A FORMAL TOTAL SYNTHESIS OF THE MARINE DITERPENOID DIISOCYANOADOCIANE

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This thesis contains no material previously submitted for a degree in any other University, and to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference is made in the text.

Kelly Ann Fairweather

The chemists are a strange class of mortals, impelled by an almost maniacal impulse to seek their pleasures amongst smoke and vapour, soot and flames, poisons and poverty, yet amongst all these evils I seem to live so sweetly that I would rather die than change places with the King of Persia.

Johann Joachim Becher, *Physica Subterranea* (1667)

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This thesis describes a formal total synthesis of the marine diterpenoid, diisocyanoadociane (**1.10**).

Chapter 1 provides a brief survey of isonitrile marine natural products, including the isolation, biological function, biosynthesis and previous synthetic studies of these compounds. A strategy for the synthesis of diisocyanoadociane is also introduced.

Chapter 2 covers our problems with the previous synthetic sequence to ketone **1.95**, and our efforts to improve it by utilising an epoxidation to install the required carbonyl group.

The first half of Chapter 3 discusses the Birch reduction of the A-ring, and investigations into the proposed reductive acylation and alkylation reactions. The second half covers an alternative approach to elaboration of the A-ring, and a successful synthesis of an intermediate (**3.36**) bearing a quaternary centre with the correct stereochemistry for C-7 in the natural product.

Chapter 4 discusses an improved synthesis of aldehyde **1.98**, in particular an alternative method for cyclopropanation. This chapter will also cover the Birch reduction of the A-ring, and a successful synthesis of an intermediate (**4.17**) bearing both quaternary centres with the correct stereochemistry for C-7 and C-20 in the natural product.

Chapter 5 covers the difficulties encountered with the intramolecular Michael reaction, and the successful synthesis of a tetracyclic precursor (**1.87**) to diisocyanoadociane (**1.10**).

Chapter 6 discusses our studies towards the deoxygenation and dealkylation to obtain dicarboxylic acid **1.62**. The second part of this chapter will discuss the use of the Curtius rearrangement to complete the stereocontrolled formal total synthesis of Diisocyanoadociane (**1.10**).

The following abbreviations have been used throughout this thesis:

Ac	Acetyl
AcOH	Acetic acid
AIBN	2,2'-azobisisobutyronitrile
APT	Attached Proton Test
Bn	Benzyl
Bu	Butyl
<i>t</i> -Bu	<i>tert</i> -Butyl
<i>m</i> -CPBA	<i>meta</i> -Chloroperoxybenzoic Acid
d	Days
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DEPT	Distortionless Enhancement by Polarisation Transfer
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
DMP	Dess-Martin Periodinane
EI	Electron Impact
Et	Ethyl
EtOAc	Ethyl Acetate
h	Hours
HMPA	Hexamethylphosphoramide
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
IR	Infrared
<i>J</i>	Coupling Constant
LiHMDS	Lithium Hexamethyldisilazane
LDA	Lithium Diisopropylamide
LRMS	Low Resolution Mass Spectrometry
Me	Methyl
MgSO ₄	Anhydrous Magnesium Sulfate
Min	Minutes
MOM	Methoxymethyl
m.p.	Melting Point
NaHMDS	Sodium Hexamethyldisilazane

NMR	Nuclear Magnetic Resonance
nOe	Nuclear Overhauser Effect
Ph	Phenyl
ppm	Parts Per Million
<i>i</i> -Pr	Isopropyl
Py	Pyridine
rt	Room Temperature
TBAF	Tetrabutylammonium Fluoride
TBDMS	<i>tert</i> -Butyldimethylsilyl
Tf	Triflyl
TFA	Trifluoroacetic Acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
Ts	<i>para</i> -Toluenesulfonyl

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CHAPTER 1

Introduction

1. Introduction

The search for new antimalarial agents has become increasingly important over the last two decades, since malaria has regained its status as an extremely serious threat to the health and economic well-being of the human race in tropical and semitropical regions.¹ Of particular concern is the increasing resistance of the malaria parasite *Plasmodium falciparum* against the drugs currently in clinical use.

1.1 Isolation

Since the discovery of the antimalarial activity of axisonitrile-3 **1.1**,² much research has been focused on the isolation of compounds known to contain isonitrile and related functionalities, in order to determine whether structurally similar natural products demonstrate similar biological activity. Interestingly, the isonitrile group is rarely observed in terrestrial metabolites,³ and as such the focus has been on the isolation of these compounds from marine organisms. Approximately 80 marine diterpenoids from three classes of isonitriles and isothiocyanates have been isolated to date from marine sponges, including three acyclic diterpenes, e.g. **1.2**, 46 derivatives based on the kalihinane skeleton **1.3** and 30 derivatives based on, the amphilectane skeleton **1.4** and its derivatives, namely cycloamphilectane **1.5** and isocycloamphilectane **1.6**.³

The first marine isocyano diterpene (**1.2**) was isolated from a mixture of cyclic sesquiterpenoids found in a *Halichondria* species, by Burreson *et al.* in 1974.⁴ The corresponding isothiocyanate and formamide were also isolated. These three compounds now appear to be an exception, as the majority of diterpenoid isonitriles are polycyclic.

In 1983 Scheuer and coworkers^{5,6} isolated several novel multifunctional isonitriles from marine sponges in the genus *Acanthella*. Compounds **1.7** and **1.8** are two such

examples isolated from *Acanthella* sponges in Guam. Recently, **1.7** and similar compounds were demonstrated to have significant *in vitro* antimalarial activity.^{1,7}

Wells and coworkers^{8,9} isolated diisocyanoadociane **1.10** along with five other isonitriles in 1976 from a marine sponge belonging to the genus *Amphimedon* (ex. *Adocia*)^{3,8,10} collected near Townsville, Australia on the Great Barrier Reef. Subsequently **1.10** and other diterpenoids have been isolated from the marine sponge *Cymbastela hooperi*.¹¹

In 1996 Wright and coworkers¹¹ isolated the series of 15 diterpenes **1.9-1.23** from the marine sponge *Cymbastela hooperi*, which were found to contain isocyanate, isothiocyanate and isonitrile functionalities (Figure 1.1). The biological activity of these compounds has since been investigated. Of these 15 diterpenes, all, with the exception of **1.9**, demonstrated significant antiplasmodial activity when tested for biological activity *in vitro* against two clones of the malaria parasite *Plasmodium falciparum*. The activity of the compounds towards the mammalian KB cell line was also tested in order to calculate an experimental selectivity index (SI), which indicates whether the observed antiplasmodial activity is a specific or general toxic effect. Results showed that compounds **1.10** and **1.13**, in particular, display antiplasmodial potency and selectivity that rivals the *in vitro* results obtained with some clinically-used antimalarial drugs.¹¹ Surprisingly, the closely related compounds **1.11** and **1.12** show considerably less activity than compounds **1.10** and **1.13**, and much lower selectivity indexes (Table 1.1).

Figure 1.1: Diterpenes Isolated from the Marine Sponge *Cymbastela Hooperi*

Compound	KB cells IC ₅₀ (ng/mL)	Clone D6 IC ₅₀ (ng/mL)	Clone D6 SI	Clone W2 IC ₅₀ (ng/mL)	Clone W2 SI
1.10	4700	4.7	1000	4.3	1100
1.11	1600	45.1	35.5	28.5	56.1
1.12	2000	74.9	26.7	56.1	35.7
1.13	4300	3.2	1340	2.5	1710
chloroquine 1.25	17400	3.8	4600	50.5	340
quinine	>20000	19.4	>1030	54.6	>370
mefloquine	3500	11.5	300	3.8	920
artemisinin	>20000	2.8	>7140	2.1	>9400

Table 1.1 Cytotoxicity of Compounds 1.10-1.13 and Antimalarial Standards to KB Cells and *P. falciparum* Clones D6 and W2

Table 1.1 shows that compound **1.10** demonstrates antiplasmodial potency to *P. falciparum* clones D6 and W2 with IC₅₀ values of 4.7 and 4.3 ng/mL, respectively. By comparison, the antimalarial drug, chloroquine (CQ) (**1.25**), shows antiplasmodial potency to *P. falciparum* clones D6 and W2 with IC₅₀ values of 3.8 and 50.5 ng/mL, respectively. Thus, although compound **1.10** exhibits a somewhat less potent activity than that of CQ against the growth of CQ-sensitive D6 clones of *P. falciparum*, compound **1.10** exhibits a much more potent activity than CQ against the growth of CQ-resistant W2 clones of *P. falciparum*. In contrast, compound **1.13** exhibits more potent activity than CQ against both D6 and W2 clones of *P. falciparum*, with IC₅₀ values of 3.2 and 2.5 ng/mL, respectively.

More recently a new diterpene **1.24** was isolated from the apolar extract of the Vanuatu sponge *Axinella sp.*¹² This diterpenoid has a tetracyclic carbon skeleton characterized by a rarely found *cis*-A,B ring junction, and a double bond between the 11 and 12 positions.

1.2 Biological Activity

The malaria parasite feeds by degrading haemoglobin in an acidic food vacuole, producing free heme (FP) moieties as a by-product. At the pH of the food vacuole, the FP in oxyhemoglobin is oxidised from the Fe(II) state to the Fe(III) state with the

consequent production of a 0.5 molar equivalent of hydrogen peroxide. Both FP and hydrogen peroxide are toxic molecules that the parasite needs to destroy or neutralize. If allowed to accumulate, high levels of the FP molecules would destroy the parasite membranes. The parasite disposes of the FP partly by sequestration into a crystalline form, known as hemozoin, and partly by non-enzymatic degradation processes.¹³ Chloroquine (CQ) **1.25** and a number of other quinoline antimalarial drugs exert their activity by inhibiting FP detoxification, causing a build-up of toxic FP molecules that eventually destroy the integrity of the malaria parasite membranes.

In an attempt to understand why a series of diterpene isonitriles and isothiocyanates (**1.9-1.23**, Figure 1.1) had differential antiplasmodial activity¹ and also to derive a more detailed structure-activity relationship (SAR) for them, Wright and coworkers¹³ undertook a quasi-atomistic receptor modelling study to generate a 3D pseudoreceptor envelope about the molecular ensemble of interest. Following the modelling study, the axisonitrile-3 **1.1** and three of the diterpene isonitriles **1.10**, **1.15** and **1.16** isolated from the marine sponge *Cymbastela hooperi* were used to gain an understanding of the molecular basis of the antimalarial action of these compounds. The isonitrile compounds **1.1** and **1.10**, having the most potent antimalarial activity, were shown to interact with FP and prevent its destruction and conversion to β -hematin (the form of FP present in hemozoin).

Diisocyanoadociane (**1.10**) and **1.13**, which display the most potent antimalarial activity of the diterpenes **1.9-1.23**, possess an isonitrile (in the case of **1.10**) or an isocyanate (in the case of **1.13**) group in the α -orientation at C-20 (Figure 1.2)*. All compounds lacking these potentially interacting functionalities are at least 10-fold less active. However, compounds **1.11** and **1.12** also possess an isonitrile group at C-20, and their activity is approximately 10-fold less than compounds **1.10** and **1.13** (Table 1.1). Therefore, the functionality at C-20 cannot be solely responsible for the biological activity.

* These structures are based on the isocycloamphilectane skeleton **1.6**, the numbering of which derives from the amphilectane skeleton **1.4**.³

Figure 1.2

From their molecular modelling studies, Wright and coworkers¹³ were able to conclude that the most significant structural feature for receptor complementarity of the active diterpenes was the overall lipophilic rigid molecular core comprising at least a tricyclic framework with an equatorial-oriented isonitrile group at C-7. An additional electrostatic-governed interaction close to C-20 of the common ring framework is also essential for activity, as well as a further hydrophobic region above the ring plane. This suggests that the 'receptor' for these isonitriles within the malaria parasite is hydrophobic in nature but capable of forming electrostatic interactions with functional groups on the drug surface.

The interaction of some terpene isonitriles with FP was also investigated. First, the effect of the isonitrile compounds on the visible absorption spectrum of FP was examined. The mixing of FP with compounds **1.1** and **1.10** produced a marked effect on the absorption spectrum of FP, which is consistent with the formation of mono- or bis-coordinated drug-FP complexes. In addition, **1.15** and **1.16**, two isonitrile compounds that show little antimalarial activity, showed little effect on the FP absorption spectrum, indicating that no coordination complex was formed between the FP and **1.15** or **1.16**. Thus, the ability to form a coordination complex with FP appears to correlate with the antimalarial activity of the compounds.

To investigate further the nature of the complex formed between the isonitrile compounds and FP, 1 : 1 mixtures were subjected to electrospray ionisation mass spectrometry (ESI-MS). It was found that **1.10** preferentially forms a 2 : 1 complex with FP, while **1.1** preferentially binds in a 1 : 1 complex with FP. The binding in the complexes most likely occurs via a coordinate bond between the axially-oriented group (-NC in the case of **1.1** and **1.10**) and the iron within the porphyrin. The resultant complexes are further stabilised by van der Waals-type interactions between the porphyrin and the respective ligands.

From the studies carried out by Wright and coworkers¹³ it appears that the active isonitriles exert their activity by interfering with a range of FP detoxification processes, analogous to that of quinoline antimalarial drugs. These processes include: inhibiting the decomposition of hydrogen peroxide, inhibiting the peroxidative destruction of FP and the glutathione-mediated break down of FP, and interfering with β -hematin formation. These combined effects appear to lead to a build up of toxic moieties which irreversibly damage proteins and lipids within the parasite.

1.2.1 Synthetic Antimalarial Analogues of Isonitrile Diterpenoids

In the course of research exploiting the chemistry of arene tricarbonyl chromium (0) complexes, Schmalz and coworkers¹⁴ were able to synthesis analogues of marine isonitrile diterpenoids based on natural products. **1.26** and **1.27** are examples based on the amphilectane skeleton **1.4**.

The samarium (II) iodide mediated cyclisation of an imine possessing an arene tricarbonylchromium complex such as in **1.28** gives rise to tricyclic products such as **1.29** and **1.30**. These products were then converted into the corresponding isonitriles **1.31** and **1.32** by standard procedures, after oxidative decomplexation to remove the chromium species and hydrogenolysis to remove the benzyl nitrogen protecting group (Scheme 1.1).

Scheme 1.1: Samarium Iodide Mediated Cyclisation

An analogue with an unsaturated side-chain, as found in some of the natural products (such as **1.27**), was also synthesised. In this case, to avoid any undesired hydrogenation of the side-chain double bond under the hydrogenolysis conditions, an *O*-allyl oxime derivative was used, rather than the benzyl protected derivative. Under similar conditions as seen in Scheme 1.1, both cyclisation and the *N*-deprotection proceeded in a single synthetic operation. The resulting amine (**1.34**) could be converted into the corresponding isonitrile (**1.35**) by standard procedures (Scheme 1.2).

The synthetic analogues **1.31**, **1.32** and **1.35**, as well as a nitrile derivative of **1.35**, were entered into an *in vitro* assay using the well known antimalarial compounds chloroquine (**1.25**) and artemisinin as standards. Antiplasmodial activity was then determined using two strains of *P. falciparum* (NF54 and KI). All of the isonitriles were tested and found to exhibit significant antimalarial activity. By comparison, the nitrile derivative was found to be virtually inactive, thus confirming the importance of the isonitrile group for biological activity.

The synthetic analogues **1.31**, **1.32** and **1.35** when tested had activities one order of magnitude lower than those of their natural counterparts. Compound **1.31**, in which the isonitrile group has the configuration of that seen in the natural product, was almost twice as active as its diastereomer **1.32**. Interestingly, the introduction of the unsaturated side-chain resulted in minimal increase in biological activity.

These results reveal the general antimalarial potential of structurally simplified analogues.

1.3 Biosynthesis

The biosynthesis of diisocyanoadociane is not straightforward. It has been postulated that **1.10** is terpene-derived and results from methyl migration during a unique

cyclisation of a C₂₀ precursor.^{8,10,15} At least three different foldings of the C₂₀ precursor lead to the desired skeleton (Figure 1.3).¹⁵

Figure 1.3

The biochemical origin of the isocyanide groups in **1.10** and other isocyanide containing marine natural products has been an area of much investigation since their isolation. It has been established through incorporation studies with sodium [¹⁴C] cyanide that the isonitrile carbons are derived by functionalisation of a terpene precursor using inorganic cyanide.¹⁰ In more recent studies it has been shown through labelling with sodium [¹⁴C] thiocyanate that inorganic thiocyanate in addition to cyanide is utilised by *A. terpens* for isocyanide biosynthesis, confirming that cyanide and thiocyanate are used interchangeably in marine sponges for terpene functionalisation (Figure 1.4). Furthermore, organic isothiocyanates are utilised by *A. terpens* as precursors to isocyanides.¹⁶

Figure 1.4

It is surprising that a marine invertebrate would utilise cyanide in view of the known role of cyanide as a potent cytochrome oxidase inhibitor. Since *Amphimedon sp.*, like many other sponges, contains bacterial symbionts, it is not clear whether the animal host or the bacterial symbiont is responsible for the uptake of cyanide. Many strains of

bacteria are known to have developed cyanide insensitive respiratory chains, or to generate inorganic cyanide from amino acids. However, other isocyanide-producing sponges are known to contain negligible amounts of symbionts, which is consistent with the uptake of the cyanide directly into the sponge cells. Demonstration of the functionalisation of **1.10** also fits with the uptake of cyanide directly into the sponge cells.¹⁷

The origin of the cyanide accumulated in **1.10** by *Amphimedon sp.* has been investigated. The concentration of cyanide in sea water is presumably negligible, except perhaps in industrially polluted waters. Hence, by analogy with terrestrial metabolic processes such as the biosynthesis of cyanogenic glycosides or ethylene, the ultimate source of the cyanide may be an amino acid. Several amino acids have been tested as potential precursors of diisocyanoadociane, including [U-¹⁴C]alanine, [U-¹⁴C]leucine, [2-¹⁴C]glycine, and [guanidino-¹⁴C]arginine. In each case, precursor uptake could be demonstrated both by loss of ¹⁴C from the incubation medium and subsequent detection of ¹⁴C in the sponge tissue. However, none of these precursors generated labelled diisocyanoadociane. Sponges contain many unusual amino-acids along with the common protein amino-acids, and it is highly plausible that one of these specific amino acids may act as a cyanide precursor.¹⁵

1.4 Previous Synthetic Studies

1.4.1 Total Synthesis of a Diisonitrile Tricyclic Diterpene

A member of the isonitrile diterpene family, **1.46**, an analogue of the tricyclic diterpene **1.19**, has been synthesised by Piers and Llinas-Brunet in a 20 step synthesis from stannane **1.38** (Scheme 1.3).¹⁸ The bicyclic intermediate was obtained by the one-pot conversion of **1.38** into the corresponding trifluoromethane sulfonate, followed by a Pd (0)-catalysed intramolecular coupling reaction. A Diels-Alder reaction was then used to give the tricyclic compound **1.40** as the major product after base-catalysed equilibration. A dissolving metal reduction on compound **1.41** was employed to give the all *trans*-ring system **1.42**, as required for the natural product. Worthy of note in this synthesis is the stereospecific incorporation of the isonitrile groups into **1.46**. This was achieved in four steps from the diacid **1.43**, via the corresponding dicarbamate **1.44** and diformamide **1.45** (Scheme 1.3).

Scheme 1.3: Total Synthesis of 1.46

1.4.2 Total Synthesis of a Member of the Kalihinane family

The first total synthesis of Kalihinol C (**1.52**), a member of the Kalihinane family of marine diterpenoids, has recently been reported by Wood and coworkers.¹⁹ Of interest in this synthesis is the installation of the equatorial nitrogen at C-10 by aziridination of the *exo*-methylene derivative **1.47**. The desired aziridine **1.48** was formed with 5 : 1 diastereoselectivity. Later in the sequence this terminal aziridine could be treated with Super-Hydride[®] to give the corresponding tertiary amine, and subsequent treatment with ammonium azide gave the azido-alcohol **1.50**. Treatment of intermediate **1.50** with sodium metal then resulted in simultaneous tosyl deprotection and azide reduction to afford the bisamine **1.51**. Formylation and dehydration were then employed to give Kalihinol C (**1.52**) in 39% over the three steps (Scheme 1.4).

1.4.3 Total Synthesis of Diisocyanoadociane (1.10)

As previously mentioned, diisocyanoadociane (**1.10**) was the first of the unusual diterpene isonitriles from the sponge *Amphimedon* to be isolated. The skeleton of the molecule consists of four cyclohexane rings, all *trans*-fused and in a chair conformation, with two isonitrile groups. The skeleton is unusual in that the rings have no angular methyl substituents. The unusual structure, biosynthesis, and potent biological activity of this compound have given rise to a great deal of interest amongst chemists and biochemists. Interestingly, only one total synthesis of diisocyanoadociane (**1.10**) exists to date. Corey and Magriotis achieved an enantioselective (60% e.e.) total synthesis of **1.10** in 27 steps from the acid chloride **1.53** (Scheme 1.5), thus allowing assignment of the absolute configuration.²⁰ The observed enantiomeric excess of 60% was in accordance with that determined for the first chiral intermediate, which was obtained via a diastereoselective Michael addition to convert the ethylene ketal **1.54** to the diester **1.55**, using menthol as a chiral auxiliary. The tetracyclic skeleton was then obtained from two intramolecular Diels-Alder cycloadditions. The first of these reactions occurred stereoselectively, resulting in the *trans*-fused adduct **1.57**, which has the correct stereochemistry for the natural product. The second intramolecular Diels-Alder reaction gave two diastereomeric products resulting from *cis* addition to each of the two faces of the dienophile **1.58**, with a ratio of 1.5 : 1 in favour of the desired adduct **1.59**. The more stable all *trans*-fused tetracyclic skeleton **1.60** was obtained at a later stage in the synthesis through base catalysed epimerisation. The two isocyanide groups were

then introduced in a single biomimetic operation on the bistrifluoroacetate **1.61**, by treatment with trimethylsilyl cyanide and titanium tetrachloride. A mixture of four diastereomeric diisonitriles was obtained in a total overall yield of 70%, including **1.10** in unspecified yield (Scheme 1.5).

Scheme 1.5: Total Synthesis of Diisocyanoadociane (**1.10**)

1.5 ANU Strategy for the Synthesis of Diisocyanoadociane (**1.10**)

As in the Piers synthesis (Section 1.4.1)¹⁸ we planned to utilise the Curtius rearrangement of the corresponding acyl azide of dicarboxylic acid **1.62** for the stereoselective incorporation of the isonitrile groups (Scheme 1.6).

Scheme 1.6: Curtius Rearrangement of **1.62**

Worthy of note is that Garson and coworkers^{15,21}, during the course of [¹⁴C]-labelling studies into the biochemical origin of the isocyanide groups, obtained amine **1.63** by

direct hydrolysis of diisocyanoadociane (**1.10**). Subsequently they were able to carry out formylation and dehydration reactions to reconstitute the natural product **1.10**.

To prepare the dicarboxylic acid **1.62** Mander and Crabtree devised the following plan (Scheme 1.7).

Scheme 1.7: Synthetic Plan for Diacid 1.62

Methodology towards the tricyclic aldehyde **1.65** had been well established previously in the group.^{22,23} It was envisaged that the tetracyclic skeleton (**1.67**) of the natural product could be obtained by an intramolecular Michael reaction on an all *trans*-fused tricyclic enone intermediate **1.66**. As this reaction is reversible, the thermodynamically most stable *trans*-fused product would be expected.

1.5.1 Work Carried Out by Crabtree

In work by Crabtree²⁴ a tetracyclic skeleton **1.69** with the desired *trans-anti-trans*-stereochemistry at all but two bridgehead carbons (labelled *), and the quaternary centre with the correct stereochemistry in the A-ring, was completed in 18 steps from aldehyde **1.65**. The key intramolecular Michael addition produced a 70% yield of **1.69** from **1.68** (Scheme 1.8).

Starting with aldehyde **1.65** as a building block, a 1,4-dissolving metal reduction was carried out on the corresponding ester **1.70** to give the *cis*-fused product **1.71**, a result that was unexpected (Scheme 1.9).

The 1,4-reduction of octalones to give a *trans*-ring fusion, by contrast, is well precededented.²⁵ The observed *cis*-ring fusion in compound **1.71** can be explained by analysis of the possible conformations of the radical benzylic anion intermediate that result on conjugate reduction (Figure 1.5).

Only the two radical benzylic anion intermediates **1.72** and **1.73** satisfy the orbital overlap requirements between the β -carbon and the enolate system. In the case of **1.73**, which would lead to a *trans*-fused product, the exocyclic ester function is in the plane of the aromatic ring, resulting in a severe *peri* interaction. In the conformation **1.72**, that acts as the precursor to the *cis*-fused product, this destabilising *peri* interaction is avoided. Thus, the product with a *cis*-ring fusion is observed in the above dissolving metal reduction.

Also worthy of note is the reduction of the angular ester group in **1.70** to the corresponding hydroxymethyl derivative. This reduction is not expected in the absence of an alcohol. It was presumed that the ammonia in the reaction must act as a proton

source for this reduction as well as the β -protonation of the benzylic anion intermediate formed from the 1,4-reduction of the enone system.

Elaboration of the ester group in compound **1.71** was then carried out in order to install the side chain required for formation of the fourth ring. A Birch reduction, followed by careful control of the double bond isomerisation, formed the α,β -enone **1.76** without removal of the acid sensitive protecting group (Scheme 1.10).

Scheme 1.10: Birch Reduction of the A Ring

Reductive acylation then resulted in the formation of the required A,B-*trans* ring fusion and gave a modest yield of the β -keto ester **1.77**.²⁶ Alkylation followed to introduce the desired axial methyl group in compound **1.78** (Scheme 1.11).

Scheme 1.11: Reductive Acylation and Alkylation

Alkylation along the axial vector under stereoelectronic control (Figure 1.6) for this type of compound is well preceded,²⁷ provided that there is no undue steric hindrance.^{28,29}

Figure 1.6

The introduction of the enone double bond was the next step in the reaction sequence. Selenium based chemistry was utilised for this transformation, but the yields were poor. Furthermore, in order to avoid the formation of the cyclic ether **1.81**, it was necessary to remove the MOM ether protecting group before the enone function could be installed. Nevertheless, a small quantity of enone **1.68** was obtained (Scheme 1.12).

Scheme 1.12: Formation of Enone 1.68

Initial attempts to perform the base catalysed intramolecular Michael reaction utilising DBU, and potassium *t*-butoxide in *t*-butyl alcohol, were unsuccessful, but potassium carbonate in methanol, was found to give the tetracycle **1.69** in 71% yield (Scheme 1.13).

Scheme 1.13: Intramolecular Michael Addition

A major problem with the route outlined above is the formation of the *cis*-ring fusion between the B and D-rings early in the reaction sequence. In order to correct the stereochemistry to give the all *trans*-fused tetracycle, epimerisation would need to occur at two bridgehead carbons (labelled *). The oxidation of the olefinic bond to the corresponding ketone **1.82** and deprotection of the angular methoxymethyl group has the potential to allow for both removal of the angular group (retro-aldol reaction) and epimerisation on treatment with base. However, in order to allow for the concomitant epimerisation at the other bridgehead carbon, the other ketone group must also remain. This presents an additional problem, as if the epimerisation is successful, both ketone groups will have identical local environments within the product (**1.83**). Thus, differentiation between the two ketone groups may be difficult if not impossible (Scheme 1.14).

Scheme 1.14: Correction of *cis*-Ring Fusion

1.5.2 A Revised Approach

In order to avoid the problems associated with the B,D *cis*-ring fusion, a new approach was devised, in which the B,D *trans*-ring fusion could be established by means of a retro-Claisen reaction, before the key intramolecular Michael addition (Scheme 1.15).

Scheme 1.15: Revised Synthesis of Diacid **1.62**

As a prelude to the current research,³⁰ an analogue of ketone **1.85** was synthesised in a 12 step sequence, shown in Scheme 1.16. Tricyclic precursor **1.88** was synthesised according to methodology developed previously in the group.²²⁻²⁴ Alcohol **1.88** was then protected as the TBDMS ether **1.89**, and a hydroboration reaction was carried out on the less sterically hindered double bond to produce the alcohol **1.90**. After further manipulations, the tetrasubstituted double bond in enone **1.91** was reduced by means of a 1,4-conjugate reduction affording the *cis*-ring fused product **1.92**, although in poor yield. The *cis*-ring fusion was later corrected to give the desired *trans*-ring fused product **1.95** via a retro-Claisen reaction on keto-aldehyde **1.94**. Although the benzoate bearing side chain in **1.95**, which was eventually to be used in the formation of the fourth ring to complete the tetracycle, has the incorrect stereochemistry (confirmed by X-ray crystallography³⁰) for the formation of the natural product, it was believed that this stereocentre could be corrected by epimerisation at a later stage in the synthesis.

Scheme 1.16: Synthesis of Ketone 1.95

Ketone **1.95** was further elaborated with the formation of the quaternary centre which becomes the isonitrile bearing centre in the D-ring (C-20) of **1.10** (Scheme 1.17). We hoped to obtain intermediate **1.98** via the methylation of the exocyclic enolate of aldehyde **1.97**, which could be obtained after a Wittig reaction on ketone **1.95**. We expected alkylation of aldehyde **1.97** to occur along the less sterically crowded equatorial vector,³¹ but unfortunately, our attempts to incorporate an equatorial methyl group at C-1 (C-20 in the natural product) in the D-ring by alkylation of aldehyde **1.97** were unsuccessful (Scheme 1.17).

The required equatorial methyl group in **1.98**, however, was installed by an acid-catalysed-ring-opening reaction of the methoxy cyclopropane moiety in **1.99**.³² This intermediate was obtained from ketone **1.95** via the enol ether **1.96** by employing a Wittig reaction followed by subjecting the resulting enol ether **1.96** to Simmons-Smith conditions, or treating with diazomethane and a catalytic amount of palladium acetate. The methoxy cyclopropane **1.99** was then treated with concentrated hydrochloric acid in acetone at reflux to obtain the methylated derivative **1.98** with the required stereochemistry, as confirmed by one dimensional nuclear Overhauser enhancement (nOe) NMR experiments³⁰ (Figure 1.18).

In view of this result, the methoxy cyclopropanated precursor **1.99** must have been formed by addition of the methylene unit to the exo face of the enol ether **1.96** (Figure 1.7).

1.6 Current Study

The aim of the current study has been to blend and improve the procedures established thus far into a cohesive route to diisocyanoadociane (**1.10**).

The formation and relative stereochemistry of the two isonitrile bearing quaternary carbons, C-7 and C-20 in the A and D-rings respectively of diisocyanoadociane (**1.10**), has previously been established separately on similar tricyclic intermediates as discussed.^{24,30} As mentioned above, a synthetic route to aldehyde **1.98**, with the correct stereochemistry for the quaternary centre at C-20 and the desired *trans*-fusion between the B and D-rings, had been achieved. We envisaged applying the Birch derived methodology developed by Crabtree (Scheme 1.10 and 1.11) to afford the carboxylic

acid **1.101**, with the consequential elaboration of the quaternary centre in the A-ring. Based on this work, the β -keto ester **1.102** would be obtained via a reductive acylation²⁶ of the enone **1.101** corresponding to **1.100** after a Birch reduction of the aromatic ring. The axial methyl group at C-7 could then be introduced by alkylation of the corresponding enolate of the β -keto ester **1.102**, under stereoelectronic control (Figure 1.6), to give compound **1.103** (Scheme 1.19). The use of a dissolving metal reduction in order to facilitate the regioselective installation of the required acyl group would also result in the formation of the A,B-*trans* ring fusion required in our target **1.102**.

Following on from work carried out by Crabtree²⁴ it was envisaged that the tetracyclic skeleton **1.87** of the natural product could be obtained by an intramolecular Michael reaction on an all *trans*-fused tricyclic enone intermediate **1.86**. As this reaction is reversible, the thermodynamically most stable *trans*-fused product, with an equatorial methyl group next to the carbonyl function, would be expected. As mentioned above, from earlier work³⁰ we expected the ketone bearing side chain to have the incorrect stereochemistry for the formation of the all *trans*-fused tetracycle. However, it appeared plausible to invert the configuration at C-1 at the same time as inducing the planned intramolecular Michael reaction. Deoxygenation and demethylation would then follow to give the dicarboxylic acid **1.62** (Scheme 1.20).

Scheme 1.20: Proposed Intramolecular Michael Reaction

CHAPTER 2

Improved synthesis of Ketone 1.95

2. Improved Synthesis of Ketone 1.95

This chapter will cover our problems with the previous synthetic sequence to ketone 1.95, and our efforts to improve it by utilising an epoxidation to install the required carbonyl group.

As already discussed, ketone **1.95** was previously synthesised by a 12 step sequence from alcohol **1.88** (Scheme 1.16, Chapter 1).³⁰ A major problem with this route to **1.95** is the many additional steps required, owing to numerous protecting group manipulations, oxidations and reductions. Furthermore, there are steps in the sequence with unacceptable yields. For example, the best yield that could be obtained in the hydroboration reaction to form **1.90**, even after extensive attempts to optimize the reaction, was at best 69%, but more commonly 45-55%. By far the most problematic step in the sequence, however, was the 1,4-conjugate reduction of **1.91**, which gave a dismal yield (45%) of the required intermediate **1.92**.

Scheme 2.1: Hydroboration and 1,4-Conjugate Reduction

In contrast, when this reaction was applied to the simpler enone **2.1**, the reduced product **2.2** was obtained in 75% yield (Scheme 2.2).

Scheme 2.2: 1,4 Conjugate Reduction of Enone 2.1

In view of the higher yield, it was decided to reduce the tetrasubstituted double bond before elaboration of the less sterically hindered double bond. To this end, attention

was focused on the synthesis of enone **2.1**, which was previously obtained by a three step procedure shown in scheme 2.3.

The allylic alcohol **1.88** could be obtained in high yield as a single diastereomer of unspecified stereochemistry from **1.65**, as previously reported by Crabtree,²⁴ then oxidation with Dess-Martin periodinane (DMP)³³ gave enone **2.1** in modest yield.

In the present study, it was found that enone **2.1** could be synthesised in one step by Friedel Crafts acylation^{34,35} of the styrene bond in **1.64**, using aluminum chloride as the Lewis acid and propionyl chloride at -78 °C in DCM. Not only were two steps saved by utilising the acylation reaction, but the reaction time for acylation was also reduced from 7 days to 20 minutes (Scheme 2.4).

We ascertained that it is important to carry out the Friedel Crafts acylation reaction at -78 °C. Initially the reaction was attempted at room temperature, whereupon none of the desired enone was obtained. Instead, a puzzling tetracyclic compound was isolated, and eventually assigned the structure **2.3**. The ¹H NMR spectrum exhibited a doublet at 2.21 ppm and a quartet at 6.61 ppm, each with a coupling constant of 7.6 Hz which could be attributed to the methyl group and proton respectively on the exocyclic double bond. It was thought that the desired acylated compound **2.1** was formed initially, then

the aromatic ring cyclised onto the carbonyl carbon, followed by dehydration to form the external double bond. A proposed mechanism is outlined in Scheme 2.5.

Scheme 2.5: Proposed Mechanism for the Formation of 2.3

The 1,4-reduction was then carried out as before by the addition of enone **2.1** to lithium metal dissolved in freshly distilled ammonia, followed by quenching with isoprene, then treatment with aqueous ammonium chloride after removal of ammonia to give **2.2** in 75% yield (Scheme 2.2).

Scheme 2.2: 1,4 Conjugate Reduction of Enone 2.1

Like the example shown in Scheme 1.9, (Chapter 1), the enone **2.1** underwent reduction of the angular methoxycarbonyl group, to the corresponding hydroxymethyl derivative, and gave the product **2.2** assumed to have a *cis*-ring fusion by analogy with the Crabtree example (**1.71**, Scheme 1.9 and Figure 1.5). Once the required reduced product **2.2** was synthesised in large quantities with acceptable yields, our focus turned to improving the “oxygenation” of the double bond. In view of the lack of success in producing high yields of the alcohol **1.90** utilising a hydroboration reaction, Scheme 2.1 (discussed in Chapter 1, Section 1.5.2), we went in search of an alternative approach.

To this end, we decided to explore an epoxidation based route. In preparation for the planned epoxidation reaction, compound **2.4** was synthesised bearing suitable protecting

groups. The free hydroxy group in **2.2** was first protected as the MOM ether, followed by reduction of the ketone group with lithium aluminum hydride. Protection of the resulting free alcohol as the benzoate gave compound **2.4** as one epimer in 90% yield over the three steps. An epoxidation reaction was then carried out by treatment of olefin **2.4** with *m*-CPBA, using sodium bicarbonate as a buffer, to give the epimeric epoxides **2.5** in 60% yield. The formation of the epoxides was evident by analysis of the ^1H NMR spectrum, from the presence of two new singlets at 2.82 ppm due to the major epoxide epimer and 2.90 ppm due to the minor epoxide epimer; also the singlet due to the double bond proton in the starting material at 5.04 ppm had disappeared. We then attempted to perform a 1,2-hydride shift using the Lewis acid boron trifluoride diethyl etherate at 0 °C. Rather than the desired ketone, however, a mixture of products was formed. The structure of the major product appeared to be **2.6** (Scheme 2.6). The 1,2-hydride shift of compound **2.5** was also attempted at -78 °C, but no reaction occurred.

The product **2.6** can be derived from cyclisation of the angular MOM ether onto the D-ring with the consequential opening of the epoxide to give a tertiary alcohol and loss of a methyl group (Scheme 2.7).

In view of this result, it was decided to replace the MOM protecting group with an acetate function. Initially the hydroxymethyl substituent of compound **2.2** was protected as the acetate, but, on reduction of the ketone (sodium borohydride in this case), two epimeric alcohol products in a ratio of 1 : 5 were obtained. It appeared that the steric bulk of the MOM protecting group was such that it allowed hydride to approach only one face. Therefore, compound **2.4** was synthesised as described above, followed by removal of the MOM protecting group by heating in methanol with hydrochloric acid to afford the parent alcohol, which was subsequently protected as the acetate **2.7** in 81% yield over the two steps. With the acetate installed, the epoxidation was carried out as before to give the epimeric epoxides **2.8** in 85% yield. In this case, the 1,2-hydride shift occurred smoothly on treatment with boron trifluoride diethyl etherate at 0 °C, to give **2.9** as a mixture of 2-C epimers in 75% yield (Scheme 2.8).

Next, ketone **2.9** was treated with potassium hydroxide in ethanol to remove the acetoxymethyl group and establish the required *trans*-ring fusion at the carbon alpha to the ketone group by a retro-aldol reaction.³⁶ Under these conditions, the C-2 centre also underwent epimerisation thereby affording **1.95** in 70% yield (Scheme 2.9).

In summary, by the use of the above methodology, we were able to improve the synthetic sequence to ketone **1.95** to produce acceptable yields and a reduction in the total number of steps.

CHAPTER 3

Birch Reduction and Elaboration of the A-Ring

3. Birch Reduction and Elaboration of the A-ring

The first half of this chapter will discuss the Birch reduction of the A-ring, and investigations into the proposed reductive acylation and alkylation reactions. The second half covers an alternative approach to the elaboration of the A-ring, and a successful synthesis of an intermediate (3.36) bearing a quaternary centre with the correct stereochemistry at C-1 (equivalent to C-7 in the natural product).

3.1 Birch Reduction

We decided to explore the Birch reduction, and the ensuing chemistry to install the quaternary centre in the A-ring, on the readily accessible intermediate **1.95**. This compound has the required *trans*-ring fusion for the D and B rings, but it lacks the functionality at C-1 (equivalent to the C-20 quaternary centre in the natural product).

Thus, ketone **1.95** was reduced with L-selectride[®] ³⁷ to afford 88% of the alcohol **3.1** as one epimer.* Reduction with the less bulky reducing agent, sodium borohydride, gave two epimeric alcohols in a 2 : 1 ratio. The alcohol **3.1** was then converted to the MOM ether **3.2** in 86% yield. Because of concerns over the stability of the benzoate function in the Birch reduction, replacement by the TBDMS group was undertaken. Thus, the benzoate group was removed by heating **3.2** with sodium ethoxide in ethanol, affording alcohol **3.3** in 95% yield. We then attempted to install the desired TBDMS group using TBDMSCl in DMF and a catalytic amount of imidazole, a method commonly used for this conversion.³⁸ Unfortunately, even after stirring this reaction mixture for 2 days, only 52% of the desired TBDMS ether **3.4** was obtained, based on recovered starting material. However, we were pleased to find that a good yield of **3.4** could be obtained within 20 minutes by using a method developed by Corey³⁹, whereby the alcohol **3.3** was treated with TBDMSOTf and 2,6-lutidine in DCM (Scheme 3.1).

* The stereochemistry of the alcohol **3.1** was confirmed at a later stage in the synthesis by X-ray crystallography (see Figure 5.3, Chapter 5)

Scheme 3.1: Formation of a Suitable TBDMS Ether

The Birch reduction of **3.4** proved to be stubborn. We attempted the reduction of **3.4** to **3.5** with both methanol and ethanol as the proton sources, but no reaction occurred. We believed that in both the above cases, the respective alcohol was reacting faster with the dissolved lithium metal than compound **3.4**. We hypothesised that better results could be obtained using the less reactive reagent, *t*-butyl alcohol, as the proton source. Acting on this hypothesis, we repeated the Birch reduction on a small scale (*ca.* 100 mg) using *t*-butyl alcohol as the proton source, and stirring for 40 minutes gave 100% conversion of compound **3.4** to the dihydroanisolet moiety **3.5**. Unfortunately, on a larger scale this reaction resulted in a large amount of recovered starting material. After having tried a range of reaction times and conditions, it was finally found that the best results could be obtained by stirring at -40 °C for 3 hours with *t*-butyl alcohol as the proton source and a large excess (50 equivalents) of lithium metal. Presumably, the bulky side chain interferes with solvation of the intermediate aromatic radical-anion.

The dihydroanisolet moiety **3.5** was then isolated, and on treatment with a mixture of acetic acid, THF and water (4 : 2 : 1),⁴⁰ the β,γ -enone **3.6** was obtained. Conversion to the desired α,β -enone **3.7** occurred on treatment with anhydrous hydrogen chloride gas in THF to give a yield of 71% over the three steps. The conversion of **3.6** to **3.7** needed to be followed closely, as when the reaction was left for longer than 20 minutes we started to see more polar products by TLC, which could be attributed to deprotection of the MOM and TBDMS ethers (Scheme 3.2).

The formation of the α,β -enone **3.7** was evident by a distinctive singlet in the ^1H NMR spectrum at 5.81 ppm owing to the proton on the carbon-carbon double bond.

3.2 Reductive Acylation of Enone **3.7**

It was planned to set up the C-1 (equivalent to C-7 in the natural product) quaternary centre in the A-ring by reductive acylation of a suitable enone, followed by alkylation of the resulting β -keto ester. We expected this alkylation to occur under stereoelectronic control to give the required axial methyl group for the natural product, as for the conversion of **1.77** to **1.78** by Crabtree shown in Scheme 1.11 (discussed in Section 1.5.1).

Reductive acylation has been a topic of extensive studies previously in our laboratories.^{26,41} During these studies a relatively mild, reliable method for preparing β -keto esters with good ambidoselectivity was established. This methodology involves forming the required enolate by reduction with dissolved lithium metal in ammonia, followed by trapping the enolate at $-78\text{ }^\circ\text{C}$ in ether with methyl cyanoformate, then warming to $0\text{ }^\circ\text{C}$ before quenching with water. Greater than 95% ambidoselectivity had been displayed by the reagent for the C-terminus of the enolate using this procedure,

although in earlier studies, varying amounts of the enol carbonate products were isolated, using THF instead of ether as the solvent. Examples of reactions utilising this methodology are shown in Scheme 3.3.

Scheme 3.3: Examples of Reductive Acylations

It was suggested in mechanistic studies carried out by Crabtree²⁴ that the acylation proceeds via an aldol type intermediate. If these aldol intermediates were relatively long-lived under the reaction conditions, equilibrium would be set up between the *ortho* complex **3.14** and the aldol intermediate **3.15**. The aldol derivative **3.15** would then be stabilised by chelation of the lithium cation between the carbonyl oxygen and the alkoxy anion. However, in the case of **3.14**, the lithium cation can only co-ordinate to the oxygen anion. Therefore, the aldol intermediate **3.15** would be stabilised relative to the *ortho* intermediate **3.14**, displacing the equilibrium in the desired direction, and yielding the β -keto ester (**3.12**) as the major product on work-up (Scheme 3.4).

Scheme 3.4: Intermediates in the Reductive Acylation

The increased ambidoselectivity in ether relative to THF was also explained by the fact that diethyl ether is a poor solvating medium for the lithium cation. This poor solvation allows a relatively strong chelate to form between the *C*-acylated aldol intermediate and the cation, displacing the equilibrium in Scheme 3.4 in favour the desired *C*-acylated product. However, THF solvates the lithium cation to a greater extent, so the chelate is less stable.

Reductive acylation was attempted on enone **3.7** following the methodology described above. The first reaction was attempted on a small scale (*ca.* 20 mg), and gave the β -keto ester **3.16** in less than 20% yield. The reaction was repeated on a larger scale to give three products in poor yield; the desired product **3.16** was formed, but we also isolated its regioisomer (in its enol form **3.17**) and the product of simple 1,4-reduction **3.18** (Scheme 3.5).

Scheme 3.5: Reductive Acylation of Enone **3.7**

Analysis by ¹H NMR spectroscopy provided evidence for the formation of **3.16**, in that a doublet arising from the proton on the carbon bearing the ester group was present at 3.12 ppm with a diaxial coupling constant of 11.7 Hz. Furthermore a singlet at 3.75 ppm due to the ester group was observed. On the other hand, the regioisomer **3.17** exhibited a singlet at 3.73 ppm due to the ester group, and a singlet at 12.08 ppm due to the enol proton.*

In view of the poor results obtained so far in this reaction, some model studies were undertaken on the simpler enone **3.11**, which has been previously acylated in high yield

* The location of the ester function was confirmed by 2D NMR studies on the methylated derivative (see section 3.2.2).

(as shown in Scheme 3.3). The reductive acylation of **3.11**, following the previously developed methodology, resulted in none of the desired β -keto ester **3.12**, but rather its regioisomer **3.19** and the *O*-acylated product **3.13**. This reaction was followed by TLC analysis, and a great change was noticed after warming to 0 °C. After this observation, the experiment was repeated, quenching with water at -78 °C. From this experiment the desired β -keto ester **3.12** was obtained in 12% yield, plus two cyanohydrin compounds **3.20** and **3.21** in 21% and 31% yield respectively. The cyanohydrin compounds were converted to the β -keto ester **3.12** when treated with mild base. However, in order to avoid the isolation of these cyanohydrin compounds the experiment was repeated, quenching at -78 °C with 2 *M* lithium hydroxide rather than water, and followed until only one compound could be seen by TLC analysis. To our delight this resulted in the isolation of the desired β -keto ester **3.12** in 70% yield[†] (Scheme 3.6).

Scheme 3.6: Model Studies on Reductive Acylation Reaction

This new methodology was then applied to enone **3.7**, and the desired β -keto ester **3.16** was obtained in 40% yield. Although the yield of **3.16** was still quite low, it was a vast improvement on the previous attempts (Scheme 3.7).

[†] The NMR data for compounds shown in Scheme 3.6 are in accordance to that previously recorded by S.R. Crabtree, Ph.D. thesis, ANU, 1990.

Scheme 3.7: Improved Reductive Acylation of Enone 3.7

In an attempt to improve the methodology further, a two step procedure was investigated. The enolate resulting from the dissolving metal reduction was first trapped as the TMS enol ether.⁴² The enolate was then liberated in the second step on treatment with *n*-butyllithium and finally trapped with methyl cyanoformate. Applying this procedure to enone **3.7** gave ester **3.17** and a poor yield of the desired acylated product **3.16** (Scheme 3.8).

Scheme 3.8: Two Step Acylation Procedure

The best result we were able to obtain for the reductive acylation to give **3.16** was, despite our best efforts, a yield of only 40%. However, we were able to obtain enough acylated material to investigate the subsequent alkylation reaction.

3.3 Stereochemistry at the β -position of the Reductive Acylation Products

As briefly mentioned in Chapter 1, the 1,4-reduction of octalones to give a *trans*-ring fusion is well precededented.²⁵ The stereochemistry at the β -position is established by the protonation of an allylic anion intermediate. In the reduction step of the conversion of **3.7** to **3.16**, there are two possible allylic anion intermediates, **3.23** and **3.24**, which satisfy the orbital overlap requirements between the β -carbon and the enolate system.

Intermediate **3.23** has less severe 1,3-diaxial interactions than **3.24**, so it can be assumed that the kinetically favoured transition state structure will be based on the more stable conformation **3.23**, which leads to the observed *trans*-ring fusion.[▼]

3.4 Attempted Alkylation of β -keto ester **3.16**

There are numerous methods for the alkylation of β -keto esters. The methods we attempted for the alkylation of **3.16** to **3.25** are listed below:

- *Sodium hydride and iodomethane in THF at room temperature.* Alkylations of substrates very similar to that of the β -keto ester **3.16** have been carried out previously using this method.²⁴ When this methodology was applied to **3.16**, a complex mixture of products was obtained which contained none of the methylated product **3.25**.
- *Sodium hydride and iodomethane in toluene at 80 °C.*⁴³ When applied to **3.16**, only a trace amount of the product **3.25** was obtained.
- *Potassium carbonate and iodomethane in acetone at reflux.*⁴⁴ Only starting material was recovered using this procedure.
- *Potassium *t*-butoxide in benzene and *t*-butanol at room temperature.*⁴⁵ The best result was produced using this procedure, but only a small amount of the alkylated product **3.25** was obtained (Scheme 3.9).

Scheme 3.9: Alkylation of **3.16**

The results for the alkylation of **3.16** were disappointing, especially considering that the alkylation of **3.17** (the regioisomer of **3.16**) proceeded smoothly on treatment with sodium hydride and iodomethane to afford **3.26** in 65% yield (Scheme 3.10).

[▼] The *trans* relationship of the two bridgehead protons in the A-ring was later confirmed by X-ray crystallography on the advanced intermediates **1.87** and **5.2** (Chapter 5).

Scheme 3.10: Alkylation of 3.17, the Regioisomer of 3.16

The regiochemistry of acylation and stereochemistry of alkylation leading to **3.26** was determined by two dimensional NMR studies. The ^1H NMR spectrum of **3.26** exhibits a multiplet between 2.24-2.35 ppm due to the two protons on C-1 alpha to the carbonyl group. Upfield of this, a multiplet between 2.04-2.13 ppm was observed representing the two protons on C-4 and the proton on C-4a. Analysis of the COSY spectrum showed the C-1 protons were only coupled to themselves and one other proton at C-10a, therefore providing evidence of the observed regiochemistry of **3.26**. Accordingly, no relationship was observed between the protons on C-1 and C-4, which we would have expected if we had the other regioisomer (**3.25**). Analysis of the NOESY spectrum showed a correlation between a C-1 proton (presumably the axial proton) and the methyl group at C-3. An enhancement was also observed between the other proton at C-1 (presumably the equatorial proton) and the proton at C-10a. Furthermore, an enhancement was observed between the methyl group at C-3 and the proton at C-4a. Thus, the axial stereochemistry of the methyl group at C-3 was confirmed (Figure 3.1).

Figure 3.1

In summary, even after optimisation, the reductive acylation reaction provided a poor yield of the β -keto ester **3.16**. Furthermore, progress with the alkylation of **3.16** had not been encouraging thus far.

3.5 A New Approach

The following plan was devised as an alternative to installing the required quaternary centre in the A-ring (Scheme 3.11).

Scheme 3.11: New Strategy

A dissolving metal reduction would result in the saturated product with the A, B *trans*-ring fusion (**3.27**). Installing the α,β -enone **3.28** (which we require at a later stage for the intramolecular Michael reaction, see Chapter 5) would then “mask” C-3, allowing for regioselective acylation to form the β -keto ester **3.29**.

In methodology developed by Mander and Sethi,⁴⁶ a number of β -keto ester substrates have been prepared regioselectively from the lithium enolates of the parent ketones and methyl cyanoformate. The parent ketones were treated with LDA to form the lithium enolate, then subsequently trapped at $-78\text{ }^{\circ}\text{C}$ with methyl cyanoformate in the presence of HMPA. An example of the acylation of a steroidal compound, bearing similar structural characteristics to our tricyclic intermediates, is shown below (Scheme 3.12).

Scheme 3.12: Acylation of a Steroid

In another example, Fraser-Reid and coworkers applied the above procedure to the acylation of (*R*)-(-)-carvone **3.30** to afford ester **3.31** in quantitative yield⁴⁷ (Scheme 3.13).

Scheme 3.13: Acylation of (R)-(-)-Carvone

3.6 Synthesis of Enone 3.34

In order to install the enone in the required position, we first needed to reduce the enone **3.7** to set up the A, B *trans*-ring fusion. To this end, 1,4-reduction of **3.7** with lithium metal dissolved in ammonia, followed by an aqueous work up, gave the *trans*-fused product **3.18** in 92% yield (Scheme 3.14).

3.14: Dissolving Metal Reduction

In previous work by Crabtree the introduction of an enone double bond was carried out using selenium based chemistry, but the yields were poor (see Scheme 1.12).²⁴ However, a versatile method for the preparation of α,β -unsaturated carbonyl compounds was reported in 1978 by Saegusa and coworkers.⁴⁸ Saegusa's procedure involves the reaction of silyl enol ethers with palladium (II) acetate in acetonitrile to give regiospecific introduction of an α,β -carbon-carbon double bond to unsymmetrical ketones. It is believed an oxo- π -allyl palladium (II) complex (**3.32**) may be involved (Scheme 3.15).

Scheme 3.15: Saegusa Oxidation

It was decided to use the Saegusa oxidation to synthesis enone **3.34**. Ketone **3.18** was treated with LDA, and trapping the resulting enolates with TMSCl gave a 2 : 1 ratio of silyl enol ethers in favour of the required product **3.33**. The crude mixture was then treated with palladium (II) acetate in the presence of *p*-benzoquinone in acetonitrile to give an excellent combined yield of the enones **3.34** and **3.7** (Scheme 3.16). The

presence of *p*-benzoquinone in the reaction mixture appears to regenerate an active palladium (II) species.⁴⁸

Scheme 3.16: Application of the Saegusa Oxidation

The formation of enone **3.7** was inconvenient, but this was not an insurmountable problem, since the enone could be easily separated from enone **3.34** and recycled.

3.7 Regioselective Acylation and Alkylation

With enone **3.34** in hand, the next step involved regioselective acylation to form the required β -keto ester **3.35**. We were delighted to find that treating the lithium enolate of **3.34** with methyl cyanoformate, in the presence of HMPA at -78°C , gave a good yield of β -keto ester **3.35** with no by-products (Scheme 3.17).

Scheme 3.17: Regioselective Acylation

As discussed (Section 3.2.1), the results from alkylation studies of β -keto ester **3.16** had not been encouraging (Scheme 3.9). Nevertheless, we decided to investigate the alkylation of ester **3.35**, which only differs from **3.16** in that it possesses an α,β -carbon-carbon double bond. We were pleased to find that when **3.35** was treated with sodium hydride and iodomethane in THF at room temperature, the methylated product **3.36** was obtained in reasonable yield (Scheme 3.18).

Scheme 3.18: Alkylation Reaction

Although we expected the alkylation of **3.16** to occur under stereoelectronic control to give the required axial methyl group for the natural product (Figure 1.6, discussed in Chapter 1), we were unsure how the presence of the carbon-carbon double bond in the six-membered-ring of **3.35** would affect the stereochemical outcome of the alkylation.

Figure 1.6

In order to confirm the stereochemistry at C-1, the product **3.36** was subjected to one dimensional nuclear Overhauser enhancement (nOe) NMR experiments. An nOe enhancement was observed between the methyl group at C-1 and the proton at C-4a. This observation is only possible if the methyl group is axial* (Figure 3.1).

Figure 3.1

Thus, elaboration of the A-ring was successfully achieved (compound **3.36**), with the stereochemistry at six centres correct.

* The stereochemistry of **3.36** was further confirmed by X-ray crystallography on the advanced intermediate **5.2**, Chapter 5.

CHAPTER 4

Elaboration of the D-ring and a Cohesive Synthesis

4. Elaboration of the D-ring and a Cohesive Synthesis

The first part of this chapter will discuss an improved synthesis of aldehyde **1.98**, including an alternative method for cyclopropanation. The second and third parts will cover the Birch reduction of the A-ring, and a successful synthesis of an intermediate (**4.17**) bearing both quaternary centres with the correct stereochemistry at C-1 (C-7 in the natural product) and C-8 (C-20 in the natural product).

4.1 Improved Synthesis of Aldehyde **1.98**

As discussed (Section 1.5.2), aldehyde **1.98** with the required equatorial methyl group for the quaternary centre at C-1 (equivalent to C-20 in the natural product) in the D-ring was previously synthesised (Scheme 1.18).^{*}

The synthesis of **1.98** was achieved by employing an acid-catalysed-ring-opening reaction of a cyclopropyl precursor,³² which was obtained by a Simmons-Smith reaction.³⁰ A problem with this sequence was the low yielding Simmons-Smith reaction, which even after long reaction times would not go to completion. The Simmons-Smith reaction as initially carried out gave only 40% of the desired methoxy cyclopropane **1.99**. Under the initial conditions the zinc/copper couple from zinc dust and cuprous chloride was heated under reflux, then treated with methylene iodide to form the iodomethylzinc reagent.⁴⁹ The method developed by Furukawa and coworkers^{50,51}, whereby diethyl zinc is treated with methylene iodide to generate the iodomethylzinc reagent was also attempted, but was unsuccessful. We had also formed the methoxy cyclopropane **1.99** by treatment of the enol ether **1.96** with diazomethane

^{*} This Scheme is repeated from Chapter 1.

and a catalytic amount of palladium acetate.⁵² However, while the yield of this reaction was a vast improvement (70%) on previous attempts, a large excess of diazomethane was needed, and even then the reaction still could not be forced to completion. Given the poor yield of the Simmons-Smith reaction we decided to investigate alternative reagents.

In a recent publication by Yang, Lorenz and Shi⁵³ a new reactive species for cyclopropanation was reported. The iodomethylzinc reagent **4.1** was generated by the reaction of diethyl zinc with trifluoroacetic acid, followed by treatment of the resulting species with methylene iodide (Scheme 4.1).

Scheme 4.1: Formation of Reactive Iodomethylzinc Reagent

The reaction sequence to form the iodomethylzinc reagent **4.1** is carried out at 0 °C using DCM as the solvent, and the olefin is added directly to the reagent. The authors reported that the reaction is completed within 30 minutes at room temperature on a variety of olefin substrates.

When the above discussed cyclopropanation conditions were applied to the enol ether **1.96**, the reaction proceeded to completion within one hour at room temperature, affording the desired methoxy cyclopropane **1.99** in 80% yield after purification. However, a better result was achieved if purification was left to a later stage in the synthesis. To this end, the crude cyclopropane **1.99** was treated with hydrochloric acid to obtain the aldehyde **1.98**, followed by oxidation with sodium chlorite⁵⁴ to give the carboxylic acid **4.2** in 80% yield over the three steps (Scheme 4.2).

The problems that we had previously encountered with the Simmons-Smith reaction were therefore overcome. An alternative reagent for the cyclopropanation reaction was found that can be used to produce large quantities of carboxylic acid **4.2**.

4.2 Birch Reduction of the A-ring

The Birch reduction discussed in Chapter 3 was carried out on an intermediate **3.4** with a TBDMS ether in place of the initial benzoate protecting group (Scheme 4.3).

To replace the benzoate group of **4.2** with a TBDMS protecting group, the protection of the carboxylic acid group as the TBDMS ester is inevitable. The consequence of carrying out a Birch reduction in the presence of an ester group is that they are readily reduced under the reaction conditions, thus resulting in a cycle of changing oxidation states at the quaternary centre in the D-ring. We considered the possibility of carrying out the unavoidable *bis*-protection followed by a hydrolysis reaction to remove the

TBDMS ester, but this would result in an additional step to our sequence. Thus, we decided to attempt the Birch reduction on the benzoate **4.2**, in order to avoid the extra steps associated with changing the protecting group. The Birch reduction was carried out using lithium metal in ammonia, and *t*-butyl alcohol as the proton source (as discussed in Chapter 3.1), with the expectation that the benzoate protecting group would be lost in this reaction to give alcohol **4.3** (Scheme 4.4). Unfortunately, alcohol **4.3** was not obtained, but a small amount of a compound in which it appeared that the aromatic ring of the benzoate group had been reduced as well as the A-ring.

Scheme 4.4: Failed Birch Reduction

We also attempted the Birch reduction on the free alcohol **4.4**. Thus, treatment of **4.2** with sodium ethoxide in ethanol gave alcohol **4.4** in good yield. The alcohol **4.4** was then subjected to Birch conditions, but rather than obtaining the expected β,γ -enone, compound **4.5** was obtained in poor yield (Scheme 4.5). It was believed that this product formed via indiscriminate internal protonation from the free alcohol function.

Scheme 4.5: Internal Protonation During Birch Reduction

Given the lack of success thus far, we decided to protect the alcohol **4.4** as the TBDMS ether. Treatment of alcohol **4.4** with TBDMSOTf and 2,6-lutidine gave the *bis*-protected product **4.6** as expected. Fortunately, the selective hydrolysis of **4.6** proceeded smoothly on treatment with potassium carbonate in aqueous methanol to obtain a good yield of the TBDMS ether **4.7** over the two steps (Scheme 4.6).

Scheme 4.6: Silyl Ether Formation

The aromatic moiety in **4.7** underwent Birch reduction on treatment with lithium in ammonia and *t*-butyl alcohol at $-40\text{ }^{\circ}\text{C}$ for 3 hours. The initially formed dihydroanisole product was treated with a solution of acetic acid, THF and water (4 : 2 : 1) to obtain the β,γ -enone **4.8**, which could be converted on treatment with hydrogen chloride gas to a 1 : 1 mixture of **4.8** and the α,β -enone **4.9** in good yield. The two enone products were easily separated and **4.8** converted to additional α,β -enone **4.9** (Scheme 4.7).

Scheme 4.7: Birch Reduction of **4.7**

4.3 Elaboration of the A-ring

4.3.1 Synthesis of Enone **4.12**

The methodology outlined in Chapter 3 (Section 3.3) was now applied to enone **4.9** so as to install the required enone functionality and quaternary centre in the A-ring. To this end, the enone **4.9** was subjected to 1,4-reduction with dissolved lithium metal in ammonia, followed by methylation of the carboxylic acid with diazomethane to give the *trans*-fused product **4.10**. The alcohol **4.11** was also obtained, but was easily oxidised with DMP to give ketone **4.10** (Scheme 4.8).

Scheme 4.8: Dissolving Metal Reduction of 4.9

The next step required the Saegusa oxidation of **4.10** to furnish enone **4.12**. Previously, for the conversion of ketone **3.18** to enone **3.34** (Scheme 3.16) the silyl enol ether intermediates were synthesised in a 2 : 1 ratio in favour of the intermediate leading to the required enone **3.34**. Although enone **3.7** was also formed in this process (derived from the minor silyl enol ether intermediate), it could be easily recycled to form more of the required enone **3.34**.

Scheme 3.16: Application of the Saegusa Oxidation

In the case of ketone **4.10**, in order to recycle the unwanted enone (**4.9a**) formed after the Saegusa oxidation, the methyl ester group would initially need to be hydrolysed before the dissolving metal reduction, only to be re-esterified in the following step (Scheme 4.9).

Scheme 4.9: Proposed Recycling of Enone 4.9

Thus, our attention was focused on finding conditions to improve the ratio of silyl enol ether intermediates. The results from our studies are summarised in Table 4.1.

Base	Silylating Reagent	Ratio 4.14 : 4.15
LDA	TMSCl	2 : 1
LiTMP	TMSCl	2 : 1
LICA	TMSCl	2 : 1
Triethylamine	TMSOTf	5 : 1
2, 6- Lutidine	TMSOTf	20 : 1

Table 4.1: Silylation Studies

Table 4.1 shows that forming the enolate of **4.10** with LDA gives a 2 : 1 ratio of silyl enol ethers. It is well known that highly hindered bases, such as LDA, favour the formation of the kinetic, less substituted silyl enol ether.⁵⁵ Therefore, it was hypothesised that the use of even bulkier bases would increase this ratio. Acting on this hypothesis LDA was substituted by the bulkier bases lithium tetramethyl piperidine (LiTMP) and lithium isopropylcyclohexyl amide (LICA), respectively. In both cases a ratio of 2 : 1 was observed. Better ratios of **4.14** : **4.15** were observed when TMSOTf was used as the silylating reagent. Thus, ketone **4.10** was treated with triethylamine and TMSOTf to give a 5 : 1 ratio of the silyl enol ethers. We were pleased, however, to find that using 2,6-lutidine as the base increased the ratio to 20 : 1 in favour of the required silyl enol ether **4.14**.

The crude mixture of **4.14** and **4.15** obtained thus was then treated with palladium (II) acetate in the presence of *p*-benzoquinone to give a good yield of enone **4.12**, and a small amount of enone **4.9a** (Scheme 4.10).

Scheme 4.10: Saegusa Oxidation of 4.10

4.3.2 Regioselective Acylation and Alkylation

The acylation reaction of enone **4.12** was carried out as described in chapter 3 (Section 3.3.2). Thus, the lithium enolate of **4.12** was treated with methyl cyanoformate, in the presence of HMPA at -78°C to give the β -keto ester **4.16** in 83% yield. The β -keto ester **4.16** was then treated with sodium hydride and iodomethane to obtain the methylated product **4.17**, possessing the required axial methyl group[†] (Scheme 4.11).

Scheme 4.11: Regioselective Acylation and Alkylation to Form 4.17

We were pleased to find that the acylation of **4.12** and the alkylation of **4.16** proceeded in higher yields than that of their respective models **3.34** and **3.35** (Section 3.3.2).

[†] The stereochemistry was confirmed later by X-ray crystallography of the advanced intermediate **1.87**, Chapter 5.

The 300 MHz ^1H NMR spectrum obtained for the diester **4.17** is shown in Figure 4.1.

Figure 4.1: 300 MHz ^1H NMR of **4.17**

Assignment of the characteristic peaks shown in Figure 4.1 are as follows: the two methyl groups at the quaternary centres occur as singlets at the same chemical shift, 1.26 ppm; the two ester groups at the quaternary centres in the D-ring and the A-ring occur as singlets at 3.64 ppm and 3.72 ppm respectively; the carbon-carbon double bond protons occur as two doublet of doublets at 5.96 ppm and 7.28 ppm.

Thus, we had achieved the synthesis of intermediate **4.17** with the correct stereochemistry at seven centres, including both the quaternary centres in the A and the D-rings.

CHAPTER 5

Intramolecular Michael Addition Reaction

5. Intramolecular Michael Addition Reaction

This chapter will cover the difficulties encountered with the intramolecular Michael reaction, and the successful synthesis of a tetracyclic precursor (1.87) to diisocyanoadociane (1.10).

5.1 Introduction

As discussed in Chapter 1, it was envisaged that the tetracyclic skeleton **1.87** of the natural product (**1.10**) could be obtained by an intramolecular Michael reaction on an all *trans*-fused tricyclic enone intermediate **1.86**. As this reaction is reversible, the thermodynamically most stable *trans*-fused product would be expected (Scheme 5.1).

Scheme 5.1: Proposed Michael Reaction

We knew from previous work³⁰ that the centre at C-5 bearing the side chain has the incorrect stereochemistry for the Michael reaction to occur giving the all *trans*-fused tetracycle. However, it was believed that due to the presence of base, epimerisation of C-5 would readily occur and the Michael addition would follow.*

We decided to test the methodology on compound **3.36**, which should be an ideal model for ester **4.17** (Scheme 5.2).

Scheme 5.2: Proposed Model Michael Reaction

* Thus far numbering of the tricyclic derivatives has been based on phenanthrene. The tetracyclic structures that follow in Chapter 5 and 6 are numbered according to the isocycloamphilectane.

5.2 Model Studies towards the Intramolecular Michael Addition

5.2.1 Formation of Dione 5.1

In order to complete the synthesis of dione **5.1**, the removal of the TBDMS protecting group was required, followed by the oxidation of the resulting hydroxyl function to the ketone group. Removal of the TBDMS protecting group in the presence of the enone function, however, was not possible. For example, when ester **3.35** was treated with TBAF a mixture was produced, the major product isolated being the tetracyclic ether **5.3** (Scheme 5.3).

Scheme 5.3: Cyclic Ether Formation

Thus, the enone function needed to be “deactivated” before removal of the TBDMS protecting group. To this end, reduction of enone **3.36** under Luche conditions⁵⁶ resulted in formation of epimeric allylic alcohols **5.4** in 91% yield (Scheme 5.4).

Scheme 5.4: Luche Reduction of Enone 3.36

The reduction of **3.36** was characterised by a significant up field shift in the double bond proton at C-4 in the ^1H NMR spectrum, from 7.18 ppm to 5.96 ppm. Furthermore, a new peak was observed as a multiplet at 4.73 ppm due to the proton at C-2.

Allylic alcohol **5.4** was treated with TBAF at 65 °C in the presence of 4Å powdered molecular sieves to obtain the diol **5.5** in good yield (Scheme 5.5). Although deprotection could be conducted at room temperature, the reaction was very slow.

Scheme 5.5: Deprotection Reaction

All that remained in order to complete the synthesis of **5.1** was the oxidation of the hydroxyl groups. Thus, treatment of diol **5.5** with an excess of DMP gave the required dione **5.1** in 81% yield (Scheme 5.6).

Scheme 5.6: Double Oxidation of Diol 5.5

The formation of the dione **5.1** was evident by two new carbonyl peaks in the ^{13}C NMR spectrum at 198.9 ppm and 213.6 ppm, as well as the shift of H-4 to 6.85 ppm.

5.2.2 Intramolecular Michael Reaction

The intramolecular Michael reaction of compound **5.1** proved problematic. Initially we utilised Crabtree's conditions, i.e. potassium carbonate in methanol (see Chapter 1, Section 1.5.1), but no reaction occurred. The reaction was also attempted under reflux, but only starting material was recovered. The reaction was then attempted under the range of reaction conditions summarised in Table 5.1 below.

Conditions	Time	Result
$\text{K}_2\text{CO}_3/\text{MeOH}$ r.t and Δ	24 h	No reaction
DBU/MeOH r.t and Δ	24 h	No reaction
$\text{KO}^t\text{Bu}/t\text{-BuOH}$	24 h	Complex mixture
KH/THF	24 h	No reaction
KH/DMF	24 h	Complex mixture
HCl/MeOH	24 h	MOM deprotection

Table 5.1: Results for attempted intramolecular Michael Addition

The results shown in Table 5.1 were disappointing. Substituting DBU for potassium carbonate had no effect on the outcome of the reaction, both at room temperature and at reflux. Potassium hydride in THF also gave only recovered starting material. We hoped to increase the reactivity by substituting THF for the polar aprotic solvent DMF, but unfortunately this resulted in a complex product mixture, as did treatment with potassium *t*-butoxide in *t*-butyl alcohol. Since by this point we had had no success with base we attempted the reaction with acid, but this only resulted in deprotection of the MOM ether.

We believed that the problems with the intramolecular Michael addition were arising from the difficulty of epimerisation at C-5. An inspection of molecular models indicated that the Michael reaction was unlikely to take place with the side chain of **5.1** in the axial orientation, as it would require the D-ring to adopt a boat conformation to bring the Michael donor within bonding distance of the Michael acceptor; even then, orbital overlap would be poor. If the ketone side chain was able to take up an equatorial orientation, however, it appeared that good orbital overlap would be achieved between the reacting centres (Figure 5.1).

Figure 5.1: Inversion of Configuration at C-5

Corey and coworkers⁵⁷ encountered a difficult intramolecular Michael reaction in their work towards the synthesis of longifolene, shown in Scheme 5.7. Strong bases such as potassium *t*-butoxide and sodium methoxide led to extensive degradation of the starting material **5.6**. Weaker bases, however, were without effect at both room temperature and up to 100 °C. Eventually, it was discovered that treating **5.6** with triethylamine in ethylene glycol at 225 °C for 24 hours gave the desired product **5.7** in 10-20% yield.

Scheme 5.7: Michael Addition used in the Synthesis of Longifolene

These were not encouraging results, given that the yield of **5.7** was poor, and a number of other degradation products were obtained out of the reaction mixture. Nonetheless, we decided to apply this methodology to **5.1**, but under less forceful conditions. Initially, we attempted the reaction in the lower boiling point alcohol, *n*-butanol, in the presence of triethylamine, but no reaction occurred. We then attempted the reaction in ethylene glycol, and we discovered that treatment of **5.1** with triethylamine in ethylene glycol at 150 °C for 20 hours gave the desired tetracycle **5.2** in 30% yield based on recovered starting material (Scheme 5.8).

Scheme 5.8: Intramolecular Michael Addition of **5.1**

We terminated the reaction before the consumption of all of the starting material in order to avoid the formation of unwanted by-products. We also saw unwanted by-products if the reaction mixture was heated to temperatures above 150 °C, as revealed by the ^1H NMR spectrum. In the ^1H NMR spectrum of the crude product the integration of the β -keto ester peak at 3.76 ppm in the desired product **5.2** was significantly less than the MOM group methyl ether peak (at 3.38 ppm). Therefore we concluded that the other products were resulting from decarboxylation processes.

The 800 MHz ^1H NMR spectrum of **5.2** after purification is shown in Figure 5.2.

Figure 5.2: 800 MHz ^1H NMR spectrum of **5.2**

We were surprised to find the two methyl groups C-17 and C-18 overlapped to appear as one doublet at 1.01 ppm. Analysis of the COSY and HMQC spectra, however, confirmed the presence of the two methyl groups at this chemical shift. The methyl group at C-7 occurs as a singlet at 1.40 ppm and the ester group as a singlet at 3.76 ppm. The two protons on C-5 can be seen as distinctive multiplets at 2.36 ppm and 2.58 ppm.

The stereochemistry of **5.2** was confirmed by X-ray crystallography. Figure 5.3 shows that we had formed the all *trans*-fused tetracyclic required for the natural product. Furthermore, the quaternary centre in the A-ring possessed the desired axial methyl group, and the two secondary methyl groups were equatorial as required.[^]

[^] The numbering shown in the X-ray crystal structure of **5.2** is an arbitrary numbering system.

Figure 5.3: Crystal structure of **5.2**

Although we were successful in synthesising **5.2** with the correct stereochemistry, the best yield we could obtain from the Michael reaction was 30% based on recovered starting material. Thus, we attempted to further optimise the reaction conditions. One problem with the conditions utilised above was the difficulty of extracting the product from the ethylene glycol mixture at the end of the reaction. It was assumed that high heat was needed to activate the reaction, so ethylene glycol was substituted with the less polar high boiling point solvent xylene, but no reaction occurred. Using 1,2-dimethoxyethane or digol as the solvent was also without effect.

We decided to attempt the Michael addition under high pressure in order to activate the reaction. The advantages of using high pressure as the activation method are that generally it is a mild non-destructive method, with excellent reproducibility.⁵⁸ We hoped to carry out the reaction in methanol. Thus, **5.1** in methanol and triethylamine were subjected to 19 kbar of pressure at 25 °C for 24 hours, after which time a complex product mixture resulted which appeared to contain none of the desired product **5.2**.

In summary, despite our efforts to optimise the intramolecular Michael addition reaction, it appeared that the conversion of **5.1** to **5.2** required very specific reaction conditions, heating to at least 150 °C in ethylene glycol and triethylamine. The yield of **5.2** from this process was at best 30% based on recovered starting material, and it was postulated that the low yield was due to decarboxylation of the β -keto ester function.

5.3 Michael Addition on a Model Lacking the β -keto Ester Function

It was hypothesised that a better yield could be obtained from the intramolecular Michael addition if it was carried out on an intermediate lacking the β -keto ester group. Thus, dione **5.10** was prepared by applying the methodology described in 5.2.1 to an intermediate produced earlier in the sequence (see Chapter 3), enone **3.34**. Luche reduction of **3.34** gave epimeric allylic alcohols **5.8**, which were treated with TBAF to give 87% yield of the diols **5.9** over the two steps. Diols **5.9** then underwent a double oxidation on treatment with DMP to give the required dione **5.10** (Scheme 5.9).

Treatment of **5.10** with triethylamine in ethylene glycol at 150 °C gave the desired tetracycle **5.11** in 68% yield (Scheme 5.10).

Thus, the intramolecular Michael addition on an intermediate lacking the β -keto ester group (**5.10**) exhibited a significant improvement in yield.

5.3.1 Acylation of 5.11 and Attempted Alkylation

Given the improvement in yield of the key intramolecular Michael addition reaction, we decided to investigate the regioselective acylation of the tetracycle **5.11**. We hoped the

methyl group at C-3 would induce enough steric hindrance to shield C-5, thereby directing the approach of the electrophile to C-7 (Figure 5.4).

Figure 5.4: Lithium Enolate of 5.11

The lithium enolate of **5.11** was generated with LDA then treated with methyl cyanoformate in the presence of HMPA at -78°C to give a mixture of acylated products. A mixture of two inseparable regio-isomers **5.12** and **5.13** were isolated from the reaction mixture in 40% yield. On treatment with potassium carbonate in methanol, epimerisation of the ester group in **5.13** occurred to give **5.14**. Esters **5.12** and **5.14** could then be easily separated by chromatography on silica gel (Scheme 5.11).

Scheme 5.11: Acylation of 5.11

The structure and stereochemistry of both **5.12** and **5.14** were confirmed by one dimensional and two dimensional NMR studies. In the case of ester **5.12**, the proton on C-7 occurs as a doublet at 3.19 ppm with a coupling constant of 12.6 Hz, the size of this coupling to H-8 confirming that H-7 is axial. The stereochemistry was further confirmed by analysis of the NOESY spectrum. The proton on C-7 showed a correlation with the proton at C-13, thus confirming the stereochemistry. The equatorial proton on C-5 showed a correlation with the axial proton on C-5, the methyl group C-18, and the proton at C-4. The enhancement between the equatorial proton on C-5 and the methyl group C-18 was further confirmation of the structure of **5.12** (Figure 5.5).

Figure 5.5: NOESY Correlations of Ester 5.12

On the other hand, ester **5.14** exhibited a doublet of doublets at 3.62 ppm due to the proton on C-5 with coupling constants of 4.8 and 1.2 Hz. The size of the coupling (4.8 Hz) to H-4 indicated that the proton at C-5 was equatorial, which was further confirmed by analysis of the NOESY spectrum. The proton at C-5 showed a correlation with the proton at C-4, and with the methyl group at C-18, therefore confirming the stereochemistry and location of the ester function in **5.14** (Figure 5.6). In contrast, the proton at C-5 in ester **5.13** was observed as a doublet at 3.30 ppm with a diaxial coupling constant of 3.2 Hz.

Figure 5.6: NOESY Correlations of Ester 5.14

It was somewhat surprising that **5.14** in which the ester substituent is axial was more stable than **5.13**. Presumably the *peri*-interaction between the C-3 methyl group and the equatorial ester substituent destabilises **5.13**.

It was hoped that utilising the bulkier base lithium tetramethyl piperidine (LiTMP) to form the lithium enolate would improve the regioselectivity of the acylation reaction, but this was not the case. On the other hand, using lithium hexamethyldisilazane (LiHMDS) to form the lithium enolate gave **5.12** as the only β -keto ester product (based on the crude ^1H NMR spectrum) (Scheme 5.12).

Scheme 5.12: Regioselective Acylation of 5.11

With β -keto ester **5.12** in hand, it remained for us to install the axial methyl group at C-3 to complete the synthesis of the advanced intermediate **5.2**. Unfortunately all attempts to alkylate **5.12**, for example with sodium hydride and iodomethane (Scheme 5.13), were unsuccessful, resulting in complex product mixtures from which none of the desired product could be isolated.

Scheme 5.13: Attempted Alkylation of **5.12**

In summary, the intramolecular Michael addition reaction on an intermediate (**5.10**) lacking the β -keto ester function proceeded in good yield (68%) to give the tetracyclic intermediate **5.11**. Acylation could be directed to the required position, C-7 of **5.11**, utilising LiHMDS as the base, but all attempts to alkylate the β -keto ester **5.12** to form **5.2** were unsuccessful. This route was accordingly abandoned.

5.4 The Key Intramolecular Michael Addition Reaction

Having synthesised the tetracyclic intermediates **5.2** and **5.11**, it was decided to apply the established methodology towards the intramolecular Michael reaction of **1.86** to form the tetracyclic compound **1.87** as previously outlined in Scheme 5.1.

Thus, as illustrated in Scheme 5.14, dione **1.86** was prepared by applying the established methodology to enone **4.17**. Luche reduction of **4.17** gave epimeric allylic alcohols **5.15** in 80% yield, which were treated with TBAF to give the epimeric diols **5.16** in 84% yield, based on recovered starting material. The diol mixture **5.16** then underwent oxidation on treatment with DMP to give the required dione **1.86** in 81% yield.

Scheme 5.14: Synthesis of Dione 1.86

The intramolecular Michael reaction was carried out as described previously. Thus, dione **1.86** was treated with triethylamine in ethylene glycol at 150 °C. Surprisingly, after only four hours no starting material remained. Three products were obtained from the reaction in poor yield. A trace amount of a compound which appeared to have the structure **5.17**, the desired product **1.87** in 7% yield, and the transesterified compound **5.18** was formed as the major product with a dismal yield of 27% (Scheme 5.15).

Scheme 5.15: Initial Intramolecular Michael Addition of 1.86

Due to the increased reactivity of **1.86** relative to enones **5.1** and **5.10**, we decided to conduct the reaction at lower temperatures. It was found that at 100 °C and lower the formation of **5.17** was avoided, but unfortunately the formation of the transesterified product **5.18** could not be avoided. In fact at temperatures lower than 150 °C the transesterified enone **5.19** was also obtained as an inseparable mixture with **5.18**. The results of reducing the reaction temperature are summarised in Table 5.2.

Temperature	Reaction time	Recovered 1.86	1.87 yield*	5.18 and 5.19 yield
150 °C	4 h	0	7%	27% (5.18 only)
100 °C	18 h	12%	17% (20%)	17% (18%)
70 °C	4 d	24%	22% (30%)	29% (41%)

Table 5.2: Effect of temperature on the Intramolecular Michael Reaction of 1.86

* Yields in brackets refer to yields based on recovered starting material.

Table 5.2 shows that as the temperature decreases the yield of **1.87** increases. However, decreasing the temperature of the reaction leads to a significant increase in reaction time, and over longer reaction times the formation of the transesterified compounds **5.18** and **5.19** could not be avoided. Treatment of **1.86** with triethylamine in ethylene glycol at 70 °C for four days resulted in the best yield of **1.87** (30% based on recovered starting material). A mixture of **5.18** and **5.19** was also obtained in a 5 : 1 ratio in 41% yield, based on recovered starting material (Scheme 5.16).

Scheme 5.16: Optimised Intramolecular Michael Addition of 1.86

The formation of the transesterified products **5.18** and **5.19** was inconvenient, but not an insurmountable problem, since the ester groups were eventually hydrolysed to the dicarboxylic acid **1.62**. This conversion will be discussed further in Chapter 6[♥] (Scheme 5.17).

[♥] Originally we attempted a reverse transesterification with methanol to convert the mixture of **5.18** and **5.19** to the methyl diesters **1.86** and **1.87**. However, the reaction was unreliable and produced low yields.

Scheme 5.17: Planned Synthesis of Dicarboxylic Acid 1.62

Thus, the mixture of **5.18** and **5.19** was converted to the MOM ethers **5.20** and **5.21**, and then a reasonable amount of **5.20** could be isolated, although the separation was difficult and a pure sample of the minor product **5.21** could not be obtained (Scheme 5.18). The mixture of **5.21** and **5.20**, however, could be recycled to obtain more of the required product **5.20**.

Scheme 5.18: MOM Protection of 5.18 and 5.19

The protons on C-2' and C-3' in **5.20** appeared as two characteristic multiplets, representing two protons each in the ¹H NMR spectrum, one between 3.72-3.75 ppm and the other between 4.33-4.36 ppm. The peaks for C-2' and C-3' in the ¹³C NMR were observed at 64.2 ppm and 65.5 ppm respectively.

The 800 MHz ^1H NMR spectrum of the desired tetracyclic product **1.87** is shown in figure 5.7.

Figure 5.7: 800 MHz ^1H NMR spectrum of **1.87**

The methyl groups C-17 and C-18 occur as doublets at 0.92 and 1.02 ppm respectively. The methyl group at C-20 occurs as a singlet at 1.25 ppm and the methyl group at C-7 occurs as a singlet at 1.39 ppm. The ester group at C-20 was observed as a singlet at 3.63 ppm and the β -keto ester peak at C-7 was observed at 3.75 ppm. The multiplets exhibited at 2.35 and 2.56 ppm were assigned to the two protons on C-5.

The stereochemistry of **1.87** was confirmed by X-ray crystallography. Figure 5.8 shows that we had formed the all *trans*-fused tetracycle required for the natural product. Furthermore the quaternary methyl group in the A-ring was axial, and the quaternary methyl group in the D-ring was equatorial as required.

Figure 5.8: X-ray Structure of **1.87**

In summary, the best yield of **1.87** obtained in the intramolecular Michael addition was 30% based on recovered starting material; however, 41% of useable transesterified intermediates (**5.18** and **5.19**) were also obtained. Thus, the synthesis of the tetracyclic skeleton of diisocyanoadociane (**1.87**) was successfully achieved, with the stereochemistry at all ten centres correct.

CHAPTER 6

Deoxygenation and the Curtius Rearrangement

6. Deoxygenation and the Curtius Rearrangement

The first part of this chapter will discuss our studies towards the deoxygenation and dealkylation to obtain dicarboxylic acid **1.62**. The second part will discuss the planned Curtius rearrangement to complete the formal total synthesis of Diisocyanoadociane (**1.10**).

6.1 Introduction

As mentioned in Chapter 1 (Section 1.5, Scheme 1.6)[♦] it was planned to utilise the Curtius rearrangement of the corresponding acyl azide of dicarboxylic acid **1.62** for the stereoselective incorporation of the isonitrile groups in **1.10**.

Scheme 1.6: Proposed Curtius Rearrangement of **1.62**

In order to complete the synthesis of the skeleton of diisocyanoadociane (**1.10**) and to prepare for the Curtius rearrangement, we first needed to synthesise dicarboxylic acid **1.62**. It was envisaged that the dicarboxylic acid **1.62** could be obtained after a double deoxygenation and ester hydrolysis of the Michael products **1.87** and **5.20** (Scheme 6.1).

Scheme 6.1: Planned Synthesis of Dicarboxylic Acid **1.62**

6.2 Deoxygenation

The Wolff-Kishner reduction is a well known reaction for the reduction of carbonyl compounds to hydrocarbons. Two different variations of the method were discovered independently by Kishner in 1911⁵⁹ and by Wolff in 1912.⁶⁰ Early procedures described

[♦] This Scheme is repeated from Chapter 1.

the addition of preformed hydrazones to hot solid potassium hydroxide, or by heating with sodium ethoxide in ethanol in a sealed tube at 180 °C. In general, heating at 180 °C for six to eight hours is adequate to achieve complete reduction.⁶¹ Numerous modifications of the Wolff-Kishner reduction have been introduced over the years.⁶¹ For example, the modification discovered by Huang-Minlon⁶² in 1946, which involved heating the crude hydrazone to 180-200 °C for three to four hours with sodium or potassium hydroxide in diethylene or triethylene glycol. In 1962 Cram and coworkers⁶³ reported a modified Wolff-Kishner reduction that could be conducted at room temperature. The authors reported that the slow addition of hydrazones to a solution of sublimed potassium *t*-butoxide in anhydrous dimethyl sulfoxide at 25 °C gave the corresponding hydrocarbons in good yields. The main by-product from this procedure was an azine, whose formation is favoured by the rapid addition of hydrazone to the reaction mixture. Azine formation is a well documented side reaction of the Wolff Kishner reduction.⁶¹ (Scheme 6.2)

Scheme 6.2: Azine formation

Henbest and coworkers⁶⁴ reported an alternative to Cram's procedure, in which the hydrazones were added in a single portion to a suspension of potassium *t*-butoxide in toluene at 100-110 °C to obtain the corresponding hydrocarbons.

In 2004, these reduced temperature modifications of the Wolff-Kishner reduction were exploited by Myers and Furrow⁶⁵ for the reduction of *N*-silylhydrazones. *N*-*t*-Butyldimethylsilylhydrazones were prepared by treating the parent aldehydes or ketones with 1,2-bis(*t*-butyldimethylsilyl)hydrazine (BTBSH) and a catalytic amount of scandium trifluoromethanesulfonate. An example is shown in Scheme 6.3.⁶⁵

Scheme 6.3: Preparation of an *N*-*t*-Butyldimethylsilylhydrazone

The crude hydrazones were then subjected to Cram-type conditions at 23 °C or 100 °C with *t*-butyl alcohol added as a proton source. Outstanding yields of reduction products were achieved, and some examples of these reductions are shown in Scheme 6.4.

Scheme 6.4: Modified Wolff-Kishner Reduction

Several features of the Myers modified Wolff-Kishner reduction demonstrate it to be advantageous. First, the azine formation was not observed in the process and the two steps could be conducted in a single reaction vessel without compromising the yield of the reduction products. Second, it is milder than traditional Wolff-Kishner reactions in that reductions in most cases can be carried out at room temperature. Furthermore, the *N*-silylhydrazones exhibit improved stability over standard hydrazones with respect to handling and storage.

We decided to apply the methodology described by Myers to the model compound, **6.3**. Unfortunately, after treatment of the initially formed *N*-silylhydrazone with potassium *t*-butoxide in dimethyl sulfoxide and *t*-butyl alcohol at room temperature overnight, none of the desired product **6.4** was formed (Scheme 6.5).

Scheme 6.5: Attempted Deoxygenation of Model **6.3**

Analysis of the crude ^1H NMR showed that the ester group had been lost in the operation. Thus, given the apparent sensitivity of the β -keto ester function to strong base, this methodology was abandoned.

In 1971 Hutchins and coworkers⁶⁶ reported the mild reduction of tosylhydrazones to hydrocarbons using sodium cyanoborohydride in a 1 : 1 mixture of DMF and sulfolane at 100-105 °C. The authors reported that keto esters could be converted to the corresponding hydrocarbons without decomposition of the ester function. In 1985 Kim et al.⁶⁷ discovered that reduction of aldehydes and ketones could be achieved in one pot by treating with tosylhydrazine then zinc-modified cyanoborohydride in methanol at reflux. Several tosylhydrazones were converted cleanly into the corresponding hydrocarbons after three hours in good yield. Examples of ketone reduction with tosylhydrazine and zinc-modified cyanoborohydride have subsequently been carried out in THF at reflux.⁶⁸ We decided to test this two-step one pot procedure for the conversion of model β -keto ester **6.5** to ester **6.6**. Thus, keto ester **6.5** was treated with tosylhydrazine in THF at reflux for 16 hours, before the addition of zinc chloride and sodium cyanoborohydride and heating at reflux for an additional 16 hours to obtain ester **6.6** in 66% yield (Scheme 6.6).

Scheme 6.6: Deoxygenation of Model Ester 6.5

Given the success on model compound **6.5** we attempted the deoxygenation of compound **1.87**. To this end, dione **1.87** was treated with tosylhydrazine for 16 hours in THF at reflux. Zinc chloride and sodium cyanoborohydride were then added and the mixture was heated at reflux for an additional 24 hours to obtain a complex product mixture, from which hydrocarbon **6.1** was separated, although in the dismal yield of 5% (Scheme 6.7).

Scheme 6.7: Deoxygenation of 1.87

In view of the lack of success thus far for the deoxygenation of dione **1.87** utilising a modified Wolff-Kishner reduction, we turned our attention to alternative deoxygenation protocols.

Another method commonly used in the literature for the deoxygenation of secondary alcohols is the radical mediated Barton-McCombie reaction (Scheme 6.8).⁶⁹ This deoxygenation involves reaction of tributylstannane with the thiocarbonate or xanthate ester derived from the parent secondary alcohol to give the corresponding hydrocarbon in good yield. The driving force for the reaction is the formation of the very stable S-Sn bond. An advantage of this protocol is that it takes place under neutral conditions, making it compatible with the presence of a number of functional groups.

Scheme 6.8: The Barton-McCombie Reaction

Thus, in order to test the Barton-McCombie reaction conditions on our model compound **6.5** we first needed to reduce the ketone group. We decided to carry out the reduction under Luche reaction conditions⁵⁶, as we hoped that by binding the carbonyl group with cerium trichloride reduction would occur at only one face of the molecule, therefore avoiding the formation of epimeric products. However, this was not the case and instead reduction of ketone **6.5** under Luche reaction conditions gave the epimeric alcohols **6.7** in a 4 : 1 ratio, although in quantitative yield. Treatment of the alcohols with NaHMDS followed by carbon disulfide then iodomethane over six hours gave the epimeric xanthate esters **6.8**. Finally the xanthate esters **6.8** were treated with tributylstannane in the presence of AIBN as the radical initiator, then heated to 80 °C over five hours to obtain the ester **6.6** in 70% yield over the three steps (Scheme 6.9).

Scheme 6.9: Barton-McCombie Deoxygenation of Model Ester 6.5

The conditions for the Barton-McCombie reaction established on compound **6.5** were then applied to the synthesis of ester **6.1**. Thus, dione **1.87** was treated with sodium borohydride and cerium trichloride to give the corresponding mixture of epimeric diols. The diols were then treated with NaHMDS, carbon disulfide and iodomethane over six hours to form the corresponding epimeric xanthate esters, which could then be treated with tributylstannane in the presence of AIBN to obtain the desired hydrocarbon **6.1** in 47% yield over the three steps (Scheme 6.10).

Scheme 6.10: Barton-McCombie Deoxygenation of 1.87

The Barton-McCombie deoxygenation procedure could also be applied to the transesterified derivative **5.20** to give the corresponding hydrocarbon **6.2** in 39% yield over three steps (Scheme 6.11).

Scheme 6.11: Barton-McCombie Deoxygenation of 5.20

In both of the above cases, each time the reaction was carried out a mono-deoxygenated compound was also obtained in varying yields, which could be recovered and submitted

to the reaction conditions a second time to obtain more of the respective hydrocarbons **6.1** and **6.2**.

In summary, the Barton-McCombie reaction was identified to be the best method to achieve the deoxygenation of diones **1.87** and **5.20**. By using this reaction, the tetracyclic skeleton of the natural product (**1.10**) was successfully completed.

6.3 Dealkylation of the two Ester Groups

In order to complete the synthesis of dicarboxylic acid **1.62** we needed to carry out the dealkylation of the diesters **6.1** and **6.2**. Initially we attempted to remove the ester groups of **6.2** by base hydrolysis. Thus, treatment of **6.2** with lithium hydroxide in methanol : water (3 : 1)³⁸ at reflux overnight gave two products: **6.9** and **6.1**. The two products arose from mono-dealkylation (**6.9**) and transesterification (**6.1**), but even after prolonged reaction time, the axial ester group in the D-ring remained untouched. Thiolate mediated demethylation is known to proceed under mild conditions, and is especially suited to the dealkylation of hindered methyl esters. By employing this methodology, we were able to obtain the dicarboxylic acid **1.62** after treatment of the mixture of **6.9** and **6.1** in an HMPA solution of sodium propane thiolate at room temperature for 24 hours, although in low yield (Scheme 6.12).⁷⁰

Scheme 6.12: Dealkylation of **6.2**

A better yield was obtained for the one step thiolate mediated double demethylation of the diester **6.1**. Thus, treatment of **6.1** with a freshly prepared solution of sodium propanethiolate in HMPA over 1.5 days gave the required dicarboxylic acid **1.62** in 87% yield (Scheme 6.13).

Scheme 6.13: Thiolate Mediated Demethylation of **6.1**

hand, possesses an axial carboxylic acid group at the quaternary centre and is representative of the D-ring in compound **1.62**.

Acyl azide formation was first tested on the equatorial model compound **6.10**. We were delighted to find that on treatment with oxalyl chloride in DCM the corresponding acid chloride was obtained after less than one hour at room temperature. The DCM was removed and the crude acid chloride immediately treated with sodium azide in THF at room temperature for 18 hours to obtain the acyl azide **6.11**. Evidence for the formation of the acyl azide was provided by IR spectroscopy, which showed that a strong $\nu(\text{N}=\text{N}=\text{N})$ absorption was visible at 2130 cm^{-1} . The Curtius rearrangement then occurred rapidly on heating **6.11** in toluene at reflux for 15 minutes to obtain isocyanate **6.12**. The reaction could again be followed by IR spectroscopy as the absorption at 2130 cm^{-1} had disappeared and a new strong $\nu(\text{N}=\text{C}=\text{O})$ absorption was visible at 2256 cm^{-1} . The crude isocyanate in toluene was then treated with concentrated hydrochloric acid and heated at reflux for 20 hours to obtain the amine **6.13** in 48% yield over the four sequential steps (Scheme 6.16).

Scheme 6.16: Curtius Rearrangement of the Equatorial Model (48% over four steps)

Next, we repeated the methodology on the more sterically demanding axial model **4.2**. To this end, treatment of **4.2** with oxalyl chloride in DCM, followed by sodium azide in THF at room temperature for 24 hours gave the acyl azide **6.14**. Heating **6.14** in toluene at reflux for 15 minutes then gave the isocyanate **6.15**. The conversion of **6.14** to **6.15** could again be followed by IR spectroscopy, which showed that a strong $\nu(\text{N}=\text{N}=\text{N})$ absorption was seen at 2129 cm^{-1} for **6.14**. This absorption disappeared on conversion to **6.15** and a $\nu(\text{N}=\text{C}=\text{O})$ absorption was seen at 2259 cm^{-1} . Hydrolysis of **6.15** to the amine **6.16** was slow, and even after heating the isocyanate with concentrated hydrochloric acid in toluene at reflux for 24 hours, only 29% of the substrate was

converted to the amine **6.16**. Nevertheless, we could extract the amine from the mixture and repeat the hydrolysis reaction on the recovered isocyanate **6.15** (Scheme 6.17).

In summary, the acyl azide formation and the subsequent Curtius rearrangement was successfully carried out on two model compounds: **6.10** bearing an equatorial carboxyl group, and **4.2** bearing an axial carboxyl group. In both cases no urea by-products were observed.

6.4.2 The Key Curtius Rearrangement

We then applied the methodology established for the formation of amines **6.13** and **6.16** to the double Curtius rearrangement to form the diamine **1.63**. Thus, dicarboxylic acid **1.62** was treated with oxalyl chloride in DCM to obtain the corresponding diacid chloride, which was treated immediately with sodium azide in THF. Analysis by IR spectroscopy after 18 hours revealed that the absorption for the diacid chloride at 1781 cm^{-1} had disappeared, and a new absorption was observed at 2131 cm^{-1} due to the diacyl azide **6.17**. On heating the crude azide **6.17** in toluene at reflux for 15 minutes the double Curtius rearrangement proceeded smoothly to give diisocyanate **6.18**. Analysis of **6.18** by IR spectroscopy revealed an absorption at 2260 cm^{-1} which was assigned to the $\nu(\text{N}=\text{C}=\text{O})$ stretch. Further characterization by E.I. mass spectrometry confirmed the structure of **6.18**. Diisocyanate **6.18** was finally treated with concentrated hydrochloric acid in toluene for 18 hours to obtain the diamine **1.63** in 39% yield over the four steps (Scheme 6.18).

Scheme 6.18: Curtius Rearrangement of 1.62

Diamine **1.63** was further purified by reverse phase HPLC, and was found to give identical mass spectra, and ¹H and ¹³C NMR spectra (measured on the trifluoroacetate salts in CD₃OD), to those obtained from an authentic sample derived from hydrolysis of diisocyanoadociane (**1.10**).⁷² The 600 MHz ¹H NMR spectra for the synthetic and authentic samples of the diamine **1.63** are shown in Figure 6.1, and the ¹³C NMR spectra (obtained at 800 MHz for the synthetic sample and at 600 MHz for the authentic sample) are shown in Figure 6.2.

600 MHz ^1H NMR spectrum of the TFA salt of **1.63** (synthetic sample)

600 MHz ^1H NMR spectrum of the TFA salt of **1.63** (authentic sample)

Figure 6.1: ^1H NMR Spectra of synthetic and authentic samples of **1.63**

800 MHz ^{13}C NMR spectrum of the TFA salt of **1.63** (synthetic sample)

600 MHz ^{13}C NMR spectrum of the TFA salt of **1.63** (authentic sample)

Figure 6.2: ^{13}C NMR Spectra of synthetic and authentic samples of **1.63**

In Chapter 1 we outlined the synthetic strategy to diisocyanoadociane (**1.10**) and in that chapter we also referred to the work of Garson and coworkers,⁷² who obtained diamine **1.63** during the course of their biosynthetic studies, and subsequently were able to carry out formylation and dehydration reactions to reconstitute **1.10** (Scheme 6.19). Thus, the chemistry outlined in this chapter completes a formal total synthesis of diisocyanoadociane (**1.10**).

Scheme 6.19: Reconstitution of **1.10** by Garson and Coworkers

CHAPTER 7

Summary and Conclusions

7. Summary and Conclusions

In conclusion, we have successfully completed a formal total synthesis of diisocyanoadociane (**1.10**). The 35 step sequence to diamine **1.63** is outlined in Scheme 7.1. The sequence begins with a phenanthrenoid (**1.64**) precursor which undergoes extensive elaboration before transformation into a pyrene derived intermediate (**1.87**) by means of an intramolecular Michael reaction. Finally the nitrogen functionality is introduced via a double Curtius rearrangement.

As discussed in Chapter 1 (Section 1.4.3) Corey and Magriotis²⁰ have to date achieved the only other total synthesis of diisocyanoadociane (**1.10**). Our synthetic sequence outlined in Scheme 7.1 and Corey's sequence (summarised in Chapter 1, Scheme 1.5) are of a similar number of steps, but in our sequence additional steps were required due to compatibility problems with protecting groups and oxidation state changes. Worthy of note is that in Corey's sequence the two isonitrile groups were introduced in a single biomimetic operation to generate four diastereomeric diisonitriles, including **1.10** in unspecified yield. In our work, however, we have achieved the stereoselective incorporation of nitrogen at the two quaternary centres by utilising the Curtius rearrangement, thus theoretically facilitating the production of the natural product (**1.10**) as a single isomer at the final step.

Scheme 7.1: Synthetic Sequence to Amine 1.63

Scheme 7.1: Continued

All ten stereocentres in the skeleton of **1.10** have been introduced with the correct relative stereochemistry, but we are yet to address the issue of enantioselectivity. However, the initial Birch reductive alkylation (step 1, Scheme 7.1), if carried out on an appropriate chiral benzamide⁷³ should resolve this remaining stereochemical issue. An

alternate approach would be an asymmetric Heck reaction^{74,75} to obtain a chiral phenanthrenoid. (Scheme 7.2)

7.2: Possible Approaches to an Enantioselective Synthesis

If successful this would open the gateway to an enantioselective total synthesis of diisocyanoadociane (**1.10**) and a number of other diterpene natural products with significant *in vitro* anti-malarial activity, such as **1.11**, **1.12** and **1.13**.

CHAPTER 8

Experimental

8. Experimental

8.1 General Experimental

Melting points (m.p.) were recorded on a Reichert hot-stage and are uncorrected. Microanalyses were carried out by the Australian National University Analytical Services Unit, Canberra.

Infrared (IR) spectra ($\nu_{\max}$) were recorded on a Perkin-Elmer 683 Infrared spectrophotometer on 0.25 mm NaCl solution cells. Data are recorded as follows: wavenumber (cm^{-1}), s (strong), br (broad).

Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on three different instruments operating at the following frequencies: (a) Varian Mercury 300 spectrometer at 300 MHz. (b) Varian Inova 600 spectrometer at 600 MHz. (c) Bruker Avance 800 spectrometer at 800 MHz. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were also recorded on three different instruments operating at the following frequencies: (a) Varian Mercury 300 spectrometer at 75 MHz. (b) Varian Inova 600 spectrometer at 150 MHz. (c) Bruker Avance 800 spectrometer at 200 MHz. The instrument each sample was run on is stated. For proton spectra recorded in deuterated chloroform, the residual CHCl_3 peak was used as the internal reference (7.26 ppm), while the central peak of CDCl_3 (77.0 ppm) was used as the reference for carbon spectra. For proton spectra recorded in deuterated methanol, the residual HCD_2OD peak was used as the internal reference (3.31 ppm), while the central peak of CD_3OD (49.0 ppm) was used as the reference for carbon spectra. Data are recorded as follows: chemical shift (ppm), multiplicity (s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, dd: doublet of doublets, ddd: double doublet of doublets, dt: doublet of triplets, dq: doublet of quartets, s (br): broad singlet), coupling constant J (Hz), intensity as number of protons, and assignment (based on chemical shifts). Distortionless enhancement by polarisation transfer (DEPT) and attached proton test (APT) experiments were used in the assignment of carbon spectra.

One dimensional Nuclear Overhauser spectroscopy was conducted using the 1D-NOESY pulse sequence. Two dimensional NMR experiments were recorded on a

Varian Inova 600 spectrometer. Proton-proton correlation spectroscopy was conducted using the gCOSY pulse sequence. Short range carbon-hydrogen correlation experiments were conducted via indirect detection using the gHMQC pulse sequence. Two dimensional nuclear Overhauser spectroscopy experiments were conducted with a pulse field gradient using the NOESY pulse sequence.

Low resolution (LRMS) EI mass spectra (70 eV) and high resolution (HRMS) EI mass spectra were recorded on a Fisons VG autospec double focusing mass spectrometer. The molecular ion (M^+), if present, significant high mass ions and the more intense low mass ions are reported. Data are recorded as follows: m/z value, relative intensity as a percentage of the base peak.

Analytical thin layer chromatography (TLC) was carried out on Merck aluminum TLC plates precoated with KG60 F₂₅₄ silica. The developed plates were visualised under shortwave ultraviolet light and stained with PMA dip (15 g phosphomolybdic acid, 2.5 g cerium sulfate, 15 mL conc. sulfuric acid, 500 mL water). or a solution of potassium permanganate (3 g) and potassium carbonate (20 g) in sodium hydroxide (5%, aqueous, 5 mL) and water (200 mL). After staining, the plates were developed by heating to 180 °C. Flash chromatography was conducted according to the method of Still and coworkers,⁷⁶ with Merck Kieselgel 60 used as the adsorbent. All solvents used for elution were analytical reagent (AR) grade, and were used without further purification.

High performance liquid chromatography (HPLC) was carried out using Waters alliance 2695 HPLC pumps, and a Waters 2996 photodiode array detector set at 210 nm. Novapack C18 columns were supplied by Waters.

Reagents used in reactions were obtained commercially from the Merck or Aldrich Chemical Companies, and were used without further purification unless otherwise indicated. Tetrahydrofuran (THF), diethyl ether (ether) and benzene were purified by distillation from sodium benzophenone ketyl under nitrogen. Toluene and dichloromethane (DCM) were purified by distillation from calcium hydride under nitrogen. Triethylamine and diisopropylamine were purified by distillation from calcium hydride under nitrogen and stored over potassium hydroxide. Ethylene glycol was purified by distillation from MgSO₄ under reduced pressure and stored over 3Å

molecular sieves. Ammonia was dried with sodium metal and FeNO_3 and then distilled under an inert atmosphere as required. Sodium hydride (60% in mineral oil) was washed twice with dry petroleum ether before use. Dess-Martin periodinane was prepared by the method of Dess and Martin.⁷⁷⁻⁷⁹ Ethanol-free ethereal diazomethane was prepared from Diazald[®] (*N*-methyl-*N*-nitroso-*p*-toluenesulfonamide).⁸⁰

All moisture-sensitive reactions were conducted in flame-dried glassware under a positive pressure of dry nitrogen, unless otherwise stated. Reaction temperatures refer to the external oil bath temperatures. All organic extracts were dried with anhydrous magnesium sulfate. After filtration, the bulk of the solvent was removed using a Büchi rotary evaporator with a water aspirator. Final traces of solvent were removed under high vacuum.

8.1.1 Notes on Nomenclature

Chemical Abstracts nomenclature has been used throughout the experimental section, which are generally in accordance with the rules published by the International Union of Pure and Applied Chemistry (IUPAC).

The tricyclic compounds have been named as derivatives of phenanthrene with two possible numbering systems.

(i)

For example compound **1.64** is named as; (8a*RS*) Methyl 9,10-Dihydro-2-methoxy-7-methylphenanthrene-8a(6*H*)-carboxylate.

(ii)

For example compound **1.95** is named as; (2*RS*, 4*RS*, 4*aRS*, 10*aSR*, 1'*SR*) 4-(1'-Benzoyloxypropyl)-7-methoxy-2-methyl-3,4,4*a*,9,10,10*a*-hexahydrophenanthren-1(2*H*)-one.

The tetracyclic compounds **5.2**, **5.11**, **5.12** and **5.14** have been named as derivatives of pyrene.

For example compound **5.2** is named as; (3*RS*, 3*aSR*, 5*aSR*, 5*bSR*, 5*cSR*, 6*RS*, 7*RS*, 8*aSR*, 10*RS*, 10*aSR*) Methyl-2,9-dioxo-6-methoxmethoxy-1, 3*a*, 4, 5, 5*a*, 5*b*, 5*c*, 6, 7, 8, 8*a*, 10, 10*a*-tridecahydro-3,7,10-trimethylpyrene-3(2*H*)-carboxylate.

The tetracyclic compounds **1.87**, **5.20**, **6.1**, **6.2**, **1.62** and **1.63** are named as derivatives of isocycloamphilectane.

For example compound **1.63** is named as; Isocycloamphilectane-7,20-diamine.

8.2 Chapter 2 Experimental

(1*RS*) Methyl 2-Methoxy-1-(2'-(3''-methoxyphenyl)ethyl)-5-methylcyclohexa-2,5-diene-1-carboxylate (8.1)

Preparation in accordance to that previously recorded by S.R. Crabtree, Ph.D. thesis, ANU 1990.²⁴

A flame dried 3-necked flask, fitted with a dry ice condenser was charged with 2-methoxy-5-methylbenzoate (2.0 g, 11.1 mmol), THF (20 mL) and *t*-butyl alcohol (2.1 mL, 22.2 mmol) under nitrogen. Dry ammonia (100 mL) was then distilled into the flask cooled to $-78\text{ }^{\circ}\text{C}$, and small pieces of freshly cleaned lithium wire (0.19 g, 27.8 mg/atom) were added. The resulting blue solution was warmed to $-33\text{ }^{\circ}\text{C}$ and stirred for 15 min, before adding isoprene until the blue colour dispersed. The ammonia was then boiled off under a stream of nitrogen and the residue cooled to $-78\text{ }^{\circ}\text{C}$. 2-(3''-Methoxyphenyl)-ethyl iodide (3.2 g, 12.2 mmol) in THF (8.5 mL) was then added drop wise over 10 min and the resulting reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min, before warming to room temperature and stirring for an additional 16 h. Water (25 mL) was then added and the reaction mixture extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried over anhydrous MgSO_4 , and concentrated *in vacuo* to give a yellow oil. Purification by flash column chromatography on silica gel using ethyl acetate : hexane (1 : 9) as eluant gave the title compound **8.1** (2.0 g, 57%) as a yellow oil.

IR (thin film) cm^{-1} : 2937s (C-H), 1731s (C=O), 1695s, 1665s, 1601s, 1584s, 1491s (C=C), 1384s, 1365s, 1230br, 1168s, 1045s (C-O).

^1H NMR (300 MHz, CDCl_3) δ : 1.77 (s, 3H, 5- CH_3), 2.00 (m, 1H, H-1'), 2.31 – 2.44 (m, 3H, H-1', H-2'), 2.78 (m, 2H, H-4), 3.56 (s, 3H, $-\text{CO}_2\text{CH}_3$), 3.67 (s, 3H, 2-O CH_3), 3.78 (s, 3H, 3''-O CH_3), 4.88 (t, $J = 3.6\text{ Hz}$, 1H, H-3), 5.16 (s (br), 1H, H-6), 6.68-6.76 (m, 3H, H-2'', H-4'', H-6''), 7.16 (dd, $J = 8.4$, $J = 7.5\text{ Hz}$, 1H, H-5'').

^{13}C NMR (75 MHz, CDCl_3) δ : 22.6 (5- CH_3), 30.8 (CH_2 , C-1'), 31.3 (CH_2 , C-4), 36.1 (CH_2 , C-2'), 52.3 (1- CO_2CH_3), 52.5 (C, C-1), 54.4 (2- OCH_3), 55.1 (3''- OCH_3), 93.8 (CH, C-3), 110.8 (CH, C-4''), 113.9 (CH, C-2''), 120.7 (CH, C-6''), 121.6 (CH, C-6), 128.9 (CH, C-5''), 134.7 (C, C-5), 144.1 (C, C-1''), 152.3 (C, C-2), 159.3 (C, C-3''), 174.1 (1-CO).

LRMS (m/z): 316 (M^+ , 31%), 257 (29), 195 (18), 181 (46), 149 (70), 135 (100), 121 (43), 105 (40), 91 (43), 77 (32).

HRMS: $\text{C}_{19}\text{H}_{24}\text{O}_4$ (M^+) requires 316.1675, found 316.1677

(8a*RS*) Methyl 9,10-Dihydro-2-methoxy-7-methylphenanthrene-8a(6H)-carboxylate (1.64)

Preparation in accordance to that previously recorded by S.R. Crabtree, Ph.D. thesis, ANU 1990.²⁴

Boron trifluoride diethyl etherate (5.6 mL, 43.9 mmol) was added drop wise to a solution of ester **8.1** (12.6 g, 39.9 mmol) in DCM (250 mL) at -24°C under nitrogen. The reaction mixture was warmed to room temperature and stirred for 1 h. Water (60 mL) was then added and the resulting mixture stirred vigorously for 10 min. The organic phase was separated and the aqueous phase further extracted with DCM (2 x 50 mL). The combined organic extracts were dried over anhydrous MgSO_4 , and concentrated *in vacuo* to give a yellow solid. Trituration with hexane gave the title compound **1.64** (9.64 g, 85%) as a cream powder. A sample was crystallised from methanol to give white needle-like crystals.

m.p.: $135\text{--}138^\circ\text{C}$

IR (thin film) cm^{-1} : 2948s (C-H), 1720s (C=O), 1606s, 1572s, 1497s, 1444, 1230s, 1167, 1072.

^1H NMR (300 MHz, CDCl_3) δ : 1.78 (s, 3H, 7- CH_3), 1.80 (m, 1H, H-9), 2.45 (ddd, $J_{\text{gem}} = 13.0$, $J_{9,10} = 5.7$, $J_{9,10} = 1.6$ Hz, 1H, H'-9), 2.73-3.00 (m, 4H, H-6, H-10), 3.57 (s, 3H, 8a- CO_2CH_3), 3.78 (s, 3H, 2- OCH_3), 5.40 (s (br), 1H, H-8), 6.21 (dd, $J = 4.4$, $J = 3.2$ Hz, 1H, H-5), 6.56 (d, $J_{1,3} = 2.6$ Hz, 1H, H-1), 6.74 (dd, $J_{3,4} = 8.8$, $J_{3,1} = 2.6$ Hz, 1H, H-3), 7.53 (d, $J_{4,3} = 8.8$, 1H, H-4).

^{13}C NMR (75 MHz, CDCl_3) δ : 23.2 (7- CH_3), 27.7 (CH_2 , C-10), 32.6 (CH_2 , C-9), 34.2 (CH_2 , C-6), 48.9 (C, C-8a), 52.6 (8a- CO_2CH_3), 55.5 (2- OCH_3), 113.1 (CH, C-3), 113.2 (CH, C-1), 118.3 (CH, C-5), 123.6 (CH, C-4), 125.7 (C, C-4a), 128.1 (CH, C-8), 133.3 (C, C-7), 133.8 (C, C-10a), 136.4 (C, C-4b), 158.7 (C, C-2), 174.5 (8a-CO).

LRMS (m/z): 284 (M^+ , 58%), 226 (36), 225 (100), 224 (45), 210 (37), 209 (23), 193 (20), 179 (23), 178 (26), 166 (23), 165 (34), 152 (19).

HRMS: $\text{C}_{18}\text{H}_{20}\text{O}_3$ (M^+) requires 284.1412, found 284.1415.

Microanalysis: Calcd. for $\text{C}_{18}\text{H}_{20}\text{O}_3$: C, 76.03%; H, 7.09%. Found: C, 75.92%; H, 6.82%.

(8a*RS*) Methyl 9,10-Dihydro-5-(1'-oxopropyl)-2-methoxy-7-methylphenanthrene-8a(6*H*)-carboxylate (2.1)

Aluminum chloride (9.4 g, 70.4 mmol) was added to a solution of olefin **1.64** (5.0 g, 17.6 mmol) and propionyl chloride (4.6 mL, 53.8 mmol) in DCM (150 mL) at -78°C under nitrogen. The resulting reaction mixture was stirred for 20 min then quenched by pouring over iced water with vigorous stirring. The organic phase was separated and the aqueous phase extracted with DCM (2 x 30 mL). The combined organic extracts were washed with water, aqueous potassium dihydrogen orthophosphate, dried over anhydrous MgSO_4 and concentrated *in vacuo* to give a cream solid. Trituration with hexane gave the title compound **2.1** (4.5 g, 75%) as a cream powder. A sample was crystallised from ethyl acetate and hexane to give white crystals.

m.p.: 139-144 °C

IR (thin film) cm^{-1} : 2936s (C-H), 1729s (C=O), 1679s (C=O), 1605s, 1498s, 1445, 1264, 1239, 1166, 1070.

^1H NMR (300 MHz, CDCl_3) δ : 0.94 (t, $J_{3',2'} = 7.2$ Hz, H-3'), 1.75 (s, 3H, 7- CH_3), 1.90 (ddd, $J_{\text{gem}} = 13.5$ Hz, $J_{9,10} = 10.8$ Hz, $J_{9,10} = 7.0$ Hz, 1H, H-9), 2.23 (dq, $J = 17.7$ Hz, $J = 7.2$ Hz, 2H, H-2'), 2.57 (m, 1H, H'-9), 2.56 (d, $J_{\text{gem}} = 21.9$ Hz, 1H, H-6), 2.87 (ABdd, $J_{\text{gem}} = 17.9$ Hz, $J_{10,9} = 6.0$ Hz, 1H, H-10), 3.01 (ddd, $J_{\text{gem}} = 17.9$ Hz, $J_{10,9} = 10.8$ Hz, $J_{10,9} = 7.0$ Hz, 1H, H'-10), 3.24 (d, $J_{\text{gem}} = 21.9$ Hz, 1H, H'-6), 3.44 (s, 3H, 8a- CO_2CH_3), 3.76 (s, 3H, 2- OCH_3), 5.33 (s (br), 1H, H-8), 6.60-6.63 (m, 2H, H-1, H-3), 6.97 (d, $J_{4,3} = 8.7$ Hz, 1H, H-4).

^{13}C NMR (75 MHz, CDCl_3) δ : 8.7 (CH_3 , C-3'), 22.6 (7- CH_3), 26.7 (CH_2 , C-9), 34.3 (CH_2), 34.3 (CH_2), 35.6 (CH_2) 50.7 (C, C-8a), 52.2 (8a- CO_2CH_3), 55.1 (2- OCH_3), 111.7 (CH, C-3), 113.2 (CH, C-1), 122.3 (CH, C-4), 126.9 (C, C-4a), 130.4 (C, C-8), 131.0 (C, C-5), 132.7 (C, C-7), 135.2 (CH, C-4b), 137.8 (C, C-10a), 159.5 (C, C-2), 173.5 (8a-CO), 211.8 (1'-CO).

LRMS (m/z): 340 (M^+ , 40%), 311 (10), 281 (62), 263 (26), 251 (30), 223 (39), 209 (19), 178 (14), 165 (26), 57 (100).

HRMS: $\text{C}_{21}\text{H}_{24}\text{O}_4$ (M^+) requires 340.1675, found 340.1670.

Microanalysis: Calcd. for $\text{C}_{21}\text{H}_{24}\text{O}_4$: C, 74.09%; H, 7.11%. Found: C, 73.97%; H, 6.97%.

(7a*RS*) Methyl 4-ethylidene-5,7a,8,9-tetrahydro-2-methoxy-6-methyl-4*H*-cycopenta[*def*]phenanthrene-7a-carboxylate (2.3)

Aluminum (III) chloride (0.05 g, 0.35 mmol) was added to a solution of olefin **1.64** (0.05 g, 0.18 mmol) and propionyl chloride (0.03 mL, 0.35 mmol) in DCM (2 mL) at room temperature under nitrogen. The resulting reaction mixture was stirred for 18 h poured over iced water with vigorous stirring. The organic phase was separated and the aqueous phase extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with water (10 mL), aqueous saturated sodium bicarbonate (10 mL), dried over anhydrous MgSO_4 and concentrated *in vacuo* to give a yellow oil. Purification by flash column chromatography on silica gel using ethyl acetate : hexane (1 : 9) as eluant gave the title compound **2.3** (0.03 g, 52%) as a yellow oil.

IR (thin film) cm^{-1} : 2949 (C-H), 1725s (C=O), 1594, 1477, 1449, 1269, 1232, 1148, 1062.

^1H NMR (300 MHz, CDCl_3) δ : 1.88 (s, 3H, 6- CH_3), 2.21 (d, $J = 7.6$ Hz, 3H, 1'- CH_3), 2.56-2.92 (m, 4H, H-8, H-9), 3.22, 3.37 (2 x ABd, $J = 21.5$ Hz, 2H, H-5), 3.62 (s, 3H, 7a- CO_2CH_3), 3.81 (s, 3H, 2- OCH_3), 5.61 (s (br), 1H, H-7), 6.52 (s, 1H, H-1), 6.61 (q, $J = 7.6$ Hz, 1H, 1'-H), 6.92 (s, 1H, H-3).

^{13}C NMR (75 MHz, CDCl_3) δ : 15.3 (C-2'), 23.7 (6- CH_3), 25.7 (CH_2 , C-9), 33.3 (2 x CH_2 , C-8, C-5), 46.9, 52.3, 54.2, 55.9, 104.6 (CH, C-3), 110.1 (CH, C-1), 122.2, 126.4, 128.0, 129.6, 131.4, 137.4, 137.6, 140.2, 158.8 (C, C-2), 174.0 (7a- CO_2CH_3).

(4'*RS*, 4a'*SR*, 10a'*RS*) 1-[10a'-Hydroxymethyl-7'-methoxy-2'-methyl-4a',9',10',10a'-tetrahydrophenanthren-4' (3'*H*)-yl]-propan-1-one (2.2**)**

Preparation in accordance to that previously recorded by K.A. Fairweather, Honours thesis, ANU 2002.³⁰

Dry ammonia (480 mL) was distilled into a 3-necked flask fitted with a dry ice condenser, under nitrogen. Small pieces of freshly cleaned lithium wire (1.0 g, 152.7

mmol) were added and the resulting blue solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 15 min. A solution of ketone **2.1** (4.0 g, 11.7 mmol) in THF (200 mL) was then added drop wise over 5 min and the resulting reaction mixture was stirred for 15 min before adding isoprene drop wise until the blue colour dispersed. The ammonia was allowed to boil off under a stream of nitrogen and a saturated solution of aqueous ammonium chloride (80 mL) was added. After 15 min, water (50 mL) was added and the aqueous phase extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL) and dried over anhydrous MgSO_4 . Concentration of the organic phase *in vacuo* gave a yellow oil which was purified by flash column chromatography on silica gel using ethyl acetate : hexane (2 : 3) as eluant to give the title compound **2.2** (2.7 g, 74%) as a white solid.

m.p.: 106-109 $^{\circ}\text{C}$

IR (thin film) cm^{-1} : 3436br (C-OH), 2914s (C-H), 1701s (C=O), 1611s, 1502s, 1461, 1278, 1236, 1075, 1038.

^1H NMR (300 MHz, CDCl_3) δ : 1.04 (t, $J_{3,2} = 7.2\text{ Hz}$, 3H, H-3), 1.54 (dt, $J_{\text{gem}} = 13.2\text{ Hz}$, $J_{10',9'} = 5.1\text{ Hz}$, 1H, H-10'), 1.65 (s, 3H, 2'- CH_3), 1.75 (ddd, $J_{\text{gem}} = 13.2\text{ Hz}$, $J_{10',9'} = 10.5\text{ Hz}$, $J_{10',9'} = 5.1\text{ Hz}$, 1H, H'-10'), 1.94 (d, $J = 6.9\text{ Hz}$, 2H, H-3'), 2.35-2.56 (m, 3H, H-2, H-9'), 2.74 (ddd, $J_{\text{gem}} = 16.2$, $J_{9',10'} = 10.5\text{ Hz}$, $J_{9',10'} = 5.1\text{ Hz}$, H'-9'), 2.91 (s (br), 1H, -OH), 3.09 (ddd, $J = 10.2\text{ Hz}$, $J = 6.9\text{ Hz}$, $J = 3.3\text{ Hz}$, 1H, H-4'), 3.46, 3.60 (2 x ABd, $J = 11.1\text{ Hz}$, 2H, 10a'- CH_2), 3.71 (d, $J_{4a',4'} = 3.3\text{ Hz}$, 1H, H-4a'), 3.71 (s, 3H, 7'- OCH_3), 4.98 (s (br), 1H, H-1'), 6.54 (d, $J_{8',6'} = 2.7\text{ Hz}$, 1H, H-8'), 6.60 (dd, $J_{6',5'} = 8.6\text{ Hz}$, $J_{6',8'} = 2.7\text{ Hz}$, 1H, H-6'), 6.72 (d, $J_{5',6'} = 8.6\text{ Hz}$, 1H, H-5').

^{13}C NMR (75 MHz, CDCl_3) δ : 8.0 (CH_3 , C-3), 23.6 (2'- CH_3), 26.5 (CH_2 , C-10'), 28.5 (CH_2), 29.6 (CH_2), 34.3 (CH_2), 39.2 (C, C-10a'), 42.0 (CH, C-4a'), 50.0 (CH, C-4'), 54.9 (7'- OCH_3), 69.3 (C10a'- CH_2OH), 111.7 (CH, C-6'), 113.3 (CH, C-8'), 125.3 (CH, C-1'), 127.9 (CH, C-5'), 128.7 (C, C-4b'), 136.9 (C, C-2'), 139.1 (C, C-8a'), 157.0 (C, C-7'), 215.1 (1-CO).

LRMS (m/z): 314 (M^+ , 60%), 283 (74), 265 (26), 239 (24), 225 (84), 211 (63), 199 (16), 190 (63), 171 (44), 147 (19), 57 (100).

HRMS: $C_{20}H_{26}O_3$ (M^+) requires 314.1882, found 314.1884.

Microanalysis: Calcd. for $C_{20}H_{26}O_3$: C, 76.40%; H, 8.33%. Found: C, 76.30%; H, 8.40%.

(4'*RS*, 4a'*SR*, 10a'*RS*) 1-[10a'-Methoxmethoxy-7'-methoxy-2'-methyl-4a',9',10',10a'-tetrahydrophenanthren-4'(3'*H*)-yl]-propan-1-one (8.2)

Hünig's base (5.6 mL, 32.1 mmol) was added to alcohol **2.2** (3.36 g, 10.7 mmol) in DCM (100 mL) at 0 °C under nitrogen. Chloromethyl methyl ether (2.4 mL, 32.1 mmol) was added drop wise and the reaction mixture warmed to room temperature. DMAP (50 mg) was then added and the reaction was stirred for 24 h. The reaction mixture was cooled to 0 °C, saturated sodium bicarbonate (50 mL) was added, and stirring continued for 10 min. The organic phase was then separated and the aqueous phase was extracted with DCM (3 x 50 mL). The combined organic extracts were washed with water (50 mL), 2 *M* hydrochloric acid (50 mL), saturated sodium bicarbonate (50 mL), brine (50 mL) and dried over anhydrous $MgSO_4$. Concentration of the organic phase *in vacuo* gave the title compound **8.2** (3.8 g, 100%) as a yellow gum, which was used directly in the next step without further purification.

IR (thin film) cm^{-1} : 2933s (C-H), 1704s (C=O), 1611s, 1502s, 1462, 1377, 1279, 1236, 1151, 1108, 1042.

1H NMR (300 MHz, $CDCl_3$) δ : 1.11 (t, $J_{3,2} = 7.2$ Hz, 3H, H-3), 1.61 (m, 1H, H-10'), 1.65 (s, 3H, 2'-CH₃), 1.88 (m, 1H, H'-10'), 1.95 (d, $J = 7.2$ Hz, 2H, H-3'), 2.39-2.69 (m, 3H, H-2, H-9'), 2.79 (ddd, $J_{gem} = 16.5$, $J_{9',10'} = 11.4$ Hz, $J_{9',10'} = 5.1$ Hz, 1H, H'-9'), 3.08 (ddd, $J = 10.5$ Hz, $J = 7.2$ Hz, $J = 3.0$ Hz, 1H, H-4'), 3.38 (s, 3H, 10a'-OCH₂OCH₃), 3.39, 3.60 (2 x ABd, $J = 9.7$ Hz, 2H, 10a'-CH₂), 3.69 (d, $J_{4a',4'} = 3.0$ Hz, 1H, H-4a'), 3.75 (s, 3H, 7'-OCH₃), 4.65 (s, 2H, 10a'-OCH₂OCH₃), 5.04 (s (br), 1H, H-1'), 6.57 (d, $J_{8',6'} =$

2.7 Hz, 1H, H-8'), 6.62 (dd, $J_{6',5'} = 8.4$ Hz, $J_{6',8'} = 2.7$ Hz, 1H, H-6'), 6.71 (d, $J_{5',6'} = 8.4$ Hz, 1H, H-5').

^{13}C NMR (75 MHz, CDCl_3) δ : 8.2 (CH_3 , C-3), 23.6 ($2'\text{-CH}_3$), 26.7 (CH_2 , C-10'), 28.0 (CH_2), 30.4 (CH_2), 33.9 (CH_2), 39.4 (C, C-10a'), 41.2 (CH , C-4a'), 49.9 (CH , C-4'), 55.0 ($10\text{a}'\text{-OCH}_2\text{OCH}_3$), 55.2 ($7'\text{-OCH}_3$), 74.7 ($\text{C}10\text{a}'\text{-CH}_2\text{OH}$), 96.6 ($10\text{a}'\text{-OCH}_2\text{OCH}_3$), 111.7 (CH , C-6'), 113.5 (CH , C-8'), 125.1 (CH , C-1'), 127.8 (CH , C-5'), 128.7 (C, C-4b'), 136.2 (C, C-2'), 139.5 (C, C-8a'), 157.1 (C, C-7'), 214.2 (1-CO).

LRMS (m/z): 358 (M^+ , 46%), 283 (85), 265 (15), 239 (35), 225 (72), 211 (52), 195 (15), 171 (44), 147 (16), 57 (100).

HRMS: $\text{C}_{22}\text{H}_{30}\text{O}_4$ (MH^+) requires 359.2217, found 359.2213.

(4'*RS*, 4a'*SR*, 10a'*RS*, 1*SR* or 1*RS*) 1-[10a'-Methoxmethoxy-7'-methoxy-2'-methyl-4a',9',10',10a'-tetrahydrophenanthren-4' (3'*H*)-yl]-propan-1-ol (8.3)

A solution of ketone **8.2** (3.8 g, 10.7 mmol) in diethyl ether (40 mL) was added to a suspension of lithium aluminum hydride (0.8 g, 21.4 mmol) in diethyl ether (40 mL) at 0 °C under nitrogen. The resulting reaction mixture was warmed to room temperature and stirred for 1 h. Water (0.8 mL) was added, followed by 1 *M* sodium hydroxide (0.8 mL) and a further portion of water (0.16 mL). When a white precipitate formed, anhydrous MgSO_4 was added and the reaction mixture was filtered through a plug of Celite[®]. Concentration of the organic phase *in vacuo* gave the title compound **8.3** (3.6 g, 93%) as a white foam, which was used directly in the next step without further purification.

IR (thin film) cm^{-1} : 3478br (C-OH), 2923s (C-H), 1609s, 1500s, 1464, 1377, 1272, 1237, 1151, 1109, 1044.

¹H NMR (300 MHz, CDCl₃) δ: 0.97 (t, $J_{3,2} = 7.3$ Hz, 3H, H-3), 1.35 (m, 1H, H-10'), 1.68 (s, 3H, 2'-CH₃), 1.52-1.85 (m, 5H, H'-10', H-3', H-2), 2.15 (m, 1H, H-9'), 2.53 (ddd, $J_{gem} = 16.5$, $J_{9',10'} = 11.1$ Hz, $J_{9',10'} = 5.7$ Hz, 1H, H'-9'), 2.86 (m, 1H, H-4'), 3.31 (d, $J_{4a',4'} = 3.3$ Hz, 1H, H-4a'), 3.36 (s, 3H, 10a'-OCH₂OCH₃), 3.36, 3.53 (2 x ABd, $J = 9.3$ Hz, 2H, 10a'-CH₂), 3.77 (s, 3H, 7'-OCH₃), 3.79 (m, 1H, H-1), 4.61 (s, 2H, 10a'-OCH₂OCH₃), 5.12 (s (br), 1H, H-1'), 6.59 (d, $J_{8',6'} = 2.7$ Hz, 1H, H-8'), 6.71 (dd, $J_{6',5'} = 8.4$ Hz, $J_{6',8'} = 2.7$ Hz, 1H, H-6'), 7.40 (d, $J_{5',6'} = 8.4$ Hz, 1H, H-5').

¹³C NMR (75 MHz, CDCl₃) δ: 9.5 (CH₃, C-3), 23.8 (2'-CH₃), 26.9 (CH₂, C-10'), 29.2 (CH₂), 30.4 (CH₂), 30.7 (CH₂), 37.9 (C, C-10a'), 40.5 (CH, C-4a'), 44.0 (CH, C-4'), 55.0 (10a'-OCH₂OCH₃), 55.2 (7'-OCH₃), 72.8 (CH, C-1), 74.7 (C10a'-CH₂), 96.8 (10a'-OCH₂OCH₃), 111.9 (CH, C-6'), 113.3 (CH, C-8'), 126.8 (CH, C-1'), 129.3 (CH, C-5'), 131.3 (C, C-4b'), 135.4 (C, C-2'), 140.1 (C, C-8a'), 157.1 (C, C-7').

LRMS (m/z): 360 (M⁺, 23%), 280 (7), 267 (40), 239 (15), 227 (100), 212 (17), 173 (12), 147 (25), 84 (67).

HRMS: C₂₂H₃₂O₄ (M⁺) requires 360.2301, found 360.2301.

(4'*RS*, 4a'*SR*, 10a'*RS*, 1*SR* or 1*RS*) 1-[10a'-Methoxmethoxy-7'-methoxy-2'-methyl-4a',9',10',10a'-tetrahydrophenanthren-4'(3'*H*)-yl]-propan-1-yl benzoate (2.4)

Benzoyl chloride (3.5 mL, 29.9 mmol) was added to a solution of alcohol **8.3** (3.6 g, 9.96 mmol) in pyridine (100 mL) at room temperature under nitrogen. A catalytic amount of DMAP (5 mol %) was added and the resulting reaction mixture was stirred for 24 h. Water (50 mL) was then added, and the resulting mixture stirred for 10 min before extracting with ethyl acetate (4 x 50 mL). The combined organic extracts were washed with a saturated aqueous solution of copper sulfate (4 x 50 mL), water (50 mL), 1 M hydrochloric acid (50 mL), water (50 mL), and dried over anhydrous MgSO₄.

Concentration of the organic phase *in vacuo* gave a cream solid, which was further purified by flash column chromatography on silica gel using ethyl acetate : hexane (1 : 9) as eluant to give the title compound **2.4** (4.2 g, 84% over three steps) as a white wax.

IR (thin film) cm^{-1} : 2931s (C-H), 1711s (C=O), 1609s, 1501s, 1451, 1314, 1272, 1237, 1150, 1110, 1045.

^1H NMR (300 MHz, CDCl_3) δ : 0.91 (t, $J_{3,2} = 7.3$ Hz, 3H, H-3), 1.64 (m, 1H, H-10'), 1.74-1.94 (m, 4H, H'-10', H-3', H-2), 2.06 (m, 1H, H'-3'), 1.73 (s, 3H, 2'- CH_3), 2.45-2.76 (m, 3H, H-4', H-9'), 3.17 (d, $J_{4a',4'} = 3.0$ Hz, 1H, H-4a'), 3.34 (s, 3H, 10a'- OCH_2OCH_3), 3.35, 3.51 (2 x ABd, $J = 6.6$ Hz, 2H, 10a'- CH_2), 3.58 (s, 3H, 7'- OCH_3), 4.60, 4.64 (2 x ABd, $J = 9.3$ Hz, 2H, 10a'- OCH_2OCH_3), 5.26 (s (br), 1H, H-1'), 5.53 (ddd, $J = 9.9$ Hz, $J = 5.4$ Hz, $J = 3.9$ Hz, 1H, H-1), 6.26 (d, $J_{8',6'} = 2.7$ Hz, 1H, H-8'), 6.68 (dd, $J_{6',5'} = 8.7$ Hz, $J_{6',8'} = 2.7$ Hz, 1H, H-6'), 7.20 (d, $J_{5',6'} = 8.7$ Hz, 1H, H-5'), 7.30-7.51 (m, 3H, H-3'', H-4''), 7.74 (d, $J = 8.4$ Hz, 2H, H-2'').

^{13}C NMR (75 MHz, CDCl_3) δ : 8.2 (CH_3 , C-3), 24.0 (2'- CH_3), 26.0 (CH_2 , C-10'), 26.4 (CH_2), 29.1 (CH_2), 31.3 (CH_2), 39.1 (C, C-10a'), 40.0 (CH, C-4a'), 40.4 (CH, C-4'), 54.7 (10a'- OCH_2OCH_3), 55.0 (7'- OCH_3), 74.2 (CH, C-1), 75.4 (C10a'- CH_2), 96.6 (10a'- OCH_2OCH_3), 111.9 (CH, C-6'), 112.8 (CH, C-8'), 127.3 (CH, C-1'), 127.6 (CH, C-5'), 129.3 (Ar), 129.4 (Ar), 130.1 (Ar), 130.2 (Ar), 132.3 (C, C-4b'), 133.6 (C, C-2'), 138.3 (C, C-8a'), 156.6 (C, C-7'), 165.7 (1-OC(O)Ph).

LRMS (m/z): 464 (M^+ , 37%), 432 (5), 388 (8), 342 (8), 310 (15), 297 (16), 280 (32), 267 (100), 225 (25), 211 (17), 105(50).

HRMS: $\text{C}_{29}\text{H}_{36}\text{O}_5$ (M^+) requires 464.2563, found 464.2567.

(4'*RS*, 4a'*SR*, 10a'*RS*, 1*SR* or 1*RS*) 1-[10a'-Hydroxymethyl-7'-methoxy-2'-methyl-4a',9',10',10a'-tetrahydrophenanthren-4'(3'*H*)-yl]-propan-1-yl benzoate (**8.4**)

Concentrated hydrochloric acid (10 drops) was added to a solution of MOM ether **2.4** (4.2 g, 9.04 mmol) in methanol (80 mL). The resulting reaction mixture was stirred at 70 °C for 18 h, then a saturated solution of sodium bicarbonate was added and the methanol removed *in vacuo*. The residue was extracted with ethyl acetate (3 x 30mL) and the combined organic extracts were dried over anhydrous MgSO₄. Concentration of the organic phase *in vacuo* gave the title compound **8.4** (3.6 g, 95%) as a white foam, which was used directly in the next step without further purification.

IR (thin film) cm⁻¹: 2935s (C-H), 1709s (C=O), 1609s, 1501s, 1451, 1315, 1272s, 1114, 1070, 1041.

¹H NMR (300 MHz, CDCl₃) δ: 0.86 (t, $J_{3,2}$ = 7.5 Hz, 3H, H-3), 1.56-2.28 (m, 5H, H-10', H-3', H-2), 1.77 (s, 3H, 2'-CH₃), 2.24 (m, 1H, H'-3'), 2.47-2.54 (m, 2H, H-9'), 2.76 (m, 1H, H-4'), 3.22 (d, $J_{4a',4'}$ = 3.3 Hz, 1H, H-4a'), 3.37, 3.42 (2 x ABd, J = 10.8 Hz, 2H, 10a'-CH₂), 3.52 (s, 3H, 7'-OCH₃), 5.17 (s (br), 1H, H-1'), 5.47 (ddd, J = 9.6 Hz, J = 5.4 Hz, J = 3.3 Hz, 1H, H-1), 6.12 (d, $J_{8',6'}$ = 2.7 Hz, 1H, H-8'), 6.66 (dd, $J_{6',5'}$ = 8.6 Hz, $J_{6',8'}$ = 2.7 Hz, 1H, H-6'), 7.19 (d, $J_{5',6'}$ = 8.6 Hz, 1H, H-5'), 7.25-7.48 (m, 3H, H-3'', H-4''), 7.58 (d, J = 7.2 Hz, 2H, H-2'').

¹³C NMR (75 MHz, CDCl₃) δ: 8.2 (CH₃, C-3), 24.2 (2'-CH₃), 26.0 (CH₂, C-10'), 26.1 (CH₂), 28.6 (CH₂), 32.4 (CH₂), 39.0 (C, C-10a'), 40.8 (CH, C-4a'), 40.9 (CH, C-4'), 54.7 (7'-OCH₃), 68.8 (C10a'-CH₂), 75.3 (CH, C-1), 112.4 (CH, C-6'), 112.6 (CH, C-8'), 126.6 (CH, C-1'), 127.6 (CH, C-5'), 129.3 (Ar), 129.7 (Ar), 129.9 (Ar), 130.4 (Ar), 132.3 (C, C-4b'), 135.7 (C, C-2'), 137.1 (C, C-8a'), 156.7 (C, C-7'), 165.7 (1-OC(O)Ph).

LRMS (m/z): 420 (M^+ , 33%), 298 (21), 280 (12), 267 (100), 225 (35), 211 (20), 105 (61).

HRMS: $C_{27}H_{32}O_4$ (M^+) requires 420.2295, found 420.2298.

(4'*RS*, 4a'*SR*, 10a'*RS*, 1*SR* or 1*RS*) 1-[10a'-Acetoxymethyl-7'-methoxy-2'-methyl-4a',9',10',10a'-tetrahydrophenanthren-4'(3'*H*)-yl]-propan-1-yl Benzoate (2.7)

Acetic anhydride (3.2 mL, 34.2 mmol) was added to alcohol **8.4** (3.6 g, 8.6 mmol) in DCM (90 mL) and pyridine (2.7 mL, 34.2 mmol) at 0 °C under nitrogen. A catalytic amount of DMAP was added and the resulting reaction mixture stirred for 1 h. The reaction was quenched with water (30 mL), the organic phase separated and the aqueous residue was further extracted with DCM (2 x 20 mL). The combined organic extracts were washed with a saturated aqueous solution of copper sulfate (2 x 20 mL), water (20 mL), 1 *M* hydrochloric acid (20 mL), saturated sodium bicarbonate (20 mL), and dried over anhydrous $MgSO_4$. Concentration of the organic phase *in vacuo* gave a cream solid, which was further purified by flash column chromatography on silica gel using ethyl acetate : hexane (1 : 4) as eluant to give the title compound **2.7** (3.4 g, 81% over two steps) as a white solid.

m.p.: 108-111 °C

IR (thin film) cm^{-1} : 2935s (C-H), 1736s (C=O), 1713s (C=O), 1610s, 1501s, 1451, 1380, 1314, 1271, 1112, 1070, 1038.

1H NMR (300 MHz, $CDCl_3$) δ : 0.90 (t, $J_{3,2} = 7.5$ Hz, 3H, H-3), 1.53-1.76 (m, 4H, H-10', H-2), 1.70 (s, 3H, 2'-CH₃), 1.83-1.93 (m, 2H, H-3'), 1.99 (s, 3H, 10a'-OC(O)CH₃), 2.44 (m, 1H, H-9'), 2.63-2.73 (m, 2H, H'-9', H-4'), 3.18 (d, $J_{4a',4'} = 3.0$ Hz, 1H, H-4a'), 3.60 (s, 3H, 7'-OCH₃), 3.84, 4.19 (2 x ABd, $J = 10.8$ Hz, 2H, 10a'-CH₂), 5.10 (s (br),

^1H , H-1'), 5.50 (ddd, $J = 9.9$ Hz, $J = 5.1$ Hz, $J = 3.6$ Hz, 1H, H-1), 6.31 (d, $J_{8',6'} = 2.4$ Hz, 1H, H-8'), 6.68 (dd, $J_{6',5'} = 8.4$ Hz, $J_{6',8'} = 2.4$ Hz, 1H, H-6'), 7.20 (d, $J_{5',6'} = 8.4$ Hz, 1H, H-5'), 7.31-7.57 (m, 3H, H-3'', H-4''), 7.80 (d, $J = 7.2$ Hz, 2H, H-2'').

^{13}C NMR (75 MHz, CDCl_3) δ : 8.1 (CH_3 , C-3), 20.6 ($-\text{OC}(\text{O})\text{CH}_3$), 23.6 ($2'-\text{CH}_3$), 25.8 (CH_2 , C-10'), 26.3 (CH_2), 29.4 (CH_2), 30.5 (CH_2), 38.0 (C, C-10a'), 39.7 (CH, C-4a'), 40.0 (CH, C-4'), 54.5 ($7'-\text{OCH}_3$), 69.5 (C10a'- CH_2), 75.1 (CH, C-1), 111.8 (CH, C-6'), 112.9 (CH, C-8'), 125.6 (CH, C-1'), 127.6 (CH, C-5'), 128.4 (Ar), 129.1 (Ar), 129.8 (Ar), 130.0 (Ar), 132.2 (C, C-4b'), 135.3 (C, C-2'), 138.3 (C, C-8a'), 156.6 (C, C-7'), 165.3 ($1-\text{OC}(\text{O})\text{Ph}$), 170.4 ($-\text{OC}(\text{O})\text{CH}_3$).

LRMS (m/z): 462 (M^+ , 50%), 340 (49), 297 (2), 280 (74), 267 (100), 225 (47), 187 (25), 105(71).

HRMS: $\text{C}_{29}\text{H}_{34}\text{O}_5$ (M^+) requires 462.2406, found 462.2409.

Microanalysis: Calcd. for $\text{C}_{29}\text{H}_{34}\text{O}_5$: C, 75.30%; H, 7.41%. Found: C, 75.38%; H, 7.64%.

(4'*RS*, 4a'*SR*, 10a'*RS*, 1*SR* or 1*RS*) 1-(10a'-Acetoxymethyl-7'-methoxy-2'-methyl-1',2'-epoxy-4a',9',10',10a'-tetrahydrophenanthren-4-yl)-propan-1-yl Benzoate (2.8)

m-CPBA (0.81 g, 4.70 mmol) was added to a mixture of olefin **2.7** (1.08 g, 2.30 mmol) and NaHCO_3 (1.70 g) in DCM (20 mL) at 0 °C under nitrogen. The resulting reaction mixture was warmed to room temperature and stirred for 2 h before 10% Na_2SO_3 (10 mL) was added. After 5 min, the organic phase was separated and the aqueous residue further extracted with DCM (2 x 15 mL). The combined organic extracts were washed with 1 *M* sodium hydroxide and brine then dried over MgSO_4 . Concentration of the organic phase *in vacuo* gave a white foam which was further purified by flash column

chromatography on silica gel using ethyl acetate : hexane (1 : 4) as eluant to give the title compound **2.8** (0.98 g, 89%) as a white foam.

IR (thin film) cm^{-1} : 2938s (C-H), 1743s (C=O), 1713s (C=O), 1610s, 1583, 1501s, 1451, 1381, 1364, 1271, 1176, 1070, 1039.

^1H NMR (300 MHz, CDCl_3) δ : 0.93 (t, $J_{3,2} = 7.5$ Hz, 3H, H-3), 1.21 (m, 1H, H-10'), 1.57-1.69 (m, 3H), 1.86-2.11 (m, 2H), 1.30 (s, 3H, 2'-CH₃), 2.03 (s, 3H, 10a'-OC(O)CH₃), 2.50-2.92 (m, 4H, H-9', H-4', H-4a), 2.81 (s, 1H, H-1' major), 2.97 (s, 1H, H-1' minor), 3.74 (s, 3H, 7'-OCH₃), 4.25 (s, 2H, 10a'-CH₂), 5.38 (m, 1H, H-1), 6.57 (d, $J_{8',6'} = 2.4$ Hz, 1H, H-8'), 6.73 (dd, $J_{6',5'} = 8.4$ Hz, $J_{6',8'} = 2.4$ Hz, 1H, H-6'), 7.10 (d, $J_{5',6'} = 8.4$ Hz, 1H, H-5'), 7.41-7.64 (m, 3H, H-3'', H-4''), 8.00 (d, $J = 7.2$ Hz, 2H, H-2'').

^{13}C NMR (75 MHz, CDCl_3) δ : 8.2 (CH₃, C-3), 20.9 (-OC(O)CH₃), 22.3 (2'-CH₃), 25.0 (CH₂, C-10'), 26.5 (CH₂), 28.6 (CH₂), 31.3 (CH₂), 35.4 (C, C-10a'), 36.2 (CH, C-4a'), 37.3 (CH, C-4'), 55.0 (7'-OCH₃), 58.3 (C, C-2'), 64.3 (CH, C-1'), 68.0 (C10a'-CH₂), 75.4 (CH, C-1), 111.7 (CH, C-6'), 113.5 (CH, C-8'), 127.1 (CH, C-5'), 128.2 (Ar), 129.3 (Ar), 130.1 (Ar), 130.4 (Ar), 132.8 (C, C-4b'), 139.5 (C, C-8a'), 157.0 (C, C-7'), 165.7 (1-OC(O)Ph), 170.7 (-OC(O)CH₃).

LRMS (m/z): 478 (M^+ , 5%), 418 (12), 356 (15), 296 (34), 267 (45), 226 (47), 173 (29), 105 (100).

HRMS: $\text{C}_{29}\text{H}_{34}\text{O}_6$ (M^+) requires 478.2355, found 478.2359.

(4*RS*, 4a*SR*, 10a*SR*, 1*SR* or 1*RS*) 10a-acetoxymethyl-4-(1'-Benzoyloxypropyl)-7-methoxy-2-methyl-3, 4, 4a, 9,10, 10a-hexahydrophenanthren-1(2*H*)-one (**2.9**)

Boron trifluoride diethyl etherate (0.52 mL, 4.10 mmol) was added drop wise to a solution of epoxide **2.8** (0.98 g, 2.05 mmol) in DCM (35 mL) at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C for 40 min before adding water (15 mL) and stirring vigorously for 10 min. The organic phase was separated, and the aqueous phase extracted with DCM (2 x 15 mL). The combined organic extracts were dried over anhydrous MgSO₄ and concentrated *in vacuo* to give a white foam. Purification by flash column chromatography on silica gel using ethyl acetate : hexane (1 : 4) as eluant gave the title compound **2.9** (0.72 g, 74%) as a white solid. A sample was crystallised from hexane to give white needle-like crystals.

m.p.: 121-123 °C

IR (thin film) cm⁻¹: 2967s (C-H), 1739s (C=O), 1709s (C=O), 1611s, 1584, 1502s, 1452, 1378, 1337, 1314, 1271, 1174, 1108, 1038.

¹H NMR (300 MHz, CDCl₃) δ: 0.89 (t, $J_{3',2'} = 7.2$ Hz, 3H, H-3'), 1.12 (d, $J = 6.3$ Hz, 3H, 2-CH₃), 1.55-2.25 (m, 6H, H-10, H-3, H-2'), 1.93 (s, 3H, 10a-OC(O)CH₃), 2.45-2.76 (m, 4H, H-9, H-4, H-2), 3.42 (s, 3H, 7-OCH₃), 3.46 (d, $J_{4a,4} = 4.2$ Hz, 1H, H-4a), 3.94, 4.36 (2 x ABd, $J = 10.8$ Hz, 2H, 10a-CH₂OH), 5.75 (ddd, $J = 10.5$ Hz, $J = 6.9$ Hz, $J = 3.6$ Hz, 1H, H-1'), 6.18 (d, $J_{8,6} = 2.7$ Hz, 1H, H-8), 6.55 (dd, $J_{6,5} = 8.6$ Hz, $J_{6,8} = 2.7$ Hz, 1H, H-6), 7.17 (d, $J_{5,6} = 8.6$ Hz, 1H, H-5), 7.26-7.50 (m, 3H, H-3'', H-4''), 7.66 (d, $J = 8.4$ Hz, 2H, H-2'').

¹³C NMR (75 MHz, CDCl₃) δ: 8.1 (CH₃, C-3'), 15.8 (2-CH₃), 20.6 (-OC(O)CH₃), 25.4 (CH₂, C-10), 25.9 (CH₂), 28.0 (CH₂), 33.2 (CH₂), 38.2 (C, C-10a), 40.7 (CH, C-4a), 41.6 (CH), 50.8 (CH), 54.3 (7-OCH₃), 67.2 (C10a-CH₂OH), 74.0 (CH, C-1'), 112.4 (CH, C-6), 112.7 (CH, C-8'), 127.4 (CH, C-5'), 127.6 (Ar), 129.0 (Ar), 129.3 (Ar), 130.0 (Ar), 132.2 (C, C-4b), 135.3 (C, C-8a), 156.9 (C, C-7), 165.1 (1'-OC(O)Ph), 170.0 (-OC(O)CH₃), 214.2 (1-CO).

LRMS (m/z): 478 (M⁺, 11%), 418 (50), 356 (53), 328 (22), 296 (50), 268 (35), 226 (47), 173 (65), 105(100).

HRMS: C₂₉H₃₄O₆ (M⁺) requires 478.2355, found 478.2362.

Microanalysis: Calcd. for $C_{29}H_{34}O_6$: C, 72.78%; H, 7.16%. Found: C, 72.99%; H, 7.25%.

(2*RS*, 4*RS*, 4*aRS*, 10*aSR*, 1'*SR*) 4-(1'-Benzoyloxypropyl)-7-methoxy-2-methyl-3,4,4*a*,9,10,10*a*-hexahydrophenanthren-1(2*H*)-one (1.95)

Acetate **2.9** (0.21 g, 0.44 mmol) was dissolved in ethanolic potassium hydroxide (0.6 g per 20 mL), and monitored by TLC until all the starting material had been consumed (ca. 1 h). The reaction mixture was neutralised with 1 *M* hydrochloric acid, the ethanol removed *in vacuo* and the residue extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL) and dried over anhydrous $MgSO_4$. Concentration of the organic phase *in vacuo* gave a brown oil which was purified by flash column chromatography on silica gel using ethyl acetate : hexane (1 : 4) as eluant to give the title compound **1.95** (0.12 g, 70%) as a cream solid. A sample was crystallised from hexane to give white crystals.

m.p: 94-95 °C

IR (thin film) cm^{-1} : 2967s (C-H), 1709s (C=O), 1611s, 1584s, 1503s, 1452s, 1316, 1275s, 1111, 1026.

1H NMR (300 MHz, $CDCl_3$) δ : 0.95 (t, $J_{3',2'} = 7.3$ Hz, 3H, H-3'), 1.11 (d, $J = 6.3$ Hz, 3H, 2- CH_3), 1.48 (m, 1H, H-10), 1.70 (dd, $J_{gem} = 14.1$ Hz, $J = 4.5$ Hz, 1H, H-3), 1.81 (m, 1H, H-2'), 1.95 (m, 1H, H'-2'), 2.17 (m, 1H, H'-10), 2.24 (ddd, $J_{gem} = 14.1$ Hz, $J = 6.0$, $J = 2.1$ Hz, 1H, H'-3) 2.45-2.53 (m, 2H, H-9), 2.73 (m, 1H, H-2), 2.99-3.05 (m, 3H, H-4, H-4a, H-10a), 3.46 (s, 3H, 7- OCH_3), 5.88 (ddd, $J = 10.8$ Hz, $J = 8.4$ Hz, $J = 3.3$ Hz, 1H, H-1'), 6.02 (d, $J_{8,6} = 2.7$ Hz, 1H, H-8), 6.52 (dd, $J_{6,5} = 8.7$ Hz, $J_{6,8} = 2.7$ Hz, 1H, H-6), 7.16-7.44 (m, 6H, H-5, H-2'', H-3'', H-4'').

^{13}C NMR (75 MHz, CDCl_3) δ : 9.2 (CH_3 , C-3'), 14.7 (2- CH_3), 22.3 (CH_2 , C-10), 27.2 (CH_2 , C-2'), 29.2 (CH_2 , C-9), 38.4 (CH_2 , C-3), 40.1 (CH , C-2), 40.4 (CH , C-10a), 46.8 (CH , C-4a), 47.3 (CH , C-4), 54.6 (7- OCH_3), 72.7 (CH , C-1'), 112.4 (CH , C-6), 112.6 (CH , C-8), 127.2 (CH , C-5), 127.9 (Ar), 129.0 (Ar), 129.2 (Ar), 132.1 (C, C-4b), 137.1 (C, C-8a), 156.4 (C, C-7), 165.8 (1'- OC(O)Ph), 211.8 (1-CO).

LRMS (m/z): 406 (M^+ , 90%), 284 (51), 242 (56), 216 (30), 187 (87), 160 (76), 128 (13), 105 (100).

HRMS: $\text{C}_{26}\text{H}_{30}\text{O}_4$ (M^+) requires 406.2144, found 406.2148.

Microanalysis: Calcd. for $\text{C}_{26}\text{H}_{30}\text{O}_4$: C, 76.82%, H, 7.44%. Found: C, 76.47%, H, 7.37%.

8.3 Chapter 3 Experimental

(1*RS*, 2*RS*, 4*RS*, 4a*SR*, 10a*SR*, 1'*SR*) 4-(1'-Benzoyloxypropyl)-7-methoxy-2-methyl-3,4,4a,9,10,10a-hexahydrophenanthren-1(2*H*)-ol (**3.1**)

L-Selectride[®] (1.7 mL of a 1.0 *M* solution in THF, 1.7 mmol) was added to ketone **1.95** (0.50 g, 1.2 mmol) in THF (5 mL) at -78 °C under nitrogen. The resulting reaction mixture was stirred for 20 min before warming to 0 °C. 10% Aqueous sodium hydroxide (7 mL) and 30% aqueous hydrogen peroxide (5 mL) were added, the solution was warmed to room temperature and stirred overnight. The mixture was then extracted with ethyl acetate (3 x 30 mL), washed with water (2 x 10 mL), saturated sodium bicarbonate solution (2 x 10 mL) and brine (10 mL). The organic phase was then dried over anhydrous MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography on silica gel using ethyl acetate : hexane (5 : 95) as eluant gave the title compound **3.1** (0.44 g, 88%) as a white foam.

IR (thin film) cm^{-1} : 2526 (C-OH), 2927s (C-H), 1709s (C=O), 1611s, 1584, 1502s, 1452s, 1316, 1275s, 1112, 1026.

^1H NMR (300 MHz, CDCl_3) δ : 0.87 (t, $J_{3',2'} = 7.2$ Hz, 3H, H-3'), 1.02 (d, $J = 6.9$ Hz, 3H, 2- CH_3), 1.37-1.72 (m, 5H), 1.75-1.87 (m, 2H), 2.01 (m, 1H), 2.16 (m, 1H), 2.40-2.70 (m, 2H), 2.82 (m, 1H, H-4), 3.21 (m, 1H, H-4a), 3.46 (s, 3H, 7- OCH_3), 3.78 (m, 1H, H-1), 5.63 (ddd, $J = 10.8$ Hz, $J = 8.1$ Hz, $J = 3.0$ Hz, 1H, H-1'), 6.01 (d, $J_{8,6} = 2.7$ Hz, 1H, H-8), 6.50 (dd, $J_{6,5} = 8.7$ Hz, $J_{6,8} = 2.7$ Hz, 1H, H-6), 7.17-7.42 (m, 6H, H-5, H-2'', H-3'', H-4'').

^{13}C NMR (75 MHz, CDCl_3) δ : 9.5 (CH_3 , C-3'), 18.5 (2- CH_3), 27.3 (CH_2), 27.4 (CH_2), 30.9 (CH_2), 32.3 (CH_2), 32.6 (CH), 37.6 (CH), 39.8 (CH), 40.7 (CH), 55.0 (7- OCH_3), 73.7 (CH, C-1'), 75.1 (CH, C-1), 112.5 (CH, C-6), 113.1 (CH, C-8), 127.7 (CH, C-5), 128.6 (Ar), 129.8 (Ar), 129.9 (Ar), 131.7 (Ar), 132.4 (C, C-4b), 137.9 (C, C-8a), 156.5 (C, C-7), 166.4 (1'- $\text{OC}(\text{O})\text{Ph}$).

LRMS (m/z): 408 (M^+ , 44%), 390 (15), 284 (5), 268 (100), 239 (26), 226 (65), 189 (40), 105 (71).

HRMS: $\text{C}_{26}\text{H}_{32}\text{O}_4$ (M^+) requires 408.2301, found 408.2301.

(1'*RS*, 2'*RS*, 4'*RS*, 4a'*SR*, 10a'*SR*, 1*SR*) 1-[7'-Methoxy-1'-methoxymethoxy-2'-methyl-1',2',4a',9',10',10a'-hexahydrophenanthrene-4'(3'*H*)-yl]-propan-1-yl benzoate (3.2)

Hünig's base (0.68 mL, 3.88 mmol) was added to alcohol **3.1** (0.52 g, 1.29 mmol) in DCM (10 mL) at 0 °C under nitrogen. Chloromethyl methyl ether (0.29 mL, 3.88 mmol) was added drop wise and the reaction mixture was warmed to room temperature. A catalytic amount of DMAP was then added and the mixture was stirred for 24 h. The reaction was then cooled to 0 °C, saturated sodium bicarbonate (10

mL) was added, and the resulting mixture stirred for 10 min. The organic phase was then separated and the aqueous phase was extracted with DCM (3 x 10 mL). The combined organic extracts were washed with water (10 mL), 2 M hydrochloric acid (10 mL), saturated sodium bicarbonate (10 mL), brine (10 mL) and dried over anhydrous MgSO_4 . Concentration *in vacuo* gave the crude product as a yellow gum, which was further purified by flash column chromatography on silica gel using ethyl acetate : hexane (5 : 95 – 20 : 80) as eluant to give the title compound **3.2** (0.50 g, 86%) as a colourless oil.

IR (thin film) cm^{-1} : 2929s (C-H), 1709s (C=O), 1611s, 1584, 1502s, 1452s, 1316, 1274s, 1147, 1039.

^1H NMR (300 MHz, CDCl_3) δ : 0.87 (t, $J_{3,2} = 7.2$ Hz, 3H, H-3), 1.00 (d, $J = 6.6$ Hz, 3H, 2'- CH_3), 1.53-1.87 (m, 7H), 2.01 (m, 1H), 2.16 (m, 1H), 2.39-2.62 (m, 2H), 2.80 (m, 1H, H-4'), 3.24 (m, 1H, H-4a'), 3.37 (s, 3H, 1'- OCH_2OCH_3), 3.46 (s, 3H, 7'- OCH_3), 4.63, 4.67 (2 x ABd, $J = 6.9$ Hz, 2H, 1'- OCH_2OCH_3), 5.63 (m, 1H, H-1), 6.00 (d, $J_{8',6'} = 2.7$ Hz, 1H, H-8'), 6.50 (dd, $J_{6',5'} = 8.7$ Hz, $J_{6',8'} = 2.7$ Hz, 1H, H-6'), 7.17-7.41 (m, 6H, H-5', H-2'', H-3'', H-4'').

^{13}C NMR (75 MHz, CDCl_3) δ : 9.1 (CH_3 , C-3), 18.6 (2'- CH_3), 27.0 (CH_2), 27.3 (CH_2), 30.4 (CH_2), 32.2 (CH_2), 33.1 (CH), 38.2 (CH), 39.7 (CH), 40.4 (CH), 54.5 (1'- OCH_2OCH_3), 56.0 (7'- OCH_3), 73.3 (CH, C-1), 83.0 (CH, C-1'), 98.4 (1'- OCH_2OCH_3), 112.1 (CH, C-6'), 112.5 (CH, C-8'), 127.2 (CH, C-5'), 128.1 (Ar), 129.1 (Ar), 129.3 (Ar), 129.5 (Ar), 131.4 (Ar), 131.7 (Ar), 132.0 (C, C-4b'), 137.6 (C, C-8a'), 156.0 (C, C-7'), 165.9 (1-OC(O)Ph).

LRMS (m/z): 452 (M^+ , 25%), 420 (40), 390 (30), 285 (60), 268 (100), 239 (26), 226 (65), 160 (30), 105 (85).

HRMS: $\text{C}_{28}\text{H}_{36}\text{O}_5$ (M^+) requires 452.2563, found 452.2562.

(1'*RS*, 2'*RS*, 4'*RS*, 4a'*RS*, 10a'*SR*, 1*SR*) 1-[7'-Methoxy-1'-methoxymethoxy-2'-methyl-1',2',4a',9',10',10a'-hexahydrophenanthrene-4' (3'*H*)-yl]-propan-1-ol (**3.3**)

Small pieces of sodium metal (0.4 g total) were added slowly to ethanol (20 mL) at room temperature under nitrogen. A solution of benzoate **3.2** (0.50 g, 1.11 mmol) in ethanol (5 mL) was added and the resulting reaction mixture heated at reflux for 24 h. The reaction mixture was warmed to room temperature, water (10 mL) was added and the ethanol removed *in vacuo*. The aqueous residue was extracted with ethyl acetate (3 x 20 mL) and the combined organic extracts dried over anhydrous MgSO_4 . Concentration of the organic phase *in vacuo* gave a yellow gum which was purified by flash column chromatography on silica gel using ethyl acetate : hexane (1 : 9) as eluant to give the title compound **3.3** (0.36 g, 95%) as a white foam.

IR (thin film) cm^{-1} : 3576 (C-OH), 2926s (C-H), 1609s, 1500s, 1464, 1256, 1147, 1038s.

^1H NMR (300 MHz, CDCl_3) δ : 0.91 (t, $J_{3,2} = 7.2$ Hz, 3H, H-3), 0.96 (d, $J = 6.3$ Hz, 3H, 2'- CH_3), 1.32 (m, 1H), 1.48-1.87 (m, 6H), 2.10 (m, 1H), 2.49 (m, 1H, H-4'), 2.71 (m, 1H), 2.88 (m, 1H), 3.28 (m, 1H, H-4a'), 3.39 (s, 3H, 1'- OCH_2OCH_3), 3.62 (m, 1H, H-1'), 3.75 (s, 3H, 7'- OCH_3), 3.88 (td, $J_{1,2} = 9.0$, $J_{1,4'} = 3.0$ Hz, 1H, H-1), 4.65, 4.68 (2 x ABd, $J = 6.9$ Hz, 2H, 1'- OCH_2OCH_3), 6.60 (d, $J_{8',6'} = 2.6$ Hz, 1H, H-8'), 6.73 (dd, $J_{6',5'} = 8.6$ Hz, $J_{6',8'} = 2.6$ Hz, 1H, H-6'), 7.29 (d, $J_{5',6'} = 8.6$ Hz, 1H, H-5').

^{13}C NMR (75 MHz, CDCl_3) δ : 9.7 (CH_3 , C-3), 18.6 (2'- CH_3), 27.3 (CH_2), 29.2 (CH_2), 30.9 (CH_2), 32.5 (CH_2), 32.9 (CH), 38.3 (CH), 40.3 (CH), 42.8 (CH), 55.1 (1'- OCH_2OCH_3), 56.1 (7'- OCH_3), 72.8 (CH, C-1), 83.0 (CH, C-1'), 98.4 (1'- OCH_2OCH_3), 112.3 (CH, C-6'), 114.3 (CH, C-8'), 128.5 (CH, C-5'), 130.8 (C, C-4b'), 139.0 (C, C-8a'), 157.2 (C, C-7').

LRMS (m/z): 348 (M^+ , 25%), 316 (35), 286 (48), 268 (23), 245 (50), 228 (100), 227 (75), 201 (27), 186 (40).

HRMS: $C_{21}H_{32}O_4$ (M^+) requires 348.2301, found 348.2304.

(1'*RS*, 2'*RS*, 4'*RS*, 4a'*SR*, 10a'*SR*, 1*SR*) 1-[7'-Methoxy-1'-methoxymethoxy-2'-methyl-1',2',4a',9',10',10a'-hexahydrophenanthrene-4' (3'*H*)-yl]-propoxy-(*t*-butyl)dimethylsilane (3.4)

t-Butyldimethylsilyl trifluoromethanesulfonate (0.36 mL, 1.55 mmol) was added drop wise to alcohol **3.3** (0.36 g, 1.03 mmol) and 2,6-lutidine (0.24 mL, 2.06 mmol) in DCM (6 mL) at room temperature under nitrogen. The resulting reaction mixture was stirred for 15 min after which time TLC analysis revealed the consumption of all starting material. Water (6 mL) was added and the organic phase separated before further extraction with DCM (2 x 10 mL). The combined organic extracts were washed with brine and dried over anhydrous $MgSO_4$. Concentration of the organic phase *in vacuo* gave a yellow gum, which was purified by flash column chromatography on silica gel using ethyl acetate : hexane (1 : 9) as eluant to give the title compound **3.4** (0.38 g, 77%) as a white gum. A sample was crystallised from hexane to give white crystals.

m.p: 69-70 °C

IR (thin film) cm^{-1} : 2929s (C-H), 1611, 1576, 1501s, 1464, 1278, 1256s, 1149, 1039s.

1H NMR (300 MHz, $CDCl_3$) δ : -0.06 (s, 3H, -SiCH₃), -0.04 (s, 3H, -SiCH₃), 0.74 (t, $J_{3,2} = 7.2$ Hz, 3H, H-3), 0.84 (s, 9H, -Si^tBu), 0.97 (d, $J = 6.6$ Hz, 3H, 2'-CH₃), 1.23-1.99 (m, 8H), 2.62-2.88 (m, 3H), 3.26 (dd, $J_{4a',10a'} = 12.0$ Hz, $J_{4a',4'} = 5.7$ Hz 1H, H-4a'), 3.39 (s, 3H, 1'-OCH₂OCH₃), 3.57 (m, 1H, H-1'), 3.78 (s, 3H, 7'-OCH₃), 3.75 (m, 1H, H-1), 4.64, 4.67 (2 x ABd, $J = 6.9$ Hz, 2H, 1'-OCH₂OCH₃), 6.56 (d, $J_{8',6'} = 2.9$ Hz, 1H, H-8'), 6.70 (dd, $J_{6',5'} = 8.4$ Hz, $J_{6',8'} = 2.9$ Hz, 1H, H-6'), 7.20 (d, $J_{5',6'} = 8.4$ Hz, 1H, H-5').

^{13}C NMR (75 MHz, CDCl_3) δ : -4.4 (SiCH_3), -3.8 (SiCH_3), 10.8 (CH_3 , C-3), 18.2 (SiC), 19.1 ($2'\text{-CH}_3$), 26.1 (Si^tBu), 28.0 (CH_2), 28.3 (CH_2), 29.3 (CH_2), 31.0 (CH_2), 34.2 (CH), 37.2 (CH), 40.3 (CH), 41.0 (CH), 55.1 ($1'\text{-OCH}_2\text{OCH}_3$), 56.0 ($7'\text{-OCH}_3$), 73.3 (CH , C-1), 83.5 (CH , C-1'), 98.4 ($1'\text{-OCH}_2\text{OCH}_3$), 111.7 (CH , C-6'), 113.4 (CH , C-8'), 128.6 (CH , C-5'), 130.5 (C , C-4b'), 138.3 (C , C-8a'), 156.7 (C , C-7').

LRMS (m/z): 462 (M^+ , 2%), 405 (27), 373 (20), 269 (7), 226 (7), 174 (14), 173 (100), 147 (10), 117 (15), 115 (11).

HRMS: $\text{C}_{27}\text{H}_{46}\text{O}_4$ (M^+) requires 462.3165, found 462.3160.

Microanalysis: Calcd. for $\text{C}_{27}\text{H}_{46}\text{O}_4\text{Si}$: C, 70.08%, H, 10.02%. Found: C, 69.82%, H, 10.10%.

(4aSR, 4bSR, 5RS, 7RS, 8RS, 8aSR, 1'SR) 4-(1'-*t*-Butyldimethylsilyloxypropyl)-8-methoxmethoxy-7-methyl-4,4a,4b,5,6,7,8,8a,9,10-decahydro-2(3H)-phenanthrenone (3.7)

Dry ammonia (100 mL) was distilled into a 3-necked flask fitted with a dry ice condenser under nitrogen. Small pieces of freshly cleaned lithium wire (0.70 g, 100 mmol) were added at $-78\text{ }^\circ\text{C}$ and the resulting blue solution was stirred for 15 min. Silyl ether **3.4** (0.93 g, 2.0 mmol) in THF (40 mL) was added over 10 min, stirred for 15 min, then *t*-butanol (40 mL) was added. The resulting blue reaction mixture was warmed to $-40\text{ }^\circ\text{C}$ and stirred for 3 h. The reaction was quenched with methanol and the ammonia allowed to boil off under a stream of nitrogen, before a saturated aqueous solution of ammonium chloride (80 mL) was added. Water (50 mL) was added after 15 min and the aqueous phase extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL) and dried over anhydrous MgSO_4 . Concentration of the organic phase *in vacuo* gave a colourless oil, which was taken up in a solution of acetic acid : THF : water (4 : 2 : 1, 50 mL) and stirred overnight under nitrogen. The solvent was removed *in vacuo* and the residue treated

with 10% aqueous sodium hydroxide until pH 10. The aqueous residue was then extracted with ethyl acetate (3 x 50 mL), dried over anhydrous MgSO_4 and concentrated *in vacuo* to give the crude $\beta\gamma$ -enone **3.6** as a colourless oil, which was used directly in the next step without further purification.

Concentrated sulfuric acid was added drop wise to sodium chloride. The resulting hydrogen chloride gas was passed through concentrated sulfuric acid and then bubbled through THF (15 mL) for ca. 1 min. The crude $\beta\gamma$ -enone **3.6** in THF (15 mL) was then added to the acidic THF and the reaction monitored by TLC. The reaction was quenched with saturated aqueous sodium bicarbonate (5 mL) when most of the starting material had been consumed and a new UV active spot was observed. The THF was removed *in vacuo* and the aqueous residue extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL) and dried over anhydrous MgSO_4 . Concentration of the organic phase *in vacuo* gave a yellow gum, which was purified by flash column chromatography on silica gel using ethyl acetate : hexane (1 : 9) as eluant to give the $\beta\gamma$ -enone **3.6** (0.06 g, 7%) as a colourless oil, and the $\alpha\beta$ -enone **3.7** (0.58 g, 64%) as a white solid (71% combined yield). A sample of the $\alpha\beta$ -enone **3.7** was crystallised from hexane to give white crystals.

(4aSR, 4bSR, 5RS, 7RS, 8RS, 8aSR, 1'SR) 4-(1'-*t*-Butyldimethylsilyloxypropyl)-8-methoxmethoxy-7-methyl-,4,4a,4b,5,6,7,8,8a,9,10-decahydro-2(3*H*)-phenanthrenone (3.7)

m.p: 78-80 °C

IR (thin film) cm^{-1} : 2930s (C-H), 1672s (C=O), 1621, 1472, 1463, 1360, 1256s, 1151, 1039s.

^1H NMR (300 MHz, CDCl_3) δ : 0.06 (s, 3H, - SiCH_3), 0.08 (s, 3H, - SiCH_3), 0.90 (s, 9H, - Si^tBu), 0.92 (t, $J_{3',2'} = 7.5$ Hz, 3H, H-3'), 0.89-0.92 (m, 3H, 7- CH_3), 1.35-1.92 (m, 10H), 2.08-2.46 (m, 6H), 2.77 (m, 1H), 3.38 (s, 3H, 8- OCH_2OCH_3), 3.42 (m, 1H, H-8), 4.07 (dt, $J_{1',5} = 7.5$ Hz, $J_{1',2'} = 4.5$ Hz, 1H, H-1'), 4.61, 4.58 (2 x ABd, $J = 6.9$ Hz, 2H, 8- OCH_2OCH_3), 5.81 (s (br), 1H, H-1).

^{13}C NMR (75 MHz, CDCl_3) δ : -4.0 (SiCH_3), -3.5 (SiCH_3), 8.6 (CH_3 , C-3'), 18.2 (SiC), 18.7 (7- CH_3), 26.1 (Si^tBu), 27.2 (CH_2), 28.4 (CH_2), 30.1 (CH_2), 30.5 (CH_2), 32.8 (CH), 35.4 (CH_2), 36.3 (CH_2), 36.7 (CH), 38.3 (CH), 40.9 (CH), 44.1 (CH), 56.3 (8- OCH_2OCH_3), 72.9 (CH , C-1'), 83.1 (CH , C-8), 98.8 (8- OCH_2OCH_3), 124.0 (CH , C-1), 167.7 (C, C-10a), 200.2 (2-CO).

LRMS (m/z): 450 (M^+ , 5%), 435 (2), 421 (5), 393 (47), 361 (6), 331 (14), 318 (76), 256 (30), 224 (40), 192 (77), 173 (91), 170 (89), 141 (65), 73 (100).

HRMS: $\text{C}_{26}\text{H}_{46}\text{O}_4\text{Si}$ (M^+) requires 450.3165, found 450.3158.

Microanalysis: Calcd. for $\text{C}_{26}\text{H}_{46}\text{O}_4\text{Si}$: C, 69.28%, H, 10.29%. Found: C, 68.94%, H, 9.90%.

(4bSR, 5RS, 7RS, 8RS, 8aSR, 1'SR) 4-(1'-*t*-Butyldimethylsilyloxypropyl)-8-methoxmethoxy-7-methyl-1,4,4b,5,6,7,8,8a,9,10-decahydro-2(3H)-phenanthrenone (3.6)

IR (thin film) cm^{-1} : 2930s (C-H), 1721s (C=O), 1677, 1471s, 1379, 1254s, 1151, 1071, 1037s.

^1H NMR (300 MHz, CDCl_3) δ : -0.10 (s, 3H, - SiCH_3), -0.02 (s, 3H, - SiCH_3), 0.82 (s, 9H, - Si^tBu), 0.84 (t, $J_{3',2'} = 7.2$ Hz, 3H, H-3'), 0.92 (d, $J = 6.6$ Hz, 3H, 7- CH_3), 1.39-1.80 (m, 10H), 2.20-2.32 (m, 2H), 2.38-2.48 (m, 3H), 2.68 (s(br), 2H, H-1), 2.74 (m, 1H), 3.40 (s, 3H, 8- OCH_2OCH_3), 3.50 (m, 1H, H-8), 3.97 (dt, $J_{1',5} = 9.0$ Hz, $J_{1',2'} = 3.9$ Hz, 1H, H-1'), 4.66 (s, 2H, 8- OCH_2OCH_3).

^{13}C NMR (75 MHz, CDCl_3) δ : -4.5 (SiCH_3), -3.5 (SiCH_3), 7.2 (CH_3 , C3'), 18.2 (SiC), 18.7 (7- CH_3), 26.2 (Si^tBu), 26.8 (CH_2), 27.9 (2 x CH_2), 29.9 (CH_2), 32.3 (CH_2), 32.5 (CH), 37.2 (CH), 39.0 (CH_2 , C3), 39.1 (CH), 40.5 (CH), 45.0 (CH_2 , C-1), 56.2 (8- OCH_2OCH_3), 71.2 (CH , C-1'), 83.2 (CH , C-8), 98.5 (8- OCH_2OCH_3), 123.7 (C, C-10a), 132.7 (C, C-4a), 212.0 (2-CO).

LRMS (m/z): 450 (M^+ , 6%), 435 (6), 393 (47), 361 (20), 330 (20), 256 (22), 214 (21), 185 (15), 173 (100), 117 (31), 74 (90).

HRMS: C₂₆H₄₆O₄Si (M⁺) requires 450.3165, found 450.3157.

(1*RS*, 4*aRS*, 4*bSR*, 5*RS*, 7*RS*, 8*RS*, 8*aSR*, 10*aSR*, 1'*SR*) Methyl 5-(1'-*t*-Butyldimethylsilyloxypropyl)-8-methoxmethoxy-7-methyl-2-oxo-3,4,4*a*,4*b*,5,6,7,8,8*a*,9,10,10*a*-dodecahydrophenanthrene-1(2*H*)-carboxylate (3.16)

Dry ammonia (10 mL) was distilled into a 3-necked flask fitted with a dry ice condenser under nitrogen. Small pieces of freshly cleaned lithium wire (0.005 g, 0.68 mmol) were added at -78 °C and the resulting blue solution stirred for 10 min. A solution of enone **3.7** (0.12 g, 0.27 mmol) in *t*-butyl alcohol (0.020 mL, 0.27 mmol) and ether (2 mL) was added drop wise, and the resulting reaction mixture stirred for 15 min. The reaction was quenched with isoprene until the blue colour dispersed, and the ammonia allowed to boil off under a stream of nitrogen. The residue was dried under high vacuum for 5 min then nitrogen was reintroduced. Ether (5 mL) was added and the reaction mixture was cooled to -78 °C. Methyl cyanoformate (0.024 mL, 0.32 mmol) was added and the reaction mixture was stirred for 15 min before quenching with lithium hydroxide (3 mL, 2 M). The reaction mixture was warmed to room temperature and monitored by TLC until only one product was observed. The reaction mixture was extracted with ether (3 x 15 mL) and the combined organic extracts were washed with water (5 mL), brine (5 mL) and dried over anhydrous MgSO₄. Concentration of the organic phase *in vacuo* gave a colourless oil which was purified by flash column chromatography on silica gel using ethyl acetate : hexane (5 : 95 - 20 : 80) as eluant to give the title compound **3.16** (0.054 g, 39%) as a colourless oil.

IR (thin film) cm^{-1} : 2930s (C-H), 1749s (C=O), 1716 (C=O), 1462, 1359, 1254, 1150, 1071, 1038.

¹H NMR (300 MHz, CDCl₃) δ: 0.06 (s, 3H, -SiCH₃), 0.07 (s, 3H, -SiCH₃), 0.91 (s, 9H, -Si^tBu), 0.88-0.95 (m, 6H, H-3', 7-CH₃), 1.13 (m, 1H), 1.32-1.83 (m, 12H), 2.12 (m, 1H), 2.27-2.42 (m, 3H), 3.12 (d, *J*_{1,10a} = 11.7 Hz, 1H, H-1), 3.35 (m, 1H, H-8), 3.39 (s,

3H, 8-OCH₂OCH₃), 3.75 (s, 3H, 1-CO₂CH₃), 3.92 (m, 1H, H-1'), 4.59, 4.62 (2 x ABd, J = 6.6 Hz, 2H, 8-OCH₂OCH₃).

¹³C NMR (75 MHz, CDCl₃) δ : -4.2 (SiCH₃), -3.2 (SiCH₃), 9.7 (CH₃, C-3'), 18.3 (SiC), 19.0 (7-CH₃), 26.1 (Si^tBu), 28.7 (CH₂), 29.3 (CH₂), 29.9 (CH₂), 30.4 (CH₂), 31.5, 33.1, 37.3, 40.4, 40.7, 41.1, 41.5, 45.8, 51.9 (1-CO₂CH₃), 56.3 (8-OCH₂OCH₃), 63.7 (CH, C-1), 73.5 (CH, C-1'), 83.5 (CH, C-8), 98.9 (8-OCH₂OCH₃), 170.2 (1-CO₂CH₃), 205.8 (2-CO).

LRMS (m/z): 453 ((M-^tBu)⁺, 73%), 373 (10), 299 (9), 201 (10), 173 (100), 115 (17).

HRMS: C₂₄H₄₁O₆Si (M-^tBu)⁺ requires 453.2672, found 453.2602.

(4a*RS*, 4b*SR*, 5*RS*, 7*RS*, 8*RS*, 8a*SR*, 10a*RS*, 1'*SR*) Methyl 5-(1'-*t*-Butyldimethylsilyloxypropyl)-8-methoxmethoxy-7-methyl-2-hydroxy-1,4,4a,4b,5,6,7,8, 8a,9,10,10a-dodecahydrophenanthrene-3(2*H*)-carboxylate (3.17)

Dry ammonia (10 mL) was distilled into a 3-necked flask fitted with a dry ice condenser under nitrogen. Small pieces of freshly cleaned lithium wire (0.004 g, 0.61 mmol) were added at -78 °C and the resulting blue solution stirred for 10 min. A solution of enone **3.7** (0.11 g, 0.24 mmol) in *t*-butyl alcohol (0.020 mL, 0.24 mmol) and ether (2 mL) was added drop wise, and the resulting reaction mixture stirred for 15 min. The reaction was quenched with isoprene until the blue colour dispersed, and the ammonia allowed to boil off under a stream of nitrogen. The residue was dried under high vacuum for 5 min then nitrogen was reintroduced. Ether (5 mL) was added and the reaction mixture was cooled to -78 °C. Methyl cyanofomate (0.020 mL, 0.26 mmol) was added and the reaction mixture was stirred for 15 min then warmed to 0 °C before quenching with water (5 mL). The reaction mixture was extracted with ether (3 x 15 mL) and the combined organic extracts washed with water (5 mL), brine (5 mL) and dried over anhydrous MgSO₄. Concentration of the organic phase *in vacuo* gave a yellow oil. The mixture was dissolved in methanol (5 mL) and potassium carbonate (0.5 g) was added.

The reaction mixture was stirred for 2 h, then the methanol removed *in vacuo* and the residue extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were dried over anhydrous MgSO_4 and concentrated *in vacuo* to give a yellow oil which was purified by flash column chromatography on silica gel using ethyl acetate : hexane (1 : 9) as eluant to give the title compound **3.17** (0.022 g, 19%) as a colourless oil. Further elution gave ketone **3.18** (0.014 g, 13%) and ester **3.16** (0.017 g, 14%).

IR (thin film) cm^{-1} : 2929s (C-H), 1743, 1718, 1663s, 1623s, 1442, 1359, 1274, 1217, 1150, 1037.

^1H NMR (300 MHz, CDCl_3) δ : 0.02 (s, 3H, - SiCH_3), 0.05 (s, 3H, - SiCH_3), 0.88 (s, 9H, - Si^tBu), 0.88-0.93 (m, 6H, H-3', 7- CH_3), 1.12 (m, 1H), 1.20-1.82 (m, 13H), 1.91-2.14 (m, 2H), 2.29 (m, 1H), 2.56 (m, 1H), 3.35 (m, 1H, H-8), 3.41 (s, 3H, 8- OCH_2OCH_3), 3.73 (s, 3H, 1- CO_2CH_3), 3.84 (m, 1H, H-1'), 4.63 (s, 2H, 8- OCH_2OCH_3), 12.08 (s, 1H, 2-OH).

^{13}C NMR (75 MHz, CDCl_3) δ : -4.4 (SiCH_3), -3.8 (SiCH_3), 10.7 (CH_3 , C-3'), 18.2 (SiC), 19.2 (7- CH_3), 26.0 (Si^tBu), 28.4 (CH_2), 28.6 (CH_2), 28.7 (CH_2), 29.6 (CH_2), 32.5, 33.6 36.6, 37.8, 38.0, 38.4, 41.7, 41.8, 51.2 (1- CO_2CH_3), 56.2 (8- OCH_2OCH_3), 73.4 (CH , C-1'), 83.9 (CH , C-8), 97.1 (C, C-3), 98.9 (8- OCH_2OCH_3), 171.1 (1- CO_2CH_3), 172.8 (C-1).

LRMS (m/z): 495 ($(\text{M-Me})^+$, 5%), 453 (100), 435 (6), 346 (13), 333 (21), 284 (31), 173 (82).

HRMS: $\text{C}_{27}\text{H}_{47}\text{O}_6\text{Si}$ (M-Me^+) requires 495.3142, found 495.3140.

(1*RS*, 4*aRS*, 4*bSR*, 5*RS*, 7*RS*, 8*RS*, 8*aSR*, 10*aSR*, 1'*SR*) Methyl 5-(1'-*t*-Butyldimethylsilyloxypropyl)-8-methoxmethoxy-1,7-methyl-2-oxo-3,4,4*a*,4*b*,5,6,7,8,8*a*,9,10,10*a*-dodecahydrophenanthrene-1(2*H*)-carboxylate (**3.25**)

Potassium *t*-butoxide (0.017g, 0.15 mmol) in *t*-butyl alcohol (1.5 mL) was added to a solution of ester **3.16** (0.039 g, 0.076 mmol) and iodomethane (9.5 μ L, 0.15 mmol) in benzene (1.5 mL) at room temperature under nitrogen. The resulting reaction mixture was stirred for 18 h, then partitioned between iced water and DCM (10 mL, 1 : 1). The organic phase was separated and the aqueous phase extracted with DCM (3 x 5 mL). The combined organic extracts were dried over anhydrous MgSO_4 and concentrated *in vacuo* to give a yellow oil. Purification by flash column chromatography on silica gel using ethyl acetate : hexane (1 : 9) as eluant gave the title compound **3.25** (0.006 g, 22%) as a colourless oil.

IR (thin film) cm^{-1} : 2927s (C-H), 1744s (C=O), 1713 (C=O), 1463, 1360, 1260, 1085, 1038.

^1H NMR (300 MHz, CDCl_3) δ : 0.05 (s, 3H, -SiCH₃), 0.06 (s, 3H, -SiCH₃), 0.91 (s, 9H, -Si^{*t*}Bu), 0.88-0.96 (m, 6H, H-3', 7-CH₃), 1.33 (s, 3H, 1-CH₃), 1.17-1.81 (m, 13H), 2.01-2.12 (m, 2H), 2.31-2.39 (m, 2H), 2.50 (m, 1H), 3.35 (m, 1H, H-8), 3.40 (s, 3H, 8-OCH₂OCH₃), 3.74 (s, 3H, 1-CO₂CH₃), 3.88 (m, 1H, H-1'), 4.60, 4.63 (2 x ABd, J = 6.6 Hz, 2H, 8-OCH₂OCH₃).

^{13}C NMR (75 MHz, CDCl_3) δ : -4.1 (SiCH₃), -3.4 (SiCH₃), 10.4 (CH₃, C-3'), 15.7 (1-CH₃), 18.4 (SiC), 19.1 (7-CH₃), 26.1 (Si^{*t*}Bu), 27.3 (CH₂), 28.9 (CH₂), 29.7 (CH₂), 29.8 (CH₂), 30.5 (CH₂), 33.3 (CH), 35.6 (CH), 37.2 (CH₂), 37.5 (CH), 41.5 (CH), 42.2 (CH), 48.1 (CH), 52.3 (1-CO₂CH₃), 56.3 (8-OCH₂OCH₃), 62.1 (C, C-1), 74.1 (CH, C-1'), 83.5 (CH, C-8), 98.9 (8-OCH₂OCH₃), 173.3 (1-CO₂CH₃), 210.4 (2-CO).

LRMS (m/z): 467 ((M-^{*t*}Bu)⁺, 12%), 387 (13), 313 (12), 201 (12), 173 (100), 115 (20), 73 (61).

HRMS: C₂₅H₄₃O₆Si (M-^{*t*}Bu)⁺ requires 467.2829, found 467.2837.

(4a*RS*, 4b*SR*, 5*RS*, 7*RS*, 8*RS*, 8a*SR*, 10a*RS*, 1'*SR*) Methyl 5-(1'-*t*-Butyldimethylsilyloxypropyl)-8-methoxmethoxy-3,7-methyl-2-hydroxy-1,4,4a,4b,5,6,7,8, 8a,9,10,10a-dodecahydrophenanthrene-3(2*H*)-carboxylate (**3.26**)

Sodium hydride (0.001g, 0.04 mmol) was added to β -keto ester **3.17** (0.022 g, 0.04 mmol) in THF (1 mL) at room temperature under nitrogen. After 5 min, iodomethane (0.003 mL, 0.05 mmol) was added and the reaction mixture stirred for 18 h. The reaction was quenched with water, and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with water (5 mL), brine (5 mL) and dried over MgSO_4 . Concentration of the organic phase *in vacuo* gave a yellow oil, which was purified by flash column chromatography on silica gel using ethyl acetate : hexane (1 : 9) as eluant to give the title compound **3.26** (0.014 g, 65%) as a colourless oil.

IR (thin film) cm^{-1} : 2929s (C-H), 1742s (C=O), 1709 (C=O), 1462, 1379, 1258, 1087, 1037.

^1H NMR (500 MHz, CDCl_3) δ : 0.00 (s, 3H, -SiCH₃), 0.04 (s, 3H, -SiCH₃), 0.89 (s, 9H, -Si^tBu), 0.92 (d, $J = 6.5$ Hz, 3H, 7-CH₃), 0.93 (t, $J_{3',2'} = 7.3$ Hz, 3H, H-3'), 1.15 (m, 1H), 1.25-1.75 (m, 10H), 1.34 (m, 1H), 1.47 (s, 3H, 3-CH₃), 1.82 (dd, $J = 14$ Hz, $J = 4.0$ Hz, 1H), 2.04-2.13 (m, 3H, H-4, H-10a), 2.24-2.35 (m, 2H, H-1), 3.34 (m, 1H, H-8), 3.39 (s, 3H, 8-OCH₂OCH₃), 3.74 (s, 3H, 3-CO₂CH₃), 3.73 (m, 1H, H-1'), 4.60, 4.62 (2 x ABd, $J = 7.3$ Hz, 2H, 8-OCH₂OCH₃).

^{13}C NMR (75 MHz, CDCl_3) δ : -4.3 (SiCH₃), -3.6 (SiCH₃), 11.9 (CH₃, C-3'), 18.2 (SiC), 19.2 (7-CH₃), 20.7 (3-CH₃), 26.0 (Si^tBu), 28.2 (CH₂), 29.4 (CH₂), 29.8 (CH₂), 32.8 (CH₂), 33.9 (CH), 37.2 (CH), 38.2 (CH, C-10a), 40.0 (CH₂, C-4), 40.5 (CH), 42.0 (CH), 43.0 (CH), 45.1 (CH₂, C-1), 52.3 (3-CO₂CH₃), 56.2 (8-OCH₂OCH₃), 57.6 (C, C-3), 74.7 (CH, C-1'), 83.9 (CH, C-8), 98.9 (8-OCH₂OCH₃), 173.4 (3-CO₂CH₃), 209.2 (2-CO).

LRMS (m/z): 467 ((M-^tBu)⁺, 76%), 423 (51), 352 (39), 308 (31), 271 (30), 229 (25), 173 (100).

HRMS: C₂₅H₄₃O₆Si (M-^tBu)⁺ requires 467.2829, found 467.2827.

(4a*RS*, 4b*SR*, 5*RS*, 7*RS*, 8*RS*, 8a*SR*, 10a*RS*, 1'*SR*) 5-(1'-*t*-Butyldimethylsilyloxypropyl)-8-methoxmethoxy-7-methyl-1,4,4a,4b,5,6,7,8,8a,9,10,10a-dodecahydro-2(3*H*)-phenanthrenone (3.18)

Dry ammonia (60 mL) was distilled into a 3-necked flask fitted with a dry ice condenser under nitrogen. Small pieces of freshly cleaned lithium wire (0.05 g, 7.59 mmol) were added at -78 °C and the resulting blue solution stirred for 10 min. A solution of enone **3.7** (1.14 g, 2.53 mmol) in *t*-butyl alcohol (0.24 mL, 2.53 mmol) and THF (20 mL) was added drop wise, and the resulting reaction mixture stirred for 20 min. The reaction was quenched with isoprene until and blue colour dispersed and the ammonia was allowed to boil off under a stream of nitrogen. A saturated solution of aqueous ammonium chloride (20 mL) was then added and stirring continued for a further 15 min. Water (10 mL) was added and the aqueous phase extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL) and dried over anhydrous MgSO₄. Concentration of the organic phase *in vacuo* gave the title compound **3.18** (1.06 g, 92%) as a colourless oil.

IR (thin film) cm⁻¹: 2929s (C-H), 1718s (C=O), 1463, 1360, 1254s, 1150, 1038s.

¹H NMR (300 MHz, CDCl₃) δ: 0.04 (s, 3H, -SiCH₃), 0.06 (s, 3H, -SiCH₃), 0.90 (s, 9H, -Si^tBu), 0.86-0.92 (m, 3H, 7-CH₃), 0.93 (t, *J*_{3,2'} = 7.2 Hz, 3H, H-3'), 1.10-1.76 (m, 14H), 2.04-2.22 (m, 2H), 2.25-2.41 (m, 4H), 3.35 (m, 1H, H-8), 3.39 (s, 3H, 8-OCH₂OCH₃), 3.88 (dt, *J*_{1',5} = 5.4 Hz, *J*_{1',2'} = 5.7 Hz, 1H, H-1'), 4.60, 4.62 (2 x ABd, *J* = 6.9 Hz, 2H, 8-OCH₂OCH₃).

^{13}C NMR (75 MHz, CDCl_3) δ : -4.3 (SiCH_3), -3.4 (SiCH_3), 10.4 (CH_3 , $\text{C}3'$), 18.3 (SiC), 19.1 (7- CH_3), 26.1 (Si^tBu), 28.8 (CH_2), 29.3 (CH_2), 29.7 (CH_2), 30.9 (CH_2), 33.3 (CH_2), 33.4 (CH), 37.7 (CH), 41.0 (CH), 41.1 (CH), 41.5 (CH), 41.6 (CH), 43.7 (CH_2), 48.7 (CH_2), 56.2 (8- OCH_2OCH_3), 73.8 (CH , $\text{C}-1'$), 83.8 (CH , $\text{C}-8$), 98.9 (8- OCH_2OCH_3), 211.7 (2-CO).

LRMS (m/z): 395 ($(\text{M}-t\text{Bu})^+$, 65%), 241 (15), 201 (10), 173(100), 115 (17), 73 (57), 45 (66).

HRMS: $\text{C}_{22}\text{H}_{39}\text{O}_4\text{Si}$ ($(\text{M}-t\text{Bu})^+$) requires 395.2618, found 395.2613.

(4a*SR*, 4b*SR*, 5*RS*, 7*RS*, 8*RS*, 8a*SR*, 10a*RS*, 1'*SR*) 5-(1'-*t*-Butyldimethylsilyloxypropyl)-8-methoxmethoxy-7-methyl-4a,4b,5,6,7,8,8a,9,10,10a-decahydro-2(1*H*)-phenanthrenone (**3.34**)

n-Butyllithium (1.30 mL of a 1.6 *M* solution in hexanes, 2.12 mmol) was added to diisopropylamine (0.30 mL, 2.12 mmol) in THF (5 mL) at -20 °C under nitrogen. The reaction mixture was stirred for 20 min, warmed to 0 °C and stirred for a further 30 min. The solution was then cooled to -78 °C and TMSCl (0.94 mL, 7.42 mmol) was added, followed by the drop wise addition of ketone **3.18** (0.48 g, 1.06 mmol) in THF (5 mL). After 20 min, the reaction was quenched by the addition of triethylamine (2 mL) and a saturated aqueous solution of sodium bicarbonate (5 mL). The mixture was extracted with ether (3 x 20 mL), and the combined extracts washed with water (5 mL) and 1 *M* citric acid (5 mL). The organic extracts were dried over anhydrous MgSO_4 and concentrated in *vacuo* to give a mixture of two silyl enol ethers (2 : 1 in favour of the desired isomer **3.33**), which were used directly in the next reaction without further purification.

A solution of the crude crude silyl enol ethers in acetonitrile (5 mL) were added to palladium acetate (0.24 g, 1.07 mmol) and *p*-benzoquinone (0.06 g, 0.54 mmol) in acetonitrile (5 mL) at room temperature under nitrogen. The resulting reaction mixture

was stirred for 30 h, then filtered through a plug of Celite[®] and washed with ether (30 mL). Concentration of the organic filtrate *in vacuo* gave a black gum which was further purified by flash column chromatography on silica gel using ethyl acetate : hexane (1 : 9) as eluant to give the title $\alpha\beta$ -enone **3.34** (0.31 g, 64%) as a white solid, and $\alpha\beta$ -enone **3.7** (0.11 g, 24%) as a white solid (88% combined yield). A sample of the title $\alpha\beta$ -enone **3.34** was crystallised from hexane to give white crystals.

m.p: 65-67 °C

IR (thin film) cm^{-1} : 2930s (C-H), 1684s (C=O), 1472, 1360, 1255s, 1148, 1039s.

^1H NMR (300 MHz, CDCl_3) δ : 0.04 (s, 3H, -SiCH₃), 0.06 (s, 3H, -SiCH₃), 0.87 (s, 9H, -Si^tBu), 0.91 (d, $J = 6.3$ Hz, 3H, 7-CH₃), 0.87-0.92 (m, 3H, H-3'), 1.24 (m, 1H), 1.39-1.81 (m, 12H), 2.13 (m, 1H, H-1), 2.26-2.52 (m, 2H, H-1, H-4a), 3.37 (m, 1H, H-8), 3.40 (s, 3H, 8-OCH₂OCH₃), 4.07 (dt, $J_{1,5} = 6.9$ Hz, $J_{1',2'} = 4.5$ Hz, 1H, H-1'), 4.62 (s, 2H, 8-OCH₂OCH₃), 5.97 (dd, $J = 9.9$ Hz, $J = 1.5$ Hz, 1H, H-3), 7.19 (d, $J = 9.9$ Hz, 1H, H-4).

^{13}C NMR (75 MHz, CDCl_3) δ : -3.7 (SiCH₃), -3.4 (SiCH₃), 8.0 (CH₃, C-3'), 18.3 (SiC), 18.9 (7-CH₃), 26.2 (Si^tBu), 27.8 (CH₂), 29.3 (CH₂), 30.7 (CH₂), 31.9 (CH₂), 32.9 (CH), 36.5 (CH), 40.1 (CH), 41.6 (CH), 42.0 (CH), 42.9 (CH), 45.5 (CH₂, C-1), 56.2 (8-OCH₂OCH₃), 72.3 (CH, C-1'), 83.7 (CH, C-8), 99.0 (8-OCH₂OCH₃), 128.8 (CH, C-3), 153.9 (CH, C-4), 200.4 (2-CO).

LRMS (m/z): 450 (M^+ , <1%), 393 ($(\text{M}-\text{tBu})^+$, 85%), 331 (12), 318 (9), 273 (5), 257 (20), 199 (10), 173 (100), 115 (21).

HRMS: $\text{C}_{26}\text{H}_{46}\text{O}_4\text{Si}$ (M^+) requires 450.3165, found 450.3169.

$\text{C}_{22}\text{H}_{37}\text{O}_4\text{Si}$ ($(\text{M}-\text{tBu})^+$) requires 393.2461, found 393.2460.

Microanalysis: Calcd. for $\text{C}_{26}\text{H}_{46}\text{O}_4\text{Si}$: C, 69.28%, H, 10.29%. Found: C, 69.74%, H, 10.15%.

(1*RS*, 4*aRS*, 4*bSR*, 5*RS*, 7*RS*, 8*RS*, 8*aSR*, 10*aSR*, 1'*SR*) Methyl 5-(1'-*t*-Butyldimethylsilyloxypropyl)-8-methoxmethoxy-7-methyl-2-oxo-4*a*,4*b*,5,6,7,8,8*a*,9,10, 10*a*-decahydrophenanthrene-1(2*H*)-carboxylate (**3.35**)

n-Butyllithium (0.64 mL of a 1.6 *M* solution in hexanes, 1.03 mmol) was added to diisopropylamine (0.014 mL, 1.03 mmol) in THF (6 mL) at -20 °C under nitrogen. The reaction mixture was stirred for 20 min, warmed to 0 °C and stirred for a further 30 min. The solution was then cooled to -78 °C, ketone **3.34** (0.31 g, 0.69 mmol) was added, and the reaction mixture warmed to 0 °C for 1 h. After cooling to -78 °C, HMPA (0.12 mL, 0.69 mmol) and methyl cyanoformate (0.08 mL, 1.03 mmol) were added. After 20 min the reaction mixture was poured into water and extracted with ether (3 x 15 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL) and dried over anhydrous MgSO₄. Concentration of the organic phase *in vacuo* gave a yellow oil which was purified by flash column chromatography on silica gel using ethyl acetate : hexane (1 : 9) as eluant to give the title compound **3.35** (0.27 g, 77%) as a colourless oil.

IR (thin film) cm⁻¹: 2931s (C-H), 1746s (C=O), 1682s (C=O), 1472, 1463, 1257s, 1151, 1040s.

¹H NMR (300 MHz, CDCl₃) δ: 0.03 (s, 3H, -SiCH₃), 0.05 (s, 3H, -SiCH₃), 0.86 (s, 9H, -Si^{*t*}Bu), 0.86-0.91 (m, 3H, 7-CH₃), 0.91 (t, *J*_{3',2'} = 7.2 Hz, 3H, H-3'), 1.17-1.82 (m, 11H), 2.02 (m, 1H), 2.27 (m, 1H), 2.62 (m, 1H, H-4a), 3.13 (d, *J*_{1,10a} = 13.2 Hz, 1H, H-1), 3.60 (m, 1H, H-8), 3.39 (s, 3H, 8-OCH₂OCH₃), 3.76 (s, 3H, 1-CO₂CH₃), 4.12 (m, 1H, H-1'), 4.59, 4.62 (2 x ABd, *J* = 6.9 Hz, 2H, 8-OCH₂OCH₃), 6.01 (dd, *J* = 10.2 Hz, *J* = 2.4 Hz, 1H, H-3), 7.25 (d, *J* = 10.2 Hz, 1H, H-4).

¹³C NMR (75 MHz, CDCl₃) δ: -3.7 (SiCH₃), -3.3 (SiCH₃), 7.3 (CH₃, C-3'), 18.3 (SiC), 18.9 (7-CH₃), 26.3 (Si^{*t*}Bu), 27.6 (CH₂), 28.8 (CH₂), 29.9 (CH₂), 31.1 (CH₂), 32.6 (CH), 36.1 (CH), 40.4 (CH), 41.3 (CH), 42.0 (CH), 44.1 (CH), 52.1 (1-CO₂CH₃), 56.3

(8-OCH₂OCH₃), 61.2 (CH, C-1), 71.9 (CH, C-1'), 83.3 (CH, C-8), 99.0 (8-OCH₂OCH₃), 127.6 (CH, C-3), 154.4 (CH, C-4), 170.6 (1-CO₂CH₃), 194.8 (2-CO).

LRMS (m/z): 451 ((M-^tBu)⁺, 51%), 389 (15), 331 (10), 269 (5), 255 (7), 199 (10), 173 (90), 115 (22), 73 (100).

HRMS: C₂₄H₃₉O₆Si ((M-^tBu)⁺) requires 451.2516, found 451.2510.

(1*RS*, 4*aRS*, 4*bSR*, 5*RS*, 7*RS*, 8*RS*, 8*aSR*, 10*aSR*, 1'*SR*) Methyl 5-(1'-*t*-Butyldimethylsilyloxypropyl)-8-methoxmethoxy-1,7-dimethyl-2-oxo-4*a*,4*b*,5,6,7,8,8*a*,9,10, 10*a*-decahydrophenanthrene-1(2*H*)-carboxylate (3.36)

Sodium hydride (0.007g, 0.29 mmol) was added to β -keto ester **3.35** (0.12 g, 0.24 mmol) in THF (2 mL) at room temperature under nitrogen. After 5 min, iodomethane (0.018 mL, 0.29 mmol) was added and the resulting reaction mixture stirred for 18 h. The reaction was quenched with water, poured into 1 *M* hydrochloric acid (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with water (5 mL), brine (5 mL) and dried over MgSO₄. Concentration of the organic phase *in vacuo* gave a yellow oil, which was purified by flash column chromatography on silica gel using ethyl acetate : hexane (1 : 9) as eluant to give the title compound **3.36** (0.082 g, 65%) as a white solid. A sample of the title β -keto ester **3.36** was crystallised from hexane to give white crystals.

m.p: 98-99 °C

IR (thin film) cm⁻¹: 2931s (C-H), 1744s (C=O), 1680s (C=O), 1471, 1461, 1256s, 1151, 1035s.

¹H NMR (300 MHz, CDCl₃) δ : 0.01 (s, 3H, -SiCH₃), 0.06 (s, 3H, -SiCH₃), 0.87 (s, 9H, -Si^tBu), 0.89 (d, *J* = 6.0 Hz, 3H, 7-CH₃), 0.90 (t, *J*_{3',2'} = 6.9 Hz, 3H, H-3'), 1.25 (s, 3H, 1-CH₃), 1.20-1.83 (m, 11H), 2.35 (m, 1H), 2.27 (m, 1H), 2.51 (m, 1H, H-4*a*), 3.33

(m, 1H, H-8), 3.37 (s, 3H, 8-OCH₂OCH₃), 3.70 (s, 3H, 1-CO₂CH₃), 4.07 (m, 1H, H-1'), 4.58, 4.61 (2 x ABd, $J = 6.6$ Hz, 2H, 8-OCH₂OCH₃), 5.93 (dd, $J = 10.5$ Hz, $J = 2.4$ Hz, 1H, H-3), 7.18 (d, $J = 10.5$ Hz, 1H, H-4).

¹³C NMR (75 MHz, CDCl₃) δ : -3.6 (SiCH₃), -3.2 (SiCH₃), 8.0 (CH₃, C-3'), 14.0 (1-CH₃), 18.4 (SiC), 18.9 (7-CH₃), 26.3 (Si^tBu and CH₂), 28.0 (CH₂), 29.3 (CH₂), 31.2 (CH₂), 32.6 (CH), 36.3 (CH), 38.3 (CH), 41.1 (CH), 41.4 (CH), 46.6 (CH), 52.3 (1-CO₂CH₃), 56.2 (8-OCH₂OCH₃), 58.8 (C, C-1), 72.9 (CH, C-1'), 83.4 (CH, C-8), 99.0 (8-OCH₂OCH₃), 126.5 (CH, C-3), 152.7 (CH, C-4), 173.3 (1-CO₂CH₃), 199.2 (2-CO).

LRMS (m/z): 465 ((M-^tBu)⁺, 17%), 403 (15), 385 (10), 345 (5), 253 (16), 227 (5), 173 (100), 133 (15), 73 (70).

HRMS: C₂₅H₄₁O₆Si ((M-^tBu)⁺) requires 465.2672, found 465.2678.

Microanalysis: Calcd. for C₂₉H₅₀O₆Si: C, 66.63%, H, 9.64%. Found: C, 66.63%, H, 9.75%.

8.4 Chapter 4 Experimental

(2'*RS*, 4'*RS*, 4a'*SR*, 10a'*SR*, 1*SR*) 1-[7'-Methoxy-1'-methoxymethylene-2'-methyl-1', 2', 4a', 9', 10', 10a'-hexahydrophenanthrene-4' (3'*H*)-yl]-propan-1-yl Benzoate (1.96)

Sodium bis(trimethylsilyl)amide (40.5 mL of a 1 M solution in THF, 40.5 mmol) was added drop wise to a stirred solution of (methoxymethyl)triphenyl phosphonium chloride (13.9 g, 40.5 mmol) in dry THF (50 mL) at 0 °C under nitrogen. After 15 min, a solution of ketone **1.95** (3.29 g, 8.09 mmol) in THF (50 mL) was added drop wise to the red solution and the reaction mixture was stirred at room temperature. After 4 h, the reaction was quenched with water (20 mL) and extracted with ethyl acetate (4 x 50 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried

over anhydrous MgSO_4 , and concentrated *in vacuo* to give a yellow oil. Purification by flash column chromatography using ether : hexane (5 : 95) as eluant gave the title compound **1.96** (2.96 g, 87%) as a colourless oil, a mixture of *E* and *Z* isomers.

IR (thin film) cm^{-1} : 2931s (C-H), 1709s (C=O), 1672s, 1610s, 1584, 1502s, 1452s, 1315, 1274s, 1224, 1146, 1112, 1045, 1026.

^1H NMR (300 MHz, CDCl_3 ; * indicates peaks belonging to minor isomer) δ : 0.84 (t, $J_{3,2} = 7.5$ Hz, 3H, H-3), 0.87* (t, $J_{3,2} = 7.5$ Hz, 3H, H-3), 1.04 (d, $J = 6.6$ Hz, 3H, 2'- CH_3), 1.34* (d, $J = 6.6$ Hz, 3H, 2'- CH_3), 1.45 (m, 1H, H-10'), 1.59-2.03 (m, 4H), 2.31-2.67 (m, 5H), 2.80-2.96 (m, 2H, H-4a', H-4'), 3.45 (s, 3H, 1'- CHOCH_3), 3.46 (s, 3H, 7'- OCH_3), 3.50* (s, 3H, 1'- CHOCH_3), 3.51* (s, 3H, 7'- OCH_3), 5.63 (s, 1H, 1'- CHOCH_3), 5.70* (s, 1H, 1'- CHOCH_3), 5.71 (m, 1H, H-1), 6.01 (d, $J_{8',6'} = 2.7$ Hz, 1H, H-8'), 6.10* (d, $J_{8',6'} = 2.7$ Hz, 1H, H-8'), 6.50 (dd, $J_{6',5'} = 8.4$ Hz, $J_{6',8'} = 2.7$ Hz, 1H, H-6'), 6.55* (dd, $J_{6',5'} = 8.4$ Hz, $J_{6',8'} = 2.7$ Hz, 1H, H-6'), 7.12 (d, $J_{5',6'} = 8.4$ Hz, 1H, H-5'), 7.18* (d, $J_{5',6'} = 8.4$ Hz, 1H, H-5'), 7.18-7.52 (m, 5H, H-2'', H-3'', H-4'').

^{13}C NMR (75 MHz, CDCl_3 ; * indicates peaks belonging to minor isomer) δ : 9.2 (CH_3 , C-3), 9.4* (CH_3 , C-3), 19.0 (2'- CH_3), 21.0* (2'- CH_3), 26.2 (CH_2), 26.3* (CH_2), 26.9 (CH_2), 27.8* (CH_2), 30.5 (CH_2), 31.3* (CH_2), 31.6 (CH_2), 32.2* (CH_2), 37.9 (CH), 38.8* (CH), 40.2 (CH), 40.4* (CH), 41.0 (CH), 41.4* (CH), 47.3 (CH), 47.6* (CH), 54.6 (7'- OCH_3), 54.7* (7'- OCH_3), 59.6 (1'- CHOCH_3), 73.6 (CH, C-1), 74.3* (CH, C-1), 112.0 (CH, C-6'), 112.5 (CH, C-8'), 112.6* (CH, C-8'), 123.8 (CH, 1'- CHOCH_3), 123.9* (CH, 1'- CHOCH_3), 127.2 (CH, C-5'), 127.3* (CH, C-5'), 127.9 (Ar), 128.0* (Ar), 129.3 (Ar), 129.6* (Ar), 129.7 (Ar), 130.8 (Ar), 131.2* (Ar), 131.9 (C, C-4b'), 132.0* (C, C-4b'), 137.6 (C, C-8a'), 138.2* (C, C-8a'), 139.4 (C, C-1'), 139.6* (C, C-1'), 156.0 (C, C-7'), 156.1* (C, C-7'), 165.6 (1-OC(O)Ph), 165.7* (1-OC(O)Ph).

LRMS (m/z): 434 (M^+ , 9%), 312 (100), 297 (2), 280 (7), 267 (10), 243 (53), 225 (4), 211 (9), 185 (4), 158 (9).

HRMS: $\text{C}_{28}\text{H}_{35}\text{O}_4$ (MH^+) requires 435.2535, found 435.2541.

(1'*RS*, 2'*RS*, 4'*RS*, 4a'*SR*, 10a'*SR*, 1*SR*) 1-[7'-Methoxy-1''-methoxy-spiro[cyclopropane-1',1']-2'-methyl-1', 2', 4a', 9', 10', 10a'-hexahydrophenanthrene-4' (3'*H*)-yl]-propan-1-yl Benzoate (**1.99**)

Diethyl zinc (24.5 mL of a 1 *M* solution in hexanes, 24.5 mmol) was added to DCM (20 mL) at 0 °C under nitrogen. Trifluoroacetic acid (1.89 mL, 24.5 mmol) in DCM (10 mL) was then added drop wise and the resulting reaction mixture stirred for 20 min. Diiodomethane (1.98 mL, 24.5 mmol) in DCM (10 mL) was then added and after 20 min enol ether **1.96** (2.96 g, 7.01 mmol) was added. The reaction mixture was warmed to room temperature and stirred for a further 20 min. The reaction was quenched with a saturated solution of ammonium chloride and extracted with DCM (3 x 50 mL). The combined organic extracts were washed with water, dried over MgSO₄ and concentrated *in vacuo* to give the title compound **1.99** (ca. 3 g) as a yellow oil. The crude product was used directly in the next step without any further purification. A sample was purified by flash column chromatography using ether : petroleum spirit (0.5 : 9.5) for characterization purposes.

IR (thin film) cm⁻¹: 2929s (C-H), 1709s (C=O), 1503s, 1455, 1273s, 1112, 1067, 1042, 1020.

¹H NMR (300 MHz, CDCl₃) * indicates peaks belonging to minor isomer) **δ**: 0.59 (d, *J* = 7.1 Hz, 3H, 2'-CH₃), 0.64 (m, 1H, H-2''), 0.86 (t, *J*_{3,2} = 7.2 Hz, 3H, H-3), 0.88* (t, *J*_{3,2} = 7.2 Hz, 3H, H-3), 0.81 (m, 1H, H'-2''), 0.97* (d, *J* = 7.1 Hz, 3H, 2'-CH₃), 1.57 (m, 1H, H-10'), 1.62-1.89 (m, 4H), 2.11-2.54 (m, 5H), 2.89 (m, 1H, H-4'), 3.10-3.23 (m, 2H, H-4a', H-1''), 3.22 (s, 3H, 1'-CHOCH₃), 3.30* (s, 3H, 1'-CHOCH₃), 3.43 (s, 3H, 7'-OCH₃), 3.45* (s, 3H, 7'-OCH₃), 5.75 (ddd, *J* = 11.1 Hz, *J* = 7.8 Hz, *J* = 3.3 Hz, 1H, H-1), 5.97 (d, *J*_{8',6'} = 2.9 Hz, 1H, H-8'), 6.49 (dd, *J*_{6',5'} = 8.4 Hz, *J*_{6',8'} = 2.9 Hz, 1H, H-6'), 6.52* (dd, *J*_{6',5'} = 8.4 Hz, *J*_{6',8'} = 2.9 Hz, 1H, H-6'), 7.14 (d, *J*_{5',6'} = 8.4 Hz, 1H, H-5'), 7.17-7.45 (m, 5H).

^{13}C NMR (75 MHz, CDCl_3 * indicates peaks belonging to minor isomer) δ : 9.2 (CH_3 , C-3), 9.8* (CH_3 , C-3), 10.8 (CH_2 , 1'- CH_2), 16.6 (2'- CH_3), 18.4* (2'- CH_3), 25.3 (CH_2), 27.0 (CH_2), 29.8 (CH_2), 30.5 (CH_2), 31.3 (CH_2), 32.1* (CH_2), 32.9 (C, C-1'), 33.1* (C, C-1'), 38.6 (CH), 38.9* (CH), 38.4 (CH), 41.8 (CH), 42.0* (CH), 45.7 (CH), 46.0* (CH), 54.6 (7'- OCH_3), 54.7* (7'- OCH_3), 57.8 (1'- CHOCH_3), 58.1* (1'- CHOCH_3), 59.7 (1'- CHOCH_3), 60.0* (1'- CHOCH_3), 73.7 (CH, C-1), 74.0* (CH, C-1), 112.0 (CH, C-6'), 112.2 (CH, C-8'), 112.4* (CH, C-8'), 127.2 (CH, C-5'), 127.4* (CH, C-5'), 127.9 (Ar), 128.1* (Ar), 129.3 (Ar), 129.7* (Ar), 131.6 (C, C-4b'), 131.9* (C, C-4b'), 137.5 (C, C-8a'), 138.2* (C, C-8a'), 155.9 (C, C-7'), 156.0* (C, C-7'), 165.7 (1- OC(O)Ph).

LRMS (m/z): 448 (M^+ , 15%), 326 (68), 294 (11), 284 (65), 268 (85), 251 (21), 239 (34) 225 (100), 211 (23), 197 (20), 185 (14).

HRMS: $\text{C}_{29}\text{H}_{36}\text{O}_4$ (M^+) requires 448.2614, found 448.2615.

(1*RS*, 2*RS*, 4*RS*, 4*aSR*, 10*aSR*, 1'*SR*) 4-(1'-Benzoyloxypropyl)-7-methoxy-1,2-methyl-3,4,4*a*,9,10,10*a*-hexahydrophenanthrene-1(2*H*)-carbaldehyde (**1.98**)

Concentrated hydrochloric acid (4 mL) was added to cyclopropane **1.99** (3 g, 7 mmol) in acetone (80 mL) and heated at reflux for 10 h. Water (10 mL) was then added and the acetone removed *in vacuo*. The mixture was extracted with ethyl acetate (4 x 10 mL) and the combined organic extracts washed with brine (10 mL), saturated sodium bicarbonate (10 mL) then water (10 mL). The organic phase was dried over anhydrous MgSO_4 and concentrated *in vacuo* to give the title compound **1.98** (3 g) as a yellow oil which was used in the next step without further purification. A sample was purified by flash column chromatography for characterization purposes, on silica gel using ether : hexane (5 : 95) as eluant to give the title compound as a white solid. A sample was crystallised from ethyl acetate : hexane to give white crystals.

m.p: 150-152 °C

IR (thin film) cm^{-1} : 2917s (C-H), 1709s (C=O), 1610s, 1503s, 1453, 1273s, 1108.

^1H NMR (300 MHz, CDCl_3) δ : 0.90 (t, $J_{3',2'} = 7.3$ Hz, 3H, H-3'), 1.01 (d, $J = 6.7$ Hz, 3H, 2- CH_3), 1.35 (s, 3H, 1- CH_3), 1.26 (m, 1H, H-10), 1.65 (m, 1H, H-2'), 1.77–1.93 (m, 3H, H'-2', H-3, H-2), 2.07–2.20 (m, 3H, H'-3, H'-10, H-10a), 2.47–2.50 (m, 2H, H-9), 2.98 (m, 1H, H-4), 3.40 (m, 1H, H-4a), 3.44 (s, 3H, 7- OCH_3), 5.72 (ddd, $J = 10.8$ Hz, $J = 7.8$ Hz, $J = 2.7$ Hz, 1H, H-1'), 5.99 (d, $J_{8,6} = 2.7$ Hz, 1H, H-8), 6.50 (dd, $J_{6,5} = 8.4$ Hz, $J_{6,8} = 2.7$ Hz, 1H, H-6), 7.17–7.42 (m, 6H, H-5, H-2'', H-3'', H-4''), 9.93 (s, 1H, 1-CHO).

^{13}C NMR (75 MHz, CDCl_3) δ : 9.1 (CH_3 , C-3'), 17.2 (2- CH_3), 19.9 (1- CH_3), 24.0 (CH_2 , C-10), 26.8 (CH_2 , C-2'), 31.1 (CH_2 , C-9), 35.5 (CH_2 , C-3), 35.6 (CH , C-2), 40.6 (CH , C-4), 41.7 (CH , C-4a), 43.3 (CH , C-10a), 51.9 (C, C-1), 54.7 (7- OCH_3), 72.8 (CH , C-1'), 112.3 (CH , C-6), 112.4 (CH , C-8), 127.3 (CH , C-5), 127.9 (Ar), 129.3 (Ar), 129.4 (Ar), 132.0 (C, C-4b), 137.3 (C, C-8a), 156.3 (C, C-7), 165.7 (1'- $\text{OC}(\text{O})\text{Ph}$), 207.7 (1-CHO).

LRMS (m/z): 434 (M^+ , 10%), 336 (68), 312 (12), 283 (11), 231 (74), 215 (100), 199 (24), 185 (23).

HRMS: $\text{C}_{28}\text{H}_{34}\text{O}_4$ (M^+) requires 434.2457, found 434.2452.

(1*RS*, 2*RS*, 4*RS*, 4a*SR*, 10a*SR*, 1'*SR*) 4-(1'-Benzoyloxypropyl)-7-methoxy-1,2-methyl-3,4,4a,9,10,10a-hexahydrophenanthrene-1(2*H*)-carboxylic acid (4.2)

Aldehyde **1.98** (3.25 g, 7.02 mmol) was dissolved in a mixture of acetonitrile (200 mL), hydrogen peroxide (24 mL of a 30% w/v solution) and sodium hydrogen phosphate buffer (24 mL, pH 2). The solution was cooled to 0 °C and sodium chlorite (1.27 g, 14.0 mmol) was added. The resulting reaction mixture was stirred for 5 h then diluted with ethyl acetate (150 mL) and washed with water (100 mL). The organic phase was

separated and the aqueous layer extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL), dried over MgSO_4 and concentrated *in vacuo* to give a yellow solid. Purification by flash column chromatography using ethyl acetate : petroleum spirit (1 : 4) with 1% acetic acid as eluant gave the title compound **4.2** (2.52 g, 80% over three steps) as a white solid. A sample was crystallised from ether : hexane to give white crystals.

m.p: 203-205 °C

IR (thin film) cm^{-1} : 3289br (C-OH), 2938s (C-H), 1709s (C=O), 1689s (C=O), 1606, 1503, 1450, 1275s, 1109.

^1H NMR (300 MHz, CDCl_3) δ : 0.87 (t, $J_{3',2'} = 7.5$ Hz, 3H, H-3'), 1.00 (d, $J = 6.6$ Hz, 3H, 2- CH_3), 1.39 (s, 3H, 1- CH_3), 1.09–2.34 (m, 8H, H-2', H-3, H-2, H-10, H-10a), 2.37–2.58 (m, 2H, H-9), 2.86 (m, 1H, H-4), 3.44 (s, 3H, 7- OCH_3), 3.55 (m, 1H, H-4a), 5.64 (ddd, $J = 10.5$ Hz, $J = 7.5$ Hz, $J = 2.7$ Hz, 1H, H-1'), 5.99 (d, $J_{8,6} = 2.7$ Hz, 1H, H-8), 6.51 (dd, $J_{6,5} = 8.4$ Hz, $J_{6,8} = 2.7$ Hz, 1H, H-6), 7.15–7.41 (m, 6H, H-5, H-2'', H-3'', H-4'').

^{13}C NMR (75 MHz, CDCl_3) δ : 9.0 (CH_3 , C-3'), 17.4 (2- CH_3), 23.2 (1- CH_3), 24.6 (CH_2 , C10), 26.6 (CH_2 , C-2'), 30.9 (CH_2 , C-9), 34.5 (CH_2 , C-3), 35.4 (CH, C-2), 39.8 (CH, C-4), 39.9 (CH, C-4a), 42.5 (CH, C-10a), 49.9 (C, C-1), 54.6 (7- OCH_3), 73.2 (CH, C-1'), 112.2 (CH, C-6), 112.4 (CH, C-8), 127.3 (CH, C-5), 127.9 (Ar), 129.3 (Ar), 129.5 (Ar), 131.4 (Ar), 132.0 (C, C-4b), 137.2 (C, C-8a), 156.1 (C, C-7), 165.9 (1'- $\text{OC}(\text{O})\text{Ph}$), 181.1 (1- CO_2H).

LRMS (m/z): 450 (M^+ , 90%), 328 (68), 283 (30), 240 (46), 231 (42), 213 (31), 159 (26), 105 (100).

HRMS: $\text{C}_{28}\text{H}_{34}\text{O}_5$ (M^+) requires 450.2406, found 450.2406.

Microanalysis: Calcd. for $\text{C}_{28}\text{H}_{34}\text{O}_5$: C, 74.64%, H, 7.61%. Found: C, 74.43%, H, 7.67%.

(1*RS*, 2*RS*, 4*RS*, 4*aSR*, 10*aSR*, 1'*SR*) 4-(1'-hydroxypropyl)-7-methoxy-1,2-methyl-3,4,4*a*,9,10,10*a*-hexahydrophenanthrene-1(2*H*)-carboxylic acid (**4.4**)

Sodium (2 g) was slowly added to the benzoate **4.2** (2.52 g, 5.62 mmol) in ethanol (120 mL) at room temperature under nitrogen. The reaction mixture was heated at reflux for 2 d, then water (50 mL) was added and the ethanol removed *in vacuo*. The residue was treated with 1 *M* hydrochloric acid until pH 5 and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried over MgSO₄ and concentrated *in vacuo* to give the crude product as a yellow solid. Purification by flash column chromatography using ethyl acetate : petroleum spirit (1 : 9) with 1% acetic acid as eluant gave the title compound **4.4** (1.24 g, 65%) as a white foam and recovered starting material **4.2** (0.97 g, 35%) which was re-submitted to the reaction conditions and purified as above to give more of the title compound **4.4** (1.38 g total, 73%).

IR (thin film) cm⁻¹: 3546br (C-OH), 2934s (C-H), 1694s (C=O), 1610s, 1500s, 1464, 1256s, 1157.

¹H NMR (300 MHz, CDCl₃) δ: 0.92 (t, $J_{3',2'} = 7.5$ Hz, 3H, H-3'), 0.96 (d, $J = 6.6$ Hz, 3H, 2-CH₃), 1.26-1.67 (m, 6H), 1.34 (s, 3H, 1-CH₃), 1.97 (td, $J = 12.0$ Hz, $J = 1.5$ Hz, 1H), 2.08 (m, 1H), 2.57 (m, 1H, H-4), 2.68-2.89 (m, 2H, H-9), 3.59 (m, 1H, H-4*a*), 3.74 (s, 3H, 7-OCH₃), 3.94 (m, 1H, H-1'), 6.58 (d, $J_{8,6} = 2.7$ Hz, 1H, H-8), 6.73 (dd, $J_{6,5} = 8.7$ Hz, $J_{6,8} = 2.7$ Hz, 1H, H-6), 7.29 (d, $J_{5,6} = 8.7$ Hz, 1H, H-5).

¹³C NMR (75 MHz, CDCl₃) δ: 9.5 (CH₃, C-3'), 17.3 (2-CH₃), 23.2 (1-CH₃), 24.5 (CH₂), 29.0 (CH₂), 31.3 (CH₂), 34.4 (CH₂), 35.4 (CH), 39.8 (CH), 42.0 (CH), 43.1 (CH), 49.7 (C, C-1), 55.0 (7-OCH₃), 72.8 (CH, C-1'), 112.3 (CH, C-6), 114.1 (CH, C-8), 128.0 (CH, C-5), 130.9 (C, C-4*b*), 138.5 (C, C-8*a*), 157.2 (C, C-7), 180.7 (1-CO₂H).

LRMS (m/z): 346 (M^+ , 75%), 328 (15), 283 (11), 241 (25), 199 (26), 187 (66), 174 (100), 161 (37).

HRMS: $C_{21}H_{30}O_4$ (M^+) requires 346.2144, found 346.2143.

(1*RS*, 2*RS*, 4*RS*, 4*aSR*, 10*aSR*, 1'*SR*) 4-(1'-*t*-butyldimethylsilyloxypropyl)-7-methoxy-1,2-methyl-3,4,4*a*,9,10,10*a*-hexahydrophenanthrene-1(2*H*)-carboxylic acid (4.7)

t-Butyldimethylsilyl trifluoromethanesulfonate (1.43 mL, 6.23 mmol) was added drop wise to alcohol **4.4** (0.72 g, 2.08 mmol) and 2,6-lutidine (0.97 mL, 8.32 mmol) in DCM (20 mL) at room temperature under nitrogen. After 15 min water (20 mL) was added and the organic phase was separated then the aqueous layer extracted with DCM (2 x 20 mL). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give the crude *bis*-protected product as a yellow gum.

Potassium carbonate (10% in water 10 mL) was added to a solution of the TBDMS ester in THF : MeOH (1 : 3, 40 mL) and stirred at room temperature for 1 h 45 min. The methanol was removed *in vacuo*, the residue treated with 1 *M* hydrochloric acid until pH 5 and then extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow oil. Purification by flash column chromatography on silica gel using ethyl acetate : hexane (1 : 9) with 1% acetic acid as eluant gave the title compound **4.7** (0.78 g, 81%) as a white solid. A sample was crystallised from hexane to give white crystals.

m.p: 172-173 °C

IR (thin film) cm^{-1} : 3500br (C-OH), 2929s (C-H), 1692s (C=O), 1611, 1502s, 1472, 1255s, 1079.

^1H NMR (300 MHz, CDCl_3) δ : -0.11 (s, 3H, -SiCH₃), -0.07 (s, 3H, -SiCH₃), 0.80 (s, 9H, -Si^{*t*}Bu), 0.75-0.84 (m, 3H, H-3'), 0.98 (d, $J = 6.6$ Hz, 3H, 2-CH₃), 1.87-2.16 (m, 8H), 1.33 (s, 3H, 1-CH₃), 2.68-2.84 (m, 3H), 3.53 (dd, $J_{4a,10a} = 12.0$ Hz, $J_{4a,4} = 4.5$ Hz, 1H, H-4a), 3.77 (s, 3H, 7-OCH₃), 3.87 (m, 1H, H-1'), 6.54 (d, $J_{8,6} = 2.7$ Hz, 1H, H-8), 6.70 (dd, $J_{6,5} = 8.7$ Hz, $J_{6,8} = 2.7$ Hz, 1H, H-6), 7.23 (d, $J_{5,6} = 8.7$ Hz, 1H, H-5).

^{13}C NMR (75 MHz, CDCl_3) δ : -4.5 (SiCH₃), -3.9 (SiCH₃), 9.8 (CH₃, C-3), 17.7 (2-CH₃), 18.2 (SiC), 23.5 (1-CH₃), 25.2 (CH₂), 26.1 (Si^{*t*}Bu), 28.7 (CH₂), 31.4 (CH₂), 31.9 (CH₂), 36.8 (CH), 39.2 (CH), 39.4 (CH), 43.6 (CH), 49.6 (C, C-1), 55.2 (7-OCH₃), 72.7 (CH, C-1'), 111.8 (CH, C-6), 113.2 (CH, C-8), 128.4 (CH, C-5), 131.1 (C, C-4b), 137.4 (C, C-8a), 156.7 (C, C-7), 181.4 (1-CO₂H).

LRMS (m/z): 460 (M^+ , 15%), 437 (17), 405 (50), 403 (98), 283 (23), 241 (23), 173 (100), 117 (70).

HRMS: $\text{C}_{27}\text{H}_{44}\text{O}_4\text{Si}$ (M^+) requires 460.3009, found 460.3007.

Microanalysis: Calcd. for $\text{C}_{27}\text{H}_{44}\text{O}_4\text{Si}$: C, 70.39%, H, 9.63%. Found: C, 70.06%, H, 9.49%.

(1*RS*, 2*RS*, 4*RS*, 4a*SR*, 4b*SR*, 10a*SR*, 1'*SR*) 4-(1'-*t*-Butyldimethylsilyloxypropyl)-2-methyl-7-oxo-3,4,4a,4b,5,6,7,9,10,10a-decahydrophenanthrene-1(2*H*)-carboxylic acid (4.9)

Dry ammonia (200 mL) was distilled into a 3-necked flask fitted with a dry ice condenser under nitrogen. Small pieces of freshly cleaned lithium wire (1.65 g, 245.3 mmol) were added at -78 °C and the resulting blue solution was stirred for 15 min. Silyl ether **4.7** (2.26 g, 4.91 mmol) in THF (50 mL) was added over 10 min, stirred for 15 min, then *t*-butanol (50 mL) was added. The blue reaction mixture was warmed to -40 °C and stirred for 3 h. The reaction was then quenched with methanol and the ammonia

allowed to boil off under a stream of nitrogen before a saturated aqueous solution of ammonium chloride (80 mL) was added. After 15 min water (50 mL) was added and the aqueous phase adjusted to pH 5 with 1 M hydrochloric acid then extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL) and dried over anhydrous MgSO_4 . Concentration of the organic phase *in vacuo* gave a colourless oil, which was taken up in a solution of acetic acid : THF : water (4 : 2 : 1, 50 mL) and stirred for 2 h under nitrogen. The solvent was removed *in vacuo* and the aqueous residue was extracted with ethyl acetate (3 x 50 mL) then dried over anhydrous MgSO_4 . Concentration of the organic phase *in vacuo* gave the crude $\beta\gamma$ -enone **4.8** as a colourless oil, which was used directly in the next reaction without purification. Concentrated sulfuric acid was added drop wise to sodium chloride. The resulting hydrogen chloride gas was passed through concentrated sulfuric acid and then bubbled through THF (35 mL) for 1 min. The crude $\beta\gamma$ -enone **4.8** in THF (35 mL) was then added to the acidic THF then the reaction was monitored by TLC until half of the starting material had been consumed, and a new UV active spot was observed. Concentration of the organic phase *in vacuo* gave a yellow gum, which was purified by flash column chromatography on silica gel using ethyl acetate : hexane (1 : 9 – 1 : 4) with 1% acetic acid as eluant to give the $\beta\gamma$ -enone **4.8** (1.31 g, 39%) as a colourless oil, and the $\alpha\beta$ -enone **4.9** (1.20 g, 35%) as a white foam (74% combined yield).

(1RS, 2RS, 4RS, 4aSR, 4bSR, 10aSR, 1'SR) 4-(1'-*t*-Butyldimethylsilyloxypropyl)-1,2-dimethyl-7-oxo-3,4,4a,4b,5,6,7,9,10,10a-decahydrophenanthrene-1(2H)-carboxylic acid (4.9)

IR (thin film) cm^{-1} : 2932s (C-H), 1694s (C=O), 1671 (C=O), 1472, 1462, 1256s, 1208.

^1H NMR (300 MHz, CDCl_3) δ : 0.07 (s, 3H, -SiCH₃), 0.08 (s, 3H, -SiCH₃), 0.89 (s, 9H, -Si^tBu), 0.91 (t, $J_{3',2'} = 7.5$ Hz, 3H, H-3'), 0.86-0.94 (m, 3H, 2-CH₃), 1.26 (s, 3H, 1-CH₃), 1.05-2.31 (m, 14H), 2.34-2.45 (m, 2H, H-6), 2.91 (m, 1H, H-4b), 4.16 (dt, $J = 8.4$ Hz, $J = 3.9$ Hz, 1H, H-1'), 5.79 (s, 1H, H-8).

^{13}C NMR (75MHz, CDCl_3) δ : -3.8 (SiCH₃), -3.3 (SiCH₃), 7.4 (CH₃, C3'), 17.6 (2-CH₃), 18.2 (SiC), 23.9 (1-CH₃), 26.1 (Si^tBu), 27.0 (CH₂), 28.0 (CH₂), 28.4 (CH₂), 33.1 (CH₂), 35.2 (CH), 35.3 (CH), 35.7 (CH₂), 36.2 (CH₂), 39.0 (CH), 43.5 (CH), 46.3 (CH),

50.1 (C, C-1), 72.3 (CH, C-1'), 123.7 (CH, C-8), 167.8 (C, C-8a), 180.2 (1-CO₂H), 200.9 (7-CO).

LRMS (m/z): 448 (M⁺, 1%), 319 (80), 345 (15), 316 (100), 273 (21), 224 (48), 173 (91).

HRMS: C₂₆H₄₄O₄Si (M⁺) requires 448.3009, found 448.3010.

(1*RS*, 2*RS*, 4*RS*, 4*aSR*, 10*aSR*, 1'*SR*) 4-(1'-*t*-Butyldimethylsilyloxypropyl)-1,2-dimethyl-7-oxo-3,4,4*a*,5,6,7,8,9,10,10*a*-decahydrophenanthrene-1(2*H*)-carboxylic acid (4.8)

IR (thin film) cm⁻¹: 2931s (C-H), 1721s (C=O), 1694 (C=O), 1472, 1463, 1254s, 1075s.

¹H NMR (300 MHz, CDCl₃) δ: -0.10 (s, 3H, -SiCH₃), -0.01 (s, 3H, -SiCH₃), 0.82 (s, 9H, -Si^{*t*}Bu), 0.87 (t, *J*_{3',2'} = 7.5 Hz, 3H, H-3'), 0.91 (d, *J* = 6.6 Hz, 3H, 2-CH₃), 1.28 (s, 3H, 1-CH₃), 1.44-2.20 (m, 11H), 2.26-2.38 (m, 2H), 2.41-2.46 (m, 2H), 2.67 (s(br), 2H, H-8), 2.70-2.90 (m, 2H), 4.05 (dt, *J* = 9.9 Hz, *J* = 3.3 Hz, 1H, H-1').

¹³C NMR (75 MHz, CDCl₃) δ: -4.6 (SiCH₃), -3.4 (SiCH₃), 6.6 (CH₃, C-3'), 17.5 (2-CH₃), 18.2 (SiC), 23.6 (1-CH₃), 24.6 (CH₂), 26.2 (Si^{*t*}Bu), 27.5 (CH₂), 28.2 (CH₂), 30.5 (CH₂), 34.3 (CH₂), 35.3 (CH), 36.0 (CH), 39.1 (CH₂), 41.7 (CH), 42.2 (CH), 44.7 (CH₂, C-8), 49.8 (C), 70.7 (CH, C-1'), 122.8 (C, C-8a), 133.0 (C, C-4b), 181.2 (1-CO₂H), 212.2 (7-CO).

LRMS (m/z): 391 ((M-^{*t*}Bu)⁺, 50%), 316 (70), 277 (22), 224 (21), 173 (100), 147 (43), 73 (79).

HRMS: C₂₂H₃₅O₄Si ((M-^{*t*}Bu)⁺) requires 391.2305, found 391.2304.

(1*RS*, 2*RS*, 4*RS*, 4*aSR*, 4*bRS*, 8*aRS*, 10*aSR*, 1'*SR*) 4-(1'-*t*-
 Butyldimethylsilyloxypropyl)-1,2-dimethyl-7-oxo-3,4,4*a*,4*b*,5,6,7,8,8*a*,9,10,10*a*-
 dodecahydrophenanthrene-1(2*H*)-carboxylic acid (**8.5**)

Dry ammonia (70 mL) was distilled into a 3-necked flask fitted with a dry ice condenser under nitrogen. Small pieces of freshly cleaned lithium wire (0.056 g, 8.22 mmol) were added at $-78\text{ }^{\circ}\text{C}$ and the resulting blue solution was stirred for 10 min. A solution of enone **4.9** (1.23 g, 2.74 mmol) in *t*-butanol (0.26 mL, 2.74 mmol) and THF (40 mL) was added drop wise, and the resulting reaction mixture was stirred for 30 min at $-33\text{ }^{\circ}\text{C}$. The reaction was quenched with isoprene until the blue colour dispersed, and the ammonia was allowed to boil off under a stream of nitrogen. A saturated solution of aqueous ammonium chloride (40 mL) was then added and stirring continued for a further 15 min. Water (10 mL) was added and the aqueous phase adjusted to pH 5 with 1 *M* hydrochloric acid then extracted with ethyl acetate (3 x 40 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL) and dried over anhydrous MgSO_4 . Concentration of the organic phase in *vacuo* gave a yellow oil (1.24 g, a mixture of the title compound **8.5** and alcohol **8.6**) which was used directly in the next step without further purification. A sample of **8.5** was purified by flash column chromatography for characterization purposes, on silica gel using ether : hexane (1 : 9) with 1% acetic acid as eluant to give the title compound as a white solid.

m.p.: 181-184 $^{\circ}\text{C}$

IR (thin film) cm^{-1} : 3300br (C-OH), 2931s (C-H), 1716s (C=O), 1695 (C=O), 1472, 1462, 1254s, 1079.

^1H NMR (300 MHz, CDCl_3) δ : 0.08 (s, 6H, - SiCH_3), 0.86 (d, $J = 6.6\text{ Hz}$, 3H, 2- CH_3), 0.91 (s, 9H, - Si^tBu), 0.92 (t, $J_{3',2'} = 7.5\text{ Hz}$, 3H, H-3'), 1.23 (s, 3H, 1- CH_3), 0.98-2.45 (m, 20H), 4.02 (m, 1H, H-1').

^{13}C NMR (75 MHz, CDCl_3) δ : -4.2 (SiCH₃), -3.0 (SiCH₃), 8.9 (CH₃, C-3'), 17.8 (2-CH₃), 18.4 (SiC), 23.7 (1-CH₃), 26.2 (Si^tBu), 28.0 (CH₂), 28.7 (CH₂), 30.9 (CH₂), 32.1 (CH₂), 33.7 (CH₂), 35.6 (CH), 36.1 (CH), 40.9 (CH), 42.0 (CH), 43.4 (CH), 43.7 (CH), 44.1 (CH₂, C-5), 48.4 (CH₂, C-8), 50.1 (C, C-1), 72.9 (CH, C-1'), 181.2 (1-CO₂H), 212.3 (7-CO).

LRMS (m/z): 393 ((M-^tBu)⁺, 67%), 255 (12), 215 (13), 173 (100), 145 (11), 115 (19).

HRMS: $\text{C}_{22}\text{H}_{37}\text{O}_4\text{Si}$ ((M-^tBu)⁺) requires 393.2461, found 393.2466.

(1*RS*, 2*RS*, 4*RS*, 4*aSR*, 4*bRS*, 8*aRS*, 10*aSR*, 1'*SR*) Methyl 4-(1'-*t*-Butyldimethylsilyloxypropyl)-7-1,2-dimethyl-7-oxo-3,4,4*a*,4*b*,5,6,7,8,8*a*,9,10,10*a*-dodecahydrophenanthrene-1(2*H*)-carboxylate (**4.10**)

A freshly prepared solution of diazomethane in ether (120 mL) was added to the crude carboxylic acids **8.5** and **8.6** (2 g) in ether (50 mL) at 0 °C. The yellow reaction mixture was stirred for 30 min, and the excess diazomethane and ether blown off with a stream of nitrogen. Purification by flash column chromatography using ethyl acetate : petroleum spirit (1 : 9) as eluant gave the title compound **4.10** (1.2 g, 55% over two steps) as a colourless oil, and alcohol **4.11** (0.45 g, 21% over the two steps) which was subsequently converted to **4.10** by oxidation with DMP (a total of 76% yield over two steps).

(1*RS*, 2*RS*, 4*RS*, 4*aSR*, 4*bRS*, 8*aRS*, 10*aSR*, 1'*SR*) Methyl 4-(1'-*t*-Butyldimethylsilyloxypropyl)-1,2-dimethyl-7-oxo-3,4,4*a*,4*b*,5,6,7,8,8*a*,9,10,10*a*-dodecahydrophenanthrene-1(2*H*)-carboxylate (**4.10**)

IR (thin film) cm^{-1} : 2952s (C-H), 1721s (C=O), 1472, 1462, 1255, 1145.

^1H NMR (600 MHz, CDCl_3) δ : 0.08 (s, 3H, -SiCH₃), 0.09 (s, 3H, -SiCH₃), 0.78 (d, J = 7.2 Hz, 3H, 2-CH₃), 0.92 (s, 9H, -Si^tBu), 0.93 (t, $J_{3,2'} = 7.2$ Hz, 3H, H-3'), 0.79 (m,

^1H , H-10), 1.09 (m, 1H, H-9), 1.24 (s, 3H, 1-CH₃), 1.26-1.35 (m, 2H, H-8a, H-5), 1.48-1.75 (m, 8H, H-2', H-4b, H-3, H-2, H-10a, H'-9), 1.85 (m, 1H, H-4a), 1.95 (m, 1H, H'-10), 2.06 (m, 1H, H-8), 2.18 (m, 1H, H-4), 2.27 (m, 1H, H'-8), 2.30-2.34 (m, 2H, H-6), 2.44 (m, 1H, H'-5), 3.62 (s, 3H, 1-CO₂CH₃), 4.03 (dt, $J = 7.2$ Hz, $J = 4.2$ Hz, 1H, H-1').

^{13}C NMR (75 MHz, CDCl₃) δ : -4.2 (SiCH₃), -3.0 (SiCH₃), 8.7 (CH₃, C-3'), 17.8 (2-CH₃), 18.2 (SiC), 23.9 (2-CH₃), 26.2 (Si^tBu), 28.1 (CH₂, C-10), 28.6 (CH₂, C-2'), 30.9 (CH₂, C-5), 32.4 (CH₂, C-3), 33.7 (CH₂, C-9), 35.7 (CH), 36.1 (CH, C-4), 40.9 (CH₂, C-6), 42.0 (CH, C-4b), 43.5 (CH, C-8a), 44.0 (CH, C-4a), 44.3 (CH), 48.5 (CH₂, C-8), 50.3 (C, C-1), 50.6 (1-CO₂CH₃), 72.9 (CH, C-1'), 175.0 (1-CO₂CH₃), 211.8 (7-CO).

LRMS (m/z): 407 ((M-^tBu)⁺, 91%), 255 (28), 215 (18), 173 (100), 145 (13), 115 (27).

HRMS: C₂₃H₃₉O₄Si ((M-^tBu)⁺) requires 407.2618, found 407.2621.

(1*RS*, 2*RS*, 4*RS*, 4a*SR*, 4b*RS*, 8a*RS*, 10a*SR*, 1'*SR*) Methyl 4-(1'-*t*-Butyldimethylsilyloxypropyl)-1,2-dimethyl-7-hydroxy-3,4,4a,4b,5,6,7,8,8a,9,10,10a-dodecahydrophenanthrene-1(2*H*)-carboxylate (4.11)

IR (thin film) cm⁻¹: 3411br (C-OH), 2929s (C-H), 1720s (C=O), 1461, 1387, 1254, 1079.

^1H NMR (300 MHz, CDCl₃) δ : 0.06 (s, 6H, -SiCH₃), 0.77 (d, $J = 6.3$ Hz, 3H, 2-CH₃), 0.90 (s, 9H, -Si^tBu), 0.88-0.92 (m, 3H, H-3'), 0.86-2.20 (m, 24H), 3.61 (s, 3H, 1-CO₂CH₃), 3.90 (m, 1H, H-1').

^{13}C NMR (75 MHz, CDCl₃) δ : -4.4 (SiCH₃), -3.2 (SiCH₃), 9.7 (CH₃, C-3'), 17.9 (2-CH₃), 18.3 (SiC), 23.9 (1-CH₃), 26.1 (Si^tBu), 28.4 (CH₂), 28.8 (CH₂), 30.3 (CH₂), 31.6, 33.4, 35.4, 36.0, 36.6, 41.1, 42.6, 43.1, 43.6, 44.7, 50.3 (1-CO₂CH₃), 50.5 (C, C-1), 70.5 (CH, C-7), 73.1 (CH, C-1'), 175.4 (1-CO₂CH₃).

LRMS (m/z): 466 (M⁺, 2%), 465 (5), 437 (96), 421 (28), 409 (78), 407 (83), 393 (44), 351 (89), 330 (100).

HRMS: C₂₇H₅₀O₄Si (M⁺) requires 466.3478, found 466.3465.

(1*RS*, 2*RS*, 4*RS*, 4*aSR*, 4*bSR*, 8*aRS*, 10*aSR*, 1'*SR*) Methyl 4-(1'-*t*-Butyldimethylsilyloxypropyl)-1,2-dimethyl-7-oxo-3,4,4*a*,4*b*,7,8,8*a*,9,10,10*a*-decahydrophenanthrene-1(2*H*)-carboxylate (4.12)

Trimethylsilyl trifluoromethanesulfonate (1.52 mL, 8.39 mmol) was added drop wise to ketone **4.10** (1.30 g, 2.80 mmol) and 2,6-lutidine (1.30 mL, 11.19 mmol) in DCM (30 mL) at 0 °C under nitrogen. Water (15 mL) was added and the organic phase was separated before further extraction of the aqueous layer with DCM (2 x 15 mL). The combined organic extracts were then washed with brine and dried over anhydrous MgSO₄. Concentration of the organic phase *in vacuo* gave a mixture of two silyl enol ethers (20 : 1, 6,7-enol ether : 7,8-enol ether). The crude silyl enol ethers in acetonitrile (30 mL) were added to palladium acetate (0.63 g, 2.80 mmol) and *p*-benzoquinone (0.15 g, 1.40 mmol) in acetonitrile (30 mL) at room temperature under nitrogen. The resulting reaction mixture was stirred for 30 h, then filtered through a plug of Celite® and washed with ether (60 mL). Concentration *in vacuo* gave a black gum, which was purified by flash column chromatography on silica gel using ethyl acetate : petroleum spirit (1 : 9) as eluant to give the title $\alpha\beta$ -enone **4.12** (1.03 g, 79%) as a white solid, and $\alpha\beta$ -enone **4.9a** (0.051 g, 4%) as a white foam (83% combined yield). A sample of the title $\alpha\beta$ -enone **4.12** was crystallised from hexane to give white crystals.

(1*RS*, 2*RS*, 4*RS*, 4*aSR*, 4*bSR*, 8*aRS*, 10*aSR*, 1'*SR*) Methyl 4-(1'-*t*-Butyldimethylsilyloxypropyl)-1,2-dimethyl-7-oxo-3,4,4*a*,4*b*,7,8,8*a*,9,10,10*a*-decahydrophenanthrene-1(2*H*)-carboxylate (4.12)

m.p: 99-101 °C

IR (thin film) cm⁻¹: 2933s (C-H), 1722s (C=O), 1684s (C=O), 1472s, 1463, 1253s, 1195.

¹H NMR (300 MHz, CDCl₃) δ : 0.05 (s, 3H, -SiCH₃), 0.08 (s, 3H, -SiCH₃), 0.79 (d, *J* = 6.6 Hz, 3H, 2-CH₃), 0.87 (s, 9H, -Si^{*t*}Bu), 0.93 (t, *J*_{3',2'} = 7.2 Hz, 3H, H-3'), 0.87 (m,

^1H , H-10), 1.25 (s, 3H, 1-CH₃), 1.18 (m, 1H, H-9), 1.46-1.69 (m, 8H), 1.80 (m, 1H), 1.96-2.14 (m, 2H, H-8, H-10), 2.35-2.41 (m, 2H, H-8, H-4), 2.55 (m, 1H, H-4b), 3.62 (s, 3H, 1-CO₂CH₃), 4.17 (dt, $J = 8.7$ Hz, $J = 3.9$ Hz, 1H, H-1'), 5.97 (m, 1H, H-6), 7.27 (dd, $J = 9.0$ Hz, $J = 1.8$ Hz, 1H, H-5).

^{13}C NMR (75 MHz, CDCl₃) δ : -3.7 (SiCH₃), -3.3 (SiCH₃), 6.9 (CH₃, C-3'), 17.7 (2-CH₃), 18.3 (SiC), 23.9 (1-CH₃), 26.2 (Si^tBu), 27.4 (CH₂), 27.7 (CH₂), 32.4 (CH₂), 33.1 (CH₂), 35.1 (CH), 35.4 (CH), 41.6 (CH), 42.3 (CH), 43.7 (CH), 44.7 (CH), 45.3 (CH₂, C-8), 50.5 (C, C-1), 50.7 (1-CO₂CH₃), 71.6 (CH, C-1'), 128.7 (CH, C-6), 154.1 (CH, C-5), 175.0 (1-CO₂CH₃), 200.2 (7-CO).

LRMS (m/z): 405 ((M-^tBu)⁺, 93%), 330 (22), 270 (25), 213 (14), 173 (100), 115 (33).

HRMS: C₂₃H₃₇O₄Si ((M-^tBu)⁺) requires 405.2461, found 405.2459.

(1*RS*, 2*RS*, 4*RS*, 4*aSR*, 4*bSR*, 10*aSR*, 1'*SR*) Methyl 4-(1'-*t*-Butyldimethylsilyloxypropyl)-1,2-dimethyl-7-oxo-3,4,4*a*,4*b*,5,6,7,9,10,10*a*-decahydrophenanthrene-1(2*H*)-carboxylate (4.9a)

IR (thin film) cm⁻¹: 2952s (C-H), 1722s (C=O), 1676s (C=O), 1472s, 1388, 1256s, 1206.

^1H NMR (300 MHz, CDCl₃) δ : 0.08 (s, 3H, -SiCH₃), 0.09 (s, 3H, -SiCH₃), 0.78 (d, $J = 6.3$ Hz, 3H, 2-CH₃), 0.90 (s, 9H, -Si^tBu), 0.92 (t, $J_{3',2'} = 7.2$ Hz, 3H, H-3'), 1.28 (s, 3H, 1-CH₃), 0.86-2.48 (m, 16H), 2.91 (m, 1H, H-4b), 3.61 (s, 3H, 1-CO₂CH₃), 4.18 (dt, $J = 9.0$ Hz, $J = 3.6$ Hz, 1H, H-1'), 5.77 (s, 1H, H-8).

^{13}C NMR (75 MHz, CDCl₃) δ : -3.8 (SiCH₃), -3.3 (SiCH₃), 7.4 (CH₃, C-3'), 17.6 (2-CH₃), 18.2 (SiC), 24.1 (1-CH₃), 26.1 (Si^tBu), 27.1 (CH₂), 28.0 (CH₂), 28.5 (CH₂), 33.3 (CH₂), 35.3 (CH₂), 35.3 (CH), 35.7 (CH), 36.4 (CH₂, C-6), 39.0 (CH), 43.7 (CH), 46.6 (CH), 50.3 (C, C-1), 50.8 (1-CO₂CH₃), 72.3 (CH, C-1'), 123.8 (CH, C-8), 167.2 (C, C8a), 174.7 (1-CO₂CH₃), 200.3 (7-CO).

LRMS (m/z): 405 ((M-^tBu)⁺, 95%), 330 (94), 270 (92), 224 (94), 173 (100), 115 (89).

HRMS: $C_{23}H_{37}O_4Si$ ($(M-^tBu)^+$) requires 405.2461, found 405.2460.

(1*RS*, 4*aRS*, 4*bSR*, 5*RS*, 7*RS*, 8*RS*, 8*aSR*, 10*aSR*, 1'*SR*) Dimethyl 5-(1'-*t*-Butyldimethylsilyloxypropyl)-7,8-dimethyl-2-oxo-4*a*,4*b*,5,6,7,9,10,10*a*-octahydrophenanthrene-1,8(2*H*, 8*aH*)-dicarboxylate (4.16**)**

n-Butyllithium (1.0 mL of a 1.6 *M* solution in hexanes, 1.60 mmol) was added to diisopropylamine (0.22 mL, 1.60 mmol) in THF (10 mL) at -20 °C under nitrogen. The reaction mixture was stirred for 20 min, warmed to 0 °C and stirred for a further 30 min. The solution was cooled to -78 °C, ketone **4.12** (0.37 g, 0.80 mmol) in THF (10 mL) was added, and then stirred for 1 h at 0 °C. The reaction mixture was then cooled to -78 °C, HMPA (0.14 mL, 0.80 mmol) was added followed by methyl cyanoformate (0.12 mL, 1.60 mmol). After 20 min the mixture was poured into water and extracted with ether (3 x 15 mL). The combined organic extracts were washed with water (10 mL), brine (10mL) and dried over anhydrous $MgSO_4$. Concentration of the organic phase *in vacuo* gave a yellow oil, which was purified by flash column chromatography on silica gel using ethyl acetate : hexane (1 : 9) as eluant to give the title compound **4.16** (0.35 g, 83%) as a colourless oil.

IR (thin film) cm^{-1} : 2952s (C-H), 1746s (C=O), 1722s (C=O), 1681s (C=O), 1472s, 1462s, 1254s, 1149.

1H NMR (300 MHz, $CDCl_3$) δ : 0.05 (s, 3H, -SiCH₃), 0.07 (s, 3H, -SiCH₃), 0.79 (d, J = 6.6 Hz, 3H, 7-CH₃), 0.86 (s, 9H, -Si^{*t*}Bu), 0.93 (t, $J_{3',2'} = 7.2$ Hz, 3H, H-3'), 1.26 (s, 3H, 8-CH₃), 0.90 (m, 1H, H-9), 1.17 (m, 1H, H-10), 1.47-1.72 (m, 6H), 1.82 (m, 1H), 1.95-2.14 (m, 3H, H-4b, H-9, H-10), 2.38 (m, 1H, H-5), 2.69 (m, 1H, H-4a), 3.10 (d, $J_{1,10a} = 12.9$ Hz, 1H, H-1), 3.62 (s, 3H, 8-CO₂CH₃), 3.76 (s, 3H, 1-CO₂CH₃), 4.22 (dt, J = 9.3 Hz, J = 3.6 Hz, 1H, H-1'), 6.03 (dd, J = 10.2 Hz, J = 2.7 Hz, 1H, H-3), 7.33 (dd, J = 10.2 Hz, J = 1.8 Hz, 1H, H-4).

^{13}C NMR (75 MHz, CDCl_3) δ : -3.6 (SiCH_3), -3.2 (SiCH_3), 6.4 (CH_3 , C-3'), 17.7 (7- CH_3), 18.3 (SiC), 23.9 (8- CH_3), 26.2 (Si^tBu), 27.1 (CH_2 , C-9), 27.4 (CH_2), 30.4 (CH_2), 33.3 (CH_2), 34.8 (CH), 35.2 (CH), 42.6 (CH), 42.7 (CH), 43.6 (CH), 44.4 (CH), 50.5 (C, C-8), 50.8 (8- CO_2CH_3), 52.0 (1- CO_2CH_3), 60.9 (CH , C-1), 71.4 (CH , C-1'), 127.5 (CH , C-3), 154.3 (CH , C-4), 170.5 (1- CO_2CH_3), 174.7 (8- CO_2CH_3), 194.6 (2-CO).

LRMS (m/z): 463 ($(\text{M}^t\text{Bu})^+$, 93%), 405 (49), 388 (50), 329 (67), 269 (47), 213 (40), 173 (100).

HRMS: $\text{C}_{25}\text{H}_{39}\text{O}_6\text{Si}$ ($(\text{M}^t\text{Bu})^+$) requires 463.2516, found 463.2514.

(1*RS*, 4*aRS*, 4*bSR*, 5*RS*, 7*RS*, 8*RS*, 8*aSR*, 10*aSR*, 1'*SR*) Dimethyl 5-(1'-*t*-Butyldimethylsilyloxypropyl)-2-oxo-1,7,8-trimethyl-4*a*,4*b*,5,6,7,9,10,10*a*-octahydrophenanthrene-1,8(2*H*, 8*aH*)-dicarboxylate (**4.17**)

Sodium hydride (0.018 g, 0.76 mmol) was added to the β -keto ester **4.16** (0.33 g, 0.64 mmol) in THF (10 mL) at room temperature under nitrogen. After 5 min iodomethane (0.048 mL, 0.76 mmol) was added and the reaction mixture stirred for 18 h. The reaction was quenched with water and extracted with ethyl acetate (4 x 10 mL). The combined organic extracts were washed with water (5 mL), brine (5 mL) and dried over MgSO_4 . Concentration of the organic phase *in vacuo* gave a yellow oil which was purified by flash column chromatography on silica gel using ethyl acetate : petroleum spirit (1 : 9) as eluant to give the title compound **4.17** (0.30 g, 88%) as a white solid. A sample was crystallized from hexane to give white crystals.

m.p: 47-50 $^{\circ}\text{C}$

IR (thin film) cm^{-1} : 2950s (C-H), 1741s (C=O), 1721s (C=O), 1679s (C=O), 1461, 1258s, 1212.

^1H NMR (300 MHz, CDCl_3) δ : 0.04 (s, 3H, -SiCH₃), 0.09 (s, 3H, -SiCH₃), 0.79 (d, J = 6.6 Hz, 3H, 7-CH₃), 0.89 (s, 9H, -Si^tBu), 0.93 (t, $J_{3',2'} = 7.2$ Hz, 3H, H-3'), 1.26 (s, 6H, 1-CH₃, 8-CH₃), 0.91 (m, 1H, H-9), 1.25 (m, 1H, H-10), 1.47-1.68 (m, 6H), 1.81 (m, 1H), 2.01 (m, 1H, H-9), 2.08-2.26 (m, 2H, H-10, H-4b), 2.38 (m, 1H, H-5), 2.56 (m, 1H, H-4a), 3.64 (s, 3H, 8-CO₂CH₃), 3.72 (s, 3H, 1-CO₂CH₃), 4.19 (dt, $J = 8.7$ Hz, $J = 3.9$ Hz, 1H, H-1'), 5.96 (dd, $J = 10.4$ Hz, $J = 2.7$ Hz, 1H, H-3), 7.28 (dd, $J = 10.4$ Hz, $J = 1.5$ Hz, 1H, H-4).

^{13}C NMR (75 MHz, CDCl_3) δ : -3.6 (SiCH₃), -2.9 (SiCH₃), 6.9 (CH₃, C-3'), 14.1 (1-CH₃), 17.6 (7-CH₃), 18.4 (SiC), 23.8 (8-CH₃), 26.3 (Si^tBu), 26.7 (CH₂, C-9), 27.4 (CH₂), 27.9 (CH₂), 33.3 (CH₂), 35.1 (CH), 35.2 (CH), 39.3 (CH), 43.5 (CH), 44.5 (CH), 46.2 (CH), 50.6 (C, C-8), 50.8 (8-CO₂CH₃), 52.2 (1-CO₂CH₃), 58.6 (C, C-1), 72.0 (CH, C-1'), 126.3 (CH, C-3), 152.8 (CH, C-4), 173.2 (1-CO₂CH₃), 174.8 (8-CO₂CH₃), 199.1 (2-CO).

LRMS (m/z): 477 ((M-^tBu)⁺, 84%), 459 (22), 419 (37), 357 (38), 343 (53), 283 (22), 173 (100).

HRMS: C₂₆H₄₁O₆Si (M-^tBu)⁺ requires 477.2672, found 477.2669.

8.5 Chapter 5 Experimental

(1*RS*, 4*aRS*, 4*bRS*, 5*RS*, 7*RS*, 8*RS*, 8*aSR*, 10*aSR*, 1'*SR*) 4,1'-Epoxy-7-methyl-1-methoxycarbonyl-8-methoxmethoxy-5-(1'-propyl)-2-oxo-1,3,4*a*,4*b*,5,6,7,8,8*a*,9,10,10*a*-dodecahydrophenanthrene (5.3)

Tetrabutyl ammonium fluoride (0.30 mL of a 1 M solution in THF, 0.30 mmol) was added to a solution of silyl ether **3.35** (0.022 g, 0.043 mmol) in THF (1 mL) containing powdered 4Å molecular sieves at room temperature under nitrogen. The reaction mixture was stirred overnight, then water (5 mL) was added and the mixture extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with water

(5 mL), brine (5 mL) and dried over MgSO_4 . Concentration of the organic phase *in vacuo* gave a yellow oil which was purified by flash column chromatography on silica gel using ether : hexane (1 : 1) as eluant to give the title compound **5.3** (0.002 g, 12%) as a white foam.

IR (thin film) cm^{-1} : 2926s (C-H), 1747s (C=O), 1715 (C=O), 1455, 1257, 1151, 1091, 1037.

^1H NMR (300 MHz, CDCl_3) δ : 0.90 (t, $J_{3',2'} = 7.5$ Hz, 3H, H-3'), 0.96 (d, $J = 6.9$ Hz, 3H, 7- CH_3) 1.15-2.01 (m, 14H), 2.40 (m, 1H, H-3), 2.81 (dd, $J = 13.2$ Hz, $J = 5.1$ Hz, 1H, H'-3), 3.08 (d, $J_{1,10a} = 11.4$ Hz, 1H, H-1), 3.39 (s, 3H, 8- OCH_2OCH_3), 3.50 (m, 1H, H-8), 3.65-3.75 (m, 2H, H-4, H-1'), 3.76 (s, 3H, 1- CO_2CH_3), 4.60 (s, 2H, 8- OCH_2OCH_3).

^{13}C NMR (75 MHz, CDCl_3) δ : 9.3 (CH_3 , C-3'), 18.3 (7- CH_3), 26.2 (CH_2), 28.5 (CH_2), 29.7 (CH_2), 32.7 (CH_2), 33.0, 33.4, 37.0, 40.3, 44.5, 45.9, 48.6, 52.1 (1- CO_2CH_3), 56.1 (8- OCH_2OCH_3), 63.5 (CH, C-1), 71.3 (CH, C-4), 75.3 (CH, C-1'), 80.4 (CH, C-8), 98.2 (8- OCH_2OCH_3), 169.7 (1- CO_2CH_3), 202.9 (2-CO).

LRMS (m/z): 394 (M^+ , 5%), 365 (38), 319 (25), 303 (85), 173 (20), 45 (100).

HRMS: $\text{C}_{22}\text{H}_{34}\text{O}_6$ (M^+) requires 394.2355, found 394.2361.

(1*RS*, 4*aSR*, 4*bSR*, 5*RS*, 7*RS*, 8*RS*, 8*aSR*, 10*aSR*, 1'*SR*) Methyl 5-(1'-*t*-Butyldimethylsilyloxypropyl)-1,7-dimethyl-2-hydroxy-8-methoxmethoxy-4*a*,4*b*,5,6,7,8,8*a*,9,10,10*a*-decahydrophenanthrene-1(2*H*)-carboxylate (**5.4**)

Cerium (III) chloride heptahydrate (4.8 mL of a 0.1 *M* solution in MeOH, 0.48 mmol) was added to ketone **3.36** (0.23 g, 0.44 mmol) in MeOH (3 mL) at -78 °C under nitrogen. Sodium borohydride (0.05 g, 0.44 mmol) was added portion wise over 40 min, allowing the reaction mixture to warm to 0 °C. The reaction was quenched with

water (2 mL), and the methanol removed *in vacuo*. The aqueous residue was then extracted with ethyl acetate (4 x 20 mL). The combined organic extracts were washed with saturated sodium bicarbonate solution (10 mL), brine (10 mL), and dried over MgSO_4 . Concentration of the organic phase *in vacuo* gave the epimeric alcohols **5.4** (0.21 g, 91%) as a white foam, which was used without further purification.

IR (thin film) cm^{-1} : 3464br (C-OH), 2928s (C-H), 1726s (C=O), 1463, 1387, 1257s, 1152, 1038s.

^1H NMR (300 MHz, CDCl_3 , major epimer) δ : 0.05 (s, 3H, OSiCH_3), 0.06 (s, 3H, OSiCH_3), 0.90 (s, 9H, OSi^tBu), 0.85-0.93 (m, 6H, 7- CH_3 , H-3'), 1.09 (s, 3H, 1- CH_3), 1.10-1.75 (m, 12H), 2.00 (m, 1H), 2.17 (m, 1H), 3.30 (m, 1H, H-8), 3.39 (s, 3H, 8- OCH_2OCH_3), 3.72 (s, 3H, 1- CO_2CH_3), 3.94 (m, 1H, H-1'), 4.58, 4.62 (2 x ABd, $J = 6.9$ Hz, 2H, 8- OCH_2OCH_3), 4.73 (m, 1H, H-2), 5.52 (m, 1H, H-3), 5.96 (m, 1H, H-4).

^{13}C NMR (75 MHz, CDCl_3 , major epimer) δ : -4.0 (SiCH_3), -3.4 (SiCH_3), 9.2 (CH_3 , C-3'), 9.4 (1- CH_3), 18.4 (SiC), 19.0 (7- CH_3), 26.2 (Si^tBu), 26.5 (CH_2), 28.5 (CH_2), 29.7 (CH_2), 30.1 (CH_2), 33.0 (CH), 37.4 (CH), 38.3 (CH), 41.3 (CH), 41.7 (CH), 46.5 (CH), 51.9 (1- CO_2CH_3 and C1), 56.2 (8- OCH_2OCH_3), 73.3 (CH, C-1'), 73.4 (CH, C-2), 83.7 (CH, C-8), 99.0 (8- OCH_2OCH_3), 129.1 (CH, C-3), 130.3 (CH, C-4), 177.1 (1- CO_2CH_3).

LRMS (m/z): 467 ($(\text{M}^t\text{Bu})^+$, 2%), 405 (8), 347 (11), 313 (15), 253 (31), 204 (17), 173 (100), 133 (29), 73 (52).

HRMS: $\text{C}_{25}\text{H}_{43}\text{O}_6\text{Si}$ ($(\text{M}^t\text{Bu})^+$) requires 467.2829, found 467.2825.

(1*RS*, 4*aSR*, 4*bSR*, 5*RS*, 7*RS*, 8*RS*, 8*aSR*, 10*aSR*, 1'*SR*) Methyl 5-(1'-Hydroxypropyl)-1,7-dimethyl-2-hydroxy-8-methoxmethoxy-4*a*,4*b*,5,6,7,8,8*a*,9,10,10*a*-decahydrophenanthrene-1(2*H*)-carboxylate (5.5**)**

Tetrabutyl ammonium fluoride (0.97 mL of a 1 M solution in THF, 0.97 mmol) was added to a solution of silyl ether **5.4** (0.17 g, 0.32 mmol) in THF (10 mL) containing powdered 4Å molecular sieves at room temperature under nitrogen, then heated to 65 °C overnight. The reaction mixture was cooled to room temperature, water (5 mL) added and the mixture extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with water (5 mL), brine (5 mL) and dried over MgSO₄. Concentration of the organic phase *in vacuo* gave a yellow oil which was purified by flash column chromatography on silica gel using ethyl acetate : hexane (2 : 3 – 4 : 1) as eluant to give the epimeric diols **5.5** (0.096 g, 73%) as a white foam.

IR (thin film) cm⁻¹: 3469br (C-OH), 2928s (C-H), 1720s (C=O), 1455, 1381, 1259, 1150, 1037s.

¹H NMR (300 MHz, CDCl₃, major epimer) δ: 0.87 (d, *J* = 4.8 Hz, 3H, 7-CH₃), 0.98 (t, *J*_{3',2'} = 7.2 Hz, 3H, H-3'), 1.07 (s, 3H, 1-CH₃), 0.88-1.71 (m, 12H), 2.07 (m, 1H), 2.23 (m, 1H, H-4a), 3.32 (m, 1H, H-8), 3.38 (s, 3H, 8-OCH₂OCH₃), 3.71 (s, 3H, 1-CO₂CH₃), 3.86 (m, 1H, H-1'), 4.58, 4.61 (2 x ABd, *J* = 6.7 Hz, 2H, 8-OCH₂OCH₃), 4.72 (m, 1H, H-2), 5.47 (m, 1H, H-3), 6.06 (m, 1H, H-4).

¹³C NMR (75 MHz, CDCl₃, major epimer) δ: 9.0 (CH₃, C-3'), 9.5 (1-CH₃), 18.8 (7-CH₃), 26.5 (CH₂), 28.5 (CH₂), 29.7 (CH₂), 31.4 (CH₂), 32.4 (CH), 38.9 (CH), 39.4 (CH), 41.5 (CH), 42.1 (CH), 46.2 (CH), 51.9 (1-CO₂CH₃ and C1), 56.2 (8-OCH₂OCH₃), 71.8 (CH, C-1'), 73.4 (CH, C-2), 83.5 (CH, C-8), 99.0 (8-OCH₂OCH₃), 128.3 (CH, C-3), 131.2 (CH, C-4), 177.2 (1-CO₂CH₃).

LRMS (m/z): 392 ((M-H₂O)⁺, 5%), 330 (22), 271 (23), 253 (25), 213 (25), 204 (21), 145 (72), 131 (25), 105 (26), 45 (100).

HRMS: C₂₃H₃₆O₅ (M-H₂O)⁺ requires 392.2563, found 392.2560.

(1*RS*, 4*aSR*, 4*bSR*, 5*RS*, 7*RS*, 8*RS*, 8*aSR*, 10*aSR*) Methyl 5-(1'-oxopropyl)-1,7-dimethyl-8-methoxmethoxy-2-oxo-4*a*,4*b*,5,6,7,8,8*a*,9,10,10*a*-decahydrophenanthrene-1(2*H*)-carboxylate (5.1**)**

Dess-Martin periodinane (0.50 g, 1.17 mmol) was added to diol **5.5** (0.12 g, 0.29 mmol) in DCM (10 mL) at room temperature under nitrogen. After 1.5 h, the reaction mixture was stirred with 1 *M* sodium thiosulfate (5 mL) and a saturated solution of sodium bicarbonate (5 mL) until the cloudiness disappeared. The organic phase was separated and the aqueous phase extracted with DCM (3 x 10 mL). The combined organic extracts were dried over anhydrous MgSO_4 and concentrated *in vacuo* to give a white solid. Purification by flash column chromatography on silica gel using ethyl acetate : hexane (1 : 9) as eluant gave the title compound **5.1** (0.096 g, 81%) as a white foam.

IR (thin film) cm^{-1} : 2931s (C-H), 1741s (C=O), 1703s (C=O), 1678s (C=O), 1456, 1254, 1149 1032s.

^1H NMR (300 MHz, CDCl_3) δ : 0.93 (d, $J = 6.6$ Hz, 3H, 7- CH_3), 1.04 (t, $J_{3',2'} = 7.2$ Hz, 3H, H-3'), 1.24 (s, 3H, 1- CH_3), 1.22-1.46 (m, 3H), 1.55-1.66 (m, 4H), 1.87 (m, 1H), 2.24-2.44 (m, 4H), 2.69 (m, 1H, H2'), 3.27 (m, 1H, H-5), 3.60 (m, 1H, H-8), 3.38 (s, 3H, 8- OCH_2OCH_3), 3.72 (s, 3H, 1- CO_2CH_3), 4.60 (s, 2H, 8- OCH_2OCH_3), 5.95 (dd, $J = 10.4$ Hz, $J = 3.0$ Hz, 1H, H-3), 6.85 (d, $J = 10.4$ Hz, 1H, H-4).

^{13}C NMR (75 MHz, CDCl_3) δ : 7.9 (CH_3 , C-3'), 13.6 (1- CH_3), 18.3 (7- CH_3), 26.3 (CH_2), 28.5 (CH_2), 30.5 (CH_2), 32.2 (CH_2), 35.7 (CH), 38.2 (CH), 39.7 (CH), 41.7 (CH), 46.3 (CH), 46.4 (CH), 52.3 (1- CO_2CH_3), 56.2 (8- OCH_2OCH_3), 58.9 (C, C-1), 82.9 (CH, C-8), 98.9 (8- OCH_2OCH_3), 127.6 (CH, C-3), 149.6 (CH, C-4), 173.0 (1- CO_2CH_3), 198.9 (2-CO), 213.6 (1'-CO).

LRMS (m/z): 406 (M^+ , 10%), 344 (38), 285 (27), 255 (11), 227 (50), 213 (13), 57 (89), 45 (100).

HRMS: $C_{23}H_{34}O_6$ (M^+) requires 406.2355, found 406.2353.

(3*RS*, 3*aSR*, 5*aSR*, 5*bSR*, 5*cSR*, 6*RS*, 7*RS*, 8*aSR*, 10*RS*, 10*aSR*) Methyl 2,9-dioxo-6-methoxmethoxy-1,3*a*,4,5,5*a*,5*b*,5*c*,6,7,8,8*a*,10,10*a*-tridecahydro-3,7,10-trimethylpyrene-3(2*H*)-carboxylate (5.2**)**

Enone **5.1** (0.048 g, 0.12 mmol) in ethylene glycol (5 mL) and triethylamine (0.5 mL) was heated to 150 °C under nitrogen for 20 h. Water was then added and the resulting emulsion extracted with pentane : DCM (2 : 1, 5 x 10 mL). The combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product mixture as a yellow oil. Purification by flash column chromatography on silica gel using ethyl acetate : hexane (1 : 9 – 2 : 3) as eluant gave the title compound **5.2** (0.011 g, 31% based on recovered starting material) as a white solid. A sample was crystallized from methanol to give white needle like crystals.

m.p: 127-129 °C

IR (thin film) cm^{-1} : 2929s (C-H), 1738s (C=O), 1709s (C=O), 1678s (C=O), 1455, 1363, 1271, 1244, 1032.

1H NMR (800 MHz, $CDCl_3$) δ : 1.01 (d, $J = 6.4$ Hz, 6H, 7- CH_3 , 10- CH_3), 1.37-1.68 (m, 11H, H-4, H-5, H-5*a*, H-5*b*, H-5*c*, H-7, H-8, H-10*a*), 1.40 (s, 3H, 3- CH_3), 2.14-2.21 (m, 2H, H-8*a*, H-3*a*), 2.26 (m, 1H, H-10), 2.36 (m, 1H, H-1), 2.58 (dd, $J = 14.4$ Hz, $J = 4.0$ Hz, 1H, H-1), 3.39 (m, 1H, H-6), 3.38 (s, 3H, 6- OCH_2OCH_3), 3.76 (s, 3H, 3- CO_2CH_3), 4.59, 4.61 (2 x ABd, $J = 7.2$ Hz, 2H, 8- OCH_2OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ : 11.1 (10- CH_3), 15.5 (3- CH_3), 18.7 (7- CH_3), 27.0 (CH_2 , C-5), 27.5 (CH_2 , C-4), 28.3 (CH_2 , C-8), 35.8 (CH, C-7), 42.4 (CH_2 , C-1), 43.9 (CH), 44.5 (CH), 45.3 (CH), 46.4 (CH), 48.8 (CH), 49.8 (CH, C-10), 52.4 (CH), 52.8 (3- CO_2CH_3), 56.2 (6- OCH_2OCH_3), 61.6 (C, C-3), 81.9 (CH, C-6), 98.7 (6- OCH_2OCH_3), 172.8 (3- CO_2CH_3), 208.1 (2-CO), 209.9 (9-CO).

LRMS (m/z): 406 (M^+ , 5%), 344 (10), 285 (8), 277 (12), 245 (34), 215 (31), 130 (26), 55 (27), 45 (100).

HRMS: $C_{23}H_{34}O_6$ (M^+) requires 406.2355, found 406.2345.

(4aSR, 4bSR, 5RS, 7RS, 8RS, 8aSR, 10aRS, 1'SR) 5-(1'-*t*-Butyldimethylsilyloxypropyl)-8-methoxmethoxy-7-methyl-4a,4b,5,6,7,8,8a,9,10,10a-decahydrophenanthrene-2(1H)-ol (5.8)

Cerium (III) chloride heptahydrate (9.3 mL of a 0.1 *M* solution in MeOH, 0.93 mmol) was added to ketone **3.34** (0.38 g, 0.84 mmol) at -78 °C under nitrogen. Sodium borohydride (0.064 g, 1.68 mmol) was added portion-wise over 40 min, allowing the reaction mixture to warm to 0 °C. The reaction was quenched with water (2 mL), and the methanol removed *in vacuo*. The aqueous residue was then extracted with ethyl acetate (4 x 20 mL). The combined organic extracts were washed with saturated sodium bicarbonate solution (10 mL), brine (10 mL), and dried over $MgSO_4$. Concentration of the organic phase *in vacuo* gave the title compound **5.8** (0.38 g, 100%) as a white foam, which was used without further purification.

IR (thin film) cm^{-1} : 3401br (C-OH), 2928s (C-H), 1471, 1462, 1387, 1253, 1150, 1039.

1H NMR (300 MHz, $CDCl_3$) δ : 0.04 (s, 3H, -SiCH₃), 0.05 (s, 3H, -SiCH₃), 0.88 (s, 9H, -Si^{*t*}Bu), 0.87-0.92 (m, 6H, 7-CH₃, H-3'), 1.10-1.70 (m, 14H), 1.90 (m, 1H), 2.00 (m, 1H), 2.19 (m, 1H), 3.32 (m, 1H, H-8), 3.39 (s, 3H, 8-OCH₂OCH₃), 3.89 (m, 1H, H-1'), 4.33 (m, 1H, H-2), 4.60, 4.62 (2 x ABd, *J* = 6.6 Hz, 2H, 8-OCH₂OCH₃), 5.63 (m, 1H, H-3), 5.95 (m, 1H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$) δ : -4.1 (SiCH₃), -3.8 (SiCH₃), 9.9 (CH₃, C-3'), 18.2 (SiC), 19.0 (7-CH₃), 26.0 (CH₂), 26.1 (Si^{*t*}Bu), 28.3 (CH₂), 29.0 (CH₂), 30.0 (CH₂), 32.1, 33.4, 37.4, 40.1 (CH), 40.5 (CH), 42.0 (CH), 42.4 (CH), 56.0 (8-OCH₂OCH₃), 68.2

(CH, C-2), 73.2 (CH, C-1'), 84.0 (CH, C-8), 98.8 (8-OCH₂OCH₃), 130.8 (CH, C-3), 131.5 (CH, C-4).

LRMS (m/z): 452 (M⁺, 5%), 423 (22), 402 (100), 391 (54), 372 (84), 361 (25), 333 (51), 315 (12).

HRMS: C₂₆H₄₈O₄Si (M⁺) requires 452.3322, found 452.3318.

(4a*SR*, 4b*RS*, 5*RS*, 7*RS*, 8*RS*, 8a*SR*, 10a*RS*, 1'*SR*) 5-(1'-hydroxypropyl)-8-methoxmethoxy-7-methyl-4a,4b,5,6,7,8,8a,9,10,10a-decahydrophenanthrene-2(1*H*)-ol (5.9)

Tetrabutyl ammonium fluoride (2.52 mL of a 1 *M* solution in THF, 2.52 mmol) was added to a solution of silyl ether **5.8** (0.38 g, 0.84 mmol) in THF (20 mL) containing powdered 4Å molecular sieves at room temperature under nitrogen, then heated to 65 °C overnight. The reaction mixture was cooled to room temperature, water (10 mL) added and the mixture extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL) and dried over MgSO₄. Concentration of the organic phase *in vacuo* gave a yellow oil which was purified by flash column chromatography on silica gel using ethyl acetate : hexane (2 : 3 – 4 : 1) as eluant to give the title compound **5.9** (0.24 g, 87% over two steps) as a white foam.

IR (thin film) cm⁻¹: 3396br (C-OH), 2906s (C-H), 1463, 1450, 1442, 1148, 1143, 1044, 1039.

¹H NMR (300 MHz, CDCl₃) δ: 0.88 (d, *J* = 5.7 Hz, 3H, 7-CH₃), 0.98 (t, *J*_{3',2'} = 7.5 Hz, 3H, H-3'), 1.13-1.68 (m, 15H), 1.96-2.14 (m, 3H), 3.32 (m, 1H, H-8), 3.40 (s, 3H, 8-OCH₂OCH₃), 3.86 (td, *J*_{1,2} = 8.6 Hz, *J*_{1,4'} = 2.7 Hz, 1H, H-1'), 4.31 (m, 1H, H-2), 4.62 (s, 2H, 8-OCH₂OCH₃), 5.61 (m, 1H, H-3), 6.07 (m, 1H, H-4).

^{13}C NMR (75 MHz, CDCl_3) δ : 9.7 (CH_3 , C-3'), 18.9 (7- CH_3), 28.4 (CH_2), 29.9 (CH_2), 31.2 (CH_2), 32.2 (CH_2), 32.7, 39.4, 40.4, 41.0 (CH), 41.7 (CH), 41.8 (CH), 43.5 (CH), 56.2 (8- OCH_2OCH_3), 68.6 (CH, C-2), 71.9 (CH, C-1'), 83.8 (CH, C-8), 99.0 (8- OCH_2OCH_3), 130.2 (CH, C-3), 132.3 (CH, C-4).

LRMS (m/z): 320 ($(\text{M}-\text{H}_2\text{O})^+$, 7%), 288 (7), 258 (50), 240 (29), 201 (42), 69 (68), 57 (79), 45 (100).

HRMS: $\text{C}_{20}\text{H}_{32}\text{O}_3$ ($\text{M}-\text{H}_2\text{O}$) $^+$ requires 320.2351, found 320.2356.

(4a*SR*, 4b*SR*, 5*RS*, 7*RS*, 8*RS*, 8a*SR*, 10a*RS*, 1'*SR*) 5-(1'-oxopropyl)-8-methoxmethoxy-7-methyl-4a,4b,5,6,7,8,8a,9,10,10a-decahydro-2(1*H*)-phenanthrenone (5.10)

Dess-Martin periodinane (1.20 g, 2.84 mmol) was added to diol **5.9** (0.24 g, 0.71 mmol) in DCM (40 mL) at room temperature under nitrogen. After 1.5 h, the reaction mixture was stirred with a mixture of 1 *M* sodium thiosulfate (10 mL) and a saturated solution of sodium bicarbonate (10 mL) until the cloudiness disappeared. The organic phase was separated and the aqueous phase extracted with DCM (3 x 20 mL). The combined organic extracts were dried over anhydrous MgSO_4 and concentrated *in vacuo* to give a white solid. Purification by flash column chromatography on silica gel using ethyl acetate : hexane (3 : 7) as eluant gave the title compound **5.10** (0.18 g, 76%) as a white solid.

m.p: 109-111 $^{\circ}\text{C}$

IR (thin film) cm^{-1} : 2929s (C-H), 1700s (C=O), 1682s (C=O), 1460, 1445, 1403, 1222, 1150, 1089, 1031.

^1H NMR (300 MHz, CDCl_3) δ : 0.93 (d, $J = 6.6$ Hz, 3H, 7- CH_3), 1.03 (t, $J_{3',2'} = 7.2$ Hz, 3H, H-3'), 1.27-1.77 (m, 9H), 1.86 (m, 1H), 2.11-2.44 (m, 4H), 2.67 (m, 1H, H2'), 3.27 (m, 1H, H-5), 3.40 (m, 1H, H-8), 3.40 (s, 3H, 8- OCH_2OCH_3), 4.62 (s, 2H, 8- OCH_2OCH_3), 5.97 (dd, $J = 10.2$ Hz, $J = 3.0$ Hz, 1H, H-3), 6.91 (dd, $J = 10.2$ Hz, $J = 1.7$ Hz, 1H, H-4).

^{13}C NMR (75 MHz, CDCl_3) δ : 7.8 (CH_3 , C-3'), 18.3 (7- CH_3), 29.4 (CH_2), 30.3 (CH_2), 31.9 (CH_2), 32.1 (CH_2), 35.9, 39.1, 41.6, 41.8, 42.9, 45.4, 46.1, 56.1 (8- OCH_2OCH_3), 83.1 (CH, C-8), 98.8 (8- OCH_2OCH_3), 129.8 (CH, C-3), 150.6 (CH, C-4), 199.9 (2-CO), 213.8 (1'-CO).

LRMS (m/z): 334 (M^+ , 20%), 272 (49), 215 (30), 200 (48), 188 (19), 57 (50), 45 (100).

HRMS: $\text{C}_{20}\text{H}_{30}\text{O}_4$ (M^+) requires 334.2144, found 334.2146.

(3a*RS*, 5a*SR*, 5b*SR*, 5c*SR*, 6*RS*, 7*RS*, 8a*SR*, 10*RS*, 10a*SR*) 6-Methoxmethoxy-1,3a,4,5,5a,5b,5c,6,7,8,8a,10a-dodecahydro-7,10-dimethylpyrene-2,9(3*H*, 10*H*)-dione (5.11)

Enone **5.10** (0.069 g, 0.21 mmol) in ethylene glycol (6 mL) and triethylamine (0.6 mL) was heated to 150 °C under nitrogen for 20 h. Water was then added and the resulting emulsion extracted with pentane : DCM (2 : 1, 5 x 10 mL). The combined organic extracts were washed with brine (5 mL), dried over MgSO_4 and concentrated *in vacuo* to give a yellow oil. Purification by flash column chromatography on silica gel using ethyl acetate : hexane (4 : 6) as eluant gave the title compound **5.11** (0.047 g, 68%) as a white foam.

IR (thin film) cm^{-1} : 2930s (C-H), 1711s (C=O), 1447, 1365, 1252, 1150, 1044.

^1H NMR (300 MHz, CDCl_3) δ : 0.99 (d, $J = 6.6$ Hz, 6H, 7- CH_3 , 10- CH_3), 1.16-1.89 (m, 12H), 2.07-2.46 (m, 5H), 2.62 (m, 1H, H-1), 3.36 (s, 3H, 6- OCH_2OCH_3), 3.38 (m, 1H, H-6), 4.59 (s, 2H, 8- OCH_2OCH_3).

^{13}C NMR (75 MHz, CDCl_3) δ : 11.2 (10- CH_3), 18.7 (7- CH_3), 27.4 (CH_2), 28.2 (CH_2), 33.3 (CH_2), 35.8, 40.7, 43.8, 46.5, 47.3, 48.1, 49.3, 49.4, 49.9, 54.5, 56.1 (6- OCH_2OCH_3), 82.1 (CH, C-6), 98.7 (6- OCH_2OCH_3), 209.2 (2-CO), 210.5 (9-CO).

LRMS (m/z): 334 (M^+ , 40%), 302 (15), 272 (57), 193 (10), 186 (11), 124 (12), 45 (100).

HRMS: $\text{C}_{20}\text{H}_{30}\text{O}_4$ (M^+) requires 334.2144, found 334.2143.

(3*RS*, 3*aSR*, 5*aSR*, 5*bSR*, 5*cSR*, 6*RS*, 7*RS*, 8*aSR*, 10*RS*, 10*aSR*) Methyl 2,9-dioxo-6-methoxmethoxy-1,3*a*,4,5,5*a*,5*b*,5*c*,6,7,8,8*a*,9*a*,10,10*a*-tetradecahydro-7,10-dimethylpyrene-3(2*H*)-carboxylate (5.12**)**

n-Butyllithium (0.12 mL of a 1.6 M solution in hexanes, 0.20 mmol) was added to diisopropylamine (0.028 mL, 0.20 mmol) in THF (2 mL) at -20°C under nitrogen. The reaction mixture was stirred for 20 min, warmed to 0°C and stirred for a further 30 min. The solution was then cooled to -78°C , ketone **5.11** (0.044 g, 0.13 mmol) was added, and the reaction mixture warmed to 0°C for 1 h. After cooling to -78°C , HMPA (0.024 mL, 0.13 mmol) and methyl cyanoformate (0.016 mL, 0.20 mmol) were added. After 20 min the reaction mixture was poured into water and extracted with ether (3 x 10 mL). The combined organic extracts were washed with water (5 mL), brine (5 mL) and dried over anhydrous MgSO_4 . Concentration of the organic phase *in vacuo* gave a yellow oil which was purified by flash column chromatography on silica gel using ethyl acetate : hexane (1 : 9) as eluant to give compounds **5.12** and **5.13** (0.016 g, 37%) as an inseparable mixture. The mixture of **5.12** and **5.13** was then treated with potassium carbonate (0.20 g) in methanol (2 mL) overnight. Water was then added and the methanol removed *in vacuo*. The aqueous residue was extracted with ether (3 x 5 mL)

and dried over MgSO_4 . Concentration of the organic phase *in vacuo* gave a colourless oil which was purified by flash column chromatography on silica gel using ethyl acetate : hexane (1 : 9) as eluant to give methyl esters **5.12** (0.014 g, 88%) and **5.14** (1.9 mg, 12%).

(3*RS*, 3*aSR*, 5*aSR*, 5*bSR*, 5*cSR*, 6*RS*, 7*RS*, 8*aSR*, 10*RS*, 10*aSR*) Methyl 2,9-dioxo-6-methoxmethoxy-1,3*a*,4,5,5*a*,5*b*,5*c*,6,7,8,8*a*,9*a*,10,10*a*-tetradecahydro-7,10-dimethylpyrene-3(2*H*)-carboxylate (5.12**)**

IR (thin film) cm^{-1} : 2928s (C-H), 1745s (C=O), 1710s (C=O), 1456, 1366, 1252, 1151, 1033.

^1H NMR (600 MHz, CDCl_3) δ : 0.99 (d, J = 6.0 Hz, 3H, 7- CH_3) 1.00, (d, J = 6.6 Hz, 3H, 10- CH_3), 1.19-1.70 (m, 11H), 1.80-1.91 (m, 2H), 2.13-2.20 (m, 2H), 2.74 (dd, J = 13.8 Hz, J = 4.2 Hz, 1H, H-1), 3.19 (d, J = 12.6 Hz, 1H, H-3), 3.37 (s, 3H, 6- OCH_2OCH_3), 3.39 (m, 1H, H-6), 3.77 (s, 3H, 3- CO_2CH_3), 4.59, 4.60 (2 x ABd, J = 6.6 Hz, 2H, 8- OCH_2OCH_3).

^{13}C NMR (150 MHz, CDCl_3) δ : 11.2 (10- CH_3), 18.7 (7- CH_3), 27.4 (CH_2), 27.9 (CH_2), 31.8 (CH_2), 35.8 (CH), 43.0 (CH), 43.8 (CH), 46.2 (CH_2 , C-1), 47.2 (CH), 48.2 (CH), 48.8 (CH), 49.7 (CH), 52.1 (3- CO_2CH_3), 52.6 (CH), 56.3 (6- OCH_2OCH_3), 63.3 (CH, C-3), 81.9 (CH, C-6), 98.7 (6- OCH_2OCH_3), 169.7 (3- CO_2CH_3), 203.6 (2-CO), 209.9 (9-CO).

LRMS (m/z): 392 (M^+ , 19%), 360 (5), 330 (22), 244 (18), 215 (6), 124 (6), 45 (100).

HRMS: $\text{C}_{22}\text{H}_{32}\text{O}_6$ (M^+) requires 392.2199, found 392.2194.

(1*RS*, 3*aRS*, 5*aSR*, 5*bSR*, 5*cRS*, 6*RS*, 7*RS*, 8*aSR*, 10*RS*, 10*aSR*) Methyl 2,9-dioxo-6-methoxmethoxy-3,3*a*,4,5,5*a*,5*b*,5*c*,6,7,8,8*a*,9*a*,10,10*a*-tetradecahydro-7,10-dimethylpyrene-1(2*H*)-carboxylate (5.14**)**

IR (thin film) cm^{-1} : 2928s (C-H), 1712s (C=O), 1449, 1357, 1252, 1165, 1041.

^1H NMR (600 MHz, CDCl_3) δ : 1.00 (d, $J = 6.0$ Hz, 3H, 7- CH_3) 1.02, (d, $J = 6.6$ Hz, 3H, 10- CH_3), 1.21-1.71 (m, 10H, H-3a, H-4, H-5, H-5a, H-5b, H-7, H-8, H-10a), 1.80 (m, 1H, H'-4), 2.15 (q, $J = 10.6$ Hz, 1H, H-5c), 2.21 (m, 1H, H-8a), 2.35 (m, 1H, H-3), 2.58 (m, 1H, H-10), 2.64 (m, 1H, H'-3), 3.37 (s, 3H, 6- OCH_2OCH_3), 3.38 (m, 1H, H-6), 3.62 (dd, $J = 4.8$ Hz, $J = 1.2$ Hz, 1H, H-1), 3.73 (s, 3H, 1- CO_2CH_3), 4.59, 4.61 (2 x ABd, $J = 6.9$ Hz, 2H, 8- OCH_2OCH_3).

^{13}C NMR (150 MHz, CDCl_3) δ : 11.2 (10- CH_3), 18.7 (7- CH_3), 27.3 (CH_2), 28.3 (CH_2), 33.2 (CH_2), 35.7 (CH), 41.4 (CH), 43.7 (CH), 43.8 (CH), 45.8 (CH_2 , C-3), 46.2 (CH), 47.3 (CH), 52.1 (2 x CH), 52.4 (3- CO_2CH_3), 56.2 (6- OCH_2OCH_3), 59.3 (CH, C-1), 82.2 (CH, C-6), 98.8 (6- OCH_2OCH_3), 168.9 (1- CO_2CH_3), 204.1 (2-CO), 210.5 (9-CO).

LRMS (m/z): 392 (M^+ , 34%), 330 (19), 215 (51), 170 (20), 45 (100).

HRMS: $\text{C}_{22}\text{H}_{32}\text{O}_6$ (M^+) requires 392.2199, found 392.2200.

(3*RS*, 3a*SR*, 5a*SR*, 5b*SR*, 5c*SR*, 6*RS*, 7*RS*, 8a*SR*, 10*RS*, 10a*SR*) Methyl 2,9-dioxo-6-methoxmethoxy-1,3a,4,5,5a,5b,5c,6,7,8,8a,9a,10,10a-tetradecahydro-7,10-dimethylpyrene-3(2*H*)-carboxylate (5.12**)**

Lithium bis(trimethylsilyl)amide (0.13 mL of a 1 *M* solution in THF, 0.13 mmol) was added to ketone **5.11** (0.029 g, 0.087 mmol) at -78 °C under nitrogen. The reaction mixture was then warmed to 0 °C for 1 h, then cooled to -78 °C before adding HMPA (0.015 mL, 0.087 mmol) and methyl cyanofomate (0.010 mL, 0.13 mmol). After 20 min the reaction mixture was poured into water and extracted with ether (3 x 10 mL). The combined organic extracts were washed with water (5 mL), brine (5 mL) and dried over anhydrous MgSO_4 . Concentration of the organic phase *in vacuo* gave a yellow oil which was treated with potassium carbonate (0.20 g) in methanol (2 mL) overnight. Water was then added and the methanol removed *in vacuo*. The aqueous residue was extracted with ether (3 x 5 mL) and dried over MgSO_4 . Concentration of the organic

phase *in vacuo* gave the title compound **5.12** (~0.02 g) as a colourless oil which was not purified further.

(1*RS*, 4*aSR*, 4*bSR*, 5*RS*, 7*RS*, 8*RS*, 8*aSR*, 10*aSR*, 1'*SR*) Dimethyl 5-(1'-*t*-Butyldimethylsilyloxypropyl)-2-hydroxy-1,7,8-trimethyl-4*a*,4*b*,5,6,7,9,10,10*a*-octahydrophenanthrene-1,8(2*H*, 8*aH*)-dicarboxylate (5.15**)**

Ketone **4.17** (0.36 g, 0.67 mmol) in MeOH (10 mL) was added to cerium (III) chloride heptahydrate (0.28 g, 0.74 mmol) under nitrogen. The solution was cooled to -78°C , sodium borohydride (0.03 g, 0.74 mmol) was added and the mixture gradually warmed to 0°C over 50 min. The reaction was quenched with water and the methanol was removed *in vacuo*. The aqueous residue was extracted with ethyl acetate (4 x 30 mL), then the combined organic extracts washed with brine (10 mL), back-extracted with ethyl acetate (2 x 10 mL) and dried over MgSO_4 . Concentration of the organic phase *in vacuo* gave two epimeric products, which were purified by flash column chromatography on silica gel using ethyl acetate : petroleum spirit (1.5 : 8.5) as eluant to give the major alcohol (0.27 g, 75%) and the minor alcohol (0.02 g, 5%) as white solids. A sample of the major alcohol **5.15** was crystallised from ether to give white crystals.

m.p: $133\text{--}136^{\circ}\text{C}$

IR (thin film) cm^{-1} : 3497br (C-OH), 2951s (C-H), 1723s (C=O), 1468s, 1387, 1255s, 1212.

^1H NMR (300 MHz, CDCl_3 , major epimer) δ : 0.05 (s, 3H, - SiCH_3), 0.08 (s, 3H, - SiCH_3), 0.76 (d, $J = 6.6$ Hz, 3H, 7- CH_3), 0.88 (s, 9H, - Si^tBu), 0.91 (t, $J_{3',2'} = 7.2$ Hz, 3H, H-3'), 0.85 (m, 1H, H-9), 1.06 (s, 3H, 1- CH_3), 1.22 (s, 3H, 8- CH_3), 1.18 (m, 1H, H-10), 1.46-1.77 (m, 8H), 1.89-2.10 (m, 3H), 2.31 (m, 1H, H-5), 3.63 (s, 3H, 8- CO_2CH_3), 3.70 (s, 3H, 1- CO_2CH_3), 4.09 (m, 1H, H-1'), 4.73 (m, 1H, H-2), 5.51 (m, 1H, H-3), 6.05 (m, 1H, H-4).

^{13}C NMR (75 MHz, CDCl_3 , major epimer) δ : -3.9 (SiCH_3), -3.0 (SiCH_3), 7.9 (CH_3 , C-3'), 9.1 (1-CH_3), 17.7 (7-CH_3), 18.4 (SiC), 23.9 (8-CH_3), 26.3 (Si^tBu), 26.9 (CH_2), 28.0 (CH_2), 28.4 (CH_2), 32.8 (CH_2), 35.4 (CH), 36.0 (CH), 39.5 (CH), 44.0 (CH), 44.5 (CH), 46.2 (CH), 50.6 ($2 \times \text{C}$, C-8 and C-1), 50.8 ($8\text{-CO}_2\text{CH}_3$), 51.9 ($1\text{-CO}_2\text{CH}_3$), 72.2 (CH , C-1'), 73.2 (CH , C-2), 128.8 (CH , C-3), 130.6 (CH , C-4), 175.2 ($1\text{-CO}_2\text{CH}_3$), 177.1 ($8\text{-CO}_2\text{CH}_3$).

LRMS (m/z): 479 ($(\text{M}^t\text{Bu})^+$, 53%), 419 (82), 404 (79), 387 (80), 361 (41), 355 (33), 345 (100).

HRMS: $\text{C}_{26}\text{H}_{43}\text{O}_6\text{Si}$ ($(\text{M}^t\text{Bu})^+$) requires 479.2829, found 479.2830.

Microanalysis: Calcd. for $\text{C}_{30}\text{H}_{52}\text{O}_6\text{Si}$: C, 67.12%, H, 9.76%. Found: C, 67.43%, H, 10.00%.

(1*RS*, 4*aSR*, 4*bSR*, 5*RS*, 7*RS*, 8*RS*, 8*aSR*, 10*aSR*, 1'*SR*) Dimethyl 5-(1'-Hydroxypropyl)-2-hydroxy-1,7,8-trimethyl-4*a*,4*b*,5,6,7,9,10,10*a*-octahydrophenanthrene-1,8(2*H*, 8*aH*)-dicarboxylate (5.16**)**

Tetrabutyl ammonium fluoride (1.51 mL of a 1 *M* solution in THF, 1.51 mmol) was added to the TBDMS ether **5.15** (0.27 g, 0.50 mmol) in THF (20 mL) containing powdered 4Å molecular sieves at room temperature under nitrogen, then the mixture was heated to 65 °C for 36 h. The reaction mixture was cooled to room temperature, water (5 mL) was added and the mixture extracted with ethyl acetate (4 x 20 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL) and dried over MgSO_4 . Concentration of the organic phase *in vacuo* gave a yellow oil, which was purified by flash column chromatography on silica gel using ethyl acetate : hexane (2 : 3 – 4 : 1) as eluant to give the title compound **5.16** (0.15 g, 84% based on recovered starting material) as a white solid.

m.p: 164-165 °C

IR (thin film) cm^{-1} : 3497br (C-OH), 2948s (C-H), 1718s (C=O), 1459, 1387, 1256, 1211.

^1H NMR (300 MHz, CDCl_3) δ : 0.75 (d, $J = 6.9$ Hz, 3H, 7- CH_3), 0.84 (m, 1H, H-9), 0.98 (t, $J_{3',2'} = 7.5$ Hz, 3H, H-3'), 1.05 (s, 3H, 1- CH_3), 1.21 (s, 3H, 8- CH_3), 1.20 (m, 1H, H-10), 1.31-1.99 (m, 10H), 2.14 (m, 1H, H-5), 2.26 (m, 1H, H-4a), 3.63 (s, 3H, 8- CO_2CH_3), 3.69 (s, 3H, 1- CO_2CH_3), 3.91 (td, $J = 8.7$ Hz, $J = 2.7$ Hz, 1H, H-1'), 4.72 (m, 1H, H-2), 5.49 (m, 1H, H-3), 6.10 (m, 1H, H-4).

^{13}C NMR (75 MHz, CDCl_3) δ : 9.2 (1- CH_3), 9.5 (CH_3 , C-3'), 17.9 (7- CH_3), 24.1 (8- CH_3), 27.2 (CH_2), 28.3 (CH_2), 28.6 (CH_2), 33.6 (CH_2), 35.4 (CH), 38.6 (CH), 40.1 (CH), 44.4 (CH), 44.8 (CH), 46.2 (CH), 50.7 (C, C-8 or C-1), 51.1 (8- CO_2CH_3), 52.1 (C, C-8 or C-1), 52.2 (1- CO_2CH_3), 71.9 (CH, C-1'), 73.5 (CH, C-2), 128.7 (CH, C-3), 131.4 (CH, C-4), 175.4 (1- CO_2CH_3), 177.5 (8- CO_2CH_3).

LRMS (m/z): 404 ($(\text{M}-\text{H}_2\text{O})^+$, 20%), 386 (20), 345 (41), 327 (44), 285 (51), 278 (56), 221 (70), 189 (67), 161 (100).

HRMS: $\text{C}_{24}\text{H}_{36}\text{O}_5$ ($(\text{M}-\text{H}_2\text{O})^+$) requires 404.2563, found 404.2562.

(1*RS*, 4*aSR*, 4*bSR*, 5*RS*, 7*RS*, 8*RS*, 8*aSR*, 10*aSR*) Dimethyl 5-(1'-Oxopropyl)- 2-oxo-1,7,8-trimethyl-4*a*,4*b*,5,6,7,9,10,10*a*-octahydrophenanthrene-1,8(2*H*, 8*aH*)-dicarboxylate (1.86)

Dess-Martin periodinane (0.45 g, 1.07 mmol) was added to diol **5.16** (0.15 g, 0.36 mmol) in DCM (10 mL) at 0 °C under nitrogen. After 1.5 h, the reaction mixture was stirred with 1 *M* sodium thiosulfate (5 mL) and a saturated aqueous solution of sodium bicarbonate (5 mL) until the cloudiness disappeared. The organic phase was separated and the aqueous phase extracted with DCM (3 x 15 mL). The combined organic extracts were dried over anhydrous MgSO_4 and concentrated *in vacuo* to give a white solid. Purification by flash column chromatography on silica gel using ethyl acetate :

hexane (1 : 9) as eluant gave the title compound **1.86** (0.12 g, 81%) as a white solid. A sample was crystallised from ether/hexane to give white crystals.

m.p: 143-145 °C

IR (thin film) cm^{-1} : 2947s (C-H), 1736s (C=O), 1720s (C=O), 1678s (C=O), 1458, 1377, 1263.

^1H NMR (300 MHz, CDCl_3) δ : 0.82 (d, $J = 6.9$ Hz, 3H, 7- CH_3), 0.78 (m, 1H, H-9), 1.04 (t, $J_{3',2'} = 7.2$ Hz, 3H, H-3'), 1.23 (s, 6H, 1- CH_3 , 8- CH_3), 1.17-1.51 (m, 2H), 1.68-1.75 (m, 2H), 1.93-2.44 (m, 7H), 2.69 (m, 1H, H-2'), 3.35 (m, 1H, H-5), 3.63 (s, 3H, 8- CO_2CH_3), 3.71 (s, 3H, 1- CO_2CH_3), 5.96 (dd, $J = 10.5$ Hz, $J = 2.7$ Hz, 1H, H-3), 6.88 (dd, $J = 10.5$ Hz, $J = 1.5$ Hz, 1H, H-4).

^{13}C NMR (75 MHz, CDCl_3) δ : 7.9 (CH_3 , C-3'), 13.5 (1- CH_3), 17.2 (7- CH_3), 22.9 (8- CH_3), 26.7 (CH_2 , C-9), 27.5 (CH_2 , C-10), 32.2 (CH_2 , C-6), 35.4 (CH), 35.5 (CH_2 , C-2'), 38.9 (CH), 41.5 (CH), 44.6 (CH), 46.0 (CH), 46.1 (CH, C-5), 49.9 (C, C-8), 50.9 (8- CO_2CH_3), 52.3 (1- CO_2CH_3), 58.7 (C, C-1), 127.6 (CH, C-3), 149.5 (CH, C-4), 172.9 (1- CO_2CH_3), 174.8 (8- CO_2CH_3), 198.8 (2-CO), 213.9 (1'-CO).

LRMS (m/z): 418 (M^+ , 94%), 358 (58), 299 (59), 241 (61), 213 (20), 159 (22), 121 (21), 57 (100).

HRMS: $\text{C}_{24}\text{H}_{34}\text{O}_6$ (M^+) requires 418.2355, found 418.2354.

Microanalysis: Calcd. for $\text{C}_{24}\text{H}_{34}\text{O}_6$: C, 68.88%, H, 8.19%. Found: C, 68.89%, H, 8.12%.

($\pm$)-Dimethyl 2,6-Dioxo-isocycloamphilectan-7,20-dicarboxylate (1.87**)**

Enone **1.86** (0.058g, 0.14 mmol) in ethylene glycol (3 mL) and triethylamine (0.3 mL) was heated to 70 °C under nitrogen for 4 d. Water was then added and the resulting mixture extracted with pentane : DCM (2 : 1, 3 x 10 mL). The aqueous phase was then saturated with sodium chloride and further extracted with pentane : DCM (2 : 1, 3 x 10 mL). The combined organic extracts were washed with water (5 mL), brine (5 mL), dried over MgSO_4 and concentrated *in vacuo* to give the crude product mixture as a yellow oil. Purification by flash column chromatography on silica gel using ethyl acetate : petroleum spirit (1.5 : 8.5) as eluant gave the title compound **1.87** (0.013 g, 30% based on recovered starting material) as a white solid and an inseparable mixture of **5.18** and **5.19** (0.018 g, 41% based on recovered starting material) as a colourless oil. A sample of **1.87** was crystallised from methanol to give white needle like crystals.

m.p: 174-175 °C

IR (thin film) cm^{-1} : 2950s (C-H), 1732s (C=O), 1712s (C=O), 1456, 1434, 1380, 1235, 1091.

^1H NMR (800 MHz, CDCl_3) δ : 0.92 (d, J = 6.4 Hz, 3H, 17- CH_3), 0.91 (m, 1H, H-10), 1.02 (d, J = 7.2 Hz, 3H, 18- CH_3), 1.17 (m, 1H, H-11), 1.24 (m, 1H, H-14), 1.25 (s, 3H, 16- CH_3), 1.33 (m, 1H, H-9), 1.39 (s, 3H, 19- CH_3), 1.39-1.44 (m, 2H, H'-9, H-15), 1.59 (m, 1H, H-13), 1.66 (m, 1H, H-4), 1.74 (m, 1H, H'-14), 1.84 (m, 1H, H-12), 1.95 (dq, J = 13.6 Hz, J = 2.4 Hz, 1H, H'-10), 2.15-2.19 (m, 2H, H-8, H-1), 2.28 (m, 1H, H-3), 2.35 (m, 1H, H-5), 2.56 (dd, J = 14.4 Hz J = 4.0 Hz, 1H, H'-5), 3.63 (s, 3H, 20- CO_2CH_3), 3.75 (s, 3H, 7- CO_2CH_3).

^{13}C NMR (150 MHz, CDCl_3) δ : 11.1 (18- CH_3), 15.5 (19- CH_3), 17.4 (17- CH_3), 23.3 (16- CH_3), 26.4 (CH_2 , C-10), 27.4 (CH_2 , C-9), 29.5 (CH_2 , C-14), 39.6 (CH, C-15), 42.3 (CH_2 , C-5), 44.6 (CH, C-13), 45.1 (CH, C-8), 46.3 (CH, C-12), 48.4 (CH, C-4), 49.5 (C, C-20), 49.6 (CH, C-3), 51.0 (CH, C-11), 51.1 (20- CO_2CH_3), 52.4 (7- CO_2CH_3), 52.4 (CH, C-1), 61.4 (C, C-7), 172.7 (7- CO_2CH_3), 174.4 (20- CO_2CH_3), 207.9 (6-CO), 209.9 (2-CO).

LRMS (m/z): 418 (M^+ , 40%), 400 (78), 358 (51), 341 (100), 281 (60), 229 (50), 211 (54).

HRMS: $C_{24}H_{34}O_6$ (M^+) requires 418.2355, found 418.2354.

Microanalysis: Calcd. for $C_{24}H_{34}O_6$: C, 68.88%, H, 8.19%. Found: C, 68.65%, H, 7.91%.

(±)-7-(2'-Methoxmethoxyethyl) 20-Methyl 2,6-Dioxo-isocycloamphilectan-7, 20-dicarboxylate (5.20)

Hünig's base (0.15 mL, 0.86 mmol) was added to a mixture of alcohols **5.18** and **5.19** (0.077 g, 0.17 mmol) in DCM (5 mL) at 0 °C under nitrogen. Chloromethyl methyl ether (0.065 mL, 0.86 mmol) was added drop wise and the reaction mixture was warmed to room temperature. A catalytic amount of DMAP was then added and the reaction mixture stirred for 24 h. The reaction mixture was cooled to 0 °C, saturated aqueous sodium bicarbonate (5 mL) was added, and the resulting mixture stirred for 10 min. The organic phase was separated and the aqueous phase was extracted with DCM (3 x 10 mL). The combined organic extracts were washed with water (5 mL), 1 M hydrochloric acid (5 mL), saturated aqueous sodium bicarbonate (5 mL), brine (5 mL) and dried over anhydrous $MgSO_4$. Concentration of the organic phase *in vacuo* gave a yellow gum which was purified by flash column chromatography on silica gel using ethyl acetate : hexane (1 : 4) as eluant to give the title compound **5.20** (0.036 g, 43%) as a colourless oil and a mixture of esters **5.21** and **5.20** (0.026, 31%) as a colourless oil.

IR (thin film) cm^{-1} : 2931s (C-H), 1736s (C=O), 1712s (C=O), 1459, 1380, 1254, 1091.

1H NMR (300 MHz, $CDCl_3$) δ : 0.91 (d, $J = 6.9$ Hz, 3H, 17- CH_3), 0.87 (m, 1H, H-10), 1.01 (d, $J = 6.6$ Hz, 3H, 18- CH_3), 1.12-2.04 (m, 10H), 1.24 (s, 3H, 16- CH_3), 1.38 (s, 3H, 19- CH_3), 2.11-2.40 (m, 4H), 2.57 (dd, $J = 14.4$ Hz $J = 3.9$ Hz, 1H, H-5), 3.35 (s, 3H, 2'- OCH_2OCH_3), 3.61 (s, 3H, 20- CO_2CH_3), 3.72-3.75 (m, 2H, 2'-H), 4.33-4.36 (m, 2H, 1'-H), 4.62 (s, 2H, 2'- OCH_2OCH_3).

^{13}C NMR (75 MHz, CDCl_3) δ : 11.1 (CH_3), 15.4 (CH_3), 17.4 (CH_3), 23.3 (CH_3), 26.3 (CH_2), 27.4 (CH_2), 29.5 (CH_2), 39.6 (CH), 42.2 (CH_2), 44.5 (CH), 45.0 (CH), 46.3 (CH), 48.3 (CH), 49.5 (C), 49.6 (CH), 50.9 (CH), 51.0 ($20\text{-CO}_2\text{CH}_3$), 52.4 (CH), 55.2 ($2'\text{-OCH}_2\text{OCH}_3$), 61.4 (C), 64.2 (CH_2 , C-1'), 65.5 (CH_2 , C-2'), 96.4 ($2'\text{-OCH}_2\text{OCH}_3$), 172.1 ($7\text{-CO}_2\text{R}$), 174.4 ($20\text{-CO}_2\text{CH}_3$), 207.8 (6-CO), 209.9 (2-CO).

LRMS (m/z): 492 (M^+ , 4%), 460 (19), 386 (20), 358 (41), 299 (37), 281 (38), 229 (30), 45 (100).

HRMS: $\text{C}_{27}\text{H}_{40}\text{O}_8$ (M^+) requires 492.2723, found 492.2726.

8.6 Chapter 6 Model Studies Experimental

(1*SR*, 4*aRS*, 8*aSR*)-Methyl decahydro-1-methylnaphthalene-1-carboxylate (6.6)

Method A: Tosylhydrazine (0.65 g, 3.48 mmol) was added to ketone **6.5** (0.65 g, 2.90 mmol) in THF (15 mL) under nitrogen. The resulting mixture was heated at reflux for 18 h. The reaction was then cooled to room temperature before adding zinc chloride (0.55 g, 4.06 mmol) and sodium cyanoborohydride (0.26 g, 4.06 mmol). The suspension was then heated to reflux for 24 h. The mixture was cooled to room temperature and saturated sodium bicarbonate was added. The residue was extracted with ether (4 x 20 mL) then the combined organic extracts were washed with 1 *M* hydrochloric acid (5 mL), water (5 mL) and dried over MgSO_4 . Concentration *in vacuo* gave the crude product as a colourless oil, which was purified by flash column chromatography using ether : petroleum spirit (1 : 9) as eluant to give the title compound **6.6** (0.40 g, 66%) as a colourless oil.

Method B: ketone **6.5** (0.10 g, 0.45 mmol) in MeOH (5 mL) was added to cerium (III) chloride heptahydrate (0.18 g, 0.49 mmol) under nitrogen. The solution was cooled to 0 °C, and sodium borohydride (0.02 g, 0.49 mmol) was added. The reaction was stirred for 30 min then quenched with water, and the methanol removed *in vacuo*. The aqueous

residue was extracted with ethyl acetate (3 x 10 mL) then the aqueous phase saturated with sodium chloride, and further extracted with ethyl acetate (2 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over MgSO_4 and concentrated *in vacuo* to give a mixture of two epimeric alcohols **6.7** (0.11 g), which were used directly in the next step without purification.

The crude alcohols **6.7** (0.11 g, 0.49 mmol) were dissolved in THF (5 mL) and Sodium bis(trimethylsilyl)amide (0.97 mL of a 1 M solution in THF, 0.97 mmol) was added at room temperature under nitrogen. The resulting reaction mixture was stirred for 2 h then carbon disulfide (0.058 mL, 0.97 mmol) was added. The reaction mixture was stirred for 2 h then iodomethane (0.06 mL, 0.97 mmol) was added. The mixture was stirred for an additional 2 h then quenched with acetic acid (0.5 mL) and diluted with saturated ammonium chloride solution (5 mL). The resulting aqueous mixture was extracted with ethyl acetate (4 x 10 mL). The combined organic extracts were dried over MgSO_4 and concentrated *in vacuo* to give a mixture of two epimeric xanthate esters **6.8** (0.13 g), which were used directly in the next step without purification.

The crude xanthate esters **6.8** (0.13 g, 0.41 mmol) were dissolved in toluene (5 mL) then tributyl tin hydride (0.22 mL, 0.82 mmol) and a catalytic amount of AIBN was added. The reaction mixture was heated to a 100 °C for 1 h, after which time starting material remained so excess tributyl tin hydride (0.15 mL, 0.56 mmol) and AIBN (catalytic) were added. After 1 h at 100 °C the toluene was removed *in vacuo* and the residue purified by flash column chromatography on silica gel using ether : petroleum spirit (5 : 95) as eluant to give the title compound **6.6** (0.062 g, ~70% over 3 steps) as a colourless oil.

IR (thin film) cm^{-1} : 2924s (C-H), 1730s (C=O), 1447, 1383, 1263, 1227, 1142, 1105.

^1H NMR (300 MHz, CDCl_3) δ : 0.87-1.78 (m, 16H, H-2, H-3, H-4, H-4a, H-5, H-6, H-7, H-8, H-8a), 1.11 (s, 3H, 1- CH_3), 3.65 (s, 3H, 1- CO_2CH_3).

^{13}C NMR (75 MHz, CDCl_3) δ : 15.0 (1- CH_3), 21.0 (CH_2 , C-3), 26.4, 26.7, 28.4 (CH_2 , C-6, C-7 and C-8), 34.0, 34.8 (CH_2 , C-4 and C-5), 36.4 (CH, C-4a), 37.4 (CH_2 , C-2), 46.7 (C, C-1), 47.1 (CH, C-8a), 51.6 (1- CO_2CH_3), 179.0 (1- CO_2CH_3).

LRMS (m/z): 210 (M^+ , 52%), 178 (50), 151 (91), 123 (31), 101 (38), 95 (100).

HRMS: C₁₃H₂₂O₂ (M⁺) requires 210.1620, found 210.1619.

(1*SR*, 4*aRS*, 8*aSR*)-decahydro-1-methylnaphthalene-1-carboxylic acid (6.10)

Method A: Lithium hydroxide (0.28 g, 6.71 mmol) was added to a solution of ester **6.6** (0.28 g, 1.34 mmol) in methanol : water (3 : 1, 10 mL) and the resulting reaction mixture was heated at reflux for 24 h. The methanol was then removed *in vacuo*, and the aqueous residue extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were washed with brine, dried over MgSO₄ and concentrated *in vacuo* to give a colourless oil. Purification by flash column chromatography using ethyl acetate : petroleum spirit (5 : 95) with 1% acetic acid as eluant gave the title compound **6.10** (0.11 g, 42%) as a colourless oil.

Method B: Freshly distilled propane thiol (0.70 mL, 7.72 mmol) was added to a degassed suspension of sodium hydride (0.24 g, 10 mmol) in HMPA (5 mL) at room temperature under nitrogen. The resulting reaction mixture was stirred for 2 h, then left to stand for 1h.

An aliquot of the thiolate solution prepared above (0.38 mL, 0.57 mmol) was added to a solution of ester **6.6** (0.039 g, 0.19 mmol) in HMPA (0.4 mL) at room temperature under nitrogen. The reaction mixture was stirred for 14 h, after which time ethyl acetate (5 mL) was added and the crude carboxylic acid was extracted with water : saturated sodium bicarbonate (2 : 1, 3 x 10 mL). The combined aqueous washings were treated with 1 M hydrochloric acid until pH 2 then the solution was extracted with ethyl acetate (4 x 5 mL). The combined organic extracts were washed with a saturated copper (II) chloride solution (2 x 5 mL), brine (5 mL) and dried over MgSO₄. Concentration of the organic phase *in vacuo* gave a yellow gum, which was purified by flash column chromatography on silica gel using ethyl acetate : petroleum spirit (1 : 9) as eluant to give the title compound **6.10** (0.031 g, 83%) as a colourless oil.

IR (thin film) cm^{-1} : 3000br (C-OH), 2923s (C-H), 1696s (C=O), 1447, 1404, 1294, 1277, 1244, 1164.

^1H NMR (300 MHz, CDCl_3) δ : 0.85-1.82 (m, 16H, H-2, H-3, H-4, H-4a, H-5, H-6, H-7, H-8, H-8a), 1.11 (s, 3H, 1- CH_3).

^{13}C NMR (75 MHz, CDCl_3) δ : 14.8 (1- CH_3), 21.0 (CH_2 , C-3), 26.4, 26.8, 28.4 (CH_2 , C-6, C-7 and C-8), 34.0, 34.9 (CH_2 , C-4 and C-5), 36.4 (CH , C-4a), 37.4 (CH_2 , C-2), 46.5 (C, C-1), 46.9 (CH , C-8a), 185.5 (1- CO_2H).

LRMS (m/z): 196 (M^+ , 63%), 178 (46), 151 (72), 123 (54), 110 (49), 96 (52), 95 (100).

HRMS: $\text{C}_{12}\text{H}_{20}\text{O}_2$ (M^+) requires 196.1463, found 196.1466.

(1*SR*, 4a*RS*, 8a*SR*)-decahydro-1-methylnaphthalen-1-amine (6.13)

Oxalyl chloride (0.13 mL, 1.50 mmol) was added to the dicarboxylic acid **6.10** (0.029 g, 0.15 mmol) in DCM (3 mL) at room temperature under nitrogen. After 1.5 h, analysis by IR spectroscopy revealed a peak at 1783 cm^{-1} , due to the formation of an acid chloride. The reaction mixture was concentrated *in vacuo* and dried under high vacuum for 5 min.

The crude acid chloride was taken up in THF (3 mL) and sodium azide (0.098 g 1.50 mmol) was added. The resulting reaction mixture was stirred for 18 h, after which time analysis by IR spectroscopy revealed the disappearance of the peak at 1783 cm^{-1} , and the formation of a peak at 2130 cm^{-1} , due to the formation of an acyl azide. The reaction mixture was then diluted with water (5 mL) and extracted with ethyl acetate (5 x 5 mL). The combined organic extracts were then dried over MgSO_4 and concentrated *in vacuo* to give the crude acyl azide **6.11** as a yellow oil.

Toluene (3 mL) was added to the crude acyl azide **6.11** and the resulting solution was heated to reflux for 15 min then cooled to room temperature. Analysis by IR spectroscopy revealed a new peak at 2256 cm^{-1} , and the disappearance of the peak at 2130 cm^{-1} , indicating that the desired isocyanate **6.12** had formed. Concentrated hydrochloric acid (0.3 mL) was then added to the isocyanate in toluene and the mixture

heated to 100 °C for 20 h. After cooling the solution to room temperature, the mixture was extracted with water (2 x 10 mL). The combined aqueous layers were treated with 10% aqueous sodium hydroxide until pH 10, then extracted with chloroform (3 x 15 mL). The combined organic extracts were dried over MgSO₄ and concentrated to give the title compound **6.13** (0.012 g, 48% over four steps) as a white wax.

IR (thin film) cm⁻¹: 3351br (NH₂), 2922 (C-H), 1715, 1598, 1448, 1378, 1260, 1171, 1092.

¹H NMR (300MHz, CDCl₃) δ: 0.76-1.85 (m, 18H, 1-NH₂, H-2, H-3, H-4, H-4a, H5, H-6, H-7, H-8, H-8a), 0.97 (s, 3H, 1-CH₃).

LRMS (m/z): 167 (M⁺, 18%), 149 (37), 124 (58), 105 (34), 81 (26), 70 (100).

HRMS: C₁₁H₂₁N (M⁺) requires 167.1674, found 167.1676.

(1*RS*, 2*RS*, 4*RS*, 4a*SR*, 10a*SR*, 1'*SR*) 4-(1'-Benzoyloxypropyl)-7-methoxy-1,2-methyl-3,4,4a,9,10,10a-hexahydrophenanthrene-1(2*H*)-amine (6.16)

Oxalyl chloride (0.11 mL, 1.30 mmol) was added to the dicarboxylic acid **4.2** (0.056 g, 0.13 mmol) in DCM (3 mL) at room temperature under nitrogen. After 1.5 h, analysis by IR spectroscopy revealed a peak at 1779 cm⁻¹, due to the formation of an acid chloride. The reaction mixture was concentrated *in vacuo* and dried under high vacuum for 5 min.

The crude acid chloride was taken up in THF (3 mL) and sodium azide (0.081 g 1.30 mmol) was added. The resulting reaction mixture was stirred for 18 h, after which time analysis by IR spectroscopy revealed the disappearance of the peak at 1779 cm⁻¹, and the formation of a peak at 2129 cm⁻¹, due to the formation of an acyl azide. The reaction mixture was then diluted with water (5 mL) and extracted with ethyl acetate (5

x 5 mL). The combined organic extracts were then dried over MgSO_4 and concentrated *in vacuo* to give the crude acyl azide **6.14** as a yellow oil.

Toluene (3 mL) was added to the crude acyl azide **6.14** and the resulting solution was heated to reflux for 15 min then cooled to room temperature. Analysis by IR spectroscopy revealed a new peak at 2259 cm^{-1} , and the disappearance of the peak at 2129 cm^{-1} , indicating that the desired isocyanate **6.15** had formed. Concentrated hydrochloric acid (0.3 mL) was then added to the isocyanate in toluene and the mixture heated to $100\text{ }^\circ\text{C}$ for 24 h. After cooling the solution to room temperature, the mixture was extracted with water (2 x 10 mL). The combined aqueous layers were treated with 10% aqueous sodium hydroxide until pH 10, then extracted with chloroform (3 x 15 mL). The combined organic extracts were dried over MgSO_4 and concentrated to give the title compound **6.16** (0.015 g, 29% over four steps) as a white wax and recovered isocyanate **6.15** (~0.04 g).

(1*RS*, 2*RS*, 4*RS*, 4*aSR*, 10*aSR*, 1'*SR*) 4-(1'-Benzoyloxypropyl)-7-methoxy-1,2-methyl-3,4,4*a*,9,10,10*a*-hexahydrophenanthrene-1(2*H*)-isocyanate (6.15)

IR (thin film) cm^{-1} : 2924 (C-H), 2260 (N=C=O), 1709, 1611, 1502, 1463, 1273.

^1H NMR (300 MHz, CDCl_3) δ : 0.87 (t, $J_{3',2'} = 7.2\text{ Hz}$, 3H, H-3'), 1.04 (d, $J = 5.7\text{ Hz}$, 3H, 2- CH_3), 1.11-2.59 (m, 13H, 1- CH_3 , H-2', H-3, H-2, H-10, H-10*a*, H-9), 3.12 (m, 1H, H-4), 3.42 (s, 3H, 7- OCH_3), 3.55 (m, 1H, H-4*a*), 5.57 (ddd, $J = 10.5\text{ Hz}$, $J = 8.1\text{ Hz}$, $J = 3.0\text{ Hz}$, 1H, H-1'), 5.99 (d, $J_{8,6} = 3.0\text{ Hz}$, 1H, H-8), 6.51 (dd, $J_{6,5} = 8.7\text{ Hz}$, $J_{6,8} = 3.0\text{ Hz}$, 1H, H-6), 7.16-7.42 (m, 6H, H-5, H-2'', H-3'', H-4'').

LRMS (m/z): 447 (M^+ , 65%), 404 (10), 316 (20), 282 (82), 240 (100), 228 (60), 225 (41).

HRMS: $\text{C}_{28}\text{H}_{33}\text{NO}_4$ (M^+) requires 447.2410, found 447.2406.

(1*RS*, 2*RS*, 4*RS*, 4*aSR*, 10*aSR*, 1'*SR*) 4-(1'-Benzoyloxypropyl)-7-methoxy-1,2-methyl-3,4,4*a*,9,10,10*a*-hexahydrophenanthrene-1(2*H*)-amine (6.16)

LRMS (m/z): 421 (M^+ , 10%), 404 (10), 282 (52), 240 (100), 225 (12), 105 (37).

HRMS: $C_{27}H_{35}NO_3$ (M^+) requires 421.2619, found 421.2617.

8.7 Chapter 6 Experimental

(±)-Dimethyl Isocycloamphilectane-7,20-dicarboxylate (6.1)

Dione **1.87** (0.028 g, 0.067 mmol) in MeOH (2 mL) was added to cerium (III) chloride heptahydrate (0.056 g, 0.15 mmol) under nitrogen. The solution was cooled to 0 °C, and sodium borohydride (0.01 g, 0.26 mmol) was added in four batches over 2 h, until TLC revealed the consumption of all starting material. The reaction was quenched with water and the methanol was removed *in vacuo*. The aqueous residue was extracted with ethyl acetate (3 x 10 mL), then the aqueous phase saturated with sodium chloride, and extracted with ethyl acetate (2 x 10 mL). The combined organic extracts were washed with brine (10 mL) and dried over $MgSO_4$. Concentration of the organic phase *in vacuo* gave the desired product as a mixture of four epimeric alcohols (0.028g), which was used directly in the next step without further purification.

The crude diols (0.028 g, 0.066 mmol) were dissolved in THF (3 mL) and Sodium bis(trimethylsilyl)amide (0.26 mL of a 1 M solution in THF, 0.26 mmol) was added at room temperature under nitrogen. The resulting reaction mixture was stirred for 2 h then carbon disulfide (0.016 mL, 0.26 mmol) was added. The reaction mixture was stirred for 2 h and then iodomethane (0.016 mL, 0.26 mmol) was added. After a further 2 h, the reaction was quenched with acetic acid (0.5 mL) and diluted with a saturated aqueous ammonium chloride solution, before extracting with ethyl acetate (4 x 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product as a mixture of four epimeric xanthates (~0.40 g), which was used directly in the next step without further purification.

The crude xanthate esters (~0.40 g, 0.066 mmol) were dissolved in toluene (3 mL) and tributyl tin hydride (0.071 mL, 0.26 mmol) was added under nitrogen. A catalytic amount of AIBN was added and the reaction mixture heated to 80 °C for 2.5 h, after which time starting material remained so excess tributyl tin hydride (0.03 mL, 0.11

mmol) and AIBN (catalytic) were added. After 1 h at 80 °C TLC revealed the consumption of all starting material. The toluene was removed *in vacuo* and the residue purified by flash column chromatography on silica gel using ethyl acetate : petroleum spirit (5 : 95) as eluant to give the title compound **6.1** (7.1 mg, 27% over 3 steps) as a white oil, and a mono-deoxygenated product (11 mg, 40% over 3 steps), which was recycled to give the title compound **6.1** (5.1 mg), (12.2 mg, 47% total yield of the title compound over three steps).

IR (thin film) cm^{-1} : 2925s (C-H), 1726s (C=O), 1456, 1260, 1160, 1097.

^1H NMR (600 MHz, CDCl_3) δ : 0.68 (ddd, $3xJ = 10.8$ Hz, 1H), 0.83 (d, $J = 6.6$ Hz, 3H, 17- CH_3), 0.86 (d, $J = 6.6$ Hz, 3H, 18- CH_3), 0.74-0.91 (m, 4H), 1.08 (s, 3H, 16- CH_3), 1.19 (s, 3H, 19- CH_3), 0.96-1.21 (m, 4H), 1.23-1.45 (m, 5H), 1.53-1.63 (m, 3H), 1.72-1.85 (m, 3H), 3.62 (s, 3H, 20- CO_2CH_3), 3.64 (s, 3H, 7- CO_2CH_3).

^{13}C NMR (150 MHz, CDCl_3) δ : 15.1 (16- CH_3), 17.4 (17- CH_3), 19.9 (18- CH_3), 23.4 (19- CH_3), 25.2 (CH_2), 27.2 (CH_2), 28.5 (CH_2), 36.7 (CH_2 and CH), 38.4 (CH_2), 40.5 (CH), 41.0 (CH), 42.7 (CH_2 , C-6), 45.0 (CH), 45.4 (CH), 46.2 (CH), 46.6 (C), 48.2 (CH), 50.2 (C), 50.3 (CH), 50.7 (CO_2CH_3), 51.7 (CO_2CH_3), 175.3 (20- CO_2CH_3), 179.1 (7- CO_2CH_3).

LRMS (m/z): 390 (M^+ , 25%), 330 (100), 271 (92), 217 (24), 201 (20), 149 (34), 81 (53), 69 (98).

HRMS: $\text{C}_{24}\text{H}_{38}\text{O}_4$ (M^+) requires 390.2770, found 390.2763.

($\pm$)-7-(2'-Methoxmethoxyethyl) 20-Methyl-isocycloamphilectan-7,20- dicarboxylate (6.2)

Dione **5.20** (0.019 g, 0.039 mmol) in MeOH (2 mL) was added to cerium (III) chloride heptahydrate (0.032 g, 0.085 mmol) under nitrogen. The solution was cooled to 0 °C, and sodium borohydride (0.006 g, 0.16 mmol) was added in four batches over 2 h, until TLC revealed the consumption of all starting material. The reaction was quenched with water and the methanol was removed *in vacuo*. The aqueous residue was extracted with ethyl acetate (3 x 10 mL), then the aqueous phase saturated with sodium chloride, and extracted with ethyl acetate (2 x 10 mL). The combined organic extracts were washed with brine (10 mL) and dried over MgSO₄. Concentration of the organic phase *in vacuo* gave the desired product as a mixture of four epimeric alcohols (0.019 g), which was used directly in the next step without further purification.

The crude diols (0.019 g, 0.038 mmol) were dissolved in THF (3 mL) and Sodium bis(trimethylsilyl)amide (0.23 mL of a 1 M solution in THF, 0.23 mmol) was added at room temperature under nitrogen. The resulting reaction mixture was stirred for 2 h then carbon disulfide (0.017 mL, 0.23 mmol) was added. The reaction mixture was stirred for 2 h and then iodomethane (0.014 mL, 0.23 mmol) was added. After a further 2 h, the reaction was quenched with acetic acid (0.5 mL) and diluted with a saturated aqueous ammonium chloride solution, before extracting with ethyl acetate (4 x 10 mL). The combined organic extracts were dried over MgSO₄ and concentrated *in vacuo* to give the crude product as a mixture of four epimeric xanthates (~0.03 g), which was used directly in the next step without further purification.

The crude xanthate esters (~0.03 g) were dissolved in toluene (3 mL) and tributyl tin hydride (0.049 mL, 0.18 mmol) was added under nitrogen. A catalytic amount of AIBN was added and the reaction mixture heated to 80 °C for 2.5 h, after which time starting material remained so excess tributyl tin hydride (0.025 mL, 0.09 mmol) and AIBN (catalytic) were added. After 1 h at 80 °C TLC revealed the consumption of all starting material. The toluene was removed *in vacuo* and the residue purified by flash column chromatography on silica gel using ethyl acetate : petroleum spirit (1 : 9) as eluant to give the title compound **6.2** (7 mg, 39% over 3 steps) as a white oil, and a mono-deoxygenated product (6 mg, 33% over 3 steps).

IR (thin film) cm⁻¹: 2926s (C-H), 1725s (C=O), 1459, 1382, 1255, 1230, 1157, 1042.

¹H NMR (300 MHz, CDCl₃) δ: 0.68 (ddd, 3xJ = 9.9 Hz, 1H), 0.83 (d, J = 6.0 Hz, 3H, 17-CH₃), 0.86 (d, J = 6.3 Hz, 3H, 18-CH₃), 1.09 (s, 3H, 16-CH₃), 1.19 (s, 3H, 19-CH₃), 0.73-1.43 (m, 12H), 1.51-1.67 (m, 4H), 1.72-1.84 (m, 3H), 3.36 (s, 3H, 2'-OCH₂OCH₃),

3.61 (s, 3H, 20-CO₂CH₃), 3.69-3.73 (m, 2H, 2'-H), 4.22-4.25 (m, 2H, 1'-H), 4.62 (s, 2H, 2'-OCH₂OCH₃).

¹³C NMR (75 MHz, CDCl₃) δ: 15.1 (16-CH₃), 17.4 (17-CH₃), 19.9 (18-CH₃), 23.4 (19-CH₃), 25.2 (CH₂), 27.2 (CH₂), 28.5 (CH₂), 36.7 (CH₂ and CH), 38.4 (CH₂), 40.5 (CH), 41.0 (CH), 42.7 (CH₂, C-6), 44.9 (CH), 45.4 (CH), 46.2 (CH), 46.6 (C), 48.2 (CH), 50.2 (C), 50.3 (CH), 50.7 (20-CO₂CH₃), 55.2 (2'-OCH₂OCH₃), 63.4 (CH₂, C-1'), 65.6 (CH₂, C-2'), 96.4 (2'-OCH₂OCH₃), 175.3 (20-CO₂CH₃), 178.5 (7-CO₂R).

LRMS (m/z): 464 (M⁺, 5%), 419 (15), 372 (10), 359 (12), 331 (31), 271 (100), 215 (15), 201 (15).

HRMS: C₂₇H₄₄O₆ (M⁺) requires 464.3138, found 464.3142.

(±)-Isocycloamphilectane-7,20-dicarboxylic Acid (1.62)

Method A:

Freshly distilled propane thiol (0.35 mL, 3.87 mmol) was added to a degassed suspension of sodium hydride (0.12 g, 5.0 mmol) in HMPA (2.5 mL) under nitrogen. The reaction mixture was stirred for 2 h then left to stand for 1 h at room temperature.

An aliquot of the thiolate solution prepared above (0.19 mL, 0.30 mmol) was added to a solution of diester **6.1** (0.015 g, 0.038 mmol) in HMPA (0.3 mL) at room temperature under nitrogen. The reaction mixture was stirred for 1.5 d, after which time ethyl acetate (5 mL) was added and the crude carboxylic acid was extracted with a solution of water and saturated sodium bicarbonate (2 : 1, 3 x 10 mL). The combined aqueous washings were treated with 1 M hydrochloric acid until pH 2, then the resulting mixture was extracted with ethyl acetate (4 x 5 mL). The combined organic extracts were washed with saturated copper (II) chloride solution (2 x 5 mL), brine and dried over MgSO₄. Concentration of the organic phase *in vacuo* gave a yellow gum, which was

purified by flash column chromatography on silica gel using ethyl acetate : petroleum spirit (1 : 4) as eluant to give the title compound **1.62** (0.012 g, 87%) as a white solid

Method B:

Lithium hydroxide (13 mg, 0.30 mmol) was added to ester **6.2** (7 mg, 0.015 mmol) in methanol : water (3 : 1, 4 mL) and the reaction mixture was heated at reflux for 24 h. The reaction mixture was cooled to room temperature and the methanol removed *in vacuo*. The aqueous residue was then extracted with ethyl acetate (3 x 5 mL) and the combined organic extracts dried over MgSO₄. Concentration of the organic phase *in vacuo* gave the crude mixture (~6 mg) as a colourless oil.

An aliquot of the thiolate solution prepared in method A (0.10 mL, 0.15 mmol) was added to a solution of crude mixture (~6 mg, 0.015 mmol) in HMPA (0.3 mL) at room temperature under nitrogen. The reaction mixture was stirred for 1.5 d, after which time ethyl acetate (5 mL) was added and the crude carboxylic acid was extracted with water : saturated sodium bicarbonate solution (2 : 1, 3 x 10 mL). The combined aqueous washings were treated with 1 M hydrochloric acid until pH 2 then the residue was extracted with ethyl acetate (4 x 5 mL). The combined organic extracts were washed with a saturated copper (II) chloride solution (2 x 5 mL), brine and dried over MgSO₄. Concentration of the organic phase *in vacuo* gave a yellow gum, which was purified by flash column chromatography on silica gel using ethyl acetate : petroleum spirit (1 : 4) as eluant to give the title compound **1.62** (~1 mg, ~20% over two steps) as a white solid.

m.p: decomposed at 280 °C

IR (thin film) cm⁻¹: 3200br (C-OH), 2924s (C-H), 1693s (C=O), 1456, 1379, 1261.

¹H NMR (600 MHz, CDCl₃) δ: 0.83 (d, *J* = 6.3 Hz, 3H, 17-CH₃), 0.88 (d, *J* = 6.6 Hz, 3H, 18-CH₃), 1.05 (s, 3H, 16-CH₃), 1.16 (s, 3H, 19-CH₃).

See dimethyl ester derivative **6.1** for full ¹H NMR characterisation.

^{13}C NMR (75 MHz, CDCl_3) δ : 14.9 (16- CH_3), 17.3 (17- CH_3), 19.8 (18- CH_3), 23.4 (19- CH_3), 25.1 (CH_2), 27.0 (CH_2), 28.4 (CH_2), 36.6 (CH_2), 36.7 (CH), 38.2 (CH_2), 40.2 (CH), 40.9 (CH), 42.7 (CH_2 , C-6), 44.9 (CH), 45.4 (CH), 46.0 (CH), 46.2 (C), 48.2 (CH), 49.8, 50.1, 178.4 (20- CO_2H), 182.1 (7- CO_2H).

LRMS (m/z): 362 (M^+ , 18%), 316 (100), 298 (12), 271 (75), 262 (50), 217 (43), 201 (25), 161 (20).

HRMS: $\text{C}_{22}\text{H}_{34}\text{O}_4$ (M^+) requires 362.2457, found 362.2465.

($\pm$)-Isocycloamphilectane-7,20-diamine (1.63)

Oxalyl chloride (0.072 mL, 0.83 mmol) was added to the dicarboxylic acid **1.62** (0.015 g, 0.041 mmol) in DCM (3 mL) at room temperature under nitrogen. After 3 h, analysis by IR spectroscopy revealed a peak at 1781 cm^{-1} , due to the formation of an acid chloride. The reaction mixture was concentrated *in vacuo* and dried under high vacuum for 5 min.

The crude acid chloride was taken up in THF (3 mL) and sodium azide (0.054 g 0.83 mmol) was added. The resulting reaction mixture was stirred for 18 h, after which time analysis by IR spectroscopy revealed the disappearance of the peak at 1781 cm^{-1} , and the formation of a peak at 2131 cm^{-1} , due to the formation of an acyl azide. The reaction mixture was then diluted with water (5 mL) and extracted with ethyl acetate (5 x 5 mL). The combined organic extracts were dried over MgSO_4 and concentrated *in vacuo* to give the crude acyl azide **6.17** as a yellow oil.

Toluene (3 mL) was added to the crude acyl azide **6.17** and the resulting solution was heated to reflux for 15 min then cooled to room temperature. Analysis by IR spectroscopy revealed a new peak at 2260 cm^{-1} , and the disappearance of the peak at 2131 cm^{-1} , indicating that the desired isocyanate **6.18** had formed. Concentrated hydrochloric acid (2 mL) was then added to the isocyanate in toluene and the mixture heated to $100\text{ }^\circ\text{C}$ for 18 h. After cooling the solution to room temperature, the mixture was extracted with water (2 x 10 mL). The combined aqueous layers were treated with

10% aqueous sodium hydroxide until pH 10, then extracted with chloroform (5 x 10 mL). The combined organic extracts were dried over MgSO_4 and concentrated to give the title compound **1.63** (4.70 mg, 39% over three steps) as a white solid, which was further purified by reverse-phase HPLC on C-18 stationary phase heated to 40 °C (5-100% acetonitrile and 100-5% water gradient containing 0.1% TFA),

IR (thin film) cm^{-1} : 3368br (N-H), 2920s (C-H), 1729, 1642, 1544, 1455, 1378, 1261, 1101.

^1H NMR (600 MHz, CD_3OD , measured on TFA salt) δ : 0.78 (m, 1H), 0.86 (ddd, $3\times J = 10.2$ Hz, 1H), 0.86-0.91 (m, 1H), 0.92 (d, $J = 6.6$ Hz, 3H), 0.95 (ddd, $3\times J = 10.2$ Hz, 1H), 1.03 (d, $J = 7.2$ Hz, 3H), 1.03 (m, 1H), 1.09-1.15 (m, 2H), 1.20-1.28 (m, 2H), 1.25 (s, 3H), 1.30-1.35 (m, 3H), 1.35 (s, 3H), 1.53-1.63 (m, 3H), 1.75 (m, 1H), 1.86-1.91 (m, 2H), 1.99 (m, 1H), 2.10 (m, 1H).

^{13}C NMR (200 MHz, CD_3OD) measured on TFA salt δ : 15.6, 18.0, 20.0, 22.2, 25.8, 26.1, 26.8, 37.6, 37.8, 38.6, 40.4, 41.9, 43.1, 46.8, 47.2, 48.2, 58.0, 60.4. Two peaks obscured by CD_3OD .

LRMS (m/z): 304 (M^+ , 32%), 289 (37), 256 (9), 221 (12), 204 (25), 105 (20), 84 (100).

HRMS: $\text{C}_{20}\text{H}_{36}\text{N}_2$ (M^+) requires 304.2878, found 304.2876.

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APPENDIX ONE

Organic Letters Publication

A Formal Total Synthesis of the Marine Diterpenoid Diisocyanoadociane

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ABSTRACT

A formal total synthesis of diisocyanoadociane, a marine diterpenoid with potent antimalarial properties, has been completed. The synthesis begins with a phenanthrenoid precursor that is transformed into a pyrene-derived intermediate by means of an intramolecular Michael reaction. Nitrogen functionality is introduced via a double Curtius reaction.

Numerous diterpenes based on a wide range of carbon skeletons possessing one or more isonitrile substituents have been isolated from marine sponges.¹ Many have been shown to have significant in vitro anti-malarial activity with the most potent being diisocyanoadociane (**1**), isolated originally from an *Amphimedon* species² and subsequently from *Cymbastela hooperi*.³ The combination of biological activity⁴ with the unusual pyrene-based structure **2** has aroused the interest of synthetic chemists, and an elegant enantioselective synthesis (60% ee) based on sequential Diels–Alder cycloadditions has been reported by Corey and Magriotis.⁵ In the final stages of their synthesis, however, the isonitrile groups were introduced without diastereochemical control. This intriguing molecule had also captured our attention, and we now disclose an alternative formal synthesis of (±)-**1** in which all 10 stereogenic centers have been introduced with complete diastereoselectivity.⁶ An outline of our strategy is

provided in Scheme 1 and begins with the proposed construction of the phenanthrene derived structure **3** as illustrated.⁷

Thus, Birch reductive alkylation, then Lewis acid induced cyclization, following earlier precedents, could be expected to furnish **3** in good yield.⁸ We envisaged completion of the pyrene structure by means of the intramolecular Michael reaction **7** → **8**, and in anticipation of this step we hoped to introduce a propionyl side chain into **3** by means of a

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(6) The numbering system of the parent structure, namely “isocycloamphilectane” (**2**) is based on its presumed biogenetic relationship to the amphilectane skeleton (cf. ref 1) and will be used throughout this Letter.

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Scheme 1

Friedel–Crafts-type acylation of the styrene double bond. To maintain stereochemical control in the introduction of the isonitrile groups, we planned to establish the quaternary centers at C-7 and C-20 by stereochemically controlled α -methylation of methoxycarbonyl or formyl substituents at these loci and then apply the Curtius rearrangement to the corresponding acyl azides.⁹ As illustrated in Figure 1, we

Figure 1. Stereocontrolled elaboration of the C-7 and C-20 quaternary centers.

expected simple alkylation at C-20 to proceed along the equatorial vector (steric control), whereas to achieve “axial” alkylation at C-7, we anticipated that the involvement of the C-6 carbonyl group (stereoelectronic control) would be necessary.¹⁰

Elaboration of these two centers would necessarily be under kinetic control, as would be the stereochemistry at C-8 following Li/NH_3 reduction of enone **6**. The remaining stereogenic centers, however, should be subjected to thermodynamic control by virtue of their relationship to carbonyl groups at C-2, C-6, and C-20, respectively, at the appropriate stage of the sequence.

The first stage of the synthesis is outlined in Scheme 2. Thus, Birch reduction of methyl 2-methoxy-5-methylbenzoate with lithium and in situ alkylation followed by $\text{BF}_3 \cdot \text{Et}_2\text{O}$ -induced cyclization afforded **3** in good yield. Then, AlCl_3 -catalyzed acylation of the styrene alkene bond with propionyl chloride afforded **4**, provided that this last reaction

was carried out at -78°C ; at higher temperatures, the newly formed carbonyl function underwent intramolecular cyclization onto the aromatic ring B. To reduce the styrene bond, **4** was submitted to reduction by lithium in liquid ammonia, affording hydroxy ketone **9**, a somewhat surprising result given the absence of a proton source (other than ammonia). The all-cis structure was provisionally assigned as indicated from extensive NMR studies and is consistent with subsequent analyses. After masking the hydroxyl as a MOM ether, the carbonyl function was reduced (LiAlH_4) to give an epimerically pure alcohol of unspecified configuration that was protected as the benzoate **10**. Hydroboration proved to be unsatisfactory for the introduction of oxygen at C-20, so we examined epoxidation with a view to subsequent rearrangement to the 20-one. When the MOM group was found to interfere with epoxidation, it was replaced by acetate, and then the reaction proceeded smoothly to afford **11** as a mixture of epimers. $\text{BF}_3 \cdot \text{Et}_2\text{O}$ -induced rearrangement then gave **12**, again as a mixture of diastereomers. However, subsequent base-catalyzed hydrolysis of the acetate function with concomitant loss of the superfluous angular substituent (retro-aldol as planned) led to a single diastereomer, presumed to be **13** in the expectation that the product would possess the more stable trans-fused ring system with the 16-methyl group equatorial. To elaborate the quaternary center at C-20, a Wittig reaction was carried out with methoxymethylenetriphenyl phosphorane, followed by hydrolysis to aldehyde **15**. C-Methylation of the aldehyde was unsuccessful, however, and so we abandoned the original strategy (Figure 1a) and submitted the enol ether **14** to a modified Simmons–Smith methylenation.¹¹ The resulting cyclopropane derivative **16** was then treated with acid at reflux to give the desired aldehyde **17**.¹² NMR analysis again established the stereochemical relationships between the substituents on ring-D, the most salient feature of which was the cis relationship between the formyl group and H-12 as established by NOE difference spectra. It was thus established that methylenation had taken place on the more exposed exo face, leading to the desired diastereomer.

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Scheme 2

The next stage of the synthesis, as outlined in Scheme 3, involved extensive functional group manipulation, including repeated lithium in ammonia reductions and establishment of the second quaternary center at C-7. Thus, aldehyde **17** was oxidized to acid **18** (NaClO_2 , 80% yield from **14**)¹³ and the benzoate group replaced with a TBDMS function, following which, Birch reduction and hydrolysis in acetic acid of the dihydroanisole product afforded the expected β,γ -unsaturated enone which could be isomerized by anhydrous HCl in THF to enone **20**. A second lithium/ammonia reduction with trapping of the resulting lithium enolate by methyl cyanoformate¹⁴ afforded a modest yield of the β -keto ester **21**, but C-methylation of this intermediate using a variety of bases gave none of the desired product.

Alternatively, enone **20** was simply reduced with Li/NH_3 to **22** and the isomeric enone **23** prepared using the Saegusa

Scheme 3

procedure.¹⁵ Subsequent acylation with methyl cyanoformate,¹⁶ followed by C-methylation, then proceeded in excellent yield to afford **24**. From model studies, we expected that removal of the TBDMS group with TBAF would almost certainly result in cyclization of the liberated hydroxyl onto the enone function. The enone was therefore reduced with $\text{NaBH}_4/\text{CeCl}_3$ ¹⁷ prior to deprotection. After desilylation, a double oxidation with the Dess–Martin periodinane¹⁸ afforded dione **25** in preparation for the pivotal Michael reaction (Scheme 4).

An inspection of molecular models indicated that the Michael reaction was unlikely to take place with **25** since it would require the D-ring to adopt a boat conformation to bring the participating functions within bonding distance, and even then orbital overlap between the reacting centers would be poor. It appeared that an α -configured side chain could assume the necessary geometry, however. When treatment of **25** with a variety of bases returned starting material, it seemed that the axially oriented side chain was more stable in the β -configuration, despite its axial nature. Nevertheless, one could expect there to be a sufficient amount of the α -epimer in equilibrium to undergo the desired cyclization. After extensive experimentation, it was found that heating a solution of **25** in ethanediol and triethylamine for 4 days at 70 °C effected cyclization, conditions that were selected in

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Scheme 4

view of those reported by Corey et al. for a difficult intramolecular Michael reaction during the synthesis of longifolene.¹⁹ No other solvent was effective, and unfortunately, trans-esterification of the 7-ester function with the glycol had occurred, resulting in a 4:3 mixture of **26** and **27**, complicating subsequent manipulations. After confirming the structure of the latter compound by single-crystal X-ray analysis,²⁰ the diketone was converted into the deoxy derivative **28** by applying the Barton–McCombie deoxygenation procedure to the dixanthate derived from the 2,6-diol.²¹ After protecting **26** as the MOM ether, this product was similarly deoxygenated. Demethylation of both ester

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groups in **28** was effected with sodium propanethiolate,²² while the deoxygenated ester from **26** was treated with lithium hydroxide to hydrolyze the C-7 ester function before liberating the C-20 carboxyl with propanethiolate. Preparation of the diacyl chloride and thence the diacyl azide **29** proceeded smoothly, as did the Curtius rearrangement to **30**, which was effected by heating in toluene at reflux.²³ Hydrolysis in *concd* HCl then afforded diamine **31**, which gave identical mass spectra as well as ^1H and ^{13}C NMR spectra (measured on the TFA salts) to those obtained from an authentic sample obtained by hydrolysis of **1**. Since **31** has been reconstituted to **1**,²⁴ the formal total synthesis of diisocyanoadociane (**1**) is complete. While all 10 stereogenic centers have been introduced with the correct relative stereochemistry, we have yet to address the question of enantioselectivity. However, the initial Birch reductive alkylation, if carried out on an appropriate chiral benzamide,²⁵ should resolve this remaining stereochemical issue.

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Supporting Information Available: Experimental details and copies of selected ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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APPENDIX TWO

X-Ray Crystal Structure Reports

Figure 1. Anisotropic displacement ellipsoid plot of $C_{23}H_{34}O_6$ with labelling of selected atoms. Ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

Figure 2. Unit cell packing diagram of $C_{23}H_{34}O_6$.solvate projected down the a axis. Hydrogen atoms have been deleted for clarity.

21 Feb 2005

Crystal structure of $C_{23}H_{34}O_6$.solvate -lnm041

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Abstract

The crystal structure of $C_{23}H_{34}O_6$.solvate is reported. The solvate is most probably methanol in 1:1 ratio with $C_{23}H_{34}O_6$.

Comment

The crystallographic asymmetric unit consists of one $C_{23}H_{34}O_6$ molecule and disordered molecules of solvation. The solvate molecules give rise to an infinite chain of atomic sites running through the unit cell in the *a* direction. The sample was recrystallized from methanol, so the electron density has been modelled assuming two disordered methanol molecules of half-occupancy. As C and O sites can not be differentiated, C atom sites of occupancy 0.58 (*i.e.* (8+6)/(6×4)) were used. These sites were refined with a common isotropic displacement parameter and with restraints on bonding distances.

In other structures we have successfully used the computer program SQUEEZE within PLATON to account for the electron density in ill-defined regions of the unit cell. [Sluis, P. van der and Spek, A. L. (1990) *Acta Crystallogr., Sect. A*, 46, 194–201.] In this case the program fails: when the solvate sites are omitted from the model, solvent accessible voids are located but no positive electron density is recovered.

H atoms of the $C_{23}H_{34}O_6$ molecule were included at calculated positions and ride on the atoms to which they are bonded. H atoms of the solvation molecules were not located.

The biggest peaks in the final difference electron density map are located within the disordered solvate channel.

Experimental

The compound was prepared by KAF and recrystallized from methanol. The sample ID is KF11181c.

Crystal data $\text{C}_{23}\text{H}_{34}\text{O}_6 \cdot \text{CH}_4\text{O}$ $M_r = 438.56$

Orthorhombic

 $Pbca$ $a = 5.9302(2) \text{ \AA}$ $b = 38.9317(13) \text{ \AA}$ $c = 20.6300(6) \text{ \AA}$ $V = 4762.9(3) \text{ \AA}^3$ $Z = 8$ $D_x = 1.211 \text{ Mg m}^{-3}$ D_m not measuredMo $K\alpha$ radiation $\lambda = 0.71073 \text{ \AA}$ *Data collection*

Nonius Kappa CCD diffractometer

 φ and ω scans with CCD

Absorption correction:

by integration *via* Gaussian method (Coppens, 1970) implemented in maXus (2000) $T_{\min} = 0.976$, $T_{\max} = 0.996$

31008 measured reflections

3740 independent reflections

Cell parameters from 89702 reflections

 $\theta = 3\text{--}24^\circ$ $\mu = 0.088 \text{ mm}^{-1}$ $T = 200 \text{ K}$

Plate

Colourless

 $0.38 \times 0.27 \times 0.05 \text{ mm}$

Crystal source: ?

2051 reflections with

 $I > 2.00\sigma(I)$ $R_{\text{int}} = 0.06$ $\theta_{\max} = 24.0^\circ$ $h = -6 \rightarrow 6$ $k = -35 \rightarrow 44$ $l = -23 \rightarrow 23$

every 0 reflections

frequency: 0 min

intensity decay: none

*Refinement*Refinement on F $R = 0.0683$ $wR = 0.0551$ $S = 0.9497$

2051 reflections

275 parameters

H-atom parameters not refined

Method, part 1, Chebychev polyno-

mial, (Watkin, 1994, Prince, 1982)

$$[\text{weight}] = 1.0/[A_0 * T_0(x) + A_1 * T_1(x) \dots + A_{n-1} * T_{n-1}(x)]$$
where A_i are the Chebychev coefficientslisted below and $x = F_{\text{calc}}/F_{\text{max}}$ Method= Robust Weighting (Prince, 1982) $W =$

$$[\text{weight}] * [1 - (\Delta F / 6 * \sigma F)^2]^2$$

$$A_i \text{ are:}$$

1.60 0.141 1.25

 $(\Delta/\sigma)_{\text{max}} = 0.084634$ $\Delta\rho_{\text{max}} = 0.38 \text{ e } \text{\AA}^{-3}$ $\Delta\rho_{\text{min}} = -0.39 \text{ e } \text{\AA}^{-3}$

Extinction correction: none

Scattering factors from *International Tables*
for *X-ray Crystallography* (Vol. IV)Table 1. *Selected geometric parameters* ($\text{\AA}$, $^\circ$)

O1—C20	1.200 (4)	C5—C6	1.499 (5)
O2—C20	1.343 (4)	C5—C18	1.528 (5)
O2—C21	1.445 (4)	C6—C7	1.523 (5)
O3—C2	1.209 (4)	C7—C8	1.512 (5)
O4—C6	1.216 (5)	C7—C16	1.549 (5)
O5—C10	1.462 (4)	C8—C9	1.531 (6)
O5—C22	1.397 (4)	C9—C10	1.526 (6)
O6—C22	1.416 (5)	C9—C19	1.522 (6)
O6—C23	1.421 (5)	C10—C11	1.525 (5)
C1—C2	1.529 (5)	C11—C12	1.531 (5)
C1—C14	1.552 (5)	C11—C16	1.532 (5)
C1—C17	1.550 (5)	C12—C13	1.511 (5)
C1—C20	1.519 (5)	C13—C14	1.532 (5)
C2—C3	1.501 (5)	C14—C15	1.533 (5)
C3—C4	1.529 (5)	C15—C16	1.529 (5)
C4—C5	1.554 (5)	C51—C52	1.467 (10)
C4—C15	1.542 (4)	C53—C54	1.452 (9)

C20—O2—C21	116.8 (3)	C7—C8—C9	111.7 (3)
C10—O5—C22	114.3 (3)	C8—C9—C10	111.1 (3)
C22—O6—C23	114.1 (3)	C8—C9—C19	110.9 (4)
C2—C1—C14	111.8 (3)	C10—C9—C19	113.6 (4)
C2—C1—C17	107.1 (3)	C9—C10—O5	109.8 (3)
C14—C1—C17	111.7 (3)	C9—C10—C11	111.6 (3)
C2—C1—C20	107.7 (3)	O5—C10—C11	109.0 (3)
C14—C1—C20	110.3 (3)	C10—C11—C12	112.6 (3)
C17—C1—C20	108.0 (3)	C10—C11—C16	113.2 (3)
C1—C2—O3	120.7 (3)	C12—C11—C16	109.4 (3)
C1—C2—C3	116.3 (3)	C11—C12—C13	110.8 (3)
O3—C2—C3	122.9 (3)	C12—C13—C14	111.1 (3)
C2—C3—C4	111.2 (3)	C13—C14—C1	112.4 (3)
C3—C4—C5	111.8 (3)	C13—C14—C15	110.7 (3)
C3—C4—C15	109.6 (3)	C1—C14—C15	114.2 (3)
C5—C4—C15	112.0 (3)	C4—C15—C14	110.7 (3)
C4—C5—C6	107.6 (3)	C4—C15—C16	111.7 (3)
C4—C5—C18	112.9 (3)	C14—C15—C16	110.1 (3)
C6—C5—C18	111.8 (3)	C11—C16—C7	110.8 (3)
C5—C6—O4	124.0 (4)	C11—C16—C15	112.1 (3)
C5—C6—C7	115.3 (3)	C7—C16—C15	111.5 (3)
O4—C6—C7	120.6 (4)	C1—C20—O2	111.0 (3)
C6—C7—C8	114.0 (3)	C1—C20—O1	126.6 (3)
C6—C7—C16	106.1 (3)	O2—C20—O1	122.4 (3)
C8—C7—C16	112.5 (3)	O6—C22—O5	113.2 (3)

H atoms bonded to C atoms of the $C_{23}H_{34}O_6$ molecule were included at calculated positions and ride on the atoms to which they are bonded. H atoms of the solvation molecules were not located.

Data collection: COLLECT (Nonius BV, 1997) . Cell refinement: Denzo/Scalepack (Otwinowski & Minor, 1996) . Data reduction: Denzo/Scalepack (Otwinowski & Minor, 1996) . Program(s) used to solve structure: *SIR92* (Altomare *et al.* 1994) . Program(s) used to refine structure: *CRYSTALS* (Watkin *et al.* 2003) . Molecular graphics: *ORTEP-II* (Johnson 1976) in *teXsan* (MSC, 1992–1997) . Software used to prepare material for publication: *CRYSTALS* (Watkin *et al.* 2003) .

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Supplementary data

Table S1. Fractional atomic coordinates and equivalent isotropic displacement parameters ($\text{\AA}^2$)

$U_{\text{eq}} = (1/3)\Sigma_i\Sigma_j U^{ij} a^i a^j \mathbf{a}_i \cdot \mathbf{a}_j$.					
	Occupancy	<i>x</i>	<i>y</i>	<i>z</i>	U_{eq}
O1	1.0000	0.9587 (4)	0.69060 (8)	0.34405 (13)	0.0484
O2	1.0000	0.6012 (4)	0.69338 (7)	0.37714 (11)	0.0399
O3	1.0000	0.8015 (4)	0.74467 (6)	0.46386 (12)	0.0391
O4	1.0000	0.2678 (5)	0.65959 (7)	0.70109 (14)	0.0515
O5	1.0000	0.2802 (4)	0.56099 (6)	0.55139 (13)	0.0440
O6	1.0000	0.2904 (5)	0.52300 (7)	0.46300 (15)	0.0579
C1	1.0000	0.8734 (6)	0.68447 (8)	0.45886 (16)	0.0269
C2	1.0000	0.8184 (6)	0.71809 (10)	0.49373 (16)	0.0295
C3	1.0000	0.7989 (6)	0.71619 (9)	0.56620 (16)	0.0326
C4	1.0000	0.6362 (6)	0.68777 (8)	0.58686 (15)	0.0274
C5	1.0000	0.6036 (7)	0.68691 (9)	0.66157 (16)	0.0341
C6	1.0000	0.4543 (7)	0.65696 (10)	0.67716 (17)	0.0365
C7	1.0000	0.5450 (7)	0.62203 (9)	0.65659 (17)	0.0343
C8	1.0000	0.4034 (8)	0.59204 (10)	0.67931 (19)	0.0468
C9	1.0000	0.4920 (8)	0.55787 (10)	0.6529 (2)	0.0466
C10	1.0000	0.5067 (6)	0.55854 (9)	0.57904 (18)	0.0368
C11	1.0000	0.6472 (6)	0.58878 (9)	0.55505 (17)	0.0333
C12	1.0000	0.6585 (7)	0.59061 (9)	0.48100 (18)	0.0381
C13	1.0000	0.8130 (6)	0.61926 (8)	0.45939 (17)	0.0347
C14	1.0000	0.7338 (6)	0.65397 (8)	0.48602 (16)	0.0267
C15	1.0000	0.7190 (6)	0.65300 (8)	0.56020 (16)	0.0258
C16	1.0000	0.5673 (6)	0.62340 (9)	0.58184 (16)	0.0292
C17	1.0000	1.1302 (6)	0.67831 (10)	0.46643 (19)	0.0368
C18	1.0000	0.5092 (8)	0.72049 (10)	0.68863 (18)	0.0441
C19	1.0000	0.3552 (9)	0.52787 (11)	0.6792 (2)	0.0635
C20	1.0000	0.8235 (6)	0.68957 (9)	0.38731 (18)	0.0316
C21	1.0000	0.5311 (7)	0.70077 (12)	0.31155 (18)	0.0480
C22	1.0000	0.1993 (8)	0.53034 (10)	0.5249 (2)	0.0545
C23	1.0000	0.1897 (9)	0.54188 (12)	0.4116 (2)	0.0628
C51	0.5800	0.252 (6)	0.5980 (9)	0.2473 (17)	0.214 (5)
C52	0.5800	0.489 (6)	0.5973 (8)	0.2272 (12)	0.214 (5)
C53	0.5800	0.346 (6)	0.6021 (9)	0.2608 (15)	0.214 (5)
C54	0.5800	0.587 (7)	0.5983 (7)	0.2706 (13)	0.214 (5)
H31	1.0000	0.7423 (6)	0.73871 (9)	0.58291 (16)	0.0391
H32	1.0000	0.9511 (6)	0.71139 (9)	0.58502 (16)	0.0391
H41	1.0000	0.4842 (6)	0.69270 (8)	0.56800 (15)	0.0329
H51	1.0000	0.7539 (7)	0.68418 (9)	0.68293 (16)	0.0409
H71	1.0000	0.7003 (7)	0.61933 (9)	0.67474 (17)	0.0412
H81	1.0000	0.4062 (8)	0.59126 (10)	0.72776 (19)	0.0562
H82	1.0000	0.2448 (8)	0.59538 (10)	0.66409 (19)	0.0562
H91	1.0000	0.6498 (8)	0.55438 (10)	0.6686 (2)	0.0560
H101	1.0000	0.5814 (6)	0.53678 (9)	0.56483 (18)	0.0442
H111	1.0000	0.8021 (6)	0.58429 (9)	0.57221 (17)	0.0400
H121	1.0000	0.5037 (7)	0.59486 (9)	0.46350 (18)	0.0457
H122	1.0000	0.7168 (7)	0.56829 (9)	0.46385 (18)	0.0457
H131	1.0000	0.9690 (6)	0.61453 (8)	0.47551 (17)	0.0416
H132	1.0000	0.8141 (6)	0.62023 (8)	0.41096 (17)	0.0416
H141	1.0000	0.5772 (6)	0.65828 (8)	0.46998 (16)	0.0320
H151	1.0000	0.8730 (6)	0.64890 (8)	0.57839 (16)	0.0310
H161	1.0000	0.4145 (6)	0.62799 (9)	0.56329 (16)	0.0350
H171	1.0000	1.1728 (6)	0.65644 (10)	0.44413 (19)	0.0441

H172	1.0000	1.2147 (6)	0.69788 (10)	0.44653 (19)	0.0441
H173	1.0000	1.1689 (6)	0.67664 (10)	0.51350 (19)	0.0441
H181	1.0000	0.4918 (8)	0.71847 (10)	0.73670 (18)	0.0529
H182	1.0000	0.6151 (8)	0.73972 (10)	0.67837 (18)	0.0529
H183	1.0000	0.3589 (8)	0.72523 (10)	0.66855 (18)	0.0529
H191	1.0000	0.4160 (9)	0.50586 (11)	0.6614 (2)	0.0762
H192	1.0000	0.3660 (9)	0.52751 (11)	0.7276 (2)	0.0762
H193	1.0000	0.1939 (9)	0.53053 (11)	0.6661 (2)	0.0762
H211	1.0000	0.3632 (7)	0.70304 (12)	0.31004 (18)	0.0576
H212	1.0000	0.6019 (7)	0.72275 (12)	0.29687 (18)	0.0576
H213	1.0000	0.5796 (7)	0.68165 (12)	0.28234 (18)	0.0576
H221	1.0000	0.0317 (8)	0.53201 (10)	0.5209 (2)	0.0654
H222	1.0000	0.2389 (8)	0.51109 (10)	0.5549 (2)	0.0654
H231	1.0000	0.2623 (9)	0.53536 (12)	0.3697 (2)	0.0754
H232	1.0000	0.2110 (9)	0.56703 (12)	0.4194 (2)	0.0754
H233	1.0000	0.0249 (9)	0.53654 (12)	0.4097 (2)	0.0754

Table S2. Anisotropic displacement parameters ($\text{\AA}^2$)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O1	0.0371 (16)	0.075 (2)	0.0332 (15)	0.0009 (15)	0.0088 (13)	0.0054 (15)
O2	0.0287 (14)	0.0677 (19)	0.0232 (14)	0.0010 (13)	-0.0013 (11)	0.0077 (13)
O3	0.0449 (15)	0.0381 (15)	0.0344 (14)	0.0025 (13)	0.0062 (13)	0.0071 (12)
O4	0.059 (2)	0.0481 (17)	0.0468 (17)	-0.0038 (16)	0.0211 (16)	-0.0062 (14)
O5	0.0424 (16)	0.0291 (14)	0.0604 (18)	-0.0053 (13)	0.0032 (14)	-0.0089 (13)
O6	0.066 (2)	0.0458 (17)	0.062 (2)	0.0085 (16)	-0.0060 (17)	-0.0146 (15)
C1	0.0265 (19)	0.029 (2)	0.0254 (19)	-0.0001 (16)	-0.0009 (15)	0.0008 (15)
C2	0.0207 (18)	0.035 (2)	0.032 (2)	0.0009 (18)	-0.0003 (16)	0.0059 (18)
C3	0.039 (2)	0.0273 (19)	0.031 (2)	-0.0007 (19)	-0.0036 (18)	-0.0008 (16)
C4	0.030 (2)	0.029 (2)	0.0233 (19)	-0.0016 (17)	-0.0019 (15)	0.0002 (15)
C5	0.048 (2)	0.032 (2)	0.0226 (19)	0.0017 (19)	-0.0011 (17)	-0.0036 (16)
C6	0.051 (3)	0.038 (2)	0.0204 (19)	-0.004 (2)	0.0001 (19)	-0.0011 (17)
C7	0.045 (2)	0.033 (2)	0.0248 (19)	-0.0015 (19)	-0.0004 (17)	0.0032 (17)
C8	0.072 (3)	0.038 (2)	0.031 (2)	-0.006 (2)	0.011 (2)	0.0037 (17)
C9	0.067 (3)	0.034 (2)	0.039 (2)	0.000 (2)	0.007 (2)	0.0071 (19)
C10	0.041 (2)	0.029 (2)	0.040 (2)	0.000 (2)	0.0016 (19)	-0.0013 (17)
C11	0.037 (2)	0.028 (2)	0.034 (2)	0.0001 (18)	-0.0039 (17)	-0.0004 (16)
C12	0.048 (2)	0.031 (2)	0.035 (2)	0.002 (2)	0.0073 (19)	-0.0062 (17)
C13	0.039 (2)	0.035 (2)	0.030 (2)	-0.0020 (19)	0.0064 (18)	-0.0039 (16)
C14	0.0276 (19)	0.0277 (19)	0.0246 (19)	-0.0023 (16)	0.0021 (16)	0.0007 (14)
C15	0.0258 (19)	0.028 (2)	0.0232 (19)	0.0011 (17)	-0.0032 (16)	0.0003 (14)
C16	0.034 (2)	0.029 (2)	0.0250 (19)	0.0028 (18)	-0.0020 (16)	-0.0012 (16)
C17	0.025 (2)	0.043 (2)	0.042 (2)	-0.0005 (17)	-0.0020 (17)	-0.0015 (19)
C18	0.065 (3)	0.033 (2)	0.034 (2)	-0.002 (2)	0.005 (2)	-0.0058 (18)
C19	0.104 (4)	0.039 (3)	0.048 (3)	-0.009 (3)	0.019 (3)	0.007 (2)
C20	0.028 (2)	0.037 (2)	0.029 (2)	0.0001 (18)	0.0004 (18)	-0.0008 (17)
C21	0.042 (2)	0.069 (3)	0.033 (2)	-0.009 (2)	-0.0087 (19)	0.012 (2)
C22	0.063 (3)	0.035 (2)	0.066 (3)	-0.012 (2)	0.004 (3)	-0.010 (2)
C23	0.069 (3)	0.062 (3)	0.058 (3)	0.000 (3)	-0.001 (3)	-0.007 (2)

Table S3. *Geometric parameters* ($\text{\AA}$, $^\circ$)

O1—C20	1.200 (4)	C10—H101	1.000
O2—C20	1.343 (4)	C11—C12	1.531 (5)
O2—C21	1.445 (4)	C11—C16	1.532 (5)
O3—C2	1.209 (4)	C11—H111	1.000
O4—C6	1.216 (5)	C12—C13	1.511 (5)
O5—C10	1.462 (4)	C12—H121	1.000
O5—C22	1.397 (4)	C12—H122	1.000
O6—C22	1.416 (5)	C13—C14	1.532 (5)
O6—C23	1.421 (5)	C13—H131	1.000
C1—C2	1.529 (5)	C13—H132	1.000
C1—C14	1.552 (5)	C14—C15	1.533 (5)
C1—C17	1.550 (5)	C14—H141	1.000
C1—C20	1.519 (5)	C15—C16	1.529 (5)
C2—C3	1.501 (5)	C15—H151	1.000
C3—C4	1.529 (5)	C16—H161	1.000
C3—H31	1.000	C17—H171	1.000
C3—H32	1.000	C17—H172	1.000
C4—C5	1.554 (5)	C17—H173	1.000
C4—C15	1.542 (4)	C18—H181	1.000
C4—H41	1.000	C18—H182	1.000
C5—C6	1.499 (5)	C18—H183	1.000
C5—C18	1.528 (5)	C19—H191	1.000
C5—H51	1.000	C19—H192	1.000
C6—C7	1.523 (5)	C19—H193	1.000
C7—C8	1.512 (5)	C21—H211	1.000
C7—C16	1.549 (5)	C21—H212	1.000
C7—H71	1.000	C21—H213	1.000
C8—C9	1.531 (6)	C22—H221	1.000
C8—H81	1.000	C22—H222	1.000
C8—H82	1.000	C23—H231	1.000
C9—C10	1.526 (6)	C23—H232	1.000
C9—C19	1.522 (6)	C23—H233	1.000
C9—H91	1.000	C51—C52	1.467 (10)
C10—C11	1.525 (5)	C53—C54	1.452 (9)
C20—O2—C21	116.8 (3)	C4—C5—H51	109.179
C10—O5—C22	114.3 (3)	C6—C5—H51	110.438
C22—O6—C23	114.1 (3)	C18—C5—H51	104.856
C2—C1—C14	111.8 (3)	C5—C6—O4	124.0 (4)
C2—C1—C17	107.1 (3)	C5—C6—C7	115.3 (3)
C14—C1—C17	111.7 (3)	O4—C6—C7	120.6 (4)
C2—C1—C20	107.7 (3)	C6—C7—C8	114.0 (3)
C14—C1—C20	110.3 (3)	C6—C7—C16	106.1 (3)
C17—C1—C20	108.0 (3)	C8—C7—C16	112.5 (3)
C1—C2—O3	120.7 (3)	C6—C7—H71	108.322
C1—C2—C3	116.3 (3)	C8—C7—H71	108.324
O3—C2—C3	122.9 (3)	C16—C7—H71	107.318
C2—C3—C4	111.2 (3)	C7—C8—C9	111.7 (3)
C2—C3—H31	109.032	C7—C8—H81	108.908
C4—C3—H31	109.034	C9—C8—H81	108.912
C2—C3—H32	109.039	C7—C8—H82	108.912
C4—C3—H32	109.038	C9—C8—H82	108.908
H31—C3—H32	109.466	H81—C8—H82	109.467
C3—C4—C5	111.8 (3)	C8—C9—C10	111.1 (3)
C3—C4—C15	109.6 (3)	C8—C9—C19	110.9 (4)
C5—C4—C15	112.0 (3)	C10—C9—C19	113.6 (4)
C3—C4—H41	108.747	C8—C9—H91	108.872
C5—C4—H41	106.134	C10—C9—H91	105.883
C15—C4—H41	108.479	C19—C9—H91	106.138
C4—C5—C6	107.6 (3)	C9—C10—O5	109.8 (3)
C4—C5—C18	112.9 (3)	C9—C10—C11	111.6 (3)
C6—C5—C18	111.8 (3)	O5—C10—C11	109.0 (3)

C9—C10—H101	107.658	C1—C17—H171	109.466
O5—C10—H101	110.354	C1—C17—H172	109.468
C11—C10—H101	108.473	H171—C17—H172	109.475
C10—C11—C12	112.6 (3)	C1—C17—H173	109.466
C10—C11—C16	113.2 (3)	H171—C17—H173	109.477
C12—C11—C16	109.4 (3)	H172—C17—H173	109.476
C10—C11—H111	104.624	C5—C18—H181	109.459
C12—C11—H111	108.725	C5—C18—H182	109.476
C16—C11—H111	108.075	H181—C18—H182	109.476
C11—C12—C13	110.8 (3)	C5—C18—H183	109.466
C11—C12—H121	109.137	H181—C18—H183	109.474
C13—C12—H121	109.135	H182—C18—H183	109.476
C11—C12—H122	109.129	C9—C19—H191	109.471
C13—C12—H122	109.133	C9—C19—H192	109.470
H121—C12—H122	109.467	H191—C19—H192	109.476
C12—C13—C14	111.1 (3)	C9—C19—H193	109.459
C12—C13—H131	109.074	H191—C19—H193	109.475
C14—C13—H131	109.068	H192—C19—H193	109.477
C12—C13—H132	109.072	C1—C20—O2	111.0 (3)
C14—C13—H132	109.075	C1—C20—O1	126.6 (3)
H131—C13—H132	109.467	O2—C20—O1	122.4 (3)
C13—C14—C1	112.4 (3)	O2—C21—H211	109.472
C13—C14—C15	110.7 (3)	O2—C21—H212	109.462
C1—C14—C15	114.2 (3)	H211—C21—H212	109.476
C13—C14—H141	108.301	O2—C21—H213	109.467
C1—C14—H141	104.336	H211—C21—H213	109.476
C15—C14—H141	106.325	H212—C21—H213	109.476
C4—C15—C14	110.7 (3)	O6—C22—O5	113.2 (3)
C4—C15—C16	111.7 (3)	O6—C22—H221	108.539
C14—C15—C16	110.1 (3)	O5—C22—H221	108.534
C4—C15—H151	107.306	O6—C22—H222	108.528
C14—C15—H151	109.035	O5—C22—H222	108.526
C16—C15—H151	107.892	H221—C22—H222	109.467
C11—C16—C7	110.8 (3)	O6—C23—H231	109.464
C11—C16—C15	112.1 (3)	O6—C23—H232	109.469
C7—C16—C15	111.5 (3)	H231—C23—H232	109.476
C11—C16—H161	107.447	O6—C23—H233	109.467
C7—C16—H161	108.041	H231—C23—H233	109.476
C15—C16—H161	106.657	H232—C23—H233	109.476

O1—C20—O2—C21	-3.4 (5)	C4—C15—C16—C7	-55.6 (4)
O1—C20—C1—C2	111.7 (4)	C4—C15—C16—C11	179.5 (3)
O1—C20—C1—C14	-126.1 (4)	C5—C4—C15—C14	176.1 (3)
O1—C20—C1—C17	-3.7 (5)	C5—C4—C15—C16	53.0 (4)
O2—C20—C1—C2	-67.6 (4)	C5—C6—C7—C8	173.7 (3)
O2—C20—C1—C14	54.7 (4)	C5—C6—C7—C16	-61.9 (4)
O2—C20—C1—C17	177.0 (3)	C6—C5—C4—C15	-53.0 (4)
O3—C2—C1—C14	-139.3 (3)	C6—C7—C8—C9	175.6 (3)
O3—C2—C1—C17	98.0 (4)	C6—C7—C16—C11	-177.3 (3)
O3—C2—C1—C20	-18.0 (5)	C6—C7—C16—C15	57.1 (4)
O3—C2—C3—C4	131.0 (4)	C7—C6—C5—C18	-175.4 (3)
O4—C6—C5—C4	-115.9 (4)	C7—C8—C9—C10	-55.8 (5)
O4—C6—C5—C18	8.7 (5)	C7—C8—C9—C19	176.9 (3)
O4—C6—C7—C8	-10.2 (5)	C7—C16—C11—C10	51.4 (4)
O4—C6—C7—C16	114.1 (4)	C7—C16—C11—C12	177.8 (3)
O5—C10—C9—C8	-66.2 (4)	C7—C16—C15—C14	-179.0 (3)
O5—C10—C9—C19	59.7 (4)	C8—C7—C16—C11	-52.0 (4)
O5—C10—C11—C12	-56.9 (4)	C8—C7—C16—C15	-177.6 (3)
O5—C10—C11—C16	67.8 (4)	C8—C9—C10—C11	54.7 (4)
O5—C22—O6—C23	-78.6 (4)	C9—C8—C7—C16	54.8 (4)
O6—C22—O5—C10	-78.0 (4)	C9—C10—O5—C22	-104.6 (3)
C1—C2—C3—C4	-52.0 (4)	C9—C10—C11—C12	-178.3 (3)
C1—C14—C13—C12	-173.9 (3)	C9—C10—C11—C16	-53.6 (4)
C1—C14—C15—C4	52.7 (4)	C10—C11—C12—C13	-175.8 (3)
C1—C14—C15—C16	176.7 (3)	C10—C11—C16—C15	176.7 (3)
C1—C20—O2—C21	175.9 (3)	C11—C10—O5—C22	132.9 (3)
C2—C1—C14—C13	-170.9 (3)	C11—C10—C9—C19	-179.4 (3)
C2—C1—C14—C15	-43.6 (4)	C11—C12—C13—C14	-58.3 (4)
C2—C3—C4—C5	-176.7 (3)	C11—C16—C15—C14	56.1 (4)
C2—C3—C4—C15	58.6 (4)	C12—C11—C16—C15	-56.9 (4)
C3—C2—C1—C14	43.6 (4)	C12—C13—C14—C15	57.1 (4)
C3—C2—C1—C17	-79.0 (4)	C13—C12—C11—C16	57.5 (4)
C3—C2—C1—C20	164.9 (3)	C13—C14—C1—C17	-50.8 (4)
C3—C4—C5—C6	-176.4 (3)	C13—C14—C1—C20	69.3 (4)
C3—C4—C5—C18	59.8 (4)	C13—C14—C15—C16	-55.2 (4)
C3—C4—C15—C14	-59.3 (4)	C15—C4—C5—C18	-176.8 (3)
C3—C4—C15—C16	177.6 (3)	C15—C14—C1—C17	76.4 (4)
C4—C5—C6—C7	60.1 (4)	C15—C14—C1—C20	-163.4 (3)
C4—C15—C14—C13	-179.2 (3)		

Sample: man0503a

Compound: $C_{24}H_{34}O_6$.

X-ray Structure Report

for

Kelly A. Fairweather and Lewis N. Mander

by

Anthony C. Willis

Research School of Chemistry, Institute of Advanced Studies

Australian National University, Canberra, ACT 0200, Australia

Thursday, 18th May 2005

Figure 1. Anisotropic displacement ellipsoid plot of $C_{24}H_{34}O_6$, with labelling of selected atoms. Ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

Figure 2. Unit cell packing diagram of $C_{24}H_{34}O_6$, projected down the b axis. Hydrogen atoms have been deleted for clarity.

18 May 2005

Crystal structure of $C_{24}H_{34}O_6$ –man0503a

KELLY A. FAIRWEATHER , LEWIS N. MANDER AND ANTHONY C. WILLIS

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Abstract

The crystal structure of $C_{24}H_{34}O_6$ is reported.

Comment

The crystallographic asymmetric unit consists of one $C_{24}H_{34}O_6$ molecule.

H atoms were observed in difference electron density maps prior to their inclusion. They were included at calculated positions and then refined positionally.

The final difference electron density map was generally featureless with peaks having no chemical significance.

Experimental

The compound was prepared by KAF and recrystallized from methanol. The sample ID is KFIX79c.

Crystal data $\text{C}_{24}\text{H}_{34}\text{O}_6$ $M_r = 418.53$

Monoclinic

 $P2_1/c$ $a = 16.5386 (2) \text{ \AA}$ $b = 6.21980 (10) \text{ \AA}$ $c = 21.3466 (3) \text{ \AA}$ $\beta = 96.1116 (7)^\circ$ $V = 2183.38 (5) \text{ \AA}^3$ $Z = 4$ $D_x = 1.273 \text{ Mg m}^{-3}$ D_m not measuredMo $K\alpha$ radiation $\lambda = 0.71073 \text{ \AA}$ *Data collection*

Nonius Kappa CCD diffractometer

 φ and ω scans with CCD

Absorption correction:

by integration *via* Gaussian method (Coppens, 1970) implemented in maXus (2000) $T_{\min} = 0.969$, $T_{\max} = 0.992$

43217 measured reflections

4962 independent reflections

Cell parameters from 32292 reflections

 $\theta = 3\text{--}27^\circ$ $\mu = 0.090 \text{ mm}^{-1}$ $T = 200 \text{ K}$

Plate

Colourless

 $0.40 \times 0.25 \times 0.09 \text{ mm}$

Crystal source: ?

3711 reflections with

 $I > 2.00\sigma(I)$ $R_{\text{int}} = 0.04$ $\theta_{\max} = 27.5^\circ$ $h = -21 \rightarrow 21$ $k = -7 \rightarrow 8$ $l = -27 \rightarrow 27$

every 0 reflections

frequency: 0 min

intensity decay: none

*Refinement*Refinement on F $R = 0.0343$ $wR = 0.0432$ $S = 1.0610$

3711 reflections

373 parameters

Only coordinates of H atoms refined

Method, part 1, Chebychev polyno-

mial, (Watkin, 1994, Prince, 1982)

[weight] = $1.0/[A_0 * T_0(x) + A_1 * T_1(x) \dots$
 $+ A_{n-1}] * T_{n-1}(x)$ where A_i are the Chebychev coefficientslisted below and $x = F_{\text{calc}}/F_{\text{max}}$ Method= Robust Weighting (Prince, 1982) $W =$ [weight] * $[1 - (\Delta F / 6 * \sigma F)^2]^2$ A_i are:

0.992 0.548 0.626

 $(\Delta/\sigma)_{\text{max}} = 0.002381$ $\Delta\rho_{\text{max}} = 0.29 \text{ e } \text{\AA}^{-3}$ $\Delta\rho_{\text{min}} = -0.18 \text{ e } \text{\AA}^{-3}$

Extinction correction: none

Scattering factors from *International Tables*

for X-ray Crystallography (Vol. IV)

Table 1. *Selected geometric parameters* ($\text{\AA}$, $^\circ$)

O1—C17	1.1991 (13)	C5—C19	1.5243 (17)
O2—C17	1.3392 (14)	C6—C7	1.5100 (15)
O2—C23	1.4383 (15)	C7—C8	1.5185 (16)
O3—C2	1.2130 (13)	C7—C16	1.5395 (13)
O4—C6	1.2124 (16)	C8—C9	1.5286 (16)
O5—C21	1.2049 (14)	C9—C10	1.5560 (14)
O6—C21	1.3421 (13)	C9—C20	1.5335 (17)
O6—C24	1.4418 (15)	C10—C11	1.5682 (13)
C1—C2	1.5344 (14)	C10—C21	1.5189 (14)
C1—C14	1.5560 (13)	C10—C22	1.5407 (14)
C1—C17	1.5297 (14)	C11—C12	1.5338 (13)
C1—C18	1.5420 (15)	C11—C16	1.5381 (13)
C2—C3	1.5055 (15)	C12—C13	1.5240 (14)
C3—C4	1.5345 (15)	C13—C14	1.5294 (13)
C4—C5	1.5495 (14)	C14—C15	1.5359 (13)
C4—C15	1.5380 (13)	C15—C16	1.5455 (13)
C5—C6	1.5185 (17)		

C17—O2—C23	116.55 (10)	C10—C9—C20	112.57 (9)
C21—O6—C24	116.72 (9)	C9—C10—C11	112.21 (8)
C2—C1—C14	110.92 (8)	C9—C10—C21	110.57 (9)
C2—C1—C17	106.90 (8)	C11—C10—C21	106.38 (8)
C14—C1—C17	109.87 (8)	C9—C10—C22	107.88 (9)
C2—C1—C18	106.89 (9)	C11—C10—C22	108.40 (8)
C14—C1—C18	112.83 (8)	C21—C10—C22	111.42 (8)
C17—C1—C18	109.22 (9)	C10—C11—C12	112.12 (8)
C1—C2—O3	121.20 (10)	C10—C11—C16	115.76 (8)
C1—C2—C3	116.10 (8)	C12—C11—C16	108.78 (8)
O3—C2—C3	122.67 (9)	C11—C12—C13	111.38 (8)
C2—C3—C4	112.17 (9)	C12—C13—C14	111.19 (8)
C3—C4—C5	111.14 (9)	C13—C14—C1	111.01 (8)
C3—C4—C15	110.88 (9)	C13—C14—C15	111.13 (8)
C5—C4—C15	111.12 (8)	C1—C14—C15	113.66 (8)
C4—C5—C6	107.11 (9)	C4—C15—C14	111.02 (8)
C4—C5—C19	114.06 (11)	C4—C15—C16	111.39 (8)
C6—C5—C19	111.80 (11)	C14—C15—C16	109.45 (8)
C5—C6—O4	122.51 (11)	C7—C16—C11	110.45 (8)
C5—C6—C7	115.26 (10)	C7—C16—C15	111.23 (8)
O4—C6—C7	122.16 (11)	C11—C16—C15	110.52 (8)
C6—C7—C8	113.31 (10)	C1—C17—O2	110.62 (8)
C6—C7—C16	109.31 (9)	C1—C17—O1	125.49 (10)
C8—C7—C16	110.57 (9)	O2—C17—O1	123.89 (10)
C7—C8—C9	111.59 (10)	C10—C21—O6	112.47 (9)
C8—C9—C10	114.43 (9)	C10—C21—O5	124.99 (10)
C8—C9—C20	109.98 (10)	O6—C21—O5	122.43 (10)

H atoms were refined positionally.

Data collection: COLLECT (Nonius BV, 1997) . Cell refinement: Denzo/Scalepack (Otwinowski & Minor, 1996) . Data reduction: Denzo/Scalepack (Otwinowski & Minor, 1996) . Program(s) used to solve structure: *SIR92* (Altomare *et al.* 1994) . Program(s) used to refine structure: *CRYSTALS* (Watkin *et al.* 2003) . Molecular graphics: *ORTEP-II* (Johnson 1976) in *teXsan* (MSC, 1992–1997) . Software used to prepare material for publication: *CRYSTALS* (Watkin *et al.* 2003) .

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Supplementary data

Table S1. *Fractional atomic coordinates and equivalent isotropic displacement parameters ($\text{\AA}^2$)*

$$U_{\text{eq}} = (1/3)\Sigma_i\Sigma_j U^{ij} a^i a^j \mathbf{a}_i \cdot \mathbf{a}_j.$$

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{eq}
O1	0.54043 (5)	1.06092 (15)	0.43004 (4)	0.0426
O2	0.51053 (5)	0.71520 (14)	0.40902 (4)	0.0352
O3	0.52369 (5)	0.89611 (16)	0.28110 (4)	0.0382
O4	0.16522 (7)	0.4199 (2)	0.18955 (5)	0.0658
O5	0.16307 (6)	0.27103 (14)	0.41668 (4)	0.0417
O6	0.13636 (5)	0.43413 (13)	0.50538 (4)	0.0316
C1	0.42590 (6)	0.97247 (17)	0.35339 (5)	0.0236
C2	0.45244 (6)	0.91753 (17)	0.28855 (5)	0.0268
C3	0.38542 (7)	0.8989 (2)	0.23529 (5)	0.0306
C4	0.31669 (6)	0.75032 (18)	0.25174 (5)	0.0258
C5	0.24762 (7)	0.7381 (2)	0.19680 (5)	0.0355
C6	0.18355 (7)	0.5860 (2)	0.21720 (5)	0.0373
C7	0.14735 (6)	0.6501 (2)	0.27648 (5)	0.0287
C8	0.08219 (7)	0.4962 (2)	0.29407 (5)	0.0359
C9	0.04325 (6)	0.5748 (2)	0.35170 (5)	0.0312
C10	0.10493 (6)	0.62843 (17)	0.40981 (5)	0.0229
C11	0.18140 (6)	0.75177 (16)	0.39091 (4)	0.0210
C12	0.25046 (6)	0.75844 (18)	0.44487 (5)	0.0254
C13	0.31970 (6)	0.90321 (18)	0.42883 (5)	0.0257
C14	0.35223 (6)	0.83192 (16)	0.36769 (4)	0.0208
C15	0.28384 (6)	0.82260 (16)	0.31312 (4)	0.0214
C16	0.21577 (6)	0.67137 (16)	0.33096 (4)	0.0214
C17	0.49871 (6)	0.92722 (18)	0.40200 (5)	0.0276
C18	0.40691 (7)	1.21522 (18)	0.35297 (6)	0.0306
C19	0.27599 (10)	0.6711 (4)	0.13403 (6)	0.0562
C20	-0.02270 (8)	0.4164 (3)	0.36748 (7)	0.0455
C21	0.13647 (6)	0.42360 (17)	0.44259 (5)	0.0255
C22	0.06142 (7)	0.77291 (19)	0.45432 (5)	0.0296
C23	0.57919 (9)	0.6494 (3)	0.45177 (8)	0.0491
C24	0.17421 (9)	0.2583 (2)	0.54145 (7)	0.0417
H31	0.3640 (9)	1.039 (3)	0.2264 (7)	0.0373
H32	0.4095 (9)	0.854 (2)	0.1959 (7)	0.0373
H41	0.3402 (8)	0.606 (2)	0.2581 (6)	0.0312
H51	0.2217 (9)	0.894 (3)	0.1924 (7)	0.0424
H71	0.1243 (9)	0.795 (2)	0.2671 (7)	0.0345
H81	0.1082 (10)	0.352 (3)	0.3022 (7)	0.0430
H82	0.0393 (9)	0.485 (3)	0.2584 (7)	0.0430
H91	0.0172 (9)	0.717 (2)	0.3387 (7)	0.0374
H111	0.1630 (8)	0.902 (2)	0.3812 (6)	0.0255
H121	0.2307 (8)	0.808 (2)	0.4854 (7)	0.0310
H122	0.2713 (8)	0.609 (2)	0.4528 (6)	0.0310
H131	0.3650 (8)	0.900 (2)	0.4649 (7)	0.0311
H132	0.2978 (8)	1.051 (2)	0.4237 (6)	0.0311
H141	0.3718 (8)	0.686 (2)	0.3738 (6)	0.0254
H151	0.2587 (8)	0.970 (2)	0.3058 (6)	0.0260
H161	0.2407 (8)	0.525 (2)	0.3394 (6)	0.0261
H181	0.4005 (9)	1.262 (2)	0.3952 (7)	0.0378
H182	0.4506 (9)	1.295 (2)	0.3380 (7)	0.0378
H183	0.3567 (9)	1.245 (2)	0.3256 (7)	0.0378
H191	0.2279 (12)	0.654 (3)	0.1037 (10)	0.0687
H192	0.3108 (12)	0.782 (3)	0.1179 (9)	0.0687

H193	0.3070 (13)	0.536 (3)	0.1395 (10)	0.0687
H201	−0.0463 (10)	0.447 (3)	0.4064 (9)	0.0550
H202	−0.0006 (11)	0.268 (3)	0.3701 (8)	0.0550
H203	−0.0658 (11)	0.410 (3)	0.3323 (8)	0.0550
H221	0.0978 (9)	0.810 (2)	0.4923 (7)	0.0364
H222	0.0141 (9)	0.701 (2)	0.4692 (7)	0.0364
H223	0.0417 (9)	0.902 (2)	0.4310 (7)	0.0364
H231	0.5796 (11)	0.489 (3)	0.4497 (8)	0.0580
H232	0.5738 (11)	0.701 (3)	0.4938 (9)	0.0580
H233	0.6286 (12)	0.698 (3)	0.4383 (8)	0.0580
H241	0.1852 (10)	0.300 (3)	0.5844 (9)	0.0499
H242	0.2242 (11)	0.221 (3)	0.5276 (8)	0.0499
H243	0.1399 (10)	0.132 (3)	0.5352 (8)	0.0499

Table S2. Anisotropic displacement parameters ($\text{\AA}^2$)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O1	0.0381 (5)	0.0440 (5)	0.0432 (5)	−0.0116 (4)	−0.0073 (4)	−0.0073 (4)
O2	0.0275 (4)	0.0354 (4)	0.0404 (4)	0.0023 (3)	−0.0072 (3)	−0.0010 (3)
O3	0.0266 (4)	0.0541 (5)	0.0353 (4)	−0.0018 (4)	0.0097 (3)	−0.0091 (4)
O4	0.0738 (7)	0.0825 (8)	0.0451 (6)	−0.0413 (7)	0.0245 (5)	−0.0359 (6)
O5	0.0602 (6)	0.0249 (4)	0.0412 (5)	0.0074 (4)	0.0100 (4)	−0.0033 (3)
O6	0.0356 (4)	0.0329 (4)	0.0263 (4)	0.0030 (3)	0.0039 (3)	0.0055 (3)
C1	0.0217 (4)	0.0258 (5)	0.0235 (4)	−0.0030 (4)	0.0032 (4)	−0.0027 (4)
C2	0.0263 (5)	0.0281 (5)	0.0269 (5)	−0.0038 (4)	0.0072 (4)	−0.0025 (4)
C3	0.0292 (5)	0.0407 (6)	0.0229 (5)	−0.0043 (5)	0.0068 (4)	−0.0003 (4)
C4	0.0255 (5)	0.0327 (5)	0.0197 (4)	−0.0026 (4)	0.0043 (4)	−0.0033 (4)
C5	0.0324 (5)	0.0546 (8)	0.0193 (5)	−0.0085 (5)	0.0022 (4)	−0.0033 (5)
C6	0.0337 (6)	0.0562 (8)	0.0217 (5)	−0.0116 (5)	0.0017 (4)	−0.0091 (5)
C7	0.0244 (5)	0.0410 (6)	0.0200 (5)	−0.0057 (4)	−0.0003 (4)	−0.0027 (4)
C8	0.0292 (5)	0.0530 (7)	0.0251 (5)	−0.0149 (5)	0.0008 (4)	−0.0077 (5)
C9	0.0228 (5)	0.0428 (6)	0.0277 (5)	−0.0065 (4)	0.0014 (4)	−0.0009 (5)
C10	0.0214 (4)	0.0243 (5)	0.0234 (4)	−0.0013 (4)	0.0036 (3)	−0.0007 (4)
C11	0.0207 (4)	0.0224 (5)	0.0199 (4)	−0.0010 (3)	0.0025 (3)	−0.0014 (3)
C12	0.0242 (5)	0.0333 (6)	0.0186 (4)	−0.0054 (4)	0.0024 (4)	−0.0029 (4)
C13	0.0238 (5)	0.0323 (6)	0.0210 (4)	−0.0058 (4)	0.0029 (4)	−0.0053 (4)
C14	0.0205 (4)	0.0221 (5)	0.0199 (4)	−0.0012 (4)	0.0021 (3)	−0.0017 (4)
C15	0.0212 (4)	0.0242 (5)	0.0187 (4)	−0.0003 (4)	0.0020 (3)	−0.0017 (4)
C16	0.0213 (4)	0.0240 (5)	0.0187 (4)	−0.0010 (4)	0.0014 (3)	−0.0025 (4)
C17	0.0230 (5)	0.0342 (5)	0.0260 (5)	−0.0043 (4)	0.0043 (4)	−0.0038 (4)
C18	0.0360 (6)	0.0239 (5)	0.0333 (6)	−0.0040 (4)	0.0094 (5)	−0.0008 (4)
C19	0.0503 (8)	0.0963 (13)	0.0232 (6)	−0.0253 (9)	0.0092 (6)	−0.0149 (7)
C20	0.0335 (6)	0.0675 (10)	0.0359 (6)	−0.0234 (6)	0.0052 (5)	−0.0074 (6)
C21	0.0249 (5)	0.0237 (5)	0.0283 (5)	−0.0041 (4)	0.0043 (4)	−0.0006 (4)
C22	0.0281 (5)	0.0296 (5)	0.0327 (5)	0.0019 (4)	0.0103 (4)	−0.0011 (4)
C23	0.0351 (7)	0.0547 (9)	0.0533 (8)	0.0061 (6)	−0.0144 (6)	0.0039 (7)
C24	0.0435 (7)	0.0401 (7)	0.0401 (7)	0.0032 (6)	−0.0020 (5)	0.0131 (6)

Table S3. Geometric parameters ($\text{\AA}$, $^\circ$)

O1—C17	1.1991 (13)	C10—C22	1.5407 (14)
O2—C17	1.3392 (14)	C11—C12	1.5338 (13)
O2—C23	1.4383 (15)	C11—C16	1.5381 (13)
O3—C2	1.2130 (13)	C11—H111	0.998 (13)
O4—C6	1.2124 (16)	C12—C13	1.5240 (14)
O5—C21	1.2049 (14)	C12—H121	1.006 (14)
O6—C21	1.3421 (13)	C12—H122	0.998 (15)
O6—C24	1.4418 (15)	C13—C14	1.5294 (13)
C1—C2	1.5344 (14)	C13—H131	1.016 (14)
C1—C14	1.5560 (13)	C13—H132	0.992 (14)
C1—C17	1.5297 (14)	C14—C15	1.5359 (13)
C1—C18	1.5420 (15)	C14—H141	0.965 (14)
C2—C3	1.5055 (15)	C15—C16	1.5455 (13)
C3—C4	1.5345 (15)	C15—H151	1.012 (13)
C3—H31	0.950 (16)	C16—H161	1.006 (13)
C3—H32	1.008 (15)	C18—H181	0.965 (15)
C4—C5	1.5495 (14)	C18—H182	0.960 (15)
C4—C15	1.5380 (13)	C18—H183	0.981 (15)
C4—H41	0.979 (14)	C19—H191	0.98 (2)
C5—C6	1.5185 (17)	C19—H192	0.98 (2)
C5—C19	1.5243 (17)	C19—H193	0.98 (2)
C5—H51	1.060 (16)	C20—H201	0.974 (18)
C6—C7	1.5100 (15)	C20—H202	0.991 (19)
C7—C8	1.5185 (16)	C20—H203	0.979 (18)
C7—C16	1.5395 (13)	C22—H221	0.985 (15)
C7—H71	0.992 (15)	C22—H222	0.983 (15)
C8—C9	1.5286 (16)	C22—H223	0.984 (15)
C8—H81	1.001 (17)	C23—H231	0.997 (19)
C8—H82	0.986 (16)	C23—H232	0.967 (19)
C9—C10	1.5560 (14)	C23—H233	0.944 (19)
C9—C20	1.5335 (17)	C24—H241	0.950 (18)
C9—H91	1.011 (15)	C24—H242	0.937 (18)
C10—C11	1.5682 (13)	C24—H243	0.969 (18)
C10—C21	1.5189 (14)		
C17—O2—C23	116.55 (10)	C6—C5—H51	107.9 (8)
C21—O6—C24	116.72 (9)	C19—C5—H51	109.4 (8)
C2—C1—C14	110.92 (8)	C5—C6—O4	122.51 (11)
C2—C1—C17	106.90 (8)	C5—C6—C7	115.26 (10)
C14—C1—C17	109.87 (8)	O4—C6—C7	122.16 (11)
C2—C1—C18	106.89 (9)	C6—C7—C8	113.31 (10)
C14—C1—C18	112.83 (8)	C6—C7—C16	109.31 (9)
C17—C1—C18	109.22 (9)	C8—C7—C16	110.57 (9)
C1—C2—O3	121.20 (10)	C6—C7—H71	104.5 (8)
C1—C2—C3	116.10 (8)	C8—C7—H71	110.9 (8)
O3—C2—C3	122.67 (9)	C16—C7—H71	108.0 (8)
C2—C3—C4	112.17 (9)	C7—C8—C9	111.59 (10)
C2—C3—H31	108.1 (9)	C7—C8—H81	107.7 (9)
C4—C3—H31	109.1 (9)	C9—C8—H81	110.9 (9)
C2—C3—H32	109.1 (8)	C7—C8—H82	109.0 (9)
C4—C3—H32	113.0 (8)	C9—C8—H82	108.3 (9)
H31—C3—H32	105.1 (12)	H81—C8—H82	109.3 (13)
C3—C4—C5	111.14 (9)	C8—C9—C10	114.43 (9)
C3—C4—C15	110.88 (9)	C8—C9—C20	109.98 (10)
C5—C4—C15	111.12 (8)	C10—C9—C20	112.57 (9)
C3—C4—H41	106.8 (8)	C8—C9—H91	105.2 (8)
C5—C4—H41	108.1 (8)	C10—C9—H91	104.8 (8)
C15—C4—H41	108.7 (8)	C20—C9—H91	109.3 (8)
C4—C5—C6	107.11 (9)	C9—C10—C11	112.21 (8)
C4—C5—C19	114.06 (11)	C9—C10—C21	110.57 (9)
C6—C5—C19	111.80 (11)	C11—C10—C21	106.38 (8)
C4—C5—H51	106.2 (8)	C9—C10—C22	107.88 (9)

C11—C10—C22	108.40 (8)	O2—C17—O1	123.89 (10)
C21—C10—C22	111.42 (8)	C1—C18—H181	109.5 (9)
C10—C11—C12	112.12 (8)	C1—C18—H182	110.5 (9)
C10—C11—C16	115.76 (8)	H181—C18—H182	108.4 (13)
C12—C11—C16	108.78 (8)	C1—C18—H183	110.4 (9)
C10—C11—H111	106.0 (7)	H181—C18—H183	109.3 (12)
C12—C11—H111	108.5 (7)	H182—C18—H183	108.8 (12)
C16—C11—H111	105.2 (7)	C5—C19—H191	107.9 (12)
C11—C12—C13	111.38 (8)	C5—C19—H192	111.2 (12)
C11—C12—H121	111.7 (8)	H191—C19—H192	108.0 (16)
C13—C12—H121	109.4 (8)	C5—C19—H193	109.5 (12)
C11—C12—H122	108.6 (8)	H191—C19—H193	111.3 (17)
C13—C12—H122	109.5 (8)	H192—C19—H193	108.8 (17)
H121—C12—H122	106.2 (11)	C9—C20—H201	114.9 (10)
C12—C13—C14	111.19 (8)	C9—C20—H202	110.1 (10)
C12—C13—H131	109.3 (8)	H201—C20—H202	108.1 (15)
C14—C13—H131	110.1 (8)	C9—C20—H203	109.5 (10)
C12—C13—H132	107.5 (8)	H201—C20—H203	109.7 (14)
C14—C13—H132	109.4 (8)	H202—C20—H203	103.9 (15)
H131—C13—H132	109.3 (11)	C10—C21—O6	112.47 (9)
C13—C14—C1	111.01 (8)	C10—C21—O5	124.99 (10)
C13—C14—C15	111.13 (8)	O6—C21—O5	122.43 (10)
C1—C14—C15	113.66 (8)	C10—C22—H221	111.2 (8)
C13—C14—H141	107.4 (8)	C10—C22—H222	112.0 (9)
C1—C14—H141	107.2 (7)	H221—C22—H222	106.2 (12)
C15—C14—H141	106.0 (8)	C10—C22—H223	108.4 (8)
C4—C15—C14	111.02 (8)	H221—C22—H223	111.4 (12)
C4—C15—C16	111.39 (8)	H222—C22—H223	107.7 (12)
C14—C15—C16	109.45 (8)	O2—C23—H231	105.3 (10)
C4—C15—H151	108.0 (7)	O2—C23—H232	110.5 (11)
C14—C15—H151	109.9 (7)	H231—C23—H232	112.2 (15)
C16—C15—H151	107.0 (7)	O2—C23—H233	111.5 (11)
C7—C16—C11	110.45 (8)	H231—C23—H233	107.1 (16)
C7—C16—C15	111.23 (8)	H232—C23—H233	110.2 (16)
C11—C16—C15	110.52 (8)	O6—C24—H241	109.7 (10)
C7—C16—H161	108.1 (7)	O6—C24—H242	111.4 (10)
C11—C16—H161	109.0 (7)	H241—C24—H242	106.7 (14)
C15—C16—H161	107.3 (7)	O6—C24—H243	109.0 (10)
C1—C17—O2	110.62 (8)	H241—C24—H243	113.7 (15)
C1—C17—O1	125.49 (10)	H242—C24—H243	106.4 (14)

O1—C17—O2—C23	-1.8 (2)	C5—C4—C15—C16	57.1 (1)
O1—C17—C1—C2	107.3 (1)	C5—C6—C7—C8	178.58 (9)
O1—C17—C1—C14	-132.3 (1)	C5—C6—C7—C16	-57.6 (1)
O1—C17—C1—C18	-8.0 (2)	C6—C5—C4—C15	-56.8 (1)
O2—C17—C1—C2	-72.2 (1)	C6—C7—C8—C9	-176.19 (9)
O2—C17—C1—C14	48.2 (1)	C6—C7—C16—C11	176.08 (9)
O2—C17—C1—C18	172.45 (9)	C6—C7—C16—C15	53.0 (1)
O3—C2—C1—C14	-135.6 (1)	C7—C6—C5—C19	-175.5 (1)
O3—C2—C1—C17	-15.8 (1)	C7—C8—C9—C10	-52.7 (1)
O3—C2—C1—C18	101.0 (1)	C7—C8—C9—C20	179.4 (1)
O3—C2—C3—C4	131.2 (1)	C7—C16—C11—C10	49.5 (1)
O4—C6—C5—C4	-118.0 (1)	C7—C16—C11—C12	176.81 (9)
O4—C6—C5—C19	7.6 (2)	C7—C16—C15—C14	-177.75 (8)
O4—C6—C7—C8	-4.5 (2)	C8—C7—C16—C11	-58.5 (1)
O4—C6—C7—C16	119.3 (1)	C8—C7—C16—C15	178.39 (9)
O5—C21—O6—C24	3.5 (2)	C8—C9—C10—C11	41.9 (1)
O5—C21—C10—C9	49.7 (1)	C8—C9—C10—C21	-76.7 (1)
O5—C21—C10—C11	-72.3 (1)	C8—C9—C10—C22	161.2 (1)
O5—C21—C10—C22	169.7 (1)	C9—C8—C7—C16	60.7 (1)
O6—C21—C10—C9	-134.08 (9)	C9—C10—C11—C12	-166.70 (9)
O6—C21—C10—C11	103.84 (9)	C9—C10—C11—C16	-41.1 (1)
O6—C21—C10—C22	-14.1 (1)	C10—C11—C12—C13	-172.53 (9)
C1—C2—C3—C4	-50.6 (1)	C10—C11—C16—C15	173.08 (8)
C1—C14—C13—C12	-176.96 (8)	C10—C21—O6—C24	-172.77 (9)
C1—C14—C15—C4	54.1 (1)	C11—C10—C9—C20	168.4 (1)
C1—C14—C15—C16	177.43 (8)	C11—C12—C13—C14	-56.5 (1)
C1—C17—O2—C23	177.7 (1)	C11—C16—C15—C14	59.2 (1)
C2—C1—C14—C13	-173.70 (8)	C12—C11—C10—C21	-45.7 (1)
C2—C1—C14—C15	-47.6 (1)	C12—C11—C10—C22	74.3 (1)
C2—C3—C4—C5	178.67 (9)	C12—C11—C16—C15	-59.7 (1)
C2—C3—C4—C15	54.5 (1)	C12—C13—C14—C15	55.5 (1)
C3—C2—C1—C14	46.1 (1)	C13—C12—C11—C16	58.1 (1)
C3—C2—C1—C17	165.91 (9)	C13—C14—C1—C17	68.3 (1)
C3—C2—C1—C18	-77.2 (1)	C13—C14—C1—C18	-53.8 (1)
C3—C4—C5—C6	179.26 (9)	C13—C14—C15—C16	-56.5 (1)
C3—C4—C5—C19	55.0 (2)	C15—C4—C5—C19	179.0 (1)
C3—C4—C15—C14	-56.6 (1)	C15—C14—C1—C17	-165.53 (8)
C3—C4—C15—C16	-178.81 (8)	C15—C14—C1—C18	72.3 (1)
C4—C5—C6—C7	58.9 (1)	C16—C11—C10—C21	79.9 (1)
C4—C15—C14—C13	-179.86 (8)	C16—C11—C10—C22	-160.15 (8)
C4—C15—C16—C7	-54.6 (1)	C20—C9—C10—C21	49.8 (1)
C4—C15—C16—C11	-177.67 (8)	C20—C9—C10—C22	-72.2 (1)
C5—C4—C15—C14	179.30 (9)		

Table S4. Contact distances ($\text{\AA}$)

O1...O1 ⁱ	3.483 (2)	O3...C3 ⁱⁱ	3.503 (2)
O1...C19 ⁱⁱ	3.527 (2)	O3...C4 ⁱⁱ	3.565 (1)
O3...C2 ⁱⁱⁱ	3.369 (1)	O4...C24 ^{iv}	3.368 (2)
O3...C18 ⁱⁱⁱ	3.387 (2)	O5...C11 ^v	3.296 (1)
O3...O3 ⁱⁱ	3.4390 (7)	O5...C13 ^v	3.445 (1)
O3...O3 ⁱⁱⁱ	3.4390 (7)	O5...C12 ^v	3.526 (1)
O3...C3 ⁱⁱⁱ	3.472 (2)	O6...C20 ^{vi}	3.585 (2)

Symmetry codes: (i) $1-x, 2-y, 1-z$; (ii) $1-x, \frac{1}{2}+y, \frac{1}{2}-z$; (iii) $1-x, y-\frac{1}{2}, \frac{1}{2}-z$; (iv) $x, \frac{1}{2}-y, z-\frac{1}{2}$; (v) $x, y-1, z$; (vi) $-x, 1-y, 1-z$.

Corrections

- Page xi LiHMDS = lithium hexamethyldisilazide
- Page 13 Scheme 1.3, replace CH₂Br with CH₂Br₂
- Page 14 Scheme 1.4, replace Cu(OT)₂ with Cu(OTf)₂
- Page 15 Replace R-CN at C-20 in structure **1.10** with R-NC
- Page 23 Replace Pd(OAc)₄ with Pd(OAc)₂, and also on page 53
- Page 32 Reduction of the alcohol function in **2.2** (MOM ether derivative) gave an epimerically pure alcohol of unspecified stereochemistry
- Page 67 Invert stereochemistry at C-8 in structures **5.1** and **5.2**, table 5.1
- Page 73 Figure 5.5, replace C-12 with C-13
- Page 74 line 7, replace 3.2 Hz with 13.2 Hz