University of Sussex

Studies towards the Total Synthesis of Herbimycin A

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School of Life Sciences
Department of Chemistry
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This thesis is dedicated to my mother Hélène Roche Favier and to my grand-mothers Jacqueline Rey Roche and Andrée Reynaud Favier, for their unconditional love and support, and their wonderful recipes!

I hereby declare that this thesis has not been submitted, either in the same or different form, to this or any other University for a degree.

Signature:

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ABSTRACT

Herbimycin A (1) belongs to the ansamycin family and is a 19-membered lactam with seven stereogenic centres, making it a synthetic challenge, which was first isolated in 1979 by Omura *et al.* Herbimycin A (1) exhibits a broad spectrum of biological activities: herbicidal, inhibitor of angiogenesis and of the maturation of growth factor receptor tyrosine kinases.

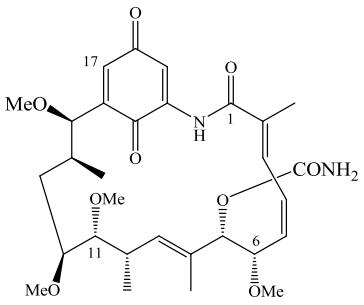

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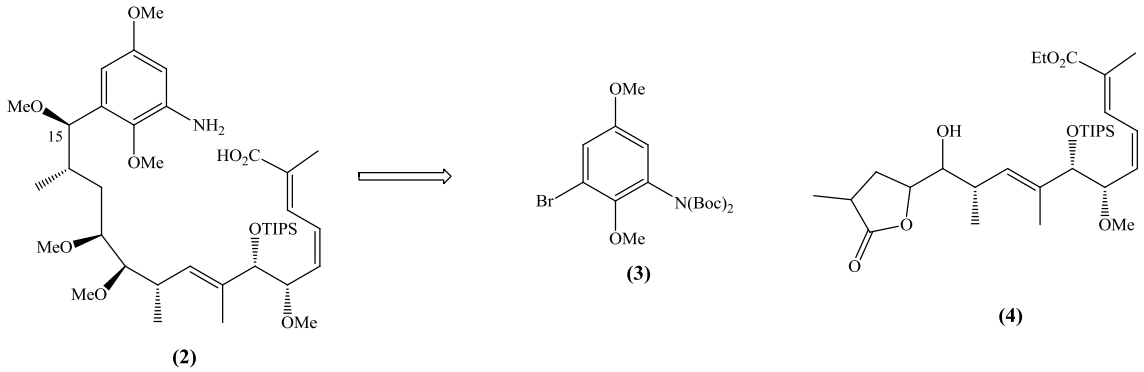
Figure 1 - Herbimycin A

Since its discovery, only three total syntheses of Herbimycin A **(1)** have been described in the literature, along with the syntheses of advanced fragments.

This thesis describes a new route to Herbimycin A **(1)**, using a wide range of chemical reactions than those used in the previous routes from the literature.

The main idea is to split Herbimycin A **(1)** into an aromatic fragment and an aliphatic fragment as shown below in Scheme 1.



Scheme 1 - Retrosynthesis highlighting both aromatic and aliphatic fragments

The synthesis of aliphatic fragment **(4)** follows up the work of Ansell and Pietsch, past members of the Parsons group.

Interesting results could be obtained and a wide range of Organic Chemistry reactions could be investigated.

ABBREVIATIONS

Ac	Acetyl
AHBA	3-amino-5-hydroxybenzoic acid
AIBN	Azobisisobutyronitrile
Aq	Aqueous
Ar	Aromatic
ATP	Adenosine triphosphate
BHT	Butylated hydroxytoluene
Bn	Benzene
Boc	Tert-butoxycarbonyl
BOP	Bis(2-oxo-2oxazolidinyl)-phosphinic
Bu	Butyl
c	Concentration
C	Carbon
CAN	Ceric ammonium nitrate
cat	catalytic
Conc.	Concentrated
^{13}C NMR	Carbon Nuclear Magnetic Resonance
Cp	Cyclopentadienyl
CSA	Camphorsulfonic acid
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DHQ	3-Dehydroquinic acid
DIBALH	Diisobutylaluminium Hydride
DIPEA	*N*,*N*-Diisopropylethylamine

DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
DMP	Dess-Martin Periodinane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMS	Dimethyl Sulfide
DMSO	Dimethyl Sulfoxide
DNA	Deoxyribonucleic acid
dr	diastereoisomeric ratio
EAC	Ehrlich ascites carcinoma
ee	enantiomeric excess
Eq.	Equivalents
EI	Electron ionization
ER	Endoplasmic reticulum
ESI	Electrospray ionization
Et	Ethyl
g	gram
h	hour
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
^{1}H NMR	Hydrogen Nuclear Magnetic Resonance
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HSP	Heat Shock Protein
IBX	2-iodoxybenzoic acid
IC	Inhibitory concentration
Imid	Imidazole
Ipc	Isopinocampheyl
IR	Infrared
L	Litre
LDA	Lithium diisopropylamide
LHMDS	Lithium bis(trimethylsilyl)amide

LRMS	Low resolution mass spectrometry
M	Molar
Me	Methyl
min	minutes
Mol	Mole(s)
MW	Molecular Weight
NBS	*N*-Bromosuccinimide
NMO	*N*-Methylmorpholine-*N*-oxide
NRK	Normal rat kidney
PDC	Pyridinium dichromate
PG	Protecting Group
Ph	Phenyl
PKS	Polyketide Synthase
ppm	part per million
PPTS	Pyridinium *p*-toluenesulfonate
Pr	Propyl
Py	Pyridine
quant.	quantitative
RCM	Ring Closure Metathesis
RNA	Ribonucleic acid
rt	Room Temperature
s	Singlet
sat.	Saturated
SRC	Sarcoma
t	Triplet
TBAF	Tetra-butylammonium fluoride
TBDPS	*Tert*-butyl diphenyl silyl
TBS	*Tert*-butyl dimethyl silyl
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl) oxidanyl
Tf	Triflate
TFA	Trifluoroacetic acid

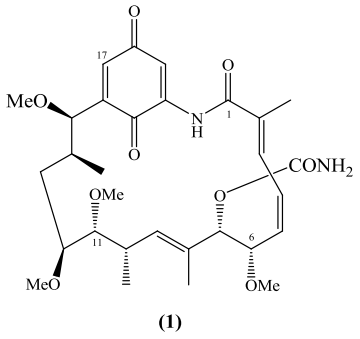
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
THP	Tetrahydropyran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
TMV	Tobacco mosaic virus
Tol	Toluene
TPAP	Tetrapropylammonium perruthenate
Tr	Trityl
ts	Temperature-sensitive
Ts	Tosyl

CHAPTER 1

HERBIMYCIN A

I. The Ansamycin Antibiotics

Herbimycin A **(1)** belongs to the family of the ansamycin macrolide antibiotics. Ansamycins are named so, because of their basket-like molecular architecture, being benzenoid or naphthalenoid aromatic compounds in which non-adjacent positions are linked by a polyketide derived aliphatic chain (Latin: ansa = handle) to form a cyclic structure[1].



(1)

Figure 2 - Herbimycin A **(1)**

One of the aliphatic-aromatic junctions is always an amide bond. These macrolactams are an interesting synthetic challenge as they contain many chiral centres.

Herbimycin A **(1)** was isolated in 1979 by Omura and co-workers from the fermentation broth of *Streptomyces hygroscopicus* strain AM-3672[2,3] pictured in Figure 3.

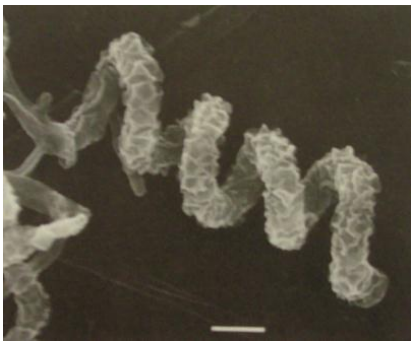
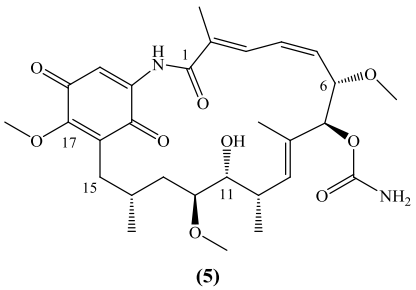


Figure 3 - *Streptomyces hygroscopicus* AM-3672[3]

It was discovered, based on detailed spectroscopic analyses[4,5] that herbimycin A **(1)** was a 19-membered lactam ring with seven stereogenic centres, a carbamate, an isolated trisubsituted (*E*)-double bond, and (*E,Z*)-diene plus a benzoquinone ring system.

The first ansamycin shown to contain a benzoquinone moiety was geldanamycin **(5)** and was isolated for the first time in 1970 from *Streptomyces hygroscopicus var*[6].



(5)

Figure 4 - Geldanamycin **(5)**

It was worth noting that several ansamycins such as herbimycin B[7] **(6)** and C[8] **(7)**, the dihydroherbimycins A[9] **(8)** and C[11] **(9)**, as well as macbecin[10] I **(10)** and II **(11)**, have a close structure to herbimycin A **(1)**.

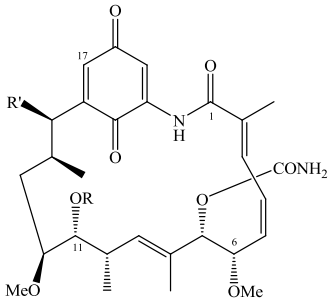


Figure 5 - The herbimycins

Herbimycin A **(1)** R=Me, R'=OMe

Herbimycin B **(6)** R=H, R'= H

Herbimycin C **(7)** R=Me, R'=H

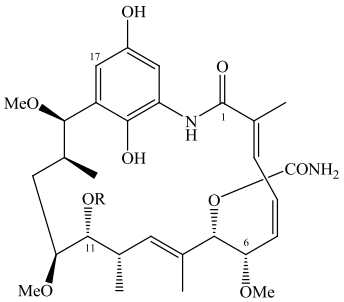


Figure 6 - The dihydroherbimycins

Dihydroherbimycin A **(8)** R= Me

Dihydroherbimycin C **(9)** R=H

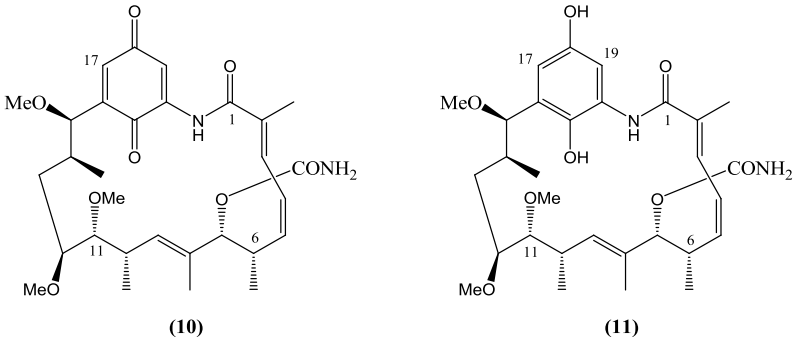
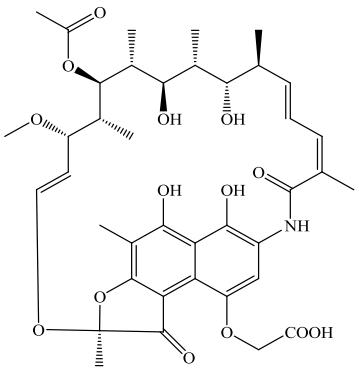


Figure 7 - Macbecin I **(10)** and macbecin II **(11)**

The natural ansamycins are split in different groups according to the nature of the aromatic moiety and the length of the aliphatic chain. Each group exhibits different biological activities.

The main prominent ones containing a naphthalenoid part and a 17-C atom chain, show selective antibacterial activity and inhibit RNA polymerase. The rifamycins, such as rifamycin B **(12)** are of clinical importance[11].



(12)

Figure 8 - Rifamycin B **(12)**

The benzenoid ansamycins with a 15-C chain include the ansamitocins, for instance, ansamitocin P-3 **(13)**, along with the maytansine[12] **(14)** known for their anti-tumour activity[13].

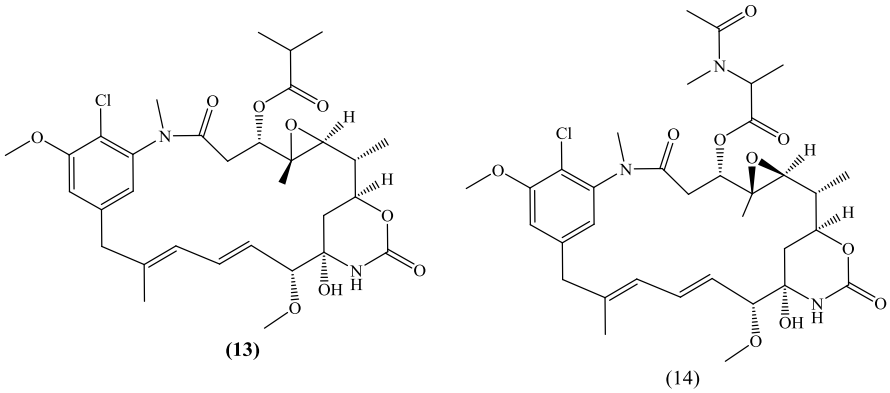


Figure 9 - Ansamitocin **(13)** and maytansine **(14)**

II. Biological Activity

1. Herbicidal activity

The herbicidal activity of herbimycin A **(1)** was tested by planting seeds of various monocotyledonous and dicotyledonous plants[2,7]. Two systems were used in treatments with herbimycin A **(1)**. The pre-emergence system was conducted before germination of the seeds and the post-emergence, 1 to 2 weeks after germination by foliar spraying. Herbicidal effects were examined after treatment with herbimycin A **(1)** and evaluated. As shown in Table 1, herbimycin A **(1)** was found to exhibit potent herbicidal activity against most mono- and di-cotyledonous plants.

	Test Plant	Pre-emergence system* (g/area)				Post-emergence system* (g/area)		
		100	50	25	12.5	100	50	25
Monocotyledon	*Oryza sativa*	2	1	1	0	0	0	0
	Echinochola crus-galli	5	5	5	4			
	Digitaria adescendens	5	5	5	4	5	4	4
	Cyperus microiria	5	5	5	5	5	5	5
Dicotyledon	*Chenopodium ficifolium*	5	5	5	4	5	5	5
	Portulaca oleracea	5	5	5	4	4	4	3
	Galinsoga ciliata	5	5	5	4	4	3	2
	Rorippa atrovirens	5	5	4	4	5	4	3

*0 = no activity; 1 = less than 20%; 2 = 20 to 40%; 3 = 40 – 70%; 4 = 70 - 90% and 5 = 90-100%.

Table 1 - Herbicidal activity of herbimycin A **(1)**

2. Anti-tobacco mosaic virus activity

Iwai and co-workers observed that both herbimycin A **(1)** and B **(6)**, macbecin I **(10)** and geldanamycin **(5)** had activities against anti-tobacco mosaic virus (TMV). TMV, one of the simplest viruses known, is an RNA virus that causes mosaic disease in tobacco and similar effects in other plants.

Figure 10 - Tobacco mosaic virus - Systemic infections of Nicotiana tabacum cv. Turk plants showing TMV-associated mosaic[14] (Photo: Karen-Beth G. Scholthof).

The obtained results of the study are compared in Table 2.

Antibiotic	Concentration (ppm)	Inhibition (%)
Herbimycin A **(1)**	25.0	95
	12.5	90
	6.2	92
	3.1	85
Herbimycin B **(6)**	25.0	100
	12.5	93
	6.2	88
	3.1	58
Geldanamycin **(5)**	25.0	99
	12.5	98
	6.2	98
	3.1	30
Macbecin I **(10)**	25.0	53

Table 2. Anti-TMV activity of herbimycins, geldanamycin and macbecin I

This finding was new in a sense that no ansamycin antibiotic had previously been reported to have herbicidal activity.

3. Inhibition of macromolecular synthesis in ts/NRK cells

Herbimycin A **(1)** was later on re-isolated as an active substance which reversed the transformed morphology of temperature-sensitive Rous sarcoma virus-infected rat cells (ts/NRK) to the normal morphology at a permissive temperature (33°C)[15].

Rous sarcoma virus is an oncogenic virus, that is, a virus capable of causing a sarcoma cancer.

Uehara and his team[16] showed that Herbimycin A **(1)** inhibited DNA synthesis with little or no inhibition of RNA and protein syntheses at the concentrations corresponding to their IC_{50}.

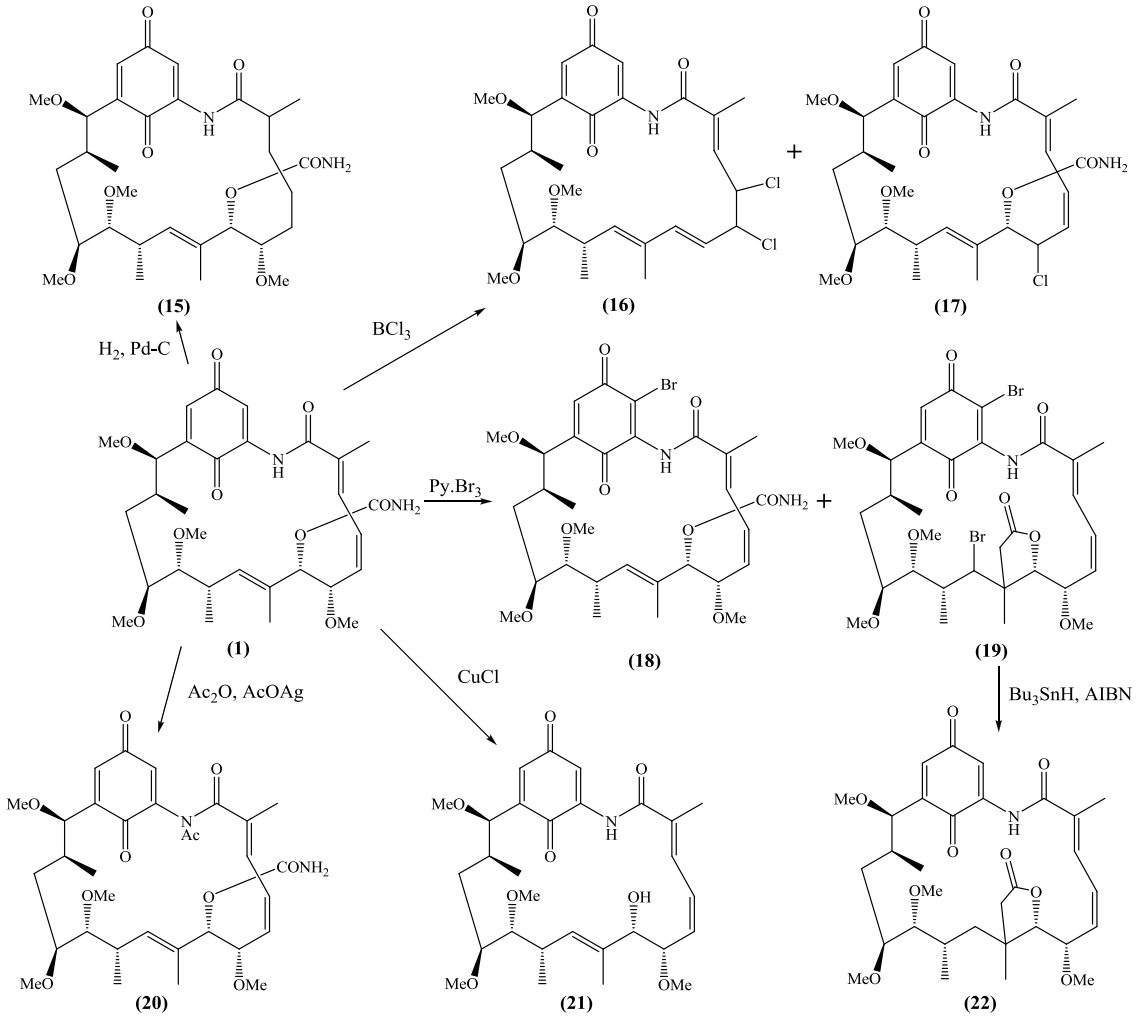
	Inhibition (%)
DNA	85.5
RNA	7.0
Protein	11.0

Table 3. Effect of herbimycin A **(1)** on macromolecular syntheses in ts/NRK cells

4. Chemical modification and antitumor activity

Several halogenated and other analogues have been synthesized, and evaluated *in vivo* regarding their activities against Ehrlich ascites carcinoma[17,18]. Ehrlich ascites carcinoma (EAC) is one of the commonest experimental tumors. EAC is referred to as an undifferentiated carcinoma which has high transplantable capability, no-regression, rapid proliferation, shorter life span, 100% malignancy and also does not have tumor-specific transplantation antigen (TSTA)[19].

EAC is similar to human tumours which are the most sensitive to chemotherapy as they are undifferentiated and as they present a rapid growth rate.


(15)
(16)
(17)
(1)
(18)
(19)
(20)
(21)
(22)
H2, Pd-C
BCl3
Py.Br3
Ac2O, AcOAg
CuCl
Bu3SnH, AIBN

Scheme 2

Some derivatives showed to be even more active than Herbimycin A (1).

Compound	Total dose (mg/kg)	Dose (mg/kg x day)	T / C (%)	Number of living*/total
Herbimycin A **(1)**	6.3	1.3 x 5	126	1/4
1 **(15)**	125	25.0 x 5	193	3/4
2 **(16)**	250	50.0 x 5	215	4/4
3 **(17)**	125	12.5 x 5	200	4/4
4 **(18)**	250	50.0 x 5	190	4/4
5 **(19)**	125	25.0 x 5	134	1/4
6 **(20)**	125	25.0 x 5	89	0/4
7 **(21)**	250	50.0 x 5	200	3/4
8 **(22)**	250	50.0 x 5	150	2/4

*Number of surviving mice at day 31.

Table 4. Antitumor activity of Herbimycin A analogues against Ehrlich ascites carcinoma

As you can notice from Table 4, the derivatives modified at the 4, 5, 6, and 7-positions of the *ansa*-chain showed particularly high activities.

5. Mechanism of anti-proliferative and anti-tumor activity

Herbimycin A specifically inhibits the cytosolic chaperone HSP 90 (Heat Shock Protein) and its endoplasmic reticulum (ER) homologue GRP 94.

Heat shock proteins are called molecular chaperones. Their production is triggered when a cell is subjected to stress situations, such as undesired chemical influences or high temperatures[20]. They prevent the non-specific aggregation of proteins and assist in their folding and refolding[21].

One of the main roles of the HSP 90 chaperone is the activation of different families of protein kinases, which play a major role in cancer[22].

Herbimycin A has anti-proliferative and anti-tumor effects: as it binds to HSP 90, inhibiting the HSP 90 - mediated conformational maturation/re-folding reaction, thereby promoting degradation of HSP 90 substrates[23,24].

SRC (sarcoma) kinases are important during the cell cycle. As a consequence, much attention is being focused in order to act on them for therapeutic purposes. A screening of natural products has been performed whose aim was the inhibition of the transforming activity of tyrosine kinase oncogenes. Herbimycin A **(1)** was found to exhibit inhibitory activity[25].

Later on, a study showed that drug-induced reversion could be achieved without any direct inhibition of the SRC phosphorylating agent but that the ansamycins directly bind to HSP 90[26].

It is known that herbimycin A **(1)** and geldanamycin **(5)** bind to the adenosine triphosphate (ATP) binding pocket of HSP 90, which is located in the *N*-terminal of the protein[27,28].

Stebbins and his team were able to obtain a crystal structure of the HSP 90 - geldanamycin complex and observed geldanamycin **(5)** bound to the ATP binding site in a C-clamp like structure, where the benzoquinone forms the top of the C and the *ansa* ring the stem and bottom (see Figure 11)[22]. This observation led to interesting conclusions regarding the structure-activity relationship of geldanamycin **(5)** and its inhibitory effects.

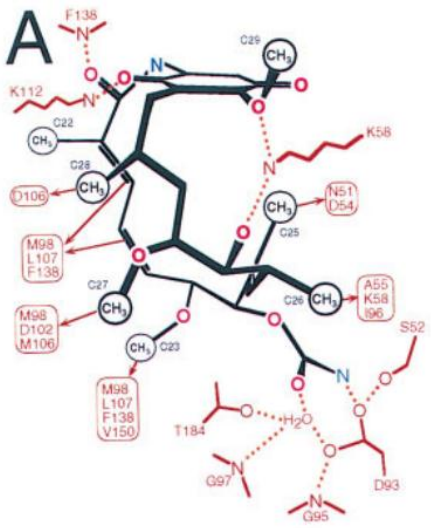
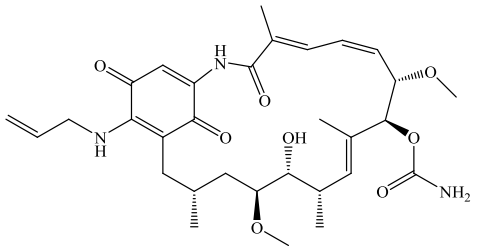


Figure 11 - X-Ray structure of HSP 90 - geldanamycin **(5)** complex by Stebbins[22]

However, due to high levels of toxicity, geldanamycin **(5)** cannot be used as a therapeutic agent. Analogues have been sought after and the main focus for structural modification is the C-17 methoxy group. Schnur *et. al.* showed that the highest potency was obtained when an amino group was present at the C-17 position[29,30].

The synthesis of 17-aminoallylgeldanamycin often referred to as 17-AAG or now tanespimycin **(23)** shown below was a major breakthrough, as it proved to be more stable and less toxic than geldanamycin **(5)**[31]. In addition, it shows a higher affinity for HSP 90 derived from tumour cells compared to normal cells[32]. Tanespimycin **(23)** has been in clinical trials since 1999. It is currently in phase II trials against melanoma[33,34], breast[35], prostate[36], and thyroid[37] cancer.

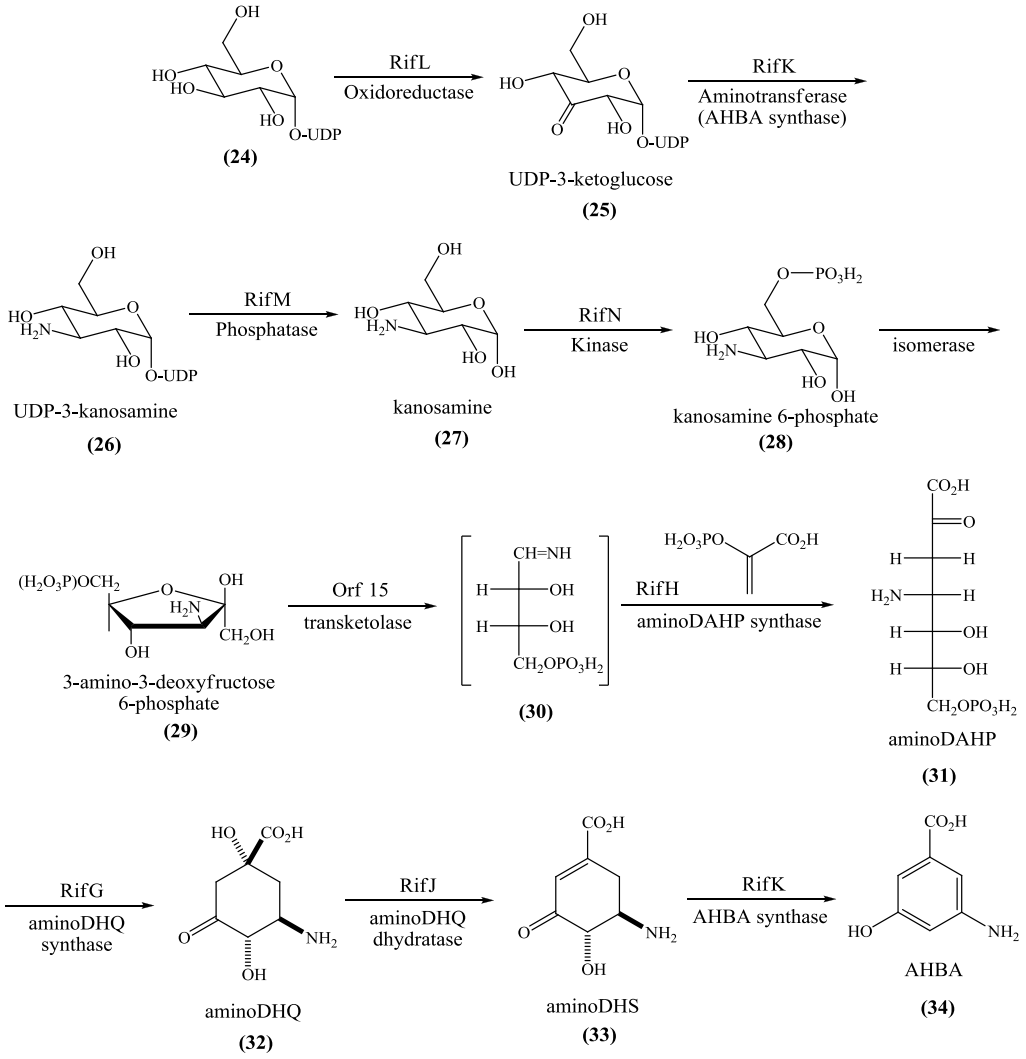


(23)

Figure 12 - Tanespimycin **(23)**

III. Biosynthesis

As mentioned earlier, Herbimycin A **(1)** is produced by *Streptomyces hygroscopicus* strains. The biosynthesis of Herbimycin A **(1)** involves at first the formation of 3-amino-5-hydroxybenzoic acid (AHBA) **(34)**, by a variant of the Shikimate pathway[38].

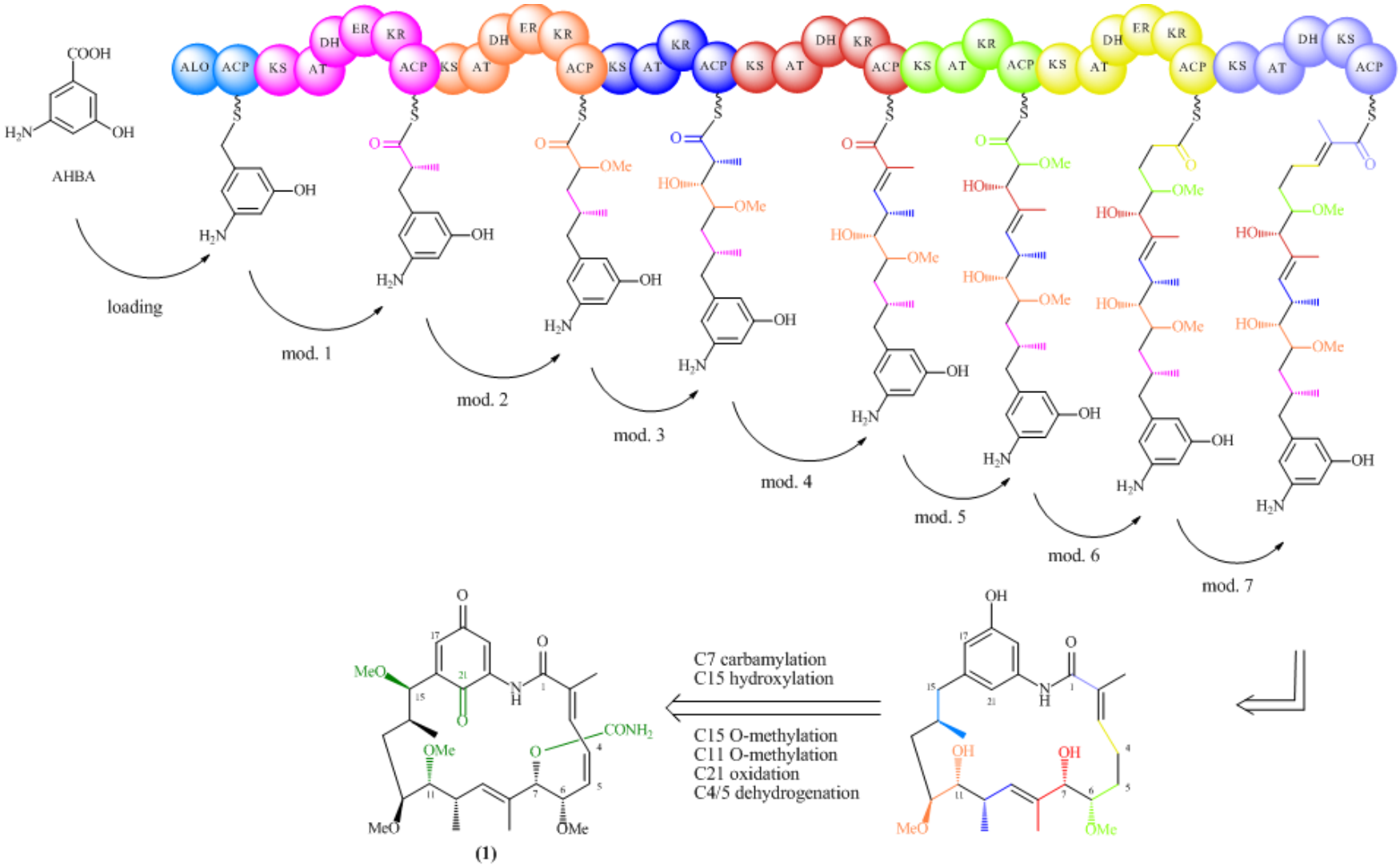


Scheme 3 – Biosynthesis of AHBA following the Shikimate pathway[38]

AHBA **(34)** then serves as the starter unit for the assembly of a polyketide to form the carbon skeleton of **(1)**. This formation is catalyzed by a special enzyme called polyketide synthase (PKS), made of sets of active sites called modules.

Each module contains the catalytic domains required for a single round of polyketide chain elongation by substrate condensations and various reductions or dehydrations. During each extension step of one unit, the polyketide chain is elongated with two carbon atoms, where the β-carbon is a keto group. Then, post-PKS tailoring steps further modify the PKS product to give **(1)**.

In 2005, Rascher *et al.*[39], from Kosan Biosciences, Inc., in California published their results about the biosynthesis of herbimycin A **(1)** obtained by gene sequencing and disruption. They proposed that C-21 oxidation, C-17 oxidation and *O*-methylation, along with C-7 carboymylation and C-4 and C-5 dehydrogenation occur after polyketide chain assembly, as outlined in Scheme 4 below.



Scheme 4 - Pathway leading to herbimycin A (1) proposed by A. Rascher[39]

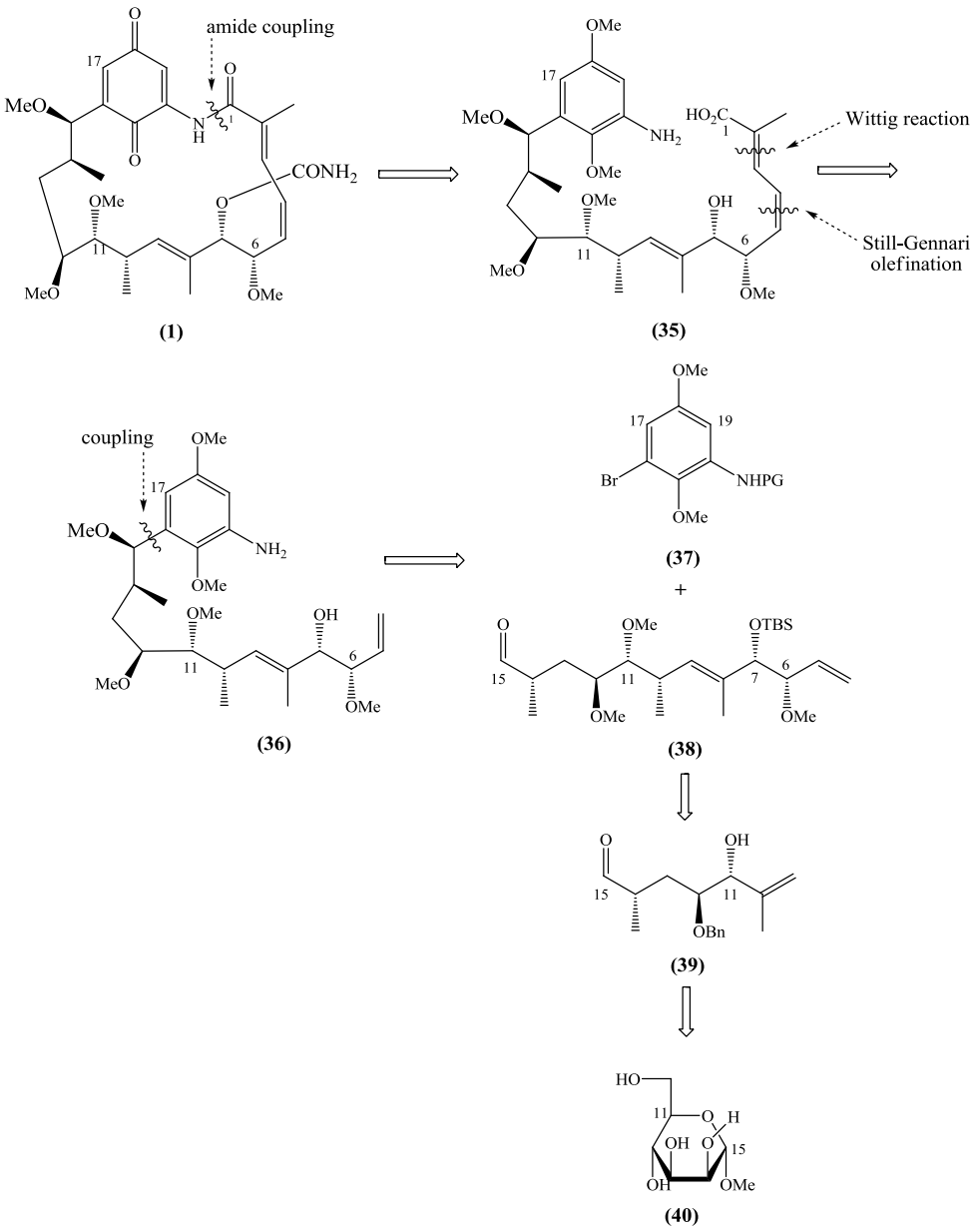
CHAPTER 2

PREVIOUS SYNTHESES

Since its discovery, only three total syntheses of herbimycin A **(1)** have been described in the literature, although there have been many syntheses of advanced fragments. In addition, related ansamycin benzoquinone compounds such as the macbecins **(10)** and **(11)** and geldanamycin **(5)** have been extensively studied in the past.

I. Tatsuta's total synthesis:

Tatsuta and co-workers[40,41] reported the first total synthesis of herbimycin A **(1)** in 1991, which also confirmed the compound's absolute stereochemistry. The retrosynthetic pathway Tatsuta and his team proposed is pictured in Scheme 5.

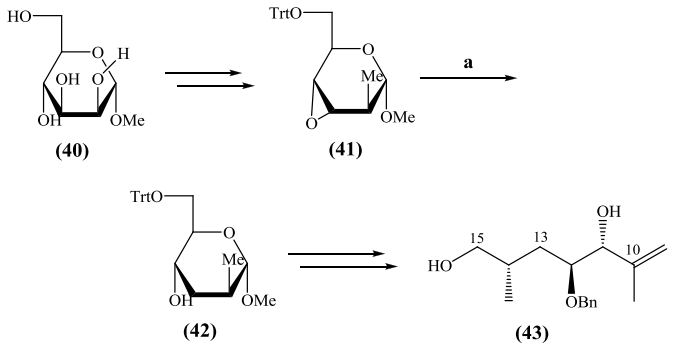


Scheme 5 – Retrosynthetic path

Formation of the quinone and construction of the carbamate unit were carried out after the macrocyclisation step to furnish herbimycin A **(1)**. Intermediate **(35)** was the result of several group manipulations, including a Still-Gennari olefination[42] and a Wittig reaction. The route the author proposed was to install both C6 and C7 chiral centres prior to performing the coupling of the aromatic unit.

As a consequence, intermediate **(36)** was divided into two portions being the aromatic chromophore **(37)** and the aliphatic aldehyde **(38)**. The aldehyde would be obtained by elongation of the the C9-C15 portion **(39)** which would again be derived from the chiral sugar, methyl α-D-mannopyranoside **(40)** (Scheme 5).

The synthesis of the aldehyde **(38)** began with conversion of methyl α-D-mannopyranoside **(40)** into the epoxide **(41)**. This was regioselectively opened using bis(1,2-dimethylpropyl)borane to give a 6:1 ratio in favour of the desired regio-isomer **(42)**, corresponding to the necessary stereochemical relationships at the C12 and C14 positions in herbimycin. The resulting alcohol **(42)** was subsequently converted to alkene **(43)** in several steps (Scheme 6).

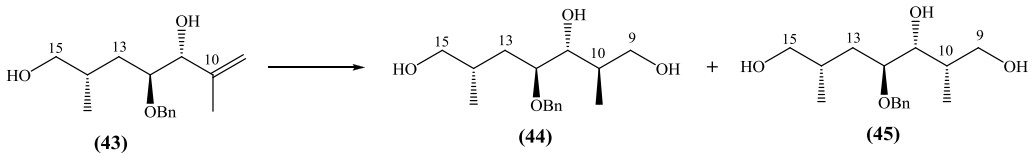


Reagents and conditions: a) Bis(1,2-dimethylpropyl)borane (8 eq), $NaBH_4$ (0.25 eq), THF, 25 °C, 83 %.

Scheme 6 – Epoxide opening

The authors introduced the *syn* relationship between the C11 alcohol and the C10 methyl substituents by treating olefin **(43)** with dicyclohexylborane in tetrahydrofuran followed by subsequent work-up with basic hydrogen peroxide to produce the undesired *anti* product **(44)** and the desired *syn* product **(45)** in 66% and 15 % yields respectively.

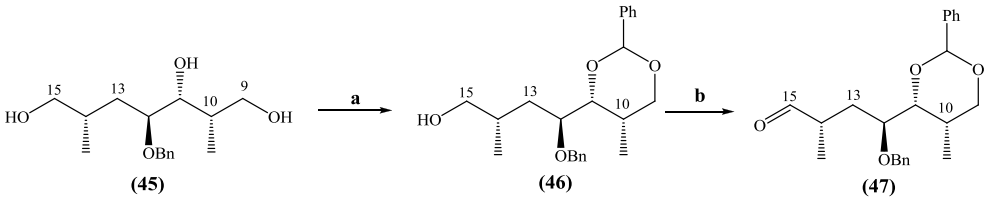
However, when borane dimethyl sulfide complex was used in tetrahydrofuran, alcohol **(45)** was formed upon hydroperoxide work-up, in an 83 % yield, with only 17 % of its undesired C10 isomer **(44)** (Scheme 7).



Reagents and conditions: $BH_3 \cdot SMe_2$, THF, 25 °C, *then* H_2O_2(aq), NaOH, 83 % of **(45)**, (dr = 1:5, (**45**:**44**)).

Scheme 7 - *Syn* selective hydroboration

The mixture of both 1,3-diol **(44)** and **(45)** was converted to the acetal using benzaldehyde dimethyl acetal in dichloromethane and a substoichiometric amount of 10-camphorsulfonic acid. Terminal alcohol **(46)** was oxidised following Swern's procedure to give aldehyde **(47)** in an 89 % (Scheme 8).

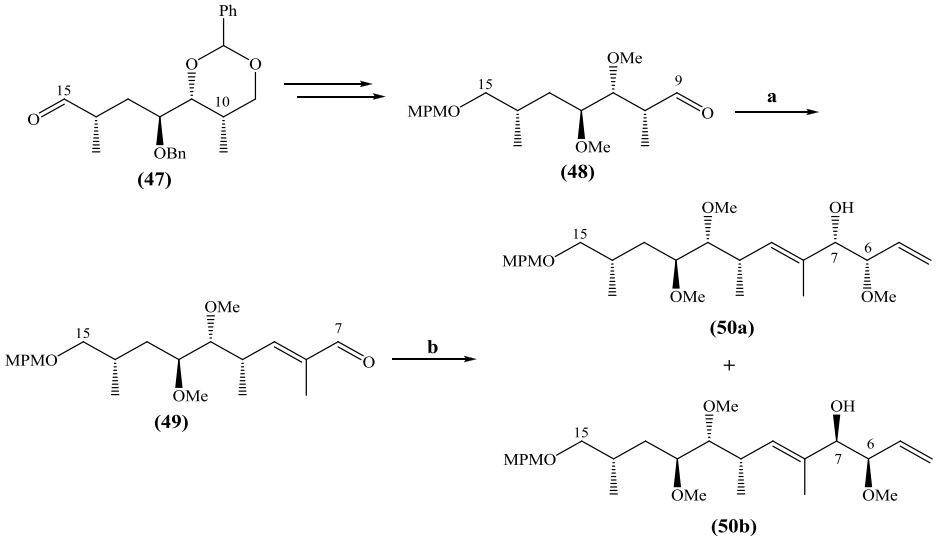


Reagents and conditions: a) $PhCH(OMe)_2$, CSA, CH_2Cl_2, 25 °C, 90 %;
b) $(COCl)_2$, Me_2SO, Et_3N, CH_2Cl_2, 89 %.

Scheme 8

Aldehyde **(48)**, obtained from intermediate **(47)** after several steps, underwent Correy-Schlessinger's olefination[43] with *N*-[2-(triethylsilyl)propylidene]-*t*-butylamine

and *s*-butyllithium in tetrahydrofuran followed by an aqueous oxalic acid work-up yielding the (*E*)-unsaturated aldehyde **(49)** in an 85% yield as a single isomer, corresponding to the C7-C15 fragment. This fragment was then allylated using [(*Z*)-3-methoxyallyl]-diisopinocampheylborane, prepared according to Brown's procedure[44] resulting in the desired C7-C6 *syn* product **(50a)** in a 76 % yield, along with a 14% yield of the undesired diastereoisomer **(50b)**.

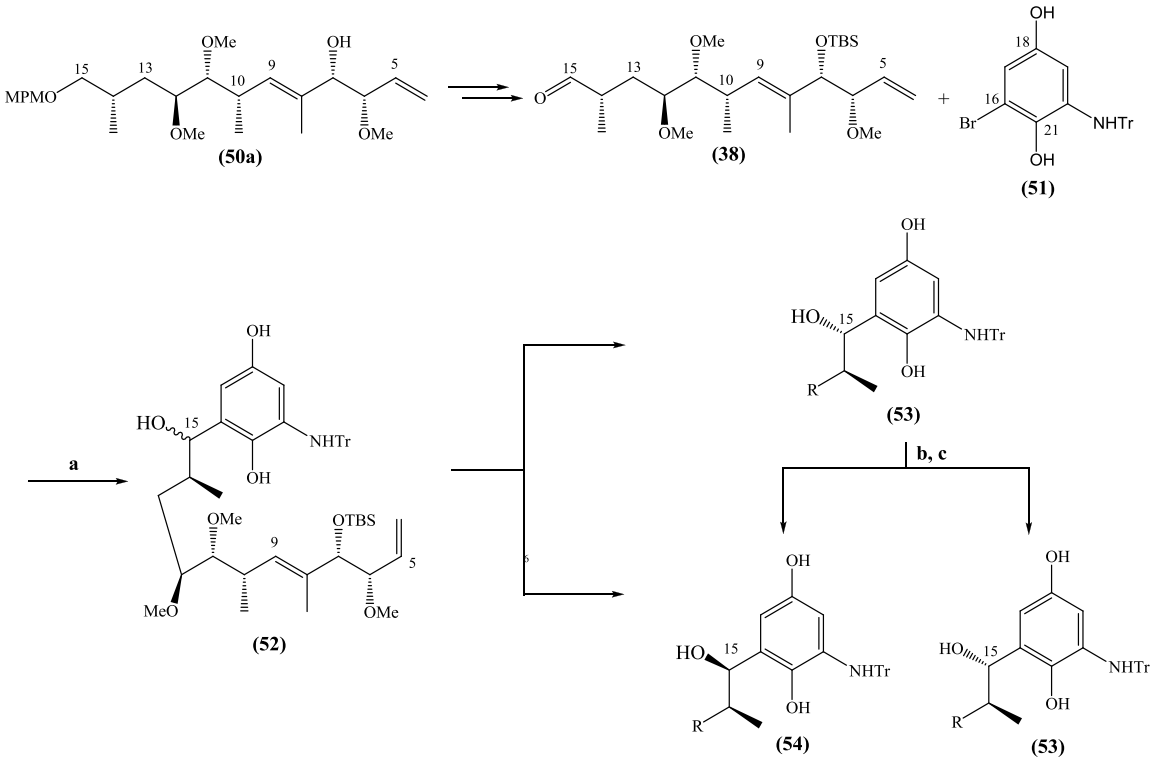


Reagents and conditions: a) *N*-[2-(triethylsilyl)-propylidene]-*t*-butylamine, *s*-BuLi, THF, -78 ºC to -20 ºC, oxalic acid work-up, 85 %; **b)** [(*Z*)-3-methoxyallyl]-diisopinocamphenylborane, THF, -78 ºC to -20 ºC, 90 %, (dr = 6:1, (**49:50**)).

Scheme 9

Once the aliphatic fragment **(38)** was obtained it was then coupled to the aromatic sub-unit **(51)**, which was prepared from 3-bromo-2,5-dimethoxyaniline in a 98% yield.[45] It led to a separable mixture of the 15*R* **(54)** and the 15*S* **(53)** isomers in a 1:1 ratio and 91 % yield. The structure of the desired diastereomer **(54)** was confirmed by comparing the proton NMR spectrum with similar intermediates that Baker *et al*. had

synthesised in their work on macbecin 1 **(10).**[46] The authors could convert the undesired isomer **(53)** to the desired one **(54)** by an oxidation-reduction procedure[47] using lithium aluminium hydride and (+)-(2*S*,3*R*)-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol (chirald®) in a solution of 1% of tetrahydrofuran in diethyl ether at -78 ºC (Scheme 10). The concentration of tetrahydrofuran in the reaction was essential to reach a 4:1 ratio of 15*R* **(54)** and 15*S* **(53)** diastereoisomers[48].

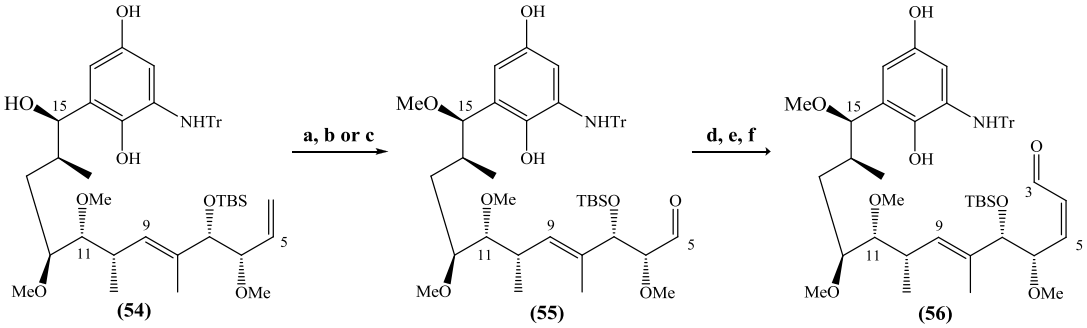


Reagents and conditions: a) *n*-BuLi, THF, -78 ºC, 91 %, (dr = 1:1, (**53:54**)); **b)** Me_2SO, Ac_2O, 95 ºC, 80 %; **c)** $LiAlH_4$, **(chirald®)**, 1 % THF/Et_2O, -78 ºC, 80 %, (dr = 4:1, (**54:53**)).

Scheme 10

The synthesis proceeded with methylation followed by cleavage of the terminal alkene using either osmium tetroxide/sodium periodate or by treatment with osmium tetroxide, 4-methylmorpholine-*N*-oxide followed by lead tetra-acetate, to give aldehyde

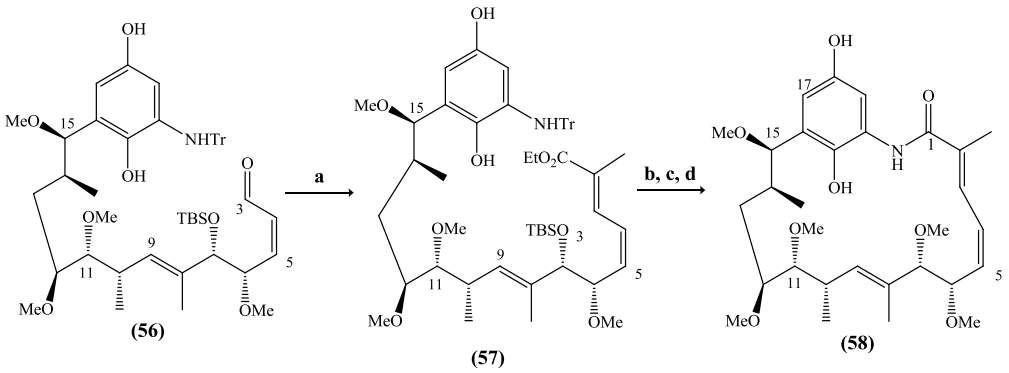
(55). The following steps were similar to those employed by Baker and his team for the total synthesis of macbecin I **(10)**[46]. A Still-Gennari olefination42 using potassium bis(trimethylsilyl)amide, 18-crown-6 in tetrahydrofuran at -78 ºC was followed by a reduction and then an oxidation leading to aldehyde **(56)** (Scheme 11).



Reagents and conditions: a) MeI, NaH, DMF, 0 °C; **b)** OsO_4-$NaIO_4$,THF-pH 7, phosphate Buffer, rt.; **c)** OsO_4-NMO, H_2O/$(Me)_2CO$, rt, *then* $Pb(OAc)_4$, AcOK, MeCN, 0 °C; **d)** $(CF_3CH_2O)_2P(O)CH_2COOMe$, $KN(SiMe_3)_2$, 18 – crown - 6, THF, -78˚C, 4 h, (63 % and 73 % respectively over three steps); **e)** DIBAL, toluene, -78˚C, 1 h; **f)** PDC, CH_2Cl_2, 25˚C , 24 h.

Scheme 11

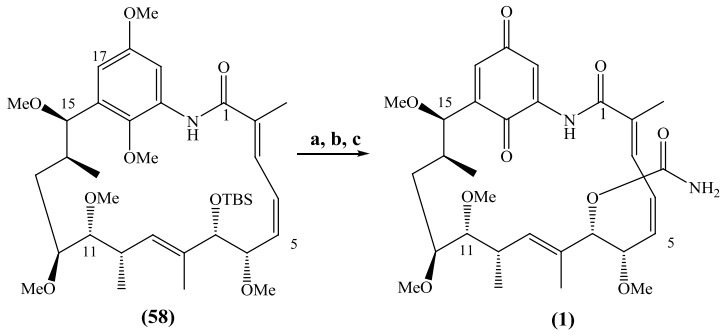
A subsequent Wittig reaction using the stabilised ylide 1-carboethoxy ethylidenetriphenylphosphorane led to the *E*/*Z*-diene **(57)** in a 70% yield over three steps. Saponification and macrolactamisation with bis(2-oxo-3-oxazolidinyl)phosphinic chloride and *N*-ethyldiisopropylamine[49] in toluene at 85ºC led to the desired macrocycle **(58)** in an overall yield of 72 % from aldehyde **(56)** (Scheme 12).



Reagents and conditions: **a)** Ph_3P=C(Me)COOEt, CH_2Cl_2, 40˚C, 22 h; **b)** 0.02% HCl-MeOH, 25˚C, 0.5 h; **c)** LiOH, 2 : 2 : 1 THF – MeOH - H_2O, 25˚C, 29 h; **d)** BOP-Cl, DIPEA, toluene, 85˚C, 15 h, , 72 % over 4 steps.

Scheme 12

Only three steps were left to reach herbimycin A **(1)**: a desilylation using tetrabutylammonium fluoride, followed by carbamoylation with sodium cyanate and trifluoroacetic acid in dichloromethane[50] and finally an oxidative de-*O*-methylation using silver (II) oxide and 1 M aqueous nitric acid in dioxane. This gave herbimycin A **(1)** in a 91% yield from **(58)** (scheme 13)[51] and also allowed Tastuta to confirm the structures absolute stereochemistry for the first time.

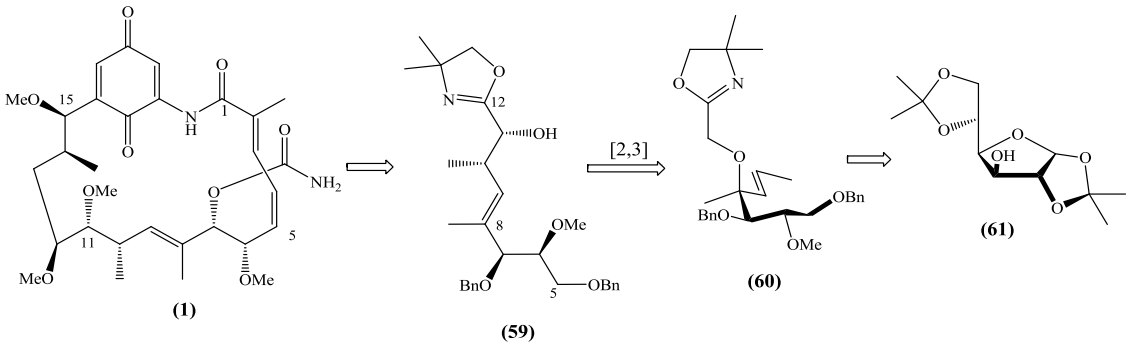


Reagents and conditions: **a)** TBAF, THF, 25 ºC, quant.; **b)** NaOCN, TFA, CH_2Cl_2, 25 ºC, 91 %; **c)** AgO, 1M HNO_3(aq), dioxane, 25 ºC, 100 % (91 % over three steps).

Scheme 13

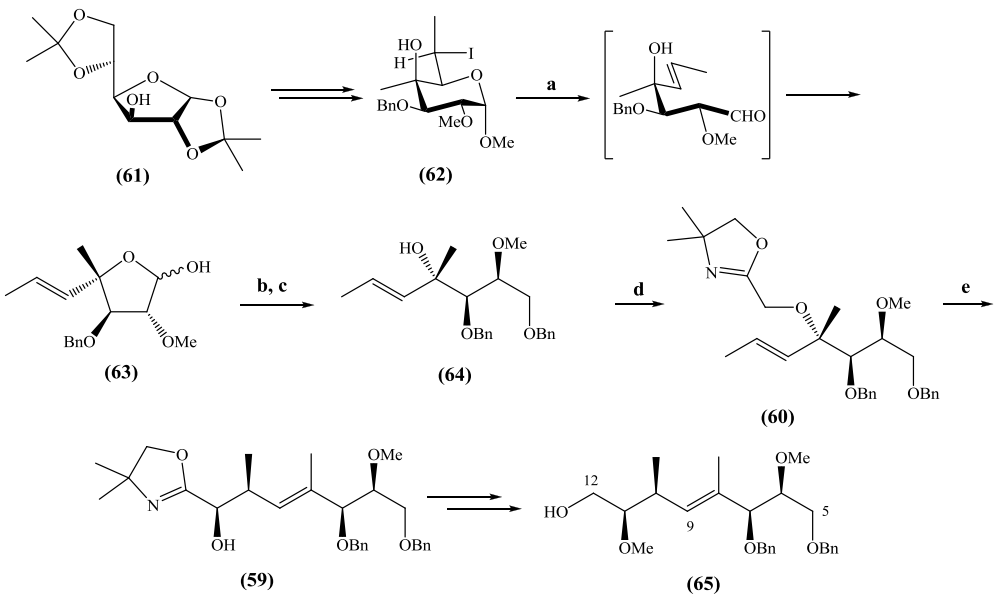
II. Kallmerten's partial synthesis

In 1993, Kallmerten[52] reported the synthesis of the C5-C12 subunit **(59)** of herbimycin A **(1)** where the key transformation was a diastereoselective [2,3] Wittig rearrangement of the glucose derived tertiary allylic ether **(60)**.



Scheme 14

Kallmerten started the synthesis with the commercially available glucofuranose **(61)** that was turned into iodo-alcohol **(62)** over eleven steps. The iodide **(62)** was then treated with Zinc dust in ethanol resulting in the cyclised lactol **(63)** as a mixture of anomers. The lactol **(63)** underwent a reduction, followed by a mono-benzylation of the resulting diol to yield tertiary allylic alcohol **(64).** Oxazoline **(60)** was then formed and was treated with lithium diisopropylamide and a [2,3] Wittig rearrangement took place to produce oxazoline **(59)** as a single product. **(59)** was then turned, after two steps, into **(65)** which corresponds to the right C5-C12 precursor of herbimycin A **(1)**, bearing 4 of its 7 chiral centres.

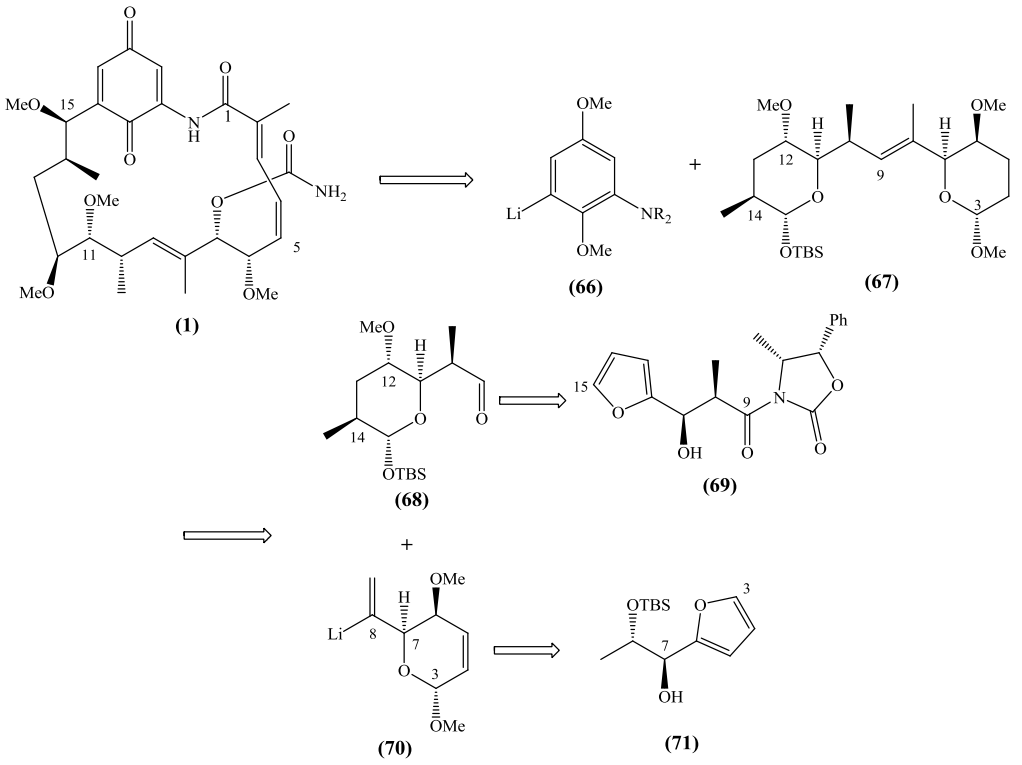


Reagents and conditions: a) Zn, EtOH; **b)** $LiBH_4$, THF; **c)** $PhCH_2Br$, NaH, DME, 79 % over three steps; **d)** KH, 2-chloromethyl-4,5-dihydro-4,4-dimethyloxazole, DME; **e)** LDA, THF, -78 to 0˚C, 78 % over two steps.

Scheme 15

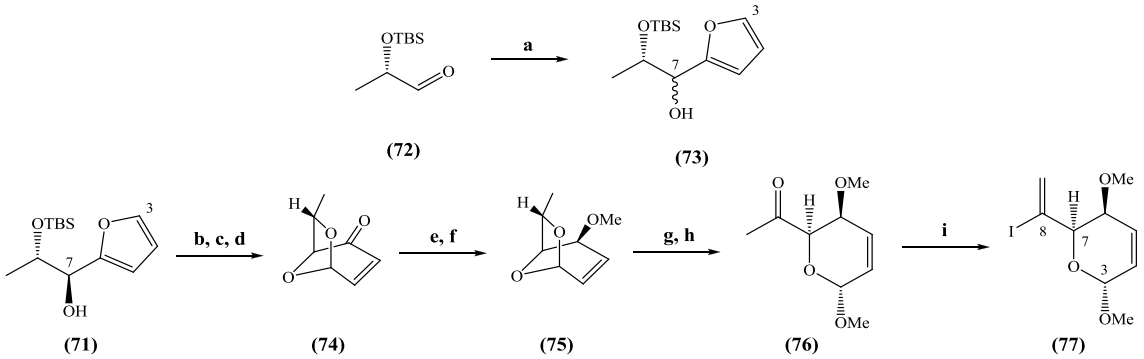
III. Martin's partial synthesis

Martin reported the synthesis of an advanced intermediate **(67)** toward the total synthesis of herbimycin A **(1)**, containing C3-C15 with the correct stereochemistry[53]. The key steps of this synthesis were the transformations of furans **(69)** and **(71)** to pyran **(68)** and dihydropyran **(70)** respectively (Scheme 16). These reactions had been previously described by Martin when he worked on the total synthesis of (+)-macbecin 1 **(10)**[54]**.** The coupling of both pyrans **(68)** and **(70)** led to the trisubstituted *E*-double bond between C8 and C9 in herbimycin.



Scheme 16

The authors started with the known aldehyde **(72)** which reacted with furyl lithium to yield a separable mixture of epimeric diols **(73)**. The desired diol **(71)** was oxidized to give the intermediate hydropyranone then cyclized under dehydrating conditions to furnish the enone **(74)**. Selective reduction of the ketone in **(74)** was performed *via* the use of Yamamoto's bulky DIBAL-BHT reagent[55], followed by methylation to give the ether **(75)**. The ketal was hydrolysed by treatment with acid and subsequently oxidised using the Swern procedure[56] to produce ketone **(76)**. The obtained ketone **(76)** was then turned into vinyl iodide **(77)** following the Barton vinyl iodine procedure[57] (Scheme 17).

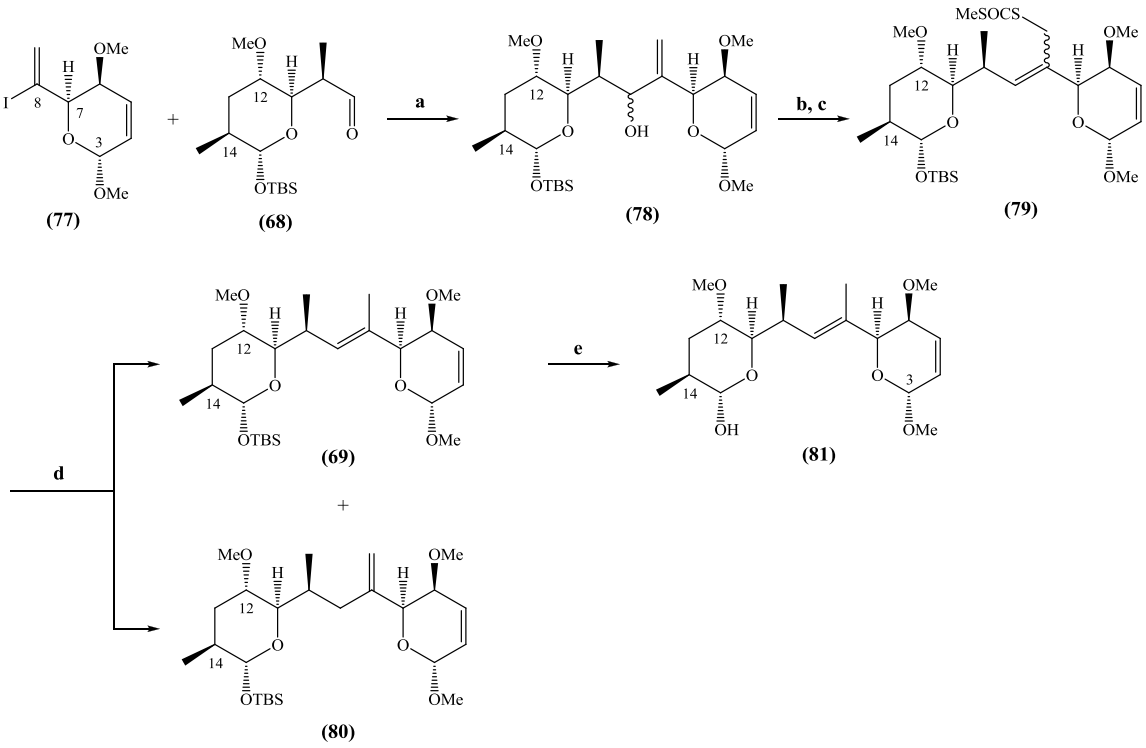


Reagents and conditions: a) furan, *n*-BuLi, THF, -70 to 0˚C; **b)** TBAF, THF, rt; **c)** O_2, CH_2Cl_2/MeOH, Me_2S; **d)** *p*-TsOH, benzene, MeCN, $MgSO_4$; **e)** DIBAL-BHT; **f)** KH, MeI; **g)** PPTS, MeOH; **h)** DMSO,$(COCl)_2$, Et_3N, CH_2Cl_2, -60˚C; **i)** NH_2NH_2, I_2, Et_3N.

Scheme 17

Then, Martin and his team proceeded to a metal-halogen exchange with **(77)** which reacted with **(68)** to give alcohol **(78)** as a mixture. **(78)** was then converted to xanthates which underwent thermal isomerization via a [3,3]-sigmatropic rearrangement leading to the mixture of allylic dithiocarbonate **(79)**.

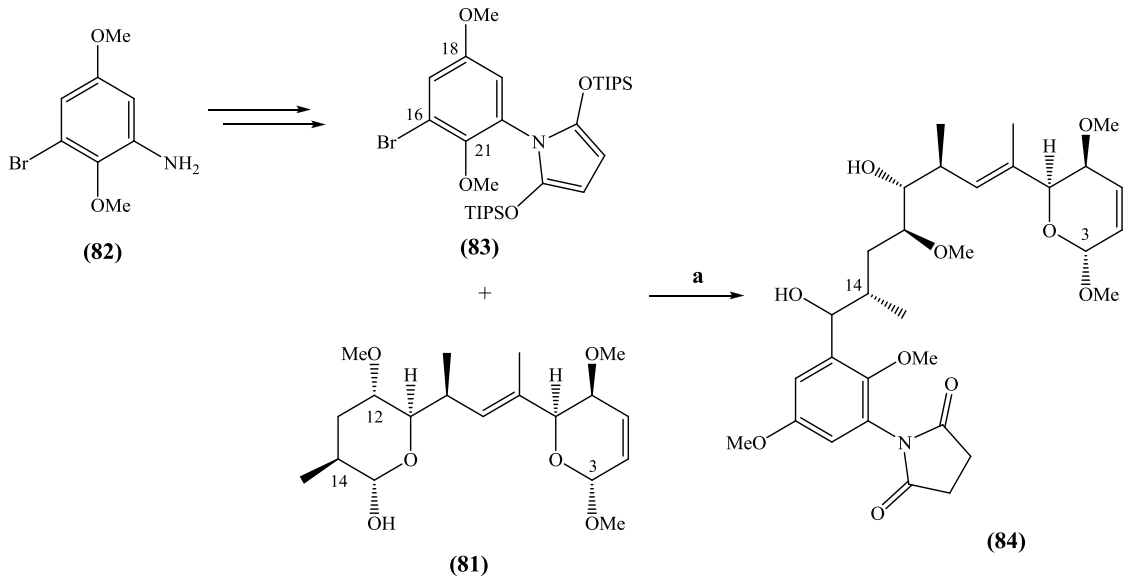
(79) was then reduced to yield alkene **(69)** along with the disusbstituted alkene **(80)**. Desired **(69)** had its silyl protecting group removed to give lactol **(81)**.



Reagents and conditions: a) *t*-BuLi, Et_2O, -95˚C; **b)** NaH, CS_2, THF, MeI; **c)** benzene, Δ; **d)** Bu_3SnH, AIBN, toluene, Δ; **e)** TBAF, HOAc, THF, rt.

Scheme 18

The authors could achieve the coupling of the aromatic fragment **(83)** with lactol **(81)** to obtain a mixture of **(84)**. The desired isomer proved to be a suitable precursor to herbimycin A **(1)** (Scheme 19).

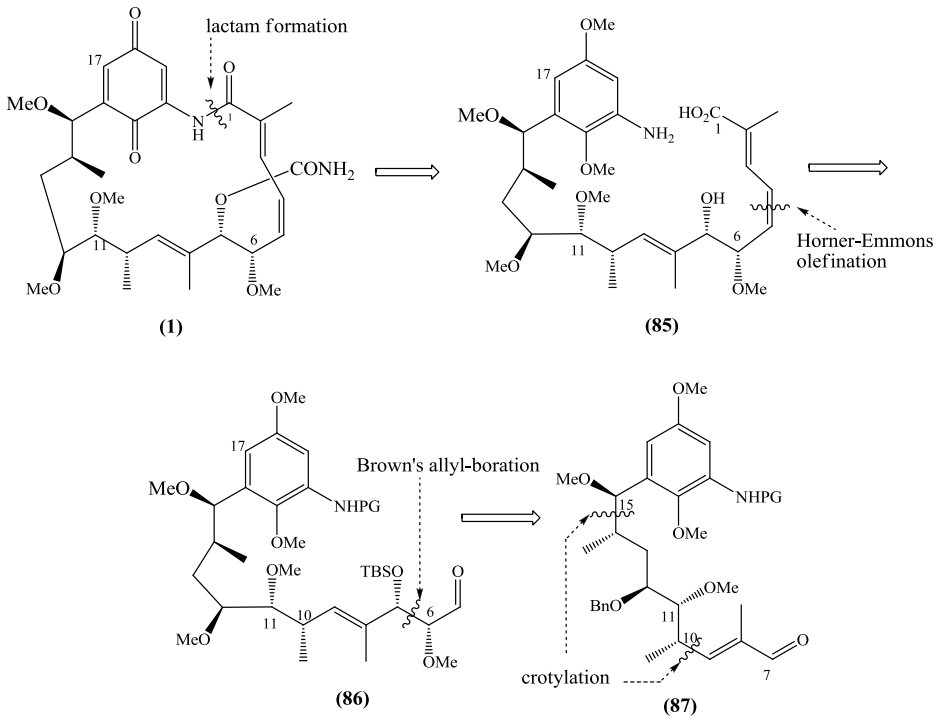


Reagents and conditions: a) *t*-BuLi, TMEDA, Et_2O, -20˚C, then dilute HCl, 38 %.

Scheme 19

IV. Panek's total synthesis

Panek and co-workers[58] published the second total synthesis of herbimycin A **(1)** in 2004. The key step of their approach was an asymmetric crotylsilation that had been previously developed for their total synthesis of macbecin **(10)**[59] which constructed four of the seven necessary stereocentres of the target molecule.



Scheme 20 –Panek's retrosynthetic route

Macro-lactamisation would be the final step and a Horner-Emmons olefination installed the sensitive E/Z-diene system. The C6-C7 bond was the result of Brown's allylation[44] and the stereo-centre at the C12 position was formed by the hydroboration reaction investigated by Panek[59].

The synthesis started with alcohol **(88)** which had been previously synthesised during Panek's total synthesis of macbecin 1 **(10)** (Figure 13)[59]:

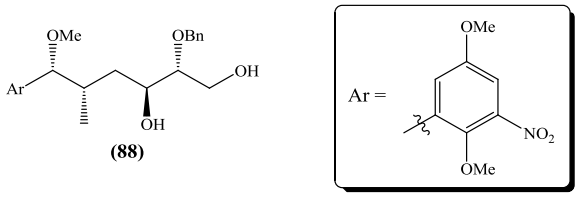
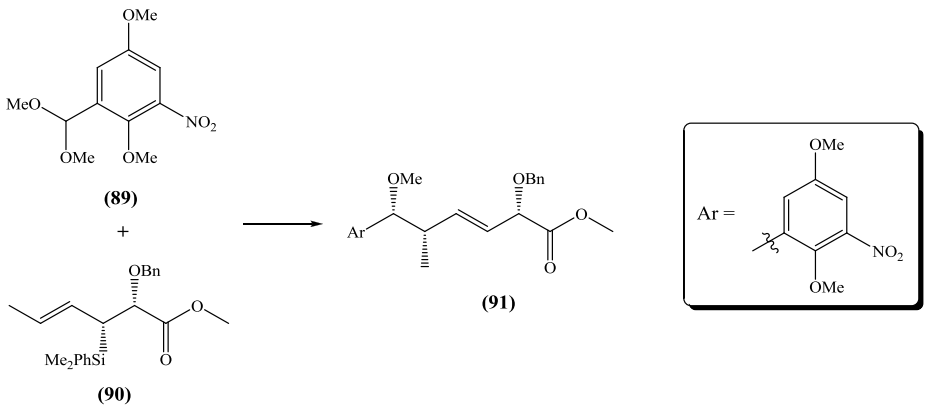


Figure 13

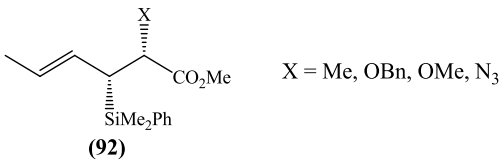
The aromatic acetal **(89)** was built from *p*-methoxyphenol[60,61] and underwent a *syn*-crotylation with (*E*)-crotyl silane **(90)** using trimethylsilyl triflate in dichloromethane at -78 °C, to give the corresponding ester **(91)** in an 89 % yield (Scheme 21).



Reagents and conditions: TMSOTf, CH_2Cl_2, -78 ºC, 89 %, (dr = >30:1);

Scheme 21

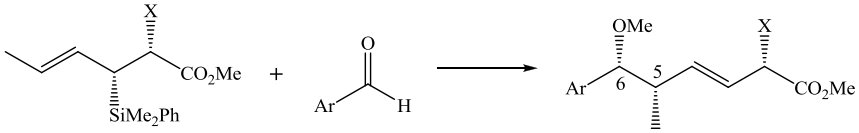
In the past, Panek had investigated *syn* crotylation reactions with (*E*)-crotyl silanes of the general structure **(92)** (Figure 14) acting as carbon nucleophiles in the addition to aldehydes and pre-formed acetals, leading to homo-allylic ethers with high stereo-selectivity[59].



(92)

Figure 14

When reacting α-methyl-β-(dimethylphenylsilyl)-(*E*)-hexenoates **(92a)** and **(92b)** with aryl acetals **(89)**, in the presence of a Lewis acid, Panek observed the preferential formation of the *E*-alkene with high *syn*-stereoselectivity. Indeed, chiral centres at the C5 and C6 positions of the products **(94a)** and **(94b)** were obtained with an e.e .of greater than 95 % (Scheme 22) [62,63].



(92) **(93)** **(94)**

X = Me **(92a)**
X = OMe **(92b)**

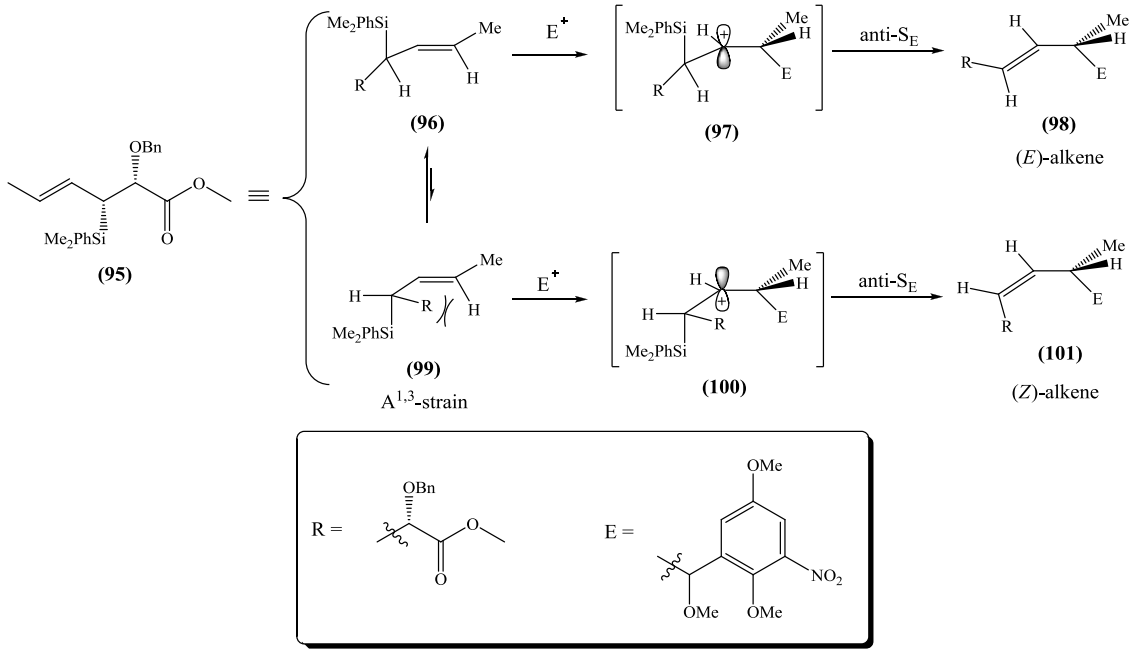
X = Me **(94a)**
X = OMe **(94b)**

Reagents and conditions: TMSOTf, CH_2Cl_2, -78 ºC

Scheme 22

The crotyl silane reagents **(92)** behaved as carbon nucleophiles, attacking the *in situ* generated oxonium ion[64] **(93)**, formed from the corresponding acetal, when treated with a Lewis acid.

Panek based his mechanism on an *anti*-S_E addition model depicted in Scheme 23[65].

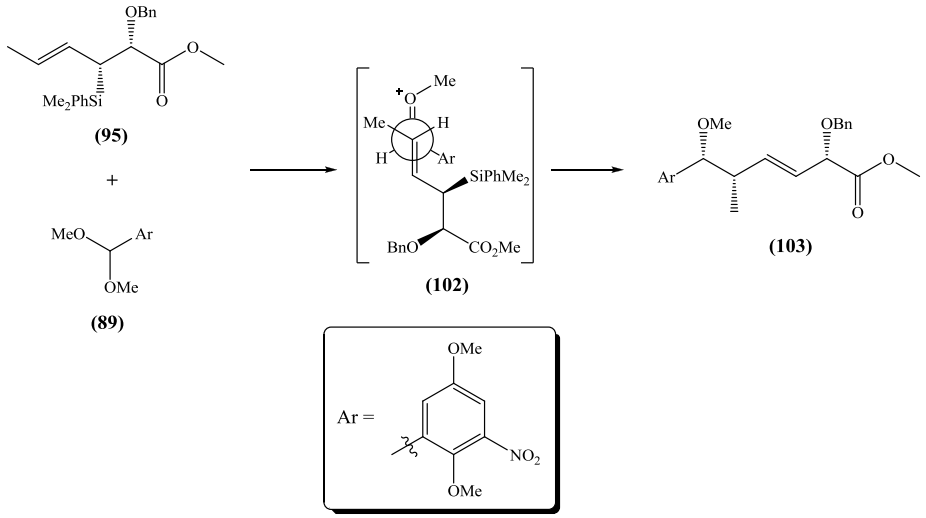


Scheme 23 - *E*-selectivity

In order not to have any steric strain ($A^{1,3}$-strain) **(99)**, the smallest substituent, in this case hydrogen, is placed in an eclipsing position to the adjacent double bond[66] yielding the favoured conformer **(96)**. The silicon moiety being bulky, it then directs the approach of the electrophile onto the opposite face of the π-system, thus giving the carbocations **(97)** and **(100)**. The C-Si bond switches then to a periplanar position with regards to the *p*-orbital through bond rotation, allowing stabilisation of the carbocation through hyperconjugation, thus giving the favoured *E*-alkene **(98)** or the unfavoured *Z*-alkene **(101)**.

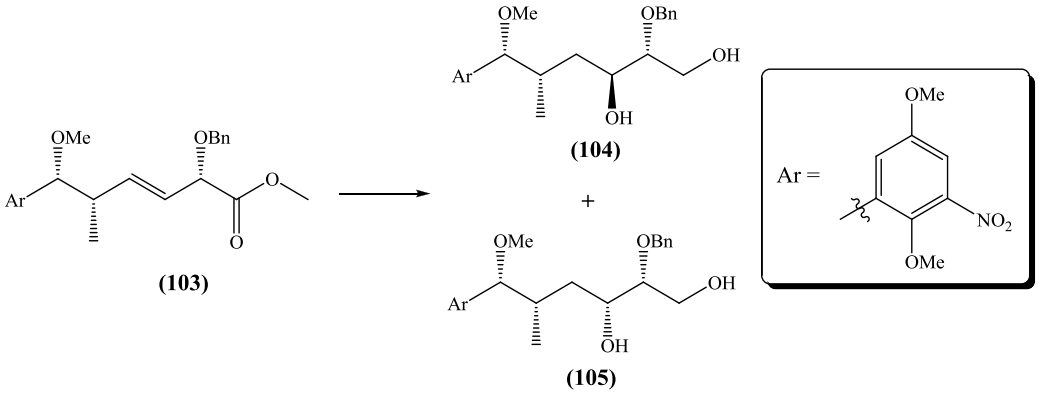
With regards to the resultant stereo-chemistry, Panek based his explanation on an antiperiplanar transition state model which described the interaction between the crotylsilane and the oxonium ion. Panek suggested that the participating π-bonds were

orientated at a 180º angle to each other. The nucleophilic carbon and the activated carbonyl adopted a co-planar *anti*-relationship (Scheme 24).



Scheme 24 – *Syn*-selectivity

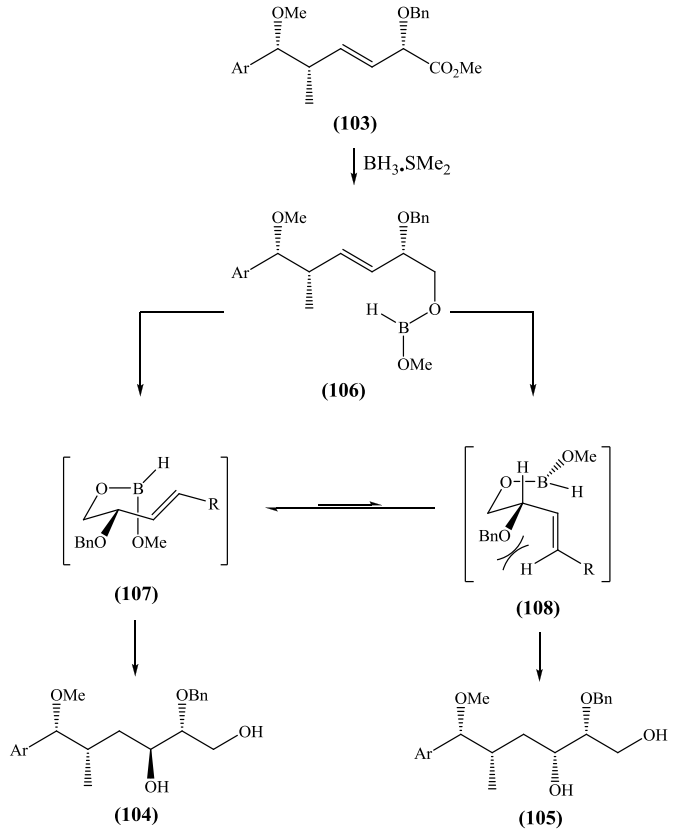
The ester **(103)** was then treated with borane dimethyl sulfide complex in tetrahydrofuran, and subsequently oxidized with alkaline hydrogen peroxide, leading to the required diol **(104)** in an 85 % yield with a dr of up to 11:1 (Scheme 25).



Reagents and conditions: $BH_3 \cdot SMe_2$, NaOOH, THF, 85 %, (dr = 11:1, (**104:105**)).

Scheme 25

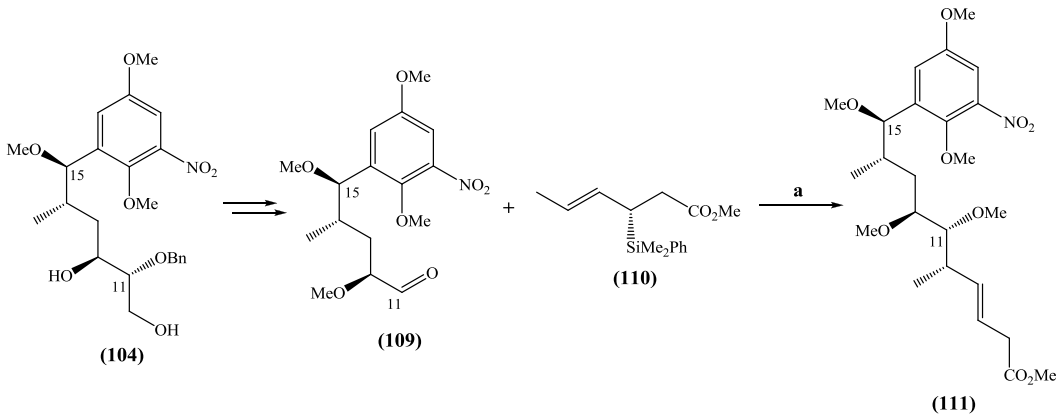
Panek proposed the following intramolecular mechanism to explain the resulting stereochemistry of this hydroboration step (Scheme 26)[67].



Scheme 26 – Intra-molecular hydroboration according to Panek[67]

As shown above the ester group was first reduced, resulting in a directing alkoxy group, thus leading to good levels of regio- and diastereoselectivity (Scheme 26)[68]. The author suggested the OBn group, adjacent to the carbonyl led to a polarization of the double bond; thus reinforcing the positional and facial selectivity in favour of the desired product.

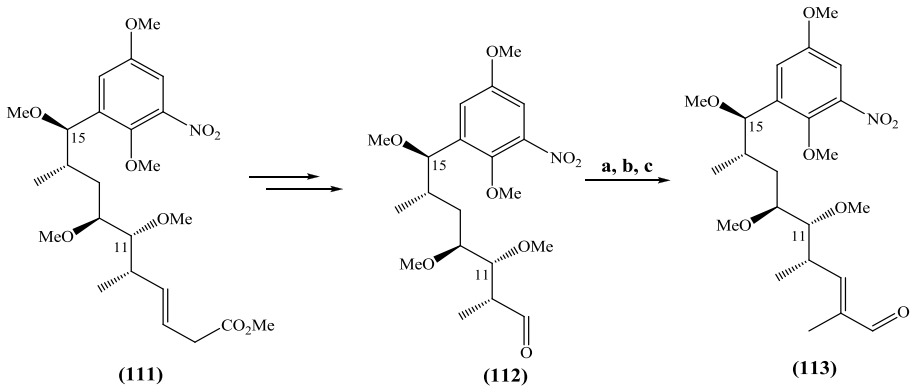
A further five steps were necessary to furnish the aldehyde **(109)** in an overall yield of 56% before performing the silyl-crotylation reaction (Scheme 27).



Reagents and conditions: a) TMSOTf, TMSOMe, 59 %, (dr = 12:1).

Scheme 27

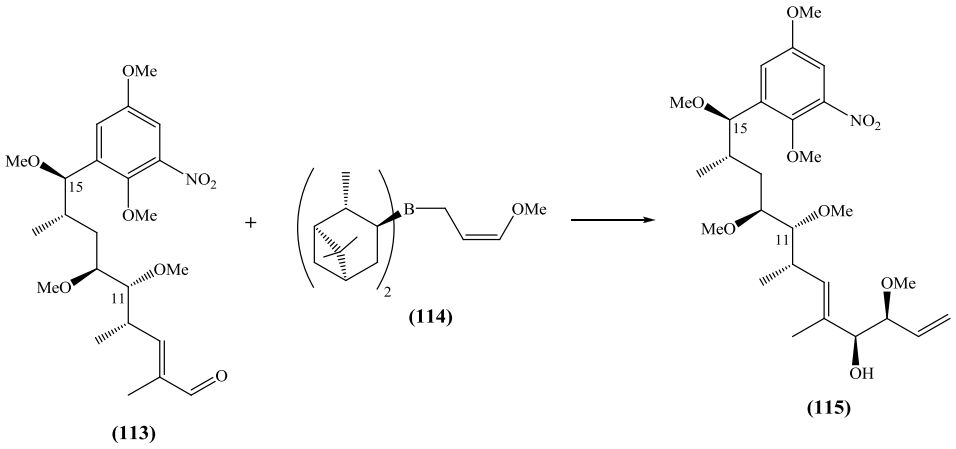
Ester **(111)** was subsequently turned into aldehyde **(112)** in a 61 % yield *via* oxidative cleavage and reduction. A Wittig olefination, followed by reduction and a Swern oxidation led to the tri-substituted *E*-alkene **(113)** in an overall yield of 57 % yield (Scheme 28).



Reagents and conditions: a) $Ph_3P=C(Me)CO_2Et$, toluene, 78 %; **b)** DIBAL-H, THF, 80 %; **c)** $(COCl)_2$, Me_2SO, 91 %.

Scheme 28

Brown allylation[44] allowed the authors to install the chiral centres at the C6 and C7 positions (Scheme 29).

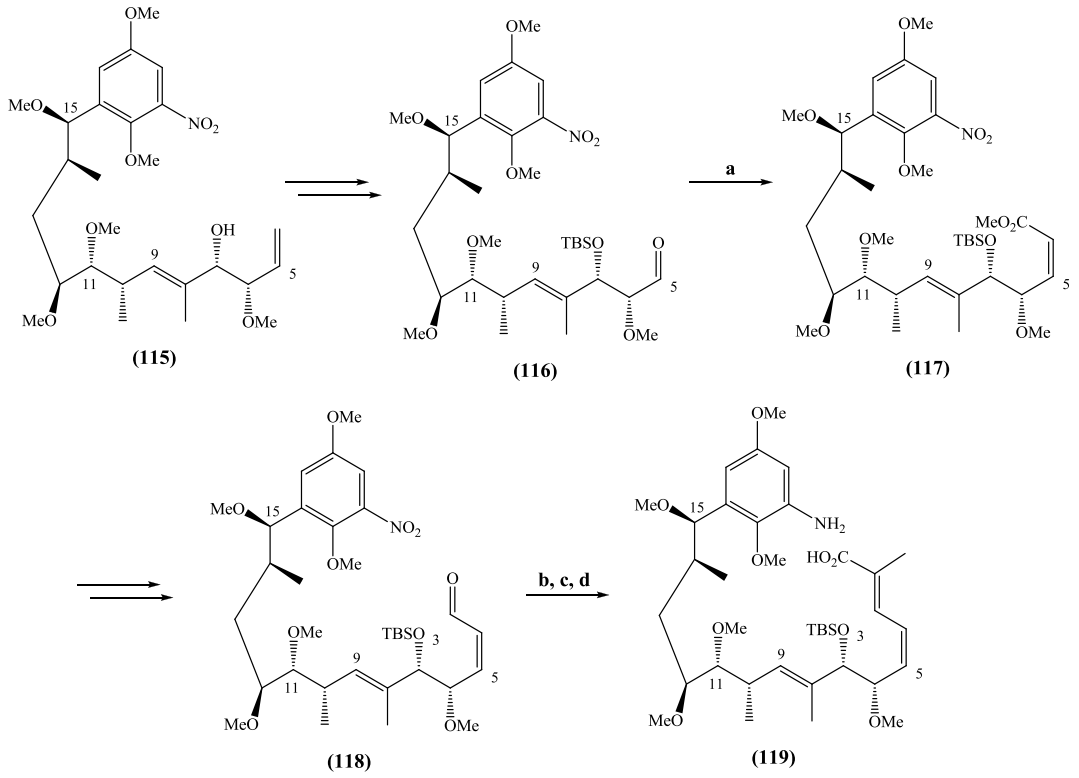


Reagents and conditions: THF, -78 ºC, 77 %.

Scheme 29

Panek used the γ-methoxyallyl organoborane reagent **(114)** derived from (-)-α-pinene to give a 77% yield of the alcohol **(108)** as a single diastereoisomer (Scheme 29)[58].

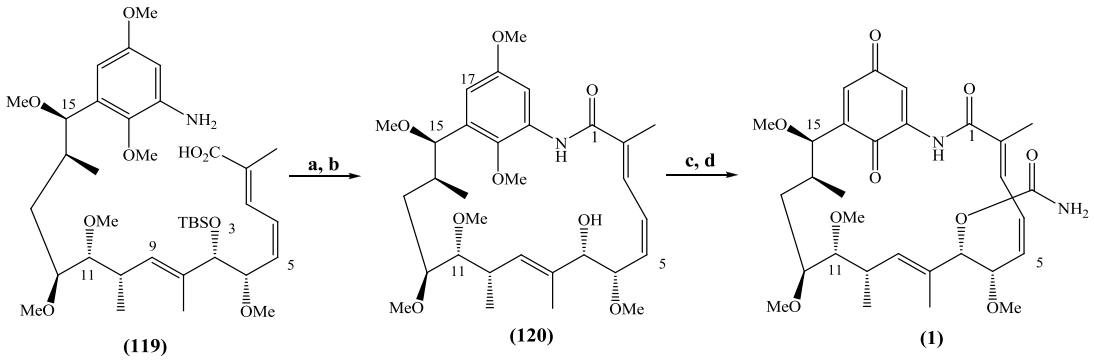
After performing a silyl protection and an oxidative cleavage of the terminal alkene **(115)**, aldehdye **(116)** underwent an olefination[69] using the Still-Gennari phosphonate[42]. The *Z*-α,β-unsaturated ester **(117)** was subsequently turned in two steps into its corresponding aldehyde **(118)** in an overall yield of 89% before being subjected to Wittig's conditions using the stabilised ylide 1-carboethoxyethylidenetriphenyl-phosphorane. The *E*/*Z*-diene system **(118)** was obtained in a 99 % yield (with a dr = >30:1, (*E*:*Z*)). The nitro group was reduced based on Lalancette's procedure[70] using $NaBH_2S_3$, which was followed by a saponification of the ethyl ester, leading to the carboxylic acid **(119)** (Scheme 30).



Reagents and conditions: a) $(CF_3CH_2O)_2P{=}O(CH_2)CO_2Me$, KHMDS, 18-crown-6, 83 %; **b)** $Ph_3P{=}C(Me)CO_2Et$, toluene, 99 %, (dr = >30:1, (*E*:*Z*)); **c)** $NaBH_2S_3$, THF, 83 %; **d)** LiOH, MeOH/THF/H_2O (2:2:1), quant.

Scheme 30

Panek then carried out the final four steps according to Tatsuta's procedure[40,41] shown on Scheme 12 and Scheme 13: macrolactamisation, desilylation and carbamate formation led to alcohol **(120)** (Scheme 31)[71]. Formation of the quinone was performed with ceric ammonium nitrate, leading to herbimycin A **(1)** in 27 steps from **(89)** and **(90)** in an overall yield of 1.1%.

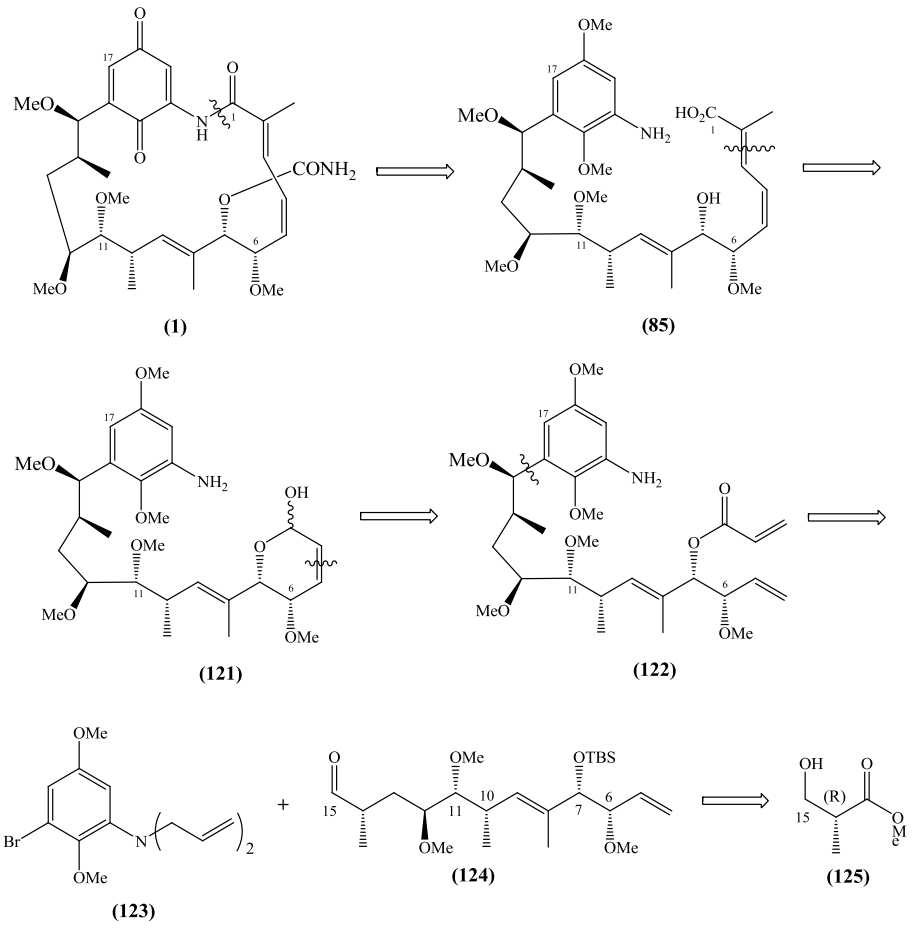


Reagents and conditions: a) BOP-Cl, DIPEA, 81 %; **b)** TBAF, 73 %;
c) $Cl_3CCONCO$, MeOH, K_2CO_3, 97 %; **d)** CAN, MeCN/H_2O (2:1), 63 %.

Scheme 31

V. Cossy's total synthesis

The most recent total synthesis of herbimycin A was that reported by the group of Cossy[72] in 2007. Their synthesis was novel in the sense that five of the structures seven chiral stereocentres of were installed based on allyl-metal methodologies, where the Z-alkene of the E/Z-diene system was installed through a Ring Closing Metathesis (RCM) [73].

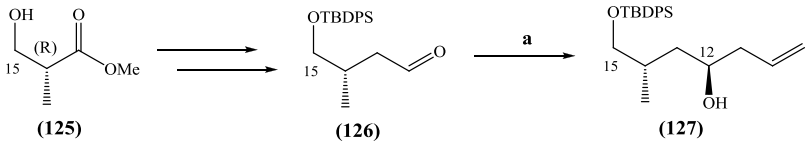


Scheme 32 – Cossy's retrosynthetic analysis[72]

The above retrosynthesis shows that the final step of the synthesis would be a macrolactamisation starting from acid **(85)**. The E-double bond of the *E*/*Z*-diene system would be set up thanks to a Wittig olefination carried out on lactol **(121)**, which would be formed *via* a ring closing metathesis of diene **(122)**. Further simplification of **(122)** led to a disconnection between herbimycin A's **(1)** aromatic portion and the C-15 methoxy aliphatic chain generating fragments **(123)** and **(124)**. The stereo-centre at C12 would be controlled by an allyltitanation and the C10, C11 and C6, C7 stereogenic centres would be the result of a *syn*-crotylboration and a *syn*-alkoxyallylboration,

respectively. The commercially available Roche® ester **(125)**, bearing the correct setereochemistry at C13, acted as the starting point for this synthesis.

To start with the synthesis of fragment **(124)**, aldehyde **(126)** was obtained in four steps from Roche ester **(125)**. Aldehyde **(126)** underwent a stereoselective allyltitanation[74,75] by treatment with Hafner's allyl titanium reagent **(*S*,*S*)-(128),** shown in Figure 15 (Scheme 33).



Reagents and conditions: a) (*S*,*S*)-(128), Et_2O, -78 ºC, 96 %, (dr = >95:5).

Scheme 33

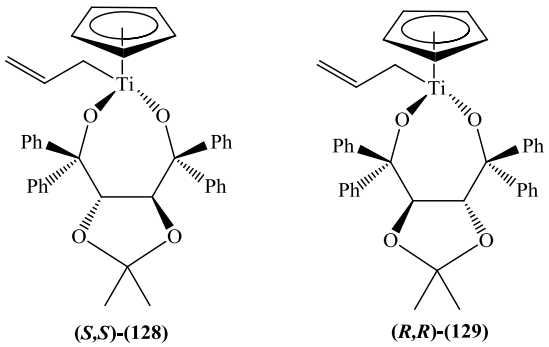
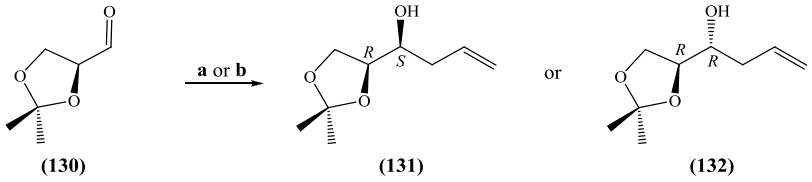


Figure 15 - Hafner's titanium reagents[74]

A range of titanium reagents derived from cyclopentadienyl titanium trichloride ($CpTiCl_3$) were investigated by Hafner and his group. The best results were obtained with titanium reagents **(128)** and **(129)** which enable the transfer of allyl groups with

very high diastereofacial selectivity[76]. Either alcohol **(131)** or **(132)** were obtained, depending if **(*R*,*R*)-(129)** or **(*S*,*S*)-(128)** was used (see Figure 15), with a diastereomeric ratio of 98:2 (Scheme 34). According to Hafner, the selectivity is more likely to be due to electronic rather than steric effects.



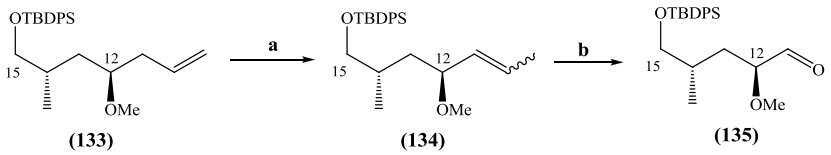
(130) **(131)** **(132)**

Reagents and conditions: a) (*R*,*R*)-(129), THF, -78 ºC, 80 % of **(131)**; **b) (*S*,*S*)-(128)**, THF, -78 ºC, 71 % of **(132)**, (dr = 98:2).

Scheme 34

Thanks to Hafner's[74] titanium reagent **(*S*,*S*)-(128)** (Figure 15), Cossy obtained alcohol **(127)** in a 96 % yield and with a 95:5 diastereomeric ratio (Scheme 34).

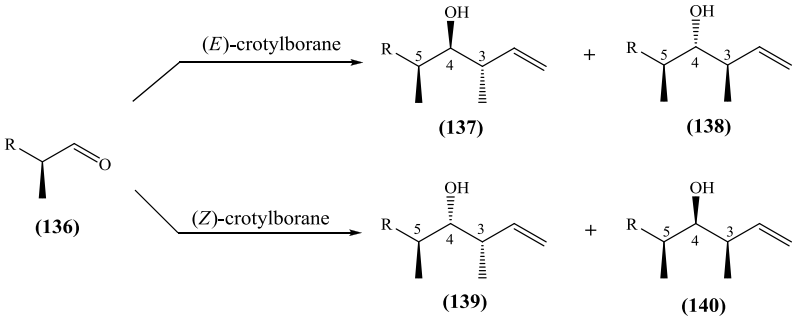
Alcohol **(127)** was then methylated before performing the isomerisation[77] of the terminal double bond of alkene **(133)** in a 98% yield using Grubbs' 2nd generation catalyst (2 mol%) (Scheme 35)[78]. Treatment of alkene **(134)** with osmium tetroxide and sodium periodate followed, generating aldehyde **(135)**, which was then used without any further purification.



Reagents and conditions: a) Grubbs II (2 mol %), *N*-allyl-*N*-tritylamine, DIPEA, toluene, 98 %; **b)** OsO_4, NMO, Me_2O/H_2O (9:1), *then* $NaIO_4$ (crude).

Scheme 35

The next step was to work on the stereocentres at C10 and C11. To do so, Cossy used tartrate crotylboronates, based on the methodology developed by Roush[79,80], where the crotylation reactions he investigated controlled the *syn*/*anti* relationships; (*E*)-crotylboronates tended to give *anti* C3-C4 alcohols **(137)** and **(138)** whereas (*Z*)-crotylboronates *syn* C3 - C4 alcohols **(139)** and **(140)** (Scheme 36). However, the diastereofacial selectivity of the aldehyde was harder to achieve.



Scheme 36 - Crotylboronation reactions investigated by Roush *et al.*[79]

During the study of the application of enantiopure tartrate ester modified crotylboronates **(141)** and **(142)** (Figure 16) and their corresponding enantiomers, Roush and co-workers observed that when they were used with α-methyl chiral aldehydes

(136), they were able to control the C4-C5 configuration as well as the C3-C4 one, thus allowing selective formation of **(137)** or **(138)** and **(139)** or **(140)** (Scheme 36)[79,80,81].

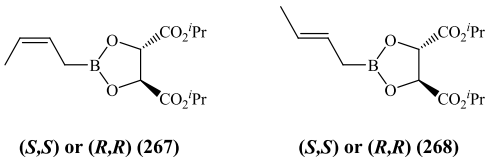
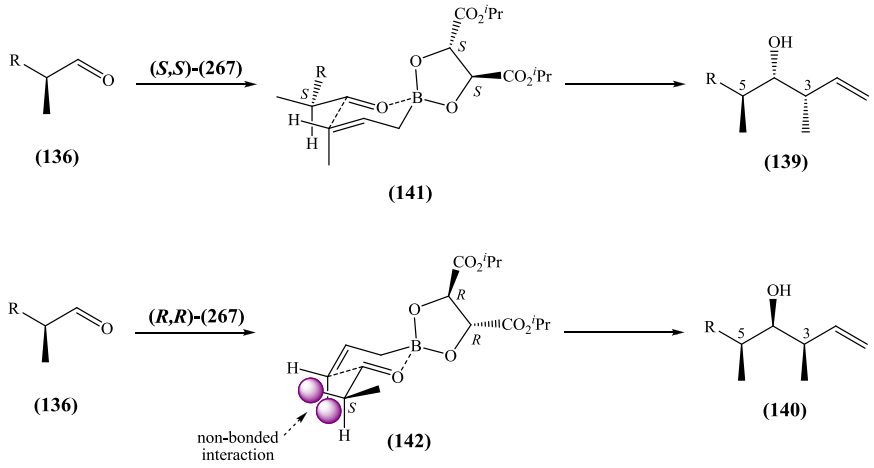
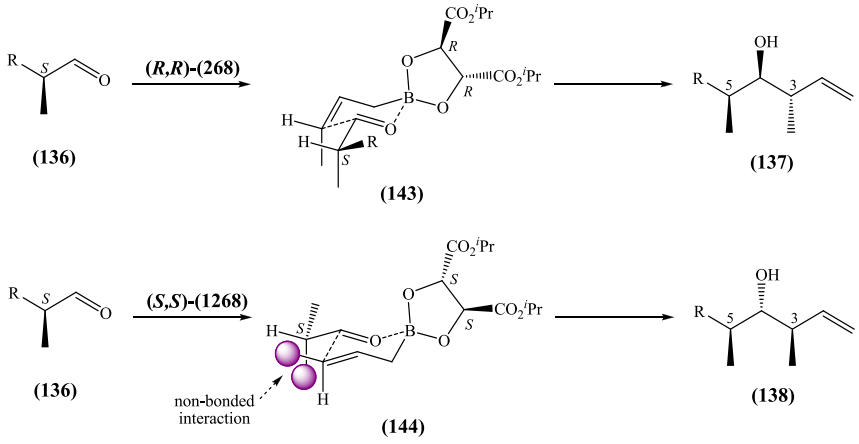


Figure 16 – (*Z*)- and (*E*)- crotylboronates[80]

Roush proposed an empirical model to describe the reactivity of **(141)** and **(142)** shown in Scheme 37 and Scheme 38[82]. Diastereoisomers **(137)** and **(139)**, formed *via* transition states **(143)** and **(141)**, each with a 3,5 *anti*-relationship are intrinsically favoured[82] whereas the 3,5-*syn* diastereoisomers **(138)** and **(140)** are intrinsically disfavoured due to the non-bonded interaction between the R group of the aldehyde and the methyl group of the crotyl reagent in transition states **(144)** and **(142)**.

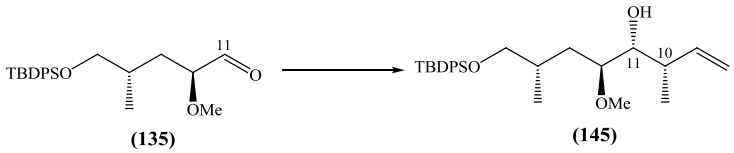


Scheme 37 - *Z*-crotylboronates



Scheme 38 - *E*-crotylboronates

This methodology was used in the synthesis of herbimycin A **(1)** by Cossy and her team (Scheme 39)[72]. They assumed the α-methoxy group in **(135)** would lead to the formation of the desired diastereoisomer **(145)** since R is larger than a methyl group. According to Roush's model, the reaction is intrinsically favoured[79]. Crotylation of aldehyde **(135)** using the *Z*-crotylboronate **(*S*,*S*)-(267)** gave the desired diastereoisomer **(145)** in a 70 % yield (Scheme 39). The formation of any other diastereoisomer was not reported.

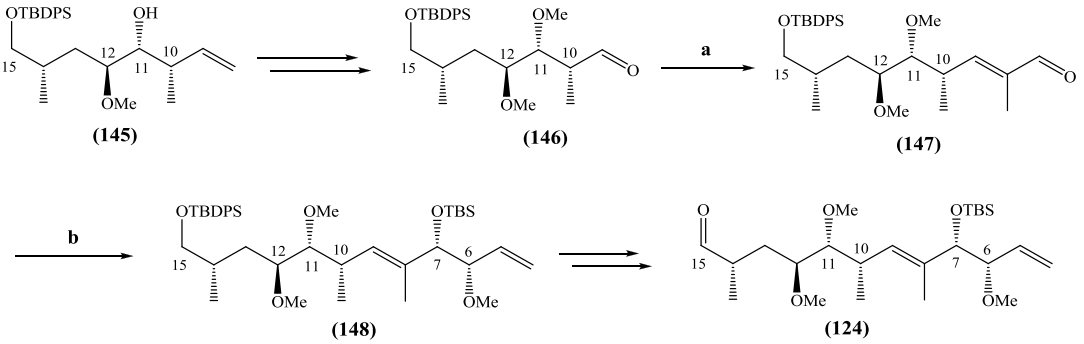


Reagents and conditions: (*S*,*S*)-(267), 4 Å MS, toluene, rt to -78 ºC, *then* 2N NaOH (aq), 0 ºC,70 %.

Scheme 39 – Crotylboronation installing both C10 and C11 stereo-centres

Successive methylation, dihydroxylation and cleavage starting from alcohol **(145)** gave aldehyde **(146)**, which then underwent a Corey-Schlessinger olefination[43] to get the α-β-unsaturated aldehyde **(147)** in a 93 % yield and an (*E*/*Z*)-ratio of 4:1.

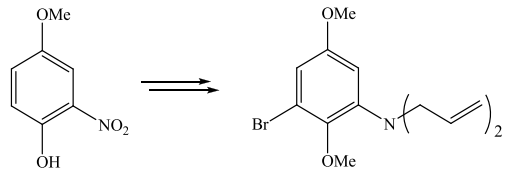
The desired C-6/C-7 *syn* product **(148)** was obtained *via* Brown's allylation in a 73% yield and a 4:1 diastereomeric ratio. Silyl protection, and selective deprotection followed by a Dess-Martin oxidation gave aldehyde **(124)** (Scheme 40).



Reagents and conditions: a) *N*-[2-(triethylsilyl)-propylidene]-*t*-butylamine, *s*-BuLi, *then* citric acid, 86 %, (4:1, (*E*:*Z*)); **b) (114)**, *s*-BuLi, THF, -78 ºC, $BF_3{\cdot}OEt_2$, -50 ºC to 0 ºC, 73 %, (dr = 4:1).

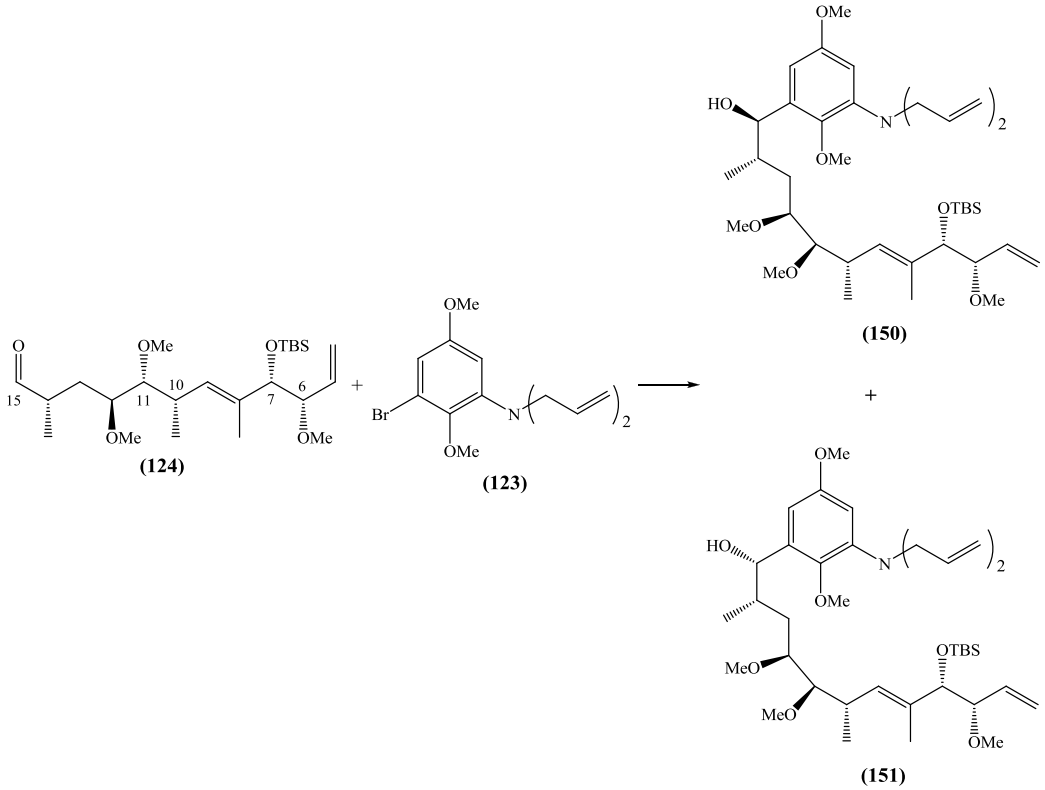
Scheme 40

The authors prepared the aromatic subunit **(123)** in 4 steps starting from commercially available 4-methoxy-2-nitrophenol **(149)** with an overall yield of 49% (Scheme 41).



Scheme 41

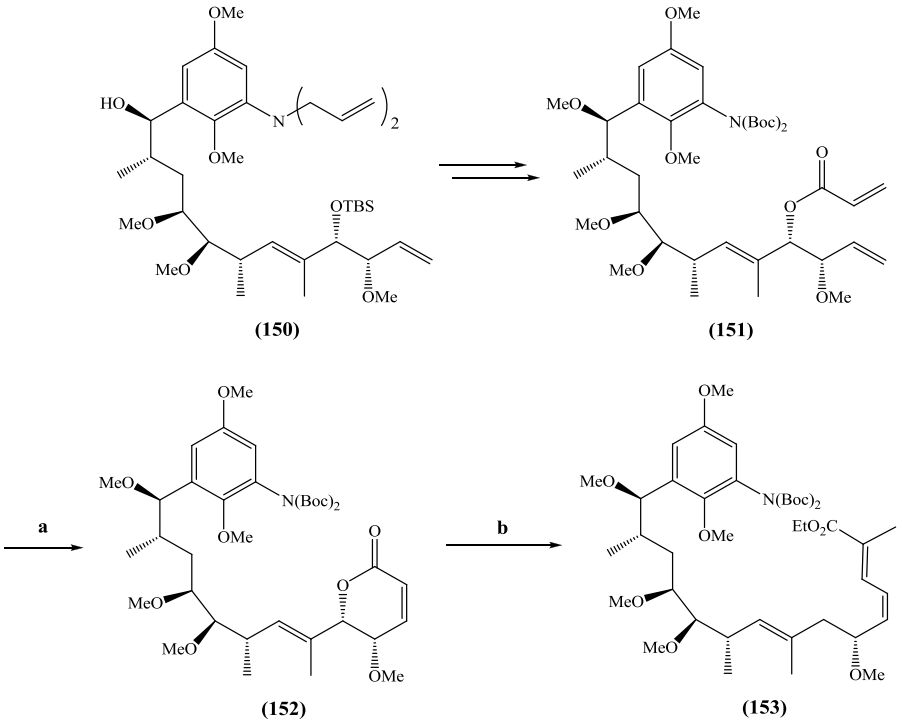
Coupling both aliphatic **(124)** and aromatic **(123)** fragments could then take place by means of a lithium halogen exchange. Cossy's team obtained a mixture of two diastereosiomers in an overall yield of 87% with a 1.6:1 ratio in favour of the desired Felkin-Ahn adduct **(150)** which could be isolated by silica gel chromatography, with a yield of 54 % (Scheme 42).



Reagents and conditions: *n*-BuLi, Et_2O, -78 °C to rt, *then* -78 °C, **(150)**, 87 %, (dr = 1.6:1, (**150**:**151**)).

Scheme 42 – Coupling reaction

The synthesis went on with the desired enantiomer **(150)** which underwent several steps leading to diene **(151)**. Grubb's 2nd generation catalyst was then used to perform a RCM with diene **(151)** to give lactone **(152)**, which was converted to the corresponding lactol. The sensitive *E*/*Z*-diene system was subsequently installed using the stabilized ylide 1-carboethoxyethylidenetriphenylphosphorane (Scheme 43)[83].

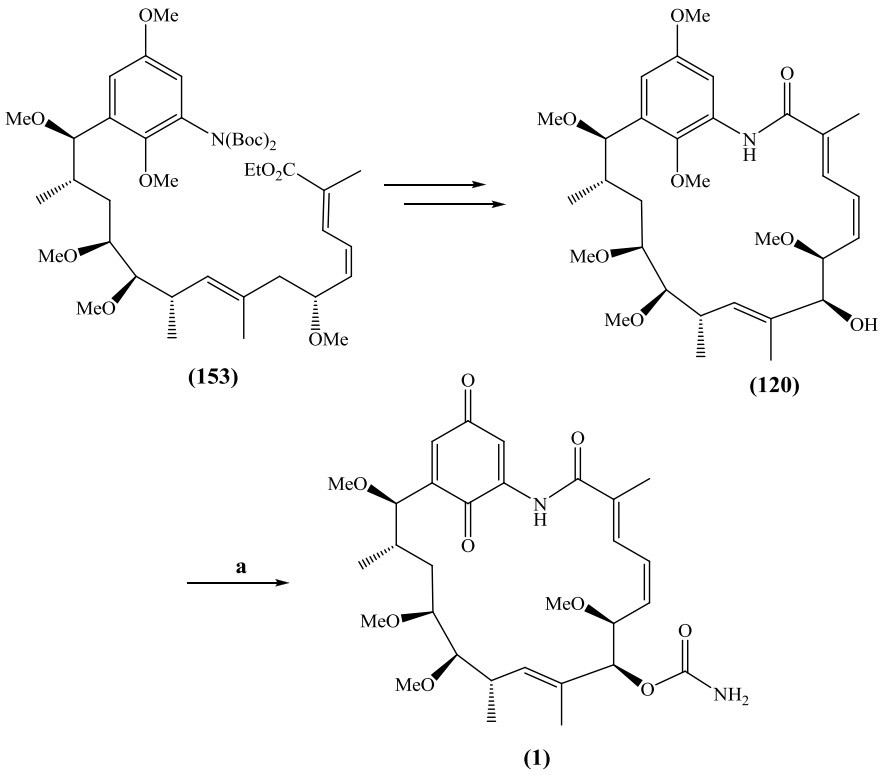


Reagents and conditions: a) Grubbs II (20 mol %), toluene, Δ, 72 %; **b)** DIBAL-H, Et_2O, -78 °C. *then* $Ph_3P{=}C(Me)CO_2Et$, toluene, Δ, (9:1, (*E*:*Z*)), (87 % over two steps).

Scheme 43

The end of the synthesis was based on the one Tatsuta[40] and Panek[58] reported (Scheme 44). The amine function of intermediate **(153)** was deprotected and a saponification was achieved before realizing the bis(2-oxo-3-oxazolidinyl)phosphinic chloride mediated macrocylization to give amide **(120)**.

Finally, a carbamate was formed at the desired C7 and the aromatic ring was oxidized by reaction with ceric ammonium nitrate to obtain herbimycin A **(1)** in 30 steps with an overall yield of 1.5 %.



Reagents and conditions: a) i) Cl_3CONCO, K_2CO_3, MeOH; ii) CAN (36 % over two steps).

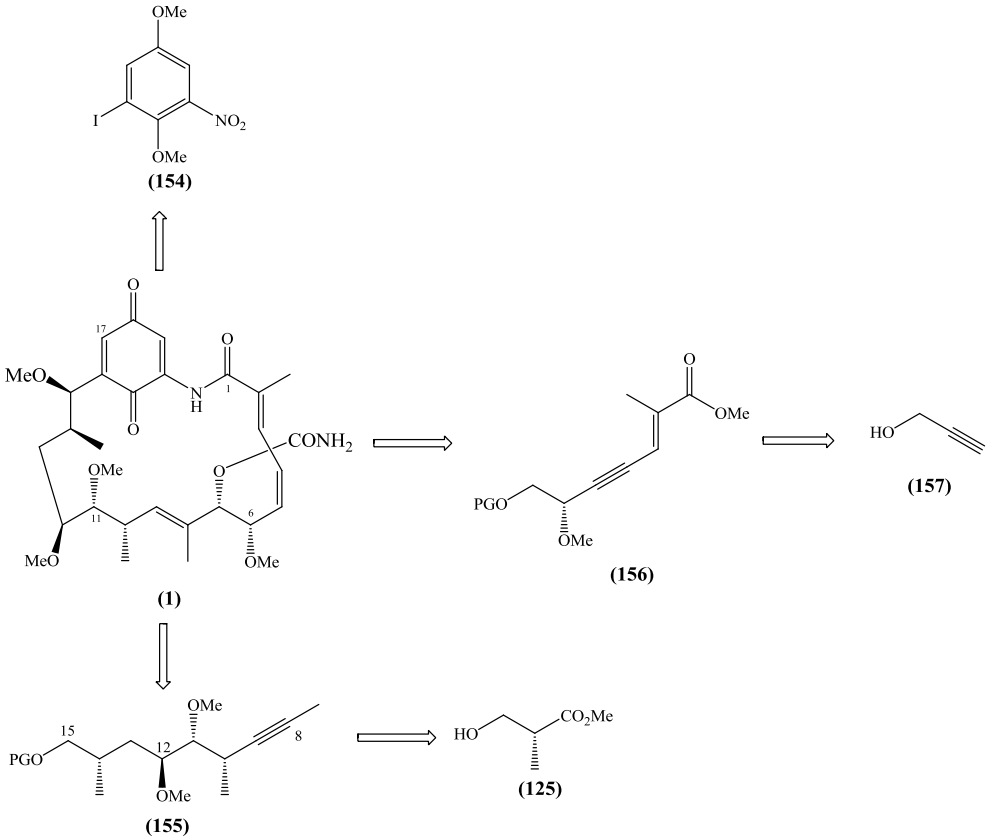
Scheme 44

In her synthesis, Cossy obtained the C5-C15 fragment *via* a concise and efficient route when compared with the synthesis of the same fragment reported by Tatsuta[40].

VI. Ardisson's partial synthesis

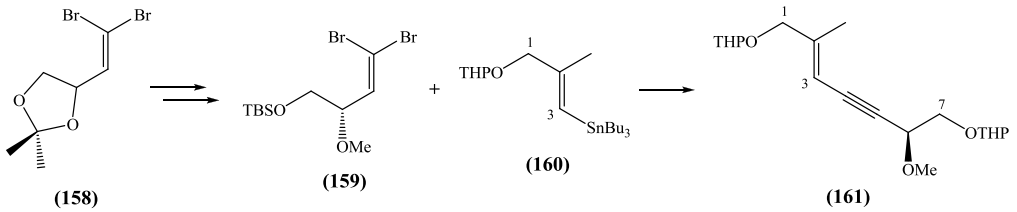
Ardisson and his team reported the construction of the three C16-N22 **(154)**, C1-C7 **(156)** and C8-C15 **(155)** segments of herbimycin A **(1)** in an attempt to develop its convergent synthesis (Scheme 45).

The key steps developed in this synthesis are an asymmetric Sharpless epoxidation[84,85] and a diastereoselective Hoppe crotylation[86] leading to fragment **(155)**.



Scheme 45

The synthesis of the C1-C7 fragment began with the conversion of dibromide **(158)** to the silyl ether **(159)** in three steps in an overall yield of 45 % (Scheme 46). Based on Shen's methodology[87], enyne **(161)** was formed by reacting **(159)** and **(160)** with dichloro bis-acetonitrile palladium ($Pd(CH_3CN)_2Cl_2$), copper (I) iodide and diisopropylethylamine in dimethylformamide at 85 °C, to give the desired enyne **(161)** in a 63 % yield.

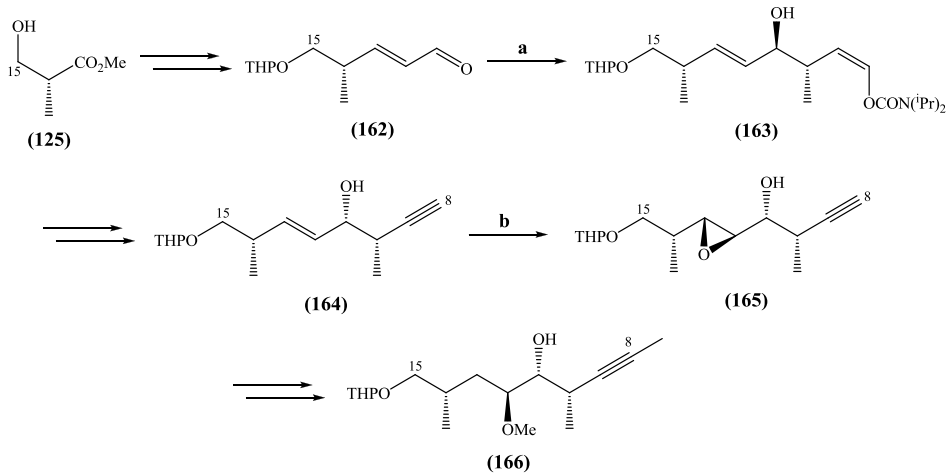


(158) **(159)** **(160)** **(161)**

Reagents and conditions: $Pd(CH_3CN)_2Cl_2$ (15 mol %), CuI (30 mol %), (1.5 eq), DMF, 85 °C, 63 %.

Scheme 46

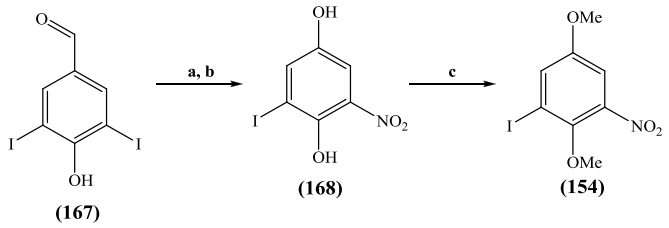
The C8-C15 fragment was formed starting with alcohol **(125)**, which was turned into aldehyde **(162)** in six steps in a 50 % yield (Scheme 47). The aldehyde **(162)** subsequently underwent a Hoppe crotylation resulting in alcohol **(163)** in an 85 % yield as a single diastereoisomer. Alcohol **(163)** was then converted to alkyne **(164)** in three steps in an overall yield of 22%. Sharpless epoxidation was then carried out on alkene **(164)** which was treated with D-(-)-diethyltartrate to give **(165)** in an 85 % yield as a single diastereoisomer. The synthesis of the C8-C15 fragment ended up with two additional steps to yield alkyne **(166)** in an overall yield of 42 %.



Reagents and conditions: a) (*E*)-crotyl (diisopropyl)carbamate (2.6 eq), 1.6 M *n*-BuLi (2.4 eq), (-)-sparteine (2.3 eq), -78 °C, *then* $Ti(Oi\text{-}Pr)_4$ (6 eq), pentane, -50 °C to -78 °C, *then* **(162)**, 85 %; **b)** D-(-)-diethyl tartrate (1.2 eq), TBHP (2 eq), CH_2Cl_2, -25 °C, 85 %.

Scheme 47

The aromatic sub-unit **(154)** was formed in three steps from the commercially available di-iodo compound **(167)** in an overall yield of 55 % (Scheme 48).



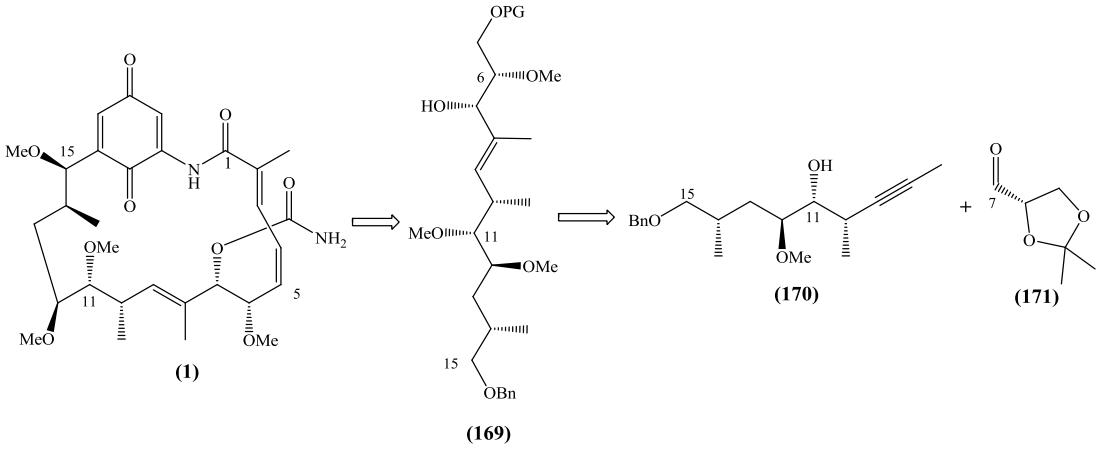
Reagents and conditions: a) $NaNO_2$, HOAc, 80 °C, 80 %; **b)** *m*-CPBA, CH_2Cl_2, 4 °C, 80 %; **c)** KOH, MeI, 20 °C, 85 %.

Scheme 48

To the best of our knowledge, the coupling of fragments **(154)**, **(155)** and **(156)** has not been reported yet.

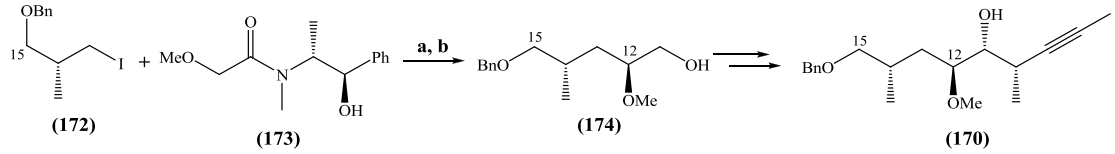
VII. Micalizio's partial synthesis

Micalizio and his team developed a general convergent route[88] to the C5 –C15 subunits of the ansamycin antibiotics herbimycin A **(1)**, geldanamycin **(5)** and macbecin 1 **(10)**. The key step in this synthesis would be the mediated coupling of alkyne **(170)** with aldehyde **(171)** (Scheme 49).



Scheme 49

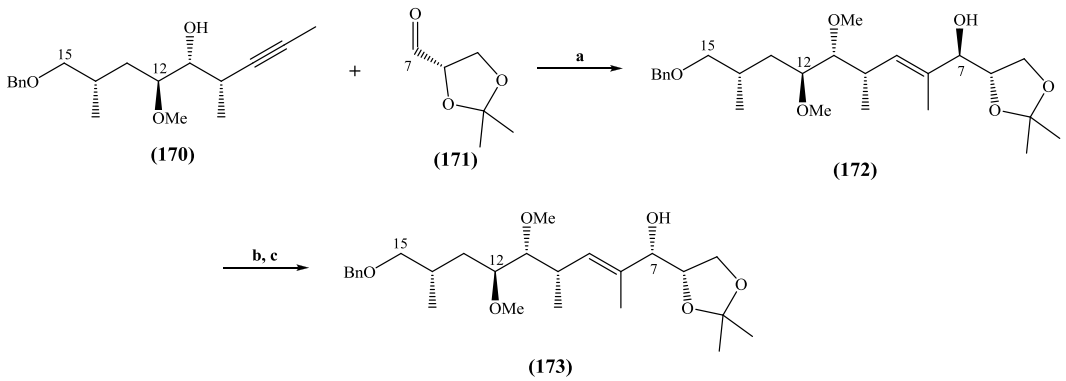
Roche iodide **(172)**[89] was first coupled to amide **(173)** based on Myers' alkylation[90] followed by the cleavage of the chiral auxiliary agent. Alcohol **(174)** was obtained in a 70 % yield (Scheme 50). Two additional steps lead to alkyne **(170)** in an overall yield of 50 %.



Reagents and conditions: a) LDA, THF, -78 °C to rt.; **b)** $BH_3 \cdot NH_3$, LDA, THF, (70 % over two steps), (dr = 4:1).

Scheme 50

A stereoselective titanium mediated coupling reaction between alkyne **(170)** and aldehyde **(171)** using $ClTi(O\textit{i}\text{-}Pr)_3$ provided the C5-C15 fragment of herbimycin A **(1)** (Scheme 51). Alcohol **(172)** was thus obtained in a 58 % yield as the major isomer in a 5:1 ratio of regioisomers and a 3:1 ratio of diastereoisomers in favour of the C7 undesired diastereoisomer[91]. Oxidation of alcohol **(172)** to the ketone using Dess-Martin periodinane[92] was followed by a stereo-selective reduction using L-selectride[93] to give the desired C7 diastereo-isomer required for herbimycin A **(1)** corresponding to the C5-C15 fragment **(173)** as the major diastereoisomer in an 84 % yield and a 20:1 ratio of diastereoisomers with regards to the C7 position (Scheme 51).



Reagents and conditions: a) NaH, MeI, THF *then* $ClTi(O\textit{i}\text{-}Pr)_3$, *c*-$C_5H_9MgCl$ -78 to -30 °C, *then* -78 °C, $BF_3{\cdot}OEt_2$, **(171)**, 58 %, (dr = 3:1, **(172:173)**); **b)** Dess-Martin periodinane, CH_2Cl_2; **b)** L-Selectride, 84 % over two steps, (dr = 20:1, **(173:172)**)

Scheme 51

The advantage of the route Micalizio developed is that it can also be applied to the synthesis of geldanamycin **(5)** and macbecin 1 **(10)**.

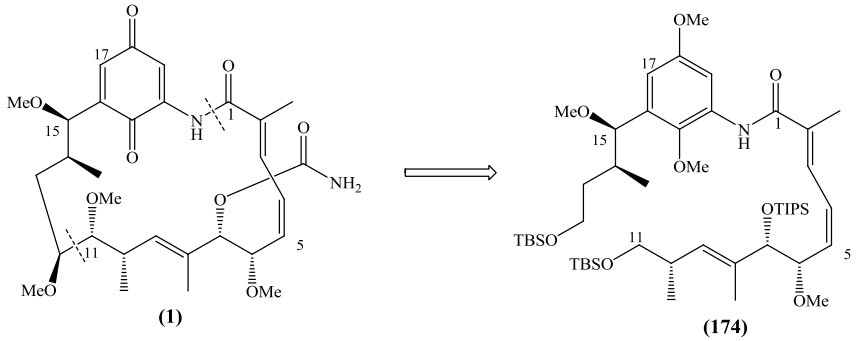
CHAPTER 3

RESULTS AND DISCUSSION

I. Previous Parsons'group study

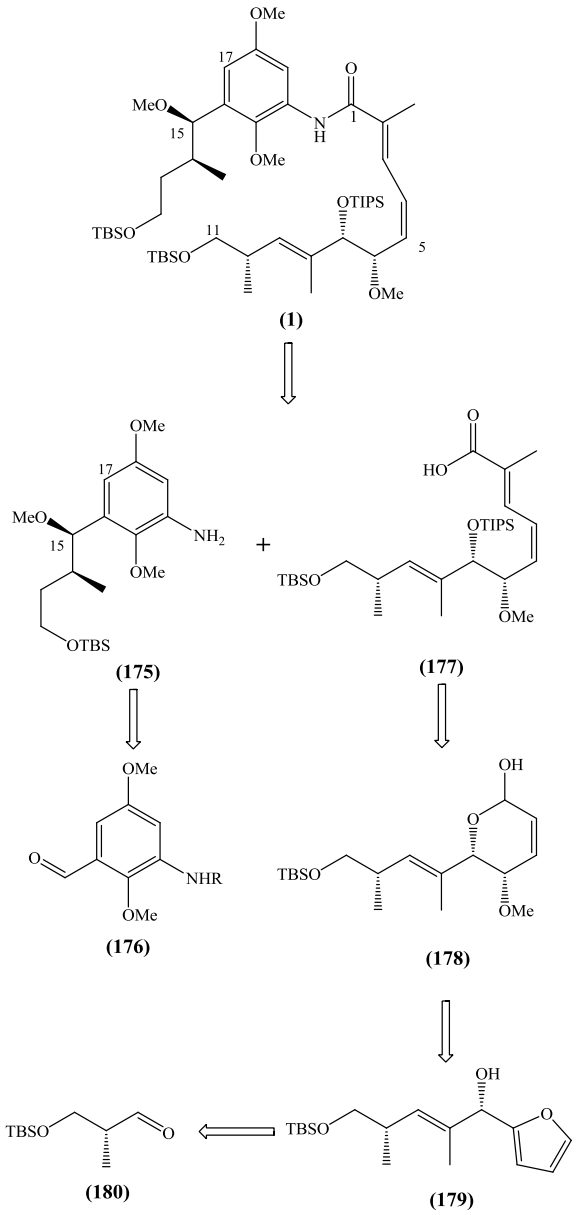
Dr. Ansell[94], a former member in the Parsons group, worked on the total synthesis of herbimycin A **(1)**. His study led to a concise, novel and divergent route to the advanced intermediate **(174)**.

The route proposed was to assemble the C11 and C12 stereo-centres as the last step in the macrocyclic assembly, using Pedersen's method[95].



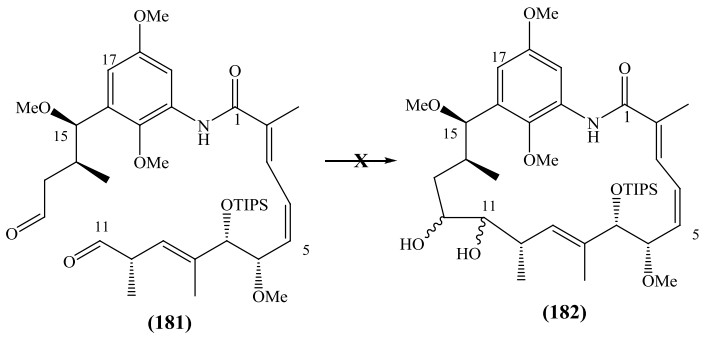
Scheme 52

This advanced intermediate was derived from the coupling of an aromatic **(175)** and an aliphatic fragment **(177)** whose retrosynthesis is presented below.



Scheme 53 – Ansell's retrosynthetic analysis

With intermediate **(174)** in hand, Ansell converted it to the di-aldehyde **(181)** with the aim of achieving macro-cyclisation with ($VCl_3(THF)_3$), in conjunction with activated zinc dust based on Pedersen's protocol[95]. Unfortunately, this did not proceed to give the desired product.

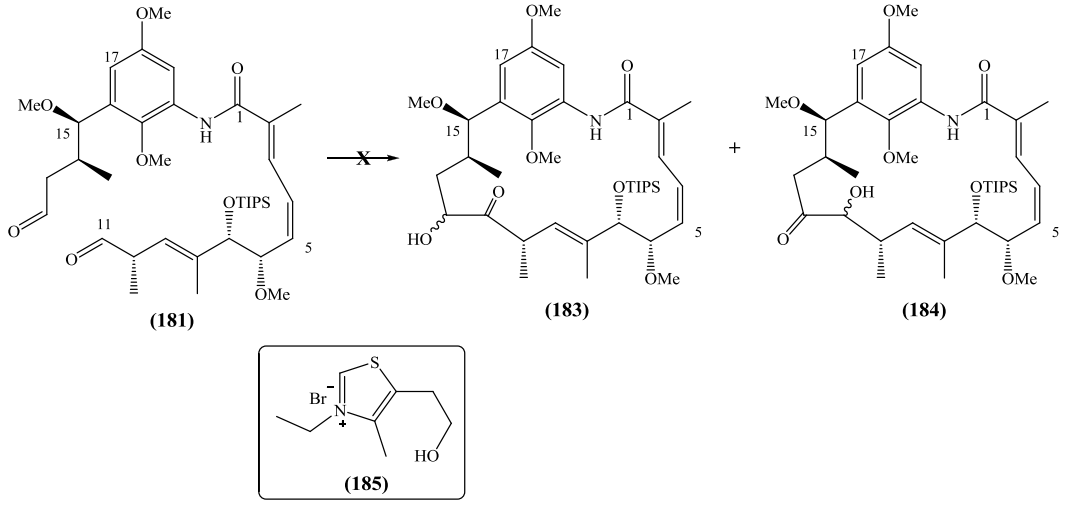


Reagents and conditions: $VCl_3(THF)_3$, Zn, THF, rt.

Scheme 54 – Mc Murry approach

This work was continued by Dr. Inga Pietsch[96] who further studied the Pedersen coupling, without success, and also worked on alternative approaches, such as the Mc Murry coupling[97] which uses a low valent titanium species, and the Stetter approach[98] with the macrocyclisation of the di-aldehyde **(181)**.

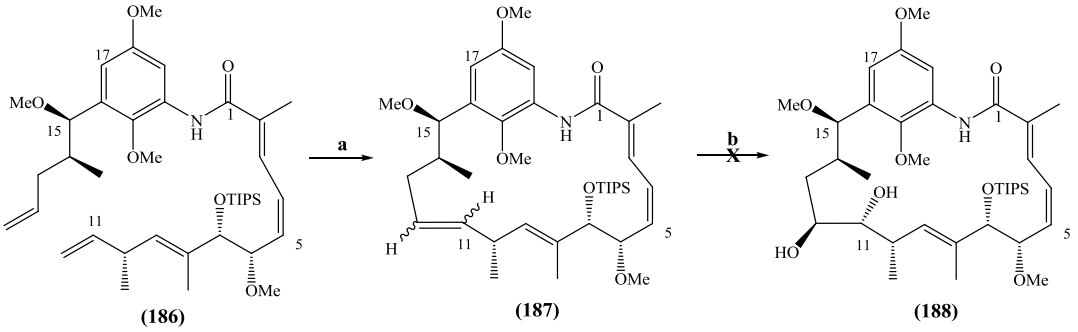
However, neither of these reactions resulted in the formation of the desired C11-C12 bond.



Reagents and conditions: **(185)**, DBU, *t*-BuOH, 40 ºC.

Scheme 55 - Stetter approach

The final attempt was attempted *via* RCM of the dialkene followed by selective dihydroxylation[99] and succeeded in producing the C11-C12 bond, but the desired diol **(188)** could not be installed.



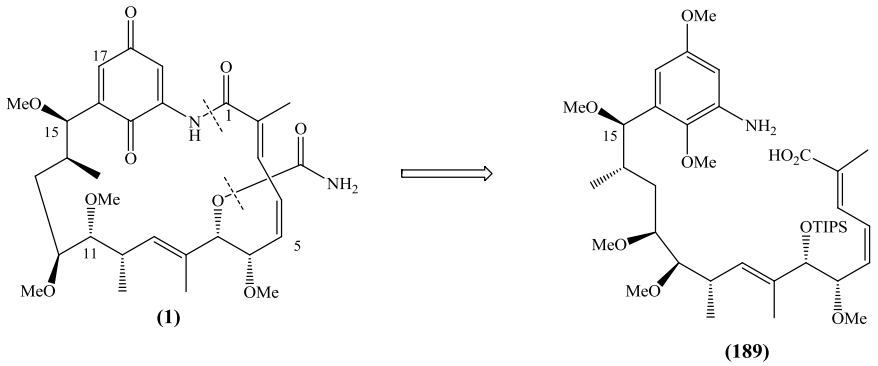
(186) **(187)** **(188)**

Reagents and conditions: a) Grubbs II[nd] generation catalyst, 10 mol %, CH_2Cl_2, approx. 43 %; *b)* OsO_4, K_2CO_3, $K_3Fe(CN)_6$, $(DHQ)_2$-Phal.

Scheme 56 – RCM and dihydroxylation approach

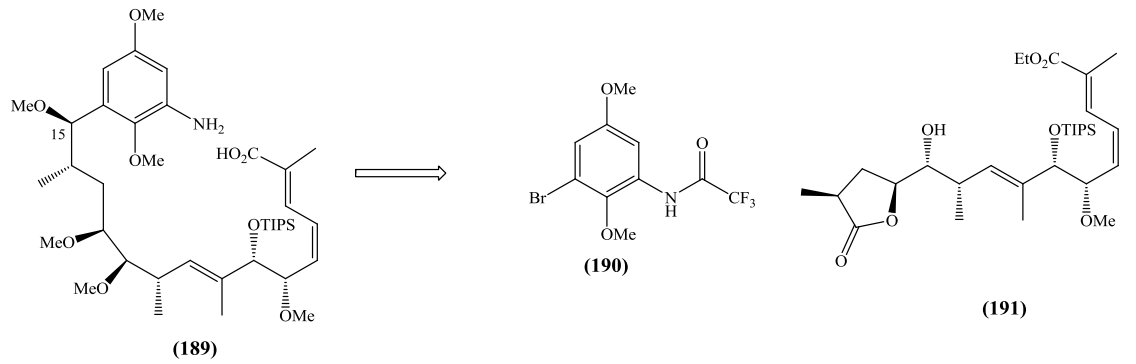
II. Retrosynthetic analysis

In this thesis, a brand new approach to herbimycin A **(1),** was envisaged in a mostly linear way. The first disconnection would be the amide bond, at the C1 position, whose coupling had been previously studied by Tatsuta[40,41].



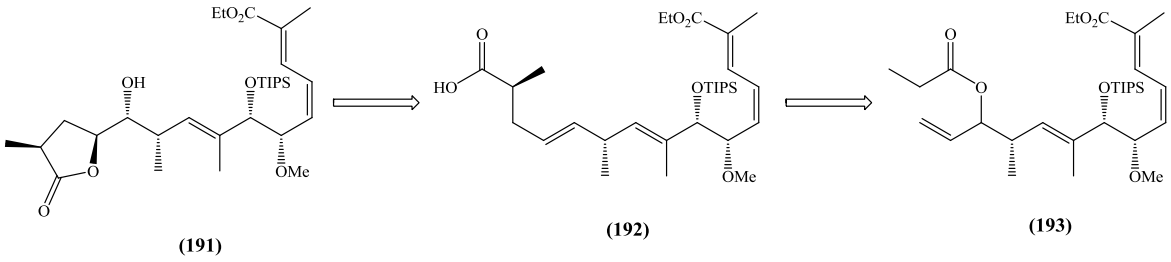
Scheme 57

A further series of disconnections then divided herbimycin A into two fragments: one an aliphatic **(191)** and the other a tetra substituted aromatic **(190)**.



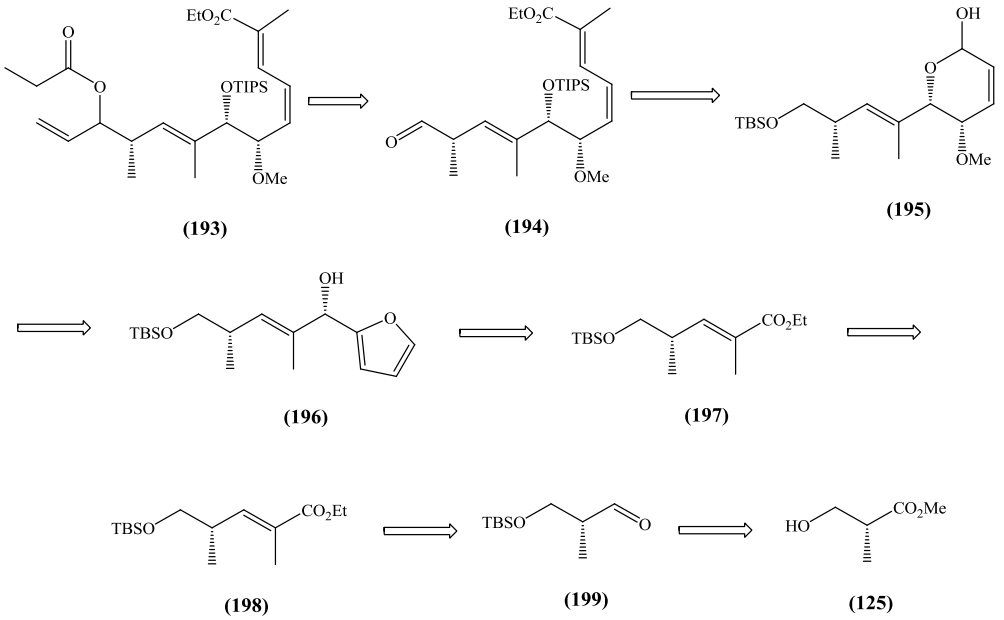
Scheme 58

The lactone fragment **(191)** would be obtained *via* the oxidative lactonization of the primary carboxylic acid **(192)**. This key step will be important in setting up the desired chirality in the final molecule.



Scheme 59

The primary acid **(192)** could be derived from the propionate **(193)** *via* an Ireland-Claisen rearrangement[100,101,102].



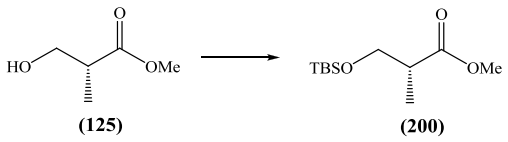
Scheme 60

Propionate **(193)** would be obtained from aldehyde **(194)** after a two steps, which itself would be the result of an oxidation and deprotection of alcohol **(195)**. The E/Z-diene system could be achieved through a ring expansion[103] of furyl alcohol **(196)**. This alcohol **(196)** is chiral and could be installed following a procedure devised by Terashima[104] starting from the corresponding furyl ketone. The *E*-olefin **(198)** would be the result of a Wittig reaction from aldehyde **(199)**, with the ultimate starting material being the commercially available Roche's ester **(125)**. This ester had been used previously by Cossy[72] and provides a starting point as it bears the desired C10 chiral center.

III. Initial attempt toward the aliphatic lactone fragment (191)

The synthesis of the aliphatic fragment commenced with following the procedures developed by Drs. Ansell[94] and Pietsch[96].

The initial step of the synthesis was to protect the alcohol of the chiral ester **(125)** using a silicon group in order to manipulate the ester.

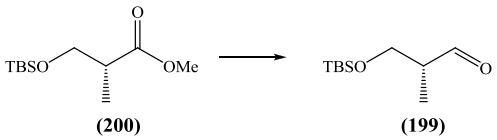


(125) **(200)**

Reagents and conditions: TBSCl, imidazole, DMAP (7%), CH_2Cl_2, 95%.

Scheme 61

Initially, it was attempted to obtain the aldehyde **(199)** directly from the ester by the use of DIBAL, however, despite using only one equivalent of DIBAL, the best yield obtained was only 60 % (Scheme 62).

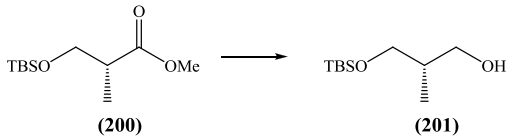


(200) **(199)**

Reagents and conditions: DIBAL-H (1 eq), CH_2Cl_2, -78˚C, 60%.

Scheme 62

It was therefore thought more efficient to reduce to the alcohol and subsequently oxidize back up to the aldehyde **(199)**. Extra equivalents of DIBAL were then used to give alcohol **(201)** in a 90 % yield (Scheme 63).

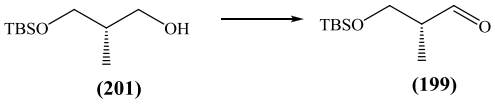


(200) **(201)**

Reagents and conditions: DIBAL-H, CH_2Cl_2, -78˚C, 90%.

Scheme 63

This was followed by oxidation to the aldehyde **(199),** obtained in an 85 % yield applying Parikh-Doering's conditions[105], using sulfur trioxide pyridine complex in dichloromethane and dimethyl sulfoxide.

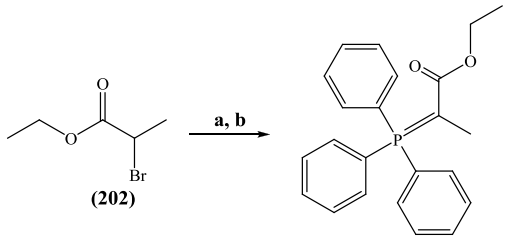


(201) **(199)**

Reagents and conditions: SO_3·Py, DMSO, CH_2Cl_2, Et_3N, 85%.

Scheme 64

The ylide, 1-carboethoxy ethylidenetriphenylphosphorane was freshly prepared from ethyl 2-bromopropanoate in toluene. The reaction mixture was stirred at 60˚C for four hours. It was important not to go over 60˚C as beyond that temperature, the reaction mixture became viscous and the intermediate bromide salt was not obtained (Scheme 65).

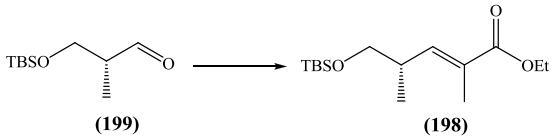


(202) **(203)**

Reagents and conditions: a) PPh_3, Tol., 60˚C; *b)* 1M NaOH, CH_2Cl_2, 70%.

Scheme 65

This ylide **(203)** was then used to insert the *E*-double bond thanks to a Wittig reaction, leading to ester **(198)** in an 80% yield (Scheme 66).

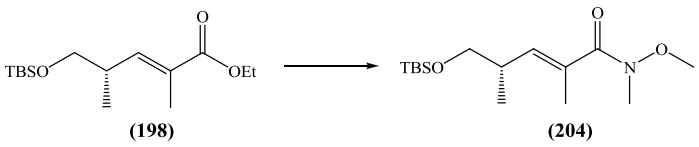


(199) **(198)**

Reagents and conditions: $Ph_3P{=}C(Me)CO_2Et$, Tol., 60˚C, 80%.

Scheme 66

The next step consisted in reaching Weinreb amide[106,107] **(204)**. The main advantage in using a Weinreb amide is that over addition of organometallic reagents can be avoided. The major advantage of this method over addition of organometallic reagents to more typical acyl compounds is that it avoids the common problem of over-addition. **(204)** had then to be formed in order to only have a single addition of furyllithium to obtain furylketone **(205)**.

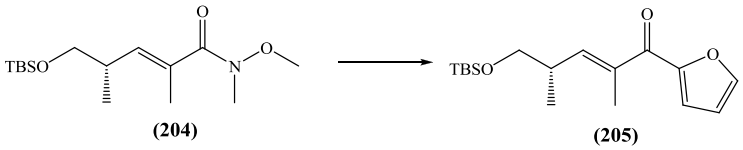


Reagents and conditions: (MeO)NH(Me).HCl, *i*-PrMgCl, THF, -5˚C, 4 h, 70%.

Scheme 67

Ester **(198)** was converted to Weinreb amide **(204)** in a 70 % yield with recovery of the starting material **(198)** which could then be used again.

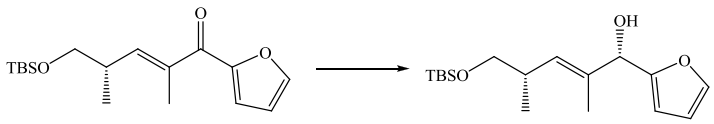
The following step was the addition of furyllithium, which was freshly prepared, to give furyl ketone **(205)** in a 95 % yield (Scheme 68).



Reagents and conditions: furan, *n*-BuLi, THF, 0˚C, then -5˚C, 95%.

Scheme 68

The following step was the reduction of the furyl ketone **(205)** to the alcohol **(196)**, following the procedure developed by Terashima and his team[104,108] (Scheme 69).



(205) **(196)**

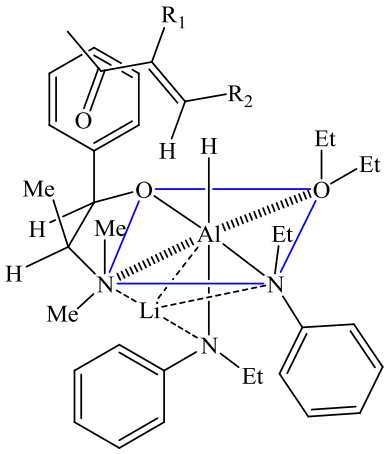
Reagents and conditions: $LiAlH_4$, Et_2O, (–)-*N*-methylphedrine, reflux, *then N*-ethylaniline, reflux, *then* -100˚C, 60%.

Scheme 69

Terashima discovered that a chiral reducing agent could be prepared from lithium aluminium hydride by reacting it with (-)-*N*-methylephedrine and *N*-ethylaniline. This was formed successfully to convert unsaturated ketones to their corresponding alcohols in high optical purity (78 % to 98 % ee) and high yields (92 % to 100 %).

Terashima showed that the reduction using (-)-*N*-methylephedrine favoured the formation of the *S*-enantiomer.

Presented below is one of the most likely transition states the authors proposed. The ketone comes in from the upper face of the complex from the least hindered angle of approach.



where R_1 = alkyl or H

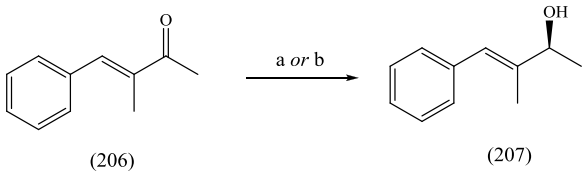
and R_2 = alkyl or aryl

Figure 17 - Transition state proposed by Terashima

Following Terashima's initial procedure, *N*-ethylaniline was then used, acting as the achiral amine additive (Scheme 69). The reducing agent was prepared just beforehand with lithium aluminium hydride which was first treated with (-)-*N*-methylephedrine at 0 ºC, followed by heating to reflux for 90 minutes. *N*-ethylaniline was then added and the reaction mixture was heated up again to reflux for a further 90 minutes. Before adding the furylketone **(205)**, the reaction mixture was cooled down to about -100 °C. The reaction mixture was stirred at this same temperature for four hours, before being quenched. Subsequent work-up and purification led to furyl alcohol **(196)** in a 61% yield.

Only later on did we found that Terashima[109] obtained a better selectivity with the reduction of 4-phenyl-3(*E*)-buten-2-one **(206)** to the desired *S*-alcohol **(*S*)-(-)-(207)**, using diphenylamine instead of *N*-ethylaniline. He also published a correction of his previous results. For instance, with the reduction of 4-phenyl-3(*E*)-buten-2-one **(206)**, the optical purity obtained with *N*-ethylaniline was 47% with a yield of 94%. When

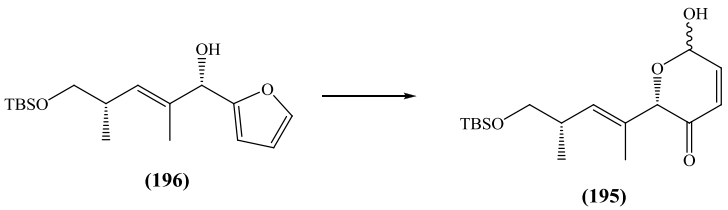
diphenylamine was employed, the optical purity reached 66% with a similar yield (97%) (Scheme 70).



Reagents and conditions: a $LiAlH_4$ (3.3 eq), (-)-N-methylphedrine (3.6 eq), N-ethylaniline (7.2 eq), 94%, 47%, ee; *b* $LiAlH_4$ (3.3 eq), (-)-N-methylphedrine (3.6 eq), diphenylamine (7.2 eq), 97%, 66%, ee.

Scheme 70 - Reduction of 4-Phenyl-3-(*E*)-buten-2-one **(206)** by Terashima

Next comes the formation of the lactol **(195)** through the ring expansion of the furyl compound **(196)** (Scheme 71).



Reagents and conditions: NBS, THF/H_2O (4:1), -5 °C, 62 %.

Scheme 71

Many reagents and conditions were tried by Ansell[94], such as bromine[110], dimethyldioxirane[111], Sharpless[112] and m-chloroperbenzoic acid[113] but the best yields were obtained with the addition of a stoichiometric amount of *N*-bromosuccinimide at 0 °C in THF and water (4:1)[103]. Georgiadis and Couladouros[103]

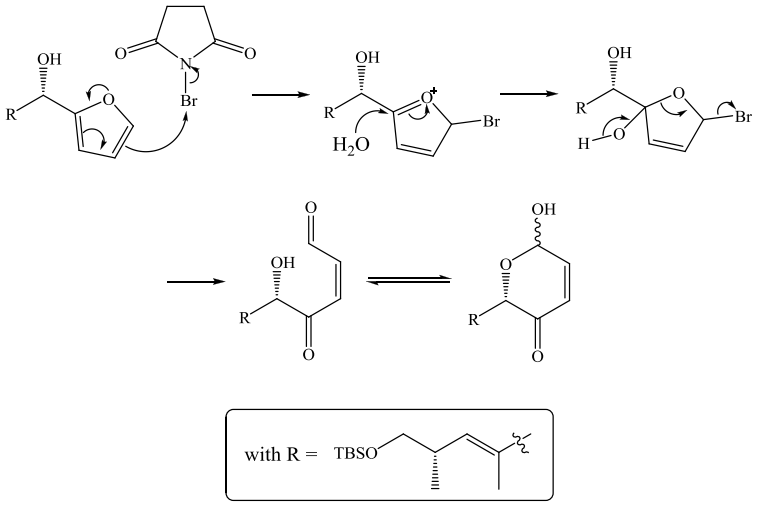
stated several conditions in order to avoid the formation of any by-products and to reach high yields:

- the temperature should be maintained below 5 °C,
- any excess of *N*-bromosuccinimide had to be destroyed in order for the subsequently liberated *in situ* bromine to be immediately consumed.

In order to remove any NBS and bromine residue, successive washings of the organic fraction were carried out with 15% aqueous sodium dithionite and 10% aqueous sodium bicarbonate.

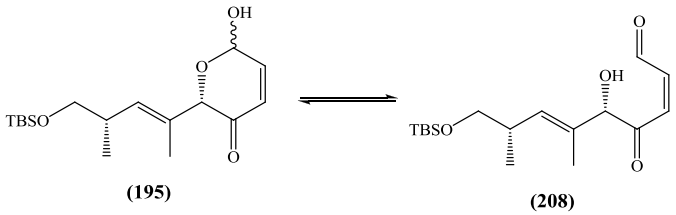
In addition, as our system proved to be acid-sensitive, neutral silica had to be used in order for the crude product to be purified by silica chromatography. Lactol **(195)** could be obtained in a 62% yield.

Regarding the mechanism of this reaction, it was believed to proceed through the intermediates pictured below in Scheme 72.



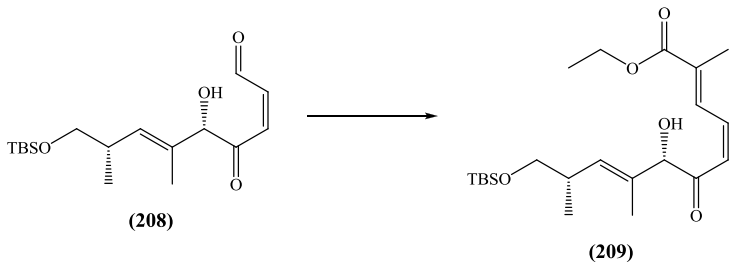
Scheme 72

The lactol **(195)** exists in equilibrium with its aldehyde form **(208)** thus allowing for reactions to take place with the carbonyl group (Scheme 73).



Scheme 73

Subsequent reaction of lactol **(195)** with Wittig ylide 1-carboethoxy ethylidenetriphenylphosphorane led to the desired E/Z-diene **(209)** in an 85% yield (Scheme 74). In order to prevent any isomerisation, the reaction was carried out at room temperature and neutral silica was used for the purification process.



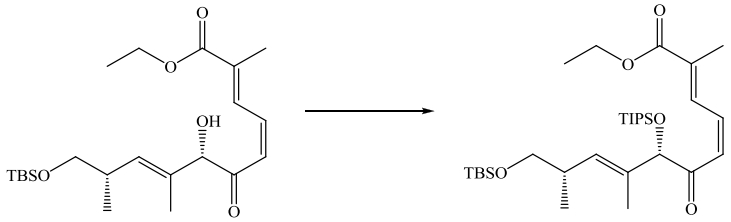
Reagents and conditions: $Ph_3P=C(Me)CO_2Et$, C_6H_6, rt, 85 %.

Scheme 74

Then, the free secondary alcohol was protected with triisopropylsilyl[114] (TIPS) in order to differentiate it from the primary alcohol which is being protected with terbutyldimethylsilyl. TIPS is one of the most sterically hindered silyl protecting groups. Reaction with tetrabutylammonium fluoride is a common method for TIPS desilylations[115]. Ogilvie and co-workers were the firsts to introduce the use of the triisopropylsilyl (TIPS) group as a selective protecting group for alcohols[116].

TIPS-protection reactions can be achieved using either triisopropylchlorosilane (TIPS-Cl), triisopropylsilane[117] or the triflate[118] (TIPS-OTf). According to Rucker[114], the best results are obtained with TIPS-OTf which was therefore what was used for this specific step.

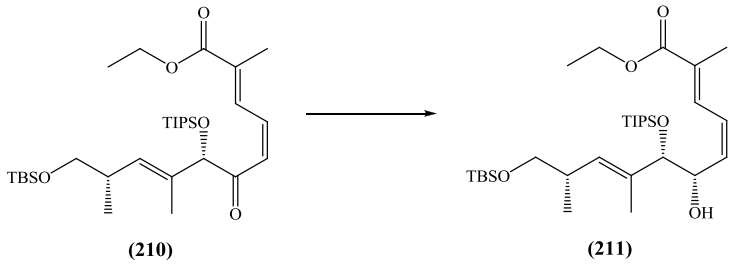
The silylation of alcohol **(209)** led to the corresponding silyl ether **(210)** in an 85 % yield.



Reagents and conditions: TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 85 %.

Scheme 75

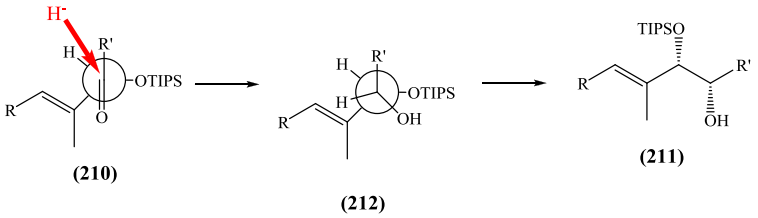
As we were then in the presence of an enone, we decided to perform Luche 1,2-reduction[119] starting from enone **(210)** down to the corresponding chiral alcohol **(211)** in a 94% yield. A high level of stereoselectivity could be obtained but a minor by-product could also be observed by proton and carbon NMR. This by-product was thought to be a diastereoisomer.



Reagents and conditions: $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, 0 °C, 94%.

Scheme 76

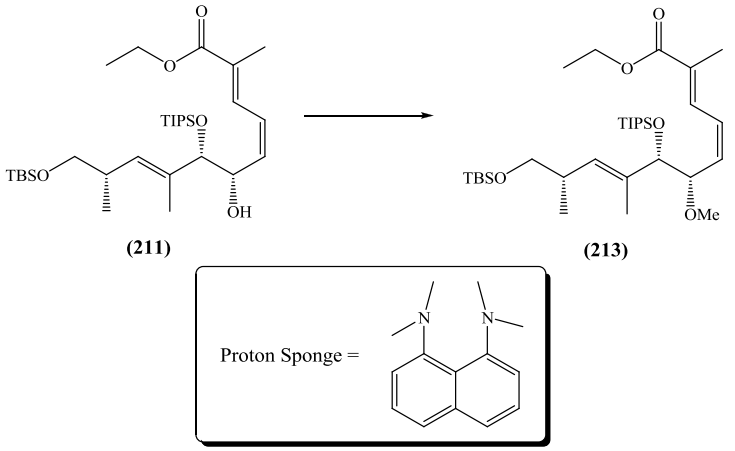
Felkin-Ahn[120] transition sate model can explain the observed diastereoselectivity. Below is presented the Felkin-Ahn transition state model (Scheme 77).



Scheme 77

Scheme 77 above shows that the hydride is likely to attack from the less hindered face with an angle of 107 ˚C with regards to the carbonyl group.

Alcohol **(211)** was then methylated using trimethyloxonium tetratfluoroborate and a proton sponge^{TM} to obtain the methyl ether **(213)** in an 89% yield (Scheme 78)[121].



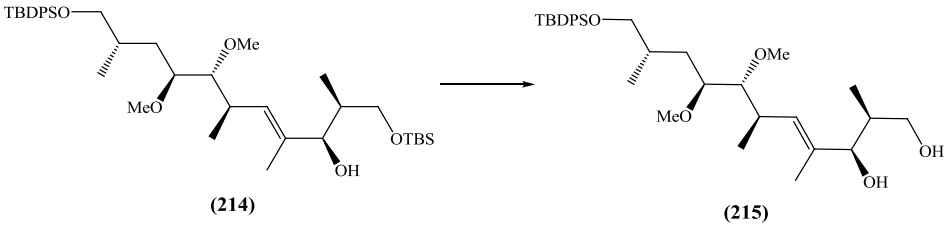
Reagents and conditions: Me_3OBF_4, Proton Sponge^{TM}, CH_2Cl_2, 89 %.

Scheme 78

Now that we have finished working on the right hand-side of the molecule, we next turned our attention to the left hand-side. The idea was to selectively remove the TBS protecting group in the presence of the TIPS group as the latter one is bulkier and,

in our case, is connected to a secondary alcohol whereas the TBS group is only connected to a primary alcohol.

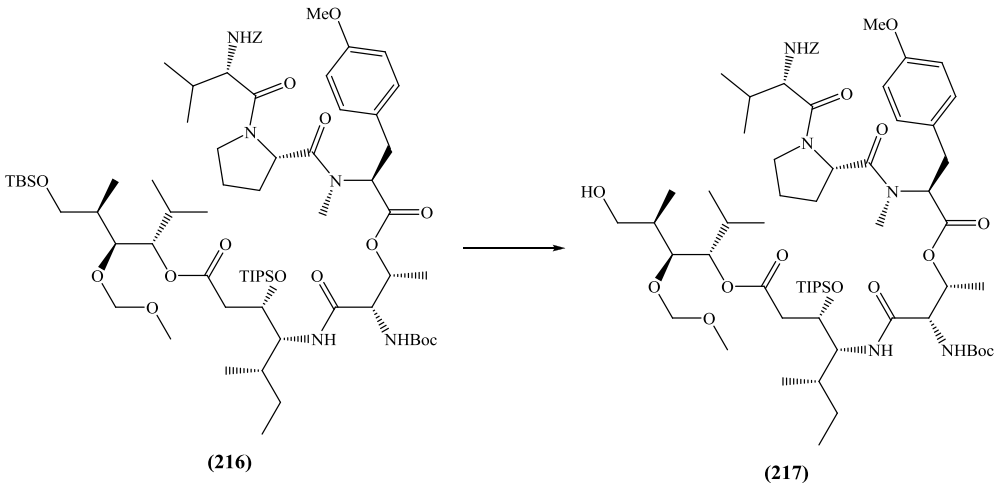
In 1991, Marshall and co-workers reported the use of acetic acid to selectively deprotect TBS ethers in the presence of other protecting groups for the synthesis of the C11-C21 fragment of Macbecin 1[122].



Reagents and conditions: AcOH, THF, H_2O, 87 %.

Scheme 79

The same conditions were used by Joullie[123] for the synthesis of didemins A, B and C, in the presence of TIPS:

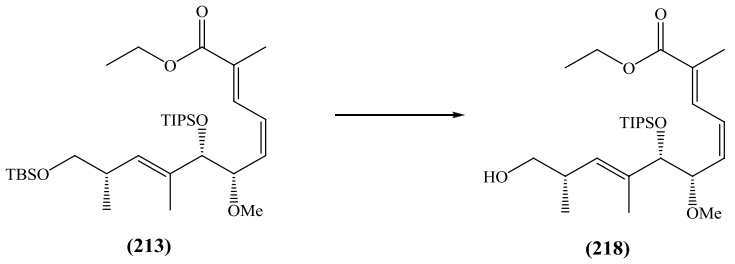


(216) **(217)**

Reagents and conditions: AcOH, THF, H_2O, 12 h, 83 %.

Scheme 80

Applying these same conditions to our substrate gave a successful result as the TBS group could be removed in a quantitative yield (Scheme 81).

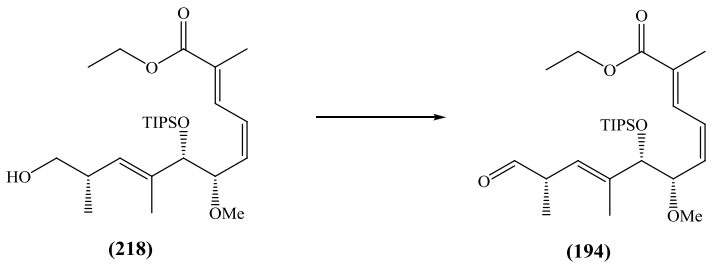


(213) **(218)**

Reagents and conditions: AcOH, THF, H_2O, overnight, 100 %.

Scheme 81

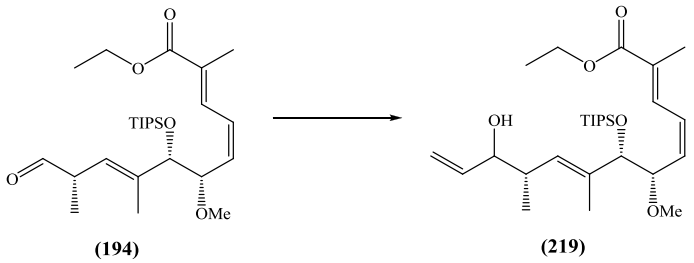
The deprotected primary alcohol **(218)** was then oxidized relying on Ley's oxidation[124] using TPAP and NMO, leading to the aldehyde **(194)** in a 70 % yield.



Reagents and conditions: NMO, TPAP, CH_2Cl_2, 70 %.

Scheme 82

Aldehyde **(194)** was then subjected to the attack of vinyl magnesium bromide, leading to allyl alcohol **(219)** in a 60 % yield (Scheme 83). Several spots were observed by thin layer chromatography, but only the ally alcohol **(219)** could be isolated after purification. Attack on the ester function of aldehyde **(194)** could explain why the yield is modest, although such by-product could not be isolated.



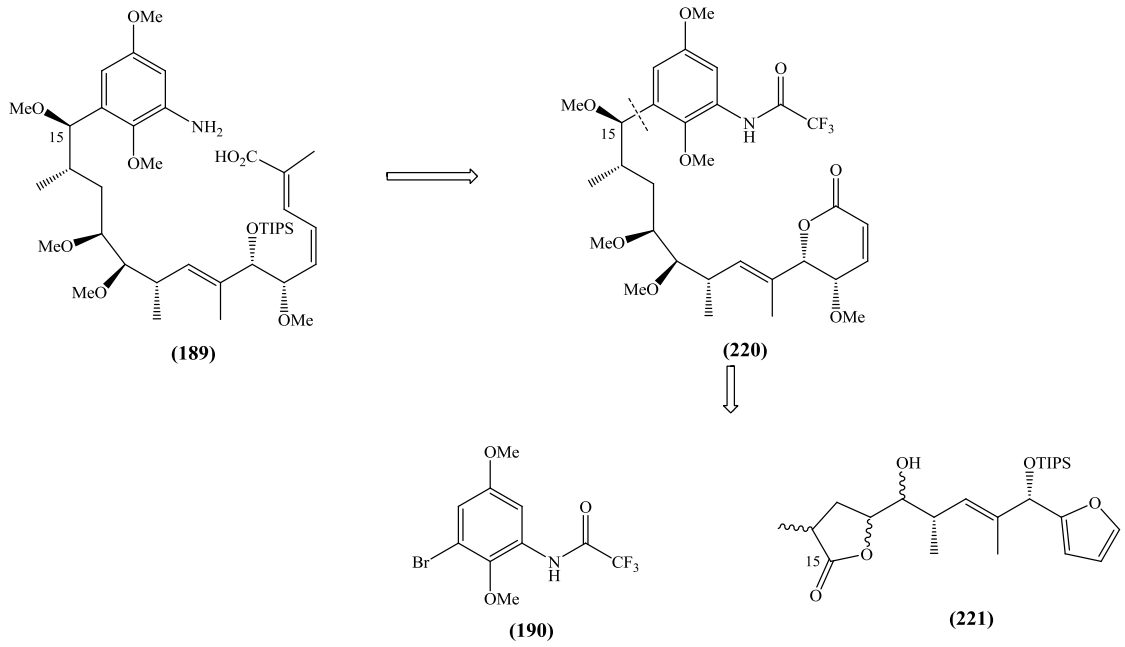
Reagents and conditions: vinyl magnesium bromide, THF, 0˚C, 60 %.

Scheme 83

At this stage, we only had a small amount in hands to go ahead. So far, 15 steps have been carried out starting from Roche ester **(125)** with an overall yield of 3 %. Due to the lack of intermediate to proceed any further, we modified our route so that the Ireland-Claisen rearrangement could be performed at an earlier stage in the synthesis of the aliphatic fragment.

IV. Alternative Approach to the Aliphatic Fragment

Below is shown our new retrosynthetic analysis:



Scheme 84

The main difference with our strategy is the aliphatic sub-units:

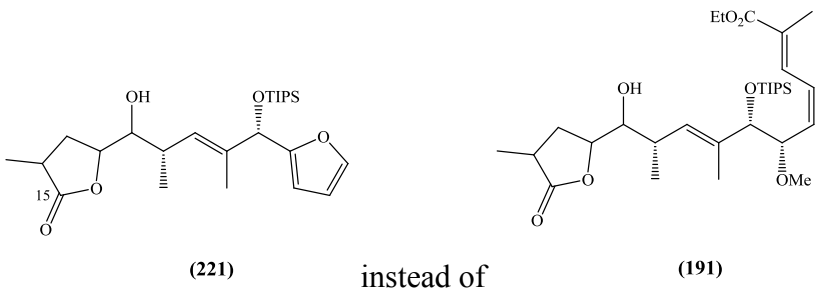
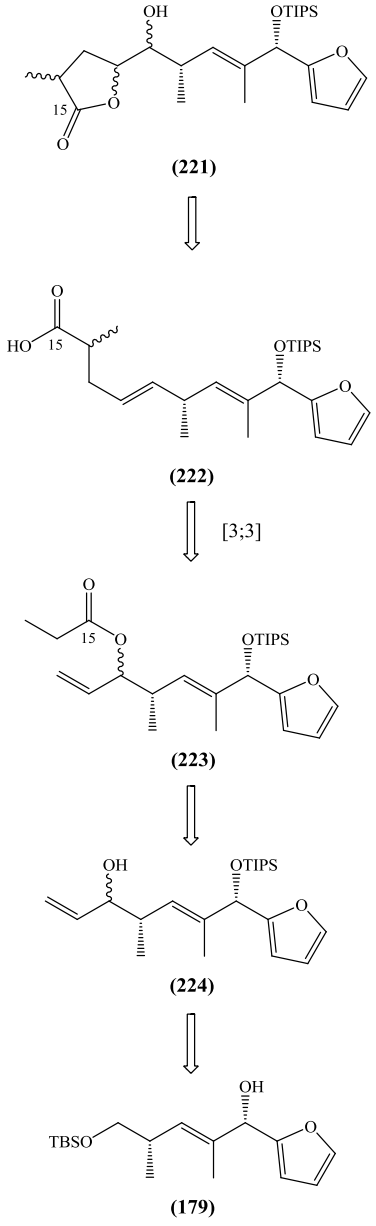


Figure 18

We decided not to worry about the ring extension step and leave the furyl ring untouched. Our new target was then the aliphatic fragment **(223)** whose retrosynthesis is presented in Scheme 85 below.



Scheme 85

The target lactone **(221)** would be formed from the acid **(222)**. This acid **(222)** would be derived from the sigmatropic rearrangement of the propionate **(223)** using the Ireland-Claisen protocol.

We hoped this propionate **(223)** could be synthesized from the already available alcohol **(224)** *via* protection of the secondary alcohol and manipulation of the protected primary alcohol **(179)**.

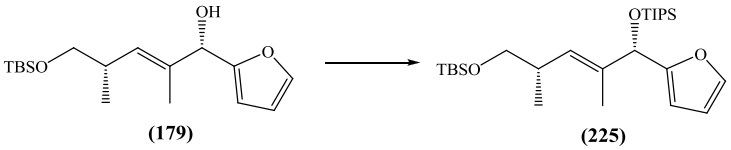
Therefore, we started again with chiral alcohol **(179)** which we could synthesize earlier and decided to protect it using the triisopropylsilyl group and different conditions were carried out:

Entry	Reagent	Base	Solvent	Yield
1	TIPS-OTf	Et_3N	CH_2Cl_2	20 %
2	TIPS-OTf	$^{i}Pr_2NEt$	CH_2Cl_2	18 %
3	TIPS-OTf	2,6-lutidine	CH_2Cl_2	40 %
4	TIPS-OTf	2,6-lutidine	benzene	32 %

Table 5

On Table 5 above, the highest yield was obtained in CH_2Cl_2 using 2,6-lutidine. The alcohol **(179)** was taken up in dichloromethane and the temperature was cooled down to 0 °C before adding 2,6-lutidine. The reactive mixture was then stirred at 0 °C for about ten minutes and tri-isopropylsilyl trifluoromethanesulfonate added dropwise.

The reactive mixture was warmed up to ambient temperature and stirred overnight to produce, after work up and purification, the disilylated compound **(225)** in a 40 % yield (Scheme 86).

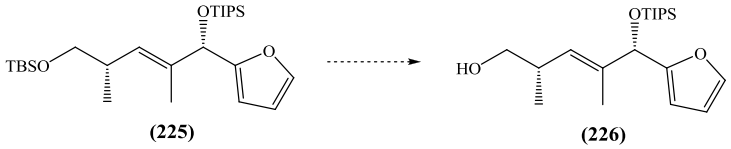


(179) **(225)**

Reagents and conditions: TIPS-OTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 40 %.

Scheme 86

Attempts were made to selectively remove the TBS protecting group in the presence of the TIPS group.



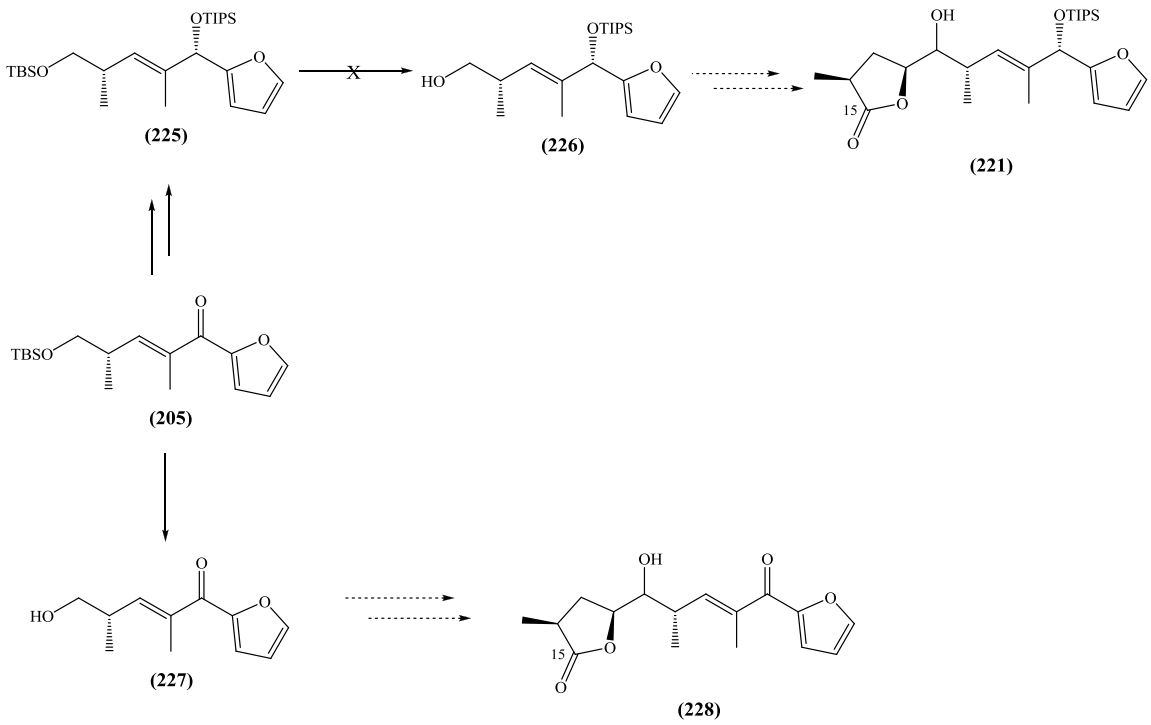
(225) **(226)**

Scheme 87

As the TIPS group being bulky and connected to a secondary alcohol compared to the TBS group connected to a primary alcohol, we thought the deprotection step would work. Acid hydrolysis, using 1% HC1 in ethanol, along with base hydrolysis, using 5% NaOH in ethanol, and fluoride cleavage, using TBAF in THF, did not work. The conditions applied earlier with a mixture of glacial acetic acid, water and THF did not work either.

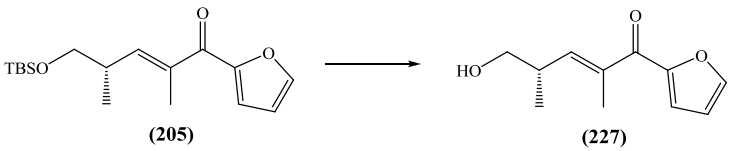
Unfortunately, the reaction did not proceed for our substrate **(226)**. The reaction was carried out with a scope of different acetic acid / water / THF ratios, without any positive outcome. We ended up getting a mixture of compounds which could not be separated nor characterized.

We then had to change our strategy and decided to start from furyl ketone **(205)** (Scheme 88).



Scheme 88

The primary alcohol being protected, we then had to deprotect it, allowing us to perform further reactions.



(205) **(227)**

Reagents and conditions: $Py{\cdot}Br_3$ (5 %), MeOH, rt, 3 hours, 80 %.

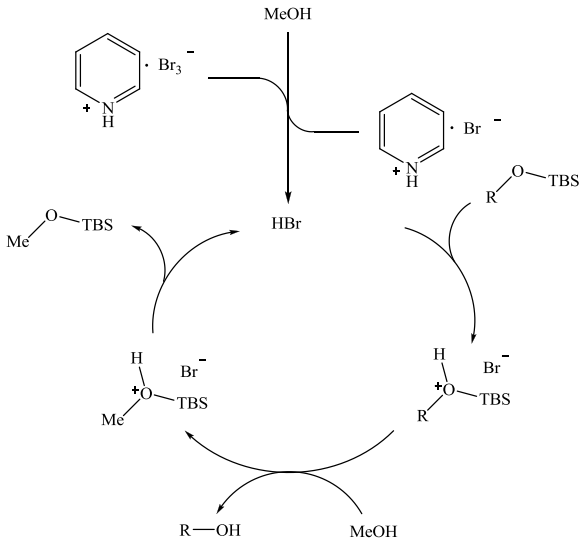
Scheme 89

A series of reagents were tried (HCl, TBAF, H_2SO_4) but the best yield was obtained using pyridinium tribromide.

Recently, Jennings and co-workers[125] discovered that a substoichiometric amount of pyridinium tribromide ($Py.Br_3$) in methanol could chemoselectively deprotect primary TBS ethers in the presence of other protecting groups.

5 mol % of pyridinium tribromide was added to a solution of the protected alcohol in methanol at a temperature of -20˚C. After 3 hours, the reaction went to completion and after purification, the free alcohol was obtained in an 80 % yield.

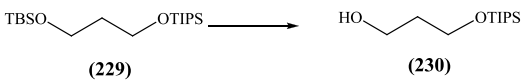
The mechanism the authors proposed is shown in Scheme 90.



Scheme 90

Jennings assumed that pyridinium tribromide provides a small amount of HBr, and enters into a catalytic process. Along with the formation of HBr, protonation of the TBS ether should provide the oxonium cation, followed by a nucleophilic displacement with MeOH, thus cleaving the silyl ether and furnishing the desired alcohol. Final deprotonation of the secondary oxonium cation regenerates the acid catalyst, thus making the protocol catalytic in HBr.

Moreover, the authors observed that pyridinium tribromide could selectively deprotect a primary TBS in the presence of TIPS as shown below:

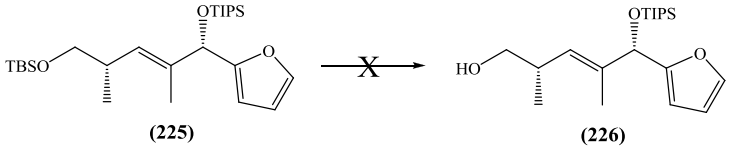


(229) **(230)**

Reagents and conditions: 5 % $Py.Br_3$, MeOH, 87 %

Scheme 91

We then went back to our issue dealing with the selective deprotection of TBS in the presence of TIPS on our substrate **(225)**. The same conditions as those in Scheme 91 were attempted but once again, without a positive outcome.

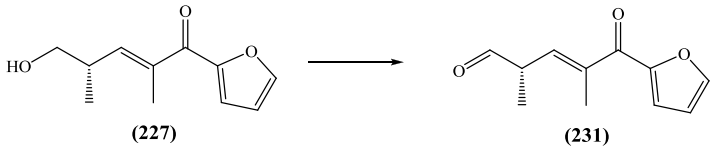


(225) **(226)**

Reagents and conditions: 5 % $Py.Br_3$, MeOH, 0 %.

Scheme 92

Therefore, we moved on to the oxidation of alcohol **(227)** to the aldehyde **(231)**.



(227) **(231)**

Scheme 93

A variety of common oxidizing reagents were employed (Table 10), including: pyridinium dichromate (PDC)[126], (2,2,6,6-tetramethylpiperidin-1-yl) oxidanyl (TEMPO)[127], 2-iodoxybenzoic acid (IBX)[128] and tetrapropylammonium perruthenate (TPAP)[124]. Unfortunately, all those reactions did not proceed with the exception of Ley's oxidation where an aldehyde peak could be observed on the proton NMR, but in a very low ratio.

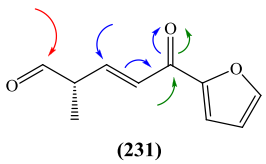
The use of Parikh-Doering conditions[105] did lead to the aldehyde **(231)** but in a modest yield (Entry 7, Table 7).

The best result was obtained by using Dess Martin periodinane (DMP)[128] which proved to be the best reagent. In addition, the purification was much simplified in comparison to the Parikh-Doering reaction as there is no dimethyl sulfide involved.

Entry	oxidizing agent	Solvent	Yield (%)
1	PDC	CH_2Cl_2	SM
2	TEMPO, NaCl, KBr	CH_2Cl_2	SM
3	IBX	Acetone	SM
4	IBX	EtOAc	SM
5	IBX	$CHCl_3$	SM
6	TPAP, NMO	CH_2Cl_2	traces
7	$Py.SO_3$, NEt_3, DMSO (rt)	CH_2Cl_2	50
7	$Py.SO_3$, NEt_3, DMSO (30˚C)	CH_2Cl_2	50
8	DMP	CH_2Cl_2	67

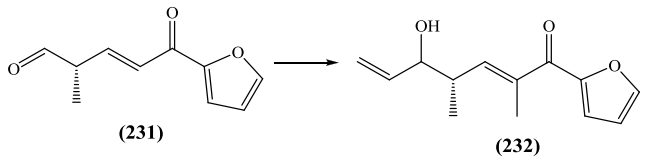
Table 6

With aldehyde **(231)** in hand, a Grignard[129] reaction using vinyl magnesium bromide allowed us to obtain allylic alcohol **(232)** in a 60 % yield when 1 equivalent of the Grignard reagent was used. 1.2 equivalents was also used and the reaction was quenched after 4 hours as we feared the Grignard reagent could have attacked different electrophilic centres (Figure 19). Either way, the starting aldehyde **(231)** that did not react could still be recovered and used again.



(231)

Figure 19



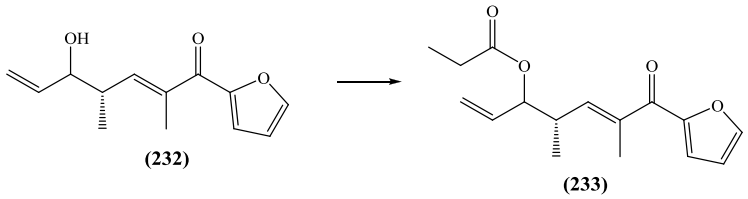
(231) (232)

Entry	Conditions	Eq.	Time	Solvent	Yield (%)
1	CH_2=CHMgBr	1.2	4 hours	THF	55
2	CH_2=CHMgBr	1	4 hours	THF	53
3	CH_2=CHMgBr	1	18 hours	THF	60

Scheme 94 & Table 7

The addition of vinylmagnesium bromide was not diastereoselective as the presence of diastereoisomers could be observed in the NMR spectra. Separation could not be achieved.

Allylic propionate **(233)** was formed by reaction of alcohol **(232)** with propionyl chloride at 0˚C with 2,6-lutidine as a base (Scheme 95).

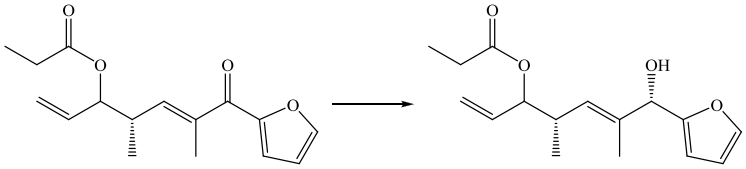


(232) (233)

Reagents and conditions: propionyl chloride, 2,6-lutidine, CH_2Cl_2, 0˚C, 89 %.

Scheme 95

The stereoselective reduction of the ketone was conducted using Terashima's conditions were carried out, but the main difference with our substrate is that two carbonyl groups are present. Therefore, only 1 equivalent of the reducing agent was used, and the proportions of the other reagents where altered accordingly. Alcohol **(234)** was obtained in a 71% yield. With this reaction, we were expecting to obtain a mixture of diastereoisomers, which unfortunately could not be separated.

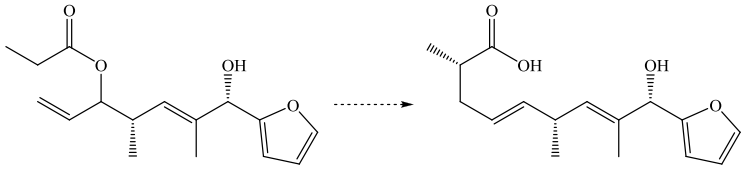


(233) **(234)**

Reagents and conditions: $LiAlH_4$, Et_2O, (−)-*N*-methylphedrine, reflux, *then N*-ethylaniline, reflux, *then* -100˚C, 71%.

Scheme 96

We were then ready to investigate the Ireland-Claisen rearrangement[130] starting from allylic propionate **(234)**.

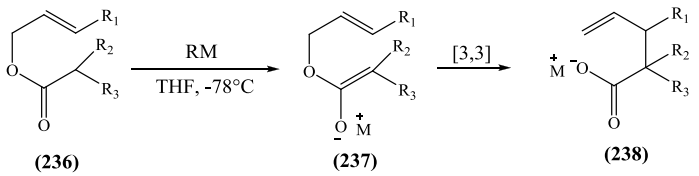


(234) **(235)**

Reagents and conditions: DMPU, LiHMDS, TMSCl, THF, 0˚C.

Scheme 97

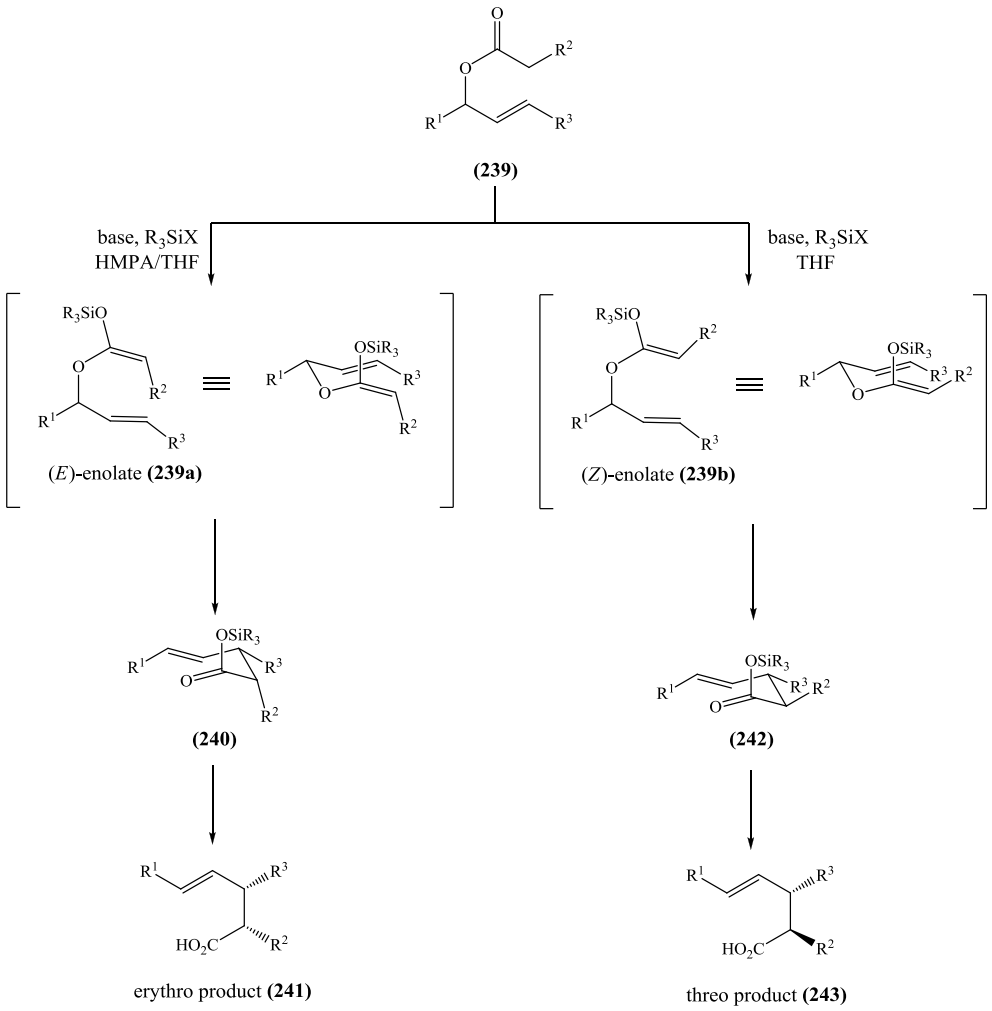
The Ireland-Claisen rearrangement refers to the [3,3] rearrangement of allylic esters **(236)** as ester enolates **(237)** to give α,β-unsaturated carboxylic acids **(238)** (Scheme 98).



(236) **(237)** **(238)**

Scheme 98 – Ireland-Claisen rearrangement

Regarding the geometry of the products of the Ireland-Claisen rearrangement, it can be predicted by looking at the stereochemistry of the double bonds involved in the ketene acetal rearragenment. The (E)-enolate **(239a)** predominantly gives an *erythro* product **(241)**, whereas the (Z)-enolate one **(239b)** gives a *threo* compound **(243)** as the main product (Scheme 99). Ireland suggested the rearrangement proceeds through a four centered "chair-like" transition state, as shown below, thus allowing stereo-selection of the products[131].



Scheme 99

The geometry of the silyl ketene acetal can be controlled during the ester enolization step by varying the solvent system. The formation of the (Z)-enolates is favored by THF as the solvent, whereas using an HMPA/THF combination favors the formation of the (E)-enolate (lithium enolate). Depicted in Figure 20 below are the two competing pericyclic, six-membered chair-like transition states (**I** and **II**) for the deprotonation step. Transition state I **(244)**, leading to the *Z*-enolate, would be destabilized by an unfavorable 1,2-interaction between R and OR'. On the other hand,

transition state II **(245)**, the one leading to the *E*-enolate, would be destabilized by an unfavorable 1,3-diaxial interaction between R and the axial isopropyl group of the base. In the absence of HMPA, the 1,3-diaxial interactions predominate. In the presence of HMPA, the 1,2-interactions predominate, which may be rationalized by the assumption that the lithium-enolate oxygen distance is increased due to the decreased Lewis acidity of the lithium cation in the presence of external Lewis basic ligands, like HMPA. A looser cyclic transition state would weaken the transannular interactions and the 1,2-interactions are more important (Figure 20).

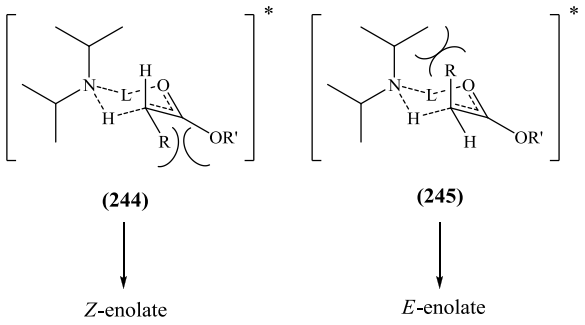
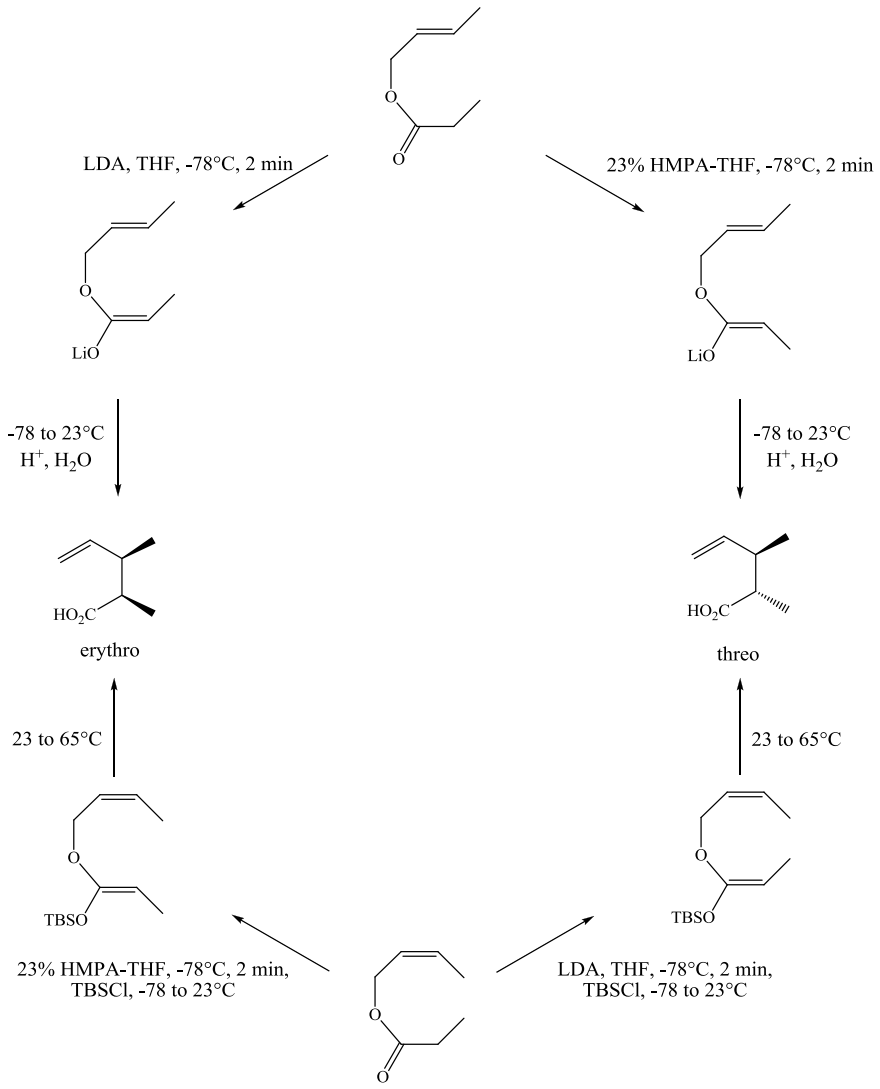


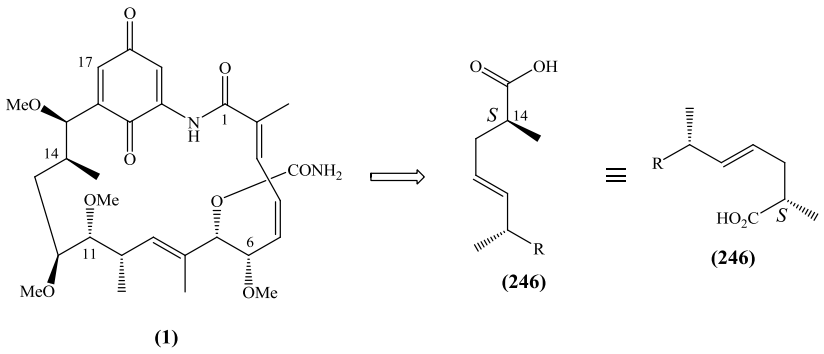
Figure 20

In addition, the stereochemistry of the allylic bond (*cis* or *trans*) is retained on silylation and both compounds predominantly give the erythro and the threo isomers on rearrangement (Scheme 100).



Scheme 100

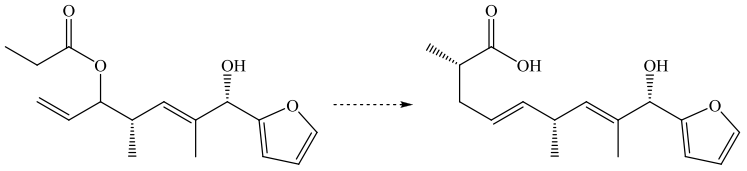
In our case, there is no substituent on the initial double bond. Also, we have to pay attention to the stereo-chemistry of C14 of hebimycin A (Scheme 21).



Scheme 101

We were interested in getting the *S* enantiomer through this rearrangement. Therefore, we need to go through the (*E*)-silyl enol ether, thus using a coordinating solvent, such as DMPU and HMPA, during the reaction.

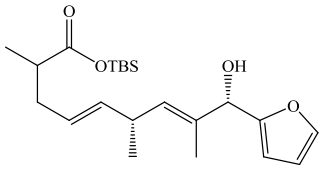
Different conditions, described in Table 12, were tried. Due to the toxicity of HMPA, DMPU was first used as the coordinating solvent. Different trapping agents (TMSCl and TBSCl) and bases (LHMDS, LDA) were also used, without any success (entry 1-5).



(234) (235)

Entry	Base	Solvent	Trapping agent	Temperature (˚C)	Yield (%)
1	LHMDS	THF/DMPU	TMSCl	-78˚ to rt	decomp.
2	LHMDS	THF/DMPU	TMSCl	-78 to 50	decomp.
3	LHMDS	THF/DMPU	TBSCl	-78 to rt/50	decomp.
4	LDA	THF/DMPU	TMSCl	-78 to rt/50	decomp.
5	LDA	THF/DMPU	TBSCl	-78 to rt/50	decomp.
6	LDA	THF/HMPA	TBSCl	-78 to rt	silyl ester **(247) (**traces)

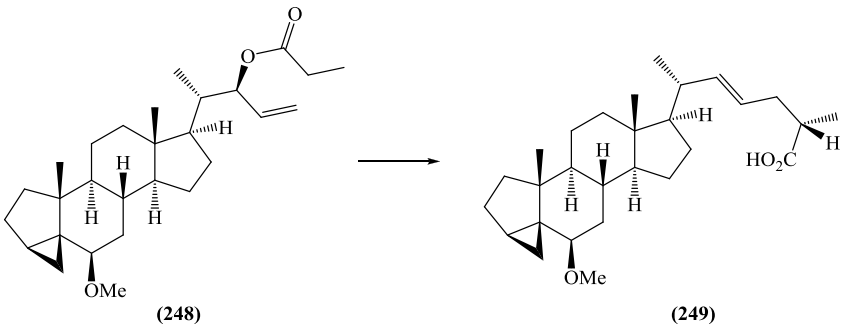
Scheme 102 & Table 8



(247)

Figure 21

However, Giroux and Corey[132] have recently developed a pathway for the stereo-controlled elaboration of dafachronic A. Reaction of allylic propionate **(248)** with LDA in THF-HMPA at -78 °C produced an enol silyl ether which without isolation was heated at reflux to undergo a highly stereo-selective Ireland-Claisen rearrangement, yielding acid **(249)** (Scheme 102).

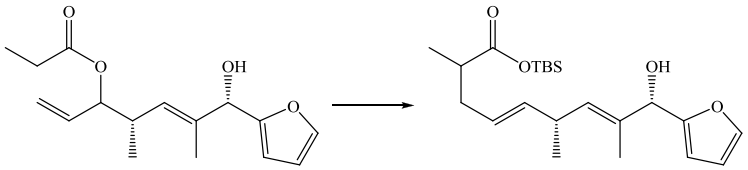


(248) (249)

Reagents and conditions: LDA, TBSCl, THF-HMPA, -78˚C to rt, 7 h, 66 %.

Scheme 103

We therefore tried the same conditions on our substrate **(234)** (Table 12, Entry 6). However, we noticed that the silyl group was not removed. Indeed, the mixture was only warmed up to room temperature.



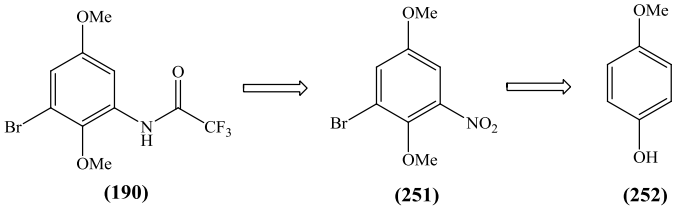
(234) (250)

Scheme 104

The next logical step was then to perform the reaction again with the same conditions with heating the reaction mixture. However, due to the lack of intermediate, this step could not be carried out.

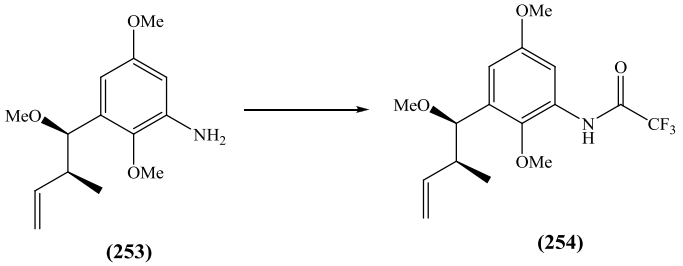
V. Attempts toward the Aromatic Fragment

Our target was the aromatic sub-unit **(190)** presented in Scheme 105 below along with our retrosynthetic route. This advanced aromatic fragment **(190)** would be obtained starting from commercially available 4-methoxyphenol **(252)** that would undergo successive nitration, bromination and methylation. The nitro group would then be reduced to the amine which could then be modified.



Scheme 105

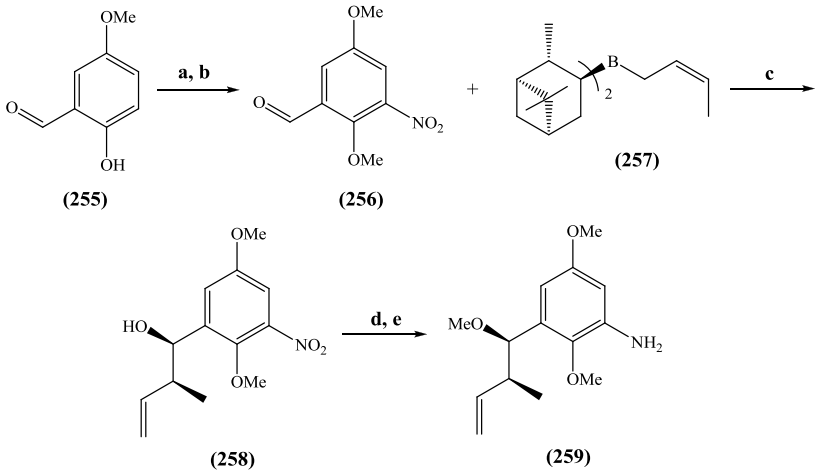
Previously in the Parsons' group, Ansell[94] successfully converted aniline **(253)** into trifluoroacetamide **(254)**[133].



Reagents and conditions: TFAA, Et_3N, CH_2Cl_2, 0˚C, 92%.

Scheme 106

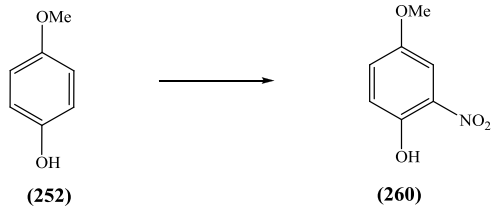
Ansell obtained the aniline fragment starting with commercially available 2-hydroxy-5-methoxybenzaldehyde which was successively nitrated and methylated. Aldehyde **(255)** was then subjected to Brown's crotylation[134] to insert the C14-C15 stereocentres in a single step (Scheme 106).



Reagents and conditions: a) HNO_3, AcOH, 10°C to 20 °C, 61 %; *b)* MeI, Ag_2O, CHCl3, 40 °C, 64 %; *c)* H_2O_2, 3 M NaOH, 89 %; *d)* MeI, NaH, THF, 0 °C, 90 %; *e) conc.* HCl, Sn, EtOH, 98 %.

Scheme 107

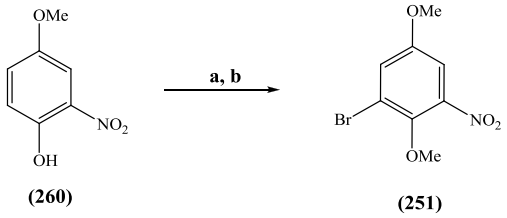
We then decided to protect our amine with the trifluoroacetamide group. Following Cossy's procedure[72], the synthesis of the aromatic fragment started with commercially available 4-methoxyphenol **(252)**, which was nitrated using sodium nitrite and glacial acetic acid in ethanol. The reactive mixture was heated to reflux for 2 hours, leading to the nitro compound **(260)** in a 70 % yield (Scheme 107).



Reagents and conditions: $NaNO_3$, AcOH, EtOH, 54 %.

Scheme 108

Regioselective *ortho*-bromination of the aromatic ring, followed by methylation using dimethylsulfate and potassium carbonate allowed us to obtain **(251)** in a 90 % yield (Scheme 108).

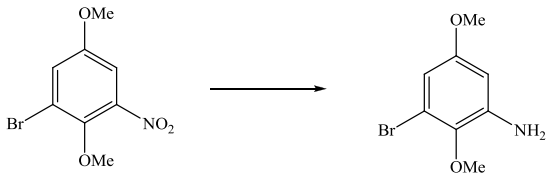


Reagents and conditions: a) Br_2, AcONa, AcOH, 76 %;

b) Me_2SO_4, K_2CO_3, acetone, reflux, 90 %.

Scheme 109

The next step consisted in the selective reduction of the nitro group using iron powder and acetic acid in water (Scheme 110).

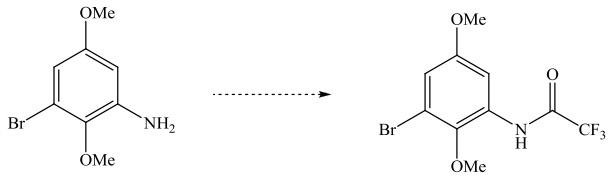


(251) **(261)**

Reagents and conditions: Fe, AcOH, H_2O, reflux, 86%

Scheme 110

The next logical step was then to turn the amine into trifluoroacetamide, but due to time constrains, this step could not be performed.



(261) **(190)**

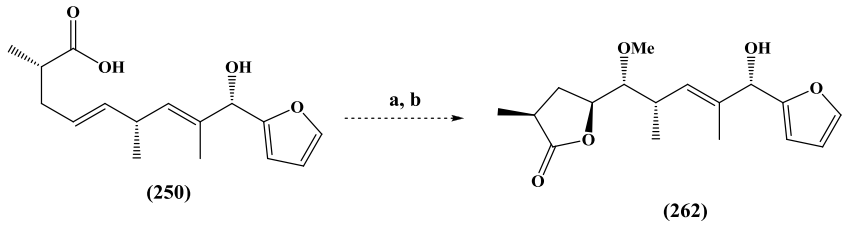
Reagents and conditions: TFAA, Et_3N, CH_2Cl_2, 0 °C

Scheme 111

VI. Conclusion and future work

To conclude, the route to herbimycin A **(1)** developed in this thesis proved to be very challenging as it had to be rethought several times. The synthesis was split into two parts, being the synthesis of the aromatic portion and the synthesis of the aliphatic fragment. The key step leading to the latter one, being the Ireland-Claisen rearrangement, seems to work although it still needs to be optimized.

Once the Ireland-Claisen will have been optimized, the next step would be a lactonization, with the resulting alcohol being methylated.

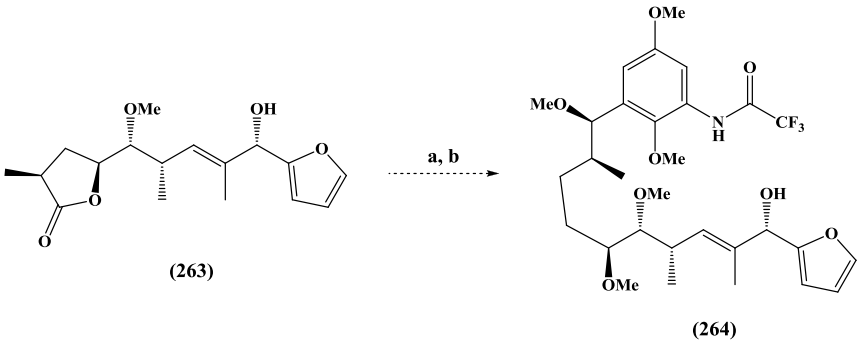


(250) (262)

Reagents and conditions: a) AD mix α, tBuOH, H_2O; *b)* MeI, NaH, DMF, 0 °C.

Scheme 112

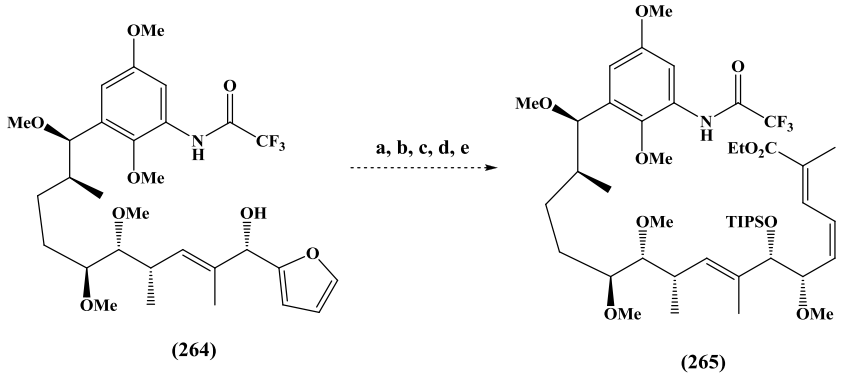
Then, the aromatic compound would be coupled with the aliphatic fragment, with once again the resulting alcohol being methylated.



Reagents and conditions: a) **(190)** *n*-BuLi, Et_2O, -78 °C to rt, *then* -78 °C; *b)* MeI, NaH, DMF, 0 °C.

Scheme 113

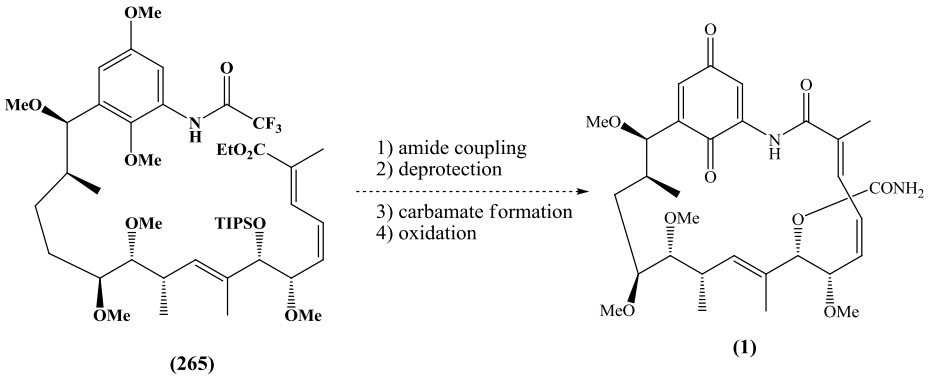
The right hand side of the molecule would be allowed to go through a ring expansion, followed by a Wittig reaction in order to insert all the necessary carbon atoms. The following steps are similar to those carried out earlier on during the first route of the synthesis of herbimycin A **(1)** (Scheme 114).



Reagents and conditions: a) NBS, THF/H_2O (4:1), -5 °C; *b)* $Ph_3P{=}C(Me)CO_2Et$, C_6H_6, rt;
c) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; d) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, 0 °C;
e) Me_3OBF_4, Proton Sponge™, CH_2Cl_2.

Scheme 114

The total synthesis would be achieved by performing an amide coupling, followed by silyl deprotection, carbamate formation and quinone formation to yield herbimycin A **(1)** (Scheme 115).



(265) **(1)**

Scheme 115

CHAPTER 4

EXPERIMENTAL

I. General Experimental Detail

Reactions requiring anhydrous conditions were conducted by using flame-dried glassware.

Anhydrous Et_2O and tetrahydrofuran were distilled from sodium in the presence of benzophenone. CH_2Cl_2, benzene, toluene, DMF, triethylamine, and ethyl acetate were distilled from calcium hydride prior to use. Methanol and ethanol were distilled from activated magnesium turnings using a crystal of iodine. All other grade solvents were used as received for routine purposes from Fischer scientific. Chemical reagents were commercially available, and used without further purification unless otherwise stated.

All reactions were monitored, where appropriate, by analytical thin layer chromatography using Merck glass backed plates pre-coated with 0.25 mm layer of silica gel 60 F_{254} containing a fluorescent indicator. Visualisation was achieved with Ultra Violet florescence radiation (254 nm), and/or by staining with alkaline potassium permanganate, vanillin, or phosphomolybdic acid dips. Purification by flash column chromatography was carried according to Still's procedure[135] using Fisher Scientific silica 60A (35-70 mesh).

^1H NMR spectra were recorded using a Varian VNMRS operating at 500 MHz. Samples were run at ambient probe temperature using $CDCl_3$ as the solvent, unless otherwise stated. Residual isotopic solvent ($CHCl_3$, δ_H = 7.27 ppm) was used as the internal reference. Chemical shifts (δ) are quoted in parts per million (ppm), and coupling constants (*J*) are measured in Hertz (Hz). The following abbreviations are used to describe the multiplicity of a given signal: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad singlet; app, apparent.

^{13}C NMR spectra were recorded using a Varian VNMRS operating at 125 MHz. Samples were run at ambient probe temperature using $CDCl_3$ as the solvent, unless otherwise stated. Residual isotopic solvent ($CHCl_3$, δ_C = 77.00 ppm) was used as the internal reference. Chemical shifts (δ) are quoted in parts per million (ppm). Carbon spectra assignments are supported by DEPT and correlation experiments.

The numbering of all the compounds mentioned in this section is arbitrary, with the sole intention to aid in the assignment of protons and carbons in the relevant spectra. As such, they do not necessarily correspond with that of the I.U.P.A.C. system.

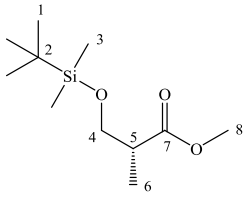
Infrared spectra (IR) were recorded on a Perkin-Elmer FT-IR 298 (1710) spectrometer, with absorption maxima (ν_{max}) measured in cm^{-1}. Some samples were prepared as either a thin film (liquids) or a solution in CH_2Cl_2 (solids) between sodium chloride plates, and other samples were directly placed on a universal attenuated total reflectance sampling accessory.

Mass spectrometry data were recorded by Dr. Alaa Abdul-Sada on a Bruker Daltronics Apex III 4.7T using positive electro-spray ionization (+'ve ESI), and a Fisons Instrument VG Autospec using positive electron impact (+'ve EI), with methanol as the solvent. Only molecular ions, fractions from molecular ions and other major peaks are reported as mass/charge (m/z) ratios. The following abbreviations are used to describe the experiment: HRMS, high resolution mass spectrometry; LRMS, low resolution mass spectrometry.

Optical rotations were recorded using a Bellingham-Stanley ADP440 polarimeter with a 1 cm-path length cell. Optical rotation $[\alpha]_D$ data are given in units $10^{-1}deg.cm^2.g^{-1}$, and solution concentrations are given in g/100 cm^{-3}.

II. Experimental Procedures

Methyl (2*R*)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-2-methylpropanoate (200)



(200)

To a stirred solution of *tert*-butyldimethylsilyl chloride (15.0 g, 100 mmol) in CH_2Cl_2 (220 mL) under an atmosphere of nitrogen at 0 °C, was added imidazole (6.8 g, 100 mmol) as a single portion. The resulting reaction mixture was stirred for five minutes and a solution of (*R*)-(3)-hydroxy-2-methylpropionate **(200)** (7.8 g, 66 mmol) in CH_2Cl_2 (50 mL) was added drop wise. The reaction mixture was stirred for a further ten minutes and *N*,*N*-dimethylaminopyridine (0.8 g, 6.6 mmol) was added as a single solid portion. The reaction mixture was allowed to warm up to room temperature overnight and was then quenched with water (300 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (4 x 100 mL). The organic phases were combined and dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography (3 % Et_2O : petroleum ether) yielded silyl ether **(200)** as a clear oil (14.5 g, 95 %).

R_f 0.40 (2 % Et_2O : petroleum ether).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.73 (1 H, dd, *J* 7.0 Hz, 9.6 Hz, H-4), 3.63 (3 H, s, H-8), 3.61-3.58 (1 H, m, H-4), 2.66-2.55 (1 H, m, H-5), 1.09 (3 H, d, *J* 7.2 Hz, H-6), 0.83 (9 H, s, H-1), -0.01 (6 H, s, H-3).

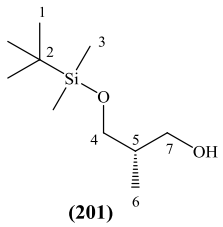
^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3 (C-7), 65.2 (C-4), 51.4 (C-8), 42.4 (C-5), 25.7 (C-1), 18.1 (C-2), 13.4 (C-6), -5.6 (C-3).

HRMS (ESI) *m*/*z* = 255.1374 (*calc.* 255.1387) $C_{11}H_{24}O_3SiNa$ [M + Na].

ν_{max} (thin film)/cm^{-1} 2955, 2931, 2886, 2859, 1744 (C=O), 1472, 1464, 1436.

$[\alpha]_D^{28}$ -20.2º (*c* 1.57 in $CHCl_3$).

Methyl (2*R*)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-2-methylpropanol (201)



(201)

To a stirred solution of ester **(200)** (10.0 g, 43 mmol) in CH_2Cl_2 (250 mL) at -78 °C under an atmosphere of nitrogen, was added diisobutylaluminium hydride (95 mL of a 1 M solution in CH_2Cl_2, 95 mmol) drop wise over four hours. The reaction mixture was allowed to warm up to room temperature overnight and was quenched with a cold solution of potassium sodium tartrate (54 g) and water (300 mL). The resulting cloudy solution was stirred until it became clear and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 150 mL). The organic layers were combined, dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure to yield alcohol **(201)** as a clear oil. (8.3 g, 90 %).

R_f 0.24 (20 % Et_2O : petroleum ether).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74 (1 H, dd, *J* 4.1 Hz, 9.6 Hz, H-7), 3.65-3.58 (2 H, m, H-4), 3.54 (1 H, dd, *J* 7.8 Hz, 9.5 Hz, H-7), 2.0-1.88 (1 H, m, H-5), 0.89 (9 H, s, H-1), 0.83 (3 H, d, *J* 6.8 Hz, H-6), 0.07 (6 H, s, H-3).

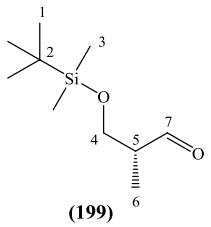
^{13}C NMR (125 MHz, $CDCl_3$) δ 68.5 (C-7), 67.9 (C-4), 37.0 (C-5), 25.8 (C-1), 18.1 (C-2), 13.0 (C-6), -5.7 (C-3).

HRMS (ESI) *m/z* = 227.1428 (*calc.* 227.1438) $C_{10}H_{24}O_2SiNa$ [M + Na].

ν_{max} (thin film)/cm^{-1} 3366 (br, OH), 2956, 2930, 2886, 2859, 1472, 1464, 1389, 1362, 1256, 1091, 1040, 939, 837, 776, 667.

$[\alpha]_D^{29}$ -10.6º (*c* 1.70 in $CHCl_3$).

Methyl (2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-methylpropanal (199)



(199)

To a stirred solution of alcohol **(201)** (13.5 g, 67 mmol) in CH_2Cl_2 (275 mL) under an atmosphere of nitrogen, was added triethylamine (47.1 mL, 335 mmol) at 0 °C. A solution of sulfurtrioxide pyridinium complex (42.6 g, 268 mmol) in dimethylsulfoxide (55 mL) was added drop wise over four hours. The resulting reaction mixture was allowed to warm up to room temperature overnight and was quenched with a saturated solution of aqueous ammonium chloride (100 mL). The layers were separated and the aqueous phase was extracted with Et_2O (7 x 100 mL). The organic layers were combined, washed with a solution of saturated sodium chloride (100 mL), dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography (5 % Et_2O : petroleum ether) yielded aldehyde **(199)** as a pale yellow oil (11.5 g, 85 %)

R_f 0.45 (8 % Et_2O : petroleum ether).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.72 (1H, d, *J* 1.5 Hz, H-7), 3.85 (1 H, dd, *J* 10.2 Hz, 5.0 Hz, H-4), 3.80 (1 H, dd, *J* 10.1 Hz, 6.2 Hz, H-4), 2.57-2.46 (1 H, m, H-5), 1.07 (3 H, d, *J* 6.9 H-6), 0.86 (9 H, s, H-1), 0.04 (6 H, s, H-3).

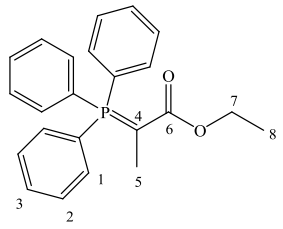
^{13}C NMR (125 MHz, $CDCl_3$) δ 204.7 (C-7), 63.4 (C-4), 48.8 (C-5), 25.7 (C-1), 18.2 (C-2), 10.2 (C-6), -5.6 (C-3).

LRMS (EI) *m/z* 203 ([M+H]+, 36 %), 185 (14), 161 (100), 133 (25), 75 (55).

ν_{max} (thin film)/cm^{-1} 2957, 2931, 2885, 2859, 2713, 1736 (C=O), 1473, 1464, 1390, 1362, 1256, 1099, 1033, 1007, 939, 838, 815, 777, 668, 342.

$[\alpha]_D^{31}$ -44.3º (*c* 1.98 in $CHCl_3$).

1-carbo-ethoxyethylidenetriphenylphosphorane (203)



(203)

Ethyl 2-bromopropanoate (14.9 mL, 115 mmol) was added drop wise to a stirred solution of triphenylphosphine (30.0 g, 115 mmol) in toluene (150 mL). The reaction mixture was heated at 60 °C and a white precipitate was formed. The mixture was then stirred for 4 hours and toluene was evaporated under vacuum. Et_2O (200 mL) was then added to the crude mixture and left stirring vigorously for 2 hours. Filtration yielded the bromide salt as a white powder.

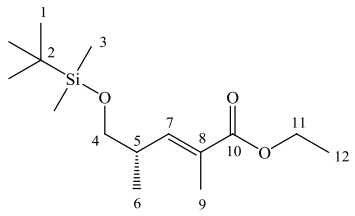
The obtained salt was then dissolved in CH_2Cl_2 (200 mL) and 1M aq NaOH (115 mL, 115 mmol) was added to the solution. The mixture was stirred for 20 minutes after which the organic phase was separated and the aqueous layer extracted with CH_2Cl_2 (2 x 50ml). The combined organic extracts were dried on magnesium sulfate and concentrated under reduced pressure to give **(203)** as a light yellow powder (29.0 g, 70 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.7-7.4 (15 H, m, H-1,2,3) 3.71 (2 H, q, H-7), 1.61 (3 H, d, H-5) 0.45 (3 H, t, H-8).

ν_{max} (thin film)/cm^{-1} 1624, 1589, 1431, 1187, 1088.

mp 157 °C (*litt*. 157-159) °C.

Ethyl (2*E*,4*R*)-5-{[*tert*-butyl(dimethyl)silyl]oxy}-2,4-dimethyl-2-pentenoate (198)



(198)

To a stirred solution of phosphorane **(203)** (11.6 g, 32 mmol) in toluene (100 mL), was added a solution of aldehyde **(199)** (5.0 g, 25 mmol) in toluene (50 mL) at room temperature. The reaction mixture was then heated at reflux for thirty six hours and was subsequently allowed to cool down to room temperature. The solvent was removed under reduced pressure and the crude was taken up in hexane (100 mL). The resulting white precipitate was filtered off and the same process was repeated twice. The remaining solution was concentrated under reduced pressure and the crude material was purified by flash column chromatography (2 % Et_2O : petroleum ether) to give alkene **(198)** as a colorless oil (5.4 g, 80 %).

R_f 0.47 (15 % Et_2O : petroleum ether).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.55 (1 H, d, *J* 10.2 Hz, H-7), 4.23-4.11 (2 H, m, H-11), 3.49 (2 H, d, *J* 6.0 Hz, H-4), 2.74-2.62 (1 H, m, H-5), 1.85 (3 H, s, H-9), 1.29 (3 H, t, *J* 7.2 Hz, H-12), 1.00 (3 H, d, *J* 6.6 Hz, H-6), 0.87 (9 H, s, H-1), 0.03 (6 H, s, H-3).

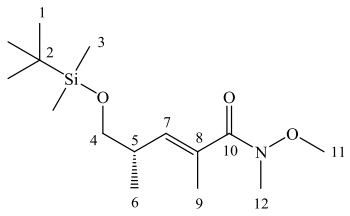
^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1 (C-10), 144.4 (C-7), 127.8 (C-8), 67.0 (C-4), 60.3 (C-11), 36.2 (C-5), 25.8 (C-1), 18.9 (C-2), 16.1 (C-6), 14.2 (C-12), 12.6 (C-9), -5.5 (C-3).

HRMS (ESI) *m*/*z* = 309.1828 (*calc.* 309.1856) $C_{15}H_{30}O_3SiNa$ [M + Na].

ν_{max} (thin film)/cm^{-1} 2956, 2928, 2857, 1711 (C=O), 1468, 1234, 1085, 832.

$[\alpha]_D^{25.5}$ -4.5º (*c* 1.79 in $CHCl_3$).

(2*E*,4*R*)-5-{[*tert*-butyl(dimethyl)silyl]oxy}-*N*-methoxy-*N*-2,4-trimethyl-2-pentenoamide (204)



(204)

To a stirred solution of ester **(198)** (4.1 g, 15 mmol) in tetrahydrofuran (150 mL) was added *N*,*O*-dimethylhydroxylamine hydrochloride (2.2 g, 22.5 mmol) as a single solid portion at room temperature under a nitrogen atmosphere. The reaction mixture was cooled to -20 °C and *iso*-propylmagnesium chloride (22 mL of a 2.0 M solution in tetrahydrofuran, 44 mmol) was added drop wise ensuring that the temperature remained below -5 °C. The reaction mixture was stirred at -5 °C (methanol and ice bath) for four hours, before being quenched by a solution of saturated aqueous ammonium chloride (100 mL). The layers were then separated and the aqueous phase was extracted with Et_2O (2 x 50 mL). The combined organic extracts were dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography (35 % Et_2O : petroleum ether) and the Weinreb amide **(204)** was obtained as a yellow oil (3.2 g, 70 %).

R_f 0.26 (40 % Et_2O : petroleum ether).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.62 (1H, d, *J* 7.9 Hz, H-7), 3.64 (3 H, s, H-11), 3.53-3.42 (2 H, m, H-4), 3.22 (3 H, s, H-12), 2.68-2.59 (1 H, m, H-5), 1.88 (3 H, s, H-9), 0.99 (3 H, d, *J* 6.6 Hz, H-6), 0.88 (9 H, s, H-1), 0.03 (6 H, s, H-3).

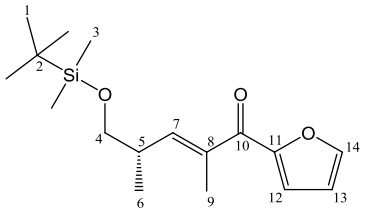
^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6 (C-10), 136.2 (C-7), 131.0 (C-8), 67.3 (C-4), 60.8 (C-11), 35.4 (C-12), 33.9 (C-5), 25.9 (C-1), 18.3 (C-2), 16.5 (C-6), 14.1 (C-9), -5.4 (C-3).

HRMS (ESI) *m*/*z* = 302.2136 (*calc.* 302.2146) $C_{15}H_{32}O_3NSi$ [M + H].

ν_{max} (thin film)/cm^{-1} 2957, 2930, 2896, 2858, 1741, 1655 (C=O), 1460, 1363, 1257, 1098, 1028, 1007, 837, 777, 666.

$[\alpha]_D^{26}$ -5.5º (*c* 1.74 in $CHCl_3$).

(2*E*,4*R*)-5-{[*tert*-butyl(dimethyl)silyl]oxy}-1-(2-furyl)-2,4-dimethyl-2-penten-1-one (205)



(205)

To a stirred solution of furan (3.80 mL, 52 mmol) in tetrahydrofuran (100 mL) at -78 °C under an atmosphere of nitrogen was added *n*-butyllithium (20.8 mL of a 2.5 M solution in hexanes, 52 mmol) drop wise. The reaction mixture was allowed to warm up to -5 °C over four hours. The resultant yellow solution of 2-furyl-lithium was added drop wise to a stirred solution of Weinreb amide **(204)** (10.5 g, 35 mmol) in tetrahydrofuran (500 mL) at 0 °C under an atmosphere of nitrogen over thirty minutes. The reaction mixture was stirred overnight at room temperature, before being quenched by pouring into an iced cooled solution of saturated aqueous ammonium chloride (300 mL). The layers were separated and the aqueous phase extracted with Et_2O (3 x 250 mL). The combined organic extracts were dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (10 % Et_2O : petroleum ether) and furyl ketone **(205)** was isolated as a yellow oil (10.0 g, 95 %).

R_f 0.54 (20 % Et_2O : petroleum ether).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59-7.58 (1H, m, H-14), 7.03 (1H, d, *J* 3.6 Hz, H-12), 6.48-6.46 (1H, m, H-13), 6.42 (1H, d, *J* 9.6 Hz, H-7), 3.59-3.49 (2H, m, H-4), 2.83-2.74 (1H, m, H-5), 1.94 (3H, s, H-9), 1.02 (3H, d, *J* 6.8 Hz, H-6), 0.86 (9H, s, H-1), 0.02 (6H, s, H-3).

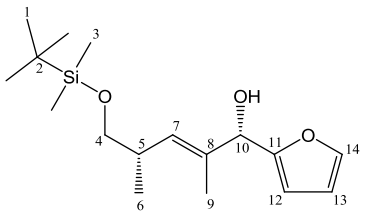
^{13}C NMR (125 MHz, $CDCl_3$) δ 185.1 (C-10), 151.8 (C-11), 146.5 (C-14), 145.8 (C-13), 135.6 (C-8), 119.4 (C-12), 111.5 (C-7), 67.1 (C-4), 36.4 (C-5), 25.8 (C-1), 18.2 (C-2), 16.1 (C-6), 12.8 (C-9), -5.5 (C-3).

HRMS (ESI) ***m/z*** = 331.1696 (*calc.* 331.1670) $C_{17}H_{28}O_3SiNa$ [M + Na].

ν_{max} (thin film)/cm^{-1} 2930, 1648 (C=O), 1561, 1467, 1389, 1297, 1253, 1091, 1031, 837, 776, 666.

$[\alpha]_D^{28}$ -12.3º (*c* 2.21 in $CHCl_3$).

5-(tert-Butyl-dimethyl-silanyloxy)-1-furan-2-yl-2,4-dimethyl-pent-2-en-1-ol (196)



(196)

(1*R*),(2*S*)-(-)-*N*-methylephedrine (4.0 g, 22.1 mmol) in Et_2O (60 mL) was added drop wise to a stirred solution of lithium aluminium hydride (820 mg, 21.5 mmol) in Et_2O (20 mL) at 0 °C under an atmosphere of nitrogen. The reaction mixture was heated to reflux for two hours, before being allowed to cool to room temperature. A solution of freshly distilled *N*-ethylaniline (5.7 mL, 45.5 mmol) in Et_2O (20 mL) was added drop wise and the reaction mixture was heated to reflux for a further two hours. The reaction mixture was cooled to -100 °C and a solution of furyl ketone **(205)** (2.0 g, 6.5 mmol) in Et_2O was added drop wise. The reaction mixture was stirred at -100 °C for four hours, before subsequently being quenched by pouring into an ice cooled aqueous solution of sodium potassium tartrate (16.0 g) and water (150 mL). The solution was allowed to warm to room temperature overnight. The layers were separated and the aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with a solution of saturated aqueous copper sulfate (100 mL), a solution of saturated aqueous sodium chloride (2 x 100 mL) dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (3 % Et_2O : petroleum ether) and furyl alcohol **(196)** was isolated as a yellow oil (1.23 g, 60 %).

R_f 0.21 (20 % Et_2O : petroleum ether).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (1H, s, H-14), 6.33 (1H, s, H-12), 6.23 (1H, s, H-13), 5.40 (1H, d, *J* 10 Hz, H-7), 5.11 (1H, s, H-10), 3.52-3.41 (2H, m, H-4), 2.65-2.60

(1H, m, H-5), 1.66 (3H, s, H-9), 1.23 (1H, br, OH), 1.00 (3H, d, *J* 10 Hz, H-6), 0.90 (9H, s, H-1), 0.04 (6H, s, H-3).

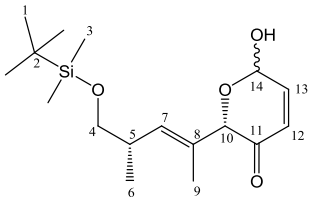
^{13}C NMR (125 MHz, $CDCl_3$) δ 155 (C-11), 142 (C-14), 134 (C-8), 130 (C-13), 110 (C-12), 106 (C-7), 73.2 (C-10), 67.7 (C-4), 35.3 (C-5), 25.9 (C-1), 18.3 (C-2), 17.2 (C-6), 13.0 (C-9), 5.33 (C-3).

HRMS (ESI) *m*/*z* = 333.1860 (*calc.* 333.1856) $C_{17}H_{30}O_3SiNa$ [M + Na].

ν_{max} (thin film)/cm^{-1} 3412 br (CHOH), 2929, 2857, 1472, 1388, 1256, 1088, 1007, 836, 776, 734, 666.

$[\alpha]_D^{28}$ +4.69º (*c* 1.28 in $CHCl_3$).

(*S*)-2-((*S*,*E*)-5-(*t*-Butyldimethylsilyloxy)-4-methylpent-2-en-2-yl)-6-hydroxy-2*H*pyran-3(6*H*)-one (195)



(195)

To a stirred solution of alcohol **(196)** (1.0 g, 3.23 mmol) in tetrahydrofuran (80 mL) and water (20 mL) was added *N*-bromosuccinimide (575 mg, 3.23 mmol) as a single portion at -5 °C under a nitrogen atmosphere. The dark yellow reaction mixture was stirred at the same temperature for one hour, before addition of a solution of 10 % aqueous potassium iodide (50 mL). The solution was allowed to warm to room temperature, the layers were then separated and the aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with a solution of 15 % aqueous sodium dithionite (100 mL), followed by a solution of 10 % aqueous sodium bicarbonate (100 mL). The organic extracts were dried over magnesium sulfate, filtered and most of the solvent was removed under reduced pressure. To avoid decomposition 1-2 mL of solvent was retained. The crude material was purified by flash column chromatography using neutral silica (20 % Et_2O : petroleum ether) and lactol **(195)** was isolated as a yellow oil (653 mg, 62 %, 2 diastereoisomers with a 1:4 ratio).

R_f 0.29 (40 % Et_2O : petroleum ether).

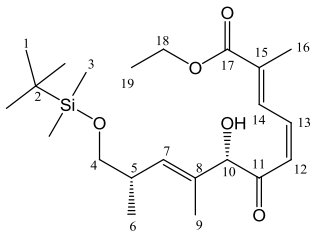
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 (1H, dd, *J* 2.5 Hz, *J* 10.2 Hz, H-13), 6.13 (1H, d, *J* 10.4 Hz, H-12) 5.71-5.63 (1H, m, H-14), 5.29 (1H, d, *J* 8.9 Hz, H-7), 4.91-4.85 (1H, m, H-10), 3.56-3.30 (2H, m, H-4), 2.69-2.53 (1H, m, H-5), 1.64 (3H, s, H-9), 1.0 (3H, d, *J* 6.2 Hz, H-6), 0.88 (9 H, s, H-1), 0.03 (6H, s, H-3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 195.0 (C-11), 144.5 (C-13), 135.5 (C-7), 130.2 (C-8), 128.1 (C-12), 87.9 (C-14), 80.7 (C-10), 67.5 (C-4), 35.3 (C-5), 25.9 (C-1), 18.4 (C-2), 17.0 (C-6), 13.1 (C-9), -5.4 (C-3).

HRMS (ESI) *m/z* = 349.1803 (*calc.* 349.1806) $C_{17}H_{30}O_4SiNa$ [M + Na].

ν_{max} (thin film)/cm^{-1} 3376 (br, O-H), 2957, 2930 and 2868 (m, C-H), 1691 (m, C=O), 1469.

(2*E*,4*Z*,7*S*,8*E*,10*S*)-Ethyl 11-(*t*-butyldimethylsilyloxy)-7-hydroxy-2,8,10-trimethyl-6-oxoundeca-2,4,8-trienoate (209)



(209)

To a stirred solution of lactol **(195)** (500 mg, 1.53 mmol) in dry benzene was added phosphorane **(203)** (1.11g, 3.06 mmol) as a single portion at room temperature under a nitrogen atmosphere. The reaction mixture was stirred for 48 hours, before removing the solvent under reduced pressure. The crude material was purified by flash column chromatography using neutral silica (10 % Et_2O : petroleum ether) and alcohol **(209)** was isolated as a yellow oil (533 mg, 85 %).

R_f 0.27 (20 % Et_2O : petroleum ether).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (1H, d, *J* 12.0 Hz, H-14), 6.90 (1H, dd app. t, *J* 11.8 Hz, H-13), 6.34 (1H, d, *J* 11.7, H-12), 5.48 (1H, d, *J* 9.5 Hz, H-7), 4.56 (1H, s, H-10), 4.26 (2H, q, *J* 6.8 Hz, H-18), 3.56-3.38 (2H, m, H-4), 2.67-2.52 (1H, m, H-5), 2.04 (3H, s, H-9/H-16), 1.47 (3H, s, H-9/H-16), 1.34 (3H, t, *J* 6.7 Hz, H-19), 0.99 (3H, d, *J* 4.9 Hz, H-6), 0.88 (9H, s, H-1), 0.04 (6H, s, H-3).

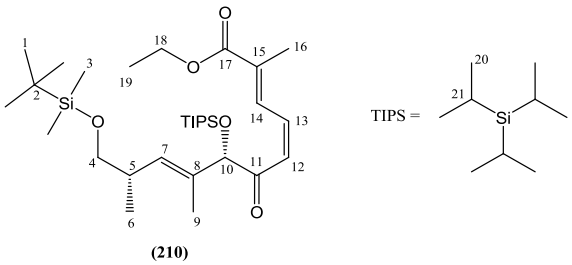
^{13}C NMR (125 MHz, $CDCl_3$) δ 199.9 (C-11), 167.7 (C-17), 138.4 (C-13), 137.7 (C-15/C-8), 136.2 (C-7), 132.4 (C-15/C-8), 132.1 (C-14), 123.5 (C-12), 84.0 (C-10), 67.2 (C-4), 61.2 (C-18), 35.6 (C-5), 25.9 (C-1), 18.4 (C-2), 17.0 (C-6), 14.2 (C-19), 12.8 (C-16/C-9), 11.2 (C-16/C-9), -5.3 (C-3).

HRMS (ESI) *m*/*z* = 433.2384 (*calc.* 433.2381) $C_{22}H_{38}O_5SiNa$ [M + Na].

ν_{max} (thin film)/cm^{-1} 3470 (br, O-H), 2962, 2927 and 2859 (m, C-H), 1714 (s, C=O), 1620 (w, C=C), 1581, 1240, 1082, 1030.

$[\alpha]_D^{32}$ -110.8º (*c* 1.57 in $CHCl_3$).

(2*E*,4*Z*,7*S*,8*E*,10*S*)-Ethyl 11-(*t*-butyldimethylsilyloxy)-2,8,10-trimethyl-6-oxo-7-(triisopropylsilyloxy)undeca-2,4,8-trienoate (210)



(210)

To a stirred solution of alcohol **(209)** (500 mg, 1.22 mmol) in CH_2Cl_2 (20 mL) was added 2,6-lutidine (0.43 mL, 3.66 mmol) at 0 °C under a nitrogen atmosphere, followed by triisopropylsilyl trifluoromethanesulfonate (0.66 mL, 2.44 mmol) drop wise. The reaction mixture was stirred at 0 °C for three hours, before adding to a solution of saturated aqueous sodium bicarbonate (100 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography using neutral silica (2.5 % Et_2O : petroleum ether) and silyl ether **(210)** was isolated as a bright yellow oil (587 mg, 85 %).

R_f 0.41 (5 % Et_2O : petroleum ether).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (1H, d, *J* 13.2 Hz, H-14), 6.91-6.77 (1H, m, H-13), 6.63 (1H, d, *J* 12.8 Hz, H-12), 5.66 (1H, d, *J* 9.0 Hz, H-7), 4.42 (1H, s, H-10), 4.23 (2H, q, *J* 6.7 Hz, H-18), 3.52-3.30 (2H, m, H-4), 2.64-2.51 (1H, m, H-5), 2.00 (3H, s, H-9/H16), 1.60 (3H, s, H-9/H-16), 1.32 (3H, t, *J* 7.1 Hz, H-19), 1.05-1.0 (21H, m, H-20 and H-21), 0.95 (3H, d, *J* 6.6 Hz, H-6), 0.87 (9H, s, H-1), 0.02 (6H, s, H-3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 199.9 (C-11), 168.0 (C-17), 136.9 (C-13), 135.7 (C-15/C-8), 132.8 (C-14), 132.2 (C-15/C-8), 131.1 (C-7), 125.0 (C-12), 83.7 (C-10), 67.6

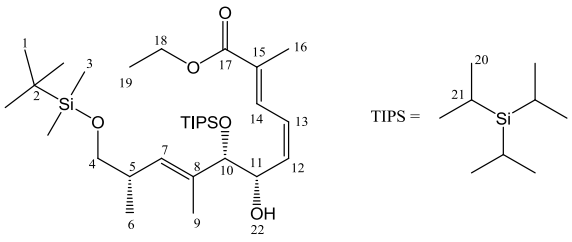
(C-4), 61.0 (C-18), 35.2 (C-5), 25.9 (C-1), 18.3 (C-2), 17.9 (C-20), 17.0 (C-6), 14.2 (C-19), 13.1 (C-16/C-9), 12.6 (C-16/C-9), 12.0 (C-21), -5.4 (C-3).

HRMS (ESI) *m/z* = 589.3737 (*calc*. 589.3715) $C_{31}H_{58}O_5Si_2Na$ [M + Na].

ν_{max} (thin film)/cm^{-1} 2932 and 2863 (m, C-H), 1710 (s, C=O), 1577, 1466, 1385, 1240, 1090, 834.

$[\alpha]_D^{28}$ +43.9^o (*c* 1.22 in $CHCl_3$).

(2*E*,4*Z*,6*S*,7*S*,8*E*,10*S*)-Ethyl 11-(*t*-butyldimethylsilyloxy)-6-hydroxy-2,8,10-trimethyl-7-(triisopropylsilyloxy)undeca-2,4,8-trienoate (211)



(211)

To a stirred solution of enone **(210)** (500 mg, 0.88 mmol) in methanol (20 mL) was added cerium trichloride heptahydrate (4.85 mL of a 0.2 M solution in methanol, 0.97 mmol), at 0 °C under a nitrogen atmosphere, followed by sodium borohydride (37 mg, 0.97 mmol) as multiple portions. The effervescent mixture was stirred at 0 °C for three hours, before removing the solvent under reduced pressure. The resultant material was taken up in CH_2Cl_2 (20 mL), washed with a solution of saturated aqueous sodium chloride (50 mL), and the aqueous layer was then extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography using neutral silica (10 % Et_2O : petroleum ether) and the resultant alcohol **(211)** was isolated as a pale yellow oil (470 mg, 94 %).

R_f 0.19 (10 % Et_2O : petroleum ether).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (1H, d, *J* 11.3 Hz, H-14), 6.39 (1H, dd app. t, *J* 12.1 Hz, H-13), 5.69-5.63 (1H, m, H-12), 5.14 (1H, d, *J* 5.5 Hz, H-7), 4.53 (1H, dd app. t, *J* 7.7 Hz, H-11), 4.26-4.11 (2H, m, H-18), 3.95 (1H, d, *J* 7.5 Hz, H-10), 3.51-3.40 (1H, m, H-4), 3.34-3.24 (1H, m, H-4), 2.52-2.37 (1H, m, H-5), 1.91 (3H, s, H-9/H-16), 1.65 (3H, s, H-9/H-16), 1.32-1.20 (3H, m, H-19), 1.07 (21H, br, s, H-20 and H-21), 0.88-0.81 (12H, m, H-1 and H-6), 0.02 (6H, s, H-3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2 (C-17), 136.5 (C-12), 133.5 (C-8/C-15), 132.6 (C-7), 132.5 (C-14), 128.8 (C-8/C-15), 126.5 (C-13), 82.2 (C-10), 69.7 (C-11), 67.2

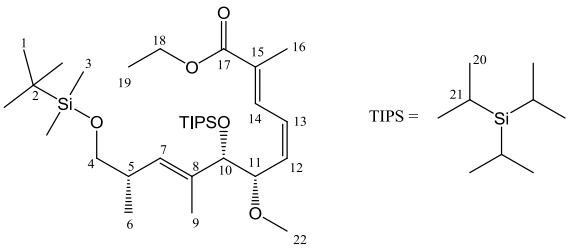
(C-4), 60.6 (C-18), 35.2 (C-5), 25.9 (C-1), 18.4 (C-2), 18.1 (C-20), 16.6 (C-6), 14.3 (C-19), 12.9 (C-21), 12.3 (C-9/C-16), 12.3 (C-9/C-16), -5.5 (C-3).

HRMS (ESI) *m/z* = 591.3873 (*calc.* 591.3871) $C_{31}H_{60}O_5Si_2Na$ [M + Na].

ν_{max} (thin film)/cm^{-1} 3530 (br, O-H), 2927 and 2859 (s, C-H), 1710 (s, C=O), 1462, 1389,1248, 1082.

$[\alpha]_D^{30}$ -22.4º (*c* 1.32 in $CHCl_3$).

(2*E*,4*Z*,6*S*,7*S*,8*E*,10*S*)-Ethyl 11-(*t*-butyldimethylsilyloxy)-6-methoxy-2,8,10-trimethyl-7-(triisopropylsilyloxy)undeca-2,4,8-trienoate (213)



(213)

To a stirred solution of alcohol **(211)** (400 mg, 0.70 mmol) in CH_2Cl_2 (50 mL) was added proton sponge^{TM} (1,8-bis(dimethylamino)naphthalene) (480 mg, 2.24 mmol) at room temperature under a nitrogen atmosphere, followed by trimethyloxonium tetrafluoroborate (310 mg, 2.10 mmol) as multiple portions. The reaction mixture was stirred for five hours, before the addition of CH_2Cl_2 (150 mL) and of an aqueous solution of 1 M sodium dihydrogen phosphate (150 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were washed with a solution of saturated aqueous sodium chloride (100 mL), dried over sodium sulfate, filtered and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography using neutral silica (5 % Et_2O : petroleum ether) and ester **(213)** was isolated as a yellow oil (362 mg, 89 %).

R_f 0.18 (25 % Et_2O : petroleum ether).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (1H, d, *J* 12.0 Hz, H-14), 6.43 (1H, dd, *J* 11.4 Hz, 11.6 Hz, H-13), 5.49-5.45 (1H, m, H-12), 5.14-5.06 (1H, m, H-7), 4.25-4.21 (2H, m, H-18), 4.12-4.09 (2H, m, H-10 and H-11), 3.46 (1H, dd, *J* 5.1 Hz, 9.7 Hz, H-4), 3.38-3.32 (1H, m, H-4), 3.27 (3H, s, H-22), 2.51-2.42 (1H, m, H-5), 1.94 (3H, s, H-9/H-16), 1.58 (3H, s, H-9/H-16), 1.31 (3H, t, *J* 7.1 Hz, H-19), 1.11-1.04 (24H, m, H-6, H-20 and H-21), 0.88 (9H, s, H-1), 0.02 (6H, s, H-3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4 (C-17), 135.6 (C-12), 134.8 (C-8/C-15), 132.5 (C-14), 130.9 (C-7), 128.9 (C-8/C-15), 126.8 (C-13), 80.8 (C-10/C-11), 80.6 (C-10/

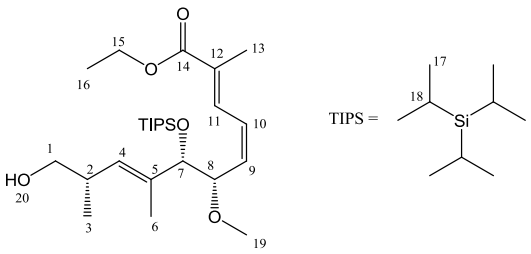
C-11), 67.5 (C-4), 60.6 (C-18), 56.8 (C-22), 35.1 (C-5), 25.9 (C-1), 18.3 (C-2), 18.0 (C-20), 16.9 (C-6), 14.3 (C-19), 12.7 (C-21), 12.4 (C-16), 11.8 (C-9), -5.3 and -5.4 (C-3).

HRMS (ESI) *m/z* = 605.4015 (*calc.* 605.4028) $C_{32}H_{62}O_5Si_2Na$ [M + Na].

ν_{max} (thin film)/cm^{-1} 2940, 2863 (s, C-H), 1710 (s, C=O), 1466, 1389, 1363, 1252, 1094, 881.

$[\alpha]_D^{33}$ -12.6º (*c* 2.38 in $CHCl_3$).

(2*E*,4*Z*,6*S*,7*S*,8*E*,10*S*)-Ethyl 11-hydroxy-6-methoxy-2,8,10-trimethyl-7-(triisopropylsilyloxy)undeca-2,4,8-trienoate (218)



(218)

To a stirred solution of **(213)** (200 mg, 0.35 mmol) in tetrahydrofuran (5 mL) was added a pre-mixed solution of glacial acetic acid (5 mL) and water (2.5 mL) drop wise at room temperature under a nitrogen atmosphere. The reaction mixture was stirred overnight, before adding toluene (10 mL) and removing the solvent under reduced pressure. This process was repeated twice. The crude material was purified by flash column chromatography using neutral silica (20 % Et_2O : petroleum ether) and alcohol **(218)** was isolated as a clear oil (164 mg, 100 %).

R_f 0.18 (20 % Et_2O : petroleum ether).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (1H, d, *J* 12.0 Hz, H-11), 6.44 (1H, dd app. t, *J* 11.4 Hz, H-10), 5.53-5.38 (1H, m, H-9), 5.10 (1H, d, *J* 9.5 Hz, H-4), 4.20 (2H, q, *J* 7.0 Hz, H-15), 4.14-4.05 (2H, m, H-7 and H-8), 3.42-3.29 (2H, m, H-1), 3.24 (3H, s, H-19), 2.62-2.48 (1H, m, H-2), 1.91 (3H, s, H-6/H-13), 1.66 (1H, br, s, H-20), 1.59 (3H, s, H-6/H-13), 1.29 (3H, t, *J* 7.0 Hz, H-16), 1.04-1.00 (21 H, m, H-17 and H-18), 0.85 (3H, d, *J* 6.6 Hz, H-3).

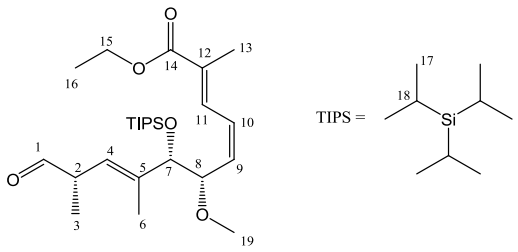
^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7 (C-14), 137.2 (C-5/C-12), 135.9 (C-9), 132.6 (C-11), 130.7 (C-4), 129.6 (C-5/C-12), 127.4 (C-10), 80.9 (C-7/C-8), 80.8 (C-7/C-8), 67.9 (C-1), 61.1 (C-15), 57.2 (C-19), 35.5 (C-2), 18.4 (C-17), 16.9 (C-3), 14.7 (C-16), 13.7 (C-6/C-13), 12.8 (C-18), 12.7 (C-6/C/-13).

HRMS (ESI) *m/z* = 491.3155 (*calc.* 491.3163) $C_{26}H_{48}O_5SiNa$ [M + Na].

ν_{max} (thin film)/cm^{-1} 3468 (br, O-H), 2944 and 2867 (m, C-H), 1703 (m, C=O), 1635 (w, C=C), 1464, 1389, 1368, 1254, 1190, 1106, 1067, 1034, 997, 910, 883, 811, 735, 680, 648.

$[\alpha]_D^{33}$ -20.4º (*c* 1.52 in $CHCl_3$).

(2*E*,4*Z*,6*S*,7*S*,8*E*,10*S*)-Ethyl 6-methoxy-2,8,10-trimethyl-11-oxo-7-(triisopropylsilyloxy)undeca-2,4,8-trienoate (194)



(194)

To a stirred solution of alcohol **(218)** (107 mg, 0.23 mmol) in CH_2Cl_2 (10 mL) was added 4 Å MS and *N*-methylmorpholine-*N*-oxide (32 mg, 0.27 mmol) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred for 30 minutes, before addition of tetrapropylammonium peruthenate (4 mg, 0.011 mmol) as a single portion. The reaction mixture was stirred for one hour, before removing the solvent under reduced pressure. The crude material was immediately purified by flash column chromatography (5 % Et_2O : petroleum ether) and aldehyde **(194)** was isolated as a clear oil (75 mg, 70 %).

R_f 0.5 (20 % Et_2O : petroleum ether).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.46 (1H, d, *J* 1.7 Hz, H-1), 7.46 (1H, d, *J* 12.0 Hz, H-11), 6.49-6.44 (1H, m, H-10), 5.46 (1H, dd app. t, *J* 10.3, H-9), 5.20 (1H, d, *J* 9.3, H-4), 4.24-4.12 (4H, m, H-7, H-8 and H-15), 3.27 (3H, s, H-19), 3.25-3.18 (1H, m, H-2), 1.93 (3H, s, H-6/H-13), 1.66 (3H, s, H-6/H-13), 1.30 (3H, t, *J* 7.1 Hz, H-16), 1.12-1.02 (12 H, m, H-3, H-17 and H-18).

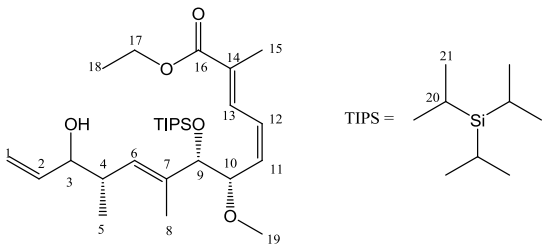
^{13}C NMR (125 MHz, $CDCl_3$) δ 200.8 (C-1), 168.2 (C-14), 140.1 (C-5/C-12), 135.0 (C-9), 132.1 (C-11), 129.5 (C-5/C-12), 127.3 (C-10), 123.8 (C-4), 80.5 (C-7/C-8), 79.6 (C-7/C8), 60.7 (C-15), 56.8 (C-19), 46.0 (C-2), 18.0 (C-17), 17.9 (C-3), 14.3 (C-16), 13.6 (C-6/C-13), 12.4 (C-18), 12.3 (C-6/C-13).

HRMS (ESI) *m/z* = 489.2999 (*calc.* 489.3007) $C_{26}H_{46}O_5SiNa$ [M + Na].

ν_{max} (thin film)/cm^{-1} 2936 and 2865 (s, C-H), 1711 (s, C=O), 1463, 1246, 1096.

$[\alpha]_D^{22}$ +41.7° (*c* 0.67 in $CHCl_3$).

11-Hydroxy-6-methoxy-2,8,10-trimethyl-7-triisopropylsilanyloxy-trideca-2,4,8,12-tetraenoic acid ethyl ester (219)



(219)

To a stirred solution of aldehyde **(194)** (310 mg, 1.63 mmol) in tetrahydrofuran (10 mL) under an atmosphere of nitrogen, was added vinyl magnesium bromide (1.63 mL, 1.63 mmol) drop wise at 0˚C and the reaction mixture was stirred at room temperature overnight and was then quenched with a solution of saturated ammonium chloride (10 mL). The aqueous layer was then extracted with Et_2O (3 x 10 mL). The organic extracts were combined and washed with brine (30 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Flash chromatography (gradient of 0 to 15 % of Et_2O in petroleum ether) afforded alcohol **(219)** as an orange oil (215 mg, 60 %).

R_f 0.50 (20 % diethyl ether : petroleum ether).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.53-6.45 (1H, m, H-12), 5.89-5.77 (1H, m, H-2), 5.48 (1H, m, H-11), 5.23 (1H, m, H-6), 5.18-5.07 (2H, m, H-1), 4.27 (2H, m, H-17), 4.25-4.11 (2H, m, H-9 and H-10), 3.91 (1H, m, H-3), 3.28 (3H, s, H-19), 2.37 (1H, m, H-4), 1.95 (1H, m, H-8 or H-15), 1.66 (1H, m, H-8 or H-15), 1.32 (3H, t, *J* 10 Hz, H-18), 1.14-1.04 (18H, d, *J* 10 Hz, H-19), 1.00 (1H, m, H-5), 0.97 (3H, q, *J* 10 Hz, H-20).

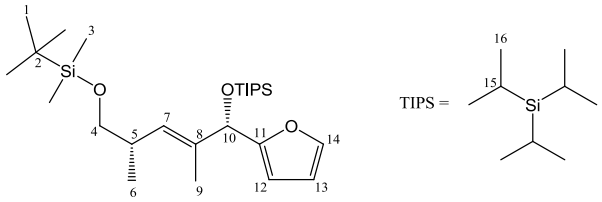
^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0 (C-16), 139.1 (C-2), 137.8 (C-7 or C-14), 137.3 (C-7 or C-14), 135.6 (C-11), 132.4 (C-13), 129.0 (C-6), 127.2 (C-12), 115.3 (C-1), 80.7

(C-9 or C-10), 76.5 (C-3), 60.7 (C-9 or C-10), 60.3 (C-17), 56.7 (C-19), 21.7 (C- 4), 18.1 (C-21), 16.0 (C-20), 14.3 (C-18), 13.3 (C-8 or C-15), 12.6 (C-5), 12.5 (C-8 or C-15).

HRMS (ESI) *m/z* = 517.3318 (*calc.* 517.3320) $C_{28}H_{50}O_5SiNa$ [M + Na].

ν_{max} (thin film)/cm^{-1} 2952, 1699, 1463, 1254, 1100, 907, 730.

2-[5-(tert-Butyl-dimethyl-silanyloxy)-2,4-dimethyl-1-triisopropylsilanyloxy-pent-2-enyl]-furan (224)



(224)

To a stirred solution of furyl acohol **(196)** (1.0 g, 3.2 mmol) in CH_2Cl_2 (50 mL) at 0 °C under an atmosphere of nitrogen, was added 2,6-lutidine (1.2 mL, 9.7 mmol) and the reaction mixture was stirred at 0 °C for ten minutes. Then, tri-isopropylsilyl trifluoromethanesulfonate (1.8 mL, 6.4 mmol) was added drop wise at 0 °C. The reaction mixture was warmed to room temperature and stirred overnight and subsequently quenched with a solution of saturated aqueous sodium hydrocarbonate (40 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The organic extracts were combined and dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (100 % petroleum ether) and the disilylated alcohol **(224)** was isolated as a colorless oil (70 mg, 40 %).

R_f 0.73 (10 % Et_2O : petroleum ether).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (1H, m, H-14), 6.28 (1H, m, H-12), 6.19 (1H, m, H-13), 5.41 (1H, d, *J* 9.35 Hz, H-7), 3.34-3.54 (2H, m, H-4), 2.53-2.59 (1H, m, H-10), 1.58 (3H, d, *J* 1.1Hz, H-6), 1.51 (3H, s, H-9), 1.25 (1H, m, H5), 1.01-1.12 (18H, m, H-16), 0.96 (3H, m, H-15), 0.90 (9H, s, H-1), 0.04 (6H, s, H-3).

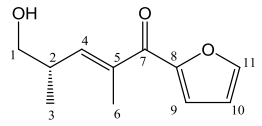
^{13}C NMR (125 MHz, $CDCl_3$) δ 156.8 (C-11), 141.1 (C-14), 135.6 (C-8), 129.3 (C-13), 109.9 (C-12), 105.8 (C-7), 74.4 (C-10), 67.7 (C-4), 35.2 (C-5), 25.9 (C-1), 18.0 (C-2), 17.9 (C-16), 17.1 (C-6), 12.3 (C-15), 12.1 (C-9), -5.4 (C-3).

HRMS (ESI) *m/z* = 489.3178 (*calc.* 489.3191) $C_{26}H_{50}O_3Si_2Na$ [M + Na].

ν_{max} (thin film)/cm^{-1} 2927, 2865, 1463, 1252, 1083, 833.

$[\alpha]_D^{29}$ +13.4º (*c* 0.54 in $CHCl_3$).

(S,E)-1-(furan-2-yl)-5-hydroxy-2,4-dimethylpent-2-en-1-one (227)



(227)

To a stirred solution of protected alcohol **(205)** (3.3 g, 10.7 mmol) in methanol (50 mL) at room temperature and under an atmosphere of nitrogen, was added pyridinium tribromide (320 mg, 0.53 mmol) and the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was then quenched with sodium bicarbonate (20 mL). The aqueous layer was then extracted (3 x 20 mL) with ethyl acetate. The combined organic extracts were dried with anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Flash chromatography (20 % Et_2O : petroleum ether) afforded alcohol **(227)** as a yellowish oil (1.67 g, 80 %).

R_f 0.37 (80 % Et_2O : petroleum ether).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (1H, dd, *JA* 1.7 Hz, *JB* 0.7 Hz, H-11), 7.08 (1H, dd, *JC* 3.5 Hz, *JB* 0.7 Hz, H-9), 6.52-6.51 (1H, dd, *JC* 3.5 Hz, *JA* 1.7 Hz, H-10), 6.43-6.41 (1H, d, *J* 11 Hz, H-4), 3.36-3.55 (2H, m, H-1), 2.90-2.87 (1H, m, H alkoxy), 2.00 (3H, s, H-6), 1.41 (1H, m, H-2), 1.10-1.09 (3H, d, *J* 8.8 Hz, H-3).

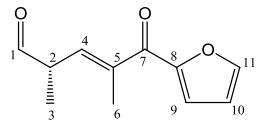
^{13}C NMR (125 MHz, $CDCl_3$) δ 185 (C-7), 153 (C-8), 157 (C-11), 145 (C-10), 137 (C-5), 119 (C-9), 112 (C-4), 68 (C-1), 37 (C-2), 16 (C-3), 14 (C-6).

HRMS (ESI) *m/z* = 217.0834 (*calc.* 217.0835) $C_{11}H_{14}O_3Na$ [M + Na].

ν_{max} (thin film)/cm^{-1} 3422, 2960, 2928, 1622, 1463.

$[\alpha]_D^{25}$ -8.6º (*c* 0.53 in $CHCl_3$).

5-Furan-2-yl-2,4-dimethyl-5-oxo-pent-3-enal (231)



(231)

To a stirred solution of alcohol **(227)** (2.2 g, 11.3 mmol) in CH_2Cl_2 (200 mL) at room temperature and under an atmosphere of nitrogen, was added Dess-Martin periodinane (7.2 g, 17.0 mmol) and the reaction mixture was stirred at room temperature overnight. The reaction mixture was then quenched with sodium thiosulfate (100 mL) and sodium bicarbonate (100 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 x 100 mL). The organic extracts were combined and washed with brine (100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Flash chromatography (10 % Et_2O : petroleum ether) afforded aldehyde **(231)** as a yellowish oil (1.44 g, 67 %).

R_f 0.57 (80 % Et_2O : petroleum ether).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.45 (1H, s, H-1), 7.61 (1H, dd, *JA* 1.7 Hz, *JB* 0.7 Hz, H-11), 7.27 (1H, d, *JB* 0.7 Hz, H-9), 6.65 (1H, d, *J* 9.7 Hz, H-4), 6.58-6.57 (1H, dd, *J* 3.7 Hz, *JA* 1.7Hz, H-10), 4.46-4.43 (1H, m, H-2), 1.88 (3H, s, H-6), 1.42-1.40 (3H, d, *J* 7 Hz, H-3).

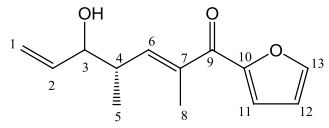
^{13}C NMR (125 MHz, $CDCl_3$) δ 194 (C-1), 188 (C-7), 152 (C-8), 151 (C-11), 139 (C-10), 139 (C-5), 118 (C-9), 113 (C-4), 42 (C-2), 17 (C-3), 9.5 (C-6).

HRMS (ESI) *m/z* = 215.0679 (*calc.* 215.0679) $C_{11}H_{12}O_3Na$ [M + Na].

ν_{max} (thin film)/cm^{-1} 1671, 1463.

$[\alpha]_D^{25}$ +3.6º (*c* 0.55 in $CHCl_3$).

1-Furan-2-yl-5-hydroxy-2,4-dimethyl-hepta-2,6-dien-1-one (232)



(232)

To a stirred solution of aldehyde **(231)** (1.25 g, 6.51 mmol) in tetrahydrofuran (50 mL) under an atmosphere of nitrogen, was added vinyl magnesium bromide (6.51 mL, 6.51 mmol) drop wise at 0˚C and the reaction mixture was stirred at room temperature overnight. The reaction mixture was then quenched with a solution of saturated ammonium chloride (40 mL). The aqueous layer was then extracted with Et_2O (3 x 50 mL). The organic extracts were combined and washed with brine (100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Flash chromatography (gradient of 0 to 15 % of Et_2O in petroleum ether) afforded alcohol **(232)** as an orange oil (0.86 g, 60 %).

R_f 0.40 (50 % Et_2O : petroleum ether).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (1H, d, *J* 1Hz, H-13), 7.20-7.18 (1H, m, H-11), 6.53 (1H, m, H-12), 5.86-5.77 (1H, m, H-2), 5.62-5.61 (1H, d, *J* 9.5 Hz, H-6), 5.30-5.17 (2H, m, H-1), 4.54 (1H, d, *J* 4.8 Hz, H-3), 4.16-4.12 (1H, m, H-4), 1.73 (3H, s, H-8), 1.62 (1H, s, alkoxy), 1.30-1.26 (3H, m, H-5).

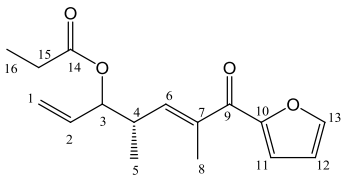
^{13}C NMR (125 MHz, $CDCl_3$) δ 191 (C-9), 152 (C-10), 146 (C-13), 139 (C-2), 138 (C-7), 126 (C-11), 117 (C-6), 115 (C-1), 112 (C-12), 78 (C-3), 41 (C-4), 17 (C-5), 12 (C-8).

HRMS (ESI) *m/z* = 243.0994 (*calc.* 243.0992) $C_{13}H_{16}O_3Na$ [M + Na].

ν_{max} (thin film)/cm^{-1} 3441 (alcohol), 2927, 1659, 1464.

$[\alpha]_D^{26}$ +22.9º (*c* 1.01 in $CHCl_3$).

Propionic acid 5-furan-2-yl-2,4-dimethyl-5-oxo-1-vinyl-pent-3-enyl ester (233)



(233)

To a stirred solution of alcohol **(232)** (160 mg, 0.73 mmol) in CH_2Cl_2 (10 mL) under an atmosphere of nitrogen was added 2-6 lutidine (0.08 mL, 0.87 mmol) at 0˚C. The reaction mixture was stirred at 0˚C for 10 minutes and propionyl chloride (0.08 mL, 0.87 mmol) was added drop wise at 0˚C. The reaction mixture was then allowed to warm up to room temperature, stirred overnight and was then quenched with a 2M aqueous solution of hydrochloric acid (5 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 x 50 mL). The organic extracts were combined, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Flash chromatography (10 % Et_2O : petroleum ether) afforded ester **(233)** as a yellowish / orange oil (180 mg, 89 %).

R_f 0.63 (50 % Et_2O : petroleum ether).

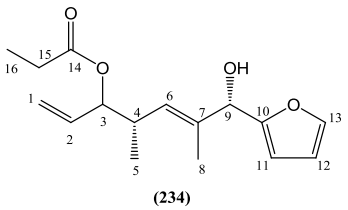
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (1H, d, *J* 0.6 Hz, H-13), 7.19-7.17 (1H, m, H-11), 6.53-6.52 (1H, m, H- 12), 5.75-5.73 (1H, m, H-2), 5.63 (1H, d, *J* 9 Hz, H-6), 5.59 (1H, m, H-4), 5.25-5.15 (2H, m, H-1), 4.15-4.08 (1H, m, H-3), 2.37-2.32 (2H, m, H-15), 1.74 (1H, s, H-8), 1.28-1.26 (3H, m, H-5), 1.15-1.12 (3H, m, H-16).

^{13}C NMR (125 MHz, $CDCl_3$) δ 190.3 (C-9), 173.1 (C-14), 152.1 (C-10), 146.3 (C-13), 135.1 (C-2/6), 134.5 (C-7), 127.4 (C-2/6), 117.4 (C-11/12), 116.9 (C-1), 112.2 (C-11/12), 78.8 (C-3), 41.3 (C-4), 27.9 (C-15), 17.2 (C-5/8), 13.2 (C-5/8), 9.1 (C-16).

HRMS (ESI) *m/z* = 299.1259 (*calc.* 299.1254) $C_{16}H_{20}O_4Na$ [M + Na].

ν_{max} (thin film)/cm^{-1} 2980, 1735, 1677, 1465.

(4S,7S,E)-7-(furan-2-yl)-7-hydroxy-4,6-dimethylhepta-1,5-dien-3-yl propionate (234)



(234)

To a stirred solution of lithium aluminium hydride (275 mg, 7.24 mmol) in Et_2O (10 mL) at 0 °C under an atmosphere of nitrogen, was added a solution of (1*R*),(2*S*)-(-)-*N*-methylephedrine (1.3 g, 7.24 mmol) in Et_2O (30 mL) drop wise. The reaction mixture was submitted to reflux for two hours, before being allowed to cool to room temperature. A solution of freshly distilled *N*-ethylaniline (1.82 mL, 14.5 mmol) in Et_2O (10 mL) was added drop wise and the reaction mixture was submitted to reflux for a further two hours. The reaction mixture was cooled down to -100 °C and a solution of furyl ketone **(233)** (1.2 g, 4.34 mmol) in Et_2O (30 mL) was added drop wise. The reaction mixture was stirred at -100 °C for four hours, before subsequently being quenched by pouring into an ice cooled aqueous solution of sodium potassium tartrate (10 g) and water (50 mL). The solution was allowed to warm to room temperature overnight. The layers were separated and the aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with a solution of saturated aqueous copper sulfate (50 mL), a solution of saturated aqueous sodium chloride (2 x 50 mL) dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (5 % Et_2O : petroleum ether) and furyl alcohol **(234)** was isolated as a clear oil (860 mg, 71 %).

R_f 0.35 (30 % Et_2O : petroleum ether).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (1H, s, H-13), 6.33 (1H, dd, *J* 2.6, 10 Hz, H-12), 6.25 (1H, dd, *J* 2.6, 10 Hz, H-11), 5.82 (1H, m, H-2), 5.59 (1H, t, *J* 6.0 Hz, H-3), 5.43 (1H, d, *J* 10 Hz, H-6), 5.30-5.26 (2H, m, H-1), 4.42 (1H, d, *J* 7.85 Hz, H-4), 2.95 (1H, m,

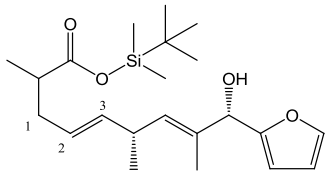
H-9), 2.36 (2H, m, H-15), 1.67 (3H, d, *J* 13 Hz, H-5), 1.08 (3H, m, H-16), 0.89 (3H, d, 6.75 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ 173 (C-14), 155 (C-10), 142 (C-13), 135 (C-2), 130 (C-7), 129 (C-6), 116 (C-1), 110 (C-12), 107 (C-11), 79 (C-3), 72 (C-4), 38 (C-9), 28 (C-15), 17 (C-8), 13 (C-5), 9 (C-19).

HRMS (ESI) *m*/*z* = 301.1414 (*calc.*301.1410) $C_{16}H_{22}O_4SiNa$ [M + Na].

ν_{max} (thin film)/cm^{-1} 3459, 2979, 2930, 2876, 1729, 1358, 1182.

(4E,6R,7E,9S)-tert-butyldimethylsilyl-9-(furan-2-yl)-9-hydroxy-2,6,8-trimethyl nona-4,7-dienoate (247)



(247)

To a stirred solution of diisopropylamine (0.76 mL, 5.5 mmol) in tetrahydrofuran (25 mL) was added *n*-butyllithium (2.2 mL, 2.5M in hexanes, 5.5 mmol) at 0 °C. The solution was stirred at 0 °C for 15 min and cooled to -78 °C. Hexamethylphosphoramide (1.9 mL, 11.0 mmol) and tetrahydrofuran (1.9 mL) were then successively added. The solution became light yellow and after 10 min, a solution of propionate **(234)** (300 mg, 1.1 mmol) in tetrahydrofuran (2 µL) was slowly added. The resulting solution was stirred at -78 °C for 45 min by which time the color became bright yellow. A solution of *tert*-butyldimethylsilyl chloride (1.32 mg, 8.8 mmol) in tetrahydrofuran (30 mL) was then added. The solution became light yellow and after 15 min at -78 °C the reaction mixture was gradually warmed to rt over 2h. The solution was then stirred at rt. for 7 h and quenched with 1M aqueous hydrochloric acid (50 mL). The aqueous phase was extracted with ethyl acetate (3 x 50 mL). The organic extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient from 10 % ethyl acetate : petroleum to 30 % ethyl acetate : petroleum) to afford the corresponding silyl ester **(247)** (traces) as a colourless oil.

R_f 0.75 (5 % Et_2O : petroleum ether).

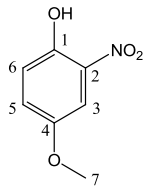
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (1H, d, J 14 Hz, H-16), 6.27 (1H, t, J 11 Hz, H-15), 6.10 (1H, m, H-14), 6.01 (1H, t, J 14 Hz, H-6) 5.47 (1H, m, H-5), 5.23 (1H, d, J 10 Hz, H-9), 4.45 (1H, m, H-12), 2.94 (1H, m, H-7), 2.54 (1H, m, H-2), 2.23 (2H, m, H-4),

1.70 (3H, d, J 11 Hz, H-8), 1.19 (3H, m, H-3), 1.02 (3H, m, H-11), 0.87 (9H, d, J 14 Hz, H-19), 0.11 (6H, s, H-17).

^{13}C NMR (125 MHz, $CDCl_3$) δ 181 (C-1), 156 (C-13), 141 (C-16), 137 (C-6), 134 (C-9), 123 (C-5), 110 (C-15), 105 (C-14), 73 (C-12), 40 (C-2), 39 (C-7), 38 (C-10), 36 (C-4), 26 (C-19), 18 (C-18), 17 (C-3), 16 (C-11), 14 (C-8), -5 (C-17).

HRMS (ESI) *m*/*z* = 415.2265 (*calc.* 415.2275) $C_{22}H_{36}O_4SiNa$ [M + Na].

4-methoxy-2-nitrophenol (260)



(260)

To a stirred solution of 4-methoxy-2-phenol **(252)** (0.67 g, 0.54 mmol) in ethanol (50 mL) was added glacial acetic acid (2 mL) at room temperature, followed by a solution of sodium nitrite (0.6 g, 0.9 mmol) in ethanol (30 mL) drop wise over 30 minutes. The resulting mixture was stirred overnight and subsequently quenched with 20% aqueous potassium hydroxide solution (50 mL). Et_2O (100 mL) was then added to the solution which was stirred 30 minutes. The layers were then separated and the aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (100 % toluene) and 4-methoxy-2-nitrophenol **(260)** was isolated as an orange solid (0.5 g, 54 %).

R_f 0.82 (Toluene).

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.40 (1H, s, OH), 7.52 (1H, d, *J* 2.0 Hz, H-3), 7.24 (1H, dd, *J* 2.0, 8.4 Hz, H-5), 7.10 (1H, d, *J* 8.4 Hz, H-6), 3.84 (3H, s, H-7).

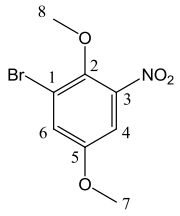
^{13}C NMR (125 MHz, $CDCl_3$) δ 153.0 (C-4), 150.5 (C-1), 134.0 (C-2), 127.7 (C-5), 121.3 (C-6), 106.1 (C-3), 56.4 (C-7).

LRMS (EI) *m/z* = 169 (*calc.*169.137) $C_7H_7NO_4$.

ν_{max} (thin film)/cm^{-1} 3227, 1523, 1244, 1216, 1027.

mp 82°C (lit.[136] 83°C).

1-bromo-2,5-dimethoxy-3-nitrobenzene (251)



(251)

To a stirred solution of 4-methoxy-2-nitrophenol **(260)** (8.31 g, 49.2 mmol) in glacial acetic acid (50 mL) was added a solution of bromine (2.5 mL, 49.2 mmol) in glacial acetic acid (10 mL) over 40 min. After stirring for 30 minutes at room temperature and heating at reflux for 5 hours, the reaction mixture was poured into water (750 mL) and acidified with conc. hydrochloric acid (10 mL). After filtration and drying, the desired 2-bromo-4-methoxy-6-nitrophenol was obtained as an orange solid (9.3 g, 76%). 2-bromo-4-methoxy-6-nitrophenol (9.3 g, 37.4 mmol) was then taken up in dry acetone (300 mL), and potassium carbonate (15.5 g, 112 mmol) and dimethyl sulfate (7.1 mL, 74.8 mmol) were added. The reaction mixture was heated at reflux for 5 hours and was then concentrated under reduced pressure. The residue was purified by flash chromatography (100 % toluene) and the desired aryl bromide **(251)** was obtained as a yellow solid (8.8 g, 90 %).

R_f 0.75 (Toluene).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (1H, d, *J* 3.1 Hz, H-4), 7.28 (1H, d, *J* 3.1Hz, H-6), 3.96 (s, 3H, H-7), 3.83 (s, 3H, H-8).

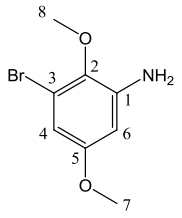
^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5 (C-5), 145.0 (C-2), 144.5 (C-3), 123.8 (C-6), 120.1 (C-1), 109.2 (C-4), 62.7 (C-7), 56.3 (C-8).

LRMS (EI) ***m*/*z*** = 261 and 263 (1:1 ratio).

ν_{max} (thin film)/cm^{-1} 1524, 1341, 1229, 1077, 1043, 984, 860, 777.

mp 98°C (lit.[137] 98-98.5 °C).

3-bromo-2,5-dimethoxyaniline (**261**)



(261)

To a stirred suspension of nitro compound **(251)** (1.0 g, 3.8 mmol) in water (13 mL) were added glacial acetic acid (0.15 mL) and iron (powder, 1.5 g). After 1.5 h of heating at reflux, the reaction mixture was filtered. The aqueous layer was basified with a saturated aqueous solution of sodium carbonate and extracted with ethyl acetate (2x 50 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure to provide the crude aniline (**261)** as a brown viscous oil (758 mg, 86%).

^{1}H NMR (500 MHz, $CDCl_3$) δ6.45 (1H, d, *J* = 3.0 Hz, H-4); 6.23 (1H, d, *J* = 2.5 Hz, H-6); 3.93 (2H, b, NH_2); 3.78 (3H, s, H-6); 3.71 (3H, s, H-4).

^{13}C NMR (125 MHz, $CDCl_3$) δ δ 156.9 (C-5), 141.7 (C-2), 138.7 (C-1), 117.1 (C-3), 107.1 (C-4), 101.3 (C-6), 59.9 (C-8), 55.7 (C-7).

HRMS (ESI) ***m*/*z*** = 231, 233 (1:1 ratio).

ν_{max} (thin film)/cm^{-1} 3468, 3370, 2936, 2830, 1612, 1565, 1486, 1431, 1222, 1152, 1037, 990, 832.

CHAPTER 5

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