PART II

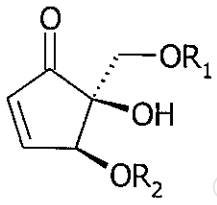
SYNTHESIS OF PENTENOMYCIN

PART II

SYNTHESIS OF PENTENOMYCIN

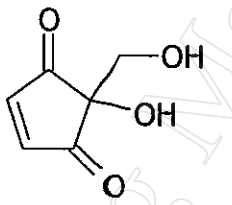
1. Introduction

Natural products containing the highly oxygenated cyclopentanoid skeleton have recently attracted considerable attention, because in many cases they exhibit interesting biological activities.[1-5] For example, the pentenomycin group, of compounds (**1-7**) have been demonstrated to have moderate to strong *in vitro* activity against a variety of both gram-positive and gram-negative bacteria, including *Neisseria meningitidis* and *Neisseria gonorhocae*. The potential pharmacological importance of the cyclopentenone structural unit, including that found in pentenomycins, suggests that it might be the reactive functionality in a variety of structurally complex antitumor agents.



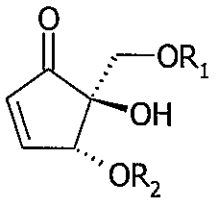
Pentenomycins

1, R_1=R_2=H (I)
2, R_1=H, R_2=Ac (II)
3, R_1=Ac, R_2=H (III)



Dehydropentenomycin

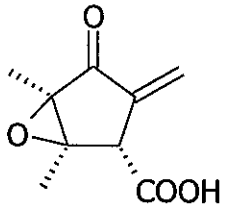
4



Epipentenomycins

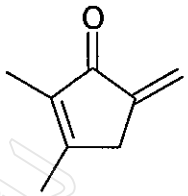
5, R_1=R_2=H (I)
6, R_1=H, R_2=Ac (II)
7, R_1=Ac, R_2=H (III)

Some structurally related cyclopentanoid antibiotics are the methylenomycins A (**8**) and B (**9**),[6] the known antitumor agent sarcomycin (**10**),[7] and xanthocidin (**11**).[8]



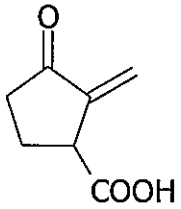
Methylenomycin A

8



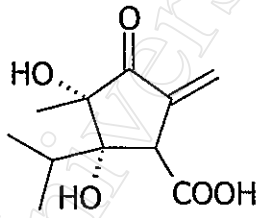
Methylenomycin B

9



Sarcomycin

10



Xanthocidin

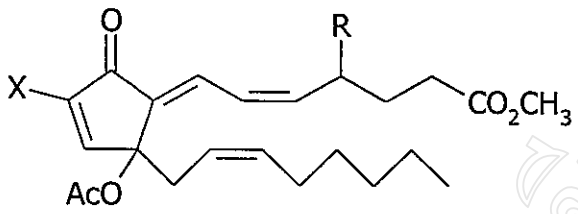
11

Interestingly, the didemnenones (**12**) that have been isolated from the Carribbean tunicate *Tridemnum cf. cyanaphorum* and the South Pacific tunicate *Didemnum voeltzkowi,* exhibit a broad-range of antimicrobial and antileukemic activities.[9]

Didemnenones

12

A series of marine eicosanoids related to the prostaglandins, such as the clavulones (**13**)[10] (claviridinones), a marine prostanoid isolated from the Okinawan soft coral, *Clavulariaviridis* and the punaglandins (**16**),[11] have reported to have a remarkable cytotoxicity in both *in vitro* and *in vivo* studies. The non-naturally occurring arylidene cyclopentenediones (**15**) also showed reasonable *in vitro* antitumor activity.[12]



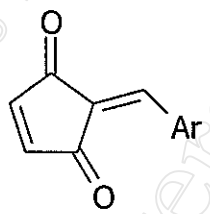
Clavulones X=H, R=OAc

13

Haloclavulones X=Cl, Br or I

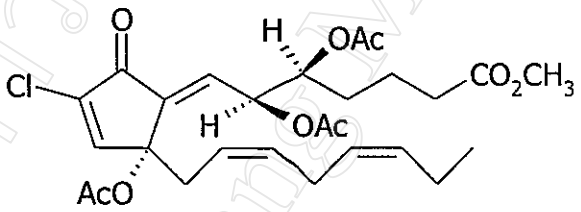
R=H

14



Arylidene cyclopentenediones

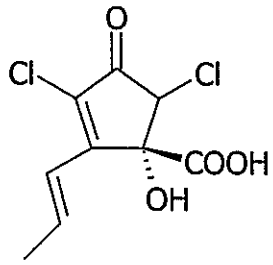
15



Punaglandins

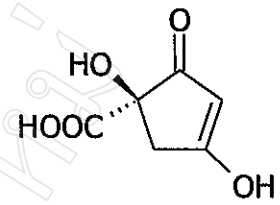
16

Other cyclopentenone natural products are the bioactive compounds cryptosporiopsin (**17**),[13,14,15] kjellmanianone (**18**),[16,17,18] reductiomycin (**19**),[19,20] and terrein (**20**).[21,22] The pentenomycins are new members of this group of substances.



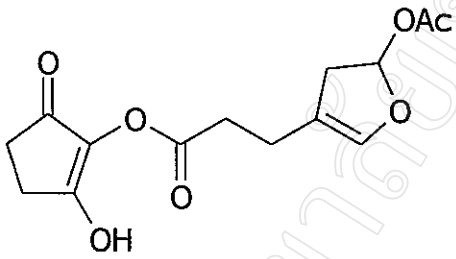
Cryptosporiopsin

17



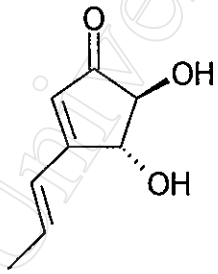
Kjellmanianone

18



Reductiomycin

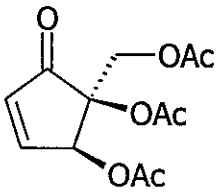
19



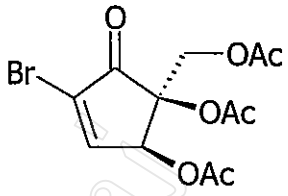
Terrein

20

Pentenomycin I (**1**), an amorphous powder, and pentenomycin II (**2**), a syrup, were first isolated in 1973 by Umino and co-workers[1,2] from aerobically culture broths of a mutant strain of *Streptomyces eurythermus*. Structural assignments including the relative stereochemistry were derived through spectroscopic measurements, preparation of the triacetate of pentenomycin I (**21**) and X-ray crystallographic analysis of the derived bromotriacetate (**22**). The latter not only confirmed the proposed structures but also defined the absolute stereochemistry to be *4S, 5S*.[3]



21



22

Three years later (1976), Shomura *et al.*[23] isolated pentenomycin III (**3**) from *Streptovercillium eurocidicum* SF-1768, a strain known to produce pentenomycin II (**2**). In the same year, three additional antibiotics (C-2254, A II and A I) **5**, **6** and **7** were isolated by the Hatano group[24] from *Streptomyces lavendolygriseus* C-2254; initially their structures were postulated to have the epimeric arrangement of hydroxyl substituents. However, shortly thereafter, Hatano *et al.*[24] demonstrated that they were, in fact, identical with pentenomycins I-III.[25]

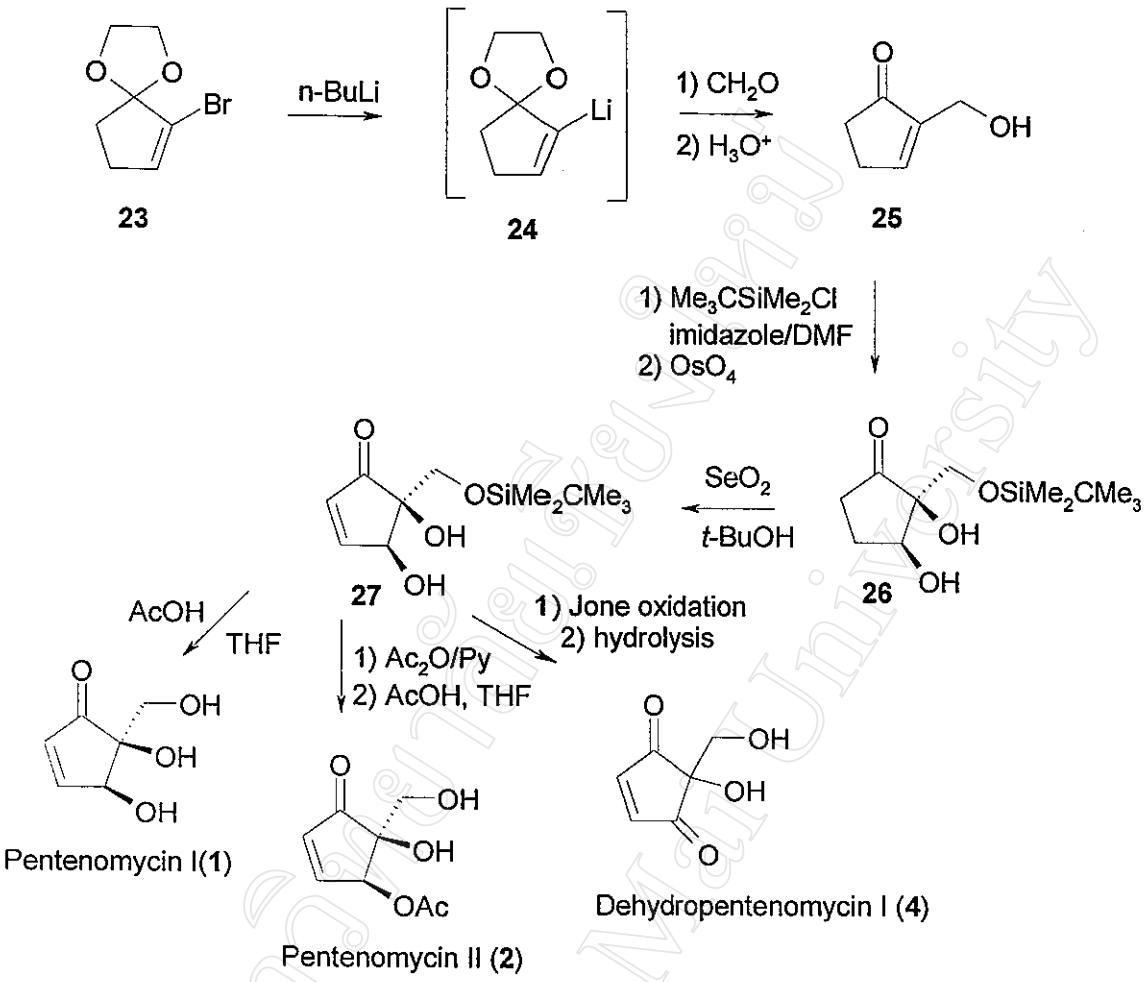
In 1978, Noble *et al.*[4] reported the isolation of **4**, a simple oxidation product of pentenomycin I (**1**), termed dehydropentenomycin I (**4**). The assignment of structure in this case was based solely on spectroscopic evidence.

Finally, Bernillon *et al.*[5] reported the first isolation of (-)-epipentenomycin I (5) from carpophores of *Peziza sp.*, collected on horse manure.

The pentenomycin I-III (**1**, **2** and **3**) are representatives of a small but rapidly growing family of antibiotics, all of which possess the highly oxygenated cyclopentenone ring. Because of their interesting biological activities and because they have been isolated in a very small amounts, synthesis would thus provide larger amounts of these compounds to study their biology and methods to prepare new derivatives or analogues. A summary of previous syntheses of the pentenomycins follows.

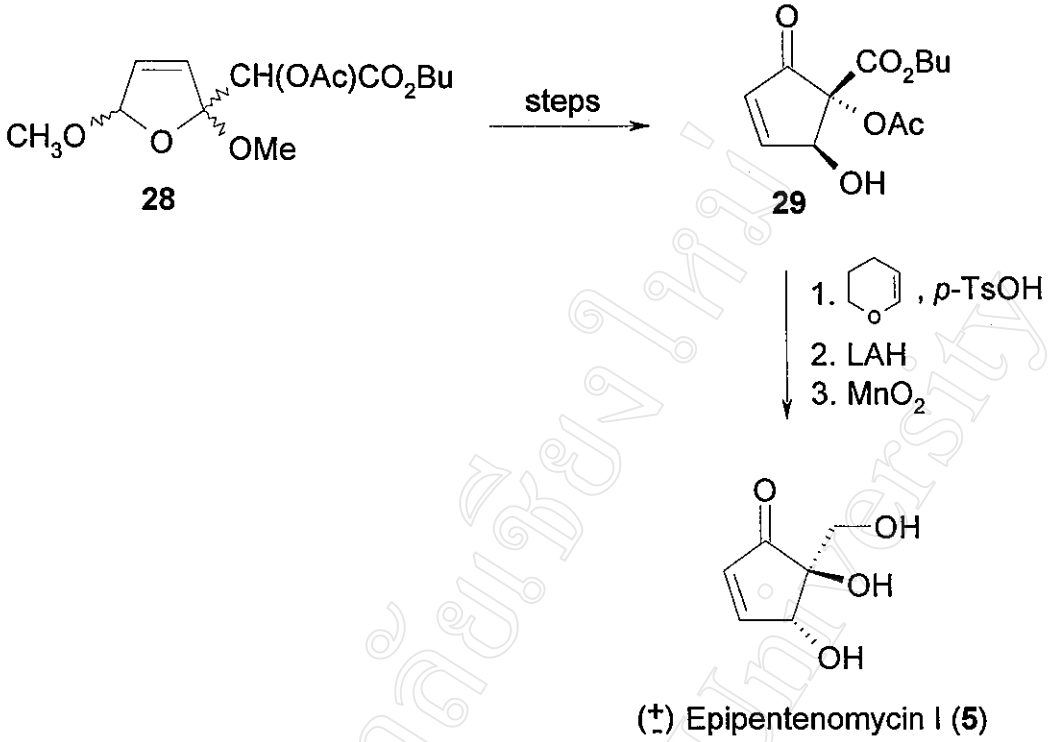
Synthesis of (±) –Pentenomycins and (±)-Epipentenomycins

The synthesis of (±)-pentenomycin I (**1**), (±)-pentenomycin II (**2**) and dehydropentenomycin I (**4**), exploiting a versile latent α-ketovinyl anion equivalent, was demonstrated by Smith, III *et al.*[26] as shown in Scheme 1. Treatment of ketal (**23**) with *n*-butyllithium gave the vinyl anion (**24**), which was then reacted with HCHO (g) and the resulting product was deketalised to give the cyclopentenone (**25**). The primary hydroxyl was protected with *tert*-butyldimethylsilyl chloride and then *cis*-dihydroxylation with osmium tetroxide gave the *cis*-diol (**26**). Dehydrogenation with selenium dioxide in *tert*-butanol gave **27**, which was: 1) hydrolysed to (±) pentenomycin I; 2) acetylated and then hydrolysed to (±) pentenomycin II; and 3) oxidised (Jones method) and then hydrolysed to dehydropentenomycin I.



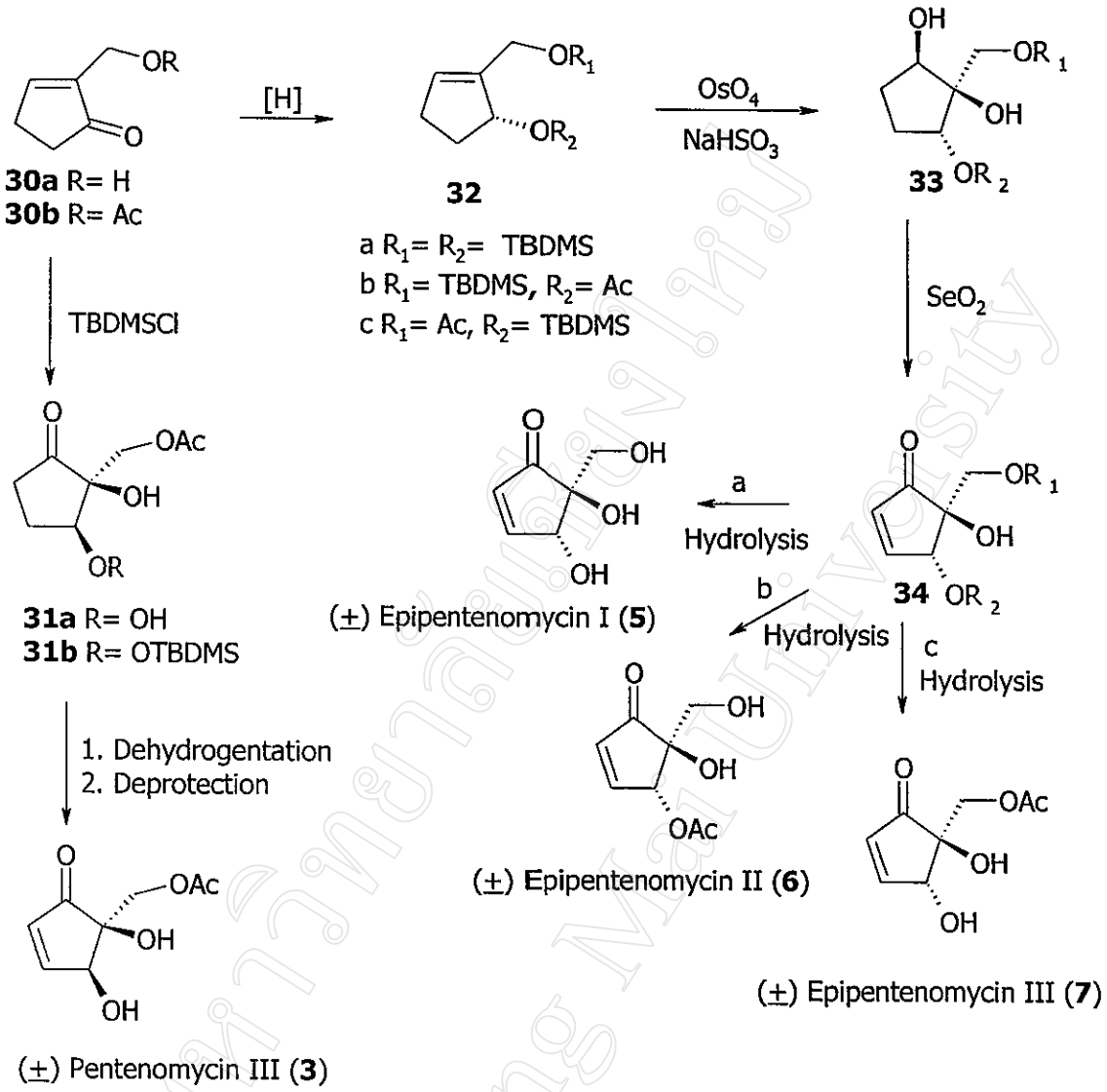
Scheme 1

(±) Epipentenomycin I (**5**) was first synthesised by Sono *et al.*[25] using the acid catalysed transformation of a 2,5-dihydro-2,5-dimethoxyfuran (**28**) to give, after several steps, the cyclopentenone derivative (**29**), which was a key intermediate in the synthesis of (±) epipentenomycin I (**5**) (Scheme 2).



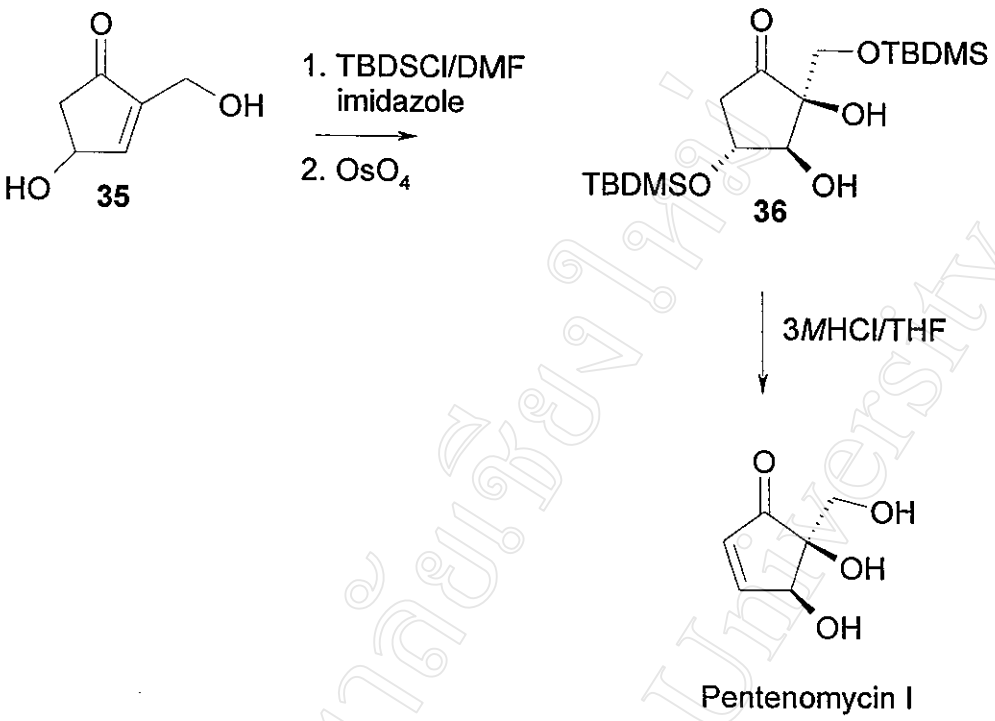
Scheme 2

In 1982, Smith, III *et al.* [27] once again reported a stereocontrolled total synthesis of (±) pentenomycin I-III (**1-3**) and their epimers (**5-7**), and dehydropentenomycin I (**4**). The synthesis of pentenomycin I and II and dehydropentenomycin I followed the same strategies discussed previously in Scheme 1.[26] However, in the synthesis of pentenomycin III, the diol acetate (**31a**) was protected as the monosilyl ether (**31b**) which was dehydrogenated by employing SeO_2. Deprotection of the secodary hydroxy group afforded (±) pentenomycin III (Scheme 3). The synthesis of epipentenomycin I-III involved protection of the hydroxy group followed by reduction to afford compound (**32**, R_1= TBDMS, R_2= OH). The OsO_4 *cis*-dihydroxylation of **32** gave compound **33** in a highly stereoselective manner. Application of the SeO_2 dehydrogenation led to the cyclopentenone (**34**), which was converted to the epipentenomycin series.



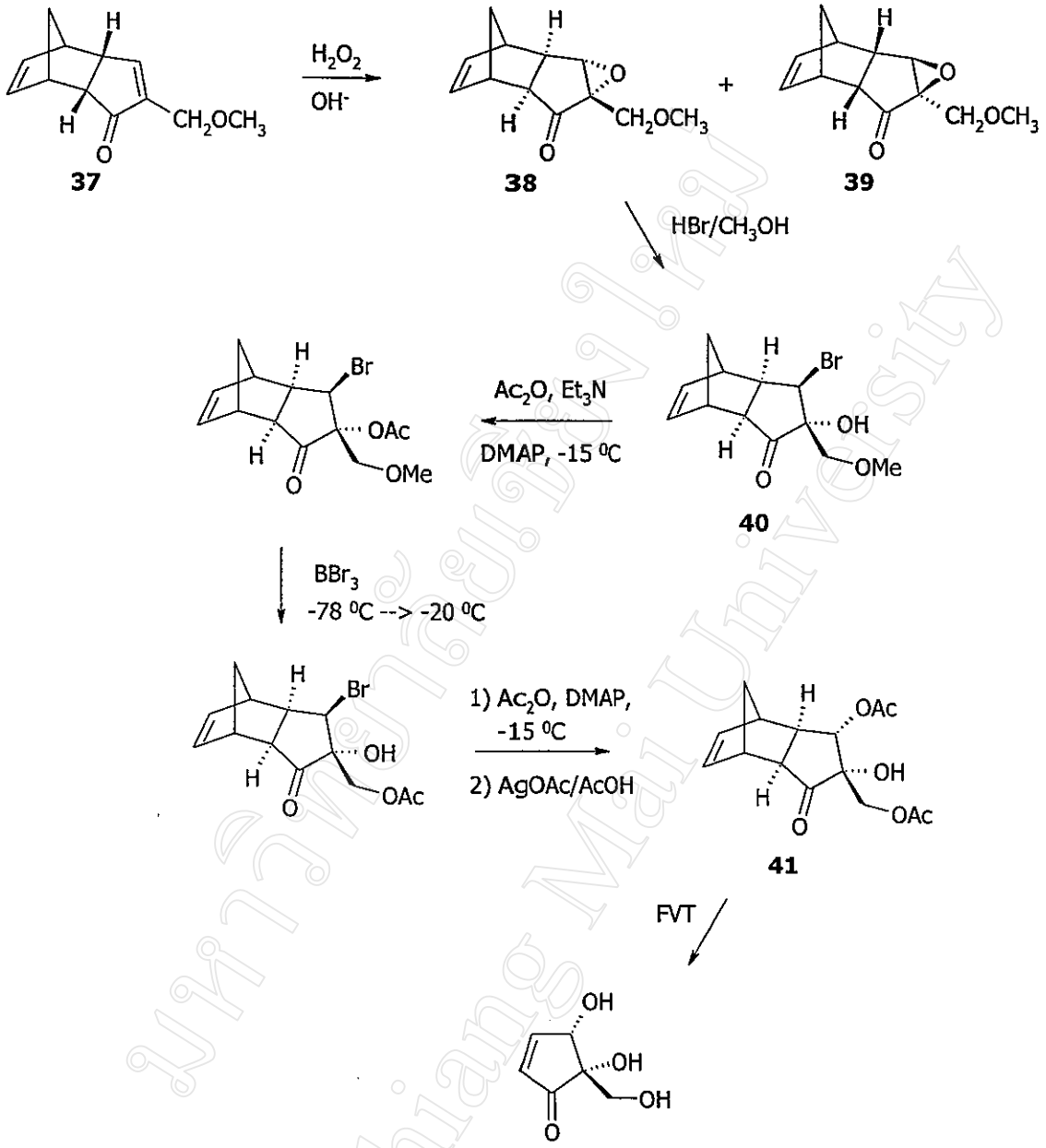
Scheme 3

A similar synthesis has been described by Stoodley[28] starting from 4-hydroxy-2-hydroxymethyl-2-cyclopentenone (**35**) as shown in Scheme 4. Treatment of **35** with *t*-butyldimethylsilyl chloride (TBDMSCl) and imidazole followed by *cis*-dihydroxylation gave (±) diol (**36**). Hydrolysis of **36** using 3M-hydrochloric acid and tetrahydrofuran gave (±) pentenomycin I (**1**).



Scheme 4

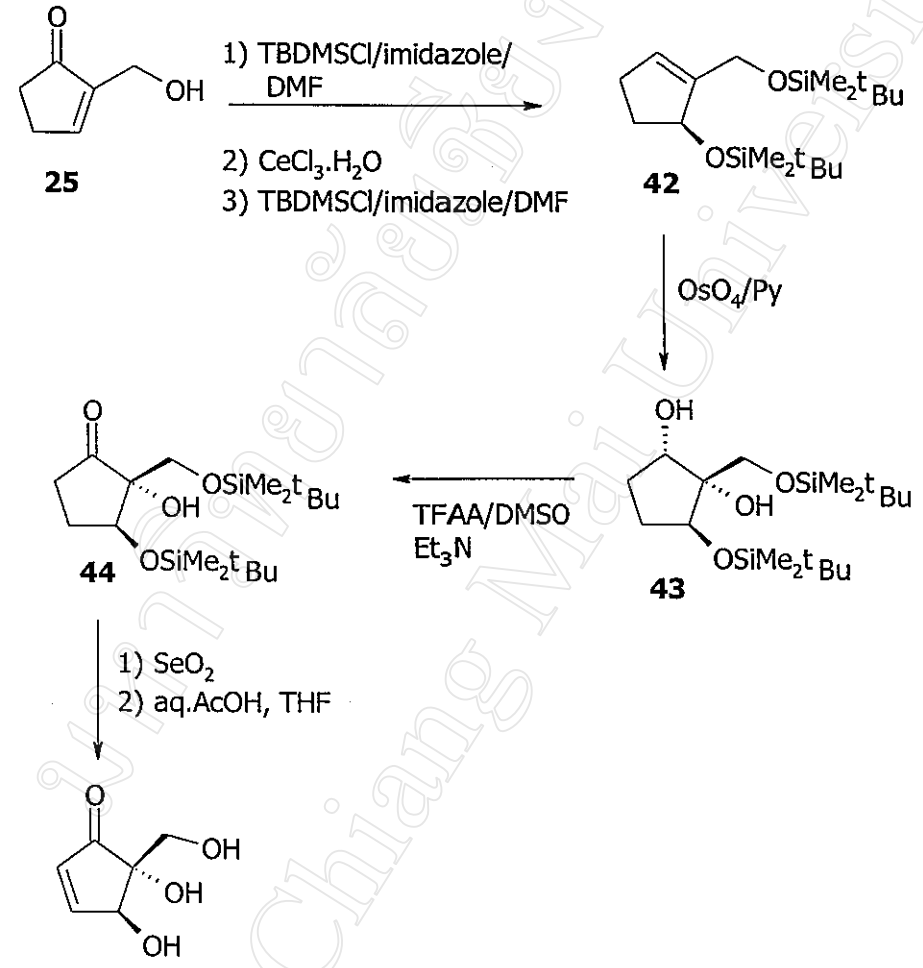
In 1982, Zwanenburg[29] reported a total synthesis of (±)-pentenomycins by flash vacuum thermolysis (FVT) of substituted tricyclo[5.2.1.0]decanones as shown in Scheme 5. The precursor for pentenomycin, 4-methoxymethyltricyclodecenone (**37**) was prepared from furan derivatives.[29] Selective oxidation of **37** with hydrogen peroxide afforded the epoxides (**38**) and (**39**). Treatment of these epoxides with a concentrated solution of hydrobromic acid in methanol converted only **38** into the bromohydrin (**40**). Acetylation of **40** with acetic anhydride followed by treatment with BBr_3 and then acylation with Ac_2O and treatment with AgOAc gave the tertiary alcohol (**41**). Flash vacuum thermolysis (525 °C/ 0.04 Torr) of **41** gave (±) pentenomycin I (**1**).



(±)-Pentenomycin I (**1**)

Scheme 5

The (±)-epipentenomycin series of compounds were prepared by some diastereoselective reactions by Smith, III[30] as shown in Schemes 6. The synthesis of (±) epipentenomycin I (**5**) involved protection and reduction of compound **25** to afford **42**. *Cis*-dihydroxylation of **42** provided the diol (**43**). Oxidation of **43** followed by dehydrogenation and hydrolysis of the silyl groups of **44** afforded (±)- epipentenomycin I (**5**). The syntheses of (±)-epipentenomycin II and III proceeded in a similar manner.

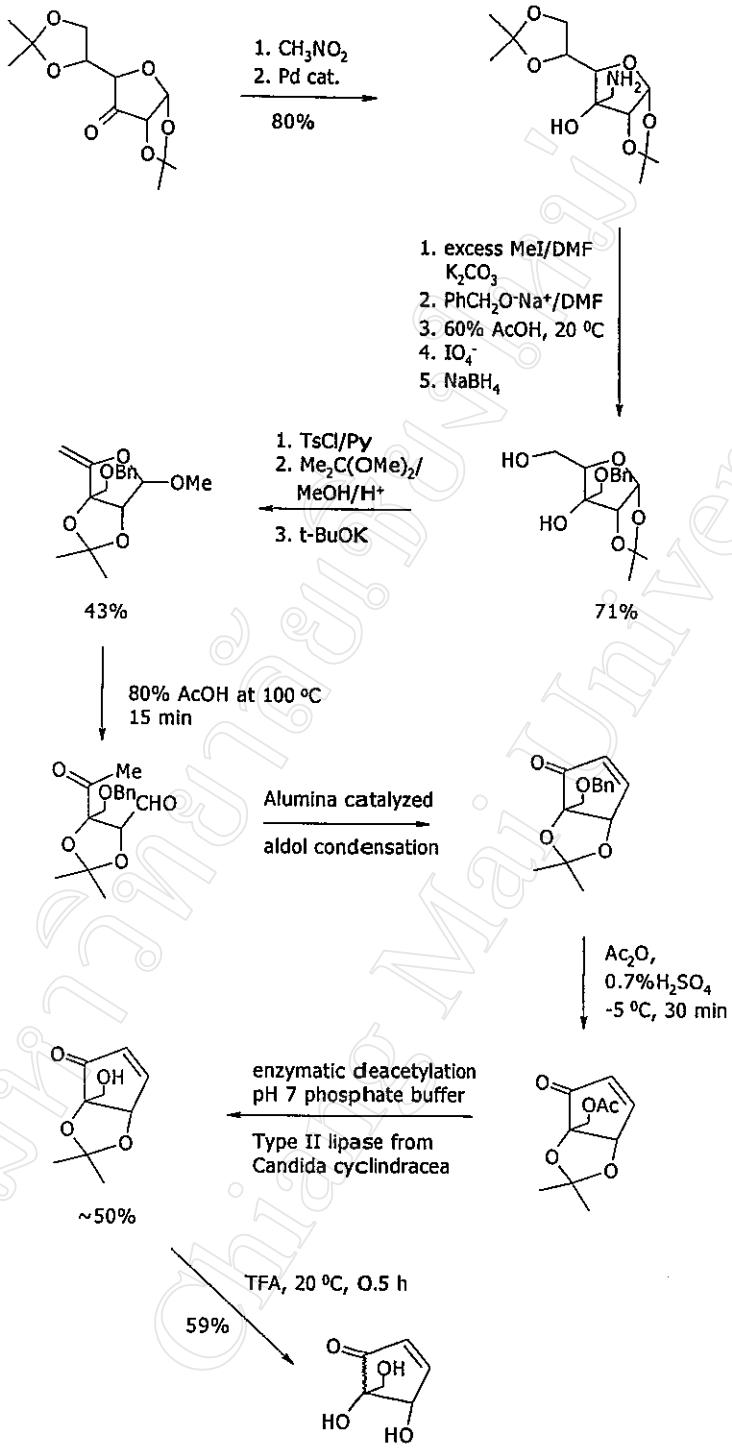


Scheme 6

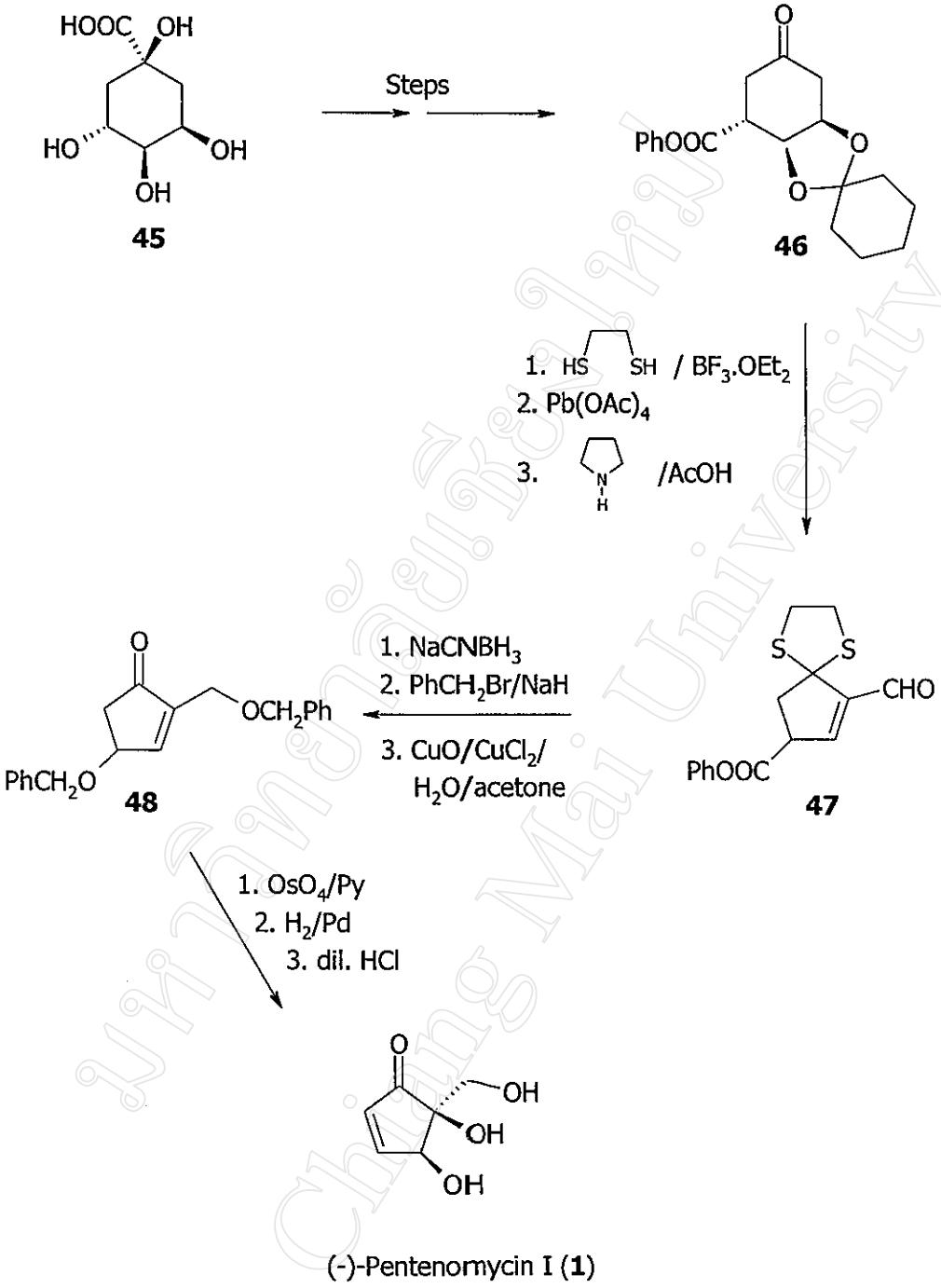
Synthesis of optically active pentenomycins

Verheyden and co-workers[31] reported the synthesis of pentenomycin and its simpler analogue 6-deoxypentenomycin in enantiomerically pure starting form from carbohydrates. The synthesis proceeded by conversion of 3-benzyloxymethyl and 3-methyl derivatives of 1,2,5,6-di-*O*-isopropylidene-α-*D*-allofuranose, respectively, into the pen-4-eno-furanosides. Acidic hydrolysis of the latter gave the related 4-ketoaldehydes which underwent intramolecular aldol condensation to form the appropriately substituented 2-cyclopenten-1-ones. These could be converted into the target compounds (Scheme 7).

Another route to (-)-pentenomycin (**1**) was described starting from *D*-(-)-quinic acid (**45**)[28] (Scheme 8). *D*-(-)-quinic acid (45) was converted into cyclohexanone **46**. Treatment of **46** with ethane-1,2-dithiol and boron trifluoride. etherate ($BF_3.OEt_2$) resulted in protection of the ketone as its thioketal and deprotection of the 1,2-*cis* diol group. Oxidative cleavage of the diol with lead(IV) acetate followed by an intramolecular aldol like reaction (via a pyrrolinium intermediate) gave the cyclopentene-carbaldehyde (**47**). Compound **47** was converted into cyclopentenone **48** by reduction of the aldehyde, protection of the resulting diol as the dibenzyl ether and thioketal hydrolysis. *Cis*-dihydroxylation of cyclopentenone **48** followed by hydrogenolysis and addition of dilute hydrochloric acid afforded (-) pentenomycin (**1**) as shown in Scheme 8.


1. CH_3NO_2
2. Pd cat.
80%
1. excess MeI/DMF
K_2CO_3
2. $PhCH_2O^-Na^+$/DMF
3. 60% AcOH, 20 °C
4. IO_4^-
5. $NaBH_4$
1. TsCl/Py
2. $Me_2C(OMe)_2$/
MeOH/H^+
3. t-BuOK
43%
71%
80% AcOH at 100 °C
15 min
Alumina catalyzed
aldol condensation
Ac_2O,
0.7%H_2SO_4
-5 °C, 30 min
enzymatic deacetylation
pH 7 phosphate buffer
Type II lipase from
Candida cyclindracea
~50%
TFA, 20 °C, 0.5 h
59%
(-)-Pentenomycin I (1)

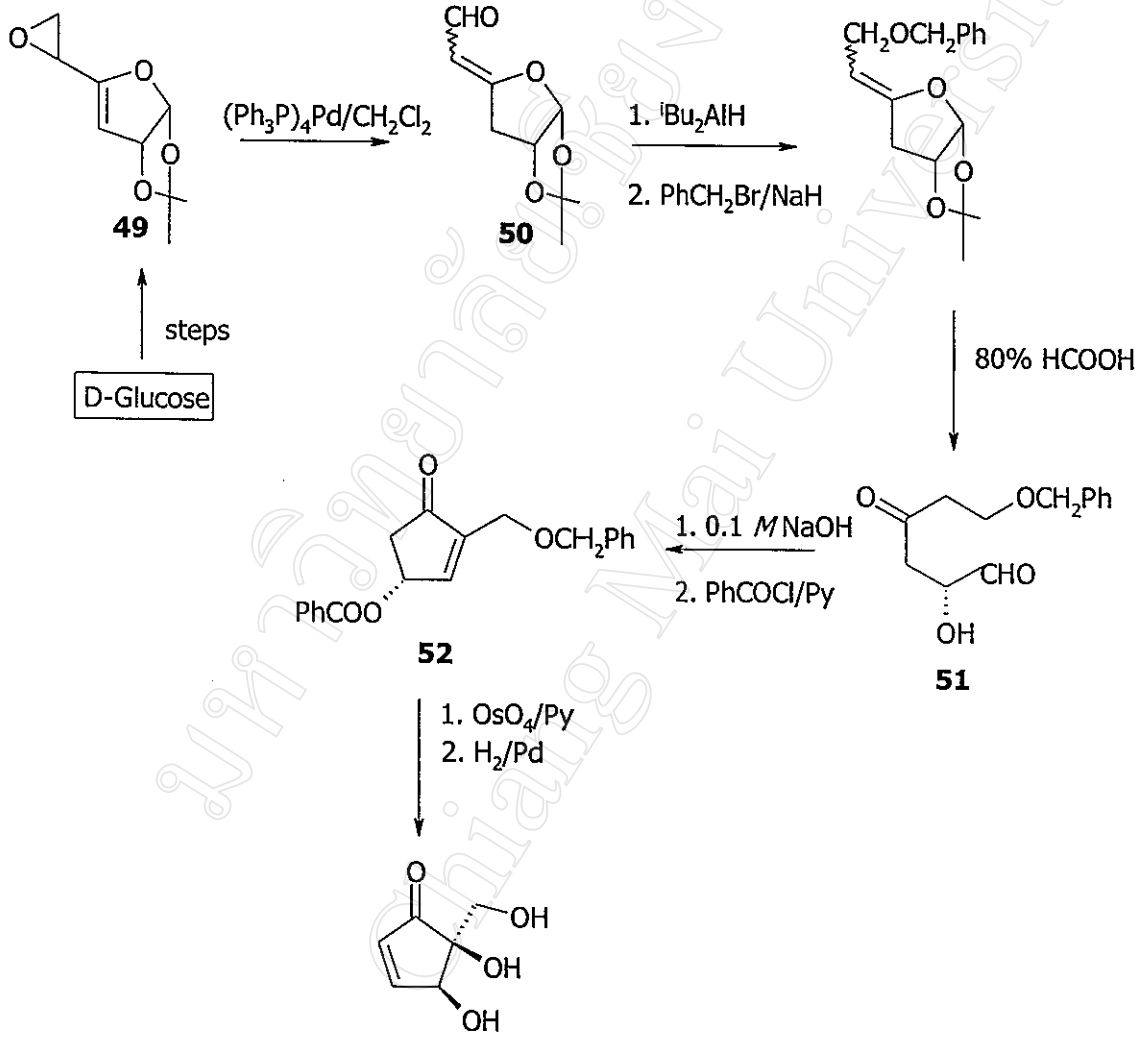
Scheme 7



(-)-Pentenomycin I (**1**)

Scheme 8

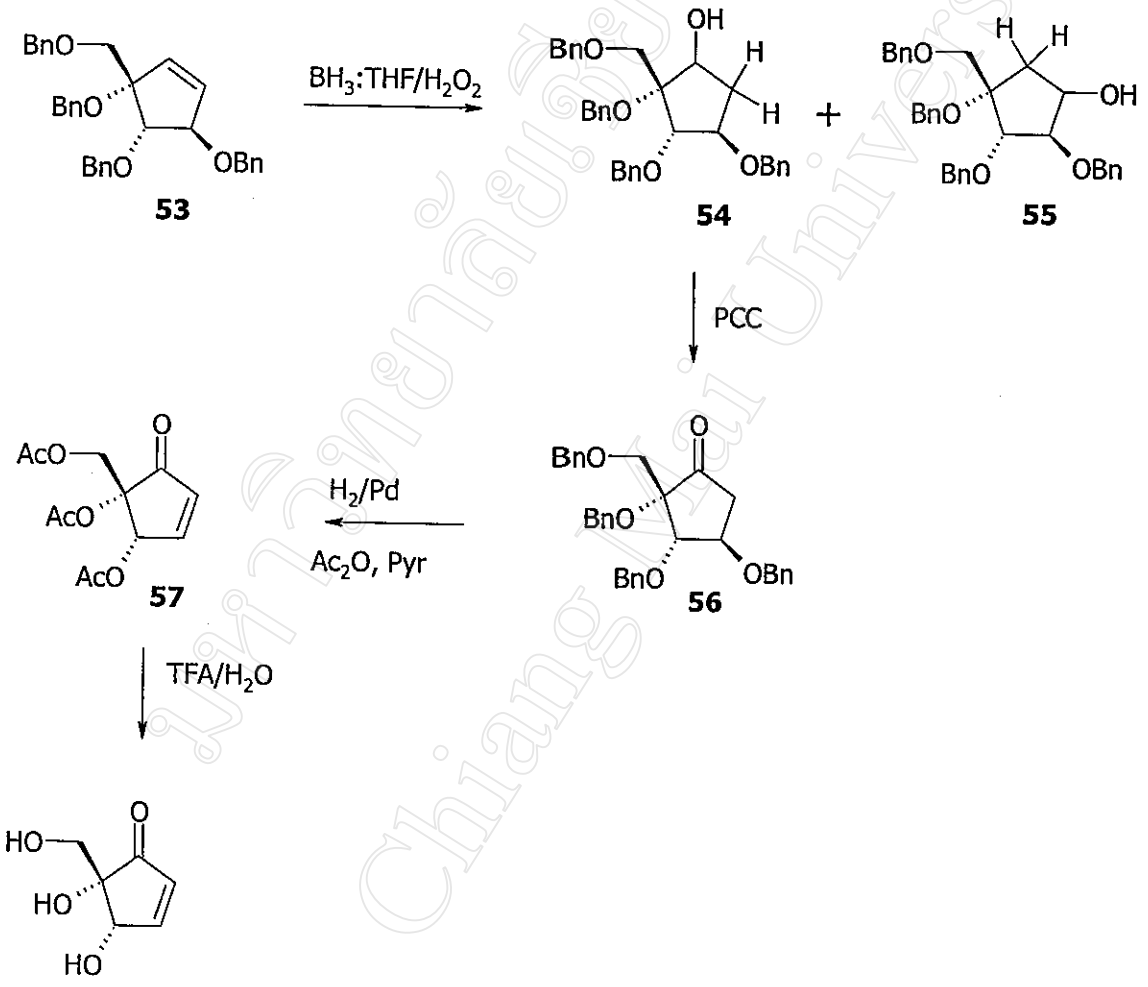
In 1984, Das[32] reported an alternative synthesis of (-)-pentenomycin I (**1**) by transforming *D*-glucose into (*R*)-4-hydroxy-2-benzyloxymethylcyclopent-2-en-1-one (**52**) (Scheme 9). The synthesis involved $(Ph_3P)_4Pd$-catalysed rearrangement of epoxide **49**, prepared from D-glucose, to give the aldehyde (**50**) as an E/Z mixture. Sequential reduction, benzylation and hydrolysis of **50** yielded **51**. Intramolecular aldol condensation-dehydration of **51** gave cyclopentenone **52**, a known precursor of (-)-pentenomycin I (**1**).



(-)-Pentenomycin I (**1**)

Scheme 9

Recently, a total synthesis of (-)-pentenomycin starting from a protected polyhydroxy cyclopentene (**53**) has been reported by Yousef Al-Abed[33] as shown in Scheme 10. The compound (**53**) was treated with BH_3.THF to give the two regioisomeric alcohols (**54**) and (**55**). Alcohol **54** was oxidised by PCC to afford the corresponding ketone (**56**), which underwent hydrogenolysis and then acetylation with pyridine/ acetic anhydride to furnish the acetylated enone (**57**). Deprotection of the acetate (**57**) afforded (-)-pentenomycin I (**1**).



(-) pentenomycin I (**1**)

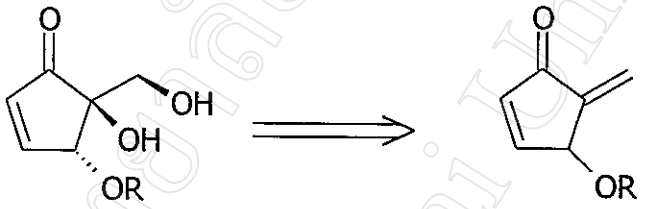
Scheme 10

2. Objective

The objective of this part of the project was to synthesise pentenomycins, by a potentially simple, efficient and useful synthetic method that could be adapted in the future to the synthesis of analogues for future structure-activity studies and to the synthesis of enantiomerically pure products.

3. Proposed synthetic approaches to pentenomycins

A retrosynthetic analysis for the preparation of pentenomycins suggests that they could be obtained by di-hydroxylation of 3-alkoxyl-2-methylene-4-cyclopentenone (**58**) (Scheme 11).



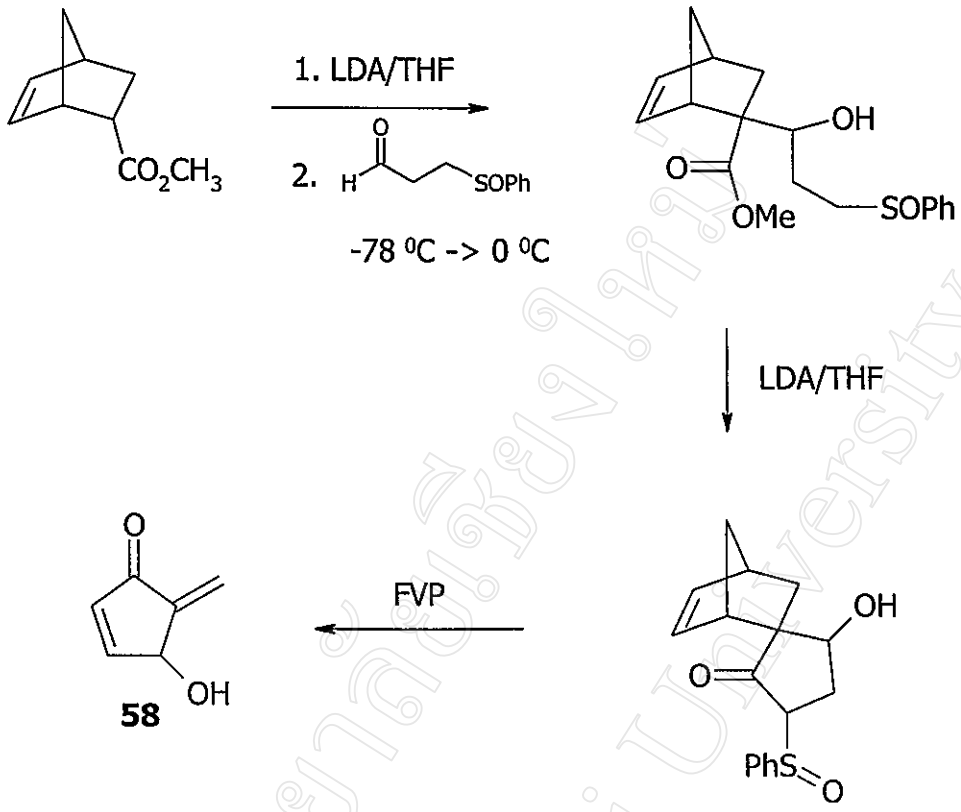
58

Scheme 11

4. Results and Discussion

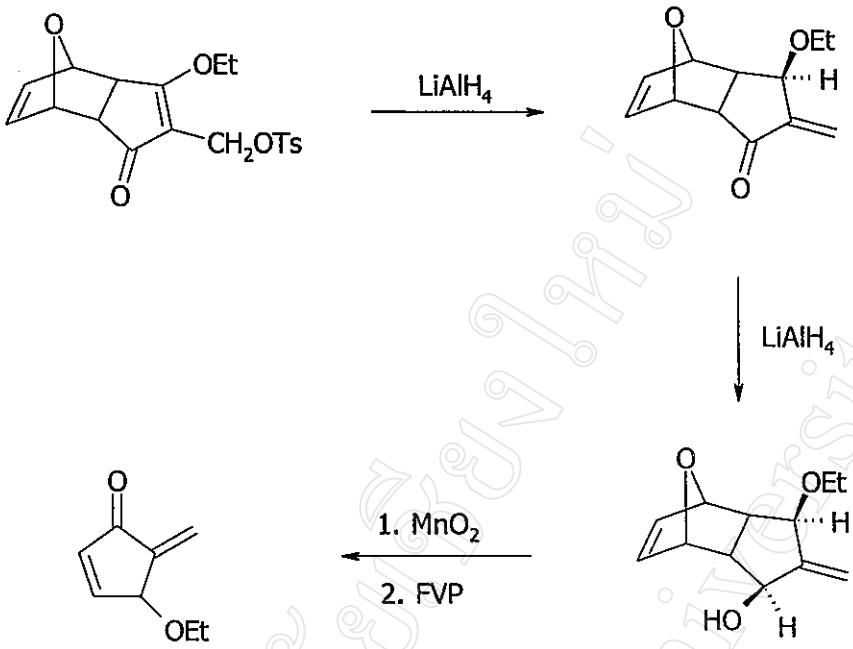
4.1 Synthesis of cyclopentenones prior to pentenomycins

Pohmakotr[34] has extensively demonstrated the synthesis of 3-hydroxy-2-methylene-4-cyclopentenone (**58**, R=H) (Scheme 12) which is a useful starting material to the pentenomycins. This method involved flash vacuum pyrolysis (FVP) in the final synthetic step to give **58** (R=H).

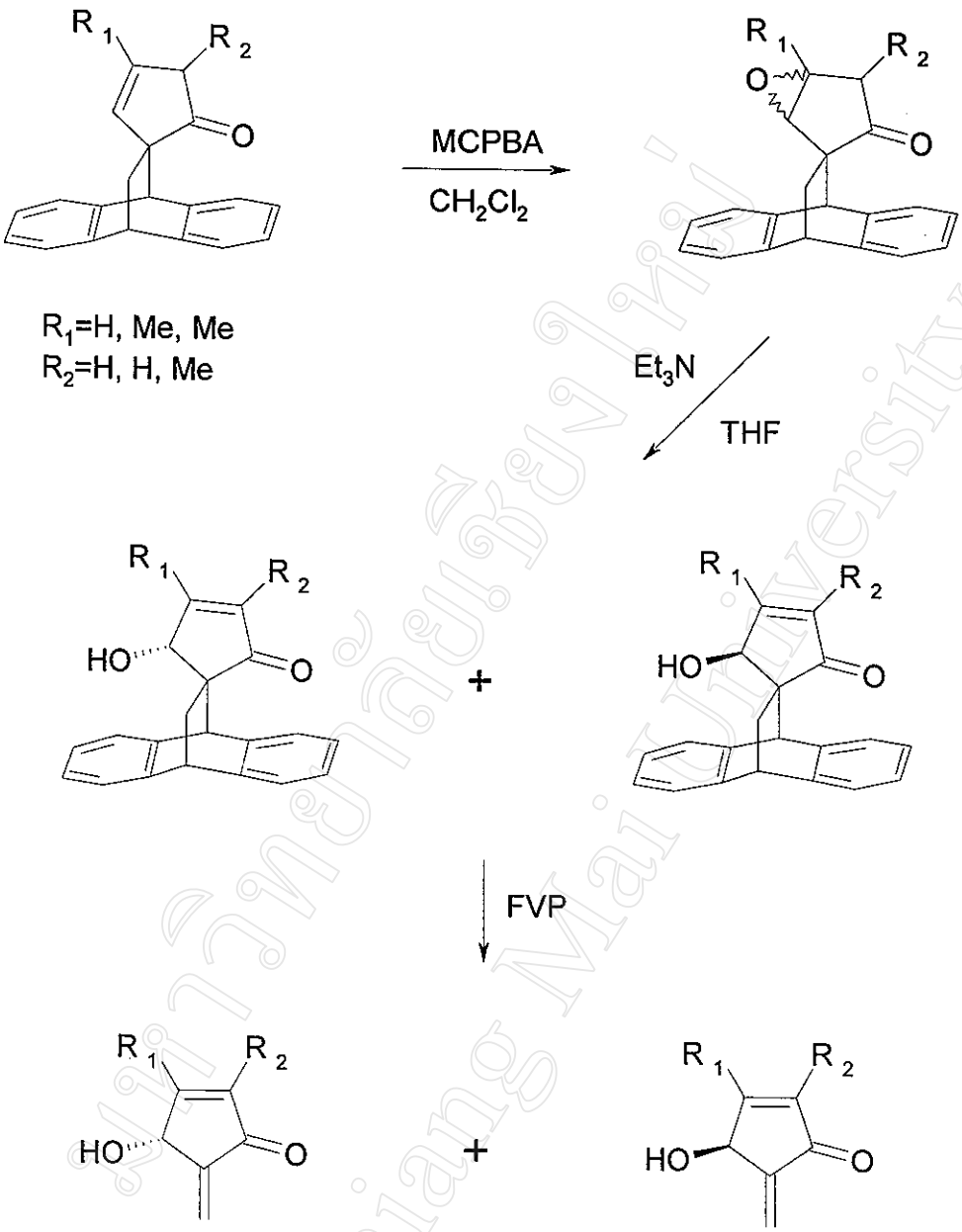


Scheme 12

The other synthetic routes leading to compounds of the type **58** are shown in Schemes 13[35] and 14.[36] The functionalised cyclopentenones were obtained from both routes after chemical manipulation of the preformed cyclopentenone nucleus followed by retro-Diels-Alder reactions, under FVP conditions.

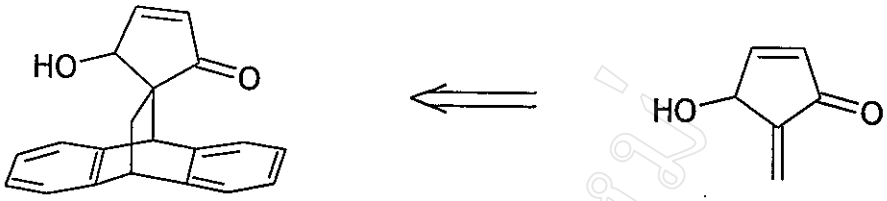


Scheme 13



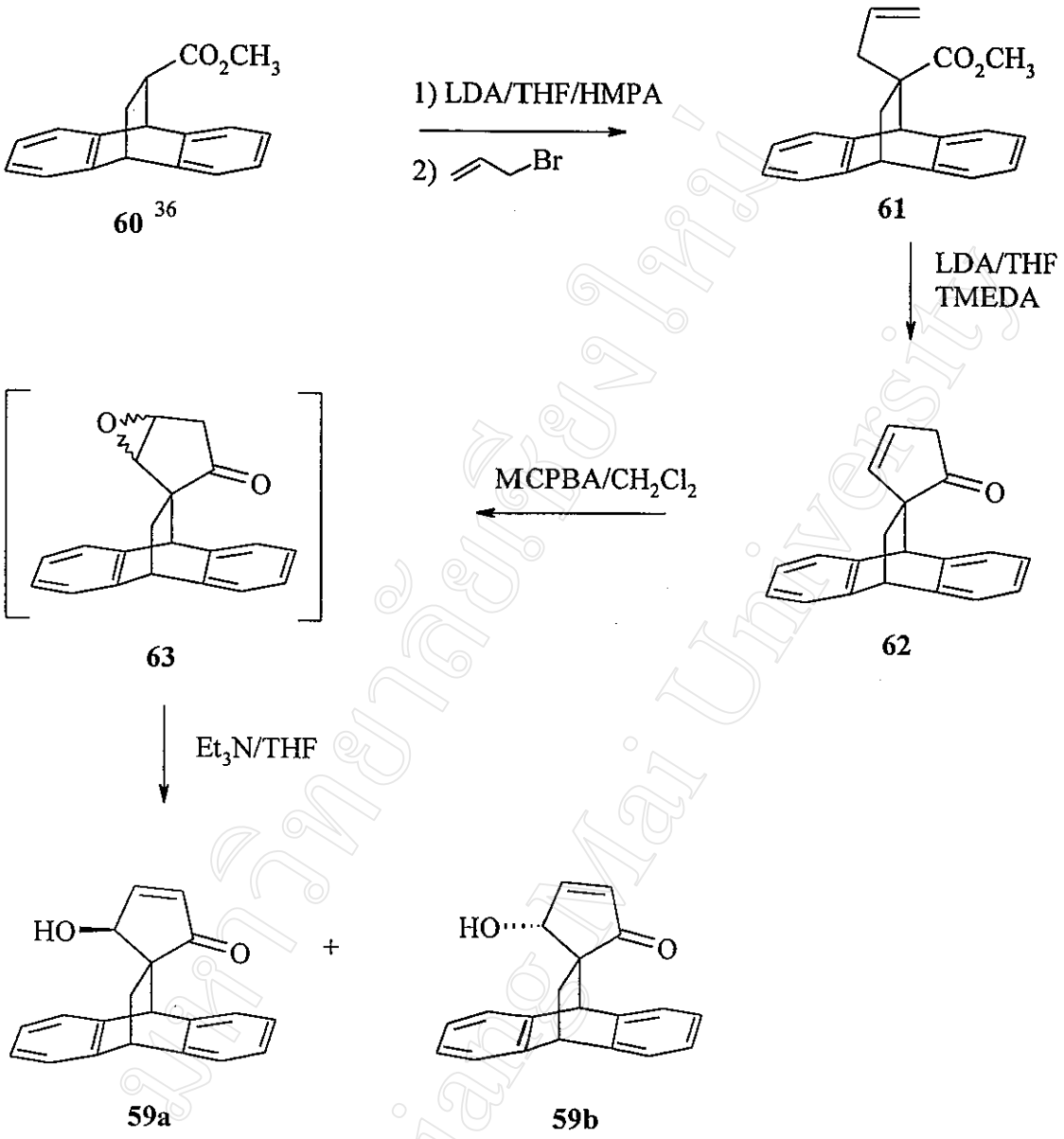
Scheme 14

Di-hydroxylation of compounds of the type **58** could well be a valuable method for the synthesis of many polyoxygenated cyclopentenoid antibiotics such as pentenomycins. The synthetic route to prepare **58** (R= H) was based upon the method developed by Thebtaranonth[36] using anthracene adducts as building blocks.



59 **58**

The two diastereoisomers of compound **59**[36,37] were prepared according to the literature as shown in Scheme 15. The key intermediate in the synthesis, compound **62**, was prepared by a three-carbon annelation method.[37]

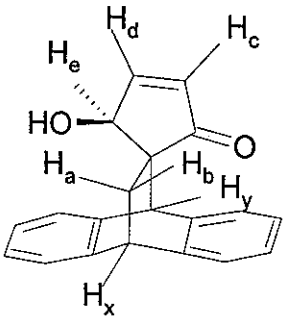


60 [36] **61** **62** **63** **59a** **59b**

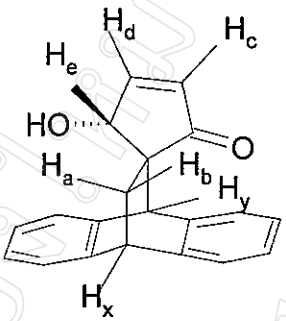
Scheme 15

The three carbon annelation of **61** using excess LDA in THF/TMEDA solution afforded **62**.[37,39] MCPBA oxidation of **62** in CH_2Cl_2 gave crude **63** which, without purification, was further treated with a catalytic amount of triethylamine in THF solution to yield, after PLC separation (silica gel PF_{254}; pure CH_2Cl_2 as eluent), **59a** and **59b** in

yields of 34% and 61% respectively (95% overall yield from **59**). The structure identification of these diastereoisomers **(59a)** and **(59b)** was based on ^{1}H-NMR and X-ray crystallography.



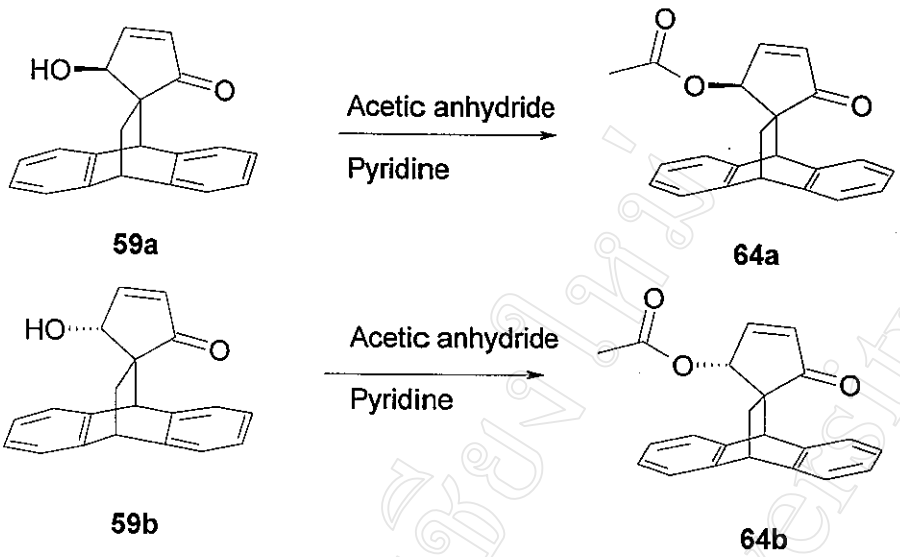
59a



59b

The ^{1}H-NMR spectrum of **59a** showed a broad singlet of one proton at δ 2.13 representing the hydroxyl group and a singlet of the proton H_e at δ 4.23, along with other peaks for protons on the aromatic ring and the olefinic protons. In the ^{1}H-NMR spectrum of **59b**, an upfield shift of 0.86 ppm for the signal generated by the hydroxyl group and a downfield shift of 0.28 ppm for the signal generated by the proton H_e were observed compared to that of the ^{1}H-NMR spectrum of **59a**. These were because of the effect of anisotropic effects of the 9,10-dihydroanthracene aromatic ring. The ^{1}H-NMR spectra of compounds (**59a**) and (**59b**) were identical with those reported in the literature.[37,39]

Acetylation of both diastereoisomer (**59a** and **59b**) using excess acetic anhydride in pyridine (Scheme 16), after purification and recrystallisation provided **64a** and **64b**, respectively as colourless crystals. The structures of **64a** and **64b** were based on the spectroscopic data. The same complex coupling pattern in the ^{1}H-NMR spectra, as described for **59a** and **59b**, were observed for **64a** and **64b**, respectively. The most salient feature of these spectra were a three-proton singlet at δ 1.77 for compound **64a** and at δ 1.97 for compound **64b** ascribable to the acetate groups. The molecular compositions, $C_{22}H_{19}O_3$ of both **64a** and **64b** were established from high resolution mass spectrometry.



Scheme 16

The structures were also confirmed unequivocally by X-ray crystallography as shown in Figure 1 and Figure 2. It is noted from the Figure 1 that the carbonyl group of the acetate moiety is pointing away from the aromatic 9,10-dihydroanthracene ring. However, from the Figure 2, the carbonyl group of the acetate moiety is pointing towards the aromatic 9,10-dihydroanthracene ring. Not only the X-ray crystallography of **64a** and **64b** confirmed their structures, they also confirmed the structures of **59a** and **59b** as well.

The X-ray structure of **64a** indicates that the acetate methyl group lies above the aromatic ring of the 9,10-dihydroanthracene system. This explains why this methyl group resonates at an unusual upfield position in the ^{1}H-NMR (δ 1.77).

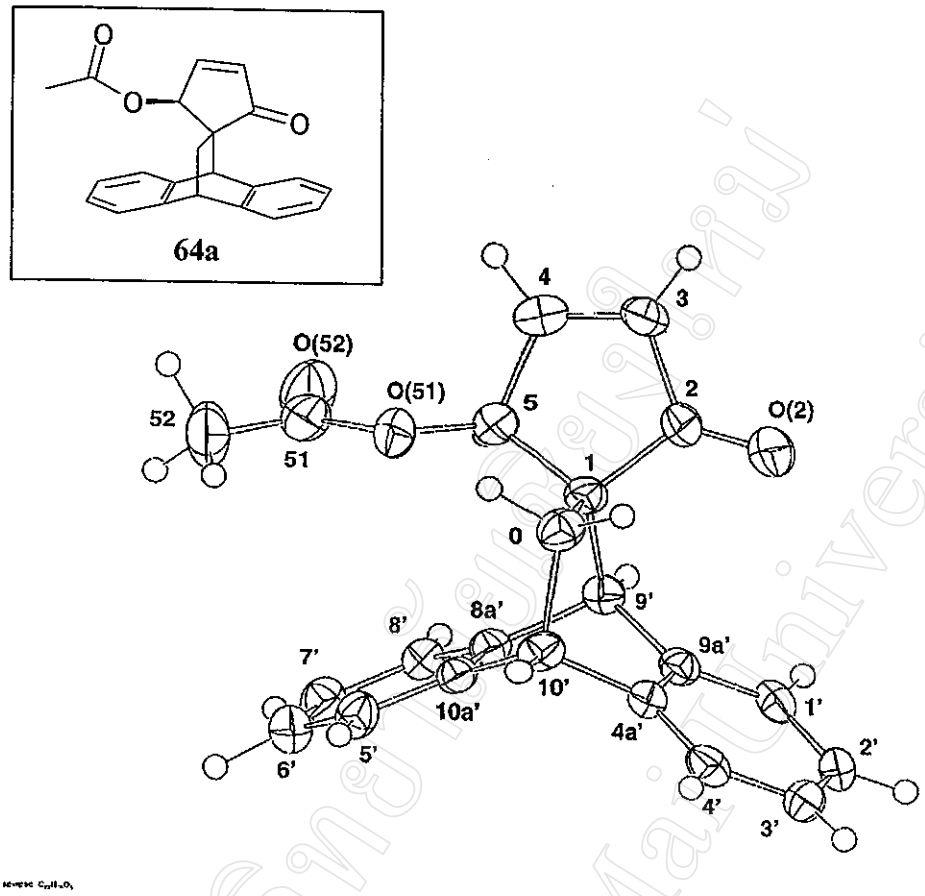


Figure 1. X-ray structure of compound **64a**

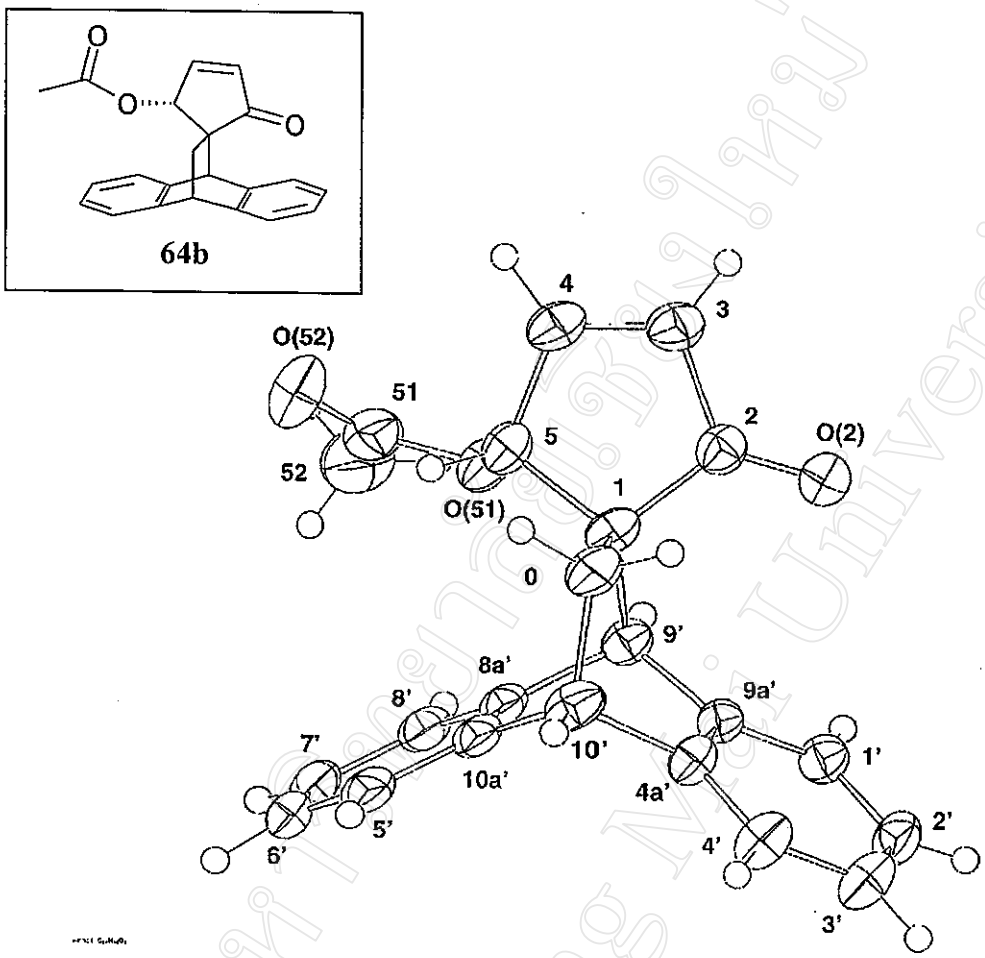
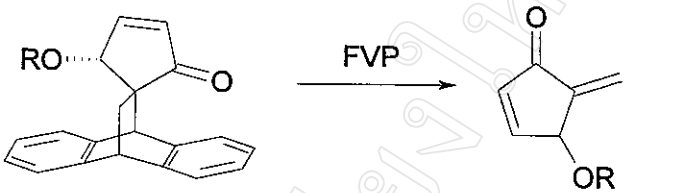


Figure 2. X-ray structure of compound **64b**

The retro-Diels-Alder reactions of **59a-b** and **64a-b** using flash vacuum pyrolysis afforded the compound **58** (R=H) and **58** (R=Ac) in yields of 94 and 78%, respectively (Scheme 17). The structural assignment of these compounds was based on their spectroscopic data.



59 R= H
64 R= Ac

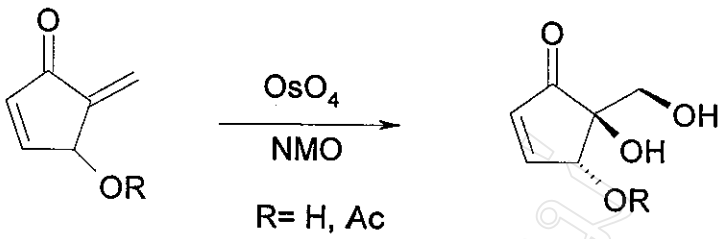
58 R= H, Ac

Scheme 17

In the ^{1}H-NMR spectrum of compound **58** (R= H) the olefinic methylene protons appeared as two singlets at δ 5.73 and 6.20, while two sets of doublets centred at δ 6.45 and 7.53 were observed for the olefinic protons on the cyclopentenone ring. A board singlet at δ 2.14 was observed for the hydroxyl group, along with a singlet proton at δ 5.22 for the hydrogen adjacent to the hydroxy group. This data was in agreement with that reported in the literature.[37] The disappearance of the aromatic protons was indicative of the loss of anthracene molecule. The ^{1}H-NMR spectrum of **58** (R= Ac) showed an extra three-proton singlet at δ 2.11 which was consistent with the presence of an acetyl group. This compound is reported here for the first time and was further characterized by ^{13}C-NMR, DEPT and high resolution mass spectrometry.

4.2 Epoxidation of Cyclopentenone leading to pentenomycins

The initial work carried out was the *cis*-di-hydroxylation of **58** (R= H), employing OsO_4. It would be expected that if this conversion of **58** to pentenomycin was successful, this would lead to an efficient entry to the series of pentenomycins.

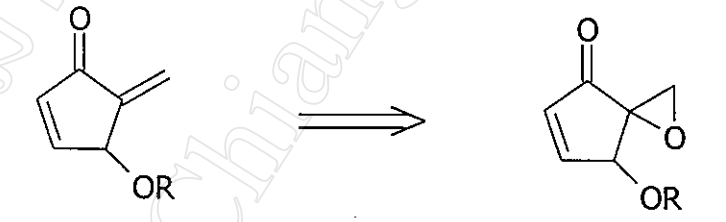


58 pentenomycins

Scheme 18

Unfortunately, all attempts at the dihydroxylation of **58** (R=H) using OsO_4 failed to give pentenomycins. Treatment of **58** (R=H) with 1.2 equivalents of OsO_4 in acetone or with a catalytic amount of OsO_4 in the presence of *N*-methylmorpholine *N*-oxide (NMO) in water and acetone gave, after reductive work-up with saturated aqueous $NaHSO_3$, a very polar compound in low yield. The structure of this compound was not determined. It should be noted that the ^{1}H-NMR spectra of the crude products obtained from these reactions indicated either oxidation of all unsaturated bonds or polymerisation of the starting material due to the lack of olefinic signals. However, further investigation employing in this route was not continued.

Another method investigated was the epoxidation of **58** followed by epoxide hydrolysis to yield the pentenomycins. Epoxidation of **58** would yield the spiro epoxide of type **66** as shown in Scheme 19.

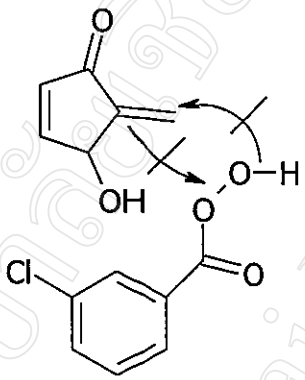


58 R=H, Ac **66** R=H, Ac

Scheme 19

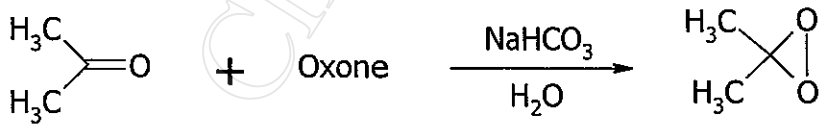
Therefore, a suitable epoxidising agent was searched according to the stability of the starting material. Firstly, epoxidation was carried out using MCPBA.

Unfortunately, the attempted epoxidation of **58** (R=H) using 1 equivalent of MCPBA in CH_2Cl_2 at 0 °C gave 100% recovered starting material and remaining reagent as indicated from TLC and ^{1}H-NMR analysis. It was also found that all attempts to improve the epoxidation by using a large excess of MCPBA and longer reaction times were unsuccessful. The failure of the reaction may be due to the electron deficient nature of the alkene (Scheme 20).



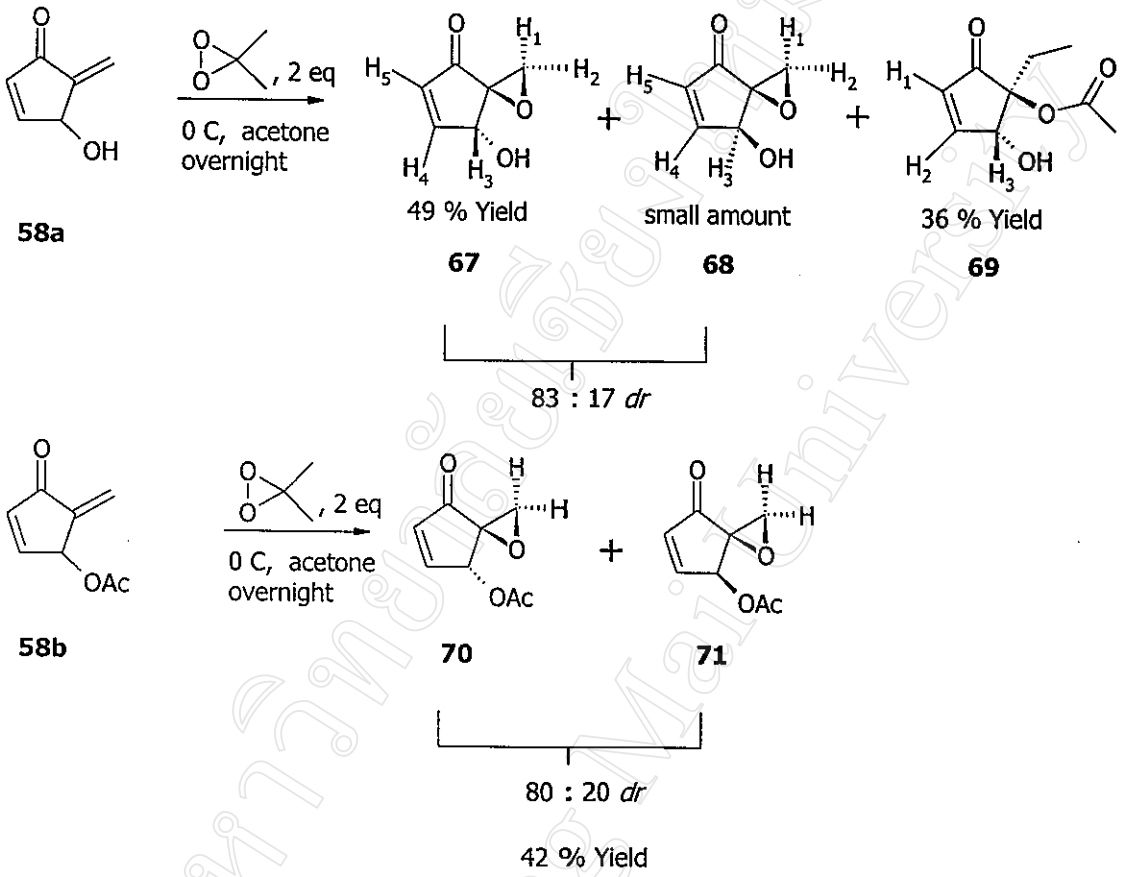
Scheme 20

The next oxidising agent investigated was dimethyldioxirane,[38] that was generated by combining oxone (potassium peroxymonosulfate, $2KHSO_4.KHSO_4.K_2SO_4$) with $NaHCO_3$ in acetone and water as shown in Scheme 21.



Scheme 21

The epoxidation of **58** using freshly prepared and distilled dimethyldioxirane under various reaction conditions provided the spiro epoxide compounds as shown in Scheme 22.



Scheme 22

Treatment of **58a** with 2 equivalents of dimethyldioxirane in acetone at 0 °C furnished the spiro epoxides **67** and **68** in a ratio of 83: 17 (as determined by ^{1}H-NMR), along with the unexpected compound (**69**). On the other hand, epoxidation of **58b** with dimethyldioxirane (2 equivalents) gave compound **70** as a major product and compound **71** as a minor product in a ratio of 80: 20 (as determined by ^{1}H-NMR). The major product **(67)** could be separated by careful preparative thin-layer chromatography (silica

(silica gel; 40% ethyl acetate in petroleum sprit as eluent). However, due to the small quantity of the minor product (**68**), a pure sample of this compound could not be obtained. Epoxides (**70**) and (**71**) could not be separated and were obtained as a mixture in 42% yield. No product corresponding to the acetate derivative of **69** could be detected.

The ^{1}H-NMR spectrum of the spiro epoxide (**67**) showed two set of doublets at δ 3.14 and 3.28 for H_1 and H_2, one singlet at δ 4.96 for H_3 and two sets of doublets at δ 6.53 and 7.69 for H_4 and H_5, along with a board singlet at δ 2.31 for the hydroxyl group. The ^{13}C-NMR spectrum of **67** indicated six different carbons in the molecule. The ^{1}H-NMR spectrum of **68** showed two set of doublets at δ 3.34 and 3.41 for H_1 and H_2, one singlet proton at δ 5.12 for H_3 and two set of doublets at δ 6.63 and 7.82 for H_4 and H_5, along with a board singlet at δ 2.32 for the hydroxyl proton. Both compounds have the molecular formula, $C_6H_7O_3$, from the HRCI mass spectra.

To determine the relative stereochemistries of the two compounds (**67**) and (**68**) all that was needed was the position of the proton H_3 relative to H_1 and H_2. As shown in Figure 3, the NOESY experiments on **67** showed no cross-peaks between H_1 or H_2 and H_3 which meant they most likely had a *trans* relationship. However, the stereochemistry of these compounds could not be unequivocally determined by NOESY experiments.

The structural assignment of the spiro epoxide (**70**) and (**71**) was also based on the spectroscopic data. A characteristic signal in the ^{1}H-NMR spectrum was a three-proton singlet at δ 2.11, which was assigned to the acetyl methyl group in both **70** and **71**. HRCI mass spectrometry showed the molecular formula, $C_8H_9O_3$, which supported the structures. The stereochemistry of compound **70** could also not be unequivocally determined by NOESY experiments, that showed no cross-peak between H_1 or H_2 and H_3, as shown in Figure 4.

However, the stereochemistry of these compounds was determined by conversion to the natural products, epipentenomycin I and epipentenomycin III, respectively, which will be discussed in section **4.3**.

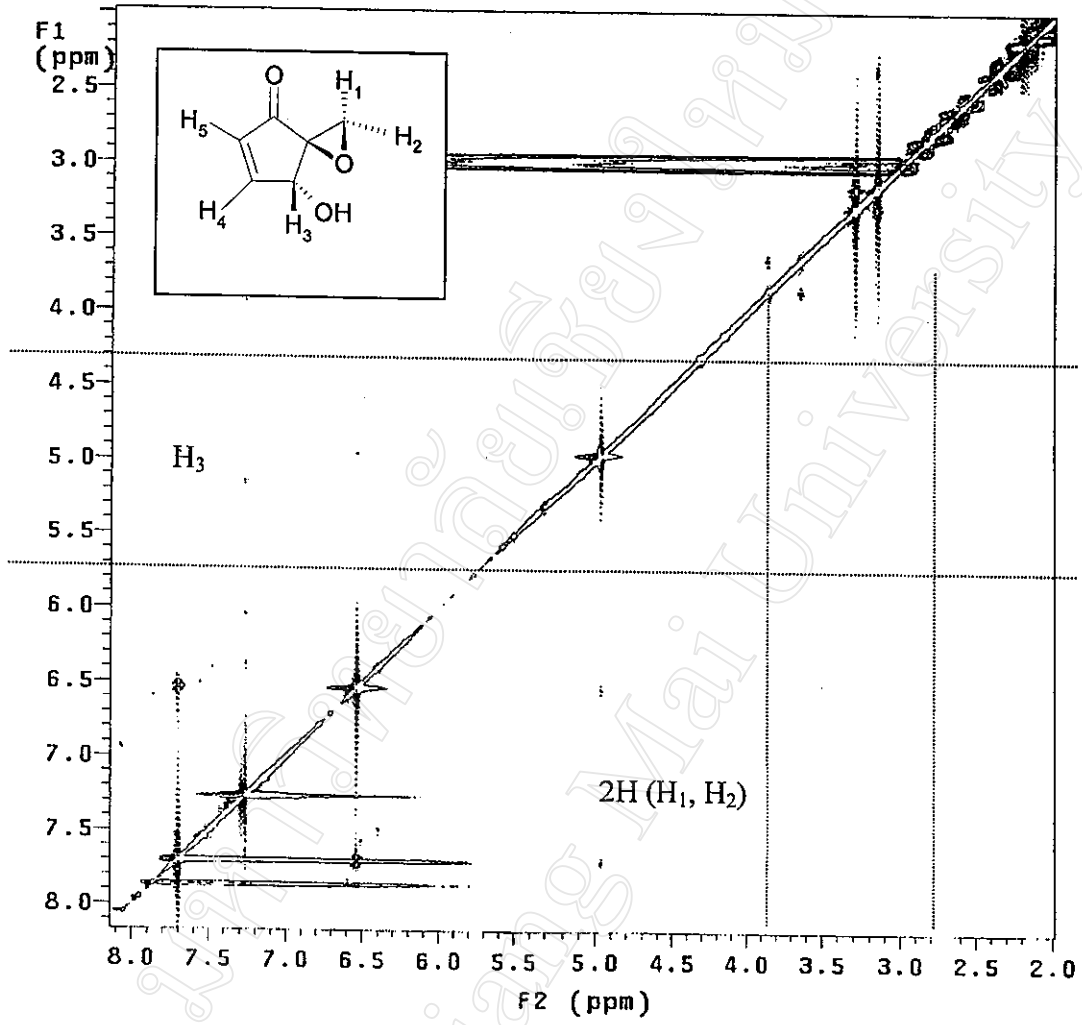


Figure 3. NOESY spectra of **67**

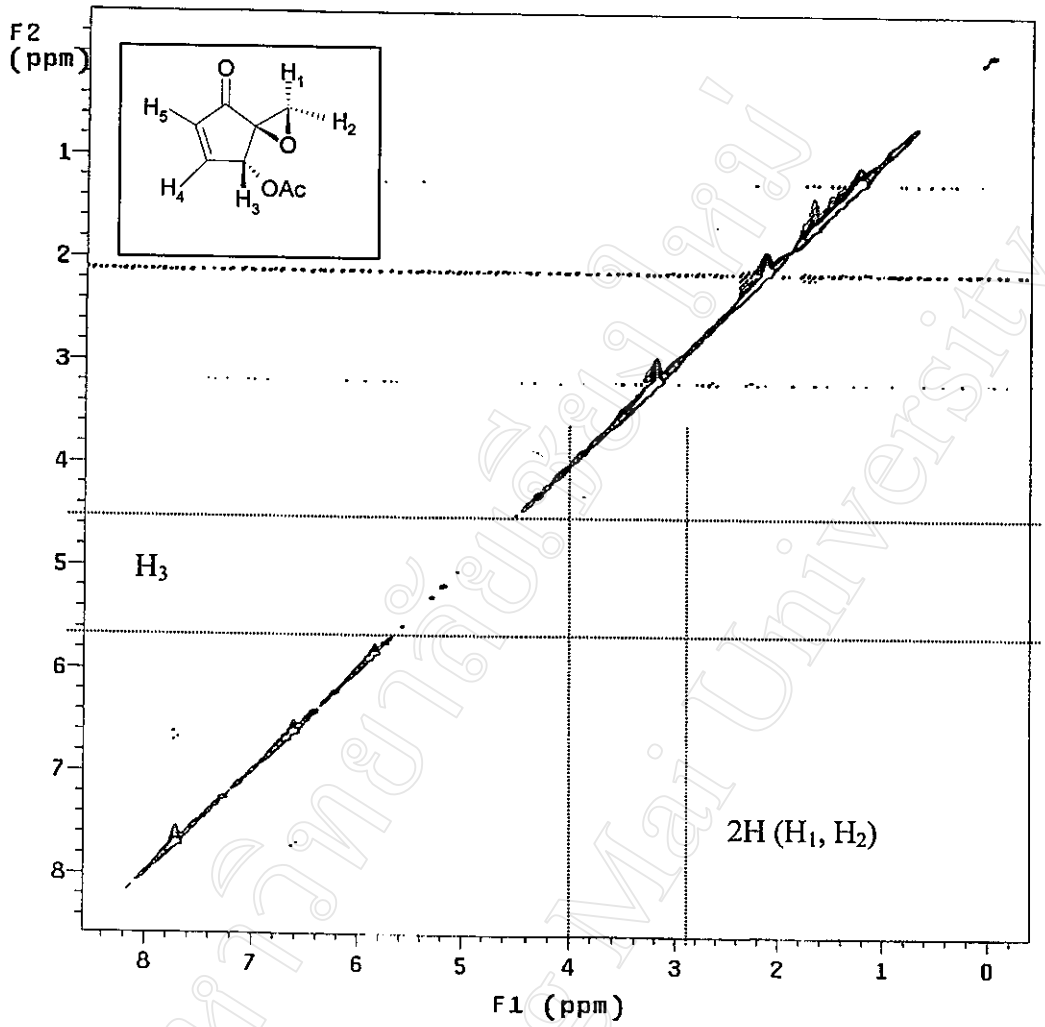
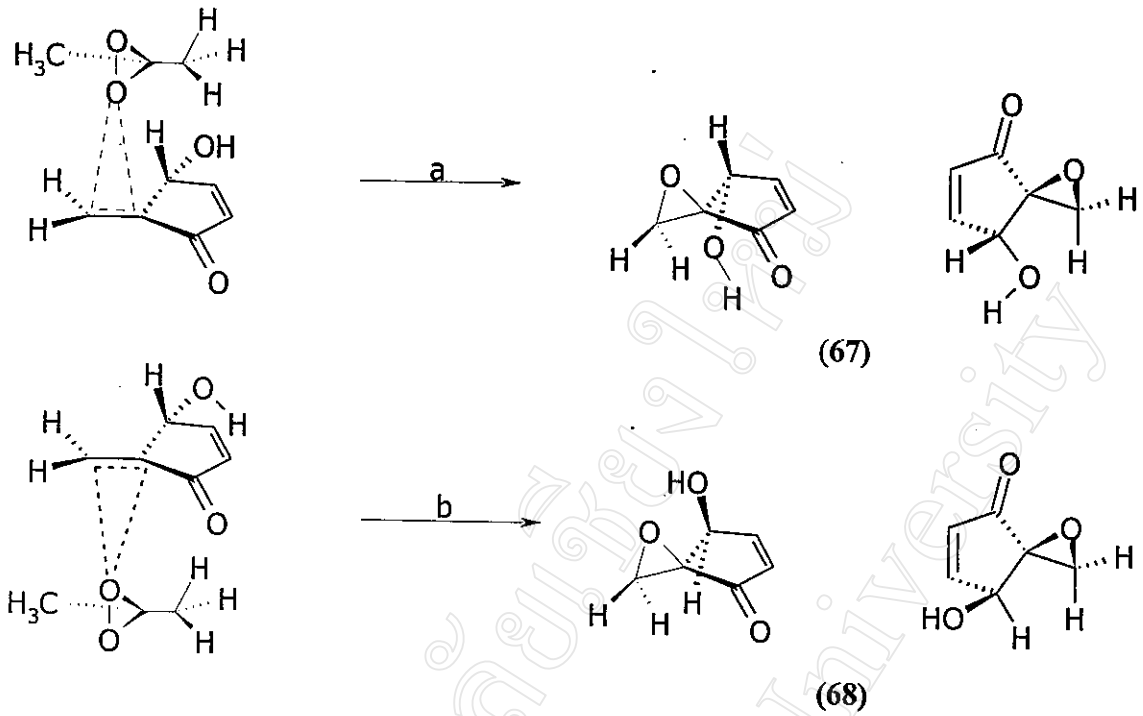


Figure 4. NOESY spectra of **70**



Scheme 23. *a*, epoxidation from the less sterically hindered side gave compound (**67**). *b*, intermolecular hydrogen bonding in the intermediate leading to the minor product (**68**).

Scheme 23 shows the possible transition state structures for the formation of compounds **67** and **68**. The preference for epoxide **67** can be rationalized as arising from addition of dimethyldioxirane to the least hindered face of diene (**58a**), that is from the face anti to the hydroxyl group as shown in step a in Scheme 23. The transition state leading to the minor product (**68**) would be disfavoured on steric grounds but favoured by intermolecular H-bonding between the reagent and the hydroxyl group as shown in Scheme 23. Clearly steric factors are more dominant and favour the formation of **67**.

The biological testing of compound **67** against both gram positive and gram negative bacteria showed that this compound had strong antibacterial activity (by Department of Biology, University of Wollongong). The results are shown in the table below (**Table 1**). However, other compounds will be tested for antibacterial activity in the near future.

Table 1. Bacteriostatic Activity of **67** (in acetone)

Concentration of **67**	*Staphylococcus aureus*	*Escherichia coli*
1 mg/ml	++	++
0.1 mg/ml	++	++
0.01 mg/ml	+	+

+ partially active

++ fully active

The epoxidation reaction of **58a** also gave the unexpected product **(69)** (36 % yield). An HRCI mass spectrum of this compound gave a parent ion, MH^+ of *m/z* 185.0794, consistent with the molecular formula, $C_9H_{13}O_4$. This suggested that extra three carbons, six hydrogens and one oxygen had been inserted into the molecule compared with compound **67**. The ^{1}H-NMR spectrum of this compound showed the presence of twelve protons at δ 0.92 (*t*, 3H, *J*=7.58 Hz, $CH_2C\underline{H}_3$), 1.71 (m, 1H, *J*=7.58 Hz, $C\underline{H}_AH_BCH_3$), 2.08 (m, 1H, *J*=7.58 Hz, $CH_A\underline{H}_BCH_3$), 2.15 (s, 3H, CH_3), 3.27 (d, OH, *J*=4.21 Hz), 5.01 (dd, 1H, *J*=2.10, 2.10 Hz), 6.30 (dd, 1H, *J*=1.68, 4.63 Hz), 7.49 (dd, 1H, *J*=1.68, 4.63 Hz). The ^{13}C-NMR and DEPT spectra presented two methyl groups at δ 8.1 and 21.1, one methylene carbon at δ 24.6, and also a quaternary carbon at δ 171.9. X-ray crystallography revealed the structure of this compound as shown in Figure 5b.

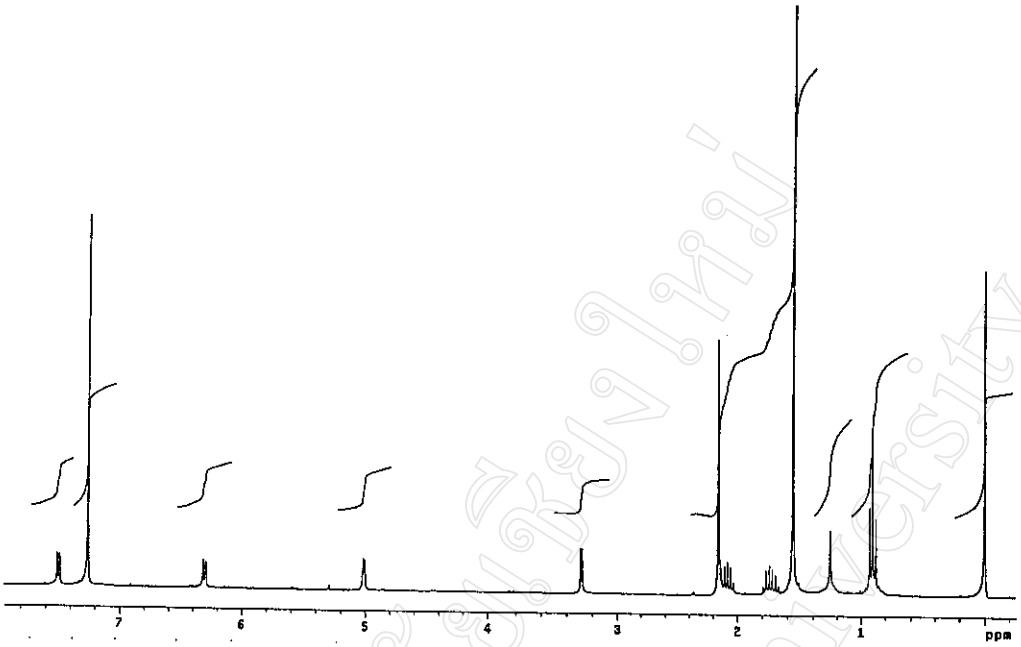


Figure 5a. The 300 MHz ^{1}H-NMR ($CDCl_3$) of compound **69**

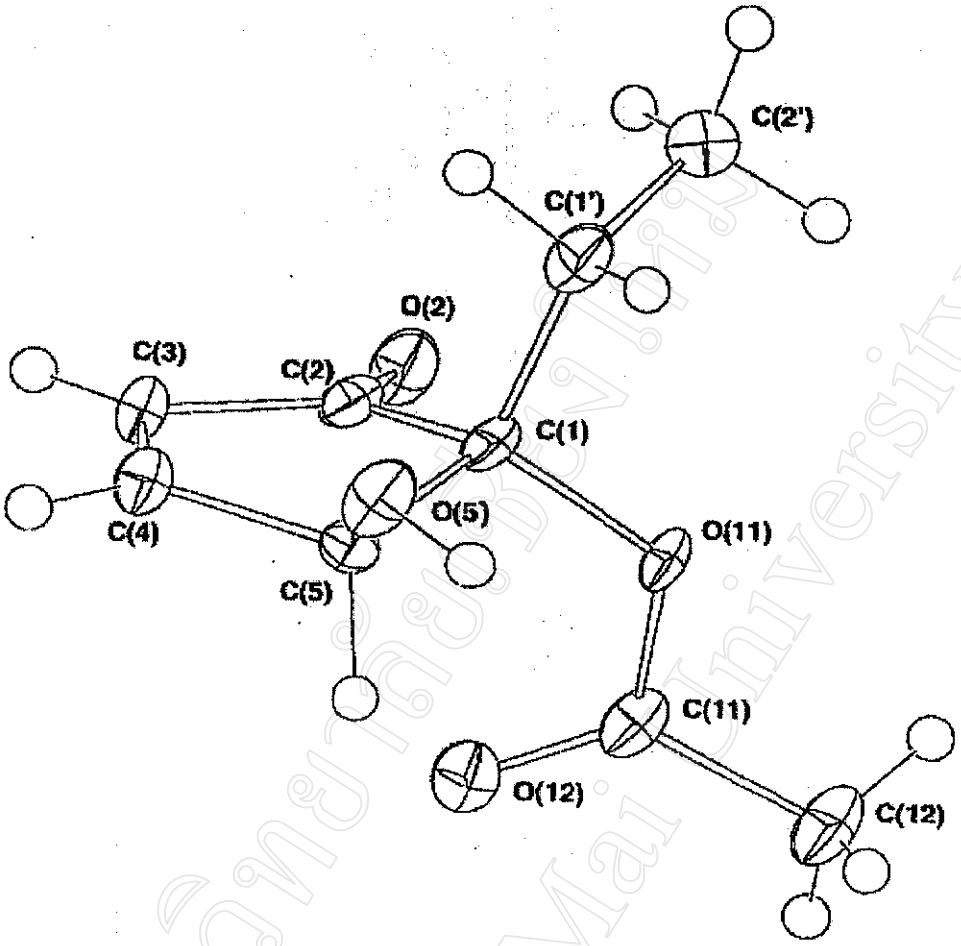
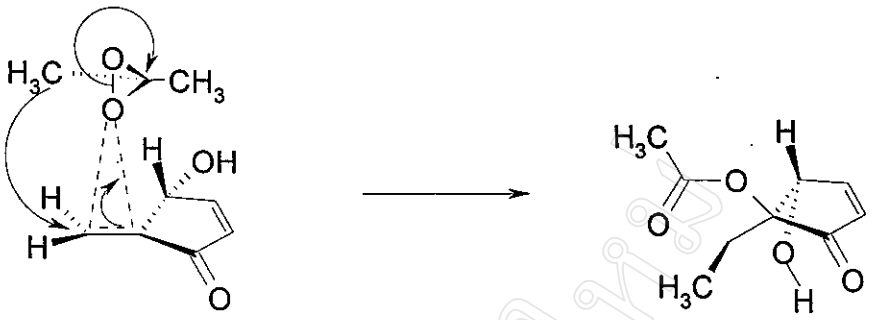


Figure 5b. X-ray structure of **69**

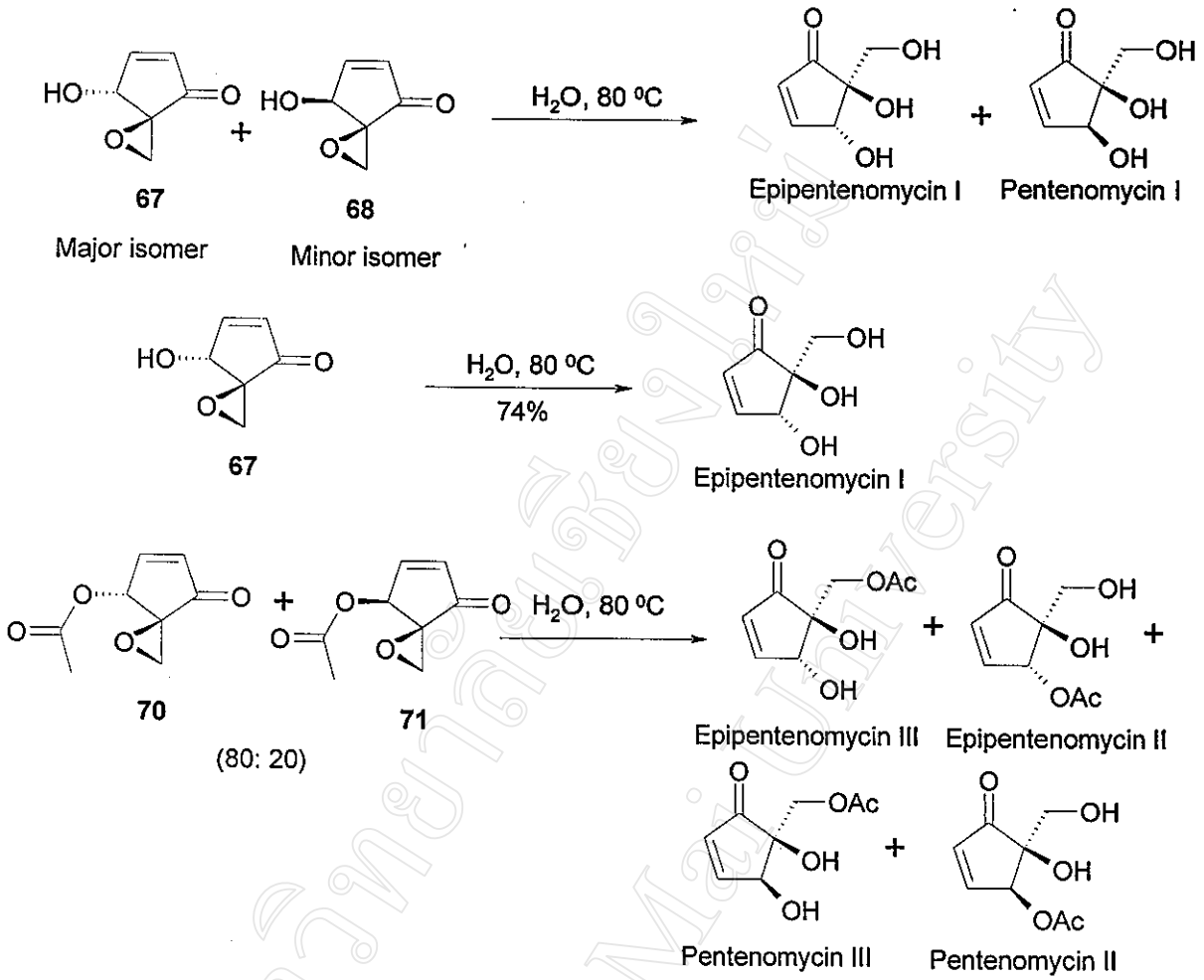
It could be seen that compound **69** might be an rearrangement product arising from one molecule of starting material and one molecule of reagent. This rearrangement involved an unusual migration of a methyl group from dimethyldioxirane to the terminal alkene carbon of **58a** (Scheme 24). The exact mechanism for this reaction is not certain.



Scheme 24

4.3 Hydrolysis of spiro epoxide leading to pentenomycins and epipentenomycins

Consideration of the structure of the compounds of **67** and **70, 68** and **71** suggested that hydrolysis of the epoxide ring could lead to pentenomycin. Normally, the hydrolysis of spiro epoxide **67** and **70, 68** and **71** should be readily achieved either by an acid or a base catalysed hydrolysis. However, due to the instability of starting material (**67** - **71**), the hydrolysis should be performed under very mild conditions. Therefore, the hydrolysis using only water, without any catalysts were attempted. A mixture (83 : 17) of **67** and **68**, pure **67** and a mixture (80 : 20) of **70** and **71** were dissolved in D_2O and heated at 80 °C. After 16 hours, the solvent was removed by freeze-drying for 6 hours to overnight to give pentenomycins and epipentenomycins in good yields (Scheme 25).



Scheme 25

Since the pentenomycins are strongly hydroscopic and soluble in water, all solvents were removed by freeze-drying. Pentenomycins showed clean spots on TLC (reverse phase, MeOH/H_2O=1:9). The ^{1}H-NMR spectra of the synthesised pentenomycins were consistent with the assigned structures and identical with those reported in the literature.[27,33-34] Hydrolysis of a mixture of **67** and **68** gave epipentenomycin I and pentenomycin I. However, the mixture could not be separated to

obtain the pure compounds but the ^{1}H-NMR spectrum was shown to have epipentenomycin I and pentenomycin I (Figture 6) when compared to the literature.[27]

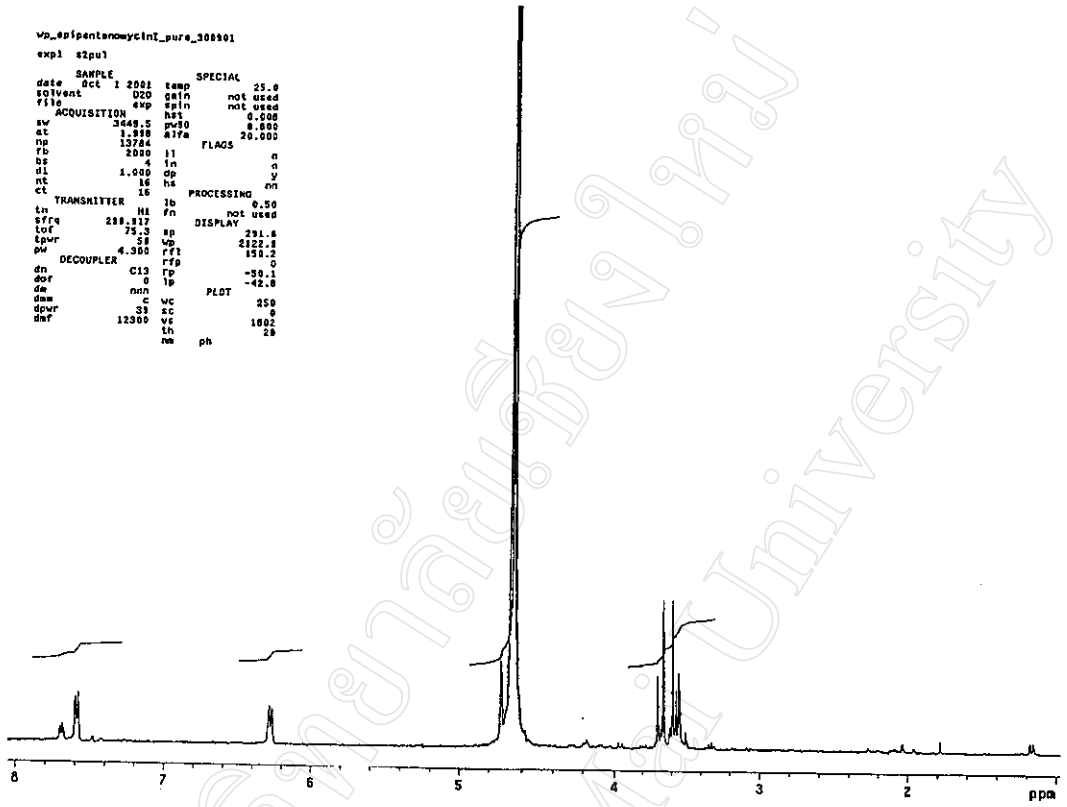


Figure 6. The 300 MHz ^{1}H-NMR (D_2O) of the mixture of epipentenomycin I (major) and pentenomycin I (minor) from the hydrolysis reaction of the mixture of **67** and **68**.

However, hydrolysis of pure racemic **67** gave only pure racemic epipentenomycin I in 74%. The ^{1}H-NMR of the product from this reaction is shown in Figure 7.

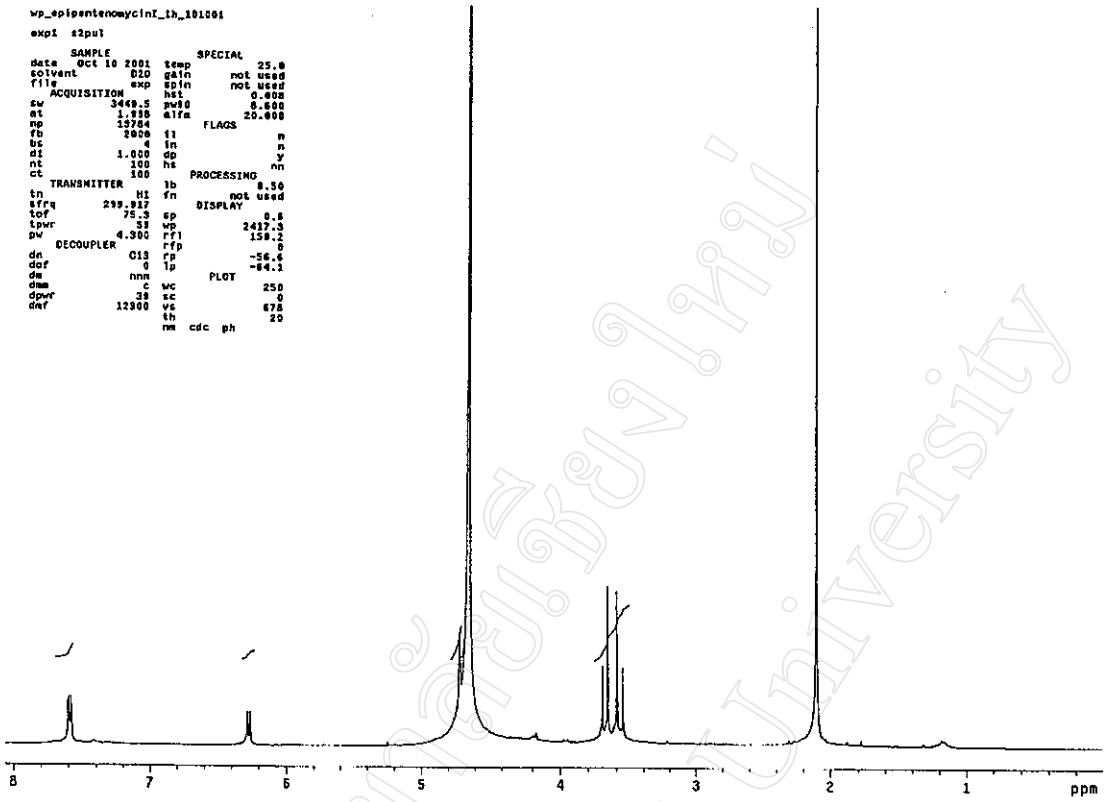


Figure 7. The 300 MHz ^{1}H-NMR (D_2O) of epipentenomycin I from the hydrolysis reaction of pure **67**.

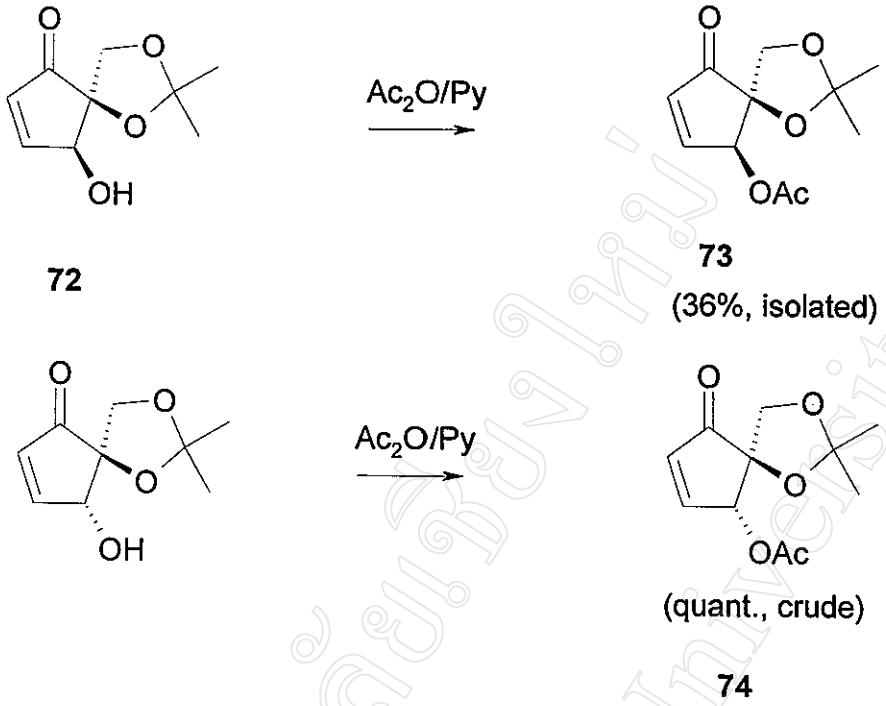
Hydrolysis of a mixture (80: 20) of **70** and **71** by heating in an NMR tube in D_2O for 16 hours gave a mixture consisting mainly of epipentenomycin II and epipentenomycin III (in approximately a 1 : 1 ratio). This was evident from the signals (AB q) at δ 4.1 for C$H_A H_B$OAc for epipentenomycin III and at d 3.58 for C$H_A H_B$OH for epipentenomycin II. Smith *et al* [27] has also observed migration of the secondary acetate in epipentenomycin II to the primary hydroxyl group to give epipentenomycin III. This migration is facilitated in epipentenomycin II because of the *cis* relationship between the primary hydroxmethyl group and the secondary hydroxyl group. Smith found that in D_2O epipentenomycin II and epipentenomycin III are in equilibrium and a mixture of both compounds is formed while in chloroform solution the equilibrium favours

epipentenomycin III exclusively. Thus the crude reaction mixture from heating **70** and **71** in D_2O was evaporated to dryness and extracted into chloroform. The ^1H NMR of this extract showed the formation of epipentenomycin III plus about 15-20% of an isomeric compound that had spectral data close, but not exactly the same, to that reported for pentenomycin III.[27] Unfortunately attempts to purify this compound to give a pure sample of epipentenomycin III were not successful. The ^1H-NMR spectrum (in $CDCl_3$) of epipentenomycin III is shown in the experimental part and was identified by ^1H-NMR spectroscopy when compared to the literature.[27] It should be noted that pentenomycin III and epipentenomycin III resulted from the migration of the acetate group from the secondary to less hindered primary positions. The formation of the migration products (epipentenomycin III and pentenomycin III) was monitored by ^1H-NMR and supported by the result of similar work by Pohmakotr *et al.*[34] having successfully completed the preparation of pentenomycin I and epipentenomycin I by the hydrolysis route shown in Scheme 26.

72

Scheme 26

This research group have also tried to use **72** as precursors for the syntheses of pentenomycin II and epipentenomycin II by treating **72** with acetic anhydride in pyridine at room temperature. The acetates **73** and **74** were obtained in good yield (Scheme 27).

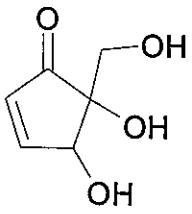


72

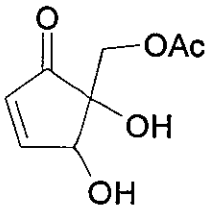
Scheme 27

The same group[34] has reported that attempts to hydrolyse **73** by the conventional method (1*N* HCl in acetone) at 0 ^{0}C to room temperature followed by freeze-drying afforded a mixture of products. From the ^{1}H-NMR analysis of the crude products, the compounds **75**, **76** and **77** were obtained during the reaction. However, these compounds were not purified. The formation of **75** originated from the primary hydrolytic product **77** (and/or **76**) by hydrolysis with the aqueous HCl. Compound **76**, on the other hand, was formed by intramolecular acetyl group migration from **77**.

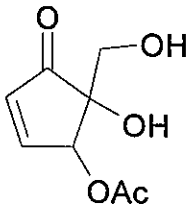
The conversion of epipentenomycin II (**6**) to epipentenomycin III (**7**) was also reported,[32] which involved intramolecular migration of the acetyl group from the secondary to the primary hydroxyl group *via* a six-membered transition state.



75



76



77

In conclusion, epipentenomycin I and III were synthesised by a short and general method. While the former compound was obtained pure the latter was obtained as an inseparable mixture (*ca* 80 : 20) with pentenomycin III. In principle, this method could be used to prepare these compounds in optically active form if the enantiomerically pure **58** (R=H, Ac) were used as starting materials.

5. Experimental

5.1 Genernal Procedures

Melting points were uncorrected.

Infrared spectra were recorded with a Jasco 810 and a FT-IR Nicolet 510 infrared spectrophotometer.

^{1}H-NMR (60 MHz) were recorded on a Hitachi 1500 spectrometer and ^{1}H-NMR (400 MHz) were recorded on a Bruker DPX400 spectrometer (Chiang Mai University and Mahidol University, Thailand). ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75 MHz) spectra were recorded on a Varian Mercury Fourier transform spectrometer. ^{1}H-NMR (500 MHz) was recorded on a Varian Inova spectrometer (University of Wollongong, Australia). Unless otherwise stated, the spectra were obtained from solutions in $CDCl_3$ and referenced to TMS. Resonances are quoted in ppm.

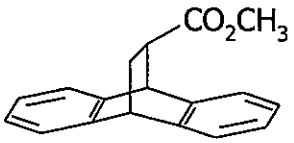
Chemical ionisation mass spectra (MS-CI) were determined using a Perkin-Elmer GC-MS (Chiang Mai University, Thailand) and a Shimadzu QP-5000 (University of Wollongong, Australia) by the direct insertion technique. High resolution CI mass spectra were determinded using a Fisons/VG Autospec-TOF-oa Mass Spectrometer (University of Wollongong, Australia).

Preparative layer chromatography was carried out on 20x20 mm glass plates coated with Kieselgel 60 F_{254} (Merck). Column chromatography with silica gel was conducted using solvents as indicated.

All reactions requiring anhydrous conditions, were conducted, in glassware that had been over dried and cooled in a desiccator, under an anhydrous nitrogen atmosphere. Anhydrous solvents were also used for such reactions. The THF used had been dried over sodium metal/benzophenone and distilled under nitrogen.

5.2 Experimental Procedures

1. Methyl 9,10-dihydro-9,10-ethanoanthracene-11-carboxylate (60)[36,37,39]



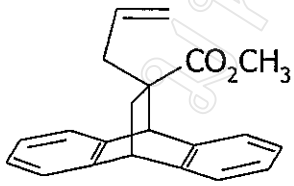
60

A mixture of anthracene (4.45 g, 25 mmol), methyl acrylate (2.58 g, 30 mmol) and xylene (25 ml) was heated in a sealed glass tube in a steel bomb apparatus at 120 ^{0}C for 24 hr. Volatile materials were removed under vacuo and purified by column chromatography (silica gel). The column was eluted with hexane until no anthracene was detected then stripped with ethyl acetate:hexane (5:95). The almost pure adduct was recrystallised from MeOH to give the monoester adduct (12 g, 91%) as colourless crystals, mp. 116-118 ^{0}C (lit.[37] mp. 117-118 °C).

IR (Nujol) υ_{max}1725, 1460, 1200, 1058, 1010, 758 cm^{-1}

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.90-2.25 (m, 2H), 2.85-2.95 (m, 1H), 3.62 (s, 3H, OMe), 4.36 (t, 1H, *J*=3 Hz), 4.72 (d, 1H, *J*=3Hz), 7.10-7.42 (m, 8H, Ar-H)

2. Methyl 11-(2-propenyl)-9,10-dihydro-9,10-ethanoanthracene-11-carboxylate (61)[36,37,39]



61

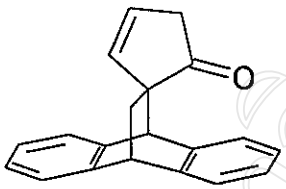
To a solution of LDA (45 mmol) in THF (200 ml) prepared according to the standard procedure, was added HMPA (30 ml) followed by a solution of the ester-adduct (**60**) (10 g, 38 mmol) in THF (100 ml) at –78 °C. The reaction mixture was stirred at 0 °C for 3 hr, allyl bromide (4.82 mole, 0.057 mole) was then introduced at –78 °C and the reaction

kept at 0 ^{0}C for 0.5 hr and at room temperature for 15 hr. The mixture was cooled to 0 ^{0}C and quenched with saturated aqueous ammonium chloride solution. The two layers were separated and the aqueous layer was extracted with THF (3x 50 mL). The organic layers were combined, dried (Na_2SO_4) and evaporated to give the solid residue. The residue was purified by column chromatography (silica gel; 5% ethyl acetate in hexane as eluent) to obtain the ester adduct (10g, 87%) as colourless crystals, mp. 56-57 °C (lit.[37] mp. 56.5-57.5 ^{0}C) (CH_2Cl_2-hexane).

IR (Nujol) υ_{max}1720, 1450, 1430, 1200, 1185, 1170, 1125, 915, 750 cm^{-1}

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.50 (dd, 1H, *J*=3 Hz), 2.65 (dd, 1H, J=3 Hz), 1.75 (dd, 1H, *J*=7 Hz), 2.35 (dd, 1H, *J*=7 Hz), 3.52 (s, 3H, OMe), 4.50 (s, 1H), 4.29 (t, 1H, *J*=3 Hz), 4.80 (d, 1H, *J*= 3 Hz), 4.96 (dd, 1H, *J*= 10 Hz), 5.52-5.72 (m, 1H), 7.00-7.39 (m, 8H, Ar-H)

3. 9',10'-Dihydro-spiro[4-cyclopentene-1,11'-(9,10)-ethanoanthracene]-2-one (62) [36,37,39]



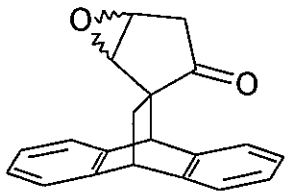
62

To a solution of LDA (36 mmol) in THF (75 mL) at –78 ^{0}C was added TMEDA (25 ml) followed by a solution of the allyl adduct (**61**) (5 g, 16 mmol) in THF (100 ml) at –78 °C and the reaction mixture then stirred at room temperature for 18 hr. The mixture was cooled down to –78 °C and saturated ammonium chloride solution was added. The organic material was extracted into dichloromethane and the organic solution was washed with water, dried ($MgSO_4$) and finally evaporated to yield the crude cyclisation product. Purification by column chromatography (silica gel; 5% ethyl acetate in hexane as a developing solvent) yielded (10 g, 87%) as colourless crystals, m.p 132-133 °C (lit.[37] 132-133 °C) (CH_2Cl_2-hexane).

IR (Nujol) υ_{max}2950, 1757, 1498, 1477, 1280, 1230, 1164, 780, 730 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ 1.65 (dd, 1H, *J*=3 Hz), 2.05 (dd, 1H, *J*=3 Hz), 2.82 (dd, 1H, *J*=2 Hz), 3.25 (dd, 1H, *J*=2 Hz), 4.10 (s, 1H), 4.42 (t, 1H, *J*=7 Hz, *J*= 2 Hz, *J*=2 Hz), 5.30 (dd, 1H, *J*=3 Hz), 6.13 (dd, 1H, *J*=2 Hz), 7.10-7.49 (m, 8H, Ar-H).

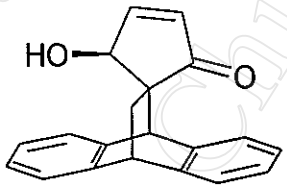
4. 9',10'-Dihydro-4,5-oxiran-spiro[cyclopentane-1,11'-(9,10)-ethano-anthracene]-2-one (63)[36,37,39]



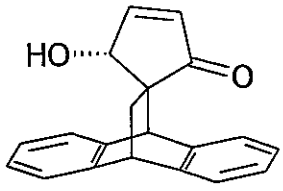
63

To a 0 °C solution of **62** (11.7 g, 43 mmol) in dry dichloromethane (100 ml) was added a solution of *m*-chloroperoxybenzoic acid (10.48 g, 51.6 mmol) in dry dichloromethane (100 ml) and the mixture left stirring overnight at room temperature. The reaction mixture was extracted with saturated aqueous sodium bicarbonate solution, washed with water, dry ($MgSO_4$), filtered and evaporated to dryness to obtain **63** (11.9 g, 96%) as a mixture of two isomers (1:1.6 parts as indicated by NMR integration). The crude product, without any further purification, was used as the starting material in the next reaction.

5. 9',10'-Dihydro-5-hydroxy-spiro[3-cyclopentene-1,11'-(9,10)-ethanoanthracene]-2-one (59)[36,37,39]



59a



59b

To a 0 °C solution of the crude epoxide (**63**) (2.13 g, 7.4 mmol) in THF (50 ml) was added triethylamine (2.06 ml, 14.8 mmol) and the mixture left stirring at room

temperature overnight. The solvents were evaporated to give the unsaturated alcohol adduct **(59a)** and **(59b)** as a mixture of 2 stereoisomers. The crude product was purified by column chromatography (silica gel; pure CH_2Cl_2 in hexane as a developing solvent) to obtain **59a** (0.72 g, 34 %) as colourless crystals from CH_2Cl_2-hexane, mp. 159-161 °C (lit.[37] 159-160 °C) and **59b** (1.3 g, 61%) as colourless crystals from CH_2Cl_2-hexane, mp. 161-162 °C (lit.[37] 163-165 °C).

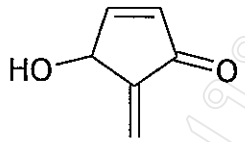
(59a) IR(KBr) υ_{max} 1710, 1400, 1340, 760 cm^{-1}

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.75, 2.10, 4.42, ABX system (dd, dd, d, 3H, J_{AB}=12 Hz, J_{AX}=J_{BX}=2.4 Hz), 2.13 (broad, 1H, OH (disappeared with D_2O)) 4.23 (s, 1H), 4.44 (s, 1H), 6.20 (d, 1H, J=6 Hz), 7.08-7.47 (m, 9H, 1H and Ar-H).

(59b) IR(KBr) υ_{max} 1700, 1460, 1165, 760 cm^{-1}

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.75, 2.25, 4.42, ABX system (dd, dd, d, 3H, J_{AB}=12.8 Hz, J_{AX}=J_{BX}=2.5 Hz), 1.27 (broad, 1H, OH (disappeared with D_2O)) 4.51 (s, 1H), 3.90 (s, 1H), 6.09, ABX system (d, 1H, J_{AB}=6 Hz, J_{AX}=J_{BX}=1.5 Hz), 6.93-7.43 (m, 9H, 1H and Ar-H).

6. 3-Hydroxy-2-methylene-4-cyclopentenone (58a)[36,37]



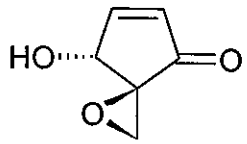
58a

Compound **59** (a, b) (500 mg) was placed in a 10 ml round-bottom flask connected to a gas phase pyrolysis apparatus and the system was subjected to high vacuum (0.05 mm). The sample was carefully pyrolysed with free-flame and the vapor passed through the heating column at 450 °C. The crude product was trapped in a U-shape glass tube immersed in a dry ice-acetone bath. The crude product was purified by preparative layer chromatography (silica gel; pure dichloromethane as eluent) to obtain **58a** (179.5 mg, 94%) as a viscous liquid.

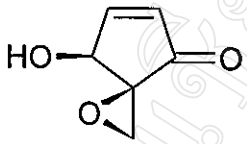
IR(Neat) υ_{max} 3350, 2900, 1700, 1650, 1400, 890 cm^{-1}

^{1}H-NMR (300 MHz $CDCl_3$): δ 2.14 (broad, 1H, OH (disappeared with D_2O)), 5.22 (s, 1H), 5.73 (s, 1H), 6.20 (s, 1H), 6.45 (d, (J=6Hz), 7.53, d, (J=6Hz).

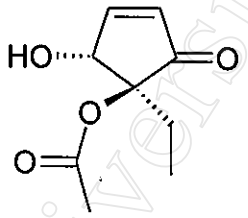
7. 3-Hydroxy-2-spiro[oxiran]-4-cyclopentenone (67, 68) and 3-hydroxy-2-acetyl-2-ethyl-4-cyclopentenone (69)



67



68



69

To a solution of **58a** (50 mg, 0.45 mmol) in acetone (5 ml) was added a solution of dioxirane (0.90 mmol, 0.07 M) in acetone at 0 °C, and the reaction was left to stir overnight at room temperature. The solvent was then evaporated to give **67** and **68** as a mixture of 2 diastereomers (dr = 83: 17 from ^{1}H-NMR). The crude product was purified by PLC (silica gel; 40% ethyl acetate in petrolium sprit as eluent) to obtain **67** (28 mg, 49%), **68** (a small amount) as a viscous liquid and **69** (30 mg, 36 % yield).

(67) ^{1}H-NMR (300 MHz, $CDCl_3$) : δ 2.31 (broad, OH), 3.14 (d, 1H, *J*=5.9 Hz), 3.28 (d, 1H, *J*=5.9 Hz), 4.96 (s, 1H,), 6.53 (dd, 1H, *J*=6.7, 1.2 Hz), 7.69 (dd, 1H, *J*=6.3, 2.1 Hz). (300 MHz, D_2O) δ 3.04 (d, 1H, *J*=5.9 Hz), 3.21 (d, 1H, *J*=5.9 Hz), 4.82 (s, 1H,), 6.43 (d, 1H, *J*=6.7 Hz), 7.76 (d, 1H, *J*=6.3 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 50.1 (CH_2), 69.8 (CH-OH), 137.7 (CH-CH-C=O), 138.6 (O=C-C-CH_2), 161.5 (CH=CH-C=O), 186.0 (C=O).

CIMS (70 eV) *m/z* (relative intensity): 127 (M^+, 100) . HRCIMS (70 eV) *m/z:* Calcd for $C_6H_7O_3$, 127.0395. Found, 127.0363 (M+).

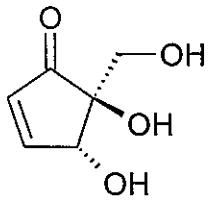
(**68**) ^{1}H NMR (300 MHz, $CDCl_3$) : δ 2.32 (broad, OH), 3.34 (d, 1H, *J*=5.9 Hz), 3.41 (d, 1H, *J*=5.9 Hz), 5.12 (s, 1H,), 6.63 (d, 1H, *J*=6.7 Hz), 7.82 (d, 1H, *J*=6.3 Hz).

(**69**), Needles from DCM/petroleum sprit, mp = 98-100 °C, ^{1}H NMR (300 MHz, $CDCl_3$) : δ 0.92 (*t,* 3H, *J*=7.58 Hz), 1.71 (m, 1H, *J*=7.58 Hz), 2.08 (m, 1H, *J*=7.58 Hz), 2.15 (s, 3H), 3.27 (d, OH, *J*=4.21 Hz), 5.01 (dd, 1H, *J*=2.10, 2.10 Hz), 6.30 (dd, 1H, *J*=1.68, 4.63 Hz), 7.49 (dd, 1H, *J*=1.68, 4.63 Hz)

^{13}C NMR (75 MHz, $CDCl_3$): δ 8.1 (CH_3), 21.6 (CH_3), 24.6 (CH_2), 75.2 (CH-OH), 89.2 (O=C-C-CH_2), 132.7 (CH=CH-C=O), 159.8 (CH=CH-C=O), 171.9 (C=O), 200.7 (CH_3C=O).

CIMS (70 eV) *m/z* (relative intensity) : 185 (M^+, 100) . HRCIMS (70 eV) *m/z:* Calcd for $C_9H_{13}O_4$, 185.0814. Found, 185.0794 (M+).

8. (±) Epipentenomycin I (5)



5

A solution of **67** (32 mg) in D_2O (1 ml) was heated overnight at 80 °C. The resulting solution was freeze-dried overnight to remove water to give (±) epipentenomycin I (**5**) (23.7 mg, 74%) as a viscous liquid.

The ^{1}H-NMR of this compound was identical to that reported in the literature.[27]

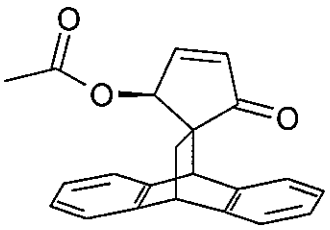
IR : 1049, 1403, 1577, 1710, 1919, 3364.

^{1}H-NMR (300 MHz, D_2O) : δ 3.57 (d, 1H, -HC*H*-OH, *J* = 11.8 Hz), 3.67 (d, 1H, -HC*H*-OH, *J* = 11.8 Hz), 4.71 (d, 1H, -*CH*-OH, *J* = 1.7 Hz), 6.27 (dd, 1H, -CO-*CH*=CH-, *J* = 6.3, 1.7 Hz), 7.58 (dd, 1H, - CO-CH=*CH*-, *J* = 5.9, 2.1 Hz)

^{13}C NMR (75 MHz, D_2O): δ 63.6, 77.6, 82.4, 132.4, 163.6.

CIMS (70 eV) *m/z* (relative intensity) : 145 (M^+, 100) .

9. 9', 10'-Dihydro-5-acetyl-spiro[3-cyclopentene-1,11'-(9,10)-ethanoanthracene]-2-one (64)



64a

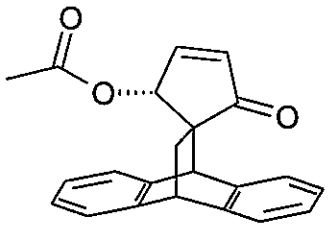
To a solution of **59a** (0.55g, 1.92 mmol) in pyridine (5 ml) was added excess acetic anhydride at room temperature and the reaction was left to stirr overnight. The solvents were then evaporated to give a white solid. Recystallization from DCM/petroleum sprit gave **64a** (0.562 g, 89 % yield) as colourless crystals, mp. 201-202 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.77 (s, 3H), 1.96 (dd, 1H, *J*= 9.7, 2.5 Hz), 2.1(dd, 1H, *J*=9.7, 2.5 Hz), 4.07 (s, 1H), 4.44 (s, 1H), 5.56 (d, 1H, *J*=1.7 Hz), 6.30 (d, 1H, *J*=5.9 Hz), 7.14-7.39 (m, 8H, 2Ar), 7.47 (dd, 1H, *J*=2.5, 3.4 Hz)

^{13}C NMR (75 MHz, $CDCl_3$): δ 20.8 (CH_3), 34.6 (CH_2), 44.6 (C-CH-Ar), 52.5 (CH_2-CH-Ar), 55.3 (O=C-C-CH_2), 78.8 (CH-O), 123.1 (ArCH), 123.3 (ArCH), 123.9 (ArCH), 125.2 (ArCH), 126.3 (ArCH), 126.4 (ArCH), 126.6 (ArCH), 126.8 (ArCH), 135.5 (CH=CH-C=O), 139.6 (CH-C-Ar), 140.9 (CH-C-Ar), 144.3 (d, *J*= 6.3Hz) (2 x CH-C-Ar), 156.6 (CH=CH-C=O), 169.6 (C=O), 206.7 (CH_3C=O).

CIMS (70 eV) *m/z* (relative intensity) : 95(14), 109(4), 153(90), 179(100), 235(14), 271(14), 331(M^+, 3).

HRCIMS (70 eV) *m/z:* Calcd for $C_{22}H_{19}O_3$, 331.1334. Found, 331.1331 (M+).



64b

To a solution of **59b** (0.50g, 1.74 mmol) in pyridine (5 ml) was added excess acetic anhydride at room temperature and the reaction was left to stirr overnight. The solvents were then evaporated to give a white solid. Recystallization from DCM/petroleum sprit gave **64b** (0.514 g, 81 % yield) as colourless crystals, mp. 180-182 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) : δ 1.95 (dd, 1H, *J*= 9.7, 2.5 Hz), 1.97 (s, 3H), 2.13 (dd, 1H, *J*=9.7, 2.5 Hz), 4.35 (s, 2H), 5.30 (s, 1H), 6.30 (d, 1H, *J*=5.9 Hz), 7.05-7.3 (m, 8H, 2Ar), 7.41 (dd, 1H, *J*=3.4, 2.5 Hz)

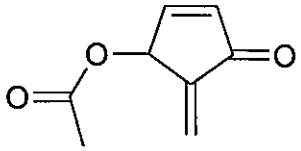
^{13}C-NMR (75 MHz, $CDCl_3$): δ 21.3 (CH_3), 40.3 (CH_2), 44.6 (C-CH-Ar), 48.4 (CH_2-CH-Ar), 55.6 (O=C-C-CH_2), 80.8 (CH-O), 123.2 (ArCH), 123.4 (ArCH), 123.8 (ArCH), 125.5 (ArCH), 125.7 (ArCH), 125.9 (ArCH), 126.2 (ArCH), 126.3 (ArCH), 136.0 (CH=CH-C=O), 140.6 (CH-C-Ar), 141.2 (CH-C-Ar), 144.3 (CH-C-Ar), 144.5 (CH-C-Ar), 156.2 (CH=CH-C=O), 169.8 (C=O), 205.8 (CH_3C=O).

CIMS (70 eV) *m/z* (relative intensity) : 153(57), 179(100), 235(14), 271(21), 331(M^+, 14).

HRCIMS (70 eV) *m/z:* Calcd for $C_{22}H_{19}O_3$, 331.1334. Found, 331.1318 (M+).

However, acetylation of a mixture of **59a** and **59b** (1:1) with acetic anhydride in pyridine gave **64a** and **64b** in 92 % yield.

10 . 3-Acetyl-2-methylene-4-cyclopentenone (58b)



58b

Compound **64a,b** (500 mg) was placed in a 10 ml round-bottom flask connected to a gas phase pyrolysis apparatus and the system was subjected to high vacuum (0.05 mm). The sample was carefully pyrolysed with free-flame and the vapor passed through the heating column at 400-450 ^{0}C. The crude product was trapped in a U-shape glass tube immersed in a liquid nitrogen bath. Crude product was purified by PLC (silica gel; 40% ehtyl acetate in petrolium sprit as eluent) to obtain **58b** (390 mg, 78%) as a viscous liquid.

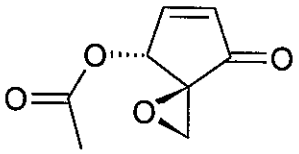
^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.11(s, 3H), 5.72 (s, 1H), 6.20 (s, 1H), 6.22(s, 1H), 6.53(d, 1H, *J*=3.32 Hz), 7.47 (dd, 1H, *J*=2.53, 3.79 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 21.3 (CH_3), 71.8 (CH-O), 120.7 (CH_2), 138.7 (CH=CH-C=O), 141.2 ($C=CH_2$), 154.6 (CH=CH-C=O), 170.8 (C=O), 193.3 (CH_3C=O)

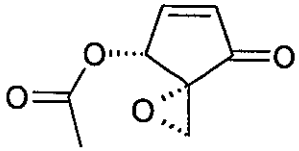
CIMS (70 eV) *m/z* (relative intensity) : 153(M^+, 100).

HRCIMS (70 eV) *m/z:* Calcd for $C_8H_9O_3$, 153.0551. Found, 153.0552 (M+).

11. 3-Acetyl-2-spiro[oxiran]-4-cyclopentenone (70 and 71)



70



71

To a solution of **58b** (48 mg, 0.31 mmol) in acetone (5 ml) was added a solution of dioxirane (0.90 mmol, 0.07 M) in acetone at 0 °C, and the reaction was left to stir overnight at room temperature. The solvent was then evaporated to give **70** and **71** as a mixture of 2 diastereomers (dr = 80 : 20 from ^{1}H-NMR). The clude product was purified by preparative layer chromatography (silica gel, dichloromethane) to obtain a mixture of **70** and **71** (22mg, 42%) as a viscous liquid.

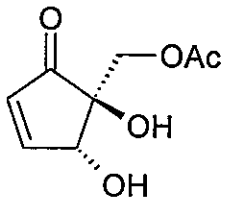
(**70**) , ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.11 (s, 3H), 3.18 (d, 2H, *J*=3.8 Hz), 5.83 (s, 1H), 6.60 (d, 1H, *J*=6.3 Hz), 7.70 (dd, 1H, *J*=2.5, 2.1 Hz). ^{1}H NMR (300 MHz, D_2O): δ 2.03 (s, 3H), 3.08 (d, 1H, *J*=5.5, Hz), 3.18 (d, 1H, *J*=5.5, Hz), 5.85 (s, 1H), 6.59 (d, 1H, *J*=6.3 Hz), 7.76 (d, 1H, *J*=6.7 Hz).

^{13}C-NMR (75 MHz, $CDCl_3$) : δ 21.1 (CH_3), 51.1 (CH_2), 72.5 (C̲H-O), 137.4 (C̲H=CH-C=O), 138.5 (O=C-C̲-CH_2), 158.0 (CH=C̲H-C=O), 170.0 (C=O), 198.4 (CH_3C̲=O)

CIMS (70 eV) *m/z* (relative intensity) : 169(M^+, 100) . HRCIMS (70 eV) *m/z:* Calcd for $C_8H_9O_4$, 169.0500. Found, 169.0496 (M+).

(**71**), ^{1}H-NMR (300 MHz, $CDCl_3$) : δ 2.11 (s, 3H), 3.18 (d, 2H, *J*=3.8 Hz), 5.83 (s, 1H), 6.60 (d, 1H, *J*=6.3 Hz), 7.70 (dd, 1H, *J*=2.5, 2.1 Hz)

12. Epipentenomycin III



(7)

A mixture of compounds **70** and **71** ratio (80:20) (13 mg) in D_2O (1 ml) was heated overnight (monitored by ^{1}H-NMR) at 80 °C. The resulting solution was freeze-dried overnight to remove water. The crude mixture was extracted with dichloromethane and purified using preparative layer chromatography (silica gel, dichloromethane) to give 4-hydroxy-5-acetylmethyl-2-cyclopentenone ((±) epipentenomycin III) (**7**) as a viscous liquid plus about 20% of an isomeric compound, that was most likely pentenomycin III (4 mg, 21.74%).[27] The ^{1}H-NMR showed peaks which identified the major product as epipentenomycin III when compared that reported in the literature.[27]

^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.07 (s, 3H, OAc), 4.22 (d, 1H, -HC*H*-OAc, *J*=11.7 Hz), 4.42 (d, 1H, -HC*H*-OAc, *J*=11.7 Hz), 4.90 (d, 1H, -*CH*-OH, *J*=4.6 Hz), 6.34 (dd, 1H, CO-*CH*=CH-, *J*=2.53, 1.68 Hz), 7.53 (dd, 1H, -CO-CH=*CH*-, *J*= 2.53, 1.68 Hz).

^{1}H-NMR (300 MHz, D_2O): δ 1.95 (s, 3H, OAc), 4.13 (d, 1H, -HC*H*-OAc, *J* = 11.7 Hz), 4.21 (d, 1H, -HC*H*-OAc, *J* = 11.7 Hz), 4.74 (d, 1H, -*CH*-OH, *J* = 1.5 Hz), 6.28 (dd, 1H, -CO-*CH*=CH-, *J* = 6.3, 1.7 Hz), 7.57 (dd, 1H, - CO-CH=*CH*-, *J* = 4.8, 1.5 Hz)

6. References

1. K. Umino, T. Furumai, N. Matsuzawa, Y. Awataguchi, Y. Ito and T. Okuda, *J. Antibiot.*, 1973, **26**, 506.
2. K. Umino, N. Takeda, Y. Ito and T. Okuda, *Chem. Pharm. Bull.*, 1974, **22**, 1233.
3. K. Umino, K. Kolera, K. Aoe and T. Date, *Chem. Pharm. Bull.*, 1974, **22**, 1963.
4. M. Noble, D. Noble and R. A. Fletton, *J. Antibiot.*, 1978, **31**, 15.
5. J. Bernillon, J. F. Bonvin, M. T. Pommier and N. Arpin, *J. Antibiot.*, 1989, **13**, 1430.
6. a. T. Haneishi, N. Kitahara, Y. Takigushi, M. Arai and S. Sugawara, *J. Antibiot.*, 1974, **27**, 386.
   b. T. Haneishi, A. Terahara, M. Arai and C. Tamura, J. Antibiot., *1974*, **27**, 393.
   c. T. Haneishi, A. Takeuchi, K. Nitta, T. Yamamoto and M. Arai, *J. Antibitot.*, 1974, **27**, 400.
7. a. H. Umezawa, T. Takenshi, K. Nitta, T. Yamamoto and S. Yamaoka, *J. Antibiot.*, 1953, **6**, 101.
   b. H. Umezawa, T. Takenshi, K. Nitta, Y. Okami, T. Yamamoto and S. Yamaoka, *J. Antibiot.*, 1953, **6**, 153.
8. a. K. Asaki and S. Suzuki, *Agric. Biol. Chem.*, 1970, **34**, 325.
   b. K. Asaki, J. Nagatsu and S. Suzuki, *J. Antibiot. Ser. A.*, 1966, **19**, 195.
9. a. C. J. Forsyth and J. Clardy, *J. Am. Chem. Soc.*, 1990, **112**, 3497.
   b. N. Lindquist, W. Fenical, D. F. Sesin, C. M. Ireland, G. D. Van Duyne, C. J. Forsyth and J. Clardy, *J. Am. Chem. Soc.*, 1988, **110**, 1308.
10. a. H. Kikushi, Y. Tsukitani, K. Iguchi and Y. Yamada, *Tetrahedron Lett.*, 1982, 5171.
    b. H. Kikushi, Y. Tsukitani, K. Iguchi and Y. Yamada, *Tetrahedron Lett.*, 1983, 1549.
    c. K. Iguchi, Y. Yamada, H. Kikushi and Y. Tsukitani, *Tetrahedron Lett.*, 1983, 4433.
11. a. B. J. Baker, R. K. Okuda, P. T. K. Yu and P. J. Scheuer, *J. Am. Chem. Soc.*, 1985, **107**, 2976.
    b. H. Nagaoka, H. Miyaoka, Y. Miyakoshi and Y. Yamada, *J. Am. Chem. Soc.*, 1986, 5019.
12. S. Inayama, K. Mamoto, T. Shibata and T. Hirose, *J. Med. Chem.*, 1976, **19**, 433.

13. W. J. Mc Gahren, J. H. Van Den Hende and L. A. Mitscher, *J. Am. Chem. Soc.*, 1969, **91**, 157.

14. M. A. Stillwell, F. A. Wodd and G. M. Strunz, Can. *J. Microb.*, 1969, **15**, 501.

15. G. M. Strunz and A. S. Court, *Experientia.*, 1970, **26**, 714.

16. M. Nakayama, Y. Fukuoka, H. Nozaki, A. Matsuo and S. Hayashi, *Chem. Lett.*, 1980, 1243.

17. H. Iric, J. Katakawa, M. Tomita and Y. Mitzuno, *Chem. Lett.*, 1981, 637.

18. D. Boschelli, A. B. Smith, O. D. Stringer, R. H. Jenkins and F. A. Davis, *Tetrahedron Lett.*, 1981, **22**, 4385.

19. K. H. Hirayama, K. Shimizu, K. Shirahata, K. Ueno and G. Tamura, *Agric. Biol. Chem.*, 1980, **44**, 2083.

20. K. Shimizu and A. Tamura, *J. Antibiot.*, 1980, **44**, 2083.

21. M. Raistrick and G. Smith, *J. Biochem.*, 1935, **29**, 606.

22. D. H. R. Barton and E. J. Miller, *J. Chem. Soc.*, 1955, 1028.

23. Shomura, T.; Hoshida, J; Kondo, Y.; Watanabe, H.; Omoto, S.; Inouye, S.; Niida, T. *Kenkyu Nempo* 1976, 16, 1. Shoumura, T.; *et al.* (Meiji Seika). Japanese Kokai, 19276- 82, July 20, 1976.

24. Hatano, K.; Izawa, M.; Hasegawa, T.; Tonida, S.; Asai, M.; Iwasaki, H.; Yamano, T. *J. Takeda Res. Lab.*, 1976, **38**, 22.

25. T. Sono, Y. Matsumura, S. Shinichiro and M. Suzuki, *Chem. Lett.*, 1980, **12**, 1619.

26. S. J. Branca and A. B. Smith, III, *J. Am. Chem Soc.*, 1978, **100**, 7767.

27. A. B. Smith, III, S. J. Branca, N. N. Pilla and M. A. Guaciaro, *J. Org. Chem.*, 1982, **47**, 1855.

28. R. J. Stoodley, J D. Elliott, M. Hetmanski, M. N. Palfreyman and N. Purcell, *Tetrahedron Lett.*, 1983, **24**, 965 and references therein.

29. B. Zwanenburg, A. J. H. Klunder and J. M. J. Verlaak, *Tetrahedron Lett.*, 1982, **23**, 5463.

30. A. B. Smith, III and N. C. Pilla, *Tetrahedron Lett.*, 1980, **21**, 4691.

31. J. P. H. Verheyden, A. C. Richadson, R. S. Bhatt, B. D. Grant, W. L. Fitch and J. G.

Moffatt, *Pure&Appl. Chem.*, 1978, **50**, 1363.

32. S. Achab, J. P. Cosson and B. C. Das, *J. Chem. Soc., Chem. Comm.*, 1984, 1040.
33. S. Mohindra and A. Yousef, *Tetrahedron Lett.*, 2000, **41**, 4291 and references therein.
34. M. Pohmakotr and S. Popuang, *Tetrahedron Lett.*, 1991, **32**, 275.
35. A. A. M. Houwen-Claassen, A. J. H. Klunder and B. Zwanenberg, *Tetrahedron*, 1989, **45**, 7149.
36. N. Chantarasiri, P. Dinprasert, C. Thebtaranonth, Y. Thebtaranonth and C. Yenjai, *J. Chem. Soc., Chem. Commun.*, 1990, 286 and references therein.
37. C. Yenjai, *Ph.D. Thesis*, Mahidol University, 1989.
38. R. W. Murray, M. Singh, *Org. Synth.*, 1997, 74, 91
39. W. Phutdhawong, *M.Sc. Thesis*, Chiang Mai University, 1998