

DISSERTATION

STUDIES TOWARDS THE TOTAL SYNTHESIS OF
(-)-LEMONOMYCIN

Submitted by
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Chemistry

In partial fulfillment of the requirements
For the Degree of Doctor of Philosophy
Colorado State University
Fort Collins, Colorado
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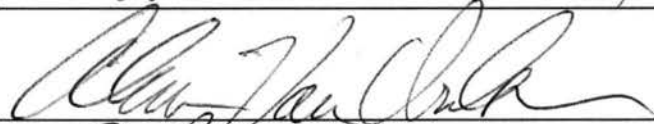
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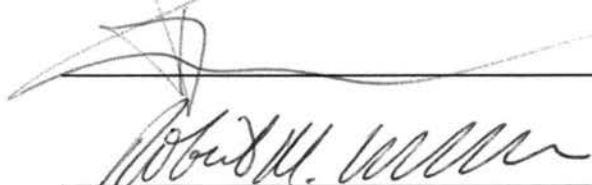
WE HEREBY RECOMMENDED THAT THE DISSERTATION
PREPARED UNDER OUR SUPERVISION BY YUYIN CHEN
ENTITLED STUDIES TOWARDS THE TOTAL SYNTHESIS OF (-)-
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Committee on Graduate Work









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ABSTRACT OF DISSERTATION

STUDIES TOWARDS THE TOTAL SYNTHESIS OF
(-)-LEMONOMYCIN

An asymmetric synthesis of the tetracyclic core of (-)-lemonomycin is presented. It features an efficient route towards a highly versatile tetrahydroisoquinoline intermediate, in which a diastereoselective Pictet-Spengler reaction has been developed.

In addition, a novel oxidation was discovered in the process of an azomethine ylide cyclization for construction of C and D rings of lemonomycin. An investigation into the mechanism of this novel oxidation has been carried out and the results discussed. The tetracyclic enamide from this process represents a highly functionalized and versatile intermediate. Interestingly, the enamide double bond proved very resistant to reduction and this transformation was fully investigated. More recently, with high-pressure hydrogenation equipment, promising leads towards hydrogenation of this enamide have been uncovered.

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CHAPTER 1

Introduction: Quinocarcin Family of Natural Products

Quinocarcin natural products are members of the tetrahydroisoquinoline family of antitumor antibiotics.¹ The nearly 60 natural products and hundreds of synthetic analogues belonging to the tetrahydroisoquinoline family have been studied thoroughly over the past 30 years, starting with the isolation of naphthridinomycin in 1974. To date, quinocarcin/ quinocarcinol, tetrazomine and lemonomycin are natural products isolated in the quinocarcin family.

In this chapter the isolation, structure determination and biological activities of quinocarcin/ quinocarcinol, tetrazomine and lemonomycin will be summarized. In addition, the strategic analysis of the syntheses of quinocarcin family of natural products will be discussed.

1.1 Isolation, Structure Determination and Biological Activity

1.1.1 Quinocarcin and Quinocarcinol

Quinocarcin (**1**) and quinocarcinol (**2**) were isolated² in 1983 from *Streptomyces melanovinacesu* nov. sp. (Figure. 1). The structure of **2** was determined by X-ray

crystallography.³ The structure of **1** was then confirmed by chemical conversion to **2** via reduction. Garner et al. reported the total synthesis of (-)-quinocarcin (**1**) in 1992, thus confirming the absolute stereochemistry.⁴

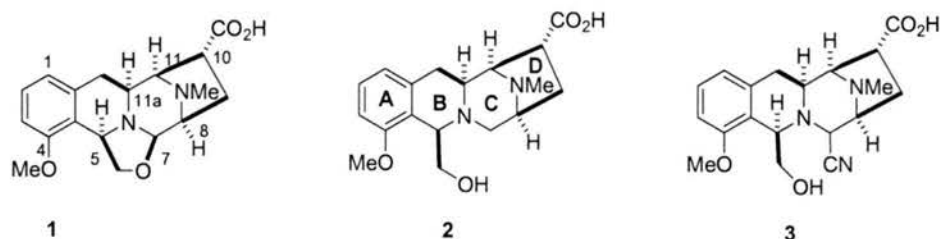


Figure 1 Quinocarcin (**1**), quinocarcinol (**2**) and DX-52-1(**3**)

Quinocarcin (**1**) and quinocarcinol (**2**) both have a core tetracyclic ring system bearing a tetrahydroisoquinoline as the AB ring and an *N*-methyl pyrrolidine as the D ring. **1** has an oxazolidine ring which quinocarcinol **2** does not have. This functionality has been shown to be the key to the mechanism of action of **1** and this will be discussed later in this chapter (Scheme 5).

Quinocarcin (**1**) has moderate activity against Gram-(+) bacteria such as *Staphylococcus aureus*, *Bacillus subtilis* and *Klebsiella pneumoniae* with MIC's of 12.5, 12.5, and 25 μ L, respectively.^{5a} It also has been shown to inhibit [³H]-thymidine incorporation in *Bacillus subtilis*. This was found to be due to inhibition of DNA polymerase, which is a manifestation of oxidative DNA cleavage.⁶ No effect was seen on RNA or protein synthesis. Quinocarcinol (**2**) has no activity against either Gram-(+) or Gram-(-) bacteria.

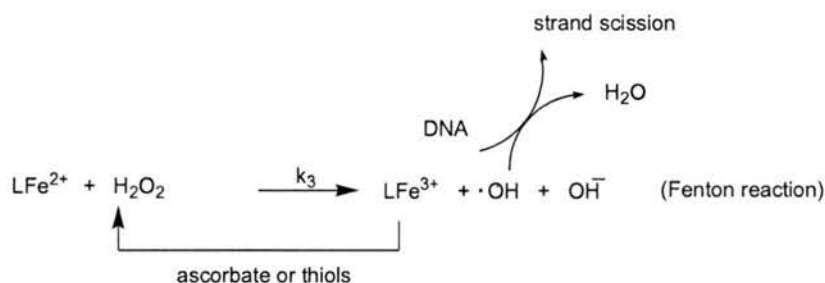
Quinocarmycin citrate (quinocarcin as its citrate salt or KW2152)^{7,8} and DX-52-1 (3) were assayed by the National Cancer Institute in a screen of 60 tumor cell lines.⁹ Both have shown promising activity with 3 showing excellent activity against several melanoma cell lines. However quinocarmycin citrate has liver toxicity, resulting in the discontinuation of clinical trials of quinocarmycin citrate in Japan. DX-52-1 on the other hand didn't show the toxicities associated with quinocarmycin citrate.

Quinocarcin (1) was first reported by Tomita et al. to mediate oxidative cleavage of DNA via superoxide production.¹⁰ Tomita's study has shown that the oxidative cleavage of DNA by 1 was inhibited by addition of oxygen free radical scavengers such as methanol and *tert*-butanol, or SOD (superoxide dismutase) and catalase. However, cleavage was enhanced by addition of DTT (dithiothreitol), but this was not required; also, it was not stimulated by addition of metal ions (Fe^{2+} or Cu^{2+}). A mechanistic explanation was not offered in this work.

Superoxide has been shown to mediate DNA strand breakage via dismutation to hydrogen peroxide via the Haber-Weiss cycle followed by Fenton-mediated generation of the diffusible and highly reactive hydroxyl radical.¹¹ With EDTA (ethylenediaminetetraacetic acid), k_1 represented the rate-determining step ($76 \text{ M}^{-1}\text{s}^{-1}$) at neutral pH (Scheme 1).

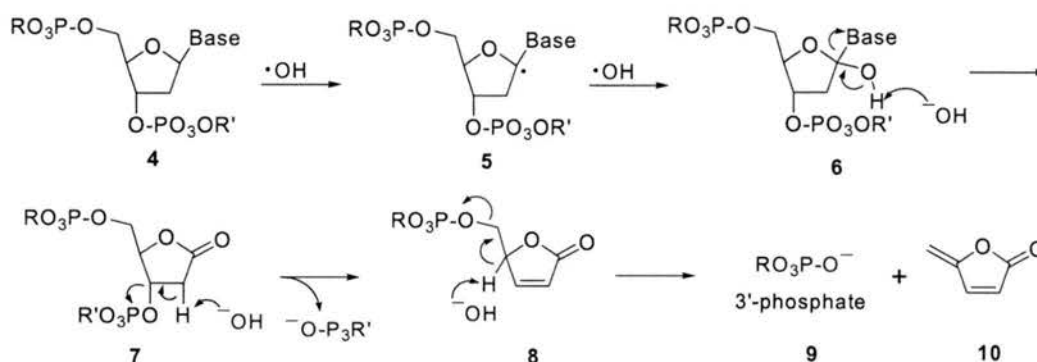


The ability of hydroxyl radical to abstract hydrogen atoms from deoxyribose is at the basis of its ability to cause oxidative damage to DNA and RNA. The diffusible and highly reactive hydroxyl radical causes damage to random nucleic acids resulting in strand scission at any base pair site. This process can be activated by addition of reducing agents such as ascorbate and thiols which provide a constant source of Fe(II) as well as superoxide, thereby facilitating the DNA-cleavage process. (Scheme 2)



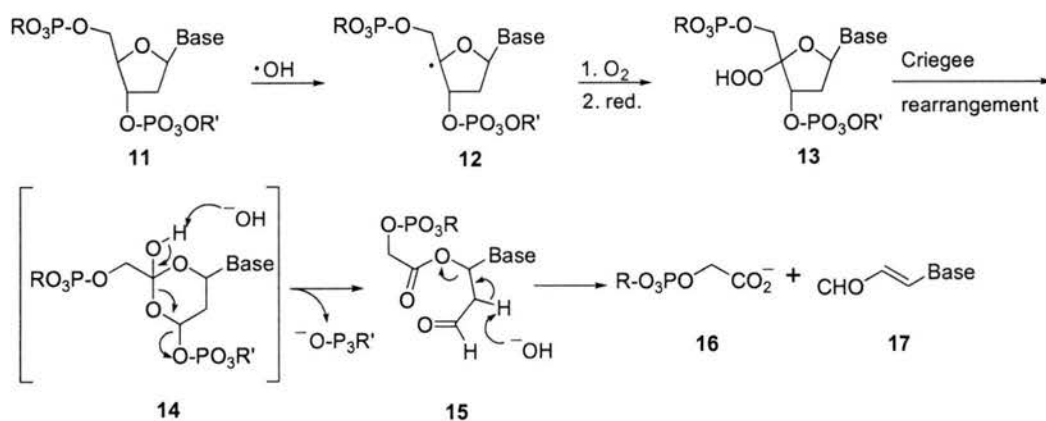
Scheme 2 Activation by ascorbate or thiols

The damage of DNA by reaction with hydroxyl radical has been shown to occur via two predominate pathways.¹² The first pathway (Scheme 3) begins with hydroxyl radical abstraction of the C-1' hydrogen from the deoxyribose **4** producing radical **5**, captured by another hydroxyl radical forms the hemi-ketal **6**, which forms lactone **7** after loss of the base. Alpha deprotonation causes strand scission of the 3'-phosphate. Deprotonation at the C-4' position affords the unstable unsaturated lactone **10** with the 3'-phosphate product **9**.



Scheme 3 C-1' hydrogen atom abstraction

In the other pathway (Scheme 4), hydroxyl radical abstracts the C-4' hydrogen atom from the deoxyribose forming the radical **12**; reaction of this radical species with molecular oxygen followed by single electron reduction results in hydroperoxide **13**. A Criegee rearrangement affords the alkaline labile intermediate **14** which decomposes to aldehyde **15** resulting in strand scission. Subsequent deprotonation affords the 3'-phosphoglycolate **16** and the base propenal **17**.

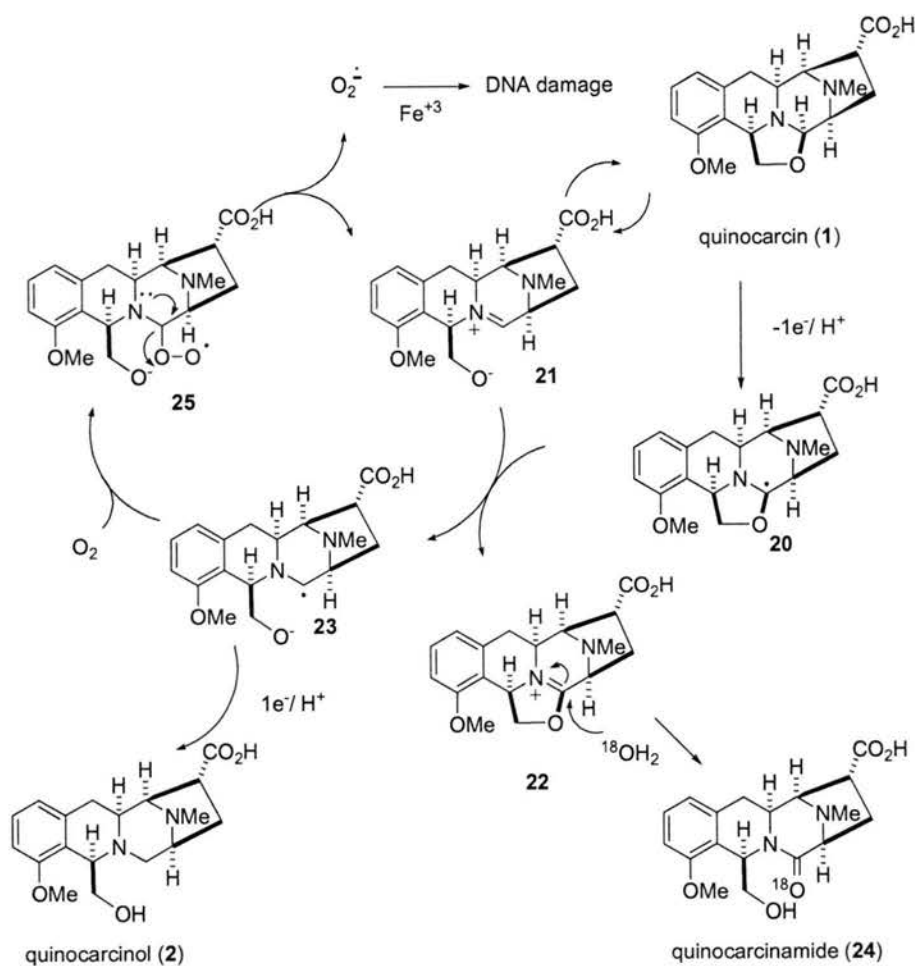


Scheme 4 C-4' hydrogen atom abstraction

In 1992, Williams et al. reported a study of superoxide formation by quinocarcin (**1**) and quinocarcin analogs.¹³ A mechanism based on the redox-disproportionation of **1** was proposed based on the following experimental results (scheme 5). When quinocarcin was allowed to stand in carefully deoxygenated water at 25°C, two new products were produced, quinocarcinol (**2**) and quincarcinamide (**24**). This supported the fact that single electron transfer from **1**, with concomitant proton loss from the oxazolidine nitrogen to the ring-opened tautomer **21**, would form radical anion **23** and the oxazolidinyl radical **20**. Radical **20** should be able to reduce a second equivalent of **21**, ultimately becoming

oxazolidinium ion **22**, which should hydrolyze to **24**. This was confirmed by a disproportionation reaction in 98% $^{18}\text{OH}_2$ generating **24** with greater than 40% ^{18}O incorporated at the amide carbonyl. Radical anion **21** subsequently abstracted a hydrogen atom (presumably from **1**) resulting in formation of **2** and regenerating radical **20**. The disproportionation reaction in D_2O generated product **2** with no incorporation of deuterium on C-7 indicated this hydrogen atom transfer.

Under aerobic conditions, radical anion **23** could react with molecular oxygen to produce peroxy radical anion **25** which, with nitrogen participation, expels one molar equivalent of superoxide, regenerating **21**. The superoxide would then go through Fenton cycling in the presence of Fe^{3+} to cause random DNA damage via hydroxyl radicals.



Scheme 5 Proposed redox cycle of quinocarcin and superoxide production

The rate of superoxide formation was determined by following the reduction of NBT (nitroblue tetrazolium) spectrophotometrically. The reduction of NBT by quinocarcin (1) was pH-dependent, exhibiting an increased rate of reduction as the pH is raised (Table 1). The authors ascribed this to the requirement for the oxazolidine nitrogen atom to be in an unprotonated state as required by the mechanisms proffered. Importantly, the formation of superoxide by 1 was extremely slow (10^4 – 10^5 times slower) relative to the rate-limiting step of the Haber-Weiss/Fenton reaction ($76 \text{ M}^{-1}\text{s}^{-1}$). This made the slow

production of superoxide by quinocarcin the overall rate limiting step in the DNA-cleavage process.

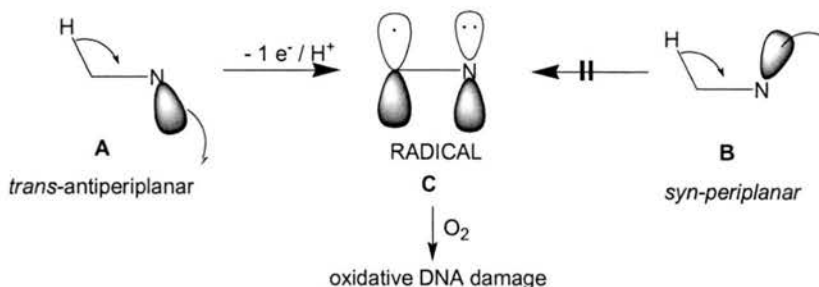
Table 1 Rate of superoxide production by quinocarcin (**1**) and analogs

Substrates	Concentration (mM)	pH	rate ($\text{M}^{-1}\text{s}^{-1} * 10^{-9}$)
2	1.0	6.0	0
1	1.0	7.0	4.2
1	1.0	8.0	11.0
26 (Figure 2)	1.0	8.0	0.41
27 (Figure 2)	1.0	8.0	0
3	1.0	8.0	0

While Tomita's study has previously shown that the addition of iron or copper salts had no stimulatory effect on the ability of **1** to cleave DNA, Williams et al. reported that the addition of the potent iron chelator desferal did, however, exhibit significant inhibition of DNA cleavage particularly at high concentration. These results supported that the DNA cleavage was indeed metal-dependent and that the low concentration of adventitious Fe^{+3} present was already in excess of that required to effect Fenton-mediated cleavage of DNA; addition of excess iron would therefore not be expected to have any additive effect. This observation also supported the hypothesis where in the limiting reagent in DNA cleavage mediated by these compounds was the slow production of superoxide.

As shown in Scheme 5, the initial step in the electron transfer between the oxazolidine and the iminium species involves 1-electron loss from the oxazolidine

nitrogen. Williams et al. predicted that the *trans*-antiperiplanar arrangement (A) of the oxazolidine methane and nitrogen lone pair should be the most favorable geometry for a 1-electron oxidation and concomitant proton loss in the redox self-disproportionation, since this arrangement provides maximum overlap in the transition state (Scheme 6). Two quinocarcin analogs **26** and **27** (Figure 2) synthesized and confirmed by x-ray analyses were used to study the effect of the stereochemistry of the nitrogen lone pair. It was found that *anti* analog **26** could produce superoxide, but *syn* analog **27** could not (Table 1). This observation supported the hypothesis that stereoelectronic control elements of oxazolidine ring system were intimately related to the biological activities of these substances. Additionally, neither quinocarcinol (**2**) nor the semi-synthetic cyano derivative of quinocarcin (DX-52-1, **3**) produced superoxide (Table 1), which further supported the notion that the oxazolidine moiety of these compounds must be “intact”.



Scheme 6 Stereoelectronic control elements of superoxide production

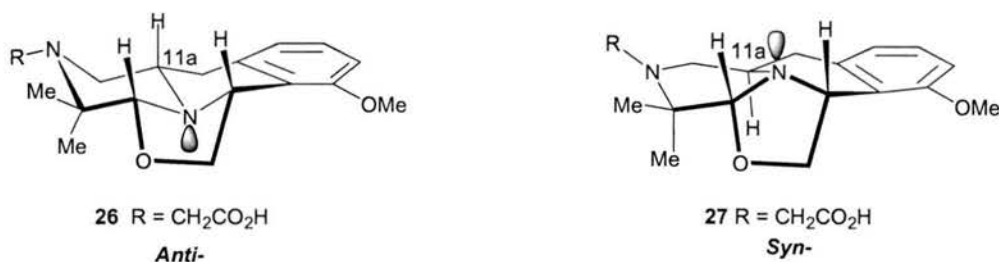


Figure 2 Quinocarcin analogs **26** and **27**

Surprisingly, netropsin analogue **28** (Figure 3), having the well-known DNA binding moiety, did cause oxygen-dependent DNA cleavage, but was not inhibited by SOD or catalase.¹⁴ In addition, the DNA cleavage patterns were not random, indicating a non-diffusible hydrogen atom abstractor. The experimental data and observation suggested that proper orientation of the drug, as dictated by the netropsin moiety, might position a drug-centered radical (a carbon centered radical) in proper geometry to abstract a hydrogen atom from the phosphoribose backbone. In the presence of oxygen, attack of the resulting radical in the phosphoribose back bone would ultimately result in scission of the DNA.

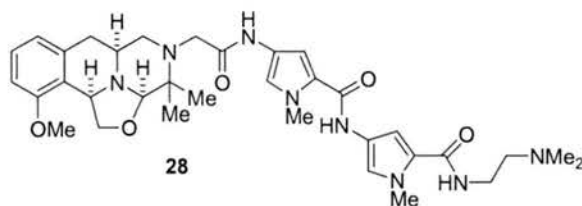
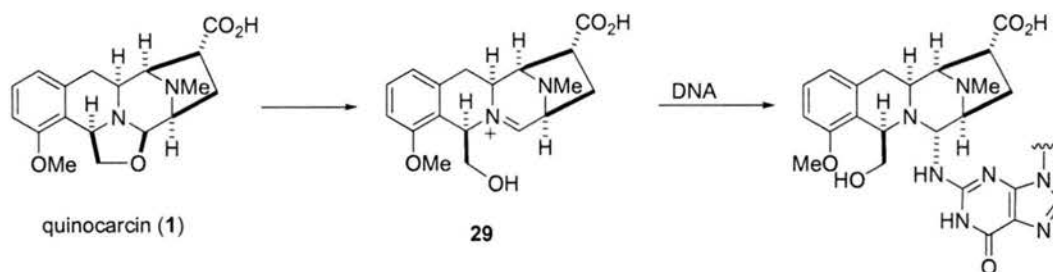


Figure 3 Netropsin analog (**28**)

In 1988, Remers *et al.* reported a molecular modeling study on the binding of quinocarcin (**1**) to DNA.¹⁵ By analogy to the mechanism of iminium formation described for the saframycins, the structurally related quinocarcin iminium species (**29**) was docked into the minor groove of DNA and several conformations were investigated (Scheme 7). This study revealed that the original, arbitrarily assigned absolute stereochemistry of quinocarcin would be a poor DNA alkylating agent. The opposite absolute

stereochemistry was suggested based on better DNA binding energies, and this was later confirmed by Garner's asymmetric synthesis of (-)-quinocarcin.⁴



Scheme 7 Proposed DNA alkylation of quinocarcin (1)

It was believed by Williams et al. that *syn* quinocarcin analog **27** would be expected to alkylate DNA in accordance with the modeling studies reported by Remers. However, no DNA alkylation was observed with **27**¹⁶, the *epi* neutropsin analog (**30**), or the *epi* phenol analog (**31**) (Figure 4). The possible reasons for this were first, the gem-dimethyl group might be too bulky to allow for DNA to approach and to be alkylated and second, the alkylation might be reversible due to displacement of the DNA by the amine lone pair.

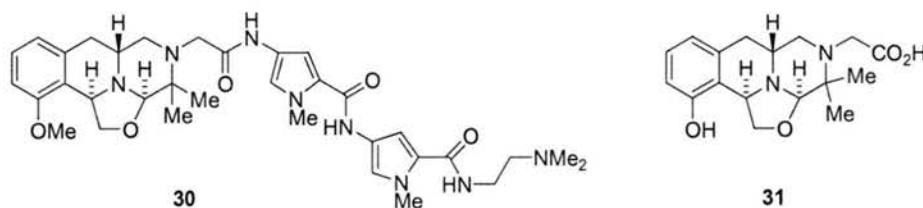


Figure 4 *epi*-Neutropsin analog (**30**) and *epi*-phenol analog (**31**)

The semi synthetic quinocarcin analogues were prepared and studied at Kyowa Hakko Kogyo Company. All of the analogues were tested in vitro against the HeLa S3 cell line along with in vivo studies against P388 leukemia. The biological activity studies of those analogues have shown¹⁷ that: 1) oxazolidine-containing analogues displayed superior activity over that for the E-ring-opened analogues; 2) presence of the free phenol in place of the methoxy constituent lowered the activity;^{16a} 3) quinone analogues showed reduced biological activities. 4) thioalkyl quinone analogues showed some increased activity. The analogues synthesized by Terashima et al. showed interesting biological activities and some of these compounds displayed increased biological activity over that for quinocarcin against P388 murine leukemia.¹⁸ Among them **32** (Figure 5) had the best activity by far ($IC_{50} = 1.0 \times 10^{-5} \mu\text{g/mL}$), exhibiting approximately 2 orders of magnitude higher potency than quinocarcin (**1**) ($IC_{50} = 3.3 \times 10^{-2} \mu\text{g/mL}$).

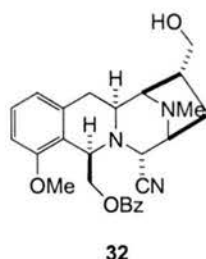


Figure 5 Terashima's quinocarcin analog **32**

1.1.2 Tetrazomine

Tetrazomine (**33**, Figure 6) was isolated at Yananouchi Pharmaceutical Company in Japan from *Saccharothrix mutabilis* sub-sp. *chichijimaensis* in 1991.¹⁹ The structure was

determined by NMR spectroscopy by the Hirayama group, but not the relative and absolute stereochemistry.²⁰ The relative and absolute stereochemistry of the 3-hydroxy pipercolic acid moiety was determined by Williams et al. in 1998.²¹ The total synthesis of (-)-tetrazomine by Williams et al. in 2001 secured both the relative and absolute stereochemistry of the natural product and is that depicted in Figure 6.²² **33** Has the same tetracyclic core and the oxazolidine ring as quinocarin (**1**). The structure similarity results in a similar mechanism of action of **33** and quinocarin (**1**), which will be discussed later in this chapter (Scheme 8).

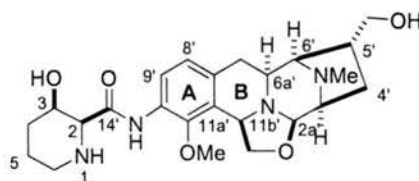


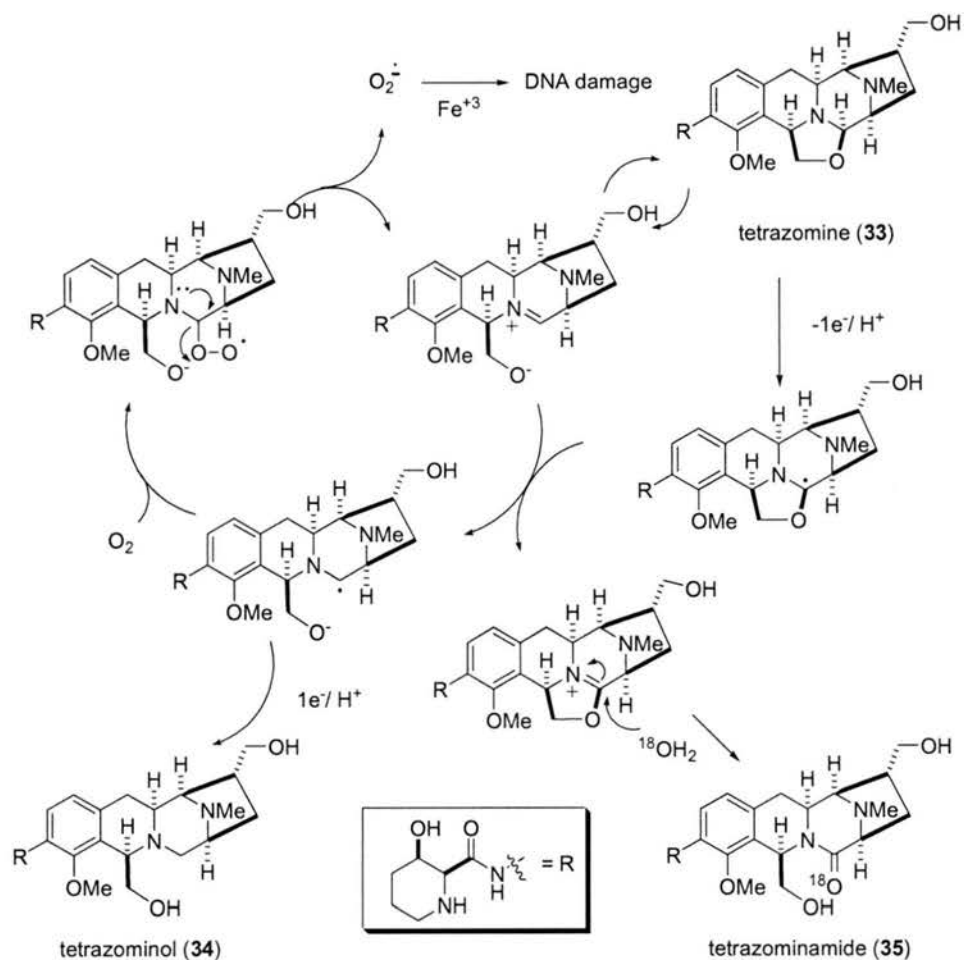
Figure 6 Tetrazomine (**33**)

Preliminary antitumor and antimicrobial assays of tetrazomine revealed that tetrazomine possesses good antimicrobial active against both Gram-(+) and Gram-(-) bacteria as illustrated in Table 2.¹⁹ It also showed that tetrazomine is active against P388 leukemia and L1210 leukemia with IC_{50} value of 0.014 and 0.0427 $\mu\text{g/mL}$ respectively. An *in vivo* study showed that tetrazomine has activity against P388 leukemia.¹⁹

Table 2 Antimicrobial activities of tetrazomine

Test organisms	MIC ($\mu\text{g/mL}$)
<i>Bacillus subtilis</i> ATCC 6633	6.25
<i>Staphylococcus aureus</i> FDA 209P JC-1	6.25
<i>Staphylococcus epidermidis</i> IID 866	25
<i>Streptococcus pyogenes</i> Cook	0.78
<i>Enterococcus faecalis</i> IID 682	6.25
<i>Enterococcus faecium</i> CAY 09-1	3.13
<i>Mycobacterium smegmatic</i> ATCC 607	12.5
<i>E. coli</i> NIHJ	1.56
<i>Citrobacter freundii</i> CAY 17-1	0.78
<i>Klebsiella pneumoniae</i> ATCC 10031	3.13
<i>Proteus vulgaris</i> OXK US	3.13
<i>Pseudomonas aeruginosa</i> NCTC 10490	6.25
<i>Pseudomonas aeruginosa</i> ATCC 8689	50

Williams et al. showed that tetrazomine (**33**), like quinocarcin (**1**), underwent a self-redox reaction to produce superoxide that can cleave DNA in a nonspecific manner (Scheme 8).²³ In a carefully deoxygenated environment, tetrazomine spontaneously disproportionated above neutral pH to give the Cannizzarro-type products tetrazominol (**34**) and tetrazominamide (**35**). Reduction of natural tetrazomine could furnish an authentic specimen of **34**. The structural assignment for **35** was based primarily on the exact mass spectrum for this material.



Scheme 8 Mechanism of superoxide formation mediated by tetrazomine (33)

Similar to quinocarcin, under aerobic conditions, the rate of superoxide formation by tetrazomine was found to be pH-dependent, with the highest rate occurring about pH 8 (Table 3). The DNA cleavage by tetrazomine, which was inhibited by addition of SOD, was not affected by the addition of Fe^{2+} and Fe^{3+} and was inhibited by addition of desferal at very high concentrations.

Table 3 Rate of superoxide formation for tetrazomine (**33**), quinocarcin (**1**) and analogs

Substrate	Concentration (mM)	pH	rate ($\text{M}^{-1}\text{s}^{-1} * 10^{-9}$)
33	1.0	6.0	2.46
33	1.0	7.0	10.6
33	1.0	8.0	17.5
1	1.0	8.0	11
26 (Figure 2)	1.0	8.0	0.41
27 (Figure 2)	1.0	8.0	0
DX-52-1 (3)	1.0	8.0	0

Williams and Scott reported the antimicrobial activity of a series of tetrazomine analogues against a Gram-(+) bacteria (*Staphylococcus aureus*) and Gram-(-) bacteria (*Klebsiella pneumoniae*).²¹ The analogues that had the same absolute stereochemistry as the natural product were much more active than those analogues containing the *ent*-tetrahydroisoquinoline core. Also, the antimicrobial activities for the aminonitriles were similar to that of the corresponding oxazolidine-containing analogues.

1.1.3 Lemonomycin

Lemonomycin (**36**, formerly called LL-AP191, Figure 7) was first isolated in 1964 from the culture broth of a strain of *Streptomyces candidus*, by a process consisting of solvent extraction, carbon absorption, and precipitation from acetone-water²⁴.

Lemonomycin precipitated appears as lemon-yellow powder, and lemonomycin hydrochloride as yellow-green powder.

Although the production, isolation, and antibacterial activity were described in this early research, the structure of lemonomycin was not disclosed until 2000²⁵. As part of a continuous program to discover new agents to overcome increasing resistance in antimicrobial chemotherapy, researchers at Wyeth-Ayerst reexamined lemonomycin and characterized its structure as **36** by using spectroscopic methods.

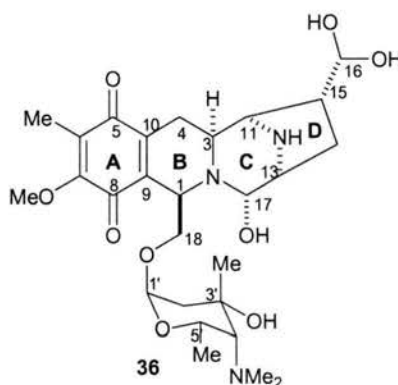


Figure 7 Lemonomycin (**36**)

36, Having the 6-methyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline-5,8-dione substructure, is a member of the tetrahydroisoquinoline family of antitumor antibiotics. Lemonomycin's structure is more related to the quinocarcin (**1**)/ tetrazomine (**33**) family, having the tetracyclic ring system containing a pyrrolidine portion, but with a fully substituted quinone moiety. The unique aspect of lemonomycin's structure is the 2,6-dideoxy-4-amino sugar attached at C-18, which is rare in nature²⁶ and is encountered the

first time in this family among nearly 60 natural products and hundreds of synthetic analogues.

Study has shown that lemomycin is a potent broad-spectrum antibiotic. It has antibacterial activity *in vitro* against both Gram-(+) and Gram-(-) bacteria (Table 4). It is quite potent against a series of staphylococci and streptococci when compared with tetracycline (A), penicillin G (B) and erythromycin (C) (Table 5).

Table 4 *In vitro* antibacterial spectrum of lemomycin

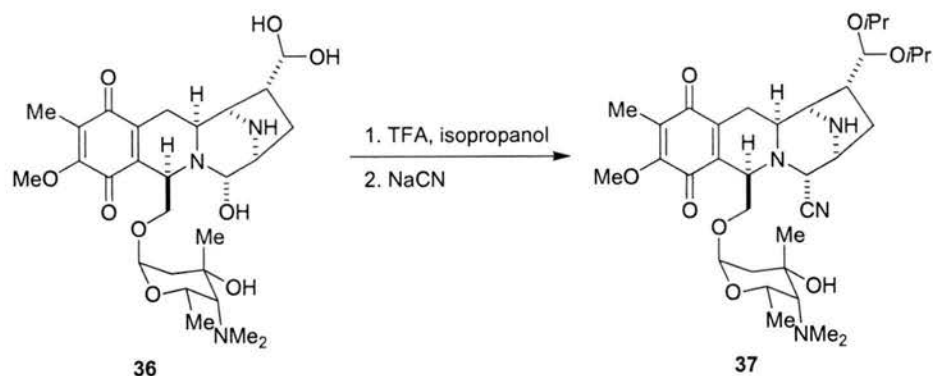
Organism	MIC ($\mu\text{g/mL}$) *
<i>Mycobacterium smegmatis</i> ATCC 607	6.2
<i>Staphylococcus aureus</i> ATCC 6548P	0.2
<i>Streptococcus faecalis</i> ATCC 8043	0.4
<i>Bacillus subtilis</i> ATCC 6633	0.05
<i>Pseudomonas fluorescens</i> ATCC 12633	1.6
<i>Protues vulgaris</i> ATCC 9484	0.4
<i>Escherichia coli</i> ATCC 9637	1.6
<i>Salmonella gallinarum</i> (Lederle 604)	0.8
<i>Clostridium sporogenes</i> ATCC 7955	>100

Minimal inhibitory concentration determined by agar dilution-streak method

Table 5 Comparison of lemomycin and tetracycline (A), penicillin G (B) and erythromycin (C) against various staphylococci and streptococci

Organism	MIC ($\mu\text{g/mL}$) *			
	Lemonomycin	A	B	C
<i>Staphylococcus aureus</i> (Lederle 4050B-122-7)	0.08	10	>100	1.5
<i>S. aureus</i> (Lederle 4050B-122-10)	0.15	>100	>100	3
<i>S. aureus</i> (Lederle 4050B-122-13)	0.15	2.5	0.08	3
<i>S. aureus</i> (Lederle 4050B-122-14)	0.15	>100	0.04	3
<i>S. aureus</i> Rose ATCC 14154	0.15	>100	>100	12.5
<i>S. aureus</i> Smith	0.04	2.5	0.8	1.5
<i>Streptococcus faecalis</i> ATCC 8043	0.4	2.5	2.5	0.4
<i>S. pyogenes</i> C203	<0.005	1.2	0.001	0.2
<i>S. pyogenes</i> (Lederle 8053B-40-2)	0.01	25	0.01	0.4
<i>S. pyogenes</i> (Lederle 8053B-40-3)	0.01	100	0.01	0.4
<i>S. Pyogenes</i> NY5	<0.005	2.5	0.01	0.4
<i>Streptococcus</i> sp. λ -Strep. 11	5.0	>100	2.5	1.5
<i>Streptococcus</i> sp. λ -Strep. 80	2.5	>100	2.5	1.5

Researchers at Wyeth-Ayerst reported lemomycin's antibiotic activity against a variety of antibiotic-resistant bacterial strains. The MIC of lemomycin was measured to be 0.4 and 0.2 $\mu\text{g/mL}$ for methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium* respectively. In addition to the antibiotic activity, lemomycin and its derivative **37** (Scheme 9) also showed *in vitro* activity against a human colon tumor cell line (HCT116) and their respective IC_{50} 's were measured as 0.36 and 0.26 $\mu\text{g/mL}$.

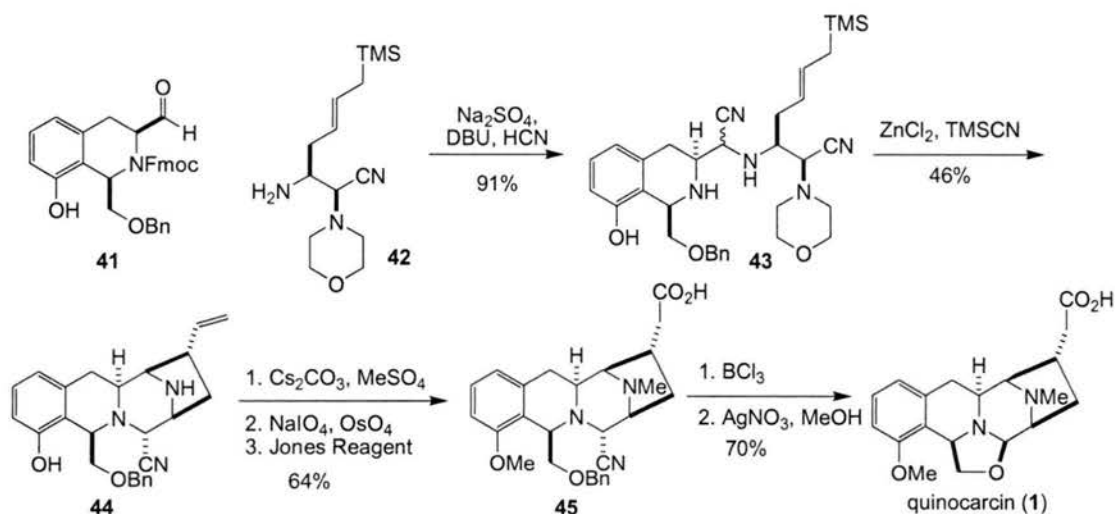


So far there are no studies of the mechanism of action of lemonmycin reported.

Since the first synthesis of ($\pm$)-quinocarcinol by Danishefsky et al. in 1985, extensive study has been made in the synthesis of the quinocarcin family of natural products. Williams and Scott's review article¹ has covered the synthetic work of the quinocarcin family before the year 2002. This edition will cover several more synthetic studies of quinocarcin family since 2002. It will also discuss different strategies toward construction of D ring and AB ring system in the general tetracyclic core.

1.2.1 Recent Progresses

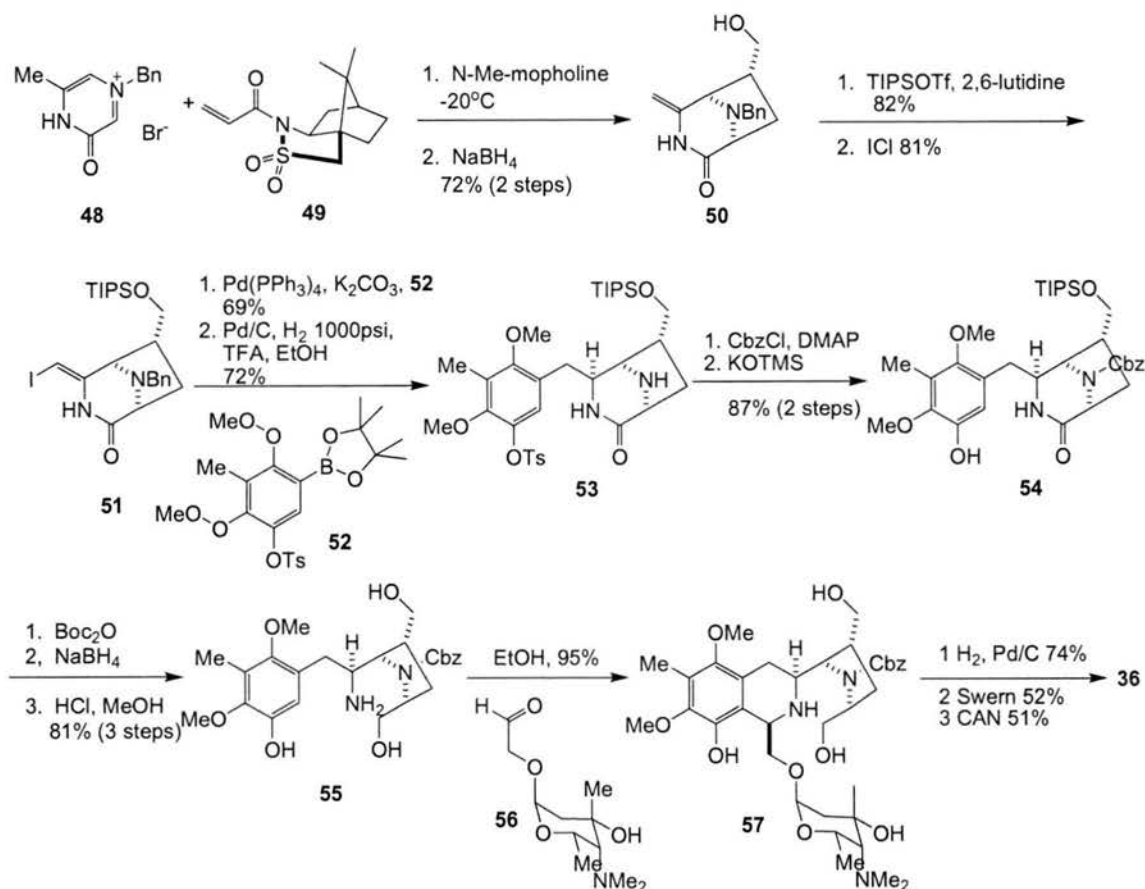
In 2005, Myers et al. extended their approach of direct condensation of α -amino aldehyde derivatives used in the synthesis of (-)-saframycin A to the synthesis of (-)-quinocarcin (**1**) (Scheme 10).²⁷ Condensation of the known compounds **41** and **42** in presence of sodium sulfate afforded the corresponding imine. Without isolation, the imine intermediate was treated with DBU followed by methanolic hydrogen cyanide leading to Strecker product **43** in 91% yield. Treatment with zinc chloride in the presence of trimethylsilyl cyanide afforded the cyanopiperazine intermediate **44** in 46% yield. Bismethylation followed by oxidative cleavage of the olefin and further oxidation afforded carboxylic acid **45** in 64% yield. Debenzylation using boron trichloride, followed by treatment with silver nitrate in aqueous methanol completed the conversion to **1** in 70% yield.



Scheme 10 Myers' total synthesis of quinocarcin (**1**)

So far there is only a single report of the synthesis of (-)-lemonomycin (**36**), which was carried out by Stoltz et al.²⁸ and two synthetic studies published by Fukuyama²⁹ and Magnus respectively³⁰.

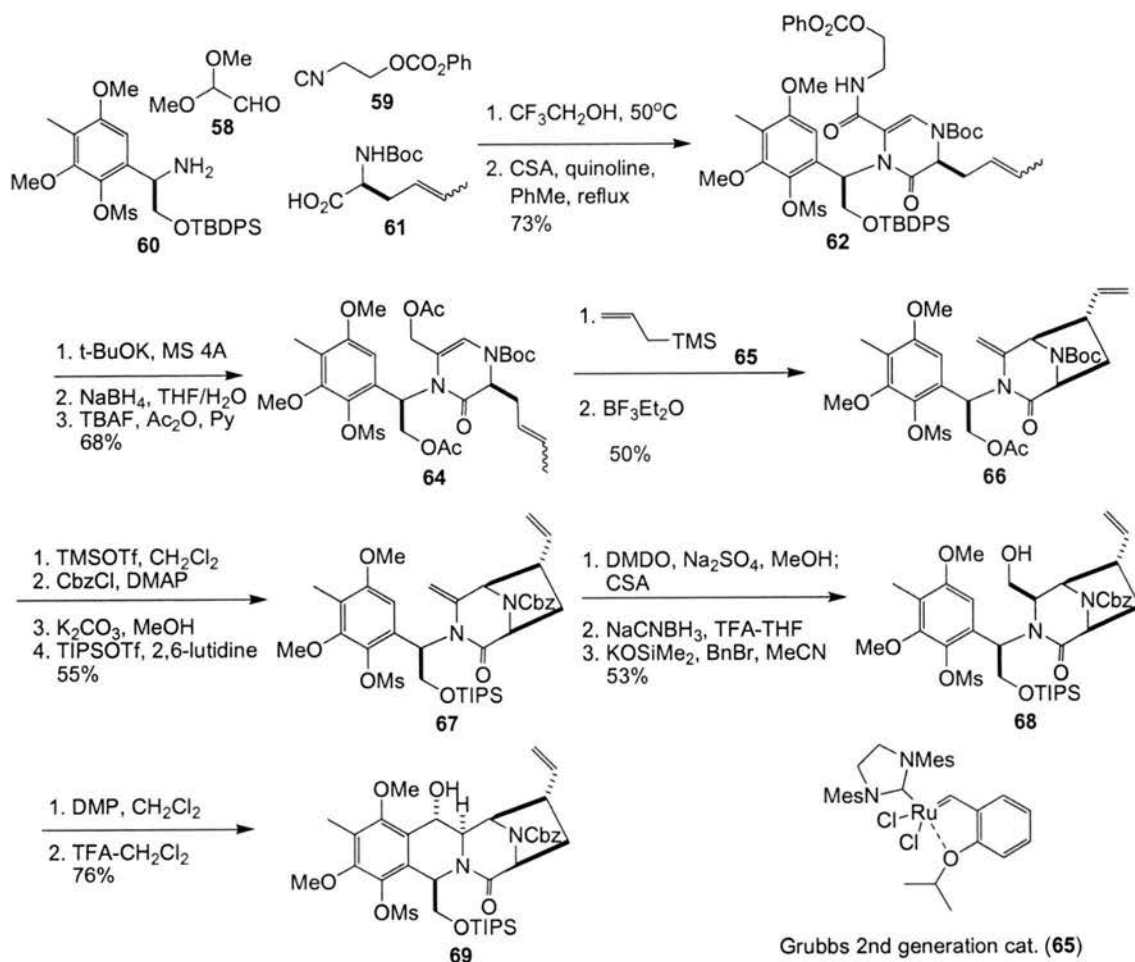
Stoltz et al. completed the total synthesis of **36** in 2003 (Scheme 11).²⁸ Their synthesis features a dipolar cyclization using oxidopyrazinium salt **48** and Oppolzer sultam-derived acrylamide **49** to produce a cycloadduct, which upon treatment with NaBH₄ in EtOH provided alcohol **50** in 72% yield and 94% ee. After protection of the free hydroxyl functionality as a silyl ether, iodination produced Z-iodoenamide **51** as a single isomer. Suzuki coupling of iodide **51** with boronic ester **52** afforded aryl enamide, which upon hydrogenation under 1000 psi generated **53** in 72% yield. Protection of the secondary amine using CbzCl followed by liberation of the phenol by KOTMS, yielded amide **54** in 87%. Activation of the amide with Boc₂O, with concomitant protection of the phenol, allowed the amide in **54** to be reduced by NaBH₄. After removal of the Boc groups and the TIPS ether by methanolic HCl, compound **55** generated in 81% yield. Pictet-Spengler cyclization of **55** with **56** generated **57** as a single diastereomer in 95% yield. Hydrogenolytic cleavage of the Cbz group, a double Swern oxidation and treatment with CAN provided **36**.



Scheme 11 Stoltz's total synthesis of (-)-lemonomycin (**36**)

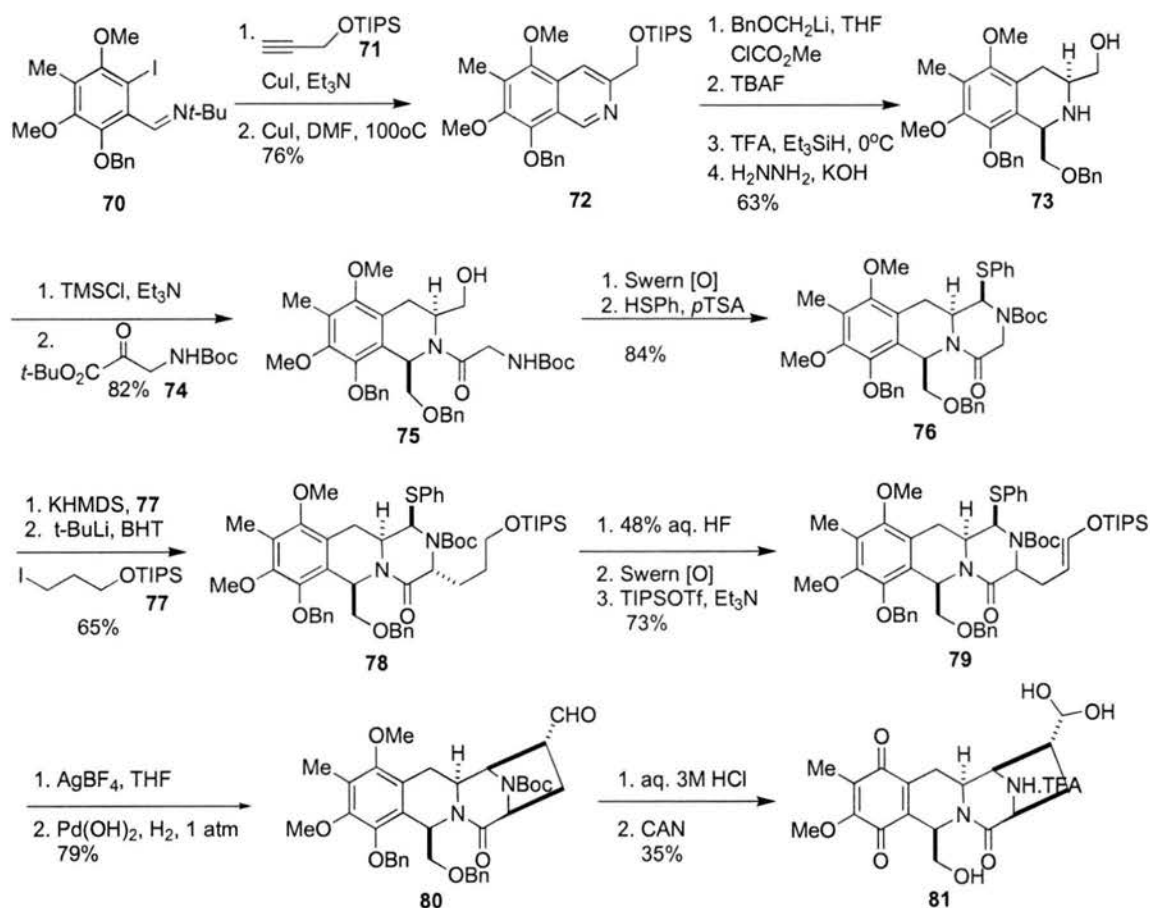
Fukuyama et al. reported their synthetic studies on **36** in 2003 (Scheme 12).²⁹ An Ugi four component condensation of **58-61** afforded a dipeptide, which was then transformed to the cyclic enamide **62** by treatment with CSA. Upon treatment with *t*-BuOK, the oxazolidinone was formed smoothly and was then reduced to the corresponding alcohol. Removal of the TBDPS ether and protection as acetate furnished **64** in 68% yield. Cross-metathesis of **64** and allyltrimethylsilane (**66**) in the presence of Grubbs 2nd generation catalyst (**65**) generated the cyclization precursor in 51% yield. Upon treatment with $\text{BF}_3 \cdot \text{Et}_2\text{O}$, generation of the conjugated acyliminium cation and

subsequent cyclization of the allylsilane moiety proceeded immediately to provide **66** with complete stereoselectivity in almost quantitative yield. After exchange of the protecting group from Boc to Cbz and from acetate to TIPS ether, **67** was generated in 55% yield. DMDO oxidation of **67**, ionic reduction of the acyliminium ion, followed by treatment with KOSiMe₃ and BnBr furnished the benzyl ether **68** in 53% yield. After oxidation of the alcohol **68** with Dess-Martin periodinane, treatment of the resulting aldehyde with TFA induced the desired cyclization to afford **69**.



Scheme 12 Fukuyama's synthetic studies on (-)-lemonomycin (**36**)

In 2005 Magnus et al. reported their synthesis of the glycon portion of ($\pm$)-lemonomycin (Scheme 13).³⁰ A modified Larock isoquinoline synthesis using *o*-isoimine **70** and acetylene **71** generated the isoquinoline **72** in 76% yield. Treatment of **72** with benzyl oxymethyl lithium and quenching with methyl chloroformate, followed by addition of TBAF, generated an oxazolidinone dihydrosioquinoline derivative. This was reduced by ionic hydrogenation giving 1,3-*cis*-substituted tetrahydroisoquinoline, which was then hydrazinolized to amino alcohol **73** in 63% yield. The amine **73** was coupled as its TMS ether with mixed anhydride **74**. The silyl ether was then removed upon acidic workup giving **75** in 82% yield. Swern oxidation of **75** generated a hemiaminal, which was converted to thioaminal **76** as a single diastereomer. Alkylation of **76** with iodide **77** gave a single diastereomer, which could be epimerized to the desired isomer **78** with minimal degradation. After removal of the silyl ether, followed by oxidation of the resulting alcohol to aldehyde, a silyl enol ether formation generated the cyclisation precursor **79**. The *N*-acyliminium cyclization was promoted with thiophilic AgBF₄, providing aldehyde **80** as a single diastereomer. After removal of the benzyl ether and the Boc group on nitrogen, oxidation of phenol with CAN finished the ($\pm$)-lemonomycinone amide **81**.



Scheme 13 Magnus' total synthesis of (±)-lemonomycinone amide **81**

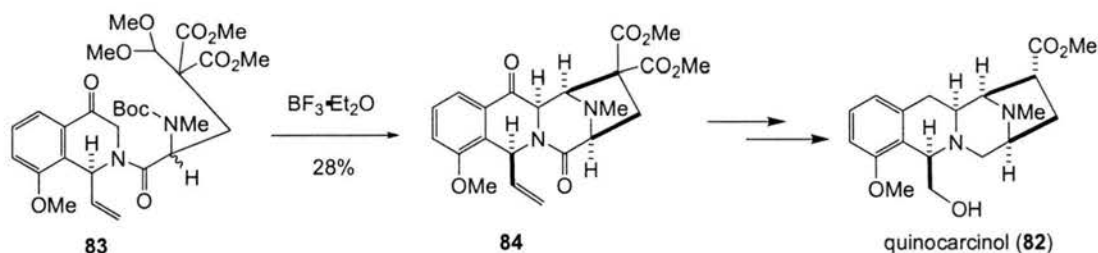
1.2.2 Strategic Analysis

In these previously reported synthetic studies of the quinocarcin family of natural products, much of the effort has been focused on the construction of the pyrrolidine unit, the D ring, and the tetrahydroisoquinoline unit (AB ring system).

1.2.2.1 D Ring Construction

Three general methods for constructing the D ring have appeared in the literature, *N*-acyliminium/iminium cyclization, dipolar cyclization and functionalization of pyrrolidine derivatives.

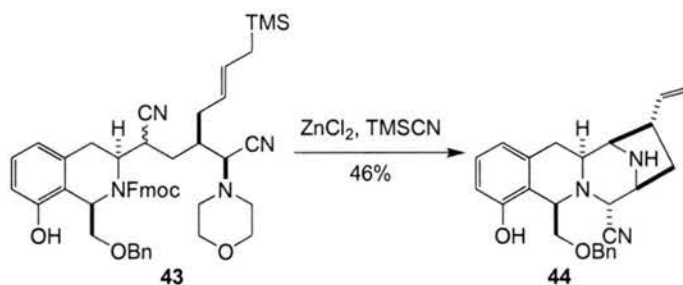
In the synthesis of (±)-quinocarcinol (**82**) in 1985, Danishefsky et al. employed the first iminium ion cyclization (Scheme 14) to install the pyrrolidine unit.³¹ Treatment of ketone **83** with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ liberated the secondary amine and the aldehyde. The consequent condensation generated the iminium ion, which then cyclized with the activated ketone functionality to form the tetracycle **84** in 28%, as only one of the possible four diastereomers.



Scheme 14 Danishefsky's iminium ion cyclization

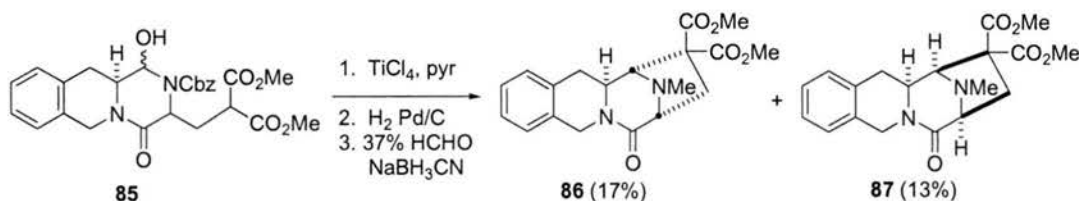
20 Years after Danishefsky's synthesis, Myers et al. set the second example of applying iminium ion cyclization to construct the pyrrolidine unit in the total synthesis of (-)-quinocarcin (**1**) (Scheme 15).²⁷ Treatment of the bis-amino nitrile **43** with zinc chloride generated a piperazine iminium ion intermediate, which subsequently cyclized with the allylsilane moiety giving the pyrrolidine **44** in 46% yield as the desired stereoisomer. The

sequence of bicyclization involving initial formation of the C-ring followed by formation of the D-ring proved to be critical to achieving proper stereochemistry of the D-ring.



Scheme 15 Myer's iminium ion cyclization (Scheme 9)

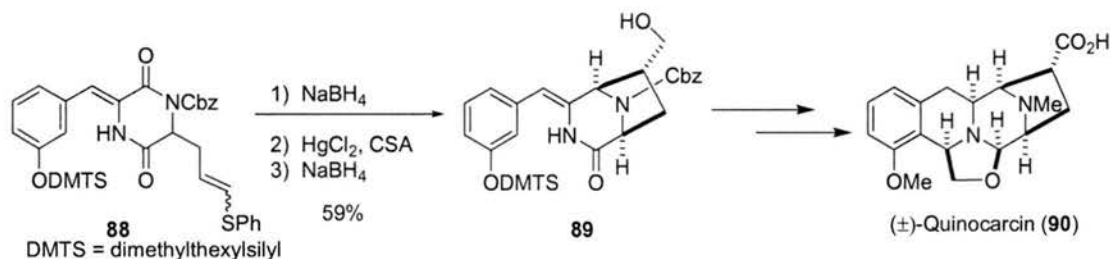
The first *N*-acyliminium cyclization was reported in Saito and Hirata's synthetic study toward quinocarcin in 1987 (Scheme 16). Malonate **85** cyclized in an intramolecular fashion via an *N*-acyliminium ion, which was generated by treatment of **85** with titanium tetrachloride.³² Subsequent Cbz removal and *N*-methylation afforded the two diastereoisomers **86** and **87** in comparable yields.



Scheme 16 Saito and Hirata's *N*-acyliminium ion cyclization

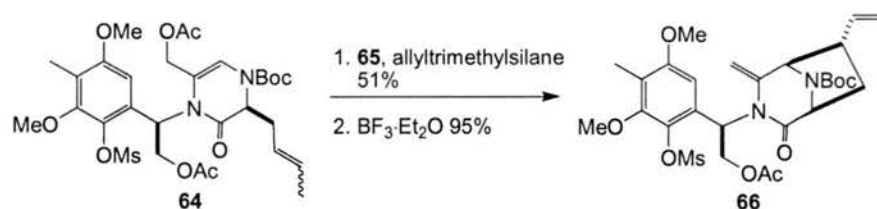
Following Saito and Hirata, Fukuyama employed *N*-acyliminium ion-mediated cyclization for the total synthesis of ($\pm$)-quinocarcin (**90**) in 1988 (Scheme 17).³³ After

reduction of the activated lactam **88**, HgCl₂ and CSA (camphorsulfonic acid) promoted the thio-enol to cyclize with the resulting *N*-acyliminium ion to form the bicyclic compound **89** in 59% yield.



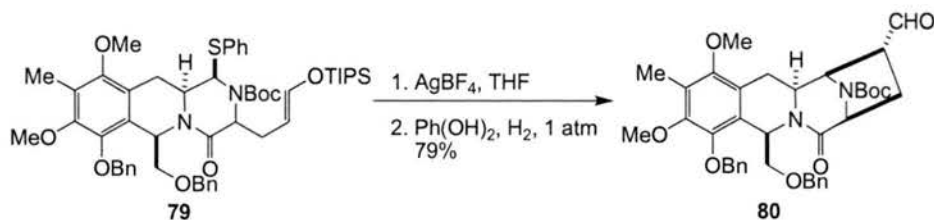
Scheme 17 Fukuyama's *N*-acyliminium ion cyclization

Most recently, Fukuyama et al. in their synthetic studies toward (-)-lemonomycin (**36**) constructed the pyrrolidine ring utilizing a conjugated *N*-acyliminium ion, which was generated by treatment of the RCM product of **64** with BF₃·Et₂O.²⁹ The subsequent cyclization of the allylsilane moiety generated **66** with complete stereoselectivity in almost quantitative yield (Scheme 18).



Scheme 18 Fukuyama's *N*-acyliminium ion cyclization

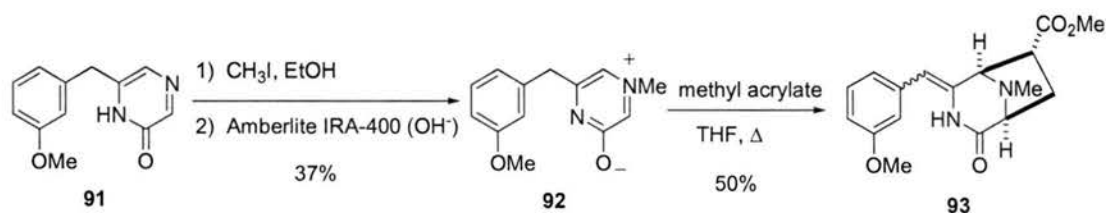
Magnus et al. in their synthesis of the aglycon portion of ($\pm$)-lemonomycin applied an *N*-acyliminium cyclization to substrate **79** promoted with thiophilic AgBF_4 . After the *N*-acyliminium ion formation, it cyclized with the silyl enol moiety to generate the pyrrolidine **80** as a single diastereoisomer (Scheme 19).³⁰



Scheme 19 Magnus' *N*-acyliminium ion cyclization

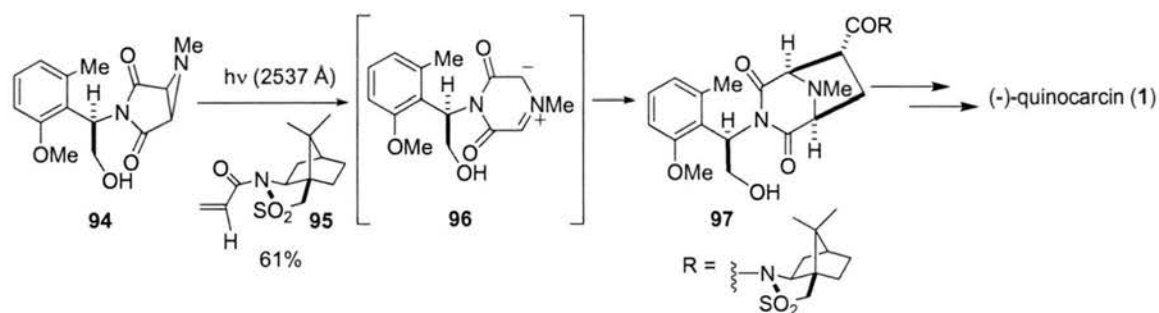
The other widely used method for constructing the pyrrolidine unit is 1,3-dipolar cycloaddition. A variety of ways for generating the azomethine ylide have been explored in the synthesis of quinocarcin family of natural products.

In 1990, Joule et al. first reported their 1,3-dipolar cyclization approach to quinocarcin (Scheme 20).³⁴ An oxidopyrazinium salt **92** was generated from **91** by quaternization followed by deprotonation. After dipolar species **92** was trapped with methyl acrylate, the cycloadduct **93** was obtained in 50% yield with the desired relative stereochemistry on the pyrrolidine ring.



Scheme 20 Joule's 1,3-dipolar cyclization

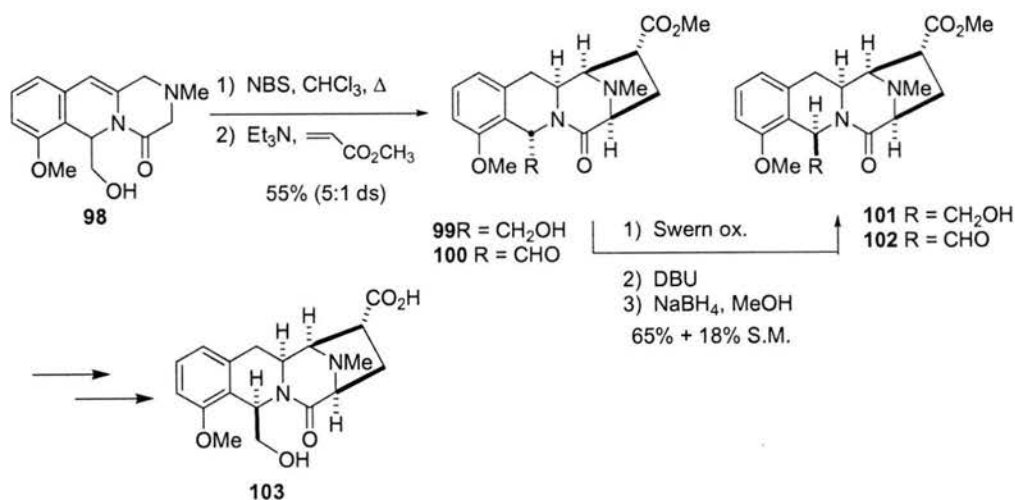
In the first asymmetric synthesis of (-)-quinocarcin (**1**) in 1992, Garner et al. utilized the azomethine ylide **96** formed via irradiation of aziridine **94** (Scheme 21).³⁵ When trapped with Oppolzer's sultam **95**, it afforded the desired bicyclic cycloadduct **97** in 61% yield via an *exo-si* attack on the olefin.



Scheme 21 Garner's 1,3-dipolar cyclization

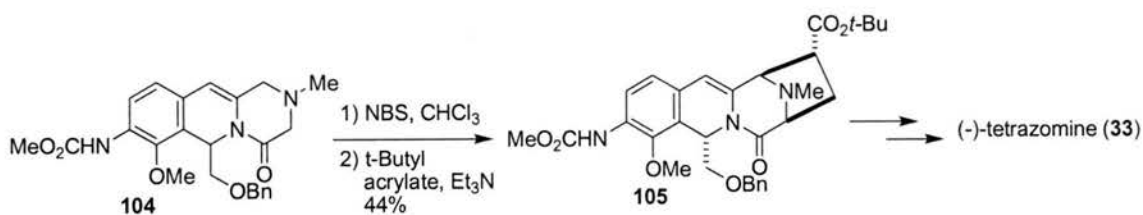
In 1995, Williams et al. utilized a 1,3-dipolar cycloaddition in the synthesis of (±)-quinocarcinamide (**103**) (Scheme 22).³⁶ The azomethine ylide was generated by NBS oxidation of the allylic amine **98** followed by deprotonation using triethylamine. After trapping with methyl acrylate, the cycloadducts **99** and **101** were formed in a 5:1 ratio

with desired relative stereochemistry on the pyrrolidine ring. Epimerization of the C-1 center was required at a later stage.



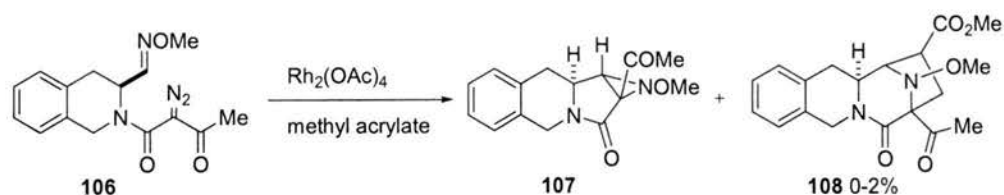
Scheme 22 Williams' 1,3-dipolar cyclization

The same methodology was applied to the total synthesis of (-)-tetrazomine (**33**) in 2001 (Scheme 23).²² When *t*-butyl acrylate was employed, the 1,3-dipolar cyclization of the azomethine ylide generated from **104** afforded the cycloadduct **105** in improved diastereoselectivity.



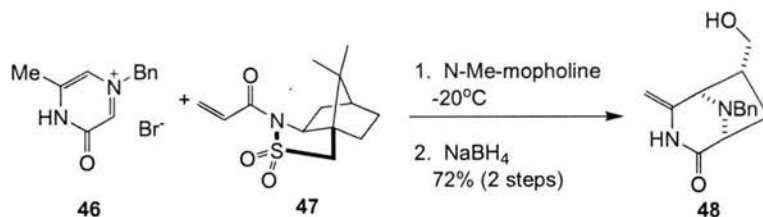
Scheme 23 Williams' 1,3-dipolar cyclization

In 1996, McMills et al. attempted to form an azomethine ylide via a rhodium-catalyzed carbene cyclization (Scheme 24).³⁷ Unfortunately, upon treatment of **106** with the rhodium catalyst, the desired tetracycle **108** could only be detected in very small amounts. Aziridine **107** was the major product in all attempts. Further investigation of this reaction is needed on photolytic opening of the aziridine ring to the azomethine ylide as well as extension to substrates with differentially substituted diazo-moieties and other C=N species such as imines, hydrazones and silylimines.



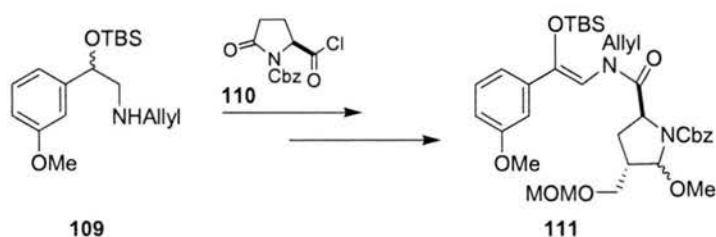
Scheme 24 McMills' 1,3-dipolar cyclization

Most recently, Stoltz et al. developed Joule's 1,3-dipolar cycloaddition for the total synthesis of (-)-lemonomycin in 2003.²⁸ In situ generation of oxidopyrazinium salt by deprotonation of bromide salt **46** followed by treatment of Oppolzer sultam-derived acrylamide **47** afforded the cycloadduct **48** in 72% yield and 94% ee (Scheme 25).



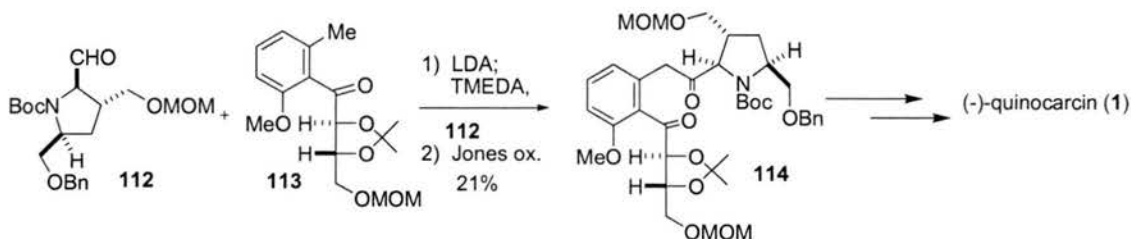
Scheme 25 Stoltz's 1,3-dipolar cyclization

To construct the pyrrolidine moiety, some efforts also were made towards functionalizing pyrrolidine derivatives. Weinreb et al. reported their synthetic studies on quinocarin in 1990 (Scheme 26).³⁸ A functionalized pyrrolidine **111** was synthesized from coupling the acid chloride **110** with allyl amine **109**. The acid chloride **110** was converted from L-glutamic acid.



Scheme 26 Weinreb's pyrrolidine derivative functionalization

Terashima et al. in their synthesis of (-)-quinocarin (Scheme 27),³⁹ converted L-glutamic acid to a fully functionalized pyrrolidine **112** bearing all the desired stereochemistry, which was then coupled to the aromatic unit **113** at later stage.

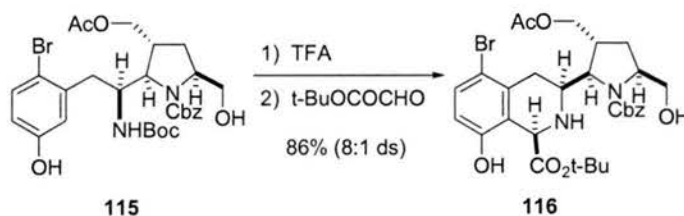


Scheme 27 Terashima's pyrrolidine derivative functionalization

1.2.2.2 AB Ring Construction

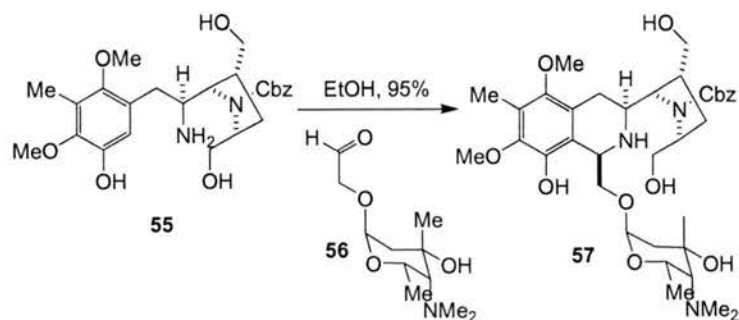
Construction of the tetrahydroisoquinoline unit (the AB ring system), is another key to the synthesis of the quinocarcin family of natural products.

For closure of the B ring, the Pictet-Spengler reaction is one of the most widely employed methods in the synthesis of the tetrahydroisoquinoline moiety as it enables the C-1 center to be generated in a stereoselective manner. In the quinocarcin family of natural products, it has been first applied in Fukuyama's total synthesis of ($\pm$)-quinocarcin. After removal of the Boc group on substrate **115**, the resulting TFA salt was converted to tetrahydroisoquinoline **116** in 86% yield as 8:1 mixture favoring the *cis*-isomer (Scheme 28).³³



Scheme 28 Fukuyama's Pictet-Spengler reaction

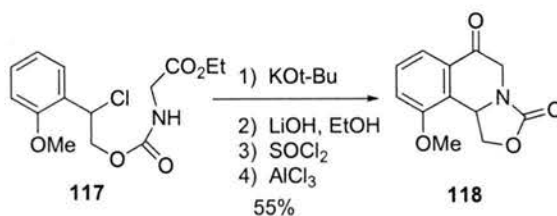
In Stoltz's total synthesis of (-)-lemonomycin in 2003, the TFA salt of primary amine **55** was cyclized to give tetrahydroisoquinoline **57** in 95% yield as a single diastereomer (Scheme 29).²⁸



Scheme 29 Stoltz's Pictet-Spengler reaction

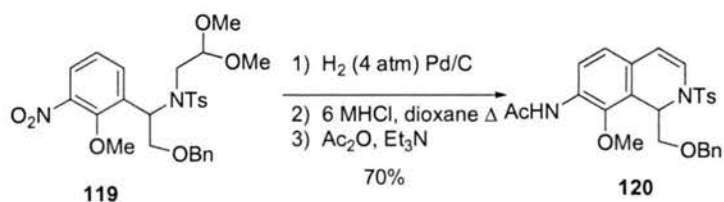
Later in Myers' total synthesis of (-)-quinocarcin, *cis*-tetrahydroisoquinoline **41** was again derived from a primary amine using the Pictet-Spengler reaction (Scheme 29).³⁰

Aromatic electrophilic alkylation is another general method applied for closure of the B ring. A Freidel-Crafts reaction was employed in Williams' total synthesis of ($\pm$)-quinocarcinamide to generate isoquinoline **118** via an acid chloride derived from **117** (Scheme 30).³⁶

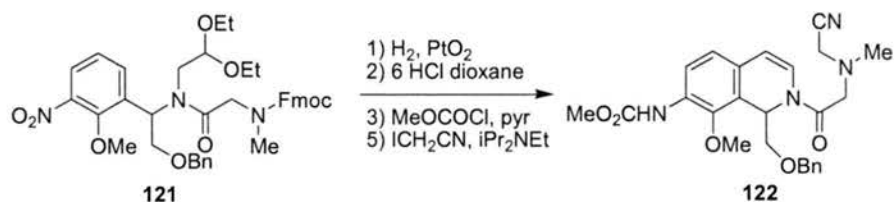


Scheme 30 Williams's Freidel-Crafts reaction

A modified Pomeranz-Fritsch reaction has been utilized in Kaufman's synthesis of the AB ring system of tetrazomine (Scheme 31)⁴⁰ and Williams' total synthesis of (-)-tetrazomine (Scheme 32)²² to generate dihydroisoquinoline **120** and **122** respectively.

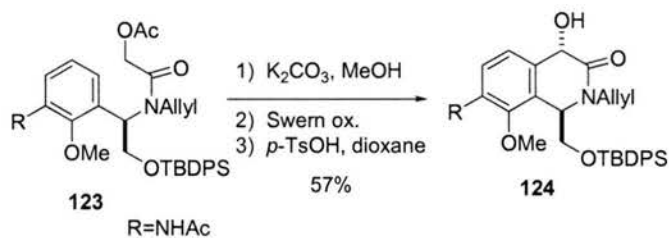


Scheme 31 Kaufman's modified Pomeranz-Fritsch reactions

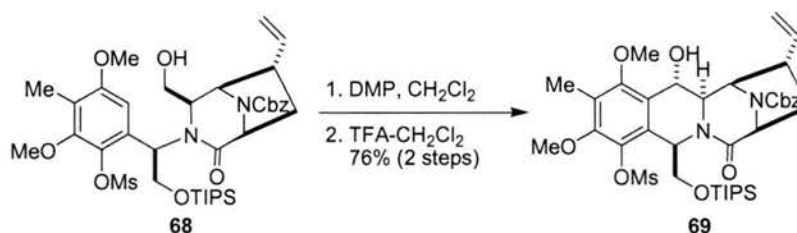


Scheme 32 Williams' modified Pomeranz-Fritsch reactions

Similarly secondary alcohols **124**, and **69** were generated by modified Pomeranz-Fritsch reaction by using the corresponding aldehydes in Wipf's synthesis of an optically active AB-ring system of tetrazomine (Scheme 33) and Fukuyama's synthetic studies on (-)-lemonomycin (Scheme 34), respectively.²⁹

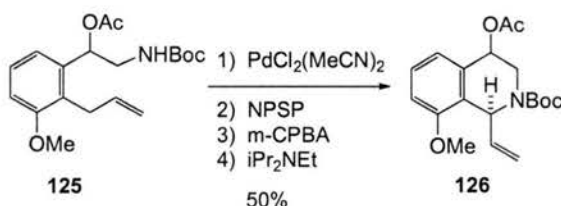


Scheme 33 Wipf's modified Pomeranz-Fritsch reactions

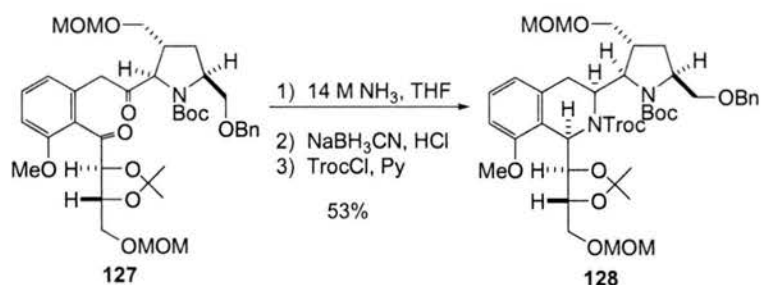


Scheme 34 Fukuyama's modified Pomeranz-Fritsch reactions

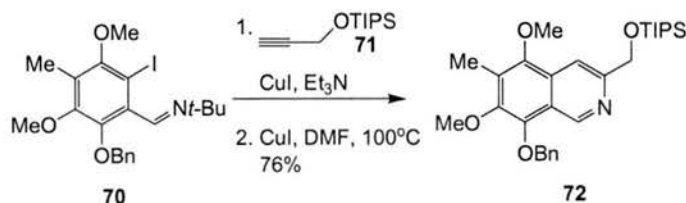
Other methods for closure of the B ring includes Danishefsky's intramolecular *N*-alkylation using an alkyl selenium compound derived from **125** (Scheme 35).⁴¹ Condensation of ammonia with aromatic ketone **127** was employed in Terashima's total synthesis of (-)-quinocarcin (Scheme 36).¹⁸ More recently, a Larock isoquinoline synthesis to afford **72** in Magnus' total synthesis of (±)-lemonomycinone analogue was carried out (Scheme 37).³⁰



Scheme 35 Danishefsky's intramolecular *N*-alkylation



Scheme 36 Terashima's condensation



Scheme 37 Magnus' modified Larock isoquinoline synthesis

With extensive synthetic studies of the quinocarcin family of natural products reported, different strategies towards the tetracyclic core construction were discussed in this section. *N*-acyliminium/iminium cyclization and dipolar cyclization have proven to be quite efficient strategies to construct the pyrodilene ring, D ring. Functionalization of a pyrrolidine derivative has also been utilized in the total synthesis of the natural products. Traditional methods of tetrahydroisoquinoline formation, such as the Pictet-Spengler reaction and a modified Pomeranz-Fritsch cyclization, have also often been used in the synthesis of this family of natural products. New approaches employed in this area include Stoltz's Suzuki coupling for connection of the A and B ring and Magnus' modification of Larock's dihydroisoquinoline synthesis.

CHAPTER 2

Efforts Towards the Total Synthesis of (-)-Lemonomycin

2.1 Objectives

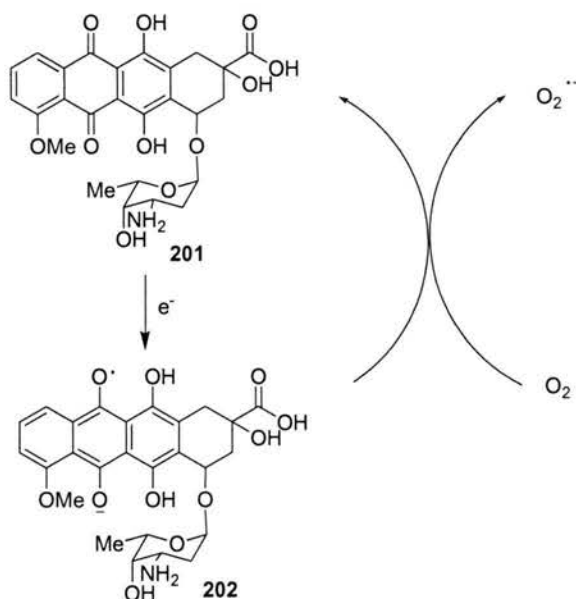
2.1.1 Study of Mechanism of Action of (-)-Lemonomycin

As described in chapter 1, lemonomycin (**36**) is a potent broad-spectrum antibiotic. Lemonomycin **36** and its derivative **37** (Scheme 9) also showed *in vitro* activity against the human colon tumor cell line (HCT116) and their respective IC₅₀'s were measured as 0.36 and 0.26 µg/mL. Despite this, there have been no studies on the mechanism of action of **36**.

One of the goals of the project is to study the mechanism of action of lemonomycin. It has been shown in the Williams' lab that the mechanism of action for quinocarcin (**1**) and tetrazomine (**33**) involves a self-redox disproportionation reaction to produce superoxide that can cause cleavage of DNA in a nonspecific manner (Scheme 5 and 8).¹³ ²³ The oxazolidine moiety involved in this process is crucial and must be "intact". Unlike **1** and **33**, lemonomycin (**36**), which lacks the oxazolidine functionality, might display a different mechanism of action.

However, it is also well known that quinone-containing compounds can cause DNA damage by a mechanism involving quinone-participated oxygen reduction and

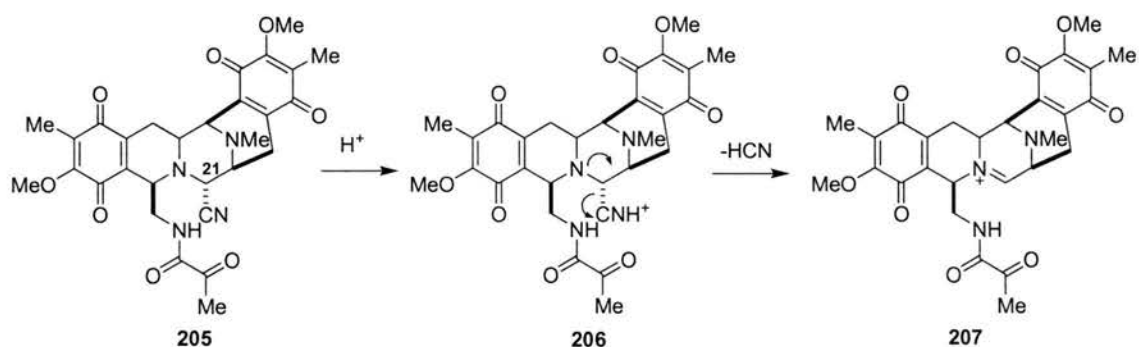
superoxide formation. This is illustrated by doxorubicin (**201**), a member of the anthracyclines family. A single electron reduction of the drug by reducing agents such as ascorbate, DTT (*in vitro*) or NADPH-cytochrome-P-450 reductase (*in vivo*), produces hydroquinone radical **202**, which is then believed to reduce molecular oxygen to superoxide (Scheme 38). The superoxide can then be processed to an activated species by the aforementioned metal-dependent process (Scheme 1), ultimately resulting in damage to DNA. Similar mechanisms for O_2 -activation resulting in DNA-damage have been proposed for adriamycin, streptonigrin and mitomycins, all of which contain analogous quinone moieties.⁴²



Scheme 38 Superoxide production by doxorubicin (**201**).

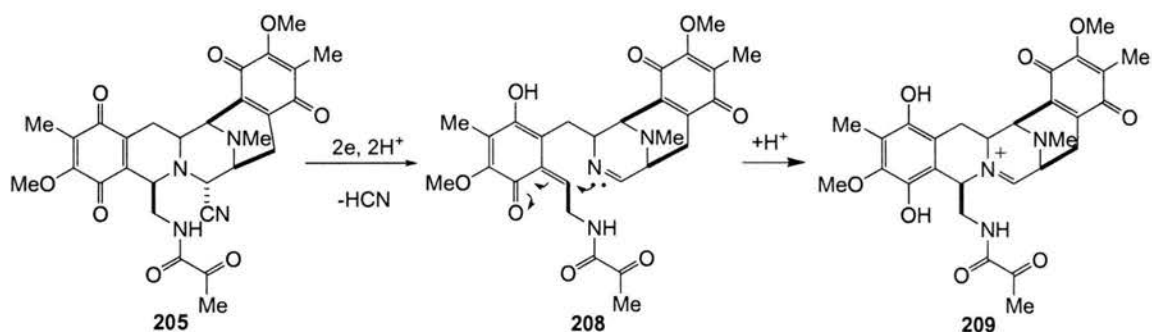
In addition, the mechanism of action studies of saframycin A (**205**) has shown that having either a nitrile or hydroxyl functionality at C-21 allowed for the formation of an

electrophilic iminium species, which can alkylate DNA. The original proposed mechanism (Scheme 39) for alkylation had the nitrile being protonated (**206**) and leaving as HCN to form the iminium ion **207**.⁴³ The DNA was then able to form a covalent bond with the drug.



Scheme 39 Mechanism of action of saframycin A (**205**)

Lown has proposed another mechanism, based on the fact that the DNA alkylating ability of saframycin A was enhanced upon reduction to the hydroquinone. (Scheme 40).⁴⁴ The phenol could lose a proton causing the B ring to open, which in turn eliminated cyanide. The imine **208** can attack the exocyclic olefin forming iminium ion **209**, which can then alkylate DNA.



Scheme 40 Mechanism of action of the hydroquinone form of saframycin A (**205**)

Because lemonomycin bears the quinone moiety and a leaving group at the equivalent position of saframycin A's leaving group, it would be interesting to see if lemonomycin would cause oxygen-dependant DNA damage via a quinone mediated oxygen reduction and superoxide formation. Alternatively, lemonomycin may cause DNA alkylation via a mechanism related to that of saframycin A.

When the unique structural aspects of lemonomycin are taken into account, there will be more interesting questions to answer. Could the aldehyde, now in its hydrate form, serve as an active site for DNA alkylation? In addition could the sugar affect DNA binding by any sequence recognition?

At the time the project was began, no synthetic route toward lemonomycin was available. In order to obtain enough material for the mechanism of action study, another goal of this project was to develop a total synthesis of lemonomycin.

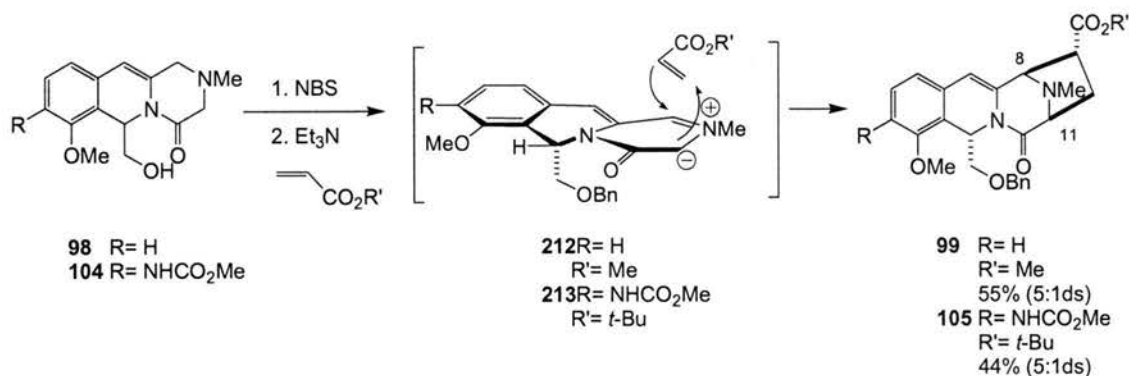
2.2.2 Develop of Total Synthesis of (-)-Lemonomycin

2.2.2.1 Existing Total Synthesis and Synthetic Studies

As described in chapter 1, to date, one total synthesis of (-)-lemonomycin was reported by Stoltz²⁸ and two synthetic studies have been reported by Fukuyama²⁹ and Magnus³⁰. Stoltz et al. developed a modified Joule's 1,3-dipolar cycloaddition. Fukuyama and Magnus both utilized an *N*-acyliminium ion, which cyclized with an allylsilane and a thio-enol ether respectively.

2.2.2.2 Previous Work in the Williams' Group

In the total synthesis of quinocarcinamide (**103**) and tetrazomine (**33**),^{36, 22} Williams et al. performed an 1,3-dipolar cycloaddition to construct the D rings efficiently through an NBS-mediated azomethine ylide. In this reaction, tricyclic dihydroisoquinolines **98** and **104** were required to generate the imminium salt by treatment with NBS refluxing in chloroform (Scheme 41). After generating the azomethine ylide **212** and **213** by adding triethylamine at 0 °C, treatment with acrylate provided cycloadducts **99** and **105** possessing the correct regiochemistry and *exo*-configuration.

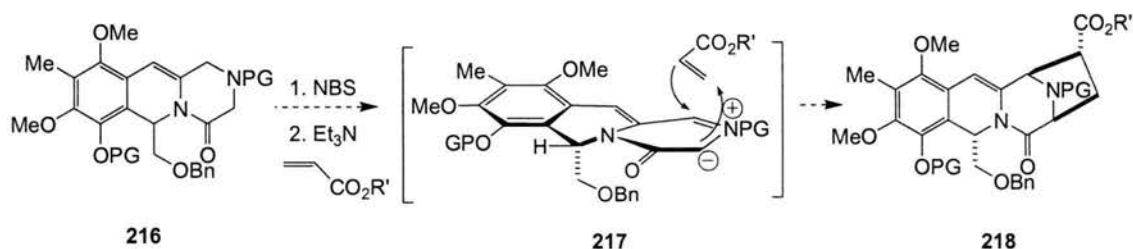


Scheme 41 NBS mediated azomethine generation and 1,3-dipolar cycloaddition

The regiochemical outcome of the cycloaddition reaction results from the major canonical form of the azomethine ylide **212** or **213**, in which the negative charge is effectively localized on the carbon α to the amide carbonyl. Due to the cyclic nature of the **212** and **213**, the cycloadducts formed are forced to have the correct relative stereochemical configuration between the C-8 and C-11 (quinocarcin numbering). The

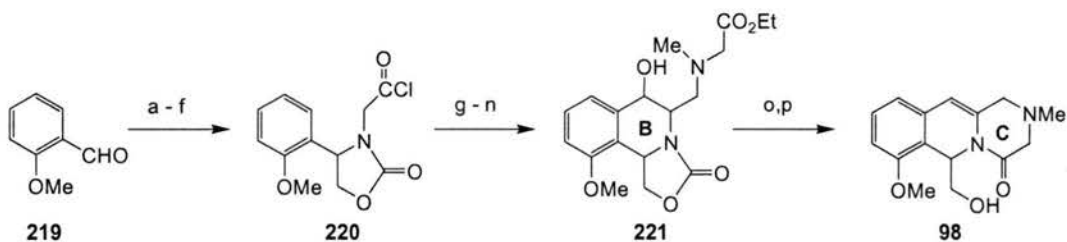
approach of the dipolarophile is presumably governed by the conformation of the ylide, which positions the hydroxymethyl group in a pseudoaxial orientation effectively shielding the bottom face of the ylide and favoring formation of the observed major isomer.

This 1,3-dipolar cycloaddition could potentially be applied to the synthesis of the tetracyclic core **218** of lemomycin (**36**) by using azomethine ylide **217** (Scheme 42). Thus, a similar tricycle dihydroisoquinoline **216** would need to be prepared.



Scheme 42 Proposed D ring construction in lemomycin

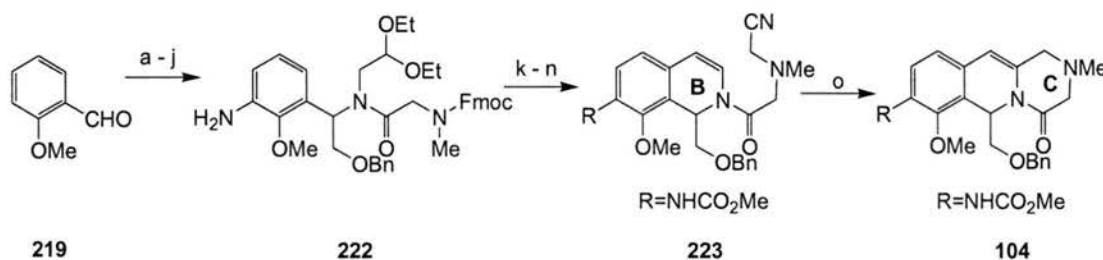
Furthermore, the chemistry for constructing the tricycle dihydroisoquinoline **98** and **104** in the synthesis of quinocarcinamide (**103**) and tetrazomine (**33**) could also be applied to the synthesis of **216**. In the synthesis of quinocarcinamide (Scheme 43), Flannagan and Williams have employed acid chloride **220**, which was derived from aldehyde **219** in 6 steps, to construct the B ring using Friedel-Craft conditions. After proper modification, an amino ethylester **221** was obtained in 7 steps and it was used to build up the C ring by constructing the amide bond to give the tricycle **98**.



Conditions: a. $(\text{CH}_3)_3\text{SiI}$, NaOH, $n\text{-Bu}_4\text{NBr}$. b. COCl_2 , cat. H_2O . c. $\text{H}_2\text{NCH}_2\text{CO}_2\text{Et}$, NaHCO_3 , 53% (3 steps). d. $\text{KO}t\text{-Bu}$. e. LiOH, EtOH. f. SOCl_2 . g. AlCl_3 , 55% (4 steps). h. LDA, CNCO_2Et . i. NaBH_3CN , HOAc, 68% (2 steps). j. LiOH, EtOH. k. SOCl_2 , tol. l. NaBH_4 , EtOH, 42% (3 steps). m. MsCl , Et_3N . n. $\text{MeNHCH}_2\text{CO}_2\text{Et}$, 96% (2 steps). o. LiOH, EtOH. p. DCC, HOBT, 53% (2 steps).

Scheme 43 Construction of tricyclic dihydroisoquinoline **98**

In the synthesis of tetrazomine (Scheme 44), Scott and Williams applied a modified Pomeranz-Fritsch reaction to construct the B ring using ethyl acetal **222**. The acetal **222** was synthesized in 10 steps from the same aldehyde **219** Flanagan used. The C ring was prepared by iminium ion cyclization of the aminonitrile **223** using $\text{Ag}(\text{OTf})$ in the presence of TFA and TFAA to afford tricycle **104**.



Conditions: a. $(\text{CH}_3)_3\text{SiI}$, NaOH, $n\text{-Bu}_4\text{NI}$. b. NaN_3 , H_2O , acetone. c. NaH, BnBr. d. H_2 , Pd/C. e. KNO_3 , TFAA. f. 2M LiOH, EtOH 46% (6 steps). h. $\text{BrCH}_2\text{CH}(\text{OMe})_2$, K_2CO_3 . i. Fmoc-Sarcocine-Cl, DMAP, 61% (2 steps). j. H_2 , PtO_2 . k. 6N HCl, 90°C . l. MeOCOC_2Cl , Py. m. pyrrolidine. n. ICH_2CN , $i\text{-Pr}_2\text{NEt}$, 86% (5 steps). o. AgOCOCF_3 , TFAA, TFA, 93%.

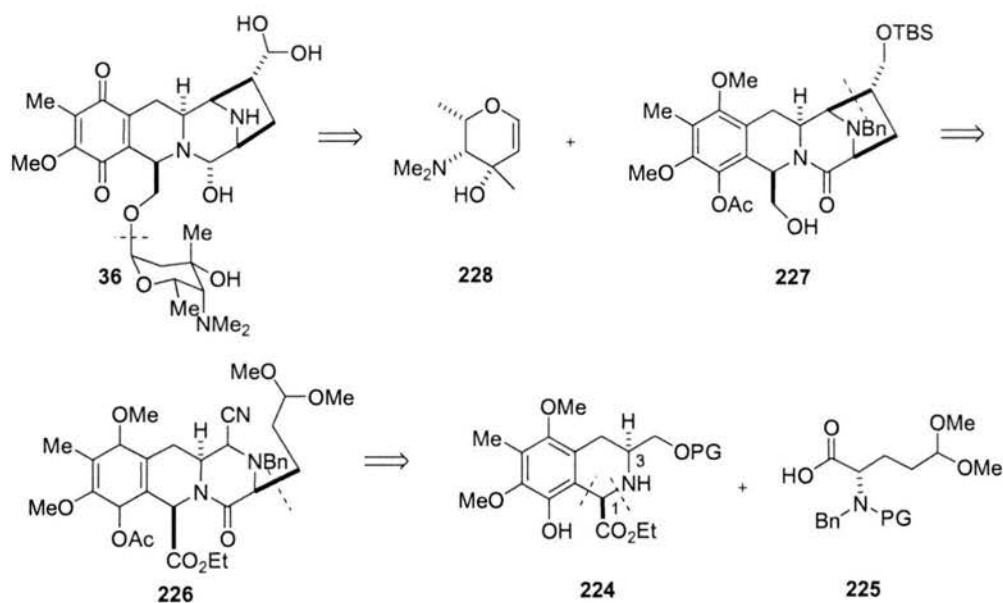
Scheme 44 Construction of tricyclic dihydroisoquinoline **104**

Although these previous strategies seem readily applicable to the synthesis of lemomycin, limitations existed in using this 1,3-dipolar cycloaddition strategy. First, the olefin in the tricycle dihydroisoquinoline substrates, which was found to be necessary for the oxidation of the amine for the 1,3-dipolar cycloaddition, doesn't exist in the target natural products. Therefore another reduction step would be required to remove the olefin. Secondly, the stereochemistry at C-1, which controls the facial selectivity of the dipolarophile, is opposite to the stereochemistry of the target natural products. As a result, an epimerization step would be needed to access the desired stereochemistry that is present in the natural products. Considering these two drawbacks, it was decided to explore an alternative synthetic route toward lemomycin.

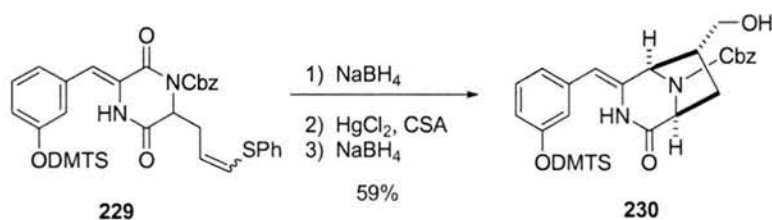
2.2 Original Plan

Our original plan (Scheme 45) was to first construct the tetracyclic ring system **227** of lemomycin (**36**) and carry out a late-stage installation of the 2-deoxy-sugar moiety by glycosidation with glycal **228**. For the tetracyclic core **227**, we planned to construct the B ring using a diastereoselective Pictet-Spengler cyclization to give **224**. Generation of the desired stereochemistry at C-1 required for the natural product, which could be controlled by the stereochemistry at C-3, will be investigated. After coupling with a suitable glycine derivative **225**, which will introduce another stereo center, and conversion of the TBS ether to an aldehyde, the substrate **224** could be transformed into the aminonitrile substrate **226** or other suitable iminium ion precursor. An intramolecular

Mannich type cyclization would install the D ring with all the desired stereochemistry to afford **227**. A related *N*-acyliminium cyclization of **229** generating tetracycle **230** (Scheme 46) was employed by Fukuyama in the synthesis of quinicarcin and lends supports the expected stereochemistry outcome in our system.³³



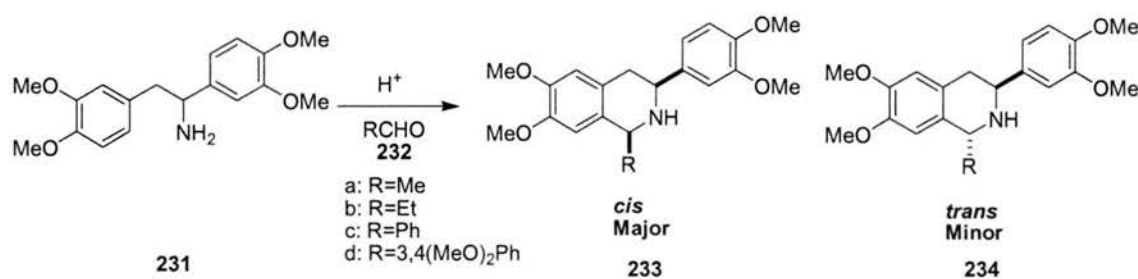
Scheme 45 Original retrosynthetic analysis



Scheme 46 Fukuyama's *N*-acyliminium cyclization

2.3 Construction of the B Ring

The synthesis of lemomycin began from the construction of the B ring, a tetrahydroisoquinoline derivative **224**. The classical methods for isoquinoline synthesis⁴⁵ include the Bischler-Napieralski cyclization/reduction, the Pictet-Spengler reaction and various Pomeranz-Fritsch cyclizations. In an early study, it has been shown that *cis*-1,3-disubstituted tetrahydroisoquinoline **233a-d** could be obtained in a highly diastereoselective fashion through a Pictet-Spengler cyclization using primary amine **231** (Scheme 47).⁴⁶ With different aldehydes **232a-d**, under acidic conditions, the *cis* selectivity of the cyclization increases with the bulk of the R group (Table 6).

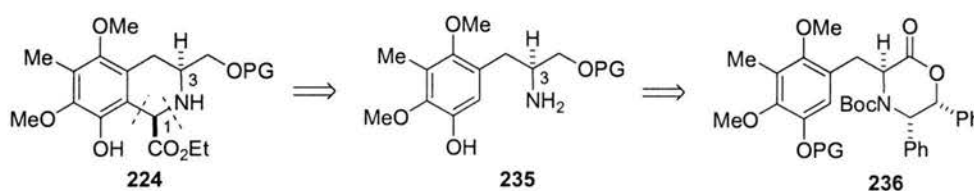


Scheme 47 Pictet-Spengler cyclization of amine **231**

Table 6 Selectivity of Pictet-Spengler cyclization of primary amine **31**

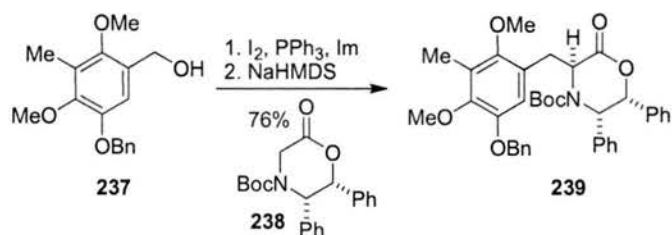
	233a: 234a	233b: 234b	233c: 234c	233d:234d
Yield (%)	75: 9.5	65: 7	81: 2.8	74: 2
Ratio	8: 1	9: 1	30: 1	37: 1

Inspired by this result, it was decided to prepare substrate **224** using a Pictet-Spengler reaction with enantiomerically pure β -arylethylamine derivative **235** (Scheme 48). For preparation of the β -arylethylamine derivative **235**, it was considered to utilize 4-Boc-5,6-diphenylmorpholine-2-one (N-Boc-Williams' lactone, **238**) derived **236**.⁴⁷ It would not only establish the absolute stereochemistry at C-3 but also potentially provide access to a variety of β -arylethylamine derivatives besides **235**.



Scheme 48 Retrosynthetic analysis of tetrahydroisoquinoline **224**

Beginning with known alcohol **237**,⁴⁸ it was found that conversion to the benzyl iodide and direct coupling with N-Boc-William's lactone **238** could give the desired product **239** in over 76% yield (Scheme 49). The initial attempts to convert **237** to the benzyl bromide were abandoned due to the low yields under variety of conditions. From coupling product **239**, four β -arylethylamine derivatives **240**, **241**, **242**, and **243** (Figure 8) were prepared and tested under Pictet-Spengler cyclization conditions.



Scheme 49 Formation of coupling product **239**

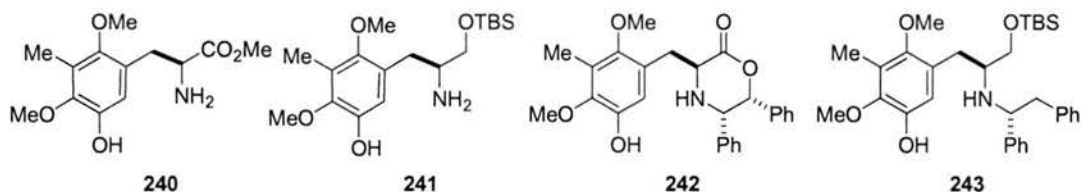
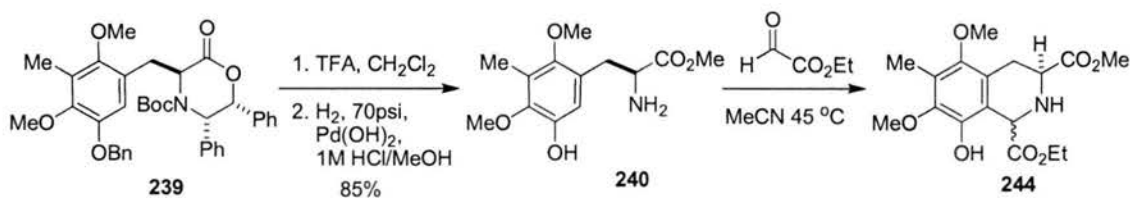


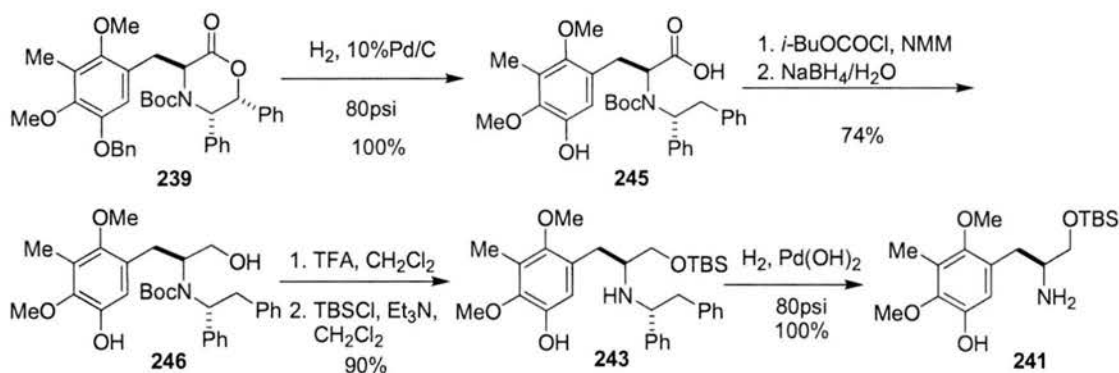
Figure 8 β -arylethylamine derivatives **240**, **241**, **242** and **243**

Primary amines **240** and **241** most closely related to the substrate **231** used in the known system (Scheme 47) were investigated first. Amino ester **240** was synthesized from the coupling product **239** by treatment with TFA⁴⁹ to remove the *N*-Boc group, followed by hydrogenation in 1M HCl·MeOH, resulting in concomitant removal of the chiral template and methyl ester formation (Scheme 50). The Pictet-Spengler reaction of **240** with ethyl glyoxalate in acetonitrile at 40°C over 1 day produced **244** in a maximum yield of 30% as an inseparable mixture of both *cis* and *trans* products.



Scheme 50 Preparation and Pictet-Spengler reaction of amino ester **240**

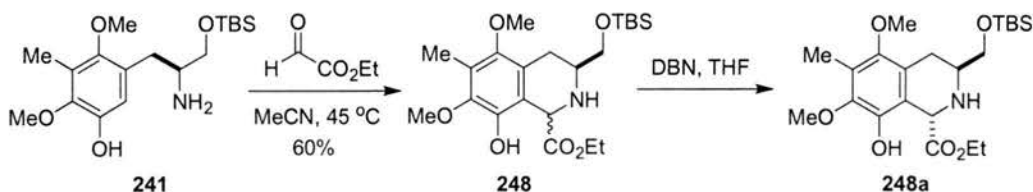
Primary amino alcohol **241** was initially obtained in a poor yield from direct reduction of the methylester **240** using LiBH_4 followed by TBS ether protection. Due to this low yield, a revised route was employed. The lactone **239**, with a Boc-protected nitrogen, could be opened under hydrogenation conditions with concomitant removal of the benzyl group on the phenol (Scheme 51). The resulting carboxylic acid **245** was reduced to alcohol **246** via the mixed anhydride using NaBH_4 . Subsequent Boc-deprotection followed by TBS protection of the primary alcohol gave **243**. Finally, the desired primary amine **241** was obtained by another hydrogenation reaction. Each step in this revised route can be carried out on a multigram scale in good to excellent yields.



Scheme 51 Preparation of the primary amino alcohol derivative **241**

The Pictet-Spengler reaction of substrate **241** under the same conditions employed previously gave the product **248** in an improved 60% yield. However, no diastereoselectivity was observed for the reaction and the diastereoisomers could not be separated (Scheme 52). Furthermore, epimerization of the product mixture **248** using

DBN only generated the undesired *trans* isomer **248a**. The stereochemistry of **248a** was confirmed by nOe data (Figure 9) and later experimental results (Scheme 62).



Scheme 52 Preparation and epimerization of Pictet-Spengler cyclization product **248**

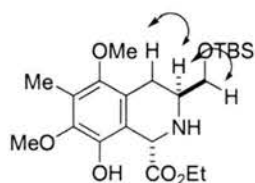
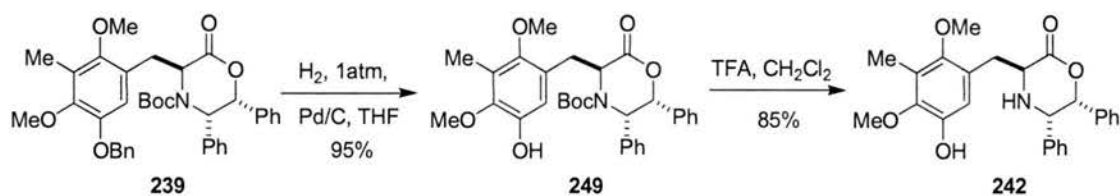
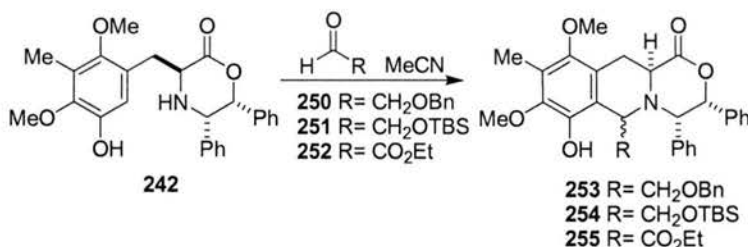


Figure 9 nOe correlation of **248a**

Because of the low diastereoselectivity provided by the primary amines **240** and **241**, secondary amines were investigated. The secondary amine **242** was prepared from the coupling product **239** by first removing the benzyl ether on phenol under hydrogenation conditions, followed by Boc-deprotection with TFA (Scheme 53). Pictet-Spengler reaction of this secondary amine **242** using different aldehydes (**250-252**) generated the corresponding products (**253-255**) in excellent yields, but with low diastereoselectivity (Scheme 54, Table 7). The *trans*: *cis* ratios of all the reaction products were determined by the ^1H -NMR. Further attempts to epimerize the C-1 center of **255** were unsuccessful.



Scheme 53 Preparation of secondary amine substrate **242**



Scheme 54 Pictet-Spengler cyclization of substrate **242**

Table 7 Pictet-Spengler cyclization of substrate **242**

Aldehyde	Temp. (°C)	Time (h)	Yield (%)	<i>trans</i> : <i>cis</i>
250	50	12	253 88	1: 0.6
251	65	24	254 80	0.4: 1
252	82	12	255 90	1: 0.4

The diastereomeric mixture of **253** was found to be separable and the relative stereochemistry of both *trans* isomer **253a** and *cis* isomer **253b** were assigned by nOe measurements (Figure 10). It appeared that the two methine protons (H^b and H^c) on the chiral template were diagnostic protons. Those belonging to the *cis* isomer have higher chemical shifts than those belonging to the *trans* isomer.

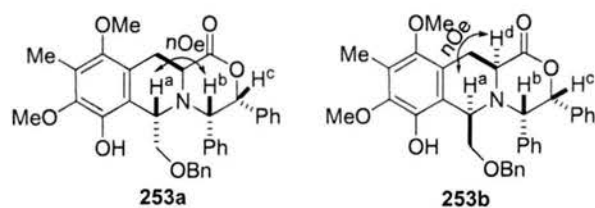
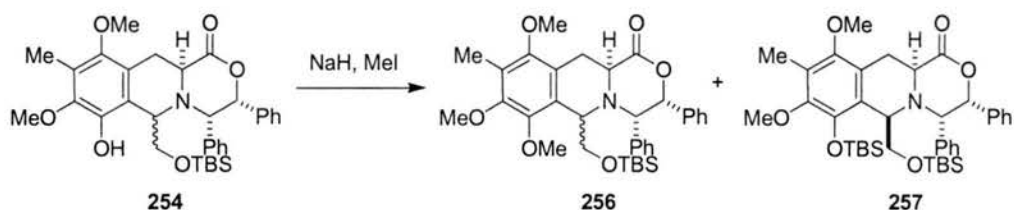


Figure 10 nOe correlation of **253a** and **253b**

The inseparable mixture of product **254** had a similar NMR pattern as **253**. In order to confirm the relative stereochemistry, diastereomeric mixture **254** was converted to the corresponding phenol methyl ether **256** by treatment with NaH and MeI (Scheme 55). Interestingly, a by-product **257** was generated and turned out to be crystalline. An X-ray structure of **257** was obtained (Figure 11) and confirmed that the chemical shift of the methine protons on the auxiliary belonging to the *cis* isomer are higher than those belongs to the *trans* isomer.



Scheme 55 Phenol methyl ether **256** formation and phenol TBS ether **257** formation

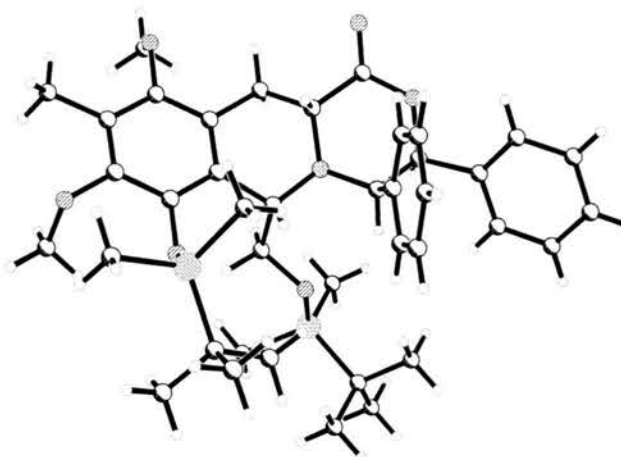


Figure 11 ORTEP illustration of compound **257**

The nOe data of the mixture of inseparable product **255** was obtained (Figure 12). Because the signals of the mixture were well separated, the nOe data clearly supported the conclusion we had drawn about the methine protons.

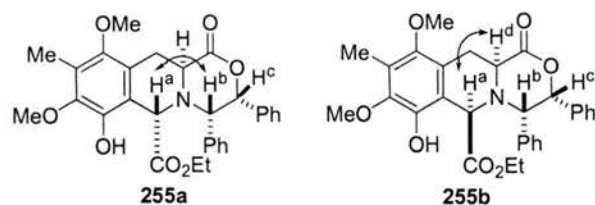
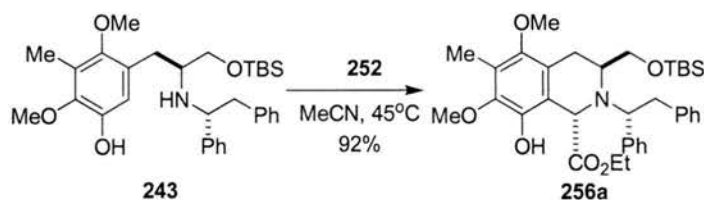


Figure 12 nOe correlation of **255a** and **255b**

When secondary amine **243** together with ethylglyoxolate were react in acetonitrile at 45 °C, the Pictet-Spengler reaction generated the cyclization product **256** in an

excellent yield and diastereoselectivity, but favoring the *trans* isomer in a 96: 4 *trans*: *cis* ratio (Scheme 56). The relative stereochemistry of the *trans* isomer **256a** was assigned by nOe data (Figure 13). The ratio of *cis* isomer to *trans* isomers was determined by ^1H -NMR.



Scheme 56 Pictet-Spengler cyclization of **243**

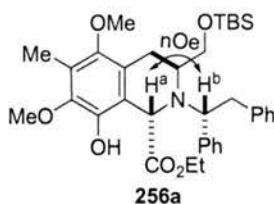
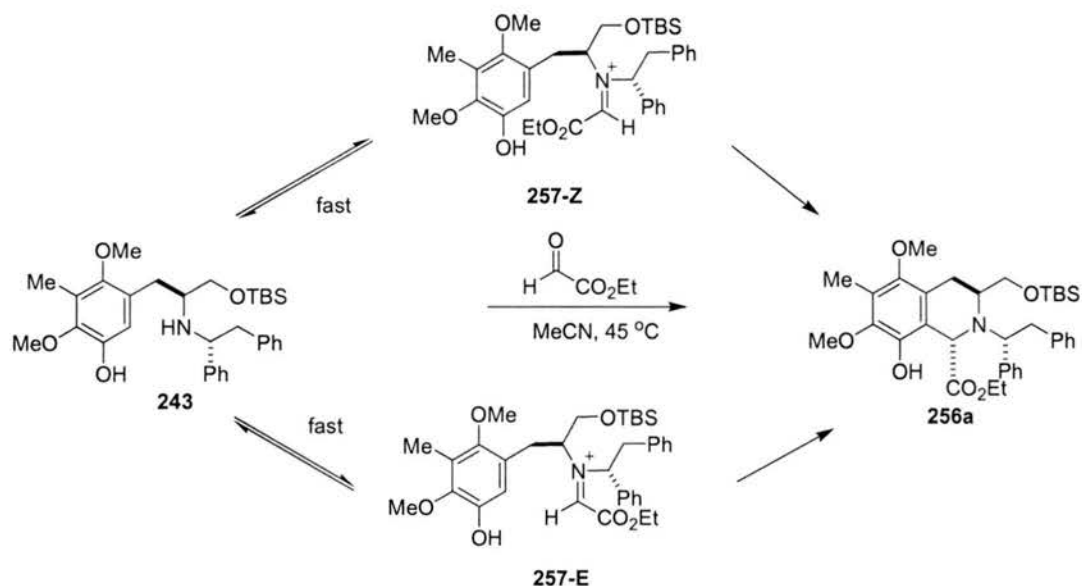


Figure 13 nOe correlation of **256a**

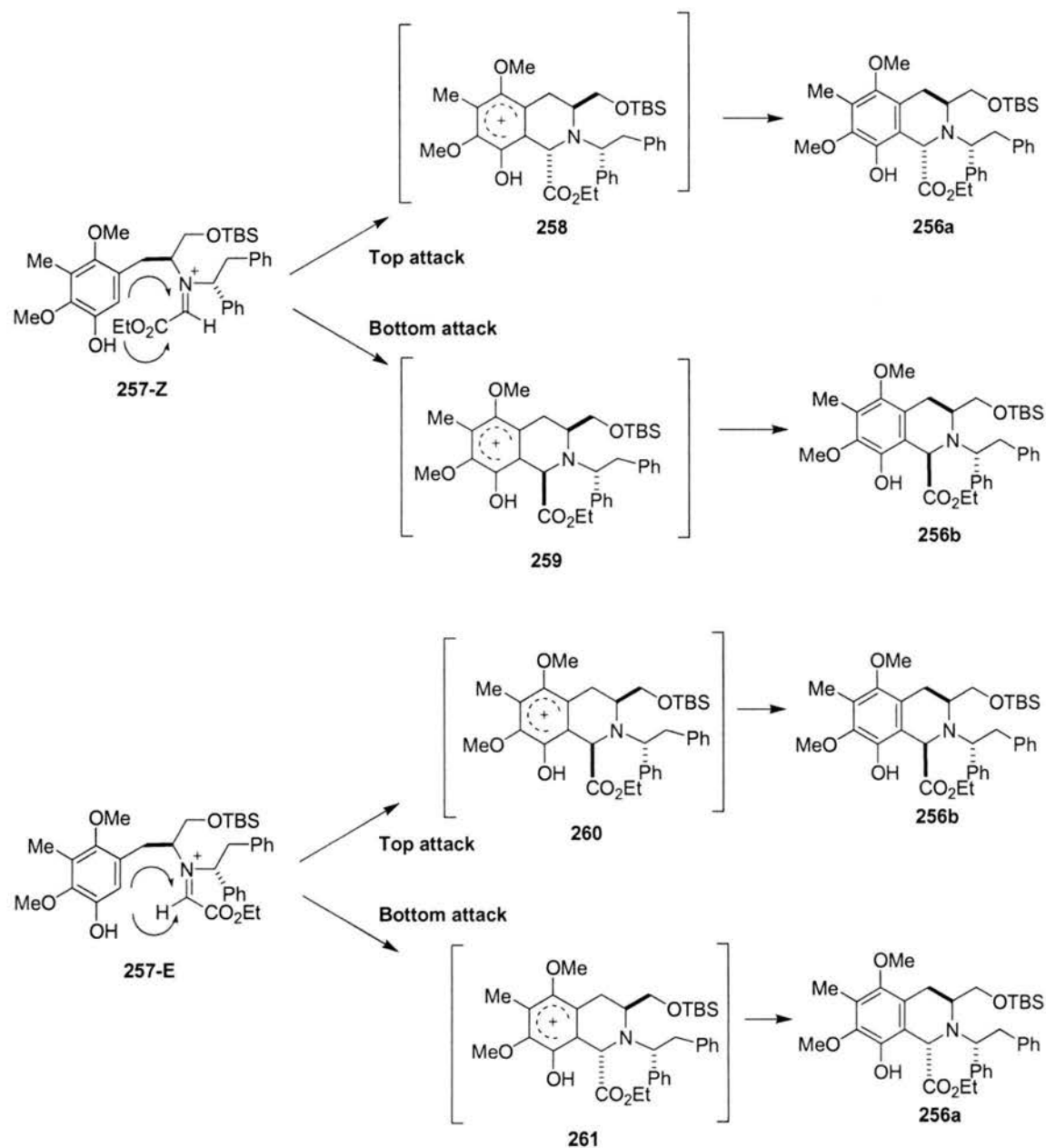
It is interesting to consider why the secondary amine **243** can form the *trans* product **256a** selectively. Under the reaction conditions employed above, the Pictet-Spengler reaction of secondary amine **243** with ethyl glyoxalate should proceed by reversible formation of an iminium ion of both *Z* (**257-Z**) and *E* (**257-E**) isomers, followed by electrophilic aromatic substitution (Scheme 57).



Scheme 57 Pictet-Spengler reaction via iminium ion intermediate

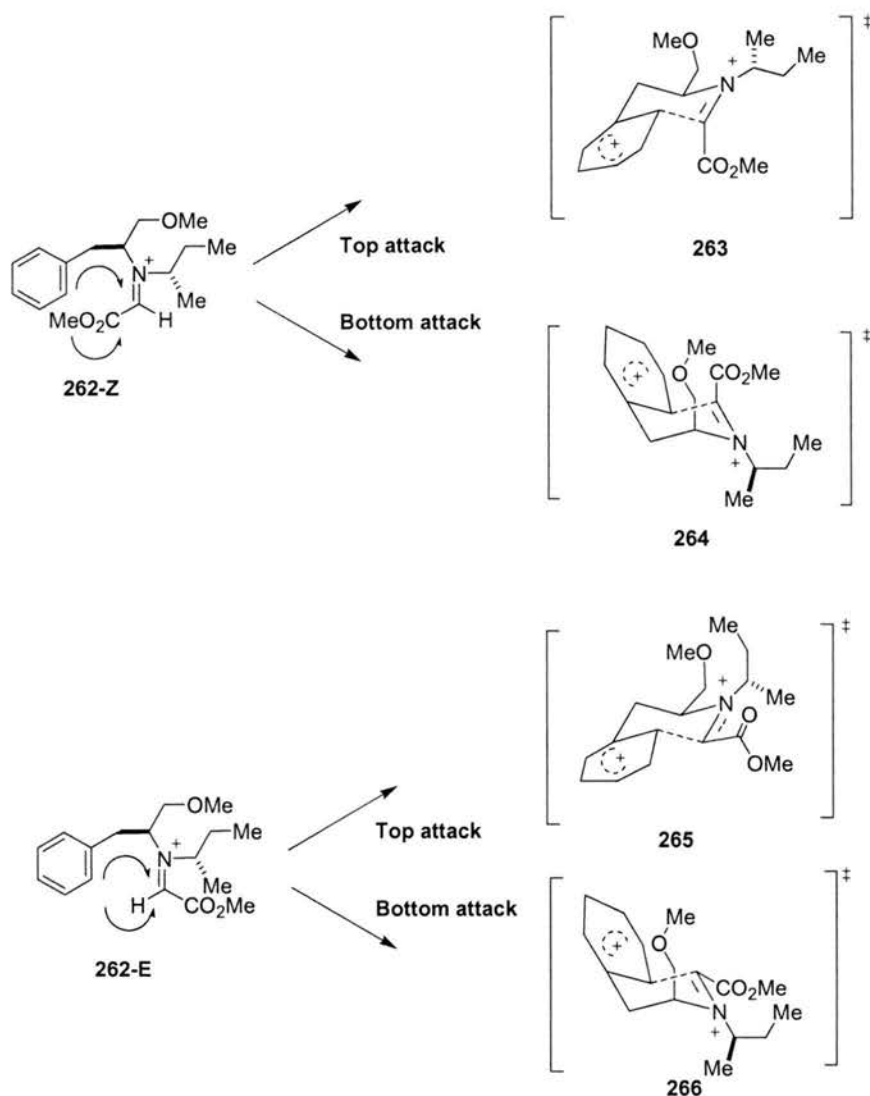
The general mechanism for electrophilic aromatic substitution involves π -complex formation, which in general is rapidly reversible and in many cases the equilibrium constant is small. In order for a substitution to occur, a “ σ -complex” must be formed. The σ -complex is an intermediate in which a σ bond is formed at the site of substitution resulting in a cyclohexadienyl cation. Formation of the σ -complex is usually the rate-determining step in electrophilic aromatic substitution. Therefore, The good *trans* selectivity of the Pictet-Spengler reaction with substrate **243** could be explained based on the difference of activation energy of σ -complex generated from the secondary iminium ion **257-Z** and **257-E**.

From each secondary iminium ion **257-Z** and **257-E**, two possible σ -complexes bearing different stereochemistry at C-1 can be formed, resulting from top or bottom attack on the corresponding iminium ion (Scheme 58).



Scheme 58 Electrophilic aromatic substitution of **257-Z** and **257-E**

In order to compare the activation energy for the formation of the σ -complexes from **257-Z** and **257-E**, a transition state energy calculation was carried out using Spartan⁵⁰ on the models **262-Z** and **262-E** (Scheme 59).



Scheme 59 Transition states **263-266** of the Friedel-Craft reaction of **262-Z** and **262-E**

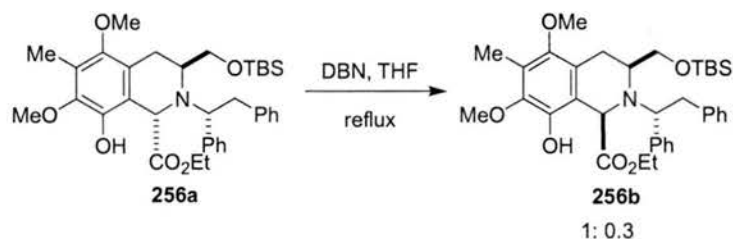
The energy calculation of the transition state **263-266** using HF/6-31G* showed (Table 8) that **266** was the lowest in energy at 4.81 kcal/mol lower than **264**, the second lowest in energy. Based on this model calculation, it can be proposed that the *trans*

product **256b** was generated through bottom attack of **257-E** through the intermediate **261**.

Table 8 The energy calculation of the transition state **263-266** by using HF/6-31G*

	263	264	265	266
E (hartrees)	-937.661403	-937.663419	-937.660377	-937.671088
$\Delta E_{266/264}$ (kcal/mol)	$(E_{264} - E_{266}) * 627.5 = 4.81$			

Since the *cis* product was the desired one for the intramolecular Mannich-type cyclization strategy, epimerization of the *trans* isomer **256a** was carried out. Treatment with DBN in refluxing THF for 24 h gave the desired product **256b** in a 1: 0.3 *cis*: *trans* ratio (Scheme 60). Unfortunately, the product mixture was inseparable until further transformations were carried out.

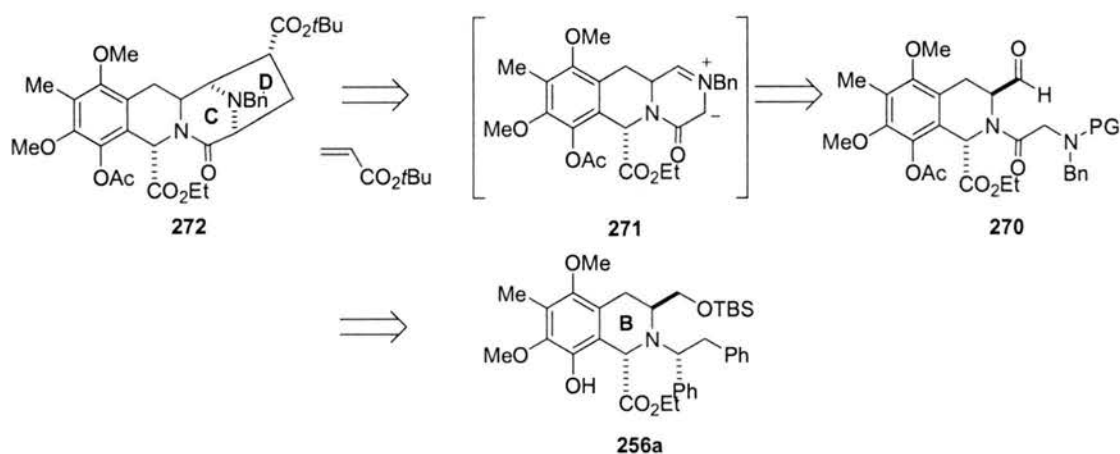


Scheme 60 Epimerization of **256a**

2.4 Revised Synthetic Plan

At this stage the B ring of lemomycin had been constructed in excellent yield and diastereoselectivity. However, the Pictet-Spengler reaction favors the undesired *trans* diastereoisomer and to follow our original plan, an epimerization had to be employed to

obtain the *cis* isomer. In addition, because the diastereoisomeric mixture was inseparable, the undesired *trans* isomer couldn't be recycled, resulting in a 25% waste of material. In Williams' synthesis of quinocarcinamide (**103**) and tetrazomine (**33**), the same C-1 center had been set up opposite to that required for the natural product (Scheme 41). However, this stereocenter then correctly controlled the diastereoselectivity of the subsequent azomethine ylide dipolar cyclization. Since epimerization cannot be avoided, it was decided to take advantage of the C-1 stereochemistry and employ an azomethine ylide (**271**) mediated cyclization to construct both the C and D ring (**272**). Azomethine ylide **271** can be derived from the *trans* isomer **256** (Scheme 61). This modified approach could be more efficient than the original one.



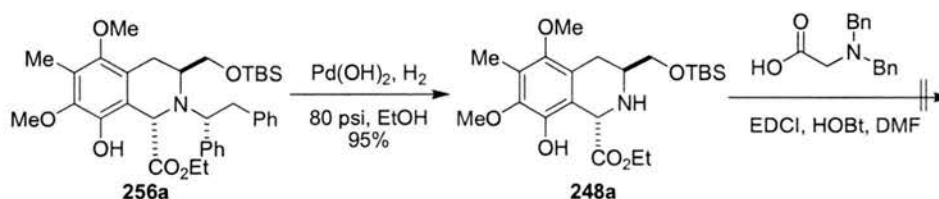
Scheme 61 Revised synthetic plan for the tetracyclic ring system **272**

There are many ways to prepare azomethine ylides.⁵¹ Based on substrate **256a**, it was planned to employ a condensation-deprotonation strategy to build up

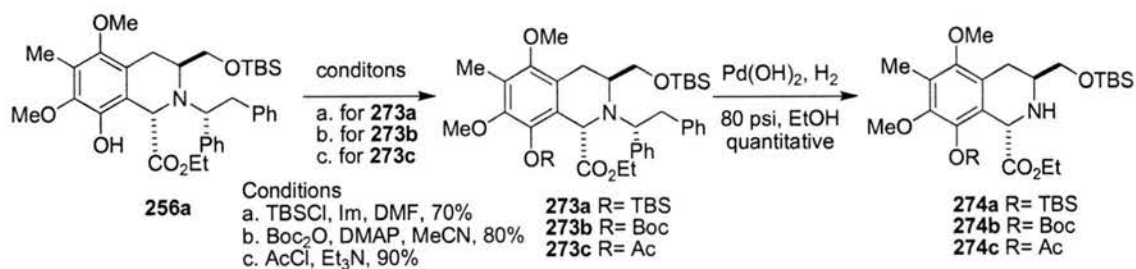
tetrahydroisoquinoline azomethine ylide intermediate **271** from aldehyde **270**, which could be derived from the *trans* isomer **256a** by standard manipulations.

2.5 Preparation of the Cycloaddition Precursor

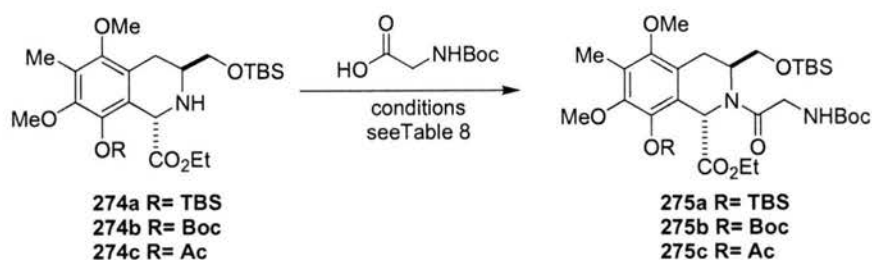
Towards the cycloaddition precursor aldehyde **270**, various glycine derivatives were explored for coupling to the tetrahydroisoquinoline core derived from **256a** (Scheme 62). After hydrogenation, secondary amine **248a** was obtained from **256a** in quantitative yield. However, **248a** failed to couple with *N,N*-dibenzyl glycine using EDCI and HOBT in DMF. This problem may have arisen from the presence of the free phenol, therefore compound **256a** was converted to three different phenol ethers (**273a-c**), before removal of the chiral template on nitrogen under hydrogenation conditions to generate the amines **274a-c** (Scheme 63). Different coupling conditions were explored on each of the three amines with commercially available *N*-Boc glycine (Scheme 64). It was found out that after converting the *N*-Boc glycine to its corresponding isobutyl anhydride, the coupling reaction generated the corresponding desired products **275a-c** in good yields for all three cases (Table 9).



Scheme 62 Formation and coupling reaction of **248a**



Scheme 63 Formation and coupling reaction of **273a-c**

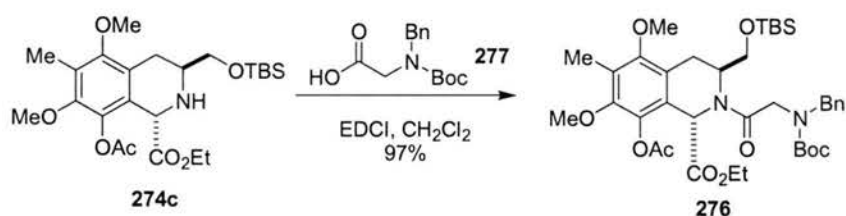


Scheme 64 Coupling reaction of **274a-c** with *N*-Boc glycine

Table 9 Conditions for coupling reaction of **274a-c**

Conditions	SM	Product (yield)
$(\text{COCl})_2$, Et_3N , DMAP, CH_2Cl_2	274a	275a (10%)
	274b	NA
	274c	NA
	274a	NA
EDCI, HOBT, DMAP, DMF	274b	275b 35%
	274c	275c 30%
	274a	275a 60%
<i>i</i> -BuOCOC Cl , NMM, DMF	274b	275b 80%
	274c	275c 71%

N-benzyl-(Boc) glycine (**277**)⁵² was then coupled to the amine **274c**, which has the most compatible functional groups for the rest of the synthesis (Scheme 65). Unfortunately, the optimized condition using mixed anhydride didn't work well with this glycine derivative. After investigating various conditions (Table 10), it was found that using EDCI in a concentrated CH₂Cl₂ solution, the coupling reaction proceeded to give the desired product **276** in an almost quantitative yield.

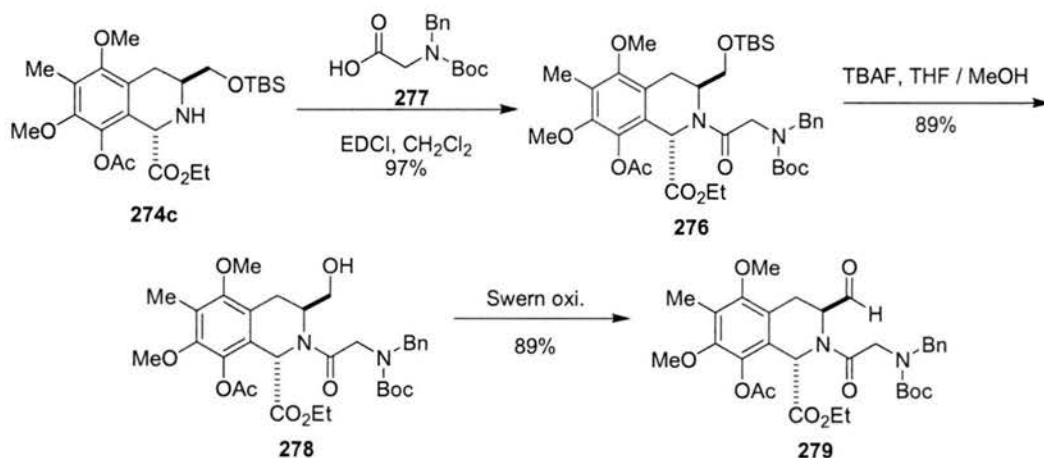


Scheme 65 Coupling reaction of substrate **274c**

Table 10 Conditions for coupling reaction of substrate **274c**

Conditions	Results
274c (1.0 eq.), 277 (2.0 eq.), <i>i</i> -BuOCOC ₂ H ₅ (2.0 eq.), NMM (2.1 eq.)	276 53%
274c (1.0 eq.), 277 (2.0 eq.), (COCl) ₂ (2.4eq), CH ₂ Cl ₂ /DMF	No product
274c (1.0 eq.), 277 (2.0 eq.), EDCI (1.5 eq.), HOBT (1.0 eq.), 12h	276 : 274c = 1: 5
274c (1.0 eq.), 277 (2.0 eq.), EDCI(1.5 eq.), HOBT (1.0 eq.), Et ₃ N (2.0 eq.), 12h	No product
274c (1.0 eq.), 277 (2.0 eq.), EDCI, (1.5 eq.), CH ₂ Cl ₂ (1M), reflux, 12h	276 (56%)
274c (1.0 eq.), 277 (2.0 eq.), EDCI, (1.5 eq.), CH ₂ Cl ₂ (1M), 2days	276 (97%)

After removing the TBS ether using TBAF in MeOH buffered THF solution, the resulting alcohol **278** was oxidized to corresponding aldehyde **279** under Swern oxidation conditions (Scheme 66). With this aldehyde in hand, we were ready to investigate the key cycloaddition reaction.

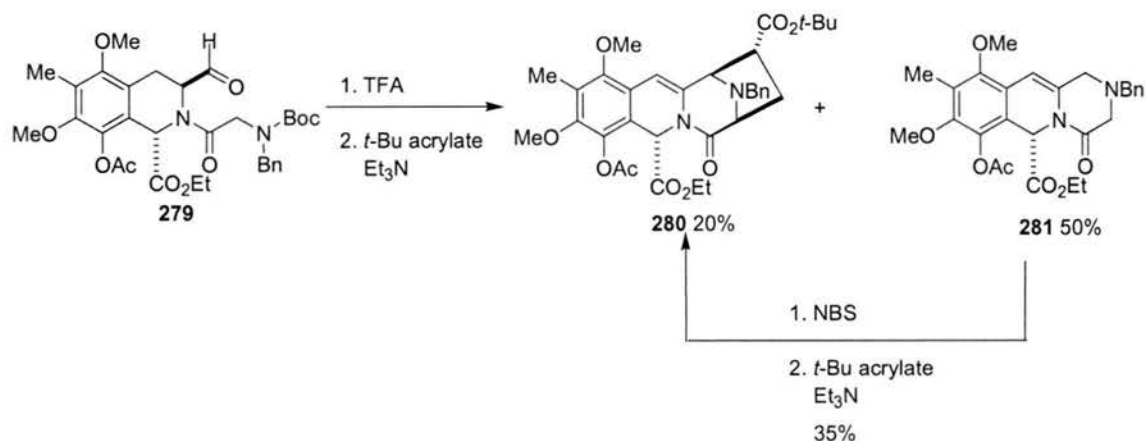


Scheme 66 Formation of aldehyde **279**

2.6 Construction of C and D Ring

Following our revised plan to generate azomethine ylide **271** by condensation-deprotonation strategy, the aldehyde **279** was treated with TFA to remove the Boc protecting group. After concentration of the reaction mixture to remove most of the TFA, Et₃N was added in the presence of *t*-Bu acrylate. Interestingly, the products isolated from this reaction were dihydroisoquinoline tetracycle **280** in around 20% yield, bearing the desired stereochemistry on the D ring, and dihydroisoquinoline tricycle **281** in 50% yield (Scheme 67). The structure of the tetracyclic **280** was confirmed by x-ray crystallography (Figure 14). The proposed structure of the tricycle **281** was consistent with its spectroscopic data. In addition, when tricycle **281** was treated with NBS followed by

Et₃N in presence of *t*-Bu acrylate, the reaction generated tetracycle **280** in 35% yield. The same type of transformation has been employed in the synthesis of quinocarcinamide (**103**) and tetrazomine (**33**) (Scheme 41).



Scheme 67 Formations of **280** and **281**

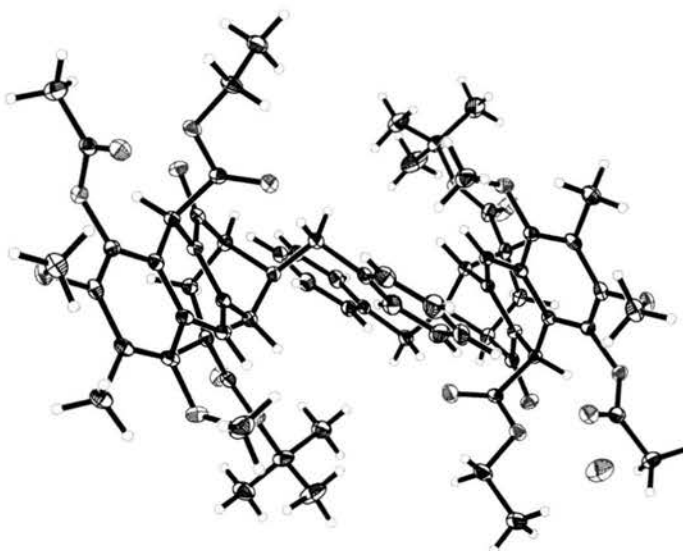
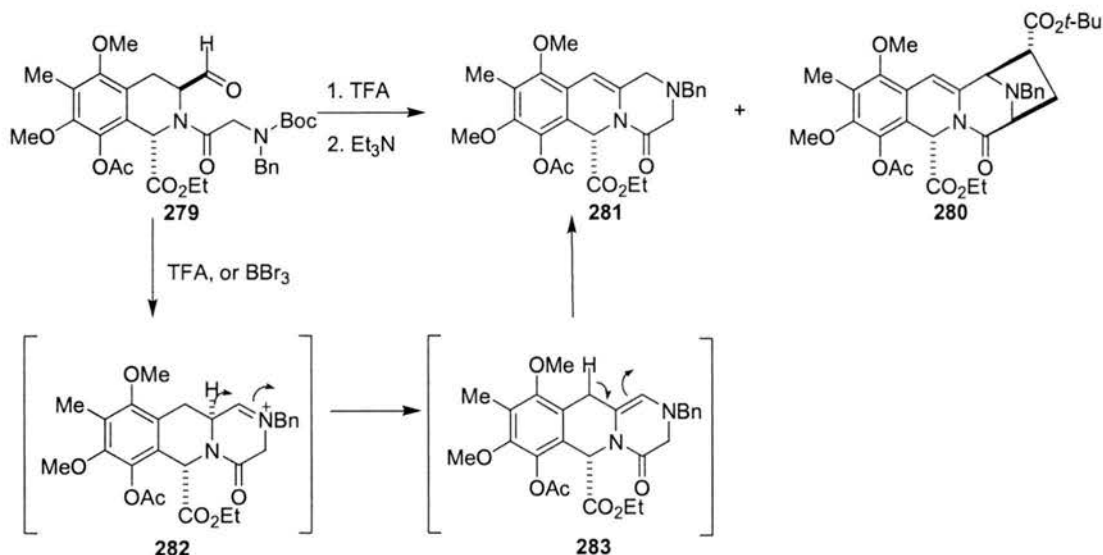


Figure 14 ORTEP illustration of compound **280**

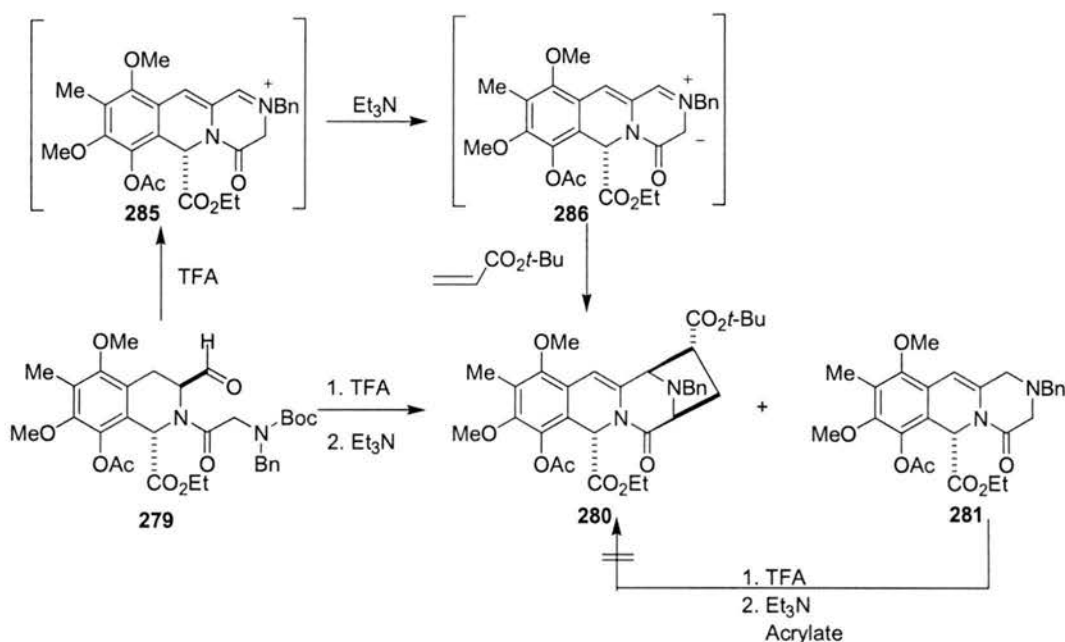
When compound **279** was treated with acid (3M HCl in MeOH, BBr₃, or TMSOTf) other than TFA to remove the Boc group, tricycle product **281** was isolated as the only product. When BBr₃ was used, tricycle **281** was generated in 75% yield. It is reasonable to assume that tricycle **281** could be generated from tautomerization of the iminium ion **282** under acidic conditions (Scheme 68).



Scheme 68 Mechanistic proposal for tricycle **281** formation

Tetracycle **280** had to be generated through the dihydroisoquinoline **286** by an oxidation reaction (Scheme 69). When tricycle **281** was treated with TFA, followed by Et₃N in the presence of *t*-Bu acrylate, only starting material was recovered. This observation suggested that the oxidation did not take place after formation of tricycle **281**. Meanwhile, the mass spectrum of the reaction mixture generated by treatment of **279** with TFA indicated the presence of **285** with a mass of 493.1975 (HRMS (FAB) calcd. For C₂₇H₂₉N₂O₇ (M⁺): 493.1975). Therefore, it was concluded that the oxidation was a competitive reaction with tautomerization and both reactions took place upon treatment

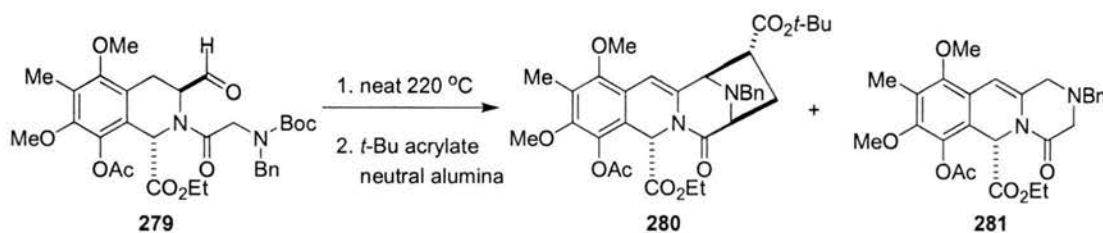
of **279** with TFA, prior to the formation of the desired azomethine ylide by treatment with Et_3N .



Scheme 69 Mechanistic proposal for tetracycle **280** formation

Since oxidation product **280** can be generated in a significant amount only when TFA was used, TFA, a known single electron oxidant was suspected to be the oxidant.⁵³ However, we were unable to detect any reduced forms of TFA *i.e* trifluoroacetaldehyde or trifluoroethanol, from the reaction of **279** with TFA.

When thermal conditions were employed to remove the Boc group from **279**, followed by addition of neutral alumina in the presence of *t*-Bu acrylate, the reaction gave both products **280** and **281** in a 1: 1 ratio, though in very poor yield of 15% (Scheme 70). Therefore, it is believed that TFA facilitated oxidation, but molecular oxygen is most likely the oxidant in this reaction.



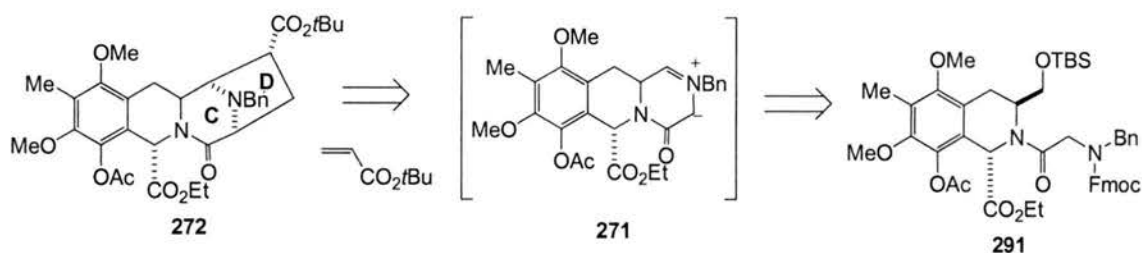
Scheme 70 Formation of **280** and **281** under thermal condition

The detailed mechanism of the oxidation was not yet clear. Some of our observations are as follows. Upon treatment of **279** with TFA under oxygen (1 atm), there was no identifiable product isolated from the cycloaddition (Scheme 67). It could be possible that over-oxidation resulted in decomposition. When radical scavenger di-tert-butyl phenol was employed, oxidation product **280** was generated in a comparable yield as where no radical scavenger was used. This suggested that the oxidation mechanism might not involve a radical species. Finally, absence of light had no effect on the production of **279**.

It has been shown that oxidation and tautomerization took place during *N*-Boc removal, before the formation of azomethine ylide by Et_3N addition. As expected, any attempts to avoid oxidation by excluding oxygen in the reaction system only resulted in generation of the tautomerization product **281** without any detectable amount of desired tetracycle **272**. It appeared that the tautomerization was unavoidable when *N*-Boc substrate **279** was employed in this condensation-deprotonation two-step procedure of azomethine ylide formation.

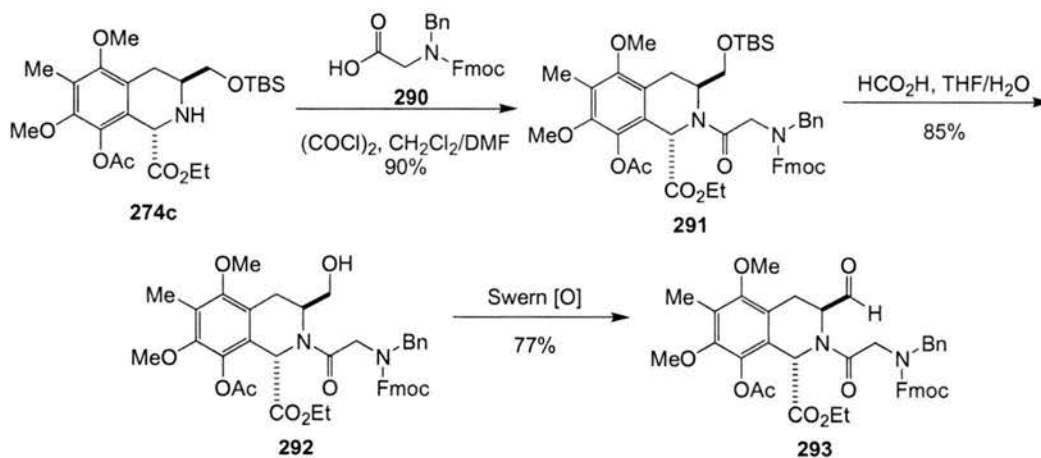
In order to limit the exposure time of the iminium ion to the reaction condition, thus to create a better chance for azomethine ylide **271** formation, it was decided to prepare substrate **291** using (*N*-Fmoc)Bn glycine as the coupling partner (Scheme 71). It was

hoped that when base was used to remove the Fmoc from **291**, formation of iminium ion and azomethine ylide could be accomplished in the same step.



Scheme 71 Condensation-deprotonation one step strategy of **271** formation

From the secondary amine **274c**, (*N*-Fmoc)Bn glycine⁵⁴ was coupled using its acid chloride to give the desired product **291** in 82% yield (Scheme 72). Due to the base-sensitivity of the Fmoc group, the TBS ether was removed under acidic conditions. Formic acid was found to be the best choice and gave the free alcohol **292** in 80%, which was then oxidized to the corresponding aldehyde **293** in 77% yield by Swern oxidation.



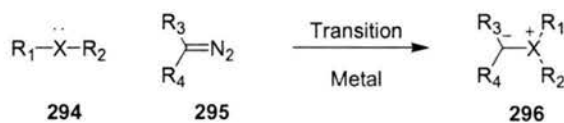
Scheme 72 Preparation of aldehyde **293** from secondary amine **274c**.

When aldehyde **293** was treated with various bases such as Et₃N, piperidine, TBAF, in the presence of *t*-Bu acrylate, decomposition was observed in all cases. Interestingly, no hemiaminal intermediate, tautomerization product or cycloaddition product was ever isolated from these reactions. It was fairly certain that the Fmoc was removed successfully, as indicated by the existence of fluorene in the crude reaction mixture. It was therefore highly probable that the iminium ion formed from the condensation decomposed under the basic conditions of the reaction.

2.7 Attempts at Alternative Azomethine Ylide Generation

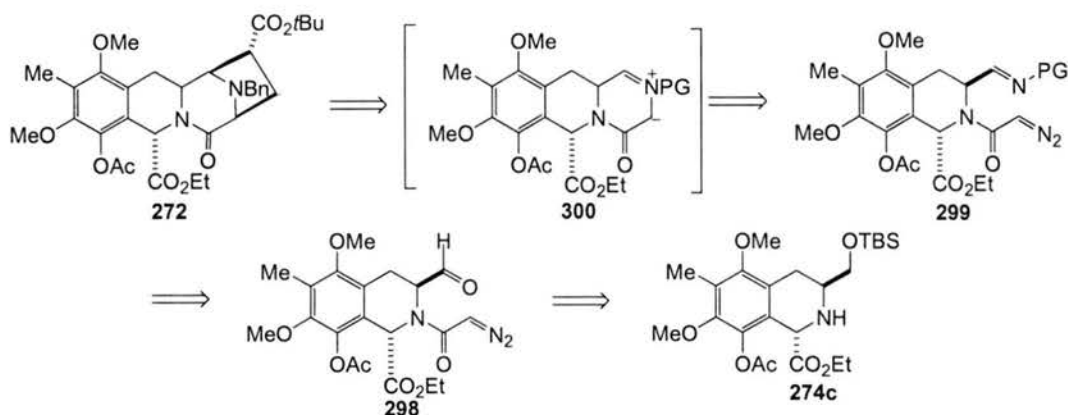
During the condensation-deprotonation-cycloaddition experiments, it was shown that the fate of the iminium ion intermediate **282** was uncertain, since it could lead to the tautomerization product **281** under acidic conditions, the oxidation product **280** under air with assistance of TFA, or be destroyed under basic conditions. All these scenarios compete with the formation of the desired azomethine ylide **271**.

Therefore, it was decided to develop an alternative approach to generate the azomethine ylide in one step, which wouldn't proceed via the iminium ion intermediate. It is known that electrophilic carbenes (generated from the metal-catalyzed decomposition of diazo compounds **295**) function as Lewis acids by interacting with a pair of nonbonding electrons contributed by a Lewis base (**294**). If the Lewis base is an uncharged species, the end result of such an acid-base reaction is an ylide (**296**) (Scheme 73).⁵⁵



Scheme 73 Ylide **296** generation using electrophilic carbene

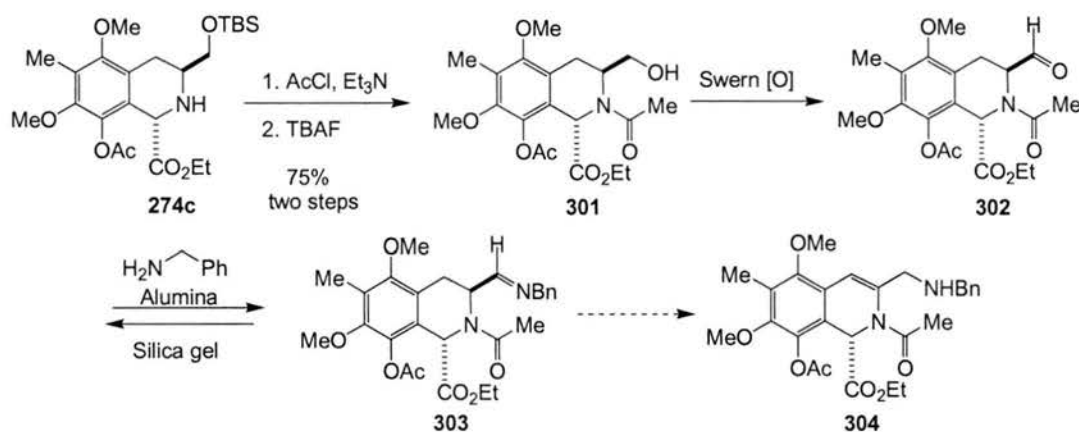
We envisioned that an electrophilic carbene produced from the metal-catalyzed decomposition of diazo compound **299** could be employed towards the synthesis of **272** via azomethine ylide **300** (Scheme 74).⁵⁶ The α -diazo carbonyl compound **299**, bearing an imine functionality could be prepared by condensation of aldehyde **298** with a suitable amine. The aldehyde **298** could be derived from the available intermediate **274c** before or after a suitable α -carbonyl diazo moiety was installed.



Scheme 74 Alternative route for **272** formation using diazo-compound **299**

A potential problem with this route is the possibility that imine **299** could undergo tautomerization to a styrene amine derivative. To test this possibility, a condensation reaction was set up by using aldehyde **302** and benzyl amine (Scheme 75).

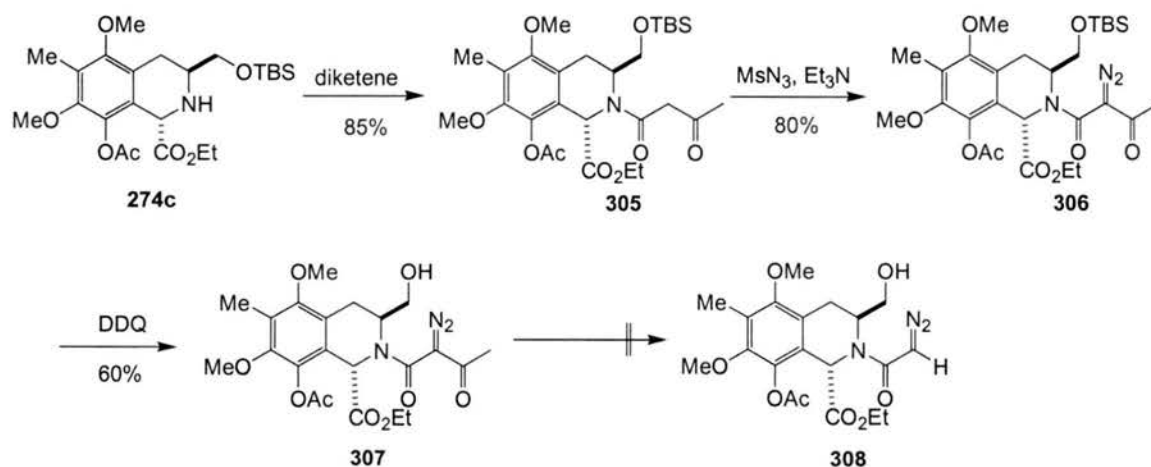
Aldehyde **302** was prepared from the available intermediate **274c** by a sequence of *N*-acylation, removal of TBS ether and a Swern oxidation. The condensation of aldehyde **302** was carried out with benzyl amine in the presence of neutral alumina. After three hours, the NMR of the crude reaction mixture showed that the aldehyde peak around 9.5 ppm had disappeared and there was a new peak around 7.0 ppm. Attempts to purify the reaction mixture by preparative TLC resulted in recovery of the starting material. The NMR data confirmed the formation of imine **303**, while the recovery of the starting material suggested that imine **303** didn't tautomerize to styrene amine **304** under the reaction conditions.



Scheme 75 Preparation and condensation reaction of aldehyde **302**

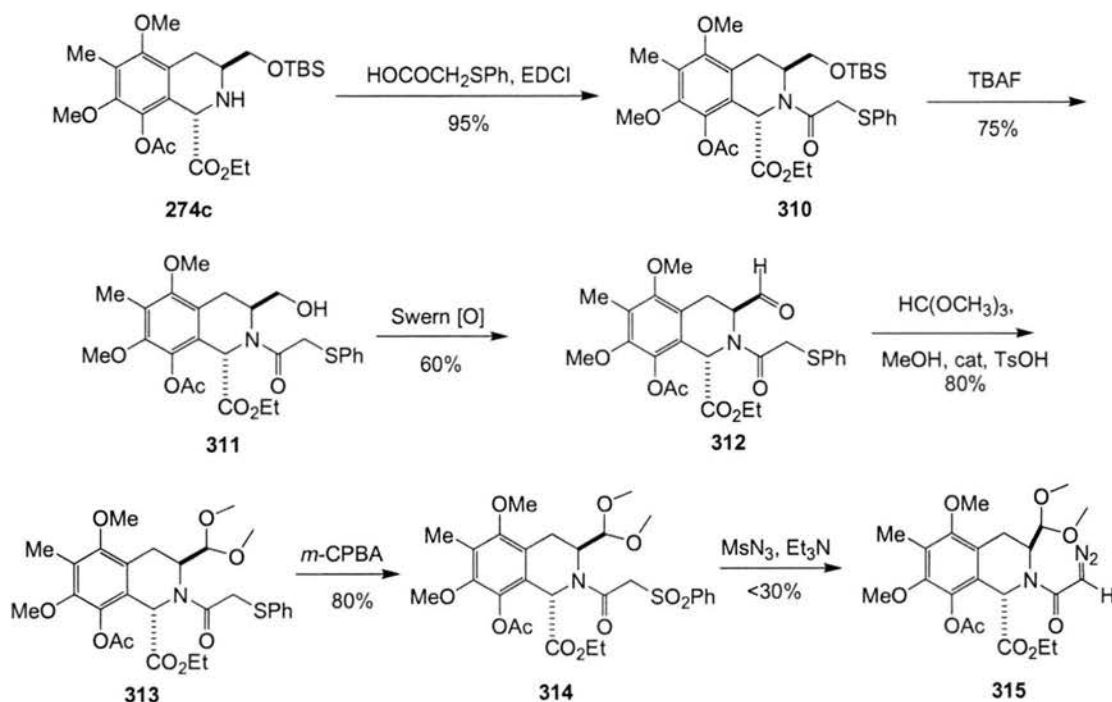
Having established the feasibility of the condensation reaction, the synthesis of aldehyde **298** was investigated. It was planned to install the α -carbonyl diazo moiety before the aldehyde formation. Coupling reactions of the secondary amine **274c** with glyoxylic acid tosylhydrazone⁵⁷ using coupling reagent such as DCC and EDCI or its corresponding acid chloride or succinimide⁵⁸ were all unsuccessful.

Therefore attention was turned towards the standard diazo-transfer reaction. β -Keto amide **305** was generated in 85% yield by treatment of **274c** with diketene. In the presence of Et_3N , the diazo-transfer reaction proceeded successfully with MsN_3 in acetonitrile to give **306** in 80% yield (Scheme 76). However, the removal of the TBS ether was problematic. The diazo functionality was not stable under acidic conditions or with different fluoride reagents. When basic conditions were employed, the acetate was also removed resulting in the formation of a phenoxide. Any attempt to neutralize the phenoxide only resulted in destruction of the diazo functionality. Eventually, it was discovered that DDQ⁵⁹ or CAN could remove the TBS ether to afford the free alcohol in good yield. In the case of DDQ, only a catalytic amount of the oxidant was needed to generate **307** in 60%. However, the hydrolysis of **307** to **308** failed under a variety of conditions (LiOH , KOH , pyrrolidine). It was also found that the oxidation of alcohol **307** to the corresponding aldehyde couldn't be achieved under a number of conditions.



Scheme 76 Preparation of diazo compound **307**

Following these observations a revised route was investigated. It was decided to install the α -carbonly diazo moiety after aldehyde formation. Also, in order to have a better chance for hydrolysis at later stage, **310** was prepared in 95% yield by coupling **274c** with phenylthioacetic acid (Scheme 77). Removal of the TBS ether with TBAF and Swern oxidation of the resulting alcohol provided aldehyde **312**. This was then protected as methyl acetal **313**, which could be removed in the presence of the diazo functionality under oxidation conditions like DDQ. These steps proceeded without any epimerization at C-3 as confirmed by nOe studies (Figure 15). Oxidation of the phenylsulfide group to a sulfone provided **314**, which was equivalent to a β -keto amide with activated methylene protons. The diazo transfer reaction of **314** with MsN_3 and Et_3N generated a product whose proton NMR was consistent with the proposed structure **315**. In addition, the IR indicated the presence of the diazo functionality having a characteristic stretch at 2107cm^{-1} . However, the yield of this reaction was poor making it difficult to access usable quantities of **315**. Therefore, further investigations employing different azide sources are currently being investigated.



Scheme 77 Preparation of diazo compound **315**

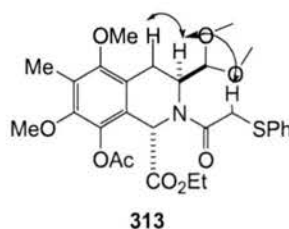
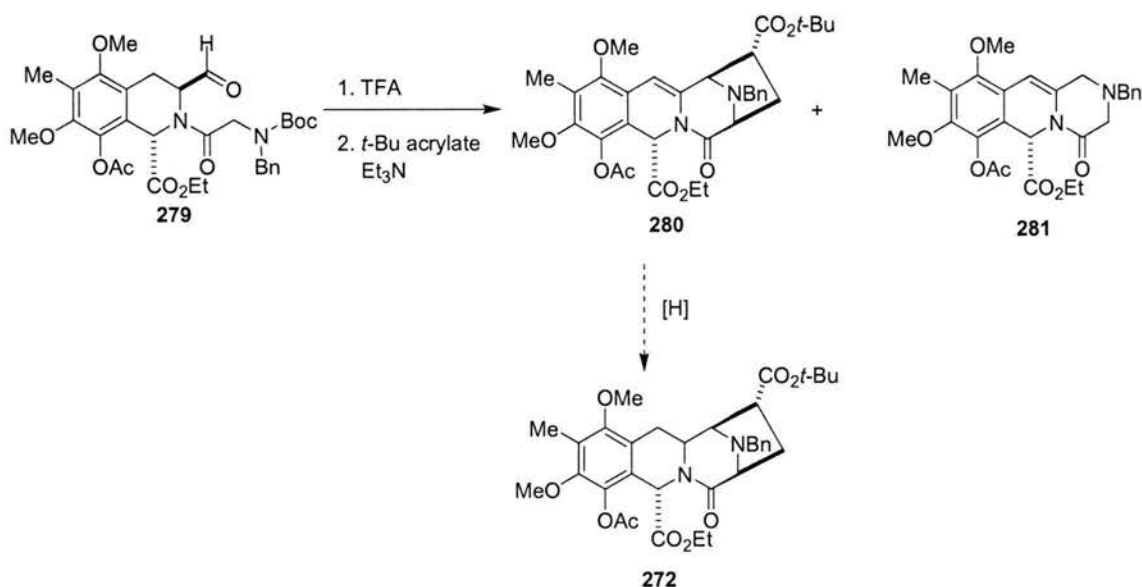


Figure 15 nOe correlation of compound **313**

2.8 Further Elaboration

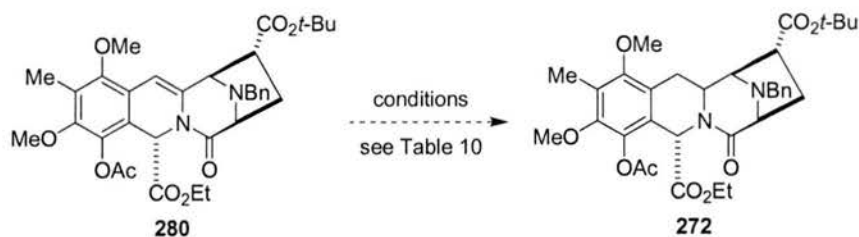
While we were investigating ways to directly generate the desired saturated tetracycle **272**, it was also noticed that tetracycle **280**, bearing all the desired stereochemistry on the D ring, could potentially be reduced to **272** to continue the synthesis (Scheme 78).



Scheme 78 Potential reduction of **280** to generate **272**

Because of the competitive tautomerization that led to the product **281**, the yield of the product **280** was poor. Optimization of oxidation product **280** was carried out focusing on the step of treatment of **279** with TFA, where the oxidation is thought to take place. The best conditions found were treatment of aldehyde **266** in a 0.1M chloroform solution, with 50 equivalents of TFA at room temperature in a flask with a 100 times volume of air (cf solvent) sealed for 4 hours. After concentration of the reaction mixture to remove most of the TFA, the same amount of chloroform was added at 0 °C under Ar, followed by 20 equivalents of *t*-Bu acrylate and 10 equivalents of Et₃N. After removal of the ice bath, the reaction was stirred at room temperature overnight. Under these optimized conditions, the oxidation product **280** could be isolated in over 70% yield as a single diastereoisomer. With a good route to **280** in hand, we were ready to investigate its elaboration.

After the first couple attempts at reducing the double bond, it became apparent that it was a challenging transformation. Hydrogenation of substrate **280**, under 1300 to 1500 psi hydrogen, with different catalysts (Raney-Ni, Rh/C, Rh/Alumina, Rh(OAc)₂, RhCl₃, Wilkinsons' Ir/C, Crabtree's, Pd/C, PdCl₂, Pd(OH)₂), only resulted in recovering starting materials (Scheme 79, Table 11).



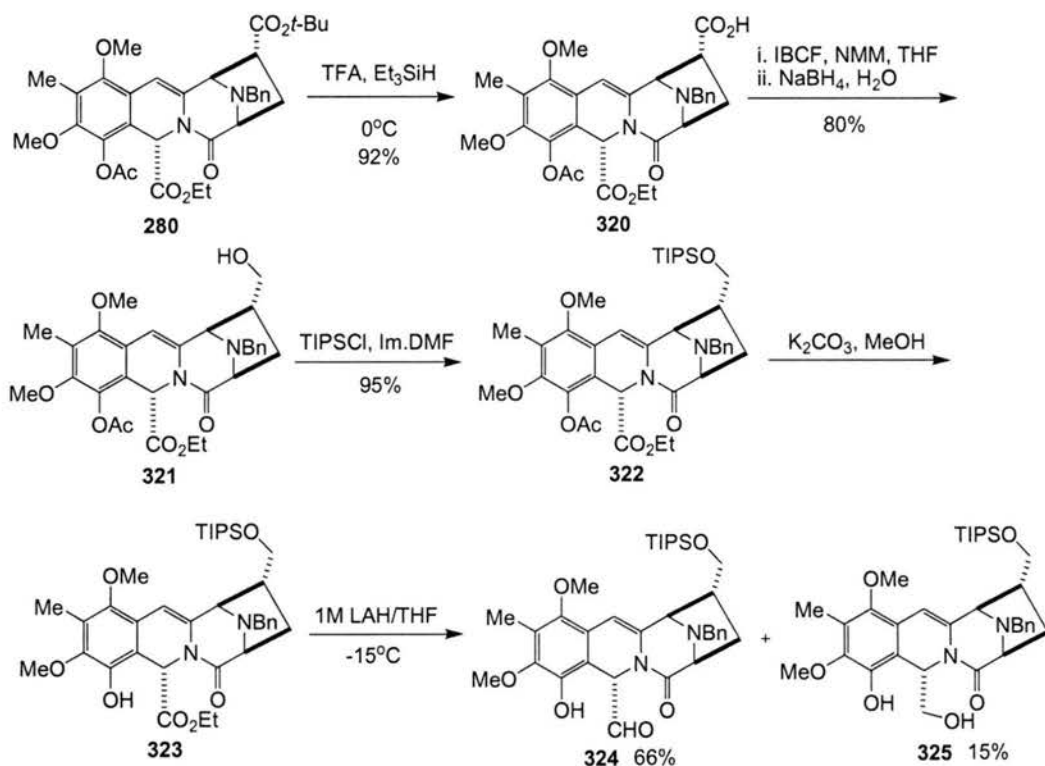
Scheme 79 Attempted reduction of **280**

Table 11 Attempted reduction of **280**

Substrate	Catalyst	H ₂ (psi)	Tmep.	Results
280	Raney-Ni	1500	r.t.	SM
280	Rh/C	1300	r.t.	SM
280	Rh/Alumina	1300	r.t.	SM
280	Rh(OAc) ₂	1500	r.t.	SM
280	RhCl ₃	1500	r.t.	SM
280	Willkinsons'	1500	r.t.	SM
280	Ir/C	1300	r.t.	SM
280	Crabtree's	1500	r.t.	SM
280	Pd/C	1300	r.t.	SM
280	PdCl ₂	1300	r.t.	SM
280	Pd(OH) ₂	1300	r.t.	SM

Since the reduction of the double bond could be employed at later stage of the synthesis, the further elaboration of tetra cycle **280** was explored in an effort to generate alternative reduction substrates.

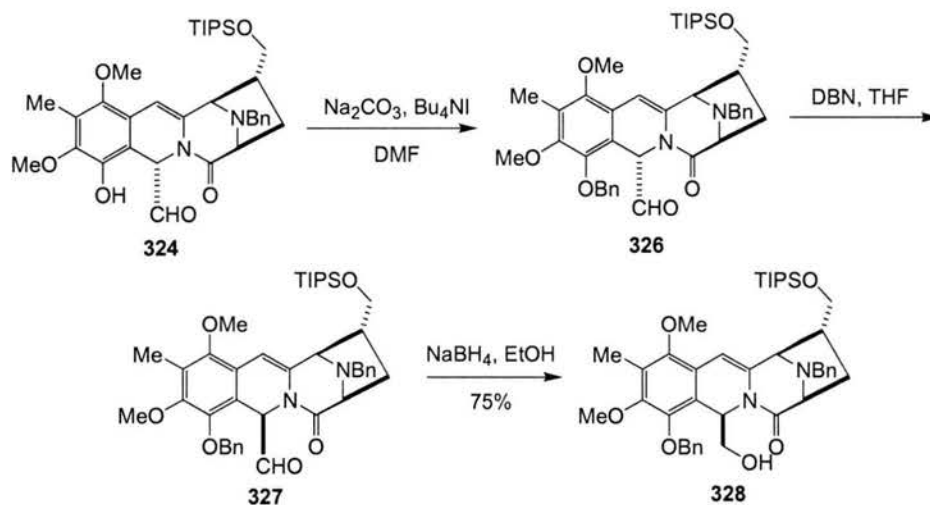
The next goal for further elaboration at this stage was to epimerize the C-1 center. In order to do that the tert-butyl ester **280** was converted to triisopropyl silyl ether **322** (Scheme 80). This was achieved by first converting **280** to acid **320** in 92% yield using a combination of TFA and Et₃SiH. Reduction of the corresponding mixed anhydride of **320** gave the alcohol **321** in 80% yield, which was then protected as tri-isopropyl silyl ether **322** in 95% yield. The epimerization of substrate **322** or its free phenol **323** both failed. When **322** was treated with DBU or DBN, hydrolysis of the acetate took place to give phenol **323** without any epimerization product and when EtONa or *t*-BuONa were employed, the reaction caused decomposition of both **322** and **323**. When NaHMDS, LDA and NaH were used, the deuteration experiments showed that no deprotonation took place at the C-1 center in each case. Instead, the ester **323** was reduced to its corresponding aldehyde **324**. Different hydride reagents (DIBAL, LiBH₄, super hydride, LAH) were used under various conditions (-78°C to refluxing in THF or ether). It was found out that treatment of **323** with 1 equivalent of 1M LAH in THF at -15°C could generate the aldehyde **324** in around 70% yield together with 10-15% corresponding alcohol **325**.



Scheme 80 Preparation of aldehyde **324**

Epimerization of aldehyde **324** using DBN resulted in decomposition of the starting material. However, when protected as benzyl ether, **326** could be epimerized to **327** by using DBN (Scheme 81). Unfortunately, the yields for both the phenol protection and the epimerization were very poor due to the base sensitivity of the starting materials. For the phenol protection, attempts to avoid using bases were unsuccessful. Triflic acid catalyzed benzylation using benzyl trichloroacetimidate proceeded very slowly and caused mainly decomposition of the starting materials. Ag_2O worked well on small scales under 20 mg, however the reaction preceded very slowly when more than 100 mg of starting material was used and extensive decomposition was also observed. When AgBF_4 was used, there was no reaction at 0°C but decomposition at room temperature. When NaH and KHMDS

was used there was no reaction at 0 °C; it did proceed slowly at room temperature, but was accompanied by extensive decomposition. Finally, when a variety of bases (Im., pyridine, DBU, K₂CO₃, Na₂CO₃, NaHCO₃) were screened, Na₂CO₃ was found to generate the desired aldehyde in a maximum yield of 60%. To optimize the epimerization step, an NMR reaction was set up. When 0.5 equivalent of DBN was used in 0.05 M **326** in 6d-THF solution, it was found out that the equilibrium of this epimerization reaction could be reached in 20 minutes at room temperature without significant loss of the starting materials. The reaction generated a mixture of products in a 1 to 0.6 ratio favoring the *cis* product **327**. After reduction using NaBH₄, the alcohol **328** was obtained in 75% yield.

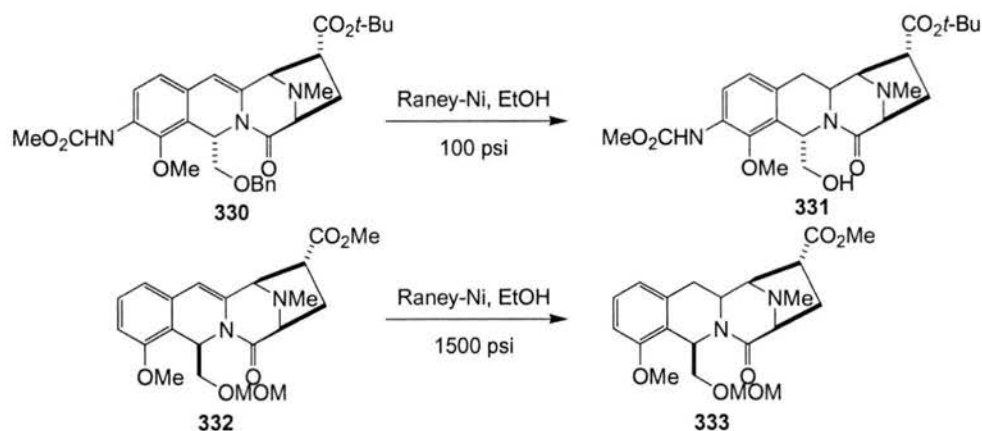


Scheme 81 Preparation of alcohol **328**

2.9 Attempted Reduction

Once alcohol **327** was obtained with the epimerized C-1 center, it allowed access to different substrates, which could be used to investigate the reduction of the enamide in

tetracycle **280**. In the case of tetrazomine(**33**) and quinocarcinamide (**103**), hydrogenation was carried out on similar substrates **330** and **332** successfully to generate **331** and **333** respectively (Scheme 82). It is interesting to notice that in case of **330** only 100 psi of hydrogen was required. This could be rationalized by either the stereochemistry of the C-1 center on substrate **330** aiding the alcohol to deliver the catalyst from the bottom face of the molecule or the difference in the electronic property of the benzene ring of **330**, which may lower the energy barrier for the hydrogenation.



Scheme 82 Existing examples of hydrogenation of **330** and **332**

Based on these rationales, different substrates that may be more susceptible to hydrogenation were prepared. Substrates **335** and **336** (Figure 16) were prepared aiming to alter the stereo-effect, having different stereochemistry at C-1. **335** Has the free alcohol, which might help deliver the catalyst from the bottom face of the molecule. Alternatively, **336** bearing the opposite stereochemistry at C-1 to **297**, has a more open bottom face for the catalyst to approach. Substrates **337** **338**, **339** and **340** (Figure 17) having electron poorer aromatic rings than **280** were prepared. In addition, substrate **337** and **338** were prepared as it was anticipated that they would be able to survive acidic conditions that may need to be employed in order to reduce the alkene. Unfortunately, no

desired product was isolated from the reaction using any of these substrates with a variety of catalysts, temperatures or the addition of acid (Scheme 83, Table 12).



Figure 16 Substrates **335** and **336** concerning the steric effect

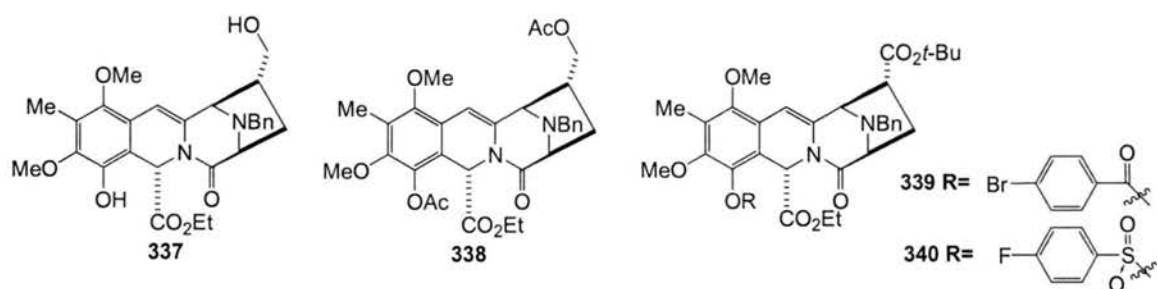
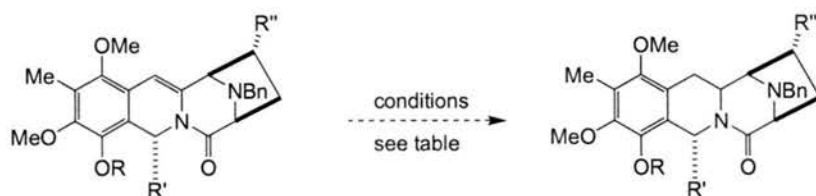


Figure 17 Substrates **337**, **338**, **339** and **340** concerning the electronic effect



Scheme 83 Hydrogenation of substrate **335-340**

Table 12 Hydrogenation of substrate **335-340**

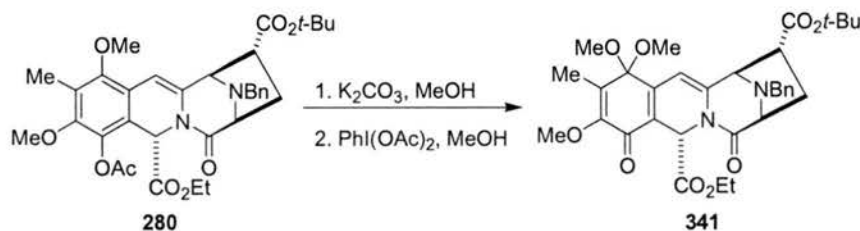
Substrate	Catalyst	H ₂ (psi)	°C	Results
335	Raney-Ni	1300	r.t.	SM
336	Willkinsons'	1500	r.t.	Shown vinyl proton
335/337	Rh/C	1500	65	SM
335/337	RhCl ₃	1500	65	SM

335/337	Pd(OH) ₂	1500	65	SM
335	Ir/C	1300	r.t.	SM
339	Raney-Ni	1000 / 500	r.t.	No desired product / SM
340	Raney-Ni	1000 / 500	r.t.	No desired product / SM
337/338	Pd/C, TFA	1300	r.t.	Removal of N-Bn

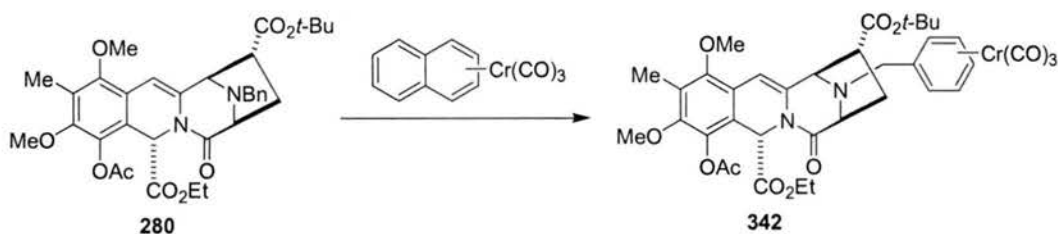
It was also noticed that the double bond was conjugated with both the electron rich benzene ring and the electron-withdrawing amide. To make the system simpler reduction of the amide in the conjugated system was attempted. However reduction with different hydrides reagents (LAH, LiEt₃BH, LiH₂NBH₃⁶⁰) under various conditions (from 0°C to refluxing in THF or ether) were unsuccessful. Cp₂ZrHCl, an effective reagent for reduction of tertiary amides⁶¹ and alkenes, also failed to deliver any of the desired reduction products. Attempted electrophilic activation of the amide⁶² for reduction by trifluoromethanesulfonic anhydride and pyridine was also failed, with only starting material being recovered from the reaction.

Aiming to dramatically change the conjugated system, **280** was converted to quinone ketal **341** (Scheme 84). However, attempted reduction of **341** by using hydrogenation at 110 psi in the presence of Pd/C or PdCl₂ didn't generate any desired product. The reduction was also not successful when L-selectride was applied. Another attempt involved the synthesis of the arene-Cr(CO)₃ complex of **280**, in order to dramatically change the electronic property of the benzyl ring.⁶³ However, the reaction of **280** with naphthalene Cr(CO)₃ complex⁶⁴ generated **342** having Cr(CO)₃ complexed with the benzyl ring in the N-benzyl functionality (Scheme 85). At this stage, a clean method

for the removal of the N-Bn had not been found, therefore further investigation of forming the desired $\text{Cr}(\text{CO})_3$ complex of **280** was abandoned.



Scheme 84 Preparation of quinone ketal **341**



Scheme 85 Preparation of compound **342**

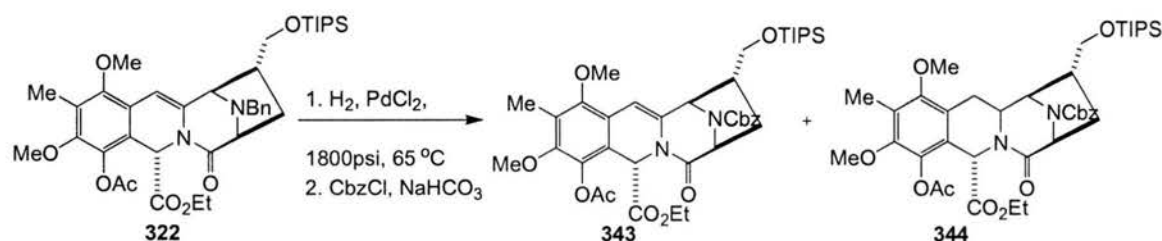
Using substrates with this conjugated system, other reduction conditions were investigated. Ionic reduction, diimide reduction, hydrogen transfer reaction using HCOOH and Pd black and SmI_2 reduction gave mainly recovered starting materials. Birch reduction caused the decomposition of the starting material due to the presence of such an electron rich aromatic ring. Attempts to modify the double bond by oxidative addition reactions such as dihydroxylation, hydroboration, oxymercuration, halogenation, or radical reactions also didn't yield any promising leads.

Most recently, a good high-pressure reactor allows us to manipulate the hydrogenation reaction at 2000 psi, 65 °C. Promising results have been achieved by using freshly made Raney-Ni. The crude NMR of these reactions showed a single product without the vinyl proton (Table 13, entry 5 and 6). However, the product seemed to be

unstable and any attempt to isolate it by preparative TLC resulted in decomposition. In addition, the reactivity of the Raney-Ni was different from batch to batch and had a very short bench lifetime. This made it difficult to obtain repeatable results when Raney-Ni was used. When PdCl₂ was employed with substrate **328**, under 1800 psi and 65 °C, the crude hydrogenation reaction products were treated with CbzCl in MeOH with NaHCO₃. Two products have been isolated from this reaction. The major product was **343**, while the other one doesn't have the vinyl proton in ¹H-NMR, but didn't have the correct mass. After extensive NMR study, it was concluded that it was not the desired product **344** (Scheme 86).

Table 13 Hydrogenation of substrate **280**, **322**, **325** and **328**

Entry	Substrate	Catalyst	psi	Temp	Results
1	280/325 /328	Ra-Ni (A)	2,000	r.t.	de-Bn+SM
2	325	Willkinson	2,000	65 °C	SM
3	325	Ru black	2,000	65 °C	SM
4	280	Rh/Alumina	2,000	65 °C	de-Bn+SM
5	325/328	Ra-Ni (A)	2,000	65 °C	Promising product
6	280	Ra-Ni (B)	1,500	65 °C	Promising product
7	322	PdCl ₂	1,800	65 °C	Promising product



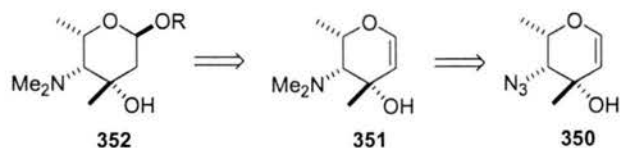
Scheme 86 Reduction of **322**

2.10 Preparation of the Sugar Moiety

As described in chapter one, lemomycin is unique in bearing a sugar moiety, which has been encountered the first time in the tetrahydroisoquinoline family. Moreover, the 2,6-dideoxy-4-amino sugar is rare in nature and has been found in only two unrelated natural product families.²⁶ The synthesis of 2-deoxy glycosides⁶⁵ is a small but important niche in the field of carbohydrate chemistry. The preparation of the 2-deoxyglycosyl function has been found in several important antibiotic families, like anthracycline antibiotics,⁶⁶ aureolic acid family of antitumor antibiotics,⁶⁷ avermectin antibiotics⁶⁸ and landomycin antibiotics.⁶⁹

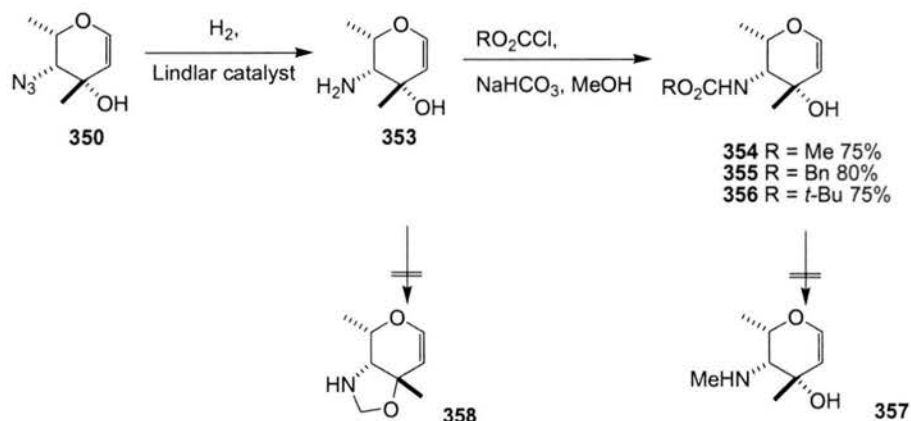
Glycal is a very versatile synthetic intermediate especially in the synthesis of 2-deoxy glycoside. When only hydrogen is attached to C-2, will the thermodynamic effect in tetrahydropyran will favor the axial linkage of the electronegative functional group on C-1. The acid-catalyzed activation of glycals is a general method for 2-deoxyglycosyl transformations. However, it was accompanied by varying degrees of Ferrier reaction,⁷⁰ where the oxygen constituent at C-3 is eliminated to form an allylic carbonium ion. Falck and Mioskowski showed that use of triphenylphosphine hydrogen bromide suppressed the Ferrier reaction pathway, thus making the direct method of glycal activation general and useful.⁷¹ In addition, a simple glycal can be converted to other glycosyl donors, which can be activated in different ways.^{72, 65}

It was planned to use glycal **351** as an intermediate to synthesize the 2-deoxyglycoside in lemomycin (**352**). The glycal **351** could be derived from the known compound **350** (Scheme 87).⁷³



Scheme 87 synthetic analysis of **352**

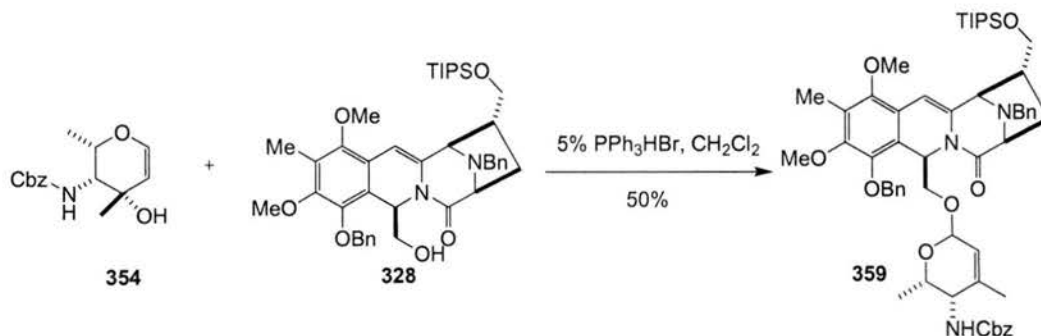
Hydrogenation of **350** using Lindlar's catalyst afforded a primary amine **353** (Scheme 88), which could be protected in the form of different carbamates (**354-355**). Reduction of methyl carbamate **354** and benzyl carbamate **355** using LAH in refluxing THF failed to generate the methyl group in **357**. Treatment of formaldehyde with the crude hydrogenation product **353** didn't afford any isolatable oxazolidine product **358**. Synthesis of *N*-dimethyl glycal **351** is still under investigation.



Scheme 88 Preparation of glycal **354-355**

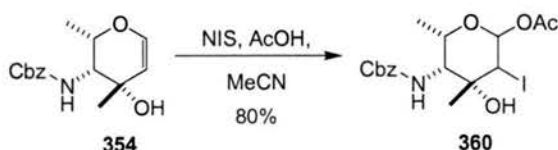
With **354** in hand, glycosidation of tetracycle **328** was investigated. When **354** was activated by $\text{PPh}_3\cdot\text{HBr}$, the glycosidation reaction only generated the Ferrier reaction product **359** (Scheme 89). The reason for this might come from use of excess $\text{PPh}_3\cdot\text{HBr}$. Because of the limited amount of the glycosyl acceptor, the reaction scale was limited to

5-10 mg, which made it difficult to measure catalytic amounts of $\text{PPh}_3\cdot\text{HBr}$. The use of a pre-prepared $\text{PPh}_3\cdot\text{HBr}$ solution in CH_2Cl_2 only caused deactivation of the reaction. Therefore, an optimized route for producing sufficient amount of glycosyl acceptor **328** was required and is still under investigation.



Scheme 89 Glycosidation of **328** with **354**

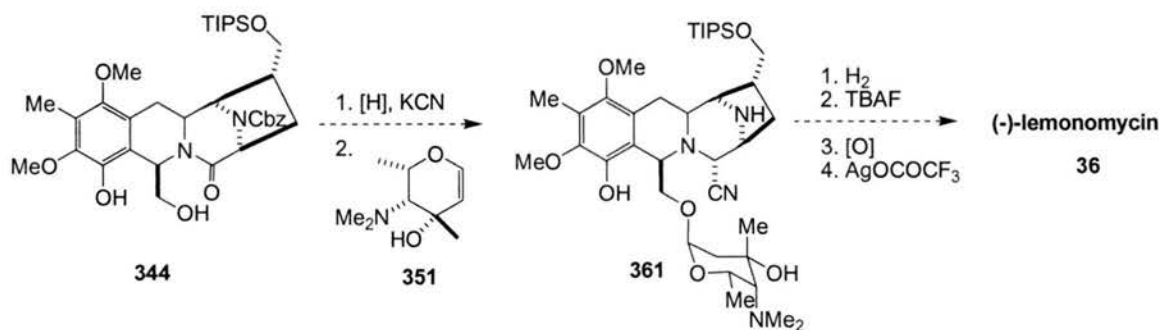
Glycals have also been activated using a variety of halogen sources.^{65, 72} The halogenated glycoside can be easily reduced to the desired 2-deoxyglycoside. When glycal **354** was treated with NIS in presence of AcOH, the reaction generated the desired glycoside **360** (Scheme 90). However, when treated **354** with NIS, no glycosidation took place with glycosyl acceptor **328**. When glycoside **358** was activated with TMSOTf or $\text{BF}_3\cdot\text{Et}_2\text{O}$, the reaction didn't proceed in presence of the glycosyl acceptor **328**.



Scheme 90 Glycosidation of **354**

Conversion of the glycal **354** to other types of glycosyl donors, with or without a functional group on C-2, is still under investigation.

Ideally, once a good protocol of reduction is developed, the tetracycle **344** will be reduced to its corresponding aminonitrile and coupled with glycal **351** to afford **361**. After removal of the Cbz protecting group and liberation of the alcohol, two consecutive oxidations will furnish the quinone and aldehyde functionalities. Finally, conversion of the animonitrile to hemiaminal will complete the synthesis of (-)-lemonomycin (**36**) (Scheme 91).



Scheme 91 Synthetic plan towards total synthesis of (-)-lemonomycin

2.11 Conclusion

Towards the total synthesis of (-)-lemonomycin, the tetracycle **328** has been prepared. A diastereoselective Pictet-Spengler reaction has been developed to construct the AB ring system (**256**), which has been applied in the total synthesis of (-)-jorumycin, (-)-renieramycin G.⁷⁴ The choice of using secondary amine **243**, with a bulky chiral

template on nitrogen, controlled the excellent diastereoselectivity of this reaction. An interesting oxidation facilitated dihydroisoquinoline azomethine ylide formation to construct the C and D ring (**280**) efficiently. Although the detailed mechanism of this oxidation is still not clear, it has been postulated that molecular oxygen is most likely to be the oxidant and that TFA facilitates the process. In addition, it was proved that the oxidation took place at the stage of treatment of **279** with TFA.

Intensive effort has been made into the highly challenging reduction of the enamide. It appears that Raney-Ni is the more promising catalyst. When the Raney-Ni had a good activity, it was able to reduce **280**, **325** and **328** under hydrogen at 1500 psi and 65 °C.

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- ⁶⁷ (a) *Studies on the Synthesis of Aureolic Acid Antibiotics: Highly Stereoselective Synthesis of Aryl 2-Deoxy-glycosides via the Mitsunobu Reaction and Synthesis of the Olivomycin A-B Disaccharide.* Roush, W. R.; Lin, X. J. *Am. Chem. Soc.* **1995**, *117*, 2236-2250. (b) *Aureolic acid antibiotics: a simple method for 2-deoxy- β -glycosidation.* Ramesh, S.; Kaila, N.; Grewal, G.; Frank, R. W. *J. Org. Chem.* **1990**, *55*, 5-7.
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- ⁶⁹ *Efficient Synthesis of the Hexasaccharide Fragment of Landomycin A: Using Phenyl 2,3-O-Thionocarbonyl-1-thioglycosides as 2-Deoxy-glycoside Precursors.* Yu, B.; Wang, P. *Org. Lett.* **2002**, *4*, 1919-1922.

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⁷⁴ *Asymmetric Total Syntheses of (-)-Jorumycin, (-)-Renieramycin G, 3-epi-Jorumycin, and 3-epi-Renieramycin G*. Lane, J. W.; Chen, Y.; Williams, R. M. *J. Am. Chem. Soc.* **2005**, 127, 12684-12690.

Experimental Section

3.1 General Procedures

Unless otherwise noted, materials were obtained from commercially available sources and used without further purification. Toluene, diethyl ether, THF and dimethyl formamide were degassed with argon and passed through a solvent system (J.C. Meyer of glass Contour). The molecular sieves were activated by heating at 150 °C at 1 mm Hg for 3h in a vacuum oven.

All reactions involving hydroscopic substances were conducted with flames or oven dried glassware under an inert atmosphere (Ar) dried by passage of atmospheric gases through a column packed with CaSO₄.

Chromatographic separations were performed with EM Science TLC plates (silica gel 60, F254, 20 x 20cm x 250µm) or with EM Science 230-240 mesh silica gel under positive air pressure. Reactions and chromatographic fractions were monitored and analyzed with EM Science TLC plates. Visualizations on TLC were achieved with ultraviolet light and heating of TLC plates submerged in a 5% solution of phosphomolybic acid in 95% ethanol.

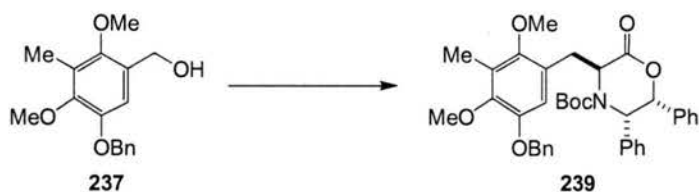
Infrared spectra were recorded on a Perkin-Elmer 1600 series FT-IR as thin films from methylene chloride and are reported as λ_{max} in wavenumbers (cm⁻¹).

Nuclear magnetic resonance (NMR) spectra were acquired using a Bruker AC-300, Varian 300 or 400 spectrometers. NMR chemical shifts are given in parts per million (ppm) relative to internal CHCl₃, DMSO, or methanol. Proton (¹H) NMRs are tabulated in the following order: number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q,

quartet; and m, multiplet) and coupling constant in hertz. When appropriate, the multiplicity of a signal is denoted as "br" to indicate that the signal was broad.

Mass spectra were obtained on Fisons VG Autospec. Optical rotations were obtained on a Rudolph Research automatic polarimeter Autopol III.

3.2 Preparation of Compounds

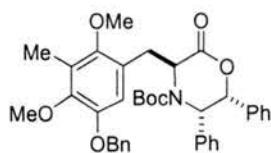


3-(5-Benzyloxy-2,4-dimethoxy-3-methyl-benzyl)-2-oxo-5,6-diphenyl-morpholine-4-carboxylic acid tert-butyl ester (239)

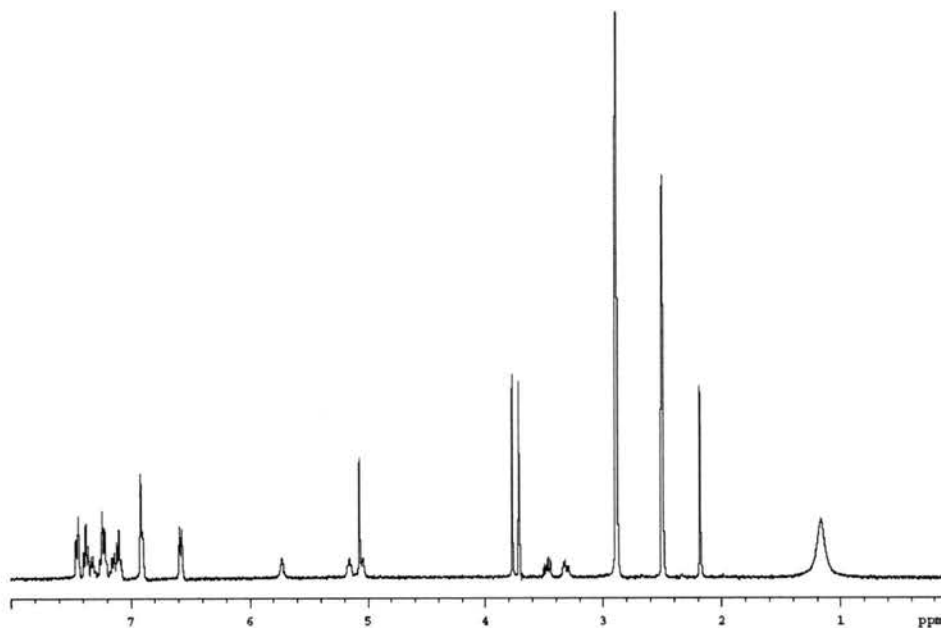
I₂ (3.96 g, 15.6 mmol) was added to a solution of PPh₃ (4.09 g, 15.6 mmol) in CH₂Cl₂ (104 mL) at 0 °C. After the yellow slurry was stirred for 5 min, a solution of **237** (3.00 g, 10.4 mmol) and imidazole (1.06 g, 31.2 mmol) in CH₂Cl₂ (69 mL) was added dropwise by cannula. After stirring for 30 minutes at 0 °C, the reaction mixture was diluted with CH₂Cl₂ (100 mL) and washed successively with 5% NaHSO₃ (20 mL), H₂O (10 mL), brine (10 mL). After drying (Na₂SO₄) and concentration under reduced pressure, the crude product was used for the next stage.

N-Boc-Williams' lactone **238** (4.03 g, 10.4 mmol) was dissolved in THF (80 mL), cooled down to -78 °C and then NaHMDS (11.40 mL, 11.4 mmol) was added dropwise. After the reaction mixture was stirred for 30 min, solution of the crude benzyl iodide in THF (50 mL) was dropped in. After 4h at -78 °C the reaction was poured into EtOAc (300 mL) and washed with saturated aqueous NH₄Cl (30 mL) followed by brine. The organic layer was dried (Na₂SO₄), concentrated under reduced pressure and purified by flash chromatography (silica, 6:1 hexane:AcOEt) affording **239** (4.93 g, 76% yield from **237**). ¹H NMR (400 MHz, DMSO, 120°C): δ 1.17 (9H, bs), 2.18 (3H, s), 3.50 (1H, 1/2 ABX, *J*_{AB} = 13.6 Hz), 3.40 (1H, 1/2 ABX, *J*_{AB} = 13.2 Hz), 3.71 (3H, s), 3.77 (3H, s), 5.07

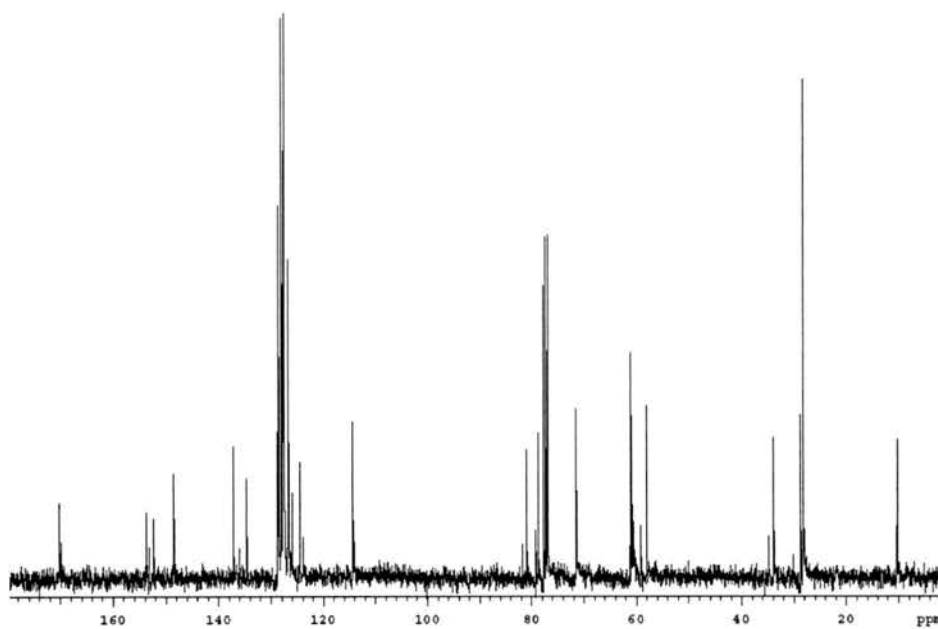
(3H, m), 5.16 (1H, m), 5.73 (1H, s), 6.60 (2H, m), 6.91 (3H, m), 7.49- 7.07 (11H, m), ^{13}C NMR (75 MHz, CDCl_3 , mixture of rotamers): δ 10.3, 10.4, 28.3, 28.7, 33.9, 34.8, 58.1, 59.2, 60.4, 60.8, 61.0, 61.3, 71.4, 71.5, 78.7, 79.2, 81.0, 81.7, 114.1, 114.4, 123.9, 124.5, 126.0, 126.6, 127.5, 127.6, 127.7, 127.9, 128.0, 128.5, 128.7, 134.6, 126.0, 137.2, 148.3, 148.6, 152.4, 153.1, 153.8, 169.7, 170.1, IR (NaCl, depos. from CH_2Cl_2): 2932, 2359, 1757, 1700, 1240cm^{-1} . $[\alpha]_{\text{D}}^{25} = +24.1$ ($c=1.0$, CH_2Cl_2). HRMS (FAB) calcd for $\text{C}_{38}\text{H}_{41}\text{NO}_7$ (MH^+) 623.2883; found 623.2887. Mp: 182-183 °C.



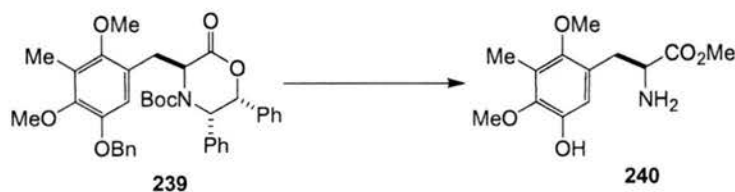
239



^1H NMR, 400 MHz, DMSO, 120°C, filename: YY-II-151.120°C

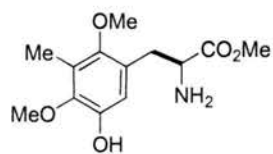


^{13}C NMR, 75 MHz, CDCl_3 , filename: YY-II-443.13C

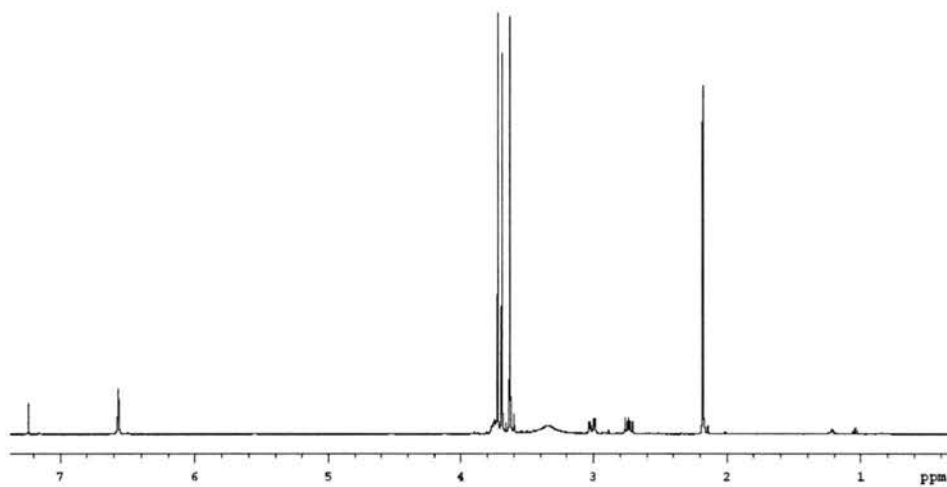


2-Amino-3-(5-hydroxy-2,4-dimethoxy-3-methyl-phenyl)-propionic acid methyl ester
(**240**)

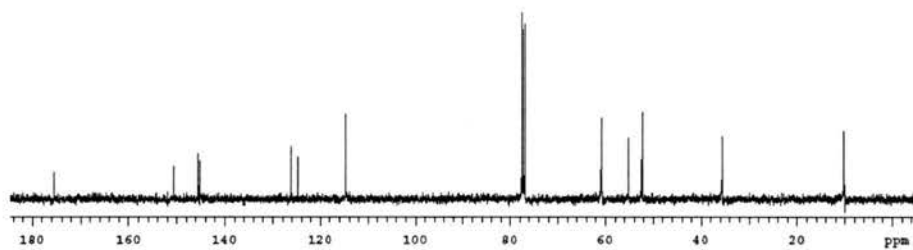
To a solution of **239** (0.10 g, 0.16 mmol) in CH_2Cl_2 (3 mL) was added TFA (0.12 mL, 1.6 mmol). After 4 hours the reaction mixture was concentrated under reduced pressure. The crude product was used without further purification for the subsequent hydrogenation. A pressure tube containing the crude product in 1M HCl in MeOH (5 mL) was purged with argon for 5 minutes. 20% Pd(OH)₂ (10 mg) was then added to the mixture and the tube pressurized to 70 psi with hydrogen gas. The tube was then purged another 2 times with hydrogen and stirred for 24 hours under 70 psi. After releasing the pressure the reaction mixture was filtered through a pad of celite, washed with MeOH (20 mL) and concentrated under reduced pressure. The resulting residue was diluted with CH_2Cl_2 (20 mL) and washed with sat. NaHCO_3 (2 mL), brine (2 mL). The organic layer was dried (Na_2SO_4), concentrated down and purified by flash chromatography (silica, 10:1 CH_2Cl_2 : MeOH) affording **240** (37 mg, 85% yield from **239**). ^1H NMR (400 MHz, CDCl_3): δ 2.18 (3H, s), 2.73 (1H, dd, $J = 8.7, 13.6$ Hz), 3.01 (1H, dd, $J = 4.3, 13.6$ Hz), 3.34 (2H, bs), 3.63 (3H, s), 3.69 (3H, s), 3.72 (3H, s), 3.75 (1H, m), 6.57 (1H, s), ^{13}C NMR (100 MHz, CDCl_3): δ 10.1, 35.6, 52.3, 55.1, 60.7, 60.8, 114.7, 124.8, 126.2, 145.2, 145.6, 150.7, 175.6, IR (NaCl, depos. from CH_2Cl_2): 3359, 3294, 2950, 1738, cm^{-1} , HRMS (FAB) calcd for $\text{C}_{13}\text{H}_{20}\text{NO}_5$ (MH^+) 270.1341; found 270.1329.



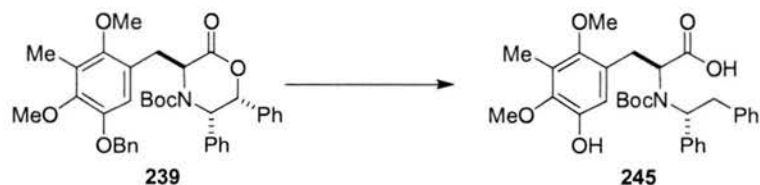
240



¹H NMR, 400 MHz, CDCl₃, filename: YY-IV-043

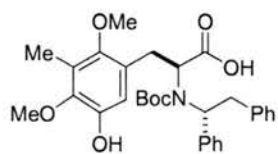


¹³C NMR, 100 MHz, CDCl₃, filename: YY-IV-043.13C

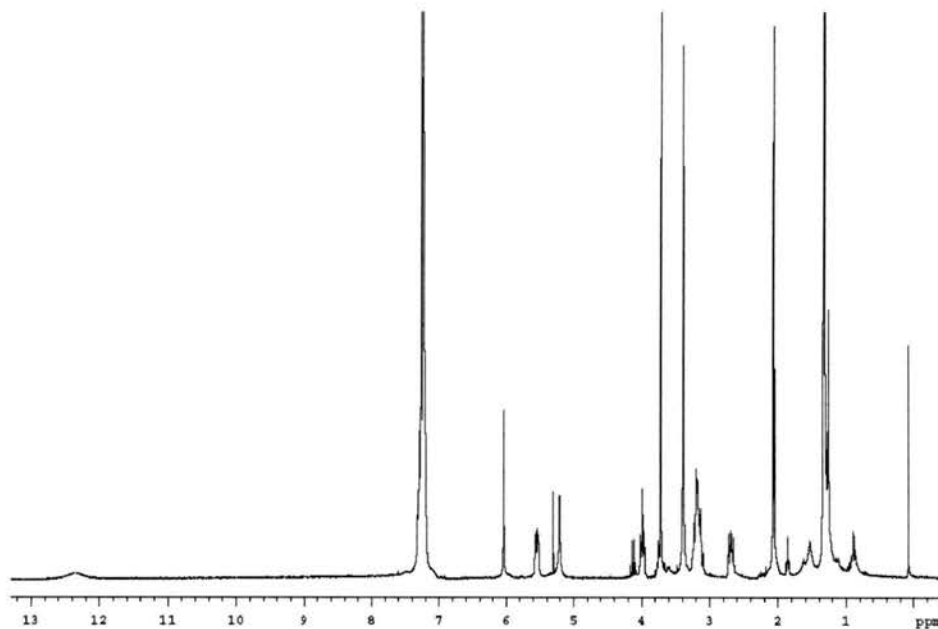


2-[tert-Butoxycarbonyl-(1,2-diphenyl-ethyl)-amino]-3-(5-hydroxy-2,4-dimethoxy-3-methyl-phenyl)-propionic acid (245**)**

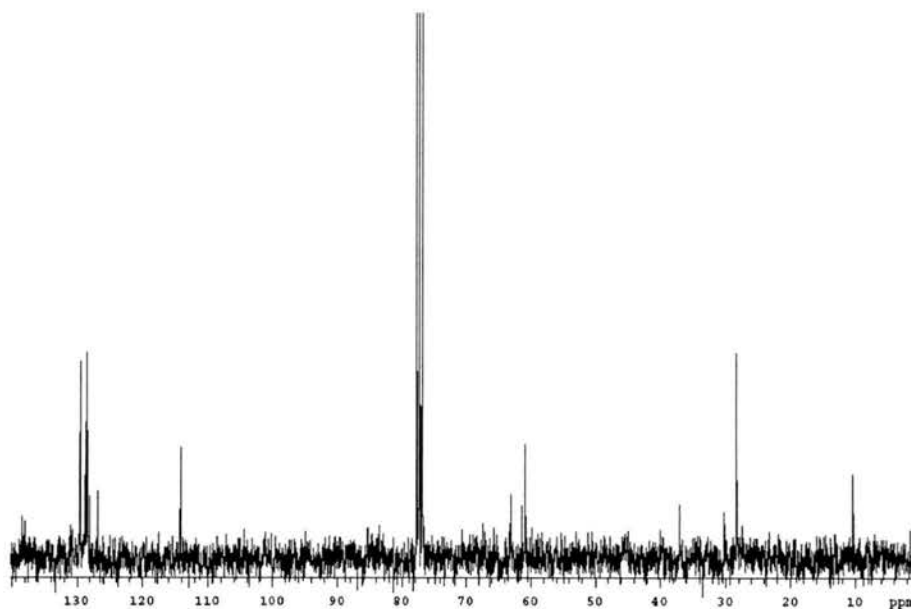
A pressure tube containing **239** (1.5 g, 2.40 mmol) in absolute ethanol (60 ml) was purged with argon for 15 minutes, 10% Pd/C (300 mg) was then added to the mixture and the tube pressurized to 70 psi with hydrogen gas. The tube was purged another 2 times with hydrogen and the pressurized tube then stirred for 24 hours. After releasing the pressure the reaction mixture was filtered through a pad of celite and concentrated under reduced pressure. The resulting residue was purified by chromatography (silica, 1:1 hexane:AcOEt) affording **245** (1.2g, 93% yield). ^1H NMR (300MHz, CDCl_3 , mixture of rotamers, major isomer was reported): 1.32 (9H, s), 2.07 (3H, s), 2.67 (1H, dd, $J = 8.4$, 14.1 Hz), 3.18 (3H, m), 3.39 (3H, s), 3.72 (3H, s), 4.0 (1H, t, $J = 7.8$ Hz), 5.21 (1H, s), 5.54 (1H, dd, $J = 4.2$, 10.2 Hz), 6.04 (1H, s), 7.18-7.35 (10H, m), 12.37 (1H, br). ^{13}C NMR (75 MHz, CDCl_3 , mixture of rotamers): δ 10.2, 28.3, 30.1, 37.2, 60.9, 61.3, 63.1, 114.2, 126.8, 128.0, 128.3, 128.5, 128.7, 129.5, 138.3, 144.9. IR (NaCl, depos. from CH_2Cl_2): 3384, 3029, 2931, 1692, 1482, 1453, 1418, 1160 cm^{-1} . HRMS (FAB) calcd. For $\text{C}_{31}\text{H}_{38}\text{NO}_7$ (MH^+): 536.2648, Found: 536.2650. $[\alpha]_{\text{D}}^{25} = +20.5$ ($c = 1.0$, CH_2Cl_2).



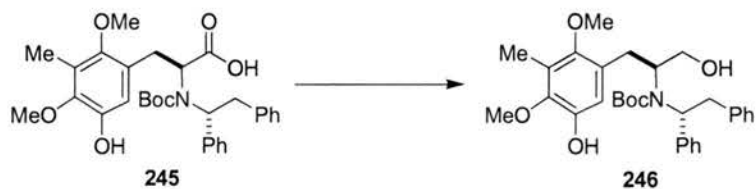
245



^1H NMR, 300 MHz, CDCl_3 , filename: YY-II-445



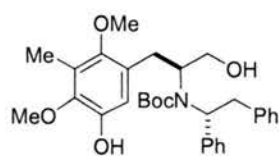
^{13}C NMR, 75 MHz, CDCl_3 , filename: YY-II-455.13C



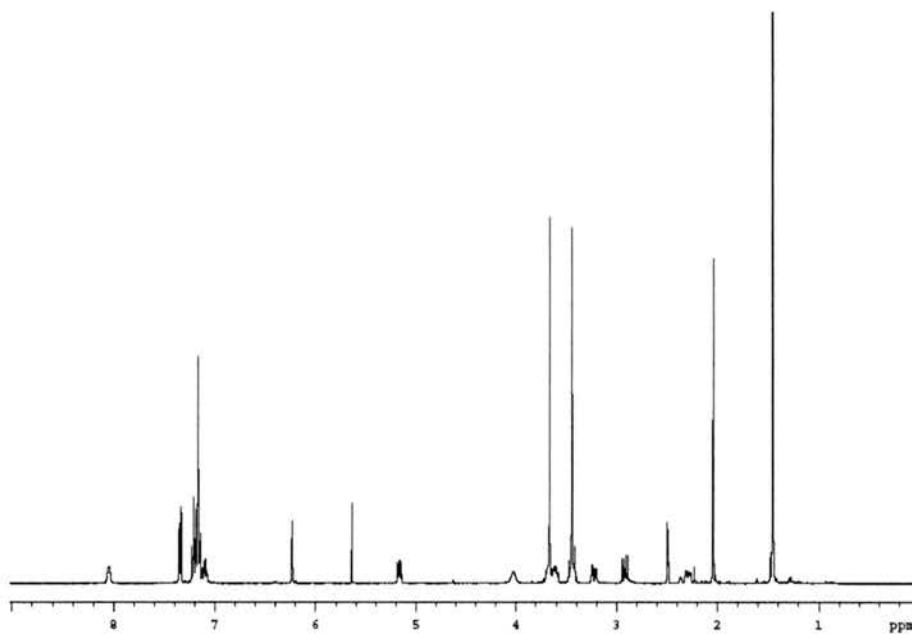
(1,2-Diphenyl-ethyl)-[2-(5-hydroxy-2,4-dimethoxy-3-methyl-phenyl)-1-

hydroxymethyl-ethyl]-carbamic acid tert-butyl ester (246**)**

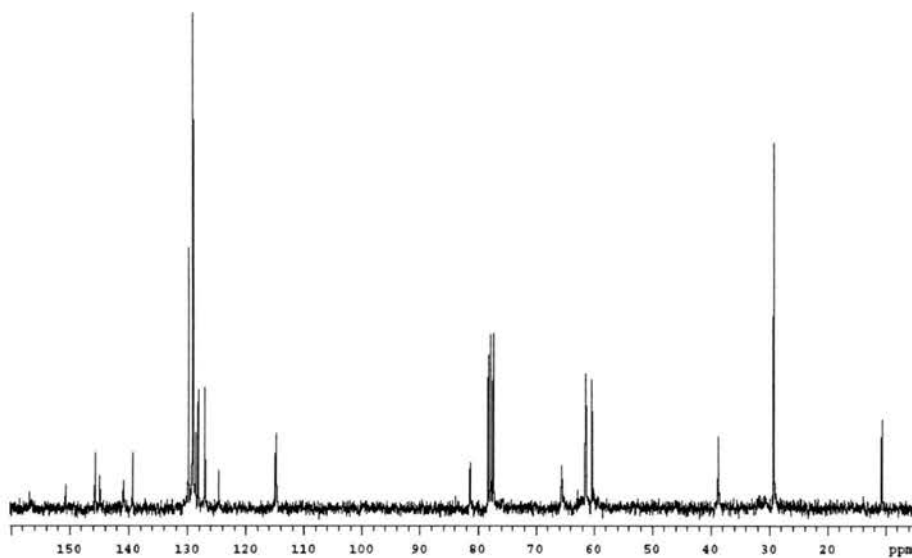
To a solution of **245** (6.4 g, 11.90 mmol) in THF (237 mL), NMM (1.3 mL, 11.90 mmol) was added followed by isobutylchloroformate (1.6 mL, 11.90 mmol). After stirring at room temperature for 20 minutes, the resulting reaction mixture was filtered through Celite and added to an ice-cold suspension of NaBH₄ (2.3 g, 60 mmol) in water (120 mL). The reaction mixture was stirred at 0 °C for 3 hours and then quenched with 1M HCl (50 mL). The resulting mixture was stirred for another hour at 0 °C and then extracted with EtOAc, washed with brine and dried (Na₂SO₄). After concentration under reduced pressure, the resulting residue was purified by flash chromatography (silica, 4:1 hexane:AcOEt) affording **246** (4.6 g, 75% yield from **245**). ¹H NMR (400 MHz, DMSO, 120°C): δ 1.42 (9H, s), 2.00 (3H, s), 2.23 (1H, m), 2.87 (1H, dd, *J* = 8.1, 13.8 Hz), 3.17 (1H, m), 3.40 (3H, s), 3.34–3.47 (2H, m), 3.60 (3H, s), 3.60–3.70 (2H, m), 4.05 (1H, bs), 5.15 (1H, dd, *J* = 3.2, 9.1 Hz), 6.18 (1H, s), 7.03–7.33 (10H, m), 8.08 (1H, bs). ¹³C NMR (75 MHz, CDCl₃, mixture of rotamers): δ 10.7, 29.3, 38.7, 60.4, 61.3, 61.4, 65.5, 81.3, 114.8, 124.6, 127.0, 128.1, 128.6, 129.0, 129.8, 139.3, 140.8, 144.9, 145.7, 150.6, 156.9. IR (NaCl, depos. from CH₂Cl₂): 3389, 2973, 2930, 1660, 1452, 1165 cm⁻¹. HRMS (FAB) calcd. For C₃₁H₄₀NO₆ (MH⁺): 522.2856, Found: 522.2879. [α]_D²⁵ = +34.2 (*c* = 1.0, CH₂Cl₂)



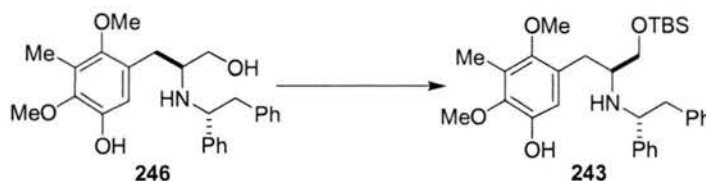
246



^1H NMR, 400 Hz, DMSO, 120°C, filename: YY-II-157.120°C



^{13}C NMR, 75 MHz, CDCl_3 , filename: YY-II-453.13C

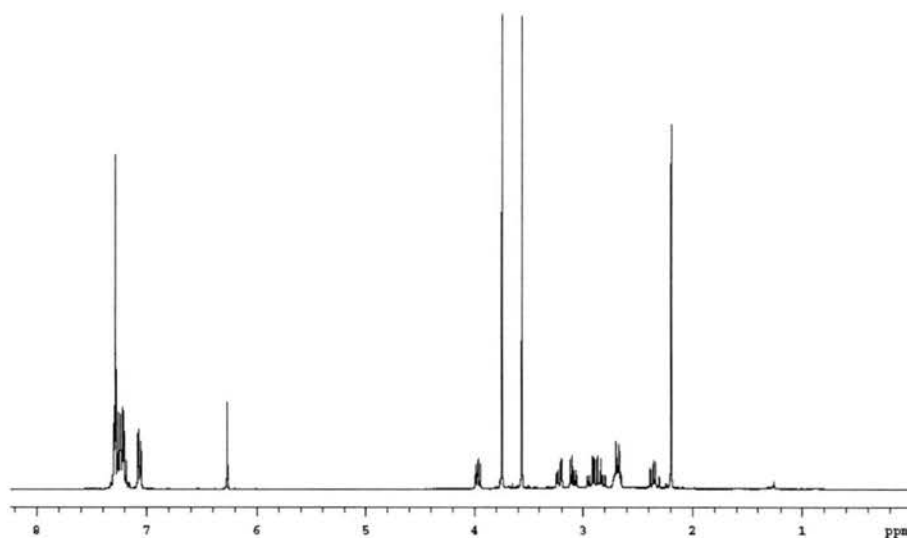
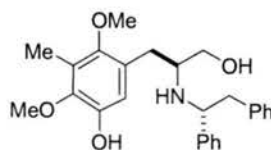


5-((S)-3-(tert-butyldimethylsilyloxy)-2-((R)-1,2-diphenylethylamino)propyl)-2,4-dimethoxy-3-methylphenol (243)

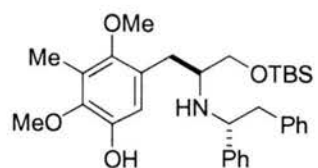
To a solution of **246** (4.6 g, 8.80 mmol) in CH_2Cl_2 (176 mL), TFA (33.9 mL, 44.00 mmol) was added dropwise at room temperature and the resulting solution was stirred for 40 minutes. The reaction mixture was diluted with CH_2Cl_2 (500 mL), washed with water (50 mL) saturated aqueous NaHCO_3 (50 mL), brine (50 mL) and dried (Na_2SO_4). After concentration under reduced pressure, the resulting crude amine used directly without further purification. ^1H NMR (300MHz, CDCl_3): 2.20 (3H, s), 2.34 (1H, dd, $J = 9, 15.6$ Hz), 2.69 (2H, m), 2.83 (1H, dd, $J = 8.7, 13.5$ Hz), 2.93 (1H, dd, $J = 3.9, 10.8$ Hz), 3.09 (1H, dd, $J = 5.7, 11.1$ Hz), 3.22 (1H, dd, $J = 3.9, 10.8$ Hz), 3.56 (3H, s), 3.75 (3H, s), 3.97 (1H, dd, $J = 6.0, 8.4$ Hz), 6.27 (1H, s), 7.05-7.30 (10H, m).

To a stirred solution of the crude amine in CH_2Cl_2 (880 mL) was added TBSCl (2.65 g, 17.6 mmol) followed by Et_3N (3.7 mL, 26.40 mmol). After 19 hours the mixture was washed with saturated aqueous NH_4Cl , brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (silica, 6:1 hexane:AcOEt) affording **243** (4.15 g, 88% yield from **246**). ^1H NMR (300MHz, CDCl_3): δ -0.05 (6H, s), 0.84 (9H, s), 2.20 (3H, s), 2.53 (1H, dd, $J = 7.5, 13.2$ Hz), 2.70 (2H, m), 2.88 (2H, m), 3.33 (1H, s), 3.35 (1H, s), 3.50 (3H, s), 3.76 (3H, s), 3.94 (1H, t, $J = 6.6$ Hz), 6.46 (1H, s), 7.00-7.30 (10H, m). ^{13}C NMR (75 MHz, CDCl_3): δ -5.0, 10.3, 18.6, 26.3, 32.0, 46.0, 57.4, 60.8, 61.0, 62.6, 65.8, 114.5, 124.2, 126.2, 127.0, 127.7, 128.2, 128.9, 129.5, 139.0, 144.2, 144.2, 145.0, 150.6. IR (NaCl, depos. from CH_2Cl_2): 3341, 3061,

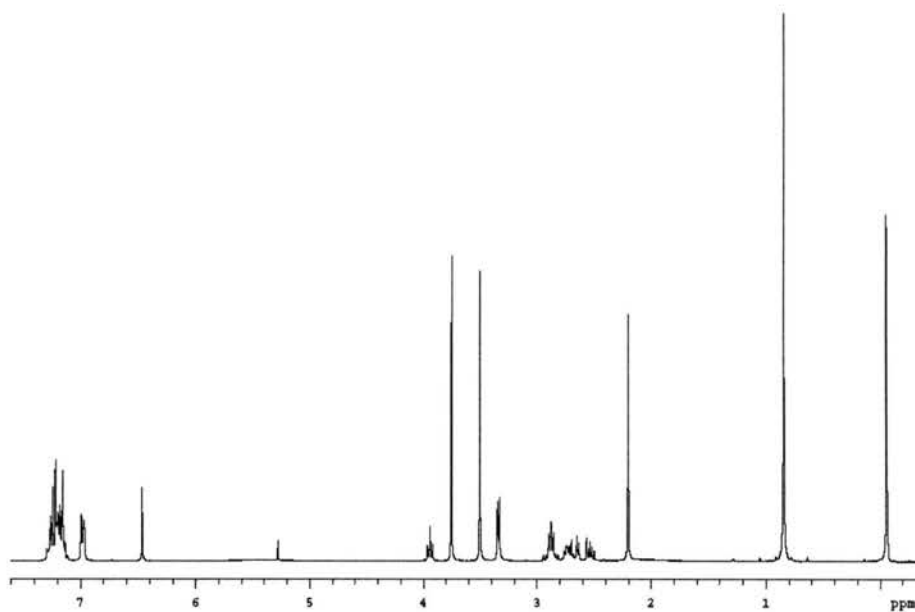
3027, 2951, 2929, 2855, 1601, 1481, 1453 cm^{-1} . HRMS (FAB) calcd. For $\text{C}_{32}\text{H}_{46}\text{NO}_4\text{Si}$ (MH^+): 536.3196, Found: 536.3197. $[\alpha]_{\text{D}}^{25} = -4.9$ ($c = 1.0$, CH_2Cl_2).



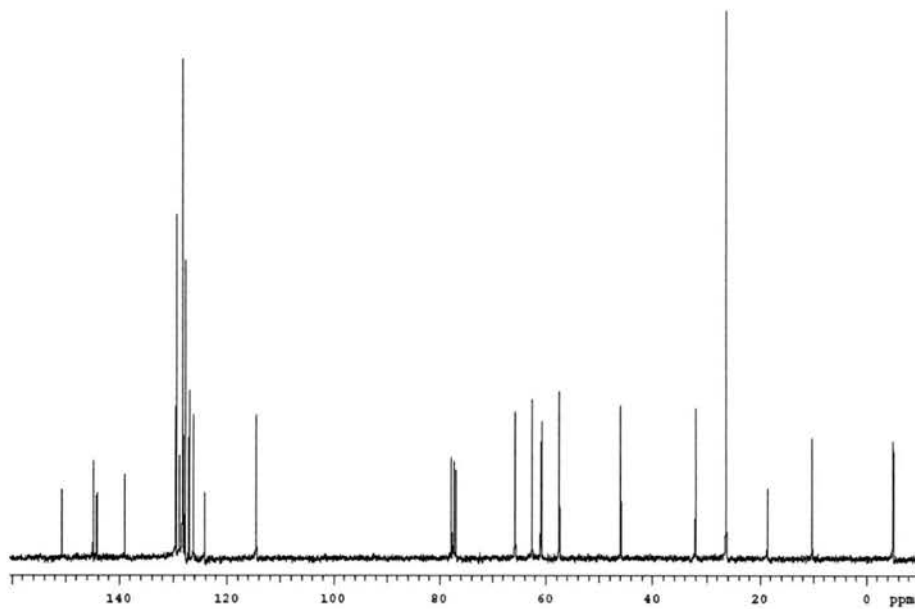
^1H NMR, 300 MHz, CDCl_3 , filename: YY-I-344



243



^1H NMR, 300 MHz, CDCl_3 , filename: YY-II-160

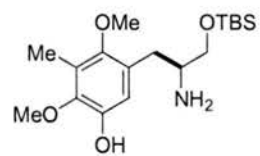


^{13}C NMR, 75 MHz, CDCl_3 , filename: YY-II-160.13C

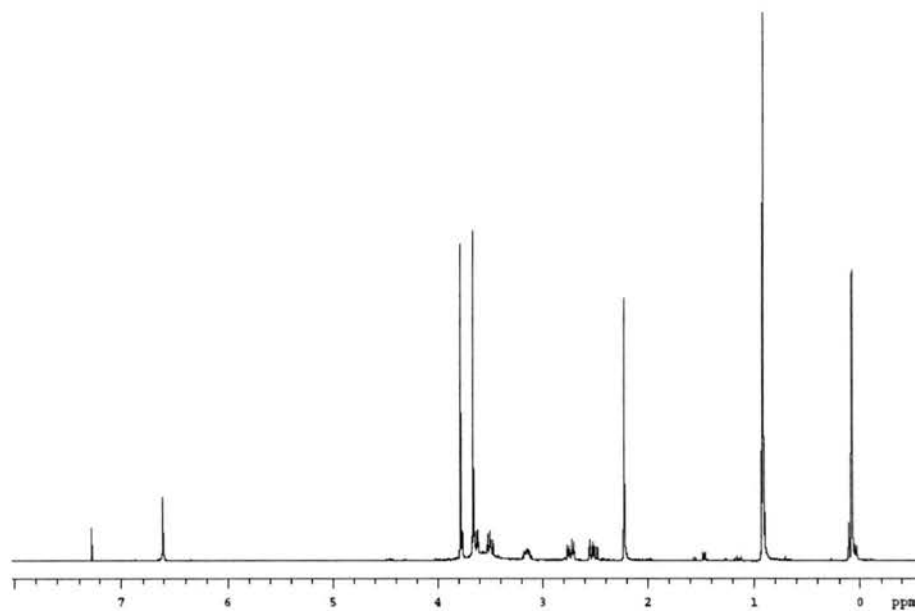


**(S)-5-(2-amino-3-(tert-butyldimethylsilyloxy)propyl)-2,4-dimethoxy-3-methylphenol
(241)**

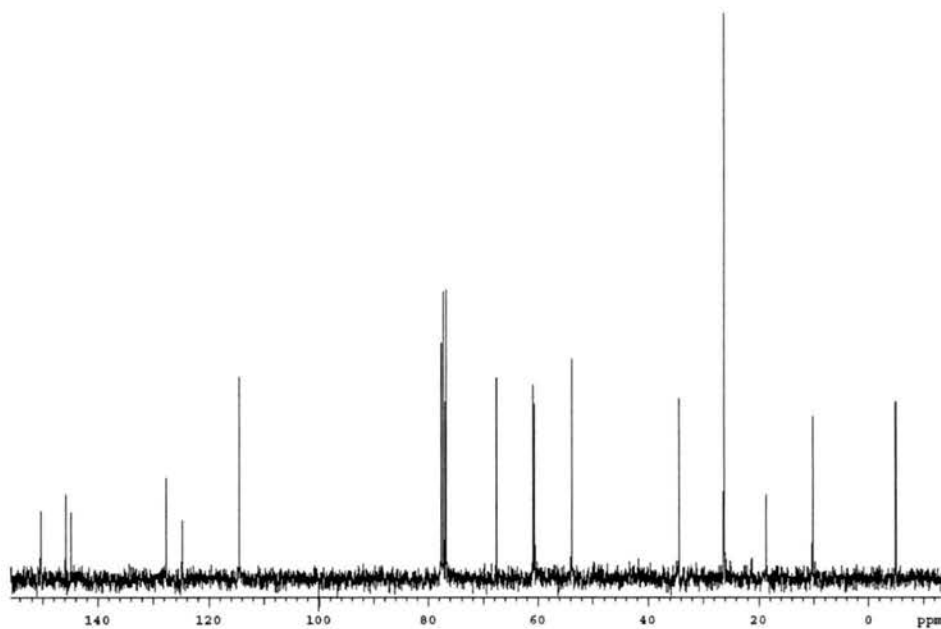
A pressure tube containing **243** (100 mg, 0.19 mmol) in absolute ethanol (5 ml) was purged with argon for 5 minutes, 20% Pd(OH)₂ (10 mg) added to the mixture and the tube pressurized to 70 psi with hydrogen gas. The tube was then purged another 2 times with hydrogen. The pressurized tube was then stirred for 24 hours at 70 psi. After releasing the pressure the reaction mixture was filtered through a pad of celite and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (silica, 20:1 EtOAc:MeOH) affording **241** (66 mg, 95% yield from **243**). ¹H NMR (300MHz, CDCl₃): δ 0.07 (6H, s), 0.92 (9H, s), 2.23 (3H, s), 2.52 (1H, 1/2 ABX, *J*_{AB} = 8.6 Hz), 2.74 (1H, 1/2 ABX, *J*_{AB} = 5.1 Hz), 3.15 (1H, m), 3.50 (1H, 1/2 ABX, *J*_{AB} = 6.4 Hz), 3.60-3.68 (1H, m), 3.66 (3H, s), 3.79 (3H, s), 6.61 (1H, s). ¹³C NMR (75 MHz, CDCl₃): δ -5.0, 10.2, 18.6, 26.2, 34.3, 53.9, 60.7, 60.9, 67.6, 114.5, 124.9, 127.7, 144.9, 145.8, 150.4. IR (NaCl, depos. from CH₂Cl₂): 3356, 2952, 2930, 2856 cm⁻¹. HRMS (FAB) calcd. For C₁₈H₃₄NO₄Si (MH⁺): 356.2257, Found: 356.2261.



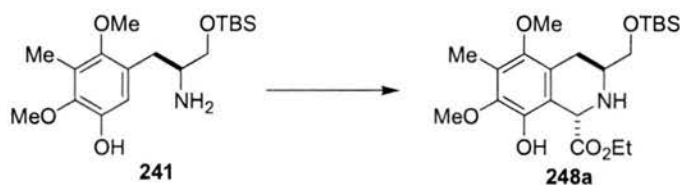
241



^1H NMR, 300 MHz, CDCl_3 , filename: YY-#-038



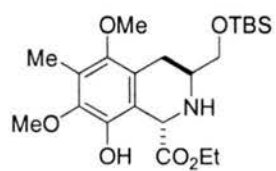
^{13}C NMR, 75 MHz, CDCl_3 , filename: YY-#-038.13C



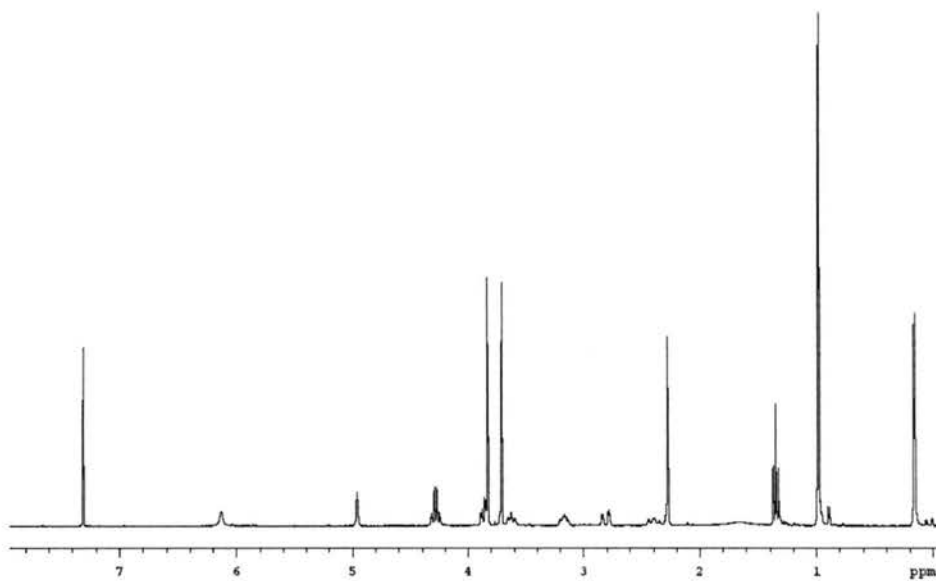
ethyl 3-((tert-butyldimethylsilyloxy)methyl)-8-hydroxy-5,7-dimethoxy-6-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (248**)**

To a solution of **241** (20 mg, 0.06 mmol) in MeCN (1 mL) was added glyoxalate (17 μ L, 0.09 mmol). The reaction mixture was warmed to 45 °C and stirred for 16 hours. After concentrated under reduced pressure, the resulting residue was purified by chromatography (silica, 6:1 EtOAc:Hexane) affording **248** of two diastereomers (16 mg, 62% yield from **241**).

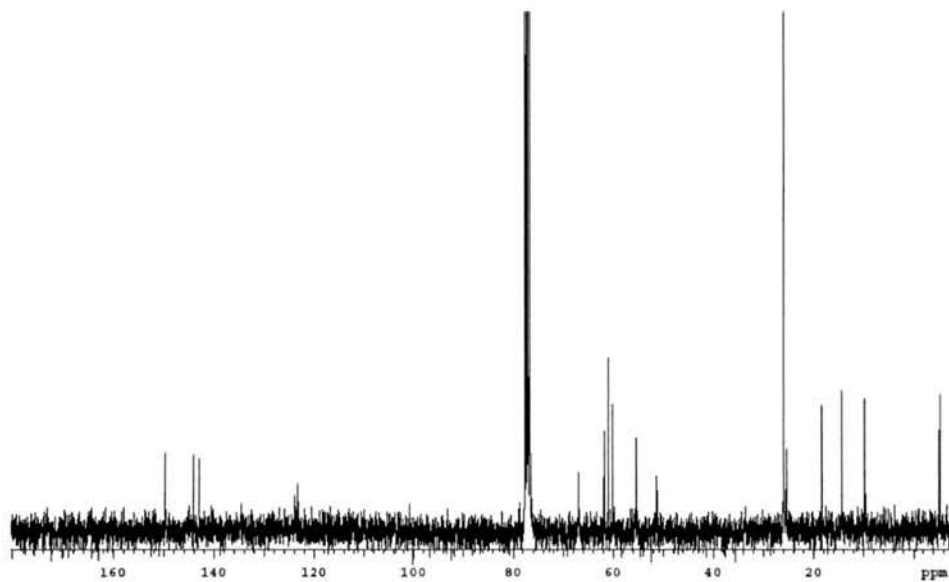
To a solution of **248** (16 mg, 0.04 mmol) in THF (0.80 mL) was added DBN (2 μ L, 0.02 mmol). After stirring for 12 hours, the reaction mixture was quenched with saturated NH_4Cl (1 mL) and extracted with EtOAc(10 mL). The organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (silica, 6:1 hexane:AcOEt) affording **248a** (13 mg, 80% yield from **248**). ^1H NMR (300MHz, CDCl_3): δ 0.15 (3H, s), 0.17 (3H, s), 1.00 (9H, s), 1.35 (3H, t, J = 7.0 Hz), 2.28 (3H, s), 2.40 (1H, dd, J = 11.3, 15.5 Hz), 2.81 (1H, dd, J = 3.7, 16.8 Hz), 3.18(1H, m), 3.63 (1H, m), 3.71 (3H, s), 3.83 (3H, s), 3.87 (1H, 3.7, 10.0 Hz), 4.28 (2H, m), 4.96 (1H, s), 6.13 (1H, m). ^{13}C NMR (75 MHz) (CDCl_3): δ -5.3, -5.2, 9.7, 14.4, 18.4, 25.5, 26.0, 51.3, 55.3, 60.0, 60.9, 61.7, 66.9, 123.5, 143.0, 144.2, 150.0. HRMS (FAB) calcd. For $\text{C}_{22}\text{H}_{38}\text{NO}_6$ Si (MH^+): 440.2468, Found: 440.2479.



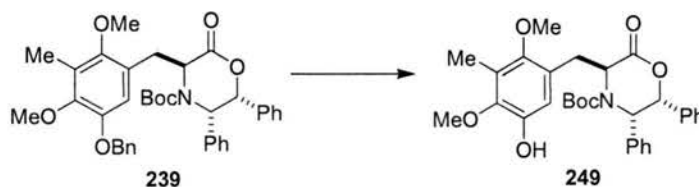
248a



¹H NMR, 300 MHz, CDCl₃, filename: YY-#039

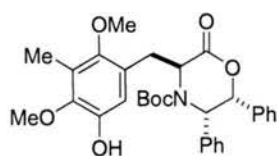


¹³C NMR, 75 MHz, CDCl₃, filename: YY-#-039.13C

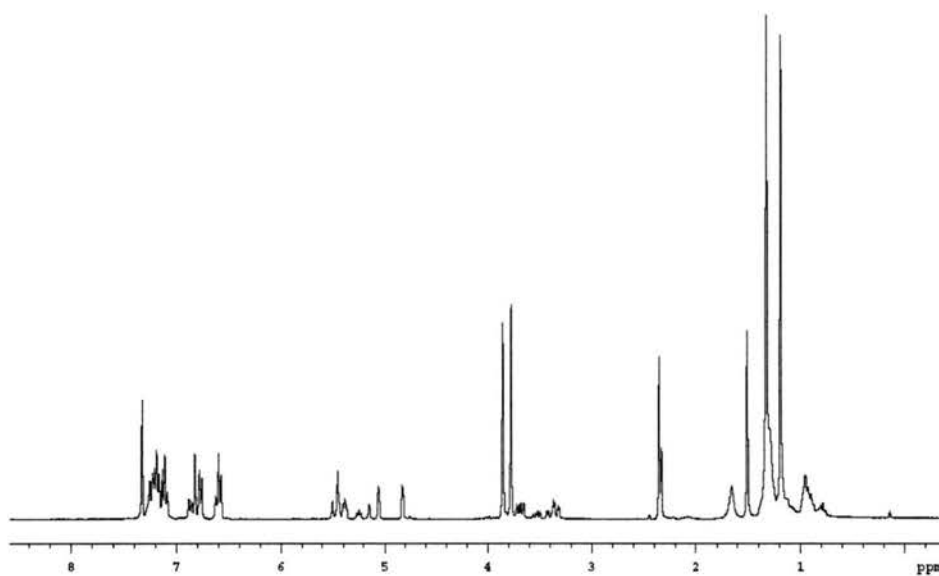


(3S,5S,6R)-tert-butyl 3-(5-hydroxy-2,4-dimethoxy-3-methylbenzyl)-2-oxo-5,6-diphenylmorpholine-4-carboxylate (249**)**

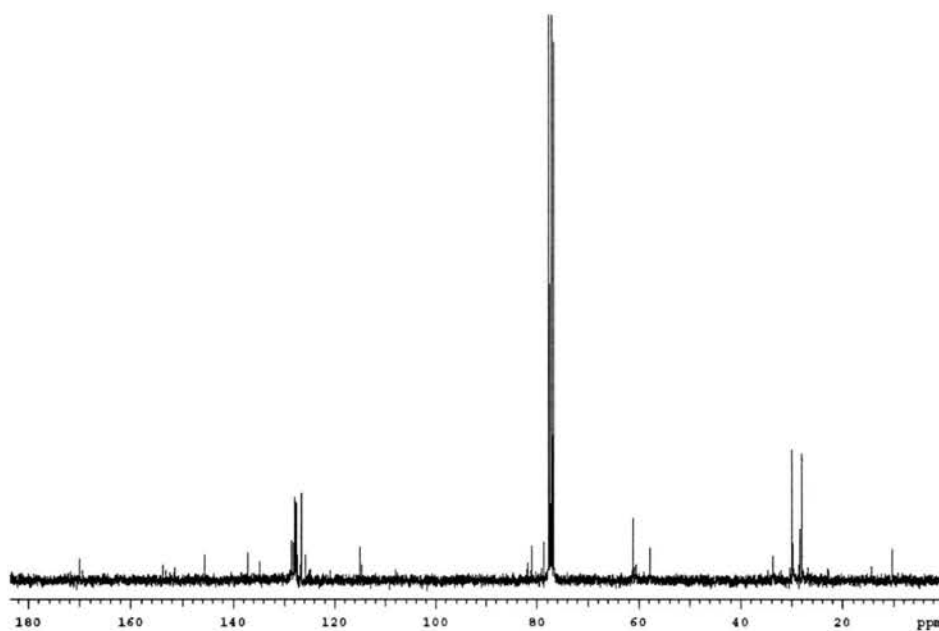
A solution of **239** (100 mg, 0.16 mmol) in THF (10 mL) was purged with argon for 5 min and 5% Pd/C (10 mg) was then added. The reaction mixture was then stirred under a hydrogen balloon for 12h. After this time, the reaction mixture was filtered through a pad of celite and concentrated under reduced pressure. The resulting residue was purified by chromatography (silica, 3:1 Hexane: EtOAc) affording **249** (81 mg, 95% yield from **239**). ^1H NMR (300MHz, CDCl_3 , mixture of rotamers in 1: 0.5 ratio): 1.33 (13.5H, s), 2.33 (1.5H, s), 2.35 (3H, s), 3.37 (1.5H, m), 3.53 (0.5H, dd, $J= 7.4, 13.4$ Hz), 3.69 (1H, dd, $J=7.1, 13.4$ Hz), 3.78 (4.5H, s), 3.86 (4.5H, s), 4.83 (1H, s), 5.05 (1H, s), 5.15 (0.5H, s), 5.25 (0.5H, t, $J= 5.6$ Hz), 5.38 (1H, t, $J= 5.6$ Hz) 5.45 (1.5H, s), 5.50 (0.5H, s), 6.55-7.38 (15H, m). ^{13}C NMR (75 MHz, CDCl_3 , mixture of rotamers): δ 10.2, 28.0, 28.5, 29.9, 33.7, 57.8, 61.0, 78.6, 80.9, 81.8, 114.6, 115.1, 125.8, 126.6, 126.7, 127.4, 127.5, 127.7, 127.9, 128.0, 128.1, 128.5, 134.7, 137.1, 145.5, 151.5, 153.7, 169.9



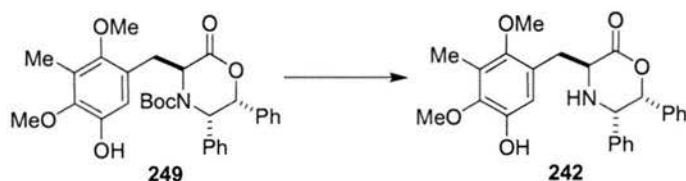
249



^1H NMR, 300 MHz, CDCl_3 , filename: YY-I-181

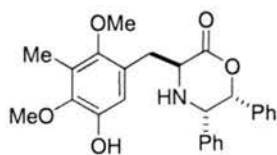


^{13}C NMR, 75 MHz, CDCl_3 , filename: YY-I-181.13C

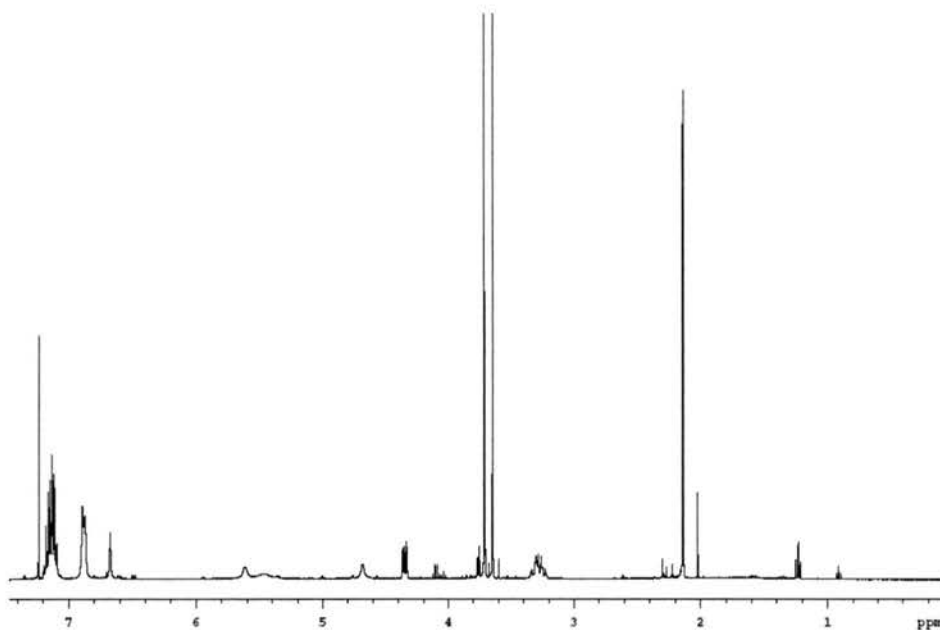


(3S,5S,6R)-3-(5-hydroxy-2,4-dimethoxy-3-methylbenzyl)-5,6-diphenylmorpholin-2-one (242)

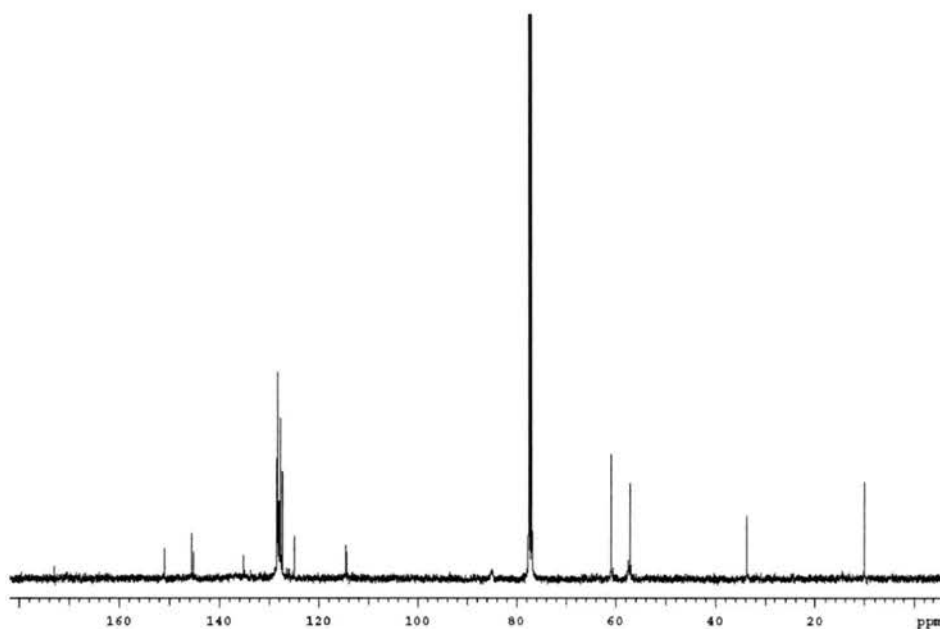
To a solution of **249** (81 mg, 0.15 mmol) in CH_2Cl_2 (3 mL), was added TFA (0.12 mL, 1.5 mmol). After stirring for 4 h, the reaction was quenched with H_2O (0.5 mL), washed with saturated NaHCO_3 (2 x 0.5 mL) and brine. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (silica, 1:1 hexane:AcOEt) affording **242** (55 mg, 85% yield from **249**). ^1H NMR (400MHz, CDCl_3): δ 2.14 (3H, s), 3.20-3.37 (2H, m), 3.65 (3H, s), 3.71 (3H, s), 4.35 (1H, dd, $J = 4.7, 9.2$ Hz), 4.69 (1H, s), 5.46 (1H, bs), 5.62 (1H, s), 6.67 (1H, s), 6.83-7.20 (10H, m). ^{13}C NMR (100 MHz) (CDCl_3): δ 10.1, 33.7, 57.1, 60.9, 114.5, 127.4, 127.8, 128.1, 128.3, 128.4, 135.1, 145.2, 145.6, 151.0, 173.0. IR (NaCl, depos. from CH_2Cl_2): 3330, 2938, 1731 cm^{-1} . HRMS (FAB) calcd. For $\text{C}_{26}\text{H}_{28}\text{NO}_5$ (MH^+): 434.1967, Found: 434.1969.



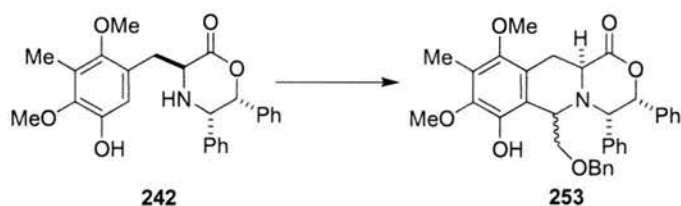
242



^1H NMR, 400 MHz, CDCl_3 , filename: YY-I-127

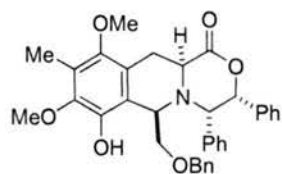


^{13}C NMR, 100 MHz, CDCl_3 , filename: YY-I-127.13C

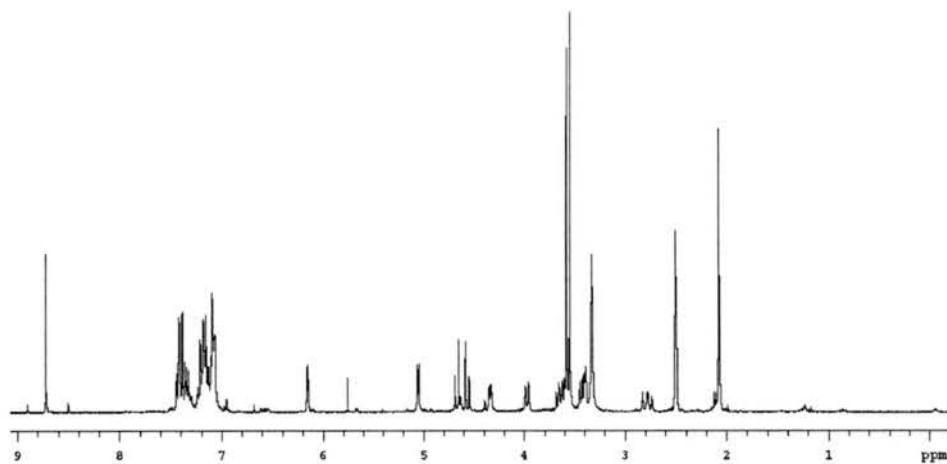


(3R,4S,11aS)-6-(benzyloxymethyl)-7-hydroxy-8,10-dimethoxy-9-methyl-3,4-diphenyl-3,4,11,11a-tetrahydro-[1,4]oxazino[4,3-b]isoquinolin-1(6H)-one (253)

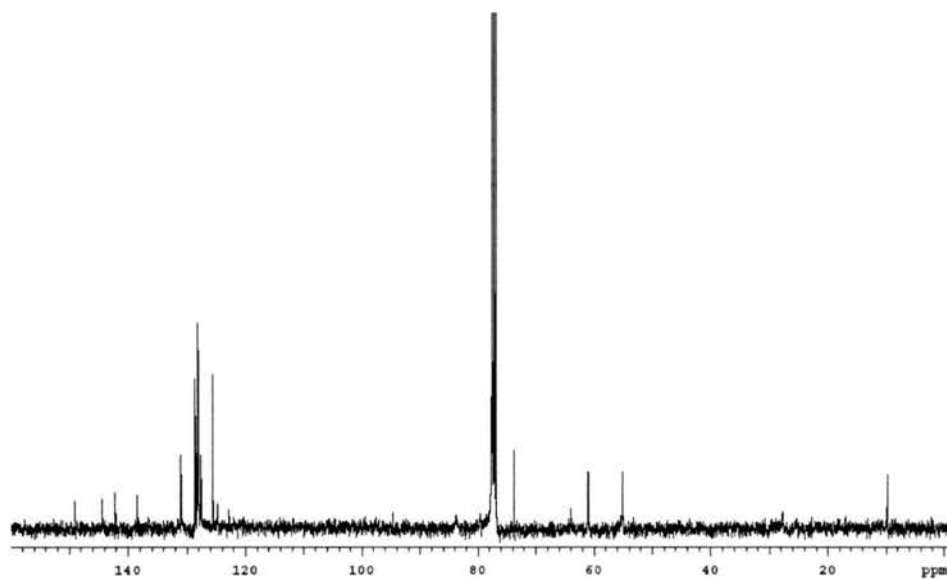
To a solution of **242** (95 mg, 0.22 mmol) in MeCN (2.2 mL), was added **250** (50 mg, 0.33 mmol) and the reaction warmed to 50 °C. After stirring for 20 h the reaction was concentrated under reduced pressure. The residue was purified by flash chromatography (silica, 6:1 hexane:AcOEt) affording a mixture of **253a** and **253b** (110 mg, 88% yield from **242**). For the *cis* isomer ¹H NMR (300MHz, DMSO): δ 2.08 (3H, s), 2.78 (1H, dd, *J*=11.7, 15.6 Hz), 3.37-3.47 (2H, m), 3.55 (3H, s), 3.58 (3H, s), 3.64 (1H, dd, , *J*= 1.8, 9.3 Hz), 3.97 (1H, dd, *J*= 1.8, 9.2 Hz), 4.34 (1H, d, *J*= 6.4 Hz), 4.56 (1H, d, *J*= 11.9 Hz), 4.67 (1H, d, *J*= 11.9 Hz), 5.06 (1H, d, *J*= 3.8 Hz), 6.15 (1H, d, *J*= 4.0 Hz), 7.03-7.46 (15H, m), 8.72 (1H, s). ¹³C NMR (100 MHz, CDCl₃): δ 9.8, 55.1, 61.0, 73.7, 125.6, 127.6, 128.0, 128.2, 128.5, 128.7, 131.0, 138.4, 142.2, 144.4, 149.1. IR (NaCl, depos. from CH₂Cl₂): 3409, 2927, 1739, 1453 cm⁻¹. HRMS (FAB) calcd. For C₃₅H₃₆NO₆ (MH⁺): 566.2543, Found: 566.2534. For the *trans* isomer ¹H NMR (300MHz, DMSO): δ 2.11 (3H, s), 2.84 (1H, dd, *J*= 5.7, 17.2 Hz), 3.22 (1H, dd, *J*= 11.9, 17.2 Hz), 3.42 (1H, dd, *J*= 2.7, 10.4 Hz), 3.53 (3H, s), 3.64 (3H, s), 3.74 (1H, dd, *J*= 8.2, 10.1 Hz), 4.29 (1H, dd, *J*= 2.9, 7.7 Hz), 4.37 (2H, s), 4.61 (1H, d, *J*= 4.8 Hz), 4.68 (1H, dd, *J*= 5.5, 11.4 Hz), 5.65 (1H, d, *J*= 4.6 Hz), 6.90-7.36 (15H, m), 8.48 (1H, s).



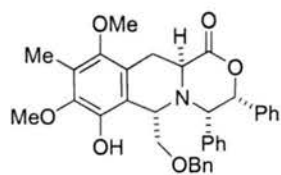
253b



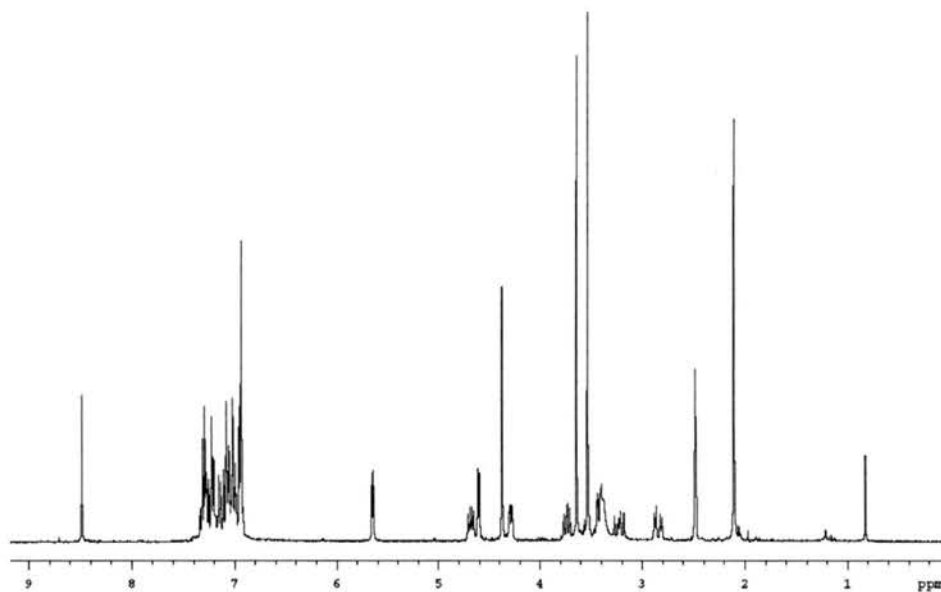
^1H NMR, 300 MHz, DMSO, filename: YY-I-120



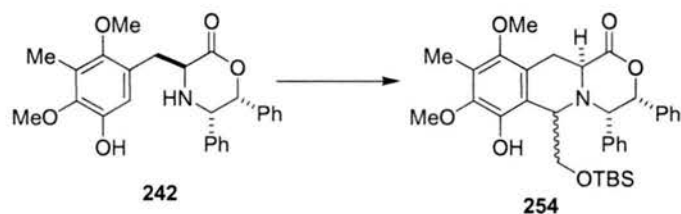
^{13}C NMR, 100 MHz, CDCl_3 , filename: YY-I-120.13C



253a

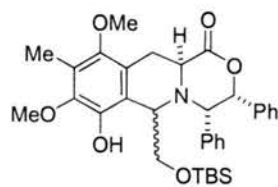


^1H NMR, 300 MHz, DMSO, filename: YY-I-111

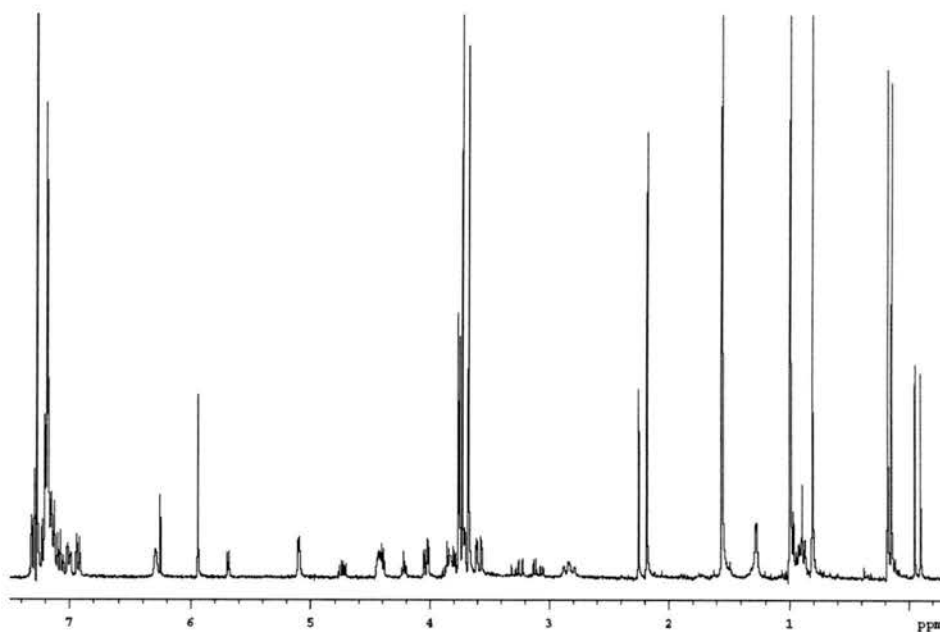


**(3R,4S,11aS)-6-((tert-butyldimethylsilyloxy)methyl)-7-hydroxy-8,10-dimethoxy-9-methyl-3,4-diphenyl-3,4,11,11a-tetrahydro-[1,4]oxazino[4,3-b]isoquinolin-1(6H)-one
(254)**

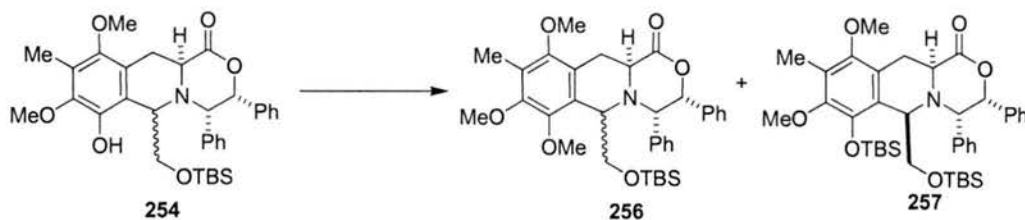
To a solution of **242** (526 mg, 1.2 mmol) in MeCN (4 mL), was added **251** (313 mg, 1.8 mmol) and the reaction was warmed to 65 °C. After 24 h the reaction was concentrated under reduced pressure and the residue was purified by flash chromatography (silica, 6:1 hexane:AcOEt) affording a mixture of **254** (564 mg, 80% yield from **242**). ¹H NMR (300MHz, CDCl₃, mixture of two diastereomers) : δ -0.09 (1.2H, s), -0.05 (1.2H, s), 0.15 (3H, s), 0.18 (3H, s), 0.81 (3.6H, s), 1.00 (9H, s), 2.28 (3H, s), 2.25 (1.2H, s), 2.80 (1H, t, *J*= 11.7 Hz), 3.08 (0.4H, dd, *J*= 5.9, 17.8 Hz), 3.27 (1H, dd, *J*= 11.4, 17.2 Hz), 3.59 (1H, dd, *J*= 2.8, 11.4 Hz), 3.68 (3H, s), 3.71 (0.4H, m), 3.73 (3H, s), 3.75 (1.2H, s), 3.76 (1.2H, s), 3.84 (1.8H, m), 4.04 (1H, dd, *J*= 3.7, 9.7Hz), 4.22 (0.4H, t, *J*= 5.3Hz), 4.42 (1.4H, m), 4.73 (1H, dd, *J*= 6.0, 11.0 Hz), 5.10 (1H, d, *J*= 4.0 Hz), 5.69 (0.4H, d, *J*= 4.6 Hz), 5.94 (1H, s), 6.25 (0.4H, s), 6.30 (1H, m), 6.90-7.34 (14H, m).



254

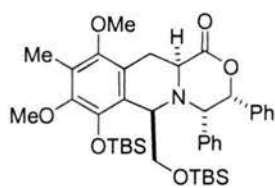


¹H NMR, 300 MHz, CDCl₃, filename: YY-I-170

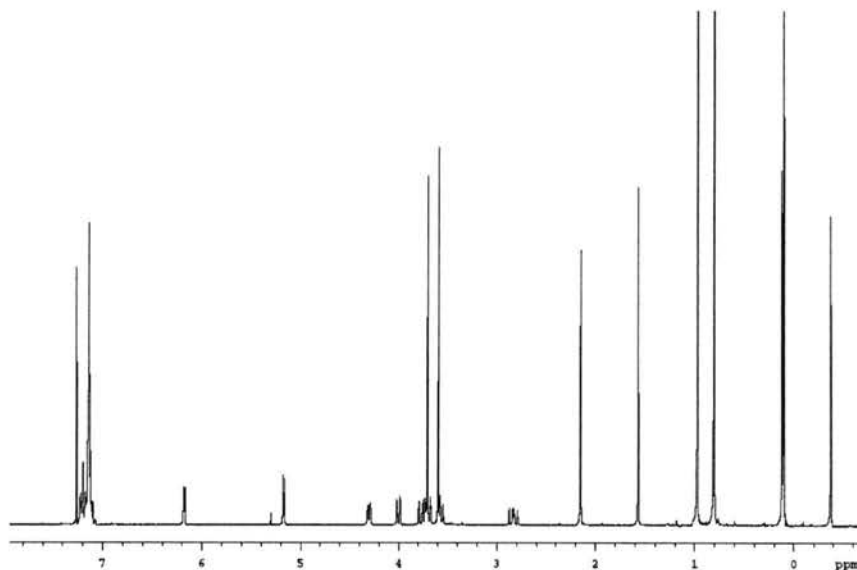


(3R,4S,6R,11aS)-7-(tert-butyldimethylsilyloxy)-6-((tert-butyldimethylsilyloxy)methyl)-8,10-dimethoxy-9-methyl-3,4-diphenyl-3,4,11,11a-tetrahydro-[1,4]oxazino[4,3-b]isoquinolin-1(6H)-one (257)

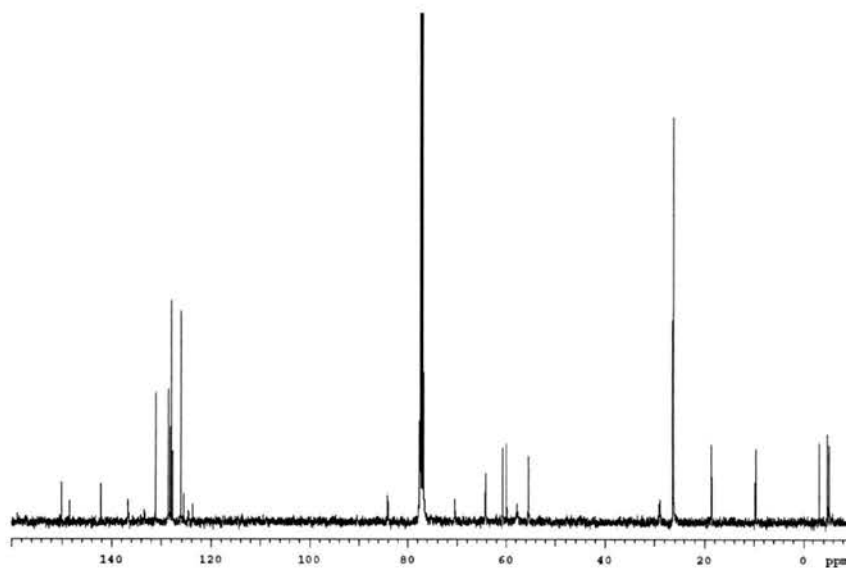
To a solution of **254** (564 mg, 0.95 mmol) in DMF (1.9 mL) was added NaH (50 mg, 1.24 mmol) at 0°C. After stirring for 20min, MeI (77 μ L, 1.24 mmol) was added to the reaction mixture and the reaction warmed to r.t. After 2 h the reaction was quenched with sat. aq. NH_4Cl (2 mL) and diluted with ether (50 mL). After washing with H_2O (10 mL), the organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (silica, 10:1 hexane:AcOEt) affording **257** as by product. ^1H NMR (300MHz, CDCl_3): δ -0.38 (3H, s), 0.10 (6H, s), 0.12 (3H, s), 0.81 (9H, s), 0.97 (9H, s), 2.15 (3H, s), 2.83 (1H, dd, J = 11.5, 15.6 Hz), 3.57 (1H, m), 3.59 (3H, m), 3.66- 3.81 (2H, m), 3.71 (3H, s), 4.00 (1H, dd, J =2.1, 9.3 Hz), 4.30 (1H, d, J =7.3 Hz), 5.17 (1H, d, J =4.0 Hz), 6.18 (1H, d, J =4.0 Hz), 7.06-7.28 (10H, m). ^{13}C NMR (100 MHz, CDCl_3): δ -5.2, -5.1, -4.8, -3.2, 9.7, 18.5, 18.7, 26.3, 29.0, 55.5, 57.8, 59.9, 60.7, 64.2, 70.4, 84.1, 123.6, 124.6, 125.6, 126.1, 127.7, 128.1, 128.6, 131.2, 133.4, 136.6, 142.1, 148.5, 150.1 IR (NaCl, depos. from CH_2Cl_2): 2953, 2930, 2857, 1745 cm^{-1} . HRMS (FAB) calcd. for $\text{C}_{40}\text{H}_{58}\text{NO}_6\text{Si}_2$ (MH^+): 704.3803, Found: 704.3781.



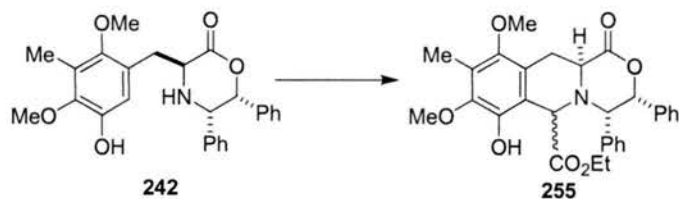
257



^1H NMR, 300 MHz, CDCl_3 , filename: YY-diTBS-Pictet

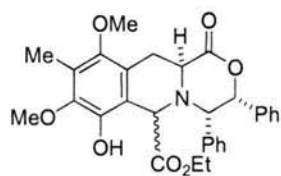


^{13}C NMR, 100 MHz, CDCl_3 , filename: YY-diTBS-Pictet.13C

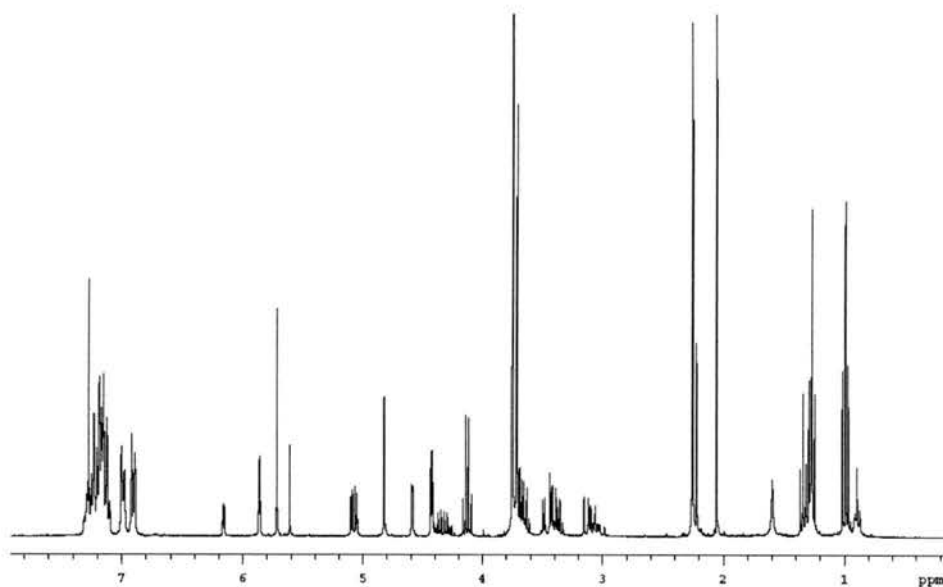


(3R,4S,11aS)-ethyl 7-hydroxy-8,10-dimethoxy-9-methyl-1-oxo-3,4-diphenyl-1,3,4,6,11,11a-hexahydro-[1,4]oxazino[4,3-b]isoquinoline-6-carboxylate (255)

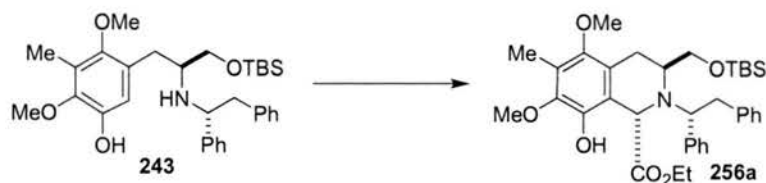
To a solution of **242** (13 mg, 0.03 mmol) in MeCN (0.6 mL), was added **252** (8.5 μ L, 0.04 mmol) and the reaction heated to reflux. After 12 h the reaction was concentrated under reduced pressure and the residue purified by flash chromatography (silica, 6:1 hexane:AcOEt) affording a mixture of **255** (13 mg, 90% yield from **242**). ^1H NMR (300MHz, CDCl_3 , mixture of two diastereomers in 1: 0.4 ratio) : δ 0.99 (3H, t, $J=7.1$ Hz), 1.34 (1.2H, t, $J=7.2$ Hz), 2.28 (1.2H, s), 2.26 (3H, s), 3.08 (1.4H, m), 3.42 (2H, m), 3.66 (1.4H, m), 3.71 (2.4H, s), 3.75 (6H, s), 4.33 (0.8H, m), 4.4 (1H, d, $J=3.5$ Hz), 4.59 (0.8H, m), 4.82 (1H, s), 5.08 (1H, dd, $J=4.8, 12.0$ Hz), 5.61 (0.4H, s), 5.72 (1H, s), 5.86 (1H, d, $J=3.5$ Hz), 6.16 (0.4H, d, $J=3.6$ Hz), 6.84-7.32 (14H, m).



255

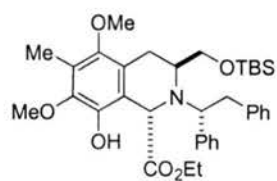


^1H NMR, 300 MHz, CDCl_3 , filename: YY-I-152

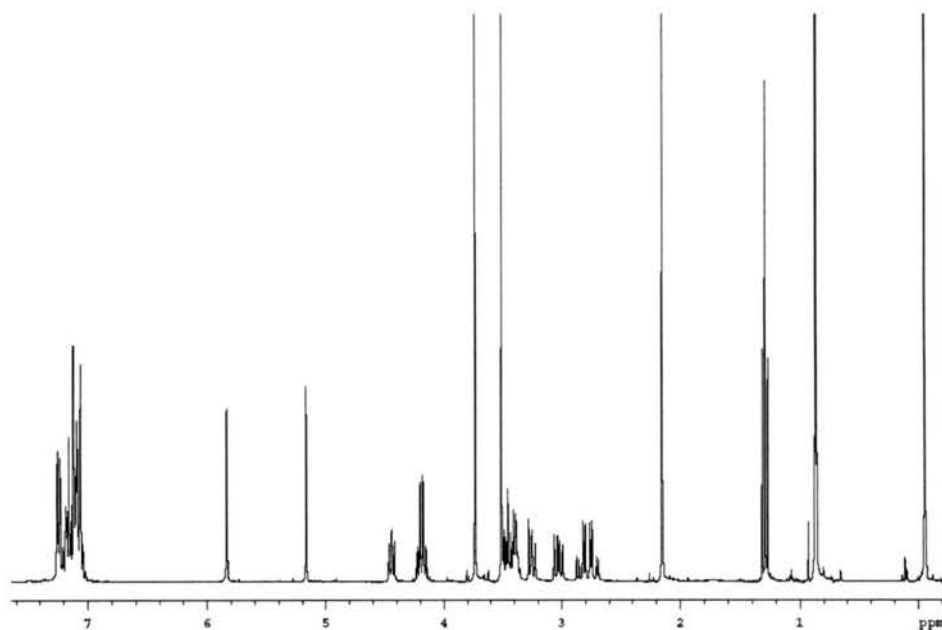


3-(tert-Butyl-dimethyl-silanyloxymethyl)-2-(1,2-diphenyl-ethyl)-8-hydroxy-5,7-dimethoxy-6-methyl-1,2,3,4-tetrahydro-isoquinoline-1-carboxylic acid ethyl ester (256a)

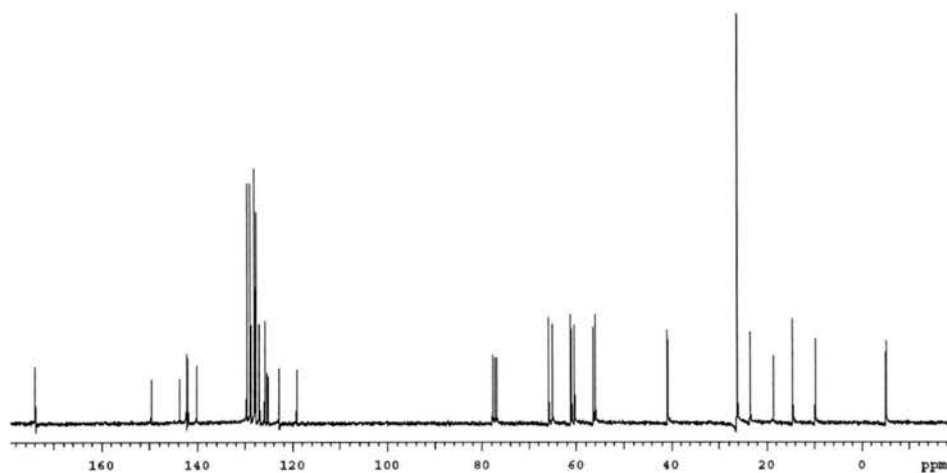
To a solution of **243** (6.25 g, 11.66 mmol) in CH₃CN (116 mL), was added glyoxalate (3.5 mL, 17.5 mmol) and the reaction warmed to 40°C. After 3.5 days at 40 °C, the reaction mixture was concentrated under reduced pressure, and purified by flash chromatography (silica, 3:1 hexane:AcOEt) affording **256a** (6.65g, 92% yield from **243**). ¹H NMR (300MHz, CDCl₃): δ -0.06 (6H, s), 0.87 (9H, s), 1.30 (3H, t, *J*= 7.2 Hz), 2.15 (3H, s), 2.72 (1H, dd, *J*=4.8, 16.2 Hz), 2.83 (1H, dd, *J*=7.8, 17.1 Hz), 3.02 (1H, dd, *J*=8.4, 13.5 Hz), 3.25 (1H, dd, *J*=7.2, 9.9 Hz), 3.44 (3H, m), 3.51 (3H, s), 3.74 (3H, s), 4.19 (2H, m), 4.44 (1H, t, *J*= 6.3 Hz), 5.17 (1H, s), 5.84 (1H, s), 7.02-7.28 (10H, m). ¹³C NMR (75 MHz) (CDCl₃): δ -5.0, 9.9, 14.6, 18.6, 22.5, 26.3, 40.8, 56.0, 56.5, 60.4, 61.0, 61.3, 65.1, 65.9, 119.2, 122.9, 125.4, 126.0, 127.1, 127.8, 128.1, 130.0, 140.2, 142.0, 142.3, 143.7, 150.0, 173.9. IR (NaCl, depos. from CH₂Cl₂): 3423, 3028, 2952, 2930, 2855, 1729, 1463, 1413 cm⁻¹. HRMS (FAB) calcd. for C₃₆H₅₀NO₆ Si(MH⁺) : 620.3407, Found: 620.3389. [α]_D²⁵ = -38.8 (c=1.0, CH₂Cl₂).



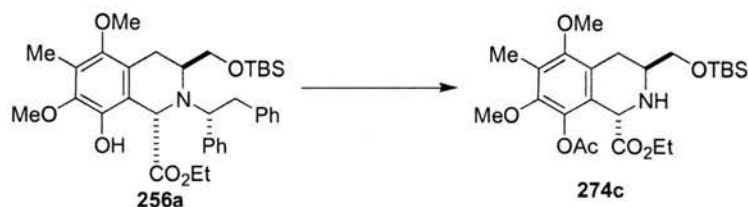
256a



^1H NMR, 300 MHz, CDCl_3 , filename: YY-II-161



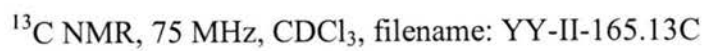
^{13}C NMR, 75 MHz, CDCl_3 , filename: YY-II-161.13C

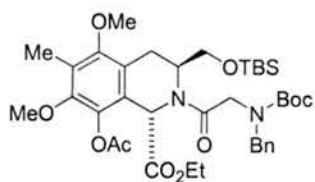


8-Acetoxy-3-(tert-butyl-dimethyl-silanyloxymethyl)-5,7-dimethoxy-6-methyl-1,2,3,4-tetrahydro-isoquinoline-1-carboxylic acid ethyl ester (274c)

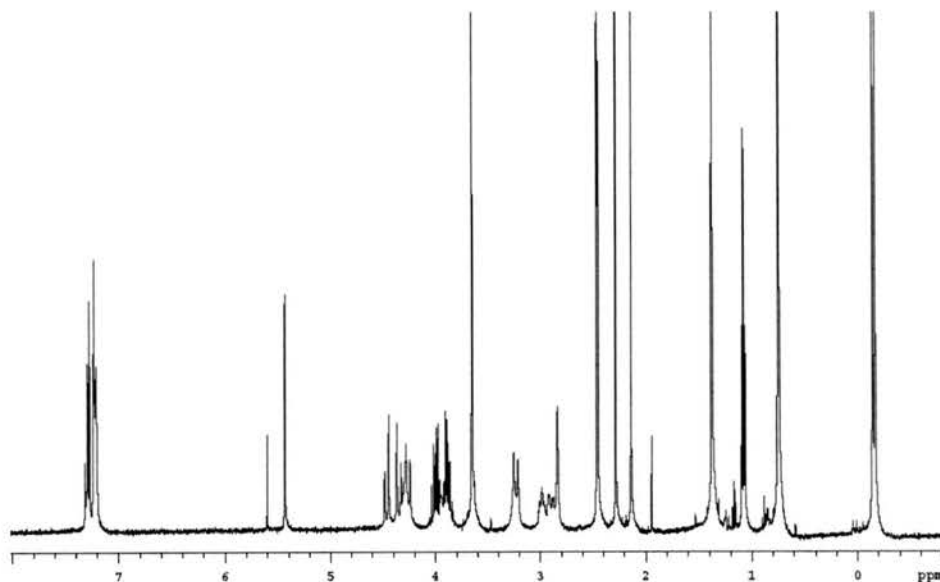
To a solution of **256a** (6.65 g, 10.70 mmol) in CH_2Cl_2 was added Et_3N (4.5 mL, 32.10 mmol) dropwise at 0°C followed by AcCl (0.84 mL, 11.8 mmol). After 30 minutes at 0°C , the reaction mixture was filtered through 1g silica. The filtrate was concentrated under reduced pressure and the crude acetate was used in the next step.

A pressure tube containing the crude acetate (7.0 g) in absolute ethanol (280 ml) was purged with argon for 15 minutes, $\text{Pd}(\text{OH})_2$ (700 mg) added to the mixture and the tube pressurized to 80 psi with hydrogen gas. The tube was then purged another 2 times with hydrogen. After 2 days, the pressure was released and the reaction filtered through a pad of celite. After concentration under reduced pressure, the residue was purified by chromatography (silica, 1:1 hexane:AcOEt) affording **274c**. (1.2g, 93% yield from **256a**). ^1H NMR (300MHz, CDCl_3): δ -0.08 (6H, d, $J=4.5$ Hz), 0.91 (9H, s), 1.26 (3H, t, $J=7.2$ Hz), 2.22 (3H, s), 2.27 (3H, s), 2.38 (1H, m), 2.76 (1H, dd, $J=3.9, 16.5$ Hz), 3.20 (1H, m), 3.58 (1H, m), 3.7 (6H, s), 3.80 (1H, dd, $J_1=3.3, J_2=9.9$ Hz), 4.18 (2H, q, $J=7.2, 14.4$ Hz), 4.69 (1H, s); ^{13}C NMR (75 MHz, CDCl_3): δ -5.0, -4.9, 10.1, 14.62, 18.6, 20.8, 25.6, 26.2, 50.5, 55.8, 60.0, 61.5, 67.0, 124.2, 124.8, 124.9, 138.1, 148.8, 154.7, 168.4, 172.1; IR (NaCl, depos. from CH_2Cl_2): 2932, 2856, 1770, 1736, 1199, 1109, 837 cm^{-1} . HRMS (FAB) calcd. For $\text{C}_{24}\text{H}_{40}\text{NO}_7\text{Si}$ (MH^+): 482.2574, Found: 482.2573. $[\alpha]_D^{25} = -20.6$ ($c=1.0$, CH_2Cl_2).

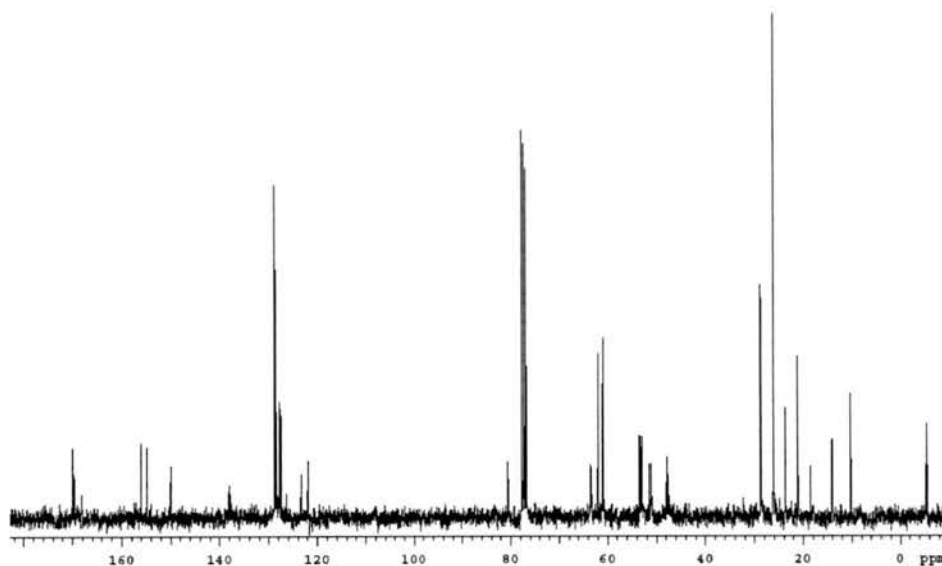




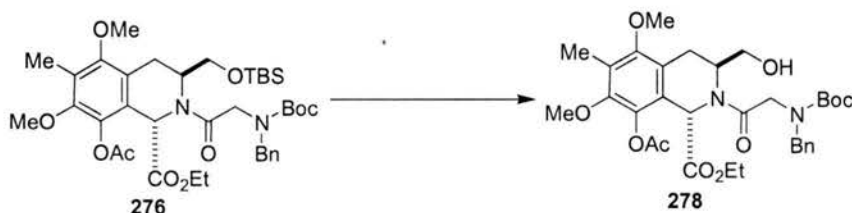
276



^1H NMR, 400 MHz, DMSO, 120°C, filename: YY-III-232.120°C

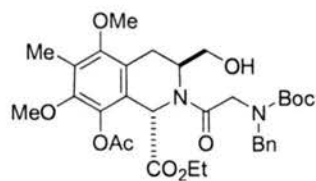


^{13}C NMR, 75 MHz, CDCl_3 , filename: YY-III-232.13C

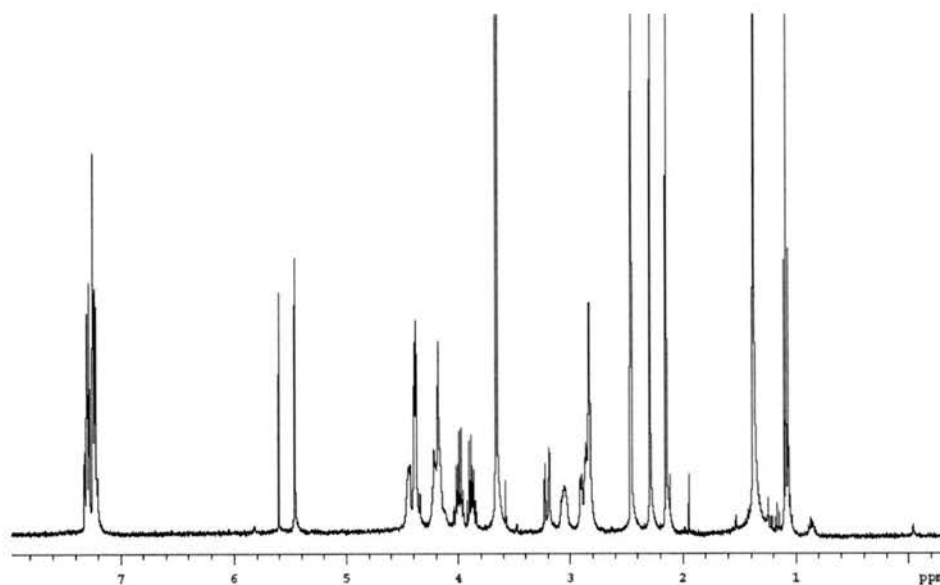


8-Acetoxy-2-[2-(benzyl-tert-butoxycarbonyl-amino)-acetyl]-3-hydroxymethyl-5,7-dimethoxy-6-methyl-1,2,3,4-tetrahydro-isoquinoline-1-carboxylic acid ethyl ester
(278)

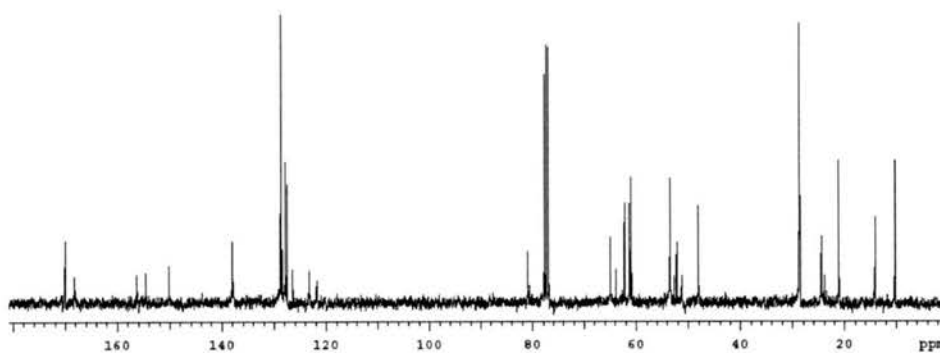
To a solution of **276** (1.08 g, 1.5 mmol) in THF/ MeOH (16 mL/ 1 mL) was added TBAF (1M in THF, 1.8 mL, 1.8 mmol) and the reaction was stirred at r.t. for 18 h. After this time the reaction was quenched with sat. aq. NH_4Cl (5 mL) and diluted with EtOAc (200 mL). The organic layer was washed with brine and dried (Na_2SO_4). After concentration under reduced pressure the resulting residue was purified by flash chromatography (silica, 3:1 hexane:AcOEt) affording **278** (0.82 g, 89% yield). ^1H NMR (400MHz, DMSO, 120°C): δ 1.13 (3H, t, J = 6.7 Hz), 1.42 (9H, s), 2.19 (3H, s), 2.33 (3H, s), 2.93 (1H, dd, J = 15, 5.4 Hz), 3.10 (1H, bs), 3.25 (1H, d, J = 15.7 Hz), 3.69 (3H, s), 3.70 (3H, s), 3.86–4.10 (2H, m), 4.14–4.30 (3H, m), 4.40–4.54 (3H, m), 5.50 (1H, s), 7.23–7.38 (5H, m). ^{13}C NMR (75 MHz, CDCl_3 , mixture of rotamers): δ 10.3, 14.1, 21.1, 23.9, 24.5, 28.6, 28.7, 48.0, 51.1, 52.7, 53.4, 53.5, 60.9, 61.3, 62.2, 63.8, 65.0, 80.9, 121.7, 123.3, 126.4, 127.5, 128.4, 128.7, 137.9, 138.1, 150.2, 154.5, 156.4, 168.1, 170.0. IR (NaCl, depos. from CH_2Cl_2): 3463, 2937, 1778, 1699, 1411, 1200 cm^{-1} . HRMS (FAB) calcd. For $\text{C}_{32}\text{H}_{43}\text{N}_2\text{O}_{10}$ (MH^+) : 615.2918, Found: 615.2912. $[\alpha]_{\text{D}}^{25} = +68.8$ ($c=1.0$, CH_2Cl_2).



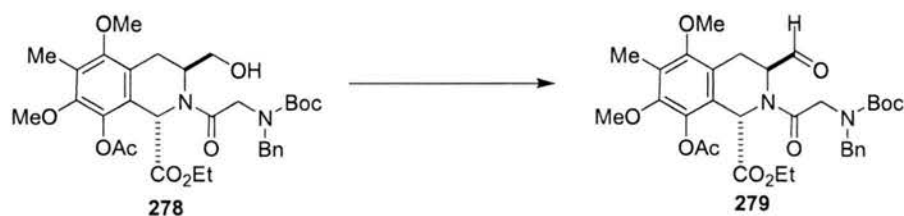
278



^1H NMR, 400 MHz, DMSO, 120°C, filename: YY-III-246.120°C



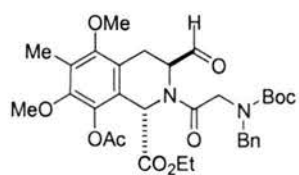
^{13}C NMR, 300 MHz, CDCl_3 , filename: YY-III-246.13C



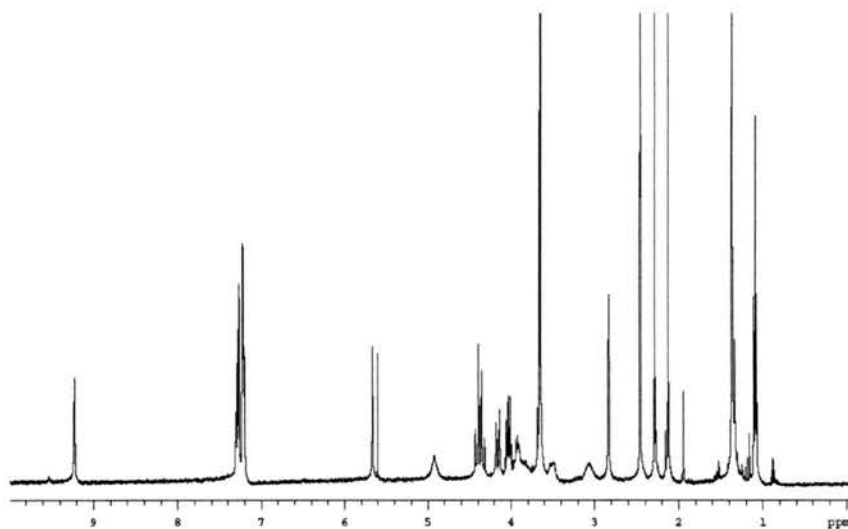
8-Acetoxy-2-[2-(benzyl-tert-butoxycarbonyl-amino)-acetyl]-3-formyl-5,7-dimethoxy-6-methyl-1,2,3,4-tetrahydro-isoquinoline-1-carboxylic acid ethyl ester
(279)

To a solution of $(\text{COCl})_2$ (0.17 mL, 1.95 mmol) in CH_2Cl_2 (3.25 mL) at -78°C , was added DMSO (0.18 mL, 2.60 mmol) dropwise. After 5 minutes a solution of **278** (400 mg, 0.65 mmol) in CH_2Cl_2 (5.00 mL) was added dropwise. After a further 45 minutes, Et_3N (0.90 mL, 6.5 mmol) was added to the reaction mixture and it was kept at -78°C for 5 min and then warmed to 0°C . The reaction was then quenched with and diluted with CH_2Cl_2 (20 mL). The organic layer was washed with saturated NH_4Cl (3 mL) followed by brine and dried (Na_2SO_4). After concentration under reduced pressure the resulting residue was purified by flash chromatography (silica, 3:1 hexane:AcOEt) affording **279** (0.32 g, 80% yield). ^1H NMR (400 MHz, DMSO, 120°C): δ 1.13 (3H, t, $J = 7.0$ Hz), 1.41 (9H, s), 2.17 (3H, s), 2.33 (3H, s), 3.11 (1H, bs), 3.54 (1H, m), 3.69 (3H, s), 3.70 (3H, s), 3.81–4.02 (2H, m), 4.02–4.12 (1H, m), 4.20 (1H, d, $J = 17.0$), 4.37 (1H, d, $J = 15.6$ Hz), 4.45 (1H, d, $J = 15.6$ Hz), 4.97 (1H, bs), 5.71 (1H, s), 7.18–7.38 (5H, m), 9.27 (1H, s). ^{13}C NMR (100 MHz, CDCl_3 , mixture of rotamers): δ 10.1, 13.9, 14.4, 20.9, 21.0, 22.0, 23.3, 28.5, 29.9, 47.1, 47.8, 50.9, 53.1, 53.4, 53.7, 60.0, 60.3, 60.8, 60.9, 61.1, 62.3, 62.8, 80.9, 81.1, 121.4, 121.8, 122.3, 126.8, 127.7, 128.1, 128.2, 128.6, 128.8, 137.5, 137.9, 150.3, 150.7, 153.9, 155.8, 168.2, 170.0, 173.1, 198.9, 199.3, 201.0. IR (NaCl, depos. from

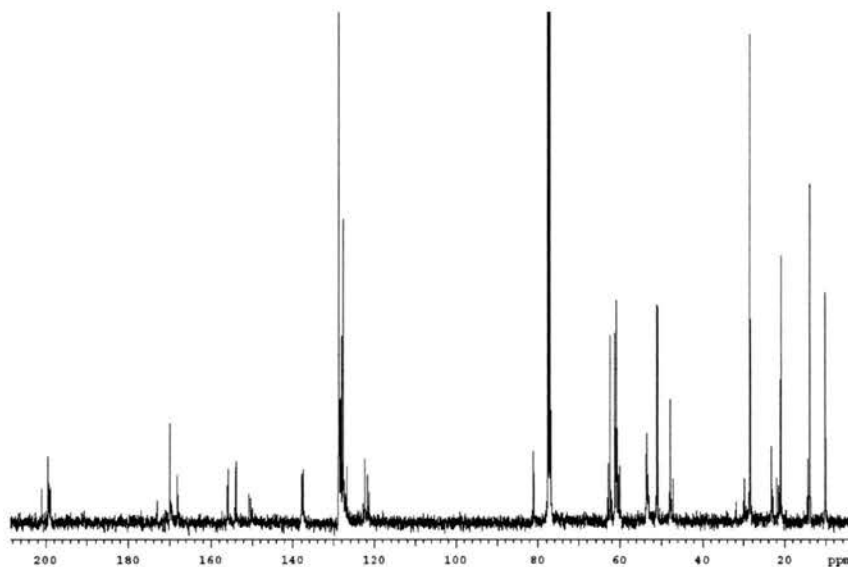
CH₂Cl₂): 3450, 2978, 1776, 1741, 1411, 1200 cm⁻¹. HRMS (FAB) calcd. For
C₃₂H₄₁N₂O₁₀ (MH⁺): 613.2761, Found: 613.2765. $[\alpha]_D^{25} = +50.8$ (c=1.0, CH₂Cl₂).



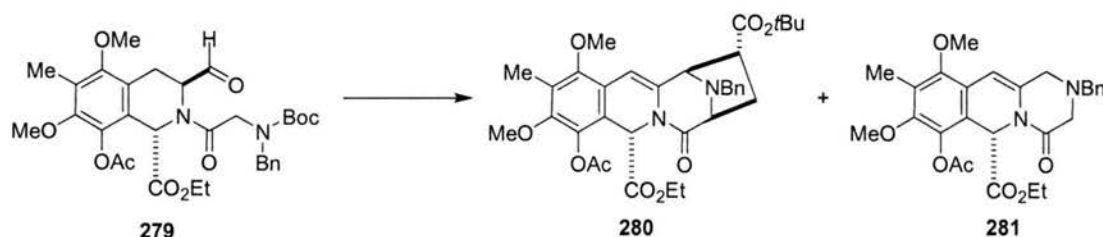
279



^1H NMR, 400 Hz, DMSO, 120°C, filename: YY-III-368.120°C



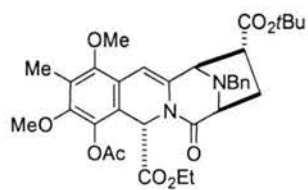
^{13}C NMR, 100 Hz, CDCl_3 , filename: YY-II-209.13C



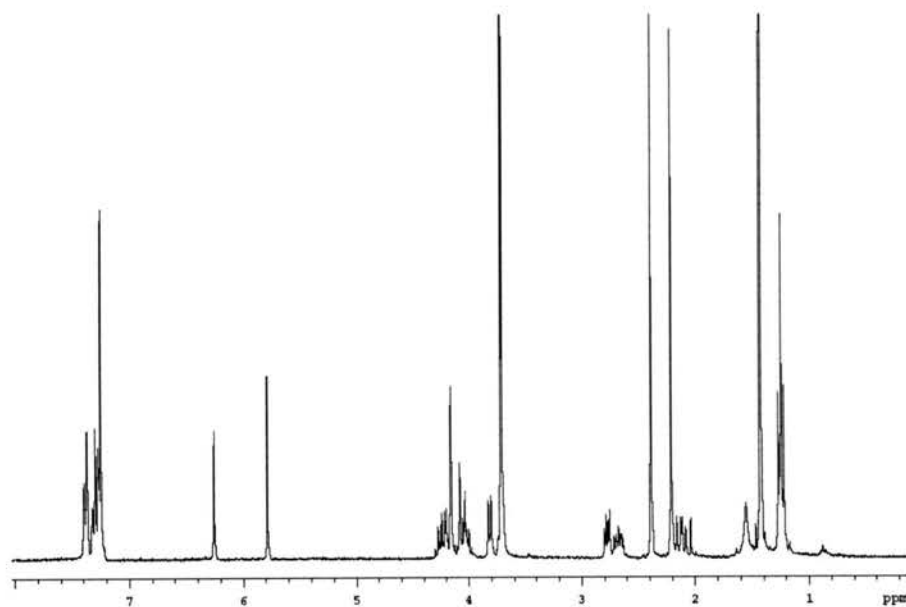
To a solution of **279** (165 mg, 0.27 mmol) in CHCl_3 (2.7 mL) in 250 mL round bottom flask was added TFA (1.10 mL, 13.50 mmol). The flask was left open to the air and then sealed with a glass stopper. After 3.5 h the solvent and TFA were removed under reduced pressure and the resulting residue was dissolved with CHCl_3 (2.7 mL). To this reaction mixture was added *t*-butyl acrylate (0.80 mL, 5.40 mmol) and Et_3N (0.37 mL, 2.7 mmol) at 0°C . The reaction was warmed to r.t. and was stirred for 3 h. The reaction mixture was then diluted with EtOAc (20 mL) and washed with saturated NH_4Cl . The organic layer was washed with brine and dried (Na_2SO_4). After concentration under reduced pressure, the resulting residue was purified by flash chromatography (silica, 3:1 hexane:AcOEt) affording **280** (0.11 g, 67% yield). ^1H NMR (300 MHz, CDCl_3): δ 1.25 (3H, t, $J=7.3$ Hz), 1.44 (9H, s), 2.13 (1H, dd, $J=9.7, 13.9$ Hz), 2.22 (3H, s), 2.40 (3H, s), 2.67 (1H, m), 2.79 (1H, dd, $J=4.6, 9.5$ Hz), 3.71 (3H, s), 3.72 (3H, s), 3.82 (1H, dd, $J=7.4$ Hz), 3.93–4.31 (4H, m), 4.17 (1H, s); 5.80 (1H, s), 6.27 (1H, s), 7.20–7.43 (5H, m). ^{13}C NMR (100 MHz) (CDCl_3): δ 9.9, 14.2, 21.1, 28.2, 32.1, 50.1, 51.3, 51.6, 60.9, 61.7, 62.3, 63.0, 64.1, 81.5, 97.8, 116.9, 120.9, 126.7, 127.3, 128.4, 128.9, 137.4, 138.2, 138.5, 150.0, 151.2, 168.2, 168.6, 170.9, 171.9. IR (NaCl, depos. from CH_2Cl_2): 2978, 1741, 1692, 1202 cm^{-1} . HRMS (FAB) calcd. For $\text{C}_{34}\text{H}_{41}\text{N}_2\text{O}_9$ (MH^+): 621.2812, Found: 621.2805. $[\alpha]_{\text{D}}^{25} = -48.2$ ($c=1.0$, CH_2Cl_2).

281 (15mg, 11%). ^1H NMR (40 MHz) (CDCl_3): δ 1.17 (3H, t, $J=7.3$ Hz), 2.19 (3H, s), 2.35 (3H, s), 3.38–3.61 (4H, m), 3.65 (2H, s), 3.68 (3H, s), 3.69 (3H, s), 3.95 (1H, m),

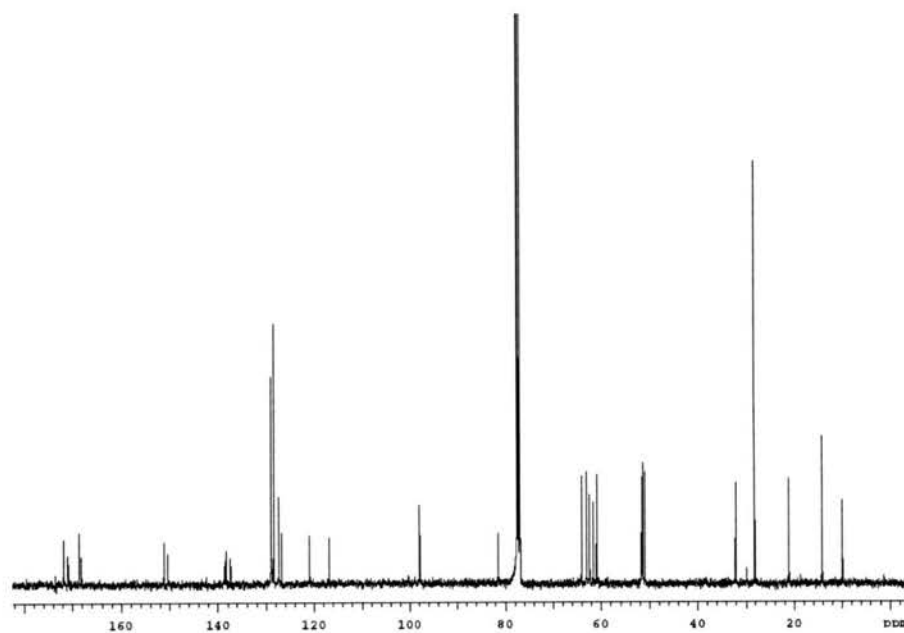
4.15 (1H, m), 5.81 (1H, s), 6.34 (1H, s), 7.24–7.34 (5H, m). ^{13}C NMR (100 MHz, CDCl_3):
 δ 9.9, 14.1, 21.1, 50.8, 53.5, 57.5, 60.7, 60.9, 61.5, 62.4, 100.0, 117.6, 120.6, 126.6, 127.9,
128.7, 129.3, 133.1, 136.8, 138.1, 150.3, 151.4, 166.4, 168.1, 168.5. HRMS (FAB) calcd.
For $\text{C}_{274}\text{H}_{31}\text{N}_2\text{O}_7$ (MH^+): 495.2131, Found: 495.2119.



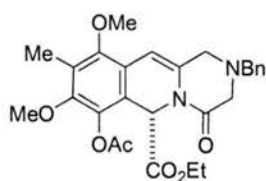
280



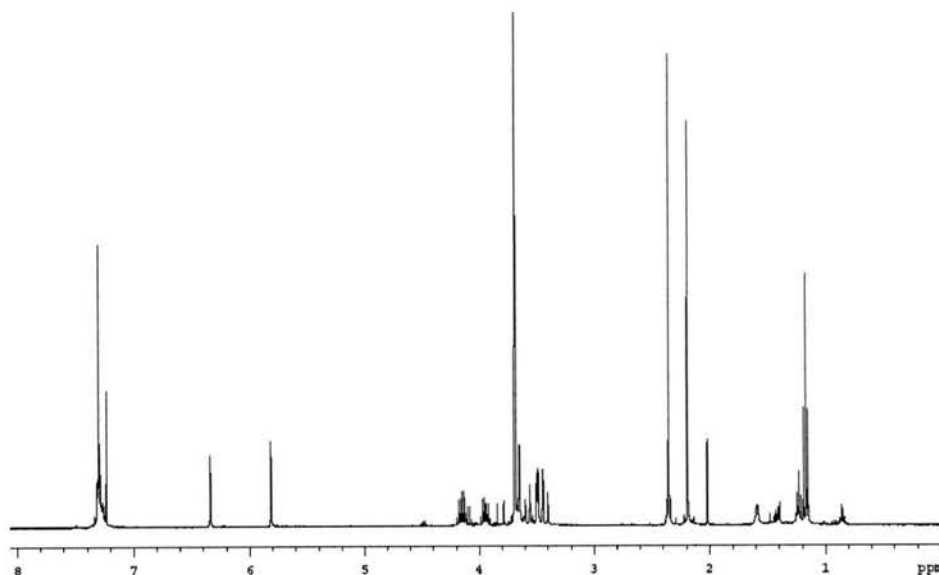
^1H NMR, 400 MHz, CDCl_3 , filename: YY-IV-001



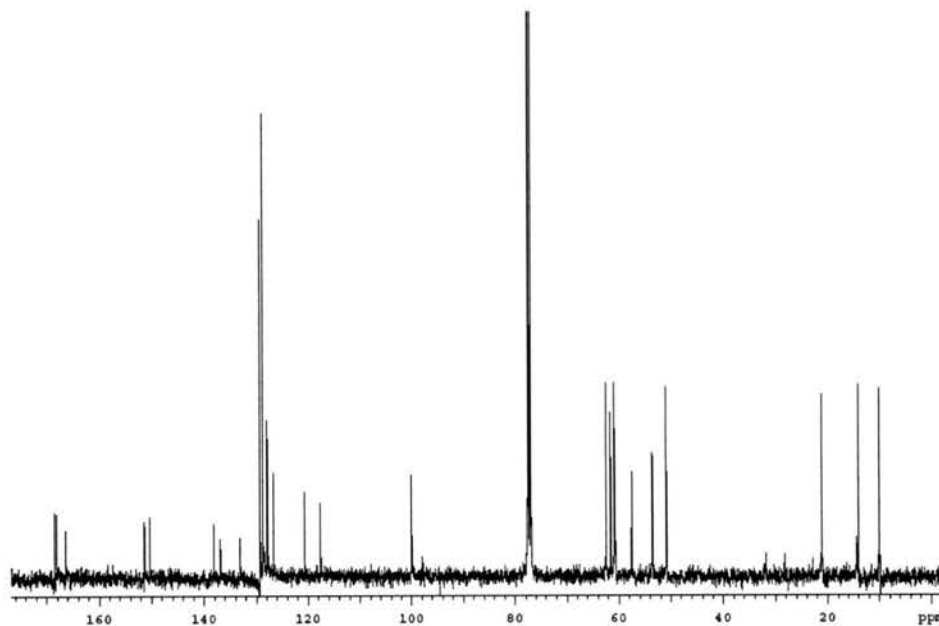
^{13}C NMR, 100 MHz, CDCl_3 , filename: YY-IV-001.13C



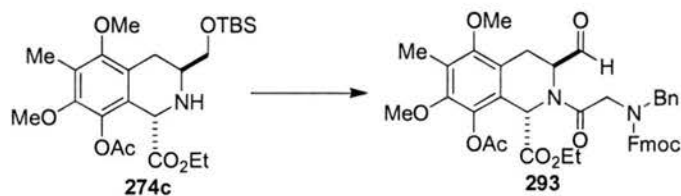
280



^1H NMR, 400 MHz, CDCl_3 , filename: YY-IV-063



^{13}C NMR, 100 MHz, CDCl_3 , filename: YY-IV-063.13C



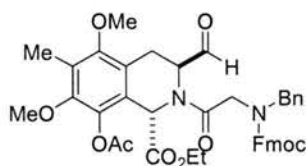
(1S,3S)-ethyl 2-(2-((((9H-fluoren-9-yl)methoxy)carbonyl)(benzyl)amino)acetyl)-8-acetoxy-3-formyl-5,7-dimethoxy-6-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (293)

To a solution of *N*-Bn(Fmoc) glycine (120 mg, 0.30 mmol) in CH₂Cl₂ (1 mL) at 0 °C was added DMF (1 drop, catalytic) followed by (COCl)₂ (40 μL, 0.40 mmol). After stirring for 30 minutes, the reaction mixture was concentrated under reduced pressure and redissolved in CH₂Cl₂ (1 mL). To this solution was added **274c** (100 mg, 0.20 mmol) followed by 2,6-lutidine (30 μL, 0.3 mmol). After stirring for 12 hours the reaction was quenched by saturated NH₄Cl and extracted with EtOAc. The organic layer was washed with brine and dried (Na₂SO₄). After concentration under reduced pressure, the resulting residue was purified by flash chromatography (silica, 6:1 hexane:AcOEt) affording **291** (138 mg, 82% yield).

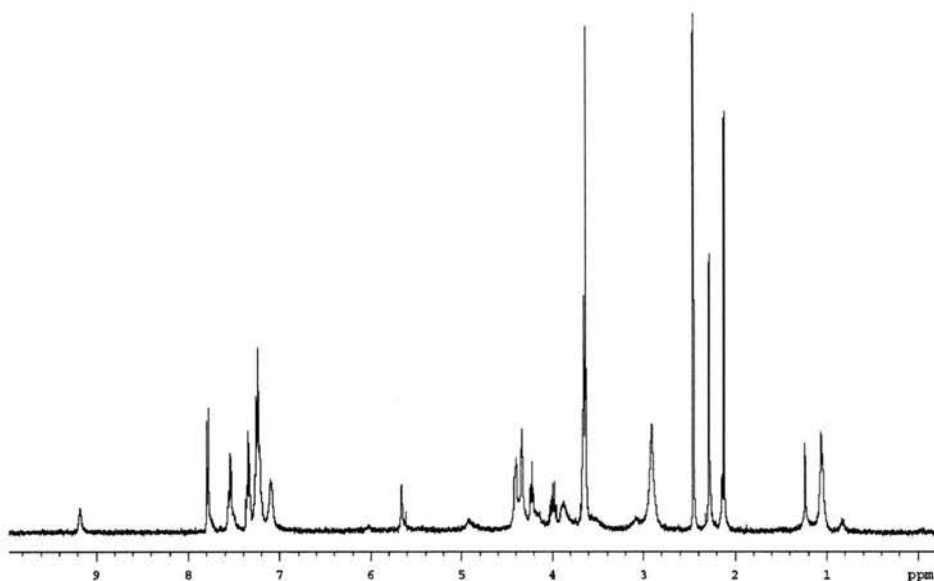
To a solution of **291** (170 mg, 0.20 mmol) was added a THF: HCOOH: H₂O (6: 3: 1) solution (3.40 mL). After stirring for 20 hours, the reaction was quenched with saturated NaHCO₃ and extracted with EtOAc. The organic layer was washed with brine and dried (Na₂SO₄). After concentration under reduced pressure, the resulting residue was purified by flash chromatography (silica, 4:1 hexane:AcOEt) affording **292** (118 mg, 80% yield).

To a solution of oxalyl chloride in CH₂Cl₂ (0.18 mL) at -78 °C was added DMSO (12 μL). 5 minutes later, a solution of **292** (27 mg, 0.04 mmol) in CH₂Cl₂ (0.45 mL) was added and the reaction stirred for another 1 h. Et₃N (0.05 mL, 0.36 mmol) was then added

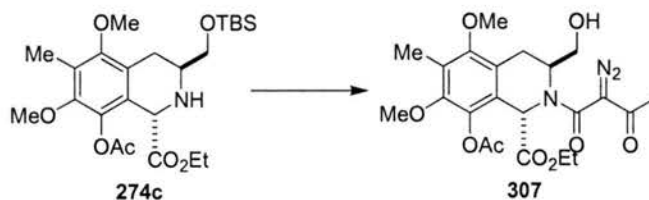
and the reaction mixture warmed up to 0 °C and stirred for a further 10 minutes. The reaction mixture was then diluted with Et₂O, washed with 50% saturated NH₄Cl, brine and dried (Na₂SO₄). After concentration under reduced pressure, the resulting residue was purified by flash chromatography (silica, 4:1 hexane:AcOEt) affording **293** (20 mg, 77% yield). ¹H NMR (400 MHz) (DMSO, 110 °C): δ 1.06 (3H, bs), 2.12 (3H, s), 2.28 (3H, s), 3.10(1H, m), 3.51(1H, m), 3.64 (3H, s), 3.66 (3H, s), 3.78–4.04 (3H, m), 4.18–4.49 (6H, m), 4.91 (1H, m), 5.66 (1H, s), 7.06–7.84 (13H, m), 9.18 (1H, s). HRMS (FAB) calcd. For C₄₂H₄₃N₂O₁₀ (MH⁺): 735.2918, Found: 735.2923



293



¹H NMR, 400 MHz, DMSO, 110 °C filename: YY-II-417.110 °C



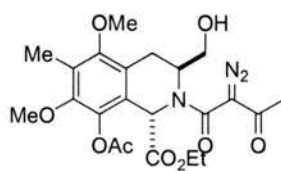
(1S,3S)-ethyl 8-acetoxy-2-(2-diazo-3-oxobutanoyl)-3-(hydroxymethyl)-5,7-dimethoxy-6-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (307)

To a solution of **274c** (100 mg, 0.21 mmol) in THF (0.42 mL) was added DMAP (2.5 mg, 0.02 mmol) followed by diketene (20 μ L, 0.25 mmol). After stirring for 1 hour, the reaction was quenched by saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (silica, 4:1 hexane:AcOEt) affording **305** (107 mg, 90% yield).

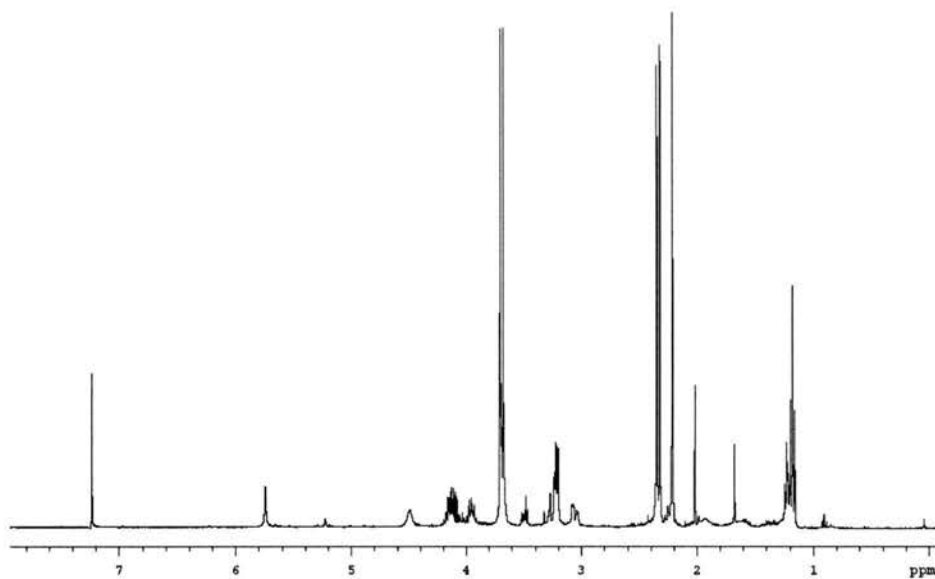
To a solution of **305** (210 mg, 0.36 mmol) in MeCN (3.7 mL) at 0 $^\circ\text{C}$ was added MsN_3 (225 mg, 1.86 mmol) followed by Et_3N (0.26 mL, 1.86 mmol). After warming to room temperature and stirring for 12 hours, the reaction was diluted with CH_2Cl_2 and washed with brine. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (silica, 4:1 hexane:AcOEt) affording **306** (192 mg, 87 % yield).

To a solution of **306** (56 mg, 0.09 mmol) in MeCN: H_2O (9: 1) (0.30 mL) was added DDQ (2.15 mg, 0.01 mmol). After stirring for 8 hours the reaction mixture was diluted with CH_2Cl_2 and washed with brine. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (silica, 25:1 CH_2Cl_2 :MeOH) affording **307** (26 mg, 60 % yield). ^1H NMR (400 MHz, CDCl_3): δ 1.20 (3H, t, J = 7.14 Hz), 2.23 (3H, s), 2.34 (3H, s), 2.37 (3H,

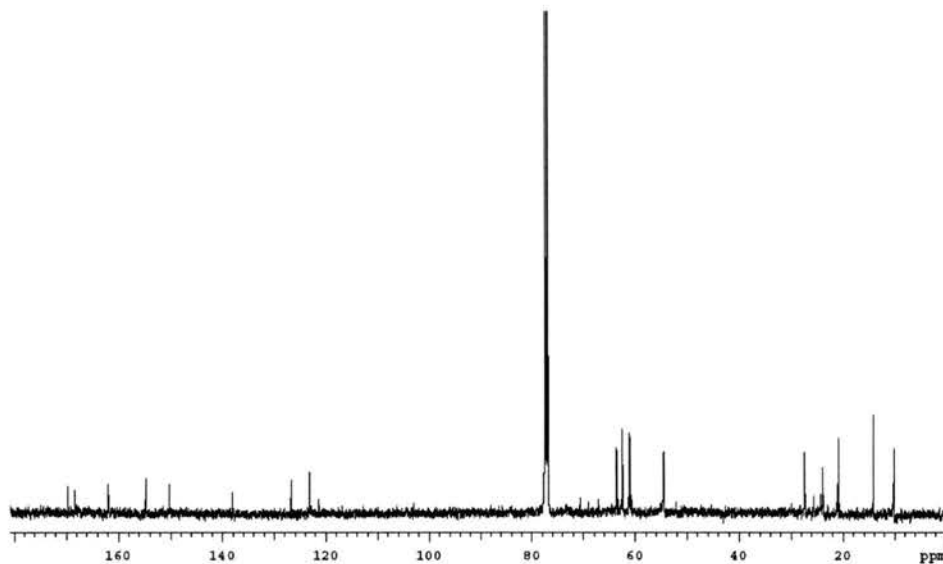
s), 3.08 (1H, dd, $J = 5.3, 15.6$ Hz), 3.28 (2H, m), 3.50 (1H, m), 3.70 (3H, s), 4.73 (3H, s), 3.98 (1H, m), 4.15 (1H, m), 4.52 (1H, m), 5.77 (1H, s). ^{13}C NMR (100 MHz, CDCl_3): δ 10.1, 14.0, 20.9, 23.9, 27.3, 54.5, 54.6, 121.4, 123.2, 126.8, 138.0, 150.2, 154.8, 161.9, 168.3, 169.7. IR (NaCl, depos. from CH_2Cl_2): 3456, 2941, 2117, 1741, 1199 cm^{-1} . HRMS (FAB) calcd. For $\text{C}_{22}\text{H}_{28}\text{N}_3\text{O}_9$ (MH^+): 478.1826, Found: 478.1824.



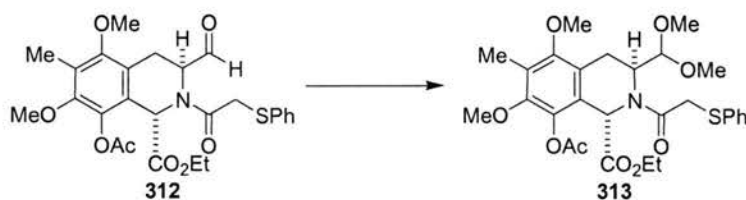
307



^1H NMR, 400 MHz, CDCl_3 , filename: YY-III-115.3

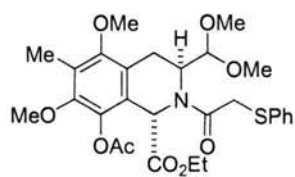


^{13}C NMR, 100 MHz, CDCl_3 , filename: YY-III-115.3.13C

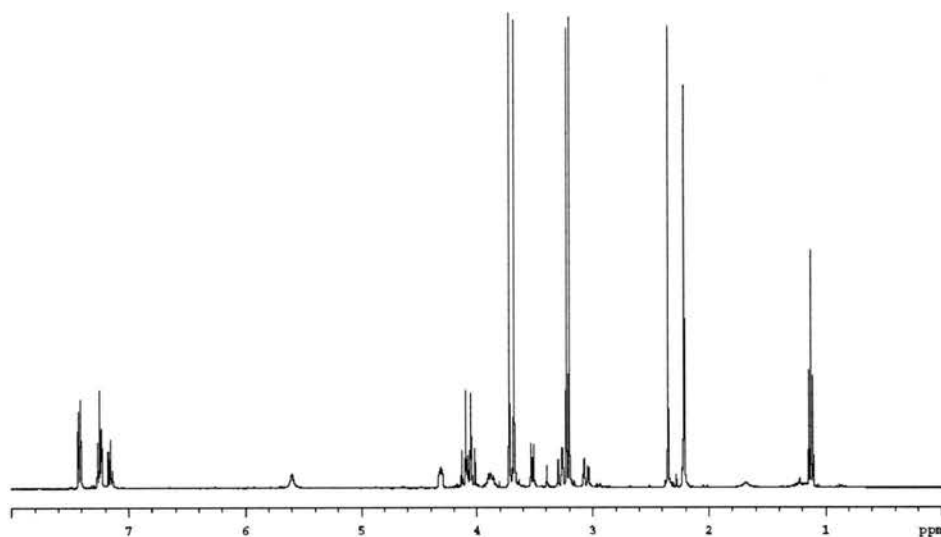


(1S,3S)-ethyl 8-acetoxy-3-(dimethoxymethyl)-5,7-dimethoxy-6-methyl-2-(2-(phenylthio)acetyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (313)

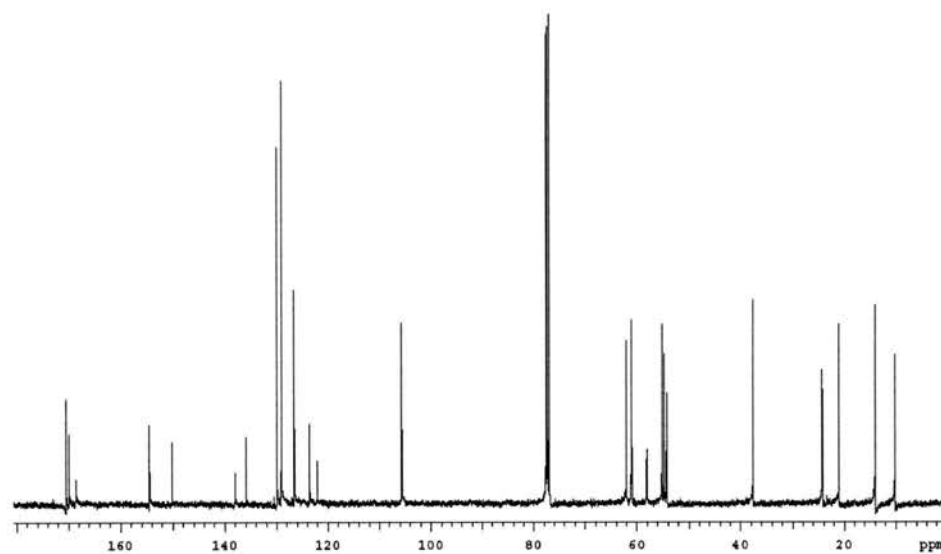
312 (40mg, 0.08 mmol) was dissolved in TsOH/MeOH (1 mg/mL) solution (1.48 mL) and trimethyl orthoformate (85 μ L, 0.78 mmol) added dropwise. The reaction mixture was then warmed to 40°C for 8 hours. After this time the reaction was diluted with EtOAc (10 mL), washed with saturated aqueous Na₂CO₃ (1 mL) and brine. The organic layer was dried (Na₂SO₄), concentrated under reduced pressure and the resulting residue purified by flash chromatography (silica, 2:1 hexane:AcOEt) affording **313** (33 mg, 76%). ¹H NMR (400 MHz, CDCl₃): δ 1.13 (3H, t, J = 7.3 Hz), 2.21 (3H, s), 2.35 (3H, s), 3.05 (1H, dd, J = 4.5, 14.9 Hz), 3.20 (3H, s), 3.22 (3H, s), 3.52 (1H, d, J = 8.3 Hz), 3.68 (3H, s), 3.72 (3H, s), 3.87 (1H, m), 4.03 (1H, d, J = 14.5 Hz), 4.08 (1H, m), 4.12 (1H, d, J = 14.5 Hz), 4.32 (1H, m), 5.60 (1H, s), 7.12- 7.44 (5H, m). ¹³C NMR (100 MHz, CDCl₃): δ 10.1, 13.9, 21.0, 24.2, 37.6, 54.1, 54.7, 55.1, 58.0, 60.9, 61.0, 61.9, 105.7, 122.1, 123.6, 126.5, 126.6, 129.6, 130.0, 135.9, 138.1, 150.2, 154.5, 168.6, 169.9, 170.5, IR (NaCl, depos. from CH₂Cl₂): 3057, 2939, 2835, 1742, 1650 cm⁻¹. HRMS (FAB) calcd. For C₂₈H₃₆N₁O₉S (MH⁺): 562.2111, Found: 562.2107. $[\alpha]_D^{25}$ = +59.2 (c=1.0, CH₂Cl₂).



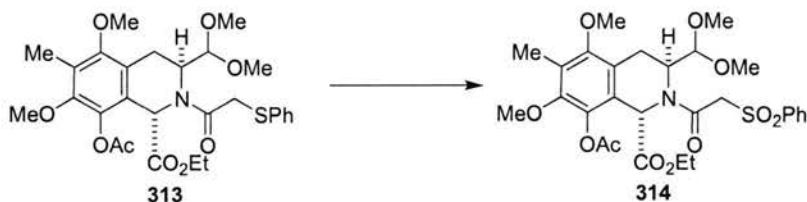
313



¹H NMR, 400 MHz, CDCl₃, filename: YY-III-243

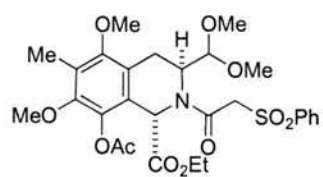


¹³C NMR, 100 MHz, CDCl₃, filename: YY-IV-243.13C

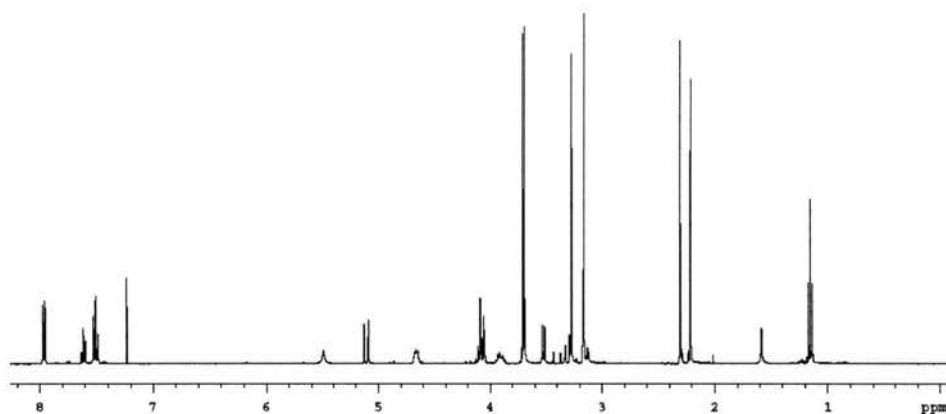


(1S,3S)-ethyl 8-acetoxy-3-(dimethoxymethyl)-5,7-dimethoxy-6-methyl-2-(2-(phenylsulfonyl)acetyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (314)

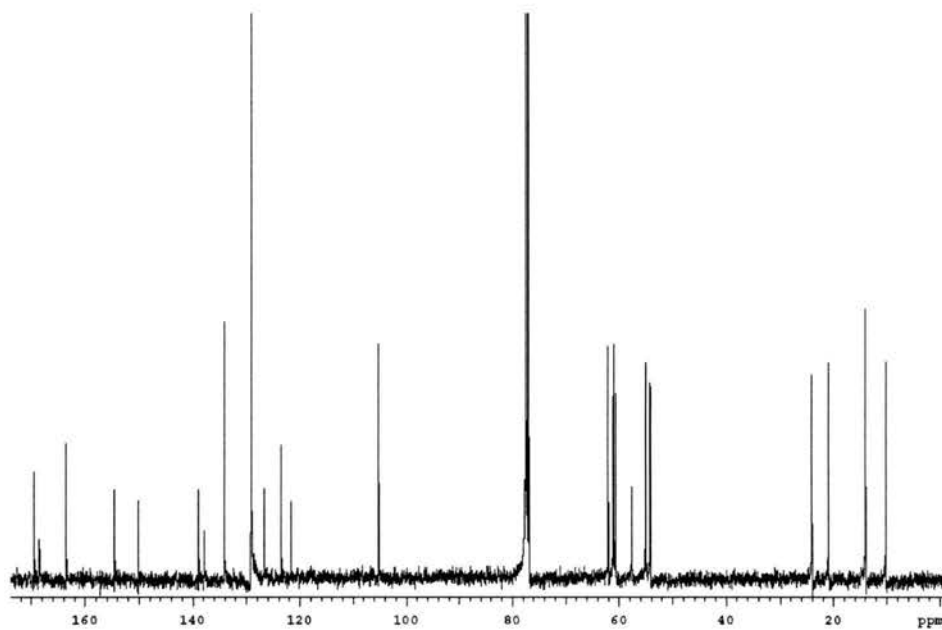
To a solution of **313** (17 mg, 0.03 mmol) in CH_2Cl_2 (0.15 mL) was added *m*-CPBA (10.45 mg, 0.06 mmol) at 0°C . The reaction was warmed to r.t. and after 40 min, was quenched with saturated aqueous NaHCO_3 (0.5 mL) and diluted with CH_2Cl_2 (5 mL). The organic layer was then washed with brine and dried (Na_2SO_4). After concentration under reduced pressure, the resulting residue was purified by flash chromatography (silica, 1:1 hexane:AcOEt) affording **314** (15 mg, 83%). ^1H NMR (400 MHz, CDCl_3): δ 1.15 (3H, t, $J = 7.2$ Hz), 2.21 (3H, s), 2.31 (3H, s), 3.15 (1H, 1/2 ABX, $J_{\text{AB}} = 5.1$ Hz), 3.16 (3H, s), 3.27 (3H, s), 3.31 (1H, 1/2 ABX, $J_{\text{AB}} = 2.3$ Hz), 3.50 (1H, d, $J = 8.3$ Hz), 3.69 (3H, s), 3.71 (3H, s), 3.91 (1H, m), 4.08 (2H, m), 4.67 (1H, m), 5.11 (1H, d, $J = 14.5$ Hz), 5.49 (1H, s), 7.46–7.99 (5H, m). ^{13}C NMR (100 MHz, CDCl_3): δ 10.1, 14.0, 20.9, 24.0, 54.1, 54.2, 55.0, 57.6, 60.6, 60.9, 61.1, 61.9, 105.1, 121.6, 123.5, 126.7, 129.1, 129.2, 134.1, 137.9, 138.9, 150.2, 154.6, 163.5, 168.5, 169.5, IR (NaCl, depos. from CH_2Cl_2): 2939, 1774, 1742, 1200 cm^{-1} . HRMS (FAB) calcd. For $\text{C}_{28}\text{H}_{36}\text{N}_1\text{O}_{11}\text{S}$ (MH^+): 594.2009, Found: 594.1998. $[\alpha]_{\text{D}}^{25} = +60.6$ ($c=0.5$, CH_2Cl_2).



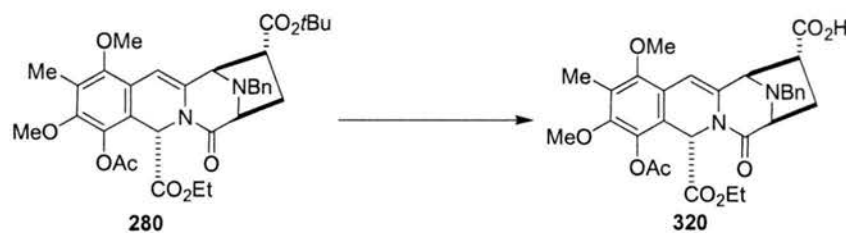
314



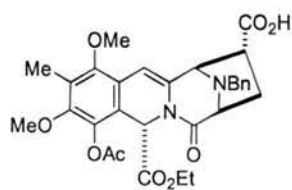
^1H NMR, 400 MHz, CDCl_3 , filename: YY-IV-065



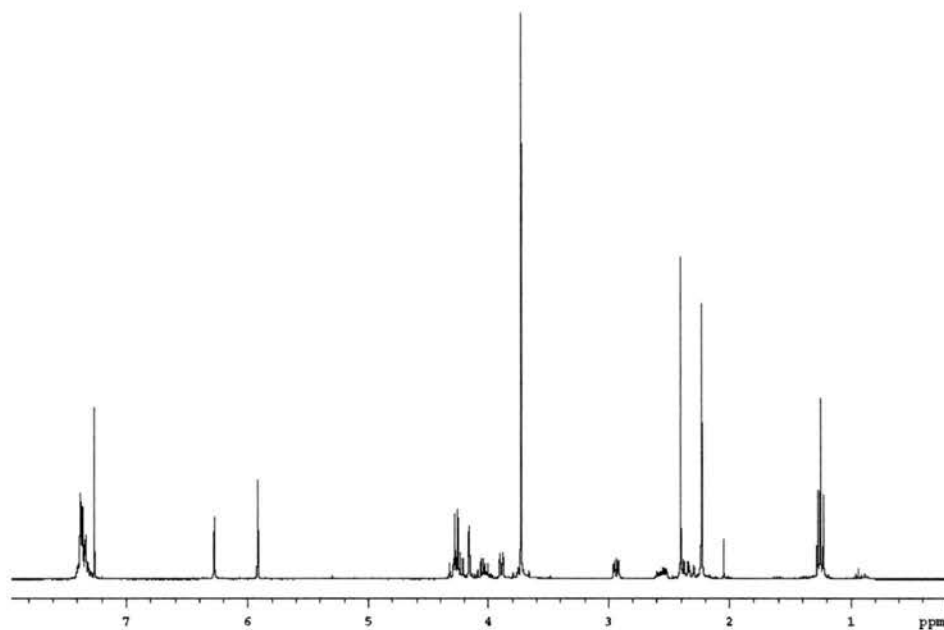
^{13}C NMR, 400 MHz, CDCl_3 , filename: YY-IV-065.13C



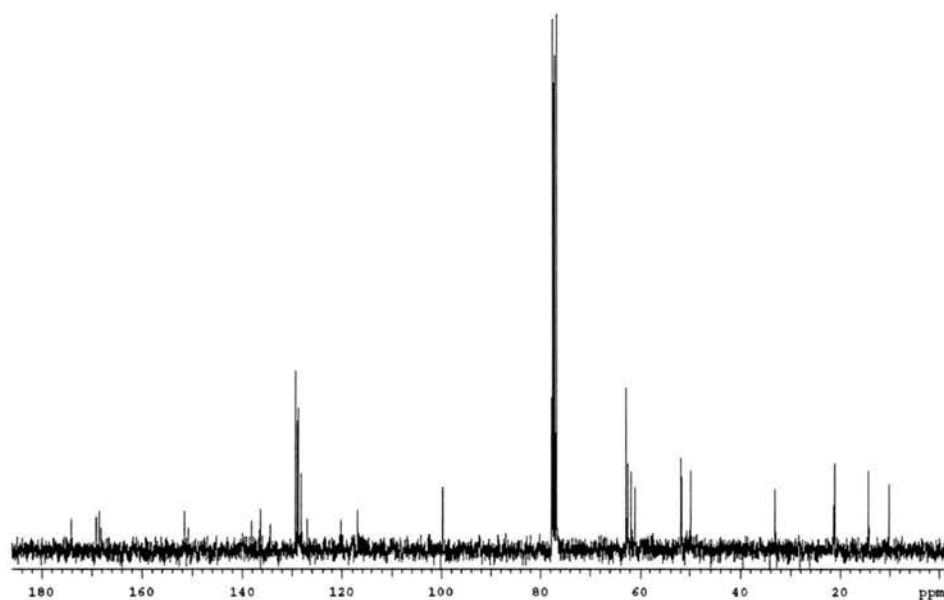
To a solution of **280** (455 mg, 0.73 mmol) in CH_2Cl_2 (2.8 mL) at 0°C , was added Et_3SiH (1.17 mL, 7.30 mmol), followed by TFA (2.83 mL, 36.68 mmol). The resulting mixture was cooled to 5°C . After 24 h the reaction was quenched with H_2O (10 mL) and diluted with CH_2Cl_2 (200 mL). The organic phase was washed with saturated aqueous NaHCO_3 , brine and dried (Na_2SO_4). After concentration under reduced pressure, the resulting residue was purified by flash chromatography (silica, 1:2 hexane:AcOEt) affording **320** (0.38 g, 92% yield). ^1H NMR (300 MHz, CDCl_3): δ 1.25 (3H, t, $J=7.3$ Hz), 2.23 (3H, s), 2.34 (1H, dd $J=9.5, 14.2$), 2.40 (3H, s), 2.56 (1H, m), 2.94 (1H, $\frac{1}{2}$ ABX, $J_{\text{AB}}=3.5$ Hz), 3.73 (6H, s), 3.89 (1H, dd, $J=8.2$ Hz), 4.03 (1H, m), 4.16 (1H, s), 4.27 (3H, m), 5.92 (1H, s), 6.28 (1H, s), 7.20–7.43 (5H, m). ^{13}C NMR (75 MHz, CDCl_3): δ 10.2, 14.3, 21.2, 33.1, 49.8, 51.6, 51.8, 61.0, 61.8, 62.4, 62.7, 99.8, 100.1, 116.8, 120.3, 127.1, 128.2, 128.9, 129.4, 134.5, 136.5, 138.2, 150.8, 151.6, 168.0, 168.4, 169.2, 174.1. IR (NaCl, depos. from CH_2Cl_2): 2940, 1741, 1692, 1202 cm^{-1} . HRMS (FAB) calcd. For $\text{C}_{30}\text{H}_{33}\text{N}_2\text{O}_9$ (MH^+): 565.2186, Found: 565.2185. $[\alpha]_{\text{D}}^{25} = -19.9$ ($c=1.0$, CH_2Cl_2).



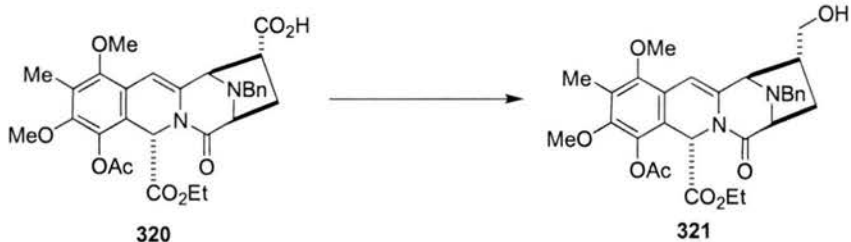
320



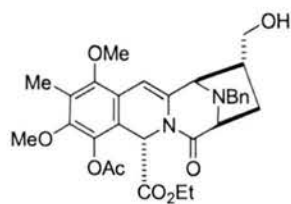
^1H NMR, 300 MHz, CDCl_3 , filename: YY-III-377.1



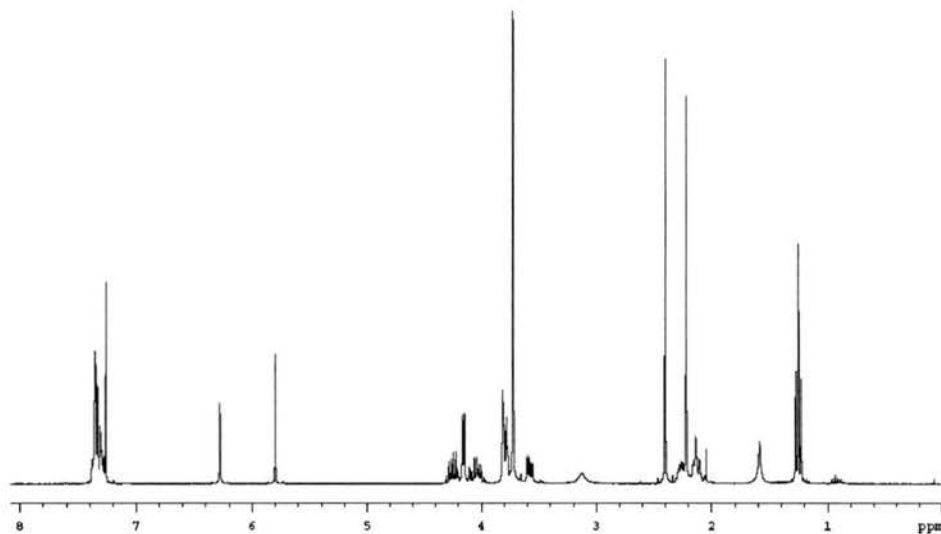
^{13}C NMR, 75 MHz, CDCl_3 , filename: YY-III-377.1.13C



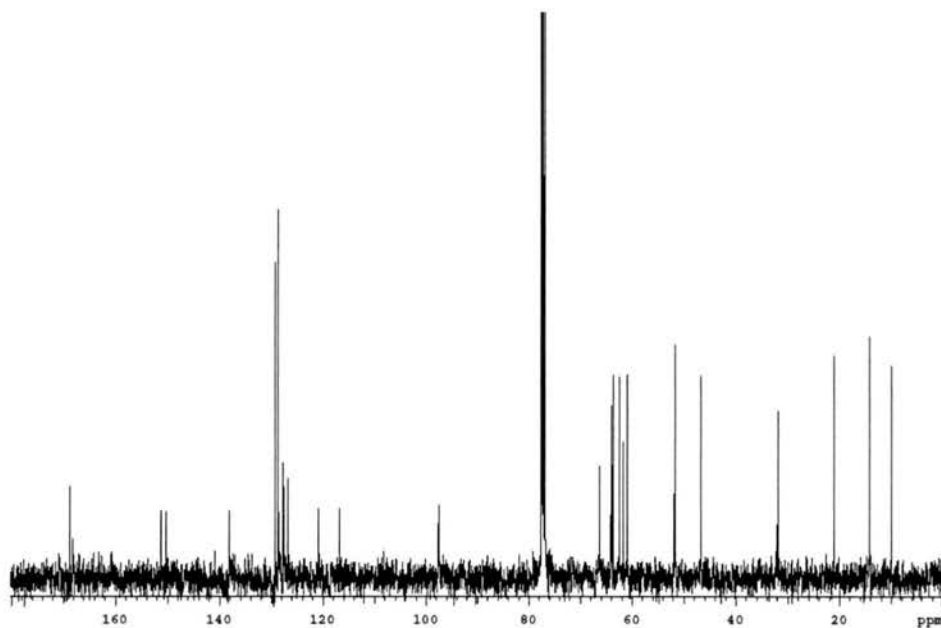
To a solution of **3207** (240 mg, 0.6 mmol) in THF (12 mL) at 0 °C was added NMM (0.080 mL, 0.72 mmol), followed by isobutylchloroformate (0.085 mL, 0.66 mmol). The reaction was then warmed to room temperature and after 20 min was filtered through Celite and added to an ice cold suspension of NaBH₄ (227 mg, 6 mmol) in water (12 mL). The reaction mixture was stirred at 0 °C for 20 minutes and then quenched with 1M HCl (6 mL). The resulting mixture was stirred for another 30 minutes at 0 °C and then extracted with EtOAc, washed with brine and dried (Na₂SO₄). After concentration under reduced pressure, the resulting residue were purified by flash chromatography (silica, 1:1 hexane:AcOEt) affording **321** (270 mg, 80% yield from **320**). ¹H NMR (300 MHz, CDCl₃): δ 1.25 (3H, t, *J*= 7.3 Hz), 2.14 (2H, m), 2.22 (3H, s), 2.26 (1H, m), 2.40 (3H, s), 3.12 (1H, bs), 3.58 (1H, dd, *J*= 5.7, 10.6 Hz), 3.72 (3H, s), 3.73 (3H, s), 3.80 (3H, m), 4.03 (1H, m), 4.16 (1H, dd, *J*= 5.6 Hz), 4.26 (1H, m), 5.80 (1H, s), 6.28 (1H, s), 7.27–7.41 (5H, m). ¹³C NMR (75 MHz, CDCl₃): δ 9.9, 14.1, 21.1, 31.9, 46.7, 51.7, 60.9, 61.6, 62.5, 63.7, 64.1, 66.3, 97.5, 116.7, 121.0, 126.8, 127.7, 128.7, 129.4, 138.2, 150.3, 151.3, 168.2, 168.8. IR (NaCl, depos. from CH₂Cl₂): 3465, 2940, 1742, 1688, 1203 cm⁻¹. HRMS (FAB) calcd. For C₃₀H₃₅N₂O₈ (MH⁺): 551.2393, Found: 551.2387. [α]_D²⁵ = +6.8 (c=1.0, CH₂Cl₂).



321



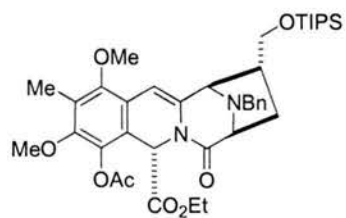
^1H NMR, 300 MHz, CDCl_3 , filename: YY-III-430.pure



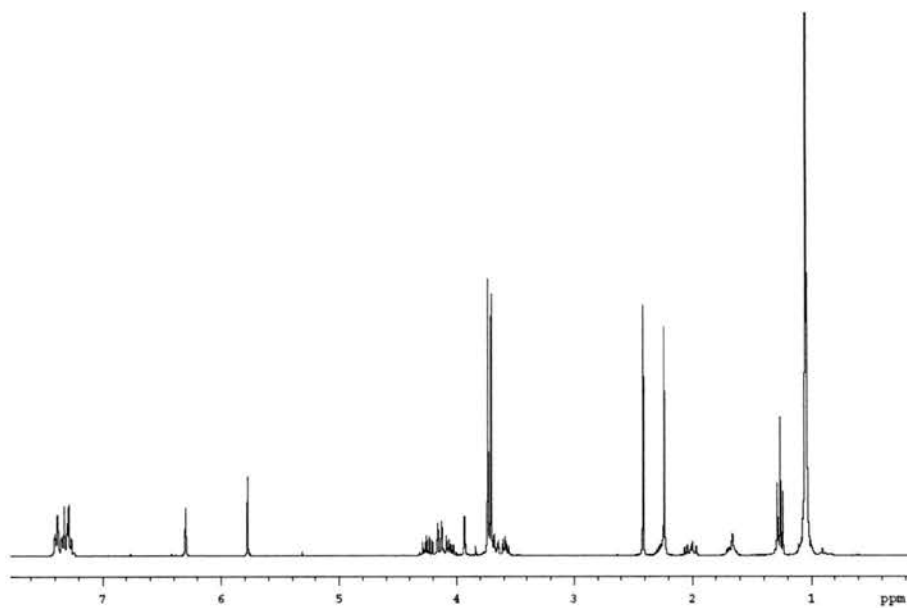
^{13}C NMR, 100 MHz, CDCl_3 , filename: YY-III-430.pure.13C



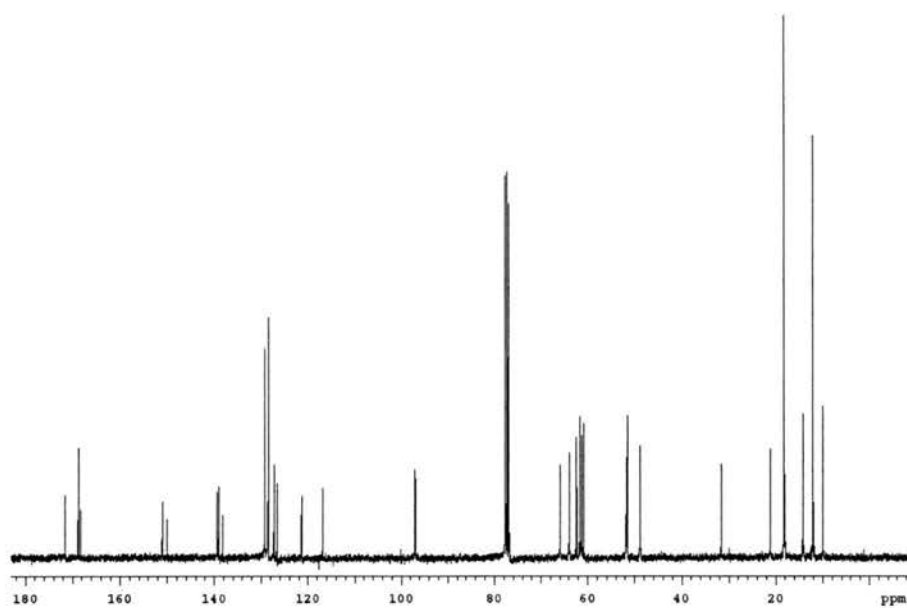
To a solution of **321** (190 mg, 0.35 mmol) in DMF (3.5 mL), was added TIPSCl (90 μ L, 0.42 mmol) followed by Imid. (60 mg, 0.875 mmol). After stirring for 12 hours, the reaction mixture was diluted with Et₂O (25 mL) and washed with H₂O (5 mL), brine (5 mL) and dried (Na₂SO₄). After concentration under reduced pressure, the resulting residue were purified by flash chromatography (silica, 3:1 hexane:AcOEt) affording **322** (235 mg, 95% yield). ¹H NMR (300 MHz, CDCl₃): δ 1.05 (21H, bs), 1.26 (3H, t, J = 7.4 Hz), 1.67 (1H, m), 2.02 (1H, m), 2.24 (3H, s), 2.28 (1H, m), 2.42 (3H, s), 3.58 (1H, dd, J = 5.9, 9.9 Hz), 3.63-3.77 (2H, m.), 3.70 (3H, s), 3.73 (3H, s), 3.93 (1H, s), 4.05 (1H, m), 4.10 (1H, d, J = 13.5, Hz), 4.18 (1H, d, J = 13.5, Hz), 4.26 (1H, m), 5.78 (1H, s), 6.30 (1H, s), 7.21-7.43 (5H, m). ¹³C NMR (75 MHz, CDCl₃): δ 9.9, 12.1, 14.2, 18.2, 21.1, 31.1, 48.8, 51.5, 51.7, 60.9, 61.3, 61.7, 62.3, 63.9, 65.9, 97.0, 116.9, 121.4, 126.6, 127.2, 128.4, 129.2, 138.2, 139.0, 139.3, 194.9, 151.1, 168.3, 168.8, 171.5; IR (NaCl, depos. from CH₂Cl₂): 2941, 2865, 1743, 1690, 1202 cm⁻¹. HRMS (FAB) calcd. For C₃₉H₅₅N₂O₈Si (MH⁺): 707.3727, Found: 707.3720. $[\alpha]_D^{25}$ = -43.7 (c=1.0, CH₂Cl₂).



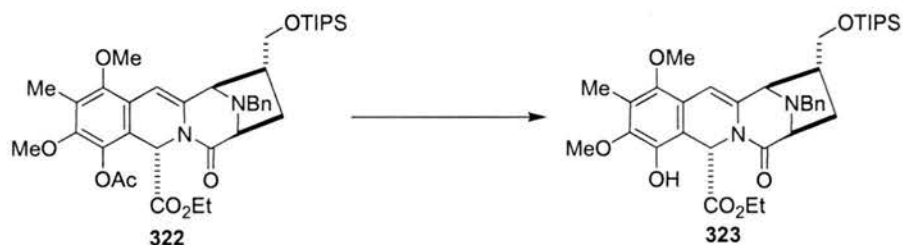
322



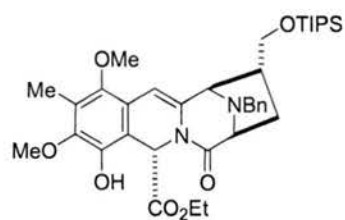
^1H NMR, 300 MHz, CDCl_3 , filename: YY-IV-020



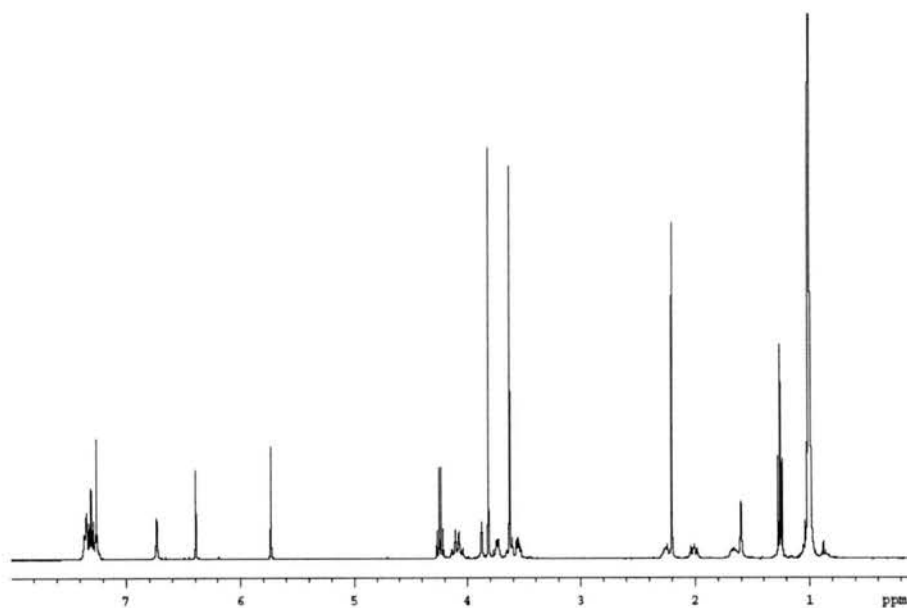
^{13}C NMR, 75 MHz, CDCl_3 , filename: YY-IV-020.13C



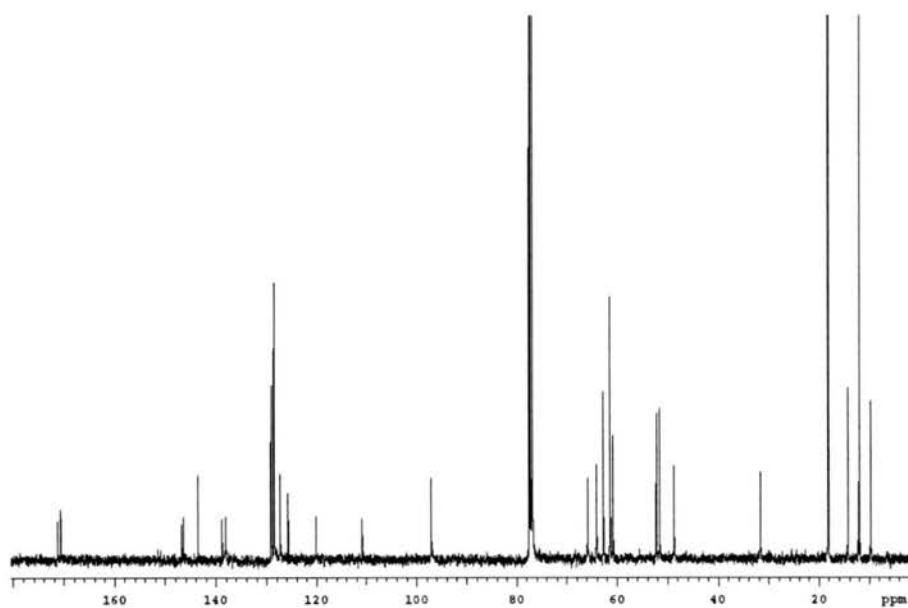
To a MeOH (89 mL) solution of **322** (250 mg, 0.35 mmol) was added K_2CO_3 (244 mg, 1.77 mmol) and after 2 h the reaction was quenched with 1M HCl (3.4 mL) to pH < 7. The MeOH was removed under reduced pressure and the resulting residue was diluted with EtOAc, washed with brine and dried (Na_2SO_4). After concentration under reduced pressure, the resulting residue was purified by flash chromatography (silica, 6:1 hexane:AcOEt) affording **323** (223 mg, 96% yield). ^1H NMR (400 MHz, CDCl_3): δ 1.00 (21H, bs), 1.26 (3H, t, J = 7.3 Hz), 1.67 (1H, m), 2.02 (1H, m), 2.20 (3H, s), 2.27 (1H, m), 3.55 (1H, dd, J = 5.9, 9.9 Hz), 3.63 (3H, s), 3.63 (1H, m), 3.74 (1H, d, J = 5.9 Hz), 3.82 (3H, s), 3.88 (1H, s), 4.10 (2H, m), 4.20 (1H, d, J = 7.3 Hz), 4.24 (1H, d, J = 7.3 Hz), 5.74 (1H, s), 6.40 (1H, s), 6.74 (1H, s), 7.22-7.40 (5H, m). ^{13}C NMR (100 MHz) (CDCl_3): δ 9.7, 12.1, 14.3, 18.2, 31.7, 48.8, 51.7, 52.3, 60.9, 61.5, 62.8, 64.1, 65.9, 97.2, 110.9, 125.7, 127.2, 128.5, 129.1, 138.2, 138.8, 143.6, 146.4, 146.8, 170.7, 171.3. IR (NaCl, depos. from CH_2Cl_2): 3390, 2941, 2864, 1740, 1689, 1639 cm^{-1} . HRMS (FAB) calcd. For $\text{C}_{37}\text{H}_{53}\text{N}_2\text{O}_7\text{Si}$ (MH^+): 665.3622, Found: 665.3612. $[\alpha]_{\text{D}}^{25}$ = -52.2 (c = 1.0, CH_2Cl_2).



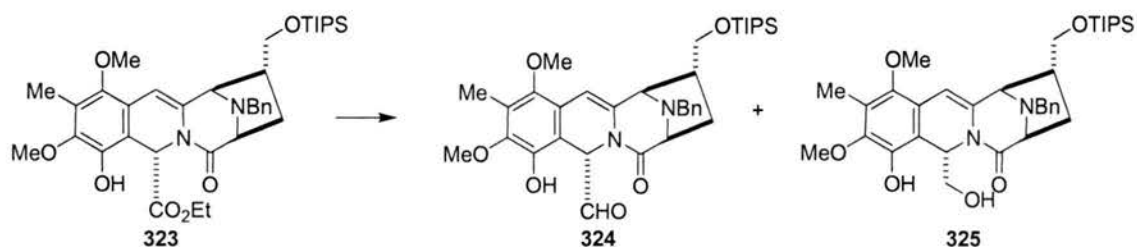
323



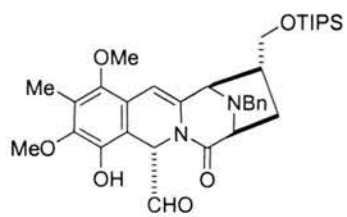
^1H NMR, 400 MHz, CDCl_3 , filename: YY-IV-023



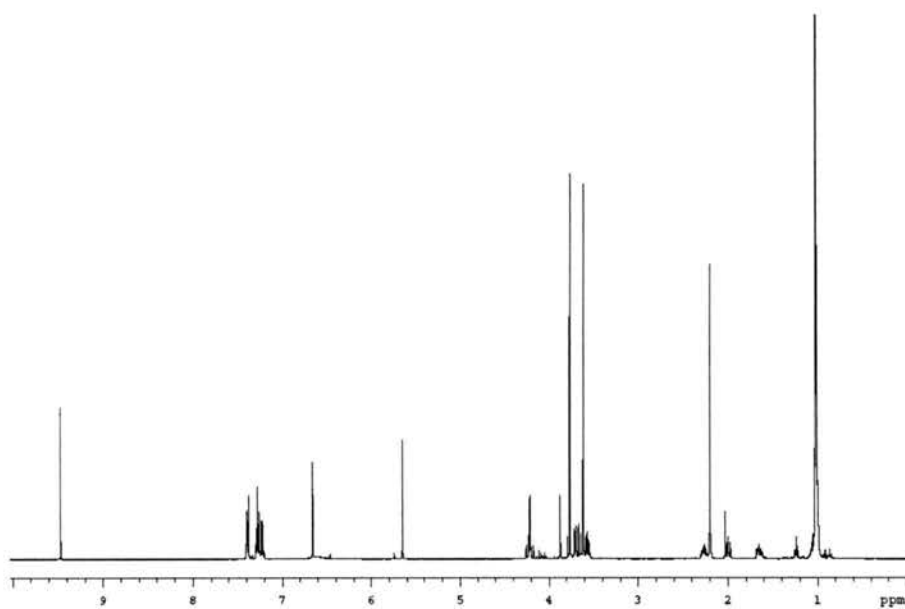
^{13}C NMR, 100 MHz, CDCl_3 , filename: YY-IV-023.13C



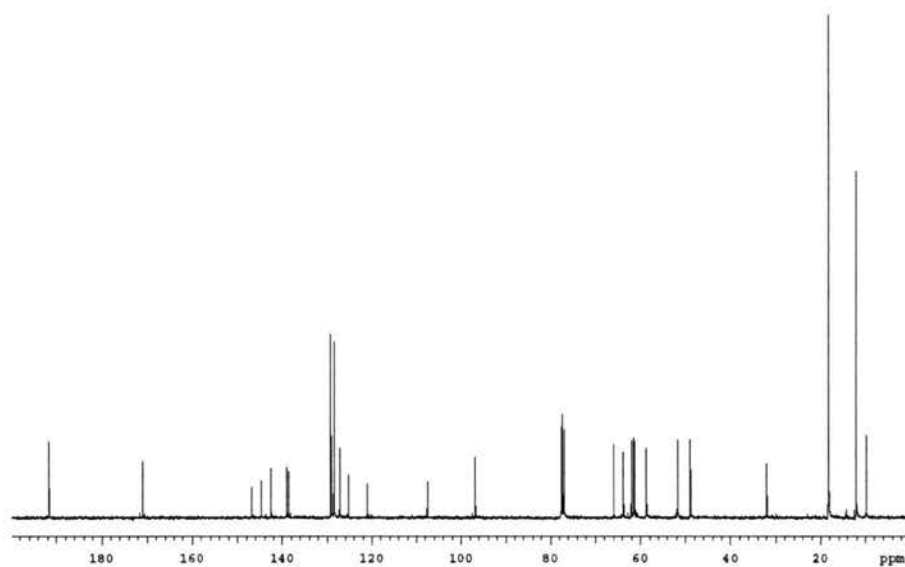
To a THF (3.6 ml) solution of **323** (118 mg, 0.18 mmol) was added 1M LAH in THF (0.18 mL, 0.18 mmol) at -10°C . After 10 min the reaction was quenched with 1M HCl (0.2 mL), diluted with EtOAc, washed with brine and dried (Na_2SO_4). After concentration under reduced pressure, the resulting residue was purified by flash chromatography (silica, 6:1 hexane:AcOEt) affording **324** (74 mg, 66%) and **325** (23 mg, 21%). $R_f = 0.6$ and 0.4 respectively (1:1 hexane : AcOEt). ^1H NMR (400 MHz, CDCl_3): δ 1.02 (21H, bs.), 1.65 (1H, m), 2.00 (1H, dd, $J = 8.5, 12.4$ Hz), 2.20 (3H, s), 2.27 (1H, m), 3.56 (1H, dd, $J = 5.1, 9.2$ Hz), 3.61 (3H, s), 3.68 (2H, m), 3.76 (3H, s), 3.87 (1H, s), 3.88 (1H, s), 4.19 (1H, d, $J = 13.4$ Hz), 4.24 (1H, d, $J = 13.4$ Hz), 5.64 (1H, s), 6.66 (1H, s), 7.20-7.40 (5H, m), 9.47 (1H, s). ^{13}C NMR (100 MHz) (CDCl_3): δ 9.8, 12.1, 18.2, 31.9, 48.8, 51.8, 58.6, 61.2, 61.5, 62.0, 65.9, 96.8, 107.5, 120.9, 125.3, 127.2, 128.4, 129.2, 138.6, 139.0, 124.6, 144.7, 146.8, 170.9, 191.6. IR (NaCl, depos. from CH_2Cl_2): 3362, 2941, 2865, 1740, 1674, 1636 cm^{-1} . HRMS (FAB) calcd. For $\text{C}_{35}\text{H}_{49}\text{N}_2\text{O}_6\text{Si}$ (MH^+): 621.3359, Found: 621.3370. $[\alpha]_D^{25} = -34.0$ ($c=1.0$, CH_2Cl_2)



324

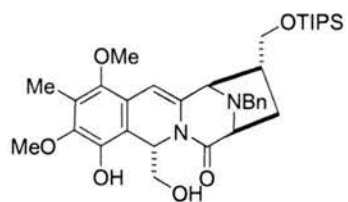


^1H NMR, 400 MHz, CDCl_3 , filename: YY-IV-035.1

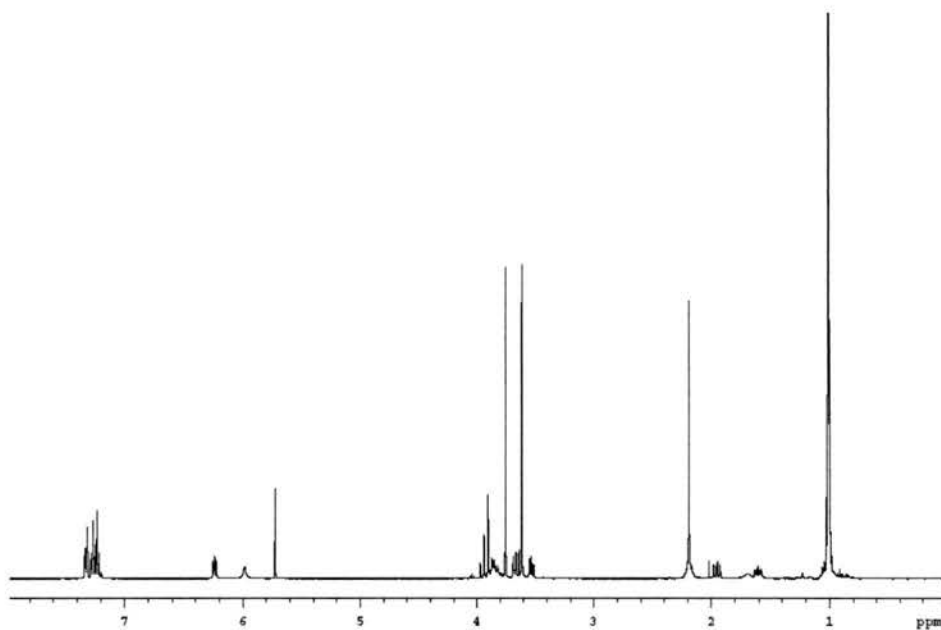


^{13}C NMR, 100 MHz, CDCl_3 , filename: YY-IV-035.1.13C

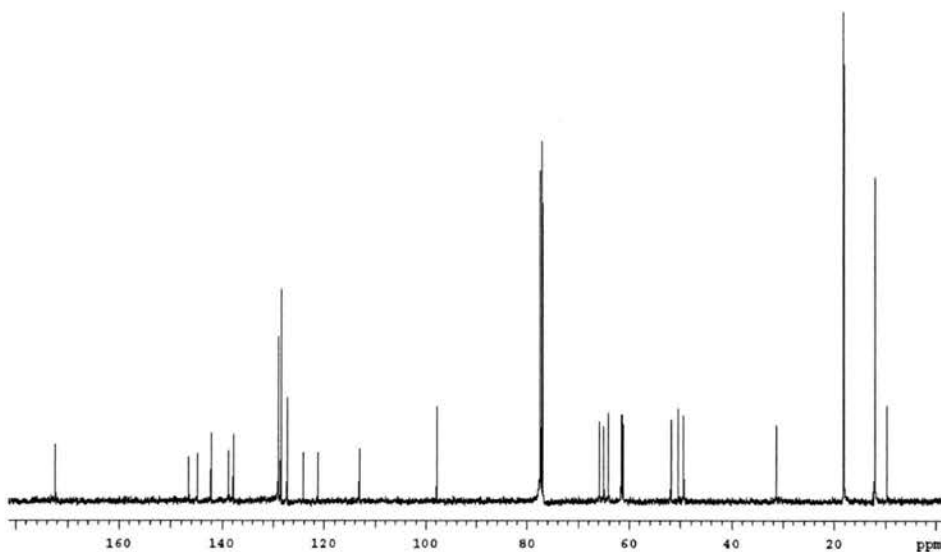
For compound **325**: ^1H NMR (400 MHz, CDCl_3): δ 1.01 (21H, m), 1.60 (1H, m), 1.96 (1H, dd, $J = 9.6, 13.4$ Hz), 2.19 (3H, s), 2.13-2.24 (2H, m), 3.53 (1H, dd, $J = 5.1, 9.6$ Hz), 3.61 (3H, s), 3.65 (2H, m), 3.75 (3H, s), 3.79-3.99 (5H, m), 5.73 (1H, s), 5.99 (1H, bs), 6.24 (1H, dd, $J = 4.5, 7.2$ Hz), 7.18-7.36 (5H, m). ^{13}C NMR (100 MHz) (CDCl_3): δ 9.7, 12.1, 18.2, 31.3, 49.4, 50.4, 51.9, 61.2, 61.4, 61.6, 64.0, 65.0, 65.8, 97.9, 113.1, 121.2, 124.1, 127.3, 128.5, 129.0, 137.9, 138.6, 142.1, 144.8, 146.4, 172.4. IR (NaCl, depos. from CH_2Cl_2): 3389, 2940, 2864, 1668, 1632, 1463cm^{-1} . HRMS (FAB) calcd. For $\text{C}_{35}\text{H}_{51}\text{N}_2\text{O}_6\text{Si}$ (MH^+): 623.3516, Found: 623.3526. $[\alpha]_{\text{D}}^{25} = -50.0$ ($c=1.0$, CH_2Cl_2).



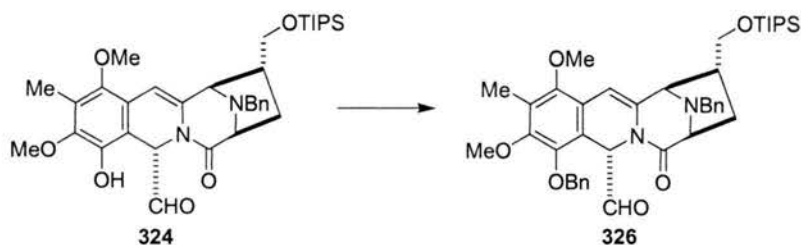
325



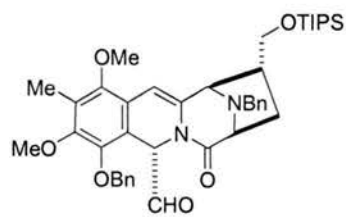
^1H NMR, 400 MHz, CDCl_3 , filename: YY-IV-035.2



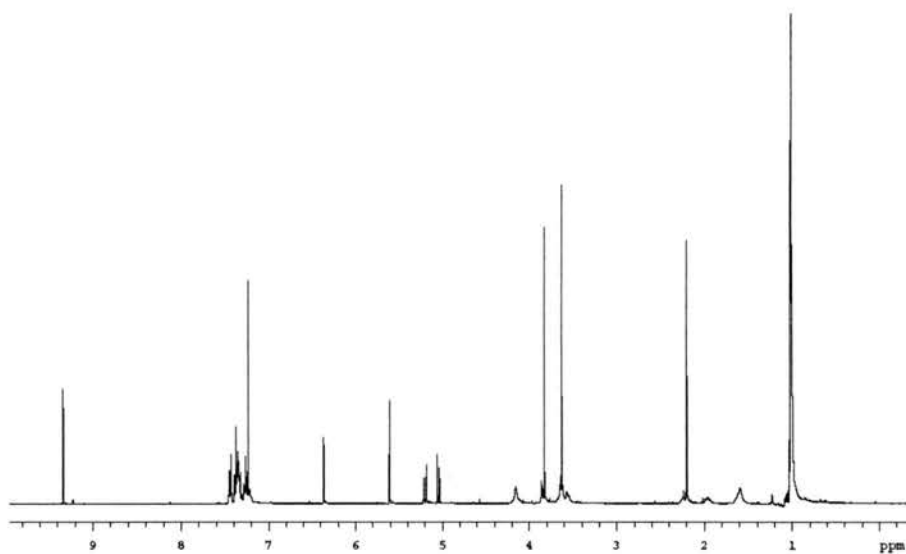
^{13}C NMR, 100 MHz, CDCl_3 , filename: YY-IV-035.2 .13C



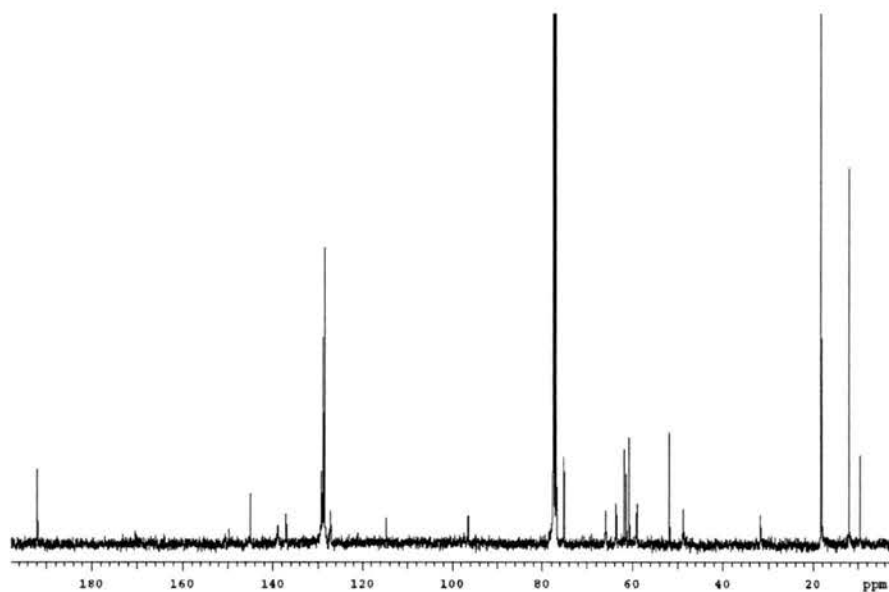
To a solution of **324** (50 mg, 0.08 mmol) in DMF (0.2 mL) was added in Bu₄NI (3.7 mg, 0.01 mmol), BnBr (4.6 μ L, .012 mmol), followed by NaCO₃ (13.6 mg, .016 mmol). After stirring for 2 h, the reaction mixture was quenched with 1M HCl (mL) and diluted with Et₂O. The organic layer was then washed with water (1 mL), brine (1 mL) and dried (Na₂SO₄). After concentration under reduced pressure the resulting residue was purified by flash chromatography (silica, 6:1 hexane:AcOEt) affording **326** (37 mg, 66%). ¹H NMR (400 MHz, CDCl₃): δ 1.01 (21H, m), 1.61 (1H, m), 1.96 (1H, m), 2.20 (3H, s), 2.24 (1H, m), 3.56 (1H, m), 3.62 (3H, s), 3.60-3.68 (2H, m), 3.83 (3H, s), 3.86 (1H, s), 4.16 (2H, m), 5.07 (1H, d, J = 10.9 Hz), 5.22 (1H, d, J = 10.9 Hz), 5.61 (1H, s), 6.37 (1H, s), 7.17-7.47 (10H, m), 9.33 (1H, s). ¹³C NMR (100 MHz) (CDCl₃): δ 9.6, 12.1, 18.2, 31.7, 48.8, 51.7, 59.0, 60.7, 61.3, 61.8, 63.6, 65.9, 75.2, 96.4, 114.7, 127.2, 128.4, 128.5, 128.9, 129.2, 137.0, 138.8, 145.0, 149.8, 170.4, 191.9, IR (NaCl, depos. from CH₂Cl₂): 2941, 2865, 1740, 1688, 1636 cm⁻¹. HRMS (FAB) calcd. For C₄₂H₅₅N₂O₆Si (MH⁺): 711.3829, Found: 711.3836. $[\alpha]_D^{25}$ = -52.4 (c=1.0, CH₂Cl₂).



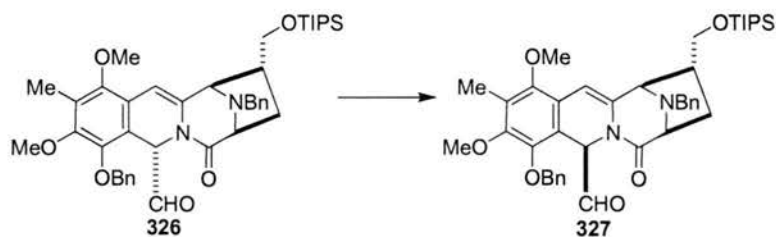
326



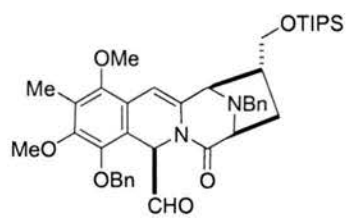
^1H NMR, 400 MHz, CDCl_3 , filename: YY-IV-036.1



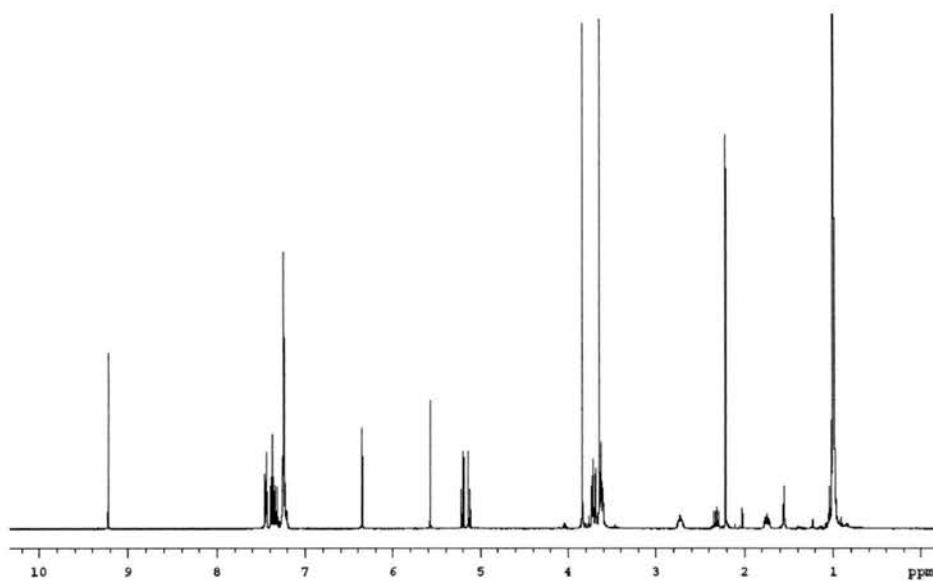
^{13}C NMR, 100 MHz, CDCl_3 , filename: YY-IV-036.1.13C



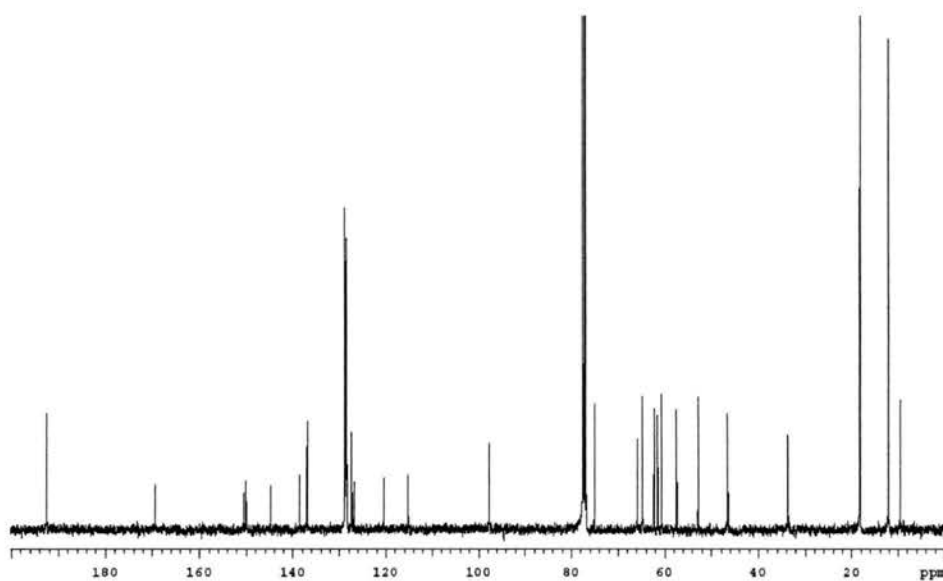
To a solution of **326x** (100 mg, 0.14 mmol) in THF (2.8 mL) was added in DBN (8.65 μ L, 0.07 mmol) and the reaction stirred for 30 min at r.t.. The reaction was then quenched with 1M HCl (1 ml), extracted with EtOAc and the organic layer washed with brine and dried (Na_2SO_4). After concentration under reduced pressure, the resulting residue was purified by flash chromatography (silica, 10:1 hexane:AcOEt) affording **III-327** (50 mg, 50%) and unreacted starting material (40 mg, 40%). ^1H NMR (400 MHz, CDCl_3): δ 1.00 (21H, m), 1.75 (1H, m), 2.21 (3H, s), 2.32 (1H, dd, $J = 9.2, 13.0$ Hz), 2.73 (1H, m), 3.65 (3H, s), 3.59-3.66 (3H, m), 3.68-3.75 (3H, m), 3.84 (3H, s), 5.12 (1H, d, $J = 11.1$ Hz), 5.20 (1H, d, $J = 11.1$ Hz), 5.58 (1H, s), 6.35 (1H, s), 7.20-7.48 (10H, m), 9.22 (1H, s). ^{13}C NMR (100 MHz, CDCl_3): δ 9.6, 12.2, 18.2, 33.7, 46.5, 52.8, 57.4, 60.7, 61.4, 62.3, 64.7, 65.9, 70.1, 97.8, 115.2, 127.4, 128.5, 128.6, 128.7, 128.9, 137.0, 138.5, 144.9, 150.0, 150.6, 169.3, 192.5 IR (NaCl, depos. from CH_2Cl_2): 2941, 2865, 1738, 1688, 1645 cm^{-1} . HRMS (FAB) calcd. For $\text{C}_{42}\text{H}_{55}\text{N}_2\text{O}_6\text{Si}$ (MH^+): 711.3829, Found: 711.3836. $[\alpha]_{\text{D}}^{25} = +105.5$ ($c=1.0$, CH_2Cl_2).



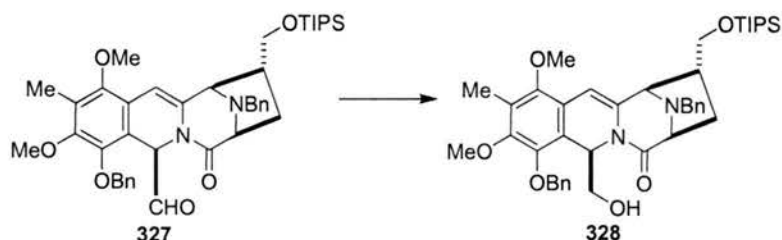
327



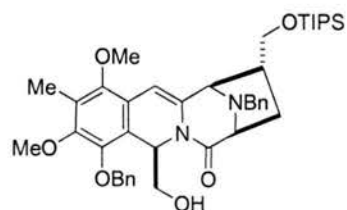
^1H NMR, 400 MHz, CDCl_3 , filename: YY-IV-087.2



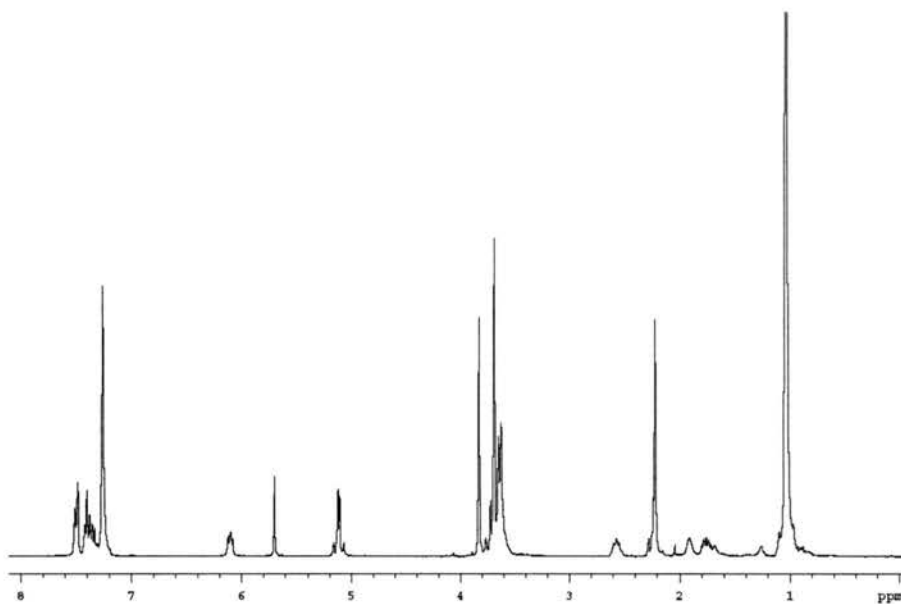
^{13}C NMR, 100 MHz, CDCl_3 , filename: YY-IV-087.13C



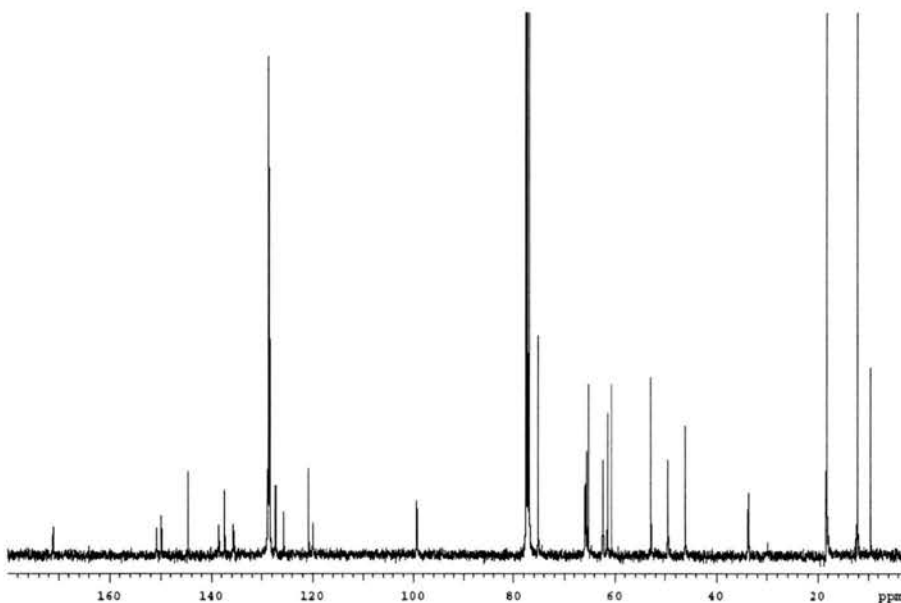
To a solution of **327** (53 mg, 0.08mmol) in EtOH (3.7 mL), was added NaBH₄ (11 mg, 0.3 mmol) at 0°C. After stirring for an hour at this temperature, the reaction mixture was quenched with 1M HCl (0.1 mL) and diluted with EtOAc. After washing with brine the organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (silica, 3:1 hexane:AcOEt) affording **328** (40 mg, 75%). ¹H NMR (400 MHz, CDCl₃): δ 1.00 (21H, m), 1.74 (1H, m), 1.85 (1H, bs), 2.19 (3H, s), 2.22 (1H, m), 2.55 (1H, m), 3.52-3.71 (8H, m), 3.66 (3H, s), 3.80 (3H, s), 5.09 (2H, dd, , *J*= 11.8, 19.8 Hz), 5.68 (1H, s), 6.07 (1H, dd, , *J*= 4.7, 8.3 Hz), 7.18- 7.52 (10H, m). ¹³C NMR (100 MHz, CDCl₃): δ 9.5, 12.2, 18.2, 33.7, 46.1, 49.5, 52.8, 60.6, 61.4, 62.4, 65.2, 65.6, 65.8, 75.2, 99.2, 119.9, 150.8, 125.7, 127.3, 128.4, 128.5, 128.6, 128.8, 135.7, 137.3, 138.5, 144.6, 149.8, 150.8, 171.1. IR (NaCl, depos. from CH₂Cl₂): 3450, 2940, 2864, 1674, 1635 cm⁻¹. HRMS (FAB) calcd. For C₄₂H₅₇N₂O₆Si (MH⁺): 713.3986, Found: 713.3996. [α]_D²⁵= +70.5 (c=1.0, CH₂Cl₂).



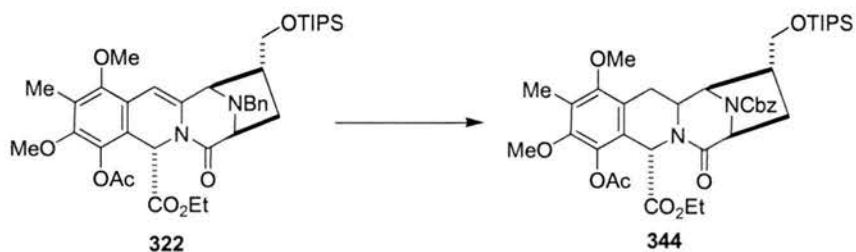
328



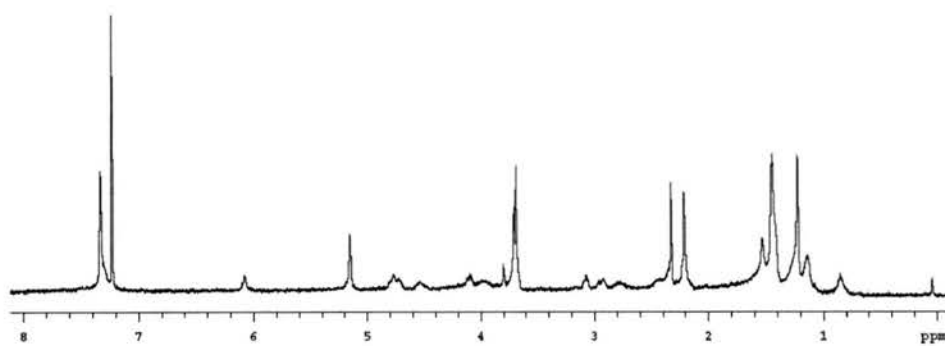
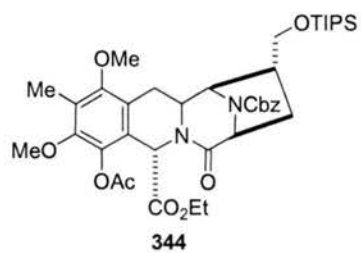
^1H NMR, 400 MHz, CDCl_3 , filename: YY-III-451.3



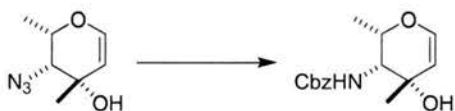
^{13}C NMR, 100 MHz, CDCl_3 , filename: YY-III-451.3.13C



A pressure reactor containing **322** (10 mg, 0.014 mmol) and PdCl₂ (1.3 mg) in absolute ethanol (0.5 ml) was purged with hydrogen gas for three times. After the reactor was pressurized to 1800 psi with hydrogen gas, the reaction was stirred at 65 °C for 2 days. After the pressure was released, the reaction filtered through a pad of celite. The resulting reaction mixture was concentrated under reduced pressure and the residue was dissolve in MeOH. To this methanol solution, CbzCl (1 μL, 0.03 mmol) was added, followed by NaHCO₃ (2.5 mg 0.03 mmol). After stirring for over night, the reaction mixture was filter through a pad of clite, and concentrated under reduced pressure. The resulting residue was purified by prep-TLC (silica, 1:1 hexane:AcOEt) affording **344** (1 mg, 10%). ¹H NMR (400 MHz, CDCl₃): δ 1.14 (3H, bs), 1.22- 1.53 (21H, m), 2.15 (1H, m), 2.22 (3H, s), 2.23 (3H, s), 2.45 (1H, m), 2.76 (1H, m), 2.93 (1H, m), 3.07 (1H, m), 3.69 (3H, s), 3.71 (3H, s), 3.80 (1H, s), 3.96 (1H, m), 4.10 (1H, m), 3.54 (1H, m), 4.76 (2H, m), 5.16 (2H, s), 5.68 (1H, s), 6.08 (1H), 7.33 (5H, m).



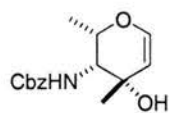
¹H NMR, 400 MHz, CDCl₃, filename: YY-IV-092B.2



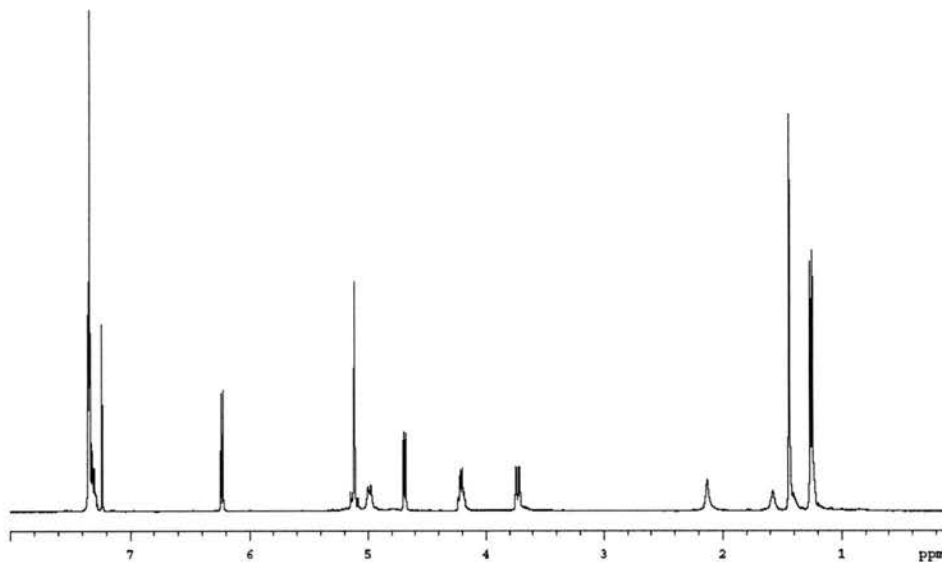
benzyl (2S,3R,4S)-4-hydroxy-2,4-dimethyl-3,4-dihydro-2H-pyran-3-ylcarbamate

(355)

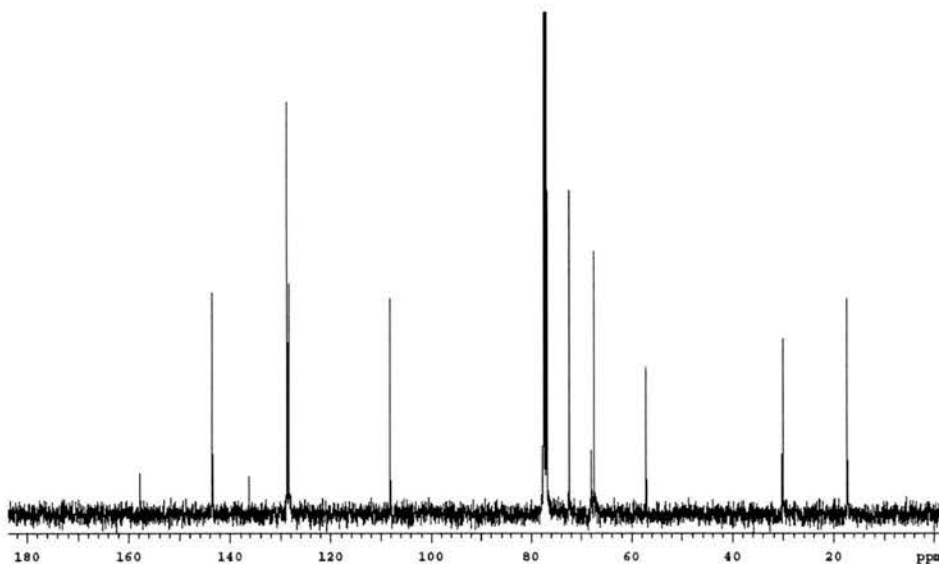
To a solution of **350** (48 mg, 0.28 mmol) in MeOH (30 mL) was added Lindlar catalyst (100 mg). After being purged with argon, the reaction mixture was stirred under 1 atm hydrogen for 1 hour. After filtered through a celite pad, the reaction mixture was concentrated down under reduced pressure. The resulting residue was dissolved in THF (5.6 mL) and was added CbzCl (48 μ L, 0.56 mmol) followed by NMM (61 μ L, 0.34 mmol) at 0 °C. After warmed to room temperature and stirred for 30 minutes, the reaction mixture was filtered through a celite pad and concentrated down. The resulting residue were purified by flash chromatography (silica, 3:1 hexane:AcOEt) affording **355** (54 mg, 70%). ^1H NMR (400 MHz, CDCl_3): δ 1.25 (3H, d, J = 6.6 Hz), 1.44 (3H, s), 2.13 (1H, bs), 3.73 (1H, d, J = 10.4 Hz), 4.20 (1H, dd, J = 6.6, 13.0 Hz), 4.68 (1H, d, J = 10.4 Hz), 5.00 (1H, d, J = 9.2 Hz), 5.12 (2H, s), 6.23 (1H, d, J = 6.2 Hz), 7.26- 7.37 (5H, m). ^{13}C NMR (100 MHz, CDCl_3): δ 17.3, 30.1, 57.1, 67.5, 68.0, 72.4, 108.2, 128.4, 128.5, 128.8, 136.3, 143.5, 157.8 IR (NaCl, depos. from CH_2Cl_2): 3426, 1706, cm^{-1} . HRMS (FAB) calcd. For $\text{C}_{15}\text{H}_{20}\text{N}_1\text{O}_4$ (MH^+): 278.1392, Found: 278.1392.



355



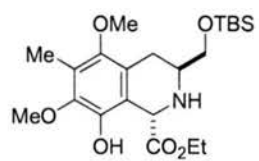
^1H NMR, 400 MHz, CDCl_3 , filename: YY-III-466

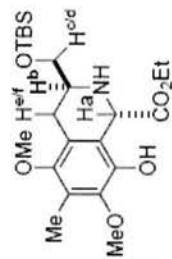


^{13}C NMR, 100 MHz, CDCl_3 , filename: YY-III-466.13C

Appendix 1

nOe on compound **248a**

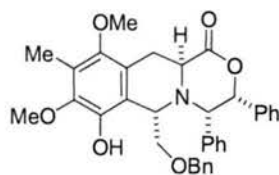


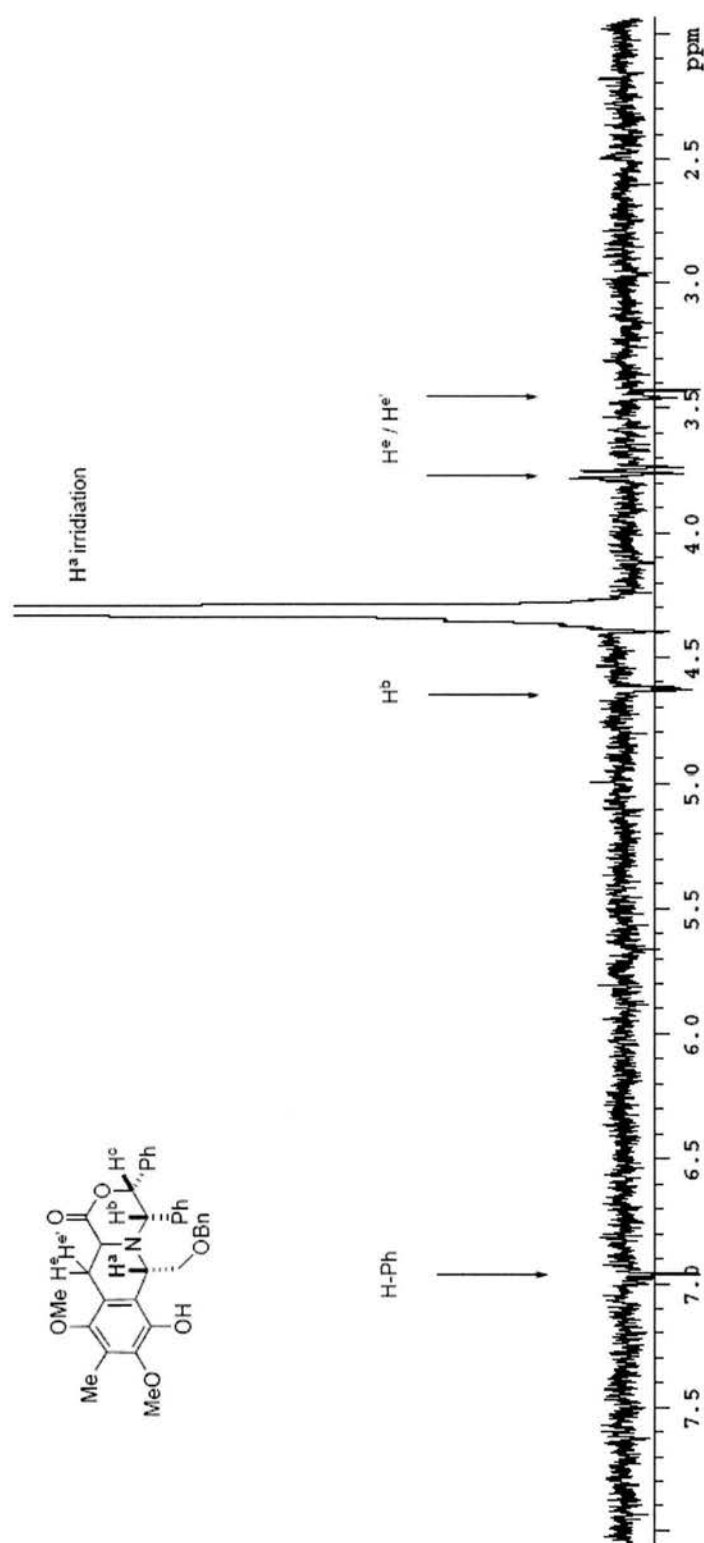


180

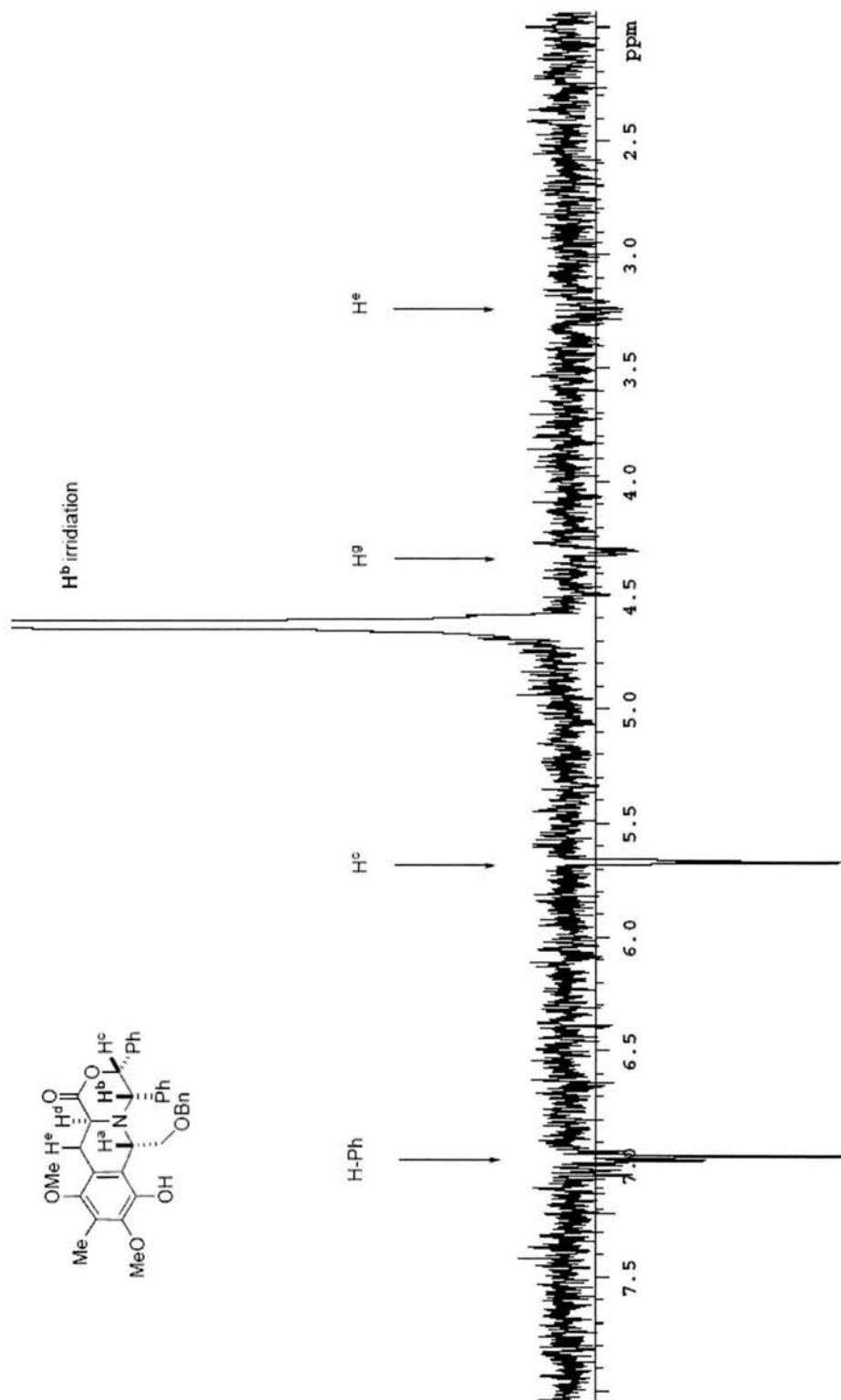
Appendix 2

nOe on compound **253a**





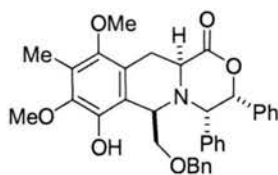
nOe, 400 MHz, DMSO, filename: YY-I-111.nOe.Ha

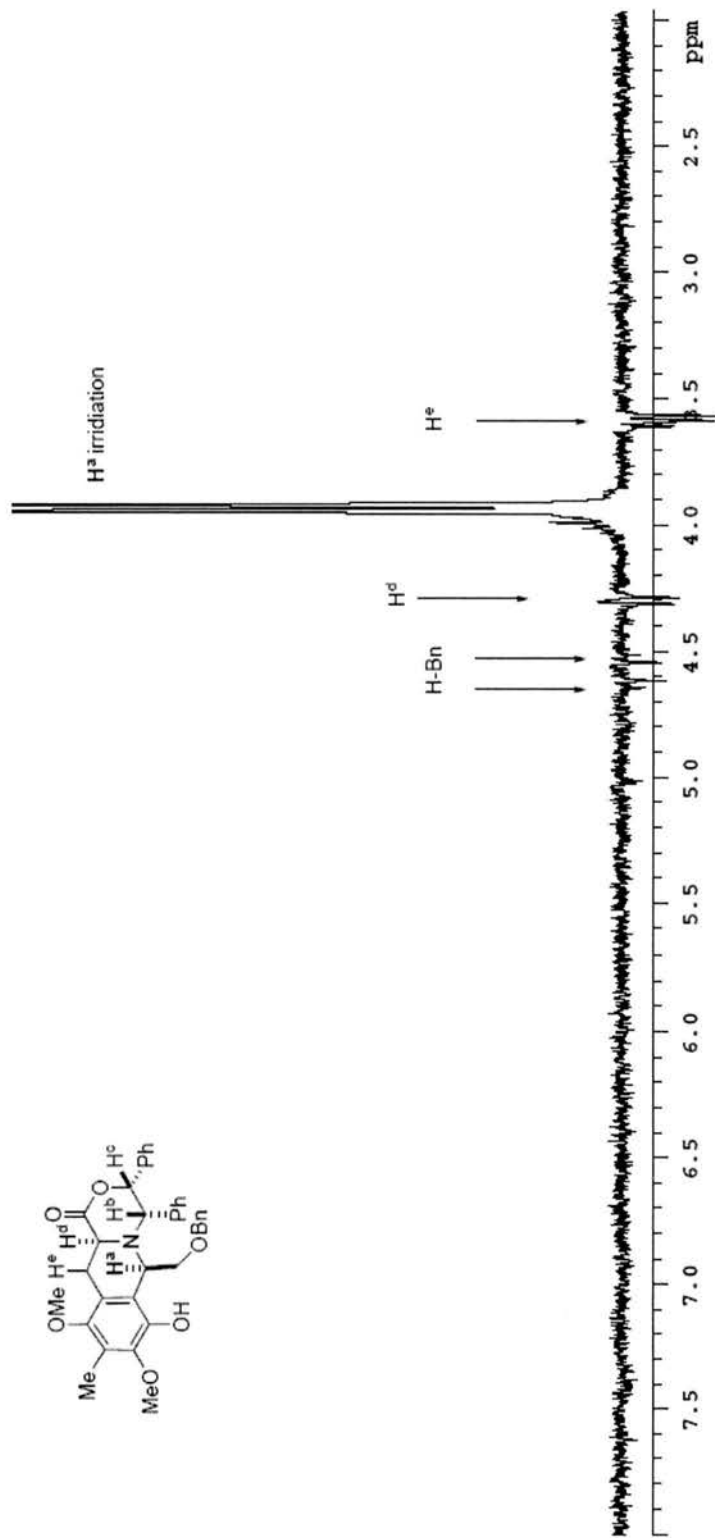
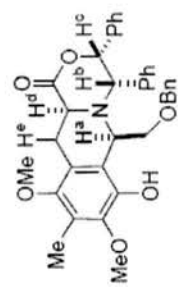


nOe, 400 MHz, DMSO, filename: YY-I-111.nOe.Hb

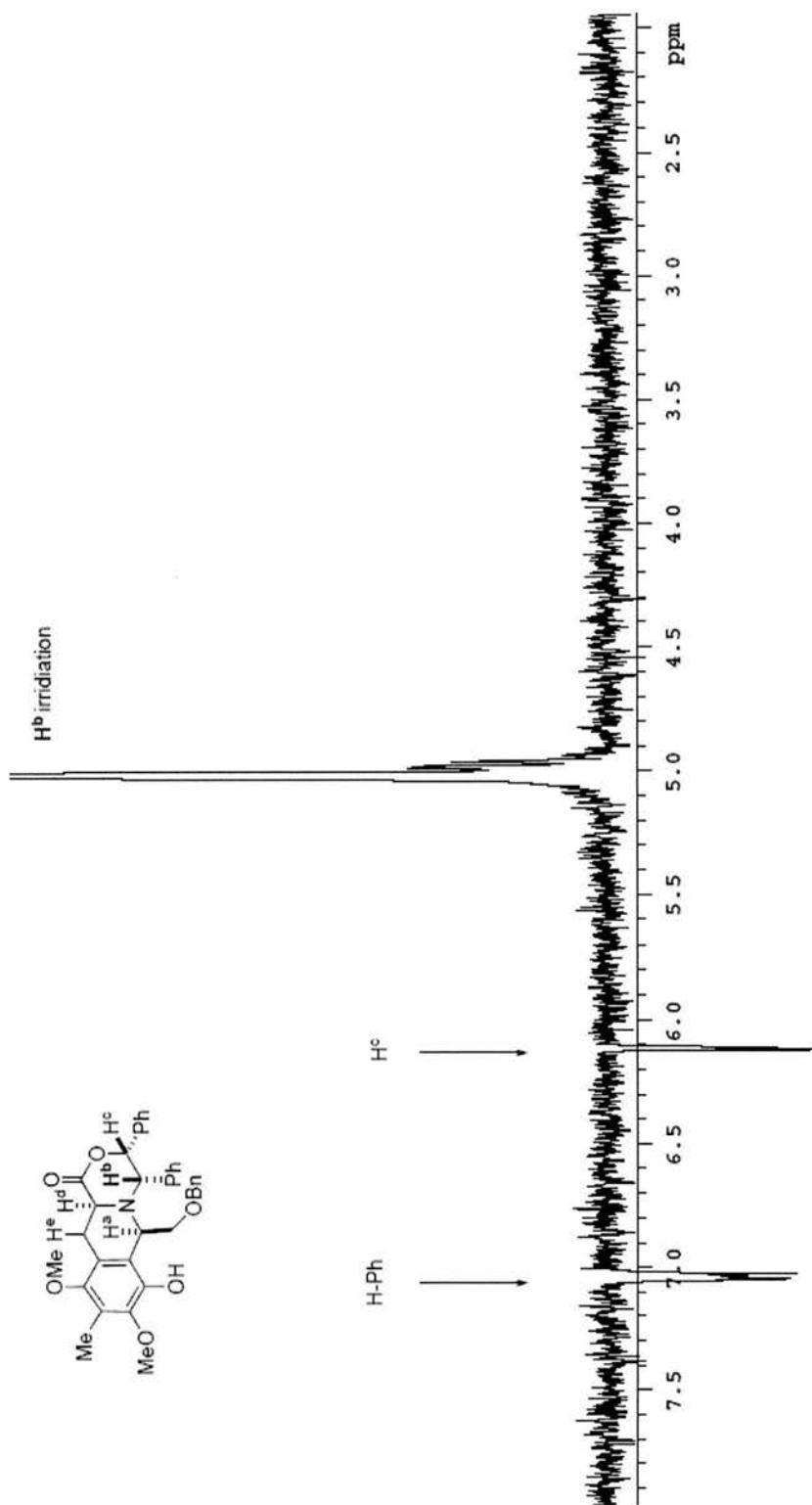
Appendix 3

nOe on compound **253b**





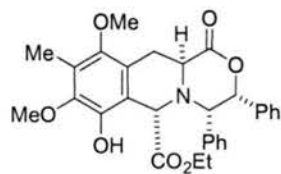
nOe, 400MHz, DMSO, filename: YY-I-120.nOe.Ha.

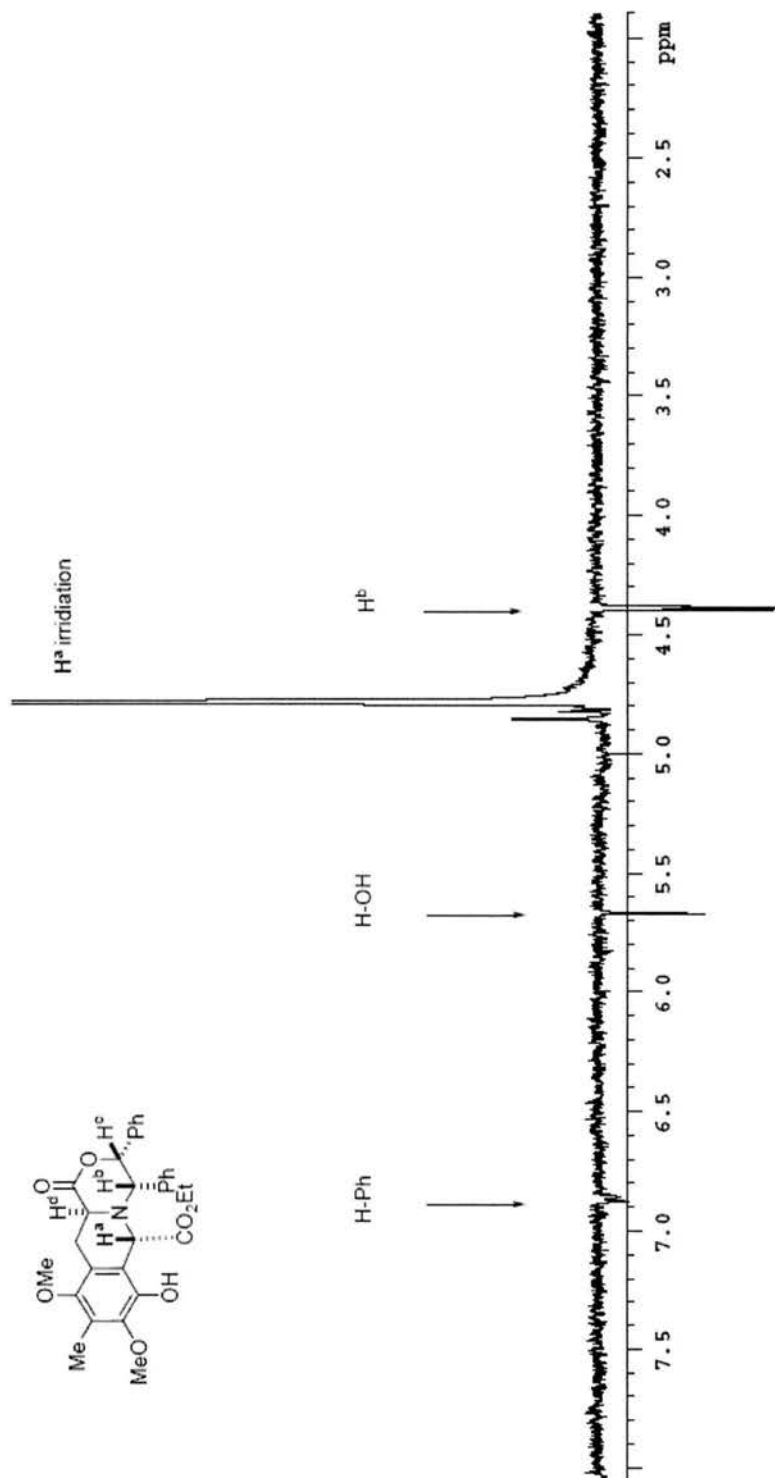


nOe, 400MHz, DMSO, filename: YY-I-120.nOe.Hb.

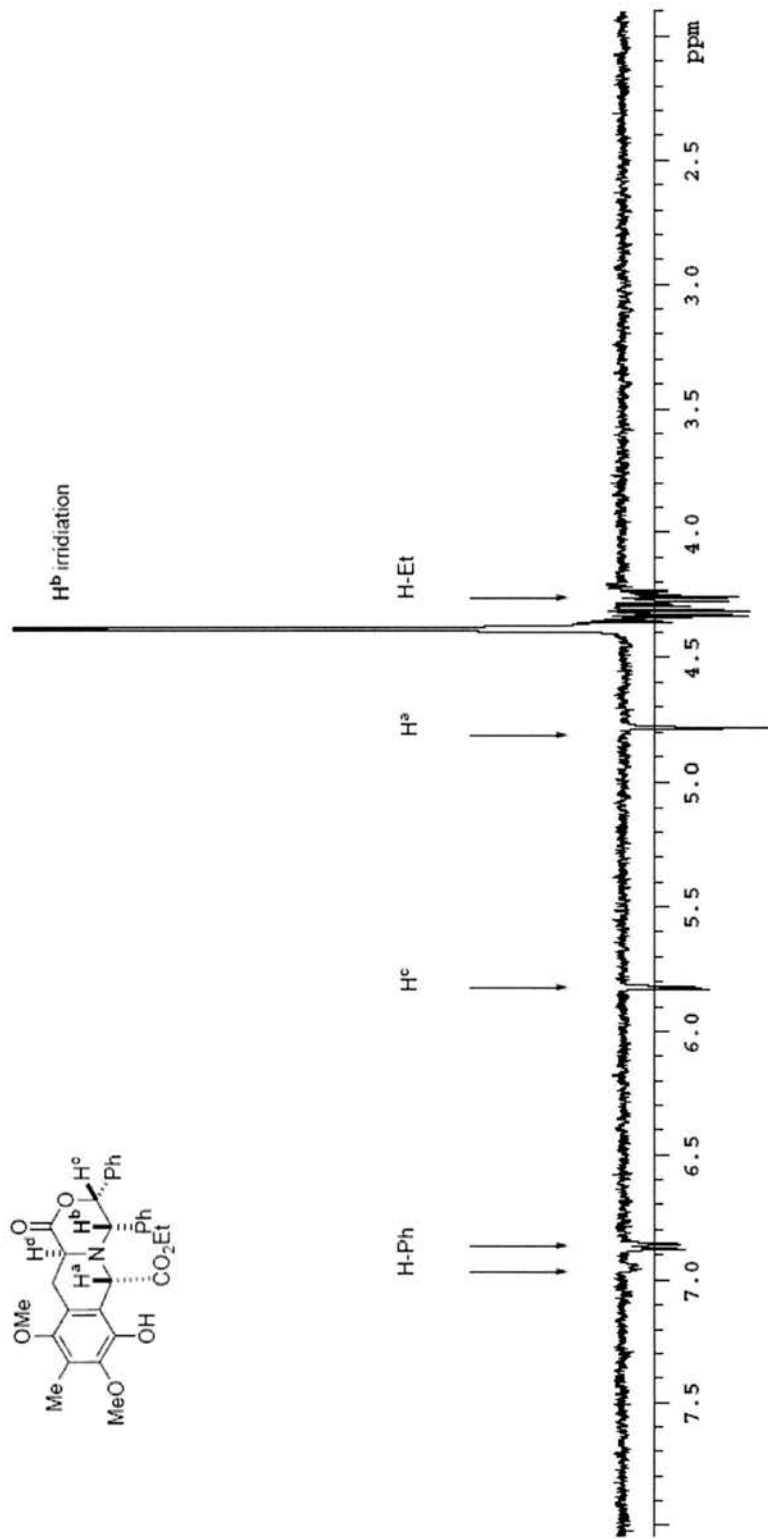
Appendix 4

nOe on compound **255a**





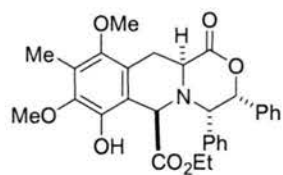
nOe, 400 MHz, CDCl_3 , filename: YY-I-157nOe.anti.Ha

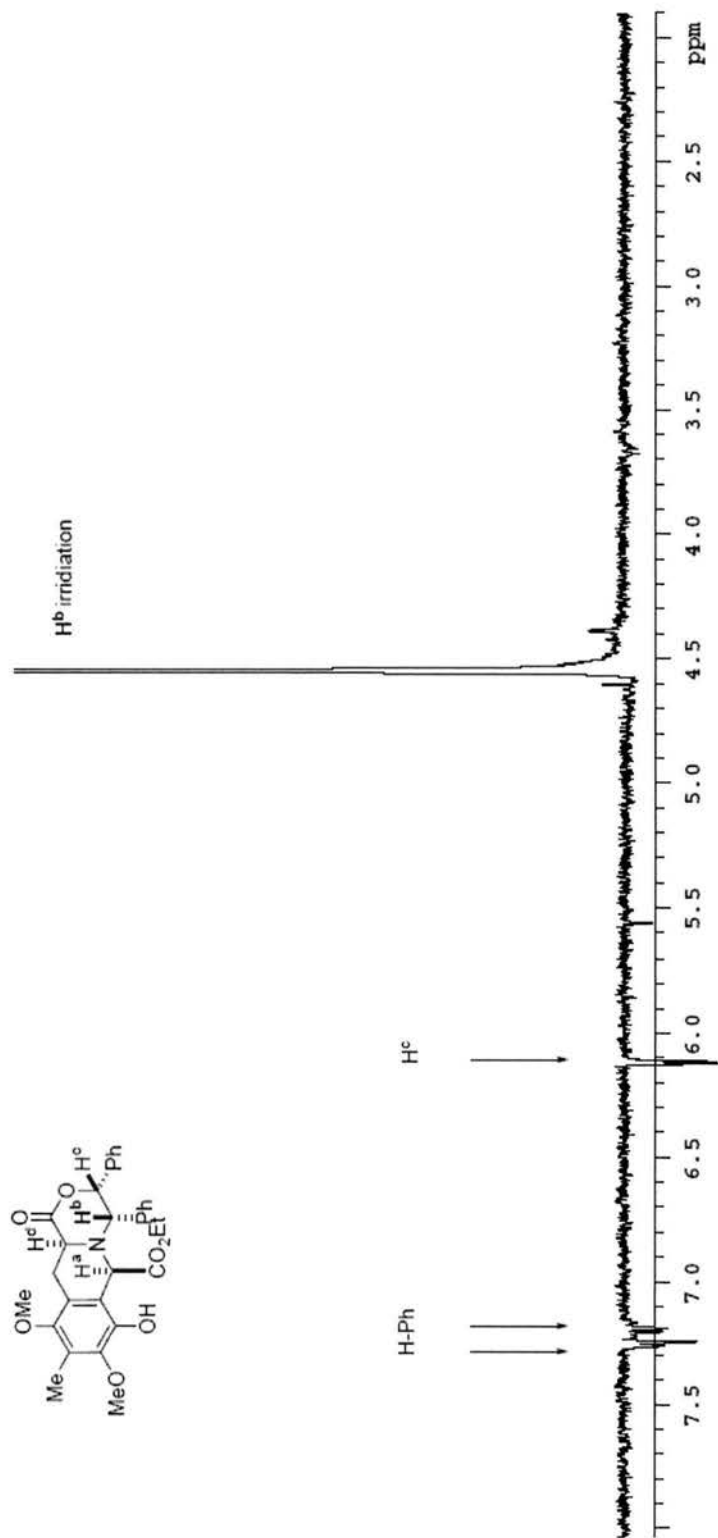


nOe, 400 MHz, CDCl_3 , filename: YY-I-157nOe.anti.Hb

Appendix 5

nOe on compound **255b**

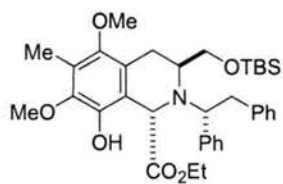


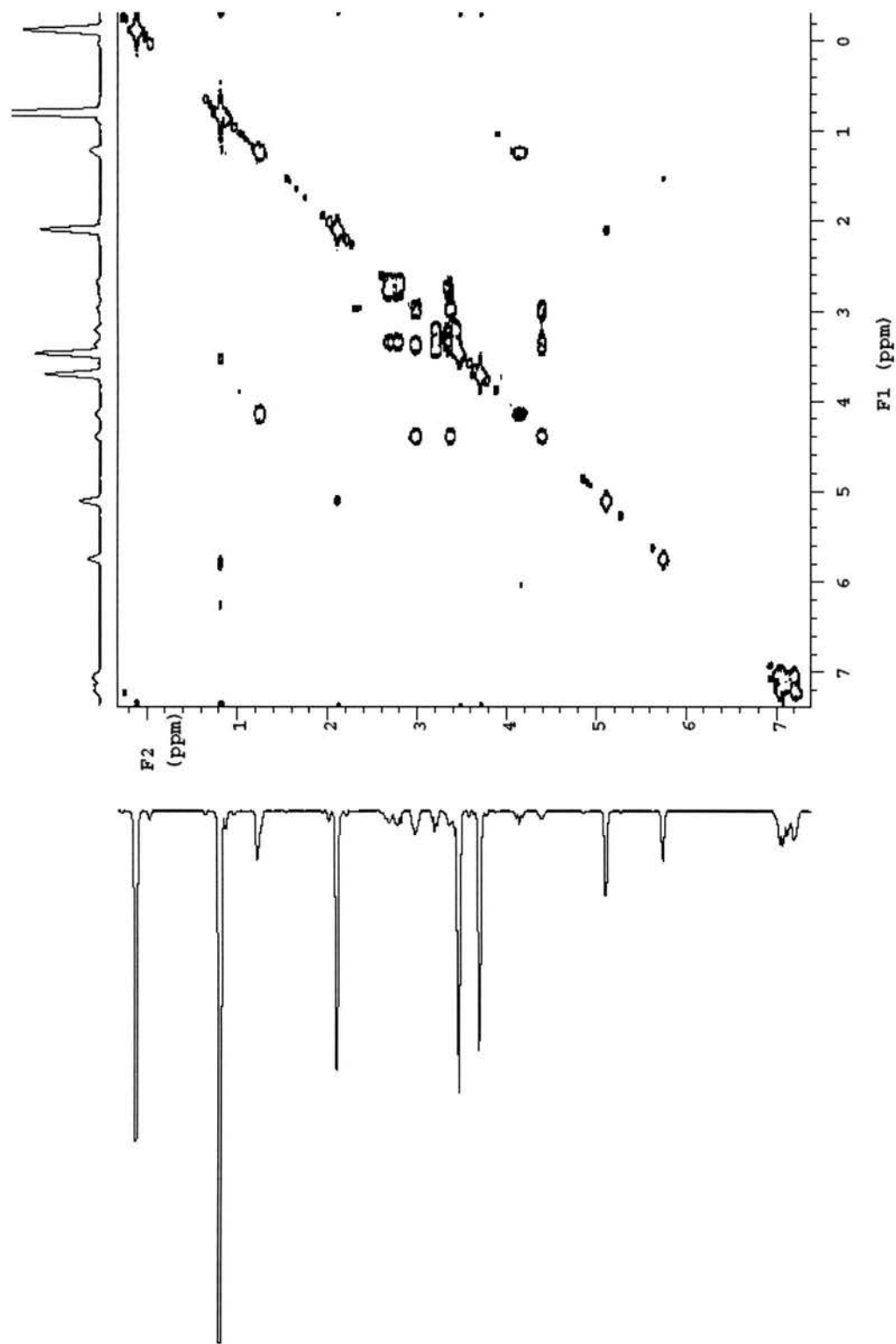


nOe, 400 MHz, $CDCl_3$, filename: YY-I-157nOe.syn.Hb

Appendix 6

g-COSY and nOe on compound **256a**

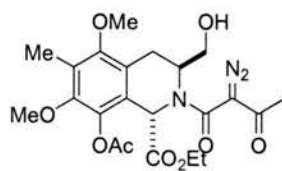


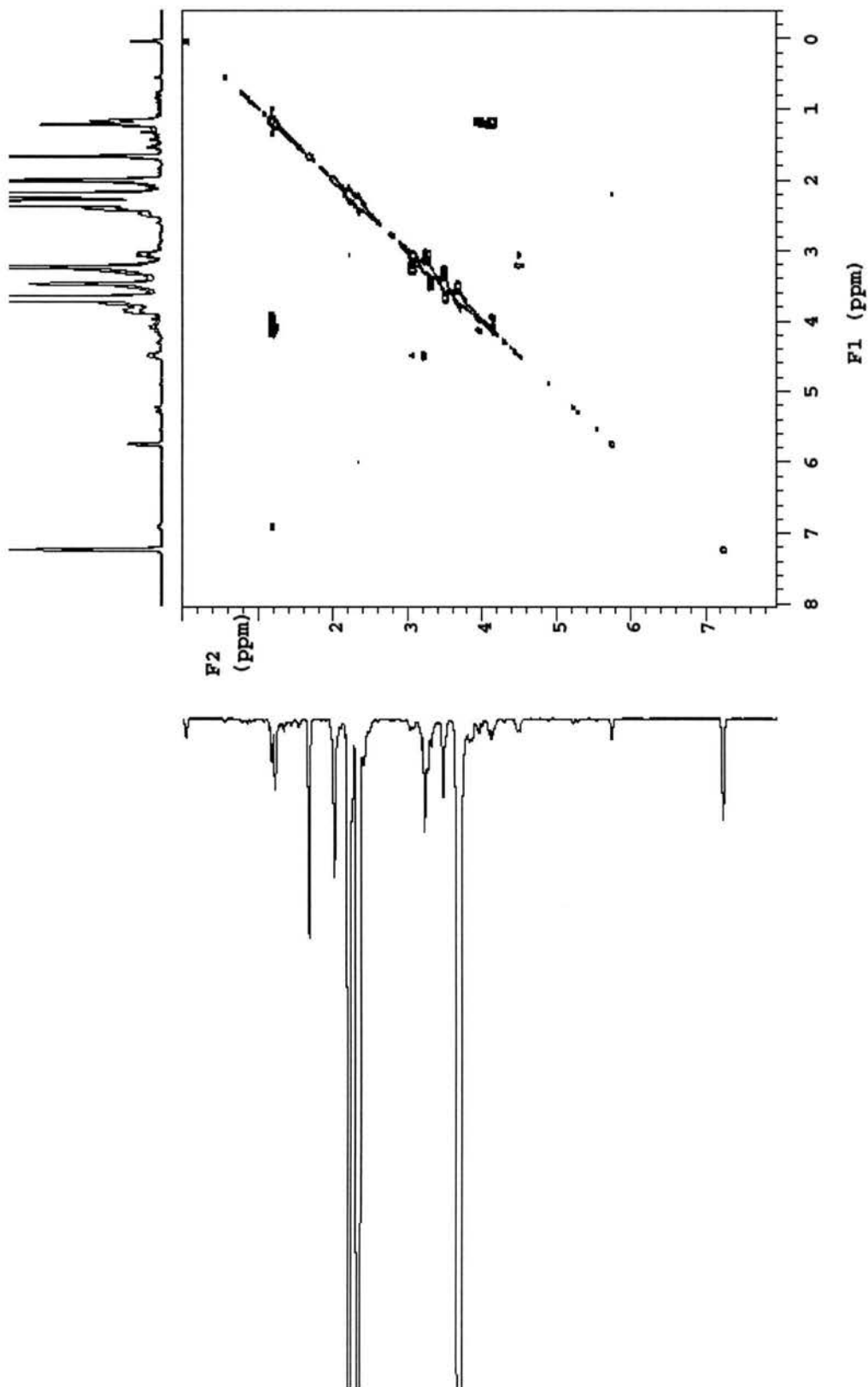


g-COSY, 400 MHz, CDCl₃, filename: YY-I-263.COSY

Appendix 7

g-COSY on compound **307**

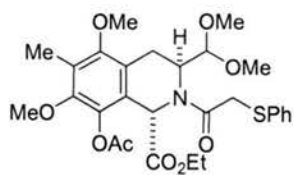


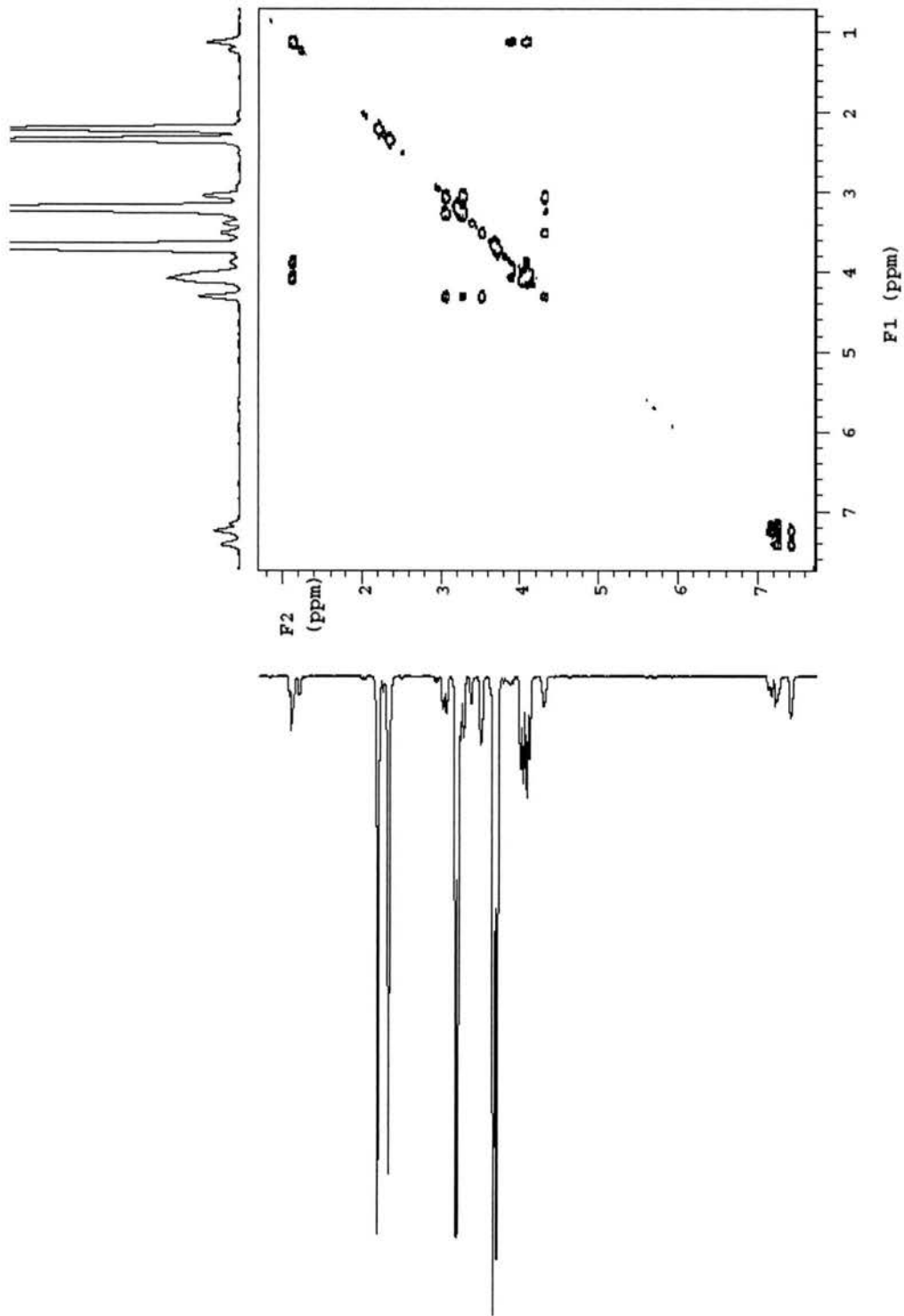


^1H NMR, 400 MHz, CDCl_3 , filename: YY-III-115.3.gCOSY

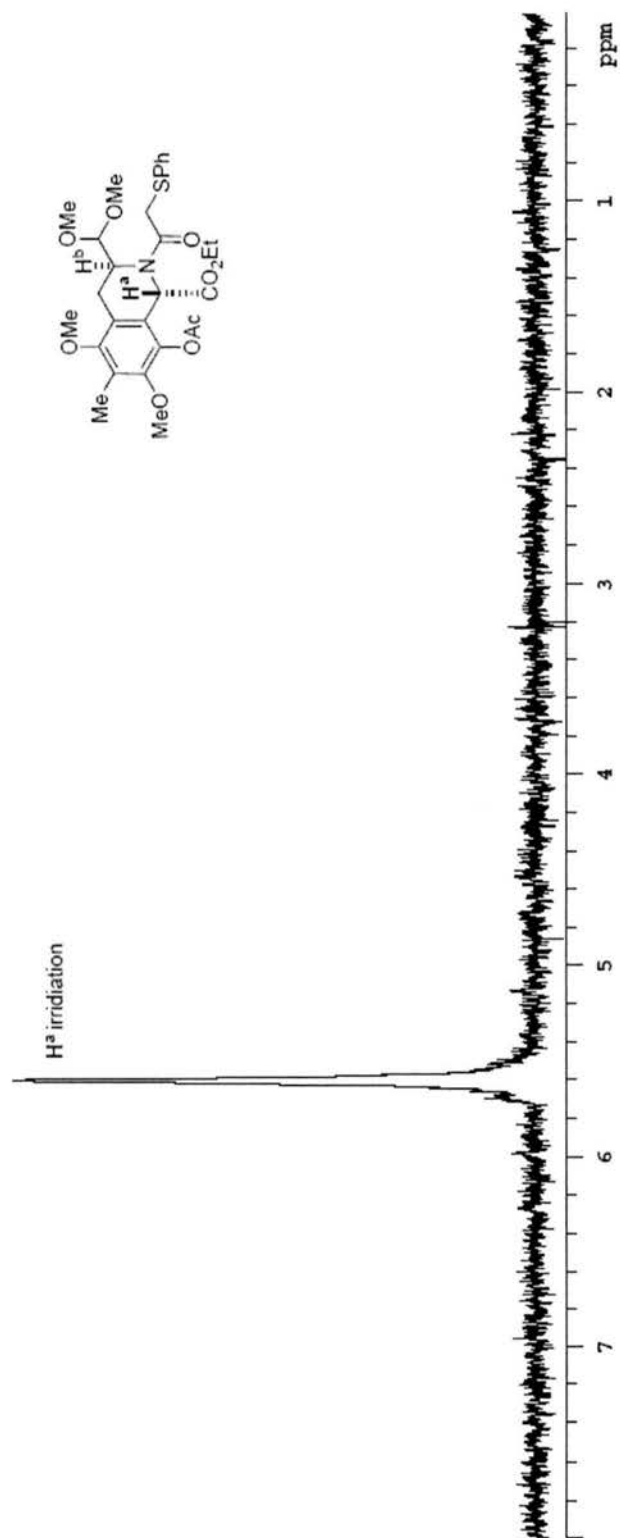
Appendix 8

g-COSY, nOe and CHSQC on compound **313**

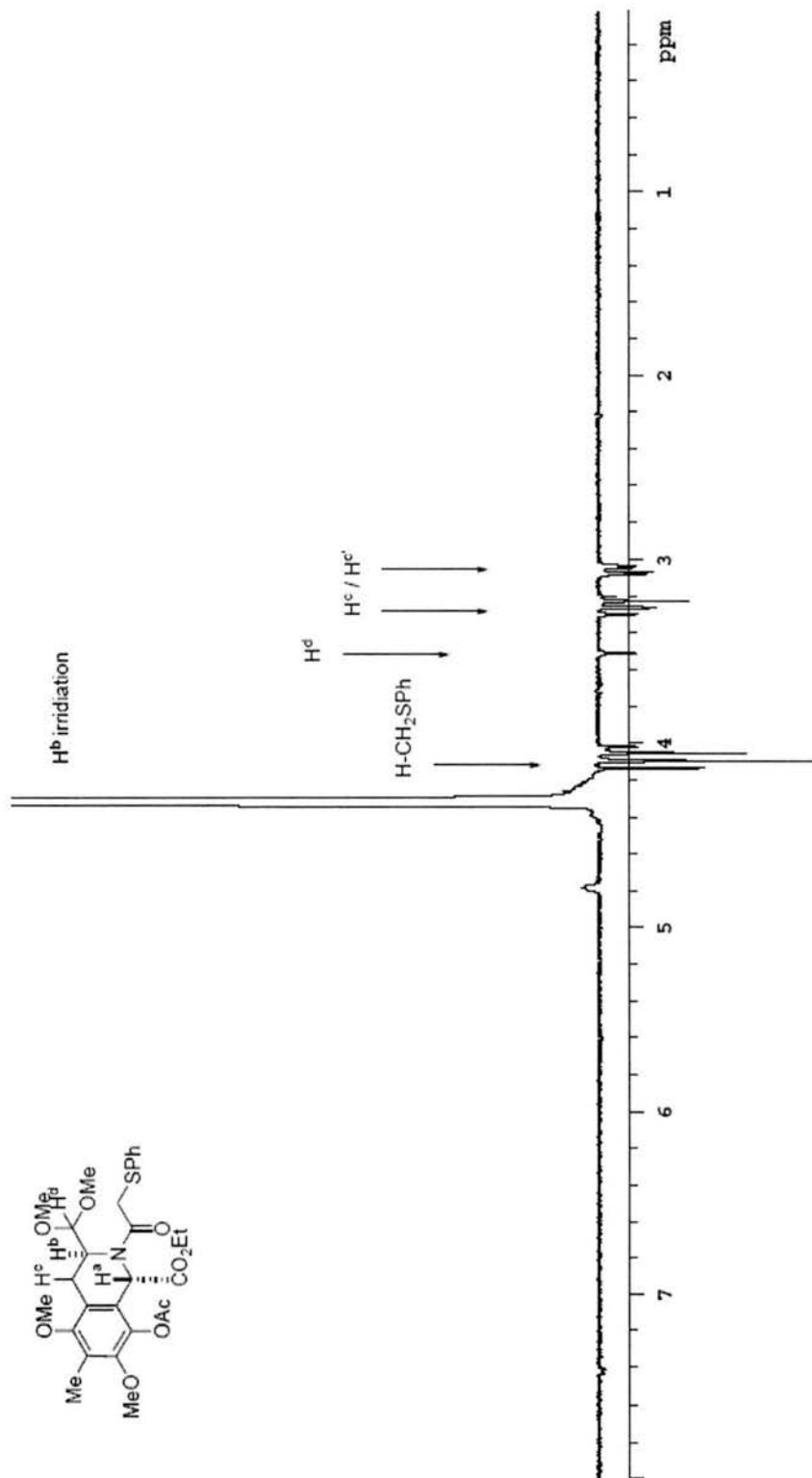




gCOSY, 400MHz, CDCl₃, filename: YY-III-243.gCOSY

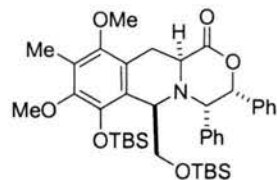


NOSY1D, 400MHz, CDCl₃, filename: YY-III-243.nOe.Ha



NOSY1D, 400MHz, CDCl_3 , filename: YY-III-243.nOe.Hb

Appendix 9



257

Table 1. Crystal data and structure refinement for rw106.

Identification code	rw106	
Empirical formula	C ₄₀ H ₅₇ N O ₆ Si ₂	
Formula weight	704.05	
Temperature	373(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 12.5855(15) Å	$\alpha = 90^\circ$.
	b = 12.6808(17) Å	$\beta = 90^\circ$.
	c = 24.795(3) Å	$\gamma = 90^\circ$.
Volume	3957.2(9) Å ³	
Z	4	
Density (calculated)	1.182 Mg/m ³	
Absorption coefficient	0.134 mm ⁻¹	
F(000)	1520	
Crystal size	0.48 x 0.40 x 0.31 mm ³	
Theta range for data collection	1.64 to 28.34°.	
Index ranges	-16 ≤ h ≤ 16, -16 ≤ k ≤ 16, -32 ≤ l ≤ 31	
Reflections collected	37176	
Independent reflections	9613 [R(int) = 0.0428]	
Completeness to theta = 28.34°	99.0 %	
Absorption correction	multi-scan	
Max. and min. transmission	0.9595 and 0.9383	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	9613 / 0 / 443	
Goodness-of-fit on F ²	1.028	
Final R indices [I > 2sigma(I)]	R1 = 0.0406, wR2 = 0.0929	
R indices (all data)	R1 = 0.0549, wR2 = 0.0992	
Largest diff. peak and hole	0.427 and -0.275 e.Å ⁻³	

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for rw106m. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U(\text{eq})$
Si(2)	4160(1)	225(1)	1705(1)	19(1)
Si(1)	-942(1)	-329(1)	1595(1)	20(1)
C(1)	1975(2)	-1214(1)	-128(1)	18(1)
C(2)	1870(2)	-126(1)	-382(1)	18(1)
C(3)	2390(1)	659(1)	-14(1)	18(1)
C(4)	2894(1)	1562(1)	-216(1)	17(1)
C(5)	3461(1)	2243(1)	119(1)	19(1)
C(6)	3529(2)	1987(1)	663(1)	20(1)
C(7)	3054(1)	1079(1)	875(1)	18(1)
C(8)	2454(1)	429(1)	536(1)	17(1)
C(9)	1802(1)	-453(1)	784(1)	17(1)
C(10)	1284(2)	-2304(1)	612(1)	17(1)
C(11)	613(2)	-2923(1)	207(1)	19(1)
C(12)	1608(1)	-2068(1)	-519(1)	19(1)
C(13)	1922(2)	2309(2)	-933(1)	28(1)
C(14)	3999(2)	3218(1)	-92(1)	25(1)
C(15)	3401(2)	3302(2)	1315(1)	34(1)
C(16)	5330(2)	1109(2)	1765(1)	33(1)
C(17)	4544(2)	-916(2)	1280(1)	27(1)
C(18)	3647(2)	-150(2)	2393(1)	23(1)
C(19)	4493(2)	-817(2)	2678(1)	38(1)
C(20)	2614(2)	-782(2)	2355(1)	45(1)
C(21)	3459(2)	844(2)	2729(1)	46(1)
C(22)	863(2)	87(1)	1063(1)	20(1)
C(23)	-1879(2)	-500(2)	1024(1)	33(1)
C(24)	-987(2)	1068(2)	1833(1)	34(1)
C(25)	-1251(2)	-1276(2)	2157(1)	24(1)
C(26)	-612(2)	-1009(2)	2663(1)	42(1)
C(27)	-2449(2)	-1213(2)	2283(1)	34(1)
C(28)	-989(2)	-2409(2)	1981(1)	32(1)
C(29)	2290(1)	-2876(1)	796(1)	18(1)

C(30)	3075(2)	-3243(1)	443(1)	21(1)
C(31)	3966(2)	-3762(1)	638(1)	26(1)
C(32)	4091(2)	-3933(2)	1185(1)	30(1)
C(33)	3308(2)	-3600(2)	1535(1)	31(1)
C(34)	2420(2)	-3077(2)	1344(1)	24(1)
C(35)	465(2)	-4055(1)	377(1)	20(1)
C(36)	-228(2)	-4256(2)	802(1)	23(1)
C(37)	-312(2)	-5262(2)	1019(1)	27(1)
C(38)	287(2)	-6077(2)	807(1)	28(1)
C(39)	956(2)	-5892(2)	374(1)	28(1)
C(40)	1047(2)	-4881(2)	158(1)	24(1)
O(1)	1066(1)	-2912(1)	-331(1)	22(1)
O(2)	1856(1)	-2050(1)	-984(1)	25(1)
O(3)	2854(1)	1762(1)	-765(1)	20(1)
O(4)	4094(1)	2659(1)	1001(1)	24(1)
O(5)	3135(1)	857(1)	1416(1)	20(1)
O(6)	278(1)	-631(1)	1392(1)	23(1)
N(1)	1408(1)	-1232(1)	385(1)	17(1)

Table 3. Bond lengths [$\text{\AA}$] and angles [$^\circ$] for rw106m.

Si(2)-O(5)	1.6803(13)
Si(2)-C(17)	1.854(2)
Si(2)-C(16)	1.857(2)
Si(2)-C(18)	1.8840(19)
Si(1)-O(6)	1.6599(14)
Si(1)-C(23)	1.856(2)
Si(1)-C(24)	1.868(2)
Si(1)-C(25)	1.880(2)
C(1)-N(1)	1.458(2)
C(1)-C(2)	1.522(2)
C(1)-C(12)	1.525(3)
C(2)-C(3)	1.500(2)
C(3)-C(8)	1.396(2)
C(3)-C(4)	1.401(2)
C(4)-O(3)	1.386(2)
C(4)-C(5)	1.393(3)
C(5)-C(6)	1.389(3)
C(5)-C(14)	1.504(2)
C(6)-O(4)	1.390(2)
C(6)-C(7)	1.400(2)
C(7)-O(5)	1.374(2)
C(7)-C(8)	1.400(2)
C(8)-C(9)	1.519(2)
C(9)-N(1)	1.483(2)
C(9)-C(22)	1.531(2)
C(10)-N(1)	1.480(2)
C(10)-C(11)	1.529(3)
C(10)-C(29)	1.528(3)
C(11)-O(1)	1.451(2)
C(11)-C(35)	1.509(2)
C(12)-O(2)	1.195(2)
C(12)-O(1)	1.352(2)
C(13)-O(3)	1.425(2)
C(15)-O(4)	1.426(3)

C(18)-C(21)	1.529(3)
C(18)-C(20)	1.530(3)
C(18)-C(19)	1.533(3)
C(22)-O(6)	1.427(2)
C(25)-C(26)	1.530(3)
C(25)-C(28)	1.537(3)
C(25)-C(27)	1.542(3)
C(29)-C(34)	1.394(3)
C(29)-C(30)	1.399(3)
C(30)-C(31)	1.387(3)
C(31)-C(32)	1.383(3)
C(32)-C(33)	1.380(3)
C(33)-C(34)	1.384(3)
C(35)-C(36)	1.390(3)
C(35)-C(40)	1.390(3)
C(36)-C(37)	1.388(3)
C(37)-C(38)	1.383(3)
C(38)-C(39)	1.383(3)
C(39)-C(40)	1.394(3)
O(5)-Si(2)-C(17)	109.26(8)
O(5)-Si(2)-C(16)	110.79(8)
C(17)-Si(2)-C(16)	108.03(10)
O(5)-Si(2)-C(18)	104.08(8)
C(17)-Si(2)-C(18)	114.06(9)
C(16)-Si(2)-C(18)	110.60(10)
O(6)-Si(1)-C(23)	109.24(9)
O(6)-Si(1)-C(24)	110.05(9)
C(23)-Si(1)-C(24)	109.41(11)
O(6)-Si(1)-C(25)	105.60(8)
C(23)-Si(1)-C(25)	111.03(9)
C(24)-Si(1)-C(25)	111.44(10)
N(1)-C(1)-C(2)	109.38(14)
N(1)-C(1)-C(12)	113.31(15)
C(2)-C(1)-C(12)	110.74(14)
C(3)-C(2)-C(1)	108.23(14)

C(8)-C(3)-C(4)	119.50(16)
C(8)-C(3)-C(2)	118.63(15)
C(4)-C(3)-C(2)	121.60(16)
O(3)-C(4)-C(5)	119.37(16)
O(3)-C(4)-C(3)	118.86(16)
C(5)-C(4)-C(3)	121.74(16)
C(6)-C(5)-C(4)	117.73(16)
C(6)-C(5)-C(14)	120.05(17)
C(4)-C(5)-C(14)	122.21(16)
C(5)-C(6)-O(4)	118.34(16)
C(5)-C(6)-C(7)	122.02(17)
O(4)-C(6)-C(7)	119.64(16)
O(5)-C(7)-C(6)	120.30(16)
O(5)-C(7)-C(8)	120.40(15)
C(6)-C(7)-C(8)	119.22(16)
C(3)-C(8)-C(7)	119.69(16)
C(3)-C(8)-C(9)	121.28(16)
C(7)-C(8)-C(9)	118.78(15)
N(1)-C(9)-C(8)	113.57(14)
N(1)-C(9)-C(22)	110.01(14)
C(8)-C(9)-C(22)	105.70(14)
N(1)-C(10)-C(11)	106.25(14)
N(1)-C(10)-C(29)	117.50(15)
C(11)-C(10)-C(29)	114.18(15)
O(1)-C(11)-C(35)	108.33(14)
O(1)-C(11)-C(10)	112.47(14)
C(35)-C(11)-C(10)	111.91(15)
O(2)-C(12)-O(1)	118.57(17)
O(2)-C(12)-C(1)	121.47(17)
O(1)-C(12)-C(1)	119.72(16)
C(21)-C(18)-C(20)	109.5(2)
C(21)-C(18)-C(19)	108.07(18)
C(20)-C(18)-C(19)	109.23(19)
C(21)-C(18)-Si(2)	109.81(15)
C(20)-C(18)-Si(2)	111.59(14)
C(19)-C(18)-Si(2)	108.55(14)

O(6)-C(22)-C(9)	111.74(14)
C(26)-C(25)-C(28)	109.09(19)
C(26)-C(25)-C(27)	109.63(18)
C(28)-C(25)-C(27)	108.39(18)
C(26)-C(25)-Si(1)	110.94(15)
C(28)-C(25)-Si(1)	110.03(13)
C(27)-C(25)-Si(1)	108.71(14)
C(34)-C(29)-C(30)	117.80(17)
C(34)-C(29)-C(10)	118.31(17)
C(30)-C(29)-C(10)	123.86(16)
C(31)-C(30)-C(29)	120.76(18)
C(32)-C(31)-C(30)	120.5(2)
C(33)-C(32)-C(31)	119.3(2)
C(32)-C(33)-C(34)	120.53(19)
C(33)-C(34)-C(29)	121.09(19)
C(36)-C(35)-C(40)	119.30(17)
C(36)-C(35)-C(11)	117.63(17)
C(40)-C(35)-C(11)	122.87(17)
C(37)-C(36)-C(35)	120.61(19)
C(38)-C(37)-C(36)	119.88(18)
C(37)-C(38)-C(39)	119.95(18)
C(38)-C(39)-C(40)	120.32(19)
C(35)-C(40)-C(39)	119.89(18)
C(12)-O(1)-C(11)	121.47(14)
C(4)-O(3)-C(13)	113.97(14)
C(6)-O(4)-C(15)	111.61(15)
C(7)-O(5)-Si(2)	124.82(12)
C(22)-O(6)-Si(1)	120.20(11)
C(1)-N(1)-C(10)	113.41(14)
C(1)-N(1)-C(9)	114.11(14)
C(10)-N(1)-C(9)	113.13(14)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for rw106m. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

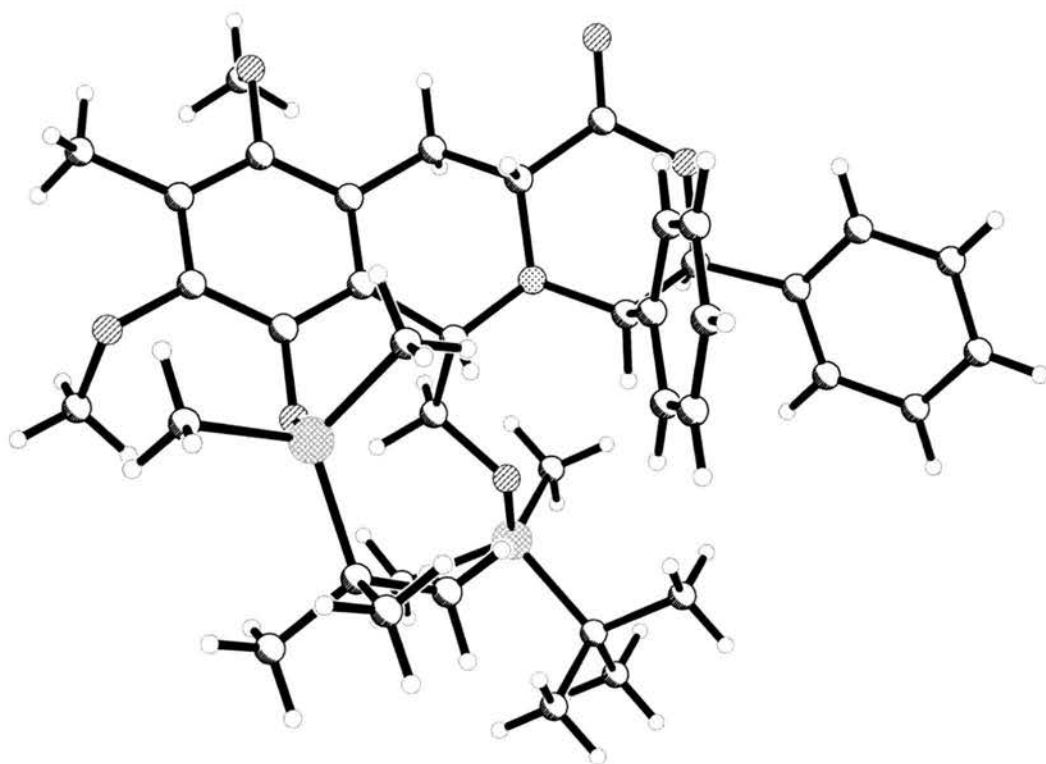
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Si(2)	20(1)	16(1)	20(1)	1(1)	-1(1)	-1(1)
Si(1)	21(1)	20(1)	19(1)	-1(1)	2(1)	-2(1)
C(1)	19(1)	18(1)	17(1)	0(1)	-1(1)	-1(1)
C(2)	22(1)	16(1)	17(1)	1(1)	-1(1)	-1(1)
C(3)	17(1)	15(1)	22(1)	0(1)	1(1)	1(1)
C(4)	18(1)	16(1)	17(1)	3(1)	2(1)	3(1)
C(5)	20(1)	13(1)	24(1)	1(1)	1(1)	0(1)
C(6)	21(1)	16(1)	25(1)	-2(1)	-1(1)	-1(1)
C(7)	19(1)	17(1)	18(1)	0(1)	2(1)	1(1)
C(8)	17(1)	14(1)	19(1)	1(1)	3(1)	1(1)
C(9)	20(1)	14(1)	16(1)	1(1)	0(1)	-3(1)
C(10)	21(1)	13(1)	19(1)	2(1)	1(1)	-2(1)
C(11)	22(1)	17(1)	18(1)	2(1)	1(1)	-1(1)
C(12)	20(1)	14(1)	22(1)	1(1)	-2(1)	1(1)
C(13)	32(1)	26(1)	24(1)	4(1)	-5(1)	7(1)
C(14)	31(1)	16(1)	28(1)	5(1)	0(1)	-5(1)
C(15)	41(1)	27(1)	33(1)	-12(1)	2(1)	-5(1)
C(16)	27(1)	26(1)	46(1)	5(1)	-8(1)	-7(1)
C(17)	29(1)	25(1)	28(1)	-1(1)	2(1)	3(1)
C(18)	26(1)	24(1)	19(1)	2(1)	0(1)	2(1)
C(19)	40(1)	41(1)	32(1)	15(1)	3(1)	10(1)
C(20)	41(1)	67(2)	27(1)	10(1)	3(1)	-26(1)
C(21)	69(2)	42(1)	27(1)	-6(1)	8(1)	14(1)
C(22)	24(1)	14(1)	23(1)	2(1)	5(1)	-2(1)
C(23)	40(1)	33(1)	26(1)	8(1)	-6(1)	-14(1)
C(24)	38(1)	27(1)	37(1)	-4(1)	8(1)	2(1)
C(25)	23(1)	30(1)	19(1)	3(1)	2(1)	-2(1)
C(26)	49(2)	57(2)	21(1)	9(1)	-5(1)	-12(1)
C(27)	30(1)	39(1)	34(1)	7(1)	11(1)	1(1)
C(28)	33(1)	27(1)	35(1)	9(1)	7(1)	3(1)
C(29)	20(1)	12(1)	23(1)	2(1)	-3(1)	-4(1)

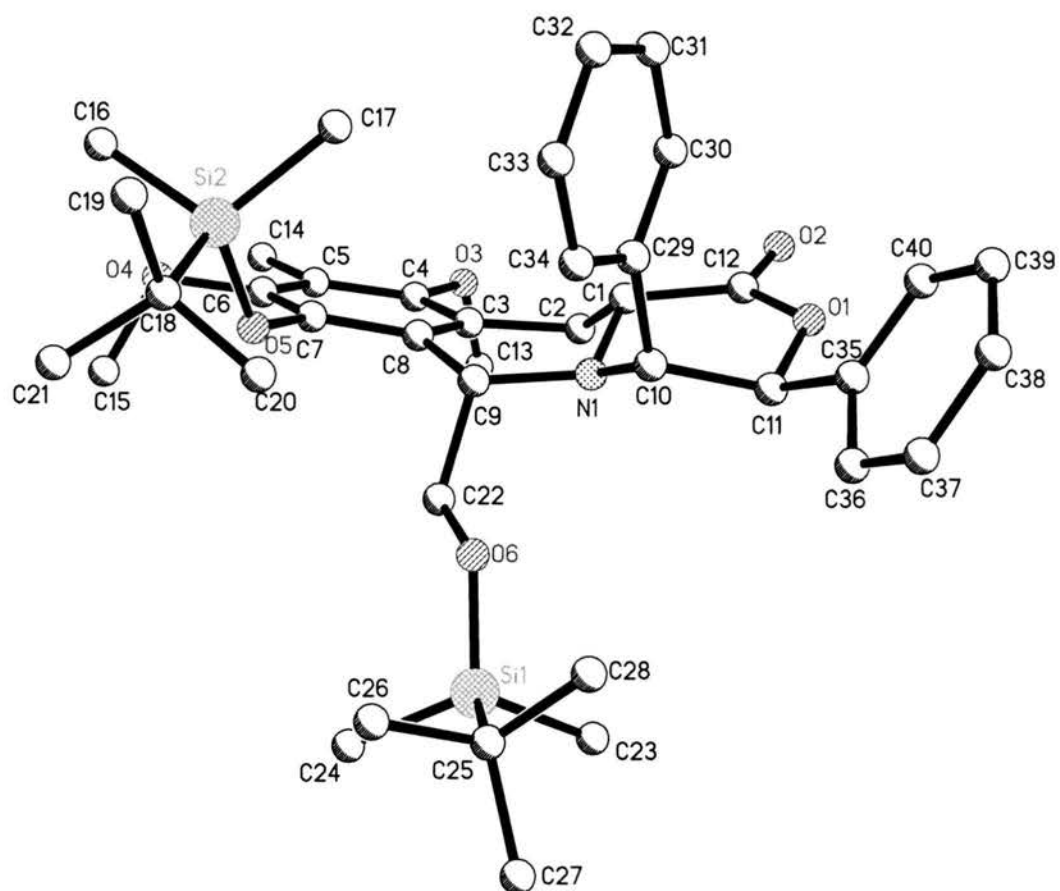
C(30)	23(1)	14(1)	24(1)	2(1)	-2(1)	-2(1)
C(31)	23(1)	16(1)	37(1)	3(1)	0(1)	-1(1)
C(32)	26(1)	20(1)	44(1)	10(1)	-11(1)	-1(1)
C(33)	39(1)	26(1)	27(1)	8(1)	-8(1)	-5(1)
C(34)	29(1)	19(1)	23(1)	1(1)	-1(1)	-5(1)
C(35)	19(1)	17(1)	22(1)	-1(1)	-5(1)	-4(1)
C(36)	26(1)	21(1)	23(1)	-3(1)	1(1)	-6(1)
C(37)	31(1)	27(1)	23(1)	3(1)	0(1)	-9(1)
C(38)	35(1)	19(1)	32(1)	5(1)	-8(1)	-8(1)
C(39)	32(1)	17(1)	34(1)	-3(1)	-3(1)	0(1)
C(40)	27(1)	21(1)	25(1)	0(1)	1(1)	-3(1)
O(1)	29(1)	18(1)	19(1)	0(1)	-1(1)	-5(1)
O(2)	38(1)	18(1)	19(1)	-1(1)	3(1)	0(1)
O(3)	24(1)	19(1)	19(1)	4(1)	1(1)	2(1)
O(4)	28(1)	17(1)	26(1)	-1(1)	-5(1)	-5(1)
O(5)	24(1)	17(1)	18(1)	1(1)	-1(1)	0(1)
O(6)	24(1)	20(1)	25(1)	3(1)	7(1)	-2(1)
N(1)	22(1)	11(1)	17(1)	0(1)	1(1)	-2(1)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^{-3}$) for rw106m.

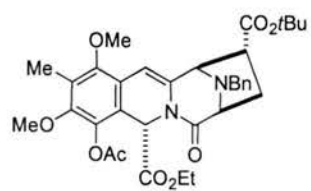
	x	y	z	U(eq)
H(1A)	2730	-1334	-52	22
H(2A)	2212	-117	-732	22
H(2B)	1126	50	-429	22
H(9A)	2232	-819	1055	20
H(10A)	842	-2224	935	21
H(11A)	-90	-2591	189	22
H(13A)	1949	2422	-1316	41
H(13B)	1885	2977	-752	41
H(13C)	1306	1898	-846	41
H(14A)	3870	3281	-472	37
H(14B)	4749	3170	-28	37
H(14C)	3720	3827	90	37
H(15A)	3815	3754	1544	50
H(15B)	2954	2862	1533	50
H(15C)	2969	3724	1080	50
H(16A)	5579	1293	1412	49
H(16B)	5885	753	1959	49
H(16C)	5131	1737	1956	49
H(17A)	4799	-667	938	41
H(17B)	3937	-1362	1225	41
H(17C)	5095	-1309	1457	41
H(19A)	4239	-1018	3028	56
H(19B)	5133	-412	2715	56
H(19C)	4635	-1438	2469	56
H(20A)	2376	-962	2711	68
H(20B)	2737	-1415	2152	68
H(20C)	2081	-366	2178	68
H(21A)	3195	648	3079	69
H(21B)	2948	1285	2551	69
H(21C)	4116	1221	2769	69

H(22A)	1125	661	1285	24
H(22B)	395	385	793	24
H(23A)	-1700	-14	741	49
H(23B)	-2590	-364	1145	49
H(23C)	-1832	-1209	890	49
H(24A)	-818	1531	1539	51
H(24B)	-479	1165	2118	51
H(24C)	-1686	1226	1965	51
H(26A)	-789	-1496	2945	64
H(26B)	-778	-304	2777	64
H(26C)	134	-1058	2585	64
H(27A)	-2617	-1692	2571	51
H(27B)	-2849	-1402	1968	51
H(27C)	-2628	-508	2390	51
H(28A)	-1155	-2888	2269	48
H(28B)	-247	-2459	1896	48
H(28C)	-1402	-2588	1668	48
H(30A)	2999	-3138	74	25
H(31A)	4483	-3998	398	31
H(32A)	4696	-4268	1315	36
H(33A)	3378	-3728	1903	37
H(34A)	1900	-2856	1586	28
H(36A)	-640	-3712	941	28
H(37A)	-769	-5387	1306	32
H(38A)	240	-6749	955	34
H(39A)	1347	-6444	228	33
H(40A)	1497	-4760	-133	29





Appendix 10



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Table 1. Crystal data and structure refinement for RW103.

Identification code	rw103 (YuYin Chen/Williams)		
Empirical formula	C ₆₈ H ₈₀ N ₄ O ₁₉		
Formula weight	1257.36		
Temperature	173(2) K		
Wavelength	0.71073 Å		
Crystal system	Monoclinic		
Space group	P2(1)		
Unit cell dimensions	a = 12.6954(11) Å	α = 90°.	
	b = 18.2894(16) Å	β = 90.994(2)°.	
	c = 13.7914(12) Å	γ = 90°.	
Volume	3201.8(5) Å ³		
Z	2		
Density (calculated)	1.304 Mg/m ³		
Absorption coefficient	0.095 mm ⁻¹		
F(000)	1336		
Crystal size	0.52 x 0.37 x 0.28 mm ³		
Theta range for data collection	1.48 to 26.37°.		
Index ranges	-15<=h<=15, 0<=k<=22, 0<=l<=17		
Reflections collected	6767		
Independent reflections	6767 [R(int) = 0.0000]		
Completeness to theta = 26.37°	100.0 %		
Absorption correction	Multi-scan		
Max. and min. transmission	0.9738 and 0.9520		
Refinement method	Full-matrix least-squares on F ²		
Data / restraints / parameters	6767 / 1 / 821		
Goodness-of-fit on F ²	1.141		
Final R indices [I>2sigma(I)]	R1 = 0.0413, wR2 = 0.1046		
R indices (all data)	R1 = 0.0463, wR2 = 0.1086		
Absolute structure parameter	-0.1(7)		
Extinction coefficient	0.0138(11)		
Largest diff. peak and hole	0.383 and -0.489 e.Å ⁻³		
Comment: Water molecule in lattice. No protons assigned.			

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for RW103. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U(\text{eq})$
O(1)	9473(2)	1364(1)	-2990(1)	25(1)
O(2)	10136(2)	716(1)	-4229(1)	23(1)
O(3)	10815(2)	1541(1)	-5993(1)	20(1)
O(4)	12225(2)	1074(1)	-5188(2)	26(1)
O(5)	12419(2)	2510(1)	-6340(1)	22(1)
O(6)	10832(2)	4210(1)	-4110(2)	24(1)
O(7)	4754(2)	3903(1)	-4123(2)	31(1)
O(8)	6161(2)	4444(1)	-3397(2)	26(1)
O(9)	7378(2)	1094(1)	-4684(2)	24(1)
N(1)	8233(2)	2153(1)	-4330(2)	16(1)
N(2)	6602(2)	2477(1)	-3042(2)	18(1)
C(1)	9219(2)	1799(2)	-4642(2)	17(1)
C(2)	13493(2)	2424(2)	-6005(2)	27(1)
C(3)	8266(2)	2830(2)	-3842(2)	18(1)
C(4)	9146(2)	3230(2)	-3798(2)	19(1)
C(5)	10891(2)	3528(2)	-4537(2)	20(1)
C(6)	11699(2)	3376(2)	-5191(2)	20(1)
C(7)	11693(2)	2691(2)	-5640(2)	20(1)
C(8)	10884(2)	2194(2)	-5468(2)	18(1)
C(9)	10079(2)	2354(2)	-4839(2)	17(1)
C(10)	10066(2)	3034(2)	-4365(2)	18(1)
C(11)	7223(2)	3079(2)	-3440(2)	18(1)
C(12)	7353(2)	1715(2)	-4350(2)	18(1)
C(13)	6359(2)	2052(2)	-3929(2)	19(1)
C(14)	5903(2)	2644(2)	-4605(2)	20(1)
C(15)	6470(2)	3346(2)	-4264(2)	18(1)
C(16)	5686(2)	3920(2)	-3922(2)	21(1)
C(17)	5517(2)	5023(2)	-2911(2)	28(1)
C(18)	6343(3)	5452(2)	-2345(3)	43(1)
C(19)	4983(3)	5502(2)	-3667(3)	39(1)
C(20)	4759(3)	4660(2)	-2225(2)	32(1)

C(21)	11572(3)	4338(2)	-3342(3)	41(1)
C(22)	12483(2)	3963(2)	-5457(2)	25(1)
C(23)	11523(2)	999(2)	-5763(2)	22(1)
C(24)	11238(3)	318(2)	-6313(2)	30(1)
C(25)	9602(2)	1272(2)	-3842(2)	18(1)
C(26)	10640(2)	207(2)	-3548(2)	25(1)
C(27)	9856(2)	-340(2)	-3168(2)	27(1)
C(28)	7109(2)	2040(2)	-2264(2)	23(1)
C(29)	7374(2)	2507(2)	-1390(2)	20(1)
C(30)	8408(2)	2532(2)	-1041(2)	31(1)
C(31)	8666(3)	2914(2)	-201(3)	43(1)
C(32)	7888(4)	3284(2)	291(2)	46(1)
C(33)	6867(3)	3282(2)	-62(3)	41(1)
C(34)	6604(2)	2892(2)	-908(2)	30(1)
N(1A)	3230(2)	3298(1)	1503(2)	17(1)
N(2A)	1551(2)	2973(1)	188(2)	20(1)
O(1A)	4305(2)	4169(1)	215(2)	33(1)
O(2A)	5224(2)	4683(1)	1435(1)	25(1)
O(3A)	5826(2)	3845(1)	3259(1)	21(1)
O(4A)	7257(2)	4358(1)	2569(2)	27(1)
O(5A)	7439(2)	2871(1)	3561(1)	23(1)
O(6A)	5855(2)	1269(1)	1157(2)	23(1)
O(7A)	-110(2)	1416(2)	1522(2)	53(1)
O(8A)	1097(2)	1077(1)	438(2)	25(1)
O(9A)	2369(2)	4353(1)	1847(2)	27(1)
C(1A)	4220(2)	3644(2)	1830(2)	17(1)
C(2A)	8508(2)	2965(2)	3237(2)	28(1)
C(3A)	3254(2)	2630(2)	985(2)	17(1)
C(4A)	4141(2)	2241(2)	923(2)	18(1)
C(5A)	5902(2)	1928(2)	1651(2)	19(1)
C(6A)	6711(2)	2053(2)	2342(2)	20(1)
C(7A)	6703(2)	2715(2)	2832(2)	20(1)
C(8A)	5899(2)	3220(2)	2676(2)	19(1)
C(9A)	5085(2)	3083(2)	2022(2)	16(1)
C(10A)	5076(2)	2424(2)	1503(2)	17(1)
C(11A)	2196(2)	2370(2)	587(2)	18(1)

C(12A)	2344(2)	3734(2)	1504(2)	20(1)
C(13A)	1342(2)	3393(2)	1071(2)	20(1)
C(14A)	914(2)	2804(2)	1752(2)	22(1)
C(15A)	1491(2)	2103(2)	1424(2)	20(1)
C(16A)	721(2)	1498(2)	1136(2)	27(1)
C(17A)	500(2)	433(2)	67(2)	28(1)
C(18A)	-542(3)	669(3)	-371(4)	56(1)
C(19A)	418(4)	-127(2)	863(3)	52(1)
C(20A)	1210(3)	150(2)	-721(3)	42(1)
C(21A)	6640(3)	1192(2)	422(2)	34(1)
C(22A)	7488(2)	1452(2)	2593(2)	26(1)
C(23A)	6552(2)	4395(2)	3129(2)	24(1)
C(24A)	6289(3)	5019(2)	3782(2)	32(1)
C(25A)	4572(2)	4196(2)	1055(2)	20(1)
C(26A)	5676(3)	5215(2)	768(2)	29(1)
C(27A)	6054(3)	5854(2)	1362(3)	38(1)
C(28A)	2033(2)	3404(2)	-591(2)	23(1)
C(29A)	3424(2)	2956(2)	-1715(2)	22(1)
C(30A)	2375(2)	2940(2)	-1437(2)	20(1)
C(31A)	1657(2)	2520(2)	-1982(2)	25(1)
C(32A)	1998(3)	2138(2)	-2789(2)	30(1)
C(33A)	3040(3)	2168(2)	-3064(2)	29(1)
C(34A)	3756(2)	2573(2)	-2524(2)	28(1)
W(1)	3678(2)	5300(2)	3105(2)	58(1)

Table 3. Bond lengths [$\text{\AA}$] and angles [$^\circ$] for RW103.

O(1)-C(25)	1.201(3)	C(13)-C(14)	1.535(4)
O(2)-C(25)	1.339(3)	C(14)-C(15)	1.543(4)
O(2)-C(26)	1.461(3)	C(15)-C(16)	1.527(4)
O(3)-C(23)	1.372(3)	C(17)-C(20)	1.514(4)
O(3)-C(8)	1.398(3)	C(17)-C(19)	1.514(5)
O(4)-C(23)	1.190(4)	C(17)-C(18)	1.516(5)
O(5)-C(7)	1.386(3)	C(23)-C(24)	1.499(4)
O(5)-C(2)	1.441(3)	C(26)-C(27)	1.511(4)
O(6)-C(5)	1.381(3)	C(28)-C(29)	1.511(4)
O(6)-C(21)	1.423(4)	C(29)-C(34)	1.385(4)
O(7)-C(16)	1.211(3)	C(29)-C(30)	1.391(4)
O(8)-C(16)	1.338(4)	C(30)-C(31)	1.386(5)
O(8)-C(17)	1.502(3)	C(31)-C(32)	1.385(6)
O(9)-C(12)	1.225(4)	C(32)-C(33)	1.377(6)
N(1)-C(12)	1.375(3)	C(33)-C(34)	1.402(5)
N(1)-C(3)	1.410(3)	N(1A)-C(12A)	1.379(4)
N(1)-C(1)	1.480(3)	N(1A)-C(3A)	1.415(3)
N(2)-C(11)	1.466(3)	N(1A)-C(1A)	1.472(3)
N(2)-C(28)	1.477(4)	N(2A)-C(13A)	1.468(3)
N(2)-C(13)	1.477(3)	N(2A)-C(28A)	1.474(4)
C(1)-C(9)	1.519(4)	N(2A)-C(11A)	1.475(3)
C(1)-C(25)	1.537(4)	O(1A)-C(25A)	1.203(3)
C(3)-C(4)	1.335(4)	O(2A)-C(25A)	1.319(3)
C(3)-C(11)	1.515(4)	O(2A)-C(26A)	1.463(3)
C(4)-C(10)	1.462(4)	O(3A)-C(23A)	1.378(4)
C(5)-C(10)	1.405(4)	O(3A)-C(8A)	1.401(3)
C(5)-C(6)	1.407(4)	O(4A)-C(23A)	1.194(4)
C(6)-C(7)	1.398(4)	O(5A)-C(7A)	1.390(3)
C(6)-C(22)	1.513(4)	O(5A)-C(2A)	1.446(3)
C(7)-C(8)	1.395(4)	O(6A)-C(5A)	1.385(3)
C(8)-C(9)	1.382(4)	O(6A)-C(21A)	1.440(4)
C(9)-C(10)	1.406(4)	O(7A)-C(16A)	1.199(4)
C(11)-C(15)	1.552(4)	O(8A)-C(16A)	1.327(4)
C(12)-C(13)	1.529(4)	O(8A)-C(17A)	1.487(4)

O(9A)-C(12A)	1.226(4)	C(13A)-C(14A)	1.535(4)
C(1A)-C(9A)	1.523(4)	C(14A)-C(15A)	1.548(4)
C(1A)-C(25A)	1.542(4)	C(15A)-C(16A)	1.524(4)
C(3A)-C(4A)	1.336(4)	C(17A)-C(19A)	1.506(5)
C(3A)-C(11A)	1.519(4)	C(17A)-C(18A)	1.508(5)
C(4A)-C(10A)	1.459(4)	C(17A)-C(20A)	1.514(5)
C(5A)-C(10A)	1.398(4)	C(23A)-C(24A)	1.496(4)
C(5A)-C(6A)	1.407(4)	C(26A)-C(27A)	1.502(5)
C(6A)-C(7A)	1.388(4)	C(28A)-C(30A)	1.513(4)
C(6A)-C(22A)	1.513(4)	C(29A)-C(34A)	1.389(4)
C(7A)-C(8A)	1.390(4)	C(29A)-C(30A)	1.392(4)
C(8A)-C(9A)	1.382(4)	C(30A)-C(31A)	1.401(4)
C(9A)-C(10A)	1.403(4)	C(31A)-C(32A)	1.391(5)
C(11A)-C(15A)	1.552(4)	C(32A)-C(33A)	1.383(5)
C(12A)-C(13A)	1.530(4)	C(33A)-C(34A)	1.381(5)

C(25)-O(2)-C(26)	116.5(2)
C(23)-O(3)-C(8)	117.5(2)
C(7)-O(5)-C(2)	116.1(2)
C(5)-O(6)-C(21)	115.2(2)
C(16)-O(8)-C(17)	120.2(2)
C(12)-N(1)-C(3)	122.6(2)
C(12)-N(1)-C(1)	115.5(2)
C(3)-N(1)-C(1)	120.3(2)
C(11)-N(2)-C(28)	116.5(2)
C(11)-N(2)-C(13)	101.0(2)
C(28)-N(2)-C(13)	113.5(2)
N(1)-C(1)-C(9)	112.0(2)
N(1)-C(1)-C(25)	108.9(2)
C(9)-C(1)-C(25)	109.1(2)
C(4)-C(3)-N(1)	121.4(2)
C(4)-C(3)-C(11)	123.8(2)
N(1)-C(3)-C(11)	114.8(2)
C(3)-C(4)-C(10)	121.2(3)
O(6)-C(5)-C(10)	117.6(2)
O(6)-C(5)-C(6)	119.8(2)
C(10)-C(5)-C(6)	122.3(3)
C(7)-C(6)-C(5)	117.6(2)
C(7)-C(6)-C(22)	121.9(3)
C(5)-C(6)-C(22)	120.4(3)
O(5)-C(7)-C(8)	117.6(3)
O(5)-C(7)-C(6)	121.5(2)
C(8)-C(7)-C(6)	120.5(2)
C(9)-C(8)-C(7)	121.5(3)
C(9)-C(8)-O(3)	117.8(2)
C(7)-C(8)-O(3)	120.5(2)
C(8)-C(9)-C(10)	119.6(2)
C(8)-C(9)-C(1)	120.8(2)
C(10)-C(9)-C(1)	119.6(2)
C(5)-C(10)-C(9)	118.4(3)
C(5)-C(10)-C(4)	122.5(3)
C(9)-C(10)-C(4)	118.8(2)

N(2)-C(11)-C(3)	113.1(2)
N(2)-C(11)-C(15)	100.5(2)
C(3)-C(11)-C(15)	111.0(2)
O(9)-C(12)-N(1)	121.4(3)
O(9)-C(12)-C(13)	122.9(2)
N(1)-C(12)-C(13)	115.7(2)
N(2)-C(13)-C(12)	111.4(2)
N(2)-C(13)-C(14)	101.7(2)
C(12)-C(13)-C(14)	111.0(2)
C(13)-C(14)-C(15)	103.5(2)
C(16)-C(15)-C(14)	111.3(2)
C(16)-C(15)-C(11)	112.8(2)
C(14)-C(15)-C(11)	103.8(2)
O(7)-C(16)-O(8)	124.9(3)
O(7)-C(16)-C(15)	123.4(3)
O(8)-C(16)-C(15)	111.7(2)
O(8)-C(17)-C(20)	109.1(2)
O(8)-C(17)-C(19)	110.0(3)
C(20)-C(17)-C(19)	113.7(3)
O(8)-C(17)-C(18)	102.6(2)
C(20)-C(17)-C(18)	110.3(3)
C(19)-C(17)-C(18)	110.6(3)
O(4)-C(23)-O(3)	123.4(3)
O(4)-C(23)-C(24)	127.2(3)
O(3)-C(23)-C(24)	109.4(2)
O(1)-C(25)-O(2)	125.1(2)
O(1)-C(25)-C(1)	124.6(2)
O(2)-C(25)-C(1)	110.3(2)
O(2)-C(26)-C(27)	111.2(2)
N(2)-C(28)-C(29)	111.2(2)
C(34)-C(29)-C(30)	119.2(3)
C(34)-C(29)-C(28)	121.4(3)
C(30)-C(29)-C(28)	119.4(3)
C(31)-C(30)-C(29)	120.9(3)
C(32)-C(31)-C(30)	119.7(3)
C(33)-C(32)-C(31)	120.0(3)

C(32)-C(33)-C(34)	120.3(3)
C(29)-C(34)-C(33)	119.9(3)
C(12A)-N(1A)-C(3A)	121.7(2)
C(12A)-N(1A)-C(1A)	116.3(2)
C(3A)-N(1A)-C(1A)	120.0(2)
C(13A)-N(2A)-C(28A)	114.1(2)
C(13A)-N(2A)-C(11A)	100.9(2)
C(28A)-N(2A)-C(11A)	115.9(2)
C(25A)-O(2A)-C(26A)	116.7(2)
C(23A)-O(3A)-C(8A)	118.1(2)
C(7A)-O(5A)-C(2A)	115.1(2)
C(5A)-O(6A)-C(21A)	114.0(2)
C(16A)-O(8A)-C(17A)	121.5(2)
N(1A)-C(1A)-C(9A)	111.9(2)
N(1A)-C(1A)-C(25A)	109.0(2)
C(9A)-C(1A)-C(25A)	110.1(2)
C(4A)-C(3A)-N(1A)	121.2(2)
C(4A)-C(3A)-C(11A)	123.4(2)
N(1A)-C(3A)-C(11A)	115.2(2)
C(3A)-C(4A)-C(10A)	121.4(3)
O(6A)-C(5A)-C(10A)	117.8(2)
O(6A)-C(5A)-C(6A)	119.9(2)
C(10A)-C(5A)-C(6A)	122.0(3)
C(7A)-C(6A)-C(5A)	117.4(2)
C(7A)-C(6A)-C(22A)	122.2(3)
C(5A)-C(6A)-C(22A)	120.1(3)
C(6A)-C(7A)-C(8A)	121.1(2)
C(6A)-C(7A)-O(5A)	121.4(3)
C(8A)-C(7A)-O(5A)	117.3(3)
C(9A)-C(8A)-C(7A)	121.3(3)
C(9A)-C(8A)-O(3A)	117.8(2)
C(7A)-C(8A)-O(3A)	120.5(2)
C(8A)-C(9A)-C(10A)	119.2(2)
C(8A)-C(9A)-C(1A)	121.3(2)
C(10A)-C(9A)-C(1A)	119.4(2)
C(5A)-C(10A)-C(9A)	118.9(2)

C(5A)-C(10A)-C(4A)	122.2(2)
C(9A)-C(10A)-C(4A)	118.4(2)
N(2A)-C(11A)-C(3A)	112.5(2)
N(2A)-C(11A)-C(15A)	100.9(2)
C(3A)-C(11A)-C(15A)	110.4(2)
O(9A)-C(12A)-N(1A)	121.3(3)
O(9A)-C(12A)-C(13A)	122.9(3)
N(1A)-C(12A)-C(13A)	115.8(2)
N(2A)-C(13A)-C(12A)	112.2(2)
N(2A)-C(13A)-C(14A)	102.2(2)
C(12A)-C(13A)-C(14A)	110.4(2)
C(13A)-C(14A)-C(15A)	103.2(2)
C(16A)-C(15A)-C(14A)	111.9(2)
C(16A)-C(15A)-C(11A)	114.2(2)
C(14A)-C(15A)-C(11A)	103.8(2)
O(7A)-C(16A)-O(8A)	125.4(3)
O(7A)-C(16A)-C(15A)	122.7(3)
O(8A)-C(16A)-C(15A)	111.9(2)
O(8A)-C(17A)-C(19A)	109.2(3)
O(8A)-C(17A)-C(18A)	110.5(3)
C(19A)-C(17A)-C(18A)	114.5(4)
O(8A)-C(17A)-C(20A)	102.3(2)
C(19A)-C(17A)-C(20A)	109.9(3)
C(18A)-C(17A)-C(20A)	109.8(3)
O(4A)-C(23A)-O(3A)	123.5(3)
O(4A)-C(23A)-C(24A)	127.7(3)
O(3A)-C(23A)-C(24A)	108.8(3)
O(1A)-C(25A)-O(2A)	125.0(3)
O(1A)-C(25A)-C(1A)	124.2(3)
O(2A)-C(25A)-C(1A)	110.8(2)
O(2A)-C(26A)-C(27A)	107.4(3)
N(2A)-C(28A)-C(30A)	113.0(2)
C(34A)-C(29A)-C(30A)	121.0(3)
C(29A)-C(30A)-C(31A)	118.7(3)
C(29A)-C(30A)-C(28A)	119.3(3)
C(31A)-C(30A)-C(28A)	121.9(3)

C(32A)-C(31A)-C(30A)	119.8(3)
C(33A)-C(32A)-C(31A)	120.8(3)
C(34A)-C(33A)-C(32A)	119.8(3)
C(33A)-C(34A)-C(29A)	119.9(3)

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for RW103. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	31(1)	23(1)	22(1)	2(1)	1(1)	3(1)
O(2)	25(1)	19(1)	25(1)	6(1)	4(1)	7(1)
O(3)	19(1)	20(1)	20(1)	0(1)	1(1)	0(1)
O(4)	22(1)	27(1)	29(1)	3(1)	-1(1)	3(1)
O(5)	17(1)	31(1)	20(1)	4(1)	2(1)	0(1)
O(6)	23(1)	17(1)	33(1)	-2(1)	-2(1)	-2(1)
O(7)	21(1)	35(1)	37(1)	-4(1)	-4(1)	8(1)
O(8)	21(1)	20(1)	37(1)	-5(1)	5(1)	3(1)
O(9)	25(1)	17(1)	31(1)	-5(1)	2(1)	-2(1)
N(1)	14(1)	16(1)	19(1)	0(1)	1(1)	1(1)
N(2)	19(1)	19(1)	16(1)	0(1)	2(1)	-1(1)
C(1)	15(1)	16(1)	19(1)	1(1)	1(1)	1(1)
C(2)	16(1)	34(2)	30(2)	5(1)	1(1)	0(1)
C(3)	19(1)	16(1)	17(1)	2(1)	-1(1)	2(1)
C(4)	20(1)	16(1)	21(1)	1(1)	-3(1)	0(1)
C(5)	21(1)	16(1)	24(1)	5(1)	-4(1)	-2(1)
C(6)	17(1)	19(1)	24(1)	7(1)	-4(1)	-3(1)
C(7)	16(1)	26(2)	17(1)	6(1)	0(1)	1(1)
C(8)	19(1)	17(1)	17(1)	0(1)	-3(1)	2(1)
C(9)	16(1)	19(1)	17(1)	3(1)	-5(1)	0(1)
C(10)	17(1)	16(1)	21(1)	2(1)	-3(1)	1(1)
C(11)	16(1)	19(1)	18(1)	1(1)	-1(1)	1(1)
C(12)	18(1)	19(1)	18(1)	4(1)	0(1)	-1(1)
C(13)	16(1)	21(1)	19(1)	-1(1)	2(1)	-2(1)
C(14)	18(1)	22(1)	20(1)	1(1)	-1(1)	3(1)
C(15)	17(1)	21(1)	18(1)	2(1)	2(1)	1(1)
C(16)	21(1)	22(1)	21(1)	5(1)	1(1)	2(1)
C(17)	25(2)	20(2)	40(2)	-4(1)	10(1)	4(1)
C(18)	36(2)	33(2)	60(2)	-23(2)	10(2)	-2(2)
C(19)	46(2)	26(2)	45(2)	7(2)	16(2)	12(2)
C(20)	37(2)	26(2)	35(2)	0(1)	13(1)	3(1)

C(21)	49(2)	33(2)	40(2)	-10(2)	-13(2)	-1(2)
C(22)	21(1)	23(2)	31(2)	5(1)	-1(1)	-6(1)
C(23)	23(1)	19(1)	23(1)	3(1)	9(1)	0(1)
C(24)	29(2)	23(2)	39(2)	-4(1)	7(1)	-1(1)
C(25)	15(1)	17(1)	21(1)	1(1)	2(1)	-2(1)
C(26)	22(1)	21(1)	32(2)	8(1)	1(1)	7(1)
C(27)	32(2)	19(2)	30(2)	5(1)	-2(1)	0(1)
C(28)	30(2)	20(1)	19(1)	3(1)	1(1)	4(1)
C(29)	22(1)	21(1)	18(1)	4(1)	1(1)	-2(1)
C(30)	26(2)	33(2)	34(2)	6(1)	-5(1)	0(1)
C(31)	48(2)	43(2)	37(2)	4(2)	-18(2)	-10(2)
C(32)	80(3)	34(2)	23(2)	4(1)	-12(2)	-23(2)
C(33)	63(2)	27(2)	33(2)	-5(1)	24(2)	-3(2)
C(34)	27(2)	32(2)	31(2)	1(1)	8(1)	-1(1)
N(1A)	14(1)	18(1)	21(1)	-1(1)	0(1)	0(1)
N(2A)	17(1)	22(1)	19(1)	-1(1)	1(1)	4(1)
O(1A)	42(1)	34(1)	25(1)	5(1)	-7(1)	-16(1)
O(2A)	27(1)	24(1)	25(1)	5(1)	-4(1)	-8(1)
O(3A)	21(1)	21(1)	20(1)	-2(1)	0(1)	-3(1)
O(4A)	23(1)	28(1)	31(1)	2(1)	1(1)	-5(1)
O(5A)	16(1)	35(1)	19(1)	4(1)	-3(1)	-3(1)
O(6A)	19(1)	18(1)	31(1)	-1(1)	4(1)	1(1)
O(7A)	37(1)	62(2)	60(2)	-32(2)	28(1)	-28(1)
O(8A)	23(1)	23(1)	29(1)	-4(1)	4(1)	-7(1)
O(9A)	26(1)	22(1)	32(1)	-6(1)	-2(1)	6(1)
C(1A)	16(1)	17(1)	18(1)	-2(1)	-1(1)	0(1)
C(2A)	18(1)	37(2)	28(2)	6(1)	-4(1)	-4(1)
C(3A)	18(1)	16(1)	17(1)	1(1)	1(1)	-3(1)
C(4A)	17(1)	17(1)	19(1)	1(1)	3(1)	-2(1)
C(5A)	18(1)	17(1)	21(1)	3(1)	4(1)	-4(1)
C(6A)	15(1)	23(1)	22(1)	9(1)	3(1)	-1(1)
C(7A)	15(1)	28(2)	17(1)	5(1)	-1(1)	-4(1)
C(8A)	22(1)	17(1)	17(1)	1(1)	2(1)	-4(1)
C(9A)	14(1)	19(1)	16(1)	2(1)	2(1)	-1(1)
C(10A)	16(1)	18(1)	18(1)	3(1)	2(1)	-2(1)
C(11A)	15(1)	20(1)	19(1)	-1(1)	1(1)	-2(1)

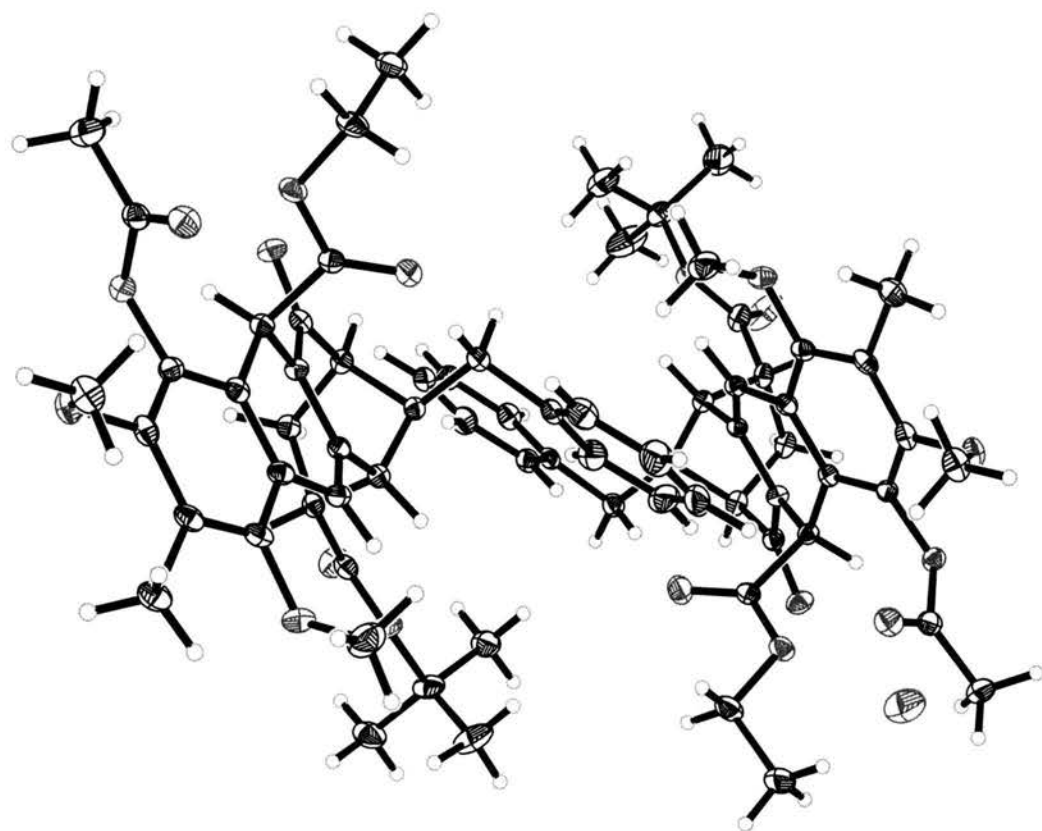
C(12A)	20(1)	21(1)	20(1)	-1(1)	1(1)	2(1)
C(13A)	14(1)	27(2)	21(1)	-3(1)	-1(1)	3(1)
C(14A)	15(1)	31(2)	20(1)	-4(1)	1(1)	-1(1)
C(15A)	17(1)	28(2)	17(1)	-1(1)	2(1)	-4(1)
C(16A)	25(2)	34(2)	23(1)	-4(1)	4(1)	-8(1)
C(17A)	25(2)	27(2)	32(2)	-6(1)	-3(1)	-8(1)
C(18A)	37(2)	49(2)	82(3)	-29(2)	-26(2)	9(2)
C(19A)	76(3)	37(2)	42(2)	-2(2)	1(2)	-31(2)
C(20A)	45(2)	35(2)	46(2)	-14(2)	11(2)	-9(2)
C(21A)	39(2)	28(2)	34(2)	-5(1)	14(1)	-2(1)
C(22A)	22(1)	27(2)	29(2)	6(1)	0(1)	2(1)
C(23A)	26(1)	21(1)	24(1)	2(1)	-10(1)	-4(1)
C(24A)	41(2)	22(2)	32(2)	-5(1)	-8(1)	-3(1)
C(25A)	19(1)	17(1)	22(1)	2(1)	1(1)	2(1)
C(26A)	30(2)	25(2)	30(2)	9(1)	-3(1)	-8(1)
C(27A)	50(2)	25(2)	37(2)	4(1)	-6(2)	-12(2)
C(28A)	24(1)	23(2)	21(1)	2(1)	-1(1)	2(1)
C(29A)	22(1)	22(1)	22(1)	2(1)	2(1)	-4(1)
C(30A)	22(1)	20(1)	19(1)	4(1)	-2(1)	1(1)
C(31A)	20(1)	31(2)	25(1)	4(1)	-4(1)	-2(1)
C(32A)	36(2)	26(2)	28(2)	-2(1)	-11(1)	-3(1)
C(33A)	41(2)	24(2)	21(1)	2(1)	6(1)	4(1)
C(34A)	26(2)	31(2)	28(2)	2(1)	7(1)	-3(1)
W(1)	57(2)	48(2)	69(2)	-12(2)	12(2)	-2(2)

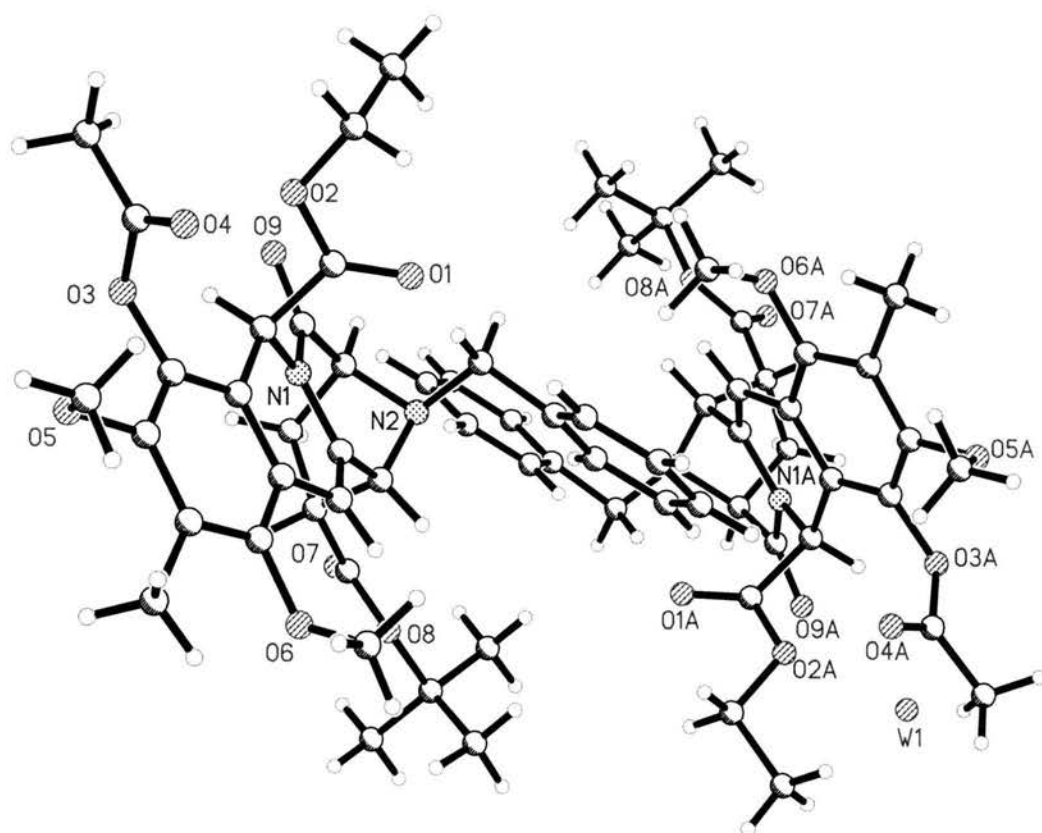
Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^{-3}$) for RW103.

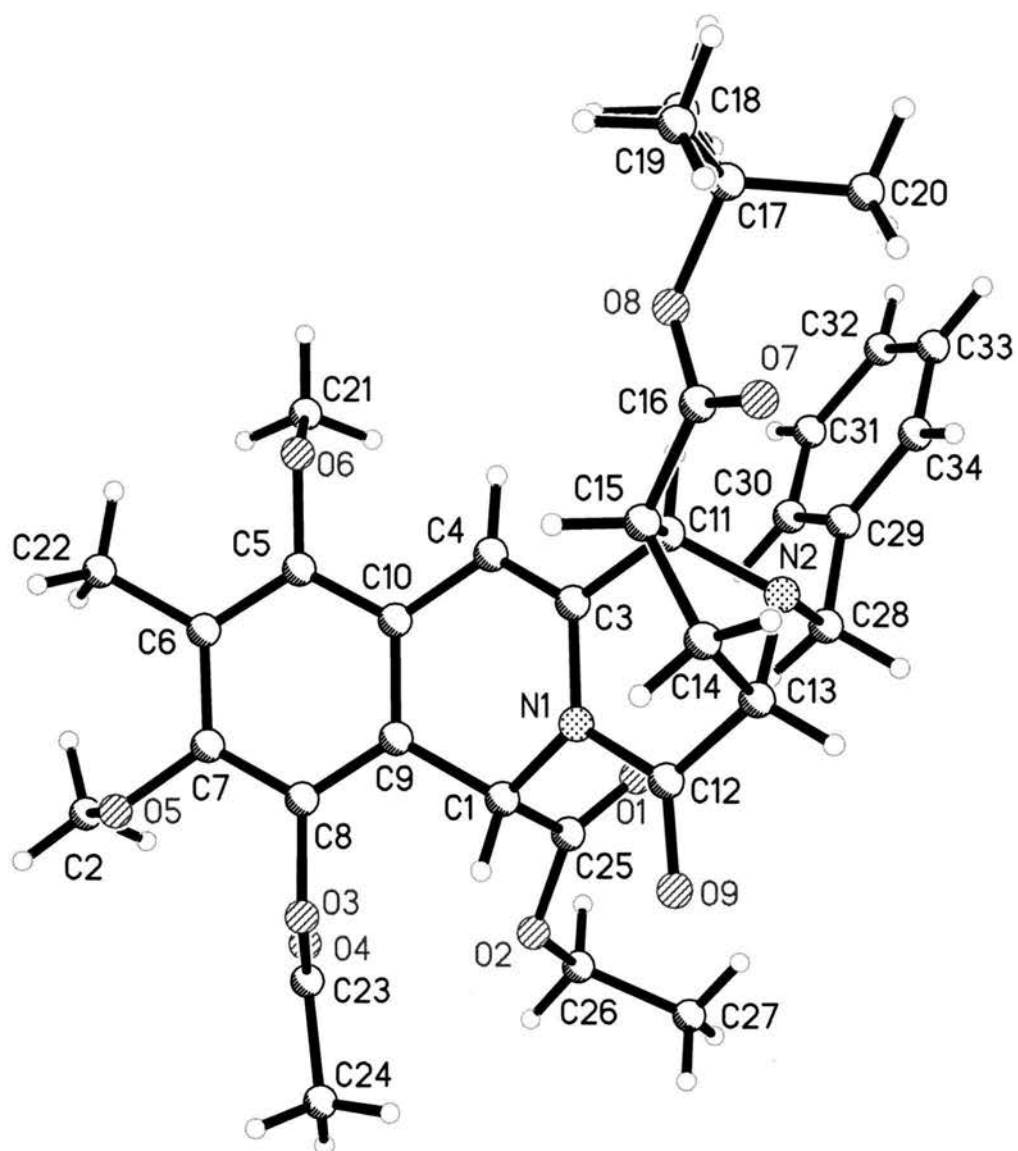
	x	y	z	U(eq)
H(1A)	9071	1513	-5248	20
H(2A)	13937	2295	-6554	40
H(2B)	13531	2035	-5517	40
H(2C)	13742	2884	-5718	40
H(4A)	9174	3649	-3392	23
H(11A)	7333	3471	-2943	21
H(13A)	5821	1667	-3798	22
H(14A)	5131	2687	-4532	24
H(14B)	6058	2535	-5291	24
H(15A)	6891	3550	-4807	22
H(18A)	6678	5134	-1858	65
H(18B)	6009	5866	-2022	65
H(18C)	6877	5634	-2790	65
H(19A)	5516	5716	-4088	58
H(19B)	4596	5894	-3345	58
H(19C)	4491	5207	-4058	58
H(20A)	5155	4363	-1753	49
H(20B)	4271	4347	-2595	49
H(20C)	4360	5036	-1883	49
H(21A)	11468	4830	-3081	61
H(21B)	12289	4295	-3589	61
H(21C)	11469	3976	-2828	61
H(22A)	12363	4399	-5061	38
H(22B)	12394	4087	-6145	38
H(22C)	13201	3782	-5337	38
H(24A)	11742	-70	-6148	45
H(24B)	11260	417	-7011	45
H(24C)	10527	163	-6141	45
H(26A)	10953	485	-2998	30
H(26B)	11215	-55	-3876	30

H(27A)	10214	-674	-2713	41
H(27B)	9555	-621	-3710	41
H(27C)	9293	-82	-2833	41
H(28A)	7762	1816	-2511	28
H(28B)	6630	1641	-2071	28
H(30A)	8945	2284	-1382	37
H(31A)	9373	2921	35	51
H(32A)	8059	3539	873	55
H(33A)	6338	3545	269	49
H(34A)	5899	2893	-1150	36
H(1AA)	4087	3915	2446	21
H(2AA)	8971	3072	3795	41
H(2AB)	8534	3372	2775	41
H(2AC)	8744	2516	2920	41
H(4AA)	4162	1836	492	21
H(11B)	2290	1976	93	21
H(13B)	797	3777	940	24
H(14C)	142	2751	1673	26
H(14D)	1086	2919	2438	26
H(15B)	1952	1924	1969	24
H(18D)	-998	850	142	85
H(18E)	-880	251	-695	85
H(18F)	-425	1058	-845	85
H(19D)	1125	-248	1111	78
H(19E)	80	-569	606	78
H(19F)	-3	72	1389	78
H(20D)	1885	-3	-433	63
H(20E)	1329	538	-1196	63
H(20F)	873	-268	-1045	63
H(21D)	6562	715	107	50
H(21E)	7344	1229	722	50
H(21F)	6549	1580	-62	50
H(22D)	7997	1631	3080	39
H(22E)	7861	1305	2008	39
H(22F)	7109	1030	2853	39
H(24D)	6798	5416	3692	47

H(24E)	6318	4855	4458	47
H(24F)	5578	5197	3624	47
H(26C)	5137	5375	286	34
H(26D)	6271	4993	417	34
H(27D)	6364	6221	935	56
H(27E)	6586	5689	1836	56
H(27F)	5458	6070	1702	56
H(28C)	2654	3667	-321	27
H(28D)	1520	3774	-827	27
H(29A)	3920	3233	-1346	27
H(31B)	939	2498	-1802	30
H(32B)	1510	1851	-3156	36
H(33B)	3262	1911	-3624	34
H(34B)	4474	2589	-2705	34







List of Abbreviations

Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
Alloc	allyloxycarbonyl
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
Bz	benzoyl
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
CSA	camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBALH	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
DTT	dithiothreitol
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
Fmoc	9-fluorenylmethoxycarbonyl
HOBt	1-hydroxybenzotriazole
Im	imidazol-1-yl
NaHMDS	sodium bis(trimethylsilyl)amide
KHMDS	potassium bis(trimethylsilyl)amide
LAH	lithium aluminum hydride
<i>m</i> CPBA	<i>m</i> -chloroperoxybenzoic acid
MOM	methoxymethyl
Ms	methanesulfonyl
NBS	<i>N</i> -bromosuccinimide
NBT	nitro blue tetrazolium chloride
NIS	<i>N</i> -Iodosuccinimide
NMM	4-methylmorpholine
NPSP	<i>N</i> -phenylselenophthalimide
PCC	pyridinium chlorochromate
PMB	<i>p</i> -methoxybenzyl
PPTS	pyridinium <i>p</i> -toluenesulfonate
Pyr	pyridine
TBAF	tetrabutylammonium fluoride
TBS	<i>tert</i> -butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran

TIPS	Triisopropylsilyl
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TMS	trimethylsilyl
Troc	2,2,2-trichloroethoxycarbonyl
Ts	<i>p</i> -toluenesulfonyl

Asymmetric Total Syntheses of (–)-Jorumycin,
(–)-Renieramycin G, 3-*epi*-Jorumycin, and
3-*epi*-Renieramycin G

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Abstract: The total synthesis of (–)-jorumycin (**1**) and (–)-renieramycin G (**2**) has been accomplished in 25 and 23 steps, respectively, from 5-benzyloxy-2,4-dimethoxy-3-methyl-benzyl alcohol. The synthesis features a substrate-tunable stereoselective intramolecular Pictet–Spengler-type reaction for the construction of the key pentacyclic core of both targets, bearing either the natural configuration or the epimeric configuration at C-3. With access to a C-3 *epi*-pentacyclic framework, 3-*epi*-jorumycin (**32**) and 3-*epi*-renieramycin G (**34**) were also successfully synthesized. Furthermore, preliminary biological evaluation of 3-*epi*-jorumycin (**32**), in addition to relevant synthetic intermediates, revealed that significant cytotoxicity had been retained in these compounds. Therefore, these early studies constitute the basis for a new structure activity relationship (SAR) investigation for this class of antitumor antibiotics.

Introduction

The antitumor antibiotics belonging to the tetrahydroisoquinoline family have been studied thoroughly, and numerous natural products within the class have been isolated.¹ (–)-Jorumycin (**1**), a member of this family, was isolated from the mantle and mucus of the pacific nudibranch *Jorunna funebris* (Figure 1).² (–)-Jorumycin (**1**) is closely related to the saframycins (**6–8**), members of the renieramycin family (**2–4**), and, most notably, Ecteinascidin 743 (**5**), which was demonstrated to be a highly promising, exceedingly potent antitumor agent currently in phase II/III clinical trials.³ In general, the tetrahydroisoquinoline family of alkaloids include potent cytotoxic agents that display a range of biological properties such as antitumor and antimicrobial activities.¹ Consistent with other members in the group, (–)-jorumycin (**1**) also harbors potent biological activities. Specifically, **1** has shown activity against NIH 3T3 tumor cells (100% of inhibition at 50 ng/mL) and has displayed cytotoxicity (IC₅₀ 12.5 ng/mL) against other tumor cell lines at very low concentrations. Additionally, **1** was shown to inhibit the growth of various Gram-positive bacteria (e.g., *Bacillus subtilis*, *Staphylococcus aureus*) at a concentration lower than 50 ng/mL.² An efficient semisynthesis of **1** from a closely related natural product, renieramycin M (**4**), was recently reported by Saito and co-workers.⁴

(–)-Renieramycin G (**2**) was isolated from the marine sponge *Xestospongia caycedoi* by Davidson in 1992 (Figure 1).⁵ Despite

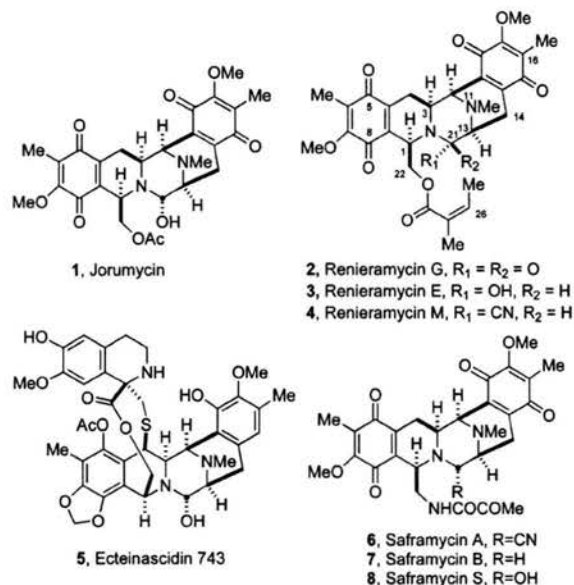


Figure 1. Tetrahydroisoquinoline alkaloids.

having an amide carbonyl residue at C-21, **2** was reported to retain cytotoxicity against human cancer cells with MIC values of 0.5 and 1.0 $\mu\text{g/mL}$ against KB and LoVo cell lines, respectively.⁵ This is surprising in light of the fact that virtually all biologically active members of this family of tetrahydroisoquinoline alkaloids possess a carbinolamine or cyano function at C-21 that permits the formation of a potent, electrophilic

(1) For a review, see: Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669–1730.

(2) Fontana, A.; Cavaliere, P.; Wahidulla, S.; Naik, C. G.; Cimino, G. *Tetrahedron* **2000**, *56*, 7305–7308.

(3) Aune, G. J.; Furuta, T.; Pommier, Y. *Anti-Cancer Drugs* **2002**, *13*, 545–555.

(4) Saito, N.; Tanaka, C.; Koizumi, Y.-i.; Suwanborirux, K.; Amnuoyopol, S.; Pummangura, S.; Kubo, A. *Tetrahedron* **2004**, *60*, 3873–3881.

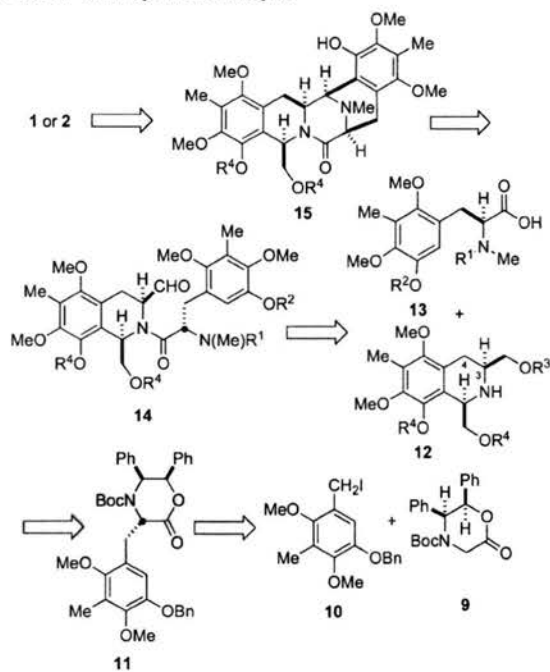
(5) Davidson, B. S. *Tetrahedron Lett.* **1992**, *33*, 3721–3725.

iminium ion species that has been implicated in the formation of covalent bonds to DNA and possibly other biomacromolecules.¹

Previously, our laboratory reported an efficient method for the construction of a highly functionalized pentacyclic tetrahydroisoquinoline relevant to the ecteinascidin, saframycin, safracin, and renieramycin families of antitumor alkaloids.^{6a} The approach, which was based on the use of sequential asymmetric Staudinger and Pictet–Spengler cyclization reactions, ultimately afforded a pentacyclic core containing an alkene group at the C3–C4 position (renieramycin numbering). Further employment of this intermediate in the synthesis of relevant natural product targets mandates retention of the alkene (for cribrastatin 4), saturation, or, in the case of the ecteinascidins and bioxalomyces, heteroatom functionalization at C3–C4 position. As part of a program directed toward efficient, asymmetric total syntheses of relevant members of the tetrahydroisoquinoline family,⁶ improvements were sought with respect to the construction of a necessarily versatile pentacyclic ring system that would be of potential use in accessing a variety of these targets. We report here a general method to construct a saturated pentacyclic ring system that should prove useful for the asymmetric total synthesis of several members of this family of natural products and congeners. The utility of this approach is demonstrated here through the first asymmetric total syntheses of (–)-jorumycin (1) and (–)-renieramycin G (2). Furthermore, en route to 1 and 2, a serendipitous discovery afforded a method to efficiently and selectively access a related pentacyclic intermediate, epimeric at the C-3 position. The C-3-*epi*-pentacycle was subsequently employed in the synthesis of 3-*epi*-jorumycin (32) and 3-*epi*-renieramycin G (34). The biological activity of this hitherto unreported stereochemical series is also reported herein.

Our strategy for the total synthesis of (–)-jorumycin (1) and (–)-renieramycin G (2) is illustrated in Scheme 1. Nucleophilic coupling between the appropriately functionalized aryl iodide 10 and chiral glycine template 9^{7,10} would afford intermediate 11. Based on the intrinsic symmetry of 1 and 2, coupling partners 12 and 13, representing the western and eastern halves of our targets, respectively, can both be derived from 11. Importantly, compound 12 will bear full saturation at the C3–C4 position (renieramycin numbering), obviating the difficult reduction required through our previous approach.^{6a} Cyclization substrate 14 would be available through a convergent coupling between intermediates 12 and 13 followed by oxidation at the appropriate primary alcohol position. An intramolecular Pictet–

Scheme 1. Retrosynthetic Analysis



Spengler condensation through the aldehyde group of intermediate 14 would provide the versatile pentacyclic intermediate 15. Our intermediate 15 would provide 1 or 2 through straightforward functional group manipulations and should prove useful in the synthesis of related targets and their congeners.

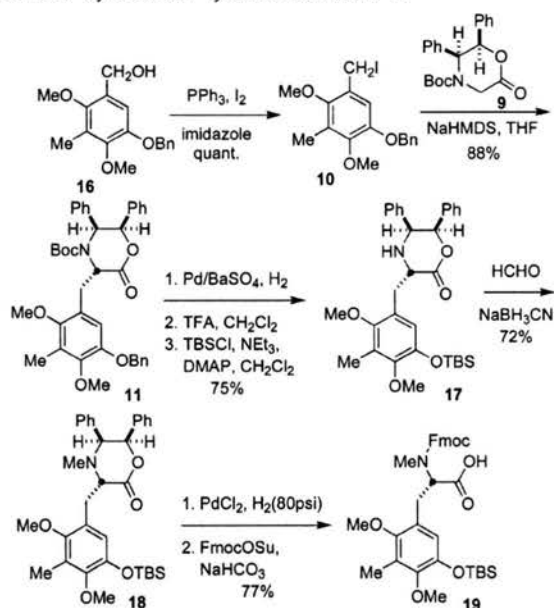
Results and Discussion

Historically, numerous synthetic efforts toward members of the saframycin and renieramycin families of antitumor antibiotics have exploited a symmetry-based approach.⁸ Such a strategy is logical because, unlike Et-743 which contains a pseudo-symmetrical pentacyclic core,^{6a,b,9} the saframycins and renieramycins possess a symmetrical substitution pattern on both the eastern and the western arene units. Indeed, the notion of employing a single common intermediate in a stereoselective and highly symmetrical approach toward any member of the saframycin or renieramycin families was pioneered by Myers

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Scheme 2. Synthesis of Tyrosine Derivative 19



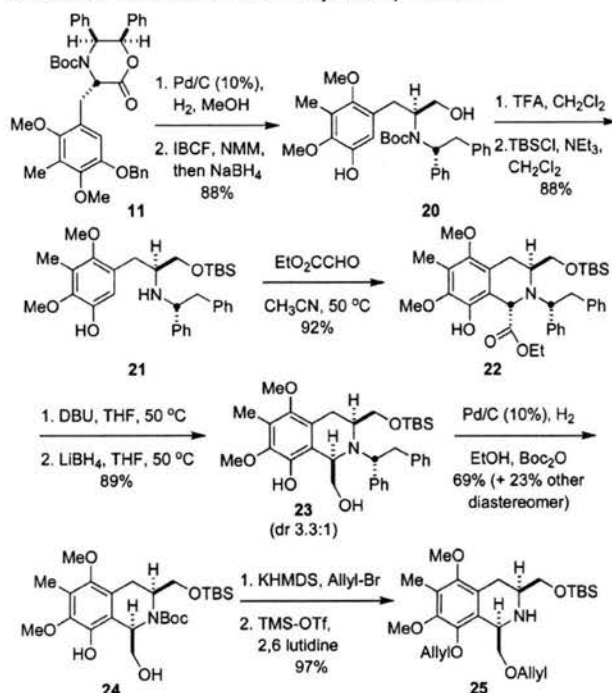
and co-workers in their elegant total synthesis of (–)-saframycin A.^{8a} The efficiency of this strategy ultimately culminated in a viable solid-phase route to saframycin A and analogues.^{8b}

Our universal building block, compound **11**, was readily available through straightforward methods (Scheme 2).^{6b} Initially, alcohol **16**^{8c} was converted to the corresponding benzyl iodide derivative **10** in quantitative yield. However, compound **10** was found to be unstable and was therefore utilized crude through immediate condensation with the sodium enolate of oxazinone **9** to afford the alkylation product **11** in 88% yield.^{7,10}

Conversion of compound **11** to the requisite amino acid component **13** (Scheme 1), representing the eastern half of **1** and **2**, proceeded as follows. The *O*-benzyl group of **11** was initially removed by catalytic hydrogenation to give the corresponding phenol, followed by removal of the *N*-*t*-Boc protecting group by treatment with TFA to afford an amine intermediate. Subsequent re-protection of the phenol group of this intermediate as the corresponding *O*-TBS ether under standard conditions afforded compound **17** in 75% for three steps. The requisite *N*-Me group was then installed through reductive amination of the secondary amine group in **17** producing *N*-methyl lactone **18** in 72% yield. Removal of the chiral auxiliary in compound **18** by catalytic hydrogenation, followed by protection of the secondary amine as the corresponding Fmoc derivative, furnished amino acid **19** in 77% yield for two steps.

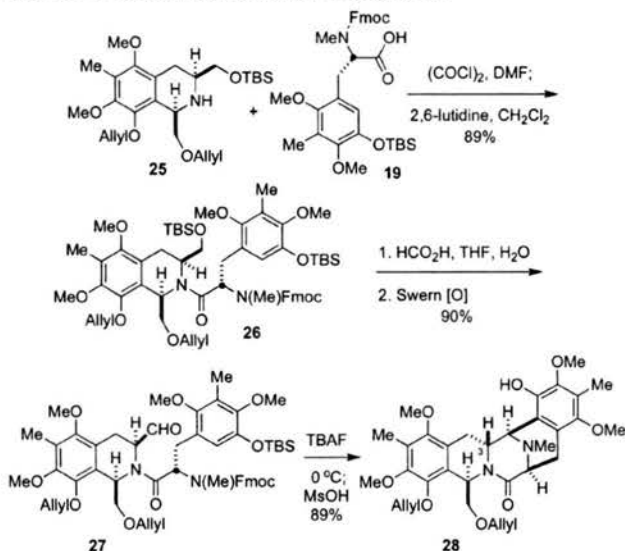
With the eastern tyrosine derivative in hand, synthesis of tetrahydroisoquinoline component **12**, representing the western half of **1** and **2**, commenced as above, from compound **11** (Scheme 3). Initially, subjection of compound **11** to catalytic hydrogenation conditions affected removal of the *O*-benzyl group as well as partial cleavage of the chiral auxiliary, affording a carboxylic acid intermediate. The carboxylic acid group in this intermediate was subsequently converted to the corresponding primary alcohol through a mixed-anhydride reduction producing compound **20** in 88% yield for two steps. Removal of the *N*-*t*-Boc protecting group in compound **20** by treatment with TFA followed by selective protection of the free primary alcohol as the corresponding *O*-TBS ether under standard

Scheme 3. Construction of Tetrahydroisoquinoline 25



conditions afforded compound **21** in 88% yield for two steps. Treatment of this substance with ethyl glyoxylate afforded the corresponding *anti*-tetrahydroisoquinoline **22** as a single stereoisomer in 92% yield.

Consistent with prior observations regarding peptide couplings of similarly functionalized amine substrates with sterically demanding carboxylic acid partners,^{6a} a syn relationship with respect to the C-1 and C-3 positions was determined to be required for a successful marriage of the eastern and western core units. Therefore, equilibration of the *anti*-carboethoxy group in **22** with DBU^{9p,q} afforded an inseparable (3.3:1) mixture of diastereomers in favor of the ester intermediate bearing the desired syn configuration at C-1. Conversion of the ester group in this intermediate to the corresponding primary alcohol was accomplished by subjecting the product mixture to reductive conditions (LiBH₄), successfully producing compound **23** (dr 3.3:1) in 89% yield. Exchange of the chiral auxiliary in compound **23** for the corresponding *N*-*t*-Boc protecting group was accomplished in one step by hydrogenolysis of the isomeric mixture in the presence of Boc₂O. This operation afforded the desired substance **24** in 69% yield in addition to 23% of the corresponding *anti*-isomer, which, at this juncture, were easily separated by conventional flash chromatography. In addition to providing a pair of chromatographically separable isomers, the functional group exchange installed appropriate, temporary protection at the nitrogen position on compound **24**. Nitrogen protection was found to be essential for subsequent protecting group installation at the two remaining free alcohol positions, and, furthermore, the *N*-*t*-Boc group could be easily removed under conditions compatible with the overall protection strategy. Therefore, bis-allyl protection of the free alcohol positions in compound **24** afforded a fully protected carbamate intermediate. Finally, the *N*-*t*-Boc group was selectively removed under Lewis-acid conditions, producing compound **25** in excellent yield for two steps. Importantly, the allyl ether groups were chosen for their orthogonal characteristics with respect to the

Scheme 4. Construction of 3-*epi*-Pentacycle 28

other protecting groups present. Additionally, it was reasoned that the compact size of these groups would minimize steric shielding of the secondary amine and improve the reactivity of compound **25** for coupling with compound **19**.

With straightforward access to compounds **19** and **25** bearing the appropriate features necessary for the convergent peptide coupling, the stage was set for joining the eastern and western halves of **1** and **2**. Amino acid **19** was initially converted into the corresponding acid chloride by treatment with oxalyl chloride and was then coupled to compound **25** in the presence of 2,6-lutidine to afford the desired peptide **26** in 89% yield (Scheme 4).

The next step entailed installation of the requisite aldehyde group in compound **26** to produce the desired cyclization substrate **14** (Scheme 1). Therefore, initial selective removal of the *O*-TBS group at the relevant primary hydroxyl position afforded a free alcohol intermediate, which was subsequently converted to the corresponding aldehyde **27** through a Swern protocol¹¹ (oxalyl chloride, DMSO, NEt₃) in excellent yield for two steps. Cyclization of compound **27** was accomplished in a one-pot procedure. Initial treatment of compound **27** with TBAF simultaneously removed the phenolic *O*-TBS and *N*-Fmoc groups, producing an iminium intermediate through collapse of the resulting free secondary amine group onto the aldehyde group. Subsequent treatment of this reactive intermediate in situ with excess MeOH promoted nucleophilic attack of the electron-rich eastern arene unit onto the electrophilic iminium species. This reaction generated compound **28**, exclusively, in 89% yield bearing the opposite configuration at C-3 with respect to the natural products. The structure of compound **28** was subsequently confirmed through single-crystal X-ray analysis (Figure 2).

The observed epimerization at C-3 was quite unexpected. On one hand, Danishefsky and co-workers obtained a 3-*epi*-pentacyclic intermediate en route to cribrastatin IV (renieramycin H) through an intramolecular C3–C11 bond-forming Mannich condensation.¹² On the other hand, Corey and co-

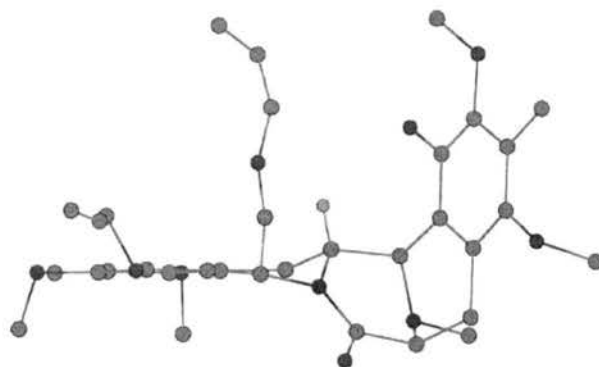


Figure 2. X-ray structure of 3-*epi*-pentacycle **28**.

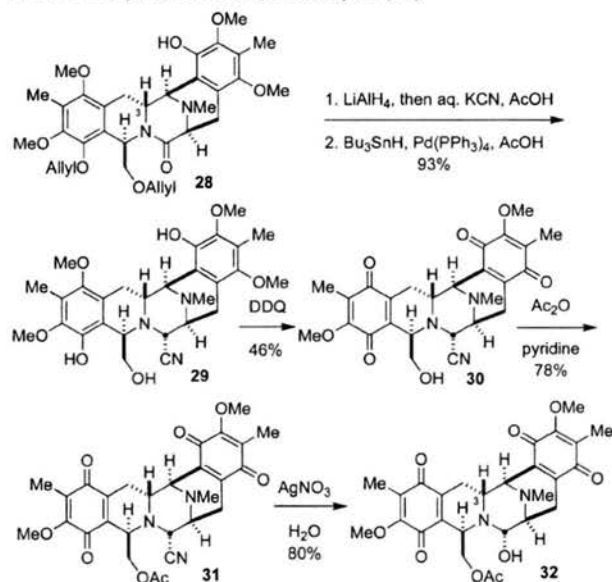
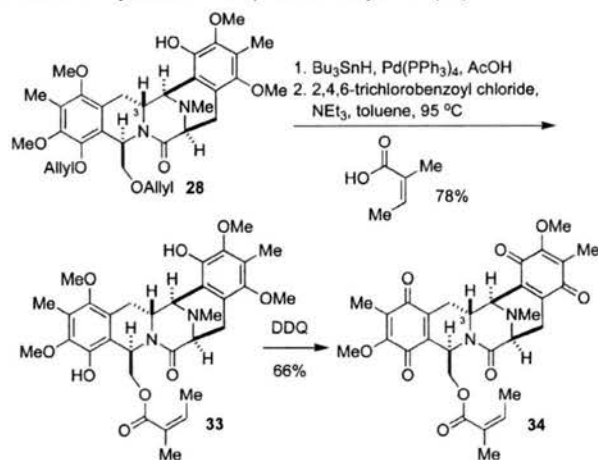
workers, in their groundbreaking total synthesis of Et-743, deployed a hemi-aminoacetal derivative to effect a C19–C11 bond-forming process that selectively cyclized to a key pentacyclic intermediate bearing the natural configuration at C-3.^{9a,b} Although the C3-*epi* cyclization conundrum posed an initial obstacle with respect to the synthesis of **1** and **2**, the efficient route to compound **28** fortuitously presented a unique opportunity. Indeed, selective access to a pentacyclic intermediate bearing the opposite configuration at C-3 would, in turn, provide a gateway to a hitherto unexplored series of C3-*epi*-tetrahydroisoquinoline natural product analogues. Structure–activity relationships (SARs) have been reported on potent analogues of saframycin A (**6**) by Myers and co-workers,^{8b,d} and Corey, Schreiber, and co-workers have prepared synthetic analogues of Et-743 (**5**) (e.g., phthalascidin, Pt-650) that maintained virtually the same cytotoxicity as the parent natural product.^{9c} Additionally, studies by Ong and co-workers toward the development of a pentacyclic scaffold mimic of saframycin A resulted in a compound of diminished potency with respect to the parent natural product.^{8k} However, to date SAR investigations have not addressed the cytotoxicity profiles of epimeric members of the tetrahydroisoquinoline family bearing the pentacyclic skeleton characteristic of the saframycins. The specific global conformations of these compounds will most likely reflect the individual stereochemical configurations contained within the pentacyclic system. Therefore, one could hypothesize that a structural modification of this variety could manifest into a significantly altered backbone conformation for the epimeric analogues relative to their respective natural product counterparts. These structural differences could, in turn, enhance or diminish the ability of these epimeric compounds to participate in noncovalent and covalent binding in the minor groove of DNA.¹³

With these thoughts in mind, we turned our attention toward the conversion of compound **28** to the C-3-*epi* variants of compounds **1** and **2**, 3-*epi*-jorumycin (**32**) and 3-*epi*-renieramycin G (**34**), respectively. The synthesis of 3-*epi*-jorumycin (**32**) commenced with conversion of the amide group in compound **28** to the corresponding aminonitrile (Scheme 5). This conversion entailed initial reduction of the amide group (LiAlH₄, THF) followed by trapping of the resulting carbinolamine group with cyanide (aqueous KCN, AcOH) affording the desired aminonitrile intermediate. Subsequent reductive removal of the allyl groups from this species afforded compound **29** in 93% yield for two steps. Initial DDQ oxidation of the

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Scheme 5. Synthesis of 3-*epi*-Jorumycin (**32**)Scheme 6. Synthesis of 3-*epi*-Renieramycin G (**34**)

hydroquinone units in compound **29** afforded bis-quinone **30** in 46% yield. The primary hydroxyl group in compound **30** was then acylated to give compound **31** in 78% yield. Treatment of compound **31** with aqueous AgNO_3 cleanly afforded 3-*epi*-jorumycin (**32**) in 80% yield. The relative configurations at the aminonitrile and carbinolamine positions (C-21) of compounds **30** and **32**, respectively, were verified through ^1H NMR coupling constant analysis.¹⁴

With our first epimeric target in hand, efforts were then directed toward the conversion of compound **28** to 3-*epi*-renieramycin G (**34**). Thus, initial removal of the allyl groups in compound **28** afforded a triol intermediate (Scheme 6). Selective acylation of the primary alcohol group in this intermediate with angelic acid was accomplished under modified Yamaguchi conditions¹⁵ to afford compound **33** in 78% yield

(14) 2D NOE analyses of compounds **29**–**32** were inconclusive in regards to establishing the respective configurations at C-21. However, the coupling constants (J 's) between H-21 and H-13 were successfully measured for compounds **30** and **32** at 1.9 and 2.1 Hz, respectively. Based on dihedral angles derived from energy-minimized structures of **30** and **32** bearing both possible configurations at C-21, these J 's were consistent with the respective assigned stereochemistries at this position.

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Table 1. Antiproliferative Activity of 3-*epi*-Jorumycin (**32**) and Related Synthetic Intermediates^a

compound	cell line	
	A549	HCT-116
29	> 10	> 10
30	6.2	4.4
31	5.1	2.0
32	> 10	4.9

^a Values reported are GI_{50} in μM .

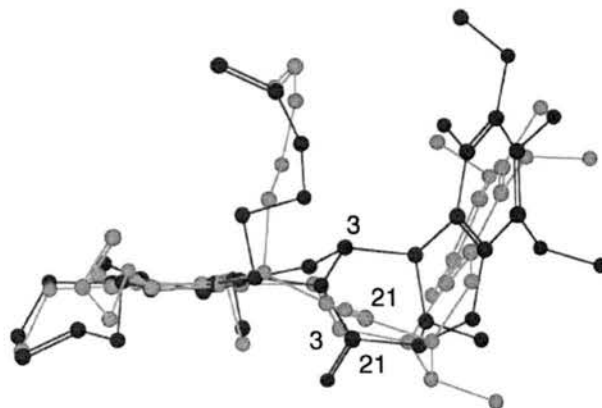
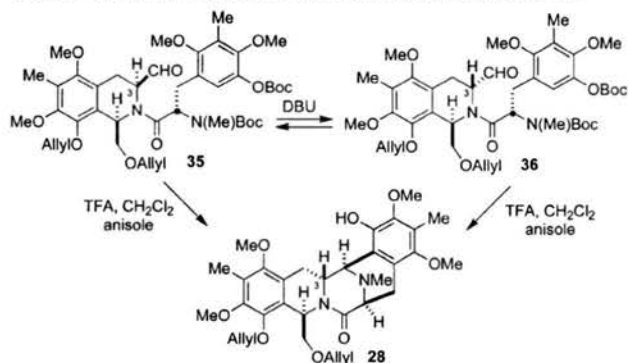


Figure 3. Overlay of compounds **28** (red) and **41** (gray).

for two steps. Subsequent DDQ oxidation of the hydroquinone units in compound **33** to the corresponding bis-quinone produced 3-*epi*-renieramycin G (**34**) in 66% yield.

Preliminary cytotoxicity assays were conducted on compounds **29**–**32** to determine whether antiproliferative activity had been retained. Compounds **29**–**32** were screened against two human cancer cell lines (A549 and HCT-116) (Table 1), and results revealed low micromolar inhibition profiles for all compounds tested, verifying the retention of antitumor potential for this new class of agents despite the inversion of configuration at C-3. However, as (–)-jorumycin (**1**) and presumably related intermediates are known to be unstable,² accurate determinations of relative cytotoxicity for the 3-*epi* analogues in comparison to the parent natural products (**1** and **2**) would have to be conducted simultaneously. This requirement, therefore, provided additional motivation for the development of a viable synthetic route to our original targets, compounds **1** and **2**.

It is quite significant that the C-3-*epi* substances display substantial cytotoxicity, and this was quite unexpected based on an initial consideration of the anticipated substantial change in geometry that the C-3-*epi* stereochemistry would render on C-21, the well-accepted site of DNA alkylation within the saframycin-ecteinascidin family of antitumor agents.¹ To gain some preliminary insight into the C-3-*epi* series, we have compared the geometry of compound **28** as revealed through X-ray analysis with the energy minimized geometry of **41** (vide infra) as shown in the overlay presented in Figure 3. While these are both amide-containing substrates, the overall spatial arrangements of the C-21 carbon atom in both substrates are found in a surprisingly similar region of space when the left-hand A–B ring systems are overlapped. This preliminary modeling exercise provides the reasonable expectation that the C-3-*epi* compounds, such as **30** and **31**, should be functionally capable of alkylating the exocyclic amine group of guanine residues in the minor groove of DNA in a fashion similar to that established for the

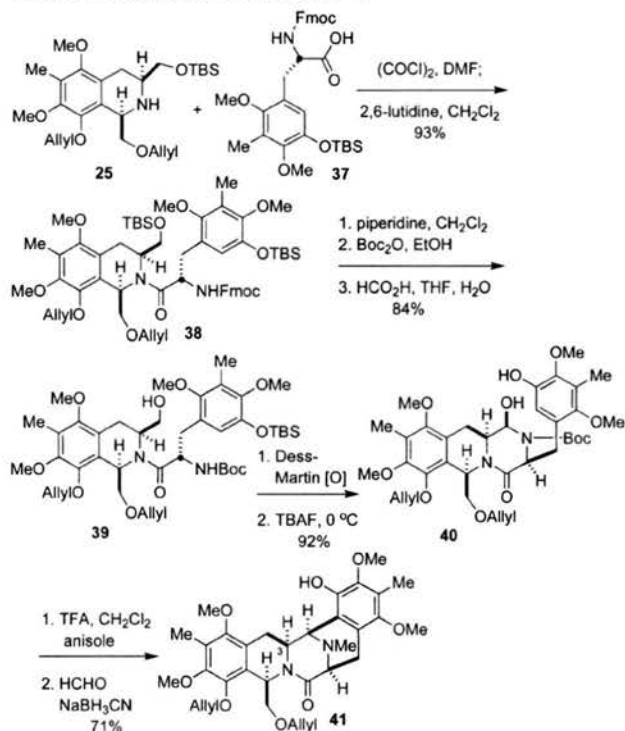
Scheme 7. Cyclization Studies on Alternate Substrates **35**, **36**

natural products.¹ Efforts to explore the biochemical reactivity of these compounds are presently under study and will be the subject of a separate disclosure.

Access to the natural substances **1** and **2** required a method for the synthesis of a versatile pentacyclic intermediate (**15**) bearing the natural configuration at C-3. To achieve this goal, a thorough investigation was conducted to determine a viable route to obviate the undesired epimerization at C-3. The cyclization of our original substrate, compound **27**, was initially conducted under basic conditions (TBAF) followed by treatment of the incipient iminium intermediate with excess acid (MsOH). Therefore, it was initially conjectured that perhaps the epimerization was mediated by base. This postulate seemed reasonable based on previous reports by Corey and co-workers of similar cyclizations whereby iminium formation and subsequent cyclization were both conducted under acidic conditions to successfully afford compounds bearing the natural configuration at C-3.^{9a,b}

To test our theory, a cyclization substrate bearing acid-labile protecting groups at the relevant positions was desired. This new protection strategy would also permit access to a C-3-*epi* cyclization substrate through deliberate base-mediated equilibration at the C-3 aldehyde position (renieramycin numbering). The epimeric substrate would serve to determine the dependence, if any, of the initial configuration at C-3 on the stereochemical outcome of the cyclization. In accord with this strategy, compound **35**, bearing Boc protection at the nitrogen and phenol positions, was synthesized by straightforward methods from peptide **26**.¹⁶ Subsequent treatment of compound **35** with DBU effectively equilibrated the configuration at C-3, affording a diastereomeric mixture of **35** and **36** (dr ~1:1, Scheme 7). Subjection of compounds **35** and **36**, individually, to TFA afforded exclusively, the 3-*epi* pentacycle **28**, which is consistent with the behavior of compound **27** (Scheme 4).

These studies on compounds **35** and **36** confirmed that the stereochemical outcome of the cyclization at C-3 under these conditions was independent of the initial substrate configuration at C-3, and, importantly, this confirmed that the epimerization was pervasive even in the absence of base. Guided by these preliminary findings, extensive studies were then conducted to determine the appropriate cyclization substrate and reaction conditions necessary to maintain the desired configuration at the C-3 position. These efforts ultimately led to the discovery

Scheme 8. Synthesis of Pentacycle **41**

of compound **40**, a modified substrate lacking a methyl group at the nitrogen position and bearing a free phenol group on the eastern arene unit.

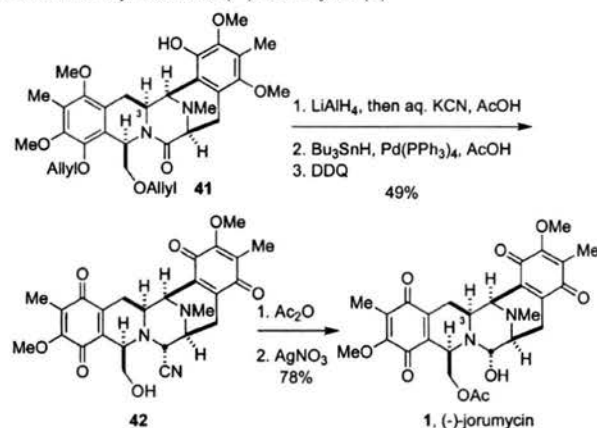
Preparation of compound **40** proved straightforward and commenced with the coupling of modified amino acid **37**,¹⁷ through its corresponding acid chloride, to compound **25** in the presence of 2,6-lutidine to afford the desired peptide **38** in 93% yield (Scheme 8). The *N*-Fmoc group in compound **38** was then removed with piperidine, and the resulting free amine was reprotected as the corresponding Boc carbamate to afford the desired intermediate. Selective removal of the *O*-TBS protecting group at the primary hydroxyl position in this intermediate was accomplished under acidic conditions producing alcohol **39** in 84% yield for three steps. Subsequent oxidation of the primary hydroxyl group in **39** to the corresponding aldehyde through the agency of the Dess–Martin reagent¹⁸ resulted in a hemi-aminal intermediate. Removal of the phenolic *O*-TBS group in the intermediate produced compound **40** as a single diastereomer (hemi-aminal configuration established by 2D ROESY NMR) in 92% yield for two steps. Gratifyingly, subjection of substrate **40** to TFA afforded a pentacyclic compound in high yield bearing the desired natural configuration at C-3. Installation of the *N*-Me group in this intermediate through reductive amination with formaldehyde produced compound **41** in 71% yield for two steps, appropriately endowed for conversion to the natural alkaloids.

The modified cyclization strategy proceeding through compound **40** was somewhat less convergent than our previous route to 3-*epi*-pentacycle **28** due to necessary protecting group manipulations and a late-stage installation of the requisite *N*-Me group. Nonetheless, the specific structural features of compound

(16) Compound **35** was prepared from peptide **26** through the following sequence: (1) TBAF, THF, room temperature; then excess Boc_2O ; (2) Boc_2O , EtOH, room temperature; (3) Dess–Martin [O].

(17) Compound **37** was prepared from amine **17** in two steps: (1) PdCl_2 , EtOH, H_2 ; (2) FmocOSu, aqueous NaHCO_3 , CH_2Cl_2 (see Supporting Information).
(18) Dess, B. D.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.

Scheme 9. Synthesis of (–)-Jorumycin (1)

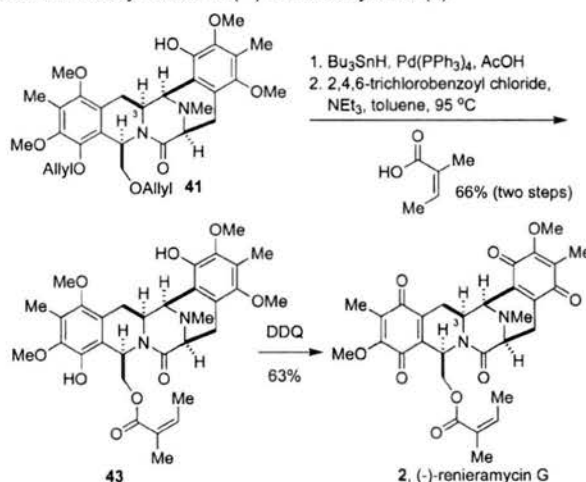


40 were found to be crucial to the success of the cyclization. Indeed, any attempts to cyclize substrates incorporating an acid labile group at the eastern phenolic position or an *N*-Me group resulted only in the production of 3-*epi*-pentacycle products in addition to undesired byproducts.

With compound **41** in hand, we initially endeavored to complete the synthesis of (–)-Jorumycin (**1**). In accord with the route to 3-*epi*-Jorumycin (**32**), conversion of the amide group in compound **41** to the corresponding aminonitrile proceeded as before (LiAlH_4 , THF, then aqueous KCN, AcOH). Subsequent reductive removal of the allyl groups in this intermediate afforded the corresponding triol. Oxidation of the hydroquinone units in the triol intermediate afforded the bis-quinone **42** in 49% yield for three steps. Importantly, spectroscopic data from compound **42** matched data from the same intermediate reported previously by Saito and co-workers in their semisynthesis of (–)-Jorumycin (**1**) from renieramycin M (**4**).⁴ The primary hydroxyl group in compound **42** was then acylated to give an acetate intermediate, after which treatment of this intermediate with aqueous silver nitrate cleanly afforded (–)-Jorumycin (**1**) in 78% yield for two steps (Scheme 9). The synthetic Jorumycin had spectral data consistent with that previously reported for the natural substance² and for the material derived through semisynthetic methods.⁴

Consistent with our route to 3-*epi*-renieramycin G (**34**), conversion of compound **41** to (–)-renieramycin G (**2**) proved straightforward. Initial removal of the *O*-allyl groups from compound **41** afforded a triol intermediate, which was subjected to selective acylation of the primary alcohol group with angelic acid under modified Yamaguchi conditions¹⁵ as above, to afford compound **43** in 66% yield for two steps. Subsequent DDQ oxidation of the hydroquinone units in compound **43** to the

Scheme 10. Synthesis of (–)-Renieramycin G (2)



corresponding bis-quinone produced (–)-renieramycin G (**2**) in 63% yield (Scheme 10). The synthetic (–)-renieramycin G had spectral data fully consistent with those previously reported for the natural substance.^{5,19}

Conclusion

The asymmetric total syntheses of (–)-Jorumycin (**1**) and (–)-renieramycin G (**2**) have been accomplished in 25 and 23 steps, respectively. Additionally, 3-*epi*-Jorumycin (**32**) and 3-*epi*-renieramycin G (**34**) were also successfully synthesized, the former of which, including related synthetic intermediates, displayed significant cytotoxicity in preliminary biological evaluation. Efforts to utilize this approach for the concise asymmetric synthesis of other members of the renieramycin family, the ecteinascidins, saframycins, as well as the safracins and some mechanistically inspired analogues, including epimers, are currently under study in our laboratories.

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Supporting Information Available: Complete experimental and spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA0535918

(19) We were unable to acquire an authentic specimen of natural renieramycin G from Prof. B. S. Davidson (ref 5) with which to compare our synthetic sample. The isolation paper (ref 5) notes that the natural product was unstable. Furthermore, an optical rotation for this natural product has heretofore not been recorded.

An Improved Synthesis of Optically Pure 4-Boc-5,6-Diphenylmorpholin-2-one and 4-Cbz-5,6-Diphenylmorpholin-2-one

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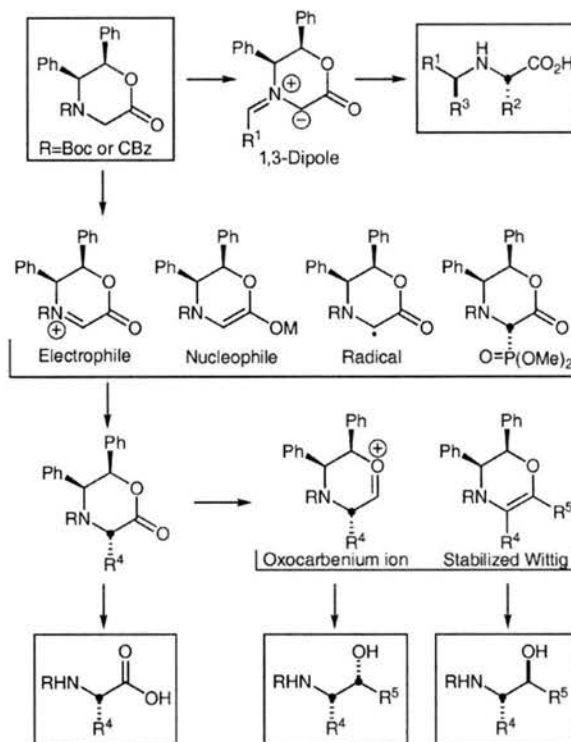
Abstract: A convenient synthesis of optically pure 4-Boc-5,6-diphenylmorpholin-2-one and 4-Cbz-5,6-diphenylmorpholin-2-one by reaction of (+)- or (-)-2-amino-1,2-diphenylethanol with ethyl bromoacetate, followed by N-protection, and *p*-TsOH-mediated ring-closure is described. The title compounds can be used as synthons for the asymmetric synthesis of N-protected α -amino acids. These lactones are quite stable to storage and handling.

Key words: amino acids, asymmetric synthesis, lactones, 2-amino-1,2-diphenylethanol, ring-closure

It is well-established that (+)- and (-)-4-*tert*-butoxycarbonyl-5,6-diphenylmorpholin-2-ones, as well as the corresponding 4-benzyloxycarbonyl compounds, are useful intermediates for the asymmetric synthesis of α -amino acid derivatives.^{1–3} These intermediates serve as chiral, non-racemic templates for the construction of α -amino acids, which are found in a large number of biologically important metabolites and natural products (Scheme 1).⁴ Several methods have been developed for the asymmetric synthesis of α -amino acids such as alkylation of chiral Schiff bases, catalytic asymmetric C-H, C-C and C-N bond forming reactions and the asymmetric Strecker reaction among other methods.⁴ However, none of these methods can provide the range of chemical reactivity for C-C bond-forming processes that the morpholinone-based chiral templates provide. The great versatility that these glycine templates offer for preparing structurally diverse amino acids in high optically purity has been illustrated in the synthesis of several complex alkaloid natural products.^{1–3} Among the transformations reported for these glycine templates is the asymmetric [1,3] dipolar cycloaddition reaction, which enables diastereoselective double alkylation in the construction of densely functionalized pyrrolidines (Scheme 1).^{2p,3c} We have also demonstrated that the methylene carbon of the morpholinone can be coupled with a variety of electrophiles and nucleophiles to provide optically pure α -homologated amino acids after cleavage of the chiral template. Furthermore, the morpholinone can be selectively *trans*-homologated through Wittig olefination^{2a} followed by reduction. Alternatively, the morpholinone can be *cis*-homologated through Lewis acid-mediated addition of allylsilane to the

intermediate oxocarbenium ion generated from the corresponding hemiacetal.^{2a,5}

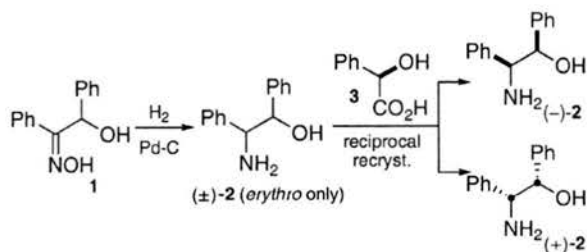
A variety of both reductive and oxidative conditions have been developed for removing the chiral auxiliary from the functionalized adducts to generate the corresponding amino acid or amino alcohol products.¹ Furthermore, the lactones are quite stable to storage and handling.



Scheme 1 Synthesis of L- and D-amino acid derivatives from morpholinones

Our group has reported the synthesis of the title compounds starting from benzoin and have reported a practical procedure for the synthesis of (5*S*,6*R*)-4-*tert*-butoxycarbonyl-5,6-diphenylmorpholin-2-one (**6**) from (1*R*,2*S*)-(-)-2-amino-1,2-diphenylethanol [(-)-**2**].⁶ Herein, we wish to report an improved and more efficient preparation starting from non-racemic amino alcohols (+)- and (-)-**2**. The non-racemic amino alcohols, (1*R*,2*S*)-(-)-2-amino-1,2-diphenylethanol and (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol, are commercially available. Alterna-

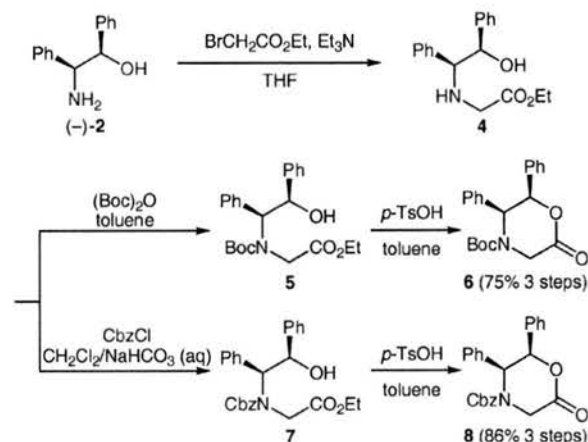
tively, these compounds can be easily prepared by converting benzoin to its corresponding oxime (**1**),⁷ followed by stereoselective oxime reduction which gives exclusively, the *erythro*-amino alcohol,⁸ and subsequent optical resolution of the resulting *erythro*-amino alcohol ($\pm$)-**2** (Scheme 2). This robust reduction that can be performed on a large scale, provides the racemic amino alcohols as a crystalline solid in a high state of purity. Resolution was accomplished through reciprocal crystallization of the corresponding (–)-mandelic acid salts.⁹ The new protocol provides higher resolution efficiency and requires fewer recrystallizations than the fractional L-glutamic acid resolution reported previously.^{6a,8} Alternatively, the non-racemic amino alcohols can be prepared through initial lipase resolution of benzoin, followed by requisite oxime formation and subsequent reduction.¹⁰



Scheme 2 Preparation of (1*R*,2*S*)-(–)-2-amino-1,2-diphenylethanol and (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol⁷

Following resolution, either (+)- or (–)-**2** was reacted with ethyl bromoacetate to form the corresponding chiral glycinate as illustrated for compound **4** in Scheme 3. Our previously reported procedure was reported on a 25 g (117 mmol) scale and was accomplished by slow addition of Et₃N (2.0 equiv) to a solution of either (+)- or (–)-**2** and ethyl bromoacetate (1.5 equiv) in anhydrous THF (0.26 M).⁵ After stirring for 20 hours at room temperature, the crude product was isolated and was subsequently recrystallized from absolute ethanol to yield 29 g (84%) of the enantiomerically pure glycinate bearing the desired configuration. We have since found that this reaction can be significantly improved by changing the addition sequence of the reagents. Specifically, slow addition of ethyl bromoacetate to the amino alcohol/Et₃N/THF solution resulted in complete reaction after an additional 1 hour of stirring at room temperature. We were able to decrease the quantities of Et₃N (1.55 equiv) and THF (0.45 M) required, and successfully conducted the reaction in reagent grade THF, obviating the use of anhydrous solvent. Importantly, the resulting crude product was isolated in adequate purity as a solid after rinsing with water and can be subjected to subsequent transformations without recrystallization. Furthermore, **4** and the corresponding antipode can now be routinely prepared on >100 g scale (0.5 mol) using this modified procedure.

Amine **4** [from (–)-**2**, 0.5 mol] was then acylated by reaction with either di-*t*-butyl dicarbonate [(Boc)₂O] or benzyl chloroformate (CbzCl). Our previous procedure for pre-



Scheme 3 Synthesis of (5*S*,6*R*)-4-*t*-Boc-5,6-diphenylmorpholin-2-one and (5*S*,6*R*)-4-Cbz-5,6-diphenylmorpholin-2-one from (1*R*,2*S*)-(–)-2-amino-1,2-diphenylethanol

paring **5** entailed refluxing **4** with (Boc)₂O (2.0 equiv) in a biphasic CHCl₃/aqueous NaHCO₃–NaCl mixture for 20 hours. This was followed by an aqueous work-up, drying of the organic layer overnight, and removal of excess (Boc)₂O (5 mmHg, 130 °C) to afford **5** (33.2 g, 99% from **4**). Alternatively, due to efforts to obviate the use of chlorinated solvents, it was discovered that the reaction could be performed in toluene. Therefore, a solution of (Boc)₂O (1.35 equiv) in toluene was slowly added to crude **4** in refluxing toluene. After 10 hours, a portion of the solvent was distilled from the reaction mixture effecting azeotropic removal of excess water that remained from the isolation of **4** in the previous step. The resulting solution of **5** in toluene was used in the following step, therefore avoiding product isolation. This modified procedure is advantageous in that it (1) requires less (Boc)₂O reagent; (2) obviates halogenated solvents, (3) utilizes a solvent that can, in practice, be recycled, and (4) is significantly more time efficient.

If the *N*-Cbz lactone **8** is ultimately desired, Schotten–Bauman acylation conditions are used to produce **7** from intermediate **4** as previously described (1.1 equiv CbzCl, sat. NaHCO₃ solution, CH₂Cl₂).⁸ Interestingly, by applying minor modifications to the original procedure,⁸ including maintaining the reaction at 0 °C rather than room temperature and slowly adding CbzCl to the biphasic mixture of **4** in aqueous NaHCO₃/CH₂Cl₂, we were able to reduce the reaction time from 12 hours to one hour.

Reaction of the crude *N*-protected products, **5** or **7**, with catalytic amounts of *p*-TsOH promotes ring-closure to **6** and **8**, respectively. The former protocol entailed refluxing the esters (**5** or **7**) in benzene with catalytic *p*-TsOH (0.1 equiv) using a Soxhlet extractor packed with CaCl₂ to remove water from the reaction. However, in accord with our recently developed distillation protocol, the reaction could be successfully performed in toluene. Therefore, removal of a portion of the reaction solvent through simple distillation, as before, effected azeotropic dehydration of

the reaction. This modification effectively provides the desired morpholinones after three distillation cycles. Finally, the products are recrystallized from ethanol or toluene to provide optically pure 4-Boc-5,6-diphenylmorpholin-2-one (**6**) and 4-Cbz-5,6-diphenylmorpholin-2-one (**8**) in 75% and 86% yield, respectively, over three steps. Importantly, while the modified procedure requires three days for completion, the previous procedure typically required six to seven days and yielded 59% and 66% of **6** and **8**, respectively, over three steps.

Utilizing this convenient procedure, it is possible to prepare optically pure 4-Boc-5,6-diphenylmorpholin-2-one and 4-Cbz-5,6-diphenylmorpholin-2-one on a 100 g scale with reproducibly high yields. Exclusion of air during the synthesis was not necessary, and the entire sequence from benzoin was accomplished without any chromatographic separations. The products can be stored on the shelf at room temperature over several years without decomposition.

Procedure for the Preparation of (5S,6R)-4-(*t*-Butoxy-carbonyl)-5,6-diphenylmorpholin-2-one (**6**)

(1R,2S)-(-)-2-Amino-1,2-diphenylethanol [(**-**)-**2**, 106 g, 0.5 mol] was dissolved in a mixture of THF (1100 mL, ACS grade) and Et₃N (108 mL, 78.4 g, 0.775 mol, 1.55 equiv) with gentle warming. Ethyl bromoacetate (86 mL, 129 g, 0.775 mol, 1.55 equiv) was slowly dropped into the vigorously stirred solution over 1 h at r.t. The reaction was stirred for an additional 1 h, then cooled to 0 °C and filtered. The filter cake was thoroughly rinsed with ice cold THF (2 × 100 mL). The combined filtrates were evaporated to dryness, and the solid residue was washed with warm H₂O (500 mL, 50 °C), dissolved in toluene (600 mL), and brought to reflux temperature. A solution of di-*t*-butyl dicarbonate (147 g, 0.675 mol, 1.35 equiv) in toluene (400 mL) was slowly added to the stirred mixture over 2 h. The reaction remained at reflux for an additional 10 h, then 300–500 mL of solvent was distilled off to remove any residual water. The reaction volume was adjusted back to 1000 mL with fresh toluene, *p*-TsOH·H₂O (9.52 g, 0.05 mol, 0.1 equiv) was added, and the excess solvent was slowly distilled until approx. 500 mL remained. The reaction was cooled to r.t., the resulting crystals were collected by filtration, rinsed with toluene–hexane (1:3, 200 mL), followed by hexane (200 mL). The mother liquor and washes were combined, and the solvent was removed by distillation (until 300 mL remained). The cooling, filtration, and washing sequence was repeated to provide a second crop of crystals. The washes and mother liquors were again combined along with additional *p*-TsOH·H₂O (2.38 g, 0.012 mol, 0.025 equiv) and the sequence was repeated to provide a third crop of crystals. The combined solids were recrystallized from ethanol to give the product as a white crystalline solid (132 g, 75%); mp 207 °C; [α]_D²² –87.3 (c 1.0, CH₂Cl₂). IR (NaCl, CH₂Cl₂): 3050, 2975, 1755, 1690, 1380, 1255, 1150, 1100, 1045 cm⁻¹. ¹H NMR (200 MHz, DMSO-*d*₆ vs. DMSO, 120 °C): δ = 1.25 (9 H, s), 4.52 (2 H, d, *J* = 1 Hz), 5.16 (1 H, d, *J* = 3 Hz), 6.17 (1 H, d, *J* = 3 Hz), 6.63–6.68 (2 H, m), 7.00–7.30 (8 H, m). Anal. Calcd for C₂₁H₂₃NO₄: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.08; H, 6.44; N, 3.98.

(5R,6S)-4-(*t*-Butoxycarbonyl)-5,6-diphenylmorpholin-2-one is obtained from the antipode, (1S,2R)-(+)-2-amino-1,2-diphenylethanol, using the procedure described above. Mp 207 °C; [α]_D²² +87.3 (c 1.0, CH₂Cl₂).

Procedure for the Preparation of (5S,6R)-4-(Benzyloxy-carbonyl)-5,6-diphenylmorpholin-2-one (**8**)

(1R,2S)-(-)-2-Amino-1,2-diphenylethanol [(**-**)-**2**, 106 g, 0.5 mol] was dissolved in a mixture of THF (1100 mL, ACS grade) and Et₃N (108 mL, 78.4 g, 0.775 mol, 1.55 equiv) with gentle warming. Ethyl bromoacetate (86 mL, 129 g, 0.775 mol, 1.55 equiv) was slowly dropped into the vigorously stirred solution over 1 h at r.t. The reaction was stirred for an additional 1 h, then cooled to 0 °C and filtered. The filter cake was thoroughly rinsed with ice cold THF (2 × 100 mL). The combined filtrates were evaporated to dryness and the residue diluted with CH₂Cl₂ (750 mL) and sat. NaHCO₃ (750 mL). The mixture was cooled in ice and benzyl chloroformate (83 mL, 98.8 g, 0.55 mol, 1.1 equiv) was slowly added to the stirred solution over 1 h. The reaction was stirred for an additional 1 h at 0 °C, and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (2 × 100 mL), and the combined organic extracts were washed with H₂O and dried (Na₂SO₄). The solvent was removed, the residue was dissolved in toluene (1100 mL, ACS grade), *p*-TsOH·H₂O (9.52 g, 0.05 mol, 0.1 equiv) was added, and the excess solvent was slowly distilled at atmospheric pressure until approximately 500 mL remained. The reaction was then cooled to r.t. The resulting crystals were collected by filtration, and subsequently rinsed with toluene–hexane (1:3, 300 mL), followed by hexane (300 mL, 163 g, 84%). The mother liquor and washes were combined and evaporated to dryness under reduced pressure, and the residue was recrystallized from toluene to provide a second crop of product (2.43 g, 2%). The combined crops afforded 166 g (86%) of white crystalline product. Mp 206–207 °C; [α]_D²² –68.7 (c 1.0, CH₂Cl₂). IR (NaCl, paraffin oil): 1745, 1705, 1455, 1440, 1375, 1325, 1215, 1120, 1055 cm⁻¹. ¹H NMR (200 MHz, DMSO-*d*₆ vs. TMS, 120 °C): δ = 4.60 (2 H, ABq, *J* = 18 Hz), 5.06 (2 H, ABq, *J* = 13 Hz), 5.29 (1 H, d, *J* = 3 Hz), 6.20 (1 H, d, *J* = 3 Hz), 6.66 (1 H, s), 6.60 (1 H, s), 7.00–7.30 (13 H, m). Anal. Calcd for C₂₄H₂₁NO₄: C, 74.40; H, 5.46; N, 3.61. Found: C, 73.85; H, 5.38; N, 3.50.

(5R,6S)-4-(Benzyloxycarbonyl)-5,6-diphenylmorpholin-2-one is obtained from the antipode, (1S,2R)-(+)-2-amino-1,2-diphenylethanol using the procedure described above. Mp 206–207 °C; [α]_D²² +68.7 (c 1.0, CH₂Cl₂).

Acknowledgment

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FORMATION OF THE C₃-C₄ UNSATURATED FRAMEWORK OF CRIBROSTATIN 4 VIA DEAD-MEDIATED OXIDATION OF AN ALLYLIC TERTIARY AMINE

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Abstract – The formal synthesis of the tetrahydroisoquinoline alkaloid cribrostatin 4 (**1**) is described. The synthesis features as a key step a DEAD-mediated oxidation of an allylic tertiary amine to an iminium ion immediately followed by a Pictet-Spengler cyclization to form the pentacyclic skeleton of cribrostatin 4.

INTRODUCTION

The tetrahydroisoquinoline family of antitumor agents comprise a clinically significant family of antitumor drugs.¹ Within this family, four main structural motifs are noteworthy. The tetrahydroisoquinolines that are represented by quinocarcin, tetrazomine, lemonomycin, and the bioxalomycins are biosynthetically derived from phenylalanine (or tyrosine) and glutamic acid. The second sub-type, which includes ecteinascidin 743 (**3**), the saframycins (**6**), jorumycin (**5**) and members of the renieramycin family (**1**, **2**), are biosynthetically derived from two tyrosine units. With respect to the chemically reactive functionality within this family, several members (quinocarcin, tetrazomine, bioxalomycins) contain a fused oxazolidine ring while others contain either a carbinolamine or an α -aminonitrile at C-21 (eg., ecteinascidin 743, lemonomycin, saframycin A). Cribrostatin 4 (**1**, also named renieramycin H) was independently isolated from the blue sponge *Cribrochalina* collected in reef passages in the Republic of Maldives by Petit and from the bright blue sponge *Haliclona cribicutis* by Parameswaran and coworkers.² One unique structural feature of cribrostatin 4 (**1**) and renieramycin I (**2**), is the presence of the C₃-C₄ benzylic olefinic residue (Figure 1). Seminal work by Danishefsky and coworkers led to the disclosure of the first total synthesis of cribrostatin 4 (**1**) via a “lynchpin Mannich”

cyclization protocol to establish the pentacyclic core.³ The Danishefsky strategy effectively installed the C₃-C₄ benzylic olefin *via* C4-ketone reduction and dehydration.³ As part of our long-standing interest in the chemistry and biology of the tetrahydroisoquinoline alkaloids,^{1,4-9} we recently reported the asymmetric total synthesis of cribrostatin 4⁵ *via* a C₃-C₄ fused tricyclic β -lactam species which served as an efficient precursor for the creation of the C₃-C₄ benzylic olefin.⁶ Cribrostatin 4 displays low micromolar antimicrobial and antitumor activities compared with the most potent members of this family, such as ecteinascidin 743 (**3**), phtalascidin 650 (**4**), jorumycin (**5**) or saframycin S (**6**) that exhibit nanomolar cytotoxic activities.¹ The extraordinary activity of the latter compounds is due to the presence of a carbinolamine (or functional equivalent) moiety at C₂₁ that allows the formation of a potent electrophilic iminium ion species implicated in the formation of covalent bonds with DNA.¹ Thus, we speculate that the cytotoxic activity of cribrostatin 4 (**1**) should be significantly increased by introducing a carbinolamine function at C₂₁ in place of the amide carbonyl residue in the natural product. The synthesis of analogues of ecteinascidin-743, phtalascidin 650, jorumycin or saframycin S bearing a C₃-C₄ alkene might provide a valuable platform from which to explore the stereo-electronic influence of the C₃-C₄ double bond on the reactivity of the electrophilic iminium ion species as this relates to cytotoxic activity. We report herein a new method to access the desired C₃-C₄ unsaturated pentacyclic skeleton.

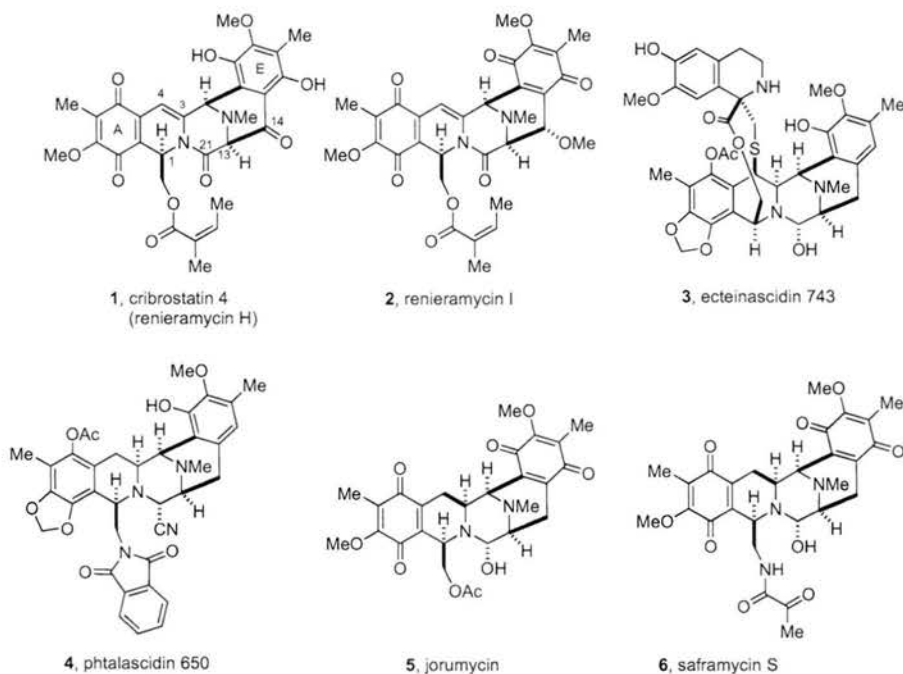
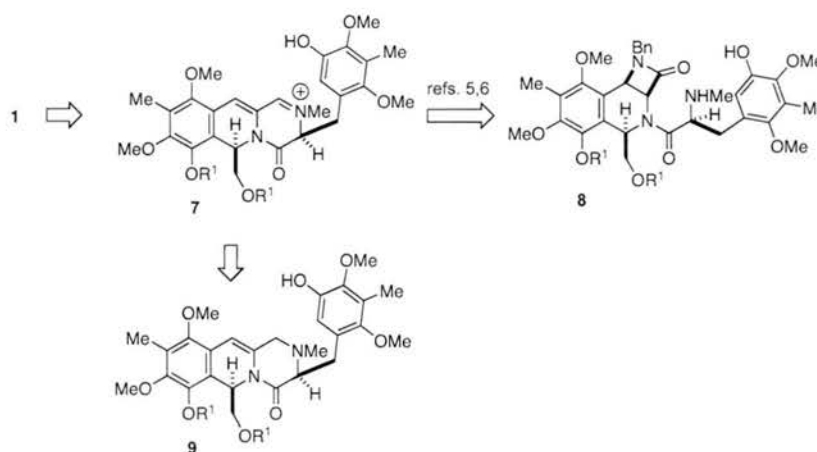


Figure 1. Tetrahydroisoquinoline alkaloids.

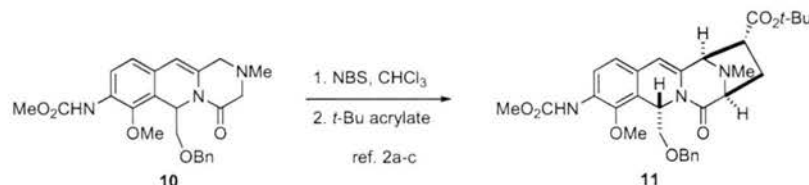
RESULTS AND DISCUSSION

Our retrosynthesis is based on the Pictet-Spengler cyclization of the conjugated iminium ion intermediate **7**.¹ Two different strategies to form the key iminium ion species can be envisioned (Scheme 1). The first strategy relied on the reductive opening/elimination of the C₃-C₄ β -lactam in **8** immediately followed by spontaneous iminium ion formation and cyclization to the pentacyclic framework.⁶ As mentioned above, this new conceptual approach to tetrahydroisoquinolines was recently successfully conscripted for the asymmetric total synthesis of cribrostatin **4**.⁵



Scheme 1. Retrosynthesis of Cribrostatin **4**.

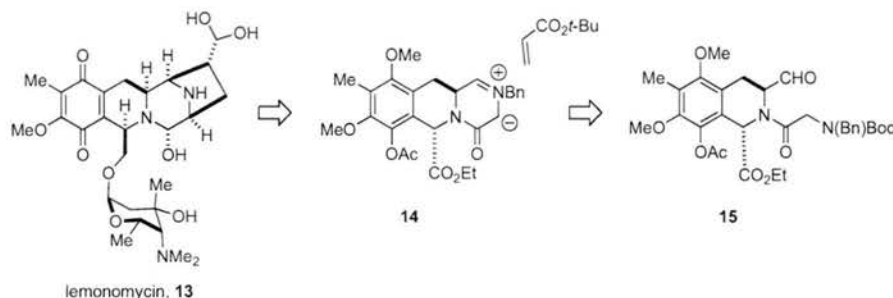
Our second option was envisioned to exploit the direct oxidation of the allylic tertiary amine **9** into the common iminium ion species **7**. This approach was inspired by our NBS-mediated oxidation of structurally related allylic tertiary amines to iminium intermediates that were then converted into azomethine ylides that underwent [1,3]-dipolar cycloadditions with acrylates, culminating with the total syntheses of tetrazomine and quinocarcinamide (Scheme 2).^{4a-c}



Scheme 2. NBS-mediated oxidation of tertiary allylic amines.

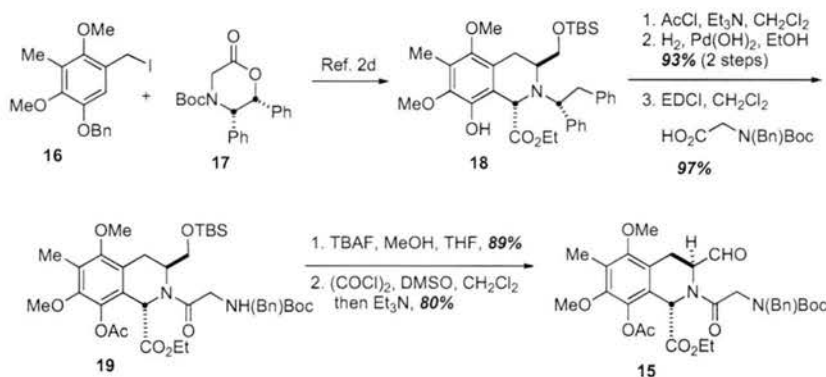
Moreover, we have observed an interesting air-mediated autoxidation of an allylic tertiary amine in the course of synthetic studies towards lemomycin, another member of the tetrahydroisoquinoline family of

antitumor antibiotics.¹⁰⁻¹² Our retrosynthesis of lemonomycin (**13**) required a [1,3]-dipolar cycloaddition between *t*-butyl acrylate and azomethine ylide **14**. The latter would be the result of the condensation of the amine and aldehyde functions in **15** after *N*-*t*-Boc removal, followed by deprotonation of the resulting iminium ion intermediate (Scheme 3).



Scheme 3. Retrosynthesis of Lemonomycin.

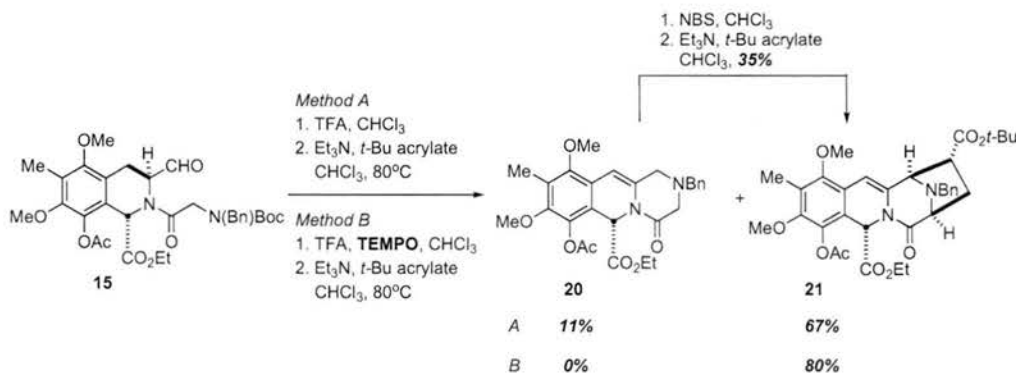
Tetrahydroisoquinoline **18** was produced from the coupling product of the chiral glycine template **17** and benzyl iodide **16** according to our previously reported protocol.¹³ Tetrahydroisoquinoline **18** was transformed to the *N*-*t*-Boc amino aldehyde **15** in five steps as described in Scheme 4.



Scheme 4. Synthesis of amino aldehyde **15**.

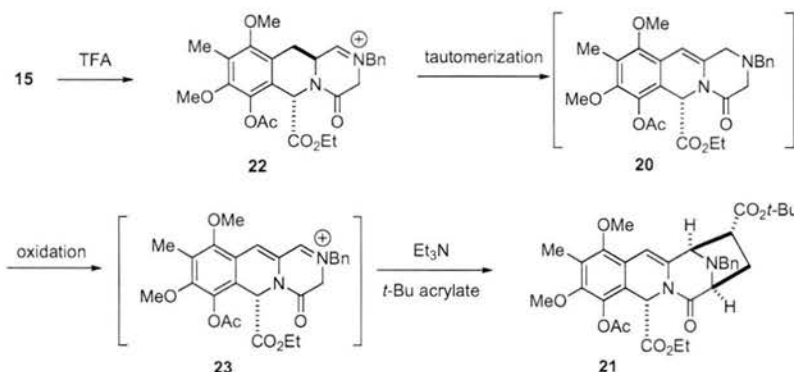
Interestingly and unexpectedly, *N*-*t*-Boc removal from **15** with TFA followed by treatment with triethylamine and *t*-butyl acrylate did not produce the expected cycloadduct but afforded the allylic tertiary amine **20** (11%) and the C₃-C₄ unsaturated tetracycle cycloadduct **21** in 67% yield (Scheme 5). We were able to selectively obtain the unsaturated cycloadduct **21** (80%) by adding TEMPO to promote the oxidation of the allylic amine during the *N*-*t*-Boc removal step. Moreover, treatment of allylic amine

20 with NBS, followed by addition of triethylamine and *t*-butyl acrylate led to the formation of the unsaturated cycloadduct **21** in 35% yield.



Scheme 5. Unexpected formation of the unsaturated tetracycle **21**.

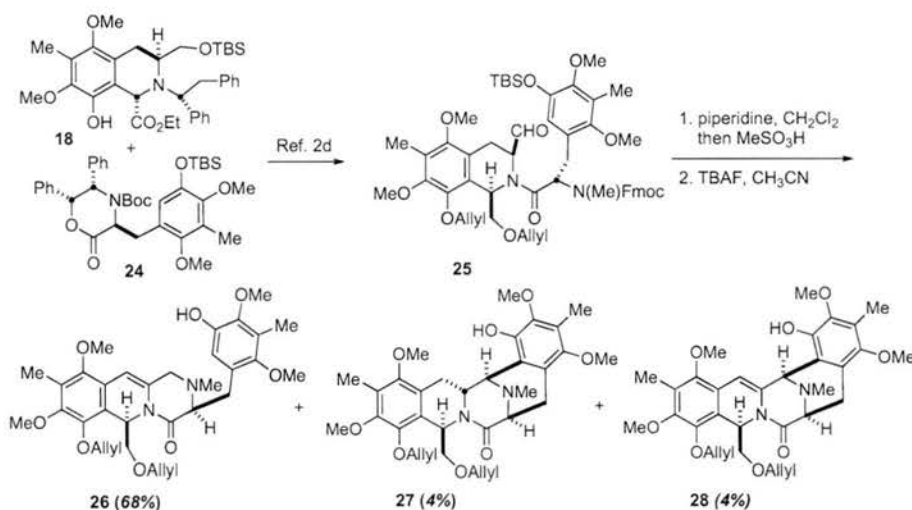
We have rationalized these results as follows: after formation of the iminium ion species **22**, rapid tautomerization led to the formation of **20** that presents a thermodynamically favored benzylic alkene. Spontaneous oxidation of this allylic tertiary amine subsequently occurs and generates the C₃-C₄ unsaturated iminium intermediate **23** that could then be engaged in the [1,3]-dipolar cycloaddition through the incipient azomethine ylide to form the observed C₃-C₄ unsaturated tetracycle **21** (Scheme 6).¹⁴ Zhu recently observed a similar spontaneous air oxidation of an allylic secondary amine to a C₃-C₄ unsaturated species in connection with synthetic studies toward lemonomycin.^{12c}



Scheme 6. Tautomerization/oxidation.

The fortuitous observation of the propensity of such allylic amines to suffer rapid and facile allylic oxidation encouraged us to apply this type of transformation to the pentacyclic framework of cribrostatin 4. The starting point for the synthesis of the allylic amine **26** was the amino aldehyde **25** obtained from tetrahydroisoquinoline **18** and amino acid precursor **24** as reported in our syntheses of 3-*epi*-renieramycin G and 3-*epi*-jorumycin (Scheme 7).^{4d} The *N*-Fmoc protecting group in **25** was removed with piperidine

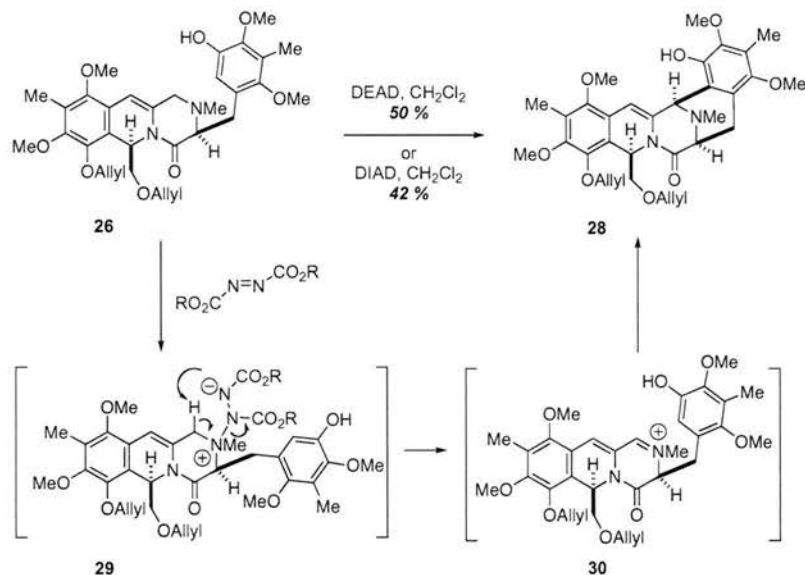
and methanesulfonic acid was subsequently added to promote the formation of the iminium species followed by migration of the double bond to the C₃-C₄ benzylic position. The *O*-TBS protecting group of the eastern phenol was then removed with TBAF to yield 68% of the desired allylic amine **26**, 4% of the 3-*epi*-pentacycle **27**^{2a} and significantly, we isolated 4% of the unsaturated pentacyclic compound **28** (Scheme 7). Moreover, after standing for ten days in an NMR tube in CDCl₃, a 10% conversion of **26** into **28** was also observed.



Scheme 7. Synthesis of allylic amine **26**.

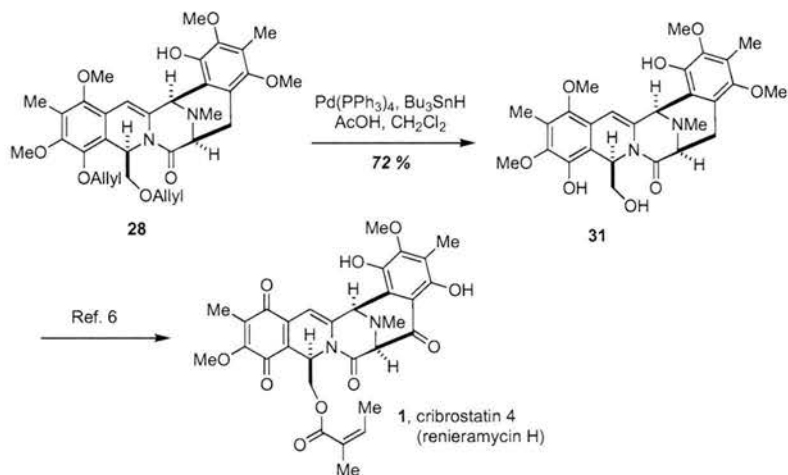
Encouraged by these promising results, we turned our efforts to find more efficient conditions for this oxidation. Numerous methods are described in the literature to form iminium species from tertiary amines.¹⁴ Among them are the Polonovski-Potier reaction,¹⁵ the use of NBS,^{4a-c} K₃Fe(CN)₆,¹⁶ or TPAP-NMO.¹⁷ These methods were all examined but unfortunately each gave mixtures of unidentified products with no attendant formation of pentacycle **28**. As noted above, TEMPO was successful in promoting the formation of the unsaturated skeleton of lemomycin from **15** but here again in this case, only the starting amine **26** was recovered when treated with TEMPO. The literature contains a few reports concerning the oxidation of tertiary amines to iminium ion intermediates mediated by azodicarboxylates, such as DEAD (diethyl azodicarboxylate).¹⁸ Indeed, treatment of **26** with DEAD in CH₂Cl₂ at room temperature for 15 h afforded the pentacycle **28** in 50% yield (Scheme 8). Replacing DEAD by DIAD (di-*isopropyl* azodicarboxylate) also afforded **28** in 42% yield. The mechanism for this oxidation presumably process through nucleophilic attack of the tertiary amine on the diazo bond of the azodicarboxylate species to form the zwitterionic intermediate **29**; subsequent β-H elimination generates

the key iminium ion species **30** immediately followed by cyclization to pentacyclic substance **28** (Scheme 8).



Scheme 8. DIAD-mediated oxidation of allylic amine **26**.

The allyl protecting groups of the phenol and the primary alcohol in **28** were then removed with Pd(PPh₃)₄ in the presence of *tri-n*-butyltin hydride and acetic acid to afford **31** (Scheme 9). As compound **31** constitutes an advanced intermediate utilized successfully in our recent asymmetric total synthesis of cribrastatin **4**, this work thus represents a formal total synthesis of cribrastatin **4**.⁵



Scheme 9. Formal total synthesis of cribrastatin **4**.

In summary, synthetic studies on lemomycin have led to the discovery of a very facile autoxidation of an electron-rich tricyclic dihydroisoquinoline. The incipient iminium ion was converted into an azomethine ylide that underwent 1,3 dipolar cycloaddition with *t*-butyl acrylate. We have thus found that azodicarboxylates can oxidize related tricyclic dihydroisoquinolines to generate synthetically useful amounts of a reactive, incipient iminium ion species that can be trapped in a Pictet-Spengler reaction to furnish the pentacyclic framework of cribrostatin 4. Currently, we are examining the reduction of the C₂₁ amide moiety within this series into carbinolamine analogues (and functional equivalents) of cribrostatin 4, that is anticipated to lead to significantly more potent cytotoxic agents capable of alkylating DNA.

EXPERIMENTAL

General procedures: Unless otherwise noted, materials were obtained from commercially available sources and used without further purification. THF and dichloromethane were degassed with argon and passed through a solvent system (J.C. Meyer of glass Contour). All reactions were conducted with flame- or oven-dried glassware under an inert atmosphere of argon unless otherwise noted. Chromatographic separations were performed with EM Science TLC plates (silica gel 60, F254, 20 x 20cm x 250µm) or with EM Science 230-240 mesh silica gel under positive air pressure. Infrared spectra were recorded on a Perkin-Elmer 1600 series FT-IR as thin films from methylene chloride and are reported as λ_{max} in wavenumbers (cm⁻¹). Nuclear magnetic resonance (NMR) spectra were acquired using Varian 300 or 400 spectrometers. NMR chemical shifts are given in parts per million (ppm) relative to internal CHCl₃, or DMSO. Mass spectra were obtained on Fisons VG Autospec. Optical rotations were obtained on a Rudolph Research automatic polarimeter Autopol III.

Compound 19: To a solution of **18** (6.65 g, 10.70 mmol) in CH₂Cl₂ was added Et₃N (4.5 mL, 32.10 mmol) dropwise at 0 °C followed by AcCl (0.84 mL, 11.8 mmol). After 30 min at 0 °C, the reaction mixture was filtered through silica gel. The filtrate was concentrated under reduced pressure and the crude acetate was used in the next step. A pressure tube containing the crude acetate (7.0 g) in absolute ethanol (280 mL) was purged with argon for 15 min, Pd(OH)₂ (700 mg) added to the mixture and the tube pressurized to 80 psi with hydrogen gas. The tube was then purged another 2 times with hydrogen. After 2 days, the pressure was released and the reaction filtered through a pad of celite. After concentration under reduced pressure, the residue was purified by chromatography (SiO₂, 1:1 hexane:AcOEt) affording the free amine. (1.2 g, 93% yield). $[\alpha]_{\text{D}}^{25} = -20.6$ (c 1.0, CH₂Cl₂). ¹H NMR (300MHz, CDCl₃): δ -0.08 (d, *J* = 4.5 Hz, 6H), 0.91 (s, 9H), 1.26 (t, *J* = 7.2 Hz, 3H), 2.22 (s, 3H), 2.27 (s, 3H), 2.38 (m, 1H), 2.76 (dd, *J* = 3.9, 16.5 Hz, 1 H), 3.20 (m, 1H), 3.58 (m, 1H), 3.73 (s, 6H), 3.80 (dd, *J* = 9.9, 3.3 Hz, 1H), 4.18 (q, *J* =

14.4, 7.2 Hz, 2H), 4.69 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3): δ -5.0, -4.9, 10.1, 14.62, 18.6, 20.8, 25.6, 26.2, 50.5, 55.8, 60.0, 61.0, 61.5, 67.0, 124.2, 124.8, 124.9, 138.1, 148.8, 154.7, 168.4, 172.1; IR (thin film): 2932, 2856, 1770, 1736, 1199, 1109, 837 cm^{-1} . HRMS (FAB+) calcd. for $\text{C}_{24}\text{H}_{40}\text{NO}_7\text{Si}$ (MH^+ , m/z) 482.2574; found 482.2573.

To a solution of the free amine (2.0 g, 4.15 mmol) in CH_2Cl_2 (2 mL) was added EDCI (1.2 g, 6.23 mmol) followed by *N*-Bn, *N*-Boc glycine (2.2 g, 8.3 mmol). After stirring for two and half days, the reaction mixture was diluted with EtOAc (200 mL), washed with water (50 mL) brine (50 mL) and dried (Na_2SO_4). After concentration under reduced pressure, the resulting residue was purified by flash chromatography (SiO_2 , 6:1 hexane:AcOEt) affording **19** (2.9 g, 97% yield). $[\alpha]_{\text{D}}^{25} = +43.7$ (c 1.0, CH_2Cl_2). ^1H NMR (400 MHz, DMSO, 120°C): δ -0.20 (d, $J = 9.8$ Hz, 6H), 0.78 (s, 9H), 1.12 (t, $J = 7$ Hz, 3H), 1.41 (s, 9H), 2.18 (s, 3H), 2.32 (s, 3H), 2.91–3.09 (m, 2H), 3.27 (d, $J = 15.8$ Hz, 2H), 3.69 (s, 6H), 3.85–4.11 (m, 3H), 4.21–4.35 (m, 2H), 4.35 (d, $J = 15.6$ Hz, 1H), 4.47 (d, $J = 15.6$ Hz, 1H), 5.47 (s, 1H), 7.16–7.41 (m, 5H). ^{13}C NMR (75 MHz, CDCl_3 , mixture of rotamers): δ -5.5, -5.3, 10.3, 14.1, 18.5, 21.1, 23.7, 26.1, 28.6, 28.7, 47.9, 51.0, 51.6, 60.1, 61.0, 62.0, 63.3, 63.6, 80.6, 121.9, 123.2, 126.3, 127.5, 127.8, 128.4, 128.7, 137.7, 138.1, 138.3, 150.0, 154.9, 156.1, 168.2, 169.8, 170.1. IR (thin film): 2931, 2857, 1780, 1743, 1703, 1667, 1411, 1120, 1117 cm^{-1} . HRMS (FAB+) calcd. for $\text{C}_{38}\text{H}_{57}\text{N}_2\text{O}_{10}\text{Si}$ (MH^+ , m/z) 729.3783; found 729.3787.

Compound 15: To a solution of **19** (1.08 g, 1.5 mmol) in THF/ MeOH (16 mL/ 1 mL) was added TBAF (1M in THF, 1.8 mL, 1.8 mmol) and the reaction was stirred at rt for 18 h. After this time the reaction was quenched with sat. aq. NH_4Cl (5 mL) and diluted with EtOAc (200 mL). The organic layer was washed with brine and dried (Na_2SO_4). After concentration under reduced pressure the resulting residue was purified by flash chromatography (SiO_2 , 3:1 hexane:AcOEt) affording the desired alcohol (0.82 g, 89% yield). $[\alpha]_{\text{D}}^{25} = +68.8$ (c 1.0, CH_2Cl_2). ^1H NMR (400MHz, DMSO, 120°C): δ 1.13 (t, $J = 6.7$ Hz, 3H), 1.42 (s, 9H), 2.19 (s, 3H), 2.33 (s, 3H), 2.93 (dd, $J = 15, 5.4$ Hz, 1H), 3.10 (bs, 1H), 3.25 (d, $J = 15.7$ Hz, 1H), 3.69 (s, 3H), 3.70 (s, 3H), 3.86–4.10 (m, 2H), 4.14–4.30 (m, 3H), 4.40–4.54 (m, 3H), 5.50 (s, 1H), 7.23–7.38 (m, 5H). ^{13}C NMR (75 MHz, CDCl_3 , mixture of rotamers): δ 10.3, 14.1, 21.1, 23.9, 24.5, 28.6, 28.7, 48.0, 51.1, 52.7, 53.4, 53.5, 60.9, 61.3, 62.2, 63.8, 65.0, 80.9, 121.7, 123.3, 126.4, 127.5, 128.4, 128.7, 137.9, 138.1, 150.2, 154.5, 156.4, 168.1, 170.0. IR (thin film): 3463, 2937, 1778, 1699, 1411, 1200 cm^{-1} . HRMS (FAB+) calcd. for $\text{C}_{32}\text{H}_{43}\text{N}_2\text{O}_{10}$ (MH^+ , m/z) 615.2918; found 615.2912.

To a solution of $(\text{COCl})_2$ (0.17mL, 1.95 mmol) in CH_2Cl_2 (3.2 mL) at -78°C , was added DMSO (0.18 mL, 2.60 mmol) dropwise. After 5 min a solution of the preceding alcohol (400mg, 0.65 mmol) in CH_2Cl_2 (5 mL) was added dropwise. After a further 45 min, Et_3N (0.90 mL, 6.5 mmol) was added to the reaction mixture and it was kept at -78°C for 5 min and then warmed to 0°C . The reaction was then quenched with

sat. aq. NH_4Cl and diluted with CH_2Cl_2 (20 mL). The organic layer was washed with sat. aq. NH_4Cl (3 mL) followed by brine and dried (Na_2SO_4). After concentration under reduced pressure the resulting residue was purified by flash chromatography (SiO_2 , 3:1 hexane:AcOEt) affording **15** (320 mg, 80% yield). $[\alpha]_{\text{D}}^{25} = +50.8$ (c 1.0, CH_2Cl_2). ^1H NMR (400 MHz, DMSO, 120°C): δ 1.13 (t, $J = 7.0$ Hz, 3H), 1.41 (s, 9H), 2.17 (s, 3H), 2.33 (s, 3H), 3.11 (bs, 1H), 3.54 (m, 1H), 3.69 (s, 3H), 3.70 (s, 3H), 3.81–4.02 (m, 2H), 4.02–4.12 (m, 1H), 4.20 (d, $J = 17.0$, 1H), 4.37 (d, $J = 15.6$ Hz, 1H), 4.45 (d, $J = 15.6$ Hz, 1H), 4.97 (br s, 1H), 5.71 (s, 1H), 7.18–7.38 (m, 5H), 9.27 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3 , mixture of rotamers): δ 10.1, 13.9, 14.4, 20.9, 21.0, 22.0, 23.3, 28.5, 29.9, 47.1, 47.8, 50.9, 53.1, 53.4, 53.7, 60.0, 60.3, 60.8, 60.9, 61.1, 62.3, 62.8, 80.9, 81.1, 121.4, 121.8, 122.3, 126.8, 127.7, 128.1, 128.2, 128.6, 128.8, 137.5, 137.9, 150.3, 150.7, 153.9, 155.8, 168.2, 170.0, 173.1, 198.9, 199.3, 201.0. IR (thin film): 3450, 2978, 1776, 1741, 1411, 1200 cm^{-1} . HRMS (FAB+) calcd. for $\text{C}_{32}\text{H}_{41}\text{N}_2\text{O}_{10}$ (MH^+ , m/z) 613.2761; found 613.2765.

Compounds 20 and 21: To a solution of **15** (165 mg, 0.27 mmol) in CHCl_3 (2.7 mL) was added TFA (1.10 mL, 13.50 mmol). The flask was left open to air and then sealed with a glass stopper. After stirring for 3.5 h, the solvent and TFA were removed under reduced pressure and the resulting residue was dissolved with CHCl_3 (2.7 mL). To this reaction mixture was added *t*-butyl acrylate (0.80 mL, 5.40 mmol) and Et_3N (0.37 mL, 2.7 mmol) at 0°C . The reaction was warmed to rt and stirred for 3 h. The reaction mixture was then diluted with EtOAc (20 mL) and washed with saturated NH_4Cl . The organic layer was washed with brine and dried (Na_2SO_4). After concentration under reduced pressure, the resulting residue was purified by flash chromatography (silica, 3:1 hexane:EtOAc) affording **21** (110 mg, 67% yield) and **20** (15 mg, 11%).

21: $[\alpha]_{\text{D}}^{25} = -48.2$ (c 1.0, CH_2Cl_2). ^1H NMR (300 MHz, CDCl_3): δ 1.25 (t, $J = 7.3$ Hz, 3H), 1.44 (s, 9H), 2.13 (dd, $J = 9.7, 13.9$ Hz, 1H), 2.22 (s, 3H), 2.40 (s, 3H), 2.67 (m, 1H), 2.79 (dd, $J = 4.6, 9.5$ Hz, 1H), 3.71 (s, 3H), 3.72 (s, 3H), 3.82 (dd, $J = 7.4$ Hz, 1H), 3.93–4.31 (m, 4H), 4.17 (s, 1H), 5.80 (s, 1H), 6.27 (s, 1H), 7.20–7.43 (m, 5H). ^{13}C NMR (100 MHz, CDCl_3): δ 9.9, 14.2, 21.1, 28.2, 32.1, 50.1, 51.3, 51.6, 60.9, 61.7, 62.3, 63.0, 64.1, 81.5, 97.8, 116.9, 120.9, 126.7, 127.3, 128.4, 128.9, 137.4, 138.2, 138.5, 150.3, 151.2, 168.2, 168.6, 170.9, 171.9. IR (thin film): 2978, 1741, 1692, 1202 cm^{-1} . HRMS (FAB+) calcd. for $\text{C}_{34}\text{H}_{41}\text{N}_2\text{O}_9$ (MH^+ , m/z): 621.2812; found: 621.2805.

20: ^1H NMR (400 MHz, CDCl_3): δ 1.17 (t, $J = 7.3$ Hz, 3H), 2.19 (s, 3H), 2.35 (s, 3H), 3.38–3.61 (m, 4H), 3.65 (s, 2H), 3.68 (s, 3H), 3.69 (s, 3H), 3.95 (m, 1H), 4.15 (m, 1H), 5.81 (s, 1H), 6.34 (s, 1H), 7.24–7.34 (m, 5H). ^{13}C NMR (100 MHz, CDCl_3): δ 9.9, 14.1, 21.1, 50.8, 53.5, 57.5, 60.7, 60.9, 61.5, 62.4, 100.0,

117.6, 120.6, 126.6, 127.9, 128.7, 129.3, 133.1, 136.8, 138.1, 150.3, 151.4, 166.4, 168.1, 168.5. HRMS (FAB+) calcd. for $C_{27}H_{31}N_2O_7$ (MH^+ , m/z): 495.2131; found: 495.2119.

Synthesis of **21** via NBS oxidation of **20** followed by 1,3 cycloaddition: To a solution of **20** (110 mg, 0.22 mmol) in $CHCl_3$ (3 mL) was added NBS (43.5 mg, 0.25 mmol) and the solution was heated to reflux for 45 min. The solution was cooled to $0^\circ C$ and *t*-butyl acrylate (660 μL) was added followed by the dropwise addition of a solution of Et_3N (245 μL , 1.76 mmol) in CH_2Cl_2 (850 μL). The reaction mixture was stirred for 3 h at rt. The solvent was then removed under reduced pressure. The crude material was diluted with CH_2Cl_2 (5 mL) and then washed with sat. aq. $NaHCO_3$ (5 mL). The organic layer was dried with Na_2SO_4 . After concentration the residue was purified by chromatography to afford **21** (48.2 mg, 35%).

Compound 26: To a solution of **25** (55 mg, 0.0580 mmol) in CH_2Cl_2 (4 mL) under argon was added piperidine (57 μL , 0.0580 mmol) and the reaction was stirred for 15 h at rt. Methansulfonic acid (150 μL) was subsequently added and the reaction was stirred at rt for an additional 2 h. The reaction mixture was then quenched with sat. aq. $NaHCO_3$ (5 mL) and diluted with CH_2Cl_2 (5 mL). The aqueous layer was washed with CH_2Cl_2 (2 x 5 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated. The crude mixture obtained was then diluted in CH_3CN (4 mL) and TBAF (30 mg, 0.115 mmol) was added. The reaction mixture was stirred for 2 h at rt and then quenched with sat. aq. NH_4Cl (5 mL) and diluted with EtOAc (5 mL). The aqueous layer was extracted with EtOAc (2 x 5 mL) and the combined organic phases were dried (Na_2SO_4). After concentration under reduced pressure the resulting residue was purified by flash chromatography (SiO_2 , 1:1 hexane:EtOAc) affording 2.7 mg of a 1:1 mixture of **27** (4%) and **28** (4%) along with the pure desired allylic amine **26** (23.5 mg, 68% yield) as a yellow oil. $[\alpha]_D^{25} = +118.4$ (c 0.25, CH_2Cl_2). 1H NMR ($CDCl_3$, 300 MHz): 2.17 (s, 3H), 2.23 (s, 3H), 2.36 (s, 3H), 3.24-3.04 (m, 2H), 3.38 (dd, $J = 11.1, 3.9$ Hz, 1H), 3.66-3.56 (m, 2H), 3.69 (s, 3H), 3.71 (s, 3H), 3.76-3.72 (m, 1H), 3.77 (s, 3H), 3.79 (s, 3H), 3.98-3.90 (m, 2H), 4.21 (dd, $J = 12.6, 5.4$ Hz, 1H), 4.58-4.53 (m, 2H), 5.14 (dd, $J = 10.5, 1.8$ Hz, 1H), 5.29-5.22 (m, 2H), 5.43 (dd, $J = 16.8, 1.8$ Hz, 1H), 5.59 (br s, 1H), 5.87 (s, 1H), 5.94-5.81 (m, 1H), 6.13 (dddd, $J = 16.5, 10.8, 5.8, 5.4$ Hz; 1H), 6.38 (dd, $J = 8.7, 3.8$ Hz, 1H), 6.81 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): 9.4, 10.0, 31.5, 42.1, 46.4, 51.0, 60.4, 60.8, 60.9, 61.4, 66.7, 69.9, 71.7, 74.2, 101.2, 113.8, 117.2, 117.9, 120.3, 121.3, 124.4, 125.2, 128.2, 130.9, 134.2, 134.8, 144.4, 144.7, 145.2, 149.3, 150.6, 168.8. TLC: $R_f = 0.65$ (SiO_2 , 1:3 hexane:EtOAc). IR (thin film): 3386, 2936, 2854, 1673, 1634, 1462, 1415, 1239, 1109, 1061, 1007. HRMS (FAB+) calcd for $C_{33}H_{43}N_2O_8$ (MH^+ , m/z) 595.3019; found 595.3017.

Compound 28: To a solution of **26** (17.0 mg, 0.029 mmol) in CH_2Cl_2 (4 mL) was added a solution of DEAD (40% in toluene) (26 mg, 0.06 mmol) in CH_2Cl_2 (0.3 mL) over 15 min and the reaction was stirred for 5 h at rt. TLC showed that the reaction was not complete and again, a solution of DEAD (40% in toluene) (25 mg, 0.06 mmol) in CH_2Cl_2 (0.3 mL) was added over 15 min and the reaction was stirred for 15 h at rt. The reaction mixture was then quenched with sat. aq. NaHCO_3 (4 mL) and diluted with CH_2Cl_2 (2 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 4 mL) and the combined organic phases were dried (Na_2SO_4). After concentration under reduced pressure the resulting residue was purified by Preparative TLC (SiO_2 , 3:7 hexane:AcOEt) affording the desired unsaturated pentacycle **28** (8.5 mg, 50%) as a yellow film. $[\alpha]_{\text{D}}^{25} = +3.5$ (c 0.28, CH_2Cl_2). ^1H NMR (CDCl_3 , 300 MHz): 2.17 (s, 3H), 2.19 (s, 3H), 2.54 (s, 3H), 3.10-2.98 (m, 2H), 3.20-3.12 (m, 2H), 3.41-3.25 (m, 2H), 3.65 (s, 3H), 3.72-3.69 (m, 1H), 3.73 (s, 3H), 3.75 (s, 3H), 3.76 (s, 3H), 4.51 (app d, $J = 5.8$ Hz, 2H), 4.63 (s, 1H), 4.91-4.83 (m, 2H), 5.41-5.21 (m, 3H), 5.55 (s, 1H), 6.09 (dddd, $J = 17.1, 10.5, 5.8, 5.8$ Hz, 1H), 6.19 (dd, $J = 7.5, 3.9$ Hz, 1H), 6.26 (s, 1H). ^{13}C NMR (CDCl_3 , 75 MHz): 9.4, 9.7, 28.9, 41.7, 46.9, 56.4, 60.2, 60.4, 60.8, 61.0, 61.4, 70.1, 71.9, 74.2, 102.5, 116.4, 117.9, 119.7, 120.3, 121.4, 122.2, 122.9, 125.1, 132.4, 134.2, 135.1, 142.2, 143.8, 144.7, 149.6, 149.9, 150.7, 168.2. TLC: $R_f = 0.35$ (SiO_2 , 1:3 hexane:EtOAc). IR (thin film): 3306, 2930, 2851, 1675, 1637, 1463, 1414, 1108, 1058, 1005 cm^{-1} . HRMS (FAB+) calcd for $\text{C}_{33}\text{H}_{41}\text{N}_2\text{O}_8$ (MH^+ , m/z) 593.2863; found 593.2847.

Compound 31: To a solution of **28** (5.0 mg, 0.00840 mmol) in CH_2Cl_2 (1 mL) was successively added AcOH (7.5 mg, 0.126 mmol), $\text{Pd}(\text{PPh}_3)_4$ (5 mg, 0.00433 mmol), and Bu_3SnH dropwise (17.7 μL , 0.0672 mmol). The reaction was stirred 2 h, then quenched with sat. aq. NaHCO_3 (3 mL) and diluted with CH_2Cl_2 (3 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 3 mL) and the combined organic phases were dried (Na_2SO_4). After concentration under reduced pressure the resulting residue was purified by Preparative TLC (SiO_2 , AcOEt) affording the desired triol **31** (3.1 mg, 72%) as a white film. $[\alpha]_{\text{D}}^{25} = +5.3$ (c 0.15, CH_2Cl_2). ^1H NMR (300 MHz, CDCl_3): 1.80 (br, 1H), 2.19 (s, 6H), 2.54 (s, 3H), 3.20-3.15 (m, 3H), 3.31 (dd, $J = 10.3, 5.1$ Hz, 1H), 3.62 (s, 3H), 3.70 (s, 3H), 3.72 (s, 3H), 3.73 (s, 3H), 3.73-3.70 (m, 1H), 4.65 (s, 1H), 5.61 (s, 1H), 5.75 (br, 1H), 6.10 (dd, $J = 6.9, 5.1$ Hz, 1H), 6.27 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3): 9.9, 29.4, 41.7, 49.3, 56.5, 60.4, 60.8, 61.0, 61.1, 61.7, 64.5, 102.9, 114.3, 119.4, 119.9, 121.7, 123.4, 124.0, 132.1, 142.0, 142.3, 144.1, 147.2, 149.9, 169.3. IR (thin film): 3345, 2930, 2855, 1633, 1465, 1414, 1308, 1257, 1107, 1054, 1003, 798, 736. HRMS (FAB+) calcd for $\text{C}_{27}\text{H}_{33}\text{N}_2\text{O}_8$ ($\text{M}+\text{H}^+$, m/z) 513.2236; found 513.2237. This substance proved to be identical to that obtained by a distinct route previously.⁶

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