SYNTHETIC STUDIES TOWARD SELECTED MEMBERS OF THE PYRROLE-IMIDAZOLE ALKALOIDS: AXINELLAMINE, KONBU'ACIDIN AND PALAU'AMINE

A Dissertation

by

MANUEL ZANCANELLA

Submitted to the Office of Graduate Studies of
Texas A&M University
in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

August 2010

Major Subject: Chemistry

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Approved by:

Chair of Committee,	Daniel Romo
Committee Members,	David E. Bergbreiter
	Daniel A. Singleton
	Thomas D. McKnight
Head of Department,	David H. Russell

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ABSTRACT

Synthetic Studies Toward Selected Members of the Pyrrole-imidazole Alkaloids: Axinellamine, Konbu'acidin and Palau'amine.

(August 2010)

Manuel Zancanella, B.S., University of Texas at Tyler

Chair of Advisory Committee: Dr. Daniel Romo

The pyrrole imidazole alkaloids (PIA) is an ever-growing family of structurally related natural products isolated from several species of sponges which now features more than one hundred memebrs. Their complex molecular architectures, and in some cases, significant biological activities, have made these alkaloids the synthetic targets of a number of research groups across the world. In our approach, following early biosynthetic proposal by Kinnel and Scheuer and Al-Mourabit and Potier, it was envisioned that several of these alkaloids, namely palau'amine, axinellamine, konbu'acidin, styloguanidine and massadine, could be derived from a common chlorocyclopentane precursor through different modes of intramolecular cyclization.

Building on the work done previously in our research group by Dr. Anja Dilley, Dr. Paul Dransfield, and Dr. Shaohui Wang, my investigations led to the synthesis of the angular *aza*-triquinane core of axinellamine and the peculiar *trans*-azabicyclo[3.3.0]octane core of palau'amine. In my further studies mono- and bis-pyrrole advanced intermediates were synthesized that contain *the complete carbon framework* of the target natural products. However, attempts to induce the pivotal, potentially biomimetic cyclizations expected to deliver the cores of the target alkaloids proved to be rather challenging, resulting in inconsistent and irreproducible results and leading to the exploration of an alternative, "abiotic" approach.

My efforts in this direction resulted in the synthesis of a pentacyclic enamine precursor to styloguanidine and a pentacyclic carbinolamine suitable for the synthesis of palau'amine. Final attempts to complete the target natural products were however unsuccessful.

DEDICATION

To my mother, Annamaria

"…fatti non foste a viver come bruti,
ma per seguir virtute e canoscenza"

Dante Alighieri, *The Divine Comedy*,
Canto XXVI, *118-120*.

ACKNOWLEDGEMENTS

I would like to thank my advisor Prof. Daniel Romo for the opportunity and both, for the challenge of my project, and for the unwavering guidance through it. Working in his lab has been a privilege and a pleasure. I thank him also for welcoming my family and I into his house for much needed breaks from chemistry.

My deepest gratitude goes to my committee members, Prof. David Bergbreiter, Prof. Daniel Singleton and Prof. Thomas McKnight. Although our interactions during my graduate career have been brief, they have been very significant. I am especially grateful to Prof. McKnight for agreeing to serve on my committee with virtually no notice. Sincere thanks also to Prof. Brian Connell and Prof. Jiong Yang; Friday's joint group meetings have been an invaluable learning experience.

My gratitude and admiration go to Dr. Anja Dilley and Dr. Paul Dransfield; in my world they are the true giants whose shoulders I stood on. I did not have the pleasure to personally interact with Dr. Dilley, however her pioneering efforts provided a solid foundation for my work and are deeply appreciated. I was on the other hand, immensely fortunate in my graduate studies to be taken under the wings of Dr. Dransfield and Dr. Andy Mitchell, both of whom are brilliant chemists, inspiring mentors and above all, true friends. Maybe one day Andy, you will use your outstanding teaching abilities to help me make some sense of college football rankings.

I am very grateful to the many collaborators I had the fortune to work with throughout the years: Dr. Liang Tang, Dr. Shaohui Wang and especially Dr. Yonggang Wang. I am truly humbled by the quality of his work and by the depth of his chemical insight. I could not have hoped for a better teammate. I would also like to acknowledge the significant contributions of several undergraduate collaborators who did the "dirty" work of providing large amounts of starting materials under my tyranny. Randy Suders, Louis Robinett, and Alice Cole, your help was invaluable, and I hope that maybe you learned something along the way as well.

My deepest appreciation is also extended to other "seniors" in the lab who led by example, including Dr. Ke "Mister" Kong and Dr. Richard Duffy, and the post-docs Dr.

Ziad Moussa and Dr. Gil Ma, for helping me become a better researcher. Much gratitude goes to my peers for sharing the graduate journey with me, making it an enjoyable and rich experience. Thanks in particular to Kay Morris and Henry Nguyen in the Romo group and others who chose different paths, especially Todd Hudnall, Chris Dorsey, Nathan Rife and Brandon Chance.

Thank you also to all other fellow group members, past and present for their help, encouragement, insight, and definitely for the fun; Dr. Sung Wook Cho, Dr. Vikram Purohit, Gang Liu, Supakarn "Ta" Chamni, JC Reyes, and more recently Morgan Shirley, Dr. Caroline Leverett, Dr. Omar Robles, Dr, Chunxiao Xu, Dr. Fang Li, Mikail Abbasov, Alfred Tuley and Kevin Arendt.

A very special thanks to my "neighbor" and fellow coffee-drinker Dr. Changsuk "Chef" Lee. My time in the lab would definitely not have been the same without him. I am forever in awe of his knowledge of Asian cuisine and Japanese animation. To you, my friend, I say "*Ban-kai!*" and best of luck.

Thank you to my mother, Annamaria for instilling in me the love of learning and for always encouraging me to go "the extra mile" in the quest for knowledge. Though thousands of miles away, her presence is as strong as ever. Thanks to my father, Antonio, for teaching me that it is never too late to make a change, and for far more than his financial support throughout the years.

A heartfelt thank you to Mr. George Mayes, who solemnly promised to kick my behind if I ever quit. George, I am glad you don't have to do that.

Finally, there are no words that can appropriately describe the love, trust and support that my wife, Julie, has given me throughout the years. I could not, and I would not have done this without you. You are my anchor to sanity and you know that I would be "sad and lonely" without you.

Lastly, thank you to my daughter Sarah, for making me discover emotions I did not know I could have. Maybe one day you will read this and understand what daddy was doing when he was not home.

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CHAPTER I

INTRODUCTION: ENANTIOSELECTIVE SYNTHESES OF THE PYRROLE-IMIDAZOLE ALKALOIDS

1.1 Structural Diversity and Biosynthesis of the Pyrrole-Imidazole Alkaloids

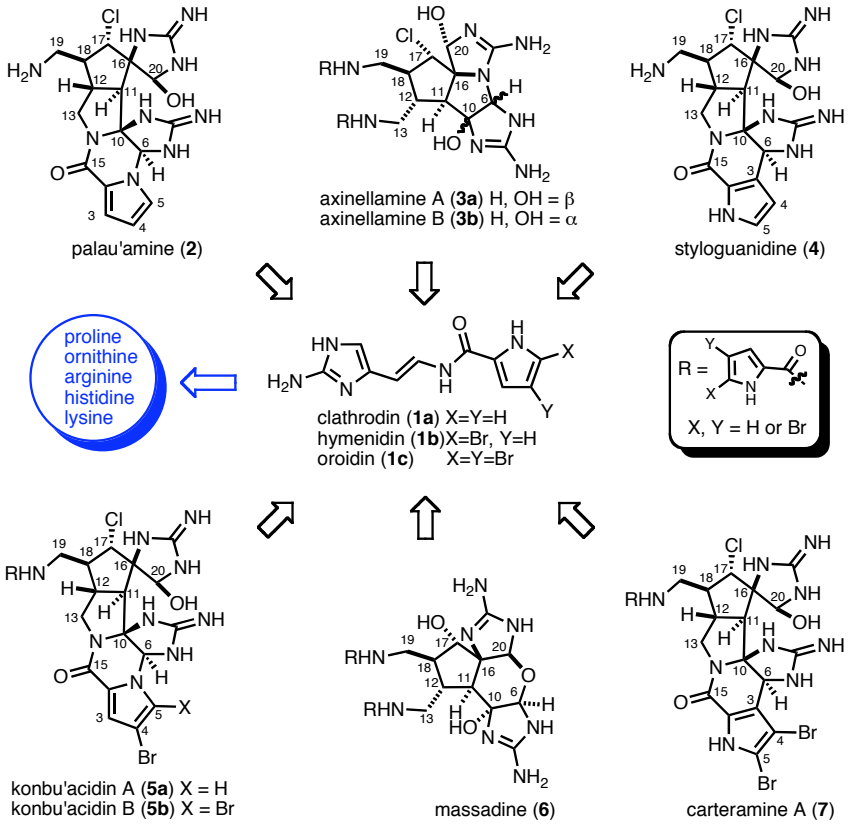


Figure 1.1. Structural complexity and common descent of selected pyrrole-imidazole alkaloids.

The pyrrole-imidazole alkaloids (PIAs henceforth) constitute a biogenetically unique family of natural products, which to date have been isolated exclusively from several species of marine sponges. A small sampling of theses metabolites, relevant to the present work is shown above.

This dissertation follows the style of the *Journal of Organic Chemistry*.

Already numbering more than one hundred and fifty members, new congeners continue to be detected and characterized while at the same time known metabolites are isolated from new sources, and their intriguing structural complexity, rich and compact stereochemical content, high N to C ratio (~1:2), and increasingly studied biological activities are attracting a growing number of researchers from numerous disciplines world-wide.

It has been proposed that the more complex members of this family are forged in nature *via* dimerization and additional intramolecular cyclization events of oroidin and congeners (**1a-c**), derived in turn from naturally occurring aminoacids [1] (Figure 1.1), giving rise to a great number of diverse constructs. This presumed biosynthetic common descent is one of the guiding principles of our strategy for the synthesis of selected PIAs (*vide infra*).

While biosynthetic details are completely lacking, biomechanistic analysis of isolated PIAs and successful synthetic strategies premised on speculative biosynthetic pathways have provided some indirect evidence regarding biosynthetic feasibility. Insofar that inherent reactivity of biosynthetic intermediates may offer clues about actual biosynthetic pathways, isolation of an increasing number of putative biosynthetic intermediates has also been extremely important in developing biogenetic hypotheses. The evolution of these pathways appears to be based in large part on the very interesting ambivalent reactivity embedded in the 2-aminoimidazole nucleus (Figure 1.2). Thus, great efforts have been devoted to unveiling the mechanistic and stereochemical details of reactions involving these pivotal intermediates.

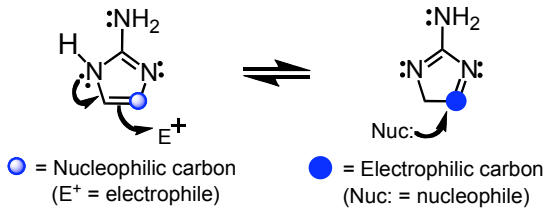
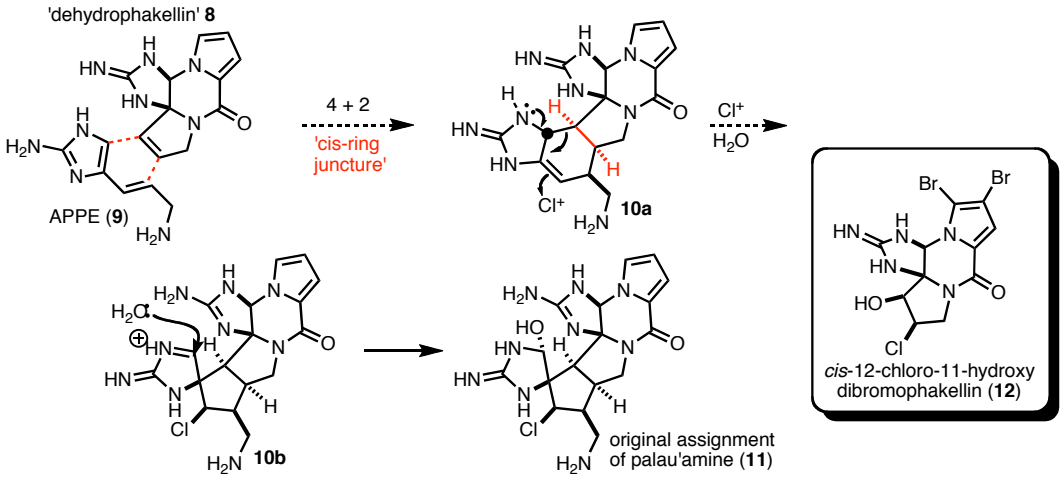


Figure 1.2. Dual reactivity of the common 2-aminoimidazole nucleus found in the PIAs.

The chemical reactivity and hypothetical chemical pathways leading to complex PIA metabolites were reported by Al-Mourabit in 2001.[2] Extension of these hypotheses to include stereochemical relationships, especially in light of the structural revision of palau'amine (discussed in Chapter II)[3] and extension to the recently isolated tetrameric PIA members, was reported by Köck and Baran in a 2007 mini-review.[4] In addition, several review articles have compiled synthetic advances within the PIA metabolites and partial descriptions of biosynthetic aspects of selected members of this family.[5]

One of the first biosynthetic proposals for the generation of higher order PIA however was advanced by Kinnel and Scheuer[6] who envisioned a Diels-Alder cycloaddition between a hypothetical 'dihydrophakellin' dienophile and aminoimidazolyl propeneamine (AAPE). A subsequent chloroperoxidase-initiated oxidation/ring-contraction event would deliver the hexacyclic core of the originally assigned structure of palau'amine (**11**).[7] In addition, the isolation of *cis*-12-chloro-11-hydroxybromoisophakellin (**12**)[8] resulting from chlorohydration of the hypothetical 'dihydrophakellin' which would serve as a dieneophile in the proposed Diels-Alder reaction, seemed to support this hypothesis.

Scheme1.1



However, it should be noted that the *cis*-stereochemistry of the chlorohydrin found in this metabolite suggests chlorohydroxylation of the *trans*-alkene found in oroidin

followed by cyclization to the phakellin core and points to an alternative Diels-Alder process. Indeed, the revision of the azabicyclo[3.3.0]octane core of palau'amine to the *trans*-ring fusion[3] suggested that if a [4+2] cycloaddition does occur to deliver a cyclohexene adduct intermediate, it must involve a non-cyclic dienophile (*e.g.* oroidin) possessing an *E* olefin geometry to provide the observed *trans* relative stereochemistry common to several higher order PIAs (*vide infra)*.

The landmark universal chemical pathway for the formation of higher PIA members known up to 2000, proposed by Al-Mourabit and Potier[2] and subsequent refinements thereof (*vide supra*), involves the dimerization of clathrodine (**1a**) (and brominated derivatives) tautomers, and the decisive first C-C bond establishes the propensity for numerous cascades of cyclization reactions with nucleophilic and electrophilic reacting position varying with the tautomer engaged in the dimerization step.

Recently, based on DFT and *ab initio* calculations Zipse advanced some doubts about the purported stability of some of these tautomers, thereby questioning their involvement in biosynthetic reactions,[9] however, the fact that all the dimeric PIAs isolated during the last decade fit in the general chemical pathway suggested for their formation, seems to attest to the soundness of this proposal. In addition, the revision of palau'amine's relative configuration gave even more consistency to the hypothesis, revealing complete uniformity of stereochemical relationships within the PIA dimer subclass.

Among the possible first C-C dimerization bonds, a C7-C7' dimer[1] provides the highest potential for the generation of the greatest structural diversity, and when analyzing various congeners having a C7-C7' connection (C12-C18 bond in the dimeric PIAs), it appears that all could be derived from intermediates A and B (Scheme 1.2) via different modes of intramolecular oxidative cyclizations.

Intermediate A could undergo an enzymatic chloro-hydroxylation, followed by intramolecular cyclization generating intermediate B, establishing the common

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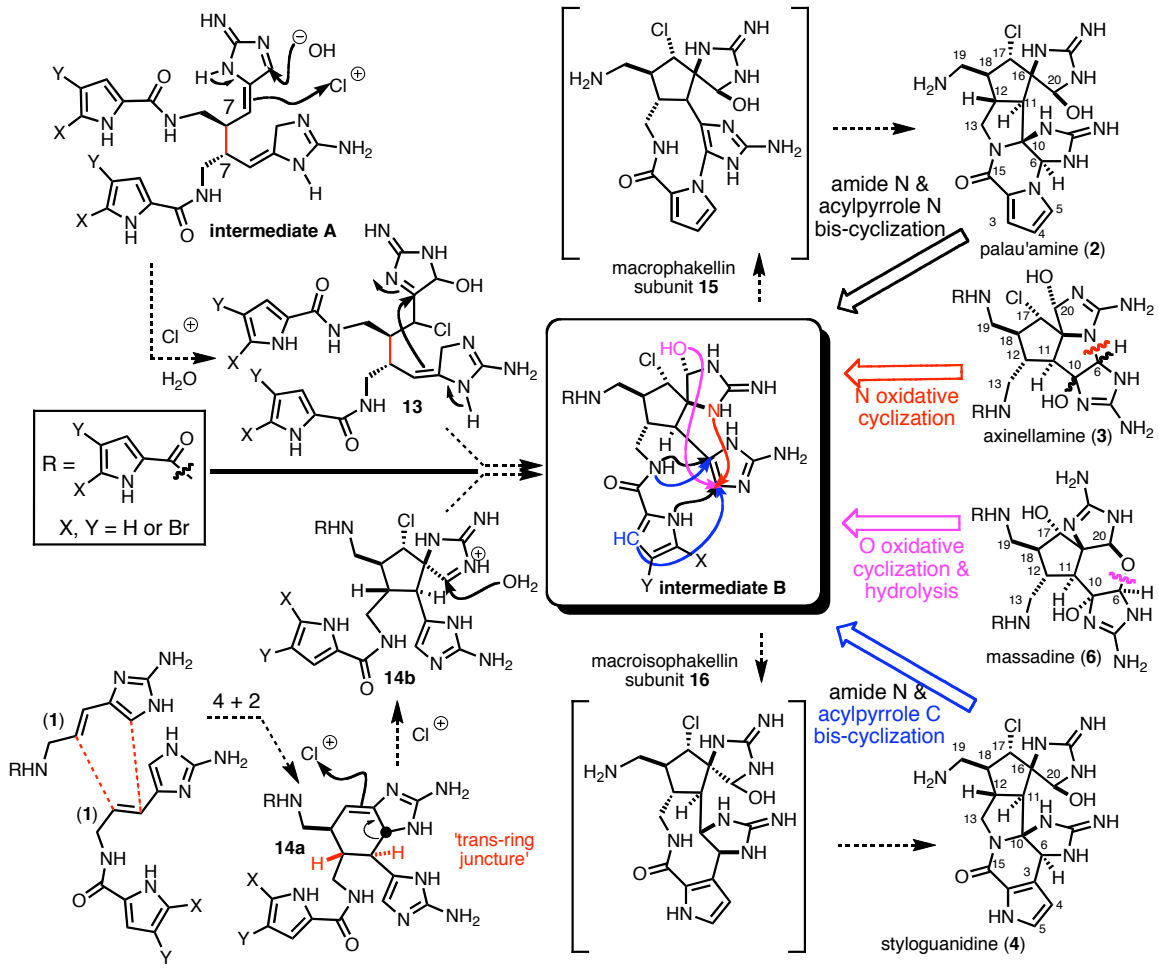
[1] The numbering of the linear precursors differs from the numbering of the PIA dimers. Throughout this document the original palau'amine numbering system[7] will be used for the dimeric PIAs.

spirocyclic subunit. The different modes of proposed oxidative cyclizations summarized below, would then deliver the variety of complex molecular architectures observed in these metabolites. In particular, oxidative cyclization of the spiroguanidine hemiaminal nitrogen onto the pendant aminoimidazole would give rise to the structure of axinellamine (**3**), while attack of the C20 oxygen in a similar fashion would generate massadine (**6**), after hydrolysis (*vide infra*). Alternatively, a bis-cyclization of the C12 pyrrole carboxamide side chain would deliver palau'amine (**2**) (N14, N1 cyclization) and styloguanidine (**4**) (N14, C3 cyclization). Whether these transformations occur in a concerted fashion or proceed instead through the fleeting macrocyclic intermediates **15** and **16** remains the subject of speculation.

Scheme1.2

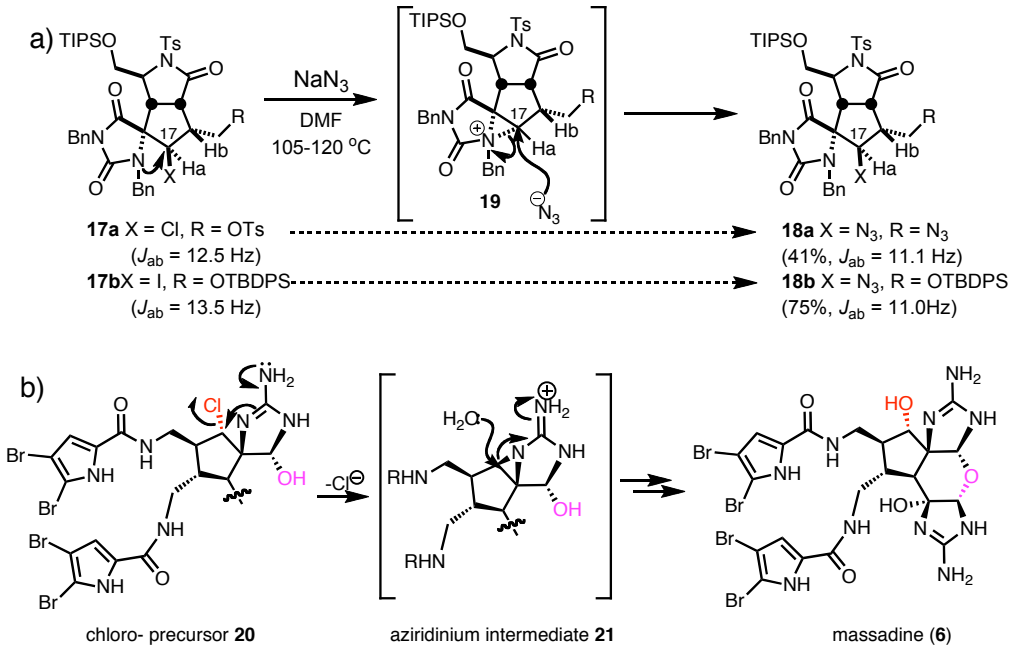


Differing only at the C19 amine terminus and in the bromine content, konbu'acidin and carteramine (Figure 1.1) would be derived in a similar fashion as palau'amine and styloguanidine respectively, from the halogenated clathrodine analogs.

Finally, it is important to note that intermediate B, putative common precursor to several higher order PIAs, could also be derived *via* a variation of the "Diels-Alder"/oxidative ring contraction sequence posited by Kinnel and Scheuer involving two units of the linear precursors.

In the dimeric PIA subclass, massadine (**6**) stands out, as it is the only metabolite featuring a pyran core and a hydroxy substituent in place of the otherwise ubiquitous chlorine. In spite, or perhaps because of this apparent oddity, speculations on its biogenesis were rather scarce, until in 2006 our group reported that an unexpected displacement of the chloride on cyclopentanes **17** by azide surprisingly proceeded with retention of configuration.[10] It was concluded that a mechanism involving neighboring group participation of the spiroaminoimidazole might be in operation involving aziridinium species **19**. It was also postulated that a similar process could account for the biosynthesis of massadine (**6**) from an earlier chlorinated precursor **20**, through a similar aziridinium intermediate **21** (Scheme 1.3).

Scheme 1.3



Confirmation of this hypothesis came in 2007 when Baran and Köck provided direct evidence for this pathway by isolating one such chlorinated precursor and reporting its rapid conversion into massadine (**6**) in an aqueous medium at 60 ºC. They also advanced an excellent analysis as to the reason why this peculiar behavior is not observed in any other PIA metabolite, namely due to the favorable geometrical disposition and the dihedral angle between the aminoimidazole nitrogen and the chlorine atom.[11]

1.2 Enantioselective Syntheses of the Pyrrole-Imidazole Alkaloids

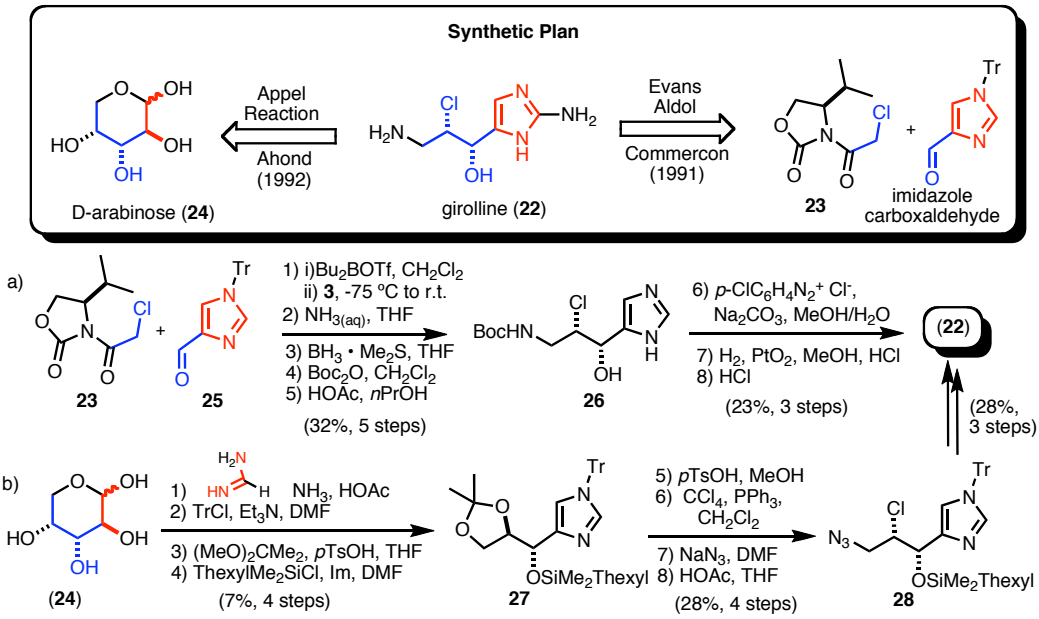
Given the immense structural diversity and architectural complexity of the PIAs, it is understandable that efforts toward the asymmetric, total synthesis of these marine alkaloids have been a very prolific domain of study for chemical synthesis. Numerous synthetic groups continue to be active in the area and a significant amount of progress has been achieved recently, including the first completed enantioselective syntheses of monomeric PIAs and racemic syntheses of long elusive, complex dimeric alkaloids. A detailed and exhaustive account of the synthetic endeavors in this area goes beyond the scope of the present review, however mention must be made of the outstanding contributions by Overman,[12] Horne,[13] Carreira,[14] Otha,[15] Lovely,[16] Harran,[17] and Chen,[18] along with many others, whose asymmetric syntheses are discussed herein. In addition, interesting methodologies leading to the construction of key structural subunits of these alkaloids have been presented by Gin,[19] Gleason,[20] and Nishizawa.[21] Furthermore, a majority of the synthetic work toward the PIAs is the subject of several recent reviews.[5]

The enantioselective synthesis of natural products is paramount to subsequent studies of bioactivity including pharmacology, cellular receptor isolation, and structure-activity studies (SAR) for potential drug discovery and development. For this reason only enantioselective routes to PIA's are described herein with the exception of the landmark synthesis of racemic palau'amine.

One of the earliest marine PIAs isolated is girolline (**22**) in 1988[22] (a.k.a. girodazole), which despite lacking a pyrrole sub-unit is always included in any discussion about PIAs as it is proposed to be derived from the same simple precursor to many of the more complex alkaloids in this family.[1] Shortly after its isolation, synthetic efforts by Ahond and Commerçon led to the elucidation of the absolute configuration of girolline.

In his approach Commerçon[23] employed an Evan's aldol strategy to establish the chlorohydrin relative and absolute stereochemistry. Subsequently, Ahond and Poupat[24] disclosed a chiral pool approach that generated the target stereochemical relationship via elaboration of *D*-arabinose (**24**).

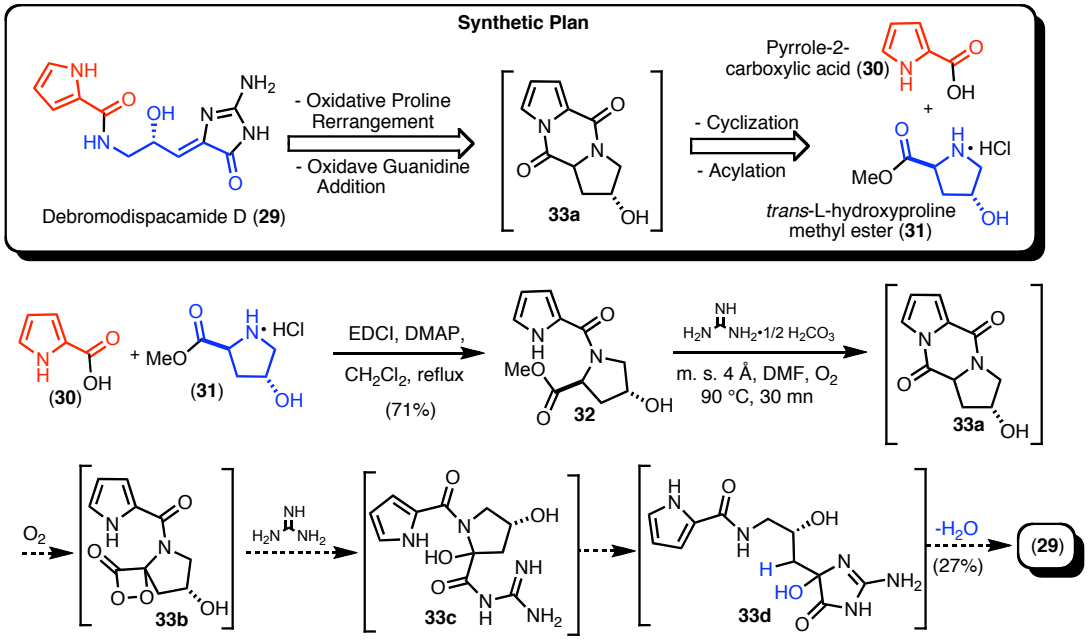
Scheme 1.4



Despite several completed syntheses, many of the simpler "linear" PIAs either lack any stereogenic centers (*e.g.* oroidin and analogues) or are naturally occurring as racemates (*e.g.* midpacamide, [25] dispacamides C and D, [26] and tauroacidin B [27]). Yet other hydroxylated metabolites which showed optical rotation were revealed, upon further investigation, to exist as non-racemic mixtures of enantiomers like tauroacidin A[27] and mukanadin A (which, despite having been isolated two years later is identical to dispacamide D).[28] Debromodispacamide D (**29**) possessing a single carbinol stereogenic center was also isolated as a racemate, and its synthesis in optically active form starting from hydroxyproline (Scheme 1.5)[29] and subsequent stability studies were instrumental in confirming that racemization does not occur during the purification process. The key step was an intriguing, presumably biomimetic oxidative reaction that generated the

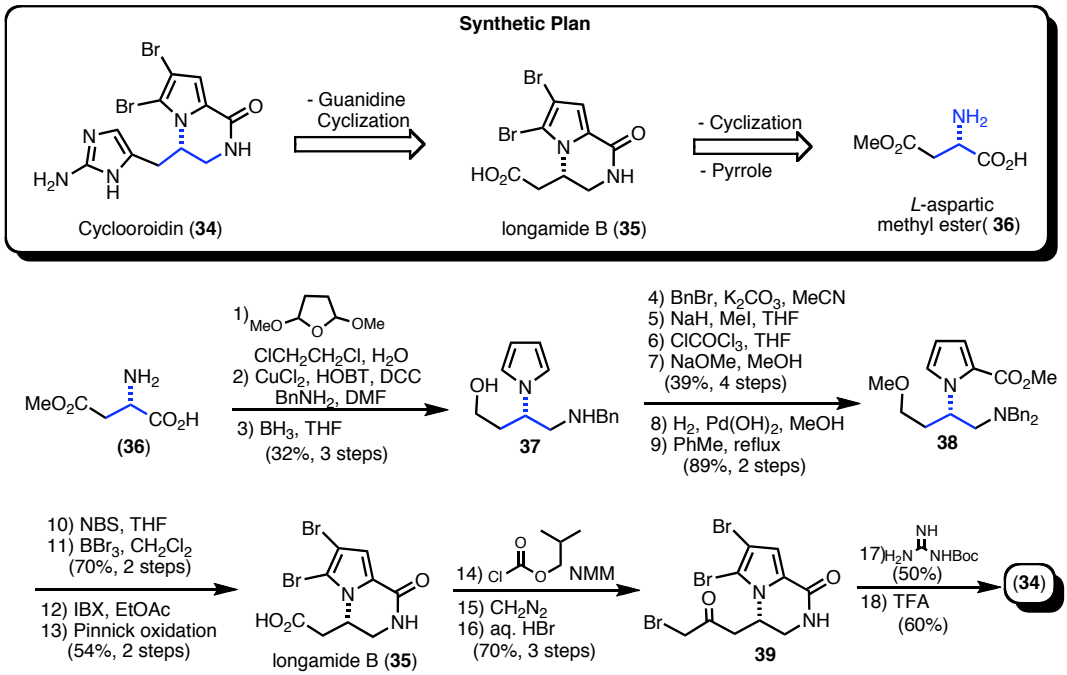
aminoimidazolone moiety *via* the fragmentation of a proposed spirocyclic dioexetanone (**33b**) intermediate.

Scheme 1.5



A presumed intramolecular oxidative cyclization introduces elements of stereochemistry also in cyclooroidin (**34**) and in the slagenins (**40**). After two racemic syntheses, the absolute configuration of natural cyclooroidin was confirmed by synthesis in 2006 by Pelloux-Leon and Minassian, [30] expanding on their previous synthesis of the related longamide B (**35** Scheme 1.6). [31] After conversion of the carboxylate moiety in this natural product into the corresponding mixed anhydride, sequential treatment with diazomethane and aqueous hydrogen bromide delivered the optically active bromoketone **39**. Subsequent reaction with Boc-guanidine generated the aminoimidazole ring, and cleavage of the carbamate protecting group delivered the target product.

Scheme 1.6

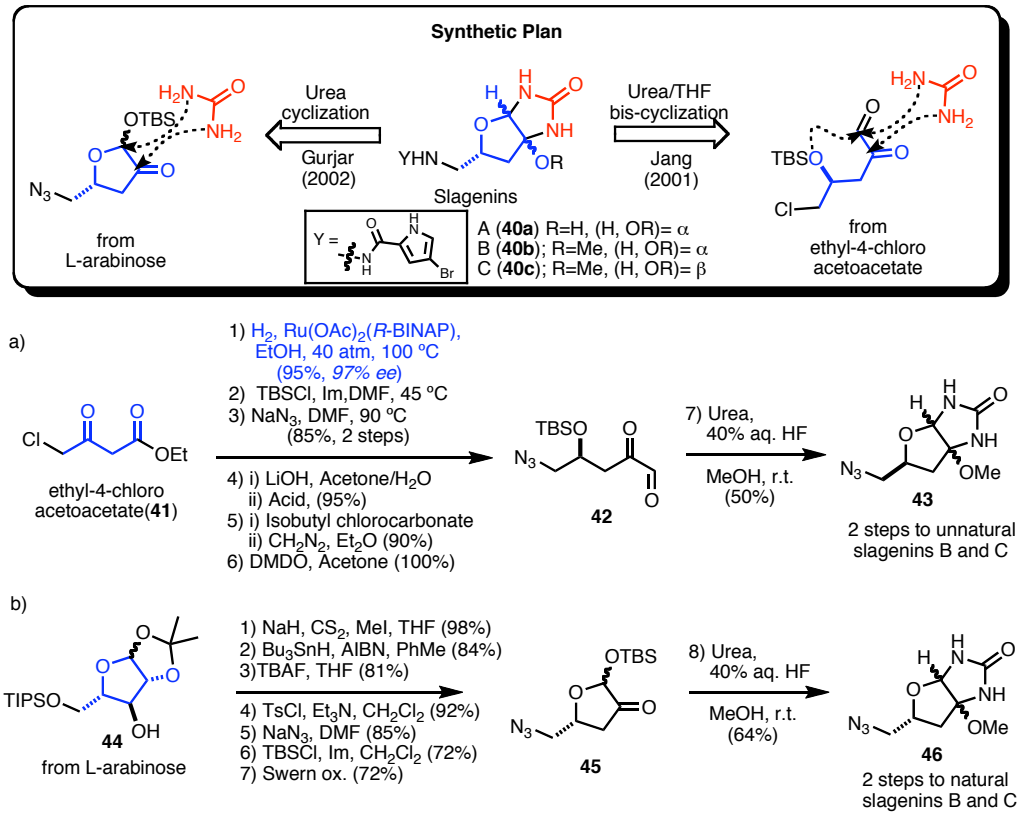


The absolute configuration of the slagenins (**40**) was established by Jang, who completed the first total synthesis of the antipodes of natural slagenins B and C (Scheme 1.7a). [32] After Noyori reduction of ethyl-4-chloroacetoacetate (**41**), the newly generated alcohol was protected as the TBS ether. Azide displacement of the terminal chloride, was then followed by conversion of the ethyl ester to glyoxal 4**2**. One pot intermolecular urea cyclization/intamolecular THF annulation then generated a 50% yield of a 9:5 (H, OMe α to β) mixture of inseparable diastereomeric bicyclic cores of the target products **43**. Finally, azide reduction and acylation of the resulting primary amines delivered the slagenins antipodes, which could be separated by column chromatography.

The following year Jang[33] and Gurjar[34] independently but virtually simultaneously arrived at the synthesis of the natural enantiomers starting from *L*-xylose (not shown) and *L*-arabinose (Scheme 1.7b) respectively. In Gurjar's approach starting from known L-arabinose derivative **44**, Barton-McCombie deoxygenation of the free hydroxyl, was followed by azide displacement on the activated primary alcohol and selective protection

and oxidation to generate the 2-ulose derivative **45**. Intermolecular urea cyclization in the presence of hydrogen fluoride and methanol, then generated an inseparable mixture of the bicyclic cores of natural slagenin B and C **46**. The natural products were then completed by installation of the pyrrole side chain as described above.

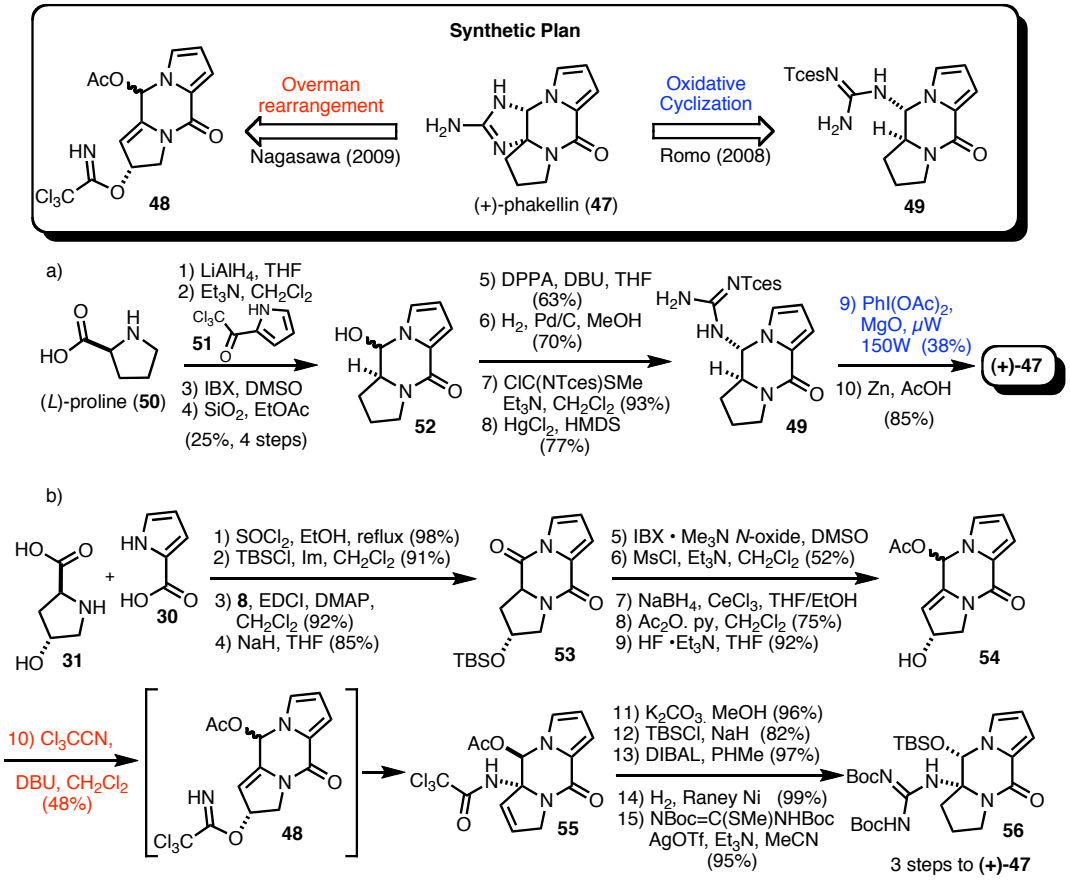
Scheme 1.7



While no significant biological activity has yet been reported for phakellin (**47**), several groups actively pursued its synthesis given that it is one of the simplest tetracyclic PIA congeners and for at least two additional reasons. One motivation was the hypothesis first proposed by Sharma who suggested that an elusive antibiotic activity was in fact possibly due to phakellin proposed to be an unidentified "natural product. A second motivation was the possibility of using phakellin annulation strategies in total synthesis approaches toward palau'amine (*vide supra*). The synthesis of (+)-phakellin by

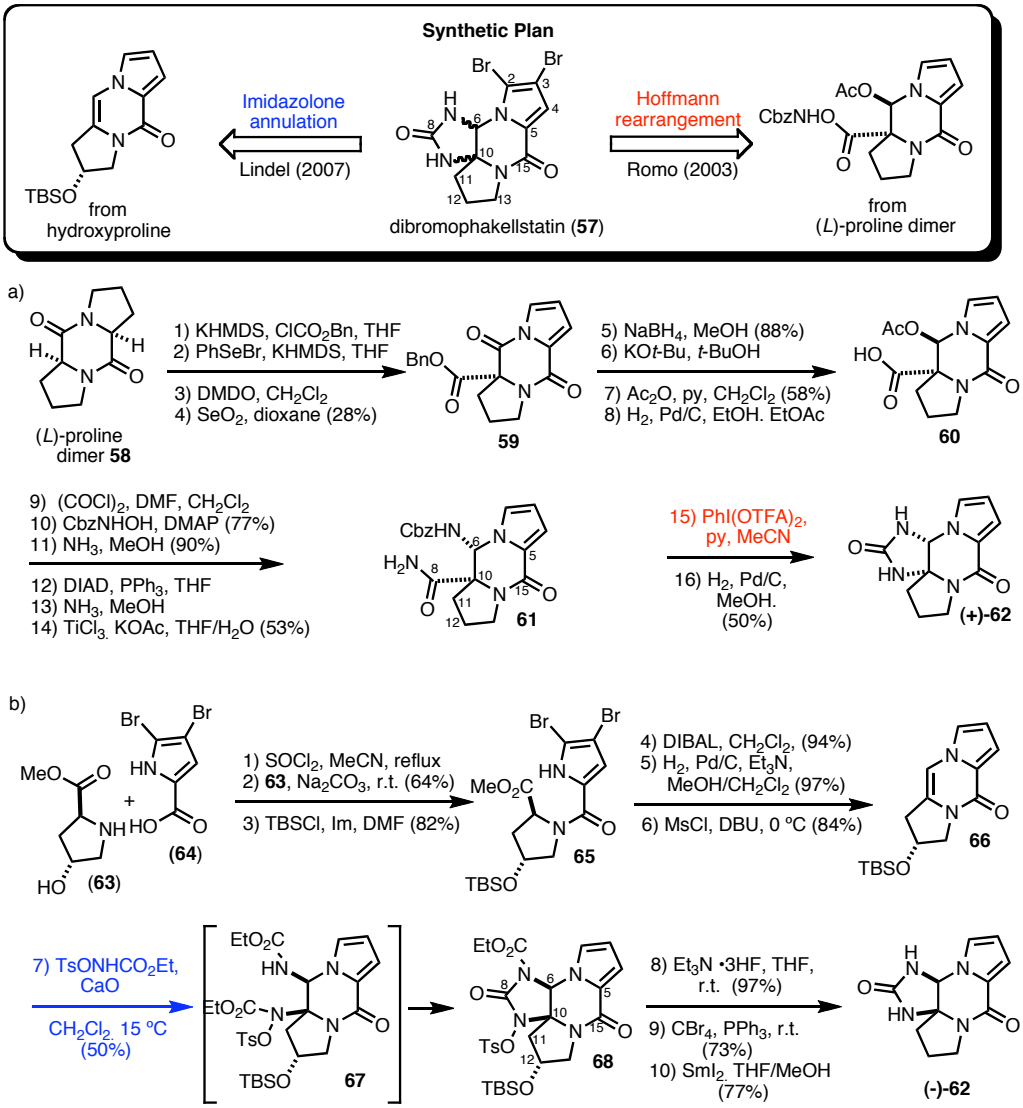
Romo[35] began with *L*-proline (**50**) and trichloroacetylpyrrole (**51**) to construct the tricyclic ketopiperazine **52**. Installation of the pendant guanidine then set the stage for the key microwave-mediated oxidative cyclization leading to the formation of the target product. The strategy employed by Nagasawa[36] for the synthesis of (+)-phakellin (**47**) started with the construction of hydroxyketopiperazine **53** from hydroxyproline (**31**) and pyrrole carboxylic acid (**30**). Overman rearrangement of the trichloroacetylimidate transient intermediate **48** obtained from treatment with trichloroacetylnitrile then installed the tertiary amide precursor to the required guanidine. Intramolecular cylization of pendant guanidine **56** finally delivered the desired product.

Scheme 1.8



The tetracyclic phakellstatins (**57**), which appear to be hydrolyzed phakellins (**47**), have attracted significant interest because of their biological activity and since their isolation a number of racemic syntheses have been reported.[37]

Scheme 1.9

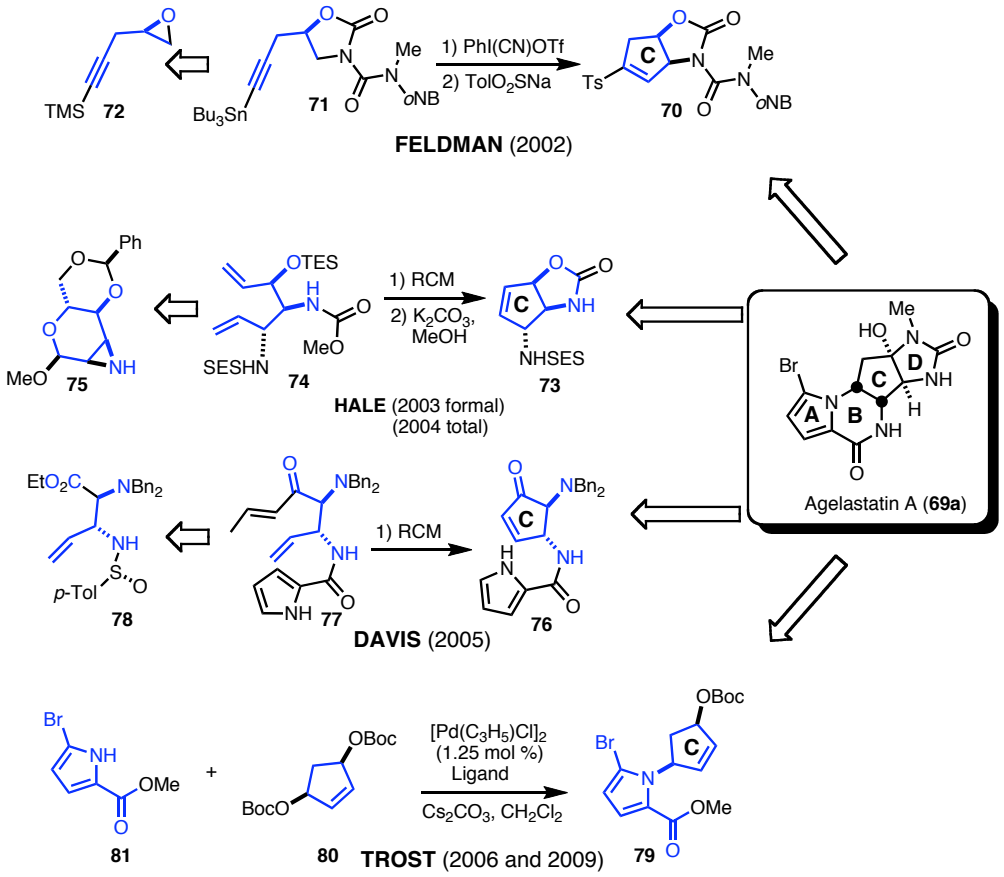


The first asymmetric synthesis of (+)-phakellstatin ((**+**)-**57**), the enantiomer of the natural product, was completed by Romo in 2003.[38] This synthesis employed a desymmetrization strategy of a diketopiperazine **58** (Scheme 1.9a) derived from

dimerization of proline and a Hoffman rearrangment simultaneously introduced the C10-N9 bond and formed the final cyclic urea. The synthesis confirmed the absolute configuration of the natural product. In 2007, Lindel disclosed the completion of the synthesis of the natural (-)-enantiomer starting with the quick construction of optically active tricyclic enamide **66** from hydroxyproline methyl ester (**63**) and dibromopyrrole carboxylic acid (**64**) (Scheme 1.9b). The key step then involved a diastereoselective, intermolecular 3-component imidazolone cyclization proceeding through the presumed transient bis-carbamate intermediate **67**.[39]

Of all monomeric PIAs, agelastatin (**69**) has garnered the most synthetic interest and this is undoubtedly due to its potent antitumor activity. Eight asymmetric syntheses have been reported to date along with a several racemic approaches.[40] While unique and creative, each synthesis features an appended acyl-pyrrole moiety, which enables a late-stage cyclization of the pyrrole and a pendant urea onto the C ring. These ring closures construct the B and D rings respectively, delivering the tetracyclic core of agelastatin. Thus, the primary differences in synthetic approaches are mainly the routes taken to the optically active, functionalized C ring. Enantioselective strategies to agelastatin along with starting materials employed are summarized in Schemes 1.10 and 1.1. Feldman was the first to synthesize the natural enantiomers of agelastatin A and B.[41] In his strategy, the intra-molecular oxidative cyclization of acetylene **71**, readily obtained from (*R*)-epichlorohydrin **72**, generated cyclopentene **70** a precursor efficiently elaborated to the ABC ring system of the agelastatins. In 2003 Hale reported a formal synthesis of agelastatin A[42] constructing enantiospecifically an advanced intermediate previously reported as a racemate by Weinreb.[43] Several manipulations of the known aziridine **75** led to diene **74**, which was readily converted to cyclopentene **73** *via* ring-closing metathesis. The following year cyclopentene **73** was advanced through a 9-step route generating several hundred milligrams of enantiomerically pure agelastatin A. [44] In Davis's 2005 synthesis the key intermediate cyclopentenone **76** was forged by alkylation of sulfinimine **78** and ring closing metathesis of the advanced allyl-enone **77**. [45] The asymmetric allylic alkylation (AAA) protocol reported by Trost in 2006, [46] and again in 2009 [47] rapidly assembled the pyrrole-cyclopentene **79**, precursor to the ABC ring system of agelastatin A. Remarkably, the target was then completed efficiently in only 8 steps.

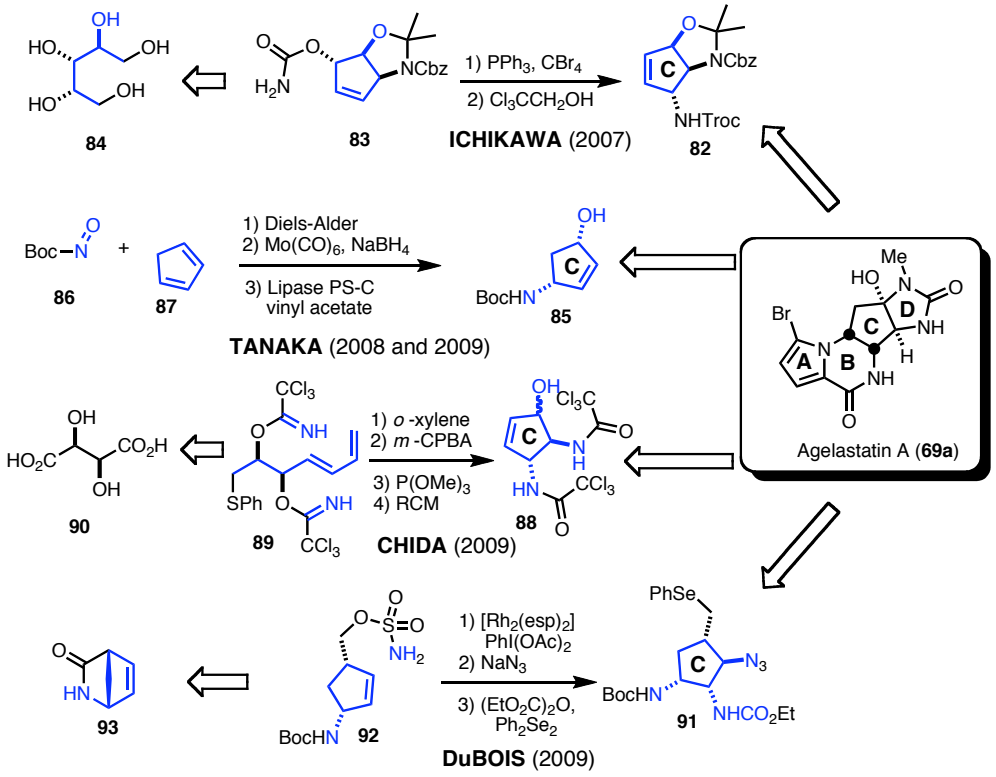
Scheme 1.10



In 2007 Ichikawa constructed the functionalized C ring **82** *via* a [3,3]-sigmatropic rearrangement of an allylic isocyanate, which proceeded very efficiently with complete transfer of chirality.[48] The synthesis disclosed by Tanaka and Yoshimitsu in 2008 commenced with the hetero Diels-Alder cycloaddition of pentadiene **87** and acylnitroso dienophile **86**, followed by reductive N-O cleavage and enzymatic resolution, which delivered the enantiomerically pure C ring precursor **85**.[49] The same approach was also utilized in their second generation synthesis completed the following year.[50] Also in 2009 the strategy employed by Chida featured an elegant sequential Overman/Mislow-Evans rearrangement of bistrichloroimidate **89** followed by ring-closing metathesis that established cyclopentene **88**.[51] In 2009, Du Bois disclosed an 11-step synthesis of (-)-agelastatin A,[52] hinging on a new catalytic intramolecular aziridination method applied to

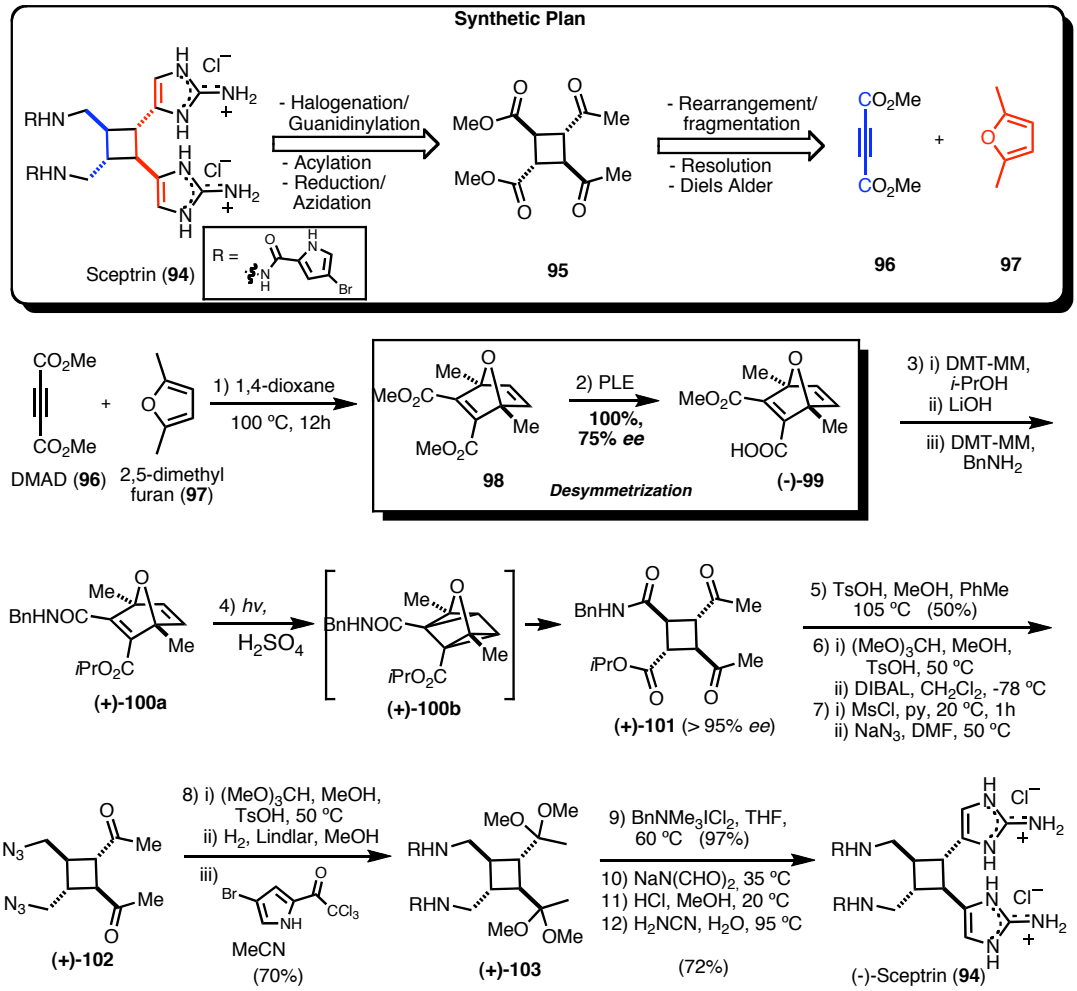
sulfonamide **92**, followed by sequential regioselective ring openings affording the completely functionalized C ring **91**.

Scheme 1.11



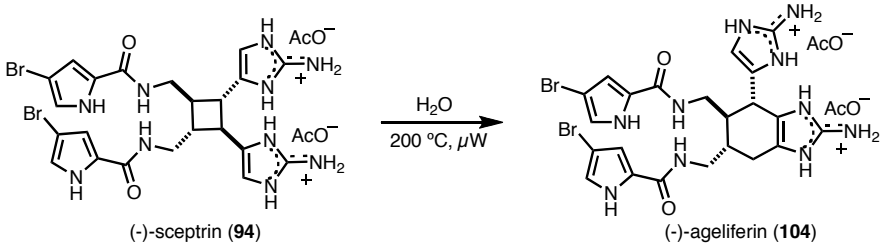
Sceptrin (**94**) is one of the simplest "dimeric" PIAs and it has been proposed as the natural precursor of the more complex and highly sought-after members of the family (e.g. palau'amine). After two racemic syntheses appeared virtually simultaneously, Baran revised his original approach and established the key optically active cyclobutane intermediate **99** through the enzymatic resolution of the previously reported Diels Alder adduct **98**, followed by photo-induced oxaquadricyclane rearrangement. Introduction of the bromopyrrole side-chains and aminoimidazole annulation, then completetd the first and still only enantioselective synthesis of sceptrin (**94**) (Scheme 1.12).[53]

Scheme 1.12



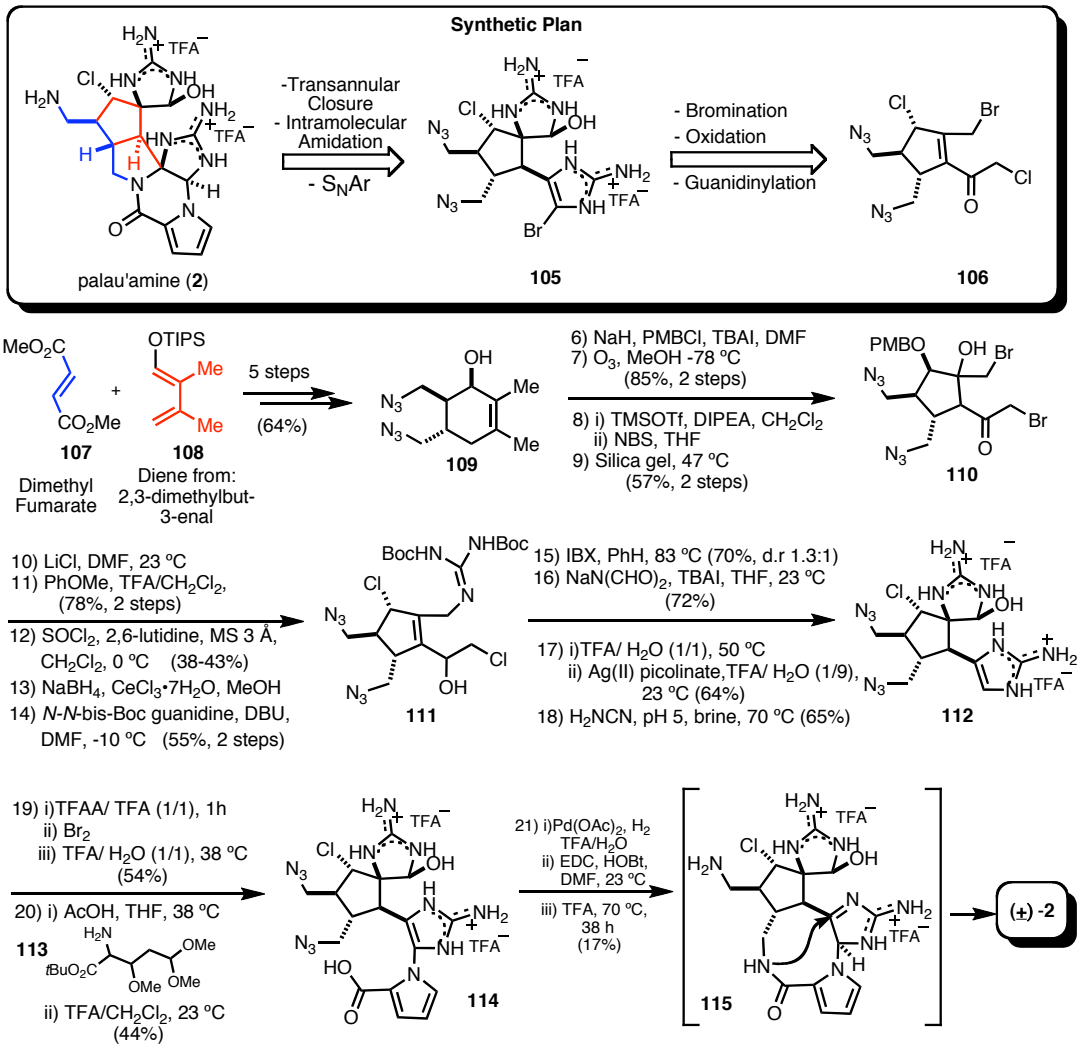
Expanding on early investigations in the Baran laboratory that led to the discovery that sceptrin (**94**) could be induced to ring expand in an aqueous medium at high temperatures, this group disclosed the first enantioselective synthesis of (–)-ageliferin ((-)-**104**) (Scheme 1.13) and its antipode (not shown). [53]

Scheme 1.13



Baran's recent synthesis of the long elusive palau'amine (**2**)[54] represents an outstanding accomplishment and raises the bar for future endeavors in the PIAs field, and is therefore included here, despite being racemic.

Scheme 1.14



Starting from the previously reported chlorocyclopentane precursor **110**, guanidine annulation and Silver-mediated oxidation of the unprotected resulting aminoimidazole generated the spirocyclic core of the target product. After construction of the pendant aminoimidazole, treatment with bromine and pyrrole precursor **113** followed by cyclization delivered biz-azide **114**. Following reduction of the azide functionalities, chemical ligation of the pyrrole carboxylate moiety and the vicinal primary amine then established a "macropalau'amine" advanced intermediate **115**. Finally, acid promoted transannular cyclization afforded the strained azabicyclo [3.3.0] core of palau'amine (**2**).

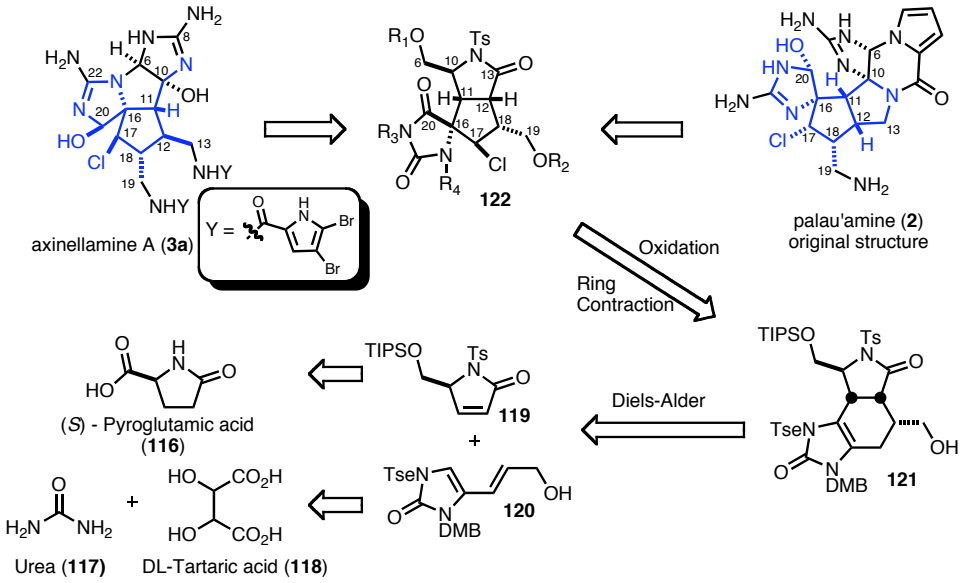
CHAPTER II

PREVIOUS WORK IN THE ROMO GROUP

2.1 Unified Strategy Toward the Axinellamines and the Original Structure of Palau'amine: Synthesis of a Common Chlorocyclopentane Precursor

At the onset of our investigation into the pyrrole-imidazole alkaloids we were inspired by the biosynthetic proposals by Kinnel and Scheuer[6] and Al-Mourabit and Potier[2] (see Chapter I). Intrigued by the homogeneity of their structural features, in our approach we sought to emulate the presumed natural pathway and develop a unified strategy for the synthesis of both palau'amine[6,7] and axinellamine[55] from a common chlorocyclopentane intermediate such as **122** (Scheme 2.1). In our strategy we envisioned a late-stage, simultaneous introduction of the guanidine moieties from corresponding urea precursors, which would be more manageable from a polarity and solubility standpoint. This approach would also give us an opportunity to probe potentially as of yet unidentified "oxo" analogues of specific natural products for biological activity. Phakellstatin (**57**) (see Chapter I), for instance displayed greater bioactivity than its *de facto* congener phakellin (**47**), in which the urea functionality is replaced by a guanidine.

Scheme 2.1



In chlorocyclopentane **122** three of the six rings of palau'amine (highlighted in Scheme 2.1) would already be established, and a few modifications (notably the epimerization at C12) would also make **122** a viable precursor for the synthesis of axinellamine. Following biosynthetic suggestions, **122** would be generated via an oxidation/ring contraction event from tricycle **121**, which in turn is the Diels Alder adduct of a vinyl-imidazolone diene **120** and a pyrrolidinone dienophile **119**, derived from commercially available and inexpensive materials. Preliminary work in our group by Dr. Anja Dilley[56] led to the identification of the crucial factors that affect the selectivity in the key Diels-Alder cycloaddition. High levels of facial selectivity had previously been reported for related systems[57] as a consequence of the expected approach of the diene from the less sterically hindered face of the dienophile, resulting in two potential *endo* transition states arrangements.

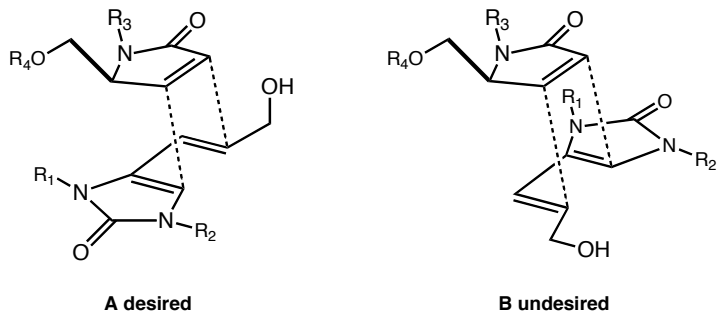
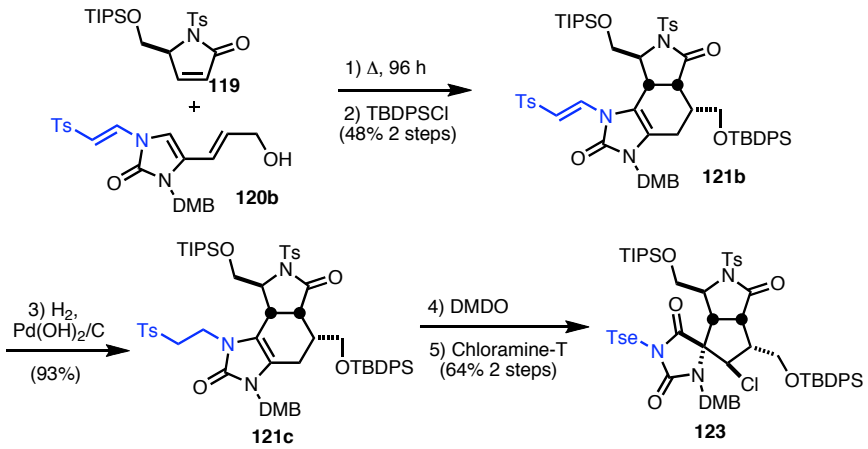


Figure 2.1. Potential *endo* transition state arrangements in the Diels Alder reaction.

Control on the regiochemistry on the other hand proved to be strongly related to the substitution of the imidazolone nitrogens of the diene. It was found that an electron-donating group on the nitrogen proximal to the alkyl substituent (R_1) paired with an electron-withdrawing group on the distal nitrogen (R_2) led to the exclusive generation of the desired adduct **121** through transition state **A** (Figure 2.1). Although the nature of the protecting group on the hydroxyl moiety of the dienophile (R_4) had no bearing on the outcome of the cycloaddition it was noted that a tosyl substituent on the nitrogen (R_3) gave consistently better yields under milder reaction conditions, than the initially employed carbamate (Boc) protection. By contrast however, the following oxidation step (*vide infra*) gave dismal results and it become apparent that a significantly different

electronic environment was required. To address this issue an "electronically switchable" protecting group was developed; thus the electron-withdrawing tosylvinyl group (Tsv), that provided the desired regiochemistry in the Diels Alder reaction exclusively, could be efficiently converted to the electron-donating tosylethyl (Tse) moiety under standard hydrogenation conditions. This change then provided the appropriate environment for the required oxidation, leading to good yields of key spirochlorocyclopentane **123**.[58]

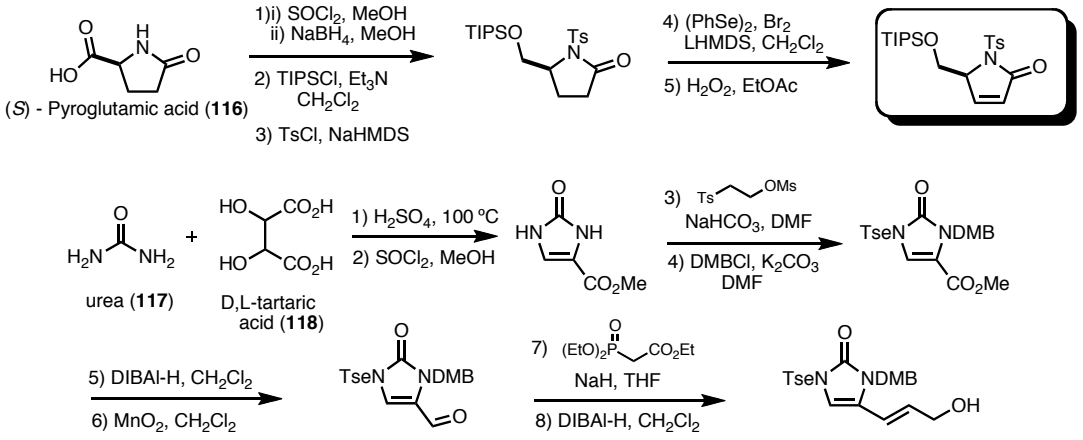
Scheme 2.2



Due to a rather tedious synthesis of the Tsv-diene, and the occurrence of some undesired side reaction however, it was decided to introduce the Tse group directly in the diene, prior to the Diels Alder step. Even though the cycloaddition was significantly affected, resulting in a 2.5:1 mixture of regioisomers, the overall reaction sequence was decidedly more efficient, and the undesired adduct could easily be separated *via* MPLC or simple column chromatography.

The synthesis of the Diels Alder partners is summarized in Scheme 2.3. The choice of the indicated protecting groups came as a result of the intensive investigations by Dr. Dilley,[56a] later expanded upon by Dr. Dransfield.[59] These endeavors predate my involvement with the project and a detailed account has been published.[59] Upon repetition and scale-up of these procedures however, further improvements were made and remarkably the 8-step synthesis of the diene could be performed entirely without the need for column chromatography purification and has been carried out in decagram scale.

Scheme 2.3



In addition recent studies that I personally performed using chiral HPLC (Figure 2.2) revealed that the desired Diels Alder product was enantiomerically pure, confirming that no epimerization of the dienophile occurred under the standard heating reaction conditions.

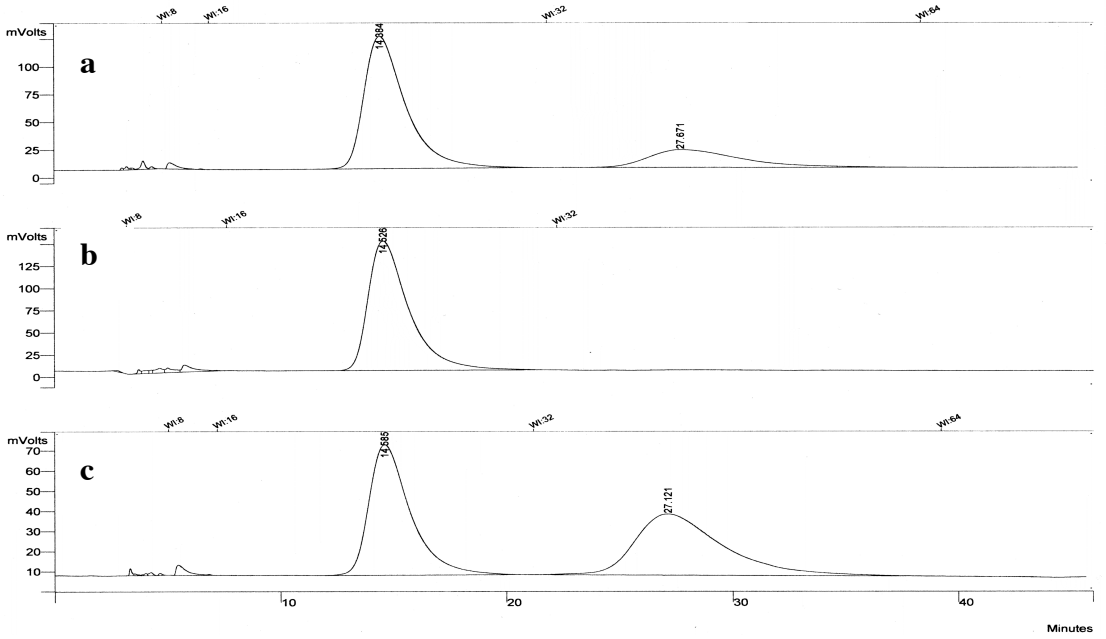
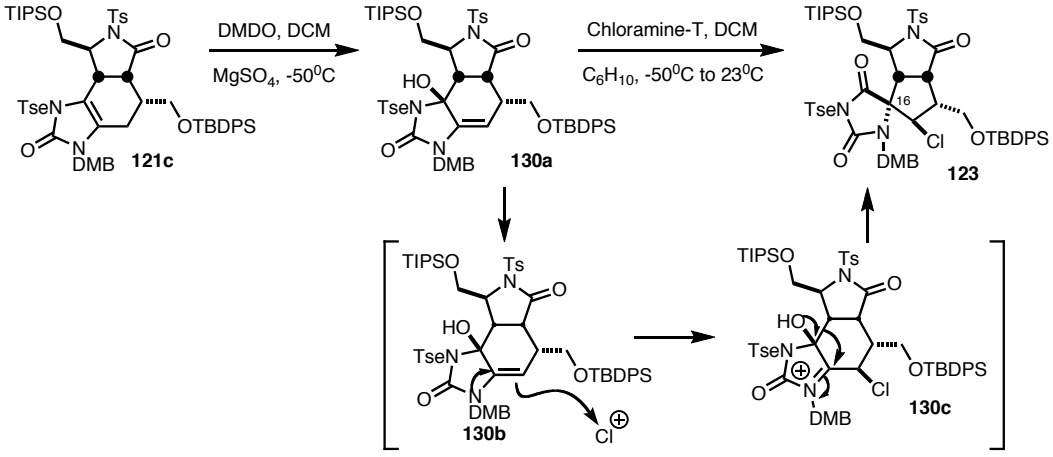


Figure 2.2. HPLC analysis of the D A adduct **121**; a) co-injection. b) pure **121**. c) racemic control.

By contrast when the cycloaddition was carried out under microwave irradiation,[60] which greatly shortened the reaction time but required higher temperatures, partial to complete erosion of enantiomeric purity was observed.

Following biosynthetic suggestions (see Chapter I) the Diels Alder adduct **121c** was oxidized with freshly prepared dimethyldioxirane (DMDO) and the resulting crude allylic alcohol **130a** was treated with a commercially available source of electrophilic chlorine (*N*-chlorosuccinimide or Chloramine-T) triggering the semi-pinnacol rearrangement that delivered the desired tricyclic intermediate **123** with *complete diastereoselectivity* for the key spirocyclic quaternary center (C16). [2]

Scheme 2.4



It is noteworthy that the reaction temperature for the DMDO oxidation step was crucial, resulting in a very clean conversion at –50ºC, but generating increasing amounts of byproducts at lower temperatures. In addition, it was observed that in the following step the chlorinated product was often isolated with varying amounts of tosylamine (not reported before), which refused to be separated by column chromatography. This however did not seem to have any effect on the subsequent reaction, after which the impurity was easily separated. It was later, and entirely serendipitously discovered that

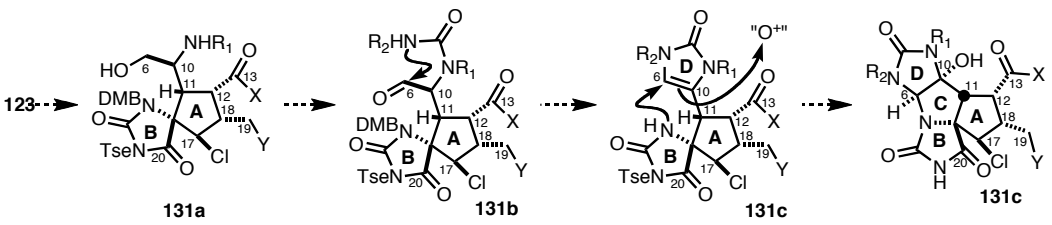
[2] Numbering for compounds throughout this dissertation follows the original numbering system introduced by Kinnel and Scheuer in the palau'amine isolation and characterization publication.[6]

the tosylamine impurity could be selectively precipitated in benzene and separated by simple filtration. As anticipated (*vide supra*) chlorocyclopentane **123** constitutes the point of divergence in our unified approach to both the axinellamines (**3**) and palau'amine (**2**). The work done in our group in these directions prior to my involvement is summarized below.

2.2 First Generation Approach to the Core of the Axinellamines

In the original approach to the axinellamines the necessary C12 epimerization was envisioned to come at a later stage, giving priority instead to the construction of the C and D rings of the tetracyclic core (**131c** in Scheme 2.5).

Scheme 2.5

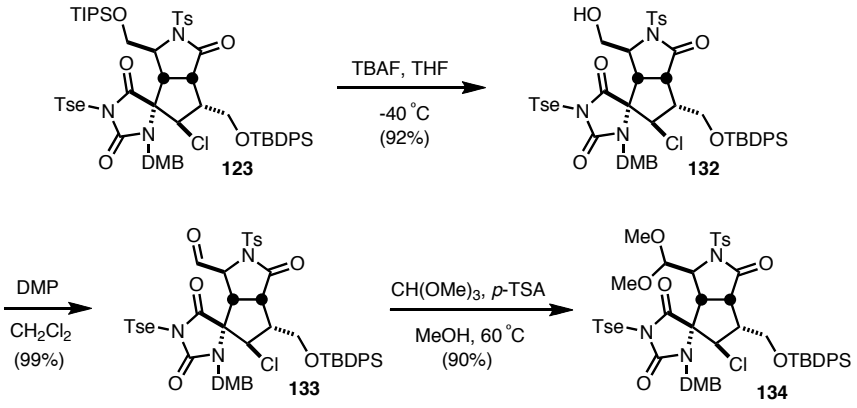


Following biosynthetic inferences it was proposed that an oxidative cyclization of the "lactam" nitrogen of the spirohydantoin onto a pendant imidazolone would deliver the fully functionalized carbon skeleton of the axinellamines (**131c** Scheme 2.5). The imidazolone would in turn derive from nucleophilic opening of the northern lactam of **123**, followed by cyclization of a protected urea onto an aldehyde (**131b → 131c**). This route would also provide a carbonyl moiety at C12, following lactam opening, suitable for the required projected epimerization.

Although I have personally performed multiple times all the reactions described in this section, occasionally exploring alternatives and or making slight modifications (*vide infra*), it must be emphasized that only the latest optimized approach is described which represents but a small sampling of the extensive synthetic investigations pioneered by Dr. Paul Dransfield,[61] and a detail account of these studies will not be included herein.

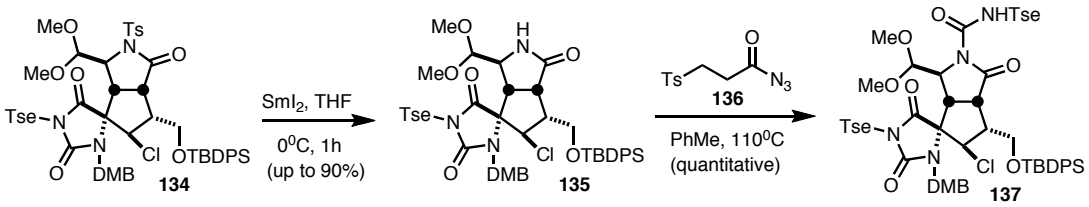
Selective TIPS desilylation of spirocycle **123** then, using one equivalent of TBAF at –40 ºC proceeded typically in a very efficient manner without affecting the more robust TBDPS protecting group (Scheme 2.6). Oxidation of the free hydroxy functionality using Dess Martin periodinane (DMP) at room temperature followed by treatment of the crude aldehyde **133**, with trimethylorthoformate in MeOH at 60 ºC in the presence of *p*-TSA, provided dimethyl acetal **134** in generally excellent yields.

Scheme 2.6



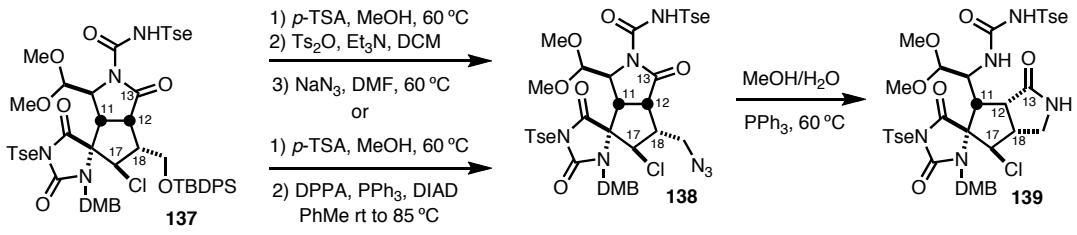
Cleavage of the tosyl protecting group from the northern lactam was efficiently accomplished by treatment of **134** with 2 equivalents of freshly prepared samarium iodide (SmI_2) in THF at 0ºC (Scheme 2.7). Installation of the required protected urea in **137** was achieved by heating intermediate **135** to 110ºC in toluene with 10 equivalents of tosylethylacylazide **136**. Under these conditions **136** undergoes a Curtius rearrangement generating *in situ* an isocyanate that reacts with the nucleophilic lactam nitrogen in **135** leading to quantitative yields of the desired urea. Remarkably, no base was required in this procedure.

Scheme 2.7



At this point, our strategy required the opening of the northern lactam to allow for the subsequent reaction of the pendant urea to generate the imidazolone necessary for the key late-stage oxidative cyclization that would deliver the tetracyclic core of axinellamine. After fruitless attempts to generate the imidazolone first, and then open the lactam,[61] we considered an intramolecular nucleophilic lactam opening, and it was reasoned that a nitrogen nucleophile in the C18 side-chain would be ideal for this purpose as it would also introduce a key feature of the natural product. Thus, conversion of protected alcohol **137** to azide **138** was achieved by a three-step sequence (Scheme 2.8), involving removal of the TBDPS group under acidic conditions, activation of the free hydroxyl moiety with tosyl anhydride, and displacement of the tosylate with sodium azide. Treatment of **138** with PPh_3 in $MeOH/H_2O$, then generated the desired amine nucleophile which efficiently proceeded in the same pot to open the northern lactam, providing urea **139** in good yield.

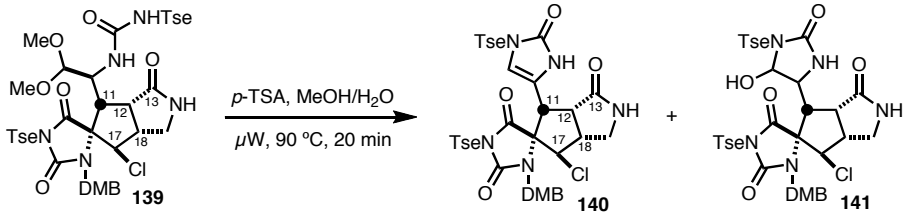
Scheme 2.8



Alternatively, I investigated the direct installation of the azide on the free alcohol under Mitsunobu conditions using diphenylphosphoryl azide (DPPA). Although this protocol efficiently provided the desired azide **138**, eliminating one step in the overall sequence, a significant amount of triphenylphosphine oxide byproduct was generated which could not be separated by silica gel chromatography. As in the following step, however, more triphenylphosphine oxide was generated and previous results had shown that urea **139** could be obtained in excellent purity, it was decided to subject the semi-purified intermediate to the reaction conditions. Indeed, very pure urea **139** was isolated after flash chromatography, albeit in a modest 20% yield for the two steps. Overall the original three-step sequence proved to be more efficient.

Urea **139** is the last fully characterized intermediate generated by Dr. Dransfield and a brief account on further studies he initiated, which I integrated and expanded is introduced below and will be further discussed in Chapter VI. Microwave irradiation of urea **139** promoted cyclization onto the dimethylacetal delivering the anticipated imidazolone **140** along with varying amounts of carbinolamine **141**.

Scheme 2.9

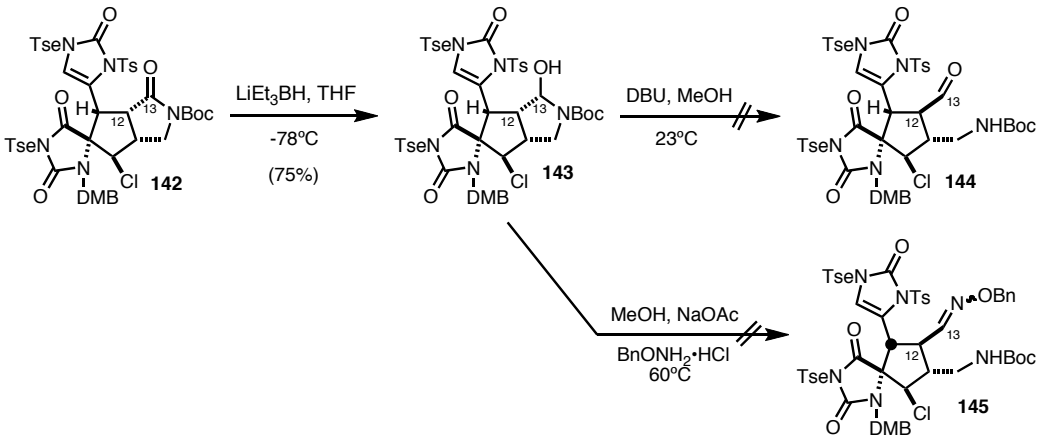


139 **140** **141**

After orthogonal protection of the free nitrogens (discussed in Chapter VI), efforts were than focused on the reversal of configuration at C12, to deliver the "all-*trans*" relative stereochemistry of the chlorocyclopentane core (A ring) of the axinellamines.

In our initial approach to this issue we envisioned reducing the Boc-lactam to the corresponding carbinolamine and promoting epimerization of the equilibrating aldehyde tautomer under basic conditions (Scheme 2.10).

Scheme 2.10



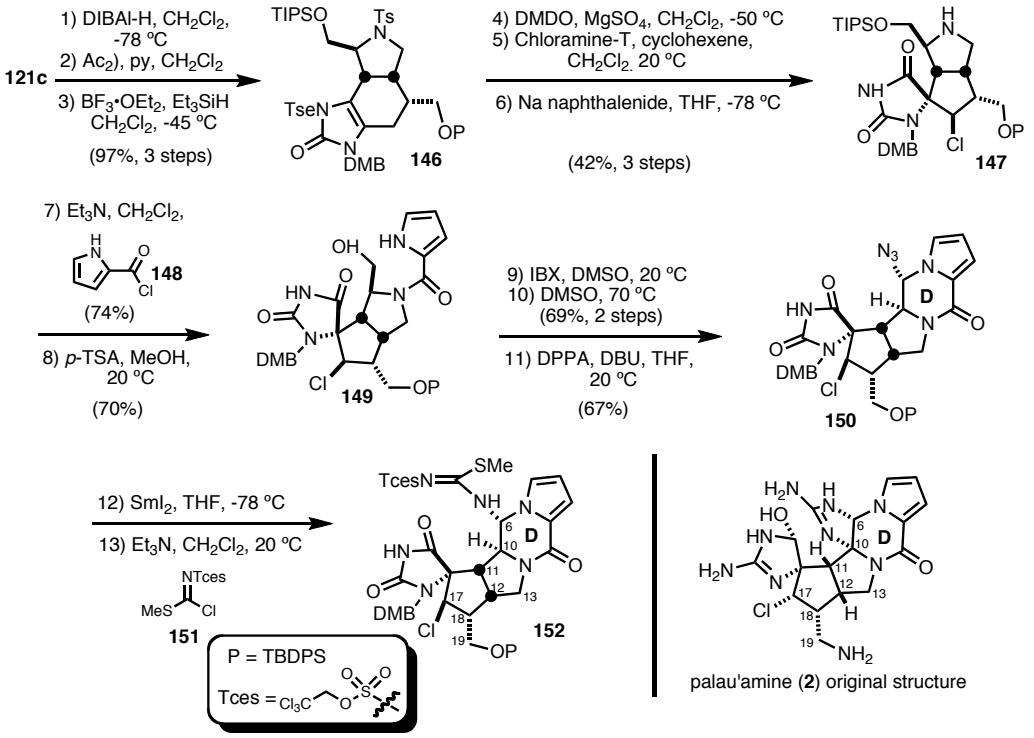
While the reduction proceeded smoothly generating the expected aminal **143** in good yield, several attempts to invert the stereochemistry as anticipated (Scheme 2.10), resulted in sluggish reactions and no significant products could be isolated.

Given these discouraging results and the lengthy route that provided only small amounts of advanced intermediates, it was decided at this point that the epimerization at C12 should be addressed earlier in the synthetic sequence. Ideally, this approach would be overall shorter and require less protecting groups. Work done in this direction is detailed in Chapter III.

2.3 *Epi*-palau'amine Investigation and Palau'amine Structural Revision

As explained above, spirocycle **123** was the projected point of divergence in our common intermediate strategy toward the synthesis of palau'amine, as it featured the completely functionalized tricyclic core of the target alkaloid (Scheme 2.1), with the exception of the chlorine-bearing C17. Several attempts to adjust the stereochemistry of this center to match that of the natural product were unsuccessful[62] and a C17 *epi*-palau'amine became our target. Investigations in this direction, carried out by Shaohui Wang, led to the synthesis of pentacycle **152** (Scheme 2.11). Once again the sequence presented herein only describes the latest successful approach and in the interest of conciseness the details of the synthetic studies that led to it will not be discussed here.

Scheme 2.11

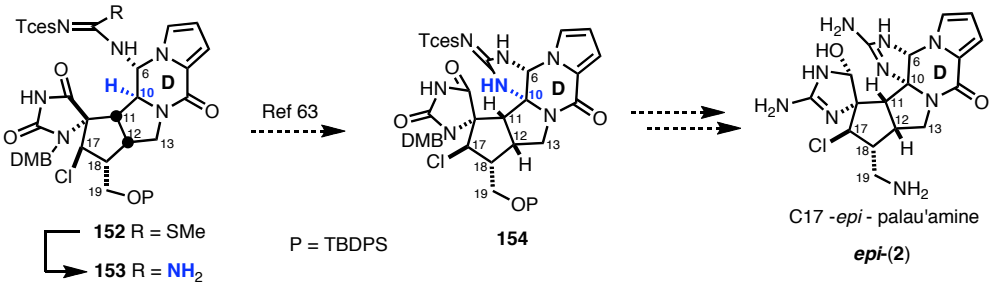


After initial attempts to reduce the lactam in spirocycle **123** to the corresponding pyrrolidine, it was discovered that this transformation gave significantly better results on the protected Diels Alder adduct **121c**. Thus, treatment with DIBAL-H, followed by activation of the resulting carbinolamine with acetic anhydride and Lewis acid-mediated hydride substitution efficiently generated pyrrolidine **146**. Oxidative ring contraction as described before, followed by single-electron-transfer cleavage of the sulfone protecting groups provided chlorocyclopentane **147** in modest yield over the three steps. Acylation of the pyrrolidine nitrogen with pyrrole carbonyl chloride **148** then, followed by selective cleavage of the TIPS ether set the stage for the construction of the D ring of palau'amine. Surprisingly, after oxidation of the primary alcohol with IBX at room temperature the anticipated cyclization of the pyrrole nitrogen onto the newly generated aldehyde did not occur and more forcing conditions had to be utilized to accomplish this transformation (step 10, Scheme 2.11). Introduction of an azide functionality under Mitsunobu conditions then, followed by reduction to the corresponding amine and treatment with

151, generated pseudothiourea **152** which is the most advanced fully characterized intermediate prepared by Dr. Wang.

At this point, generation of a pendant guanidne by displacement of the thiomethyl substituent with a nitrogen source would provide a suitable precursor for the completion of the synthesis. Following recent literature reports by DuBois,[63] it was envisioned that intramolecular C-H amination at C10, would deliver the completely functionalized hexacyclic core of palau'amine. The projected C17 epimer of the natural product would then be completed by reduction and guanidinylation of the spirocyclic hydantoin and introduction of the primary amine at C19.

Scheme 2.12



Although our synthetic efforts delivered gratifying results, as we were exploring the final steps of our strategy, independent but virtually simultaneous reports from the groups of Matsunaga,[3d] Kock,[3c] and Quinn[3a,b] appeared that called into question the original structural assignment of palau'amine. In particular, based on new and improved spectroscopic data all agreed that the stereochemistry at C12 and C17 had to be inverted.

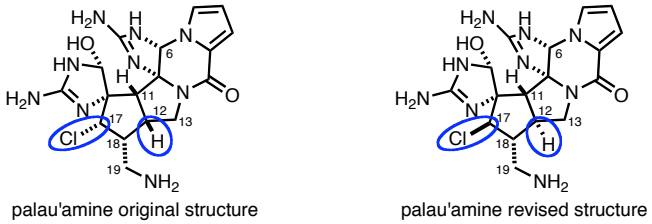
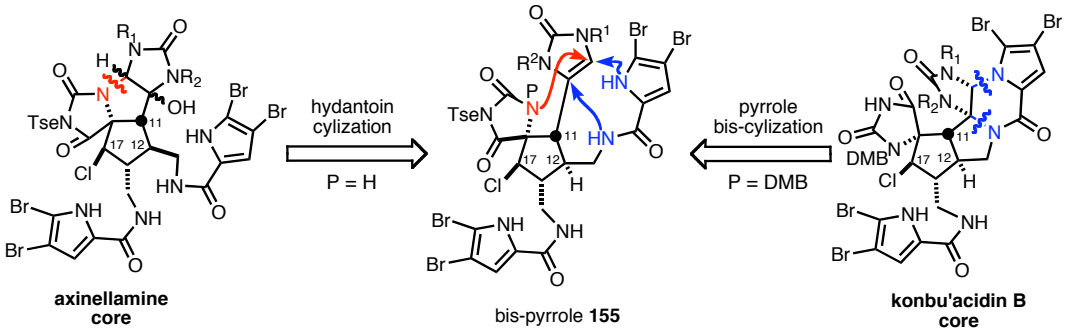


Figure 2.3. Original and revised structure of palau'amine.

If, from a biosynthetic perspective this assessment was sound, and in retrospect, fitting as virtually all PIAs now exhibited identical stereochemical relationships, it introduced on the other hand a very peculiar structural feature. Palau'amine (and by extension the related konbu'acidins (**5**)[64] and styloguanidines (**4**);[65] see Chapter I) now featured a *trans*-[3.3.0]-azabicyclooctane (*i.e.* two five-membered rings *trans*-fused), a construct that, as reported by Kock and Baran,[4] is exceedingly rare in natural products.

We realized at this point that our advanced intermediate pentacycle **152** was indeed an epimer of the natural alkaloid, albeit a C12 epimer and not a C17 epimer as originally thought. Fortunately in the course of our investigation toward the synthesis of the axinellamines we had already identified conditions to effect the desired inversion of stereochemistry at C12 (Chapter III). We reasoned that this provided us with an opportunity to revise our common intermediate approach, allowing us to potentially delay the point of divergence until much later in the synthesis. Recognizing that the newly isolated konbu'acidin B[3a] and the known axinellamines possessed identical carbon frameworks we envisioned that a bis-pyrrole intermediate such as **155** could give rise to the fully functionalized cores of either or both targets in one step through different modes of intramolecular cyclization (Scheme 2.13). In this scenario the spirohydantoin DMB protecting group would be the discriminating element that would allow us to select a specific mode of cyclization. Development and implementation of this strategy will be expanded upon in Chapter VI.

Scheme 2.13



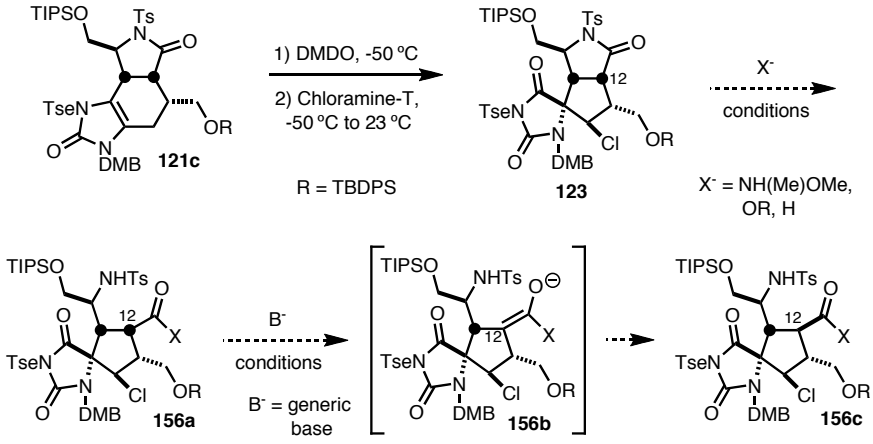
CHAPTER III

EARLY STAGE C12 EPIMERIZATION STRATEGY TOWARD THE SYNTHESIS OF THE AXINELLAMINES*

3.1 Initial Early C12 Epimerization Studies Toward Axinellamine

After the unsuccessful attempts to effect the late stage C12 epimerization required for the synthesis of the axinellamines as projected in our original strategy (see Chapter II), we revised our approach and initiated studies to address this key issue earlier in the synthetic sequence. We reasoned that the most convenient point to investigate the necessary inversion of configuration was after the establishment of the crucial spirocyclic system. Nucleophilic opening of the lactam moiety in tricycle **123** would provide a carboxylate functionality suitable for epimerization via equilibration of the intermediate enolate species **156b** (Scheme 3.1).

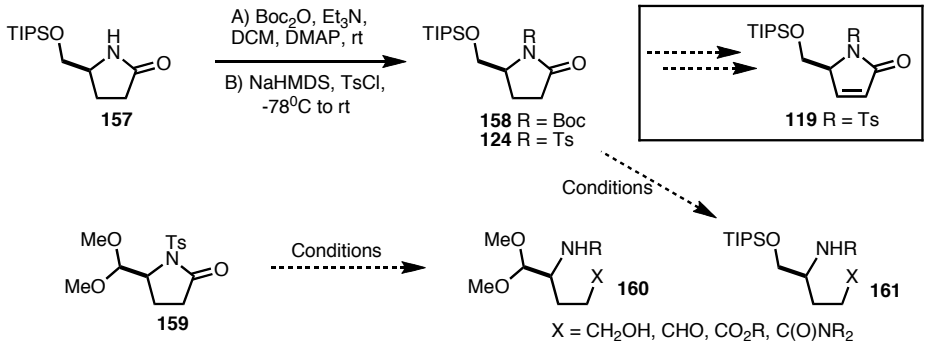
Scheme 3.1



* Part of this chapter is reprinted with permission from "Facile Synthesis of the Trans-Fused Azabicyclo[3.3.0]octane Core of the Palau'amines and the Tricyclic Core of the Axinellamines from a Common Intermediate" by Zancanella, M. A.; Romo, D. *Org. Lett.* **2008**, *10*, 3685-3688. Copyright 2008 American Chemical Society.

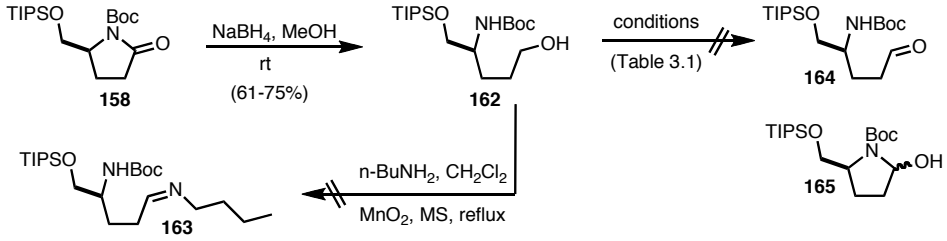
To investigate the reactivity of the northern lactam, we decided to initiate a model study, and we reasoned that diene precursor (**124** or **158** Scheme 3.2) would provide a convenient and readily accessible substrate that would adequately mimic the real system. In addition, dimethyl acetal **159**, which had been previously prepared and was available in large quantities, could also provide valuable information as to the reactivity of these systems.

Scheme 3.2



In initial trials, both the TIPS protected lactam **158** (R = Boc) and dimethyl acetal **159** reacted with excess $NaBH_4$ in alcoholic solvent to deliver modest yields of the corresponding primary alcohols. Further manipulation of the former substrate however proved not to be trivial.

Scheme 3.3



Attempts to oxdize the primary alcohol moiety to the corresponding aldehyde **164** under a variety of conditions (Table 3.1) resulted in rather sluggish reactions with no discernible desired product. In some cases spectroscopic data seemed to be consistent with carbinolamine **165**, although identity of this product could not be unambiguously established. An attempt to oxidize the alcohol moiety in the presence of an amine to trap the presumed unstable aldehyde intermediate[66] led only to complete recovery of the starting material.

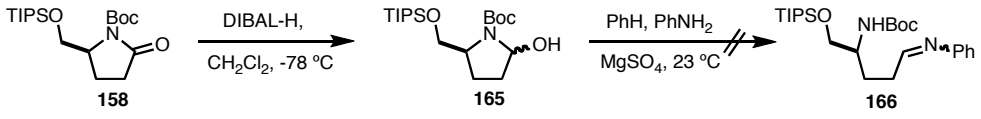
Table 3.1 Attempted oxidaton of amino alcohol **162**.

Entry	Conditions	Outcome
1	DMP[a], 23 ºC	Fast reaction but no aldehyde. Sluggish NMR. Probably aminal **165**.
2	SO_3/py, 23 ºC	Reaction time 2 h. No aldehyde. Unidentified product.
3	Swern[b]	Aldehyde signal at 9.5 ppm on crude ^{1}H NMR. Lost after work-up
4	Swern[c]	No Reaction. Probably bad Swern reagent
5	Swern[c]	Aldehyde signal at 9.5 ppm on crude ^{1}H NMR. Lost after column.

a = Dess-Martin Periodinane; **b** = addition of substrate to Swern reagent. **c** = addition of Swern reagent to substrate.

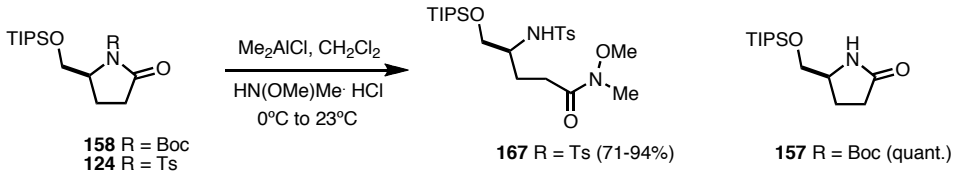
Treatment of Boc-lactam **158** with DIBAL-H under standard conditions cleanly delivered the expected mixture of carbinolamines **165**. After exposing the crude material to aniline, in an attempt to isolate a stable imine derivative however, multiple products were generated (by TLC analysis) that could not be separated and characterized, furthermore no starting material could be recovered.

Scheme 3.4



Reaction of boc-lactam **158** with methoxy-methylamine in the presence of an aluminum Lewis acid to generate the corresponding Weinreb amide derivative **167**, led instead to the fast, quantitative cleavage of the carbamate protecting group. By contrast, when the analog tosyl-lactam **124** was subjected to identical reaction conditions, excellent yields of the desired amide could be isolated after 24 hours at ambient temperature.

Scheme 3.5



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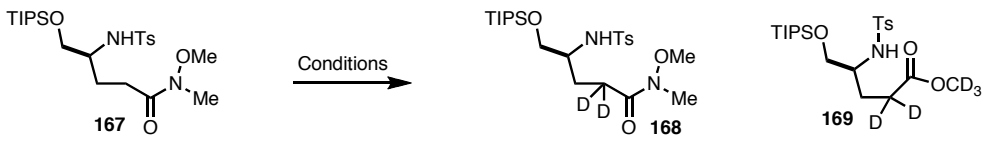
With a suitable substrate in hand we then tried to establish the propensity of this system to undergo enolization, by attempting to introduce deuterium labels alpha to the carbonyl of the Weinreb amide under basic conditions. Most conditions surveyd led to recovery of unaltered starting material. DBU in CD_3OD at room temperature for 24 h, NaHMDS at –78ºC for 30 min. then quenched with D_2O, and LiHMDS at –78ºC for 30 min. then quenched with D_2O, all gave no deuterium incorporation.

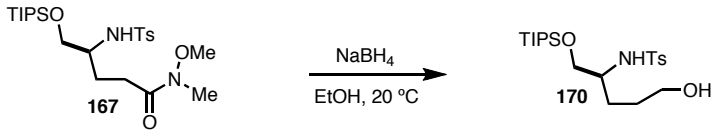
Heating the substrate in CD_3OD to 80ºC for 20h in the presence of DBU led to the isolation of a new product, which by preliminary ^1H NMR analysis was assigned structure **169** (Scheme 3.6). This compound was presumably formed either by deuterium incorporation followed by nucleophilic attack of CD_3O^- onto the amide, or by the reverse order of events.

Scheme 3.6



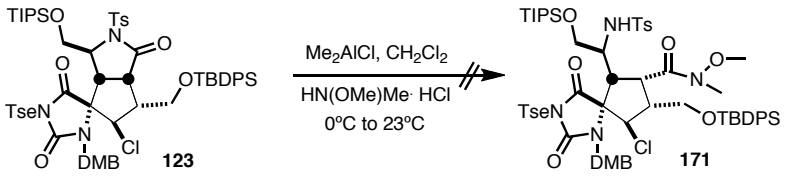
Reduction of the amide moiety proceeded pleasingly smoothly under mild conditions. Interestingly when MeOH was used instead of EtOH, a large excess of reducing reagent and longer time were required to drive the reaction to completion. Use of $LiAlH_4$ in THF solution led to very sluggish reaction and no detectable amounts of desired product were generated. Several other conditions resulted in no reaction.

Scheme 3.7



Having identified promising conditions for the lactam opening, and gained good insight on the propensity of the resulting open derivative to undergo enolization we returned to the real system **123**, with reason to believe that the key C12 epimerization would be readily accomplished. Unfortunately we soon discovered that the reactivity of the model system did not parallel that of more complex advanced synthetic intermediates.

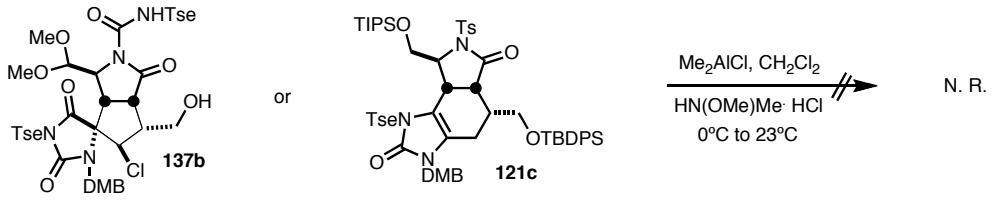
Scheme 3.8



Several runs of the established conditions for the lactam opening to the corresponding Weinreb amide on chlorocyclopentane **123** (Scheme 3.8), led to no reaction even after extensive heating (60 ºC for 10 hours). Equally disappointing results were obtained under the same conditions on more advanced intermediate **137b** and Diels

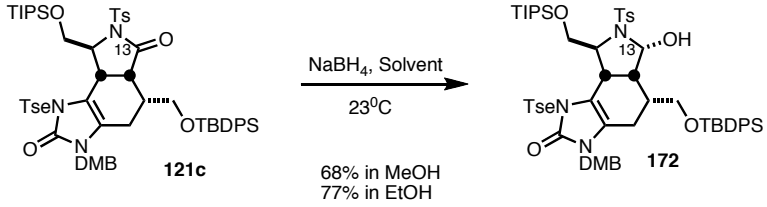
Alder adduct **121c**, in both instances leading to nearly complete recovery of unreacted starting materials.

Scheme 3.9



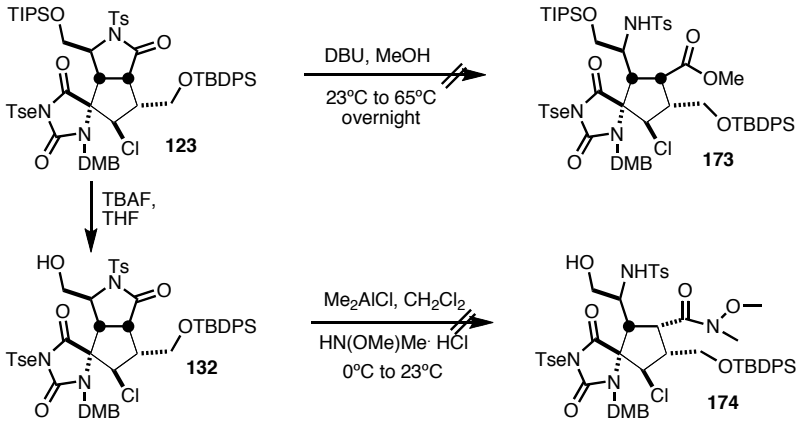
Further confirmation that the tricyclic substrates showed very different reactivity than the monocylic model system was provided by the reaction with $NaBH_4$. While the model system was converted exclusively to the corresponding open amino-alcohol (*vide supra*), the Diels Alder adduct **121c** provided good yields of the half-reduced carbinolamine in both MeOH and EtOH. In this particular instance it seems plausible to infer that, even if after initial reduction the lactam ring is opened, the constraint imposed by the tricyclic system places the tosylamine and the aldehyde termini in close proximity so that the closed aminal tautomer is exclusively favored over the open amino-alcohol form. The stereochemistry at C13 was not firmly established, but significantly, the reaction provided complete diastereoselectivity. The structure indicated in Scheme 3.10 is the kinetic product deriving from hydride attack on the concave face of the tricyclic system. The opposite configuration would be expected if a transient open amino-aldehyde species was generated in the process.

Scheme 3.10



Other attempts to open the tosyl lactam under basic conditions using methanol as the nucleophile provided no reaction even at relatively high temperatures and after prolonged reaction times. Similarly, a further run of the established conditions for the generation of the Weinreb amide (Scheme 3.5) on alcohol **132**, obtained from selective cleavage of the TIPS ether (*vide supra*) led to complete recovery of the starting material.

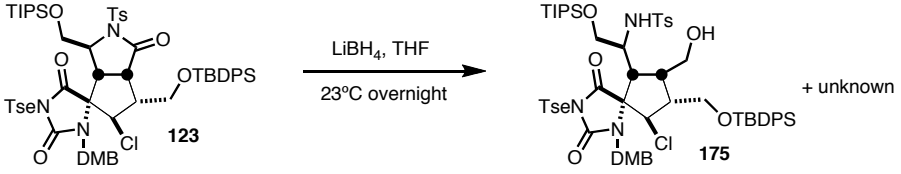
Scheme 3.11



3.2 Successful Lactam Opening and C12 Epimerization Toward Axinellamine

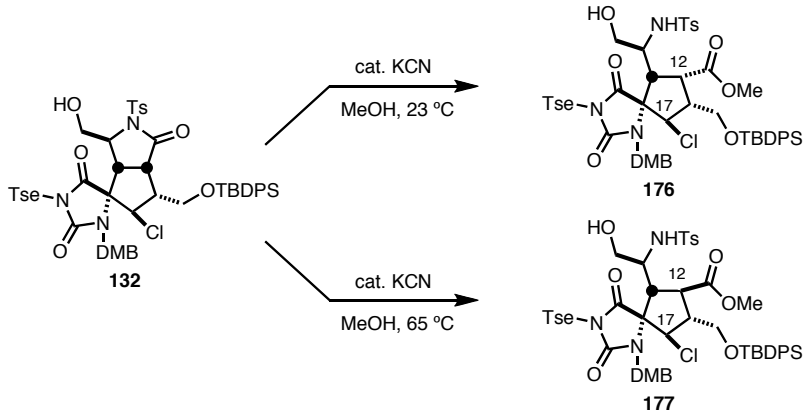
Eventually, the tosyl-lactam ring could be opened to primary alcohol **175** using excess $LIBH_4$ after overnight stirring at ambient temperature, albeit a significant amount of an unknown byproduct was also generated in the process. Although this undesired side reaction could be minimized by using a controlled excess of reagent, optimization of this procedure was not pursued in light of more promising results obtained with an alternative approach that was being investigated concomitantly (Scheme 3.13).

Scheme 3.12



Using a procedure with which Dr. Dransfield had had some success (on a different substrate) it was discovered that treatment of TIPS deprotected spirocycle **132** with catalytic KCN in MeOH at room temperature delivered after extended reaction time (up to 4 days) a methyl ester, as confirmed by the appearance of a diagnostic signal at δ 3.83 ppm (s, 3H OCH_3) in the ^1H NMR spectrum (C_6D_6). As the product and the starting material had identical Rf values, the reaction could not be monitored by TLC and after 4 days a 9:1 mixture of the two species (the product being the major) was isolated. The product was tentatively assigned structure **176**, which is consistent with mass spectrometry data; *m/z* = 1082 (M+Na) and *m/z* = 1098 (M+K). The stereochemistry at C12 could not be unequivocally assigned, as interpretation of the 1D and 2D NMR data was made difficult by the overlap of key signals. In an attempt to shorten the reaction time, in a second run heat was applied to the reaction mixture.

Scheme 3.13



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As predicted, nearly complete loss of starting material was observed in less than 18 hours, leading to the isolation of ~ 60% of a pure methyl ester. Unexpectedly however, although the mass spectrometry data were identical to those of **176**, the ^1H NMR spectrum of this material (identified as **177**) was entirely different (Figure 3.1).

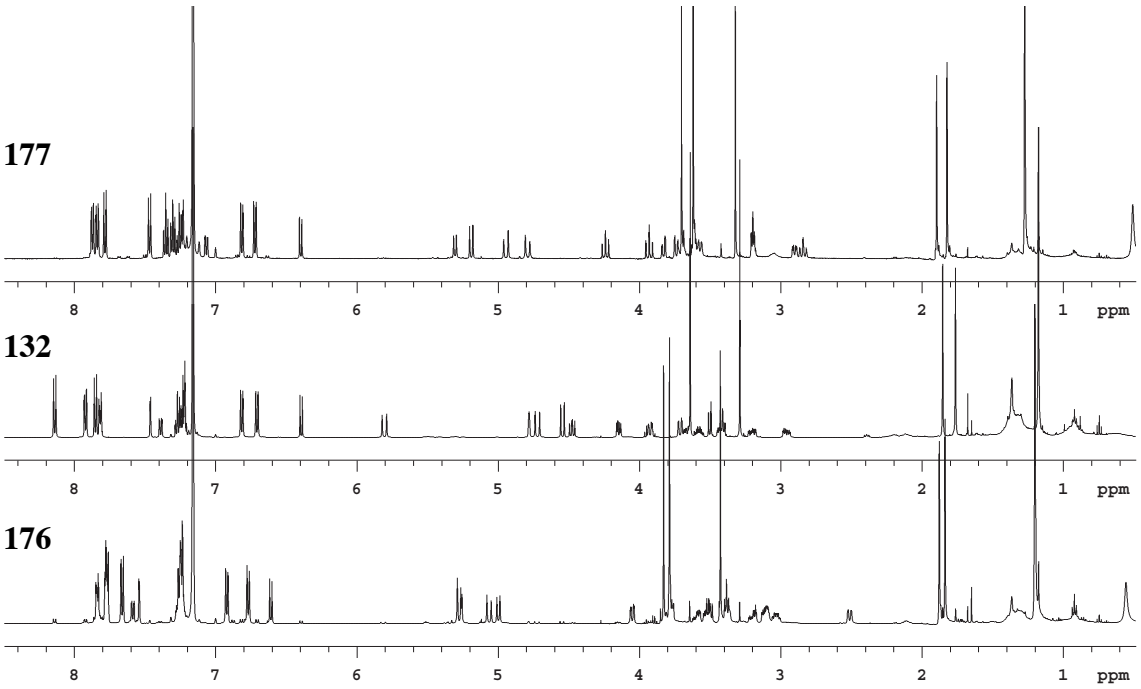
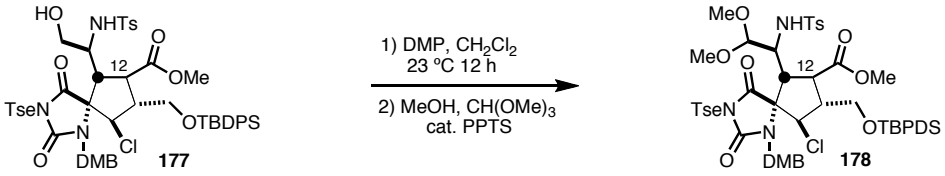


Figure 3.1. Spectral comparison of methyl esters **176** and **177**.

It seemed conceivable at his point to deduce that methyl esters **176**, and **177** were a pair of C12 epimers, but further spectroscopic evidence to unambiguously assess this possibility was required. In addition, these initial promising results provided the impetus for further investigations aimed at optimizing the reaction conditions and possibly gaining an insight into the mechanistic details of the transformation.

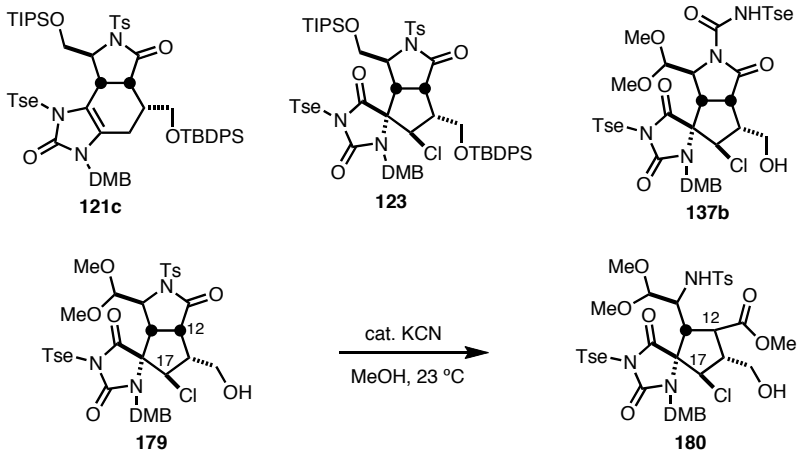
Initial attempts to explore further reactivity of ester **177** (which was presumed to be the epimerized one) using conditions utilized before (see Chapter II) resulted in quite sluggish reactions but provided nonetheless modest yields of dimethyl acetal **178** Assignment of the stereochemistry at C12 remained at this point elusive.

Scheme 3.14



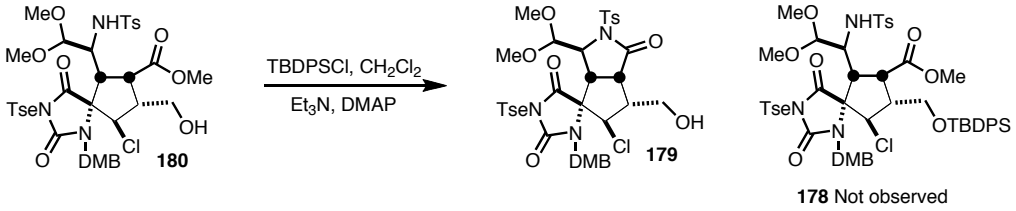
Further studies seemed to indicate that the lactam opening reaction required both a free hydroxy moiety, and a tosylated lactam to proceed to the formation of a methyl ester. When substrates **121c**, **123** and **137b** were subjected to the reaction conditions in fact, only unreacted starting materials were recovered even after prolonged reaction times. On the other hand, treatment of advanced intermediate **179** led to complete and clean conversion to methyl ester **180** in less than 24 hours at room temperature, as confirmed by the appearance of diagnostic signals at δ 3.70 ppm (s, 3H OCH_3) and δ 4.70 ppm (d, 1H NH) in the ^1H NMR spectrum (C_6D_6).

Scheme 3.15



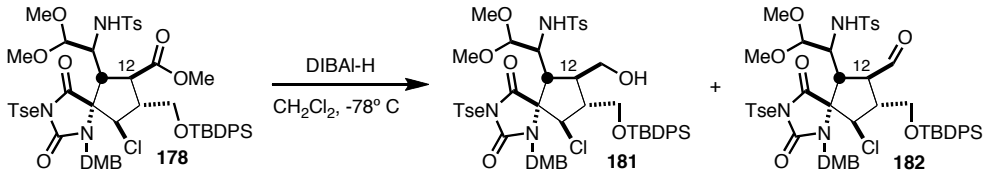
The isolation of ester **180** provided a convenient opportunity to more accurately characterize these systems as well as to gain more insight into their reactivity. Protection of the free alcohol as the TBDPS ether would in fact generate an intermediate that had previously been observed (**178** in Scheme 3.14), and spectroscopic comparison of the two substrates would be extremely valuable. Surprisingly however, when ester **180** was treated with TBDPSCl under standard conditions the only product isolated was the starting lactam **179**, presumably deriving from intramolecular attack of the sulfonamide onto the methyl ester. Although direct comparison with acetal **178**, synthesized from the ester **177** (presumably epimerized at C12) was not possible, this result seemed to provide indirect evidence that the configuration of C12 had not been inverted in **180** after lactam opening at room temperature.

Scheme 3.16



Interestingly on the other hand the attempted reduction of the methyl ester moiety in dimethyl acetal **178** using DIBAl-H resulted in an approximately equimolar (by comparison of key signals in the crude ^{1}H NMR spectra) mixture of the desired alcohol **181** and the half-reduced corresponding aldehyde **182**.

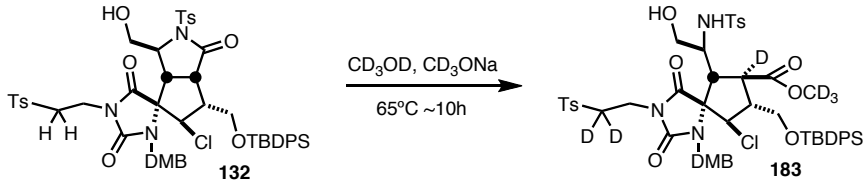
Scheme 3.17



The isolation of a stable aldehyde provided further strong, albeit indirect evidence that the stereochemistry at C12 of the starting methyl ester **177** had been inverted upon lactam opening. It seemed plausible in fact to expect that if the C12 center was not epimerized, the sulfonamide nitrogen would easily attack the available vicinal electrophile, as had presumably been observed before (Scheme 3.16), generating, in this instance, a carbinolamine. Conversely, after epimerization, the aldehyde would be on the opposite face of the chlorocyclopentane core with respect to the sulfonamide, and interaction between these two termini would appeared to be highly unlikely, as it would give rise to a very strained bicyclic system housing two *trans*-fused five-membered rings. Were a carbinolamine to form under these circumstances, it seems reasonable to anticipate that it would easily revert back to the thermodynamically more stable open aldehyde tautomer.

Strong evidence for the C12 epimerization was finally provided by a deuterium incorporation study. Treatment of lactam **132** with freshly prepared deuterated sodium methoxide, in deuterated methanol solution under the established heating conditions (Scheme 3.13) cleanly generated a new product that based on mass data and ^{1}H NMR comparison with amino alcohol **177** was assigned as deuterated ester **183**.

Scheme 3.18



The NMR comparison in particular (Figure 3.2) showed that although the two spectra were virtually identical, some significant changes had occurred in key diagnostic signals.

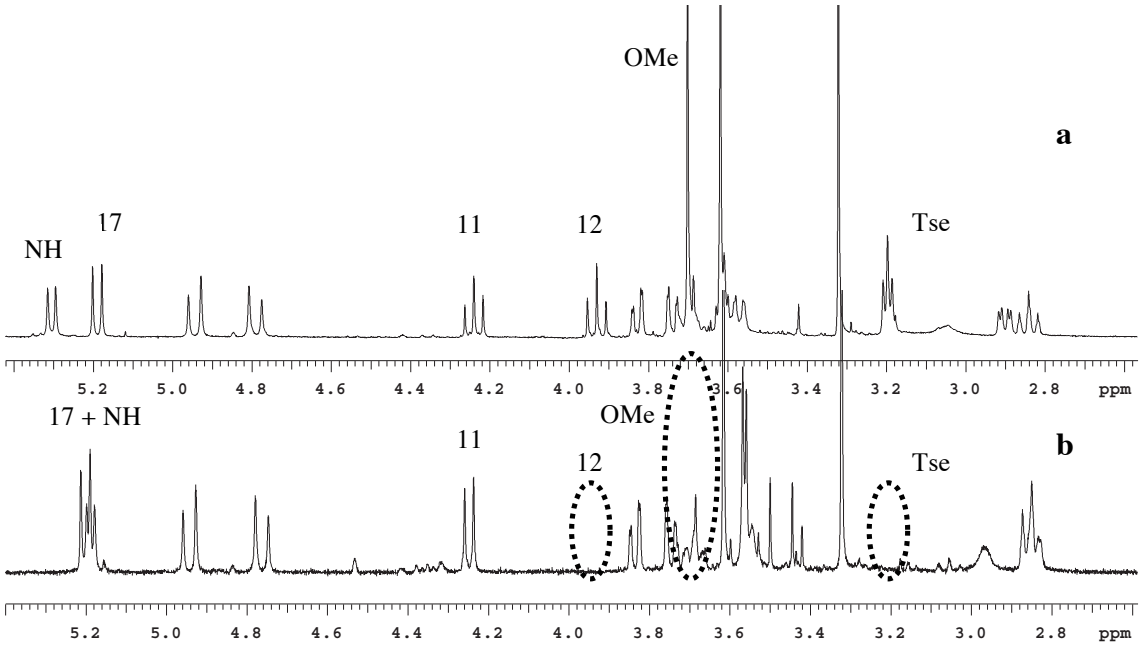


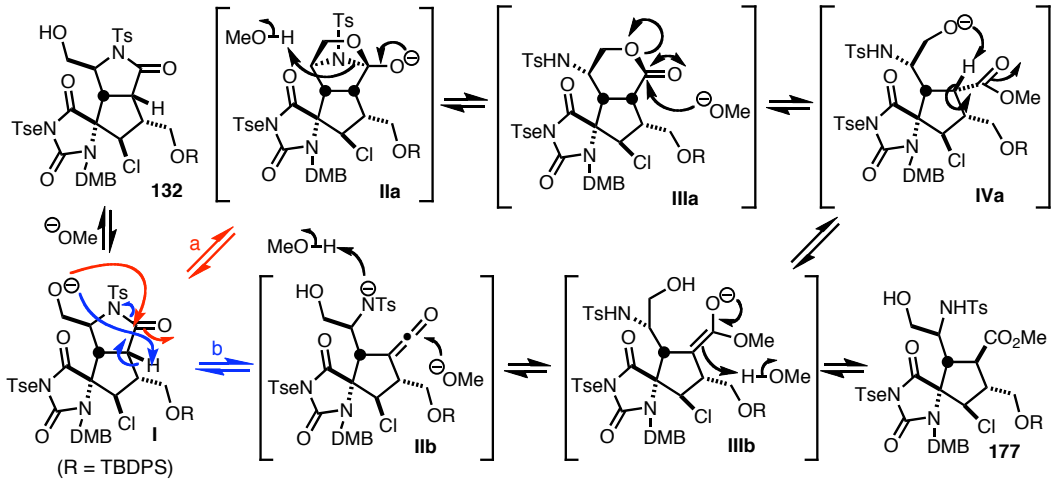
Figure 3.2. Spectral comparison of a) aminoalcohol **177** and b) deuterated ester **183**.

Namely, the methoxy signal of the methyl ester had disappeared, which indicated the formation of the expected deuterated methyl ester, also confirmed by mass data. Most importantly however, the signal relative to H12 had also disappeared and the multiplicity of the vicinal H11 proton had changed from a doublet of doublets (apparent triplet) to a doublet, which was consistent with the incorporation of a deuterium atom at C12 (α to the methyl ester), supporting in turn the formation of the enolate transient intermediate necessary for the desired inversion of stereochemistry. In addition, though unexpectedly, deuterium incorporation α to the sulfone in the Tse protecting group was also observed, as determined by the disappearance of the relative signal in the ^{1}H NMR (Figure 3.2). In retrospect, given the enhanced acidity of these protons due to the presence of the sulfone, this outcome is not surprising, and it could potentially account for the relative low yield of the process. It is conceivable, in fact, that under the basic reaction conditions, proton abstraction at the α position of to the sulfone could trigger cleavage of the Tse group.

Unfortunately several attempts to isolate this presumed by product met with no success and the possibility of its existence remained a mere speculation.

Considering the experimental information accumulated up to this point, a plausible mechanistic rationale for the C12 epimerization could be advanced (Scheme 3.19).

Scheme 3.19

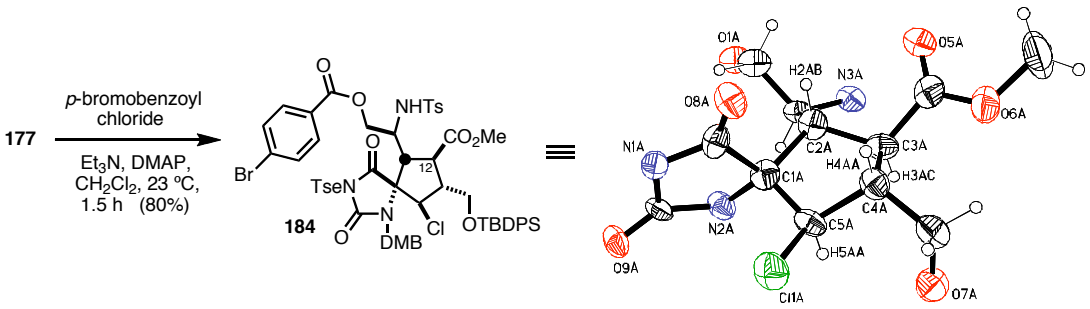


Given the non-reactivity of substrates featuring a protected northern primary alcohol (either as the TIPS ether or the dimethyl acetal (*vide supra*) it seemed reasonable to conclude that direct attack of a methoxy nucleophile on the lactam carbonyl was highly unlikely. On the other hand if this lack of reactivity were to be the consequence of steric hindrance generated by the protecting group, impeding the approach of the nucleophile, this avenue would return to be a viable one once the protecting group was removed. The result obtained with dimethyl acetal **179** however (Scheme 3.15) seemed not to support this assessment, as the desired methyl ester was in fact generated as the sole product. It appeared that a reasonable alternative could involve the alkoxide generated on the free alcohol under the reaction conditions, acting either as an internal nucleophile or an internal base, or potentially as both. We envisioned that the newly generated alkoxide **I** could attack the lactam carbonyl (path a) generating a bicyclic tetrahedral intermediate such as **IIa**, which could then collapse providing neutral pyranone **IIIa**. Nucleophilic

methoxide attack on the carbonyl of this system would then deliver a methyl ester **IVa** regenerating the initial alkoxide. This could in turn act as a base abstracting the α-proton of the methyl ester, giving rise to the corresponding enolate **IIIb**, which could then be reprotonated under the reaction conditions generating the thermodynamically favored epimerized ester **177**. Alternatively, the initial alkoxide, acting as a base, could directly abstract the α-proton of the tosyl lactam (path b) generating transient ketene species **IIb**, which could be trapped by methoxide providing the same enolate **IIIb**, thus leading to the thermodynamic product.

The evidence gathered up to this point supported the desired C12 epimerization, and methyl ester **177** was advanced to further studies that are described in the following Chapters. The results obtained in the course of these studies provided ulterior confirmation of the required inversion of configuration, but it was not until several months later that we were able to obtain crystallographic confirmation of the proposed structure.

Scheme 3.20



Reaction of ester **177** with *p*-bromobezoyl chloride provided benzoate derivative **184** which, after several attempts, could be recrystallized, providing crystals suitable for X-ray analysis. The crystal structure obtained (shown in Scheme 3.20 devoid of protecting groups for clarity) not only clearly confirmed the "all-*trans*" arrangement of the substituents on the chlorocyclopentane core, but also provided unequivocal evidence of the correct configuration of the key spirocyclic hydantoin, which had been assigned on the basis of extensive NMR analysis.

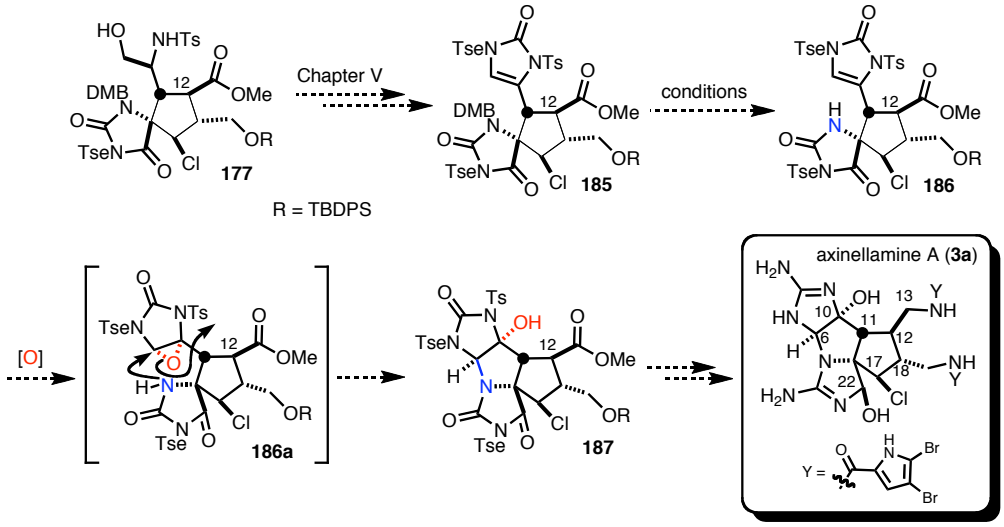
CHAPTER IV

SYNTHESIS OF THE CORE OF AXINELLAMINE AND PALAU'AMINE FROM A COMMON CHLOROCYCLOPENTANE PRECURSOR*

4.1 DMB Deprotection Studies

With the structure of the C12 epimerized ester **177** firmly secured and some promising preliminary results for the formation of the northern pendant imidazolone (discussed in Chapter V), we then focused our efforts on the removal of the DMB protection from the spirohydantoin "lactam" nitrogen, in order to generate the required nucleophile for the projected intramolecular oxidative cyclization that would deliver the tetracyclic core of the axinellamines (**187**, Scheme 4.1).

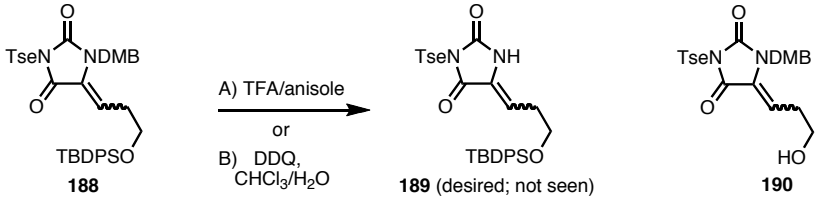
Scheme 4.1



* Part of this chapter is reprinted with permission from "Facile Synthesis of the Trans-Fused Azabicyclo[3.3.0]octane Core of the Palau'amines and the Tricyclic Core of the Axinellamines from a Common Intermediate" by Zancanella, M. A.; Romo, D. *Org. Lett*. **2008**, *10*, 3685-3688. Copyright 2008 American Chemical Society.

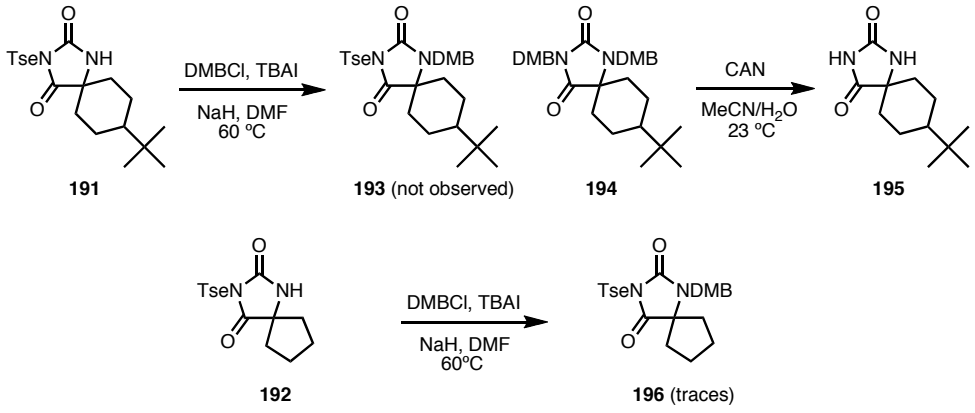
Even though the literature precedents for the cleavage of activated benzyl ethers were abundant and quite encouraging, our preliminary investigations on a simplified model system (Scheme 4.2) provided mostly sluggish and inconsistent results, leading to undesired outcomes or generating complex mixture of products that could not be neatly separated and characterized. Reaction of hydantoin **188** with trifluoroacetic acid (TFA) in the presence of anisole for instance, led to complete cleavage of the TBDPS group leaving the target DMB ether unaltered. On the other hand treatment with dichlorodicyanoquinone (DDQ) gave no appreciable reaction even after overnight stirring.

Scheme 4.2



These initial inconclusive results led to consider different model systems, and having large quantities of Tse-spirohydantoins **191** and **192** in hand from previous endeavors, we anticipated that protection of the free nitrogen would quickly provide convenient platforms to thoroughly investigate the desired transformation. The seemingly trivial benzylation of the free nitrogens of **191** and **192** however, proved in fact to be unexpectedly problematic.

Scheme 4.3

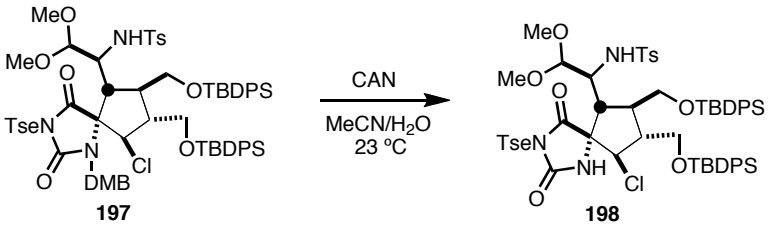


In the case of *t*-butyl-cyclohexyl derivative **191** the use of excess sodium hydride promoted the cleavage of the base-sensitive Tse group resulting in the alkylation of both nitrogens generating bis-DMB hydantoin **194**. Though unplanned, this result provided nonetheless a suitable material for DMB deprotection studies, and it was therefore treated with ceric ammonium nitrate (CAN) resulting in complete loss of starting material in less than one hour. Appearance of the expected aldehyde signals in the crude ^{1}H NMR spectrum confirmed the desired oxidative cleavage of the benzyl groups, however the deprotected spirohydantoin **195** was not isolated and characterized.

Several attempts to introduce the DMB moiety onto the cyclopentyl hydantoin **192** resulted in slow and incomplete reactions generating only trace amounts of desired product **196**. Deprotection studies on very small amounts of material were deemed not worthwhile at this juncture, and this model study was abandoned.

Pleasingly, testing dimethyl acetal **197**, a potential advanced intermediate *en route* to the axinellamines (discussed in Chapter V), provided the first breakthrough. Treatment with CAN under the conditions identified in the course of the model study in fact, led to rather clean cleavage of the DMB group. The required reaction time could not be exactly identified in this instance because what was initially thought to be unreacted starting material by TLC analysis, proved instead to be the aldehyde byproduct of the oxidative cleavage. Due to the small scale of the reaction, the exact yield could not be determined either.

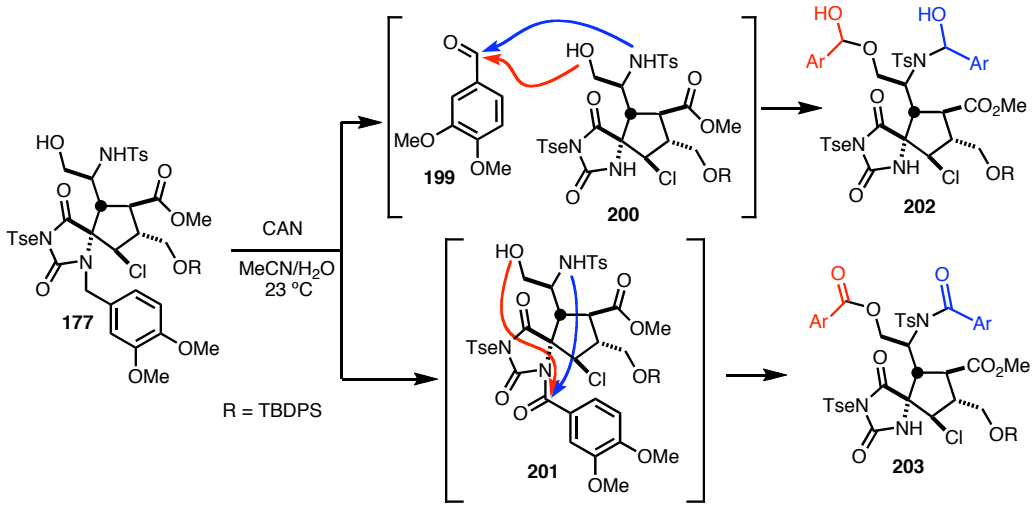
Scheme 4.4



After a few fruitless attempts to remove the DMB protection from the advanced imidazolone **185** (discussed in Chapter V), it was decided to explore an early

deprotection on the C12-epimerized methyl ester **177** (Scheme 4.1). Treatment of the starting material with 2 equivalents of CAN (in MeCN/H_2O 4:1) at room temperature seemed to lead to no reaction (by TLC) after overnight stirring. Adding excess (4 more equivalents) reagent and increasing the temperature (55ºC for 16h) seemed to have no effect. Upon analysis of the ^{1}H NMR spectrum of the crude material however it was discovered that a reaction had indeed occurred as confirmed by the appearance of the very diagnostic DMB aldehyde signals. Disappointingly however, the characteristic methoxy signals of the DMB group were still clearly visible in the two products isolated after purification. Based on these preliminary observations a potential scenario began to emerge in which, under the reaction conditions the aldehyde byproduct **199** generated by the oxidative cleavage was captured by either of the nucleophilic termini of the amino alcohol **200** (Scheme 4.5), generating either a stable hemi-acetal (red path) or a stable carbinolamine (blue path). Alternatively it is plausible to envision that CAN could promote complete benzylic oxidation of the DMB group generating transient extended imide **201**, which could in turn be the target of the nucleophilic attack of the amino alcohol (*intra-* or *inter*-molecularly), resulting in the formation of either an ester or an amide. The relatively small scale of these preliminary trials however, did not allow at this point for a complete, unambiguous characterization of the byproducts obtained.

Scheme 4.5



Treatment of the starting material with TFA and anisole at room temperature led to complete recovery of the unreacted amino-alcohol. Heating to 65ºC overnight resulted in the isolation of a mixture of products, tentatively assigned (based on ^{1}H NMR analysis) as the free diol **204**, and the mono- and/or bis- corresponding TFA derivatives **205** (Figure 4.1). In all the products the DMB group appeared to have remained unaltered. Given the small scale of the reaction and the sluggish outcome, resolution of the complex mixture by purification was not attempted.

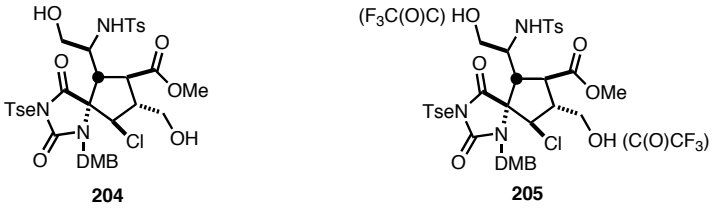
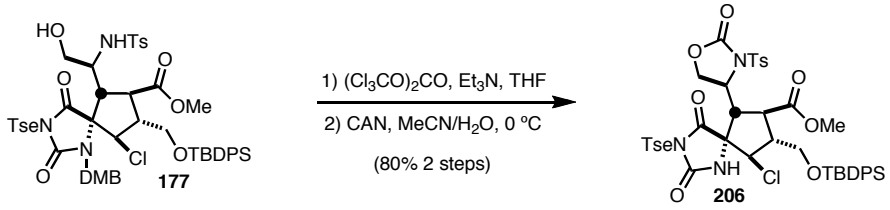


Figure 4.1. Potential products of the TFA/anisole reaction.

The above results seemed to have established that DMB cleavage with CAN could potentially be facile provided that the presumed departing aldehyde be properly trapped or that any possibility of latent nucleophilic attack be prevented. To test the latter approach the amino alcohol termini were blocked by the formation of the corresponding oxazolidinone using triphosgene. Gratifyingly, the resulting crude material underwent smooth and fast DMB cleavage under the established reaction conditions (5 equivalents of CAN in 3:1 MeCN/H_2O at 0ºC for 1 hour) generating a remarkable 80% yield of desired product **206** over the two steps.

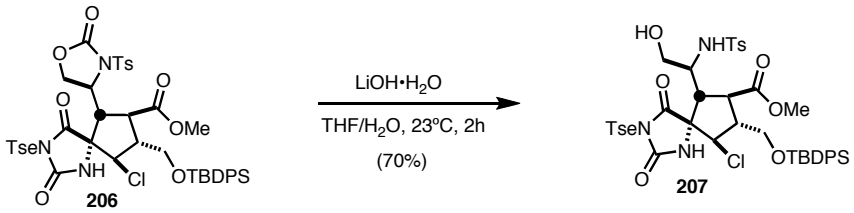
Scheme 4.6



Interestingly, the *des*-DMB product **206** was *less* polar than the starting material, although it was UV active it was *not* stained by Cerium Ammonium Molybdate (typically used for these molecules), and had an Rf value virtually identical to that of DMB aldehyde (**199**, Scheme 4.5). In spite of this, however, separation of the two species by flash column chromatography proved to be extremely easy.

It was also pleasing to find that the cleavage of the oxazolidinone proceeded efficiently with lithium hydroxide at room temperature, liberating the initial amino alcohol functionality with good yield (70% after purification). The methyl ester did not appear to be affected during the process, although partial hydrolysis of this moiety to the corresponding acid could account for the mass balance of the reaction. As the presumed acid however could not be detected, this remains only a speculation.

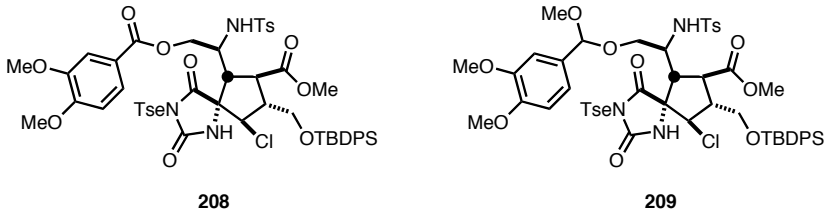
Scheme 4.7



Although the above result constituted a significant progress, we reasoned that this approach was not optimal, as it required the introduction of a temporary new functionality, lengthening in turn the overall synthetic sequence, for the sole purpose of removing a protecting group. We sought therefore to find efficient ways to trap the oxidized DMB species (*vide supra*) so that the deprotection could be performed on the "open" amino alcohol. We envisioned that using an excess of a nucleophilic additive in the reaction mixture could, in principle, sequester the departing aldehyde, or cleave the activated imide resulting from benzylic over-oxidation.

The addition of 1,3-propanediol led to the isolation of the desired product **207** in approximately 50% yield along with a second, more polar product which by ^{1}H NMR and

MS analysis was identified as diester **208**, and which seemed to be consistent with the mechanistic considerations presented in Scheme 4.5. Namely, the DMB methoxycarbenium intermediate (generated after single electron transfer) reacts with water (or the oxygen nucleophile additive), and either eliminates DMB aldehyde (observed in the crude ^{1}H NMR) leading to the formation of the desired product, or intramolecularly acylates the pendant alcohol generating **208** (Figure 4.2). This assessment seems to be supported also by the isolation of mixed acetal **209** when methanol was substituted for water and no additive was used.



208 **209**

Figure 4.2. Byproducts of the DMB removal on the unprotected amino alcohol.

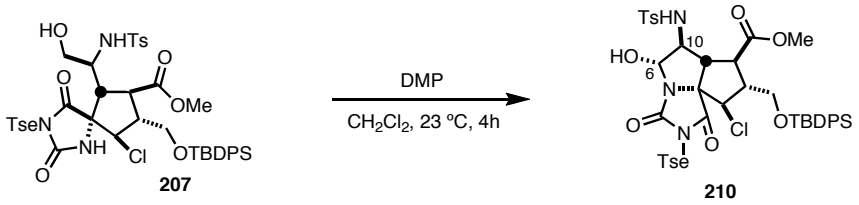
Surprisingly, the use of ethanolamine (expected to mimic the amino alcohol moiety) as additive under the same reaction conditions led to complete recovery of unaltered starting material even after prolonged reaction time and increased temperature.

4.2 Synthesis of the Angular *Aza*-Triquinane Core of the Axinellamines

With small amounts of newly generated *des*-DMB amino alcohol in hand we decided to explore the intramolecular cyclization that would deliver the tricyclic core of the axinellamines. We reasoned based on molecular model analysis, that given the close proximity of the hydantoin free nitrogen to the carbinol carbon C6, oxidation of the alcohol to the corresponding aldehyde would provide a convenient electrophile that could, in turn, potentially trigger the desired cyclization *in situ*. As anticipated, treatment with DMP pleasingly led to the isolation of a modest yield (~38%) of tricyclic aminal **210** as confirmed by the appearance in the ^{1}H NMR of aminal proton 6 at δ 5.89 ppm , and by the complete absence of any aldehyde signals in the crude ^{1}H NMR. The tentative

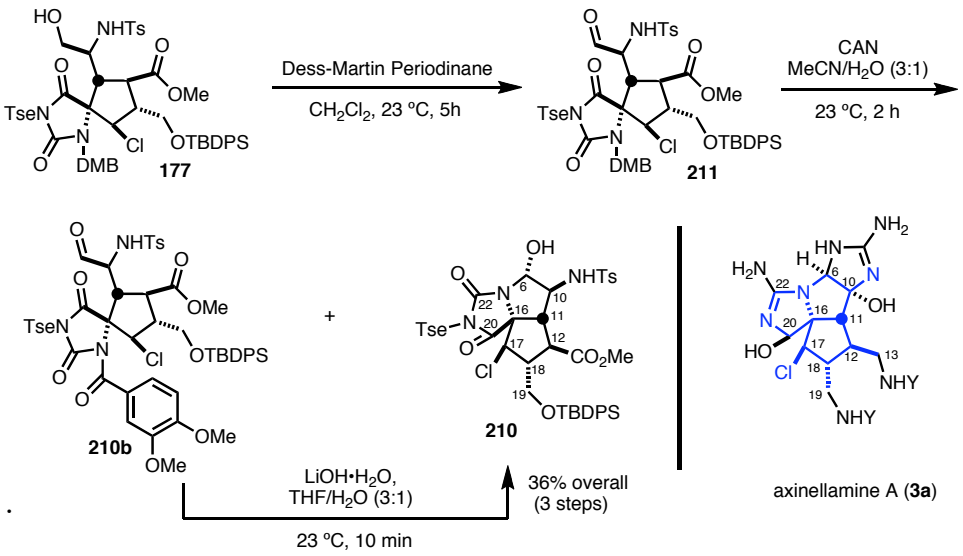
assignment of the stereochemistry at C6 was made on the basis of coupling constants and model analysis.

Scheme 4.8



Isolation of **210** attested to the predicted ease of cyclization of the hydantoin nitrogen in the presence of an adequate electrophilic moiety. This result prompted us to explore an alternative, more direct approach to arrive at carbinolamine **210**, and it was envisioned that inverting the order of events could deliver the desired outcome. Thus, oxidation of the DMB protected amino alcohol with DMP cleanly generated a stable aldehyde, which was carried on to the next step without purification. Treatment of the crude material with CAN then, under the established conditions, led to the isolation of a modest yield of a product that was spectroscopically identical to aminal **210**, along with a major byproduct that could not, in the early trials, be unambiguously identified.

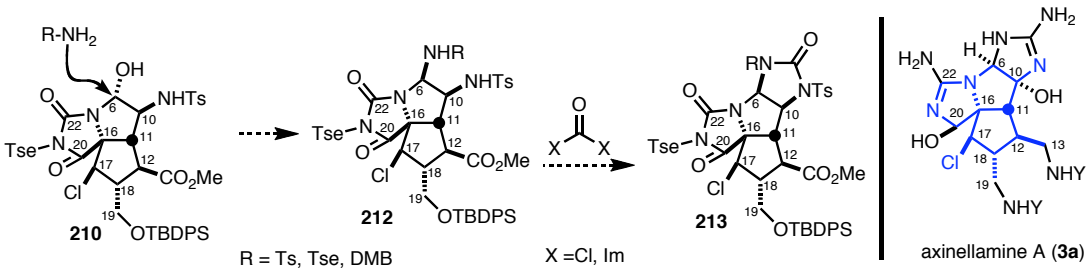
Scheme 4.9



Much later, further experimentation provided strong indirect evidence that the major byproduct of the CAN reaction was the over-oxidized benzoate derivative **210b**. Following literature precedents then,[67] this material was briefly exposed to typical hydrolysis conditions (LiOH THF/H_2O at ambient temperature for 10 minutes) cleanly generating additional aminal **210**, in modest yield for the overall, 3-step process. Aminal **210** featured the completely functionalized tricyclic core of the axinellamines (highlighted in Scheme 4.9), and it was deemed to be a suitable precursor for the completion of the synthesis of the target natural products. Investigations in this direction were however brief, as our efforts were geared toward the development of a potentially biomimetic approach to the PIA's (discussed in Chapter V), and eventually this admittedly *abiotic* strategy was abandoned.

As discussed above, the stereochemistry of the carbinolamine center (C6) could not be unambiguously established, but it was assumed to be *trans* to the sulfonamide at C10 based on model, and stereoelectronic considerations. Our first efforts therefore, were aimed at inverting the configuration of this center with a nitrogen nucleophile in order to generate a *syn* diamine **212**, which could then be annulated using triphosgene (or analogs), closing the D ring thereby delivering the complete carbon framework of the axinellamine core **213** (Scheme 4.10).

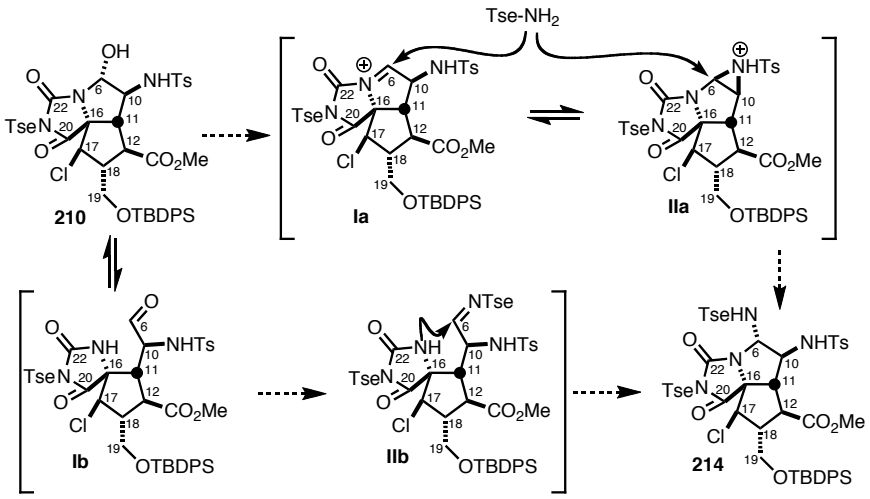
Scheme 4.10



Thus, treatment of aminal **210**, with tosylethylamine at 50ºC (no reaction was observed between 0ºC and 23ºC), resulted in clean and complete conversion to bis-amine **214** (Scheme 4.11; confirmed by 1 and 2D ^{1}H NMR, and mass data) with up to 64% yield

after purification. Based on coupling constant analysis this product seemed to have retained the original C6/C10 *trans* relative stereochemistry, indicating that the transformation could proceed *via* an acyliminium **Ia** and/or an aziridinium transient intermediate **IIa** (Scheme 4.11).

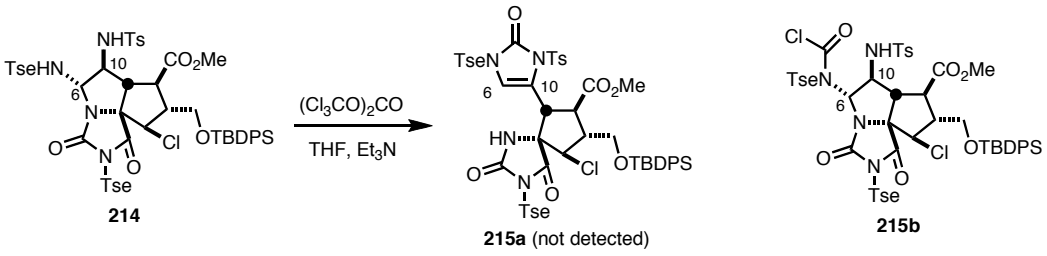
Scheme 4.11



In addition a pathway that involves the aldehyde tautomer of the starting material **Ib** undergoing imine formation followed by intramolecular ring closure **IIb** is also a viable option. Even though the acyliminium and the imine transient intermediate could potentially give rise to mixtures of C6 epimers, it is plausible to assume (as a single product was consistently isolated) that under the reaction conditions they would equilibrate converging to the thermodynamically favored *trans* species. In the case of the aziridinium intermediate **IIa** it would be reasonable to expect a mixture of regioisomers, with the amine nucleophile attacking either C6 or C10. As this outcome was however not observed we inferred that an aziridinium intermediate was either not formed or was never present in significant concentration to interact with the incoming nucleophile (i.e. the indicated equilibrium lies far to the left).

In an attempt to investigate the reactivity of diamine **214** we envisioned that treatment with triphosgene as projected (*vide supra*), could potentially provide either an advanced intermediate viable to complete the synthesis of the target product (imidazolone **215a** in Scheme 4.12), or at least, indirect evidence to support the stereochemical assignment of C6.

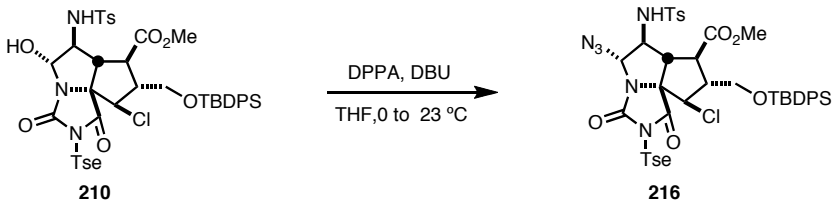
Scheme 4.12



The fact that no reaction occurred under standard conditions between 0 ºC and 20 ºC seemed to be a clear indication that the two amine functionalities lied on opposite faces of the core pyrrolidine ring and could therefore not be simultaneously engaged by the electrophile. Use of more forcing conditions (50 ºC for 4.5 h) on the crude recovered starting material led to complete conversion to a new product, which based on NMR and mass spectrometry data was assigned as carbamoyl chloride **215b**. Constructs like **215b**, which may be expected to be significantly labile, have in fact been reported to be remarkably stable, [68] and in some cases, amenable to silica gel purification.

Having gathered abundant evidence that the substitution reaction at C6 was under thermodynamic control, we tried to overcome this bias using Mitsunobu conditions, which typically involve S_N2 displacement of an activated alcohol. Unfortunately using diphenyl phosphoryl azide (DPPA) at 0 ºC did not result in any appreciable reaction, but led to complete conversion upon increasing the temperature to ambient level. Once again, based on coupling constant analysis, the newly formed azide **216** appeared to have retained the original configuration, seemingly deriving from thermodynamically controlled nucleophilic addition to a transient acyliminium species (see **Ia** in Scheme 4.11).

Scheme 4.13



As anticipated, our main focus was to develop a biomimetic, unified route to axinellamine and palau'amine, therefore the *abiotic* efforts described above were eventually abandoned, and the investigations toward the synthesis of a common late-stage precursor (discussed in Chapter V) that were performed concomitantly, regained priority.

4.3 Synthesis of the *Trans*-azabicyclo[3.3.0]octane Core of Palau'amine

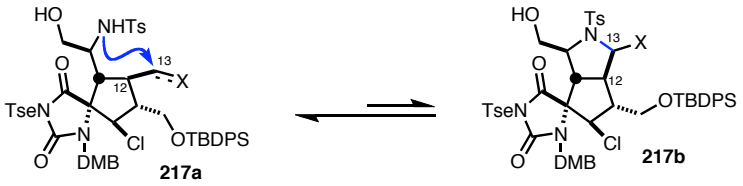
In our unified strategy toward palau' amine and axinellamine, spirohydantoin **123** was to be the point of divergence (see Chapter II) as this tricyclic structure featured the completely functionalized ABC core of palau'amine (**2**), but required an inversion of configuration at C12 to match the stereochemical relationships found in axinellamine (**3**) (*vide supra*).

While our studies on the epimerization of C12 were ongoing, the structural revision of palau'amine (see Chapter II)[3] appeared in the literature, presenting convincing evidence that the original assignment of the relative stereochemistry of key centers in the chlorocylopentane substructure was incorrect. The revised configuration of C12 and C17 revealed that the spirocyclic cores of axinellamine and palau'amine were in fact identical, supporting a common biosynthetic origin.

Having identified efficient conditions to invert the C12 configuration (see Chapter III) we reasoned that intermediate ester **177**, already shown to be a suitable precursor to the azatriquinane core of axinellamine **210** (*vide supra*), could in principle lead also to the construction of the revised ABC substructure of palau'amine. To this end we envisioned that nucleophilic attack of the sulfonamide onto an adequate electrophile at C13 would regenerate the pyrrolidine substructure of the natural product. At first analysis (Scheme 4.14) however, and based on previous results (see Chapter III) it appeared that

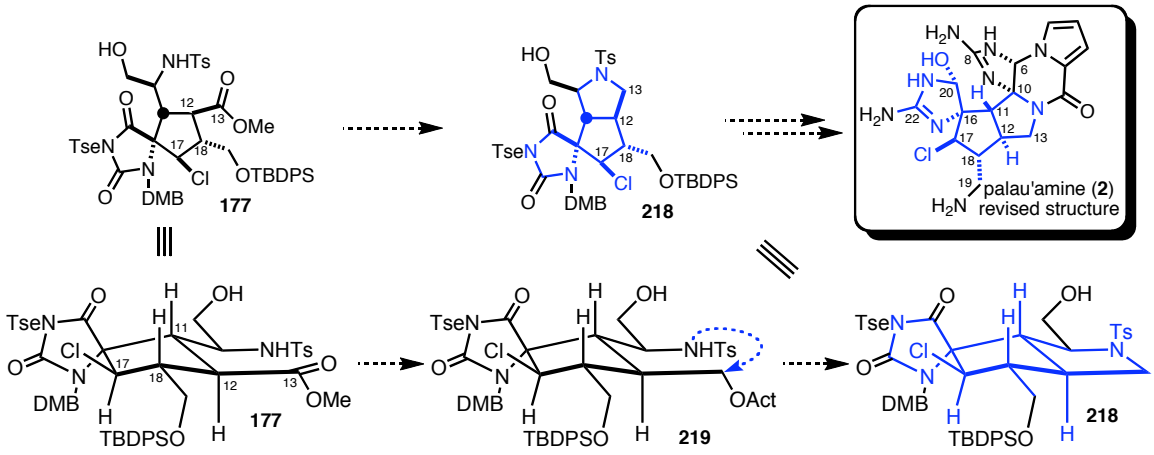
the two reacting termini, lying on opposite faces of the chlorocyclopentane core, would either not be properly oriented to interact constructively or would lead to regeneration of the starting substrate **217a** *via* thermodynamic equilibration to relieve the strain of the *trans* [3.3.0] bicyclic system **217b**.

Scheme 4.14



Upon examination of molecular models however, we reasoned that in the presumed thermodynamically preferred conformation of methyl ester **177**, in which all the substituents around the chlorocyclopentane core adopt a *pseudo*-equatorial arrangement, it seemed that the sulfonamide and C13 could be in close enough proximity to react efficiently. In addition, to overcome the issue of possible equilibrating tautomers (Scheme 4.14) we envisioned an S_N2 pathway, in which the loss of an adequate leaving group from C13 in **219** would render the process irreversible, generating a double envelope structure that appeared not to be as highly strained as originally assumed.

Scheme 4.15

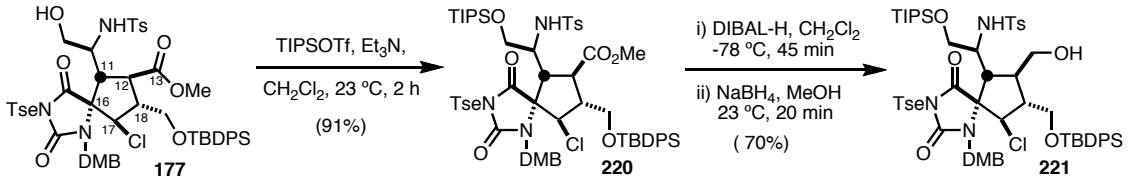


After a brief survey of the literature we were pleased to find that sulfonamides often act as nucleophiles under Mitsunobu conditions (a fact supported also by our findings on related systems discussed in Chapter VI), thus reduction of the methyl ester to the corresponding primary alcohol would provide a substrate suitable for the projected *intra*-molecular displacement, leading to the target *trans* bicyclic system.

At the onset of our investigation in this direction we reasoned that protection of the primary alcohol at C6 would be necessary to eliminate any potential regioselectivity issues arising from competing cylization of the sulfonamide resulting in the formation of an aziridine. It was decided that use of a triisopropylsilyl (TIPS) ether would be convenient, as it would facilitate the comparison of spectroscopic data with similar intermediates generated in our previous studies toward the original structure of palau'amine (see Chapter I).

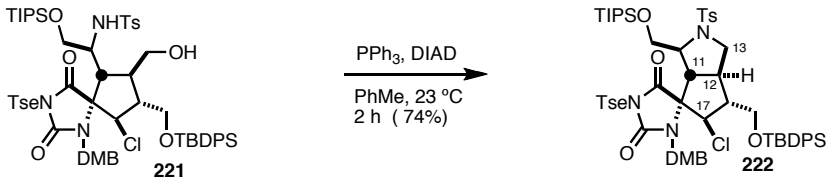
The reduction of the ester moiety in the protected amino alcohol **220** using DIBAL under standard conditions was unexpectedly sluggish resulting in the formation of a mixture of the desired primary alcohol **221** and the corresponding aldehyde (not shown). It is plausible that coordination of the aluminum reagent with the basic sulfonamide was the reason for the reduced reactivity that led to the observed partial reduction. Attempts to drive the reaction to completion by increasing the temperature resulted in the formation of complex, intractable mixtures of unidentified products. However, brief exposure of the crude mixture obtained after shortened treatment with DIBAL at low temprature to sodium borohydride at ambient temperature quickly completed the reduction leading to the isolation of synthetically useful yields of target alcohol.

Scheme 4.16



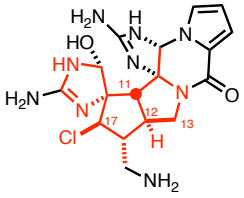
The synthesis of alcohol **221** set the stage for the projected intramolecular ring closure and we were delighted to find that under standard Mitsunobu conditions at ambient temperature the desired cyclization occurred efficiently, generating consistently good yields of *trans*-azabicyclo [3.3.0] octane **222**.

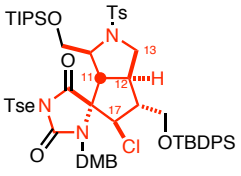
Scheme 4.17



Evidence for the stereochemistry of this bicyclic intermediate was garnered by comparison of the coupling constants of several key protons of pyrrolidine **222** with those reported for palau'amine by Quinn[3b] (Table 4.1). The coupling constants indeed correlated well further confirming the revised stereochemistry of palau'amine *i.e.* the *trans*-azabicyclo[3.3.0]octane core.

Table 4.1. Coupling constant comparison between **222** and natural palau'amine.





proton	**palau'amine**[b] mult (*J*)[c]	**222** mult (*J*)[c]
11	d (14.4)	dd (14.5. 10.0)
12	dddd (14.6, 10.2, 9.0, 7.2)	dddd (14.5, 11.0, 10.5, 6.5)_
13 α	dd (10.2, 7.2)	dd (11.0, 6.5)
13 β	t (10.2)	t (11.0)
17	d (9.0)	d (10.5)

In addition, selected nOe enhancements for tricycle **222** also corroborated the relative stereochemistry and the conformation of this rather rigid, spirotricyclic system (Figure 4.3).

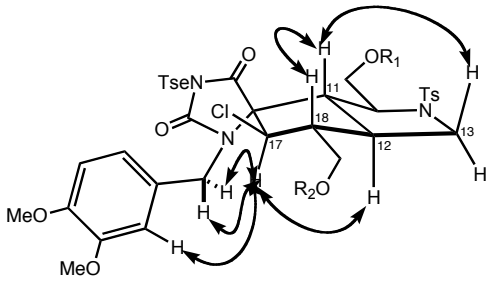
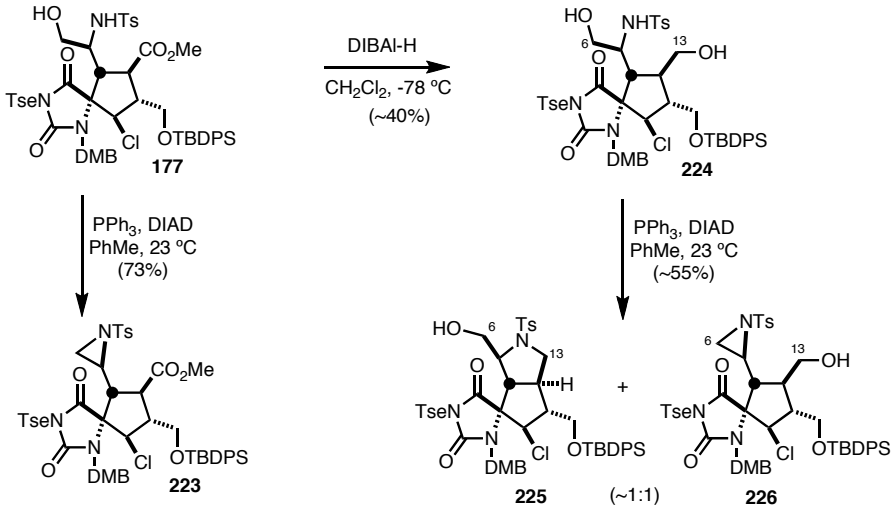


Figure 4.3. Selected nOe enhancements in tricycle **222**.

Once the structure of tricycle **222** had been convincingly established we became interested in assessing whether the aziridine mode of cyclization that we had sought to prevent (*vide supra*) was indeed a viable avenue of reaction for methyl ester **177**, and if so, to what extent as compared to the ring closure leading to the desired pyrrolidine. As we had correctly anticipated, exposure of methyl ester **177** to the established Mitsunobu condition provided the aziridine **223** deriving from nucleophilic displacement of the activated alcohol at C6 from the adjacent sulfonamide. It is noteworthy that this reaction required the use of excess reagent and prolonged time but nonetheless generated the expected product in good yields. Having determined that aziridine cyclization was, in fact possible we endeavored to assess how competitive this alternative reaction manifold was with the desired pyrrolidine annulation, and we envisioned that aminodiol **224** would provide us with a quick insight into the relative reactivity at C6 and C13 Reduction of the ester moiety in **177** with DIBAL was once again rather sluggish, and as before we ascribed the reduced reactivity of the aluminum reagent to the abundance of Lewis basic sites in the substrate. In this particular instance only partial conversion to the desired product was observed, with only traces of the half-reduced aldehyde. Resubjecting the crude material to the reaction conditions for prolonged time completed the conversion, generating however only modest yields of the target diol **224**.

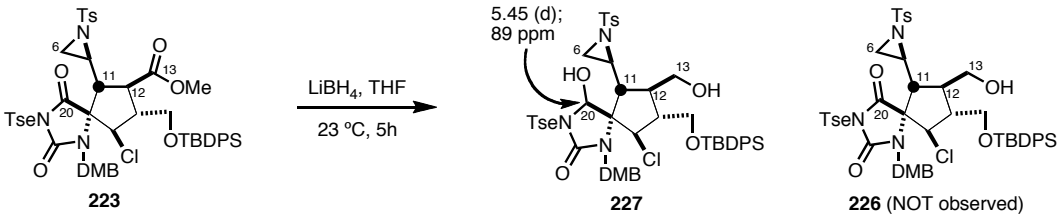
Scheme 4.18



Under the established Mitsunobu conditions this diol generated virtually equal amounts of pyrrolidine **225** and aziridine **226** (by comparison of key signals in the crude ^{1}H NMR spectrum), confirming that the two modes of intra molecular cyclization were indeed competitive. It is noteworthy that under standard conditions the relative rate of a 5-*exo-tet* ring closure is several orders of magnitude higher than a 3-*exo-tet* annulation[69] however, the result of our competition experiment revealed that in our setting, likely due to the inherent strain of the *trans* conformation of the nascent bicyclic system, the rate of 5-membered ring formation was greatly slowed.

The structures of both pyrrolidine **225** and aziridine **226**, were assigned by NMR and mass data, and the former could further be confirmed by comparison of spectroscopic data with the product deriving from selective TIPS deprotection of tricyclic system **222** (Scheme 4.17), using TBAF as previously discussed (see Chapter II). Conversely, attempts to corroborate the structure of **226** by similar comparison with the ^{1}H NMR spectrum of the product derived from reduction of the ester functionality in aziridine **223**, were thwarted by the unexpected reactivity of this substrate (Scheme 4.19).

Scheme 4.19



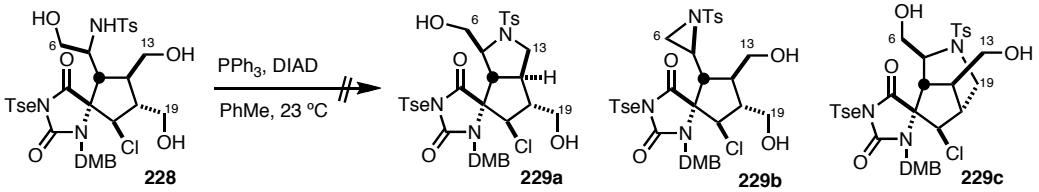
Using either DIBAL or lithium borohydride, in fact, the reaction led to the generation of excellent yields of C20 aminal **227** as indicated by the appearance of a new signal in the ^{1}H NMR at $\delta = 5.45$ ppm which is consistent with a carbinolamine proton. In addition, this signal correlated (HMQC analysis) to a carbon at $\delta = 89$ ppm, also consistent with a carbinolamine carbon. Disappearance of the lactam carbonyl signal from the ^{13}C NMR ($\delta = 173$ ppm) and mass spectrometric analysis (M+H, M+Na and M+K all matching) further corroborated the structural assignment. Designation of the relative stereochemistry at C20 however, remained unfortunately elusive.

It must be underlined at this point that reaction at C20 was not observed, under a variety of conditions in virtually any other synthetic intermediates that were generated in this, and other studies. Given that all the targeted PIA's feature a guanidine hemiaminal moiety, and considered that preliminary (but admittedly not exhaustive) investigations in our projected approach returned no satisfactory conditions to adjust the oxidation level of this key center, we envisioned this unforeseen carbinolamine to be a potentially viable precursor to the synthesis of the natural products of interest. Further investigations in this direction however (discussed in Chapter VII), revealed that the newly generated free hydroxy functionality of the C20 carbinolamine was significantly reactive, resulting in undesired outcomes and veritable synthetic dead-ends, suggesting that the originally planned late-stage reduction would be the preferred course of action.

A "three-way" competition experiment with aminotriol **228**, obtained in low yields from global silyl deprotection of alcohol **221** (TBAF/AcOH), resulted in a very sluggish and inconclusive outcome. Although complete loss of starting material was observed,

because of the small scale of the reaction none of the potential, expected products **229a-c** could be isolated and unambiguously characterized.

Scheme 4.20



4.4 Conclusions

The asymmetric synthesis of the angular azatriquinane core of the axinellamines and the *trans*-azabicyclo[3.3.0]octane core of palau'amine from a common cyclization precursor was described. In the course of these investigations, suitable conditions for the efficient cleavage of the DMB protection were identified and significant insight into the stereoelectronic factor governing the key projected intra molecular cyclizations was obtained. Although our interest lied in developing a potentially biomimetic strategy for the synthesis of the selected PIA's the synthetic intermediates discussed above remain viable precursor for an admittedly *abiotic* approach.

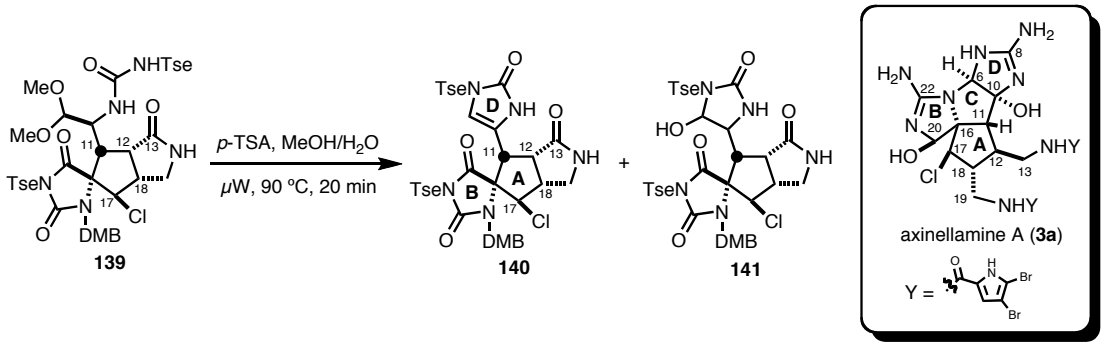
CHAPTER V

STUDIES TOWARD THE CONSTRUCTION OF THE D RING OF THE AXINELLAMINES

5.1 Original Late Stage C12 Epimerization Approach to Axinellamine

As previously discussed (Chapter II), at the time of my initial involvement with the synthesis of the PIA's, the working strategy toward axinellamine involved a late stage C12 epimerization, focusing instead on the establishment of the tetracyclic core. Pioneering work by Dr. Dransfield had generated relatively large amounts of advanced intermediate **139**, and preliminary studies had shown that under microwave irradiation and acid catalysis the urea would cyclize onto the dimethyl acetal delivering the corresponding imidazolone **140**, thereby introducing the precursor to the D ring of the axinellamines (Scheme 5.1 inset).

Scheme 5.1



The reaction conditions however had not been optimized and varying amounts of undesired carbinolamine **141** were consistently detected in the crude reaction mixture, with extreme instances in which **141** was the only product isolated. In addition, scale up above 20 mg of starting material proved not to be straightforward resulting in inconsistent, and irreproducible outcomes. Furthermore, carbinolamine **141** appeared to

be resistant to ulterior manipulations, in attempts to dehydrate it to the desired imidazolone, returning unaltered starting material under a variety of conditions.

After preliminary attempts to reproduce Dr. Dransfield's results, aimed at preparing synthetically useful amounts of imidazolone **140** in order to further study the advanced steps in our original projected strategy (*vide infra*), I endeavored to optimize the reaction conditions of this key transformation. At first analysis it appeared that the solvent mixture, and in particular the amount of water used, might play a crucial role in the outcome of the reaction and indeed investigations in this direction, summarized in table 5.1, seemed to support this assessment.

Table 5.1. Investigations of the imidazolone cyclization reaction conditions.

Entry	Scale	MeOH/H_2O	Rxn Time (min)	Heat	Outcome
1	12 mg	1/0[a]	20+20	μW, 90 ºC	**NR**[b]
2	10 mg	0.5ml/1drop	20+20+20+20	μW, 90 ºC	Mostly **141** + **X**[c]
3	10 mg	0/1	20	μW, 100 ºC	1:1 **140**:**139** (no **141**)
4	20 mg	1/3	40+ 20	μW, 90 ºC	3:1 (**140** :**141**) 43% Y[d]
5	21 mg	1/5	20	μW, 100 ºC	**140** 65% Y[d]
6	44 mg	1/5	20+20	μW, 100 ºC	**140** 48% Y (2 steps)[e]
7	52 mg	1/5	40+30	μW, 100 ºC	4:1 (**140** :**141**) 50% C[f]
8	49 mg	1/5	20+20	μW, 100 ºC	10:1 (**140** :**141**) 60% C
9	52 mg	1/5	20+10	μW, 100 ºC	**140**+traces **141** 70% C
10	167 mg	1/7	210	95 ºC[g]	**140**+ traces **139**

a = 3 Å Molecular sieves also used; b = No Reaction; c = Unidentified product; d = Refers to isolated yield; e = Refers to isolated yield after tosylation of the imidazolone nitrogen; f = Refers to conversion as determined by comparison of key signals in the crude ^{1}H NMR spectrum; g = Conventional heating in an oil bath. Unmeasured catalytic amounts of *p*-TSA were used in all reactions.

When only methanol in presumed anhydrous conditions (entry 1) was used, no reaction was observed even after resubjecting the reaction mixture to further heating. The

use of "catalytic" amount of water led to a very slow conversion to a mixture of aminal **141** and an unidentified product **X**, with no traces of desired imidazolone **140** detected. With only water as solvent and an increased operating temperature (entry 3) partial conversion to the desired product was observed, with no discernible formation of aminal **141** or any other undesired products. Reasoning that the partial conversion could be due to the poor solubility of the starting material in aqueous media we opted to use small amounts of methanol co-solvent (entry 4-10), and this, along with small adjustments in the reaction time and operating temperature led to markedly improved results. In a 1:3 $MeOH/H_2O$ solvent system at 90 ºC for 40 consecutive minutes minimal reaction occurred, but after resubjecting the crude material to increased temperature (100 ºC) a modest yield of a ~3:1 mixture of desired imidazolone **140** to aminal **141** was formed. When a 1:5 ($MeOH/H_2O$) mixture of solvents was used at 100 ºC for 20 minutes (entry 5) a 65% yield of desired product was isolated and no traces of aminal **141** and unreacted starting material could be detected. With promising conditions in hand we next attempted to double the reaction scale (entries 6-9) and eventually up to 70% conversion to the desired imidazolone with minimal formation of aminal by product could be obtained. Comparable results could be obtained on a much larger scale (entry 10) under conventional heating in an oil bath resulting in the generation of synthetically useful yields of desired product, albeit requiring a significantly longer reaction time.

No other solvent system were investigated but in retrospect, it seems evident that the use of methanol in the presence of a dimethyl acetal was a poor strategic choice, and that other solvents (*i.e.* acetone, see Chapter VII) could have provided better results.

It must be mentioned at this point that although TLC analysis and mass spectrometry data were indicative of a single product, the ^1H NMR of imidazolone **140** was not very pristine, even after several rounds of careful purification. We reasoned that partial tautomerism (**140a/140b**) in the imidazolone ring, driven by the formation of an aromatic hydroxyimidazole system (Figure 5.1) could account for the observed lack of definition. In addition, potential hindered rotation around the C11-C10 bond could give rise to rotamers (**140c/140d**), and the presence of multiple species in solution could also lead to a poorly resolved ^1H NMR, however, variable temperature NMR experiments to

assess this possibility were not performed. The presence of an unidentified byproduct having a similar Rf value to the target product could also not be excluded *a priori*.

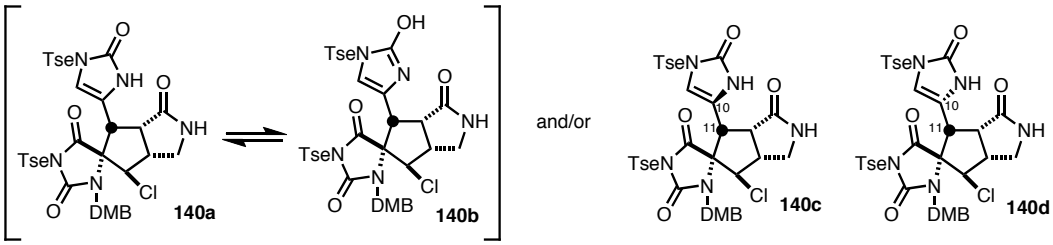


Figure 5.1. Possible tautomers and/or rotamers of imidazolone **140**

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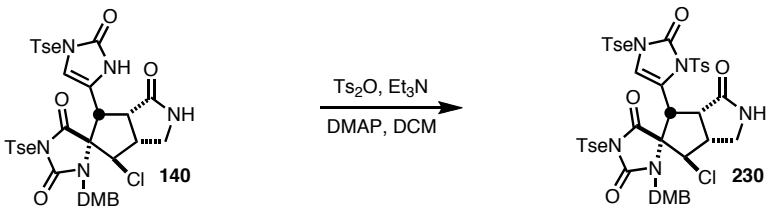
Interestingly, after treatment with tosyc anhydride, the ^{1}H NMR spectrum of the resulting protected imidazolone **230** was very neat and well resolved. Therefore, after the first attempts to purify the precursor did not returned spectroscopically pristine product, the crude material was carried on to the protection step and purified afterwards.

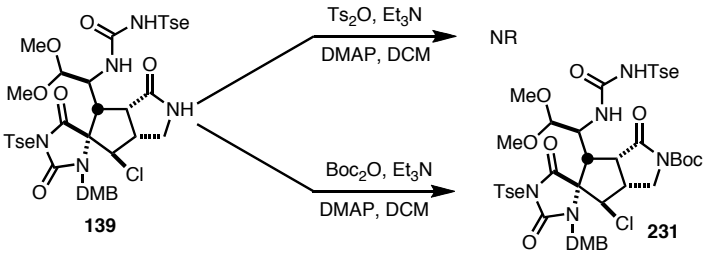
Scheme 5.2



The selective tosylation of the imidazolone could be easily confirmed as the chemical shift of the two free nitrogen protons of **140** were significantly different and clearly identifiable in the ^{1}H NMR spectrum. In addition, under the same reaction conditions urea cyclization precursor **139** remained unaltered, suggesting that the lactam

nitrogen was inert toward tosylation. On the other hand, treatment with Boc anhydride proceeded smoothly to deliver the corresponding carbamate protection on the lactam nitrogen.

Scheme 5.3



A further tosylation reaction however, provided puzzling results that potentially did not support the above assessment. When the crude material from the conventional heating reaction (table 1, entry 10) was subjected to the established reaction conditions in fact, a very slow conversion was observed, and although the expected tosylimidazolone was the major product isolated, significant amounts of another material were obtained as well. Based on ^{1}H NMR data comparison with the desired product (partial spectra shown in Figure 5.2) this unexpected material was tentatively assigned as tosylamine **232**, which could be generated by reaction of the tosylating reagent at the lactam nitrogen site, followed by intramolecular ring opening by the adjacent imidazolone free nitrogen. Full characterization of this compound was not achieved and assignment of the indicated structure remains purely speculative.

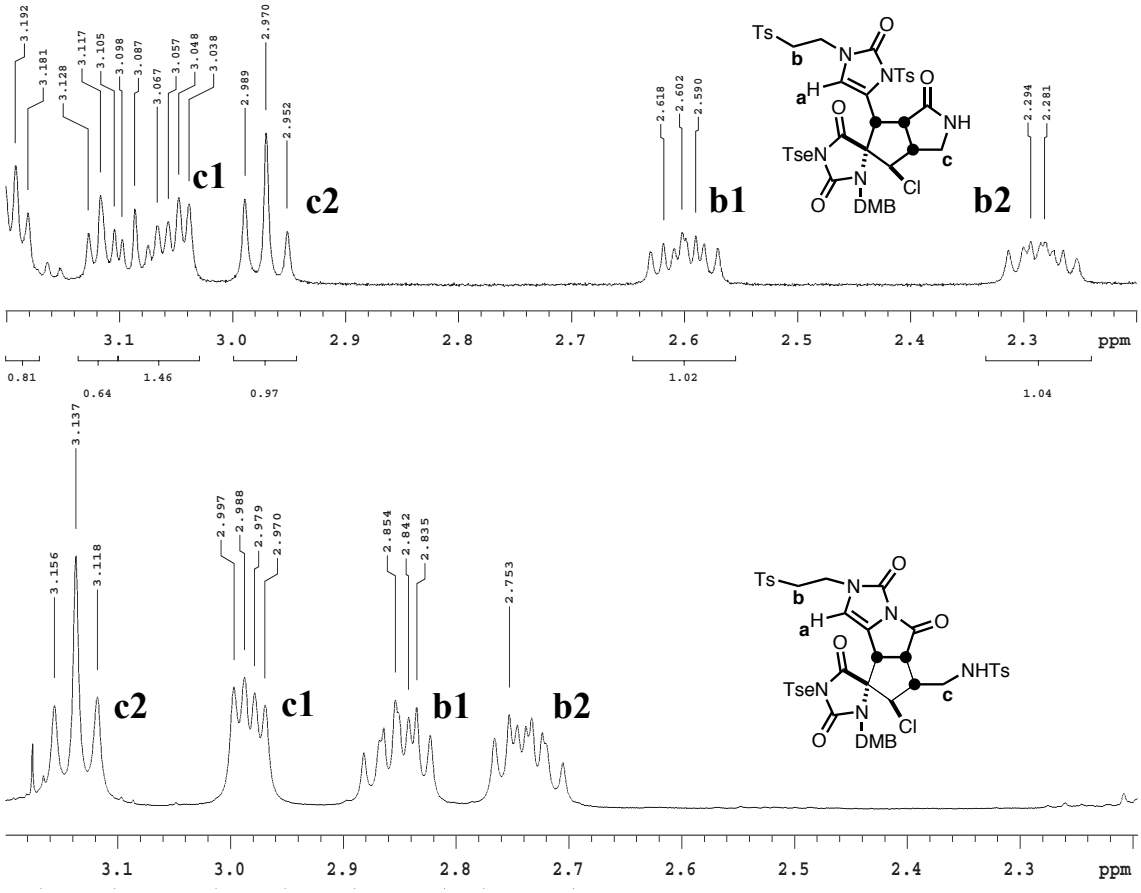
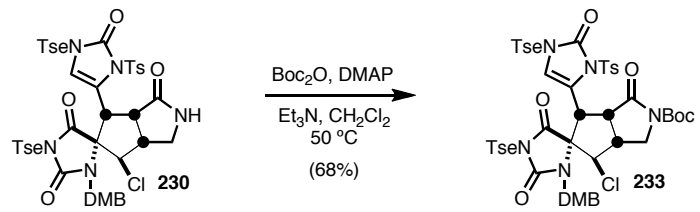


Figure 5.2. Spectral comparison of tosylimdazolone **230** and presumed tosylamine **232**.

Treatment of tosyl imidazolone **230** with Boc anhydride cleanly delivered, as expected, good yields o the fully protected product **233**. Remarkably, when imidazolone **140**, was treated with Boc anhydride the bis-carbamate resulting from reaction at both nitrogen sites was the only product isolated in modest yield (not shown).

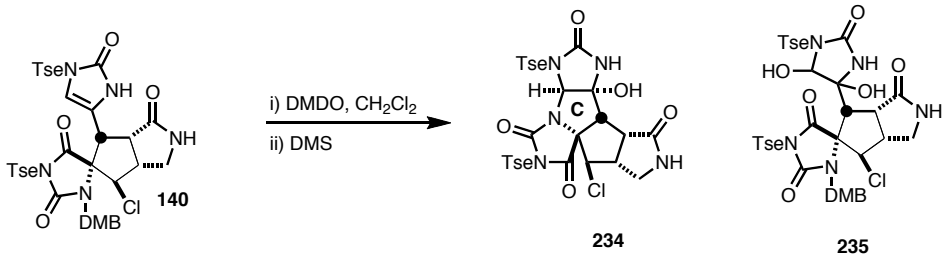
Scheme 5.4



5.2 Further Studies Along The Original Route Toward Axinellamine

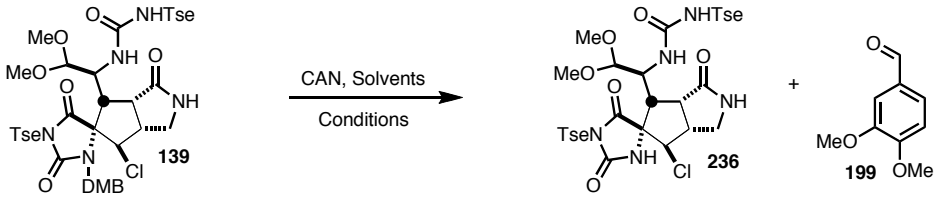
Imidazolone **140** featured the complete carbon framework of the core of axinellamine (**3**), and we anticipated that the projected intramolecular oxidative cyclization of the spirohydantoin "lactam" nitrogen would establish the C ring of the tetracyclic scaffold of the natural product (Scheme 5.5). In our initial approach we envisioned that under the reaction conditions required for the oxidation of the imidazolone unsaturation, the DMB protecting group could be cleaved triggering the desired intramolecular ring closure *in situ*. Treatment of imidazolone **140** with freshly prepared dimethyldioxirane (DMDO), however, led to the slow formation of several products, the major of which was tentatively assigned as diol **235** by ^{1}H NMR analysis after purification. The desired tetracycle **234** was not detected.

Scheme 5.5



In light of these first results it became apparent that it was necessary to identify conditions for the efficient removal of the DMB protecting group to increase the reactivity of the hydantoin nitrogen and to trigger the desired cyclization. Once again, we envisioned that under the acidic conditions required for the formation of the imidazolone, this cyclization might happen *in situ*, therefore we initiated our DMB cleavage investigations on the imidazolone precursor **139**, using ceric ammonium nitrate (CAN).[70]

Table 5.2. Attempted DMB cleavage on urea **139**.



Entry	Scale	Solvents	CAN[a]	Temp/Time	Outcome
1	2.4 mg	MeCN/H_2O (3:1)	3 equiv.	23 ^{0}C/1 h	Mix[b] + **199**
2	1 mg	MeCN/H_2O (4:1)	1.9 equiv.	23 ^{0}C/24 h	Mix[b] + **199**
3	1 mg	MeCN/pH 7 buffer (4:1)	1.9 equiv.	23 ^{0}C/24 h	Mix[b] + **199**
4	2 mg	MeCN/H_2O (9:1)	2 equiv.	0 ^{0}C/1.5 h	Mix[b] + **199**

a = the reagent was added as a solution in the indicated solvent mixture; b = multiple products were detected' separation was not attempted

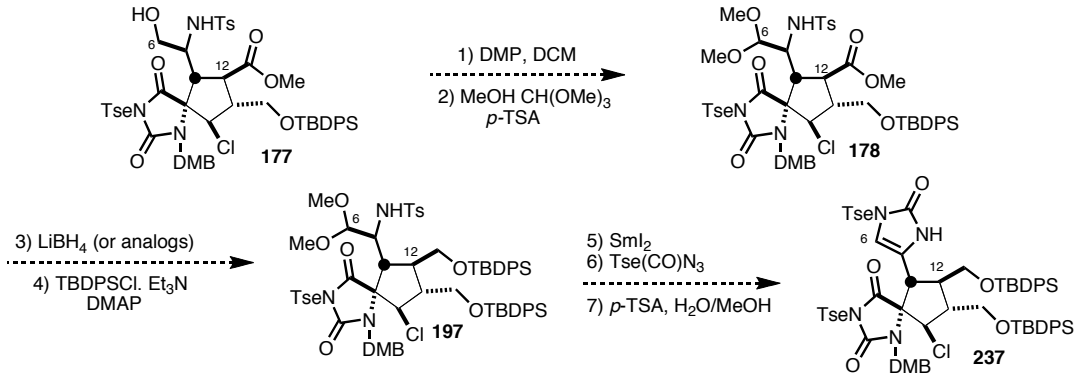
In all cases (see Table 5.2), analysis of the crude ^{1}H NMR revealed discernible signals ascribable to dimethoxy benzaldehyde **199**, which is consistent with the expected oxidative cleavage of the DMB group, on the other hand however very sluggish outcomes were obtained in all cases. Multiple products appeared to have formed, and given the small scale of these reactions, separation and characterization was not attempted. Equally inconclusive results, with sluggish reactions were obtained under the same conditions with imidazolone **140** and tosylimidazolone **230** (not shown) and resolution of the complex mixtures of products was not attempted.

With fully protected imidazolone **233** in hand I attempted to expand on the preliminary results obtained by Dr. Dransfield aimed at inverting the stereochemistry at C12 via equilibration of the aldehyde tautomer of the carbinolamine obtained by selective reduction of the Boc lactam. This carbinolamine proved not to be extremely stable and significant loss of material occurred by decomposition. Furthermore, as already discussed in Chapter II, these investigations returned no positive results, and the original route was abandoned, and a new strategy featuring an early C12 epimerization (discussed in Chapter III) was developed and implemented.

5.3 New Early C12 Epimerization Approach to Axinellamine

With the structure of amino alcohol **177** still not unambiguously assigned (see Chapter III), we carried on assuming that the C12 configuration had been inverted, and we refocused our efforts toward the construction of the imidazolone precursor to the D ring of the axinellamines. Unequivocal confirmation of the reversal of configuration at C12 was achieved during the course of these preliminary advanced investigations and a detailed account is described in Chapter III. In our initial approach to this endeavor we reasoned that proceeding through the cyclization of a pendant urea onto an exposed or masked aldehyde (*i.e.* a dimethyl acetal) would be the best course of action, as most of the chemistry involved had already been studied and optimized (Scheme 5.6).

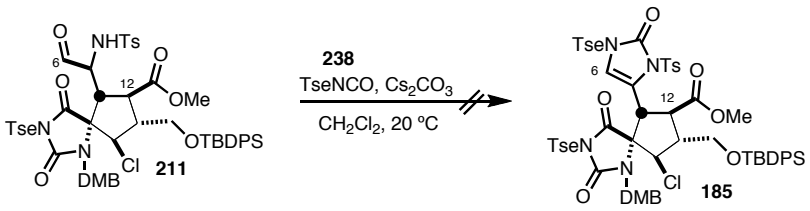
Scheme 5.6



Initial attempts to oxidize the free primary alcohol of methyl ester **177** using Dess Martin periodinane (DMP) as before (see Chapter II) were rather sluggish but provided nonetheless small amounts of desired aldehyde **211** that could be utilized crude in the following steps. Thus treatment with trimethyl orthoformate in methanol under acid catalysis, as anticipated generated modest yields of dimethyl acetal **178**.

In a first attempt to access the target imidazolone annulation we treated crude aldehyde **211** with previously generated tosylethyl isocyanate **238**, following a methodology recently reported by Trost[71]. Unfortunately, with our substrate the reaction proved to be extremely untidy, and no significant products were isolated.

Scheme 5.7

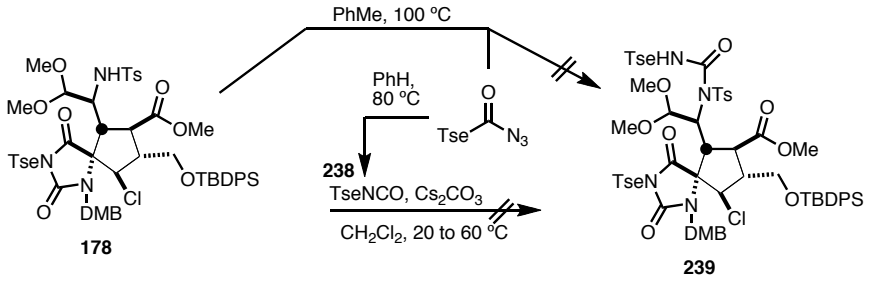


In a second run, starting material and Tse(CO)N_3 were heated together in PhH at 80ºC. Formation of TseNCO **238** was observed by TLC, but the aldehyde seemed not to react. After cooling to room temperature Cs_2CO_3 was added resulting in the formation of new products. The major product isolated did not show any aldehyde or methyl ester signals, but could not be unambiguously assigned. In a third run TseNCO **238** (freshly prepared) was added over 30 min to a solution of starting material and Cs_2CO_3 at 0ºC then the mixture was allowed to reach room temperature and stirred for ~15h. After column purification a mixture (~1:1) of products was isolated which promisingly showed extra tosyl signals and no aldehydes. Attempts to isolate and characterize the potential products however met with no success.

Reasoning that the sluggish reaction obtained thus far could be due to the low purity of the aldehyde obtained by DMP oxidation we decided to explore alternative protocols in order to improve the yield and the quality of this key intermediate. Disappointingly however, under a variety of conditions (SO_3•Py in DMSO/CH_2Cl_2, pyridinium chlorochromate in CH_2Cl_2, and stoichiometric tetrapropylammonium perruthenate in CH_2Cl_2) no improvement could be obtained. In the end use of DMP for prolonged reaction times (up to 48 h) provided the best results and the crude material could be taken on to the acetal formation delivering satisfactory yields (up to 75% for the two steps) of desired product. With sizeable amounts of dimethyl acetal **178** in hand we then tried to introduce a pendant urea by reaction of the sulfonamide with Tse isocyanate **238**. As before, addition of freshly prepared reagent to the reaction mixture and prolonged heating (12 hours) only led to partial recovery of the starting material with no desired product formed. When the isocyanate was generated *in situ* however (by heating a

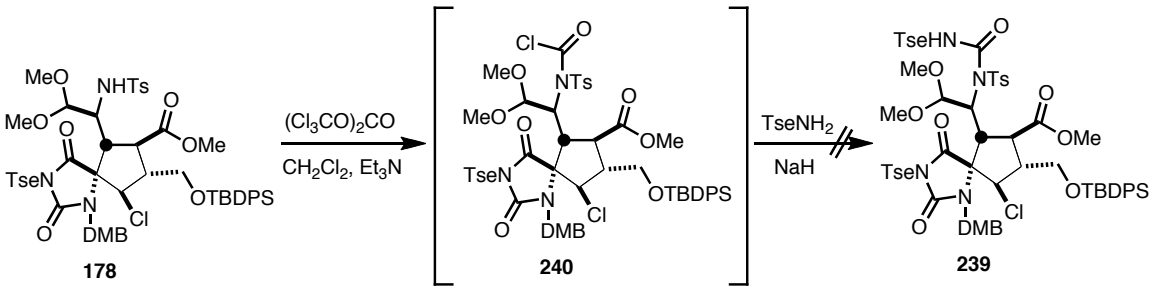
mixture of starting material and tosylethyl acyl azide in a sealed tube) partial conversion to a mixture of two products was observed. The two products refused to be separated by column chromatography (one spot by TLC) and based on analysis of the ^{1}H NMR of the purified mixture they appeared to be a pair of diastereomers, which however could not be confirmed as the desired urea **239**.

Scheme 5.8



A stepwise approach involving the generation of a carbamoyl chloride intermediate **240**, which would then further react with a nitrogen source to deliver the target urea resulted in an intractable mixture, and no significant products could be discerned. Tse amine was chosen as the nucleophile to facilitate the characterization of new products by spectroscopic comparison with similar substrates previously obtained. Attempts to isolate the potentially stable carbamoyl chloride intermediate (see Chapter IV) also met with no success.

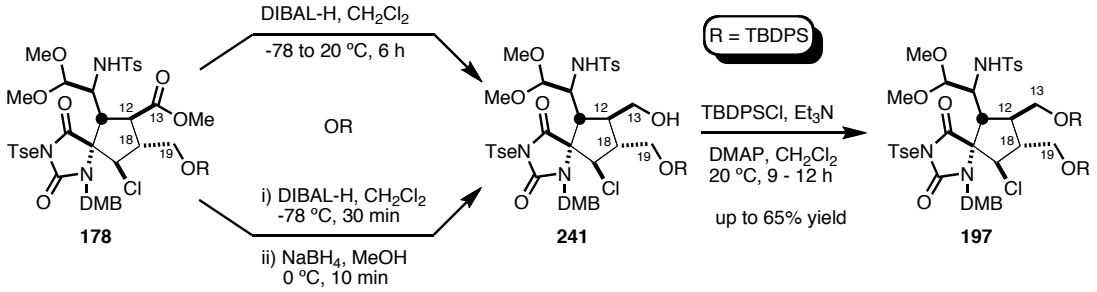
Scheme 5.9



We reasoned at this point that the decreased nucleophilicity of the sulfonamide was hindering the interaction with the electrophile, and we also considered that the methyl ester functionality might be somehow interfering, offering a potential alternative manifold of reaction leading to unidentified products. As this functionality required to be removed anyway to allow for installation of the pyrrole carboxamide side chain of the natural product, this task took priority in our investigation. We envisioned that reduction to the corresponding primary alcohol and protection as the same silyl ether (TBDPS) as the C18 chain would be the most convenient course of action as it would eventually allow for efficient, simultaneous manipulation of both side chains.

Initial attempts to effect the reduction using DIBAL, were rather sluggish, with minimal reaction observed at the standard operating temperature, and with undesired side reaction occurring at higher temperatures, leading to poor isolated yield of not very pristine target alcohol after purification. The semi pure material could however taken on to the protection step generating modest yields of bis-silyl ether **197**. It was soon discovered however (as already discussed in Chapter IV, although this was chronologically the first instance) that treatment of the starting material with DIBAL at low temperature for a shorter time, followed by brief exposure of the crude mixture to methanolic sodium borohydride at 0 ºC, provided the desired primary alcohol in sufficient purity to be advanced to the next step, without the need for further purification. Etherification under the condition discussed above then, afforded synthetically useful amounts of the target bis-silyl ether in greatly improved yields (up to 65% for the three steps).

Scheme 5.10



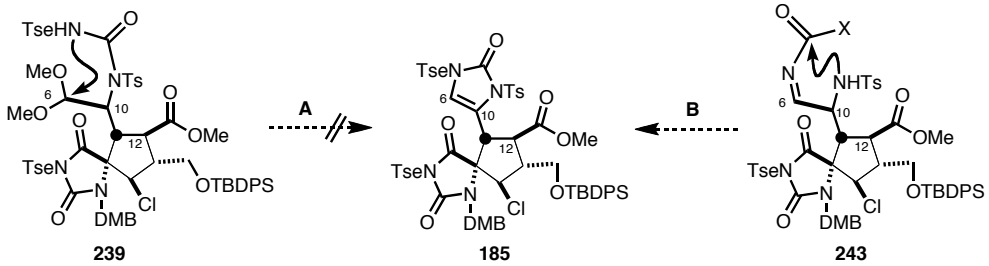
We were also pleased to find that under the CAN conditions described above cleavage of the DMB protecting group was cleanly affected on this advanced intermediate, albeit seemingly requiring a significantly longer reaction time (~ 40 hours).

Scheme 5.11

This result was significant in that it demonstrated that although the developed conditions were suitable for the removal of the key DMB protection, this transformation was however rather capricious and apparently highly substrate-dependent.

With perceived significant progress made on several fronts, we returned to the still unresolved issue of the construction of the imidazolone ring required for the pivotal intra molecular cyclization projected to deliver the tetracyclic core of the axinellamines (**3**). As our initial investigations aimed at emulating the successes obtained in previous endeavors had returned discouraging results (*vide supra*) we sought alternative approaches.

Scheme 5.12

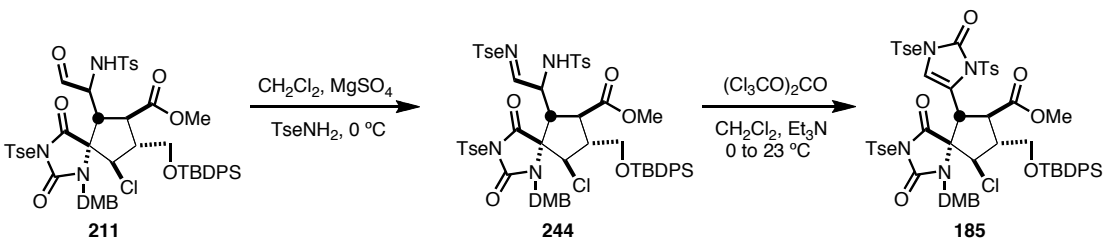


We reasoned that if using the sulfonamide to append the required urea was in fact problematic (**A** Scheme 5.12), a plausible alternative course of action would be to reverse

the order of events, introducing a carboxamide electrophile on the alcohol terminus and force the poorly nucleophilic sulfonamide to cyclize onto it, in a stepwise or potentially concerted fashion (**B** Scheme 5.12).

Thus, treatment of aldehyde **211** with $TseNH_2$ [72] led to complete conversion to a new product (which was assumed to be the desired imine **244**) in 2 hours at 0ºC. Once again Tse amine was chosen for the ease of comparison with previously obtained similar compounds. The crude product was azeotroped and treated with triphosgene at ambient temperature with overnight stirring. After purification the ^{1}H NMR spectrum was consistent with the desired product **185** (appearance of vinyl imidazolone proton signal at $\delta = 6.70$ ppm; consistent with previous observations) and the ^{13}C NMR spectrum showed a new signal at $\delta \sim 151$ ppm, ascribable to a urea carbonyl. Mass spectrometric analysis also seemed to confirm formation of the target product (observed M+Na; M+K values matched the calculated mass). Soon afterwards the reaction was repeated on a slightly larger scale (~40 mg of crude aldehyde) leading to a ~30% isolated yield (two steps) of the desired product. It is noteworthy that starting from the aminoalcohol precursor of aldehyde **211** the desired imidazolone **185** product can be obtained in three steps requiring only one purification.

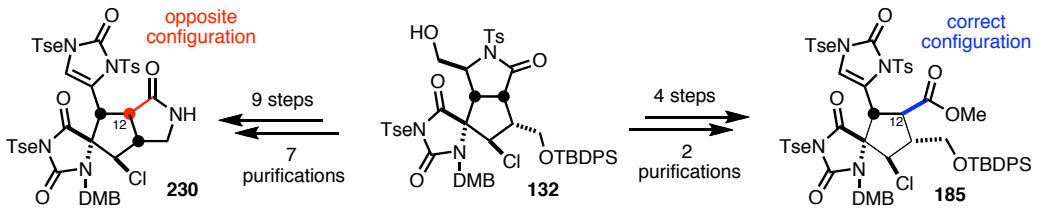
Scheme 5.13



Two facts must be highlighted at this point. Firstly, this new approach to the construction of the key imidazolone significantly shortened the synthetic route, as compared to the original strategy (*vide supra*). Starting from spirotricyclic intermediate **132** (Chapter III), in fact, nine steps and seven column chromatography purifications

were necessary to arrive at tosylimidazolone **230**. With the newly developed approach on the other hand, only four transformation and two column chromatography purifications were required to access imidazolone **185** from the same starting point. In addition imidazolone **185** featured the correct configuration at C12, matching the relative stereochemistry of the target natural product, an issue that had proved problematic to address with tosylimidazolone **230** (see Chapter II).

Scheme 5.14

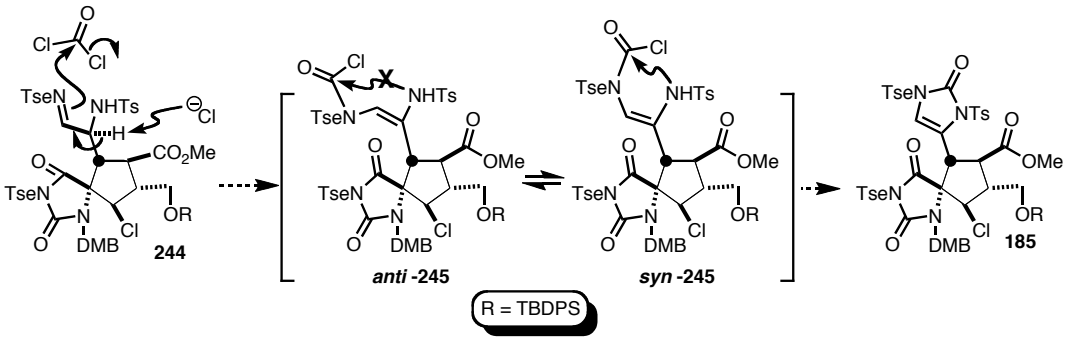


Secondly, it must be underlined that although this new approach appears in other documents,[62] which preceded the present manuscript in publication, *it was therein not properly credited*. The original work is described in Scheme 5.13 and additional studies and optimizations will be further expanded upon below.

After this first exhilarating breakthrough we encountered unforeseen difficulties in obtaining reproducible results. After meticulous investigation it was discovered that the lack of consistency could be ascribed to the solvent source, which puzzlingly however seemed to have no discernible deleterious effects on most other reactions. A detailed account of these investigations serves no purpose in this context, and it will suffice to say that as a result we opted to use tetrahydrofuran as solvent in place of dichloromethane. With this change, consistently better and reproducible result could be obtained leading to the isolation of up to 57% yield of the desired imidazolone after overnight reaction at ambient temperature. Initial attempts to increase the operating temperature (to 50 ºC) seemed to have no effect (by TLC analysis) on the outcome, however it was later found that the reaction time could be greatly reduced (to just a few hours) and the yields seemed to be consistently better (*vide infra*) when the transformation was run at 60 ºC. It seems

reasonable to envision that the reaction could proceed through the formation of a bis-enamine intermediate **245** generated after deprotonation at C10. The acidity of this site could be enhanced by initial non-bonded interaction of the imine nitrogen with a phosgene equivalent. The termini of the bis-enamine could be in a *syn* arrangement with respect to the double bond thereby placing the electrophilic carbamoyl chloride in close proximity to the sulfonamide leading to ring closure. If, on the other hand the termini are in an *anti* arrangement, constructive interaction of the sulfonamide with the presumed carbamoyl chloride cannot occur, and this fleeting intermediate could be hydrolyzed upon work-up leading to a decrease yield. Alternatively, equilibration of the two geometric isomers could result in increased productive interactions, boosting the formation of the desired product. It is easy to see in this scenario how increased operating temperatures would facilitate this equilibration, reducing the reaction time and ultimately increasing the yield.

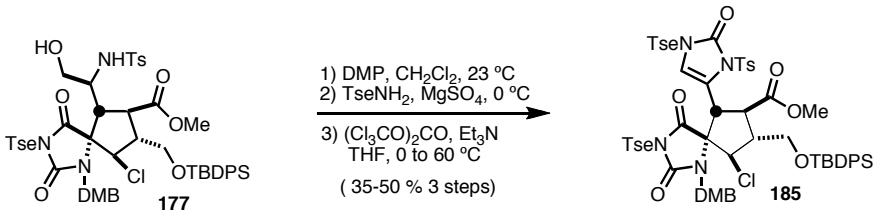
Scheme 5.15



Use of a different carbonyl source, namely carbonyl diimidazole (CDI), led only to partial recovery of the starting material, even after prolonged reaction time (15 hours) at 65 ºC. An attempt to condense imine formation and imidazolone cyclization in a "one-pot" transformation resulted in an extremely sluggish reaction with no significant product isolated or starting material recovered.

Eventually, through refinement of the reaction conditions the three-step synthesis of imidazolone **185** from amino alcohol **177** could be run on a 100 mg scale consistently obtaining synthetically useful yields (up to 50 % for the three steps) of desired product.

Scheme 5.16



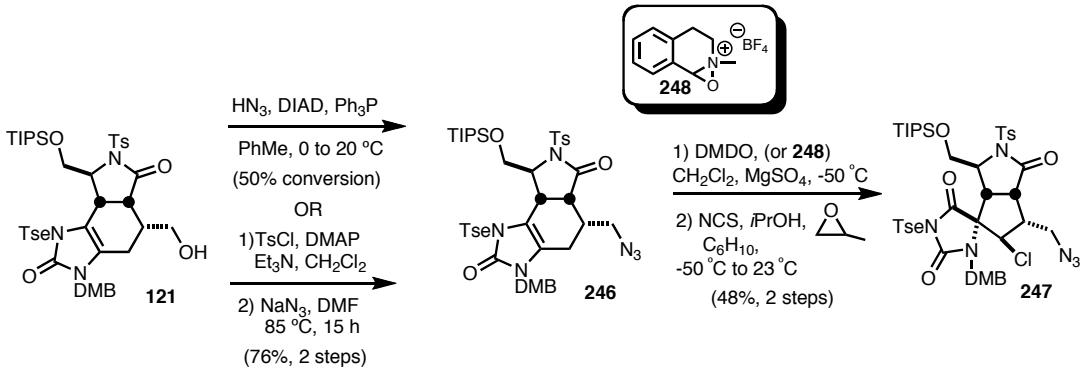
The first two reactions appear to be quantitative, as both crude ^{1}H NMR are pristine and are tainted only by residual reagents that seem however, not to interfere with the following transformations. For the reasons presented above I believe that the cause for the decrease in the overall efficiency of the sequence lies solely in the third step, but with sizeable amounts of imidazolone **185** consistently generated in good purity, and in the interest of moving the project forward, further optimization was not pursued.

5.4 Further Improvement: Synthesis of an Azide Imidazolone

More recently, in light of the structural revision of palau'amine we realized that our original unified approach to the synthesis of selected PIA's could be modified to delay the point of divergence to a much later common intermediate in the synthetic route (discussed below). We reasoned also that the early introduction of a nitrogen "handle" on the C18 side chain would improve the overall efficiency, decreasing the number of steps, and minimizing deceivingly trivial, but potentially costly manipulations on advanced precious intermediates. It was decided that introduction of an azide at C19 would provide a convenient masked amine functionality that could be easily liberated (for palau'amine (**2**)), and acylated (for axinellamine (**3**) and konbu'acidin (**5**)) in the later stages of the synthesis.

Thanks to the excellent work by Dr. Yonggang Wang, my collaborator on the project, the desired modification was promptly achieved. It must be made clear that although I have personally performed all the reactions described below (Scheme 5.17), credit for the adjustment of the original reaction conditions to suit our new needs and optimization of the related experimental procedures goes entirely to Dr. Wang.

Scheme 5.17

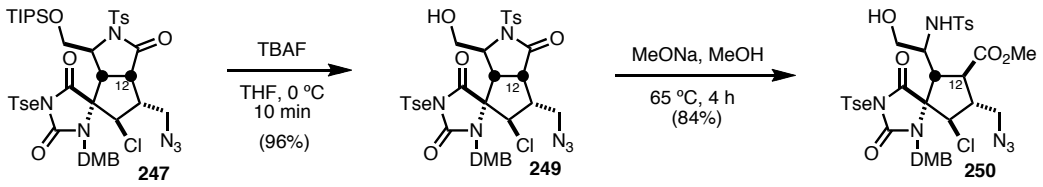


Thus, treatment of Diels Alder adduct **121** with freshly prepared hydrazoic acid under typical Mitsunobu conditions led to only partial conversion to the desired product with large amounts of unreacted starting material recovered after a long and tedious purification process. Alternatively, two-step activation of the free alcohol as the corresponding tosylate followed by displacement with sodium azide generated the target material in good yields, in gram-scale reactions. Azide **246** was then exposed to freshly prepared DMDO as before, and the crude intermediate stable allylic alcohol (see Chapter II) was treated with *N*-chlorosuccinimide in the presence of propylene oxide and cyclohexene generating modest yields of the desired chlorinated spirohydantoin **247**. Use of chloramine-T, as previously reported, led in this instance to sluggish reactions and lowered yields. In addition, due to the problematic preparation of large amounts of DMDO, this two-step sequence was only suitable for relatively small (in these early stages of the synthesis) reaction scales (only few hundred milligrams). In order to streamline the synthesis we sought alternative oxidation protocols, and Dr, Wang found

that the use of readily available oxaziridnium reagent **248** (inset in Scheme 5.17) allowed to process up to six grams of azide **246** at a time, providing comparable yields of spirotricycle **247** in synthetically useful amounts.

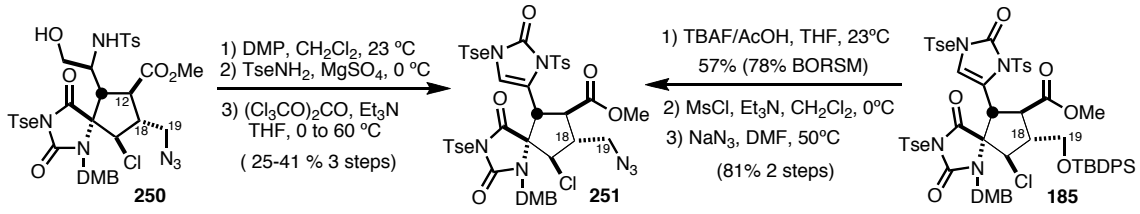
The silyl protection cleavage and subsequent lactam opening with concomitant reversal of configuration at C12 under the established conditions proceeded smoothly, consistently providing excellent yields of methyl ester **250**.

Scheme 5.18



First attempts to construct the imidazolone substructure from amino alcohol **250** under the conditions previously identified (*vide supra*) seemed not to present any problems and the desired product **251** (Scheme 5.19) could be isolated in modest yields, that were however comparable with previous results.

Scheme 5.19

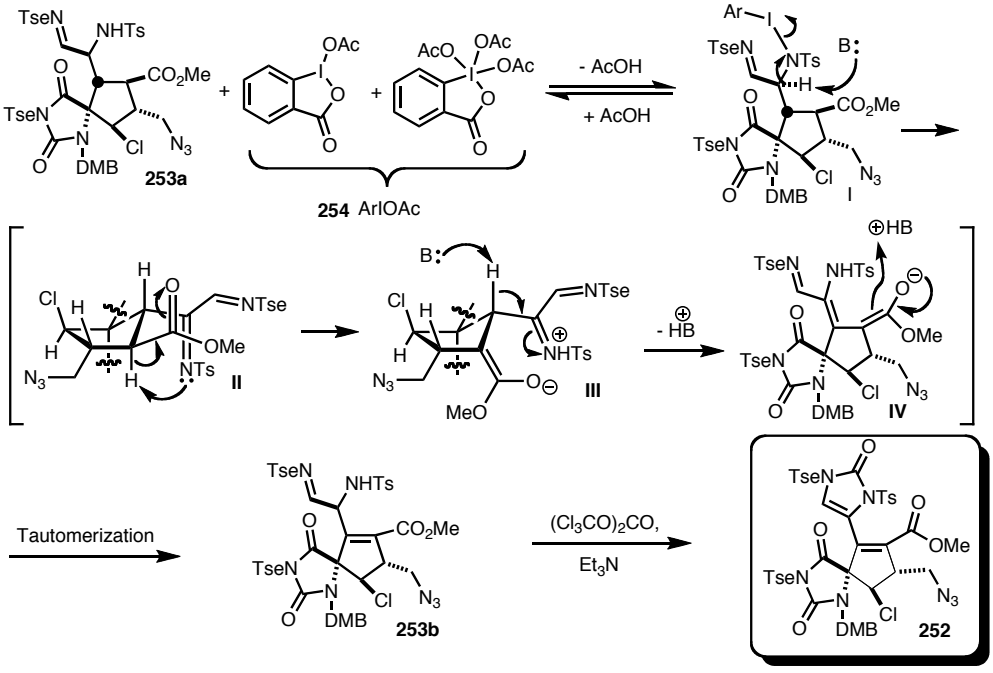


Further confirmation of the structural assignment of the newly generated product was obtained by manipulation of the C18 side chain of imidazolone **185**. Cleavage of the

TBDPS silyl ether, followed by activation of the free alcohol and displacement with sodium azide under standard conditions returned a material that was spectroscopically identical to the compound obtained via the three-step imidazolone annulation protocol.

Further runs of the cyclization sequence however, led to the isolation of significant amounts of over-oxidized enone **252** (Scheme 5.20) along with the desired product, with extreme cases in which **252** was the only material generated.

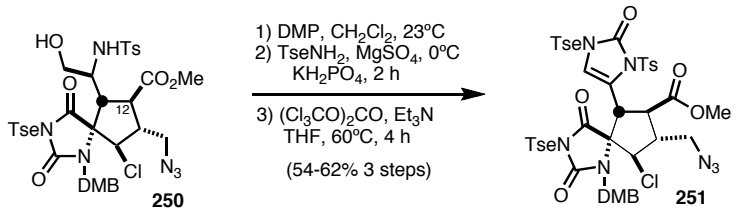
Scheme 5.20



Dr. Wang proposed that residual Dess Martin reagent and/or related byproducts present (**254** Scheme 5.20) in the crude aldehyde material could interact with the intermediate presumed imine **235a** leading to oxidation of the sulfonamide. Abstraction of the proton α to the methyl ester **II** (much more accessible in this species than in the highly congested TBDPS analog) would generate an extended enolate **III**. Reprotonation and tautomerization would then regenerate the amino-imine **235b**, which would proceed to ring closure with triphosgene as before. Dr. Wang postulated that removal of the DMP

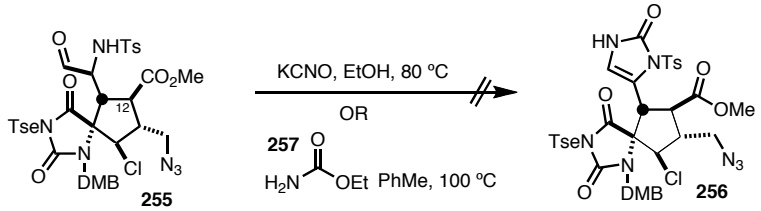
byproducts prior to imine formation, which would in turn be run under buffered conditions, could reduce the potential for this undesired reaction manifold. Thus, washing the crude aldehyde material with a saturated solution of sodium thiosulfate ($Na_2S_2O_3$), followed by imine formation in the presence of potassium phosphate monobasic (KH_2PO_4) provided a material that upon treatment with triphosgene, under unmodified conditions, led to the consistent isolation of markedly improved yields (up to 60% for the three steps on a 200 mg scale) of the desired imidazolone **251** with no discernible detection of the over-oxidized enone.

Scheme 5.21



Two attempts to generate a semi-protected imdazolone **256** reacting aldehyde **255** with either potassium isocyanate or urethane **257** at high temperatures led to extremely sluggish reactions with no significant products detected.

Scheme 5.22

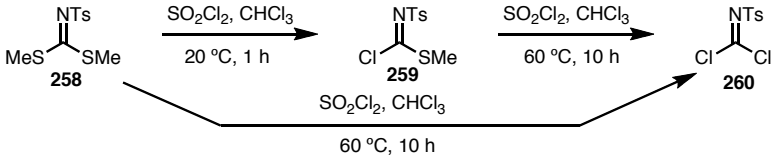


5.5 Synthesis of an Amino-Imidazole D Ring Analog

As already discussed (Chapter II) in our original strategy we had projected delaying the introduction of the amino-imidazole moieties to the final stages of the synthesis envisioning a simultaneous transformation of the northern urea and the southern hydantoin. During the course of the investigations described above we realized that an installation of the northern aminoimidazole could prove beneficial for the advanced stages of the synthesis, as it would more closely mimic the species involved in the presumed biogenetic key oxidative cyclizations. We anticipated that the established imidazolone cyclization protocol (*vide supra*) could readily be modified with the use of a nitrogen-containing "phosgene analog" which would, upon interaction with the reported amino-imine, deliver the desired cyclic guanidine.

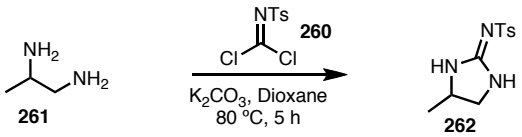
One such phosgene analog could be easily prepared from commercially available bis-methylthio methylenetosylsulfonamide **258**, by heating with sulfuryl chloride in a chloroform solution. Interestingly, after brief reaction at room temperature the mono-chloride species **259** was readily obtained but prolonged heating was required for displacement of the second thiomethyl group.

Scheme 5.23



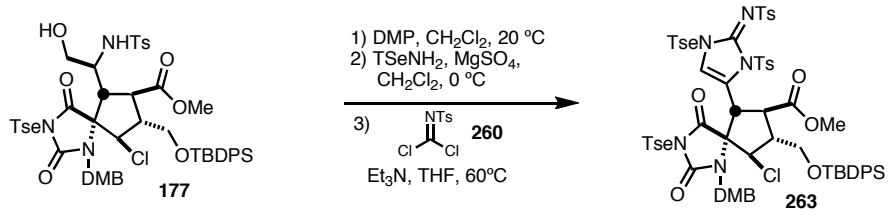
Before experimenting on the real system imine dichloride **260** was tested on propane diamine **261**, and after a few hours complete loss of starting material was observed. Although spectroscopic data of the purified product were unclear and inconclusive, mass spectrometric analysis seemed to suggest formation of the indicated cyclic guanidine **262**.

Scheme 5.24



Pleasingly, the first attempts to use imine dichloride **260** *in lieu* of triphosgene in our established cyclization protocol delivered modest yields (up to 37% for the three steps) of the target per-tosylated cyclic guanidine **263**.

Scheme 5.25

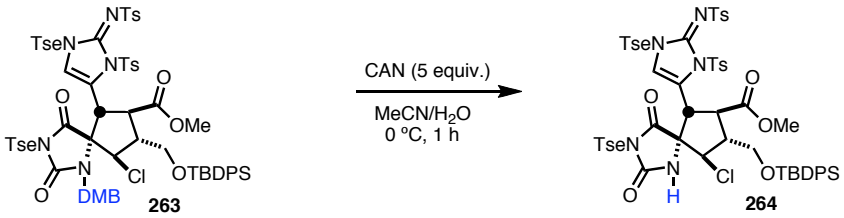


Use of toluene as solvent led to minimal reaction after several hours at 80 ºC, and resubjecting the crude material using Hünig's base in place of triethylamine seemed not to result in any significant improvements. When the reaction was run in acetonitrile in the presence of Hünig's base better yields of semi-pure (the material did not appear pristine by NMR analysis even after multiple rounds of purification) desired product could be isolated after prolonged time *at ambient temperature*, requiring however multiple resubjections of the crude mixture to the reaction conditions. Increasing the temperature in these instances seemed to have no effect on the rate of conversion.

Having accumulated enough material for further studies we began to investigate the cleavage of selected protecting groups in order to arrive at a suitable substrate to explore the key oxidative cyclization to the tetracyclic core of axinellamine (**3**).

It was encouraging to find that under the established conditions, oxidative cleavage of the DMB protection proceeded relatively well.

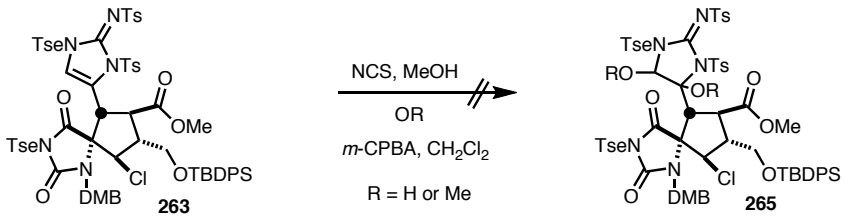
Scheme 5.26



Treatment of the advanced per-tosylated guanidine **263** with 5 equivalents of at CAN at 0 ºC in fact, gave a fast, and for the most part, clean conversion to a new product which was consistent by mass with the desired de-benzylated target **264**. D_2O wash revealed the presence of an exchangeable proton at δ = 6.57 ppm (consistent with the lactam nitrogen proton), and a signal ascribable to the vinyl proton of the cyclic guanidine (δ = 6.6 ppm) was also present.

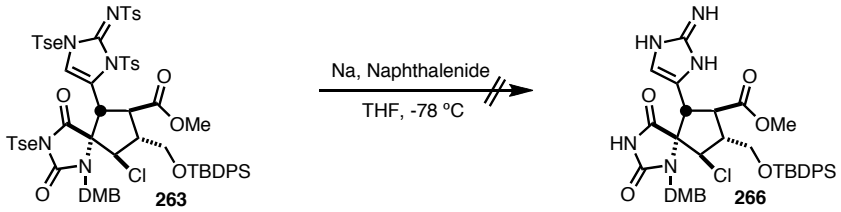
Initial attempts to test the reactivity of the double bond of the cyclic guanidine **263** seemed to suggest that the presence of the tosyl group rendered this functionality, virtually inert. Attempted oxidations under NCS or *m*-CPBA activation, did not lead to any significant reaction (by crude ^{1}H NMR analysis), and given the small scale of these studies, recovery of the starting material was not attempted.

Scheme 5.27



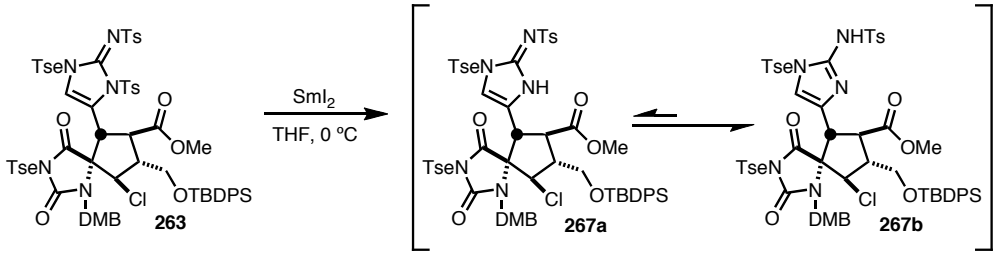
To increase the reactivity of the cyclic guanidine toward oxidation we attempted the removal of all the sulfone protecting groups using freshly prepared sodium naphthalenide. Given the small scale of the reaction, the greatly reduced molecular weight of the potential product and its unknown polarity, these endeavors were mostly inconclusive.

Scheme 5.28



Selective removal of one tosyl group could be achieved using commercially available samarium diiodide in THF solution. It is reasonable to assume that the tosyl group was removed from the imidazole ring nitrogen as this would lead, trough tautomerization, to the establishment of an aromatic protected amino-imidazole **267b**.

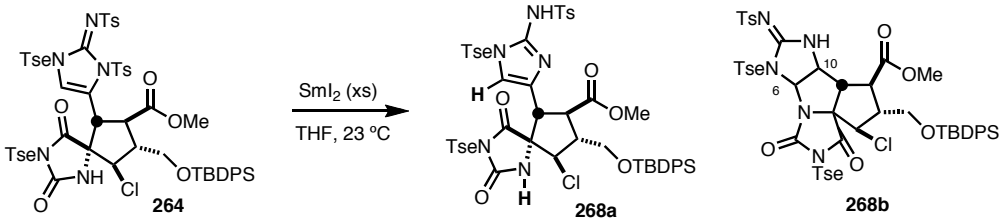
Scheme 5.29



Treatment of the newly generated product with NCS in MeOH under the same conditions described in Scheme 5.27 resulted in the formation of a new product (as confirmed by the disappearance of the very diagnostic vinyl proton signal), which however could not be unequivocally assigned. This result was however significant in that

our reasoning that removal of the tosyl group from the amino-imidazole would render the desired double bond more prone to oxidation appeared to have been correct. Further confirmation of our reasoning came from the attempted oxidation of the desired double bond in the DMB-deprotected, fully tosylated analogue **264** no reaction was observed by TLC analysis, and only starting material was recovered. When this same intermediate however was exposed to excess amounts (~ 20 equiv.) of samarium diiodide, complete conversion to a new product containing only three tosyl groups was observed.

Scheme 5.30



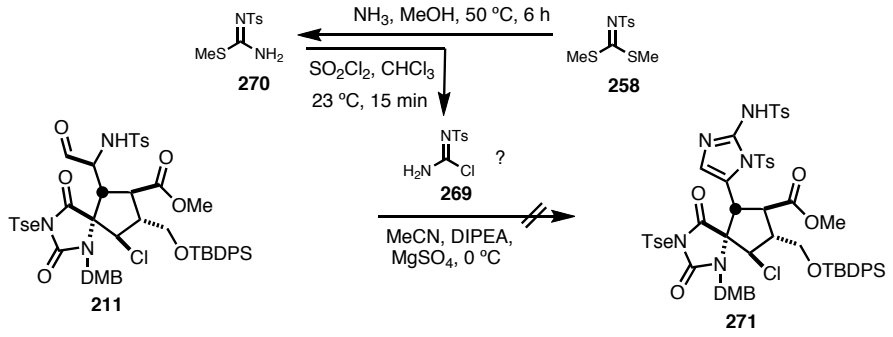
The mass was consistent with the expected amino-imidazole **268a** but the absence in the ^{1}H NMR spectrum of the very diagnostic signals for the vinyl proton and the hydantoin lactam proton suggested formation of the tetracyclic structure **268b**, deriving from intramolecular cyclization. Unfortunately, only a sub-milligram amount of **268b** could be isolated so unambiguous confirmation of its structure as well as assignment of the relative stereochemistry at C10 and C6 was not possible.

These encouraging results provided the impetus to continue our investigations, disappointingly however, further attempts to generate more per-tosylated cyclic guanidine **263** to expand on these initial promising findings proved to be fruitless. Even utilizing conditions that had previously been successful in providing modest amounts of desired product, only sluggish reactions with inconsistent and irreproducible results and no recovery of starting material were obtained.

Alternative approaches to the construction of related aminoimidazole surrogates were equally dismal. Attempted reaction of aldehyde **211** with imido chloride **269**

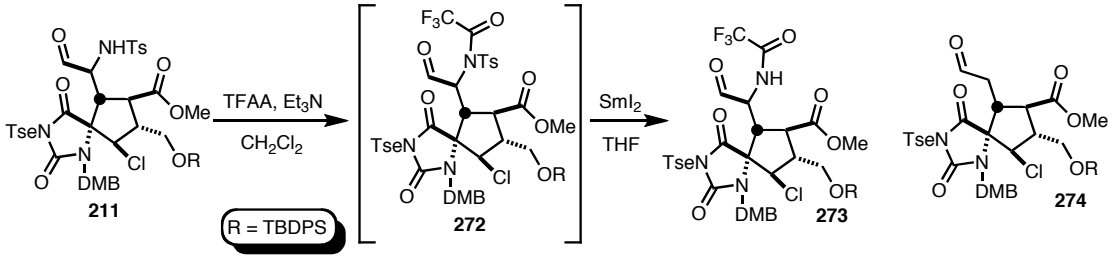
prepared from isothiourea **270** (readily available in turn, from commercially available bis-methylthio methylenetosylsulfonamide **250**) was extremely sluggish and no significant products or starting material could be detected in the crude ^{1}H NMR. It must be clarified that, although isothiourea **270** could easily be confirmed by NMR and mass data, assignment of **269** could not be unequivocally secured. In a separate experiment, use of isothiourea **270** directly on aldehyde **211**, led to the recovery of the starting material.

Scheme 5.31



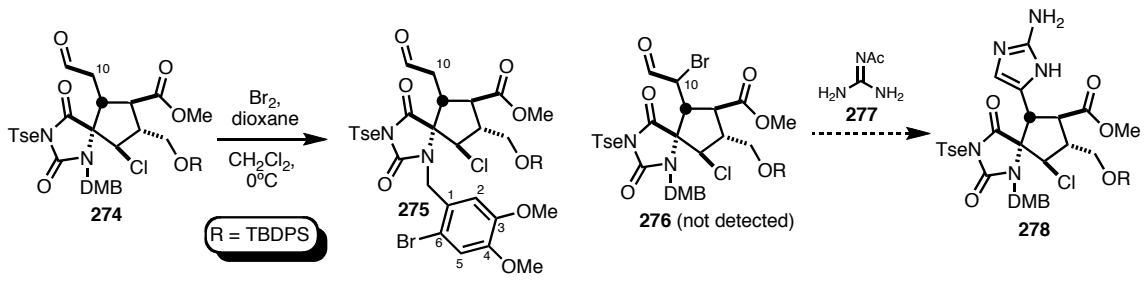
A few attempts to use commercially available cyanamide on aldehyde **211** or dimethyl acetal **197** to directly introduce the amino-imidazole ring, resulted in partial recovery of the starting materials even after heating up to 70 ºC. Reasoning, as before that the presence of the tosyl group was significantly decreasing the nucleophilicity of the amine we tried to identify conditions to remove the sulfone protecting group. Several trials in this direction using a variety of conditions were unsuccessful, but utilizing a two-step protocol developed in our group by Dr. Ziad Moussa[73] appeared to provide promising results. Thus treatment of aldehyde **211** with trifluoroacetic anhydride, followed by exposure of the crude material to samarium diiodide returned a product that was consistent by preliminary NMR observations with the desired trifluoroacetamide **273**. Upon further detailed 1 and 2D NMR analysis however (and confirmation by mass spectrometry data), the product was identified as des-amino aldehyde **274**.

Scheme 5.32



In a final attempt to make use of this unexpected substrate and garner further insight into the reactivity of these systems we envisioned that introduction of a halogen to the open α position of the aldehyde would provide yet another viable starting material for a one-step amino-imidazole synthesis. A brief survey of the literature in fact, showed that α-halo carbonyl compounds readily react with acetylguanidines to deliver the corresponding cyclic guanidines (Scheme 5.33). α-bromination of aldehydes is also widely reported. In our specific instance however, treatment of aldehyde **211** with bromine under common conditions[74] led only to the generation of a modest yield of aldehyde **275** clearly deriving from electrophilic aromatic substitution on the highly electron-rich DMB ring. Substitution at the 6 position of the aromatic ring was confirmed by appearance in the ^{1}H NMR spectrum of two singlets at δ = 6.92 ppm and δ = 7.01 ppm, in place of the typical DMB pattern (d-dd-d).

Scheme 5.33



Although certainly disappointing, though in hindsight not entirely unexpected, this result may seem, it is important to note here that it exposed avenues of reactivity that we had not previously considered and it also set a precedent that quickly provided great insight into the outcomes of later investigations.

In light of these results, further investigations toward the direct construction of the northern amino-imidazole ring were not pursued, and our efforts were refocused on the original approach involving a late-stage bis-guanidinylation.

5.6 Conclusions

Efficient methodologies for the construction of an imidazolone precursor to the D ring of the axinellamines featuring the correct C12 configuration were developed and later optimized in collaboration with Dr. Yonggang Wang. The new approach (4 steps) significantly shortened the existing synthetic route (9 steps), also requiring far less purification of the intermediates. Preliminary investigations toward the direct synthesis of the northern amino imidazole ring of the target natural product returned promising, albeit inconsistent results. Further exploration of these reactivity avenues I believe is warranted.

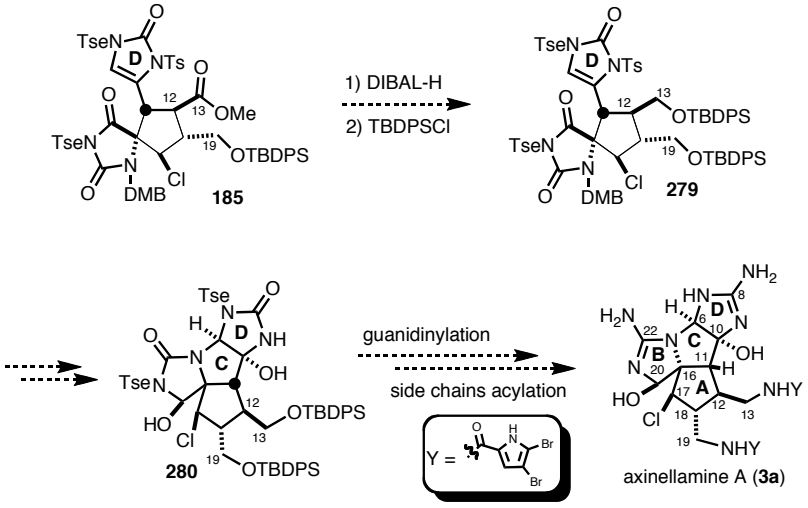
CHAPTER VI

BIOINSPIRED STRATEGIES TOWARD AXINELLAMINE, KONBU'ACIDIN AND PALAU'AMINE

6.1 Initial Studies Toward Axinellamine

After the first successful, though yet unoptimized syntheses of the imidazolone precursor to the D ring of the axinellamines, in order to move the project forward we endeavored to investigate the key cyclization that would deliver the tetracyclic core of the target natural product. As before (see Scheme 5.6 and related text), we projected that reduction of the ester moiety and protection of the resulting primary alcohol as the same silyl ether as the one already present at C19 would provide a convenient way to simultaneously manipulate both side chains in the late stages of the synthesis, once the core had been established.

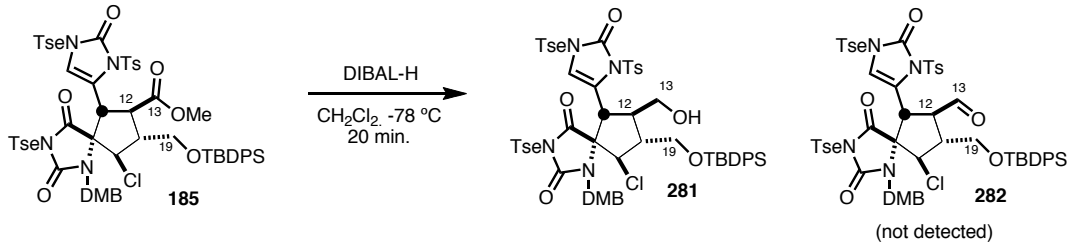
Scheme 6.1



We were pleased to find that treatment of methyl ester **185** with DIBAL under standard reaction conditions quickly and cleanly generated the desired primary alcohol **281** with no intermediate aldehyde **282** observed. It appeared that our previous

assessment (Scheme 5.9 and related text) that the proximity of a Lewis basic site (namely a sulfonamide), would hinder the reactivity of the aluminum reagent was correct.

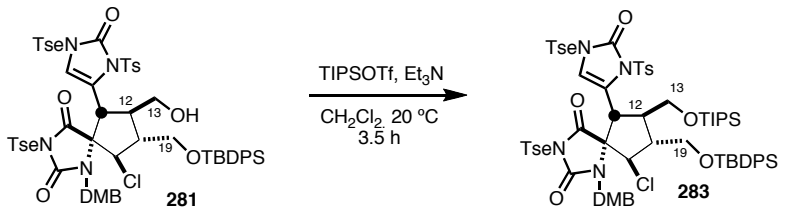
Scheme 6.2



When crude alcohol **281** was exposed to TBDPS chloride however, no reaction was observed by TLC analysis even after prolonged reaction time (19 hours) and indeed after column chromatography purification, unaltered starting material was recovered almost entirely. Considering that perhaps unknown impurities in the crude starting material had compromised the reactivity of the reagents, the procedure was repeated on the recovered purified material only to arrive at the same outcome.

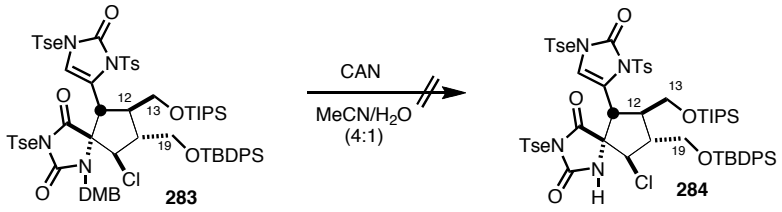
As this reaction had worked before on dimethyl acetal **178** (Scheme 5.10), we reasoned that in imidazolone **281** the C13 alcohol might lie in a rather congested region of space and we postulated that a smaller protecting group might be required. Indeed, when the smaller, and more reactive triisopropyl silyl triflate was used etherification of the free alcohol occurred readily. The protection step could eventually be run on the crude alcohol, generating modest yields of the desired product (54 % for the two steps).

Scheme 6.3



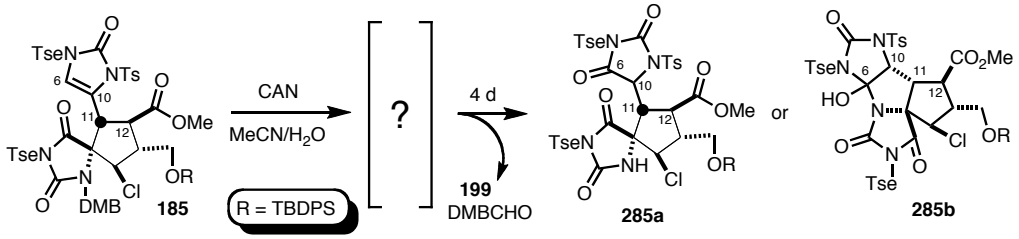
With small amounts of bis-silylether **283** in hand we proceeded to try and find suitable conditions to cleave the DMB protecting group in order to liberate the spirohydantoin "lactam" nitrogen for the projected intra molecular cyclization that would deliver the core of axinellamine. Several runs using ceric ammonium nitrate (CAN) did not provide any reaction at ambient temperature even after prolonged time (up to 40 hours). Increasing the operating temperature seemed to result in minimal reaction, as traces of the diagnostic signals of the aldehyde byproduct (**199** see Chapter IV) began to appear in the crude ^{1}H NMR, however no significant products could be isolated after column chromatography. It is important to note that these studies were performed early on, and the optimized conditions described in Chapter IV had not been identified yet.

Scheme 6.4



An interesting result was however obtained, albeit entirely serendipitously, in the course of these investigations when methyl ester **185** was subjected to the tested reaction conditions.

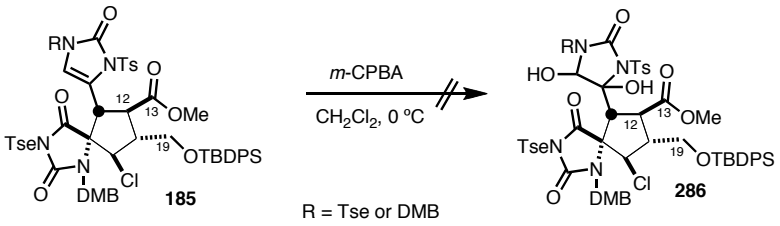
Scheme 6.5



Treatment of the DMB-protected imidazolone **185** with CAN (5 equiv.) for 1 hour at 0 ºC in fact, led to the isolation of a stable (purified by column) intermediate which still contained a "DMB" moiety. This unidentified intermediate was unintentionally left in $CDCl_3$ solution and very slowly (followed by ^1H NMR) released DMBCHO and was completely and cleanly converted to a new product. After re-purification of the mixture the isolated product was consistent by ^1H and 2D NMR as well as MS data with either bis-hydantoin **285a** or tetracycle **285b**. A 2D heteronuclear NMR investigation (HMBC) was not conclusive due to the minute amount of material, however ^{13}C NMR revealed the appearance of a new signal at δ = 170 ppm, which is consistent with a lactam carbonyl. This appeared to indicate that the correct structure was bis-hydantoin **285a** and several literature precedents confirmed that similar oxidations are not uncommon.

Concomitant early attempts to test the reactivity of the imidazolone double bond toward oxidation provided sluggish reactions and inconclusive results, and our focus shifted to the direct synthesis of an amino-imidazole precursor to the D ring of axinellamine (see Chapter V).

Scheme 6.6

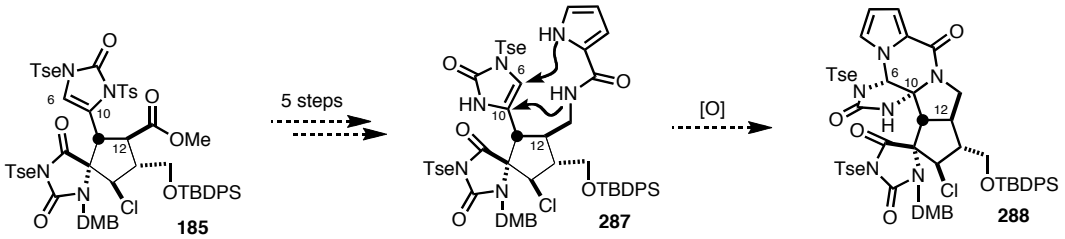


6.2 First Generation Synthesis of a Mono-Pyrrole Precursor to Palau'amine

As our studies toward the synthesis of axinellamine (**3**) (see Chapter V and 6.1 above) were well underway, the structural revision of palau'amine (**2**) appeared,[3] unifying these two natural products from a relative stereochemistry standpoint. We realized that the chlorocyclopentane core of our newly synthesized imidazolone **185** possessed all the correct stereochemical relationships found in both alkaloids and we

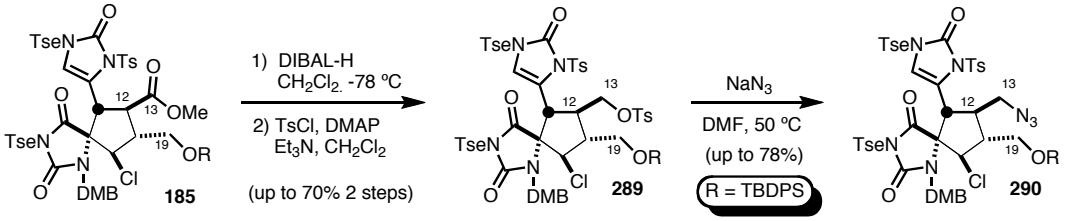
envisioned that introduction of a pyrrole carboxamide functionality on the C12 side chain (Scheme 6.7) would readily give us an opportunity to investigate a presumed biomimetic bis-cyclization[2] eading to the hexacyclic core of palau'amine. We projected that trivial manipulations, namely reduction of the ester moiety, introduction of an azide on the resulting primary alcohol followed by reduction and acylation of the corresponding primary amine would quickly deliver the required cyclization precursor **287**.

Scheme 6.7



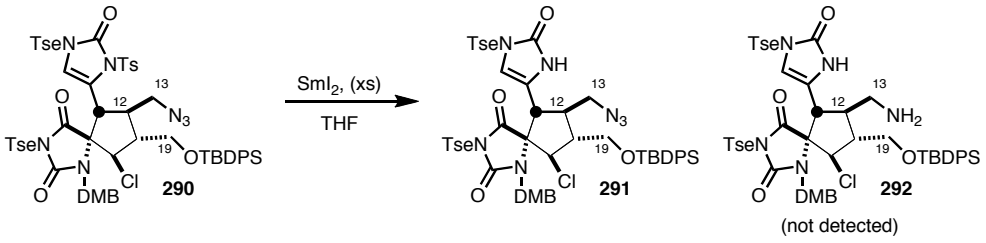
Initial attempts to introduce the azide directly on the free primary alcohol under Mitsunobu conditions met with no success, whereas the typical two-step protocol involving activation with tosyl chloride followed by displacement with sodium azide consistently provided good yields of the desired product **290**. Eventually the tosylation reaction could be run on the crude alcohol obtained after DIBAL reduction improving the overall efficiency of the sequence.

Scheme 6.8



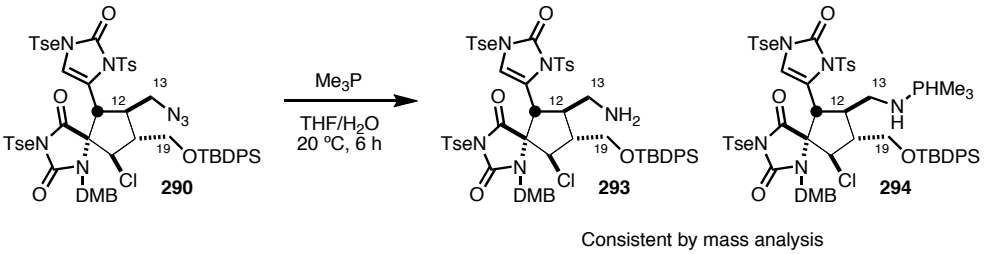
At this point following precedents set by Dr. Shaohui Wang in his pioneering studies[62] on this project we attempted to effect a simultaneous azide reduction and tosyl deprotection using samarium diiodide. The removal of the tosyl group from the imidazolone under these conditions, though expected was at the onset deemed inconsequential, however later findings (discussed in Chapter V) demonstrated that this was in fact necessary to activate the imidazolone toward oxidation. It is noteworthy that contrary to what reported by Dr. Wang, in my hands this manipulation proved to be surprisingly problematic, and in most instances, treatment of azide **290** with either commercially available, or freshly prepared samarium diiodide led only to cleavage of the sulfone leaving the azide unaltered.

Scheme 6.9



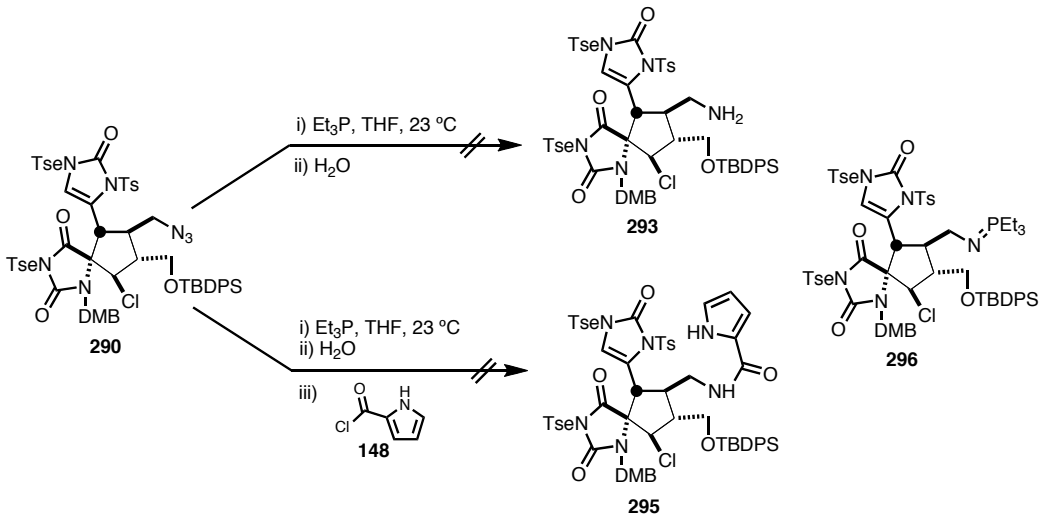
Resubjecting the crude or purified detosylated azide **291** to the reaction conditions even using large excesses (up to 15 equivalents) of reagent at ambient temperature for prolonged time only led to recovery of the starting material. Similarly, treatment with phosphines in a THF/H_2O solvent mixture for up to 17 hours only returned unaltered azide **291.** Under the latter conditions tosylated azide **290** underwent a very sluggish reaction and ^{1}H NMR analysis of the crude material revealed formation of several products. Mass spectrometry data showed peaks consistent with the desired amine **293** (M+H, M+Na and M+K), with phosphinamine **294** along with others that could not be reconciled with any plausible products.

Scheme 6.10



When triphenylphospine was used instead only partial conversion was observed at room temperature after overnight stirring. This appeared to be an indication that perhaps the target azide in **290** was significantly hindered. Heating to 50ºC for a few hours led to nearly complete conversion, but the isolated product in this case was different than before and could not be unequivocally assigned. Use of the less sterically demanding triethylphosphine, which had provided excellent results on simple azides (not shown) either trying to arrive at the free amine or to the target pyrrole, led to the isolation of a product that was consistent (confirmed by mass) with phosphine-imine **296**.

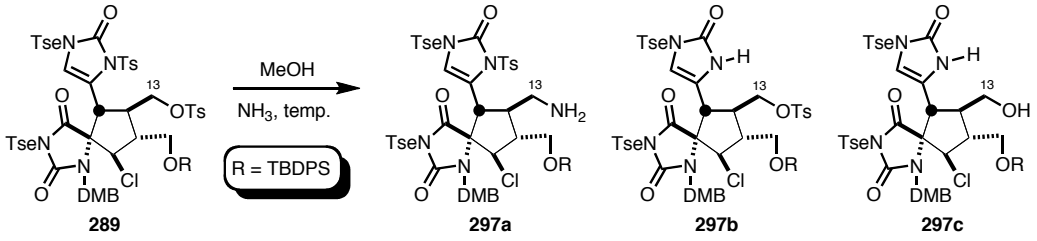
Scheme 6.11



Apparently after formation of this intermediate hydrolysis to the amine did not occur, and consequently the desired acylation did not take place. Several literature precedents confirmed that trialkyl phosphinimine (even primary ones) can indeed be quite stable and resistant to hydrolysis. Attempts to hydrolize phosphinimine **296** by prolonged exposure to water with heating, and under basic (Cs_2CO_3) or acidic conditions (2M HCl) were fruitless.

Alternative reduction protocols, such as hydrogenation in the presence of a palladium catalyst resulted in extremely sluggish reactions with no significant products being detected. At this point it was decided to explore different approaches to install the amine functionality at C13 that did not require the intermediacy of an azide. We envisioned that displacement of the tosylate precursor by ammonia (or an analog thereof) could be a suitable strategy, which would also remove one step from the overall sequence. Although this procedure finds ample precedent in the literature, in our case stirring a solution of **289** in MeOH saturated with gaseous ammonia in a sealed vial for 15 h resulted in the complete conversion to de-tosylated imidazolone **297b** (confirmed by mass).

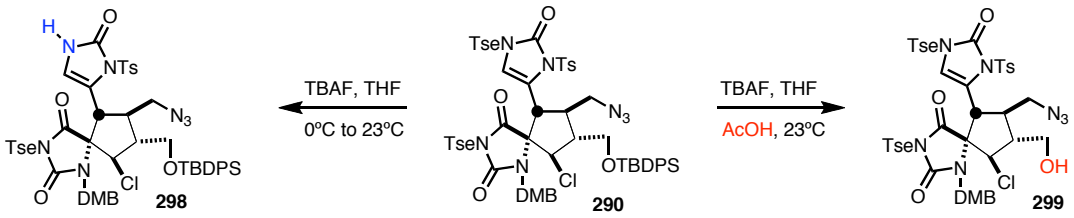
Scheme 6.12



Resubjecting this crude material to the reaction conditions but increasing the temperature to 70ºC resulted in the cleavage of the S-O bond of the tosylate generating alcohol **297c** with only traces of the desired amine **297a** detected by mass spectrometric analysis. When the reaction was run in THF under the same conditions[75] no reaction was detected even after prolonged reaction time.

Having gathered evidence that seemed to indicate that the C13 position of our substrate was unexpectedly but significantly hindered, we reasoned that removal of the bulky TBDPS protecting group from the C19 alcohol could in principle decongest the space around the desired reacting site allowing for easier approach of potential nucleophiles. In a first run, treatment of azide **290** with excess TBAF led to the complete cleavage of the imidazolone Tse group. This outcome was rationalized considering that the mild acidity of the sulfone α protons (see Chapter III) could be in this setting greatly enhanced by conjugation through the imidazolone unsaturation with the electron-withdrawing tosyl moiety.

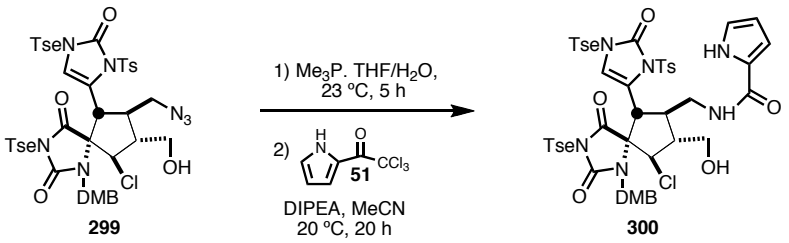
Scheme 6.13



In addition, the formation upon removal of the Tse group, of an aromatic hydroxy imidazole tautomer (see Scheme 5.29) could provide a significant driving force for this reaction manifold. The use of buffered conditions seemed to be an appropriate course of action at this juncture, and indeed addition of quantitative amounts of acetic acid to the reaction mixture (Scheme 6.13) completely reversed the chemoselectivity leading to the isolation of the desired desilylated alcohol **299** in up to 72% yield.

With free alcohol **299** in hand we were pleased to confirm that our assessment (*vide supra*) was correct. Without the hindrance of the TBDPS group the azide reduction proceeded efficiently using phosphines, and after some experimentation the crude amine could directly be acylated with commercially available trichloroacetylpyrrole generating modest yields (~ 40 % for the 2 steps) of cyclization precursor **300**.

Scheme 6.14



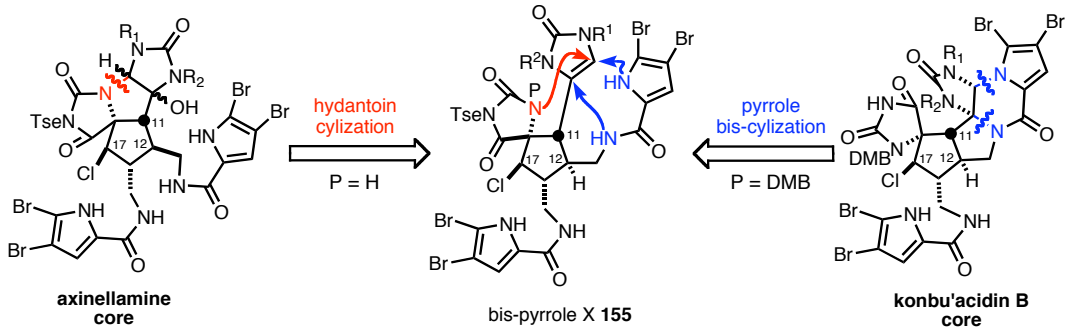
This material featured *the complete carbon framework of palau'amine* (**2**) however, oxidative cyclization experiments to generate the hexacyclic core of the target natural product (see Scheme 6.7) were never performed on this substrate.

6.3 Bis-Pyrrole Cyclization Precursor Toward Axinellamine and Konbu'acidin

One of the recently isolated new PIA's that called into question the original structural assignment of palau'amine was konbu'acidin B[3a] (**5**, see Chapter I). This alkaloid attracted our interest as it featured the hexacyclic core of palau'amine (**2**) but the level of bromination of the axinellamines (**3**), Indeed, the two natural products share a virtually identical framework and differ only in connectivities. Consistent with the proposal by Al Mourabit and Potier in fact, these two metabolites could derive from a common biogenetic precursor. Intrigued by their similarities we set out to emulate the presumed biosynthetic pathway by synthesizing one such precursor, namely bis-pyrrole **155**, which could lead in one step, *via* different modes of intra molecular cyclization, to either (or both) cores of the target alkaloids (Scheme 6.15). We had previously demonstrated that the spirohydantoin "lactam" nitrogen could in fact interact with a pendant electrophile, cyclizing to the ABC core of axinellamine (see Chapter III), and we envisioned that in this complex scenario the DMB protecting group would be the controlling element that would allow to select the desired mode of intramolecular cyclization. In the presence of this blocking group the anticipated facile hydantoin cyclization onto the pendant imidazolone would be precluded, and pyrrole carboxamide bis-cyclization should be favored. By contrast, after removal of the DMB the axinellamine pathway was expected to take precedence. It is also plausible that the two

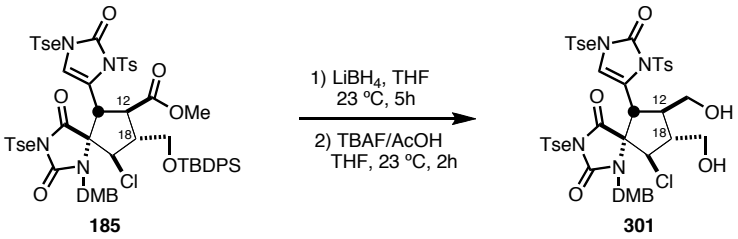
reaction avenues might be in competition leading to the formation of mixture of the two products, which would support a common biogenetic origin.

Scheme 6.15



Initial manipulation of the C12 and C18 side chains of imidazolone **185** proved to be trivial and proceeded uneventfully using conditions that we had previously identified, to generate modest yields (up to 58% for the two steps) of diol **301.**

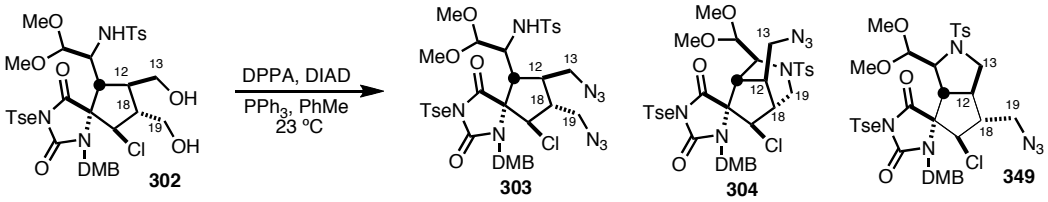
Scheme 6.16



At this point we envisioned that direct installation of azide functionalities on the free alcohol side chains under Mitsunobu conditions would be the most efficient way to proceed, even though previous experimentation on analog diol **302** had given unexpected results (Scheme 6.17) leading to the isolation of what was originally thought to be spirotricyclic mono-azide **304**, deriving from intramolecular nucleophilic attack of the sulfonamide on the activated alcohol at C19. It was discovered only recently however

that intramolecular cyclization occurs in fact *via* displacement of the C13 alcohol generating *trans*-azabicyclo octane **349** (discussed in Chapter VII).

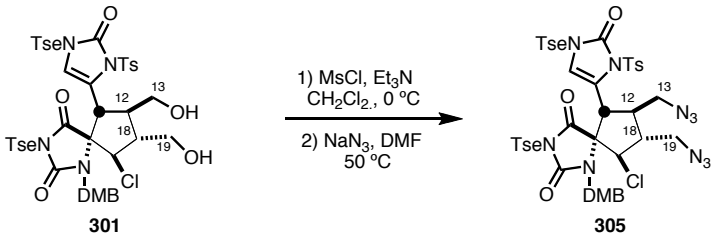
Scheme 6.17



In this case, we reasoned that the absence of the internal nucleophile (*i.e.* the sulfonamide) should prevent similar undesired reactions. The fact that imidazolone **301** provided no discernible reaction under the same reaction conditions attests that the reactivity of these two substrates was indeed profoundly dissimilar.

We therefore resorted once again to a two-step procedure involving treatment of the free alcohols with mesyl chloride, followed by displacement of the activated mesylates by sodium azide under standard conditions. This immediately provided satisfactory results leading to the consistent isolation of good yields of bis-azide **305** (70-74% for the two steps).

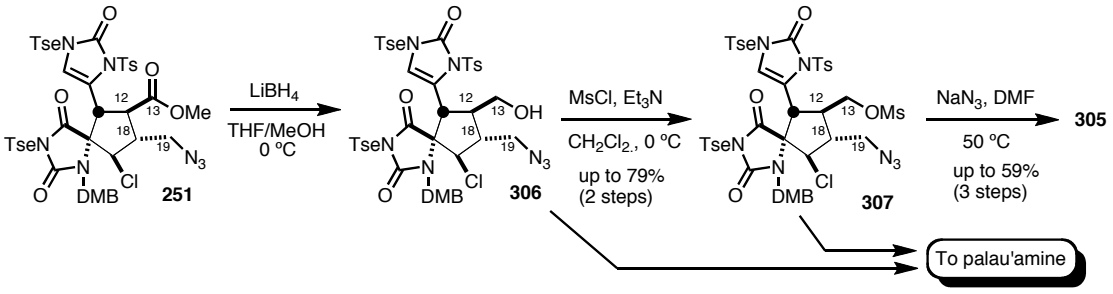
Scheme 6.18



In later trials starting from azide imidazolone **251** (discussed in Chapter V) bis-azide **305** could be obtained through similar transformations with overall good efficiency (52-59% for the three steps). In addition we envisioned that the intermediate alcohol **306**

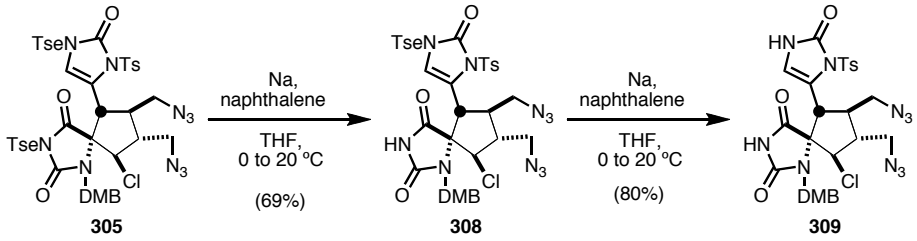
and mesylate **307** along this route could be convenient point of divergence in pursuit of the synthesis of palau'amine (discussed in the section 6.4 below).

Scheme 6.19



With a robust synthetic sequence to access bis-azide **305** in hand we projected that under single-electron-transfer conditions, namely using sodium naphthalenide, a global deprotection of the sulfone protecting group and concomitant reduction of the azide functionalities could occur delivering, after selective acylation of the primary amine moieties, the cyclization precursor that we had set out to synthesize (*vide supra*). Although not resulting in the desired outcome, preliminary studies in this direction were not entirely discouraging. In a first run **305** was treated with excess of freshly pre-prepared reagent (13 equiv.) and stirred at –78ºC for 3 hours. The mixture was then quenched with *t*-BuOH and the solvents were evaporated. After prep TLC the only product isolated (~25 % yield) was mono-deprotected imidazolone **308**.

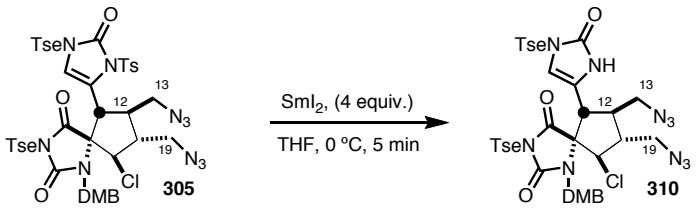
Scheme 6.20



In a second run of the reaction a sub-stoichiometric amount of naphthalene and excess sodium were directly added to a THF solution of the starting material and the resulting mixture was stirred at 0ºC for 6 hours and then at ambient temperature overnight. After aqueous workup and column purification a 69% yield of **308** was isolated. Subjecting the isolated **308** to the above conditions led to the generation of mono-tosylated imidazolone **309** in ~ 80% yield).

Treatment of bis-azide **305** with freshly prepared samarium diiodide led, as before (Scheme 6.9) only to the selective cleavage of the imidazolone tosyl group (68% yield obtained consistently in multiple runs) leaving the azide functionalities unaltered.

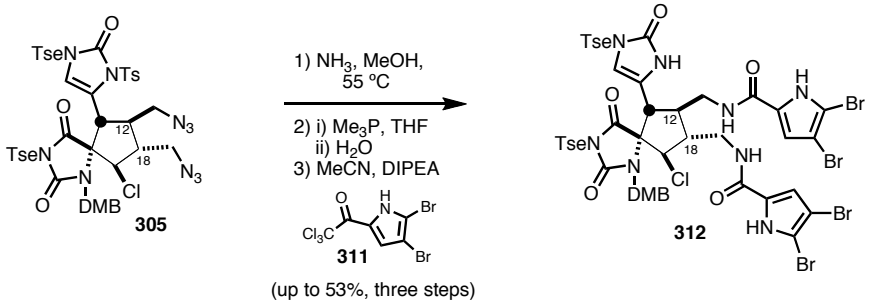
Scheme 6.21



A few other efforts to arrive at a complete detosylation either from **309** or from **305** met with no success, therefore it was decided that imidazolone **310** (already shown to be activated toward oxidation) would be advanced to the investigation of the key oxidative cyclization, delaying the removal of the Tse groups to the later stages of the synthesis. Several attempt to reduce the azide functionalities under a variety of conditions such as Mg in MeOH under sonication[76] and hydrogenation in the presence of palladium of platinum catalysts led only to partial recovery of unaltered starting material. Once again, the use of phosphines provided far superior results generating after acylation of the crude bis-amine intermediate with dibromo-trichloroacylpyrrole **311**, useful yields (up to 50% for the two steps) of the target bis-pyrrole cyclizaton precursor (Scheme 6.22). After some experimentation, using the detosylation conditions fortuitously discovered in earlier studies (*vide supra*) we could run the three-step sequence shown in Scheme 6.22 *in one pot without any work-up of the intermediates*. A single column chromatography

purification at the end of the three steps afforded bis-pyrrole **312**, featuring *the complete carbon framework* of both axinellamine and konbu'acidin, in overall good yields.

Scheme 6.22

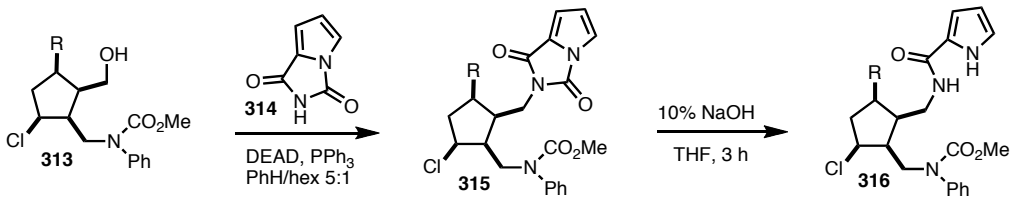


Investigations of the projected, presumed biomimetic oxidative cyclization of this material leading to the hexacyclic core of konbu'acidin B (**5b**) are discussed in section 6.5 below.

6.4 Second Generation Synthesis of a Mono-Pyrrole Precursor Toward Palau'amine

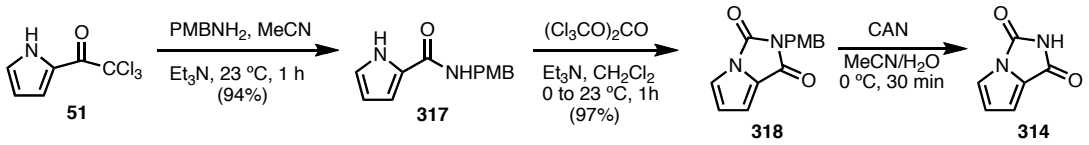
As anticipated above, in our unified strategy we envisioned mesylate **307** and alcohol **306** (Scheme 6.19) as potential points of divergence toward the synthesis of the non-brominated palau'amine (**2**). Our first efforts in this direction were inspired by work done in the Shair group at Harvard[77] involving direct installation of acylpyrrole precursors **314** onto a primary alcohol under Mitsunobu conditions, followed by mild basic hydrolysis to liberate the carboxamide functionality.

Scheme 6.23



Having found the reported syntheses of pyrrole hydantoin **314** not to be satisfactory, we developed a new approach and after brief optimization the target reagent could readily be synthesized from commercially available trichloroacetylpyrrole. Although the last step was usually low-yielding (not accurately determined), the entire sequence could be run in a few hours furnishing synthetically useful amounts of pure, crystalline reagent.

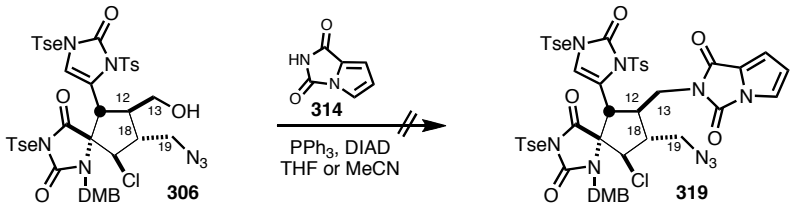
Scheme 6.24



While our investigation was in progress a publication by Lovely[16h] appeared demonstrating the utility of this reagent in the total synthesis of nagelamide D.

Disappointingly however, in our setting no reaction was detected with alcohol **306** resulting in complete recovery of unaltered starting material even after prolonged time at higher temperatures (50 ºC). It appeared that the space surrounding the C13 center was still too congested (see Scheme 6.11 and related text), and would either not accommodate a bulky activating agent (such as triphenylphosphine) and/or not allow the approach of a large nucleophile.

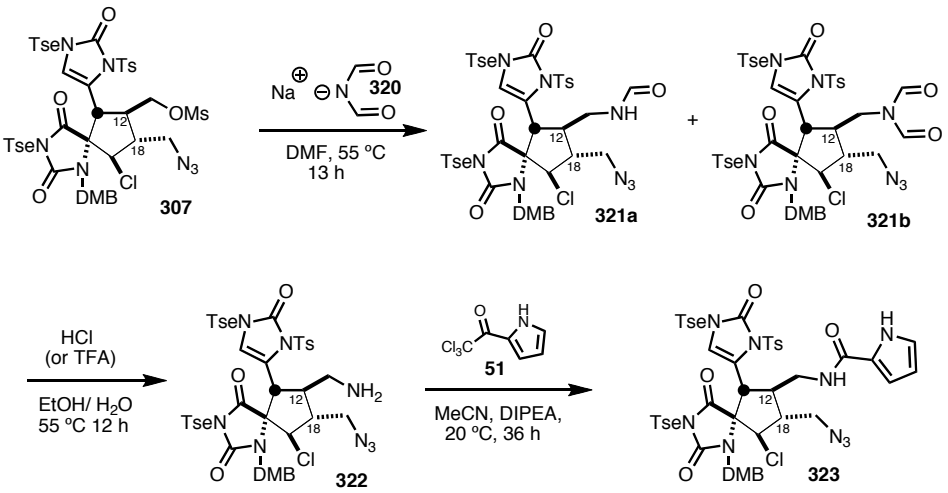
Scheme 6.25



Further studies of this procedure were not performed and it was decided at this point that mesylate **307** would provide better opportunities for the differentiation of the C12 and C18 side chains.

Initial attempts to use ammonia as the nitrogen source to displace the activated alcohol led only to complete, clean cleavage of the imidazolone tosyl group *without affecting the mesylate*. By contrast, treatment with commercially available diformylimide **320** in DMF, generated a virtually equimolar mixture of mono- and bis-formylated amines **321** (as expected per literature precedent)[78] Under strong acidic conditions the crude mixture converged to amine **322** (detected only by TLC analysis), and subsequent acylation of this presumed material provided modest amounts of mono-pyrrole **323**.

Scheme 6.26

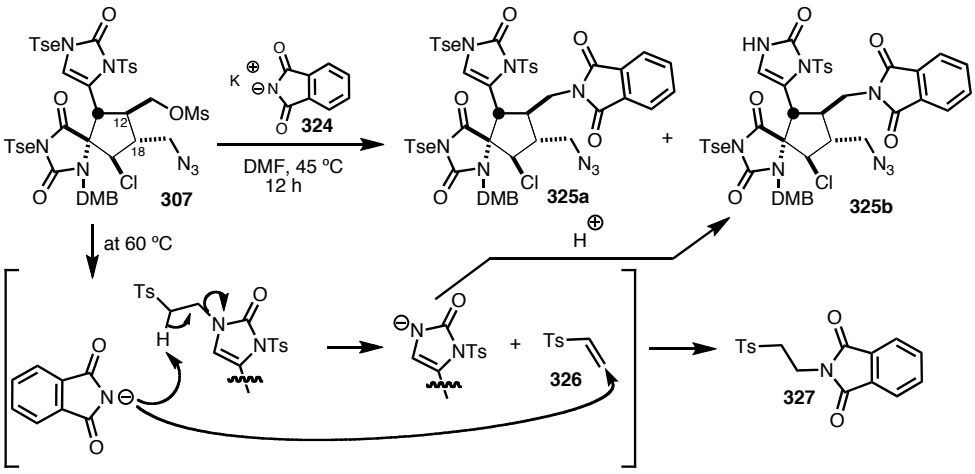


Although the procedure in the literature precedent was reported to be highly efficient (granted on much less complex substrates), and was eventually optimized to a one-pot protocol, the sequence in Scheme 6.26 was extremely sluggish (mainly due to the acid hydrolysis step) and could not be improved, prompting us to seek alternatives.

Use of potassium phthalimide **324** immediately provided far better results and after brief adjustment of the reaction conditions consistently led to the isolation of good yields (65-73%) of the desired product. Interestingly, when the reaction was run at slightly

higher temperature (60 ºC vs. 45 ºC) only minor amounts of the desired phthalimide **325a** were detected, with a mono-detosylated analog being the major product being isolated. The undesired product was identified as **325b** directly by ^{1}H NMR and mass data, and indirectly by the concomitant isolation of tosylethylphthalimide **327**. We have already discussed how the enhanced acidity of the α proton of the sulfone renders this group unusually labile (*vide supra*). Thus it is plausible to envision that phthalimide could act as a base, liberating a vinyl sulfone **326**, which is in turn trapped *via* conjugate addition by a second equivalent of phthalimide.

Scheme 6.27

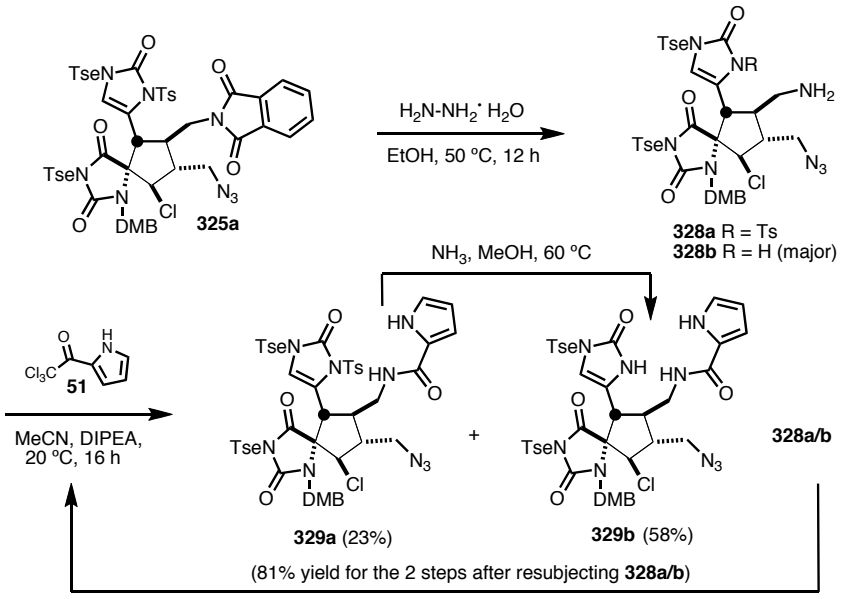


Loss of this Tse moiety was not desirable at this juncture as it was later proven to hinder the removal of the tosyl protection necessary for activation of the imidazolone toward oxidation; therefore lowering the operating temperature from 60 to 45 ºC minimized this unwanted side reaction.

The phthalimide moiety in **325a** was readily cleaved using hydrazine under standard conditions liberating the corresponding amine. It was noticed that in the process concomitant partial detosylation occurred and mass data confirmed that, in this instance it was the imidazolone tosyl group that was being cleaved. As this suited our needs (*vide*

supra) we tried to maximize this detosylation by increasing the reaction time from two to twelve hours. After this time increased, though not complete tosyl cleavage was obtained, and the crude mixture of amines **328a/b** was advanced to the acylation step, leading to the isolation of the expected mono-pyrrole carboxamides **329**, along with some unreacted amine precursors. These were resubjected to the reaction conditions generating additional desired products for an overall yield of 81% (2 steps).

Scheme 6.28



In a later experiment pyrrole **329a** could be efficiently converted to the detosylated analog **329b**, using the conditions indicated in Scheme 6.28. In this instance however, the two products, which were easily separated by column chromatography, proved to be useful for preliminary, comparative studies of the projected oxidative cyclization (discussed below), as both featured the *complete carbon framework* of palau'amine.

6.5 Oxidative Cyclization Studies

In our initial investigation of the presumed biomimetic intramolecular bis-cyclization that generates the hexacyclic core of palau'amine and konbu'acidin (study of the axinellamine mode of cyclization was postponed) we opted to monitor our reactions *via* LC/MS. This analytical technique would not only provide mass data and valuable information on the neatness of the reactions but it would also allow us to operate at a sub-milligram level, minimizing the use of precious advanced synthetic intermediates. In addition the presence of multiple bromine atoms in our substrates, which give rise to very characteristic isotopic patterns in the mass spectra (Figure 6.1), would allow us to identify significant products even in very sluggish reactions, as these patterns can be easily and accurately predicted.[79]

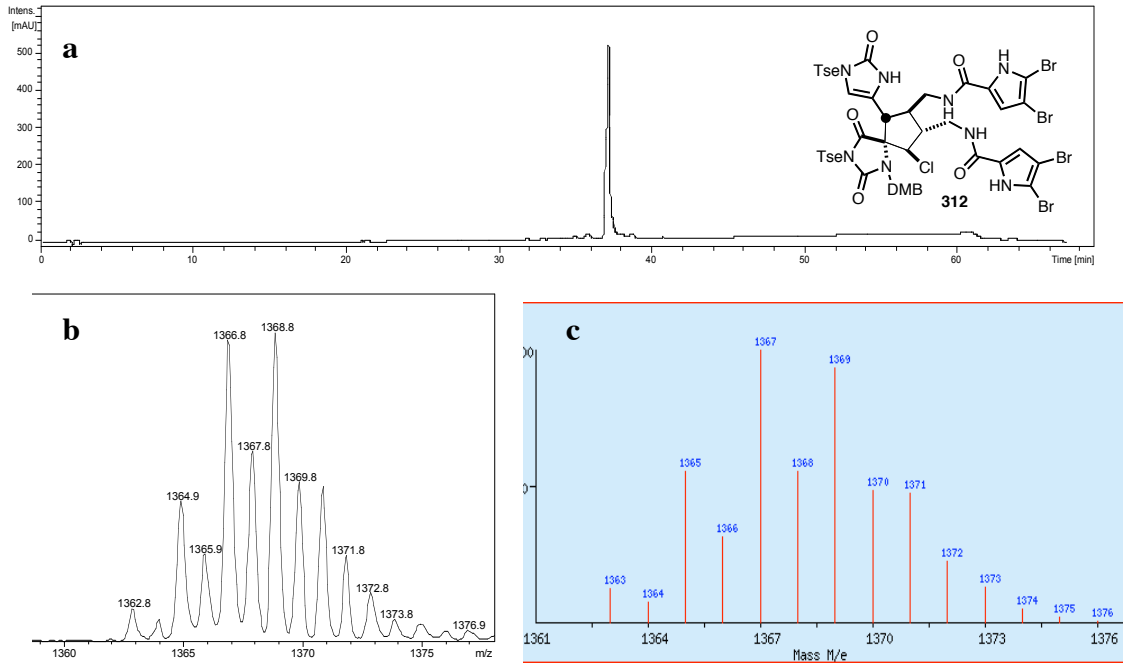


Figure 6.1. a) HPLC trace for bis-pyrrole **312**. b) observed and c) predicted[79] M+Na cluster for bis-pyrrole **312**.

Literature precedents for the desired oxidative cyclization were quite encouraging, as in several instances polycyclic alkaloids of the PIA family were obtained from linear precursors through intramolecular ring closures triggered by a variety of activating

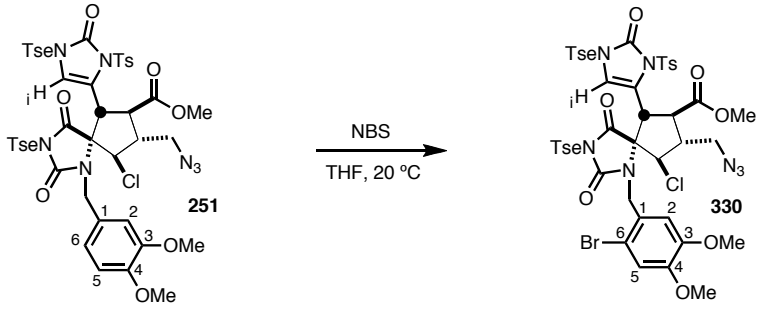
agents. Namely, the pioneering work by Büchi,[80] later emulated by Horne[13c] and more recent reports by Chen[18b] and Al Mourabit[29] provided us with promising starting points in our endeavors. Preliminary results along these guidelines however, quickly demonstrated that in our complex setting, the desired transformations would not be trivial. Intractable mixtures of unidentifiable materials were in fact obtained when bis-dibromopyrrole **312** was exposed to excess amounts of *N*-bromosuccinimide (NBS), and no significant insight could be garnered at this point. Equally dismal outcomes resulted from the use of a hypervalent iodine reagent ($PhI(OAc)_2$) and no noteworthy information could be derived from LC/MS data analysis. In yet another run using NBS in an acidic medium (TFA) the only significant LC/MS data could not be reconciled to any plausible outcomes, and an experiment using *N*-chlorosuccinimide (NCS) as the activating agent inexplicably seemed to result in complete decomposition.

In all the above experiments, given the exceedingly small scale of the reactions (0.25-1.5 mg range) no work-up was performed to prevent loss of material and after evaporation of the solvents the crude residues were subjected to LC/MS analysis. The realization that this might have had in fact, a significant impact on the outcome provided the first potential breakthrough. In a subsequent run with NBS as the activating agent in a THF solution, despite the small scale, the reaction mixture was quenched with a saturated solution of sodium thiosulfate ($Na_2S_2O_3$), diluted with ethyl acetate, dried and concentrated. Although the HPLC trace was not remarkably neat the major cluster in the mass spectrum and its isotopic pattern were clearly consistent with the addition of *two* bromine atoms and the loss of *four* hydrogens, which was highly indicative of an oxidation. Identification of the product remained at this point elusive, and a tentative assignment was advanced only after meticulous investigations (*vide infra*).

Also, if on one hand the result was encouraging, on the other hand it exposed potential reactivity avenues that we had not previously considered, namely the competing bromination in our substrate of moieties other than the target imidazolone. Recalling that electrophilic aromatic substitution of the DMB ring had previously been observed (see Chapter V), we set out to systematically investigate the reactivity of our substrates toward halogenation.

When azide imidazolone **251** was treated with an excess of NBS, a slow reaction was observed by TLC and the only product isolated was shown to be monobrominated derivative **330** (Scheme 6.29) by the change in the ^{1}H NMR spectrum of the very diagnostic DMB aromatic signals (Figure 6.2).

Scheme 6.29



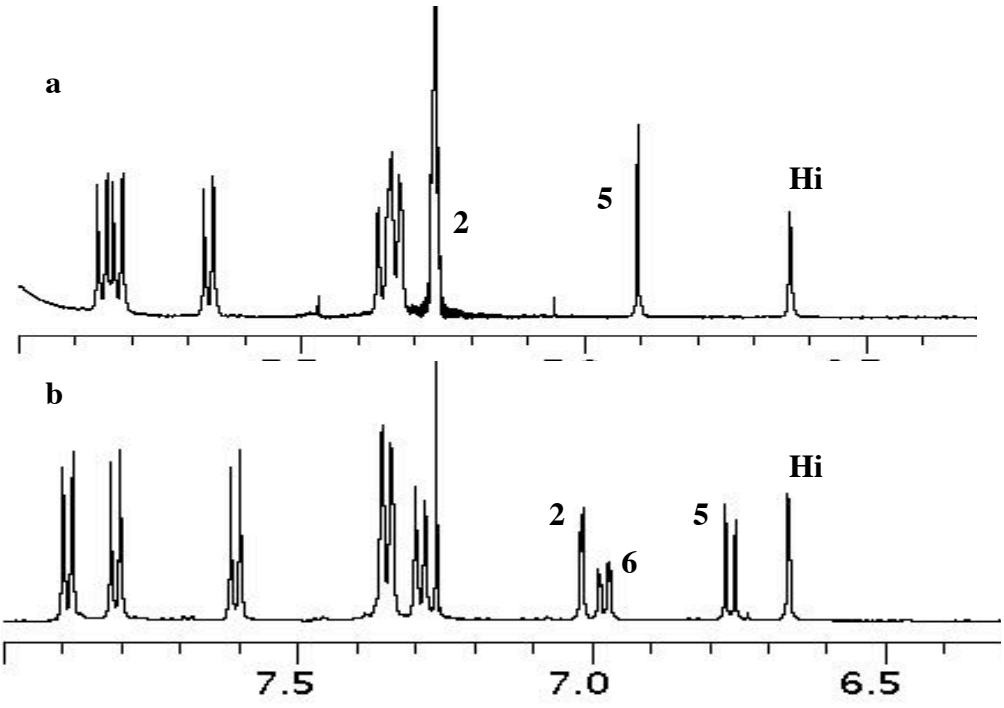


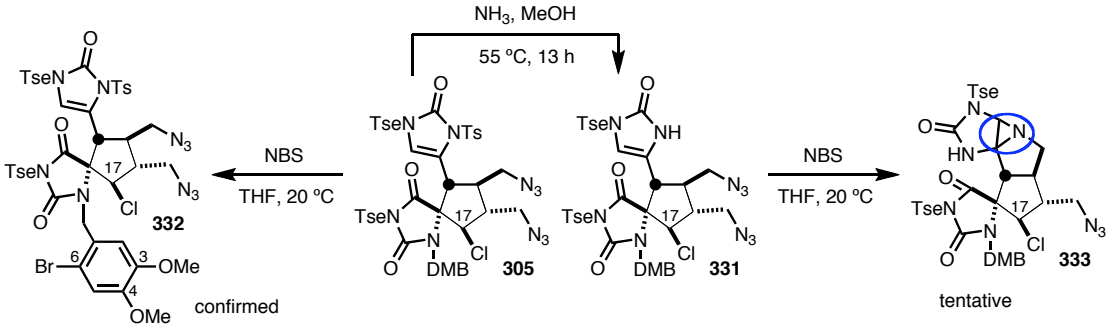
Figure 6.2. Spectroscopic comparison of the aromatic region of the ^{1}H NMR spectra of a) azide imidazolone **251** and b) brominated derivative **330**.

Incorporation of a bromine atom was confirmed by the isotopic pattern of the M+H, M+Na and M+K clusters in the mass spectrum. Exposure of this material to a large excess (> 150 equiv.) of NBS reagent led to no further reaction even after several hours.

This study clearly showed that incorporation of halogens in the very electron-rich DMB ring was quite facile although not remarkably fast. In addition, presumably because of steric hindrance this system can only accommodate one bromine atom even in the presence of a large excess of reagent. Lastly, but perhaps most importantly, as observed in many previous instances the tosyl-protected imidazolone was confirmed to be completely inert toward oxidation, as the diagnostic vinyl proton signal remained virtually unchanged in the ^{1}H NMR spectrum (Figure 6.2). Monobromination of the DMB ring was also clearly confirmed in bis-azide **305**, leaving the imidazolone unaltered, while a completely different outcome was observed once the tosyl group was removed.

When detosylated bis-azide **331** was subjected to the same reaction conditions in fact (Scheme 6.29), a much more sluggish reaction occurred, though a major product was observed in the crude ^{1}H NMR spectrum. After several rounds of careful purification analysis of the spectroscopic data of this compound revealed some very interesting features. ALL three DMB aromatic signals were clearly visible whereas the imidazolone vinyl proton was missing.

Scheme 6.30



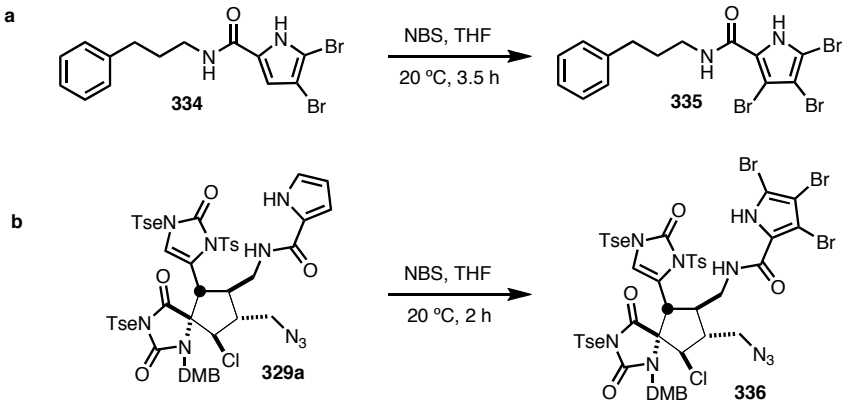
The NH signal on the imidazolone was also clearly visible, and all protecting groups were still present. In addition, the H17 coupling constant was a perfect match for

palau'amine (9.0 Hz) suggesting the formation of the strained *trans*-bicyclic system, and finally the isotopic pattern of the mass peaks indicated that no bromine atom had been incorporated, which seemed to suggest that it did indeed activate the imidazolone and was subsequently extruded (which was the kind of reactivity we had sought to obtain). In light of these observations the product was tentatively assign as aziridine **333**.

Later bromination experiments on substrates featuring free or protected amines on the side chains returned mostly inconclusive results, and coupling constant analysis of the only usable data obtained seemed to suggest that the "palau'amine cyclization" had not occurred.

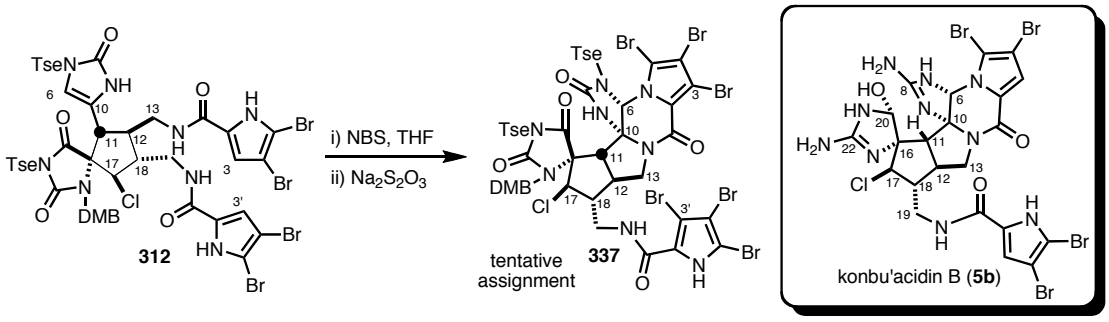
Continuing on our systematic investigation, we became aware of several reports in the literature[81] indicating that pyrroles were prone to *extensive halogenation*, which prompted us to explore this unexpected reaction manifold on our substrates. Indeed, under the established reaction conditions model carboxamide **334** quickly incorporated a bromine atom in the available position of the pyrrole, and toslylated imidazolone **329a** reacted equally promptly delivering a single product. Analysis of the ^{1}H NMR spectrum of the purified material revealed that *all* aromatic pyrrole signals had disappeared and the isotopic pattern in the salient mass peaks confirmed the presence of three bromines. It is also noteworthy that in this instance, the DMB ring *was not affected*, suggesting that incorporation of bromine on the pyrrole was much faster.

Scheme 6.31



On the basis of the results of the investigations described above we could advance a tentative assignment of the structure of the product detected by LC/MS in the only significant oxidative cyclization experiment we performed (*vide supra*). As discussed, mass data suggested the incorporation of two bromine atoms and a possible oxidation, which appeared to be consistent with hexabrominated hexacyclic compound **337** (Scheme 6.31). This assessment was, of course, extremely promising because if confirmed, compound **337** would feature *the completely functionalized carbon skeleton of konbu'acidin B* ((**5b**)inset in Scheme 6.31).

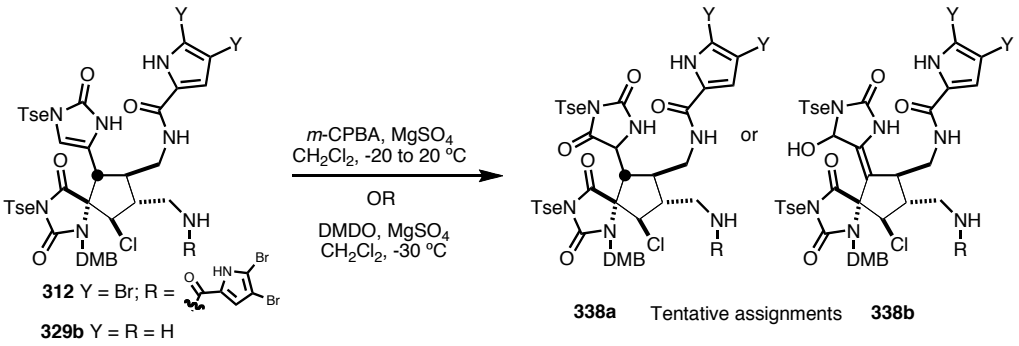
Scheme 6.32



Extremely dishearteningly however, all attempts to scale up this reaction in order to obtain adequate amounts of product for a complete spectroscopic characterization resulted in sluggish, inconsistent outcomes that provided only unintelligible or inconclusive data. In addition analysis of the coupling constants of key signals in the only significant ^{1}H NMR spectra obtained seemed to suggest that the desired oxidative cyclization *had not occurred*. Use of different solvents (MeCN, MeOH, CD_3OD and CH_2Cl_2) and different activating agents (NCS) were fruitless, and a better insight in the inner workings of this transformation had to await further experimentation.

Reasoning that the established competitive halogenation of the pyrroles was hindering our understanding of the reactivity of the imidazolone we sought alternatives means of oxidation.

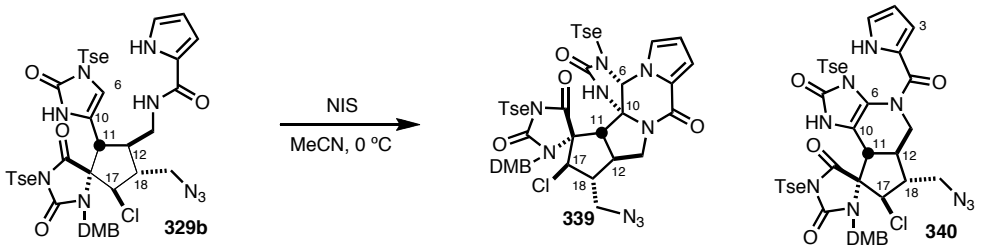
Scheme 6.33



Treatment of both bis-dibromopyrrole **312** and mono-pyrrole **329b** with either *m*-CPBA or DMDO immediately resulted in much cleaner reactions leading to complete conversions to what appeared to be single products by TLC analysis. In most instances however, crude ^{1}H NMR analysis revealed the presence or two or more species. After careful purification the major products could be separated and spectroscopic data clearly showed that only the imidazolone had reacted. It was equally evident on the other hand that no cyclization had occurred as confirmed by the presence in the ^{1}H NMR spectrum of the N-H signals of the pyrrole carboxamide. Based on incomplete mass and NMR data the products were tentatively assigned either as bis-hydantoins **338a** or allylic carbinolamines **338b** (Scheme 6.33). No further experiments in this direction were performed.

Our final investigations on the oxidative cyclization of mono-pyrrole **329b** provided another deceiving breakthrough. Treatment of this substrate with a carefully measured stoichiometric amount of *N*-iodosuccinimide (NIS) in MeCN solution at 0 ºC quickly led to complete loss of starting material. LC/MS analysis of the crude material revealed that the mass of the major species present was consistent with the desired product **339** (Scheme 6.34). The compound could be isolated and the mass was reconfirmed, but due to the scarcity of the material however, the ^{1}H NMR spectrum remained inconclusive.

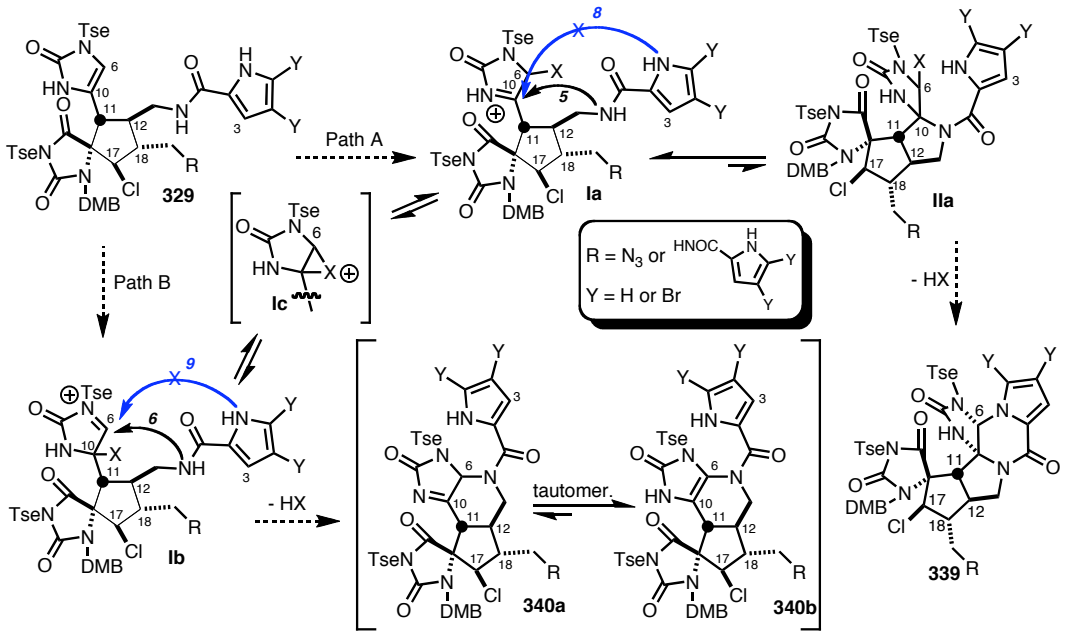
Scheme 6.34



Pleasingly, although only partial conversion was observed, the result could be reproduced, furnishing an adequate amount of product for a detailed ^{1}H NMR analysis. Disappointingly, examination of the coupling constants of key signals and the presence of the pyrrole N-H signal were not consistent with hexacycle **339**, and based on the available data the product of the above reaction was tentatively assigned as piperidine derivative **340** (Scheme 6.34). Interestingly this material was cleanly converted into a new species upon resting in a DMSO-d_6 solution for several days. The new product remains unfortunately unidentified.

In light of all the evidence gathered in the investigations discussed above some speculations could be made on the factors governing these reactions, and a plausible mechanistic rationale could be advanced. In particular it seems reasonable to ascribe the failure to attain the desired reactivity to the inherent ring strain of key presumed intermediates, the inadequate nucleophilicity of the pyrrole nitrogens and the abundance of competing reaction manifolds, which could potentially lead to the formation of deceiving structural isomers. These ruminations, relative to both the bis- and mono-pyrrole substrates, are summarized in Scheme 6.35.

Scheme 6.35



In the presence of an activating agent (generalized as X), acyliminium **Ia** (path A) could arise. This species could be potentially engaged by either the amide nitrogen, or the pyrrole nitrogen of the C12 side chain. Given the established low nucleophilicity of the pyrrole nitrogen, coupled with the formation of an 8-membered ring, the former appears to be the more likely possibility. The pyrrolidine intermediate **IIa** thus formed, due to the strain generated by the *trans* fusion with the core chlorocyclopentane, would revert to the initial acyliminium **Ia** extremely faster than if could proceed to the hexacyclic species **339** by nucleophilic attack of the pyrrole nitrogen at C6. Acyliminium **Ia** could then equilibrate, *via* "onium" intermediate **Ic** to isomeric acyliminium **Ib**. The generation of this species directly from the starting material (path B) also, cannot be excluded *a priori*. Acyliminium **Ib**, could then be engaged by the C12 side chain in the same fashion as before. Once again, formation of a 9-membered ring by attack of the pyrrole nitrogen at C6 appears improbable, and the 6-membered ring piperidine **340** would be generated instead. The ring strain in this system would be far smaller than in spirocyclic

intermediate **IIa**, allowing for elimination of "HX" delivering acyl imine **340a**. Although these constructs are reported to be, in some instances, relatively stable, tautomerization would quickly re-establish the pseudo-aromatic imidazolone. These species and hexacycle **339** are structural isomers and in the absence of detailed, pristine spectroscopic data could easily be misassigned.

After a few fruitless attempts to remove all the sulfone protecting groups in order to further explore the desired oxidative cyclization, this presumed biomimetic strategy was abandoned.

6.6 Conclusions

Two mono-pyrrole carboxamides featuring the *complete carbon framework of palau'amine* and a bis-dibromopyrrole imidazolone featuring the *complete carbon frameworks of* the axinellamines and konbu'acidin B were synthesized. Extensive, though not exhaustive investigations of the presumed biomimetic modes of intra-molecular oxidative cyclization generating the polycyclic cores of the natural products however, did not provide the desired outcomes. Considering the insight obtained in our studies, we ascribe the failure of this strategy to the inherent ring strain of key intermediates leading to the targets, the inadequate nucleophilicity of the pyrrole nitrogens, and several competing reaction manifolds often resulting in the generation of deceiving structural isomers.

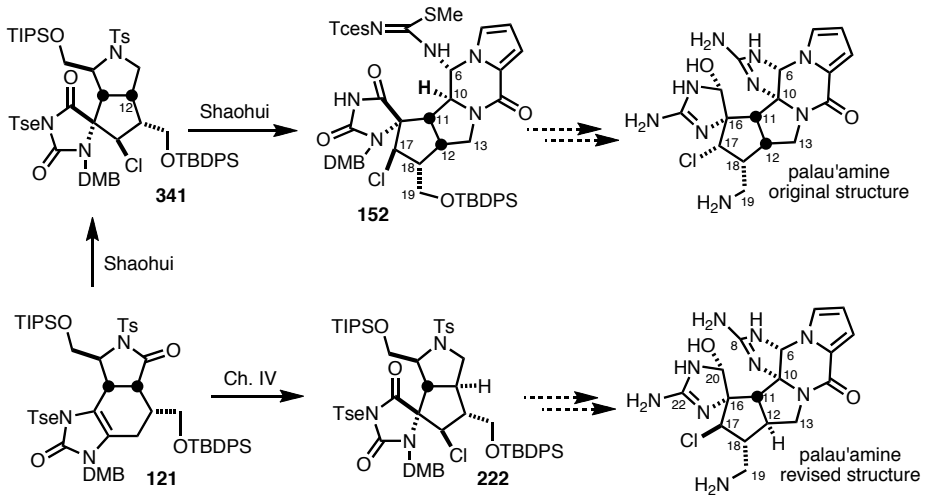
CHAPTER VII

ABIOTIC STRATEGIES TOWARD PALAU'AMINE AND STYLOGUANIDINE

7.1 Second Generation Synthesis of the *Trans*-azabicyclo[3.3.0]octane Core of Palau'amine

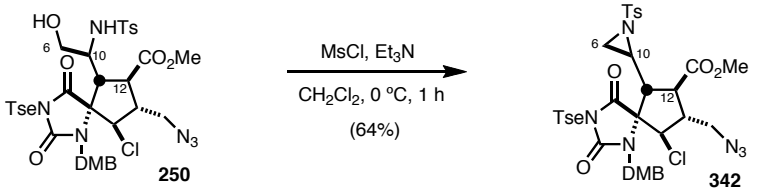
Given the disheartening results obtained in our bioinspired strategy aimed at emulating the presumed biosynthetic intra-molecular oxidative cyclization generating several PIA's it was decided to return to the admittedly abiotic approach pioneered by Dr. Shaohui Wang (see Chapter II), which had been abandoned shortly after the structural revision of palau'amine.[3] As discussed above (Chapter III) in the course of our investigations toward the synthesis of the axinellamines we had identified conditions to effect the key reversal of stereochemistry at C12 of the chlorocyclopentane core shared by all these metabolites. These studies had culminated in the synthesis of the peculiar *trans*-azabicyclo[3.3.0]octane core of the revised palau'amine (Chapter IV) and we envisioned that this material could be elaborated to the target natural product following the original route, and anticipating only minor refinements.

Scheme 7.1



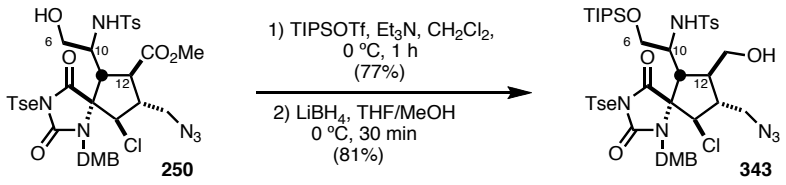
We set out therefore to prepare an analog of **222** using our newly synthesized azide methyl ester **250** (Chapter V). In earlier, unrelated studies we already discovered that the intra-molecular cyclization of the sulfonamide in ester **250**, onto the adjacent primary alcohol generating the corresponding aziridine **342**, which had been achieved on the TBDPS analog under Mitsunobu conditions (Chapter IV), could easily be triggered by simple treatment with mesyl chloride. We reasonably anticipated that similar conditions could be applied toward the synthesis of the pyrrolidine.

Scheme 7.2



Use of the procedures that had been successful in our previous studies immediately provided gratifying results. Both protection of the free primary alcohol as the TIPS ether, and reduction of the ester moiety proceeded uneventfully generating good yields of cyclization precursor **343**.

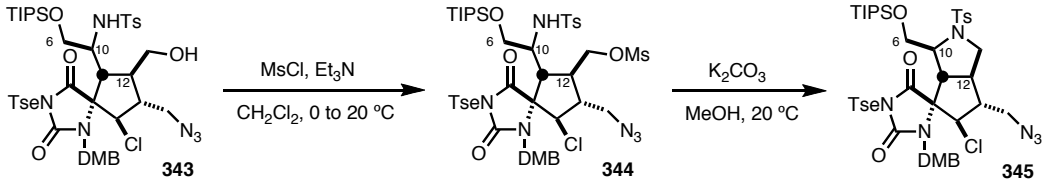
Scheme 7.3



Not expecting the cyclization to the *trans*-azabicyclo[3.3.0]octane system to be quite as facile as the generation of the aziridine (Scheme 7.2), we anticipated to isolate a stable intermediate mesylate, and then in a separate experiment induce the desired

intramolecular ring closure. Indeed, after treatment with mesyl chloride and aqueous work up, the crude material could be purified by preparative TLC, affording a modest yield (not quantified) of mesylate **344**. We were then pleased to find that stirring the activated alcohol in a methanol solution in the presence of potassium carbonate (K_2CO_3) cleanly promoted the projected cyclization providing tricyclic system **345**, as confirmed by mass spectrometry data and analysis of the coupling constants of diagnostic signals in the ^{1}H NMR spectrum.

Scheme 7.4



This early success prompted us to refine the overall approach, and in particular we sought to circumvent the cumbersome reprotection of the C6 alcohol, which had however been useful in the early stages of our investigations (Chapter IV), for spectroscopic comparison purposes.

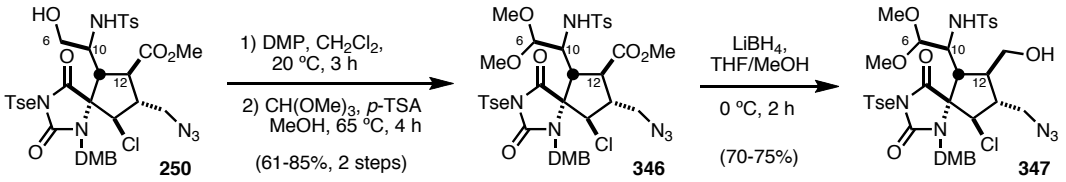
7.2 Third Generation Synthesis of the *Trans*-azabicyclo[3.3.0]octane Core of Palau'amine

In the original approach to the core of palau'amine (**2**) (see Scheme 2.10) the C6 alcohol was carried on to the late stages of the synthesis as the silyl ether, until it was conveniently liberated and oxidized to the corresponding aldehyde. This moiety was then engaged by a pendant pyrrole to generate a stable carbinolamine, thus establishing the D ring of the natural product. Committed to these guidelines we reasoned that in the revised approach, an early oxidation of the C6 to the required aldehyde, would be the most efficient course of action. We envisioned that masking the aldehyde as the corresponding acetal would afford a stable surrogate that could be safely advanced through several

chemical operations in the early stages of the synthesis, while in turn providing an adequate electrophile for the projected key ring closure.

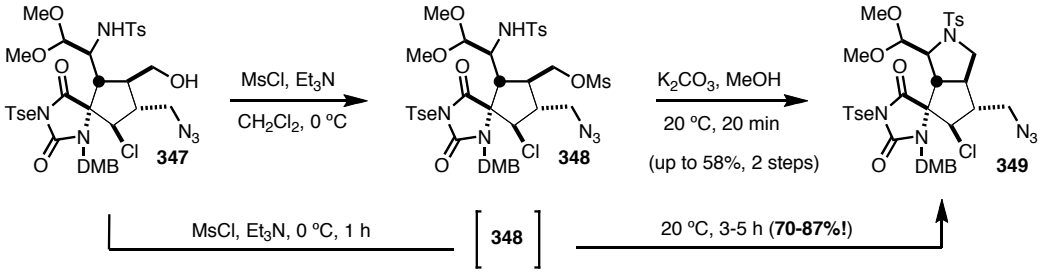
Once again the use of established procedures allowed us to quickly and efficiently generate sizeable amounts of the required cyclization precursor **347** (Scheme 7.5).

Scheme 7.5



With alcohol **347** in hand the stage was set for the key ring closure, and as expected under the previously devised conditions (Scheme 7.4) modest yields of the desired *trans* system **349** were obtained. Suspecting that the intra-molecular cyclization in this setting might be in fact, more facile that we had originally predicted we reasoned that increasing the operating temperature could promote the process. Indeed we were pleased to find that after formation of mesylate **348** at 0 ºC, allowing the reaction mixture to warm to ambient temperature led to the clean generation of the target product, which could eventually be isolated in markedly improved yields.

Scheme 7.6



It is reasonable to envision that under the previous conditions, the unanticipated partial formation of the cyclized product **349**, which was unknowingly discarded after purification of the desired intermediate, could account for the lower efficiency of the initial runs.

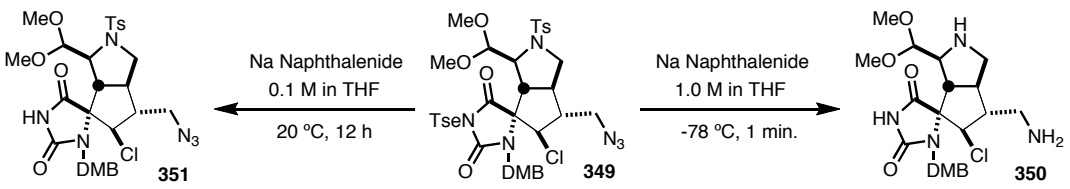
7.3 Synthesis of the D Ring Cyclization Precursor

Having devised a robust protocol for the synthesis of the pivotal *trans*-azabicyclo[3.3.0]octane system establishing the key sterochemical relationships in the core of the revised structure of palau'amine we focused on the projected construction of the D ring (*vide supra*). Installation of the necessary pendant pyrrole moiety required the prior removal of the tosyl protecting group from the pyrrolidine nitrogen.

This transformation had previously been accomplished using an excess of freshly prepared sodium naphthalenide, and indeed this proved eventually to be the most efficient method to arrive at the target cyclization precursor. Initial investigations in this direction however exposed some key issues that required small but significant adjustments of the original procedure.

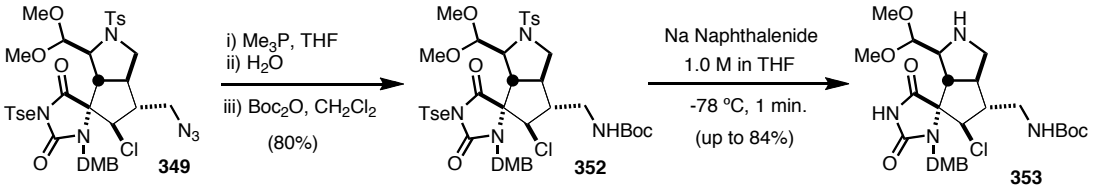
Treatment of a THF solution of tricyclce **349** and naphthalene with sodium metal or addition of a large excess of a 0.1 molar solution of pre-prepared sodium naphthalenide to a THF solution of the starting material provided no reaction at 0 ºC. After overnight stirring at ambient temperature on the other hand, clean cleavage of the Tse group was observed without affecting the pyrrolidine tosylate (product **351**, Scheme 7.7).

Scheme 7.7



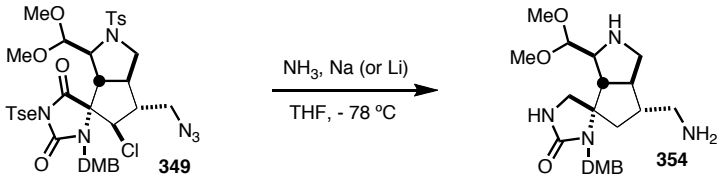
Use of a 1 molar solution of freshly prepared sodium naphthalenide however resulted in greatly increased reactivity and complete detosylation, along with reduction of the azide functionality to the corresponding primary amine **350** was obtained in minutes at –78 ºC. Although potentially useful, isolation of detosylated tricycle **350**, either directly or after acylation of the primary amine proved to be rather problematic. In addition, in some instances deceivingly fast reactions were observed that led to the formation of only partially detosylated amines. We reasoned that better results could be obtained after preemptive reduction and acylation of the interfering azide, and in fact, deprotection of carbamate **352** proceeded smoothly under the optimized conditions leading to the isolation of good yields of pyrrolidine **353.**

Scheme 7.8



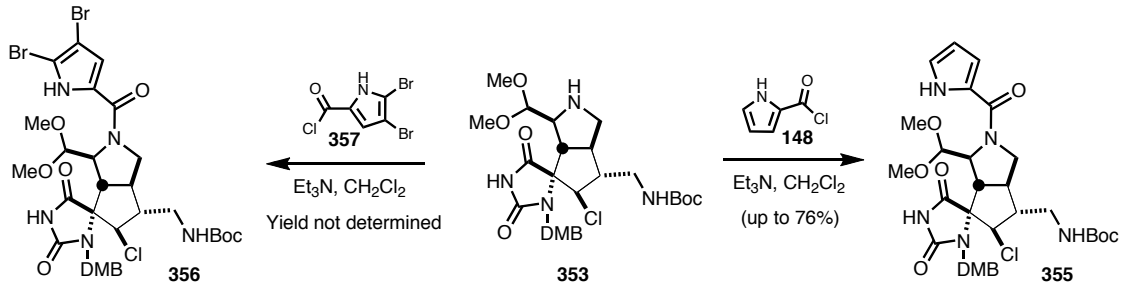
As anticipated above, alternative procedure that were tested for the cleavage of the tosyl group gave unsatisfactory outcomes. In particular treatment of azide **349** with magnesium metal in methanol solution under sonication did not provide any discernible reaction and unaltered starting material was recovered even after extended reaction time (> 30 h). At the opposite extreme, dissolving metal (Li or Na) conditions (Scheme 7.9) led to indiscriminate extensive reduction, annihilating several functionalities effectively resulting in a synthetic dead end (**354**).

Scheme 7.9



With tricycle **353** in hand, installation of an acyl pyrrole on the pyrrolidine nitrogen delivered the pivotal cyclization precursors for the construction of the D ring of palau'amine. Following once again the guidelines set forth by Dr. Wang's previous studies, use of freshly prepared acyl chlorides (**148** and **357**) provided fast reactions at ambient temperature, compared to acylations using commercially available trichloroketone analogs, which require higher temperatures and extended reaction times. The target pyrrole cyclization precursor **355** was isolated, under these conditions in good yield and purity, whereas dibrominated analog **356** was not pristine by ^{1}H NMR analysis and an accurate yield could not be determined. The reasons that prompted the synthesis of this modified cyclization precursor are discussed below.

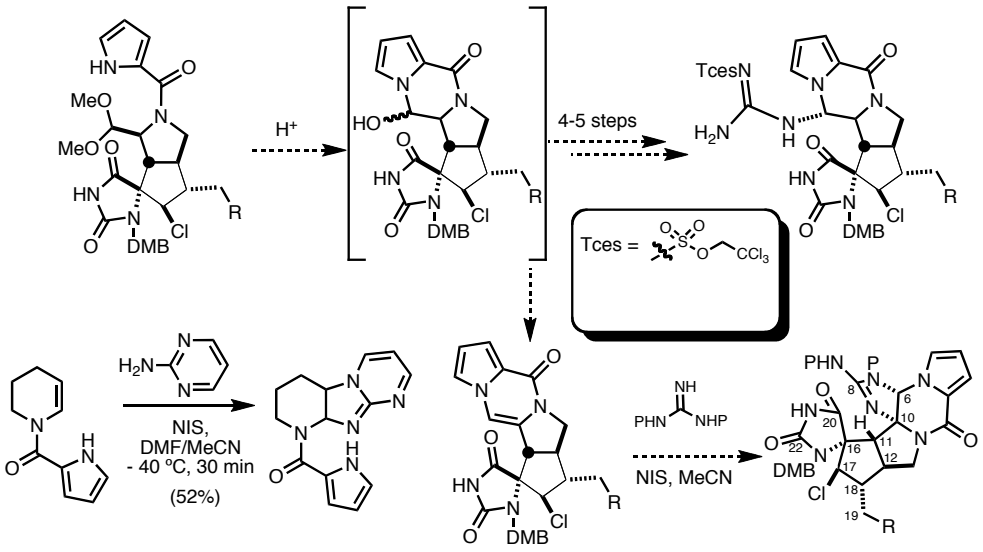
Scheme 7.10



7.4 Studies Toward the Construction of the D ring of Palau'amine

In our early exploration of reported procedures suitable for the late stages of our projected synthesis we became intrigued by a methodology for the generation of cyclic guanidines developed by Al Mourabit[82] in his synthetic approach to dibromoagelaspongine (inset in Scheme 7.10).

Scheme 7.11

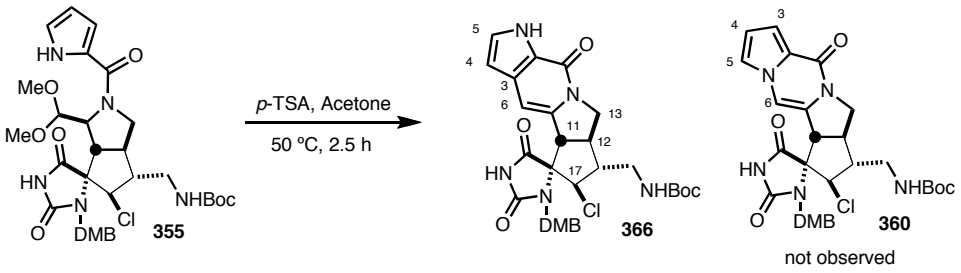


It was reported therein that enamine **363** could be activated with *N*-iodosuccinimide (NIS) to promote the inter-molecular addition of a guanidine surrogate such as the 2-aminopirymidine **365**, or alternatively a protected guanidine (such as **361**), to deliver the a 2-aminoimidazole ring system **364**. At this juncture we considered that following Dr. Wang's original procedures would take us from dimethyl acetal **355**, through 5 or 6 steps to generate a pendant guanidine **359** set up for a late stage cyclization triggered by activation of the C10 C-H bond (see Chapter II). We reasoned that if the expected carbinolamine **358**, obtained by acid promoted cyclization of the pyrrole onto the dimethyl acetal could be forced to eliminate water (perhaps under the same acidic conditions), we could arrive at system **360**, which is suitable for this procedure, removing

several steps from the overall sequence. Although the loss of the C10 stereocenter could potentially translate into a poor facial selectivity, we were confident that the inherent conformational bias of the substrate would work to our advantage. Molecular model analysis in fact (not shown), seemed to indicate that the approach of the activating agent would occur from the most exposed β face, necessarily guiding the guanidine nucleophile to attack at the α face, thereby establishing the stereochemical relationships found in palau'amine (**362** in Scheme 7.11).

If on one hand we were pleased to find that treatment of dimethyl acetal **355** with *para*-toluenesulfonic acid (*p*-TSA) in an acetone solution at 50 ºC had triggered the kind of reactivity that we had hoped for, on the other hand we had not anticipated where it would lead us.

Scheme 7.12



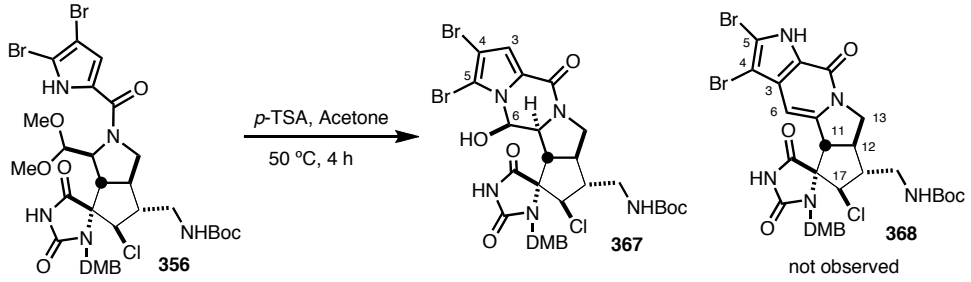
Analysis of the ^{1}H NMR ($CDCl_3$) spectrum of the purified product in fact, revealed the absence of the signals relative to the acetal and the appearance of a new signal at δ = 6.1 ppm ascribable to the vinyl proton at C6, which suggested formation of the desired enamine **360** (Scheme 7.12). In addition, LC/MS data of the crude material and mass spectrometry analysis of the purified product provided values consistent with the expected outcome. However, the presence in the ^{1}H NMR spectrum of the very diagnostic pyrrole N-H signal (δ = 9.4 ppm) and the significant change in the multiplicity of the C4 and C5 pyrrole signals provided strong evidence for a C3 mode of cyclization that had generated the pentacyclic core of the styloguanidines **366** (Chapter I).

Different modes of pyrrole cyclization had been previously reported by Al Mourabit,[83] and in retrospect this result was not entirely unexpected. In particular, in early

synthetic efforts toward dibromophakellin and ugibohlin, al Mourabit had discovered that in a non-brominated pyrrole the C3 mode of cyclization was preferred under acidic conditions, whereas the N1 cyclization was selected in a neutral medium. By contrast, bromination of the C4 and C5 position of the pyrrole rendered the N1 cyclization the exclusive avenue of reactivity under either set of conditions resulting in the formation of a stable carbinolamine.

As mentioned above, these observations prompted us to explore the reactivity of the dibromopyrrole advanced intermediate **356** (Scheme 7.13), and under the same acidic conditions as before, only partial (~50%) conversion was detected after several hours. Despite very similar polarities, the only product formed and the starting material could be separated via preparative TLC (60% EtOAc/Hexanes, 6 elutions; Rf product ~ 0.6, Rf SM ~ 0.5).

Scheme 7.13



Analysis of the ^{1}H NMR spectrum of the new material revealed the absence of the diagnostic signals of the dimethyl acetal and the pyrrole N-H. In addition, the pyrrole C3 singlet was clearly visible and no traces of aldehyde signals could be detected. Furthermore LC/MS data of the purified material confirmed a single product, and the isotopic pattern of the significant mass cluster was consistent with carbinolamine **367**. The stereochemical assignment of the C6 center was advanced solely on the basis of thermodynamic considerations and upon spectroscopic comparison with similar materials provided by a colleague (Dr. Chunxiao Xu). Although the evidence gathered strongly

supports the indicated structural assignment, the minute amount of product obtained prevented an exhaustive spectroscopic characterization and this assessment must be considered tentative. Finally, the partial conversion even after extended reaction time seemed to attest to the low nucleophilicity of the pyrrole nitrogen that had however apparently been enhanced by the effect of the bromine substituents, which could also be responsible for the complete inhibition of the C3 cyclization manifold.

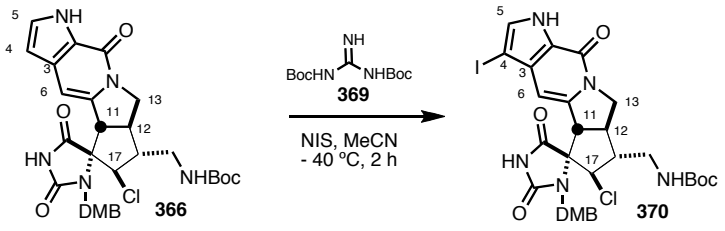
7.5 Guanidinylation Studies

With the small amounts of enamine **366** generated only few attempts to generate the final ring of the styloguanidine skeleton using the methodology reported by Al Mourabit (Scheme 7.11) could be endeavored. The results however, were significant and although our investigation ultimately did not lead to the synthesis of the target products, valuable insight on the reactivity of these systems was obtained.

In a first experiment, drop-wise addition of a solution of NIS to a cold (-40 ºC) MeCN solution of the starting material and excess bis-Boc-guanidine **369** resulted in complete loss of the starting material in 2 hours. As the progress of the reaction proved impossible to monitor by TLC, the indicated time was arbitrarily chosen.

LC/MS analysis of the crude material indicated the formation of two major products containing one and two iodine atoms respectively. After preparative TLC purification, the mono-iodinated product **370** was separated and the ^{1}H NMR spectrum clearly showed substitution at the C4 pyrrole position, as attested by the disappearance of the relative signal and the change in the multiplicity of the remaining pyrrole signal from a doublet to a singlet.

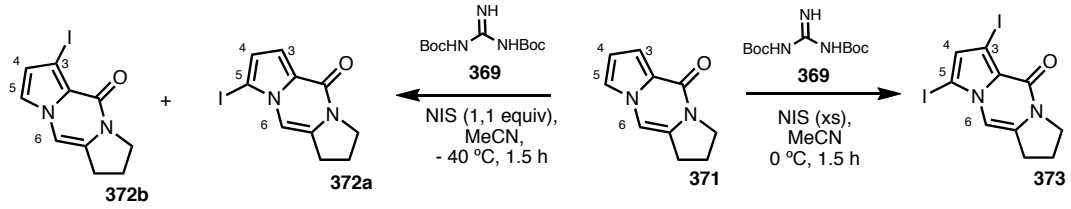
Scheme 7.14



The diiodinated product, apparently present only in significantly smaller quantity, could not be isolated. Further iodination at C5 on the pyrrole or substitution of the C6 vinyl proton are plausible reaction avenues that might have led to the generation of this material.

A brief model study performed on the simplified substrate **371**, (kindly provided by Dr. Xu) featuring the N1 mode of cyclization, led to further insight on the reactivity of these peculiar ring systems.

Scheme 7.15



Under the same condition as before, treatment with a stoichiometric amount of NIS resulted in the formation of a nearly equimolar mixture of inseparable mono-iodinated regioisomers **372a** and **372b**, whereas in the presence of excess reagent at higher temperature complete diiodination (**373**, Scheme 7.15) was confirmed by mass and ^{1}H NMR data. In both cases the enamine appeared to remain unaltered.

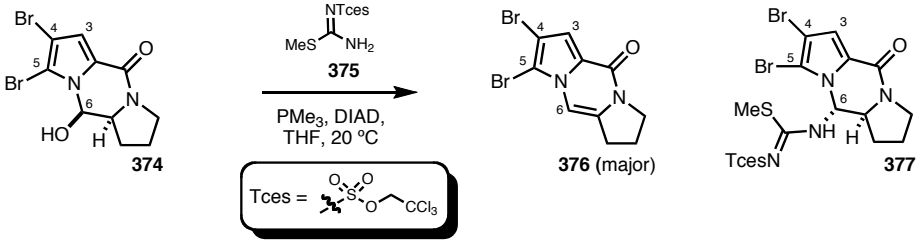
Two further experiments on sub-milligram amounts of enamine **366** were performed, and the results therefore only analyzed by LC/MS. Using chloramine-T (a commercially available source of electrophilic chlorine) the formation of a mono-chlorinated product, presumably arising by substitution at C4 as seen before, was detected. Treatment with *m*-CPBA in the presence of an excess bis-Boc guanidine reagent provided inconclusive results.

Interestingly, later theoretical calculations (performed by Mikail Abbasov) revealed interesting features of enamine **366**. According to the data, the C6-C10 unsaturation was part of an extended conjugation with the pyrrole ring, suggesting that, as observed

experimentally, it would not behave as an isolated double bond. In addition, it was found that while the C6 vinyl carbon had the highest HOMO coefficient, the C4 on the pyrrole held the highest negative natural charge making it, as observed, the most prone to be engaged by an electrophile. Lastly in the molecule's lowest energy conformation (global minimum) the DMB aromatic ring was shown to lie parallel to the DE ring system, presumably because of π-π interactions with the pyrrole ring. In this scenario the projected approach of a guanidine nucleophile from the α face (*vide supra*) would be unfeasible, therefore we set out to remove this hindrance by attempting to cleave the DMB protecting group under the conditions previously identified (Chapter IV). Unfortunately, this resulted in an extremely sluggish reaction on the last available material, thus ending our investigations on this substrate.

Having failed to generate any significant amount of carbinolamine **367** we resorted to study model system **374** (once again generously provided by Dr. Xu) to garner some initial information about the potential reactivity of this substrate. Treatment with pseudothiourea **375** under typical Mitsunobu conditions led to the formation of the elimination product **376** as the overwhelmingly major one, with only minimal amounts of the desired target **377** detected by ^{1}H NMR, and confirmed by LC/MS data.

Scheme 7.16



Although far from satisfactory this procedure has potential for optimization, and it could provide a more efficient entry into the projected urea cyclization precursor (Scheme 7.10) for the synthesis of dibromopalau'amine. An attempt to activate carbinolamine **374** with mesyl chloride in the presence of pseudothiourea **375,** resulted

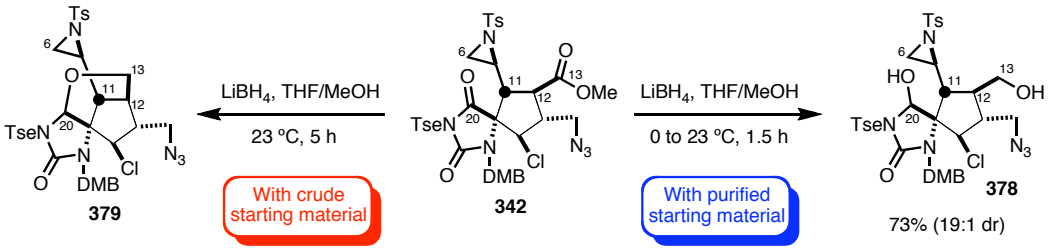
only in partial conversion to the elimination product **376**. Finally carbinolamine **374** proved to be remarkably stable under acidic conditions (*p*-TSA) with the starting material being recovered unaltered even after prolonged stirring at 80 ºC.

7.6 Other Salient Studies

As anticipated in Chapter IV the required reduction of the C20 lactam to the aminal functionality found in several PIA's (including palau'amine and axinellamine) could not be achieved under a variety of conditions in any of our synthetic intermediates with the exception of aziridine **223** (Scheme 4.19) We thought that this serendipitous but significant result warranted more investigation, and having recently synthesized azide aziridine **342** (Scheme 7.2) we saw a convenient opportunity to further explore the possibility of using this intermediate as a precursor to the synthesis of the natural products of interest.

Using the established reduction conditions excellent results were immediately obtained and the desired carbinolamine **378** was isolated in good yield with remarkable diastereoselectivity, although the configuration at C20 was not unambiguously established.

Scheme 7.17



Unexpectedly however, when crude starting material was subjected to the same conditions the peculiar spirotricyclic system **379** was exclusively generated. This product presumably arises from activation of the C13 alcohol by residual mesyl chloride from the previous reaction (Scheme 7.2) followed by intramolecular displacement by the newly

generated C20 hydroxy moiety, and examination of molecular models confirmed that this functionality was in fact, in close proximity to C13.

Further studies seemed to show that this carbinolamine provided competitive reaction manifolds in other settings as well (not shown), however this could not be unequivocally established. Although I believe that this system remains a worthy candidate for the development of an efficient approach to key functionalities found in the PIA's, it appears that the originally planned late-stage reduction would be the preferred course of action.

7.7 Conclusions

A robust protocol for the synthesis of the pivotal *trans*-azabicyclo[3.3.0]octane core of the revised structure of palau'amine was devised. Investigations on the projected crucial intra-molecular pyrrole cyclization provided significant insight into the key factors governing this transformation. In particular, introduction of bromine substituents at C4 and C5 of the pyrrole ring appeared to increase the nucleophilicity of the nitrogen, promoting the desired interaction with the pendant electrophile, delivering the pentacyclic core of dibromopalau'amine. By contrast, under similar operating conditions a C3 cyclization manifold was preferred in a non-brominated pyrrole, resulting in the formation of a styloguanidine potential precursor.

CHAPTER VIII

CONCLUSIONS

The pyrrole-imidazole alkaloids are an ever-growing family of marine metabolites that already features well over one hundred members and new congeners continue to be detected and characterized. Efforts in this field have proliferated in recent years leading to the development of a wealth of remarkable synthetic strategies, which have often culminated in exquisite total syntheses. Our approach to the synthesis of selected members of this family of alkaloids, premised on the biosynthetic proposals by Kinnel and Scheuer and Al Mourabit and Potier involves a Diels Ader cycloaddition followed by and oxidative ring contraction to generate a pivotal spirocyclic common precursor.

With this intermediate as a starting point, a chlorocyclopentane methyl ester featuring the stereochemical relationships found in the cores of several related natural products, was synthesized and its structure was secured by extensive NMR experiments and X-ray crystallographic analysis. The viability of this key intermediate to generate diverse molecular constructs *via* various mode of *intra*-molecular cyclization was demonstrated by the synthesis of the angular azatriquinane core of axinellamine and the *trans*-azabicyclo[3.3.0]octane core of the recently revised structure of palau'amine. In addition, studies on the amino alcohol functionality of this pivotal intermediate led to the construction of an imidazolone ring precursor to the northern amino-imidazole of palau'amine, axinellamine, styloguanidine, konbu'acidin and massadine. This approach significantly shortened the previously established route to a comparable analog.

Further elaboration of this system produced a bis-dibromopyrrole advanced intermediate featuring the *complete carbon framework* of the axinellamines and konbu'acidin B, and two mono-pyrrole analogs both featuring the *complete carbon framework* of palau'amine and styloguanidine. Attempts to emulate the presumed biomimetic *intra*-molecular modes of oxidative cyclization leading to the cores of the indicated natural products were not successful, presumably because of the inherent ring strain of key reactive intermediates, the inadequate nucleophilicity of the pyrrole nitrogens and the abundance of competitive reaction manifolds.

Starting from an analog of the pivotal chlorocyclopentane methyl ester described above, prepared in collaboration with Dr. Yonggang Wang, a robust route to a new *trans*-azabicyclo[3.3.0]octane system was devised. This served as the starting point for the development of an abiotic strategy toward palau'amine premised on the pioneering work in our group by Dr. Shaohui Wang, resulting in the synthesis of a pyrrole cyclization precursor and a dibrominated analog. Investigations on the reactivity of these substrates aimed at the construction of the piperazine ring of palau'amine revealed different modes of ring closure. A pyrrole C3 cyclization led to the construction of a pentacyclic enamine precursor to styloguanidine, while an alternative N1 annulation ensued in the dibrominated congener generating a stable carbinolamine suitable for the completion of palau'amine. The assignment of the latter though strongly supported by spectroscopic evidence remained tentative. Finally, attempts to construct the northern amino-imidazole ring of styloguanidine by direct guanidinylation of the enamine precursor failed presumably because of the unexpected conjugation of the enamine double bond with the pyrrole effectively reducing its propensity for oxidation.

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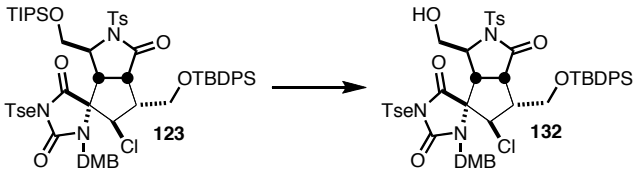
APPENDIX A

EXPERIMENTAL AND SELECTED SPECTRAL DATA

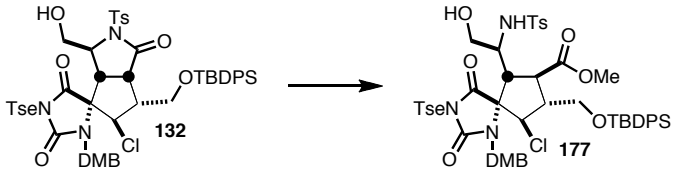
EXPERIMENTAL PROCEDURES

General Procedures: All non-aqueous reactions were carried out under nitrogen atmosphere in oven-dried (120 ºC) glassware. Dichloromethane (CH_2Cl_2), acetonitrile (MeCN) and toluene (PhMe) were obtained from a MBraun solvent system passing HPLC grade solvents through activated alumina. Tetrahydrofuran (THF) was distilled from a sodium/benzophenone ketyl. Triethylamine (99% Acros) was distilled from calcium hydride. Methanol (MeOH), ethyl acetate (EtOAc), hexanes, acetone and chloroform were used without purification. Other chemicals were purchased from Aldrich or Acros and used as received without further purification. Analytical thin layer chromatography (TLC) was performed using aluminum-backed silica gel $60F^{254}$ (Merck, 250 μm thickness). Plates were visualized under UV light (at 254 nm) and/or by staining with ceric ammonium molybdate followed by heating. Deuterated solvents were purchased from either Aldrich or Cambridge Isotopes and used as received. Flash column chromatography was performed using 60Å Silica Gel (Baker, 230-400 mesh) as a stationary phase.

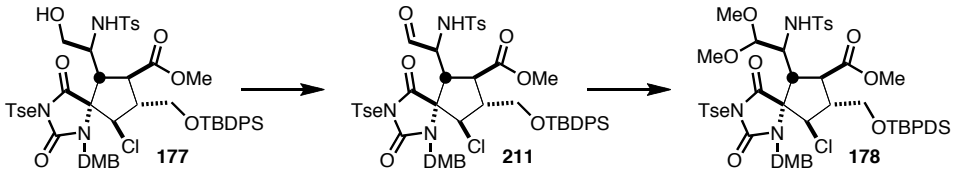
^{1}H NMR chemical shifts are reported as δ values in ppm relative to $CDCl_3$ (7.27 ppm), benzene-d_6 (7.16 ppm), CD_3OD (3.31 ppm), acetone-d_6 (2.05 ppm) or DMSO-d_6 (2.50 ppm). ^{1}H NMR coupling constants (J) are reported in Hertz (Hz) and multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br s (broad singlet), dd (doublet of doublets), dt (doublet of triplets), dq (doublet of quartets), ddd (doublet of doublets of doublets). Deuteriobenzene (benzene-d_6), deuteriochloroform ($CDCl_3$), CD_3OD, or DMSO-d_6 served as internal standard (128.30 ppm, 77.23 ppm, 49.00 ppm, or 39.50 ppm respectively) for all ^{13}C spectra. Mass spectra were obtained at the Center for Chemical Characterization and Analysis at TAMU. Infrared spectra were obtained as thin film on NaCl plates. Optical rotations were recorded at 589 nm using a 250 μL cell.



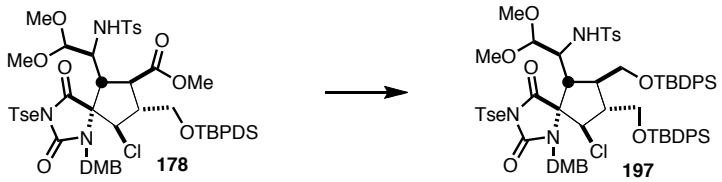
Alcohol 132: To a solution of chlorocyclopentane **123** (200 mg, 0.169 mmol) in 20 mL of anhydrous THF at -45 °C was added TBAF (1.0 M in THF, 180 μL, 0.180 mmol). The reaction mixture was stirred for 2 h while allowing to reach -20 °C. It was then quenched with 10 mL of pH 7 buffer, allowed to reach 20 ºC and extracted with EtOAc (3 x 15 mL). The combined organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (60:40) gave 138 mg (79%) of alcohol **132** as a white foam: R_f = 0.59 (60% EtOAc/Hexanes); $[\alpha]_D^{23}$ = -26.1 (*c* = 1.70, CH_2Cl_2); IR (thin film): 3063, 2932, 2856, 1717, 1652, 1518, 1457, 1144, 1113 cm^{-1}; ^1H NMR (500 MHz, benzene-d_6): δ 8.14 (d, *J* = 8.0 Hz, 2H), 7.91 (m, 2H), 7.85 (d, *J* = 8.0 Hz, 2H), 7.80 (m, 2H), 7.46 (d, *J* = 2.0 Hz, 1H), 7.38 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.21-7.29 (m, 6H), 6.81 (d, *J* = 8.0 Hz, 2H), 6.71 (d, *J* = 8.0 Hz, 2H), 6.37 (d, *J* = 8.0 Hz, 1H), 5.80 (d, *J* = 15.5 Hz, 1H), 4.79 (s, 1H), 4.71 (d, *J* = 16.0 Hz, 1H), 4.54 (d, *J* = 12.5 Hz, 1H), 4.47 (dd, *J* = 8.5, 10.5 Hz, 1H), 4.14 (dd, *J* = 4.0, 10.5 Hz, 1H), 3.93-3.96 (m, 1H), 3.73 (d, *J* = 11.5 Hz, 1H), 3.65-3.70 (m, 1H), 3.64 (s, 3H), 3.54-3.61 (m, 1H), 3.50 (d, *J* = 8.5 Hz, 1H), 3.40-3.46 (m, 2H), 3.29 (s, 3H), 3.19-3.24 (m, 1H), 2.94-2.99 (m, 1H), 1.86 (s, 3H), 1.76 (s, 3H), 1.17 (s, 9H), 0.99 (bs, 1H); ^{13}C NMR (125 MHz, benzene-d_6): δ 173.2, 171.9, 156.9, 150.3, 149.9, 145.1, 145.0, 136.3, 136.2, 136.0, 135.8, 134.1, 133.8, 130.1, 130.0, 129.9, 129.8, 129.5, 129.3, 129.0, 128.3, 121.6, 113.0, 112.1, 76.7, 63.8, 60.7, 60.6, 60.2, 55.8, 55.4, 50.8, 48.9, 48.1, 46.8, 46.0, 33.3, 27.2, 21.2, 19.6; MS (MALDI) calcd for $C_{52}H_{58}ClN_3O_{11}S_2Si$ $[M+H]^+$: 1028, $[M+Na]^+$: 1050, $[M+K]^+$: 1066; found $[M+H]^+$: 1028, $[M+Na]^+$: 1050, $[M+K]^+$: 1066.



Ester 177. To a stirred solution of alcohol **132** (250 mg, 0.243 mmol) in 30 mL MeOH at room temperature was added 3.2 mL of a freshly prepared solution of NaOMe in MeOH (0.23 M, 0.729 mmol), and after stirring at ambient temperature for 25 min, the mixture was heated to 65°C and stirred for 18 h. The reaction mixture was then cooled to 20 ºC and quenched with 20 mL of a saturated solution of NH_4Cl. Water (20 mL) was then added, the mixture was extracted with EtOAc (3 x 45 mL) and the combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (60:40 → 40:60) gave 197 mg (76%) of ester **177** as a colorless foam: *Rf* = 0.46 (60% EtOAc/Hexanes); $[\alpha]_D^{19.7}$ 26.0 (*c* 2.20, CH_2Cl_2); IR (thin film) 3511, 3271, 2934, 2857, 1776, 1717, 1596, 1516, 1453, 1149, 814, 704 cm^{-1}; ^1H NMR (500 MHz, benzene-d_6) δ 7.85 (d, *J* = 7.0 Hz, 2H), 7.83-7.81 (m, 4H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.35 (app t, *J* = 8.0 Hz, 2H), 7.30 (app. t, *J* = 8.0 Hz, 2H), 7.27-7.24 (m, 3H), 7.05 (dd, *J* = 1.5, 8.0 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 2H), 6.76 (d, *J* = 8.5 Hz, 2H), 6.41 (d, *J* = 8.5 Hz, 1H), 5.62 (d, *J* = 9.5 Hz, 1H), 5.15 (d, *J* = 11.5 Hz, 1H), 4.93 (d, *J* = 16.0 Hz, 1H), 4.86 (d, *J* = 16.0 Hz, 1H), 4.18 (dd, *J* = 11.5, 11.5 Hz, 1H), 3.94 (dd, *J* = 11.5, 11.5 Hz, 1H), 3.82 (dd, *J* = 11.0, 2.0 Hz, 1H), 3.74 (s, 3H), 3.72-3.69 (m, 4H), 3.63 (s, 3H), 3.60 (dd, *J* = 12.0, 2.5 Hz, 1H), 3.38-3.34 (m, 2H), 3.33 (s, 3H), 3.05 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.78 (app. dd, *J* = 11.5, 11.5 Hz, 1H), 1.91 (s, 3H), 1.84 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (125 MHz, benzene-d_6) δ 175.0, 173.6, 157.7, 150.7, 150.0, 145.2, 143.2, 140.0, 136.5, 136.4, 136.0, 134.3, 133.5, 130.6, 130.5, 130.4, 130.2, 129.32, 129.28, 128.7, 128.6, 128.5, 128.3, 127.4, 120.8, 112.6, 112.1, 74.8, 62.2, 60.8, 58.4, 56.0, 55.6, 55.3, 52.85, 52.79, 49.8, 48.7, 46.9, 46.6, 33.9, 30.6, 27.7, 21.5, 20.1; MS (MALDI) calcd for $C_{53}H_{62}ClN_3O_{12}S_2Si$ $[M+Na]^+$: 1082, $[M+K]^+$: 1098; found $[M+Na]^+$: 1082, $[M+K]^+$: 1098.

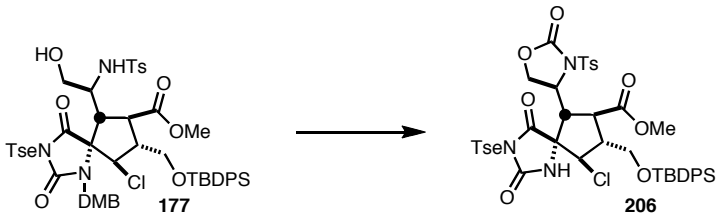


Dimethyl Acetal 178.To a stirred solution of alcohol **132** (123 mg, 0.116 mmol) in 10 mL CH_2Cl_2 at 20 ºC was was added Dess Martin periodinane (82 mg, 0.193 mmol) in one portion. The mixture was stirred at 23ºC for 4 h then it was diluted with Et_2O (~ 20 mL) and filtered through a thick pad of Celite. The solvent was removed *in vacuo* affording a white foam. This crude material (**211**) was dissolved in 4.5 mL of MeOH and 3.0 mL of trimethylorthoformate was added at 20 ºC. The resulting mixture was heated to 65 ºC and stirred for 16 h, then cooled to 20 ºC, and about half of the solvents were removed *in vacuo*. pH 7 buffer solution was then added (~ 10 mL) and the mixture was extracted with EtOAc (3 X 10 mL) and the combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (60:40) gave 46 mg (63%) of dimethyl acetal **178** as a colorless foam: *Rf* = 0.62 (80% EtOAc/Hexanes); ^{1}H NMR (500 MHz, benzene-d_6) δ 7.82 (d, *J* = 8.0 Hz, 2H), 7.78 (d, *J* = 8.5 Hz, 2H), 7.68 (app d, *J* = 8.0 Hz, 4H), 7.39 (d, *J* = 1.5 Hz, 1H), 7.34 (app t, *J* = 7.0 Hz, 2H), 7.29 (app t, *J* = 8.0 Hz, 2H), 7.24 (app t, *J* = 7.5 Hz, 2H), 7.00 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 2H), 6.75 (d, *J* = 8.0 Hz, 2H), 6.27 (d, *J* = 8.5 Hz, 1H), 5.46 (d, *J* = 16.5 Hz, 1H), 5.40 (d, *J* = 9.0 Hz, 1H), 5.00 (d, *J* = 11.5 Hz, 1H), 4.86 (d, *J* = 16.5 Hz, 1H), 4.09-3.93 (m, 5H), 3.84 (td, *J* = 8.5, 4.0 Hz, 1H), 3.73 (dd, *J* = 11.0, 1.5 Hz, 1H), 3.66 (s, 3H), 3.64 (s, 3H), 3.50 (dd, *J* = 11.5, 7.0 Hz, 2H), 3.24 (s, 3H), 2.87 (s, 3H), 2.86 (s, 3H), 2.59 (app dd, *J* = 11.5, 11.5 Hz, 1H), 1.90 (s, 3H), 1.84 (s, 3H), 1.18 (s, 9H); ^{13}C NMR (125 MHz, benzene-d_6) δ = 174.6, 173.6, 157.3, 150.9, 150.0, 144.9, 143.3, 139.2, 136.8, 136.42, 136.41, 134.6, 133.5, 130.5, 130.4, 129.9, 129.6, 129.1, 128.7, 128.6, 128.5, 128.1, 128.0, 120.5, 112.5, 112.0, 105.9, 74.8, 61.1, 58.2, 56.7, 56.4, 56.1, 55.6, 54.5, 53.6, 52.5, 50.0, 48.7, 46.7, 46.1, 34.0, 30.5, 27.6, 21.51, 21.47 20.0.



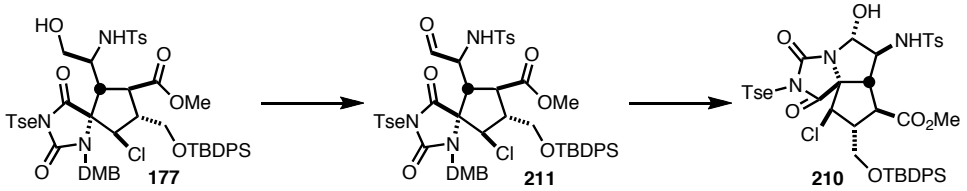
Bis-silylether 197: To a stirred solution of dimethyl acetal **178** (11.6 mg, 0.0105 mmol) in 1.0 mL of CH_2Cl_2 cooled to –78 ºC was added DIBAL-H (xs) dropwise. The mixture was stirred at to –78 ºC for 30 minutes then it was quenched by the addition of MeOH (0.8 mL). The mixture was then allowed to warm to 20 ºC, and a solution of saturated Rochelle's salt was added (~ 2 mL). The resulting mixture was stirred vigorously for 2 h, and then it was extracted with EtOAc (3 X 10 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was dissolved in MeOH (1.0 mL), cooled to 0 ºC and treated directly with an excess of $NaBH_4$. After 10 minutes H_2O was added (~ 1 mL) and the mixture was allowed to warm to 20 ºC then it was extracted with EtOAc (3 X 10 mL). The combined organic phase was washed with brine (1 X 10 mL) then it was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was dissolved in CH_2Cl_2 (2 mL) and TBDPSCl (xs) was added at 20 ºC, followed by Et_3N (~ 0.15 mL, xs) and a small crystal of DMAP. The mixture was stirred at 20 ºC for 9 h then it was concentrated *in vacuo*. Purification of the residue by flash chromatography on SiO_2 eluting with hexanes/EtOAc (70:30 → 50:50) gave bis-silylether **178** as a colorless foam (9 mg, 65% overall yield). R_f = 0.71 (60% EtOAc/Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.0 Hz, 2H), 7.69 (app d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.63 (app d, *J* = 6.5 Hz, 2H), 7.49 (app d, *J* = 8.0 Hz, 2H), 7.44 (app d, *J* = 7.5 Hz, 2H), 7.41-7.32 (m, 12H), 7.26-7.23 (m, 4H) 7.00 (d, *J* = 2.0 Hz, 1H), 6.71 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.28 (d, *J* = 8.5 Hz, 1H), 5.85 (d, *J* = 9.5 Hz, 1H), 5.16 (d, *J* = 16.0 Hz, 1H), 4.61 (d, *J* = 16.0 Hz, 1H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.02 (dd, *J* = 10.5, 3.0 Hz, 1H), 3.91-3.88 (m, 2H), 3.79 (s, 3H), 3.71 (d, *J* = 9.0 Hz, 1H), 3.61 (s, 3H), 3.61-3.56 (m, 2H), 3.48-3.43 (m, 3H), 3.38 (dd, *J* = 11.0, 2.0 Hz, 1H), 3.13 (dd, *J* = 11.0, 7.5 Hz, 1H), 3.05 (s, 3H), 2.97 (s, 3H), 3.0-2.9 (m, 1H), 2.46 (s, 3H), 2.42 (s, 3H), 2.18 (app. t, *J* = 11.5 Hz, 1H), 1.10 (s, 9H), 0.99 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 156.7, 149.1, 148.5, 145.4, 143.4, 138.6, 135.96, 135.93, 135.77, 135.71 133.7,

132.8, 132.72, 132.66, 130.3, 130.2, 130.1, 130.0, 129.8, 129.5, 129.1, 128.5, 128.1, 128.0, 127.8, 127.4, 120.1, 110.97, 110.91, 106.6, 75.7, 64.8, 60.3, 57.6, 56.9, 56.4, 56.0, 55.7, 53.3, 53.2, 46.9, 46.8, 46.0, 40.6, 33.15, 29.9, 27.22, 27.20 21.9, 21.7, 19.53, 19.45; MS (MALDI) calcd for $C_{70}H_{84}ClN_3O_{12}S_2Si2$ $[M+Na]^+$: 1336, $[M+K]^+$: 1352; found $[M+Na]^+$: 1336, $[M+K]^+$: 1352.



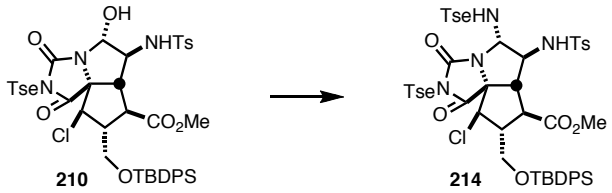
Oxazolidinone 206: To a stirred solution of **177** (9.8 mg, 0.00924 mmol) in 0.9 mL of THF cooled to 0 ºC was added triethylamine (xs), followed by a few crystals of triphosgene, and the mixture was stirred at 0 ºC for 1 h. The reaction was then quenched at 0 ºC by the addition of a saturated solution of $NaHCO_3$, and the organic solvent was evaporated under reduced pressure. The aqueous residue was extracted with EtOAc (3 X 10 mL) and the combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford a white crystalline solid. This crude material was dissolved in 1.0 mL of MeCN/H_2O (3:1) and the solution was cooled to 0ºC. Ceric ammonium nitrate (25.4 mg; 0.0463 mmol) was then added in one portion and the resulting mixture was stirred at 0ºC for 1 h, The mixture was then diluted with EtOAc (~ 10 mL) and washed with brine (3 X 10 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (70:30 → 50:50) gave oxazolidinone **206** as a colorless foam (6.9 mg, 80% overall yield of **206** for the 2 steps). R_f = 0.48 (50% EtOAc/Hexanes); IR (thin film) 1786, 1723, 1447, 1172, 1146 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.5 Hz, 2H), 7.80 (d, *J* = 8.5 Hz, 2H), 7.75 (app dd, *J* = 8.0, 2.0 Hz, 2H), 7.72 (app dd, *J* = 8.0, 1.5 Hz, 2H), 7.45-7.39 (m, 10H), 6.57 (br s, 1H), 4.81 (ddd, *J* = 9.5, 5.0, 1.5 Hz, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.51 (dd, *J* = 9.5, 9.5 Hz, 1H), 4.15 (dd, *J* = 9.5, 5.0 Hz, 1H), 3.99-3.81 (m, 4H), 3.76 (dd, *J* = 11.0, 11.0 Hz, 1H), 3.73 (s, 3H), 3.61 (ddd, *J* = 15.0, 9.5, 4.0 Hz, 1H), 3.42 (ddd, *J* = 14.5,

6.5, 3.5 Hz, 1H), 3.36 (dd, *J* = 11.5, 1.5 Hz, 1H), 2.80 (dddd, *J* = 11.5, 11.5, 2.5, 2.5 Hz, 1H), 2.48 (s, 3H), 2.47 (s, 3H), 1.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 172.7, 155.6, 152.7, 146.6, 145.8, 136.00, 135.98, 135.0, 133.8, 133.0, 130.43, 130.39, 129.97, 129.95, 128.7, 127.94, 127.93, 71.1, 70.6, 62.3, 58.4, 55.3, 52.80, 52.79, 50.9, 48.3, 43.25, 33.1, 29.9, 27.0, 26.9, 22.0, 21.9, 19.6; MS (MALDI) calcd for $C_{45}H_{50}ClN_3O_{11}S_2Si$ $[M+Na]^+$: 958, $[M+K]^+$: 974; found $[M+Na]^+$: 958, $[M+K]^+$: 974.



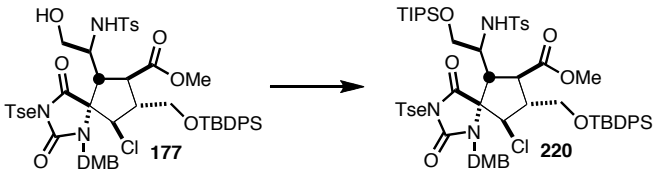
Carbinolamine 210: To a stirred solution of **177** (12 mg, 0.011 mmol) in 1.5 mL of CH_2Cl_2 at 23ºC was added Dess-Martin periodinane (10 mg, 0.024 mmol) in one portion. The mixture was stirred at 20ºC for 5 h, then it was diluted with Et_2O (~ 10 mL) and filtered through a thick pad of Celite. The solvent was removed *in vacuo* affording a white foam. This crude material (**211**) was dissolved in 1.5 mL of MeCN/H_2O (3:1) and the solution was cooled to 0ºC. Ceric ammonium nitrate (30 mg; 0.056 mmol) was then added in one portion and the resulting mixture was stirred at 0ºC for 2 h, The mixture was then diluted with EtOAc (~ 15 mL) and washed with brine (~ 15 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (70:30 → 60:40 → 35:65) gave carbinolamine **210** (not quantified) along with benzoyl aldehyde **210b** (not quantified). **210b** was dissolved in 0.8 mL of THF/H_2O and LiOH•H_2O was added at 23ºC. After 10 min the reaction mixture was quenched with NH_4Cl (~ 5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (70:30 → 60:40 → 35:65) gave carbinolamine **210** as a colorless foam (3.7 mg, 36% overall yield of **210** for the 3 steps). R_f = 0.43 (50% EtOAc/Hexanes); $[\alpha]_D^{19.5}$ 31.3 (*c* 0.0032, $CHCl_3$); IR (thin film) 3470, 3269, 2928, 2854, 1782, 1723, 1146

cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.5 Hz, 2H), 7.77 (d, *J* = 8.5 Hz, 2H), 7.61-7.63 (m, 4H), 7.35-7.43 (m, 8H), 7.31 (d, *J* = 8.5 Hz, 2H), 6.26 (d, *J* = 6.5 Hz, 1H), 5.88 (d, *J* = 3.0 Hz, 1H), 4.72 (d, *J* = 12.0 Hz, 1H), 4.23 (ddd, *J* = 15.0, 10.0, 2.5 Hz, 1H), 3.99 (d, *J* = 7.0 Hz, 1H), 3.86 (dd, *J* = 11.0, 2.0 Hz, 1H), 3.83 (dd, *J* = 11.0, 1.5 Hz, 1H), 3.74 (ddd, *J* = 15.0, 6.0, 3.0 Hz, 1H), 3.63 (ddd, *J* = 15.0, 10.5, 3.0 Hz, 1H), 3.41 (s, 3H), 3.32 (dd, *J* = 11.5, 10.0 Hz, 1H), 3.25 (ddd, *J* = 15.0, 6.0, 2.5 Hz, 1H), 3.05 (d, *J* = 10.5 Hz, 1H), 3.03 (br s., 1H), 2.66 (app t, *J* = 11.5 Hz, 1H), 2.46 (s, 3H), 2.42 (s, 3H), 1.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 170.9, 157.7, 145.9, 143.6, 137.7, 135.8, 135.0, 133.07, 133.05, 130.4, 130.02, 129.96, 128.7, 127.9, 127.2, 92.4, 79.9, 65.3, 61.6, 58.0, 54.6, 52.3, 51.7, 51.4, 45.4, 33.0, 27.0, 21.9, 21.8, 19.6; MS (MALDI) calcd for $C_{44}H_{50}ClN_3O_{10}S_2Si$ $[M+Na]^+$: 930, $[M+K]^+$: 946; found $[M+Na]^+$: 930, $[M+K]^+$: 946.



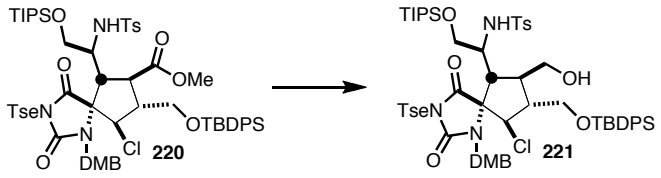
Bis-amine 214: To a stirred solution of carbinolamine **210** (3.8 mg, 0.00418 mmol) in 0.6 mL of CH_2Cl_2 at 23ºC was added $MgSO_4$ (tip of a microspatula), followed by tosylethylamine (xs). The mixture was heated to 50 ºC for 4.5 h then cooled to 20 ºC, filtered through a fritted funnel and concentrated *in vacuo*, Due to minimal reaction (by ^1H NMR) the crude material was resubjected to the reaction conditions for 2 h achieving complete conversion. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (70:30 → 50:50) gave bis-amine **214**. R_f = 0.43 (50% EtOAc/Hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.5 Hz, 2H), 7.81 (d, *J* = 7.5 Hz, 2H), 7.77 (d, *J* = 7.0 Hz, 2H), 7.64-7.60 (m, 4H), 7.44-7.37 (m, 10H), 7.33 (d, *J* = 7.5 Hz, 2H), 6.23 (d, *J* = 8.0 Hz, 1H), 5.07 (app. s 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.19-4.11 (m, 1H), 3.86-3.78 (m, 1H), 3.84 (d, *J* = 8.0 Hz, 1H), 3.74 (d, *J* = 8.0 Hz, 1H), 3.65-3.61 (m, 1H), 3.46 (s, 3H), 3.43-3.38 (m, 1H), 3.25-3.04 (m, 4H), 3.22 (dd, *J* = 11.0, 11.0 Hz, 1H), 3.08 (d *J* = 9.5 Hz, 1H), 2.71 (app t, *J* = 11.5 Hz, 1H), 2.47 (s, 6H), 2.44 (s, 3H), 2.26-2.22 (m, 1H),

1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.47, 171.42, 158.9, 145.9, 145.2, 143.7, 137.9, 136.15, 135.75, 135.1, 133.1, 133.0, 130.4, 130.3, 130.1, 128.7, 128.3, 128.0, 127.2, 83.39, 83.34, 80.3, 66.3, 61.1, 58.3, 54.9, 53.85, 52.34, 52.31, 51.5, 51.1, 46.3, 39.4, 33.15, 29.9, 27.0, 21.90, 21.89, 19.65; MS (MALDI) calcd for $C_{53}H_{61}ClN_4O_{11}S_3Si$ $[M+H]^+$: 1089 $[M+Na]^+$: 1111, $[M+K]^+$: 1127; found $[M+H]^+$: 1089 $[M+Na]^+$: 1111, $[M+K]^+$: 1127.



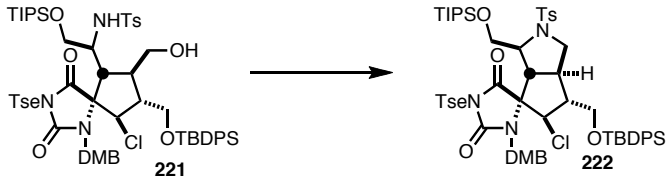
TIPS-Ester 220: To a stirred solution of ester **177** (18 mg, 0.0170 mmol) in 1.8 mL of CH_2Cl_2 at 20 ºC was added Et_3N (10 μL, 0.07 mmol), followed by TIPSOTf (6 μL, 0.04 mmol). The reaction mixture was stirred for 1 h at 20 ºC and then it was diluted with 15 mL of EtOAC and quenched with 10 mL of saturated NH_4Cl solution. The mixture was washed once with brine (15 mL) and the organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude orange oil by flash chromatography on SiO_2 eluting with hexanes/EtOAc (90:10 → 85:15 → 70:30) gave 19 mg (91%) of TIPS-ester **220** as a colorless foam: R_f = 0.52 (40% EtOAc/Hexanes); $[\alpha]_D^{19.5}$ 24.8 (*c* 0.0105, CH_2Cl_2); IR (thin film) 3366, 2949, 2866, 1780, 1726, 1442, 1149 cm^{-1}; ^{1}H NMR (500 MHz, benzene-d_6) δ 7.88 (d, *J* = 8.5 Hz, 2H), 7.86 (dd, *J* = 8.0, 1.0 Hz, 2H), 7.82 (dd, *J* = 8.0, 1.0 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.24-7.36 (m, 7H), 7.06 (dd, *J* = 8.5, 1.5 Hz, 1H) 6.83 (d, *J* = 8.5 Hz, 2H), 6.70 (d, *J* = 8.5 Hz, 2H), 6.50 (d, *J* = 8.5 Hz, 1H), 5.29 (d, *J* = 9.5 Hz, 1H), 5.16 (d, *J* = 11.5 Hz, 1H), 5.00 (d, *J* = 16.0 Hz, 1H), 4.93 (d, *J* = 16.5 Hz, 1H), 4.29 (dd, *J* = 12.0, 10.5 Hz, 1H), 3.93 (app t, , *J* = 11.5, Hz, 1H), 3.82-3.92 (m, 2H), 3.67-3.77 (m, 4H), 3.69 (s, 3H), 3.61 (s, 3H) 3.55 (ddd, *J* = 14.5, 8.5, 6.0 Hz, 1H), 3.34 (s, 3H), 3.28 (dd, *J* = 10.5, 3.5 Hz, 1H), 3.07 (dt, *J* = 14.5, 5.5 Hz, 1H), 2.64 (app. t, *J* = 11.5 Hz, 1H), 1.91 (s, 3H), 1.81 (s, 3H), 1.26 (s, 9H), 1.02-1.07 (m, 21H); ^{13}C NMR (125 MHz, benzene-d_6) δ 173.5, 172.6, 157.4, 150.4, 149.4, 144.6, 143.0, 139.6, 136.05, 135.9, 135.8, 133.8, 133.0, 130.1, 130.0, 129.9, 129.8, 129.0, 128.8, 128.2, 128.0,

127.8, 126.8, 119.8, 112.2, 111.0, 74.5, 63.1, 60.7, 57.8, 55.65, 55.25, 54.0, 52.5, 51.9, 49.0, 46.7, 46.3, 46.1, 33.6, 27.2, 21.05, 20.99, 19.6, 18.10, 18.09, 12.1; MS (MALDI) calcd for $C_{62}H_{82}ClN_3O_{12}S_2Si_2$ $[M+Na]^+$: 1238, $[M+K]^+$: 1254; found $[M+Na]^+$: 1238, $[M+K]^+$: 1254



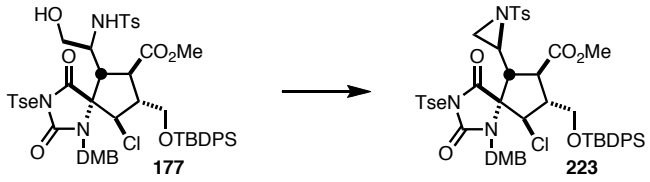
TIPS-alcohol 221: To a stirred solution of **220** (19 mg, 0.016 mmol) in 2.5 mL of CH_2Cl_2 cooled to -78 ºC was added DIBAl-H (8.5 µL, 0.048 mmol) dropwise. The mixture was stirred at -78 ºC for 55 min. then quenched with 1.5 mL of MeOH, then allowed to warm to 20 ºC, Rochelle's salt solution (~15 mL) was then added and the resulting cloudy mixture was stirred vigorously for 3.5 h. Water (~10 mL) was then added and the mixture was extracted with EtOAC (3 x 20 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was dissolved in 2.5 mL of MeOH, cooled to 0ºC and treated directly with excess $NaBH_4$. After 40 min. water (~10 mL) was added and the mixture was allowed to 20 ºC while stirring. The mixture was then extracted with EtOAC (3 x 15 mL), and the organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (80:20 →70:30) gave 12 mg (67%) of TIPS-alcohol **221** as a colorless foam: R_f = 0.43 (40% EtOAc/Hexanes); $[\alpha]_D^{20.5}$ 16.7 (*c* 0.012, $CHCl_3$); IR (thin film) 3493, 2925, 2863, 1774, 1717, 1451, 1146 cm^{-1}; ^1H NMR (500 MHz, benzene-d_6) δ 7.89 (d, *J* = 8.5 Hz, 2H), 7.79 (d, *J* = 6.5 Hz, 2H), 7.75 (d, *J* = 7.0 Hz, 2H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.32-7.37 (m, 4H), 7.26 (d, *J* = 1.5 Hz, 1H), 7.25 (app s, 1H), 7.23 (d, *J* = 1.5 Hz, 1H), 7.09 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 2H), 6.74 (d, *J* = 8.5 Hz, 2H), 6.67 (d, *J* = 10.0 Hz, 1H), 6.46 (d, *J* = 8.5 Hz, 1H), 5.46 (d, *J* = 16.5 Hz, 1H), 5.01 (d, *J* = 11.5 Hz, 1H), 4.96 (d, *J* = 16.5 Hz, 1H), 4.18-4.21 (m, 1H), 3.89 (dd, *J* = 10.5, 2.0 Hz, 1H), 3.84 (dd, *J* = 11.0, 2.0 Hz, 1H), 3.72-3.78 (m, 2H), 3.61-3.67 (m,

1H), 3.63 (s, 3H), 3.56 (dd, *J* = 11.0, 2.0 Hz, 1H), 3.55 (dd, *J* = 10.5, 3.0 Hz, 1H), 3.49 (app t, *J* = 9.5 Hz, 1H), 3.46 (dd, *J* = 9.5, 3.5 Hz, 1H), 3.42 (dd, *J* = 8.5, 5.0 Hz, 1H), 3.33 (m, 3H), 3.30 (dd, *J* = 11.5, 5.5 Hz, 1H), 3.16-3.23 (m, 1H), 3.06 (br. s, 1H), 3.00 (dt, *J* = 10.0, 5.0 Hz, 1H), 2.32 (app t, *J* = 11.5 Hz, 1H), 1.88 (s, 3H), 1.81 (s, 3H), 1.23 (s, 9H), 1.00-1.06 (m, 21H); ^{13}C NMR (125 MHz, benzene-d_6) δ 174.1, 157.4, 150.45, 149.5, 144.7, 142.8, 140.7, 136.3, 136.1, 135.9, 133.9, 133.2, 130.4, 130.2, 130.0, 129.9, 129.8, 129.3, 128.4, 128.2, 128.0, 127.05, 120.2, 112.2, 111.7, 76.4, 66.8, 65.45, 61.0, 58.8, 55.75, 55.4, 53.1, 52.0, 50.0, 47.2, 46.7, 41.95, 33.7, 27.4, 21.2, 21.1, 19.65, 18.3, 18.2, 12.1; MS (MALDI)_calcd for $C_{61}H_{82}ClN_3O_{11}S_2Si_2$ $[M+Na]^+$: 1210, $[M+K]^+$: 1226; found $[M+Na]^+$: 1210, $[M+K]^+$: 1226.



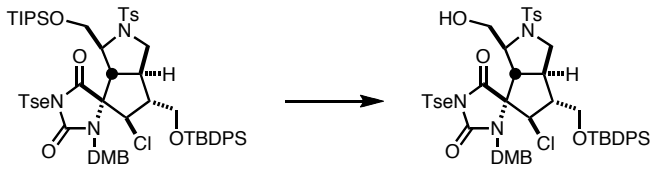
Azabicyclooctane 222: A mixture of TIPS-alcohol **221** (8.5 mg, 0.0072 mmol) and triphenyhlphosphine (4.0 mg, 0.015 mmol) was azeotroped with PhMe (300 μL) under vacuum for 4 h. PhMe (1.6 mL) was then added under N_2 at 20 ºC, followed by DIAD (3 μL, 0.015 mmol). The mixture was stirred at 20 ºC for 2.5 h and then it was concentrated *in vacuo*. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (90:10 → 70:30) provided a semi-pure material contaminated with DIAD byproduct. Further purification by flash chromatography on SiO_2 eluting with $CHCl_3$/acetone (100:0 → 99:1) gave 6.2 mg (74%) of azabicyclooctane **222** as a colorless foam: R_f = 0.30 (30% EtOAc/Hexanes); $[\alpha]_D^{20.7}$ –29.0 (*c* 0.0062, $CHCl_3$); IR (thin film), 2940, 2863, 1774, 1723, 1448, 1149 cm^{-1}; ^{1}H NMR (500 MHz, benzene-d_6) δ 7.87 (d, *J* = 8.5 Hz, 2H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.61 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.56 (dd, *J* = 7.5, 2.0 Hz, 2H), 7.20-7.27 (m, 6H), 7.08 (d, *J* = 2.0 Hz, 1H), 6.82 (d, *J* = 8.5 Hz, 2H), 6.72 (d, *J* = 8.5 Hz, 2H), 6.52 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.47 (d, *J* = 8.0 Hz, 1H), 5.11 (d, *J* = 16.5 Hz, 1H), 4.43 (d, *J* = 9.5 Hz, 1H), 4.31 (dd, *J* = 10.5, 4.5 Hz, 1H), 4.15 (dd, *J* = 10.5, 2.0 Hz, 1H), 4.04 (dd,

J = 11.0, 5.5 Hz, 1H), 3.98 (ddd, *J* = 14.5, 7.5, 5.5 Hz, 1H), 3.80 (dt, *J* = 14.5, 6.0 Hz, 1H), 3.72-3.76 (m, 1H), 3.69 (s, 3H), 3.64 (d, *J* = 16.5 Hz, 1H), 3.47 (dd, *J* = 14.5, 10.5 Hz, 1H). 3.35-3.41 (m, 2H), 3.30 (s, 3H), 3.27 (dd, *J* = 11.0, 5.0 Hz, 1H), 3.20 (dt, *J* = 14.5, 6.0 Hz, 1H), 3.01 (app t, *J* = 11.0 Hz, 1H), 1.91 (s, 3H), 1.85-1.95 (m, 2H), 1.81 (s, 3H), 1.25-1.27 (m, 21H), 0.93 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 155.45, 150.1, 149.05, 145.4, 144.2, 135.63, 135.57, 135.5, 135.4, 132.9, 132.5, 130.32, 130.30, 130.2, 128.7, 128.6, 128.14, 128.06, 127.8, 118.7, 110.95, 109.8, 70.3, 65.6, 64.1, 61.8, 58.35, 56.3, 56.15, 56.0, 52.75, 51.4 50.0, 47.3, 44.9, 33.4, 26.9, 21.90, 21.88, 19.2, 18.16, 18.15, 12.2; MS (MALDI) calcd for $C_{61}H_{80}ClN_3O_{10}S_2Si_2$ $[M+H]^+$: 1170, $[M+Na]^+$: 1192, $[M+K]^+$: 1208; found $[M+H]^+$: 1170, $[M+Na]^+$: 1192, $[M+K]^+$: 1208.



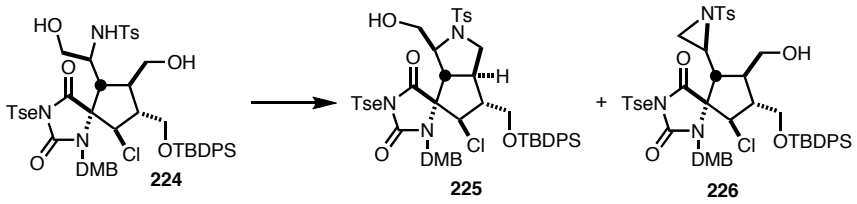
Aziridine 223: A mixture of ester **177** (4.5 mg, 0.0042 mmol) and triphenyhlphosphine (2.3 mg, 0.0088 mmol) was azeotroped with PhMe (50 μL) under vacuum for 2 h. PhMe (1.0 mL) was then added under N_2 at 20 ºC, followed by DIAD (2 μL, 0.010 mmol). The mixture was stirred at 20 ºC for 2 h and then it was concentrated *in vacuo*. Crude ^{1}H NMR analysis showed a ~ 2:1 mixture of **177** and **223** (respectively). The crude material was resubjected to the reaction conditions, stirred for 3 h and concentrated *in vacuo*. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (70:30 → 60:40) gave 3.2 mg (73%) of aziridine **223** as a colorless foam: R_f = 0.48 (50% EtOAc/Hexanes); IR (thin film), 2954, 2860, 1774, 1725, 1451, 1146 cm^{-1}; ^{1}H NMR (500 MHz, benzene-d_6) δ 7.83 (d, *J* = 8.0 Hz, 2H), 7.82 (d, *J* = 7.0 Hz, 2H), 7.80 (d, *J* = 8.5 Hz, 2H), 7.74 (d, *J* = 7.0 Hz, 2H), 7.39 (app t, *J* = 7.5 Hz, 2H), 7.34 (d, *J* = 2.0 Hz, 1H), 7.23-7.31 (m, 4H), 6.89 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 2H), 6.67 (d, *J* = 8.0 Hz, 2H), 6.36 (d, *J* = 8.5 Hz, 1H), 5.21 (d, *J* = 16.0 Hz, 1H), 5.01 (d, *J* = 11.5 Hz, 1H), 4.67 (d, *J* = 15.5 Hz, 1H), 3.95 (dd, *J* = 11.0, 2.0 Hz, 1H), 3.85 (dd, *J* = 11.0, 2.0 Hz, 1H), 3.75

(dd, *J* = 10.5, 7.5 Hz, 1H), 3.64 (s, 3H), 3.49-3.60 (m, 3H), 3.39 (s, 3H), 3.29-3.34 (m, 1H), 3.32 (s, 3H), 3.18-3.23 (m, 2H), 3.00 (ddd, *J* = 15.0, 7.0, 4.0 Hz, 1H), 2.38 (d, *J* = 4.0 Hz, 1H), 2.30 (d, *J* = 6.5 Hz, 1H), 1.83 (s, 3H), 1.82 (s, 3H), 1.24 (s, 9H); ^{13}C NMR (125 MHz, benzene-d_6) δ 172.9, 172.35, 157.1, 150.8, 150.2, 144.7, 144.3, 136.4, 136.32, 136.26, 134.5, 133.3, 130.52, 130.49, 130.15, 129.9, 129.7, 129.3, 121.1, 112.9, 112.3, 75.2, 59.5, 59.4, 56.0, 55.6, 52.2, 51.3, 49.5, 49.2, 46.8, 46.4, 40.5, 35.1, 33.7, 27.7, 27.6, 21.4, 20.0; MS (MALDI) calcd for $C_{53}H_{60}ClN_3O_{11}S_2Si$ $[M+Na]^+$: 1064, $[M+K]^+$: 1080; found $[M+Na]^+$: 1064, $[M+K]^+$: 1080.

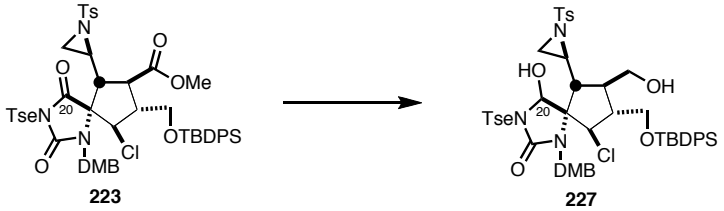


Azabicyclooctane 225: To a stirred solution of azabicyclooctane **222** (6.2 mg, 0.0053 mmol) in 0.5 ml of THF cooled to –35 ºC was added TBAF (10 μL, 0.01 mmol) dropwise and the mixture was stirred at –20 ºC for 1.5 h. The reaction was then quenched with 1 ml of pH 7 buffer and the mixture was allowed to warm to 20 ºC. Brine (~0.5 mL) was then added and the mixture was extracted with EtOAc (3 x 7 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (90:10 → 70:30 → 50:50) gave 3.3 mg (61%) of azabicyclooctane **225** as a colorless solid: R_f = 0.24 (50% EtOAc/Hexanes); IR (thin film), 3503, 2934, 2857, 1774, 1717, 1457, 1152 cm^{-1}; ^{1}H NMR (500 MHz, benzene-d_6) δ 7.84 (d, *J* = 8.5 Hz, 2H), 7.82 (d, *J* = 8.5 Hz, 2H), 7.68 (dd, *J* = 8.0, 2.0 Hz, 2H), 7.54 (dd, *J* = 8.0, 2.0 Hz, 2H), 7.20-7.25 (m, 6H), 6.98 (d, *J* = 2.5 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 2H), 6.74 (d, *J* = 8.0 Hz, 2H), 6.62 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.53 (d, *J* = 8.5 Hz, 1H), 5.06 (d, *J* = 16.5 Hz, 1H), 4.49 (d, *J* = 9.5 Hz, 1H), 4.45 (dd, *J* = 10.0, 4.5 Hz, 1H), 3.93-3.98 (m, 1H), 3.81-3.89 (m, 2H), 3.72 (d, *J* = 16.5, 1H), 3.64-3.69 (m, 1H), 3.65 (s, 3H), 3.45-3.41 (m, 3H), 3.38 (d, *J* = 3.5 Hz, 2H), 3.33 (s, 3H), 2.94 (dd, *J* = 14.0, 10.5 Hz, 1H), 2.74 (app t, *J* = 10.5 Hz, 1H), 2.57 (br s., 1H), 1.92 (s, 3H), 1.78-1.90 (m, 2H), 1.82 (s, 3H), 0.90 (s, 9H); ^{13}C NMR (125 MHz, benzene-d_6) δ 171.8, 156.5, 151.3, 150.2,

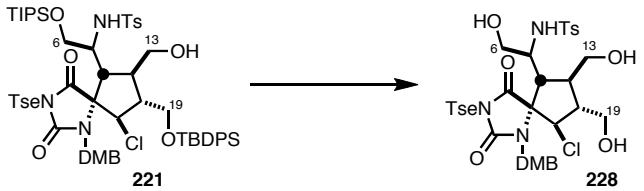
144.8, 143.8, 136.6, 136.3, 136.1, 135.95, 133.20, 133.15, 130.7, 130.56, 130.52, 130.3, 129.8, 129.0, 118.9, 112.7, 111.0, 71.0, 66.7, 64.3, 61.1, 60.8, 58.4, 56.3, 55.9, 53.3, 51.3 50.1, 45.85, 45.2, 33.9, 27.0, 21.5, 21.4, 19.4; MS (MALDI) calcd for $C_{52}H_{60}ClN_3O_{10}S_2Si$ $[M+Na]^+$: 1036; found $[M+Na]^+$: 1036.



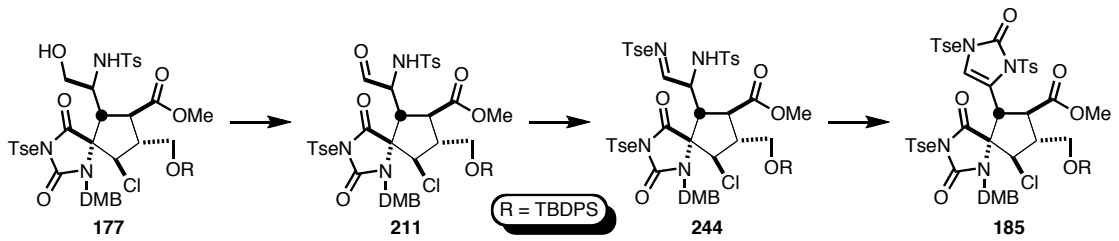
Aziridine 226: A mixture of diol **224** (3.5 mg, 0.0034 mmol) and triphenyhlphosphine (3.8 mg, 0.0145 mmol) was azeotroped with PhMe (50 μL) under vacuum for 1.5 h. PhMe (1.0 mL) was then added under N_2 at 20 ºC, followed by DIAD (2 μL, 0.010 mmol). The mixture was stirred at 20 ºC for 2 h and then it was concentrated *in vacuo*. Crude ^{1}H NMR analysis showed a ~ 1:1 mixture of azabicyclooctane **225** and aziridine **226**. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (70:30 → 60:40 → 50:50) gave ~2 mg (~55%) of a mixture of azabicyclooctane **225** and aziridine **226**. The two products were separated by prep TLC eluting with hexanes/EtOAc (75:25, 30 elutions): Characterization for azabicyclooctane **225** is reported above. Aziridine **226**: R_f = 0.24 (50% EtOAc/Hexanes); IR (thin film) 3532, 2928, 2854, 1771, 1714, 1451, 1149 cm^{-1}; ^{1}H NMR (500 MHz, benzene-d_6) δ 7.80 (dd, J = 8.0, 1.5 Hz, 2H), 7.75-7.79 (m, 4H), 7.73 (d, J = 8.0, Hz, 2H), 7.38 (app t, J = 7.5, Hz, 2H), 7.34 (d, J = 2.0, Hz, 1H), 7.23-7.33 (m, 4H), 6.92 (dd, J = 8.0, 2.0 Hz, 1H), 6.74 (d, J = 8.0 Hz, 2H), 6.65 (d, J = 8.0 Hz, 2H), 6.46 (d, J = 8.5 Hz, 1H), 5.00 (d, J = 11.5 Hz, 1H), 4.94 (d, J = 15.5 Hz, 1H), 4.69 (d, J = 16.0 Hz, 1H), 3.99-4.03 (m, 1H), 3.86-3.89 (m, 1H), 3.85 (dd, J = 10.5, 2.0 Hz, 1H), 3.78 (dd, J = 10.5, 2.0 Hz, 1H), 3.67 (s, 3H), 3.51-3.55 (m, 2H), 3.36 (s, 3H), 3.12-3.21 (m, 2H), 2.93-3.00 (m, 2H), 2.83 (app t, J = 11.0 Hz, 1H), 2.62 (dd, J = 10.0, 7.5 Hz, 1H), 2.43 (d, J = 5.0 Hz, 1H), 2.30 (m,1H), 2.16 (d, J = 6.5 Hz, 1H), 1.81 (s, 3H), 1.80 (s, 3H), 1.23 (s, 9H); MS (MALDI) calcd for $C_{52}H_{60}ClN_3O_{10}S_2Si$ $[M+Na]^+$: 1036, $[M+K]^+$: 1052; found $[M+Na]^+$: 1036, $[M+K]^+$: 1052.



Carbinolamino alcohol 227: To a stirred solution of aziridine **223** (2.8 mg, 0.0027 mmol) in 0.6 mL THF cooled to 0 ºC was added a 2M solution of $LiBH_4$ in THF (xs). After 1 h the mixture was allowed to warm to 20 ºC and stirred for an additional 5 h then it was quenched by the addition of a saturated solution of NH_4Cl (~ 1 mL). After stirring vigorously for 15 minutes the mixture was extracted with EtOAc (3 X 5 mL) and the combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (70:30 → 40:60 → 20:80) gave ~3 mg (~99%, ~3.6:1 dr at C20) of carbinolamino alcohol **227**: R_f = 0.35 (50% EtOAc/Hexanes); ^{1}H NMR (500 MHz, benzene-d_6) δ 7.89-7.86 (m, 4H), 7.81 (d, J = 8.0, Hz, 2H), 7.69 (d, J = 8.0, Hz, 2H), 7.43 (d, J = 2.0 Hz, 1H), 7.36 (app td, J = 7.5, 4.0, Hz, 4H), 7.29-7.26 (m, 1H), 7.27 (dd, J = 7.5, 3.0 Hz, 2H), 6.72 (d, J = 7.5 Hz, 2H), 6.71 (d, J = 8.0 Hz, 2H), 6.68 (d, J = 8.0 Hz, 2H), 5.45 (d, J = 11.0 Hz, 1H) 5.05 (d, J = 12.0 Hz, 1H), 4.85 (d, J = 15.5 Hz, 1H), 4.65 (d, J = 15.5 Hz, 1H), 3.96 (dd, J = 11.0, 3.0 Hz, 1H), 3.85 (ddd, J = 15.0, 7.0, 4.0 Hz, 1H), 3.75-3.70 (m, 1H), 3.69 (dd, J = 11.0, 2.0 Hz, 1H), 3.65 (s, 3H), 3.52-3.44 (m, 1H), 3.48 (s, 3H), 3.17 (d, J = 11.0 Hz, 1H), 3.17-3.13 (m, 1H), 3.04 (ddd, J = 10.5, 6.5, 4.5 Hz, 1H), 2.89 (ddd, J = 14.5, 7.0, 4.5 Hz, 1H), 2.76-2.72 (m, 1H), 2.54 (app dd, J = 11.0, 11.0 Hz, 1H), 2.27 (d, J = 4.5 Hz, 1H), 2.22 (dd, J = 10.0, 5.0 Hz, 1H), 2.19 (d, J = 6.0 Hz, 1H), 2.13 (br. s, 1H) 1.82 (s, 6H), 1.31 (s, 9H); ^{13}C NMR (125 MHz, benzene-d_6) δ 159.7, 150.6, 150.1, 144.6, 144.3, 137.3, 136.54, 136.47, 136.4, 136.3, 134.1, 133.5, 132.7, 132.6, 132.1, 130.6, 130.5, 130.2, 130.0, 121.9, 114.0, 112.5, 89.0, 70.9, 66.2, 59.7, 59.3, 56.1, 55.9, 54.4, 49.6, 46.65, 45.45, 44.2, 43.35, 35.4, 34.9, 27.7, 21.44, 21.41, 20.0; MS (MALDI) calcd for $C_{52}H_{62}ClN_3O_{10}S_2Si$ $[M+Na]^+$: 1038, $[M+K]^+$: 1054; found $[M+Na]^+$: 1038, $[M+K]^+$: 1054.

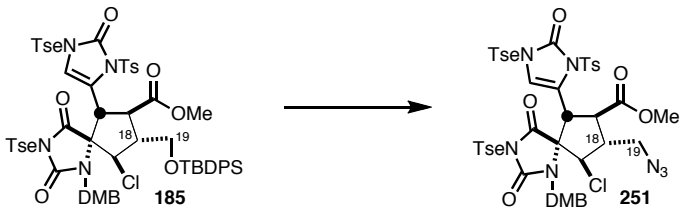


Aminotriol 228: To a stirred solution of alcohol **221** (6.1 mg, 0.0051 mmol) in 1.0 mL THF at 20 ºC was added AcOH (50 µL). The mixture was then cooled to 0 ºC and TBAF was added (xs). After 2 h the mixture was allowed to warm to 20 ºC and stirred for an additional 7 h then it was diluted with EtOAc (~ 5 mL) and washed with a saturated solution of $NaHCO_3$ (~ 2 mL). The aqueous phase was back extracted with EtOAc (1 X 5 mL) and the combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Having observed partial, non-selective desilylilation, the crude mixture was resubjected to the reaction conditions and stirred at 20 ºC for 12 h, then worked up as before. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (50:50 → 30:70 → 20:80) gave ~1.5 mg (~25%) of aminotriol **228**: R_f = 0.12 (60% EtOAc/Hexanes); IR (thin film): 3508, 3289, 2928, 2857, 1770, 1714, 1454, 1152 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.5, Hz, 2H), 7.61 (d, *J* = 8.5, Hz, 2H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 8.8, Hz, 2H), 7.05 (d, *J* = 1.5 Hz, 1H), 6.98 (dd, *J* = 8.0,1.5 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 2H), 6.04 (br s, 1H), 4.81 (d, *J* = 16.5 Hz, 1H), 4.55 (d, *J* = 16.0 Hz, 1H), 4.50 (d, *J* = 11.0 Hz, 1H), 3.97-3.80 (m, 5H), 3.88 (s, 3H), 3.87 (s, 3H), 3.74 (dd, *J* = 11.5, 4.5 Hz, 1H), 3.56-3.44 (m, 3H), 3.37 (app d, *J* = 11.0 Hz, 1H), 2.96 (dd, *J* = 11.5, 4.5 Hz, 1H), 2.79 (dd, *J* = 8.5, 8.5 Hz, 1H), 2.62-2.56 (m, 1H), 2.47 (s, 3H), 2.46-2.43 (m, 1H), 2.41 (s, 3H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 157.0, 149.1, 148.7, 145.9, 143.8, 138.65, 134.7, 130.4, 130.0, 128.9, 128.7, 126.8, 120.9, 111.8, 111.1, 75.9, 65.3, 62.9, 59.6, 59.2, 56.15, 56.0, 54.0, 52.0, 47.6, 47.0, 46.3, 42.7, 33.2, 21.95, 21.8; MS (MALDI) calcd for $C_{36}H_{44}ClN_3O_{11}S_2$ $[M+Na]^+$: 816, $[M+K]^+$: 832; found $[M+Na]^+$: 816, $[M+K]^+$: 832.



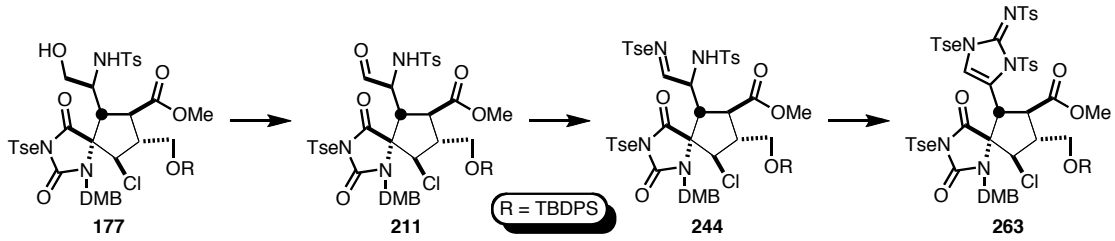
Imidazolone 185. To a solution of ester **177** (109 mg, 0.103 mmol) in 10.0 mL of CH_2Cl_2 was added Dess Martin periodinane (72 mg, 0.170 mmol), and the resulting reaction mixture was stirred at 20 °C for 3.5 h. Upon completion of the reaction as indicated by TLC, anhydrous ether (Et_2O, ~20 mL) was added and the mixture was filtered through a pad of Celite. Removal of solvents *in vacuo* afforded the desired aldehyde. The crude aldehyde **211** was dissolved in 10.0 mL of anhydrous CH_2Cl_2 and cooled to 0 °C. To the solution was added $MgSO_4$ (~100 mg) and $TseNH_2$ (23 mg, 0.115 mmol) and the reaction mixture was stirred at 0 ºC for 1 h then warmed to 20 ºC. Removal of $MgSO_4$ by filtration and concentration *in vacuo* yielded the Tse-imine intermediate **244**, which was used directly without further purification. The Tse-imine was dissolved in 11.0 mL of anhydrous THF and cooled to 0 °C. To the solution was added Et_3N (50 μL, 0.354 mmol) and triphosgene (30 mg, 0.101 mmol) sequentially. The reaction mixture was warmed to 20 ºC and stirred for 30 min, then it was sealed, heated to 60 °C and stirred for 4 h. A saturated $NaHCO_3$ solution (20 mL) was then added and the resulting mixture was cooled to 20 ºC and partitioned between water (20 mL) and EtOAc (3 x 30 mL). The combined organic phase was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (60:40 → 50:50 → 40:60) gave 65 mg (50% 3 steps) of imidazolone **185** as a colorless solid: R_f = 0.63 (60% EtOAc/Hexanes); $[\alpha]_D^{23}$ = -44.7 (*c* = 0.75, CH_2Cl_2); IR (thin film): 3100-3600, 2955, 2931, 1723, 1640, 1516, 1451, 1318, 1146, 814, 705 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8.0 Hz, 2H), 7.83 (d, *J* = 8.5 Hz, 2H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.61 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.52 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.36-7.45 (m, 10H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 2.0 Hz, 1H), 6.81 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.50 (d, *J* = 1.0 Hz, 1H), 6.37 (d, *J* = 8.0 Hz, 1H), 4.95 (d, *J* = 16.0 Hz, 1H), 4.79 (dd, *J* = 10.5, 1.0 Hz, 1H), 4.49 (d, *J* = 11.5 Hz, 1H), 4.11 (d, *J* = 16.0 Hz, 1H), 3.80-3.96 (m, 4H), 3.76 (s, 3H), 3.68 (s, 3H), 3.62 (s, 3H), 3.51-3.59 (m, 2H), 3.43 (t, *J* =

11.0 Hz, 1H), 3.36-3.40 (m, 1H), 3.14 (dt, *J* = 14.5, 5.0 Hz, 1H), 2.89 (app t, *J* = 11.5 Hz, 1H), 2.44 (s, 9H), 1.07 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.3, 171.6, 156.6, 150.7, 149.1, 148.4, 146.3, 145.7, 145.15, 136.1, 135.8, 135.71, 135.69, 133.9, 132.9, 132.75, 130.4, 130.31, 130.25, 130.15, 129.9, 129.5, 129.05, 128.5, 128.04, 128.00, 127.98, 120.2, 118.6, 115.1, 111.4, 110.7, 73.15, 59.2, 58.1, 56.0, 55.8, 54.3, 52.75, 52.74, 46.6, 44.3, 43.6, 42.7, 38.05, 33.7, 27.2, 22.0, 21.89, 21.88, 19.6; MS (MALDI) calcd for $C_{63}H_{69}ClN_4O_{14}S_3Si$ $[M+Na]^+$: 1287, $[M+K]^+$: 1303; found $[M+Na]^+$: 1287, $[M+K]^+$: 1303. HRMS (ESI) calcd for $C_{63}H_{69}ClN_4O_{14}S_3Si$ $[M+Li]^+$: 1271.3590; found: 1271.3604.



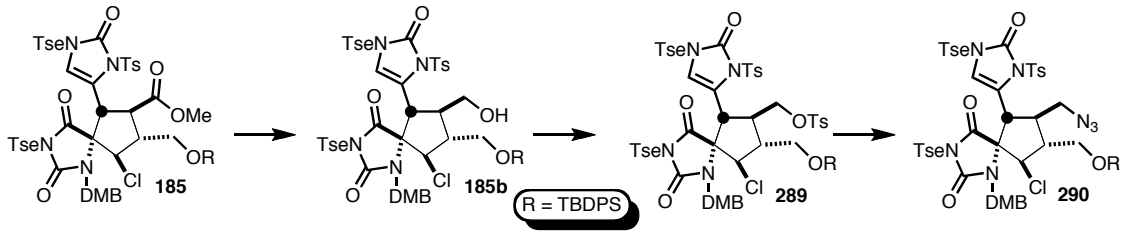
Imidazolone azide 251: To a solution of imidazolone **185** (13 mg, 0.00103 mmol) in 3.6 mL of THF was added AcOH (~ 50 µL, xs), followed by TBAF (~ 150 µL, xs) and the resulting mixture was stirred at 20 ºC for 8.5 h, adding additional TBAF every hour. The mixture was then diluted with EtOAc (~ 20 mL), washed with a saturated solution of $NaHCO_3$ (~ 15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (50:50 → 40:60 → 0:100) gave 6 mg (57%) of the desired alcohol intermediate and 3.5 mg (27%) of starting imidazolone **185**. The purified alcohol was dissolved in 2 mL of CH_2Cl_2 and cooled to 0 ºC. Et_3N was then added (~ 4 µL, xs), followed by MsCl (~ 2 µL, ~0.02 mmol), and the resulting mixture was stirred at 0 ºC for 1h. Water was then added (~ 4 mL) and the mixture was extracted with EtOAc (3 X 5 mL), and the combined organic phase was dried over $MgSO_4$, filterd and concentrated *in vacuo*. The crude material was dissolved in 1.3 mL of anhydrous DMF, and NaN_3 (7.5 mg, 0.115 mmol) was added in one portion. The resulting mixture was heated to 50 ºC for 12 h then it was allowed to cool t0 20 ºC. Water (~20 mL) was added, the mixture was extracted with EtOAc (3 X 15 mL), and the combined organic phase was washed with water (1 X 10 mL) and brine (1 X 15 mL) then it was dried over $MgSO_4$, filterd and concentrated *in vacuo*. Purification by flash

chromatography on SiO_2 eluting with hexanes/EtOAc (60:40 → 40:60 → 30:70) gave 5 mg (81% over the two steps) of imidazolone azide **251**: R_f = 0.39 (60% EtOAc/Hexanes); IR (thin film): 2954, 2931, 2108, 1777, 1723, 1450, 1146 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8.5 Hz, 2H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.359 (d, *J* = 8.0 Hz, 2H), 7.361 (d, *J* = 8.0 Hz, 2H) 7.30 (d, *J* = 8.5 Hz, 2H), 7.02 (d, *J* = 2.0 Hz, 1H), 6.98 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 6.66 (d, *J* = 1.0 Hz, 1H), 5.02 (d, *J* = 16.0 Hz, 1H), 4.73 (dd, *J* = 9.5, 1.0 Hz, 1H), 4.18 (d, *J* = 11.0 Hz, 1H), 4.00-3.90 (m, 2H), 3.93 (d, *J* = 15.5 Hz, 1H), 3.83 (dd, *J* = 13.0, 2.5 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 3.66 (dd, *J* = 13.0, 2.5 Hz, 1H), 3.53 (tdd, *J* = 15.0, 14.0, 6.0 Hz, 2H), 3.38 (ddd, *J* = 14.0, 9.0, 4.5 Hz, 1H), 3.14 (ddd, *J* = 14.5, 5.5, 3.5 Hz, 1H), 3.04 (dd, *J* = 11.0, 11.0 Hz, 1H), 2.98 (app tt, *J* = 11.0, 2.5 Hz, 1H), 2.45 (s, 6H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 171.1, 156.3, 150.7, 149.0, 148.7, 146.4, 145.85, 145.2, 136.0, 135.7, 133.9, 130.45, 130.3, 130.0, 129.5, 129.0, 128.4, 127.9, 121.3, 118.3, 115.4, 112.0, 111.0, 73.0, 59.4, 56.03, 55.98, 54.5, 53.15, 52.7, 48.4, 44.6, 44.3, 43.85, 42.1, 37.9, 33.7, 22.0, 21.9; MS (MALDI) calcd for $C_{47}H_{50}ClN_7O_{13}S_3$ $[M+H]^+$: 1052, $[M+Na]^+$: 1074, $[M+K]^+$: 1090; found $[M+H]^+$: 1052, $[M+Na]^+$: 1074, $[M+K]^+$: 1090.



Guanidine 263. To a solution of ester **177** (10 mg, 0.0094 mmol) in 1.0 mL of CH_2Cl_2 was added Dess Martin periodinane (6 mg, 0.0141 mmol), and the resulting reaction mixture was stirred at 20 °C for 4 h. Upon completion of the reaction as indicated by TLC, anhydrous ether (Et_2O, ~5 mL) was added and the mixture was filtered through a pad of Celite. Removal of solvents *in vacuo* afforded the desired aldehyde. The crude aldehyde **211** was dissolved in 1.0 mL of anhydrous CH_2Cl_2 and cooled to 0 °C. To the

solution was added $MgSO_4$ (tip of a microspatula) and $TseNH_2$ (2.5 mg, 0.0125 mmol) and the reaction mixture was stirred for 1.5 h at 0 ºC. Removal of $MgSO_4$ by filtration and concentration *in vacuo* yielded the Tse-imine intermediate **244**, which was used directly without further purification. The Tse-imine (half the material from the previous reaction) was dissolved in 0.7 mL of anhydrous THF and to the solution was added Et_3N (~4 μL, 0.028 mmol) and imine dichloride **260** (~3 mg, 0.012) sequentially. The resulting, reaction mixture was heated to 60 °C and stirred for 4 h, then allowed to cool to 20 ºC and quenched by the addition of a saturated $NaHCO_3$ solution (5 mL). The organic solvent was evaporated *in vacuo* and the aqueous residue was extracted with EtOAc (3 X 5 mL) and the combined organic phase dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (60:40 → 50:50) gave 2.5 mg (~37% over the 3 steps) of guanidine **263** as a yellow oil: R_f = 0.30 (50% EtOAc/Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (d, *J* = 8.5 Hz, 2H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.53 (d, *J* = 7.0 Hz, 2H), 7.43-7.29 (m, 14H), 7.11 (app s, 1H), 7.02 (d, *J* = 8.5 Hz, 2H), 6.98 (s, 1H), 6.88 (app d, *J* = 8.5 Hz, 1H), 6.41 (d, *J* = 8.5 Hz, 1H), 4.95 (d, *J* = 16.0 Hz, 1H), 4.88 (d, *J* = 11.5 Hz, 1H), 4.59 (d, *J* = 11.5 Hz, 1H), 4.48 (dd, *J* = 16.0, 7.0 Hz, 1H), 4.13 (d, *J* = 16.5 Hz, 1H), 3.89-3.86 (m, 2H), 3.80 (s, 3H), 3.83-3.74 (m, 2H), 3.71 (s, 3H), 3.65 (s, 3H), 3.53-3.46 (m, 3H), 3.49 (dd, *J* = 11.5, 11.5 Hz, 3H), 2.84 (app t, *J* = 11.5 Hz, 1H), 2.50 (s, 3H), 2.43 (s, 6H), 2.38 (s, 3H) 1.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.2, 171.4, 156.7, 149.2, 148.6, 146.5, 145.7, 145.2, 144.4, 142.8, 140.4, 136.1, 135.95, 135.7, 133.0, 132.67, 132.64, 130.4, 130.3, 130.2, 130.0, 129.6, 129.5, 129.34, 129.26, 128.4, 128.04, 128.02, 127.97, 126.7, 122.8, 120.25, 119.35, 111.6, 110.8, 73.2, 59.4, 57.9, 56.1, 55.78, 55.75, 52.87, 52.84, 52.7, 46.8, 44.7, 44.4, 43.2, 41.85, 33.75, 29.9, 27.2, 22.0, 21.9, 19.6; MS (MALDI) calcd for $C_{70}H_{76}ClN_5O_{15}S_4Si$ $[M+H]^+$: 1418; found $[M+H]^+$: 1418.

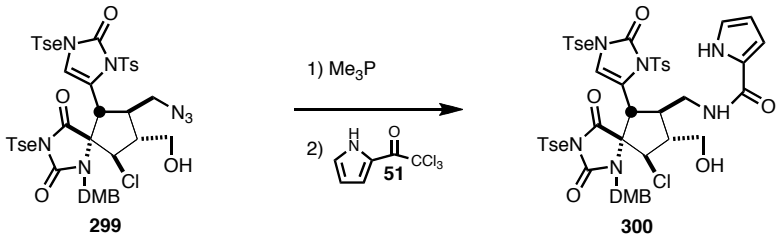


Azide 290: To a solution of imidazolone **185** (33 mg, 0.0261 mmol) in 5.0 mL of CH_2Cl_2 at -78 °C was added DIBAl-H (~ 50 μL, 0.28 mmol) and the mixture was stirred for 30 min, then quenched with 3 mL of MeOH, and allowed to warm to 20 ºC. Rochelle's salt solution was then added (~ 5 mL) and the mixture was stirred vigorously for 4 h. The mixture was then transferred into a separatory funnel and partitioned between water (10 mL) and EtOAc (4 X 25 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*, To a mixture of crude alcohol **185b** and TsCl (16 mg, 0.082 mmol) in 4.5 mL of anhydrous CH_2Cl_2, was added triethylamine (40 μL, 0.32 mmol) and a few crystals of DMAP. The reaction mixture was stirred vigorously at 20 ºC for 15 h then it was quenched with 5 mL of pH 7 buffer partitioned between water (10 mL) and EtOAc (3 X 15 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (60:40 → 50:50 → 40:60) gave 23 mg (64%) of tosylate **289** as a colorless foam. To the tosylate **289** in a dry flask was added NaN_3 (11 mg, 0.17 mmol) and anhydrous DMF (2.4 mL). The flask was sealed and the reaction mixture was heated to 50 °C and stirred for 12.5 h. After cooling to 20 ºC then, the mixture was partitioned between water (20 mL) and EtOAc (3 X 15 mL), and the combined organic phase was washed with water and brine, then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (50:50) gave 13 mg (62%) of azide **290** as a light yellow foam: R_f = 0.49 (60% EtOAc/Hexanes); $[\alpha]_D^{23}$ = -12.8 (*c* = 1.20, CH_2Cl_2); IR (thin film): 2931, 2857, 2102, 1774, 1720, 1593, 1516, 1454, 1318, 1149, 1025, 814, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.5 Hz, 2H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.63 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.53 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.34-7.48 (m, 10H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.00 (d,

J = 2.0 Hz, 1H), 6.80 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.51 (d, *J* = 8.5 Hz, 1H), 6.40 (d, *J* = 1.5 Hz, 1H), 4.84 (d, *J* = 16.0 Hz, 1H), 4.46 (d, *J* = 11.5 Hz, 1H), 4.12 (d, *J* = 8.5 Hz, 1H), 4.10 (d, *J* = 16.5 Hz, 1H), 3.81-3.97 (m, 6H), 3.79 (s, 3H), 3.70 (s, 3H), 3.54 (ddd, *J* = 9.5, 5.5, 4.0 Hz, 2H), 3.67 (dd, *J* = 12.5, 3.5 Hz, 1H), 3.25-3.28 (m, 2H), 3.15 (dt, *J* = 14.5, 5.0 Hz, 1H), 2.53 (m, 2H), 2.44 (s, 9H), 1.11 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 156.8, 150.6, 149.0, 148.4, 146.4, 145.7, 145.2, 136.1, 135.8, 135.7, 134.2, 132.8, 132.7, 130.5, 130.4, 130.33, 130.29, 130.0, 129.5, 128.8, 128.45, 128.3, 128.1, 128.0, 120.3, 118.8, 114.95, 111.45, 110.8, 73.9, 59.1, 58.1, 56.1, 55.85, 54.3, 52.75, 52.3, 45.9, 44.49, 44.43, 39.05, 37.9, 33.7, 29.9, 27.3, 22.0, 21.91, 21.89, 19.6; MS (MALDI) calcd for $C_{62}H_{68}ClN_7O_{12}S_3Si$ $[M+Na]^+$: 1284, $[M+K]^+$: 1300; found $[M+Na]^+$: 1284, $[M+K]^+$: 1300.

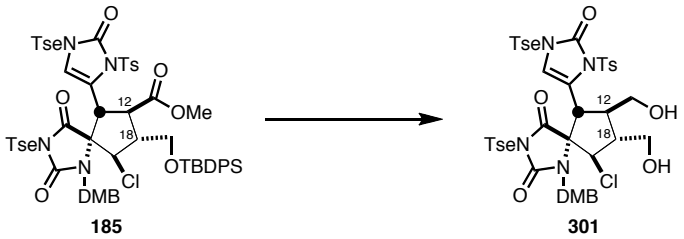
Azide 299: To a solution of azide **290** (13 mg, 0.010 mmol) in 3.0 mL of THF at 20 °C buffered with 0.5 mL AcOH, was added TBAF (~150 μL, 0.15 mmol) and the mixture was stirred for 5 hours during which, additional TBAF was added as needed to drive the reaction to completion. The reaction mixture was then diluted with EtOAc (20 mL) and washed with saturated $NaHCO_3$ solution (2 x 15 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*, Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (40:60 → 20:80 → 0:100) gave 7.6 mg (72%) of azide **299** as a colorless foam: R_f = 0.33 (80% EtOAc/Hexanes); IR (thin film): 3485, 2102, 1714, 1455, 1146; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (d, *J* = 8.5 Hz, 2H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 4H), 7.28 (d, *J* = 8.5 Hz, 2H), 6.96 (d, *J* = 2.0 Hz, 1H), 6.94 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.75 (d, *J* = 8.5 Hz, 1H), 6.64 (app s, 1H), 4.84 (d, *J* = 15.5 Hz, 1H), 4.38 (d, *J* = 11.0 Hz, 1H), 4.12 (d, *J* = 7.5 Hz, 1H), 4.03 (d, *J* = 16.0 Hz, 1H), 3.90-3.96 (m, 3H), 3.82-3.86 (m, 3H), 3.82 (s, 3H), 3.78 (s, 3H), 3.61 (app d, *J* = 5.5 Hz, 2H), 3.54 (m, 2H), 3.30 (ddd, *J* = 14.5, 5.0, 5.0 Hz, 1H), 3.15 (dt, *J* = 14.5,

5.0 Hz, 1H), 2.48-2.61 (m, 2H), 2.44 (s, 6H), 2.43 (s, 3H), 1.79 (br s. 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.45, 156.5, 150.6, 148.8, 148.4, 146.4, 145.8, 145.2, 135.9, 135.7, 134.2, 130.4, 130.3, 130.0, 129.6, 128.8, 128.4, 127.9, 121.0, 118.7, 115.4, 111.9, 111.1, 74.1, 58.9, 57.4, 56.1, 56.0, 54.4, 52.8, 52.7, 45.8, 44.4, 44.2, 39.6, 37.7, 33.6, 22.0, 21.9; MS (MALDI) calcd for $C_{46}H_{50}ClN_7O_{12}S_3$ $[M+H]^+$: 1024 $[M+Na]^+$: 1046, $[M+K]^+$: 1062; found $[M+H]^+$: 1024 $[M+Na]^+$: 1046, $[M+K]^+$: 1062.



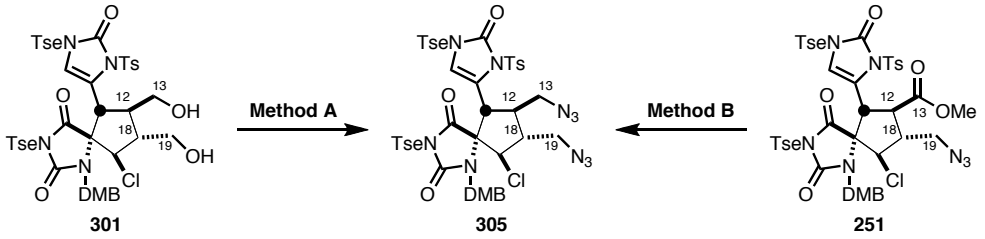
Cyclopentyl Pyrrolo amide 300: To a solution of azide **299** (4.2 mg, 0.004 mmol) in 1.0 mL of THF/H_2O (3:2) at 20 °C, was added Me_3P (1M solution in THF, ~20 μL, 0.02 mmol) and the mixture was stirred for 5 hours. The solvents were then evaporated and the dry crude material was dissolved in 1.0 mL of MeCN. DIPEA (~3 μL, 0.016 mmol) was added at 20 °C, followed by 2-(trichloroacetyl)-pyrrole **51** (~ 3 mg, 0.014 mmol), the flask was sealed to avoid loss of solvent through evaporation and the reaction mixture was stirred at 20 ºC overnight. The solvent was then evaporated and the residue was purified by flash chromatography on SiO_2 eluting with EtOAc/MeOH (100:0 → 95:5) affording 1.8 mg (40%) of amide pyrrole **300** as a colorless solid: R_f = 0.13 (5% MeOH/EtOAc); IR (thin film): 3378, 1717, 1454, 1146; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.40 (br s, 1H), 7.83 (d, *J* = 8.5 Hz, 2H), 7.82 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 6.94 (d, *J* = 2.0 Hz, 1H), 6.87-6.90 (m, 2H), 6.84 (t, *J* = 5.5 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 6.69 (d, *J* = 1.5 Hz, 1H), 6.55-6.57 (m, 1H), 6.21 (dd, *J* = 6.5, 2.5 Hz, 1H), 4.84 (d, *J* = 15.5 Hz, 1H), 4.23 (d, *J* = 11.5 Hz, 1H), 4.09 (dd, *J* = 10.0, 1.5 Hz, 1H), 4.01 (d, *J* = 15.5 Hz, 1H), 3.92-3.97 (m, 2H), 3.80-3.88 (m, 2H), 3.81 (s, 3H), 3.78 (s, 3H), 3.71 (dd, *J* = 11.5, 4.0 Hz, 1H), 3.59 (app t, *J* = 5.5 Hz, 2H), 3.47-3.58 (m, 3H), 3.21-3.27 (m, 1H), 3.09 (dt, *J* = 14.5, 5.5 Hz, 1H), 2.59-2.66 (m, 1H), 2.52-2.57 (m, 1H), 2.45 (s, 3H), 2.44 (s, 3H), 2.42 (s, 3H), 2.07 (br s, 1H); MS (MALDI) calcd for $C_{51}H_{55}ClN_6O_{13}S_3$ $[M+H]^+$:

1091 $[M+Na]^+$: 1113, $[M+K]^+$: 1129; found $[M+H]^+$: 1091 $[M+Na]^+$: 1113, $[M+K]^+$: 1129.



Diol 301. To a solution of imidazolone **185** (61 mg, 0.048 mmol) in 12.0 mL of anhydrous THF was added $LiBH_4$ (200 µL, 0.4 mmol), and the resulting reaction mixture was stirred at 20 °C for 8 h, adding additional reagent in 50 µL portions to dirve the reaction to completion as monitored by TLC. A saturated solution of NH_4Cl (~ 20 mL) was then added, and the mixture was extracted with EtOAc (3 X 25 mL), and the combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* affording a white foam. This crude material was dissolved in 12.0 mL of anhydrous THF and AcOH (300 µL) was added followed by TBAF (500 µL, 0.5 mmol). The resulting mixture was stirred at 20 ºC for 2 h, then diluted with EtOAc (~ 30 mL), and washed with a saturated solution of $NaHCO_3$, then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (30:70 → 0:100) and MeOH/EtOAc (3:97) gave 28 mg (58% 2 steps) of diol **301** as an off-white foam: R_f = 0.09 (80% EtOAc/Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.5 Hz, 2H), 7.82 (d, *J* = 8.5 Hz, 2H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 7.5 Hz, 2H), 7.35 (d, *J* = 7.5 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 6.95 (d, *J* = 2.0 Hz, 1H), 6.92 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.76 (d, *J* = 8.5 Hz, 1H), 6.64 (d, *J* = 1.0 Hz, 1H), 4.84 (d, *J* = 15.5 Hz, 1H), 4.18 (d, *J* = 12.0 Hz, 1H), 4.10 (d, *J* = 16.0 Hz, 1H), 4.05 (dd, *J* = 10.5, 1.0 Hz, 1H), 396-3.91 (m, 4H), 387-3.82 (m, 4H), 3.83 (s, 3H), 3.78 (s, 3H), 3.78 (dd, *J* = 17.0, 12.0 Hz, 1H), 3.71 (dd, *J* = 11.0, 4.0 Hz, 1H), 3.65 (dd, *J* = 11.0, 5.0 Hz, 1H), 3.54 (tdd, *J* = 15.0, 14.0, 6.0 Hz, 2H), 3.29 (app dt, *J* = 15.0, 6.0 Hz, 1H), 3.15 (app dt, *J* = 15.0, 6.0 Hz, 1H), 2.68-2.61 (m, 1H), 2.45 (s, 6H), 2.44 (s, 3H), 2.36-2.29 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.7, 156.6, 150.7, 148.85, 148.3, 146.3, 145.8, 145.3, 135.8, 135.6, 134.2, 130.39, 130.35, 130.0, 129.4, 128.7, 128.3, 127.9, 120.5, 118.75, 115.65, 111.5, 111.1, 73.9, 63.7, 60.6, 60.2, 60.0, 56.1, 556.0, 54.1, 52.8, 47.1, 44.8, 44.5, 42.4, 37.8, 33.5, 29.9,

22.0, 21.9, 21.3, 14.4; MS (MALDI) calcd for $C_{46}H_{51}ClN_4O_{13}S_3$ $[M+H]^+$: 999, $[M+Na]^+$: 1021, $[M+K]^+$: 1037; found $[M+H]^+$: 999, $[M+Na]^+$: 1287, $[M+K]^+$: 1303.

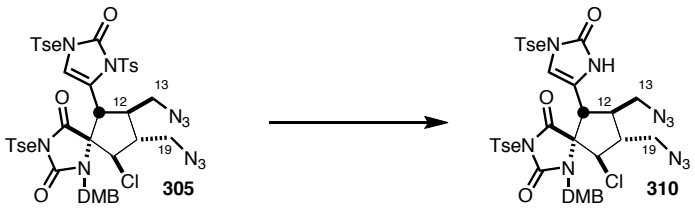


Bis-azide 305. **Method A**: To a solution of diol **301** (20.5 mg, 0.0205 mmol) in 5.0 mL of anhydrous CH_2Cl_2 cooled to 0 ºC was added Et_3N (100 µL, 0.707 mmol), followed by MsCl (40 µL, 0.52 mmol) and the resulting reaction mixture was stirred at 0 °C for 1 h. Water (~ 10 mL) was then added, and the mixture was allowed to warm to 20 ºC then extracted with EtOAc (2 X 25 mL), and the combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. This crude material was dissolved in 4.0 mL of anhydrous DMF and NaN_3 (26.7 mg, 0.41 mmol) was added in one portion. The resulting mixture was heated to 50 ºC and stirred for 13 h, then allowed to cool to 20 ºC. Water (~ 50 mL) was then added, and the mixture was then extracted with EtOAc (3 X 30 mL), and the combined organic phase was washed with water (1 X 20 mL) and brine (1 X 20 mL) then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (50:50 → 20:80) gave 16 mg (74% 2 steps) of bis-azide **305** as an off-white foam.

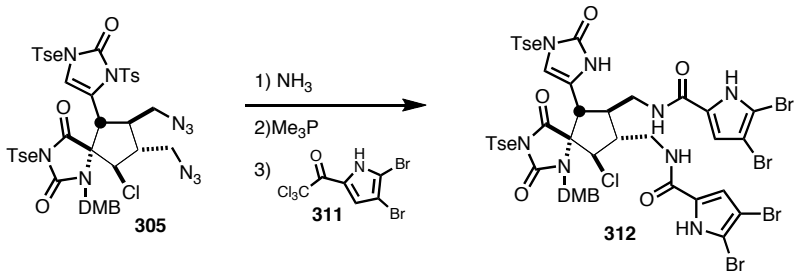
Bis-azide 305. Method B: To a solution of imidazolone azide **251** (222 mg, 0.211 mmol) in 6 mL of anhydrous THF/MeOH (95:5) cooled to 0 ºC was added $LiBH_4$ (1.3 mL, 2.6 mmol), and the resulting reaction mixture was stirred at 0 °C for 10 minutes. A saturated solution of NH_4Cl (~10 mL) was then slowly added and the mixture was allowed to warm to 20 ºC while stirring vigorously for 10 minutes. The mixture was then extracted with EtOAc (3 X 15 mL), and the combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was dissolved in 15 mL of anhydrous CH_2Cl_2 and cooled to 0 ºC, then Et_3N (100 µL, 0.707 mmol) was added,

followed by MsCl (40 μL, 0.52 mmol) and the resulting reaction mixture was stirred at 0 °C for 5 h. A saturated solution of $NaHCO_3$ (~ 15 mL) was then added, and the mixture was allowed to warm to 20 ºC then the organic layer was separated. The aqueous residue was extracted with EtOAc (2 X 10 mL), and the combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. This crude material[1] this was dissolved in 9 mL of anhydrous DMF and NaN_3 (92 mg, 1.41 mmol) was added in one portion. The resulting mixture was heated to 50 ºC and stirred for 15 h, then allowed to cool to ambient temperature. Water (~ 30 mL) was then added, followed by brine (~ 5 mL) and the mixture was extracted with EtOAc (3 X 25 mL), and the combined organic phase was washed with water (2 X 20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (50:50 → 20:80) gave 127 mg (58% 3 steps) of bis-azide **305** as an off-white foam: R_f = 0.33 (75% EtOAc/Hexanes); $[\alpha]_D^{21}$ = -22.4 (*c* = 0.0134, CH_2Cl_2); IR (thin film): 3124, 3064, 2934, 2106, 1772, 1719, 1594, 1455, 1148 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.87 (d, *J* = 8.5 Hz, 2H), 7.82 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.36 (app d, *J* = 8.0 Hz, 4H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.00 (d, *J* = 2.0 Hz, 1H), 6.96 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 6.63 (d, *J* = 1.0 Hz, 1H), 4.94 (d, *J* = 15.5 Hz, 1H), 4.20 (d, *J* = 11.5 Hz, 1H), 4.09 (dd, *J* = 9.5, 1.0 Hz, 1H), 4.03-3.92 (m, 3H), 3.96 (d, *J* = 15.5 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.68 (ddd, *J* = 16.0, 13.0, 3.0 Hz, 2H), 3.58 (app d, *J* = 5.5 Hz, 2H), 3.53 (ddd, *J* = 6.0, 5.0, 3.0 Hz, 2H), 3.32 (ddd, *J* = 8.0, 7.0, 5.0 Hz, 1H), 3.17 (ddd, *J* = 14.5, 6.0, 3.5 Hz, 1H), 2.65 (app dt, *J* = 11.0, 3.0 Hz, 1H), 2.454 (s, 3H), 2.450 (s, 3H), 2.44 (s, 3H), 2.29 (ddd, *J* = 14.0, 11.0, 6.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.3, 156.4, 150.6, 149.0, 148.6, 146.5, 145.8, 145.2, 136.0, 135.7, 134.1, 130.4, 130.3, 130.0, 129.45, 128.85, 128.4, 127.9, 121.2, 118.2, 115.4, 112.0, 111.0, 73.6, 59.6, 56.03, 55.98, 54.45, 52.75, 52.3, 48.2, 44.4, 43.7, 43.1, 40.2, 37.8, 33.6, 22.0, 21.9; MS (MALDI) calcd for $C_{46}H_{49}ClN_{10}O_{11}S_3$ $[M+H]^+$: 1049, $[M+Na]^+$: 1071, $[M+K]^+$: 1087; found $[M+H]^+$: 1049, $[M+Na]^+$: 1071, $[M+K]^+$: 1087.

[1] NOTE: this mesylate intermediate was alternatively purified at this stage (on SiO_2 eluting with hexanes/EtOAc (40:60 → 20:80)) and used for the synthesis of phthalimide **325a**.



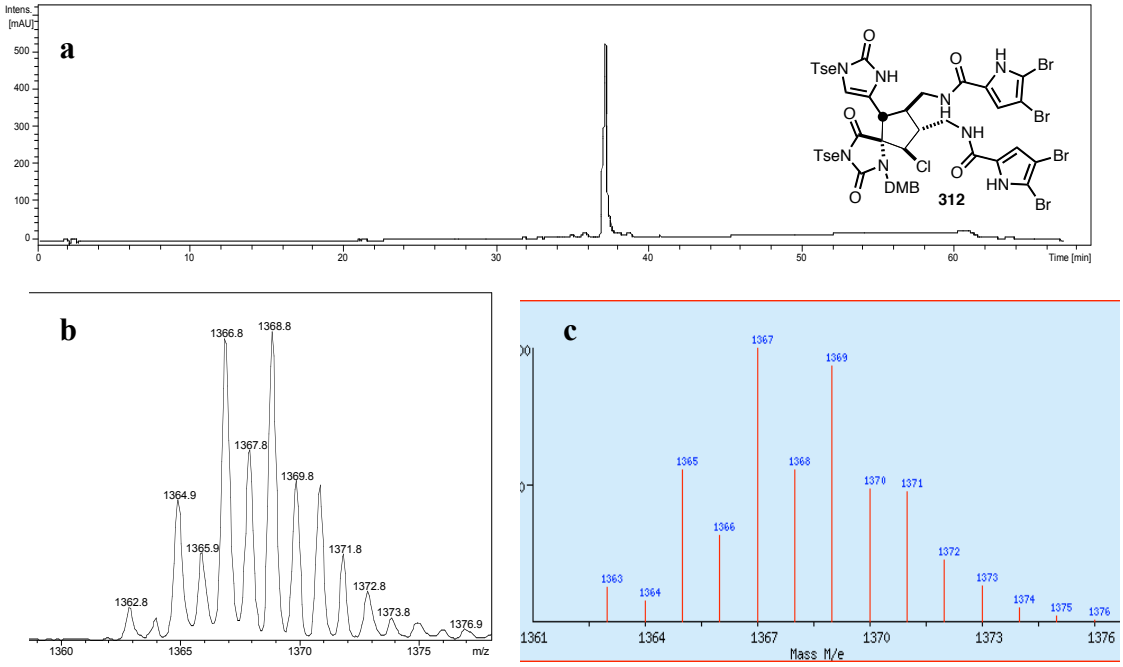
Bis-azide 310. To a solution of bis-azide **305** (23.6 mg, 0.0225 mmol) in 8.0 mL of anhydrous THF cooled to 0 ºC was added a ~ 0.06 M solution of freshly prepared SmI_2, as needed to dive the reaction to completion, as monitored by TLC. The reaction was quenched by the addition of a saturated solution of $NaHCO_3$ (~10 mL) and it was allowed to warm to 20 ºC. A saturated solution of $Na_2S_2O_3$ (~ 8 mL) was then added and the mixture was extracted with EtOAc (3 X 25 mL), and the combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford a yellow foam. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (50:50 → 0:100) gave 13.5 mg (68%) of detosylated bis-azide **310** as an off-white foam: R_f = 0.67 (EtOAc); IR (thin film): 3340, 2928, 2102, 1771, 1717, 1682, 1451, 1146 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.76 (br s, 1H), 7.89 (d, *J* = 8.5 Hz, 2H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 9.0 Hz, 2H), 6.96 (d, *J* = 2.0 Hz, 1H), 6.91 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.78 (d, *J* = 8.5 Hz, 1H), 6.47 (app t, *J* = 1.5 Hz, 1H), 4.97 (d, *J* = 16.5 Hz, 1H), 4.20-4.11 (m, 2H), 4.13 (d, *J* = 11.5 Hz, 1H), 3.94 (d, *J* = 16.0 Hz, 1H), 3.89 (ddd, *J* = 15.0, 7.0, 3.5 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.76 (dd, *J* = 13.0, 2.5 Hz, 2H), 3.68-3.59 (m, 4H), 3.57-3.52 (m, 2H), 3.50 (dd, *J* = 10.5, 1.0 Hz, 1H), 3.36 (ddd, *J* = 14.0, 6.0, 4.0 Hz, 1H), 2.65 (app tt, *J* = 11.0, 3.0 Hz, 1H), 2.47 (s, 3H), 2.44 (s, 3H), 2.40-2.33 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.75, 155.8, 153.9, 149.2, 148.8, 145.9, 145.5, 136.5, 134.8, 130.4, 130.3, 129.2, 128.7, 128.0, 120.7, 116.4, 111.4, 111.2, 111.0, 73.4, 59.55, 56.01, 55.98, 55.2, 51.8, 51.2, 48.0, 45.2, 44.3, 43.7, 39.3, 37.5, 33.15, 29.9, 21.94, 21.87; MS (MALDI) calcd for $C_{39}H_{43}ClN_{10}O_9S_2$ $[M+H]^+$: 895, $[M+Na]^+$: 917, $[M+K]^+$: 933; found $[M+H]^+$: 895, $[M+Na]^+$: 917, $[M+K]^+$: 933.



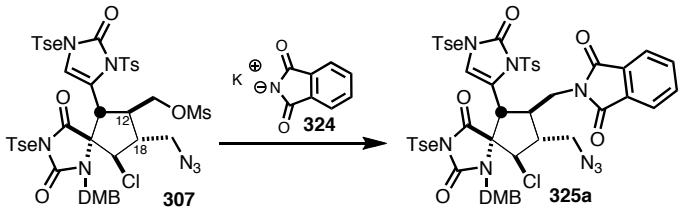
Bis-dibromopyrrole 312. A solution of bis-azide **305** (57 mg, 0.0540 mmol) in 8.0 mL of MeOH cooled tat 20 ºC was bubbled with $NH_{3(g)}$ for ~ 15 minutes. The reaction vessel was then sealed and heated at 55 ºC for 44 h, then allowed to cool to 20 ºC and concentrated *in vacuo*. The crude material (spectroscopically identical to bis-azide **310**) was dissolved in 6.5 mL of THF and cooled to 0 ºC. Trimethylphosphine (1M in THF, 220 μL, 0.220 mmol) was then added drop-wise and the mixture was stirred at 0 ºC for 1.5 h. Water (~ 50 μL) was added and the mixture was allowed to warm to 20 ºC and stirred for an additional 3.5 h, then concentrated *in vacuo*. The crude material was dissolved in ~ 3 mL of HPLC grade benzene and reconcentrated *in vacuo*. After two cycles, the crude material appeared as a yellow foam. This crude material was dissolved in 5 mL of MeCN, dibromo-trichloroacylpyrrole **311** (70 mg, 0.189 mmol) was added in one portion, followed by diisopropylethylamine (125 μL, 0.717 mmol) and the resulting mixture was stirred at 20 ºC for 17 h, then concentrated *in vacuo* to afford a yellow foam. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (50:50 → 0:100), then with MeOH/EtOAc (5:95) gave 39 mg (53% for the 3 steps) of bis-pyrrole **312** as a white solid: R_f = 0.39 (EtOAc); IR (thin film): 3351, 3124, 2925, 2851, 1771, 1714, 1682, 1629, 1454, 1143 cm^{-1}; ^1H NMR (500 MHz, CD_3OD): δ 7.83 (d, *J* = 8.5 Hz, 2H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 6.92 (d, *J* = 2.0 Hz, 1H), 6.89 (s, 1H), 6.81 (s, 1H), 6.72 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.63 (d, *J* = 8.5 Hz, 1H), 6.47 (d, *J* = 1.5 Hz, 1H), 4.65 (d, *J* = 16.5 Hz, 1H), 4.16 (d, *J* = 11.5 Hz, 1H), 4.04 (d, *J* = 16.5 Hz, 1H), 3.89-3.54 (m, 8H), 3.79 (s, 3H), 3.69 (s, 3H), 3.53 (dd, *J* = 10.5, 1.0 Hz, 1H), 3.45-3.27 (m, partially overlapping with solvent peak, 4H), 2.67 (app tt, *J* = 11.5, 4.0 Hz, 1H), 2.48 (s, 3H), 2.45 (s, 3H), 2.44-2.37 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD): δ 173.0, 161.2, 160.9, 156.2, 153.7, 148.9, 148.3, 145.6, 145.3, 136.0, 134.7, 129.8, 129.75, 129.5, 128.3, 127.8, 127.3, 127.2, 119.6, 117.35, 113.4, 113.0, 111.3,

110.0, 110.9, 105.1, 105.0, 98.7, 98.6, 73.9, 60.9, 55.0, 53.75, 51.0, 45.0, 43.7, 43.55, 41.6, 39.0, 37.0, 36.8, 32.7, 29.3, 20.3, 20.2; MS (MALDI) calcd for $C_{39}H_{43}ClN_{10}O_9S_2$ $[M+Na]^+$: 1363; found $[M+Na]^+$: 1363.

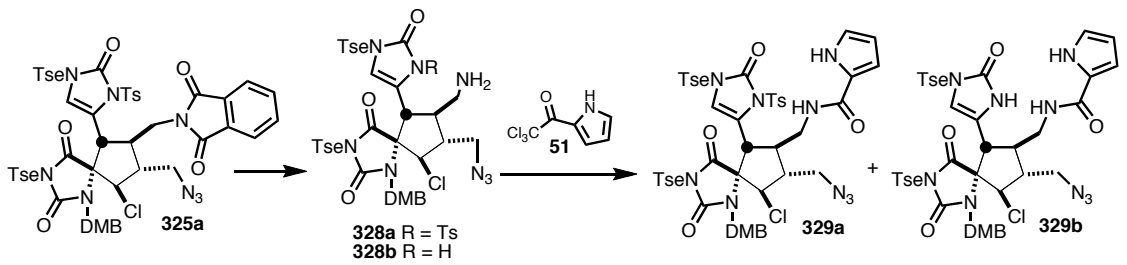
Spectroscopic data in DMSO-d_6: ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.72, (br s, 1H), 12.70 (br s, 1H), 10.00 (d, J = 1.0 Hz, 1H), 8.18 (app q, J = 6.5 Hz, 2H), 7.81 (d, J = 8.5 Hz, 2H), 7.79 (d, J = 8.5 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 6.99 (s, 1H), 6.88 (s, 1H), 6.81 (d, J = 1.5 Hz, 1H), 6.64 (dd, J = 8.5, 1.5 Hz, 1H), 6.59 (d, J = 8.5 Hz, 1H), 6.38 (app s, 1H), 4.30 (d, J = 16.5 Hz, 1H), 4.17 (d, J = 11.5 Hz, 1H), 3.97 (d, J = 16.5 Hz, 1H), 3.77-3.67 (m, 4H), 3.69 (s, 3H), 3.65-3.58 (m, 3H) 3.62 (s, 3H), 3.57-3.52 (m, 4H), 3.53 (dt, J = 14.0, 5.0 Hz, 1H), 3.29 (this signal is detected by 2D correlations but it is completely covered by the water peak from the solvent; 1H), 2.42 (s, 6H), 2.42 (this signal is detected by 2D correlations but it is completely covered by the solvent peak; 1H) 2.29-2.23 (m, 1H).



a) HPLC trace for bis-pyrrole **312**. b) observed and c) predicted M+Na cluster for bis-pyrrole **312**



Phthalimide 325a: To a solution of mesylate **307** (17 mg, 0.02154 mmol) in 2.7 mL of dry DMF was added potassium phthalimide **324** (7.4 mg, 0.0399 mmol) in one portion, and the resulting reaction mixture was stirred at 45 °C for 12, then allowed to warm to 20 ºC. Water (~20 mL) was added, followed by brine (~ mL) and the mixture was extracted with EtOAc (3 X 25 mL). The combined organic phase was washed with water (2 X 15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford a yellow oil. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (60:40 → 30:70) gave 13 mg (73%) of phthalimide **325a** as a white solid: R_f = 0.37 (50% EtOAc/Hexanes; 3 elutions); IR (thin film): 2931, 2108, 1771, 1714, 1640, 1451, 1143 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.0 Hz, 2H), 7.87 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.77 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.02 (d, *J* = 2.0 Hz, 1H), 6.95 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.75 (d, *J* = 8.5 Hz, 1H), 6.70 (d, *J* = 1.5 Hz, 1H), 5.02 (d, *J* = 15.5 Hz, 1H), 4.25 (dd, *J* = 10.5, 1.5 Hz, 1H), 4.11 (d, *J* = 11.0 Hz, 1H), 3.98 (dd, *J* = 13.0, 2.5 Hz, 1H), 3.93-3.85 (m, 4H), 3.82 (s, 3H), 3.80 (d, *J* = 15.5 Hz, 1H), 3.79 (s, 3H), 3.76-3.69 (m, 2H), 3.64 (dd, *J* = 13.0, 2.5 Hz, 1H), 3.43 (ddd, *J* = 10.0, 6.0, 3.0 Hz, 2H), 3.37 (ddd, *J* = 14.0, 8.0, 6.0 Hz, 1H), 3.10 (app dt *J* = 14.5, 5.0 Hz 1H), 2.59 (app tt, *J* = 11.0, 2.5 Hz, 1H), 2.54-2.50 (m, 1H), 2.48 (s, 3H), 2.43 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.0, 168.95, 156.2, 150.4, 148.8, 148.5, 146.0, 145.55, 144.9, 135.7, 135.5, 134.45, 131.6, 130.2, 130.0, 129.8, 129.44, 129.41, 128.1, 127.8, 123.6, 121.3, 118.8, 114.2, 112.15, 110.7, 72.9, 59.8, 55.79, 55.77, 55.74, 55.72, 54.1, 52.4, 47.35, 44.1, 42.9, 42.6, 39.1, 37.6, 37.4, 33.35, 29.7, 21.8, 21.6; MS (MALDI) calcd for $C_{54}H_{53}ClN_8O_{13}S_3$ $[M+H]^+$: 1153, $[M+Na]^+$: 1175, $[M+K]^+$: 1191; found $[M+H]^+$: 1153, $[M+Na]^+$: 1175, $[M+K]^+$: 1191.



Pyrrole 329b: To a solution of phthalimide **325a** (7 mg, 0.00607 mmol) in 2.0 mL of absolute EtOH was added hydrazine (xs) and the resulting mixture was heated to 55 ºC for 15 h then it was allowed to cool to 20 ºC and concentrated *in vacuo* to afford a mixture of amines **328a/b**. The crude material[2] was dissolved in 2.0 mL of MeCN and trichloroacetylpyrrole **51** (2 mg, 0.00941 mmol) was added in one portion, followed by diisopropylethylamine (~ 25 μL, xs). The resulting mixture was stirred at 20 ºC for 17 h then it was concentrated *in vacuo*. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (30:70 → 10:90 → 0:100) gave tosylated pyrrole **329a** (1 mg, 15%), pyrrole **329b** (3 mg, 51%) and a mixture of amines **328a/b** (not quantified). The latter was resubjected to the reaction conditions generating additional **329a** (0.6 mg, overall 23% yield), and **329b** (0.4 mg, overall 58% yield), Spectroscopic data for pyrrole **329b**: R_f = 0.26 (EtOAc); IR (thin film): 3366, 2925, 2108, 1771, 1714, 1682, 1457, 1146 cm^{-1}; ^1H NMR (500 MHz, CD_3OD): δ 7.88 (d, *J* = 8.5 Hz, 2H), 7.81 (d, *J* = 8.5 Hz, 2H), 7.455 (d, *J* = 8.0 Hz, 2H), 7.449 (d, *J* = 8.5 Hz, 2H), 6.96 (d, *J* = 2.0 Hz, 1H), 6.87 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.85 (dd, *J* = 2.5, 1.0 Hz, 1H), 6.84 (d, *J* = 8.5 Hz, 1H), 6.67 (dd, *J* = 3.5, 1.0 Hz, 1H), 6.60 (d, *J* = 1.5 Hz, 1H), 6.11 (dd, *J* = 3.5, 2.5 Hz, 1H), 4.76 (d, *J* = 16.0 Hz, 1H), 4.20 (d, *J* = 11.0 Hz, 1H), 3.99 (d, *J* = 16.5, Hz, 1H), 3.96-3.79 (m, 6H), 3.78 (s, 3H), 3.77 (s, 3H), 3.65-3.61 (m, 4H), 3.60 (dd, *J* = 14.0, 4.5 Hz, 1H), 3.51 (dd, *J* = 10.0, 1.5 Hz, 1H), 3.49 (dd, *J* = 14.0, 5.5 Hz, 1H), 2.60-2.49 (m, 2H), 2.48 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD): δ 174.3, 164.2, 157.6, 155.1, 150.3, 149.9, 147.0, 146.7, 137.5, 136.35, 131.2, 130.9, 129.7, 129.25, 126.7, 123.2, 121.5, 118.8, 112.8, 112.7, 112.6, 111.7, 110.3, 75.0, 61.3, 56.4, 55.0, 52.5, 46.4, 45.4, 45.1, 41.1, 40.9, 38.3, 21.65,

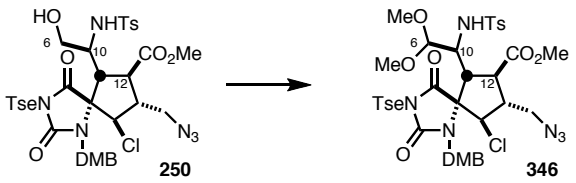
[2] In a separate experiment the two amines were separated and purified *via* preparative HPLC; spectroscopic data (^1H NMR) are reported here, and ^1H NMR spectra are attached below.

21.62; MS (MALDI) calcd for $C_{44}H_{58}ClN_9O_{10}S_2$ $[M+Na]^+$: 984, $[M+K]^+$: 1000; found $[M+Na]^+$: 984, $[M+K]^+$: 1000.

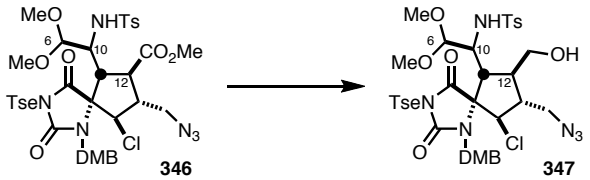
Spectroscopic data for amine **328a** (R = Ts): ^{1}H NMR (500 MHz, CD_3OD): δ 8.49 (br s, 1H), 7.89 (d, *J* = 8.5 Hz, 2H), 7.83 (d, *J* = 8.5 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 2.0 Hz, 1H), 7.00 (app s, 1H), 6.92 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.83 (d, *J* = 8.5 Hz, 1H), 4.83 (d, *J* = 16.0 Hz, 1H), 4.31 (d, *J* = 11.5 Hz, 1H), 4.05 (d, *J* = 16.0 Hz, 1H), 4.04 (app d, *J* = 9.5 Hz, 1H), 3.90-3.80 (m, 5H), 3.782 (s, 3H), 3.778 (s, 3H), 3.67 (dd, *J* = 13.5, 4.0 Hz, 1H), 3.53-3.42 (m, 4H), 3.12 (dd, *J* = 14.0, 4.5 Hz, 1H), 3.03 (dd, *J* = 14.0, 4.5 Hz, 1H), 2.66 (app tt, *J* = 11.0, 3.5 Hz, 1H), 2.50-2.4 (m, 1H, partially overlapping with the next signal), 2.46 (s, 3H), 2.45 (s, 3H), 2.44 (s, 3H).

Spectroscopic data for amine **328b** (R = H): ^{1}H NMR (500 MHz, CD_3OD): δ 8.51 (br s, 1H), 7.93 (d, *J* = 8.5 Hz, 2H), 7.81 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.00 (d, *J* = 2.0 Hz, 1H), 6.91 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.85 (d, *J* = 8.5 Hz, 1H), 6.71 (app s, 1H), 4.78 (d, *J* = 16.5 Hz, 1H), 4.29 (d, *J* = 11.5 Hz, 1H), 4.05-3.97 (m, 3H), 3.97 (d, *J* = 16.5 Hz, 1H), 3.90 (app dt, *J* = 9.0, 6.0 Hz, 1H), 3.82 (dd, *J* = 13.0, 2.5 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.68-3.65 (m, 3H), 3.54 (app dd, *J* = 12.0, 5.5 Hz, 2H), 3.51 (app d, *J* = 9.5 Hz, 1H), 3.23 (dd, *J* = 13.0, 3.5 Hz, 1H), 3.09 (dd, *J* = 13.0, 6.5 Hz, 1H), 2.63 (app tt, *J* = 11.0, 3.5 Hz, 1H), 2.56-2.5 (m, 1H), 2.49 (s, 3H), 2.46 (s, 3H).

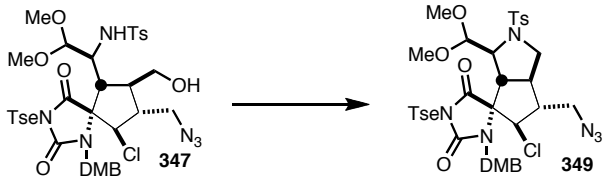
Spectroscopic data for pyrrole **329a**: R_f = 0.59 (EtOAc); ^{1}H NMR (500 MHz, CD_3OD): δ 7.83 (d, *J* = 8.5 Hz, 2H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 2.0 Hz, 1H), 6.98 (app s, 1H), 6.94 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.87 (dd, *J* = 2.5, 1.5 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.60 (app dt, *J* = 4.0, 1.5 Hz, 1H), 6.09 (app t, *J* = 3.0 Hz, 1H), 4.9 (d, *J* = 16.0 Hz, 1H; this signal is completely covered by the H_2O peak from the solvent), 4.24 (d, *J* = 11.0 Hz, 1H), 4.00 (d, *J* = 16.0, Hz, 1H), 3.87-3.63 (m, 5H), 3.781 (s, 3H), 3.778 (s, 3H), 3.72 (app t, *J* = 7.0 Hz, 1H), 3.67 (dd, *J* = 13.0, 2.0 Hz, 1H), 3.51-3.40 (m, 6H), 2.63-2.60 (m, 2H), 2.46 (s, 3H), 2.45 (s, 3H), 2.43 (s, 3H).



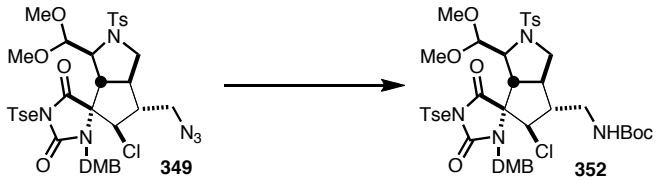
Acetal 346. To a solution of ester **250** (55.5 mg, 0.0655 mmol) in 1.5 mL of CH_2Cl_2 was added Dess-Martin periodinane (45 mg, 0.106 mmol), and the resulting reaction mixture was stirred at 20 °C for 3 h. Upon completion of the reaction as indicated by TLC, anhydrous ether (Et_2O, ~10 mL) was added and the mixture was filtered through a pad of Celite. Removal of solvents *in vacuo* afforded the desired aldehyde. The crude aldehyde was dissolved in 3.0 mL MeOH, and trimethylorthoformate (2.0 mL) was added, followed by a few crystals of *p*-toluenesulfonic acid. The reaction flask was fitted with an air condenser and the mixture was heated to 65 ºC for 4 h then allowed to cool to 20 ºC. A saturated $NaHCO_3$ solution (~ 15 mL) was then added and the resulting mixture was extracted with EtOAc (3 x 15 mL), and the combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (70:30 → 40:60) gave 48.3 mg (83% 2 steps) of acetal **346** as a colorless foam: R_f = 0.58 (70% EtOAc/Hexanes); IR (thin film): 3280, 2931, 2836, 2108, 1774, 1714, 1516, 1451, 1149 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.5 Hz, 2H), 7.01 (d, *J* = 2.0 Hz, 1H), 6.96 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 5.25 (d, *J* = 16.0 Hz, 1H), 4.99-4.96 (m,1H), 4.25 (d, *J* = 16.0 Hz, 1H), 4.16 (d, *J* = 11.5 Hz, 1H), 3.95-3.82 (m, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 3.84 (s, 3H), 3.77 (app t, *J* = 3.0 Hz, 1H), 3.56 (dd, *J* = 13.0, 2.5 Hz, 1H), 3.48-3.38 (m, 5H), 3.15 (s, 3H), 3.13 (app t, *J* = 12.0 Hz, 1H; partially overlapping with the previous signal), 3.03 (s, 3H), 2.47 (s, 3H), 2.45 (s, 3H), 2.38 (app tt, *J* = 11.5, 3.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.0, 172.1, 156.2, 149.2, 148.8, 145.3, 144.0, 137.3, 135.3, 130.1, 129.7, 128.7, 128.2, 127.1, 120.3, 110.85, 110.80, 105.2, 73.5, 59.7, 57.2, 56.5, 55.9, 55.8, 52.81, 52.76, 52.72, 47.5, 46.85, 46.3, 46.05, 45.5, 33.05, 21.7, 21.5; MS (MALDI) calcd for $C_{39}H_{47}ClN_6O_{12}S_2$ $[M+Na]^+$: 913, $[M+K]^+$: 929; found $[M+Na]^+$: 913, $[M+K]^+$: 929.



Alcohol 347. To a solution of acetal **346** (48 mg, 0.0538 mmol) in 2.5 mL of anhydrous THF/MeOH (95:5) cooled to 0 ºC was added $LiBH_4$ (0.16 mL, 0.32 mmol), and the resulting reaction mixture was stirred at 0 °C for 2 h, adding additional reagent every 30 minutes. A saturated solution of NH_4Cl (~10 mL) was then slowly added and the mixture was allowed to warm to 20 ºC while stirring vigorously for 10 minutes. The mixture was then extracted with EtOAc (3 X 15 mL), and the combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (60:40 → 20:80) gave 34.5 mg (74%) of alcohol **347** as a colorless foam: R_f = 0.37 (50% EtOAc/Hexanes); IR (thin film): 3497, 3272, 2937, 2256, 2105, 1770, 1714, 1593, 1451, 1152 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8.5 Hz, 2H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 2.0 Hz, 1H), 6.83 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.62 (app d, *J* = 10.5 Hz, 1H), 5.19 (d, *J* = 16.0 Hz, 1H), 4.12 (d, *J* = 11.5 Hz, 1H), 4.01 (d, *J* = 16.0 Hz, 1H), 3.93 (d, *J* = 3.0 Hz, 1H), 3.93-3.87 (m, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 3.84 (ddd, *J* = 14.0, 5.5, 3.5 Hz, 1H), 3.57-3.51 (m, 2H), 3.49-3.37 (m, 3H), 3.24 (s, 3H), 3.15 (s, 3H), 2.85 (dd, *J* = 11.5, 5.0 Hz, 1H), 2.48-2.45 (m, 1H; signal completely overlapping with the next signal; detected through 2D correlations), 2.47 (s, 3H), 2.42 (s, 3H), 2.13 (app tt, *J* = 11.5, 3.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.0, 156.05, 149.0, 148.6, 145.3, 143.8, 138.2, 135.3, 130.1, 129.8, 128.9, 128.2, 126.9, 120.4, 111.1, 110.7, 106.3, 75.4, 64.7, 59.7, 57.9, 57.1, 55.8, 55.7, 52.8, 52.3, 47.7, 47.3, 45.6, 45.0, 41.2, 32.95, 21.65, 21.5; MS (MALDI) calcd for $C_{38}H_{47}ClN_6O_{11}S_2$ $[M+Na]^+$: 885, $[M+K]^+$: 901; found $[M+Na]^+$: 885, $[M+K]^+$: 901.

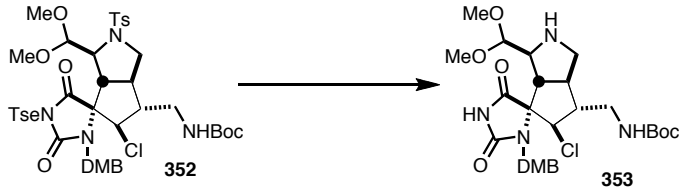


Pyrrolidine 349. To a solution of alcohol **347** (33 mg, 0.0382 mmol) in 3.0 mL of anhydrous CH_2Cl_2 cooled to 0 ºC was added Et_3N (50 µL, 0.35 mmol), followed by MsCl (~ 3 µL, 0.0388 mmol) and the resulting reaction mixture was stirred at 0 °C for 2 h. It was then allowed to warm to 20 ºC and it was stirred for an additional 5.5 h, and then concentrated *in vacuo*. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (70:30 → 50:50) gave 28 mg (87%) of pyrrolidine **349** as a colorless foam: R_f = 0.28 (50% EtOAc/Hexanes); IR (thin film): 2937, 2256, 2105, 1777, 1717, 1593, 1516, 1451 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.87 (d, *J* = 8.5 Hz, 2H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 6.81 (d, *J* = 2.0 Hz, 1H), 6.72 (d, *J* = 8.5 Hz, 1H), 6.16 (dd, *J* = 8.5, 2.0 Hz, 1H), 5.08 (d, *J* = 16.0 Hz, 1H), 4.68 (d, *J* = 2.5 Hz, 1H), 3.95 (app dt, *J* = 14.0, 7.5 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.85-3.78 (m, 2H), 3.83 (d, *J* = 9.5 Hz, 1H), 3.58 (s, 3H), 3.49 (app dt, *J* = 14.0, 7.5 Hz, 1H), 3.43-3.35 (m, 3H), 3.27 (s, 3H), 3.19 (dd, *J* = 15.0, 10.5 Hz, 1H), 3.11 (app t, *J* = 11.0 Hz, 1H); 3.10 (d, *J* = 16.0 Hz, 1H), 2.93 (dd, *J* = 12.5, 6.0 Hz, 1H), 2.49 (s, 3H), 2.47 (s, 3H), 2.02 (dddd, *J* = 11.5, 9.5, 6.0, 3.5 Hz, 1H), 1.40 (dddd, *J* = 15.0, 11.0, 11.0, 6.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 155.8, 149.9, 149.0, 145.2, 144.6, 135.5, 134.5, 130.3, 130.1, 128.8, 128.35, 127.6, 118.8, 110.4, 110.0, 104.8, 69.7, 63.3, 59.4, 58.6, 56.3, 56.2, 55.9, 52.7, 52.5, 50.8, 49.7, 47.1, 45.6, 44.4, 33.1, 21.70, 21.68; MS (MALDI) calcd for $C_{38}H_{45}ClN_6O_{10}S_2$ $[M+Na]^+$: 867, $[M+K]^+$: 883; found $[M+Na]^+$: 867, $[M+K]^+$: 883.



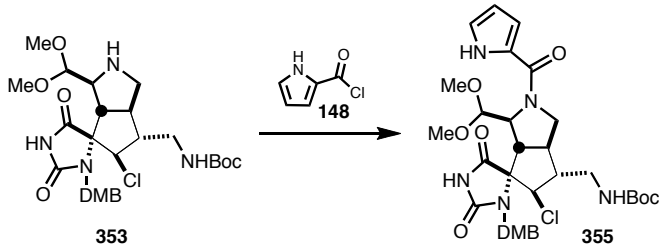
Boc-amine 352. To a solution of pyrrolidine **349** (28 mg, 0.0331 mmol) in 3.0 mL of anhydrous THF cooled to 0 ºC was added trimethylphosphine (1M in THF, ~50 µL, 0.05 mmol) drop-wise and the mixture was stirred at 0 ºC for 1.5 h. Water (~ 100 µL) was

added and the mixture was allowed to warm to 20 ºC and stirred for an additional 2 h, then concentrated *in vacuo*. The crude material was dissolved in ~ 0.5 mL of HPLC grade benzene and it was reconcentrated, then dried under vacuum. The crude dry material was then dissolved in 3.0 mL of CH_2Cl_2 and Boc_2O (xs) was added in one portion. After stirring at 20 ºC for 1 h, the mixture was concentrated *in vacuo* to afford a clear oil. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (80:20 → 50:50) gave 24 mg (80%) of Boc-amine **352** as a colorless foam: R_f = 0.29 (40% EtOAc/Hexanes, 4 elutions); IR (thin film): 3390, 2934, 1777, 1720, 1593, 1516, 1454, 1158 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.87 (d, *J* = 8.5 Hz, 2H), 7.84 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 6.76 (d, *J* = 8.5 Hz, 1H), 6.74 (app s, 1H), 6.23 (app d, *J* = 7.0 Hz, 1H), 4.95 (d, *J* = 16.0 Hz, 1H), 4.67 (d, *J* = 1.5 Hz, 1H), 4.47 (app dd, *J* = 8.0, 5.5 Hz, 1H), 3.98-3.90 (m, 2H), 3.88 (s, 6H), 3.86 (app d *J* = 7.0 Hz, 1H), 3.84-3.76 (m, 2H), 3.65 (d, *J* = 10.0 Hz, 1H), 3.58 (s, 3H), 3.47 (app dt, *J* = 14.5, 7.5 Hz, 1H), 3.37 (app dt, *J* = 14.5, 7.5 Hz, 1H), 3.24 (s, 3H), 3.13 (dd, *J* = 15.0, 10.5 Hz, 1H); 3.11 (app t, *J* = 11.0 Hz, 1H), 2.96-2.80 (m, 2H), 2.86 (d, *J* = 16.0 Hz, 1H), 2.46 (s, 3H), 2.43 (s, 3H), 1.85 (app dq, *J* = 10.0, 3.5 Hz, 1H), 1.54 (s, 9H), 1.50-1.45 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 156.2, 155.7, 149.8, 148.9, 145.2, 144.3, 135.5, 134.4, 130.2, 130.0, 129.1, 128.4, 128.0, 118.8, 110.8, 109.9, 104.9, 79.9, 70.0, 64.4, 59.5, 58.2, 56.18, 56.15, 55.9, 52.75, 51.7, 49.7, 47.5, 44.1, 40.4. 33.1, 28.5, 21.69, 21.66; MS (MALDI) calcd for $C_{43}H_{55}ClN_4O_{10}S_2$ $[M+Na]^+$: 941; found $[M+Na]^+$: 941.



Pyrrolidine 353. To a stirred solution of Boc-amine **352** (16.9 mg, 0.0184 mmol) in 1.0 mL of anhydrous THF cooled to -78 ºC was added freshly prepared sodium

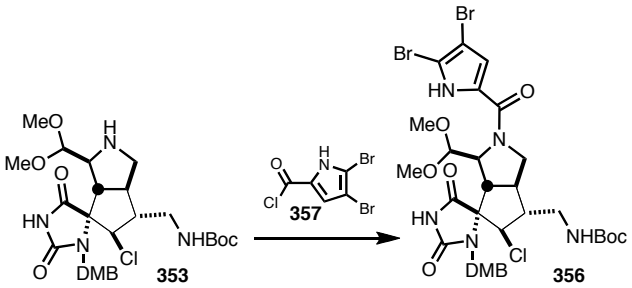
naphthalenide (1M in THF) [3] drop-wise until the completion of the reaction as indicated by the persistence of the deep dark color of the reagent solution. PH 7 buffer solution (~ 4 mL) was then added and the mixture was allowed to warm to 20 ºC with vigorous stirring. The mixture was then extracted with EtOAc (3 X 8 mL; the aqueous layer was saturated with solid NaCl before the last extraction) and the combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (80:20 → 40:60) and then with MeOH/EtOAc (15:85) gave 8.4 mg (78%) of pyrrolidine **353** and 3.8 mg (22%) of unreacted Boc-amine **352**. Resubjecting the latter to the reaction conditions provided additional pyrrolidine **353** (0.6 mg, overall yield 84%) as a colorless foam; IR (thin film): 3423, 2934, 1771, 1717, 1646, 1513, 1259, 1161 cm^{-1}; ^1H NMR (500 MHz, CD_3OD): δ 7.02 (br s, 1H), 6.94 (br s, 2H), 4.75 (d, *J* = 16.5 Hz, 1H), 4.47 (d, *J* = 16.0 Hz, 1H), 4.25 (d, *J* = 10.5 Hz, 1H), 4.05 (d, *J* = 7.5 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.29 (s, 3H), 3.21 (s, 3H), 3.18 (dd *J* = 14.5, 3.5 Hz, 1H), 3.10 (dd *J* = 10.5, 6.5 Hz, 1H), 2.99 (dd, *J* = 14.5, 8.5 Hz, 1H), 2.90 (dd, *J* = 11.0, 7.5 Hz, 1H), 2.61 (dd, *J* = 14.5, 11.0 Hz, 1H), 2.56 (app t, *J* = 10.5 Hz, 1H), 2.25-2.18 (m, 1H), 2.06-1.96 (m, 1H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.2, 156.3, 156.0, 149.6, 148.7, 129.7, 119.4, 111.0, 110.2, 107.0, 79.7, 71.75, 65.8, 57.8, 55.87, 55.85, 55.5, 54.1, 53.3, 49.7, 49.0, 46.4, 44.25, 40.0, 28.35; MS (MALDI) calcd for $C_{27}H_{39}ClN_4O_8$ $[M+H]^+$: 583; found $[M+H]^+$: 583.



Pyrrole 355. To a stirred solution of pyrrolidine **353** (3.8 mg, 0.00652 mmol) and acyl chloride **148** (1.6 mg, 0.0124 mmol) in 0.8 mL of anhydrous CH_2Cl_2 at 0 ºC was added

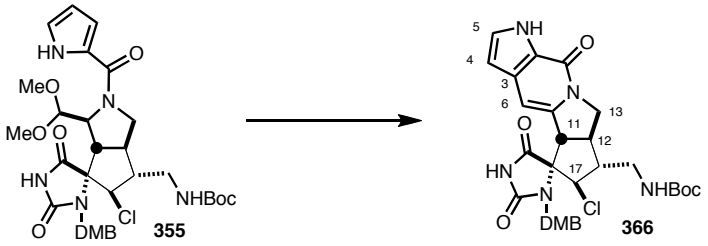
[3] Preparation: 128 mg of naphthalene were dissolved in 1 mL of anhydrous THF at 20 ºC and 3 small pieces of sodium metal (washed with hexanes) were added in one portion. The mixture was stirred for 1 h at 20 ºC during which time a deep dark color developed. The solution (1 M) was used directly.

Et_3N (~ 5 µL, 0.0353 mmol) and the resulting mixture was stirred at 20 ºC for 4.5 h, then it was concentrated *in vacuo*. The procedure was repeated on 4.4 mg (0.00755 mmol) of **353** (with 2.2 mg, 0.0170 mmol of **148**) and the crude materials were combined Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (80:20 → 0:100) gave 5.9 mg (76% overall) of pyrrole **355**; Rf 0.39 (EtOAc); IR (thin film): 3369, 3275. 2931, 1771, 1720, 1593, 1516, 1436 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6): δ 10.62 (br s, 1H), 7.05 (br s, 1H), 6.99 (dt, *J* = 2.5, 1.5 Hz, 1H), 6.94 (app d, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 6.57 (br s, 1H), 6.23 (app t, *J* = 6.0 Hz, 1H), 6.20 (dd, *J* = 6.0, 2.5 Hz, 1H), 4.96 (d, *J* = 16.0 Hz, 1H), 4.91 (br s, 1H), 4.41 (d, *J* = 16.0 Hz, 1H), 4.24 (dd, *J* = 9.0, 6.5 Hz, 1H), 4.21 (d, *J* = 10.0 Hz, 1H), 4.00 (dd, *J* = 11.0, 2.5 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.40 (t, *J* = 9.5 Hz, 1H), 3.31 (s, 3H), 3.29 (s, 3H), 3.26-3.22 (m, 1H), 3.18 (dd *J* = 14.5, 11.0 Hz, 1H), 3.02 (app dt *J* = 14.0, 8.0 Hz, 1H), 2.32-2.24 (m, 1H), 2.22-2.16 (m, 1H), 1.36 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.7, 162.1, 156.2, 156.0, 149.65, 148.8, 129.6, 124.7, 123.6, 121.8, 119.1, 113.3, 111.2, 110.0, 109.9, 102.4, 79.9, 72.1, 65.0, 58.6, 57.6, 56.1, 55.9, 51.8, 49.5, 46.95, 44.5, 40.2, 29.7, 28.3; MS (MALDI) calcd for $C_{32}H_{42}ClN_5O_9$ $[M+H]^+$: 676, $[M+Na]^+$: 698, $[M+K]^+$: 714; found $[M+H]^+$: 676, $[M+Na]^+$: 698, $[M+K]^+$: 714.



Dibromoyrrole 356. To a stirred solution of pyrrolidine **353** (8.4 mg, 0.0144 mmol) in 1.0 mL of anhydrous CH_2Cl_2 at 0 ºC was added acyl chloride **357** (7.8 mg, 0.027 mmol) as a solution in 0.1 mL of CH_2Cl_2, followed by Et_3N (~ 10 µL, 0.0707 mmol) and the resulting mixture was stirred at 20 ºC for 0.5 h, then it was concentrated *in vacuo*. Purification by flash chromatography on SiO_2 eluting with hexanes/EtOAc (80:20 → 0:100) and then with MeOH/EtOAc (15:85) gave a semi-pure material (not quantified). Further purification by preparative TLC (60% EtOAc/Hexanes, 6 elutions, Rf 0.50), gave

pure dibromopyrrole **356** (yield not determined); Rf 0.50 (60% EtOAc/Hexanes, 6 elutions); IR (thin film): 3177, 2928, 1771, 1717, 1593, 1513, 1436 cm^{-1}; ^1H NMR (500 MHz, CD_3OD): δ 7.00 (br s, 1H), 6.97 (app d, *J* = 8.0 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 6.65 (br s, 1H), 4.82 (d, *J* = 16.5 Hz, 1H), 4.41 (d, *J* = 16.5 Hz, 1H), 4.16 (d, *J* = 10.0 Hz, 1H), 4.02 (dd, *J* = 9.0, 6.0 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.75 (dd, *J* = 11.5, 2.5 Hz, 1H), 3.39 (app t, *J* = 10.0 Hz, 1H), 3.35 (s, 3H), 3.34 (s, 3H), 3.15-3.09 (m, 2H), 3.00 (dd *J* = 14.0, 9.5 Hz, 1H), 2.20-2.06 (m, 2H), 1.36 (s, 9H); ^{13}C NMR (125 MHz, CD_3OD): δ 174.5, 162.2, 159.2, 158.55, 150.8, 150.3, 131.9, 127.9, 121.2, 116.9, 113.1, 112.1, 106.8, 103.9, 100.0, 80.4, 73.8, 66.4, 58.7, 58.5, 56.43, 56.39, 55.7, 55.4, 51.2, 48.0, 44.7, 41.4, 28.8; MS (MALDI) calcd for $C_{32}H_{40}Br_2ClN_5O_9$ $[M+Na]^+$: 854; found $[M+Na]^+$: 854.



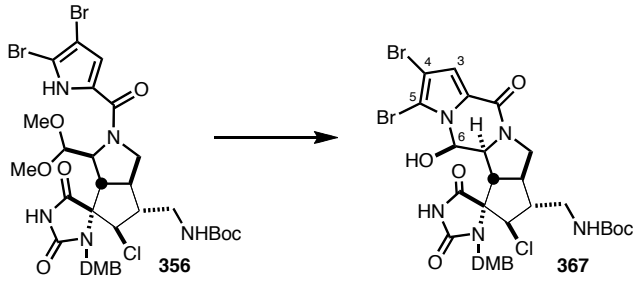
Enamine 366. To a stirred solution of pyrrole **355** (3.0 mg, 0.00444 mmol) in 0.8 mL of acetone at 20 ºC was added *p*-toluenesulfonic acid (a few small crystals) and the mixture was heated to 50 ºC for 2.5 h, then it was allowed to cool to 20 ºC. A satirated solution of $NaHCO_3$ was then added (~ 1 mL) and the organic solvent was evaporated under a flow of nitrogen. The aqueous residue was extracted with EtOAc (3 X 5 mL) and the combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by preparative TLC (30% EtOAc/Hexanes 3 elutions, 50% EtOAc/Hexanes 2 elutions, 100% EtOAc 2 elutions; Rf 0.20), gave pure enamine **366** (yield not determined). ; Rf 0.14 (60% EtOAc/Hexanes, 6 elutions); ^1H NMR (500 MHz, CD_3OD): δ 7.25 (d, *J* = 2.7 Hz, 1H), 6.92 (d, *J* = 2.0 Hz, 1H), 6.75 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.62 (d, *J* = 8.5 Hz, 1H), 6.25 (d, *J* = 2.7 Hz, 1H), 6.01 (d, *J* = 1.5 Hz, 1H), 4.58 (dd, *J* = 10.5, 6.5 Hz, 1H), 4.57 (d, *J* = 16.0 Hz, 1H), 4.42 (d, *J* = 16.0 Hz, 1H), 4.35 (d, *J* = 9.5 Hz, 1H), 3.86 (dd, *J* = 15.0, 1.5 Hz, 1H), 3.77 (s, 3H), 3.62 (s, 3H), 3.55 (app. t, *J* = 10.5 Hz, 1H), 3.31 (this signal is completely covered by the solvent peak but is identified through 2D

correlation, 1H), 3.08 (dd, J = 14.0, 8.0 Hz, 1H), 2.59 (dddd, J = 15.0, 10.5, 10.0, 6.5 Hz, 1H), 2.39-2.30 (m, 1H), 1.49 (s, 9H); MS (MALDI) calcd for $C_{30}H_{34}ClN_5O_7$ $[M+H]^+$: 612, $[M+Na]^+$: 634; found $[M+H]^+$: 612, $[M+Na]^+$: 634.

Coupling constant comparison with values reported originally for styloguanidine

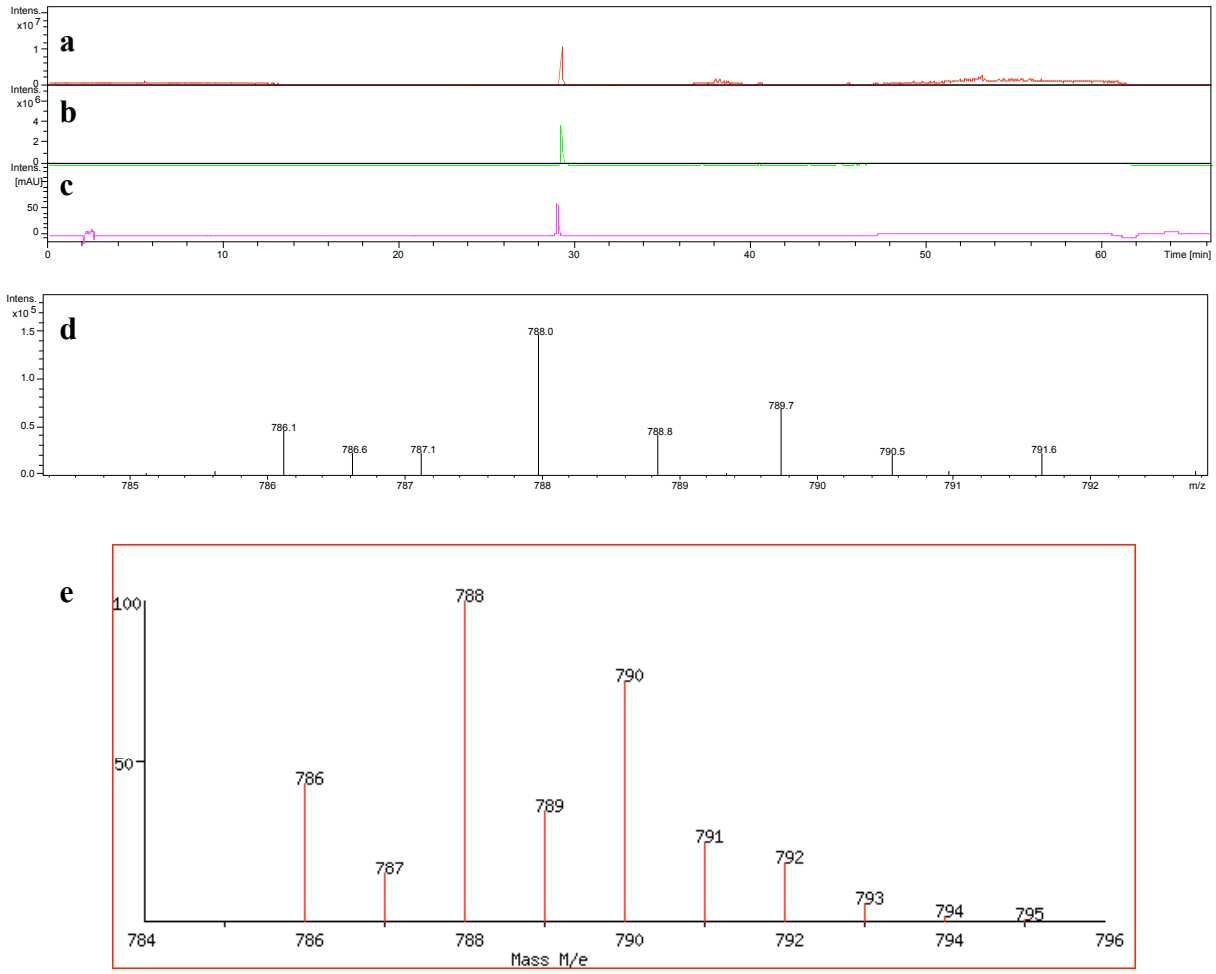
Proton	**366** mult (J)[a]	**styloguanidine** mult (J)[a]
4	d (2.7)	d (2.7)
5	d (2.7)	d (2.7)
6	d (1.5)	s
11	dd (15.0, 1.5)	d (14.2)
12		m[b]
	dddd (15.0, 10.5, 10.5, 6.0)	dddd (14.6, 10.2, 9.0, 7.2)[c]
13	dd (10.5, 6.5)	dd (10.4, 7.2)
13	d (10.5)	d (10.4)
17	d (9.5)	d (8.3)

a = values are in Hertz. b = originally reported multiplicity. [65] c = as reported by Quinn for palau'amine. [3b]

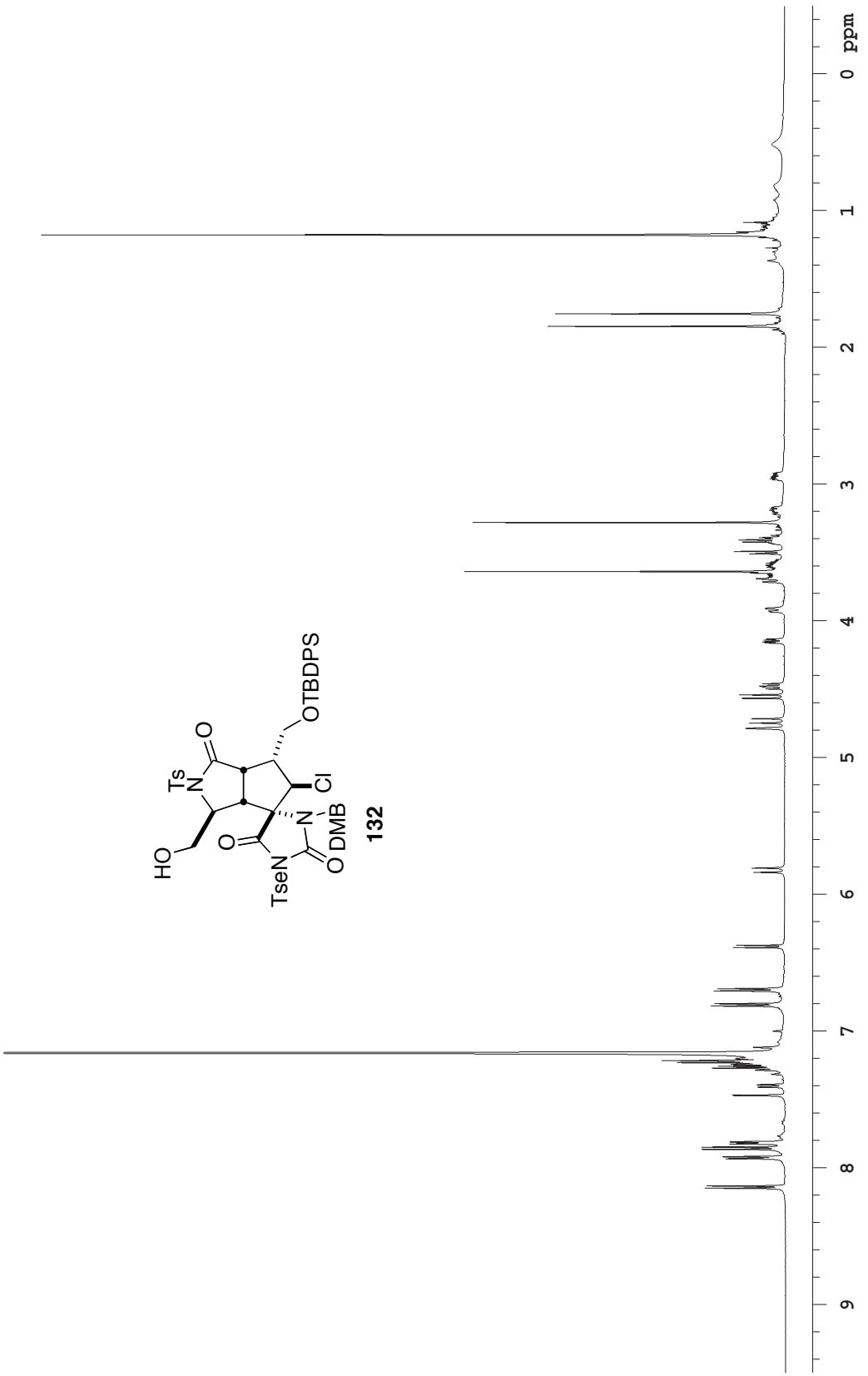


Carbinolamine 367. To a stirred solution of dibromopyrrole **356** (not quantified) in 1 mL of acetone at 20 ºC was added *p*-toluenesulfonic acid (a few small crystals) and the mixture was heated to 50 ºC for 4 h, then it was allowed to cool to ambient temperature. A satirated solution of $NaHCO_3$ was then added (~ 1 mL) and the organic solvent was evaporated under a flow of nitrogen. The aqueous residue was extracted with EtOAc (3 X 5 mL) and the combined organic phase was dried over $MgSO_4$, filtered and concentrated

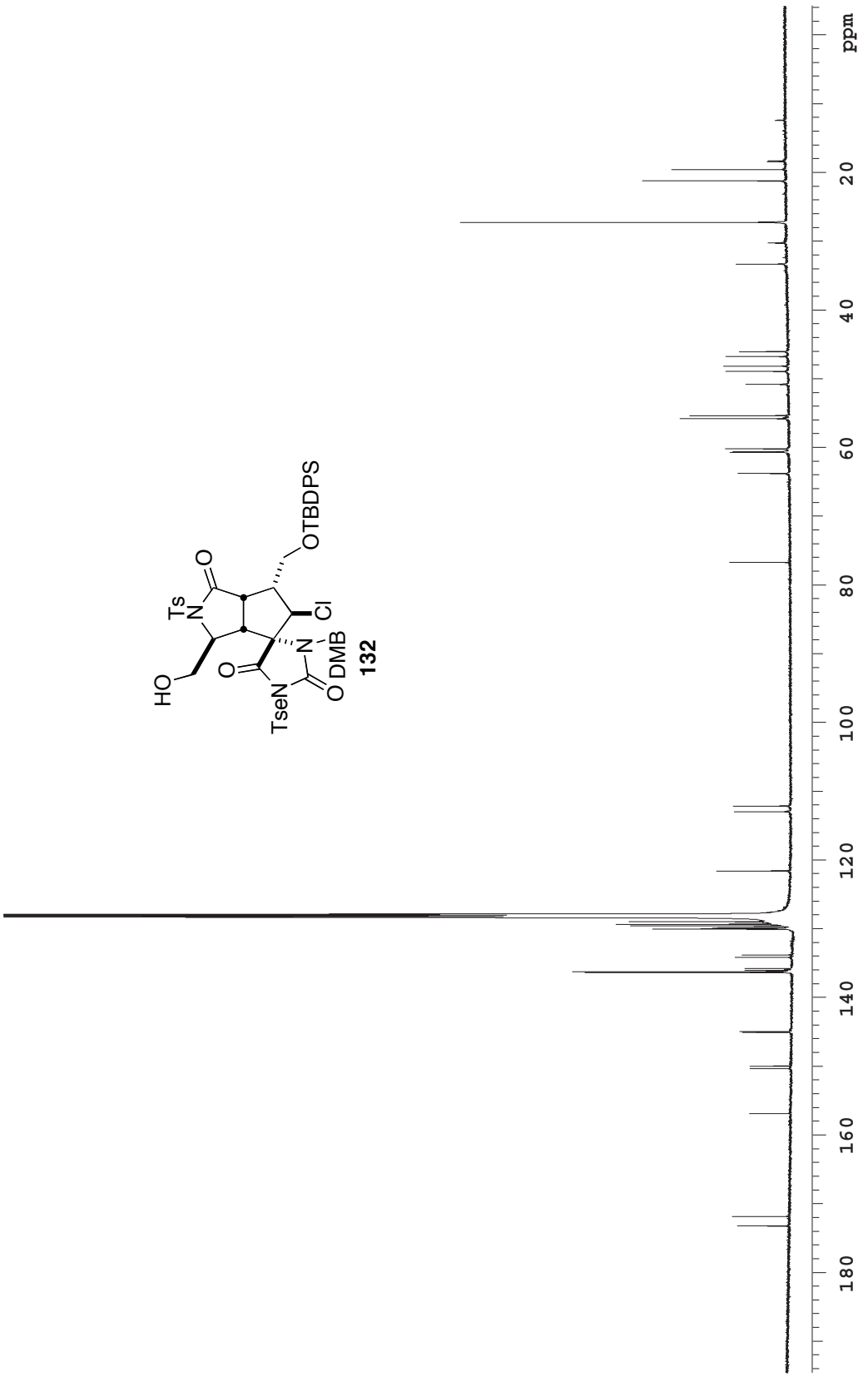
in vacuo. Purification by preparative TLC (60% EtOAc/Hexanes 6 elutions) gave carbinolamine **367** (Rf 0.6; yield not determined) and recovered dibromopyrrole **356** (Rf 0.5; yield not determined); LC/MS data are reported below.



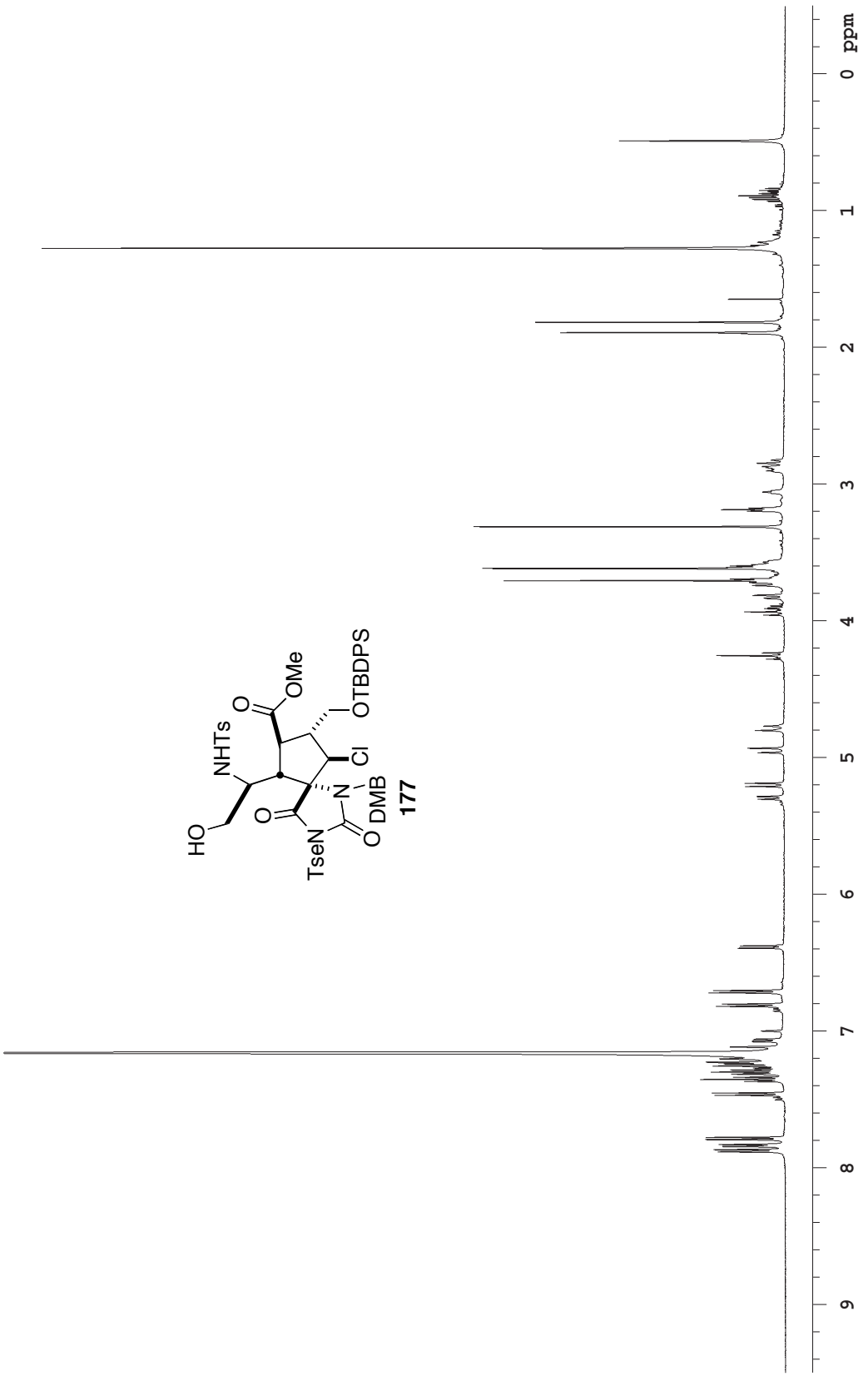
a) Total ion count b) mass (positive mode) c) HPLC trace d) observed M+H cluster and e) predicted M+H cluster for carbinolamine **367**



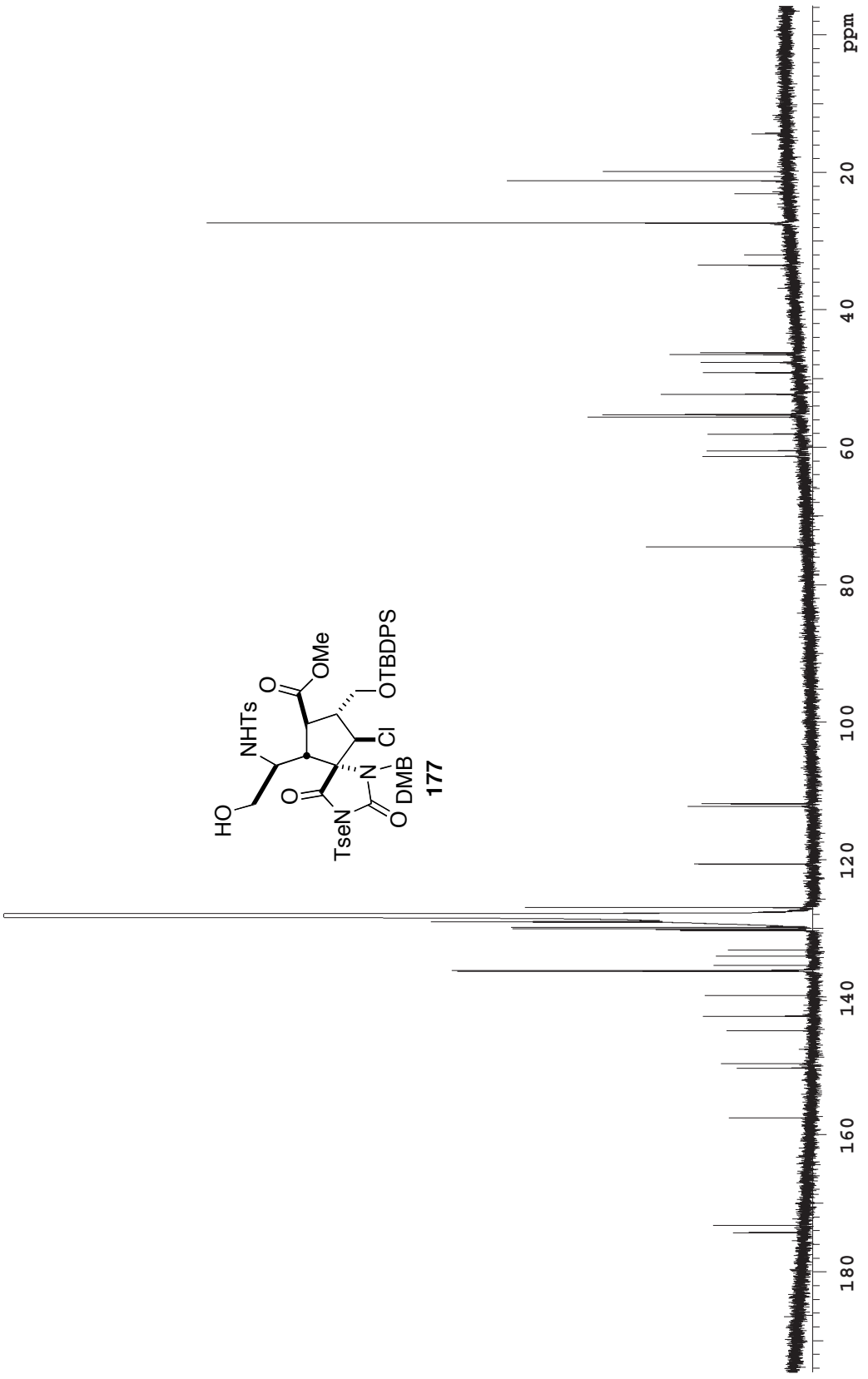
^{1}H NMR spectrum of alcohol **132** (in benzene-d_6)



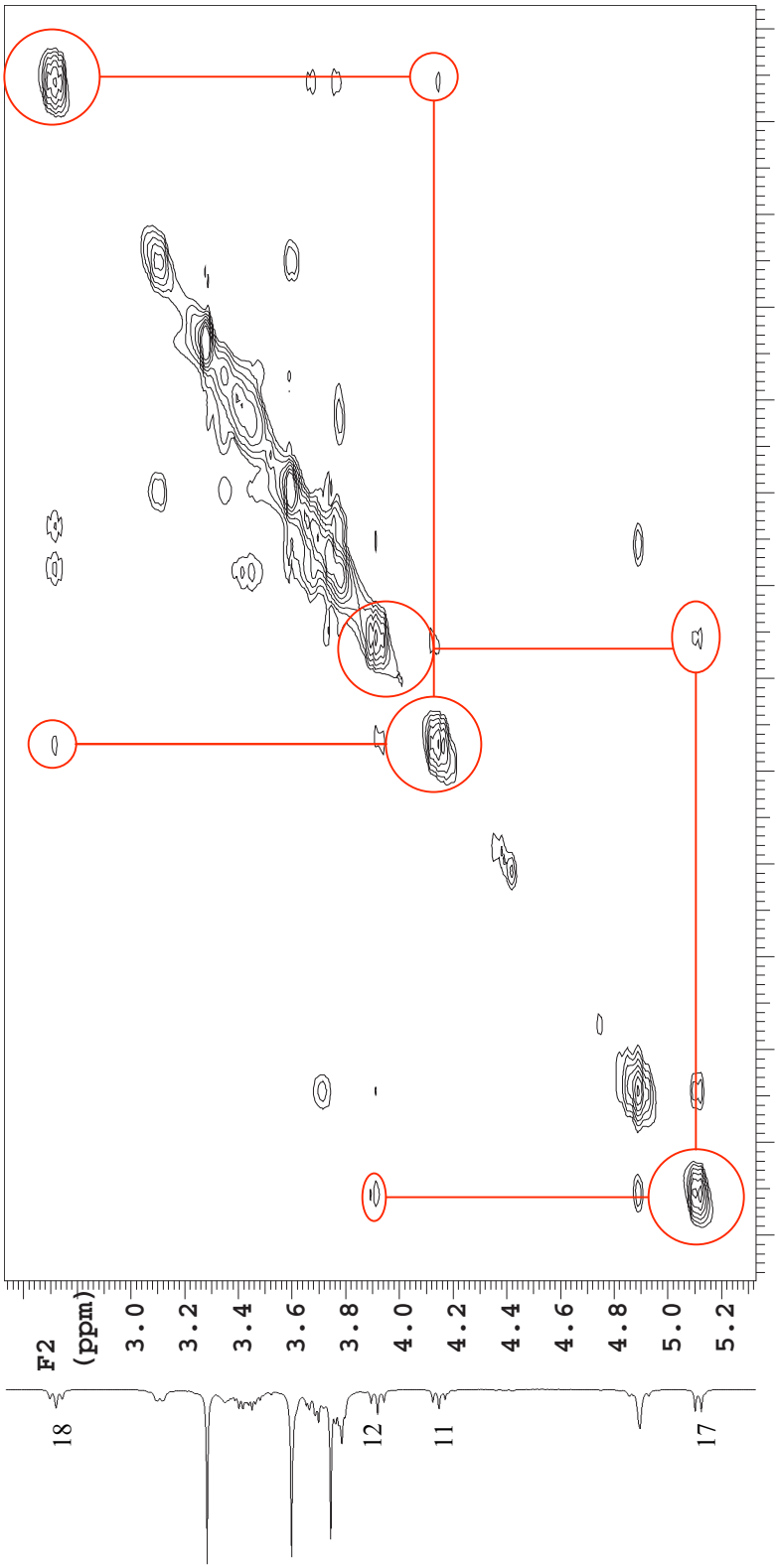
^{13}C NMR spectrum of alcohol **132** (in benzene-d_6)



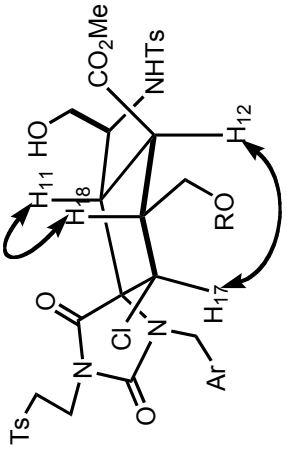
^{1}H NMR spectrum of ester **177** (in benzene-d_6)



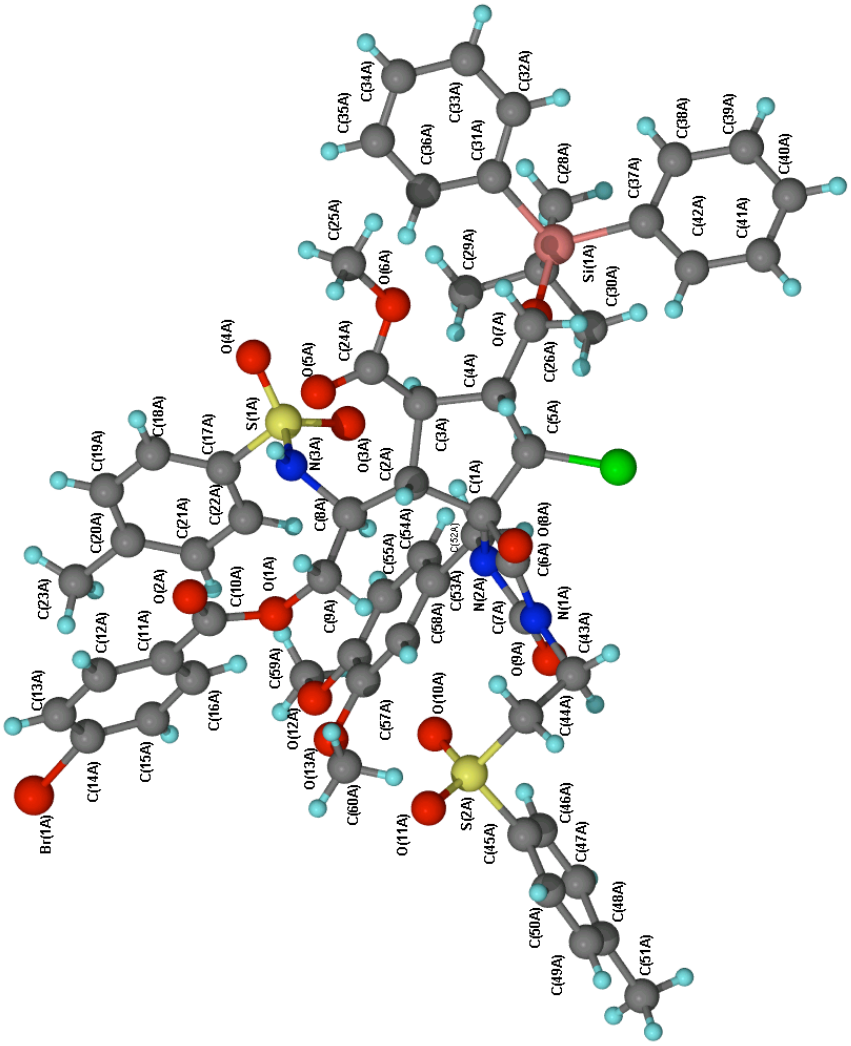
^{13}C NMR spectrum of ester **177** (in benzene-d_6)



2D NOESY spectrum of ester **177** (expansion; in benzene-d_6)



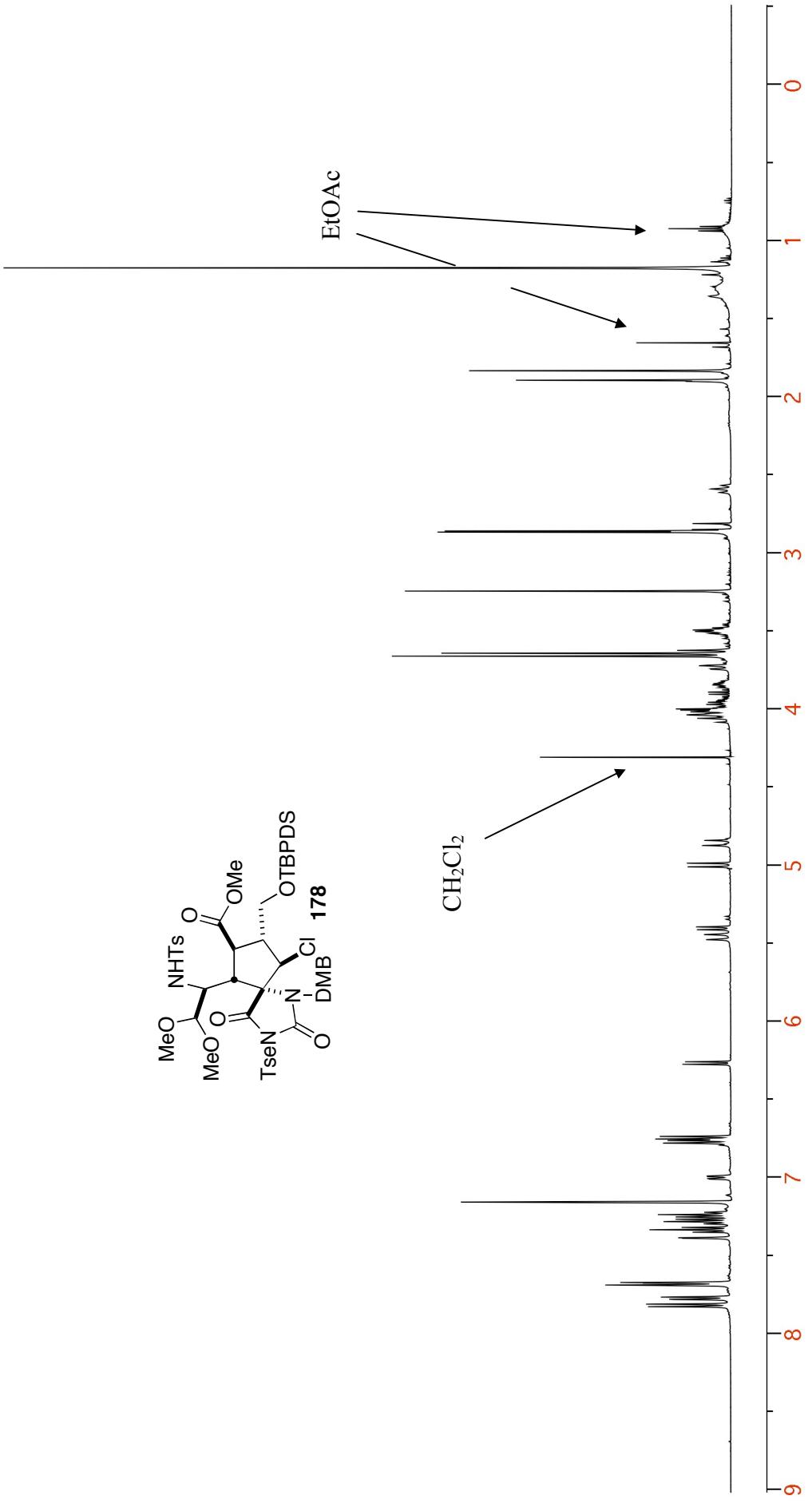
Ester **177** (R = TBDPS)



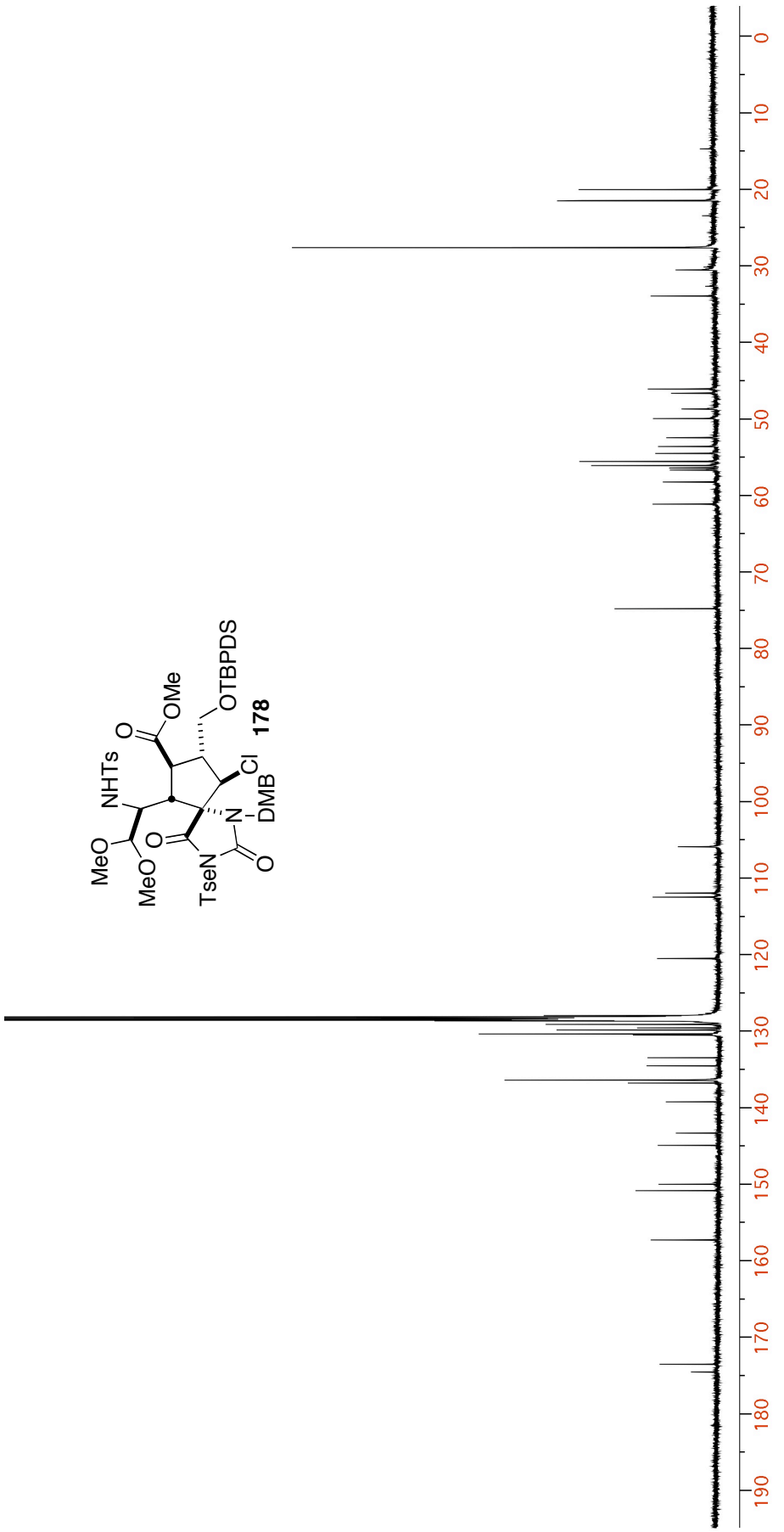
X-ray Crystal structure of bromobenzoate ester **184**

Table 1. Crystal data and structure refinement for ester **184**

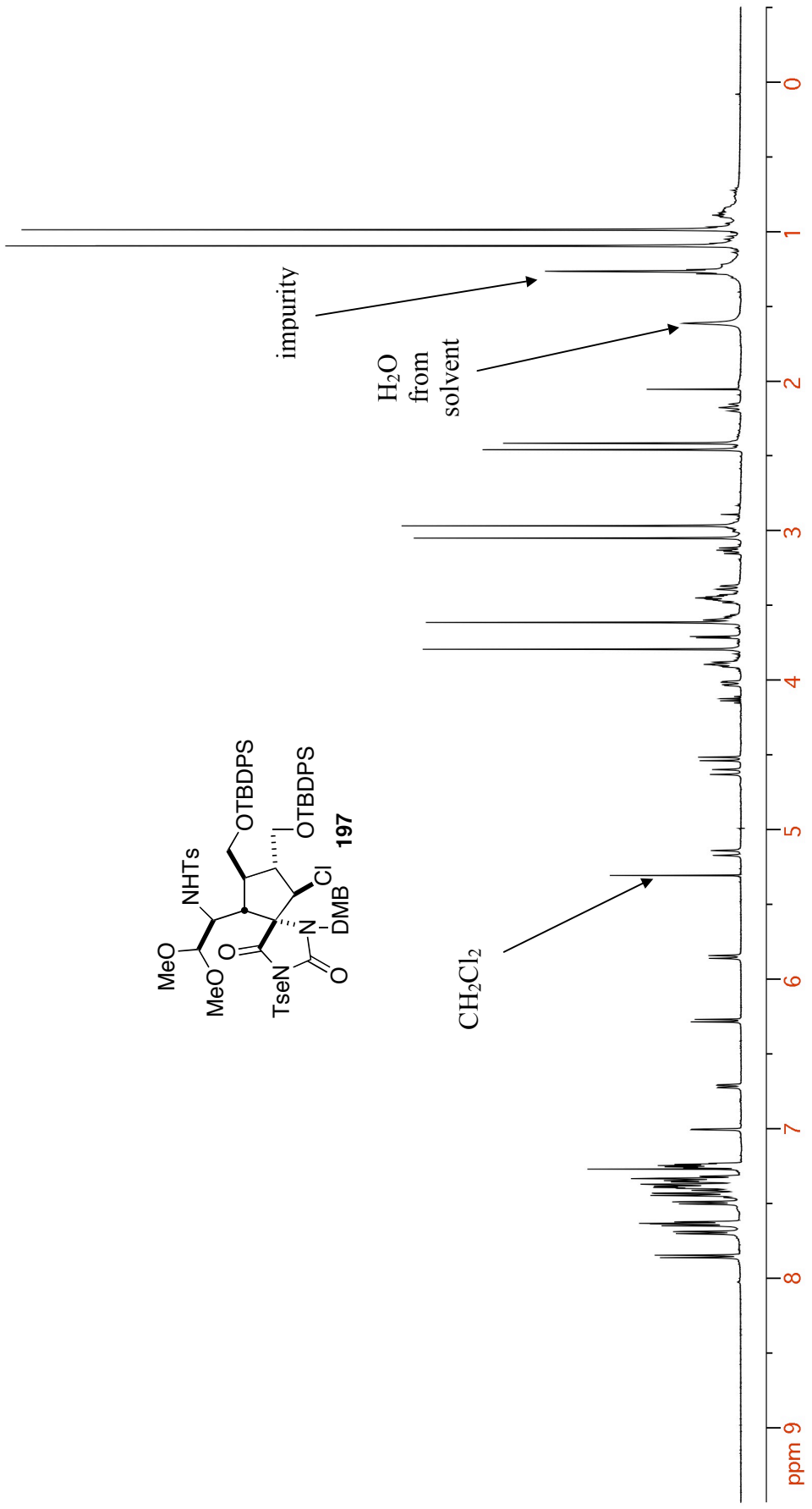
Identification code	dr68	
Empirical formula	C_{60} H_{65} Br Cl N_3 O_{13} S_2 Si	
Formula weight	1243.72	
Temperature	110(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 12.230(3) Å	α= 90°.
	b = 30.116(7) Å	β= 96.462(13)°.
	c = 33.616(9) Å	γ = 90°.
Volume	12303(5) $Å^3$	
Z	8	
Density (calculated)	1.343 Mg/m^3	
Absorption coefficient	2.657 mm^{-1}	
F(000)	5184	
Crystal size	0.20 x 0.10 x 0.01 mm^3	
Theta range for data collection	3.03 to 60.00°.	
Index ranges	-13<=h<=13, -33<=k<=33, -37<=l<=37	
Reflections collected	94122	
Independent reflections	17537 [R(int) = 0.2192]	
Completeness to theta = 60.00°	95.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9739 and 0.6186	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	17537 / 0 / 1476	
Goodness-of-fit on F^2	1.000	
Final R indices [I>2sigma(I)]	R1 = 0.0685, wR2 = 0.1255	
R indices (all data)	R1 = 0.1840, wR2 = 0.1688	
Extinction coefficient	0.00032(2)	
Largest diff. peak and hole	0.650 and -0.437 $e.Å^{-3}$	



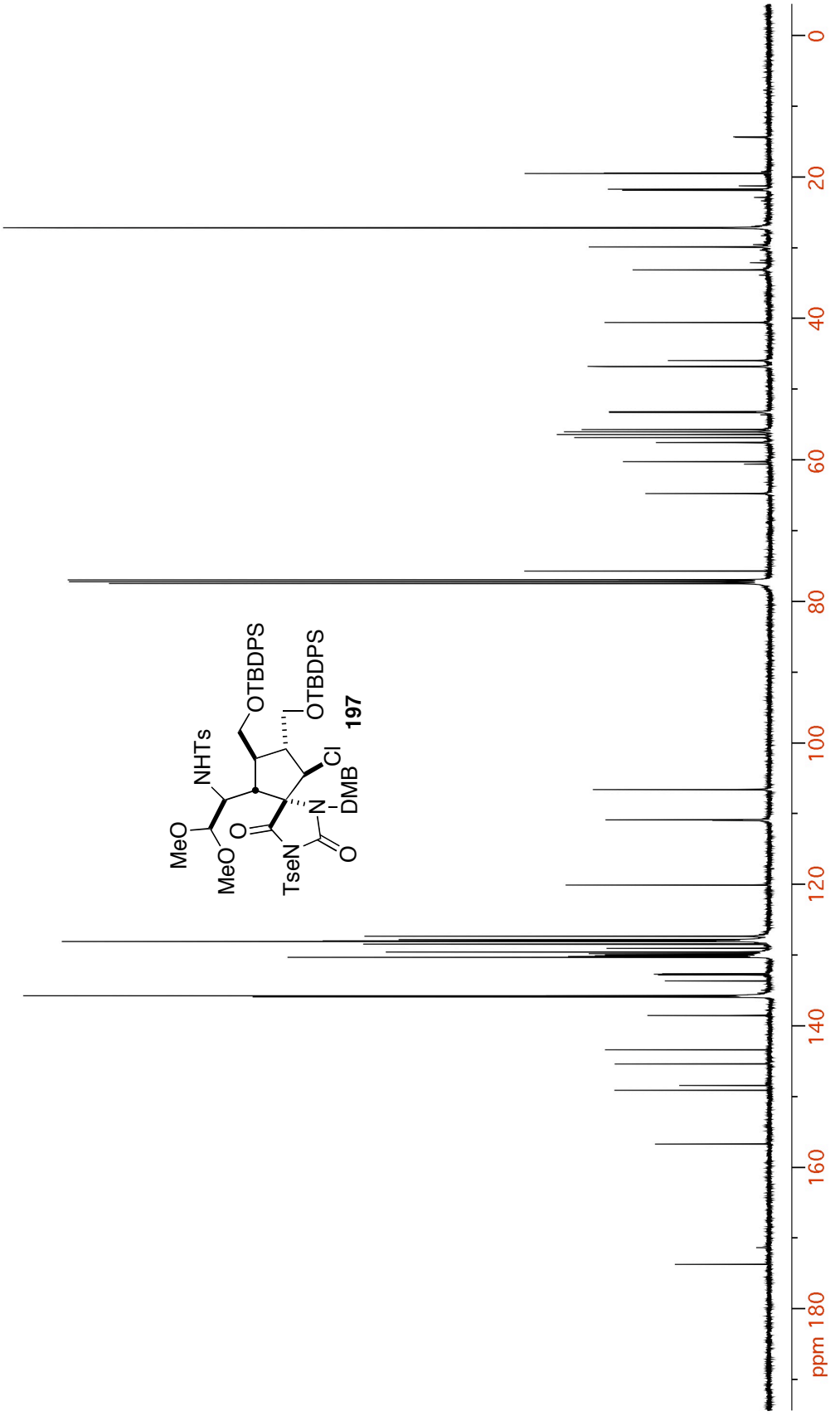
^{1}H NMR spectrum of dimethyl acetal **178** (in benzene-d_6)



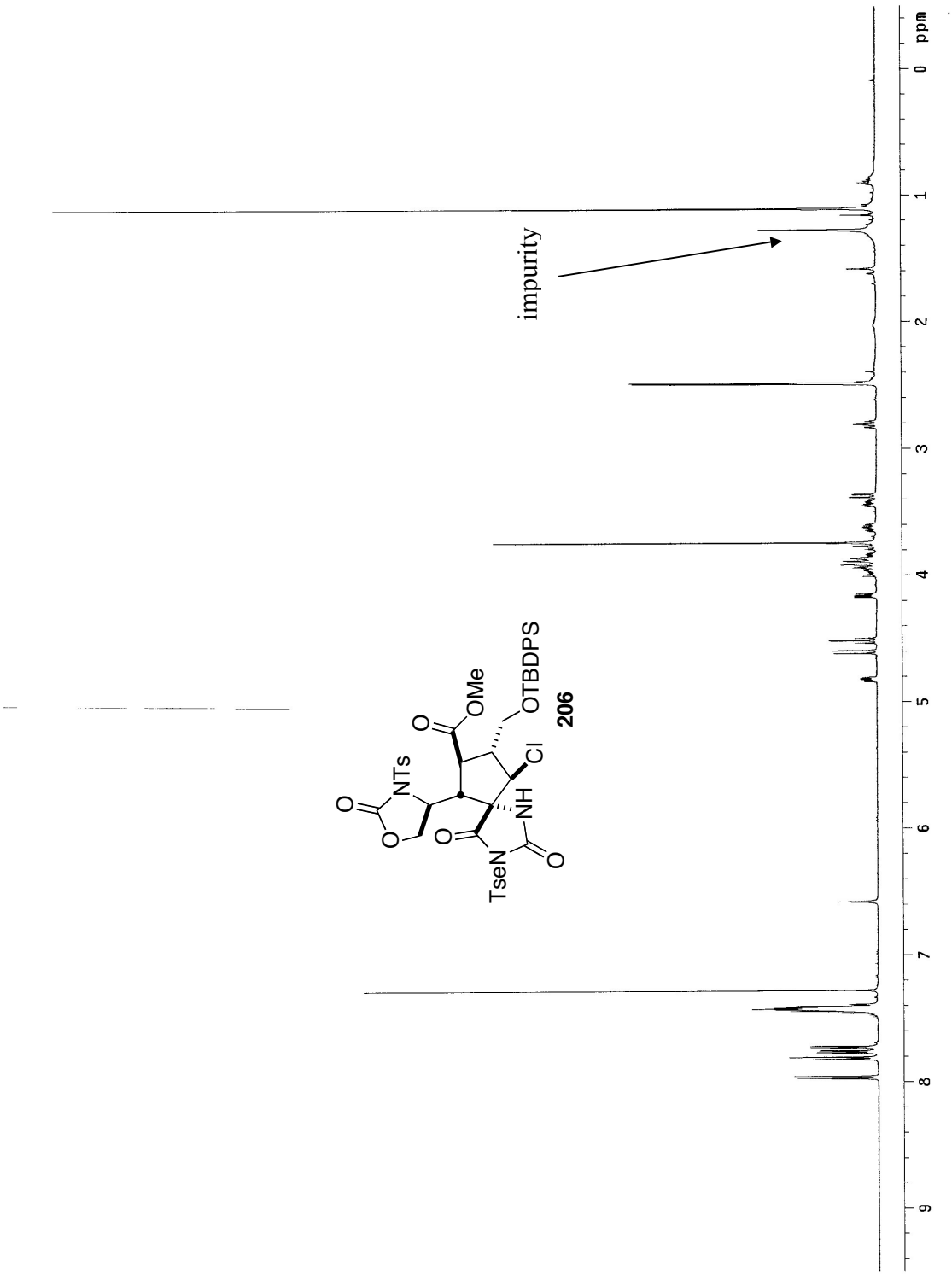
^{13}CNMR spectrum of dimethyl acetal **178** (in benzene-d_6)



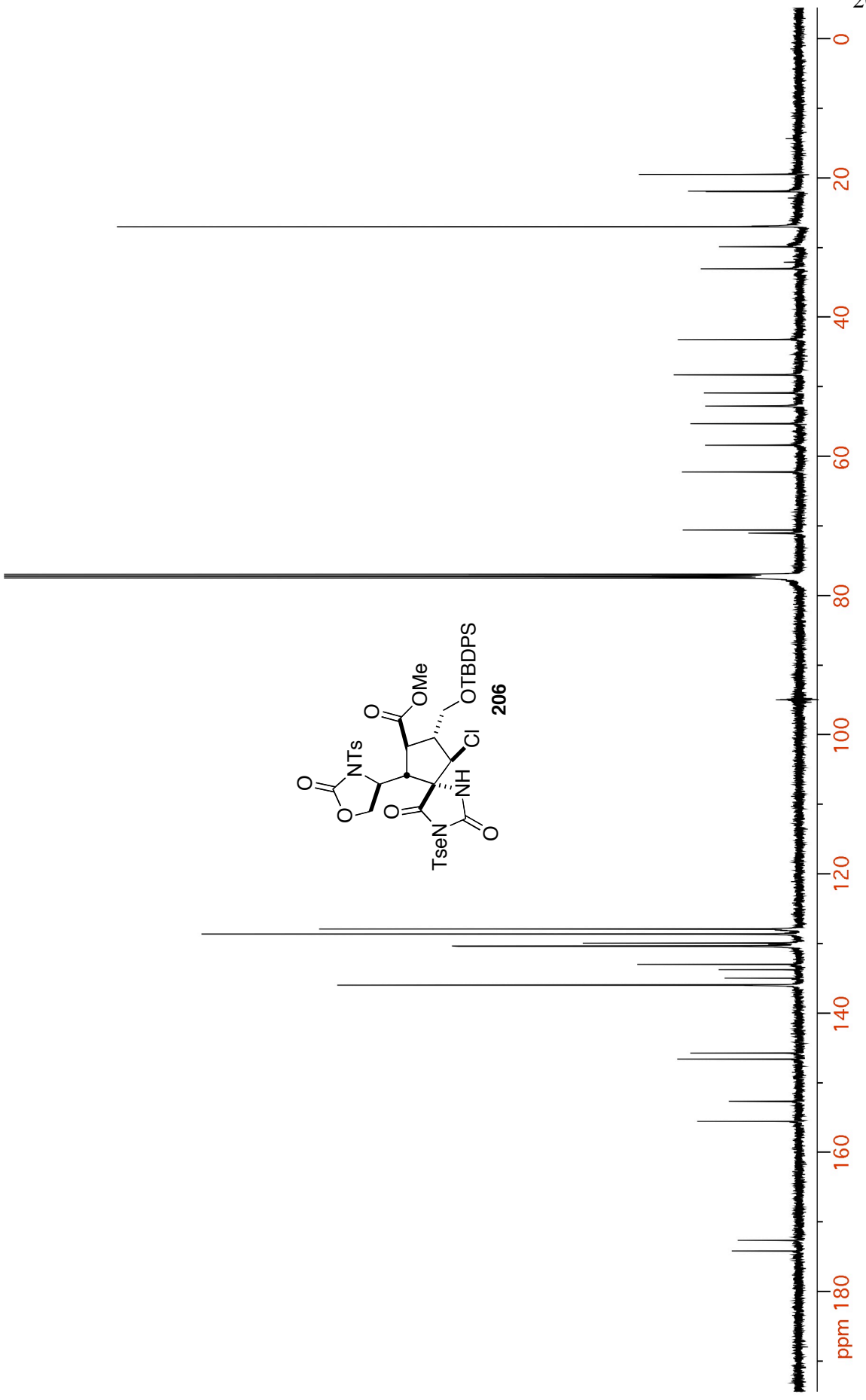
^{1}H NMR spectrum of bi-silylether **197** (in $CDCl_3$)



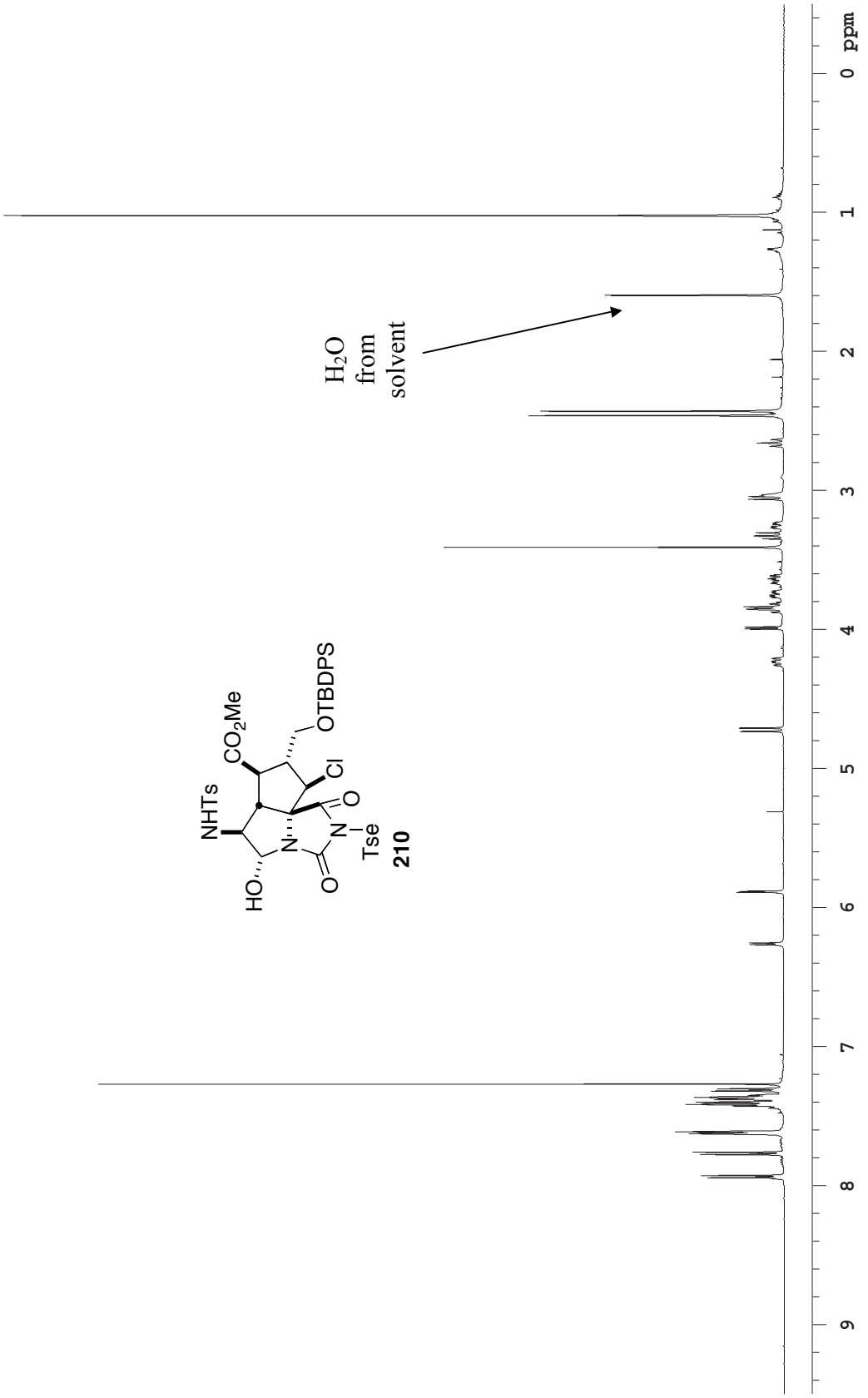
^{13}C NMR spectrum of bi-silylether **197** (in $CDCl_3$)



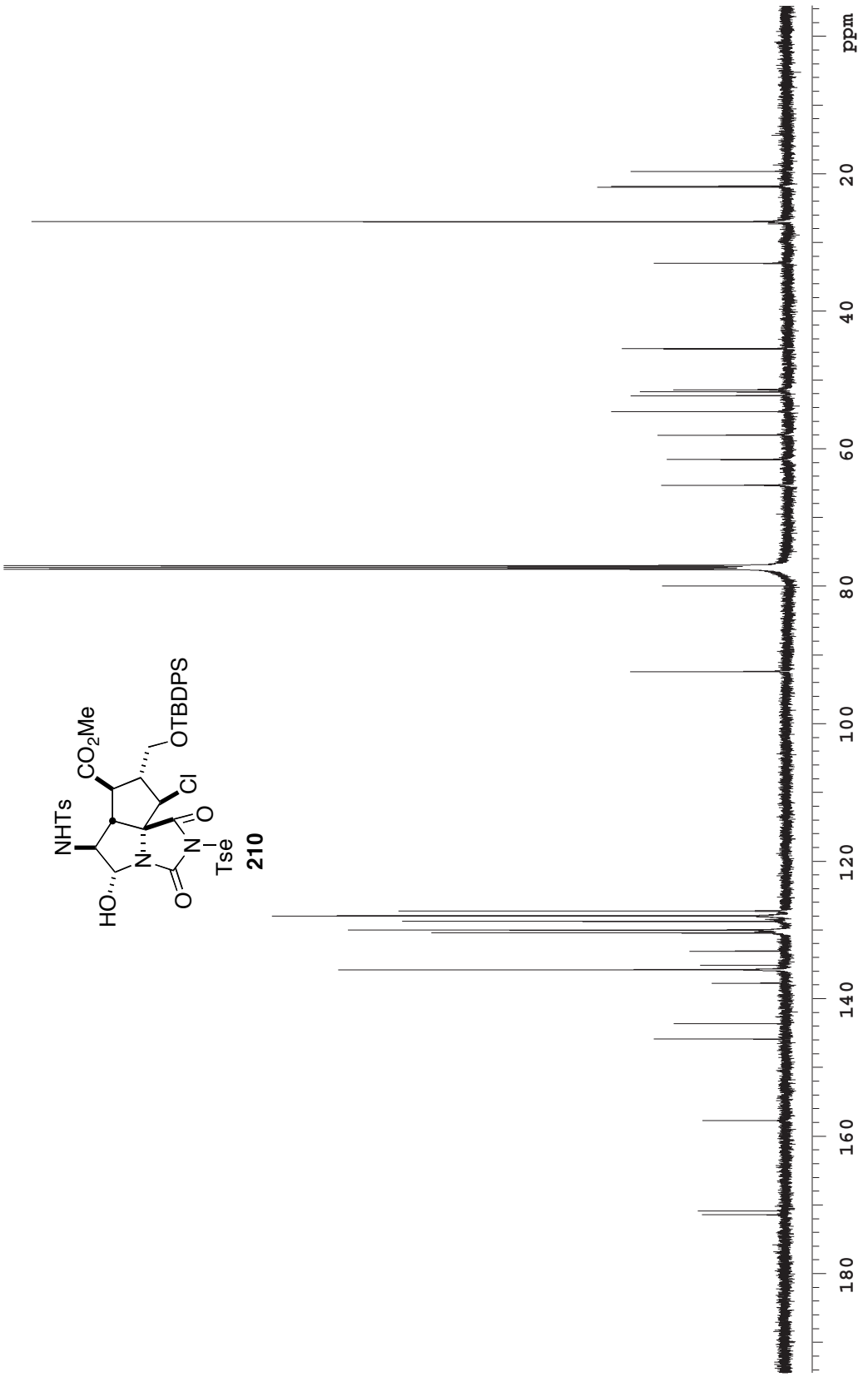
^{1}H NMR spectrum of oxazolidinone **206** (in $CDCl_3$)



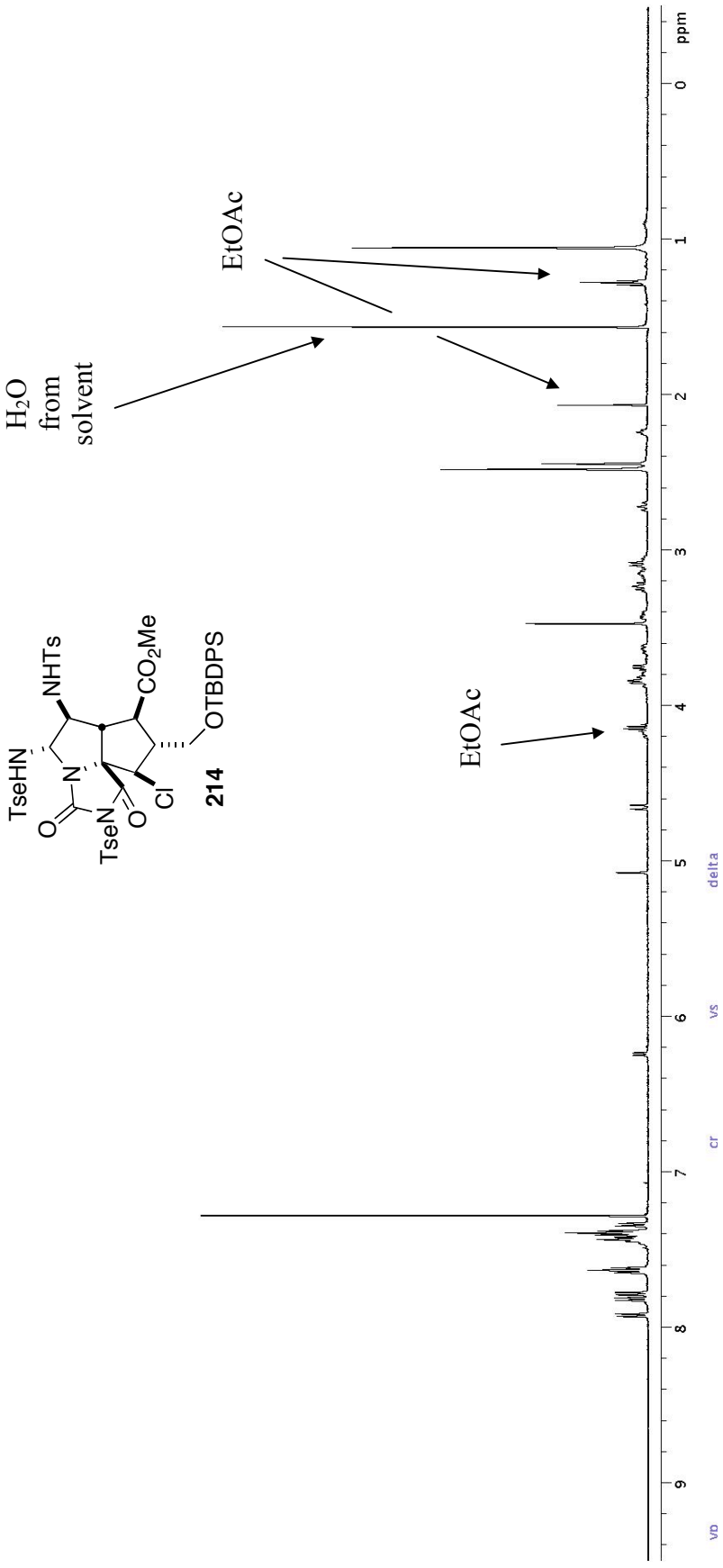
^{13}C NMR spectrum of oxazolidinone **206** (in $CDCl_3$)



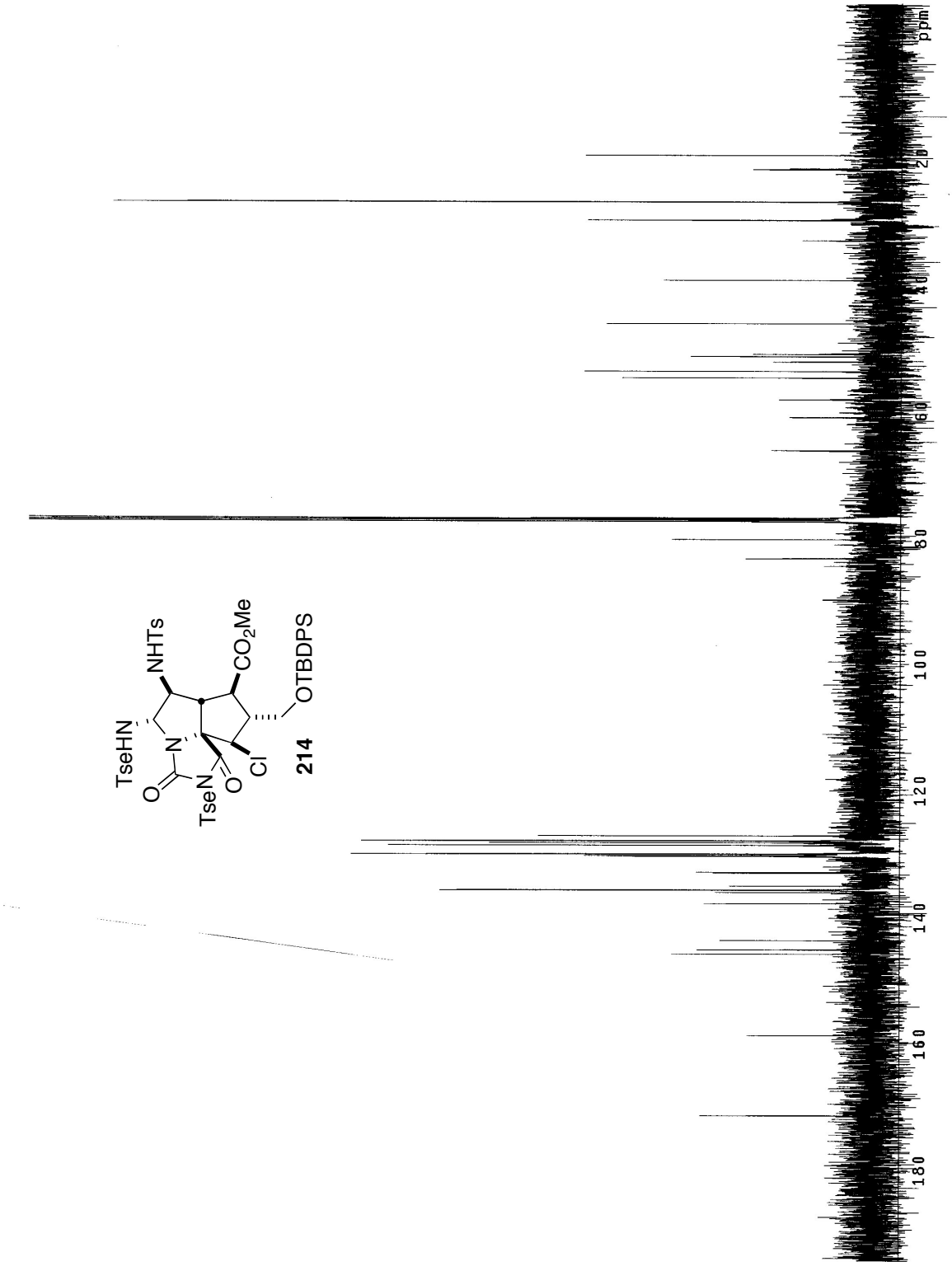
^{1}H NMR spectrum of carbinolamine **210** (in $CDCl_3$)



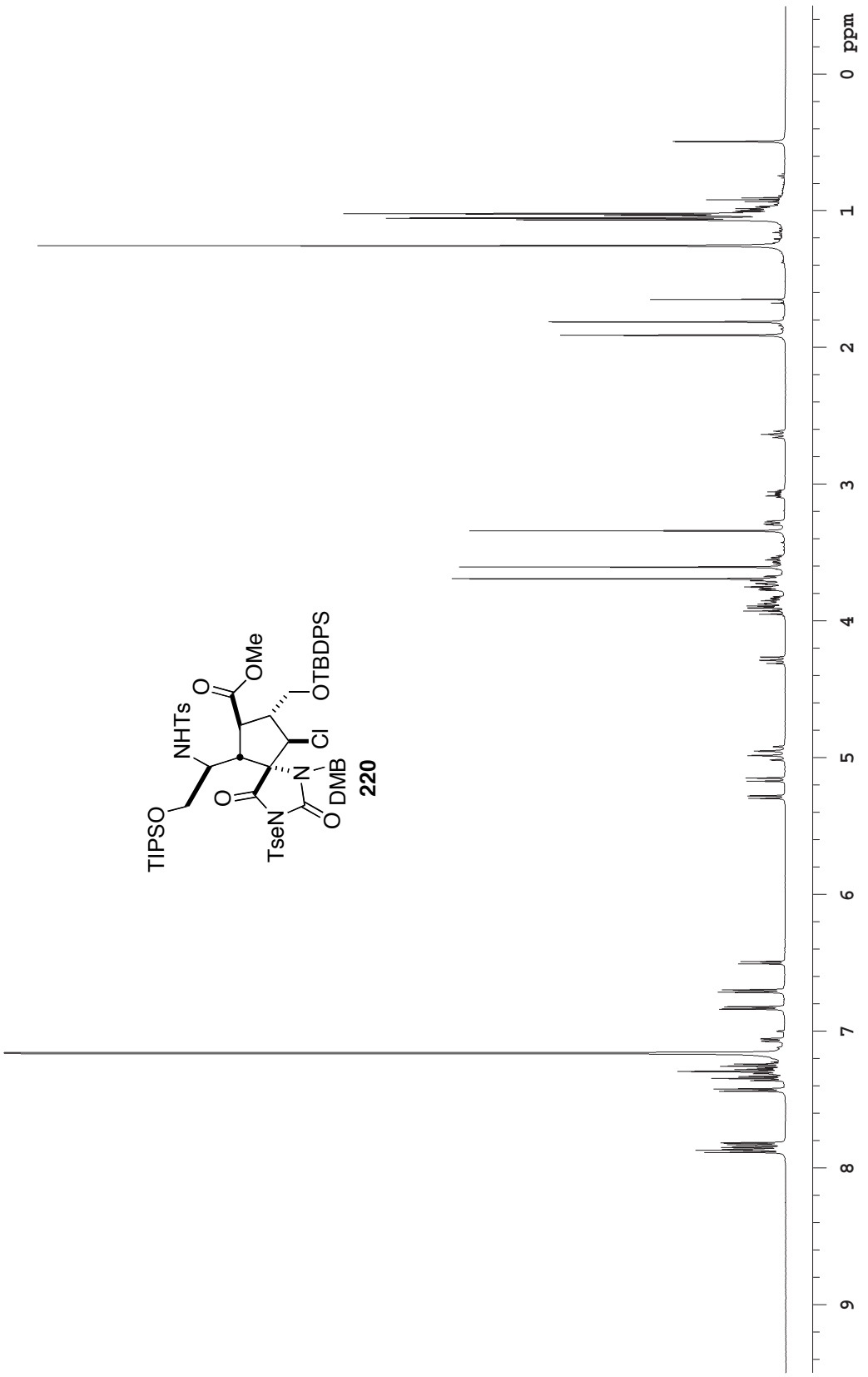
^{13}C NMR spectrum of carbinolamine **210** (in $CDCl_3$)



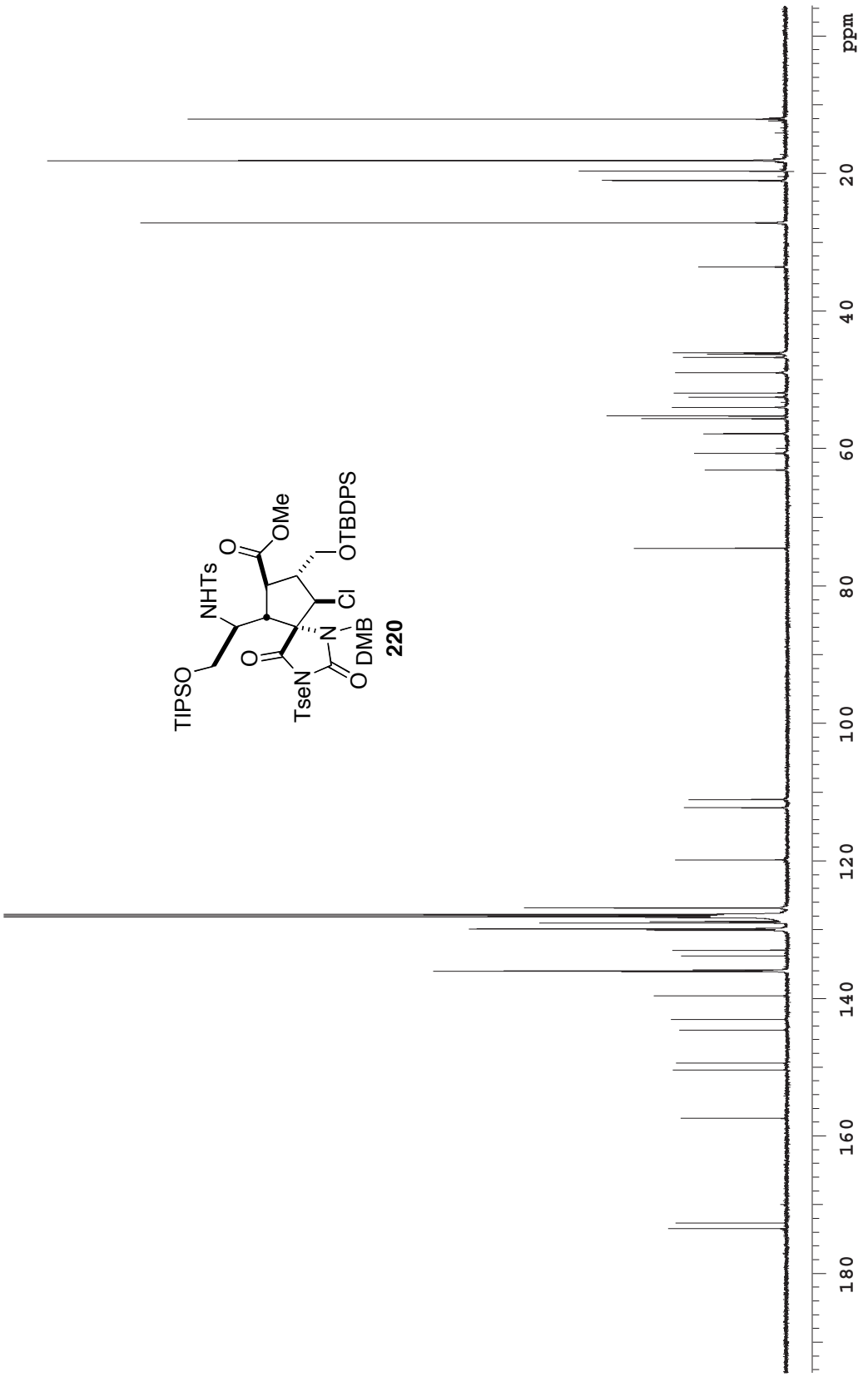
^{13}C NMR spectrum of bis-amine **214** (in $CDCl_3$)



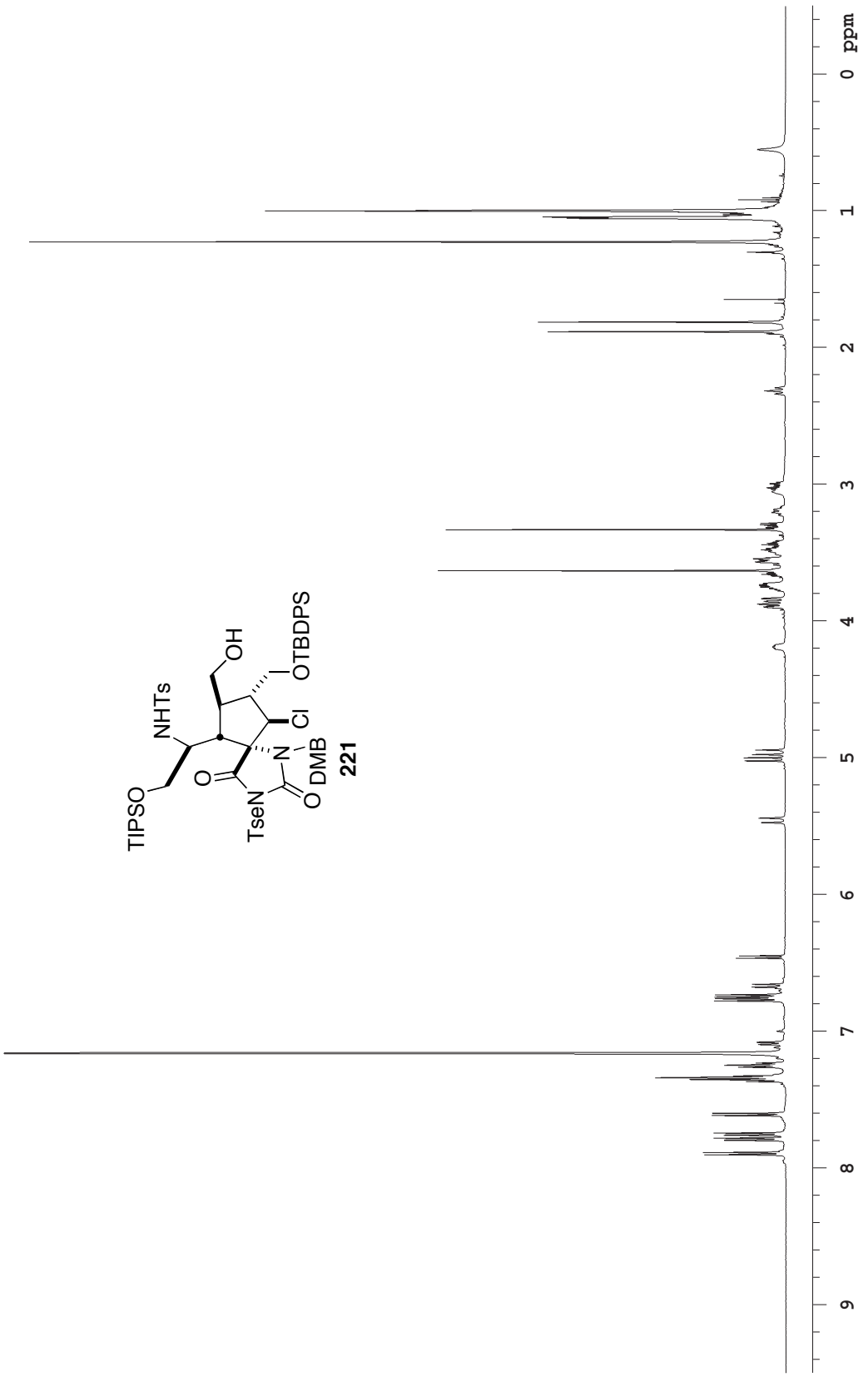
^{13}C NMR spectrum of bis-amine **214** (in $CDCl_3$)



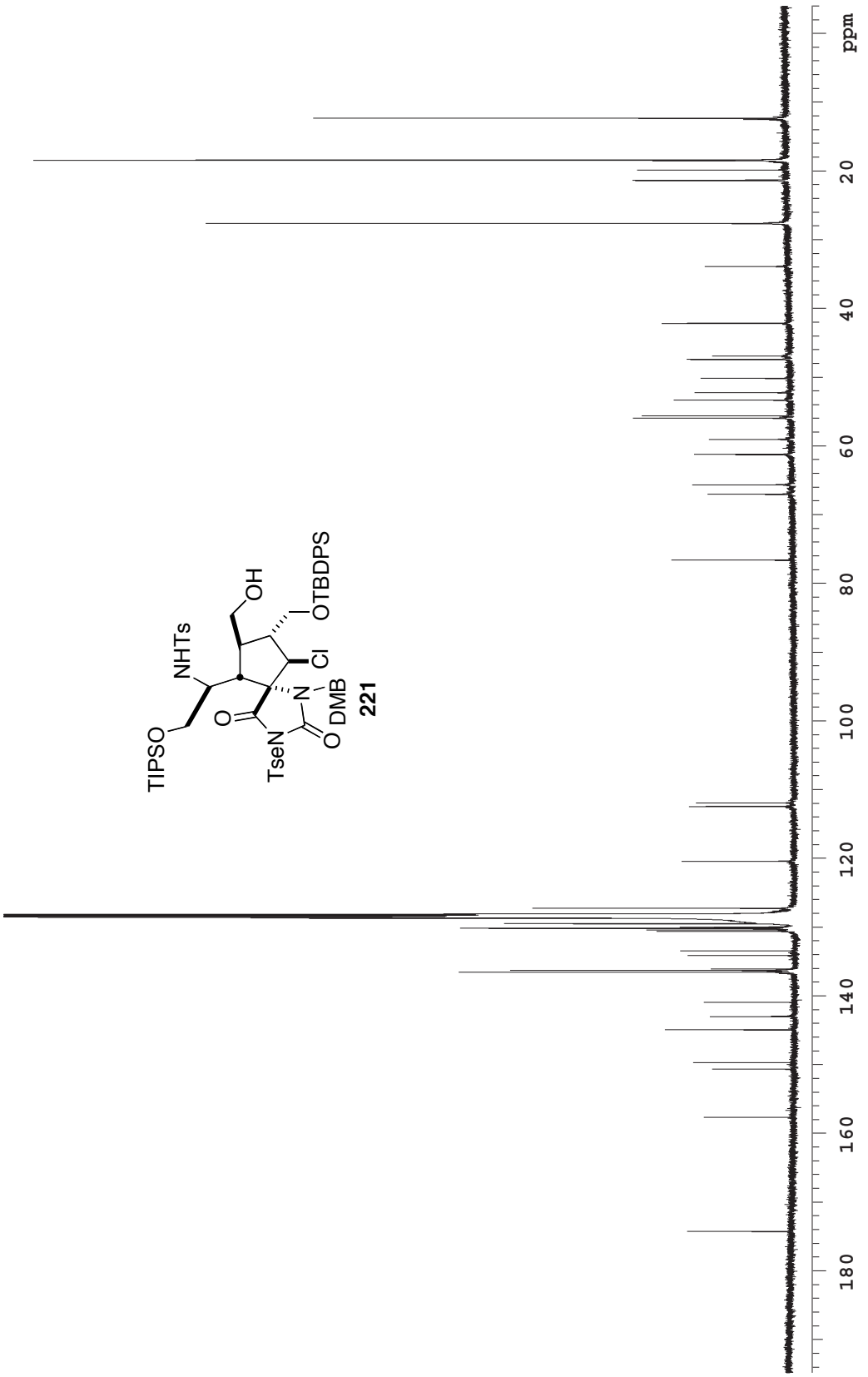
^{1}H NMR spectrum of TIPS-ester **220** (in benzene-d_6)



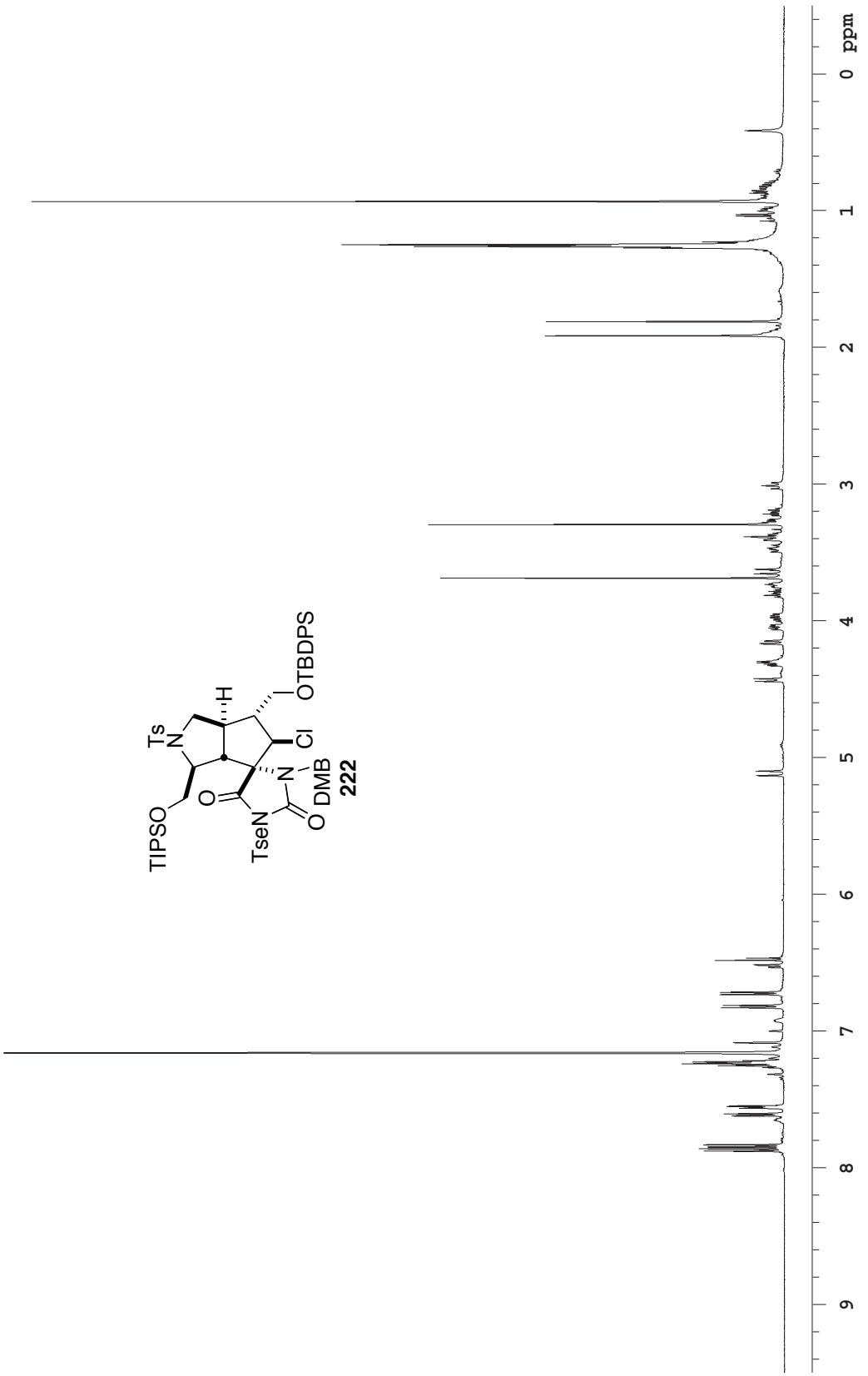
^{13}C NMR spectrum of TIPS-ester **220** (in benzene-d_6)



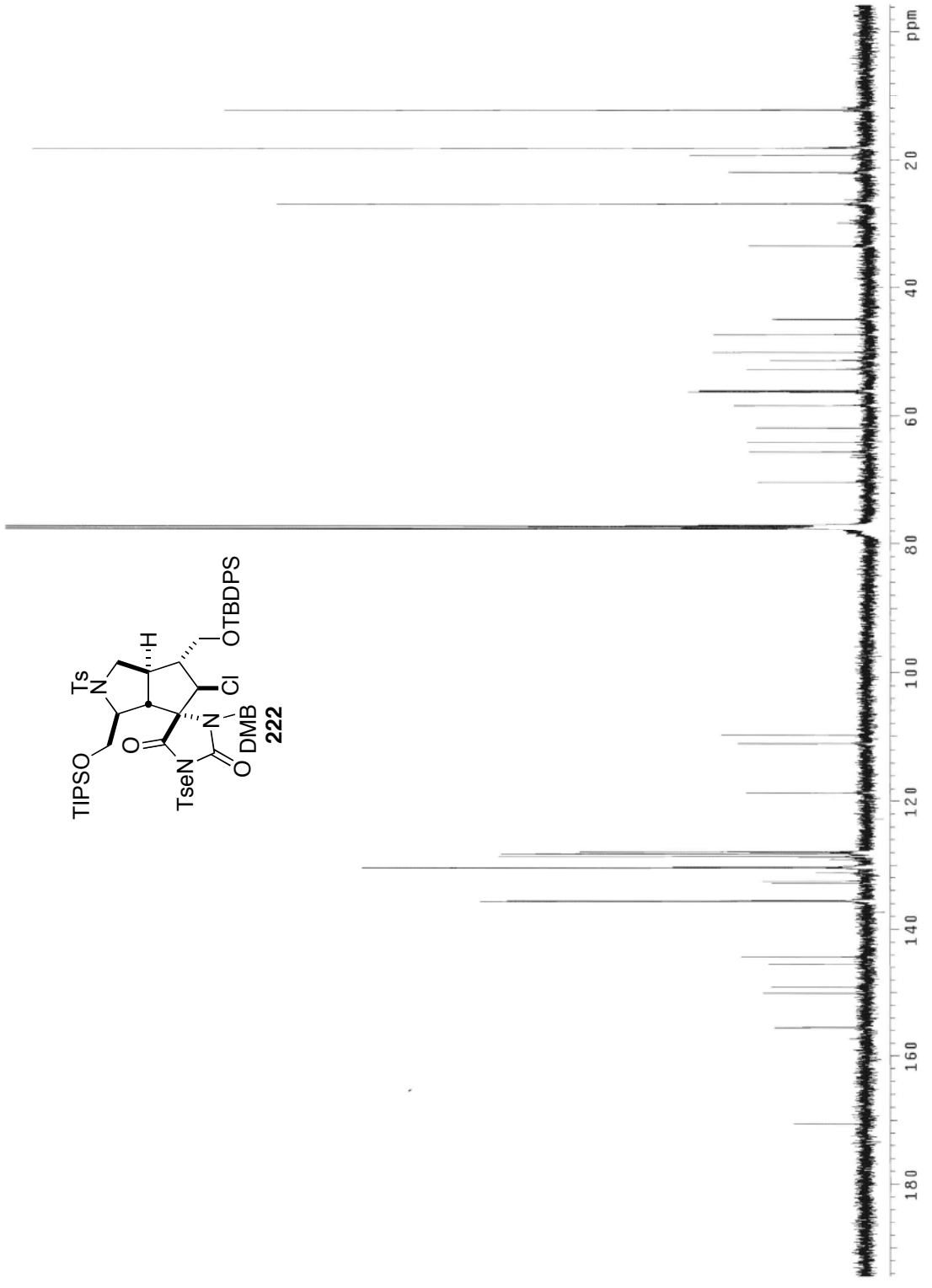
^{1}H NMR spectrum of alcohol **221** (in benzene-d_6)



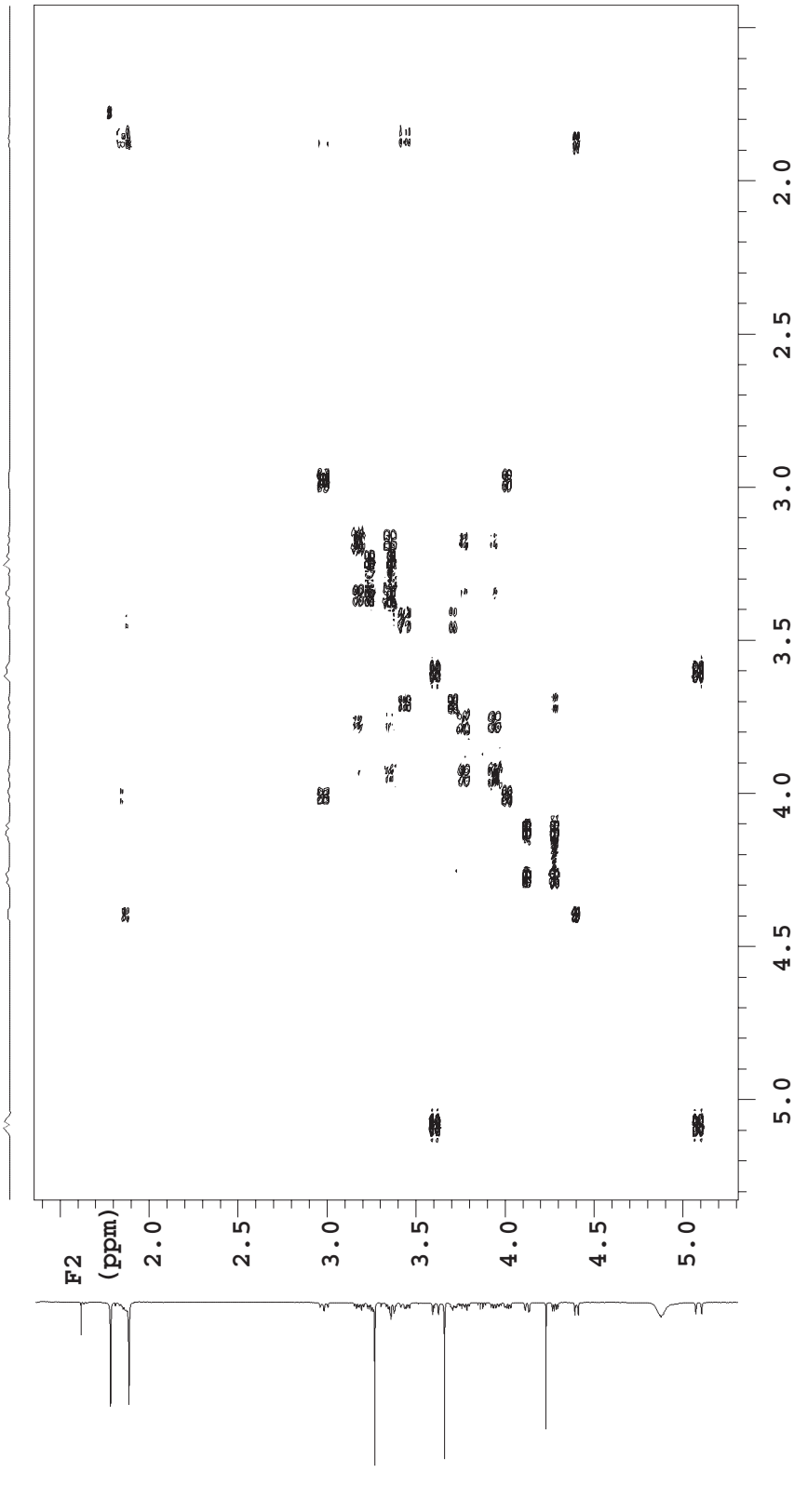
^{13}C NMR spectrum of alcohol **221** (in benzene-d_6)



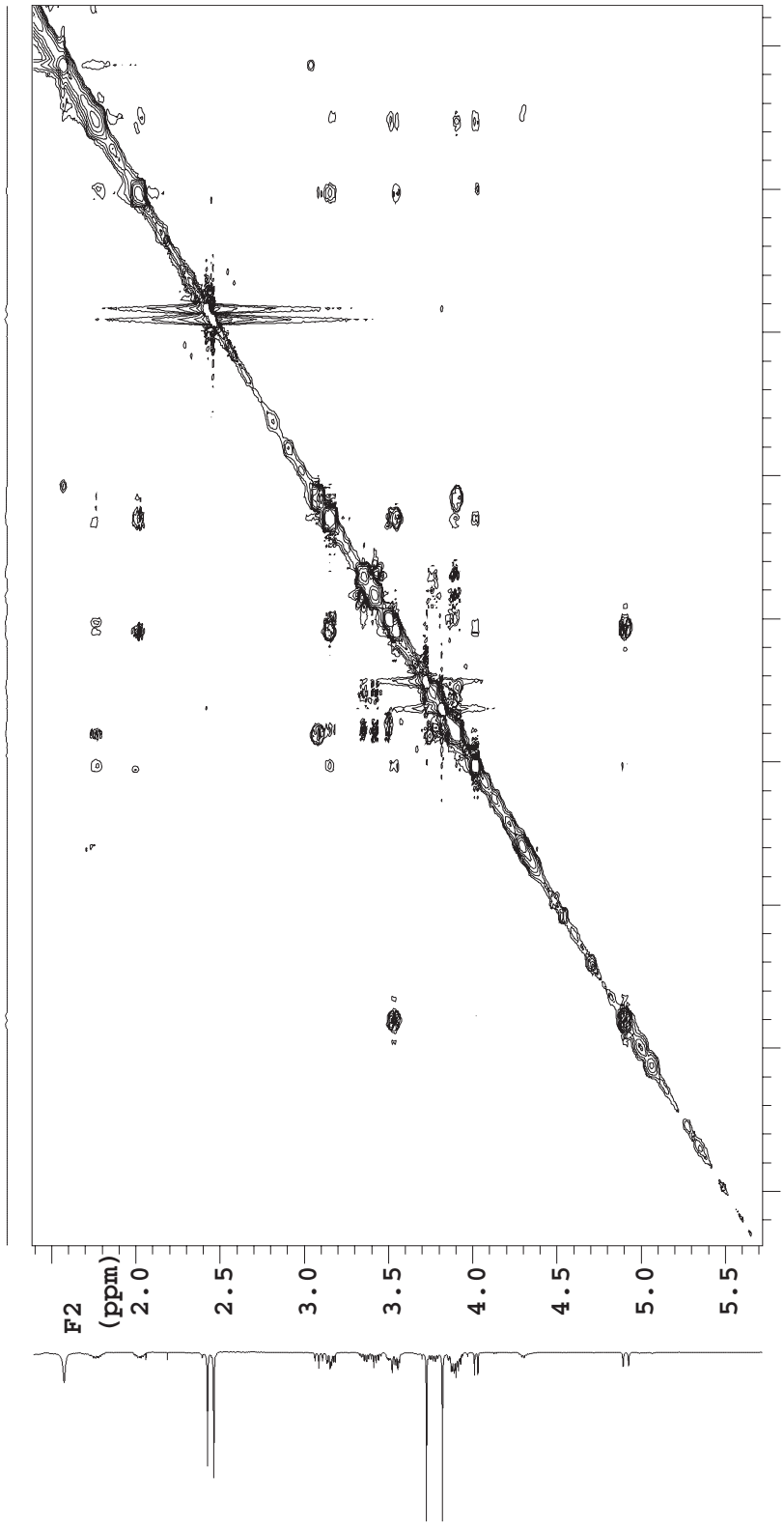
^{1}H NMR spectrum of azabicyclooctane **222** (in benzene-d_6)

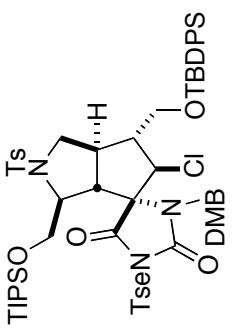


^{13}C NMR spectrum of azabicyclooctane **222** (in CDCl3)

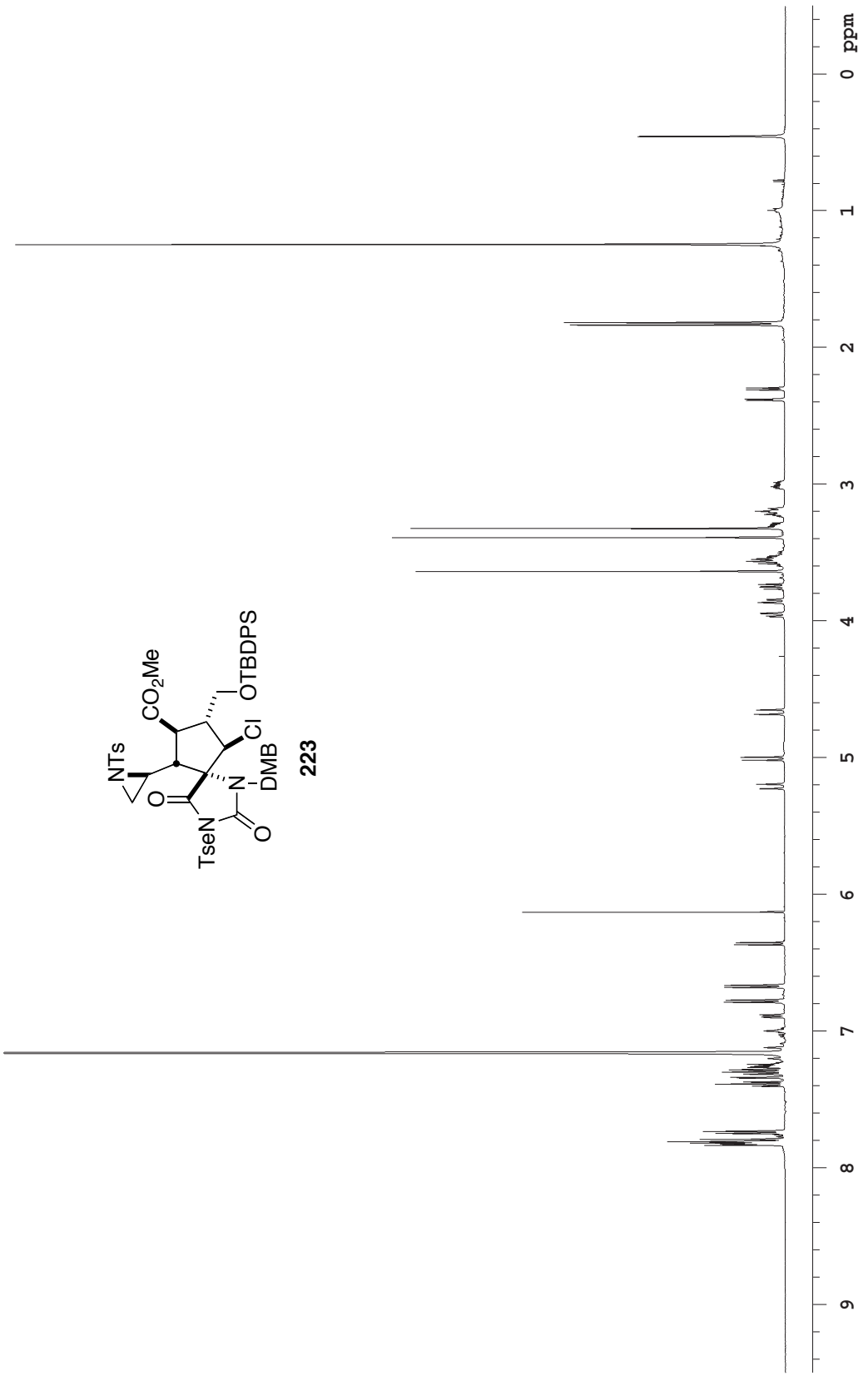


gDQCOSY spectrum of azabicyclooctane **222** (in benzene-d_6; expansion)

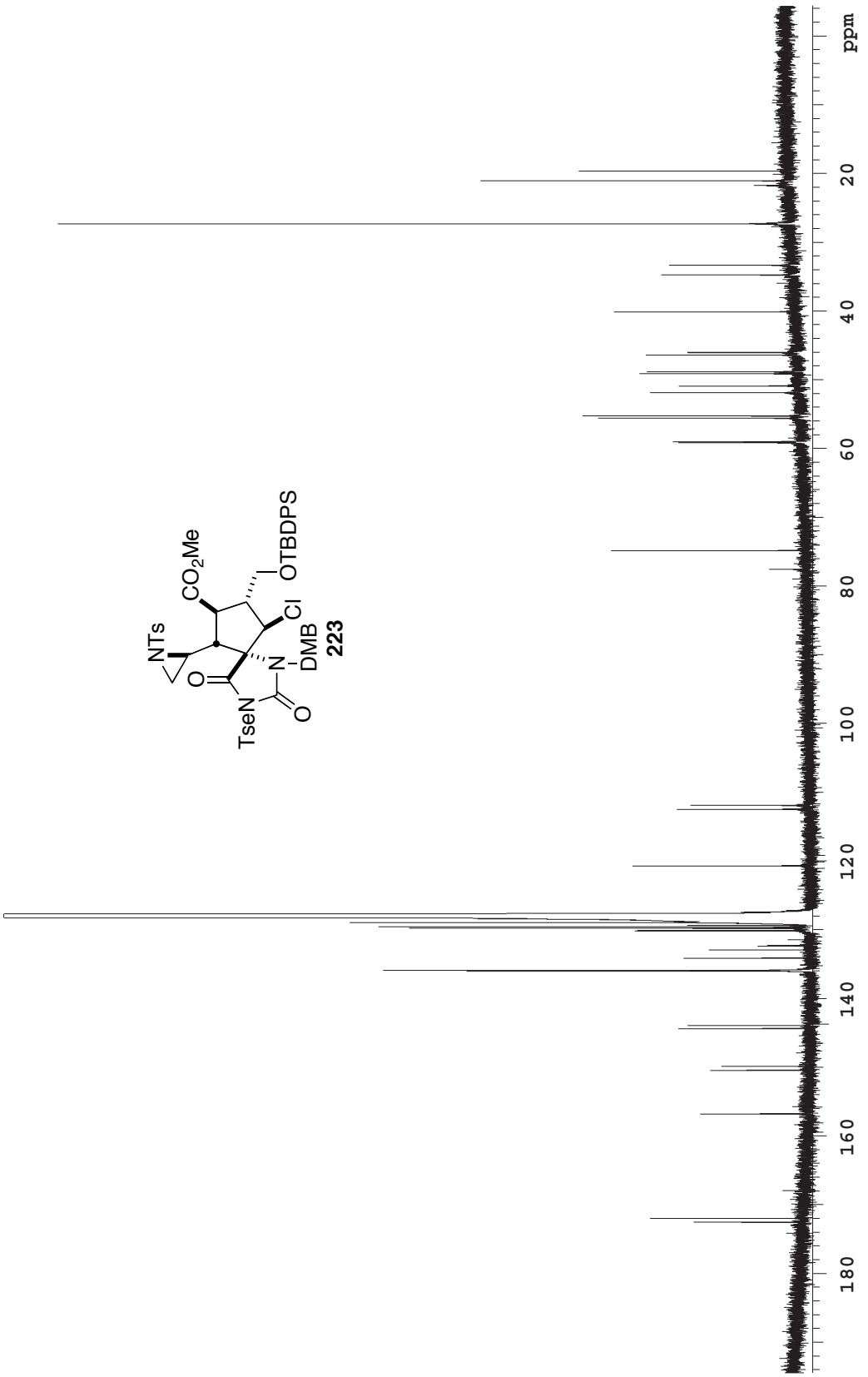




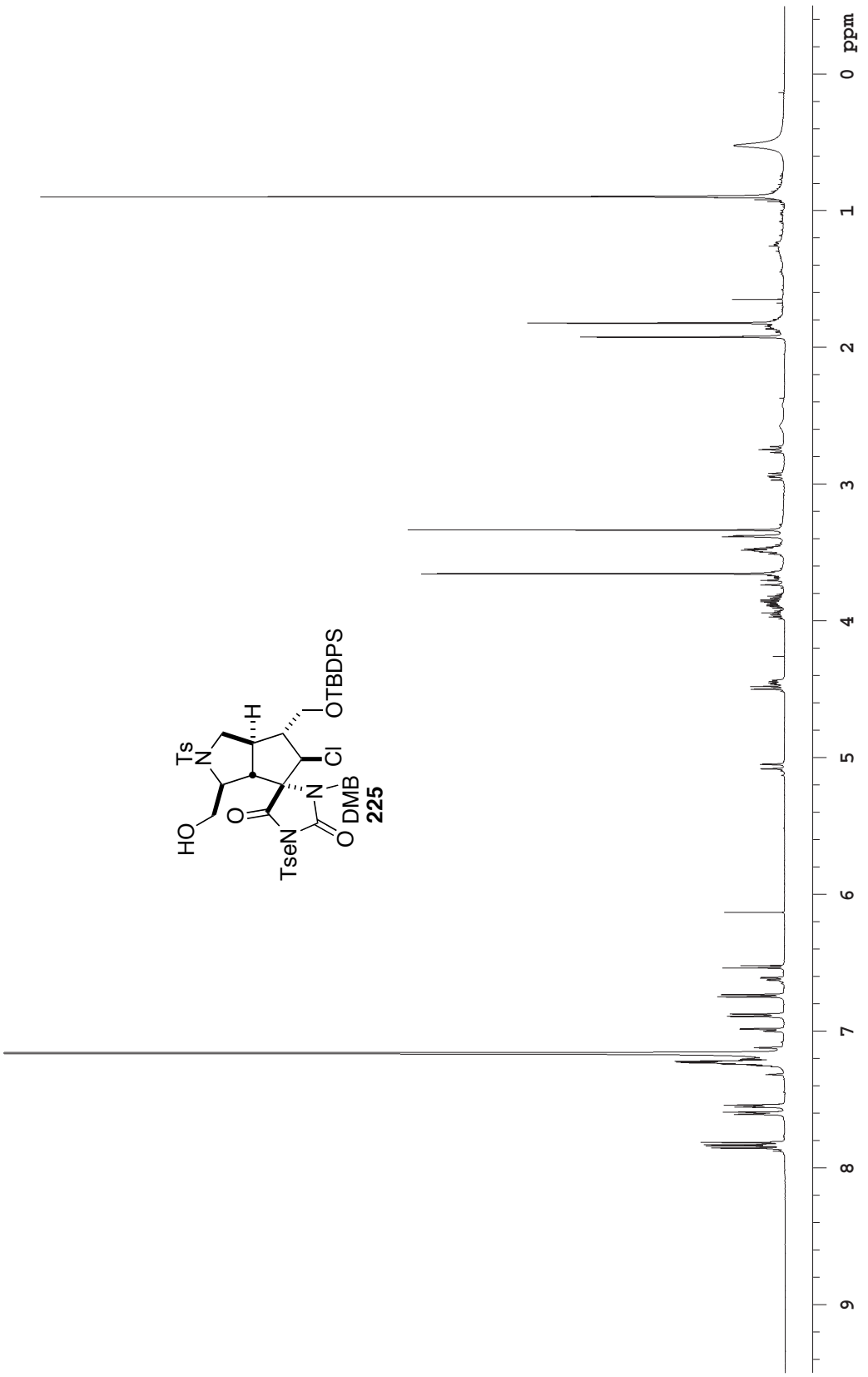
2D NOESY spectrum of azabicyclooctane **222** (in $CDCl_3$; expansion)



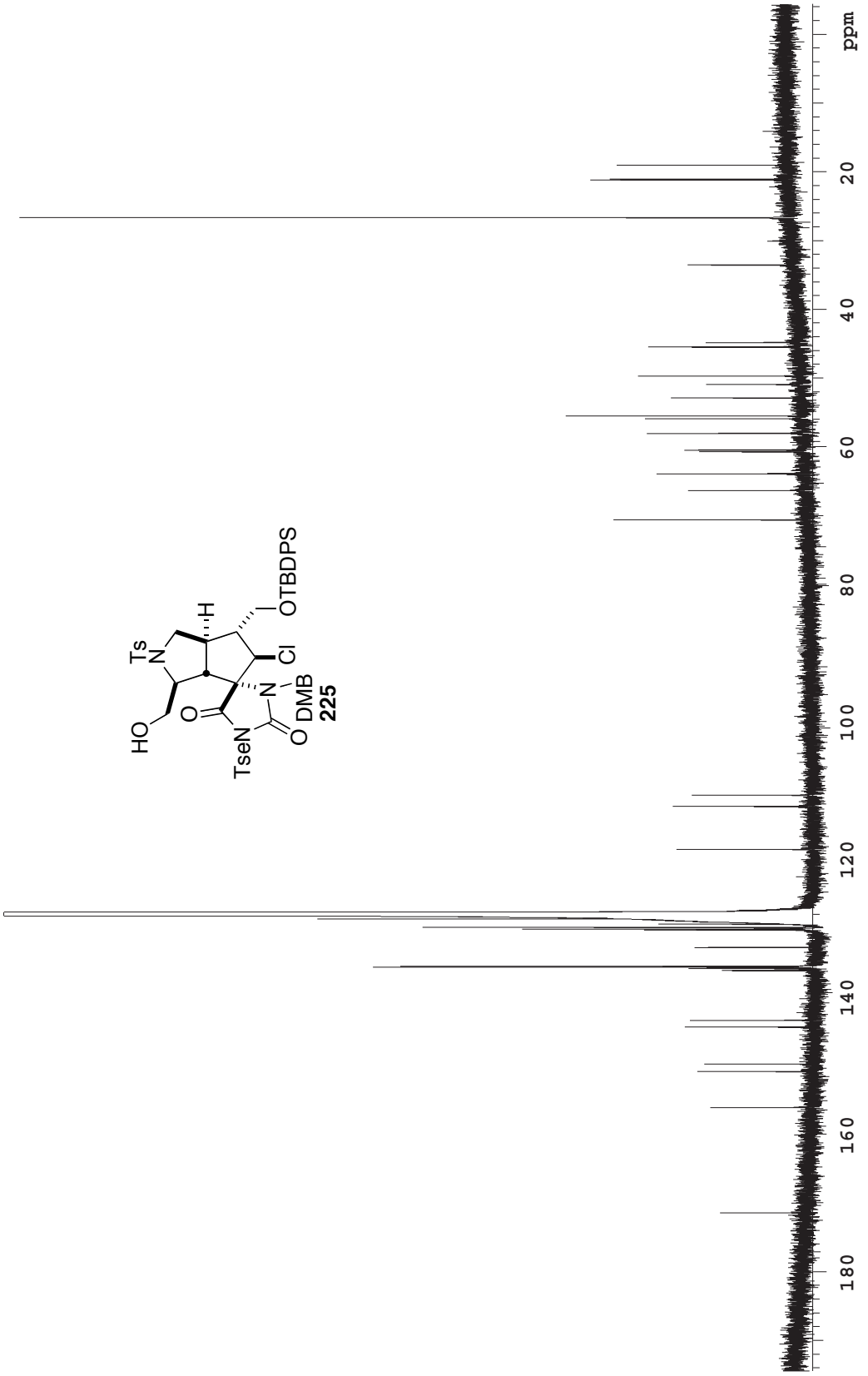
^{1}H NMR spectrum of aziridine **223** (in benzene-d_6)



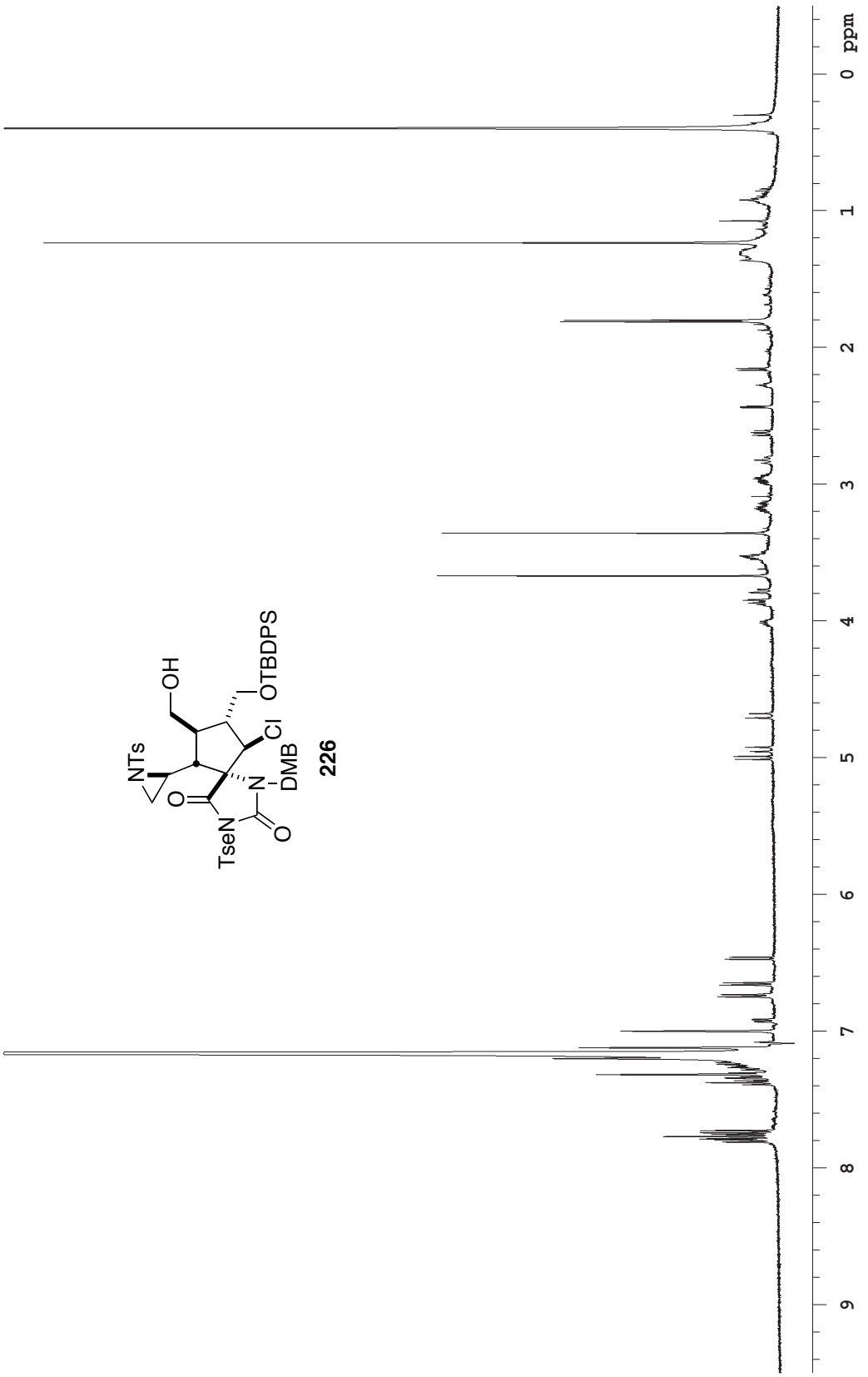
^{13}C NMR spectrum of aziridine **223** (in benzene-d_6)



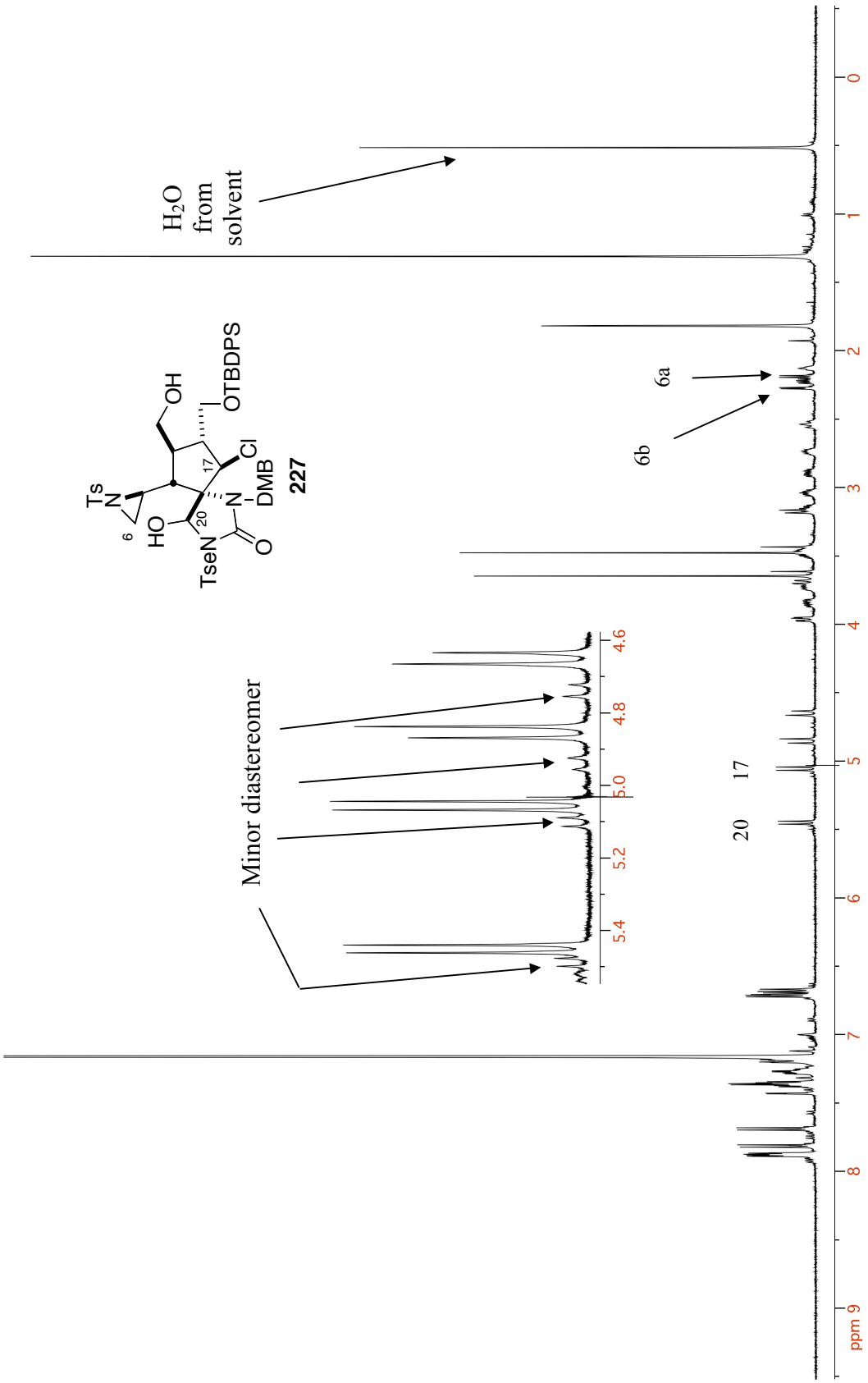
^{1}H NMR spectrum of azabicyclooctane **225** (in benzene-d_6)



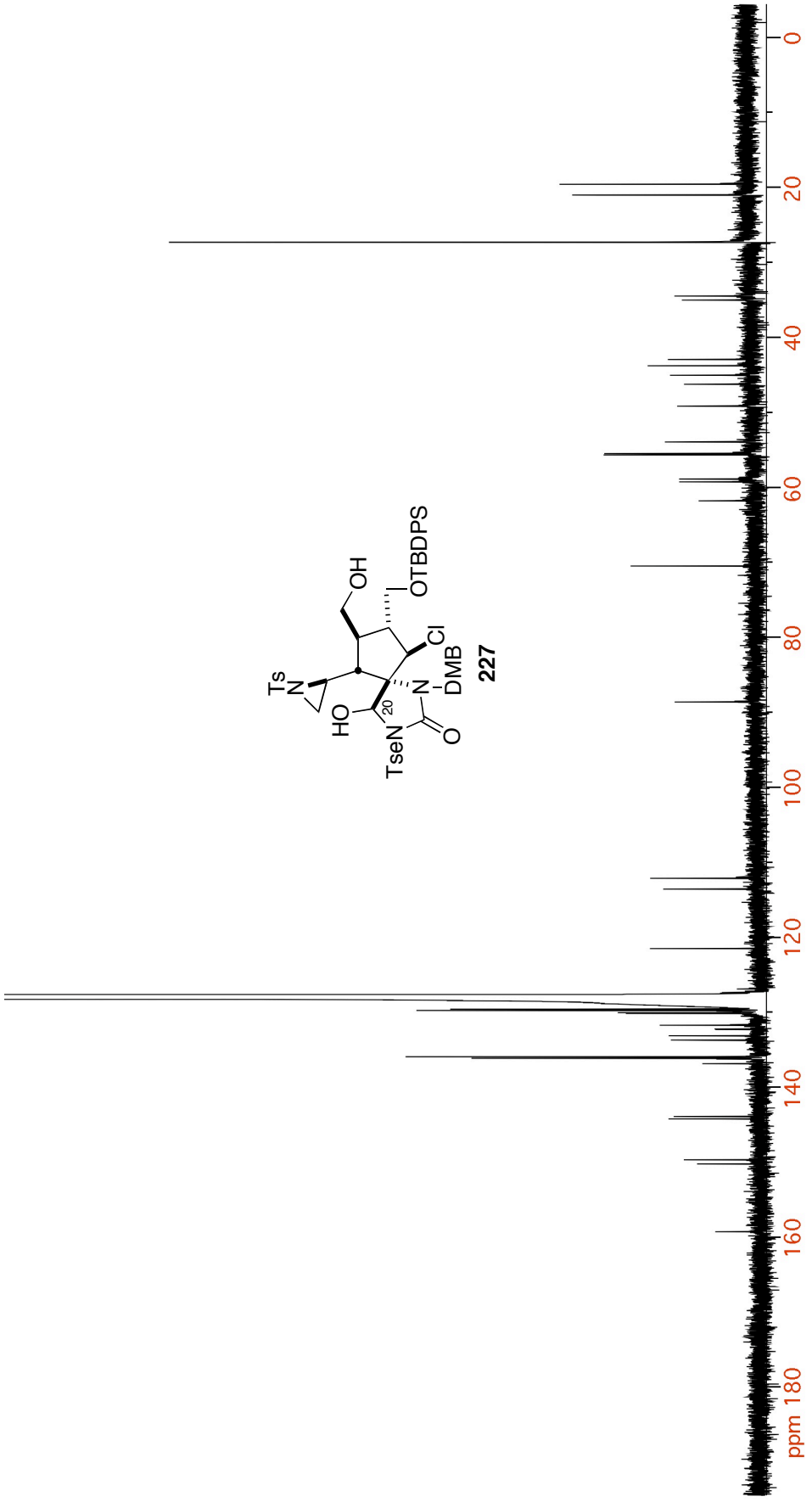
^{13}C NMR spectrum of azabicyclooctane **225** (in benzene-d_6)



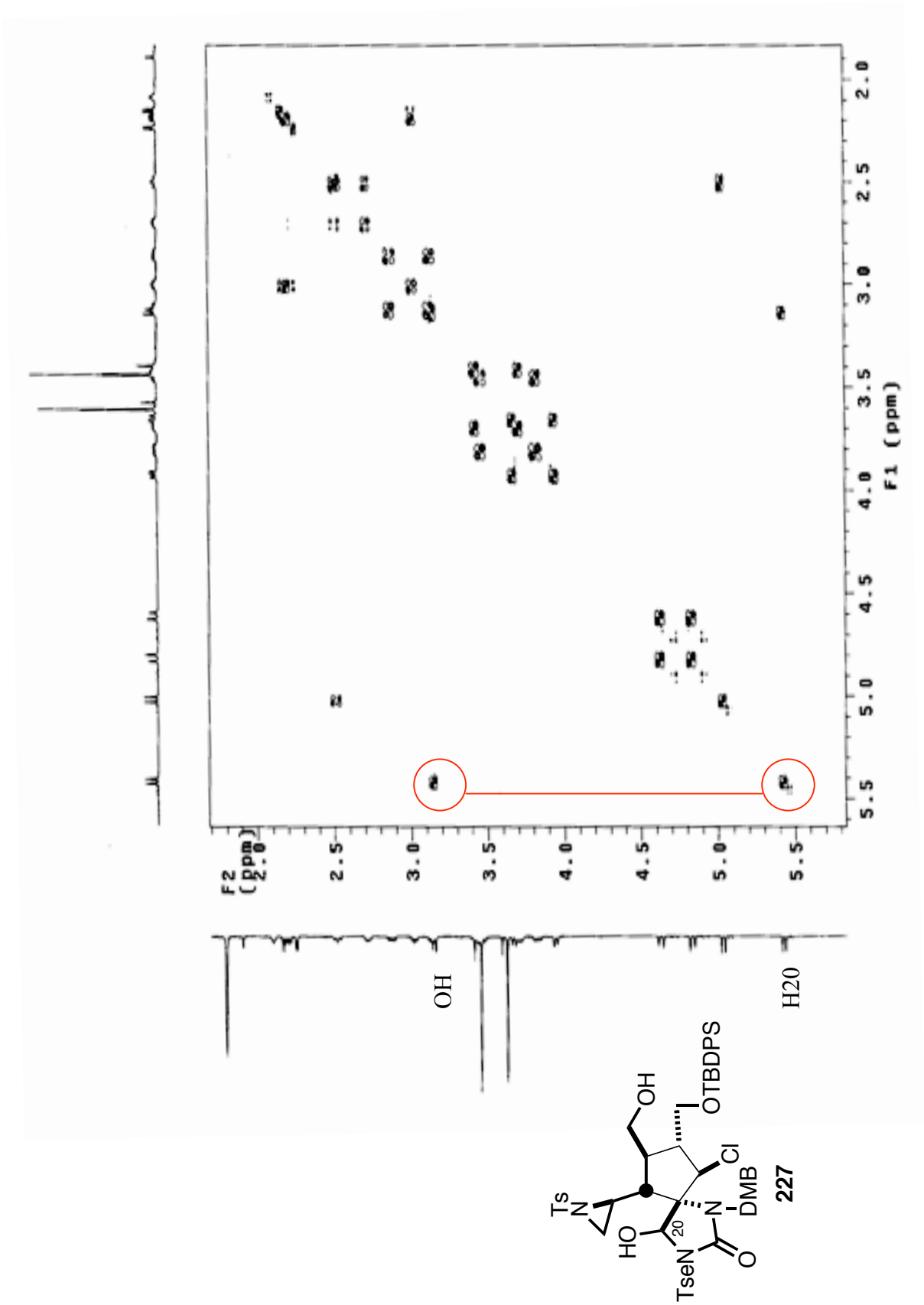
^{1}H NMR spectrum of aziridine **226** (in benzene-d_6)



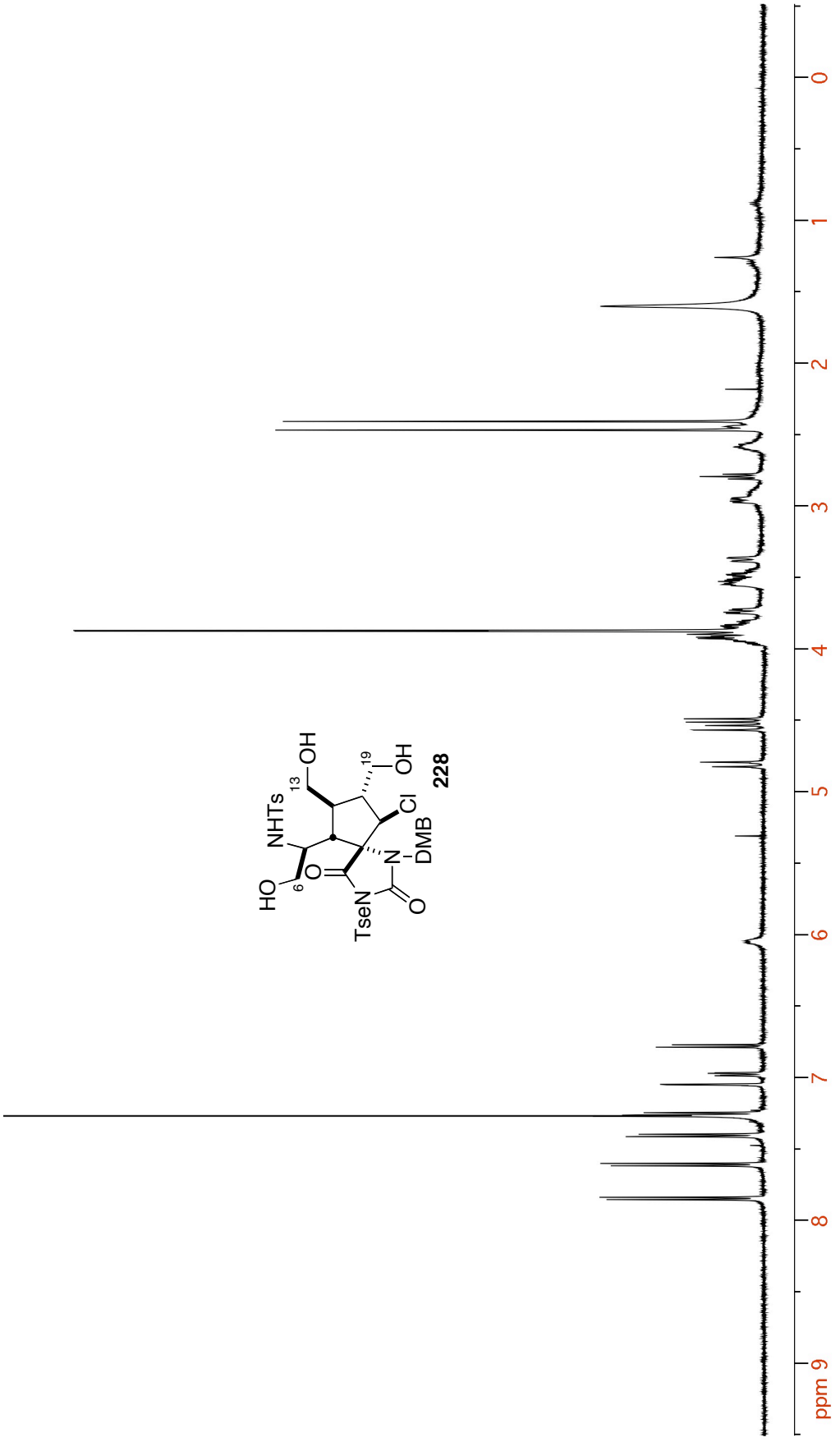
^{1}H NMR spectrum of carbinolo alcohol **227** (in benzene-d_6)



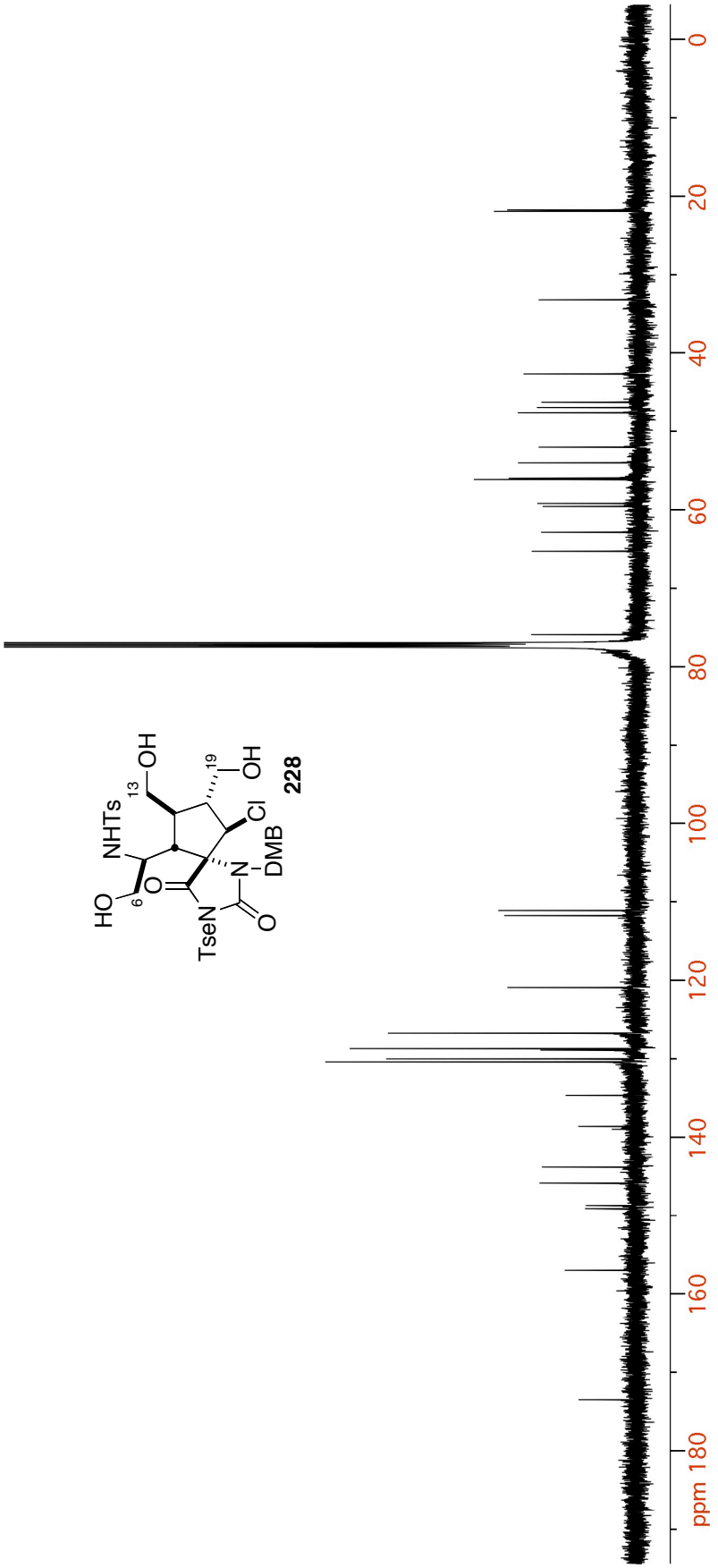
^{13}C NMR spectrum of carbinolo alcohol**227** (in C_6D_6)



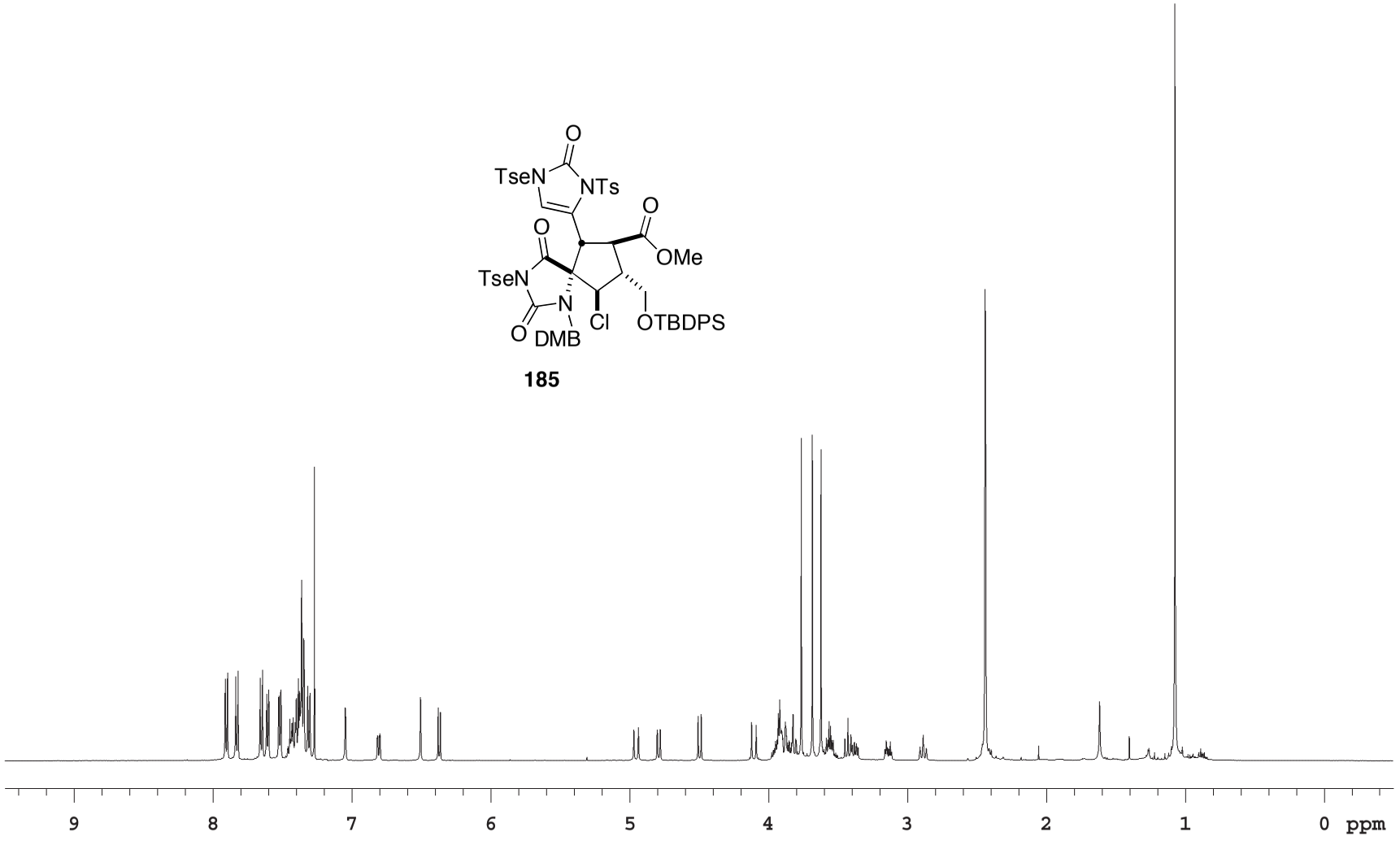
GDQCOSY spectrum of carbinolo alcohol **227** (in $CDCl_3$)



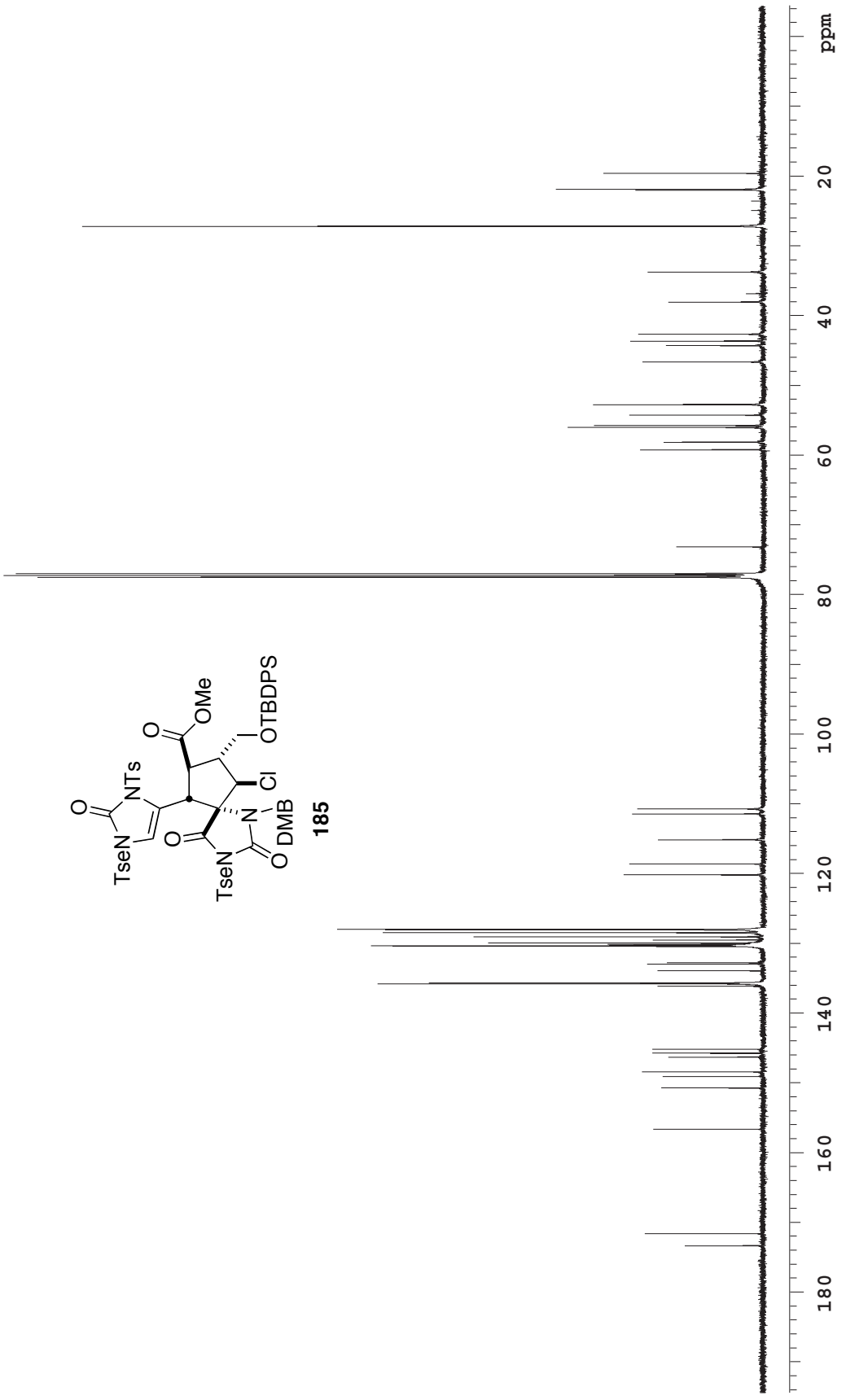
^{1}H NMR spectrum of aminotriol **228** (in $CDCl_3$)



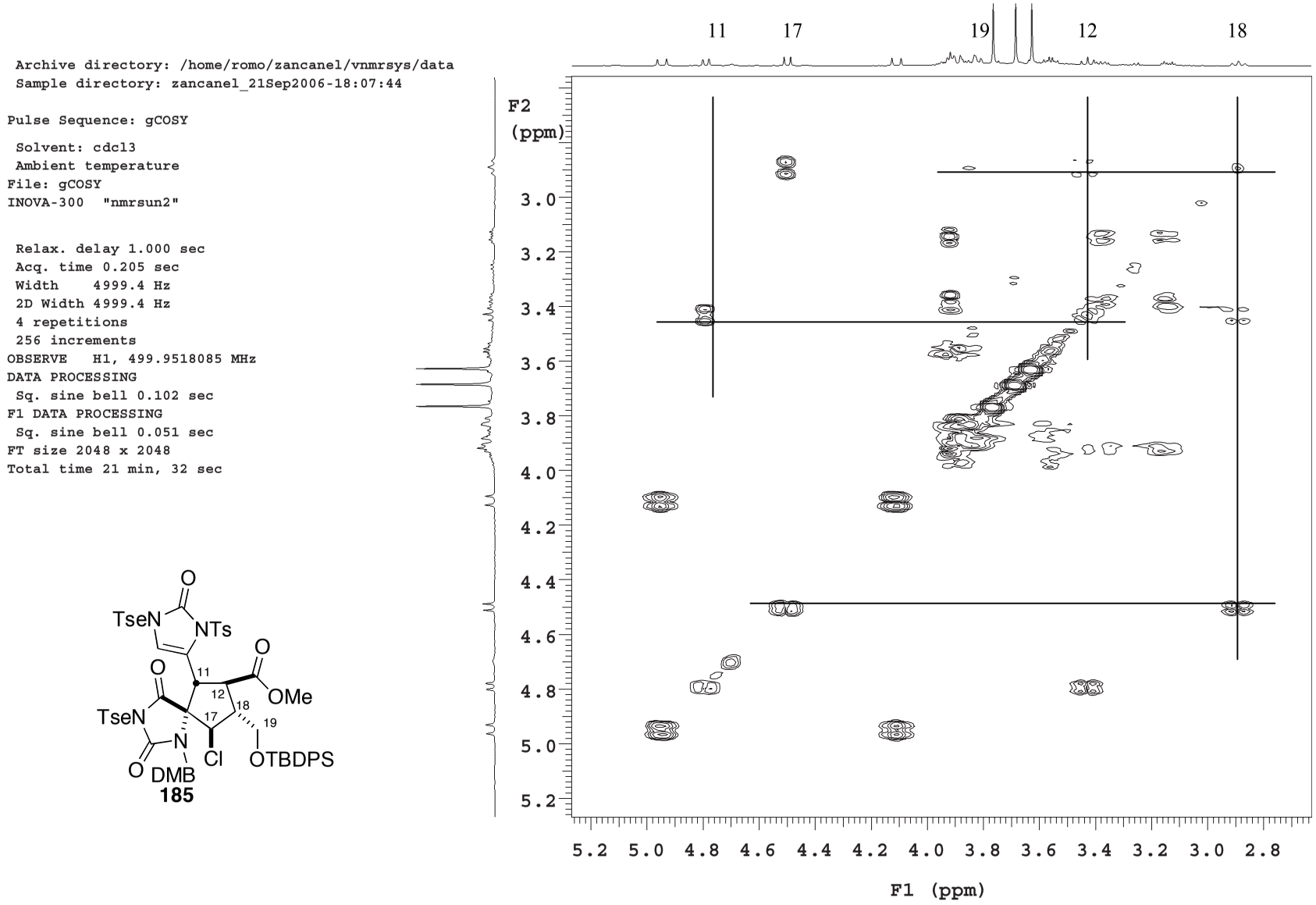
^{13}C NMR spectrum of aminotriol **228** (in $CDCl_3$)



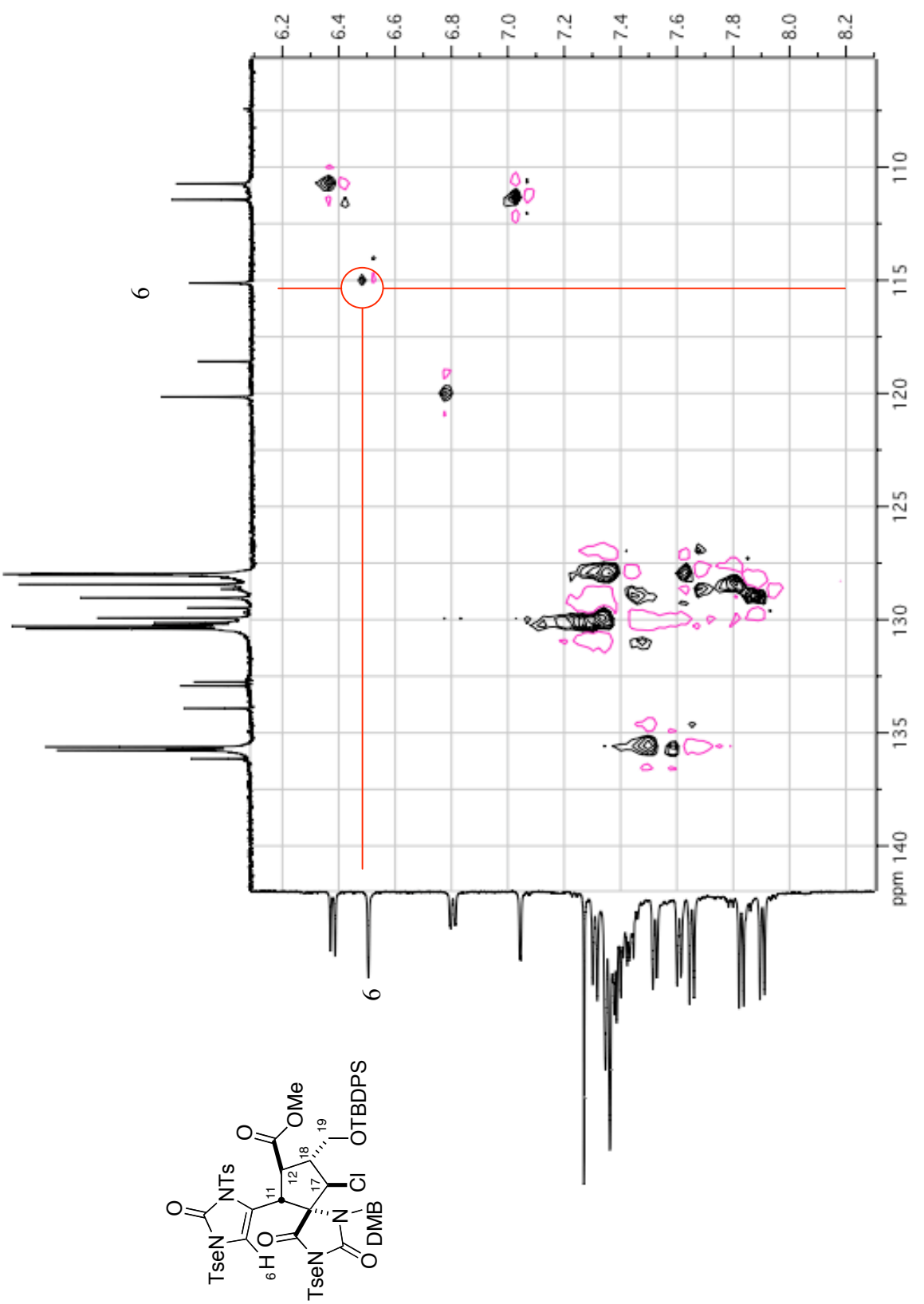
^{1}H NMR spectrum of imidazolone **185** (in $CDCl_3$)



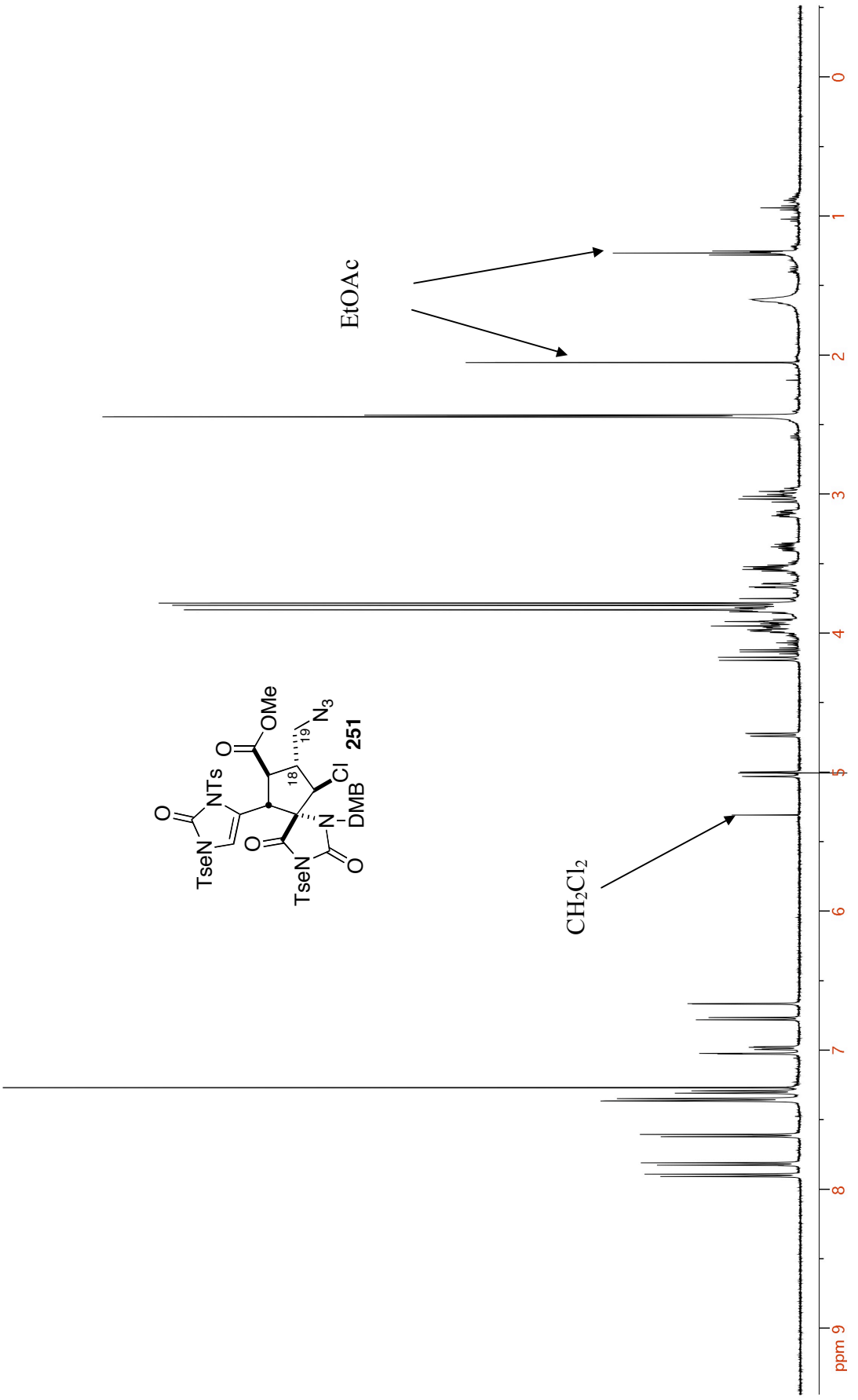
^{13}C NMR spectrum of imidazolone **185** (in $CDCl_3$)



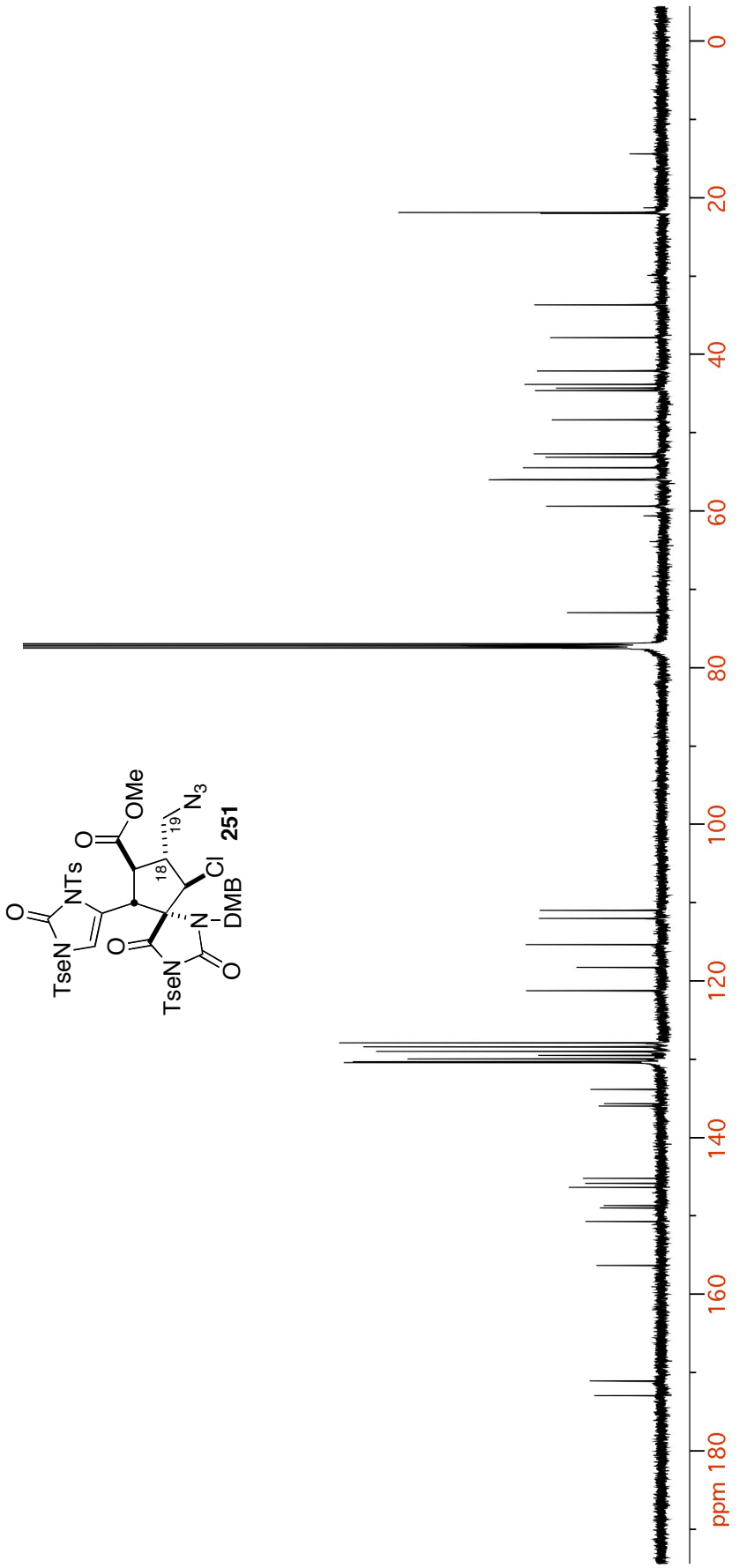
^{1}H-^{1}H gCOSY spectrum of imidazolone **185** (in $CDCl_3$; expansion)



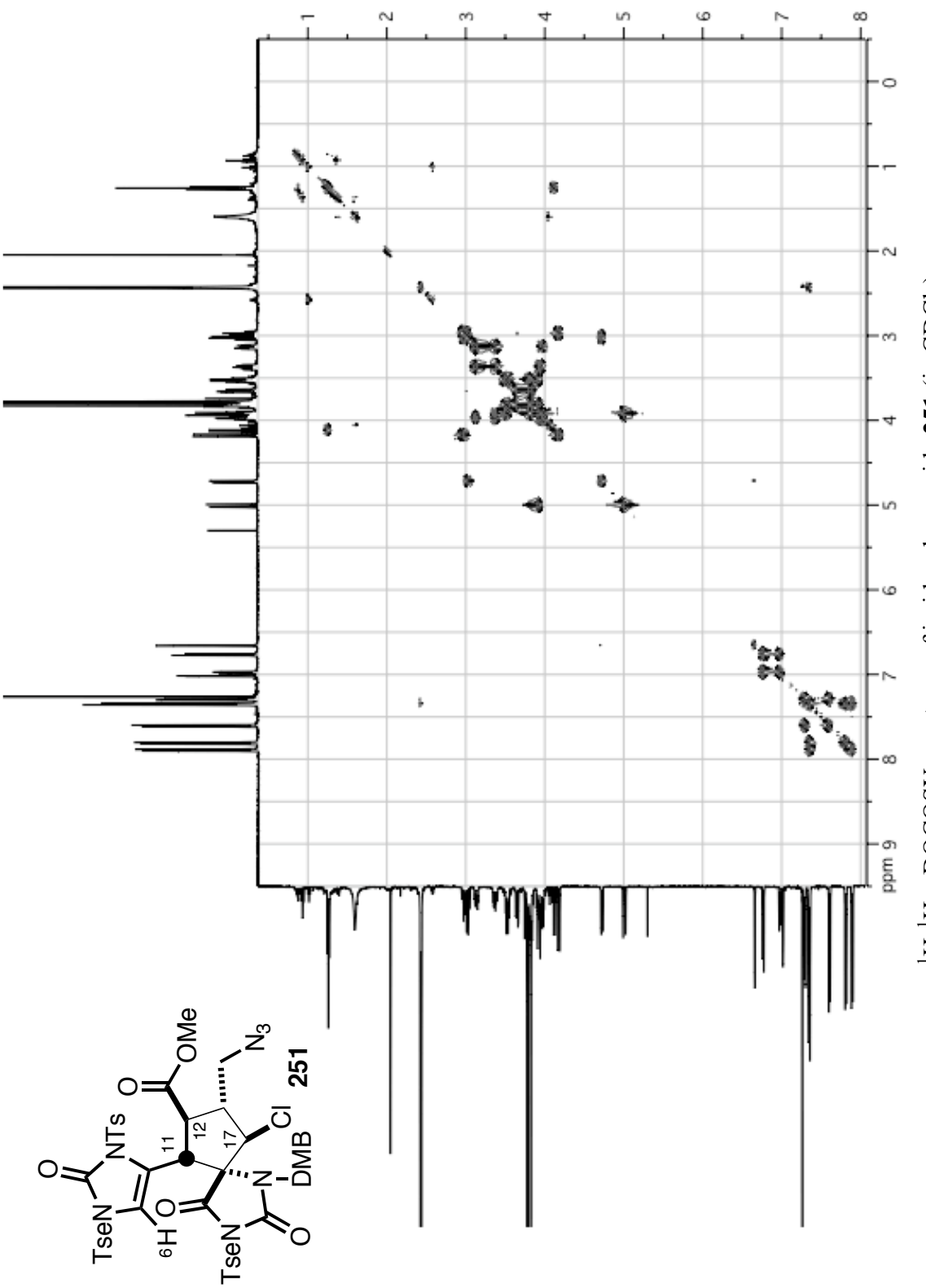
gHMQC spectrum of imidazolone **185** (in $CDCl_3$; expansion)



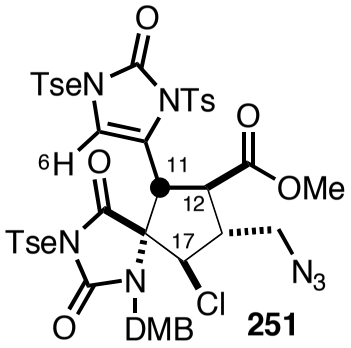
^{1}H NMR spectrum of imidazolone azide **251** (in $CDCl_3$)

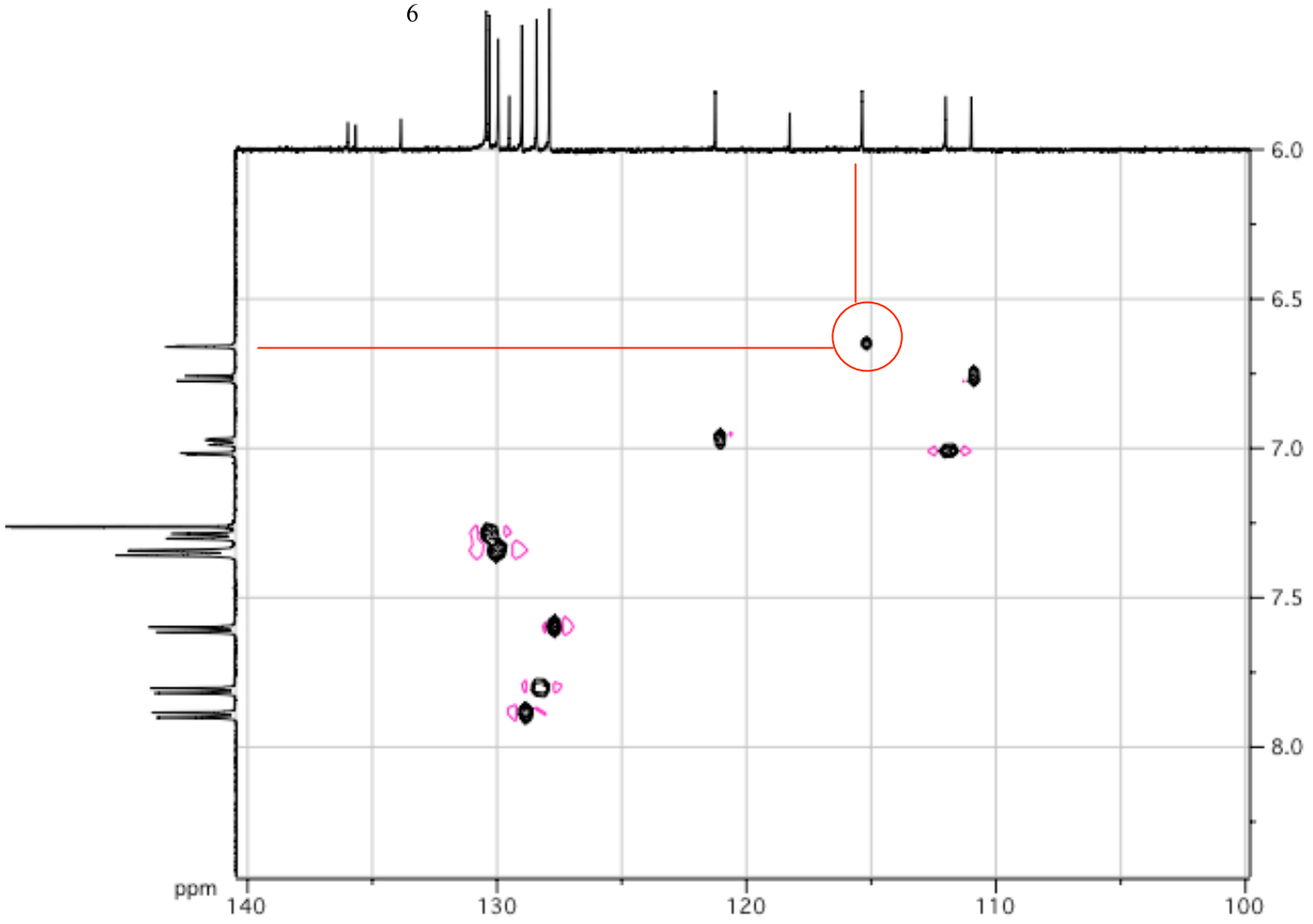


^{13}C NMR spectrum of imidazolone azide **251** (in $CDCl_3$)

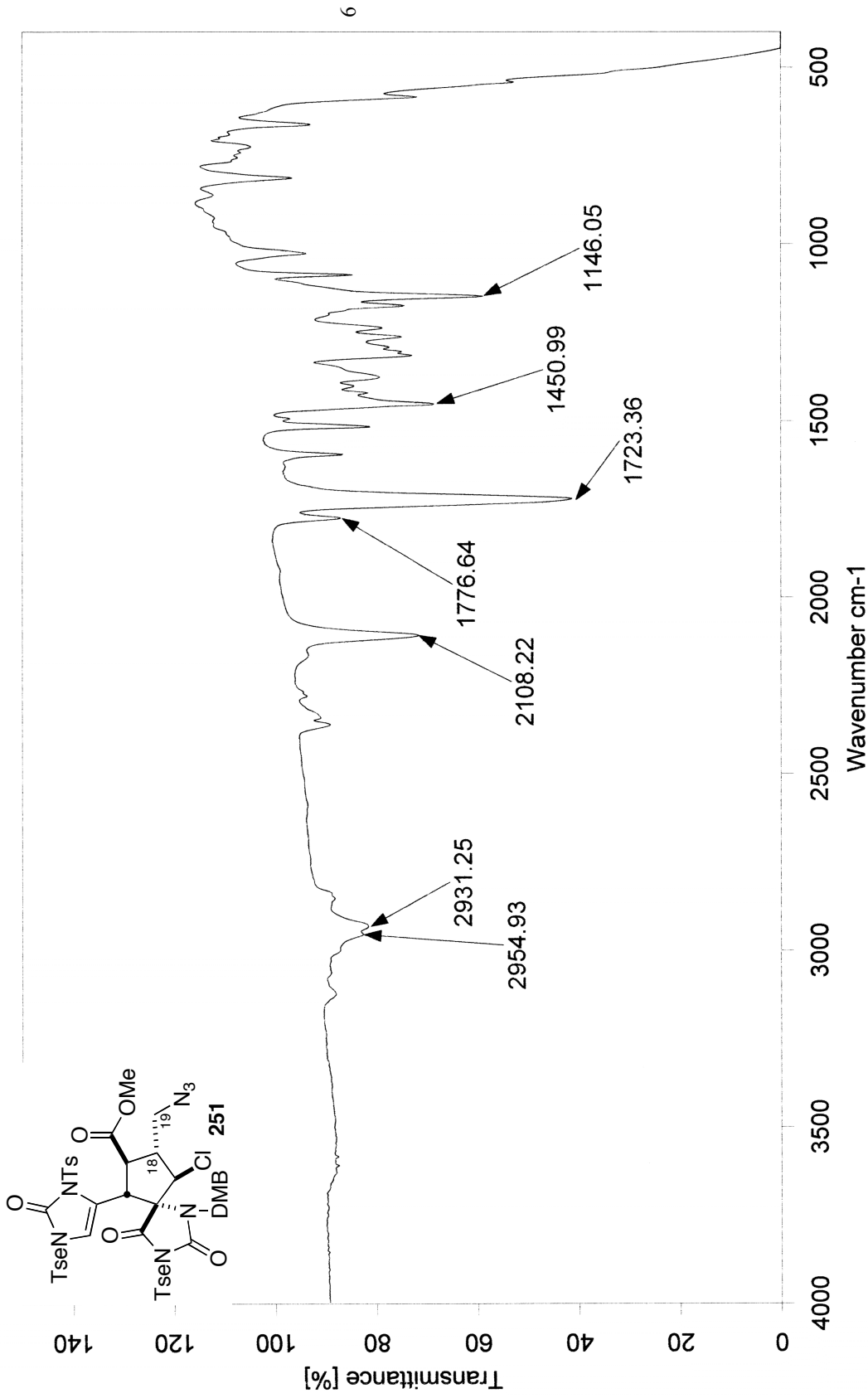


^{1}H-^{1}H gDQCOSY spectrum of imidazolone azide **251** (in $CDCl_3$)

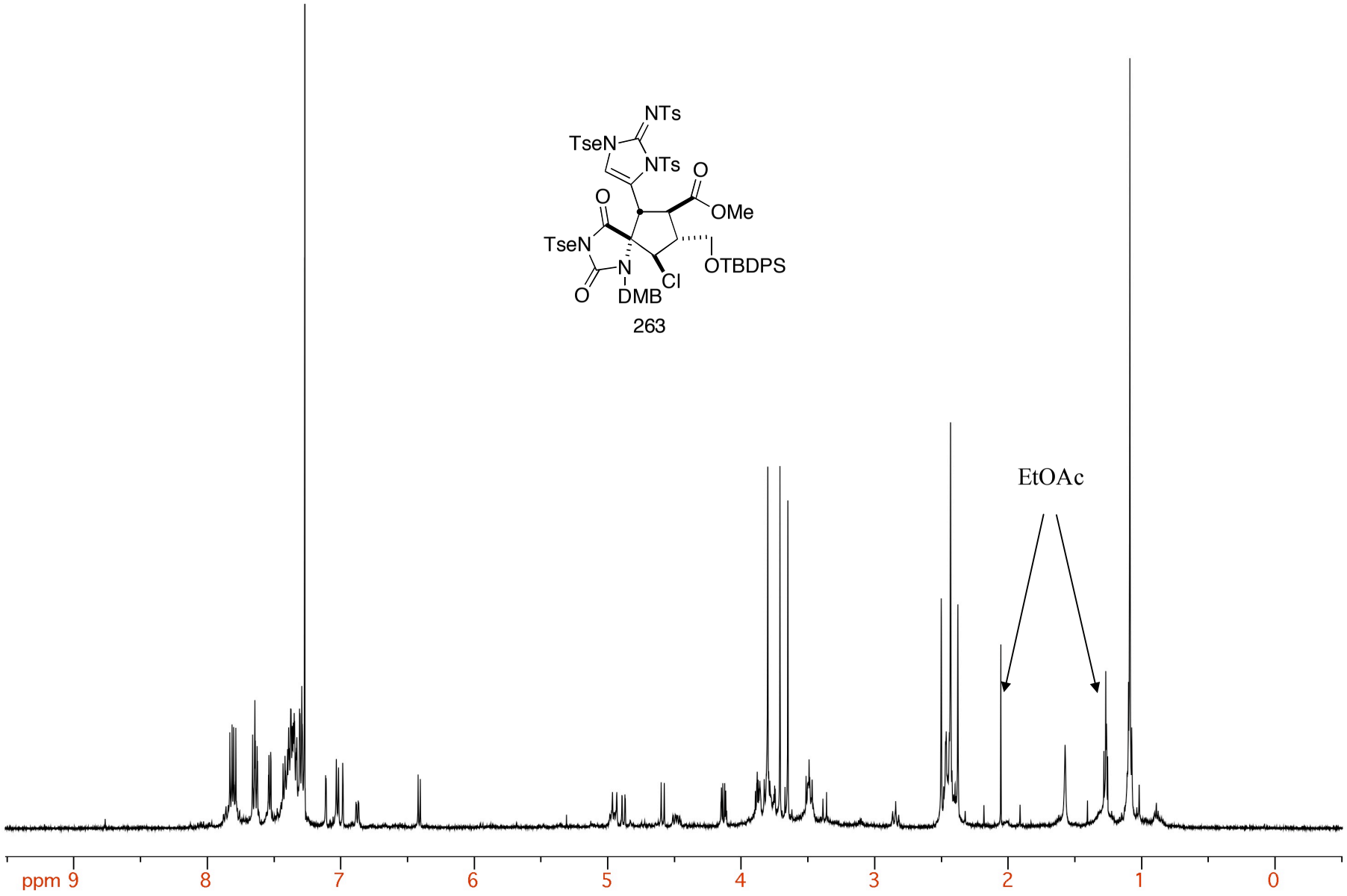




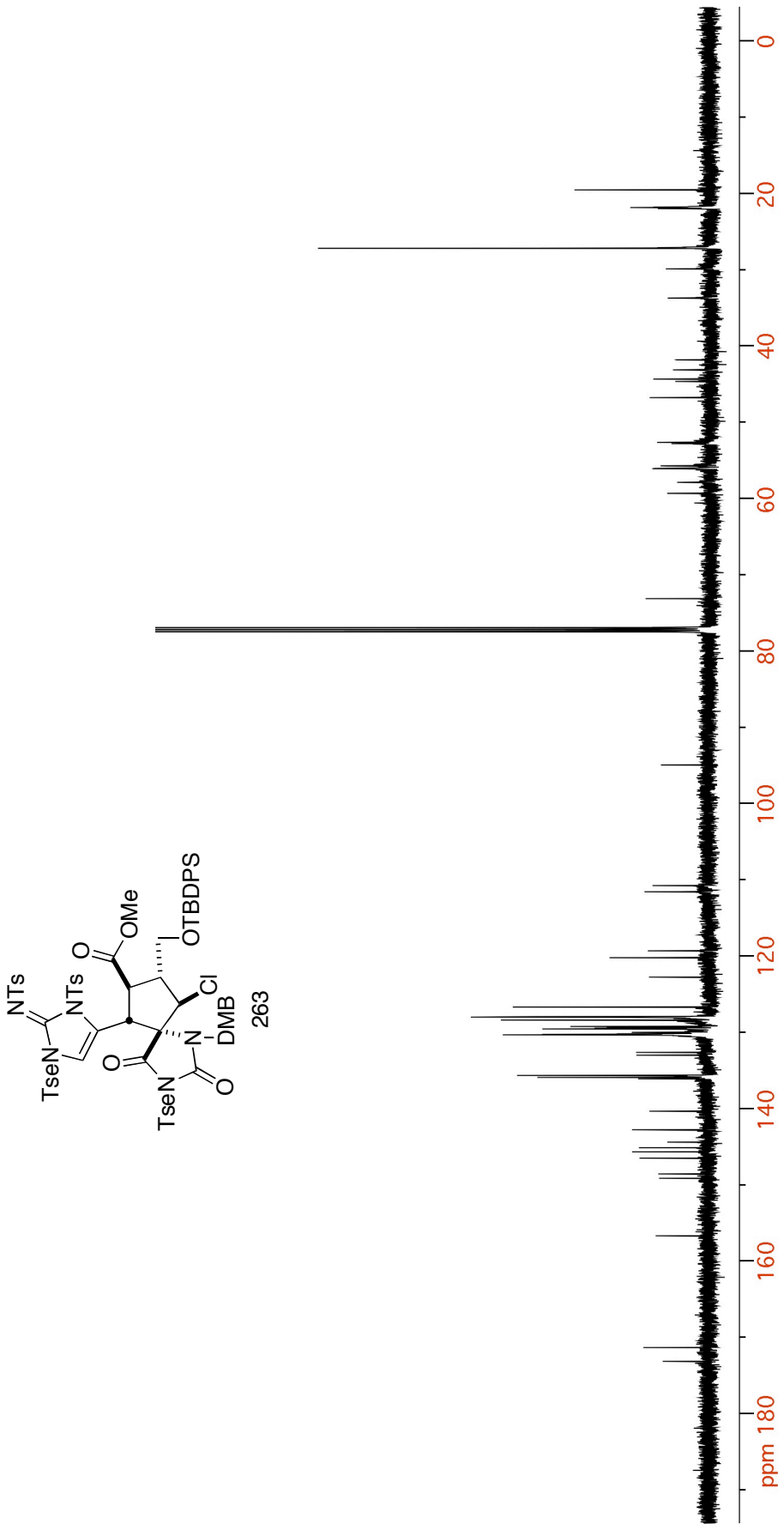
gHMQC spectrum of imidazolone azide **251** (in $CDCl_3$; expansion)



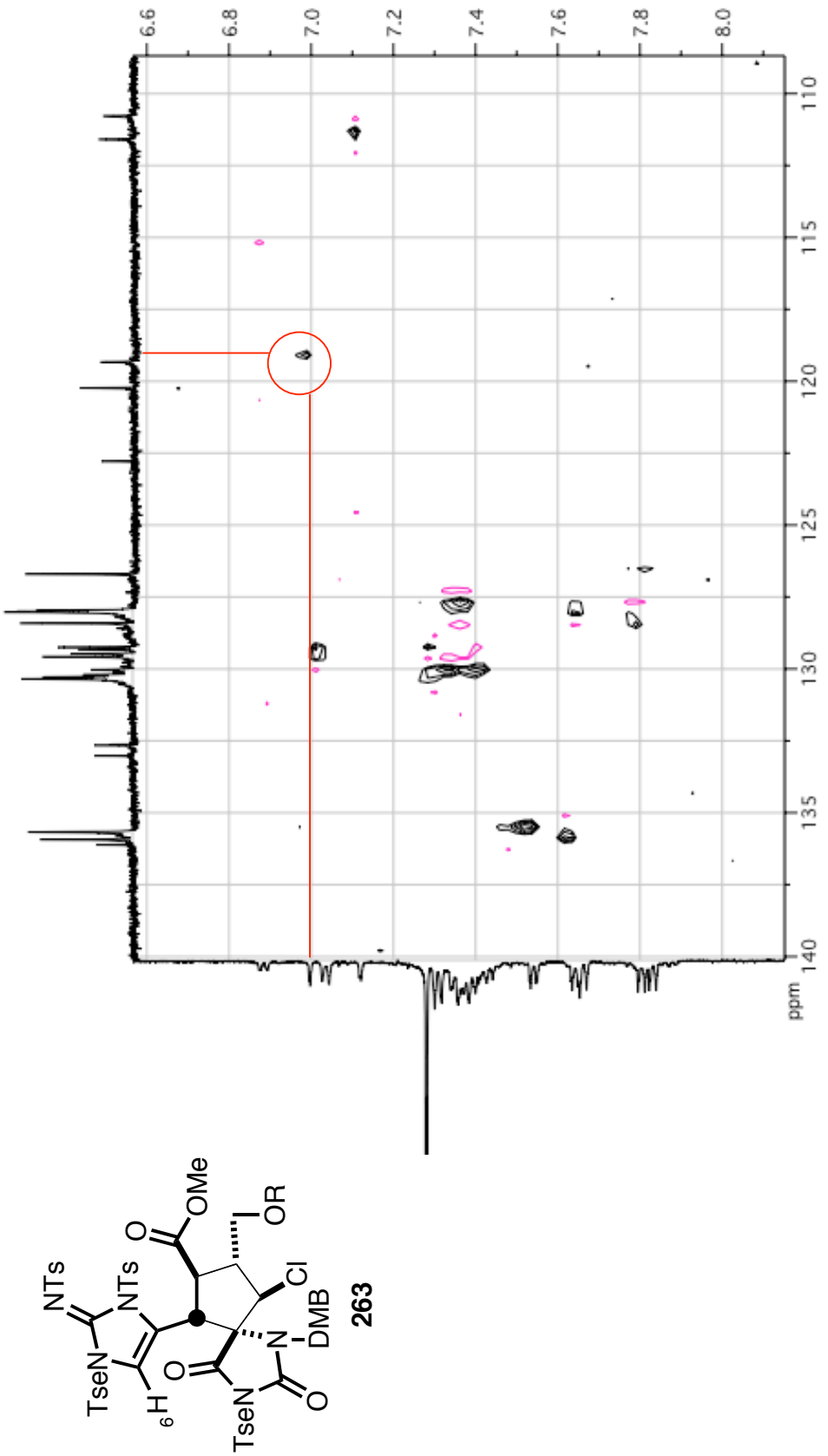
IR spectrum of imidazolone azide **251** (thin film on NaCl plate)



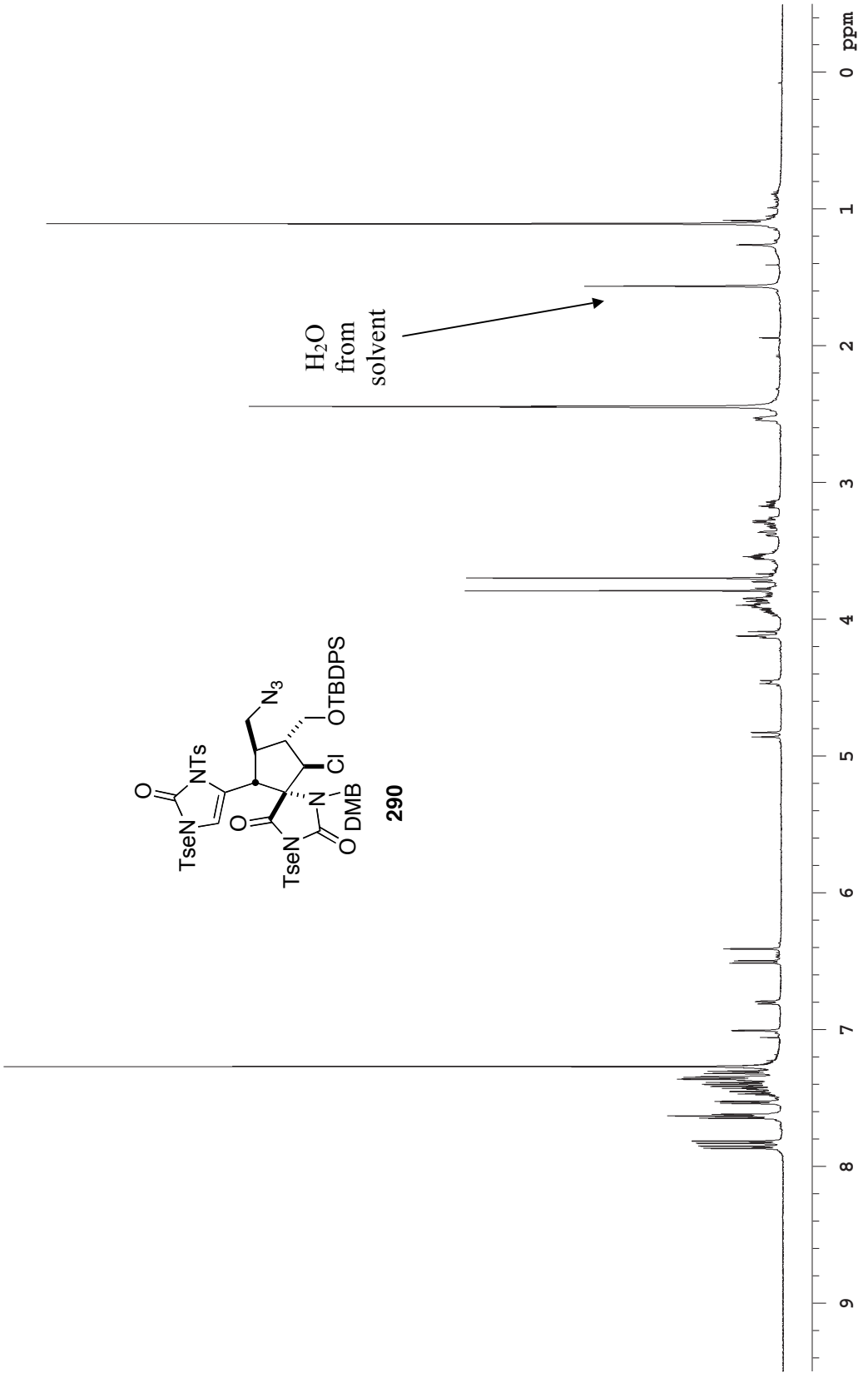
^{1}H NMR spectrum of guanidine **263** (in $CDCl_3$)



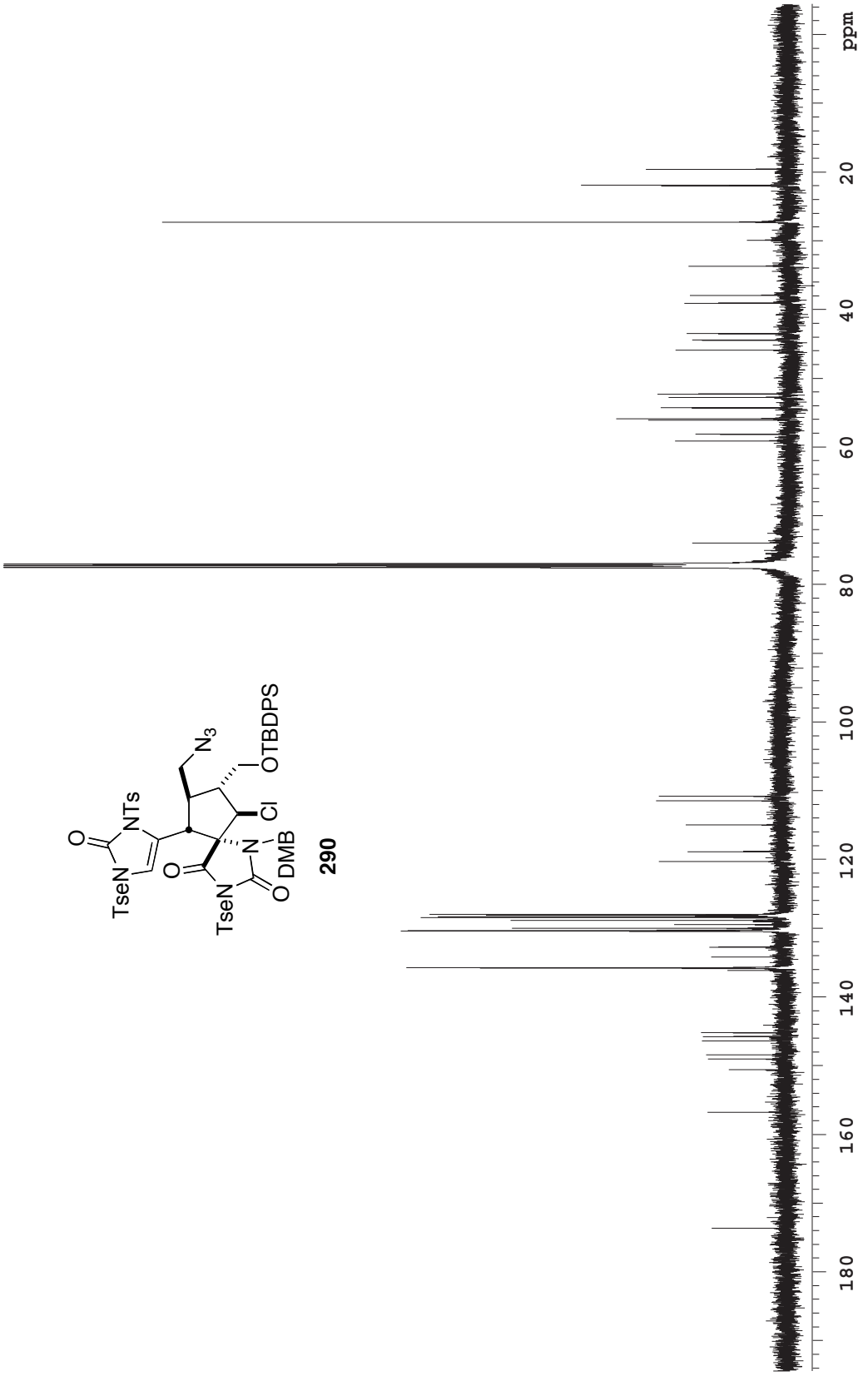
^{13}C NMR spectrum of guanidine **263** (in $CDCl_3$)



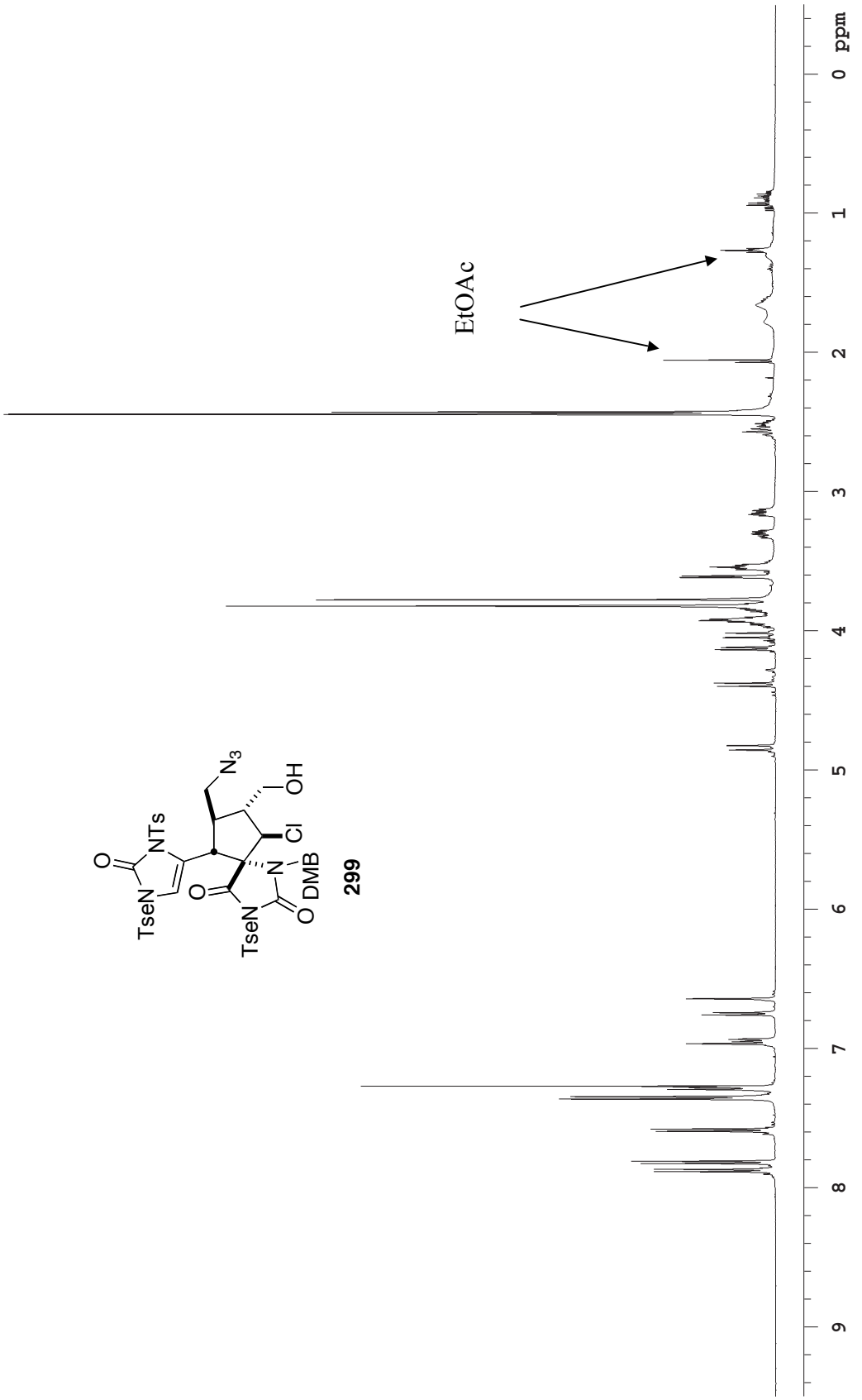
gHMQC spectrum of guanidine **263** (in $CDCl_3$; expansion)



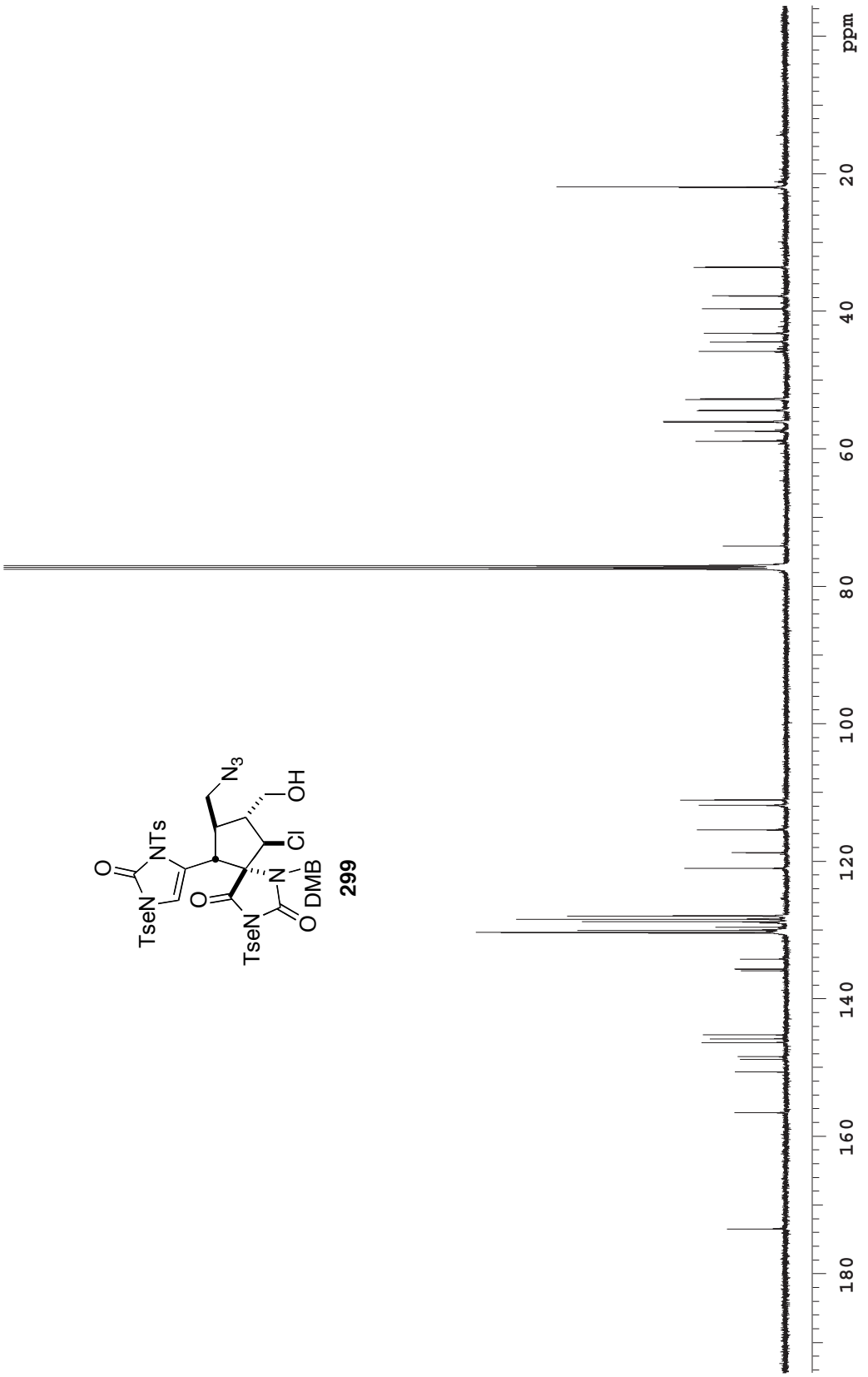
^{1}H NMR spectrum of azide **290** (in $CDCl_3$)



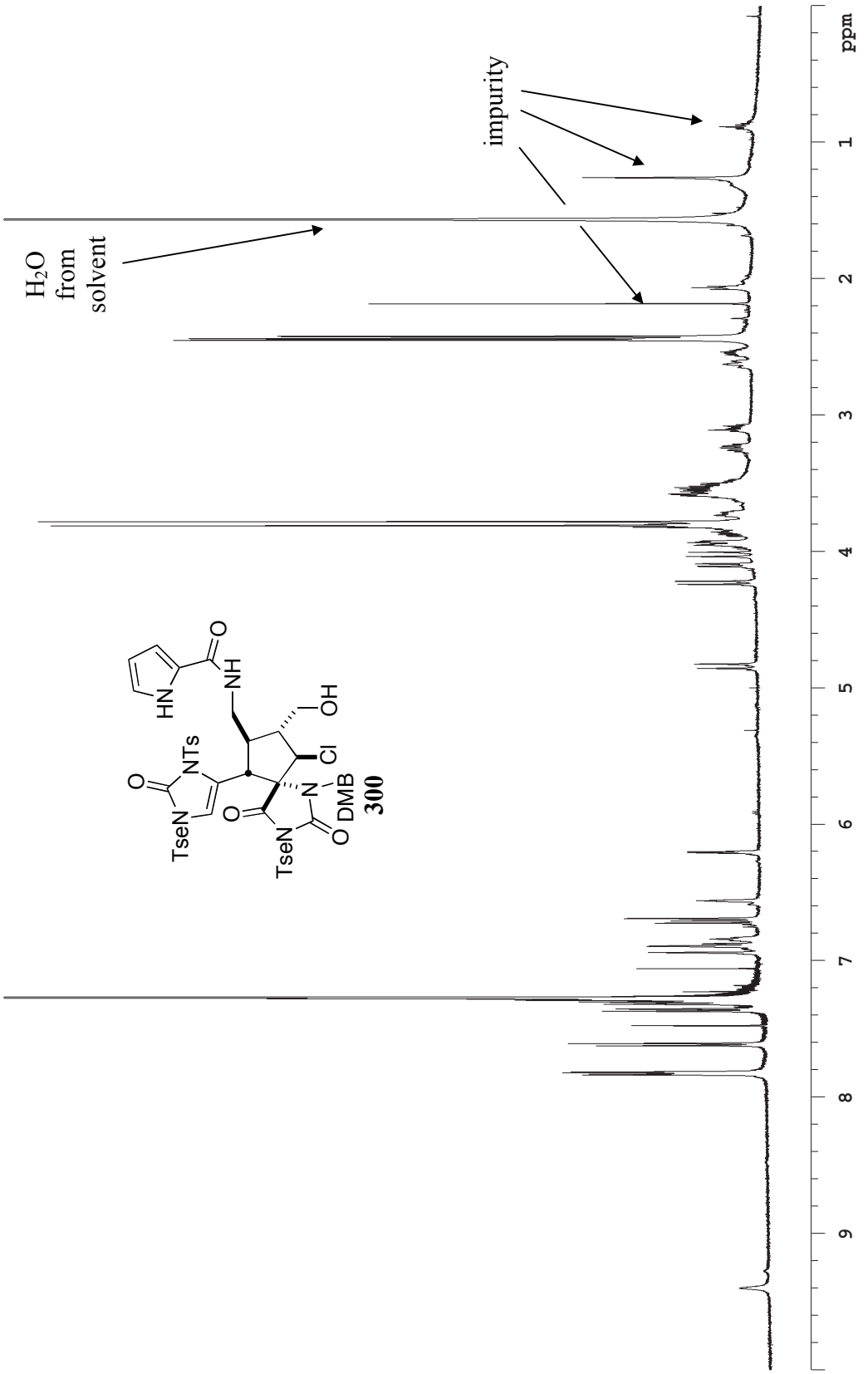
^{13}C NMR spectrum of azide **290** (in $CDCl_3$)



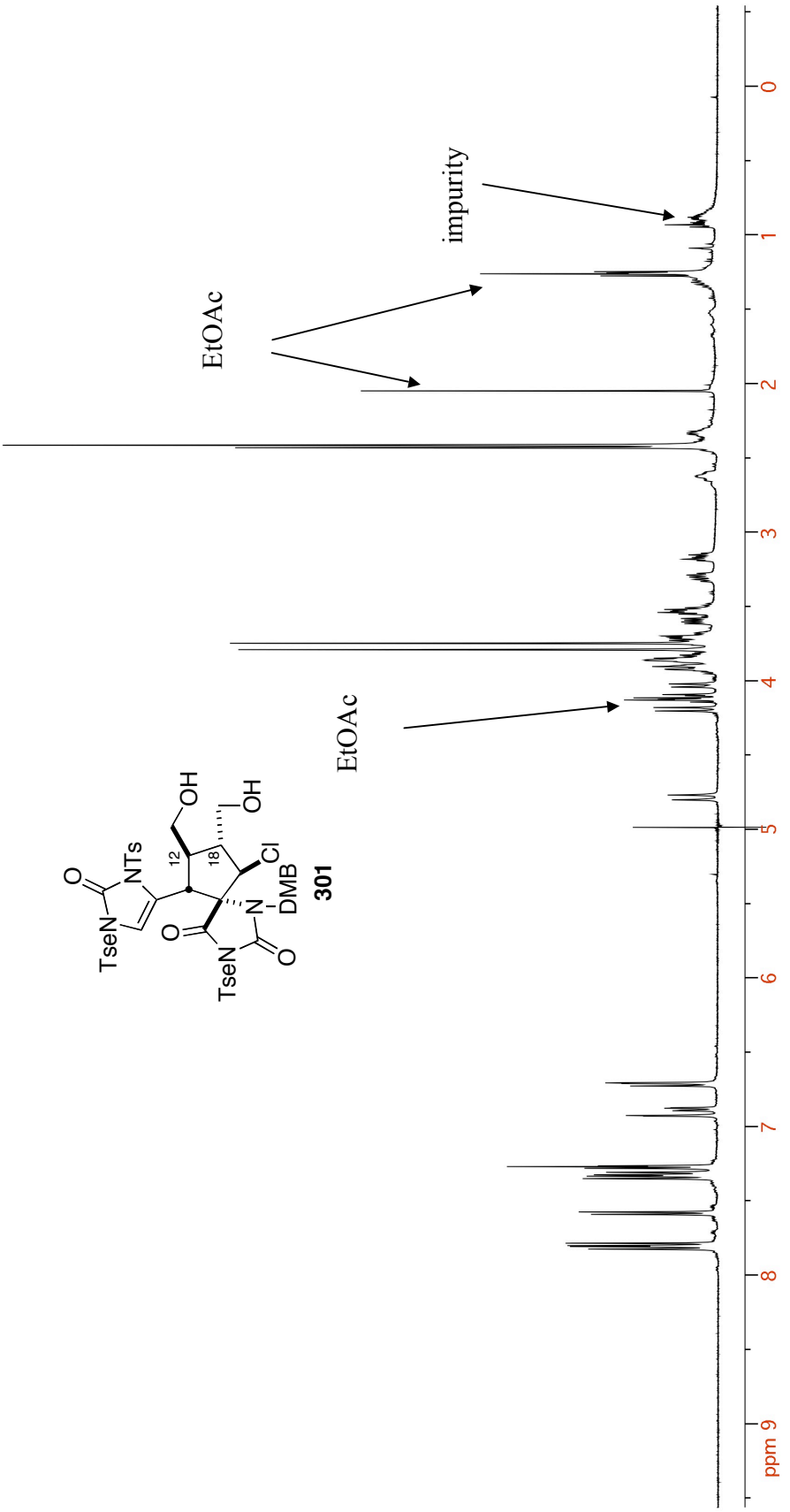
^{1}H NMR spectrum of azide **299** (in $CDCl_3$)



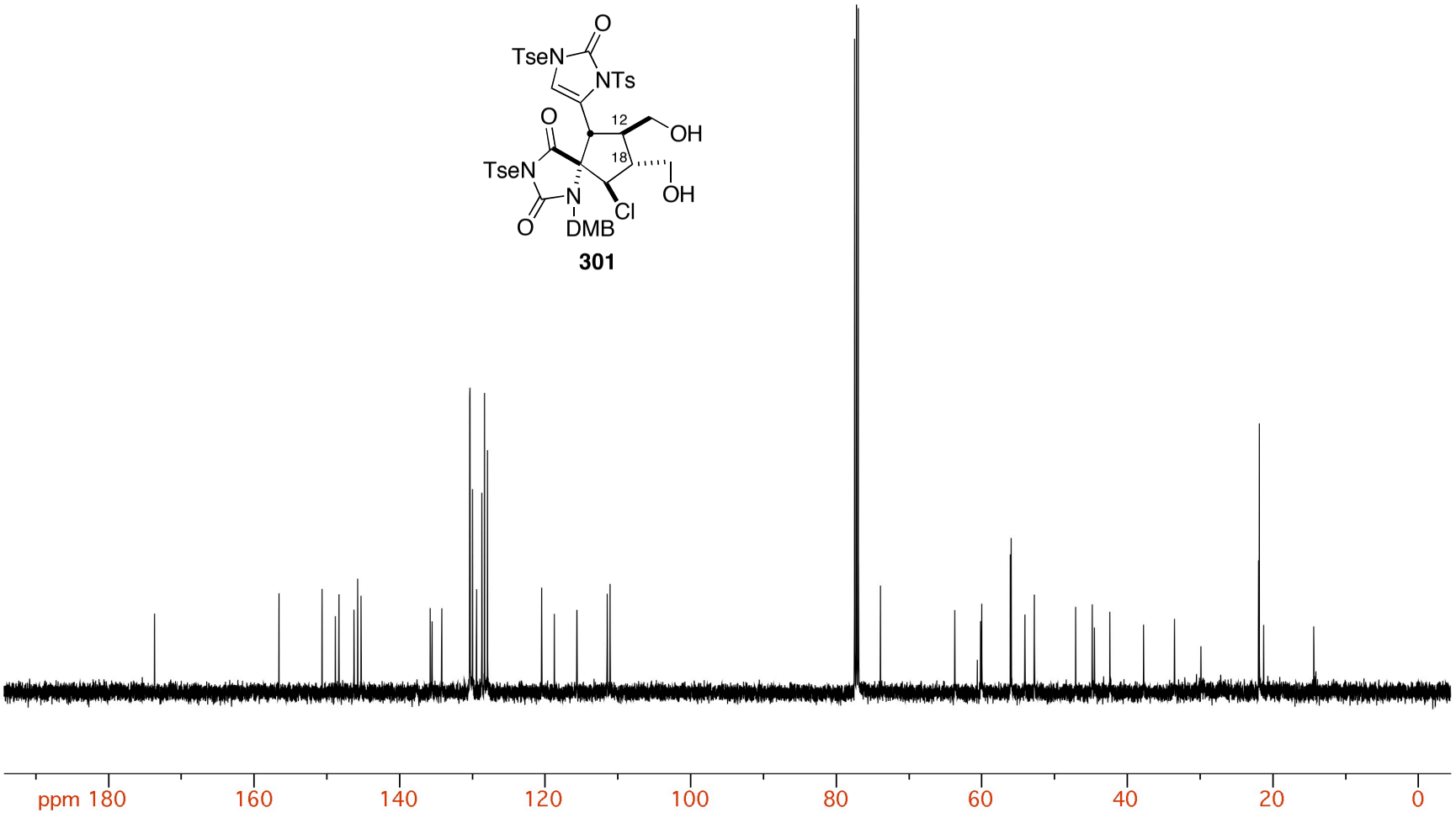
^{13}C NMR spectrum of azide **299** (in $CDCl_3$)



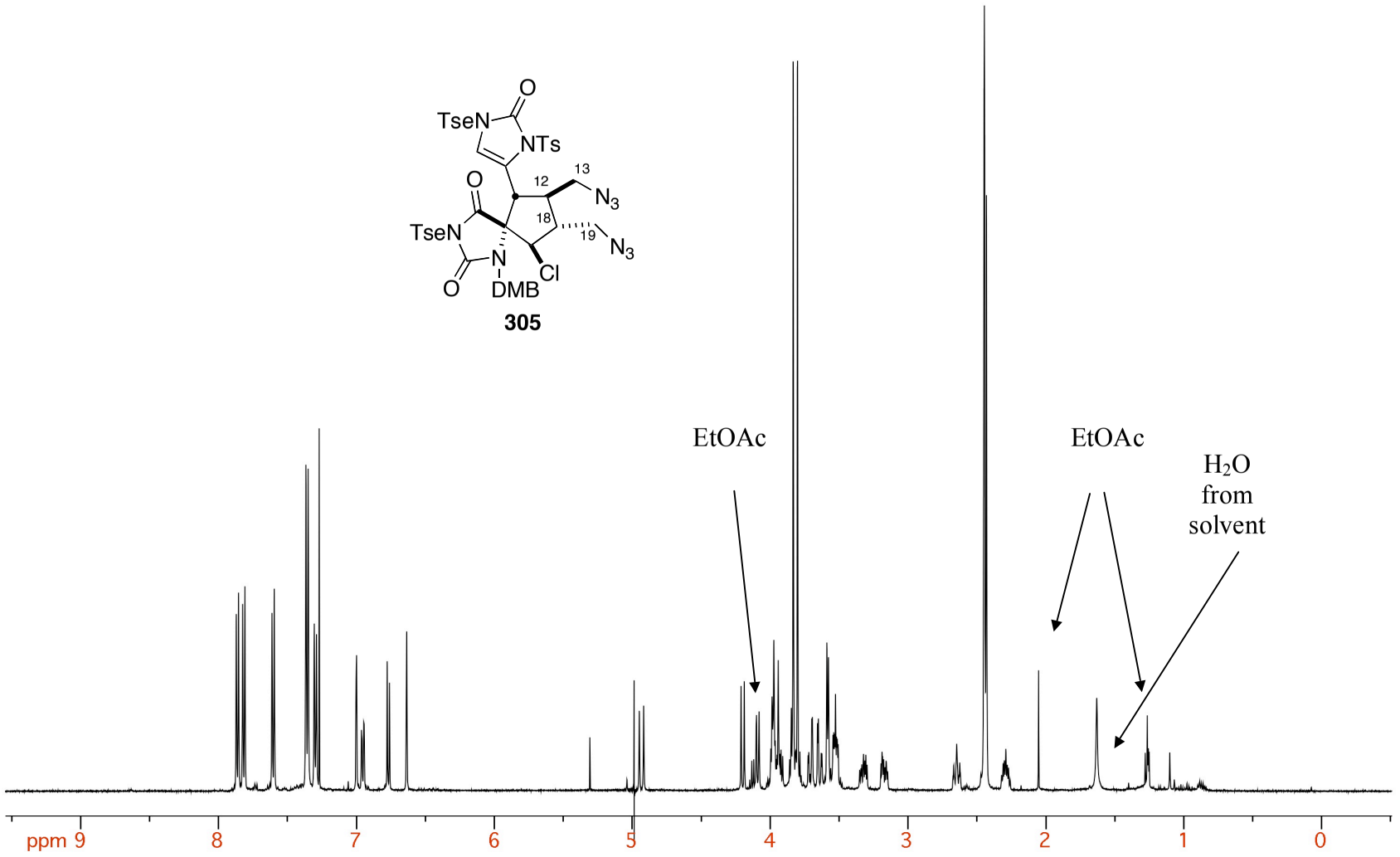
^{1}H NMR spectrum of pyrrolo amide **300** (in $CDCl_3$)



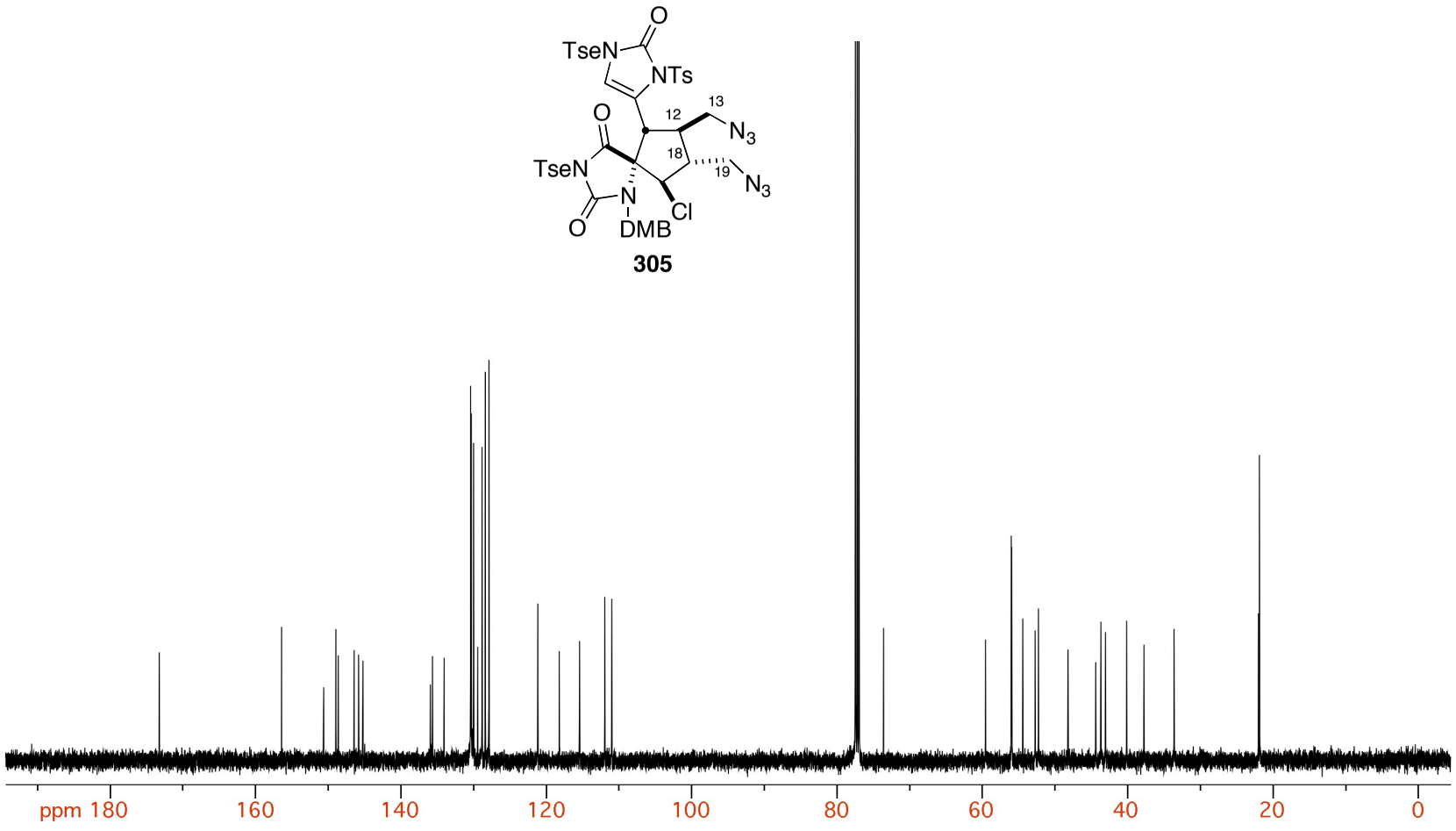
^{1}H NMR spectrum of diol **301** (in $CDCl_3$)



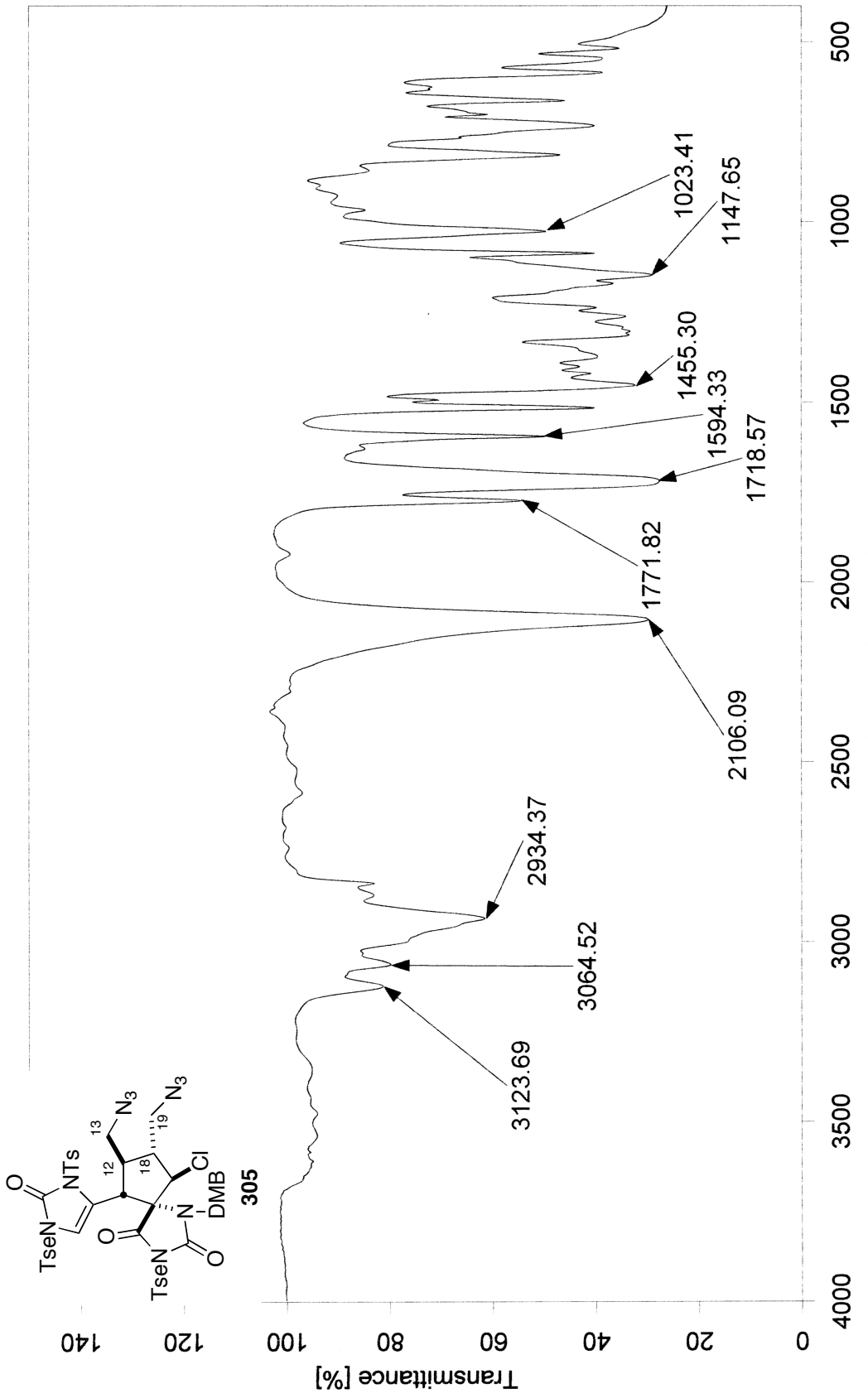
^{13}C NMR spectrum of diol **301** (in $CDCl_3$)



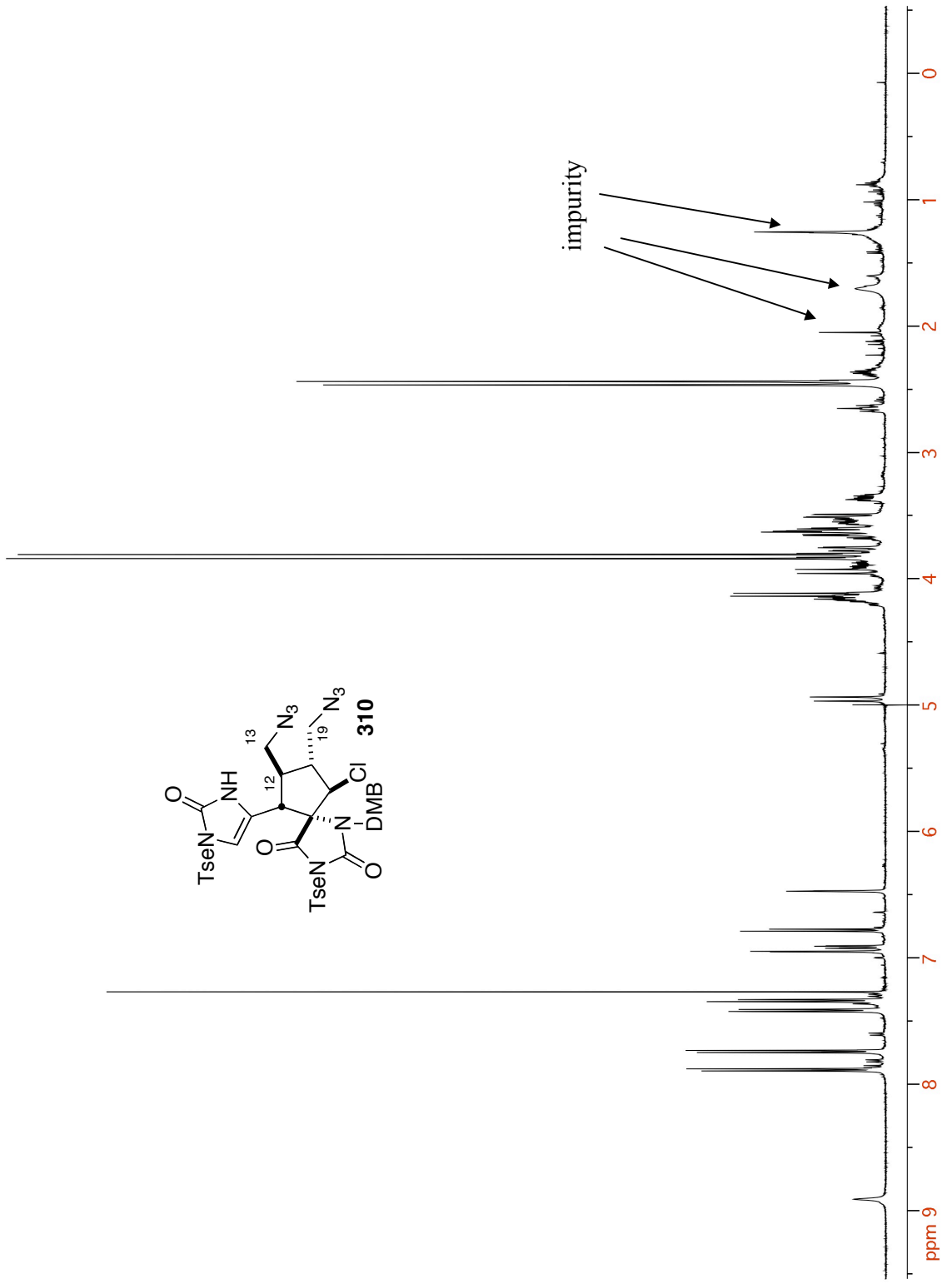
^{1}H NMR spectrum of bis-azide **305** (in $CDCl_3$)



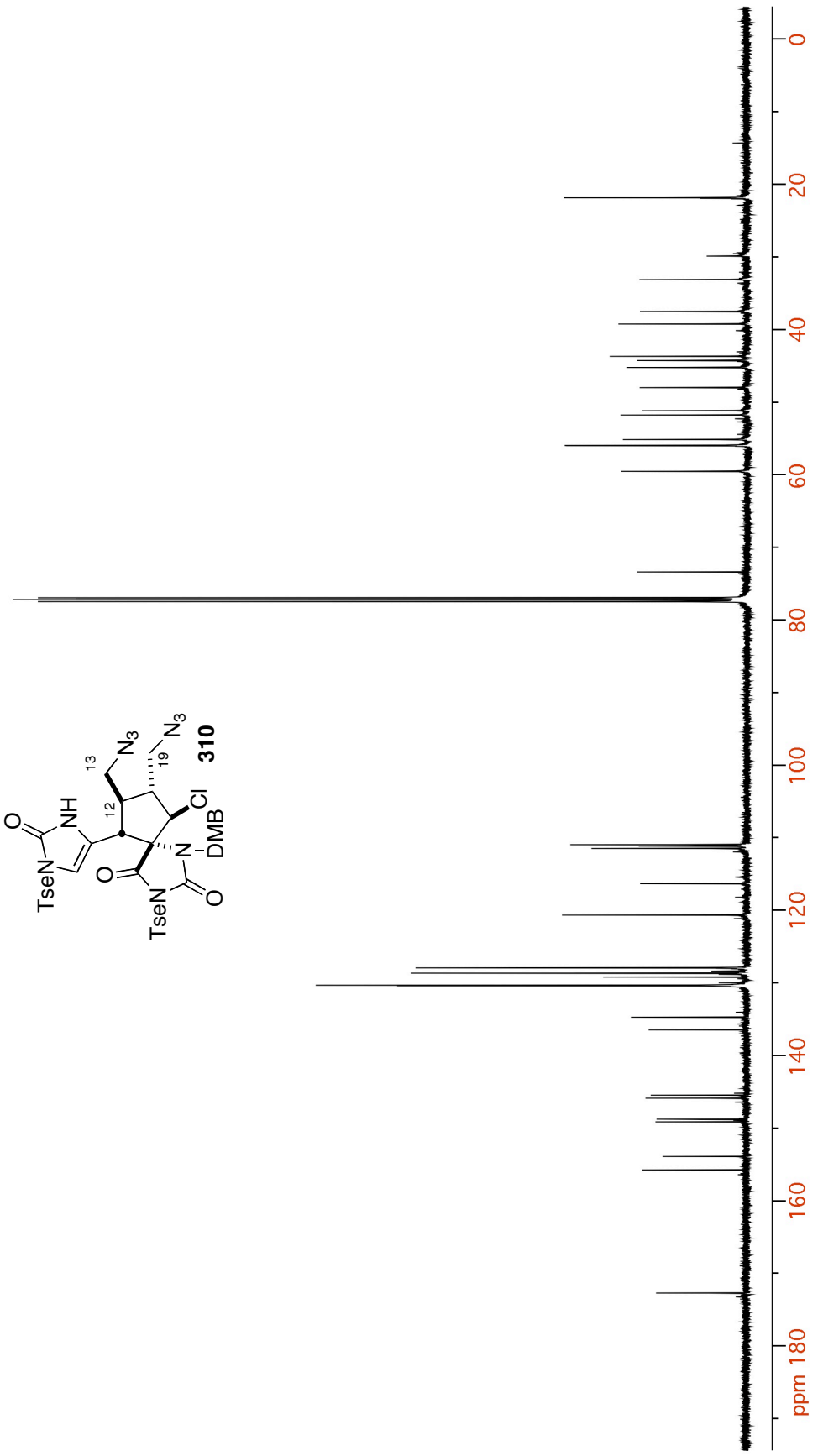
^{13}C NMR spectrum of bis-azide **305** (in $CDCl_3$)



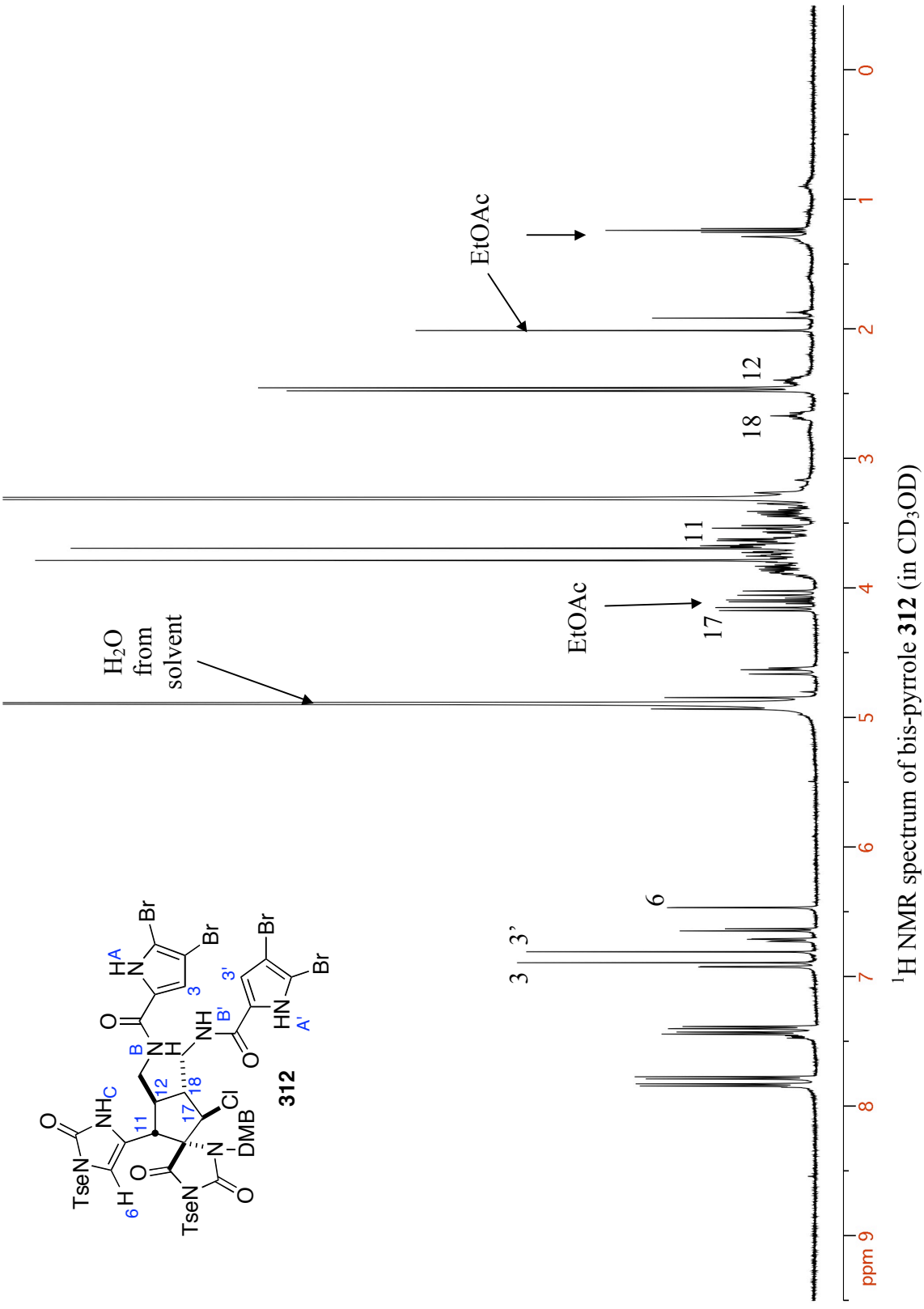
IR spectrum of bis-azide **305** (thin film on NaCl plate)



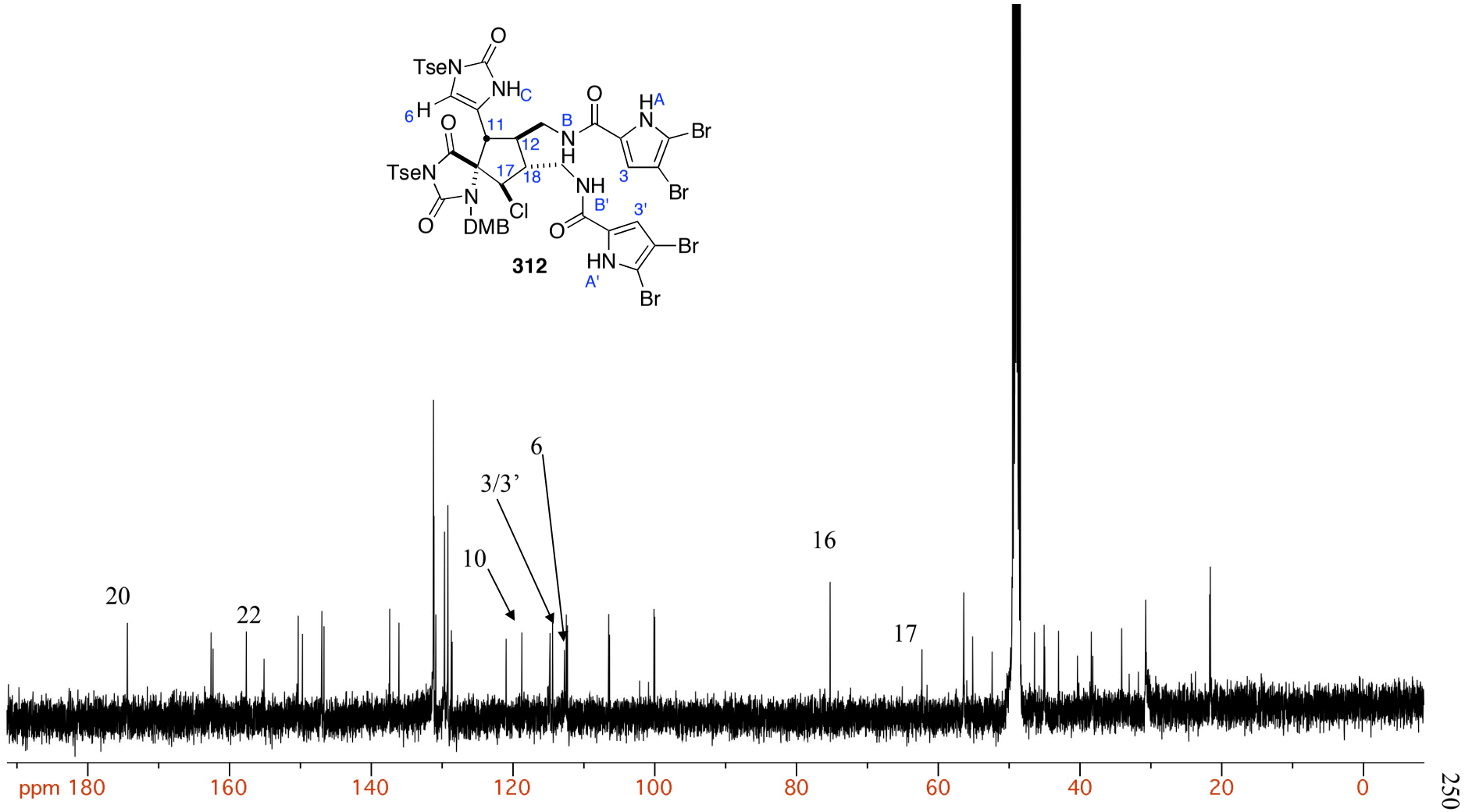
^{1}H NMR spectrum of bis-azide **310** (in $CDCl_3$)



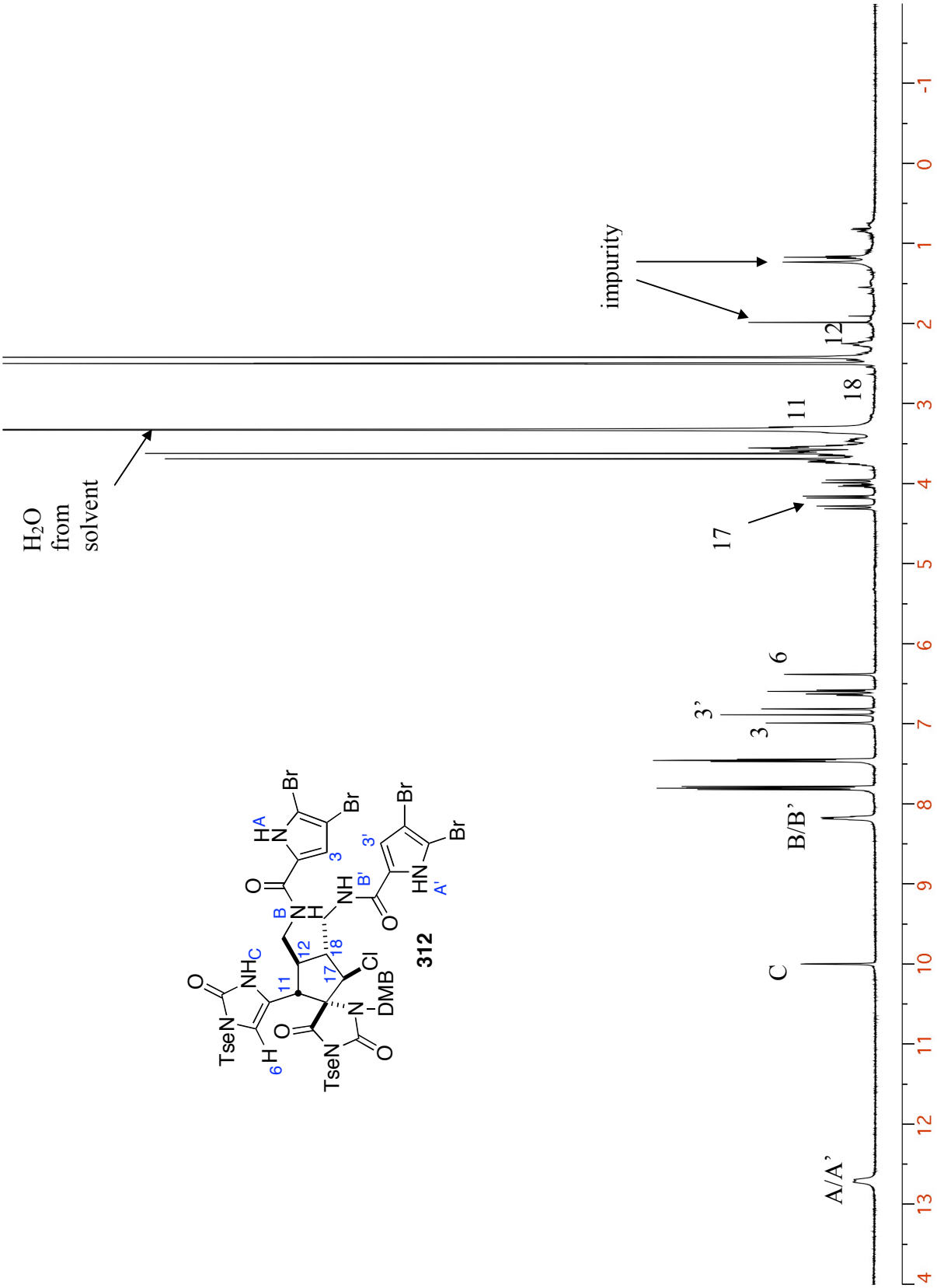
^{13}C NMR spectrum of bis-azide **310** (in $CDCl_3$)



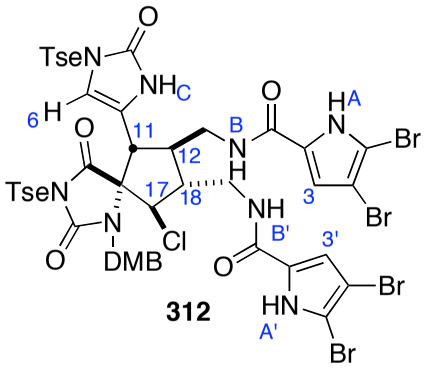
^{1}H NMR spectrum of bis-pyrrole **312** (in CD_3OD)



^{13}C NMR spectrum of bis-pyrrole **312** (in CD_3OD)

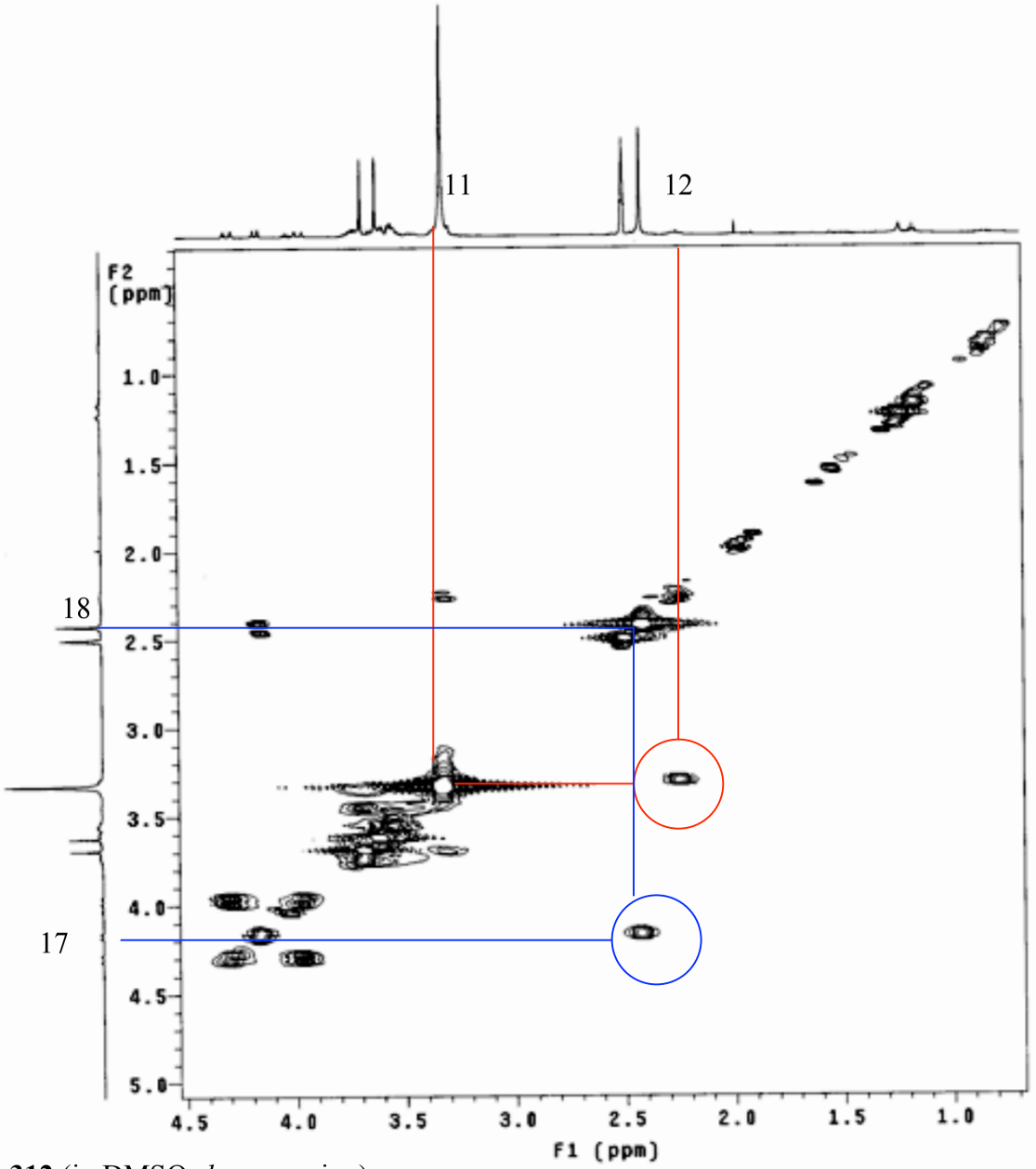


^{1}H NMR spectrum of bis-pyrrole **312** (in DMSO-d_6)

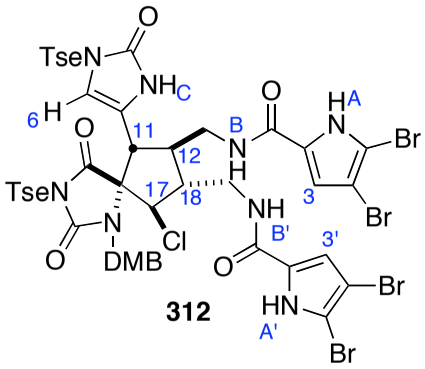


312

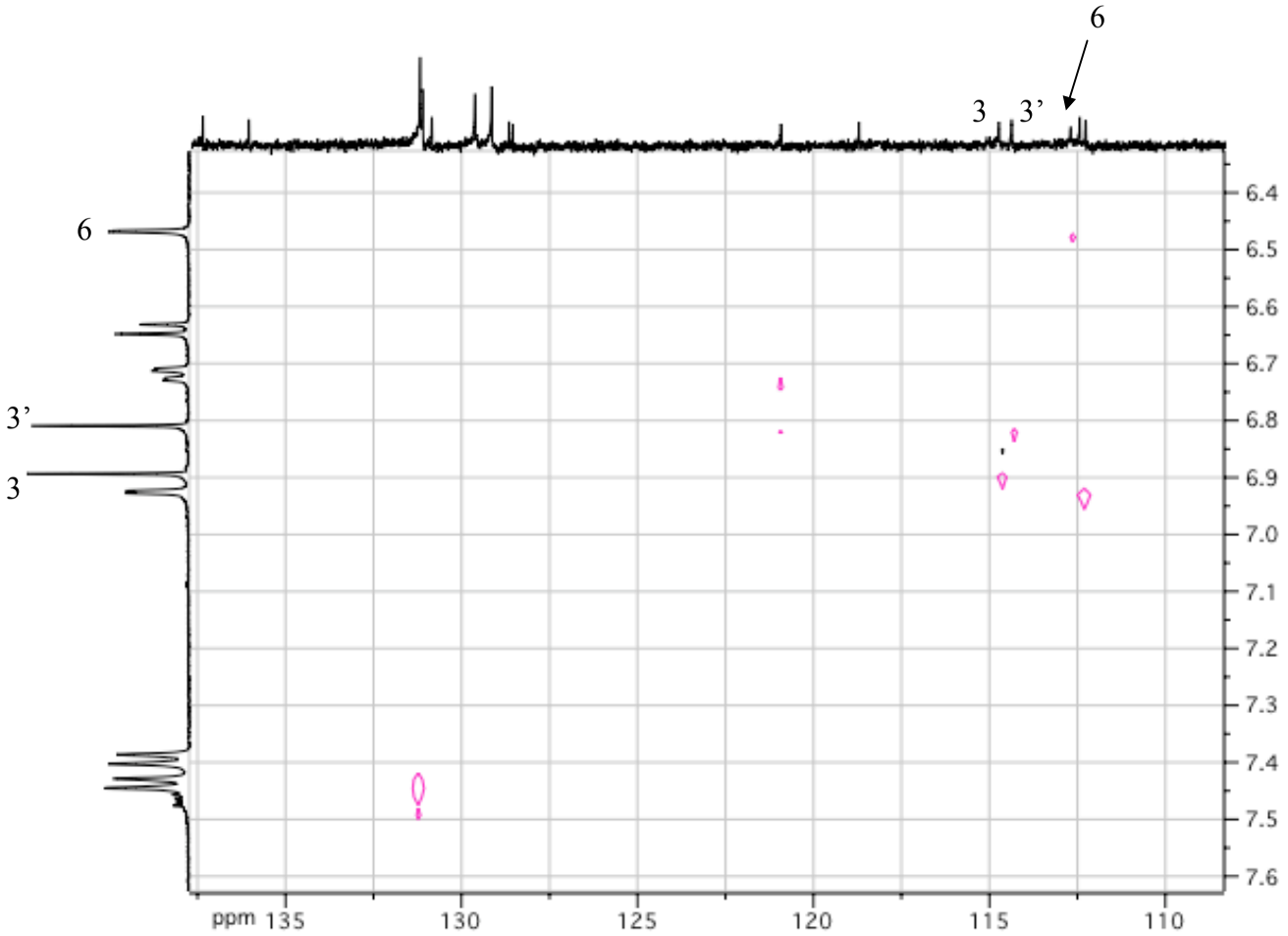
2D correlations:
H17 identifies H18 covered by solvent peak (blue)
H12 identifies H11 covered by water peak from solvent (red)



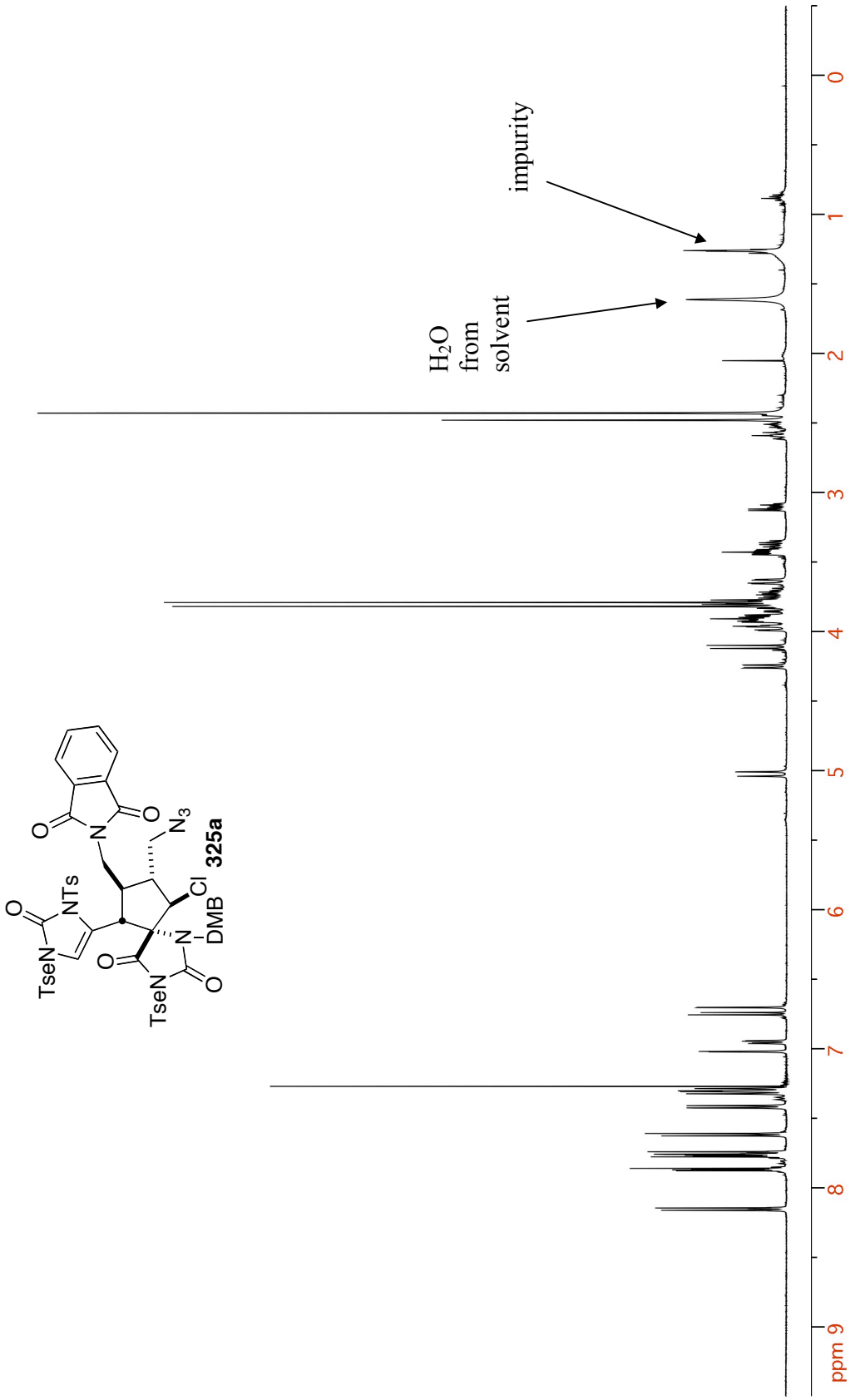
^{1}H-^{1}H gCOSYspectrum of bis-pyrrole **312** (in DMSO-d_6; expansion)



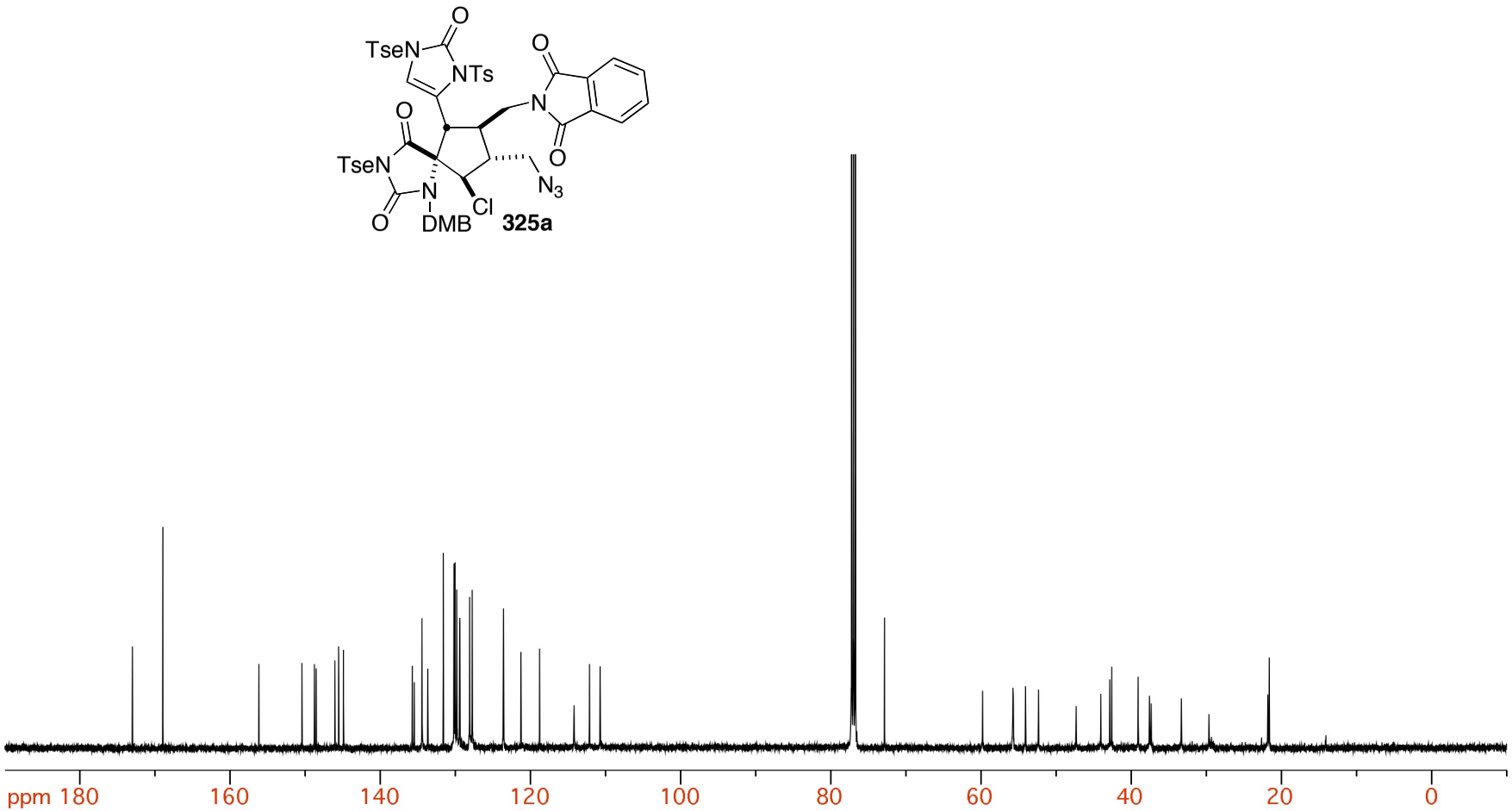
312



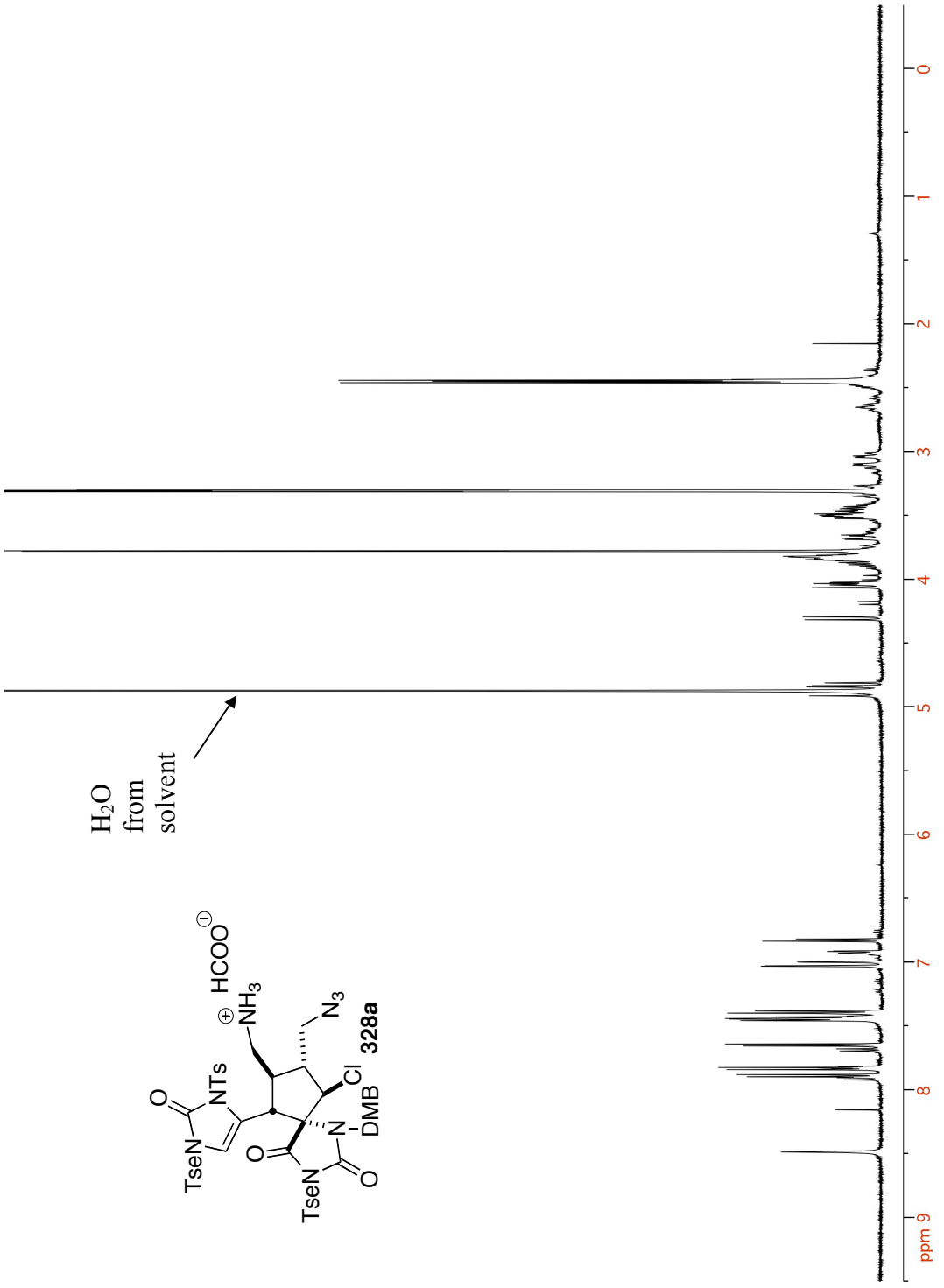
HMQC spectrum of bis-pyrrole **312** (in CD_3OD; expansion)



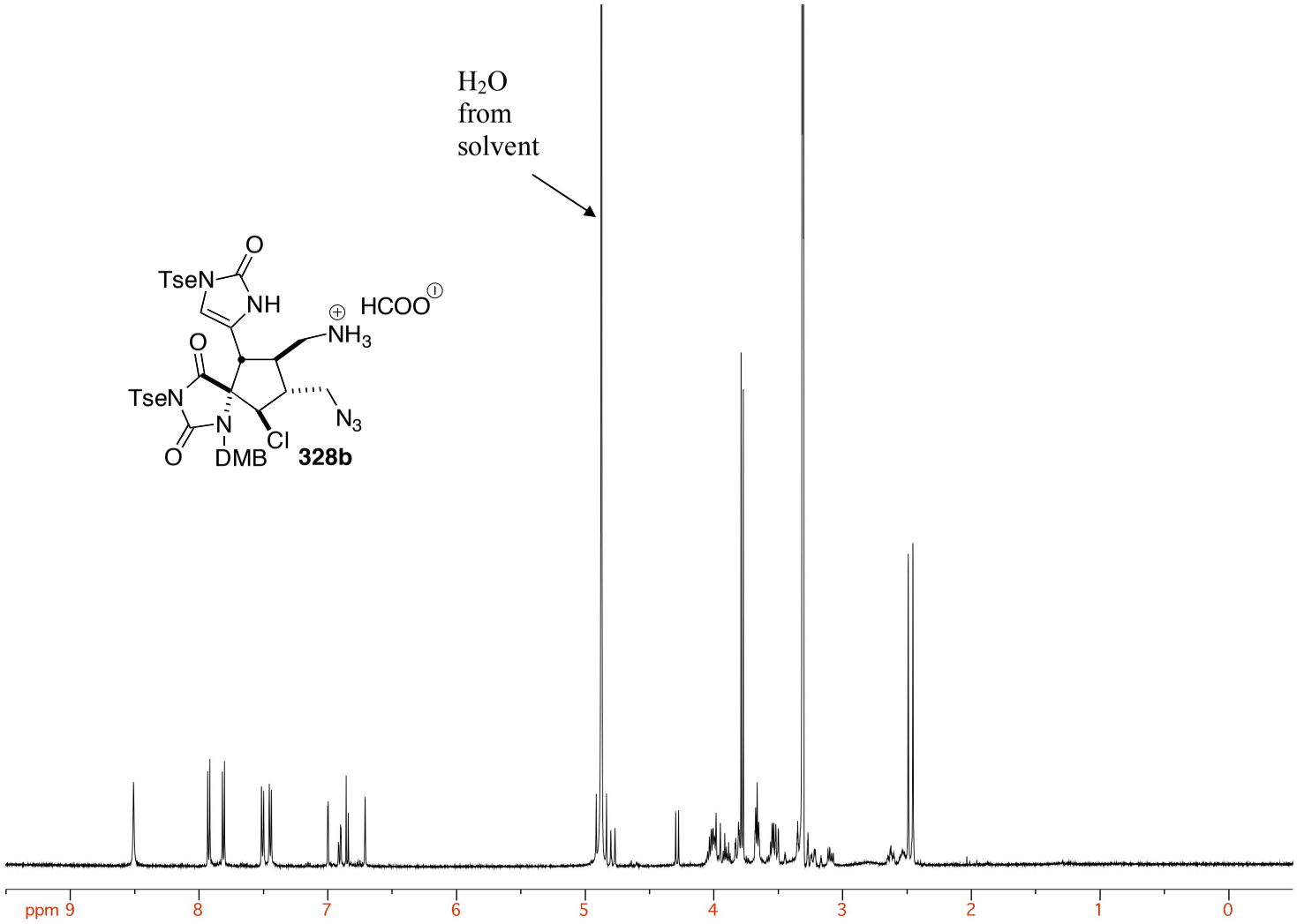
^{1}H NMR spectrum of phthalimide **325a** (in $CDCl_3$)



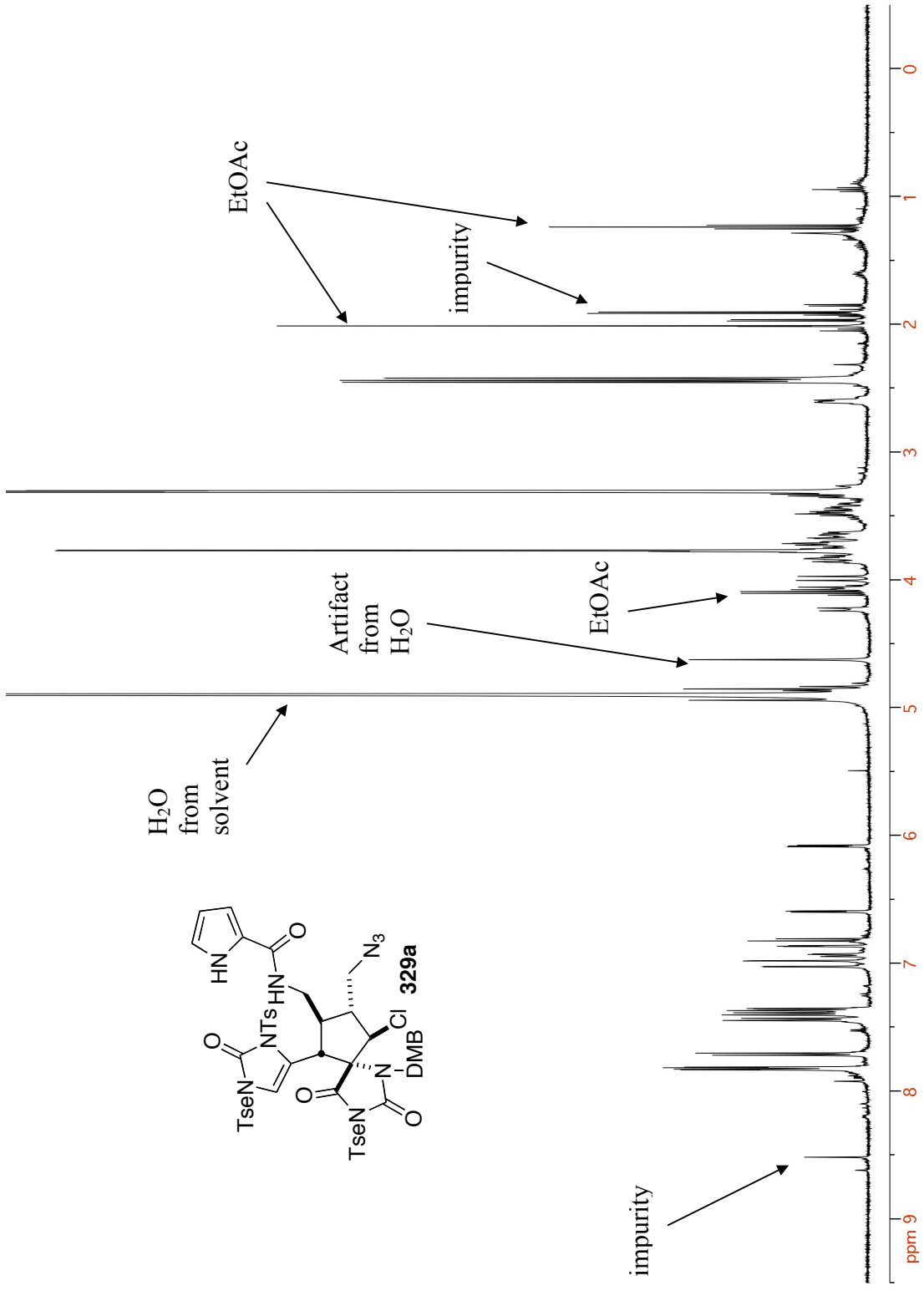
^{13}C NMR spectrum of phthalimide **325a** (in $CDCl_3$)



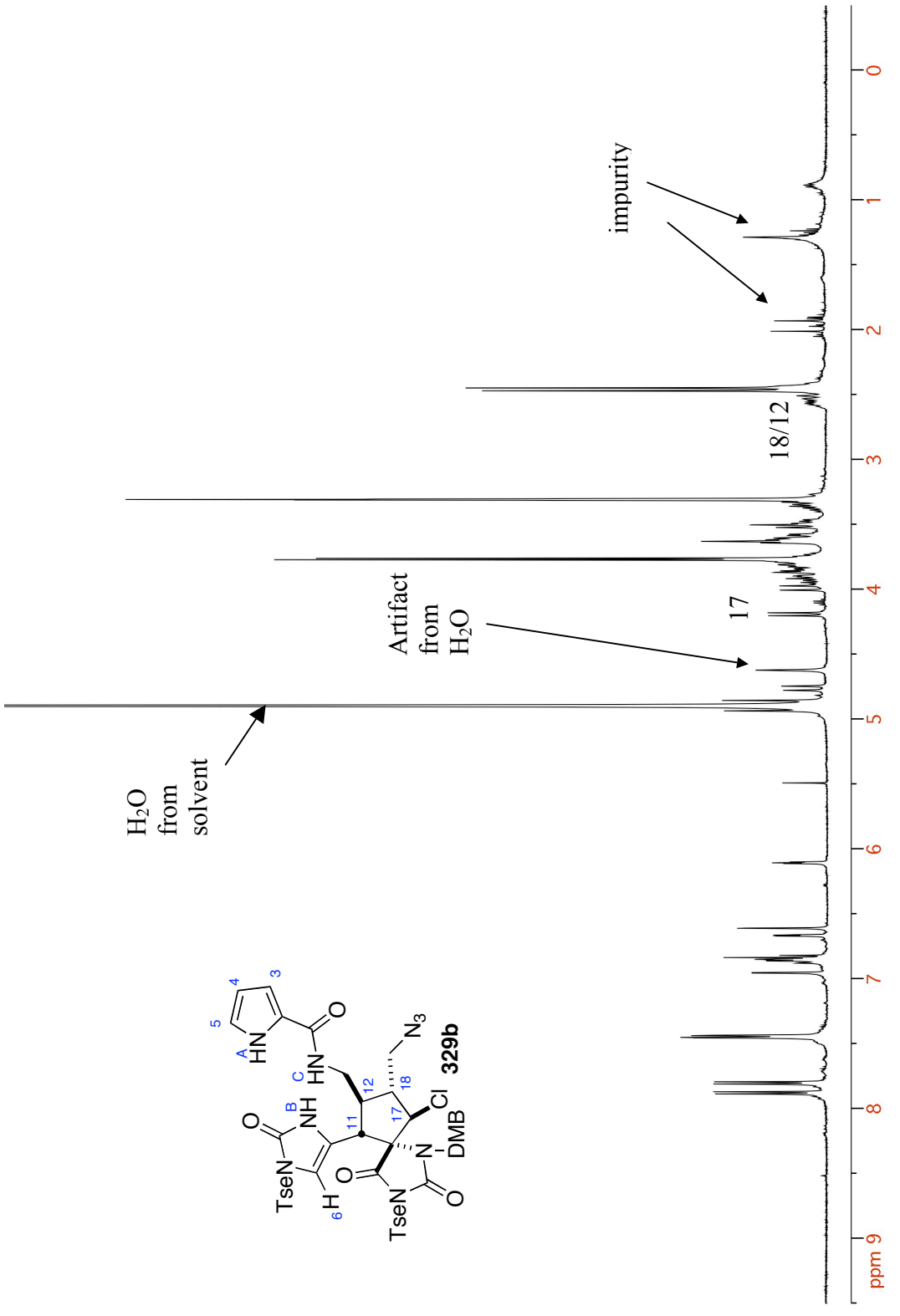
^{1}H NMR spectrum of amine **328a** (formate salt after preparative HPLC purification; in CD_3OD)



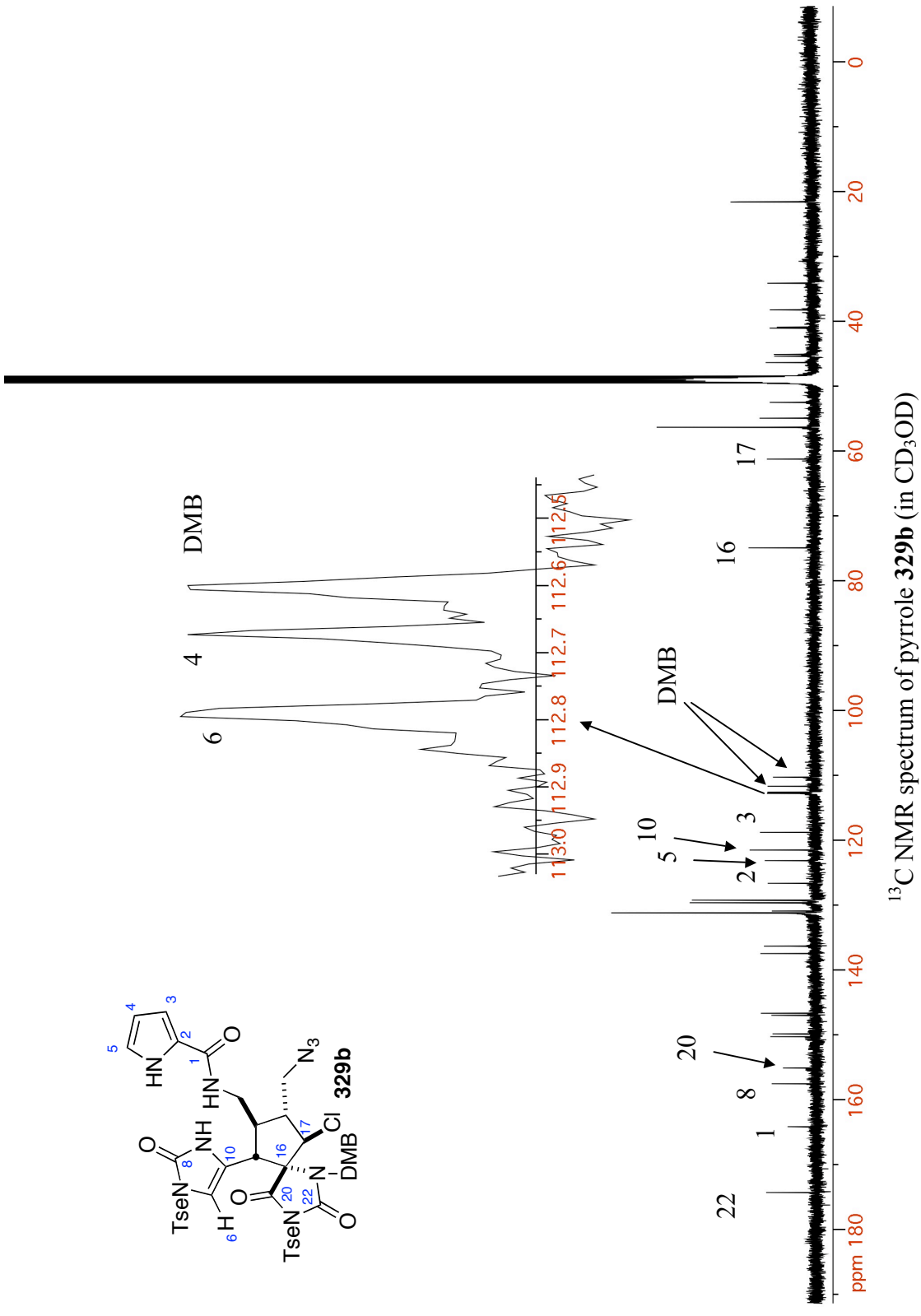
^{1}H NMR spectrum of amine **328b** (formate salt after preparative HPLC purification; in CD_3OD)



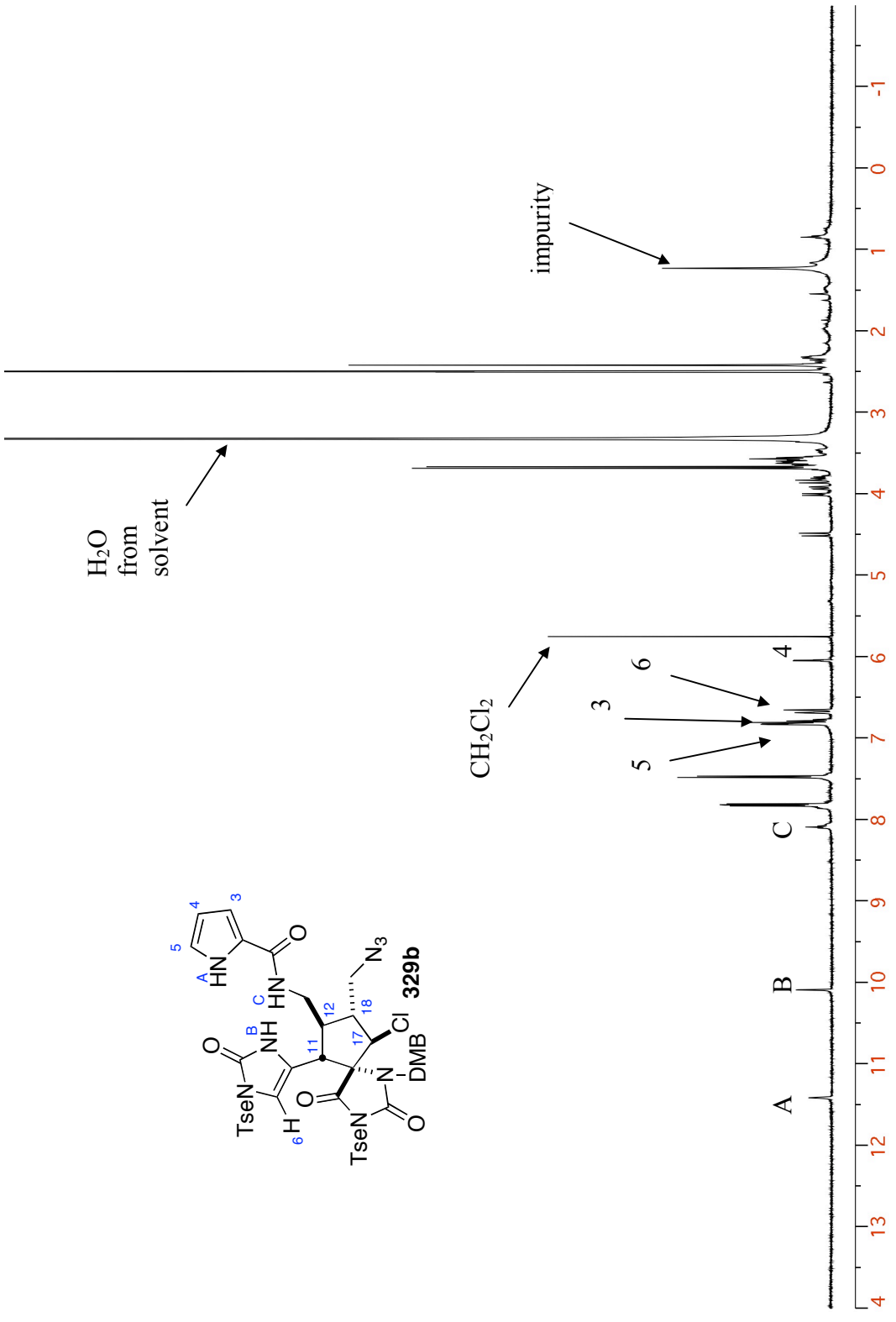
^{1}H NMR spectrum of pyrrole **329a** (in CD_3OD)



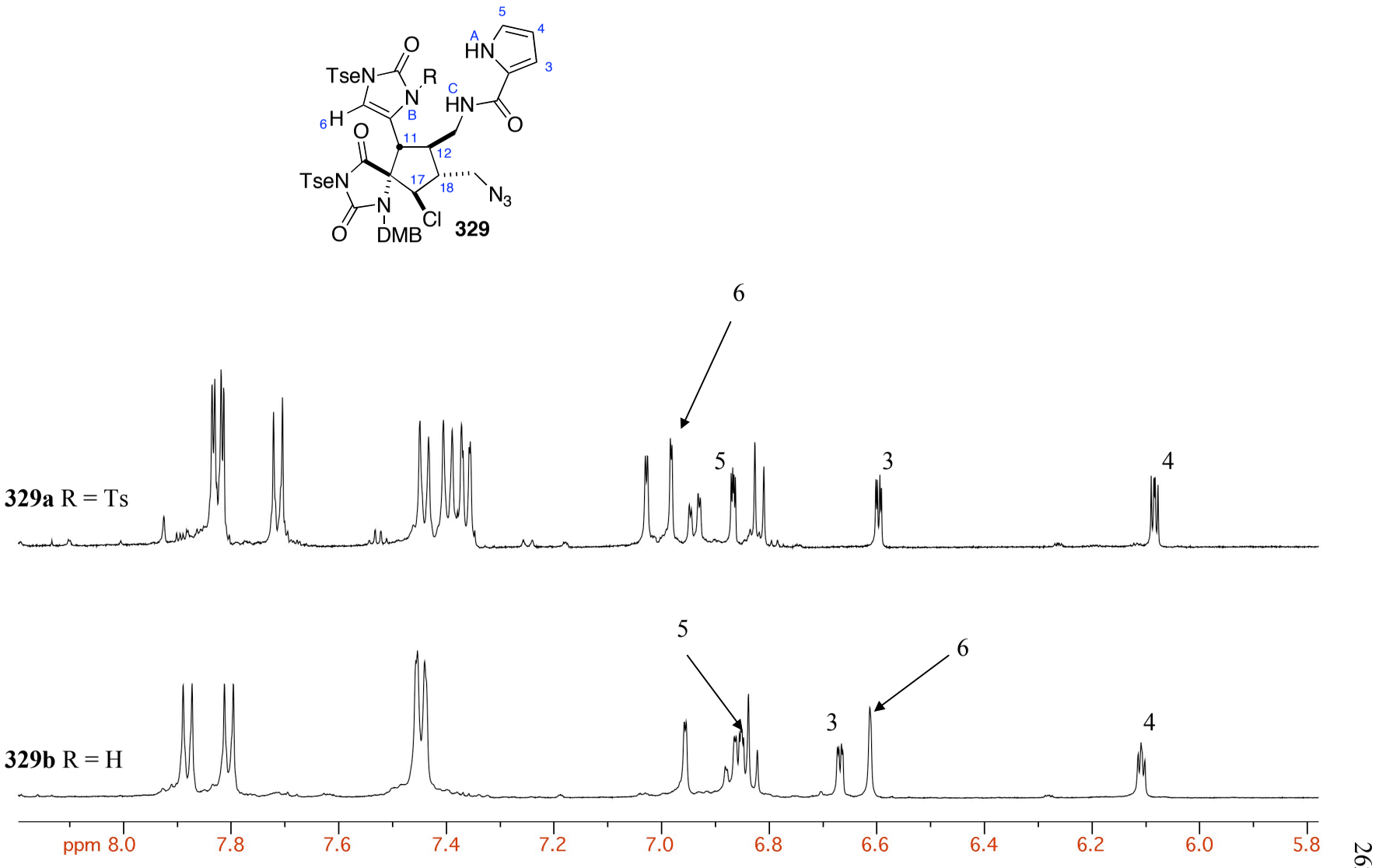
^{1}H NMR spectrum of pyrrole **329b** (in CD_3OD)



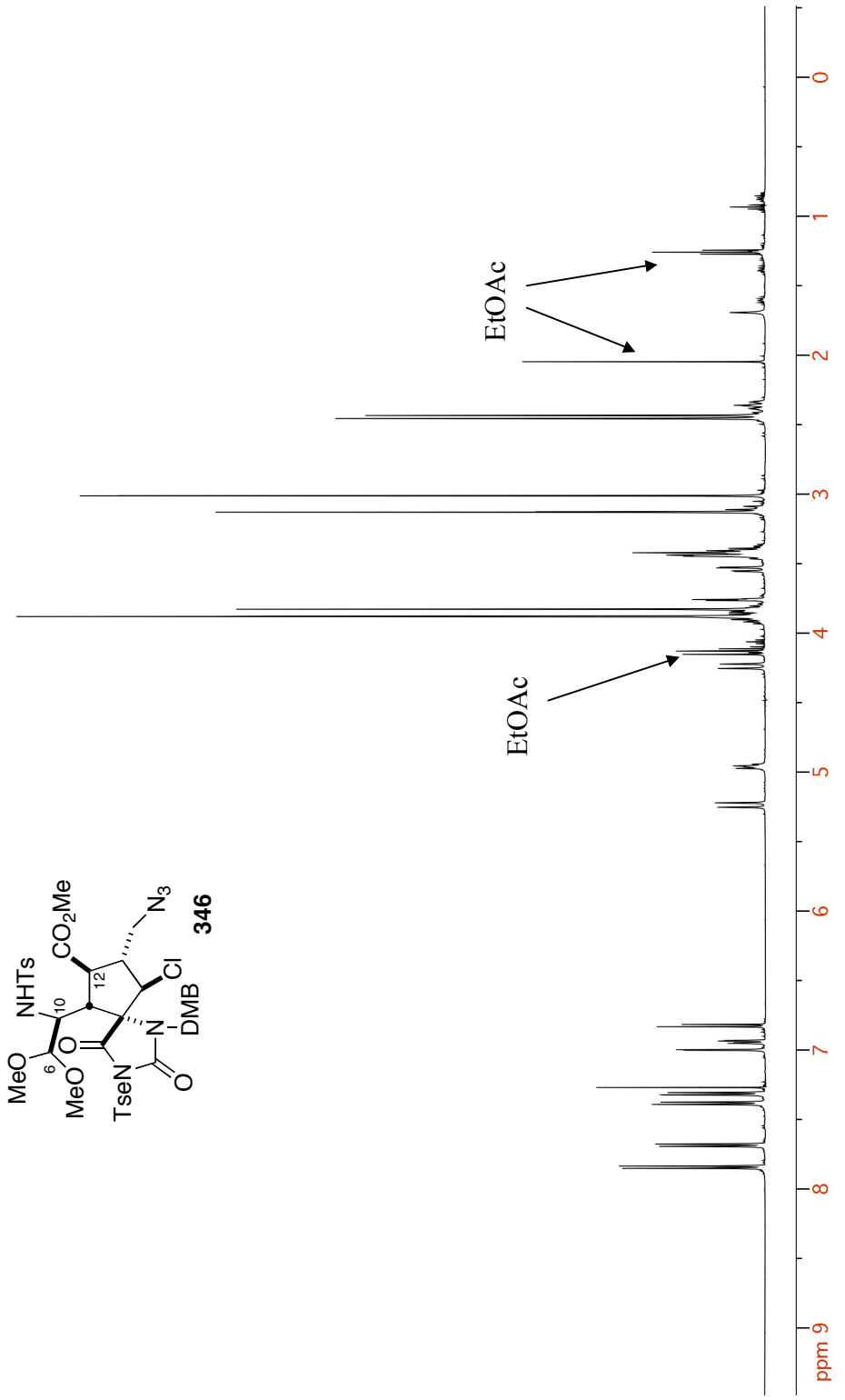
^{13}C NMR spectrum of pyrrole **329b** (in CD_3OD)



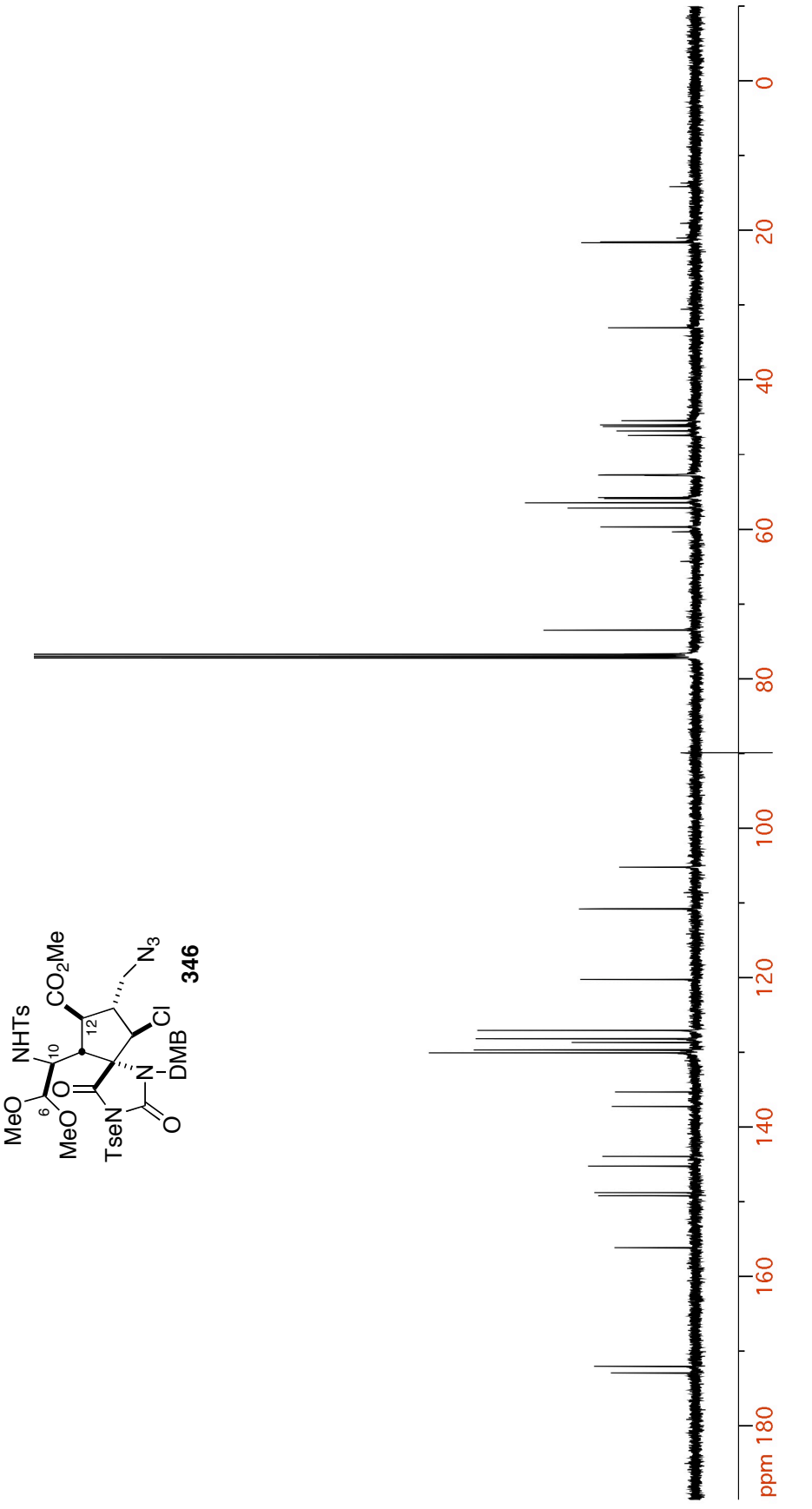
^{1}H NMR spectrum of pyrrole **329b** (in DMSO-d_6)



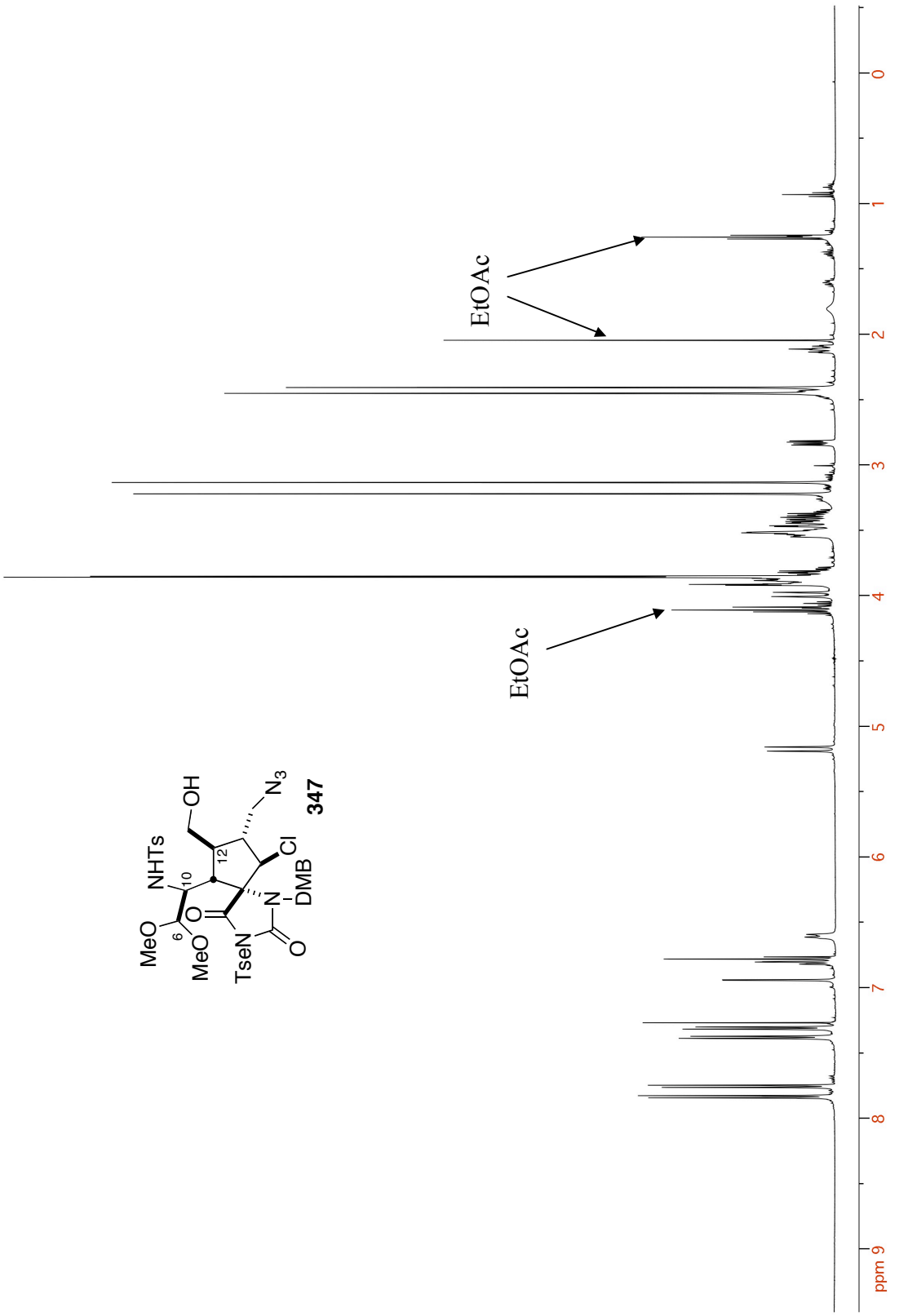
[1]H NMR spectra of tosylated pyrrole **329a** and pyrrole **329b** (in CD_3OD; expansion): shift of H6



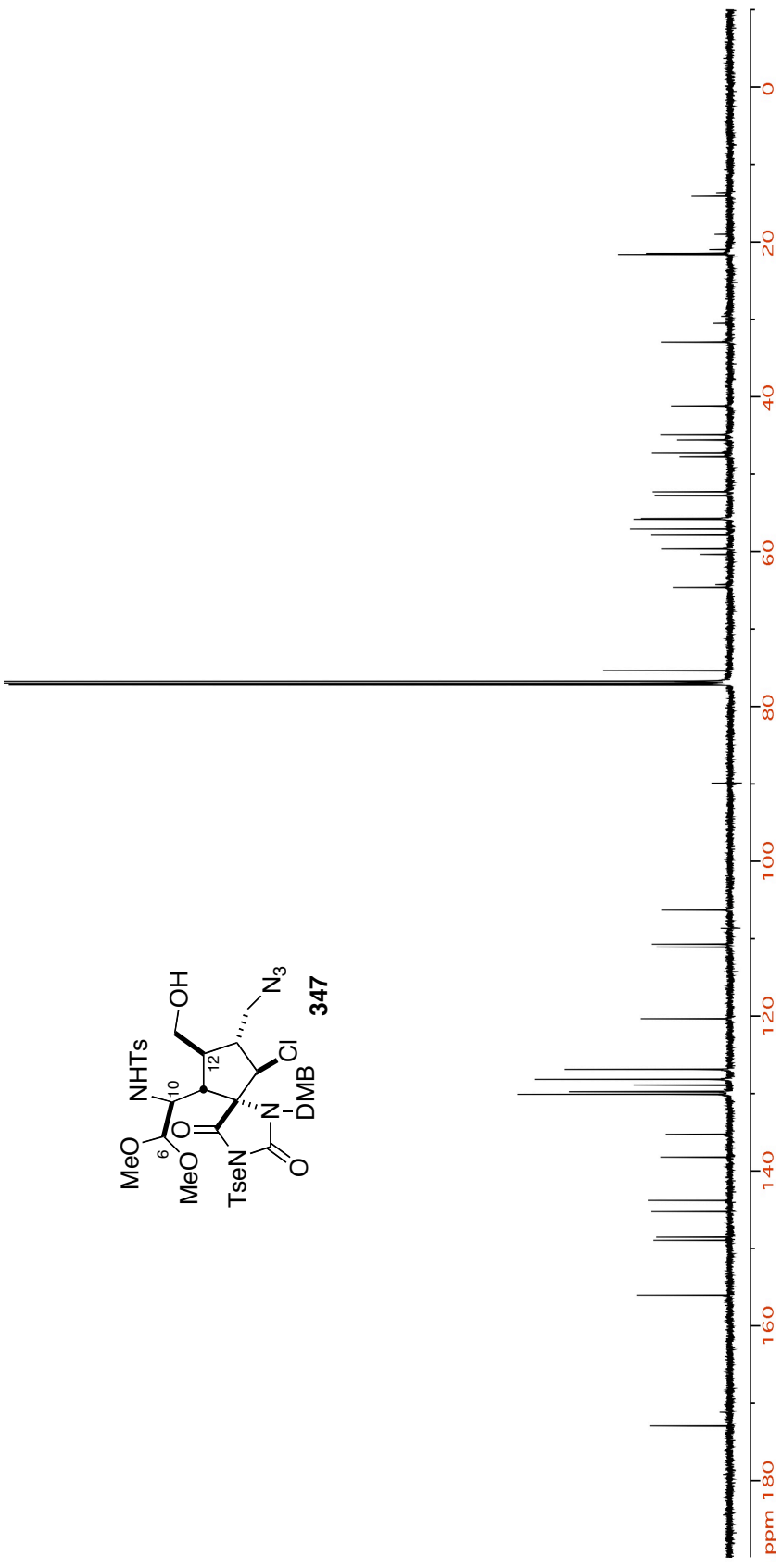
^{1}H NMR spectrum of acetal **346** (in $CDCl_3$)



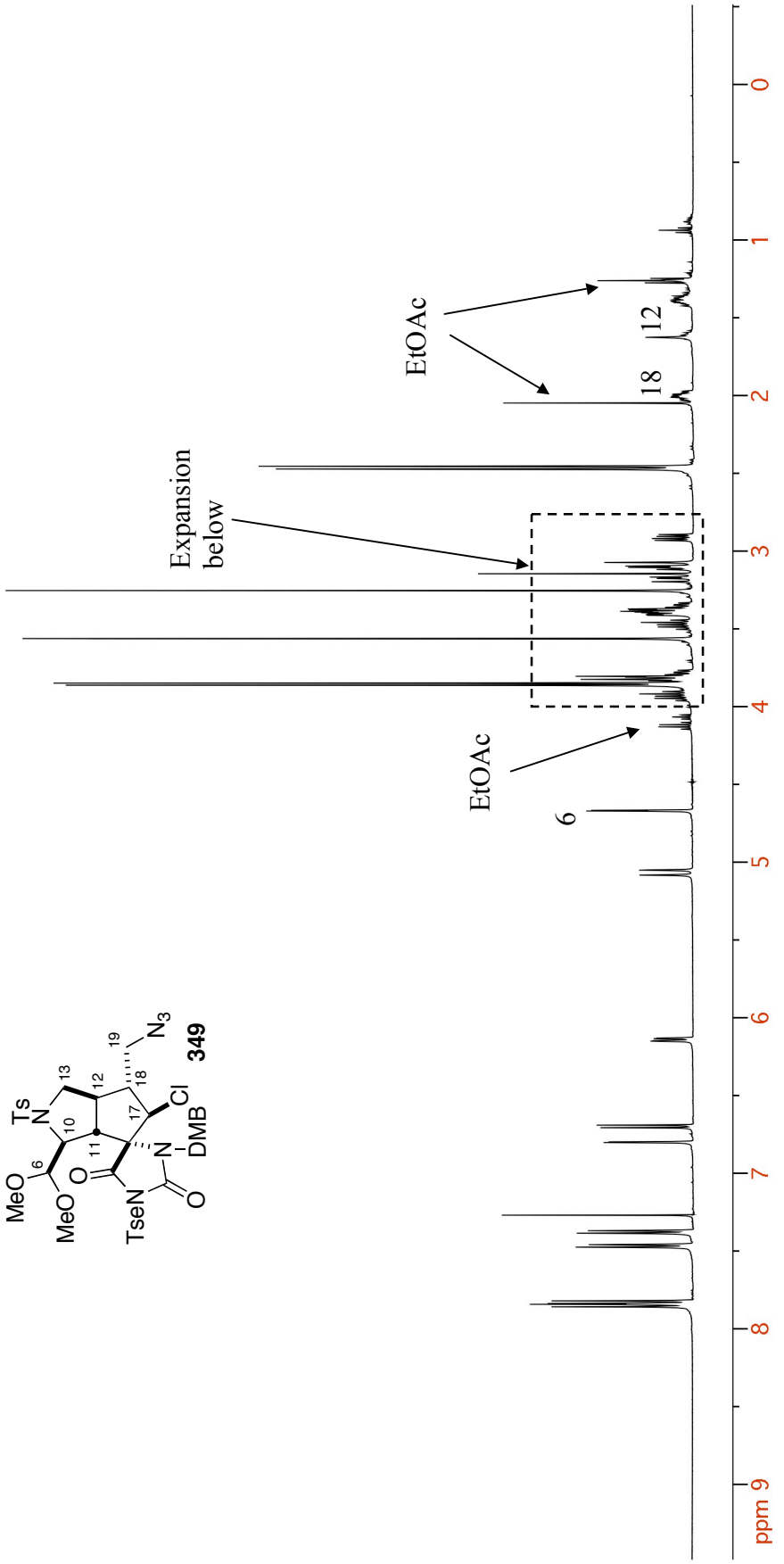
^{13}C NMR spectrum of acetal **346** (in $CDCl_3$)



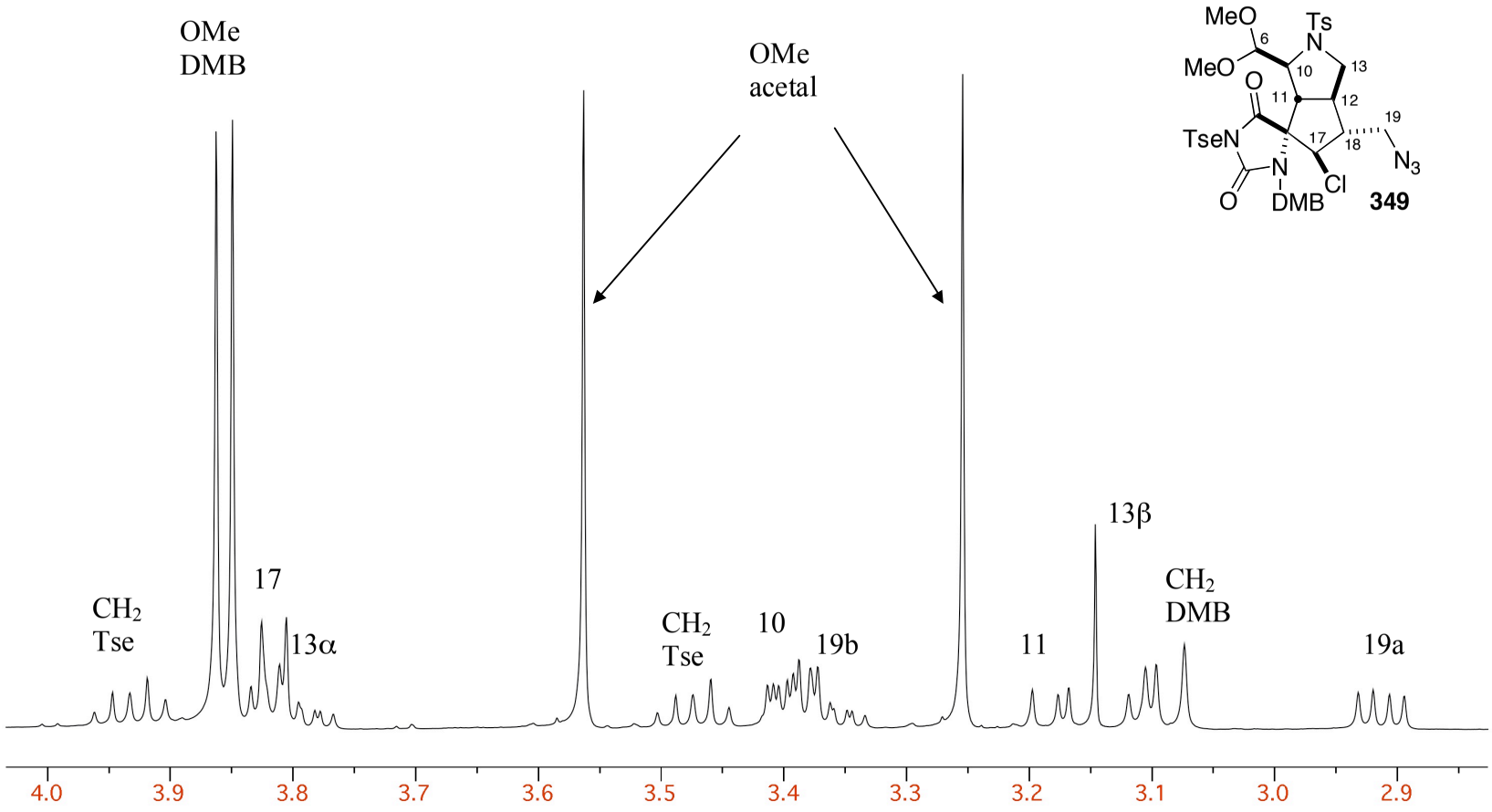
^{1}H NMR spectrum of alcohol **347** (in $CDCl_3$)



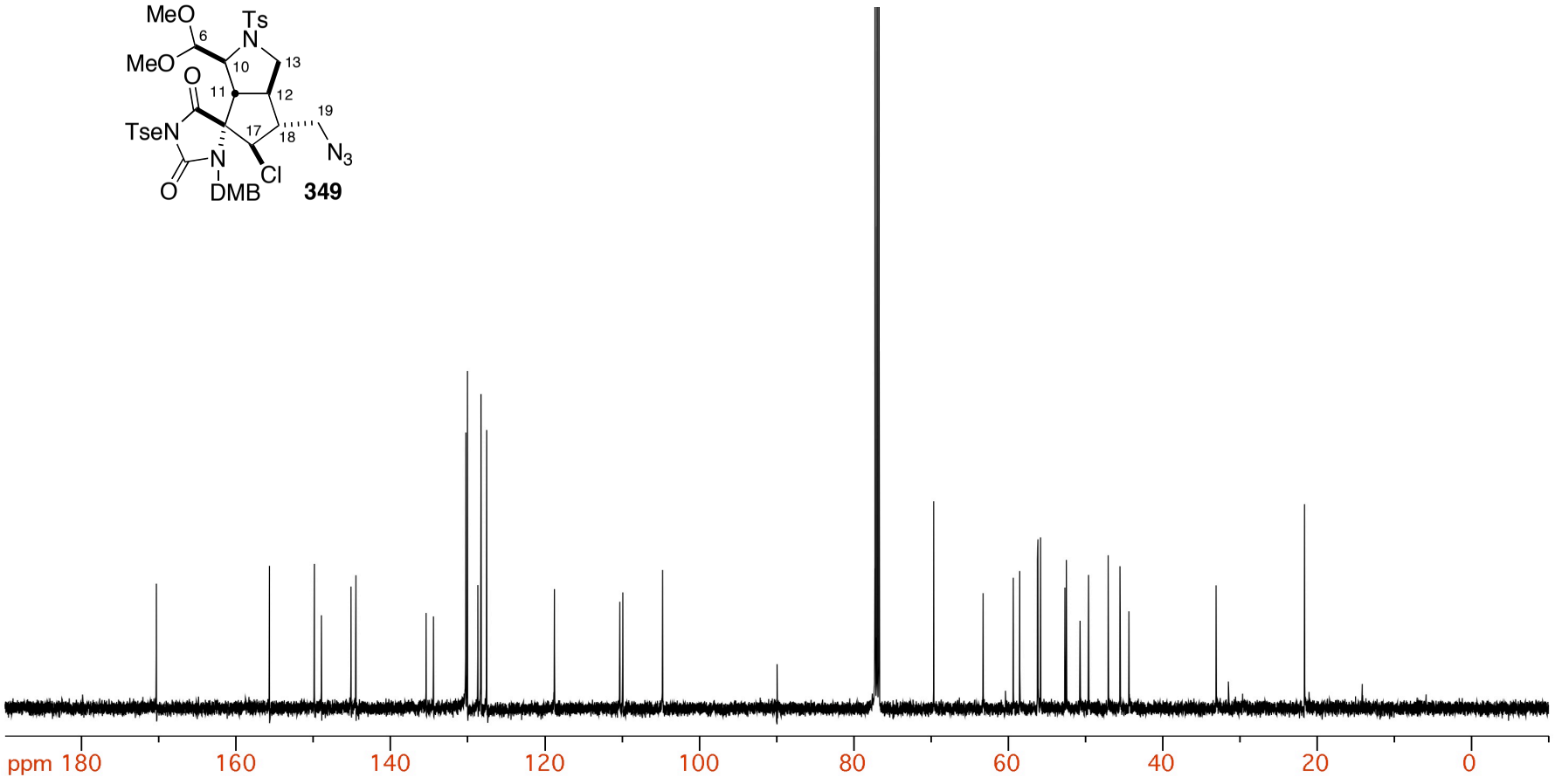
^{13}C NMR spectrum of alcohol **347** (in $CDCl_3$)



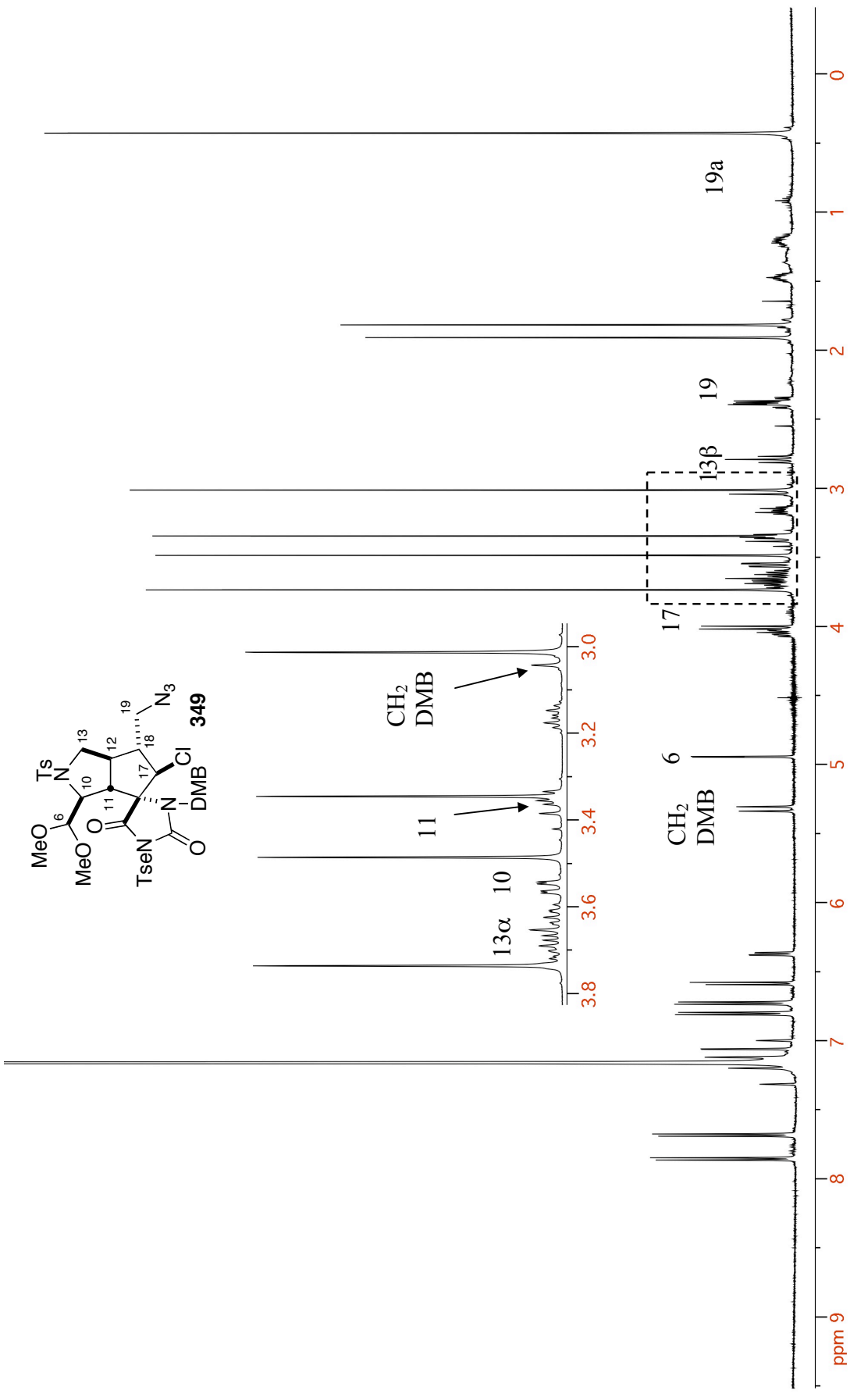
^{1}H NMR spectrum of pyrrolidine **349** (in $CDCl_3$)



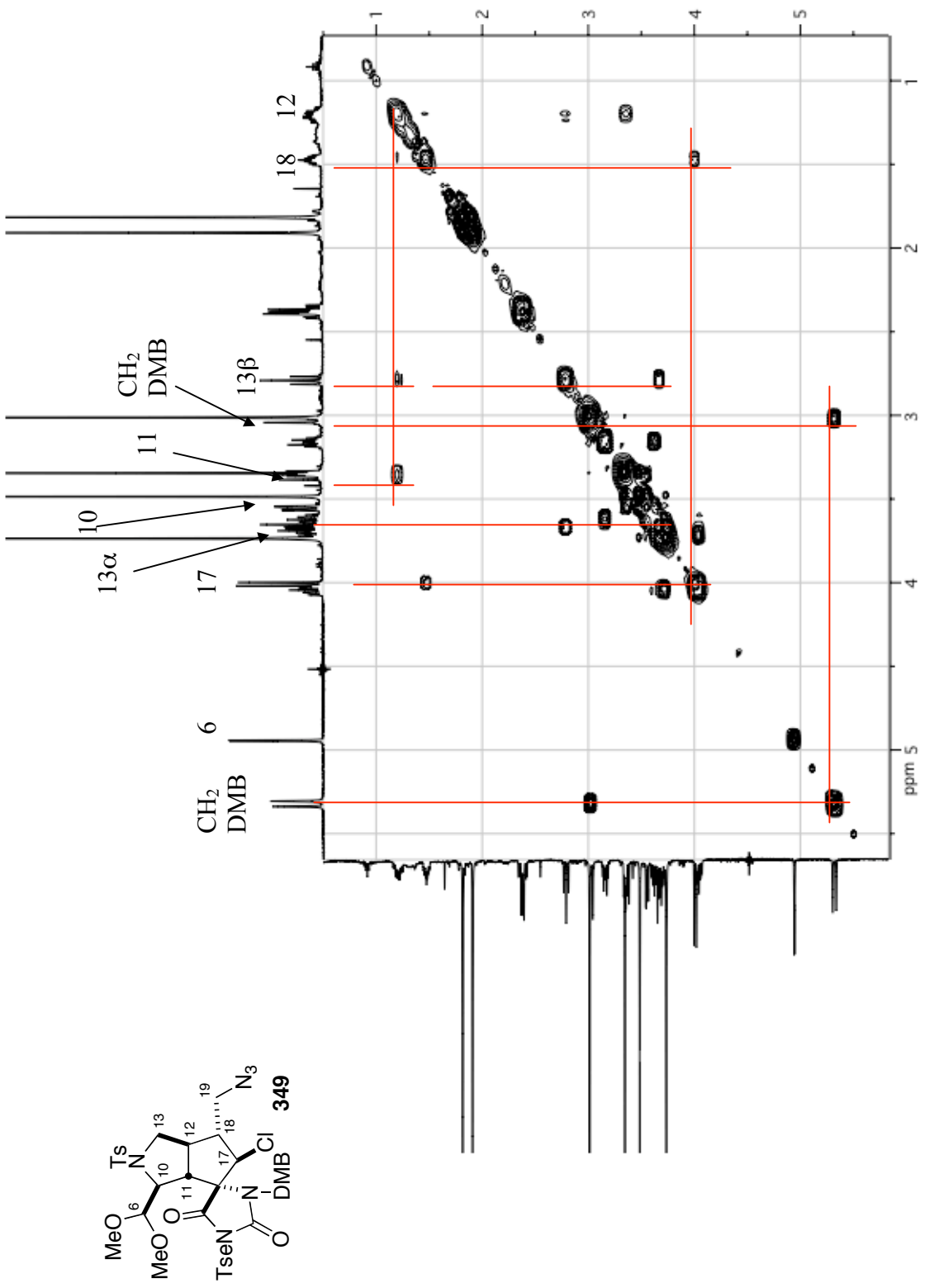
^{1}H NMR spectrum of pyrrolidine **349** (in $CDCl_3$; expansion)



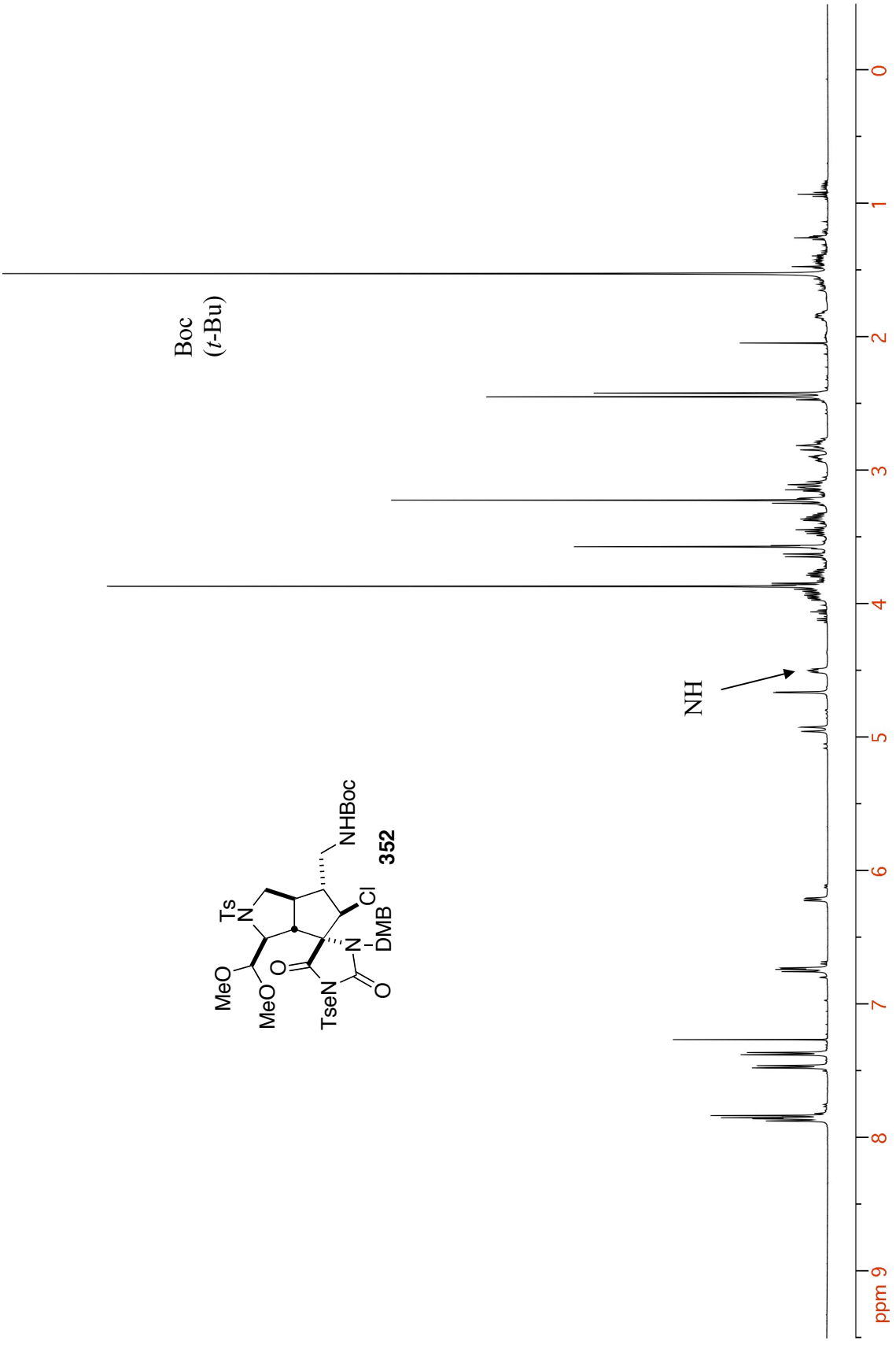
^{13}C NMR spectrum of pyrrolidine **349** (in $CDCl_3$)



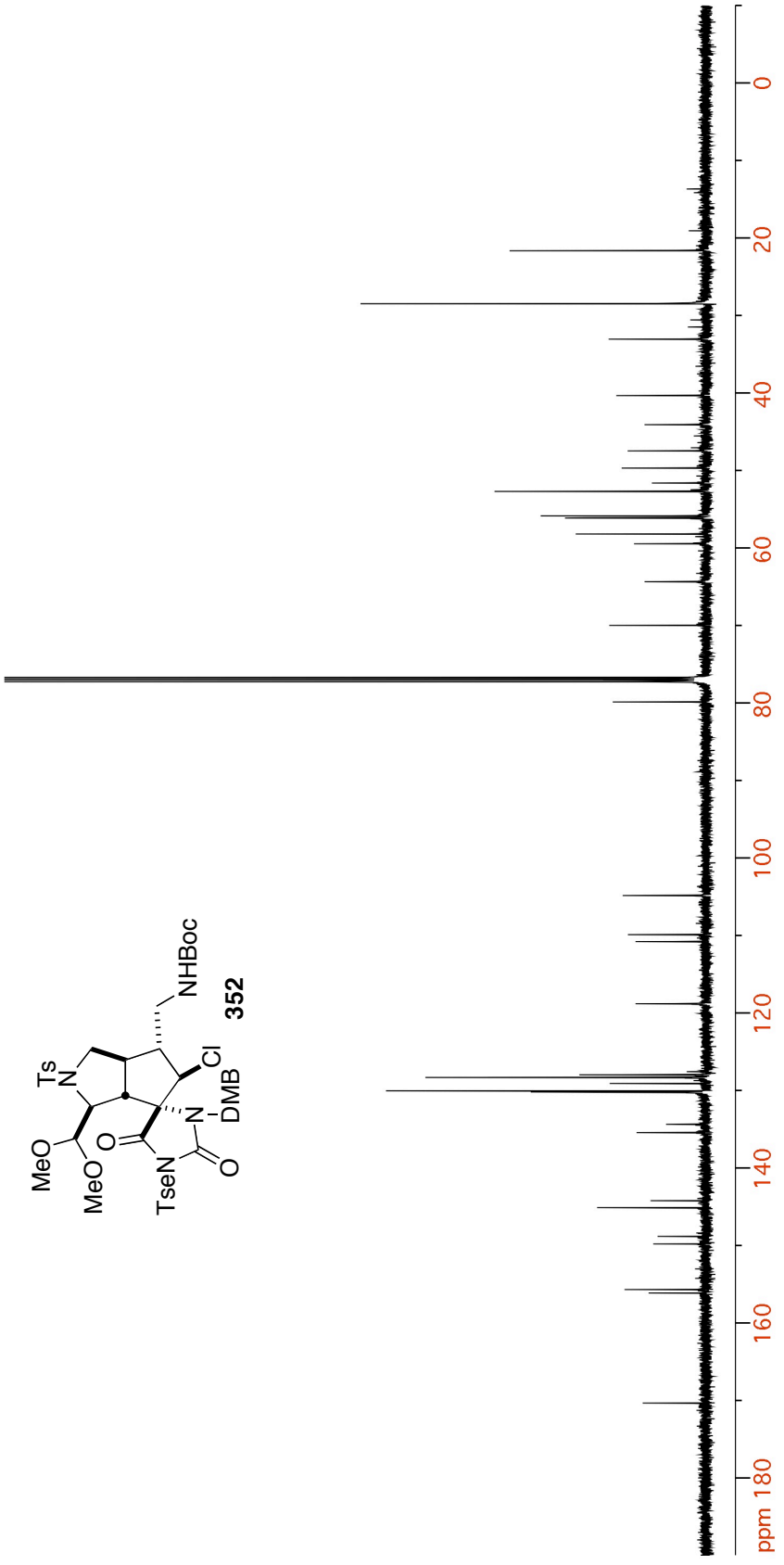
^{1}H NMR spectrum of pyrrolidine **349** (in benzene-d_6)



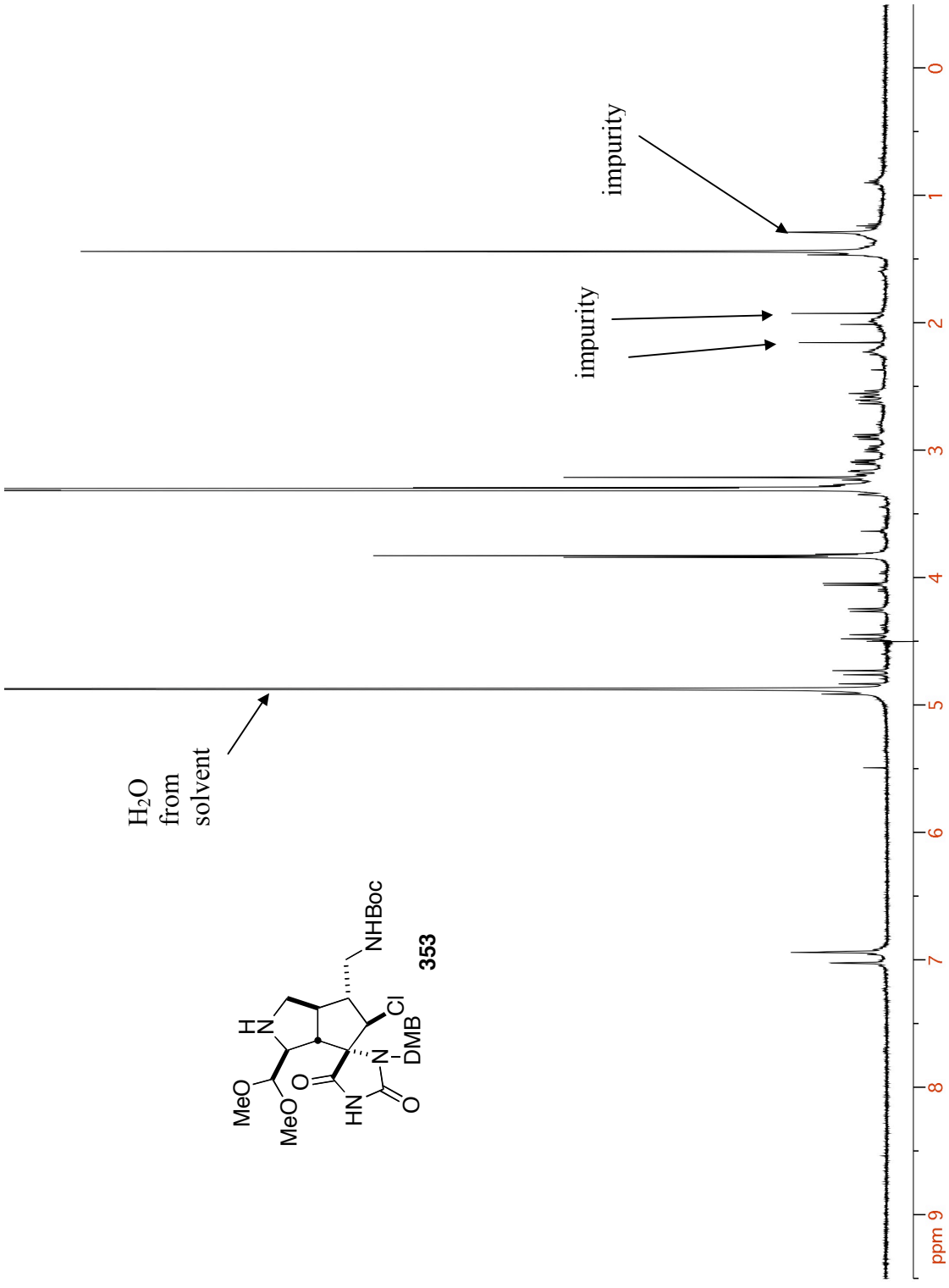
^{1}H-^{1}H-gCOSY NMR spectrum of pyrrolidine **349** (in benzene-d_6; expansion)



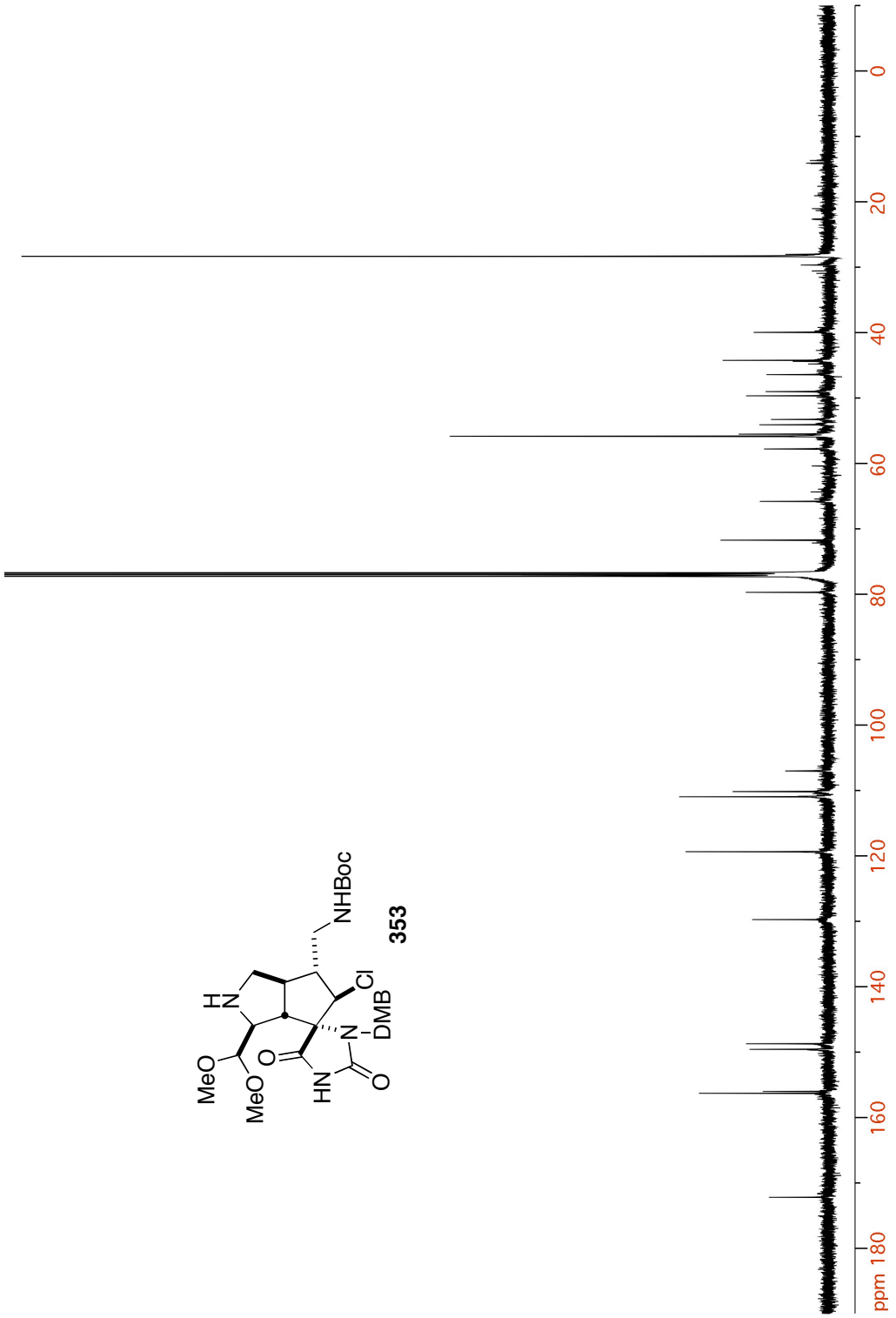
^{1}H NMR spectrum of Boc-amine **352** (in $CDCl_3$)



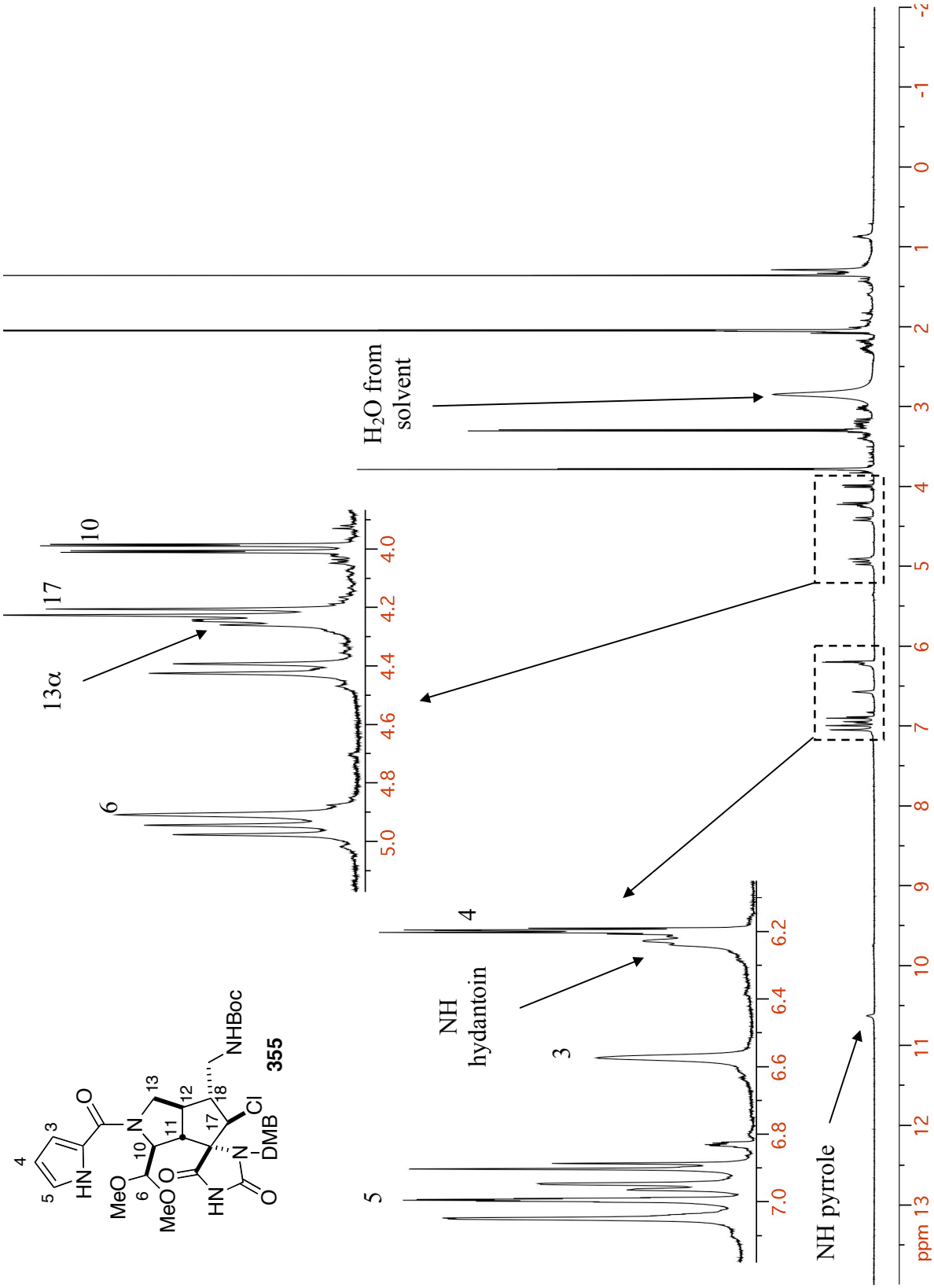
^{13}C NMR spectrum of Boc-amine **352** (in $CDCl_3$)



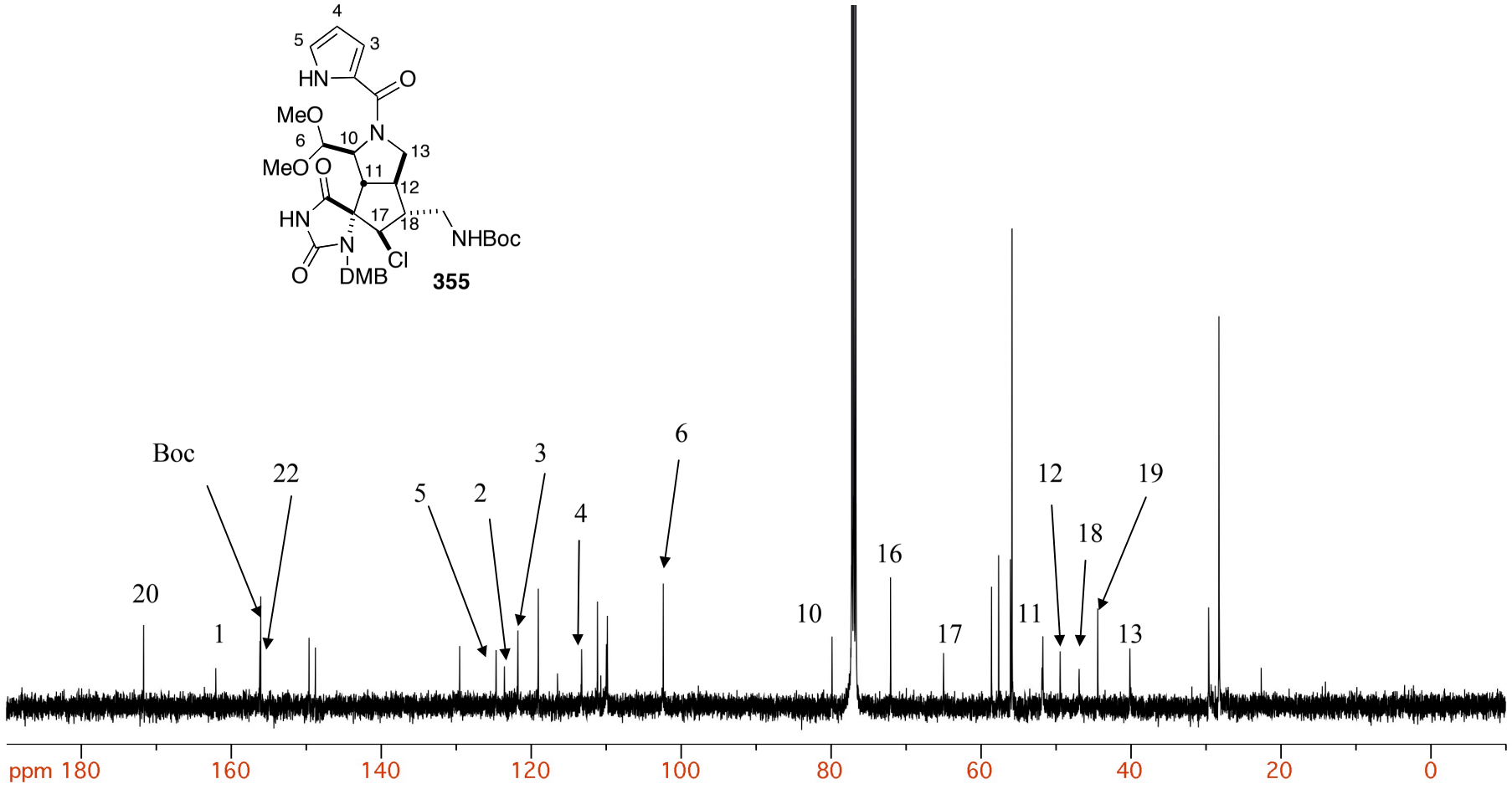
^{1}H NMR spectrum of pyrrolidine **353** (in CD_3OD)



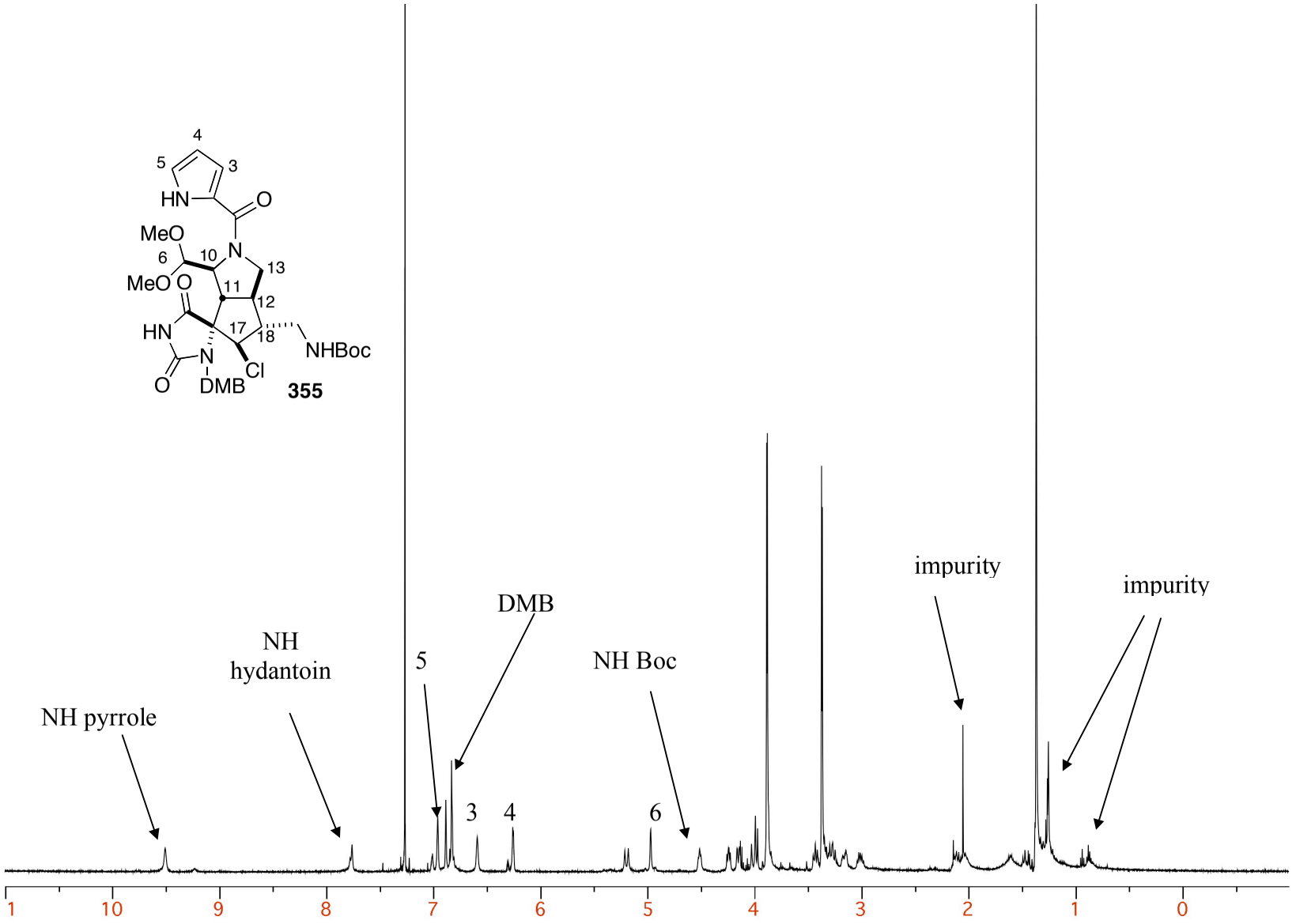
^{13}C NMR spectrum of pyrrolidine **353** (in $CDCl_3$)



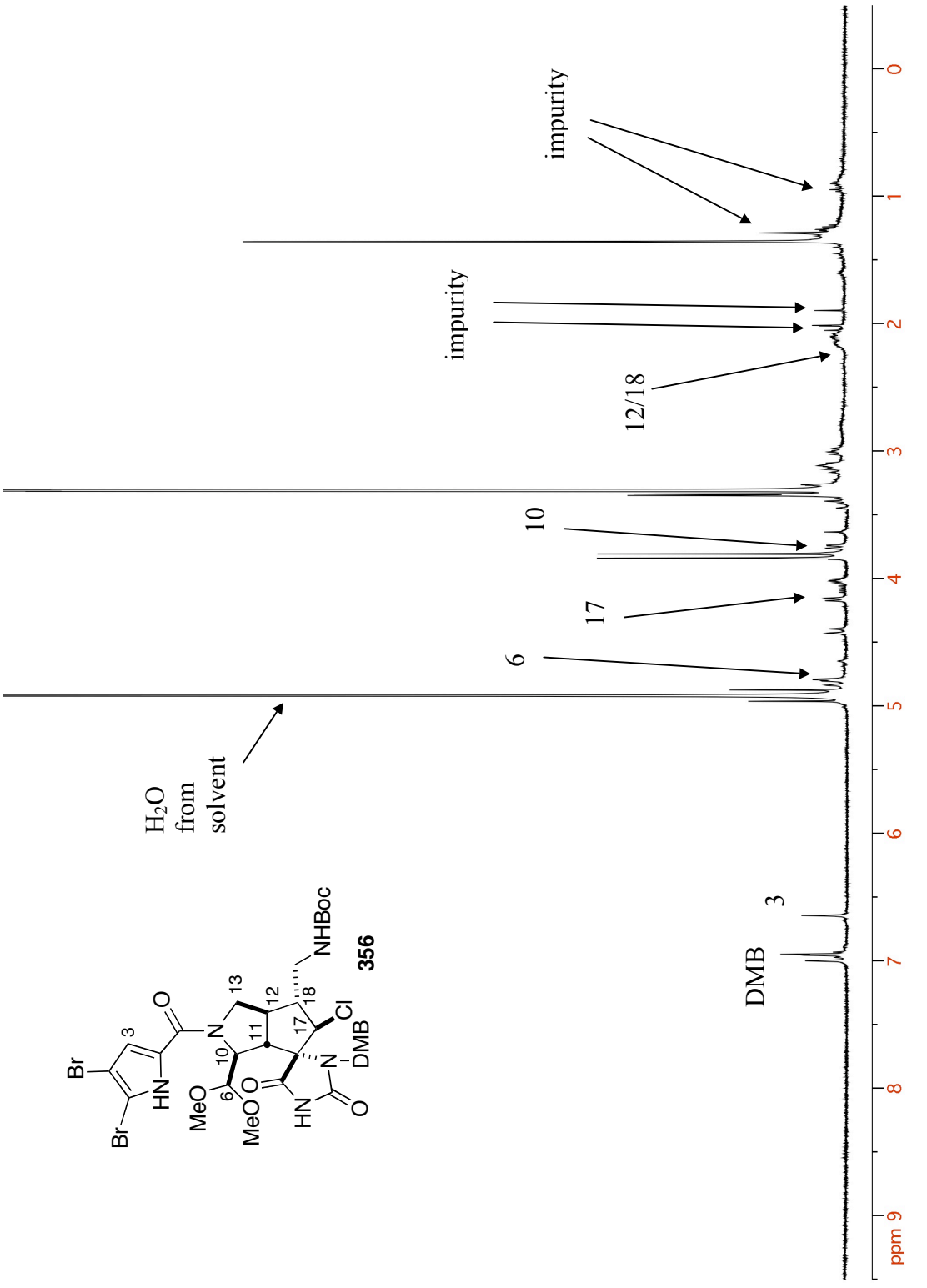
^{1}H NMR spectrum of pyrrole **355** (in acetone-d_6)



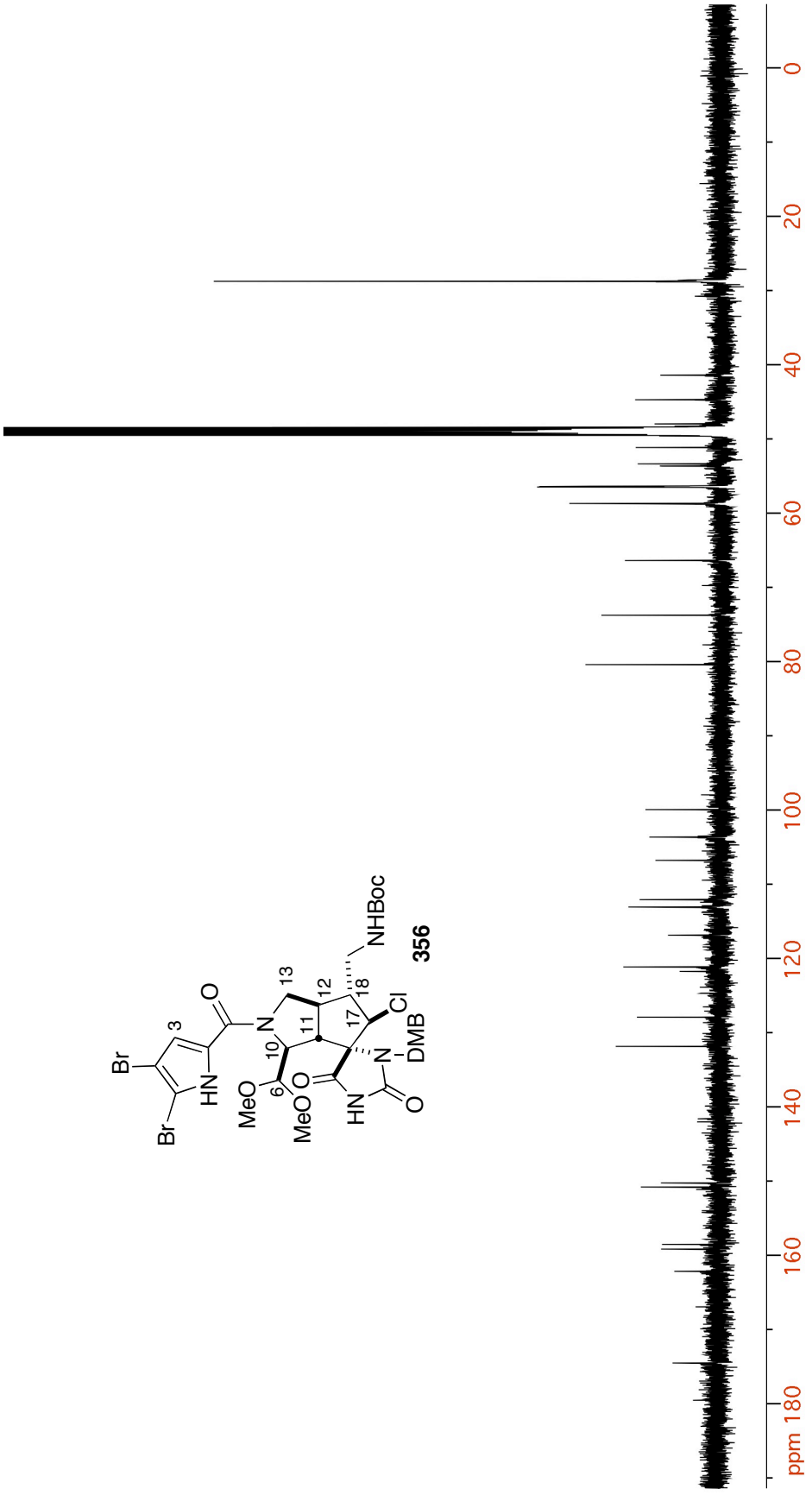
^{12}C NMR spectrum of pyrrole **355** (in $CDCl_3$)



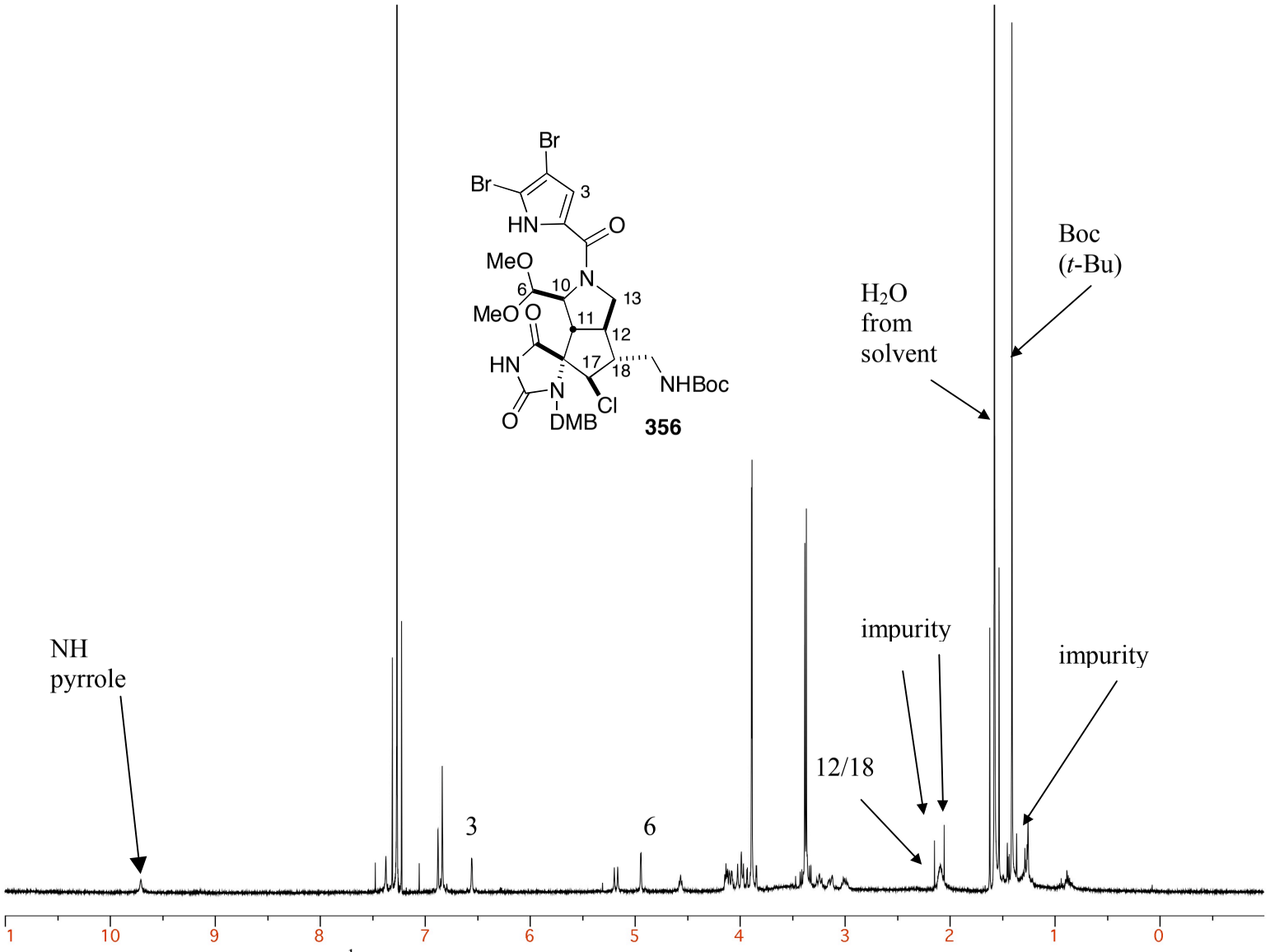
^{1}H NMR spectrum of pyrrole **355** (in $CDCl_3$)



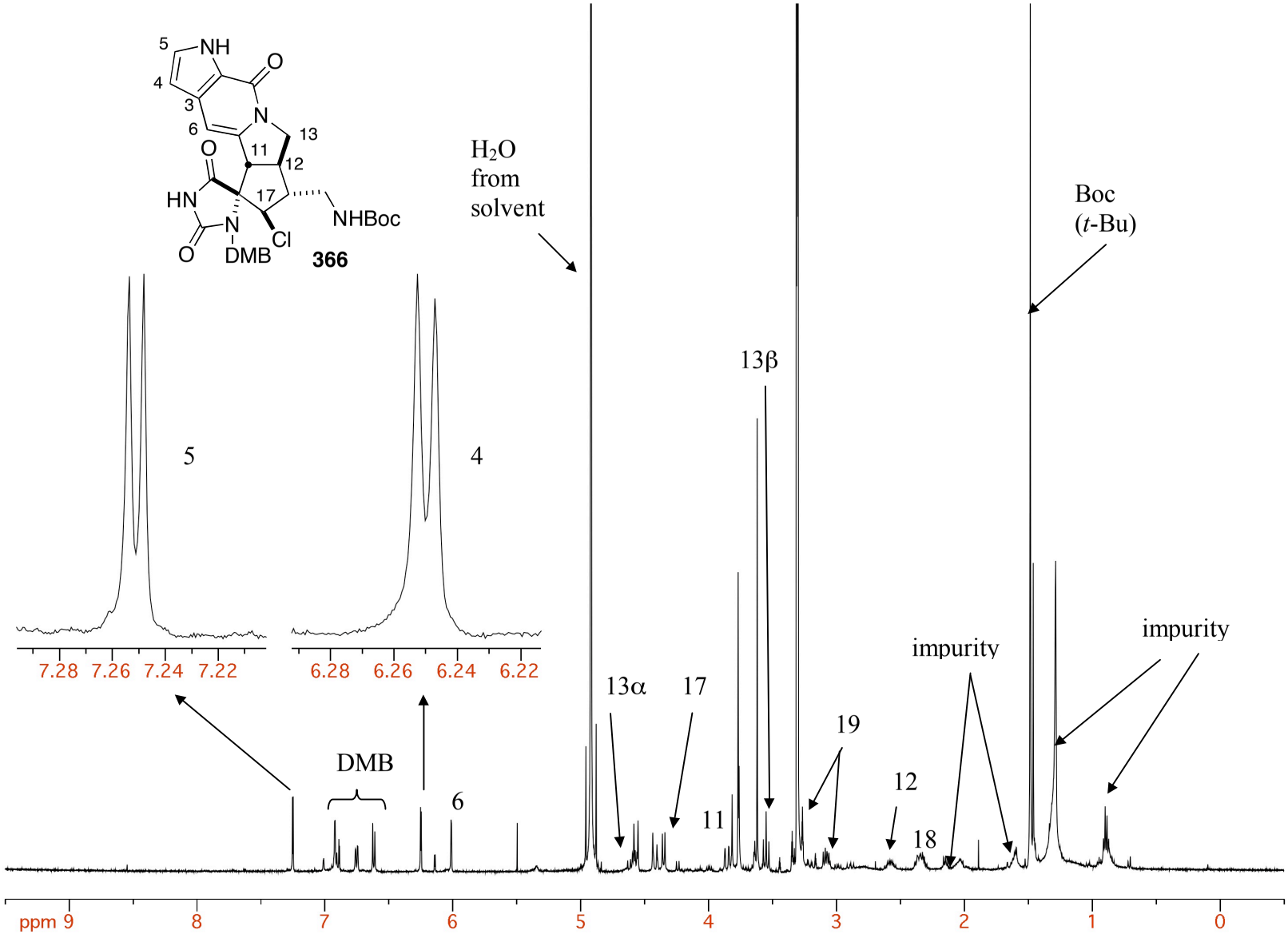
^{1}H NMR spectrum of dibromopyrrole **356** (in CD_3OD)



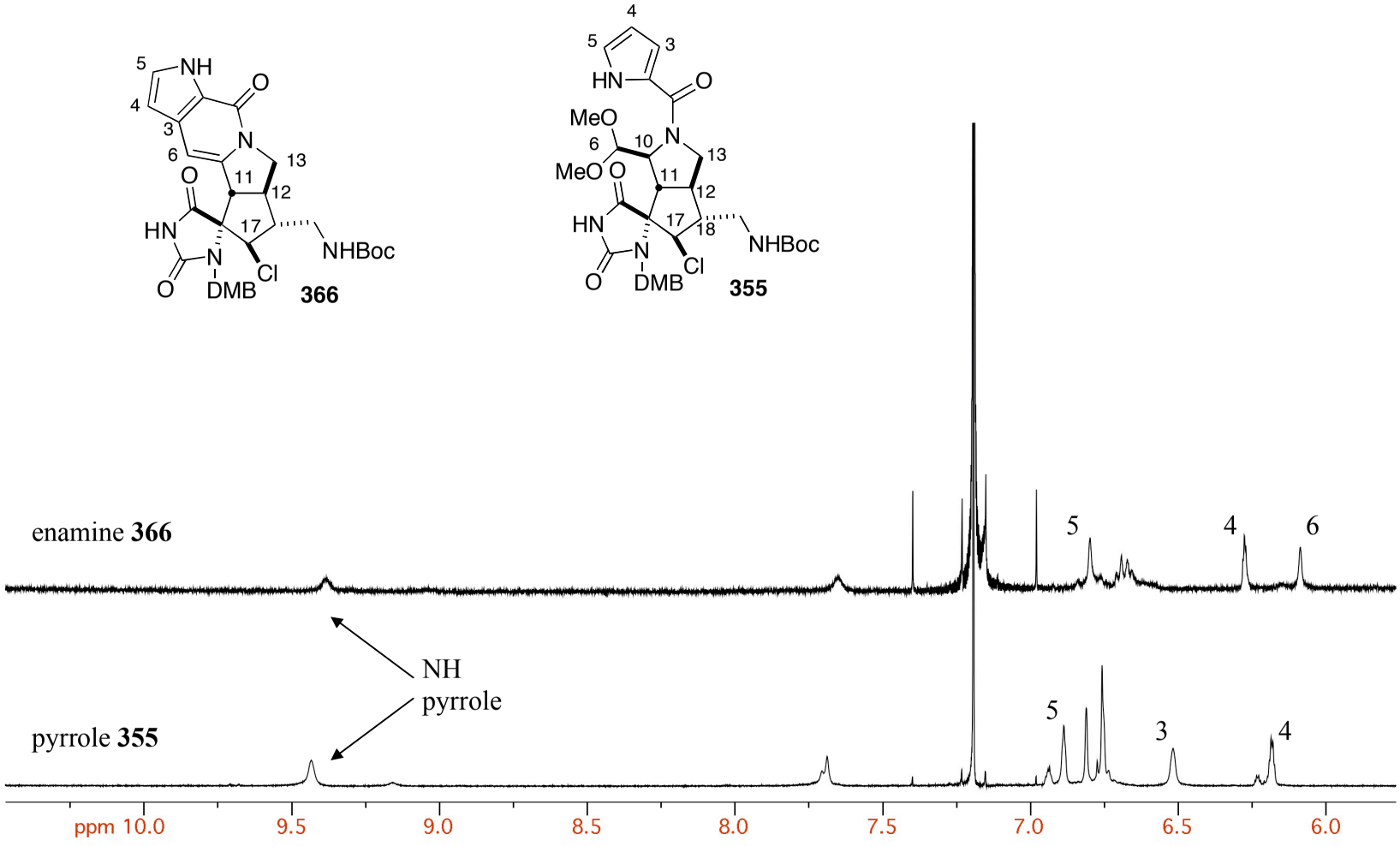
^{12}C NMR spectrum of dibromopyrrole **356** (in CD_3OD)



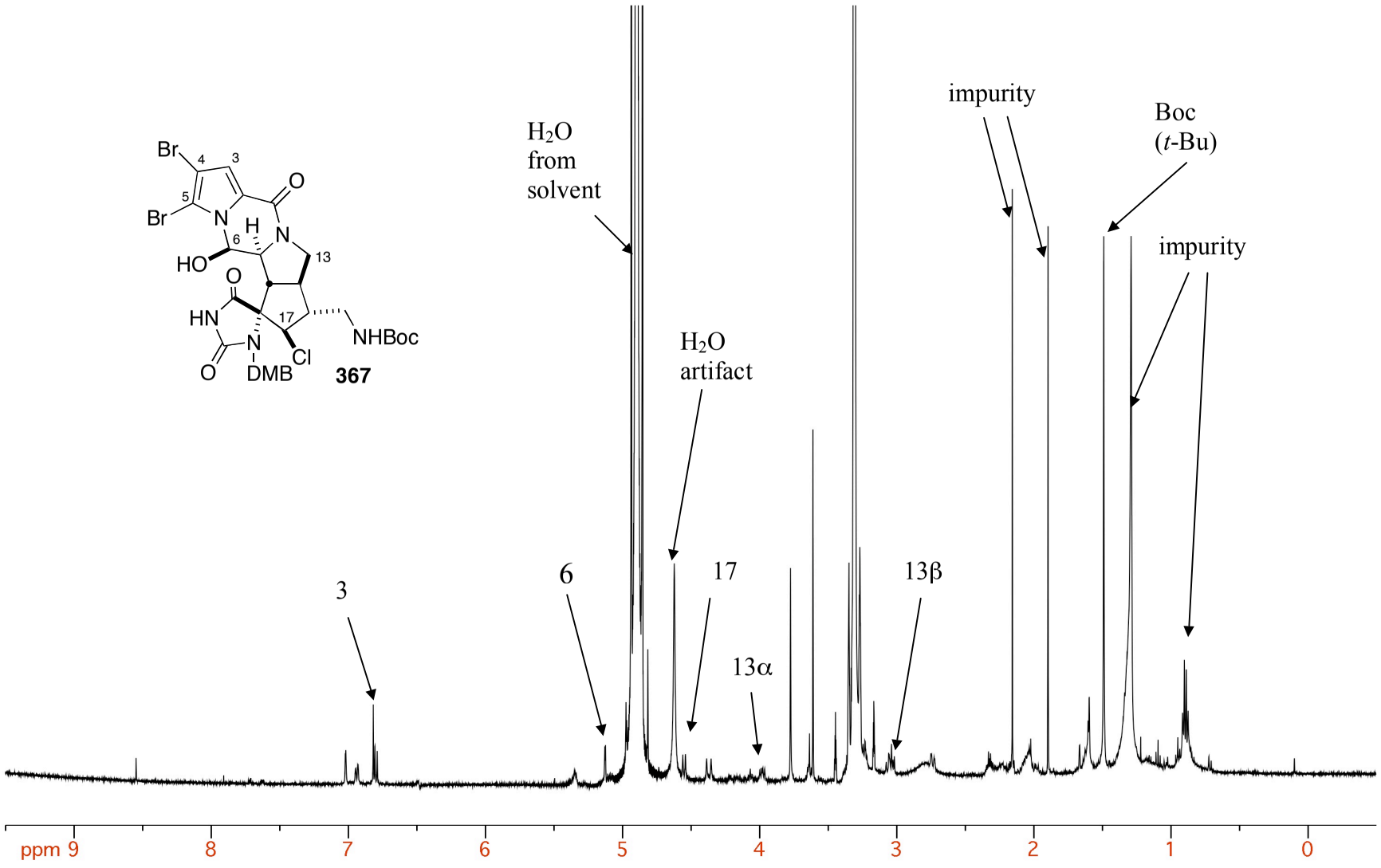
^{1}H NMR spectrum of dibromopyrrole **356** (in $CDCl_3$)



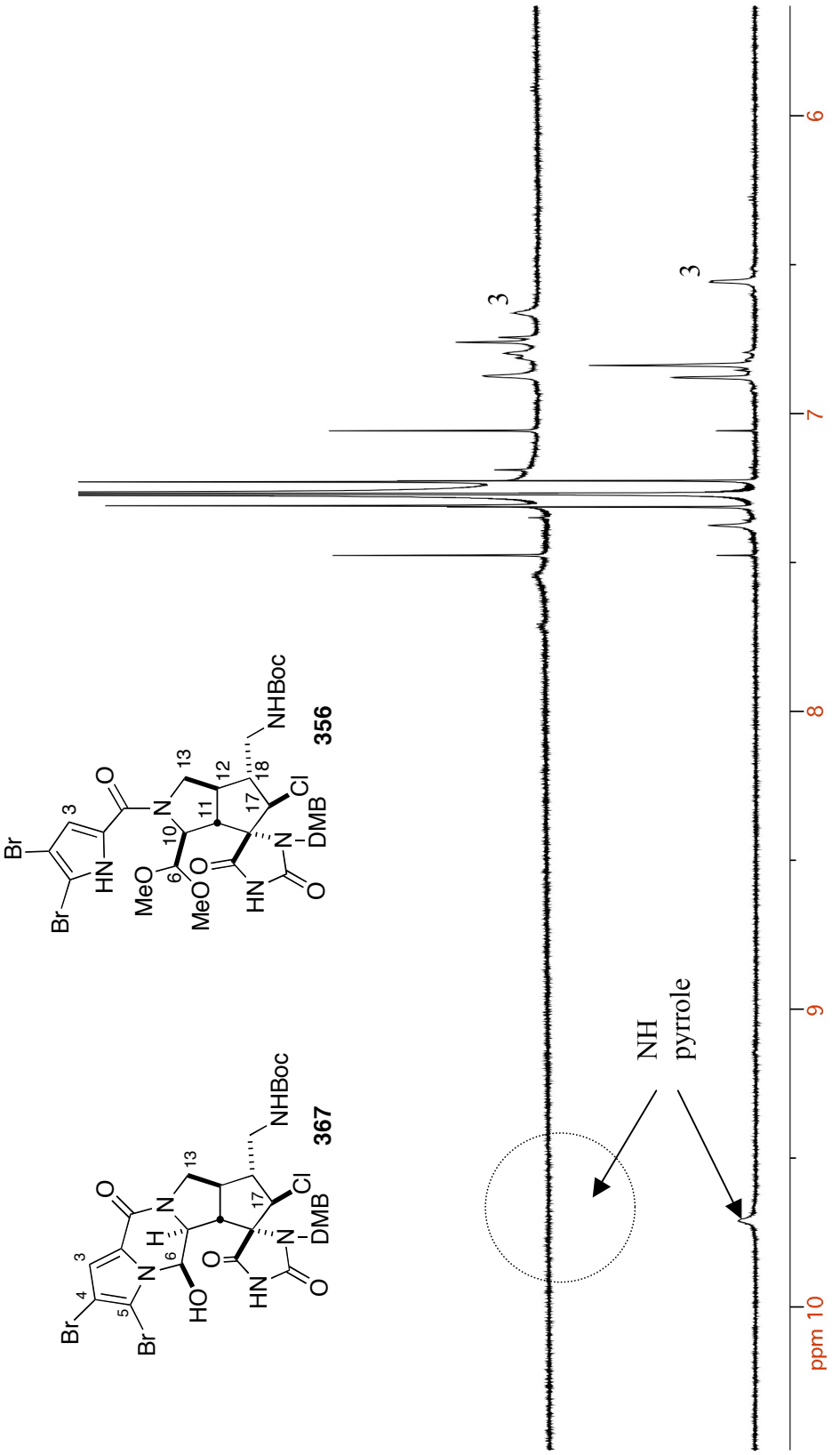
^{1}H NMR spectrum of enamine **366** (in CD_3OD)



^{1}H NMR spectra of pyrrole **355** and enamine **366** (in $CDCl_3$; expansion)



^{1}H NMR spectrum of tentative carbinolamine **367** (in CD_3OD)



^{1}H NMR spectra of sibromopyrrole **356** and tentative carbinolamine **367** (in $CDCl_3$; expansionn)

APPENDIX B

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Publications

Facile Synthesis of the Trans-Fused Azabicyclo[3.3.0]octane Core of the Palau'amines and the Tricyclic Core of the Axinellamines from a Common Intermediate. Zancanella, M. A.; Romo, D. *Org. Lett.* **2008**, *10*, 3685-3688.

Total Synthesis and Comparative Analysis of Orlistat, Valilactone, and a Transposed Orlistat Derivative: Inhibitors of Fatty Acid Synthase. Ma, G.; Zancanella, M. A.; Oyola, Y.; Richardson, R.; Smith, J. W.; Romo, D. *Org. Lett.* **2006**, *8*, 4497-4500.

Honors

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2000-2002 President's List – Tyler Junior College

2001-2004 Presidential Scholarship – University of Texas at Tyler

2002-2004 Dean's List - University of Texas at Tyler

2002-2004 President's Honor Roll - University of Texas at Tyler

2003-2004 Who's Who Among Students in American Universities and Colleges