Cascade Approaches to Polycyclic Natural Products

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ABSTRACT

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Chapter 1. Total Syntheses of Dalesconols A and B

Dalesconols A and B are two rigid, strained, polyphenolic natural products of polyketide origin that were originally isolated as part of a program seeking to identify novel immunosuppressants. The total syntheses of these two molecules was accomplished through the use of a Friedel–Crafts/oxidative Friedel–Crafts cascade sequence in which the same carbon of the framework was used as both nucleophile and electrophile in one pot to form the core, and a unique benzylic oxidation was developed to install oxygenated functionality in the final steps of the route. Preliminary biological screening was also performed to assess the immunosuppressive activity of the natural products and related synthetic intermediates.

Chapter 2. The Azaphenalene-Containing Coccinellid Defensive Alkaloids

The coccinellid defensive alkaloids are a diverse array of molecules utilized by various species of ladybug to ward off predators. In particular, the azaphenalene structural subclass of these molecules displays rich complexity with respect to stereochemistry, oxidation state, and oligomeric assemblies, posing many challenges for characterization and synthesis. Biosynthetic pathways are discussed, and a survey of previous synthetic efforts towards this oligomeric class of alkaloids is also provided in order to frame current challenges in this area of alkaloid chemistry.

Chapter 3. Development of a Programmable Synthetic Strategy to Access the Oligomeric Azaphenalene Alkaloids: Total Syntheses of Monomers and Biomimetic Dimerization

The development of a synthetic program to access many of the oligomeric members of the azaphenalene alkaloids is presented through the use of a key intermediate specifically designed to target both monomeric and higher order structures. In terms of monomeric natural products, the total syntheses of (–)-propyleine, (–)-isopropyleine, precoccinelline, formal total synthesis of coccinelline, and enantioselective formal total syntheses of hippodamine, convergine, hippocasine, and hippocasine oxide are presented. The total syntheses of (–)-propyleine and (–)-isopropyleine are the first enantioselective total syntheses of these molecules and are also the shortest and highest yielding reported to date. Attempts at a biomimetic dimerization cascade of monomeric frameworks to access homodimers psylloborine A and isopsylloborine A resulted in the formation of a non-natural dimeric framework.

Chapter 4. Development of a Programmable Synthetic Strategy to Access the Oligomeric Azaphenalene Alkaloids: Non-Biomimetic Syntheses of Homodimeric Frameworks

The first total syntheses of (–)-psylloborine A and (–)-isopsylloborine A were achieved through a non-biomimetic, cascade-based assembly of the homodimeric azaphenalene core employing the key intermediate developed in the first-generation approach. Through the use of two enamine-driven, cascade-based processes, a total of five rings and four stereocenters were set in only two distinct synthetic operations, and the development of the second cascade sequence featured the use of a uniquely designed activating group for the terminating step. A discussion of implications for these studies in oligomeric alkaloid synthesis is also provided.

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"The most exciting phrase to hear in science, the one that heralds new discoveries, is not 'Eureka!' but 'That's funny…'"

-Isaac Asimov

"Human judges can show mercy. But against the laws of nature, there is no appeal."

-Arthur C. Clarke

Dedicated to my family

List of Abbreviations

ATPH	aluminum tris(2,6-diphenylphenoxide)
CSA	camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIPEA	*N,N*-diisopropylethylamine
DMAP	*N,N*-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
EWG	electron-withdrawing group
GC-MS	gas chromatography-mass spectrometry
HNR	hydroxynaphthalene reductase
HPLC	high-performance liquid chromatography
HWE	Horner-Wadsworth-Emmons
IR	infrared
KHMDS	potassium bis(trimethylsilyl)amide
*m*CPBA	*meta*-chloroperoxybenzoic acid
MMFF	Merck molecular force field
MOM	methoxymethyl

Ms	methanesulfonyl
MS4A	4-Angstrom molecular sieves
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
PKS	polyketide synthase
PDBBA	potassium diisobutyl-*tert*-butoxyaluminum hydride
PPA	polyphosphoric acid
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TFE	2,2,2-trifluoroethanol
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TIPS	tri(isopropyl)silyl
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMG	*N,N,N',N'*-tetramethylguanidine
TMS	trimethylsilyl
Ts	toluenesulfonyl
UV	ultraviolet

PREFACE

The projects discussed in this thesis cover the total syntheses of molecules in two different areas of natural products chemistry: polyphenols and alkaloids. While these two classes generally have little in common, the studies detailed herein have employed cascade-based strategies to access the rigid, strained cores contained within all selected targets. The ability of cascade chemistry to rapidly form high levels of molecular complexity and introduce elements of considerable difficulty, such as rigid fused-ring systems and quaternary chiral centers, has been applied to the chosen molecules. The results of these studies have demonstrated the power of cascade-based core formation to rapidly assemble complex, polycyclic architectures in two different classes of natural products.

CHAPTER 1

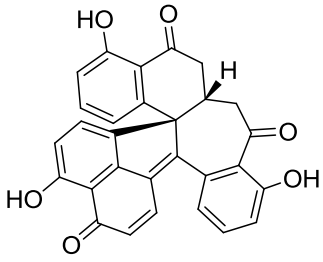
Total Syntheses of Dalesconols A and B

Section 1.1 Isolation, Biosynthesis and Biological Screening of Dalesconols A, B, and Related Metabolites

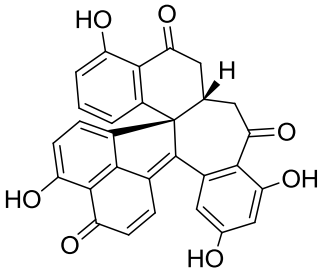
Section 1.1.1 Isolation

In 2008, as part of a program seeking to identify new classes of potent immunosuppressants, Tan and co-workers identified and characterized the polyketide-derived polyphenols dalesconol A and B (**1** and **2**, Figure 1) from a culture of *Daldinia eschsholzii* IFB-TL01 residing inside the gut of the mantis species *Tenodora aridifolia*.[1] In 2009, Lin and co-workers reported isolation of **1** and **2**, naming them sporothrin A and B, as well as a third metabolite **5** named sporothrin C, from endophytic fungus *Sporothrix* sp. #4335 that grows on the inshore mangrove tree *Kandelia candel*.[2] The Tan group issued follow-up reports in 2011[3] and 2012[4] on further isolation work and biosynthetic studies of **1** and **2** as well as structurally related dalesconol C (**3**), biosynthetic precursor to **1** daeschol A (**4**), dalmanol A (**7**), and various other related polyketide-derived polyphenolic metabolites. Furthermore, in their 2011 report, Tan and co-workers reported isolation of a metabolite matching the spectral data for sporothrin C and amended the structure to that of **6**.

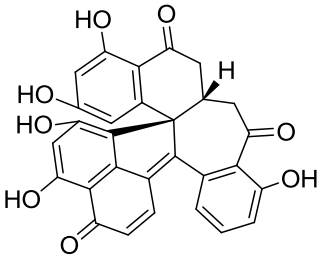
Figure 1. Dalesconol A, B, C and Related Metabolites



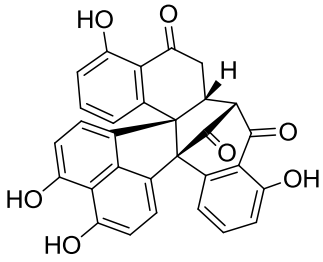
1: dalesconol A (sporothrin C)



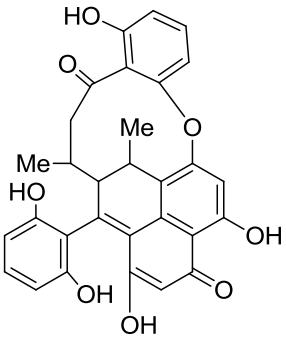
2: dalesconol B (sporothrin B)



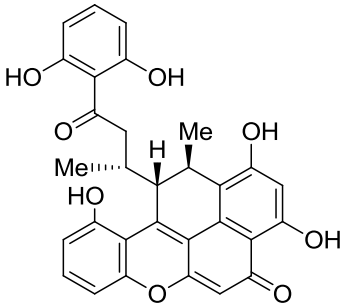
3: dalesconol C



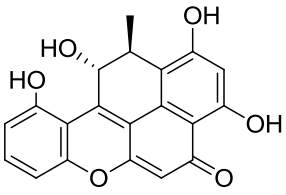
4: daeschol A



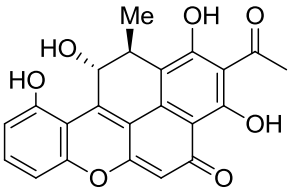
5: initially proposed structure of sporothrin C



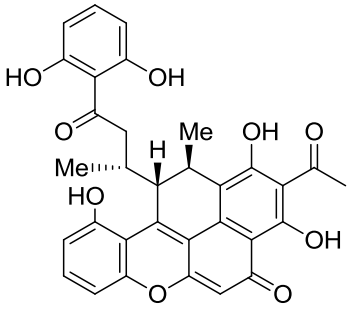
6: revised sporothrin C



7: dalmanol A



8: acetodalmanol A



9: acetodalmanol B

Section 1.1.2 Biosynthesis

Feeding experiments performed by the Tan group using ^{13}C-labeled acetate revealed that dalesconols A and B are of polyketide origin, and subsequent study of polyketide synthase (PKS) gene coding found that five PKS domains are involved in the

formation of these metabolites: a ketosynthase domain, an acyltransferase domain, two acyl carrier proteins, and a thioesterase-claisen cyclase domain. The biosynthetic pathway outlined in Scheme 1 shows the experimentally-supported biogenesis for dalesconols A–C (**1** – **3**), daeschol A (**4**), dalmanol A (**7**), and sporothrin C (**6**).

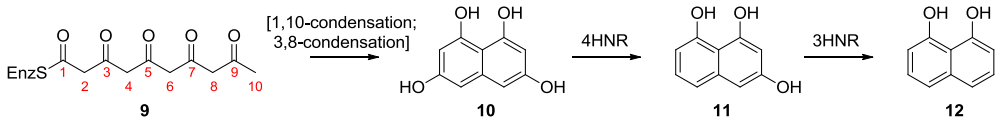
Tan and co-workers experimentally demonstrated that the dalesconols and related metabolites form through the union of polyketide fragments via pathways shown in Scheme 1. A five-acetate fragment bound to an enzyme (**9**) can undergo condensations between C-1/C-10 and C-3/C-8 to deliver, upon tautomerization, tetrahydroxynaphthalene fragment **10** (Figure 2A). This material (**10**) can then be reduced to a trihydroxynaphthalene fragment **11** or a dihydroxynaphthalene fragment **12** through the action of hydroxynaphthalene reductases (HNR). Combining these fragments through oxidative radical mechanisms (Figure 2B), two fragments of **12** can deliver binaphthyl **13**, which can further combine with **11** to give **14**. At this stage, **14** can oxidatively form the required bonds to give daeschol A (**4**), a natural product that readily undergoes oxidative decarboxylation to give dalesconol A (**1**). A similar pathway exists for dalesconol B in which two hydroxynaphthalene fragments **12** and a fragment of **10** combine, and dalesconol C is formed through a similar union of three hydroxynaphthalene fragments **11**. It is noteworthy that unlike daeschol A (**4**), neither daeschol B (**16**) nor daeschol C (**19**) have been isolated and are proposed biosynthetic intermediates only. Finally, dalesconols A–C were isolated with roughly 67% *ee* favoring the (–) enantiomer. Theoretical calculations for atropisomerism of the binaphthol radicals in this biosynthetic pathway (oxidized **13** and **17**) binding to a laccase enzyme found in

the producing organism revealed that the atropisomers leading to the (–) enantiomer of **1** – **3** were favored roughly two to one over the (+) precursor.

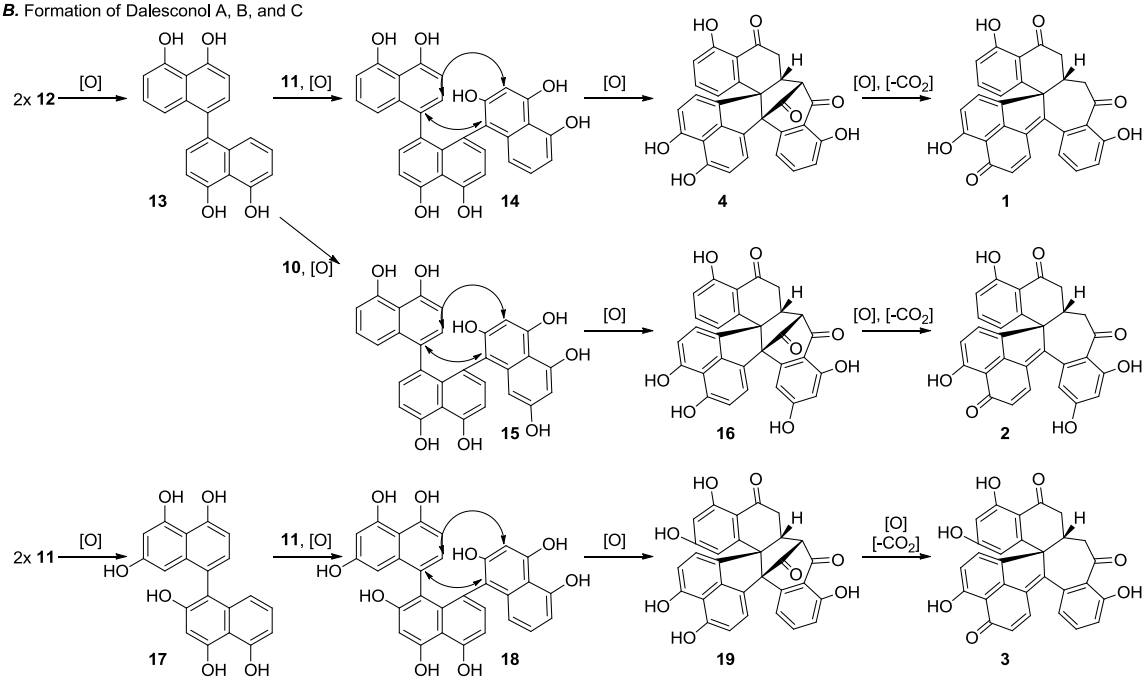
In contrast to the dalesconols, metabolites containing the dalmanol core require polyketide **9** to undergo a condensation between C-1 and C-6 to deliver **20** (Figure 2C). This fragment can undergo condensation with phenol **10** with a subsequent oxidation state adjustment delivering **21**, a molecule requiring only slight chemical adjustment to ultimately deliver dalmanol A (**7**). Dalmanol A can be converted further to the Tan group's revised structure for sporothrin C (**6**) through reductive coupling with another molecule of polyketide fragment **20**. Finally, both acetodalmanol A (**8**) and B (**9**) merely require a modified version of **20** with an extra acetate unit for biosynthesis.

Scheme 1. Biosynthesis of the Dalesconols and related metabolites

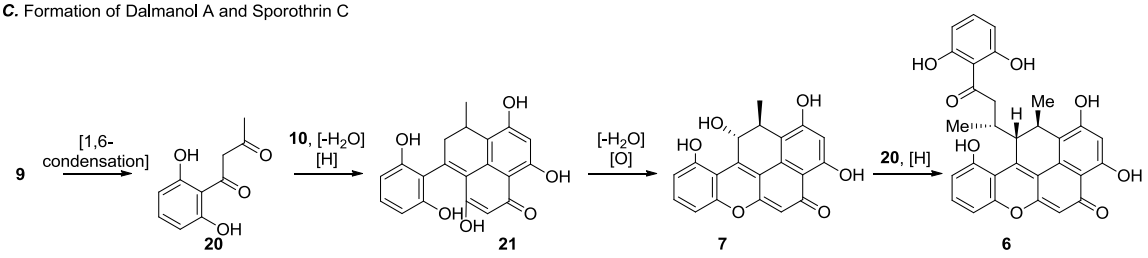
A. Biosynthesis of hydroxynaphthalene fragments



B. Formation of Dalesconol A, B, and C



C. Formation of Dalmanol A and Sporothrin C



Section 1.1.3 Biological Screening

In addition to structure elucidation and biosynthetic studies, the Tan group also performed immunosuppressant assays measuring T-cell proliferation. These efforts revealed that **1** and **2** had activity comparable to cyclosporin A, but with significantly reduced background cytotoxicity (Table 1). The toxicity associated with cyclosporin A

and other immunosuppressants such as FK506, rapamycin, and corticosteroids is well-documented and highlights the need for development of new therapies in this area.[5] Other metabolites shown in Figure 1 displayed less activity. Since the natural products were isolated in only modest enantiomeric excess, both the racemate and individual enantiomers were tested, with the racemates for dalesconol A and B displaying slightly greater potency than the individual enantiomers. This unique activity could be explained if both enantiomers are participating cooperatively with the target of interest, a phenomenon recently documented for an unrelated system by Breinbauer and co-workers. [6] It is also possible that these numbers could be within experimental error; unfortunately, Tan and co-workers did not provide error bars for their immunosuppressant data on dalesconol A and B. Either way, we felt that the potential for an effective alternative to cyclosporin A merited synthetic exploration of **1** and **2**. On top of their immunosuppressant potential, Lin and co-workers reported modest antitumor activity for dalesconol A and B, and acetylcholine esterase inhibition for dalesconol A.

Table 1. Biological Activity Reported by the Tan Group for Dalesconol A, B, C and Related Metabolites:

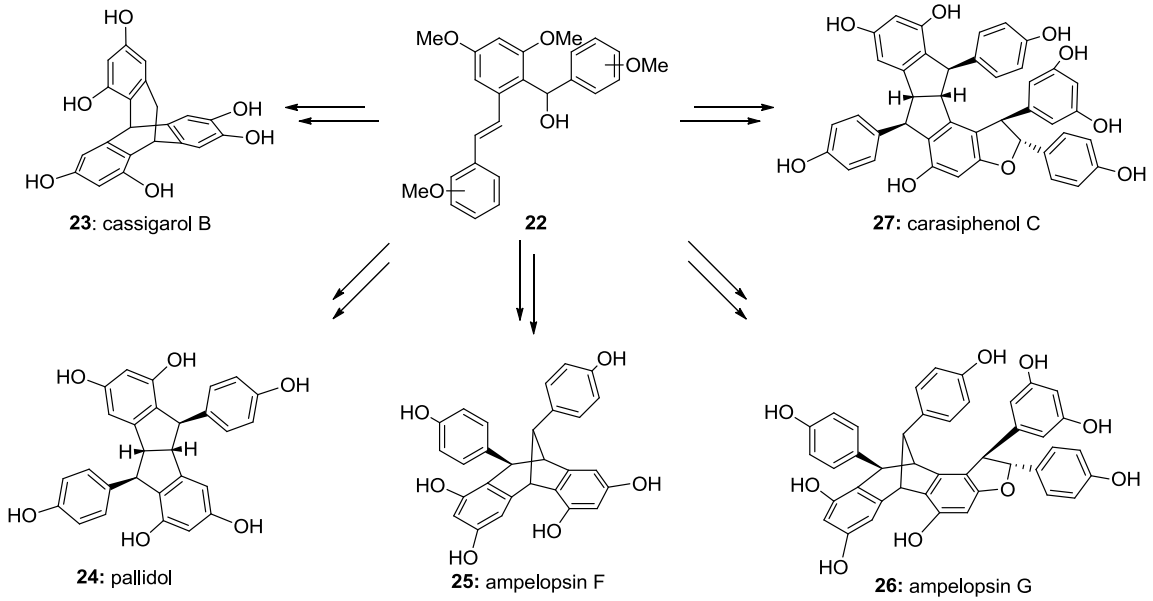
Compound	ConA-induced (μg/mL)	Cytotoxicity (μg/mL)	Selectivity Index
1: dalesconol A	0.16	>80.00	>500
(+)-1: (+)-dalesconol A	0.29	>80.00	>276
(-)-1: (-)-dalesconol A	0.58	>80.00	>138
2: dalesconol B	0.25	>80.00	>320
(+)-2: (+)-dalesconol B	0.47	>80.00	>170
(-)-2: (-)-dalesconol B	0.47	>80.00	>170
3: dalesconol C	>10.00	not tested	
4: daeschol A	>10.00	>80.00	
(+)-4: (+)-daeschol A	5.96 ± 0.06	>80.00	>13.4
(-)-4: (-)-daeschol A	>10.00	>80.00	
6: sporothrin C	>10.00	not tested	
7: dalmanol A	>10.00	>80.00	
(+)-7: (+)-dalmanol A	1.72 ± 0.10	>80.00	>46.5
(-)-7: (-)-dalmonol A	5.56 ± 0.17	>80.00	>14.4
8: acetodalmanol A	5.00 ± 0.55	>80.00	>16.0
9: acetodalmanol B	2.62 ± 0.15	12.84 ± 0.36	4.9
(+)-9: (+)-acetodalmanol B	0.87 ± 0.05	14.34 ± 0.42	16.5
(-)-9: (-)-acetodalmonol B	2.14 ± 0.15	10.04 ± 0.71	4.7
cyclosporin A	0.06 ± 0.002	11.20 ± 0.68	187

Section 1.2 Retrosynthetic Analysis

Our retrosynthetic analysis was inspired by earlier efforts in our group to synthesize members of the resveratrol class of oligomeric polyphenols.[7] As shown in Figure 2, the common triaryl intermediate **22** has been employed in cascades of various complexity to deliver a number of architectures, including [3.2.2]-, [3.2.1]-, and [3.3.0]-bicyclic frameworks (**23** – **25**). Furthermore, elaboration of relevant polycyclic scaffolds into dihydrofuran-containing natural products (**26** and **27**, reported after our work on dalesconols A and B)[8] significantly enhanced the generality of our group's synthetic

approach utilizing key triaryl intermediate **22**. This privileged scaffold has allowed access to nearly all of the polycyclic diversity within the resveratrol class of oligomeric natural products. We envisioned that similarly rapid formation of the dalesconol core could be realized from a related triaryl structure.

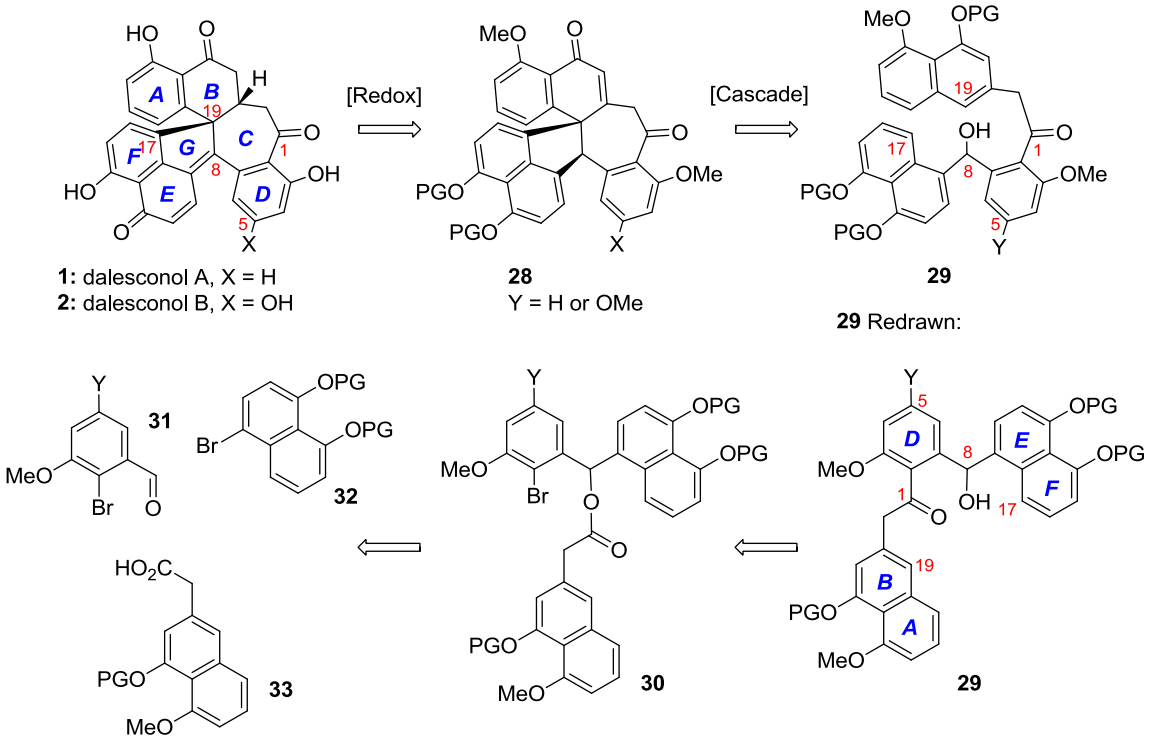
Figure 2. Privileged Triaryl Intermediate Used to Access Oligomeric Resveratrol-Based Natural Products



As illustrated in Scheme 2, our synthetic approach to **1** and **2** was based primarily on the idea that an appropriately functionalized triaryl intermediate such as **29** could be converted into the desired dalesconol core of general form **28** in a single cascade operation. The key cascade step would employ a Friedel–Crafts cyclization between C-19 and C-8 initiated by ionization of the C-8 hydroxyl group to form the seven-membered C-ring, and a subsequent oxidative Friedel–Crafts reaction via activation of the B-ring would unite C-17 and C-19 to form the five-membered G-ring. These processes would utilize C-19 as both nucleophile and electrophile in the same pot to transform it into the lone quaternary carbon of the natural product targets. Subsequent adjustments in

oxidation state and phenol deprotection would then complete the target molecules. While the processes outlined would not render the synthesis of **1** and **2** asymmetric, we did desired a strategy that would deliver both enantiomers for biological testing, and it has been shown by the Tan group that each enantiomer can be resolved by chiral HPLC. Therefore, if the synthesis outlined here could provide access to racemic **1** and **2**, then the individual enantiomers of these targets could be easily accessed, as well.

Scheme 2. Retrosynthetic Analysis of Dalesconol A and B



The differing oxidation pattern between **22** and our proposed triaryl intermediate **29** demanded that slightly different synthetic construction be developed from that employed in the syntheses of oligomeric, resveratrol-based natural products. Thus, we selected an intramolecular *O* to *C* acyl migration, specifically an anionic homo-Fries rearrangement,[9] of ester **30** to deliver our desired connectivity. In turn, ester **30** was envisioned to be easily assembled from simple aromatic building blocks **31** – **33** using

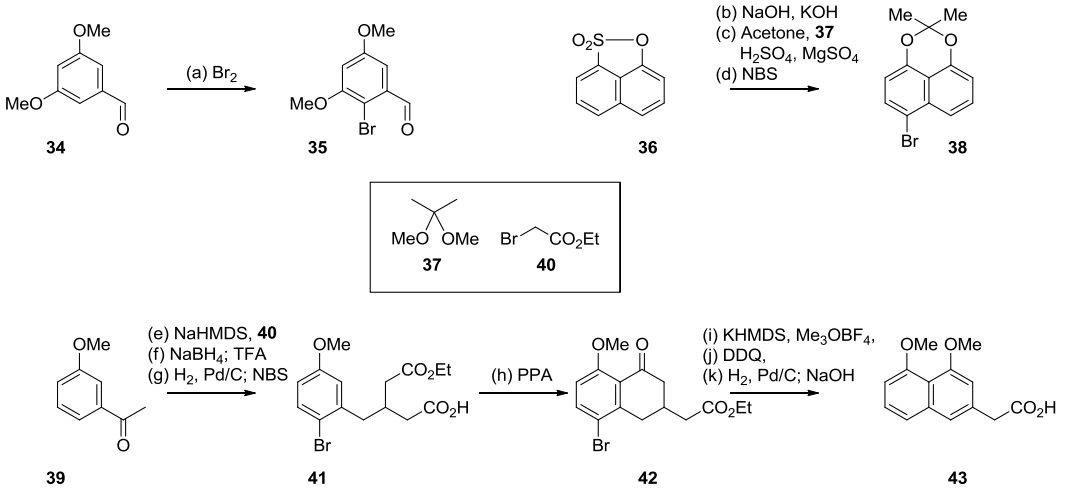
routine transformations. This proposed strategy provided flexibility such that material **31** could be generated with either a hydrogen atom or a protected phenol at C-5 to deliver either **1** or **2**, respectively.

Section 1.3 Total Synthesis

Section 1.3.1 First Generation Approach to Triaryl Intermediate and Core Formation

Our synthetic explorations began with the preparation of our three aromatic building blocks **35**, **38**, and **43** towards dalesconol B. As shown in Scheme 3, aldehyde **35** was synthesized in one step in 72% yield via bromination of commercially available 3,5-dimethoxybenzaldehyde **34**. Naphthalene diol derivative **38** was synthesized in three steps from recrystallized 1,8-naphthosultone **36**. Crystalline **36** was first subjected to an alkali fusion reaction in 53% yield utilizing a KOH and NaOH melt at 210 °C.[10] Straightforward acetonide protection of the resultant diol with acetone and H_2SO_4 proceeded in 30% yield, and aromatic bromination with NBS in 78% yield delivered the target fragment **38**.

Scheme 3. Synthesis of Aromatic Building Blocks for Dalesconol B



Reagents and conditions: (a) Bromine, AcOH, 72% (b) KOH/NaOH/**36** (5/1/1 by weight), 210°C, 53% (c) Acetone, **37**, H_2SO_4, $MgSO_4$, 30% (d) NBS, 78% (e) NaHMDS, **40**; NaHMDS, **40**, 58% (f) $NaBH_4$; TFA (g) H_2, Pd/C; NBS (h) PPA, 66% over 3 steps (i) KHMDS, Me_3OBF_4, 54% (j) DDQ, 79% (k) H_2, Pd/C; NaOH, 89%

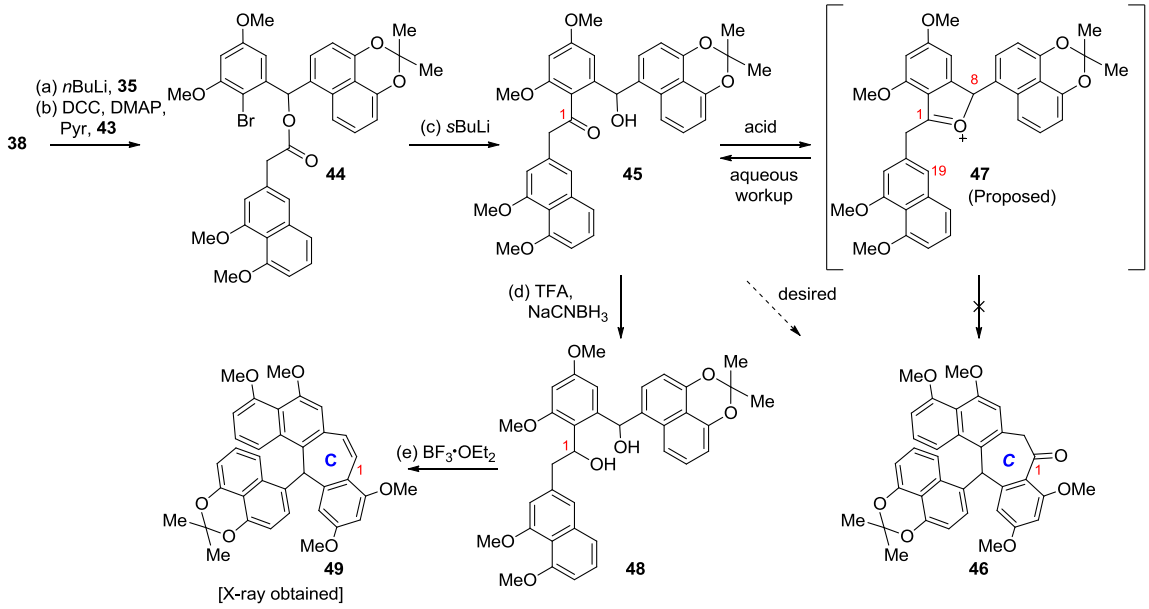
Naphthyl acetic acid derivative **43** required slightly more synthetic ingenuity, and its synthesis began with bis-alkylation of 3'-methoxyacetophenone **39** with ethyl bromoacetate **40** in 58% yield. Subsequent reduction with $NaBH_4$ provided a benzylic alcohol which could undergo acid-catalyzed desymmetrizing lactonization. Hydrogenative opening of the resulting benzylic lactone followed by NBS-mediated installation of a bromine blocking group delivered acid **41**. This acid underwent Friedel–Crafts cyclization after suspension in polyphosphoric acid to deliver ketone **42** in 66% yield. Enolate formation with KHMDS and *O*-methylation with Meerwein's salt provided 54% yield of the desired enol ether. Subsequent DDQ oxidation aromatized the substrate in 79% yield, and hydrogenative bromine removal and ester hydrolysis delivered acid target **43** in a one pot process in 89% yield.

Lithium halogen exchange on protected naphthalene diol **38** and subsequent exposure to aldehyde **35** delivered a biaryl alcohol (not shown) in 67% yield (Scheme 4).

Formation of ester **44** was achieved in 61% yield via DCC coupling of this alcohol with acid **43** in the presence of pyridine and DMAP catalysts. With ester **44** in hand, the homo-anionic Fries conditions could now be explored as a means to deliver our desired triaryl intermediate **45**. As might be expected, exposure to *n*BuLi failed to lithiate **44** and instead attacked the ester carbonyl. Exposure to *t*BuLi or *s*BuLi at –78 °C unfortunately failed to deliver any desired migration product; only debrominated starting material was obtained. Confused as to how our material could be undergoing lithium-halogen exchange but not migrating as desired, we quenched a migration attempt with D_2O in an effort to follow the anionic charge. It was feared that the acidic α-protons on our ester could perform an intramolecular aryl anion quench via a seven-membered transition state. As suspected, we found that immediately after lithium halogen exchange, intramolecular deprotonation between the lithiated aromatic position and the ester α-carbon was forming an enolate and quenching both our desired nucleophile and electrophile.

To circumvent this issue, lithium-halogen exchange was performed at –95°C and the reaction mixture was slowly warmed to –78°C to deliver the desired product in 28% yield. An intermediate temperature in this range was required for the desired reaction, as no acyl migration was observed at –95°C. The yield for this process was lower than desired due to our inability to completely shut down the intramolecular proton transfer side reaction. Fortunately, debrominated starting material and product **45** were separable, thereby allowing the dehalogenated starting material to be recycled through ester cleavage, rebromination of the resultant biaryl alcohol (not shown), and DCC coupling to re-form **44**.

Scheme 4. First Generation Approach to C Ring



Reagents and conditions: (a) *n*BuLi, **35**, 67% (b) DCC, DMAP, Pyridine, **43**, 61% (c) *s*BuLi, 28% (d) TFA, $NaCNBH_3$, 99% (e) BF_3OEt_2, 99%

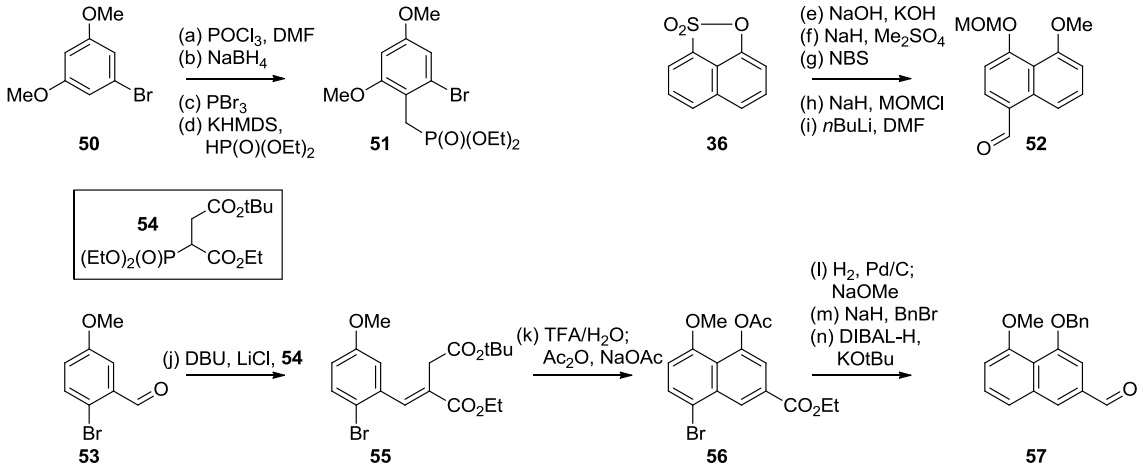
Pressing forward, we exposed triaryl alcohol **45** to a variety of acidic and dehydrative conditions in an attempt to form the seven-membered C ring found in **46**. Frustratingly, starting material was always recovered unchanged. We hypothesized that the C-1 carbonyl of **45** was bridging into the C-8 carbocation to form an oxacarbenium ion stabilized by the neighboring dimethoxyarene (**47**). It seems likely that this five-membered ring intermediate placed the desired nucleophile, C-19 on the B-ring, too far away to attack C-8, and the speed with which the C-1 carbonyl could trap the benzylic carbocation at C-8 prevented any seven-membered C-ring from forming. Upon aqueous workup, **47** could be hydrolyzed back to starting material **45**, explaining why we observed no overall reaction process under the explored conditions. To test this hypothesis, we reduced the C-1 carbonyl of **45** to an alcohol in quantitative yield using TFA and $NaCNBH_3$ and found that this new triaryl intermediate **48** smoothly cyclized with accompanying dehydration of the C-1 alcohol under a variety of acidic conditions to

give cyclized intermediate **49**. An X-ray crystal structure of **49** was obtained, confirming its structure.

Pleasingly, this result validated our approach for C-ring formation, but our triaryl intermediate could not contain the C-1 ketone. Given the low yield for the Fries rearrangement used to produce ester **45**, we redesigned the assembly of our triaryl intermediate to employ higher-yielding chemistry already developed for the resveratrol oligomer project in our lab. We hoped that late-stage benzylic oxidation of C-1 would provide the desired ketone.

Section 1.3.2 Second Generation Approach to Triaryl Intermediate and Core Formation

Scheme 5. Synthesis of Redesigned Aromatic Building Blocks for Dalesconol B



Reagents and conditions: (a) $POCl_3$, DMF, 99% (b) $NaBH_4$, 96% (c) PBr_3, 96% (d) KHMDS, $HP(O)(OEt)_2$, 94% (e) NaOH, KOH, 53% (f) NaH, Me_2SO_4, 99% (g) NBS, 98% (h) NaH, MOMCl, 99% (i) *n*BuLi, DMF, 96% (j) DBU, LiCl, **54**, 99% (k) TFA/H_2O; NaOAc, Ac_2O, 83% (l) H_2, Pd/C; NaOMe, 99% (m) NaH, BnBr, 77% (n) DIBAL-H, KO*t*Bu, 67%

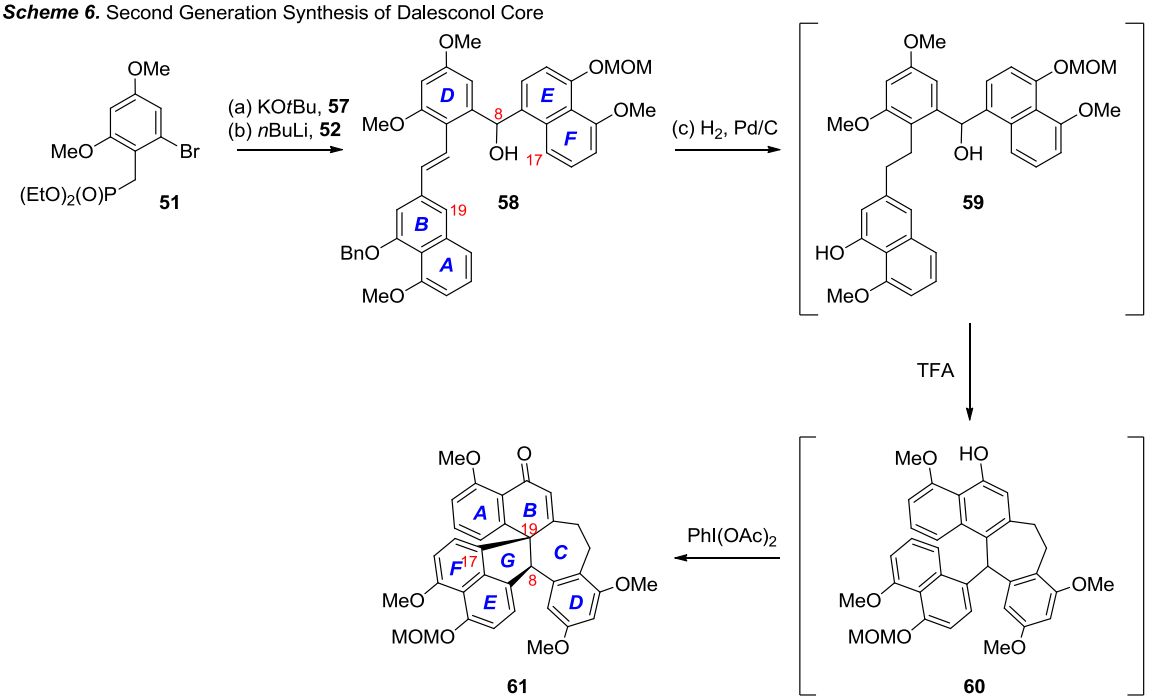
Focusing on redesigned building blocks **51**, **53**, and **58** congruent with the chemistry used for assembly of resveratrol triaryl intermediate **22**, we developed straightforward, multigram syntheses of our starting materials (Scheme 5). Beginning with dimethoxybromobenzene (**50**), Vilsmeier–Haack formylation, transformation of the resultant aldehyde into a benzyl bromide, and phosphonate anion attack delivered aryl phosphonate **51** in 86% overall yield across four steps. This process was used to prepare over 10 g of **51** in a single batch. Naphthaldehyde **52** was synthesized in 49% overall yield from sultone **36** again starting with an alkali fusion reaction to give 1,8-naphthalene diol (not shown) as in the first generation building block synthesis. Subsequent monoprotection with NaH and Me_2SO_4, selective bromination,[11] methoxymethyl ether protection, and lithium-halogen exchange followed by exposure to DMF provided over 20 g of **52**.

Finally, aldehyde **57** was obtained in five steps and 42% overall yield from commercially available benzaldehyde derivative **53**. This synthesis began with a Horner–

Wadsworth–Emmons reaction of **53** using phosphonate **54** as a Stobbe reaction surrogate, providing diester **55** in good yield. Indeed, classical Stobbe condensation as a means to form a variant of **55** was capricious and difficult to reproduce, especially on scale. Subsequent one-pot *t*-butyl ester removal and Friedel–Crafts acylation provided naphthalene ester **56**, with one-pot removal of the bromine blocking group and acetate cleavage followed by benzyl protection and ester reduction to the aldehyde delivering the desired product (**57**). It should be noted that controlled DIBAL-H reduction to deliver the aldehyde was difficult to achieve, especially on scale, and often yielded a significant quantity of over-reduced alcohol. The reagent formed by admixing DIBAL-H with KO*t*Bu, termed potassium diisobutyl *t*-butoxy aluminum hydride (PDBBA), provided far better yields of the desired aldehyde and was reproducible even on large scale.[12] This process was used to prepare multigram quantities of aldehyde **57**.

With these fragments in hand, we were able to unite them into our new triaryl intermediate **58**, providing decagram quantities of this material for cascade development. An initial Horner–Wadsworth–Emmons reaction between the anion derived from phosphonate **51** and aldehyde **57** united the two pieces in 87% yield, and exposure of the resultant stilbene derivative to *n*BuLi and aldehyde **52** delivered triaryl intermediate **58** in 67% yield (Scheme 6). Fortunately, this process was much higher yielding than the route to first generation triaryl intermediate **45**. With this new key intermediate in hand, we could now press forward with our key goal of transforming this triaryl scaffold into the dalesconol core. Extensive studies and optimization resulted in the cascade sequence shown in Scheme 6.

Scheme 6. Second Generation Synthesis of Dalesconol Core



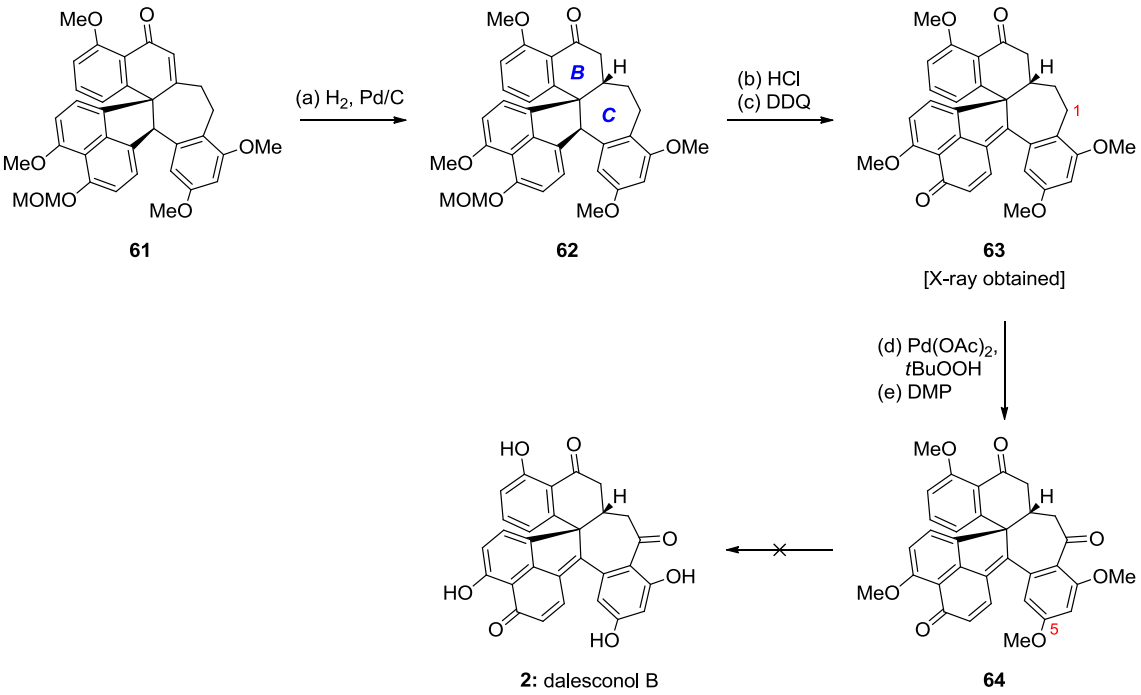
Reagents and conditions: (a) KO*t*Bu, **57**, 87% (b) *n*BuLi, **52**, 67% (c) H_2, Pd/C; TFA; $PhI(OAc)_2$, 32% overall

Unsurprisingly, the *trans*-olefin contained in **58** prevented C-ring formation from occurring in initial studies, so it was determined that hydrogenation of this olefin would be required for productive cascade-based core formation. The benzyl protecting group on the B-ring phenol was selected so that its removal would accompany olefin hydrogenation, positioning the sole deprotected phenol as a reactive handle for oxidative G-ring formation in our cascade sequence. With these two factors set, hydrogenation would prepare substrate **58** for a double ring-forming sequence. In the event, **58** was taken up in a mixture of ethyl acetate and ethanol (2:3) and subjected to one atmosphere of H_2 gas in the presence of a full equivalent of 10% Pd/C. Under these specific conditions, the benzyl protecting group was excised and the stilbene double bond was reduced in quantitative yield. Use of any other solvent combinations or ratios, as well as catalytic loadings of palladium, led to significant amounts of material in which the C-8 hydroxyl group was reduced as well. After filtration and solvent removal, the crude

residue (**59**) was resuspended in 2,2,2-trifluoroethanol and treated with one equivalent of TFA at –45 °C for 15 minutes. During this time, the desired Friedel–Crafts reaction to form the seven-membered C-ring proceeded as previously observed for diol **48** (Scheme 4) between C-19 and C-8, to give intermediate **60**. Without isolating this material, $PhI(OAc)_2$ was subsequently added to the same pot at –45 °C and 20 minutes of additional reaction time converted the strategically deprotected phenol on the B-ring into an oxidized material with a *para*-disposed carbocation at C-19. This electrophile was engaged by the electron-rich F-ring at C-17 to fashion the complete dalesconol core as expressed in **61**.[13] Overall, these operations provided **61** in 32% yield upon isolation, thereby accounting for an average efficiency of 75% per step based on the four distinct operations outlined in this cascade sequence.

Section 1.3.3 Redox Adjustment of the Dalesconol B Core and Global Deprotection

Scheme 7. Dalesconol Core to Permethylated Dalesconol B



Reagents and conditions (a) H_2 Pd/C, 84% (b) HCl, 99% (c) DDQ, 82% (d) $Pd(OAc)_2$, *t*BuOOH, 42% (e) DMP, 99%

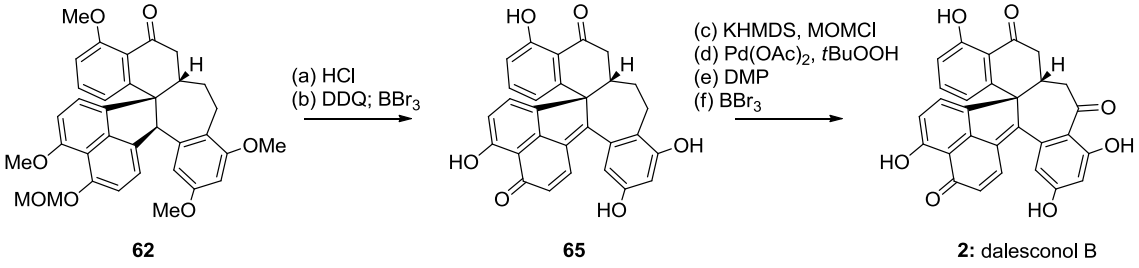
Having achieved the critical, core-forming operation, the completion of dalesconol B (**2**) required several adjustments in oxidation state prior to removal of the phenolic protecting groups. The first of these events, hydrogenation of the enone double bond in **61**, proceeded as desired in 84% yield when performed in a 3:1 mixture of EtOH and EtOAc at 25 °C (Scheme 7). This step provided **62** as a single diastereomer of unknown configuration, although it was assumed that hydrogen delivery from the more exposed top face of the molecule (as drawn) would deliver the desired *cis*-fused six-seven B/C ring junction. Occasionally, over reduction of the ketone functionality to an alcohol accompanied olefin hydrogenation. Changing solvents from the conditions described

above or prolonging reaction times without careful monitoring produced significant amounts of the undesired alcohol. Fortunately, if obtained, this material could be recycled to **62** via facile Dess–Martin oxidation.[14] Pressing forward, quantitative removal of the methoxymethyl ether protecting group via exposure to aqueous HCl and DDQ-mediated oxidation[15] converted **62** into the corresponding *para*-quinone methide **63** in 82% yield. An X-ray crystal structure of **63** confirmed the stereochemistry of the B/C ring junction as the *cis*-fusion needed to access the target structure.

At this stage, only benzylic oxidation of the C-1 position and global demethylation remained to deliver dalesconol B (**2**). Unfortunately, a variety of conventional oxidants failed to effect any transformation on **63**, and those that did merely decomposed the molecule. Arriving at the conclusion that C-1 is not as activated as one would expect an electron-rich benzylic position to be, we began investigating oxidative methods developed for less activated allylic systems and found that a procedure developed by Yu and Corey employing $Pd(OAc)_2$ and *t*BuOOH affected the desired oxidation.[16] Even this successful oxidation was sluggish, however, and it required three days of reaction time with more catalyst and co-oxidant added once per day to give 42% yield of the C-1 alcohol. This result is intriguing, as only ketone or peroxide products were reported by Yu and Corey. A similar procedure employing $Mn(OAc)_3$ instead of $Pd(OAc)_2$ also produced the C-1 alcohol, albeit in lower yield.[17] Unfortunately, these protocols were not amenable to scale-up and had to be performed on small scale in parallel in order to produce enough material to carry forward with the synthesis. Clearly, benzylic oxidation on unique, recalcitrant systems like the dalesconol framework needs more attention.

Nevertheless, we had achieved C-1 oxygenation, and quantitative Dess–Martin oxidation of the C-1 alcohol to permethylated dalesconol B **64** allowed us to begin screening conditions for deprotection. Unfortunately, we could never demethylate the C-5 phenol, and monomethylated dalesconol B was obtained with various methods employing Lewis acids such as BBr_3 and TMSI. We observed that the three phenols that were unveiled successfully have neighboring carbonyls to aid in chelation with a Lewis acid for deprotection. The C-5 methyl ether, on the other hand, does not. Furthermore, the newly installed ketone at C-1 is withdrawing electron density from the D ring, directly decreasing the Lewis basicity of the C-5 methyl ether. Without a neighboring carbonyl to aid in chelation, this decrease in Lewis basicity could be enough to prevent productive coordination with a Lewis acid reagent. This analysis led us to believe that globally deprotecting prior to C-1 oxidation and reprotecting with a more labile group than a methyl ether might enable us to finish the target.

Scheme 8. Engame of the First Total Synthesis of Dalesconol B



62 **65** **2:** dalesconol B

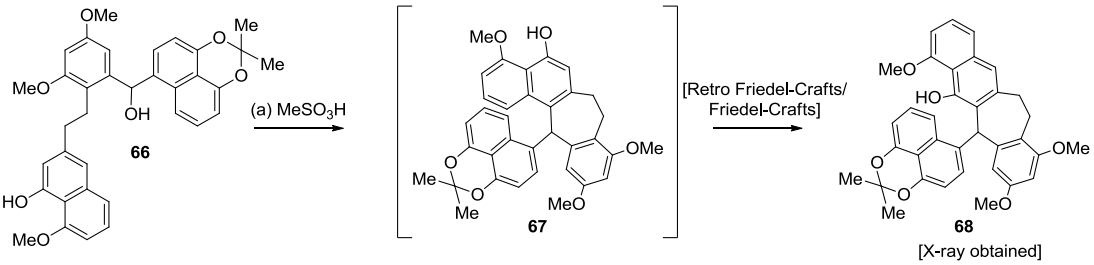
Reagents and conditions: (a) HCl, 99% (b) DDQ; BBr_3, 73% (c) KHMDS, MOMCl, 91% (d) $Pd(OAc)_2$, *t*BuOOH, 42% (e) DMP, 99% (f) BBr_3, 73%

Going back to reduced core **62**, we were able to smoothly remove the lone methoxymethyl ether protecting group via exposure to aqueous hydrochloric acid (Scheme 8). Modifying our DDQ mediated *para*-quinone methide formation, we developed a procedure in which DDQ and boron tribromide were added sequentially to

the same pot, unveiling all four free phenols to deliver *des*-oxo dalesconol B **65** in 73% yield. This intermediate only required installation of the C-1 ketone to reach our target structure. Unfortunately, attempts to oxidize **65** were met with repeated failure. Therefore, pushing ahead with our plan to employ a more labile protecting group, we reprotected all four free phenols as methoxymethyl ethers in 91% yield. Fortunately, benzylic oxidation using the Yu/Corey procedure worked similarly on this substrate as on **63**, delivering the C-1 alcohol again in 42% yield. Facile Dess–Martin oxidation and swift exposure to BBr_3 at –78 °C smoothly unveiled all four free phenols to deliver the target molecule, dalesconol B (**2**) in 73% yield. Therefore, a total of 15 operations in the longest linear sequence, with only half of these occurring after the preparation of our key intermediate **58**, were needed to achieve the total synthesis. To date, over 20 mg of dalesconol B have been prepared.

Section 1.3.4 Unanticipated Skeletal Rearrangements

Scheme 9. Structural rearrangment involving *para*- to *ortho*-Friedel-Crafts regiochemical switch

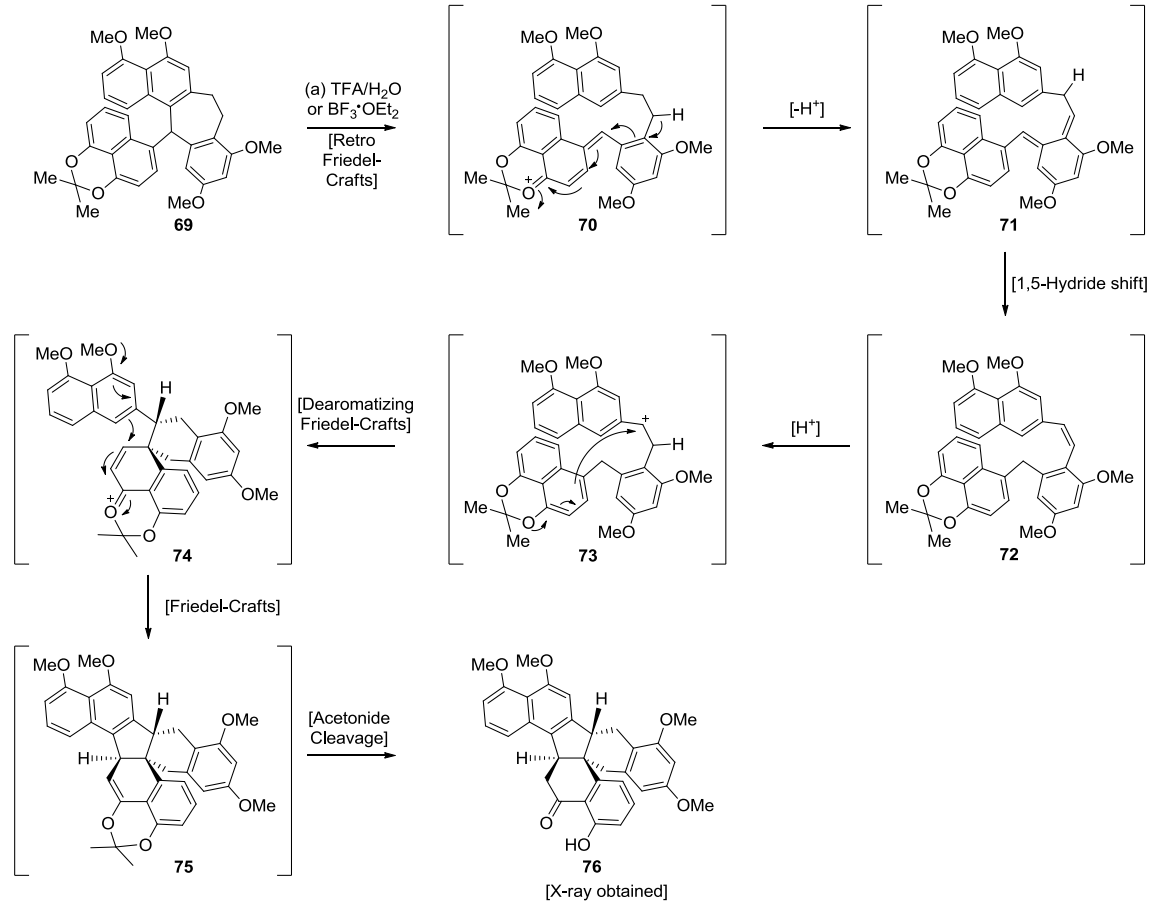


Reagents and conditions: (a) $MeSO_3H$, 77%

It is important to stress, however, that the sequence delineated above, particularly core-forming cascade transforming **58** into **61**, required several iterations to achieve. The main challenge was that subtle change of reaction conditions or the mere alteration or

absence of a protecting group resulted in unanticipated skeletal rearrangements. For instance, exposure of a molecule with a free phenol on the B ring such as triaryl intermediate **66** to a stronger acid than that used in our productive sequence led to an alternate seven-membered ring adduct **68** (Scheme 9). We believe that this structure, which was confirmed by X-ray crystallographic analysis, is the product of a retro-Friedel–Crafts/Friedel–Crafts sequence as **67** was observed during the course of the reaction by thin-layer chromatography, though it was not isolated upon completion. On the basis of the evaluation of X-ray crystal structures and related intermediates, materials of general architecture **68** appear to have less steric strain than those resembling **67**. Thus, rearrangement to the thermodynamically more stable product occurs. MMFF94 calculations predict that rearranged product **68** is 6.8 kcal/mol more stable than the desired product **67**. Indeed, if seven-membered cascade intermediate **60** is not quenched or reacted further with hypervalent iodine as described in Scheme 6, it, too, will rearrange to an *ortho*-alkylated seven-membered ring architecture resembling **68**. The desired product resulting in the union of C-8 and C-19 is, we believe, the kinetic outcome for this ring-forming reaction.

Scheme 10. Proposed Mechanism for Rearrangement to Novel Architecture **76**

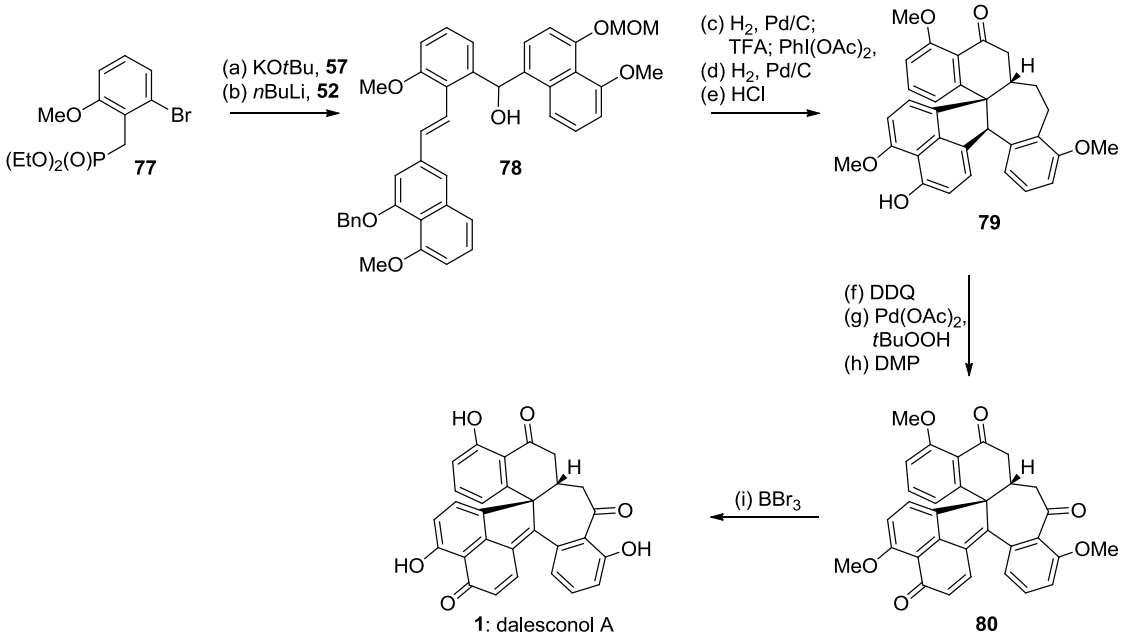


Reagents and conditions: (a) BF_3•OEt_2, 59%

Additionally, a fully protected seven-membered ring intermediate such as **69** can also rearrange into a novel architecture (Scheme 10). Both protic and Lewis acids caused this rearrangement to occur with accompanying loss of the acetonide protecting group to give unique polycycle **76**. The exact mechanism for this is not entirely understood, but we have provided a proposal for one plausible pathway initiated by a retro-Friedel–Crafts reaction.

Section 1.3.5 Total Synthesis of Dalesconol A

Scheme 11. Total Synthesis of Dalesconol A



Reagents and conditions: (a) KO*t*Bu, **57**, 79% (b) *n*BuLi, **52**, 51% (c) H_2, Pd/C; TFA; $PhI(OAc)_2$, 27% overall (d) H_2 Pd/C, 65% (e) HCl, 99% (f) DDQ, 77% (g) $Pd(OAc)_2$, *t*BuOOH, 41% (h) DMP, 99% (i) BBr_3, 66%

Finally, we wished to determine if our developed synthetic route for dalesconol B could also be applied to dalesconol A (**1**). As shown in Scheme 10, we achieved this goal starting with phosphonate **77**,[18] obtained from *ortho*-anisaldehyde through the same general sequence of events as those described for phosphonate **51** used in the synthesis of dalesconol B. The sole difference between these two phosphonates is the lack of a C-5 methyl ether. Notably, this C-5 methyl ether was the lone methyl ether that was resistant to cleavage in the synthesis of dalesconol B and required us to perform the late stage demethylation/reprotection sequence with methoxymethyl ethers. Thus, we hoped to avoid the need for such a protecting group switch in the synthesis of dalesconol A. Pleasingly, when we applied the developed route to dalesconol A, we were able to obtain the target natural product in one step shorter than the 15-step sequence required for

dalesconol B. As predicted, the lack of the C-5 phenol in the D ring does not appear to fundamentally modify reactivity of any substrates in the route towards dalesconol A, although slight changes in reaction time and temperature were required for some individual steps to reach completion. Especially intriguing is that the late-stage benzylic oxidation sequence appeared to proceed at the same rate in the route to dalesconol A as it does for dalesconol B, even with the loss of an electron donating group at C-5, further highlighting the uniqueness of our system. As a testament to the strength of the developed chemistry, in our first attempt to execute this sequence, we were able to obtain a characterizable amount of **1** from only 100 mg of *o*-anisaldehyde starting material. The yields and experimental description for this synthesis presented here and in the experimental section represent additional, larger pushes of material.

Section 1.3.6 Total Syntheses Summary

In conclusion, we were able to realize our goal of developing a short, direct route to dalesconols A and B (**1** and **2**) in 0.6% and 1.3% overall yield, respectively, that is capable of providing both natural products and has enabled a more comprehensive evaluation of biochemical potential (vide infra). Key elements of this work include a one-pot cascade which sequentially forged two rings and the lone quaternary carbon, itself used as both nucleophile and electrophile in the same pot, to complete the entire polycyclic core of the targets from an expanded version of our group's triaryl intermediate used in resveratrol oligomer synthesis; a unique benzylic oxidation to forge the C-1 ketone on a particularly unreactive framework; and the demonstration that

alteration of phenol protecting groups or reaction conditions could afford a number of unique structures in addition to the target molecules. The ability to obtain not only core **61**, but also rearranged structures **68** and **76** from intermediates of general structure **58**, reaffirms their power as privileged starting materials for the controlled generation of a variety of distinct architectures.[19]

Section 1.4 Screening Immunosuppressive Activity of Dalesconol B and Synthetic Analogues

Having completed the total syntheses of dalesconols A and B (**1** and **2**), we wished to further evaluate the biological activity of the target structures themselves as well as synthetic intermediates. In collaboration with Professor Sankar Ghosh and Dr. Hyunju Oh at the Columbia University Medical Center, **2**, an oxidized analogue of dalesconol B (**21**), and the other synthetic intermediates shown in Figures 4, 6, and 8 were screened for biological activity. We did not produce enough dalesconol A to screen it in this initial assay, but the C-1 *des*-oxo derivative **91** was evaluated. The ConA-induced T-cell proliferation assay used by the Tan group in their original communication on dalesconol A and B was repeated by Dr. Oh with our synthetic materials using cyclosporin A as an internal control, with all samples submitted blind.[20] The results are shown in Figure 3, 5, and 7.

Figure 3. Immunosuppression Data for Compounds TCS001 – TCS007

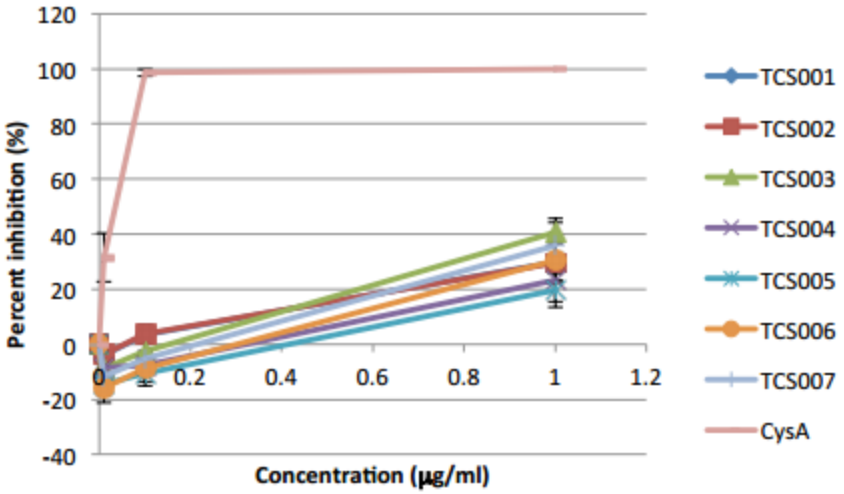
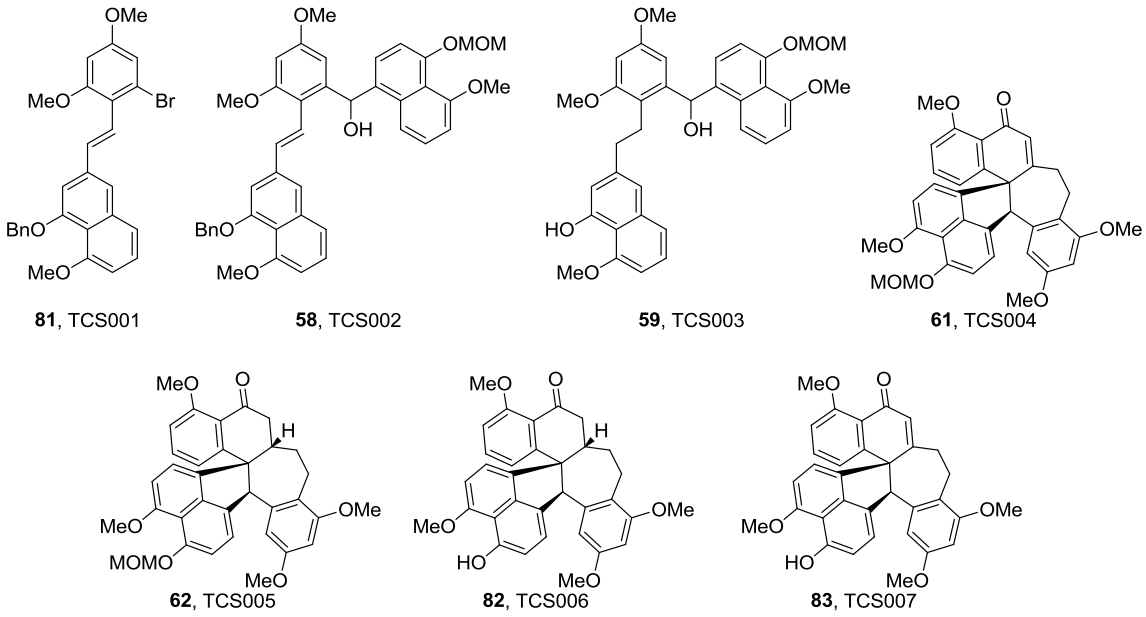


Figure 4. TCS001 - TCS007 for Immunosuppressant Screen



As displayed in Figure 3, none of the intermediates in the compound set TCS001 – TCS007 (Figure 4) demonstrated immunosuppressant activity comparable to cyclosporin A in the performed screen at concentrations <1 µg/mL. At 1 µg/mL, modest activity was observed for this set of compounds.

Figure 5. Immunosuppression Data for Compounds TCS008 – TCS014

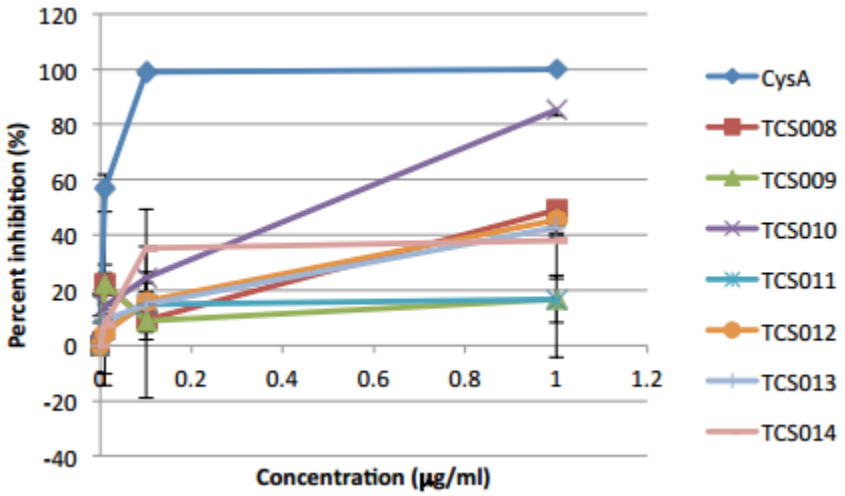
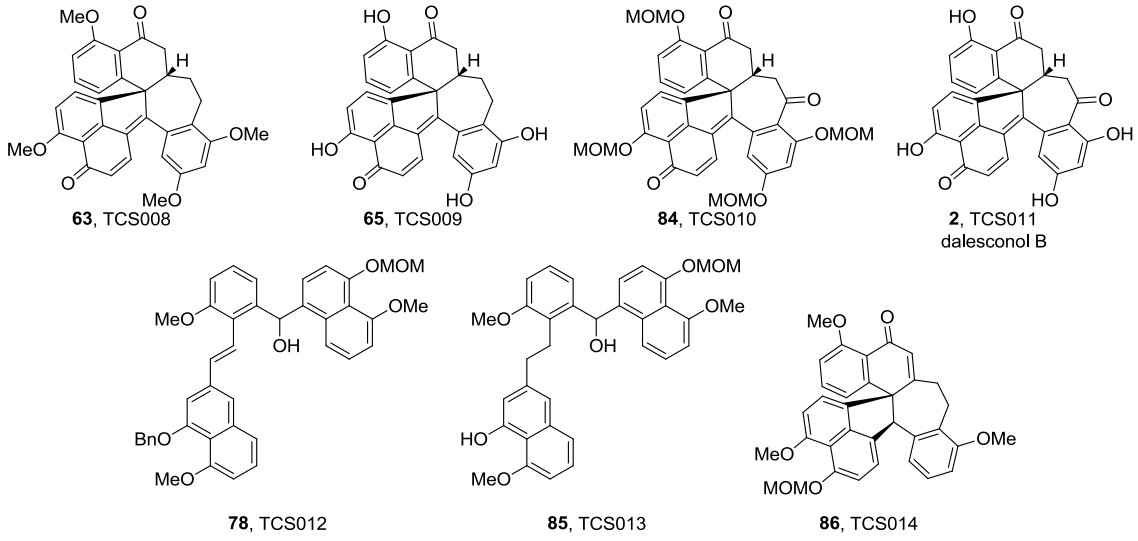


Figure 6. TCS008 - TCS014 for Immunosuppressant Screen



As displayed in Figure 5, none of the intermediates in the compound set TCS008 – TCS014 (Figure 6) demonstrated immunosuppressant activity comparable to cyclosporin A in the performed screen at concentrations <1 µg/mL. At 1 µg/mL, modest activity was observed for this set of compounds similar to the first set (Figure 4) with TCS010 (**84**), a methoxymethylether protected derivative of dalesconol B (**2**),

demonstrating >80% inhibition at 1 µg/mL. Interestingly, the immunosuppressant activity of **2** (blinded as TCS011) observed in this assay was markedly lower than that reported by Tan and co-workers.

Figure 7. Immunosuppression Data for TCS015 – TCS021

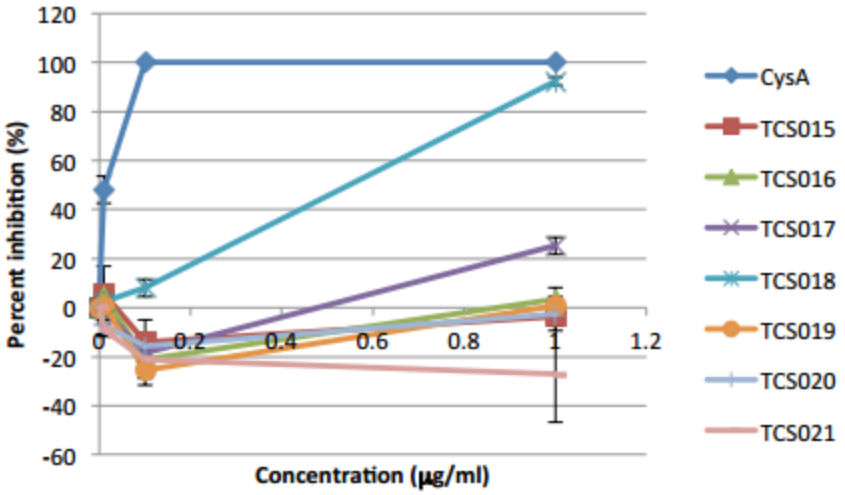
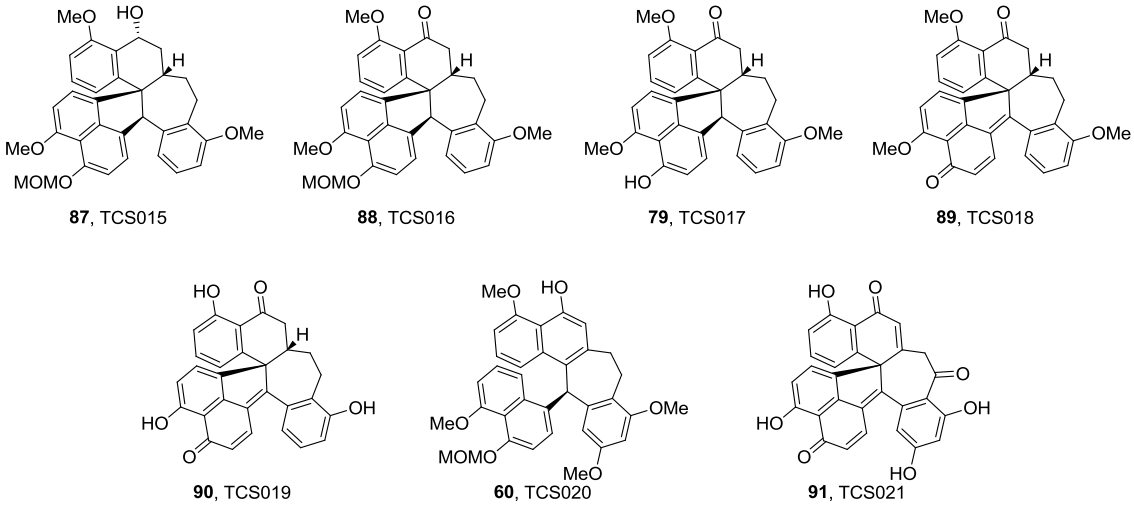
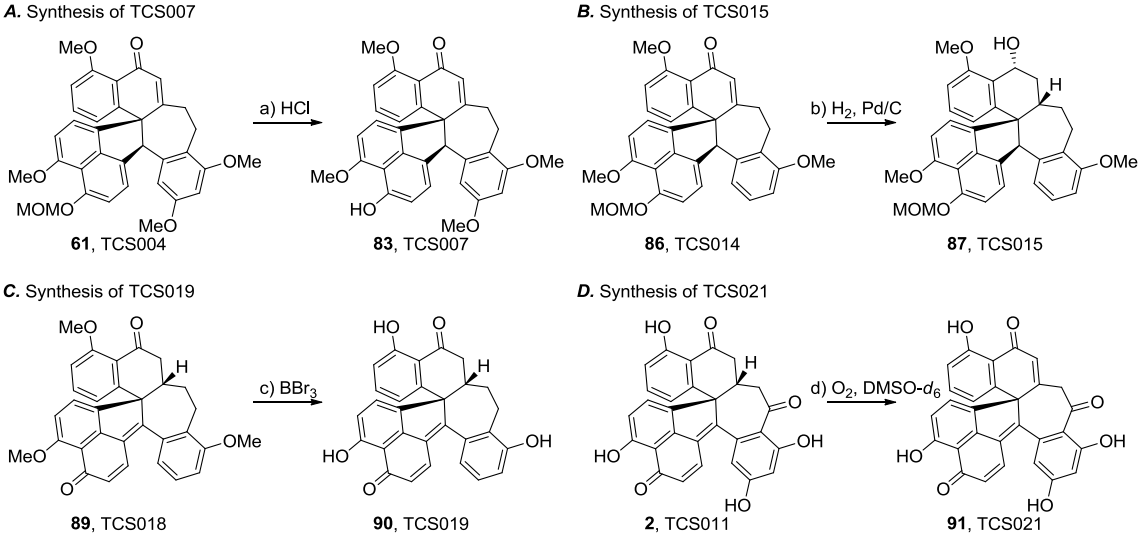


Figure 8. TCS015 - TCS021 for Immunosuppressant Screen



As displayed in Figure 5, none of the intermediates in the compound set TCS015 – TCS021 (Figure 8) demonstrated immunosuppressant activity comparable to cyclosporin A in the performed screen at concentrations <1 µg/mL, including TCS021 (**91**), an oxidized derivative of **2**. At 1 µg/mL, modest activity was observed for TCS017 (**79**), and TCS018 (**89**, oxidized variant of **79**), a C-1 *des*-oxo, methyl ether protected variant of **1**, demonstrated >90% inhibition at 1 µg/mL.

Scheme 12. Synthesis of Screening Compounds not Contained in Dalesconol A and B Synthetic Routes



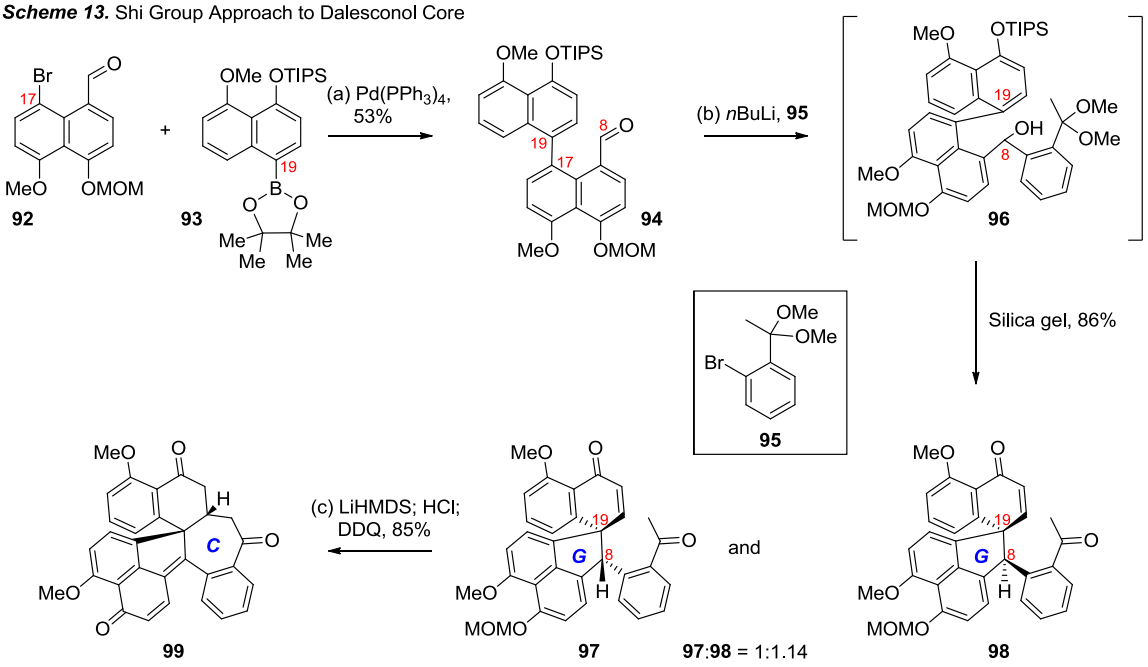
Reagents and conditions: (a) HCl, 99% (b) H_2, Pd/C, 20% (c) BBr_3, 75% (d) O_2, DMSO-d_6, 50%

It is unfortunate that we were unable to observe the level of immunosuppression for dalesconol B as the Tan group reported in their 2008 communication, and we do not have an explanation for this discrepancy. Additional experiments on this molecule would be beneficial to fully elucidate its immunosuppressive potential.

Section 1.5 Shi Group Work Towards the Dalesconol Core

In 2011, after we had published our total synthesis of dalesconol A and B, Shi and co-workers reported a concise approach to the dalesconol skeleton.[21] The assembly of the aromatic starting materials **92** and **93** made use of the chemistry we reported for the synthesis of our own building block **52**.

Scheme 13. Shi Group Approach to Dalesconol Core



As shown in Scheme 13, the Shi group began the union of their starting materials via Suzuki coupling of bromide **92** and boronic ester **93** to deliver binaphthyl aldehyde **94**, forming the bond between C-19 and C-17. Subsequent lithiation of aryl bromide **95** and nucleophilic attack of the C-8 aldehyde in **94** formed transient alcohol **96**. In practice, this unstable material was immediately subjected to silica gel to deprotect the dimethyl ketal and, more importantly, undergo a dearomatizing Friedel-Crafts reaction, forming the G-ring through ionization of the C-8 hydroxyl group. Unfortunately, this bond-forming event between C-19 and C-8 gave a nearly 1:1 mixture of diastereomers **97** and **98**. Although the penultimate structure has destroyed the C-8 stereocenter formed in this reaction through stable quinone-methide formation, only **97** would form the C-ring in the next step.

Separating the two diastereomers, **97** was treated with base to initiate Michael addition to form the C-ring. Treatment in the same pot with aqueous hydrochloric acid

removed the sole methoxymethyl ether protecting group, and addition of DDQ oxidized the newly-unveiled free phenol to the desired quinone-methide functionality of **99**; this deprotection/oxidation sequence is similar to the one we employed for the same transformation. The Shi group's approach to a protected dalesconol core was achieved in an impressive nine steps, though the final reported structure does lack the oxygenation pattern of the D-ring observed in either **1** or **2**.

It is worth noting that the Shi group formed the C- and G-rings in the opposite order from our approach. We formed the C-ring first and used the newly-installed chiral center at C-8, later destroyed through quinone-methide formation, to guide the formation of each of the two remaining chiral centers in a diastereoselective fashion. The Shi group, in contrast, first formed the G-ring in a non-diastereoselective manner, and suffered a loss of nearly half their material at this stage. Nevertheless, the Shi group was able to accomplish a nine step synthesis of dalesconol core **99** utilizing aromatic building blocks **92**, **93**, and **95** employing a similar C and G ring-forming strategy to our own; however, this work does offer additional lessons regarding the unique reactivity of these frameworks.

Section 1.6 Conclusion

In summary, we were able to realize our goal of developing a direct route to dalesconol A and B (**1** and **2**) in 14 and 0.6% overall yield and 15 steps and 1.3% overall yield, respectively, that is capable of providing both natural products, as well as several synthetic analogues, and enabled further evaluation of their biochemical potential. Key

elements of this work include a one-pot cascade which sequentially forged two rings and the lone chiral quaternary carbon to complete the entire dalesconol core and a unique benzylic oxidation. Our own biological testing performed in collaborative studies with Professor Sankar Ghosh did not reveal the same levels of activity we expected based on the Tan group's screens, and additional testing would be beneficial to elucidate the immunosuppressive activity of these natural products. Finally, a rapid core synthesis by the Shi group employing an alternative order of C- and G-ring formation took advantage of unique reactivities in the dalesconol framework and inadvertently highlighted the stereoselectivity we achieved through the use of our core-forming cascade.

Acknowledgements

Dr. Audrey Ross is acknowledged for early synthetic work on the route to dalesconols A and B. Prof. Sankar Ghosh and Dr. Hyunju Oh are acknowledged for performing the relevant immunosuppression assays on intermediates we provided. Prof. Gerard Parkin, Dr. Wesley Sattler, and Dr. Aaron Sattler are acknowledged for X-ray crystallographic analysis of noted intermediates. Dr. Yasuhiro Itagaki is acknowledged for mass spectrometric analysis. Dr. John Decatur and Dr. George Suckenick are acknowledged for NMR assistance.

Section 1.7 References

1. Y. L. Zhang, H. M, Ge, W. Zhao, H. Dong, Q. Xu, S. H. Li, J. Li, J. Zhang, Y. C. Song, R. X. Tan, *Angew. Chem.* **2008**, *120*, 5907 – 5910; *Angew. Chem. Int. Ed.* **2008**, *47*, 5823 – 5826.

2. L. Wen, X. Cai, F. Xu, Z. She, W. Chan, L. L. P. Vrijmoed, E. B. G. Jones, Y. Lin, *J. Org. Chem.* **2009**, *74*, 1093 – 1098.

3. Y. L. Zhang, J. Zhang, N. Jiang, Y. H. Lu, L. Wang, S. H. Xu, W. Wang, G. F. Zhang, Q. Xu, H. M. Ge, J. Ma, Y. C. Song, R. X. Tan, *J. Am. Chem. Soc.* **2011**, *133*, 5931 – 5940.

4. W. Fang, S. Ji, N. Jiang, W. Wang, G. Y. Zhao, S. Zhang, H. M. Ge, Q. Xu, A. H. Zhang, Y. L. Zhang, Y. C. Song, J. Zhang, R. X. Tan, *Nat. Comm.* **2012**, *3*, 1039.

5. (a) B. D. Kahan, *Nat. Rev. Immunol.* **2003**, *3*, 831 – 838. (b) H. Hackstein, W. Thomson, *Nat. Rev. Immunol.* **2004**, *4*, 24 – 34.
6 M. Mentel, W. Blankenfeldt, R. Breinbauer, *Angew. Chem. Int. Ed.* **2009**, *48*, 9084 – 9087.

7. (a) S. A. Snyder, A. L. Zografos, Y. Lin, *Angew Chem. Int. Ed.* **2007**, *46*, 8186 – 8191. (b) S. A. Snyder, S. P. Breazzano, A. G. Ross, Y. Lin, A. L. Zografos, *J. Am . Chem. Soc.* **2009**, *131*, 1753 – 1765.

8. S. A. Snyder, A. Gollner, M. I. Chiriac, *Nature* **2011**, *474*, 461 – 466.

9. K. C. Nicolaou, K. Koide, M. E. Bunnage, *Chem. Eur. J.* **1995**, *1*, 454 – 466.

10. (a) M. Poirier, M. Simard, J. D. Wuest, *Organometallics* **1996**, *15*, 1296 – 1300. (b) S. A. Snyder, Z.-Y. Tang, R. Gupta, *J. Am. Chem. Soc.* **2009**, *131*, 5744 – 5745.

11. M. C. Carreño, J. L. García Ruano, G. Sanz, M. A. Toledo, A. Urbano, *Synlett* **1997**, *11*, 1241 – 1242.

12. (a) M. Chae, J. Song, D. An, *Bull. Korean Chem. Soc.* **2007**, *28*, 2517 – 2518. (b) J. I. Song, D. K. An, *Chem. Lett.* **2007**, *36*, 886 – 887. (c) M. S. Kim, Y. M. Choi, D. K. An, *Tetrahedron Lett.* **2007**, *48*, 5061 – 5064.

13. The use of PhI(OAc)2 to forge such types of systems is, of course, well known. For selected examples, see: (a) Y. Kita, T. Takada, M. Gyoten, H. Tohma, M. H. Zenk, J. Eichhorn, *J. Org. Chem.* **1996**, *61*, 5857 – 5864. (b) Y. Kita, M. Arisawa, M. Gyoten, M. Nakajima, R. Hamada, H. Tohma, T. Takada, *J. Org. Chem.* **1998**, *63*, 6625 – 6633. (c) H. Tohma, H. Morioka, S. Takizawa, M. Arisawa, Y. Kita, *Tetrahedron* **2001**, *57*, 345 – 352. (d) I. R. Baxendale, S. V. Ley, C. Piutti, *Angew. Chem. Int. Ed.* **2002**, *41*, 2194 – 2197. (e) C. J. Lion, D. A. Vasselin, C. H. Schwalbe, C. S. Matthews, M. F. G. Stevens, A. D. Westwell, *Org. Biomol. Chem.* **2005**, *3*, 3996 – 4001. (f) I. R. Baxendale, J. Deeley, C. M. Griffiths-Jones, S. V. Ley, S. Saaby, G. K. Tranmer, *Chem. Commun.* **2006**, 2566 – 2568. (g) D. R. Kelly, S. C. Baker, D. S. King, D. S. de Silva, G. Lord, J. P. Taylor, *Org. Biomol. Chem.* **2008**, *6*, 787 – 796. However, to the best of our knowledge, the transformation has never been used in such a cascade event as described here. For excellent reviews on such reactions in synthesis, see: (h) L. Pouységu, D. Deffieux, S. Quideau, *Tetrahedron* **2010**, *66*, 2235–2261. (i) S. Quideau, L. Pouységu, D. Deffieux, *Curr. Org. Chem.* **2004**, *8*, 113–148.

14. For precedent that the desired hydrogenation could be achieved without loss of the benzylic ketone, see (a) T. Kametani, H. Kondoh, M. Tsubuki, T. Honda, *J. Chem. Soc. Perkin Trans. 1*, **1990**, 5 – 10. (b) D. H. Miles, D.-S. Lho, V. Chittawong, A. M. Payne, *J. Org. Chem.* **1990**, *55*, 4034 – 4036.

15. For a general reference on DDQ, see: D. R. Buckle in *Encyclopedia of Reagents for Organic Synthesis, Vol. 3* (Ed.: L. A. Paquette), Wiley, Chichester, **1995**, pp. 1299 – 1704.

16. (a) J.-Q. Yu, E. J. Corey, *Org. Lett.* **2002**, *4*, 2727 – 2730. (b) J.-Q. Yu, E. J. Corey, *J. Am. Chem. Soc.* **2003**, *125*, 3232 – 3233.

17. T. K. M. Shing, Y.-Y. Yeung, P. L. Su, *Org. Lett*. **2006**, *8*, 3149 – 3151.

18. M. Rawat, V. Prutyanov, W. D. Wulff, *J. Am. Chem. Soc.* **2006**, *128*, 11044 – 11053.

19. M. Welsh, S. A. Snyder, B. S. Stockwell, *Curr. Opin. Chem. Biology* **2010**, *14*, 347 – 361.

20. (a) L. Shen, Y. H. Ye, X. T. Wang, H. L. Zhu, C. Xu, Y. C. Song, H. Li, R. X. Tan, *Chem. Eur. J.* **2006**, *12*, 4393 – 4396. (b) J. Li, J. Chen, C. S. Gui, L. Zhang, Y. Qin, Q. Xu, J. Zhang, H. Liu, X. Shen, H. L. Jiang, *Bioorgan. Med. Chem.* **2006**, *14*, 2209 – 2224.

21. Y. Fan, P. Feng, M. Liu, Y. Shi, *Org. Lett.* **2011**, *13*, 4494 – 4497.

Section 1.8 Experimental Section

General Procedures. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), acetonitrile (MeCN), toluene, benzene, diethyl ether (Et_2O) and methylene chloride (CH_2Cl_2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and an ethanolic solution of phosphomolybdic acid and cerium sulfate, and heat as developing agents. SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker DRX-300, DRX-400, DMX-500 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, br = broad, AB = AB quartet, app = apparent. IR spectra were recorded on a Perkin-Elmer 1000 series FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded in the Columbia University Mass Spectral Core facility on a JOEL HX110 mass spectrometer using the MALDI (matrix-assisted laser-desorption ionization) technique.

Abbreviations. PPA = polyphosphoric acid, DMAP = *N,N*-dimethylaminopyridine, DCC = *N,N'*-dicyclohexylcarbodiimide, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, PDBBA = potassium diisobutyl-*tert*-butoxyaluminum hydride, KHMDS = potassium bis(trimethylsilyl)amide, MOM = methoxymethyl, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, TFE = 2,2,2-trifluoroethanol.

Aldehyde 35. 3,5-dimethoxybenzaldehyde (3.0 g, 18.1 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (8.0 mL) and AcOH (7.0 mL) at 25 °C. Br_2 (0.96 mL, 18.6 mmol, 1.03 equiv) was dissolved in AcOH (1.0 mL) and added at 25 °C to give an orange solution. Over the course of 5 min, the reaction turned into a green solid. The reaction was quenched by addition of H_2O (50 mL), and the crude reaction mixture was extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The resultant pink solid was purified by flash column chromatography (silica gel, hexanes/EtOAc, 1/1) to give the desired product (3.2 g, 72% yield) as a white solid. Alternatively, this material can be purchased commercially.

Naphthalene Derivative 38. Solid KOH (100 g, 1780 mmol, 18.4 equiv) was heated to 210 °C in a stainless steel pot until a partial melt formed. NaOH (20.0 g, 500 mmol, 5.15 equiv) was then added, at which time the melt became transparent. 1,8-Naphthosultone (20.0 g, 97.0 mmol, 1.0 equiv) which had been recrystallized from CH_2Cl_2 was then added in a single portion at 210 °C followed by vigorous stirring for 5 min during which time yellow gaseous clouds were evolved. The darkly colored reaction contents were kept at 210 °C with occasional manual stirring for 40 min; upon completion the reaction contents were slowly cooled to 0 °C. Water (1.4 L) and concentrated H_2SO_4 (150 mL) were added to slowly dissolve the dark, solid reaction

contents. The resultant aqueous phase was extracted with Et_2O (5 × 300 mL), and the combined organic extracts were then washed with water (400 mL) and brine (400 mL), dried ($MgSO_4$), and concentrated. The resultant crude brown solid was purified by flash column chromatography (silica gel, hexanes/Et_2O, 1/1) to give 1,8-naphthalenediol (8.23 g, 53% yield) as a white solid. This reaction was repeated several times to obtain large quantities of the desired product. Next, a portion of this material (3.5 g, 21.9 mmol, 1.0 equiv) was dissolved in acetone (50 mL) at 25 °C. $MgSO_4$ (5 g), 2,2-dimethoxypropane (5.3 mL, 43.8 mmol, 2.0 equiv), and concentrated H_2SO_4 (5.3 mL) were added sequentially at 25 °C. The resultant cloudy brown solution was degassed with an Argon balloon for 20 minutes and stirred for 2 h at 25 °C. Upon completion, the crude reaction mixture was poured into concentrated aqueous NH_4OH (50 mL). The resultant crude reaction mixture was extracted with EtOAc (5 × 75 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated. The resultant crude brown solid was purified by flash column chromatography (silica gel, hexanes/EtOAc, 4/1) to give the desired product (1.28 g, 30% yield) as a pale yellow solid. This reaction was performed several times to obtain large amounts of material. Pressing forward, this material (4.30 g, 21.5 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (100 mL) at 25 °C. NBS (3.80 g, 21.5 mmol, 1.0 equiv) was added in a single portion at 25 °C, and the resultant solution was stirred for 1 h at 25 °C over which time it darkened from pale yellow to dark brown. At this time, another aliquot of NBS (3.0 g, 17.0 mmol, 0.79 equiv) was added at 25 °C and the resultant dark brown solution was stirred for 30 min at 25 °C. Upon completion, the reaction mixture was quenched by addition of 1 M NaOH (100 mL). The crude reaction mixture was extracted with EtOAc (3 × 75 mL), and the combined organic extracts were

dried ($MgSO_4$) and concentrated. The resultant crude brown solid was purified by flash column chromatography (silica gel, hexanes/EtOAc, 4/1) to give protected naphthalene diol **38** (4.7 g, 78% yield) as an orange oil. **38**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, J = 9.0 Hz, 1 H), 7.67 (d, J = 9.0 Hz, 1 H), 7.52 (dd, J = 9.0, 6.0 Hz, 1 H), 6.94 (d, J = 9 Hz, 1 H), 6.75 (d, J = 9 Hz, 1 H) 1.66 (s, 6H).

Acid 41. 3'-methoxyacetophenone (4.57 mL, 33.3 mmol, 1.0 equiv) was dissolved in THF (75 mL) at 25 °C. The resultant pale yellow solution was cooled to –78 °C and NaHMDS (0.95 M in THF, 38.0 mL, 35.0 mmol, 1.05 equiv) was added at –78 °C. The resultant orange solution was stirred for 30 min at –78 °C after which time ethyl bromoacetate (3.82 mL, 33.3 mmol, 1.0 equiv) was added in a single portion at –78 °C. A cloudy precipitate began to form almost immediately. The reaction was allowed to warm slowly over the course of 2 h to –20 °C. At this time, the reaction mixture was cooled to –78 °C and a second aliquot of NaHMDS (0.95 M in THF, 38.0 mL, 35.0 mmol, 1.05 equiv) was added at –78 °C. The resultant bright green solution was stirred for 30 min at –78 °C after which time ethyl bromoacetate (3.82 mL, 33.3 mmol, 1.0 equiv) was added in a single portion at –78 °C. The solution quickly turned orange and thickened due to the formation of more precipitate. The reaction was allowed to warm slowly over the course of 2 h to –20 °C. Upon completion, the reaction was quenched by addition of saturated aqueous NH_4Cl (100 mL). The crude reaction mixture was extracted with EtOAc (3 × 75 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated. The resultant crude brown oil was purified by flash column chromatography (silica gel, hexanes/EtOAc, 9/1) to give the desired product (6.2 g, 58% yield) as a yellow oil. This material (6.2 g, 19.3 mmol, 1.0 equiv) was dissolved in THF (100 mL) and H_2O (20 mL)

at 25 °C. To the resultant pale yellow solution was added $NaBH_4$ (1.46 g, 38.5 mmol, 2.0 equiv) at 25 °C, which caused rapid evolution of gas. The resultant pale yellow solution was stirred at 25 °C for 1 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous $NaHCO_3$ (30 mL). The crude reaction mixture was extracted with CH_2Cl_2 (3 × 75 mL), and the combined organic extracts were dried ($MgSO_4$) with added TFA (0.5 mL) for 2 h. Upon completion, this mixture was concentrated. This material was carried forward without additional purification. This material was dissolved in EtOH at 25 °C (100 mL). Pd/C (10%, 535 mg, 0.503 mmol, 0.026 equiv) was added, and the reaction contents were placed under an atmosphere of H_2 at 25 °C. The reaction was allowed to stir for 14 h at 25 °C. Upon completion, the catalyst was removed by filtration and the crude mixture was concentrated. The crude isolate was dissolved in CH_2Cl_2 (100 mL) and cooled to 0 °C. NBS (1.72 g, 9.65 mmol, 0.5 equiv) was added at 0 °C and the resultant yellow solution was allowed to stir at 0 °C for 45 min. At this time, another aliquot of NBS (1.72 g, 9.65 mmol, 0.5 equiv) was added in a single portion at 0 °C. The resultant orange solution was stirred for 75 min at 0 °C. Upon completion, the reaction was quenched by addition of H_2O (100 mL). The crude reaction mixture was extracted with EtOAc (3 × 75 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated to give acid **41** as the desired crude product. It was carried forward without additional purification. **41**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (br s, 1 H), 7.42 (d, J = 9.0 Hz, 1 H), 6.81 (d, J = 3.0 Hz, 1 H), 6.65 (dd, J = 9.0, 3.0 Hz, 1 H), 4.13 (q, J = 9.0 Hz, 2 H), 3.78 (s, 3 H), 2.84 – 2.74 (m, 4 H), 2.49 – 2.43 (m, 3 H), 1.26 (t, J = 9.0 Hz, 3 H).

Ketone 42. Crude acid **41** prepared above was suspended in PPA (140 g) and warmed to 75 °C. The resultant orange oil was stirred for 3 h at 75 °C over which time it turned dark brown. Upon completion, the reaction contents were cooled to 0 °C and quenched by the addition of ice and H_2O (500 mL). The crude reaction mixture was extracted with EtOAc (5 × 200 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated. The resultant crude brown oil was purified by flash column chromatography (silica gel, hexanes/EtOAc, 9/1 to 4/1) to give ketone **42** (4.33 g, 66% yield) as a yellow oil. **42**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, J = 9.0 Hz, 1 H), 6.78 (d, J = 9.0 Hz, 1 H), 4.16 (q, J = 9.0 Hz, 2 H), 3.81 (s, 3 H), 3.79 – 3.76 (m, 1 H), 3.29 – 3.24 (m, 1 H), 2.80 – 2.40 (m, 5 H), 1.26 (t, J = 9.0 Hz, 3 H).

Acid 43. Ketone **42** (4.32 g, 12.7 mmol, 1.0 equiv) was dissolved in THF (85 mL) and cooled to –78 °C. KHMDS (0.5 M in Toluene, 30.4 mL, 15.2 mmol, 1.2 equiv) was added in a single portion at –78 °C and the resultant bright yellow solution was stirred for 35 min at –78 °C. Trimethyloxonium tetrafluoroborate (3.76 g, 25.4 mmol, 2.0 equiv) was added in a single portion at –78 °C and the reaction mixture was rapidly warmed to 25 °C. After stirring for 1 h at 25 °C, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (100 mL). The crude reaction mixture was extracted with EtOAc (5 × 50 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated. The resultant crude brown oil was purified by flash column chromatography (silica gel, hexanes/EtOAc, 2/1) to give the desired product (2.45 g, 54% yield) as a yellow oil. This material (2.45 g, 6.90 mmol, 1.0 equiv) was dissolved in PhH (60 mL) at 25 °C. DDQ (1.72 g, 7.59 mmol, 1.0 equiv) was added in a single portion and the resultant dark yellow solution was warmed to 80 °C. The resultant dark green solution was stirred for

2.5 h at 80 °C. Upon completion, the reaction contents were cooled to 25 °C and concentrated. The resultant green solid was purified by flash column chromatography (silica gel, hexanes/EtOAc, 4/1) to give the desired product (1.93 g, 79% yield) as a yellow solid. A portion of this material (965 mg, 2.73 mmol, 1.0 equiv) was dissolved in EtOH (20 mL) at 25 °C. Pd/C (10%, 100 mg, 0.094 mmol, 0.034 equiv) was added, and the reaction contents were placed under an atmosphere of H_2 at 25 °C. The reaction was allowed to stir for 3.5 h at 25 °C. Upon completion, the catalyst was removed by filtration and the crude mixture was concentrated. The crude isolate was dissolved in MeOH (27 mL) at 25 °C. Aqueous NaOH (1 M, 5.46 mL, 5.46 mmol, 2.0 equiv) was added in a single portion at 25 °C and the reaction contents were allowed to stir at 25 °C for 4 h. Upon completion, the reaction was quenched by addition of 1 M HCl (11 mL). The crude reaction mixture was extracted with EtOAc (5 × 20 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated to give acid **43** (600 mg, 89% yield) as a brown solid. **43**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, J = 6.0 Hz, 1 H), 7.34 (d, J = 3.0 Hz, 1 H), 7.29 (d, J = 3.0 Hz, 1 H), 6.83 (dd, J = 6.0, 3.0 Hz, 1 H), 6.77 (d, J = 3.0 Hz, 1 H), 3.97 (s, 3 H), 3.96 (s, 3 H), 3.75 (s, 2 H).

Triaryl Ester 44. Naphthalene derivative **38** (763 mg, 2.73 mmol, 1.0 equiv) was dissolved in THF (5 mL) at 25 °C, cooled to –78 °C, and *n*-BuLi (1.35 M in hexanes, 2.03 mL, 2.73 mmol, 1.0 equiv) was then added dropwise. The resultant darkened reaction contents were then stirred for 20 min at –78 °C. A solution of aldehyde **35** (670 mg, 2.73 mmol, 1.0 equiv) in THF (7 mL) was then added dropwise and the resultant orange solution was stirred was warmed to 25 °C. The reaction was stirred for 30 min at 25 °C. Upon completion, the reaction contents were quenched with saturated NH_4Cl (10 mL),

poured into water (10 mL), and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. The resultant crude orange solid was purified by flash column chromatography (silica gel, hexanes/EtOAc, 4/1) to give the desired product (814 mg, 67% yield) as a yellow solid. A portion of this material (253 mg, 0.569 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (4.4 mL) and pyridine (1.1 mL) at 25 °C. Acid **43** (140 mg, 0.569 mmol, 1.0 equiv), DMAP (44 mg, 0.361 mmol, 0.63 equiv) and DCC (129 mg, 0.626 mmol, 1.1 equiv) were added sequentially, and the resultant bright yellow solution was stirred at 25 °C for 17 h over which time white solid slowly precipitated. Upon completion, the reaction was concentrated and redissolved in Et_2O (5 mL). Precipitated solids were removed by filtration through a celite pad and the crude reaction mixture was concentrated. The resultant crude brown oil was purified by flash column chromatography (silica gel, hexanes/EtOAc, 9/1) to give ester **44** (233 mg, 61% yield) as a white foam. **44**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (s, 1 H), 7.58 (d, *J* = 9.0 Hz, 1 H), 7.40 (d, *J* = 9.0 Hz, 1 H), 7.37 (m, 2 H), 7.33 (d, *J* = 9.0 Hz, 1 H), 6.99 (d, *J* = 6.0 Hz, 1 H), 6.87 (d, *J* = 6.0 Hz, 1 H), 6.83 (d, *J* = 6.0 Hz, 1 H), 6.73 (s, 1 H), 6.67 (d, *J* = 6.0 Hz, 1 H), 6.42 (d, *J* = 3.0 Hz, 1 H), 6.35 (d, *J* = 3.0 Hz, 1 H), 3.97 (s, 3 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 3.81 (s, 2 H), 3.34 (s, 3 H), 1.65 (s, 6 H).

Triaryl alcohol 45. Ester **44** (200 mg, 0.297 mmol, 1.0 equiv) was dissolved in THF (2.4 mL) and Et_2O (0.6 mL) and cooled to –95 °C. *s*-BuLi (1.14 M in cyclohexane, 0.31 mL, 0.356 mmol, 1.2 equiv) was added dropwise at –95 °C. After 15 min, thin layer chromatography (silica gel, hexanes/EtOAc, 1/1) revealed that lithium halogen exchange was occurring, and aliquots of *s*-BuLi (1.14 M in cyclohexane, 0.05 mL, 0.059 mmol, 0.2

equiv) were added to the reaction mixture at –95 °C every 20 min until thin layer chromatography revealed complete consumption of starting material. At this time, the reaction was allowed to warm slowly from –95 °C to –78 °C. The reaction was then allowed to stir at –78 °C for 45 min. Upon completion, the reaction was quenched by the addition of saturated aqueous NH_4Cl (10 mL) and turned bright red. The crude reaction mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. The resultant crude yellow oil was purified by flash column chromatography (silica gel, hexanes/EtOAc, 1/1) to give the triaryl alcohol **45** (50 mg, 28% yield) as a yellow foam. This reaction was repeated several times to obtain larger amounts of material. **45**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.0 Hz, 1 H), 7.64 (d, *J* = 1.6 Hz, 1 H), 7.52 (app t, *J* = 8.0 Hz, 1 H), 7.38 (d, *J* = 1.6 Hz, 1 H), 7.33 (d, *J* = 8.0 Hz, 1 H), 7.22 (d, *J* = 8.0 Hz, 2 H), 6.94 (d, *J* = 8.0 Hz, 1 H), 6.78 (d, *J* = 8.0 Hz, 1 H), 6.71 (dd, *J* = 8.0, 4.0 Hz, 1 H), 6.50 (d, *J* = 2.0 Hz, 1 H), 6.45 (s, 1 H), 6.39 (d, *J* = 2.0 Hz, 1 H), 4.03 (s, 3 H), 3.96 – 3.93 (m, 1 H), 3.93 (s, 3 H), 3.80 (s, 3 H), 3.78 – 3.75 (m, 1 H), 3.77 (s, 3 H), 1.54 (s, 6 H).

Triaryl diol 48. Triaryl alcohol **45** (130 mg, 0.219 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (13 mL) and cooled to 0 °C. Sodium cyanoborohydride (1.40 g, 21.9 mmol, 100 equiv) was added in a single portion at 0 °C and the reaction was stirred vigorously to form a white, cloudy suspension. TFA (17 µL, 0.219 mmol, 1.0 equiv) was added in a single portion at 0 °C. After 5 min, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL). The crude reaction mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with water (20 mL)

and brine (20 mL), dried ($MgSO_4$), and concentrated to give the desired triaryl diol **48** (128 mg, 99% yield) as a yellow oil. **48**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.8 Hz, 1 H), 7.38 (dd, *J* = 8.4, 7.2 Hz, 1 H), 7.24 (t, *J* = 7.6 Hz, 1 H), 7.02 (d, *J* = 8.0 Hz, 1 H), 7.02 (d, *J* = 8.0 Hz, 1 H), 7.00 (s, 1 H), 6.87 (d, *J* = 7.6 Hz, 1), 6.74 (d, *J* = 8.0 Hz, 1 H), 6.69 (d, *J* = 2.0 Hz, 1 H), 6.61 (d, *J* = 7.6 Hz, 1 H), 6.48 (d, *J* = 2.0 Hz, 1 H), 6.44 (d, *J* = 2.0 Hz, 1 H), 6.24 (d, *J* = 7.6 Hz, 1 H), 6.08 (d, *J* = 2.0 Hz, 1 H), 5.70 – 5.65 (m, 1 H), 3.97 (s, 3 H), 3.93 (s, 3 H), 3.67 (s, 3 H), 3.67 (s, 3 H), 3.55 (s, 3 H), 3.39 (dd, *J* = 14.0, 3.6 Hz, 1 H), 3.23 (dd, *J* = 13.6, 6.0 Hz, 1 H), 1.66 (s, 3 H), 1.64 (s 3 H).

Cycloheptene 49. Diol **48** (105 mg, 0.176 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (5 mL) and cooled to –78 °C. BF_3•OEt_2 (0.22 mL, 1.76 mmol, 10.0 equiv) was added dropwise at –78 °C and the resultant purple solution was stirred with slow warming from –78 °C to 0 °C over the course of 2 h. Upon completion, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL). The crude reaction mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated to give the desired cycloheptene **49** (97 mg, 99% yield) as a yellow oil. A small portion of this material was recrystallized (CH_2Cl_2/MeOH, 1/1) for X-ray crystallographic analysis. **45**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.7 Hz, 1 H), 7.57 (t, *J* = 8.4 Hz, 1 H), 7.17 (d, *J* = 11.7 Hz, 1 H), 7.10 (d, *J* = 8.7 Hz, 1 H), 6.97 (d, *J* = 7.8 Hz, 1 H), 6.90 (t, *J* = 7.5 Hz, 1 H), 6.86 (d, *J* = 1.2 Hz, 1 H), 6.75 – 6.60 (m, 4 H), 6.62 (d, *J* = 7.5 Hz, 1 H), 6.52 (d, *J* = 8.1 Hz, 1 H), 6.44 (d, *J* = 2.1 Hz, 1 H), 4.00 (s, 3 H), 3.92 (s, 3 H), 3.90 (s, 3 H), 3.84 (s, 3 H), 1.59 (s, 3 H), 1.57 (s, 3 H).

Phosphonate 51. 3,5-dimethoxybromobenzene **50** (10.0 g, 46.1 mmol, 1.0 equiv) was dissolved in DMF (21 mL, 277 mmol, 6.0 equiv) and cooled to 0 °C. $POCl_3$ (12.8 mL, 138 mmol, 3.0 equiv) was added dropwise, and the now orange reaction contents were warmed to 90 °C and stirred for 6 h. Upon completion, the reaction contents were poured into ice water (100 mL), quenched by the slow addition of solid KOH until a pH 14 was obtained, and allowed to stir for 12 h. Once achieved, the crude material was extracted with Et_2O (3 × 100 mL). The combined organic extracts were then washed with water (3 × 75 mL) and brine (75 mL), dried ($MgSO_4$), and concentrated to give the desired aldehyde (11.2 g, 99% yield) as a white solid.[1] Pressing forward without any additional purification, this newly prepared material (11.2 g, 45.7 mmol, 1.0 equiv) was suspended in MeOH (250 mL) and cooled to 0 °C. $NaBH_4$ (3.45 g, 91.4 mmol, 2.0 equiv) was added portionwise and the reaction contents were stirred for 30 min at 0 °C. Upon completion, the reaction contents were poured into water (100 mL) and the residual organic solvent was concentrated. The reaction contents were redissolved in EtOAc (150 mL), poured into water (50 mL), and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with water (75 mL) and brine (75 mL), dried ($MgSO_4$), and concentrated to give alcohol **S-1** (10.8 g, 96%) as a white solid. **S-1:** R_f = 0.44 (silica gel, hexanes/EtOAc, 1/1); IR (film) ν_{max} 3327 (br), 2941, 2834, 1609, 1568, 1456, 1411, 1215, 1148, 1033, 1000; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (d, *J* = 2.4 Hz, 1 H), 6.41 (d, *J* = 2.4 Hz, 1 H), 4.80 (d, *J* = 6.0 Hz, 2 H), 3.83 (s, 3 H), 3.79 (s, 3 H), 2.17 (t, *J* = 6.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 159.5, 125.5, 121.5, 108.9, 98.3, 59.9, 55.9, 55.6; HRMS (MALDI-FTMS) calcd for $C_9H_{11}BrO_3^+$ [M^+] 245.9892, found 245.9907. Pressing forward without any additional purification, this newly prepared material (10.8

g, 43.9 mmol, 1.0 equiv) was dissolved in Et_2O (350 mL) and pyridine (0.53 mL, 6.58 mmol, 0.15 equiv) and PBr_3 (4.15 mL, 43.9 mmol, 1.0 equiv) were added sequentially at 25 °C. The reaction contents were then stirred for 4 h at 25 °C. Upon completion, the reaction contents were quenched by the addition of water (200 mL), and extracted with EtOAc (3 × 75 mL). The combined organic extracts were washed with water (100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated to give the desired bromide (13.1 g, 96%) as a white solid. [Note: this product quickly decomposes on standing once it is neat and should be carried forward immediately]. Finally, KHMDS (0.5 M in toluene, 152 mL, 75.8 mmol, 1.8 equiv) was added to a stirred solution of diethyl phosphite (10.8 mL, 84.2 mmol, 2.0 equiv) in THF (60 mL) at 0 °C, and the resultant solution was stirred for 15 min. A solution of the freshly prepared bromide (13.1 g, 42.1 mmol, 1.0 equiv) in THF (60 mL) was then added, and the reaction contents were stirred for 12 h with slow warming to 25 °C. Upon completion, the reaction contents were quenched with saturated NH_4Cl (75 mL), poured into water (50 mL), and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with water (75 mL) and brine (75 mL), dried ($MgSO_4$), and concentrated to give phosphonate **51** (14.6 g, 94%) as a colorless oil. **51**: R_f = 0.20 (silica gel, EtOAc); IR (film) ν_{max} 2981, 2937, 2906, 2839, 1603, 1569, 1485, 1463, 1438, 1412, 1303, 1276, 1224, 1200, 1159, 1034, 965; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (d, *J* = 2.4 Hz, 1 H), 6.36 (d, *J* = 2.4 Hz, 1 H), 4.01 (dq, *J* = 7.2, 7.2 Hz, 4 H), 3.77 (s, 3 H), 3.73 (s, 3 H), 3.36 (d, *J* = 21.6 Hz, 2 H), 1.22 (t, *J* = 7.2 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 158.8, 125.5 (d, *J* = 6.9 Hz), 113.9 (d, *J* = 10.4 Hz), 109.0, 98.0, 61.7 (d, *J* = 5.9 Hz), 55.6 (d, *J* = 23.5 Hz), 27.5 (d, *J* = 140.3 Hz), 16.3 (d, *J*

= 5.6 Hz); HRMS (MALDI-FTMS) calcd for $C_{13}H_{21}BrPO_5^+$ [M + H^+] 367.0310, found 367.0319.

Aldehyde 52. Solid KOH (100 g, 1780 mmol, 18.4 equiv) was heated to 210 °C in a stainless steel pot until a partial melt formed. NaOH (20.0 g, 500 mmol, 5.15 equiv) was then added, at which time the melt became transparent. 1,8-Naphthosultone (20.0 g, 97.0 mmol, 1.0 equiv) which had been recrystallized from CH_2Cl_2 was then added in a single portion at 210 °C followed by vigorous stirring for 5 min during which time yellow gaseous clouds were evolved. The darkly colored reaction contents were kept at 210 °C with occasional manual stirring for 40 min; upon completion the reaction contents were slowly cooled to 0 °C. Water (1.4 L) and concentrated H_2SO_4 (150 mL) were added to slowly dissolve the dark, solid reaction contents. The resultant aqueous phase was extracted with Et_2O (5 × 300 mL), and the combined organic extracts were then washed with water (400 mL) and brine (400 mL), dried ($MgSO_4$), and concentrated. The resultant crude brown solid was purified by flash column chromatography (silica gel, hexanes/Et_2O, 1/1) to give 1,8-naphthalenediol (8.23 g, 53% yield) as a white solid. This reaction was repeated several times to obtain large quantities of the desired product. Next, 1,8-naphthalenediol (14.84 g, 92.8 mmol, 1.0 equiv) was dissolved in THF (200 mL) and cooled to 0 °C. NaH (60% dispersion in mineral oil, 3.71 g, 92.8 mmol, 1.0 equiv) was added portionwise and the reaction contents were stirred at 0 °C for 10 min; Me_2SO_4 (8.77 mL, 92.8 mmol, 1.0 equiv) was then added dropwise at 0 °C. The reaction contents were stirred for 14 h with slow warming from 0 °C to 25 °C. Upon completion, the contents were quenched by the addition of saturated NH_4Cl (100 mL). They were then poured into water (100 mL) and extracted with EtOAc (3 × 50 mL). The combined

organic extracts were washed with water (75 mL) and brine (75 mL), dried ($MgSO_4$), and concentrated. The resultant crude grey solid was purified by flash column chromatography (silica gel, hexanes/Et_2O, 2/1) to give monomethylated phenol **S-2** (16.0 g, 99%) as a white solid. **S-2**: R_f = 0.71 (silica gel, hexanes/EtOAc, 2/1); IR (film) ν_{max} 3361 (br), 3057, 2945, 2843, 1739, 1630, 1612, 1582, 1452, 1404, 1261, 1196, 1119, 1076, 964, 813, 753, 674; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1 H), 7.43 (dd, *J* = 8.0, 0.8 Hz, 1 H), 7.36 (app t, *J* = 8.0 Hz, 1 H), 7.31 (app t, *J* = 8.0 Hz, 1 H), 7.30 (dd, *J* = 8.0, 1.2 Hz, 1 H), 6.89 (dd, *J* = 7.6, 1.2 Hz, 1 H), 6.78 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 154.5, 136.7, 127.7, 125.6, 121.8, 118.8, 115.1, 110.4, 103.9, 56.1; HRMS (MALDI-FTMS) calcd for $C_{11}H_{10}O_2^+$ [M^+] 174.0681, found 174.0673. Monomethylated phenol **S-2** (16.0 g, 92.0 mmol, 1.0 equiv) was dissolved in CH_3CN (300 mL) at 25 °C, NBS (16.4 g, 92.0 mmol, 1.0 equiv) was added in a single portion, and the resultant solution was stirred for 1 h at 25 °C. Upon completion, the reaction contents were concentrated and the resultant crude grey solid was purified by flash column chromatography (silica gel, hexanes/Et_2O, 1/1) to give the desired brominated product (23.0 g, 98%) as a yellow solid.[2] This brominated product (23.0 g, 91.1 mmol, 1.0 equiv) was dissolved in DMF (75 mL) and cooled to 0 °C. NaH (60% dispersion in mineral oil, 4.36 g, 109 mmol, 1.2 equiv) was added slowly and the resultant yellow solution was stirred for 10 min at 0 °C. MOMCl (10.4 mL, 137 mmol, 1.5 equiv) was then added and the resultant suspension was stirred for 1 h at 0 °C. Upon completion, the reaction contents were quenched with saturated $NaHCO_3$ (75 mL), and then were poured into water (100 mL) and extracted with Et_2O (5 × 50 mL). The combined organic extracts were washed with water (5 × 50 mL) and brine (75 mL), dried ($MgSO_4$), and

concentrated to give a crude yellow solid which was purified by flash column chromatography (silica gel, hexanes/Et_2O, 1/1) to give the desired MOM-protected product (26.8 g, 99%) as a yellow solid. This newly prepared material (26.8 g, 90.2 mmol, 1.0 equiv) was dissolved in THF (560 mL), cooled to –78 °C, and *n*-BuLi (1.6 M in hexanes, 67.7 mL, 108 mmol, 1.2 equiv) was added dropwise. The resultant darkened reaction contents were stirred for 20 min at –78 °C. DMF (27.8 mL, 361 mmol, 4.0 equiv) was then added dropwise, quickly lightening the color of the solution, and the reaction contents were stirred for 1.5 h at –78 °C. Upon completion, the reaction contents were quenched with saturated NH_4Cl (100 mL), poured into water (100 mL), and the organic solvent was removed by rotary evaporation. The crude reaction mixture was redissolved in Et_2O (100 mL) and extracted with Et_2O (3 × 75 mL). The combined organic extracts were washed with water (5 × 75 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated. The resultant crude brown solid was purified by flash column chromatography (silica gel, hexanes/CH_2Cl_2, 1/2) to give aldehyde **52** (21.3 g, 96%) as a yellow solid. **52**: R_f = 0.41 (silica gel, hexanes/EtOAc, 2/1); IR (film) ν_{max} 2937, 1680, 1616, 1574, 1518, 1277, 1219, 1152, 1112, 1058; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.22 (s, 1 H), 8.97 (dd, *J* = 8.0, 0.8 Hz, 1 H), 7.88 (d, *J* = 8.0 Hz, 1 H), 7.59 (dd, *J* = 8.4, 8.0 Hz, 1 H), 7.13 (d, *J* = 8.4 Hz, 1 H), 6.99 (dd, *J* = 8.0, 0.8 Hz, 1 H), 5.41 (s, 2 H), 3.98 (s, 3 H), 3.60 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.1, 160.1, 157.6, 139.2, 135.1, 129.8, 125.4, 117.9, 117.2, 108.7, 107.7, 95.3, 56.6, 56.4; HRMS (MALDI-FTMS) calcd for $C_{14}H_{14}O^+$ [M^+] 246.0892, found 246.0901.

Phosphonate 54. Triethyl phosphonoacetate (8.93 mL, 44.6 mmol, 1.0 equiv) was dissolved in THF (100 mL) at 25 °C and the resultant solution was cooled to 0 °C.

NaH (60% dispersion in mineral oil, 1.96 g, 49.1 mmol, 1.1 equiv) was added portionwise and the resultant suspension was allowed to stir for 10 min at 0 °C. *t*-Butyl bromoacetate (7.91 mL, 53.5 mmol, 1.2 equiv) was then added dropwise, and the solution was allowed to stir for 4 h with slow warming to 25 °C. During this time, the formation of a white precipitate occurred. Upon completion, the reaction contents were quenched with saturated NH_4Cl (75 mL), poured into water (50 mL), and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with water (75 mL) and brine (75 mL), dried ($MgSO_4$), and concentrated. The resultant crude, colorless oil was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH, 19/1) to give phosphonate **13** (14.9 g, 99%) as a colorless oil. Alternatively, this material can be purchased commercially.

Diester 55. *Meta*-anisaldehyde (6.06 g, 44.6 mmol, 1.0 equiv) was dissolved in AcOH (10 mL), Br_2 (2.75 mL, 53.6 mmol, 1.2 equiv) was then added dropwise, and the resultant solution was stirred for 36 h at 25 °C. Upon completion, the reaction contents were quenched with saturated Na_2SO_3 (50 mL), poured into water (20 mL), and extracted with Et_2O (5 × 30 mL). The combined organic layers were then washed with water (3 × 25 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated to give the desired aldehyde **53** (9.49 g, 99% yield) as a dark yellow solid. Alternatively, this aldehyde **53** can be purchased commercially. Next, aldehyde **53** (9.49 g, 44.2 mmol, 1.0 equiv) was dissolved in CH_3CN (200 mL) and then this solution was added to a stirred solution of phosphonate **54** (14.9 g, 44.2 mmol, 1.0 equiv), LiCl (2.44 g, 57.4 mmol, 1.3 equiv), and DBU (6.59 mL, 44.2 mmol, 1.0 equiv) at 25 °C. The resultant dark yellow solution was stirred for 12 h at 25 °C. Upon completion, the reaction contents were quenched by the

addition of saturated NH_4Cl (100 mL) and the organic solvent was concentrated. The contents were redissolved in EtOAc (50 mL), poured into water (50 mL), and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated to give diester **55** (17.5 g, 99% yield) as a yellow oil. **55**: R_f = 0.57 (silica gel, hexanes/EtOAc, 4/1); IR (film) ν_{max} 2979, 2936, 1724, 1643, 1590, 1569, 1465, 1285, 1238, 1194, 1156, 1097, 1019; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1 H), 7.47 (d, *J* = 8.8 Hz, 1 H), 6.94 (d, *J* = 2.8 Hz, 1 H), 6.77 (dd, *J* = 8.8, 2.8 Hz, 1 H), 4.29 (q, *J* = 7.2 Hz, 2 H), 3.76 (s, 3 H), 3.33 (s, 2 H), 1.45 (s, 9 H), 1.35 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 166.9, 158.7, 140.6, 136.3, 133.3, 128.3, 116.5, 115.0, 114.3, 81.1, 61.2, 55.5, 35.2, 28.0, 14.2; HRMS (MALDI-FTMS) calcd for $C_{18}H_{23}BrO_5^+$ [M^+] 398.0729, found 398.0746.

Naphthoate 56. Diester **55** (17.5 g, 43.8 mmol, 1.0 equiv) was dissolved in TFA (90% in water, 50 mL) and allowed to stir for 90 min at 25 °C. Upon completion, the reaction contents were concentrated and azeotroped with toluene (3 × 100 mL) to give the desired crude monoacid intermediate as a yellow solid. This newly formed material was immediately dissolved in Ac_2O (200 mL), NaOAc (5.03 g, 61.4 mmol, 1.4 equiv) was added at 25 °C, and the resultant yellow suspension was warmed to 140 °C and stirred at that temperature for 60 min. Upon completion, the darkened reaction contents were cooled to 25 °C and the organic solvent was concentrated. The reaction contents were redissolved in EtOAc (75 mL), poured into water (50 mL), and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated. The resultant crude brown solid was purified by flash column chromatography (silica gel, hexanes/EtOAc, 3/2) to give **56** (13.4 g, 83%

yield) as a yellow solid. **56**: R_f = 0.20 (silica gel, hexanes/EtOAc, 4/1); IR (film) ν_{max} 2979, 1769, 1718, 1597, 1572, 1506, 1356, 1277, 1248, 1212, 1092, 1023, 766; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (d, *J* = 1.6 Hz, 1 H), 7.74 (d, *J* = 8.4 Hz, 1 H), 7.73 (d, *J* = 1.6 Hz, 1 H), 6.81 (d, *J* = 8.4 Hz, 1 H), 4.45 (q, *J* = 7.2 Hz, 1 H), 3.93 (s, 3 H), 2.38 (s, 3 H), 1.44 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 165.4, 155.0, 147.0, 134.0, 131.1, 129.4, 128.4, 122.5, 119.8, 115.1, 108.7, 61.5, 56.4, 20.8, 14.3; HRMS (MALDI-FTMS) calcd for $C_{16}H_{15}BrO_5^+$ [M^+] 366.0103, found 366.0107.

Aldehyde 57. Naphthoate **56** (13.4 g, 36.5 mmol, 1.0 equiv) was dissolved in MeOH (150 mL) and CH_2Cl_2 (75 mL) at 25 °C. Pd/C (10%, 3.88 g, 3.65 mmol, 0.1 equiv) was added, and the reaction contents were placed under an atmosphere of H_2. After stirring the resultant suspension for 24 h at 25 °C, the reaction contents were filtered through a pad of Celite and NaOMe (5.94 g, 110 mmol, 3.0 equiv) was added portionwise to the filtrate at 0 °C. The resultant solution was warmed to 25 °C and allowed to stir for 2 h. Upon completion, the contents were cooled to 0 °C, quenched with the addition of 1 M HCl (200 mL), and concentrated. The reaction contents were redissolved in EtOAc (75 mL), poured into water (50 mL), and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated to give the desired product (8.38 g, 99%) as a yellow solid. Pressing forward without any additional purification, this newly prepared material (8.38 g, 36.1 mmol, 1.0 equiv) was dissolved in DMF (75 mL), cooled to 0 °C, and BnBr (8.57 mL, 72.2 mmol, 2.0 equiv) and NaH (60% dispersion in mineral oil, 2.89 g, 72.2 mmol, 2.0 equiv) were added sequentially. The reaction contents were stirred for 1 h at 0 °C, warmed to 25 °C, and then quenched with saturated NH_4Cl (50 mL). The

contents were then poured into water (200 mL) and extracted with Et_2O (5 × 50 mL). The combined organic extracts were washed with water (5 × 100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated. The resultant crude orange oil was purified by flash column chromatography (silica gel, hexanes/Et_2O, 3/2) to give the desired benzyl-protected product (8.95 g, 77% yield) as a yellow solid. A portion of this material (8.28 g, 25.7 mmol, 1.0 equiv) was dissolved in THF (130 mL) and cooled to –20 °C. A precooled (–30 °C) solution of 0.5 M PDBBA in THF/toluene [1/1, 46.2 mL, 23.1 mmol, 0.9 equiv, prepared by mixing KO*t*-Bu (1.0 M in THF, 23.1 mL, 23.1 mmol, 0.9 equiv) and DIBAL-H (1.0 M in toluene, 23.1 mL, 23.1 mmol, 0.9 equiv) at 25 °C for 2 h] was then added. The reaction contents were quickly warmed to 0 °C and stirred for 90 min at 0 °C. Upon completion, the reaction contents were quenched with 1 M HCl (300 mL), poured into water (50 mL), and extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with water (75 mL) and brine (75 mL), dried ($MgSO_4$), and concentrated. The resultant crude yellow solid was purified by flash column chromatography (silica gel, hexanes/Et_2O, 4/1) to give aldehyde **57** (5.03 g, 67% yield) as a yellow solid. **57**: R_f = 0.49 (silica gel, hexanes/EtOAc, 4/1); IR (film) ν_{max} 3062, 2935, 2838, 1687, 1581, 1512, 1498, 1463, 1354, 1279, 1101, 1076, 737; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1 H), 7.88 (d, *J* = 1.6 Hz, 1 H), 7.63 (d, *J* = 7.2 Hz, 2 H), 7.55–7.34 (m, 6 H), 7.03 (dd, *J* = 7.6, 1.2 Hz, 1 H), 5.27 (s, 2 H), 3.97 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.0, 157.4, 157.2, 137.0, 136.6, 134.7, 128.7, 128.4, 127.7, 127.6, 126.8, 122.1, 109.6, 102.0, 77.0, 70.9, 56.3; HRMS (MALDI-FTMS) calcd for $C_{19}H_{16}O_3^+$ [M^+] 292.1099, found 292.1093.

Key Triaryl Intermediate 58. Phosphonate **51** (5.84 g, 15.9 mmol, 1.0 equiv) was dissolved in THF (65 mL) at 25 °C and cooled to –78 °C. KO*t*-Bu (1.0 M in THF, 17.5 mL, 17.5 mmol, 1.1 equiv) was added dropwise and the resultant yellow solution was stirred for 20 min at –78 °C. A solution of aldehyde **57** (4.65 g, 15.9 mmol, 1.0 equiv) in THF (50 mL) was added dropwise to the stirring reaction contents, and the dark yellow solution was allowed to stir for 2 h with slow warming to 25 °C. Upon completion, the reaction contents were quenched with saturated NH_4Cl (50 mL) and poured into EtOAc (75 mL) and water (100 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with water (75 mL) and brine (75 mL), dried ($MgSO_4$), and concentrated. The resultant crude yellow solid was purified by flash column chromatography (silica gel, hexanes/Et_2O, 3/1) to give the desired *E*-olefin (6.99 g, 87%) as a yellow solid. A portion of this freshly prepared olefin (6.80 g, 13.5 mmol, 1.0 equiv) was dissolved in THF (70 mL) at 25 °C, cooled to –78 °C, and *n*-BuLi (1.6 M in hexanes, 12.6 mL, 20.2 mmol, 1.5 equiv) was then added dropwise. The resultant darkened reaction contents were then stirred for 20 min at –78 °C. A solution of aldehyde **52** (6.62 g, 26.9 mmol, 2.0 equiv) in THF (50 mL) was then added dropwise and the resultant orange solution was stirred for 4 h with slow warming from –78 °C to 25 °C. Upon completion, the reaction contents were quenched with saturated NH_4Cl (75 mL), poured into water (100 mL), and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with water (75 mL) and brine (75 mL), dried ($MgSO_4$), and concentrated. The resultant crude orange solid was purified by flash column chromatography (silica gel, hexanes/EtOAc, 1/1) to give the key triaryl intermediate **58** (6.09 g, 67%) as a yellow foam. **58**: R_f = 0.37 (silica gel, hexanes/EtOAc, 1/1); IR (film)

ν_{max} 3426 (br), 2936, 2835, 1584, 1463, 1272, 1151, 1101, 1056, 1029, 751; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.4 Hz, 1 H), 7.56 (d, *J* = 7.2 Hz, 2 H), 7.42–7.31 (m, 5 H), 7.28 (dd, *J* = 8.4, 8.0 Hz, 1 H), 7.20 (dd, *J* = 8.0, 0.8 Hz, 1 H), 7.08 (d, *J* = 16.4 Hz, 1 H), 7.08 (s, 1 H), 7.00 (d, *J* = 8.0 Hz, 1 H), 6.93 (d, *J* = 16.8 Hz, 1 H), 6.89 (d, *J* = 2.4 Hz, 1 H), 6.80–6.78 (m, 2 H), 6.76 (d, *J* = 8.0 Hz, 1 H), 6.68 (d, *J* = 1.2 Hz, 1 H), 6.52 (d, *J* = 2.8 Hz, 1 H), 5.26 (d, *J* = 6.4 Hz, 1 H), 5.23 (d, *J* = 6.4 Hz, 1 H), 4.86 (d, *J* = 12.0 Hz, 1 H), 4.82 (d, *J* = 11.6 Hz, 1 H), 3.90 (s, 3 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 3.57 (s, 3 H), 2.34 (d, *J* = 4.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 159.1, 157.3, 157.0, 156.0, 154.2, 143.3, 137.6, 137.4, 136.1, 134.9, 132.7, 128.2, 127.9, 127.4, 127.2 (2 C), 126.5, 126.4, 122.0, 120.9, 120.0, 118.9, 117.6, 117.3, 116.1, 112.3, 106.4, 106.2, 105.1, 104.0, 97.9, 96.6, 71.0, 70.1, 56.4, 56.1 (2 C), 55.7, 55.3; HRMS (MALDI-FTMS) calcd for $C_{42}H_{40}O_8^+$ [M^+] 672.2723, found 672.2698.

Dalesconol B Core (61). Triaryl intermediate **58** (5.69 g, 8.47 mmol, 1.0 equiv) was dissolved in EtOAc (40 mL) and EtOH (60 mL) at 25 °C. Solid Pd/C (10%, 9.01 g, 8.47 mmol, 1.0 equiv) was added and the reaction flask was charged with an atmosphere of H_2 gas at 25 °C. The reaction contents were stirred for 45 min at 25 °C, filtered through a pad of Celite, and the filtrate was concentrated. The resultant crude yellow foam was immediately redissolved in TFE (65 mL) and cooled to –45 °C. TFA (0.65 mL, 8.47 mmol, 1.0 equiv) was then added dropwise and the resultant dark purple solution was stirred for 15 min at –45 °C. Upon completion, $PhI(OAc)_2$ (3.00 g, 9.32 mmol, 1.1 equiv) was added and the resultant dark green solution was stirred for an additional 20 min at –45 °C. Upon completion, the reaction contents were quenched with saturated Na_2SO_3 (25 mL) and saturated $NaHCO_3$ (25 mL), poured into water (100 mL),

and extracted with EtOAc (3 × 75 mL). The combined organic extracts were washed with water (100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated. The resultant crude red foam was purified by flash column chromatography (silica gel, hexanes/EtOAc, 1/2) to give the polycyclic enone **61** (1.50 g, 32%) as a yellow solid. **61**: R_f = 0.38 (silica gel, hexanes/EtOAc, 1:3); IR (film) ν_{max} 2938, 2835, 1658, 1593, 1465, 1431, 1267, 1150, 1089, 1064; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (app t, *J* = 8.0 Hz, 1 H), 7.06 (d, *J* = 7.6 Hz, 1 H), 6.88 (dd, *J* = 7.6, 1.2 Hz, 1 H), 6.86 (d, *J* = 8.8 Hz, 1 H), 6.84 (d, *J* = 8.0 Hz, 1 H), 6.84 (d, *J* = 8.0 Hz, 1 H), 6.36 (d, *J* = 2.0 Hz, 1 H), 6.30 (dd, *J* = 7.6, 0.4 Hz, 1 H), 6.21 (d, *J* = 2.4 Hz, 1 H), 6.10 (d, *J* = 1.2 Hz, 1 H), 5.31 (s, 2 H), 4.91 (d, *J* = 1.2 Hz, 1 H), 4.01 (s, 3 H), 3.95 (s, 3 H), 3.74 (s, 3 H), 3.71 (s, 3 H), 3.63 (s, 3 H), 2.76 (dd, *J* = 14.4, 6.4 Hz, 1 H), 2.47 (dd, *J* = 14.4, 7.6 Hz, 1 H), 2.27 (ddd, *J* = 10.0, 10.0, 7.6 Hz, 1 H), 1.55 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.0, 159.4, 158.3 (2 C), 157.8, 155.6, 155.0, 151.9, 143.1, 141.2, 139.4, 139.0, 133.6, 131.1, 121.9, 121.4, 119.9, 119.4, 118.9, 115.9, 115.1, 109.4, 108.0, 97.7, 96.9, 77.2, 70.0, 59.6, 56.5, 56.3, 56.1, 55.6, 55.2, 35.7, 19.7; HRMS (MALDI-FTMS) calcd for $C_{35}H_{33}O_7^+$ [M + H^+] 565.2226, found 565.2223.

Hydrogenated core 62. Enone **61** (0.500 g, 0.887 mmol, 1.0 equiv) was dissolved in EtOAc (5 mL) and EtOH (15 mL) and Pd/C (10%, 0.471 g, 0.443 mmol, 0.5 equiv) was added. The reaction flask was charged with an atmosphere of H_2 gas at 25 °C and the reaction contents were stirred for 2 h at 25 °C. Upon completion, the reaction contents were filtered through a Celite pad, the filtrate was concentrated, and the resultant yellow solid was purified by flash column chromatography (silica gel, hexanes/EtOAc, 1/2) to give the desired reduction product **62** (0.420 g, 84%) as a yellow solid. **62**: R_f =

0.46 (silica gel, hexanes/EtOAc, 1/3); IR (film) ν_{max} 2939, 2835, 1678, 1593, 1464, 1432, 1269, 1149, 1070, 969, 736; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (app t, *J* = 8.0 Hz, 1 H), 7.04 (d, *J* = 7.6 Hz, 2 H), 6.94 (d, *J* = 8.0 Hz, 1 H), 6.84 (dd, *J* = 8.0, 1.2 Hz, 1 H), 6.82 (d, *J* = 8.4 Hz, 1 H), 6.39 (d, *J* = 2.4 Hz, 1 H), 6.35 (d, *J* = 2.4 Hz, 1 H), 6.04 (d, *J* = 7.2 Hz, 1 H), 5.30 (s, 2 H), 4.60 (s, 1 H), 4.03 (s, 3 H), 3.91 (s, 3 H), 3.78 (s, 3 H), 3.71 (s, 3 H), 3.62 (s, 3 H), 3.20–3.13 (m, 1 H), 2.60 (dd, *J* = 14.4, 6.0 Hz, 1 H), 2.33 (dd, *J* = 18.4, 6.0 Hz, 1 H), 2.22 (dd, *J* = 18.4, 14.0 Hz, 1 H), 1.81–1.74 (m, 1 H), 1.64–1.57 (m, 1 H), 1.39–1.31 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.2, 159.8, 158.8, 157.9, 157.2, 154.6, 151.6, 143.2, 142.4, 141.4, 139.1, 134.2, 120.9 (2 C), 120.6, 119.8, 119.6, 115.6, 115.4, 110.0, 107.9, 107.6, 97.7, 97.0, 77.2, 64.7, 56.7, 56.4, 56.1, 55.7, 55.4, 45.8, 39.1, 27.6, 19.1; HRMS (MALDI-FTMS) calcd for $C_{35}H_{34}O_7^+$ [M^+] 566.2305, found 566.2304.

Quinone methide 63. Intermediate **62** (0.200 g, 0.353 mmol, 1.0 equiv) was dissolved in THF (20 mL) at 25 °C and cooled to 0 °C. Concentrated HCl (1.16 mL, 14.1 mmol, 40.0 equiv) was added dropwise and the reaction contents were allowed to stir for 3 h with slow warming from 0 °C to 25 °C. Upon completion, the reaction contents were quenched with water (30 mL), poured into EtOAc (30 mL), and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with water (50 mL) and brine (25 mL), dried ($MgSO_4$), and concentrated. The resultant crude brown solid was purified by flash column chromatography (silica gel, hexanes/EtOAc, 1/2) to give the desired mono deprotected phenol (0.183 g, 99%) as a yellow oil. A portion of this material (33 mg, 0.0632 mmol, 1.0 equiv) was dissolved in PhH at 25 °C. To this solution was added DDQ (21 mg, 0.0759 mmol, 1.2 equiv) in a single portion at 25 °C. The resultant yellow solution was stirred at 25 °C for 1 h. Upon completion, the reaction was diluted with

EtOAc (5 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with 10% aqueous K_2CO_3 (10 mL), dried ($MgSO_4$), and concentrated. The resultant crude yellow solid was purified by flash column chromatography (silica gel, hexanes/EtOAc, 3/1) to give quinone methide **63** (27 mg, 82% yield). **63**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, *J* = 9.9 Hz, 1 H), 7.29 (d, *J* = 8.4 Hz, 1 H), 7.18 (t, *J* = 8.4 Hz, 1 H), 6.79 (d, *J* = 8.4 Hz, 1 H), 6.77 (d, *J* = 8.4 Hz, 1 H), 6.62 (d, *J* = 9.9 Hz, 1 H), 6.42 (s, 2 H), 6.36 (dd, *J* = 7.2, 0.9 Hz, 1 H), 3.95 (s, 3 H), 3.89 (s, 3 H), 3.82 (s, 3 H), 3.80 – 3.70 (m, 1 H), 3.76 (s, 3 H), 3.57 (dd, *J* = 17.1, 5.7 Hz, 1 H), 2.66 (dd, *J* = 17.1, 2.7 Hz, 1 H), 2.45 – 2.35 (m, 1 H), 2.35 – 2.22 (m, 1 H), 2.05 – 1.87 (m, 1 H).

Ketone 64. Quinone methide **63** (7.0 mg, 0.011 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (0.5 mL) at 25 °C open to air. K_2CO_3 (15.0 mg, 0.109 mmol, 10.0 equiv), *t*-BuOOH (5.5 M in decanes, 0.050 mL, 0.273 mmol, 25 equiv), and $Pd(OAc)_2$ (2.45 mg, 0.0109 mmol, 1.0 equiv) were added sequentially and the reaction contents were allowed to stir for 24 h at 25 °C at which time more *t*-BuOOH (5.5 M in decanes, 0.050 mL, 0.273 mmol, 25.0 equiv) and $Pd(OAc)_2$ (2.45 mg, 0.011 mmol, 1.0 equiv) were added. After 24 h of additional stirring at 25 °C, a third portion of *t*-BuOOH (5.5 M in decanes, 0.050 mL, 0.273 mmol, 25.0 equiv) and $Pd(OAc)_2$ (2.45 mg, 0.011 mmol, 1.0 equiv) were added. After another 24 h of stirring at 25 °C the reaction contents were quenched with the addition of water (2 mL), poured into EtOAc (2 mL), and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated. The resultant crude yellow oil was purified by preparative thin-layer chromatography (silica gel, CH_2Cl_2/MeOH, 97/3) to give the desired product (3.0 mg, 42%) as a yellow solid. This material (3.0 mg, 0.0046 mmol, 1.0

equiv) was then dissolved in CH_2Cl_2 (0.5 mL) at 25 °C and solid $NaHCO_3$ (3.8 mg, 0.0457 mmol, 10.0 equiv) and Dess–Martin periodinane (9.7 mg, 0.0228 mmol, 5.0 equiv) were added sequentially. The reaction contents were stirred for 2 h at 25 °C at which point they were quenched with the addition of saturated Na_2SO_3 (5 mL), and poured into water (5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with 1 M NaOH (5 mL), water (5 mL), and brine (5 mL), dried ($MgSO_4$), and concentrated to give methyl-protected dalesconol B (3.0 mg, 99% yield) as a yellow solid.

Desoxo dalesconol B (65). Intermediate **62** (0.200 g, 0.353 mmol, 1.0 equiv) was dissolved in THF (20 mL) at 25 °C and cooled to 0 °C. Concentrated HCl (1.16 mL, 14.1 mmol, 40.0 equiv) was added dropwise and the reaction contents were allowed to stir for 3 h with slow warming from 0 °C to 25 °C. Upon completion, the reaction contents were quenched with water (30 mL), poured into EtOAc (30 mL), and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with water (50 mL) and brine (25 mL), dried ($MgSO_4$), and concentrated. The resultant crude brown solid was purified by flash column chromatography (silica gel, hexanes/EtOAc, 1/2) to give the desired mono deprotected phenol (0.183 g, 99%) as a yellow oil. Pressing forward, a portion of this material (0.082 g, 0.157 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (8 mL) at 25 °C and DDQ (0.042 g, 0.152 mmol, 0.97 equiv) was added. The reaction contents were allowed to stir for 1 h at 25 °C, at which time they were then cooled to –78 °C and BBr_3 (1.0 M in CH_2Cl_2, 3.14 mL, 3.14 mmol, 20 equiv) was added dropwise. The resultant solution was stirred for an additional 12 h with slow warming from –78 °C to 25 °C. Upon completion, the reaction contents were quenched by the addition of water (15 mL),

poured into EtOAc (20 mL), and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. The resultant crude brown solid was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH, 19/1) to give the desired demethylated compound **65** (0.053 g, 73%) as a dark orange solid. **65**: R_f = 0.24 (silica gel, CH_2Cl_2/MeOH, 19/1); IR (film) ν_{max} 3425 (br), 3364 (br), 2918, 2850, 1643, 1609, 1564, 1527, 1452, 1231, 1195, 1169, 1015, 668; ^{1}H NMR (400 MHz, acetone-d_6) δ 12.71 (s, 1 H), 10.84 (br s, 1 H), 8.40 (br s, 1 H), 8.32 (br s, 1 H), 7.70 (d, *J* = 9.6 Hz, 1 H), 7.53 (d, *J* = 8.4 Hz, 1 H), 7.24 (app t, *J* = 8.0 Hz, 1 H), 6.77 (d, *J* = 8.4 Hz, 1 H), 6.74 (dd, *J* = 8.4, 1.2 Hz, 1 H), 6.70 (d, *J* = 9.6 Hz, 1 H), 6.49 (d, *J* = 2.4 Hz, 1 H), 6.46 (d, *J* = 2.4 Hz, 1 H), 6.35 (dd, *J* = 7.6, 0.8 Hz, 1 H), 3.80 (dd, *J* = 18.0, 5.2 Hz, 1 H), 3.38 (dd, *J* = 15.2, 7.6 Hz, 1 H), 2.74 (dd, *J* = 18.0, 2.0 Hz, 1 H), 2.53–2.48 (m, 1 H), 2.31 (dd, *J* = 15.2, 11.6 Hz, 1 H), 2.13–2.07 (m, 1 H), 1.92–1.83 (m, 1 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 204.7, 189.9, 165.8, 163.8, 159.5, 156.6, 155.6, 144.1, 142.6, 140.1, 138.0, 137.3, 135.8, 133.7, 132.1, 130.3, 118.9 (2 C), 117.3, 117.0, 113.9, 112.6, 104.2, 64.7, 46.8 (2 C), 34.5, 25.3; HRMS (MALDI-FTMS) calcd for $C_{29}H_{20}O_6^+$ [M^+] 464.1260, found 464.1268.

Dalesconol B (2). Deprotected compound **65** (11.0 mg, 0.024 mmol, 1.0 equiv) was dissolved in THF (1 mL), cooled to 0 °C, and KHMDS (0.5 M in toluene, 0.24 mL, 0.120 mmol, 5.0 equiv) was added dropwise. The resultant dark purple solution was then stirred for 3 min at 0 °C, at which time MOMCl (0.036 mL, 0.480 mmol, 20 equiv) was added and the solution slowly lightened to yellow as it was stirred for 20 additional min at 0 °C. Upon completion, Et_3N (0.170 mL, 1.20 mmol, 50 equiv) and MeOH (0.049 mL, 1.20 mmol, 50 equiv) were added sequentially, and the reaction contents were stirred

for 20 min at 25 °C during which time a precipitate was formed slowly. Upon completion, saturated $NaHCO_3$ (1 mL) was added and the reaction contents were stirred for 5 min more at 25 °C at which point they were poured into water (2 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated. The resultant crude yellow oil was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH, 19/1) to give the desired protected material (14.0 mg, 91%) as a yellow solid. A portion of this material (7.0 mg, 0.011 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (0.5 mL) at 25 °C open to air. K_2CO_3 (15.0 mg, 0.109 mmol, 10.0 equiv), *t*-BuOOH (5.5 M in decanes, 0.050 mL, 0.273 mmol, 25 equiv), and $Pd(OAc)_2$ (2.45 mg, 0.0109 mmol, 1.0 equiv) were added sequentially and the reaction contents were allowed to stir for 24 h at 25 °C at which time more *t*-BuOOH (5.5 M in decanes, 0.050 mL, 0.273 mmol, 25.0 equiv) and $Pd(OAc)_2$ (2.45 mg, 0.011 mmol, 1.0 equiv) were added. After 24 h of additional stirring at 25 °C, a third portion of *t*-BuOOH (5.5 M in decanes, 0.050 mL, 0.273 mmol, 25.0 equiv) and $Pd(OAc)_2$ (2.45 mg, 0.011 mmol, 1.0 equiv) were added. After another 24 h of stirring at 25 °C the reaction contents were quenched with the addition of water (2 mL), poured into EtOAc (2 mL), and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated. The resultant crude yellow oil was purified by preparative thin-layer chromatography (silica gel, CH_2Cl_2/MeOH, 97/3) to give the desired product (3.0 mg, 42%) as a yellow solid. This procedure was repeated several times to obtain large quantities of the desired product. This material (30.0 mg, 0.046 mmol, 1.0 equiv) was then dissolved in CH_2Cl_2 (1 mL) at 25 °C and solid $NaHCO_3$ (38.3 mg, 0.457 mmol, 10.0 equiv) and Dess–Martin

periodinane (96.7 mg, 0.228 mmol, 5.0 equiv) were added sequentially. The reaction contents were stirred for 2 h at 25 °C at which point they were quenched with the addition of saturated Na_2SO_3 (5 mL), and poured into water (5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with 1 M NaOH (5 mL), water (5 mL), and brine (5 mL), dried ($MgSO_4$), and concentrated to give MOM-protected dalesconol B (30.0 mg, 99% yield) as a yellow solid. A portion of this material (28.0 mg, 0.043 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (4 mL), cooled to –78 °C, and then BBr_3 (1.0 M in CH_2Cl_2, 1.07 mL, 1.07 mmol, 25.0 equiv) was added quickly and the purple reaction contents were allowed to stir for 15 min at –78 °C. Upon completion, the now brown reaction contents were poured into water (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. The resultant crude orange solid was purified by column chromatography (silica gel, CH_2Cl_2/MeOH, 19/1) to give dalesconol B (**2**, 15.0 mg, 73% yield) as a red solid. **2**: R_f = 0.35 (silica gel, CH_2Cl_2/MeOH, 19/1); IR (film) ν_{max} 3520 (br), 3300 (br), 3020 (br), 2918, 2849, 1704, 1646, 1613, 1524, 1453, 1260, 1218, 1197, 845; ^{1}H NMR (300 MHz, acetone-d_6) δ 12.61 (br s, 1 H), 12.24 (br s, 1 H), 8.05 (d, *J* = 9.9 Hz, 1 H), 7.66 (d, *J* = 8.1 Hz, 1 H), 7.14 (app t, *J* = 8.1 Hz, 1 H), 6.83 (d, *J* = 8.4 Hz, 1 H), 6.79 (d, *J* = 9.9 Hz, 1 H), 6.66 (d, *J* = 7.5 Hz, 1 H), 6.66 (d, *J* = 2.1 Hz, 1 H), 6.27 (d, *J* = 2.4 Hz, 1 H), 6.03 (d, *J* = 6.9 Hz, 1 H), 3.50 (dd, *J* = 16.8, 6.9 Hz, 1 H), 3.39 (dd, *J* = 13.8, 7.5 Hz, 1 H), 3.12 (br m, 1 H), 2.91 (dd, *J* = 16.8, 4.5 Hz, 1 H), 2.75 (dd *J* = 13.5, 2.7 Hz, 1 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 204.2, 203.0, 189.7, 166.4, 164.3, 163.7, 162.4, 159.7, 144.9, 143.2, 142.1, 139.5, 137.8, 135.4, 133.3, 132.9, 128.7, 119.5, 118.3, 116.9, 115.2, 114.7, 114.2, 113.2, 104.5, 65.0, 50.4, 42.8, 37.2;

HRMS (MALDI-FTMS) calcd for $C_{29}H_{19}O_7^+$ [M+H$^+$] 479.1131, found 479.1154. The spectroscopic data for **2** matched that as described by Lin and co-workers;[3] a full comparison table of NMR data is provided at the end of this section.

Skeletal Rearrangement Product 68. Triaryl intermediate **66** (8.0 mg, 0.014 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (0.5 mL) and cooled to –78 °C. Methanesulfonic acid (0.007 mL, 0.113 mmol, 8.0 equiv) was then added at –78 °C and the resultant solution was stirred for 1 h with slow warming to 0 °C. Upon completion, the reaction contents were quenched with saturated $NaHCO_3$ (2 mL), poured into water (2 mL), and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated. The resultant crude yellow oil was purified by preparative thin layer chromatography (silica gel, hexanes/Et_2O, 2/1) to give the cyclized and rearranged product **68** (6.0 mg, 77% yield) as a colorless oil. The product was crystallized from CH_2Cl_2/MeOH (1/1) to obtain material suitable for X-ray crystallographic analysis. **68**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.1 (s, 1 H), 7.96 (dd, *J* = 8.4, 0.8 Hz, 1 H), 7.26 – 7.10 (m, 4 H), 6.98 (s, 1 H), 6.75 – 6.72 (m, 3 H), 6.59 (s, 2 H), 6.40 (d, *J* = 2.4 Hz, 1 H), 4.10 (s, 3 H), 3.79 (s, 3 H), 3.79 (s, 3 H), 3.39 (td, *J* = 13.6, 4.8 Hz, 1 H), 3.05 (ddd, *J* = 18.0, 5.2, 3.6 Hz, 1 H), 2.89 – 2.75 (m, 1 H), 2.51 (ddd, *J* = 13.6, 5.2, 3.2 Hz, 1 H), 1.64 (s, 3 H), 1.62 (s, 3 H).

Skeletal rearrangement 76. Intermediate **69** (18.0 mg, 0.032 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (1.0 mL) and cooled to –78 °C. BF_3•OEt_2 (0.040 mL, 0.320 mmol, 10.0 equiv) was added dropwise and the resultant red solution was stirred for 7 h with slow warming to 25 °C. Upon completion, the reaction contents were quenched with saturated $NaHCO_3$ (2 mL), poured into water (2 mL), and extracted with EtOAc (3 ×

5 mL). The combined organic extracts were washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated. The resultant crude yellow oil was purified by flash column chromatography (silica gel, hexanes/Et_2O, 2/1) to give the polycyclic product **76** (9.8 mg, 59% yield) as a colorless oil. The product was crystallized from CH_2Cl_2/MeOH (1/1) to obtain material suitable for X-ray crystallographic analysis. **76**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.63 (s, 1 H), 7.43 (t, *J* = 8.0 Hz, 1 H), 7.34 (dd, *J* = 8.0, 1.2 Hz, 1 H), 6.85 (dd, *J* = 8.4, 1.2 Hz, 1 H), 6.82 (d, *J* = 7.2 Hz, 1 H), 6.77 (s, 1 H), 6.68 (dd, *J* = 7.6, 0.8 Hz, 1 H), 6.31 (d, *J* = 2.0 Hz, 1 H), 6.06 (d, *J* = 7.4 Hz, 1 H), 3.13 (dd, *J* = 16.8, 5.2 Hz, 1 H), 3.05 – 2.90 (m, 3 H), 2.83 (dd, *J* = 16.8, 12.8 Hz, 1 H).

Phosphonate 77. *o*-Anisaldehyde (10.0 g, 73.4 mmol, 1.0 equiv) was dissolved in EtOH (150 mL) at 25 °C, *N,N'*-dimethylethylenediamine (8.70 mL, 80.8 mmol, 1.1 equiv) was added, and the reaction contents were stirred at 25 °C for 24 h before being filtered through a pad of $MgSO_4$ and concentrated to afford the desired imidazolidine (15.0 g, 99% yield) as a white solid. Without any additional purification, this material (15.0 g, 72.8 mmol, 1.0 equiv) was dissolved in Et_2O (250 mL) and cooled to –40 °C. *t*-BuLi (1.7 M in pentane, 100 mL, 170 mmol, 2.34 equiv) was then added dropwise over 1 h at –40 °C. Upon completion, the resultant orange reaction contents were warmed slowly to –20 °C, stirred for an additional 7 h, and then transferred by cannula over 5 min into a flask containing $(CBrCl_2)_2$ (55.3 g, 170 mmol, 2.34 equiv) in Et_2O (250 mL) at 0 °C. The reaction contents were then stirred for 12 h, during which time they were warmed to 25 °C; upon completion, the solution was recooled to 0 °C and 1 M HCl (500 mL) was added slowly. The resultant solution was stirred for 1 h at 0 °C, quickly warmed to 25 °C, and then quenched by the addition of water (500 mL). The reaction

contents were then extracted with EtOAc (3 × 250 mL), and the combined organic extracts were washed with water (500 mL) and brine (250 mL), dried ($MgSO_4$), and concentrated.[4] The resultant crude yellow solid was purified by flash column chromatography (silica gel, hexanes/EtOAc, 9/1) to give the desired brominated product (8.12 g, 52% yield) as a white solid. This material (8.12 g, 37.8 mmol, 1.0 equiv) was suspended in MeOH (100 mL) at 25 °C and cooled to 0 °C. $NaBH_4$ (2.88g , 75.6 mmol, 2.0 equiv) was added portionwise and the reaction contents were stirred for 1 h at 0 °C. Upon completion, the reaction contents were quenched with water (100 mL) and concentrated. The reaction contents were redissolved in EtOAc (100 mL), poured into water (100 mL), and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with water (150 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated to afford the desired alcohol (7.83 g, 96%) as a white solid. Pressing forward without any additional purification, this newly prepared material (7.83 g, 36.1 mmol, 1.0 equiv) was dissolved in Et_2O (180 mL) and pyridine (0.437 mL, 5.41 mmol, 0.15 equiv) and PBr_3 (3.41 mL, 36.1 mmol, 1.0 equiv) were added sequentially at 25 °C. The reaction contents were then stirred for 4 h at 25 °C. Upon completion, the reaction contents were quenched by the addition of water (100 mL), poured into water (100 ml), and extracted with EtOAc (3 × 150 mL). The combined organic extracts were washed with water (200 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated to give the desired bromide (10.0 g, 99%) as a white solid. [Note: This product quickly decomposes on standing once it is neat and should be carried forward immediately.] Finally, KHMDS (0.5 M in toluene, 129 mL, 64.5 mmol, 1.8 equiv) was added to a solution of diethyl phosphite (9.19 mL, 71.4 mmol, 2.0 equiv) in THF (100 mL) at 0 °C and stirred for 15 min. To this

solution was added dropwise a solution of the freshly prepared bromide (10.0 g, 35.7 mmol, 1.0 equiv) dissolved in THF (100 mL), and the reaction contents were stirred for 12 h with slow warming to 25 °C. Upon completion, the reaction contents were quenched with saturated NH_4Cl (150 mL), poured into water (150 mL), and extracted with EtOAc (3 × 150 mL). The combined organic extracts were washed with water (100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated to give the phosphonate **77** (10.79 g, 90%) as a colorless oil. **77**: R_f = 0.21 (silica gel, EtOAc); IR (film) ν_{max} 2981, 1589, 1572, 1466, 1435, 1267, 1082, 965, 864, 771; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.0 Hz, 1 H), 7.07 (app dt, *J* = 8.0, 2.4 Hz, 1 H), 6.81 (d, *J* = 8.4 Hz, 1 H), 4.05 (dq, *J* = 7.2, 7.2 Hz, 4 H), 3.85 (s, 3 H), 3.50 (d, *J* = 22.0 Hz, 2 H), 1.26 (t, *J* = 7.2 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4 (d, *J* = 5.4 Hz), 128.6 (d, *J* = 3.8 Hz), 125.8 (d, *J* = 7.5 Hz), 125.0 (d, *J* = 3.5 Hz), 121.6 (d, *J* = 10.6 Hz), 109.4 (d, *J* = 3.4 Hz), 61.9 (d, *J* = 6.5 Hz), 55.9, 28.3 (d, *J* = 139.0 Hz), 16.3 (d, *J* = 6.4 Hz); HRMS (MALDI-FTMS) calcd for $C_{12}H_{19}BrPO_4^+$ [M + H$^+$] 337.0204, found 337.0189.

Key Triaryl Intermediate 78. Phosphonate **77** (6.07 g, 18.0 mmol, 1.0 equiv) was dissolved in THF (75 mL) and cooled to –78 °C. KO*t*-Bu (1.0 M in THF, 19.8 mL, 19.8 mmol, 1.1 equiv) was added dropwise and the resultant yellow solution was stirred for 20 min at –78 °C. A solution of aldehyde **57** (5.26 g, 18.0 mmol, 1.0 equiv) in THF (35 mL) was then added dropwise, and the resultant dark yellow solution was stirred for an additional 3 h with slow warming to 25 °C. Upon completion, the reaction contents were quenched with saturated NH_4Cl (75 mL), poured into water (75 mL), and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with water (100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated. The resultant crude yellow

solid was purified by column chromatography (silica gel, hexanes/Et_2O, 3/1) to give the desired *E*-disposed olefin (6.76 g, 79%) as a yellow solid. A portion of this olefin (6.68 g, 14.1 mmol, 1.0 equiv) was dissolved in THF (75 mL), cooled to –78 °C, and *n*-BuLi (1.6 M in hexanes, 13.3 mL, 21.2 mmol, 1.5 equiv) was added dropwise. The resultant darkened reaction contents were stirred for 20 min at –78 °C. A solution of aldehyde **52** (6.94 g, 28.2 mmol, 2.0 equiv) in THF (40 mL) was then added dropwise at –78 °C and the resultant orange solution was stirred for 4 h with slow warming to 25 °C. Upon completion, the reaction contents were quenched with saturated NH_4Cl (100 mL), poured into water (100 mL), and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with water (100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated. The resultant crude orange solid was purified by flash column chromatography (silica gel, hexanes/EtOAc, 1/1) to give the key triaryl intermediate **78** (4.62 g, 51%) as a yellow foam. **78**: R_f = 0.65 (silica gel, hexanes/EtOAc, 1:1); IR (film) ν_{max} 3425 (br), 2935, 2834, 1616, 1584, 1465, 1381, 1272, 1101, 1073, 1054, 750; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.4 Hz, 1 H), 7.57 (d, *J* = 7.6 Hz, 2 H), 7.42–7.29 (m, 7 H), 7.25–7.22 (m, 2 H), 7.19 (d, *J* = 16.8 Hz, 1 H), 7.14 (d, *J* = 1.2 Hz, 1 H), 7.02 (d, *J* = 8.0 Hz, 1 H), 7.01 (d, *J* = 16.4 Hz, 1 H), 6.94 (dd, *J* = 8.0, 1.2 Hz, 1 H), 5.26 (d, *J* = 6.4 Hz, 1 H), 5.24 (d, *J* = 6.0 Hz, 1 H), 4.93 (d, *J* = 12.8 Hz, 1 H), 4.89 (d, *J* = 12.4 Hz, 1 H), 3.92 (s, 3 H), 3.90 (s, 3 H), 3.86 (s, 3 H), 3.58 (s, 3 H), 2.25 (d, *J* = 4.8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 157.3, 157.1, 156.1, 154.2, 142.3, 137.6, 137.4, 135.8, 134.8, 134.5, 132.9, 128.2, 128.0, 127.4, 127.2, 127.1, 126.6, 126.2, 124.9, 122.2, 121.0, 120.4, 119.9, 118.9, 116.2, 112.4, 110.1, 106.3 (2 C), 105.3, 96.7, 77.2, 71.1, 70.2,

56.4, 56.2 (2 C), 55.7; HRMS (MALDI-FTMS) calcd for $C_{41}H_{38}O_7^+$ [M^+] 642.2618, found 642.2644.

Dalesconol A Core (79). Triaryl intermediate **78** (1.51 g, 2.35 mmol, 1.0 equiv) was dissolved in EtOAc (14 mL) and EtOH (21 mL) at 25 °C. Solid Pd/C (10%, 2.50 g, 2.35 mmol, 1.0 equiv) was added and the reaction flask was charged with an atmosphere of H_2 gas at 25 °C. The reaction contents were stirred for 1 h at 25 °C, filtered through a pad of Celite, and the filtrate was concentrated. The resultant crude yellow foam was immediately redissolved in TFE (18 mL) and cooled to –45 °C. TFA (0.18 mL, 2.35 mmol, 1.0 equiv) was added dropwise and the resultant dark purple solution was stirred for 15 min at –45 °C. Upon completion, $PhI(OAc)_2$ (0.834 g, 2.59 mmol, 1.1 equiv) was added and the resultant dark green solution was stirred for an additional 20 min at –45 °C. Upon completion, the reaction contents were quenched with saturated Na_2SO_3 (15 mL) and saturated $NaHCO_3$ (15 mL), poured into water (30 mL), and extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated. The resultant crude green foam was purified by flash column chromatography (silica gel, hexanes/EtOAc, 1/2) to give the cyclized core (0.337 g, 27%) as an orange foam. A portion of this enone (0.082 g, 0.154 mmol, 1.0 equiv) was dissolved in EtOAc (2 mL) and EtOH (6 mL) and Pd/C (10%, 0.082 g, 0.077 mmol, 0.5 equiv) was added. The reaction flask was charged with an atmosphere of H_2 gas at 25 °C and the reaction contents were stirred for 2 h at 25 °C which point more Pd/C (10%, 0.082 g, 0.077 mmol, 0.5 equiv) was added and the flask was filled with a fresh atmosphere of H_2 gas. After 2 h of additional stirring at 25 °C, the reaction contents were filtered through a Celite pad, concentrated, and the resultant crude yellow foam was

purified by flash column chromatography (silica gel, hexanes/EtOAc, 1/2) to give the desired product (0.054 g, 65% yield) as a yellow foam. This product (0.054 g, 0.100 mmol, 1.0 equiv) was dissolved in THF (6 mL) at 25 °C and cooled to 0 °C. Concentrated HCl (0.248 mL, 3.00 mmol, 30.0 equiv) was added dropwise and the reaction contents were allowed to stir for 2 h with slow warming to 25 °C. Upon completion, the reaction contents were quenched with water (6 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. The resultant crude brown oil was purified by flash column chromatography (silica gel, hexanes/EtOAc, 1/2) to give the free phenol **79** (0.049 g, 99% yield) as a yellow oil. **79**: R_f = 0.50 (silica gel, hexanes/EtOAc, 1/3); IR (film) ν_{max} 3447 (br), 2935, 1678, 1610, 1587, 1464, 1428, 1263, 1072, 1038, 819, 746; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1 H), 7.20 (app t, *J* = 8.4 Hz, 1 H), 7.08 (app t, *J* = 7.6 Hz, 1 H), 7.00 (d, *J* = 7.6 Hz, 1 H), 6.86 (d, *J* = 7.6 Hz, 1 H), 6.83–6.79 (m, 4 H), 6.76 (d, *J* = 7.6 Hz, 1 H), 6.06 (d, *J* = 7.6 Hz, 1 H), 4.66 (s, 1 H), 4.11 (s, 3 H), 3.90 (s, 3 H), 3.73 (s, 3 H), 3.18–3.11 (m, 1 H), 2.71 (dd, *J* = 13.6, 6.4 Hz, 1 H), 2.32 (dd, *J* = 18.4, 6.0 Hz, 1 H), 2.06 (dd, *J* = 18.4, 14.0 Hz, 1 H), 1.83–1.66 (m, 2 H), 1.38 (ddd, *J* = 12.4, 12.4, 7.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 159.7, 157.1, 156.8, 154.2, 151.7, 142.6, 142.3, 141.7, 135.3, 134.3, 127.6, 127.0, 122.6, 122.1, 120.6, 120.2, 119.4, 112.0, 110.6, 109.9, 105.6, 77.2, 64.6, 57.0, 56.1, 56.0, 55.7, 45.7, 38.9, 27.3, 19.5; HRMS (MALDI-FTMS) calcd for $C_{32}H_{28}O_5^+$ [M^+] 492.1937, found 492.1937.

Dalesconol A (1). Intermediate **79** (32.0 mg, 0.065 mmol, 1.0 equiv) was dissolved in benzene (1 mL) at 25 °C, DDQ (18.0 mg, 0.013 mmol, 1.0 equiv) was added, and the reaction contents were stirred for 1 h at 25 °C. Upon completion, the

reaction contents were quenched by the addition of 1 M NaOH (2 mL) and water (2 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with 1 M NaOH (2 × 5 mL), water (10 mL), and brine (10 mL), dried ($MgSO_4$), and were concentrated. The resultant crude yellow solid was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH, 19/1) to give the desired quinone methide intermediate (24.5 mg, 77%) as a yellow solid. A portion of this material (5.0 mg, 0.010 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (0.5 mL) at 25 °C open to air. K_2CO_3 (14.1 mg, 0.102 mmol, 10.0 equiv), *t*-BuOOH (5.5 M in decanes, 0.046 mL, 0.255 mmol, 25.0 equiv), and $Pd(OAc)_2$ (2.3 mg, 0.010 mmol, 1.0 equiv) were added sequentially and the reaction contents were allowed to stir for 24 h at 25 °C at which time more *t*-BuOOH (5.5 M in decanes, 0.046 mL, 0.255 mmol, 25.0 equiv) and $Pd(OAc)_2$ (2.3 mg, 0.010 mmol, 1.0 equiv) were added. After 24 h of additional stirring at 25 °C a third portion of *t*-BuOOH (5.5 M in decanes, 0.046 mL, 0.255 mmol, 25.0 equiv) and $Pd(OAc)_2$ (2.3 mg, 0.010 mmol, 1.0 equiv) were added. After another 24 h of stirring at 25 °C, the reaction contents were quenched with the addition of water (2 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated. The resultant crude yellow oil was purified by preparative thin layer chromatography (silica gel, CH_2Cl_2/MeOH, 97/3) to give the desired product (2.1 mg, 41%) as a yellow oil. This material (2.1 mg, 0.004 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (0.5 mL) and solid $NaHCO_3$ (3.5 mg, 0.042 mmol, 10.0 equiv) and Dess–Martin periodinane (8.8 mg, 0.021 mmol, 5.0 equiv) were added sequentially at 25 °C. The reaction contents were stirred for 2 h at 25 °C. Upon completion, the reaction contents were quenched with the addition of saturated Na_2SO_3 (5

mL), poured into water (5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with 1 M NaOH (5 mL), water (5 mL), and brine (5 mL), dried ($MgSO_4$), and concentrated to give protected dalesconol A (2.1 mg, 99% yield) as a yellow oil. This material (2.1 mg, 0.004 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (1 mL), cooled to –78 °C, and BBr_3 (1.0 M in CH_2Cl_2, 0.064 mL, 0.064 mmol, 15.0 equiv) was added dropwise. The resultant purple solution was stirred for 5 h with slow warming to 25 °C. Upon completion, the reaction contents were quenched by the addition of water (2 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated. The resultant crude orange oil was purified by preparative thin layer chromatography (silica gel, hexanes/EtOAc, 3/1) to give dalesconol A (**1**, 1.3 mg, 66% yield) as a red solid. **1**: R_f = 0.47 (silica gel, hexanes/EtOAc, 2/1); IR (film) ν_{max} 3550 (br), 3220 (br), 3059, 2921, 2850, 1714, 1644, 1612, 1557, 1525, 1474, 1450, 1264, 1221, 1165, 846, 820; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.13 (s, 1 H), 12.00 (s, 1 H), 10.71 (s, 1 H), 7.84 (d, *J* = 9.6 Hz, 1 H), 7.45 (app t, *J* = 8.0 Hz, 1 H), 7.28 (m, specific multiplicity obscured by solvent residual peak, 1 H), 7.04 (app t, *J* = 8.0 Hz, 1 H), 6.97 (d, *J* = 7.6 Hz, 1 H), 6.94 (d, *J* = 8.4 Hz, 1 H), 6.86 (d, *J* = 8.4 Hz, 1 H), 6.80 (d, *J* = 10.0 Hz, 1 H), 6.71 (d, *J* = 7.6 Hz, 1 H), 5.86 (d, *J* = 7.6 Hz, 1 H), 3.30 (dd, *J* = 16.8, 6.0 Hz, 1 H), 3.28 (dd, *J* = 12.8, 7.2 Hz, 1 H), 2.99 (br m, 1 H), 2.89 (dd, *J* = 16.0, 5.0 Hz, 1 H), 2.84 (dd, *J* = 13.0, 3.2 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 204.5, 201.0, 188.7, 162.7, 162.1, 159.3, 143.5, 141.3, 140.1, 137.2, 136.2, 135.4, 133.6, 133.2 (2 C), 132.0, 127.3, 124.0, 120.2, 118.4 (2 C), 117.2, 117.0, 115.2, 113.6, 64.1, 50.0, 42.3, 36.6; HRMS (MALDI-FTMS) calcd for $C_{29}H_{19}O_6^+$ [M + H^+] 463.1182, found 463.1201. The spectroscopic data for **1** matched

that as described by Lin and co-workers;[3] a full comparison table of NMR data is provided at the end of this section.

Alcohol 87. Enone **86** (45 mg, 0.0843 mmol, 1.0 equiv) was dissolved in THF (0.75 mL) and EtOH (0.75 mL) and Pd/C (10%, 45 mg, 0.0421 mmol, 0.5 equiv) was added. The reaction flask was charged with an atmosphere of H_2 gas at 25 °C and the reaction contents were stirred for 1 h at 25 °C. Upon completion, the reaction contents were filtered through a Celite pad, the filtrate was concentrated, and the resultant yellow solid was purified preparative thin layer chromatography (silica gel, hexanes/EtOAc, 1/2) to give the reduction product **87** (9 mg, 20%) as a yellow oil. **87**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (t, *J* = 8.0 Hz, 1 H), 7.04 (d, *J* = 7.6 Hz, 1 H), 6.97 (d, *J* = 8.0 Hz, 1 H), 6.88 – 6.81 (m, 4 H), 6.79 (d, *J* = 8.0 Hz, 1 H), 6.69 (d, *J* = 8.0 Hz, 1 H), 6.05 (d, *J* = 7.2 Hz, 1 H), 5.29 (s, 2 H), 5.04 (dd, *J* = 10.0, 7.6 Hz, 1 H), 4.83 (d, *J* = 1.2 Hz, 1 H), 4.2 (s, 1 H), 4.00 (s, 3 H), 3.89 (s, 3 H), 3.74 (s, 3 H), 3.62 (s, 3 H), 2.66 (dd, *J* = 14.0, 5.6 Hz, 1 H), 2.55 (dd, *J* = 13.2, 8.0 Hz, 1 H), 1.82 – 1.72 (m, 2 H), 1.70 – 1.60 (m, 1 H), 1.49 – 1.35 (m, 2 H).

Des-oxo dalesconol A (90). Intermediate **89** (35 mg, 0.0714 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (3.5 mL). The resultant yellow solution was cooled to –78 °C, and BBr_3 (1.0 M in CH_2Cl_2, 1.07 mL, 1.07 mmol, 15.0 equiv) was added dropwise. The solution was stirred for 20 h and warmed slowly from –78 °C to 25 °C. Upon completion, the reaction contents were quenched by the addition of water (5 mL), poured into EtOAc (10 mL), and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. The resultant crude brown solid was purified by flash column chromatography (silica gel,

hexanes/EtOAc, 1/3) to give the desired demethylated compound **90** (24 mg, 75%) as an orange solid. **90**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.70 (s, 1 H), 10.8 (s, 1 H), 8.50 (s, 1 H), 7.64 (d, *J* = 10.0 Hz, 1 H), 7.55 (d, *J* = 8.0 Hz, 1 H), 7.22 (t, *J* = 8.0 Hz, 1 H), 7.16 (t, *J* = 8.0 Hz, 1 H), 6.97 (dd, *J* = 8.4, 0.8 Hz, 1 H), 6.90 (dd, *J* = 8.4, 1.2 Hz, 1 H), 6.77 (d, *J* = 8.4 Hz, 1 H), 6.72 (dd, *J* = 8.4, 0.8 Hz, 1 H), 6.68 (d, *J* = 10.0, 1 H), 6.36 (dd, *J* = 8.0, 1.2 Hz, 1 H), 3.81 (dd, *J* = 18.0, 5.2 Hz, 1 H), 3.51 (dd, *J* = 15.2, 7.6 Hz, 1 H), 2.76 (dd, *J* = 18.0, 2.0 Hz, 1 H), 2.60 – 2.50 (m, 1 H), 2.41 (dd, *J* = 15.2, 11.6 Hz, 1 H), 2.20 – 2.10 (m, 1 H), 2.00 – 1.85 (m, 1 H).

Dehydro-dalesconol B (91). Dalesconol B (**2**) (4.0 mg, 0.00865 mmol, 1.0 equiv) was dissolved in DMSO-d_6 at 25 °C under air. The resultant dark red solution was allowed to stand for 8 months at which point an oxidized product was observed. The material was concentrated, and the resultant crude red solid was purified by preparative thin layer chromatography (silica gel, CH_2Cl_2/MeOH/AcOH, 98/2/0.1) to give the oxidized product **91** as a red solid (2.0 mg, 50% yield). **91**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.90 (s, 1 H), 12.37 (s, 1 H), 10.54 (br s, 1 H), 7.68 (d, *J* = 10.0 Hz, 1 H), 7.32 (t, *J* = 8.0 Hz, 1 H), 7.19 (d, *J* = 8.0 Hz, 1 H), 6.84 – 6.79 (m, 4 H), 6.73 (d, *J* = 10.0 Hz, 1 H), 6.61 (d, *J* = 7.6 Hz, 1 H), 6.60 (d, *J* = 2.0 Hz, 1 H), 6.35 (d, *J* = 2.4 Hz, 1 H), 3.41 (d, *J* = 13.2 Hz, 1 H), (1 peak obscured by water).

References

[1] W. Zhang, B. I. Wilke, J. Zhan K. Watanabe, C. N. Boddy, Y. Tang, *J. Am. Chem. Soc.* **2007**, *129*, 9304.

[2] M. C. Carreño, J. L. García Ruano, G. Sanz, M. A. Toledo, A. Urbano, *Synlett* **1997**, 1241.

[3] L. Wen, X. Cai, F. Xu, Z. She, W. L. Chan, L. L. P. Vrijmoed, E. B. G. Jones, Y. Lin, *J. Org. Chem.* **2009**, *74*, 1093–1098.

[4] M. Rawat, V. Prutyanov, W. D. Wullf, *J. Am. Chem. Soc.* **2006**, *128*, 11044.

[5] Y. L. Zhang, H. M. Ge, W. Zhao, H. Dong, Q. Xu, S. H. Li, J. Li, J. Zhang, Y. C. Song, R. X. Tan, *Angew. Chem.* **2008**, *120*, 5907 – 5910; *Angew. Chem. Int. Ed.* **2008**, *47*, 5823 – 5826.

Table S1. NMR Spectral Data Comparison of Natural and Synthetic Dalesconol A (**1**) in $CDCl_3$; Coupling Constants (*J*) in Hz.

^{1}H		^{13}C	
Natural dalesconol A	**Synthetic dalesconol A**	**Natural dalesconol A**	**Synthetic dalesconol A**
12.13 (br s)	12.13 (s)	204.5	204.5
11.99 (br s)	12.00 (s)	201	201
10.70 (br s)	10.71 (s)	188.6	188.7
7.84 (d, *J* = 10.0)	7.84 (d, *J* = 9.6)	162.7	162.7
7.45 (dd, *J* = 8.4, 7.6)	7.45 (app t, *J* = 8.0)	162	162.1
7.28 (d, *J* = 8.4)	7.28 (d, *J* = 8.0)	159.3	159.3
7.04 (dd *J* = 8.4, 7.6)	7.04 (app t, *J* = 8.0)	143.6	143.5
6.97 (d, *J* = 7.6)	6.97 (d, *J* = 7.6)	141.4	141.3
6.94 (d, *J* = 8.4)	6.94 (d, *J* = 8.4)	140.1	140.1
6.85 (d, *J* = 8.4)	6.86 (d, *J* = 8.4)	137.2	137.2
6.80 (d, *J* = 10.0)	6.80 (d, *J* = 10.0)	136.2	136.2
6.71 (d, *J* = 8.4)	6.71 (d, *J* = 7.6)	135.4	135.4
5.86 (d, *J* = 7.6)	5.86 (d, *J* = 7.6)	133.5	133.6
3.30 (dd, *J* = 16.0, 6.0)	3.30 (dd, *J* = 16.8, 6.0)	133.2	133.2 (2 C)
3.28 (dd, *J* = 13.0, 7.0)	3.28 (dd, *J* = 12.8, 7.2)	133.2	
2.99 (dddd, *J* = 7.0, 6.0, 5.0, 3.0)	2.99 (br m)	132.1	132
2.90 (dd, *J* = 16.0, 5.0)	2.89 (dd, *J* = 16, 5.0)	127.3	127.3
2.84 (dd, *J* = 13.0, 3.0)	2.84 (dd, *J* = 13, 3.2)	124	124
		120.3	120.2
		118.5	118.4 (2 C)
		118.4	
		117.2	117.2
		117	117
		115.2	115.2
		113.6	113.6
		64.2	64.1
		50	50
		42.3	42.3
		36.6	36.6

Table S2. NMR Spectral Data Comparison of Natural and Synthetic Dalesconol B (**2**) in acetone-d_6; Coupling Constants (J) in Hz.

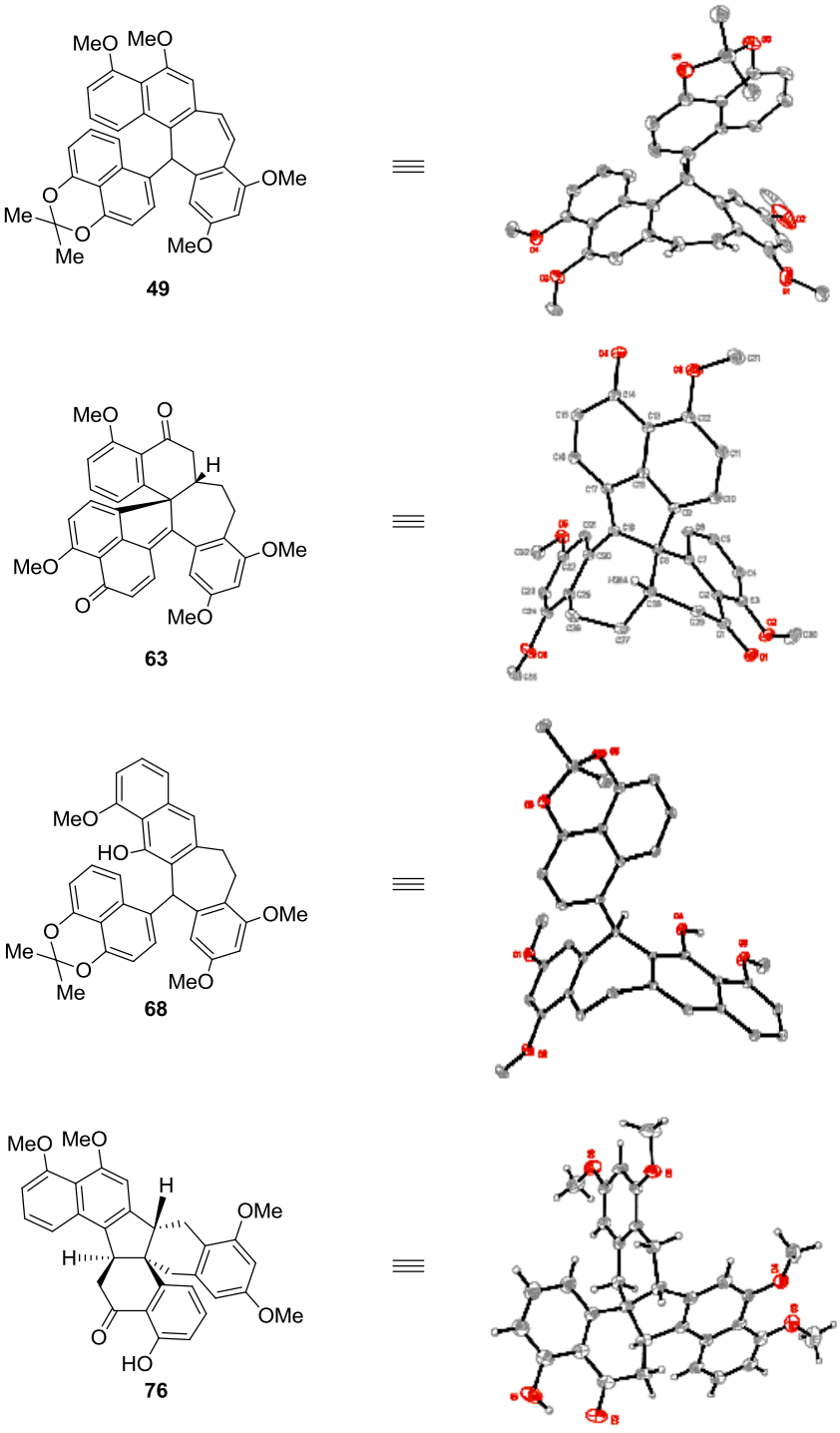
^{1}H		^{13}C	
Natural dalesconol B	**Synthetic dalesconol B**	**Natural dalesconol B**	**Synthetic dalesconol B**
12.58 (s)	12.61 (br s)	204.3	204.2
12.24 (s)	12.24 (br s)	203	203
10.77 (s)	exchanged	189.8	189.7
9.78 (br s)	exchanged	166.5	166.4
8.04 (d, J = 10.0)	8.05 (d, J = 9.9)	164.2	164.3
7.64 (d, J = 8.4)	7.66 (d, J = 8.1)		163.7
7.13 (dd, J = 8.1, 7.8)	7.14 (app t, J = 8.1)	162.7	162.4
6.82 (d, J = 8.4)	6.83 (d, J = 8.4)	159.9	159.7
6.78 (d, J = 10.0)	6.79 (d, J = 9.9)	144.9	144.9
6.66 (s)	6.66 (d, J = 2.1)	143.2	143.2
6.65 (d, J = 8.1)	6.66 (d, J = 7.5)	142.1	142.1
6.27 (s)	6.27 (d, J = 2.1)		139.5
6.02 (d, J = 7.8)	6.03 (d, J = 6.9)	137.8	137.8
3.49 (dd, J = 17, 6.6)	3.50 (dd, J = 16.8, 6.9)	135.4	135.4
3.39 (dd, J = 17, 6.6)	3.39 (dd, J = 13.8, 7.5)	134.4	
3.15 (m)	3.12 (br m)	133.3	133.3
2.90 (m)	2.91 (dd, J = 16.8, 4.5)	132.9	132.9
2.76 (m)	2.75 (dd, J = 13.5, 2.7)	132.9	
		128.7	128.7
		119.5	119.5
		118.3	118.3
		117	116.9
		115.3	115.2
		114.7	114.7
		114.2	114.2
		113.3	113.2
		104.6	104.5
		65	65
		50.4	50.4
		42.8	42.8
		37.2	37.2

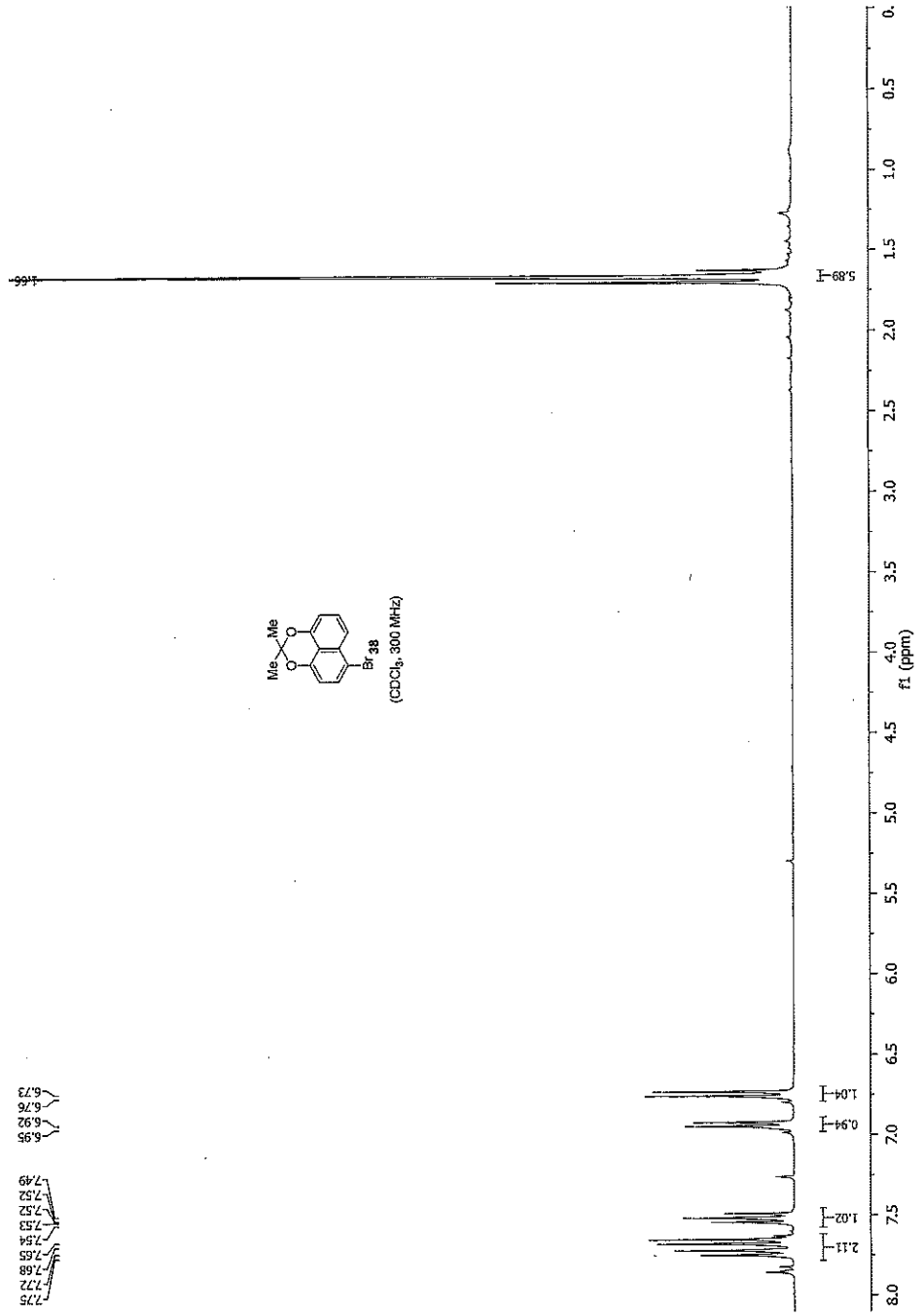
Note that all tabulated C-13 signals for natural dalesconol B in Table S2 are 1.0 ppm lower than reported as they were not referenced to the same solvent chemical shift that we used. We note that the carbon spectrum of isolated dalesconol B (**2**) taken in acetone-d_6 had 34 selected peaks for a material with only 29 distinct carbons. Our material is much purer, and can allow for a more definitive assignment in this solvent. The gaps between the two spectra indicate which we believe to be incorrectly assigned in the natural spectrum versus that identified from our synthetic material. We have taken the spectra in DMSO-d_6 as well, with the comparison table shown below with respect to Ref. 5. Note that the natural dalesconol B ^{13}C peaks were recalibrated for this comparison.

Table S3. NMR Spectral Data Comparison of Natural and Synthetic Dalesconol B (**2**) in DMSO-d_6; Coupling Constants (J) in Hz.

^{1}H		^{13}C	
Natural dalesconol B	**Synthetic dalesconol B**	**Natural dalesconol B**	**Synthetic dalesconol B**
12.39 (s)	12.39 (br s)	203.1	203.2
12.18 (s)	12.19 (br s)	202.3	202.3
10.95 (br s)	exchanged	187.9	187.9
10.66 (s)	exchanged	164.4	164.4
8.01 (d, J = 9.8)	8.01 (d, J = 9.9)	163.3	163.4
7.68 (d, J = 8.3)	7.69 (d, J = 8.4)	162.3	162.4
7.14 (t, J = 8.0)	7.14 (app t, J = 7.8)	160.7	160.7
6.81 (d, J = 9.8)	6.81 (d, J = 8.7)	157.8	157.9
6.81 (d, J = 8.3)	6.81 (d, J = 8.7)	143.5	143.5
6.67 (d, J = 8.0)	6.67 (d, J = 8.1)	141.8	141.9
6.55 (d, J = 1.9)	6.55 (s)	141	141
6.18 (d, J = 1.9)	6.18 (d, J = 2.1)	138.1	138.1
5.88 (d, J = 8.0)	5.88 (d, J = 8.1)	137	137.1
3.51 (dd, J = 16.8, 6.5)	3.52 (dd, J = 15.9, 5.7)	134.4	134.5
3.29 (dd, J = 13.2, 7.5)	3.30 (dd, J = 12.9, 7.2)	132.4	132.5
2.90 (m)	2.88 (br m)	131.5	131.5
2.81 (dd, J = 16.8, 3.5)	2.81 (dd, J = 16.2, 3.6)	127.9	128
2.62 (dd, J = 13.2, 1.9)	2.75 (dd, J = 12.6, 2.1)	118.4	118.5
		117	117.1
		115.9	115.9
		114.4	114.4
		114.2	114.3
		113.1	113.1
		111.7	111.7
		103.4	103.4
		63.4	63.5
		49.7	49.7
		41.9	41.9
		36	36.1

Figure S1. X-ray crystal structures obtained for selected intermediates.

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Me
Br
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5.89
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2.11
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6.92
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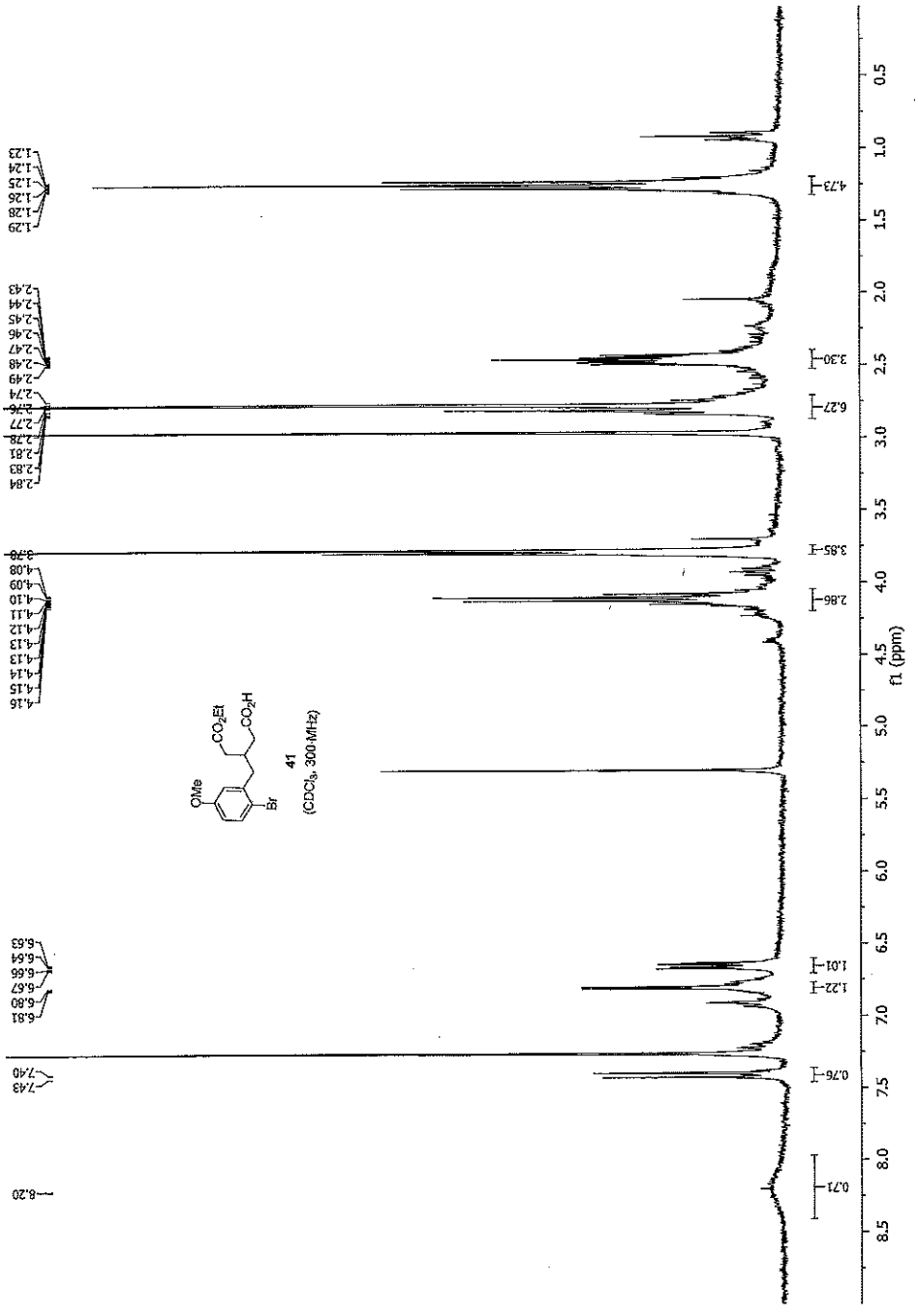
7.49
7.52
7.52
7.53
7.54
7.65
7.68
7.72
7.75
f1 (ppm)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7.40
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6.80
6.67
6.66
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6.63
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4.15
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4.13
4.12
4.11
4.10
4.09
4.08
3.78
2.84
2.83
2.81
2.78
2.77
2.76
2.74
2.49
2.48
2.47
2.46
2.45
2.44
2.43
1.29
1.28
1.26
1.25
1.24
1.23
CO2Et
CO2H
OMe
Br
41
(CDCl3, 300 MHz)
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0.76
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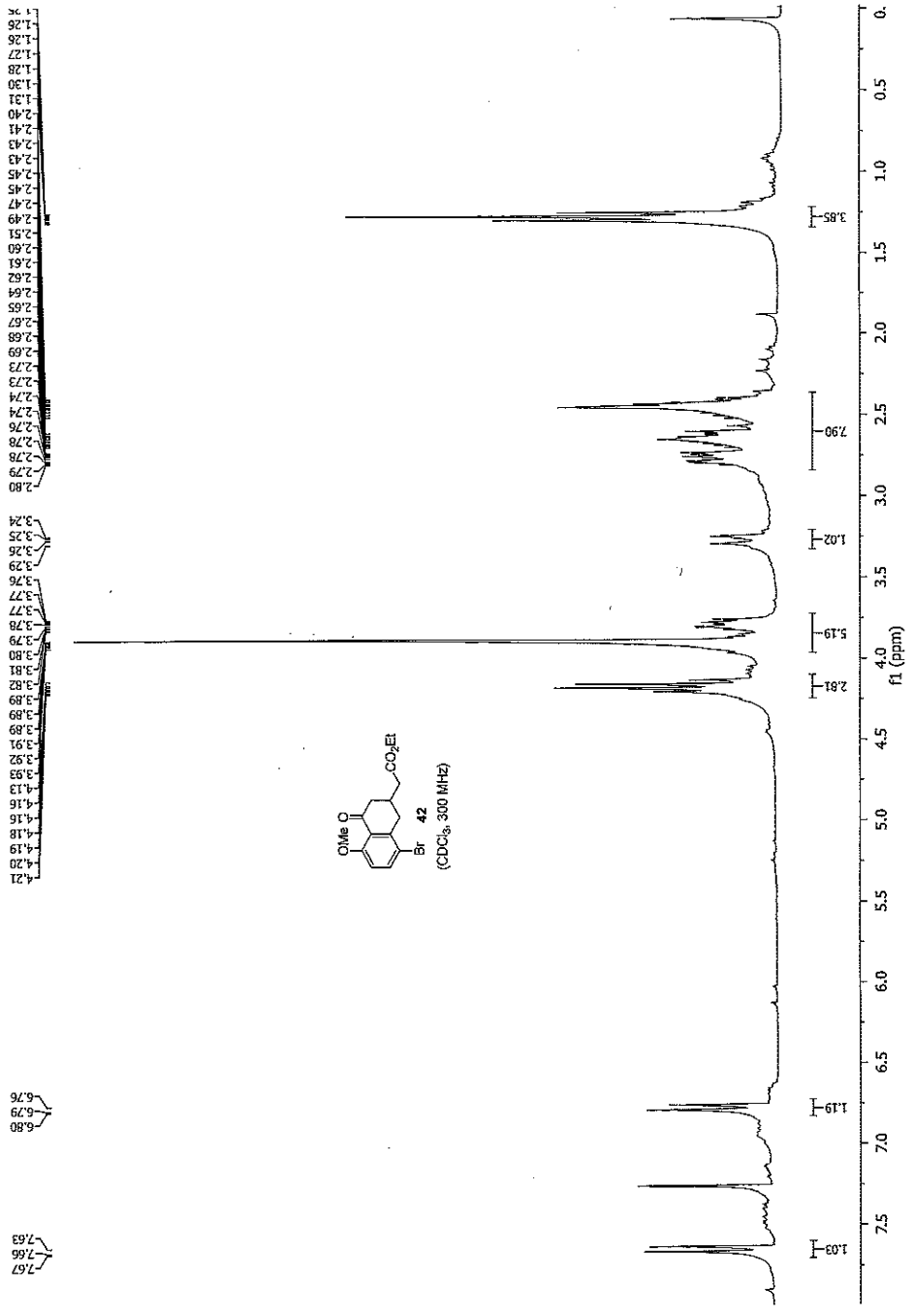
1.01
2.86
3.85
6.27
3.30
4.73
f1 (ppm)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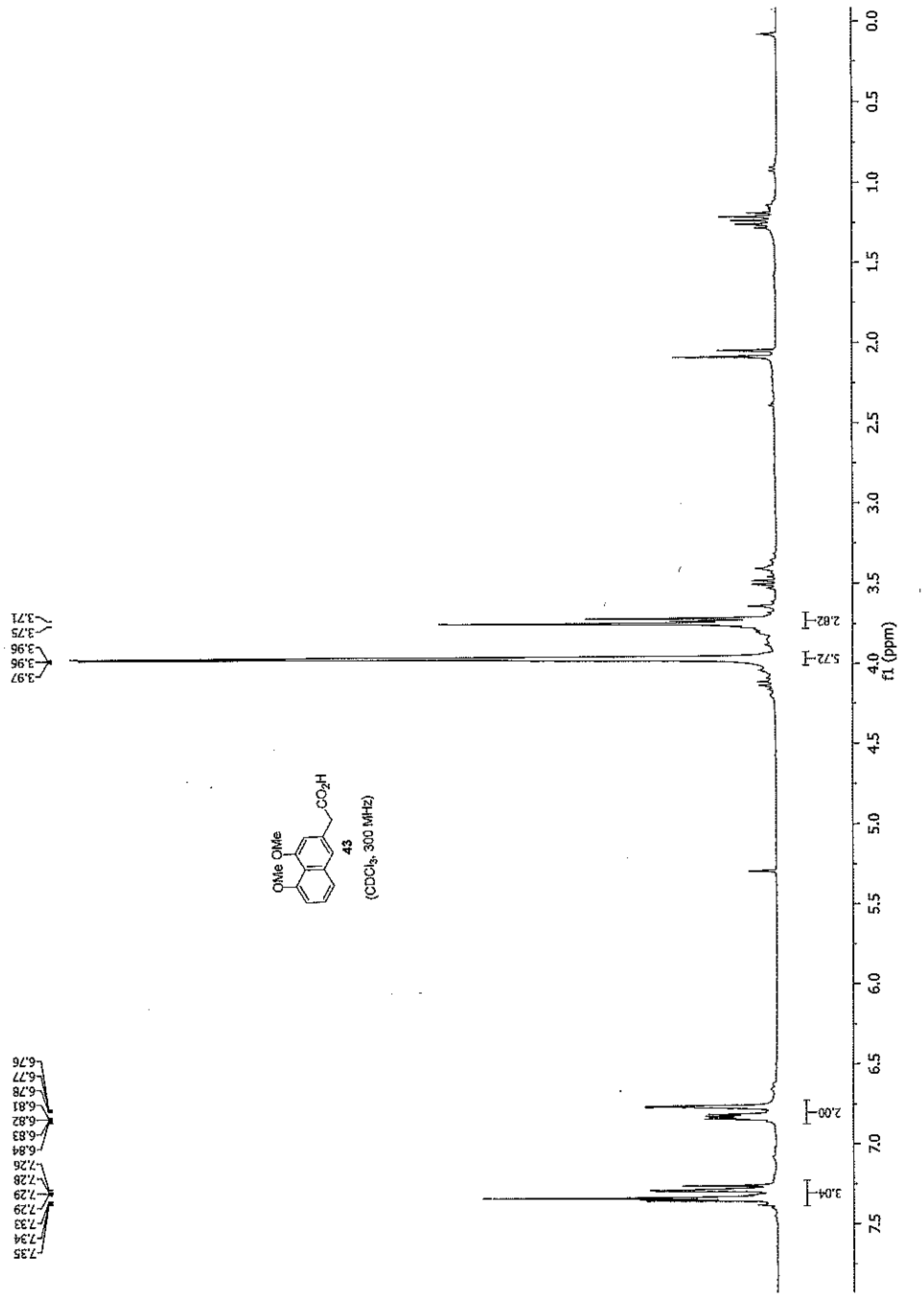
CO2Et
Br 42
(CDCl3, 300 MHz)
f1 (ppm)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3.75
3.96
3.96
3.97
6.76
6.77
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6.81
6.82
6.83
6.84
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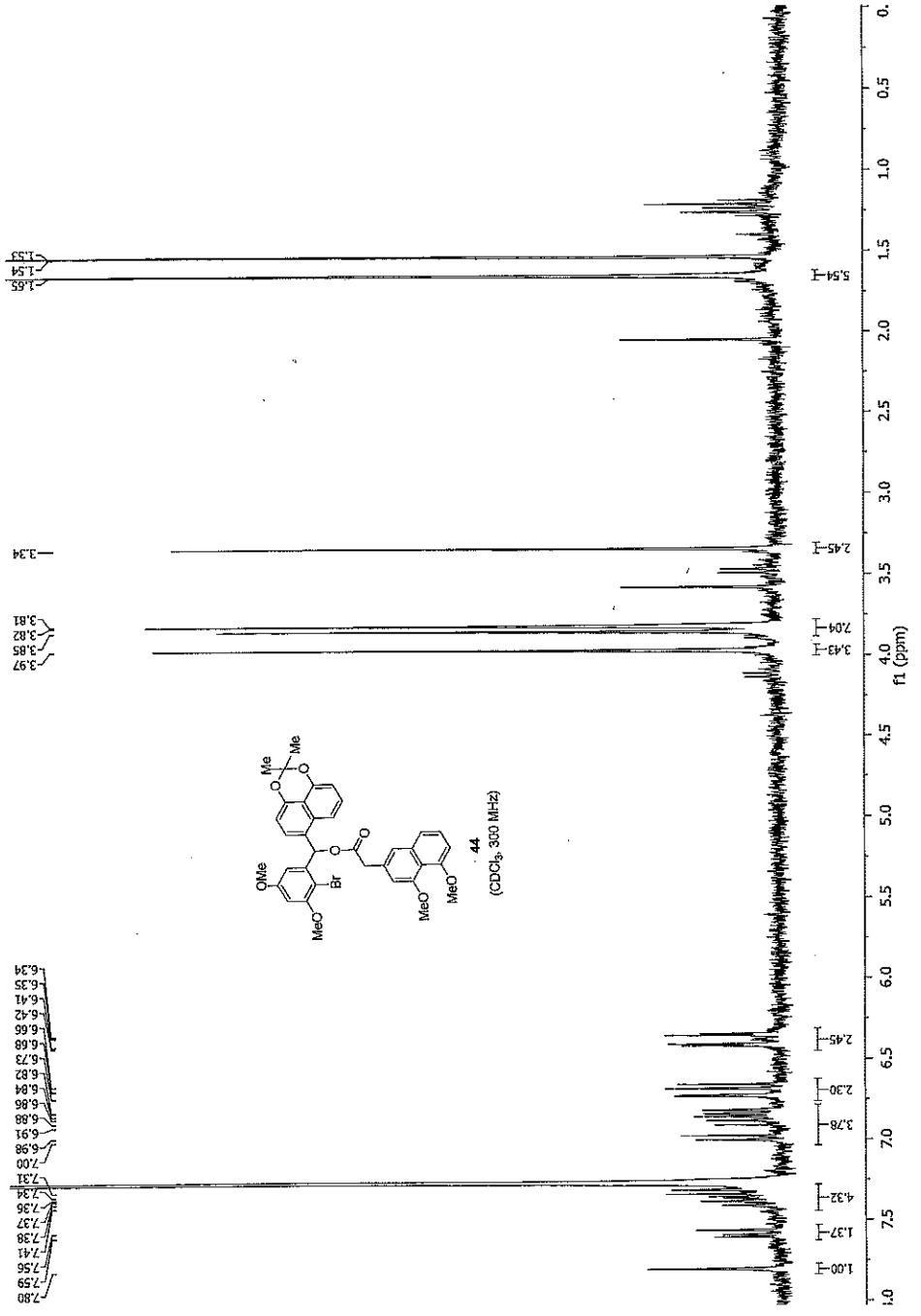
7.35
2.82
5.72
2.00
3.04
f1 (ppm)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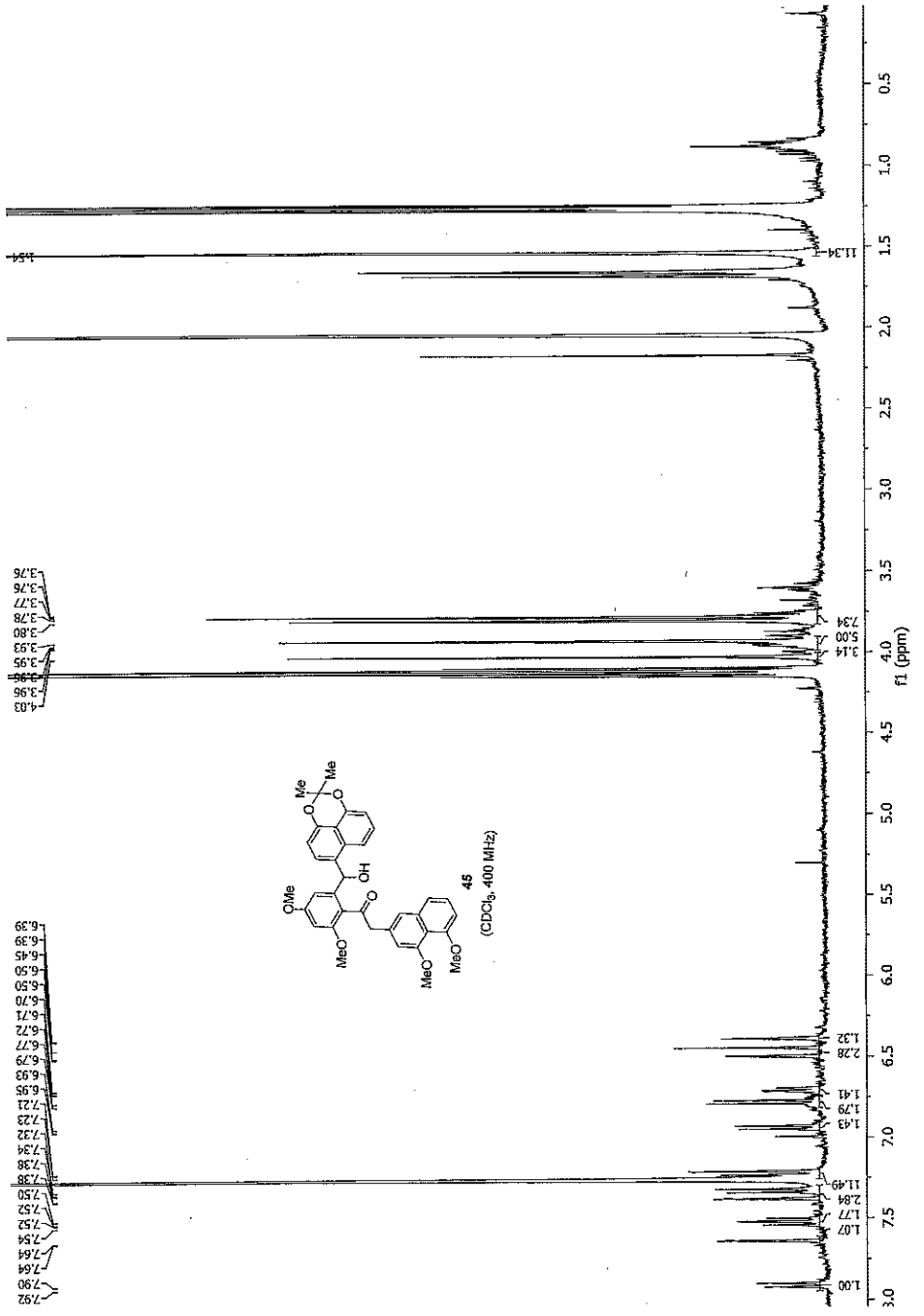
f1 (ppm)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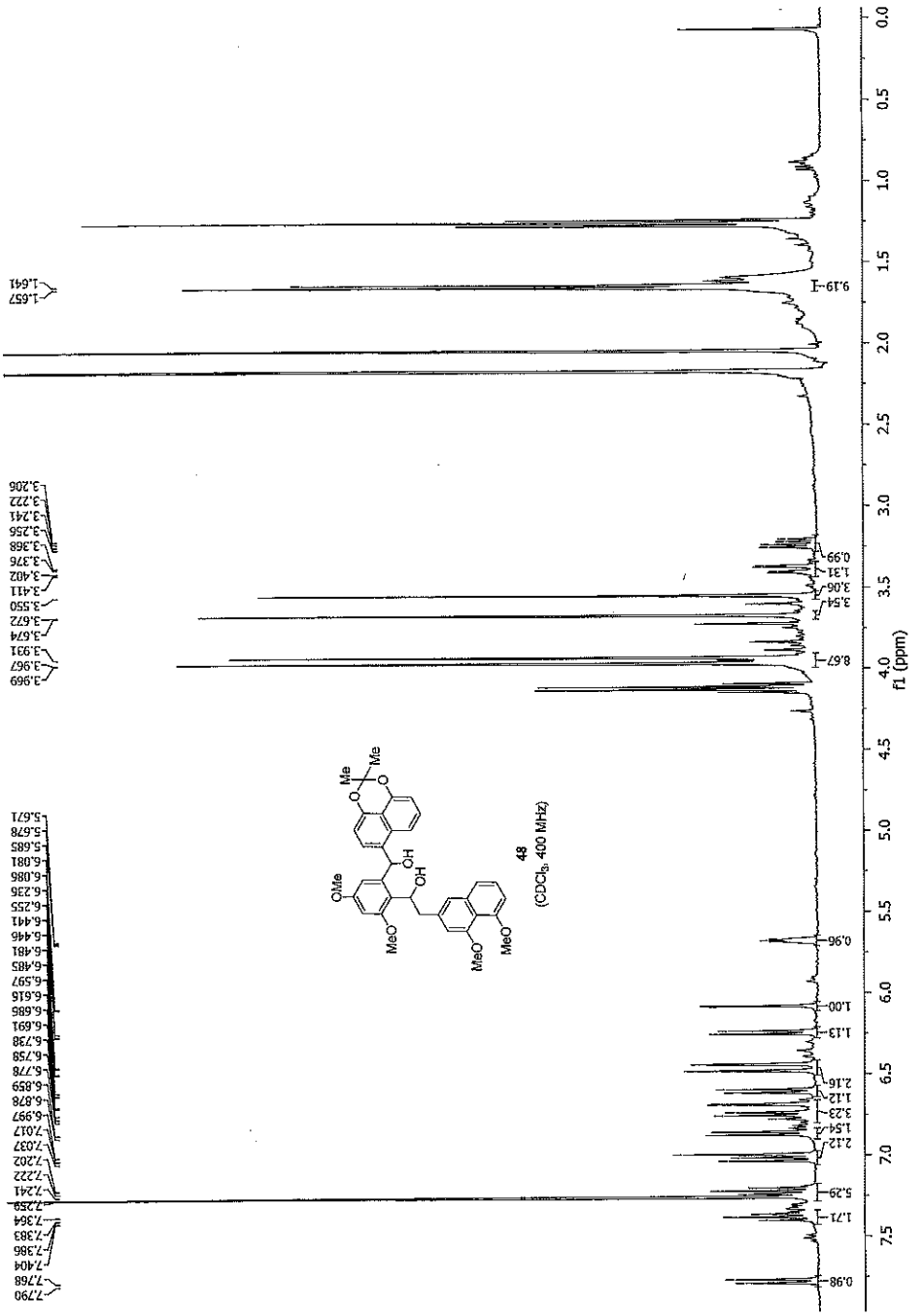
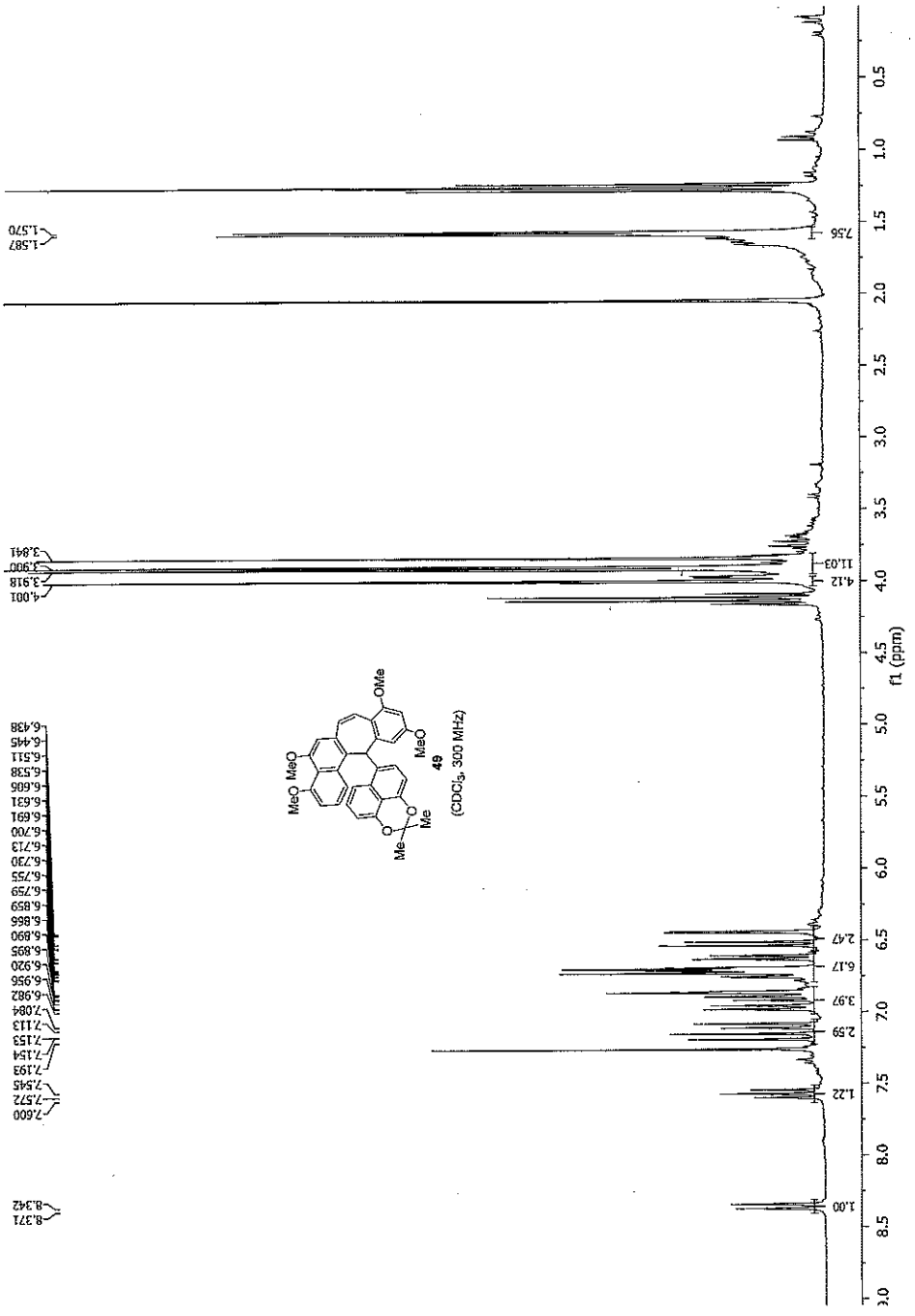
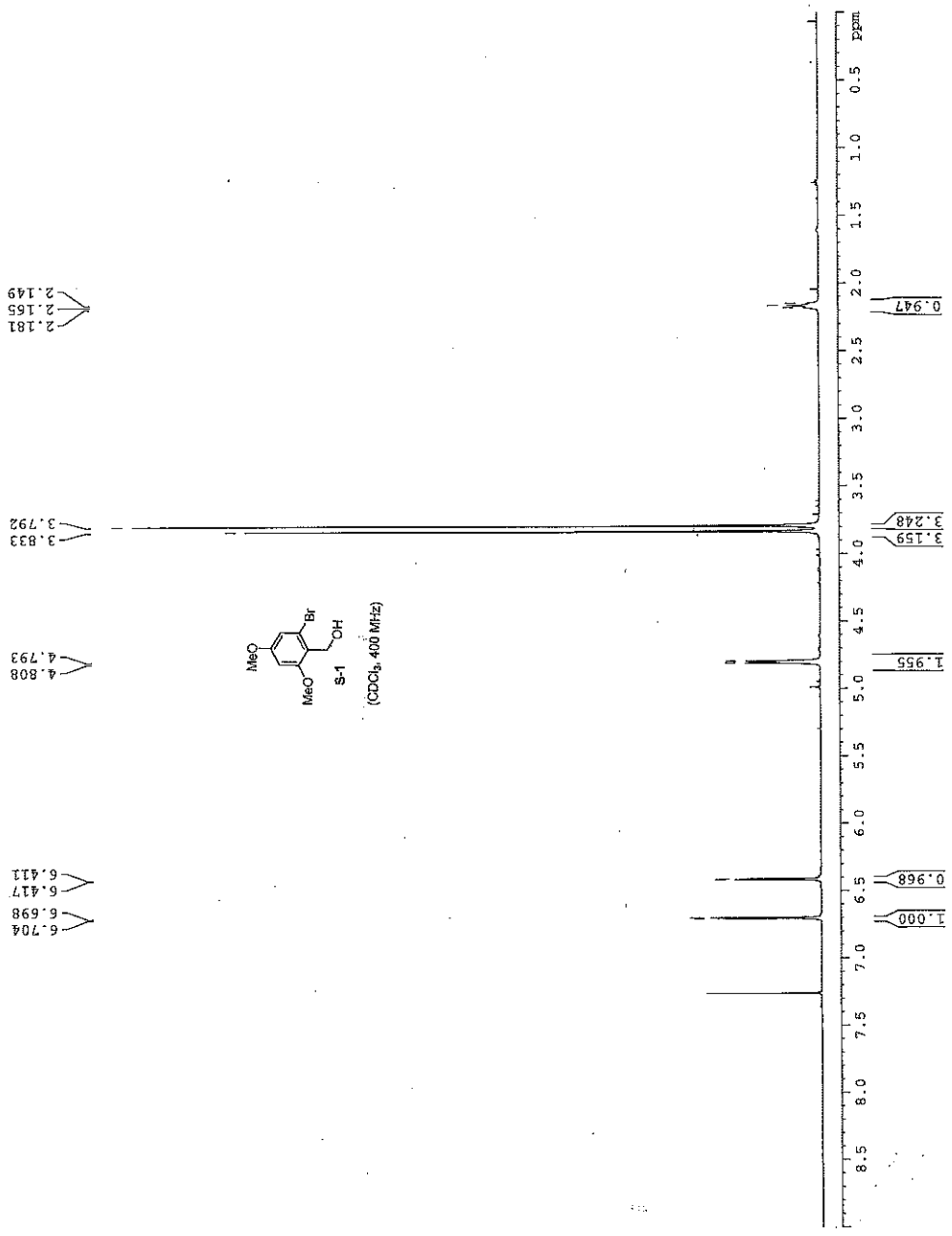
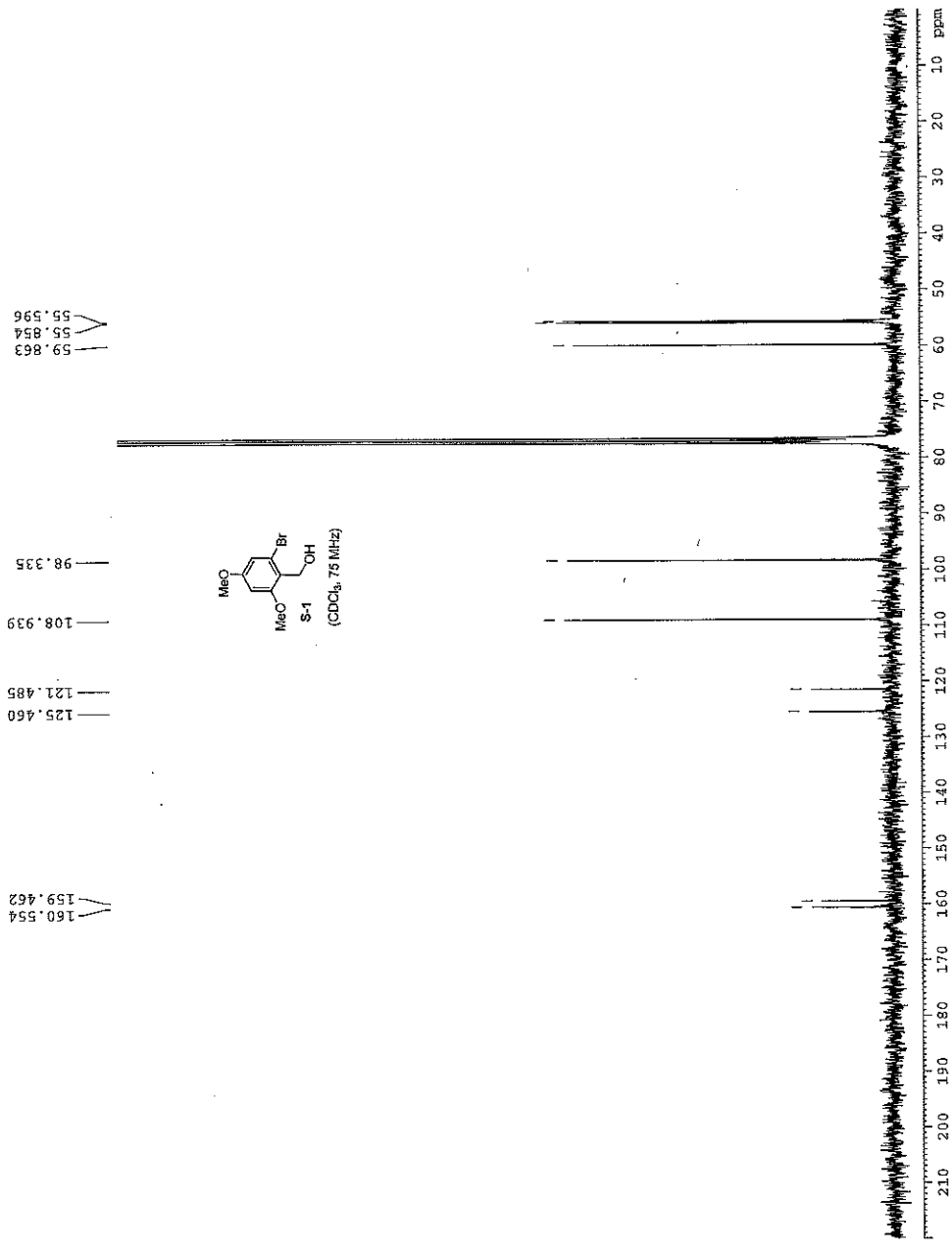
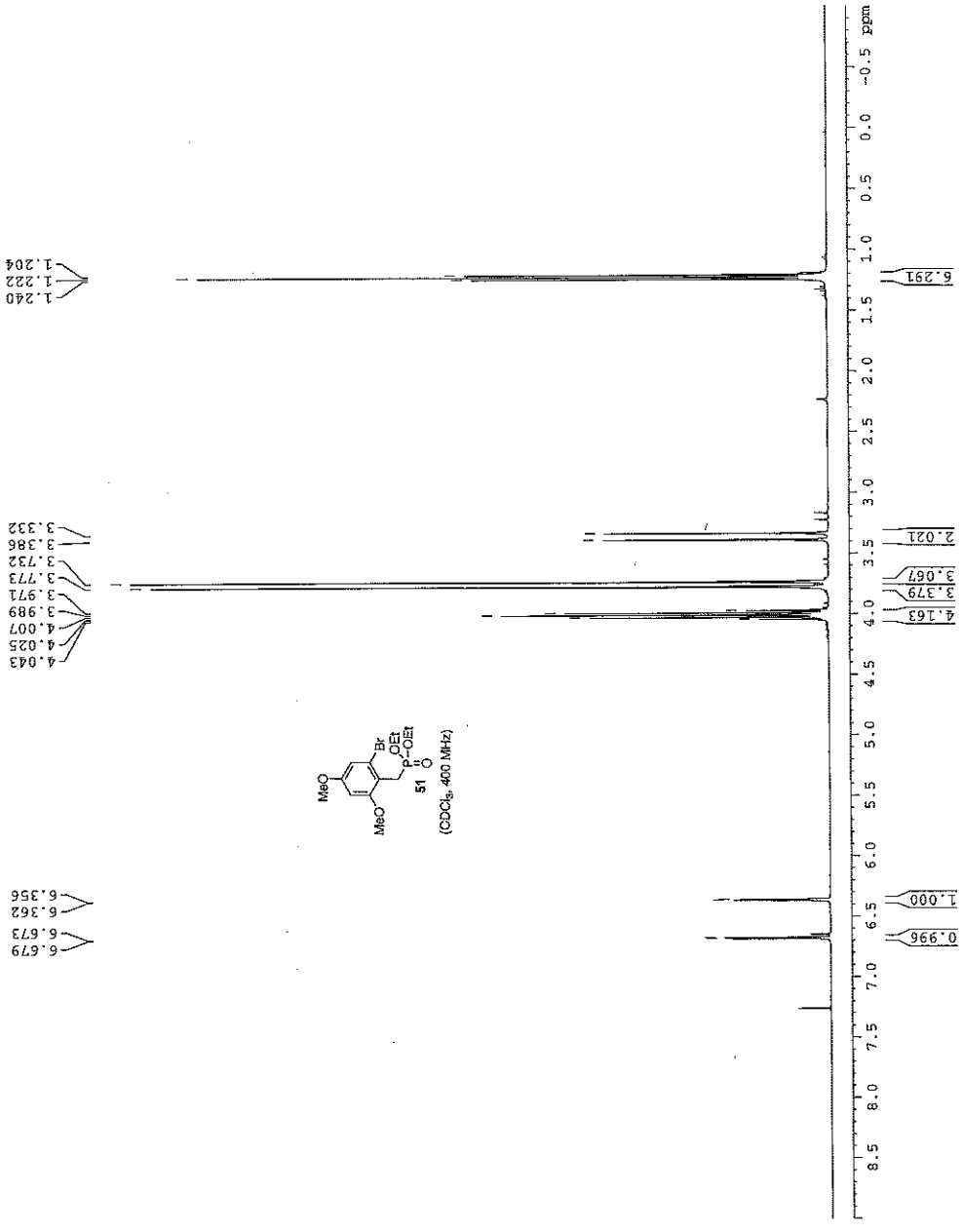
f1 (ppm)

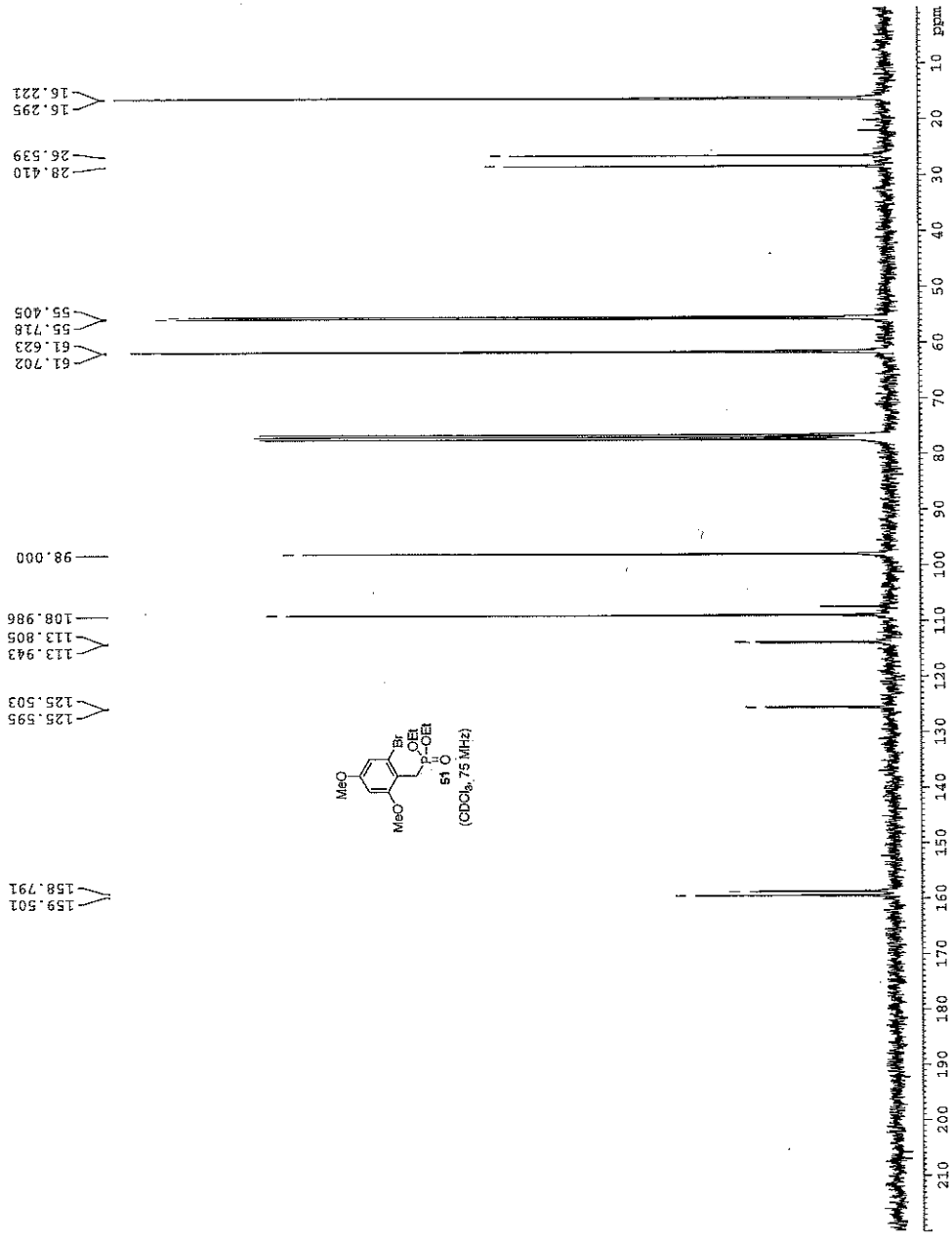

48
(CDCl3, 400 MHz)
f1 (ppm)

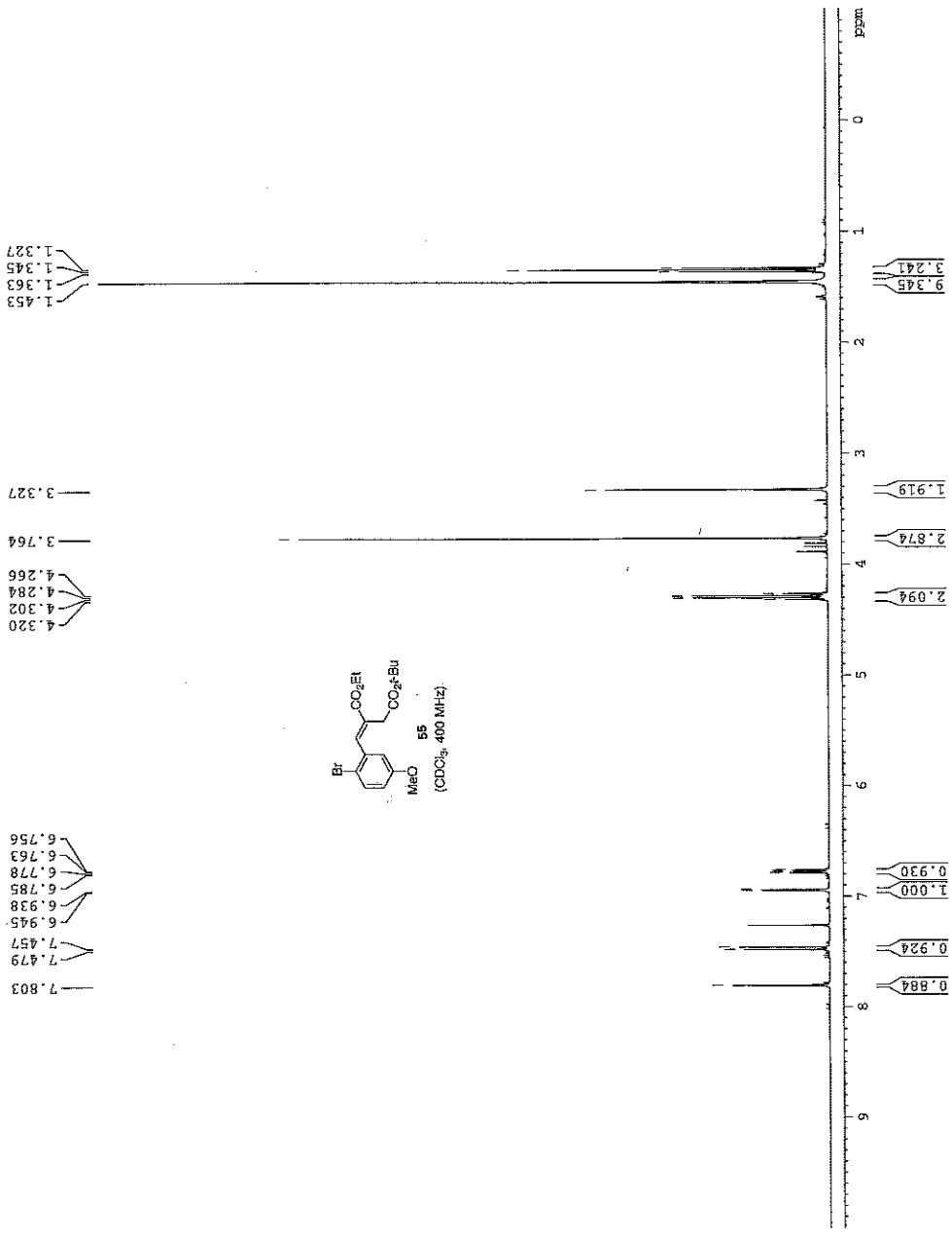

OMe
MeO
MeO MeO
Me
Me
O
O
49
(CDCl3, 300 MHz)
f1 (ppm)

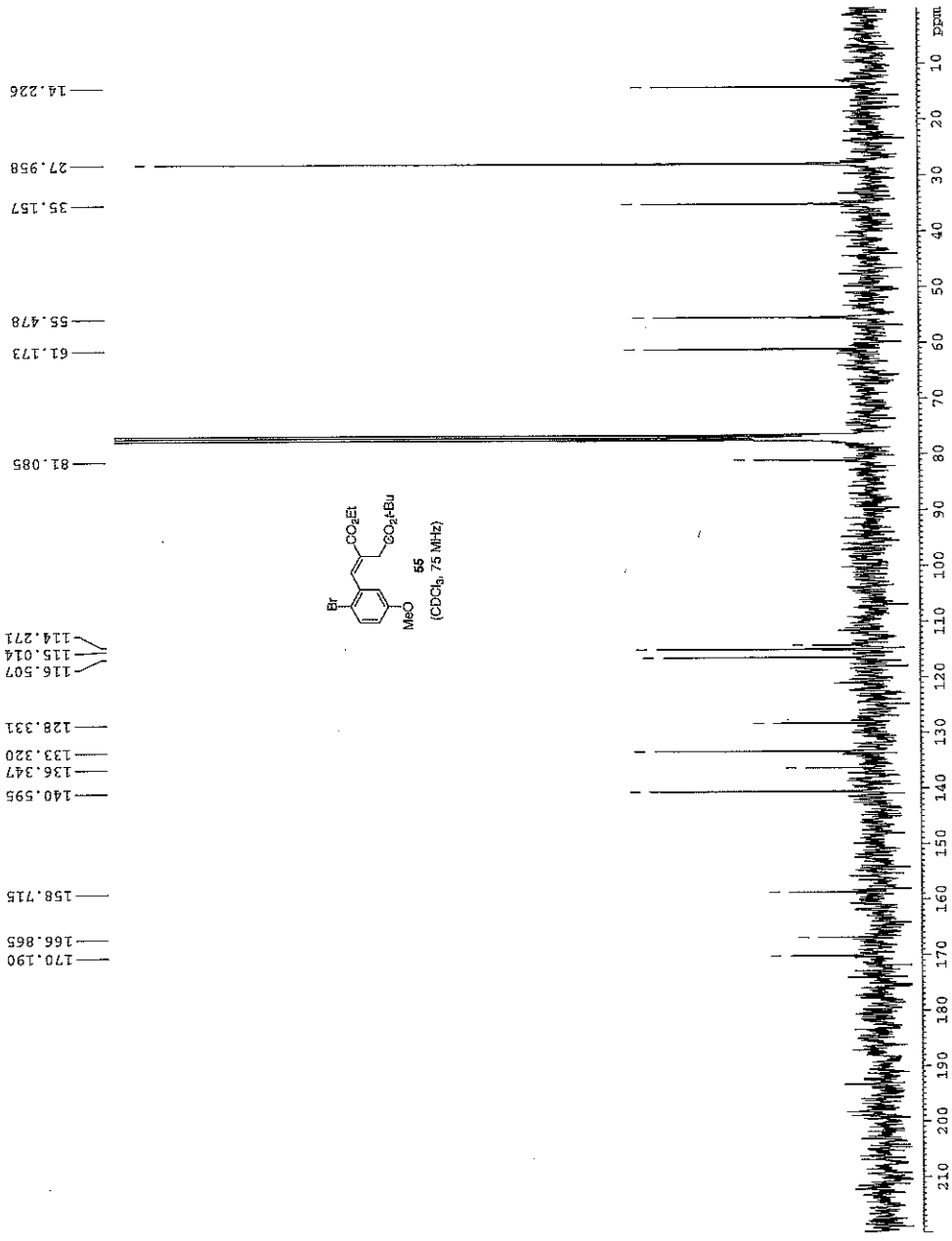

MeO
Br
OH
MeO
S-1
(CDCl3, 400 MHz)
6.704
6.698
6.417
6.411
4.808
4.793
3.833
3.792
2.181
2.165
2.149
1.000
0.968
1.955
3.248
3.159
0.947
ppm

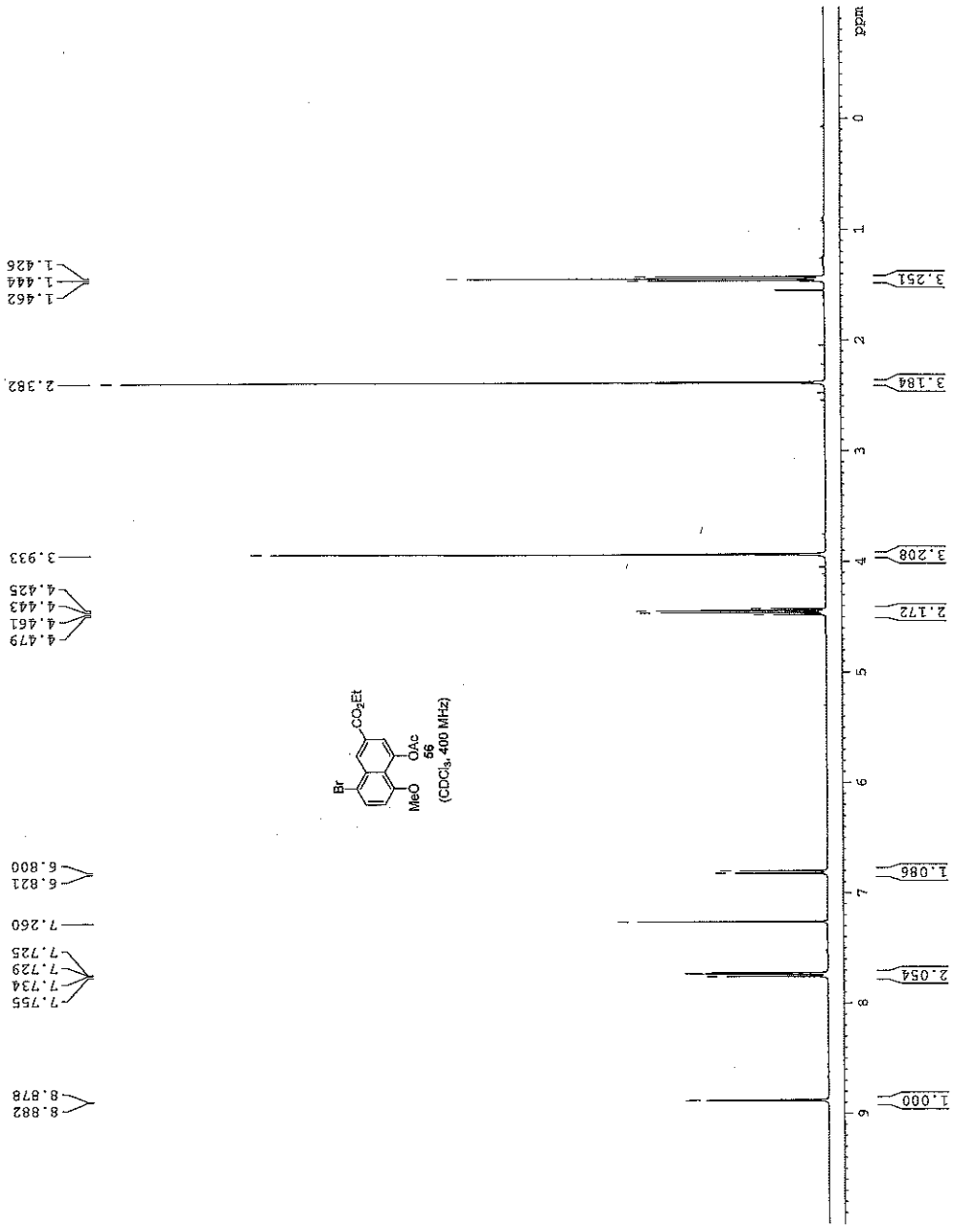

55.596
55.854
59.863
98.335
108.939
121.485
125.460
159.462
160.554
MeO
MeO
Br
OH
S-1
(CDCl3, 75 MHz)
ppm

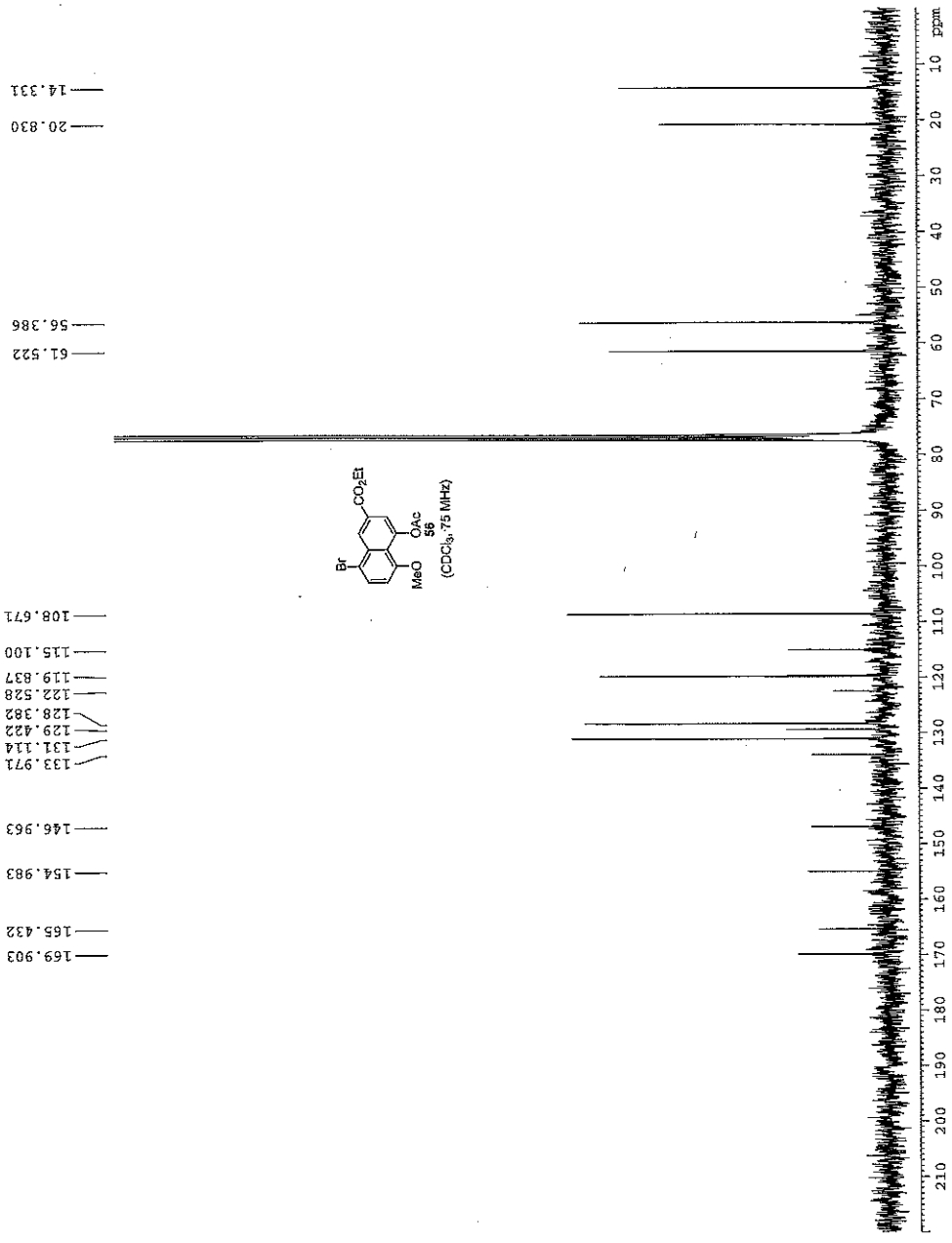

1.204
1.222
1.240
3.332
3.386
3.732
3.773
3.971
3.989
4.007
4.025
4.043
6.356
6.362
6.673
6.679
6.291
2.021
3.067
3.379
4.163
1.000
0.996
ppm
MeO
MeO
Br
OEt
P
OEt
O
51
(CDCl3, 400 MHz)

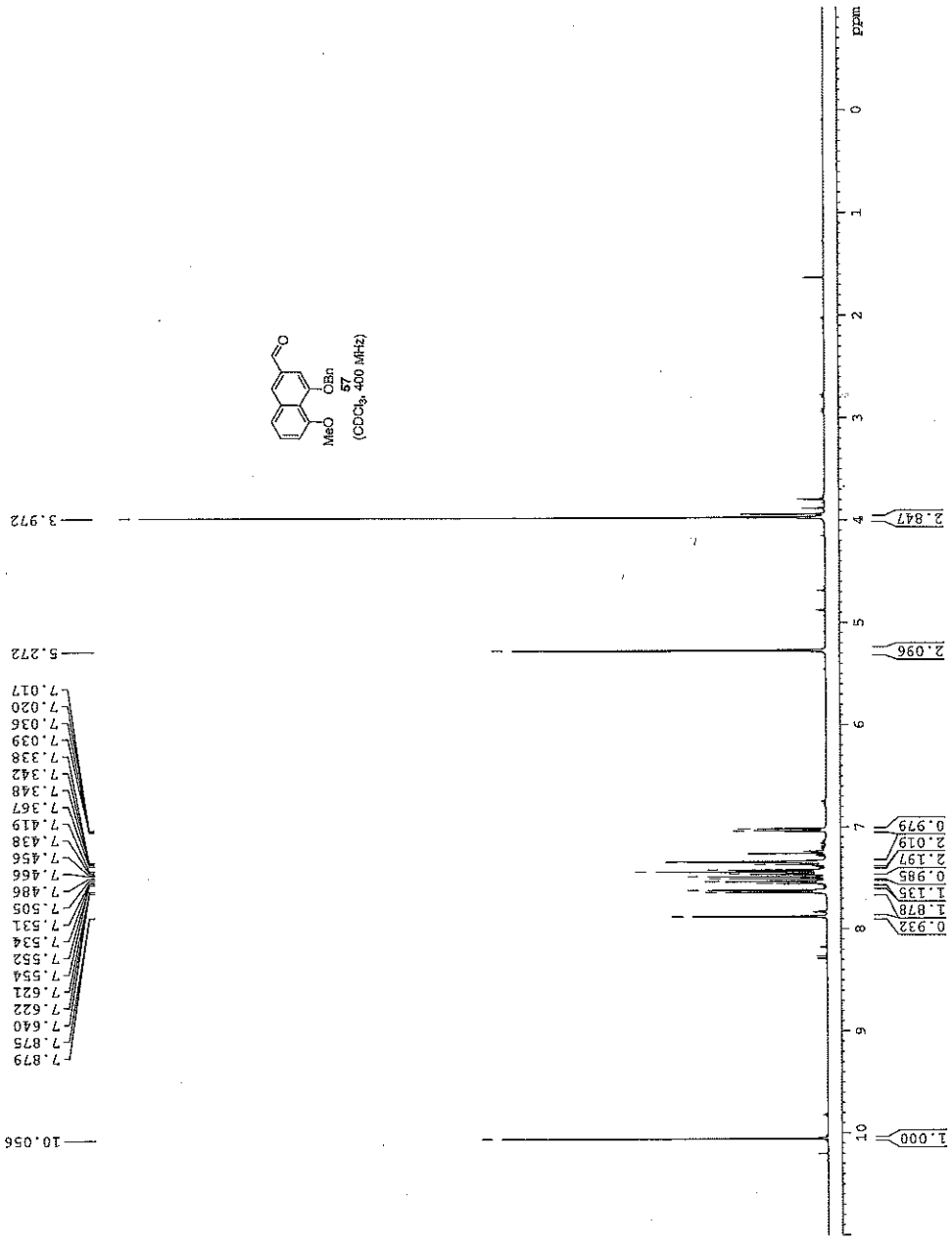

16.221
16.295
26.539
28.410
55.405
55.718
61.623
61.702
98.000
108.986
113.805
113.943
125.503
125.595
158.791
159.501
MeO
MeO
Br
OEt
OEt
51
(CDCl3, 75 MHz)
ppm

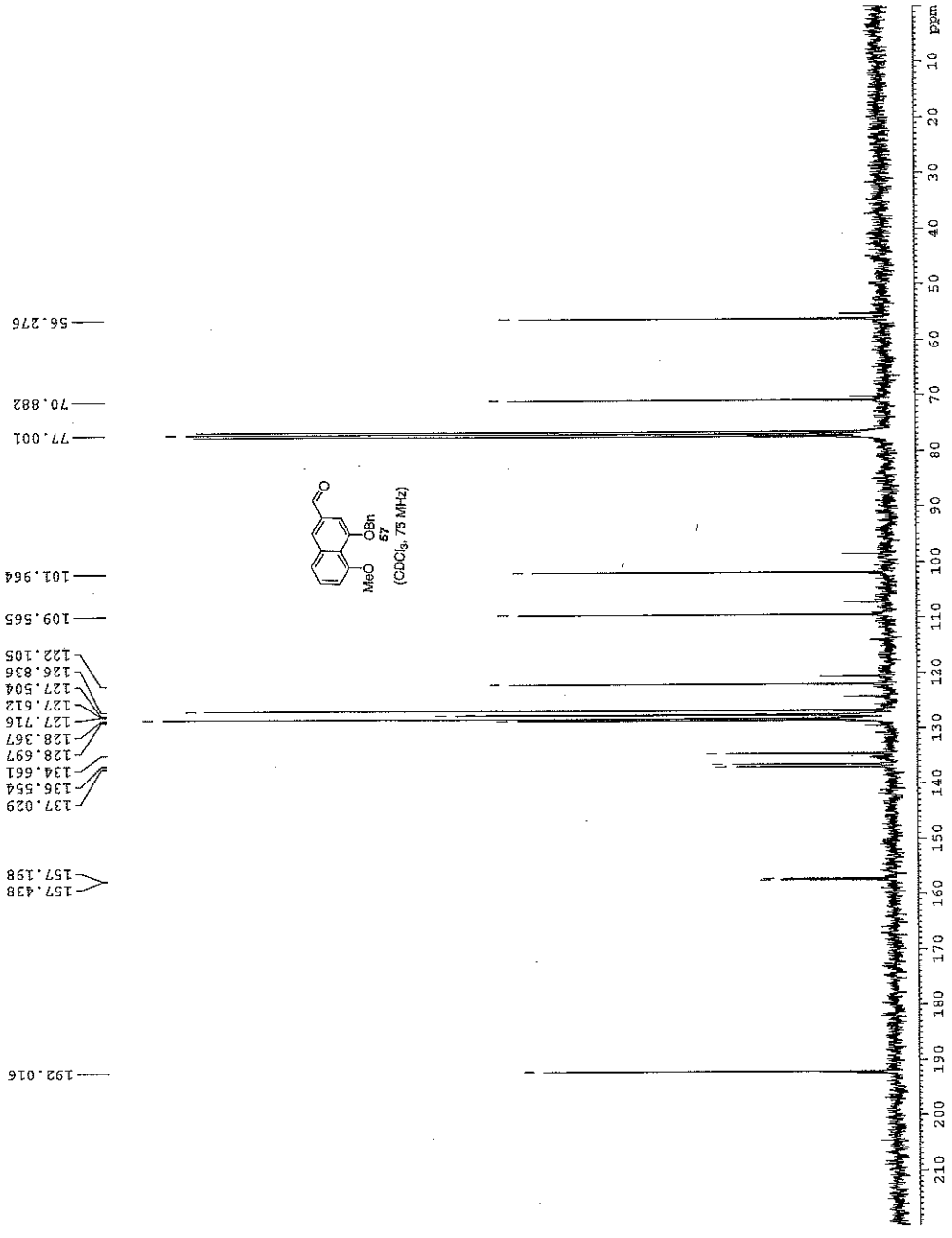

ppm
0
1
2
3
4
5
6
7
8
9
1.453
1.363
1.345
1.327
3.327
3.764
4.320
4.302
4.284
4.266
6.756
6.763
6.778
6.785
6.938
6.945
7.457
7.479
7.803
9.345
3.241
1.919
2.874
2.094
0.930
1.000
0.924
0.884
CO2Et
CO2t-Bu
Br
MeO
55
(CDCl3, 400 MHz)

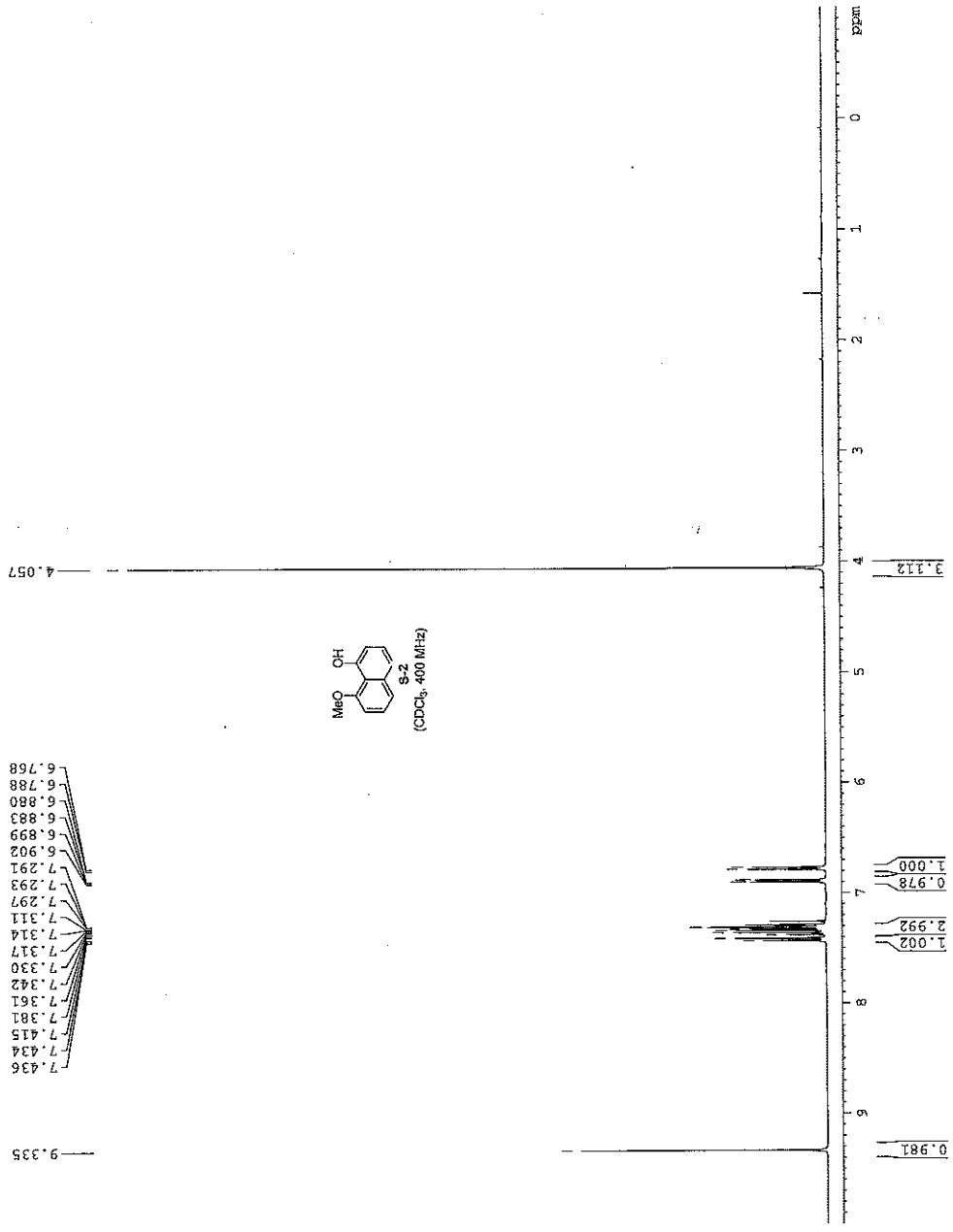

14.226
27.958
35.157
55.478
61.173
81.085
114.271
115.014
116.507
128.331
133.320
136.347
140.595
158.715
166.865
170.190
CO2Et
CO2t-Bu
Br
MeO
55
(CDCl3, 75 MHz)
ppm

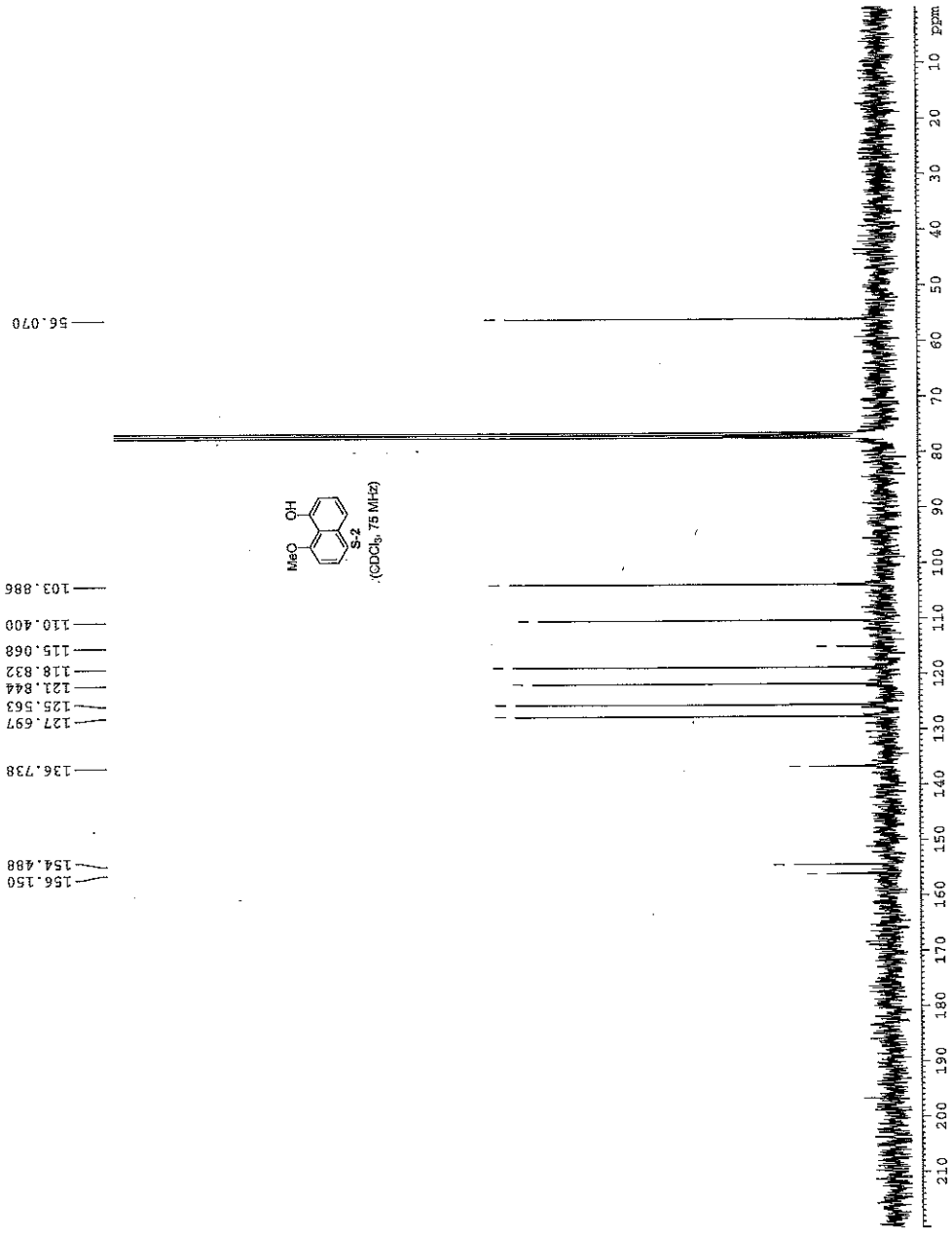

ppm
0
1
2
3
4
5
6
7
8
9
1.000
2.054
1.086
6.800
6.821
7.260
7.725
7.729
7.734
7.755
8.878
8.882
4.425
4.443
4.461
4.479
3.933
2.382
1.426
1.444
1.462
3.251
3.184
3.208
2.172
Br
CO2Et
OAc
MeO
56
(CDCl3, 400 MHz)

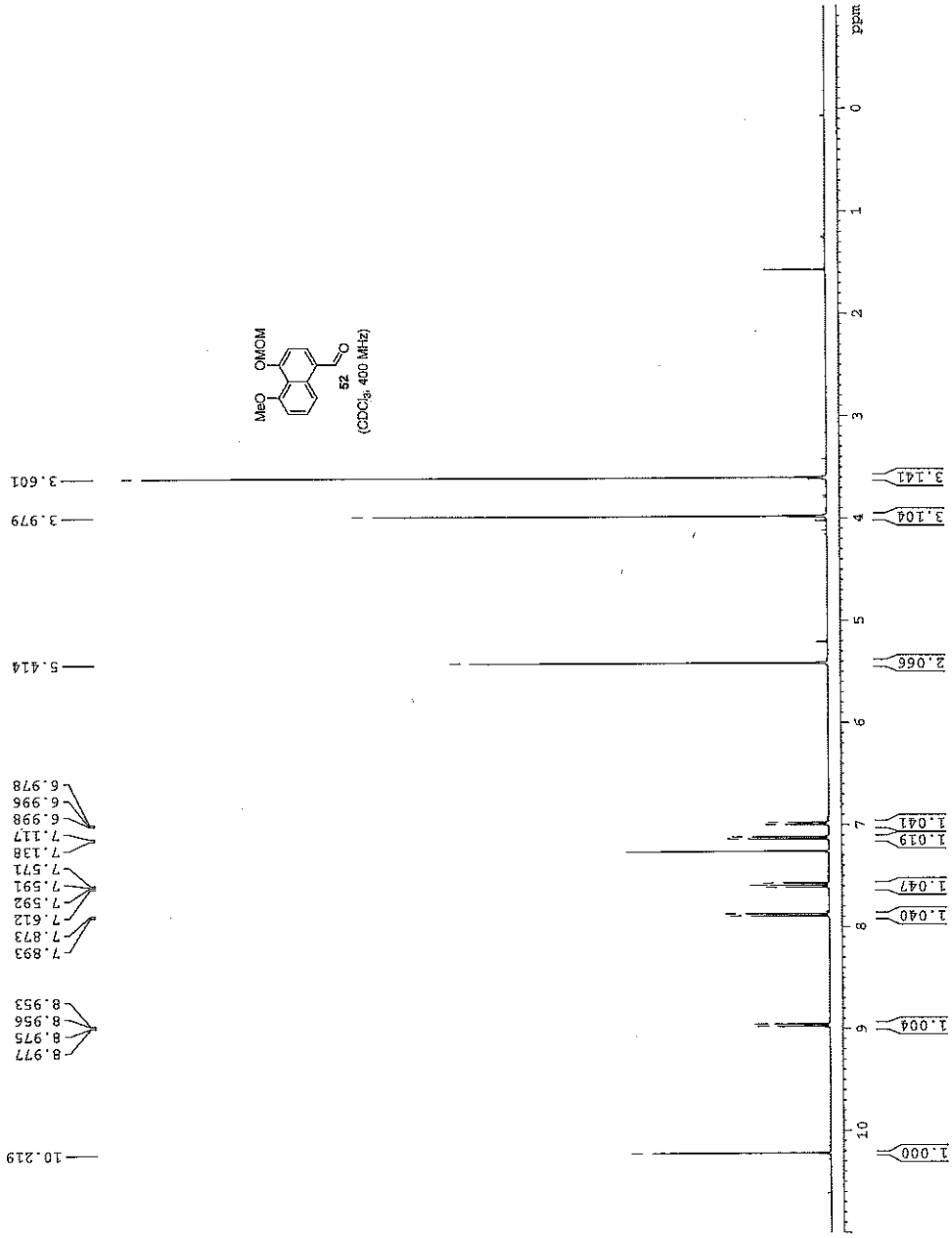

14.331
20.830
56.386
61.522
108.671
115.100
119.837
122.528
128.382
129.422
131.114
133.971
146.963
154.983
165.432
169.903
Br
MeO
OAc
56
CO_2Et
($CDCl_3$, 75 MHz)
ppm

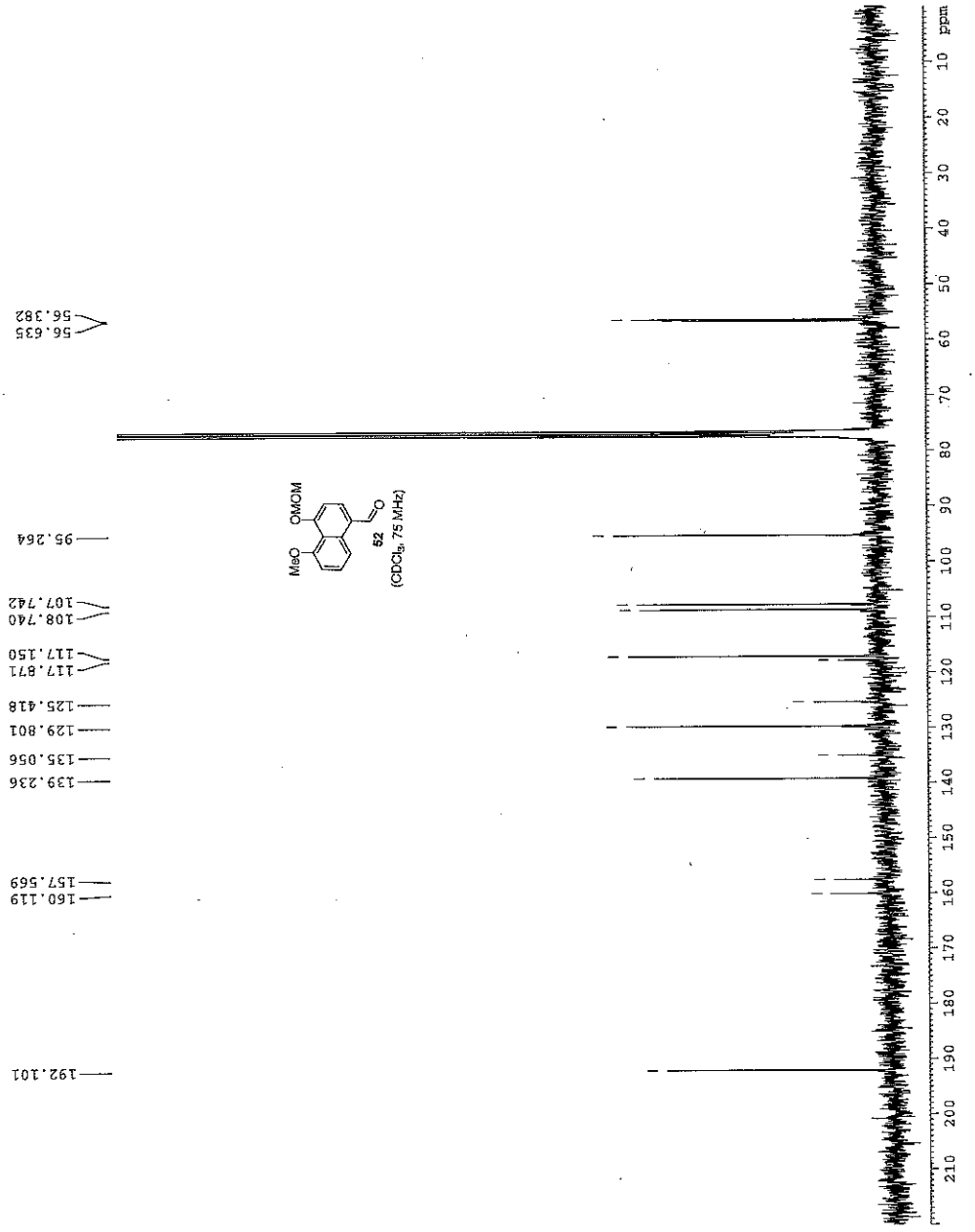

OBn
MeO
57
(CDCl3, 400 MHz)
ppm
10.056
7.879
7.875
7.640
7.622
7.621
7.554
7.552
7.534
7.531
7.505
7.486
7.466
7.456
7.438
7.419
7.367
7.348
7.342
7.338
7.039
7.036
7.020
7.017
5.272
3.972
1.000
2.096
2.847
0.979
2.019
2.197
0.985
1.135
1.878
0.932

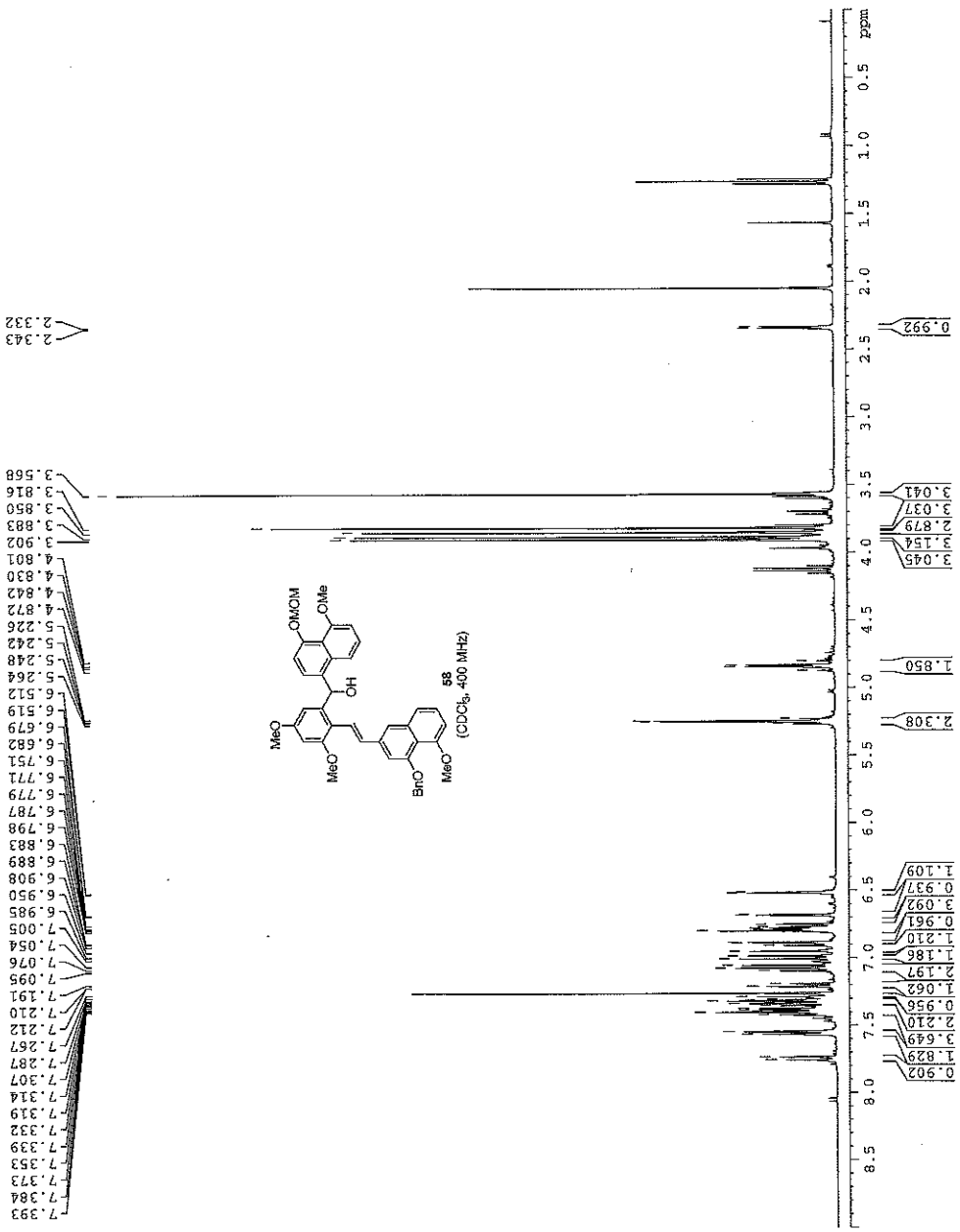

56.276
70.882
77.001
101.964
109.565
122.105
126.836
127.504
127.612
127.716
128.367
128.697
134.661
136.554
137.029
157.198
157.438
192.016
MeO
OBn
87
(CDCl3, 75 MHz)
ppm

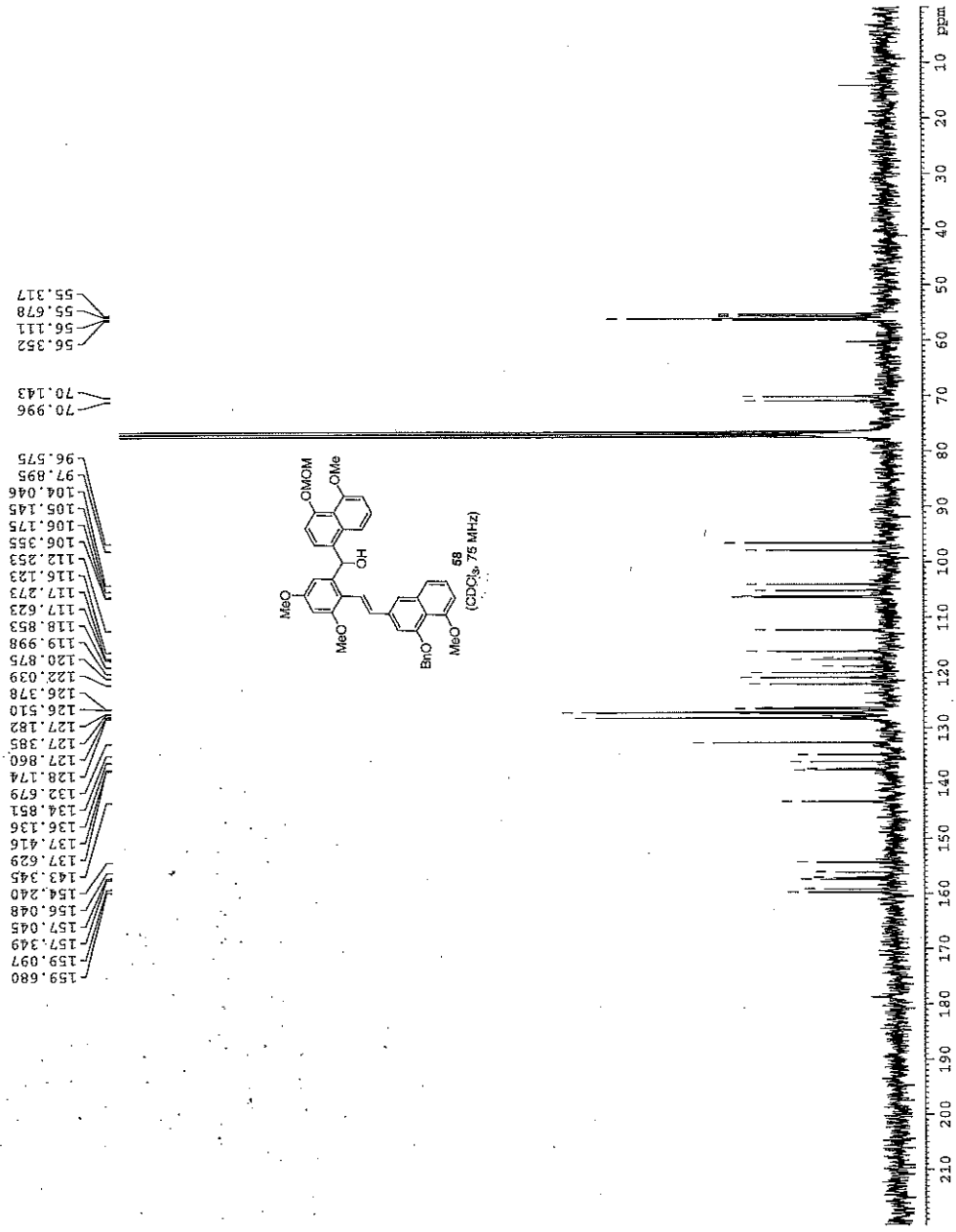

ppm
0
1
2
3
4
5
6
7
8
9
4.057
3.112
9.335
0.981
1.002
2.992
0.978
1.000
7.436
7.434
7.415
7.381
7.361
7.342
7.330
7.317
7.314
7.311
7.297
7.293
7.291
6.902
6.899
6.883
6.880
6.788
6.768
MeO
OH
S-2
(CDCl3, 400 MHz)

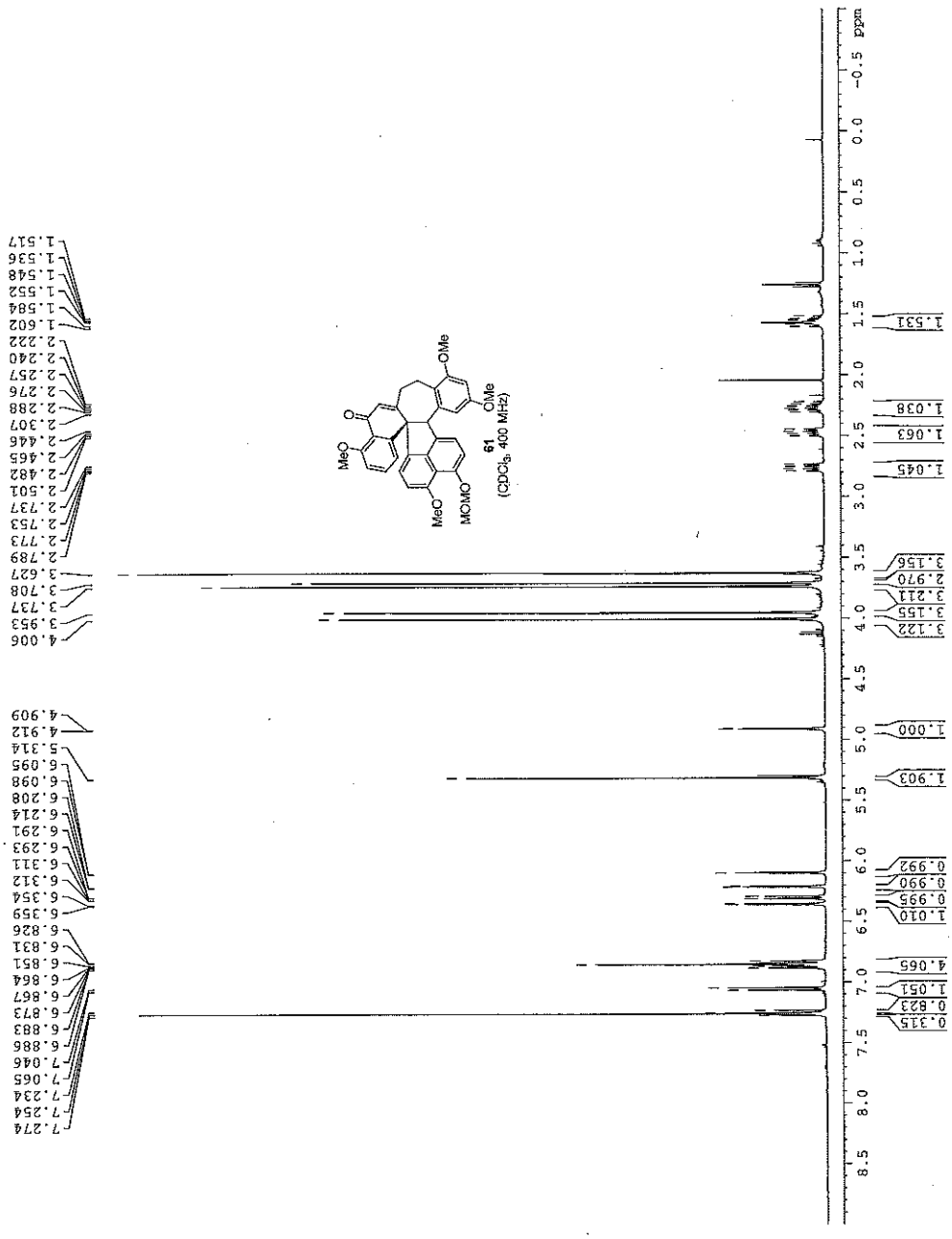

56.070
103.886
110.400
115.068
118.832
121.844
125.563
127.697
136.738
154.488
156.150
MeO
OH
S-2
(CDCl3, 75 MHz)
10 ppm

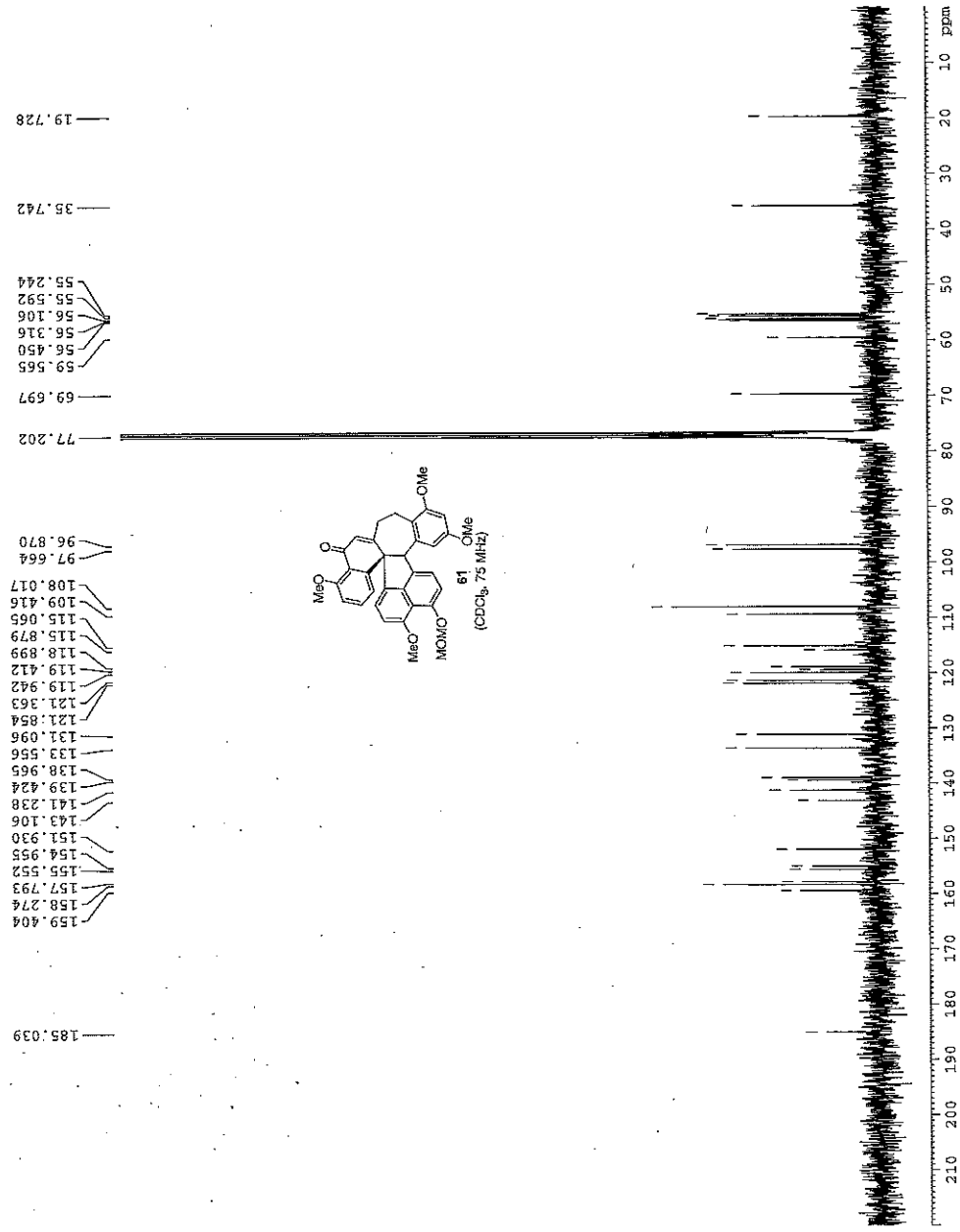

MeO
OMOM
O
52
(CDCl3, 400 MHz)
ppm
0
1
2
3
4
5
6
7
8
9
10
3.601
3.979
5.414
10.219
8.977
8.975
8.956
8.953
7.893
7.873
7.612
7.592
7.591
7.571
7.138
7.117
6.998
6.996
6.978
3.141
3.104
2.066
1.041
1.019
1.047
1.040
1.004
1.000

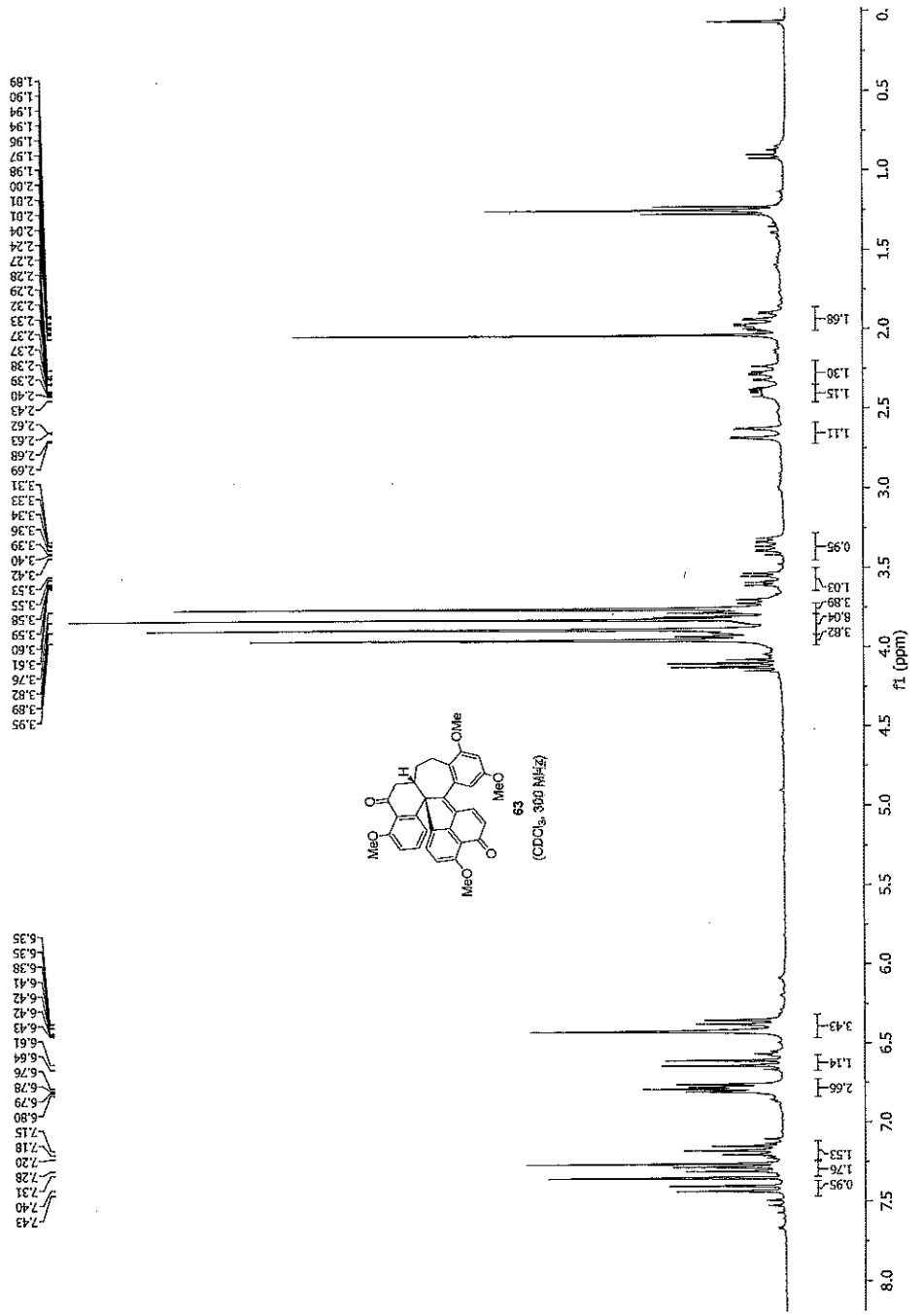

MeO
OMOM
O
52
(CDCl3, 75 MHz)
56.382
56.635
95.264
107.742
108.740
117.150
117.871
125.418
129.801
135.056
139.236
157.569
160.119
192.101
ppm

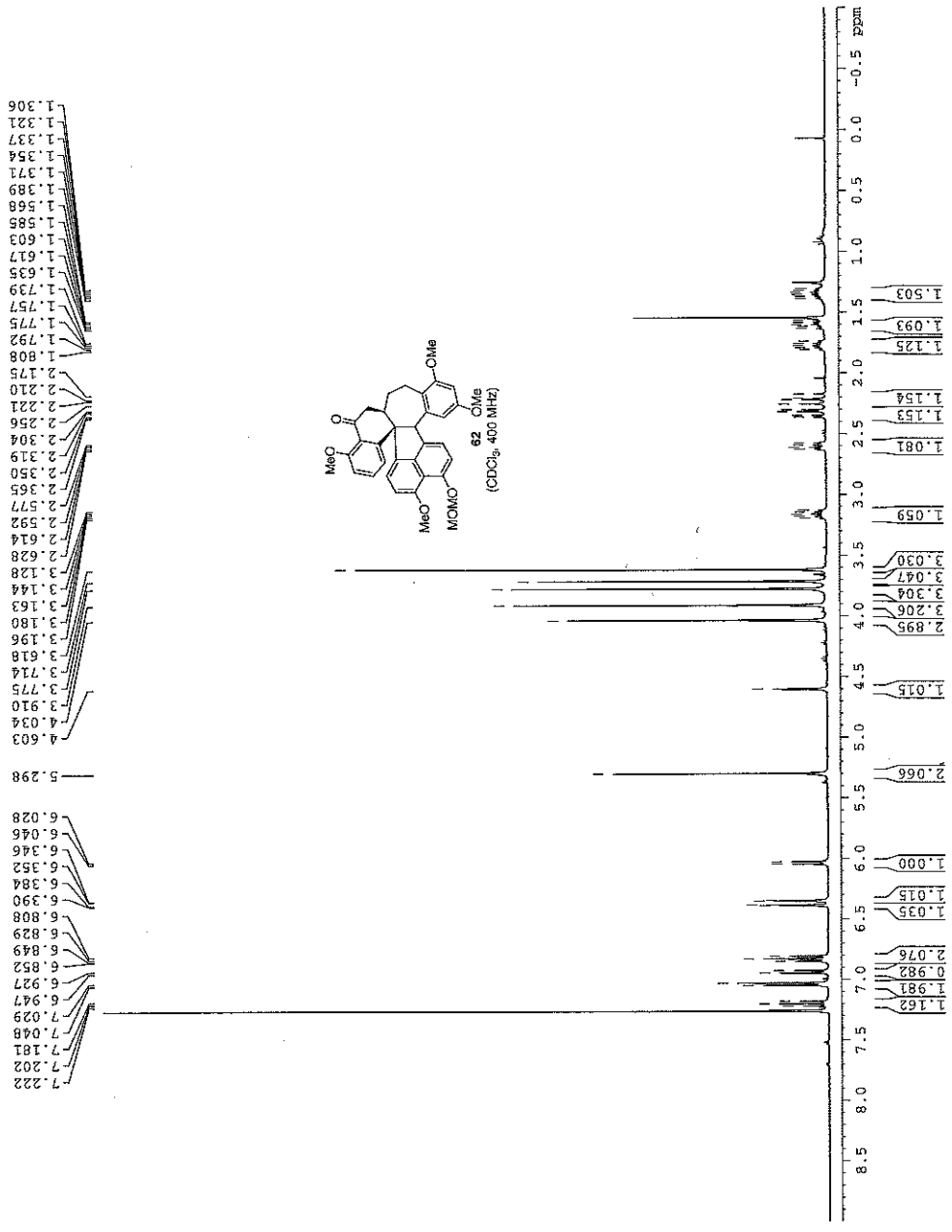

OMOM
OMe
OH
MeO
MeO
BnO
MeO
58
(CDCl3, 400 MHz)
ppm

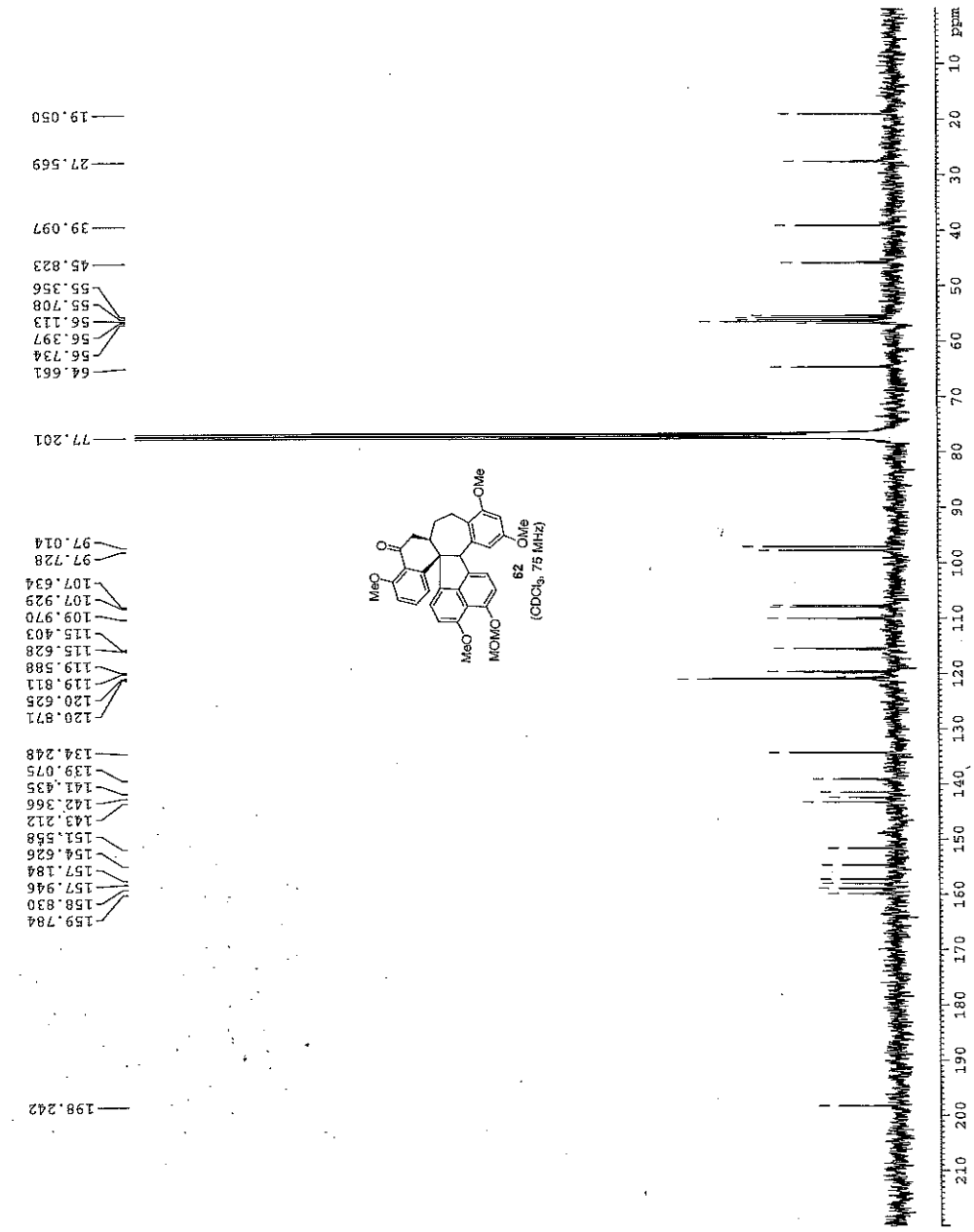

55.317
55.678
56.111
56.352
70.143
70.996
96.575
97.895
104.046
105.145
106.175
106.355
112.253
116.123
117.273
117.623
118.853
119.998
120.875
122.039
126.378
126.510
127.182
127.385
127.860
128.174
132.679
134.851
136.136
137.416
137.629
143.345
154.240
156.048
157.045
157.349
159.097
159.680
OMOM
OMe
OH
MeO
MeO
BnO
MeO
58
(CDCl3, 75 MHz)
ppm

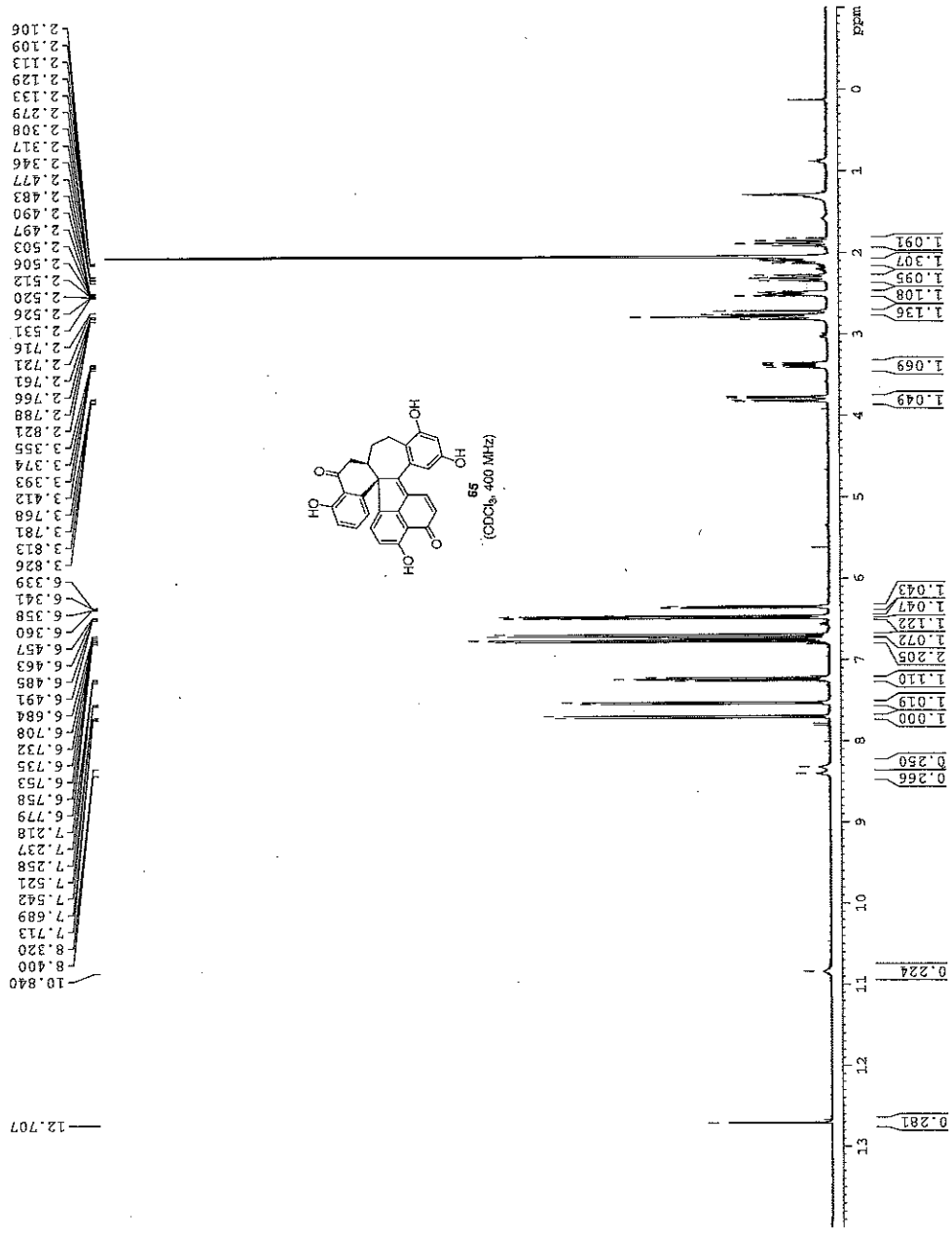

MeO
OMe
OMe
MeO
MOMO
61
(CDCl3, 400 MHz)
ppm

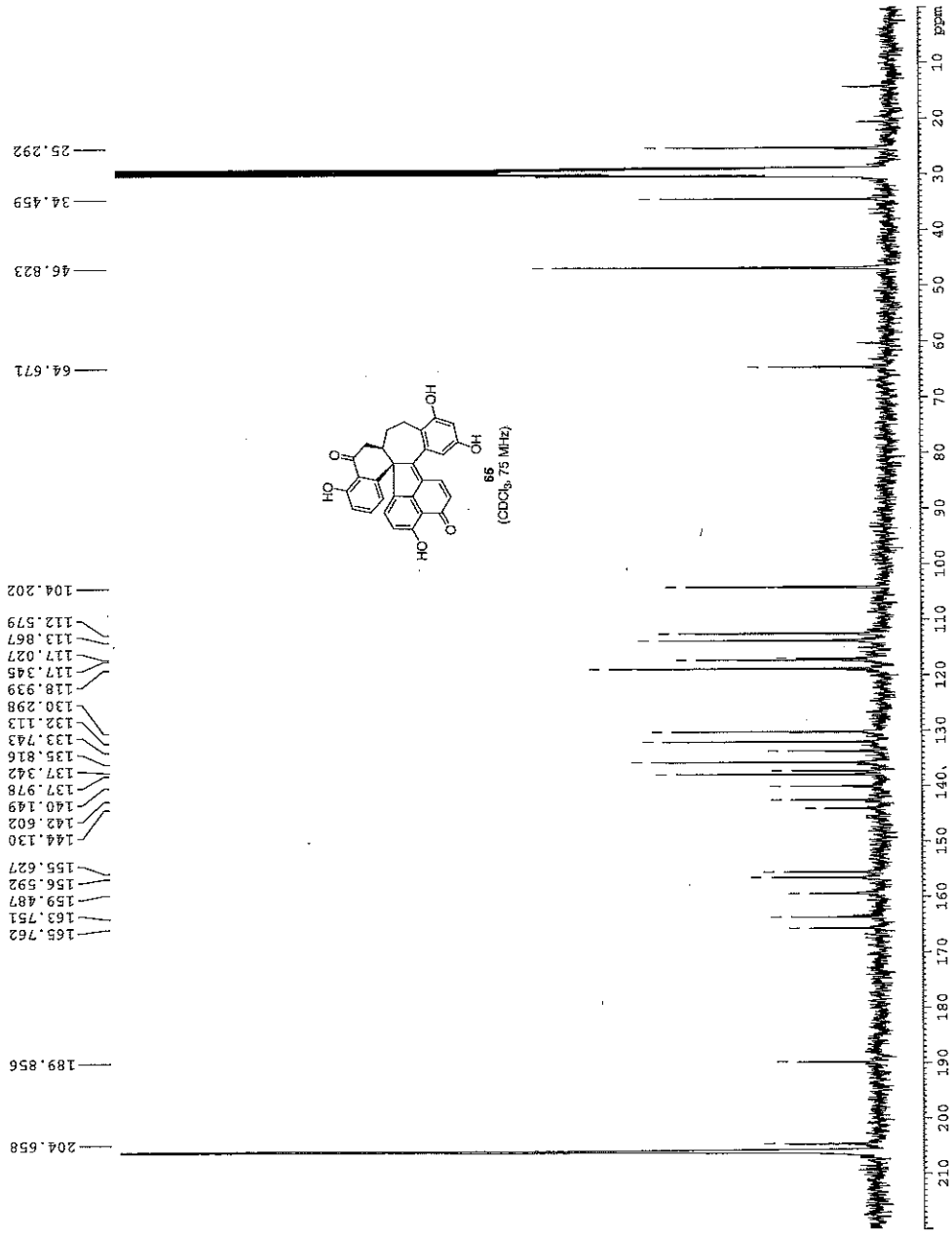

19.728
35.742
55.244
55.592
56.106
56.316
56.450
59.565
69.697
77.202
96.870
97.664
108.017
109.416
115.065
115.879
118.899
119.412
119.942
121.363
121.854
131.096
133.556
138.965
139.424
141.238
143.106
151.930
154.955
155.552
157.793
158.274
159.404
185.039
OMe
OMe
MeO
MeO
MOMO
61
(CDCl3, 75 MHz)
ppm

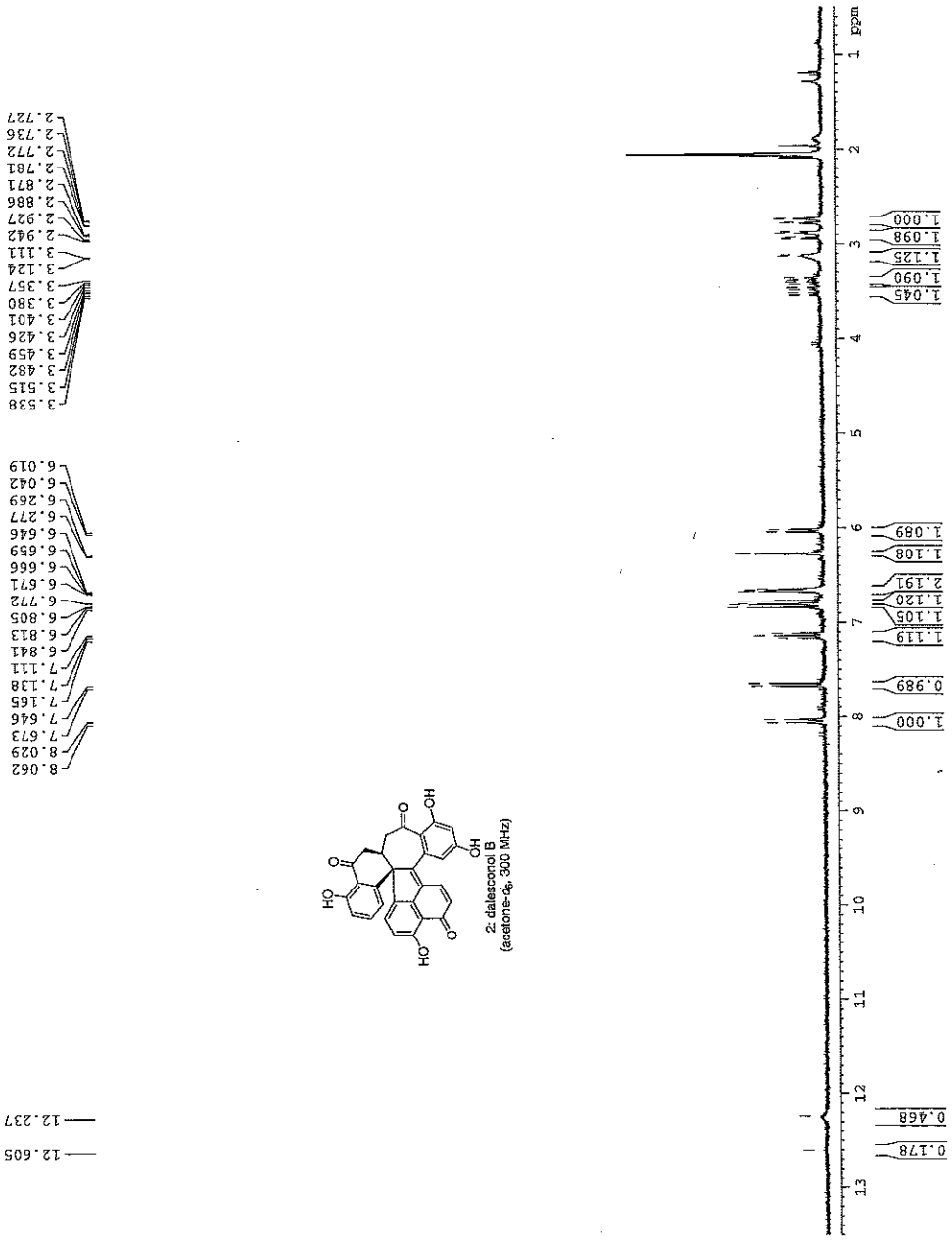

OMe
MeO
MeO
MeO
63
(CDCl3, 300 MHz)
f1 (ppm)

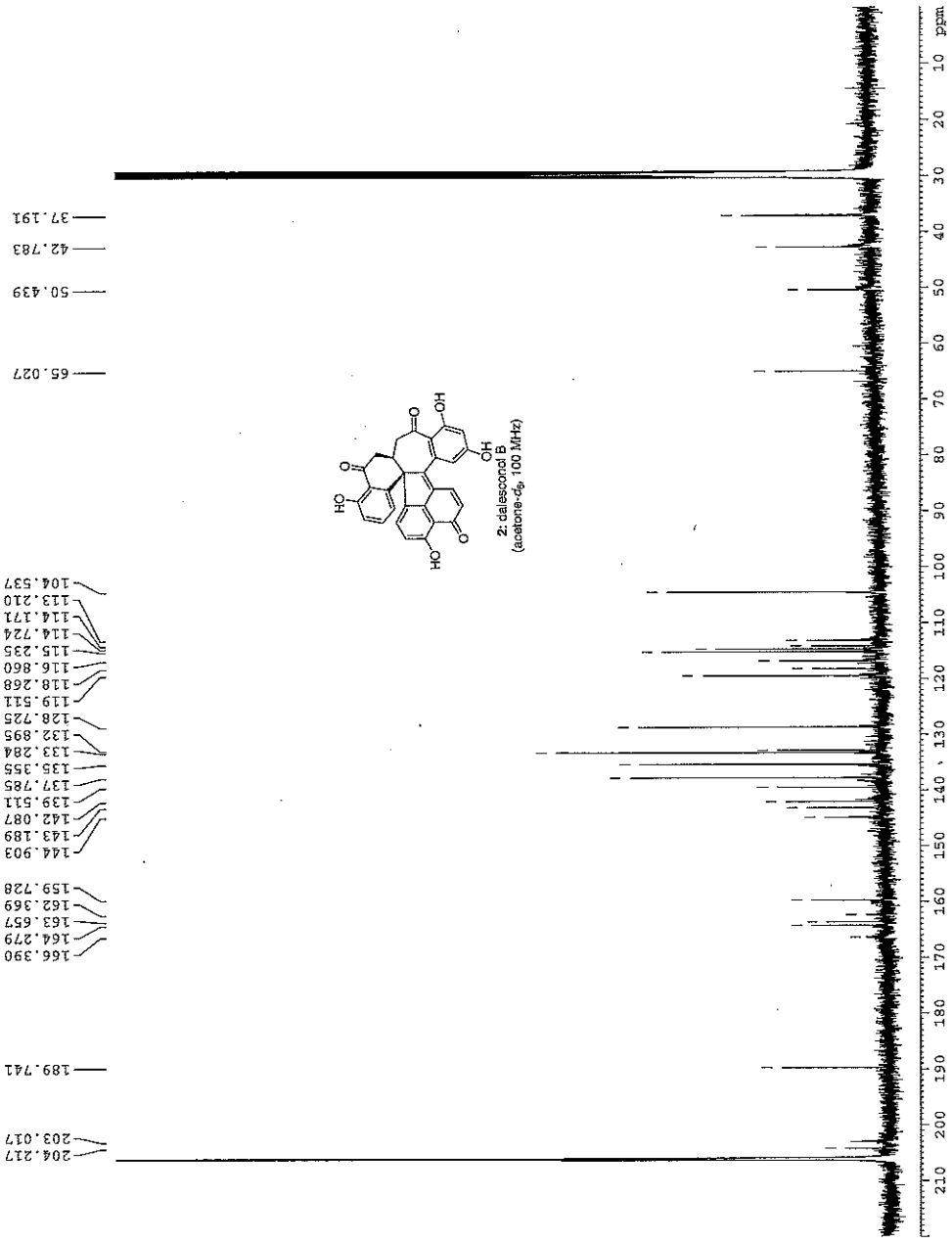

MeO
OMe
MOMO
OMe
62
(CDCl3, 400 MHz)
ppm

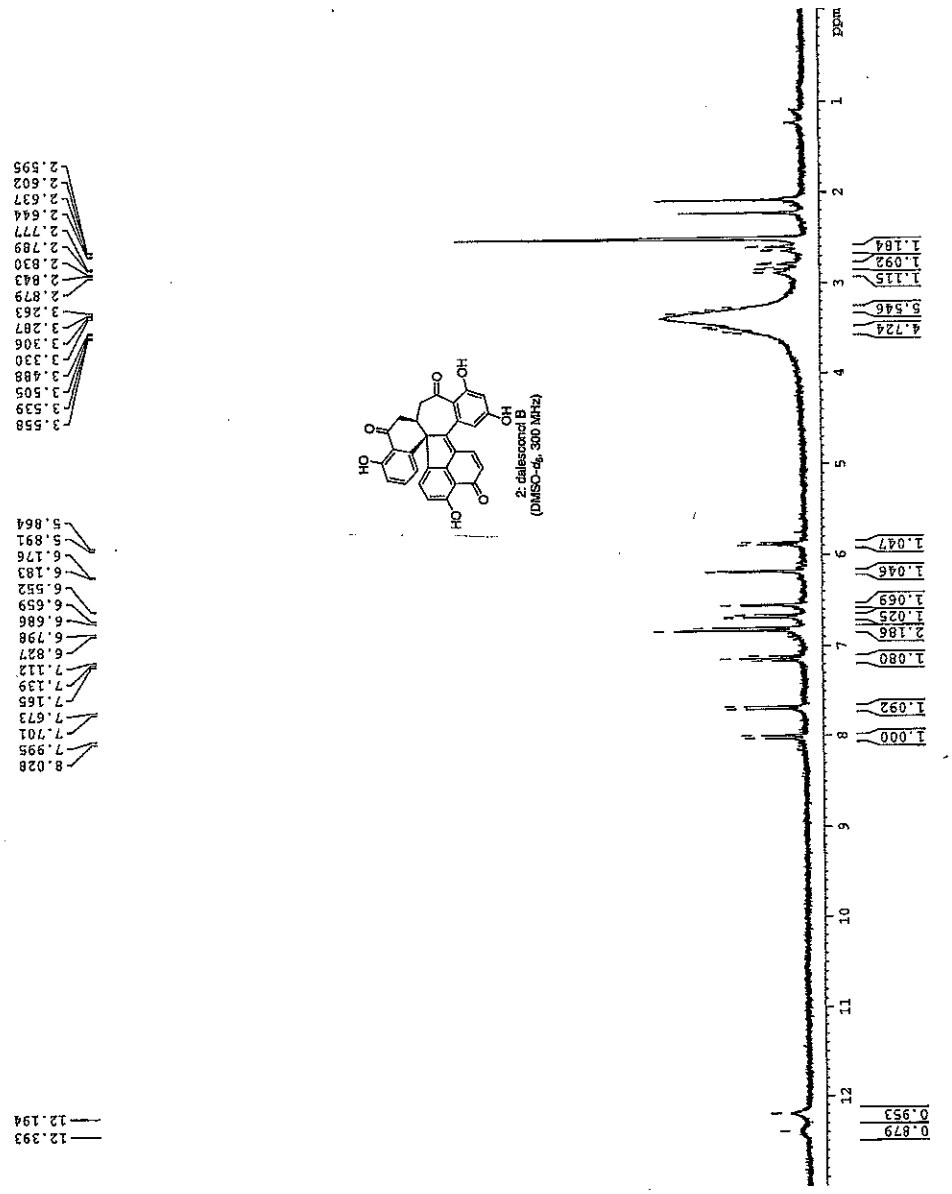

19.050
27.569
39.097
45.823
55.356
55.708
56.113
56.397
56.734
64.661
77.201
97.014
97.728
107.634
107.929
109.970
115.403
115.628
119.588
119.811
120.625
120.871
134.248
139.075
141.435
142.366
143.212
151.558
154.626
157.184
157.946
158.830
159.784
198.242
MeO
MOMO
MeO
OMe
OMe
62
(CDCl3, 75 MHz)
ppm

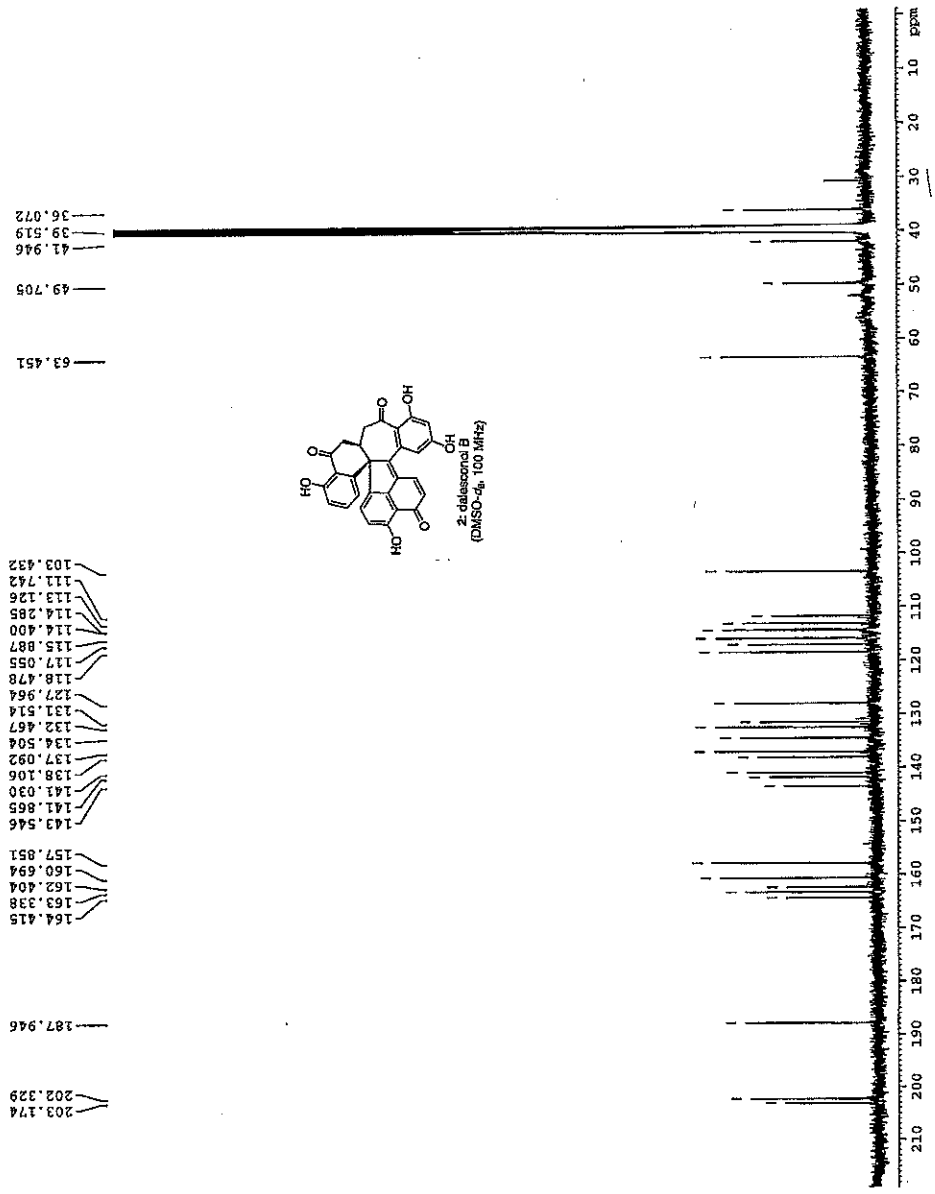

65
(CDCl3, 400 MHz)
OH
OH
HO
O
O
HO
ppm
0
1
2
3
4
5
6
7
8
9
10
11
12
13
1.091
1.307
1.095
1.108
1.136
1.069
1.049
1.043
1.047
1.122
1.072
2.205
1.110
1.019
1.000
0.250
0.266
0.224
0.281
10.840
12.707

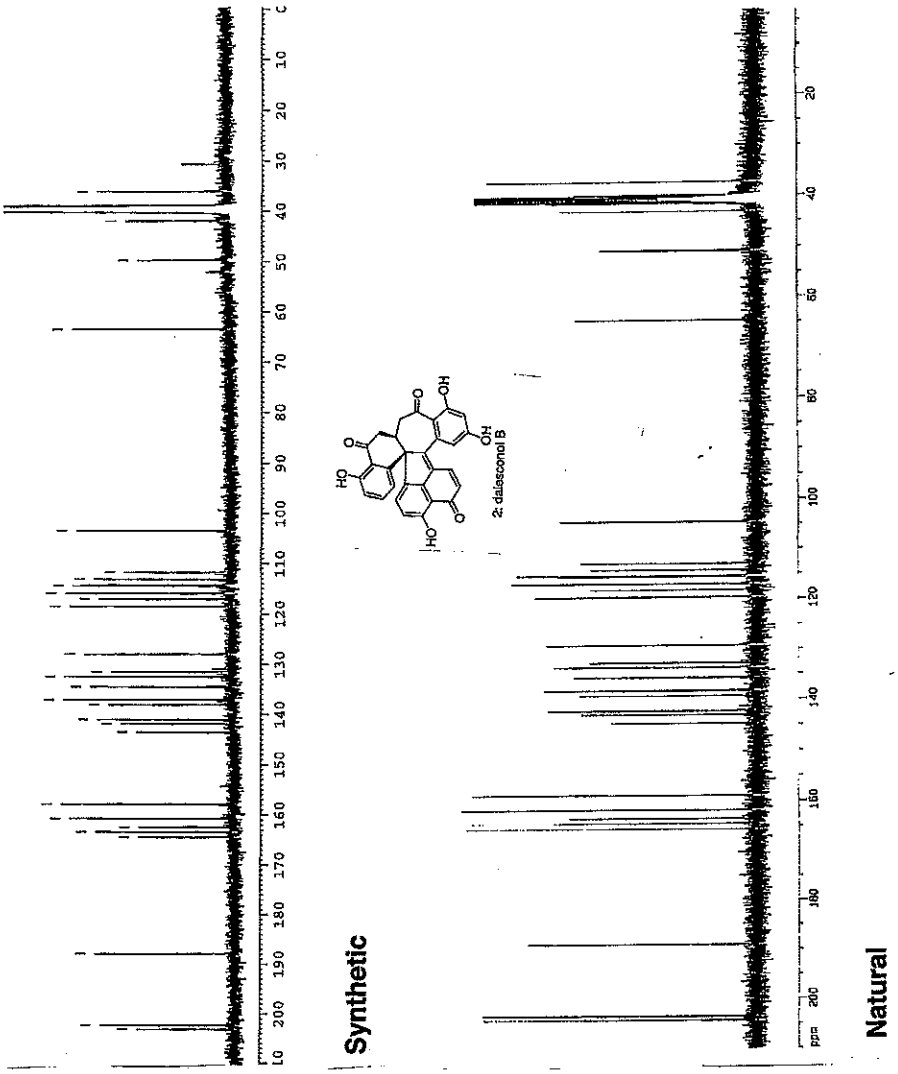

25.292
34.459
46.823
64.671
104.202
112.579
113.867
117.027
117.345
118.939
130.298
132.113
133.743
135.816
137.342
137.978
140.149
142.602
144.130
155.627
156.592
159.487
163.751
165.762
189.856
204.658
65
(CDCl3, 75 MHz)
ppm

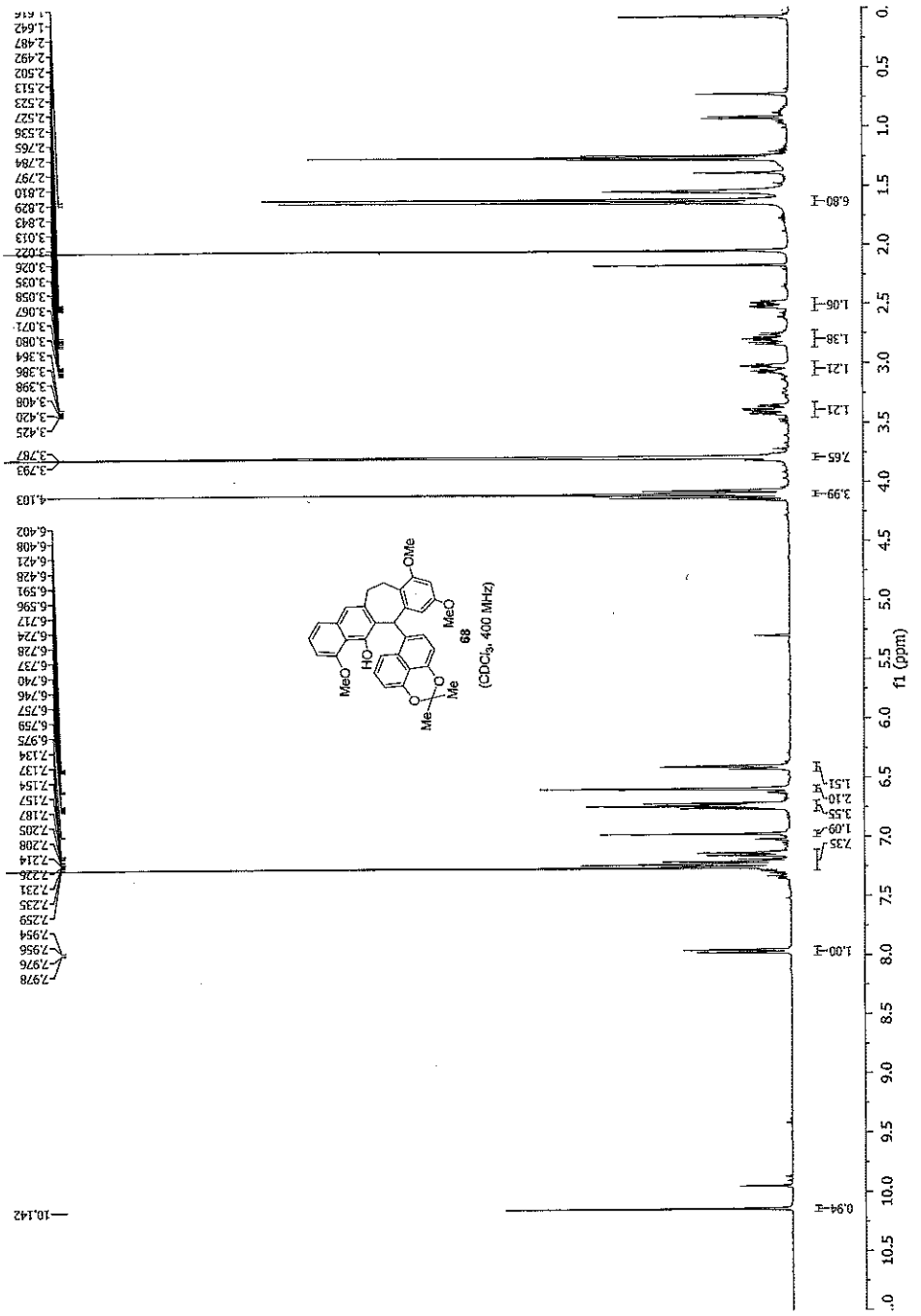

2. dalesconol B
(acetone-d_6, 300 MHz)
ppm

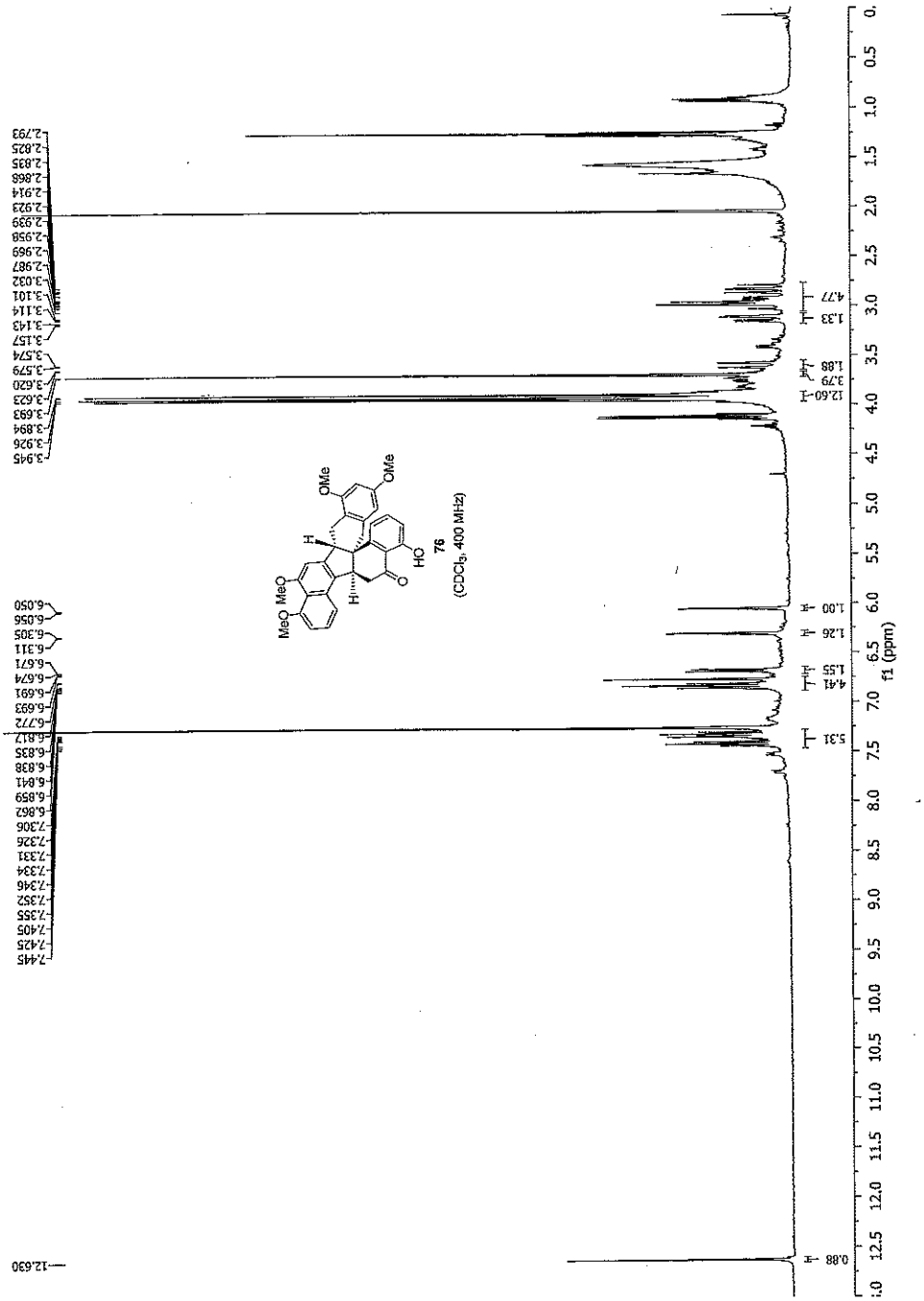

37.191
42.783
50.439
65.027
104.537
113.210
114.171
114.724
115.235
116.860
118.268
119.511
128.725
132.895
133.284
135.355
137.785
139.511
142.087
143.189
144.903
159.728
162.369
163.657
164.279
166.390
189.741
203.017
204.217
2: dalesconol B
(acetone-d6, 100 MHz)
ppm


2: dalesconol B
(DMSO-d_6, 300 MHz)
ppm


36.072
39.519
41.946
49.705
63.451
103.432
111.742
113.126
114.285
114.400
115.887
117.055
118.478
127.964
131.514
132.467
134.504
137.092
138.106
141.030
141.865
143.546
157.851
160.694
162.404
163.338
164.415
187.946
202.329
203.174
2: dalasconol B
(DMSO-d_6, 100 MHz)
ppm


Synthetic
2: dalesconol B
Natural
ppm


OMe
MeO
HO
MeO
Me
Me
68
(CDCl3, 400 MHz)
f1 (ppm)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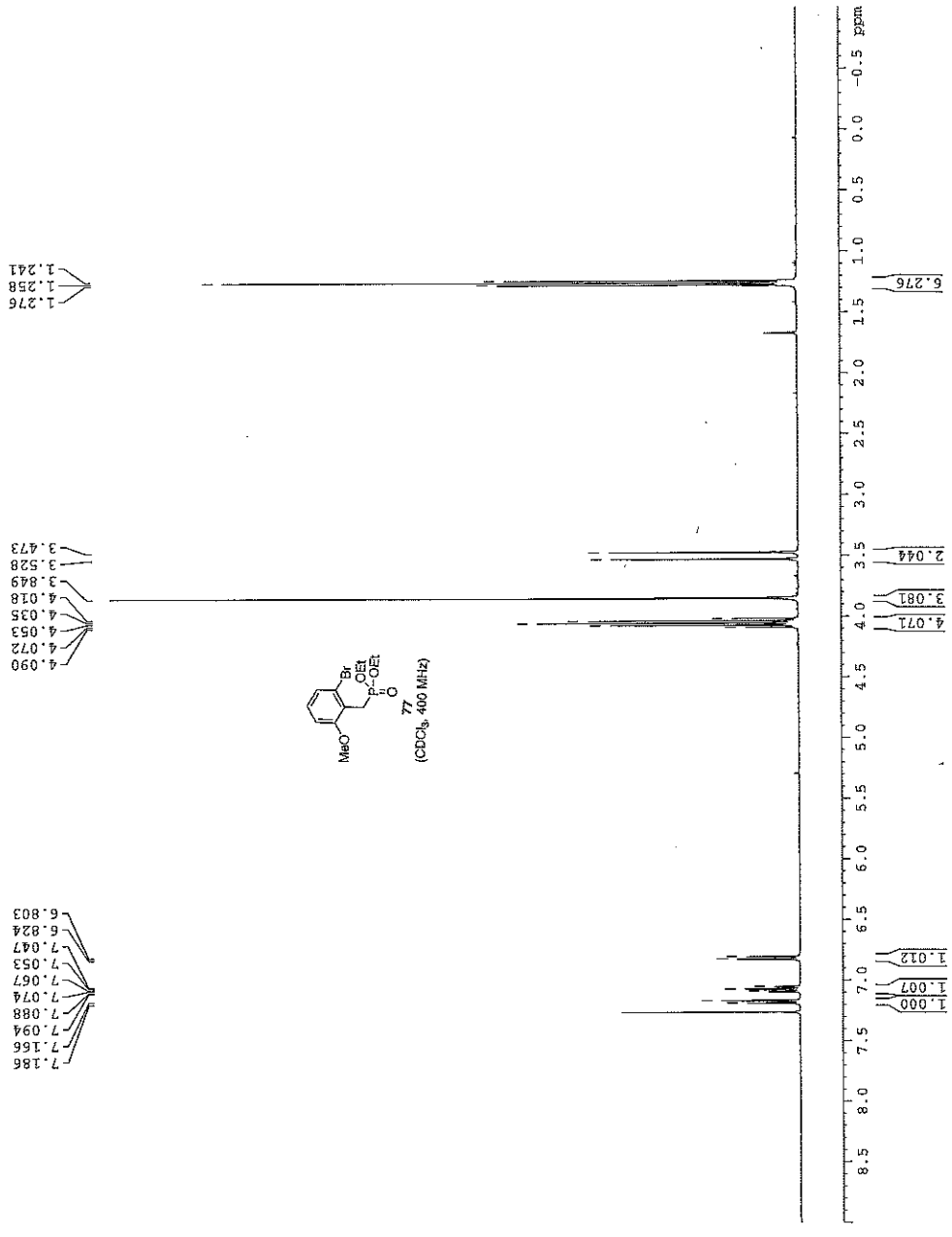
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7.047
7.053
7.067
7.074
7.088
7.094
7.166
7.186
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OEt
P
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O
MeO
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1.000
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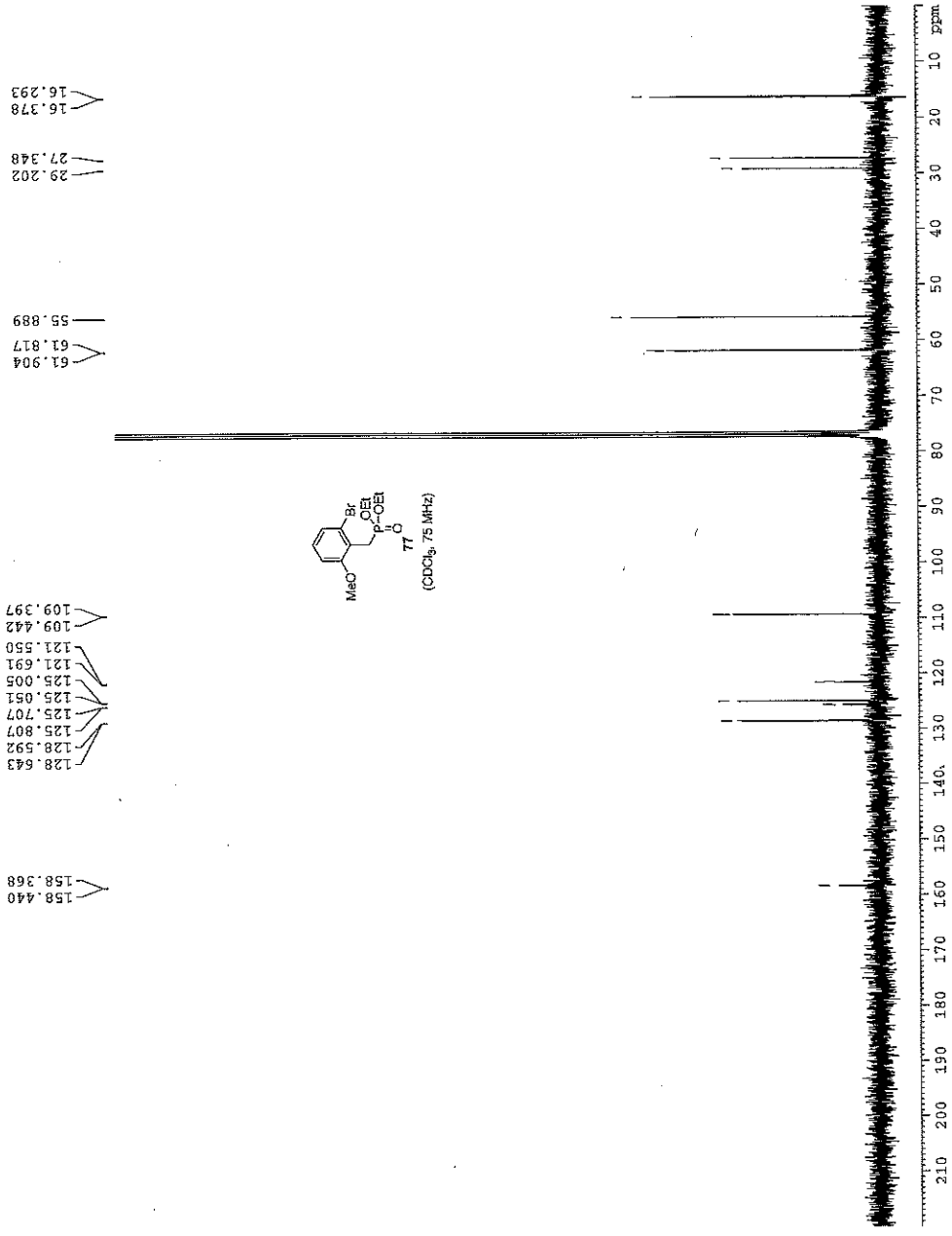
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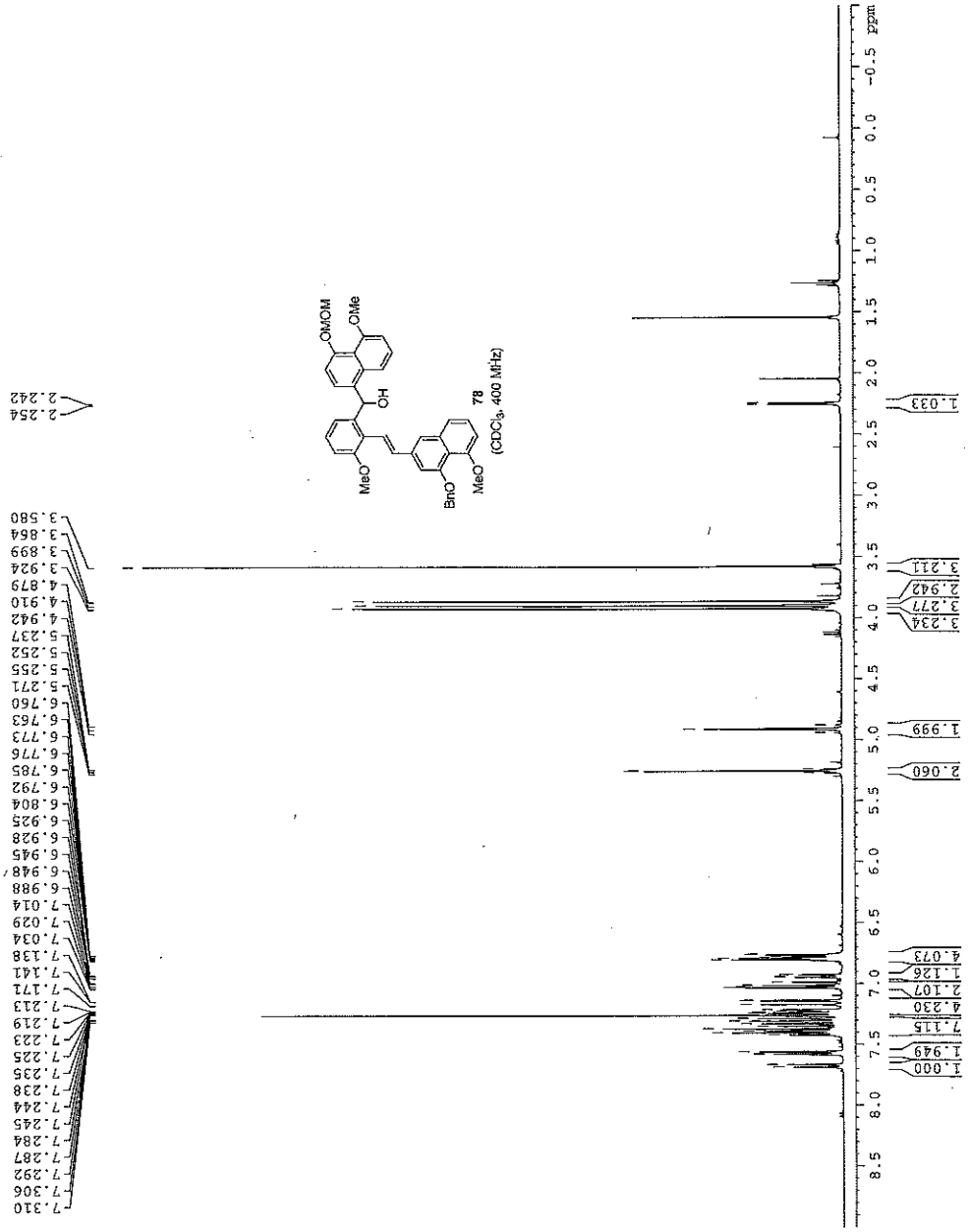
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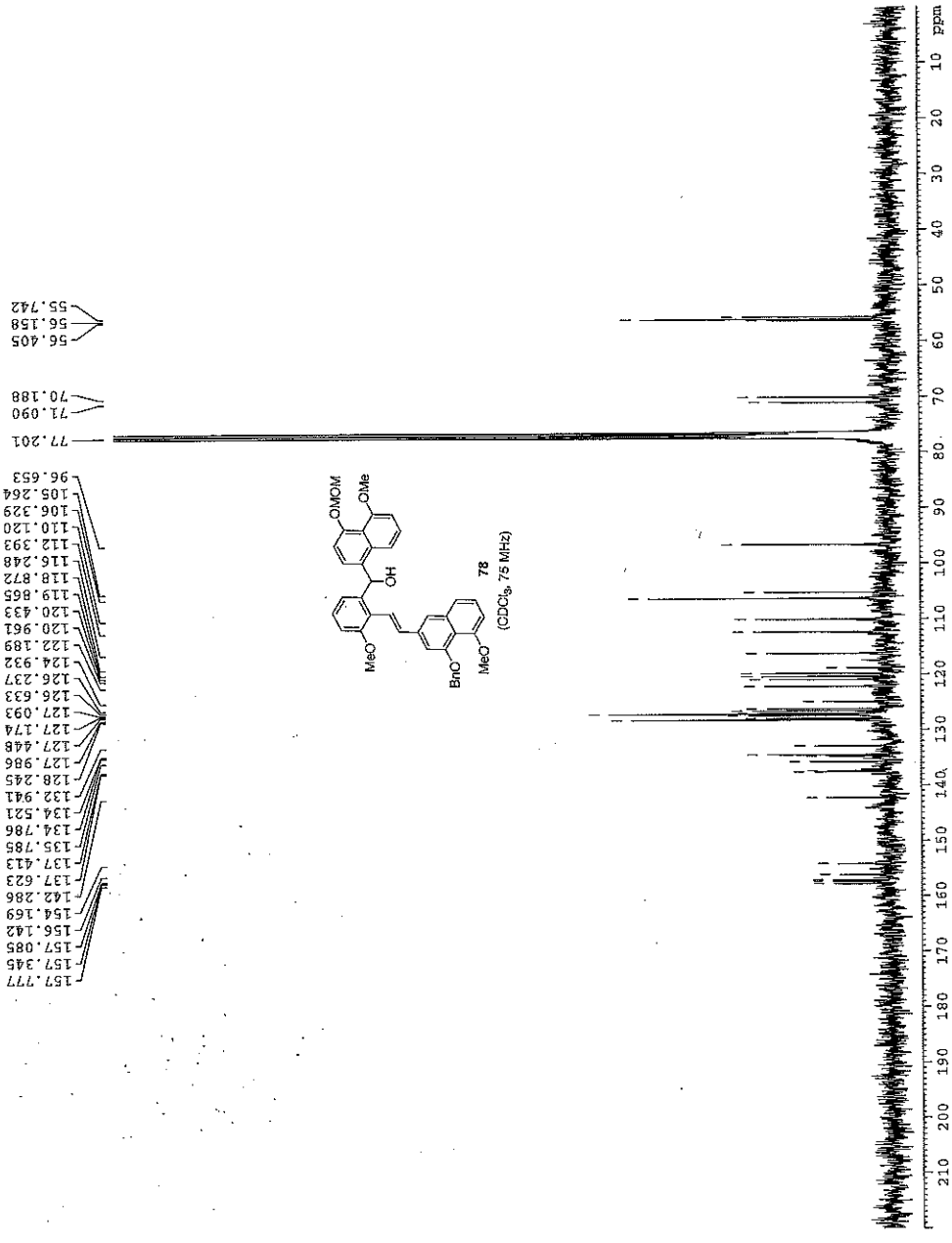
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120.433
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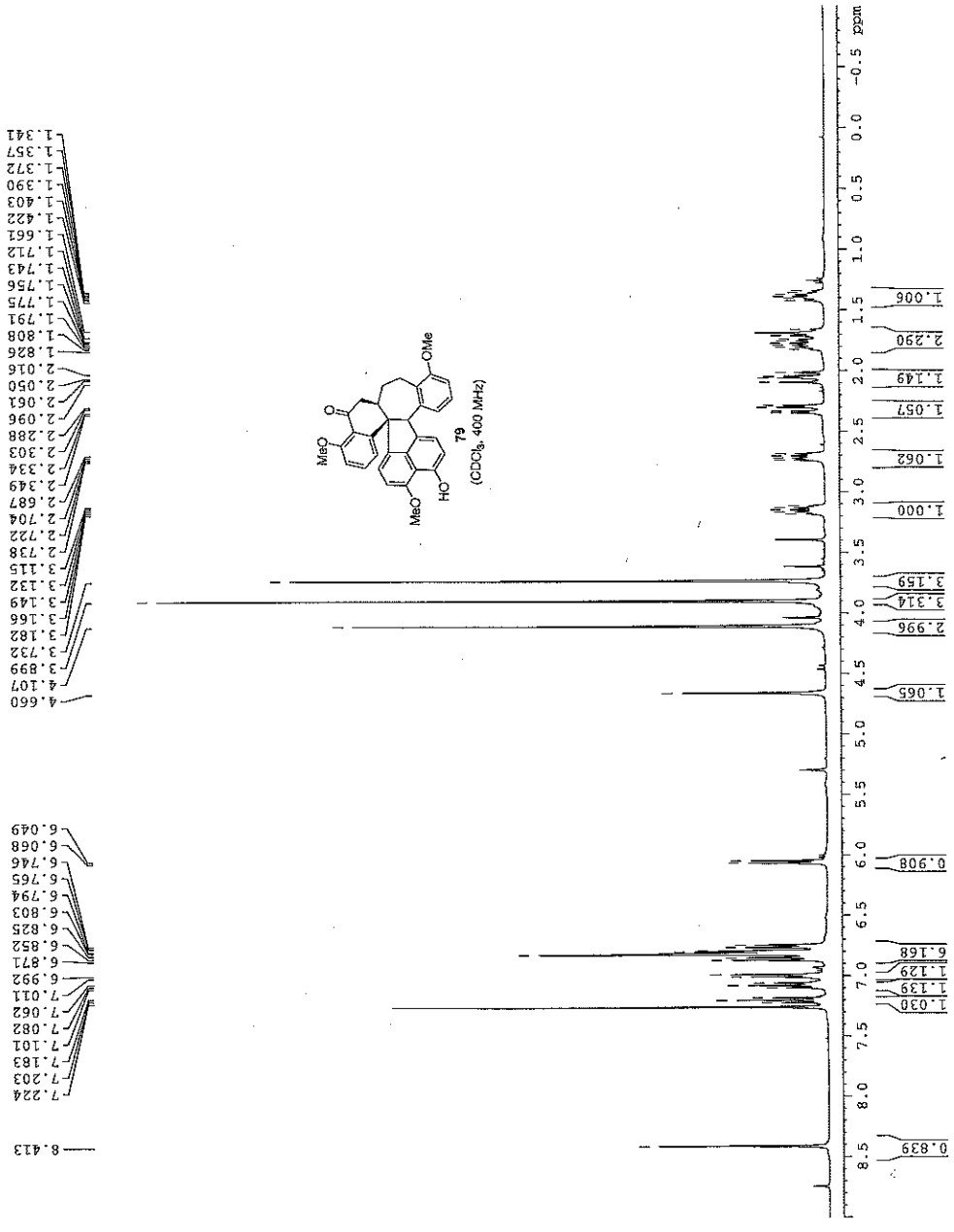
(CDCl3, 75 MHz)
ppm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HO
MeO
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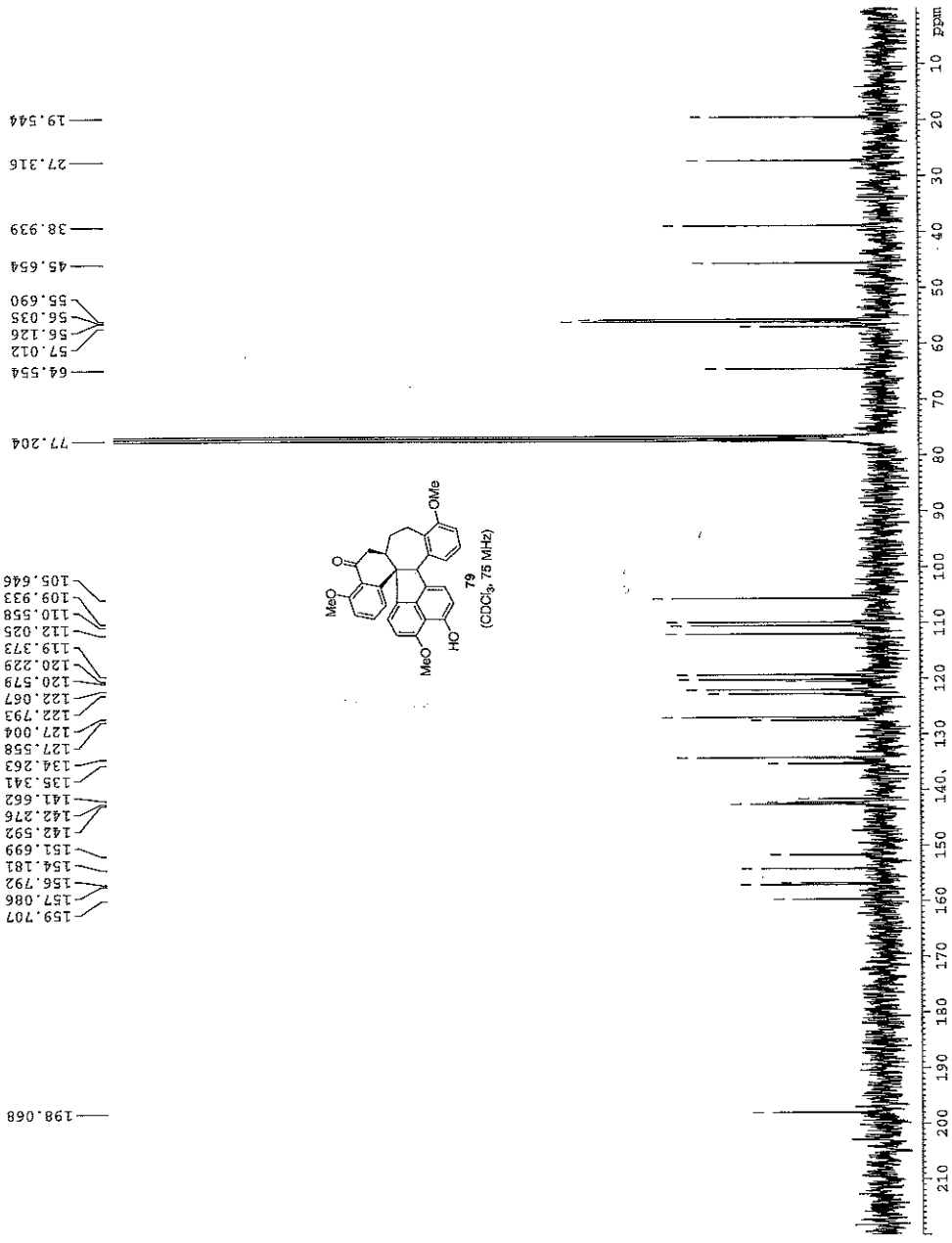
ppm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127.558
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OMe
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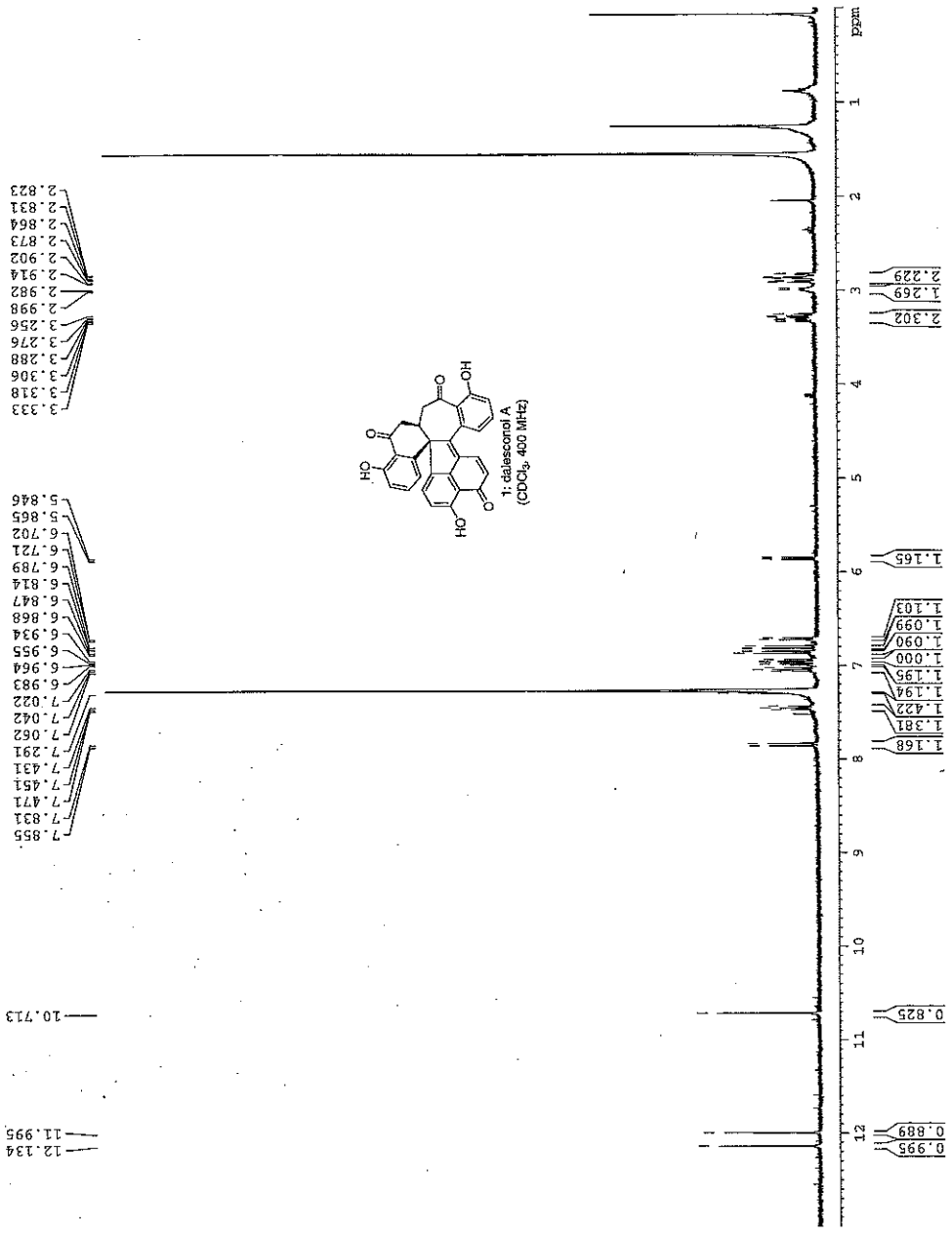
ppm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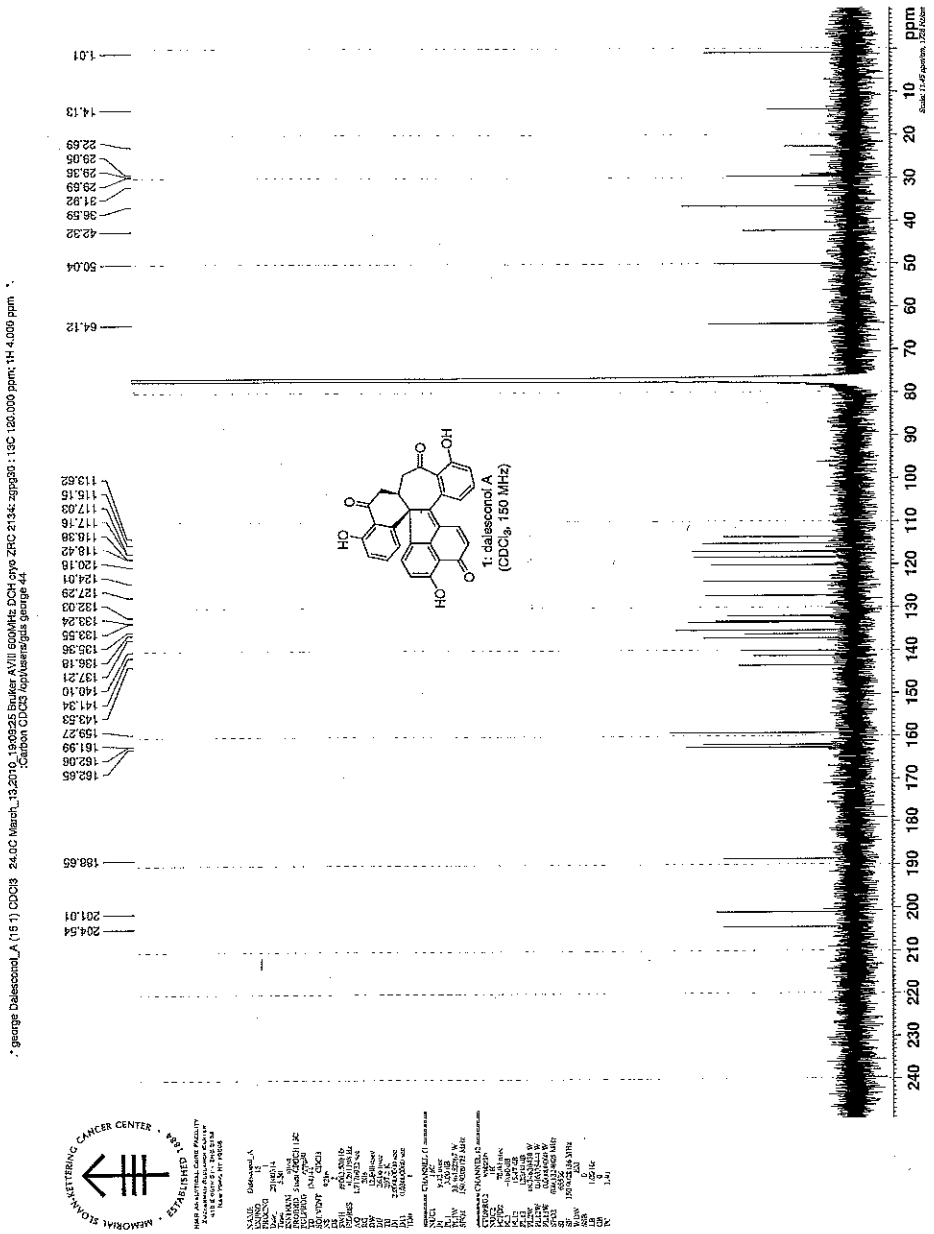
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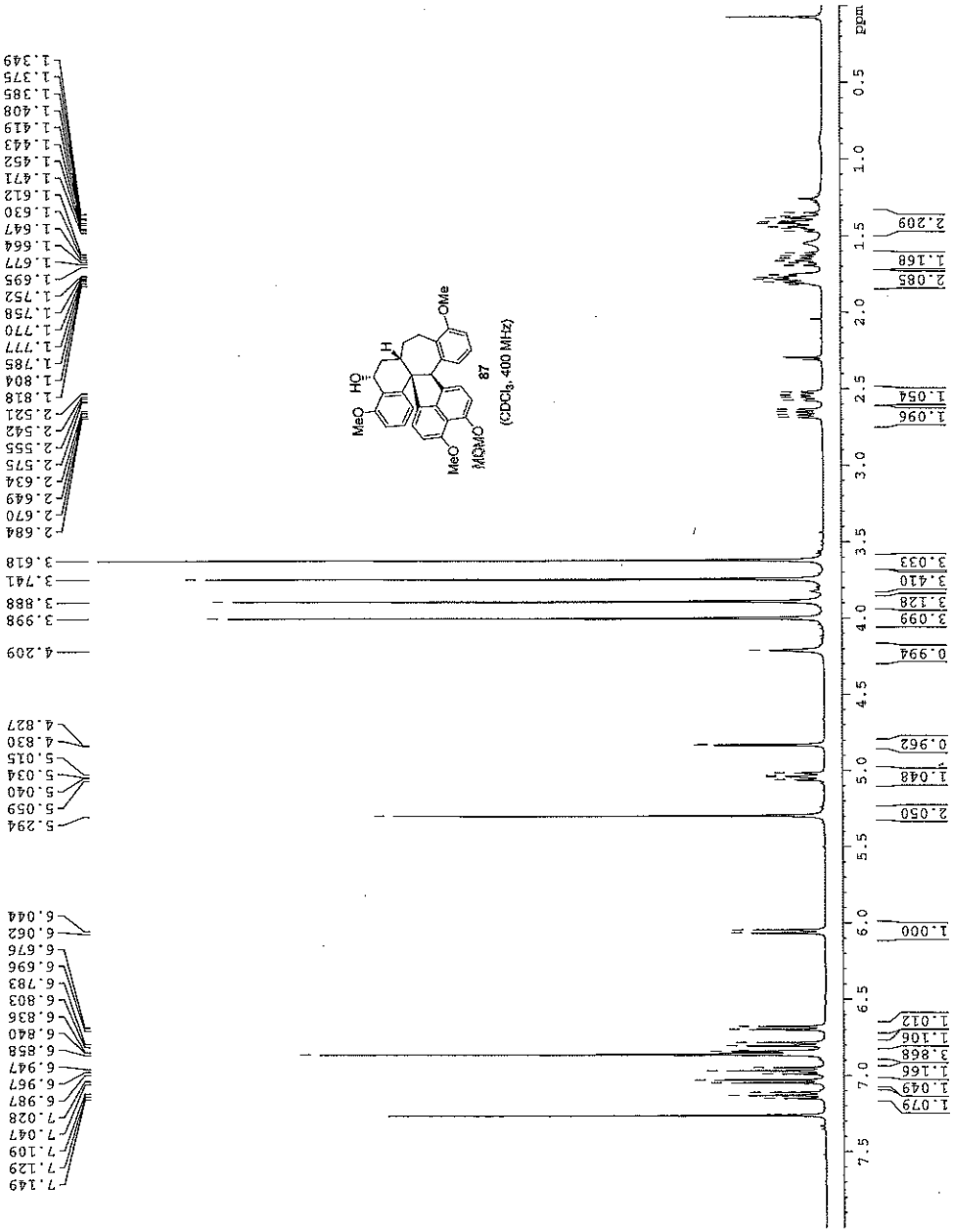
OH
ppm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OMe
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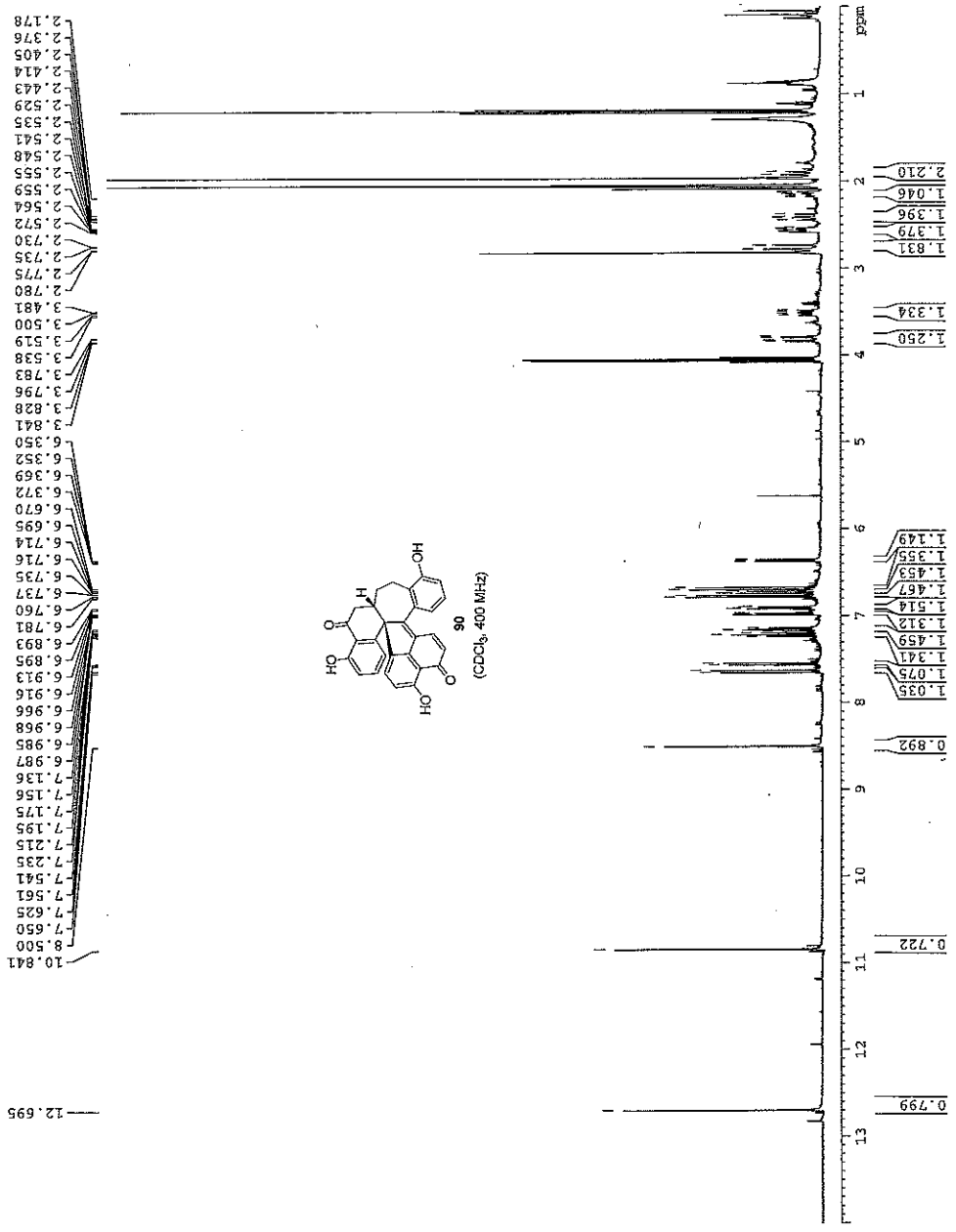
ppm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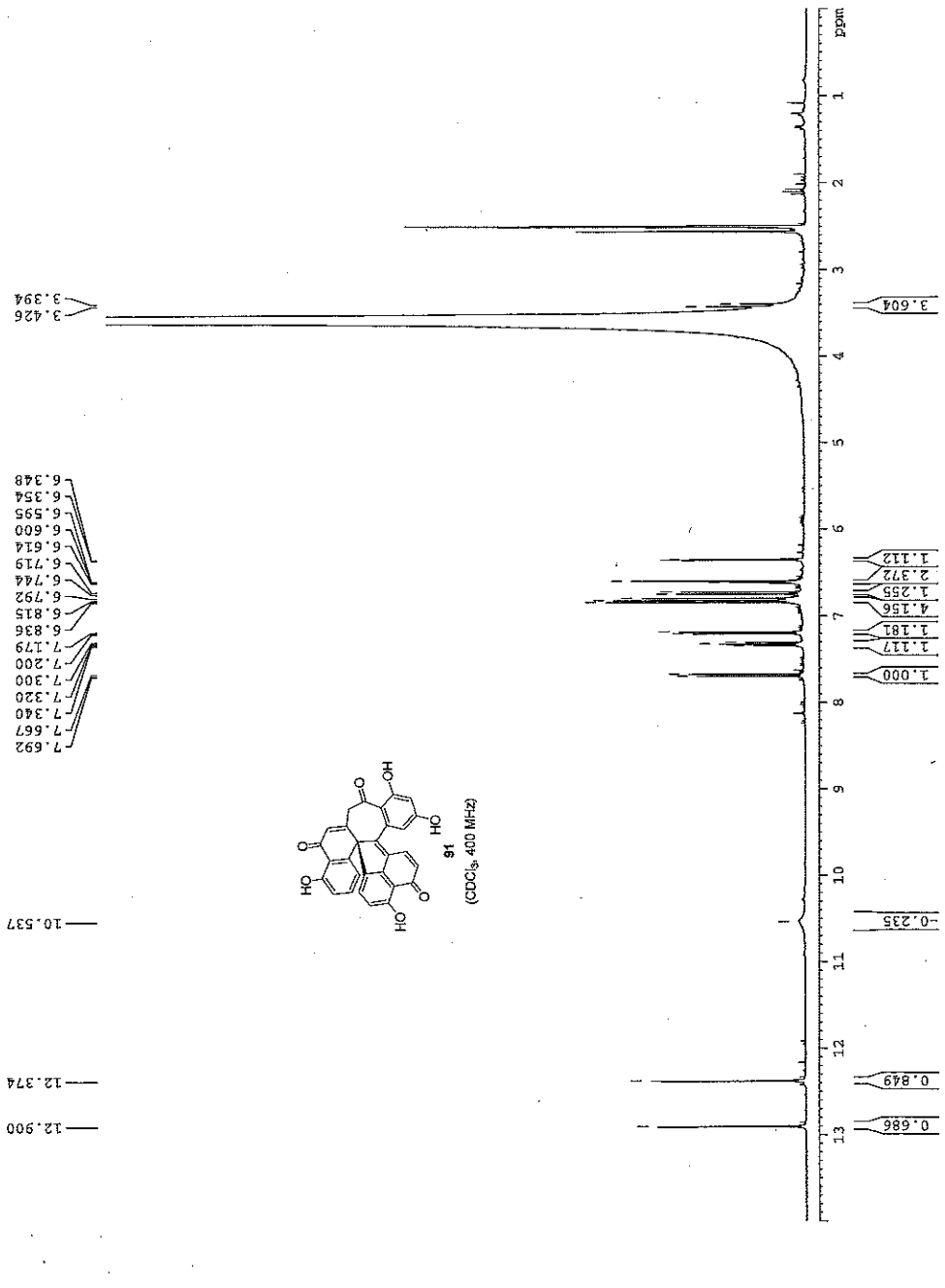
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12.374
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1.255
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1.117
1.000
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0.686
ppm
OH
HO
HO
HO
O
O
O
S1
(CDCl3, 400 MHz)

CHAPTER 2

The Azaphenalene-Containing Coccinellid Defensive Alkaloids

Section 2.1 Introduction

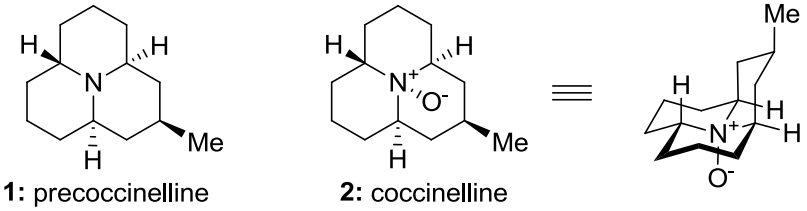
For over four decades, the natural products community has shown interest in the diverse collection of defensive alkaloids produced by many different species of ladybug.[1] When threatened, ladybugs, also known as lady bird beetles or coccinellids, emit bitter tasting drops of orange fluid from their joints called reflex blood.[2] This fluid contains defensive chemicals that have been shown to ward off predators, and the natural products covered in this chapter and shown in Figures 1 – 7 are examples of such compounds obtained from different ladybug species. It should be noted that though there are other structural subclasses of coccinellid defensive alkaloids, Chapters 2, 3, and 4 are specifically focused on those that contain a 2-methyl-perhydro-9b-azaphenalene core, particularly because this structural subtype has many variants and can be found in both monomeric and dimeric assemblies.

Structurally, the 2-methyl-perhydro-9b-azaphenalene alkaloids (henceforth referred to simply as "azaphenalenes") display a rich array of molecular complexity contained within a deceptively simple, 13-carbon skeleton. Despite the similarities of their structures, the fine levels of oxidation patterning and diastereoisomerism found in the oligomeric azaphenalene alkaloids have provided numerous challenges for isolation and synthetic chemists alike, and the remaining chapters will focus on past and present developments in this field. Isolation work, biosynthetic studies, and synthetic approaches will primarily be presented in chronological fashion in this chapter with key contributions of various investigators and marked advancements in the field receiving the most attention. Our own work towards these targets will appear in Chapters 3 and 4.

Section 2.2 Isolation

Section 2.2.1 Precoccinelline and Coccinelline

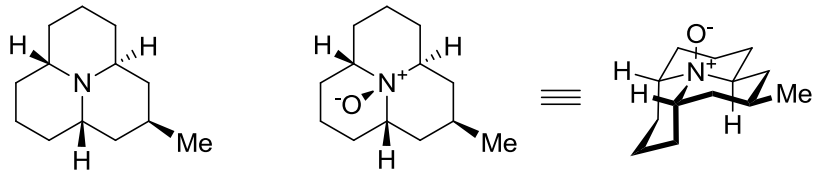
Figure 1. Saturated Monomers Precoccinelline and Coccinelline



Precoccinelline (**1**) and coccinelline (**2**), the first two azaphenalene monomers to be isolated, were reported by Tursch *et al* in 1971 as the defensive alkaloids of *Coccinella septempunctata* (Figure 1). [3] After purification over alumina, individual fractions were tasted for bitterness to determine the presence of a compound of interest, and the repellant properties of these fractions were tested on *Myrmica rubra* ants. Hungry or thirsty ants refused food or water that had been adulterated with these alkaloids. Basic structural information was originally investigated by mass spectrometry and ^{1}H NMR. A key observation made by Tursch and his team is that **2** is the *N*-oxide of **1**. Subsequently, Karlson and Losman fully assigned the framework of coccinelline as **2** through X-ray diffraction of the crystal structure of the hemihydrochloride salt.[4]

Section 2.2.2 Hippodamine and Convergine

Figure 2. Saturated Monomers Hippodamine and Convergine

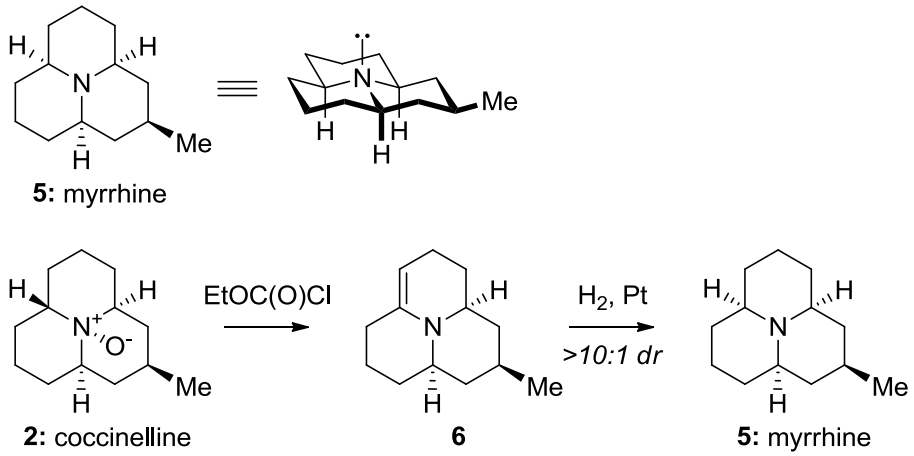


3: hippodamine **4:** convergine

Shortly after the reports on **1** and **2**, Tursch and coworkers reported two additional monomeric alkaloids of a new stereochemical configuration from *Hippodamia convergens* and named them hippodamine (**3**) and convergine (**4**, Figure 2).[5] These molecules both displayed non-symmetric structures on the basis of their ^{13}C NMR spectra, but were presumed to be racemic molecules in the original reports of their isolation due to a lack of optical activity. The structure for convergine was also originally misassigned as a hydroxylated hippodamine derivative instead of the *N*-oxide domain, an error that was corrected by an X-ray crystal structure analysis of its hydrochloride salt. This crystallographic analysis also confirmed the absolute assignment of **4** as that shown in Figure 2, and convergine hydrochloride was ultimately found to have a small, strongly solvent-dependent optical rotation. Intriguingly, this compound is levorotatory in MeOH and dextrorotatory in CH_3CN, CH_2Cl_2, and $CHCl_3$.

Section 2.2.3 Myrrhine

Figure 3. Structure of Myrrhine and its Synthesis from Coccinelline



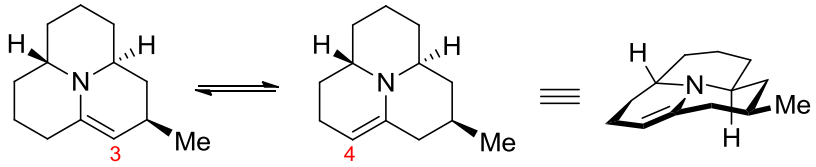
In 1975, Tursch and co-workers reported the isolation of a new monomer with all *trans* ring fusions;[i] this material was named myrrhine (**5**) based on its isolation from *Myrrha octodecimguttata* (Figure 3).[6] **5** is unique among its cousins in that it is the only saturated azaphenalene monomer to exhibit this thermodynamically most stable stereochemical configuration. Intriguingly, no *N*-oxide has been isolated from natural sources thus far, though one has been prepared synthetically. Intense Bohlmann bands in the IR spectrum for **5** confirmed that all of the protons at the ring fusions are axial and *anti* to the nitrogen lone pair. Chemical correlation between **5** and **2** further proved the structure of this new monomer; specifically, Polonovski reaction of **2** and reduction of the resulting enamine **6** from the more accessible face gave predominantly **5**. This stereochemical outcome is only possible for the azaphenalene diastereoisomers designated as myrrhine (**5**) and coccinelline (**2**) due to the known *trans*-elimination

[i] The *trans* ring fusion designation refers to the orientation of the nitrogen lone pair and the ring-fusion hydrogen atom

pathway of the Polonovski process and the arrangement of the ring fusion protons in these monomers.[7]

Section 2.2.4 Propyleine and Isopropyleine

Figure 4. Enamine-containing Monomers Propyleine and Isopropyleine



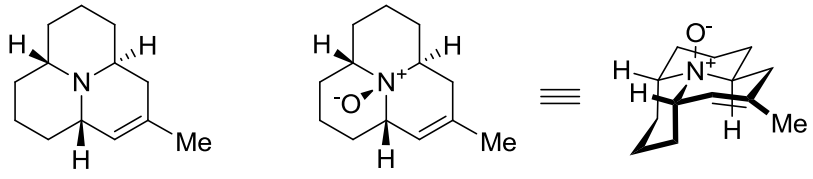
7: propyleine **8:** isopropyleine

Beyond the saturated skeletons discussed thus far, olefin-containing azaphenalene structures have also been reported. Propyleine (**7**, Figure 4) was originally described by Daloze and co-workers in 1972 to be an enamine-containing monomer from *Propylaea quattuordecimpunctata*.[8] This molecule was characterized utilizing ^{1}H NMR, IR, and UV spectroscopy. Furthermore, catalytic hydrogenation of the natural product to the known precoccinelline (**1**) helped to confirm its structure. The *trans* substitution pattern of the saturated ring and enamine olefin cause the structure of **7** to twist such that there is only partial nitrogen lone pair overlap with the olefin π-system, a phenomenon which can be observed in the UV spectrum. The isolated natural product was also observed to be levorotatory, and only one olefin isomer of the contained enamine was originally reported. Eight years later, Mueller and Thompson synthesized racemic propyleine (**7**) and reported that it is actually a minor component of an equilibrium mixture with its enamine isomer isopropyleine (**8**).[9] **7** and **8** were observed in a 1:3 ratio, respectively. Furthermore, Mueller and Thompson reported that catalytic hydrogenation

of this mixture of monomers gave a 2:1 ratio of precoccinelline (**1**) and hippodamine (**3**) and not just **1** as reported by Daloze.

Section 2.2.5 Hippocasine and Hippocasine Oxide

Figure 5. Olefin-containing monomers Hippocasine and Hippocasine Oxide

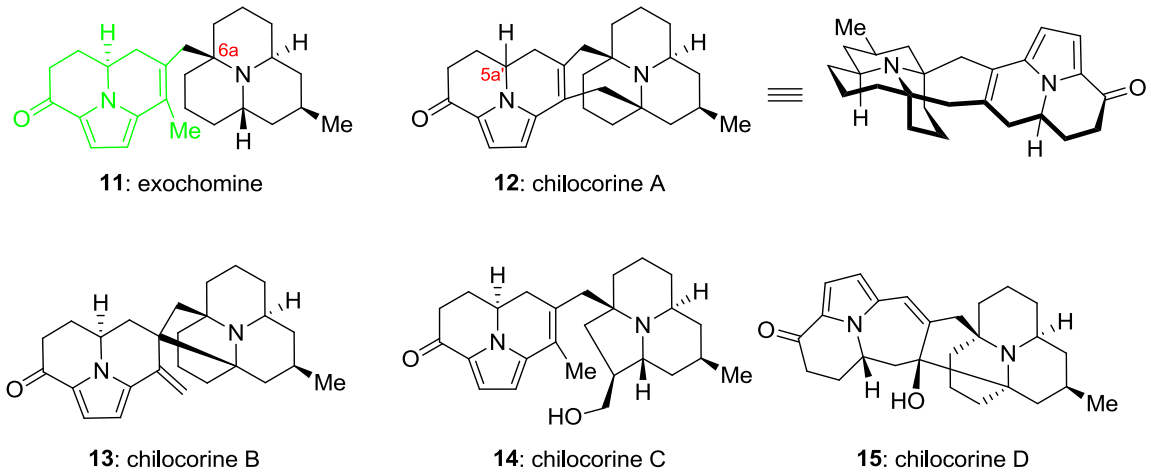


9: hippocasine **10:** hippocasine oxide

In 1976, Ayer and co-workers isolated two new olefin-containing alkaloids from *Hippodamia caseyi* which they named hippocasine (**9**) and hippocasine oxide (**10**, Figure 5).[10] These two alkaloids were assigned on the basis of ^{1}H NMR and X-ray crystallographic analysis to be a new set of olefin-containing azaphenalenes. The feature most unique to these monomers is the vinylic methyl group, a domain which was noted in the ^{1}H NMR spectrum for **10** in the original isolation report. These two new monomers (**9** and **10**) display the same ring-junction stereochemistry as that of hippodamine (**3**) and convergine (**4**), which were also present in the isolate from *H. caseyi*. Dextrorotation was reported for hippocasine oxide, but it does not appear that the absolute configuration of these monomers was assigned. As no enantioselective synthesis of either of these monomers exists, the absolute configuration is still unknown.

Section 2.2.6 Heterodimeric Coccinellid Alkaloids

Figure 6. Heterodimeric Coccinellid Alkaloids



In 1992, Daloze and co-workers reported the first example of a dimeric alkaloid from a ladybug, a heterodimer they isolated from *Exochomus quadripustulatus* and named exochomine (**11**, Figure 6).[11] Possessing a unique 3,4-dimethyloctahydro-8b-azaacenaphthalene ring system (the highlighted portion of **11**) tethered to an azaphenalene at C-6a, this molecule was assigned on the basis of a battery of NMR spectroscopy and X-ray crystallographic analysis. Furthermore, the absolute configuration of exochomine was assigned, noting that the absolute stereochemistry of the azaphenalene portion is the same as the absolute configuration observed for hippodamine and convergine, suggesting biosynthetic relevance. Interestingly, the azaacenaphthalene subunit in exochomine has never been isolated on its own from natural sources, a fact made even more surprising by subsequent isolation reports of other similar heterodimeric species.

In the years following the disclosure of exochomine's structure, four additional heterodimeric molecules were isolated, all of which are closely related to exochomine (**12 – 15**, Figure 6). Chilocorine A (**12**), originally named simply chilocorine, was isolated from *Chilocorus cacti* by Meinwald and co-workers in 1994.[12] This molecule differs from **11** in that there are two dimeric linkages, generating a seventh ring. The structure of this molecule was elucidated through the use of mass spectrometry, 1D and 2D NMR, and UV spectroscopy, but the C-5a' chiral center on the azaacenapthylene was not able to be assigned. The authors noted that if **11** and **12** are as structurally related as they appear to be, the configuration of the unassigned center within **12** is the same as that in **11**.

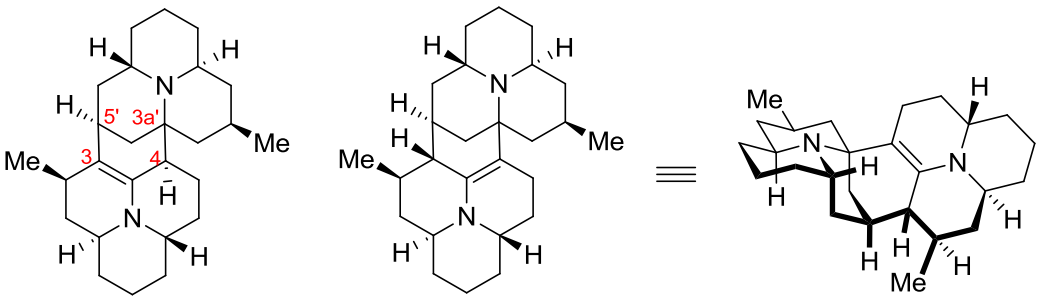
Subsequently, Meinwald and co-workers reported two new dimeric alkaloids from *Chilocorus cacti*: chilocorine B (**13**) in 1995[13] and chilocorine C (**14**) in 1998.[14] The structure of **13** was elucidated on the basis of UV spectroscopy, mass spectrometry, extensive NMR studies, and X-ray crystallographic analysis, allowing assignment of the 5a' stereocenter (as indicated within Figure 6). Chilocorine B is similar to chilocorine A in that it, too, forms a seventh ring through its dimeric linkages. Interestingly, the authors mention observing GC-MS peaks corresponding to a monomeric azaacenaphthalene like the highlighted portion of **11**, but no subsequent reports on isolation or structural elucidation of such a unique monomer exist. The structure of chilocorine C (**14**) was elucidated using similar techniques as those used for chilocorine B, although an X-ray crystal structure was not obtained, which prevented confirmation of the C-5a' ring fusion stereocenter. Again, the authors note that this stereocenter is likely the same as that observed for **11** and **13** as all of these heterodimers are likely biosynthetically related. Notably, the azaphenalene moiety contained in chilocorine C appears to have undergone

a ring contraction to form the shown hydroxymethylene substituent. This feature is unique, not being found in any other isolated member of the oligomeric coccinellid defensive alkaloid class.

Finally, chilocorine D (**15**) was reported by Daloze and co-workers in 2002 from *Chilocorus renipustulatus*.[15] This molecule was assigned on the basis of mass spectrometry, UV spectroscopy, and extensive 2D NMR analyses. Interestingly, the pyrrole-containing half of **15** is modified from all other structurally related molecules such that it is actually no longer an azaacenaphthalene, possessing instead a hydroxylated seven-membered ring. This ring system is unique to chilocorine D in this alkaloid class.

Section 2.2.7 Homodimeric Coccinellid Alkaloids Psylloborine A and Isopsylloborine A

Figure 7. Homodimeric Coccinellid Alkaloids



16: psylloborine A **17:** isopsylloborine A

In addition to heterodimeric structures, homodimers have also been isolated, though they are far fewer in number. In 1998, Schröder and Tolasch reported the isolation and characterization of a new azaphenalene-containing alkaloid from *Psyllobora vigintiduopunctata* (**16**, Figure 7).[16] Characterized through extensive 2D NMR analysis,

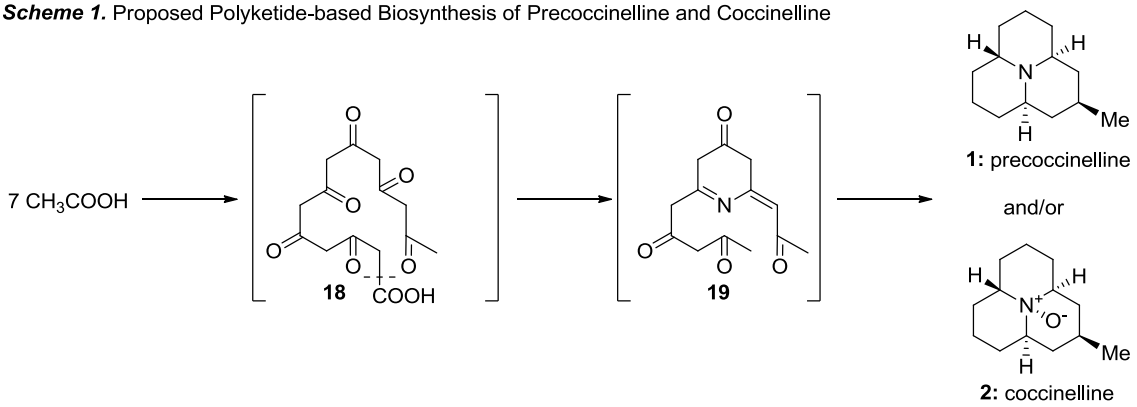
this new molecule contains a 26-carbon skeleton and two nitrogen atoms. Named psylloborine A (**16**), this complex alkaloid is a homodimer composed of two azaphenalene monomers of differing oxidation state. Compared to the monomeric azaphenalenes, the structure of psylloborine A is far more intricate, containing nine, mostly non-contiguous, stereocenters, one of which is quaternary. It also has a central, strained [3.3.1] azabicyclononene formed by the dimeric linkages.

In 1999 another homodimeric alkaloid was reported by Daloze and co-workers: isopsylloborine A (**17**). This molecule was isolated from *Halyzia 16-guttata* and *Vibidia 12-guttata*, along with minor amounts of **16**.[17] This homodimer possesses the same intricate carbon skeleton as **16** and is merely an enamine isomer of psylloborine A, possessing a similar set of challenges for both characterization and synthesis. Isopsylloborine A was characterized through extensive 2D NMR analysis through what appears to be a partial trifluoroacetate salt, though it is difficult to tell exactly which salt form was characterized from the reported data.

It is these two homodimers in particular that attracted our interest in the azaphenalene class of natural products. In Chapters 3 and 4, our explorations into the development of a family-based approach to access homodimers **16** and **17** and related monomeric structures from a common intermediate will be discussed. These studies are congruent with our group's more global interest in the synthesis of oligomeric natural products.[18] Before entering into a discussion of these efforts, however, biosynthetic studies and previous synthetic work must be examined to best understand the current state of the art at the time our studies commenced.

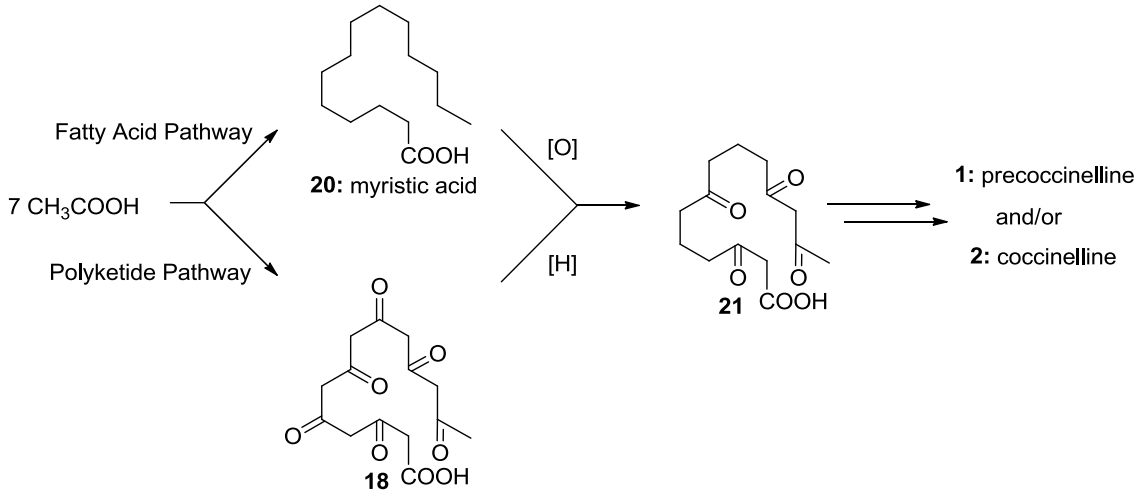
Section 2.3 Biosynthesis

Scheme 1. Proposed Polyketide-based Biosynthesis of Precoccinelline and Coccinelline



Biosynthetically, it was originally assumed that the coccinellid defensive alkaloids were produced endogenously. As noted by the Daloze team, the aphids consumed by *Coccinella septempunctata* do not contain **1** or **2**, leading to the conclusion that the ladybug must have a biosynthetic pathway for the production of these defensive chemicals. In 1975, the first biosynthetic report regarding the coccinellid defensive alkaloids by Tursch *et al*[6] led to the conclusion that a polyketide pathway (Scheme 1) was responsible for the biosynthesis of **1** and **2** on the basis of labeled acetate feeding experiments. As shown in Scheme 1, an acyclic, fourteen-carbon chain was believed to be assembled from acetate subunits, and subsequent introduction of nitrogen, cyclization pathways, and oxidation state manipulations could deliver the final alkaloids.

Scheme 2. Possibility of Fatty-Acid or Polyketide-based Biosynthesis of Precoccinelline and Coccinelline

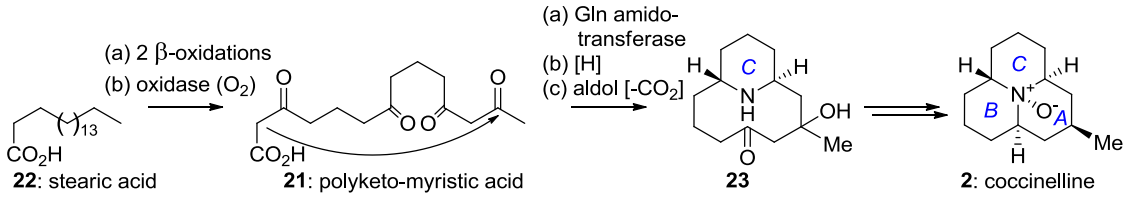


Starting in 2002, experiments reported by Braekman and co-workers modified this initial biosynthetic hypothesis to include an alternative, fatty acid pathway.[19] While the original study on coccinelline biosynthesis clearly indicated that labeled acetate was incorporated into the final structure (**2**), either a polyketide or fatty acid pathway could be operative. Furthermore, it had been shown that a structurally unrelated defensive alkaloid used by the Mexican bean beetle *Epilachna varivestis* was biosynthesized with oleic acid and L-serine, indicating that defensive chemicals produced by related insects are formed endogenously from fatty acids.[20] As shown in Scheme 2, a fatty acid pathway would require a number of oxidative manipulations, while a polyketide pathway would require enzyme-catalyzed reductions to generate coccinelline.

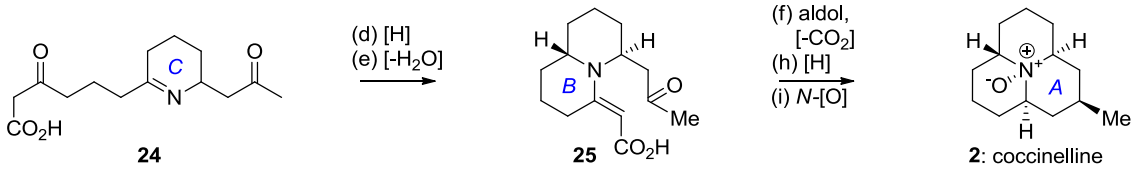
Ultimately, it was concluded that a fatty acid pathway is the operative mode of biosynthesis with the biosynthetic precursor for **2** being stearic acid (**22**) as shown in Scheme 3. Two β-oxidations could remove four carbons from the stearic acid chain and oxidation of the resultant fatty acid framework could generate polyketo-acid **21**, a myristic acid derivative. Feeding experiments with both myristic acid (**20**, 14 carbons)

and stearic acid (**22**, 18 carbons) demonstrated that **22** is the true biosynthetic precursor to the polyketo-acid **21** despite the proposed biosynthetic precursor to **2** having the same carbon count as **20**. After testing various sources of nitrogen, it was concluded that this element is incorporated into the structure by a glutamine amidotransferase; a subsequent aldol condensation and redox chemistry are then presumed to deliver coccinelline (**2**).

Scheme 3. Coccinelline Biosynthesis from Stearic Acid
A. Proposed biosynthesis of coccinelline based on biosynthetic studies



B. Our interpretation and revised proposal for coccinelline biosynthesis



Although this biosynthetic mechanism is plausible on the basis of the experimental evidence, we believe that some of the final mechanistic steps proposed may need adjustment. Specifically, we propose that nitrogenated β-keto-acid **24** condenses with a reduced C-ring amine to form the B-ring in **25** prior to closure of the A-ring. We believe this alternative, with a 6,6-fused ring system (**25**), is more reasonable than the strained [7.3.1] ring structure **23** containing a *trans* substituted C-ring; this structure would likely require significant enzymatic stabilization to prevent enamine condensation once the reactive partners are in such proximity. Indeed, while a structure such as **23** cannot be fully ruled out at this point, it would seem to be an unnecessary expenditure of energy unless such an intermediate with a strained 10-membered ring is required to

obtain the proper stereochemical outcome of **2**. We do agree, however, with Braekman *et al* that the operative pathway is likely conserved across several producing organisms of azaphenalene alkaloids on the basis of structure. We also believe that the biosynthetic studies that have been performed when compared to the wealth of structures isolated for the azaphenalene alkaloids suggests that the biosynthetic divergence occurs in the final redox manipulation steps (from **25** to **2**, for instance) which would establish different diastereomeric products and/or olefin isomers.

In terms of dimeric biosynthesis, it has been proposed that an azaphenalene and azaacenaphthalene unite to form heterodimers **11** – **15** (Figure 6) and that two azaphenalene monomers unite for homodimers **16** and **17** (Figure 7). Beyond these notions, there has been no true investigation of how these molecules arise in Nature. Our proposal for the biosynthesis of **16** and **17** will be explored at length in Chapter 3, but since this chapter surveys previous work and this section focuses specifically on experimentally validated biosynthetic hypotheses, our proposal will not be covered here.

Section 2.4 Previous Synthetic Work

In the decades since Tursch and colleagues first reported their isolation and characterization of coccinelline and precoccinelline, synthetic chemists have developed a variety of methods and strategies for the formation of the azaphenalene ring system. The following sections survey the key steps utilized by the many investigators who have demonstrated that finely honed synthetic ingenuity allows access to every monomeric structure isolated for this class. Missing from the literature are any completed studies

towards the syntheses of heterodimers **11** – **15**, and there exist no reports of any kind concerning the synthesis of homodimers psylloborine A (**16**) and isopsylloborine A (**17**). The lack of reports concerning these molecules is a major component of what attracted our initial attention to this compound collection, as many groups have already demonstrated that monomeric coccinellid defensive alkaloids are well within reach with current methods. It is with all of the following work in mind, however, that our program to develop a unified synthesis of monomers and dimers was forged.

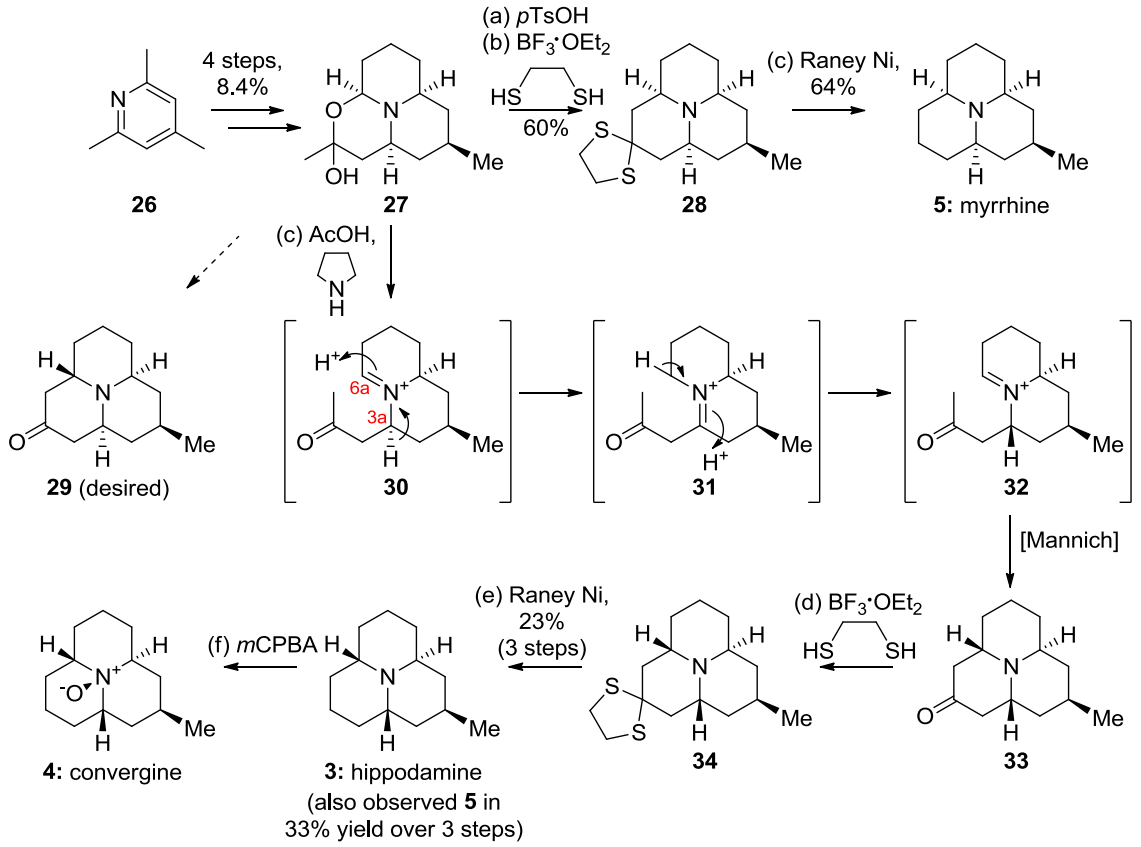
Section 2.4.1 Syntheses of Saturated Monomers through a Mannich Cascade Sequence

In 1975, Ayer and co-workers reported the first synthesis of any azaphenalene alkaloid.[21] Their strategy took advantage of a ketal/acetal ring opening/Mannich cascade starting from substrate **27**, itself prepared from 2,4,6-*sym*-collidine in 4 steps and 8.4% overall yield (Scheme 4). Varying reaction conditions enabled the preparation of either myrrhine (**5**) or hippodamine (**3**) from the same tricyclic intermediate **27**, and defunctionalization after the Mannich cascade provided three natural products (**3**, **4**, and **5**) in short order (i.e. seven, eight, and seven steps, respectively).

To obtain myrrhine, **27** merely needed to be heated with *p*TsOH in toluene to undergo dehydrative ring-opening and Mannich closure (Scheme 4). The resulting ketone was unstable and was immediately converted into dithiolane **28** with ethanedithiol and BF_3•OEt_2 in 60% yield. Finally, Raney-Ni desulfurization delivered myrrhine (**5**) in 64%

yield to complete a seven-step synthesis of the target which proceeded in 3.2% overall yield.

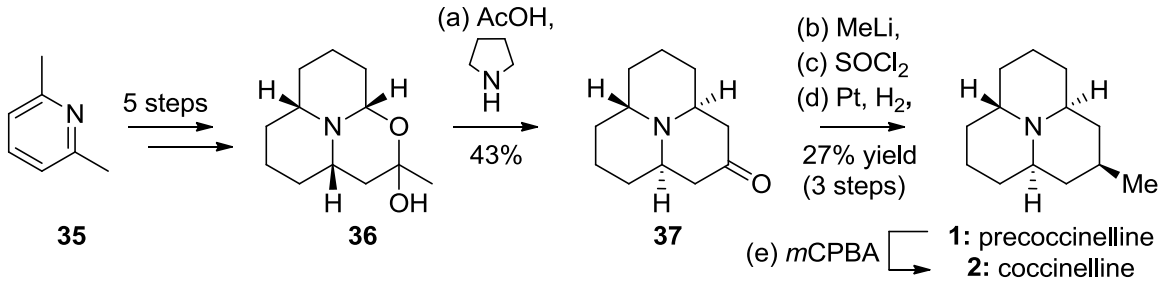
Scheme 4. Ayer's Synthesis of Myrrhine, Hippodamine and Convergine



Attempting to obtain another monomer, **27** was then treated with different conditions to undergo a similar cascade. The expected result intermediate **29**, a proposed precursor to precoccinelline (**1**), through Mannich closure of intermediate **30** on C-6a from the opposite face as that attacked to achieve myrrhine. To their surprise, however, they observed not precoccinelline, but instead hippodamine (**3**) after a similar dithiolane formation and desulfurization process as that outlined above for **5**, and **3** was easily converted into convergine (**4**) through the action of *m*CPBA (yield unreported). The result of this cascade process is surprising because it requires not only opposite facial

selectivity for the Mannich reaction at C-6a, but epimerization at C-3a, as well. This result is believed to be derived from scrambling of the iminium in **30** through proton exchange and epimerization of the acetonyl side chain. Overall, hippodamine (**3**) was obtained in seven steps and 1.9% overall yield from 2,4,6-*sym*-collidine.

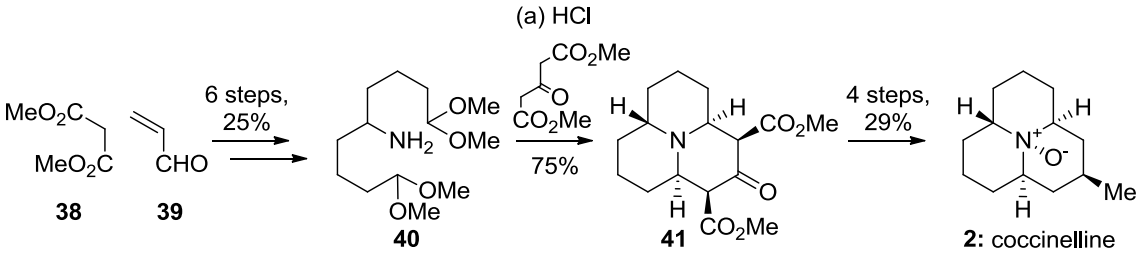
Scheme 5. Ayer's Synthesis of Precoccinelline and Coccinelline



In order to obtain precoccinelline (**1**), Ayer and co-workers employed a similar strategy but started with 2,6-lutidine instead of 2,4,6-*sym*-collidine (Scheme 5).[22] In five steps (yield unreported for one of these operations), tricyclic ketal/acetal derivative **36** was obtained similarly as described in Scheme 4. The same AcOH and pyrrolidine-mediated epimerization/Mannich cascade reaction in this case delivered the desired tricyclic ketone **37** in 43% yield with another isomer with all *trans* ring fusions (unshown) also obtained in an equal amount. Conversion of the ketone within **37** into the lone methyl group of the framework proved relatively straightforward, with precoccinelline (**1**) thusly being obtained in nine steps from 2,6-lutidine. Coccinelline (**2**) was obtained via treatment of **1** with *m*CPBA (yield unreported); overall, **2** was synthesized in ten steps. It was also reported that the *trans* ring fusion isomer of **37** could be converted into myrrhine (**5**) using the same process as that outlined to obtain **1**.

Section 2.4.2 Synthesis of Precoccinelline and Coccinelline using the Robinson-Schöpf Reaction

Scheme 6. Stevens' Synthesis of Precoccinelline and Coccinelline

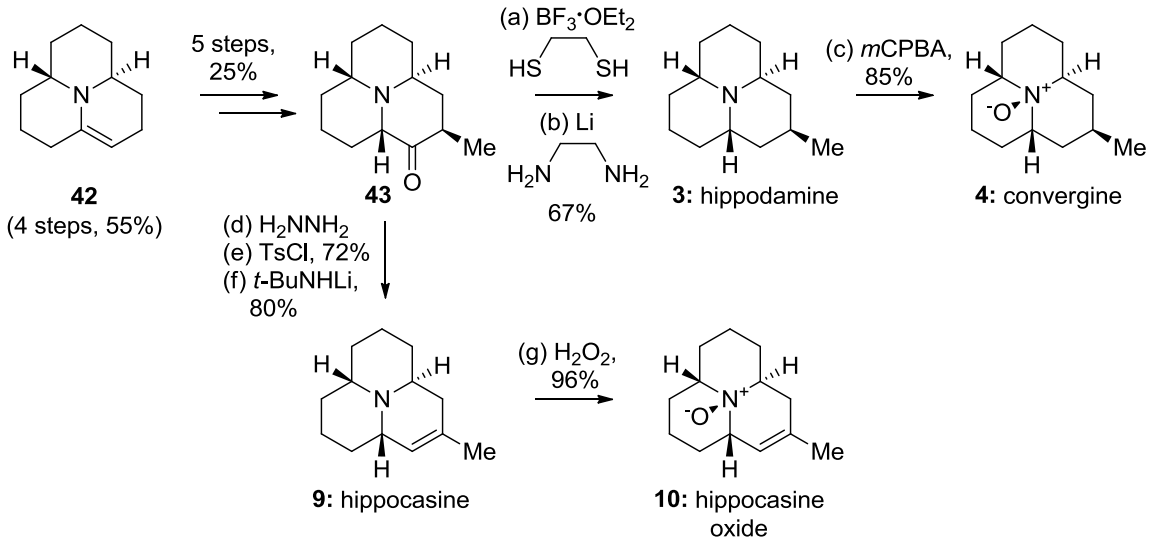


In 1979, Stevens and Lee targeted ketone **37** utilized by Ayer and co-workers in their own preparation of precoccinelline and coccinelline.[23] In this synthesis, the goal was to utilize the Robinson-Schöpf reaction, a transformation which featured prominently in the classic cascade synthesis of tropinone as a key element of ring construction.[24] Thus, key amine precursor **40** was prepared in six relatively standard steps and 25% overall yield. Subsequent treatment with HCl and acetone dicarboxylic acid methyl ester yielded tricycle **41** in 75% yield through the Robinson-Schöpf cascade reaction consisting of two Mannich reactions. This event proceeded in a diastereoselective manner, an outcome believed to be the result of axial attack of the resultant iminium for both Mannich processes. Finally, decarboxylation of **41** (to afford **37**, cf. Scheme 5) and conversion of the contained ketone into the lone methyl group delivered precoccinelline (**1**, yield unreported), and *m*CPBA of this monomer provided coccinelline (**2**) in 29% overall yield from key cascade product **41**. This approach constitutes a ten-step synthesis of **1** and an eleven-step synthesis of **2** (5.4% overall yield).

Section 2.4.3 Syntheses of all Azaphenalene Monomers from a Key Tricyclic Intermediate

Several disclosures from Mueller and co-workers from the mid-1970's into the early 1980's explored a general approach to synthesize the entire collection of azaphenalene monomers, and a full article in 1984 unified their work in a concise manner.[9,25] Enamine substrate **42** (Scheme 7) and its epimer **47** (Scheme 10) were used to access every azaphenalene monomer in Mueller's strategy, detailed below. As part of these efforts, enamine substrate **42** was converted into ketone **43** (Scheme 7), itself a common intermediate used to access six of the targeted structures. This ketone was prepared in nine steps and 14% overall yield.

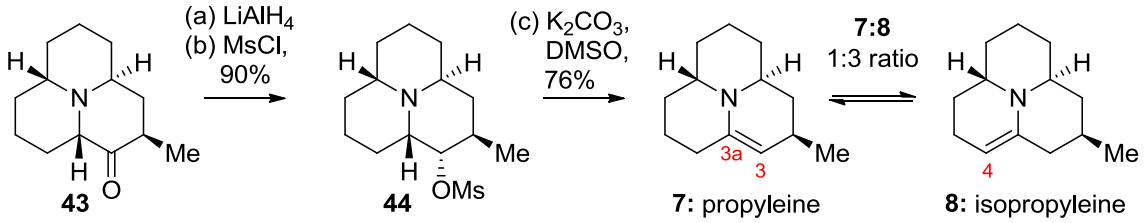
Scheme 7. Mueller's Synthesis of Hippodamine, Convergine, Hippocasine, and Hippocasine Oxide



Enamine **42** (4 steps, 55% yield from commercial materials) was used to produce ketone **43** via a series of straightforward manipulations, and this ketone intermediate was first deployed to access hippodamine (**3**), convergine (**4**), hippocasine (**9**), and hippocasine oxide (**10**) (Scheme 7). As shown, **3** was accessed from **43** through

dithiolane formation and desulfurization of the resultant material in 67% yield across two steps; overall, **3** was accessed through an eleven-step synthesis with 9.2% yield. Oxidation of **3** to **4** was accomplished in 85% yield to give a twelve-step, 7.8% overall yield of this natural product. Conversion of **43** into hippocasine (**9**) was accomplished through a three-step Bamford-Stevens protocol to generate the olefin contained in **9**, resulting in a twelve-step synthesis of hippocasine in 7.9% overall yield. Hydrogen peroxide treatment of **9** gave **10** in 96% yield, resulting in a thirteen-step synthesis of **10** in 7.6% overall yield.

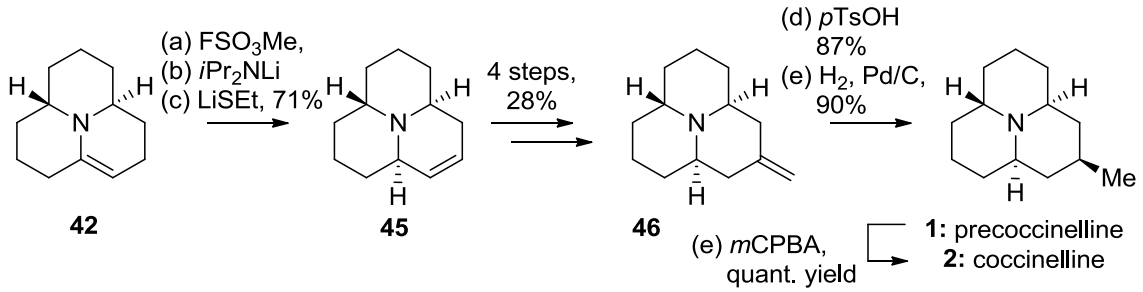
Scheme 8. Mueller's Synthesis of Propyleine and Isopropyleine



Next pursuing enamine monomers propyleine (**7**) and isopropyleine (**8**), ketone **43** was now reduced to an alcohol and converted into a mesylate leaving group (**44**) in 90% yield (Scheme 8). Treatment of this compound (**44**) with K_2CO_3 in DMSO then gave **7** and **8** as a rapidly equilibrating mixture of isomers in a 1:3 ratio. The authors discuss the possibility of this process proceeding through two different mechanisms. If elimination proceeded through an E2 process to give only **7**, equilibration of **7** to the observed mixture of **7** and **8** could occur through subsequent proton exchange. Alternatively, an E1 process could ionize the mesylate within **44**, and an iminium ion could form at C-3a after [1,2]-hydride migration. Deprotonation from either C-3 or C-4 would give **7** or **8**. The authors believe the E1 process is operative, but it cannot be ruled out that the reaction

could also proceed through an E2 pathway. Either way, it was also demonstrated that **7** and **8** rapidly interconvert in deuterated MeOH through proton exchange evidenced by disappearance of the C-3 and C-4 enamine protons within 5 minutes of NMR observation. This work reflects the only reported total synthesis of propyleine (**7**) and isopropyleine (**8**) and required twelve steps with an overall yield of 9.4% for these two compounds combined.

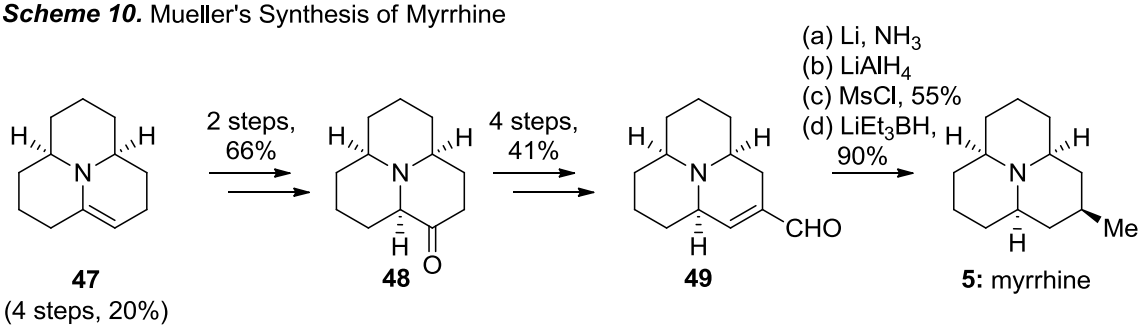
Scheme 9. Mueller's Synthesis of Precoccinelline and Coccinelline



Applying his strategy to precoccinelline (**1**), Mueller and his team again utilized tricyclic enamine **42**. First, isomerization to allylic amine **45** was accomplished in a three step process (Scheme 9). Kinetic formation of the methylammonium salt of **42** was accomplished with $MeSO_3F$, and deprotonation with LDA followed by proton capture from the ring junction established the new stereocenter. To unveil the free amine within **45**, LiSEt was used to demethylate and give the target structure in 71% yield across three steps. Four routine transformations then delivered tricycle **46**, which was also used in the synthesis of **1** by Ayer and Lee. In this case, the synthesis was finished via olefin isomerization to the more stable trisubstituted position, which increased diastereoselectivity in the reduction step from a 3:2 ratio to >97% selectivity for the desired diastereomer, precoccinelline (**1**). Unsurprisingly, peracid oxidation of **1** gave

coccinelline (**2**) in quantitative yield. Overall, **1** was obtained through this route in thirteen steps and 8.6% yield, and **2** was synthesized in fourteen steps and 8.6% yield.

Scheme 10. Mueller's Synthesis of Myrrhine

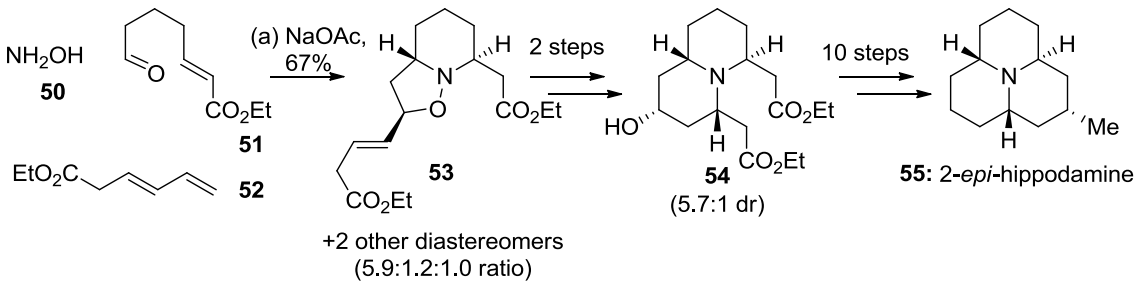


Finally, as shown in Scheme 10, Mueller was able to synthesize myrrhine (**5**) from a new tricyclic enamine **47** with both ring junction protons *syn* to one another as demanded by the target structure. This enamine was obtained in four steps and 20% overall yield from commercial materials. Carrying this tricycle through a series of relatively straightforward transformations, ketone **48** was obtained in 66% yield, and this material was converted to aldehyde **49** in four additional steps. Finally, the methyl group was set via reduction of the olefin with Li/NH_3 and reductive removal of the aldehyde oxygen in a subsequent three-step process to give **5** in 90% yield from **49**. Overall, myrrhine was achieved in fourteen steps and 13% yield, finishing Mueller's synthesis of all monomers in the azaphenalene-containing coccinellid defensive alkaloid family.

Section 2.4.4 Dieckmann Condensations to Access the Azaphenalene Ring System

In 1991, Adams and co-workers synthesized an azaphenalene core system utilizing Michael additions to build the first two piperidine rings with a Dieckmann condensation then completing the target structure.[26] As shown in Scheme 11, mixing **50** – **52** together and heating with NaOAc delivered isoxazolidine **53** along with two other diastereomers (5.9:1.2:1.0 ratio, major is **53**) in 67% combined yield through a nitrone cycloaddition. Reductive opening of the resultant isoxazole, conjugation of the olefin with the ethyl ester, and Michael addition then delivered **54** with 5.7:1 dr at the new piperidine stereocenter. In the ten steps remaining to complete 2-*epi*-hippodamine (**55**), the key operation was a Dieckmann condensation which furnished the final piperidine ring with the resulting ketone ultimately becoming the pendant methyl group. Deoxygenation of the alcohol in **54** was also required to deliver the target structure. Unfortunately, the endgame set the methyl group as the non-natural diastereomer, resulting in a synthesis of 2-*epi*-hippodamine (**55**).

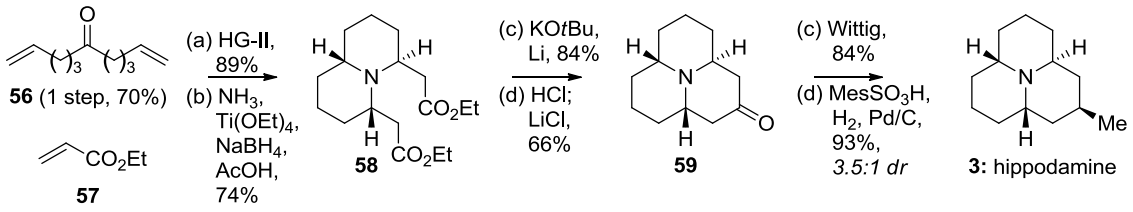
Scheme 11. Adams' Synthesis of 2-*epi*-Hippodamine



In 2005, Stockman and co-workers reported a "two-directional" approach to hippodamine (**3**) and utilized an intermediate similar to Adams' Dieckmann precursor (i. e. **54**). Originally reporting a synthesis of quinolizidine **58** through a longer route,

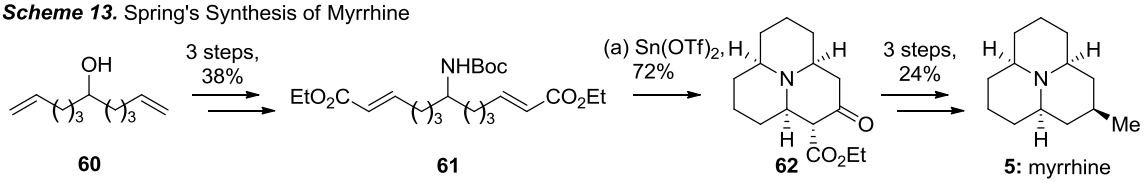
Stockman's efforts eventually streamlined the synthesis of this key material to only two steps from ketone **56** in 2008, which was itself one step away from commercial materials.[27]

Scheme 12. Stockman's Synthesis of Hippodamine



Taking ketone **56** forward, double olefin cross metathesis with **57** mediated by the Hoveyda-Grubbs second generation initiator proceeded in 89% yield and was followed by a one-pot cascade procedure consisting of reductive amination and two Michael additions. These operations collectively delivered quinolizidine **58** in 74% yield (Scheme 12). Subsequent Dieckmann condensation (84% yield) and decarboxylation (66% yield) with LiCl gave tricyclic ketone **59**. This material could undergo Wittig methylenation in 84% yield to give an olefin substrate that required only hydrogenation to deliver hippodamine. This team tested a variety of conditions, noting a poor 1:1.4 diastereomeric ratio disfavoring hippodamine for standard hydrogenation conditions with Pd/C. Subsequent work investigated a number of salts to see if the diastereomeric ratio could be affected by placing a bulky anion on the more accessible face of the molecule. Pleasingly, mesitylenesulfonic acid was found to give a 93% yield and 3.5:1 dr favoring **3**. Through this route, hippodamine (**3**) could be prepared in an impressive seven steps and 29% overall yield.

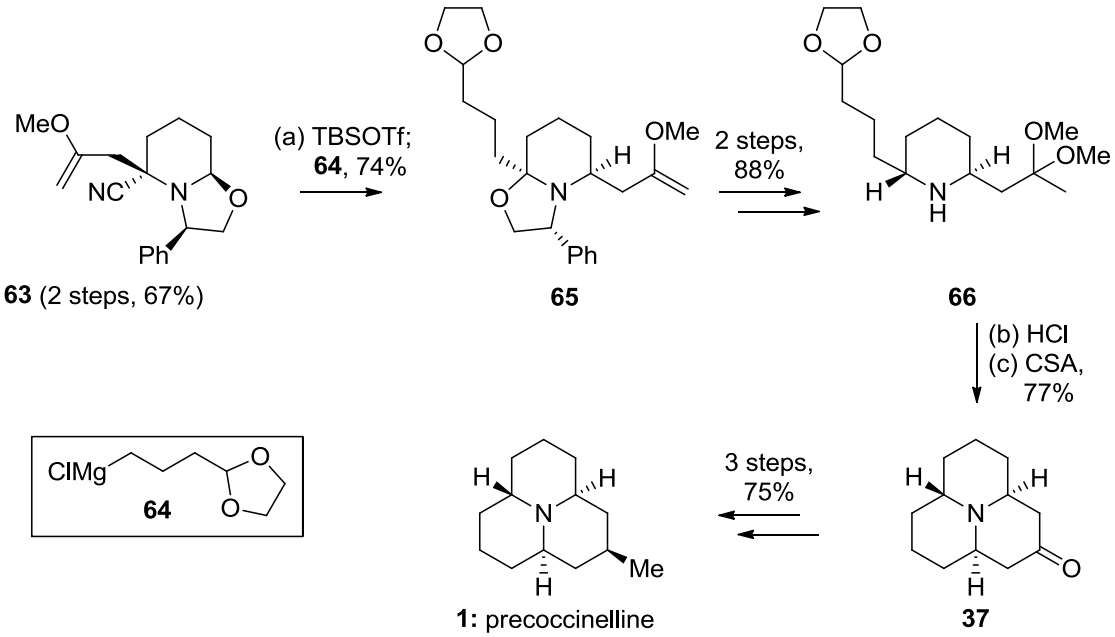
Scheme 13. Spring's Synthesis of Myrrhine



In 2009, the most recent approach to employ Dieckmann condensations in the formation of the azaphenalene core was reported by Spring and co-workers, efforts which ultimately led to myrrhine (**5**) in eight steps and 7% overall yield (Scheme 13).[28] Based on the reported yields and seven steps shown, it must be presumed that alcohol **60** is prepared in one step in very high/quantitative yield. Alcohol **60**, which is very similar to the ketone (i.e. **56**, cf. Scheme 12) employed by Stockman and co-workers, was converted into dienoate **61** in three straightforward steps and 38% overall yield. This material could then be treated with catalytic $Sn(OTf)_2$ to deliver tricycle **62** through an impressive cascade encompassing Boc removal, double Michael addition, and Dieckmann condensation. It is interesting to note that Stockman and co-workers obtained the stereochemistry necessary for hippodamine for their own Michael addition/Dieckmann strategy. Spring and co-workers noted that excess Lewis acid delivered Stockman's quinolizidine **58**, but catalytic Lewis acid gave the all *trans* ring fusion stereochemistry necessary for **5** in **62**. To finish myrrhine (**5**), decarboxylation and installation of the C-2 methyl (10:1 dr) was all that remained.

Section 2.4.5 Synthesis of Precoccinelline Employing an Aza-Cope Cascade

Scheme 14. Royer's Synthesis of Precoccinelline



In 1994, Royer and co-workers synthesized ketone **37** which, by that time, was well known to be an intermediate from which to access precoccinelline (**1**, Scheme 14).[29] Chiral functionalized piperidine **63**, formed from (–)-phenylglycinol in two steps and 67% yield, was used as starting material for this synthesis.[ii] To begin, **63** was treated with TBSOTf and Grignard reagent **64** to deliver **65** in 74% yield through a one-pot, aza-Cope/nucleophilic addition cascade reaction. Two additional steps were then required to secure intermediate **66** in 88% yield; **66** then underwent a Mannich cascade reaction similar to the one developed by Ayer as detailed in Scheme 5. The one difference here is that the cascade employed in this synthesis proceeded without the *in situ* epimerization through iminium scrambling observed by Ayer. With ketone **37** in hand, three straightforward steps were used to access precoccinelline in 75% yield in a similar

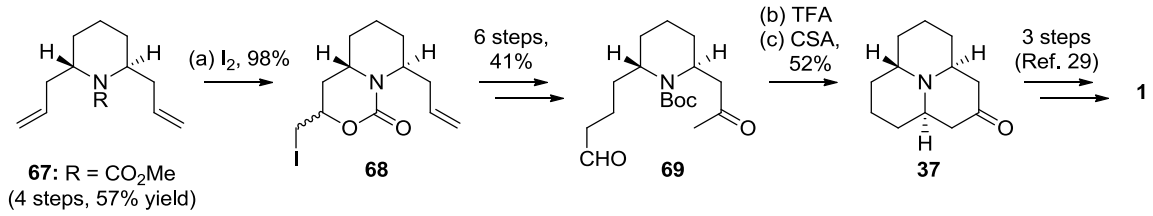
[ii] It is worth noting that hippodamine (**3**) or hippocasine (**9**) might have been a better choice of target to display the author's asymmetric method, as **1** is meso.

manner to the strategies employed by Ayer and Mueller. Overall, the total synthesis of precoccinelline was achieved by Royer and co-workers in ten steps and an impressive 25% yield.

Section 2.4.6 Synthesis of Precoccinelline Using a C_2-Symmetric Precursor

In 2002, Takahata and co-workers reported the use of a C_2-symmetric piperidine (**67**), itself prepared in four steps and 57% yield from commercial materials, to generate a variety of alkaloid skeletons, and precoccinelline (**1**) was the sole azaphenalene alkaloid pursued in these studies (Scheme 15).[30] This target was accessed by assembling ketone **37** and claiming a formal synthesis from Royer's route to the target alkaloid.[iii]

Scheme 15. Takahata's Formal Synthesis of Precoccinelline



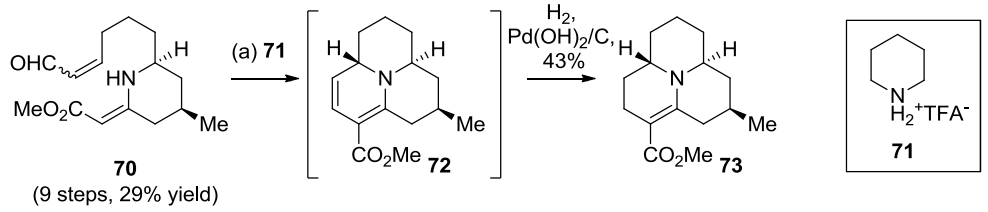
Starting from **67**, iodocyclization delivered **68** in 98% yield. Six steps were required to convert **68** into key intermediate **69** in 41% overall yield. TFA-mediated Boc deprotection and CSA catalyzed Mannich reaction delivered ketone **37** in 52% yield over both steps, which gave Takahata and co-workers a formal synthesis of precoccinelline (**1**) via Royer's route. The remaining three steps claimed are 75% overall yield, ultimately making Takahata's synthesis of **1** sixteen steps and 8.9% overall yield.

[iii] Again, **1** is an odd choice for azaphenalene synthesis from a chiral starting material, but it is likely that the symmetry of the molecule makes its synthesis easier than the hippodamine stereochemical configuration (Figures 2 and 5).

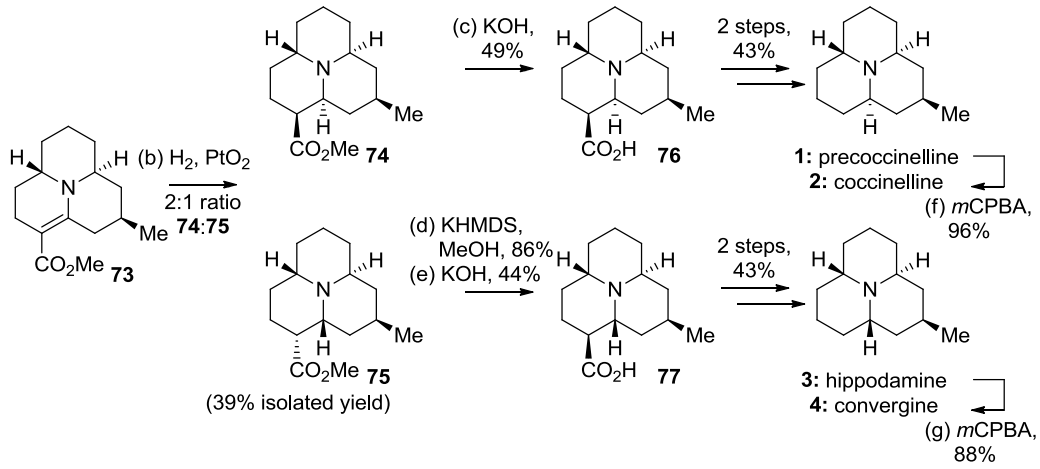
Section 2.4.7 Aza-[3 + 3] Cycloaddition Strategy to Access All Saturated Monomers

In 2003, Hsung and Gerasyuto reported the use of an aza-[3+3] cycloaddition reaction, a method developed in their group, to access all of the saturated monomers and their *N*-oxides.[31] A nine-step synthesis of aza-[3+3] precursor **70** proceeded in 29% overall yield, and this intermediate could be converted into **72** in 51% yield through treatment with piperidine salt **71** to catalyze the desired key step. In practice, however, **72** could be immediately subjected to hydrogenation conditions via a one-pot aza-[3+3]/reduction protocol to afford **73** in 43% overall yield. From here, reduction of the remaining olefin delivered **74** and **75** in a 2:1 ratio favoring the stereochemical precursor to precoccinelline (i.e. ester **74**). Hydrolysis of the ester within **74** then delivered **76** in 49% yield, and a two-step Barton decarboxylation sequence finished the target precoccinelline (**1**) in 14 steps and 4.8% overall yield. Finally, *m*CPBA-mediated oxidation of **1** delivered coccinelline (**2**) in 96% to give a fifteen-step synthesis of this monomer in 4.6% overall yield.

Scheme 16. Hsung's Aza-[3+3] Approach to Saturated Monomers
A. Key Aza-[3+3] Cycloaddition

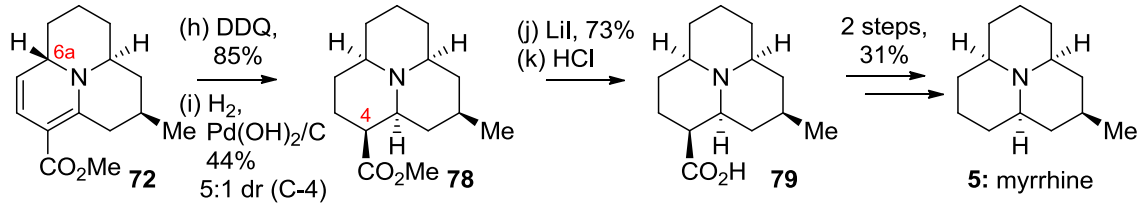


B. Synthesis of Precoccinelline, Coccinelline, Hippodamine, and Convergine



Hippodamine (**3**) was achieved through a similar sequence by the same reaction, though hydrolysis of the ester contained in **75** required KHMDS-mediated epimerization before it could be cleaved. Free acid **77** was subjected to the same two-step decarboxylation process as **76** to deliver **3** in fifteen steps and 1.3% overall yield. Oxidation of **3** delivered convergine (**4**) in 88% yield to ultimately provide this monomer in sixteen steps and 1.2% overall yield.

Scheme 17. Hsung's Synthesis of Myrrhine



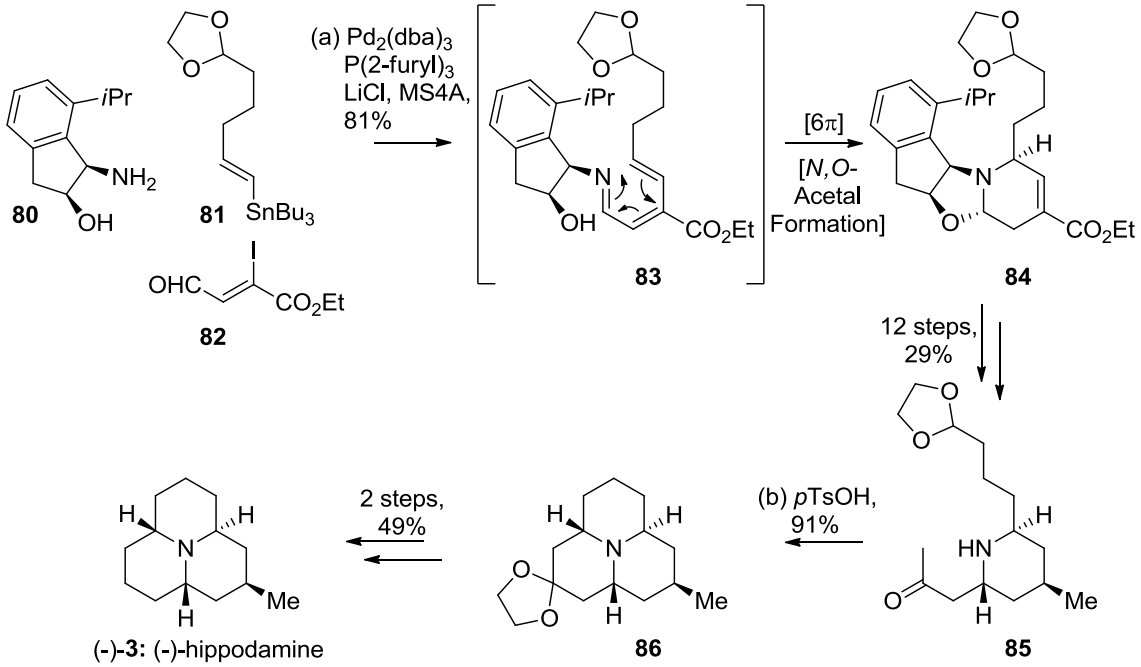
To complete their efforts in this area, the authors also accessed myrrhine (**5**) through a creative epimerization sequence at C-6a (Scheme 17). In the event, DDQ-mediated oxidation of aza-[3+3] product **72** could be performed after isolation of **72** instead of subjecting it to hydrogenation as shown in Scheme 16; the resultant pyridinium salt could be completely hydrogenated to give the all *trans* ring fusion intermediate **78** with a 5:1 diastereomeric ratio at C-4 due to small amounts of ester epimerization. Conversion of ester **78** to acid **79** was achieved in a two-step process, and Barton decarboxylation delivered myrrhine (**5**) in a total of sixteen steps and 4.3% overall yield.

Section 2.4.8 First Asymmetric Synthesis of (–)-Hippodamine

In 2013, Katsumura and co-workers reported the first asymmetric synthesis of (–)-hippodamine (–)-**3** through the use of a chiral aminoalcohol starting material. [32] Synthetic (–)-**3** reported by the authors has the same absolute configuration as that reported for convergine (**4**) when it was isolated. Since it is reasonable to assume that natural **3** and natural **4** are of the same absolute configuration as they have both been isolated from the same organism, it is also reasonable to posit that the authors have synthesized the natural antipode of **3**. This work also represents the first time that an optical rotation has been

measured for **3**, potentially establishing the specific rotation for the natural antipode of this azaphenalene monomer.

Scheme 18. Katsumura's Synthesis of (-)-Hippodamine



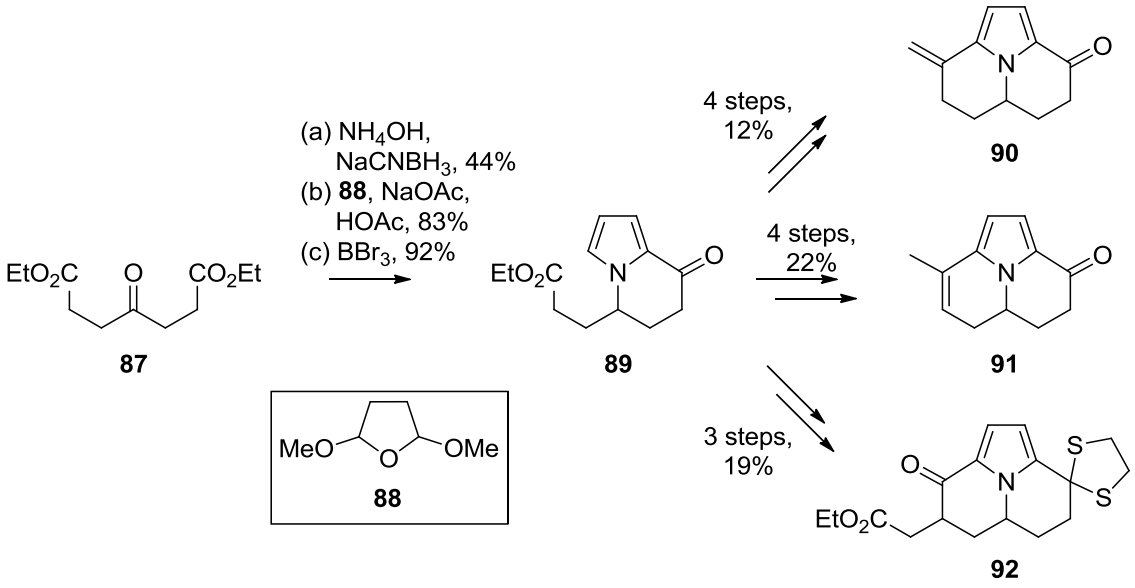
As shown in Scheme 18, dissolving chiral aminoalcohol **80**, stannane **81** (3 steps from commercial materials, 68% yield), and vinyl iodide **82** in DMF, the authors were able to employ a Stille cross-coupling of **81** and **82** followed by an imine condensation of the cross coupling product with **80** to deliver transient intermediate **83**. This species then underwent a 6π-azaelectrocyclization and *N*,*O*-acetal formation to deliver **84** in an impressive 81% yield across the entire three-component cascade process. Twelve further steps (generally routine) delivered Mannich precursor **85** in 29% yield, and this intermediate was cyclized to tricycle **86** via a deprotection/Mannich reaction/reprotection cascade sequence similar to processes developed in earlier syntheses of azaphenalene monomers. Finally, a two-step defunctionalization sequence delivered (–)-**3** in 49% yield

from **86**. This synthesis is the first enantioselective synthesis of an azaphenalene-containing coccinellid defensive alkaloid and proceeded in nineteen steps and 7.1% overall yield.

Section 2.4.9 Synthesis of the Azaacenaphthalene Subunit of the Heterodimeric Coccinellid Defensive Alkaloids

Although the heterodimeric coccinellid defensive alkaloids **11** – **15** (Figure 6) have been known for nearly two decades, there exists only one reported effort to access their unique cores through the synthesis of azaacenaphthalenes **90** – **92**.[33] Similar ring systems to **90 – 92** have been reported by other groups, as well, though not specifically with heterodimers **11** – **15** in mind as targets.[34]

Scheme 19. Meinwald's Synthesis of Functionalized Azaacenaphthylenes



As shown in Scheme 19, commercially available ketone **87** was converted to derivative **89** through reductive amination, pyrrole formation, and Friedel–Crafts

cyclization of one of the ester handles in 34% yield over three steps. Pyrrole **89** was then transformed into three derivatives, **90** – **92**, in short order and decent yield. Overall, **90** was synthesized in seven steps and 4.1% yield, **91** was synthesized in seven steps and 7.5% yield, and **92** was prepared in six steps and 6.5% yield. No subsequent reports have detailed efforts to unite **90** – **92** with azaphenalene monomers to access heterodimers **11** – **15**.

Section 2.5 Conclusion

This chapter has attempted to introduce the full wealth of isolation, biosynthetic, and synthetic studies that have been performed on the azaphenalene-containing coccinellid defensive alkaloids. During the last 40 years, nine monomeric, six heterodimeric, and two homodimeric alkaloids have been isolated, displaying an abundance of structural diversity. Biosynthetic studies on coccinelline and precoccinelline have demonstrated that these monomers are produced endogenously by the ladybug through a fatty acid pathway, and it has been postulated that all other members of this family are formed through a similar biogenesis. Finally, all monomers have been prepared synthetically utilizing a variety of classical and modern methods, although Mueller was the only investigator who reported access to every monomeric natural product employing a unified approach.

Despite the abundance of synthetic work in this area, however, there are still chemical problems to solve. In terms of challenges with the monomers, asymmetric preparation of propyleine, isopropyleine, hippocasine, and hippocasine oxide remain to

be reported. An enantioselective synthesis of convergine also has yet to be disclosed, although Katsumura's synthesis of (–)-hippodamine does constitute a formal enantioselective synthesis of the *N*-oxide, though the authors do not note this in their report.

In terms of dimeric azaphenalene-containing alkaloids, no completed syntheses have been reported. While Meinwald has reported syntheses of azaacenaphthalenes **90** – **92**, no subsequent disclosures detailing dimeric couplings exist. Furthermore, no efforts have been reported towards homodimers psylloborine A (**16**) or isopsylloborine A (**17**). Clearly, the greatest opportunity for synthetic advancement in this area of study lies in the exploration and ultimately successful preparation of dimeric architectures. Furthermore, such a program should seek to prepare the remaining monomers asymmetrically. This secondary goal is an important one since preparation of dimeric structures with racemic monomers could give non-natural diastereomers through direct dimerization strategies.

In Chapters 3 and 4, our group's efforts to access enantiomerically pure monomeric structures and homodimers psylloborine A and isopsylloborine A will be discussed in detail, keeping these challenges in mind. Our program to synthesize these alkaloids was designed in an enantioselective, late-stage divergent manner in order to develop a family-based approach to access this oligomeric class of natural products. The remainder of this thesis will discuss our own contributions to the field of azaphenalene alkaloid chemistry, and projections will be provided for the remaining synthetic studies where we believe significant discoveries can be made.

Section 2.6 References

1. Selected reviews of coccinellid defense chemical use in Nature, isolation, biosynthesis, and synthetic preparation: (a) W. A. Ayer, L. M. Browne, *Heterocycles* **1977**, *7*, 685 – 707. (b) D. Daloze, J.-C. Braekman, J. M. Pasteels, *Chemoecology* **1994/1995**, *5/6*, 173 – 183. (c) A. G. King, J. Meinwald, *Chem. Rev.* **1996** *96*, 1105 – 1122. (d) P. Laurent, J.-C. Braekman, D. Daloze, *Topics in Current Chemistry* **2005**, *240*, 167 – 229.

2. G. M. Happ, T. Eisner, *Science* **1961**, *134*, 329 – 331.

3. (a) B. Tursch, D. Daloze, M. Dupont, J. M. Pasteels, M. C. Tricot, *Experientia* **1971**, *27*, 1380 – 1381. (b) B. Tursch, D. Daloze, M. Dupont, C. Hootele, M. Kaisin, J. M. Pasteels, D. Zimmerman, *Chimia* **1971**, *25*, 307 – 308.

4. R. Karlsson, D. Losman, *J. C. S. Chem. Comm.* **1972**, 626 – 627.

5. (a) B. Tursch, D. Daloze, J. M. Pasteels, A. Cravador, J.-C. Braekman, C. Hootele, D. Zimmerman, *Bull. Soc. Chim. Belges* **1972**, *81*, 649 – 650. (b) B. Tursch, D. Daloze, J.-C. Braekman, C. Hootele, A. Cravador, D. Losman, R. Karlsson, *Tetrahedron Lett.* **1974**, *5*, 409 – 412.

6. B. Tursch, D. Daloze, J.-C. Braekman, C. Hootelé, J. M. Pasteels, *Tetrahedron* **1975**, *31*, 1541 – 1543.

7. R. T. LaLonde, E. Auer, C. F. Wong, V. P. Muralidharan, *J. Am. Chem. Soc.* **1971**, *93*, 2501 – 2506.

8. B. Tursch, D. Daloze, C. Hootele, *Chimia* **1972**, *26*, 74 – 75.

9. R. H. Mueller, M. E. Thompson, *Tetrahedron Lett.* **1980**, *21*, 1097 – 1100.

10. W. A. Ayer, M. J. Bennett, L. M. Browne, J. T. Purdham, *Can. J. Chem.* **1976**, *54*, 1807 – 1813.

11. M. Timmermans, J.-C. Braekman, D. Daloze, J. M. Pasteels, J. Merlin, J.-P., Declercq, *Tetrahedron Lett.* **1992**, *33*, 1281 – 1284.

12. K. D. McCormick, A. B. Attygalle, S.-C. Xu, A. Svatoš, J. Meinwald, M. A. Houck, C. L. Blankespoor, T. Eisner, *Tetrahedron* **1994**, *50*, 2365 – 2372.

13. X. Shi, A. B. Attygalle, J. Meinwald, M. A. Houck, T. Eisner, *Tetrahedron* **1995**, *51*, 8711 – 8718.

14. Q. Huang, A. B. Attygalle, J. Meinwald, M. A. Houck, T. Eisner, *J. Nat. Prod.* **1998**, *61*, 598 – 601.

15. P. Laurent, J.-C. Braekman, D. Daloze, J. M. Pasteels, *Tetrahedron Lett.* **2002**, *43*, 7465 – 7467.

16. F. C. Schröder, T. Tolasch, *Tetrahedron* **1998**, *54*, 12243 – 12248.

17. B. Lebrun, J.-C. Braekman, D. Daloze, P. Kalushkov, J. M. Pasteels, *Tetrahedron Lett.* **1999**, *40*, 8115 – 8116.

18. S. A. Snyder, A. M. ElSohly, F. Kontes, *Nat. Prod. Rep.* **2011**, *28*, 897 – 824.

19. (a) P. Laurent, J.-C. Braekman, D. Daloze, J. M. Pasteels, *Insect Biochemistry and Molecular Biology* **2002**, *32*, 1017 – 1023. (b) E. Haulotte, P. Laurent, J.-C. Braekman, *Eur. J. Org. Chem.* **2012**, 1907 – 1912.

20. (a) A. B. Attygalle, C. L. Blankespoor, T. Eisner, J. Meinwald, *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 12790 – 12793. (b) A. B. Attgalle, A. Svatoš, M. Veith, J. J. Farmer, J. Meinwald, S. Smedle, A. Gonzales, T. Eisner, *Tetrahedron* **1999**, *55*, 955 – 966.

21. W. A. Ayer, R. Daw, R. A. Eisner, K. Furuichi, *Can. J. Chem.* **1975**, *54*, 473 – 481.

22. W. A. Ayer, K. Furuichi, *Can. J. Chem.* **1976**, *54*, 1494 – 1495.

23. R. V. Stevens, A. W. M. Lee, *J. Am. Chem. Soc.* **1979**, *101*, 7032 – 7035.

24. (a) R. Robinson, *J. Chem. Soc.*, **1917**, *111*, 762 – 768. (b) C. Schöpf, *Angew. Chem.* **1937**, *50*, 779 – 797.

25. (a) R. H. Mueller, R. M. DiPardo, *J. Chem. Soc., Chem. Commun.* **1975**, 565 – 566. (b) R. H. Mueller, *Tetrahedron Lett.* **1976**, *34*, 2925 – 2926. (c) R. H. Mueller, M. E. Thompson, *Tetrahedron Lett.* **1979**, *22*, 1991 – 1994. (d) R. H. Mueller, M. E. Thompson, *Tetrahedron Lett.* **1980**, *21*, 1093 – 1096. (e) R. H. Mueller, M. E. Thompson, R. M. DiPardo, *J. Org. Chem.* **1984**, *49*, 2217 – 2231.

26. D. R. Adams, W. Carruthers, P. J. Crowley, *J. Chem. Soc., Chem. Commun.* **1991**, 1261 – 1263.

27. (a) M. Rejzek, R. A. Stockman, D. L. Hughes, *Org. Biomol. Chem.* **2005**, *3*, 73 – 83. (b) A. F. Newton, M. Rejzek, M.-L. Alcaraz, R. A. Stockman, *Beilstein J. Org. Chem.* **2008**, *4*, no pp. given.

28. (a) M. Díaz-Gavilán, W. R. J. D. Galloway, K. M. G. O'Connell, J. T. Hodkingson, D. R. Spring, *Chem. Commun.* **2010**, *46*, 776 – 778. (b) K. M. G. O'Connell, M. Díaz-Gavilán, W. R. J. D. Galloway, D. R. Spring, *Beilstein J. Org. Chem.* **2012**, *8*, 850 – 860.

29. C. Yue, J.-F. Nicolay, J. Royer, H.-P. Husson, *Tetrahedron* **1994**, *50*, 3139 – 3148.

30. (a) H. Takahata, H. Ouchi, M. Ichinose, H. Nemoto, *Org. Lett.* **2002**, *4*, 3459 – 3462. (b) H. Takahata, Y. Saito, M. Ichinose, *Org. Biomol. Chem.* **2006**, *4*, 1587 – 1595.

31. (a) A. I. Gerasyuto, R. P. Hsung, *Org. Lett.* **2006**, *8*, 4899 – 4902. (b) A. I. Gerasyuto, R. P. Hsung, *J. Org. Chem.* **2007**, *72*, 2476 – 2484.

32. S. Fujita, T. Sakaguchi, T. Kobayashi, H. Tsuchikawa, S. Katsumura, *Org. Lett.* **2013**, *15*, 2758 – 2761.

33. J. C. Shattuck, J. Meinwald, *Tetrahedron Lett.* **1997**, *38*, 347 – 350.

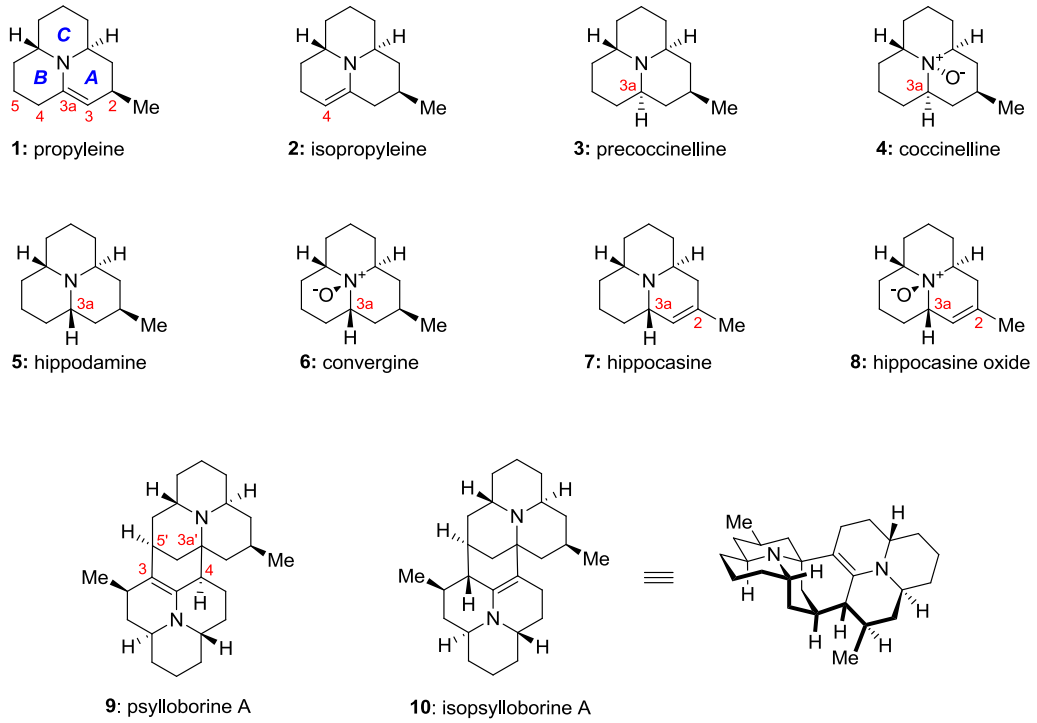
34. (a) J. Hu, X. Jiang, T. He, J. Zhou, Y. Hu, H. Hu, *J. Chem. Soc., Perkin Trans. 1* **2001**, 1820 – 1825. (b) Y.-M. Shen, G. Grampp, N. Leesakul, H.-W. Hu, J.-H. Xu, *Eur. J. Org. Chem.* **2007**, *22*, 3718 – 3726. (c) Y. Liu, H.-Y. Hu, Y. Zhang, H.-W. Hu, J.-H. Xu, *Org. Biomol. Chem.* **2010**, *8*, 4921 – 4926.

CHAPTER 3

Development of a Programmable Synthetic Strategy to Access the Oligomeric Azaphenalene Alkaloids: Syntheses of Monomers and Biomimetic Dimerization

Section 3.1 Project Goals, Retrosynthetic Analysis, and Design of Key Alcohol Intermediate

Figure 1. Targeted Members of the Oligomeric Coccinellid Alkaloid Family and 3D Representation of Homodimer Isopsylloborine A

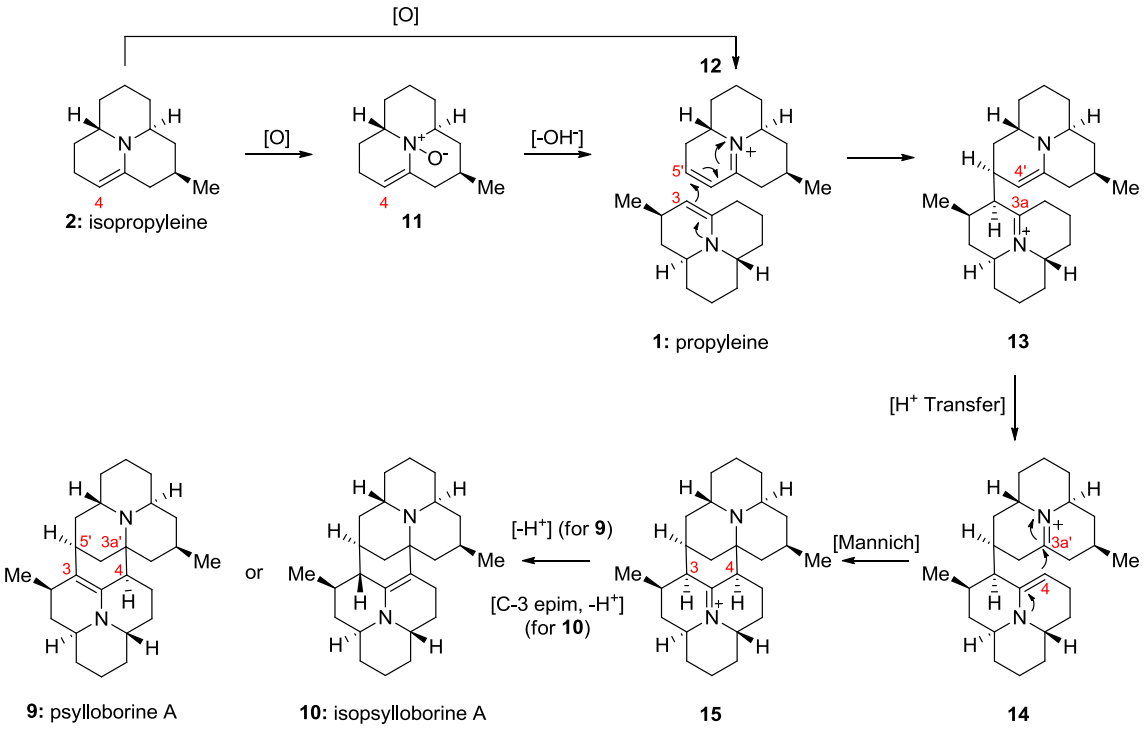


As covered in detail in the previous chapter, there has been a large amount of interest in the coccinellid family of defensive alkaloids. When threatened, ladybugs (coccinellids) secrete a mixture of alkaloids from their joints in a process known as reflex bleeding, and it is hypothesized that these alkaloids can ward off potential predators. The 2-methyl-perhydro-9b-azaphenalene structural class of these alkaloids is found in several monomeric as well as homo- and hetero-dimeric architectures (Figure 1). We selected these alkaloids as targets given the fact that these structures are congruent with our group's more global interest in oligomeric natural products. Thus, we began our synthetic forays into this family targeting monomeric frameworks (**1** – **8**) and the two known

homodimers of this class, psylloborine A (**9**) and isopsylloborine A (**10**).[i] Our goal was to develop a family-based synthetic approach that could access these oligomeric natural products from a key intermediate, a branch point that could lead to all targets and could afford a novel bond construction strategy for this class.[ii] In order to accomplish this objective, we first needed a plausible biosynthetic hypothesis for how homodimers **9** and **10** could form from simpler, monomeric species. In their isolation report on **9**, the Schröder group put forth the idea that these molecules likely form from simpler azaphenalene monomers, but no specific mechanistic rationale was given. Therefore, after careful analysis of all the structures within this family, we developed a biogenic proposal for the formation of **9** and **10**. This proposal, shown in Scheme 1, laid the foundation for our family-based synthetic approach to the oligomeric azaphenalene alkaloids.

[i] For references and detailed discussions of the isolation of these compounds, see Chapter 2
[ii] See Chapter 2 for a survey of previous synthetic approaches to the azaphenalene alkaloids

Scheme 1. Proposed Biogenesis for **1** and **2**



As indicated, it seems reasonable to presume that homodimers **9** and **10** are formed through the union of two monomeric pieces such as propyleine (**1**) and its enamine isomer isopropyleine (**2**), reported by Mueller to exist as a 1:3 mixture, respectively.[1] Based on a simple analysis of the target dimers, it is apparent that the monomeric halves of **9** and **10** differ in oxidation state, where the fully saturated half likely arises from the oxidized derivative **12** of enamine monomer **2** (Scheme 1). Curiously, no such oxidized structure has been reported, but other azaphenalene monomers do exhibit a stable, isolable oxidation product (typically the *N*-oxide) as shown in Figure 1. Intriguingly, no related *N*-oxide or otherwise oxidized variant of **1** or **2** has been reported,[iii] and the olefin found in hippocasine and its *N*-oxide (**7** and **8**, Figure

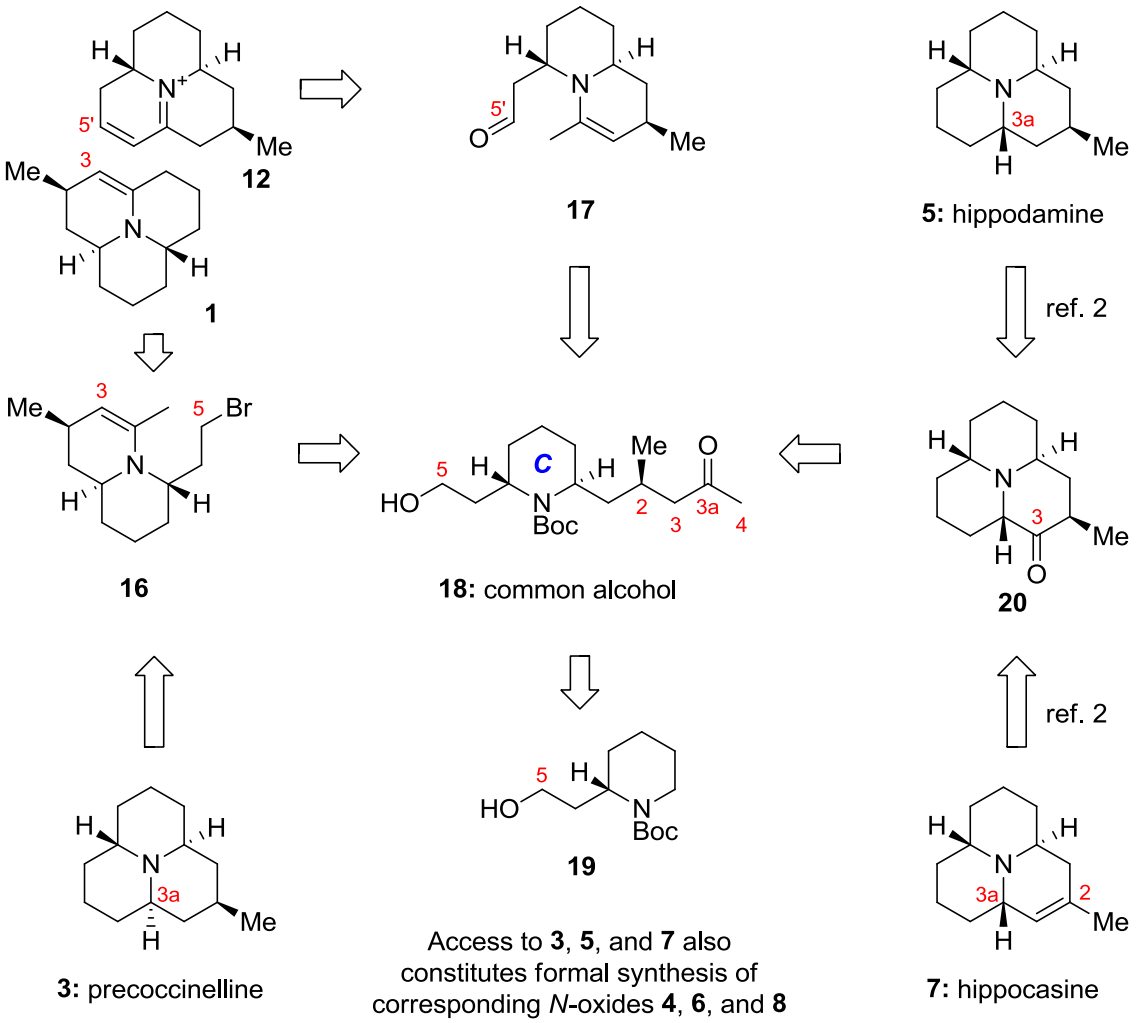
[iii] The report by Sadikov *et al* of a unique dehydro-propyleine structure (*Khimiya Prirodnykh Soedinenii* **1981**, *6*, 764 – 767) was observed only by mass spectrometry with no other analytical techniques employed, and no other isolation reports have described such a molecule.

1) is located in the wrong position to initiate a productive dimerization event. Therefore, we envisioned an oxidative event in which **2** is transformed into an extended iminium at C-5' (**12**), either through an *N*-oxide (**11**) or direct allylic hydride abstraction at C-5', generating an extended iminium (i.e. **12**) that propyleine (**1**) could engage from its C-3 position in a pseudoaxial sense to form the first of two key C-C bonds. This operation would unite the two fragments, presumably in a diastereoselective manner with a stereoelectronic preference (if not enzymatically controlled) for pseudoaxial attack at C-5' to give **13**. Proton transfer processes could mediate enamine isomerizations from **13** to **14**, with a Mannich attack then forging the second dimeric linkage between C-4 and C-3a' to give homodimeric iminium **15** in this cascade process. As this second dimeric linkage would generate a [3.3.1] bridged bicycle, C-4 should attack C-3a' on the same face from which C-5' was engaged. Deprotonation from C-3 would then provide **9**, but accessing **10** would require epimerization prior to deprotonation. We propose that the stereochemical configuration at C-3 within **10** is established through proton transfer-mediated epimerization and subsequent deprotonation of C-4. For simplicity, we have not included a depiction of such processes within Scheme 1.

Given this biosynthetic proposal, we developed a retrosynthetic plan to access extended iminium **12** and propyleine (**1**) through a strategy that would also allow for synthesis of monomeric natural products **3** – **8**, compounds not involved in the proposed dimerization. While there are many subtle stereochemical and oxidation pattern differences between all of the targeted species, each has a conserved *trans* relationship for the C-ring, an important point of emphasis for retrosynthetic design. Furthermore, the differences in the monomers of interest can all be found along the linear region between

C-2 and C-5, another key factor to take into consideration for our synthetic plan. Finally, in order to access homodimeric architectures in a controlled fashion, monomeric species would need to be prepared as single enantiomers so that direct dimerization strategies would not deliver a mixture of non-natural, diastereomeric products.

Scheme 2. Family-Based Retrosynthetic Analysis to Key Intermediate



To synthesize propyleine (**1**), we focused on bicyclic bromide **16**, which we hypothesized could form **1** through enamine isomerization and nucleophilic ring closure (Scheme 2). While the required electrophile (**12**) could conceivably be accessed directly

from isopropyleine (**2**), achieving regiochemical control could be difficult given the report that **1** and **2** rapidly interconvert as well as the fact that they possess several potential sites of oxidation. Therefore, we devised a strategy in which the higher oxidation level required at C-5' could be installed during an earlier stage of the route via aldehyde **17**. Both of these quinolizidines (i.e. **16** and **17**) could arise from alcohol **18**, which we hoped to synthesize in rapid fashion from commercially available *(S)*-1-*N*-Boc-(–)-piperidine-2-ethanol (**19**).

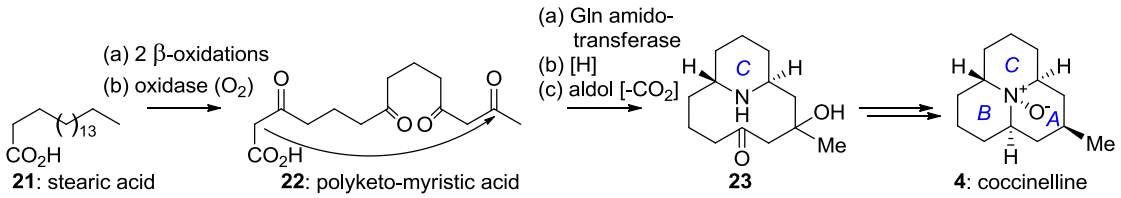
In terms of other monomeric species, precoccinelline (**3**) was envisioned to come from propyleine (**1**) itself, as it has been demonstrated by Mueller that there is a slight diastereomeric preference for reduction of the enamine monomers to **3**. We hoped to exaggerate this diastereopreference in our own studies beyond the 2:1 dr originally reported for hydrogenation conditions and achieve a controlled synthesis of **3**. Finally, ketone **20**, which we believed could be synthesized through a similar strategy as that proposed for **1**, has been shown by the Mueller group to provide rapid access to **5** – **8**.[1] Therefore, application of our route to ketone **20** would enable us to claim formal syntheses of these four monomers, as well. It is worth noting that although some of our proposed monomeric syntheses build upon the work performed by others in terms of late-stage operations, the envisioned enamine-driven ring constructions are a unique strategy not employed in any other synthetic studies of this class of natural products.[iv]

In order to facilitate these divergent synthetic routes, the envisioned key alcohol (**18**) was intentionally designed with easily differentiated functionality at either end of its

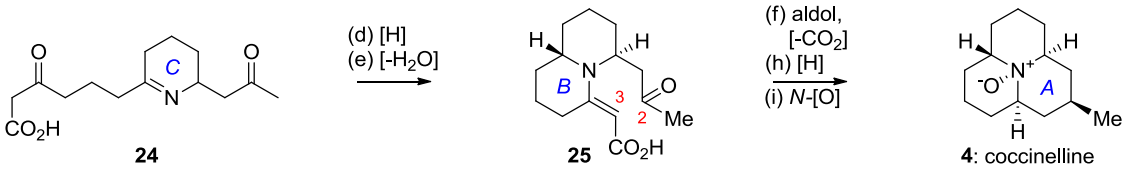
[iv] The Hsung group's use of an aza-[3+3] strategy detailed in Chapter 2 does not make use of a true enamine in the key cycloaddition step as it is conjugated to an electron withdrawing group and is therefore a vinylagous carbamate.

two side-chains, allowing subtle manipulation of the ketone, its α-carbons, and the alcohol reactive groups. In other words, the carbon chain from C-2 to C-5, highlighted above as the region of differentiation for all monomeric species of interest, would be well poised for selective chemical modification, allowing the selective synthesis of monomers and dimers through targeted and chemoselective alterations of the specifically selected functional groups within **18**.

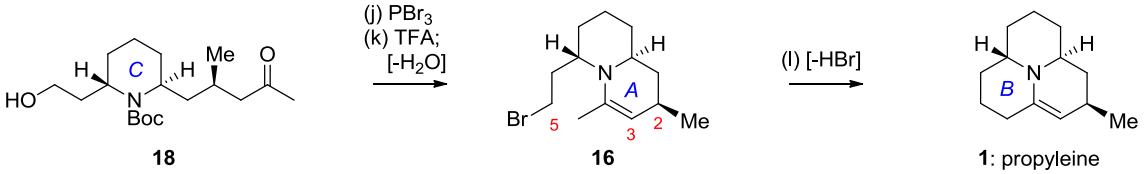
Scheme 3. Similarities Between Proposed Biosynthesis and Our Synthetic Strategy
A. Proposed biosynthesis of coccinelline from biosynthetic studies



B. Our interpretation and proposal of coccinelline biosynthesis



C. Our proposed synthetic approach to azaphenalene monomeric architectures exemplified by propyleine



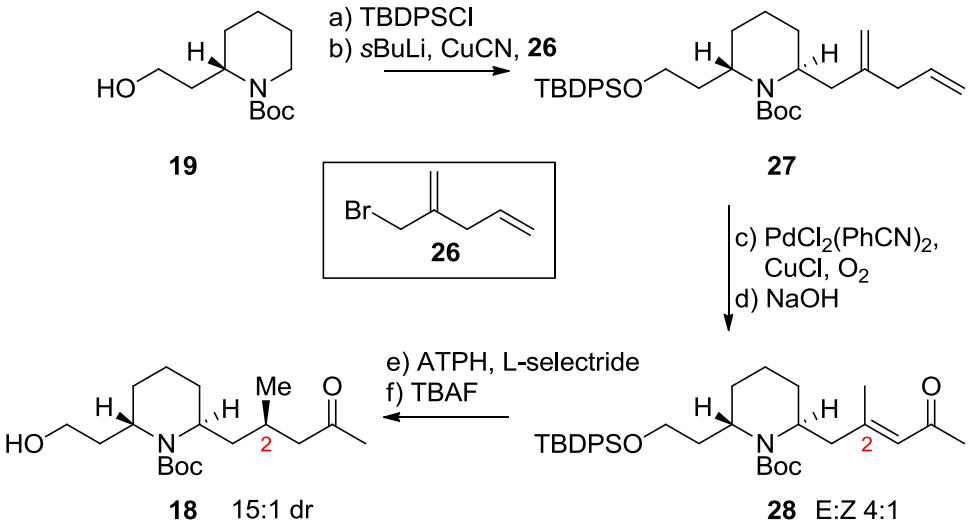
It is worth noting that such an order of ring construction and final manipulations of the C-2 to C-5 region of the tricyclic architecture proposed above is partly congruent with the biosynthetic route proposed by Braekman *et al*[2] which was partially re-interpreted by us (Scheme 3, see Chapter 2 for full discussion). As depicted in Scheme 3B and 3C, with the C-ring already in place, the A- and B-rings could form last through enamine condensation and enamine-driven nucleophilic ring closure. Braekman and co-

workers have posited that all azaphenalene natural products are likely synthesized through a similar pathway, a hypothesis we agree with on the basis of structural homology. Therefore, it seems likely that the structural differentiation observed in this class is established in the final steps of the biosynthesis. Framing our synthetic strategy around key alcohol **18** and enamine derivatives like **16** would afford excellent positioning for us to take advantage of the C-2 to C-5 region of the molecule in much the same way that we hypothesize the ladybug itself does to synthesize this oligomeric family. It was our hope that such a strategy for differentiation would prove fruitful in our synthetic studies.

Section 3.2 Synthesis

Section 3.2.1 Synthesis of Key Divergent Alcohol

Scheme 4. Rapid Synthesis of Key Alcohol



Reagents and conditions: (a) TBDPSCl, imidazole (b) *s*BuLi, TMEDA, CuCN·2LiCl, **26**, 84% over 2 steps (c) $PdCl_2(PhCN)_2$, CuCl, O_2, DMF/H_2O 10/1, 41% (d) aq. NaOH, *i*PrOH, 100% (e) 2,6-diphenyl phenol, $AlMe_3$, L-selectride, 75% (f) TBAF, 91%

Setting out to access our key alcohol (**18**), we developed a seven-step synthesis of **18** starting from commercially available *(S)*-1-*N*-Boc-(–)-piperidine-2-ethanol. Standard silylation of the starting material (**19**) followed by 2,6-*trans* selective, copper-mediated allylation with branched bromide **26** (prepared in two steps, see Section 3.5)[3] at cold temperature gave intermediate **27** in 84% yield over two steps. This new material contained all requisite carbons for the monomeric natural product targets.[4] Next, **27** was oxidized in 41% yield under Wacker conditions for 8 h at 60 °C to give the desired deconjugated enone (**29**, not shown in Scheme 4, see Scheme 5), and facile treatment with aqueous NaOH in *i*-PrOH at 25 °C could rapidly bring this enone into conjugation to give **28** in quantitative yield as a 4:1 mixture of olefin isomers. With both of these

substrates in hand, we began to develop a strategy for establishing the C-2 methyl stereocenter through diastereoselective reduction (Scheme 5).

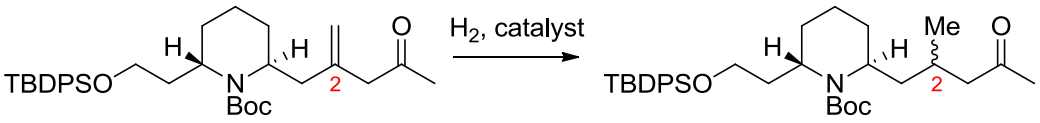
Rather unsurprisingly, simple hydrogenation using Pd/C in standard solvents yielded no diastereomeric preference with either the deconjugated or conjugated enones **29** or **28** (Scheme 5A). Attempts at substrate-directed hydrogenation in a variety of solvents using Wilkinson's catalyst ($[RhCl(PPh_3)_3]$) or Crabtree's catalyst ($[Ir(COD)(Pyr)(PCy_3)]PF_6$) on deconjugated enone **29** gave either no diastereomeric preference or a slight preference for the wrong diastereomer, a result that was not entirely unexpected. It is likely that these attempts failed to give any strong diastereomeric bias due to the olefin of interest being acyclic and relatively remote from any potential directing groups.[5]

With these results in hand, our efforts now shifted towards diastereoselective conjugate additions into the C-2 β-carbon (Scheme 5B). In initial explorations, C-2 des-methyl enone **31** (prepared through a route different from that shown in Scheme 4) was treated with $LiMe_2Cu$ at –78 °C, giving a 1:3 dr disfavoring the desired C-2 epimer. Fortunately, conjugate addition into enones has been well-studied,[6] and our research led us to evaluate the application of designer Lewis acid aluminum tris(2,6-diphenylphenoxide) (ATPH) developed by the Yamamoto group to our own system. [7]

Scheme 5. Establishing the C-2 Methyl Stereocenter Through Diastereoselective Reduction

A. Attempts at diastereoselective hydrogenation

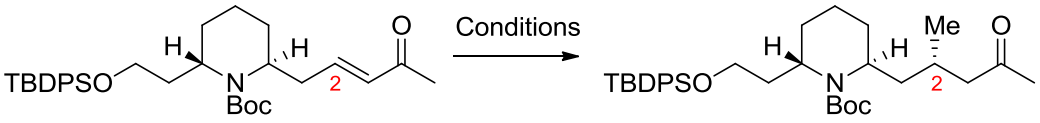
Hydrogenation Catalyst	dr (desired:undesired)
(a) Pd/C	1:1
(b) $RhCl(PPh_3)_3$	1:2
(c) $[Ir(COD)(Pyr)(PCy_3)]PF_6$	1:2



29 **30**

B. Forming the undesired C-2 stereocenter through conjugate addition of the methyl group

Conditions	dr (desired:undesired)
(d) $LiMe_2Cu$	1:3
(e) ATPH, MeLi	<1:19



31 **32**

C. Establishing the desired C-2 stereocenter through conjugate reduction

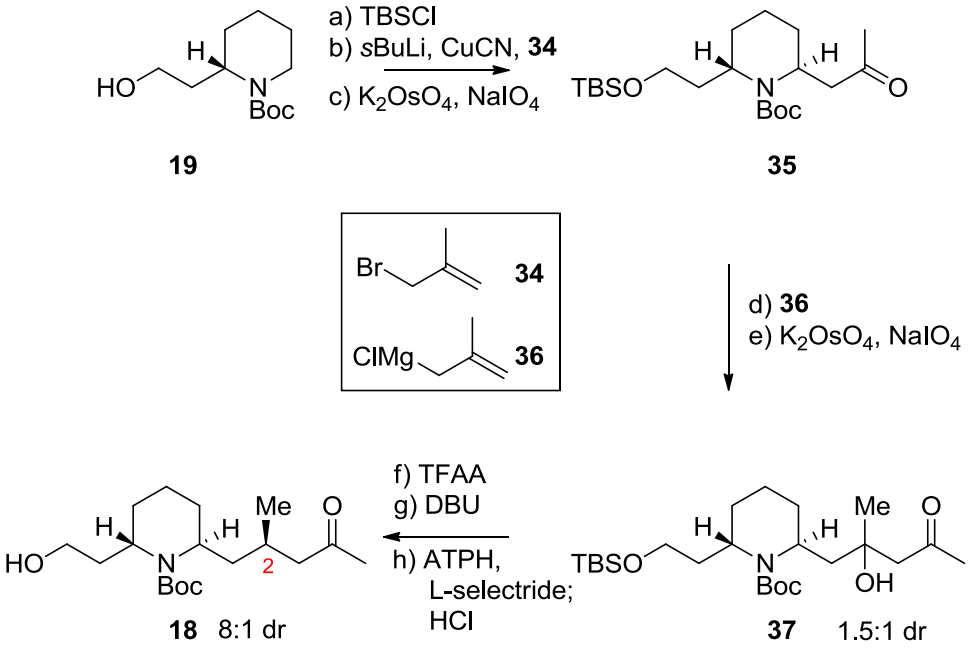
28 E:Z 4:1 **33** 15:1 dr

The Yamamoto group has extensively studied ATPH for the modification of nucleophilic additions to carbonyl-based electrophiles, reporting a variety of favorable properties. This Lewis acid has also been shown to sterically shield the carbonyl carbon in enones from nucleophilic attack. This shielding can completely change the regioselectivity for species that typically attack in a 1,2-fashion, forcing them to adopt the 1,4 mode of attack. Furthermore, ATPH can invert the diastereoselectivity of conjugate additions into cyclic systems when compared to conjugate addition in the absence of ATPH. The bulky Lewis acid is hypothesized to preferentially sit on the more accessible

face of the substrate after complexation, thereby causing the incoming nucleophile to attack from the previously less accessible face as it is now the only one available.

With these properties for ATPH in mind, we hoped to block the more accessible olefin face at which $LiMe_2Cu$ was attacking **31**. Unfortunately, ATPH is less well-studied in acyclic systems, and the complexation of enone **31** with ATPH followed by MeLi addition at –78°C yielded exclusively the wrong diastereomer. It appeared that ATPH only enhanced the innate diastereoselectivity for the undesired C-2 epimer. While this result was disappointing, it was assumed that if C-2 des-methyl enone **31** undergoes 1,4-addition from the undesired face in the presence of ATPH, perhaps trisubstituted enone **28** with the desired methyl already in place could undergo 1,4-addition of hydride from that same face. If the same facial selectivity could be achieved in this conjugate reduction as that seen in the formation of **32**, then the desired C-2 epimer **33** would be obtained. Quite gratifyingly, it was found that complexation of enone **28** with ATPH at 0 °C followed by exposure to L-selectride at –78 °C established the C-2 methyl stereocenter in 75% yield and 15:1 dr (Scheme 5C). Subsequently, standard TBAF-mediated desilylation (Scheme 4) then provided 91% yield of key alcohol **18** in seven steps from commercial materials with an overall yield of 24%.

Scheme 6. Alternative Synthesis of Key Alcohol



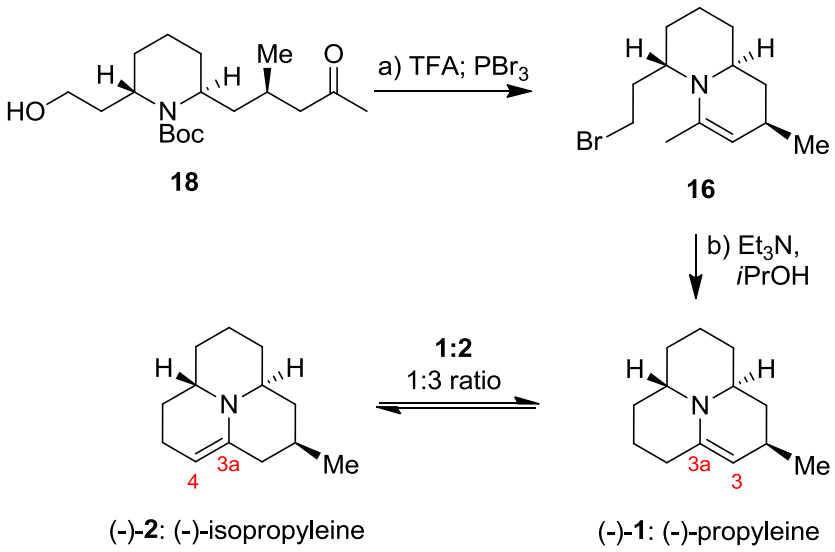
Reagents and conditions: (a) TBSCl, imidazole (b) *s*BuLi, TMEDA, CuCN·2LiCl, **34**, 92% over 2 steps (c) $K_2OsO_4{\cdot}2H_2O$, $NaIO_4$, 2,6-lutidine, 1,4-dioxane/H_2O 3/1 (d) **36** (e) $K_2OsO_4{\cdot}2H_2O$, $NaIO_4$, 2,6-lutidine, 1,4-dioxane/H_2O 3/1, 95% over 3 steps (f) TFAA, pyridine, DMAP (g) DBU, 80% over 2 steps (h) 2,6-diphenyl phenol, $AlMe_3$, L-selectride; aq. HCl, MeOH, 79%

While developing this concise synthesis of **18**, we also identified an alternative strategy to access our key alcohol that was operationally simpler and higher yielding, though it required more chemical transformations to complete (Scheme 6). The same starting material (i.e. **19**) could be TBS-protected overnight at room temperature and then allylated at –78 °C with **34** in 92% yield using the same copper-mediated procedure described previously, with subsequent Lemieux-Johnson oxidative cleavage delivering ketone **35**.[8] Moving forward, direct installation of the remaining carbons initially proved challenging. Methyl ketone **35** was unreactive to olefinating reagents that can directly form enones from ketones, and the olefin precursor to **35** (unshown) was recovered unchanged when subjected to olefin cross-metathesis conditions as an alternative mode of

enone formation. We believe the relative inertness of these substrates is due to the proximity of the desired reactive center to the bulky nitrogen protecting group. In order to circumvent this issue, the desired carbons were installed via treatment with 2-methylallylmagnesium chloride (**36**) at –78 °C which formed the tertiary alcohol product in an inconsequential 1.5:1 dr. Another Lemieux-Johnson oxidative cleavage gave hydroxy ketone **37** in 95% yield across three steps. Subsequent trifluoroacetylation at 0 °C followed by DBU-mediated elimination, also at 0 °C, then gave the required enone for diastereoselective reduction in 80% yield over two steps as a 1.5:1 mixture of olefin isomers. Finally, complexation of this mixture of isomers with ATPH at 0 °C and exposure to L-selectride at –78 °C followed by aqueous HCl quench at room temperature gave one-pot reduction and desilylation to deliver key alcohol **18** in 8:1 dr and 79% yield. Using this route, we were able to access our key intermediate in 55% overall yield and eight steps. Both this route and the one reported in Scheme 4 to alcohol **18** were employed for subsequent studies.

Section 3.2.2 Total Syntheses of (–)-Propyleine and (–)-Isopropyleine

Scheme 7. Total Syntheses of (-)-Propyleine and (-)-Isopropyleine



Reagents and conditions: (a) TFA/CH_2Cl_2, 1/1; PBr_3 (b) Et_3N, *i*PrOH, 43% over 2 steps

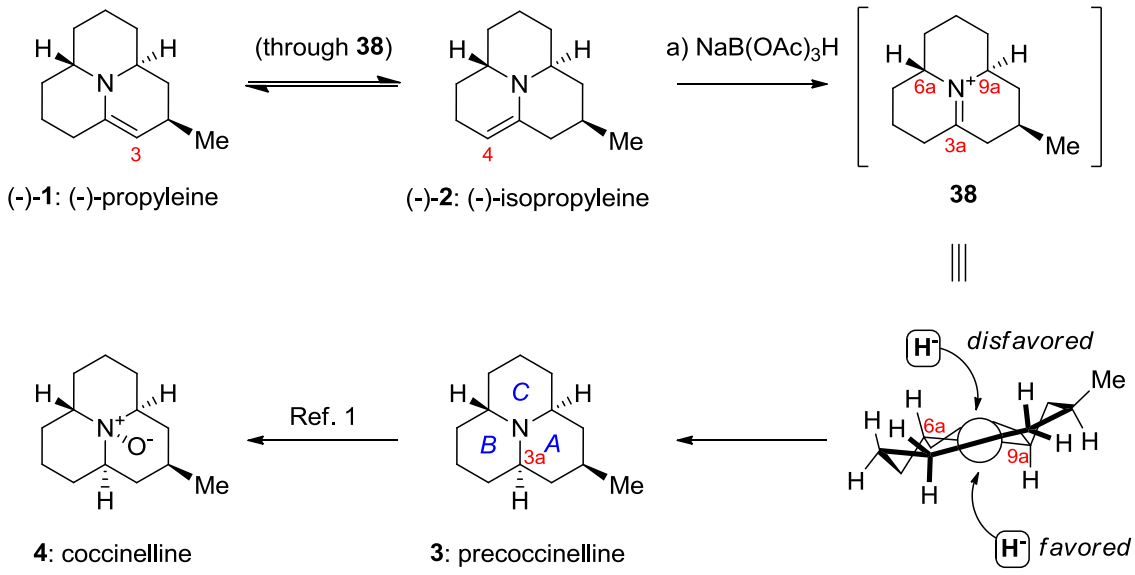
With our key alcohol in hand, we were able to realize our goal of rapidly accessing many monomeric frameworks. TFA-mediated deprotection of **18** at 0 °C and solvent removal followed by treatment of the resultant crude salt with PBr_3 in Et_2O at 70 °C in a sealed reaction vessel gave bromide **16** in a one-pot process. This bromide was carried forward crude as it proved to be highly reactive and often contained some material that had already cyclized to propyleine (**1**). Treatment of this species with Et_3N and *i*-PrOH overnight at room temperature fully cyclized this mixture to deliver (–)-propyleine ((–)-**1**) and (–)-isopropyleine ((–)-**2**) in a 1:3 ratio, respectively, in 43% yield over two steps. This ratio is the same as that reported by the Mueller group in their synthesis of this mixture of equilibrating monomers. This constitutes the shortest reported synthesis of these two molecules in only nine steps from commercial materials and proceeds in 10% overall yield. Furthermore, as the synthesized mixture of **1** and **2**

possesses the observed levorotatory property of the natural isolate, we have experimentally confirmed the absolute configuration of the natural stereocenters. It is worth noting that the stereochemistry of **1** and **2** match the absolute configuration reported for convergine (**6**), suggesting a possible biosynthetic relationship.

With these materials in hand, we could next begin exploring the synthesis of other tricyclic frameworks. We hypothesized that the prochiral *ipso* carbon, C-3a, of **1** and **2** could hold the key to accessing monomers with saturated ring fusions (**3** – **8**, Figure 1) through proper synthetic manipulation. Our approach focused on redox manipulation of this framework to synthesize either precoccinelline (**3**) or ketone **20** through divergent and chemoselective transformations.

Section 3.2.3 Total Synthesis of Precoccinelline and Formal Total Synthesis of Coccinelline

Scheme 8. Total Synthesis of Precoccinelline and Formal Total Synthesis of Coccinelline



Reagents and conditions: (a) $NaB(OAc)_3H$, 85%

We began testing our strategy through the preparation of precoccinelline (**3**). We were able to accomplish the synthesis of this monomer via reduction of **1** and **2** with $NaB(OAc)_3H$ at 0 °C in a 3.7:1 dr at C-3a and a combined yield of 85%, presumably through the intermediacy of iminium **38**, with the minor product being hippodamine (**5**). This route enabled us to access **3** in ten steps and 6.8% overall yield. A few comments must be made about the observed diastereoselectivity.

While it is possible that hydride delivery is merely occuring from a more accessible face, analysis of **38** does not appear to display a strong steric preference for one face over the other. It is also difficult to predict which face would be attacked by axial delivery of hydride due to the *trans* nature of the C-ring contained in **38**. With the

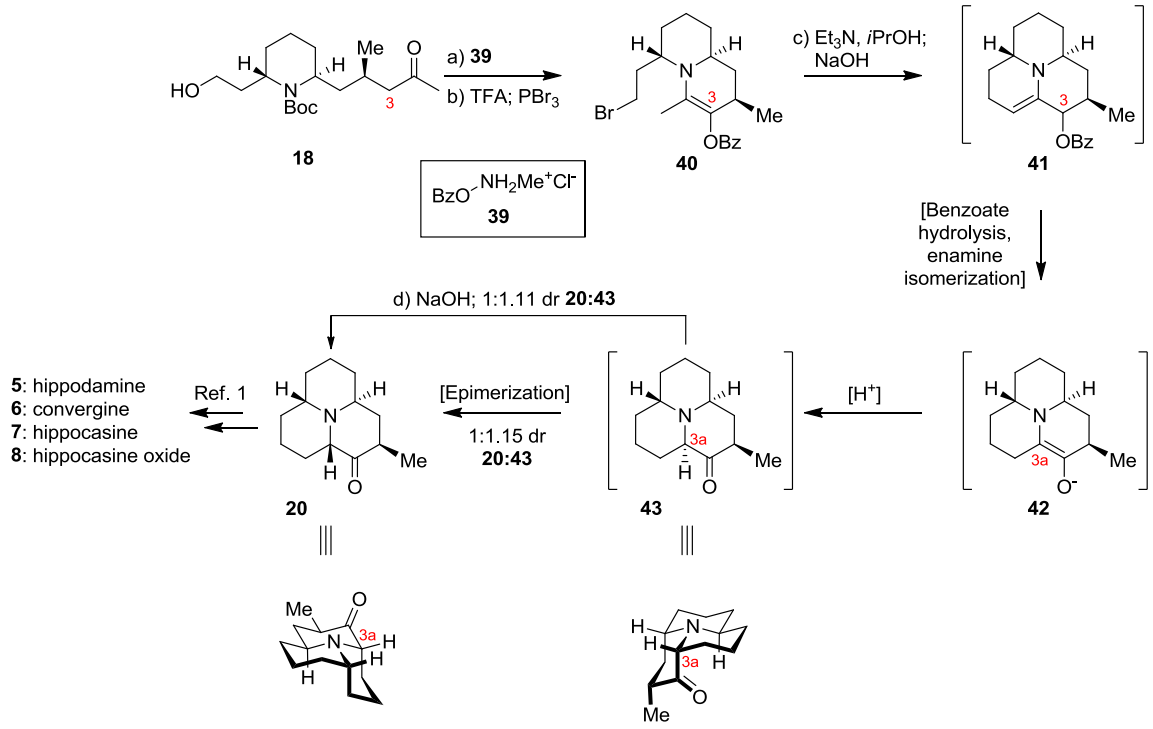
ring-fusion hydrogens at C-6a and C-9a each axially disposed, we propose that the C-ring exists as a twist boat (i.e. **38**, siting along the iminium C–N double bond in the 3D representation), making hydride delivery to the C-3a iminium axial with respect to one of the two rings irrespective of the face of delivery. However, with regard to the C-2 methyl group and the A-ring to which it is attached, hydride is preferentially delivered in an axial fashion to give the observed bias for precoccinelline (**3**). The minor hippodamine stereochemical outcome results from axial hydride delivery with respect to the B-ring which would drive the C-2 methyl axial, disfavoring this process. Finally, as has been shown by previous synthetic work in this class, **3** can be converted to its *N*-oxide, coccinelline (**4**), allowing us to claim a formal total synthesis of this oxidized monomer.[1]

Section 3.2.4 Enantioselective Formal Total Syntheses of Hippodamine, Convergine, Hippocasine, and Hippocasine Oxide

Shifting our attention to the remaining monomeric targets (**5** – **8**), we returned to key alcohol **18**. As shown in Scheme 9, utilizing an α-benzoyloxation procedure developed by Tomkinson and co-workers, we were able to install functionality at C-3 of **18** in 62% yield by exposing our key alcohol to hydroxylamine derivative **39** at room temperature for two days.[9] Subjecting this oxidized material to our one-pot TFA and PBr_3 procedure described for bromide **16** could also deliver crude bromide **40**. This material was often obtained as a mixture of bicycle **40** with small amounts of tricycle **41**. Employing *i*-PrOH and Et_3N, this mixture was fully cyclized at 40 °C to the tricyclic structure **41**, an oxidized variant of propyleine, which was subsequently treated with

aqueous sodium hydroxide at 65 °C in MeOH in the same pot to hydrolyze the benzoate ester and ultimately deliver desired ketone **20** with its C-3a epimeric ketone **43** in a 1:1.15 ratio (**20**:**43**) and 46% combined yield over two steps encompassing six distinct operations. We hypothesize that the alcohol that resulted from ester cleavage could undergo enamine isomerization and deprotonation to form amino-enolate **42**. This species could then capture a proton to give either ketone **20** or ketone **43**. After a facile chromatographic resolution, re-exposing pure ketone **43** to aqueous base established a 1:1.11 mixture of **20** to **43** in 38% combined yield, enabling the undesired ketone to be recycled. The desired ketone **20** was originally reported racemically by Mueller and co-workers in nine steps and was used to access monomeric natural products **5** – **8**.[1] Our asymmetric synthesis of **20** in ten steps constitutes formal enantioselective syntheses of these four monomers and compares favorably to the route developed by the Mueller group.

Scheme 9. Formal Enantioselective Synthesis of Hippodamine, Convergine, Hippocasine, and Hippocasine Oxide



Reagents and conditions: (a) **39**, 62% yield (b) TFA/CH_2Cl_2, 1/1; PBr_3 (c) Et_3N, *i*PrOH; NaOH, MeOH, 46% yield over 2 steps (d) NaOH, 38%

Though we were able to obtain our desired product, we were never able to form ketone **20** exclusively without its C-3a epimer. It was fortunate, however, that we were able to separate these two materials and develop a recycling process for **43** to form more of our desired ketone epimer. In initial efforts to synthesize **20**, ketone **43** was the only product observed upon hydrolysis of tricycle **41** under mild conditions at 25 °C, and it was found that extended reaction times and elevated temperature were required to form observable quantities of **20**. Furthermore, the outcome of this reaction seemed to be batch dependent, giving ratios slightly favoring to slightly disfavoring ketone **20**. Undesired ketone **43** is of the stereochemical configuration required for precoccinelline (**3**) and appears to be the kinetic outcome of benzoate hydrolysis. Thus, it is conceivable that the kinetic facial preference for axial proton capture at C-3a for amino-enolate **42** is partially

determined by the C-2 methyl group in much the same way that we hypothesize the C-2 methyl affected the diastereomeric preference for hydride delivery to **38** in Scheme 8. We also believe that the kinetic preference for ketone **43** is determined by the fact that the C-3a stereochemistry in this isomer places the C-3a proton axial with respect to the C-3 ketone, likely the kinetic preference for protonation of the enolate in **42**. Moreover, the ability to form **20** only at elevated temperatures and prolonged exposure to base is indicative of a thermodynamically controlled outcome and reversible epimerization of C-3a. This is supported by the observation that pure **20** or **43** can reform a distribution with its respective epimer when re-exposed to reaction conditions. Finally, there do not appear to be any elements within the structures of **20** and **43** that could significantly influence their relative stabilities, which would provide an explanation for the nearly 1:1 distributions observed of these compounds when exposed to reversible conditions. While it is unfortunate that ketone **20** could not be formed exclusively in the developed route, turning C-3a into an epimerizable center allowed us to work around the kinetic preference for the precoccinelline stereochemistry and form a molecule with the stereochemistry necessary for four other monomers.

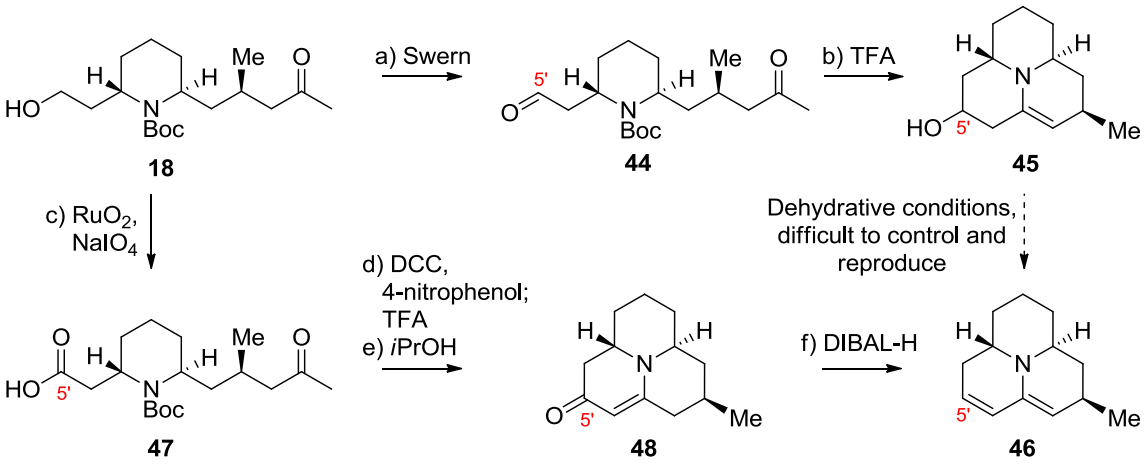
It is noteworthy that in this sequence devised to access ketone **20**, treatment of key alcohol **18** with **39** ultimately enabled the installation of an increase in oxidation level in the propyleine framework with regiocontrol. Indeed, this outcome demonstrated that our designed key intermediate does allow for selective modification at an early stage that is easily translated into tricyclic frameworks. To highlight the elegance and necessity of this approach, preliminary approaches to access ketone **20** by treating propyleine (**1**)

with an oxidant directly were not successful, requiring us to develop this non-direct, regioselective strategy to obtain our desired product.

Section 3.2.5 Attempted Biomimetic Dimerization to Form Psylloborine A and Isopsylloborine A

With all azaphenalene monomers containing a *trans*-substituted C-ring accessed, we next sought to apply our route to dimers **9** and **10**. As predicted, direct oxidation of the mixture of enamine monomers **1** and **2** to extended iminium **12** proved difficult (Scheme 1), and we embarked on our initially proposed alternative route to the biomimetic electrophile (Scheme 2), targeting dienamine **46** (the neutral form of iminium **12**) from our key alcohol. As shown in Scheme 10, Swern oxidation smoothly delivered aldehyde **44** in 94% yield from key alcohol **18**, and TFA-mediated deprotection followed by enamine condensation and spontaneous aldehyde attack delivered hydroxy tricycle **45** in 75% yield based on crude ^{1}H NMR analysis. This material was unstable, not amenable to purification, and difficult to dehydrate as desired. While we could occasionally perform the desired elimination to dienamine **46** under various conditions, these procedures were capricious, difficult to reproduce, and often led to significant amounts of decomposition. It was hypothesized that the enamine contained within the starting material for this dehydration was itself reacting with the reagents screened, and an intermediate in which this enamine was less reactive might prove more fruitful for the production of dienamine **46**.

Scheme 10. Synthesis of Electrophile for Dimerization



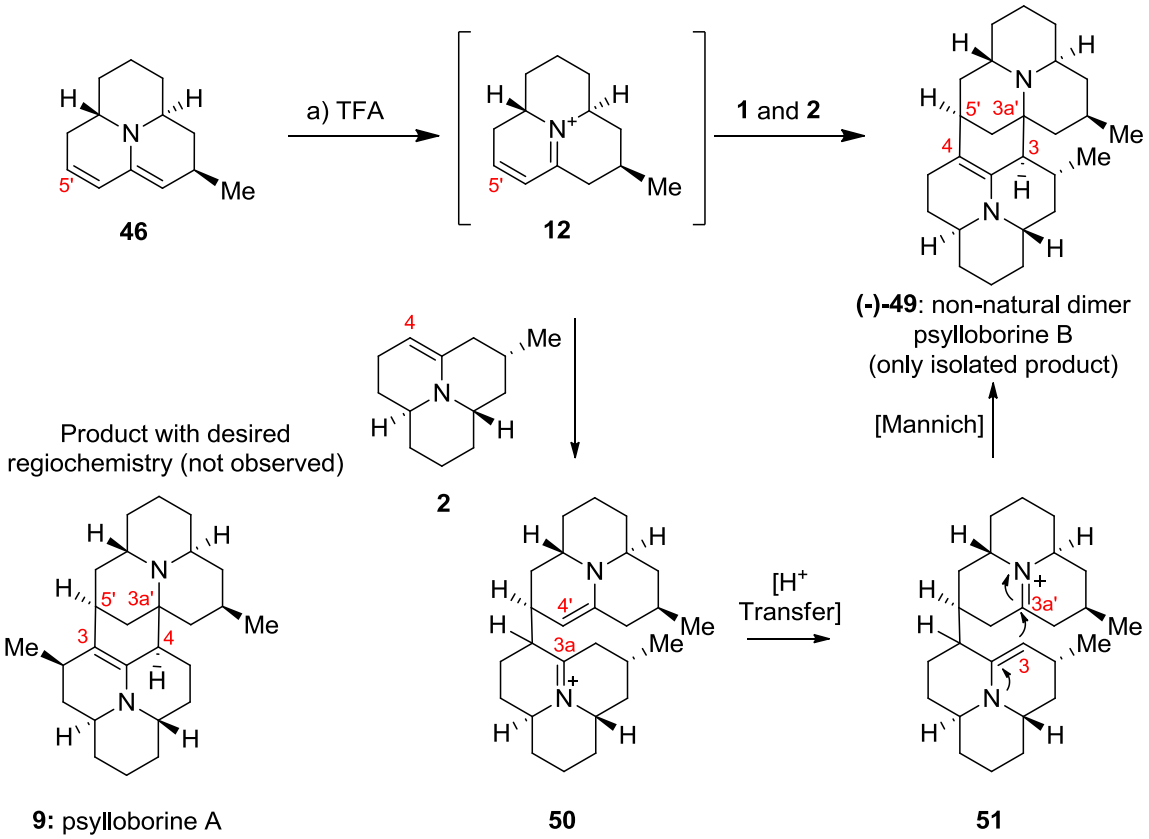
Reagents and conditions: (a) $(COCl)_2$, DMSO, Et_3N, 94% (b) TFA/CH_2Cl_2, 1/1, 75% (c) RuO_2, $NaIO_4$, acetone/H_2O 1/1, 77% (d) DCC, 4-nitrophenol, DMAP; TFA/CH_2Cl_2, 1/1 (e) *i*PrOH, 31% over 2 steps (f) DIBAL-H, 45%

In order to test this idea, we targeted tricycle **48**, a material in which the enamine functional group would likely be far less reactive masked as a vinylogous amide (or enaminone). Alcohol **18** was oxidized to carboxylic acid **47** through the action of catalytic RuO_4 in 77% yield.[10] This acid was converted into an activated ester upon exposure DCC and 4-nitrophenol at room temperature. Filtration of precipitated solids in the coupling step and concentration of the crude material was followed immediately by TFA-mediated carbamate removal at 0 °C, providing a bicyclic enamine after a careful, cold aqueous workup. Nucleophilic attack on the activated ester was promoted by *i*-PrOH at 40 °C and provided tricyclic vinylogous amide **48** in 31% yield across two steps encompassing a total of four chemical transformations. Pleasingly, vinylogous amide **48** was far easier to handle than alcohol **45**, and reduction and subsequent *in situ* elimination with DIBAL-H reproducibly gave a 45% yield of dienamine **46**, based on crude ^{1}H NMR analysis. The other major component of the crude mixture was the product of olefin

reduction (unshown). Unfortunately, dienamine **46** was unstable, difficult to purify, and had to be carried forward in crude form immediately after preparation.

Having overcome these challenges with the synthesis of **46**, we were now able to begin synthetic studies to explore our biosynthetic hypothesis. Thus, taking up the crude dienamine in CH_2Cl_2 and adding an equivalent of TFA delivered the desired extended iminium at C-5a' (**12**, Scheme 11). This species was surprisingly stable and could be observed by ^{1}H NMR if generated in a deuterated solvent. Quite excitingly, introduction of the mixture of enamine monomers **1** and **2** to this electrophilic species gave 46% yield of a dimeric product based on presumed purity of the dienamine **46**, or 21% overall yield from vinylogous amide **48**. Unfortunately, ^{1}H NMR comparison to the reported dimers **9** and **10** revealed that this material was not a known natural product, but instead a closely related structural isomer. Based on extensive 2D NMR analysis, we have assigned this material as non-natural dimer (–)-**49**, which we have named psylloborine B (See Experimental Section for more information). This product is presumed to be the result of C-4 enamine attack on C-5a' in a pseudoaxial orientation (**50**) followed by Mannich closure of the second dimeric linkage (**51**), which proceeded in the same cascade-based manner as proposed for **9** and **10** in Scheme 1. The resultant dimer, though very similar to psylloborine A (**9**), is ultimately the product of the wrong regiochemical outcome of initial nucleophilic attack. It should be noted that many related substrates and conditions other than those described here were explored but failed to provide any identifiable dimeric material, and psylloborine B was only observed for experiments performed in CH_2Cl_2.

Scheme 11. Synthesis of Non-Natural Dimer Psylloborine B (**49**)



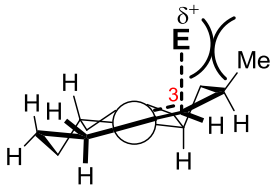
Reagents and conditions: (a) TFA, **1** and **2**, 46% from **46**, or 21% over 2 steps from **48**

We believe the observed outcome is again being steered primarily by the C-2 methyl. In theory, the enamine nucleophile has four potential sites of attack: C-3 or C-4 from the top or bottom face as shown in Figure 2. The desired, proposed pathway to **9** or **10** would be the result of initial attack from C-3. An analysis of the four possible transition states of nucleophilic attack can provide a possible explanation for the observed experimental outcome of only attack from C-3.

Figure 2. Justification for Observed Dimerization Result

A. Destabilizing interactions for C-3 regiochemistry

Steric repulsion for top-side approach



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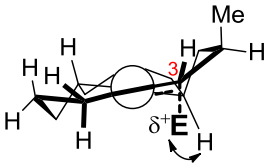
Bottom-side attack requires pseudoboat-like transition state with flag-pole interactions



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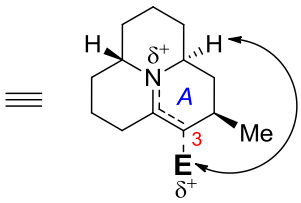
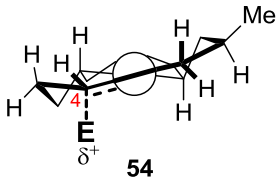


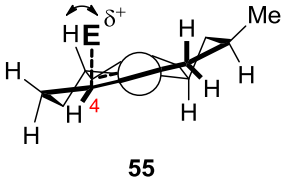
B. Transition states for C-4 regiochemistry

Bottom-side attack in pseudochair-like transition state

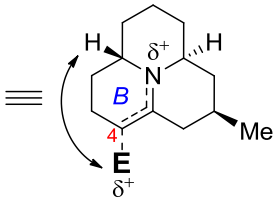


54

Top-side attack requires pseudoboat-like transition state with flag-pole interactions



55



As shown in Figure 2, transition state analysis suggests that bottom face attack from C-4 is the lowest energy pathway, explaining the observed product **49**. Nucleophilic attack from C-3 on **12** from the top face of **1** would form a favorable pseudochair-like transition state, but it also requires the incoming electrophile to approach *syn* to the C-2 methyl (**52**), likely an unfavorable steric penalty (Figure 2A, siting along C–N bond of the enamine). Similarly, pseudoaxial attack from C-3 on the bottom face of **1** *anti* to the C-2 methyl would require a pseudoboat-like transition state (**53**), also presumed to be a destabilizing factor with flagpole and eclipsing interactions in the A-ring. Finally, the B-ring containing the C-4 enamine in **2** does not have a substituent that can sterically destabilize approach of the electrophile. Therefore, the lowest energy pathway is likely a result of a pseudochair-like transition state with pseudoaxial attack from the bottom face at C-4 in **2** (**54**, Figure 2B). It is likely that the pseudoboat-like transition state **55** for

attack from the top face of C-4 in **2** is destabilized by flagpole and eclipsing interactions in the B-ring, though we cannot say for certain which face C-4 attacks from as this chiral center has been destroyed in the final dimer **49**.

To summarize the above arguments, we propose that the isolated non-natural dimer psylloborine B (**49**) arises from the C-2 methyl group raising the energy for the desired pseudochair-like transition state of attack from C-3 through steric repulsion, making bottom-face attack from C-4 the lowest energy pathway. With this result in hand, it is our opinion that these dimers may be synthesized with the proper regiochemistry in nature through an enzymatic process or the use of starting materials different from monomers **1** and **12**. Undeterred by these results, we focused on the development of a new, non-obvious dimerization strategy to synthesize **9** or **10** from our key alcohol **18**. The development of such a strategy will be the focus of Chapter 4.

Section 3.3 Conclusion and Future Directions

In conclusion, this chapter has detailed the development of our unified strategy to access monomeric and dimeric frameworks of the oligomeric coccinellid alkaloids. Employing key intermediate **18**, a material designed with chemoselective, divergent synthetic pathways in mind, total syntheses of (–)-propyleine ((–)-**1**), (–)-isopropyleine ((–)-**2**) and precoccinelline (**3**) were accomplished, as well as a formal synthesis of coccinelline (**4**) and enantioselective formal syntheses of hippodamine (**5**), convergine (**6**), hippocasine (**7**), and hippocasine oxide (**8**). Attempts at proposed biomimetic dimerization cascades were not successful in delivering homodimers **9** or **10**, but instead

gave non-natural dimer (–)**-49**. We believe this outcome is the result of the sole desymmetrizing element, the C-2 methyl group, raising the transition state energy for a productive dimerization pathway. Furthermore, we discovered in our monomeric syntheses that the C-2 methyl group appears to have a steering effect on the stereochemical outcome of transformations at the C-3a stereocenter. This effect was beneficial in our synthesis of **3**, but in the synthesis of ketone **20**, we believe epimerization was hampered by the facial preference for protonation axial with respect to the C-2 methyl group. Finally, it is our belief that a new strategy is needed to access homodimers **9** and **10**, and the results of these efforts will be described at length in Chapter 4.

Acknowledgements

Adam Trotta is acknowledged for preparation of synthetic intermediates and exploration of the epimerization strategy to obtain ketone **20** used to claim formal synthesis of hippodamine, convergine, hippocasine, and hippocasine oxide. Tara Pesce is acknowledged for preparation of synthetic intermediates. Dr. Adel ElSohly is acknowledged for helpful conversations. Dr. Yasuhiro Itagaki is acknowledged for mass spectrometric analysis. Dr. John Decatur is acknowledged for NMR assistance.

Section 3.4 References

1. For a full discussion of work done by Mueller and co-workers, see Chapter 2. A selected reference detailing these studies in full is also provided here: R. H. Mueller, M. E. Thompson, R. M. DiPardo, *J. Org. Chem.*, **1984**, *49*, 2217 – 2231.

2. (a) P. Laurent, J.-C. Braekman, D. Daloze, J. M. Pasteels, *Insect Biochemistry and Molecular Biology* **2002**, *32*, 1017 – 1023. (b) E. Haulotte, P. Laurent, J.-C. Braekman, *European J. Org. Chem.* **2012**, 1907 – 1912.

3. (a) J. G. Duboudin, B. Jousseaume, *J. Organometallic Chem.* **1979**, *168*, 1 – 11. (b) Y. Naruta, Y. Nishigaichi, K. Maruyama, *J. Org. Chem.* **1991**, *56*, 2011 – 2017.

4. D. Stead, G. Carbone, P. O'Brien, K. R. Campos, I. Coldham, A. Sanderson, *J. Am. Chem. Soc.* **2010**, *132*, 7260 -7261.

5. J. M. Brown, *Angew. Chem. Int. Ed.* **1987**, *26*, 190 – 203.

6. G. P. Howell, *Org. Process Res. Dev.* **2012**, *16*, 1258 – 1272.

7. K. Maruoko, I. Shimada, H. Imoto, H. Yamamoto, *Synlett.* **1994**, *7*, 519 – 520.

8. W. Yu, Y. Mei, Y. Kang, Z. Hua, Z. Jin, *Org. Lett.* **2004**, *6*, 3217 – 3219.

9. C. S. Beshara, A. Hall, R. L. Jenkins, K. L. Jones, T. C. Jones, N. M. Killeen, P. H. Taylor, S. P. Thomas, N. C. O. Tomkinson, *Org. Lett.* **2005**, *7*, 5729 – 5732.
10. H. Irngartinger, W. Reimann, P. Garner, P. Dowd, *J. Org. Chem.* **1988**, *53*, 3046 – 3050.

Section 3.5 Experimental Section

General Procedures. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), acetonitrile (MeCN), toluene, benzene, diethyl ether (Et_2O) and methylene chloride (CH_2Cl_2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and either an aqueous solution of ceric ammonium sulfate and ammonium molybdate and heat or an aqueous solution of potassium permanganate and sodium bicarbonate and heat as developing agents. SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker DRX-300, DRX-400, DMX-500 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, br = broad, AB = AB quartet, app = apparent. IR spectra were recorded on a Perkin-Elmer 1000 series FT-IR spectrometer. High-resolution mass spectra (HRMS) were

recorded in the Columbia University Mass Spectral Core facility on a JOEL HX110 mass spectrometer using the MALDI (matrix-assisted laser-desorption ionization) technique.

Abbreviations. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DCC = *N,N'*-dicyclohexylcarbodiimide, DCU = *N,N'*-dicyclohexylurea, DIPEA = *N,N*-diisopropylethylamine, DMAP = 4-dimethylaminopyridine, DMSO = dimethylsulfoxide, KHMDS = potassium bis(trimethylsilyl)amide, TBAF = tetra-*n*-butylammonium fluoride, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl, TFA = trifluoroacetic acid, TFAA = trifluoroacetic anhydride, TMEDA = *N,N,N',N'*-tetramethylethylenediamine.

(*S*)-1-*N*-Boc-(–)-Piperidine-2-ethanol 19. This chiral material was prepared using the following homologation procedure from (*S*)-1-*N*-Boc-pipecolic acid. Alternatively, **19** can be purchased commercially from a number of suppliers. (*S*)-1-*N*-Boc-pipecolic acid (39.8 g, 174 mmol, 1.0 equiv) was dissolved in THF (430 mL) and cooled to 0 °C. BH_3•Me_2S complex (28.8 mL, 305 mmol, 1.75 equiv) was added dropwise at 0 °C and the solution was stirred at 0 °C. After 1 h at 0 °C, the reaction mixture was warmed to 25 °C and stirred for an additional 12 h. Upon completion, the reaction mixture was cooled to 0 °C. Saturated aqueous $NaHCO_3$ (400 mL) was added slowly to quench excess reagent, and water (200 mL) was added to dissolve precipitated salts. The crude reaction was extracted with CH_2Cl_2 (4 × 500 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (3 × 300 mL) and water (3 × 300 mL), dried ($MgSO_4$), and concentrated to give crude (*S*)-1-*N*-Boc-homoprolinol (37.6 g, 100% yield) as a white solid. This material was carried forward without additional purification. Oxalyl chloride (22.6 mL, 263 mmol, 1.5 equiv) was dissolved in CH_2Cl_2

(375 mL) and cooled to –78 °C. DMSO (37.2 mL, 525 mmol, 3.0 equiv) was dissolved in CH_2Cl_2 (375 mL), cooled to –78 °C, and cannulated into the oxalyl chloride solution slowly over 1.5 h dropwise to prevent internal exotherm. Upon completion of DMSO addition, the reaction mixture was stirred at –78 °C for 25 min. During this time, a solution of (*S*)-1-*N*-Boc-homoprolinol (37.6 g, 174 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (375 mL) and cooled to –78 °C. This solution was cannulated into the reaction mixture over the course of 1 h dropwise to prevent internal exotherm. Upon completion of cannulation, the reaction mixture was stirred at –78 °C for 25 min. DIPEA (182.6 mL, 1050 mmol, 6.0 equiv) was added rapidly at this point, and the reaction mixture was slowly warmed from –78 °C to 0 °C over the course of 6 h. Upon reaching 0 °C, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (1000 mL). The crude reaction mixture was extracted with CH_2Cl_2 (3 × 300 mL). The combined organic extracts were washed with water (2 × 500 mL), saturated aqueous NH_4Cl (2 × 500 mL) and water (2 × 500 mL), dried ($MgSO_4$), and concentrated to give the desired crude aldehyde as a yellow oil in assumed quantitative yield. This crude material was immediately carried forward without additional purification. Methyl triphenylphosphonium bromide (68.7 g, 193 mmol, 1.1 equiv) was suspended in toluene (875 mL) and cooled to 0 °C. To this suspension, KHMDS (0.5 M in toluene, 385 mL, 193 mmol, 1.1 equiv) was added at 0 °C. The resultant bright yellow suspension was stirred for 30 min, and a solution of the freshly prepared aldehyde in toluene (400 mL) was rapidly cannulated into the reaction mixture. The reaction was allowed to warm from 0 °C to 25 °C for 16 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (500 mL). The crude reaction mixture was extracted

with CH_2Cl_2 (3 × 400 mL). The combined organic extracts were washed with water (2 × 500 mL), dried ($MgSO_4$), and concentrated. The resultant crude brown solid was purified by flash column chromatography (silica gel, hexanes/EtOAc, 9/1) to give the desired olefin (28.2 g, 78% yield over 2 steps) as a clear oil. BH_3•Me_2S complex (25.5 mL, 268 mmol, 2.0 equiv) was dissolved in hexanes (570 mL) and cooled to 0 °C. To this solution, 2-methyl-2-butene (57 mL, 536 mmol, 4.0 equiv) was added dropwise and the resultant clear solution was stirred at 0 °C for 3 h. The freshly prepared olefin (28.2 g, 134 mmol, 1.0 equiv) was dissolved in hexanes (510 mL), cooled to 0 °C, and cannulated dropwise into the reaction mixture over 70 min. The reaction mixture was stirred from 0 °C with slow warming to 25 °C over 3.5 h at which time thin layer chromatography revealed the complete consumption of starting material. The reaction mixture was then recooled to 0 °C. 1 M aqueous NaOH (850 mL) was added slowly with evolution of gas. Once the evolution of gas stopped, aqueous H_2O_2 (30%, 850 mL) was added slowly. The reaction mixture was allowed to warm from 0 °C to 25 °C over the course of 16 h. This crude reaction mixture was extracted with CH_2Cl_2 (3 × 1000 mL). The combined organic extracts were washed with water (1 × 1000 mL), dried ($MgSO_4$), and concentrated. The resultant crude clear oil was purified by flash column chromatography (silica gel, hexanes/EtOAc, 19/1 to 1/1) to give *(S)*-1-*N*-Boc-(–)-piperidine-2-ethanol **19** (25.2 g, 82% yield) as a clear oil.

Bromide 26. CuI (3.41 g, 17.9 mmol, 0.1 equiv) was suspended in Et_2O (180 mL) and cooled to –10 °C. Propargyl alcohol (10.5 mL, 179 mmol, 1.0 equiv) was added to the suspension, and allylmagnesium bromide (1.0 M in Et_2O, 450 mL, 450 mmol, 2.5 equiv) was rapidly cannulated into the light brown reaction mixture. The reaction initially

darkened and then thickened in consistency until a deep brown or black slurry was formed. Occasionally, mechanical stirring was arrested by the slurry and manual agitation was required to break the stir bar free from contained solids. After the addition of Grignard was complete, the reaction contents were warmed to 25 °C and stirred at 25 °C for 1 h. Upon completion, the reaction contents were cooled to 0 °C and quenched very slowly by the addition of saturated aqueous NH_4Cl (500 mL) and water (500 mL). A quench not performed very slowly will result in a runaway, violent exotherm in which large portions of reaction mixture erupt from the reaction vessel. The crude reaction mixture was extracted with Et_2O (4 × 300 mL). The combined organic extracts were dried ($MgSO_4$), and concentrated. The desired alcohol was obtained as a crude yellow oil and was carried forward without additional purification. The obtained alcohol was dissolved in hexane (195 mL) and cooled to –10 °C. Pyridine (4.35 mL, 53.9 mmol, 0.3 equiv) and PBr_3 (8.43 mL, 89.7 mmol, 0.5 equiv) were added sequentially, and the resultant cloudy yellow solution was stirred at –10 °C for 5 min. The solution was slowly warmed to 0 °C over 2 h. Upon completion, the reaction contents were cooled to 0 °C and quenched by the addition of small handfuls of ice and water (500 mL). The crude reaction mixture was extracted with pentane (4 × 100 mL). The combined organic extracts were washed with water (2 × 200 mL), saturated aqueous $NaHCO_3$ (1 × 200 mL), dried ($MgSO_4$), and concentrated until all pentane was removed. The resultant solution of bromide **26** in hexane was immediately used in the following procedure and considered to be roughly 85% yield. Alternatively, this material can be purchased commercially.

Deconjugated diene 27. *(S)*-1-*N*-Boc-(–)-piperidine-2-ethanol **19** (25.0 g, 109 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (220 mL) at 25 °C. Imidazole (14.8 g, 218

mmol, 2.0 equiv) and TBDPSCl (29.8 mL, 115 mmol, 1.05 equiv) were added sequentially to this solution at 25 °C, and a white solid quickly precipitated. The reaction was stirred at 25 °C for 19 h after which time MeOH (50 mL) was added to the reaction mixture to quench excess reagent. The reaction contents were stirred at 25 °C for 1 h more and then quenched by addition of water (500 mL). The crude reaction mixture was extracted with CH_2Cl_2 (3 × 500 mL). The combined organic extracts were washed with water (3 × 500 mL), dried ($MgSO_4$), and concentrated to give the desired silylated product as a crude clear oil. This material was carried forward crude without additional purification. A portion of this freshly prepared material (24.0 g, 51.2 mmol, 1.0 equiv) and freshly distilled TMEDA (12.3 mL, 81.9 mmol, 1.6 equiv) were dissolved in Et_2O (340 mL) and cooled to –78 °C. *s*-BuLi (1.4 M in cyclohexane, 55 mL, 76.8 mmol, 1.5 equiv) was added dropwise at –78 °C. The resultant yellow solution was then allowed to warm slowly to –45 °C and was kept at –45 °C for 1 h. At this time, the reaction mixture was cooled to –78 °C. A solution of CuCN•2LiCl complex (0.6 M in THF, 128 mL, 76.8 mmol, 1.5 equiv) was freshly prepared by dissolving CuCN (6.88 g, 76.8 mmol, 1.5 equiv) and flame-dried LiCl (6.51 g, 154 mmol, 3.0 equiv) in THF (128 mL) at 25 °C. This green solution was added dropwise to the reaction mixture at –78 °C over which time the reaction mixture slowly turned pale and then a deep orange. The resultant orange solution was stirred at –78 °C for 1 h, and then crude bromide **26** (22.5 g, 154 mmol, 3.0 equiv) was added rapidly at –78 °C. The solution immediately darkened and was allowed to warm to 25 °C over 4 h. The reaction was quenched by addition of a premixed solution of saturated aqueous NH_4Cl (300 mL) and concentrated NH_4OH (50 mL) at 25 °C and stirred at 25 °C for 1 h. The crude reaction mixture was diluted with water (300 mL)

extracted with Et_2O (4 × 300 mL). The combined organic extracts were dried ($MgSO_4$), and concentrated. The resultant crude grey oil was purified by flash column chromatography (silica gel, hexanes/EtOAc, 99/1 to 9/1) to give deconjugated diene **27** (23.6 g, 84% yield) as a clear oil. **27**: R_f = 0.62 (silica gel, hexanes/EtOAc, 9/1); $[\alpha]_D^{20}$ = –0.8° (*c* = 0.70, $CHCl_3$); IR (film) ν_{max} 3072, 2932, 2859, 1687, 1644, 1392, 1365, 1110, 703, 505; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.65 (m, 4 H), 7.44 – 7.35 (m, 6 H), 5.83 (ddt, *J* = 16.9, 10.1, 6.9 Hz, 1 H), 5.10 – 5.01 (m, 2 H), 4.80 (s, 2 H), 3.96 (dq, *J* = 8.7, 4.1 Hz, 1 H), 3.83 (dq, *J* = 9.2, 4.6 Hz, 1 H), 3.71 (t, *J* = 6.7, 1 H), 2.79 (d, *J* = 6.8 Hz, 2 H0, 2.42 (dd, *J* = 13.4, 4.6 Hz, 1 H), 2.19 (dd, *J* = 13.2, 10.0 Hz, 1 H), 2.05 – 1.95 (m, 1 H), 1.85 – 1.77 (m, 1 H), 1.77 – 1.55 (m, 6 H), 1.41 (s, 9 H), 1.05 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 146.0, 136.5, 135.7, 134.1, 129.7, 127.8, 116.3, 112.5, 79.2, 62.7, 50.4, 49.6, 40.9, 40.3, 37.7, 28.7, 27.0, 25.0, 23.2, 19.3; HRMS (MALDI-FTMS) calcd for $C_{34}H_{50}NO_3Si^+$ [M^+] 548.3560, found 548.3576.

Enone 28. Deconjugated diene **27** (23.6 g, 43.1 mmol, 1.0 equiv) was dissolved in DMF (160 mL) and water (16 mL). CuCl (4.27 g, 43.1 mmol, 1.0 equiv) and $PdCl_2(PhCN)_2$ (1.65 g, 4.31 mmol, 0.1 equiv) were added sequentially, the reaction mixture was warmed to 60 °C, and the resultant brown solution was charged with O_2 gas (1 atm) via bubbling through the solution until the reaction turned green. After stirring at 60 °C for 2 h, another portion of $PdCl_2(PhCN)_2$ (1.65 g, 4.31 mmol, 0.1 equiv) was added and O_2 gas was bubbled through the reaction mixture for 20 min. The reaction contents were then stirred at 60 °C for 2 h. At this time, another portion of $PdCl_2(PhCN)_2$ (1.65 g, 4.31 mmol, 0.1 equiv) was added and O_2 gas was bubbled through the reaction mixture for 20 min. The reaction was then stirred at 60 °C for 4 h. Upon completion, the reaction

contents were cooled to 25 °C and quenched by the addition of water (500 mL) and Et_2O (200 mL). The crude reaction mixture was extracted with Et_2O (5 × 200 mL). The combined organic extracts were washed with water (5 × 300 mL), dried ($MgSO_4$), and concentrated. The resultant crude brown oil was purified by flash column chromatography (silica gel, hexanes/Et_2O, 19/1 to 3/1) to give the desired ketone (10.0 g, 41% yield) as a yellow oil. A portion of this material (8.0 g, 14.2 mmol, 1.0 equiv) was dissolved in *i*-PrOH (140 mL) at 25 °C. 1 M aqueous NaOH (28.4 mL, 28.4 mmol, 2.0 equiv) was added in a single portion and the pale yellow reaction contents were stirred at 25 °C for 1 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (200 mL), water (200 mL) and CH_2Cl_2 (400 mL). The crude reaction mixture was extracted with CH_2Cl_2 (4 × 400 mL). The combined organic extracts were washed with water (3 × 400 mL), dried ($MgSO_4$), and concentrated to give the desired enone **28** (8.0 g, 100% yield) as a 4:1 mixture of olefins. This material was carried forward without additional purification. For characterization purposes, a portion of this material was purified using preparative thin layer chromatography (silica gel, hexanes/EtOAc, 4/1). **28**, major isomer: R_f = 0.27 (silica gel, hexanes/EtOAc, 9/1); $[\alpha]_D^{20}$ = –6.6° (*c* = 0.75, $CHCl_3$); IR (film) ν_{max} 2932, 2858, 1685, 1614, 1391, 1364, 1172, 1108, 1082, 702, 504; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.62 (m, 4 H), 7.43 – 7.35 (m, 6 H), 6.08 (s, 1 H), 4.04 – 3.96 (m, 1 H), 3.87 (dq, *J* = 9.1, 4.6 Hz, 1 H), 3.71 (t, *J* = 6.6 Hz, 1 H), 2.58 (dd, *J* = 12.7, 4.7 Hz, 1 H), 2.19 (dd, *J* = 12.8, 11.2 Hz, 1 H), 2.17 (d, *J* = 0.8 Hz, 3 H), 2.00 – 1.90 (m, 1 H), 1.85 – 1.73 (m, 3 H), 1.73 – 1.65 (m, 2 H), 1.65 – 1.53 (m, 2 H), 1.41 (s, 9 H), 1.05 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7, 156.1, 155.2, 135.7, 134.0, 133.9, 129.7, 127.8, 127.8, 125.5, 79.6, 62.6, 50.3, 49.6, 45.8, 37.7,

31.9, 28.7, 27.0; HRMS (MALDI-FTMS) calcd for $C_{34}H_{50}NO_4Si^+$ [M^+] 564.3509, found 548.3527. **28**, minor isomer: R_f = 0.40 (silica gel, hexanes/EtOAc, 9/1); $[\alpha]_D^{20}$ = +7.1° (*c* = 0.25, $CHCl_3$); IR (film) ν_{max} 2931, 2858, 1685, 1614, 1390, 1364, 1171, 1108, 1083, 703, 505; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.63 (m, 4 H), 7.42 – 7.34 (m, 6 H), 6.08 (s, 3 H), 4.13 – 4.05 (m, 1 H), 3.79 (m, 1 H), 3.68 (t, *J* = 6.8 Hz, 1 H), 3.52 (dd, *J* = 12.4, 9.2 Hz, 1 H), 2.50 (dd, *J* = 12.4, 5.6 Hz, 1 H), 2.13 (s, 3 H), 2.00 – 1.87 (m, 1 H), 1.90 (d, *J* = 0.8 Hz, 3 H), 1.82 – 1.60 (m, 4 H), 1.60 – 1.48 (m, 3 H), 1.39 (s, 9 H), 1.04 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 156.7, 155.4, 135.7, 134.1, 129.7, 127.8, 125.9, 79.3, 62.7, 50.5, 49.7, 37.7, 37.1, 32.1, 28.7, 27.0, 24.9, 24.4, 24.0, 19.3, 14.4; HRMS (MALDI-FTMS) calcd for $C_{34}H_{50}NO_4Si^+$ [M^+] 564.3509, found 564.3508.

Key Alcohol 18. 2,6-diphenyl phenol (7.08 g, 28.8 mmol, 4.5 equiv) was dissolved in CH_2Cl_2 (100 mL) at 25 °C. $AlMe_3$ (2.0 M in hexane, 4.8 mL, 9.6 mmol, 1.5 equiv) was added in a single portion at 25 °C, and the resultant yellow-orange solution evolved gas rapidly. The reaction contents were stirred at 25 °C for 40 min. The reaction contents were then cooled to 0 °C and stirred at 0 °C for 1 hr. A pre-cooled solution of enone **28** (3.60 g, 6.40 mmol, 1.0 equiv) at 0 °C in CH_2Cl_2 (35 mL + 17 mL rinse) was added dropwise over 15 min. The resultant bright yellow solution was stirred at 0 °C for 5 min, cooled to –78 °C and stirred at –78 °C for 1 h. L-selectride (1.0 M in THF, 12.8 mL, 12.8 mmol, 2.0 equiv) was added dropwise over 5 min, and the resultant yellow solution was stirred at –78 °C for 1 h. Upon completion, the reaction was quenched by the addition of 1 M aqueous HCl (150 mL) with vigorous stirring at –78 °C and immediately warmed to 25 °C and stirred at 25 °C for 30 min. The crude reaction mixture was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were washed

with water (2 × 200 mL), dried ($MgSO_4$), and concentrated. The resultant crude orange oil was purified by flash column chromatography (silica gel, hexanes/Et_2O, 19/1 to 4/1) to give the ketone product (2.71g, 75% yield) as a pale yellow oil. This reaction was repeated several times to obtain larger amounts of the desired ketone. This ketone (5.12 g, 9.06 mmol, 1.0 equiv) was dissolved in THF (45 mL) at 25 °C. TBAF (1.0 M in THF, 18.1 mL, 18.1 mmol, 2.0 equiv) was added in a single portion at 25 °C and the reaction was stirred at 25 °C for 2 h. Upon completion, the reaction contents were quenched by the addition of water (100 mL) and CH_2Cl_2 (100 mL). The crude reaction mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with water (2 × 100 mL), dried ($MgSO_4$), and concentrated. The resultant crude brown oil was purified by flash column chromatography (silica gel, CH_2Cl_2 to remove silyl fluoride byproducts, then Et_2O) to give the key alcohol **18** (2.68 g, 91% yield) as a thick yellow oil. **18**: R_f = 0.36 (silica gel, hexanes/EtOAc, 1/1); $[\alpha]_D^{20}$ = –7.6° (*c* = 0.50, $CHCl_3$); IR (film) ν_{max} 3441 (br), 2934, 2878, 1682, 1399, 1366, 1170, 1062, 876, 773; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 – 3.88 (m, 1 H), 3.87 – 3.77 (m, 1 H), 3.65 – 3.50 (m, 2 H), 2.51 (dd, *J* = 16.4, 5.2 Hz, 1 H), 2.23 (dd, *J* = 16.4, 8.0 Hz, 1 H), 2.13 (s, 3 H), 2.10 – 2.00 (m, 1 H), 1.95 – 1.55 (m, 10 H), 1.48 (s, 9 H), 1.31 (m, 1 H), 0.93 (d, *J* = 6.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.0, 156.7, 80.2, 59.5, 50.8, 50.5, 48.3, 40.7, 38.6, 30.7, 28.7, 26.6 (2 C by HSQC), 24.6, 20.8, 15.1; HRMS (MALDI-FTMS) calcd for $C_{18}H_{34}NO_4^+$ [M^+] 328.2488, found 328.2486.

Ketone 30. Deconjugated enone **29** (1.0 g, 1.78 mmol, 1.0 equiv) was dissolved in EtOAc (6.6 mL) and EtOH (2.2 mL) at 25 °C. Pd/C (10%, 378 mg, 0.385 mmol, 0.20 equiv) was added, and the reaction contents were placed under an atmosphere of H_2 at 25

°C. The reaction was allowed to stir for 13 h at 25 °C. Upon completion, the catalyst was removed by filtration and the crude mixture was concentrated to give ketone **30** (994 mg, 99% yield, 1:1 dr). **30**: ^{1}H NMR (400 MHz, $CDCl_3$) δ (2 diastereomers) 7.75 – 7.60 (m, 8 H), 7.46 – 7.30 (m, 12 H), 4.60 – 3.90 (m, 1 H), 3.85 – 3.75 (m, 1 H), 3.75 – 3.65 (m, 6 H), 2.52 (dd, *J* = 16.0, 4.4 Hz, 1 H), 2.47 (dd, *J* = 16.0, 6.0 Hz, 1 H), 2.25 – 1.30 (m, 22 H), 2.04 (s, 6 H), 1.41 (s, 9 H), 1.40 (s, 9 H), 1.04 (s, 18 H), 0.92 (d, *J* = 4.8 Hz, 3 H), 0.90 (d, *J* = 4.7 Hz, 3 H).

Ketone 32. 2,6-diphenyl phenol (46 mg, 0.188 mmol, 4.5 equiv) was dissolved in CH_2Cl_2 (0.5 mL) at 25 °C. $AlMe_3$ (2.0 M in hexane, 0.031 mL, 0.0628 mmol, 1.5 equiv) was added in a single portion at 25 °C, and the resultant yellow-orange solution evolved gas rapidly. The reaction contents were stirred at 25 °C for 40 min. The reaction contents were then cooled to –78 °C and stirred at –78 °C for 30 min. A solution of enone **31** (23 mg, 0.0418 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 ml + 0.5 mL rinse) was added dropwise over 5 min. The resultant bright yellow solution was stirred at –78 °C for 30 min. MeLi (1.6 M in Et_2O, 0.052 mL, 0.0836 mmol, 2.0 equiv) was added dropwise over 5 min, and the resultant yellow solution was stirred at –78 °C for 2 h. Upon completion, the reaction was quenched by the addition of 1 M aqueous HCl (150 mL) with vigorous stirring at –78 °C and immediately warmed to 25 °C and stirred at 25 °C for 30 min. The crude reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with water (2 × 10 mL), dried ($MgSO_4$), and concentrated. The resultant crude orange oil was purified by preparative thin layer chromatography (silica gel, hexanes/EtOAc, 4/1) to give ketone **32** (14 mg, 59% yield) as a clear oil. **32**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.62 (m, 4 H), 7.44 – 7.34 (m, 6 H), 3.98 – 3.90 (m, 1 H),

3.78 – 3.68 (m, 1 H), 3.70 (t, *J* = 6.6 Hz, 2 H), 2.47 (dd, *J* = 16.2, 6.1 Hz, 1 H), 2.23 (dd, *J* = 16.2, 7.4 Hz, 1 H), 2.09 (s, 3 H), 2.04 – 1.94 (m, 1H), 1.86 – 1.76 (m, 1 H), 1.74 – 1.36 (m, 11 H), 1.40 (s, 9 H), 1.04 (s, 9 H), 0.95 (d, *J* = 6.5 Hz, 3 H).

Alternative route to key alcohol 18:

Ketone 35. *(S)*-1-*N*-Boc-(–)-piperidine-2-ethanol **19** (19.7 g, 85.8 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (200 mL) at 25 °C. Imidazole (11.7 g, 172 mmol, 2.0 equiv) and TBSCl (14.3 g, 94.4 mmol, 1.1 equiv) were added sequentially to this solution at 25 °C, and a white solid quickly precipitated. The reaction was stirred at 25 °C for 19 h after which time MeOH (6 mL) was added to the reaction mixture to quench excess reagent. The reaction contents were stirred at 25 °C for 1 h more and then quenched by addition of water (500 mL). The crude reaction mixture was extracted with CH_2Cl_2 (3 × 500 mL). The combined organic extracts were washed with water (3 × 500 mL), dried ($MgSO_4$), and concentrated to give the desired silylated product as a crude clear oil. This material was carried forward crude without additional purification. A portion of this freshly prepared material (23.4 g, 68.2 mmol, 1.0 equiv) and freshly distilled TMEDA (16.3 mL, 109 mmol, 1.6 equiv) were dissolved in Et_2O (450 mL) and cooled to –78 °C. *s*-BuLi (1.4 M in cyclohexane, 73 mL, 102 mmol, 1.5 equiv) was added dropwise at –78 °C. The resultant yellow solution was then allowed to warm slowly to –45 °C and was kept at –45 °C for 1 h. At this time, the reaction mixture was cooled to –78 °C. A solution of CuCN•2LiCl complex (0.6 M in THF, 170 mL, 102 mmol, 1.5 equiv) was freshly prepared by dissolving CuCN (9.14 g, 102 mmol, 1.5 equiv) and flame-dried LiCl (8.65 g, 204 mmol, 3.0 equiv) in THF (170 mL) at 25 °C. This green solution was added dropwise to the reaction mixture at –78 °C over which time the reaction mixture slowly

turned pale and then a deep orange. The resultant orange solution was stirred at –78 °C for 1 h, and then 2-methylallyl bromide (**34**) (34.4 mL, 341 mmol, 5.0 equiv) was added rapidly at –78 °C. The solution immediately turned bright red, quickly faded to brownish orange, and was stirred at –78 °C for 1 h. The reaction mixture was then allowed to warm to 25 °C and stirred at 25 °C for 3 h. The reaction was quenched by addition of a premixed solution of saturated aqueous NH_4Cl (400 mL) and concentrated NH_4OH (50 mL) at 25 °C and stirred at 25 °C for 1 h. The crude reaction mixture was diluted with water (500 mL) and extracted with Et_2O (4 × 400 mL). The combined organic extracts were dried ($MgSO_4$), and concentrated. The resultant crude grey oil was purified by flash column chromatography (silica gel, hexanes/EtOAc, 4/1) to give the desired product (25.0 g, 92% yield) as a clear oil. A portion of this material (10.2 g, 25.5 mmol, 1.0 equiv) was dissolved in 1,4-dioxane (192 mL) and water (64 mL) at 25 °C. 2,6-lutidine (6.0 mL, 51 mmol, 2.0 equiv), $NaIO_4$ (21.8 g, 102 mmol, 4.0 equiv) and $K_2OsO_4•2H_2O$ (47 mg, 0.130 mmol, 0.005 equiv) were added sequentially at 25 °C. The resultant white suspension was stirred at 25 °C for 24 h over which time thick white precipitates formed. Upon completion, the reaction contents were quenched by the addition of water (300 mL) and CH_2Cl_2 (300 mL). The crude reaction mixture was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic extracts were washed with 1 M aqueous HCl (3 × 300 mL), water (2 × 300 mL), dried ($MgSO_4$), and concentrated to give the desired ketone **35** as a crude grey oil. In practice, this material was carried forward without purification. A portion of this material was purified by thin layer chromatography (silica gel, hexanes/EtOAc, 4/1) for characterization purposes. **35**: R_f = 0.43 (silica gel, hexanes/EtOAc, 4/1); $[\alpha]_D^{20}$ = +14.7° (*c* = 0.15, $CHCl_3$); IR (film) ν_{max} 2931, 2858, 1718,

1689, 1391, 1365, 1253, 1174, 1092, 836, 776; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 – 4.10 (m, 1 H), 4.01 – 3.92 (m, 1 H), 3.71 – 3.60 (m, 2 H), 2.98 (dd, *J* = 16.0, 4.4 Hz, 1 H), 2.62 (dd, *J* = 16.0 8.8 Hz, 1 H), 2.16 (s, 3 H), 1.98 – 1.88 (m, 1 H), 1.80 – 1.50 (m, 7 H), 1.44 (s, 9 H), 0.89 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.3, 155.4, 79.5, 61.5, 50.4, 48.5, 48.0, 36.8, 30.3, 28.7, 26.3, 26.1, 25.8, 18.5, 15.7, -5.2, -5.2; HRMS (MALDI-FTMS) calcd for $C_{21}H_{42}NO_4Si^+$ [M^+] 400.2883, found 400.2892.

Hydroxy ketone 37. 2-Methylallylmagnesium chloride (**36**) (0.5 M in THF, 112 mL, 56.1 mmol, 2.2 equiv) was added to a flame-dried flask and cooled to –78 °C. Crude ketone **35** (10.2 g, 25.5 mmol, 1.0 equiv) was dissolved in THF (112 mL) and cooled to 0 °C. This solution of ketone **35** was added via cannulation over 15 min to the solution of Grignard **36**. The resultant grey reaction mixture was stirred at –78 °C for 2.5 h. Upon completion, the reaction was quenched by addition of saturated aqueous NH_4Cl (200 mL) and water (200 mL). The organic and aqueous phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 300 mL). The combined organic extracts were washed with water (2 × 200 mL), dried ($MgSO_4$), and concentrated to give the desired product as a crude brown oil. Pressing forward without purification, this material was dissolved in 1,4-dioxane (192 mL) and water (64 mL) at 25 °C. 2,6-lutidine (6.0 mL, 51 mmol, 2.0 equiv), $NaIO_4$ (21.8 g, 102 mmol, 4.0 equiv) and $K_2OsO_4•H_2O$ (47 mg, 0.130 mmol, 0.005 equiv) were added sequentially at 25 °C. The resultant white suspension was stirred at 25 °C for 16 h over which time thick white precipitates formed. Upon completion, the reaction contents were quenched by the addition of water (300 mL) and CH_2Cl_2 (300 mL). The crude reaction mixture was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic extracts were washed with 1 M aqueous HCl (3 × 300 mL), water

(2 × 300 mL), dried ($MgSO_4$), and concentrated. The resultant crude black oil was purified by flash column chromatography (silica gel, hexanes/EtOAc, 4/1) to give the desired hydroxy ketone **37** (11.1 g, 95% yield, 2:1 dr) as a pale brown oil. These two diastereomers are not separable by chromatography and were characterized as a mixture. **37**: R_f = 0.42 (silica gel, hexanes/EtOAc, 2/1); IR (film) ν_{max} 3450 (br) , 3380 (br) , 2954, 2931, 2558, 1684, 1460, 1394, 1365, 1253, 1173, 1095, 836, 776; ^{1}H NMR (400 MHz, $CDCl_3$) δ (Major diastereomer) 4.72 (br s, 1 H), 4.05 – 4.00 (m, 1 H), 3.74 – 3.67 (m, 1 H), 3.63 (t, *J* = 6.6 Hz, 2 H), 2.82 (d, *J* = 16.1 Hz, 1 H), 2.55 (d, *J* = 16.2 Hz, 1 H), 2.19 (s, 3 H), 1.96 – 1.58 (m, 10 H), 1.45 (s, 9 H), 1.22 (s, 3 H), 0.89 (s, 9 H), 0.04 (s, 6 H); (Minor diastereomer) 4.94 (br s, 1 H), 4.10 – 4.05 (m, 1 H), 3.77 – 3.70 (m, 1 H), 3.63 (t, *J* = 6.6 Hz, 2 H), 2.65 (d, *J* = 15.1 Hz, 1 H), 2.60 (d, *J* = 15.1 Hz, 1 H), 2.20 (s, 3 H), 1.96 – 1.58 (m, 10 H), 1.46 (s, 9 H), 1.23 (s, 3 H), 0.89 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (2 diastereomers): 210.3, 210.2, 156.3, 80.2, 80.0, 70.9, 70.7, 61.6, 61.5, 55.1, 53.4, 49.9, 49.9, 48.7, 48.1, 46.9, 46.5, 37.6, 37.6, 32.3, 32.0, 28.7, 28.7, 27.5, 27.5, 27.1, 27.0, 26.1, 26.0, 25.0, 18.5, 14.7, -5.2; HRMS (MALDI-FTMS) calcd for $C_{24}H_{48}NO_5Si^+$ [M^+] 458.3302, found 458.3305.

Key alcohol 18. Hydroxy ketone **37** (11.1 g, 24.3 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (162 mL) at 25 °C. Pyridine (29.4 mL, 365 mmol, 15.0 equiv) and DMAP (296 mg, 2.43 mmol, 0.1 equiv) were added sequentially, the resultant pale brown solution was cooled to 0 °C. TFAA (16.9 mL, 121 mmol, 5.0 equiv) was added slowly to prevent internal exotherm at 0 °C, and the resultant dark reaction mixture was stirred at 0 °C for 90 min. Upon completion, the reaction was quenched by addition of water (150 mL). The crude reaction mixture was extracted with CH_2Cl_2 (3 × 150 mL). The combined

organic extracts were washed with water (3 × 200 mL), dried ($MgSO_4$), and concentrated. The resultant crude brown oil was dissolved in CH_2Cl_2 (120 mL) and cooled to 0 °C. DBU (5.4 mL, 36.4 mmol, 1.5 equiv) was added slowly at 0 °C and the solution darkened. After stirring at 0 °C for 5 min, the reaction mixture was allowed to warm to 25 °C. The reaction was stirred at 25 °C for 90 min. Upon completion, the reaction was diluted with CH_2Cl_2 (200 mL). The crude reaction mixture was washed with aqueous 1 M HCl (2 × 200 mL), water (200 mL), dried ($MgSO_4$), and concentrated. The resultant crude brown oil was purified by flash column chromatography (silica gel, hexanes/EtOAc, 39/1 to 9/1) to give the desired enone product (8.54 g, 80% yield) as a pale yellow oil. 2,6-diphenyl phenol (12.9 g, 52.4 mmol, 4.5 equiv) was dissolved in CH_2Cl_2 (180 mL) at 25 °C. $AlMe_3$ (2.0 M in hexane, 8.75 mL, 17.5 mmol, 1.5 equiv) was added in a single portion at 25 °C and the resultant yellow-orange solution evolved gas rapidly. The reaction contents were stirred at 25 °C for 40 min. The reaction contents were then cooled to 0 °C and stirred at 0 °C for 20 min. A portion of the enone prepared in the previous step (5.11 g, 11.6 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (60 mL + 30 mL rinse), cooled to 0 °C, and added dropwise over 20 min to the reaction contents. The resultant bright yellow solution was stirred at 0 °C for 10 min, cooled to –78 °C and stirred at –78 °C for 1 h. L-selectride (1.0 M in THF, 23.2 mL, 23.2 mmol, 2.0 equiv) was added dropwise over 2 min, and the resultant yellow solution was stirred at –78 °C for 1 h. Aqueous 1 M HCl (116 mL, 116 mmol, 10.0 equiv) and MeOH (500 mL) were then added sequentially at –78 °C and the reaction contents were immediately warmed to 25 °C and stirred at 25 °C for 1 h. Upon completion, the crude reaction mixture was diluted with CH_2Cl_2 (500 mL) and water (700 mL) and the layers were separated. The aqueous

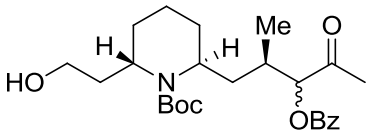
mixture was extracted with CH_2Cl_2 (5 × 300 mL). The combined organic extracts were washed with water (2 × 200 mL), dried ($MgSO_4$), and concentrated. The resultant crude orange oil was purified by flash column chromatography (silica gel, hexanes/Et_2O, 9/1 to 3/2) to give the desired alcohol **18** (3.02 g, 79% yield) as a pale yellow oil. (See characterization data above)

Propyleine (1) and isopropyleine (2). Key alcohol **18** (400 mg, 1.22 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C. TFA (10 mL) was precooled to 0 °C and added in a single portion to the solution of starting material at 0 °C. The reaction was stirred at 0 °C for 1 h. Upon completion, the crude reaction contents were concentrated. The isolated oil was dissolved in Et_2O at 25 °C. PBr_3 (0.58 mL, 6.10 mmol, 5.0 equiv) was added in a single portion with immediate formation of a milky precipitate, and the resultant light brown cloudy solution was warmed to 70 °C in a sealed reaction vessel. The reaction contents were stirred at 70 °C for 5 h. Upon completion, the reaction mixture was cooled to 0 °C and quenched by the slow addition of ice. The crude reaction contents were diluted with CH_2Cl_2 (50 mL) and 1 M aqueous NaOH (50 mL) was added. It is necessary that the solution be strongly basic for proper isolation of product. The crude reaction mixture was extracted with CH_2Cl_2 (5 × 50 mL). The combined organic extracts were dried (Na_2SO_4), and concentrated to near dryness. The crude product cannot be placed under strong reduced pressure without loss of yield. The resultant crude pale yellow oil was dissolved in CH_2Cl_2 (10 mL) at 25 °C. *i*-PrOH (7 μL) and Et_3N (0.17 mL, 1.22 mmol, 1.0 equiv) were added sequentially at 25 °C. The reaction mixture was stirred at 25 °C for 13 h. Upon completion, the reaction contents were diluted with CH_2Cl_2 (10 mL) and 1 M aqueous NaOH (10 mL). The crude reaction mixture was extracted with

CH_2Cl_2 (4 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to near dryness. The product cannot be placed under strong reduced pressure without loss of yield. The resultant crude orange oil was purified by preparative thin layer chromatography (Et_3N pretreated silica gel, hexanes/EtOAc, 19/1) to give propyleine (**1**) and isopropyleine (**2**) (101 mg, 43% yield, 1:3 ratio of **1** to **2**) as a clear oil. Due to the volatility of these materials, yield was obtained of a pure sample near dryness with solvent subtracted by NMR integration. These materials are inseparable and were characterized as a mixture. **1** and **2**: R_f = 0.74 (Et_3N pretreated silica gel, hexanes/EtOAc, 19/1); $[\alpha]_D^{20}$ = –271.7° (*c* = 1.1, $CHCl_3$); IR (film) ν_{max} 2027, 2864, 2838, 2794, 1654, 1447, 1321, 1082, 1007, 772; ^{1}H NMR (400 MHz, $CDCl_3$) δ (Key peaks for **2**, major isomer) 4.73 (m, 1 H), 3.05 (dd, *J* = 12.0, 6.0 Hz, 1 H), 2.45 (tt, *J* = 11.2, 2.4 Hz, 1 H), 0.89 (d, *J* = 6.4 Hz, 3 H); (Key peaks for **1**, minor isomer) 4.59 (s, 1 H), 3.10 (dd, *J* = 12.0, 6.0 Hz, 1 H), 2.42 (tt, obscured, 1 H), 0.95 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (**2**, major isomer) 147.4, 104.1, 56.6, 54.7, 42.9, 41.9, 33.8, 32.8, 31.3, 25.2, 22.3, 21.9, 20.0; (**1**, minor isomer) 147.2, 111.6, 57.8, 54.7, 34.3, 33.9, 33.4, 31.6, 31.5, 31.2, 26.4, 21.9 (1 C overlapping with **2)**; HRMS (MALDI-FTMS) calcd for $C_{13}H_{22}N^+$ [M^+] 192.1752, found 192.1746.

Precoccinelline (3). An equilibrium mixture of propyleine (**1**) and isopropyleine (**2**) (10.0 mg, 0.0524 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (1.0 mL) and cooled to 0 °C. $NaB(OAc)_3H$ (56 mg, 0.264 mmol, 5.0 equiv) was added in a single portion and the reaction mixture was stirred at 0 °C for 3 h. Upon completion, the reaction was quenched by addition of 1 M aqueous NaOH (2.0 mL) and water (5.0 mL) and diluted with CH_2Cl_2 (3.0 mL). The crude reaction mixture was extracted with CH_2Cl_2 (4 × 5 mL). The

combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 × 10 mL), water (2 × 10 mL), dried (Na_2SO_4), and carefully concentrated to give precoccinelline (**3**) and hippodamine (**5**) (9.5 mg, 94% crude recovery, 3.7:1 dr of **3**:**5**) as a pale yellow oil. On the basis of NMR analysis, we believe this material is pure enough to be greater than 85% yield. Due to the volatility of this compound, extended exposure to reduced pressure results in a significant loss of yield and made exact quantification of isolated yield difficult. Repeated attempts at purification utilizing various methods were often met with the significant loss of this volatile material. **3** and **5**: R_f = 0.30 (neutral alumina, Et_2O); IR (film) ν_{max} 2924, 2864, 1445, 1364, 1337, 1283, 1136, 1013, 893, 722, 622; ^{1}H NMR (400 MHz, $CDCl_3$) δ (**3**, major diastereomer) 2.96 (br d, *J* = 11.6 Hz, 2 H), 2.73 (tt, *J* = 11.4, 2.6 Hz, 1 H), 1.95 – 1.79 (m, 2 H), 1.70 – 1.59 (m, 1 H), 1.59 – 1.44 (m, 10 H), 1.28 – 1.13 (m, 2 H), 1.02 (br d, *J* = 13.3 Hz, 2 H), 0.93 (d, *J* = 6.3 Hz, 3 H); (Key peaks for **5**, minor diastereomer) 2.99 (br d, obscured, 1 H), 2.84 (tt, *J* = 11.2, 2.7 Hz, 1 H), 0.84 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (**3**, major isomer) 58.2, 48.4, 34.7, 32.7, 31.4, 31.2, 22.8, 19.9; (**5**, minor isomer) 58.9, 48.1, 43.4, 40.1, 30.5 29.5, 26.2, 25.8, 23.2, 22.6, 22.5, 19.8 (1 C overlapping with **3)**; HRMS (MALDI-FTMS) calcd for $C_{13}H_{24}N^+$ [M^+] 194.1906, found 194.1909.



S-1 (1.6:1 dr)

Benzoylated ketone S-1. Key alcohol **18** (500 mg, 1.53 mmol, 1.0 equiv) was dissolved in DMSO (3.8 mL) at 25 °C. Hydroxyl amine derivative **39** (286 mg, 1.53 mmol, 1.0 equiv) was added in a single portion at 25 °C and the resultant yellow solution was stirred at 25 °C for 2 days. Upon completion, the reaction was quenched by addition

of water (30 mL). The crude reaction mixture was extracted with Et_2O (10 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The resultant crude orange oil was purified by flash column chromatography to give the desired α-benzoyloxated product **S-1** (425 mg, 62% yield, 1.67:1 dr) as a yellow oil. These diastereomers were not separable by chromatography and were characterized as a mixture. **S-1**: R_f = 0.46 (silica gel, hexanes/EtOAc, 1/1); IR (film) ν_{max} 3442 (br), 2934, 2876, 1718, 1681, 1452, 1366, 1282, 1171, 1111, 1069, 1027, 713; ^{1}H NMR (400 MHz, $CDCl_3$) δ (Major diastereomer) 8.08 (br d, *J* = 7.2 Hz, 2 H), 7.61 (tt, *J* = 7.0, 1.5 Hz, 1 H), 7.48 (br t, *J* = 8.0 Hz, 2 H), 5.24 (d, *J* = 2.9 Hz, 1 H), 4.00 – 3.82 (m, 2 H), 3.65 – 3.55 (m, 2 H), 2.40 – 2.30 (m, 1 H), 2.21 (s, 3 H), 2.07 – 1.87 (m, 2 H), 1.83 – 1.53 (m, 8 H), 1.49 – 1.40 (m, 1 H), 1.41 (s, 9 H), 1.06 (d, *J* = 6.8 Hz, 3 H); (Minor diastereomer) 8.08 (br d, *J* = 7.2 Hz, 2 H), 7.61 (tt, *J* = 7.0, 1.5 Hz, 1 H), 7.48 (br t, *J* = 8.0 Hz, 2 H), 5.19 (d, *J* = 3.8 Hz, 1 H), 3.87 – 3.83 (m, 1 H), 3.80 – 3.72 (m, 1 H), 3.65 – 3.55 (m, 2 H), 2.40 – 2.30 (m, 1 H), 2.24 (s, 3 H), 2.07 – 1.87 (m, 2 H), 1.83 – 1.40 (m, 8 H), 1.47 (s, 9 H), 1.49 – 1.40 (m, 1 H), 1.11 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (2 diastereomers): 206.1, 205.9, 166.3, 166.2, 156.8, 133.6, 133.6, 129.9, 129.7, 129.6, 128.7, 128.7, 83.4, 82.5, 80.3, 80.3, 77.5, 77.2, 76.8, 59.8, 59.5, 50.9, 50.7, 49.3, 49.3, 37.8, 37.6, 35.2, 32.7, 32.5, 28.7, 28.6, 28.6, 27.7, 27.3, 27.3, 27.1, 27.0, 26.5, 16.6, 14.4; HRMS (MALDI-FTMS) calcd for $C_{25}H_{38}NO_6^+$ [M^+] 448.2699, found 448.2691.

Tricyclic ketone 20. A portion of **S-1** (152 mg, 0.340 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (3.7 mL) and cooled to 0 °C. TFA (3.7 mL) was added in a single portion to the stirred solution at 0 °C. The reaction was stirred at 0 °C for 1 h. Upon completion, the crude reaction contents were concentrated and dried by azeotropic

distillation with benzene. The crude isolate was dissolved in Et_2O at 25 °C. PBr_3 (0.16 mL, 1.70 mmol, 5.0 eq.) was added in a single portion with immediate formation of a milky precipitate, and the resultant light brown cloudy solution was warmed to 70 °C in a sealed reaction vessel. The reaction contents were stirred at 70 °C for 5 h. Upon completion, the reaction mixture was cooled to 0 °C and quenched by the slow addition of ice, followed by cold aqueous 1 M NaOH (5 mL). The crude reaction contents were added to CH_2Cl_2 (30 mL) and aqueous 1 M NaOH (50 mL). It is necessary that the solution be strongly basic for proper isolation of product. The crude reaction mixture was extracted with CH_2Cl_2 (5 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to give crude bicyclic bromide **40** as a yellow oil. This crude oil was dissolved in CH_2Cl_2 (4.7 mL) at 25 °C. *i*-PrOH (24 µL, 0.31 mmol, 0.912 equiv) and Et_3N (36 µL, 0.26 mmol, 0.765 equiv) were added sequentially at 25 °C. The reaction mixture was stirred at 40 °C for 4 h. Upon completion, the reaction was concentrated and redissolved in MeOH (7.2 mL) and degassed with argon at 25 °C. Aqueous 1 M NaOH was added in one portion (2.6 mL, 2.60 mmol, 10.0 equiv), and the solution was further degassed with argon at 25 °C, then heated to 65 °C and stirred for 6 h. Upon completion, the crude reaction mixture was diluted with water (10 mL) and CH_2Cl_2 (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4), and concentrated. The resultant crude yellow oil was purified by preparative thin layer chromatography (Et_3N pretreated silica gel, hexanes/EtOAc, 1/1) to afford ketone **20** (15 mg, 21%) as a clear oil and ketone **43** (17.3 mg, 25%) as a pale yellow oil. This reaction was repeated several times to obtain larger quantities of material. **20**: R_f = 0.58 (Et_3N pretreated silica gel, hexanes/EtOAc, 1/1); $[\alpha]_D^{20}$ = –83.2°

(c = 0.10, $CHCl_3$); IR (film) ν_{max} 2930, 2860, 1715, 1445, 1173, 1140, 1039; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.47 (dd, J = 12.7, 2.9, 1 H), 3.26 (tt, J = 11.1, 2.9 Hz, 1 H), 2.94 (br d, J = 12.2 Hz, 1 H), 2.57 (ddq, J = 13.0, 6.5, 6.5 Hz, 1 H), 2.03 – 1.87 (m, 3H), 1.80 – 1.65 (m, 4 H), 1.65 – 1.45 (m, 3 H), 1.35 – 1.20 (m, 2 H), 1.25 – 1.10 (m, 1 H), 1.09 – 1.01 (m, 1 H), 1.04 (d, J = 6.5 Hz, 3 H) (chemical shifts of multiplets below 2.03 ppm deconvoluted by HSQC); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.7, 71.3, 56.8, 47.9, 42.2, 40.0, 33.6, 30.1, 25.6, 22.6 (2 C by HSQC), 19.4, 14.2; HRMS (MALDI-FTMS) calcd for $C_{13}H_{22}NO^+$ [M^+] 208.1701, found 208.1703.

Recycling procedure for ketone 43:

Ketone 20. The undesired ketone **43** (34.6 mg, 0.167 mmol, 1.0 equiv) was dissolved in MeOH (4.7 mL) and degassed with argon at 25 °C. Aqueous 1 M NaOH was added (1.7 mL, 1.70 mmol, 10.2 eq.) in one portion and the solution was further degassed with argon at 25 °C. The solution was heated to 65 °C and stirred for 6 h at 65 °C. Upon completion, the crude reaction contents were diluted with water (10 mL) and CH_2Cl_2 (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The resultant crude yellow oil was purified by preparative thin layer chromatography (Et_3N pretreated silica gel, hexanes/EtOAc, 1/1) to give ketone **20** (6.2 mg, 18%) as a clear oil and ketone **43** (6.9 mg, 20%) as a pale yellow oil.

Carboxylic acid 47. Alcohol **18** (500 mg, 1.53 mmol, 1.0 equiv) was dissolved in acetone (7.6 mL) and water (7.6 mL) and cooled to 0 °C. $NaIO_4$ (1.31 g, 6.12 mmol, 4.0 equiv) and RuO_2•xH_2O (20 mg, 0.153 mmol, 0.10 equiv) were added sequentially, and the resultant grey reaction was allowed to stir at 0 °C for 90 min over which time the

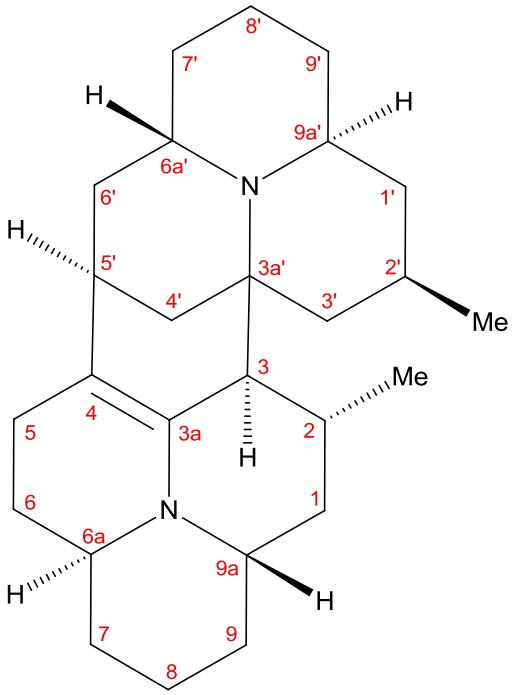
reaction turned yellowish-grey and formed a chunky precipitate. The reaction was then warmed to 25 °C and stirred at 25 °C for 30 min. Upon completion, the yellowish-grey reaction was diluted with CH_2Cl_2 (30 mL) and filtered through celite to remove precipitated solids. The crude filtrate was diluted with 1 M aqueous HCl (5 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The resultant crude black oil was purified by flash column chromatography (silica gel, hexane/EtOAc, 4/1 to 2/3) to give the carboxylic acid **47** (404 mg, 77% yield) as a clear oil. **47**: R_f = 0.48 (silica gel, hexanes/EtOAc, 1/1); $[\alpha]_D^{20}$ = –3.2° (*c* = 0.30, $CHCl_3$); IR (film) ν_{max} 3125 (br), 2934, 2882, 1714, 1688, 1459, 1394, 1367, 1251, 1169, 774; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10 – 3.90 (m, 2 H), 2.91 (dd, *J* = 15.2, 5.6 Hz, 1 H), 2.64 (dd, *J* = 15.2, 7.6 Hz, 1 H), 2.50 (dd, *J* = 16.0, 5.2 Hz, 1 H), 2.27 (dd, *J* = 16.0, 8.0 Hz, 1 H), 2.13 (s, 3 H), 2.10 – 2.00 (m, 1 H), 1.75 – 1.50 (m, 7 H), 1.47 (s, 9 H), 1.35 – 1.22 (m, 1 H), 0.93 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.2, 176.3, 155.2, 79.8, 50.7, 50.3, 48.3, 39.9, 39.3, 30.0, 28.3, 26.3, 26.0, 25.2, 20.3, 15.4; HRMS (MALDI-FTMS) calcd for $C_{18}H_{32}NO_5^+$ [M^+] 342.2280, found 342.2278.

Vinylogous amide 48. Carboxylic acid **48** (380 mg, 1.11 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (5.6 mL) at 25 °C. *Para*-nitrophenol (185 mg, 1.33 mmol, 1.2 equiv), DMAP (13 mg, 0.111 mmol, 0.10 equiv), and DCC (275 mg, 1.33 mmol, 1.2 equiv) were added sequentially at 25 °C, and the resultant bright yellow solution was stirred at 25 °C for 20 h. Upon completion, the reaction mixture was diluted with Et_2O (10 mL), filtered through celite to remove DCU byproduct, and concentrated. This material was immediately redissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C. TFA (10 mL) was pre-cooled to 0 °C and added to this solution. The resultant pale yellow reaction

mixture was stirred at 0 °C for 1 h. Upon completion, the reaction mixture was concentrated at 0 °C via rotary evaporation in an ice bath to give a crude yellow material. This crude material was dissolved in cold CH_2Cl_2 (50 mL) and washed very carefully in small portions (5 mL each) with cold saturated aqueous $NaHCO_3$ (50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The resultant crude yellow oil was immediately dissolved in CH_2Cl_2 (20 mL) at 25 °C and *i*-PrOH (14 μL) was added. The reaction mixture was warmed to 40 °C and stirred at 40 °C for 18 h. Upon completion, the reaction was diluted with CH_2Cl_2, washed with 1 M aqueous NaOH (3 × 30 mL), dried (Na_2SO_4), and concentrated. The resultant crude yellow solid was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH, 99/1 to 97/3) to give the vinylogous amide **48** (70 mg, 31% yield) as a pale yellow oil. **48**: R_f = 0.21 (silica gel, EtOAc/MeOH, 99/1); $[\alpha]_D^{20}$ = –554° (*c* = 0.35, $CHCl_3$); IR (film) ν_{max} 3434, 2947, 2869, 1613, 1532, 1452, 1255, 1148; ^{1}H NMR (500 MHz, C_6D_6) δ 5.18 (s, 1 H), 3.26 (dtd, *J* = 16.5, 6.6, 3.9 Hz, 1 H), 2.76 (tt, *J* = 11.4, 3.1 Hz, 1 H), 2.23 (t, *J* = 15.9 Hz, 1 H), 2.03 (ddd, *J* = 16.1, 3.9, 1.1 Hz, 1 H), 1.98 (ddd, *J* = 15.5, 4.7, 2.3 Hz, 1 H), 1.53 (dd, *J* = 15.5, 10.9 Hz, 1 H), 1.32 – 1.22 (m, 1 H), 1.20 – 1.05 (m, 6 H), 0.99 – 0.91 (m, 6 H), 0.59 (d, *J* = 6.8 Hz, 1 H), 0.49 (dt, *J* = 13.1, 11.6 Hz, 1 H); ^{13}C NMR (100 MHz, C_6D_6) δ 190.1, 161.9, 101.3, 54.2, 52.1, 42.4, 39.9, 38.6, 30.2, 28.1, 26.9, 21.7, 18.4; HRMS (MALDI-FTMS) calcd for $C_{13}H_{20}NO^+$ [M^+] 206.1545, found 206.1538.

Dienamine 46. Vinylogous amide **46** (23 mg, 0.112 mmol, 1.0 equiv) was dissolved in THF (0.88 mL) and 1,4-dioxane (0.22 mL) at 25 °C. DIBAL-H (1 M in toluene, 0.28 mL, 0.280 mmol, 1.0 equiv) was added in a single portion at 25 °C. Gas was quickly evolved and the reaction was stirred at 25 °C for 4 min. 1 M aqueous NaOH

(2.20 mL) was added in a single portion at 25 °C with quick evolution of gas. The reaction was stirred at 25 °C for 5 min. Upon completion, the reaction contents were diluted with water (5 mL) and CH_2Cl_2 (5 mL). The crude reaction mixture was extracted with CH_2Cl_2 (5 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to give crude product (23 mg) in full recovery as a yellow oil. Based on NMR analysis of the crude reaction mixture, roughly 45% of the crude reaction mixture is desired dienamine **46**. Due to the unstable nature of this material, it could not be purified for use or characterization. Key data is as follows. **46**: IR (film) ν_{max} 2923, 2865, 1649, 1608, 1449, 1241, 1084, 796; ^{1}H NMR (400 MHz, C_6D_6) δ (Key peaks) 6.03 (dd, *J* = 9.6, 2.9 Hz, 1 H), 5.51 (ddd, *J* = 8.9, 5.9, 2.4 Hz, 1 H), 4.63 (s, 1 H), 3.30 (ddt, *J* = 9.4, 6.1, 3.1 Hz, 1 H), 1.01 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, C_6D_6) δ (Key peaks) 143.6, 122.8, 111.7; HRMS (MALDI-FTMS) calcd for $C_{13}H_{20}N^+$ [M^+] 190.1596, found 190.1595.



(-)-49: psylloborine B

Psylloborine B (49). A portion of the crude dienamine **46** crude product mixture (45% **46**, 6 mg, 0.0132 mmol of **46**, 1.0 equiv; 0.0161 mmol amine contaminants, 1.22 equiv) was dissolved in CD_2Cl_2 (0.2 mL) at 25 °C. A solution of TFA (2.24 µL, 0.0293, 2.22 equiv) in CD_2Cl_2 (0.1 mL) was added at 25 °C. The reaction mixture was kept at 25 °C for 2 min after which time a mixture of propyleine (**1**) and isopropyleine (**2**) (6 mg, 0.0314 mmol, 2.38 equiv) dissolved in CD_2Cl_2 (0.2 mL) was added in a single portion. The reaction mixture was allowed to kept at 25 °C for 2 h. Upon completion, the reaction was quenched by the addition of 1 M aqueous NaOH (5 mL) and diluted with CH_2Cl_2 (10 mL). The crude reaction mixture was extracted with CH_2Cl_2 (5 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The resultant crude orange oil was purified by preparative thin layer chromatography (Et_3N pretreated silica gel, hexanes/EtOAc, 19/1) to give non-natural dimer **49** (2.3 mg, 46% yield based on **46**, or

21% yield over 2 steps from **48**) as a clear oil. **49**: R_f = 0.88 (Et_3N pretreated silica gel, hexanes/EtOAc, 19/1); $[\alpha]_D^{20}$ = –135.7° (*c* = 0.05, $CHCl_3$); IR (film) ν_{max} 2925, 2865, 1663, 1446, 1377, 1257, 1120, 1048; ^{1}H NMR (400 MHz, C_6D_6) δ 3.60 (br d, *J* = 13.0 Hz, 1 H), 3.06 (dd, *J* = 11.9, 5.0 Hz, 1 H), 2.71 (br t, *J* = 10.5 Hz, 1 H), 2.34 (br t, obscured, 1 H), 2.33 (q, obscured, 1 H), 2.26 (dd, *J* = 12.3, 3.2 Hz, 1 H), 2.05 (m, 1 H), 2.00 (m, 1 H), 1.99 (m, 1 H), 1.97 (m, 1 H), 1.94 (m, 1 H), 1.85 (m, 1 H), 1.85 (m, 1 H), 1.82 (m, 1 H), 1.71 (dq, *J* = 11.9, 6.7 Hz, 1 H), 1.59 (m, 1 H), 1.55 (m, 1 H), 1.49 (m, 1 H), 1.48 (m, 1 H), 1.48 (m, 1 H), 1.48 (m, 1 H), 1.45 (d, *J* = 6.1 Hz, 3 H), 1.42 (m, 1 H), 1.41 (m, 1 H), 1.39 (m, 1 H), 1.39 (m, 1 H), 1.34 (m, 1 H), 1.26 (m, 1 H), 1.24 (m, 1 H), 1.18 (m, 1 H), 1.16 (m, 1 H), 1.11 (m, 1 H), 0.98 (ddd, *J* = 12.3, 3.3, 1.8 Hz, 1 H), 0.88 (m, 1 H), 0.82 (d, *J* = 6.4 Hz, 3 H), 0.76 (dq, *J* = 12.8, 2.7 Hz, 1 H); ^{13}C NMR (125 MHz, C_6D_6) δ 145.3, 116.7, 57.3, 56.1, 55.5, 55.0, 49.7, 49.6, 48.7, 45.9, 43.6, 36.1 (2 C by HSQC), 34.4, 34.3, 31.9, 31.7 (2 C by HSQC), 29.6, 27.4, 25.2, 24.7, 23.1, 22.9, 21.1, 20.1; HRMS (MALDI-FTMS) calcd for $C_{26}H_{41}N_2^+$ [M^+] 381.3270, found 381.3272.

Figure S1. Key TOCSY, NOESY, and HMBC Correlations Confirming the Structure of Psylloborine B (**49**)

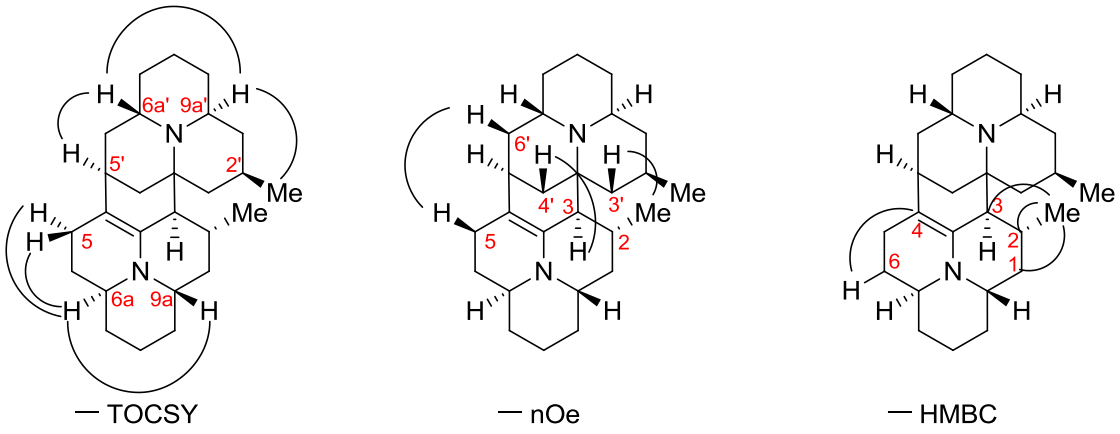


Table S1. ^{1}H and ^{13}C Data for Psylloborine B (**49**) in C_6D_6

Carbon	δ (ppm)	Proton	δ (ppm), *J* (Hz)	nOe	HMBC
C-1	45.9	**H_a-1**[a]	1.54 (m)		
		H_b-1[a]	1.38 (m)		C-2, C-9a
C-2	34.3	**H-2**	1.99 (m)		C-3a[b]
C-3	55.5	**H-3**	1.94 (m)	H_a-3', H_b-3', H_b-4'	C-2
C-3a	145.3				
C-4	116.7				
C-5	29.6	**H_a-5 (eq)**	2.03 (m)	H_b-6'	C-4
		H_b-5 (ax)	1.98 (m)	H-6a	C-3a[b], C-4
C-6	23.1	**H_a-6 (ax)**	1.71 (dq, *J* = 11.9, 6.7)	H-9a, H_b-8	C-6a
		H_b-6 (eq)	1.12 (m)	H-6a	C-4
C-6a	55	**H-6a**	3.06 (dd, *J* = 11.9, 5.6)	H_b-5, H_b-6, H_b-7	
C-7	31.7	**H_a-7**[a]	1.86 (m)		
		H_b-7[a]	1.49 (m)	H-6a	
C-8	20.1	**H_a-8 (eq)**	1.38 (m)		
		H_b-8 (ax)	1.24 (m)	H_a-6	
C-9	34.4	**H_a-9**[a]	1.42 (m)		
		H_b-9[a]	1.18 (m)		
C-9a	56.1	**H-9a**	2.34 (br t, obscured)	H_a-6, H-6a'	
C-(2Me)	24.7	**H-(2Me)**	1.46 (d, J = 6.1, 3 H)	H_b-1', H_a-3'	C-1, C-2, C-3
C-1'	43.6	**H_a-1' (eq)**	1.35 (m)		
		H_b-1' (ax)	0.88 (q, *J* = 12.1)	H-(2Me) H_a-3', H_b-9'	C-2', C-9', C-9a'
C-2'	27.4	**H-2'**	1.59 (m)	H_b-3', H_a-4', H-9a'	
C-3'	48.7	**H_a-3' (ax)**	1.81 (m)	H-3, H-(2Me), H_b-1', H-(2'Me)	C-3, C-1', C-2', C-3a', C-4', C-(2'Me)

		H_b-3' (eq)	1.17 (m)	H-3, H-2', H_b-4', H-(2'Me)	
C-3a'	57.3				
C-4'	31.9	**H_a-4' (ax)**	2.26 (dd, *J* = 12.3, 3.2)	H-2', H_a-6', H-9a'	C-3, C-4
		H_b-4' (eq)	0.98 (ddd, *J* = 12.3, 3.3, 1.8)	H-3, H_b-3'	
C-5'	36.1	**H-5'**	2.33 (m, obscured)		
C-6'	25.2	**H_a-6' (ax)**	1.96 (m)	H_a-4', H-9a'	
		H_b-6' (eq)	0.76 (dq, *J* = 12.8, 2.7)	H_a-5, H_b-7'	
C-6a'	49.7	**H-6a'**	3.60 (br d, *J* = 13.0)	H-9a	
C-7'	31.7	**H_a-7' (ax)**	1.79 (m)		
		H_b-7' (eq)	1.41 (m)	H_b-6'	
C-8'	21.1	**H_a-8' (ax)**	1.47 (m)		
		H_b-8' (eq)	1.47 (m)		
C-9'	36.1	**H_a-9' (eq)**	1.49 (m)		
		H_b-9' (ax)	1.26 (m)	H_b-1'	
C-9a'	49.6	**H-9a'**	2.71 (br t, *J* = 10.5)	H-2', H_a-4', H_a-6'	
C-(2'Me)	22.9	**H-(2'Me)**	0.82 (d, *J* = 6.4)	H_a-3', H_b-3'	C-1', C-2', C-3'

[a]Axial and equatorial assignments were not made.

[b]Crosspeak at this chemical shift could apply to one or both of these assignments

Table S2. NMR Spectral Data Comparison of Natural and Synthetic Propyleine (**1**) and Isopropyleine (**2**) in CDCl3; Coupling Constant (*J*) in Hz

^{1}H			^{13}C	
Natural Enamine Monomer	Synthetic Isopropyleine		Synthetic Isopropyleine	
Daloze	Mueller	Snyder	Mueller	Snyder
4.78 (m, 1 H)	4.75 (br s, 1 H)	4.73 (m, 1 H)	147.1	147.4
3.20 - 3.05 (m, 2 H)	3.06 (dd, *J* = 5, 1 H)	3.05 (dd, *J* = 12, 6, 1 H)	103.9	104.1
	2.46 (tt, *J* = 10, 3, 1 H)	2.45 (tt, *J* = 11.2, 2.4, 1 H)	56.3	56.6
0.92 (d, 3 H)	0.90 (d, *J* = 6, 1 H)	0.89 (d, *J* = 6.8, 3 H)	54.4	54.7
(Referenced higher than us)	(Referenced 0.1 ppm higher than us)		42.6	42.9
			41.6	41.9
			33.5	33.8
			32.5	32.8
			31.0	31.3
			25.0	25.2
			22.0	22.3
			21.6	21.9
			19.7	20.0

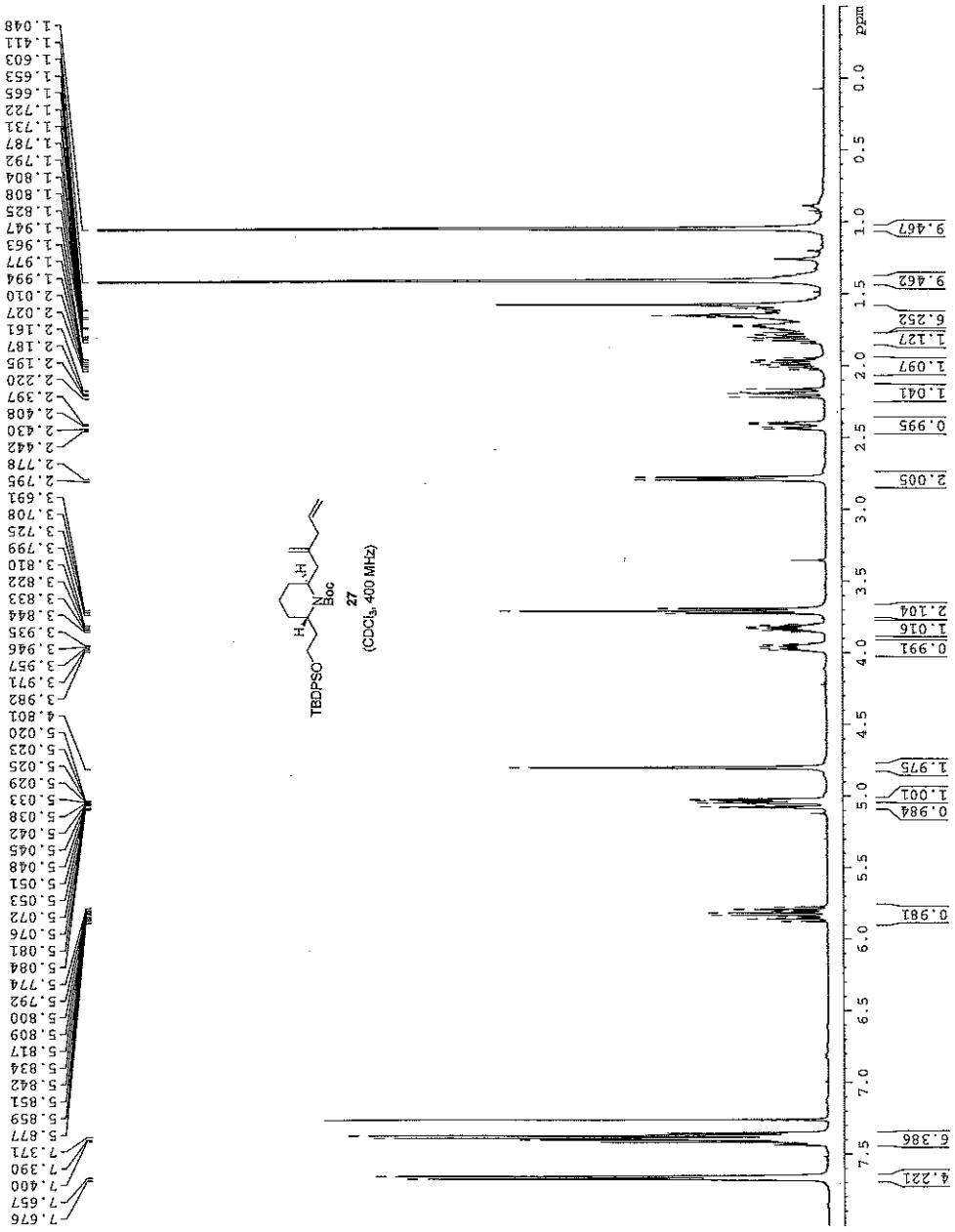
^{1}H		^{13}C	
Synthetic Propyleine		Synthetic Propyleine	
Mueller	Snyder	Mueller	Snyder
4.60 (br s, 1 H)	4.59 (s, 1 H)	147	147.2
	3.10 (dd, *J* = 12.0, 6.0, 1 H)	111.4	111.6
	2.42 (m, 1 H)		57.8
0.97 (d, *J* = 6, 3 H)	0.95 (d, *J* = 6.8, 3 H)		54.7
			34.3
			33.9
			33.4
			31.6
			31.5
			31.2
			26.4
			21.9
			(1 overlapping with isopropyleine)

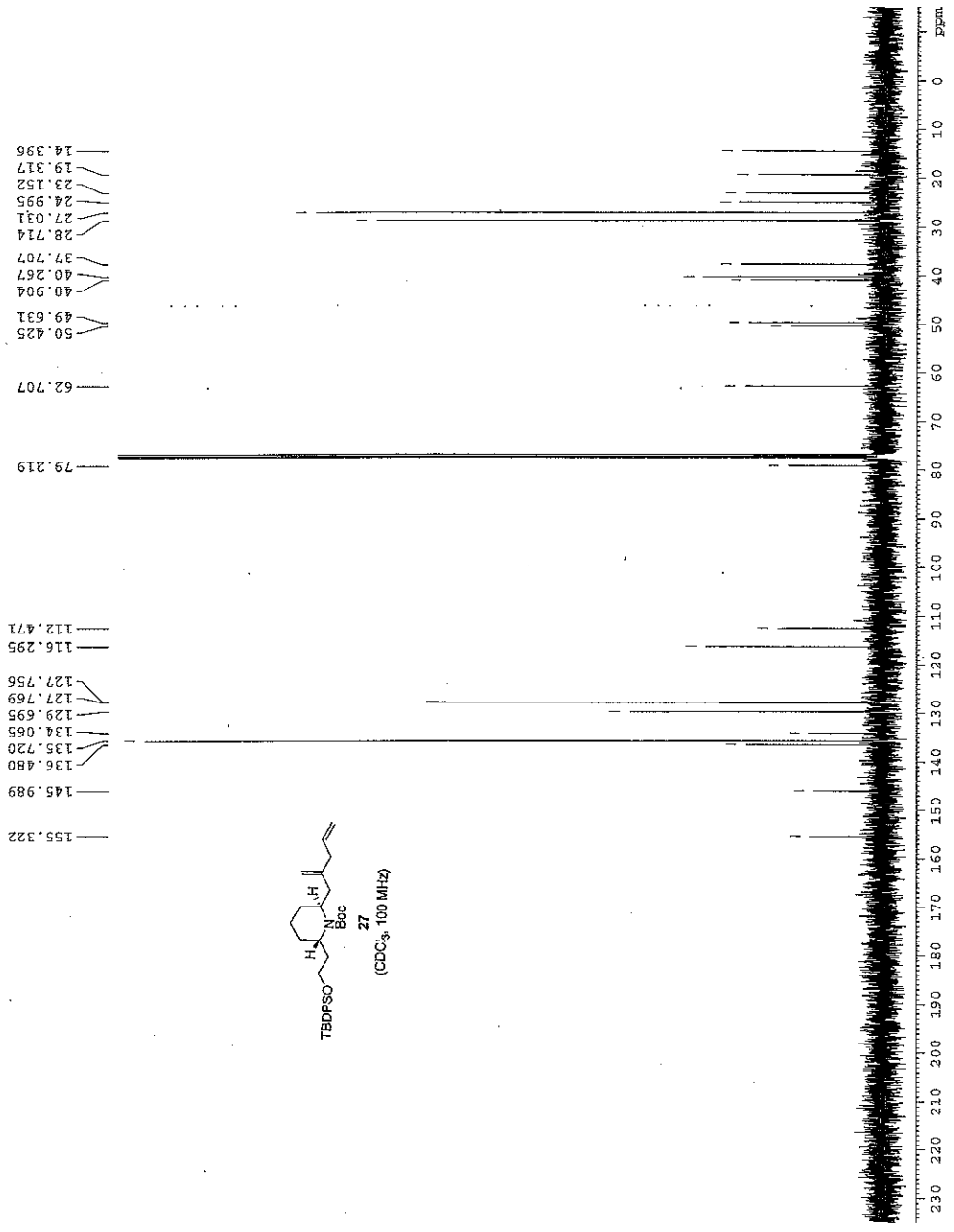
All synthetic ^{13}C chemical shift values reported by Mueller are referenced 0.2 ppm lower than us.

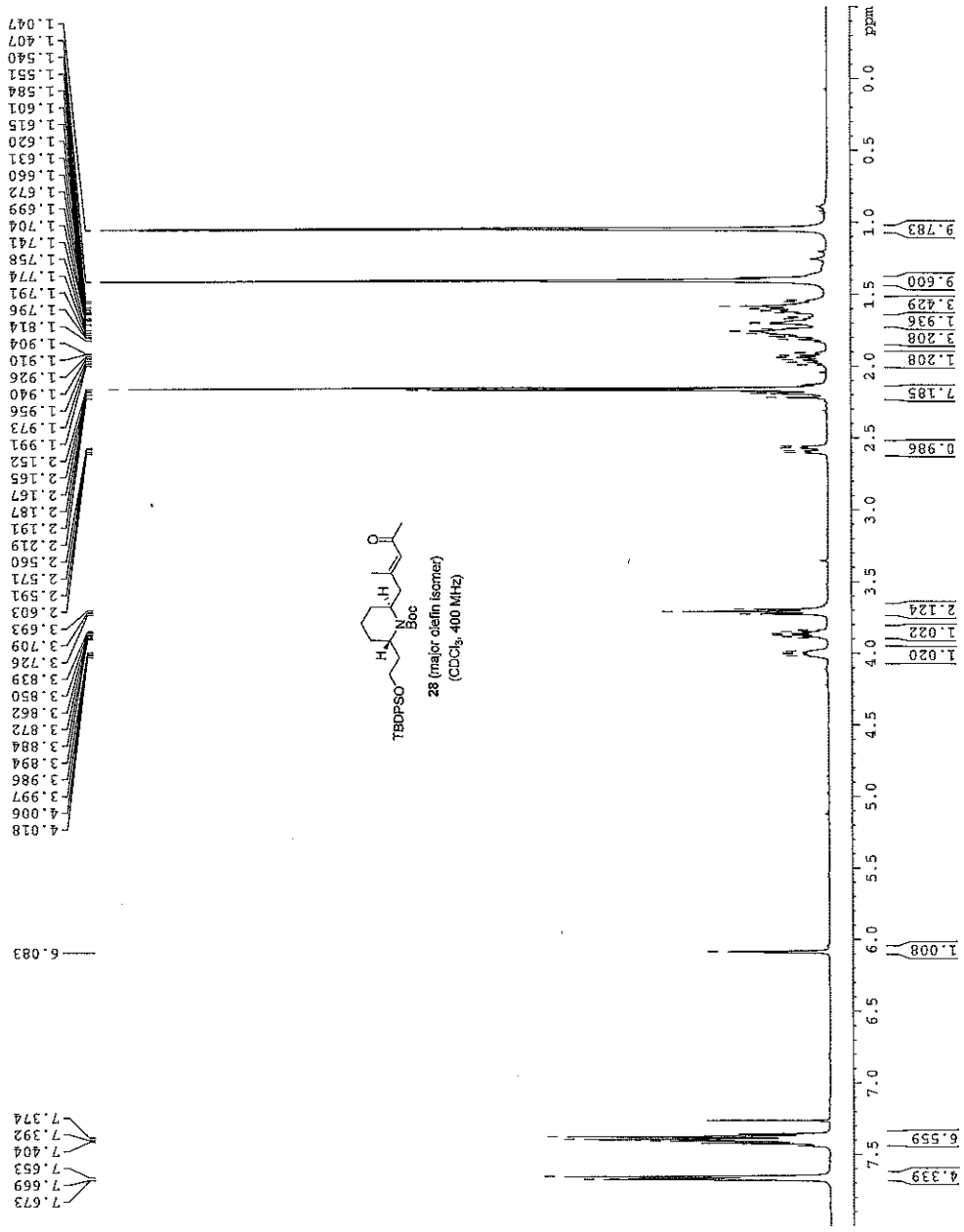
Table S3. NMR Spectral Data Comparison of Natural and Synthetic Precoccinelline (**XX**) in CDCl3; Coupling Constant (*J*) in Hz

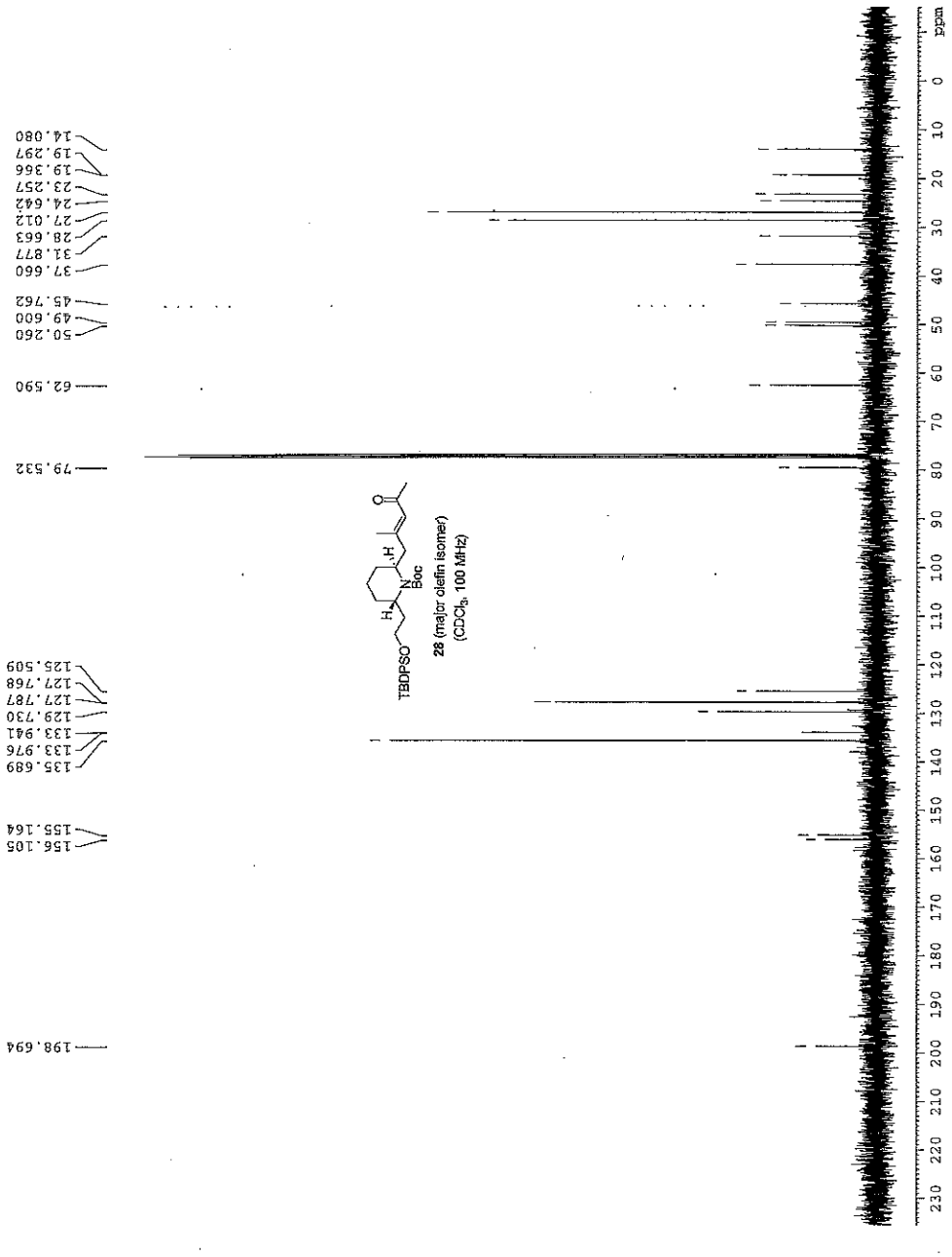
^{1}H		^{13}C	
Natural Precoccinelline	Synthetic Precoccinelline	Natural Precoccinelline	Synthetic Precoccinelline
2.95 (br d, *J* = 9.0)	2.96 (br d, *J* = 11.6, 2 H)	58.1	58.2 (2 C)
2.95 (br d, *J* = 11.5)		58.1	
2.74 (br t, *J* = 11.0)	2.73 (tt, *J* = 11.4, 2.6, 2 H)	48.3	48.4
1.88 (m)	1.95 - 1.79 (m, 2 H)	34.6	34.7 (2 C)
1.88 (m)		34.6	
1.62 (m)	1.70 - 1.54 (m)	32.6	32.7
1.56 (m)	1.57 - 1.44 (m, 10 H)	31.2	31.4 (2 C)
1.56 (m)		31.2	
1.50 (m)		31.1	31.2 (2 C)
1.50 (m)		31.1	
1.50 (m)		22.7	22.8
1.50 (m)		19.8	19.9 (2 C)
1.50 (m)		19.8	
1.50 (m)		(referenced 0.1 ppm lower than us)	
1.50 (m)			
1.50 (m)			
1.18 (m)	1.28 - 1.13 (m, 2 H)		
1.18 (m)			
1.02 (br d, *J* = 13.0)	1.02 (br d, *J* = 13.3, 2 H)		
1.02 (br d, *J* = 13.0)			
0.94 (d, *J* = 6.5, 3 H)	0.93 (d, *J* = 6.3, 3 H)		
(referenced 0.04 ppm higher than us)			

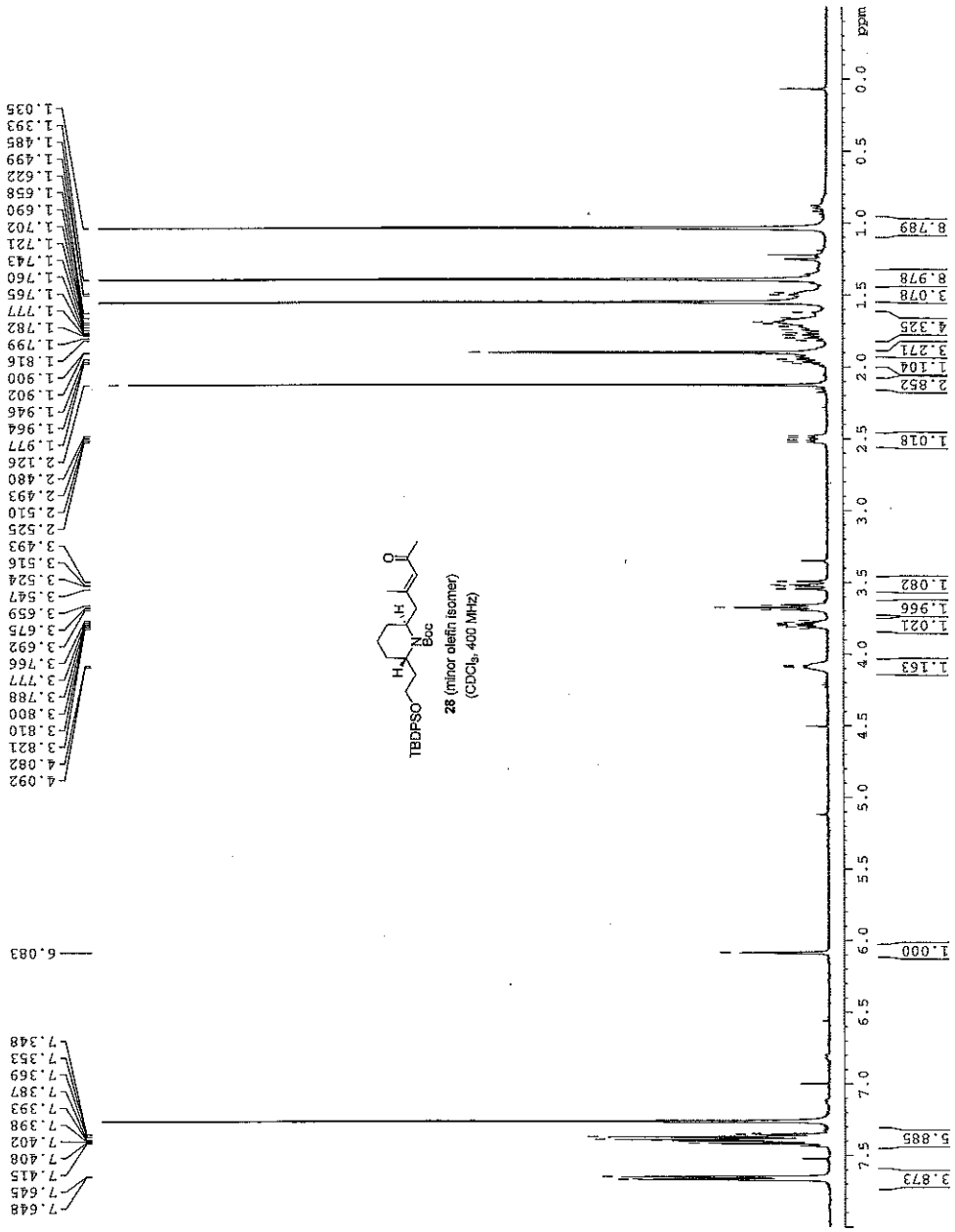
[1] Chemical shifts for precoccinelline: B. Lebrun, J. C. Braekman, D. Daloze, *Magn. Res. Chem.* **1999**, *37*, 60 – 64.

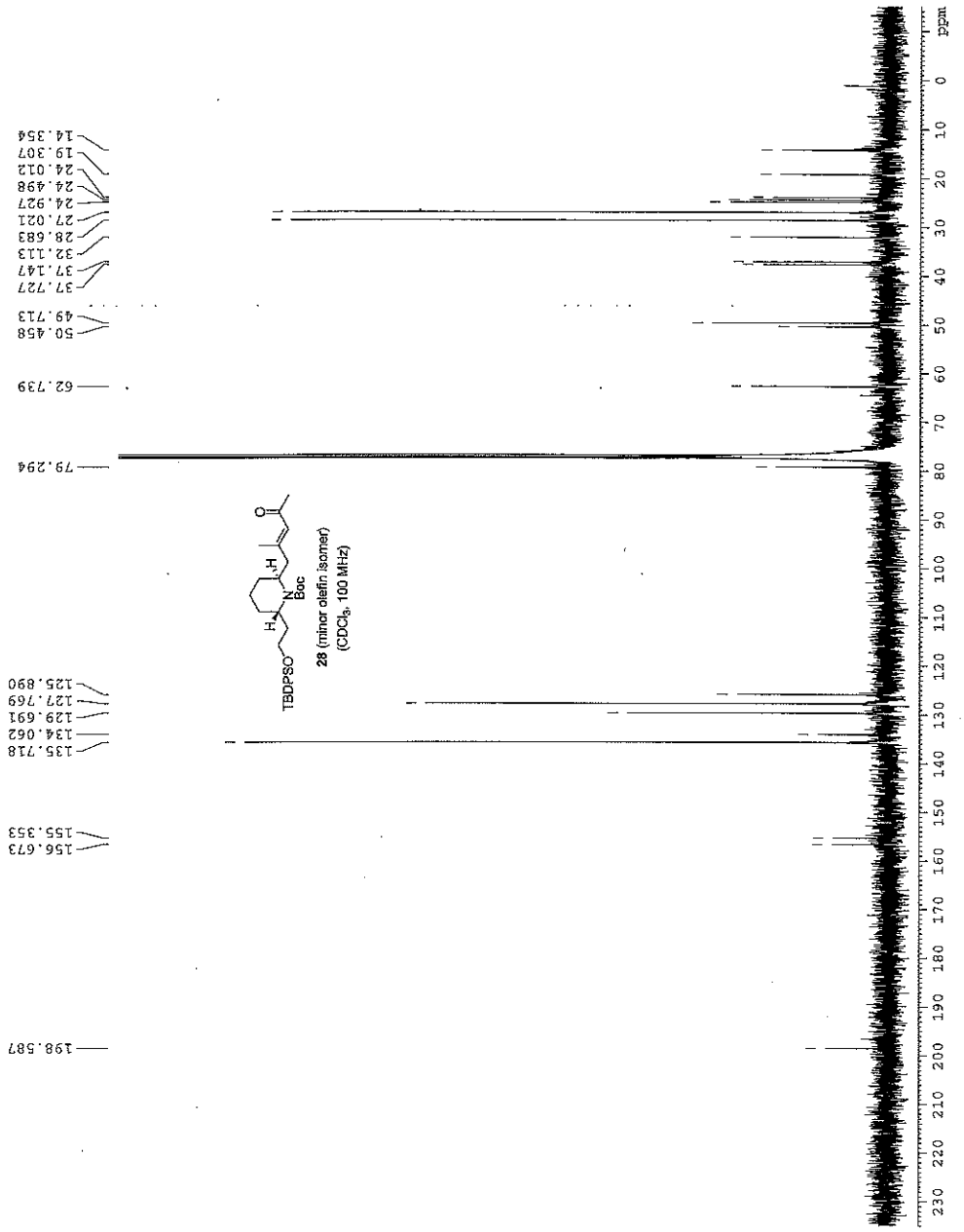

TBDPSO
Boc
27
(CDCl3, 400 MHz)
ppm
9.467
9.462
6.252
1.127
1.097
1.041
0.995
2.005
2.104
1.016
0.991
1.975
1.001
0.984
0.981
6.386
4.221

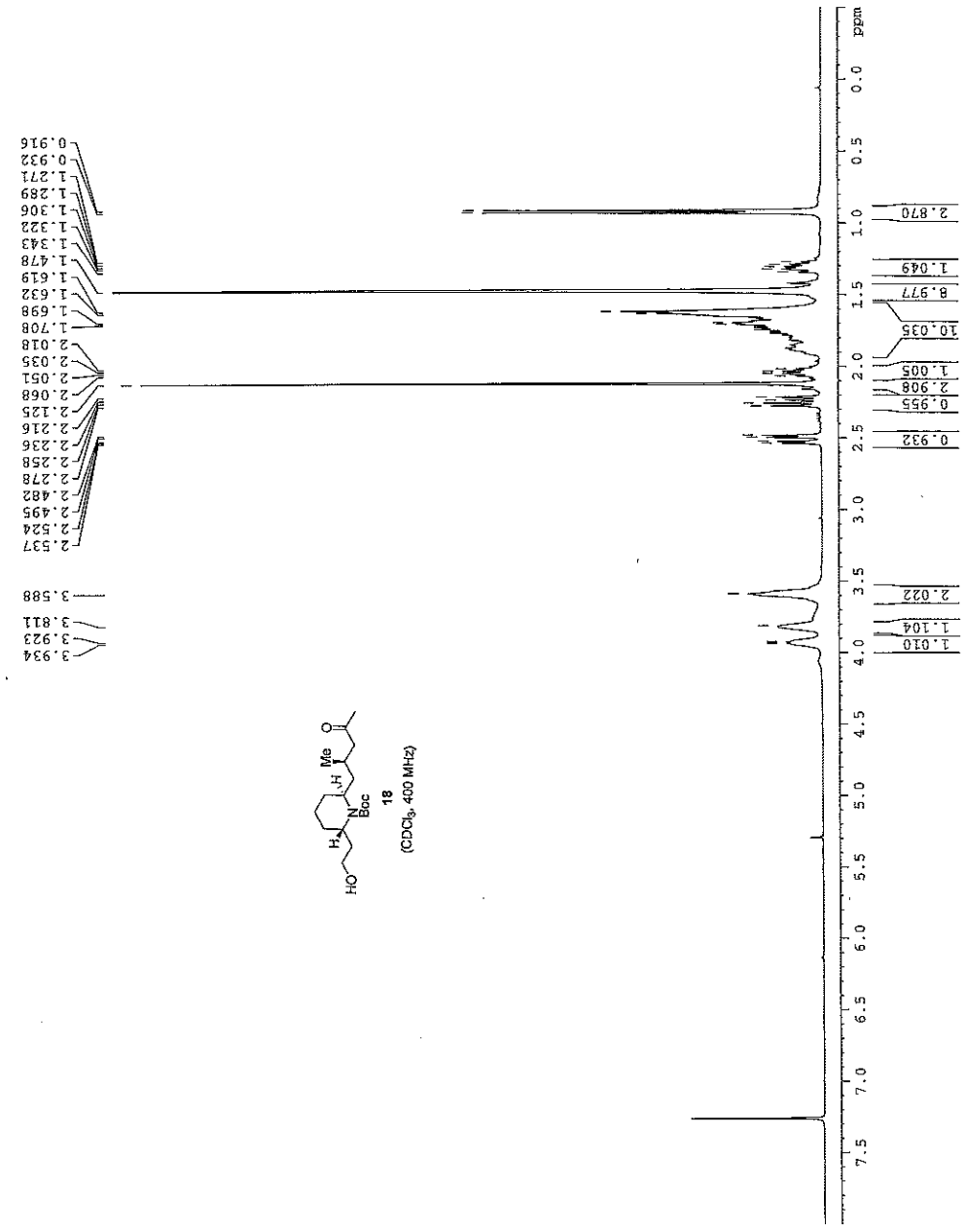

14.396
19.317
23.152
24.995
27.031
28.714
37.707
40.267
40.904
49.631
50.425
62.707
79.219
112.471
116.295
127.756
127.769
129.695
134.065
135.720
136.480
145.989
155.322
TBDPSO
Boc
27
(CDCl3, 100 MHz)
ppm

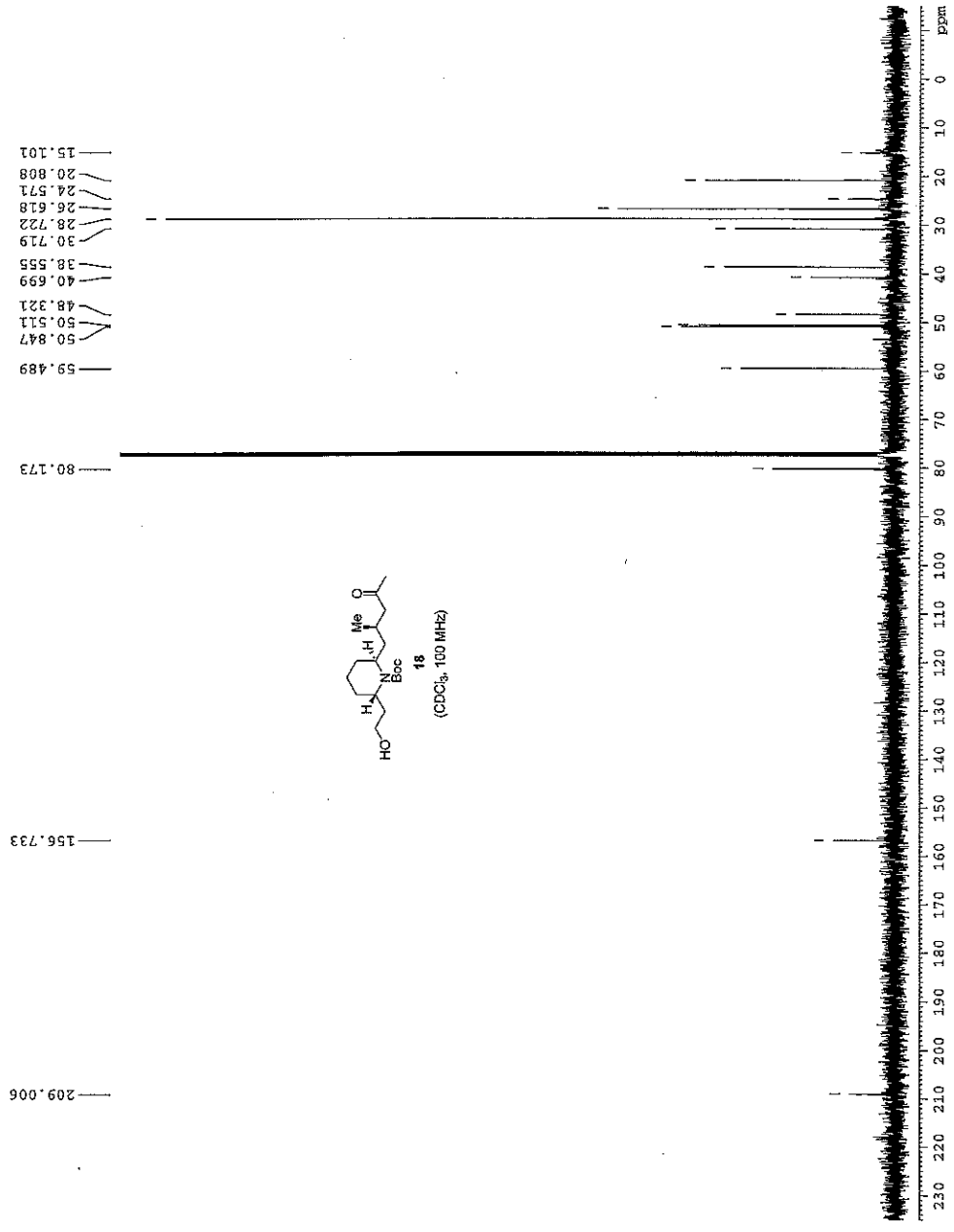

TBDPSO
Boc
28 (major olefin isomer)
(CDCl3, 400 MHz)
ppm

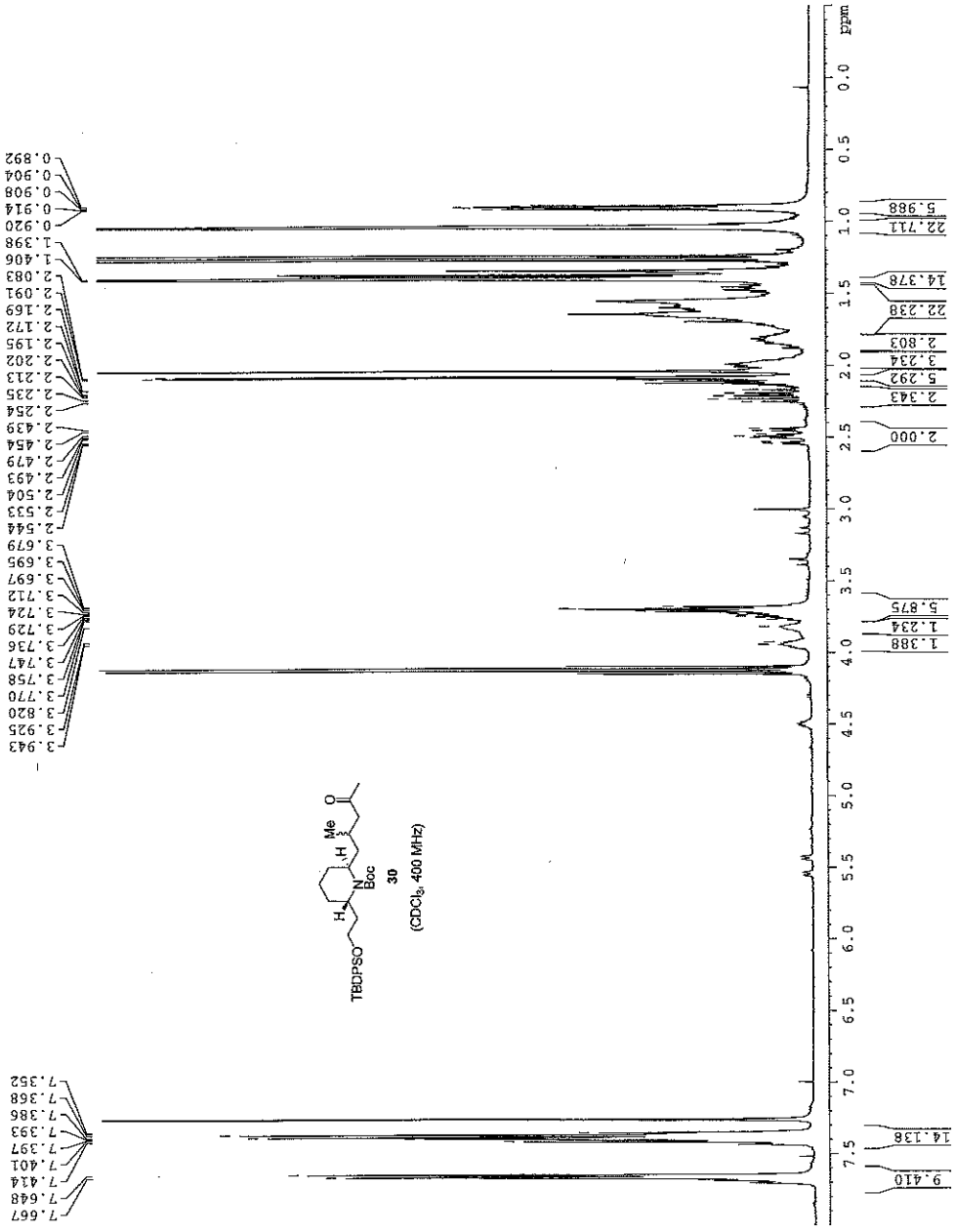

198.694
156.105
155.164
135.689
133.976
133.941
129.730
127.787
127.768
125.509
79.532
62.590
50.260
49.600
45.762
37.660
31.877
28.663
27.012
24.642
23.257
19.366
19.297
14.080
TBDPSO
Boc
28 (major olefin isomer)
(CDCl3, 100 MHz)
ppm

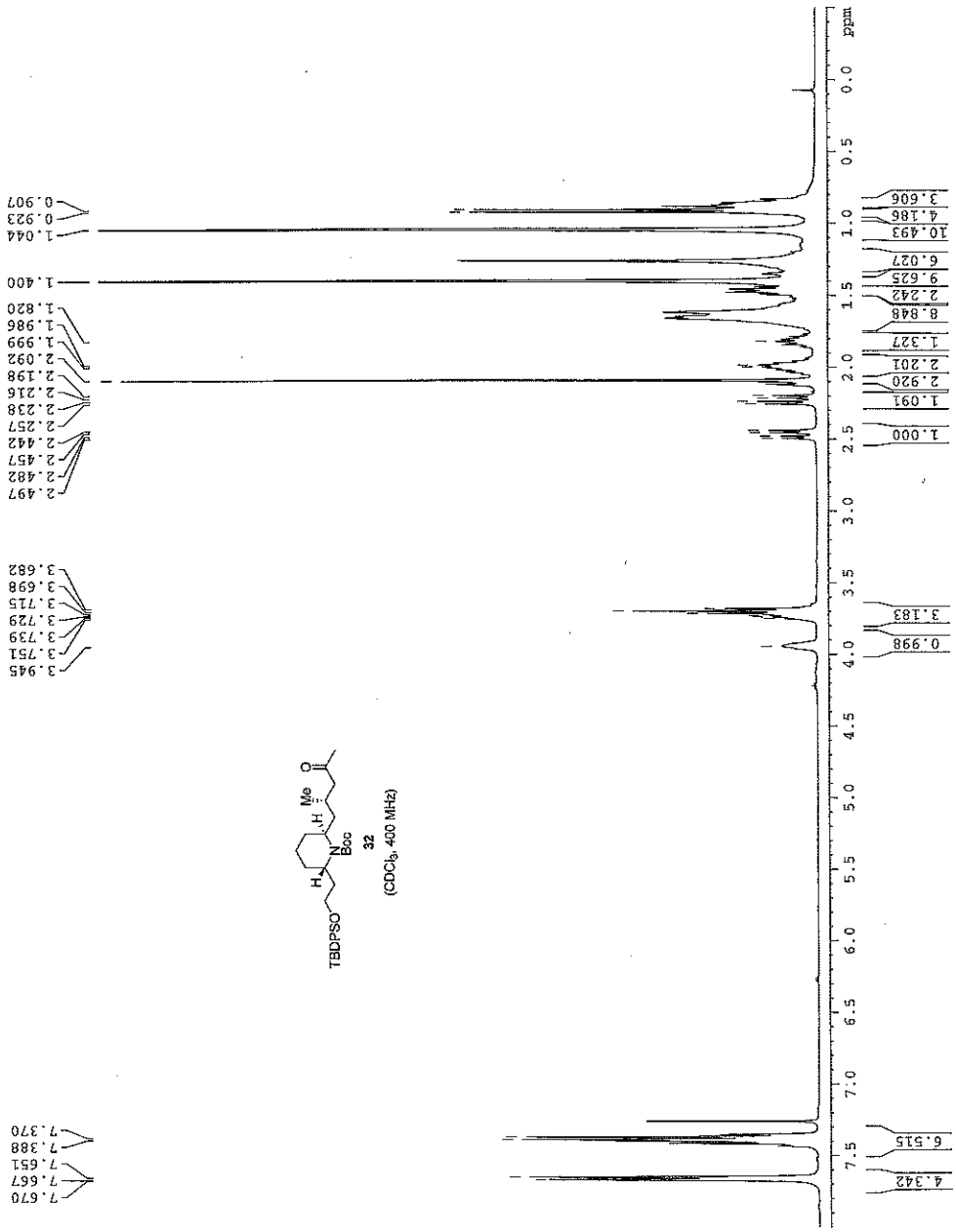

TBDPSO
Boc
28 (minor olefin isomer)
(CDCl3, 400 MHz)
ppm

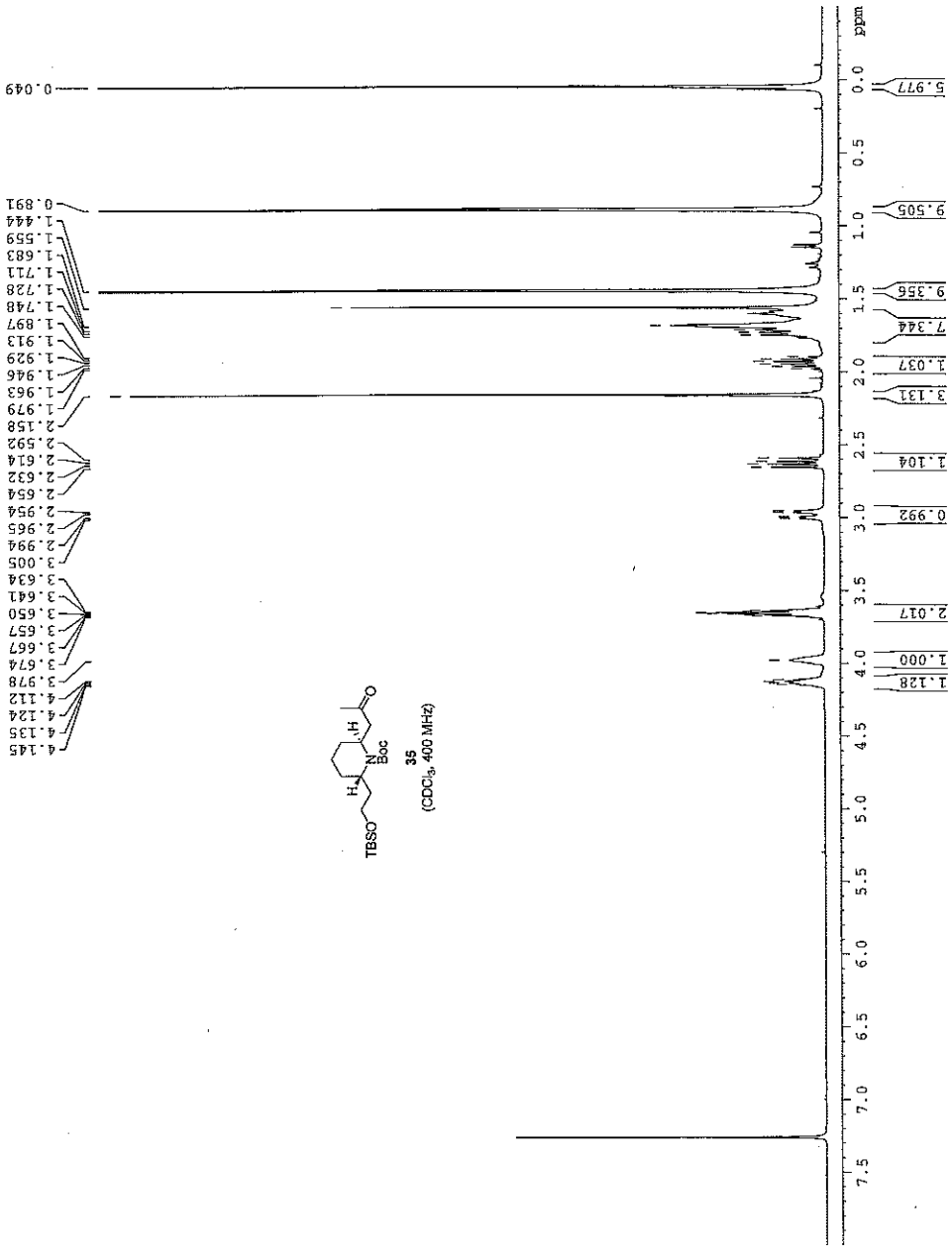

14.354
19.307
24.012
24.498
24.927
27.021
28.683
32.113
37.147
37.727
49.713
50.458
62.739
79.294
125.890
127.769
129.691
134.062
135.718
155.353
156.673
198.587
TBDPSO
Boc
28 (minor olefin isomer)
(CDCl3, 100 MHz)
ppm

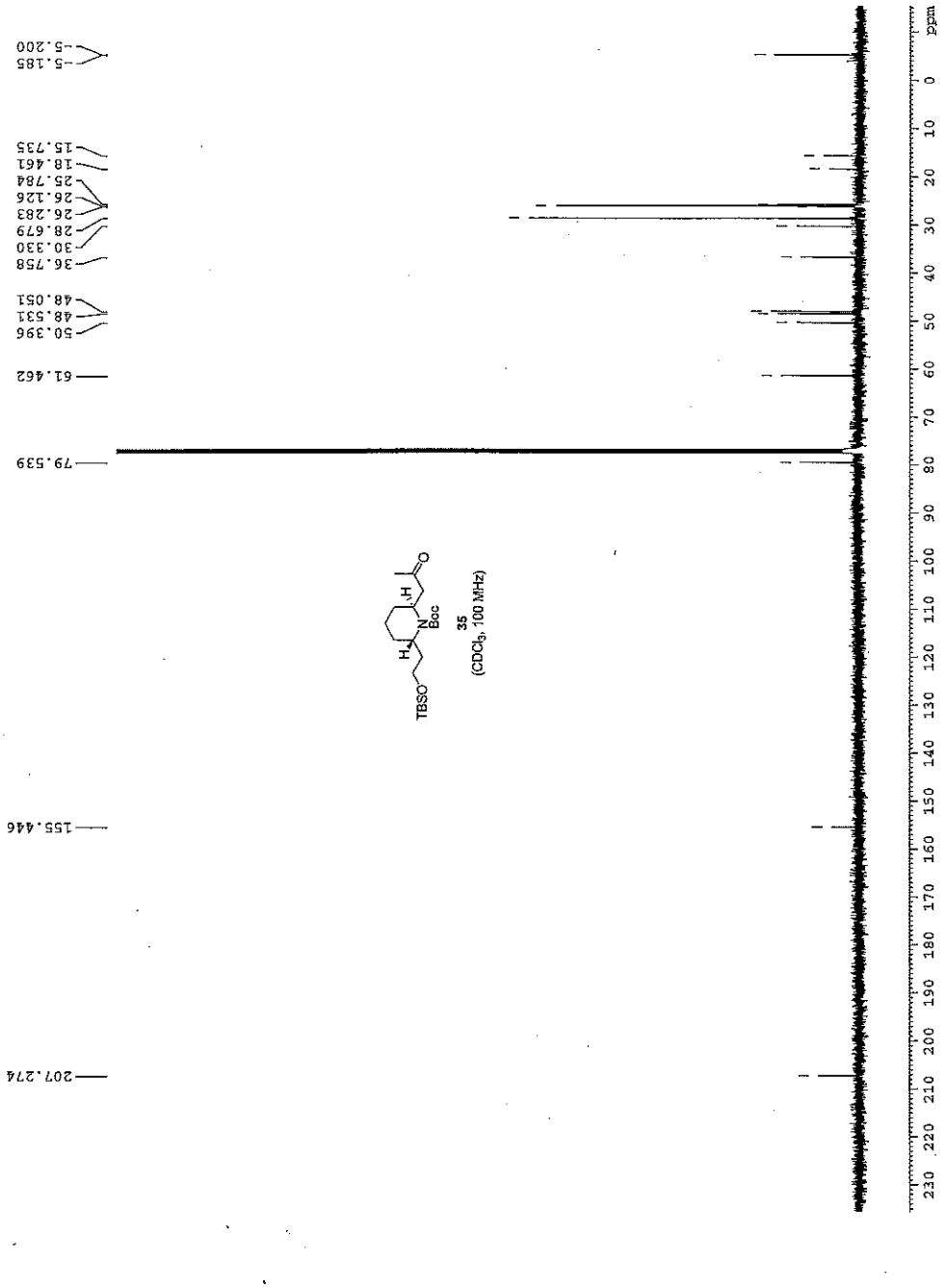

18
(CDCl3, 400 MHz)
Me
H
N
Boc
HO
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
2.870
1.049
8.977
10.035
1.005
2.908
0.955
0.932
2.022
1.104
1.010
0.916
0.932
1.271
1.289
1.306
1.322
1.343
1.478
1.619
1.632
1.698
1.708
2.018
2.035
2.051
2.068
2.125
2.216
2.236
2.258
2.278
2.482
2.495
2.524
2.537
3.588
3.811
3.923
3.934

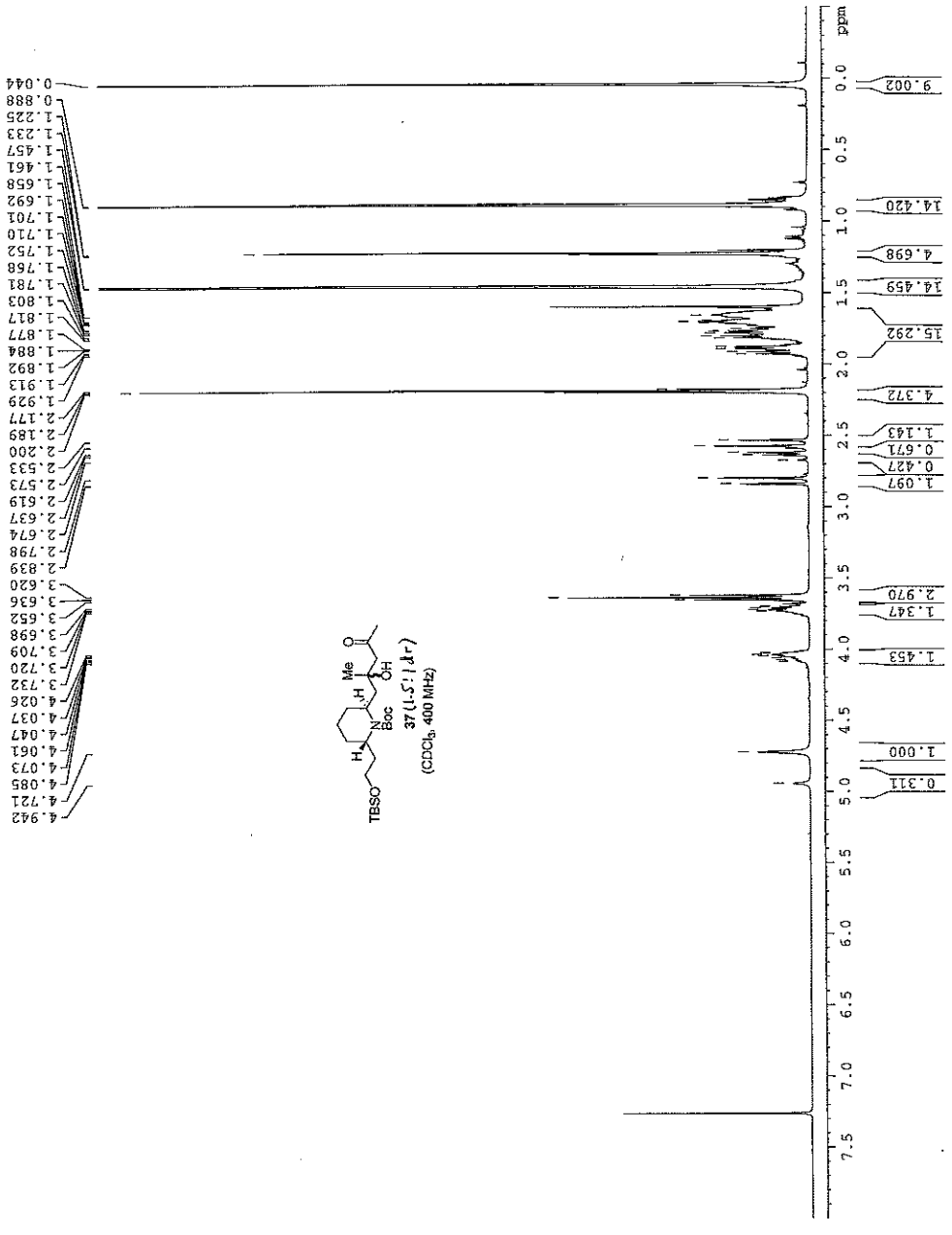

15.101
20.808
24.571
26.618
28.722
30.719
38.555
40.699
48.321
50.511
50.847
59.489
80.173
156.733
209.006
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230
Me
H
N
Boc
HO
16
(CDCl3, 100 MHz)

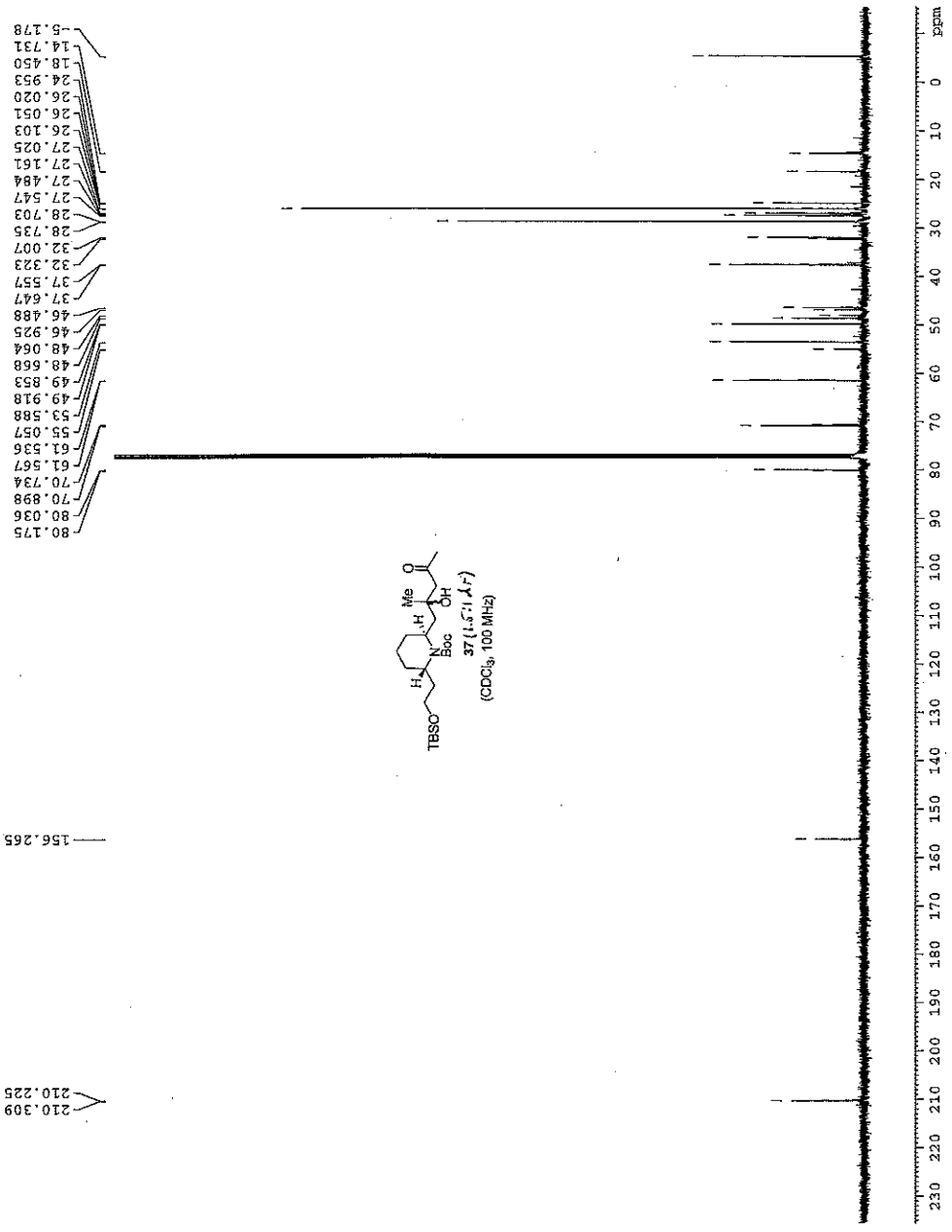

TBDPSO
Me
O
H
N
Boc
30
(CDCl3, 400 MHz)
ppm

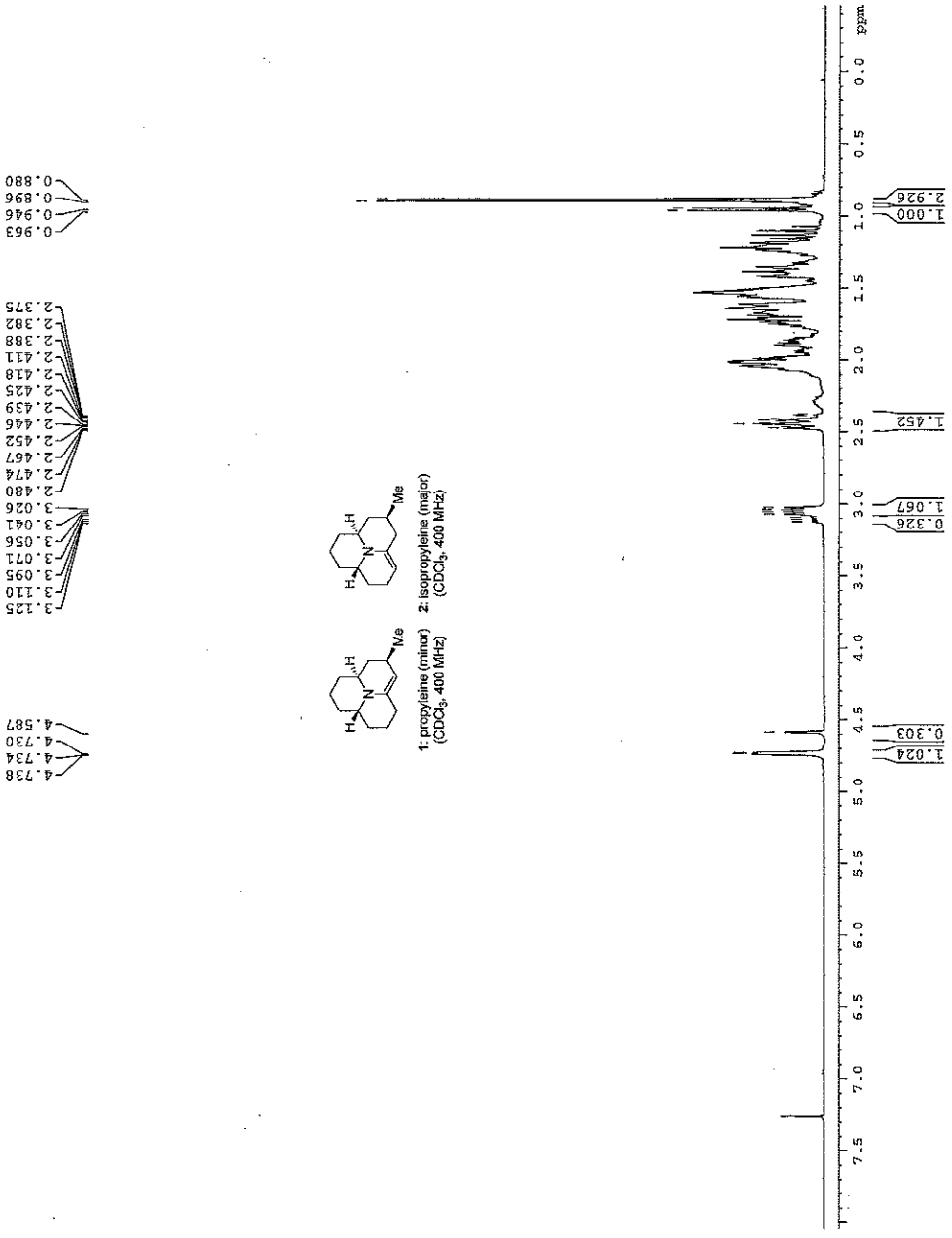

32
(CDCl3, 400 MHz)
TBDPSO
Me
Boc
ppm

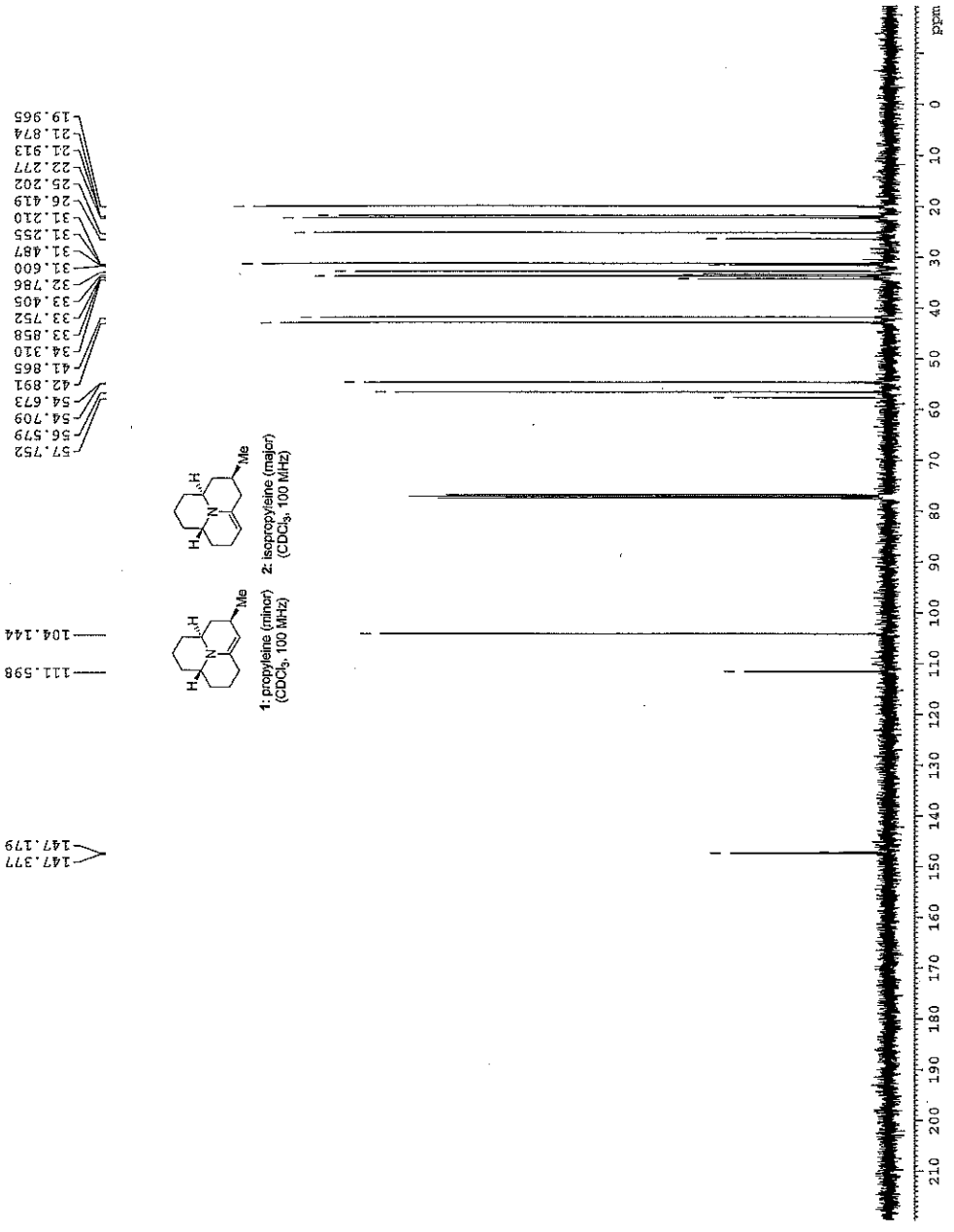

ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
5.977
9.505
9.356
7.344
1.037
3.131
1.104
0.992
2.017
1.000
1.128
0.049
0.891
1.444
1.559
1.683
1.711
1.728
1.748
1.897
1.913
1.929
1.946
1.963
1.979
2.158
2.592
2.614
2.632
2.654
2.954
2.965
2.994
3.005
3.634
3.641
3.650
3.657
3.667
3.674
3.978
4.112
4.124
4.135
4.145
TBSO
Boc
35
(CDCl3, 400 MHz)

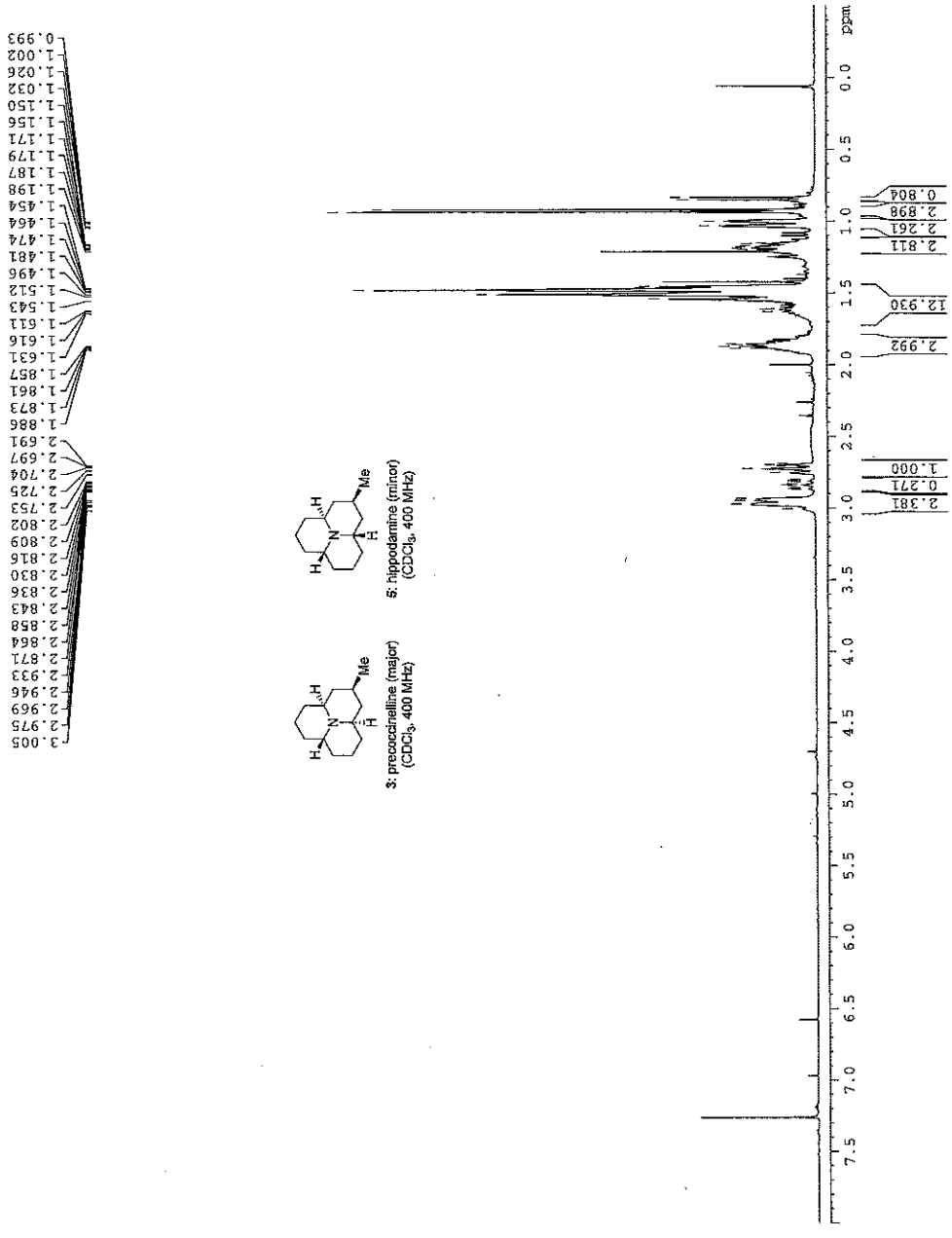

-5.200
-5.185
15.735
18.461
25.784
26.126
26.283
28.679
30.330
36.758
48.051
48.531
50.396
61.462
79.539
155.446
207.274
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230
TBSO
Boc
O
35
(CDCl3, 100 MHz)

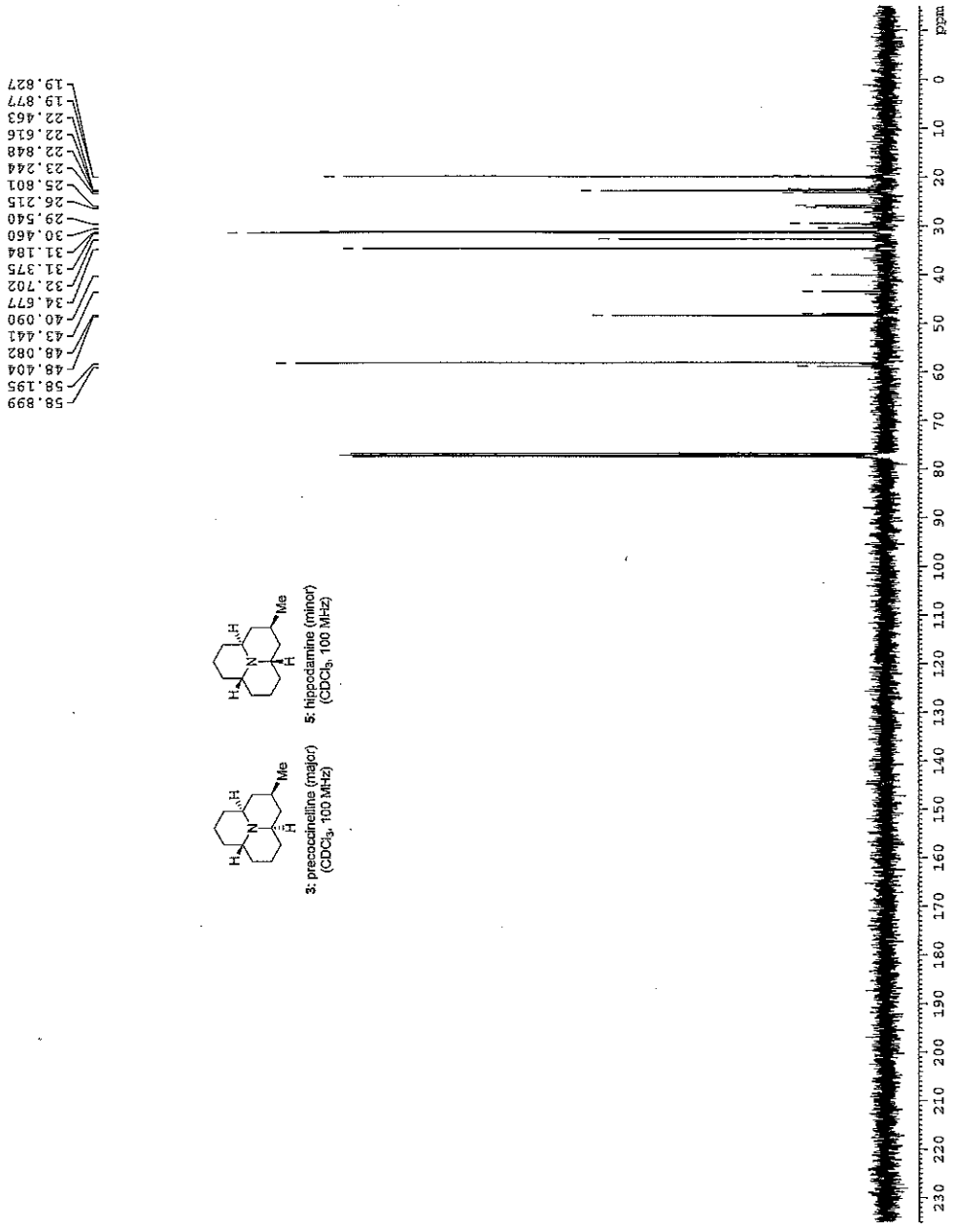

ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
9.002
14.420
4.698
14.459
15.292
4.372
1.143
0.671
0.427
1.097
2.970
1.347
1.453
1.000
0.311
0.044
0.888
1.225
1.233
1.457
1.461
1.658
1.692
1.701
1.710
1.752
1.768
1.781
1.803
1.817
1.877
1.884
1.892
1.913
1.929
2.177
2.189
2.200
2.533
2.573
2.619
2.637
2.674
2.798
2.839
3.620
3.636
3.652
3.698
3.709
3.720
3.732
4.026
4.037
4.047
4.061
4.073
4.085
4.721
4.942
TBSO
Boc
Me
OH
37 (1.5:1 dr)
(CDCl3, 400 MHz)

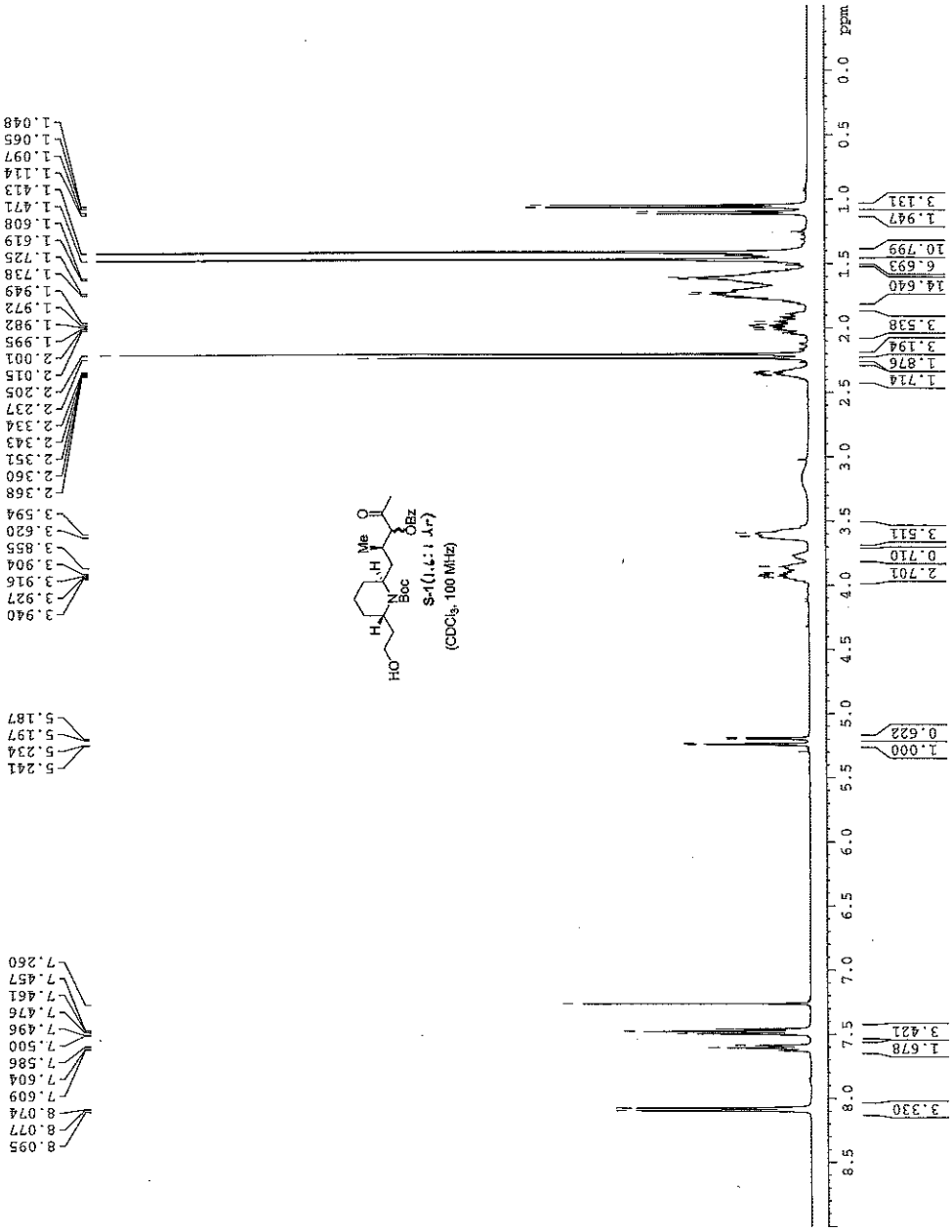

-5.178
14.731
18.450
24.953
26.020
26.051
26.103
27.025
27.161
27.484
27.547
28.703
28.735
32.007
32.323
37.557
37.647
46.488
46.925
48.064
48.668
49.853
49.918
53.588
55.057
61.536
61.567
70.734
70.898
80.036
80.175
156.265
210.225
210.309
Me
OH
N
Boc
TBSO
37 (1.5:1 dr)
(CDCl3, 100 MHz)
ppm

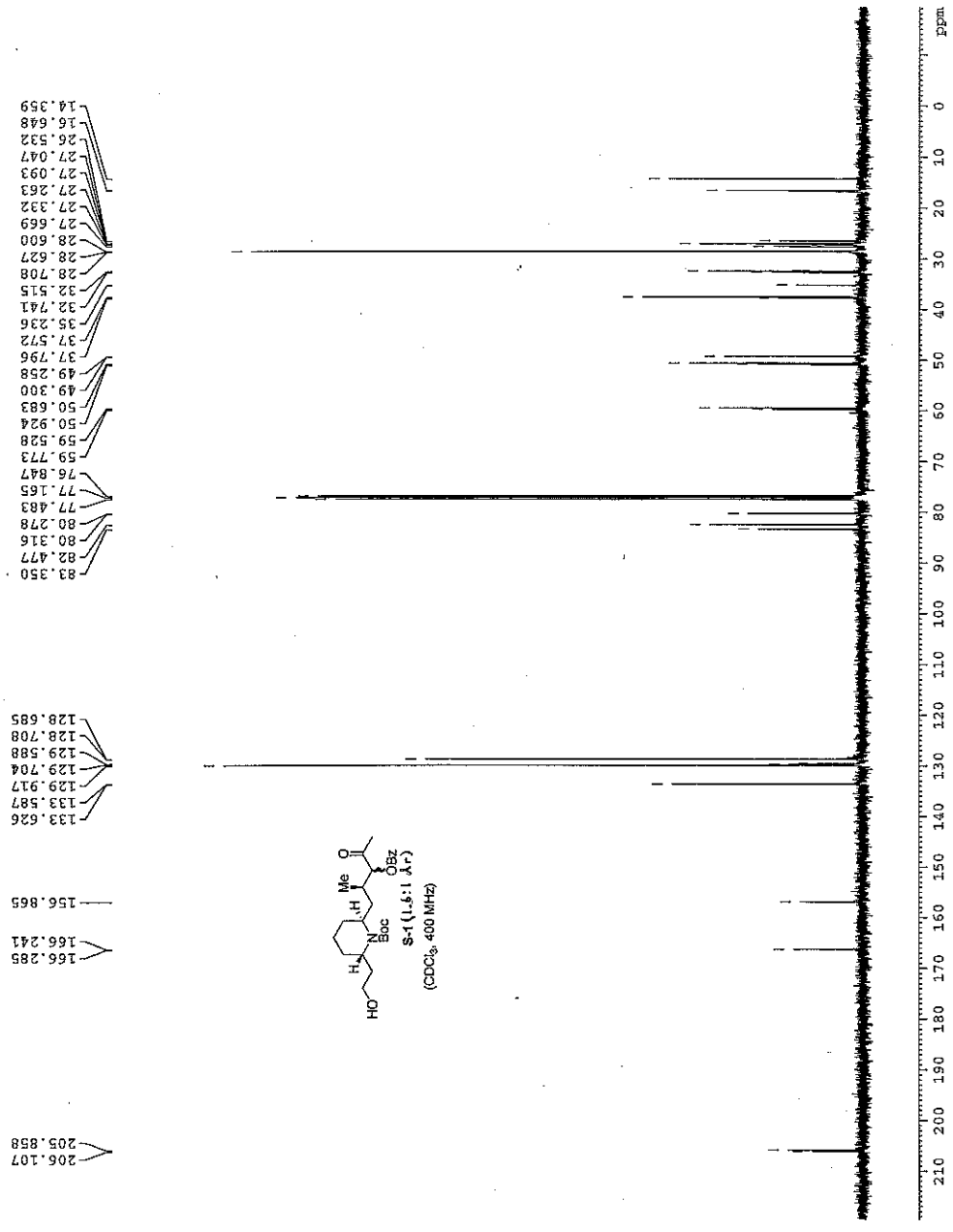

0.880
0.896
0.946
0.963
2.375
2.382
2.388
2.411
2.418
2.425
2.439
2.446
2.452
2.467
2.474
2.480
3.026
3.041
3.056
3.071
3.095
3.110
3.125
4.587
4.730
4.734
4.738
1: propyleine (minor) (CDCl3, 400 MHz)
2: isopropyleine (major) (CDCl3, 400 MHz)
1.000
2.926
1.452
0.326
1.067
1.024
0.303
ppm

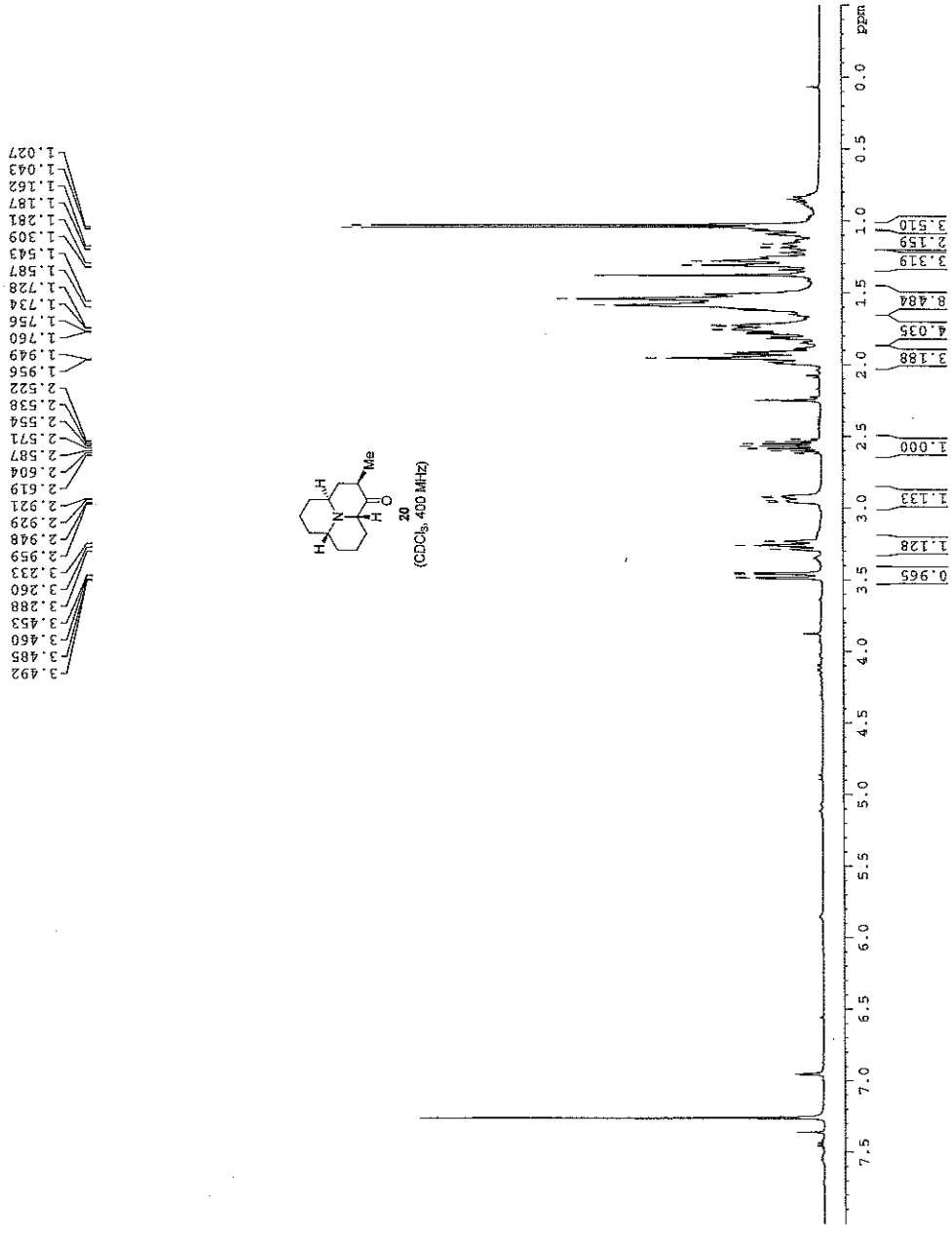

19.965
21.874
21.913
22.277
25.202
26.419
31.210
31.255
31.487
31.600
32.786
33.405
33.752
33.858
34.310
41.865
42.891
54.673
54.709
56.579
57.752
104.144
111.598
147.377
147.179
Me
H
N
H
1: propyleine (minor)
(CDCl3, 100 MHz)
Me
H
N
H
2: isopropyleine (major)
(CDCl3, 100 MHz)
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

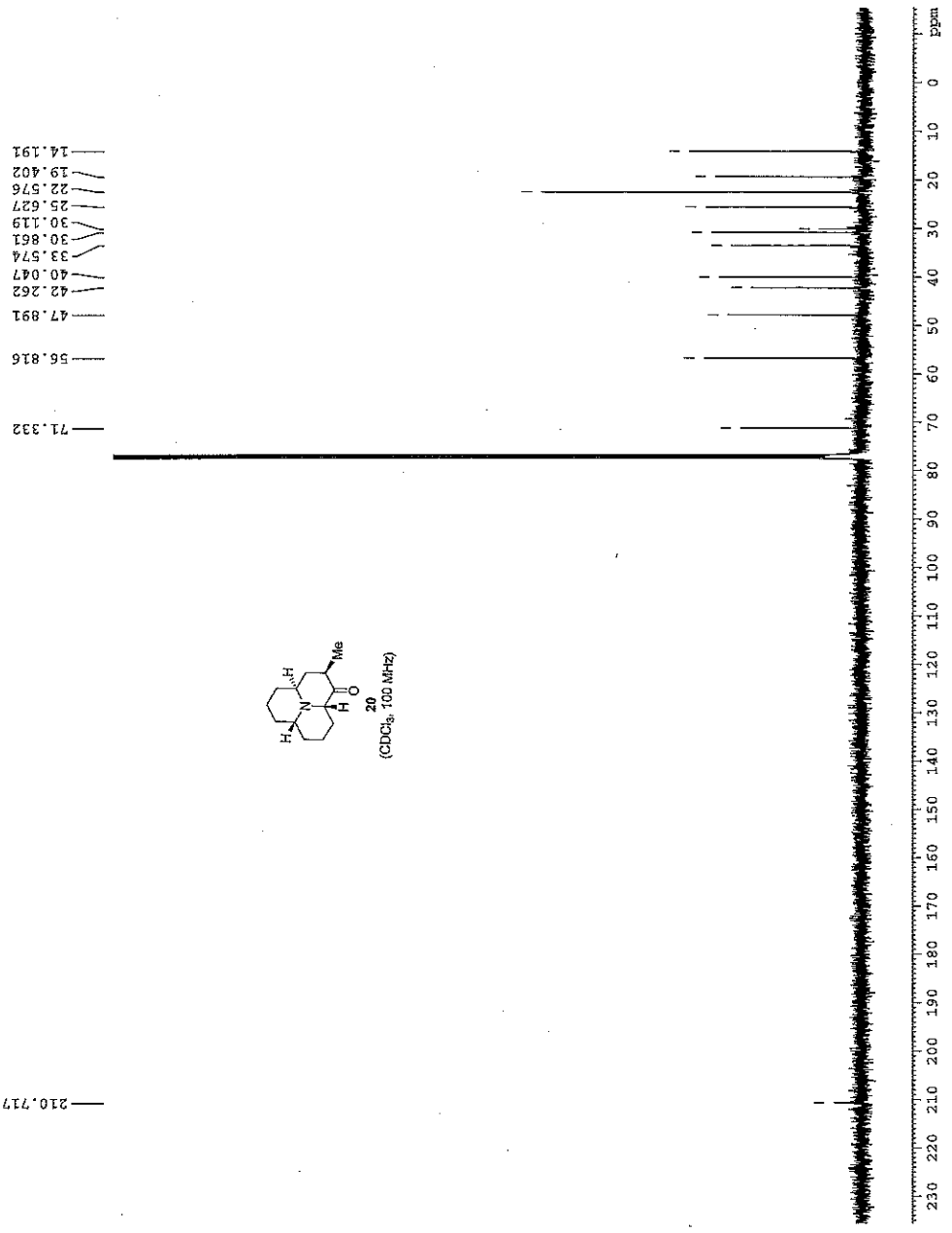

3.005
2.975
2.969
2.946
2.933
2.871
2.864
2.858
2.843
2.836
2.830
2.816
2.809
2.802
2.753
2.725
2.704
2.697
2.691
1.886
1.873
1.861
1.857
1.631
1.616
1.611
1.543
1.512
1.496
1.481
1.474
1.464
1.454
1.198
1.187
1.179
1.171
1.156
1.150
1.032
1.026
1.002
0.993
Me
H
N
H
H
3: precoccinelline (major)
(CDCl3, 400 MHz)
Me
H
N
H
H
5: hippodamine (minor)
(CDCl3, 400 MHz)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
2.381
0.271
1.000
2.992
12.930
2.811
2.261
2.898
0.804

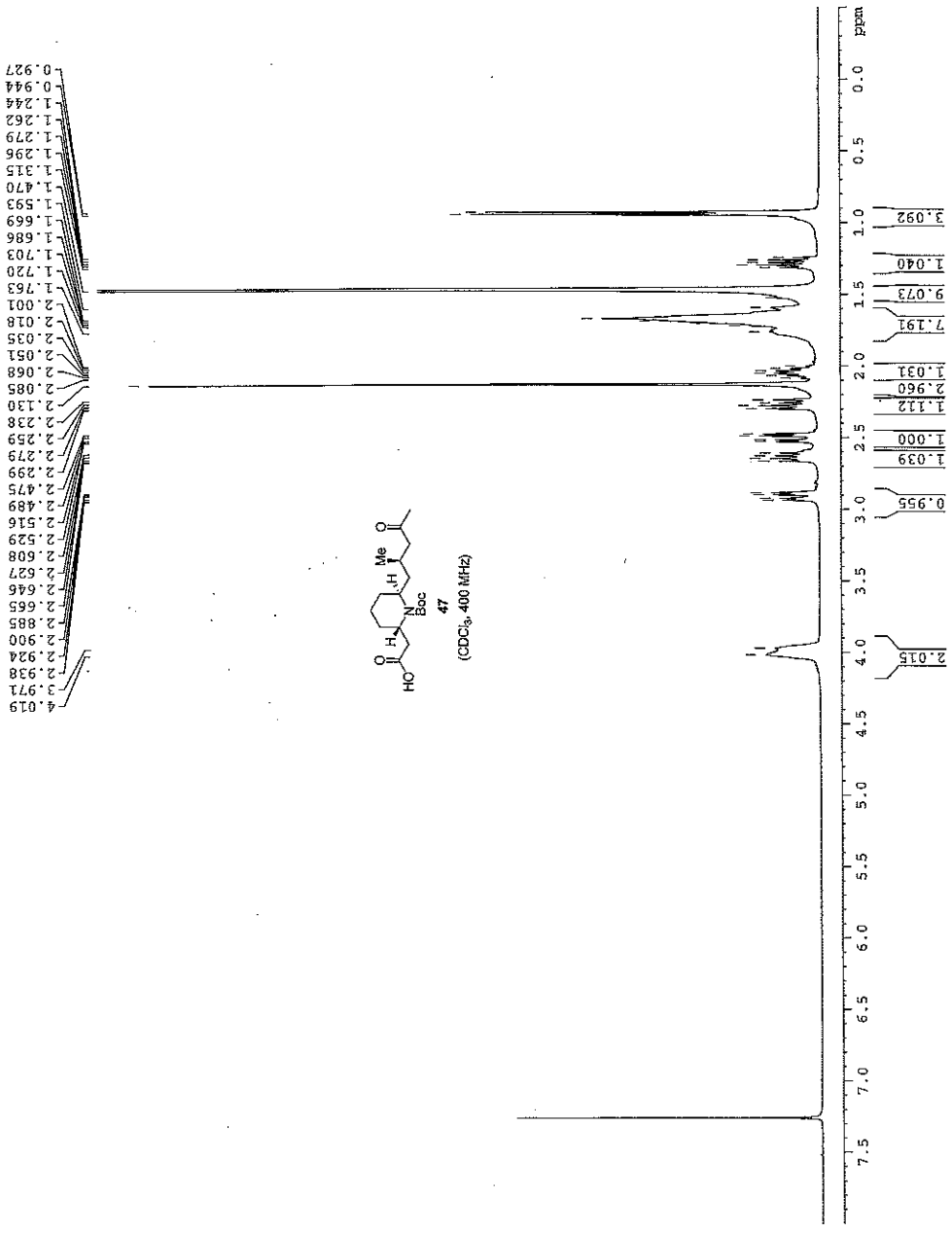

58.899
58.195
48.404
48.082
43.441
40.090
34.677
32.702
31.375
31.184
30.460
29.540
26.215
25.801
23.244
22.848
22.616
22.463
19.877
19.827
3: precocinelline (major)
(CDCl3, 100 MHz)
5: hippodamine (minor)
(CDCl3, 100 MHz)
ppm


S-1(1.4 : 1 dr)
(CDCl3, 100 MHz)
Me
OBz
Boc
HO
ppm


14.359
16.648
26.532
27.047
27.093
27.263
27.332
27.669
28.600
28.627
28.708
32.515
32.741
35.236
37.572
37.796
49.258
49.300
50.683
50.924
59.528
59.773
76.847
77.165
77.483
80.278
80.316
82.477
83.350
128.685
128.708
129.588
129.704
129.917
133.587
133.626
156.865
166.241
166.285
205.858
206.107
Me
H
N
Boc
OBz
HO
S-1 (1.9:1 dr)
(CDCl3, 400 MHz)
ppm


1.027
1.043
1.162
1.187
1.281
1.309
1.543
1.587
1.728
1.734
1.756
1.760
1.949
1.956
2.522
2.538
2.554
2.571
2.587
2.604
2.619
2.921
2.929
2.948
2.959
3.233
3.260
3.288
3.453
3.460
3.485
3.492
Me
O
H
H
H
20
(CDCl3, 400 MHz)
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
3.510
2.159
3.319
8.484
4.035
3.188
1.000
1.133
1.128
0.965


210.717
71.332
56.816
47.891
42.262
40.047
33.574
30.861
30.119
25.627
22.576
19.402
14.191
Me
H
H
N
O
20
(CDCl3, 100 MHz)
ppm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Boc
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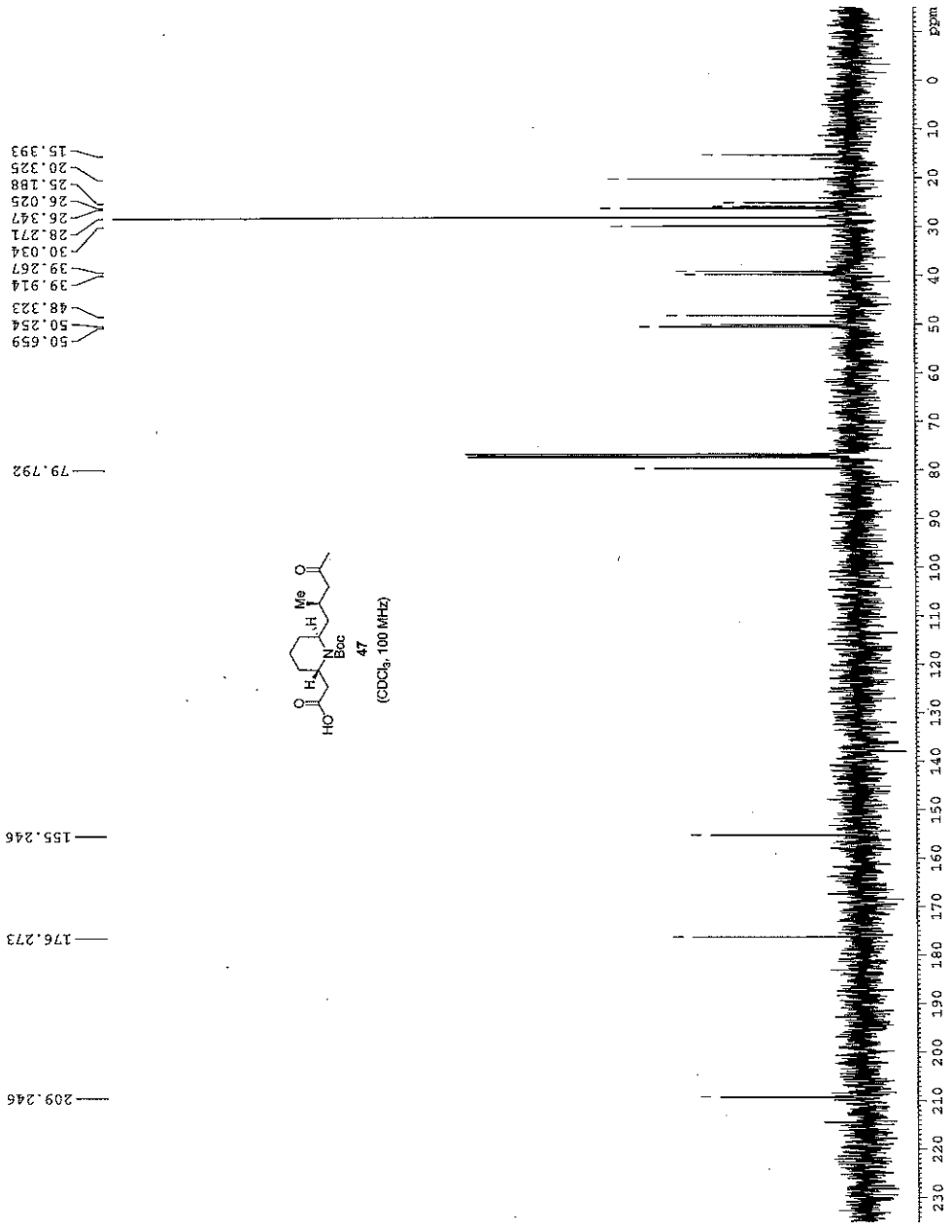
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Boc
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O
HO
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(CDCl3, 100 MHz)
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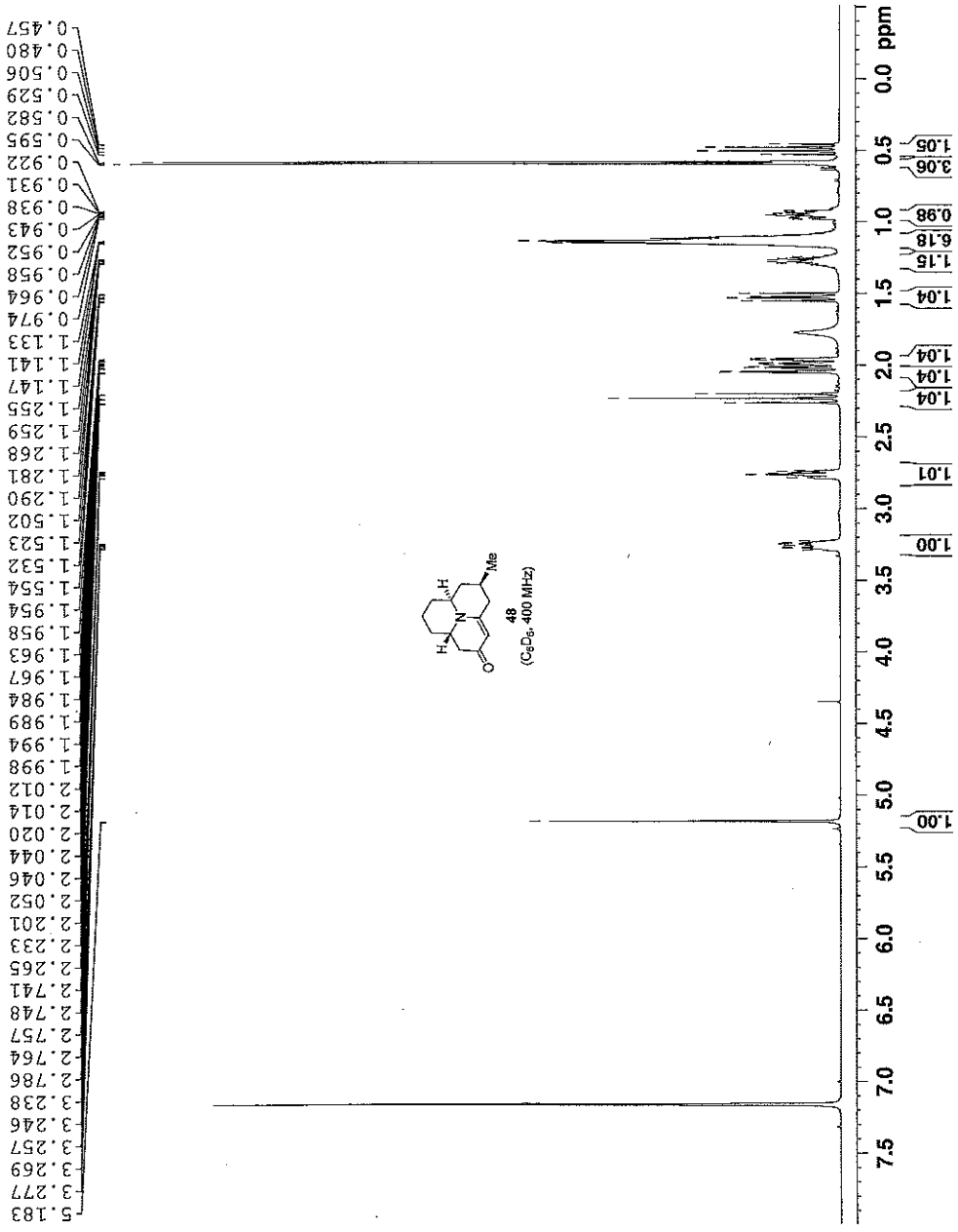
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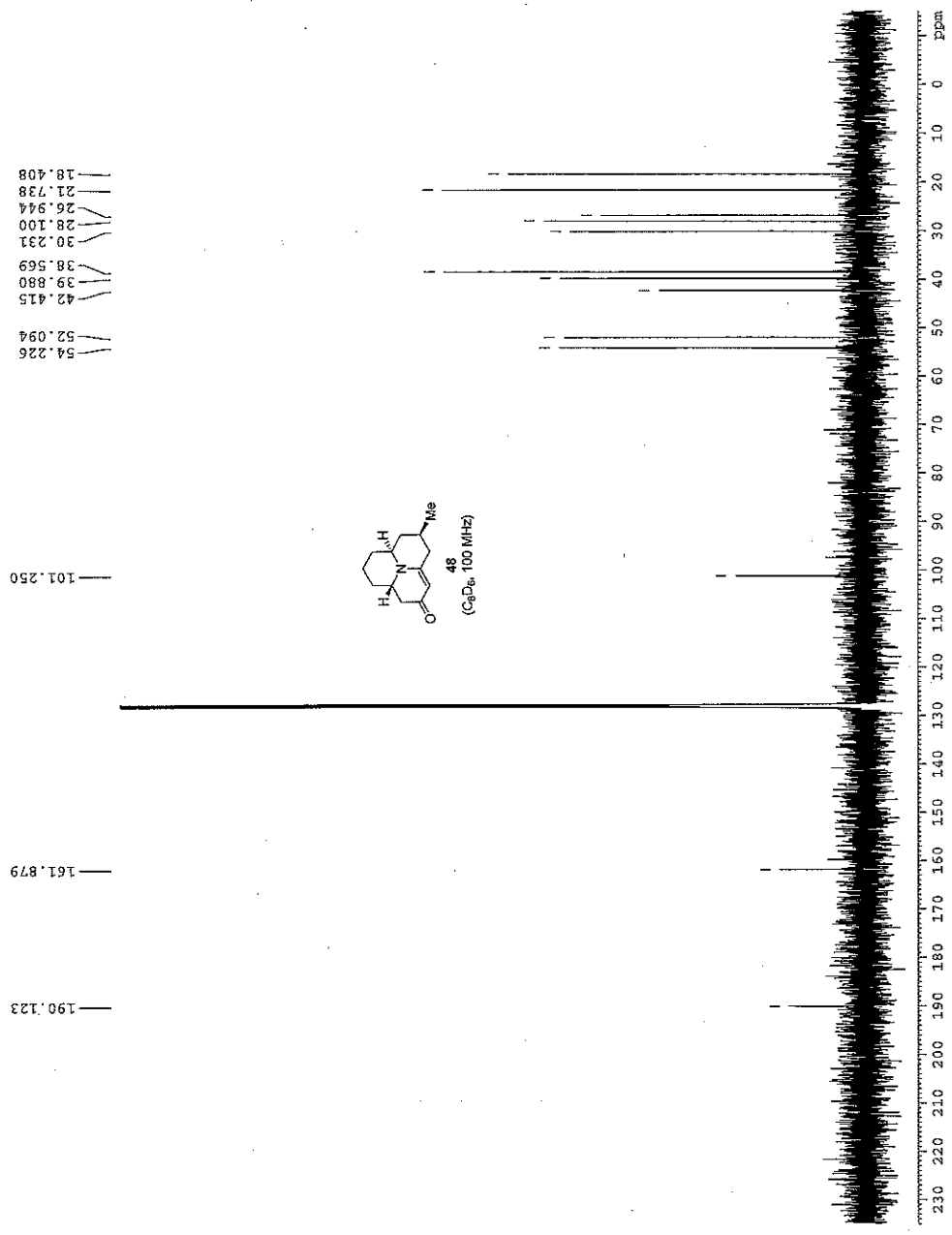
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O
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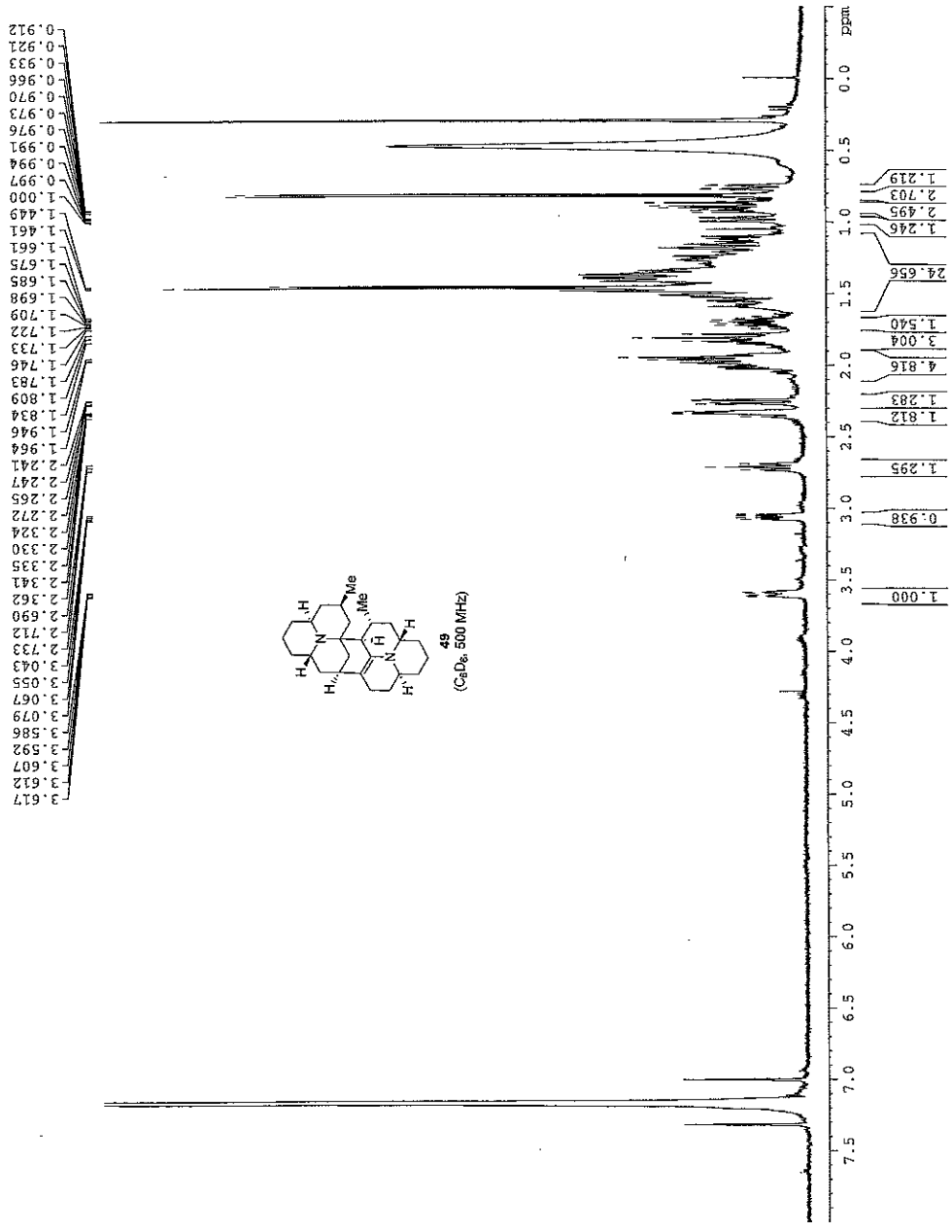
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H
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H
N
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2.495
2.703
1.219
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0.976
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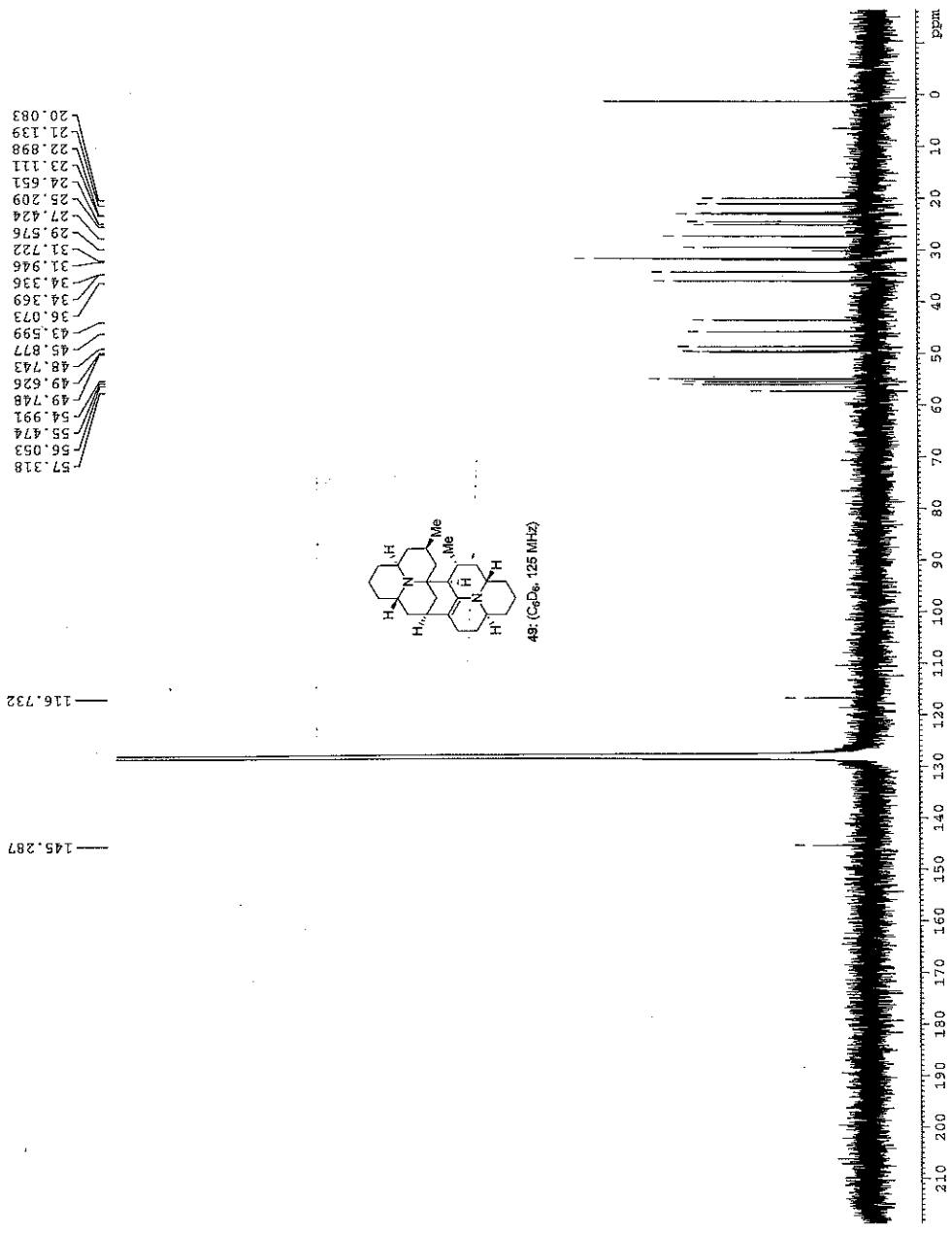
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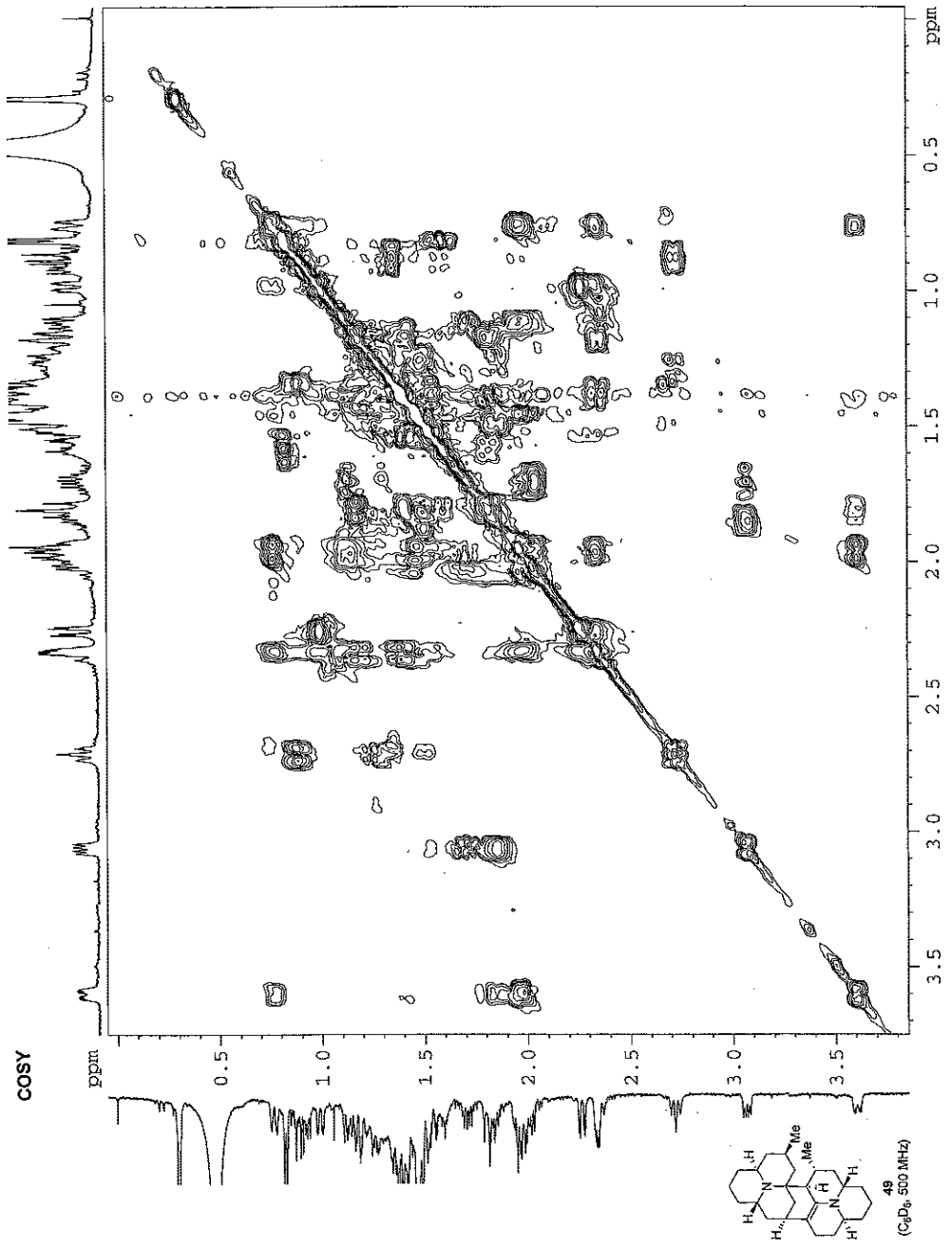
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H'
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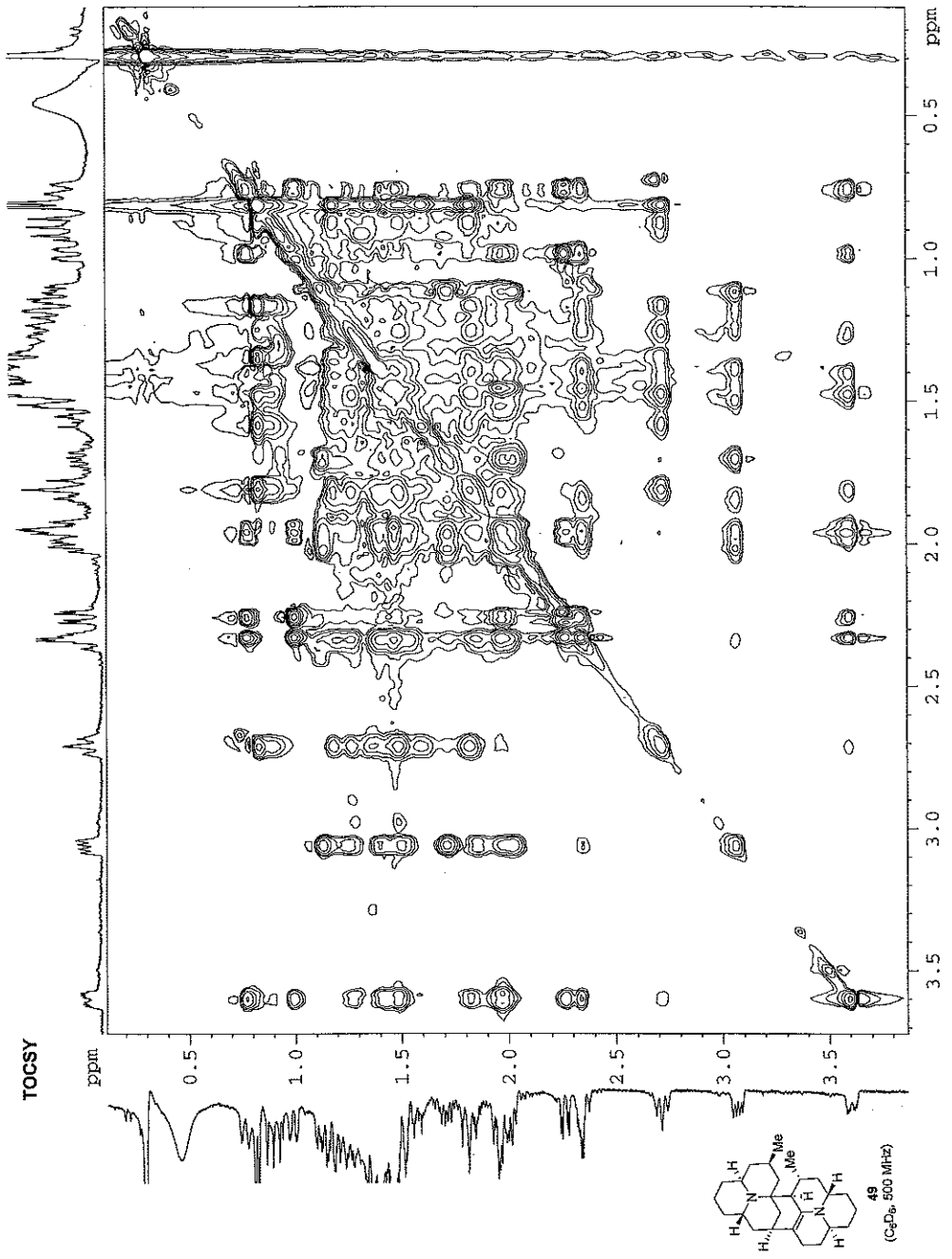
(C6D6, 500 MHz)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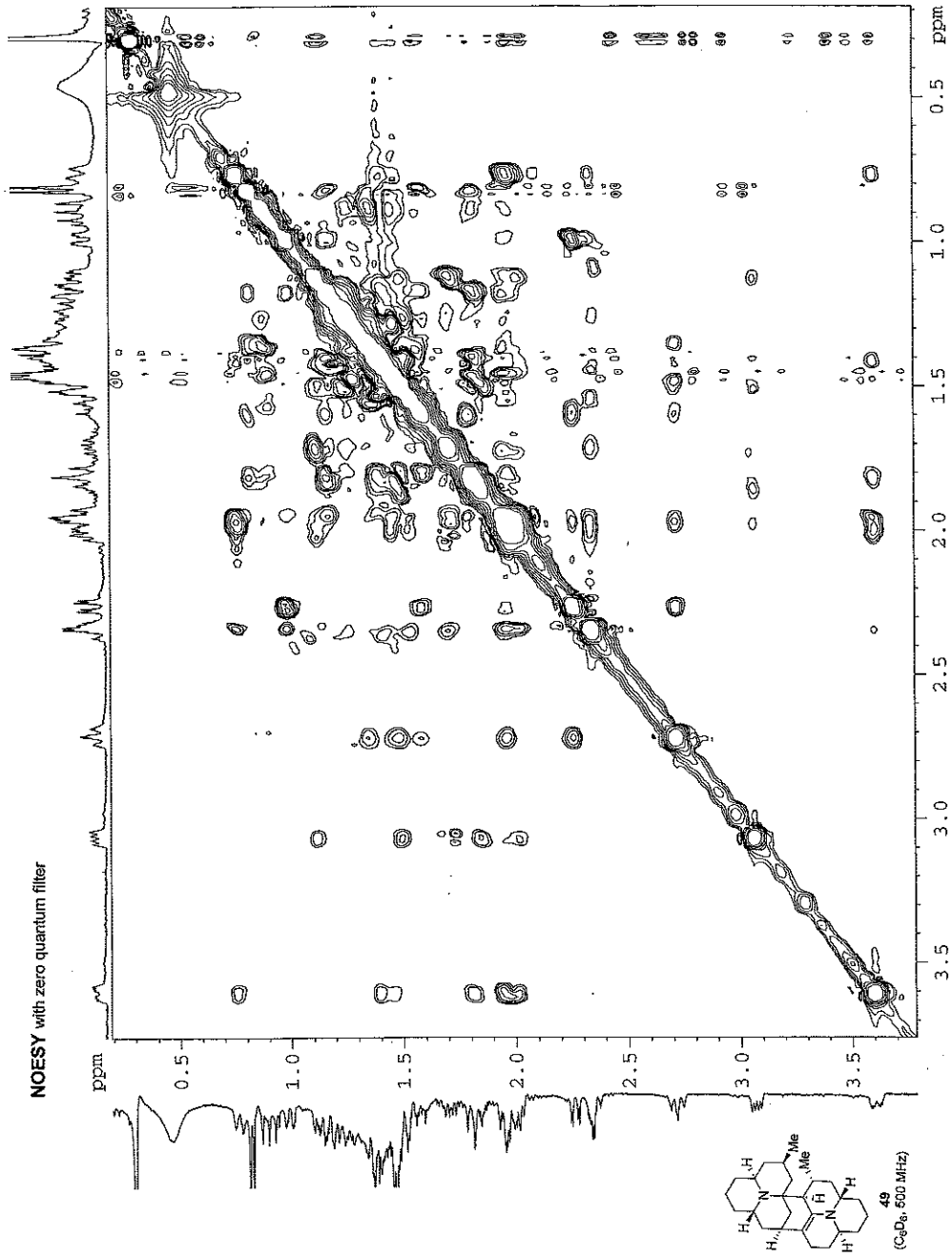
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H
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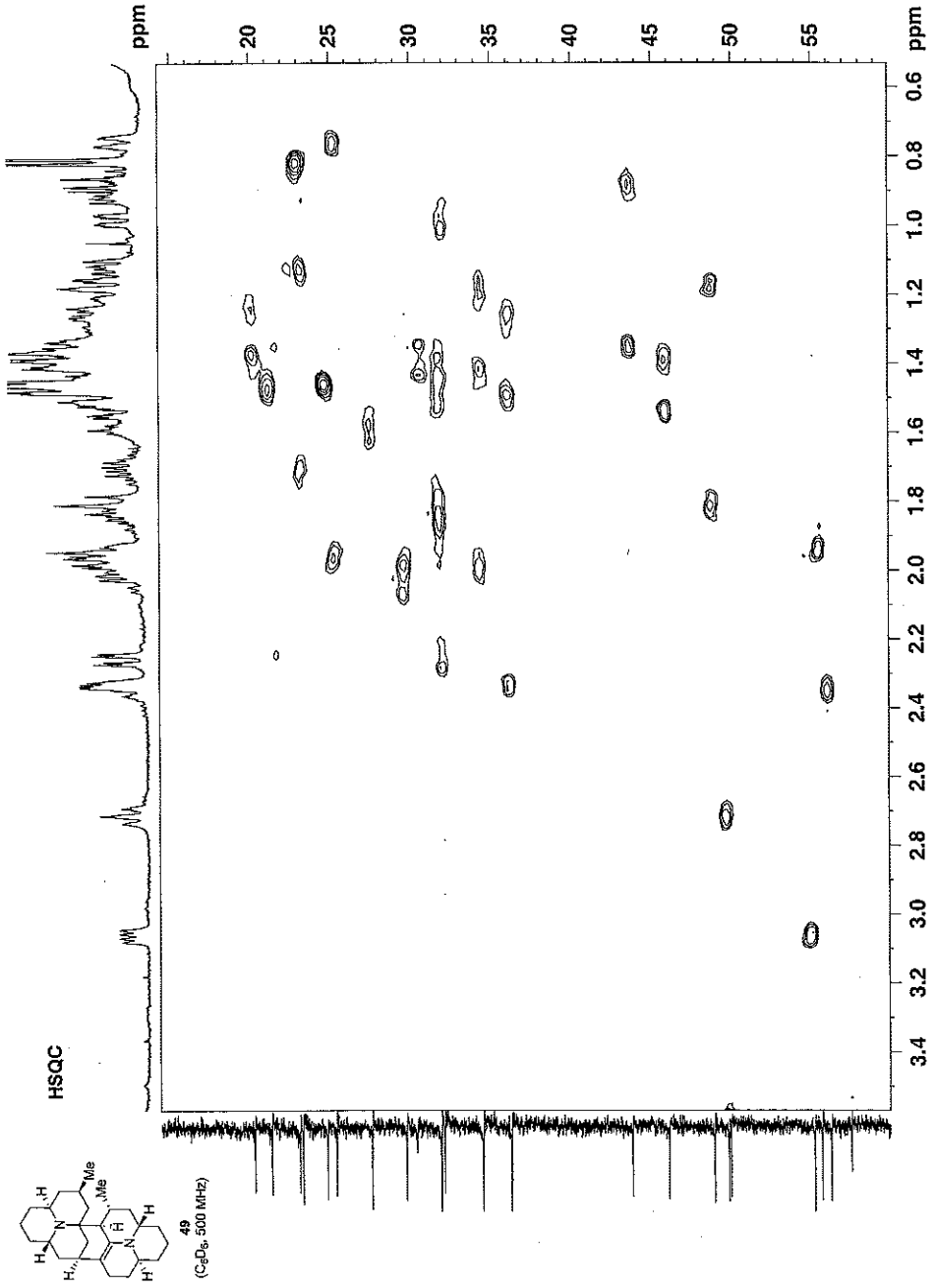
(C6D6, 500 MHz)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2.4
2.6
2.8
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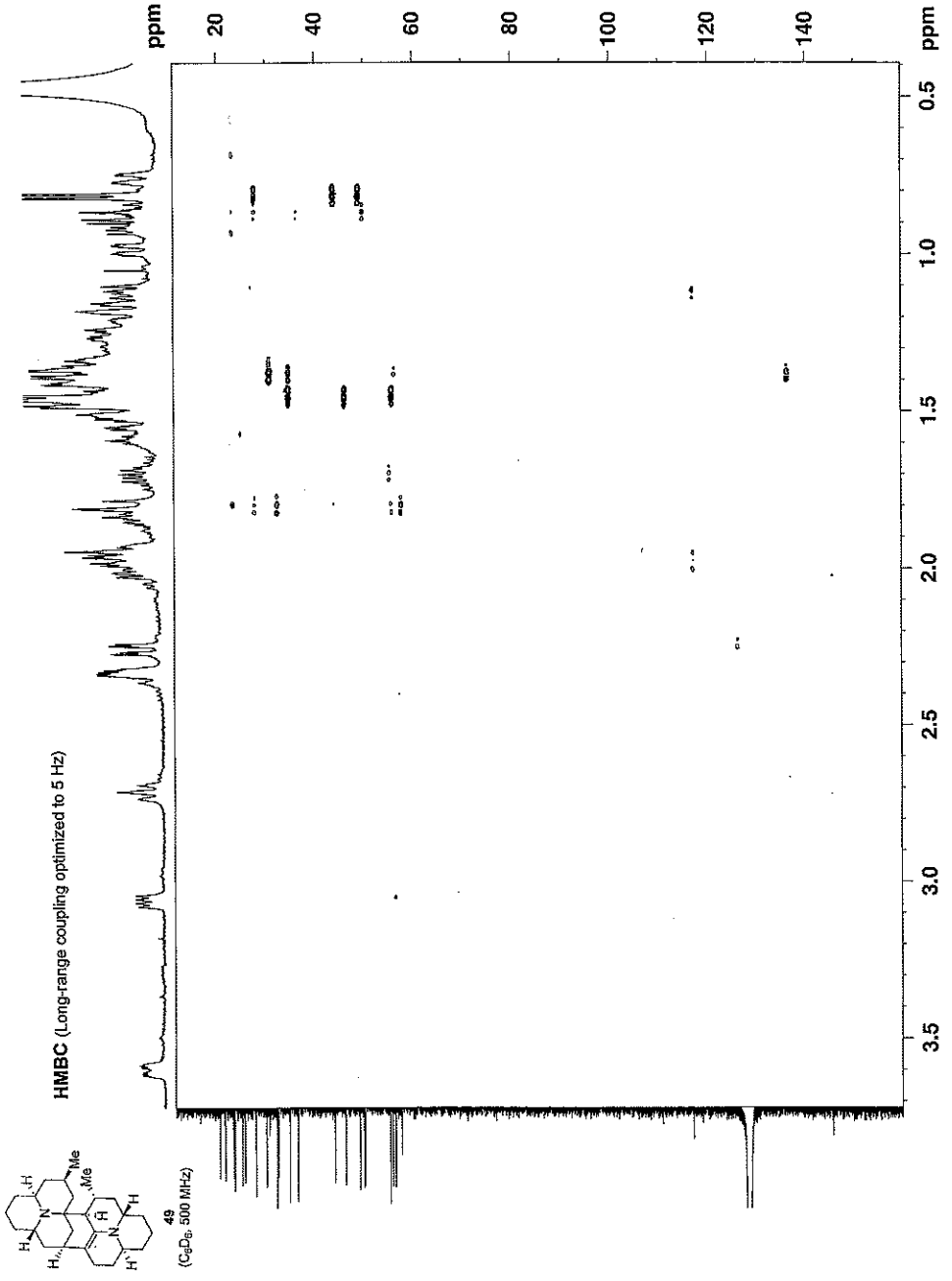
(C6D6, 500 MHz)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ppm
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H
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H
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H
N
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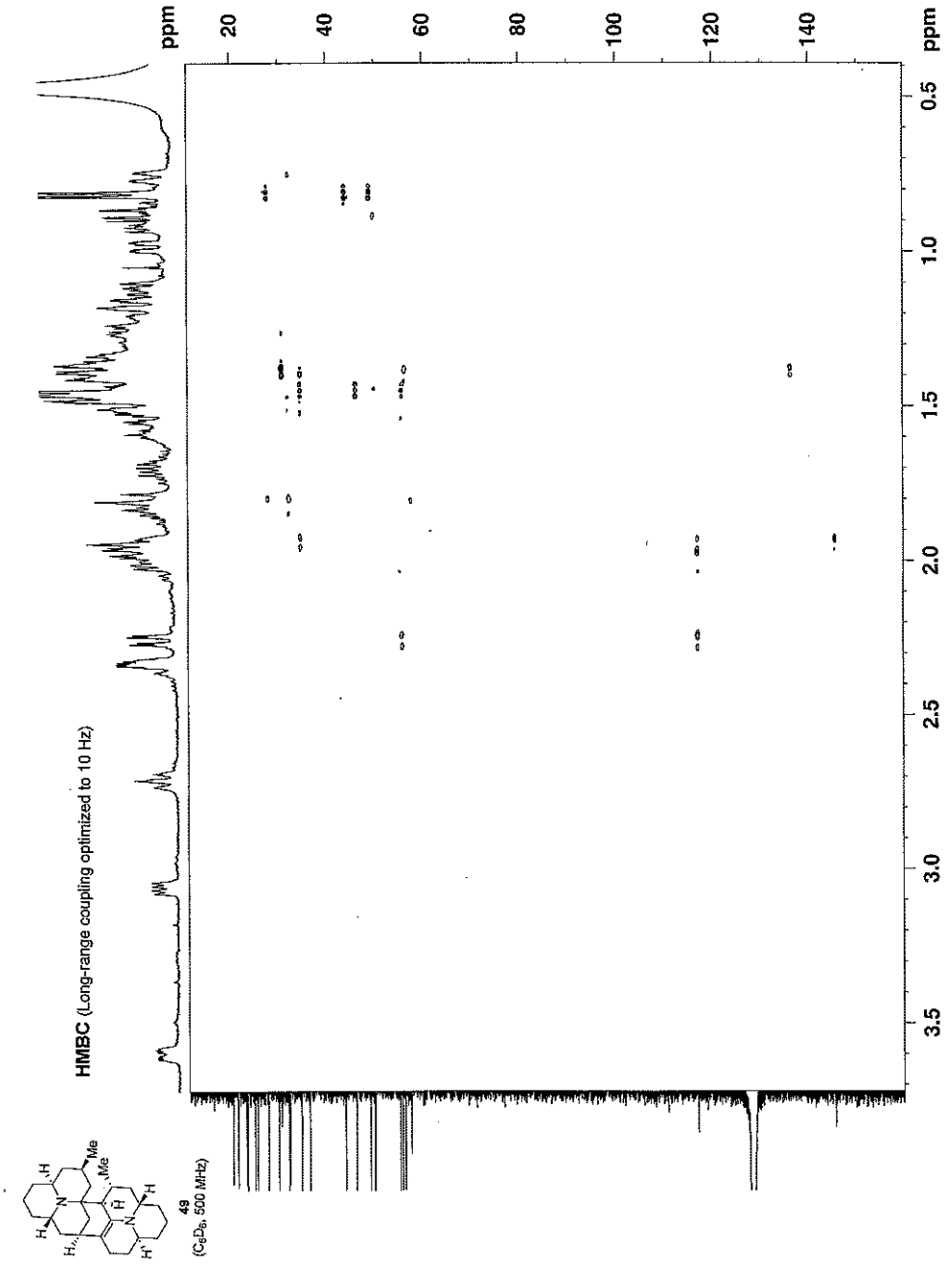
(C_6D_6, 500 MHz)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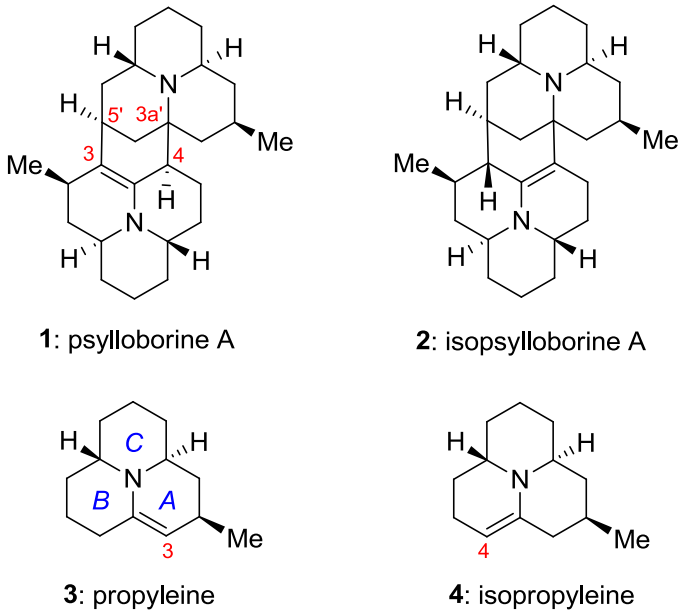
1.5
2.0
2.5
3.0
3.5
ppm

CHAPTER 4

Development of a Programmable Synthetic Strategy to Access the Oligomeric Azaphenalene Alkaloids: Non-Biomimetic Syntheses of Homodimeric Frameworks

Section 4.1 Introduction

Figure 1. Structures of Homodimers Psylloborine A and Isopsylloborine A and Related Monomers

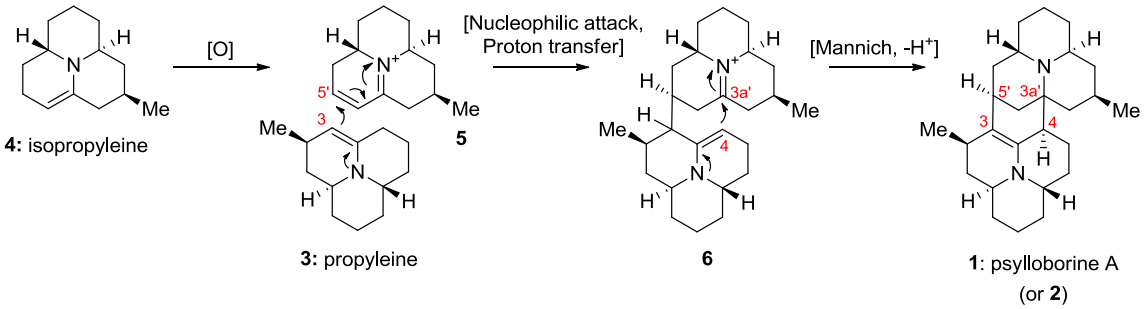


In Chapter 2, the state of the art for the field of 2-methyl-perhydro-9b-azaphenalene coccinellid defensive alkaloid chemistry was presented with an emphasis on molecular diversity and key synthetic contributions from previous investigators in this area. In Chapter 3, I outlined the development of a unified strategy to access monomeric (**3** and **4**, Figure 1, representative)[i] and homodimeric structures (**1** and **2**) of this class from a key intermediate designed specifically for synthetic divergence. Through the use of this central compound, we were able to access all monomers with a *trans* substituted C-ring and applied our approach to our proposed biosynthetic dimerization cascade, as well (Scheme 1A). Unfortunately, the product of these studies was the result of the incorrect regiochemistry of nucleophilic attack (Scheme 1B), which we believe was

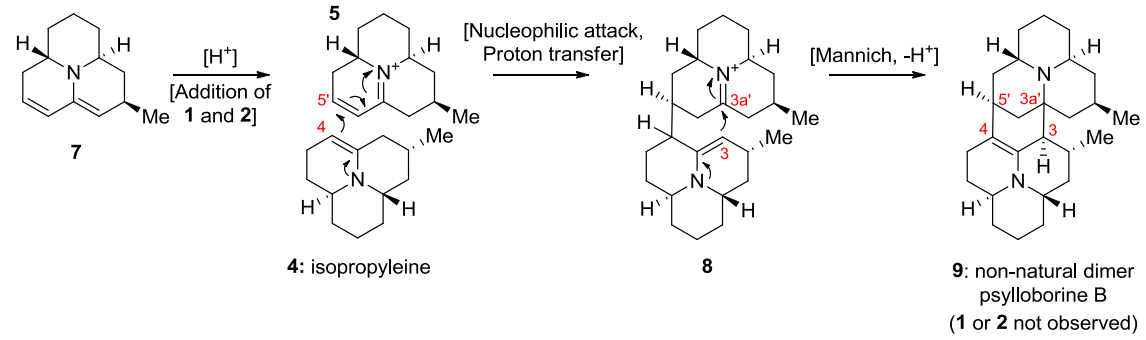
[i] For a full discussion and relevant references for monomer and dimer isolation, biosynthesis and synthetic studies, see Chapter 2.

caused by the C-2 methyl group destabilizing the transition state for attack from C-3 (See Chapter 3 for a full discussion). In this chapter, I will describe a new, non-biomimetic strategy to access homodimers psylloborine A (**1**)[1] and isopsylloborine A (**2**).[2]

Scheme 1. Possible Biosynthetic Dimerization and Attempted Synthetic Replication
A. Our Proposed Biogenesis to Account for the Formation of Psylloborine A and Isopsylloborine A



B. Result of a Biomimetic Dimerization Based on our Biosynthetic Hypothesis



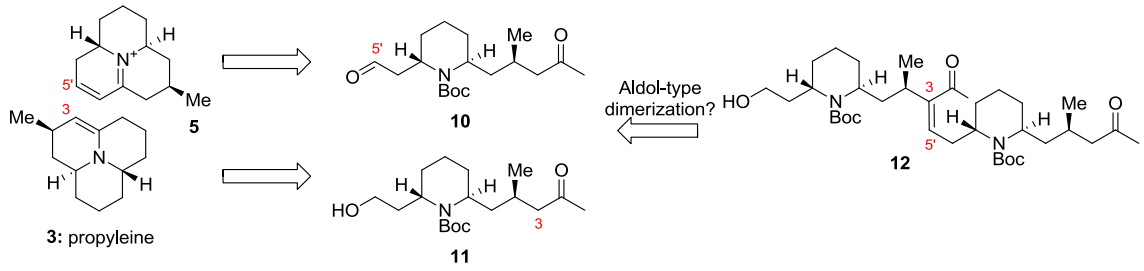
Section 4.2 Redesigned Strategy to Access Homodimeric Architectures

Faced with these disappointing results in our direct dimer synthesis, a synthetic redesign was clearly necessary in order to achieve laboratory preparation of **1** or **2**. In initial attempts to fix this regiochemical issue, we examined new uses for the synthetic precursors to the electrophile **5** and desired nucleophile **3** (Scheme 2). It had first been proposed that aldehyde **10** would enable access to the extended iminium **5**, and key alcohol **11** was used to synthesize the equilibrating mixture of enamine monomers

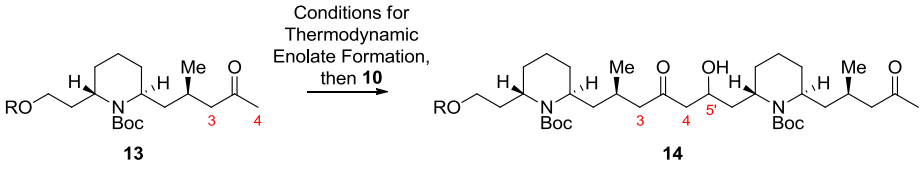
propyleine (**3**) and isopropyleine (**4**). Although uniting these fragments at C-3 and C-5' was not successful with tricyclic species as shown in Scheme 1, we believed that utilizing their synthetic precursors (**10** and **11**) or closely related derivatives may enable productive union of the two carbons of interest. Looking more closely at the alcohol precursor to propyleine, its C-3 position is the thermodynamic location for ketone enolization, itself a potential nucleophile, and the initially proposed precursor to iminium **5** was **11** with C-5' in the aldehyde oxidation state, a potential site of electrophilicity (Scheme 2A). With this analysis in mind, we began investigating aldol-type dimerizations of **10** and **13** as a way to tether the two required carbons prior to azaphenalene formation.

Scheme 2. Aldol Based Strategy for Dimerization

A. Retrosynthetic Analysis for New Strategy for C-3/C-5' Bond Construction



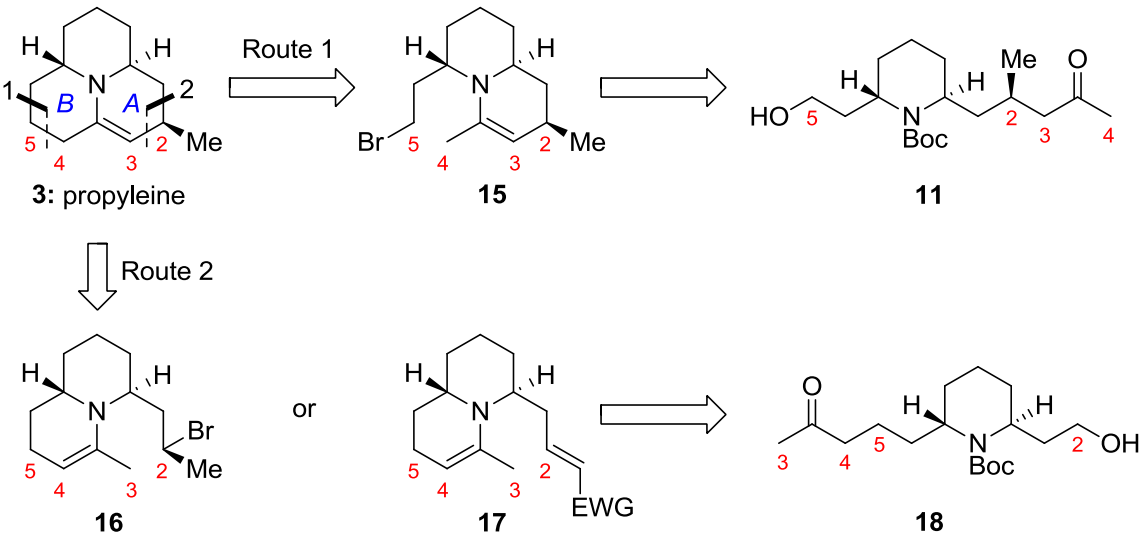
B. Results of Initial Aldol Attempts to Form the C-3/C-5' Bond



Unfortunately, this aldol-based approach did not prove as successful as imagined (Scheme 2B). The only observed product under a variety of conditions was the product of attack from C-4 on the desired aldehyde **10** to give dimeric product **14**. This outcome could be attributable to a few different factors. It is possible that there is far less inherent reactivity in a C-3 enolate than anticipated, and C-4 is a more reactive nucleophile. If this

is the case, enolate exchange from C-3 to C-4 could lead to the observed product. Alternatively, the desired product could be less stable than the observed one, and a retro-aldol process after formation of the desired product could convert it into the undesired product over the course of the reaction. Whatever the cause, it was clear desired dimer **12** was not achievable through this strategy.

Scheme 3. Alternative Retrosynthesis for Propyleine

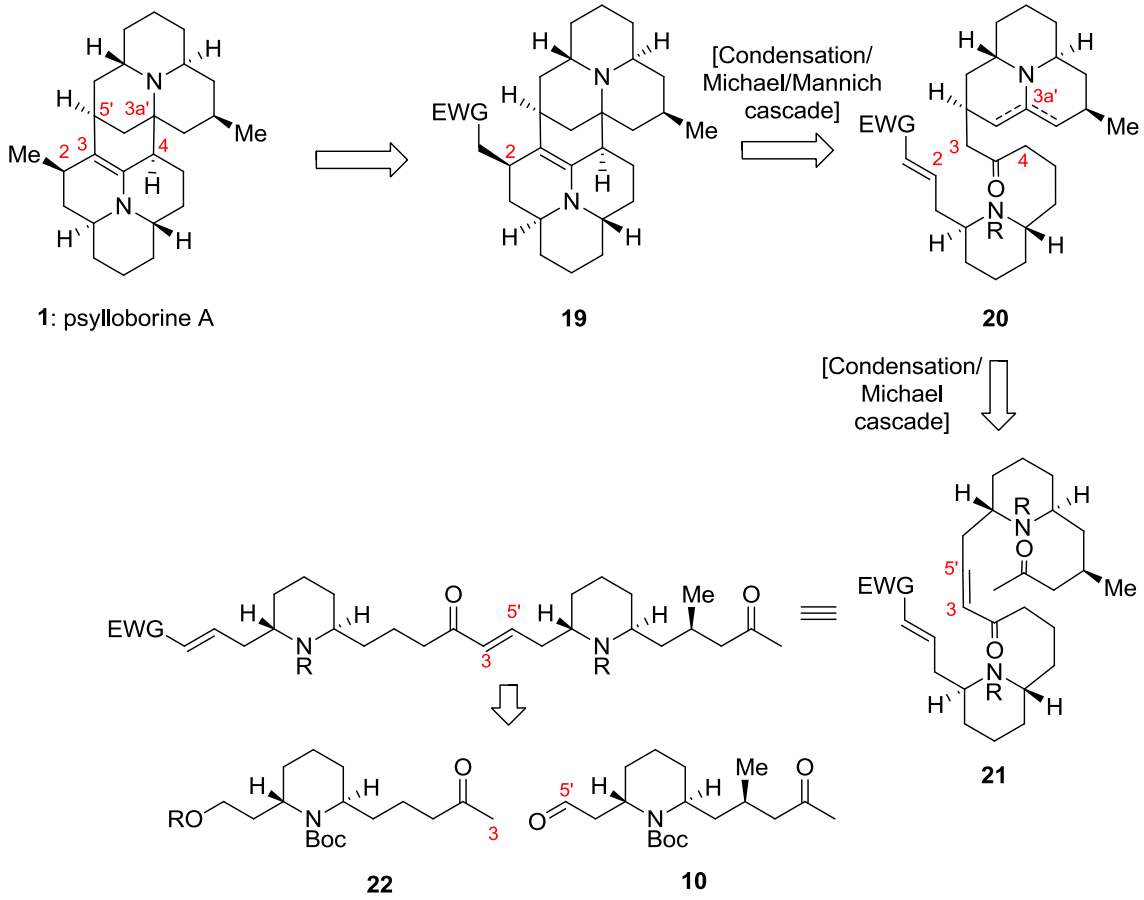


Still seeking to tether two protected, linear monomers, we elected next to exploit inherent symmetry in the azaphenalene structure. In the aldol dimerization, the problem was that the kinetic site of enolate formation (C-4) was the only site of nucleophilic attack. Fortunately, the pseudo-C_2 symmetry of propyleine (**3**) could provide us with a ready synthetic solution to this problem. Instead of forming **3** from alcohol **11** as detailed in Chapter 3 (summarized in Scheme 3, Route 1), an alternative, though very similar, bond disconnection could be made instead. In the route from **15** to **3**, formation of the C-4 to C-5 bond was the final step of the monomeric synthesis through cyclization of bromide **15** to close the B-ring. In this compound, C-2, C-3, and C-4 are already tethered.

Therefore, in key alcohol **11**, these three carbons are contained in the right-hand arm of the molecule, leaving C-5 in the left-hand arm. Alternatively, as shown in Route 2 in Scheme 3, one could imagine closing the C-2/C-3 bond to give the A-ring last via a secondary bromide **16** with the leaving group on C-2 and C-3, C-4, and C-5 already bonded linearly in this bicycle **16**. Alternatively, a substrate containing a Michael acceptor at C-2 (**17**) could also be used, and conversion of the C-2 functional handle into a methyl group after closure of the A-ring could give **3**. It was presumed that a bicycle like **17** could come from an intermediate **18** with an alcohol at C-2 allowing for rapid elaboration to a variety of Michael acceptors. These various electrophiles could be screened to determine which one(s) could easily be defunctionalized after tricycle formation to form the C-2 methyl group.

The true power of this redesigned order of ring formation, however, lies in the fact that in dissecting the molecule in a new way utilizing inherent symmetry, the C-3 to C-4 acetonyl subunit of key alcohol **11** has been moved to the other side of the molecule in new alcohol **18** with C-3 now being the most accessible carbon. This should have a profound effect on the difference in C-3 and C-4 reactivity, with C-3 now the kinetic site of enolization and the most likely site from which an aldol reaction should occur. Applying this in a broader retrosynthetic sense, Scheme 4 shows how such a strategy could be applied to dimeric targets **1** and **2** through the use of enamine-driven, cascade-based ring annulations to form the target structures.

Scheme 4. Unique Retrosynthetic Analysis Employing Tethered Monomers.



In this new approach, the envisioned ring annulations would require activating groups throughout the framework to prime the substrate for enamine-driven cascade chemistry. The product of such cascade steps would be heptacyclic core **19** requiring removal of the electron-withdrawing group appended to the C-2 methylene used in the terminating cascade (Scheme 4) in order to produce **1**. Deprotection of **20** followed by enamine condensation with the contained ketone, Michael attack onto C-2, and Mannich reaction between the C-4 enamine and C-3a' iminium could give heptacycle **19**. The tricyclic ring system contained in **20** could arise from a cascade sequence from **21** in which the required nitrogen is deprotected, condenses to form an enamine, and attacks the pendant enone at C-5'. Redrawing **21** in an open, linear fashion, it is apparent that

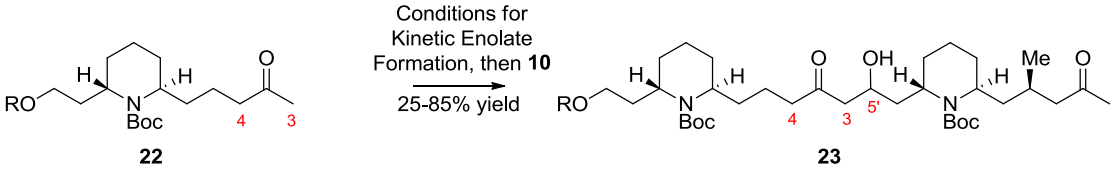
such a structure could arise from the union of building blocks **22** and **10** through the envisioned aldol reaction with kinetic enolate attack from C-3 onto C-5'. Pleasingly, testing this strategy was anticipated to be relatively facile since aldehyde **10** is a known compound from our earlier efforts (Chapter 3) and protected alcohol **22** or a relevant derivative should be accessible through similar chemistry to that employed for our key intermediate **11**.

Section 4.3 Total Synthesis of Psylloborine A and Isopsylloborine A

Section 4.3.1 Synthesis of Key Cascade Precursor

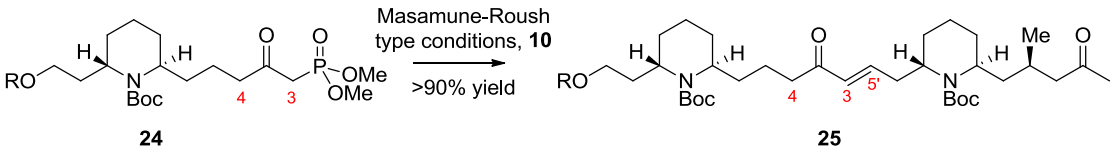
Scheme 5. Successful Dimerization of Protected Linear Monomers

A. Aldol-based dimerization



22 **23**

B. Horner-Wadsworth-Emmons-based dimerization

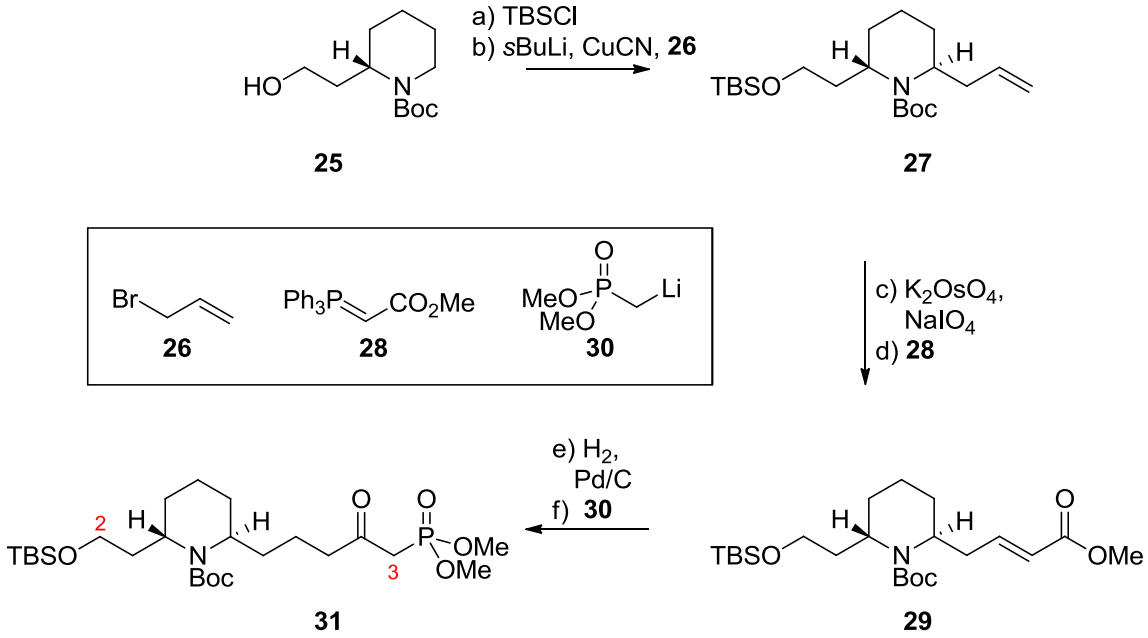


24 **25**

In the forward direction, we were pleased to find that our symmetry-based redesign of nucleophile **22** (prepared through a similar route as key alcohol **11**, unshown) did indeed provide access to the desired C-3/C-5' dimeric linkage on open frameworks utilizing aldol chemistry (**23**, Scheme 5A). Unfortunately, yields of dimer **23** were highly variable utilizing both lithium enolates and Paterson aldol[3] strategies. In optimizing this approach, we found that a Horner–Wadsworth–Emmons (HWE) coupling strategy as an

aldol surrogate was higher yielding and operationally easier than a true aldol-based approach, leading us to develop a facile synthesis of phosphonate **31** (Scheme 6).[4]

Scheme 6. Synthesis of Protected Phosphonate Monomer

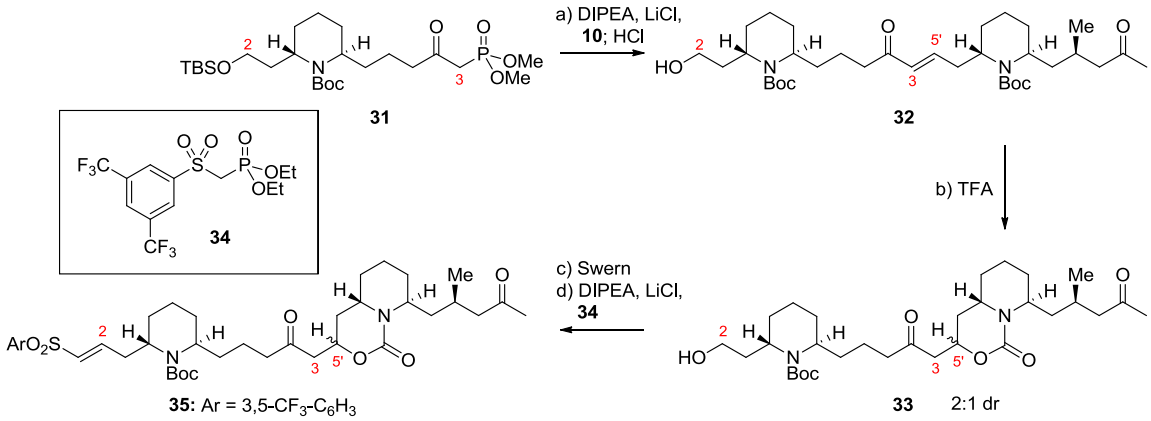


Reagents and conditions: (a) TBSCl, imidazole (b) *s*BuLi, TMEDA, CuCN·2LiCl, **26**, 91% over 2 steps (c) $K_2OsO_4 \cdot 2H_2O$, $NaIO_4$, 2,6-lutidine, 1,4-dioxane/H_2O 3/1 (d) **28**, 84% over 2 steps (e) H_2, 10% Pd/C, 97% (f) dimethyl methylphosphonate, *n*BuLi, 87%

Pleasingly, phosphonate **31** was accessed in 65% overall yield and six steps from commercial *(S)*-1-*N*-Boc-(–)-piperidine-2-ethanol (**25**), the same starting material used for key alcohol **11**. Quantitative silyl protection of the alcohol followed by deprotonation with *s*-BuLi at –45 °C and copper-mediated allylation at –78 °C gave **27** in 91% yield.[5] Carrying this material forward, Lemieux-Johnson oxidative cleavage[6] and Wittig olefination with stabilized ylide **28** at 25 °C gave ester **29** in two steps and 84% yield. The resultant methyl enoate was easily converted into the desired phosphonate fragment **31** through standard hydrogenation in 97% yield and exposure at cold temperature to

lithiate **30** in 87% yield.[7] This route is efficient and highly scalable with over 10 grams of **31** having been prepared in a single batch.

Scheme 7. Synthesis of Precursor for Core-Forming Cascades

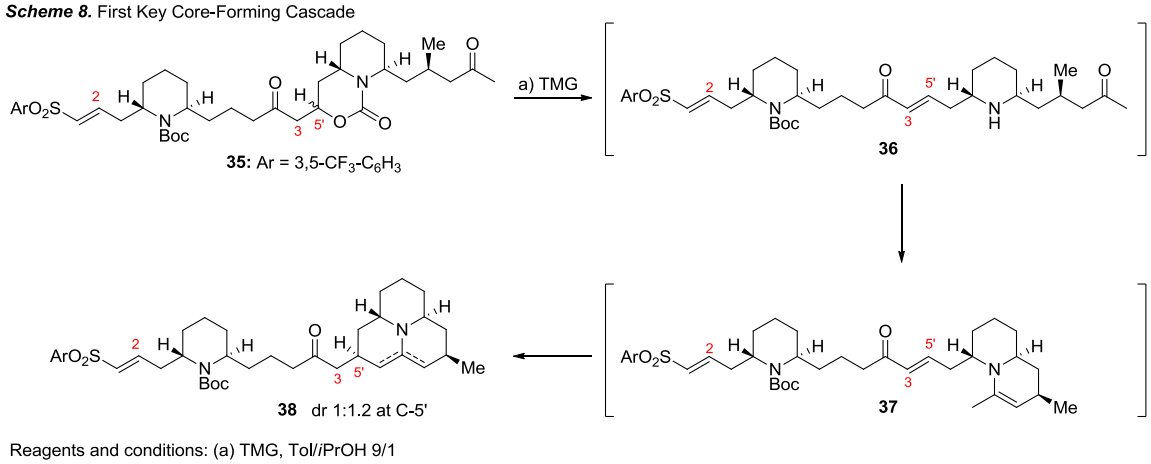


Reagents and conditions: (a) DIPEA, LiCl, **10**; aq. HCl, MeOH, 79% (b) TFA, 89% (c) $(COCl)_2$, DMSO, Et_3N (d) DIPEA, LiCl, **34**, 67% over 2 steps

Combining **31** and **10** to join C-3 and C-5' through HWE olefination utilizing Masamune-Roush conditions at 25 °C followed by HCl quench at 0 °C gave enone **32** with a free alcohol at C-2 in 79% yield (Scheme 7). At this stage, it became necessary to differentiate between the two similarly protected nitrogen atoms to allow for sequential deprotection and cascade control. Taking advantage of the nucleophilic character of the *t*-butyl carbamate, enone **32** was treated with excess TFA at –78 °C to initiate Michael addition into the C-5' position, furnishing cyclic carbamate **33** in 89% yield as an inconsequential 2:1 mixture of diastereomers. This new cyclic carbamate was acid stable but base labile, delivering the desired nitrogen differentiation. Swern oxidation of **33** provided the desired aldehyde, and olefination of this crude substrate using **34** previously reported by Alexakis and co-workers[8] gave aryl vinyl sulfone **35** in 67% yield primed to undergo a series of cyclization events to form the dimeric azaphenalene core.

4.3.2 First Core-Forming Cascade Sequence

Scheme 8. First Key Core-Forming Cascade



Reagents and conditions: (a) TMG, Tol/*i*PrOH 9/1

In the first cascade (Scheme 5), carbamate **35** was treated with TMG in a mixture of toluene and *i*-PrOH (9/1) at 25 °C to deprotonate at C-3, decarboxylate the cyclic carbamate, and reform the *trans*-enone exclusively between C-3 and C-5' in structure **36**, which was not isolated. Immediate enamine condensation formed one ring to give **37**, also a reactive intermediate in which the enamine functionality gradually closed a second ring through Michael addition at C-5' to deliver **38** over the course 6 h. Ultimately, this one pot process encompassed a deprotection and two cyclizations. Substrate **38** was not purified and needed to be carried forward immediately after preparation in order to prevent decomposition; the reactivity of the vinyl sulfone and basicity of the enamine made this material especially difficult to handle.

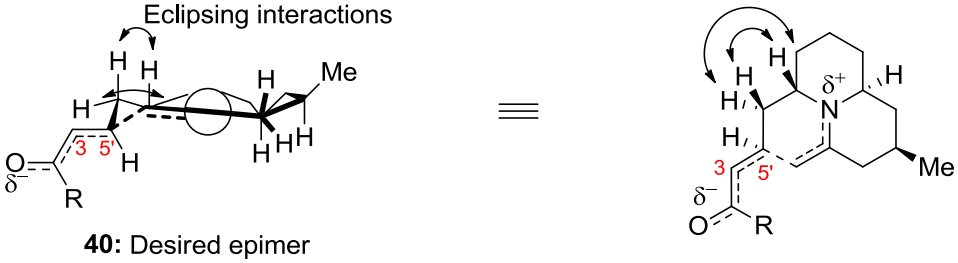
It must be noted that **38** is formed as a mixture of interconverting enamine isomers and as a 1:1.2 (pseudoaxial:pseudoequatorial) mixture of diastereomers at C-5' (pseudoaxial epimer desired, shown). In our biomimetic dimerization (Scheme 1B), an epimeric mixture at C-5' was not observed; presumably, this was the result of pseudoaxial attack at C-5'. It is unsurprising that a mixture of C-5' epimers resulted from

our new synthetic approach due to the different type of bond formation employed. The 6-(enol *endo*)-*exo*-trig closure[9] that set the C-5' stereocenter shown here likely went through a chair-like transition state with a pseudoequatorial C-5' substituent (**39**, Figure 2A). The transition state for the desired C-5' epimer would have required a boat-like transition state as depicted in **40** (Figure 2B) with two unfavorable eclipsing interactions highlighted that likely destabilized the transition state for the desired epimer.

Figure 2. Transition State Model Justifying Epimeric Mixture
A. Pseudochair-like transition state for undesired epimer

39: Undesired epimer

B. Pseudoboat-like transition state for desired epimer



40: Desired epimer

Many attempts were made to shift this result in favor of the desired epimer with the best results obtained using the conditions described above. In initial studies of this cascade, diastereomeric ratios between 1:2 and 1:3 disfavoring the desired C-5' epimer were observed. We believe the product distribution is a kinetic outcome, as resubjecting separated epimers to reaction conditions does not reform a mixture of diastereomers.[ii]

[ii] The separated epimers described here had less reactive activating groups than **38** making them more amenable to purification, see Scheme 13 in Section 4.3.5.

These results were disappointing, as we had initially hoped that a reversible reaction would enable us to recycle the undesired epimer.

Table 1. Solvent and Temperature Effect on C-5' Diastereomeric Ratio

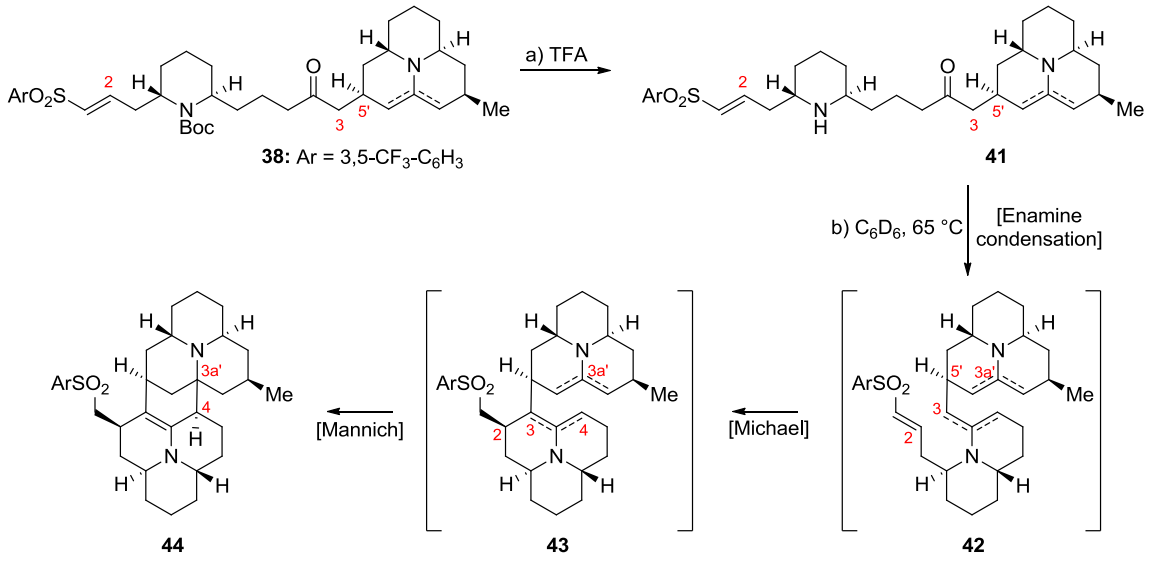
Solvent	T (°C)	C-5' dr (desired to undesired)
*i*PrOH	25	1.00 to 2.18
*i*PrOH	80	1.00 to 1.70
Toluene/*i*PrOH 9/1	**25**	**1.00 to 1.60**
Toluene/*i*PrOH 9/1	**80**	**1.00 to 1.18**
Toluene/*i*PrOH 9/1	**110**	**1.00 to 1.07**
DCE/*i*PrOH 9/1	25	1.00 to 1.98
DCE/*i*PrOH 9/1	80	1.00 to 1.47
THF/*i*PrOH 9/1	25	1.00 to 1.61
THF/*i*PrOH 9/1	80	1.00 to 1.24
DMF/*i*PrOH 9/1	25	1.00 to 1.93
DMF/*i*PrOH 9/1	80	1.00 to 1.61
Pyridine/*i*PrOH 9/1	25	1.00 to 1.81
Pyridine/*i*PrOH 9/1	80	1.00 to 1.48
TFE/*i*PrOH 9/1	25	1.00 to 1.94

With this knowledge, we attempted to affect the kinetic distribution by changing solvent and temperature (selected results in Table 1, all performed in preliminary studies with the C-2 vinyl EWG = CO_2Me). Pure *i*-PrOH was initially used because it was determined that protic solvents facilitated enamine condensation and Michael addition, but unfavorable diastereomeric ratios were observed in this medium (1:2.18 at 25 °C). Through a solvent screen, it was found that toluene and *i*-PrOH in a 9/1 mixture gave the best dr at 25 °C (1:1.6 on the substrate screened). Heating the optimal 9/1 toluene and *i*-PrOH mixture at 80 °C brought the diastereomeric ratio down from 1:1.6 to 1:1.18, and

further refluxing at 110 °C in a sealed reaction vessel gave a 1:1.07 dr. Unfortunately, the overall yield of this process began to decrease dramatically as heat was applied to the system. Therefore, 25 °C in 9/1 toluene to isopropanol were selected as the optimal temperature and solvent conditions, and it was pleasingly found that when our best results from initial studies were applied to substrate **35**, we could obtain a C-5' dr of 1:1.2. TMG was found to be the best choice to initiate decarboxylation of cyclic carbamate **35** because it did not perturb the electron-deficient functionalities present in the reaction mixture and was easily removed with a slightly basic workup at the completion of the cascade sequence. Metal alkoxides caused decomposition and by-product formation, and these bases were quickly abandoned. DBU could accomplish the desired decarboxylation but was difficult to remove from sensitive substrates after the cascade was completed. Fortunately, after expending considerable effort optimizing this reaction, the procedure described above was capable of delivering significant quantities of **38** to carry forward.

4.3.3 Second Core-Forming Cascade Sequence

Scheme 9. Second Key Core-Forming Cascade



Reagents and conditions: (a) TFA/CH_2Cl_2 1/1 (b) C_6D_6, 65 °C, 15% over 3 steps.

Pressing forward with our second cascade, substrate **38** was treated with TFA at 0 °C to remove the remaining carbamate protecting group and unveil free amine **41**. This crude amine was heated in C_6D_6 at 65 °C for 3 h to undergo the second cascade, a process which proceeded through three discreet events: enamine condensation to form one ring (**42**), Michael addition to form the second ring and set the C-2 stereocenter (**43**), and Mannich reaction between the C-4 enamine and C-3a' iminium to close the final ring, forming the [3.3.1] bicycle, the C-3a' quaternary stereocenter, and the C-4 stereocenter (**44**). In total, three rings and three stereocenters are formed in this reaction in an overall yield of 15% from cascade precursor **35**. Across the three steps from precursor **35** to heptacycle **44**, seven distinct chemical operations have occurred: two deprotections and five discreet cyclizations, resulting in an efficiency of 79% per transformation. It should be noted that although heating was found to decrease yield in the first cascade process,

this second cascade would only proceed at elevated temperature. The derivatized aryl sulfone employed here was selected after several generations of development, described in more detail in Section 4.3.4. Furthermore of the eight possible isomers that could have resulted from the second cascade process, the only observed product is the isomer that contained the psylloborine A core, and a discussion justifying this outcome is warranted.

First of all, since the Mannich attack from C-4 onto C-3a' formed the lone quaternary stereocenter as part of a [3.3.1] bridged bicycle, it must come from the same side of the electrophile as C-3, allowing only the desired stereochemical outcome for this center. Secondly, the mechanism by which the C-2 stereocenter was established (a 6-(enol *endo*)-*exo*-trig closure)[9] is similar to the process that established the C-5' stereocenter as a mixture of epimers (Section 4.3.2, Scheme 8 and Figure 2). However, this process set the C-2 stereocenter as only one epimer. We postulate that the C-2 center is established stereoselectively because the steric bulk of the tricycle attached to C-3 significantly destabilizes the boat-like transition state necessary to give the undesired C-2 epimer. This steric bulk was not present in the transition state for Michael addition into C-5', allowing both transition states to be accessed to give the diastereomeric ratio observed in that reaction.

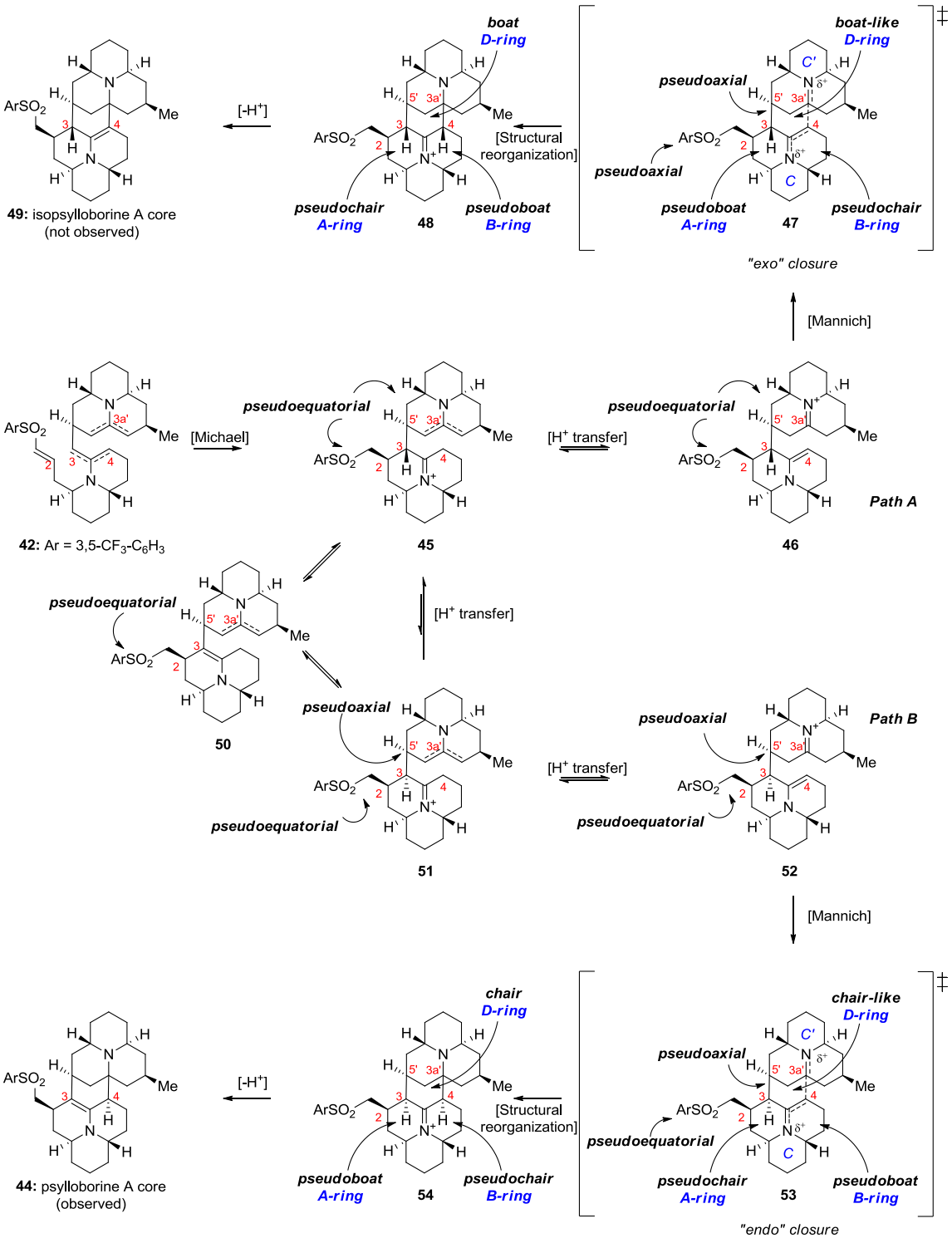
Finally, the C-4 stereochemistry and C-3 enamine isomer can be justified on the basis of the proposed pathways shown in Scheme 10, developed through the use of 3D model kits and qualitative conformational analysis. Starting with the Michael reaction between C-2 and C-3, iminium **45** should be formed with both the C-2 and C-3 substituents pseudoequatorial. This iminium could undergo proton transfer (via **50**) to iminium **51** in which C-3 has been epimerized, placing the substituent at C-3

pseudoaxial; this equilibrium likely favors the iminium **45** with both groups pseudoequatorial. Both of these iminiums (**45** or **51**) could undergo proton transfer to Mannich precursors **46** or **52**, respectively, and these two new iminiums are primed to undergo Mannich reaction to form **49** or **44**, respectively. We hypothesize that it is the choice of epimeric iminium starting material (**46** or **52**) that determines which core is ultimately formed in the reaction.

On the basis of the arguments made so far, **46** and **52** should be able to equilibrate through proton transfers and epimerization at C-3. Examining Path A, **46** could undergo Mannich reaction via transition state **47**. We have termed this the *exo* transition state because the C-ring and C'-ring are turned away from one another in this reaction, a product of the stereochemistry of C-3. In **47**, both substituents at C-2 and C-3 must be pseudoaxially disposed for proper orbital alignment of the C-4 enamine and C-3a' iminium. This destabilizing factor is further exacerbated by the fact that the A-ring must adopt a pseudoboat conformation for these groups to be pseudoaxial as the fixed nature of the tricyclic ring fusions prevents the entire A-ring from undergoing a pseudochair-pseudochair flip. Furthermore, the incipient D-ring in **47** must reside in a boat-like transition state, further destabilizing this intermediate. The result of this reaction would be the *exo* Mannich product **48** with protons at C-3 and C-4 *syn* on the *endo* face of the [3.3.1] bicycle. After structural reorganization, the A-ring in **48** would likely be a pseudochair, and the B-ring would likely be a pseudoboat. Finally, preferential deprotonation of C-4 to relieve the pseudoboat torsional strain of the B-ring could deliver the isopsylloborine A core **49**. This product was not observed, or at the very least not

isolated, in our second cascade, leading us to the conclusion that Path B, examined below, must be the operative Mannich pathway.

Scheme 10. Explanation for Second Cascade Delivering only Psylloborine A Core



If iminium **52** were to go through Mannich Path B, the psylloborine A core **44** would be the observed result, and **44** is indeed the only identifiable product of this reaction. Again, C-3 epimeric iminiums **46** and **52** should be in equilibrium via proton transfer-mediated epimerization. If iminium **52** were to undergo Mannich reaction, transition state **53** would likely be accessed to achieve the heptacyclic product **44**. This transition state **53**, termed the *endo* transition state due to the stacked nature of the C-ring and C'-ring, would have a chair-like D-ring, a pseudochair A-ring, and a pseudoboat B-ring. The C-2 substituent would be pseudoequatorial, and the A-ring would not need to change conformation into a pseudoboat in order to properly align the reactive partners as the C-3 substituent would already be pseudoaxial in this epimer. Finally, after Mannich attack and conformational readjustment, product iminium **54** would likely have a pseudoboat A-ring and pseudochair B-ring with the protons at C-3 and C-4 *syn* on the *exo* face of the newly formed bridged bicycle. Deprotonation of C-3 from the A-ring could relieve pseudoboat torsional strain and deliver **44**, the only observed product for this cascade reaction.

In examining why Path B could be favored exclusively over Path A, the destabilizing factors for each pathway must be considered, and the possibility of any stabilizing factors must also be examined. While Path B starting material **52** is likely less stable than its C-3 epimer **46**, the pseudoaxial C-3 substituent in **52** is already properly oriented for Mannich reaction once epimerized. In **46**, both the C-2 and C-3 substituents likely need to adopt pseudoaxial orientations in order to undergo Mannich reaction, forcing their A-ring into a pseudoboat (**47**). Iminium **52** does not require such unfavorable conformational readjustment for the A-ring and C-2 substituent to initiate

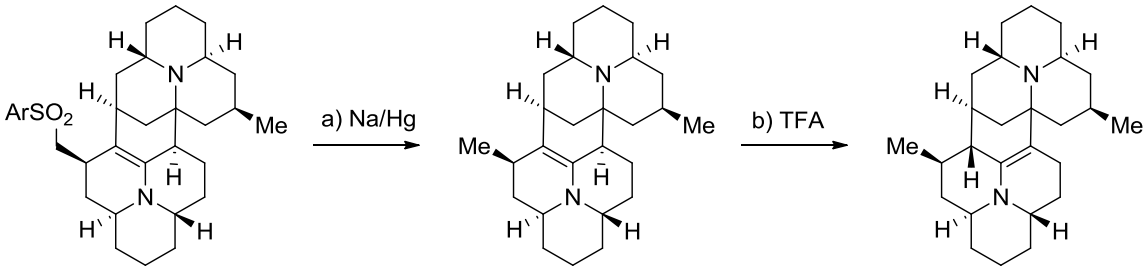
Mannich reaction. Furthermore, the *exo* transition state D-ring in **47** is boat-like, while the *endo* transition state D-ring is chair-like (**53**). Finally, stabilizing factors could also be at play; it is conceivable that the *endo* transition state has stabilizing secondary orbital overlap between the iminium and enamine nitrogen atoms. Indeed, simple orbital analysis reveals that the phase of the relevant π-orbitals would allow constructive overlap and molecular models indicate that these atoms would be in close proximity in the *endo* pathway. It is possible that this interaction contributes to the observed outcome of this cascade process.

In summary, if we consider all of the factors that could stabilize or destabilize transition states **47** and **53**, it seems likely that transition state **47** would be less favored. Indeed, **47** is the transition state that would likely lead to the isopsylloborine A core **49**, an outcome not observed for this cascade reaction. While the iminium (**46**) required to access *exo* transition state **47** is likely more stable than the one (**52**) required for *endo* transition state **53**, it seems likely that epimerization between **46** and **52** is easier than attaining the transition state (**47**) for Path A. Finally, it is possible that transition state **53** leading to psylloborine A core **44** is stabilized by secondary orbital interactions between the π-orbitals on both nitrogen atoms. As no quantum chemical calculations have been performed, it is difficult to assign with any degree of certainty the relative energies of the intermediates shown in Scheme 10. However, the discussion above offers one possible explanation for why **44** is the only observed product of this cascade sequence.

4.3.4 Endgame for the Total Syntheses of Psylloborine A and Isopsylloborine A

Finally, with desired heptacycle **44** in hand, we required only desulfonylation to complete (–)-psylloborine A ((–)-**1**). This transformation was realized via treatment of **44** with sodium amalgam[10] in *i*-PrOH at 25 °C to deliver (–)-**1** in 46% yield with 16 steps in the longest linear sequence. This represents the first total synthesis of not only this dimer, but of any azaphenalene-containing dimeric alkaloid in the coccinellid class of natural products.

Scheme 11. Synthesis of Psylloborine A and Isopsylloborine A



44: Ar = 3,5-CF_3-C_6H_3 **1**: psylloborine A **2**: isopsylloborine A

Reagents and conditions: (a) 5% Na/Hg amalgam, 46% (b) TFA, 75 °C, 75%

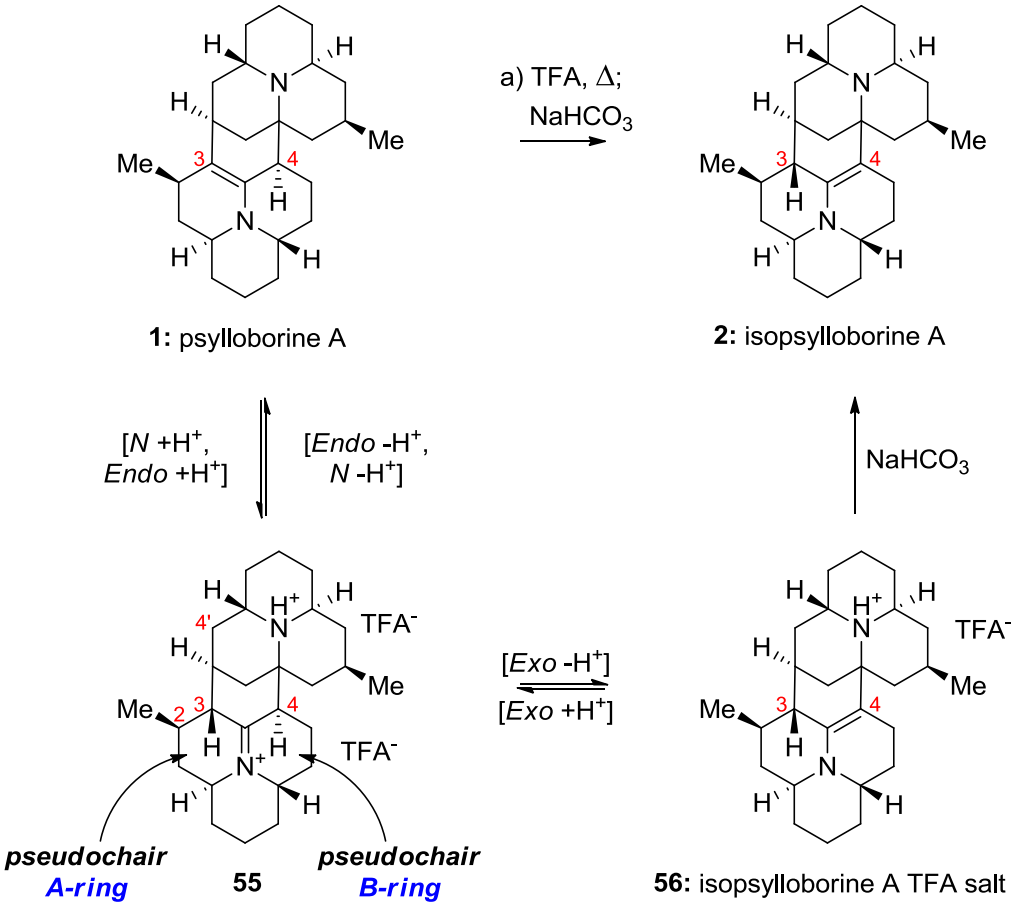
Carrying this material forward, we sought to isomerize **1** to **2**. Treating **1** with excess TFA in DCE at 75 °C for 30 min followed by a cold, mildly basic workup pleasingly transformed this dimeric material into (–)-isopsylloborine A ((–)-**2**) in 75% yield based on crude ^{1}H NMR analysis and 17 steps from commercial materials. This molecule was unstable in our hands and not amenable to several methods of purification, prompting us to characterize it as a crude material. Characterization of this compound was particularly difficult as NMR spectra of natural **2** were collected on what appears to be a partial salt form. Daloze *et al* reported broad peaks in the NMR of **2** in CD_2Cl_2, an observation we made for our dimeric material as well, and the isolation team remedied

this problem by adding TFA of unspecified stoichiometry with **2** to their NMR sample. We were able to slowly add excess TFA to our own NMR sample of **2** and obtain chemical shift values for ^{1}H and ^{13}C NMR that closely match the tabulated values for the natural isolate. Efforts to obtain original copies of spectra have been unsuccessful, so a visual comparison of the natural data and our own spectra has not been possible. Additionally, we have observed that the chemical shift values of the ^{1}H NMR for **2** with added TFA in CD_2Cl_2 are incredibly sensitive to concentration, impurities, acid content, and water content, further complicating our ability to obtain an exact match for tabulated spectral values. To verify that we did indeed synthesize **2**, we performed extensive 2D NMR analysis on the mono-TFA salt of **2** (**56**, Scheme 12) obtained by concentrating the isomerization reaction used to form isopsylloborine A. Key HMBC and nOe correlations allowed us to fully assign the structure of this dimer as **2** (See Section 4.7 for more information). Finally, the specific rotation value reported by Daloze *et al* ($[\alpha]_D = +17°$) is not in agreement with our own value for neutral **2** ($[\alpha]_D^{20} = –119.4°$) in both sign and magnitude, prompting us to obtain a specific rotation of the salt form **56**, as well, since the isolation team characterized a TFA salt form in their NMR analysis. The specific rotation value for **56** ($[\alpha]_D^{20} = +19.4°$) is in much closer agreement with that reported by the isolation team in both sign and magnitude, which may indicate that the optical rotation of the TFA salt (**56**) of natural **2** is the actual value reported in the original communication on the isolation of isopsylloborine A.

We believe the outcome of this isomerization reaction can be explained by iminium stability and protonation kinetics, and our explanation is shown in Scheme 12. We postulate that under the conditions used to make **2** (two equivalents of TFA in DCE

at 75 °C for 30 min), the tertiary amine is protonated first and does not affect subsequent equilibria. In attempts to isomerize **1** to **2** with substoichiometric amounts of TFA at elevated temperature, **1** was always recovered unchanged, suggesting that the tertiary amine protonated first (structure unshown) before the enamine at C-3, neutralizing the TFA and preventing further reaction. We postulate that the desired pathway occurs through thermodynamic protonation of the concave face of this ammonium salt (with respect to the central [3.3.1] bicycle) at C-3 to form iminium **55**, a bis-TFA salt with C-3 and C-4 protons *anti*. Convex deprotonation would deliver isopsylloborine A (**2**), as observed. We hypothesize that the activation barrier to access the concave protonation pathway is high enough that elevated temperature is required as conversion of **1** to **2** was complete only in experiments in which **1** was heated in the presence of excess TFA. In room temperature protonation experiments of **1** in CD_2Cl_2 with excess TFA, the resultant salt was converted almost exclusively back to psylloborine A (**1**) upon basic workup, though trace amounts of isopsylloborine A (**2**) were observed, suggesting that trace amounts of iminium **55** could be accessed under these conditions.

Scheme 12. Explanation for Isomerization of Psylloborine A to Isopsylloborine A



It is our belief that high temperature is required to protonate C-3 from the *endo* face (with respect to the central [3.3.1] bicycle) as the steric approach of acid at this position appears quite congested when molecular models are examined. Protonation from the *exo* face at C-3 (unshown) would give an iminium in which the A-ring is a pseudoboat (C-3 epimer of **55**, unshown) and introduces a *syn*-pentane interaction between the C-2 methyl and C-4' (labeled in **55**). Upon heating, enough energy is in the system to get over the barrier for sterically congested C-3 *endo* protonation to give iminium **55** in which both the A-ring and B-ring likely exist as pseudochairs. Finally, kinetic C-4 deprotonation from the *exo* face could give **56**, and a sodium bicarbonate

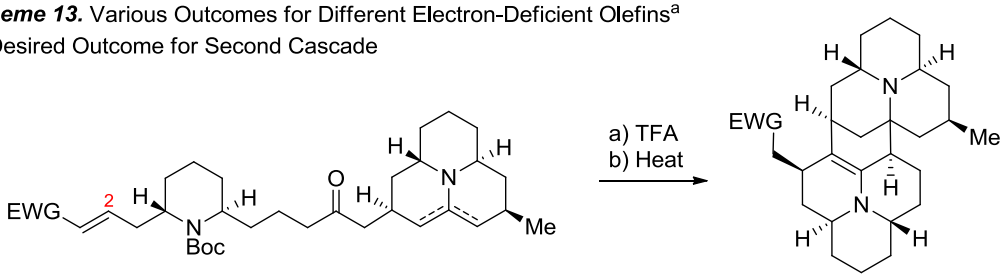
workup at room temperature could account for observed product **2**. Isolation of **56** was performed by concentration of the reaction mixture under reduced pressure to remove solvent and excess TFA, providing the stable mono-TFA salt for 2D NMR analysis.

Section 4.3.5 Development of C-2 Activating Group for the Second Cascade

The second cascade sequence described in 4.3.4 (Scheme 9 and Figure 3) required several generations of development to achieve, particularly with respect to the activating group used in Michael addition. As shown in Scheme 13, various electron-withdrawing groups utilized in the second cascade gave similar structures to **44**, but all except **44** failed to defunctionalize to **1** as desired. In preliminary development of this cascade, removing the *t*-butyl carbamate in enone **57** unveiled the free amine, which delivered heptacyclic ketone **59** when heated in *i*-PrOH (Scheme 13A). Quite pleasingly, extensive NMR analysis, particularly NOESY, enabled us to assign **59** as the structure depicted containing the stereochemical configurations and enamine isomer consistent with the psylloborine A core (See Experimental Section for more detail). Unfortunately, degradation of **59** proved unfruitful. Attempts were made to introduce functionality at either α-carbon of this ketone prior to the cascade step to aid in degradation, but these efforts were also met with failure. It was ultimately decided that other electron-deficient handles with potentially more straightforward paths to degradation were required.

Scheme 13. Various Outcomes for Different Electron-Deficient Olefins[a]

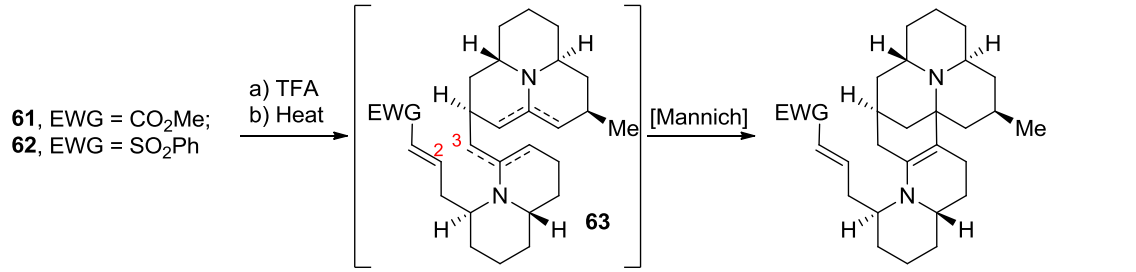
A. Desired Outcome for Second Cascade



57, EWG = C(O)Me;
38, EWG = $SO_2(mCF_3)_2Ph$;
58, EWG = SO_2pNO_2Ph

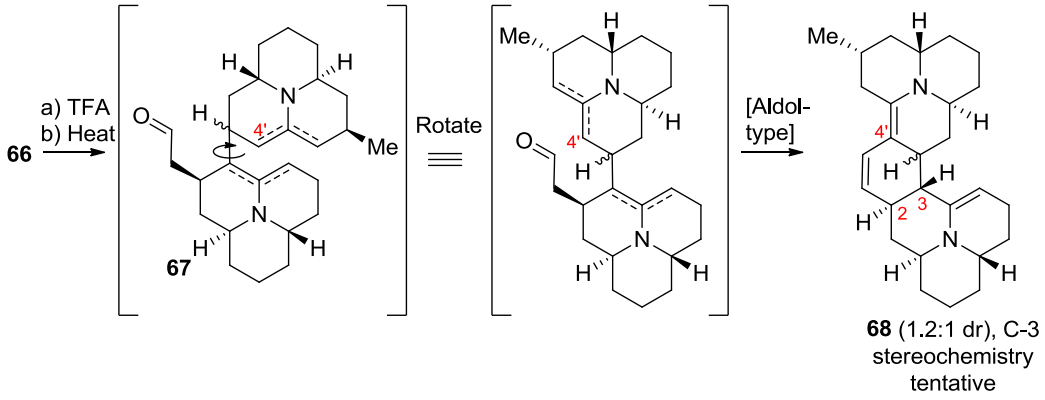
59, EWG = C(O)Me, 10%[b];
44, EWG = $SO_2(mCF_3)_2Ph$, 15%;
60, EWG = SO_2pNO_2Ph, 12%

B. Second Cascade Arrests at Mannich



64, EWG = CO_2Me, 13%;
65, EWG = SO_2Ph, no isolated yield

C. Unique Cascade With **66**, EWG = CHO



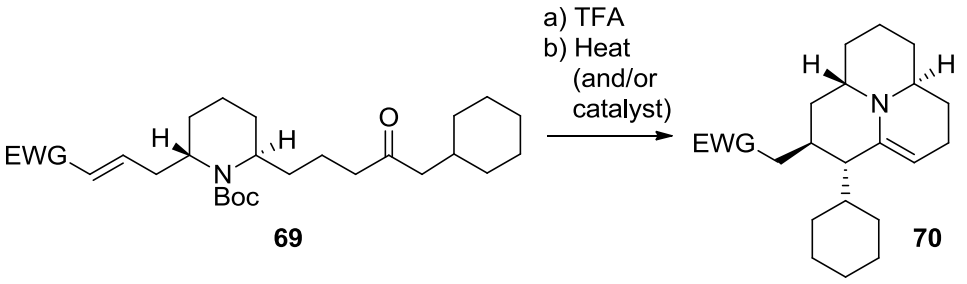
68 (1.2:1 dr), C-3 stereochemistry tentative

[a]All yields are reported overall from cascade precursor like **35**, see Section 4.7 for more information
[b]Procedure for substrate **59** requires TMG treatment after exposure to TFA

Both aldehyde and ester handles were subsequently investigated due to their similarity to a methyl ketone but potentially more direct degradation pathways. To our great surprise, when C-5' epimeric mixture (1:1.2) of enal **66** was used, dienamine hexacycle **68** was obtained as the major product (Scheme 13C). We believe this is the result of a productive enamine condensation and Michael addition to form the two

tethered monomers shown in aldehyde **67**. Sadly, rotation of the monomers into a nonproductive conformation presumably allowed an aldol-type reaction between the enamine at C-4' and the aldehyde carbonyl. Unique heptacycle **68** was isolated as a mixture of epimers and was never exhaustively assigned, but we believe the stereocenter at C-5' is the epimeric center, and the C-3 stereochemical assignment is tentative. With this result in hand, we began exploring a methyl ester activating group.

Scheme 14. Model System Used in Second Cascade Development

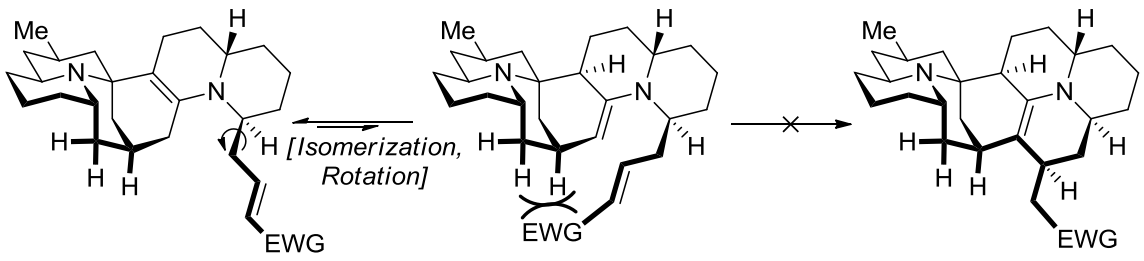


69 **70**

When ester **61** was subjected to cascade conditions, only hexacyclic enoate **64** was formed (Scheme 13B). This material is presumed to be the result of enamine condensation and Mannich attack prior to the required Michael closure. In attempts to convert hexacycle **64** into a heptacyclic product, starting material was either decomposed or recovered unchanged. The methyl enoate is clearly not as electron deficient as the enone handle in **57**, but we believe hexacycle **64** could not form the last bond specifically because Mannich reaction had happened first. In developing this step on a simpler model system (Scheme 14), we discovered that the desired Michael reaction was feasible if a thiourea catalyst was employed to further activate the enoate. When applied to **64**, however, catalytic activation failed to deliver the desired heptacyclic product. Therefore, we believe that enoate **61** is unable to form heptacyclic product because of the difficulty in attaining proper orbital overlap of the reaction partners once the strained, congested

hexacycle **64** has been formed. As depicted in Figure 3, we believe the steric penalty for bringing the reactive partners into proximity is far too high to allow Michael addition to occur once Mannich reaction has happened.

Figure 3. Possible Explanation for Cascade Arresting at Mannich for **64** or **65**



The aryl vinyl sulfone handle was next investigated due to the possibility of tuning the aryl ring to accelerate Michael addition if needed and the ease of removal of sulfones in comparison to carbon-based activating groups. When using a phenyl vinyl sulfone (**62**), we obtained several unstable materials of putative form **65** as the major products (Scheme 13B) with trace amounts of desired heptacycle (unshown) also isolated. Although this desired material was too minor to be of any synthetic use (<5% yield), it did demonstrate that aryl vinyl sulfones could undergo the full cascade reaction. Furthermore, putative hexacyclic materials like **65** resulting presumably from a Mannich reaction prior to Michael addition did not produce the desired heptacycle when resubjected to cascade conditions or urea-based catalysts. Again, successful model system work on phenyl vinyl sulfone derivatives (Scheme 14) demonstrated that the electronic demands of such a reaction could be met. We believe this constitutes a second example in this system wherein Mannich reaction prior to Michael addition precludes subsequent Michael attack. We hypothesized that if trace amounts of desired product were formed along with dead end, hexacyclic materials, then the desired heptacycle was

likely forming through initial Michael addition and subsequent Mannich reaction, a different pathway than the one leading to hexacycles like **65**.

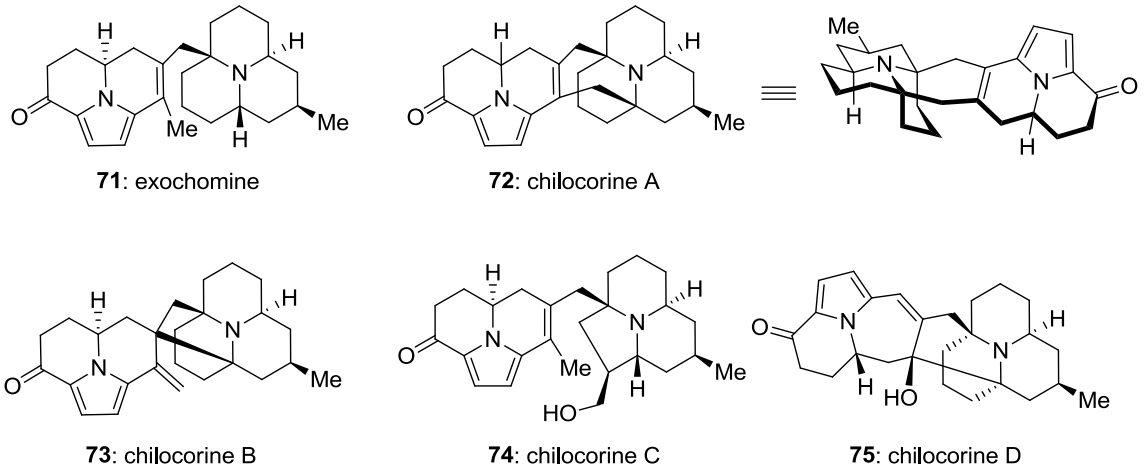
Focusing our efforts on derivatized aryl vinyl sulfones, we next investigated tuning the electronics of the aromatic ring, hoping to speed Michael addition by introducing electron-withdrawing substituents on the arene. We investigated a *para*-nitrophenyl derivative (**58**) as well as a 3,5-bis(trifluoromethyl)phenyl vinyl sulfone (**38**). Pleasingly, both of these derivatives delivered heptacyclic products (**60** and **44**, respectively). Desulfonylation with sodium-mercury amalgam proved difficult on nitro derivative **60** as the nitroarene was quickly reduced to an aniline derivative. Stronger reaction conditions were able to deliver partial desulfonylation of this material, but the harsher conditions necessary to achieve such a result also decomposed significant portions of the reaction mixture. Fortunately, 3,5-bis(trifluoromethyl) derivative **44** could be desulfonylated with sodium-mercury amalgam in 46% yield to deliver (–)-psylloborine A (**(–)-1**) as detailed in Section 4.3.4. This displays the utility of not only our cascade-based key steps, but also of the vinyl aryl sulfone as an easily tuned and removable handle to produce an equivalent of a vinyl group Michael acceptor in the context of complex molecule synthesis.

Section 4.4 Conclusion for Homodimeric Coccinellid Alkaloid Synthesis

In summary, we have achieved the first total synthesis of any natural dimeric coccinellid alkaloids through the total synthesis of (–)-psylloborine A (**1**) in 16 steps and isopsylloborine A (**2**) in 17 steps, utilizing two key enamine-driven cascade processes in

which a sum total of five rings and four stereocenters are generated from an acyclic scaffold. Key discoveries include the ability to establish productive biasing of reaction rates for competitive Michael addition and Mannich reaction in the final cascade through tuning of vinyl electron-withdrawing groups; the use of this intramolecular cascade to form the sole asymmetric, quaternary carbon; and the use of a vinyl aryl sulfone as a reactive surrogate for an unsubstituted vinyl group in a Michael addition. We believe that the outcome of these studies combined with the results discussed at length in Chapter 3 expresses the value of a family-based approach to the oligomeric coccinellid alkaloids with a key intermediate designed for synthetic divergence. We expect key alcohol **11** to be useful for ongoing studies in this class aimed at the heterodimeric coccinellid alkaloids exochomine and chilocorines A – D (**71 – 75**, Figure 4).

Figure 4. Heterodimeric Coccinellid Alkaloids



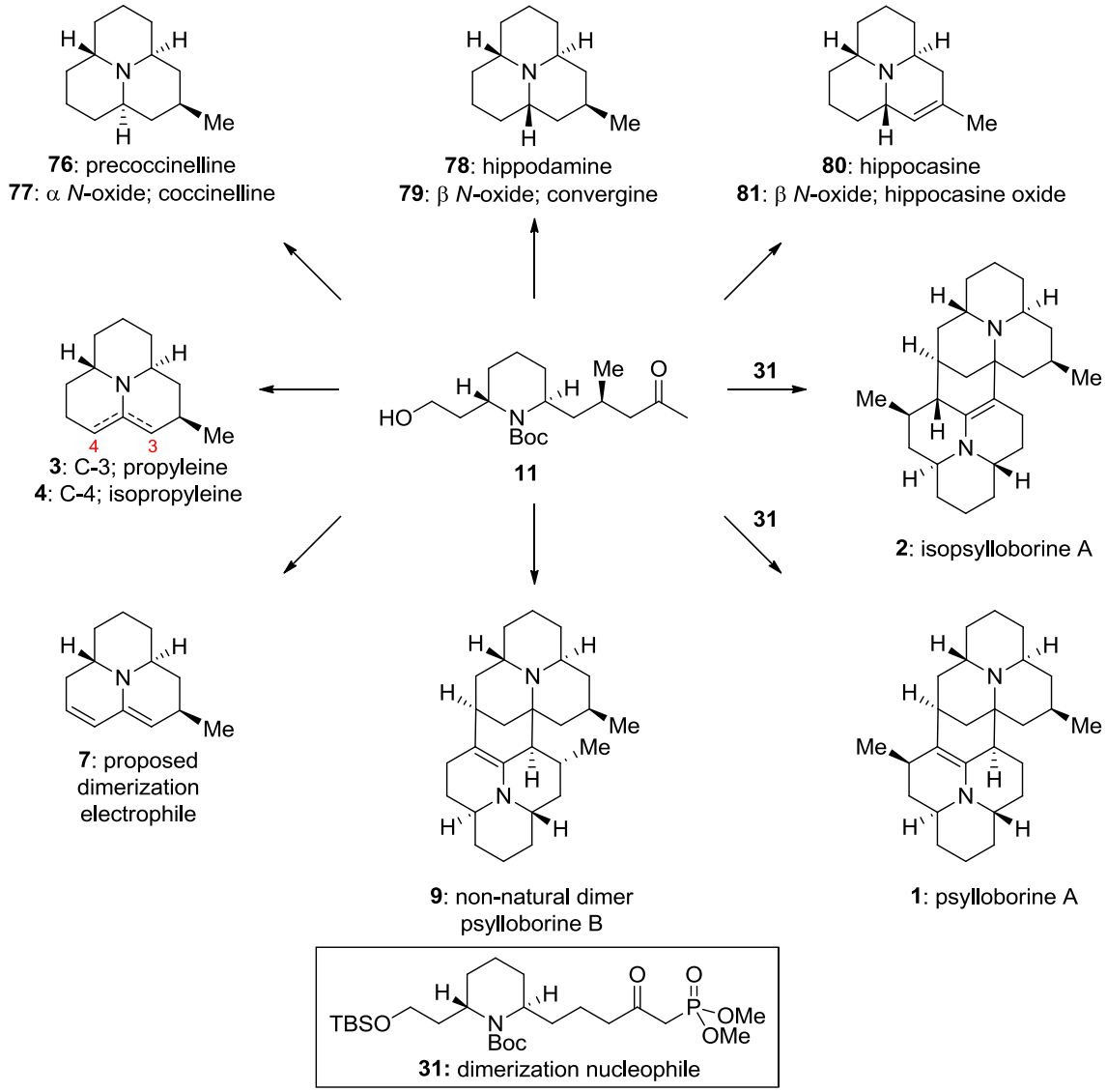
71: exochomine **72**: chilocorine A

73: chilocorine B **74**: chilocorine C **75**: chilocorine D

Section 4.5 Project Conclusion: Strategic Discussion of Oligomeric Alkaloid Synthesis

In Chapters 3 and 4, I have described the development of a unified, family-based program to access the oligomeric, azaphenalene-containing coccinellid defensive alkaloids (Summarized in Scheme 15), progressing this area of alkaloid research beyond the state-of-the-art discussed in Chapter 2. Through the chemo- and stereoselective modification of key alcohol **11**, its derivatives, and downstream synthetic products, we were able to enantioselectively access in a total or formal sense all monomeric members of this class containing a *trans* substituted C-ring (Chapter 3). Furthermore, we developed a mechanistic rationale for the formation of **1** and **2** in nature, and developed a synthesis of dienamine **7** to attempt to replicate such a union in the flask. To our disappointment, propyleine (**3**) and protonated **7** failed to deliver the desired homodimers **1** and **2**, instead forming non-natural dimer **9**, which we named psylloborine B, through initial nucleophilic attack from isopropyleine (**4**) (Section 4.1, Scheme 1B). This result is suggestive of enzymatic assistance in a dimerization event in Nature or the use of different starting materials by the ladybug.

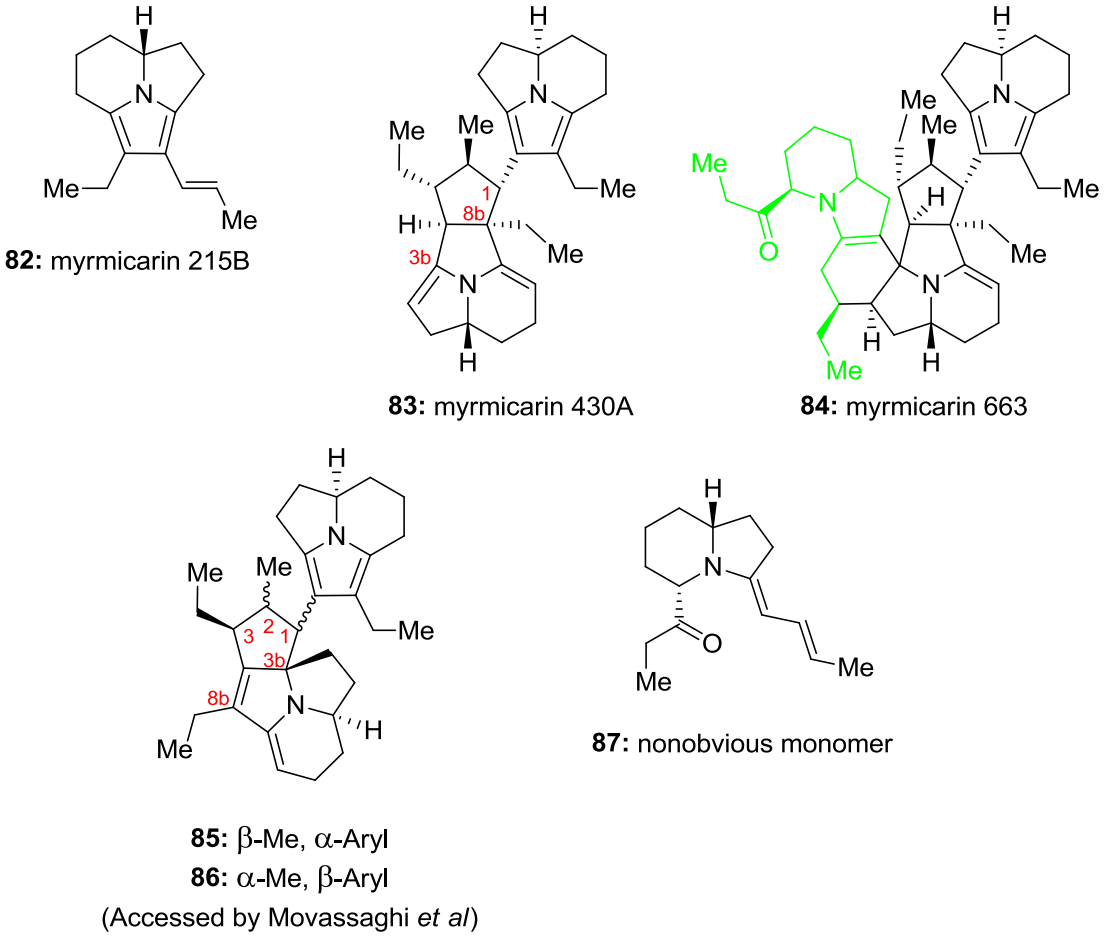
Scheme 15. Total Synthesis of Oligomeric Azaphenalene Alkaloids from a Common Intermediate



To circumvent this regiochemical issue, we developed phosphonate **31** as a non-obvious, but expected, nucleophile for dimerization with an oxidized variant of our key alcohol **11**. Pleasingly, this delivered a material that we could quickly collapse into the proper heptacyclic, homodimeric core through two key enamine-driven cascade sequences. Straightforward desulfonylation then delivered **1**, and isomerization of this homodimer provided **2**, completing the first syntheses of both natural azaphenalene homodimers and the first syntheses of any of the dimeric coccinellid alkaloids.

The lessons learned in these studies continue to add to the wealth of knowledge concerning oligomeric natural product synthesis, a research area of primary focus for our group. It has been demonstrated in numerous projects within our lab that the synthesis of oligomeric natural products from the obvious monomeric precursor is often incredibly difficult. In many cases, a different, non-obvious precursor has been developed to access higher order structures of the class of interest. While our group has applied this strategy to the helicterins[11] and resveratrol-based oligomers[12], the application of this approach to the oligomeric myrmicarin alkaloids[13] is the most related to our syntheses of the oligomeric azaphenalene alkaloids and merits some examination here. In my colleagues Dr. Adel ElSohly and Dr. Ferenc Kontes' studies, described in more detail below, a non-obvious, monomeric precursor containing only two of the three rings found in monomeric myrmicarins was employed to forge dimeric assemblies. This is quite similar to the strategy we employed in synthesizing **1** and **2**, as our precursors key alcohol **11** and phosphonate **31** each contain only one ring of the azaphenalene architecture. The successes realized by our efforts described in Chapters 3 and 4 and those reported by Dr. ElSohly and Dr. Kontes demonstrate that the use of only partially cyclized monomeric precurors in dimerization events directed at oligomeric, polycyclic alkaloid skeletons can be applied to multiple families.

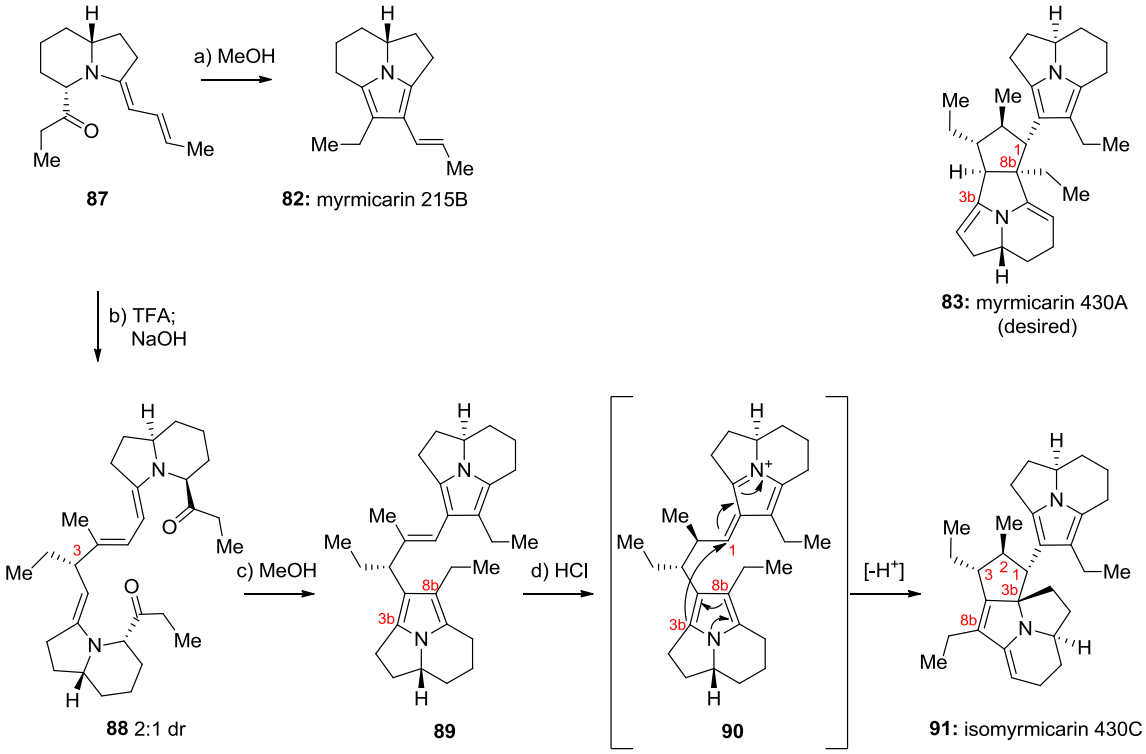
Figure 5. Oligomeric Myrmicarin Alkaloids, Non-Natural Dimer Synthesized by Movassaghi and Co-workers using Myrmicarin 215A, and Our Group's Nonobvious Monomer



More specifically, in Dr. ElSohly and Dr. Kontes' synthetic studies on the myrmicarin alkaloids targeting myrmicarin 430A (**83**) and myrmicarin 663 (**64**), indolizidine **87** was proposed as a non-obvious, potentially biosynthetic precursor to this family due to its presence in myrmicarin 663 (highlighted). Retrosynthetically disconnecting this indolizidine from **84**, it became possible to envision this trimer arising from the union of **83** and **87**. Furthermore, Movassaghi and co-workers had observed that direct dimerization of monomer myrmicarin 215B (**82**) did not produce myrmicarin 430A, instead forming non-natural dimers **85** and **86**.[14] Therefore, a rapid and expeditious

synthesis to non-obvious precursor **87** and related intermediates was developed to explore a programmable synthesis of myrmicarin oligomers (Scheme 16).

Scheme 16. Approach Developed in Our Group Towards the Oligomeric Myrmicarin Alkaloids Utilizing a Nonobvious Precursor



It was found that exposing **87** to MeOH induced Knorr pyrrole condensation to myrmicarin 215B (**82**, representative, other monomeric myrmicarin alkaloids were also synthesized from related intermediates). Turning attention towards myrmicarin 430A, attempts were made to dimerize **87** and related structures under a variety of conditions. Unfortunately, the only observed dimer was non-natural structure **91**, named isomyrmicarin 430C, the result of the wrong regiochemistry for the final ring closure (**89** to **91**, Scheme 16), forming a C-1/C-3b bond instead of the desired C-1/C-8b linkage. This undesired outcome was a result of the pyrrole in **90** possessing nucleophilicity at both C-3b and C-8b. Quantum chemical calculations performed by Dr. ElSohly indicated that isomyrmicarin 430C is the thermodynamic product for such a bond formation, and

the activation barriers for both products are very similar, indicating that neither is kinetically favored over the other. Combining the observed synthetic outcomes with the data from theoretical calculations implicates enzymatic assistance in the biosynthesis of myrmicarin 430A.

Although it was unfortunate that our group could not synthetically prepare myrmicarin 430A, the C-1 to C-3 stereotriad (indicated in **90**) established during the dimerization sequence had never before been synthesized in the natural configuration. Therefore, through the use of a non-obvious monomer for a dimerization event, the first synthesis of a myrmicarin oligomer with this stereotriad in the natural configuration was achieved, a feat in and of itself. This was achieved by taking a step back synthetically from the obvious monomer, myrmicarin 215B and unraveling one of the contained rings. By envisioning nonobvious precursor **87**, Dr. ElSohly and Dr. Kontes were able to develop a synthetically divergent intermediate that could access monomeric or dimeric species.

In the studies detailed in Chapter 3, we also experienced problems with nucleophilic regiochemistry due to an obvious dimeric precursor with multiple reactive sites, propyleine (**3**) and isopropyleine (**4**). In order to circumvent this issue, we took a synthetic step backwards, unraveled the full azaphenalene ring system, and developed a different nucleophilic precursor with only one potential site of attack (phosphonate **31**). Fortunately, we were able to utilize key alcohol **11** in a similar way to that originally envisioned with this new nucleophile and finally achieve nucleophilic regiocontrol when synthesizing the first dimeric linkage. Once we had properly tethered our monomers through a new type of dimerization, the heptacyclic structures of **1** and **2** were easily

achieved in short order, proving that key alcohol **11** is capable of delivering both monomeric and dimeric architectures of the azaphenalene class. These results allowed us to achieve our goal of employing our key alcohol **11** in a family-based, divergent synthesis of the oligomeric coccinellid alkaloids. It is our belief that **11** can also be used to access the heterodimeric coccinellid alkaloids, and studies to put this into practice are ongoing.

Acknowledgements

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Section 4.6 References

1. F. C. Schröder, T. Tolasch, *Tetrahedron* **1998**, *54*, 12243 – 12248.

2. B. Lebrun, J.-C. Braekman, D. Daloze, P. Kalushkov, J. M. Pasteels, *Tet. Lett.* **1999**, *40*, 8115 – 8116.

3. D. Menche, J. Hassfeld, J. Li, S. Rudolph, *J. Am. Chem. Soc.* **2007**, *129*, 6100 – 6101.

4. (a) M. W. Rathke, M. Nowak, *J. Org. Chem.* **1985**, *50*, 2624 – 2626. (b) R. T. Larson, M. D. Clift, R. J. Thomson, *Angew. Chem. Int. Ed.* **2010**, *51*, 2481 – 2484.

5. D. Stead, G. Carbone, P. O'Brien, K. R. Campos, I. Coldham, A. Sanderson, *J. Am. Chem. Soc.* **2010**, *132*, 7260 -7261.

6. W. Yu, Y. Mei, Y. Kang, Z. Hua, Z. Jin, *Org. Lett.* **2004**, *6*, 3217 – 3219.

7. W. R. Roush, M. Murphy, *J. Org. Chem.* **1992**, *57*, 6622 – 6629.

8. C. Bournaud, E. Marchal, A. Quintard, S. Sulzer-Mossé, A. Alexakis, *Tetrahedron: Asymmetry* **2010**, *21*, 1666 - 1673

9. (a) J. E. Baldwin, L. I. Kruse, *J. C. S. Chem. Comm.* **1977**, 233 – 235. (b) J. E. Baldwin, M. J. Lusch, *Tetrahedron* **1982**, *38*, 2939 – 2947.

10. D. A. Alonso, C. Najera, *Organic Reactions*, **2008**, *72*, 367 – 656.

11. S. A. Snyder, F. Kontes, *J. Am. Chem. Soc.* **2009**, *131*, 1745 – 1752.

12. (a) S. A. Snyder, A. L. Zografos, Y. Lin, *Angew. Chem. Int. Ed.* **2007**, *46*, 8186 – 8191. (b) S. A. Snyder, S. P. Breazzano, A. G. Ross, Y. Lin, A. L. Zografos, *J. Am. Chem. Soc.* **2009**, *131*, 1753 – 1765. (c) S. A. Snyder, A. Gollner, M. I. Chiriac, *Nature* **2011**, *474*, 461 – 466. (d) S. A. Snyder, N. E. Wright, J. J. Pflueger, S. P. Breazzano, *Angew. Chem. Int. Ed.* **2011**, *50*, 8629 – 8633. (e) S. A. Snyder, S. B. Thomas, A. C. Mayer, S. P. Breazzano, *Angew. Chem. Int. Ed.* **2012**, *51*, 4080 – 4084.

13. S. A. Snyder, A. M. ElSohly, F. Kontes, *Angew. Chem. Int. Ed.* **2010**, *49*, 9693 – 9698.

14. (a) A. E. Ondrus, M. Movassaghi, *Org. Lett.* **2009**, *11*, 2960 – 2963. (b) A. E. Ondrus, M. Movassaghi, *Chem. Commun.* **2009**, *28*, 4151 – 4165. (c) A. E. Ondrus, H. Ü. Kaniskan, M. Movassaghi, *Tetrahedron*, **2010**, *66*, 4784 – 4795.

Section 4.7 Experimental Section

General Procedures. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), acetonitrile (MeCN), toluene, benzene, diethyl ether (Et_2O) and methylene chloride (CH_2Cl_2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and either an aqueous solution of ceric ammonium sulfate and ammonium molybdate and heat or an aqueous solution of potassium permanganate and sodium bicarbonate and heat as developing agents. SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker DRX-300, DRX-400, DMX-500 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, br = broad, AB = AB quartet, app = apparent. IR spectra were recorded on a Perkin-Elmer 1000 series FT-IR spectrometer. High-resolution mass spectra (HRMS) were

recorded in the Columbia University Mass Spectral Core facility on a JOEL HX110 mass spectrometer using the MALDI (matrix-assisted laser-desorption ionization) technique.

Abbreviations. DIPEA = *N,N*-diisopropylethylamine, DMSO = dimethylsulfoxide, KHMDS = potassium bis(trimethylsilyl)amide, TBS = *tert*-butyldimethylsilyl, TFA = trifluoroacetic acid, TMEDA = *N,N,N',N'*-tetramethylethylenediamine, TMG = *N,N,N',N'*-tetramethylguanidine.

(*S*)-1-*N*-Boc-(–)-Piperidine-2-ethanol 25. This chiral material was prepared using the following homologation procedure from (*S*)-1-*N*-Boc-pipecolic acid. Alternatively, **25** can be purchased commercially from a number of suppliers. (*S*)-1-*N*-Boc-pipecolic acid (39.8 g, 174 mmol, 1.0 equiv) was dissolved in THF (430 mL) and cooled to 0 °C. BH_3•Me_2S complex (28.8 mL, 305 mmol, 1.75 equiv) was added dropwise at 0 °C and the solution was stirred at 0 °C. After 1 h at 0 °C, the reaction mixture was warmed to 25 °C and stirred for an additional 12 h. Upon completion, the reaction mixture was cooled to 0 °C. Saturated aqueous $NaHCO_3$ (400 mL) was added slowly to quench excess reagent, and water (200 mL) was added to dissolve precipitated salts. The crude reaction was extracted with CH_2Cl_2 (4 × 500 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (3 × 300 mL) and water (3 × 300 mL), dried ($MgSO_4$), and concentrated to give crude (*S*)-1-*N*-Boc-homoprolinol (37.6 g, 100% yield) as a white solid. This material was carried forward without additional purification. Oxalyl chloride (22.6 mL, 263 mmol, 1.5 equiv) was dissolved in CH_2Cl_2 (375 mL) and cooled to –78 °C. DMSO (37.2 mL, 525 mmol, 3.0 equiv) was dissolved in CH_2Cl_2 (375 mL), cooled to –78 °C, and cannulated into the oxalyl chloride solution slowly over 1.5 h dropwise to prevent internal exotherm. Upon completion of DMSO

addition, the reaction mixture was stirred at –78 °C for 25 min. During this time, a solution of (*S*)-1-*N*-Boc-homoprolinol (37.6 g, 174 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (375 mL) and cooled to –78 °C. This solution was cannulated into the reaction mixture over the course of 1 h dropwise to prevent internal exotherm. Upon completion of cannulation, the reaction mixture was stirred at –78 °C for 25 min. DIPEA (182.6 mL, 1050 mmol, 6.0 equiv) was added rapidly at this point, and the reaction mixture was slowly warmed from –78 °C to 0 °C over the course of 6 h. Upon reaching 0 °C, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (1000 mL). The crude reaction mixture was extracted with CH_2Cl_2 (3 × 300 mL). The combined organic extracts were washed with water (2 × 500 mL), saturated aqueous NH_4Cl (2 × 500 mL) and water (2 × 500 mL), dried ($MgSO_4$), and concentrated to give the desired crude aldehyde as a yellow oil in assumed quantitative yield. This crude material was immediately carried forward without additional purification. Methyl triphenylphosphonium bromide (68.7 g, 193 mmol, 1.1 equiv) was suspended in toluene (875 mL) and cooled to 0 °C. To this suspension, KHMDS (0.5 M in toluene, 385 mL, 193 mmol, 1.1 equiv) was added at 0 °C. The resultant bright yellow suspension was stirred for 30 min, and a solution of the freshly prepared aldehyde in toluene (400 mL) was rapidly cannulated into the reaction mixture. The reaction was allowed to warm from 0 °C to 25 °C for 16 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (500 mL). The crude reaction mixture was extracted with CH_2Cl_2 (3 × 400 mL). The combined organic extracts were washed with water (2 × 500 mL), dried ($MgSO_4$), and concentrated. The resultant crude brown solid was purified by flash column chromatography (silica gel, hexanes/EtOAc, 9/1) to give the desired

olefin (28.2 g, 78% yield over 2 steps) as a clear oil. BH_3•Me_2S complex (25.5 mL, 268 mmol, 2.0 equiv) was dissolved in hexanes (570 mL) and cooled to 0 °C. To this solution, 2-methyl-2-butene (57 mL, 536 mmol, 4.0 equiv) was added dropwise and the resultant clear solution was stirred at 0 °C for 3 h. The freshly prepared olefin (28.2 g, 134 mmol, 1.0 equiv) was dissolved in hexanes (510 mL), cooled to 0 °C, and cannulated dropwise into the reaction mixture over 70 min. The reaction mixture was stirred from 0 °C with slow warming to 25 °C over 3.5 h at which time thin layer chromatography revealed the complete consumption of starting material. The reaction mixture was then recooled to 0 °C. 1 M aqueous NaOH (850 mL) was added slowly with evolution of gas. Once the evolution of gas stopped, aqueous H_2O_2 (30%, 850 mL) was added slowly. The reaction mixture was allowed to warm from 0 °C to 25 °C over the course of 16 h. This crude reaction mixture was extracted with CH_2Cl_2 (3 × 1000 mL). The combined organic extracts were washed with water (1 × 1000 mL), dried ($MgSO_4$), and concentrated. The resultant crude clear oil was purified by flash column chromatography (silica gel, hexanes/EtOAc, 19/1 to 1/1) to give *(S)*-1-*N*-Boc-(–)-piperidine-2-ethanol **25** (25.2 g, 82% yield) as a clear oil.

Allylated substrate 27. *(S)*-1-*N*-Boc-(–)-piperidine-2-ethanol **25** (19.7 g, 85.8 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (200 mL) at 25 °C. Imidazole (11.7 g, 172 mmol, 2.0 equiv) and TBSCl (14.3 g, 94.4 mmol, 1.1 equiv) were added sequentially to this solution at 25 °C, and a white solid quickly precipitated. The reaction was stirred at 25 °C for 19 h after which time MeOH (6 mL) was added to the reaction mixture to quench excess reagent. The reaction contents were stirred at 25 °C for 1 h more and then quenched by addition of water (500 mL). The crude reaction mixture was extracted with

CH_2Cl_2 (3 × 500 mL). The combined organic extracts were washed with water (3 × 500 mL), dried (MgSO4), and concentrated to give the desired silylated product as a crude clear oil. This material was carried forward crude without additional purification. A portion of this freshly prepared material (23.4 g, 68.2 mmol, 1.0 equiv) and freshly distilled TMEDA (16.3 mL, 109 mmol, 1.6 equiv) were dissolved in Et_2O (450 mL) and cooled to –78 °C. *s*-BuLi (1.4 M in cyclohexane, 73 mL, 102 mmol, 1.5 equiv) was added dropwise at –78 °C. The resultant yellow solution was then allowed to warm slowly to –45 °C and was kept at –45 °C for 1 h. At this time, the reaction mixture was cooled to –78 °C. A solution of CuCN•2LiCl complex (0.6 M in THF, 170 mL, 102 mmol, 1.5 equiv) was freshly prepared by dissolving CuCN (9.14 g, 102 mmol, 1.5 equiv) and flame-dried LiCl (8.65 g, 204 mmol, 3.0 equiv) in THF (170 mL) at 25 °C. This green solution was added dropwise to the reaction mixture at –78 °C over which time the reaction mixture slowly turned pale and then a deep orange. The resultant orange solution was stirred at –78 °C for 1 h, and then allyl bromide (**26**) (29.5 mL, 341 mmol, 5.0 equiv) was added rapidly at –78 °C. The solution immediately turned bright red, quickly faded to brownish orange, and was stirred at –78 °C for 1 h. The reaction mixture was then allowed to warm to 25 °C over 1 h. The reaction was quenched by addition of a premixed solution of saturated aqueous NH_4Cl (400 mL) and concentrated NH_4OH (50 mL) at 25 °C and stirred at 25 °C for 1 h. The crude reaction mixture was diluted with water (500 mL) and extracted with Et_2O (4 × 400 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The resultant crude grey oil was purified by flash column chromatography (silica gel, hexanes/EtOAc, 9/1) to give the desired allylated product **27** (23.8 g, 91% yield) as a clear oil. **27**: R_f = 0.46 (silica gel, hexanes/EtOAc, 19/1); $[\alpha]_D^{20}$ =

–0.1° (*c* = 0.75, $CHCl_3$); IR (film) ν_{max} 2951, 2931, 2858, 1689, 1641, 1472, 1392, 1365, 1253, 1176, 1097, 836, 775; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (ddd, *J* = 17.1, 10.2, 8.2, 6.0 Hz, 1 H), 5.06 (d, *J* = 16.8 Hz, 1 H), 5.00 (d, *J* = 10.0 Hz, 1 H), 3.88 – 3.75 (m, 2 H), 3.65 (t, *J* = 6.7 Hz, 2 H), 2.50 (dt, *J* = 13.6, 5.2 Hz, 1 H), 2.19 (dt, 13.6, 9.2 Hz, 1 H), 1.97 – 1.86 (m, 1 H), 1.80 – 1.66 (m, 4 H), 1.66 – 1.58 (m, 3 H), 1.46 (s, 9 H), 0.89 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 136.4, 116.5, 79.2, 61.8, 51.9, 49.7, 39.0, 37.8, 28.7, 26.1, 25.1, 23.6, 18.5, 14.5, –5.2, –5.2; HRMS (MALDI-FTMS) calcd for $C_{21}H_{42}NO_3Si^+$ [M^+] 384.2934, found 384.2939.

Methyl enoate 29. Allylated substrate **27** (23.6 g, 61.6 mmol, 1.0 equiv) was dissolved in 1,4-dioxane (450 mL) and water (150 mL) at 25 °C. 2,6-lutidine (14.2 mL, 123 mmol, 2.0 equiv), $NaIO_4$ (52.7 g, 246 mmol, 4.0 equiv) and K_2OsO_4•$2H_2O$ (113 mg, 0.308 mmol, 0.005 equiv) were added sequentially at 25 °C. The resultant white suspension was stirred at 25 °C for 2.5 h over which time thick white precipitates formed. Upon completion, the reaction contents were quenched by the addition of water (500 mL) and CH_2Cl_2 (500 mL). The crude reaction mixture was extracted with CH_2Cl_2 (3 × 300 mL). The combined organic extracts were washed with 1 M aqueous HCl (4 × 500 mL), water (2 × 500 mL), dried ($MgSO_4$), and concentrated. The resultant crude grey oil was considered quantitative. Pressing forward without additional purification, this material was combined neat with methyl (triphenylphosphoranylidene)acetate (**28**) (25.0 g, 74.9 mmol, 1.49 equiv) at 25 °C, and CH_2Cl_2 (30 mL) was added to make a thick oil. This thick grey oil was stirred at 25 °C for 14 h. Upon completion, this oil was loaded directly onto silica gel for purification by flash column chromatography (silica gel, hexanes/EtOAc, 4/1) to give the desired methyl enoate **29** (22.8 g, 84% yield) as a clear

oil. **29**: R_f = 0.61 (silica gel, hexanes/EtOAc, 4/1); $[\alpha]_D^{20}$ = +2.2° (*c* = 0.80, $CHCl_3$); IR (film) ν_{max} 2951, 2932, 2858, 1727, 1689, 1658, 1366, 1254, 1173, 1094, 836, 776; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (ddd, *J* = 15.3, 8.4, 6.7 Hz, 1 H), 5.85 (dt, *J* = 15.7, 1.4 Hz, 1 H), 3.94 – 3.84 (m, 2 H), 3.71 (s, 3 H), 3.64 (t, *J* = 7.2 Hz, 2 H), 2.66 (dt, *J* = 12.8, 6.0 Hz, 1 H), 2.36 (dt, *J* = 17.2, 8.8 Hz, 1 H), 1.96 – 1.86 (m, 1 H), 1.83 – 1.67 (m, 4 H), 1.67 – 1.53 (m, 3 H), 1.45 (s, 9 H), 0.88 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 155.3, 146.8, 122.7, 79.6, 61.6, 51.5, 51.2, 49.8, 37.6, 28.6, 26.4, 26.1, 25.0, 24.4, 18.4, 14.5, –5.2, –5.2; HRMS (MALDI-FTMS) calcd for $C_{23}H_{44}NO_5Si^+$ [M^+] 442.2989, found 442.2978.

Phosphonate 31. Methyl enoate **29** (22.8 g, 51.7 mmol, 1.0 equiv) was dissolved in MeOH (195 mL) and EtOAc (65 mL) at 25 °C. Solid Pd/C (10%, 3.30 g, 3.10 mmol, 0.06 equiv) was added and the reaction flask was charged with an atmosphere of H_2 gas at –78 °C. The reaction was warmed to 25 °C and stirred at 25 °C for 20 h, filtered through celite, and concentrated to give the desired product (22.1 g, 97% yield) as a yellow oil. This material was carried forward without additional purification. Dimethyl methylphosphonate (4.86 mL, 45.1 mmol, 2.0 equiv) was dissolved in THF (110 mL) at 25 °C and cooled to –78 °C. *n*-BuLi (1.6 M in hexane, 31.1 mL, 49.7 mmol, 2.2 equiv) was added dropwise over 10 min at –78 °C, and the reaction contents were stirred at –78 °C for 1 h to form lithiate **30**. A portion of the hydrogenated material prepared in the previous step (10.0 g, 22.6 mmol, 1.0 equiv) was dissolved in THF (55 mL + 30 mL rinse) and added dropwise to the stirred solution of lithiate **30**. The reaction contents were allowed to warm slowly from –78 °C to –45 °C over 90 min. Upon completion, the reaction was quenched at –45 °C by the addition of saturated aqueous NH_4Cl (100 mL)

and water (50 mL). The crude reaction mixture was diluted with CH_2Cl_2 (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The resultant crude yellow oil was purified by flash column chromatography (silica gel, hexanes/EtOAc, 3/1 to pure EtOAc, then EtOAc/MeOH, 99/1 to 97/3) to give phosphonate **31** (10.6 g, 87% yield) as a pale yellow oil. **31**: R_f = 0.52 (silica gel, EtOAc); $[\alpha]_D^{20}$ = –5.5 ° (*c* = 0.95, $CHCl_3$); IR (film) ν_{max} 2953, 2931, 2856, 1715, 1684, 1393, 1366, 1255, 1092, 1032, 836, 776; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (d, *J* = 11.3 Hz, 6 H), 3.80 – 3.72 (m, 2 H), 3.63 (t, *J* = 6.7 Hz, 2 H), 3.08 (dd, *J* = 18.8, 1.4 Hz, 2 H), 2.63 (t, *J* = 6.4 Hz, 2 H), 1.97 – 1.87 (m, 1 H), 1.80 – 1.50 (m, 10 H), 1.50 – 1.40 (m, 1 H), 1.44 (s, 9 H), 0.88 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 155.6, 79.2, 61.6, 53.2, 53.1, 52.1, 49.7, 44.0, 42.0, 40.8, 37.6, 33.2, 28.7, 26.1, 25.5, 24.7, 21.0, 18.4, 15.3, –5.2; HRMS (MALDI-FTMS) calcd for $C_{25}H_{51}NO_7PSi^+$ [M^+] 536.3172, found 536.3199.

Aldehyde 10. Oxalyl chloride (0.50 mL, 5.87 mmol, 1.6 equiv) was dissolved in CH_2Cl_2 (12 mL) and cooled to –78 °C. DMSO (0.83 mL, 11.7 mmol, 3.2 equiv) was dissolved in CH_2Cl_2 (12 mL), cooled to –78 °C, and added dropwise into the oxalyl chloride solution slowly over 15 min to prevent internal exotherm. Upon completion of DMSO addition, the reaction mixture was stirred at –78 °C for 5 min. During this time, a solution of alcohol **11** (1.20 g, 3.67 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (12 mL + 6 mL rinse) at 25 °C. This solution was added dropwise into the reaction mixture over the course of 20 min to prevent internal exotherm. Upon completion of addition, the reaction mixture was stirred at –78 °C for 5 min. Et_3N (3.06 mL, 22.0 mmol, 6.0 equiv) was added rapidly at this point, and the reaction mixture was stirred at –78 °C for 20 min. The

reaction mixture was then placed in a 0 °C bath and stirred at 0 °C for 90 min. The reaction contents were quenched by the addition of saturated aqueous NH_4Cl (40 mL) and water (20 mL). The crude reaction mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with water (2 × 50 mL), saturated aqueous NH_4Cl (2 × 50 mL), water (2 × 50 mL) again, dried ($MgSO_4$), and concentrated to give aldehyde **10** (1.12 g, 94% yield) as a yellow oil. This crude material was immediately carried forward without additional purification. For characterization purposes, a portion of this material was purified using preparative thin layer chromatography (silica gel hexanes/EtOAc 1/1). **10**: R_f = 0.71 (silica gel, hexanes/EtOAc, 1/1); $[\alpha]_D^{20}$ = –1.2° (*c* = 0.85, $CHCl_3$); IR (film) ν_{max} 2933, 2374, 2728, 1716, 1682, 1456, 1391, 1366, 1329, 1169, 1096; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (t, *J* = 1.8 Hz, 1 H), 4.11 – 4.01 (m, 2 H), 3.04 (dd, *J* = 16.2, 6.9 Hz, 1 H), 2.58 (ddd, *J* = 16.5, 7.1, 1.7, 1 H), 2.45 (dd, *J* = 16.3, 5.9 Hz, 1 H), 2.28 (dd, *J* = 16.3, 7.7 Hz, 1 H), 2.12 (s, 3 H), 2.09 – 1.97 (m, 1 H), 1.77 – 1.52 (m, 9 H), 1.43 (s, 9 H), 1.21 (dt, *J* = 13.7, 7.4, 1 H), 0.93 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.2, 201.1, 155.7, 80.2, 51.4, 51.1, 49.1, 47.2, 39.7, 30.7, 28.9, 28.3, 26.6, 26.5, 20.7, 17.0; HRMS (MALDI-FTMS) calcd for $C_{18}H_{32}NO_4^+$ [M^+] 326.2331, found 326.2335.

Enone 32. Phosphonate **31** (1.84 g, 3.45 mmol, 1.0 equiv) and LiCl (584 mg, 13.8 mmol, 4.0 equiv) were suspended in CH_3CN (23 mL) at 25 °C, and DIPEA (1.20 mL, 6.90 mmol, 2.0 equiv) was added in a single portion at 25 °C, turning the solution yellow. The reaction contents were stirred at 25 °C for 30 min. Aldehyde **10** (1.12 g, 3.45 mmol, 1.0 equiv) was then dissolved in CH_3CN (12 mL + 6 mL rinse) and added dropwise over 5 min. The reaction contents were stirred at 25 °C for 4 h with formation of a cloudy

precipitate. Once aldehyde **10** was fully consumed, the reaction contents were cooled to 0 °C and 1 M aqueous hydrochloric acid (20.7 mL, 20.7 mmol, 6.0 equiv) and MeOH (20 mL) were added sequentially to generate a clear solution. The resultant solution was stirred at 0 °C for 25 min. Upon completion, the reaction contents were diluted with water (50 mL) and CH_2Cl_2 (50 mL). The crude reaction mixture was extracted with CH_2Cl_2 (4 × 40 mL). The combined organic extracts were dried ($MgSO_4$), and concentrated. The resultant crude yellow oil was purified by flash column chromatography (silica gel, hexanes/EtOAc, 9/1 to 2/3) to give enone **32** (1.68 g, 79% yield) as a pale yellow oil. **32**: R_f = 0.29 (silica gel, hexanes/EtOAc, 1/1); $[\alpha]_D^{20}$ = –13.8° (*c* = 0.80, $CHCl_3$); IR (film) ν_{max} 3444 (br), 2935, 2873, 1680, 1455, 1395, 1366, 1251, 1170, 1116, 871, 773; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (ddd, *J* = 15.2, 8.0, 6.7 Hz, 1 H), 6.11 (dt, *J* = 16.0, 1.4 Hz, 1 H), 4.08 – 4.01 (m, 1 H), 3.94 – 3.87 (m, 1 H), 3.79 – 3.73 (m, 1 H), 3.67 – 3.62 (m, 1 H), 3.62 – 3.49 (m, 2 H), 2.72 (dt, *J* = 13.3, 6.4 Hz, 1 H), 2.56 (t, *J* = 6.8 Hz, 2 H), 2.52 (dd, *J* = 14.0, 5.6 Hz, 1 H), 2.41 (dt, *J* = 16.8, 8.8 Hz, 1 H), 2.25 (dd, *J* = 16.6, 7.0 Hz, 1 H), 2.12 (s, 3 H), 2.07 – 1.97 (m, 1 H), 1.90 – 1.80 (m, 1 H), 1.80 – 1.55 (m, 17 H), 1.55 – 1.40 (m, 2 H), 1.46 (s, 9 H), 1.46 (s, 9 H), 1.34 – 1.24 (m, 1 H), 0.92 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.8, 200.2, 156.9, 155.4, 144.8, 131.9, 80.1, 79.7, 59.3, 52.3, 51.3, 50.7, 50.4, 47.8, 40.7, 39.7, 38.6, 38.0, 34.0, 30.6, 28.7, 28.6, 26.6, 25.9, 25.1, 25.0, 23.0, 21.7, 20.8, 15.1, 13.8; HRMS (MALDI-FTMS) calcd for $C_{35}H_{61}N_2O_7^+$ [M^+] 621.4479, found 621.4465.

Alcohol 33. Enone **32** (500 mg, 0.806 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (16 mL) and cooled to –78 °C. A 25 °C solution of TFA (10% v/v in CH_2Cl_2, 6.2 mL, 8.06 mmol, 10.0 equiv) was added in a single portion. The reaction was stirred at –78 °C

for 2 h. Et_3N (1.12 mL, 8.06 mmol, 10.0 equiv) was added in a single portion at –78 °C and the reaction contents were quickly warmed to 25 °C. At 25 °C, the reaction contents were diluted with CH_2Cl_2 (20 mL) and water (50 mL). The crude reaction mixture was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic extracts were washed with 0.5 M aqueous HCl (3 × 20 mL), water (3 × 20 mL), concentrated aqueous $NaHCO_3$ (40 mL), dried (Na_2SO_4), and concentrated. The resultant crude yellow oil was purified by flash column chromatography (silica gel, hexanes/EtOAc, 4/1 to pure EtOAc) to give the desired alcohol **33** (405 mg, 89% yield, dr 2:1) as a pale yellow oil. These diastereomers were inseparable and were characterized together. **31**: R_f = 0.42 (silica gel, EtOAc); IR (film) ν_{max} 3424 (br), 2933, 2872, 1708, 1675, 1431, 1398, 1365, 1170, 1116, 757; ^{1}H NMR (400 MHz, $CDCl_3$) δ (Major diastereomer, key peaks) 4.75 – 4.57 (m, 2 H), 4.08 – 3.98 (m, 1 H), 3.67 – 3.47 (m, 4 H), 2.84 (dd, *J* = 16.5, 6.1 Hz, 1 H), 2.55 (dd, *J* = 16.6, 6.4 Hz, 1 H), 2.49 (t, *J* = 6.7 Hz, 2 H), 2.11 (s, 3 H), 1.45 (s, 9 H), 0.96 (d, *J* = 6.8 Hz, 3 H); (Minor diastereomer, key peaks) 4.75 – 4.57 (m, 2 H), 4.08 – 3.98 (m, 1 H), 3.67 – 3.47 (m, 4 H), 2.93 (dd, *J* = 16.9, 6.2 Hz, 1 H), 2.67 (dd, *J* = 16.9, 6.7 Hz, 1 H), 2.49 (t, *J* = 6.7 Hz, 2 H), 2.11 (s, 3 H), 1.45 (s, 9 H), 1.00 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (2 diastereomers) 208.9, 208.6, 207.5, 207.2, 156.7, 153.7, 153.3, 80.1, 76.9, 70.9, 69.4, 59.4, 52.2, 51.1, 50.9, 49.4, 48.9, 48.5, 47.9, 47.4, 46.9, 46.7, 43.8, 43.6, 38.5, 37.2, 36.6, 36.0, 33.8, 33.7, 33.1, 33.0, 30.8, 30.7, 29.2, 28.6, 28.6, 26.0, 25.9, 25.9, 25.4, 25.3, 23.1, 21.1, 21.0, 20.4, 20.3, 19.3, 18.4, 13.8; HRMS (MALDI-FTMS) calcd for $C_{31}H_{53}N_2O_7^+$ [M^+] 565.3853, found 565.3851.

Bis(trifluoromethyl)phenyl sulfone 35. Oxalyl chloride (0.094 mL, 1.10 mmol, 1.6 equiv) was dissolved in CH_2Cl_2 (2.3 mL) and cooled to –78 °C. DMSO (0.16 mL,

2.19 mmol, 3.2 equiv) was dissolved in CH_2Cl_2 (2.3 mL), cooled to –78 °C, and added dropwise into the oxalyl chloride solution slowly over 20 min to prevent internal exotherm. Upon completion of DMSO addition, the reaction mixture was stirred at –78 °C for 5 min. During this time, a solution of alcohol **33** (386 mg, 0.685 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (2.3 mL + 1.2 mL rinse) at 25 °C. This solution was added dropwise into the reaction mixture over the course of 20 min to prevent internal exotherm. Upon completion of addition, the reaction mixture was stirred at –78 °C for 5 min. Et_3N (0.57 mL, 4.11 mmol, 6.0 equiv) was added rapidly at this point, and the reaction mixture was stirred at –78 °C for 30 min. The reaction mixture was then placed in a 0 °C bath and stirred at 0 °C for 60 min. The reaction contents were quenched by the addition of saturated aqueous NH_4Cl (10 mL) and water (5 mL). The crude reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with water (2 × 20 mL), saturated aqueous NH_4Cl (2 × 20 mL), water (2 × 20 mL) again, dried (Na_2SO_4), and concentrated to give the desired aldehyde as a crude yellow oil in full crude recovery with a 2:1 dr from the previous step. This material was immediately carried forward without additional purification. Phosphonate **34** (203 mg, 0.475 mmol, 1.0 equiv) and LiCl (40.3 mg, 0.950 mmol, 2.0 equiv) were suspended in CH_3CN (3.17 mL) at 25 °C to make a yellow suspension. DIPEA (0.17 mL, 0.950 mmol, 2.0 equiv) was added to this suspension in a single portion at 25 °C. The resultant clear suspension was stirred at 25 °C for 30 min. A portion of the crude aldehyde prepared in the previous step (267 mg, 0.475 mmol, 1.0 equiv) was dissolved in CH_3CN (1.5 mL + 1.0 mL rinse) and added to the stirring solution at 25 °C. The resultant pale yellow solution was stirred at 25 °C for 2 h. Upon completion, the reaction contents were

quenched by the addition of saturated aqueous NH_4Cl (10 mL), water (10 mL), and CH_2Cl_2 (15 mL). The crude reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The resultant crude yellow oil was purified by flash column chromatography (silica gel, hexanes/EtOAc, 9/1 to 1/1) to give bis(3,5-trifluoromethyl)phenyl sulfone **35** (267 mg, 67% yield, 2:1 dr from a previous step) as a white foam. These diastereomers were inseparable and were characterized together. **35**: R_f = 0.53 (silica gel, hexanes/EtOAc, 1/2); IR (film) ν_{max} 2934, 2869, 1714, 1681, 1629, 1362, 1333, 1280, 1144, 1105, 757, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ (Major diastereomer, key peaks) 8.34 (s, 2 H), 8.09 (s, 1 H), 7.16 – 7.06 (m, 1 H), 6.41 (d, *J* = 14.8 Hz, 1 H), 4.77 – 4.57 (m, 2 H), 3.87 – 3.79 (m, 2 H), 3.67 – 3.57 (m, 1 H), 2.87 (dd, *J* = 16.6, 6.2 Hz, 1 H), 2.58 (dd, *J* = 16.5, 6.4 Hz, 1 H), 2.51 (t, *J* = 6.8 Hz, 2 H), 2.12 (s, 3 H), 1.41 (s, 9 H), 0.97 (d, *J* = 6.5 Hz, 3 H); (Minor diastereomer, key peaks) 8.34 (s, 2 H), 8.09 (s, 1 H), 7.16 – 7.06 (m, 1 H), 6.41 (d, *J* = 14.8 Hz, 1 H), 4.77 – 4.57 (m, 2 H), 3.87 – 3.79 (m, 2 H), 3.67 – 3.57 (m, 1 H), 2.95 (dd, *J* = 16.9, 6.3 Hz, 1 H), 2.69 (dd, *J* = 16.9, 6.7 Hz, 1 H), 2.51 (t, *J* = 6.8 Hz, 2 H), 2.12 (s, 3 H), 1.41 (s, 9 H), 1.01 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (2 diastereomers) 208.9, 208.7, 207.5, 207.2, 155.4, 153.7, 153.3, 148.3, 143.9, 133.3 (q, *J* = 34.3 Hz), 130.2, 128.2, 127.0, 123.9, 121.2, 80.0, 77.4, 71.0, 69.4, 52.4, 51.1, 50.9, 50.8, 49.4, 48.9, 48.5, 47.4, 47.0, 46.8, 43.7, 43.4, 37.3, 37.0, 36.1, 33.7, 33.2, 33.1, 33.0, 33.0, 30.8, 30.7, 29.2, 28.6, 28.6, 25.5, 25.4, 24.4, 20.8, 20.7, 20.4, 20.3, 19.4, 18.4, 15.0, 14.9; HRMS (MALDI-FTMS) calcd for $C_{40}H_{55}F_6N_2O_8S^+$ [M^+] 837.3583, found 837.3575.

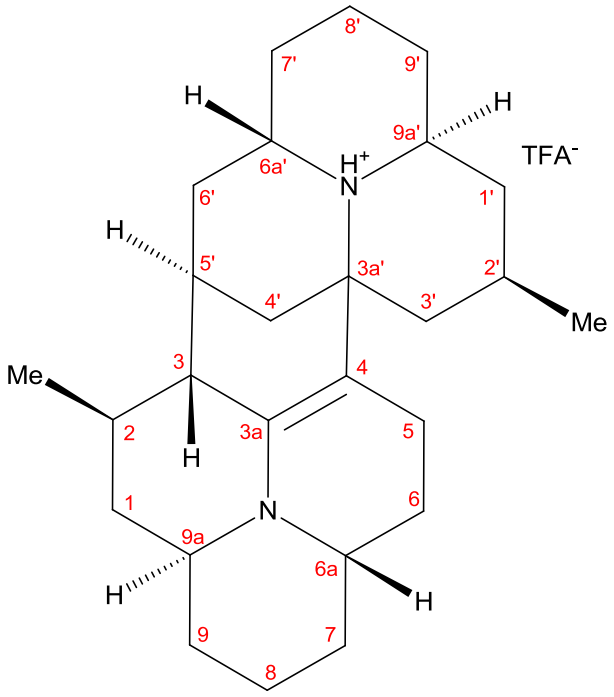
Bis(trifluoromethyl)phenyl sulfone cascade product 38. Sulfone **36** (144 mg, 0.172 mmol, 1.0 equiv) was dissolved in toluene (3.15 mL) at 25 °C. A solution of TMG (21.5 μL, 0.172 mmol, 1.0 equiv) in *i*-PrOH (0.35 mL) was added in a single portion to the reaction mixture and the resultant pale yellow solution was stirred at 25 °C for 5.5 h. Upon completion, the reaction contents were diluted with CH_2Cl_2 (30 mL). The crude reaction mixture was washed with 5% aqueous $NaHCO_3$ (5 × 40 mL), dried (Na_2SO_4), and concentrated to give the desired product (132 mg, 99% crude recovery, 1:1.2 dr by crude NMR integration) as a brown foam. This material was unstable and had to be carried forward immediately.

Bis(trifluoromethyl)phenyl sulfonyl heptacycle 44. Pressing forward without purification, the crude product of the first cascade (**38**) (132 mg containing 60 mg of desired epimer, 0.0774 mmol of desired epimer, 1.0 equiv) was dissolved in CH_2Cl_2 (1.0 mL) to give a brown solution and cooled to 0 °C. TFA (1.0 mL) was cooled to 0 °C and added to the solution of starting material in a single portion at 0 °C. The resulting pale yellow solution was stirred at 0 °C for 1 h. Upon completion, the reaction contents were diluted with CH_2Cl_2 (10 mL) and made basic in three equal portions by vigorous washing with ice cold 1 M aqueous NaOH (25 mL). The resulting aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The resultant crude yellow oil was immediately dissolved in C_6D_6 (3.0 mL) and warmed to 65 °C. The reaction was stirred at 65 °C for 3 h. Upon completion, the reaction contents were concentrated. The resultant crude brown oil was purified by preparative thin layer chromatography (Et_3N pretreated silica gel, hexanes/EtOAc, 19/1) to give heptacycle **44** (17 mg, 33% yield based on the desired epimer) as a yellow oil. **44:**

R_f = 0.60 (Et_3N pretreated silica gel, hexanes/EtOAc, 19/1); $[\alpha]_D^{20}$ = –47.0° (*c* = 0.30, $CHCl_3$); IR (film) ν_{max} 2929, 2868, 1686, 1640, 1359, 1311, 1278, 1179, 1139, 1105, 682; ^{1}H NMR (400 MHz, C_6D_6) δ 8.37 (s, 2 H), 7.57 (s, 1 H), 3.45 (dd, *J* = 13.2, 2.6 Hz, 1 H), 3.24 (d, *J* = 8.0 Hz, 1 H), 3.12 – 3.02 (m, 1 H), 3.03 (dd, *J* = 12.1, 5.8 Hz, 1 H), 2.76 (dd, *J* = 13.3, 11.4 Hz, 1 H), 2.45 (br t, *J* = 10.3, Hz, 1 H), 2.27 (br t, *J* = 10.6 Hz, 1 H), 2.18 (br s, 1 H), 2.06 – 1.92 (m, 3 H), 1.75 – 0.70 (m, 24 H), 0.77 (d, *J* = 6.4 Hz, 3 H), 0.21 (br d, *J* = 12.8 Hz, 1 H); ^{13}C NMR (100 MHz, C_6D_6) δ 149.1, 144.6, 133.3 (q, *J* = 34.4 Hz), 126.9, 124.1, 121.4, 112.6, 60.8, 56.9, 56.0, 53.5, 51.0, 49.2, 48.3, 47.2, 43.6, 37.0, 35.6, 35.5, 34.2, 33.8, 31.7, 31.4, 31.1, 30.7, 27.0, 26.8, 24.3, 22.7, 20.7, 19.8; HRMS (MALDI-FTMS) calcd for $C_{34}H_{43}F_6N_2O_2S^+$ [M^+] 657.2949, found 657.2967.

Psylloborine A (1). A portion of heptacycle **44** (15 mg, 0.0228 mmol, 1.0 equiv) was dissolved in *i*-PrOH (7.5 mL) at 25 °C, and Na/Hg amalgam (5 wt %, 2.90 g, 6.30 mmol, 276 equiv) was added in a single portion. The resultant reaction mixture was stirred vigorously at 25 °C for 75 min, during which time the solution changed from pale to bright yellow. The reaction contents were then diluted with *i*-PrOH (30 mL), filtered through Celite, and diluted with CH_2Cl_2 (100 mL). The crude reaction contents were washed with 10% aqueous $NaHCO_3$ (100 mL), the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The resultant crude yellow oil was purified by preparative thin layer chromatography (Et_3N-pretreated silica gel, hexanes/EtOAc, 19/1) to give psylloborine A (**1**, 4.0 mg, 46% yield) as a colorless, clear oil. **1**: R_f = 0.83 (Et_3N-pretreated silica gel, hexanes/EtOAc, 19/1); $[\alpha]_D^{20}$ = –31.9° (*c* = 0.10, $CHCl_3$); IR (film) ν_{max} 2924, 2856, 1740, 1646, 1454, 1377, 1374, 1262, 1129, 1094, 1065, 1052, 800, 757 cm^{-1}; ^{1}H NMR

(400 MHz, C_6D_6) δ 3.49 (br d, *J* = 12.4 Hz, 1 H), 3.21 (dd, *J* = 12.3, 6.0 Hz, 1 H), 2.67 (br t, *J* = 11.2 Hz, 1 H), 2.55 (br s, 1 H), 2.31 (m, 1 H), 2.28 (br t, *J* = 10.0 Hz, 1 H), 2.14 (m, 1 H), 2.12 (m, 1 H), 2.05 (m, 1 H), 1.93 (td, *J* = 12.8, 2.8 Hz, 1 H), 1.86 – 1.72 (m, 2 H), 1.72 (m, 1 H), 1.63 (m, 1 H), 1.56 (m, 1 H), 1.54 (m, 1 H), 1.50 (m, 1 H), 1.49 (m, 1 H), 1.45 (m, 1 H), 1.45 (m, 1 H), 1.45 (m, 1 H), 1.44 (m, 1 H), 1.39 (m, 1 H), 1.37 (m, 1 H), 1.36 (m, 1 H), 1.31 (m, 1 H), 1.28 (m, 1 H), 1.24 (m, 1 H), 1.15 (m, 1 H), 1.09 (m, 1 H), 1.09 (m, 1 H), 1.06 (d, *J* = 7.2 Hz, 3 H), 1.00 (m, 1 H), 0.87 (m, 1 H), 0.82 (m, 1 H), 0.80 (d, *J* = 6.4 Hz, 3 H), (overlapping peaks deconvoluted by HSQC); ^{13}C NMR (100 MHz, C_6D_6) δ 145.7, 118.8, 56.8, 56.3, 54.4, 50.7, 49.3, 48.7, 47.6, 43.9, 36.7, 36.0, 35.8, 34.5 (2 C by HSQC), 34.4, 31.9, 31.8, 31.4, 27.1, 26.2, 24.4, 22.8, 21.0, 20.4 20.0; ^{13}C NMR (100 MHz, CD_2Cl_2) δ 145.0, 119.8, 57.1, 56.5, 54.6, 50.6, 49.3, 48.8, 47.5, 43.9, 36.7, 35.9, 35.8, 34.5, 34.4, 34.2, 31.9, 31.8, 31.3, 27.2, 26.0, 24.3, 22.7, 20.8, 20.2, 20.0; HRMS (MALDI-FTMS) calcd for $C_{26}H_{41}N_2^+$ [M^+] 381.3270, found 381.3268.



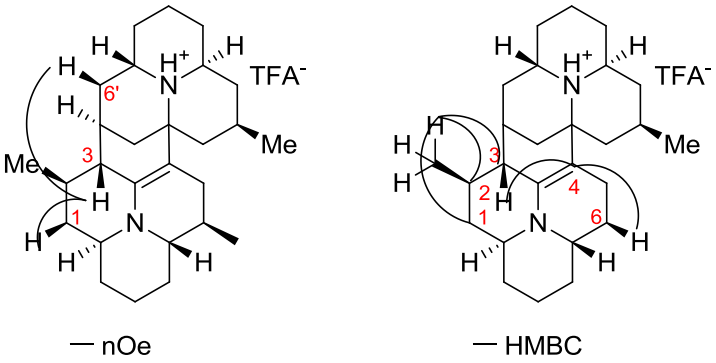
(+)-56: isopsylloborine A
TFA salt

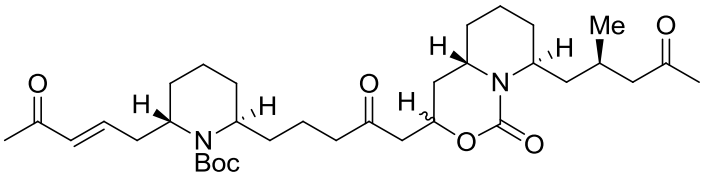
Isopsylloborine A (2) and isopsylloborine A TFA salt (56). Psylloborine A (**1**, 2.0 mg, 0.00526 mmol, 1.0 equiv) was dissolved in 1,2-dichloroethane (5.3 mL) and a solution of TFA (0.81 μL, 0.00105 mmol, 2.0 equiv) in 1,2-dichloroethane (0.1 mL) was added at 25 °C. The resultant clear solution was warmed to 75 °C and stirred for 30 min. Upon completion, the reaction contents were cooled to 25 °C and concentrated directly to give isopsylloborine A (**2**) as a trifluoroacetic acid salt (**56**) in full recovery of roughly 75% purity by crude NMR analysis. This crude isolate was then redissolved in CH_2Cl_2 (10 mL), cooled to 0 °C and washed with ice cold $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated to give isopsylloborine A (**2**) as a crude clear oil in full recovery of roughly 75% purity by crude NMR analysis. Repeated attempts to purify this material were unsuccessful due to its instability, necessitating crude characterization.

This material was characterized as the free base (**2**) [NMR analysis of **2** performed with excess TFA slowly added to the NMR sample until several peaks matched tabulated data for the natural isolate; sample also slowly formed impurities as excess TFA was added] and the trifluoroacetate salt (**56**). Extensive 2D NMR analysis was performed to unequivocally assign the structure of **56** with multiple solvents required to observe the desired nOe correlations (see Tables S3 and S4). **2**: $[\alpha]_D^{20}$ = –119.4° (*c* = 0.16, CH_2Cl_2); IR (film) ν_{max} 2924, 2854, 1685, 1459, 1383, 1271, 1207, 1123 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2 + excess TFA) δ 4.17 (br d, *J* = 13.4 Hz, 1 H), 3.80 (br d, *J* = 13.6 Hz, 1 H), 3.57 (br m), 3.34 (br t, *J* = 11.4 Hz, 1 H), 2.71 (br m, 1 H), 2.46 (m, 1 H), 2.46 (m, 1 H), 2.40 (m, 1 H), 2.30 (m, 1 H), 2.27 (m, 1 H), 2.17 (m, 1 H), 2.10 (m, 1 H), 2.10 (m, 1 H), 2.08 (m, 1 H), 2.01 (m, 1 H), 1.99 (m, 1 H), 1.88 (m, 1 H), 1.86 (m, 1 H), 1.86 (m, 1 H), 1.85 (m, 1 H), 1.82 (m, 1 H), 1.79 (m, 1 H), 1.79 (m, 1 H), 1.77 (m, 1 H), 1.75 (m, 1 H), 1.71 (m, 1 H), 1.70 (m, 1 H), 1.62 (m, 1 H), 1.62 (m, 1 H), 1.61 (m, 1 H), 1.60 (m, 1 H), 1.56 (m, 1 H), 1.56 (m, 1 H), 1.50 (m, 1 H), 1.03 (d, *J* = 6.1 Hz, 3 H), 1.00 (d, *J* = 6.1 Hz, 1 H) (overlapping peaks deconvoluted by HSQC); ^{13}C NMR (125 MHz, CD_2Cl_2 + excess TFA) δ 145.1, 127.1, 63.4, 63.2, 55.9, 55.8, 52.4, 49.5, 41.6, 39.7, 38.8, 34.9, 31.6, 31.2, 29.8, 28.5, 28.0, 26.4, 25.5, 24.8, 22.1, 21.3, 20.2, 19.3, 17.5, 16.9; HRMS (MALDI-FTMS) calcd for $C_{26}H_{41}N_2^+$ [M^+] 381.3270, found 381.3262. **56**: $[\alpha]_D^{20}$ = +19.4° (*c* = 0.20, CH_2Cl_2); IR (film) ν_{max} 3506 (br), 2929, 2855, 1672, 1459, 1197, 1130, 832, 799, 719 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) δ 10.51 (br s, 1 H), 4.31 (br d, *J* = 13.9 Hz, 1 H), 3.68 (br d, *J* = 14.2 Hz, 1 H), 3.49 (m, 1 H) 3.15 (tt, *J* = 11.6, 3.5 Hz, 1 H), 2.88 (m, 1 H), 2.41 (dd, *J* = 14.6, 3.5 Hz, 1 H), 2.39 (dd, *J* = 18.5, 6.0 Hz, 1 H), 2.32 (br s, 1 H), 2.25 (m, 1 H), 2.24 (m, 1 H), 2.24 (m, 1 H), 2.16 (m, 1 H), 2.16 (m, 1 H), 2.01 (m, 1

H), 1.96 (m, 1 H), 1.93 (m, 1 H), 1.91 (m, 1 H), 1.90 (m, 1 H), 1.81 (m, 1 H), 1.78 (m, 1 H), 1.77 (m, 1 H), 1.73 (m, 1 H), 1.73 (m, 1 H), 1.71 (m, 1 H), 1.71 (m, 1 H), 1.69 (m, 1 H), 1.66 (m, 1 H), 1.64 (m, 1 H), 1.64 (m, 1 H), 1.58 (m, 1 H), 1.55 (m, 1 H), 1.51 (m, 1 H), 1.49 (br d, *J* = 14.3 Hz, 1 H), 1.43 (br d, *J* = 13.6 Hz, 1 H), 1.00 (d, *J* = 6.3 Hz, 3 H), 1.00 d, *J* = 6.3 Hz, 3 H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 161.1, 146.5, 125.0, 118.2 or 115.9 (one of these is an impurity), 62.7, 61.5, 55.1, 54.7, 51.6, 49.4, 41.6, 40.2, 38.6, 35.0, 31.6, 31.4, 30.0, 28.4, 28.4, 26.6, 25.7, 25.1, 22.4, 21.6, 20.6, 19.5, 17.9, 17.6; ^{1}H NMR (500 MHz, CD_3CN) δ 9.32 (br s), 4.23 (br d, *J* = 13.6 Hz, 1 H), 3.68 (m, 1 H), 3.52 (br d, *J* = 13.3 Hz, 1 H), 3.22 (br t, *J* = 11.4 Hz, 1 H), 2.64 (m, 1 H), 2.43 (dd, *J* = 14.6, 3.4 Hz, 1 H), 2.37 (dd, *J* = 13.9, 6.0 Hz, 1 H), 2.31 (m, 1 H), 2.31 (br s, 1 H), 2.05 (m, 1 H), 2.04 (m, 1 H), 2.03 (m, 1 H), 2.01 (m, 1 H), 1.98 (m, 1 H), 1.96 (m, 1 H), 1.93 (m, 1 H), 1.79 (m, 1 H), 1.77 (m, 1 H), 1.77 (m, 1 H), 1.73 (m, 1 H), 1.73 (m, 1 H), 1.73 (m, 1 H), 1.63 (m, 1 H), 1.62 (m, 1 H), 1.60 (m, 1 H), 1.60 (m, 1 H), 1.60 (m, 1 H), 1.59 (m, 1 H), 1.58 (m, 1 H), 1.57 (m, 1 H), 1.54 (m, 1 H), 1.52 (m, 1 H), 1.45 (dt, *J* = 13.8, 11.7 Hz, 1 H), 1.33 (m, 1 H), 0.96 (d, *J* = 6.4 Hz, 3 H), 0.95 (d, *J* = 6.0 Hz, 3 H); ^{13}C NMR (125 MHz, CD_3CN) δ 147.5, 130.8 or 116.7 (one of these is an impurity), 124.1, 63.9, 61.3, 55.4, 55.4, 52.2, 50.4, 42.2, 41.1, 39.4, 34.8, 32.3, 31.9, 30.5, 29.1, 29.1, 27.1, 25.8, 25.1, 23.0, 21.8, 20.9, 19.7, 18.0, 17.9; HRMS (MALDI-FTMS) calcd for $C_{26}H_{41}N_2^+$ [M^+] 381.3270, found 381.3266.

Figure S1. Key selected NOESY and HMBC Correlations Confirming the Structure of **56**

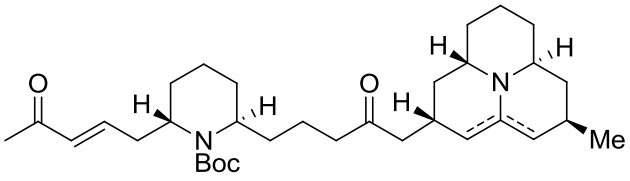




S-1 (2:1 dr)

Enone S-1. A portion of the cyclic carbamate-containing aldehyde (110 mg, 0.196 mmol, 1.0 equiv) prepared from alcohol **33** was dissolved in CH_3CN (0.8 mL) at 25 °C. 1-(Triphenylphosphoranylidene)-2-propanone (75 mg, 0.235 mmol, 1.2 equiv) was added in a single portion at 25 °C and the resultant yellow solution was heated to 80 °C. The reaction contents were stirred at 80 °C for 9 h over which time the color slowly changed from yellow to dark orange. Upon completion, the reaction contents were cooled to 25 °C and concentrated. The resultant crude orange oil was purified by preparative thin layer chromatography (silica gel, hexanes/acetone, 1/1) to give the desired enone **S-1** (70 mg, 59% yield, 2:1 dr from a previous step) as a pale yellow oil. These diastereomers were inseparable and were characterized together. **S-1**: R_f = 0.44 (silica gel, hexanes/EtOAc, 1/9); IR (film) ν_{max} 2935, 2872, 1713, 1681, 1432, 1365, 1272, 1169, 1102, 758, 731, 647; ^{1}H NMR (400 MHz, $CDCl_3$) δ (Major diastereomer, key peaks) 6.71

(dt, *J* = 16.0, 7.6 Hz, 1 H), 6.01 (d, *J* = 15.7 Hz, 1 H), 4.67 – 4.50 (m, 2 H), 3.85 – 3.75 (m, 1 H), 3.75 – 3.66 (m, 1 H), 3.60 – 3.48 (m, 1 H), 2.79 (dd, *J* = 16.6, 6.0 Hz, 1 H), 2.51 (dd, *J* = 16.7, 6.5 Hz, 1 H), 2.17 (s, 3 H), 2.06 (s, 3 H), 1.39 (s, 9 H), 0.91 (d, *J* = 6.5 Hz, 3 H); (Minor diastereomer, key peaks) 6.71 (dt, *J* = 16.0, 7.6 Hz, 1 H), 6.01 (d, *J* = 15.7 Hz, 1 H), 4.67 – 4.50 (m, 2 H), 3.85 – 3.75 (m, 1 H), 3.75 – 3.66 (m, 1 H), 3.60 – 3.48 (m, 1 H), 2.88 (dd, *J* = 17.0, 6.2 Hz, 1 H), 2.17 (s, 3 H), 2.06 (s, 3 H), 1.39 (s, 9 H), 0.95 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (2 diastereomers) 208.8, 2.08.4, 207.3, 207.0, 198.5, 155.2, 153.6, 153.2, 145.6, 132.7, 79.5, 70.8, 69.2, 51.8, 50.9, 49.2, 48.7, 48.3, 47.2, 46.7, 46.5, 43.5, 43.3, 37.9, 36.5, 35.9, 33.5, 33.5, 33.4, 32.9, 32.9, 30.6, 30.6, 29.0, 28.5, 28.2, 26.7, 25.3, 25.2, 24.3, 23.8, 23.7, 20.7, 20.7, 20.2, 20.1, 19.2, 18.3, 14.0, 14.0; HRMS (MALDI-FTMS) calcd for $C_{34}H_{55}N_2O_7^+$ [M^+] 603.4009, found 603.4014.



S-2 (1.3:1 enamine isomeric ratio)

Enone cascade product 57 and S-2. Ketone **S-1** (70 mg, 0.116 mmol, 1.0 equiv) was dissolved in toluene (2.09 mL) and *i*-PrOH (0.23 mL) at 25 °C. TMG (29 μL, 0.233 mmol, 2.0 equiv) was added in a single portion, and the resultant yellow solution was stirred at 25 °C for 6.5 h. Upon completion, the reaction contents were diluted with CH_2Cl_2 (30 mL). The crude reaction mixture was washed with 5% aqueous $NaHCO_3$ (5 × 40 mL), dried (Na_2SO_4), and concentrated. The resultant crude orange oil was purified by preparative thin layer chromatography (Et_3N pretreated silica gel, hexanes/EtOAc, 2/1) to give desired enone epimer **57** (17 mg, 27% yield, 5:1 ratio of enamine isomers) and

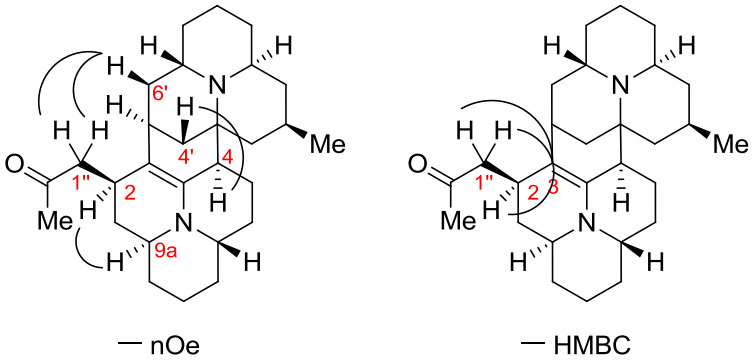
undesired enone epimer **S-2** (19 mg, 30% yield, 1.3:1 ratio of enamine isomers) as pale yellow oils. **57**: R_f = 0.55 (Et_3N pretreated silica gel, hexanes/EtOAc, 2/1); $[\alpha]_D^{20}$ = –137.5° (*c* = 0.85, $CHCl_3$); IR (film) ν_{max} 2929, 2867, 1678, 1453, 1365, 1329, 1253, 1172, 1116, 1024, 980; ^{1}H NMR (400 MHz, C_6D_6) δ (Major enamine isomer, key peaks) 6.65 (dt, *J* = 16.0, 7.2 Hz, 1 H), 6.05 (d, *J* = 16.0 Hz, 1 H), 4.88 (d, *J* = 4.4 Hz, 1 H), 3.84 – 3.74 (m, 2 H), 3.09 (dd, *J* = 12.7, 6.1 Hz, 1 H), 2.90 – 2.82 (m, 1 H), 2.66 – 2.56 (m, 1 H), 2.34 (br t, *J* = 10.8 Hz, 1 H), 2.28 (dd, *J* = 16.4, 6.9 Hz, 1 H), 1.96 (s, 3 H), 1.47 (s, 9 H), 0.84 (d, *J* = 6.4 Hz, 3 H); (Minor enamine isomer, key peaks) 6.65 (dt, *J* = 16.0, 7.2 Hz, 1 H), 6.05 (d, *J* = 16.0 Hz, 1 H), 4.63 (s, 1 H), 3.84 – 3.74 (m, 2 H), 3.11 (dd, obscured, 1 H), 2.66 – 2.56 (m, 1 H), 1.96 (s, 3 H), 1.47 (s, 9 H), 1.02 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, C_6D_6) δ (2 enamine isomers) 208.5, 208.3, 196.6, 155.3, 148.0, 14.6, 144.2, 133.1, 113.6, 107.0, 79.1, 56.1, 54.6, 52.3, 51.4, 50.1, 49.9, 44.7, 43.0, 42.9, 42.1, 38.5, 37.9, 34.0, 33.9, 33.7, 33.0, 32.0, 32.0, 31.2, 31.1, 29.8, 29.5, 28.5, 28.3, 28.0, 26.6, 25.2, 24.7, 22.5, 22.4, 21.4, 21.3, 20.4, 20.2, 15.1; HRMS (MALDI-FTMS) calcd for $C_{33}H_{53}N_2O_4^+$ [M^+] 541.4005, found 541.4017. **S-2**: R_f = 0.31 (Et_3N pretreated silica gel, hexanes/EtOAc, 2/1); $[\alpha]_D^{20}$ = –88.1° (*c* = 0.95, $CHCl_3$); IR (film) ν_{max} 2929, 2867, 1679, 1453, 1365, 1330, 1253, 1172, 1117, 980; ^{1}H NMR (400 MHz, C_6D_6) δ (Major enamine isomer, key peaks) 6.70 – 6.59 (m 1 H), 6.05 (d, *J* = 16.0 Hz, 1 H), 4.67 (s, 1 H), 3.85 – 3.70 (m, 2 H), 3.21 – 3.11 (m, 1 H), 2.92 – 2.82 (m, 1 H), 2.65 – 2.55 (m, 1 H), 1.96 (s, 3 H), 1.47 (s, 9 H), 0.84 (d, *J* = 6.4 Hz, 3 H); (Minor enamine isomer, key peaks) 6.70 – 6.59 (m 1 H), 6.05 (d, *J* = 16.0 Hz, 1 H), 4.73 (s, 1 H), 3.85 – 3.70 (m, 2 H), 3.21 – 3.11 (m, 1 H), 2.65 – 2.55 (m, 1 H), 1.96 (s, 3 H), 1.47 (s, 9 H), 1.02 (d, *J* = 6.48 Hz, 3 H); ^{13}C NMR (100 MHz, C_6D_6) δ (2 enamine isomers) 208.4, 208.1, 196.5, 155.3, 148.2,

146.4, 144.6, 133.1, 111.7, 108.0, 79.1, 56.8, 56.5, 54.7, 54.4, 52.3, 51.4, 40.0, 49.8, 43.0, 42.9, 42.8, 42.0, 40.9, 40.0, 37.9, 34.0, 33.9, 33.8, 33.7, 33.1, 32.0, 31.8, 31.3, 31.2, 29.4, 28.6, 26.7, 25.2, 24.7, 22.3, 22.1, 21.4, 21.3, 20.3, 20.2, 15.1; HRMS (MALDI-FTMS) calcd for $C_{33}H_{53}N_2O_4^+$ [M^+] 541.4005, found 541.4010.

Ketone heptacycle 59. A portion of enone **57** (15 mg, 0.0278 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (0.4 mL) to give a dark yellow solution and cooled to 0 °C. TFA (0.4 mL) was cooled to 0 °C and added to the solution of starting material in a single portion at 0 °C. The resulting pale yellow solution was stirred at 0 °C for 1 h. Upon completion, the reaction contents were diluted with CH_2Cl_2 (5 mL) and made basic in three equal portions by vigorous washing with ice cold 1 M aqueous NaOH (20 mL). The resulting aqueous layer was extracted with CH_2Cl_2 (5 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The resultant crude yellow oil was immediately dissolved in *i*-PrOH (0.55 mL) at 25 °C and TMG (7 μL, 0.0556, 2.0 equiv) was added in a single portion. The resultant dark yellow solution was stirred at 25 °C for 1 h. Upon completion, the reaction contents were diluted with CH_2Cl_2 (10 mL). The crude reaction mixture was washed with 5% aqueous $NaHCO_3$ (5 × 5 mL), dried (Na_2SO_4), and concentrated to give the desired product as a crude yellow oil. This material was immediately dissolved in *i*-PrOH (1.0 mL) and warmed to 60 °C. The reaction was stirred at 60 °C for 2.5 h. Upon completion, the reaction contents were cooled to 25 °C and concentrated. The resultant crude brown oil was purified by preparative thin layer chromatography (Et_3N pretreated silica gel, hexanes/EtOAc, 19/1) to give ketone heptacycle **59** (4.5 mg, 38% yield) as a yellow oil. **59**: R_f = 0.52 (Et_3N pretreated silica gel, hexanes/EtOAc, 19/1); $[\alpha]_D^{20}$ = –163.5° (*c* = 0.25, $CHCl_3$); IR (film)

ν_{max} 2926, 2864, 1715, 1641, 1444, 1353, 1264, 1067, 754; ^{1}H NMR (400 MHz, C_6D_6) δ 3.42 (br d, *J* = 12.4, Hz, 1 H), 3.18 – 3.11 (m, 1 H), 2.87 – 2.77 (m, 1 H), 2.65 (br t, *J* = 11.1, Hz, 1 H), 2.52 (dd, *J* = 15.0, 3.7 Hz, 1 H), 1.40 (p, *J* = 3.4 Hz, 1 H), 2.25 (br t, *J* = 10.4 Hz, 1 H), 2.10 (dd, *J* = 12.1, 3.3 Hz, 1 H), 2.11 – 2.06 (m, 1 H), 2.07 – 2.00 (m, 1 H), 1.95 (dd, *J* = 15.0, 11.1 Hz, 1 H), 1.87 (td, *J* = 12.4, 3.7 Hz, 1 H), 1.85 – 1.79 (m, 1 H), 1.78 (s, 3 H), 1.75 – 1.22 (m, 17 H), 1.21 – 1.05 (m, 3 H), 0.99 – 0.92 (m, 1 H), 0.82 (q, *J* = 12.0 Hz, 1 H), 0.81 (d, *J* = 6.4 Hz, 3 H), 0.58 (br d, *J* = 12.8 Hz, 1 H); ^{13}C NMR (100 MHz, C_6D_6) δ 206.5, 147.0, 116.2, 56.7, 56.2, 54.0, 50.9, 49.3, 48.6, 48.4, 47.5, 43.8, 37.9, 35.9, 35.7, 34.4, 34.0, 31.9, 31.6, 31.3, 30.6, 30.0, 27.1, 26.4, 24.4, 22.8, 20.9, 19.9; HRMS (MALDI-FTMS) calcd for $C_{28}H_{43}N_2O^+$ [M^+] 423.3375, found 423.3378.

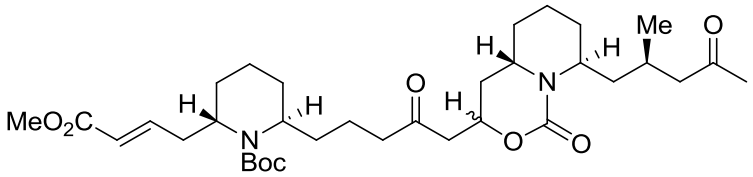
Figure S2. NOESY and HMBC Correlations Confirming the Structure of **59**



Heptacycle 68. A portion of the cyclic carbamate-containing aldehyde (105 mg, 0.187 mmol, 1.0 equiv) was dissolved in CD_3CN (0.3 mL) at 25 °C. (Triphenylphosphoranylidene)acetaldehyde (85 mg, 0.280 mmol, 1.5 equiv) was added to the reaction mixture at 25 °C and the resultant orange solution was warmed to 80 °C. The reaction mixture was kept at 80 °C for 6 h. Upon completion, the reaction contents were cooled to room temperature and concentrated. The resultant brown oil was purified by preparative thin layer chromatography (silica gel, CH_2Cl_2/acetone, 3/1) to give the

desired product (24 mg, 22% yield) and the starting aldehyde (46 mg, 44% yield) as an inseparable mixture. This reaction was repeated several times to obtain larger amounts of material. A portion of this mixture (78 mg, 0.137 mmol, 1.0 equiv, 2:1 mixture of enal to aldehyde) was dissolved in toluene (2.43 mL) and *i*-PrOH (0.27 mL) at 25 °C, and TMG (34 μL, 0.273 mmol, 2.0 equiv) was added in a single portion. The resultant yellow solution was stirred at 25 °C for 6 h. Upon completion, the reaction contents were diluted with CH_2Cl_2 (20 mL). The crude reaction mixture was washed with 5% aqueous $NaHCO_3$ (5 × 40 mL), dried (Na_2SO_4), and concentrated to give the desired product (30 mg, 65% yield, 1:1.2 dr) and cyclized aldehyde starting material contaminant. These materials were carried forward as a mixture without additional purification. This material was dissolved in CH_2Cl_2 (0.5 mL) to give a dark yellow solution and cooled to 0 °C. TFA (0.5 mL) was cooled to 0 °C and added to the solution of starting material in a single portion at 0 °C. The resulting pale yellow solution was stirred at 0 °C for 1 h. Upon completion, the reaction contents were diluted with CH_2Cl_2 (5 mL) and made basic in three equal portions by vigorous washing with ice cold 1 M aqueous NaOH (20 mL). The resulting aqueous layer was extracted with CH_2Cl_2 (5 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The resultant crude yellow oil was immediately dissolved in C_6D_6 (1.0 mL) and warmed to 80 °C. The reaction was kept at 80 °C for 2.5 h. Upon completion, the reaction contents were cooled to 25 °C and concentrated. The resultant crude brown oil was purified by preparative thin layer chromatography (Et_3N pretreated silica gel, hexanes/EtOAc, 9/1) to give unique hexacycle **68** as a yellow oil in 1.2:1 dr. **68**: ^{1}H NMR (400 MHz, C_6D_6) δ (Major diastereomer, key peaks) 6.68 (d, *J* = 10.0 Hz, 1 H), 5.38 (dd, *J* = 10.0, 2.0 Hz, 1 H), 4.93 (s, 1 H), 0.86 (d, *J* = 6.0 Hz, 3 H);

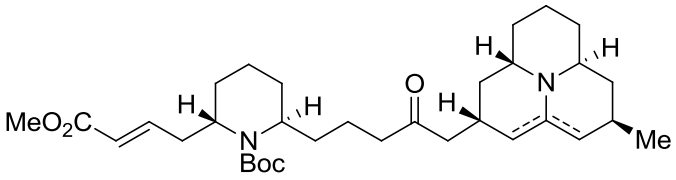
(Minor diastereomer, key peaks) 6.64 (dd, *J* = 10.4, 2.0 Hz, 1 H), 5.54 (dd, *J* = 9.6, 4.8 Hz, 1 H), 4.73 (d, *J* = 3.6 Hz, 1 H), 0.82 (d, *J* = 6.0 Hz, 3 H).



S-3 (2:1 dr)

Enoate S-3. A portion of the cyclic carbamate-containing aldehyde (110 mg, 0.196 mmol, 1.0 equiv) was combined neat with methyl (triphenylphosphoranylidene)acetate (78 mg, 0.235 mmol, 1.2 equiv) at 25 °C. CH_2Cl_2 (1.0 mL) was added to the reaction mixture and stirred open to air at 25 °C for 9 h to allow the CH_2Cl_2 to evaporate slowly so that the solution could concentrate into a uniform, yellow oil. Upon completion, the resultant crude yellow oil was purified by preparative thin layer chromatography (silica gel, hexanes/acetone, 1/1) to give the desired enoate **S-3** (88 mg, 73% yield, 2:1 dr from a previous step) as a pale yellow oil. These diastereomers were inseparable and were characterized together. **S-3**: R_f = 0.56 (silica gel, hexanes/EtOAc, 1/9); IR (film) ν_{max} 2934, 2872, 1676, 1429, 1392, 1364, 1254, 1170, 1104, 981, 758, 647; ^{1}H NMR (400 MHz, $CDCl_3$) δ (Major diastereomer, key peaks) 6.90 (ddd, *J* = 15.3, 8.3, 6.7 Hz, 1 H), 5.84 (d, *J* = 15.5 Hz, 1 H), 4.75 – 4.57 (m, 2 H), 3.88 – 3.72 (m, 2 H), 3.71 (s, 3 H), 3.65 – 3.54 (m, 1 H), 2.86 (dd, *J* = 16.7, 5.9 Hz, 1 H), 2.56 (dd, *J* = 16.7, 6.6 Hz, 1 H), 2.11 (s, 3 H), 1.45 (s, 9 H), 0.96 (d, *J* = 6.6 Hz, 3 H); (Minor diastereomer, key peaks) 6.90 (ddd, *J* = 15.3, 8.3, 6.7 Hz, 1 H), 5.84 (d, *J* = 15.5 Hz, 1 H), 4.75 – 4.57 (m, 2 H), 3.88 – 3.72 (m, 2 H), 3.71 (s, 3 H), 3.65 – 3.54 (m, 1 H), 2.94 (dd, *J* = 17.1, 6.0 Hz, 1 H), 2.11 (s, 3 H), 1.45 (s, 9 H), 1.01 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (2 diastereomers) 208.7, 208.4, 207.4, 207.1, 166.8,

155.1, 153.6, 153.2, 146.5, 122.5, 79.4, 79.4, 70.7, 69.2, 51.6, 51.4, 50.9, 50.8, 49.2, 48.7, 48.3, 47.2, 46.7, 46.5, 43.5, 43.3, 37.5, 37.1, 36.5, 35.9, 33.5, 33.5, 33.4, 32.9, 32.8, 30.6, 30.5, 29.0, 28.5, 24.2, 23.9, 23.6, 20.7, 20.2, 20.1, 18.3, 13.8; HRMS (MALDI-FTMS) calcd for $C_{34}H_{55}N_2O_8^+$ [M^+] 619.3958, found 619.3978.



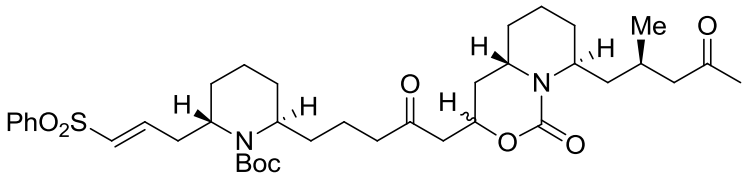
S-4 (1.3:1 enamine isomeric ratio)

Enoate cascade product 61 and S-4. Enoate **S-3** (88 mg, 0.142 mmol, 1.0 equiv) was dissolved in toluene (2.56 mL) and *i*-PrOH (0.28 mL) at 25 °C. TMG (36 μL, 0.285 mmol, 2.0 equiv) was added in a single portion, and the resultant yellow solution was stirred at 25 °C for 6.5 h. Upon completion, the reaction contents were diluted with CH_2Cl_2 (20 mL). The crude reaction mixture was washed with 5% aqueous $NaHCO_3$ (5 × 40 mL), dried (Na_2SO_4), and concentrated. The resultant crude yellow oil was purified by preparative thin layer chromatography (Et_3N pretreated silica gel, hexanes/EtOAc, 4/1) to give desired enone epimer **61** (18 mg, 23% yield, 5:1 ratio of enamine isomers) and undesired ketone epimer **S-4** (23 mg, 29% yield, 1.3:1 ratio of enamine isomers) as pale yellow oils. **61**: R_f = 0.73 (Et_3N pretreated silica gel, hexanes/EtOAc, 2/1); $[\alpha]_D^{20}$ = –155.5° (*c* = 0.90, $CHCl_3$); IR (film) ν_{max} 2929, 2868, 1722, 1685, 1656, 1438, 1366, 1325, 1272, 1173, 1117, 1036, 984, 772; ^{1}H NMR (400 MHz, C_6D_6) δ (Major enamine isomer, key peaks) 7.10 (dt, *J* = 15.4, 7.6 Hz, 1 H), 5.94 (d, *J* = 15.6 Hz, 1 H), 4.88 (d, *J* = 4.4 Hz, 1 H), 3.88 – 3.71 (m, 2 H), 3.44 (s, 3 H), 3.07 (dd, *J* = 12.8, 6.0 Hz, 1 H), 2.85 (q, *J* = 6.4 Hz, 1 H), 2.62 – 2.54 (m, 1 H), 2.35 (br t, *J* = 10.5 Hz, 1 H), 2.28 (dd, *J* = 16.4, 6.8 Hz, 1 H), 1.47 (s, 9 H), 0.84 (d, *J* = 6.4 Hz, 3 H); (Minor enamine isomer, key peaks)

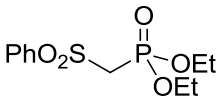
7.10 (dt, *J* = 15.4, 7.6 Hz, 1 H), 5.94 (d, *J* = 15.6 Hz, 1 H), 4.63 (s, 1 H), 3.88 – 3.71 (m, 2 H), 3.44 (s, 3 H), 3.15 – 3.08 (m, 1 H), 2.62 – 2.54 (m, 1 H), 1.47 (s, 9 H), 1.02 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, C_6D_6) δ (2 enamine isomers) 208.5, 208.3, 166.4, 155.1, 147.9, 146.8, 144.2, 123.0, 113.6, 107.1, 79.1, 56.1, 54.7, 52.2, 52.1, 51.3, 51.0, 50.1, 49.8, 44.7, 43.0, 43.0, 42.1, 38.6, 37.9, 37.7, 34.0, 33.9, 33.8, 33.0, 32.1, 32.0, 31.2, 31.2, 29.8, 29.5, 28.6, 28.0, 24.9, 24.4, 22.5, 22.4, 21.4, 21.4, 20.4, 20.2, 14.8; HRMS (MALDI-FTMS) calcd for $C_{33}H_{53}N_2O_5^+$ [M^+] 557.3954, found 557.3965. **S-4**: R_f = 0.52 (Et_3N pretreated silica gel, hexanes/EtOAc, 2/1); $[\alpha]_D^{20}$ = –91.9° (*c* = 1.15, $CHCl_3$); IR (film) ν_{max} 2929, 2867, 1721, 1685, 1656, 1438, 1366, 1327, 1272, 1171, 1116, 868, 771; ^{1}H NMR (400 MHz, C_6D_6) δ (Major enamine isomer, key peaks) 7.14 – 7.04 (m, 1 H), 5.93 (d, *J* = 15.6 Hz, 1 H), 4.67 (s, 1 H), 3.87 – 3.71 (m, 2 H), 3.44 (s, 3 H), 3.21 – 3.12 (m, 1 H), 2.92 – 2.82 (m, 1 H), 2.63 – 2.53 (m 1 H), 1.47 (s, 9 H), 0.84 (d, *J* = 6.4 Hz, 3 H); (Minor enamine isomer, key peaks) 7.14 – 7.04 (m, 1 H), 5.93 (d, *J* = 15.6 Hz, 1 H), 4.73 (s, 1 H), 3.87 – 3.71 (m, 2 H), 3.44 (s, 3 H), 3.21 – 3.12 (m, 1 H), 2.63 – 2.53 (m 1 H), 1.46 (s, 9 H), 1.02 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (100 MHz, C_6D_6) δ (2 enamine isomers) 208.4, 208.1, 166.4, 155.2, 148.2, 146.8, 146.5, 123.0, 111.6, 108.1, 79.1, 56.8, 56.5, 54.7, 54.4, 52.1, 51.4, 51.0, 49.9, 49.7, 43.0, 42.9, 42.8, 42.0, 40.9, 40.0, 37.7, 34.0, 33.8, 33.8, 33.7, 33.1, 33.1, 32.0, 31.9, 31.3, 31.2, 39.4, 38.6, 24.9, 24.4, 22.3, 22.1, 21.4, 21.3, 20.3, 20.2 14.8; HRMS (MALDI-FTMS) calcd for $C_{33}H_{53}N_2O_5^+$ [M^+] 557.3954, found 557.3965.

Enoate hexacycle 64. Enoate **62** (17 mg, 0.0306 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (0.4 mL) to give a dark yellow solution and cooled to 0 °C. TFA (0.4 mL) was cooled to 0 °C and added to the solution of starting material in a single portion at 0 °C.

The resulting pale yellow solution was stirred at 0 °C for 1 h. Upon completion, the reaction contents were diluted with CH_2Cl_2 (5 mL) and made basic in three equal portions by vigorous washing with ice cold 1 M aqueous NaOH (20 mL). The resulting aqueous layer was extracted with CH_2Cl_2 (5 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The resultant crude yellow oil was immediately dissolved in *i*-PrOH (1.0 mL) and warmed to 80 °C. The reaction was stirred at 80 °C for 2 h. Upon completion, the reaction contents were cooled to 25 °C and concentrated. The resultant crude brown oil was purified by preparative thin layer chromatography (Et_3N pretreated silica gel, hexanes/EtOAc, 3/1) to give enoate hexacycle **64** (7.5 mg, 56% yield) as a yellow oil. **64**: R_f = 0.48 (Et_3N pretreated silica gel, hexanes/EtOAc, 4/1); $[\alpha]_D^{20}$ = –4.6° (*c* = 0.43, $CHCl_3$); IR (film) ν_{max} 2926, 2847, 1726, 1656, 1631, 1437, 1268, 1181, 1139, 1082, 1054, 1012, 757; ^{1}H NMR (400 MHz, C_6D_6) δ 7.07 (dt, *J* = 15.2, 7.4 Hz, 1 H), 5.92 (dt, *J* = 15.6, 1.5 Hz, 1 H), 3.65 (br d, *J* = 13.6 Hz, 1 H), 3.50 (q, *J* = 6.0 Hz, 1 H), 3.41 (s, 3 H), 2.98 (br d, *J* = 12.0 Hz, 1 H), 2.70 (br t, *J* = 11.2 Hz, 1 H), 2.40 – 2.03 (m, 7 H), 1.98 (td, *J* = 13.4, 4.9 Hz, 1 H), 1.80 – 1.20 (m, 17 H), 1.07 (br d, *J* = 12.8 Hz, 1 H), 0.98 – 0.80 (m, 3 H), 0.92 (d, *J* = 5.9 Hz, 3 H), 0.77 (br d, *J* = 13.6 Hz, 1 H); ^{13}C NMR (100 MHz, C_6D_6) δ 166.5, 147.6, 138.0, 122.5, 108.5, 57.0, 51.5, 50.9, 49.8, 48.7, 47.9, 44.3 (2C by HSQC), 35.7, 35.4, 33.6, 31.8, 30.2, 28.8, 28.2, 28.1, 27.0, 26.3 (2C by HSQC), 23.2, 20.4, 20.0, 18.0; HRMS (MALDI-FTMS) calcd for $C_{28}H_{43}N_2O_2^+$ [M^+] 439.3325, found 439.3338.



S-5 (2:1 dr)



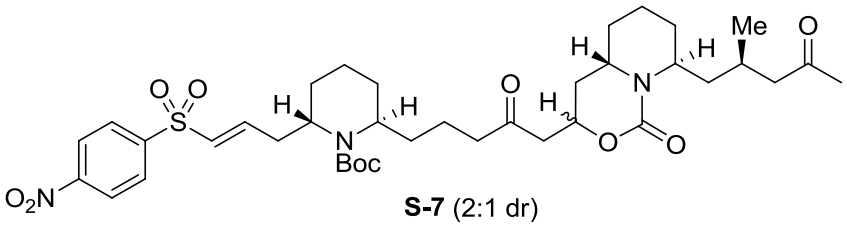
S-6

Phenyl sulfone S-5. Phosphonate **S-6** (46 mg, 0.158 mmol, 1.0 equiv) and LiCl (13.4 mg, 0.317 mmol, 2.0 equiv) were suspended in CH_3CN (1.05 mL) at 25 °C to make a clear suspension. DIPEA (0.055 mL, 0.317 mmol, 2.0 equiv) was added to this suspension in a single portion at 25 °C. The resultant clear suspension was stirred at 25 °C for 30 min. A portion of the crude aldehyde prepared from **33** (89 mg, 0.158 mmol, 1.0 equiv) was dissolved in CH_3CN (0.5 mL + 0.5 mL rinse) and added to the stirring solution at 25 °C. The resultant pale yellow solution was stirred at 25 °C for 3 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (5 mL), water (5 mL), and CH_2Cl_2 (10 mL). The crude reaction mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4), and concentrated. The resultant crude yellow oil was purified by preparative thin layer chromatography (silica gel, CH_2Cl_2/Et_2O, 1/1) to give phenyl sulfone **S-5** (79 mg, 71% yield, 2:1 dr from a previous step) as a white foam. These diastereomers were inseparable and were characterized together. **S-5:** R_f = 0.30 (silica gel, hexanes/EtOAc, 1/2); IR (film) ν_{max} 2934, 2872, 1710, 1679, 1430, 1366, 1292, 1146, 1087, 755, 597; ^{1}H NMR (400 MHz, $CDCl_3$) δ (Major diastereomer, key peaks) 7.84 (d, *J* = 7.2 Hz, 2 H), 7.58 (br t, *J* = 7.2 Hz, 1 H), 7.50 (br t, *J* = 8.0 Hz, 2 H), 6.91 (dt, *J* = 14.8, 7.6 Hz, 1 H), 6.36 (d, *J* =

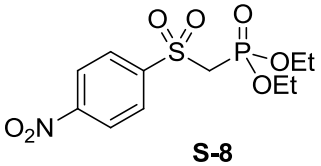
15.2 Hz, 1 H), 4.75 – 4.55 (m, 2 H), 3.81 – 3.71 (m, 2 H), 3.63 – 3.53 (m, 1 H), 2.84 (dd, *J* = 16.7, 6.1 Hz, 1 H), 2.74 (dt, *J* = 12.8, 5.9 Hz, 1 H), 2.55 (dd, *J* = 16.6, 6.4 Hz, 1 H), 2.47 (t, *J* = 6.8 Hz, 2 H), 2.19 (ddd, *J* = 13.6, 5.6, 1.9 Hz, 1 H), 2.10 (s, 3 H), 1.40 (s, 9 H), 0.95 (d, *J* = 6.5 Hz, 3 H); (Minor diastereomer, key peaks) 7.84 (d, *J* = 7.2 Hz, 2 H), 7.58 (br t, *J* = 7.2 Hz, 1 H), 7.50 (br t, *J* = 8.0 Hz, 2 H), 6.91 (dt, *J* = 14.8, 7.6 Hz, 1 H), 6.36 (d, *J* = 15.2 Hz, 1 H), 4.75 – 4.55 (m, 2 H), 3.81 – 3.71 (m, 2 H), 3.63 – 3.53 (m, 1 H), 2.92 (dd, *J* = 17.0, 6.2 Hz, 1 H), 2.74 (dt, *J* = 12.8, 5.9 Hz, 1 H), 2.67 (dd, *J* = 17.0, 6.8 Hz, 1 H), 2.47 (t, *J* = 6.8 Hz, 2 H), 2.10 (s, 3 H), 1.40 (s, 9 H), 0.99 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (2 diastereomers) 208.9, 208.6, 207.4, 207.1, 155.3, 153.7, 153.3, 144.3, 140.7, 133.4, 132.0, 129.3, 127.7, 79.8, 77.4, 70.9, 69.3, 52.2, 51.1, 50.9, 49.3, 48.9, 48.4, 47.3, 46.8, 46.7, 43.6, 43.3, 37.2, 26.6, 36.4, 36.0, 33.6, 33.2, 33.1, 33.0, 33.0, 30.7, 29.1, 28.6, 25.5, 25.3, 24.9, 24.4, 20.8, 20.7, 20.3, 20.2, 19.3, 18.4, 14.8, 14.3; HRMS (MALDI-FTMS) calcd for $C_{38}H_{57}N_2O_8S^+$ [M^+] 701.3836, found 701.3857.

Phenyl sulfone cascade product 62. Sulfone **S-5** (79 mg, 0.113 mmol, 1.0 equiv) was dissolved in toluene (2.10 mL) and *i*-PrOH (0.21 mL) at 25 °C. TMG (28.0 μL, 0.226 mmol, 2.0 equiv) in was added in a single portion to the reaction mixture and the resultant pale yellow solution was stirred at 25 °C for 7 h. Upon completion, the reaction contents were diluted with CH_2Cl_2 (20 mL). The crude reaction mixture was washed with 5% aqueous $NaHCO_3$ (5 × 40 mL), dried (Na_2SO_4), and concentrated to give the desired product (72 mg, 100% crude recovery, 1:1.2 dr, major diastereomer is a 1.3:1 mixture of enamine isomers, minor diastereomer is a 5:1 mixture of enamine isomers) as a brown foam. This material was unstable to purification and was characterized crude. **62:** IR (film) ν_{max} 2930, 2868, 1682, 1447, 1391, 1366, 1319, 1169, 1146, 1086, 757, 597; ^{1}H

NMR (400 MHz, C_6D_6) δ (Major diastereomer, major enamine isomer, key peaks) 7.95 – 7.87 (m, 2 H), 7.15 – 6.95 (m, 1 H), 7.00 – 6.91 (m, 3 H), 6.21 (d, *J* = 14.8 Hz, 1 H), 4.72 (s, 1 H), 3.85 – 3.75 (m, 1 H), 3.61 – 3.50 (m, 1 H); (Major diastereomer, minor enamine isomer, key peaks) 7.95 – 7.87 (m, 2 H), 7.15 – 6.95 (m, 1 H), 7.00 – 6.91 (m, 3 H), 6.21 (d, *J* = 14.8 Hz, 1 H), 4.76 (s, 1 H), 3.85 – 3.75 (m, 1 H), 3.61 – 3.50 (m, 1 H); (Minor diastereomer, major enamine isomer, key peaks) 7.95 – 7.87 (m, 2 H), 7.15 – 6.95 (m, 1 H), 7.00 – 6.91 (m, 3 H), 6.21 (d, *J* = 14.8 Hz, 1 H), 4.92 (d, *J* = 4.4 Hz, 1 H), 3.85 – 3.75 (m, 1 H), 3.61 – 3.50 (m, 1 H); (Minor diastereomer, minor enamine isomer, key peaks) 7.95 – 7.87 (m, 2 H), 7.15 – 6.95 (m, 1 H), 7.00 – 6.91 (m, 3 H), 6.21 (d, *J* = 14.8 Hz, 1 H), 4.65 (s, 1 H), 3.85 – 3.75 (m, 1 H), 3.61 – 3.50 (m, 1 H); ^{13}C NMR (100 MHz, C_6D_6) δ (2 diastereomers, each diastereomer has 2 enamine isomers) 208.8, 208.6, 208.5, 208.3, 155.3, 148.2, 147.9, 146.5, 144.2, 142.1, 132.8, 132.8, 129.2, 128.3, 128.1, 128.0, 127.9, 127.8, 113.6, 111.6, 108.1, 107.0, 79.3, 56.7, 56.4, 56.1, 54.7, 54.7, 54.4, 52.7, 52.7, 52.2, 51.2, 50.1, 49.9, 49.9, 49.8, 44.7, 43.0, 43.0, 42.9, 42.7, 42.1, 42.0, 40.8, 40.0, 38.5, 37.9, 36.4, 34.0, 34.0, 33.9, 33.1, 33.0, 33.0, 32.0, 32.0, 31.8, 31.3, 31.2, 30.2, 29.8, 29.5, 29.4, 28.6, 28.5, 28.3, 28.0, 26.0, 25.4, 22.5, 22.4, 22.4, 22.1, 21.3, 21.2, 20.4, 20.3, 20.2, 20.2, 16.0; HRMS (MALDI-FTMS) calcd for $C_{38}H_{55}N_2O_5S^+$ [M^+] 639.3832, found 639.3844.



S-7 (2:1 dr)



S-8

***para*-Nitrophenyl sulfone S-7.** Phosphonate **S-8** (53 mg, 0.158 mmol, 1.0 equiv) and LiCl (13.4 mg, 0.317 mmol, 2.0 equiv) were suspended in CH_3CN (1.05 mL) at 25 °C to make a pale yellow suspension. DIPEA (0.055 mL, 0.317 mmol, 2.0 equiv) was added to this suspension in a single portion at 25 °C. The resultant bright orange suspension was stirred at 25 °C for 30 min. A portion of the crude aldehyde prepared from **33** (89 mg, 0.158 mmol, 1.0 equiv) was dissolved in CH_3CN (0.5 mL + 0.5 mL rinse) and added to the stirring solution at 25 °C. The resultant pale yellow solution was stirred at 25 °C for 3 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (5 mL), water (5 mL), and CH_2Cl_2 (10 mL). The crude reaction mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The resultant crude yellow oil was purified by preparative thin layer chromatography (silica gel, CH_2Cl_2/Et_2O, 1/1) to give *para*-nitrophenyl sulfone **S-7** (79 mg, 67% yield over 2 steps, 2:1 dr from a previous step) as a white foam. These diastereomers were inseparable and were characterized together. **S-7**: R_f = 0.53 (silica gel, hexanes/EtOAc, 1/2); IR (film) ν_{max} 2933, 2872, 1709, 1678, 1607, 1531, 1432, 1349, 1328, 1147, 1085, 754; ^{1}H NMR (400 MHz, $CDCl_3$) δ (Major diastereomer, key peaks) 8.37 (d, *J* = 8.7 Hz, 2 H), 8.07 (d, *J* = 8.7 Hz, 2 H), 7.07

(dt, *J* = 14.8, 9.2 Hz, 1 H), 6.41 (d, *J* = 15.2 Hz, 1 H), 4.75 – 4.59 (m, 2 H), 3.85 – 3.75 (m, 2 H), 3.66 – 3.56 (m, 1 H), 2.86 (dd, *J* = 16.5, 6.2 Hz, 1 H), 2.57 (dd, *J* = 16.5, 6.2 Hz, 1 H), 2.21 (ddd, *J* = 13.5, 5.6, 1.8 Hz, 1 H), 2.12 (s, 3 H), 1.42 (s, 9 H), 0.97 (d, *J* = 6.6 Hz, 3 H); (Minor diastereomer, key peaks) 8.37 (d, *J* = 8.7 Hz, 2 H), 8.07 (d, *J* = 8.7 Hz, 2 H), 7.07 (dt, *J* = 14.8, 9.2 Hz, 1 H), 6.41 (d, *J* = 15.2 Hz, 1 H), 4.75 – 4.59 (m, 2 H), 3.85 – 3.75 (m, 2 H), 3.66 – 3.56 (m, 1 H), 2.97 (dd, *J* = 16.8, 6.4 Hz, 1 H), 2.68 (dd, *J* = 16.9, 6.6 Hz, 1 H), 2.12 (s, 3 H), 1.42 (s, 9 H), 1.01 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (2 diastereomers) 209.0, 208.7, 207.5, 207.2, 155.4, 143.7, 143.3, 150.7, 147.6, 146.6, 130.6, 129.2, 124.6, 80.0, 77.4, 71.0, 69.4, 52.6, 51.1, 51.0, 50.9, 49.4, 48.9, 48.5, 47.4, 47.0, 46.8, 43.7, 43.4, 37.2, 26.8, 26.7, 36.1, 33.7, 33.1, 33.0, 32.9, 30.8, 30.7, 29.8, 29.2, 25.6, 25.5, 25.3, 24.8, 20.8, 20.7, 20.3, 20.2, 19.3, 18.4, 14.8, 14.8; HRMS (MALDI-FTMS) calcd for $C_{38}H_{56}N_3O_{10}S^+$ [M^+] 746.3686, found 746.3723.

***para*-Nitrophenyl sulfone cascade product 58.** Sulfone **S-7** (79 mg, 0.106 mmol, 1.0 equiv) was dissolved in toluene (1.91 mL) and *i*-PrOH (0.21 mL) at 25 °C. TMG (26.5 μL, 0.212 mmol, 2.0 equiv) in was added in a single portion to the reaction mixture and the resultant bright yellow solution was stirred at 25 °C for 7 h. Upon completion, the reaction contents were diluted with CH_2Cl_2 (20 mL). The crude reaction mixture was washed with 5% aqueous $NaHCO_3$ (5 × 40 mL), dried (Na_2SO_4), and concentrated to give the desired product (68 mg, 94% crude recovery, 1:1.2 dr by crude NMR integration) as a brown foam. This material was unstable and had to be carried forward immediately.

***para*-Nitrophenyl sulfonyl heptacycle 60.** Pressing forward without additional purification, the crude product of the first cascade (41 mg containing 18.5 mg of desired

epimer, 0.0272 mmol of desired epimer, 1.0 equiv) was dissolved in CH_2Cl_2 (0.5 mL) to give a dark yellow solution and cooled to 0 °C. TFA (0.5 mL) was cooled to 0 °C and added to the solution of starting material in a single portion at 0 °C. The resulting pale yellow solution was stirred at 0 °C for 1 h. Upon completion, the reaction contents were diluted with CH_2Cl_2 (5 mL) and made basic in three equal portions by vigorous washing with ice cold 1 M aqueous NaOH (20 mL). The resulting aqueous layer was extracted with CH_2Cl_2 (5 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The resultant crude yellow oil was immediately dissolved in C_6D_6 (1.0 mL) and warmed to 80 °C. The reaction was stirred at 80 °C for 45 min. Upon completion, the reaction contents were concentrated. The resultant crude brown oil was purified by preparative thin layer chromatography (Et_3N pretreated silica gel, hexanes/EtOAc, 4/1) to give heptacycle **60** (4 mg, 26% yield based on the desired epimer) as a yellow oil. **60**: R_f = 0.63 (Et_3N pretreated silica gel, hexanes/EtOAc, 4/1); $[\alpha]_D^{20}$ = –26.1° (*c* = 0.25, $CHCl_3$); IR (film) ν_{max} 2927, 2864, 1683, 1638, 1607, 1531, 1445, 1348, 1304, 1151, 1086, 855, 737, 608; ^{1}H NMR (400 MHz, C_6D_6) δ 7.55 (d, *J* = 8.9 Hz, 2 H), 7.51 (d, *J* = 8.9 Hz, 2 H), 3.46 (dd, *J* = 13.2, 2.5 Hz, 1 H), 3.30 (br d, *J* = 12.8 Hz, 1 H), 3.09 (dd, *J* = 12.1, 5.9 Hz, 1 H), 3.09 – 3.00 (m, 1 H), 2.79 (dd, *J* = 13.3, 11.7 Hz, 1 H), 2.51 (br t, *J* = 11.6 Hz, 1 H), 2.28 (br s , 1 H), 2.30 – 2.23 (m, 1 H), 2.16 (dd, *J* = 12.0, 6.0 Hz, 1 H), 2.03 (br d, *J* = 12.4 Hz, 1 H), 2.03 – 1.97 (m, 1 H), 1.83 (dt, *J* = 12.7, 3.5 Hz, 1 H), 1.77 – 0.70 (m, 23 H), 0.77 (d, *J* = 6.3 Hz, 3 H), 0.34 (br d, *J* = 12.9 Hz, 1 H); ^{13}C NMR (100 MHz, C_6D_6) δ 150.5, 149.2, 146.2, 128.8, 124.4, 112.8, 60.7, 57.8, 56.9, 56.0, 53.6, 51.0, 49.2, 48.4, 47.2, 43.5, 37.0, 35.6, 35.5, 34.2, 33.9, 31.7, 31.4, 31.1, 30.6, 27.0, 24.3, 22.6,

20.8, 19.8; HRMS (MALDI-FTMS) calcd for $C_{32}H_{44}N_3O_4S^+$ [M^+] 566.3053, found 566.3064.

Table S1. NMR Spectral Data Comparison of Natural and Synthetic Psylloborine A (**1**); Coupling Constant (*J*) in Hz

^{1}H (C_6D_6)		^{13}C (CD_2Cl_2)	
Natural Psylloborine A	**Synthetic Psylloborine A**	**Natural Psylloborine A**	**Synthetic Psylloborine A**
3.49 (*J* = 12.4, 6.8, 2.4, 1.5)	3.49 (br d, *J* = 12.4)	144.9	145.0
3.21 (*J* = 11.5, 6.0, 1.7, 1.3)	3.21 (dd, *J* = 12.3, 6.0)	119.8	119.8
2.67 (*J* = 11.5, 11.2, 2.4, 2.2)	2.67 (br t, *J* = 11.2)	56.9	57.1
2.55 (*J* = 3.2, 3.2, 3.2, 3.2)	2.55 (br s)	56.3	56.5
2.32 (*J* = 11.4, 6.8, 5.8, 1.0)	2.31 (m)	54.3	54.6
2.27 (*J* = 10.0, 9.7, 3.5, 2.0)	2.28 (br t, *J* = 10.0)	50.6	50.6
2.14 (*J* = 12.0, 3.2)	2.14 (m)	49.0	49.3
2.13 (*J* = 12.0, 3.0, 1.0)	2.12 (m)	48.5	48.8
2.06 (*J* = 3.4, 3.0, 2.0)	2.05 (m)	47.2	47.5
1.93 (*J* = 12.6, 12.4, 3.2)	1.93 (td, *J* = 12.8, 2.8)	43.6	43.9
1.82 (*J* = 12.4, 12.2, 6.8, 5.0)	1.86 - 1.72 (m, 2 H)	36.4	36.7
1.79 (*J* = 12.8, 12.0, 6.0, 4.0)		35.7	35.9
1.73 (*J* = 12.6, 3.9, 2.0, 2.0)	1.72 (m)	35.6	35.8
1.64 (*J* = 12.6, 12.4, 12.0, 3.9)	1.63 (m)	34.3	34.5
1.56 (12.6, 12.4, 9.7, 3.4)	1.56 (m)	34.2	34.4
1.54 (*J* = 12.2, 12.2, 6.3, 2.0)	1.54 (m)	34.0	34.2
1.50 (*J* = 12.4, 2.4)	1.50 (m)	31.6	31.9
1.48 (*J* = 12.6, 11.8, 11.4)	1.49 (m)	31.5	31.8
1.46 (*J* = 12.2, 12.0)	1.45 (m)	31.0	31.3
1.46 (*J* = 5.8, 5.0)	1.45 (m)	26.9	27.2
1.45 (*J* = 12.8, 3.0, 2.5, 1.3)	1.45 (m)	25.7	26.0
1.44 (*J* = 12.7, 3.5, 3.0, 2.0)	1.44 (m)	24.0	24.3
1.39 (*J* = 12.4, 1.5)	1.39 (m)	22.5	22.7
1.37 (*J* = 12.2, 12.2, 6.3)	1.37 (m)	20.6	20.8
1.36 (*J* = 12.5, 4.0, 3.0, 3.0, 2.5)	1.36 (m)	20.0	20.2
1.31 (*J* = 12.8, 12.2)	1.31 (m)	19.8	20.0
1.29 (*J* = 12.4, 12.0, 11.2, 5.8)	1.28 (m)	Natural sample referenced 0.2 ppm lower than us	
1.23 (*J* = 12.5, 12.5, 12.0, 3.0, 2.0)	1.24 (m)		
1.16 (*J* = 12.7, 12.5, 10.0, 3.0)	1.15 (m)		
1.10 (*J* = 12.8, 2.0)	1.09 (m)		
1.08 (*J* = 5.8, 1.7)	1.09 (m)		
1.06 (*J* = 6.8, 3 H)	1.06 (d, *J* = 7.2, 3 H)		
1.00 (*J* = 12.0, 3.2, 1.0)	1.00 (m)		
0.88 (*J* = 12.6, 3.2, 2.4, 1.0)	0.87 (m)		
0.82 (*J* = 12.2, 12.2, 11.5)	0.82 (m)		
0.80 (*J* = 6.3, 3 H)	0.80 (d, *J* = 6.4, 3 H)		

Table S2. NMR Spectral Data Comparison of Natural and Synthetic Isopsylloborine A (**2**); Coupling Constant (*J*) in Hz

^{1}H (CD_2Cl_2 + TFA)		**^{13}C (CD_2Cl_2 + TFA)**	
Natural Isopsylloborine A	**Synthetic Isopsylloborine A**	**Natural Isopsylloborine A**	**Synthetic Isopsylloborine A**
4.17 (dq, *J* = 13.5, 3.0)	4.17 (br d, *J* = 13.4)	145.1	145.1
3.80 (bd, *J* = 12.0)	3.80 (br d, *J* = 13.6)	127.3	127.1
3.57 (br m)	3.57 (br m)	63.6	63.4
3.34 (tt, *J* = 12.0, 3.0)	3.34 (br t, *J* = 11.4)	63.5	63.2
2.67 (br m)	2.71 (br m)	56.1	55.9
2.46 (bdd, *J* = 17.5, 5.6)	2.46 (m)	56.0	55.8
2.44 (dd, *J* = 15.0, 3.5)	2.46 (m)	52.6	52.4
2.40 (br s)	2.40 (br s)	49.7	49.5
2.28 (td, *J* = 14.5, 4.5)	2.30 (m)	41.8	41.6
2.17 (m)	2.27 (m)	39.8	39.7
2.12 (m)	2.17 (m)	39.0	38.8
2.10 (m)	2.10 (m)	35.0	34.9
2.04 (m)	2.10 (m)	31.8	31.6
2.04 (m)	2.08 (m)	31.4	31.2
2.00 (m)	2.01 (m)	30.0	29.8
1.98 (m)	1.99 (m)	28.7	28.5
1.87 (m)	1.88 (m)	28.2	28.0
1.83 (m)	1.86 (m)	26.5	26.4
1.83 (m)	1.86 (m)	25.6	25.5
1.80 (m)	1.85 (m)	24.9	24.8
1.80 (m)	1.82 (m)	22.3	22.1
1.78 (m)	1.79 (m)	21.6	21.3
1.77 (m)	1.79 (m)	20.4	20.2
1.70 (m)	1.77 (m)	19.6	19.3
1.70 (m)	1.75 (m)	17.7	17.5
1.70 (m)	1.71 (m)	17.0	16.9
1.70 (m)	1.70 (m)		
1.60 (m)	1.62 (m)		
1.60 (m)	1.62 (m)		
1.60 (m)	1.61 (m)		
1.60 (m)	1.60 (m)		
1.55 (m)	1.56 (m)		
1.49 (m)	1.56 (m)		
1.48 (bd, *J* = 14.5)	1.50 (m)		
1.03 (d, *J* = 6.6, 3 H)	1.03 (d, *J* = 6.1, 3 H)		
0.99 (d, *J* = 6.6, 3 H)	1.00 (d, *J* = 6.1, 3 H)		

Table S3. ^{1}H and ^{13}C Data for Isopsylloborine A Trifluoroacetate Salt (**56**) in CD_2Cl_2

Position	δ-C (ppm), *J* (Hz)	Proton	δ (ppm), *J* (Hz)	nOe	HMBC
C-1	40.2	**H_a-1 (eq)**	1.91 (m)		C-2, C-3
		H_b-1 (ax)	1.81 (m)	H-3, H-(2Me)	C-2, C-9a
C-2	35.0	**H-2**	1.69 (m)	H-5'	C-1, C-3, C-(2Me)
C-3	49.4	**H-3**	2.24 (m)	H_b-1, H_a-5	C-3a, C-4
C-3a	146.5	**none**			
C-4	125.0	**none**			
C-5	22.4	**H_a-5 (ax)**	2.88 (m)	H-3, H-6a	
		H_b-5 (eq)	2.39 (dd, *J* = 18.5, 6.0)	H_a-3'	C-3a, C-4, C-6, C-6a
C-6	20.6	**H_a-6 (ax)**	2.01 (m)	H-9a	C-6a
		H_b-6 (eq)	1.71 (m)		C-4, C-5
C-6a	54.7	**H-6a**	3.68 (br d, *J* = 14.2)	H_a-5, H_a-7, H_b-7, H-6a'	C-8
C-7	28.4	**H_a-7**[a]	2.16 (m)	H-6a	C-6, C-6a, C-9
		H_b-7[a]	1.77 (m)	H-6a	
C-8	17.6	**H_a-8 (eq)**	1.64 (m)		
		H_b-8 (ax)	1.55 (m)	H_b-9, H-9a	C-7
C-9	31.6	**H_a-9 (ax)**	1.93 (m)		
		H_b-9 (eq)	1.78 (m)	H_b-8	
C-9a	61.5	**H-9a**	3.15 (tt, *J* = 11.6, 3.5)	H_a-6, Hb-8	
C-2(Me)	19.5	**H-2(Me)**	1.00 (d, *J* = 6.3)	H_b-1, H-5'	C-1, C-2, C-3, C-9a
C-1'	38.6	**H_a-1' (eq)**	1.73 (m)		[C-2', C-3', C-9a', C-(2'Me)][c]
		H_b-1' (ax)	1.73 (m)	H-N'	
C-2'	25.1	**H-2'**	1.96 (m)	H_b-3', H_a-4', H-9a'	
C-3'	41.6	**H_a-3' (ax)**	2.24 (m)	H_b-5, H-N'	C-1', C-2', C-3a', C-(2'Me)
		H_b-3' (eq)	1.51 (m)	H-2', H-(2'Me)	C-1', C-2'
C-3a'	62.7	**none**			
C-4'	25.7	**H_a-4' (ax)**	2.41 (dd, *J* = 14.6, 3.5)	H-2', Ha-6', H-9a'	C-3, C-4, C-3a', C-5'
		H_b-4' (eq)	1.49 (br d, *J* = 14.3)	H-5'	C-5', C-6'

C-5'	26.6	**H-5'**	2.32 (br s)	H-2, H-(2Me), H_b-4'	
C-6'	30.0	**H_a-6' (ax)**	2.25 (m)	H_a-4', H-9a'	C-7', C-6a'
		H_b-6' (eq)	1.43 (br d, *J* = 13.6)		
C-6a'	51.6	**H-6a'**	4.31 (br d, *J* = 13.9)	H-6a, H_a-7', H_b-7', H-N'	
C-7'	28.4	**H_a-7' (ax)**	2.16 (m)	H-6a', H-N'	C-6', C-6a', C-8'
		H_b-7' (eq)	1.66 (m)	H-6a'	
C-8'	17.9	**H_a-8' (eq)**	1.64 (m)		
		H_b-8' (ax)	1.58 (m)	H-9a'	
C-9'	31.4	**H_a-9' (ax)**	1.90 (m)	H-N'	C-9a'
		H_b-9' (eq)	1.71 (m)		
C-9a'	55.1	**H-9a'**	3.49 (m)	H-2', H_a-4', H_a-6', H_b-8'	
C-(2'Me)	21.6	**H-(2'Me)**	1.00 (d, *J* = 6.3)	H_b-3'	C-1', C-2', C-3', C-3a', C-9a'
N'	n/a	**H-N'**	10.51 (br s)	H_b-1', H_a-3', H-6a', H_a-7', H_a-9'	
TFA: C-1	(115.9 or 118.2)[b]	**none**			
TFA: C-2	161.1 (q, *J* = 32)	**none**			

[a]Axial and equatorial assignments were not made.

[b]One of these is an impurity.

[c]Could be assigned to H_a-1 and H_b-1 in various ways.

Table S4. ^{1}H and ^{13}C Data for Isopsylloborine A Trifluoroacetate Salt (**56**) in CD_3CN

Position	δ-C (ppm), *J* (Hz)	Proton	δ (ppm), *J* (Hz)	nOe	HMBC
C-1	41.1	**H_a-1 (eq)**	1.93 (m)	H-2	C-2, C-3
		H_b-1 (ax)	1.58 (m)		C-2, C-(2Me), C-9a[c]
C-2	34.8	**H-2**	1.73 (m)	H_a-1, H-5'	C-1, C-3, C-(2Me)
C-3	50.4	**H-3**	2.03 (m)	H-(2Me), H-5', H_b-6'	C-2, C-3a, C-4', C-6'
C-3a	147.5	**none**			
C-4	124.1	**none**			
C-5	23.0	**H_a-5 (ax)**	2.64 (m)	H-6a	C-4, C-6
		H_b-5 (eq)	2.37 (dd, *J* = 17.9, 6.0)	H_a-3', H_b-6	C-3a, C-4, C-6, C-6a, C-3a'
C-6	20.9	**H_a-6 (ax)**	2.05 (m)	H-9a	C-5, C-6a
		H_b-6 (eq)	1.63 (m)	H_b-5, H-6a	C-4, C-5
C-6a	55.4	**H-6a**	3.52 (br d, *J* = 13.3)	H_a-5, H_b-6, H_b-7, H-6a'	C-5, C-6, C-7, C-8, C-9a
C-7	29.1	**H_a-7[a]**	2.01 (m)		C-8
		H_b-7[a]	1.77 (m)	H-6a	
C-8	17.9	**H_a-8[a]**	1.59 (m)		C-9, C-9a[c]
		H_b-8[a]	1.57 (m)		C-9a[c]
C-9	32.3	**H_a-9[a]**	1.79 (m)		
		H_b-9[a]	1.52 (m)		C-8
C-9a	61.3	**H-9a**	3.22 (br t, *J* = 11.4)	H_a-6	
C-2(Me)	19.7	**H-2(Me)**	0.96 (d, *J* = 6.4)	H-3, H-5'	C-1, C-2, C-3, C-9a
C-1'	39.4	**H_a-1' (eq)**	1.77 (m)		
		H_b-1' (ax)	1.45 (dt, *J* = 13.8, 11.7)	H-(2'Me), H-N'	C-2', C-3', C-9a', C-(2'Me)
C-2'	25.1	**H-2'**	1.98 (m)	H_a-4', H-9a'	
C-3'	42.2	**H_a-3' (ax)**	1.96 (m)	H_b-5, H-N'	C-1', C-2', C-3a', C-4', C-(2'Me)
		H_b-3' (eq)	1.62 (m)		C-1'

C-3a'	63.9	**none**			
C-4'	25.8	**H_a-4' (ax)**	2.43 (dd, *J* = 14.6, 3.4)	H-2', H-9a'	C-3, C-4, C-3a', C-5', C-6'
		H_b-4' (eq)	1.54 (m)		C-5', C-6'
C-5'	27.1	**H-5'**	2.31 (br s)	H-2, H-3, H-(2Me)	C-2, C-3[d], C-3a, C-3a', C-4'
C-6'	30.5	**H_a-6' (ax)**	2.31 (m)	H_a-8', H-9a'	C-3[d], C-5', C-6a', C-7'
		H_b-6' (eq)	1.33 (m)	H-3, Hb-7'	C-3, C-4'
C-6a'	52.2	**H-6a'**	4.23 (br d, *J* = 13.6)	H-6a, Hb-7', H-N'	
C-7'	29.1	**H_a-7' (ax)**	2.04 (m)	H_b-7'[f], H_b-8'[f], H-N'	C-6', C-6a', C-8', C-9'
		H_b-7' (eq)	1.60 (m)	H-6a', H_b-6', H_a-7'[f]	
C-8'	18.0	**H_a-8' (ax)**	1.60 (m)	H_a-6', H-9a'	
		H_b-8' (eq)	1.60 (m)	H_a-7'[f]	
C-9'	31.9	**H_a-9' (ax)**	1.73 (m)	H-N'	(C-7', C-8', C-9a')[e]
		H_b-9' (eq)	1.73 (m)		
C-9a'	55.4	**H-9a'**	3.68 (m)	H-2', H_a-4', H_a-6', H_a-8'	
C-(2'Me)	21.8	**H-(2'Me)**	0.95 (d, *J* = 6.0)	H_b-1'	C-1', C-2', C-3', C-3a', C-9a'
N'	n/a	**H-N'**	9.32 (br s)	H_b-1', H_a-3', H-6a', H_a-7', H_a-9'	
TFA: C-1	(130.8 or 116.7)[b]	**none**			
TFA: C-2	161.2 (q, *J* = 33)	**none**			

[a]Axial and equatorial assignments were not made.

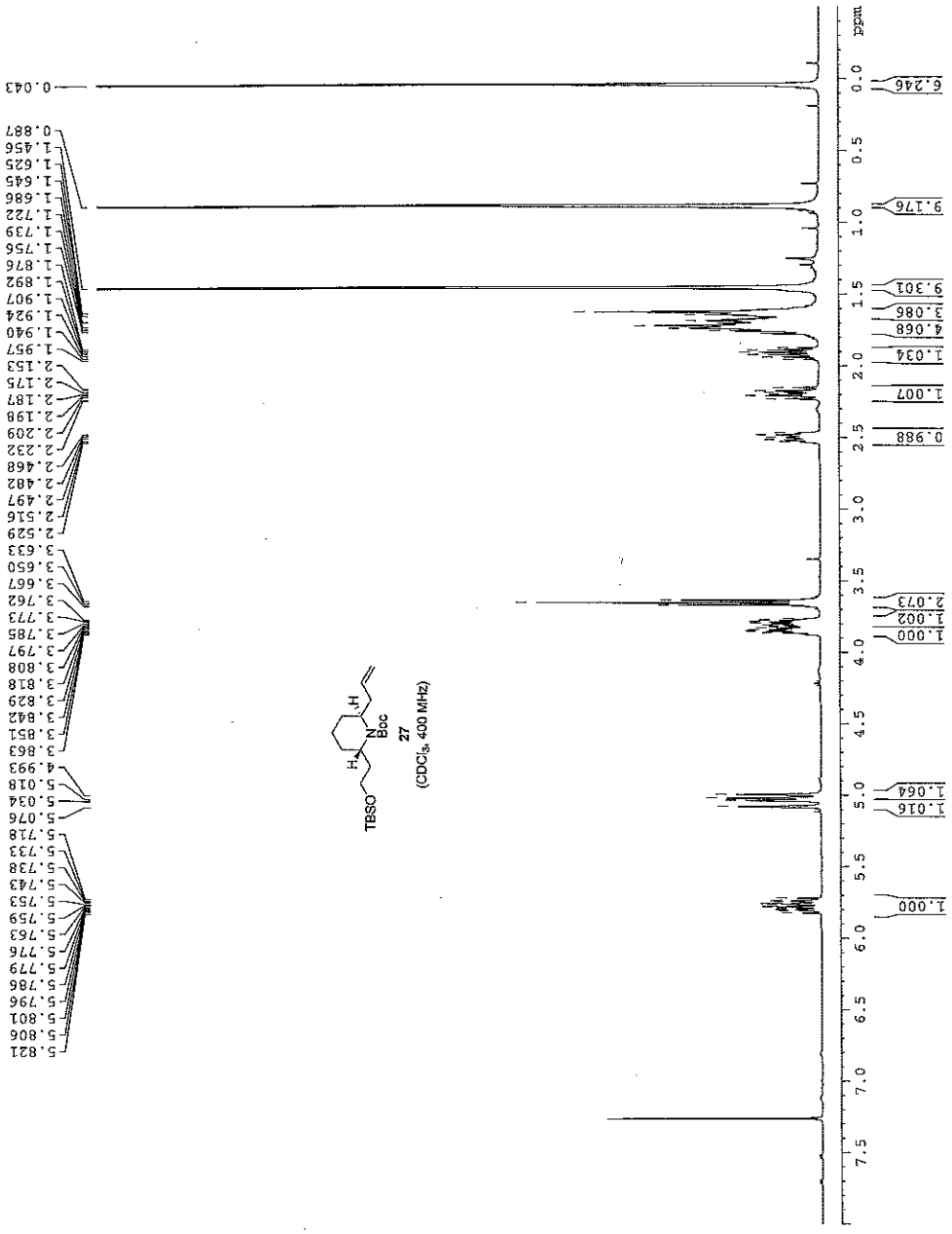
[b]One of these is an impurity.

[c]Crosspeak at this chemical shift could apply to one, two, or all of these assignments

[d]Crosspeak at this chemical shift could apply to one or both of these assignments

[e]These correlations could be assigned to H_a-9' and H_b-9' in various ways.

[f]Crosspeak could apply to one or both of these assignments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Boc
N
H
H
27
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1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
6.246
9.176
9.301
3.086
4.068
1.034
1.007
0.988
2.073
1.002
1.000
1.016
1.064
1.000
0.043
0.887
1.456
1.625
1.645
1.686
1.722
1.739
1.756
1.876
1.892
1.907
1.924
1.940
1.957
2.153
2.175
2.187
2.198
2.209
2.232
2.468
2.482
2.497
2.516
2.529
3.633
3.650
3.667
3.762
3.773
3.785
3.797
3.808
3.818
3.829
3.842
3.851
3.863
4.993
5.018
5.034
5.076
5.718
5.733
5.738
5.743
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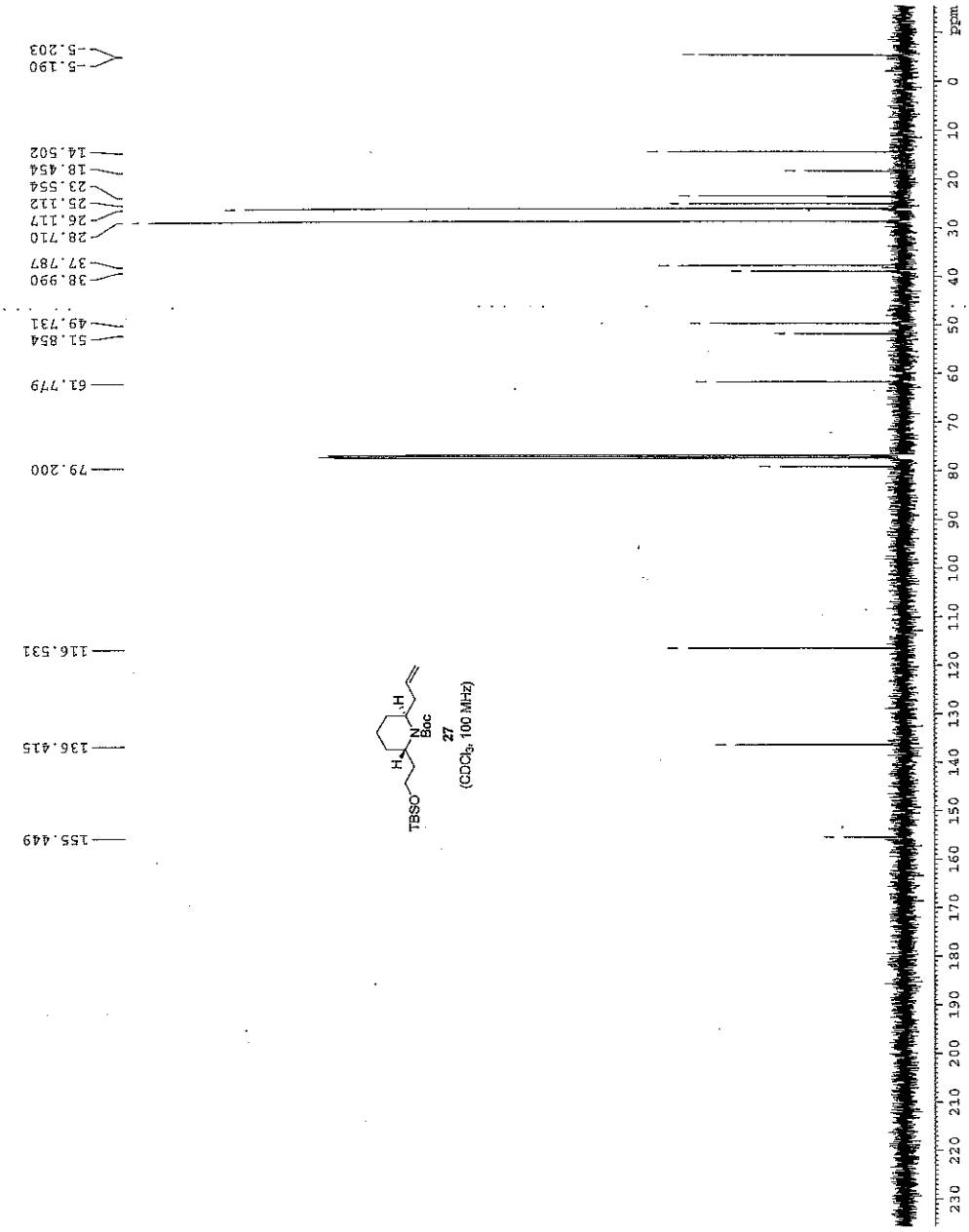
5.763
5.776
5.779
5.786
5.796
5.801
5.806
5.821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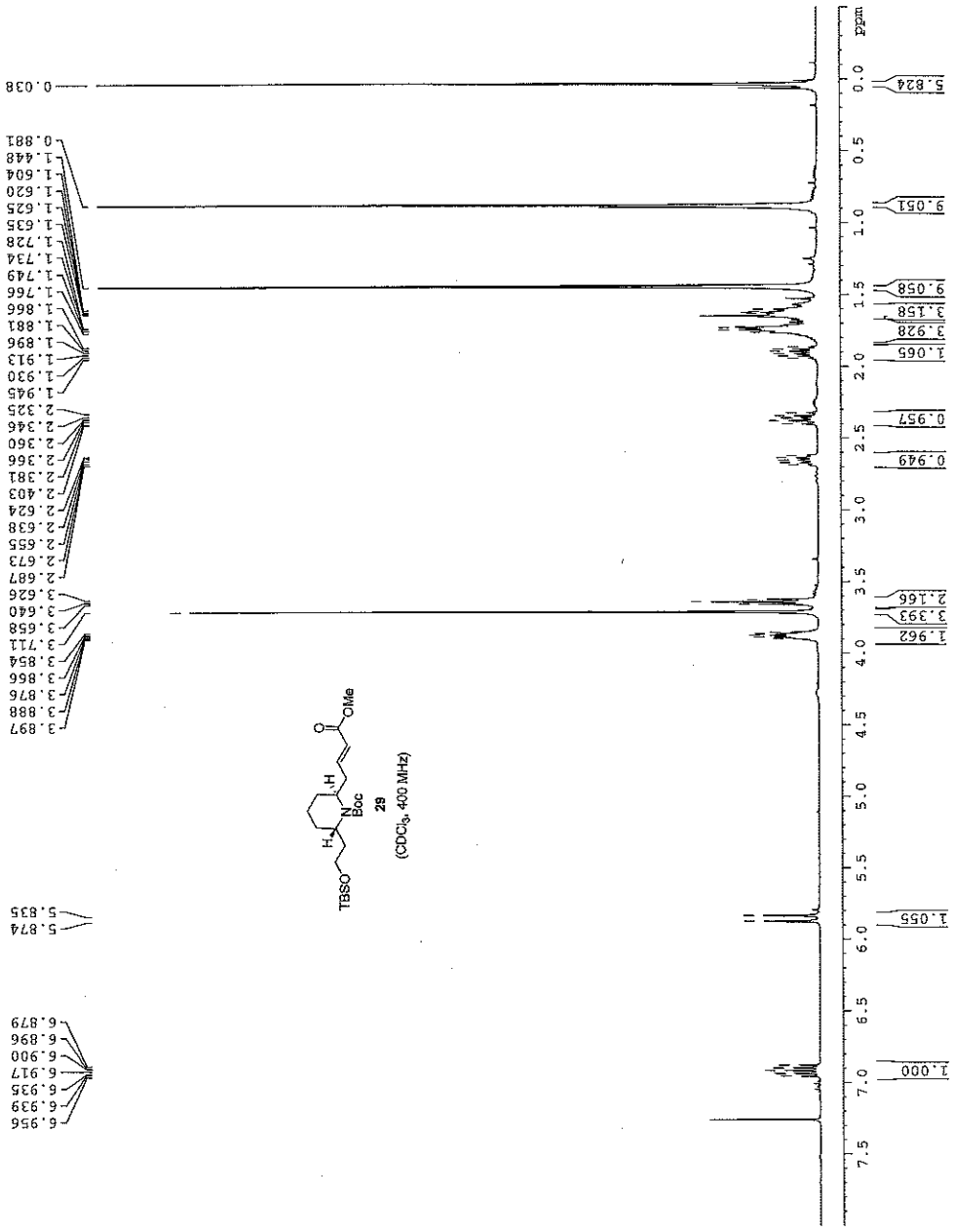
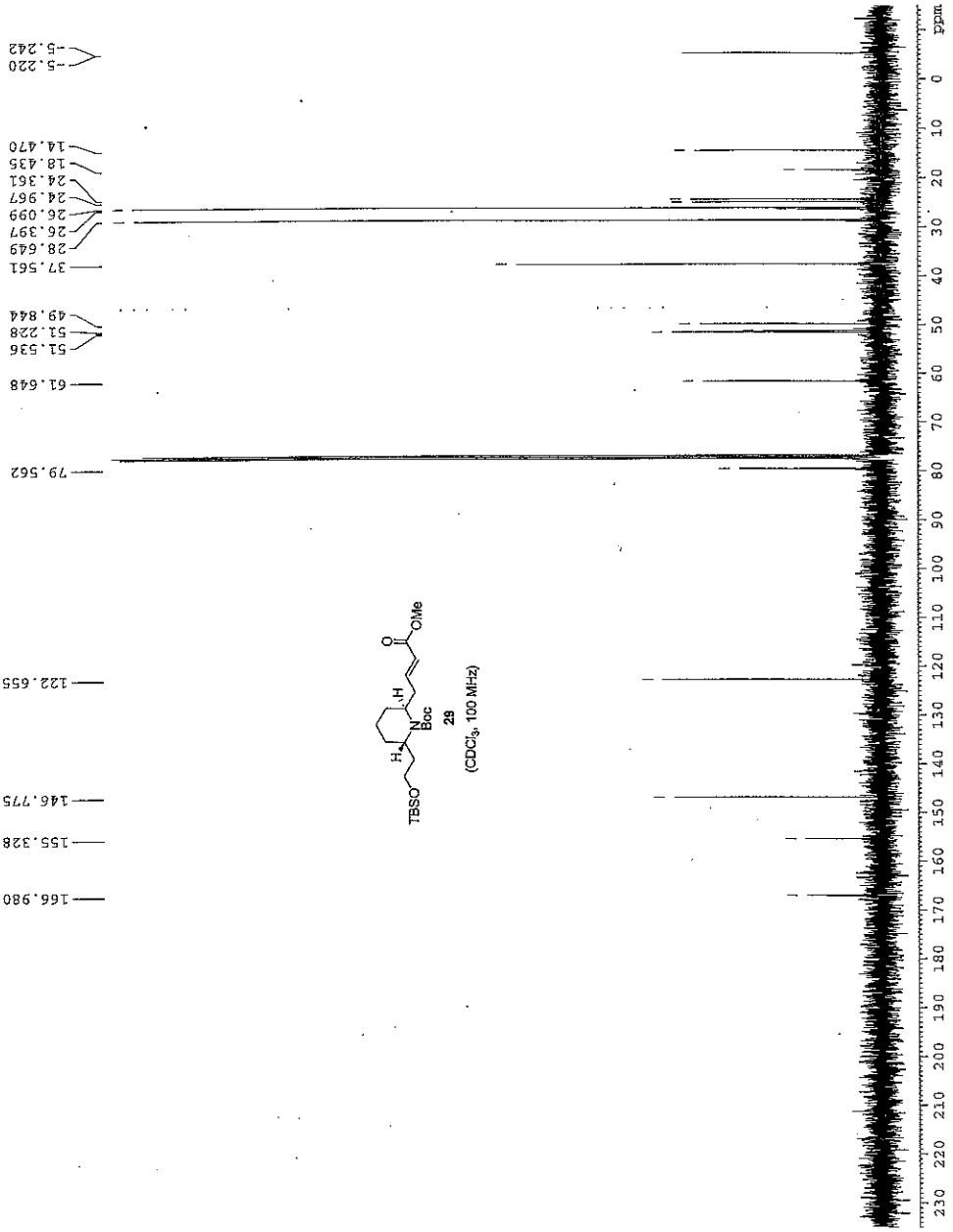
-5.190
14.502
18.454
23.554
25.112
26.117
28.710
37.787
38.990
49.731
51.854
61.779
79.200
116.531
136.415
155.449
TBSO
N
Boc
27
(CDCl3, 100 MHz)
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230


TBSO
Boc
OMe
29
(CDCl3, 400 MHz)
ppm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14.470
18.435
24.361
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28.649
37.561
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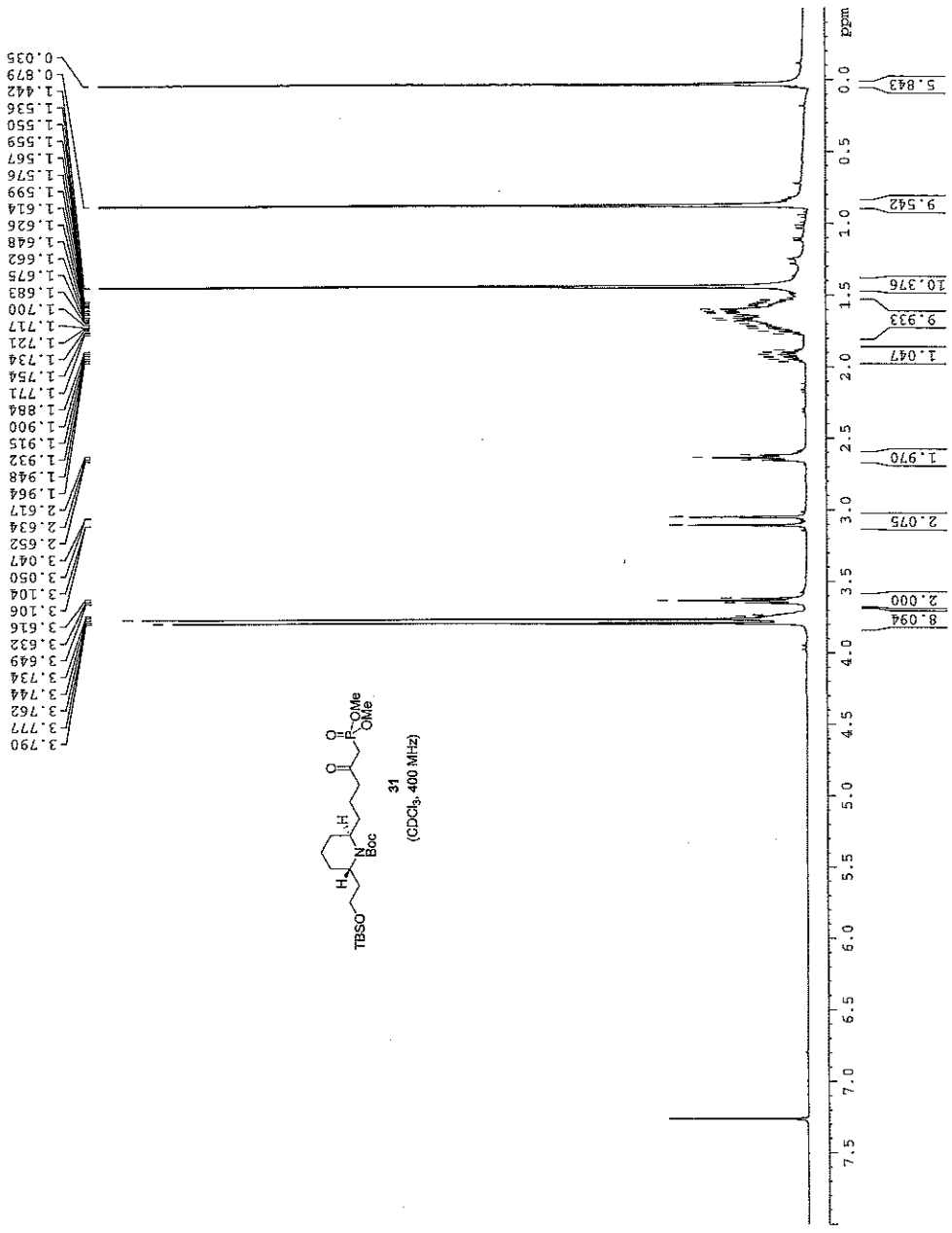
51.228
51.536
61.648
79.562
122.655
146.775
155.328
166.980
TBSO
H
N
Boc
H
OMe
O
29
(CDCl3, 100 MHz)
ppm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1.559
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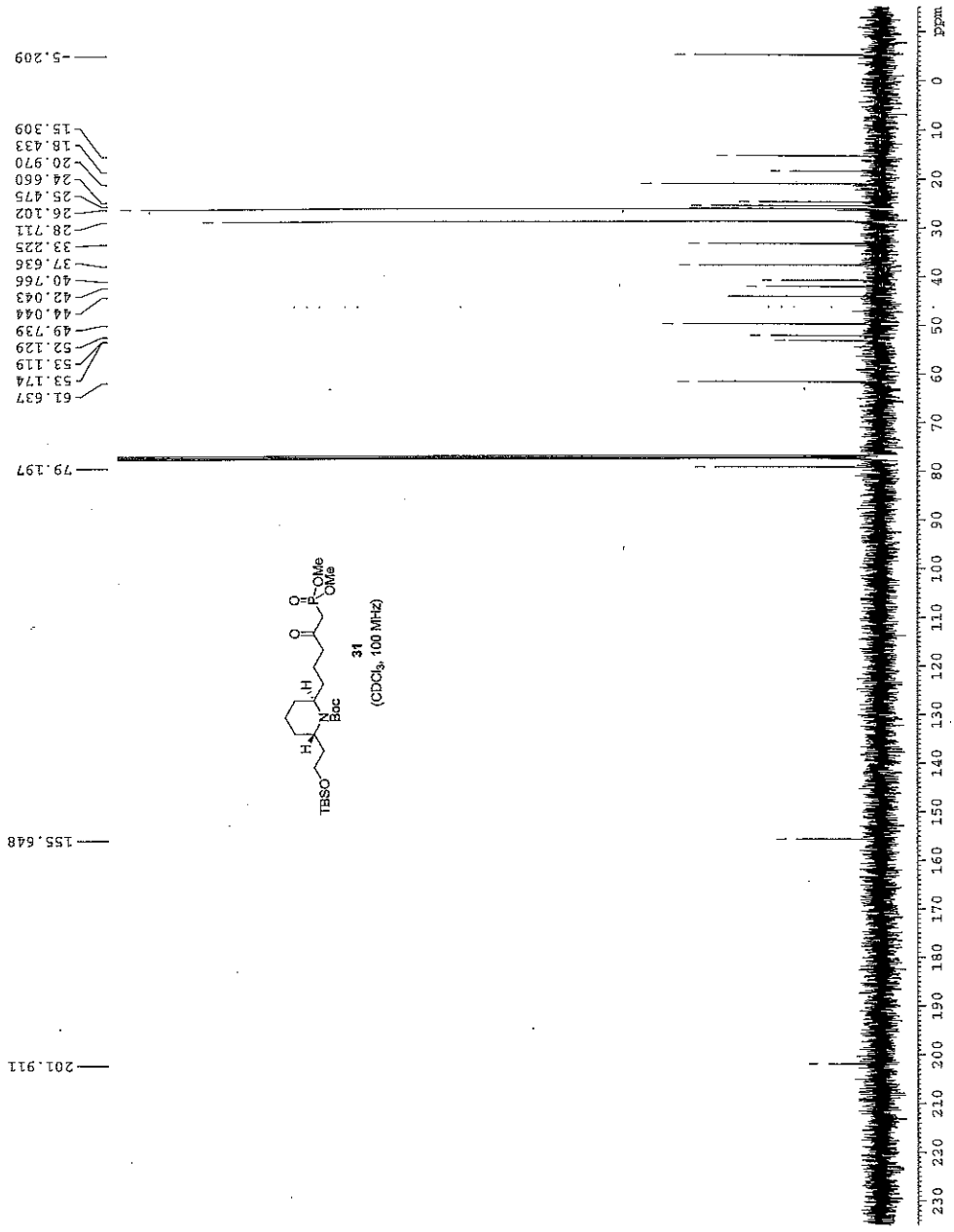
1.576
1.599
1.614
1.626
1.648
1.662
1.675
1.683
1.700
1.717
1.721
1.734
1.754
1.771
1.884
1.900
1.915
1.932
1.948
1.964
2.617
2.634
2.652
3.047
3.050
3.104
3.106
3.616
3.632
3.649
3.734
3.744
3.762
3.777
3.790
5.843
9.542
10.376
9.933
1.047
1.970
2.075
2.000
8.094
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
TBSO
Boc
OMe
OMe
31
(CDCl3, 400 MHz)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37.636
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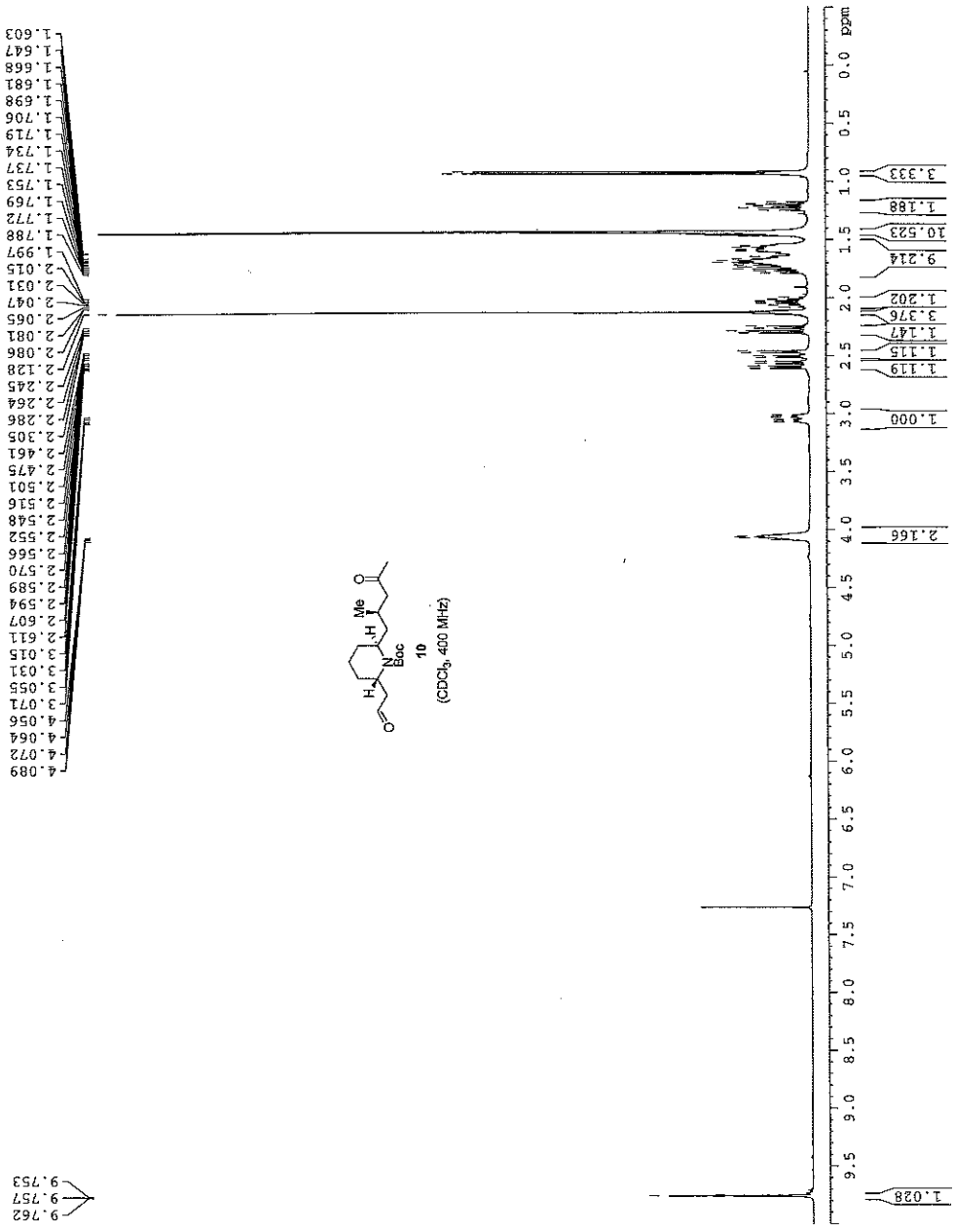
44.044
49.739
52.129
53.119
53.174
61.637
79.197
155.648
201.911
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230
TBSO
Boc
OMe
OMe
31
(CDCl3, 100 MHz)


Me
H
N
Boc
H
O
O
10
(CDCl3, 400 MHz)
ppm
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0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
3.333
1.188
10.523
9.214
1.202
3.376
1.147
1.115
1.119
1.000
2.166
1.028
9.762
9.757
9.753
4.089
4.072
4.064
4.056
3.071
3.055
3.031
3.015
2.611
2.607
2.594
2.589
2.570
2.566
2.552
2.548
2.516
2.501
2.475
2.461
2.305
2.286
2.264
2.245
2.128
2.086
2.081
2.065
2.047
2.031
2.015
1.997
1.788
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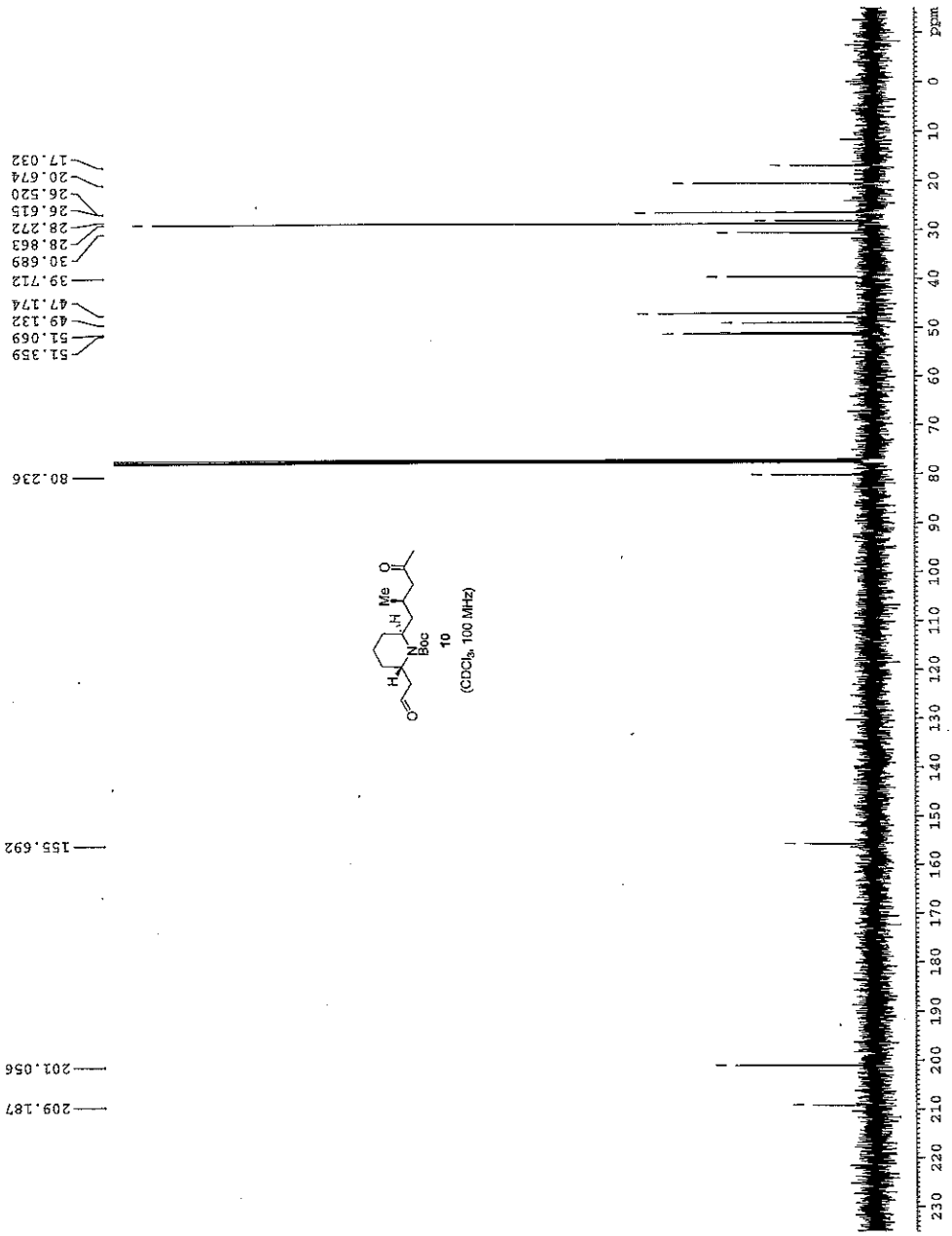
1.603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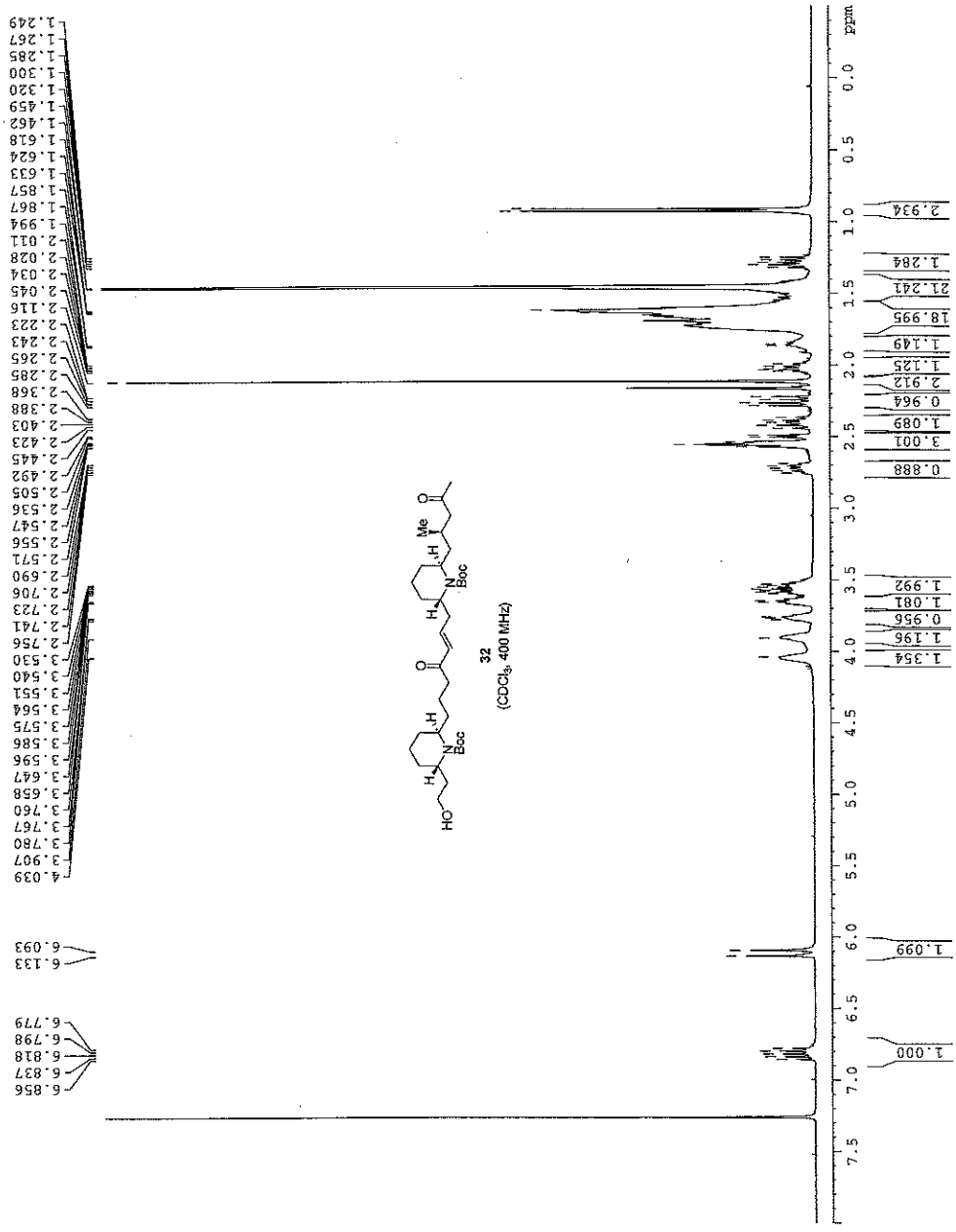
28.863
30.689
39.712
47.174
49.132
51.069
51.359
80.236
155.692
201.056
209.187
Me
O
H
N
Boc
H
O
10
(CDCl3, 100 MHz)
ppm


32
(CDCl3, 400 MHz)
Me
O
H
N
Boc
HO
ppm
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0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
2.934
1.284
21.241
18.995
1.449
1.125
2.912
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3.001
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1.992
1.081
0.956
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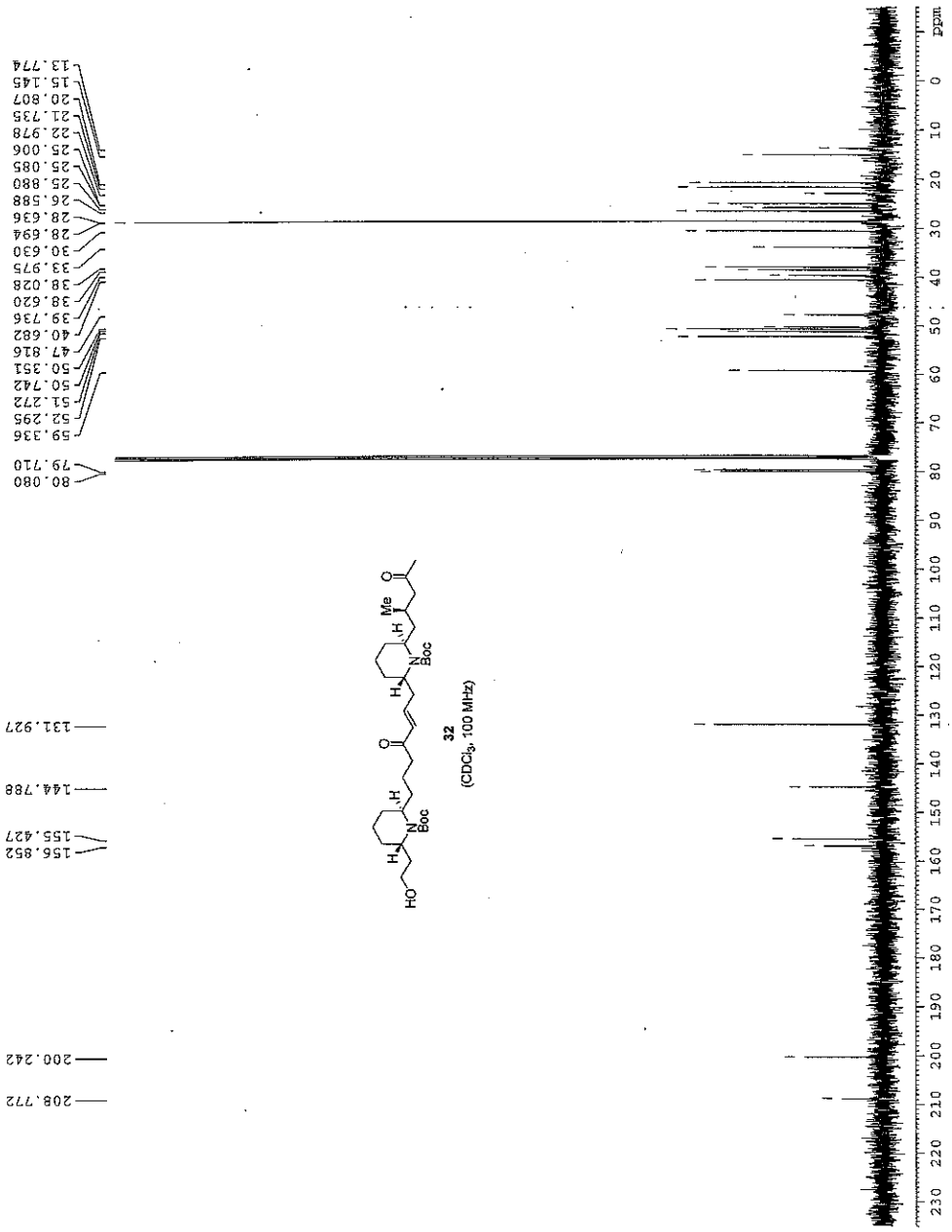
1.099
1.000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25.880
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33.975
38.028
38.620
39.736
40.682
47.816
50.351
50.742
51.272
52.295
59.336
79.710
80.080
131.927
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200.242
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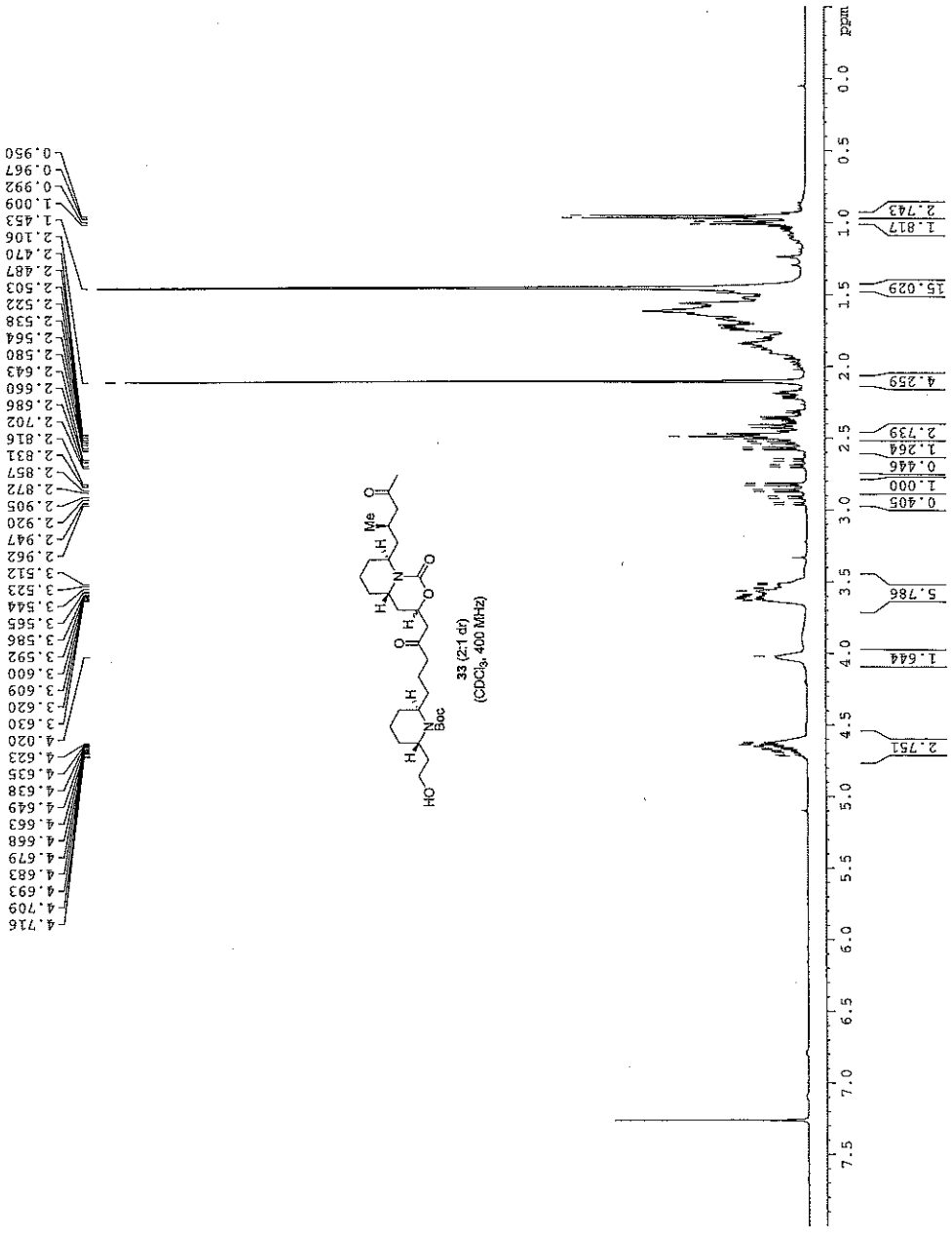
Me
H
N
Boc
O
HO
32
(CDCl3, 100 MHz)
ppm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1.453
2.106
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2.503
2.522
2.538
2.564
2.580
2.643
2.660
2.686
2.702
2.816
2.831
2.857
2.872
2.905
2.920
2.947
2.962
3.512
3.523
3.544
3.565
3.586
3.592
3.600
3.609
3.620
3.630
4.020
4.623
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4.683
4.693
4.709
4.716
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0.446
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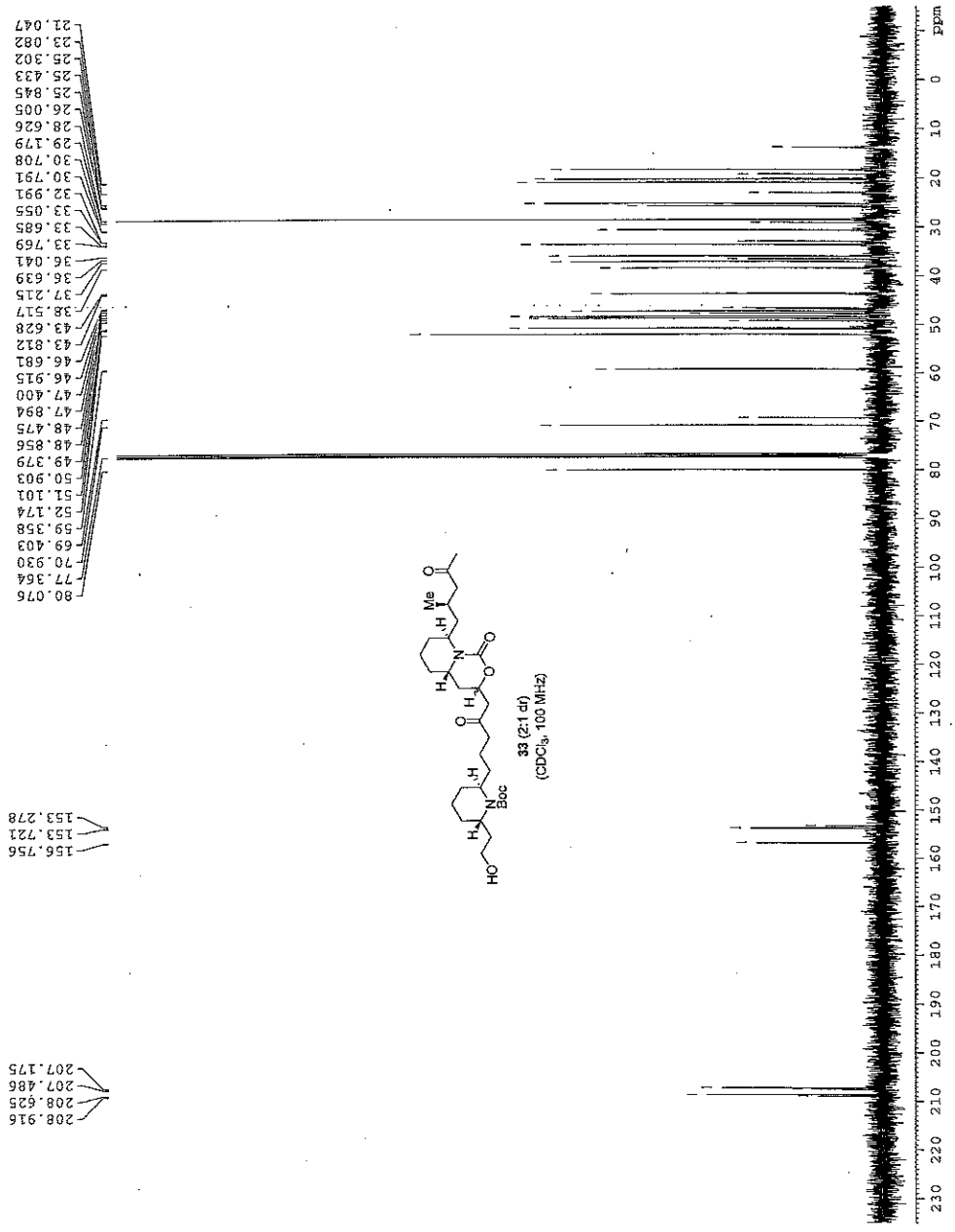
2.751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33.769
36.041
36.639
37.215
38.517
43.628
43.812
46.681
46.915
47.400
47.894
48.475
48.856
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59.358
69.403
70.930
77.364
80.076
153.278
153.721
156.756
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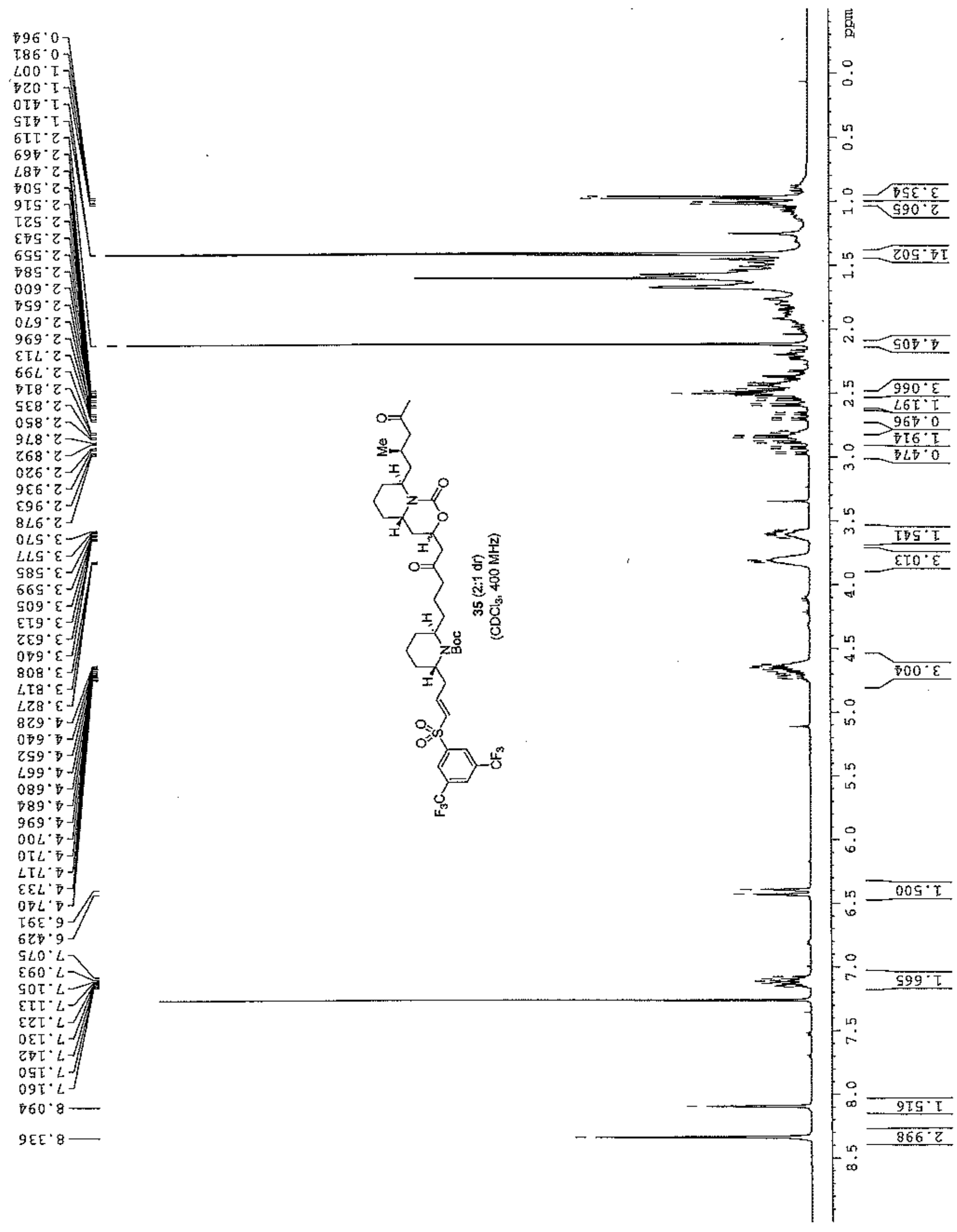
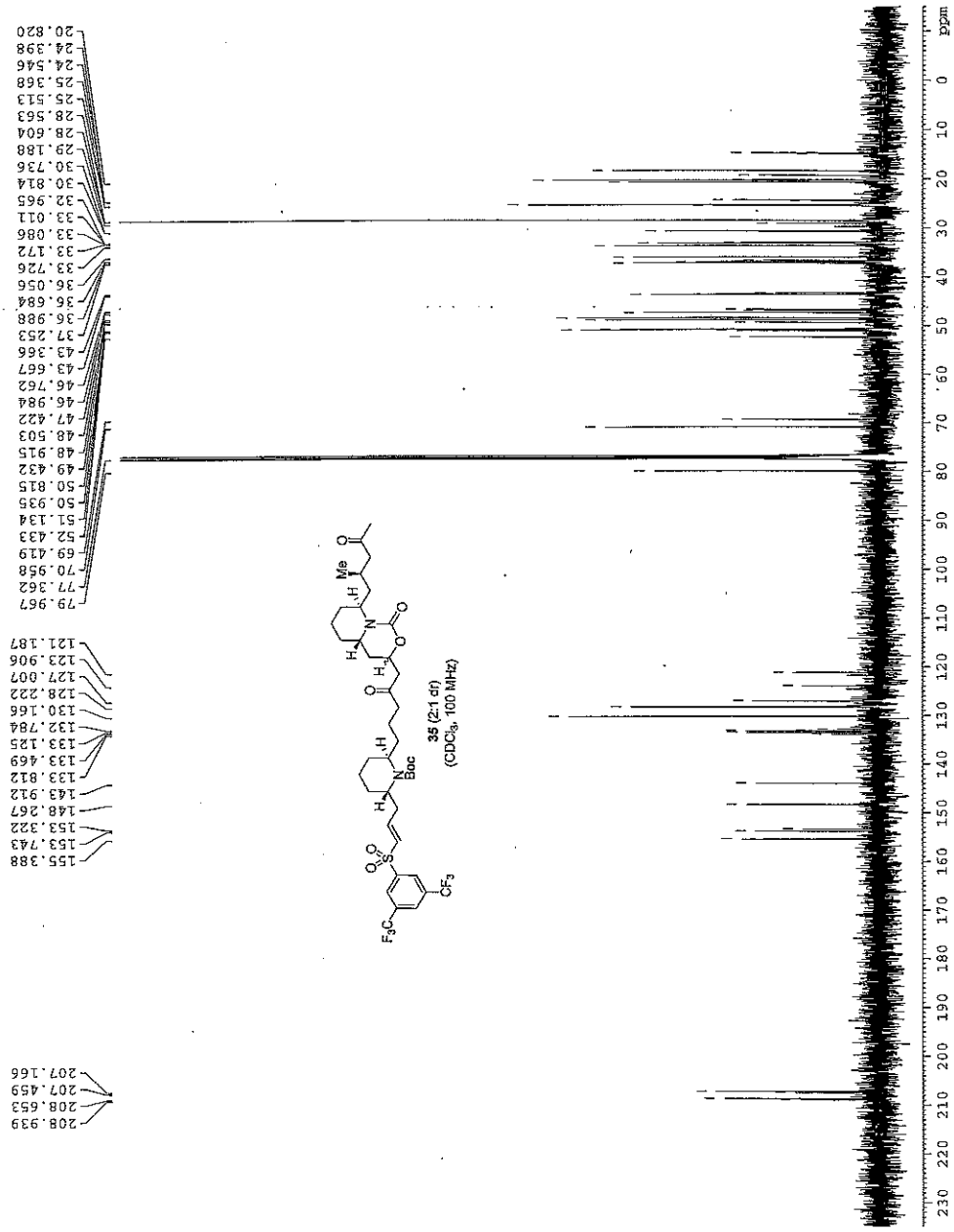
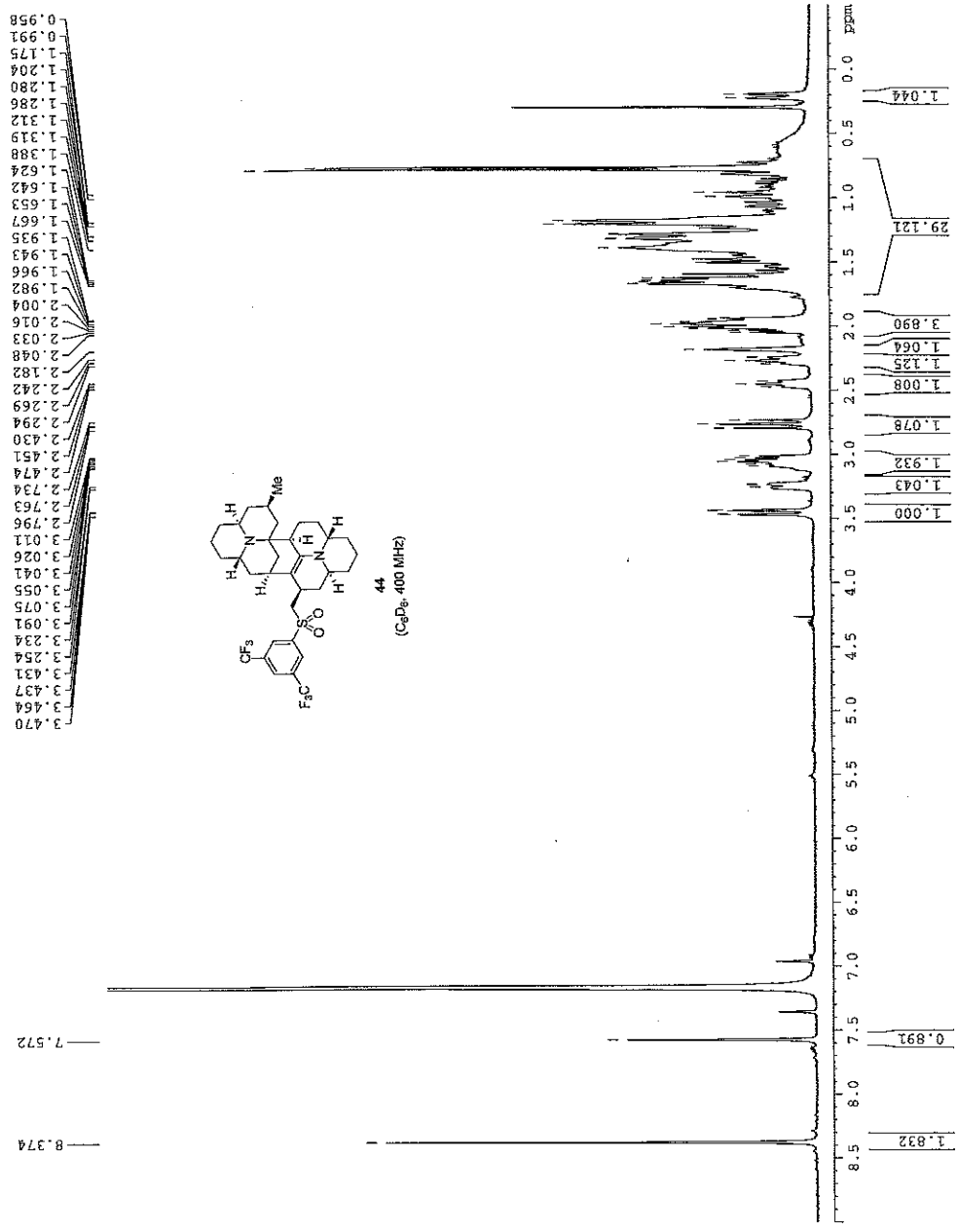
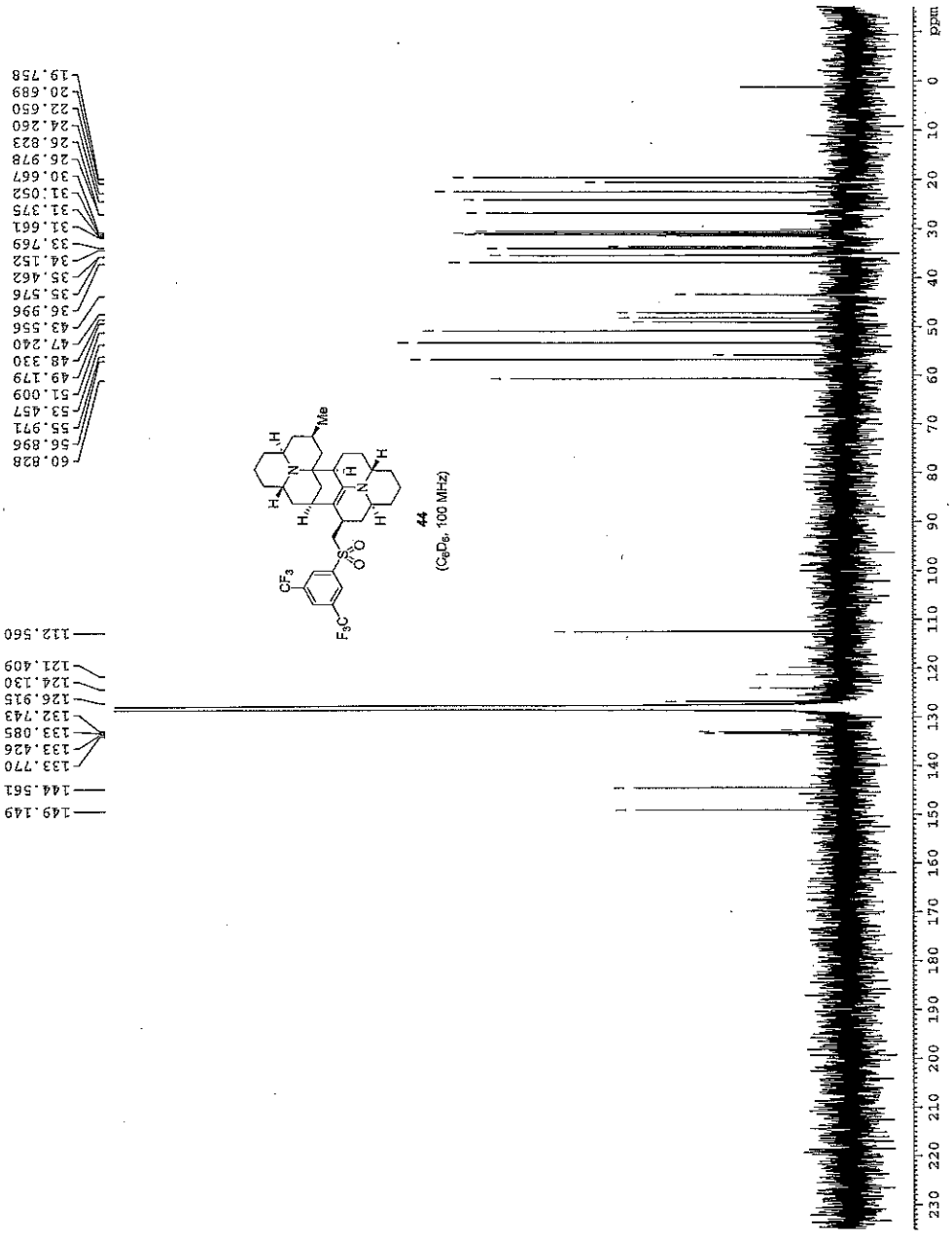
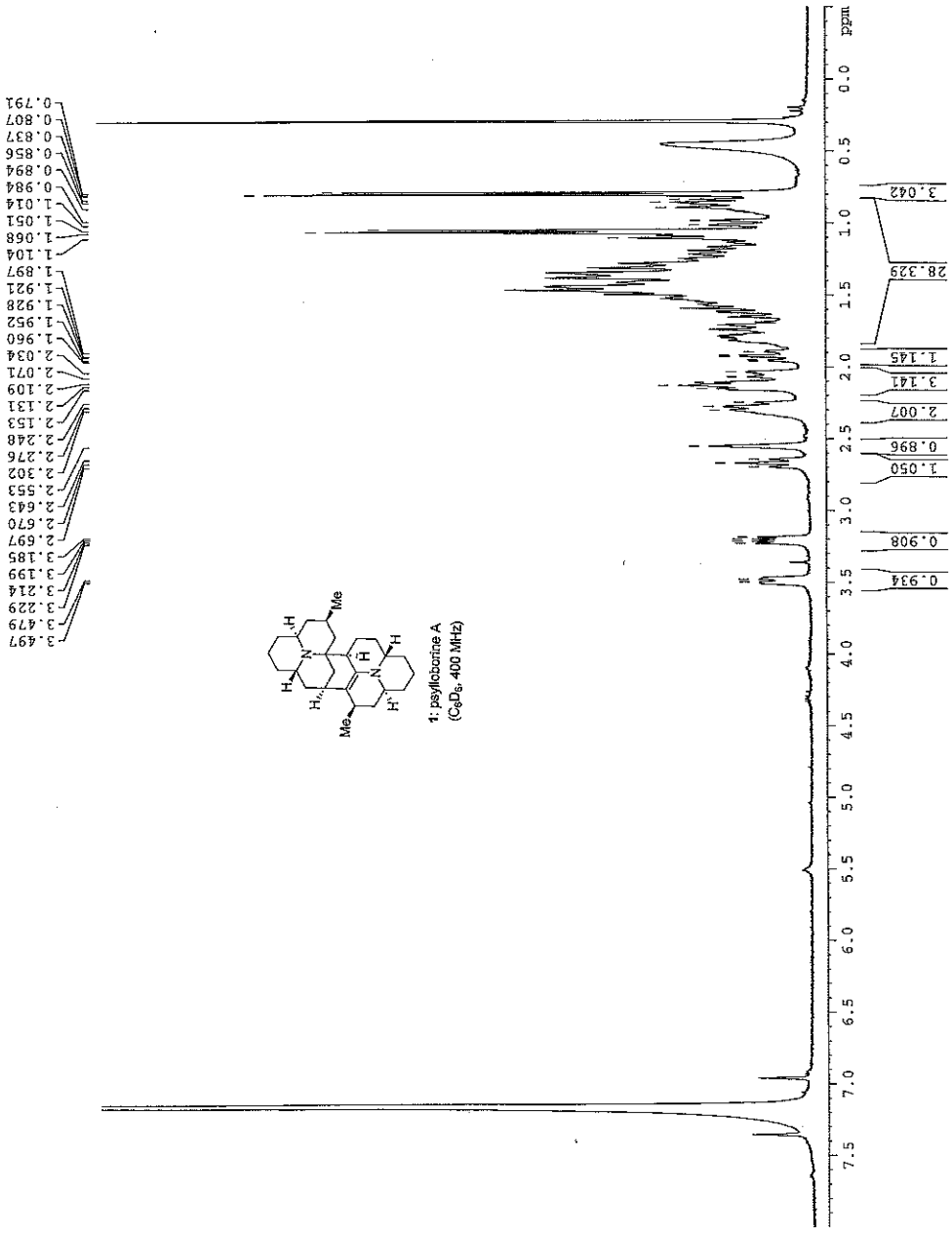
207.486
208.625
208.916
Me
Boc
HO
33 (2:1 dr)
(CDCl3, 100 MHz)
ppm

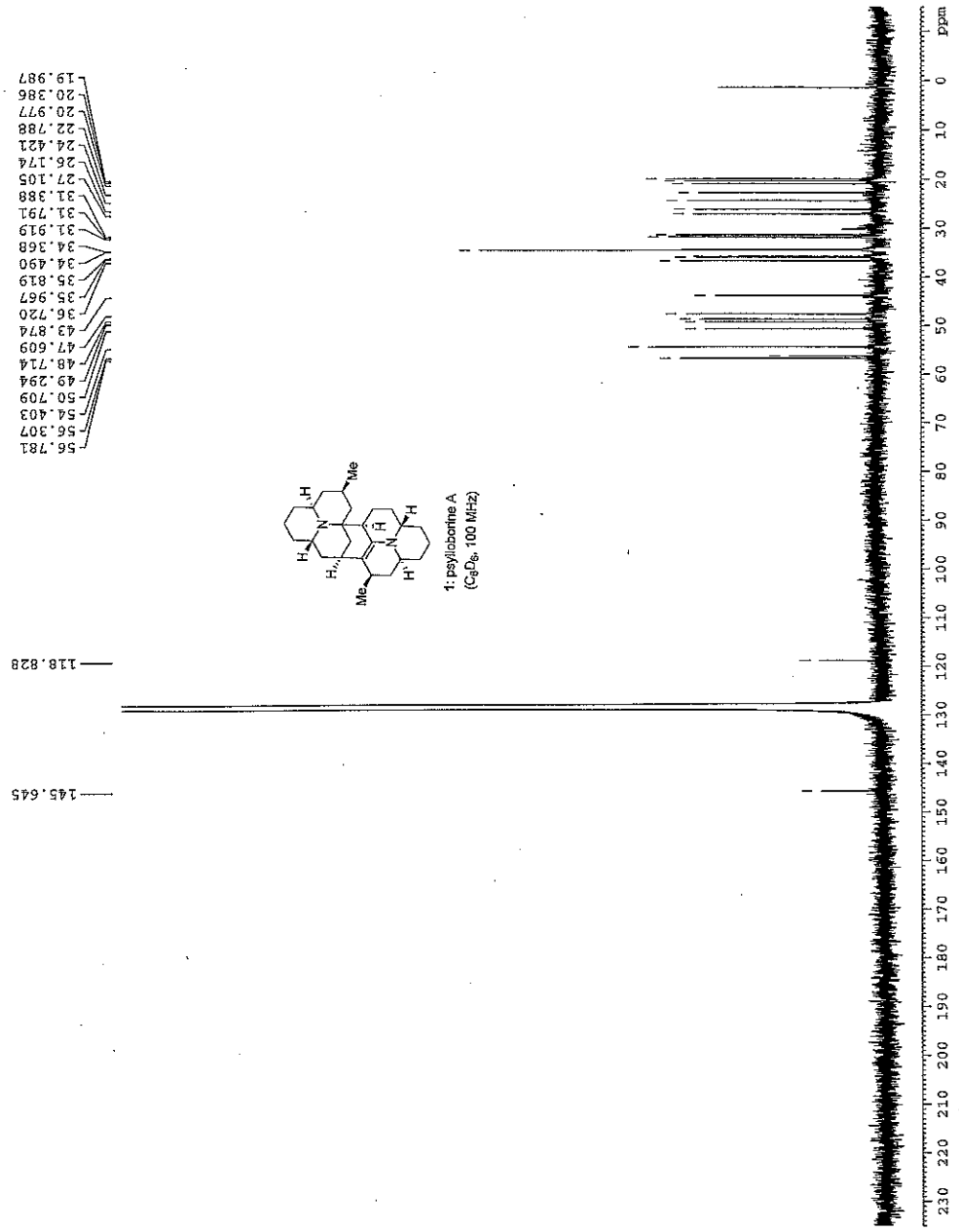

35 (2:1 dr)
(CDCl3, 400 MHz)
ppm

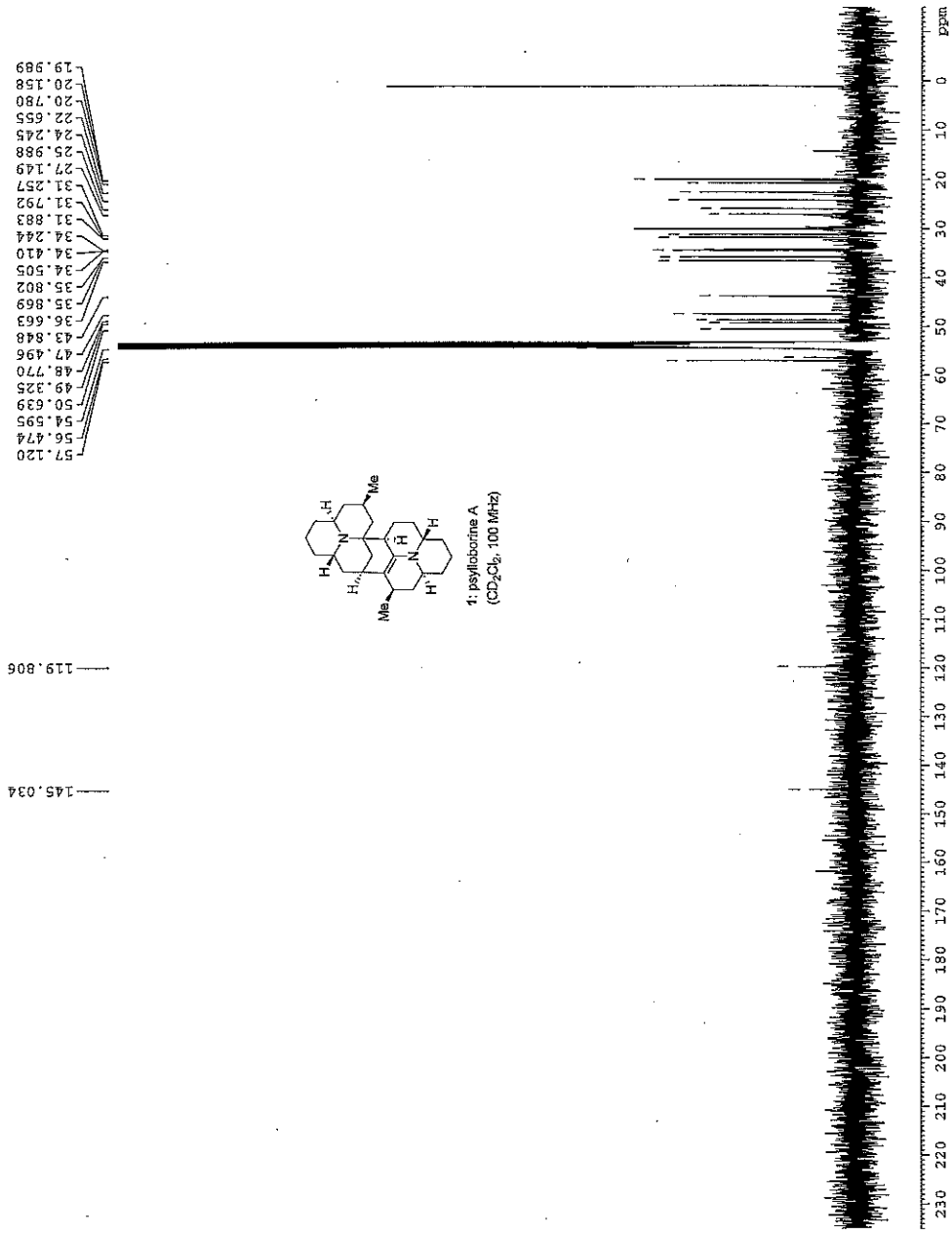

35 (2:1 dr)
(CDCl3, 100 MHz)
Me
Boc
CF3
F3C
ppm

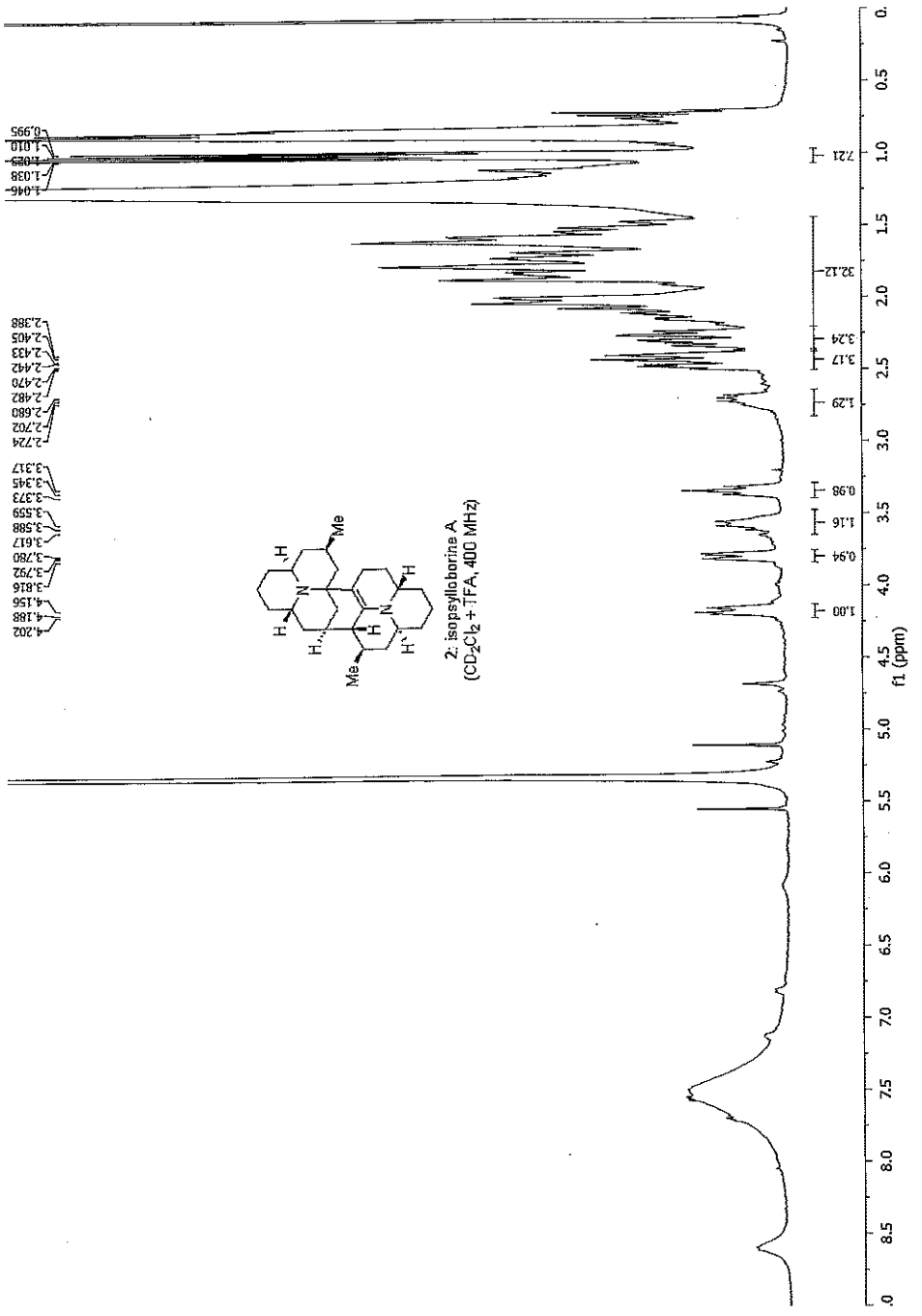

44
(C_6D_6, 400 MHz)
ppm
1.044
29.121
3.890
1.064
1.125
1.008
1.078
1.932
1.043
1.000
0.891
1.832
7.572
8.374

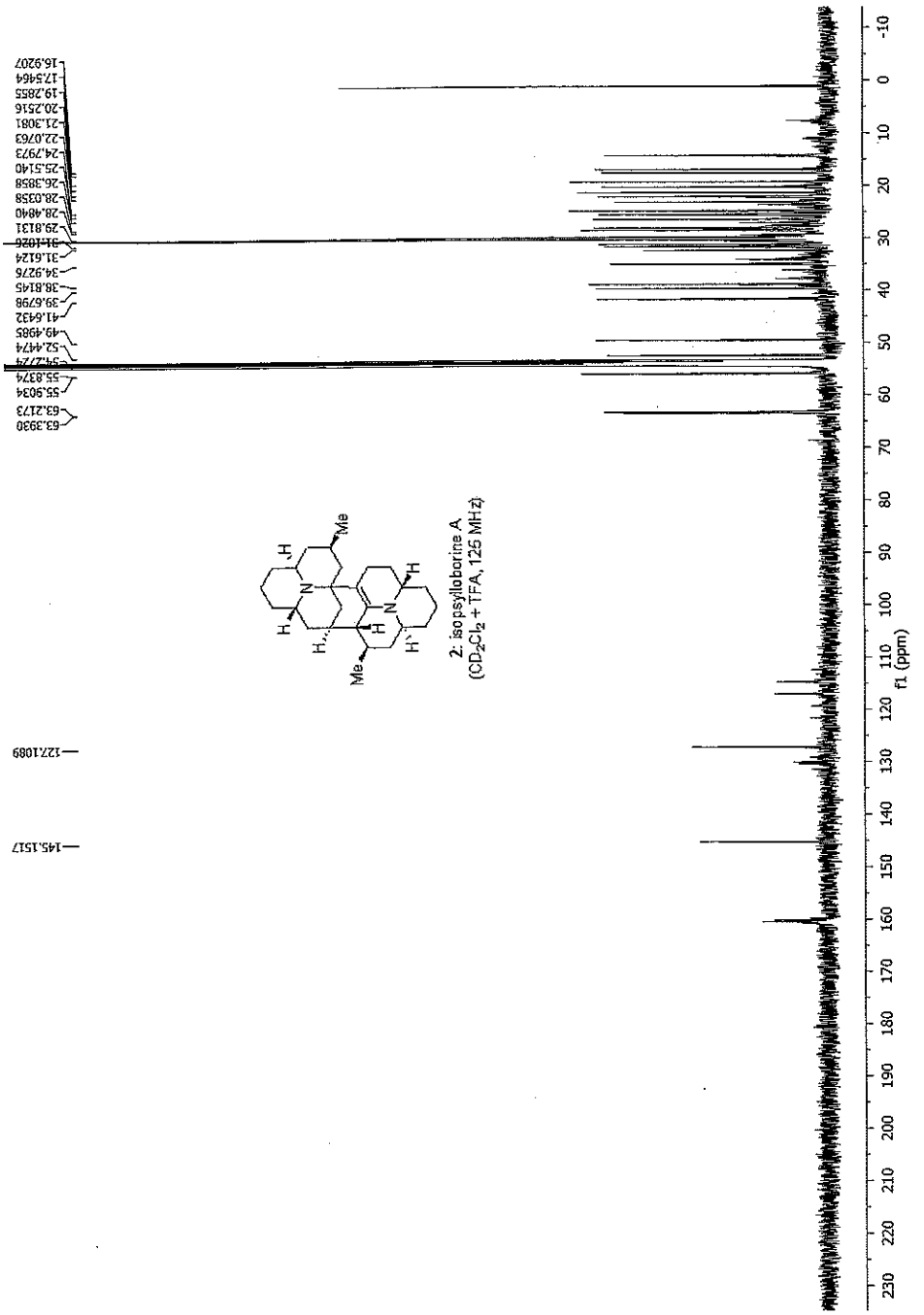

19.758
20.689
22.650
24.260
26.823
26.978
30.667
31.052
31.375
31.661
33.769
34.152
35.462
35.576
36.996
43.556
47.240
48.330
49.179
51.009
53.457
55.971
56.896
60.828
112.560
121.409
124.130
126.915
132.743
133.085
133.426
133.770
144.561
149.149
Me
CF3
F3C
44
(C6D6, 100 MHz)
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230

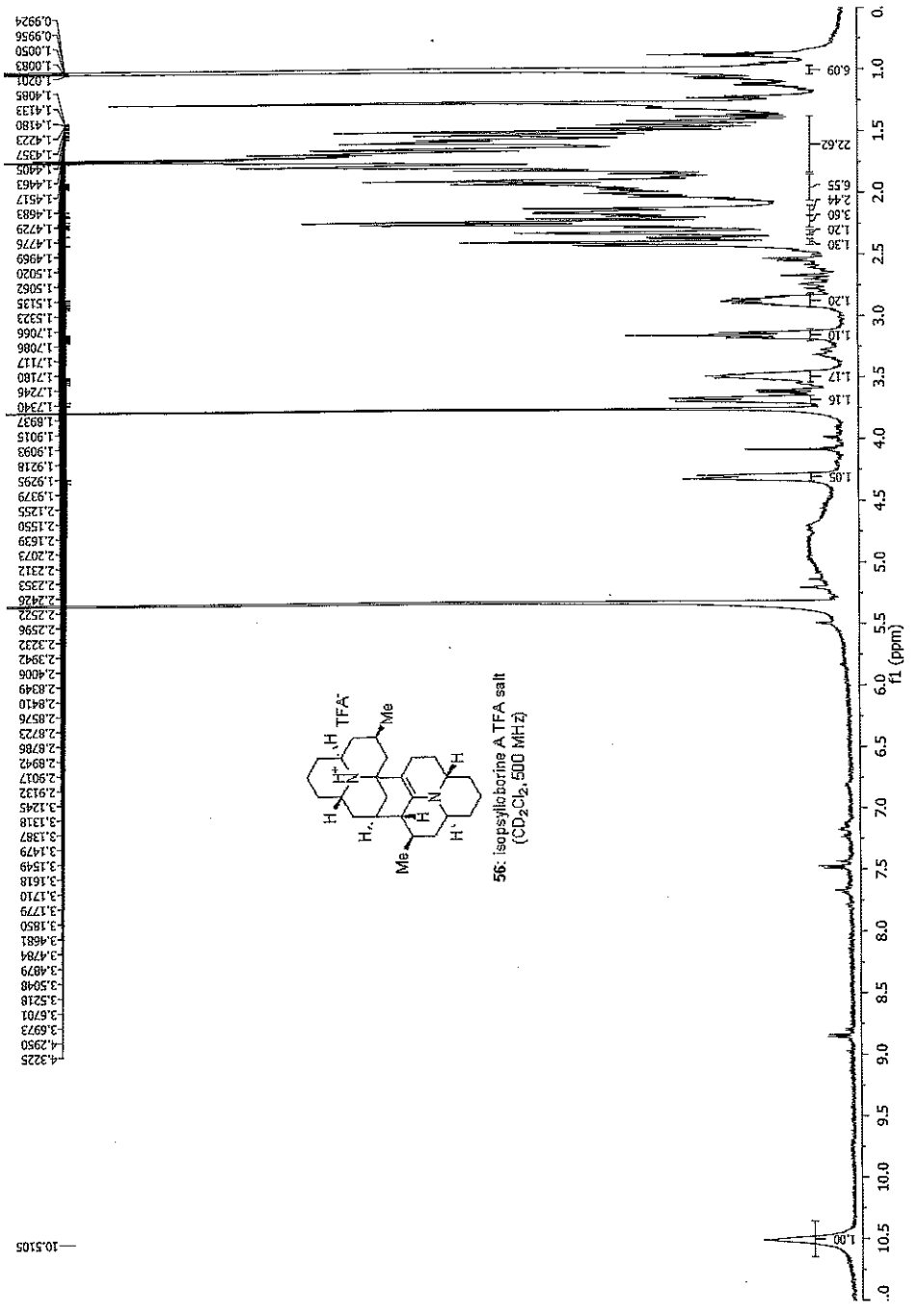

ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
3.042
28.329
1.145
3.141
2.007
0.896
1.050
0.908
0.934
0.791
0.807
0.837
0.856
0.894
0.984
1.014
1.051
1.068
1.104
1.897
1.921
1.928
1.952
1.960
2.034
2.071
2.109
2.131
2.153
2.248
2.276
2.302
2.553
2.643
2.670
2.697
3.185
3.199
3.214
3.229
3.479
3.497
Me
Me
1: psylloborine A
(C6D6, 400 MHz)


19.987
20.386
20.977
22.788
24.421
26.174
27.105
31.388
31.791
31.919
34.368
34.490
35.819
35.967
36.720
43.874
47.609
48.714
49.294
50.709
54.403
56.307
56.781
118.828
145.645
1: psylloborine A
(C6D6, 100 MHz)
ppm

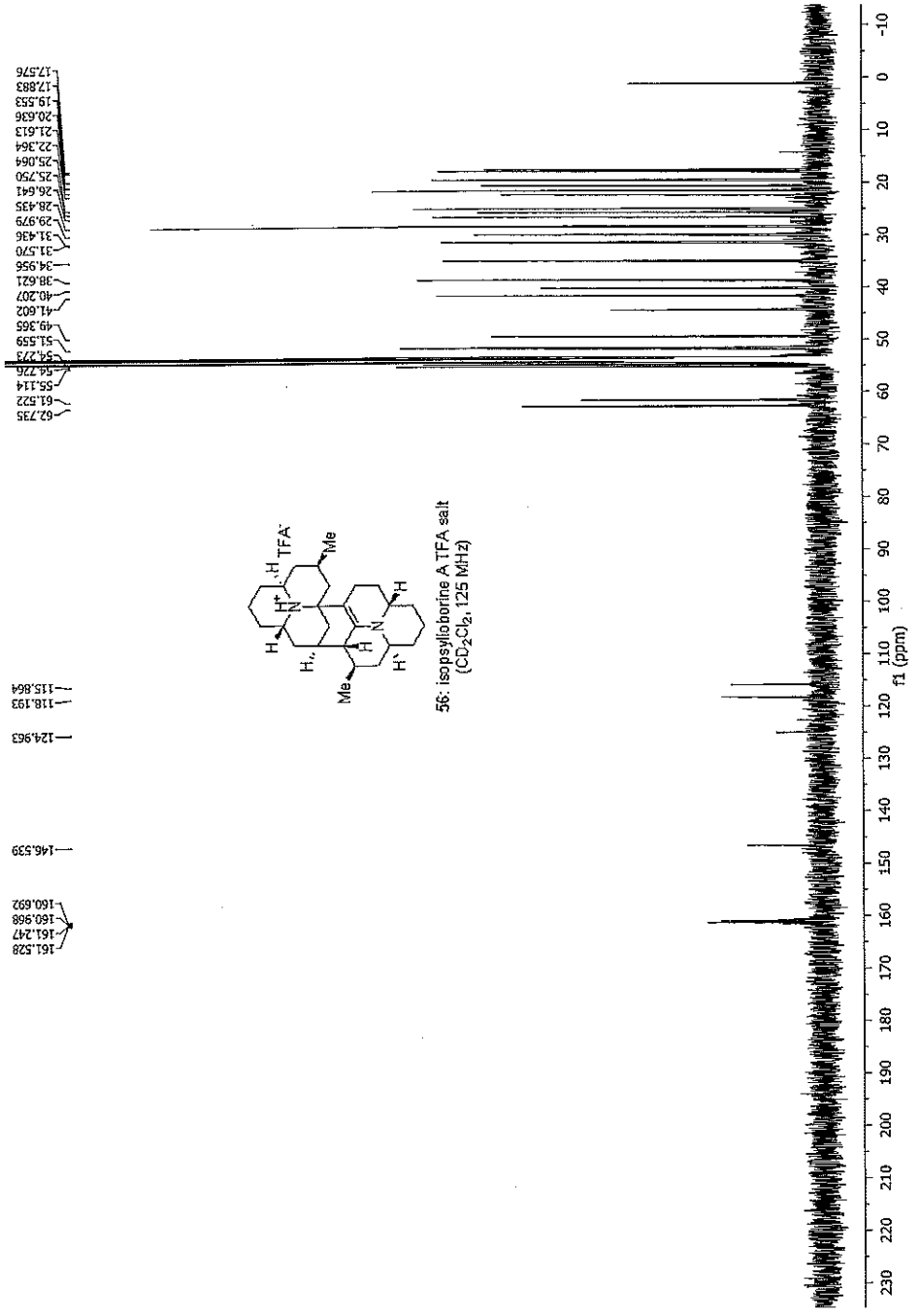

19.989
20.158
20.780
22.655
24.245
25.988
27.149
31.257
31.792
31.883
34.244
34.410
34.505
35.802
35.869
36.663
43.848
47.496
48.770
49.325
50.639
54.595
56.474
57.120
119.806
145.034
Me
Me
H
H
H
H
H
N
N
1: psyfloborine A
(CD2Cl2, 100 MHz)
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230

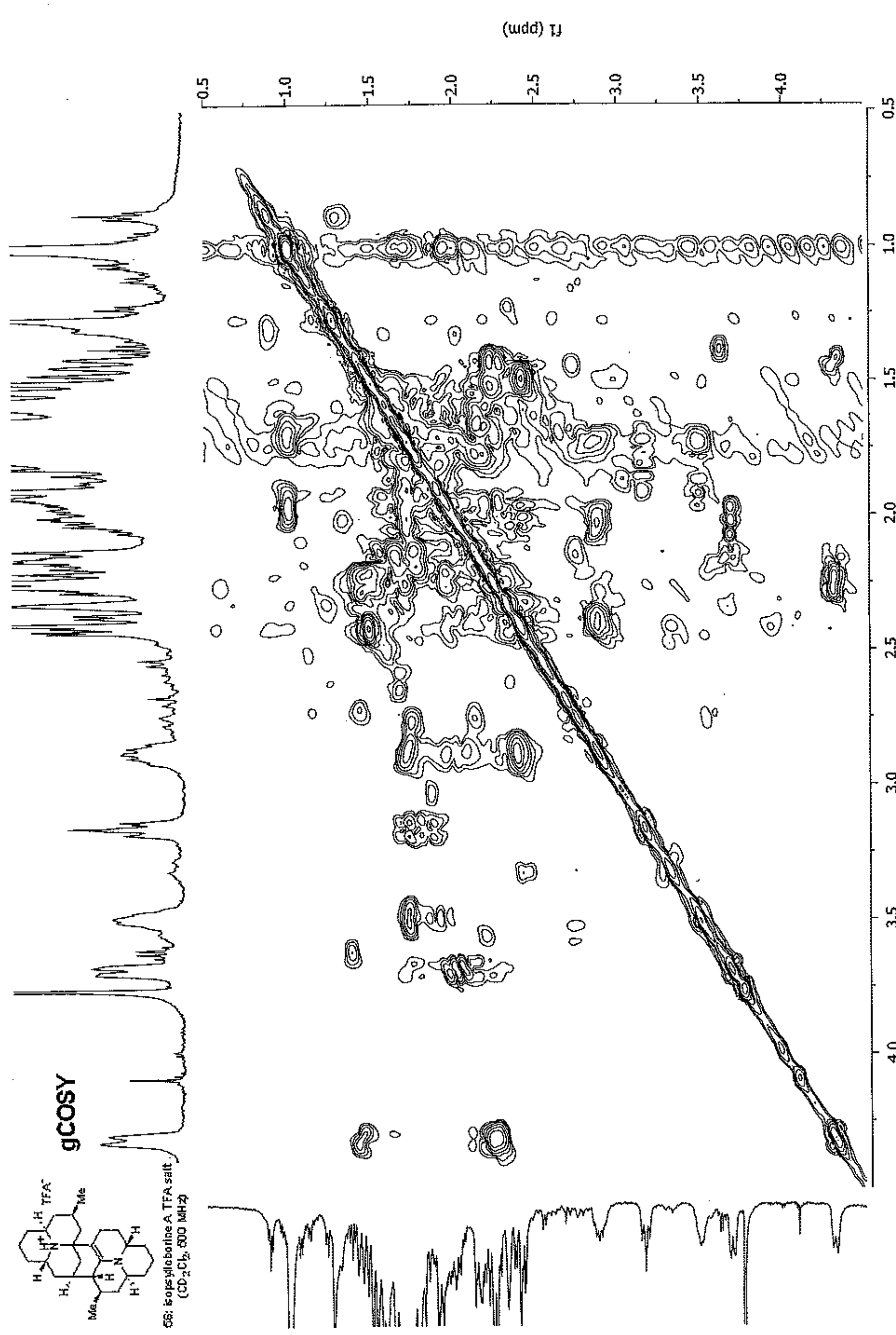

2: isopsyllaborine A
(CD2Cl2 + TFA, 400 MHz)
Me
Me
H
H
H
H
H
N
N
4.202
4.188
4.156
3.816
3.792
3.780
3.617
3.588
3.559
3.373
3.345
3.317
2.724
2.702
2.680
2.482
2.470
2.442
2.433
2.405
2.388
5.046
1.038
1.025
1.010
0.995
1.00
0.94
1.16
0.98
1.29
3.17
3.24
32.12
7.21
f1 (ppm)

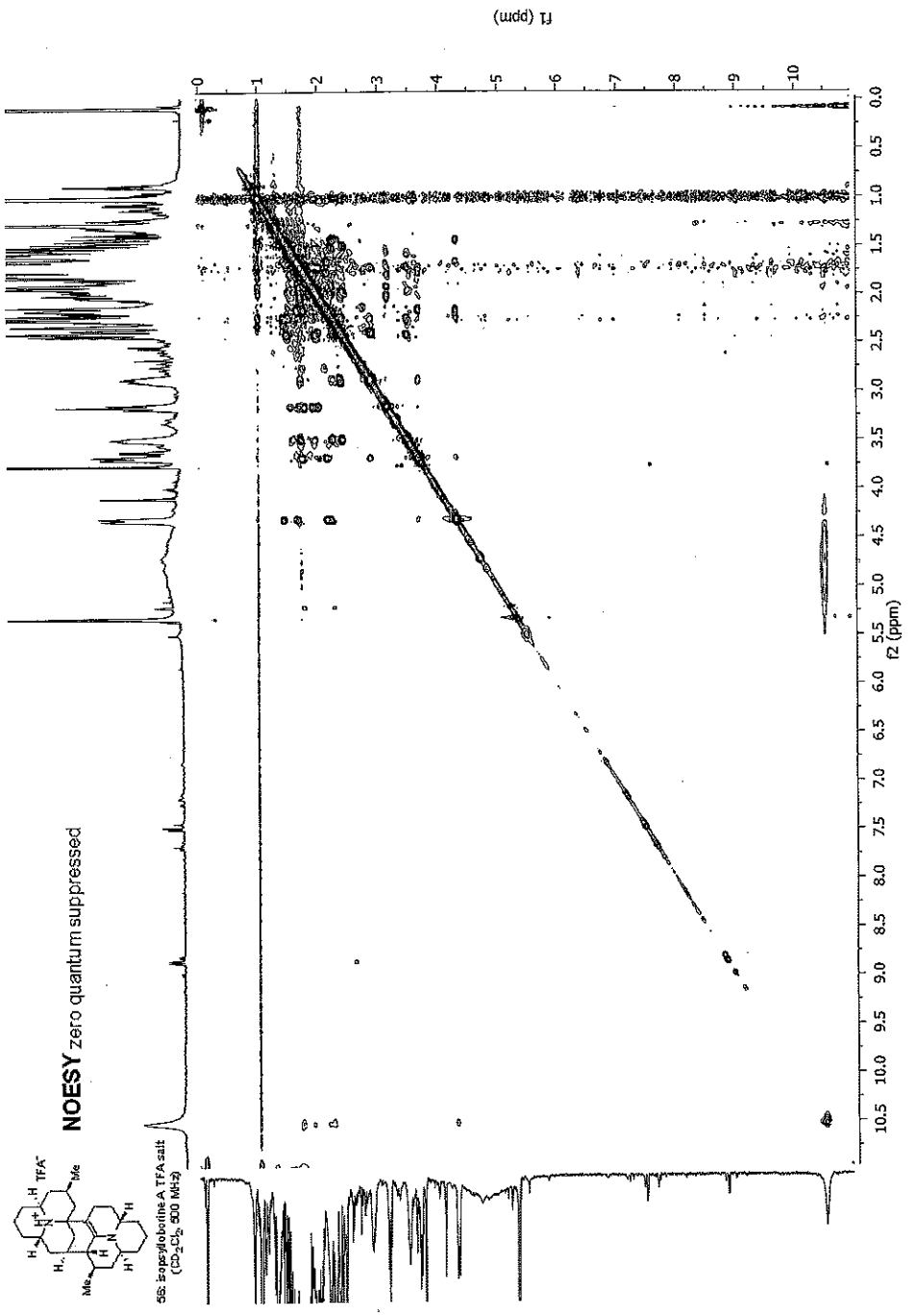

16.9207
17.5464
19.2855
20.2516
21.3081
22.0763
24.7973
25.5140
26.3858
28.0358
28.4840
29.8131
31.1026
31.6124
34.9276
38.8145
39.6798
41.6432
49.4985
52.4474
54.7274
55.3724
55.9034
63.2173
63.3930
122.1089
145.1517
2: isopsyllaborine A
(CD2Cl2 + TFA, 125 MHz)
Me
H
N
H
H
N
H
H
Me
H
f1 (ppm)

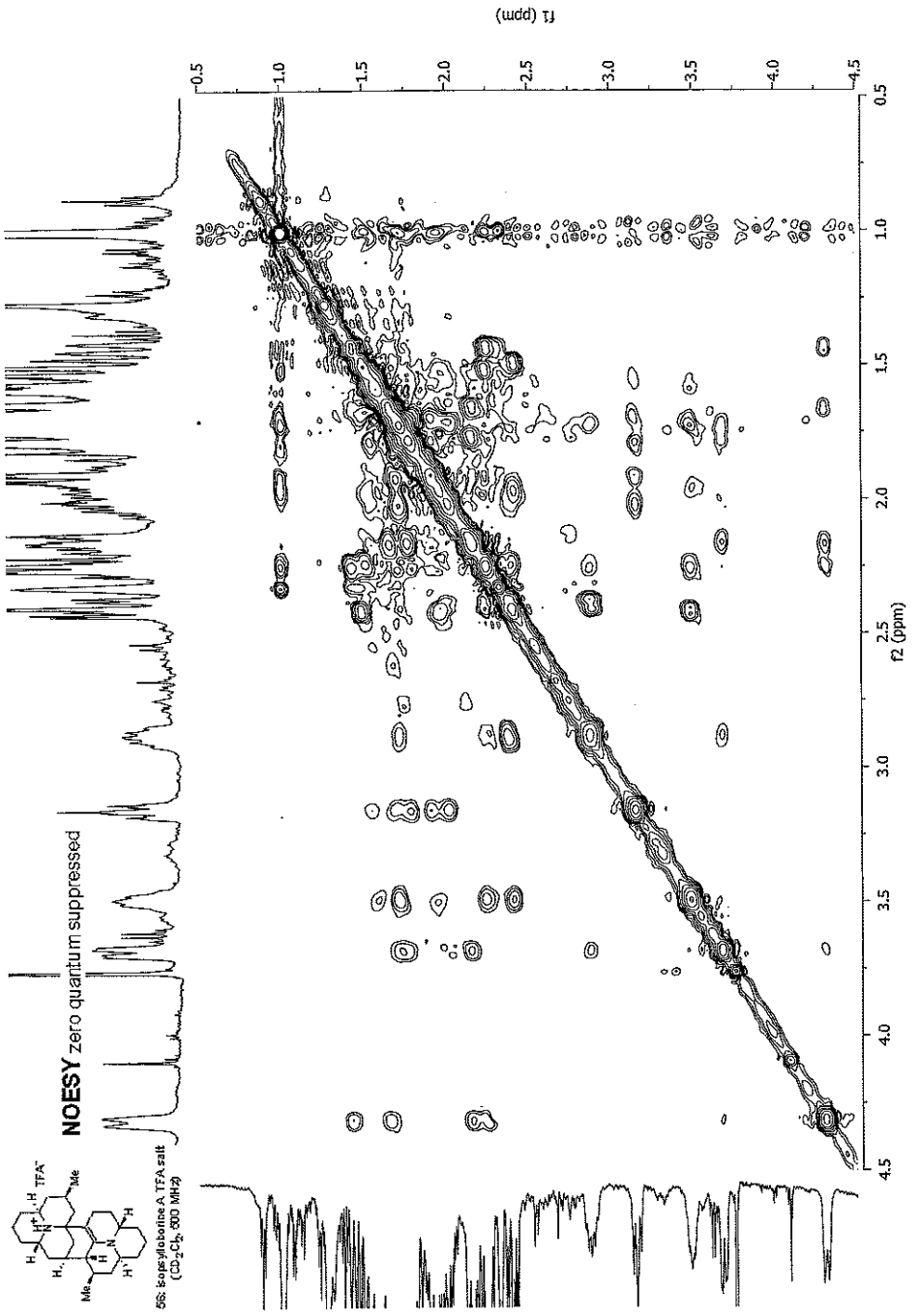


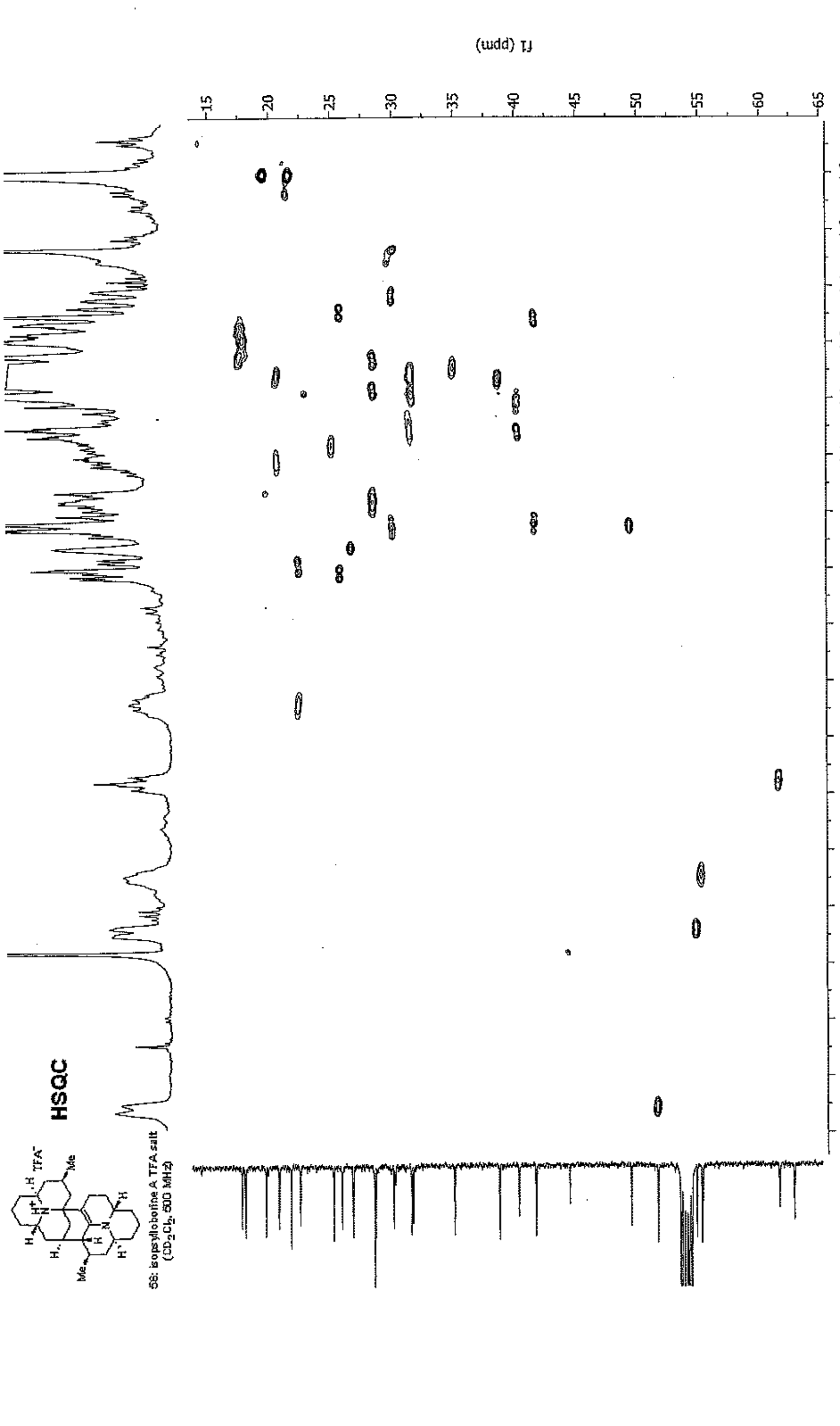
56: isopsyllicborine A TFA salt
(CD_2Cl_2, 500 MHz)

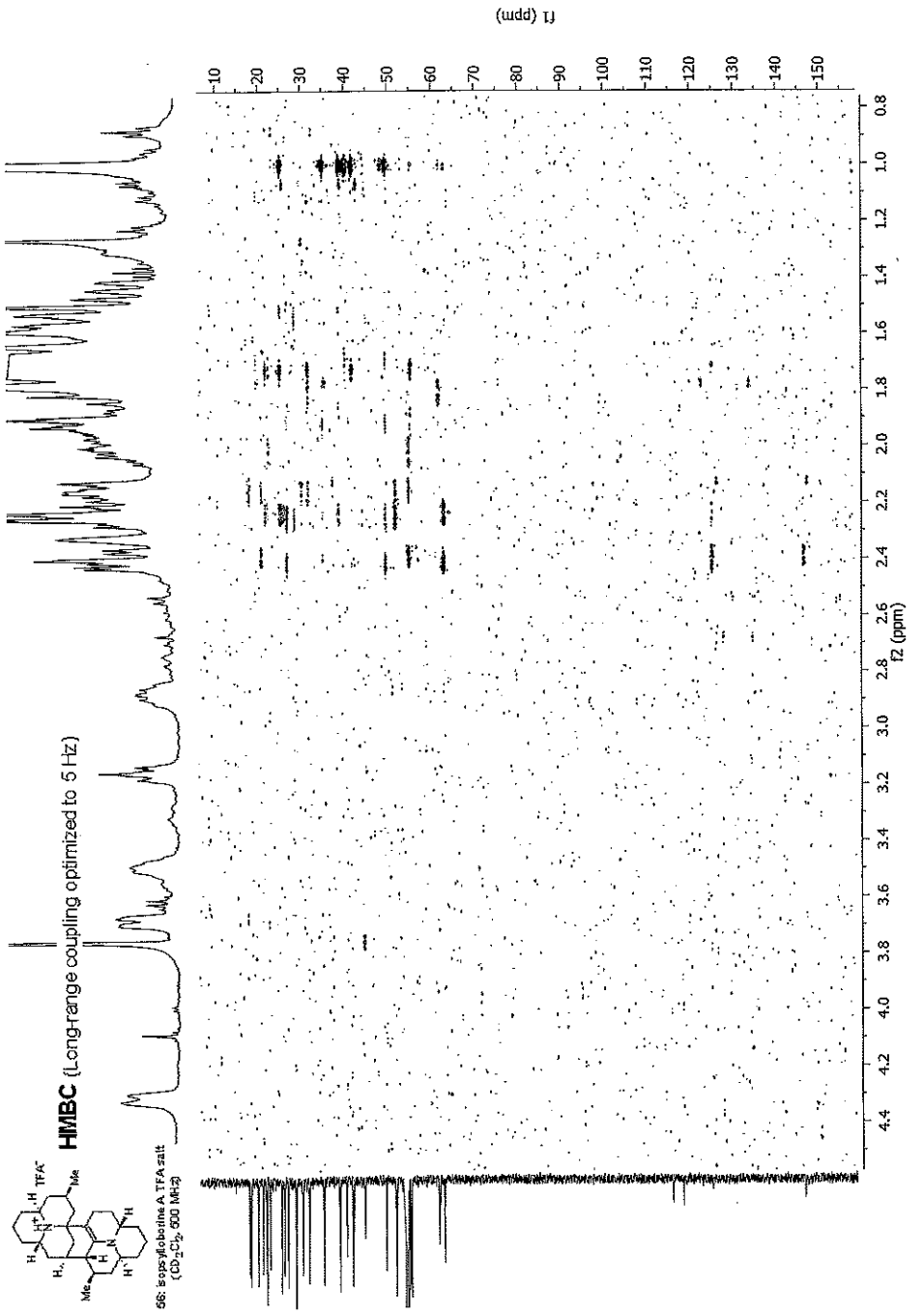

17.576
17.883
19.533
20.636
21.613
22.364
25.064
25.750
26.641
28.435
29.979
31.436
31.570
34.956
38.621
40.207
41.602
49.365
51.559
54.273
54.726
55.114
61.522
62.735
115.864
118.193
124.963
146.539
160.692
160.968
161.247
161.528
TFA
Me
Me
H
H
H
H
H
56: isopsylloborine A TFA salt
(CD_2Cl_2, 125 MHz)
f1 (ppm)

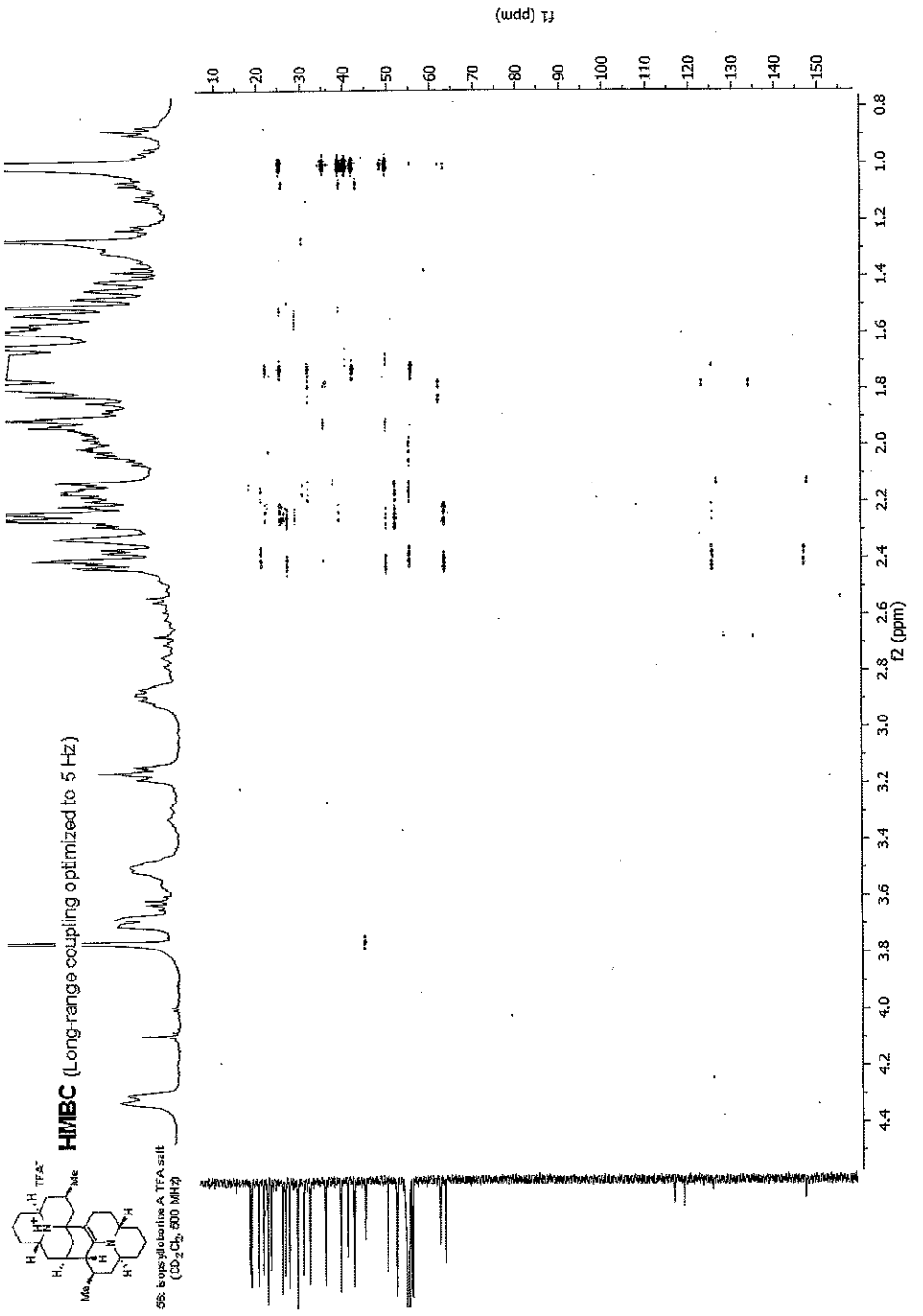

gCOSY
56: isopsylloborine A TFA salt
(CD_2Cl_2, 600 MHz)
f1 (ppm)
f2 (ppm)

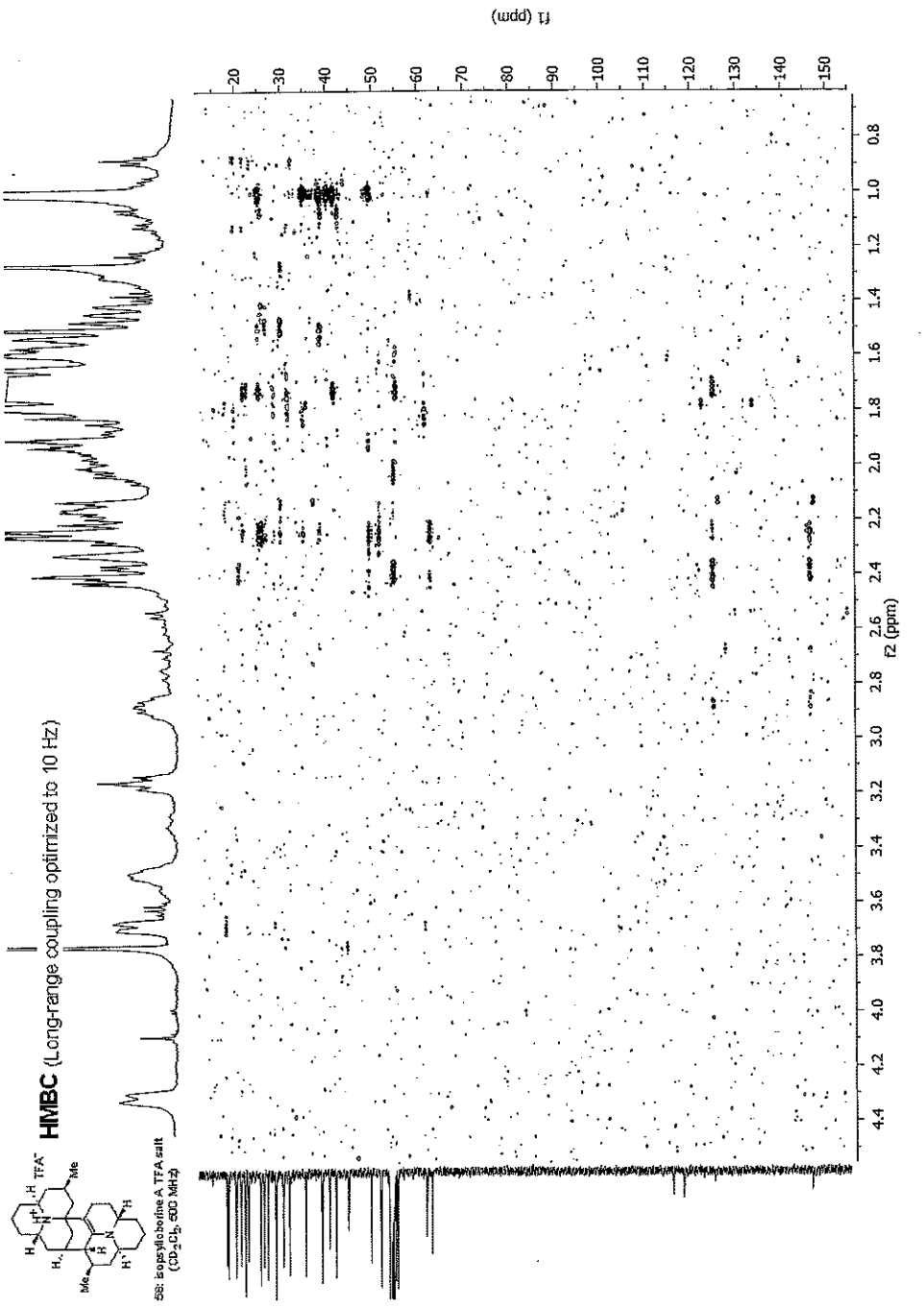

NOESY zero quantum suppressed
6S: Ispsyloborine A TFA salt
(CD2Cl2, 600 MHz)
f1 (ppm)
f2 (ppm)

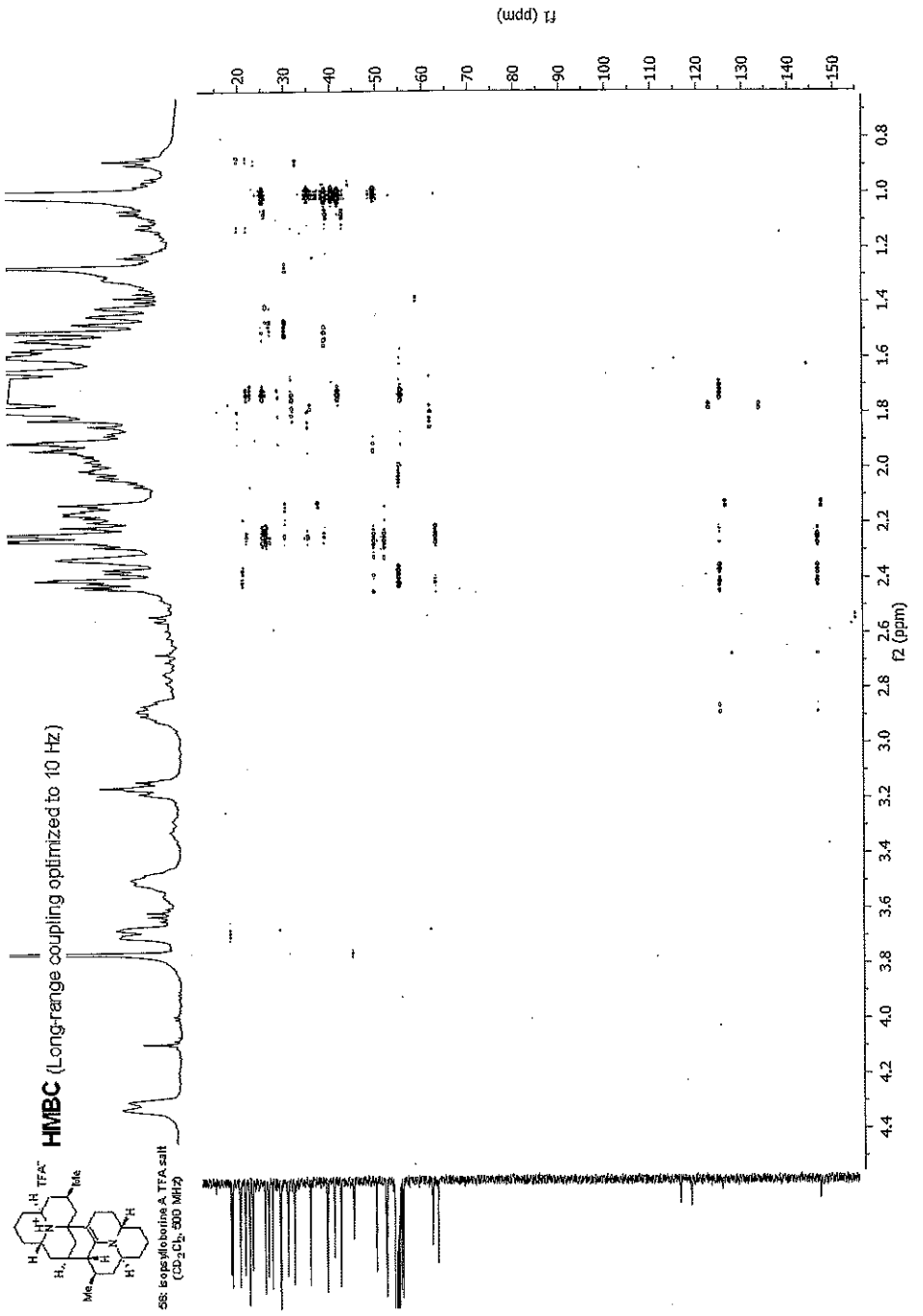

NOESY zero quantum suppressed
56: Isopsylloborine A TFA salt
(CD3-CD2-OD, 600 MHz)
f1 (ppm)
f2 (ppm)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5

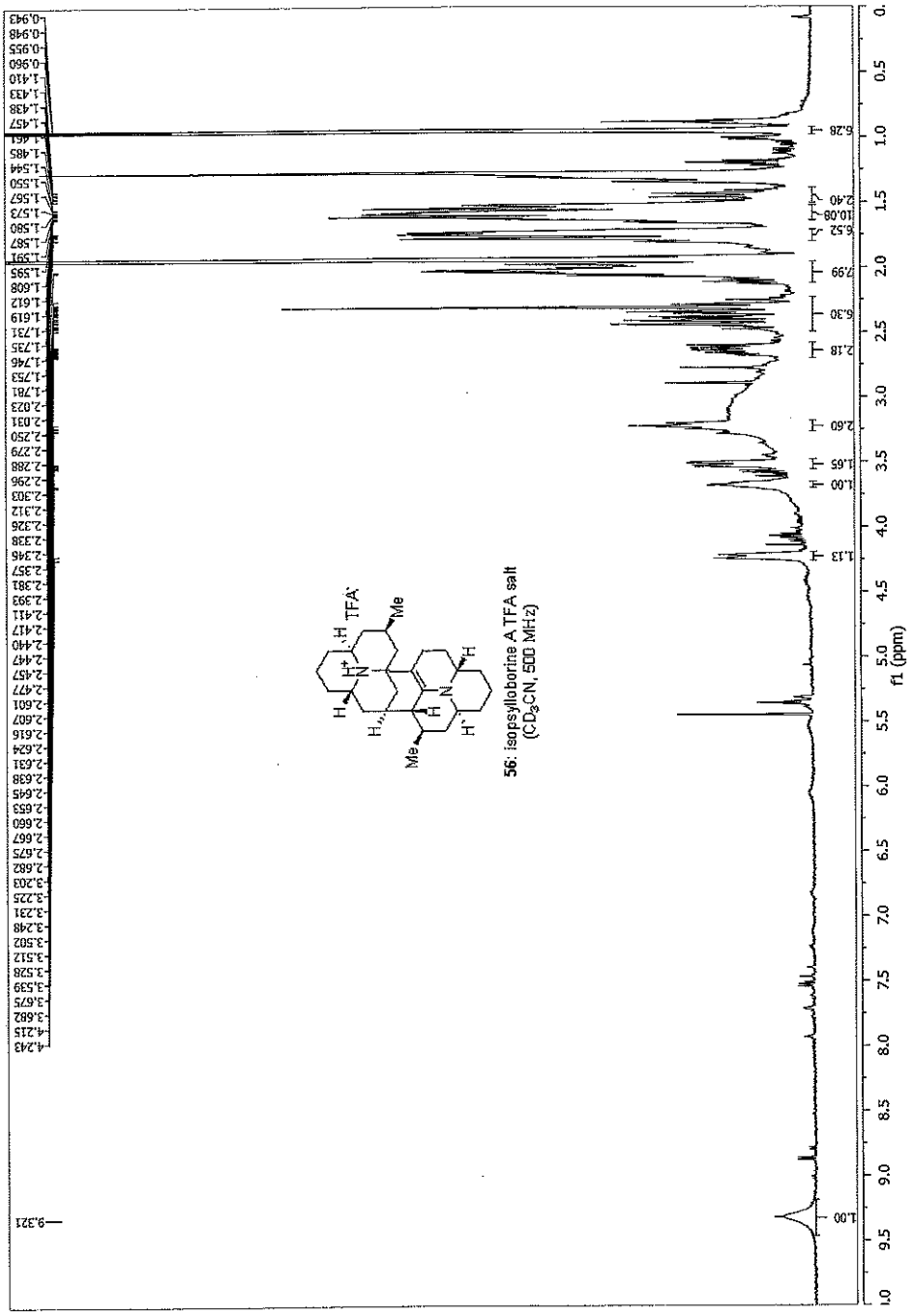

HSQC
56: isopsylloborine A TFA salt
(CD2Cl2, 500 MHz)
f1 (ppm)
f2 (ppm)

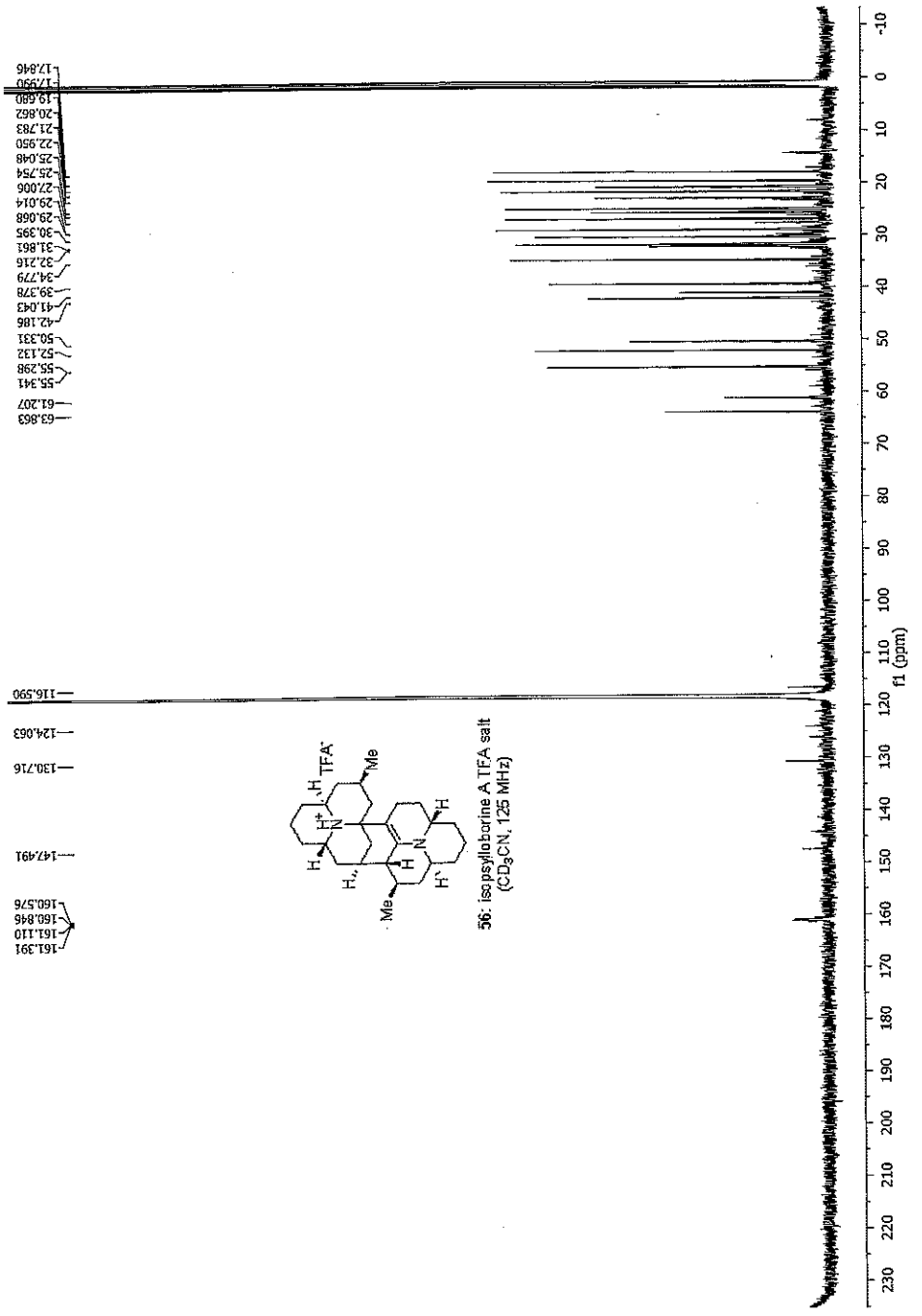

HMBC (Long-range coupling optimized to 5 Hz)
66: isopsilocaulne A TFA salt
(CD2Cl2, 600 MHz)
f1 (ppm)
f2 (ppm)

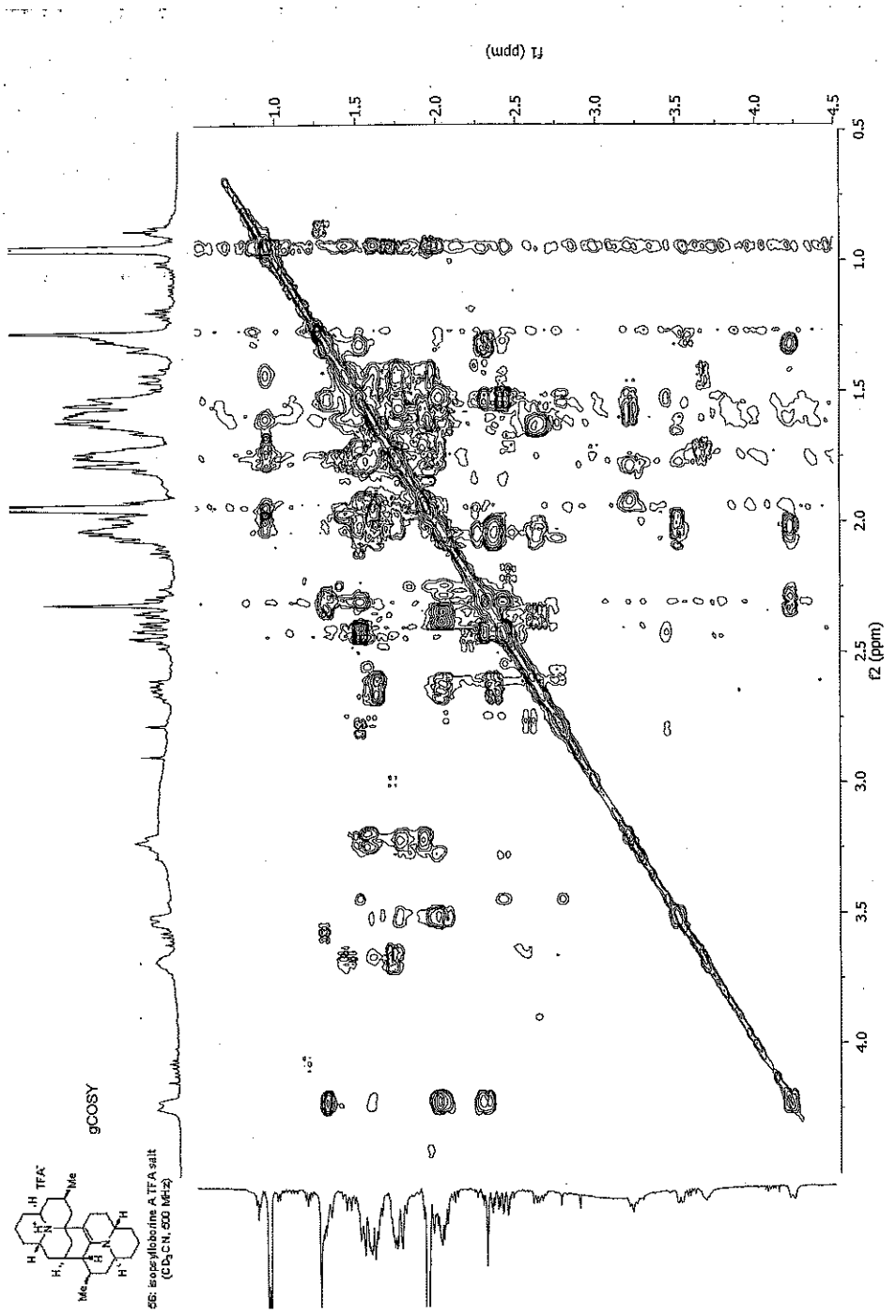

HMBC (Long-range coupling optimized to 5 Hz)
56: Isopsydlobaline A TFA salt
(CD2Cl2, 600 MHz)
f1 (ppm)
f2 (ppm)

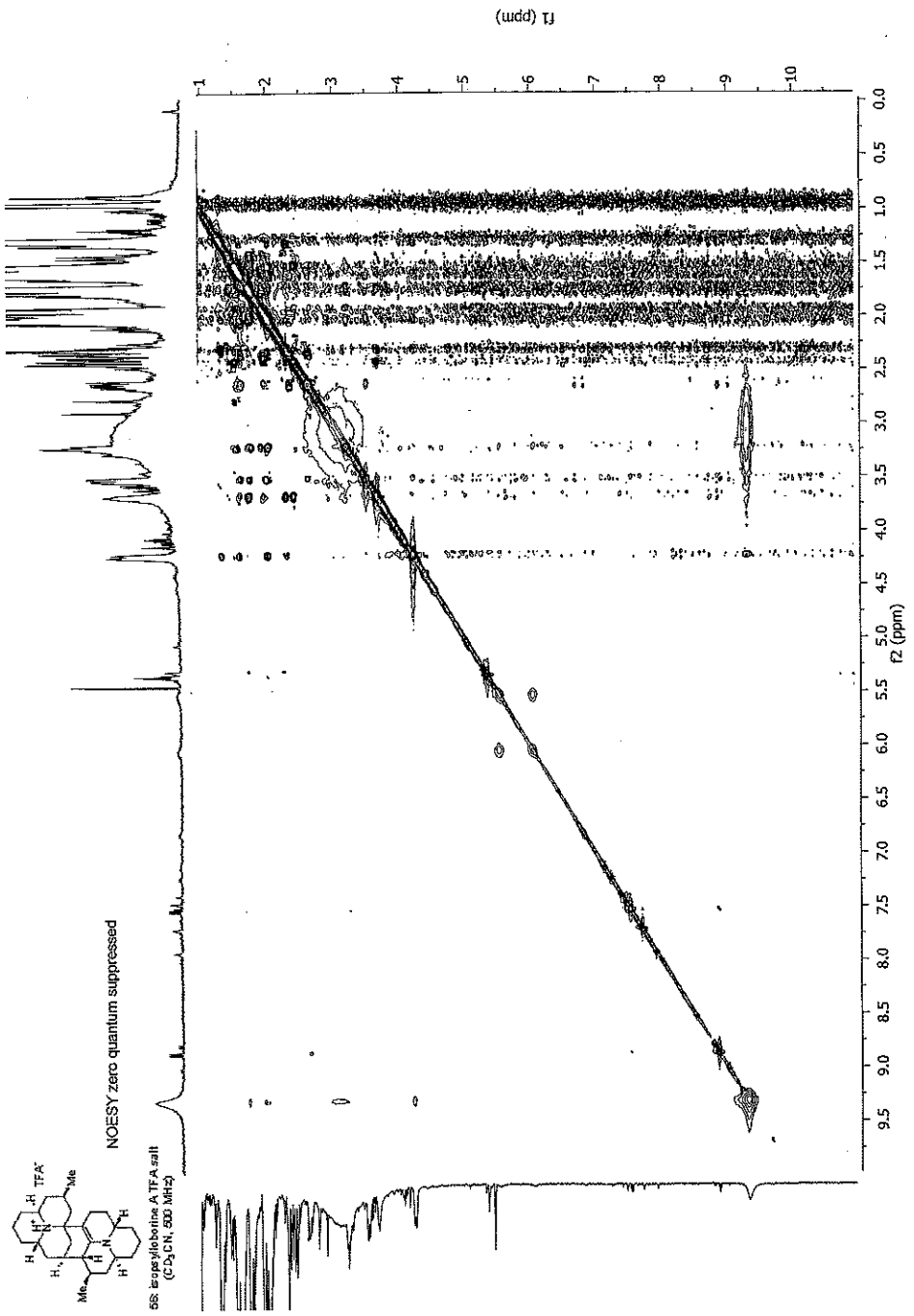

HMBC (Long-range coupling optimized to 10 Hz)
58: Isopsylloborine A TFA salt
(CD2Cl2, 600 MHz)
f1 (ppm)
f2 (ppm)

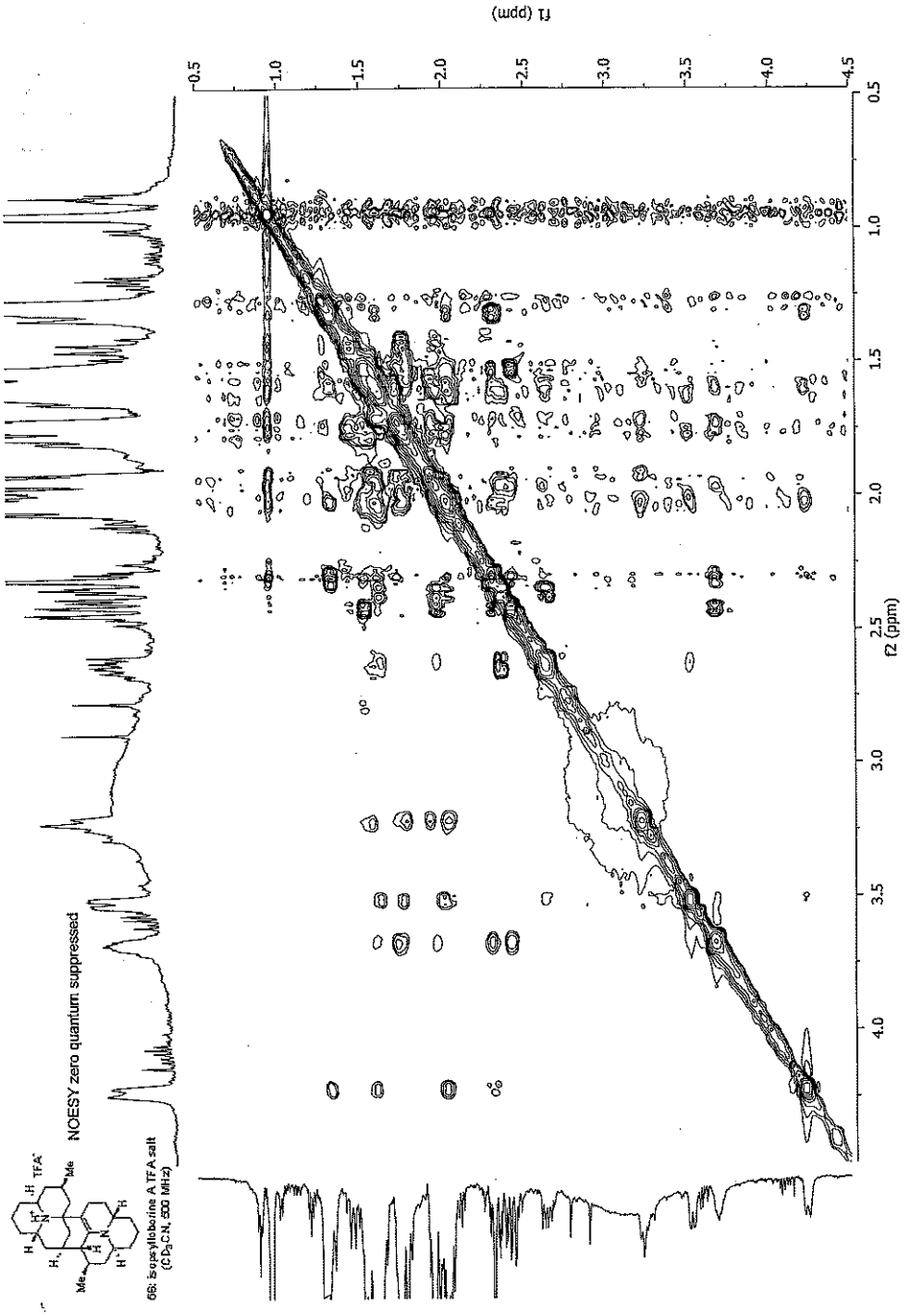

HMBC (Long-range coupling optimized to 10 Hz)
f1 (ppm)
f2 (ppm)

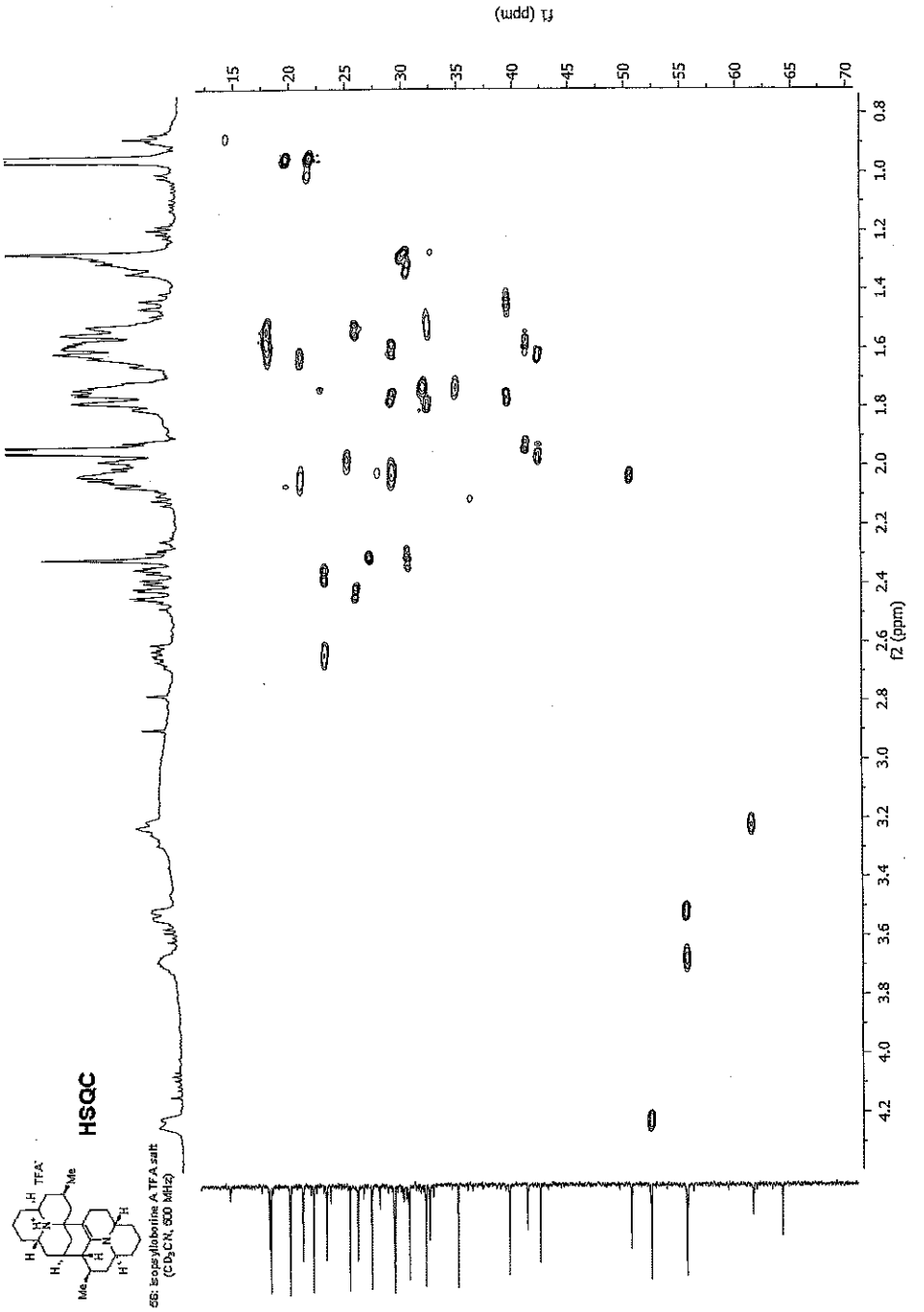

56: isopsyllaborine A TFA salt
(CD3CN, 500 MHz)
TFA
Me
Me
f1 (ppm)

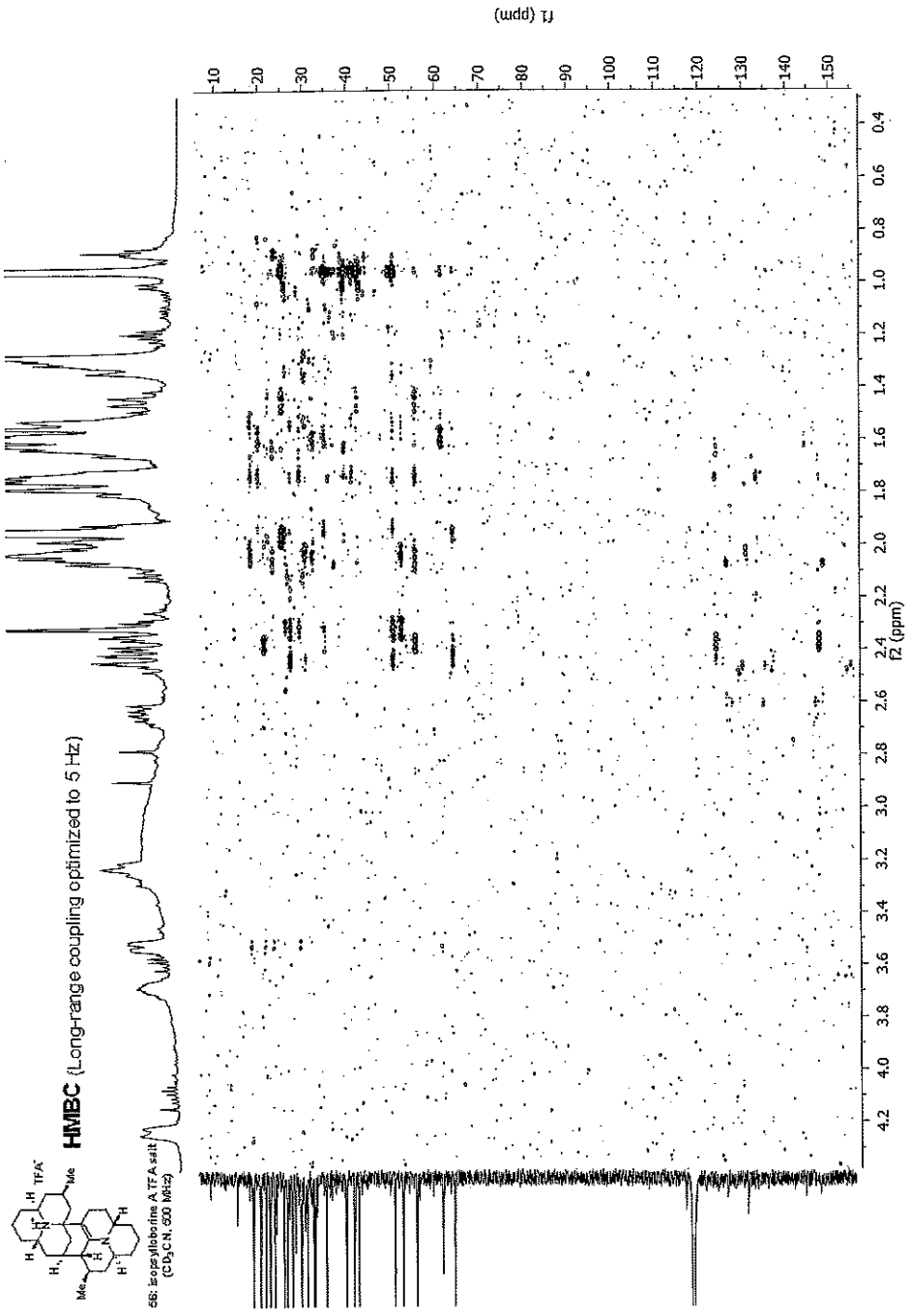

17.846
17.990
19.680
20.862
21.783
22.950
25.048
25.754
27.006
29.014
29.068
30.395
31.861
32.216
34.779
39.378
41.043
42.186
50.331
52.132
55.298
55.341
61.207
63.863
116.590
124.063
130.716
142.491
160.576
160.846
161.110
161.391
TFA⁻
Me
H
H
H
H
H
Me
56: isopsylloborine A TFA salt
(CD3CN, 125 MHz)
f1 (ppm)

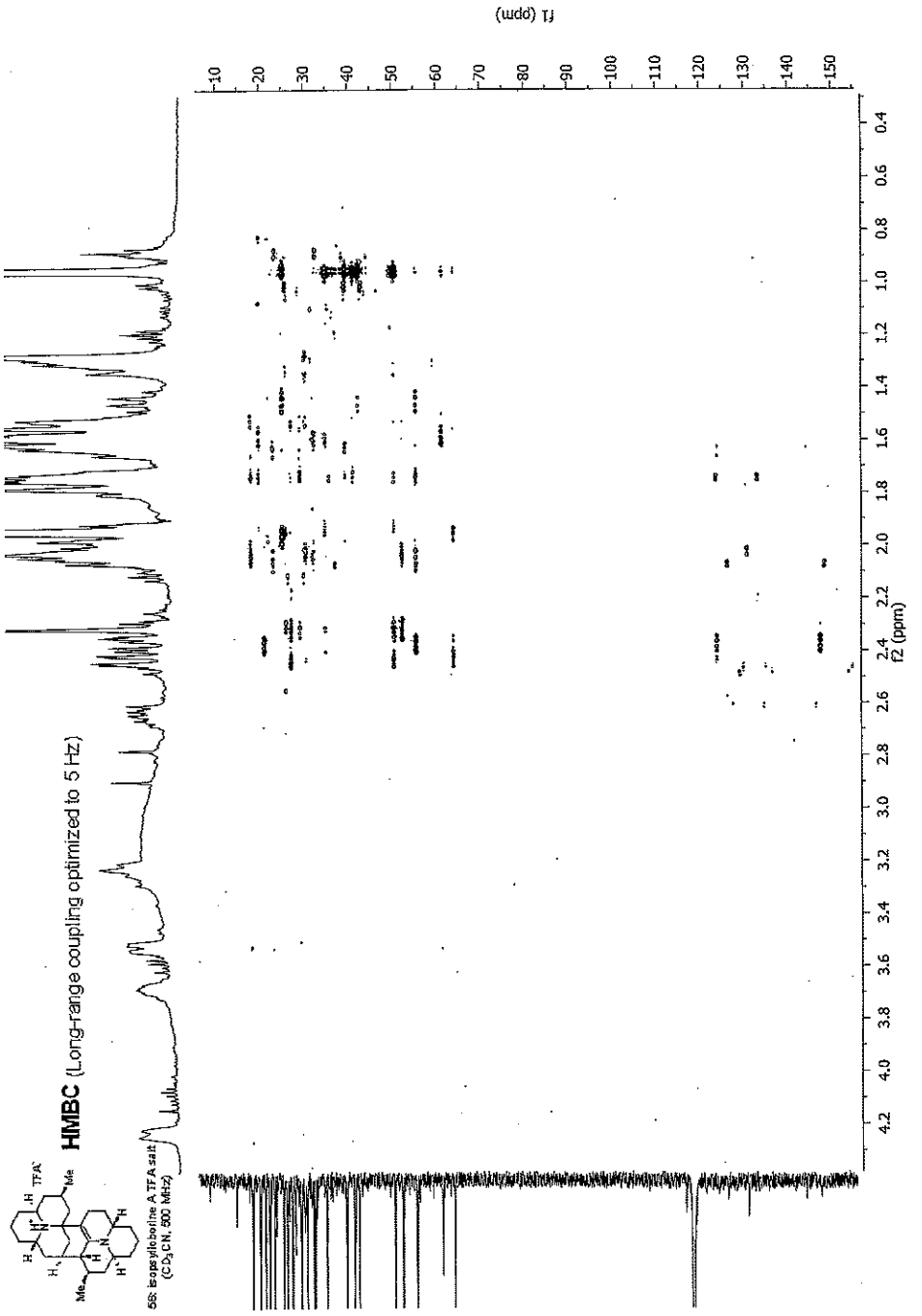

gCOSY
56: Isopsilocibine A TFA salt
(CD3CN, 500 MHz)
TFA
Me
Me
f1 (ppm)
f2 (ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
0.5

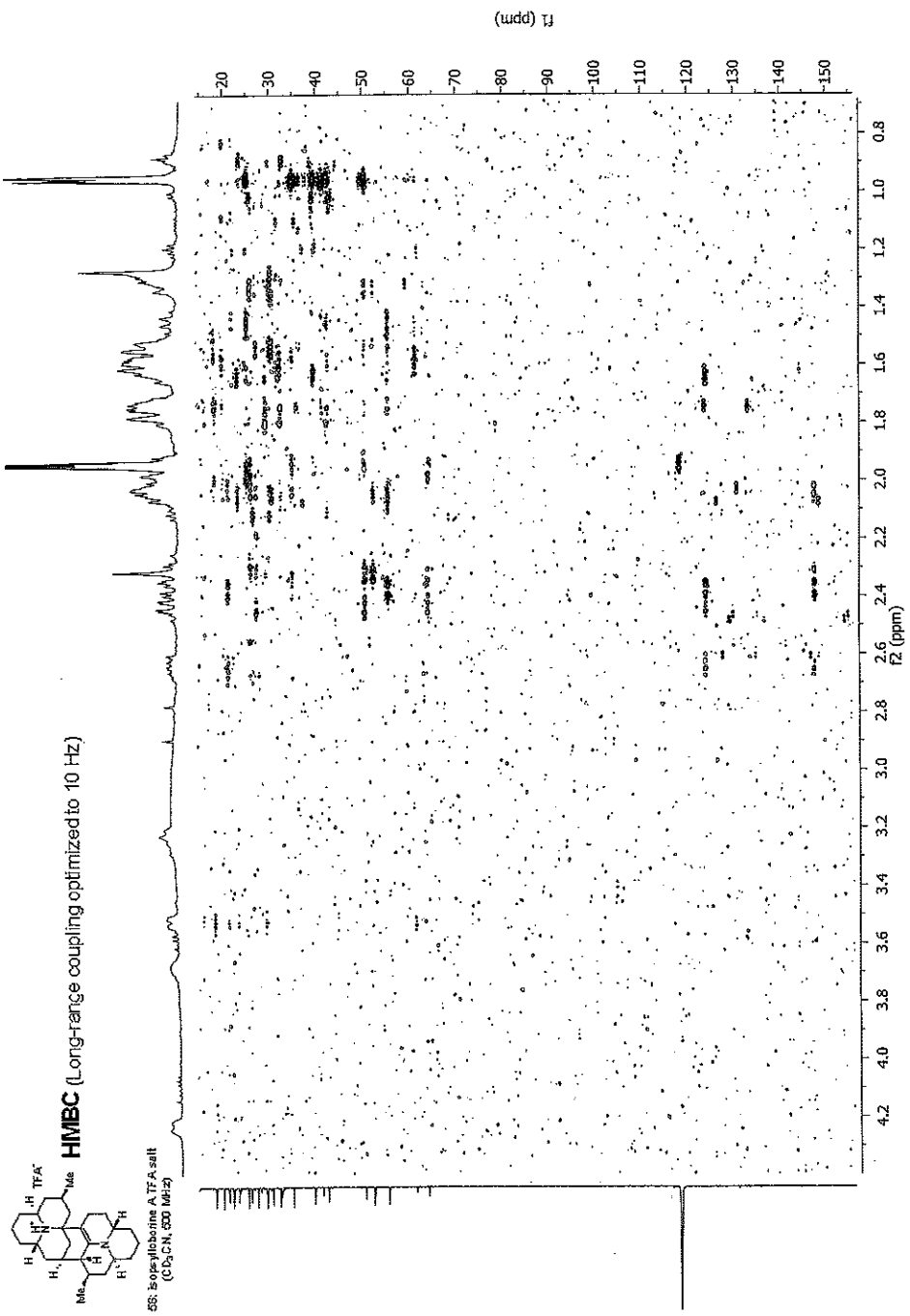

NOESY zero quantum suppressed
f1 (ppm)
f2 (ppm)
TFA
Me
Me

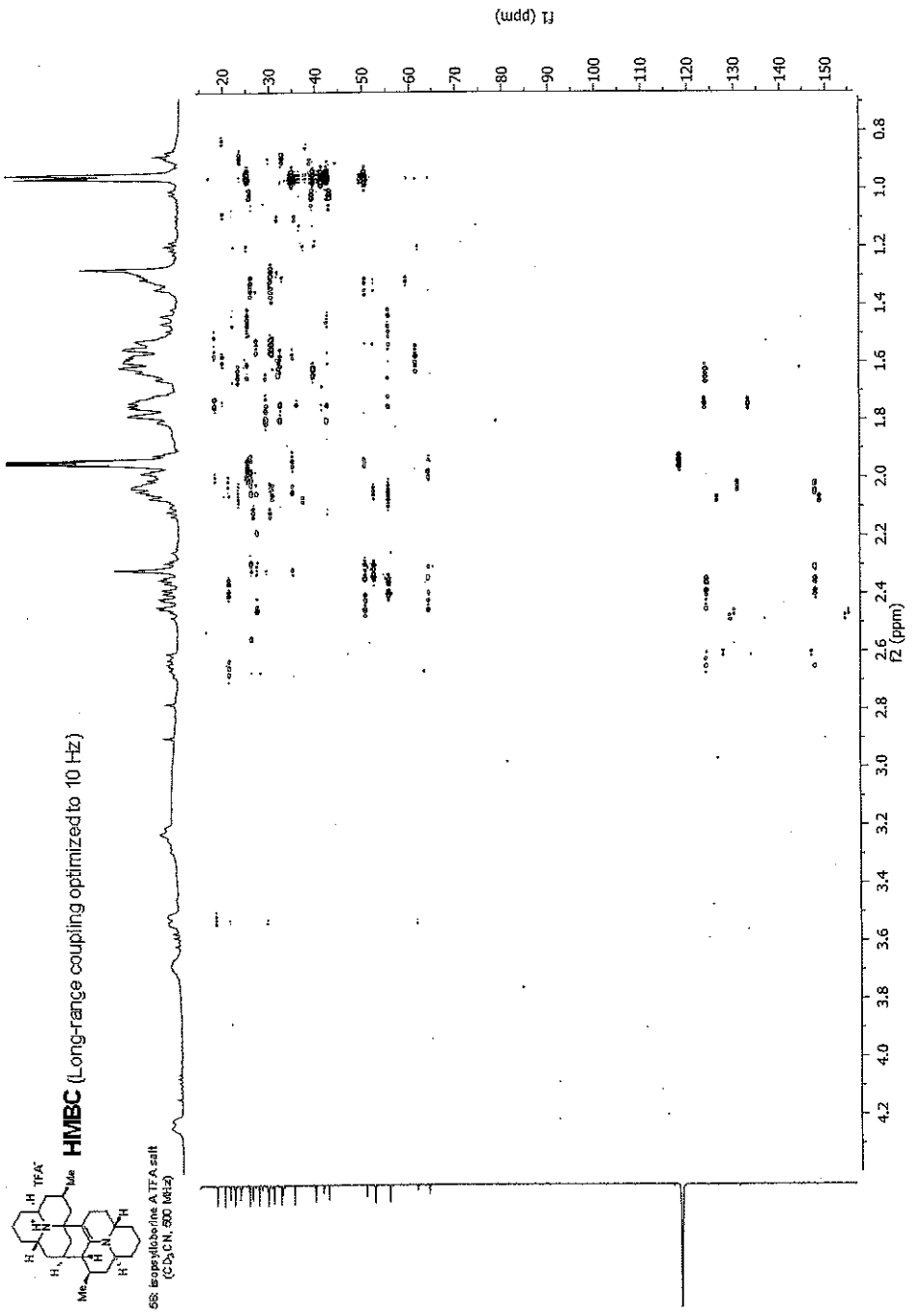

f1 (ppm)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
f2 (ppm)
NOESY zero quantum suppressed
68: isopyloborine A TFA salt
(CD3CN, 500 MHz)
TFA⁻
Me
Me

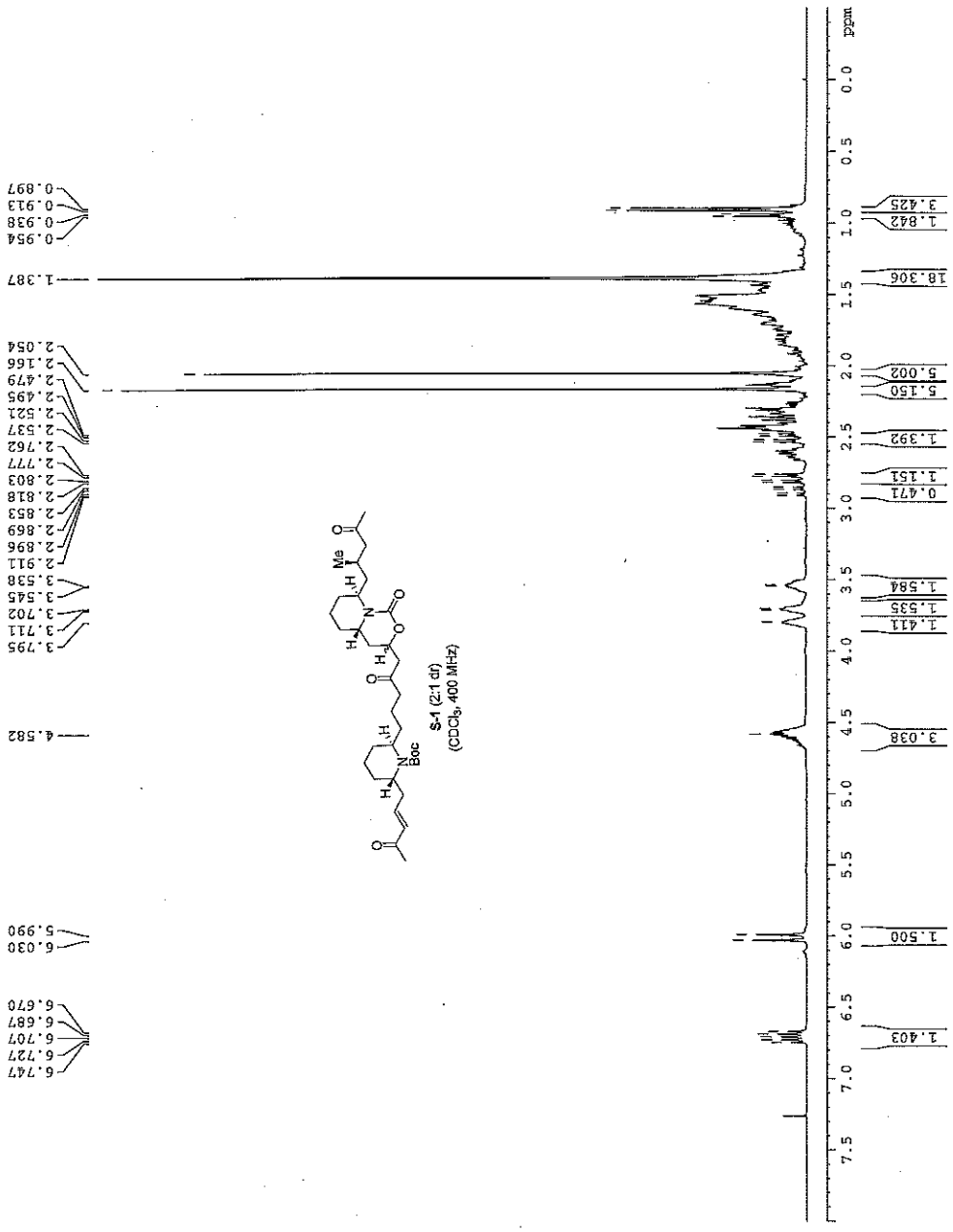

HSQC
f1 (ppm)
f2 (ppm)
TFA
Me
Me

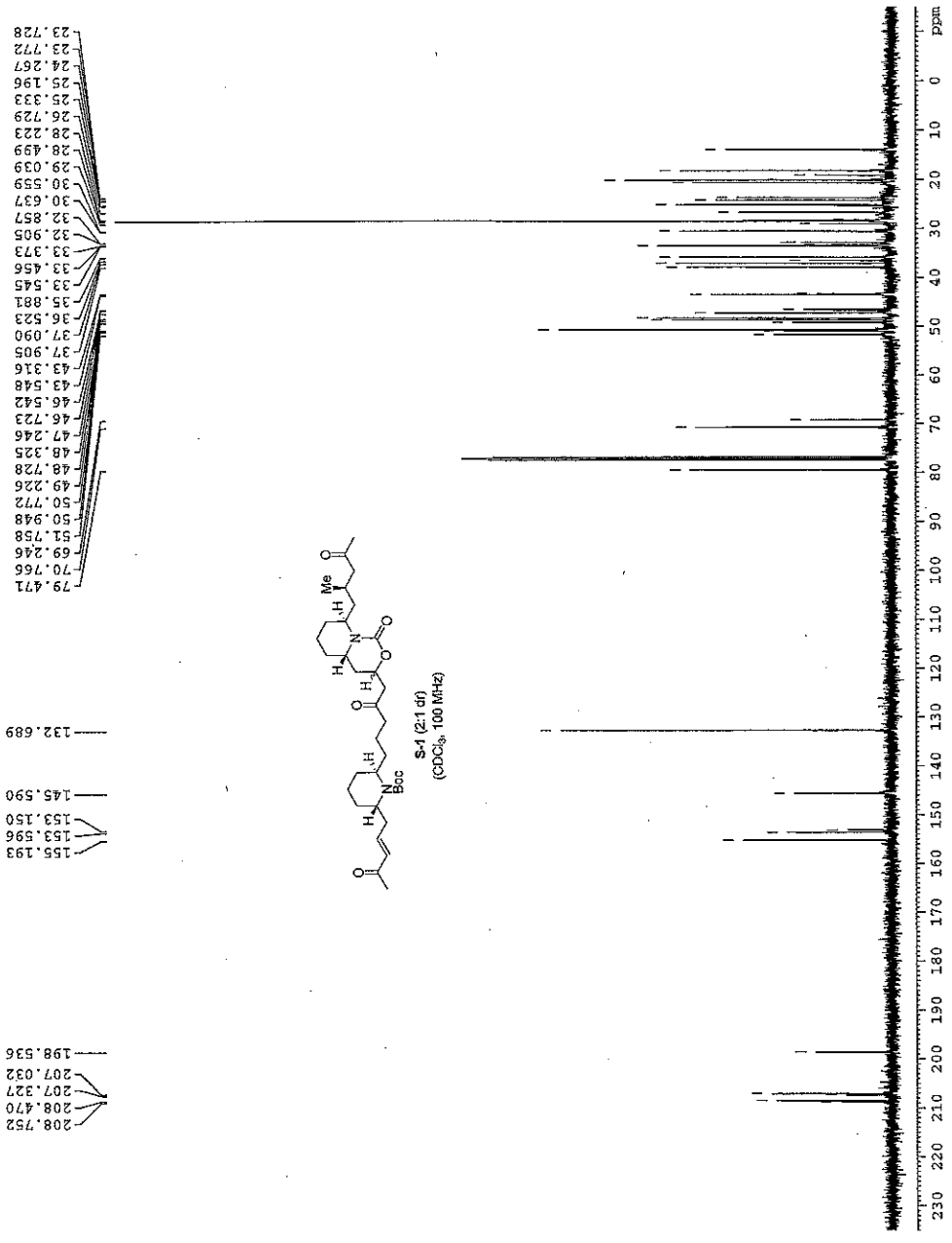

HMBC (Long-range coupling optimized to 5 Hz)
56: Isopyloborine A TFA salt
(CD3CN, 500 MHz)
f1 (ppm)
f2 (ppm)

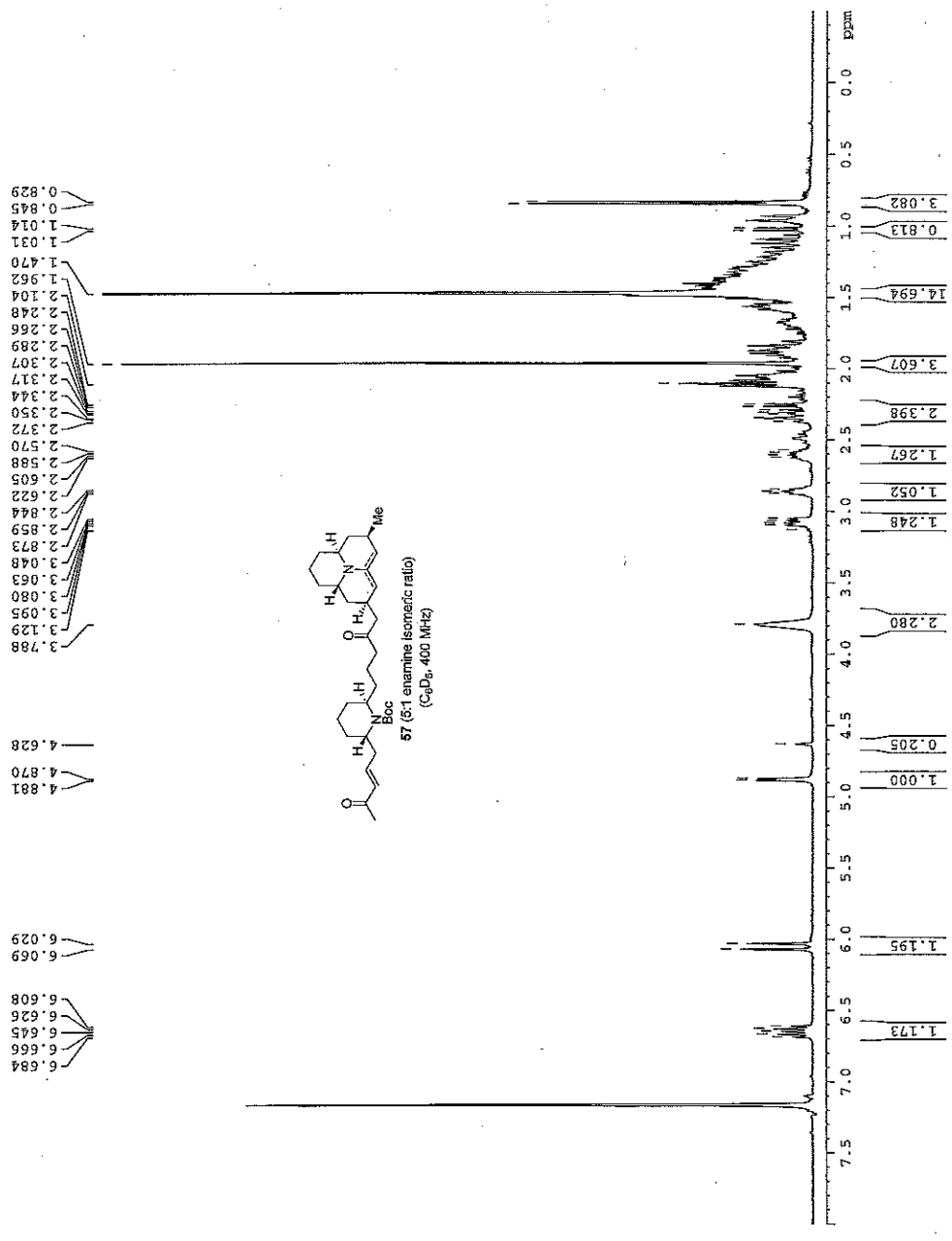

HMBC (Long-range coupling optimized to 5 Hz)
f1 (ppm)
f2 (ppm)

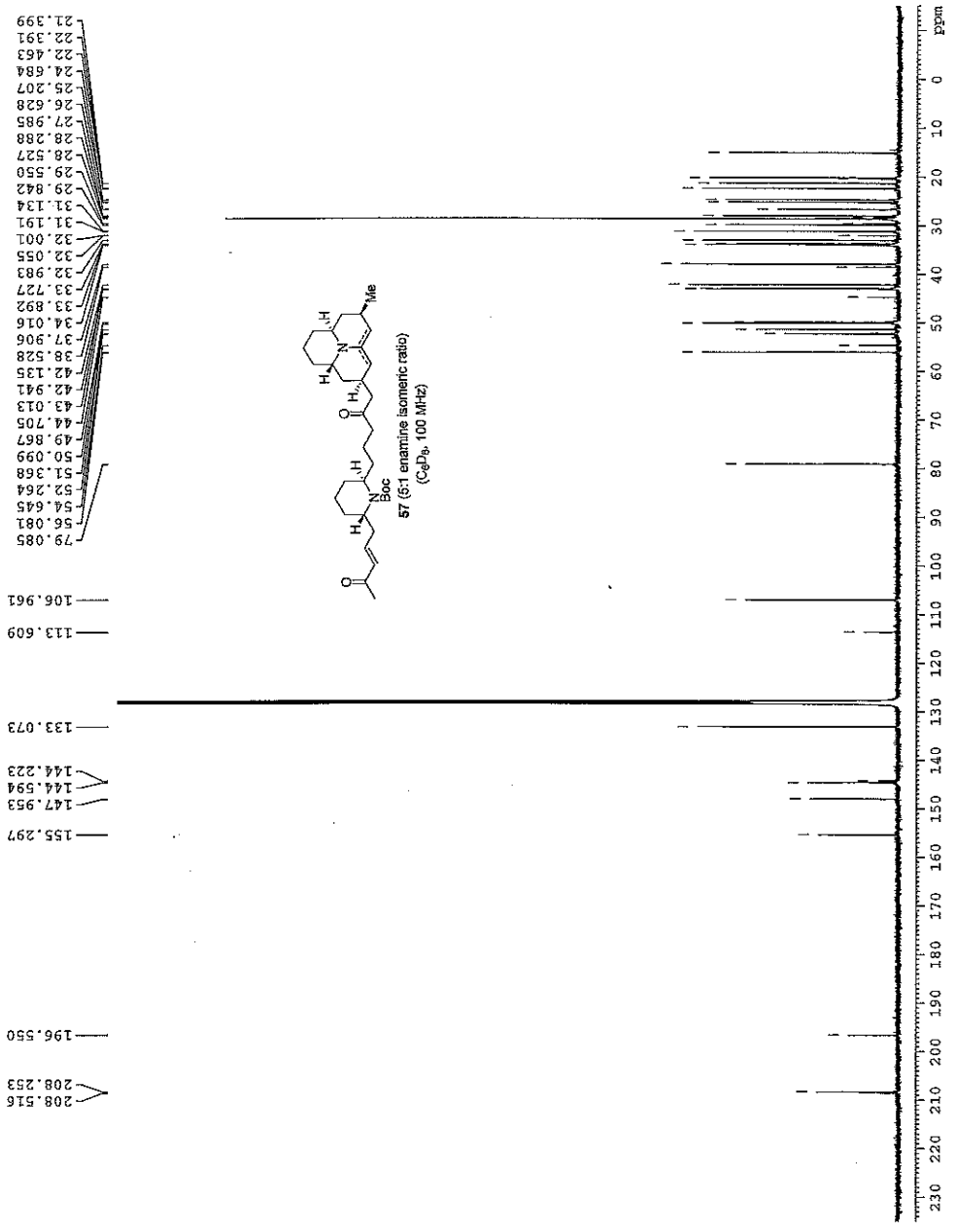

HMBC (Long-range coupling optimized to 10 Hz)
58: Isopsilocorine A TFA salt
(CD3C:N, 500 MHz)
TFA
Me
Me
f1 (ppm)
f2 (ppm)

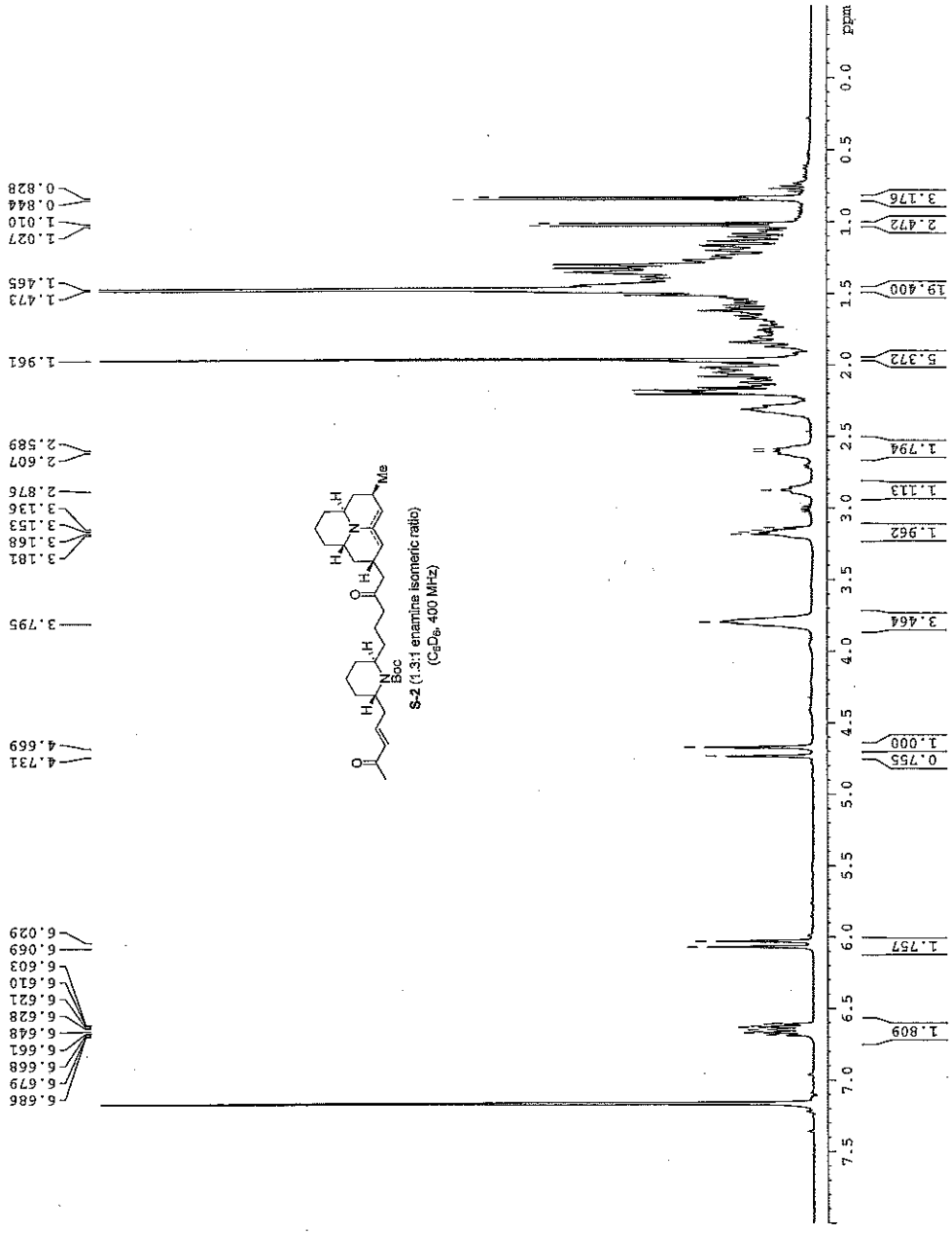

HMBC (Long-range coupling optimized to 10 Hz)
68: Isopestalotiborine A TFA salt
(CD3CN, 500 MHz)
TFA
f1 (ppm)
f2 (ppm)

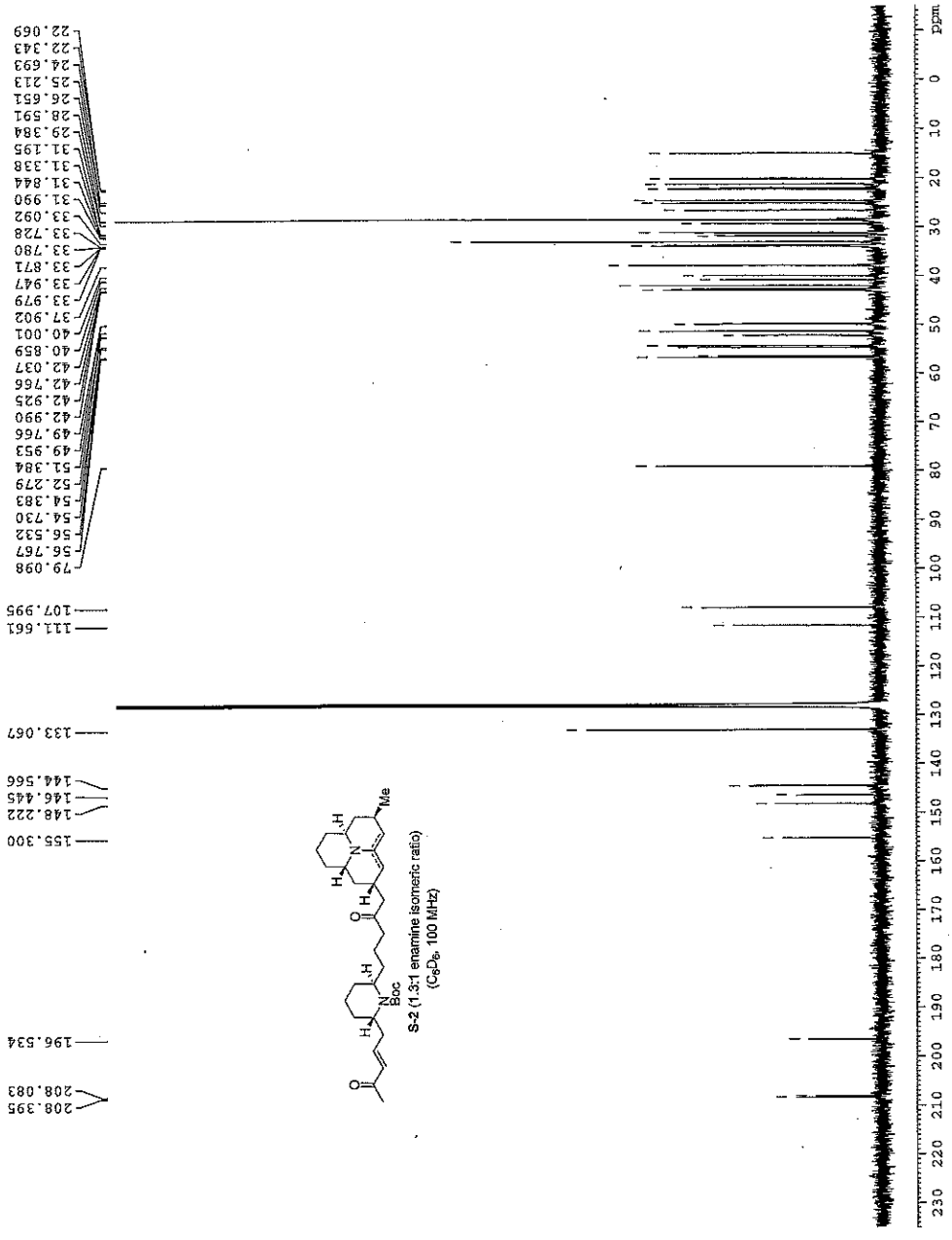

S-1 (2:1 dr)
(CDCl3, 400 MHz)
Me
Boc
ppm

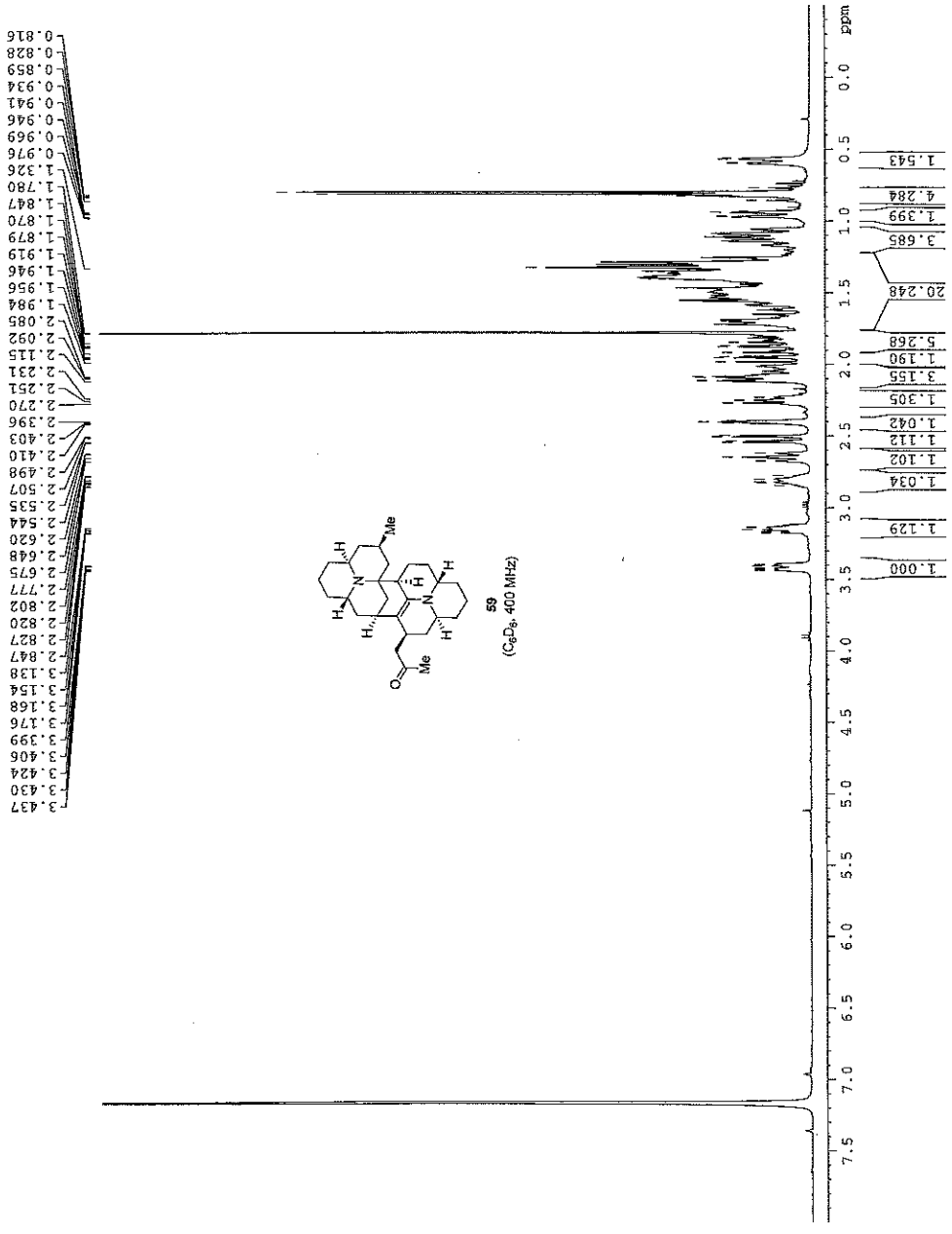

23.728
23.772
24.267
25.196
25.333
26.729
28.223
28.499
29.039
30.559
30.637
32.857
32.905
33.373
33.456
33.545
35.881
36.523
37.090
37.905
43.316
43.548
46.542
46.723
47.246
48.325
48.728
49.226
50.772
50.948
51.758
69.246
70.766
79.471
132.689
145.590
153.150
153.596
155.193
198.536
207.032
207.327
208.470
208.752
Me
Boc
S-1 (2:1 dr)
(CDCl3, 100 MHz)
ppm

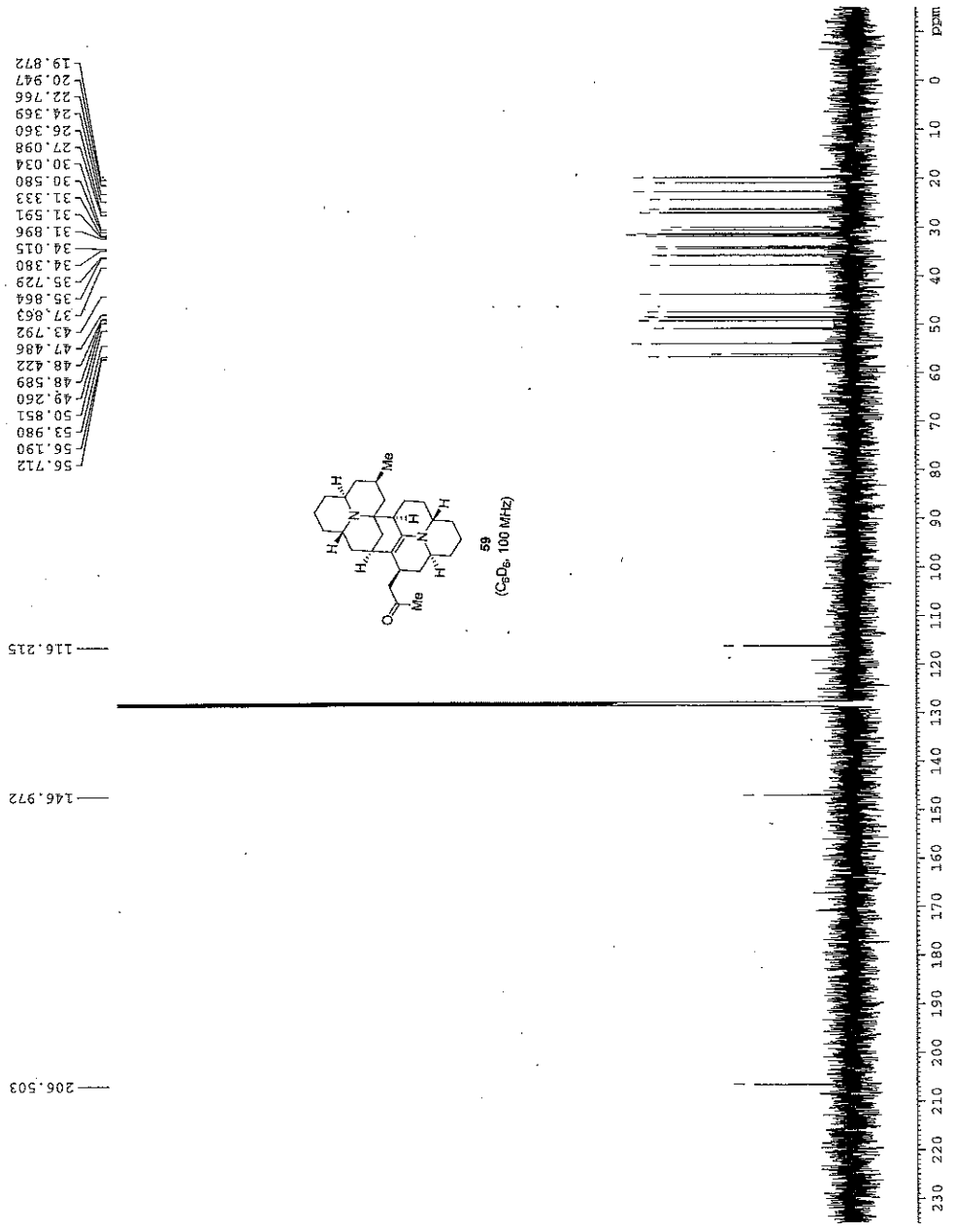

57 (5:1 enamine isomeric ratio)
(C_6D_6, 400 MHz)
Boc
Me
ppm

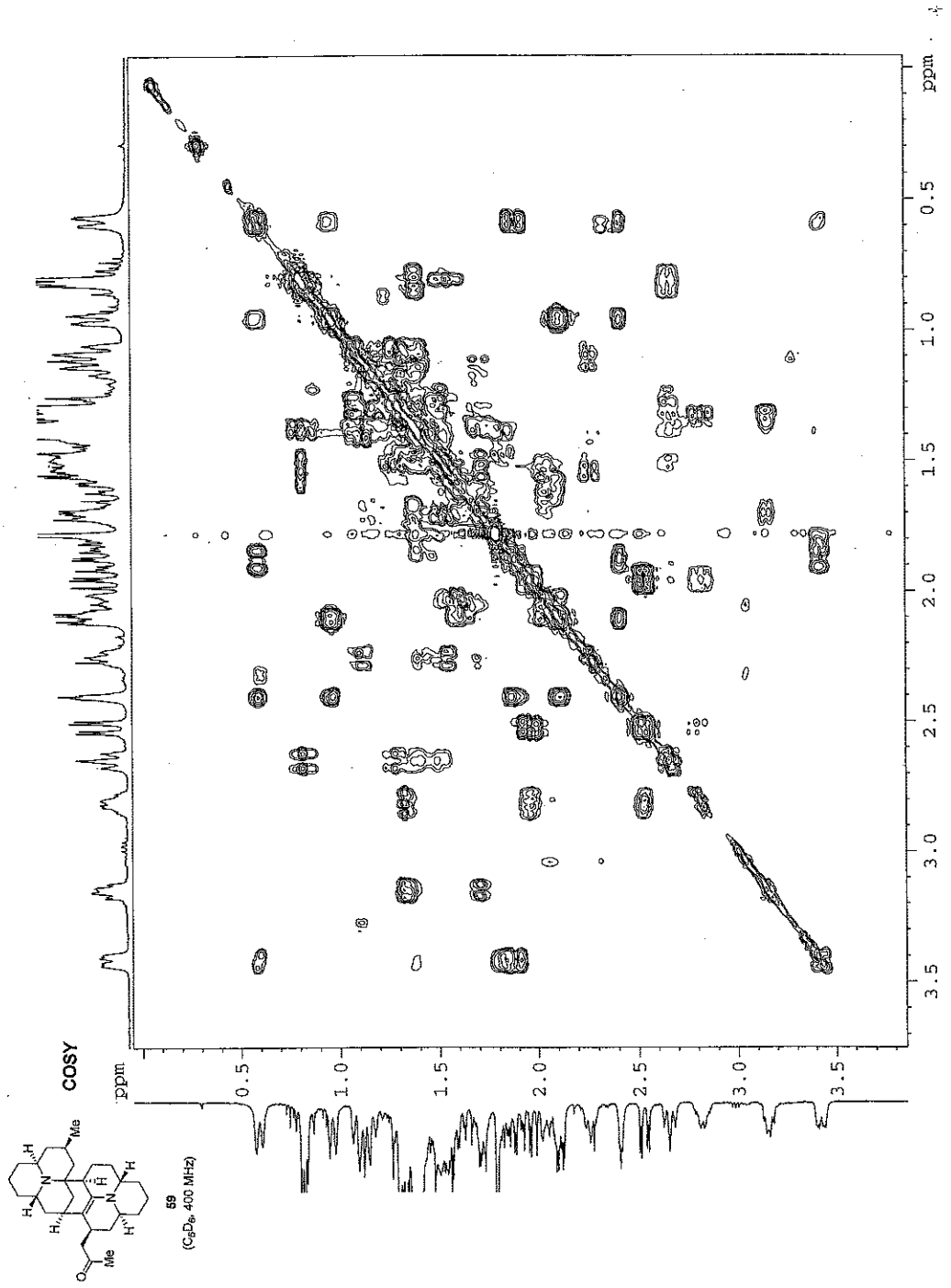

21.399
22.391
22.463
24.684
25.207
26.628
27.985
28.288
28.527
29.550
29.842
31.134
31.191
32.001
32.055
32.983
33.727
33.892
34.016
37.906
38.528
42.135
42.941
43.013
44.705
49.867
50.099
51.368
52.264
54.645
56.081
79.085
106.961
113.609
133.073
144.223
144.594
147.953
155.297
196.550
208.253
208.516
Me
Boc
57 (5:1 enamine isomeric ratio)
(C6D6, 100 MHz)
ppm

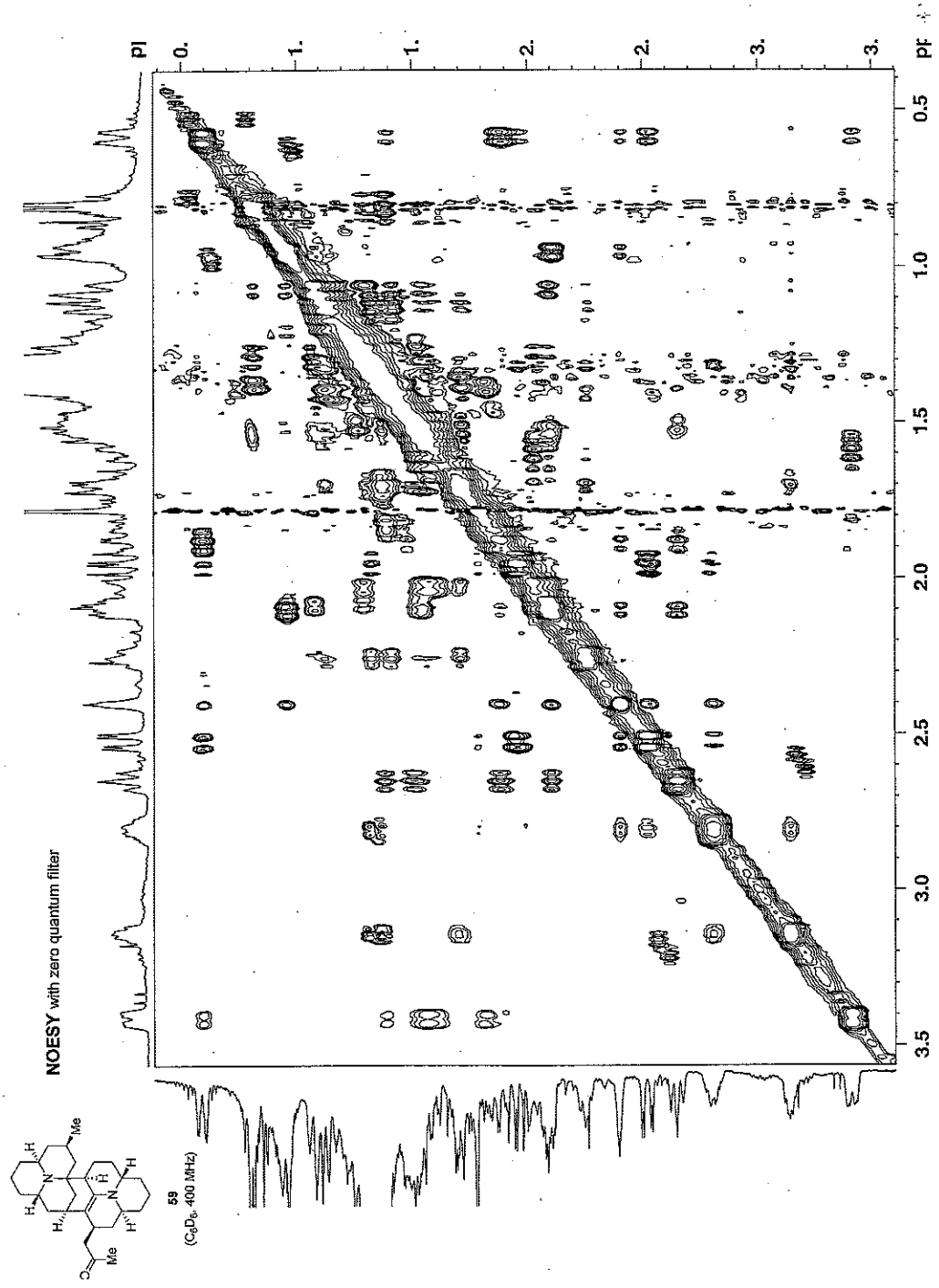

S-2 (1.3:1 enamine isomeric ratio)
(C6D6, 400 MHz)
Me
Boc
N
H
O
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
3.176
2.472
19.400
5.372
1.794
1.113
1.962
3.464
0.755
1.000
1.757
1.809
0.828
0.844
1.010
1.027
1.473
1.465
1.961
2.589
2.607
2.876
3.136
3.153
3.168
3.181
3.795
4.731
4.669
6.029
6.069
6.603
6.610
6.621
6.628
6.648
6.661
6.668
6.679
6.686

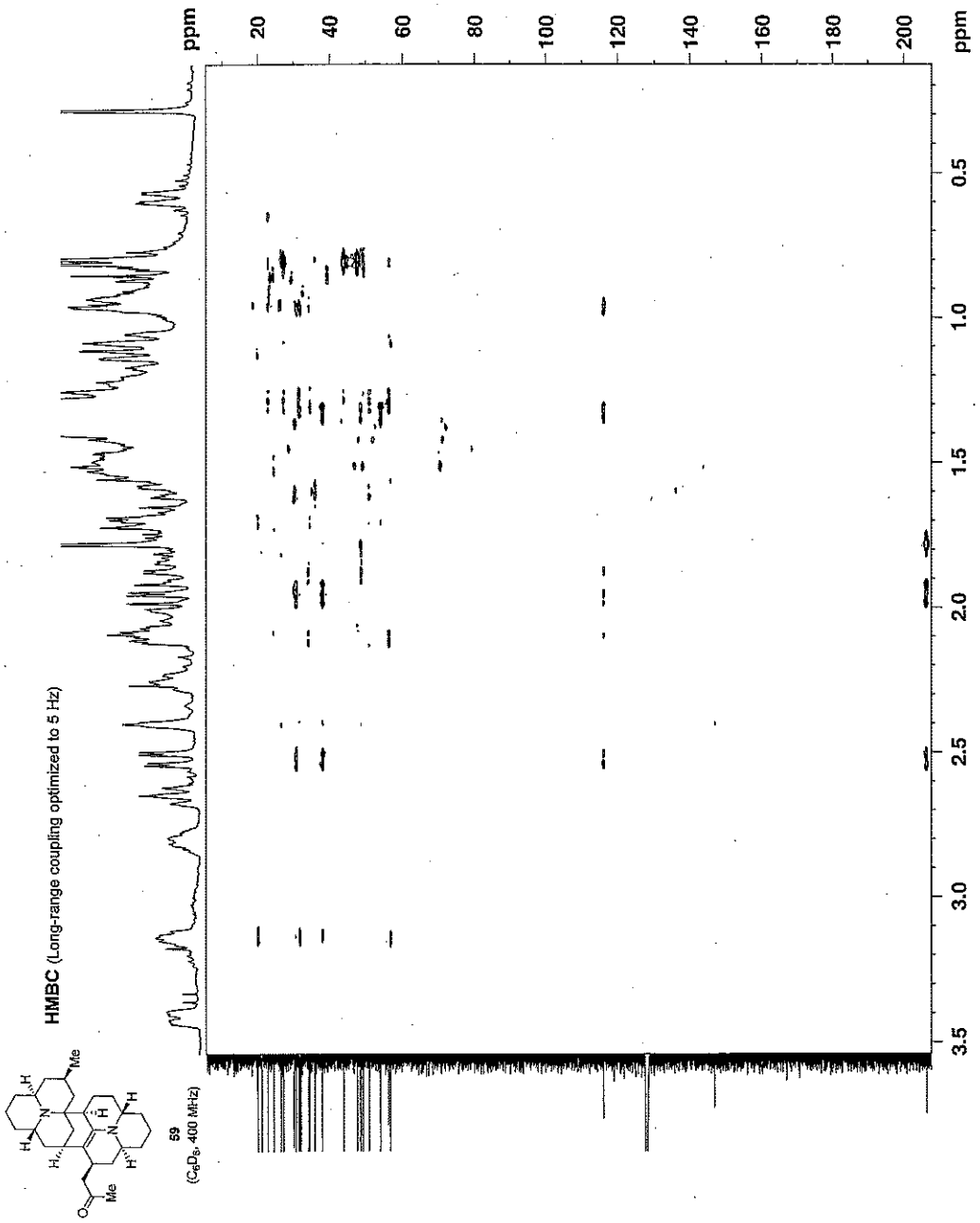

22.069
22.343
24.693
25.213
26.651
28.591
29.384
31.195
31.338
31.844
31.990
33.092
33.728
33.780
33.871
33.947
33.979
37.902
40.001
40.859
42.037
42.766
42.925
42.990
49.766
49.953
51.384
52.279
54.383
54.730
56.532
56.767
79.098
107.995
111.661
133.067
144.566
146.445
148.222
155.300
196.534
208.083
208.395
Me
H
N
H
O
H
N
Boc
H
O
S-2 (1.3:1 enamine isomeric ratio)
(C6D6, 100 MHz)
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230

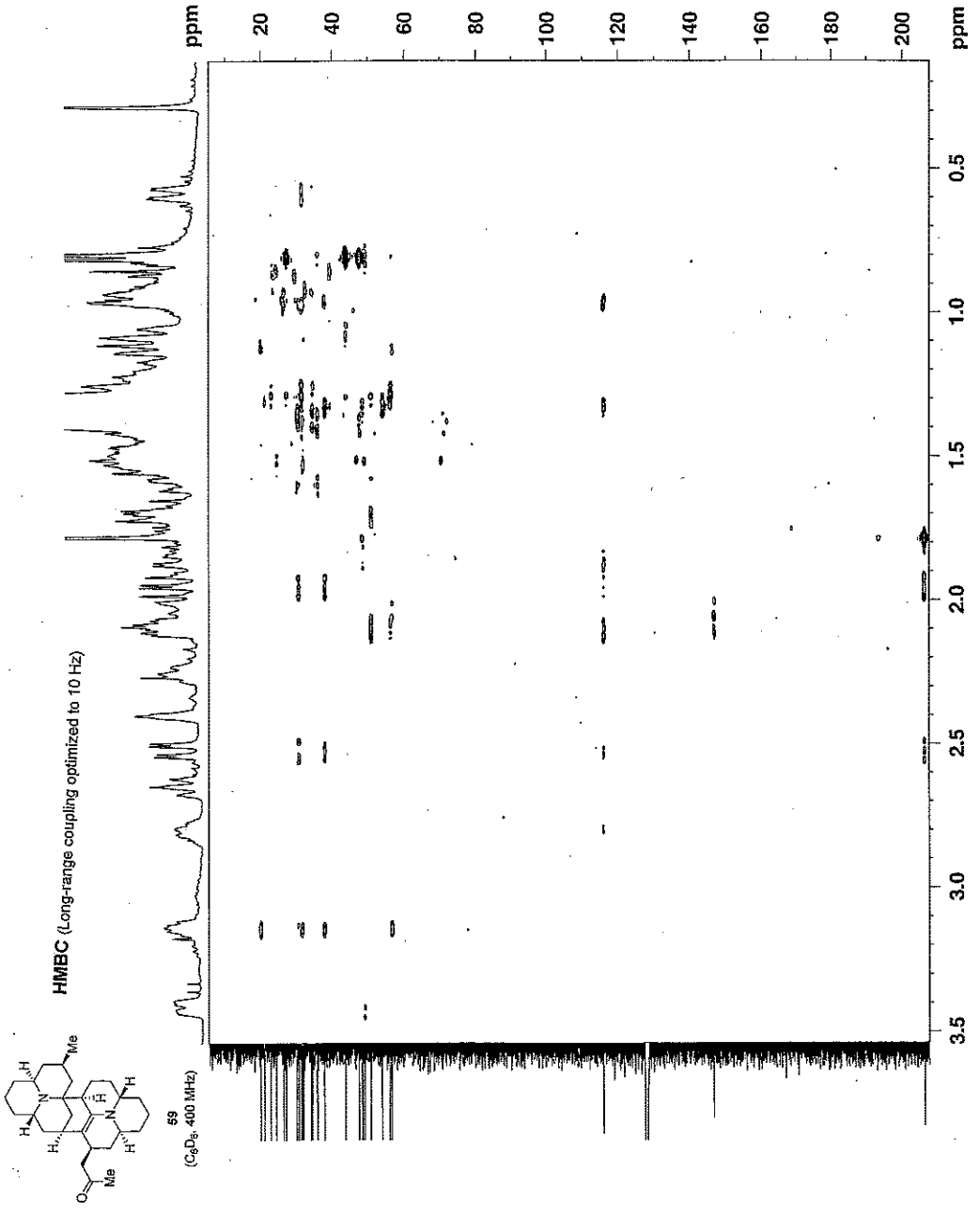

59
(C6D6, 400 MHz)
Me
Me
H
N
O
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
1.000
1.129
1.034
1.102
1.112
1.042
1.305
3.155
1.190
5.268
20.248
3.685
1.399
4.284
1.543
0.816
0.828
0.859
0.934
0.941
0.946
0.969
0.976
1.326
1.780
1.847
1.870
1.879
1.919
1.946
1.956
1.984
2.085
2.092
2.115
2.231
2.251
2.270
2.396
2.403
2.410
2.498
2.507
2.535
2.544
2.620
2.648
2.675
2.777
2.802
2.820
2.827
2.847
3.138
3.154
3.168
3.176
3.399
3.406
3.424
3.430
3.437

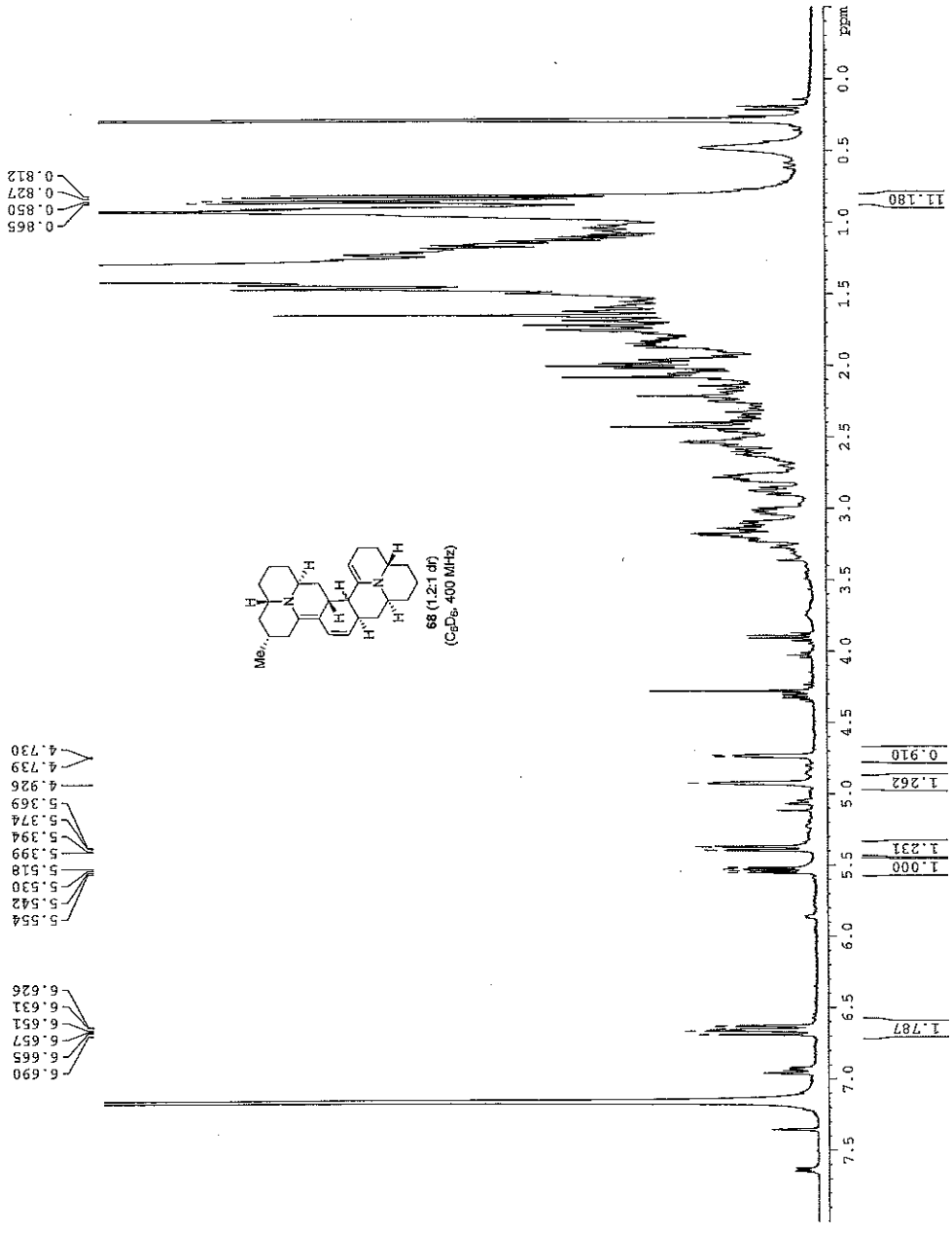

19.872
20.947
22.766
24.369
26.360
27.098
30.034
30.580
31.333
31.591
31.896
34.015
34.380
35.729
35.864
37.863
43.792
47.486
48.422
48.589
49.260
50.851
53.980
56.190
56.712
116.215
146.972
206.503
59
(C_6D_6, 100 MHz)
Me
Me
ppm

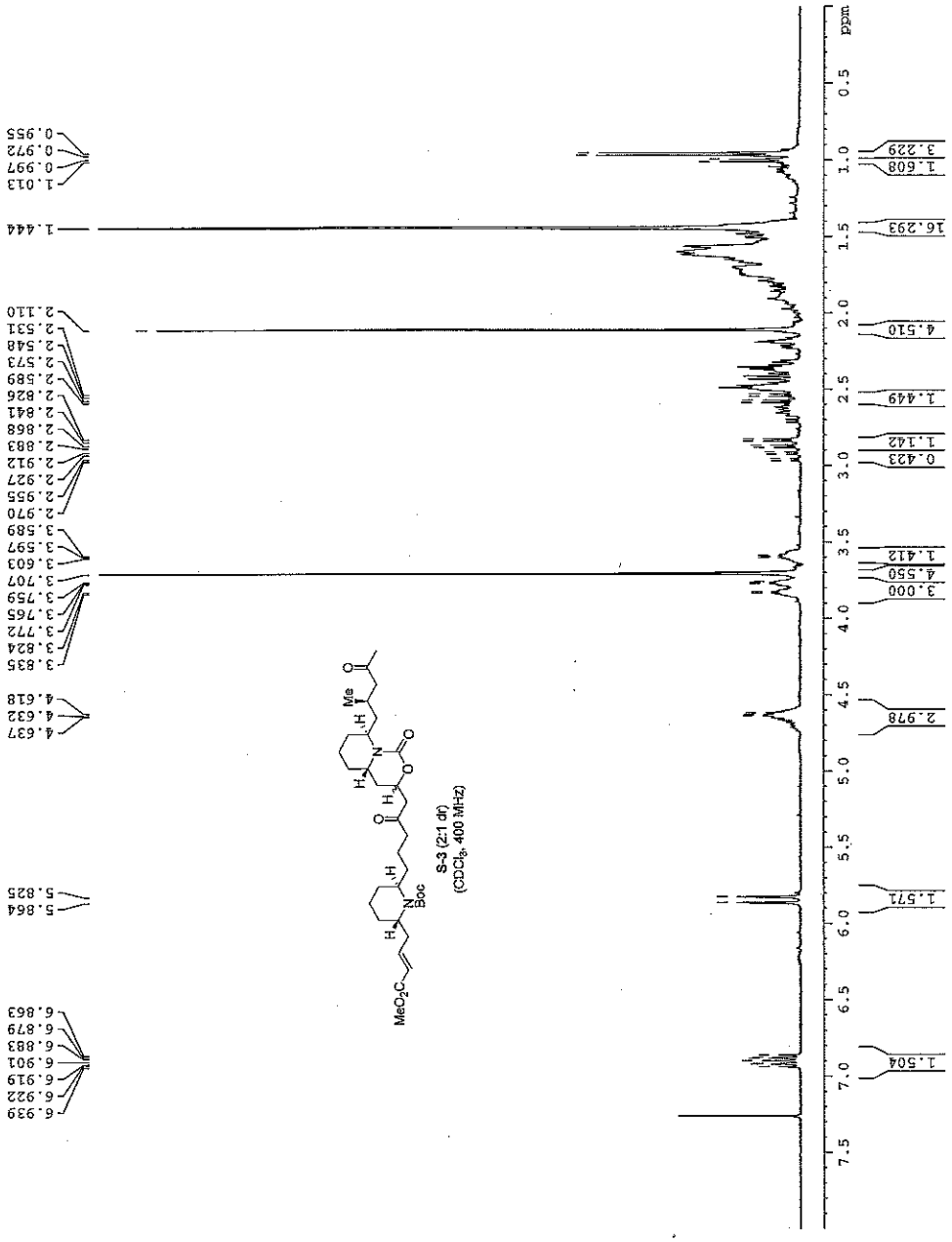

COSY
59
(C6D6, 400 MHz)
Me
Me
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5

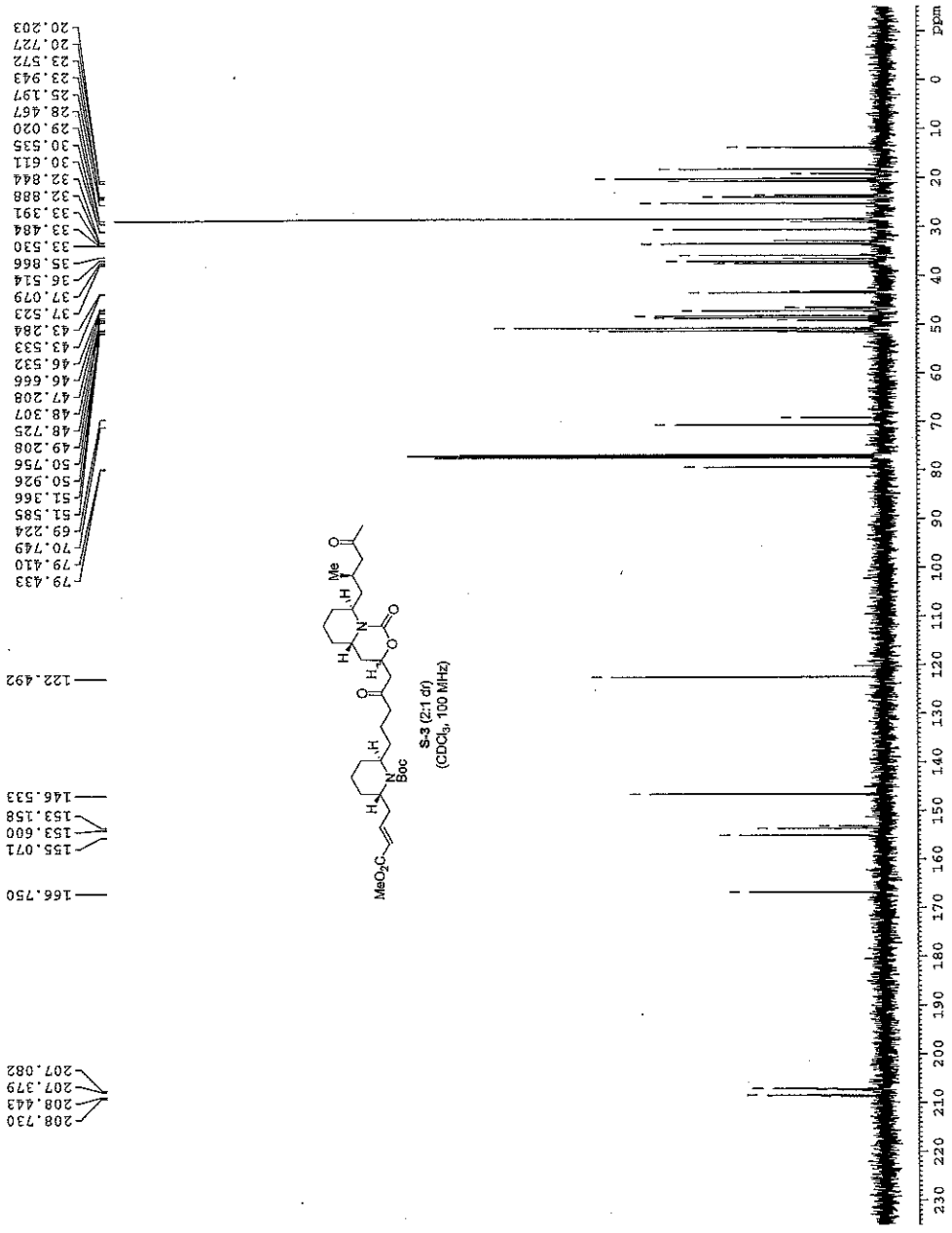

NOESY with zero quantum filter
59
(C6D6, 400 MHz)
Me
Me
H
H
H
H
H
H
H
H
O
N
N
F1
F2
0.
1.
1.
2.
2.
3.
3.
3.5
3.0
2.5
2.0
1.5
1.0
0.5

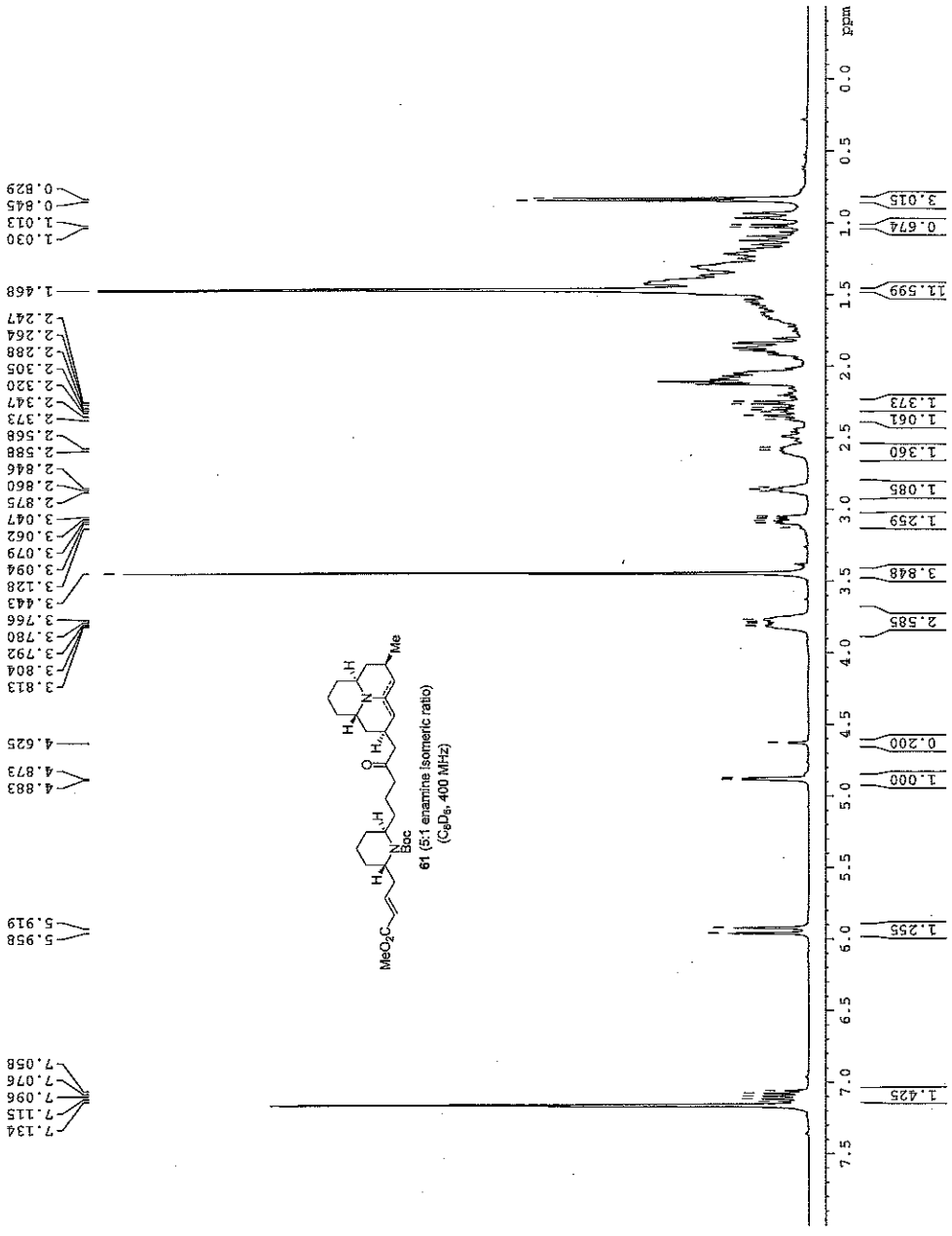

HMBC (Long-range coupling optimized to 5 Hz)
59
(C_6D_6, 400 MHz)
ppm
20
40
60
80
100
120
140
160
180
200
0.5
1.0
1.5
2.0
2.5
3.0
3.5
ppm

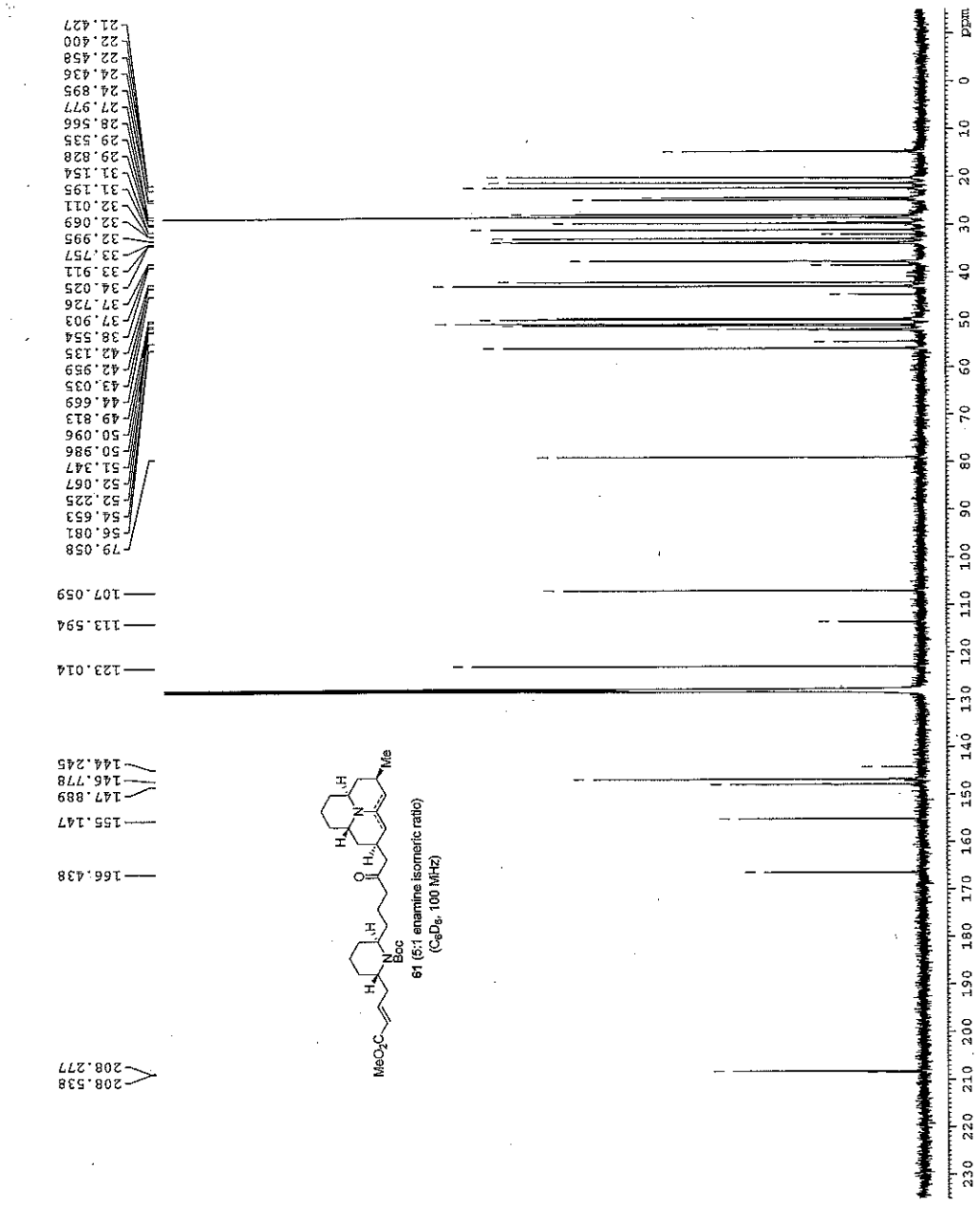

HMBC (Long-range coupling optimized to 10 Hz)
59
(C6D6, 400 MHz)
Me
Me
ppm
20
40
60
80
100
120
140
160
180
200
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5

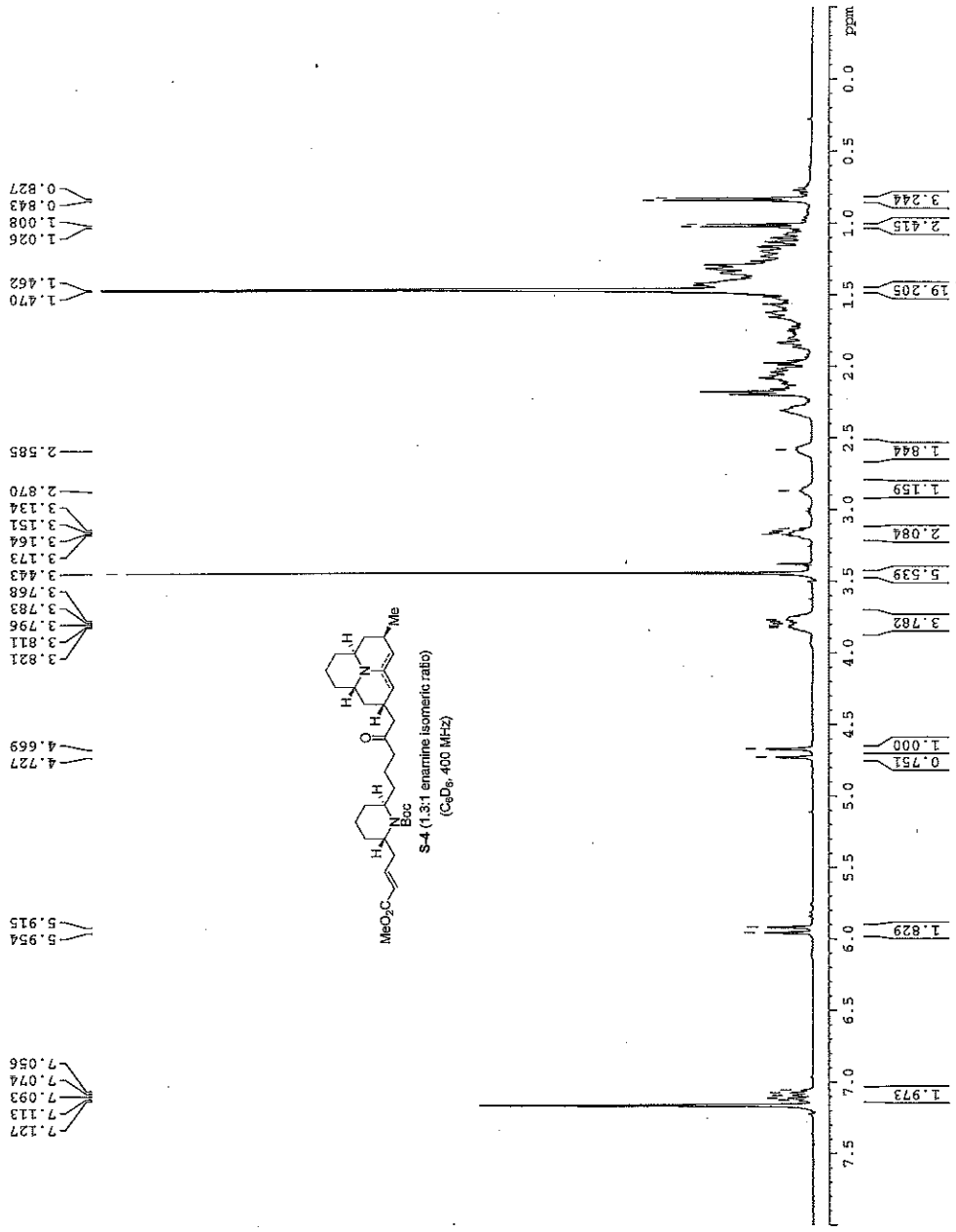

68 (1.2:1 dr)
(C_6D_6, 400 MHz)
Me
0.812
0.827
0.850
0.865
4.730
4.739
4.926
5.369
5.374
5.394
5.399
5.518
5.530
5.542
5.554
6.626
6.631
6.651
6.657
6.665
6.690
11.180
0.910
1.262
1.231
1.000
1.787
ppm

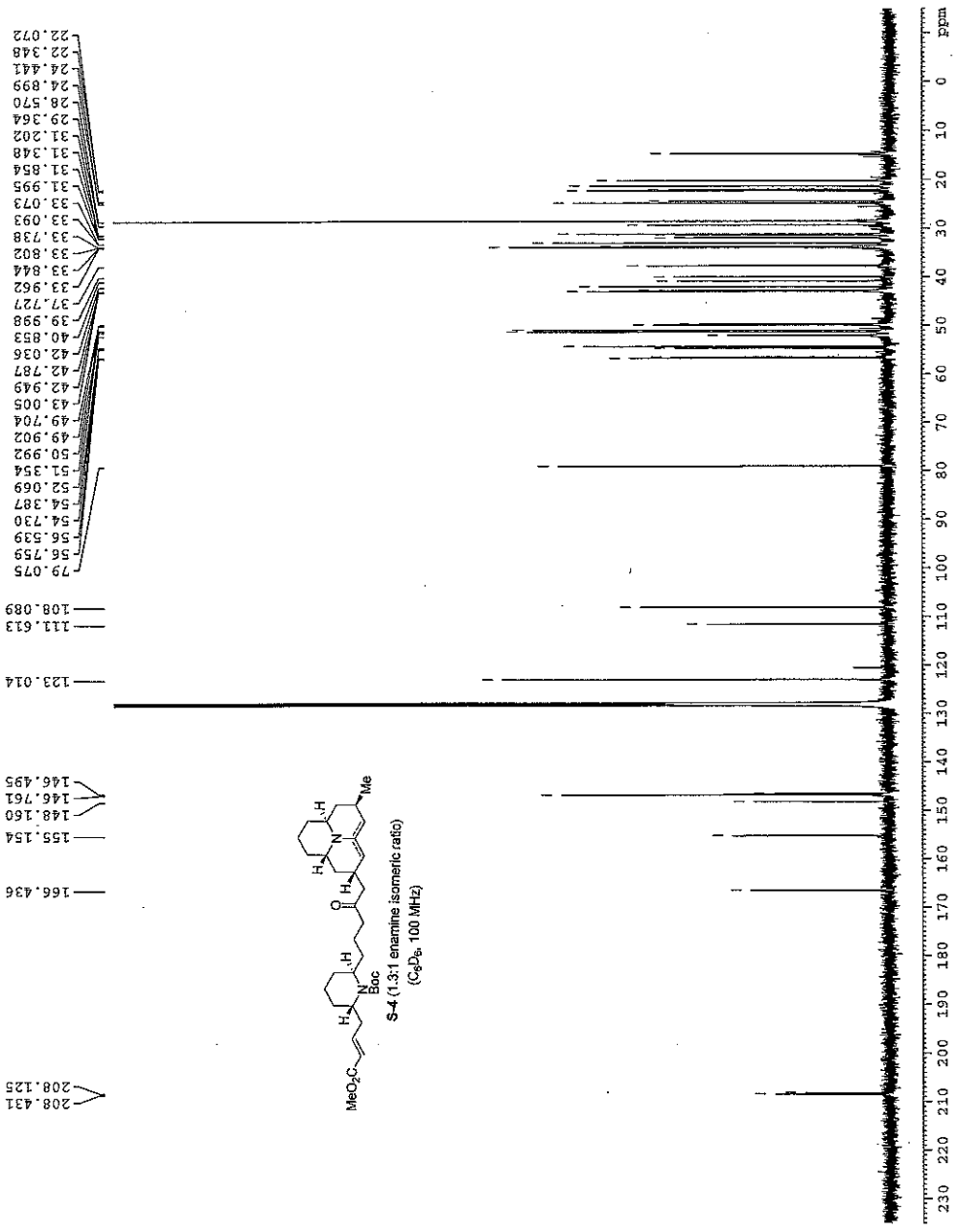

S-3 (2:1 dr)
(CDCl3, 400 MHz)
Me
Boc
MeO2C
ppm

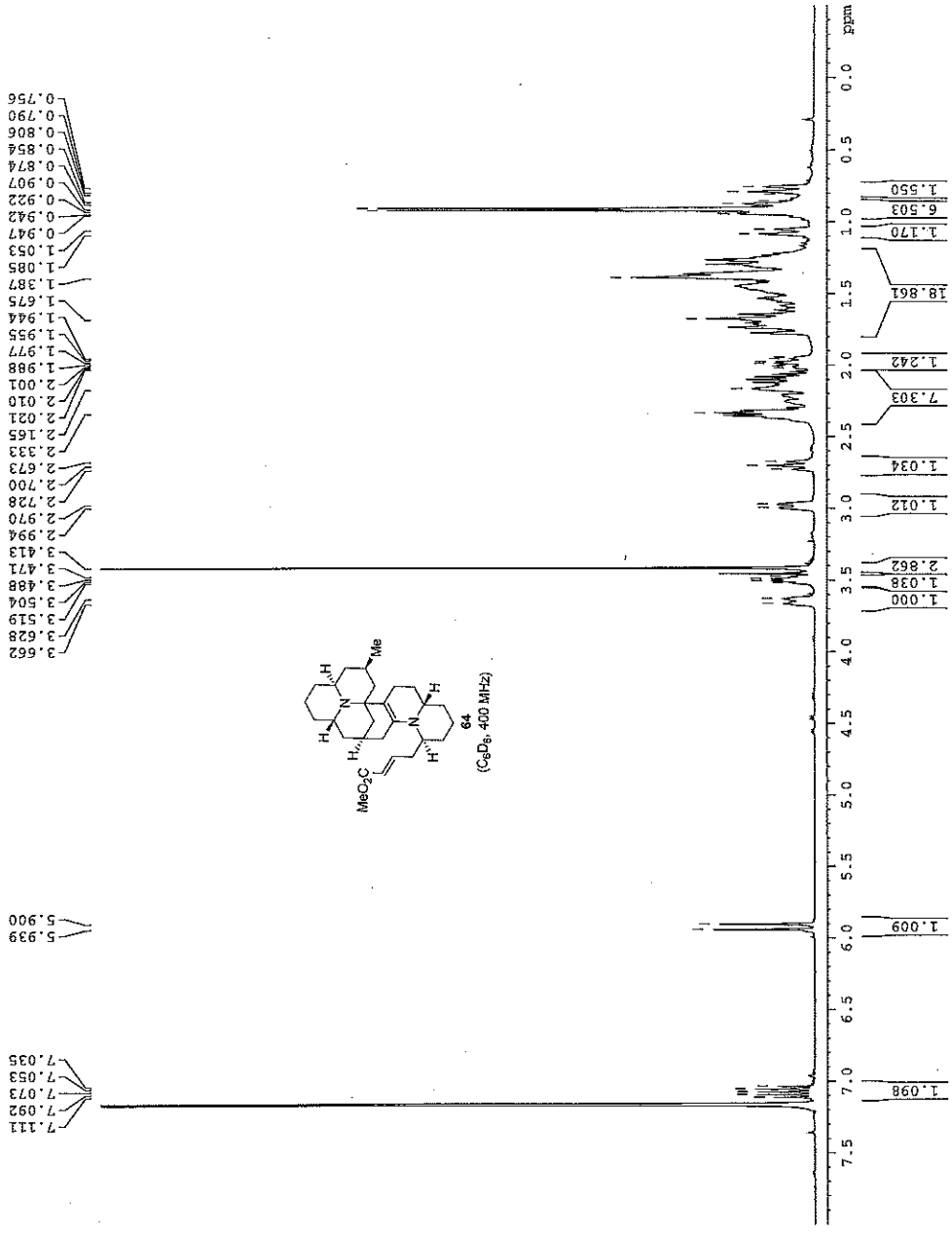

S-3 (2:1 dr)
(CDCl3, 100 MHz)
Me
Boc
MeO2C
ppm

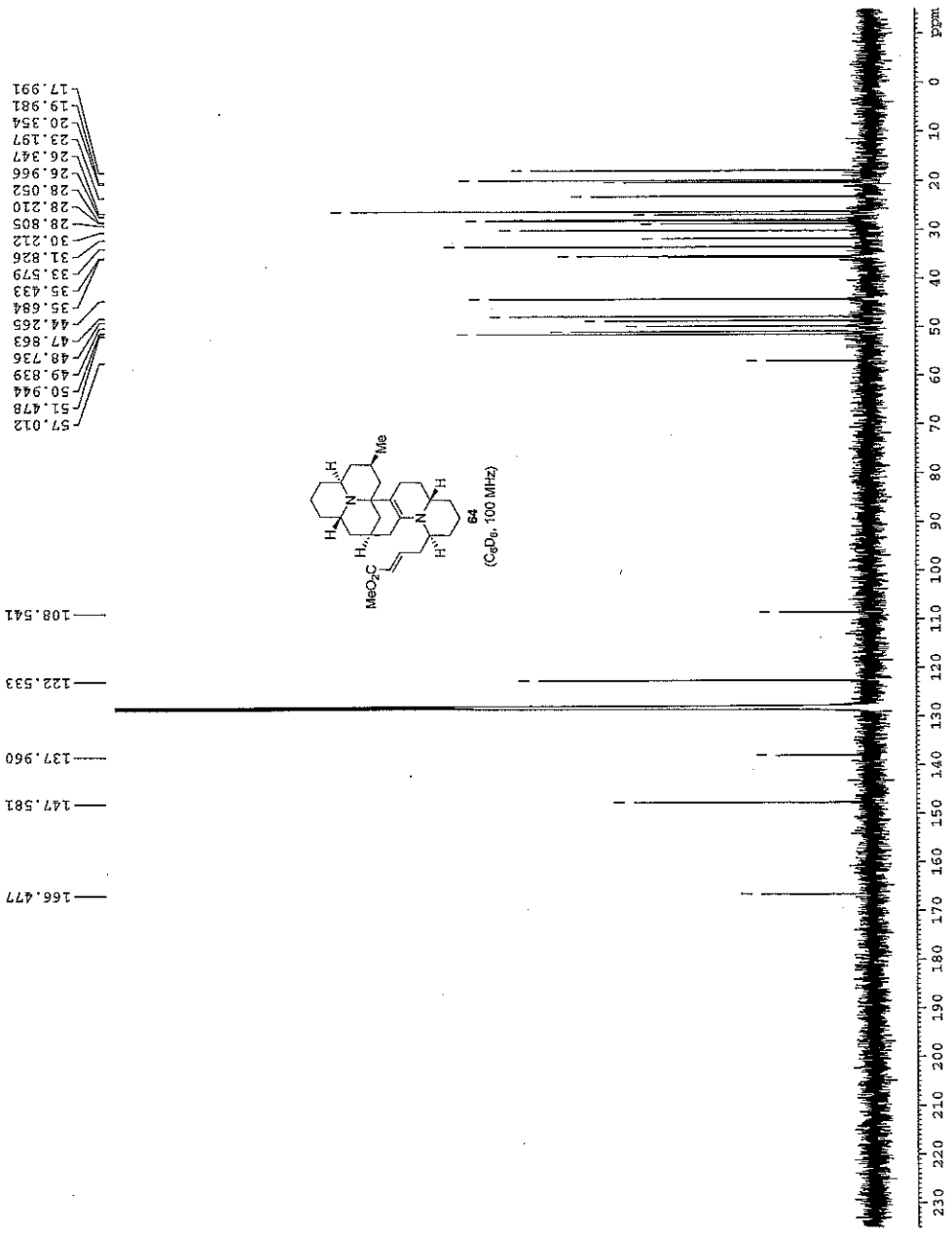

61 (5:1 enamine:isomeric ratio)
(C6D6, 400 MHz)
Boc
Me
MeO2C
ppm

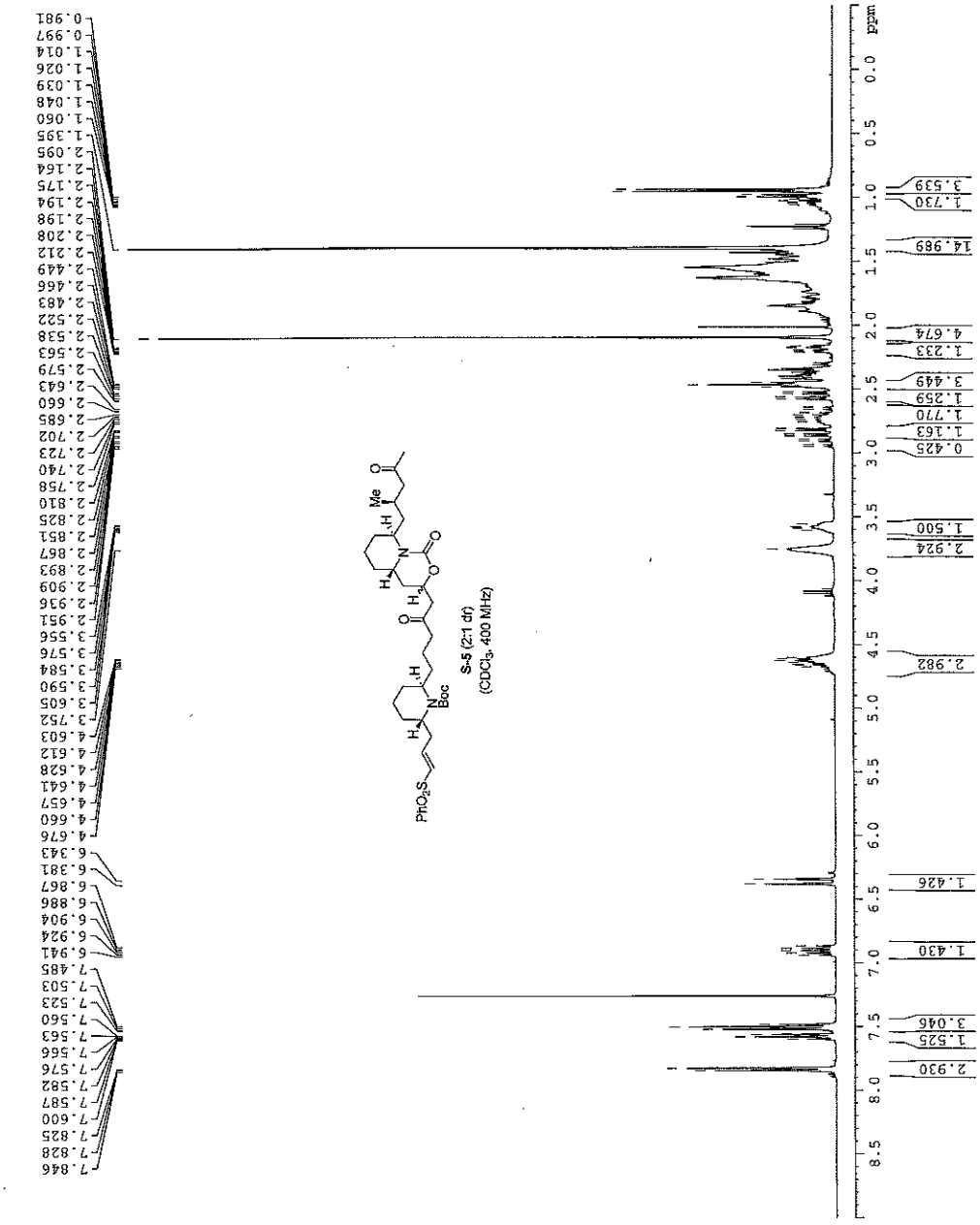

21.427
22.400
22.458
24.436
24.895
27.977
28.566
29.535
29.828
31.154
31.195
32.011
32.069
32.995
33.757
33.911
34.025
37.726
37.903
38.554
42.135
42.959
43.035
44.669
49.813
50.096
50.986
51.347
52.067
52.225
54.653
56.081
79.058
107.059
113.594
123.014
144.245
146.778
147.889
155.147
166.438
208.277
208.538
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230
Me
Boc
MeO2C
61 (5:1 enamine isomeric ratio)
(C6D6, 100 MHz)

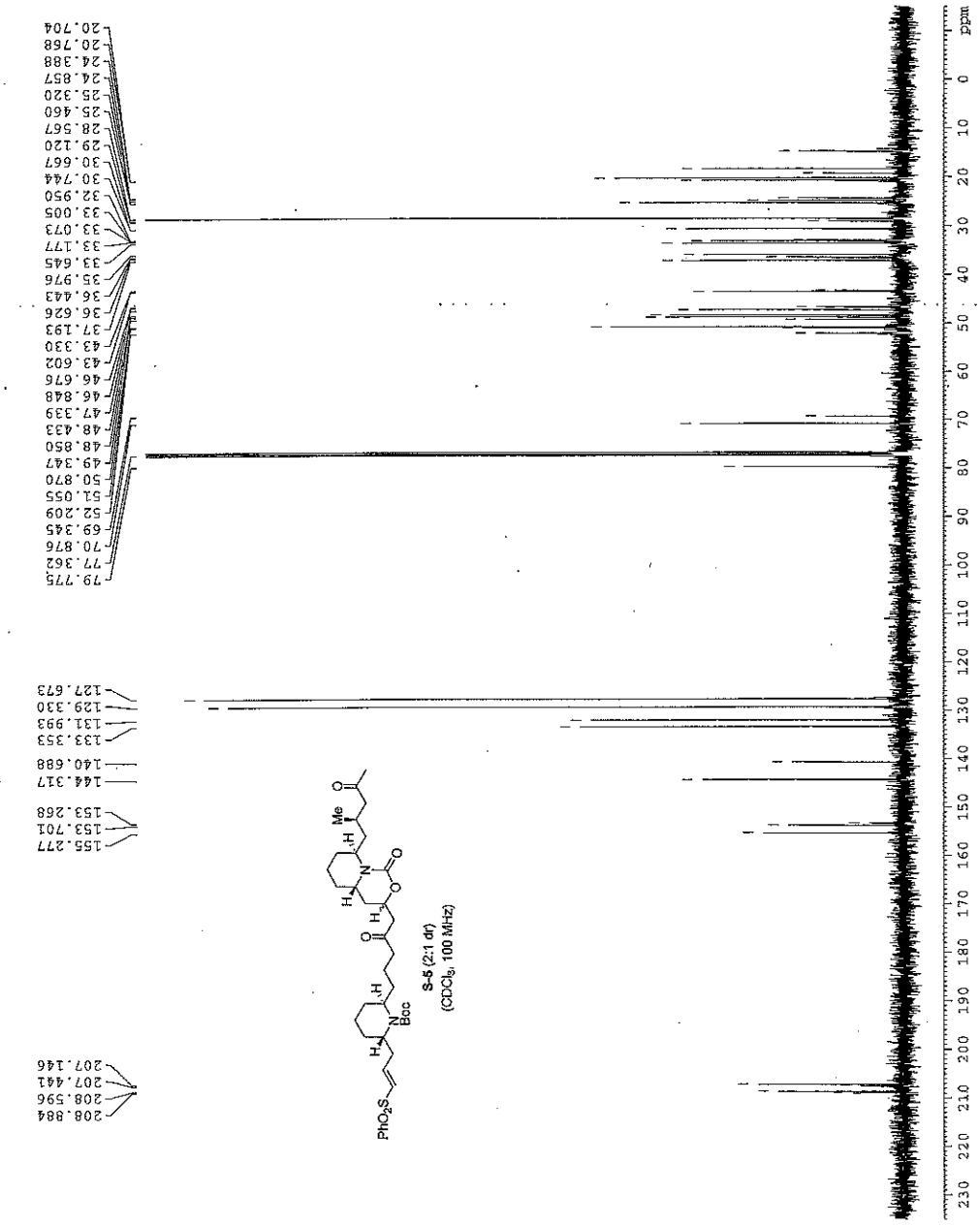

S-4 (1.3:1 enamine isomeric ratio)
(C6D6, 400 MHz)
Me
Boc
MeO2C
0.827
0.843
1.008
1.026
1.462
1.470
2.585
2.870
3.134
3.151
3.164
3.173
3.443
3.768
3.783
3.796
3.811
3.821
4.669
4.727
5.915
5.954
7.056
7.074
7.093
7.113
7.127
3.244
2.415
19.205
1.844
1.159
2.084
5.539
3.782
1.000
0.751
1.829
1.973
ppm

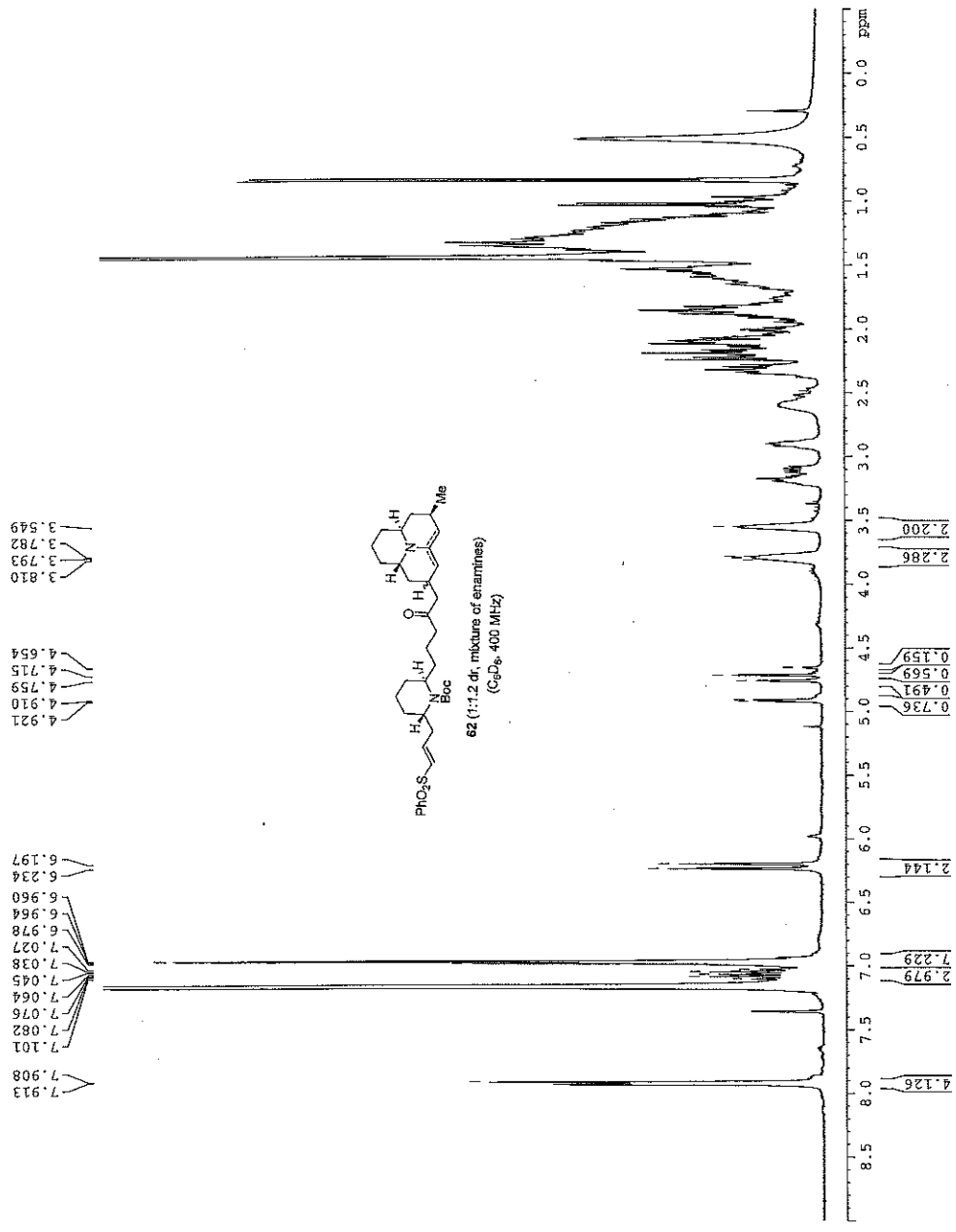

22.072
22.348
24.441
24.899
28.570
29.364
31.202
31.348
31.854
31.995
33.073
33.093
33.738
33.802
33.844
33.962
37.727
39.998
40.853
42.036
42.787
42.949
43.005
49.704
49.902
50.992
51.354
52.069
54.387
54.730
56.539
56.759
79.075
108.089
111.613
123.014
146.495
146.761
148.160
155.154
166.436
208.125
208.431
Me
H
N
H
O
H
N
Boc
H
MeO2C
S-4 (1.3:1 enamine isomeric ratio)
(C6D6, 100 MHz)
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230

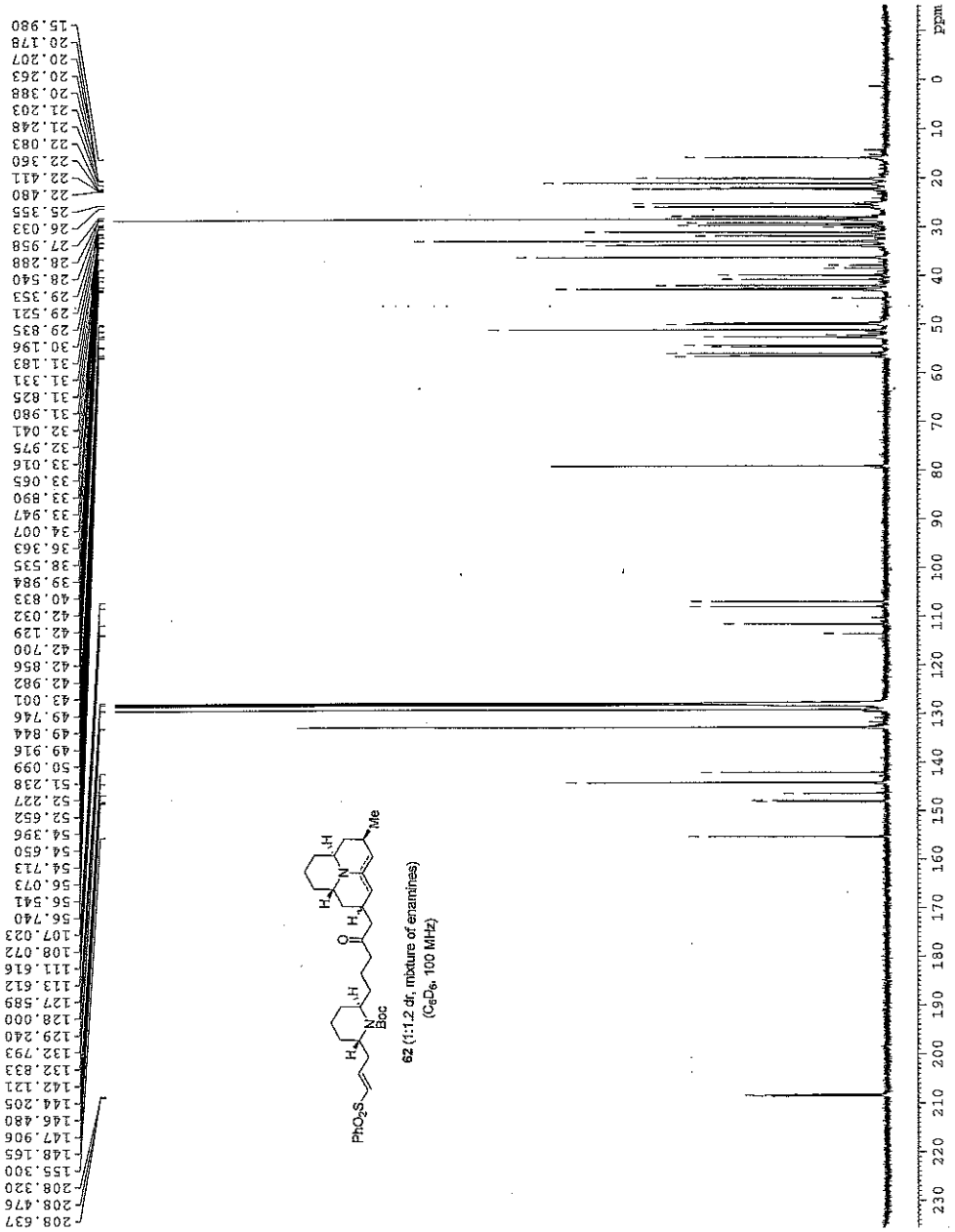

ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
1.550
6.503
1.170
18.861
1.242
7.303
1.034
1.012
2.862
1.038
1.000
1.009
1.098
0.756
0.790
0.806
0.854
0.874
0.907
0.922
0.942
0.947
1.053
1.085
1.387
1.675
1.944
1.955
1.977
1.988
2.001
2.010
2.021
2.165
2.333
2.673
2.700
2.728
2.970
2.994
3.413
3.471
3.488
3.504
3.519
3.628
3.662
5.900
5.939
7.035
7.053
7.073
7.092
7.111
Me
H
N
H
H
N
H
H
MeO2C
64
(C6D6, 400 MHz)

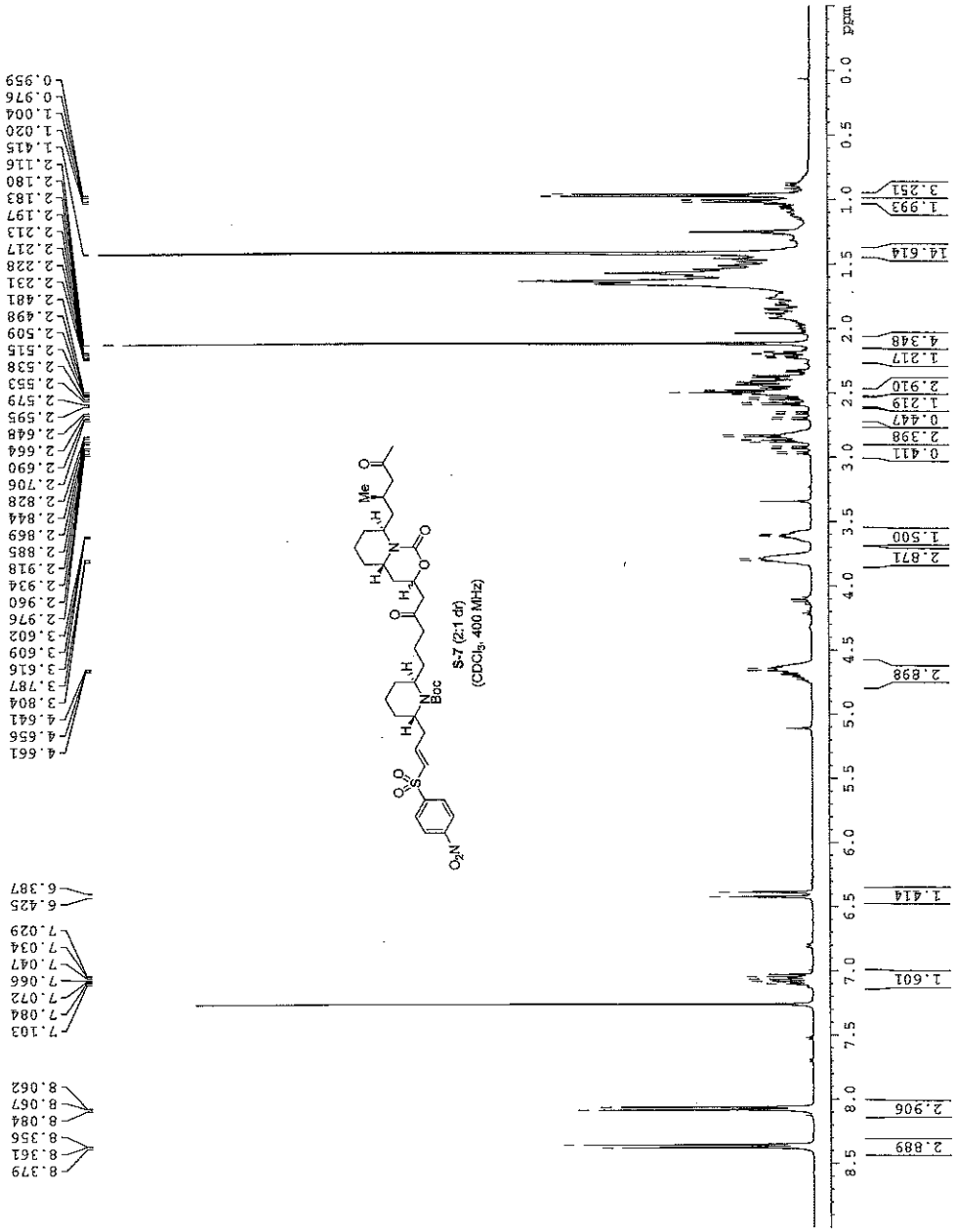

17.991
19.981
20.354
23.197
26.347
26.966
28.052
28.210
28.805
30.212
31.826
33.579
35.433
35.684
44.265
47.863
48.736
49.839
50.944
51.478
57.012
108.541
122.533
137.960
147.581
166.477
64
(C6D6, 100 MHz)
Me
MeO2C
ppm

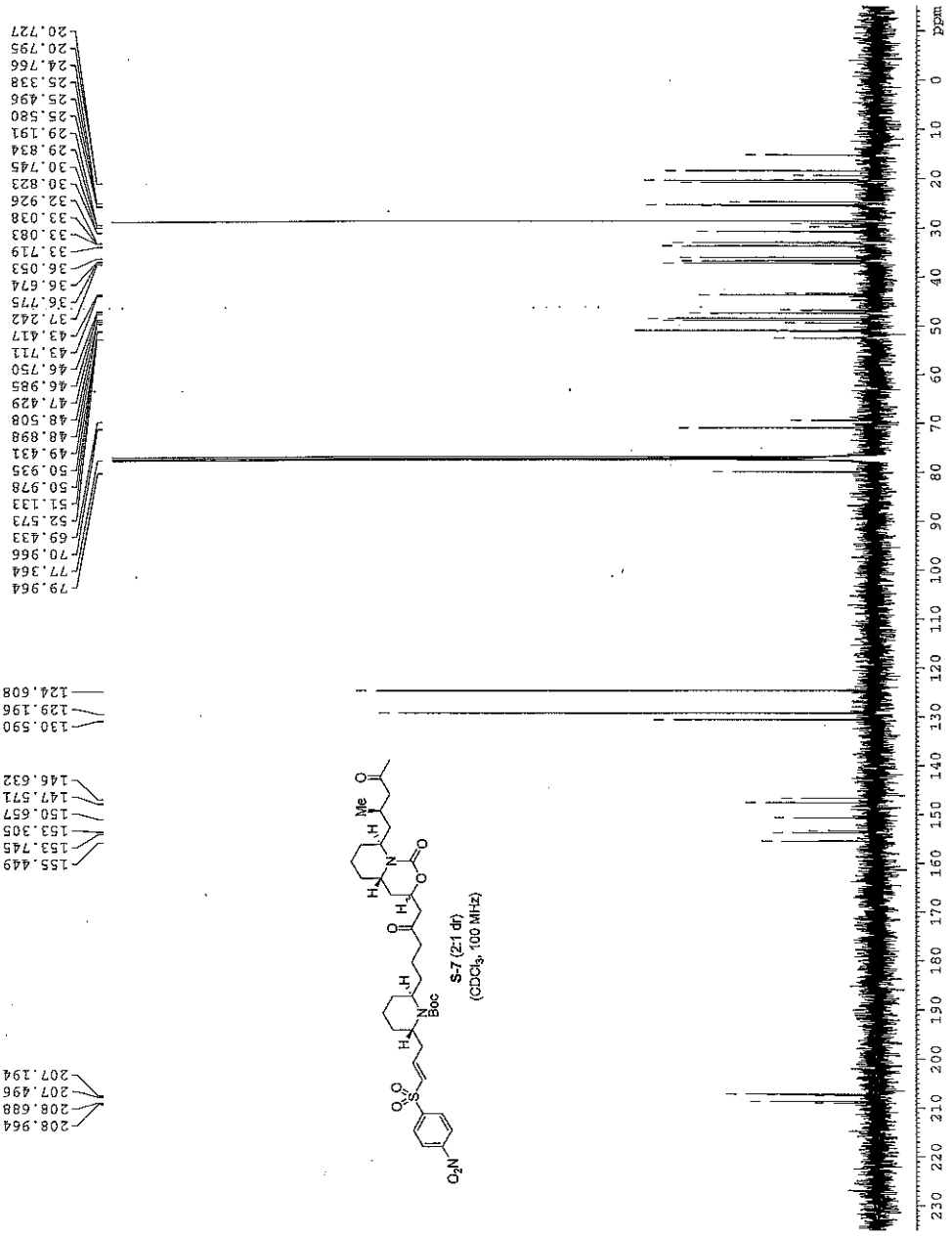

S-5 (2:1 dr)
(CDCl3, 400 MHz)
Me
Boc
PhO2S
ppm

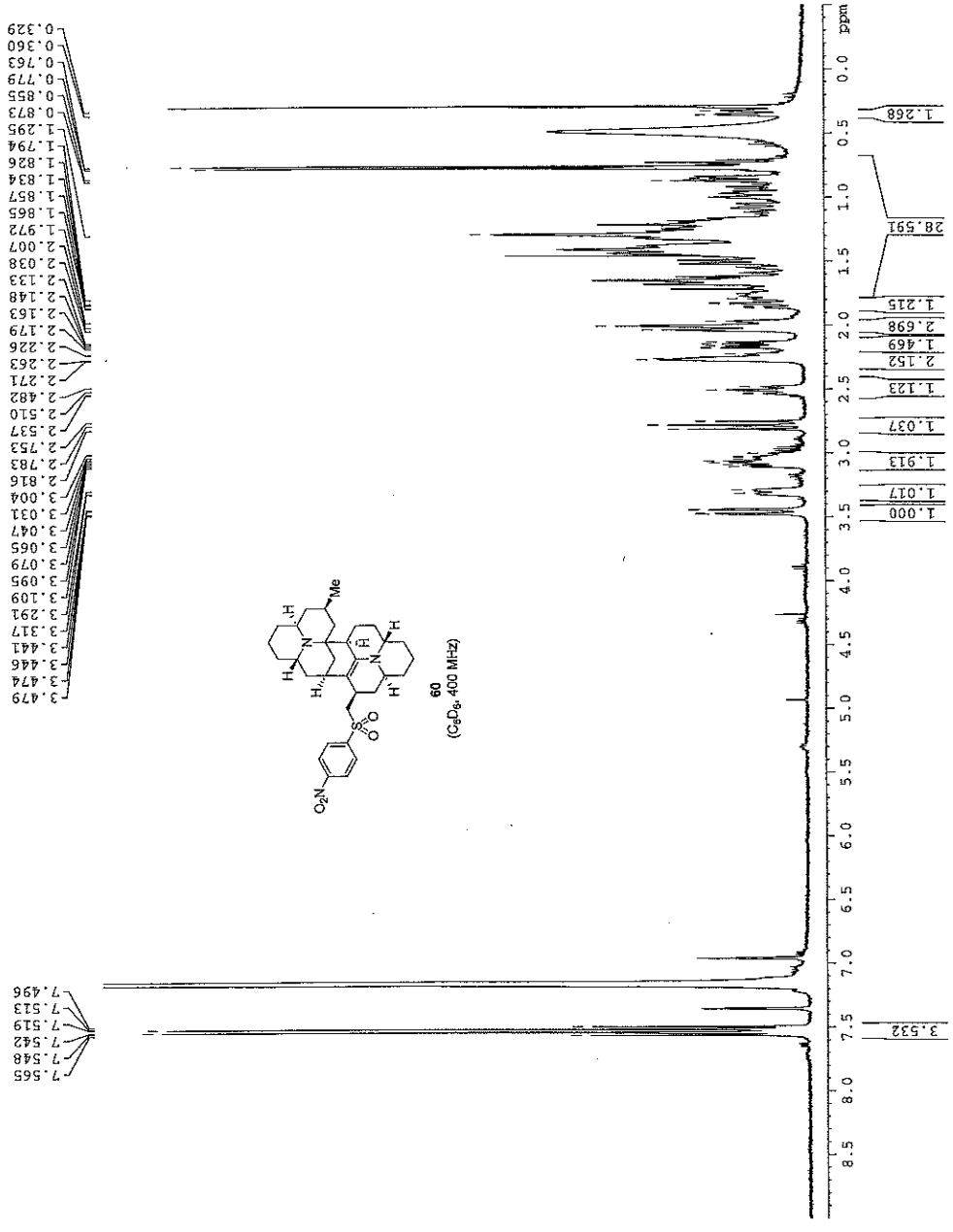

S-5 (2:1 dr)
(CDCl3, 100 MHz)
PhO2S
Boc
Me
ppm


62 (1:1.2 dr, mixture of enamines)
(C_6D_6, 400 MHz)
PhO2S
Me
Boc
7.913
7.908
7.101
7.082
7.076
7.064
7.045
7.038
7.027
6.978
6.964
6.960
6.234
6.197
4.921
4.910
4.759
4.715
4.654
3.810
3.793
3.782
3.549
4.126
2.979
7.229
2.144
0.736
0.491
0.569
0.159
2.286
2.200
ppm


PhO2S
Me
N
Boc
O
62 (1:1.2 dr, mixture of enamines)
(C6D6, 100 MHz)
ppm


S-7 (2:1 dr)
(CDCl3, 400 MHz)
Me
Boc
O2N
ppm


S-7 (2:1 dr)
(CDCl3, 100 MHz)
Me
Boc
O2N
ppm


60
(C6D6, 400 MHz)
Me
O2N
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
1.268
28.591
1.215
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2.263
2.271
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2.753
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2.816
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3.047
3.065
3.079
3.095
3.109
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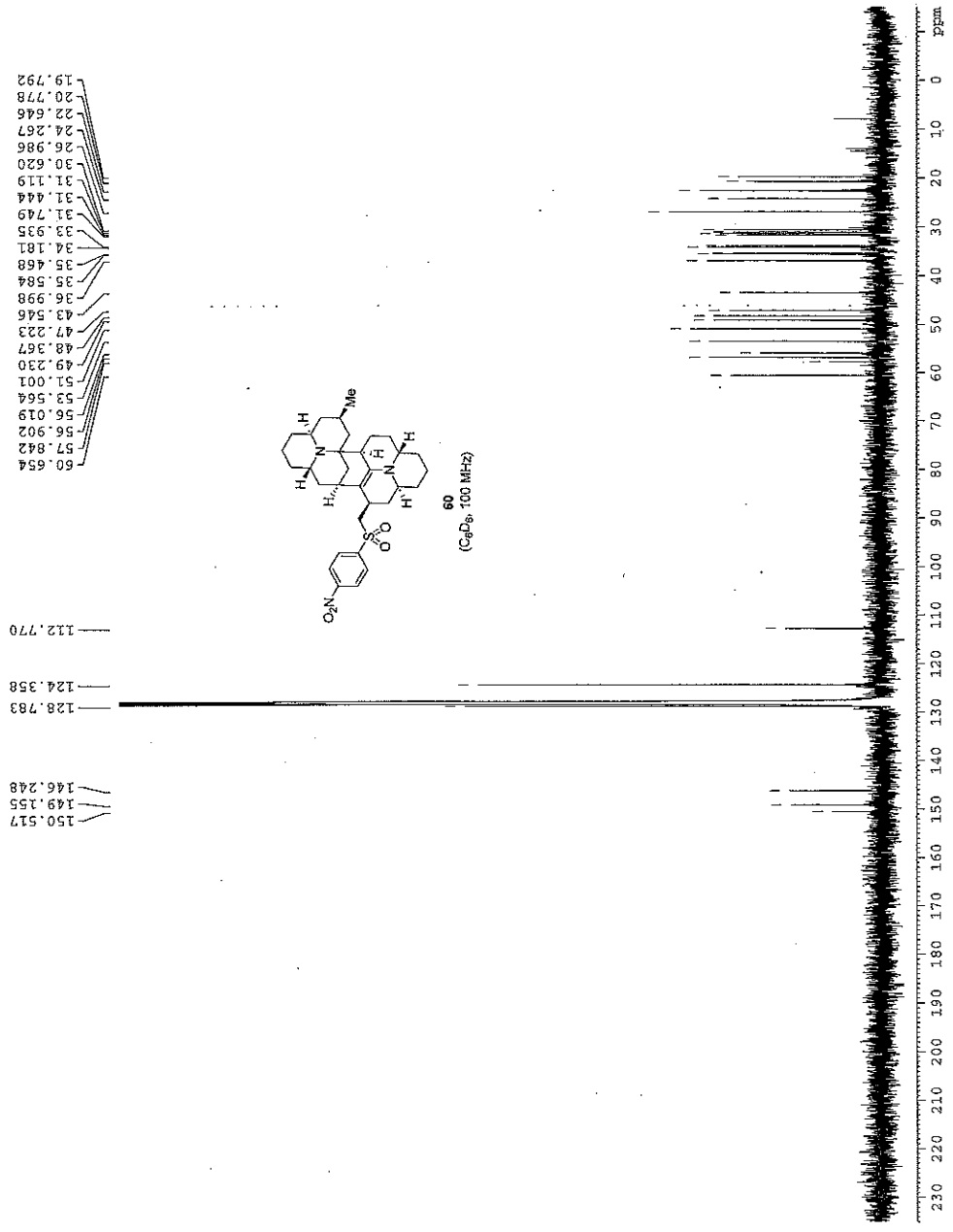
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149.155
150.517
Me
H
N
O2N
S
O
60
(C6D6, 100 MHz)
ppm