SYNTHESIS OF DIMERIC PYRROLE-IMIDAZOLE ALKALOIDS

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by

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THESIS

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To my family

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SYNTHESIS OF DIMERIC PYRROLE-IMIDAZOLE ALKALOIDS

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Dimeric pyrrole-imidazole alkaloids, also known as oroidin family of alkaloids, are a class of marine natural products with unique structural diversity and complexity. Focusing on the synthesis of the higher order dimeric pyrrole-imidazole alkaloids, my graduate work comprises two components: a synthetic study of massadine and the total synthesis of ageliferin, as describe herein.

These highly nitrogenated marine natural products possess a densely functionalized [3+2] or [4+2] dimerization core skeleton, which present significant synthetic challenges. A manganese(III)-mediated oxidative radical cyclization has been developed to construct the core skeleton of these pyrrole-imidazole dimers and its

mechanism is investigated by the methods of computational chemistry. *Ent*-15-*epi*-5,11-dioxomassadine has been synthesized by using a biomimetic oxidative ring contraction converting ageliferin skeleton to massadine skeleton with stereochemical control, followed by an oxidative cyclization to construct the oxo-bridge. An asymmetric total synthesis of ageliferin is described, featuring an early installation of 2-azidoimidazole for the oxidative radical cyclization and a phosphorus imide group as a novel protecting group for 2-aminoimidazole. These synthetic studies support the possibility that a single-electron transfer (SET) reaction and a pinacol-type rearrangement may be used in nature as a way to produce ageliferin and massadine.

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PRIOR PUBLICATIONS

1. **Xiao Wang**, Zhiqiang Ma, Jianming Lu, Xianghui Tan and Chuo Chen. Asymmetric Synthesis of Ageliferin. *J. Am. Chem. Soc*. **2011**, *133*, 15350–15353.

2. Zhiqiang Ma, Jianming Lu, **Xiao Wang** and Chuo Chen. Revisiting the Kinnel–Scheuer hypothesis for the biosynthesis of palau'amine. *Chem. Comm*. **2011**, *47*, 427–429.

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LIST OF ABBREVIATIONS

Å – ångström

Ac – acetyl, acetate

acac – acetylacetonate

aq. – aqueous

Bn – benzyl

Boc – tert-butyloxycarbonyl

BOM – benzyloxymethyl

br – broad

Bu – butyl

°C – degrees Celsius

calcd – calculated

cat. – catalytic

CBS – Corey-Bakshi-Shibata oxazaborolidine

Cbz – carboxybenzyl

CD – circular dichroism

CSA – camphorsulfonic acid

d – doublet

DCC – *N*,*N*′-Dicyclohexylcarbodiimide,

DCM – dichloromethane

DEAD – diethyl azodicarboxylate

decomp. – decomposition

DFT – density functional theory

DIBAL – diisobutylaluminium hydride

DIPEA – *N*,*N*-diisopropylethylamine

DMAP – 4-dimethylaminopyridine

DMAS – dimethylaminosulfonyl

DMB – dimethoxybenzyl

DMDO – dimethyldioxirane

DMF – *N*,*N*-dimethylformamide

DMP – Dess-Martin periodinane

DMSO – dimethyl sulfoxide

EC_{50} – half maximal effective concentration

equiv. – equivalent

ESI – electrospray ionization

Et – ethyl

g – gram(s)

gCOSY – gradient-selected Correlation Spectroscopy

GGTase I – geranylgeranyltransferase type I

h – hour(s)

HMBC – heteronuclear multiple-bond correlation spectroscopy

HMDS – bis(trimethylsilyl)amide

HMQC – heteronuclear multiple-quantum correlation spectroscopy

HPLC – high performance liquid chromatography

Hz – hertz

IBX – 2-Iodoxybenzoic acid

IC_{50} – half maximal inhibitory concentration

J – coupling constant

λ – wavelength

L – liter

m – multiplet or milli

m/z – mass to charge ratio

μ – micro

MALDI – matrix-assisted laser desorption/ionization

mCPBA – *m*-chloroperoxybenzoic acid

Me – methyl

MHz – megahertz

min – minute(s)

mmpp – magnesium monoperoxyphthalate

mol – mole(s)

Ms – methanesulfonyl (mesyl)

M.S. – molecular sieves

NBS – *N*-bromosuccinimide

NCS – *N*-chlorosuccinimide

N.D. – not detected

NIS – *N*-iodosuccinimide

NMO – *N*-Methylmorpholine *N*-oxide

NMR – nuclear magnetic resonance

nOe – nuclear Overhauser effect

NOESY – nuclear Overhauser enhancement spectroscopy

[O] – oxidation

Ph – phenyl

pH – hydrogen ion concentration in aqueous solution

PIA – pyrrole-imidazole alkaloids

PP2A – protein phosphatase 2A

ppm – parts per million

i-Pr – isopropyl

q – quartet

Red-Al – sodium bis(2-methoxyethoxy)aluminumhydride

ROESY – rotating-frame nuclear Overhauser effect correlation spectroscopy

r.t. – room temperature

R_f – retention factor

s – singlet

SEM – [2-(trimethylsilyl)ethoxy]methyl

SET – single –electon transfer

t – triplet

TBAF – tetrabutylammonium fluoride

TBAOxone – tetrabutylammonium Oxone

TBD – 1,5,7-triazabicyclo-[4.4.0]dec-5-ene

TBDPS – tert-butyldiphenylsilyl

TBS – tert-butyldimethylsilyl

Temp. – temperature

Teoc – trimethylsilylethyl carbamate

Tf – trifluoromethanesulfonyl

TFA – trifluoroacetic acid

TFE – trifluoroethanol

THF – tetrahydrofuran

TIPS – triisopropylsilyl

TLC – thin layer chromatography

TMS – trimethylsilyl

Ts – *p*-toluenesulfonyl (tosyl)

Tse – 2-(trimethylsilyl)ethyl

UV – ultraviolet

CHAPTER ONE

INTRODUCTION

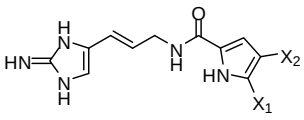
1.1 Pyrrole-Imidazole Alkaloids

In the past forty years, a series of structurally complexe pyrrole-imidazole alkaloids (PIAs) were isolated from marine sponges. These intriguing alkaloids have diverse structures and are also known as the oroidin family of alkaloids[1]. Oroidin (**1a**) was first isolated in 1971 from the sponge *Agelas oroides* (Figure 1.1.1)[2]. Several biotransformations of **1** have been observed, including oxidation, reduction, hydration, cyclization and dimerization. These modifications lead to the formation of various acyclic monomers, cyclic monomers, acyclic dimers, cyclic dimers and even tetramers. Three dimerization pathways are found among the cyclic dimers: [2+2], [3+2] and [4+2], leading to cyclobutane, cyclopentane and cyclohexene skeletons, respectively. Different bromination levels of the pyrrole, from non-brominated to di-brominated have also been found, further increasing the diversity of this family of natural products.

The structures of some representative pyrrole-imidazole alkaloids are shown in Figure 1.1.1. Sceptrin (**4**), initially isolated from *Agelas sceptrum* by Faulkner and Clardy in 1981, is the first-found cyclic oroidin dimer[3]. It bears a formal head-to-head [2+2] cycloaddtion skeleton of hymenidin (**1b**). Ageliferins (**5a-c**), which were isolated in 1986 by Rinehart and in 1990 by Kobayashi from *Agleas* sp., are the formal [4+2]

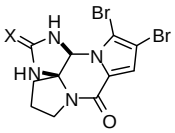
Figure 1.1.1

acyclic monomer



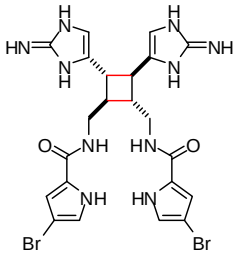
Oroidin **(1a)**, $X_1 = X_2 = Br$
Hymenidin **(1b)**, $X_1 = H$, $X_2 = Br$
Clathrodin **(1c)**, $X_1 = X_2 = H$

cyclic monomer



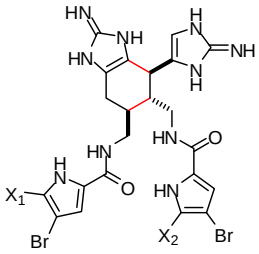
Dibromophakellstatin **(2)**, X = O
Cytotoxicin: GI_{50} 0.12–0.87 μM
Dibromophakellin **(3)**, X = NH
α_{2B} adrenoceptor agonist, EC_{50} 4.2 μM

[2+2] dimer



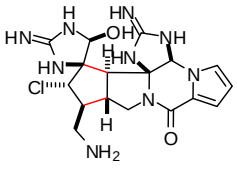
Sceptrin **(4)**
Somatostatin inhibitor, IC_{50} 0.44 μM

[4+2] dimer

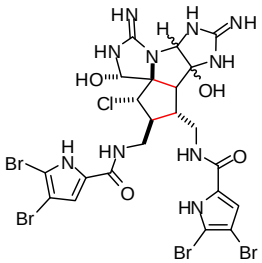


Ageliferin **(5a)**, $X_1 = X_2 = H$
Bromoageliferin **(5b)**, $X_1 = H$, $X_2 = Br$
Dibromoageliferin **(5c)**, $X_1 = X_2 = Br$
ATPase activator,
5a: 200% Δ at 30 μM
5c: 200% Δ at 1 μM

[3+2] dimer

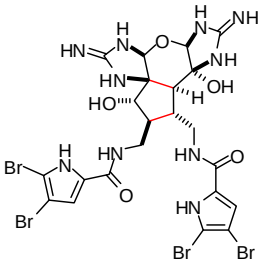


Palau'amine **(6)**
Cytotoxin (P388): IC_{50} 0.24 μM
Immunosuppressant: IC_{50} <40 nM

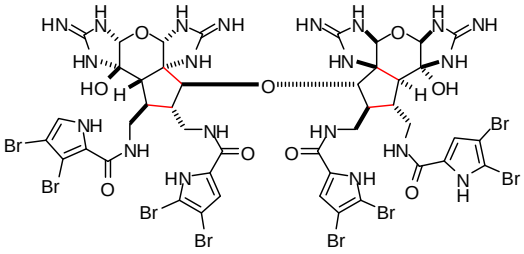


Axinellamine A (**7a**): H, OH = β
Axinellamine B (**7b**): H, OH = α
Functions unknown

tetramer



Massadine **(8)**
GGTase I inhibitor: IC_{50} 3.9 μM



Stylissadine A **(9)**
$P2X_7$ receptor antagonist: IC_{50} 0.7 μM

cycloadduct of **1**[4]. Palau'amine (**6**) was first isolated by Scheuer from *Stylotella agminata* and reported in 1993[5]. Its fully substituted [3+2] dimerization skeleton and hexacyclic ring system raise a significant challenge to synthetic chemists. Its structure was revised 14 years later[6], and the suggested revision was confirmed by total synthesis

by the Baran group in 2009[7]. In 1999 and 2003, two new [3+2] dimers, axinellamines (**7**)[8] and massadine (**8**)[9] were isolated by the Quinn and Fusetani groups from *Axinella* sp. and *Stylissa* aff. *massa* respectively. In 2006 the most complicated PIA to date, stylissadine (**9**), a dimer of massadine, was discovered by the Köck group from *Stylissa caribica*[10].

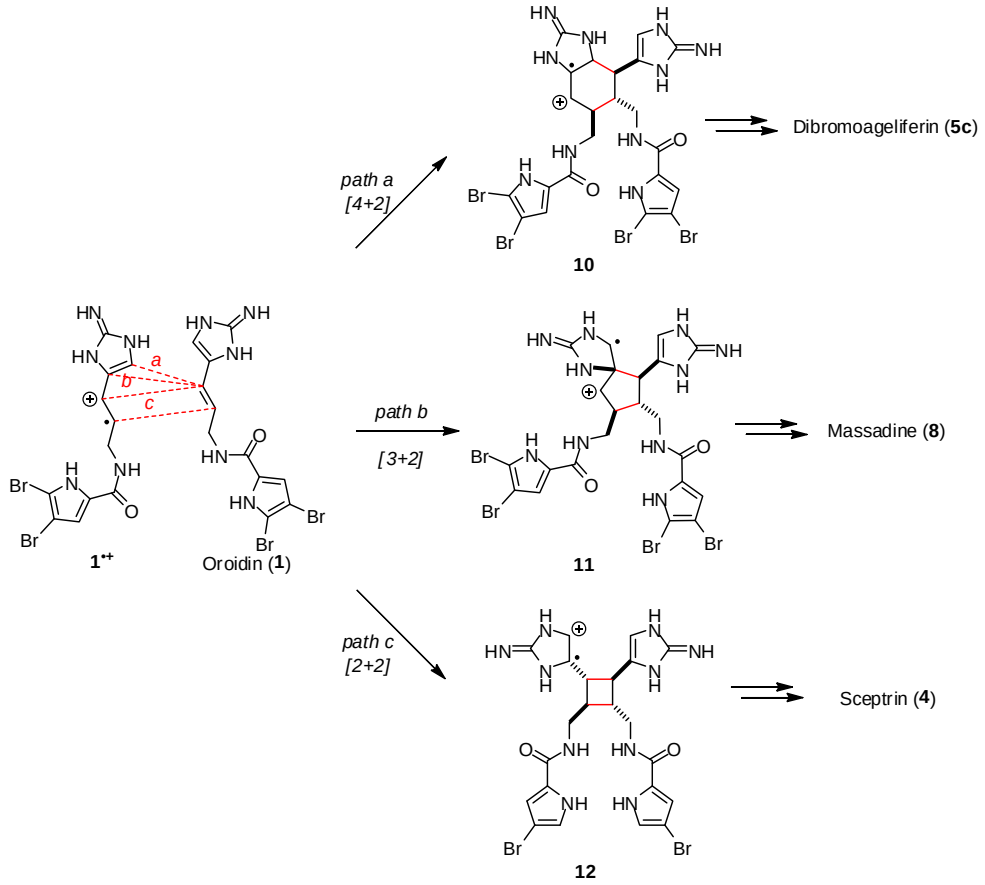
The focus of my thesis is on the synthesis of ageliferins (**5**) and massadine (**8**). Ageliferins (**5**) exhibit antimicrobial activity against both Gram-positive and Gram-negative bacteria[4a]. They are also potent actomyosin ATPase activators, increasing the ATPase activity by two-fold at micromolar concentrations. In addition, they inhibit protein phosphatase 2A (PP2A), a major serine/threonine protein phosphatase known to be critical for cellular growth and potentially implicated in the development of cancer[4b]. Massadine inhibits geranylgeranyltransferase type I (GGTase I) with an IC_{50} value of 4 μM[9].

From a structural point of view, ageliferins bear a cyclohexene ring with three contiguous stereocenters. Massadine has a fully substituted cyclopentane ring, eight contiguous stereocenters and an oxo-bridge connecting two oxidized aminoimidazole moieties. The architecturally complicated skeletons, high polarity and unusually high nitrogen abundance of these molecules (N:C:H ≈ 1:2:2) make not only the synthetic design, but also the material handling and purification challenging.

1.2 Biosynthesis of Dimeric Oroidin

One prevailing proposal for the biogenic oroidin dimerization is that the [2+2] and [4+2] dimers are generated by direct dimerization[11] and the [3+2] dimers are derived from the [4+2] dimers through an oxidative ring-contraction reaction[12]. The mismatched electronic properties of **1** make us hypothesize that the dimerization of **1** proceeds through an alternative radical mechanism (Scheme 1.2.1) rather than through a Diels-

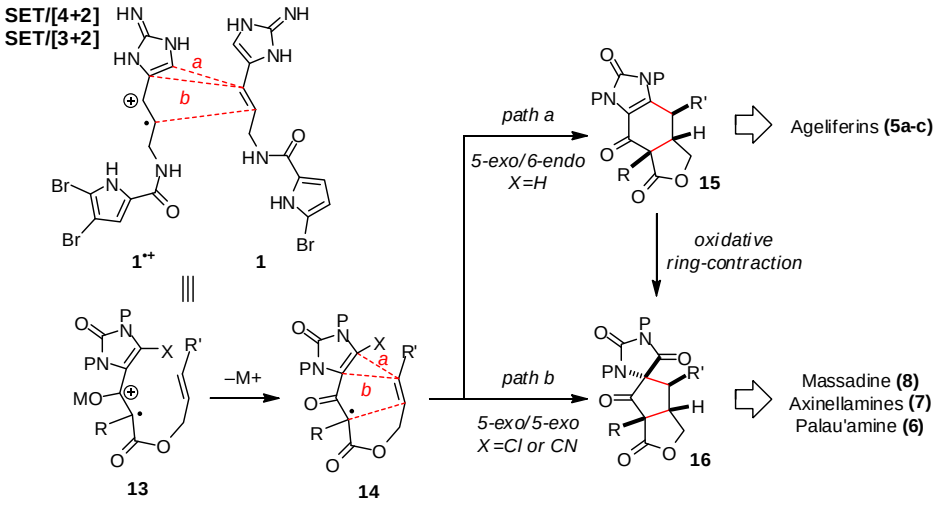
Scheme 1.2.1



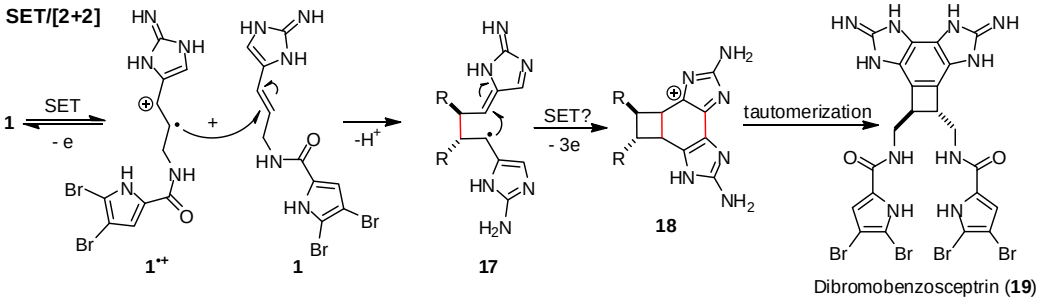
Alder reaction. A single-electron transfer (SET) oxidation of **1** would give radical cation $\mathbf{1}^{\bullet+}$ that is highly active toward cycloadditions. A [4+2] cycloaddition (path a) followed by a SET reduction would afford dibromoageliferin (**5c**); a [3+2] cycloaddition (path b) followed by a second SET oxidation and hydration would afford massadine (**8**) after further oxidation; and a [2+2] cycloaddtion (path c) followed by a SET reduction would afford sceptrin (**4**).

Previous studies in the Chen group showed that both the [4+2] and [3+2] dimerizations through radical cyclization are viable pathways (Scheme 1.2.2)[11l, 13]. We mimic the proposed cycloaddition between cation radica $\mathbf{1}^{\bullet+}$ and **1** in an intramolecular radical cascade fashion. Using a manganese(III)-mediated single-electron oxidation, we were able to obtain the [4+2] and [3+2] dimerization products **15** and **16** from **14**. We were also able to convert the [4+2] skeleton **15** to the [3+2] product **16** using a two-electron oxidative rearrangement. Recently the Molinski and Romo groups reported an enzyme-catalyzed [2+2] metabiosynthesis of dimeric oroidins supporting the possibility that dimerization goes through a SET process (Scheme 1.2.3)[14]. They successfully converted oroidin (**1**) to dibromobenzosceptrin C (**19**) using cell-free extracts obtained from *Stylissa caribica*, *Agelas conifera*, or *A. sceptrum*. They also proposed that the SET mechanism is likely involved in the cyclization. The alternative [2+2] photoaddition would be unlikely due to the lack of light where the producing sponges live[3].

Scheme 1.2.2

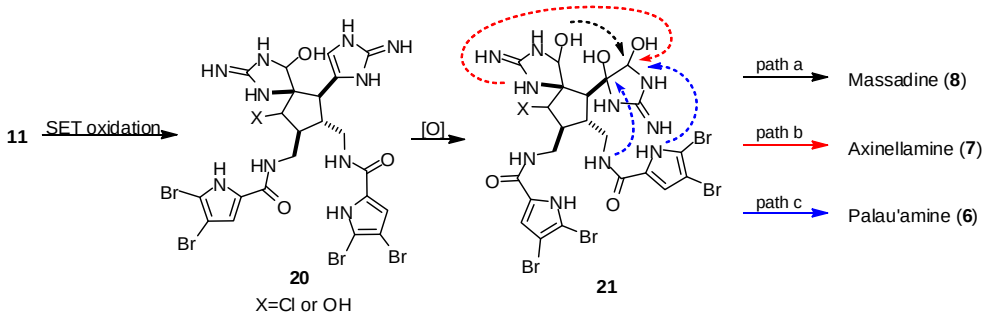


Scheme 1.2.3



The biosynthetic formation of the tetracylic skeleton of axinellamine, massadine and palau'amine involves a diverse oxidative cyclization of the [3+2] dimerization adduct **20** (Scheme 1.2.4)[111]. Oxidation of the aminoimidazole of **20** first gives **21**. Subsequent cyclization with the hemiaminal gives massadine (**8**, path a), cyclization with the cyclic guanidine gives axinellamines (**7**, path b) and cyclization with the amidopyrrole gives palau'amine (**6**, path c).

Scheme 1.2.4



1.3 Synthesis of Ageliferin and Massadine

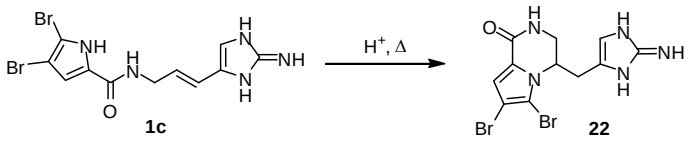
The unique molecular structures of the dimeric pyrrole-imidazole alkaloids have, over the past decades, inspired chemists to develop numerous synthetic strategies and methods. The biomimetic synthesis has been pursued by Baran[15], Ohta[16], Romo[17], Lovely[18] and us[19], while the non-biomimetic synthesis has been carried out by Overman[20], Lindel[21], Carreira[22], Austin[23], Baran[24], Birman[25], Harran[26], Shair[27], Feldman[28], Gleason[29], Gin[30] and Namba-Williams[31] groups. Some of these approaches are highlighted here.

1.3.1 Bio-Inspired Synthesis toward [4+2] and [3+2] Dimers

Among all, arguably the most biomimetic approach was developed by Romo and Lovely. In their synthesis, a Diels–Alder reaction was used to mimic the [4+2] dimerization and an oxidative ring-contraction reaction was used to convert the [4+2] skeleton to the [3+2] skeleton[17, 18]. Ohta has also used this Diels–Alder approach to achieve the racemic synthesis of 12,12'-dimethylageliferin (**25**) (Scheme 1.3.2)[16]. It was found that a more

reactive dienophile is required to react with **1** in these Diels–Alder reactions, suggesting that the biogenic dimerization of **1** is unlikely to be a thermal, uncatalyzed process. The Lindel group found that an intramolecular cyclization of **1** instead of the dimerization occurred when heating it in the presence of an acid (Scheme 1.3.1)[11k].

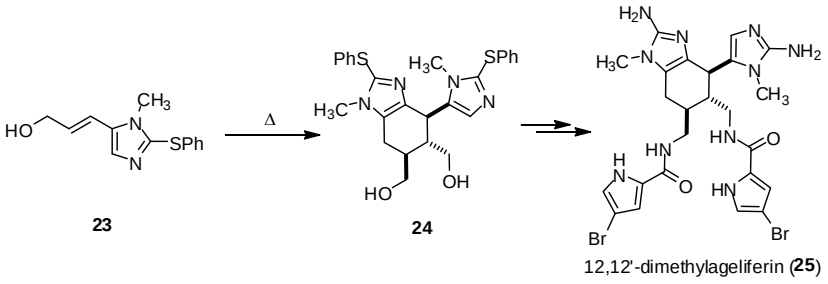
Scheme 1.3.1



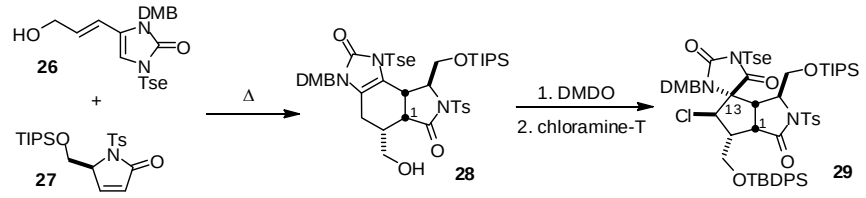
1.3.1.1 Ohta, Romo and Lovely's Synthetic Studies of Ageliferin and Massadine

The Ohta group in 2002 successfully dimerized thioimidazole **23** upon heating to generate the ageliferin cyclohexene skeleton **24** and completed the synthesis of 12, 12'-dimethylageliferin (**25**) (Scheme 1.3.2)[16]. However, only reactions with methyl protected imidazoles gave good yields.

Scheme 1.3.2

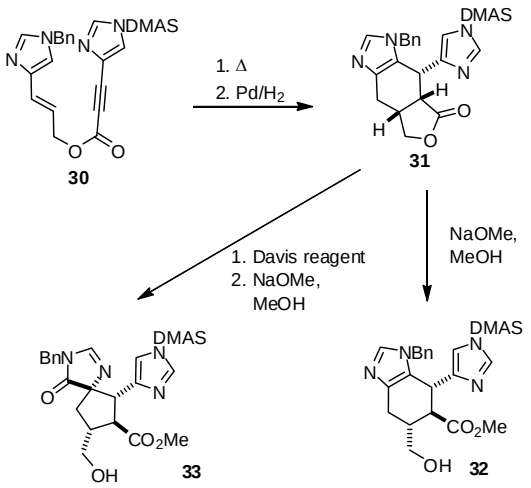


Scheme 1.3.3



The Romo group carried out the Diels-Alder reaction using a 4-vinylimidazolinone **26** as the diene and a chiral enamide **27** as the dienophile (Scheme 1.3.3)[17]. The reaction was regioselective and diastereoselective, giving the ageliferin core **28** with an undesired but epimerizable configuration at C1. Subsequently, a dioxirane oxidation of **28** followed by a chlorination reaction promoted the ring-contraction to afford the massadine skeleton **29** with a correct C-13 quaternary configuration.

Scheme 1.3.4

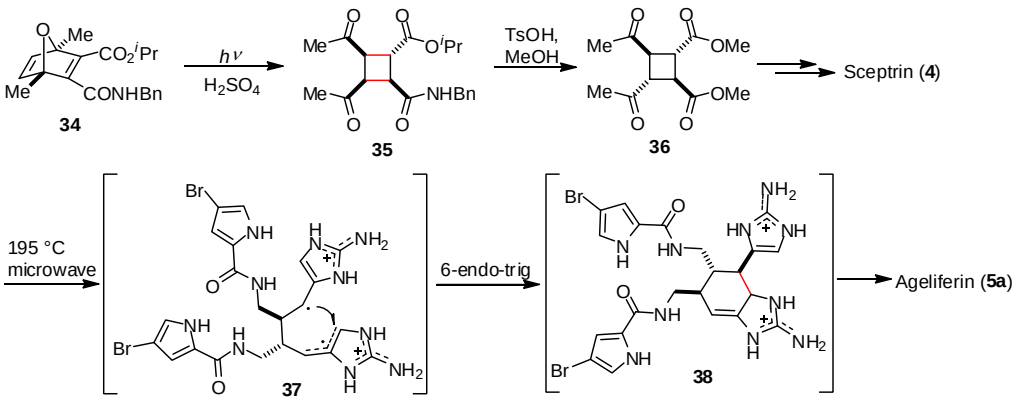


The Lovely group also reported an intramolecular Diels-Alder reaction using a vinylimidazole moiety as the diene and an alkynylimidazole as the dienophile (Scheme 1.3.4)[18]. Thermolysis of **30** followed by hydrogenation gave **31**, which was hydrolyzed and epimerized to afford **32**. Oxidation of **31** by Davis' reagent promoted the ring-contraction to afford **33** after hydrolysis and epimerization.

1.3.1.2 Baran's Synthesis of Sceptrin and Ageliferin

In 2004, the Baran group reported the first synthesis of the [2+2] dimer sceptrin (**4**)[24a]. The key step involved a [2+2] photocycloaddition of the Diels-Alder adduct **34** to give **35**, which was transformed to the sceptrin skeleton **36** (Scheme 1.3.5). Notably, the Birman group also utilized a [2+2] photocycloaddtion approach to complete the synthesis of sceptrin (**4**)[25a].

Scheme 1.3.5



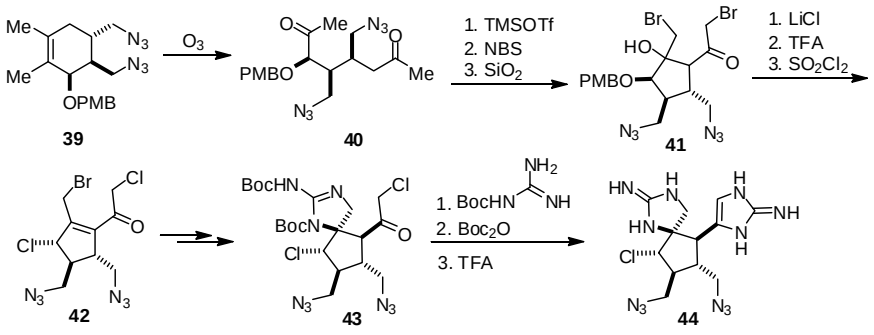
Based on the analysis of the relative contents of sceptrin (**4**) and ageliferins (**5**) in the natural samples, Baran and Köck proposed that **4** might be the biosynthetic precursor of **5**[11f-i]. They further found that **4** can be converted to **5** by microwave heating in water at 195 °C (Scheme 1.3.5)[15]. In collaboration with Houk, they found that this vinylcyclobutane-cyclohexene rearrangement occurred through the cleavage of the cyclobutane generating diradical **37**. The following radical recombination via a 6-endo-trig cyclization yielded **38**. Finally, rearomatization gave ageliferin (**5a**). The absence of the [3+2] dimers suggests the possibility of alternative biosynthetic pathways for **6**-**8**.

1.3.2 Other Approaches to [3+2] Dimers

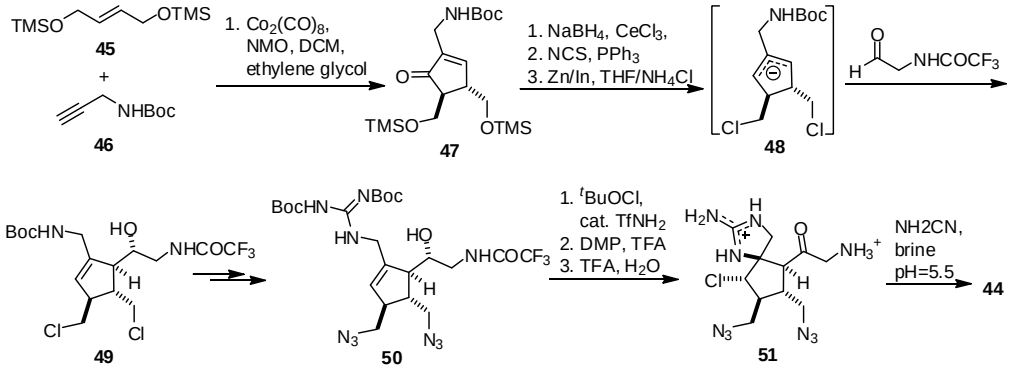
1.3.2.1 Baran's Synthesis of Axinellamine, Massadine and Palau'amine

In 2008, Baran reported the synthesis of axinellamine (**7**)[24b, c], which was the first synthesis of any of the [3+2] oroidin dimers. They found that ozonolysis of the Diels-Alder product **39** followed by an intramolecular aldol reaction and bromination provided the fully substituted cyclopentane skeleton **41** (Scheme 1.3.6). The chloride and the cyclic guanidines were then installed to give aminoimidazole **44**.

Scheme 1.3.6



Scheme 1.3.7

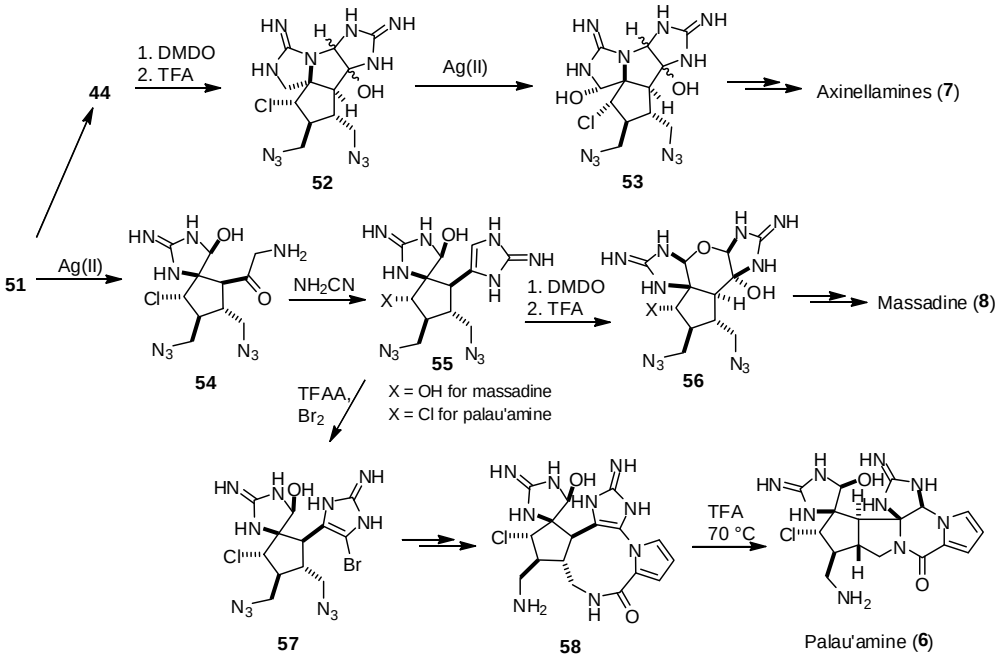


In their second generation synthesis of axinellamine, a Pauson-Khand reaction was used to construct cyclopentenone **47** (Scheme 1.3.7)[24g]. Taking advantage of the C_2 symmetry of **48,** the amino alcohol side chain was installed diastereoselectively via a desymmetrizing Barbier reation. Finally, a chloronium initiated cyclization generated the axinellamine core **51**, which was made at gram-scale in 13% overall yield in 8 steps using 4 purifications. Notably, **51** is the common intermediate for the synthesis of axinellamines (**7**), massadine (**8**) and palau'amine (**6**) (Scheme 1.3.8).

To complete the synthesis of axinellamine from **44**, a DMDO/TFA-promoted biomimetic oxidative cyclization followed by a highly chemo-, region- and stereoselective silver(II) picolinate oxidation provided hemiaminal **53**. Finally, installation of the pyrrole groups furnished axinellamines (**7**). For the synthesis of massadine (**8**), **51** was first oxidized by silver(II) picolinate and the aminoimidzole group was then introduced[24e]. During the synthesis of massadine (**8**), they found that chloride was partially hydrolyzed via an aziridinium intermediate, which was also observed by the Romo group[17f]. Oxidative

cyclization under acidic conditions suppressed the formation of the axinellamine skeleton giving **56** as a 1:3 mixture of diastereomers favoring *epi*-massadine.

Scheme 1.3.8



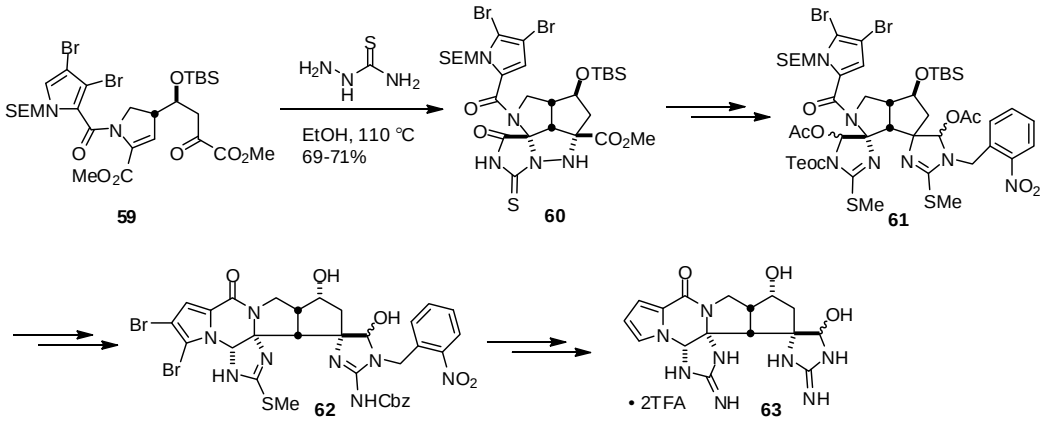
The synthetic route for palau'amine (**6**) was, however, more devious than that of axinellamines (**7**) and massadine (**8**), possibly due to higher ring strain in the cyclic system[24f]. Baran found that the biomimetic oxidative cyclization of analogs of **20** was challenging. To overcome this problem, a macrocyclic strategy was developed that used a transannular cyclization of "macropalau'amine" **58** to complete the synthesis of palau'amine (**6**). Although the ROESY study of **58** showed that the amide nitrogen was

in proximity to the aminoimidazole, only after extensive screening of conditions did they find that neat warm TFA would deliver palau'amine (**6**).

1.3.2.2 Overman's Approach to the Originally Assigned Palau'amine Structure

The first synthetic study of palau'amine (**6**) was reported by the Overman group[20a]. Their synthetic strategy was developed before the stereochemistry of **6** was revised. They developed an impressive tandem reaction, comprising a hydrazine condensation, a [3+2] cycloaddition and a thiohydantoin formation to afford **60** from **59**[20e]. Three new rings and three new stereocenters were generated in a single step, giving the *cis*-fused five-five ring system that corresponds to the originally proposed structure of palau'amine (Scheme 1.3.9). NMR analysis of the advance synthetic intermediate **63** provided support to the structural revision proposed in 2007.

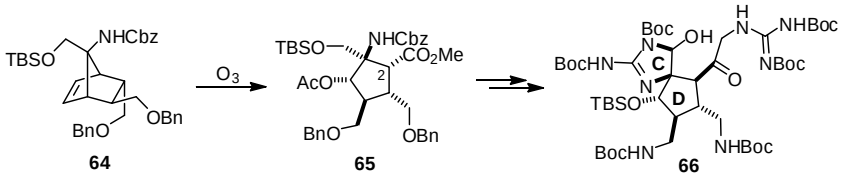
Scheme 1.3.9



1.3.2.3 Carreira's Synthesis toward Massadine

The Carreira group constructed the fully substituted cyclopentane core **65** by ozonolysis of a bicyclo[2.2.1]hept-2-ene **64** (Scheme 1.3.10), which was readily synthesized by a Diels-Alder reaction of with cyclopentadiene and succinimide[22]. The C2 carbon in **65** was epimerized under basic conditions to afford the desired stereochemistry. Installation of the spiroguanidine gave the fully functionalized massadine core **66**.

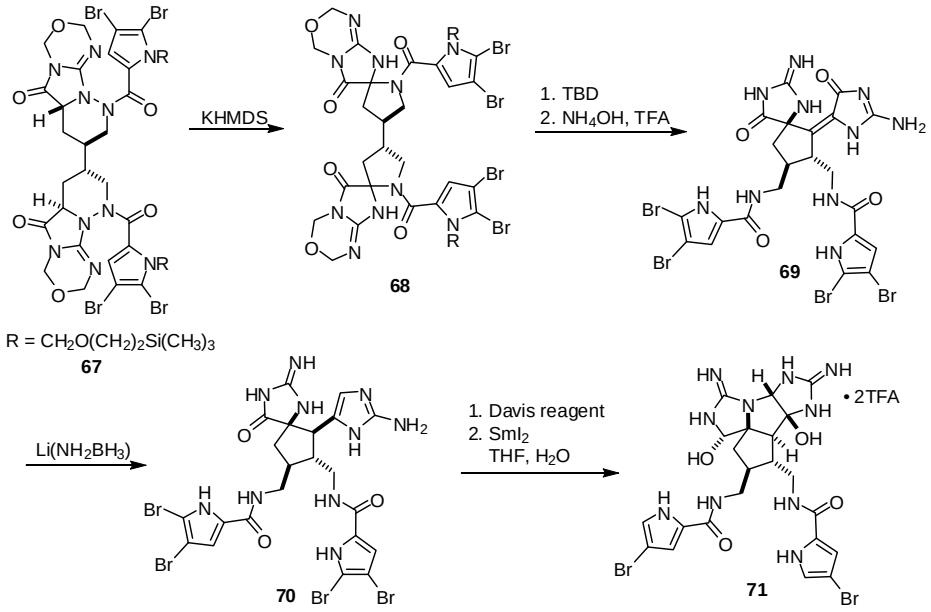
Scheme 1.3.10



1.3.2.4 Harran's Synthesis of Axinellamine Deficient in Halogen

The Harran group constructed the axinellamine core through a series of fascinating transformations (Scheme 1.3.11)[26d]. Treating C_2-symmetric **67** with KHMDS resulted in the N-N bond cleavage followed by a 5-exo-trig cyclization, affording **69** as a mixture of two diastereomers. Aminohydantoin **68** was then isomerized to give the cyclopentane core **69** upon stirring with 1,5,7-triazabicyclo-[4.4.0]dec-5-ene (TBD). After deoxygenation and an olefin migration, the des-Cl-axinellamine skeleton **70** was formed, which was transformed to **71** after 2 steps.

Scheme 1.3.11



1.4 References

(1) For reviews, see: (a) Hoffmann, H.; Lindel, T. *Synthesis*. **2003**, 1753–1783. (b) Jacquot, D. E. N.; Lindel, T. *Curr. Org. Chem*. **2005**, *9*, 1551–1565. (c) Du, H.; He, Y.; Sivappa, R.; Lovely, C. J. *Synlett*. **2006**, 965–992. (d) Köck, M.; Grube, A.; Seiple, I. B.; Baran, P. S. *Angew. Chem., Int. Ed*. **2007**, *46*, 6586–6594. (e) Weinreb, S. M. *Nat. Prod. Rep*. **2007**, *24*, 931–948. (f) Arndt, H.-D.; Riedrich, M. *Angew. Chem., Int. Ed*. **2008**, *47*, 4785–4788. (g) Heasley, B. *Eur. J. Org. Chem*. **2009**, 1477–1489. (h) Forte, B.; Malgesini, B.; Piutti, C.; Quartieri, F.; Scolaro, A.; Papeo, G. *Mar. Drugs*. **2009**, *7*, 705–753. (i) Gaich, T.; Baran, P. S. *J. Org. Chem*. **2010**, *75*, 4657–4673. (j) Al-Mourabit, A.; Zancanella, M. A.; Tilvi, S.; Romo, D. *Nat. Prod. Rep*. **2011**, *28*, 1229–1260.

(2) Isolation: (a) Forenza, S.; Minale, L.; Riccio, R. Fattorusso, E. *J. Chem. Soc., D. Chem. Commun.* **1971**, 1129–1130. Structure assignment: (b) Garcia, E. E.; Benjamin, L. E.; Fryer, R. I. *J. Chem. Soc., Chem. Commun.* **1973**, 78–79.

(3) Walker, R. P.; Faulkner, D. J.; Van Engen, D.; Clardy, J. *J. Am.Chem. Soc*. **1981**, *103*, 6772–6773.

(4) (a) Rinehart, K. L. *Pure Appl. Chem*. **1989**, *61*, 525–528. (b) Kobayashi, J.; Tsuda, M.; Murayama, T.; Nakamura, H.; Ohizumi, Y.; Ishibashi, M.; Iwamura, M.; Ohta, T.; Nozoe, S. *Tetrahedron*. **1990**, *46*, 5579–5586. (c) Keifer, P. A.; Schwartz, R. E.; Koker, M. E. S.; Hughes, R.G., Jr.; Rittschof, D.; Rinehart, K. L. *J. Org. Chem*. **1991**, *56*, 2965–2975. (d) Williams, D. H.; Faulkner, D. J. *Tetrahedron*. **1996**, *52*, 5381–5390.

(5) (a) Kinnel, R. B.; Gehrken, H. P.; Scheuer, P. J. *J. Am. Chem. Soc*. **1993**, *115*, 3376–3377. (b) Kinnel, R. B.; Gehrken, H.-P.; Swali, R.; Skoropowski, G.; Scheuer, P. J. *J. Org. Chem*. **1998**, *63*, 3281–3286.

(6) (a) Buchanan, M. S.; Carroll, A. R.; Addepalli, R.; Avery, V. M.; Hooper, J. N. A.; Quinn, R. J. *J. Org. Chem*. **2007**, *72*, 2309–2317. (b) Buchanan, M. S.; Carroll, A. R.; Quinn, R. J. *Tetrahedron Lett.* **2007**, *48*, 4573–4574. (c) Grube, A.; Köck, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2320–2324. (d) Kobayashi, H.; Kitamura, K.; Nagai, K.;

Nakao, Y.; Fusetani, N.; van Soest, R. W. M.; Matsunaga, S. *Tetrahedron Lett.* **2007**, 48, 2127–2129.

(7) Seiple, I. B.; Su, S.; Young, I. S.; Lewis, C. A.; Yamaguchi, J.; Baran, P. S. *Angew. Chem., Int. Ed*. **2010**, *49*, 1095–1098.

(8) Urban, S.; Leone, P. d. A.; Carroll, A. R.; Fechner, G. A.; Smith, J.; Hooper, J. N. A.; Quinn, R. J. *J. Org. Chem*. **1999**, *64*, 731–735.

(9) Nishimura, S.; Matsunaga, S.; Shibazaki, M.; Suzuki, K.; Furihata, K.; van Soest, R. W. M.; Fusetani, N. *Org. Lett*. **2003**, *5*, 2255–2257.

(10) (a) Grube, A.; Köck, M. *Org. Lett*. **2006**, *8*, 4675–4678. (b) Ref 6a.

(11) (a) Ref 3. (b) Ref 2c. (c) Olofson, A.; Yakushijin, K.; Horne, D. A. *J. Org. Chem*. **1997**, *62*, 7918–7919. (d) Ref 5b. (e) Al Mourabit, A.; Potier, P. *Eur. J. Org. Chem*. **2001**, 237–243. (f) Baran, P. S.; O'Malley, D. P.; Zografos, A. L. *Angew. Chem., Int. Ed*. **2004**, *43*, 2674–2677. (g) Baran, P. S.; Li, K.; O'Malley, D. P.; Mitsos, C. *Angew. Chem., Int. Ed*. **2006**, *45*, 249–252. (h) Northrop, B. H.; O'Malley, D. P.; Zografos, A. L.; Baran, P. S.; Houk, K. N. *Angew.Chem., Int. Ed*. **2006**, *45*, 4126–4130. (i) O'Malley, D. P.; Li, K.; Maue, M.; Zografos, A. L.; Baran, P. S. *J. Am. Chem. Soc*. **2007**, *129*, 4762–4775. In Ref 11f-i, the [2 + 2] dimers were suggested to be the biosynthesis precursors of the [4 + 2] dimers. (j) Travert, N.; Al-Moura, A. *J. Am. Chem. Soc*. **2004**,

126, 10252–10253. (k) Pöverlein, C.; Breckle, G.; Lindel, T. *Org. Lett.* **2006**, *8*, 819–821. (l) Ma, Z.; Lu, J.; Wang, X.; Chen, C. *Chem. Commun*. **2011**, *47*, 427–429. (m) Feldman, K. S.; Nuriye, A. Y.; Li, J. *J. Org. Chem*. **2011**, *76*, 5042–5060.

(12) (a) Ref 11d. (b) Ref 11e. (c) Ref 11i. (d) Ref 11l. (e) Ref 11m.

(13) Tan, X.; Chen, C. *Angew. Chem., Int. Ed*. **2006**, *45*, 4345–4348.

(14) Stout, E. P.; Wang, Y.; Romo, D.; Molinski, T. F. *Angew. Chem., Int. Ed*. **2012**, *51*, 1–6.

(15) (a) Ref 11f. (b) Ref 11g. (c) Ref 11h. (d) Ref 11i. Ph.D. thesis: (e) O'Malley, D. P. The Scripps Research Institute, 2008.

(16) (a) Kawasaki, I.; Sakaguchi, N.; Fukushima, N.; Fujioka, N.; Nikaido, F.; Yamashita, M.; Ohta, S. *Tetrahedron*. **2002**, *43*, 4377–4380. (b) Kawasaki, I.; Sakaguchi, N.; Khadeer, A.; Yamashita, M.; Ohta, S. *Tetrahedron*. **2006**, *62*, 10182–10192.

(17) (a) Dilley, A. S.; Romo, D. *Org. Lett*. **2001**, *3*, 1535–1538. (b) Poullennec, K. G.; Kelly, A. T.; Romo, D. *Org. Lett.* **2002**, *4*, 2645–2648. (c) Poullennec, K. G.; Romo, D. *J. Am. Chem. Soc*. **2003**, *125*, 6344–6345. (d) Dransfield, P. J.; Wang, S.; Dilley, A.; Romo, D. *Org. Lett*. **2005**, *7*, 1679–1682. (e) Dransfield, P. J.; Dilley, A. S.; Wang, S.;

Romo, D. *Tetrahedron*. **2006**, *62*, 5223–5247. (f) Wang, S.; Dilley, A. S.; Poullennecz, K. G.; Romo, D. *Tetrahedron*. **2006**, *62*, 7155–7161. (g) Tang, L.; Romo, D. *Heterocycles*. **2007**, *74*, 999–1008. (h) Wang, S.; Romo, D. *Angew. Chem., Int. Ed*. **2008**, *47*, 1284–1286. (i) Zancanella, M. A.; Romo, D. *Org. Lett*. **2008**, *10*, 3685–3688. Ph.D. thesis: (j) Poullennec, K., Texas A&M University, 2003. (k) Dilley, A., Texas A&M University, 2003. (l) Wang, S., Texas A&M University, 2007.

(18) (a) Lovely, C. J.; Du, H.; Dias, H. V. R. *Org. Lett.*, **2001**, *3*, 1319–1322. (b) He, Y.; Chen, Y.; Wu, H.; Lovely, C. J. *Org. Lett*. **2003**, *5*, 3623–3626. (c) Lovely, C. J.; Du, H.; He, Y.; Dias, H. V. R. *Org. Lett.*, **2004**, 6, 735–738. (d) Sivappa, R.; Hernandez, N. M.; He, Y.; Lovely, C. J. *Org. Lett*. **2007**, *9*, 3861–3864. (e) Lovely, C. J.; Du, H.; Sivappa, R.; Bhandari, M. R.; He, Y.; Dias, H. V. R. *J. Org. Chem*. **2007**, *72*, 3741–3749. (f) Sivappa, R.; Mukherjee, S.; Dias, H. V. R.; Lovely, C. *J. Org. Biomol. Chem*. **2009**, *7*, 3215–3218. (g) He, Y.; Krishnamoorthy, P.; Lima, H. M.; Chen, Y.; Wu, H.; Sivappa, R.; Dias, H. V. R.; Lovely C. J. *Org. Biomol. Chem.* **2011**, *9*, 2685–2701. (h) Bhandari, M. R.; Yousufuddin, M.; Lovely, C. J. *Org. Lett*. **2011**, *13*, 1382–1385. Ph.D. thesis: (i) Yu, E., University of Texas, Arlington, 2002. (j) Du, H., University of Texas, Arlington, 2004. (k) He, Y., University of Texas, Arlington, 2005. (l) Mukherjee, S., University of Texas, Arlington, 2011.

(19) (a) Ref 13. (b) Ref 11l. (c) Wang, X.; Ma, Z.; Lu, J.; Tan, X.; Chen, C. *J. Am. Chem. Soc*. **2011**, *133*, 15350–15353.

(20) (a) Overman, L. E.; Rogers, B. N.; Tellew, J. E.; Trenkle, W. C. *J. Am. Chem. Soc*. **1997**, *119*, 7159–7160. (b) Belanger, G.; Hong, F.-T.; Overman, L. E.; Rogers, B. N.; Tellew, J. E.; Trenkle, W. C. *J. Org. Chem*. **2002**, *67*, 7880–7883. (c) Katz, J. D.; Overman, L. E. *Tetrahedron*. **2004**, *60*, 9559–9568. (d) Lanman, B. A.; Overman, L. E. *Heterocycles*. **2006**, *70*, 557–570. (e) Lanman, B. A.; Overman, L. E.; Paulini, R.; White, N. S. *J. Am. Chem. Soc*. **2007**, *129*, 12896–12900. Ph.D. thesis: (f) Trenkle, W., University of California, Irvine, 2000. (g) Huang, A., University of California, Irvine, 2006. (h) Gergely, J., University of California, Irvine, 2007. (i) White, N., University of California, Irvine, 2009.

(21) (a) Ref 11k. (b) Jacobi, N.; Lindel, T.; *Eur. J. Org. Chem*. **2010**, 5415–5425. Ph.D. thesis: (c) Hoffmann, H., Universität Heidelberg, 1999. (d) Hochgürtel,M., Universität Heidelberg, 2000. (e) Jacquot, D., Ludwig-Maximilians-Universität, München, 2003. (f) Breckle, G., Ludwig-Maximilians-Universität, München, 2004. (g) Zöllinger, M., Ludwig-Maximilians-Universität, München, 2007. (h) Pöverlein, C., Ludwig-Maximilians-Universität, München, 2008.

(22) (a) Starr, J. T.; Koch, G.; Carreira, E. M. *J. Am. Chem. Soc*. **2000**, *122*, 8793–8794. (b) Breder, A.; Chinigo, G. M.; Waltman, A. W.; Carreira, E. M. *Angew. Chem., Int. Ed*. **2008**, *47*, 8514–8517. (c) Chinigo, G. M.; Breder, A.; Carreira, E. M. *Org. Lett*. **2011**, *13*, 78–81. (d) Breder, A.; Chinigo, G. M.; Waltman, A. W.; Carreira, E. M. *Chem. Eur. J*. **2011**, *17*, 12405 – 12416. Ph.D. thesis: (e) Starr, J., California Institute of Technology, 2001.

(23) (a) Koenig, S. G.; Miller, S. M.; Leonard, K. A.; Löwe, R. S.; Chen, B. C.; Austin, D. J. *Org. Lett.* **2003**, *5*, 2203 – 2206. Ph.D. thesis: (b) Koenig, S., Yale University, 2002.

(24) (a) Baran, B. S.; Zografos, A. L.; O'Malley, D. P. *J. Am. Chem. Soc.* **2004**, *126*, 3726–3727. (b) Yamaguchi, J.; Seiple, I. B.; Young, I. S.; O'Malley, D. P.; Maue, M.; Baran, P. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 3578–3580. (c) O'Malley, D. P.; Yamaguchi, J.; Young, I. S.; Seiple, I. B.; Baran, P. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 3581–3583. (d) Grube, A; Immel, S.; Baran, P. S.; and Köck, M. *Angew. Chem., Int. Ed*. **2007**, *46*, 6721–6724. (e) Su, S.; Seiple, I. B.; Young, I. S.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 16490–16491. (f) Ref 7. (g) Su, S.; Rodriguez, R. A.; Baran. P. S. *J. Am. Chem. Soc*. **2011**, *133*, 13922–13925. (h) Seiple, I. B.; Su, S.; Young, I. S.; Nakamura, A.; Yamaguchi, J.; Jørgensen, L.; Rodriguez, R. A.; O'Malley, D. P.; Gaich, T.; Köck, M.; Baran, P. S. *J. Am. Chem. Soc*. **2011**, *133*, 14710–14726.

(25) Birman, V. B.; Jiang, X. *Org. Lett*. **2004**, *6*, 2369–2371.

(26) (a) Garrido-Hernandez, H.; Nakadai, M.; Vimolratana, M.; Li, Q.; Doundoulakis, T.; Harran, P. G. *Angew. Chem., Int. Ed*. **2005**, *44*, 765–769. (b) Nakadai, M.; Harran, P. G. *Tetrahedron Lett*. **2006**, *47*, 3933–3935. (c) Li, Q.; Hurley, P.; Ding, H.; Roberts, A. G.; Akella, R.; Harran, P. G. *J. Org. Chem*. **2009**, *74*, 5909–5919. (d) Ding, H.; Roberts, A.

G.; Harran, P. G. *Angew. Chem., Int. Ed*. **2012**, *51*, 1–5. Ph.D. thesis: (e) Li, Q., University of Texas Southwestern Medical Center, 2008.

(27) Ph.D. thesis: Spoering, R., Harvard University, 2005.

(28) (a) Feldman, K. S.; Nuriye, A. Y. *Org. Lett*. **2010**, *12*, 4532–4535. (b) Ref 11m. Ph.D. thesis: (c) Skoumbourdis, A., Pennsylvania State University, 2005.

(29) (a) Cernak, T. A.; Gleason, J. L. *J. Org. Chem*. **2008**, *73*, 102–110. (b) Hudon, J.; Cernak, T. A.; Ashenhurst, J. A.; Gleason, J. L. *Angew. Chem., Int. Ed*. **2008**, *47*, 8885–8888. Ph.D. thesis: (c) Ashenhurst, R., McGill University, 2006. (d) Cernak, T., McGill University, 2007. (e) Hudon, J., McGill University, 2010.

(30) (a) Bultman, M. S.; Ma, J.; Gin, D. Y. *Angew. Chem., Int. Ed*. **2008**, *47*, 6821–6824. Ph.D. thesis: (b) Bultman, M., University of Illinois, Urbana-Champaign, 2009.

(31) (a) Namba, K.; Kaihara, Y.; Yamamoto, H.; Imagawa, H.;Tanino, K.; Williams, R. M.; Nishizawa, M. *Chem. Eur. J*. **2009**, *15*, 6560–6563. (b) Namba, K.; Inai, M.; Sundermeier, U.; Greshock, T. J.; Williams, R. M. *Tetrahedron Lett*. **2010**, *51*, 6557–6559.

CHAPTER TWO

BIOMIMETIC SYNTHESIS OF THE CORE SKELETONS OF THE PYRROLE-IMIDAZOLE DIMERS

2.1 Construction of the Ageliferin Core Structure by Intramolecular Radical Tandem Cyclization

The first part of my Ph.D. study is directed at testing the biosynthetic hypothesis of oroidin dimerization. Manganese(III) acetate is well known as an effective oxidant for enolizable carbonyl compounds. Since Corey's initial report of the intramolecular Mn(III)-promoted oxidative cyclizations of β-dicarboxylates[1], the reaction has grown in popularity and scope[2]. We envisioned that a Mn(III) oxidation of β-ketoester **72** would initiate a radical cascade cyclization reaction to give the ageliferin core skeleton **73**, establishing two C–C bonds and three stereogenic centers in a single step (Scheme 2.1.1)[3]. Indeed, we found that **73** was obtained as both a kinetic and a thermodynamic 6-endo cyclization product due to captodative effects. The initial studies were carried out by postdoctoral fellow Dr. Xianghui Tan.

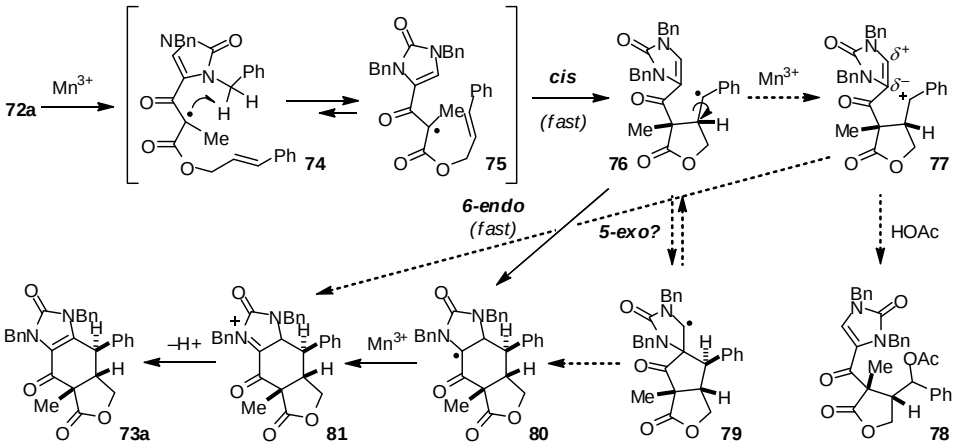
Scheme 2.1.1

72a, X = Me
72b, X = H or Cl

73a, X = Me
decomposition if X = H or Cl

The mechanism of this reaction is shown in Figure 2.1.1. Oxidation of **72** gave the α-radical that may exist as conformation **74** or **75**. We anticipate **75** to be the favored conformation for steric reasons. However, for the oxidation of **72b**, there is no α-methyl group and the unfavorable methyl/benzyl steric interaction does not exist. The α-radical would instead adopt the **74**-like conformation to minimize the dipole moment. A 1,5-hydrogen abstraction then occurred to destroy the imidazolinone group without cyclization.

Figure 2.1.1



While the Mn(III)-promoted radical cyclization reactions usually afford *trans* products, DFT calculation suggested the *cis* products to be kinetically favored. The *cis* configuration at the 5,6-ring junction in **73a** indicates that the 5-exo cyclization of **75** proceeded with kinetic control and the 6-endo cyclization of **76** was faster than the retro-5-exo-cyclization, thus providing the kinetic *cis* product. We consider the ionic 6-endo

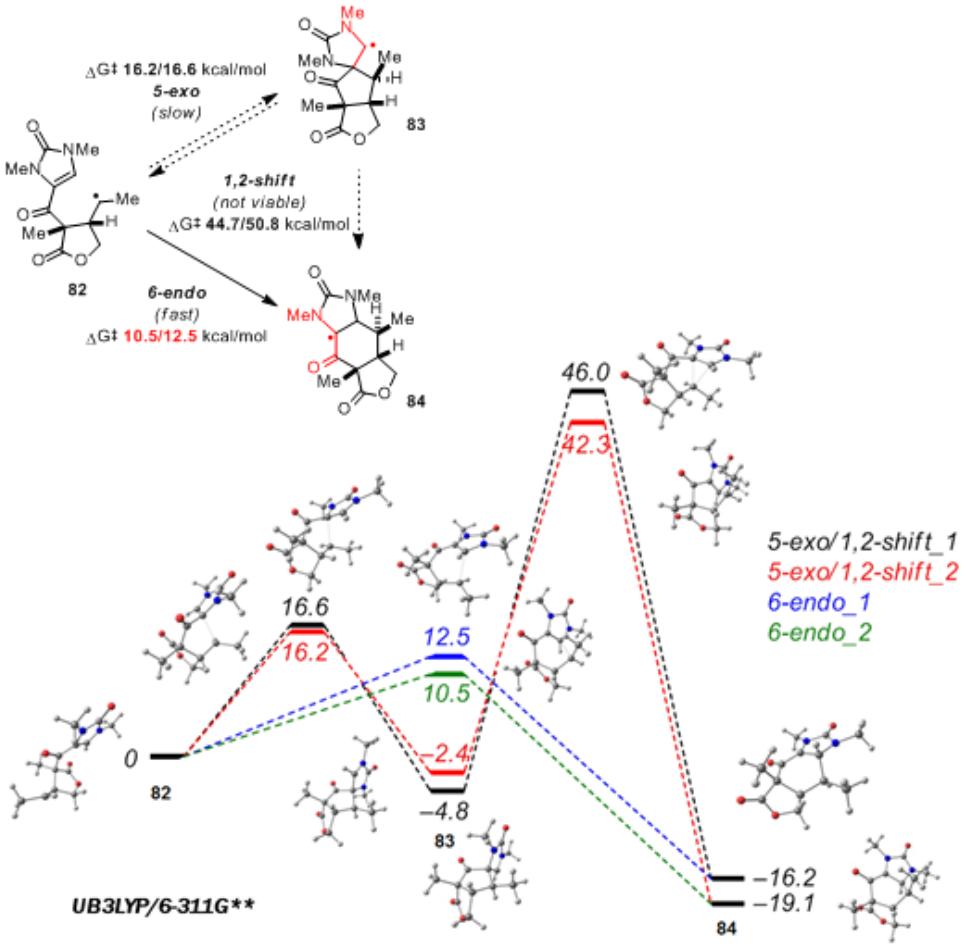
cyclization of **76** via **77** less likely because the regioselectivity and the polarization of acylimidazolinone are mismatched. Addition of $Cu(OAc)_2$, which is reported to accelerate the oxidation of secondary radicals by 350 times[3e], also had no effect on this reaction.

The regioselectivity of the cyclization of **75** and **76** is rather interesting. It is well known that the 5-exo-trig cyclization is kinetically favored over the 6-endo-trig cyclization for alkyl radicals, but the opposite is true for α-acyl radicals[2a]. Based on Houk's seminal computational studies on radical cyclization reactions, the planarity of α-acyl radicals is maintained in the transition states, causing the reversed regioselectivity[4]. However, we have observed a 5-exo-trig α-acyl radical cyclization (**75→76**) and a 6-endo-trig alkyl radical cyclization (**76→80**). We are particularly interested in the second radical cyclization step as it determines the selective formation of ageliferin or massadine core skeleton.

This step could proceed through a direct 6-endo-trig cyclization (**76→80**), a 5-exo-trig cyclization followed by a 1,2-shift (**76→79→80**), or 6-endo-trig cyclization with a equilibrium between **76** and **79**. In order to address this issue, we analyzed all these pathways with DFT calculations (Figure 2.1.2). Because the stereochemical information of the newly formed stereocenter in **83**/**84** is lost in product **73a**, we evaluated the both diastereomeric pathways. This computational study was first carried out by Dr. Chuo Chen using UHF and UB3LYP at the 6-31G** level and then refined by Kevin Cormier

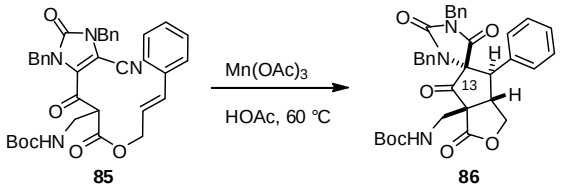
at the 6-311G** level. The result shows that the 6-endo product **84** is 11.4 or 16.7 kcal/mol more stable than the 5-exo product **83**, and the transition state energy of the 6-endo pathway is 4.1 or 5.7 kcal/mol lower than that of the 5-exo pathway, depending on the configuration of the newly generated stereocenter. The 1,2-shift is almost forbidden due to more than 40 kcal/mol energy barrier. The calculation shows the 6-exo pathway is both thermodynamically and kinetically favored, and is driven by a radical captodative stabilization.

Figure 2.1.2



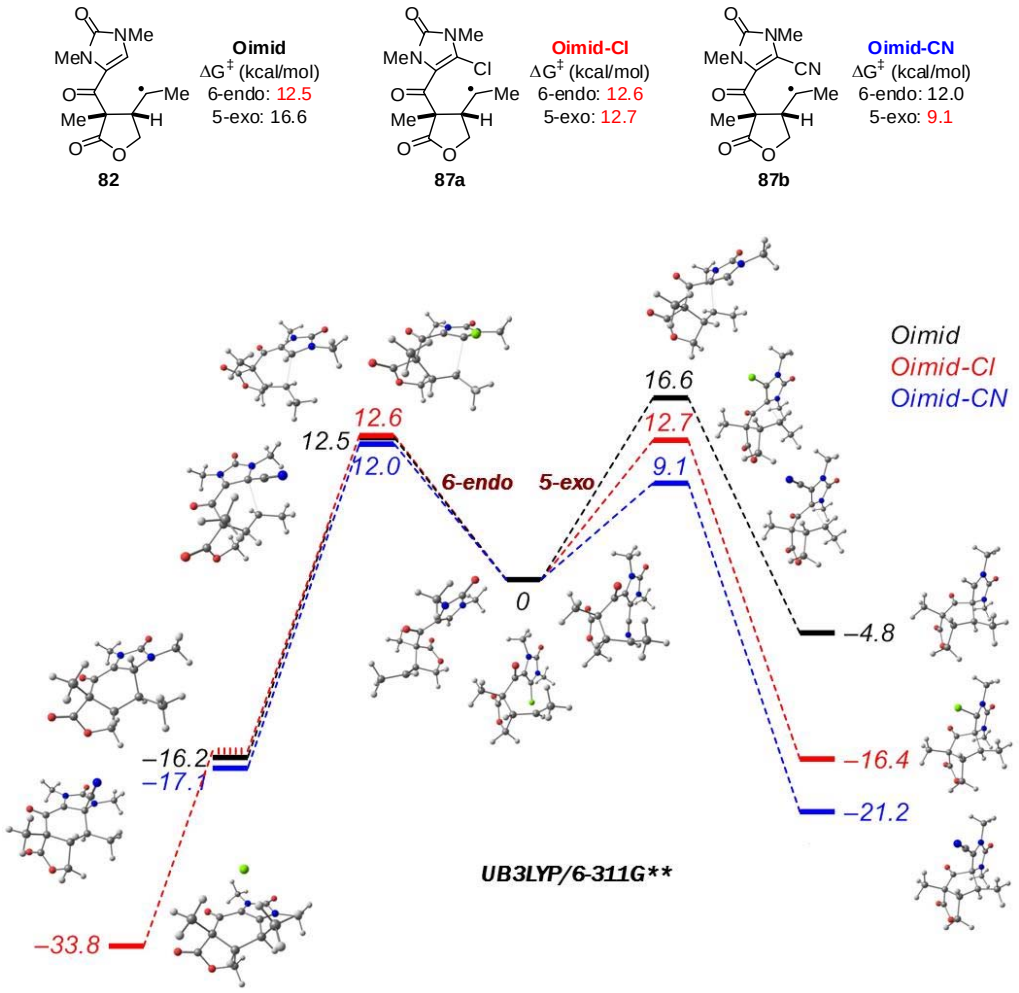
To reverse the selectivity to the 5-exo pathway for massadine skeleton, an electron withdrawing group (chloride or cyanide) was introduced to the imidazolinone to generate a captodative stabilization of the 5-exo cyclization product. Pleasingly, oxidation of **85** gave **86** bearing a massadine core skeleton as predicted (Scheme 2.1.2). This result is fully in accordance with the DFT calculation. The activation energy of the 5-exo cyclization pathway of cyanide **87b** is 2.9 kcal/mol lower than that of the 6-endo cyclization pathway, and the 5-exo cyclization product is 4.1 kcal/mol more stable (Figure 2.1.3). Thus 5-exo pathway becomes thermodynamically and kinetically favored after the modification of substrates. Unfortunately, although cyclopentane skeleton **86** was successfully obtained, the stereocenter of C13 was opposite to the nature product.

Scheme 2.1.2



85 **86**

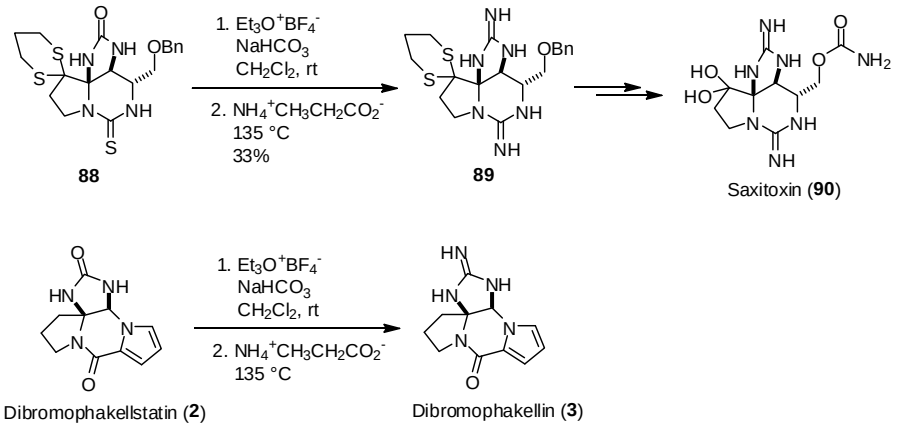
Figure 2.1.3


Oimid
ΔG‡ (kcal/mol)
6-endo: 12.5
5-exo: 16.6
82
Oimid-Cl
ΔG‡ (kcal/mol)
6-endo: 12.6
5-exo: 12.7
87a
Oimid-CN
ΔG‡ (kcal/mol)
6-endo: 12.0
5-exo: 9.1
87b
Oimid
Oimid-Cl
Oimid-CN
12.5
12.6
12.0
6-endo
5-exo
16.6
12.7
9.1
0
−4.8
−16.2
−17.1
−16.4
−21.2
−33.8
UB3LYP/6-311G**

2.2 Synthesis of *ent*-9'-*epi*-13,13'-Dioxoageliferin

Having achieved the cyclohexene core of ageliferin, its total synthesis was then pursued. One important challenge in the synthesis of oroidin dimers is the two cyclic guanidines. Since guanidine is basic, nucleophilic and polar, the previous work by Dr. Xianghui Tan relied on a late-stage conversion of urea to guanidine to avoid carrying this functional group through a long sequence of synthesis. He has demonstrated that dibromophakellstatin (**2**) can be converted to dibromophakellin (**3**) using the method that Kishi developed for the synthesis of saxitoxin (**90**) (Scheme 2.2.1)[5].

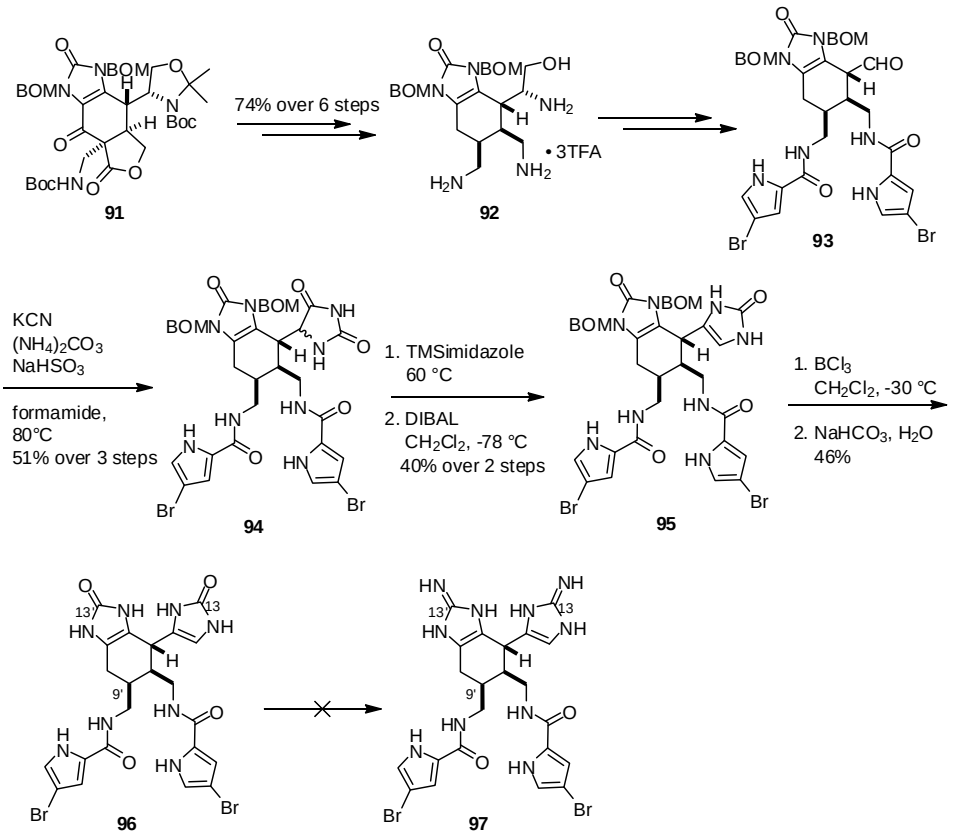
Scheme 2.2.1



The previous work toward the synthesis of ageliferin is summarized in Scheme 2.2.2. The ageliferin core **91** was prepared by the manganese(III)-mediated intramolecular radical tandem cyclization reaction. After converting to triamine **92**, the acylpyrrole was

introduced selectively to the less hindered positions. It should be noted that I found that the relative stereochemistry of the thermodynamic product of the decarboxylation of **91** was misassigned[111]. It is rather surprising to find that **92** bears *syn*-C9/C9' side-chains. The amino alcohol was then cleaved oxidatively to give **93**. A hydantoin group was then introduced by a Bucherer-Berg reaction. A two-step reduction converted **94** to imidazolinone **95**. The BOM protecting group was then removed to afford *ent*-9'-*epi*-13,13'-dioxoageliferin **96**. However, all attempts to introduce the last two nitrogen atoms failed.

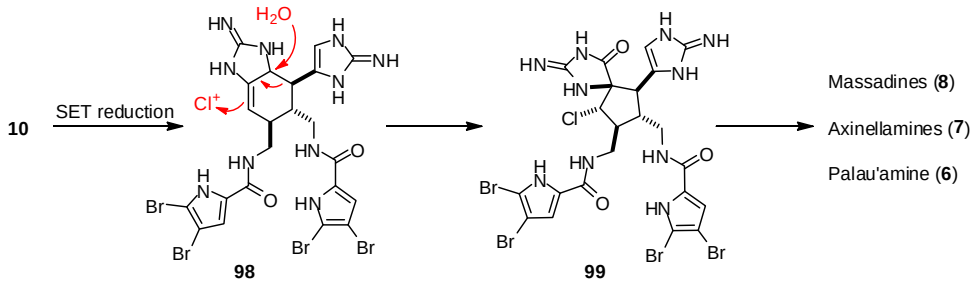
Scheme 2.2.2



2.3 Construction of the Massadine Core by Oxidative Rearrangement

Since it was difficult to construct the cyclopentane core of massadine with the correct stereocenter by the oxidative radical cyclization, we turned our attention to the oxidative rearrangement of the ageliferin skeleton for synthesizing massadine (**8**), axinellamine (**7**) and palau'amine (**6**) (Scheme 2.3.1). Both the direct and directed oxidation methods were studied in order to establish the correct spiro configuration.

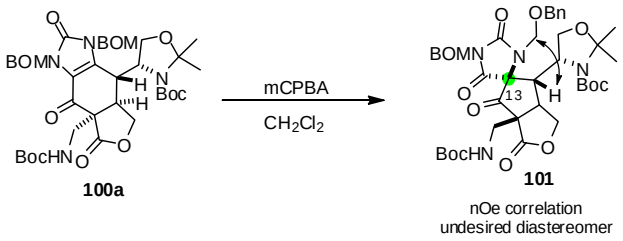
Scheme 2.3.1



2.3.1 Direct Oxidation Methods

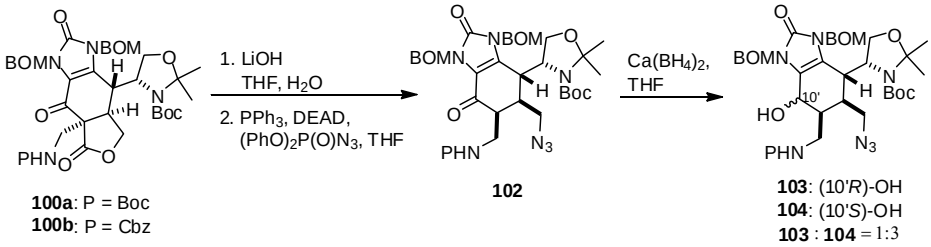
Dr. Xianghui Tan demonstrated that the oxidation of **100a** with mCPBA induced the pinacol-type oxidative ring contraction reaction affording **101** (Scheme 2.3.2). However, there was a strong stereochemical bias of **100** leading to the undesired C13 spiro configuration of **101** by oxidizing from the more accessible β-face.

Scheme 2.3.2

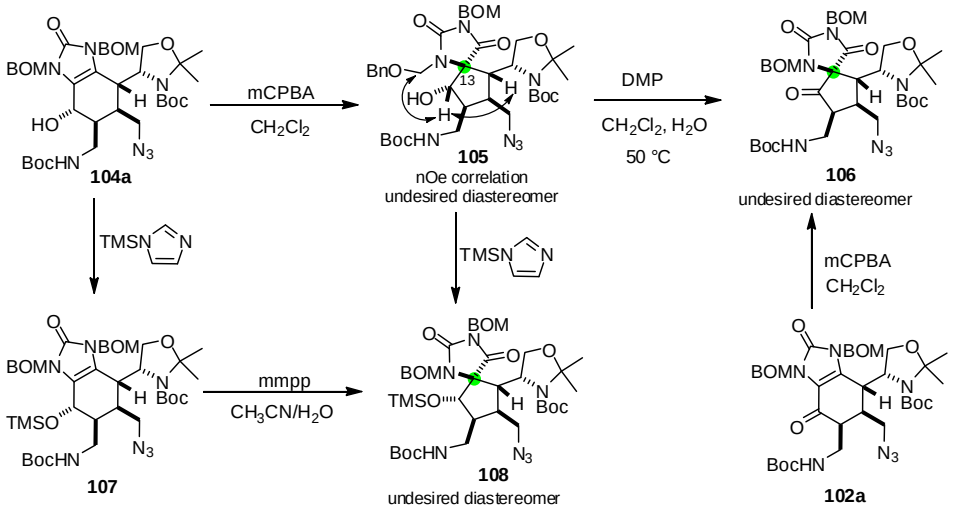


To overcome this stereochemical issue, I first decarboxylated **100** to remove the concavity of the molecule and converted the hydroxyl group to an azide by a Mitsunobu reaction (Scheme 2.3.3). However, oxidation of **102** with mCPBA also provided the undesired C13 spiro configuration. The carbonyl group of **102** was next reduced by $Ca(BH_4)_2$ to give (10'*R*)-**103** and (10'*S*)-**104** in a 1:3 ratio. I intended to use the C10 TMS ether to effectively shield the α-face, allowing oxidation to occur from the β-face. Unfortunately, oxidation of **102a**, **104a** and the TMS-protected **104a** all resulted in the undesired C13 spiro configuration (Scheme 2.3.4).

Scheme 2.3.3

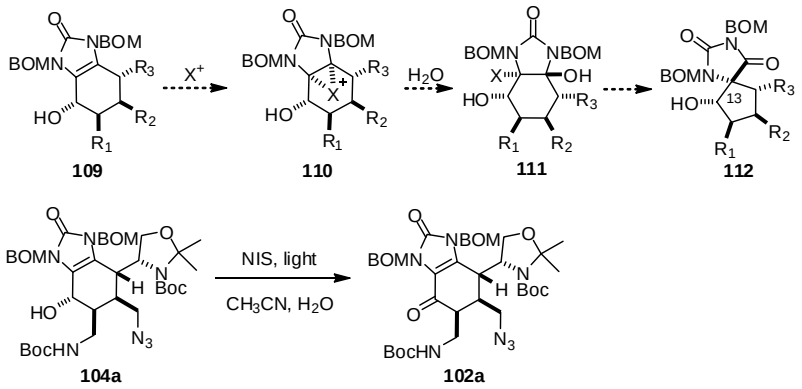


Scheme 2.3.4



To take advantage of this stereochemical bias, a stepwise halohydroxylation reaction was designed to solve this stereochemical issue (Scheme 2.3.5). It was envisioned that halogenation of **109** in an aqueous media would afford halonium ion **110**, which would hydrolyze to give anti-halohydrin **111**. The pinacol-type rearrangement would then yield **112** with the desired C13 spiro configuration. Unfortunately, reaction of **104a** with NIS under sunlight gave **102a**. No reaction occurred upon treating **102a** or **104a** with NCS, NBS, or NaClO/HCl.

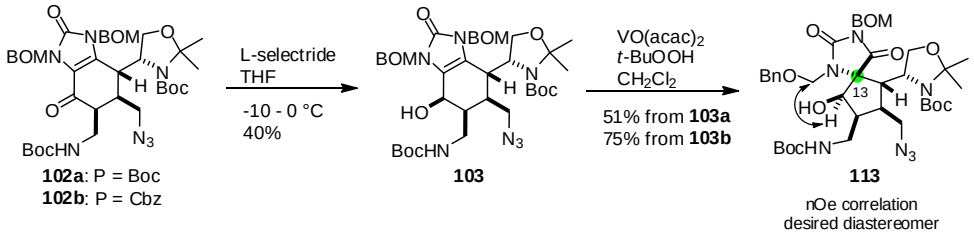
Scheme 2.3.5



2.3.2 Directed Oxidation Methods

Since the direct oxidation methods gave the desired product but with the undesired C13 spiro configuration, we turned our attention to the directed oxidation methods, aiming to direct the oxidation with the C14 hydroxyl group. Pleasingly, we found that the $VO(acac)_2$-catalyzed Sharpless allylic epoxidation of **103** gave hydantoin **113** with the desired C13 spiro configuration in high yield and >10:1 d.r[6]. The relative stereochemistry was confirmed by nOe experiment (Scheme 2.3.6).

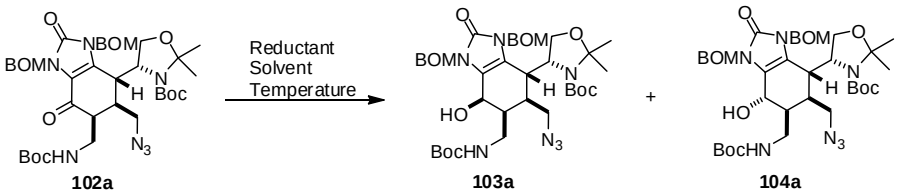
Scheme 2.3.6



To improve the regioselectivity of the reduction of **102a**, a series of reaction conditions was examined but it was found that the undesired (10'*R*)-**104a** was always obtained as the major product (Table 2.3.1), especially at lower temperature (entries 1–4). The C10' epimerization in attempt to convert (10'*R*)-**104a** to (10'*S*)-**103a** was also studied. However, the reaction was slow under acidic conditions and accompanied with Boc- and acetonide-deprotection (Table 2.3.2). The Mistunobu inversion was also hampered by the steric hindrance. Eventually, Dr. Zhiqiang Ma discovered that reduction of **102** with L-Selectride gave **103** as the major product with d.r. > 10:1 (entry 12). I subsequently found that workup of this reaction by sodium perborate converted the borane byproducts to water soluble compounds, which can be easily removed by aqueous wash.[7]

In summary, a biomimetic radical cyclization was developed to construct the ageliferin skeleton, and its mechanism was investigated; the synthesis of *ent*-9'-*epi*-13,13'-dioxoageliferin was achieved; and a directed oxidative rearrangement from ageliferin core to massadine core was realized. A synthetic study of massadine (**8**) and total synthesis of ageliferin (**5a**) will be discussed in the following chapters.

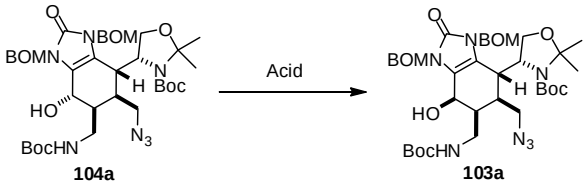
Table 2.3.1



102a **103a** **104a**

Entry	Reductant	Solvent	Temperature	Result (103a:104a)
1	$Ca(BH)_4$	THF	0 °C	<1:10
2	$Ca(BH)_4$	THF	23 °C	1:3
3	$Ca(BH)_4$	THF	50 °C	Decomposition
4	$Na(BH)_4$	EtOH/CH_2Cl_2(1:2)	50 °C	1:1.5
5	$Na(BH)_4$	MeOH	23 °C	<1:3, with Decomposition
6	$NaBH_4/CeCl_3$	MeOH	0 °C	<1:10
7	$LiBH_4$	THF	0 °C	<1:10
8	(*R*)-CBS or (*S*)-CBS	Toluene	23 °C	<1:10, with decomposition
9	Red-Al	Toluene	0 °C	No reaction
10	DIBAL	THF	-78 °C	No reaction
11	$LiAlH_4$	THF	0 °C	<1:10
12	L-Selectride	THF	-10 - 0 °C	>10:1

Table 2.3.2



Entry	Acid	Solvent	Result
1	H_2SO_4 (cat.)	Acetone, water	Boc- and acetonide-deprotection
2	TsOH (cat.)	TFE	Acetonide-deprotection
3	TsOH (cat.)	TFE, water	30% epimerization, and acetonide-deprotection
4	TsOH (cat.)	Acetone, water	Epimerization (<10% conversion after 3 days)
5	TFA (cat.)	TFE, water	No reaction at 50 °C
6	CSA (cat.)	TFE, water	No reaction at 23 °C
7	HOAc	Water	No reaction at 23 °C Acetonide-deprotection at 50 °C

2.4 References

(1) Corey, E. J.; Kang, M.-C. *J. Am. Chem. Soc*. **l984**, *106*, 5384–5385.

(2) For reviews, see: (a) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339–363. (b) Melikyan, G. G. *Org. React.* **1997**, *49*, 427–675. (c) Melikyan, G. G. *Aldrichimica Acta*. **1998**, *31*, 50–64. (d) Demir, A. S.; Emrullahoglu, M. *Curr. Org. Syn*. **2007**, *4*, 321–350. (e) Snider, B. B. *Tetrahedron*. **2009**, *65*, 10738–10744.

(3) Tan, X.; Chen, C. *Angew. Chem., Int. Ed*. **2006**, *45*, 4345–4348.

(4) Broeker, J. L.; Houk, K. N. *J. Org. Chem*. **1991**, *56*, 3651–3655.

(5) Tanino, H.; Nakata, T.; Kaneko, T.; Kishi, Y. *J. Am. Chem. Soc*. **1977**, *99*, 2818–2819.

(6) For review, see: Hoveyda, A.H.; Evans, D. A.; Fu, G. C. *Chem. Rev.*, **1993**, *93*, 1307–1370.

(7) (a) Urban, F. J.; Jasys, V. J. *Org. Proc. Res. Dev.* **2004**, *8*, 169–175. (b) Crimmins, M. T.; Ellis, J. M. *J. Org. Chem.* **2008**, *73*, 1649–1660.

CHAPTER THREE

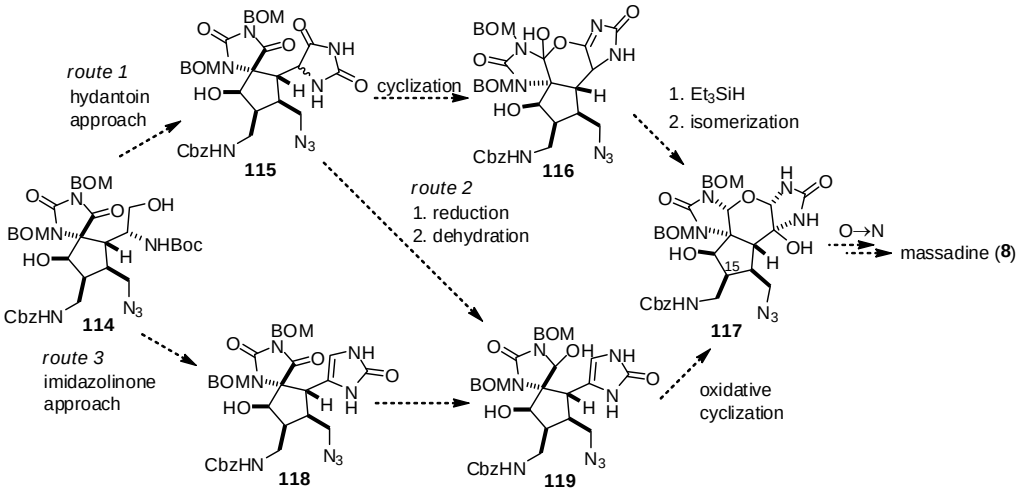
SYNTHETIC STUDIES OF MASSADINE

The previous chapter described the development of a biomimetic strategy for the synthesis of ageliferin (**5**) and massadine (**8**). This chapter entails the construction of the full skeleton of massadine (**8**). The major tasks remained are the construction of the oxo-bridge and the cyclic guanidines of **8**.

3.1 Formation of the Oxo-Bridge

As described in the previous chapter, the synthesis of saxitoxin (**90**) by Kishi and the synthesis of dibromophakellin by Feldaman[1] and us suggested that converting cyclic urea to guanidine at a late stage is feasible (Scheme 3.1.1). I therefore focused on the synthesis of **117** from **114** as the C15 stereochemical issue was not recognized by the time this study was carried out. Three distinct routes were designed to prepare **117**. In the first approach, hydantoin **115** was prepared by a Bucherer-Bergs reaction and I sought to access **117** via **116**. In the second approach, it is planned that hydantoins **115** were reduced to yield **119** and **117** was synthesized by oxidative cyclizaton. In the third approach, the imidazolinone **118** was constructed directly from **114**, followed by the hydantoin reduction to give **119** and oxidative cyclization to furnish **117**.

Scheme 3.1.1

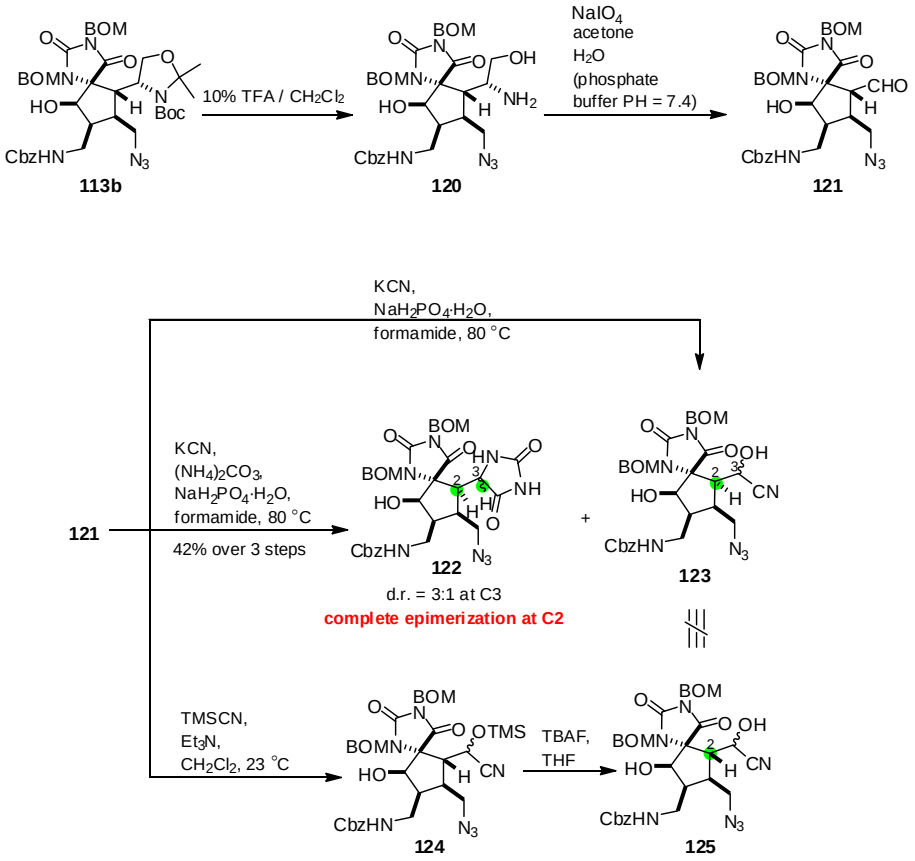


3.1.1 The Hydantoin Approach

The hydantoin approach for the synthesis of **117** was first studied (Scheme 3.1.2). The Boc and acetonide groups of the oxidative ring-contraction product **113b** were removed to give **120**. Cleavage of the amino alcohol then provided **121**, which was subjected to the Bucherer-Burg reaction under the standard conditions[2] using potassium cyanide, ammonium carbonate and sodium bisulfite to provide **122**. I found that the yield of the reaction could be improved significantly by replacing sodium bisulfite with sodium dihydrogen phosphate, giving **122** in 42% over 3 steps as a 3:1 mixture of C3-diastereomers.

The major byproduct of this Bucherer-Berg reaction was cyanohydrin **123** (~10% yield), which was the potential reaction intermediate. While it could be obtained as the only product if the reaction was carried out in the absence of ammonium carbonate, **123** could

Scheme 3.1.2



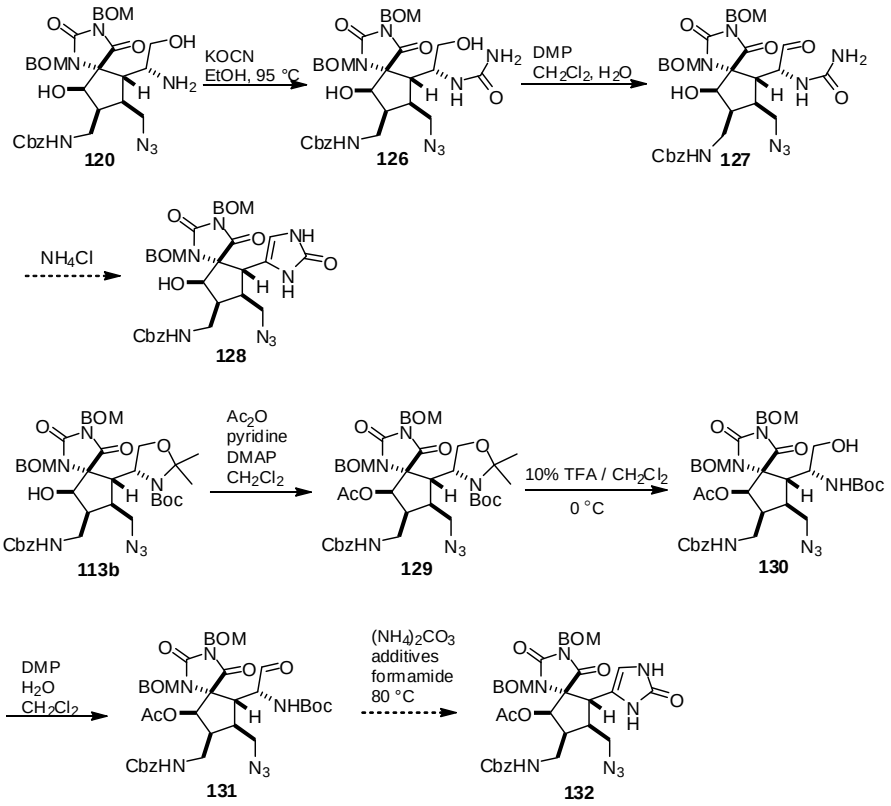
not be converted to **122** by treating it with ammonium carbonate and hydrochloric acid, trifluoroacetic acid or boron trifluoride etherate. In the meantime, Dr. Shuanhu Gao attempted to improve the synthesis of the hydantoin moiety and found that **121** could be transformed to TMS-protected cyanohydrin **124** cleanly by treating with TMSCN. Removal of the TMS group by TBAF provided **125**, which is different from **123**. Since the TMSCN reaction was carried out under much milder conditions, it is most likely that the C2 stereocenter epimerized during the Bucherer-Berg reaction. I decided not to

further pursue this route because of this C2 stereochemical issue and the difficulty in the selective reduction of the unprotected hydantoin.

3.1.2 The Imidazolinone Approach

The second approach for the synthesis of massadine (**8**) was to construct the imidazolinone moiety directly. Reaction of aminoalcohol **120** with KOCN provided urea **126**, which was oxidized to aldehyde **127** (Scheme 3.1.3). However, I was not able to induce the cyclization to deliver imidazolinone **128**. Similarly, imidazolinone **132** could

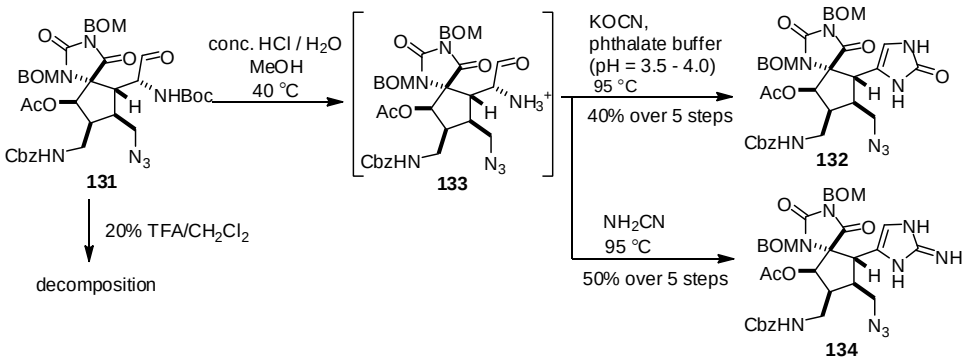
Scheme 3.1.3



not be obtained by treating **131** with ammonium carbonate under the "Bucherer-Burg conditions". The Boc-protected amino aldehyde **131** was obtained from (a) protection of the C14 alcohol, (b) removal of the acetonide and (c) oxidation of the alcohol. It is most likely that **131** is not nucleophilic enough to react with ammonium carbonate and the Boc-deprotected **131** was not stable under the reaction conditions.

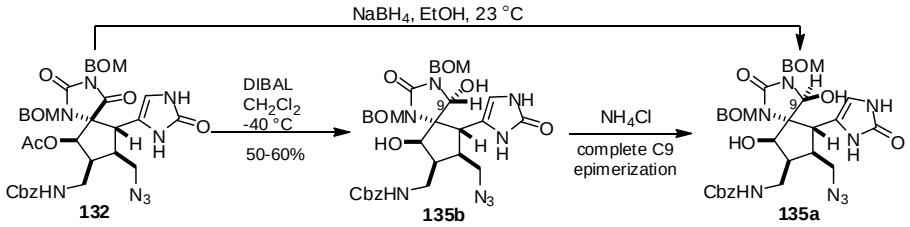
It has been reported that unprotected aminoaldehyde is stable in acidic, aqueous solutions[3]. Myers' recent studies suggest that free aminoaldehydes exist as hydrates and are stable in aqueous media below pH 5[4]. I therefore removed the Boc group of **131** with 2.4 N HCl in MeOH-H_2O at 40 °C and adjusted the pH of the solution with 3 N NaOH(aq) to 4.0 at 0 °C (Scheme 3.1.4). Subsequently treating this solution with KOCN with potassium hydrogen phthalate as the pH buffering reagent smoothly delivered imidazolinone **132** in 40% yield over 5 steps. Similarly, aminoimidazole **134** could be obtained in 50% yield by treating with cyanamide without buffer as discovered by Dr. Shuanhu Gao.

Scheme 3.1.4



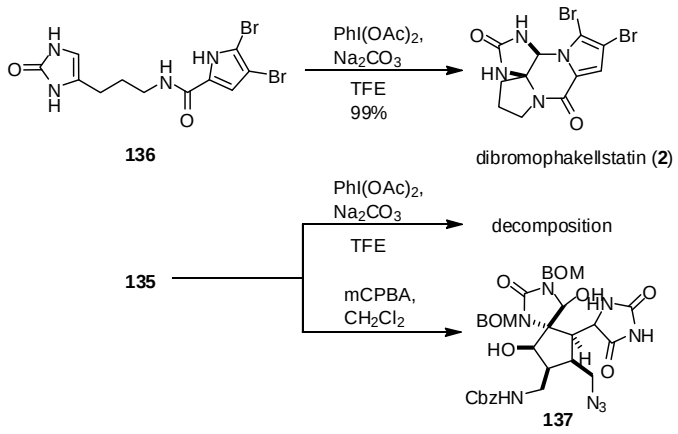
To construct the oxo-bridge of massadine (**8**), the hydantoin of **132** was reduced by sodium borohydride to provide **135a** selectively (Scheme 3.1.5). It was later found that DIBAL was a more reliable reducing agent, giving **135b** selectively in 50–60% yield after HPLC purification. Treating **135b** in ethyl acetate with saturated aqueous ammonium chloride solution converted it to **135a** completely in 10 min. The assignment of C9 configuration of **135a**/**135b** was based on the fact that **135b** was consumed faster than **135a** in the following oxidative cyclization reaction, which will be discussed in the next paragraphs. While purification of the nitrogen-containing compounds by HPLC was usually done with TFA as the additive to reduce the tailing issue, addition of 0.1% TFA to the eluents let to the decomposition of **135b**. Therefore this material is usually used without purification.

Scheme 3.1.5



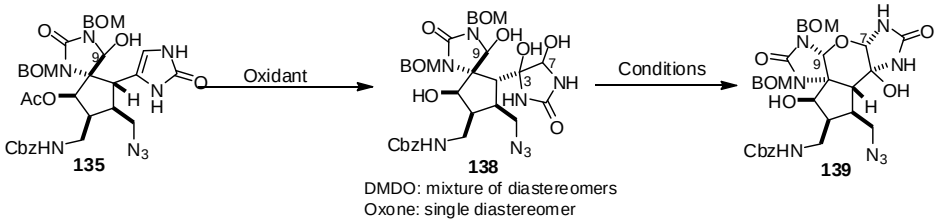
With the hemiaminal **135b** in hand, I next studied the oxidative cyclization step in attempt to complete the construction of the massadine skeleton. Dr. Jianming Lu previously showed that oxidation of **136** with bis(acetoxy)iodobenzene provided dibromophakellstatin (**2**) quantitatively (Scheme 3.1.6)[5]. Application of this method to the oxidative cyclization of **135** provided a complex mixture of products. Buffering the

Scheme 3.1.6



reaction with basic additives did not improve this reaction. Oxidation of **135** with mCPBA gave hydantoin **137**. Using the neutral oxidant DMDO gave **138** as a complex mixture of C3, C7 and C9 diastereomers (Table 3.1.1). The dehydration on **138** was not able to be induced by microwave-heating to provide **139** (entry 1).

Table 3.1.1



Entry	Oxidant	Cyclization Conditions			Yield (from 132)
		Reagent	Solvent	Temp.	
1	DMDO	Microwave	DMSO, H_2O	160-200 °C	Decomposition

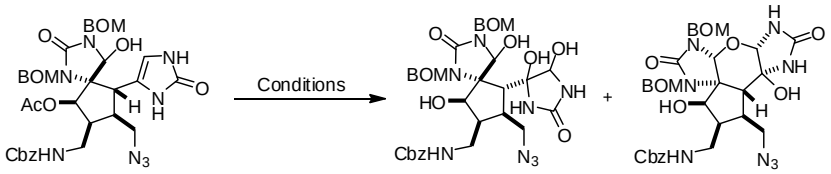
2	Oxone	$M(SO_4)_2$, M=Mg, Ca	CH_3CN	23 °C	No reaction
3	Oxone	$M(OTf)_n$, M=Sn(II), Zn, Yb, Sc	CH_2Cl_2	-40-40 °C	Decomposition
4	DMDO	$Bi(NO_3)_3 \cdot 5H_2O$	CH_3CN	23 °C	10%
5	Oxone	HCOOH		23 °C	BOM-deprotection
6	Oxone	1% H_3PO_4	CH_3CN	23 °C	<10%
7	Oxone	5% TFA	CH_2Cl_2	0 °C	15%

The cyclization of **138** under acidic conditions was next investigated. A series of Lewis acids were tested but resulted in no reaction (entry 2) or decomposition (entry 3). Eventually, it is found that treating **138** with $Bi(NO_3)_3$ gave **139** in 10% yield over 3 steps from **135a** (entry 4). However, $Bi(NO_3)_3$ is hydroscopic and the activity of the reagent reduced over time. Therefore a better protocol for this oxidative cyclization was pursued. In an effort to generate DMDO *in situ*, **135** was treated with Oxone in acetone-water and **138** could also be obtained. Later it was found that the oxidation can be performed in the absence of acetone, suggesting that Oxone oxidized imidazolinone directly. It was further realized that the cyclization of **138** could also be carried out with Brønsted acids (entries 5–7). Using Oxone as the oxidant and TFA as the dehydrating agent, **139** was obtained in 15% yield over 3 steps on a 5 mg scale of reactions.

For the oxidation of **135** by Oxone, it was found that the cyclized product **139** was formed directly in 10% yield without addition of TFA (Table 3.1.2, entry 1). It is therefore hypothesized that under the anhydrous conditions, dehydration of **138** to provide **139** would be more favorable. In contrast to Oxone, tetrabutylammonium oxone

(TBAOxone) developed by Trost has very good organic solubility[6]. Treating **138** with TBAOxone in TFE in the presence of sodium bicarbonate gave **138** and **139** in 1:1.1 and 8% yield based on HPLC, it suffered low conversion and poor ratio of **139**/**138**, however.

Table 3.1.2

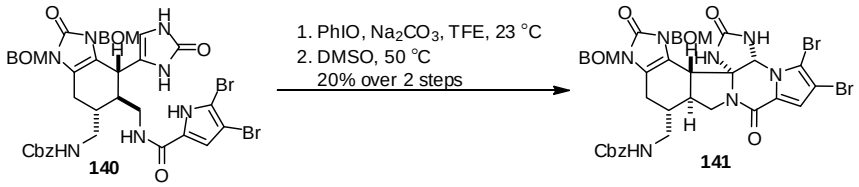


Entry	Oxidant	Solvent	Additive	Ratio of 138:139*	Conver-sion	HPLC yield of 140*
1	Oxone	Acetone/ H_2O (1:2)	$NaHCO_3$	5:1	100%	10%
2	TBAOxone	THF	$NaHCO_3$	N.D.	Decomp.	N.D.
3	TBAOxone	CH_3CN	$NaHCO_3$	N.D.	Decomp.	N.D.
4	TBAOxone	CH_2Cl_2	$NaHCO_3$	N.D.	Decomp.	N.D.
5	TBAOxone	2-Propanol	$NaHCO_3$	>20:1	100%	N.D.
6	TBAOxone	2-Propanol	$NaHCO_3$, 3Å M.S.	2.7:1	13%	3%
7	TBAOxone	TFE	$NaHCO_3$	1:1.1	31%	8%
8	PhIO	TFE	K_2CO_3	<1:10	100%	9%
9	PhIO	TFE	4 Å M.S.	7:1	31%	3%
10	PhIO	DMF	K_2CO_3	<1:10	85%	17% (40%†)
11	PhIO	DMSO	K_2CO_3	<1:10	15%	10%

*Based on UV absorption at 210nm monitored by HPLC.

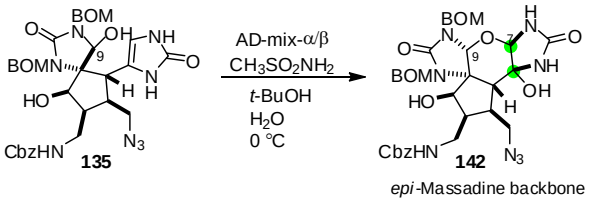
†Isolated yield.

Scheme 3.1.7



Iodosylbenzene was identified by Dr. Zhiqiang Ma as an effective reagent for the oxidative cyclization of **140** to construct the palau'amine skeleton **141** (Scheme 3.1.7). Therefore my attention was turned to promoting the oxidative cyclization of **135** by iodosylbenzene. It was eventually found that the formation of the dehydrative cyclization product **139** was favored in polar aprotic solvents (entries 10 and 11). Oxidation of **138** by iodosylbenzene in DMF in the presence of potassium carbonate gave **140** in 40% isolated yield over 2 steps. Finally, during the search for a better oxidant for this reaction, I found that oxidation of **138** with the Sharpless dihydroxylation reagent AD-mix-α or β gave the *epi*-massadine skeleton **142** in 45% HPLC yield (Scheme 3.1.8).

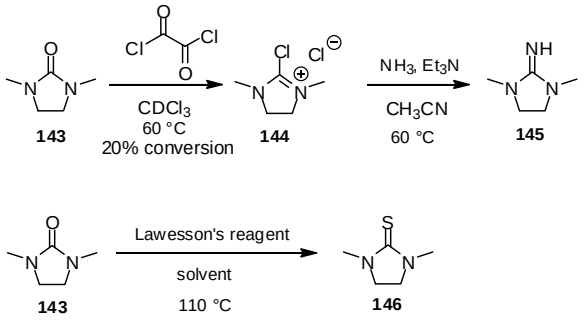
Scheme 3.1.8



3.2 Attempts to Complete the Synthesis of Massadine

With **139** in hand, the most significant remaining challenge was the conversion of the urea to guanidine. Using **143** as the model substrate to identify the proper conditions for this transformation, I found that **143** can be transformed to chlorocarboximidine **144** with oxalyl chloride with 20% conversion (Scheme 3.2.1). Reacting **144** with ammonia gave **145** in 95% NMR yield. However, only the bis-BOM deprotected product was found when treating **139** with oxalyl chloride. Attempts to react this deprotected **139** with the Meerwein's salt also failed due to its poor solubility in methylene chloride.

Scheme 3.2.1

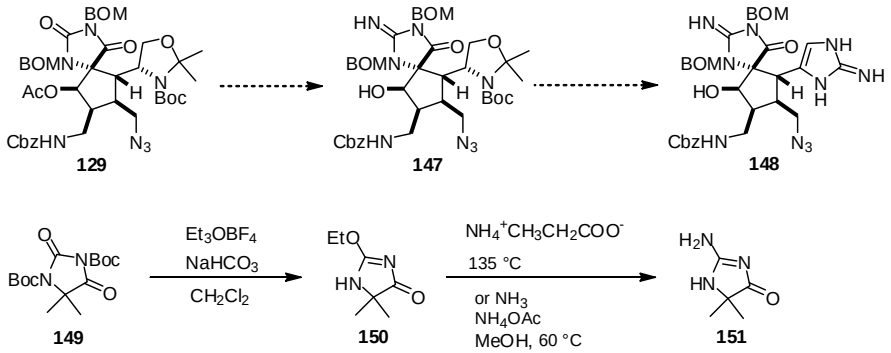


Solvent	NMR yield
CH_3CN	52%
Toluene	40%
$ClCH_2CH_2Cl$	24%
THF	15%
EtOAc	<10%
EtOH	No reaction
Acetone	No reaction

I next attempted to activate urea as thiourea toward the nucleophilic attack. To this end, it is found that **143** could be converted to **146** by treating with the Lawesson's reagent in toluene. However, no reaction occurred when treating **113b** in the same conditions, and higher temperature led to material decomposition. To overcome this issue, I found acetonitrile was an alternative solvent for this transformation, giving **146** with 52% conversion (Scheme 3.2.1). Unfortunately, treating **113b** or **139** with the Lawesson's reagent in various solvents resulted in serious decomposition of the materials.

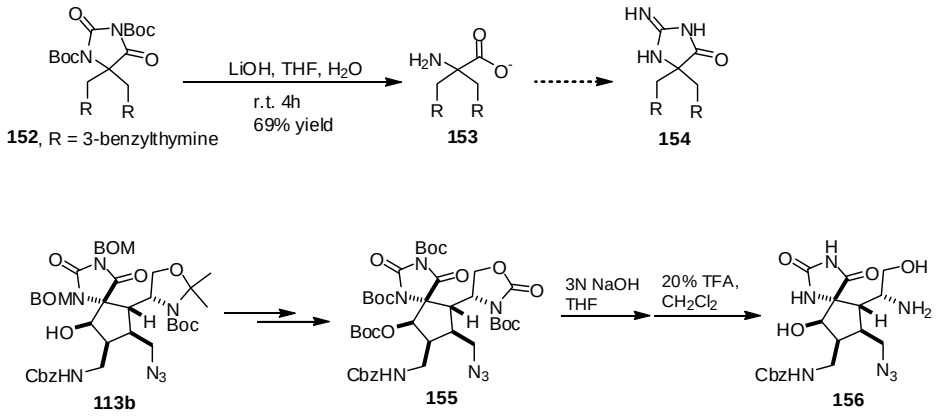
Since we were able to synthesize **134**, I planned to convert the hydantoin group of **129** to iminohydantoin (e.g., **147**) and then construct the aminoimidazole group to generate **148** (Scheme 3.2.2). Using 5,5-dimethylhydantoin as the model substrate, I found that the bis-Boc-protected **149** can react with the Meerwein's salt to give **150**. A basic workup is necessary to prevent the returning of **150** to **149** by hydrolysis. Treating **150** with ammonium propionate under Kishi's conditions or ammonia/ammonium acetate delivered iminohydantoin **151** smoothly. Unfortunately, only a trace amount of the desired product can be detected by HPLC when applying these conditions to **129**.

Scheme 3.2.2



With all the difficulties in the late stage O→N conversion on hydantoin, I turned my attention to exploring the possibility of constructing iminohydantoin from the amino acid (Scheme 3.2.3). It was reported that hydrolysis of hydantoin can be realized if electron-withdrawing groups are introduced on both nitrogen atoms[7]. For example, treating **152** with LiOH in aqueous tetrahydrofuran at ambient temperature gave **153** in 69% yield. Therefore **113b** was converted to **155** through (a) BCl_3 deprotection of BOM and acetonide, (b) conversion of the α-amino alcohol to an oxazolidinone by triphosgene and (c) a global Boc protection. However, hydrolysis of **155** under basic conditions only resulted in the cleavage of the Boc and oxazolidinone groups.

Scheme 3.2.3



In summary, *ent*-15-*epi*-5,11-dioxomassadine was obtained through (a) $VO(acac)_2$ catalyzed ring contraction, (b) installation of imidazolinone and (c) PhIO mediated oxdative cyclization. However, the late stage conversion of urea to guanidine was proved to be difficult. At this point, I decided to introduce all three nitrogen atoms of the

aminoimidazole/guanidine at an early stage. Using this strategy, the synthesis of ageliferin (**5a**) was completed, which will be discussed in the next chapter.

3.3 References

(1) Feldman, K. S.; Skoumbourdis, A. P.; Fodor, M. D. *J. Org. Chem.* **2007**, *72*, 8076–8086.

(2) (a) Bucherer, H. T.; Fischbeck, H. T. J. Prakt. Chem. **1934**, *140*, 69–89. (b) Bucherer, H. T.; Steiner, W. *J. Prakt. Chem*. **1934**, *140*, 291–316. (c) Sarges, R.; Goldstein, S. W.; Welch, W. M. *J. Med. Chem.* **1990**, 33, 1859–1865. For review, see (d) Ware, E. *Chem. Rev*. **1950**, *46*, 403–470.

(3) (a) Wiese, K. J.; Yakushijin, K.; Horne, D. A. *Tetrahedron Lett*. **2002**, *43*, 5135–5136. (b) Foley, L. H.; Büchi, G. *J. Am. Chem. Soc*. **1982**, *104*, 1776–1777. (c) Baran, P. S.; Zografos, A. L.; O'Malley, D. P. *J. Am. Chem. Soc*. **2004**, *126*, 3726–3727.

(4) Myers, A. G.; Kung, D. W.; Zhong, B. *J. Am. Chem. Soc*. **2000**, *122*, 3236–3237.

(5) Lu, J.; Tan, X.; Chen, C. *J. Am. Chem. Soc.* **2007**, *129*, 7768–7769.

(6) Trost, B. M.; Braslau, R. *J. Org. Chem*. **1988**, *53*, 532–537.

(7) Kubik, S.; Meissner, R. S.; Rebek Jr., J. *Tetrahedron Lett*. **1994**, *35*, 6635–6638.

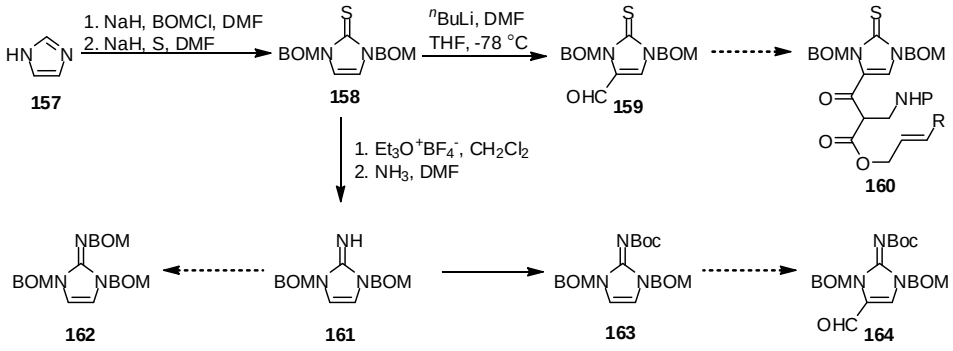
CHAPTER FOUR

TOTAL SYNTHESIS OF AGELIFERIN

4.1 Oxidative Radical Cyclization of Aminoimidazole

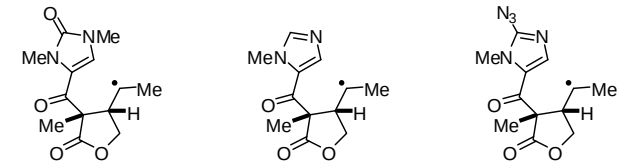
In the previous chapter, my initial strategy for the synthesis of massadine (**8**) was described. I found converting the urea group to a guanidine group at a late-stage difficult and decided to employ a strategy in which an activated urea was introduced to the guanidine group at an early stage. However, *N*,*N*'-dialkylthioimidazolinone **159** was too reactive and decomposed in the aldol reaction (Scheme 4.1.1). *N*,*N*',*N*''-trialkylaminoimidazole **162** and dialkylaminoimidazole **163** were also too labile to be introduced early. I therefore turned my attention to the protected aminoimidazole and chose to employ azidoimidazole.

Scheme 4.1.1

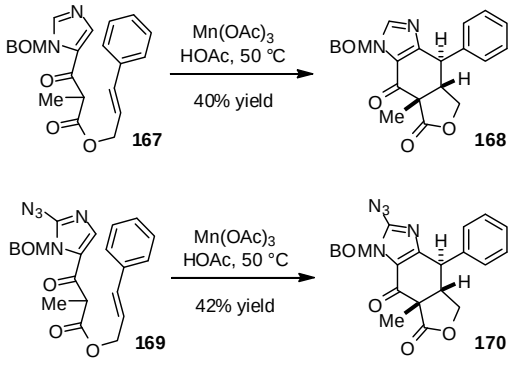


It was expected that the aromaticity of imidazole is higher than that of imidazolinone, which would be disrupted during our key Mn(III)-promoted oxidative radical cyclization reaction. We therefore first calculated the activation barrier of the Mn(III) oxidation reaction for imidazole **165** and azidoimidazole **166** to evaluate the feasibility of this plan. The calculation was first performed by Dr. Chen using UB3LYP/6-31G** and then refined by Kevin Cormier at the 6-311G** level. Based on the calculated activation barriers, the oxidative radical cyclization reactions of **165** and **166** were predicted to be equally facile as that of **82** (Figure 4.1.1). With this information in hand, Dr. Jianming Lu tested the oxidative radical cyclization of imidazole **167** and azidoimidazole **169** and obtained **168** and **169** smoothly in 40% and 42% yield (Scheme 4.1.2).

Figure 4.1.1



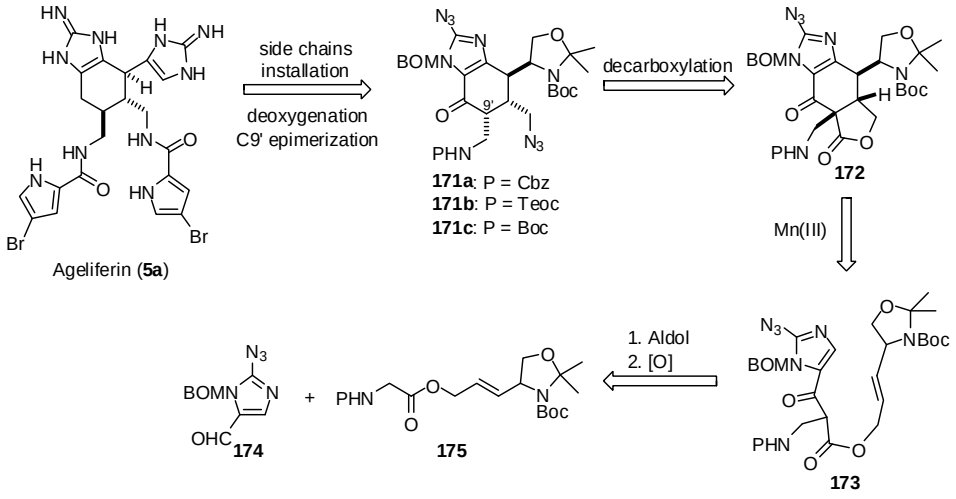
Scheme 4.1.2



4.2 Total Synthesis of Ageliferin

Encouraged by these model studies, I redesigned my synthetic approach to the oroidin dimers and set ageliferin (**5a**) as my new synthetic target. The retrosynthetic analysis is shown in Scheme 4.2.1. I planned to introduce the aminoimidazole appendage and the pyrrole groups of ageliferin (**5a**) from **171**. Azide **171** could be obtained from the oxidative radical cycliazation product **172** through decarboxylation and azidation. The azidoimidazole **173** could be constructed from azidoimidazole **174** and ester **175** via an aldol-oxidation sequence.

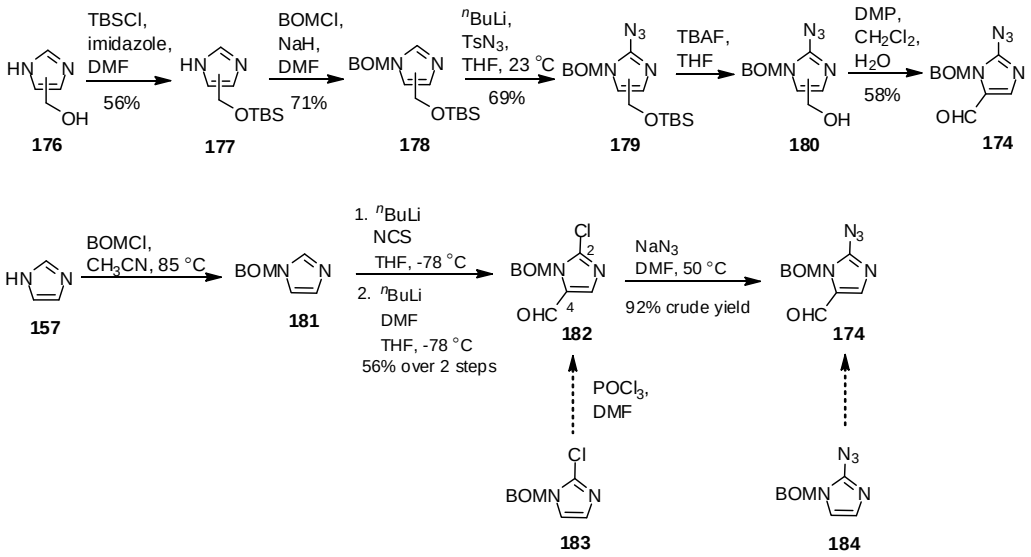
Scheme 4.2.1



The synthesis started with an improved method for the synthesis of azidoimidazole **174** (Scheme 4.2.2). The previous approach developed by Dr. Jianming Lu involves (a) TBS protection, (b) BOM protection, (c) azidation (d) removal of TBS and (e) oxidation,

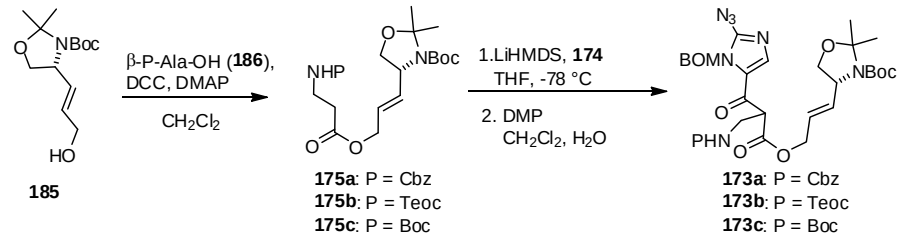
giving **174** in 5 steps with 16% yield from **176** and requiring five column chromatography purifications. I found that **174** can be prepared more efficiently by carrying out the C2-chlorination and the C4-formylation of the BOM-protected imidazole **181** in one-pot followed by an aromatic substitution of the resulting chloroimidazole **182**. Azidoimidazole **174**, which used directly for the subsequent aldol coupling, was synthesized in 52% yield over 3 steps from **181**. In the whole process, only a distillation of **181** and a recrystallization of **182** are necessary for the purification. The C4-lithiation was directed by the BOM group resulting in >10:1 regioselectivity in the formylation step. It should be noted that attempts to formylate **183** or **184** under the Vilsmeier conditions failed possibly because the C-2 chloride or azide attenuated their nucleophilicity. Lithiation of **184** was also not successful because C4-deprotonation did not occur with either *n*- or *t*-butyllithium.

Scheme 4.2.2



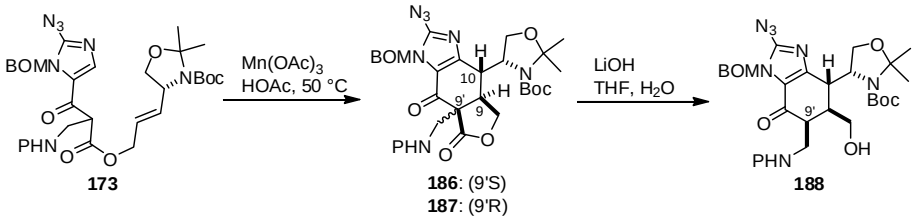
Coupling of allylic alcohol **185** and Cbz-β-Ala-OH (**186a**) by DCC afforded ester **175a** (Scheme 4.2.3). Treating **175a** with LiHMDS generated the enolate without elimination. Addition of **174** gave the corresponding aldol, which was oxidized without purification to provide **173a**. The crude **173a** can be used directly for the subsequent oxidative radical cyclization.

Scheme 4.2.3



Oxidation of **173a** with manganese(III) acetate gave the desired ageliferin core skeleton (Scheme 4.2.4). This reaction was further explored by Dr. Zhiqiang Ma, and found that the best results could be obtained by using $Mn(OAc)_3$ in acetic acid at 50–60 °C or Mn(picolinate)$_3$ in methanol at 90 °C. The products obtained were a 2.5–3:1 mixture of diastereomers **186** and **187** in 27–34% yield over 4 steps. Decarboxylation of **186** and **187** with LiOH in THF-H_2O at 23 °C for 20 min gave rise to the same product **188**, indicating that they are a pair of C9' diastereomers. The purification of the Mn(III)-promoted oxidative cyclization was therefore greatly simplified as separation of these two diastereomers was not necessary.

Scheme 4.2.4

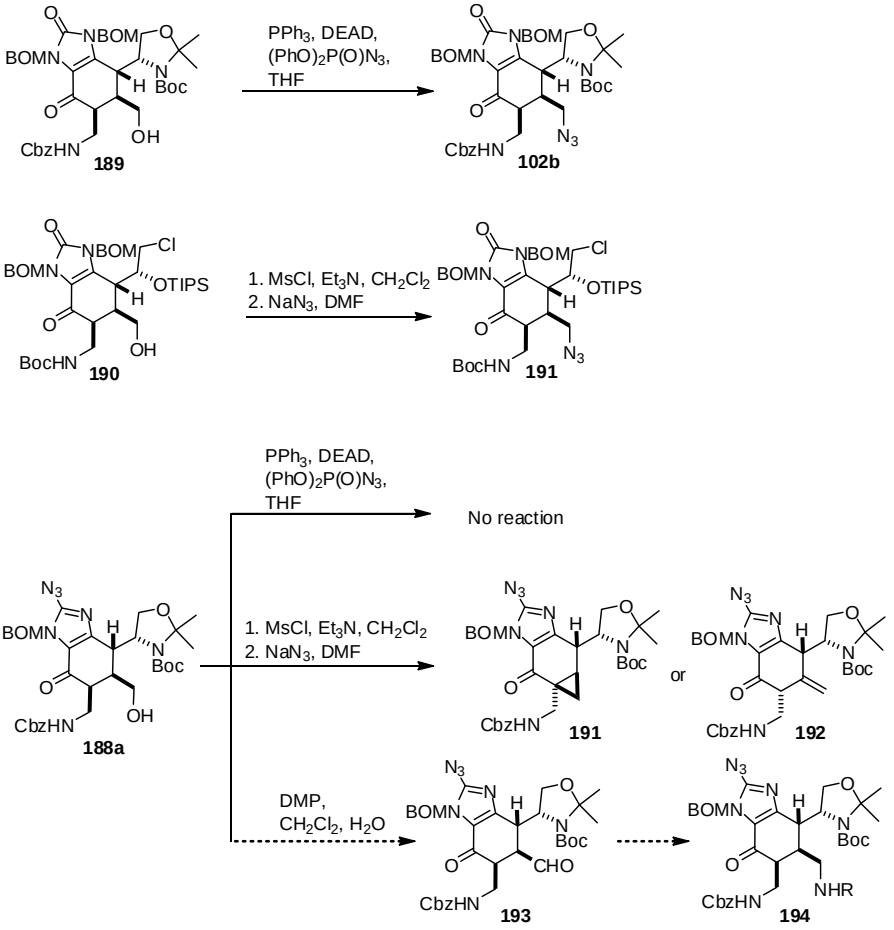


It is interesting to note that the removal of the tether by decarboxylation gave *cis*- instead of *trans*-**188**. This rather unexpected stereochemical preference presumably helps release the unfavorable steric interactions among the three side chains while maintaining the carbonyl-imidazole conjugation on a flattened half-chair cyclohexenone ring. Considering the propensity of this C9' epimerization, I decided to correct this stereochemical issue at a late stage and focus on the installation of the remaining functional groups.

Converting the hydroxyl group of **188a** to an amino group was surprisingly difficult, due presumably to the congested steric environment. The steric environment around this hydroxyl group is significantly influenced by remote functional groups (Scheme 4.2.5). For example, the hydroxyl group of imidazolinone **189** can be directly converted to an azide by a Mitsunobu reaction but this method failed for imidazolinone **190**. Nonetheless, activation of the hydroxyl group of **190** as a mesylate followed by nucleophilic substitution gave **191** smoothly. Unfortunately, neither method works for **188a**. The active Mitsunobu reagent decomposed without reacting with the hydroxyl group.

Treating the mesylate of **188a** with sodium azide under various conditions resulted only dehydration. Attempts to oxidize **174a** for a reductive amination also failed.

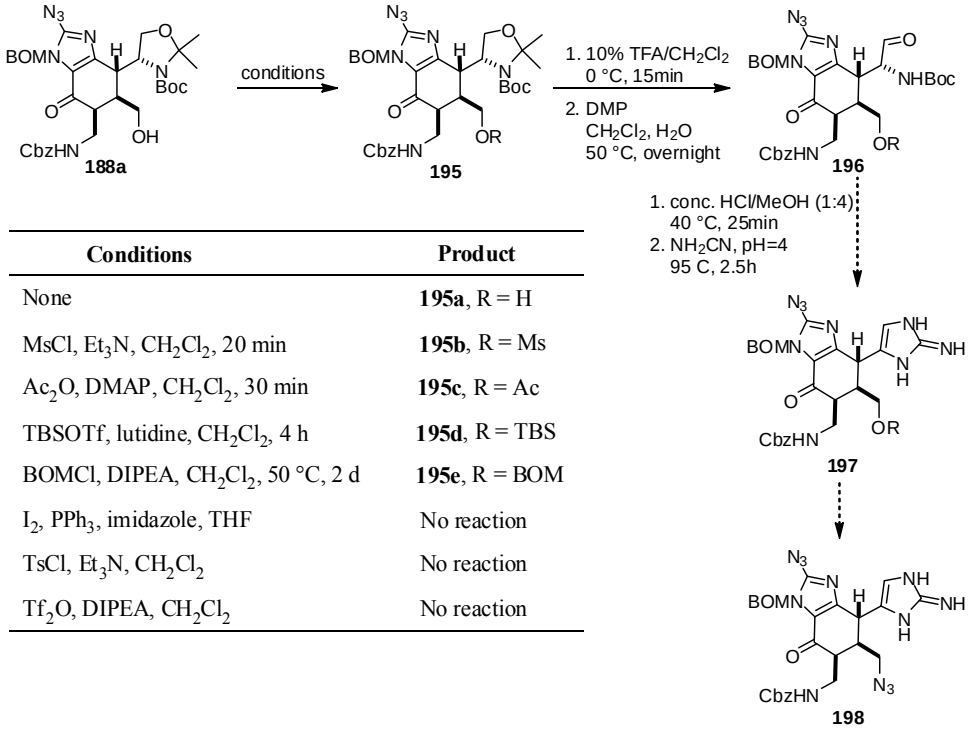
Scheme 4.2.5



An aminoimidazole group was then planned to construct first to reduce the steric congestion around the alcohol (Scheme 4.2.6). Various protecting or activating groups

for the alcohol were tested but the aminoimidazole group can only be installed to mesylate **195b** or acetate **195c** in extremely low efficiency (<5% HPLC yield).

Scheme 4.2.6

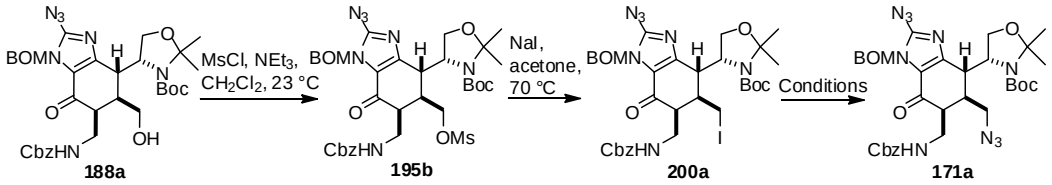


Conditions	Product
None	**195a**, R = H
MsCl, Et_3N, CH_2Cl_2, 20 min	**195b**, R = Ms
Ac_2O, DMAP, CH_2Cl_2, 30 min	**195c**, R = Ac
TBSOTf, lutidine, CH_2Cl_2, 4 h	**195d**, R = TBS
BOMCl, DIPEA, CH_2Cl_2, 50 °C, 2 d	**195e**, R = BOM
I_2, PPh_3, imidazole, THF	No reaction
TsCl, Et_3N, CH_2Cl_2	No reaction
Tf_2O, DIPEA, CH_2Cl_2	No reaction

Eventually, I found that mesylate **199a** could be converted to an iodide **200a**. For the first time, nucleophilic substitution with an azide gave an appreciable amount of azide **171a** (Scheme 4.2.7). A series of optimizations were then carried out to reduce the amount of the elimination product. Treating **199a** with a saturated solution of sodium iodide in acetone provided **200a** along with only a trace amount of the elimination product and aminoimidazole that was derived from reduction of the azidoimidazole by sodium iodide. Reacting **200a** with sodium azide in DMSO for 2 h at 60 °C or overnight

at 40 °C gave **171a** and the elimination product in a 2.5:1 ratio. Azide **171a** was isolated by HPLC in 36% yield over 4 steps. The elimination product was dominant in protic solvents (entries 1, 2), while azide substitution was more favored in polar aprotic solvents (entries 3–5). The addition of silver salt as additive allowed for the reaction to proceed at room temperature, but there was no improvement in the yield of **171a** (entries 6, 7).

Scheme 4.2.7



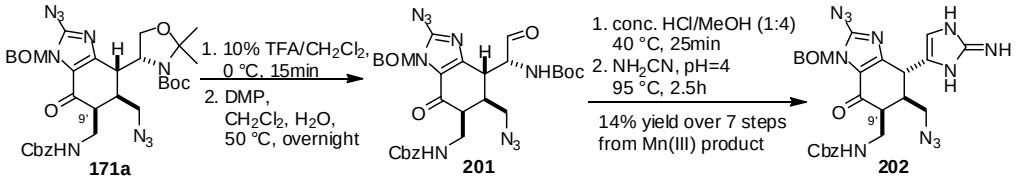
Entry	Azide	Solvent	Temp.	Additive	HPLC yield of 171a*
1	NaN_3	MeOH	60 °C		0
2	NaN_3	^{t}BuOH	60 °C		0
3	NaN_3	CH_3CN	60 °C		39%
4	NaN_3	DMF	60 °C		50%
5	NaN_3	DMSO	60 °C		71% (36%†)
6	NaN_3	DMF	23 °C	AgOAc	60%
7	NaN_3	DMSO	23 °C	AgOAc	50%

*Based on UV absorption at 280 nm.

†Isolated yield over 4 steps from lactone **186a**/**187a**.

With **171a** in hand, the second aminoimidazole and the two pyrrole groups were next introduced (Scheme 4.2.8). The acetonide protecting group of **171a** was removed first and the resulting alcohol was oxidized to **201**. The Boc group was then removed by HCl in MeOH-H_2O, followed by adjusting the pH to 4.0 by NaOH before cyanamide was added and the reaction was heated to 95 °C to provide aminoimidazole **202**. No purification was required over 7 steps, and **202** was isolated in 14% yield based on the Mn(III)-promoted oxidative cyclization product **186a**/**187a**.

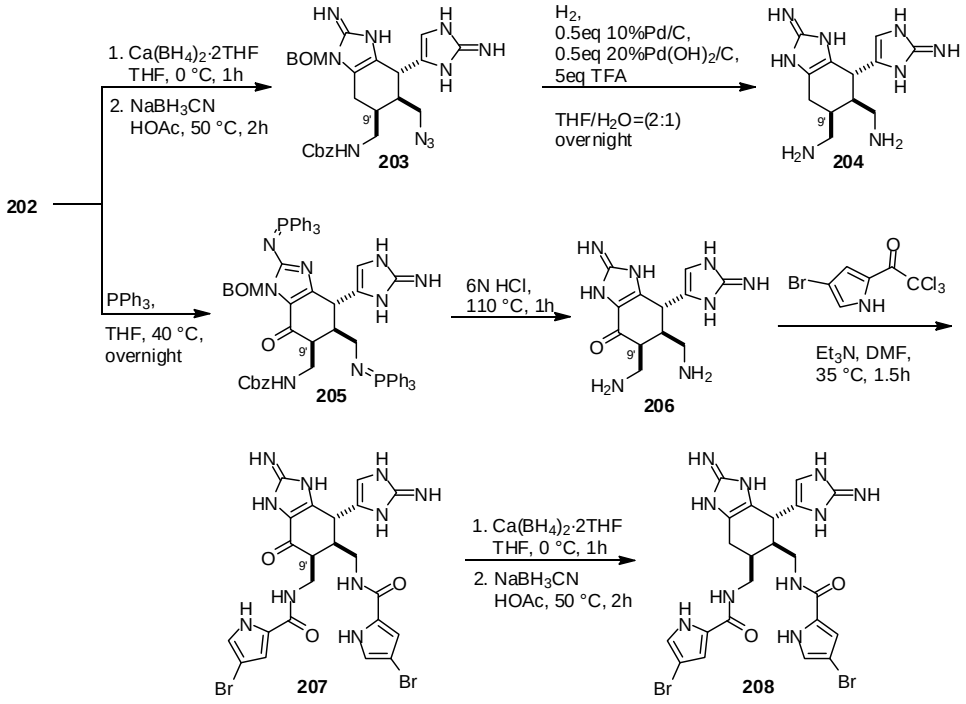
Scheme 4.2.8



To complete the synthesis of ageliferin (**5a**), **202** was deoxygentated by a sequential reduction using first $Ca(BH_4)_2$ in THF then $NaBH_3CN$ in acetic acid to give **203**, the azido group was reduced by $Ca(BH_4)_2$ at the same time (Scheme 4.2.9). Subsequently, the BOM and Cbz groups were cleaved in one step by hydrogenolysis using a large excess of palladium metal. Although **204** was detected by LC-MS from the reaction mixture, the mass recovery was very poor because of the adsorption by metal. Furthermore, purification of **204** was problematic due to its extremely high polarity with virtually no retention on reverse-phase HPLC column.

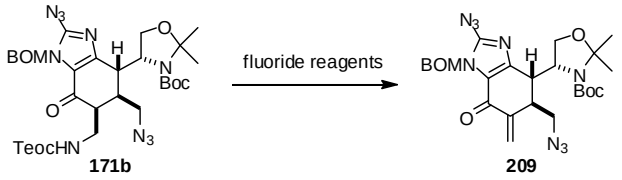
To avoid use of the palladium metal, the azido group of **202** was reduced by Staudinger reduction and the BOM and Cbz groups were hydrolyzed by 6 N HCl in boiling water. The purity of **206** was critical to the successful installation of the pyrrole groups, but similar to **204**, aminoimidazole **206** was difficult to purify. Nonetheless, a small amount of **207** was obtained and deoxygenated to **208**. The ^{1}H NMR spectrum of **195** is different from that of natural ageliferin (**5a**). It was suspected the C9' stereochemistry to be incorrect but I was not able to obtain enough material to perform thorough NMR studies. Therefore, this route was redesigned to improve the efficiency of the synthesis.

Scheme 4.2.9



First the Cbz group was replaced with a Teoc group because considerable decomposition occurred during the deprotection of Cbz. However, all attempts to remove the Teoc group on **171b** led to elimination, presumably due to the abnormal acidity of H9' (Scheme 4.2.10). As the result, Boc was used as the N7' protecting group and **171c** was prepared.

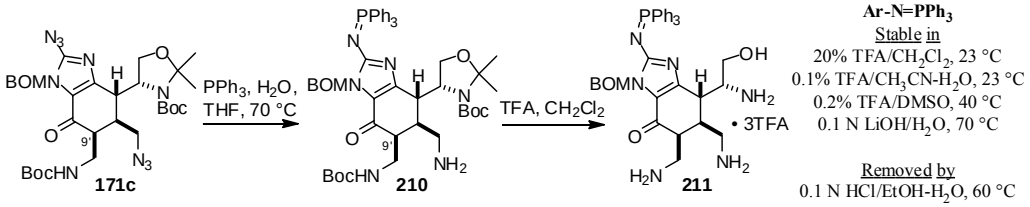
Scheme 4.2.10



The azido groups of **171c** were first reduced by Staudinger reduction (Scheme 4.2.11). The heteroaromatic azide was reduced immediately after the addition of triphenylphosphine at room temperature, but the alkyl azide was not reduced until gently heating the reaction. Interestingly, the alkyl iminophosphine was hydrolyzed under the reaction conditions, but the heteroaromatic iminophosphine was hydrolyzed only under acidic conditions. Iminophosphine **210** was stable under neutral and basic hydrolysis conditions. It was also stable under acidic anhydrous or weakly acidic aqueous conditions. By taking the advantage of the stability of this iminophosphine group, it was used as a protecting group for the aminoimidazole. Its strong UV absorbance and low polarity also facilitated the instrumental analysis and purification. The acetonide and Boc protecting groups of **210** were removed under acidic anhydrous conditions accordingly. Triamine **211** was crashed out from its ether solution as a TFA salt to remove the excess

reagents and triphenylphosphine oxide. The thorough removal of triphenylphosphine oxide was crucial to the successful installation of the pyrrole groups.

Scheme 4.2.11

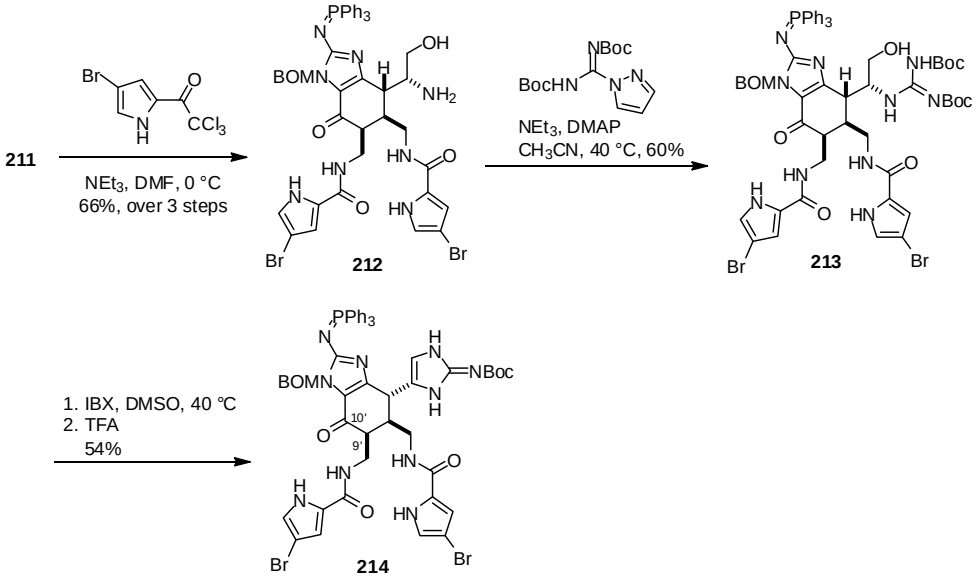


The regioselective acylation of **211** was achieved by reacting with the trichloroacetylpyrrole at 0 °C giving **212** and the mono-acylated product in a 3:1 ratio (Scheme 4.2.12). The reaction was monitored by HPLC and purified directly without workup to avoid over acylation and decomposition. The desired product **212** was isolated in 66% yield over 3 steps after HPLC purification. The mono-acylated product can be resubjected to the reaction to improve the overall efficiency. It was found that all the bromopyrrole-containing compounds in our synthesis are light-sensitive and should be stored in amber vials. The subsequent reactions were also performed with protection from light.

In order to construct the aminoimidazole moiety on **212**, an alternative, milder approach was developed without involving the use of unstable amino aldehyde. The amino group was first converted to a guanidine giving **213** in 60% yield (Scheme 4.2.12). In the absence of DMAP, the guanidine formation reaction was slow and required higher

temperature, leading to a significant amount of decomposition. The alcohol was then oxidized to an aldehyde, which slowly cyclized with the guanidine to give aminoimidazole **214** in 54% yield. Addition of 0.5 equivalent of TFA after oxidation facilitated this cyclization. IBX was found to be a milder and more efficient oxidant than the Dess-Martin reagent for the oxidation of **213**. This IBX oxidation was best performed in DMSO, although using ethyl acetate or acetonitrile allowed for an easier workup but impractically slow rate. The reaction mixture was directly purified by HPLC without workup to prevent decomposition induced by the IBX byproduct.

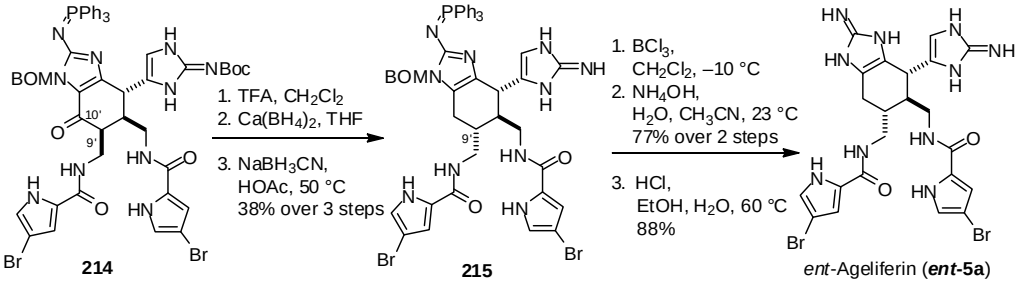
Scheme 4.2.12



Exposure of **214** under acidic conditions provided the correct C9' configuration (d.r. > 10:1) (Scheme 4.2.13). The all *anti* configuration was favored possibly because of the

reduced steric hindrance imposed by the aminoimidazole group versus the Boc- and acetonide-protected amino alcohol. The C10' carbonyl group was then removed by sequential reduction to afford protected ageliferin **215** in 38% yield over 3 steps from **214**.

Scheme 4.2.13



To complete the synthesis of ageliferin (**5a**), the benyl group of BOM was first cleaved by BCl_3, and the resulting chloromethyl group was hydrolyzed by ammonia in acetonitrile-water. Using the methanolic ammonia solution resulted in the conversion of the chloromethyl group to a MOM group. Finally, the triphenylphosphine imide group was hydrolyzed by HCl at 60 °C to afford ageliferin, whose CD spectrum indicated that *ent*-**5a** was obtained from this synthesis. In order to synthesize ageliferin in its natural enantiomeric form, *ent*-**185** was employed and **5a** was successfully obtained in 0.5% overall yield over 18 steps. Using the same sequence, dibromoageliferin (**5c**) was also synthesized in 0.5% overall yield.

4.3 Summary

In summary, biomimetic routes to access *ent*-15-*epi*-5,11-dioxomassadine (15-*epi*-5,11-dioxo-**8**) and ageliferins (**5**) have been developed. The total synthesis of both ageliferin (**5a**) and dibromoageliferin (**5c**) was achieved in 18 steps and 0.5% overall yield. These synthetic routes feature a number of key transformations: (a) an oxidative radical tandem cyclization reaction to construct the cyclohexene core of ageliferins; (b) an oxidative ring contraction reaction to convert ageliferin skeleton to massadine skeleton in a diastereoselective fashion; (c) an oxidative cyclization to construct the oxo-bridge of massadine (**8**); (d) adoption of the azidoimidazole instead of the imidazolinone as the synthetic precursor to avoid the late stage O→N transformation; (e) employment of the phosphorus imide group as a novel protecting group for 2-aminoimidazole; and (f) construction of the aminoimidazole moiety by two efficient methods. Futhermore, the studies in manganese(III) mediated oxidative radical cyclizations and $VO(acac)_2$ catalyzed ring-contraction support the possibility that a single-electron transfer (SET) reaction and a pinacol-type rearrangement may be used in nature as a way to produce **5** and **8**. Examination of the biological actitivity of **5** is currently underway.

APPENDIX A

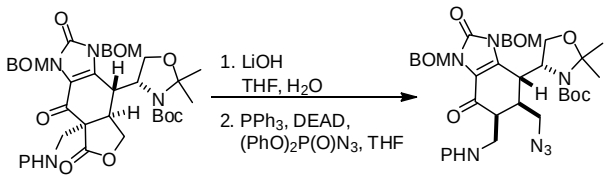
EXPERIMENTAL SECTION

General Experimental Procedures

All reactions were performed in glassware under a positive pressure of argon. The normal-phase flash column chromatography was performed as described by Still (Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925), employing EMD silica gel 60 (230–400 mesh ASTM) or deactivated silica gel (Panne, P.; Fox, J. M. *J. Am. Chem. Soc.* **2007**, *129*, 22–23, in the supporting information. For the workup, the silica gel was washed with methanol, deionized water until neutral, and again with methanol. The deactivated silica gel was air-dried at 23 °C overnight and then dried in a 110 °C oven for 30 minutes). TLC analyses were performed on EMD 250 μm Silica Gel 60 F_{254} plates and visualized by quenching of UV fluorescence (λ_{max} = 254 nm), or by staining ceric ammonium molybdate. ^{1}H and ^{13}C NMR spectra were recorded on Varian Inova-600, Inova-500, or Inova-400. Chemical shifts for ^{1}H and ^{13}C NMR spectra are reported in ppm (δ) relative to the ^{1}H and ^{13}C signals in the solvent (CDCl3: δ 7.26, 77.16 ppm; methanol-d4: δ 3.31, 49.00 ppm; DMSO-d6: δ 2.50, 39.52 ppm; benzene-d6: δ 7.16, 128.06 ppm) and the multiplicities are presented as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Mass spectra were acquired on Agilent 6120 Single Quadrupole LC/MS. Preparative HPLC was performed using a Waters Atlantis dC18 OBD 5 μm column with dimension 19×150 mm or Eclipse XDB-C18 5 μm column with dimension 9.4×250 mm. The CD spectrum was recorded on an Aviv model 62DS

spectropolarimeter in water at 25 °C.

Preparative Procedures



100a: P = Boc
100b: P = Cbz

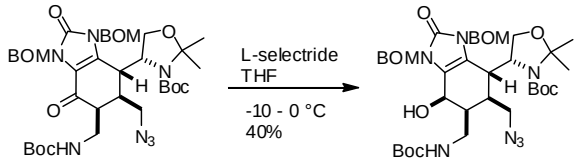
102

Azide 102b. To a solution of lactone **100b** (2.87 g, 3.53 mmol, 1.0 equiv) in tetrahydrofuran (120 mL) was added aqueous lithium hydroxide (0.34 N, 31.4 mL, 3 equiv). The reaction was stirred at 23 °C for 30 minutes. After removal of tetrahydrofuran, the mixture was partitioned between ethyl acetate (150 mL) and aqueous hydrogen chloride (0.5 N, 100 mL). The organic layer was washed with saturated sodium bicarbonate and brine, and dried over anhydrous sodium sulfate. After concentration, the crude alcohol was obtained as oil and directly used for the next step without purification. R_f = 0.1 (50% ethyl acetate–hexanes).

Diethyl azodicarboxylate (923 mg, 5.30 mmol, 1.5 equiv) and diphenylphosphoryl azide (1.46 g, 5.30 mmol, 1.5 equiv) were dropwise added to a solution of the crude alcohol and triphenylphosphine (1.39 g, 5.30 mmol, 1.5 equiv) in tetrahydrofuran (50 mL) under argon at 0 °C sequentially. The reaction was then stirred at 23 °C overnight. After removal of the solvent, the residue was purified by flash chromatography on a deactivated silica gel column (10→40% ether–hexanes, then 20% ethyl acetate–hexanes).

Azide **102b** was obtained as a white powder (1.21 g, 42% yield for two steps); R_f = 0.50 (50% ethyl acetate–hexanes); ^{1}H NMR (500 MHz, CD_3CN, 50 °C) δ 7.43 – 7.22 (m, 15H), 5.50 (d, *J* = 10.4 Hz, 1H), 5.40 (d, *J* = 10.4 Hz, 1H), 5.32 (d, *J* = 11.0 Hz, 1H), 5.17 (d, *J* = 11.0 Hz, 1H), 5.08 (s, 2H), 4.62 (s, 2H), 4.61 (d, *J* = 11.7 Hz, 1H), 4.57 (d, *J* = 11.7 Hz, 1H), 4.49-4.41 (m, 1H), 4.0-3.90 (m, 1H), 3.80 (d, *J* = 10.1 Hz, 1H), 3.74 – 3.64 (m, 2H), 3.61 (d, *J* = 11.4 Hz, 1H), 3.45 – 3.17 (m, 3H), 3.06 (d, *J* = 11.4 Hz, 1H), 2.80 – 2.73 (m, 1H), 1.59 (s, 3H), 1.48 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (125 MHz, CD_3CN, 50 °C) δ 186.4, 157.6, 155.2, 155.0, 139.9, 139.4, 138.8, 138.6, 129.8 – 128.4 (9 carbons), 118.6, 96.0, 82.2, 72.8, 72.5, 72.2, 71.9, 67.3, 59.2, 51.2, 46.4, 40.9, 39.6, 39.3, 28.8, 28.0, 24.5; MS(ESI)$^+$ calcd for $C_{43}H_{52}N_4O_{10}$ $[M+H]^+$: 810.4, found: 810.6.

Azide 102a. Lactone **100a** was converted to azide **102a** following the procedure mentioned above (67% yield over 2 steps). R_f = 0.45 (50% ethyl acetate–hexanes). ^{1}H NMR (400 MHz, Benzene-d6) δ 7.34 – 6.93 (m, 10H), 5.73 (d, *J* = 10.1 Hz, 1H), 5.58 (d, *J* = 10.1 Hz, 1H), 5.34(t, *J* = 5.2 Hz, 1H), 5.19 (d, *J* = 11.2 Hz, 1H), 5.04 (d, *J* = 11.2 Hz, 1H), 4.75 (s, 2H), 4.55 (s, 2H), 4.06 (brs, 1H), 3.63 (brs, 2H), 3.45 (d, *J* = 9.6 Hz, 1H), 3.41 – 3.31 (m, 2H), 3.18 (brs, 1H), 3.08 (brd, *J* = 7.7 Hz, 1H), 2.74 – 2.61 (brs, 1H), 2.34 (t, *J* = 11.8 Hz, 1H), 1.48 (s, 9H), 1.42 (s, 3H), 1.34 (s, 12H).



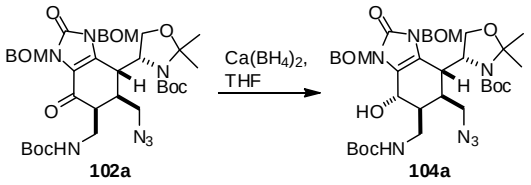
102a: P = Boc
102b: P = Cbz

103

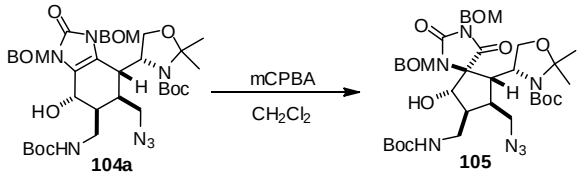
Alcohol 103a. To L-selectride (0.9 mL, 1 N in tetrahydrofuran, 7 equiv) at -10 °C was added a solution of **102a** (50 mg, 0.0645 mmol, 0.5 equiv) in tetrahydrofuran (0.25 mL), and another potion of **102a** (50 mg, 0.0645 mmol, 0.5 equiv) was added after 30 min. Then the reaction was allowed to slowly warm to 0 °C in 30 min, followed by quenching with saturated ammonium chloride solution (2 mL). After removal of tetrahydrofuran, the mixture was partitioned between ethyl acetate (3 mL) and brine (3 mL). The organic layer was then dried over anhydrous sodium sulfate. After removal of the solvent, the residue was purified by flash chromatography on a silica gel column (10→30% ethyl acetate–hexanes, then 50% ethyl acetate–hexanes). Azide **103a** was obtained as colorless oil (70 mg, 69% yield).R_f = 0.22 (50% ethyl acetate–hexanes). ^{1}H NMR (400 MHz, Benzene-d6, 50 °C) δ 7.37 – 6.95 (m, 10H), 5.33 (d, J = 10.6 Hz, 2H), 5.13 (d, J = 10.6 Hz, 2H), 4.58 (s, 2H), 4.52 (s, 2H), 4.48 (s, 1H), 3.99 (t, J = 6.6 Hz, 1H), 3.81 (d, J = 12.2 Hz, 1H), 3.58 – 3.40 (m, 2H), 3.36 (dd, J = 12.6, 2.9 Hz, 1H), 3.20 (d, J = 8.2 Hz, 1H), 2.95 (brs, 1H), 2.36 – 2.25 (m, 2H), 1.40 (s, 12H), 1.37 (s, 12H).

Alcohol 103b. Ketone **102b** (434 mg) was converted to alcohol **103b** (184 mg, 42% yield, 5→30% ethyl acetate–hexanes, then 40% ethyl acetate–hexanes) by methods described obtained above (4 equiv of L-selectride.). R_f = 0.12 (50% ethyl acetate–hexanes). ^{1}H NMR (400 MHz, Benzene-d6, 50 °C) δ 7.40 – 6.91 (m, 15H, shielded by

solvent), 5.38 (d, J = 11.1 Hz, 1H), 5.17 (d, J = 11.1 Hz, 1H), 5.13 (s, 2H), 5.26 – 4.99 (m, 2H), 4.63 (s, 2H), 4.55 (s, 2H), 4.44 (s, 1H), 4.0 (t, J = 6.8 Hz, 1H), 3.84 (d, J = 9.6 Hz, 1H), 3.65 – 3.54 (m, 2H), 3.43 (dd, J = 11.5, 5.9 Hz, 1H), 3.26 (d, J = 8.2 Hz, 1H), 2.90 (brs, 1H), 2.40 (brs, 2H), 1.41 (s, 6H), 1.35 (s, 9H).



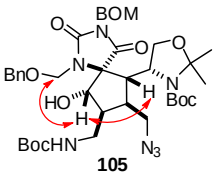
Alcohol 104a. To a solution of **102a** (60 mg, 0.077 mmol, 1.0 equiv) in tetrahydrofuran (1.2 mL) was added calcium borohydride (50 mg, 0.232 mmol, 3.0 equiv) at 0 °C, then stirred for 15 min. After removal of tetrahydrofuran, the mixture was partitioned between ethyl acetate (2 mL) and saturated ammonium chloride solution (2 mL). The organic layer was then washed with brine, and dried over anhydrous sodium sulfate. After concentration, the crude alcohol **104a** was obtained as oil containing 25% **103a**, and **104a** was directly used for the next step without purification. R_f = 0.32 (50% ethyl acetate–hexanes).



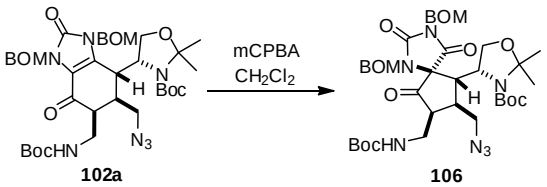
Hydantoin 105. To a solution of azide **104a** (0.12 g, 0.15 mmol, 1.0 equiv) in methylene chloride (2.0 mL) was added mCPBA (53 mg, 0.31 mmol, 2.0 equiv) at 23 °C and the

reaction was stirred overnight. After removal of solvent, the residue was partitioned between ethyl acetate (3 mL) and a solution of sodium thiosulfate (1.0 M in saturated sodium bicarbonate, 3 mL), then the organic layer was washed with brine (3 mL) and dried over sodium sulfate. After concentrating, the crude was purified by TLC to afford hydantoin **95** as colorless oil. R_f = 0.61 (50% ethyl acetate–hexanes). ^{1}H NMR (400 MHz, Benzene-d6, 50 °C) δ 7.45 – 6.90 (10H, shield by solvent), 5.11 (d, *J* = 11.3 Hz, 1H), 5.02 (dd, *J* = 13.3, 10.5 Hz, 2H), 4.80 (d, *J* = 10.9 Hz, 1H), 4.69 – 4.56 (m, 4H), 4.51 – 4.43 (m, 1H), 4.31 (d, *J* = 11.2 Hz, 1H), 3.75 – 3.65 (m, 1H), 3.33 (dd, *J* = 9.4, 5.4 Hz, 1H), 3.29 – 3.17 (m, 2H), 3.17 – 3.08 (m, 1H), 3.02 (tt, *J* = 10.8, 4.9 Hz, 2H), 2.97 – 2.85 (m, 1H), 2.62 (t, *J* = 7.7 Hz, 1H), 1.41 (s, 9H), 1.37 (s, 15H).

The relative stereochemistry of **105** was determined by nOe experiments, and nOe interactions were observed as indicated below.



105

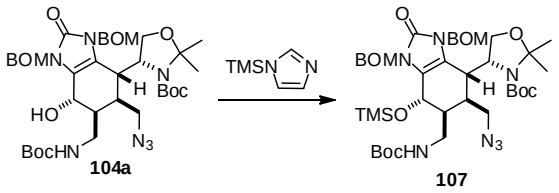


102a **106**

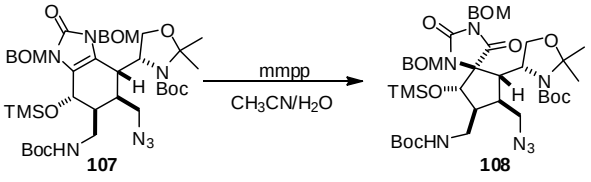
Hydantoin 106. To a solution of azide **102a** (1.0 mg, 0.0013 mmol, 1.0 equiv) in methylene chloride (0.2 mL) was added mCPBA (1 mg, 0.0058 mmol, 4.0 equiv) at

23 °C and the reaction was stirred overnight. After removal of solvent, the residue was partitioned between ethyl acetate (1 mL) and a solution of sodium thiosulfate (1.0 M in saturated sodium bicarbonate, 1 mL), and then organic layer was washed with brine (1 mL) and dried over sodium sulfate. After concentrating, the crude was purified by PTLC to afford hydantoin **106** as colorless oil. R_f = 0.65 (50% ethyl acetate–hexanes). ^{1}H NMR (400 MHz, Benzene-d6, 70 °C) δ 7.36 – 6.98 (10H, shield by solvent), 5.12 (d, *J* = 11.3 Hz, 1H), 4.97 (d, *J* = 10.1 Hz, 1H), 4.90 (d, *J* = 10.1 Hz, 1H), 4.86 (d, *J* = 11.3 Hz, 1H), 4.62 (d, *J* = 5.2 Hz, 2H), 4.56 (d, *J* = 11.9 Hz, 1H), 4.43 (d, *J* = 11.9 Hz, 1H), 4.06 (d, *J* = 9.4 Hz, 1H), 3.53 (d, *J* = 2.3 Hz, 2H), 3.47 (dd, *J* = 9.6, 6.3 Hz, 1H), 3.39 – 3.28 (m, 3H), 3.23 (t, *J* = 4.2 Hz, 1H), 3.23 (tt, *J* = 10.5, 7.5 Hz, 1H), 2.49 – 2.40 (m, 1H), 1.57 (s, 3H), 1.46 (s, 9H), 1.40 (s, 9H), 1.35 (s, 3H).

Alternate Procedure. To a solution of the alcohol **105** (1.0 mg, 0.0013 mmol, 1.0 equiv) in anhydrous methylene chloride (0.3 mL) were added Dess-Martin periodinane (5 mg, excess). The reaction was stirred at 50 °C overnight. After removal of the solvent, the residue was diluted in ethyl acetate, washed with a solution of sodium thiosulfate (1.0 M in saturated sodium bicarbonate), saturated sodium bicarbonate, and brine, and dried over anhydrous sodium sulfate. After concentration, the crude was purified by PTLC to afford hydantoin **106** as colorless oil.



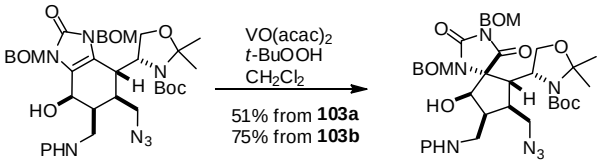
Azide 107. To a solution of alcohol **104a** (4.4mg, 0.0057 mmol, 1.0 equiv) in methylene chloride (0.2 mL) was added *N*-trimethylsilylimidazole (4.2 μL, 0.029 mmol, 5.0 equiv) and the reaction was stirred overnight before the removal of trimethylsilylimidazole under high vacuum at 50 °C. The residue was then partitioned between ethyl acetate (1 mL) and aqueous hydrochloric acid (0.1 N, 1 mL). The organic layer was then washed with saturated sodium bicarbonate (1 mL), brine (1 mL) and dried over sodium sulfate. After concentrating, the product **107** would decompose on PTLC so it was used directly for next step without purification. R_f = 0.49 (50% ethyl acetate–hexanes). ^{1}H NMR (400 MHz, Benzene-d6, 50 °C) δ 7.46 – 7.08 (10H, shield by solvent), 5.43 (d, *J* = 10.9 Hz, 1H), 5.39 (d, *J* = 10.9 Hz, 1H), 5.22 (d, *J* = 10.8 Hz, 1H), 5.07 (d, *J* = 10.8 Hz, 1H), 4.63 (s, 2H), 4.52 (d, *J* = 8.8 Hz, 2H), 4.18 (dd, *J* = 10.5, 4.2 Hz, 1H), 3.73 (d, *J* = 9.2 Hz, 2H), 3.43 – 3.28 (m, 3H), 3.24 (d, *J* = 9.4 Hz, 1H), 3.08 (dd, *J* = 11.9, 2.9 Hz, 1H), 2.91 – 2.80 (m, 1H), 2.59 (d, *J* = 10.3 Hz, 1H), 2.33 (t, *J* = 12.6 Hz, 1H), 1.64 (s, 3H), 1.55 (s, 9H), 1.44 (s, 9H), 1.35 (s, 3H), 0.24 (s, 9H).



Hydantoin 108. To a solution of azide **107** (1.0 mg, 0.0014 mmol, 1.0 equiv) in

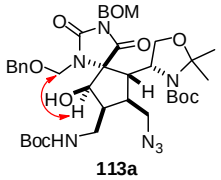
acetonitrile (0.1 mL) and water (0.1 mL) was added mmpp (1.7 mg, 80% purity, 0.0028 mmol, 2.0 equiv) at 23 °C and the reaction was stirred overnight. After removal of solvent, the residue was partitioned between ethyl acetate (1 mL) and a solution of sodium thiosulfate (1.0 M in saturated sodium bicarbonate, 1 mL), then the organic layer was washed with brine (1 mL) and dried over sodium sulfate. After concentrating, the crude was purified by TLC to afford hydantoin **108** as colorless oil. R_f = 0.58 (50% ethyl acetate–hexanes). ^{1}H NMR (400 MHz, Benzene-d6, 50 °C) δ 7.45 – 6.90 (10H, shield by solvent), 5.12 – 5.03 (m, 2H), 5.03 – 4.93 (m, 2H), 4.74 – 4.59 (m, 4H), 4.53 (d, *J* = 12.2 Hz, 1H), 4.41 (d, *J* = 11.2 Hz, 1H), 4.17 – 4.05 (m, 1H), 3.65 (d, *J* = 9.4 Hz, 1H), 3.61 – 3.53 (m, 1H), 3.53 – 3.42 (m, 1H), 3.37 (dd, *J* = 9.4, 5.3 Hz, 1H), 3.30 (dd, *J* = 12.7, 3.9 Hz, 1H), 3.16 – 3.01 (m, 2H), 3.01 – 2.87 (m, 2H), 1.58 (s, 3H), 1.44 (s, 21H), 0.00 (s, 9H).

Alternate procedure. To a 4 mL vial charged with alcohol **105** (1.0 mg) was added *N*-trimethylsilylimidazole (0.2 mL) and the reaction was stirred for 5 min before the removal of trimethylsilylimidazole under high vacuum at 50 °C. The residue was then partitioned between ethyl acetate (1 mL) and aqueous hydrochloric acid (0.1 N, 1 mL). The organic layer was then washed with saturated sodium bicarbonate (1 mL), brine (1 mL) and dried over sodium sulfate.

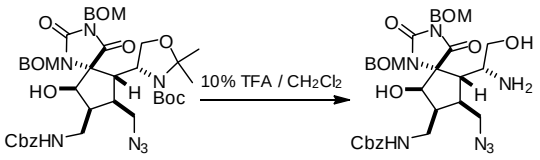


Hydantoin 113a. To a solution of alcohol **103a** (63 mg, 0.081 mmol, 1.0 equiv) in anhydrous methylene chloride was added $VO(acac)_2$ (2.2 mg, 0.0081 mmol, 0.1 equiv) and ^{t}BuOOH (37 μL, 0.202 mmol, 2.5 equiv). The reaction was stirred for 2.5 h then quenched with a solution of sodium thiosulfate (1.0 M in saturated sodium bicarbonate, 1 mL), washed with brine (2 mL), and dried over anhydrous sodium sulfate. After concentration, the crude was purified by silica gel column (10→15% ethyl acetate–hexanes) and **113a** was obtained as white powder (33 mg, 51% yield). R_f = 0.51 (50% ethyl acetate–hexanes). ^{1}H NMR (400 MHz, Benzene-d6, 50 °C) δ 7.40 – 6.91 (m, 10H), 5.37 (d, J = 11.8 Hz, 1H), 4.87 (d, J = 10.3 Hz, 1H), 4.82 (d, J = 10.3 Hz, 1H), 4.62 (d, J = 11.8 Hz, 1H), 4.54 (s, 4H), 4.10 (s, 1H), 3.91 – 3.82 (m, 1H), 3.60 (ddd, J = 15.5, 8.9, 6.6 Hz, 1H), 3.48 – 3.30 (m, 4H), 3.26 (brd, J = 12.7 Hz, 1H), 2.99 (dd, J = 10.2, 7.7 Hz, 1H), 2.94 (brs, 1H), 2.80 (tt, J = 9.2, 4.9 Hz, 1H), 1.55 (s, 3H), 1.41 (s, 9H), 1.39 (s, 9H), 1.29 (s, 3H); MS(MALDI)$^+$ calcd for $C_{40}H_{55}N_7NaO_{10}$: $[M+Na]^+$ 816.4, found: 816.4.

The relative stereochemistry of **113a** was determined by nOe experiments, and nOe interactions were observed as indicated below.

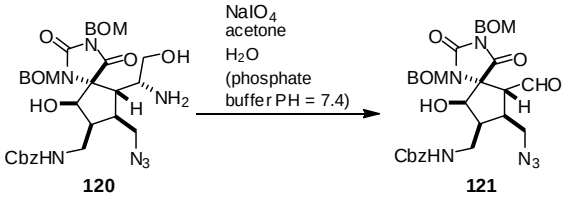


Hydantoin 113b. Alcohol **103b** (184 mg) was converted to hydantoin **113b** (140 mg, 75% yield, 15→25% ethyl acetate–hexanes) by methods described above. R_f = 0.43 (50% ethyl acetate–hexanes). ^{1}H NMR (500 MHz, DMSO-d6, 50 °C) δ 7.48 – 7.17 (m, 11H), 6.66 (brs, 1H), 5.54 (d, *J* = 5.3 Hz, 1H), 5.15 (d, *J* = 11.3 Hz, 1H), 5.08 – 4.99 (m, 2H), 4.99 – 4.91 (m, 2H), 4.88 (d, *J* = 11.3 Hz, 1H), 4.65 (s, 2H), 4.62 – 4.53 (m, 2H), 4.51 (t, *J* = 5.7 Hz, 1H), 4.33 (dd, *J* = 10.4, 5.2 Hz, 1H), 3.67 (dd, *J* = 9.5, 5.4 Hz, 1H), 3.56 (td, *J* = 13.1, 6.8 Hz, 2H), 3.44 (tq, *J* = 13.8, 7.0 Hz, 2H), 3.10 (d, *J* = 9.8 Hz, 1H), 2.68 (d, *J* = 8.9 Hz, 2H), 2.56 (p, *J* = 6.6 Hz, 1H), 1.51 (s, 3H), 1.45 (s, 9H), 1.38 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d6, 50 °C) δ 172.4, 155.7, 155.6, 152.4, 137.4, 137.2, 136.9, 128.5 – 126.5 (15 carbons), 93.4, 79.8, 77.4, 76.2, 71.6, 70.6, 70.1, 67.8, 66.0, 65.0, 55.8, 51.4, 49.5, 43.5, 41.2, 35.9, 27.6, 26.6, 23.2.

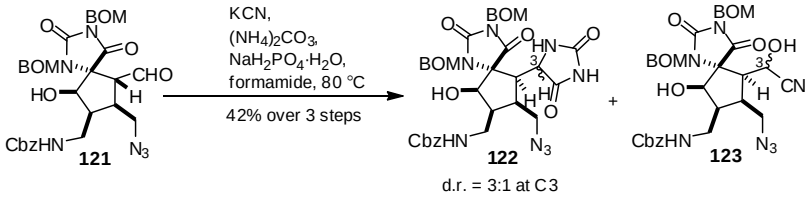


113b **120**

Aminoalcohol 120. To a vial charged with **113b** (50 mg) was added trifluoroacetic acid (10% in methylene chloride, 0.6 mL) at 23 °C. The solvent was removed after 1.5 h to afford crude aminoalcohol **120** as a colorless powder. It was used for the next step without purification. R_f = 0.38 (10% methanol–methylene chloride).



Aldehyde 121. To a solution of crude aminoalcohol **120** (50 mg) in acetone (0.4 mL) and water (0.2 mL, 0.2 N phosphate buffer pH=7.4) was added sodium periodate (50 mg). The reaction was stirred for 3 hours and then acetone was removed. The residue was partitioned between ethyl acetate (5 mL) and brine (5 mL). The organic layer was then dried over sodium sulfate and concentrated to afford crude aldehyde **121**. It was used for the next step without purification. R_f = 0.53 (10% methanol–methylene chloride).

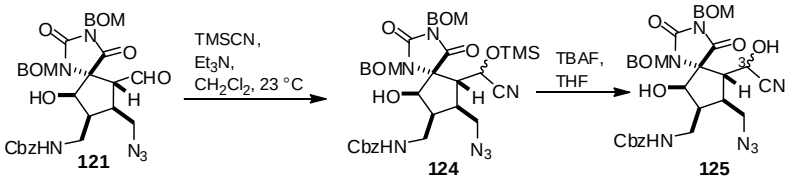


Hydantoin 122. To a solution of crude aldehyde **121** (20mg, 0.027 mmol, 1.0 equiv) in formamide (0.4 mL) were added potassium cyanide (2.7mg, 0.041 mmol, 1.5 equiv), ammonium carbonate (39mg, 0.41 mmol, 15 equiv) and sodium dihydrogen phosphate monohydrate (15mg, 0.11 mmol, 4.0 equiv). The reaction was heated to 80 °C for 10 h. The solvent was then removed under high vacuum at 60 °C, and the residue was partitioned between ethyl acetate (2 mL) and brine (1 mL). The organic layer was dried over sodium sulfate, concentrated and purified by preparative HPLC (Waters Atlantis dC18 OBD, 19×150 mm, 5 μm, eluent A: water, eluent B: acetonitrile, gradient: T = 0 min: 60% B, T = 60 min: 100% B, 5.0 mL/min) to afford the hydantoin **122** as a colorless

solid (6.4 mg, 36% yield from alcohol **113b** over three steps, retention time: 33.4 min; ^{1}H NMR (400 MHz, DMSO-d6) δ 10.81 (s, 1H), 7.90 (s, 1H), 7.59 – 7.00 (m, 15H), 5.57 (d, *J* = 6.9 Hz, 1H), 5.04 (d, *J* = 11.5 Hz, 1H), 5.03 (s, 2H), 4.93 (d, *J* = 11.5 Hz, 1H), 4.90 (s, 2H), 4.61 (q, *J* = 11.7 Hz, 2H), 4.53 (s, 2H), 4.39 (d, *J* = 9.9 Hz, 1H), 3.98 (dd, *J* = 9.6, 5.6 Hz, 1H), 3.64 (t, 2H), 3.25 (s, 2H), 2.72 – 2.66 (t, *J* = 7.5 Hz, 1H), 2.56 (brs, 2H); ^{13}C NMR (101 MHz, DMSO-d6) δ 175.1, 174.4, 157.3, 157.2, 156.0, 137.6, 137.2, 137.1, 128.5 – 127.5 (15 carbons), 78.3, 73.8, 71.9, 70.4, 69.9, 68.3, 67.8, 65.4, 56.5, 46.2, 44.9, 37.1, 36.7.

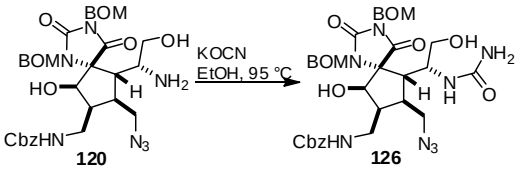
C3-diastereomer. 2.0mg, 11% yield from **113b** over three steps, retention time: 34.3 min). R_f = 0.32 (10% methanol–methylene chloride). ^{1}H NMR (400 MHz, DMSO-d6) δ 10.85 (s, 1H), 8.03 (s, 1H), 7.50 – 7.12 (m, 15H), 5.13 (dd, *J* = 24.7, 9.8 Hz, 2H), 5.06 – 4.94 (m, 2H), 4.91 – 4.77 (m, 2H), 4.62 (d, *J* = 11.5 Hz, 1H), 4.54 (d, *J* = 11.3 Hz, 1H), 4.48 (s, 2H), 4.41 (dd, *J* = 7.0, 1.9 Hz, 1H), 3.94 (dd, *J* = 11.5, 7.9 Hz, 1H), 3.68 (brs, 2H), 3.28 (s, 1H), 3.21 (dt, *J* = 10.5, 5.7 Hz, 1H), 2.74 (t, *J* = 7.4 Hz, 1H), 2.70 – 2.62 (m, 1H), 2.61 – 2.51 (m, 1H).

Cyanohydrin 123. 123 was obtained as a mixture of two C3-diastereomers (10% HPLC yield). R_f = 0.16 (50% ethyl acetate–hexanes).



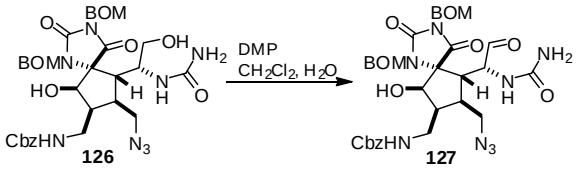
Cyanohydrin 125. To a solution of **121** (3 mg, 0.0046 mmol, 1.0 equiv) in methylene chloride (0.2 mL) was added TMSCN (2.4 μL, 0.018 mmol, 4.0 equiv) and triethylamine (0.64 μL, 0.0046 mmol, 1.0 equiv). The reaction was stirred for 1.5 h before solvent was removed to afford crude **124**. R_f = 0.50 (50% ethyl acetate–hexanes). TMS ether **124** was then dissolved in tetrahedrofuran (0.2 mL) and TBAF (1 N in THF, 10 μL) was added and the reaction was stirred for 1 h before the solvent was removed. The crude was purified by TLC to afford cyanohydrin **125** as a mixture of two C3-diastereomers. R_f = 0.40 (50% ethyl acetate–hexanes).

Differences in the NMR of **123** and **125** show that they are C2-diastereomers.

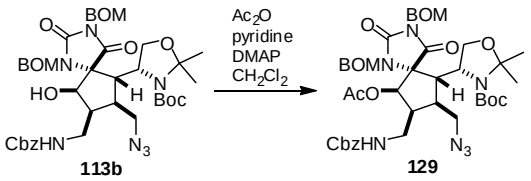


Urea 126. To a solution of aminoalcohol **120** (2.0 mg, 0.0024 mmol, 1.0 equiv) in ethanol (0.3 mL) was added potassium cyanate (0.3mg, 0.0037 mmol, 1.5 equiv) and the reaction was heated to 80 °C overnight. The solvent was then removed and the residue was partitioned between ethyl acetate (2 mL) and brine (1 mL). The organic layer was dried over sodium sulfate and concentrated to afford crude urea **126** as a white solid,

which was used for the next step without purification.

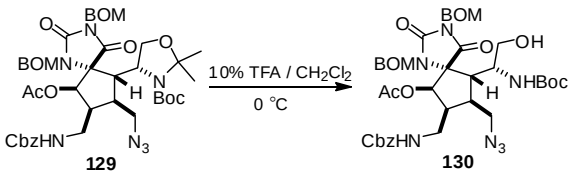


Aldehyde 127. Crude urea **126** (2 mg) was dissolved in anhydrous methylene chloride (0.2 mL), and Dess–Martin periodinane (5 mg, excess) was added to the solution at 23 °C followed by water (0.04 mg). The reaction was stirred for 4.5 h, and then an aqueous solution of 10% sodium thiosulfate/saturated sodium bicarbonate (1:1 v/v, 1 mL) was added. After stirring for another 10 min, the biphasic mixture was extracted with ethyl acetate (1 mL×3), and the organic phase was washed with saturated sodium bicarbonate (1 mL×2), dried over sodium sulfate, filtered, and concentrated to afford crude aldehyde **127** as a white powder.

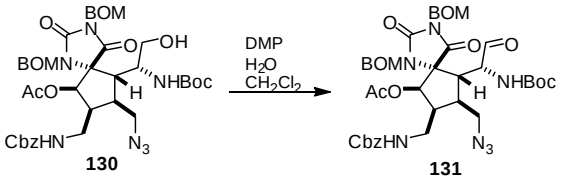


Acetate 129. To a solution of **113b** (60 mg, 0.072 mmol, 1.0 equiv) in methylene chloride (0.4 mL) were added acetic anhydride (8.2 µL, 0.087 mmol, 1.2 equiv), pyridine (6.9 µL, 0.087 mmol, 1.2 equiv) and 4-dimethylaminopyridine (0.88 mg, 0.0072 mmol, 0.1 equiv). The reaction was stirred for 1 h before the solvent was removed and the residue was partitioned between ethyl acetate (2 mL) and aqueous hydrochloric acid (1.0

N, 1 mL). The organic layer was then washed with saturated sodium bicarbonate (1 mL), brine (1 mL), dried over sodium sulfate and concentrated to afford crude acetate **129** as a white solid, which was used for the next step without purification. R_f = 0.66 (50% ethyl acetate–hexanes).

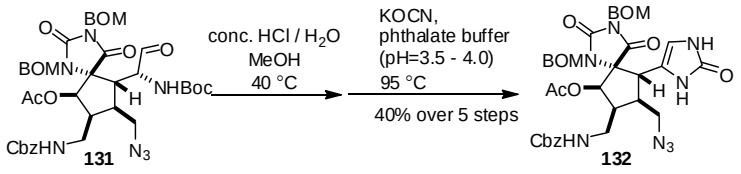


Alcohol 130. To a solution of crude **129** obtained above in methylene chloride (0.2 mL) was added trifluoroacetic acid (20% in methylene chloride, 0.2 mL) at 0 °C. The reaction was neutralized with saturated sodium bicarbonate (2 mL) after 15 min, and then diluted with ethyl acetate (5 mL). The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated to afford the crude alcohol **130** as a colorless powder. It was used for the next step without purification. R_f = 0.40 (50% ethyl acetate–hexanes).



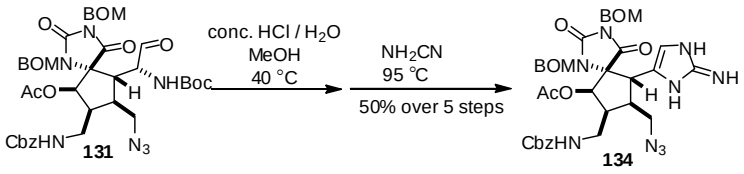
Aldehyde 131. Crude alcohol **130** obtained above was dissolved in anhydrous methylene chloride (0.4 mL), and Dess–Martin periodinane (46 mg, 0.11 mmol, 1.5 equiv) was added to the solution at 23 °C followed by water (2.0 mg, 0.11 mmol, 1.5 equiv). The

reaction was stirred for 0.5 h, and then an aqueous solution of 10% sodium thiosulfate/saturated sodium bicarbonate (1:1 v/v, 1 mL) was added. After stirring for another 10 min, the biphasic mixture was extracted with ethyl acetate (1 mL×3), and the organic phase was washed with saturated sodium bicarbonate (1 mL×2), dried over sodium sulfate, filtered, and concentrated to afford crude aldehyde **131** as a white powder. R_f = 0.41 (50% ethyl acetate–hexanes). ^{1}H NMR (500 MHz, Benzene-d6, 50 °C) δ 8.97 (s, 1H), 7.39 – 7.00 (m, 15H), 5.44 (d, *J* = 10.5 Hz, 1H), 5.26 (d, *J* = 10.9 Hz, 1H), 5.21 (d, *J* = 10.7 Hz, 1H), 5.10 (d, *J* = 12.3 Hz, 1H), 5.04 (d, *J* = 11.4 Hz, 2H), 4.74 (d, *J* = 11.9 Hz, 1H), 4.64 (s, 2H), 4.51 (s, 2H), 4.36 (d, *J* = 9.9 Hz, 1H), 3.47 (dt, *J* = 13.8, 7.0 Hz, 1H), 3.13 (dt, *J* = 14.1, 5.3 Hz, 1H), 2.85 (d, *J* = 11.4 Hz, 1H), 2.70 (d, *J* = 11.2 Hz, 1H), 2.56 (p, *J* = 9.0 Hz, 2H), 2.00 (brs, 1H), 1.47 (s, 3H), 1.37 (s, 9H).



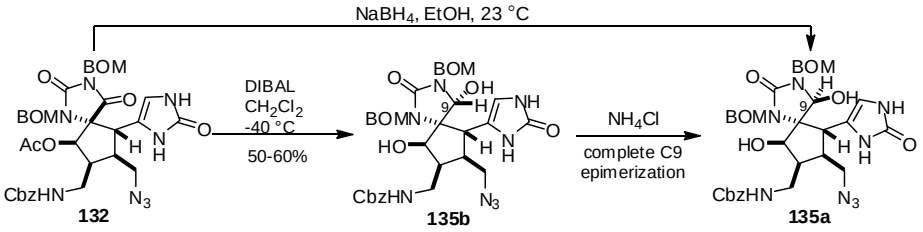
Imidazolinone 132. To a solution of the crude aldehyde **131** (55 mg) in methanol (4.8 mL) at 0 °C was added cold aqueous hydrogen chloride (12 N, 1.2 mL). The solution was stirred at 40 °C for 20 min. With the solution cooled in an ice-water bath, the pH of the solution was then adjusted to 4.0 by adding aqueous sodium hydroxide (3.0 N). Potassium cyanate (120 mg, 20 equiv) and potassium hydrogen phthalate (280mg, 20 equiv) were then added and the reaction was heated at 95 °C for 140 min. After removal of most of the methanol, the mixture was partitioned between ethyl acetate and water. The organic layer was washed with saturated sodium bicarbonate and brine, dried over

anhydrous sodium sulfate, filtered, concentrated, and then purified by preparative HPLC (Waters Atlantis dC18 OBD, 19×150 mm, 5 µm, eluent A: water, eluent B: acetonitrile, gradient: T = 0 min: 70% B, T = 40 min: 100% B, 5.0 mL/min) to afford imidazole **132** as a white solid. (21.6 mg, 43% yield over 5 steps from **113b**, retention time: 21.5 min). The reaction crude sometimes was used without purification for the next step. R_f = 0.34 (10% methanol–methylene chloride). ^{1}H NMR (500 MHz, DMSO-d6) δ 9.91 (s, 1H), 9.81 (s, 1H), 7.54 – 7.16 (m, 15H), 6.26 (s, 1H), 5.46 (d, *J* = 5.5 Hz, 1H), 5.03 (d, *J* = 11.4 Hz, 1H), 5.02 (d, *J* = 12.4 Hz, 1H), 4.98 – 4.85 (m, 3H), 4.71 (d, *J* = 11.4 Hz, 1H), 4.52 (s, 2H), 4.51 – 4.42 (m, 2H), 3.66 (dd, *J* = 12.7, 6.7 Hz, 1H), 3.51 (dd, *J* = 12.7, 6.1 Hz, 1H), 3.44 – 3.35 (m, 2H), 3.28 (dt, *J* = 13.5, 6.1 Hz, 1H), 2.97 (tq, *J* = 15.9, 7.6 Hz, 2H), 1.94 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d6) δ 171.4, 169.6, 156.1, 155.5, 155.0, 137.5, 137.4, 137.1, 128.5 – 127.0 (15 carbons), 116.1, 107.3, 78.4, 72.8, 70.4, 70.3, 70.0, 68.0, 65.3, 51.0, 46.4, 41.4, 40.8, 35.7, 20.6.



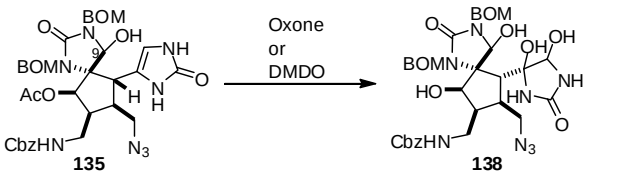
Amidazolinone 134. To a solution of the crude aldehyde **131** (15 mg) in methanol (1.2 mL) at 0 °C was added cold aqueous hydrogen chloride (12 N, 0.3 mL). The solution was stirred at 40 °C for 20 min. With the solution cooled in an ice-water bath, the pH of the solution was then adjusted to 4.0 by adding aqueous sodium hydroxide (3.0 N). Cyanamide (16 mg, 20 equiv) was then added and the reaction was heated at 95 °C for 170 min. After removal of most of the methanol, the mixture was partitioned between

ethyl acetate and water. The organic layer was washed with saturated sodium bicarbonate and brine, dried over anhydrous sodium sulfate, filtered, concentrated, and then purified by preparative HPLC (Waters Atlantis dC18 OBD, 19×150 mm, 5 µm, eluent A: water with 0.1% trifluoroacetic acid, eluent B: acetonitrile with 0.1% trifluoroacetic acid, gradient: T = 0 min: 50% B, T = 40 min: 80% B, 5.0 mL/min) to afford amidazole **134** as a white solid. (7.2 mg, 52% yield over 5 steps from **113b**, retention time: 17.5 min). ^{1}H NMR (400 MHz, Methanol-d4) δ 7.55 – 7.12 (m, 15H), 6.62 (s, 1H), 5.67 (d, *J* = 10.3 Hz, 2H), 5.10 (s, 2H), 5.08 (d, *J* = 4.2 Hz, 2H), 4.92 (d, *J* = 2.9 Hz, 2H), 4.63 (s, 2H), 4.51 – 4.32 (m, 5H), 2.93 (ddt, *J* = 12.1, 8.4, 4.3 Hz, 1H), 2.65 (dq, *J* = 10.0, 7.2 Hz, 1H).



Hemiaminal 135a. To a solution of imidazolinone **132** (4 mg, 0.0052 mmol, 1.0 equiv) in ethanol (0.2 mL) was added sodium borohydride (3 mg, excess) and stirred for 2.5 h. The reaction was quenched with acetone (0.2 mL) and the solvent was removed. The residue was then dissolved in ethyl acetate and washed with ammonium chloride, and brine, dried over sodium sulfate, and concentrated to afford **135a** as a white solid. The crude was used for the next step without purification. R_f = 0.18 (10% methanol–methylene chloride).

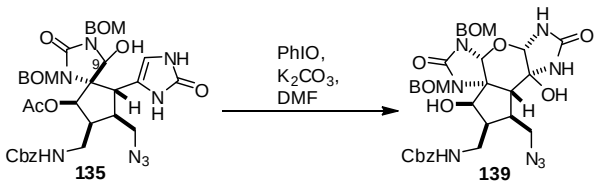
Hemiaminal 135b. To a solution of imidazolinone **132** (1 mg, 0.0013 mmol, 1.0 equiv) in methylene chloride (0.2 mL) was added DIBAL (1.0 N in methylene chloride, 7.0 µL, 5.4 equiv) at 23 °C. The reaction was then quenched with 1 mL Rochelle salt solution after 1 h, diluted with 2 mL ethyl acetate and stirred overnight. The organic layer was separated, concentrated and purified by HPLC (Eclipse XDB-C18, 9.4×250 mm, 5 µm, eluent A: water, eluent B: acetonitrile, gradient: T = 0 min: 40% B, T = 30 min: 60% B, 4.8 mL/min) to afford hemiaminal **135b** as a white solid. (0.6 mg, 60% yield, retention time: 15.0 min). R_f = 0.18 (10% methanol–methylene chloride). ^{1}H NMR (400 MHz, Methanol-d4) δ 7.45 – 7.12 (m, 15H), 6.27 (s, 1H), 5.76 (s, 1H), 5.11 – 4.97 (m, 4H), 4.82 (d, *J* = 10.9 Hz, 2H), 4.58 – 4.38 (m, 4H), 3.82 (d, *J* = 3.8 Hz, 1H), 3.72 (d, *J* = 7.9 Hz, 1H), 3.59 (dd, *J* = 12.4, 6.5 Hz, 1H), 3.51 – 3.37 (m, 3H), 3.04 – 2.90 (m, 1H), 2.64 (dt, *J* = 16.3, 7.4 Hz, 1H).



Hemiaminal 138. To a solution of hemiaminal **135** (1 mg, 0.0014 mmol, 1.0 equiv) in acetone (0.1 mL) and water (0.1 mL) were added sodium bicarbonate (3.3 mg, 0.039 mmol, 30 equiv) and Oxone (7.5 mg, 9.0 equiv) at 0 °C. The reaction was stirred overnight at the same temperature and then diluted with ethyl acetate (2 mL). The aqueous phase was extracted with ethyl acetate (1 mL × 3). The organic layers were combined and concentrated. The residue was redissolved in ethyl acetate (5 mL) and

filtered. After the removal of solvent, crude **138** was afforded as a white solid, and used for the next step without purification.

Alternate Procedure. To a solution of hemiaminal **135** (2 mg, 0.0028 mmol, 1.0 equiv) in acetone (0.1 mL) was added DMDO (248 µL, 0.0235M in acetone, 2.2 equiv) at 0 °C. The solvent was removed after 40 min and crude **138** was afforded and used for the next step without purification. R_f = 0.28 and 0.38 (10% methanol–methylene chloride).

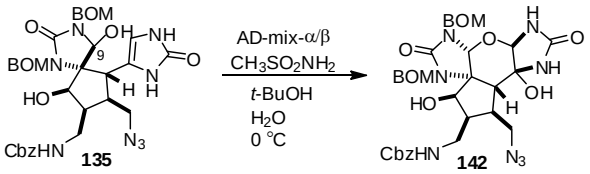


Cyclicurea 139. To a vial charged with hemianimial **135** (1.2 mg, 0.0017 mmol, 1.0 equiv) and potassium carbonate (2.0 mg, 0.014 mmol, 10 equiv) was added a suspension of iodosobenzene (1.0 mg, 0.0045 mmol, 3 equiv) in DMF (0.2 mL). The reaction was stirred for 1.5 h and became a clear solution. The reaction was then quenched with an aqueous solution of 10% sodium thiosulfate/saturated sodium bicarbonate (1:1 v/v, 1 mL) and extracted with ethyl acetate (1 mL × 4). The solvent was removed and the residue was redissolved in ethyl acetate (2 mL) and washed with brine (1 mL). Then the organic layer was dried over sodium sulfate, filtered and concentrated. The residue was purified by HPLC (Eclipse XDB-C18, 9.4×250 mm, 5 µm, eluent A: water, eluent B: acetonitrile, gradient: T = 0 min: 45% B, T = 20 min: 60% B, 4.8 mL/min) to afford **139** as a white solid (0.6 mg, 49% yield, retention time: 16.7 min). ^{1}H NMR (400 MHz, DMSO-d6) δ

9.93 (s, 1H), 8.01 (d, *J* = 3.1 Hz, 1H), 7.44 – 7.17 (m, 15H), 6.54 (s, 1H), 5.53 (s, 1H), 5.49 (d, *J* = 5.4 Hz, 1H), 5.16 (d, *J* = 3.1 Hz, 1H), 5.06 – 4.94 (m, 2H), 4.91 (d, *J* = 10.7 Hz, 1H), 4.76 (d, *J* = 11.1 Hz, 1H), 4.68 (d, *J* = 11.1 Hz, 1H), 4.55 – 4.42 (m, 3H), 4.42 (s, 2H), 4.28 (d, J = 11.3 Hz, 1H), 3.88 – 3.80 (m, 1H), 3.69 (dd, J = 11.4, 2.7 Hz, 1H), 3.22 – 3.18 (m, 1H), 3.12 – 3.01 (m, 2H), 2.87 – 2.78 (m, 1H), 2.74 (d, *J* = 5.0 Hz, 1H); MS(MALDI)$^+$ calcd for $C_{36}H_{40}N_8NaO_9$ $[M+Na]^+$: 751.3, found: 751.0.

Alternate Procedure 1. To a solution of crude hemiaminal **138** (2 mg) in acetonitrile (0.2 mL) was added bismuth nitrate (2 mg, excess) at 23 °C. The reaction was stirred 20 min before diluted with 2 mL methylene chloride and filtered. After the solvent was removed, the residue was dissolved in ethyl acetate (2 mL) and washed with brine (1 mL). The organic layer was separated, dried over sodium sulfate, filtered and concentrated. The crude was purified by HPLC under the same conditions described above to yield **139** (0.1 mg).

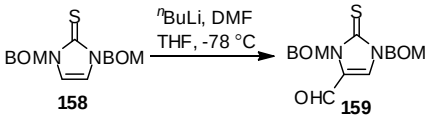
Alternate Procedure 2. To a solution of crude hemiaminal **138** (4.5 mg) in methylene chloride (0.2 mL) was added trifluoroacetic acid (10% in methylene chloride, 0.2 mL) at 0 °C. The reaction was neutralized with saturated sodium bicarbonate (2 mL) after 20 min, and then diluted with ethyl acetate (5 mL). The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude was purified by HPLC under the same conditions described above to yield **139** (0.7 mg, 15 % yield).



Cyclicurea 142. To a solution of AD-mix-α or AD-mix-β (3.7 mg) in ^{t}BuOH (0.1 mL) and water (0.14 mL) was added methanesulfonamide (0.25 mg, 1.0 equiv, in 0.4 mL ^{t}BuOH). The solution was stirred for 10 min at 0°C and then crude hemiaminal **135** (2 mg, 1.0 equiv, in 0.05 mL ^{t}BuOH) was added. The reaction was stirred at 0 °C for another 4.5 h before extracted with ethyl acetate (1 mL × 3). The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated to afford cyclicurea **142** as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.67 (s, 1H), 7.43 – 7.14 (m, 15H), 7.10 (s, 1H), 7.00 (t, *J* = 6.2 Hz, 1H), 6.22 (s, 1H), 5.48 (s, 1H), 5.40 (d, *J* = 5.1 Hz, 1H), 5.00 (d, *J* = 12.5 Hz, 1H), 4.91 (s, 1H), 4.90 (d, *J* = 12.5 Hz, 1H), 4.89 (d, *J* = 11.4 Hz, 1H), 4.82 (d, *J* = 10.9 Hz, 1H), 4.63 (d, *J* = 10.9 Hz, 1H), 4.50 (d, *J* = 11.4 Hz, 1H), 4.44 (d, *J* = 4.3 Hz, 2H), 4.41 (d, *J* = 2.4 Hz, 2H), 4.02 (s, 1H), 3.83 (d, *J* = 12.2 Hz, 1H), 3.69 (t, *J* = 4.8 Hz, 1H), 3.41 (2H, shielded by solvent), 3.00 – 2.88 (m, 1H), 2.81 – 2.69 (m, 1H), 2.64 (dt, *J* = 3.3, 1.9 Hz, 1H); MS(MALDI)$^{+}$ calcd for $C_{36}H_{40}N_8NaO_9$ $[M+Na]^{+}$: 751.3, found: 751.6.

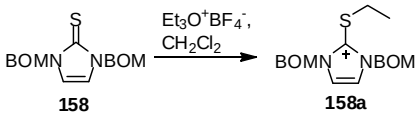
Thioimidazolinone **158.** To a solution of **157** (0.2 g, 2.94 mmol, 1.0 equiv) in DMF (5 mL) was added sodium hydride (0.129 g, 60% purity, 3.20 mmol, 1.1 equiv) slowly.

After the bubble ceased to appear, benzyl chloromethyl ether (0.86 mL, 90% purity, 6.20 mmol, 2.1 equiv) was added dropwisely and the reaction was stirred for 13 h. Another potion of sodium hydride (0.26 g, 60% purity, 6.50 mmol, 2.2 equiv) was then added, followed by sulfer powder (0.19 g, 5.90 mmol, 2.0 equiv), and the reaction was stirred for 10 h. The mixture was then quenched by saturated sodium bicarbonate (50 mL) and extracted by ether (50 mL × 3). The organic layer was filtered, dried over sodium sulfate, concentrated and purified by flash column chromatography (10%→20% ethyl acetate) to afford **158** as a colorless crystal (0.57 g, 57% yield over 2 steps from **157**). R_f = 0.56 (50% ethyl acetate–hexanes). ^{1}H NMR (400 MHz, benzene-d6) δ 7.26 (d, J = 8.2 Hz, 4H), 7.10 (t, J = 7.7 Hz, 4H) 7.04 (d, J = 6.5 Hz, 2H), 5.99 (s, 2H), 5.26 (s, 4H), 4.56 (s, 4H).



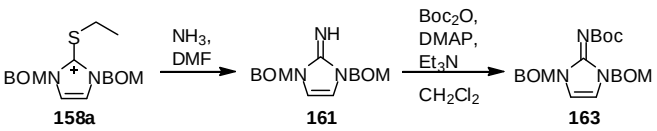
Aldehyde 159. To a solution of **159** (0.40 g, 1.18 mmol, 1.0 equiv) in THF (10 mL) was added *n*-butyllithium (0.94 mL, 2.5 M in THF, 2.35 mmol, 2.0 equiv) at -78 °C. The reaction was stirred at the same temperature for 1.5 h before DMF (0.27 mL, 3.53 mmol, 3.0 equiv) was added. The reaction was stirred for another 1 h at -78 °C and allowed to warm to room temperature overnight. The mixture was then quenched by aqueous HCl (1.0 N, 2 mL) and extracted by ether (50 mL × 3). The organic layer was filtered, dried over sodium sulfate, concentrated and used for the next step without purification. R_f = 0.51 (50% ethyl acetate–hexanes). ^{1}H NMR (400 MHz, benzene-d6) δ 8.9 (s, 1H), 7.28 (d, J = 7.1 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 7.17–6.96 (m, 6H), 6.40 (s, 1H), 5.81 (s,

2H), 5.17 (s, 2H), 4.69 (s, 2H), 4.42 (s, 2H). ^{13}C NMR (100 MHz, benzene-d6) δ 175.8, 170.5, 138.3, 137.3, 129.8, 128.7–127.5 (11 carbons), 76.2, 74.7, 72.0.



158 **158a**

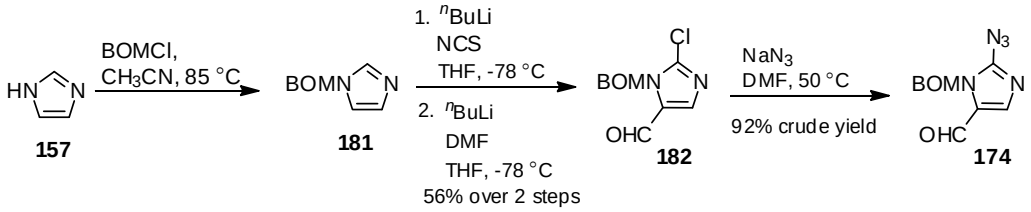
Thioimidazolinonium salt 158a. To a solution of **158** (0.10 g, 0.29 mmol, 1.0 equiv) in methylene chloride (2 mL) was added Meerwein's salt (0.87 mL, 1 N in methylene chloride, 0.87 mmol, 3.0 equiv) at room temperature and the reaction was stirred overnight. The reaction was then diluted with methylene chloride (10 mL), washed with saturated sodium bicarbonate (5 mL), brine (5 mL), dried over sodium sulfate and concentrated. The crude was used for the next step without purification. R_f = 0.41 (10% methanol–methylene chloride). ^{1}H NMR (400 MHz, benzene-d6) δ 7.85 (s, 2H), 7.34–6.96 (m, 10H), 5.40 (s, 4H), 4.52 (s, 4H), 2.51 (q, J = 9.8 Hz, 2H), 0.68 (t, J = 9.8 Hz, 3H).



158a **161** **163**

Iminoimidazole 161. A flask charged with a solution of **158a** (0.29 mmol) obtained above in DMF (3 mL) was equipped with a balloon filled with ammonia gas. The reaction was stirred overnight before the solvent was removed and afforded **161** without purification. ^{1}H NMR (400 MHz, benzene-d6) δ 9.36 (brs, 1H), 7.31–6.96 (m, 10H), 5.93 (s, 2H), 5.12 (s, 4H), 4.42 (s, 4H).

Iminoimidazole 163. To a solution of **161** (0.28 mmol, 1.0 equiv) obtained above in DMF (3 mL) were added Boc anhydride (134 μL, 0.62 mmol, 2.2 equiv) and 4-dimethylaminopyridine (6.8 mg, 0.056 mmol, 0.2 equiv). The reaction was stirred overnight before the solvent was removed, and the crude was purified by a short packed silica gel column (10–100% ethyl acetate/hexanes) to afford **163** as a white solid. ^{1}H NMR (400 MHz, benzene-d6) δ 7.26 (d, J = 6.1 Hz, 4H), 7.17–7.03 (m, 6H), 5.87 (s, 2H), 5.08 (s, 4H), 4.36 (s, 4H), 1.63 (s, 9H); MS(ESI)$^+$ calcd for $C_{24}H_{29}N_3NaO_4$ $[M+Na]^+$: 446.2, found: 446.2.

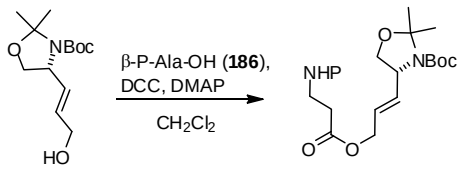


Imidazole 181. To a solution of imidazole (**157**) (48.0g, 706 mmol, 2.2 equiv) in acetonitrile (700 mL) was added benzyl chloromethyl ether (33.6 mL, 90% purity, 312 mmol, 1.0 equiv), and the reaction was refluxed at 85 °C overnight. The solvent was then removed and the crude was distilled under vacuum to afford **181** as a colorless crystal (45.6 g, 78% yield, b.p. 134–136 °C (2 mmHg)). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.35 (dd, J = 14.2, 7.0 Hz, 3H), 7.29 (d, J = 7.5 Hz, 2H), 7.14 (s, 1H), 7.09 (s, 1H), 5.33 (s, 2H), 4.44 (s, 2H).

Aldehyde 182. To a solution of *N*-(benzyloxymethyl)imidazole (**181**) (1.59 g, 8.45 mmol, 1.0 equiv) in anhydrous tetrahydrofuran (100 mL) at –78 °C was added *n*-butyllithium (5.80 mL, 9.28 mmol, 1.1 equiv, 1.6 M in hexanes) dropwisely. After stirring at –78 °C for 1 h, a solution of *N*-chlorosuccinimide (1.38 g, 10.3 mmol, 1.2 equiv) in tetrahydrofuran (50 mL) was transferred into the reaction through a stainless steel cannula over 10 min. After stirring at –78 °C for 1 h, *n*-butyllithium (15.8 mL, 25.3 mmol, 3.0 equiv, 1.6 M in hexanes) was slowly added to the reaction mixture at the same temperature, and the reaction was stirred for another 1 h. Then *N*,*N*-dimethylformamide (3.27 mL, 42.2 mmol, 5.0 equiv) was added slowly at –78 °C and the reaction was stirred for 1 h before quenched with an aqueous solution of sodium dihyrdogen phosphate (35 mL, 2.0 M). The solvents were then removed by rotary evaporator and the residue was partitioned between ethyl acetate (200 mL) and brine (100 mL). The organic layer was further washed with brine (100 mL×3), dried over sodium sulfate, filtered and concentrated. The product **182** was obtained as colorless crystals (1.18 g, 56% yield) after recrystallizing from ethyl acetate and hexanes. R_f = 0.33 (50% ethyl acetate–hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.66 (s, 1H), 7.44–7.18 (m, 5H), 5.83 (s, 2H), 4.62 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4, 142.4, 141.6, 136.6, 132.3, 128.5, 128.1, 127.5, 74.1, 71.4; MS(ESI)$^+$ calcd for $C_{12}H_{12}ClN_2O_2$ $[M+H]^+$: 251.1, found: 251.0.

Azide 174. To a solution of aldehyde **182** (1.02 g, 4.07 mmol, 1.0 equiv) in anhydrous *N*,*N*-dimethylformamide (10 mL) was added sodium azide (0.397 g, 6.10 mmol, 1.5 equiv) at 23 °C. The reaction was heated to 50 °C for 16 h. Then the reaction was

diluted with ethyl acetate (200 mL) and washed with brine (100 mL×5), dried over sodium sulfate, filtered, concentrated, and dried under high vacuum at 50 °C for 1 h. The crude product **174** was obtained as dark red oil (0.962 g, 92% crude yield), which was directly used for the next step without purification. R_f = 0.45 (50% ethyl acetate–hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.60 (s, 1H), 7.39–7.21 (m, 5H), 5.61 (s, 2H), 4.60 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.3, 148.7, 142.7, 136.9, 130.6, 128.5, 128.1, 127.7, 73.0, 71.6; MS(ESI)$^+$ calcd for $C_{12}H_{11}N_5NaO_2$ $[M+Na]^+$: 280.1, found: 280.1.



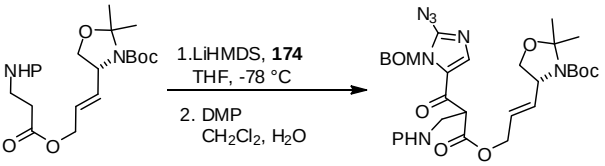
185

175a: P = Cbz
175b: P = Teoc
175c: P = Boc

Ester 175c. To a solution of allylic alcohol **185** (0.525 g, 2.04 mmol, 1.0 equiv) and Boc-β-alanine (**186c**) (0.405 g, 2.14 mmol, 1.05 equiv) in anhydrous methylene chloride (20 mL) were added *N,N'*-dicyclohexylcarbodiimide (0.442 g, 2.14 mmol, 1.05 equiv) and 4-dimethylaminopyridine (12 mg, 0.10 mmol, 0.05 equiv) at 23 °C. After stirring for 2 h, the solvent was removed. The residue was dissolved in several drops of methylene chloride, and then *N,N'*-dicyclohexylurea was crushed out with hexanes (40 mL). The suspension was filtered, dried over sodium sulfate, filtered again and concentrated to give the ester **170** as colorless oil. The crude was used directly for the next step without purification. R_f = 0.68 (50% ethyl acetate–hexanes); MS(ESI)$^+$ calcd for $C_{21}H_{37}N_2O_7$ $[M+H]^+$: 429.3, found: 429.1.

175a. R_f = 0.63 (50% ethyl acetate–hexanes). ^{1}H MNR (400 MHz, $CDCl_3$) δ 7.32 (s, 5H), 5.85 – 5.50 (m, 2H), 5.48 – 5.20 (m, 1H), 5.06 (s, 2H), 4.55 (d, J = 4.7 Hz, 2H), 4.44 – 4.15 (m, 1H), 4.01 (dd, J = 6.1, 8.9 Hz, 1H), 3.71 (dd, J = 2.0, 8.9 Hz, 1H), 3.50 – 3.37 (m, 1H), 2.53 (t, J = 5.9 Hz, 2H), 1.48 (s, 3H), 1.45 (s, 3H), 1.39 (s, 9H).

175b. R_f = 0.27 (30% ethyl acetate–hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (d, *J* = 5.9 Hz, 2H), 5.03 (brs, 1H), 4.60 (d, *J* = 4.7 Hz, 2H), 4.34 (s, 1H), 4.16 (t, *J* = 7.2 Hz, 2H), 4.04 (dd, *J* = 8.9, 6.2 Hz, 1H), 3.74 (dd, *J* = 8.9, 2.4 Hz, 1H), 3.44 (q, *J* = 6.2 Hz, 2H), 2.54 (t, *J* = 6.1 Hz, 2H), 1.60 (s, 3H), 1.52 (s, 3H), 1.46 (s, 9H), 0.98 (t, *J* = 7.2 Hz, 2H), 0.04 (s, 9H).

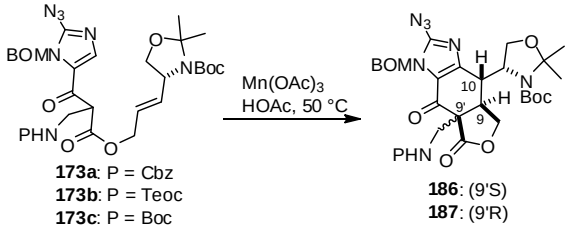


175a: P = Cbz
175b: P = Teoc
175c: P = Boc

173a: P = Cbz
173b: P = Teoc
173c: P = Boc

β-Ketoester 173c. To a solution of crude ester **175c** (0.90 g, 2.04 mmol, 1.0 equiv) in anhydrous tetrahydrofuran (10 mL) at –78 °C was added lithium bis(trimethylsilyl)amide (5.10 mL, 5.10 mmol, 2.5 equiv, 1.0 M in tetrahydrofuran) dropwisely. After stirring at –78 °C for 1 h, a solution of aldehyde **174** (0.578 g, 2.24 mmol, 1.1 equiv) in tetrahydrofuran (10 mL) was added through a stainless steel cannula over 10 min. The reaction was stirred at –78 °C for 2.5 h before quenched with an acetic acid solution in

tetrahydrofuran (2.0 mL, 1:4 v/v). The solvent was then removed by rotary evaporator. The residue was dissolved in ethyl acetate (100 mL), washed with brine (50 mL×2), dried over sodium sulfate, filtered and concentrated to afford the aldol product as pale yellow oil. This oil was dissolved in anhydrous methylene chloride (10 mL), and Dess–Martin periodinane (1.30 g, 3.06 mmol, 1.5 equiv) was added to the solution at 23 °C followed by water (55 mg, 3.06 mmol, 1.5 equiv). The white suspension was stirred for 30 min, and then an aqueous solution of 10% sodium thiosulfate/saturated sodium bicarbonate (1:1 v/v, 20 mL) was added. After stirring for another 10 min, the biphasic mixture was extracted with ethyl acetate (50 mL×3), and the organic phase was washed with saturated sodium bicarbonate (50 mL×2), dried over sodium sulfate, filtered, and concentrated to afford crude β-ketoester **173c** as pale yellow oil. R_f = 0.46 (50% ethyl acetate–hexanes); MS(ESI)$^+$ calcd for $C_{33}H_{45}N_7NaO_9$ $[M+Na]^+$: 706.3, found: 706.3.



173a: P = Cbz
173b: P = Teoc
173c: P = Boc

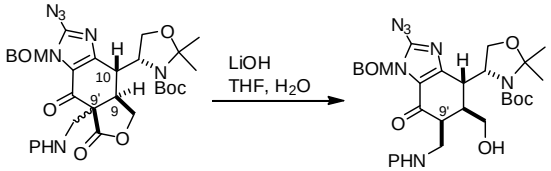
186: (9'S)
187: (9'R)

Lactone 186c and 187c. To a 50 mL flask charged with the crude **173c** obtained above and manganese(III) acetate dihydrate (1.37 g, 5.10 mmol, 2.5 equiv) was added acetic acid (15 mL) degassed by three freeze-pump-thaw cycles. The dark brown suspension was heated to 50 °C under argon for 8 h. Acetic acid was then removed and the residue was dissolved in ethyl acetate (50 mL) and a 10% aqueous sodium bisulfite solution (50 mL). The organic layer was separated and washed with brine (30 mL×2), dried over

sodium sulfate, filtered, concentrated and purified with Biotage KP-C18-HS (39 x 157 mm, 120g) column (50%→65% acetonitrile/water). The impure fractions were collected and purified by preparative HPLC (Waters Atlantis dC18 OBD, 19×150 mm, 5 μm, eluent A: water, eluent B: acetonitrile, gradient: T = 0 min: 60% B, T = 15 min: 70% B, T = 45 min: 70% B, 5.0 mL/min). Lactone **186c** was obtained as white solids (258 mg, 18% yield from **185** over 4 steps, retention time: 36 min). R_f = 0.58 (50% ethyl acetate–hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, 50 °C) δ7.44–7.12 (m, 5H), 5.96 (brs, 1H), 5.64 (d, *J* = 10.4 Hz, 1H), 5.48 (d, *J* = 10.4 Hz, 1H), 4.72–4.59 (m, 3H), 4.41 (t, *J* = 8.6 Hz, 1H), 4.29 (brs, 1H), 4.02 (brs, 1H), 3.83 (brs, 2H), 3.64 (brs, 1H), 3.17 (brs, 1H), 3.09 (t, *J* = 8.6 Hz, 1H), 1.64 (s, 3H), 1.51 (s, 9H), 1.44 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 178.0, 172.0, 156.2, 153.9, 151.5, 149.1, 137.5, 128.4, 127.8, 127.4, 124.7, 94.5, 81.3, 79.6, 73.3, 72.1, 70.0, 66.0, 60.8, 59.4, 45.0, 40.6, 38.0, 28.5, 28.4, 28.3, 24.6; MS(ESI)$^+$ calcd for $C_{33}H_{43}N_7NaO_9$ $[M+Na]^+$: 704.3, found: 704.3. Lactone **187c** was also obtained as a white solid (retention time: 34 min). ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 7.45–7.19 (m, 5H, shielded by solvent), 5.58 (d, *J* = 9.8 Hz, 1H), 5.49 (d, *J* = 9.4 Hz, 1H), 5.0–4.84 (m, 1H), 4.69 (d, *J* = 12.4 Hz,1H), 4.63 (d, *J* = 12.4 Hz,1H), 4.54 (d, *J* = 9.4 Hz, 1H), 4.44–4.28 (m, 2H), 4.27–4.18 (m, 1H), 4.18–4.08 (m, 1H), 3.78–3.64 (m, 2H), 3.50–3.39 (m, 1H), 3.39–3.24 (m, 1H), 1.60 (s, 3H), 1.56 (s, 3H), 1.49 (s, 9H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 181.3, 170.2, 155.8, 154.3, 153.7, 147.9, 137.3, 128.5, 128.1, 127.6, 124.0, 94.5, 81.5, 80.4, 73.2, 72.1, 68.7, 68.2, 59.6, 53.7, 46.3, 40.7, 40.6, 28.5, 28.3, 27.8, 24.2; MS(ESI)$^+$ calcd for $C_{33}H_{43}N_7NaO_9$ $[M+Na]^+$: 704.3, found: 704.2.

186a. β-ketoester **173a** was converted to lactone **186a** following the procedure mentioned above (19% yield from **185** over 4 steps). R_f = 0.45 (50% ethyl acetate–hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 7.40 – 7.13 (10H, shielded by solvent), 5.57 (d, *J* = 10.5 Hz, 1H), 5.45 (d, *J* = 10.5 Hz, 1H), 5.04 (d, *J* = 12.2 Hz, 1H), 4.94 (d, *J* = 12.2 Hz, 1H), 4.65 (s, 3H), 4.38 (t, *J* = 8.4 Hz, 1H), 4.32 – 4.20 (m, 1H), 4.04 – 3.89 (m, 2H), 3.82 – 3.70 (m, 1H), 3.69 – 3.59 (m, 1H), 3.09 (t, *J* = 8.6 Hz, 2H), 1.63 (s, 3H), 1.55 (s, 3H), 1.51 (s, 9H); MS(ESI)$^+$ calcd for $C_{36}H_{41}N_7NaO_9$ $[M+Na]^+$: 738.3, found: 738.2.

186b. β-ketoester **173b** was converted to lactone **186b** following the procedure mentioned above. ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 7.39 – 7.15 (m, 5H, shielded by solvent), 5.63 (d, *J* = 10.4 Hz, 1H), 5.52 (d, *J* = 10.4 Hz, 1H), 4.66 (s, 2H), 4.41 (t, *J* = 8.5 Hz, 1H), 4.29 (dd, *J* = 10.8, 6.4 Hz, 2H), 4.11 – 3.99 (m, 3H), 3.98 – 3.87 (m, 1H), 3.82 – 3.72 (m, 1H), 3.70 – 3.56 (m, 1H), 3.23 – 3.03 (m, 2H), 1.64 (s, 3H), 1.54 (s, 3H), 1.52 (s, 9H), 0.90 (t, *J* = 8.3 Hz, 2H), 0.01 (s, 9H); MS(ESI)$^+$ calcd for $C_{34}H_{47}N_7NaO_9Si$ $[M+Na]^+$: 748.3, found: 748.3.



186: (9'S)
187: (9'R)

188

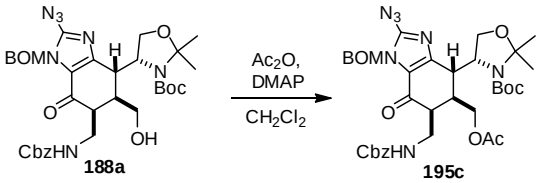
Alcohol 188c. To a solution of lactone **186c** or **187c** (0.324 g, 0.475 mmol, 1.0 equiv) in tetrahydrofuran (30 mL) was added a solution of lithium hydroxide (7.0 mL, 5.0 equiv, 0.34 N in water) at 23 °C. After stirring for 20 min, tetrahydrofuran was then removed

by rotary evaporator and the residue was partitioned between ethyl acetate (50 mL) and brine (30 mL). The organic layer was further washed with saturated sodium bicarbonate (30 mL) and brine (30 mL), dried over sodium sulfate, filtered and concentrated to afford **188c** as a colorless solid (279 mg, 90% crude yield), which was used directly for the next step without purification. R_f = 0.39 (50% ethyl acetate–hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, 50 °C) δ 7.36–7.23 (m, 5H), 5.64 (d, *J* = 10.4 Hz, 1H), 5.48 (d, *J* = 10.4 Hz, 1H), 5.21 (brs, 1H), 4.68 (d, *J* = 8.9 Hz, 1H), 4.62 (s, 2H), 4.10 (dd, *J* = 10.2, 4.9 Hz, 1H), 3.83 (dd, *J* = 8.9, 4.9 Hz, 1H), 3.74 (dd, *J* = 10.9, 3.9 Hz, 1H), 3.70–3.61 (m, 1H), 3.60–3.51 (m, 1H), 3.51–3.42 (m, 1H), 3.38 (t, *J* = 9.7 Hz, 1H), 3.34 (d, *J* = 10.2 Hz, 1H), 2.48–2.39 (m, 1H), 2.35 (t, *J* = 7.5 Hz, 1H), 1.64 (s, 3H), 1.59 (s, 3H), 1.55 (s, 9H), 1.46 (s, 9H); MS(ESI)$^+$ calcd for $C_{32}H_{45}N_7NaO_8$ $[M+Na]^+$: 678.3, found: 678.3.

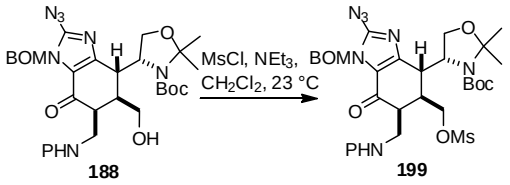
188a. Lactone **186a** was converted to alcohol **188a** following the procedure mentioned above. R_f = 0.36 (50% ethyl acetate–hexanes). ^{1}H NMR (600 MHz, $CDCl_3$, 50 °C) δ 7.44 – 7.16 (m, 10H), 5.63 (d, *J* = 10.4 Hz, 1H), 5.44 (d, *J* = 10.4 Hz, 1H), 5.09 (s, 2H), 4.68 (d, *J* = 8.7 Hz, 1H), 4.60 (s, 2H), 4.07 (dd, *J* = 10.4, 4.9 Hz, 1H), 3.81 (dd, *J* = 9.0, 4.9 Hz, 1H), 3.76 – 3.71 (m, 1H), 3.69 (dd, *J* = 10.8, 4.0 Hz, 1H), 3.58 (brs, 1H), 3.50 (brs, 2H), 3.36 (t, *J* = 9.8 Hz, 1H), 3.32 (d, *J* = 10.4 Hz, 1H), 2.45 – 2.39 (m, 1H), 1.61 (s, 3H), 1.56 (s, 3H), 1.44 (s, 9H); MS(ESI)$^+$ calcd for $C_{35}H_{43}N_7NaO_8$ $[M+Na]^+$: 712.3, found: 712.3.

188b. Lactone **186b** was converted to alcohol **188b** following the procedure mentioned above. R_f = 0.48 (50% ethyl acetate–hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ

7.41 – 7.17 (m, 5H), 5.64 (d, *J* = 10.4 Hz, 1H), 5.47 (d, *J* = 10.4 Hz, 1H), 4.69 (d, *J* = 8.7 Hz, 1H), 4.62 (s, 2H), 4.20 – 4.05 (m, 4H), 3.83 (dd, *J* = 9.0, 4.9 Hz, 1H), 3.77 – 3.64 (m, 1H), 3.72 (dd, *J* = 10.8, 4.1 Hz, 1H), 3.63 – 3.55 (m, 1H), 3.52 (d, *J* = 10.2 Hz, 1H), 3.39 (t, *J* = 9.6 Hz, 1H), 3.33 (d, *J* = 10.2 Hz, 1H), 2.44 (dt, *J* = 8.6, 4.1 Hz, 1H), 1.64 (s, 3H), 1.59 (s, 3H), 1.55 (s, 9H), 1.26 (t, *J* = 7.1 Hz, 2H), 0.05 (s, 9H).



195c. To a solution of **188a** (2 mg, 0.0028 mmol, 1.0 equiv) in methylene chloride (0.2 mL) were added acetic anhydride (0.40 μL, 0.0042 mmol, 1.5 equiv) and 4-dimethylaminopyridine (0.68 mg, 0.0056 mmol, 2.0 equiv). The reaction was stirred for 30 min before the solvent was removed and the residue was partitioned between ethyl acetate (2 mL) and aqueous hydrochloric acid (0.1 N, 1 mL). The organic layer was then washed with saturated sodium bicarbonate (1 mL), brine (1 mL), dried over sodium sulfate and concentrated to afford crude acetate **195c** as a white solid, which was used for the next step without purification. R_f = 0.58 (50% ethyl acetate–hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, 50 °C) δ 7.42 – 7.19 (m, 10H, shielded by solvent), 5.65 (d, *J* = 10.4 Hz, 1H), 5.44 (d, *J* = 10.4 Hz, 1H), 5.11 (s, 2H), 4.70 (d, *J* = 8.9 Hz, 1H), 4.63 (s, 2H), 4.12 – 4.05 (m, 2H), 3.87 – 3.73 (m, 3H), 3.63 (brs, 1H), 3.51 (brs, 1H), 3.15 (d, *J* = 10.5 Hz, 1H), 2.64 (dt, *J* = 8.8, 4.3 Hz, 1H), 1.94 (s, 3H), 1.63 (s, 3H), 1.58 (s, 3H), 1.48 (s, 9H); MS(ESI)$^+$ calcd for $C_{37}H_{45}N_7NaO_9$ $[M+Na]^+$: 754.3, found: 754.2.



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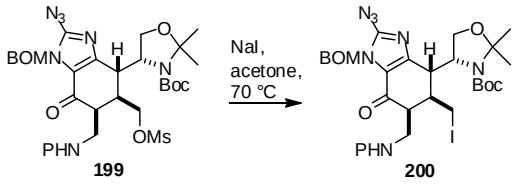
Mesylate 199c. To a solution of crude alcohol **188c** (279 mg, 0.426 mmol, 1.0 equiv) obtained above in anhydrous methylene chloride (3.0 mL) was added triethylamine (180 μL, 1.28 mmol, 3.0 equiv) followed by methanesulfonyl chloride (66 μL, 0.854 mmol, 2.0 equiv). After stirring at 23 °C for 30 min, the solvent was removed and the residue was dissolved in ethyl acetate (10 mL), washed with aqueous hydrogen chloride (8 mL, 0.1 N), saturated aqueous sodium bicarbonate (5 mL), brine (5 mL), dried over sodium sulfate, filtered and concentrated to afford the mesylate **199c** as a colorless solid. This crude product was used directly for the next step without purification. R_f = 0.40 (50% ethyl acetate–hexanes); ^{1}H NMR (500 MHz,$CDCl_3$, 50 °C) δ 7.32–7.22 (m, 5H), 5.63 (d, J = 10.3 Hz, 1H), 5.46 (d, J = 10.3 Hz, 1H), 5.15 (s, 1H), 4.70 (d, J = 9.0 Hz, 1H), 4.64 (s, 2H), 4.30 (dd, J = 10.0, 3.8 Hz, 1H), 4.07 (dd, J = 10.5, 4.9 Hz, 1H), 3.93 (t, J = 10.0 Hz, 1H), 3.82 (dd, J = 9.0, 4.9 Hz, 1H), 3.68 (s, 2H), 3.49 (s, 1H), 3.25 (d, J = 10.5 Hz, 1H), 2.90 (s, 3H), 2.81–2.69 (m, 1H), 1.65 (s, 3H), 1.59 (s, 3H), 1.55 (s, 9H), 1.45 (s, 9H); MS(ESI)$^+$ calcd for $C_{33}H_{47}N_7NaO_{10}S$ $[M+Na]^+$: 756.3, found: 756.3.

199a. Alcohol **188a** was converted to mesylate **199a** following the procedure mentioned above. R_f = 0.56 (50% ethyl acetate–hexanes); MS(ESI)$^+$ calcd for $C_{36}H_{45}N_7NaO_{10}S$ $[M+Na]^+$: 790.3, found: 790.2.

199b. Alcohol **188b** was converted to mesylate **199b** following the procedure mentioned above. R_f = 0.55 (50% ethyl acetate–hexanes).

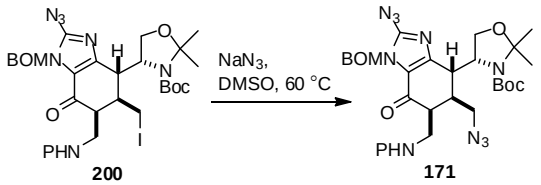


Iodide 200c. The crude mesylate **199c** obtained above was dissolved in acetone (12 mL) and sodium iodide (3.18 g, 21.2 mmol, 50 equiv) was added. After stirring at 70 °C for 2.5 h, the solvent was removed. The residue was suspended in chloroform (30 mL) and the solid was filtered off to remove most of the excess sodium iodide. After removing the solvent, the residue was dissolved in ethyl acetate (10 mL), washed with brine (5 mL×5), dried over sodium sulfate, filtered and concentrated to afford **200c** as a white solid. This crude product was used directly for the next step without purification. MS(ESI)$^+$ calcd for $C_{32}H_{44}IN_7NaO_7$ $[M+Na]^+$: 788.2, found 788.2.

200a. Mesylate **199a** was converted to iodide **200a** following the procedure mentioned above, and used without purification. ^{1}H NMR (600 MHz, $CDCl_3$, 50 °C) δ 7.42 – 7.17 (m, 10H), 5.61 (d, J = 10.4 Hz, 1H), 5.47 (d, J = 10.4 Hz, 1H), 5.12 (t, J = 10.5 Hz, 2H), 4.73 (d, J = 9.1 Hz, 1H), 4.64 (s, 2H), 4.04 (dd, J = 10.6, 5.0 Hz, 1H), 3.80 (dd, J = 9.1, 5.1 Hz, 1H), 3.76 (d, J = 12.0 Hz, 1H), 3.59 (brs, 2H), 3.43 (d, J = 10.4 Hz, 2H), 2.75 (t, J = 10.6 Hz, 1H), 2.65 (d, J = 11.8 Hz, 1H), 1.75 (s, 3H), 1.57 (s, 3H), 1.41 (s, 9H);

MS(ESI)$^+$ calcd for $C_{35}H_{42}IN_7NaO_7$ $[M+Na]^+$: 822.2, found: 822.1.

200b. Mesylate **199b** was converted to iodide **200b** following the procedure mentioned above, and used without purification; MS(ESI)$^+$ calcd for $C_{33}H_{48}IN_7NaO_7Si$ $[M+Na]^+$: 832.2, found: 832.2.

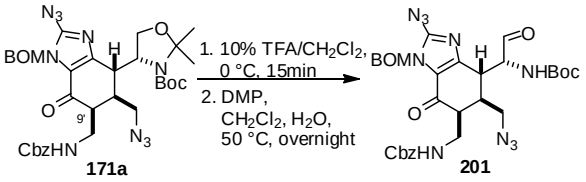


Azide 171c. The crude iodide **200c** obtained above was dissolved in anhydrous dimethyl sulfoxide (2.0 mL), then sodium azide (138 mg, 2.12 mmol, 5 equiv) was added and the reaction was heated to 60 °C for 2 h. After the solvent was removed under high vacuum, the residue was dissolved in ethyl acetate (10 mL), washed with brine (5 mL×2), dried over sodium sulfate, filtered, concentrated and purified by preparative HPLC (Waters Atlantis dC18 OBD, 19×150 mm, 5 μm, eluent A: water, eluent B: acetonitrile, gradient: T = 0 min: 70% B, T = 40 min: 100% B, 5.0 mL/min)to afford the azide **171c** as a colorless solid. (117 mg, 36% yield from lactone **172** over four steps, retention time: 28.8 min). R_f = 0.76 (50% ethyl acetate–hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.15 (m, 5H), 5.63 (d, J = 10.5 Hz, 1H), 5.46 (d, J = 10.5 Hz, 1H), 5.21 (d, J = 7.9 Hz, 1H), 4.69 (d, J = 9.1 Hz, 1H), 4.63 (s, 2H), 4.04 (dd, J = 10.6, 4.8 Hz, 1H), 3.80 (dd, J = 9.1, 4.8 Hz, 1H), 3.67 (brd, J = 13.9 Hz, 1H), 3.60 (m, 1H), 3.54 (dd, J = 11.7, 2.9 Hz, 1H), 3.48–3.34 (m, 1H), 3.23 (d, J = 10.6 Hz, 1H), 2.84 (t, J = 11.7 Hz, 1H), 2.53–2.39

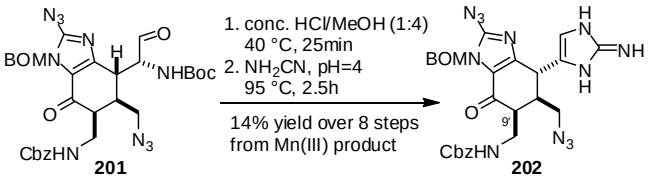
(m, 1H), 1.66 (s, 3H), 1.58 (s, 3H), 1.54 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.8, 156.4, 154.4, 151.9, 147.5, 137.4, 128.5, 128.0, 127.4, 124.0, 94.5, 81.3, 79.4, 73.1, 72.1, 65.7, 58.2, 49.5, 44.8, 41.1, 38.9, 37.3, 28.8, 28.6, 28.0, 24.8; MS(ESI)$^+$ calcd for $C_{32}H_{44}N_{10}NaO_7$ $[M+Na]^+$: 703.3, found: 703.3.

171a. Iodide **200a** was converted to azide **171a** following the procedure mentioned above, and used without purification. R_f = 0.71 (50% ethyl acetate–hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 – 7.16 (m, 10H, shielded by solvent), 5.63 (d, *J* = 10.4 Hz, 1H), 5.47 (d, *J* = 10.4 Hz, 1H), 5.18 – 5.01 (m, *J* = 7.6, 5.9 Hz, 2H), 4.71 (d, *J* = 9.6 Hz, 1H), 4.64 (s, 2H), 4.05 (dd, *J* = 10.7, 5.0 Hz, 1H), 3.80 (dd, *J* = 9.2, 4.9 Hz, 1H), 3.74 (d, *J* = 13.8 Hz, 1H), 3.68 – 3.59 (m, 1H), 3.52 (d, *J* = 12.4 Hz, 2H), 3.23 (d, *J* = 10.5 Hz, 1H), 2.89 (t, *J* = 11.6 Hz, 1H), 2.47 (dd, *J* = 10.1, 4.7 Hz, 1H), 1.65 (s, 3H), 1.58 (s, 3H), 1.43 (s, 7H); MS(ESI)$^+$ calcd for $C_{35}H_{42}N_{10}NaO_7$ $[M+Na]^+$: 737.3, found: 737.3.

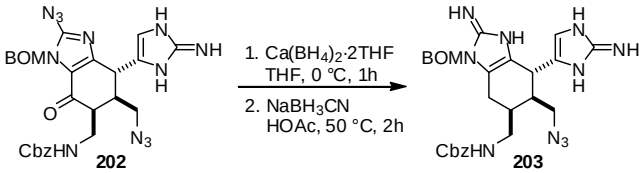
171b. Iodide **200b** was converted to azide **171b** following the procedure mentioned above. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.18 (m, 5H), 5.63 (d, *J* = 10.4 Hz, 1H), 5.48 (d, *J* = 10.4 Hz, 1H), 5.30 (brs, 1H), 4.72 (d, *J* = 9.1 Hz, 1H), 4.64 (s, 2H), 4.21 – 4.14 (m, 2H), 4.07 (dd, *J* = 10.5, 4.9 Hz, 1H), 3.81 (dd, *J* = 9.1, 4.9 Hz, 1H), 3.69 (d, *J* = 14.1 Hz, 1H), 3.62 (brs, 1H), 3.52 (d, *J* = 14.0 Hz, 2H), 3.24 (d, *J* = 10.5 Hz, 1H), 2.91 (t, *J* = 11.7 Hz, 1H), 2.49 (dt, *J* = 9.0, 3.9 Hz, 1H), 1.67 (s, 3H), 1.59 (s, 3H), 1.56 (s, 9H), 0.99 (t, *J* = 8.6 Hz, 2H), 0.05 (s, 9H); MS(ESI)$^+$ calcd for $C_{33}H_{48}N_{10}NaO_7Si$ $[M+Na]^+$: 747.3, found: 747.3.



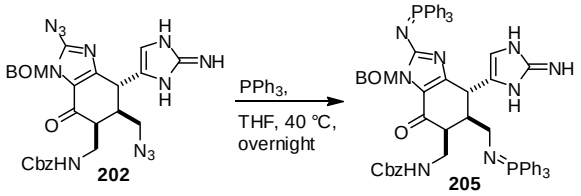
Aldehyde 201. To a solution of crude **171a** (69.0 mg, 0.0966 mmol, 1.0 equiv) in methylene chloride (0.3 mL) were added trifluoroacetic acid (20% in methylene chloride, 0.35 mL) and water (1.80 mg, 1.0 equiv)at 0 °C. The reaction was neutralized with saturated sodium bicarbonate (2 mL) after 1 h, and then diluted with ethyl acetate (5 mL). The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated to afford the crude alcohol as a colorless powder. It was used for the next step without purification. R_f = 0.40 (50% ethyl acetate–hexanes). The crude alcohol obtained above was dissolved in anhydrous methylene chloride (1.0 mL), and Dess–Martin periodinane (123 mg, 0.290 mmol, 3 equiv) was added to the solution at 23 °C followed by water (1.74 mg, 0.0966 mmol, 1.0 equiv). The reaction was heated to 50 °C for 19 h, and then an aqueous solution of 10% sodium thiosulfate/saturated sodium bicarbonate (1:1 v/v, 5 mL) was added. After stirring for another 10 min, the biphasic mixture was extracted with ethyl acetate (3 mL×3), and the organic phase was washed with saturated sodium bicarbonate (2 mL×2), dried over sodium sulfate, filtered, and concentrated to afford crude aldehyde **201** as a white powder. **201** was used directly for the next step without purification. MS(ESI)$^+$ calcd for $C_{32}H_{36}N_{10}NaO_7$ $[M+Na]^+$: 695.3, found: 695.2.



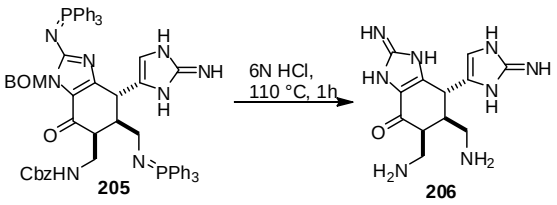
Amidazolinone 202. The aldehyde **201** obtained above was separated to two batches. To a methanol solution (4.0 mL) of half of the crude **201** at 0 °C was added cold aqueous hydrogen chloride (12 N, 1.0 mL). The solution was stirred at 40 °C for 20 min. With the solution cooled in an ice-water bath, the pH of the solution was then adjusted to 4.0 by adding aqueous sodium hydroxide (3.0 N). Cyanamide (43 mg, 20 equiv) was then added and the reaction was heated at 95 °C for 160 min. The two batches of the reaction were combined. After removal of most of the methanol, the mixture was partitioned between ethyl acetate and water. The organic layer was washed with saturated sodium bicarbonate and brine, dried over anhydrous sodium sulfate, filtered, concentrated, and then purified by HPLC (Waters Atlantis dC18 OBD, 19×150 mm, 5 μm, eluent A: water with 0.1% trifluoroacetic acid, eluent B: acetonitrile with 0.1% trifluoroacetic acid, gradient: T = 0 min: 40% B, T = 3 min: 40% B, T = 30 min: 60% B, 5.0 mL/min) to afford aminoimidazole **202** as a white solid (11.7 mg, 14% yield over 8 steps from **113b**, retention time: 19.8min). ^{1}H NMR (400 MHz, Methanol-d4) δ 7.40 – 7.12 (m, 10H), 6.42 (s, 1H), 5.66 – 5.44 (m, 2H), 5.03 (s, 2H), 4.73 – 4.53 (m, 2H), 4.22 (d, *J* = 5.0 Hz, 1H), 3.64 (ddd, *J* = 21.6, 13.5, 6.3 Hz, 2H), 3.46 – 3.34 (m, 2H), 3.00 (td, *J* = 6.6, 3.4 Hz, 1H), 2.73 – 2.56 (m, 1H); MS(ESI)$^+$ calcd for $C_{28}H_{29}N_{12}O_4$ $[M+H]^+$: 597.2, found: 597.2.



Aminoimidazole 203. To a solution of the aminoimidazole **202** (4.9 mg, 0.0069 mmol, 1.0 equiv) in tetrahydrofuran (0.4 mL) at 0 °C was added calcium borohydride bis(tetrahydrofuran) (7.4 mg, 0.034 mmol, 5.0 equiv). The reaction was stirred at 0 °C for 1 h before concentrated to dryness. The crude was kept at 0°C, and a solution of sodium cyanoborohydride (2.2 mg, 0.034 mmol, 5.0 equiv) in acetic acid (0.3 mL) was added. The reaction was then stirred at 50 °C for 2 h before concentrating and re-dissolving in ethyl acetate. The organic phase was washed with aqueous hydrogen chloride solution (1 N), saturated sodium bicarbonate, and brine, dried over anhydrous sodium sulfate, concentrated and purified by HPLC (Eclipse XDB-C18, 9.4×250 mm, 5 μm, eluent A: water with 0.1% trifluoroacetic acid, eluent B: methanol with 0.1% trifluoroacetic acid, gradient: T = 0 min: 40% B, T = 40 min: 80% B, 3.5 mL/min) to give aminoimidazole **203** (2.0 mg, 41% yield over 2 steps, retention time: 19.5 min) as a white solid. ^{1}H NMR (500 MHz, Methanol-d4) δ 7.44 – 7.20 (m, 10H), 6.38 (s, 1H), 5.31 (s, 2H), 5.12 – 5.01 (m, 2H), 4.71 – 4.60 (m, 2H), 3.96 (s, 1H), 3.66 (dd, *J* = 12.4, 4.9 Hz, 1H), 3.23 (dd, *J* = 22.6, 6.9 Hz, 2H), 3.18 (d, *J* = 6.4 Hz, 1H), 2.62 (dd, *J* = 15.0, 3.5 Hz, 1H), 2.33 – 2.08 (m, 3H); MS(ESI)$^+$ calcd for $C_{28}H_{33}N_{10}O_3$ $[M+H]^+$: 557.3, found: 557.3.

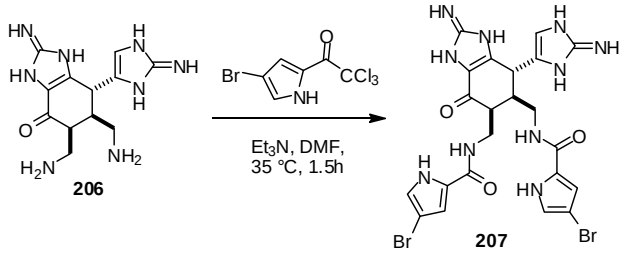


Phosphine Imide 205. To a solution of aminoimidazole **202** (0.5 mg, 0.0007 mmol, 1.0 equiv) was added triphenylphosphine (0.4mg, 0.0015 mmol, 2.2 equiv). The reaction was heated to 40 °C for 12 h before solvent was removed. The crude was used for the next step without purification. MS(ESI)$^+$ calcd for $C_{64}H_{59}N_8O_4P_2$ $[M+H]^+$: 1065.4, found: 1065.3.



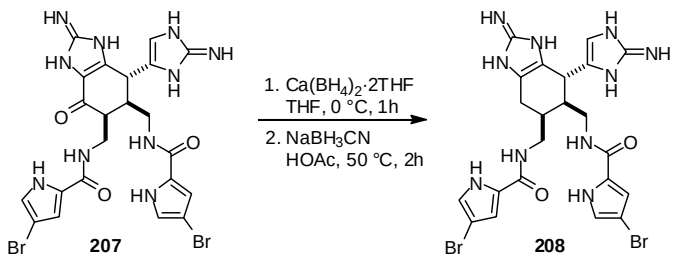
Bis-aminoimidazole 206. The crude **205** obtained above was dissolved in aqueous hydrochloric acid (6.0 N, 0.2 mL) and heated to 110 °C for 1 h. After the solvent was removed, the residue was dissolved in hydrochloric acid (0.2 mL, 1.0 N) and washed with benzene (0.2 mL × 2). The aqueous phase was concentrated and passed through a short C-18 silica gel column to remove triphenylphosphine oxide and triphenylphosphine (10% methonal in 0.1 N HCl). Then 60% of the crude was purified by HPLC (Eclipse XDB-C18, 9.4×250 mm, 5 μm, eluent A: water with 0.1% trifluoroacetic acid, eluent B: methanol with 0.1% trifluoroacetic acid, gradient: T = 0 min: 1% B, T = 5 min: 1% B, 4.8 mL/min), and aminoimidazole **206** (0.3 mg, retention time: 3.0 min) was afforded as a white solid. ^{1}H NMR (600 MHz, DMSO-d6, wet1d) δ 11.93 (s, 1H), 11.79 (s, 1H), 7.79

(brs, 3H), 7.72 (brs, 3H), 7.48 (s, 2H), 7.40 (s, 1H), 6.56 (brs, 1H), 4.24 (s, 1H), 2.95 (brs, 2H), 2.89 (d, J = 9.9 Hz, 2H), 2.71 (t, J = 10.4 Hz, 1H), one proton is missing due to solvent suppression. MS(ESI)$^+$ calcd for $C_{12}H_{19}N_8O$ $[M+H]^+$: 291.2, found: 291.2.



206 207

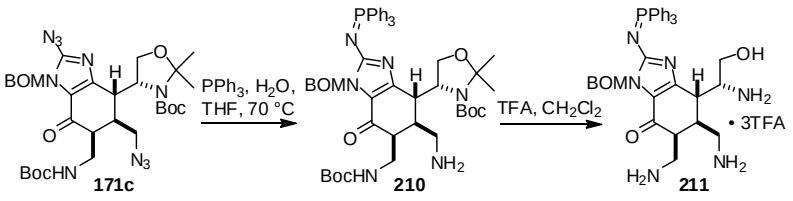
Acylpyrrole 207. The aminoimidazole **206** obtained above was separated to two batches. To a solution of **206** (0.15mg, 0.00021 mmol, 1.0 equiv) in DMF (0.2 mL) were added 4-bromo-2-(trichloroacetyl)pyrrole (0.37 mg, 0.0013 mmol, 6.0 equiv) and triethylamine (0.59 µL, 0.0042 mmol, 20 equiv), and stirred for 1.5 h at 35 °C. The two batches were combined and the solvent was removed. The residue was dissolved in aqueous trifluoroacetic acid (1% v/v, 0.8 mL), then centrifuged and white precipitate was removed. After the solvent was removed, crude **207** was obtained as a mixture of two diastereomers/regioisomers and containing 30% mono-acylation product. MS(ESI)$^+$ calcd for $C_{22}H_{23}Br_2N_{10}O_3$ $[M+H]^+$: 633.0, found: 633.0.



207 208

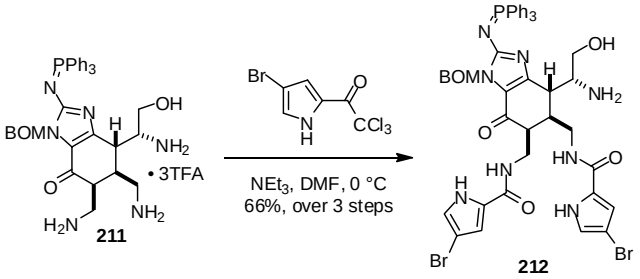
C9'-*epi*-agelifrein 208. To a solution of the crude acylpyrrole **207** (0.3 mg, 0.0042 mmol, 1.0 equiv) in tetrahydrofuran (0.2 mL) at 0 °C was added calcium borohydride bis(tetrahydrofuran) (0.45 mg, 0.0021 mmol, 5.0 equiv). The reaction was stirred at 0 °C for 1 h before quenched with aqueous trifluoroacetic acid (10% v/v, 13 μL, 40 equiv) and concentrated to dryness. The crude was used for the next step without purification. MS(ESI)$^+$ calcd for $C_{22}H_{25}Br_2N_{10}O_3$ $[M+H]^+$: 635.0, found: 635.0.

With the residue obtained above kept at 0°C, a solution of sodium cyanoborohydride (0.13 mg, 0.0021 mmol, 5.0 equiv) in acetic acid (0.2 mL) was added. The reaction was then stirred at 50 °C for 2 h before the solvent was removed. The residue was dissolve in aqueous trifluoracetic acid (2% v/v, 0.2 mL) and then the solvent was removed to afford crude **208** as a white solid. MS(ESI)$^+$ calcd for $C_{22}H_{25}Br_2N_{10}O_2$ $[M+H]^+$: 619.0, found: 619.0. The structure was not able to be confirmed by NMR.



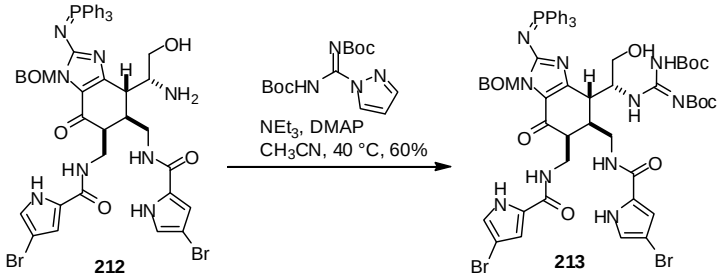
Triamine 211. To a 4 mL vial charged with azide **171c** (117 mg, 0.172 mmol, 1.0 equiv) and triphenylphosphine (112 mg, 0.427 mmol, 2.5 equiv) was added tetrahydrofuran (2.0 mL) and water (0.50 mL). The reaction was heated to 70 °C overnight. The solvent was then removed by rotary evaporator and the residue was partitioned between ethyl acetate (10 mL) and brine (5 mL). The organic layer was separated, dried over sodium sulfate,

filtered and concentrated. The residue was dissolved in methylene chloride (1 mL), and a methylene chloride solution of trifluoroacetic acid (2.0 mL, 20% v/v) was added. The reaction was stirred for 2 h before anhydrous toluene (1 mL) was added and the solvent was removed. The residue was then taken up in ethyl acetate (1 drop) and ether (3 mL) and sonicated to crash out **211** as a white solid. The solid was collected and washed with ether (10 mL) to afford crude **211** as a white powder (160 mg, 94% crude yield as calculated as a tris(trifluoroacetate) salt), which was used directly for the next step without purification. MS(ESI)$^+$ calcd for $C_{37}H_{42}N_6O_3P$ $[M+H]^+$: 649.3, found: 649.3.



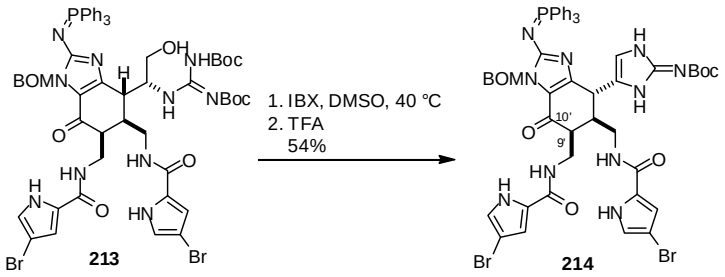
Aminoalcohol 212. To a 4 mL amber vial charged with triamine **211** (160 mg, 0.162 mmol, 1.0 equiv) was added *N*,*N*-dimethylformamide (1.0 mL) and cooled to 0 °C. 4-Bromo-2-(trichloroacetyl)pyrrole (47.1 mg, 0.162 mmol, 1.0 equiv) was then added and the reaction was stirred for 1 h at 0 °C before another portion of 4-bromo-2-(trichloroacetyl)pyrrole (33.0 mg, 0.113 mmol, 0.7 equiv) was added. The reaction was stirred at 0 °C for another 1 h before the solvent was removed under high vacuum at the same temperature. The crude mixture was purified by preparative HPLC (Waters Atlantis dC18 OBD, 19×150 mm, 5 μm, eluent A: water with 0.1% trifluoroacetic acid, eluent B: acetonitrile with 0.1% trifluoroacetic acid, gradient: T = 0 min: 35% B, T = 30 min: 80% B, 5.0 mL/min) to afford **212** as a white powder (126 mg, 66% yield from

azide **171c** over three steps and as calculated as a mono(trifluoroacetate) salt, retention time: 21.4 min). R_f = 0.26 (10% methanol–methylene chloride); ^{1}H NMR (400 MHz, CD_3OD) δ 7.89–7.72 (m, 9H), 7.72–7.59 (m, 6H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.04 (t, *J* = 7.4 Hz, 2H), 6.99–6.93 (m, 3H), 6.93–6.86 (m, 2H), 6.71 (s, 1H), 5.87 (d, *J* = 10.4 Hz, 1H), 5.78 (d, *J* = 10.4 Hz, 1H), 4.73 (d, *J* = 13.2 Hz, 1H), 4.64 (d, *J* = 13.2 Hz, 1H), 3.78 (dd, *J* = 14.0, 8.4 Hz, 1H), 3.64 (dd, *J* = 14.0, 4.5 Hz, 1H), 3.45 (dd, *J* = 14.3, 4.7 Hz, 1H), 3.36 (brd, *J* = 9.5 Hz, 1H), 3.31 (1H, shielded by CD_3OD), 3.23 (s, 1H), 3.18 (dd, *J* = 9.2, 2.1 Hz, 1H), 3.07–2.95 (m, 2H), 2.67–2.58 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 187.5, 162.78, 162.77, 162.0, 161.6, 139.8, 135.13, 135.11, 133.9, 133.8, 130.9, 130.7, 129.4, 128.6, 127.9, 127.6, 127.2, 127.0, 126.5, 123.2 (two carbons), 122.3, 113.9 (two carbons), 97.7, 97.6, 74.4, 73.0, 60.6, 53.6, 47.1, 42.6, 39.0, 38.7, 37.1; MS(ESI)$^+$ calcd for $C_{47}H_{46}Br_2N_8O_5P$ $[M+H]^+$: 991.2, found: 991.2.



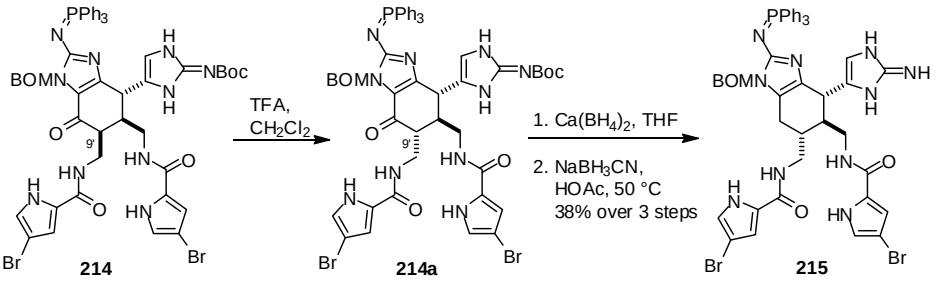
Guanidine 213. To a 4 mL amber vial charged with amine **212** (126 mg, 0.114 mmol, 1.0 equiv), *N*,*N*'-di-Boc-1*H*-pyrazole-1-carboxamidine (106 mg, 0.342 mmol, 3.0 equiv) and 4-dimethylaminopyridine (2.8 mg, 0.023 mmol, 0.2 equiv) were added acetonitrile (1.0 mL) and triethylamine (95 μL, 0.68 mmol, 6.0 equiv), and then heated to 40 °C for 24 h. After the solvent was removed, the residue was purified by preparative HPLC

(Waters Atlantis dC18 OBD, 19×150 mm, 5 μm, eluent A: water, eluent B: acetonitrile, gradient: T = 0 min: 60% B, T = 30 min: 100% B, 5.0 mL/min) to afford guanidine **213** as a white powder (84.1 mg, 60% yield, retention time: 30.1 min). R_f = 0.32 (50% ethyl acetate–hexanes); ^{1}H NMR (400 MHz, $CDCl_3$, 40 °C) δ 11.11 (s, 1H), 10.37 (s, 1H), 10.32 (s, 1H), 8.56 (s, 1H), 7.68 (dd, *J* = 12.3, 7.7 Hz, 6H), 7.56 (t, *J* = 7.2 Hz, 3H), 7.52–7.38 (m, 6H), 7.21 (s, 5H), 6.80 (s, 1H), 6.72 (s, 1H), 6.59 (s, 1H), 6.50 (s, 1H), 5.80 (s, 2H), 4.71 (s, 2H), 4.18 (t, *J* = 8.6 Hz, 1H), 3.84 (brs, 2H), 3.44–3.17 (m, 4H), 3.06 (d, *J* = 11.5 Hz, 1H), 2.99 (d, *J* = 7.9 Hz, 1H), 2.34 (brs, 1H), 1.41 (s, 9H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, 40 °C) δ 184.2, 163.2, 160.7, 160.6, 157.5, 156.1, 152.8, 152.4, 138.7, 132.8, 132.7, 129.0, 128.9, 128.3, 127.4, 127.1, 126.3, 126.0, 121.6, 121.2, 111.9, 111.8, 96.8, 96.7, 83.4, 79.5, 72.5, 70.7, 63.2, 52.3, 45.1, 40.8, 40.6, 39.3, 37.5, 28.3, 27.9; MS(ESI)$^+$ calcd for $C_{58}H_{64}Br_2N_{10}O_9P$ $[M+H]^+$: 1233.3, found: 1233.2.



Aminoimidazole 214. To a 4 mL amber vial charged with guanidine **213** (27.7 mg, 0.0224 mmol, 1.0 equiv) and 2-iodoxybenzoic acid (18.8 mg, 0.0671 mmol, 3.0 equiv) was added anhydrous dimethyl sulfoxide (0.40 mL). The reaction was heated to 40 °C for 5 h before trifluoroacetic acid (0.86 μL, 0.011 mmol, 0.5 equiv) was added and the reaction was stirred for another 5 h at the same temperature. The reaction mixture was

directly purified by preparative HPLC (Waters Atlantis dC18 OBD, 19×150 mm, 5 μm, eluent A: water with 0.1% trifluoroacetic acid, eluent B: methanol with 0.1% trifluoroacetic acid, gradient: T = 0 min: 70% B, T = 15 min: 85% B, 5.0 mL/min) without workup to afford **214** as a white powder (13.6 mg, 54% yield, retention time: 17.5 min). ^{1}H NMR (400 MHz, CD_3OD) δ 7.87–7.48 (m, 16H), 7.32–7.06 (m, 5H), 6.91 (t, *J* = 1.6 Hz, 2H), 6.78 (d, *J* = 1.5 Hz, 1H), 6.70 (d, *J* = 1.5 Hz, 1H), 5.76 (d, *J* = 10.2 Hz, 1H), 5.74 (d, *J* = 10.2 Hz, 1H), 4.67 (s, 2H), 4.37 (d, *J* = 2.7 Hz, 1H, H10), 3.88 (dd, *J* = 13.7, 7.1 Hz, 1H, H8'), 3.67 (m, 1H, H8'), 3.64 (dd, *J* = 14.2, 4.4 Hz, 1H, H8), 3.55 (dd, *J* = 14.2, 7.2 Hz, 1H, H8), 3.08 (brs, 1H), 2.71 (brs, 1H, H9), 1.56 (s, 9H); ^{13}C NMR (100 MHz, CD_3OD) δ 187.6(C10'), 162.8(C6), 162.7(C6'), 161.9(C13'), 161.6(C15'), 152.7(Boc), 142.0(C13), 139.2(Bn), 135.16(PPh_3), 135.14(PPh_3), 133.8(PPh_3), 133.7(PPh_3), 130.9(PPh_3), 130.7(PPh_3), 129.5(Bn), 128.9(Bn), 128.2(Bn), 127.8(Bn), 127.3(C11), 127.2(C5), 127.1(C5'), 126.3(C15), 123.2 (C2), 123.1(C2'), 122.6(C11'), 113.8(C4), 113.6(C4'), 97.62(C3), 97.56(C3'), 85.0(Boc), 74.0(BOM), 72.5(Bn), 45.7(C9), 39.2(C8), 37.6(C8'), 34.3(C10), 28.2(Boc); MS(ESI)$^{+}$ calcd for $C_{53}H_{52}Br_2N_{10}O_6P$ $[M+H]^{+}$: 1113.2, found: 1113.1.

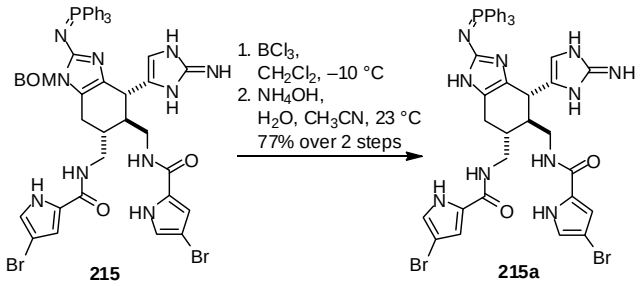


Aminoimidazole 214a. To a 4 mL amber vial charged with aminoimidazole **214** (12.0

mg, 0.0108 mmol, 1.0 equiv) was added a solution of trifluoroacetic acid in methylene chloride (0.40 mL, 20% v/v). This reaction was stirred at 23 °C and the epimerization was monitored by HPLC (Waters Atlantis dC18 OBD, 4.6×150 mm, 5 μm, eluent A: water with 0.1% trifluoroacetic acid, eluent B: acetonitrile with 0.1% trifluoroacetic acid, gradient: T = 0 min: 10% B, T = 7 min: 95% B, 0.8 mL/min; retention time: *cis*-minor 8.30 min, *trans*-major 8.55 min) until equilibrium has been reached, which requires 60–72 h. Toluene (1 mL) was then added and the solvent was removed to afford crude aminoimidazole **214a**, which was used directly for the next step without purification. MS(ESI)$^+$ calcd for $C_{48}H_{44}Br_2N_{10}O_4P$ $[M+H]^+$: 1013.2, found: 1113.1.

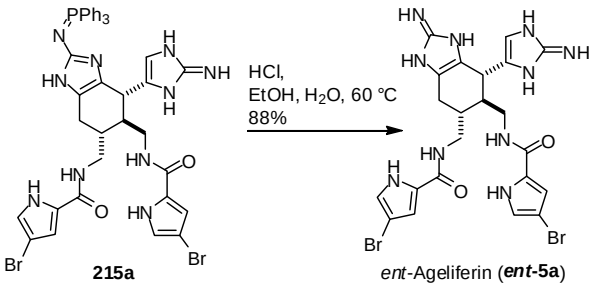
Aminoimidazole 215. To crude **214a** obtained above in tetrahydrofuran (0.40 mL) was added calcium borohydride bis(tetrahydrofuran) (11.0 mg, 0.0514 mmol, 5.0 equiv). The reaction was stirred at 23 °C for 3 h before the solvent was removed. This residue was then dissolved in acetic acid (0.40 mL) and sodium cyanoborohydride (3.5 mg, 0.056 mmol, 5.0 equiv) was added. After heating at 50 °C for 6 h, the solvent was removed and the residue was purified by preparative HPLC (Waters Atlantis dC18 OBD, 19×150 mm, 5 μm, eluent A: water with 0.1% trifluoroacetic acid, eluent B: methanol with 0.1% trifluoroacetic acid, gradient: T = 0 min: 60% B, T = 20 min: 80% B, 5.0 mL/min) to afford **215** as a white powder. (4.5 mg, 38% yield from **214** over three steps and as calculated as a mono(trifluoroacetate) salt, retention time: 24.2 min). ^{1}H NMR (400 MHz, CD_3OD) δ 7.79–7.63 (m, 9H), 7.63–7.52 (m, 6H), 7.15–7.02 (m, 5H), 7.00 (d, *J* = 1.5 Hz, 1H), 6.99 (d, *J* = 1.5 Hz, 1H), 6.96 (d, *J* = 1.5 Hz, 1H), 6.85 (d, *J* = 1.5 Hz, 1H), 6.28 (s, 1H), 5.61 (d, *J* = 11.0 Hz, 1H), 5.41 (d, *J* = 11.0 Hz, 1H), 4.67 (d, *J* = 12.9 Hz, 1H), 4.61

(d, *J* = 12.9 Hz, 1H), 3.74 (dd, *J* = 14.6, 3.8 Hz, 1H), 3.61 (dd, *J* = 14.0, 2.6 Hz, 1H), 3.49 (d, *J* = 6.6 Hz, 1H), 3.44 (dd, *J* = 14.6, 4.5 Hz, 1H), 3.18 (dd, *J* = 13.6, 9.3 Hz, 1H), 2.90 (dd, *J* = 16.4, 4.0 Hz, 1H), 2.48 (ddd, *J* = 16.4, 7.2, 1.8 Hz, 1H), 2.18–2.03 (m, 1H), 2.03–1.92 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 163.2, 163.0, 148.9, 148.1, 138.9, 134.9, 134.9, 133.7, 133.6, 130.7, 130.6, 129.5, 128.8, 128.2, 128.03, 127.98, 127.2, 127.1, 126.9, 124.6, 123.4, 123.2, 118.3, 114.5, 113.7, 112.0, 97.8, 97.7, 73.2, 72.4, 44.3, 42.7, 39.7, 37.0, 32.6, 23.1; MS(ESI)$^+$ calcd for $C_{48}H_{46}Br_2N_{10}O_3P$ $[M+H]^+$: 999.2, found: 999.1.



Aminoimidazole 215a. To a 4 mL amber vial charged with aminoimidazole **215** (3.2 mg, 0.0029 mmol, 1.0 equiv) was added methylene chloride (0.30 mL). The reaction was cooled to –40 °C before a methylene chloride solution of boron trichloride (87.5 µL, 0.0875 mmol, 30 equiv) was added. Then the reaction was warmed to –10 °C and stirred for 20 min. An acetonitrile solution of concentrated aqueous ammonium hydroxide (0.200 mL, 1:4 v/v) was then added and the reaction was stirred for another 30 min at 23 °C. After the solvent was removed, the residue was purified by HPLC (Eclipse XDB-C18, 9.4×250 mm, 5 µm, eluent A: water with 0.1% trifluoroacetic acid, eluent B: acetonitrile with 0.1% trifluoroacetic acid, gradient: T = 0 min: 30% B, T = 10 min: 50%

B, 4.8 mL/min) to afford **215a** as a white powder (2.2 mg, 77% yield as calculated as a mono(trifluoroacetate) salt, retention time: 11.4 min). ^{1}H NMR (400 MHz, CD_3OD) δ 7.69–7.59 (m, 9H), 7.59–7.51 (m, 6H), 6.97 (d, *J* = 1.5 Hz, 1H), 6.94 (d, *J* = 1.5 Hz, 1H), 6.93 (d, *J* = 1.5 Hz, 1H), 6.83 (d, *J* = 1.5 Hz, 1H), 6.78 (s, 1H), 3.81 (d, *J* = 7.6 Hz, 1H), 3.77 (dd, 14.4, 4.2 Hz, 1H), 3.67 (dd, *J* = 13.8, 3.3 Hz, 1H), 3.50 (dd, *J* = 14.4, 4.9 Hz, 1H), 3.35 (1H), 2.77 (dd, *J* = 16.0, 5.2 Hz, 1H), 2.46 (ddd, *J* = 16.0, 7.7, 2.4 Hz, 1H), 2.33–2.18 (m, 1H), 2.19–2.07 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 163.2, 162.9, 149.3, 149.2, 133.80, 133.77, 133.1, 133.0, 130.0, 129.9, 127.5, 127.2, 127.1, 123.3, 123.1, 122.8, 119.1, 114.2, 113.6, 113.0, 97.7, 97.6, 44.1, 42.8, 40.0, 37.2, 33.3, 23.7; MS(ESI)$^{+}$ calcd for $C_{40}H_{38}Br_2N_{10}O_2P$ $[M+H]^{+}$: 879.1, found: 879.0.



***ent*-Ageliferin (*ent*-5a).** To a 1.8 mL amber vial charged with aminoimidazole **202a** (4.5 mg, 0.0045 mmol, 1.0 equiv) was added ethanol (50 μL) and aqueous HCl (50 μL, 0.20 N). The reaction was heated at 60 °C for 6 h and purified directly by HPLC (Eclipse XDB-C18, 9.4×250 mm, 5 μm, eluent A: water with 0.1% trifluoroacetic acid, eluent B: acetonitrile with 0.1% trifluoroacetic acid, gradient: T = 0 min: 20% B, T = 8 min: 40% B, 4.8 mL/min) without workup to afford ***ent*-5** as a white powder (3.4 mg, 88% yield as calculated as a bis(trifluoroacetate) salt, retention time: 8.5 min). ^{1}H NMR (600 MHz,

CD_3OD) δ 6.97 (dd, *J* = 1.5, 0.7 Hz, 1H), 6.94 (dd, *J* = 1.5, 0.7 Hz, 1H), 6.93 (dd, *J* = 1.5, 0.7 Hz, 1H), 6.83 (dd, *J* = 1.5, 0.7 Hz, 1H), 6.78 (s, 1H), 3.82 (d, *J* = 7.3 Hz, 1H), 3.78 (dd, *J* = 14.6, 4.2 Hz, 1H), 3.67 (dd, *J* = 14.0, 3.4 Hz, 1H), 3.50 (dd, *J* = 14.6, 4.9 Hz, 1H), 3.32 (dd, *J* = 14.0, 9.1 Hz, 1H), 2.77 (ddd, *J* = 16.4, 5.4, 1.2 Hz, 1H), 2.47 (ddd, *J* = 16.4, 8.0, 2.4 Hz, 1H), 2.28–2.23 (m, 1H), 2.15–2.11 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 163.2, 162.9, 149.24, 149.18, 127.5, 127.2, 127.1, 123.3, 123.1, 122.8, 119.1, 114.2, 113.6, 113.0, 97.7, 97.6, 44.1, 42.8, 40.0, 37.2, 33.3, 23.7; MS(ESI)$^+$ calcd for $C_{22}H_{25}Br_2N_{10}O_2$ $[M+H]^+$: 619.1, found: 619.0.

Ageliferin (5a). Alcohol *ent*-**185** was converted to ageliferin (**5a**) by methods described above.

Dibromoageliferin (5c). Alcohol *ent*-**185** was converted to dibromoageliferin (**5c**) following the similar procedure described above, by using 4,5-dibromo-2-(trichloroacetyl)pyrrole instead of 4-bromo-2-(trichloroacetyl)pyrrole as the acylation reagent. TFA salt: ^{1}H NMR (500 MHz, Methanol-d4) δ 6.97 (s, 1H), 6.85 (s, 1H), 6.79 (s, 1H), 3.81 (d, *J* = 7.2 Hz, 1H), 3.73 (dd, *J* = 14.4, 4.4 Hz, 1H), 3.63 (dd, *J* = 14.1, 3.4 Hz, 1H), 3.50 (dd, *J* = 14.4, 4.7 Hz, 1H), 3.33 (dd, *J* = 14.1, 8.5 Hz, 1H), 2.76 (dd, *J* = 16.5, 5.5 Hz, 1H), 2.45 (ddd, *J* = 16.5, 7.8, 2.4 Hz, 1H), 2.30 – 2.20 (m, 1H), 2.16 – 2.07 (m, 1H). HCl salt: ^{1}H NMR (600 MHz, Methanol-d4) δ 7.02 (s, 1H), 6.89 (s, 1H), 6.79 (s, 1H), 3.84 (d, *J* = 6.8 Hz, 1H), 3.72 (dd, *J* = 14.6, 4.3 Hz, 1H), 3.62 (dd, *J* = 14.0, 2.9 Hz, 1H), 3.51 (dd, *J* = 14.6, 4.8 Hz, 1H), 3.35 (dd, *J* = 14.0, 9.3 Hz, 1H), 2.77 (dd, *J* = 16.5, 5.3 Hz, 1H), 2.48 (dd, *J* = 16.5, 7.4 Hz, 1H), 2.30 – 2.23 (m, 1H), 2.20 – 2.14 (m, 1H).

Part of material decomposed during concentrating in HCl. MS(ESI)$^+$ calcd for $C_{22}H_{23}Br_4N_{10}O_2$ $[M+H]^+$: 774.9, found: 774.6.

APPENDIX B

COMPARISON OF SPECTRAL DATA WITH NATURAL AGELIFERINS

Comparison of the ^{1}H NMR Chemical Shifts and Coupling Constants of Ageliferins (5a) in CD_3OD

	Natural sample·HCl*	Synthetic sample·TFA
2	6.96 (d, *J* = 1.5 Hz)	6.94 (dd, *J* = 1.5, 0.7 Hz)
2'	6.97 (d, *J* = 1.5 Hz)	6.97 (dd, *J* = 1.5, 0.7 Hz)
4	6.85 (d, *J* = 1.5 Hz)	6.83 (dd, *J* = 1.5, 0.7 Hz)
4'	6.94 (d, *J* = 1.5 Hz)	6.93 (dd, *J* = 1.5, 0.7 Hz)
8a	3.50 (dd, *J* = 14, 5 Hz)	3.50 (dd, *J* = 14.6, 4.9 Hz)
8b	3.77 (dd, *J* = 14, 4.5 Hz)	3.78 (dd, *J* = 14.6, 4.2 Hz)
8'a†	3.33 (dd, *J* = 14, 4.5 Hz)	3.32 (dd, *J* = 14.0, 9.1 Hz)
8'b	3.64 (dd, *J* = 14, 3 Hz)	3.67 (dd, *J* = 14.0, 3.4 Hz)
9	2.16 (m)	2.15 – 2.11 (m)
9'	2.27 (m)	2.28 – 2.23 (m)
10	3.83 (brd, *J* = 7 Hz)	3.82 (d, *J* = 7.3 Hz)
10'a	2.48 (ddd, *J* = 16, 8, 2.5 Hz)	2.47 (ddd, *J* = 16.4, 8.0, 2.4 Hz)
10'b	2.78 (ddd, *J* = 16, 5.5, 1.5 Hz)	2.76 (ddd, *J* = 16.4, 5.4, 1.2 Hz)
15	6.79 (brs)	6.78 (s)

*****Kobayashi, J.; Tsuda, H.; Murayama, T.; Nakamura, H.; Ohizumi, Y.; Ishibashi, M.; Iwamura, M. *Tetrahedron*. **1990**, *46*, 5579–5586.

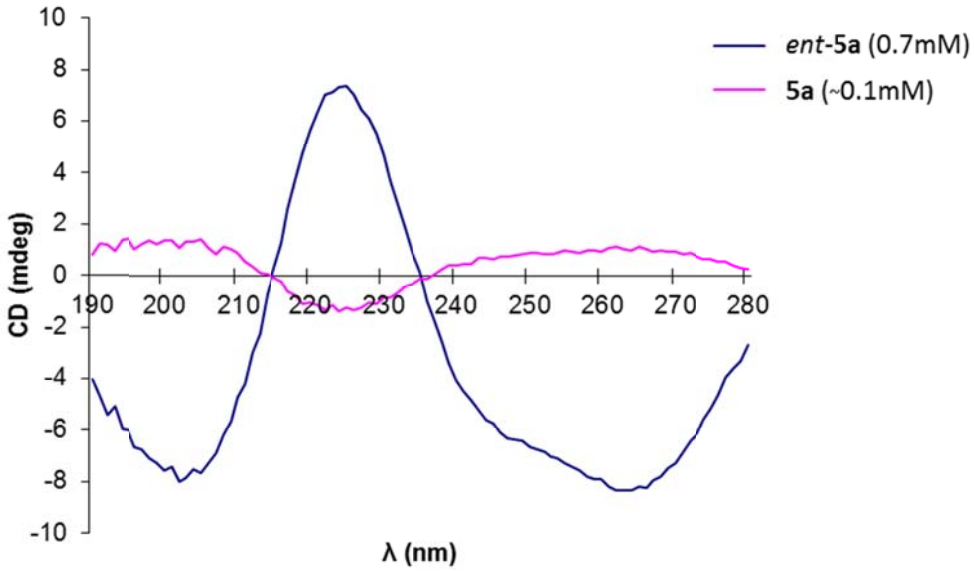
Comparison of the ^{13}C NMR Chemical Shifts of Ageliferins (5a) in CD_3OD

	Natural sample·HOAc*	Baran's reported synthetic sample·TFA†	Synthetic sample·TFA
2	123.2	123.3	123.3
2'	123.0	123.1	123.1
3	97.7	97.7	97.7
3'	97.6	97.6	97.6
4	114.2	114.3	114.2
4'	113.6	113.8	113.6
5	127.3	127.3	127.2
5'	127.3	127.2	127.1
6	163.1	163.2	163.2
6'	162.9	163.0	162.9
8	40.6	40.0	40.0
8'	43.0	42.9	42.8
9	43.8	44.0	44.1
9'	37.4	37.3	37.2
10	34.3	33.4	33.3
10'	23.8	23.9	23.7
11	131.4	127.6	127.5
11'	123.0	122.8	122.8
13	150.2	149.4	149.24
13'	149.4	149.3	149.18
15	112.4	113.1	113.0
15'	122.3	119.3	119.1

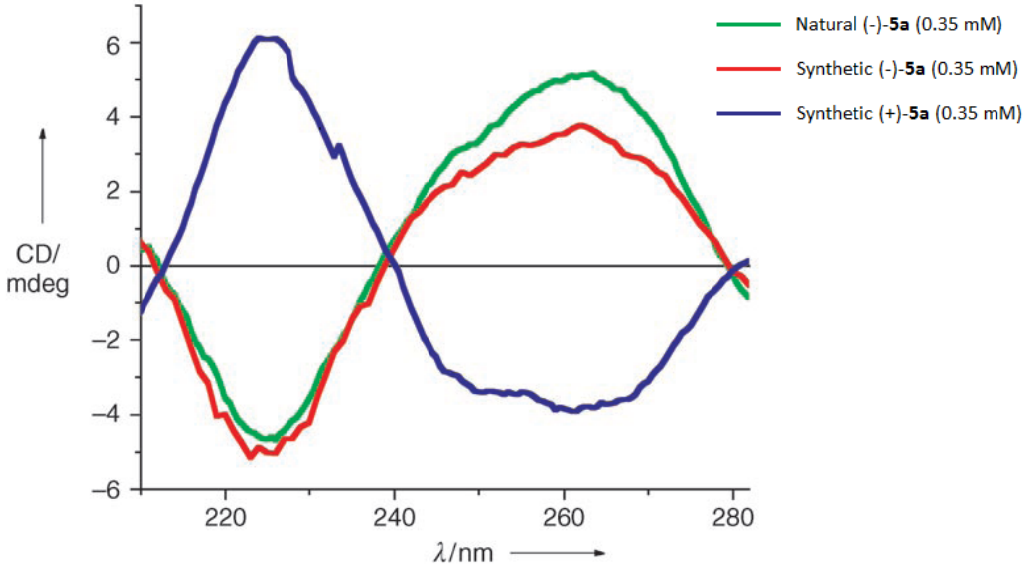
*****Kobayashi, J.; Tsuda, H.; Murayama, T.; Nakamura, H.; Ohizumi, Y.; Ishibashi, M.; Iwamura, M. *Tetrahedron*. **1990**, *46*, 5579–5586.

†O'Malley, D. P.; Li, K.; Maue, M.; Zografos, A. L.; Baran, P. S. *J. Am. Chem. Soc*. **2007**, *129*, 4762–4775.

CD Spectra of Ageliferin



Reported CD Spectra of Ageliferin by Baran*



*Baran, P. S.; Li, K.; O'Malley, D. P.; Mitsos, C. *Angew. Chem., Int. Ed*. **2006**, *45*, 249–252.

Comparison of the ^{1}H NMR Chemical Shifts and Coupling Constants of Dibromoageliferins (5c) in CD_3OD.

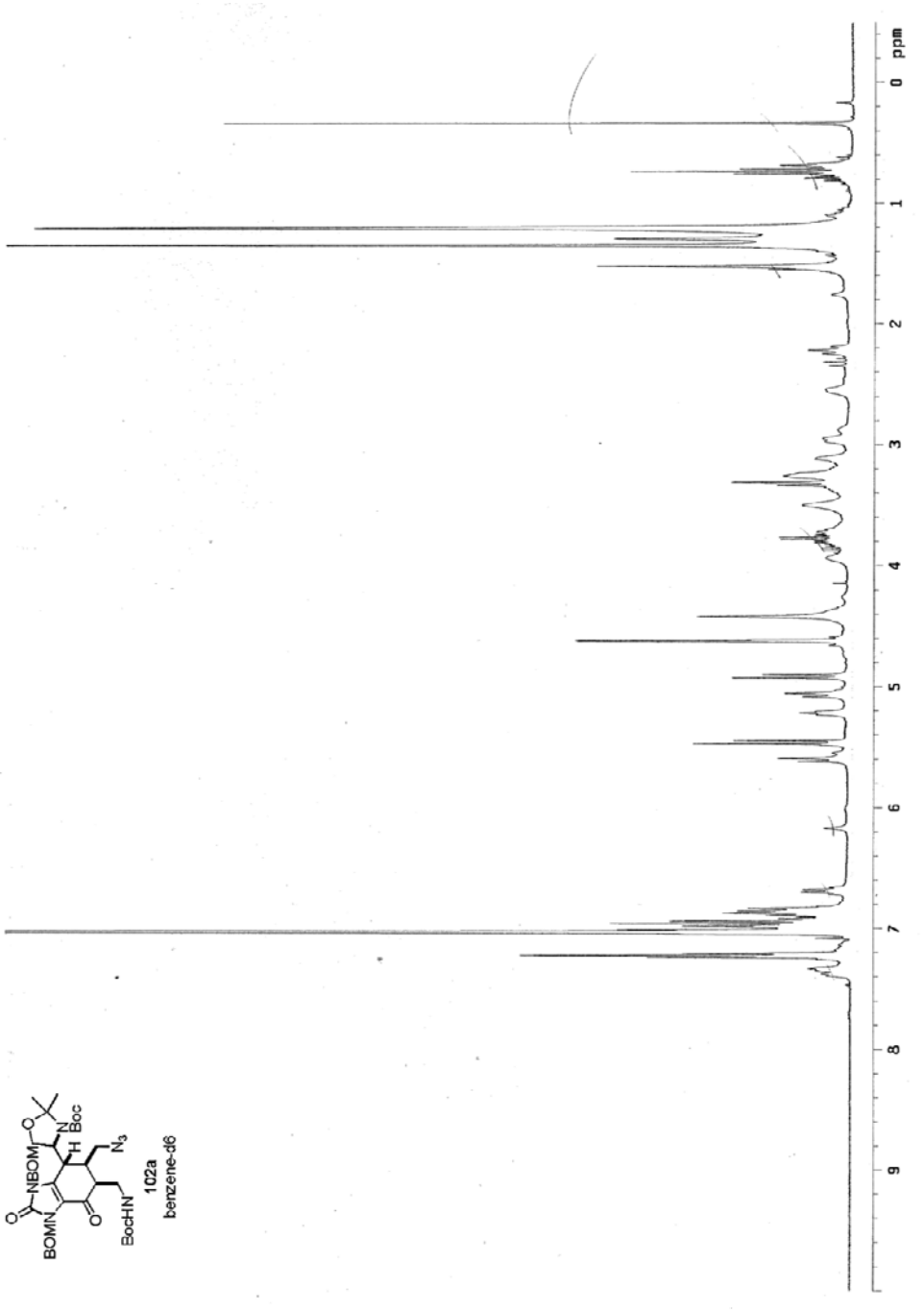
	Natural sample·HCl*	**Synthetic sample·HCl**	**Synthetic sample·TFA**
4	6.92 (brs)	6.89 (s)	6.85 (s)
4'	7.05 (brs)	7.02 (s)	6.97 (s)
8a	3.55 (dd, *J*=14.5, 4.5 Hz)	3.51 (dd, *J*=14.6, 4.8 Hz)	3.50 (dd, *J*=14.4, 4.7 Hz)
8b	3.76 (dd, *J* = 14.5, 4 Hz)	3.72 (dd, *J*=14.6, 4.3 Hz)	3.73 (dd, *J*=14.4, 4.4 Hz)
8'a†	3.30	3.35 (dd, *J*=14.0, 9.2 Hz)	3.33 (d, *J* = 14.1, 8.5 Hz)
8'b	3.66 (dd, *J* = 14, 3 Hz)	3.62 (dd, *J*=14.0, 2.9 Hz)	3.63 (dd, *J*=14.1, 3.4 Hz)
9	2.20 (m)	2.20 – 2.14 (m)	2.16 – 2.07 (m)
9'	2.30 (m)	2.30 – 2.23 (m)	2.30 – 2.20 (m)
10	3.87 (brd, *J* = 7 Hz)	3.84 (d, *J* = 6.8 Hz)	3.81 (d, *J* = 7.2 Hz)
10'a	2.51 (dd, *J* = 16, 8 Hz)	2.48 (dd, *J*=16.5, 7.4 Hz)	2.45 (ddd, *J* = 16.5, 7.8, 2.4 Hz)
10'b	2.81 (dd, *J* = 16, 5.5 Hz)	2.77 (dd, *J*=16.5, 5.3 Hz)	2.76 (dd, *J*=16.5, 5.5 Hz)
15	6.83 (brs)	6.79 (s)	6.79 (s)

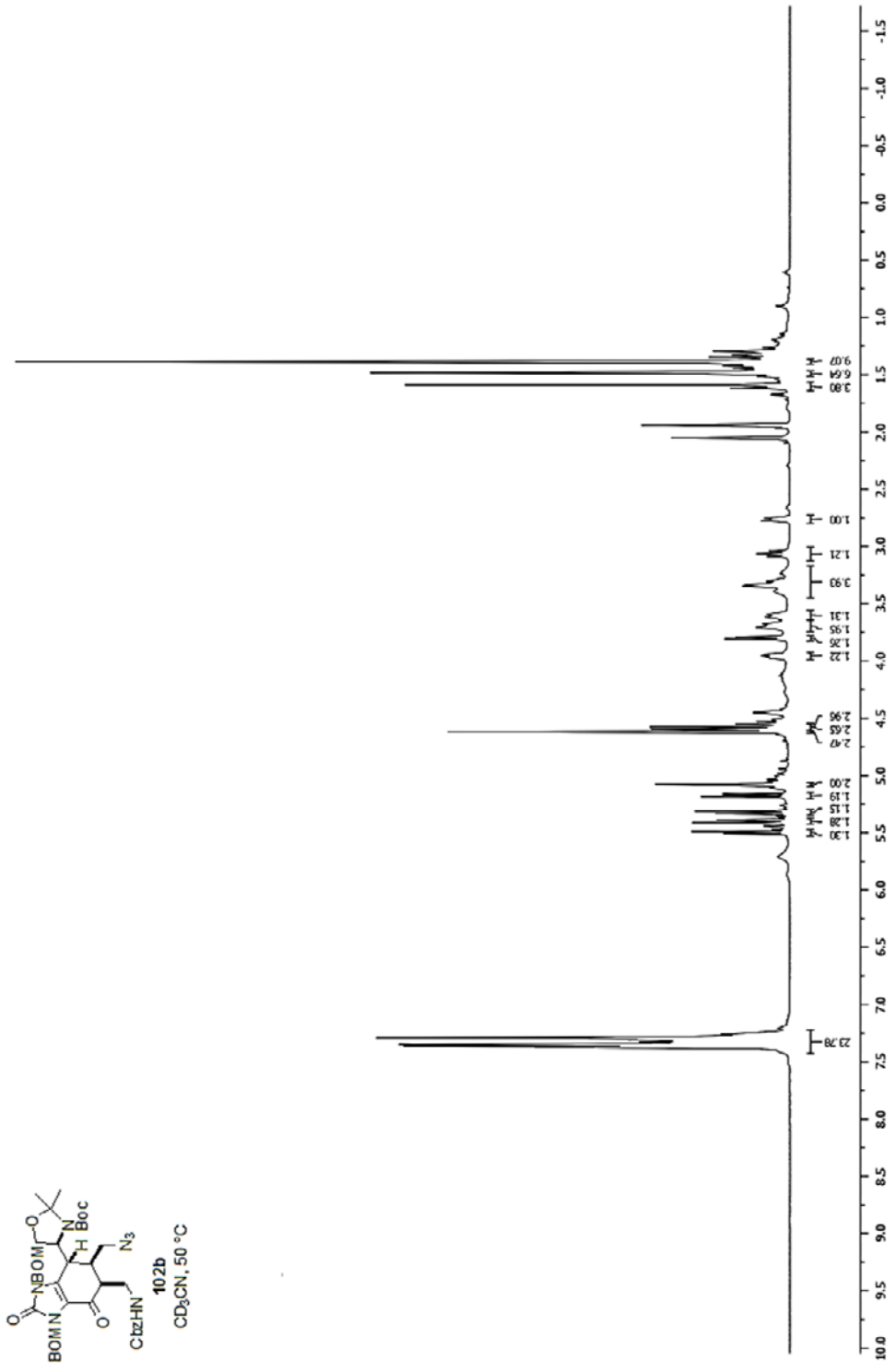
*****Kobayashi, J.; Tsuda, H.; Murayama, T.; Nakamura, H.; Ohizumi, Y.; Ishibashi, M.; Iwamura, M. *Tetrahedron*. **1990**, *46*, 5579–5586.

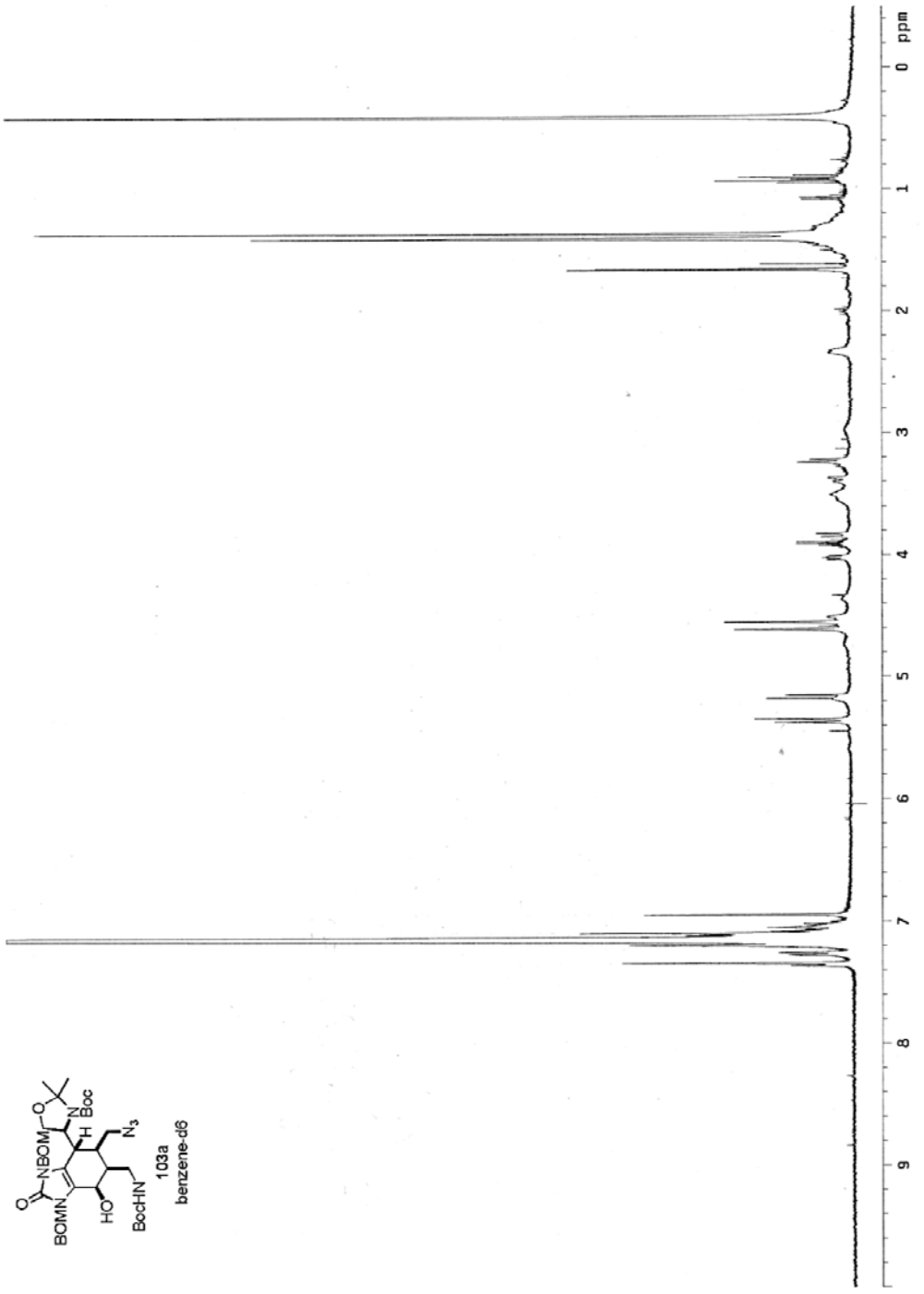
†Overlaps with the signal of methanol.

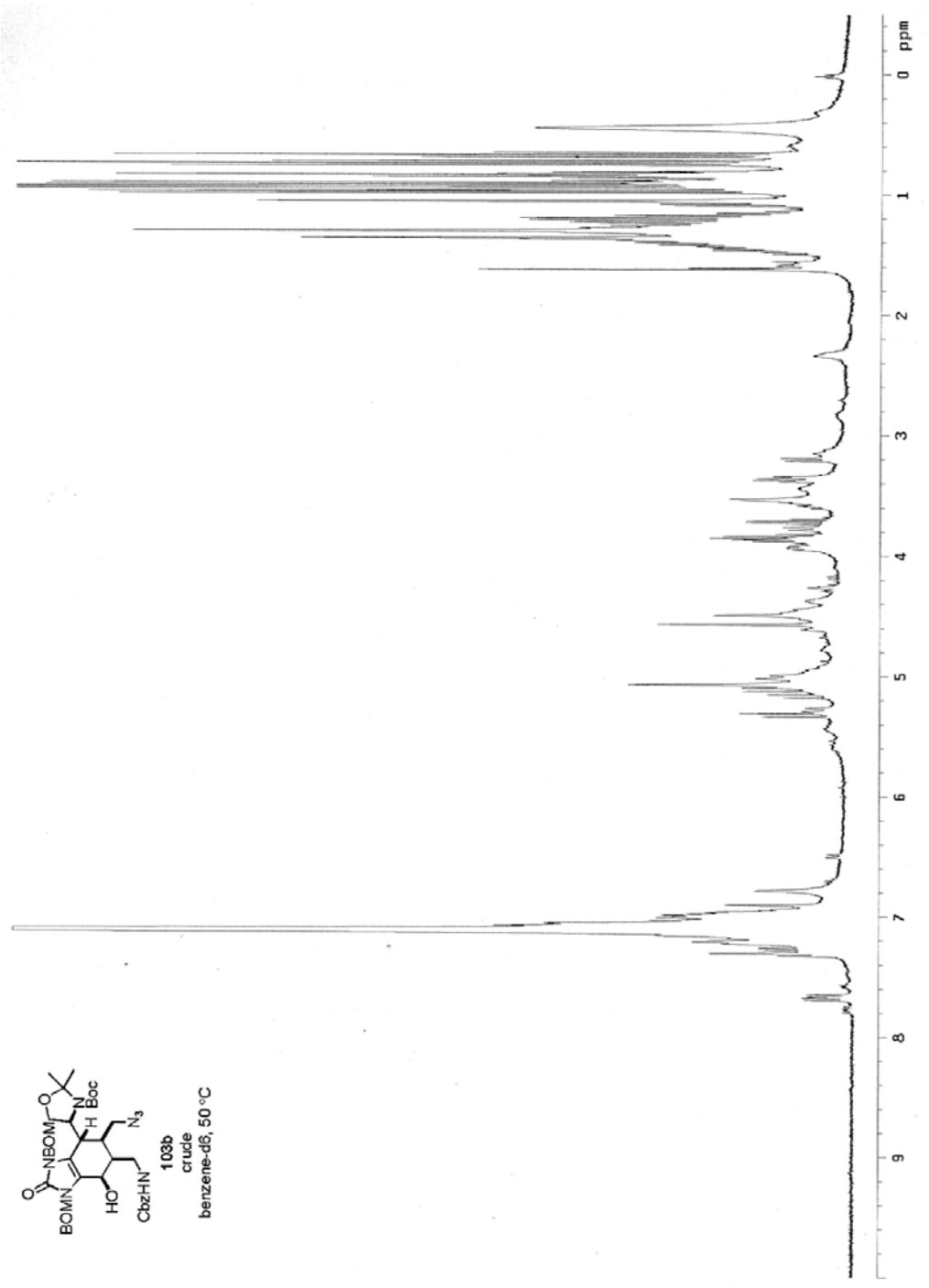
APPENDIX C

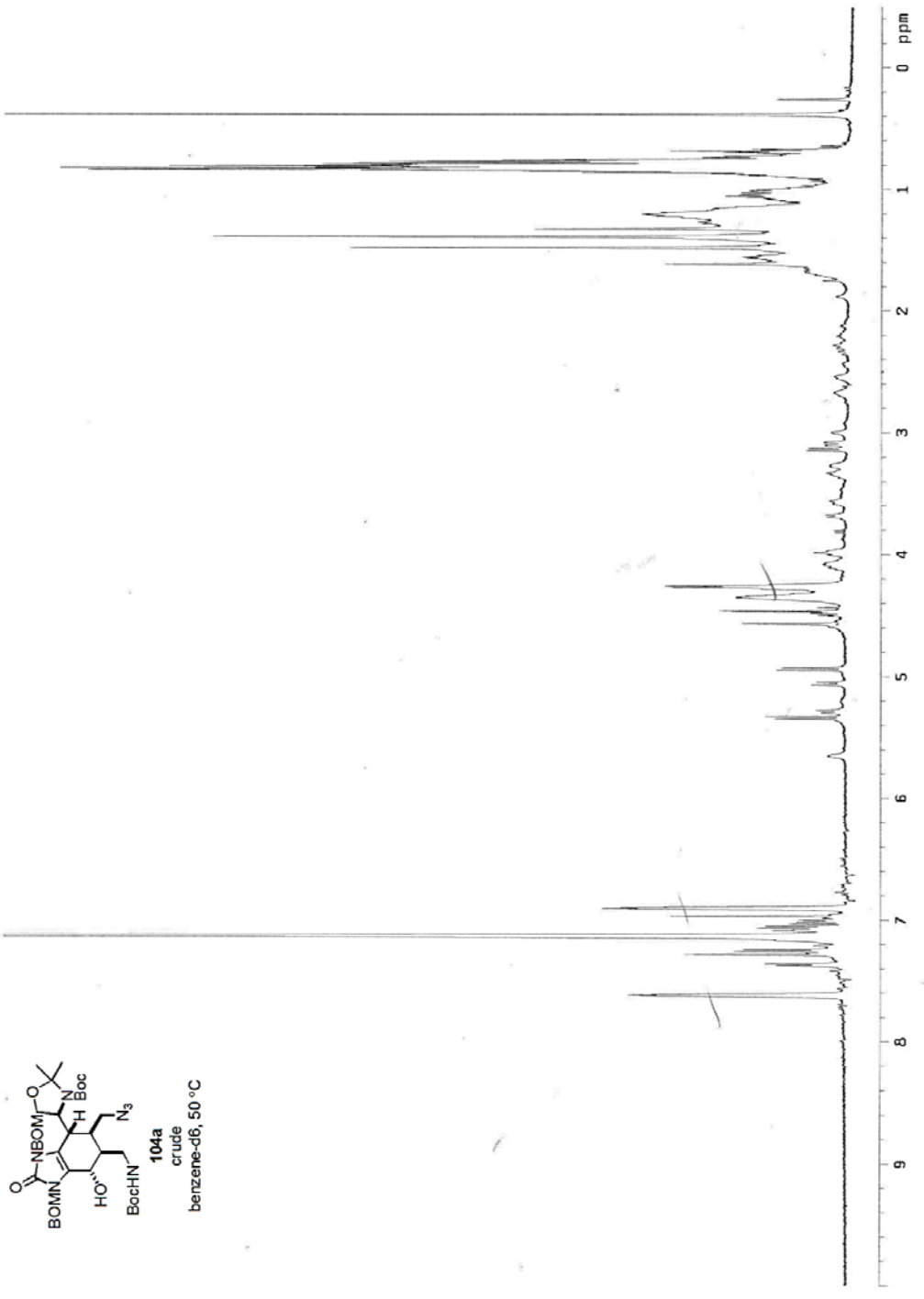
SPECTRA RELEVANT TO THE SYNTHESIS

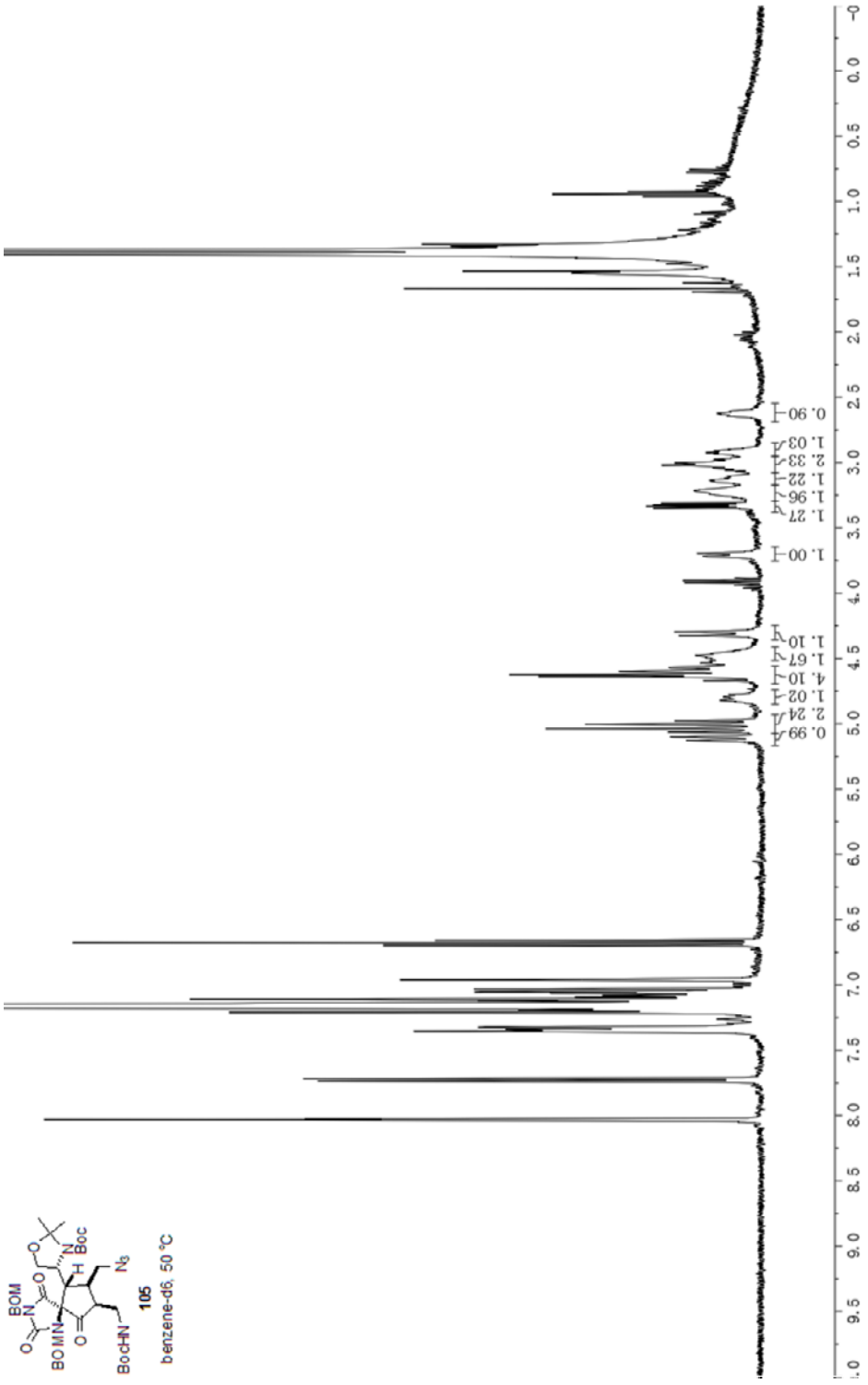


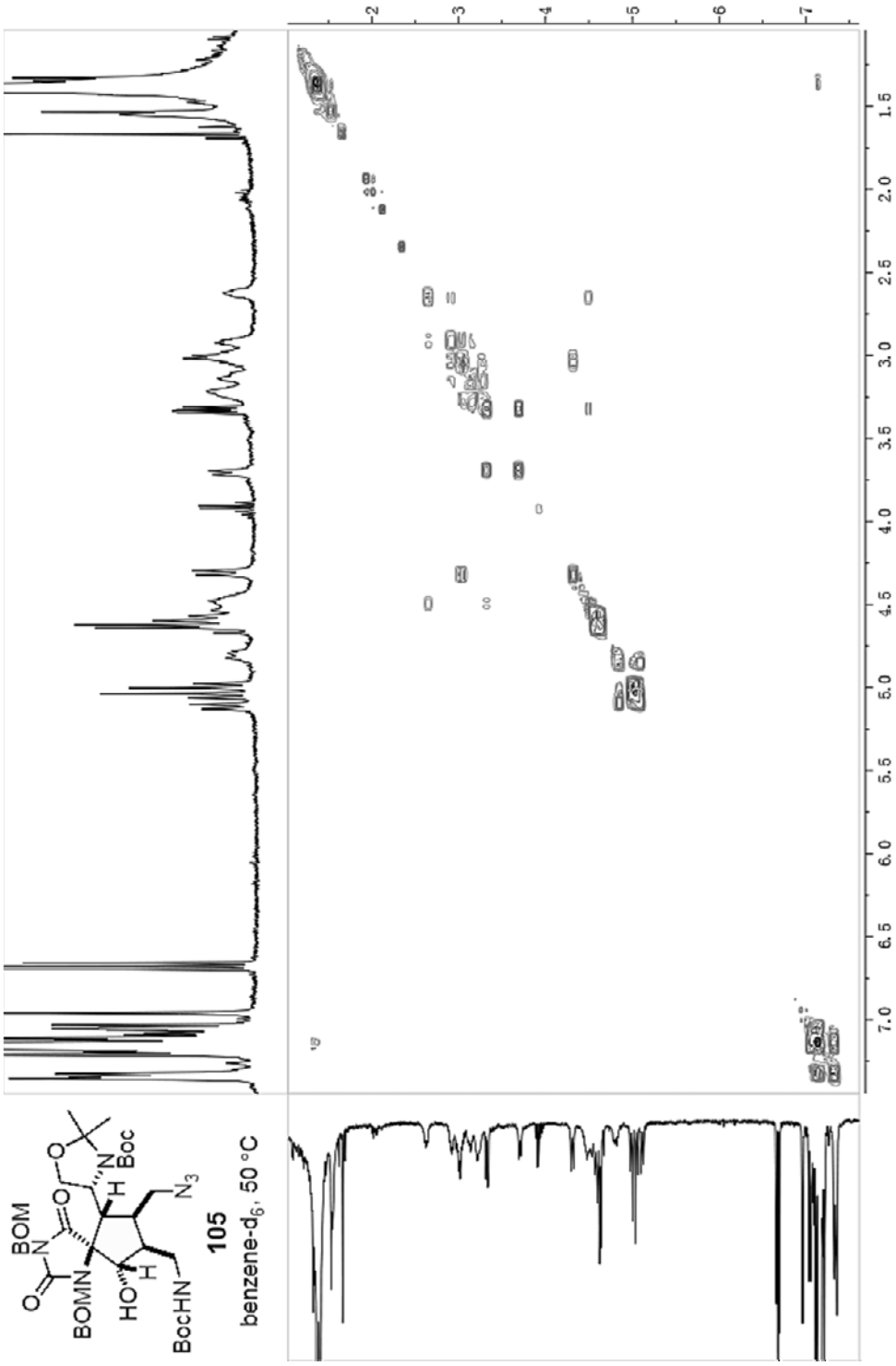

BOMN
NBOM
O
O
O
N
H Boc
N3
CbzHN
102b
CD3CN, 50 °C

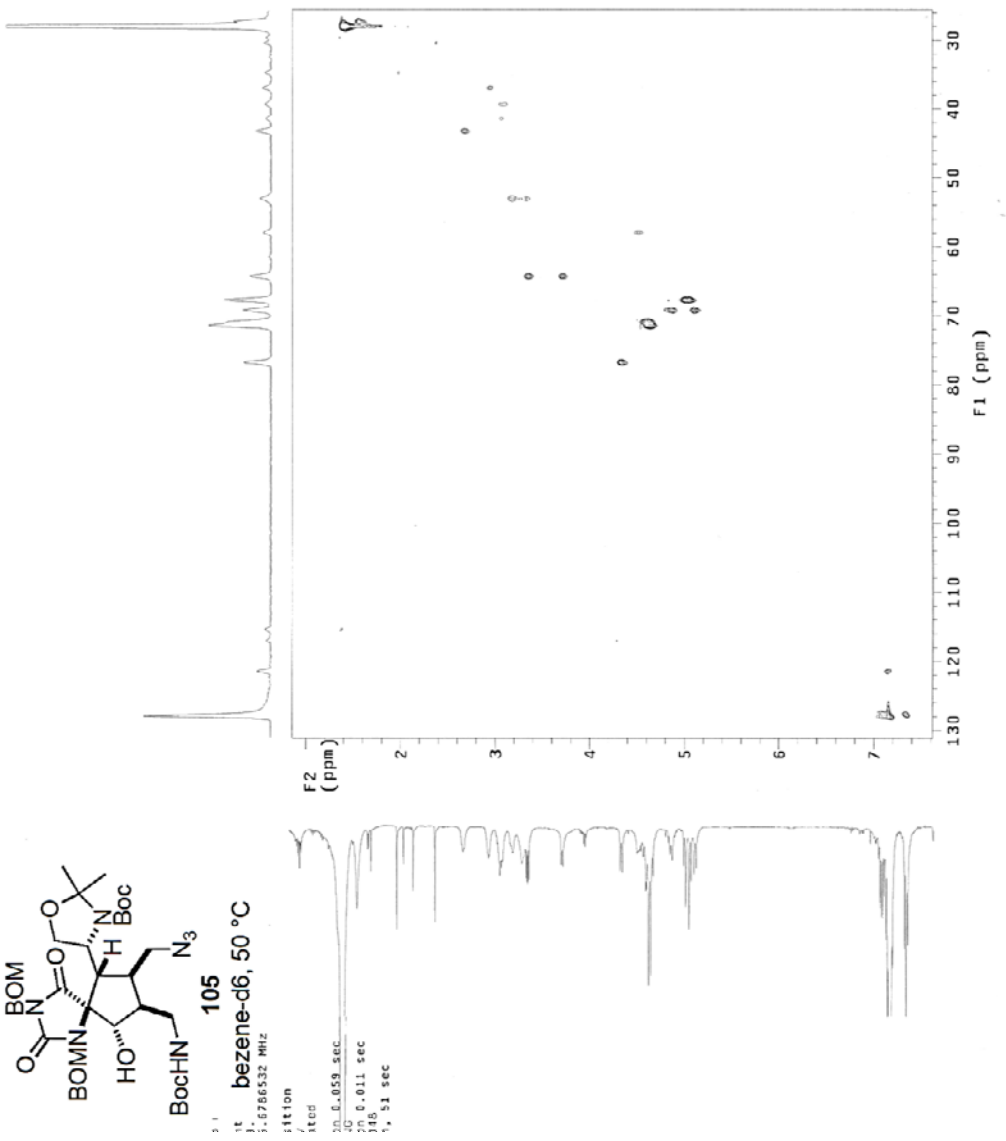

BOMN
NBOM
O
O
N
Boc
H
HO
BocHN
N3
103a
benzene-d6
9
8
7
6
5
4
3
2
1
0 ppm

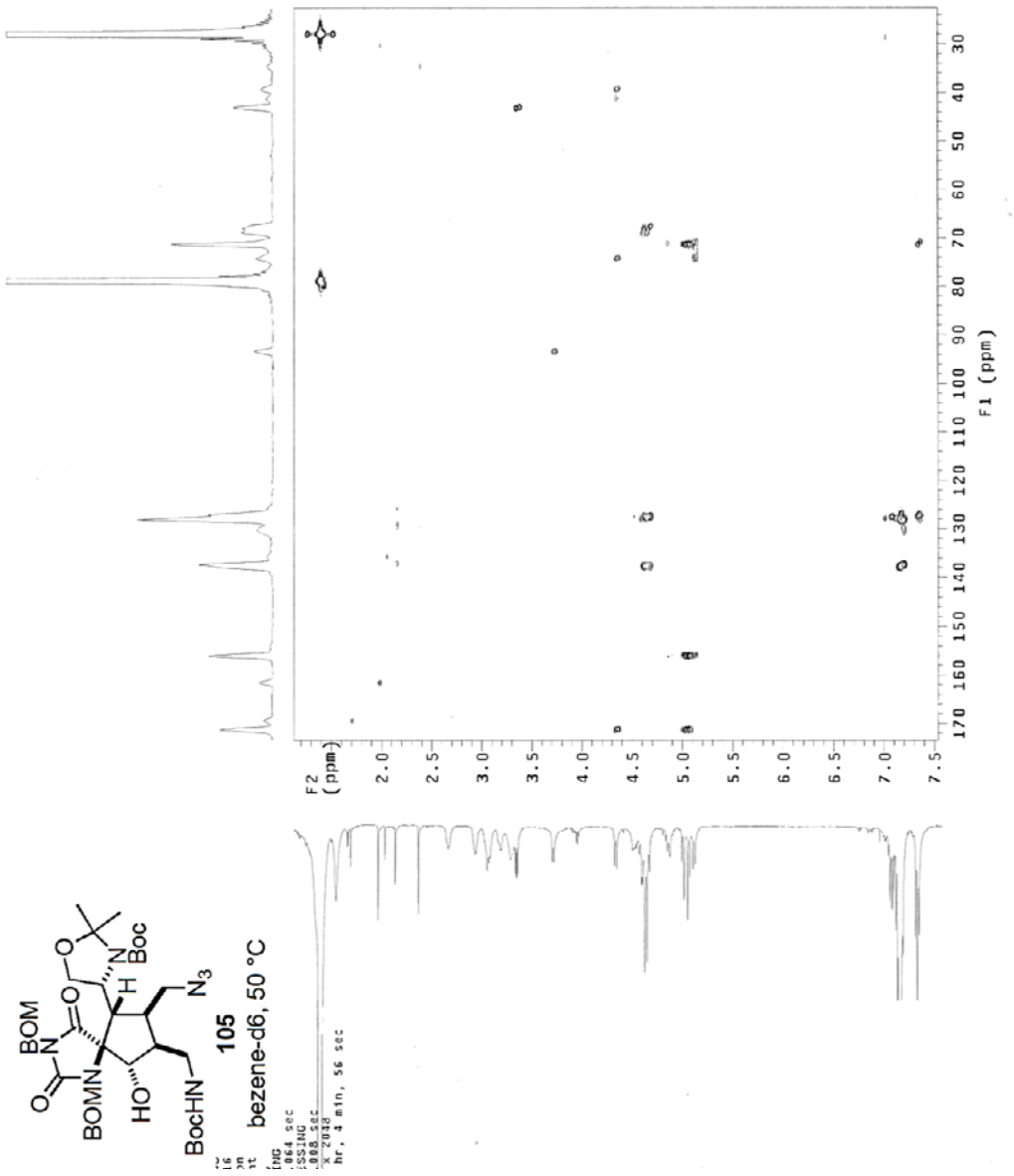

103b
crude
benzene-d6, 50 °C
0 ppm

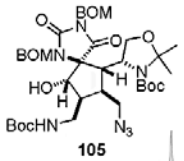

NBOM
N Boc
H
N3
O
BOMN
HO
BocHN
104a
crude
benzene-d6, 50 °C
9
8
7
6
5
4
3
2
1
0 ppm


BOM
BOMN
BocHN
N3
Boc
105
benzene-d6, 50 °C
0.90
1.03
2.33
1.22
1.96
1.27
1.00
1.10
1.67
4.10
1.02
2.24
0.99


BOM
N
O
O
BOMN
HO
H
H
N
Boc
O
O
N3
BocHN
105
benzene-d6, 50 °C
2
3
4
5
6
7
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0

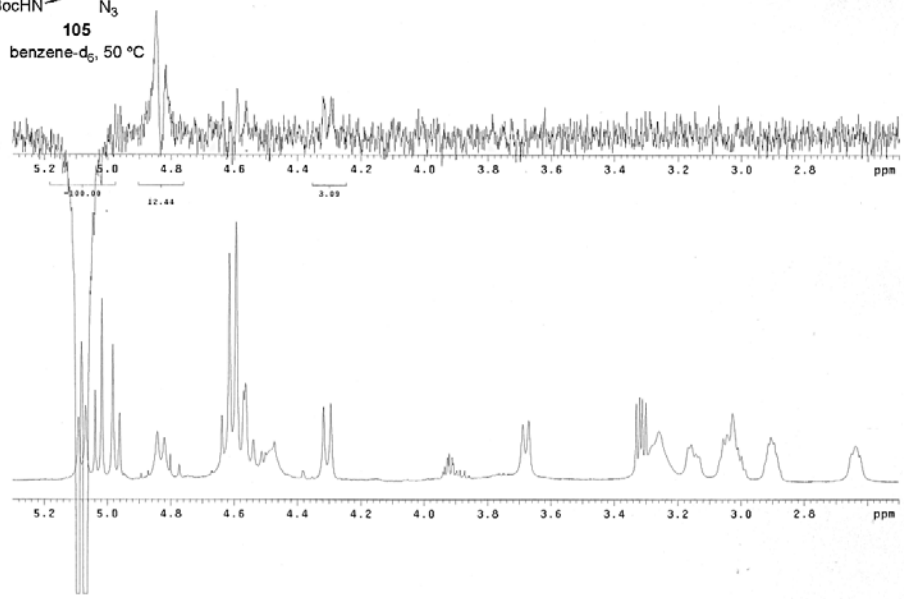

BOM
BOMN
HO
BocHN
N3
Boc
105
bezene-d6, 50 °C
F2 (ppm)
F1 (ppm)

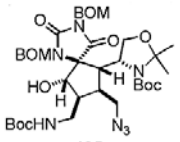

BOM
BOMN
HO
BocHN
Boc
N_3
105
bezene-d6, 50 °C
F2 (ppm)
F1 (ppm)



105

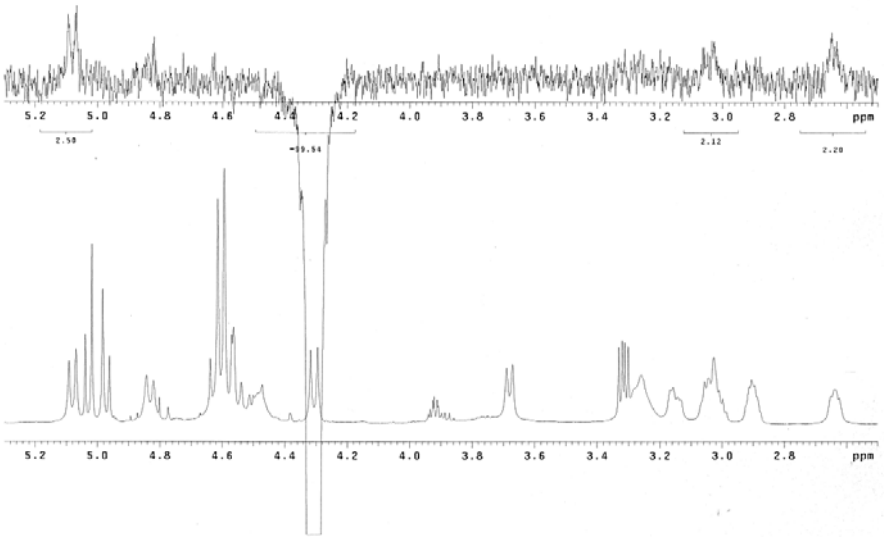
benzene-d_5, 50 °C

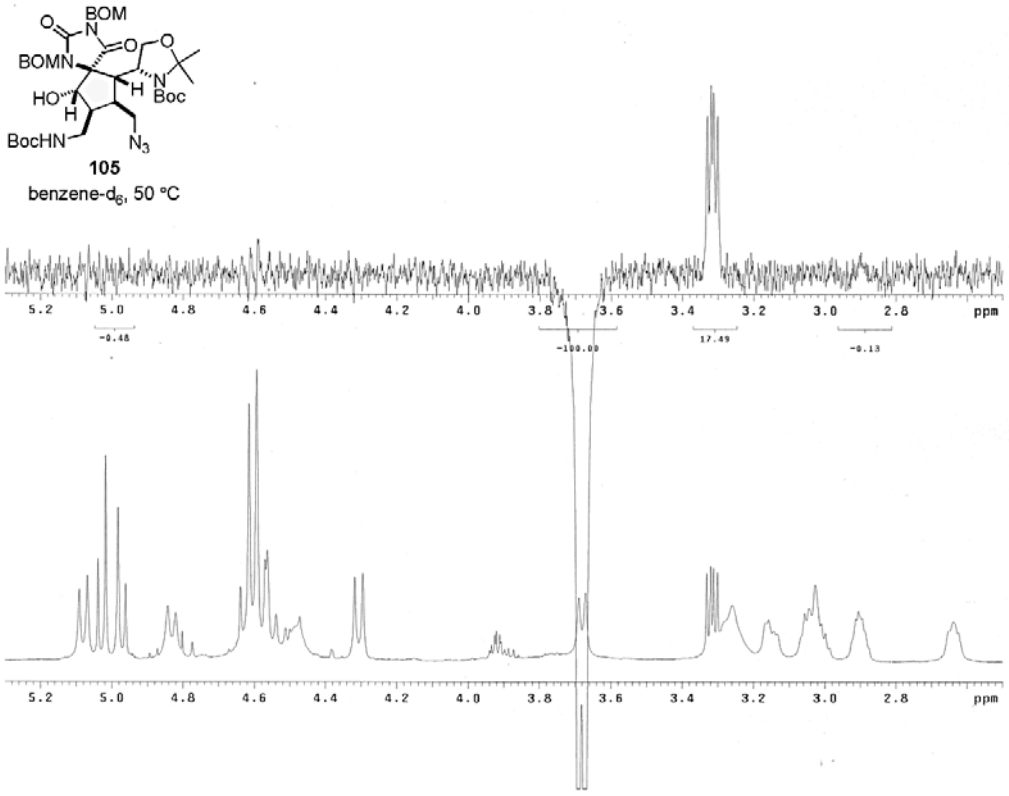


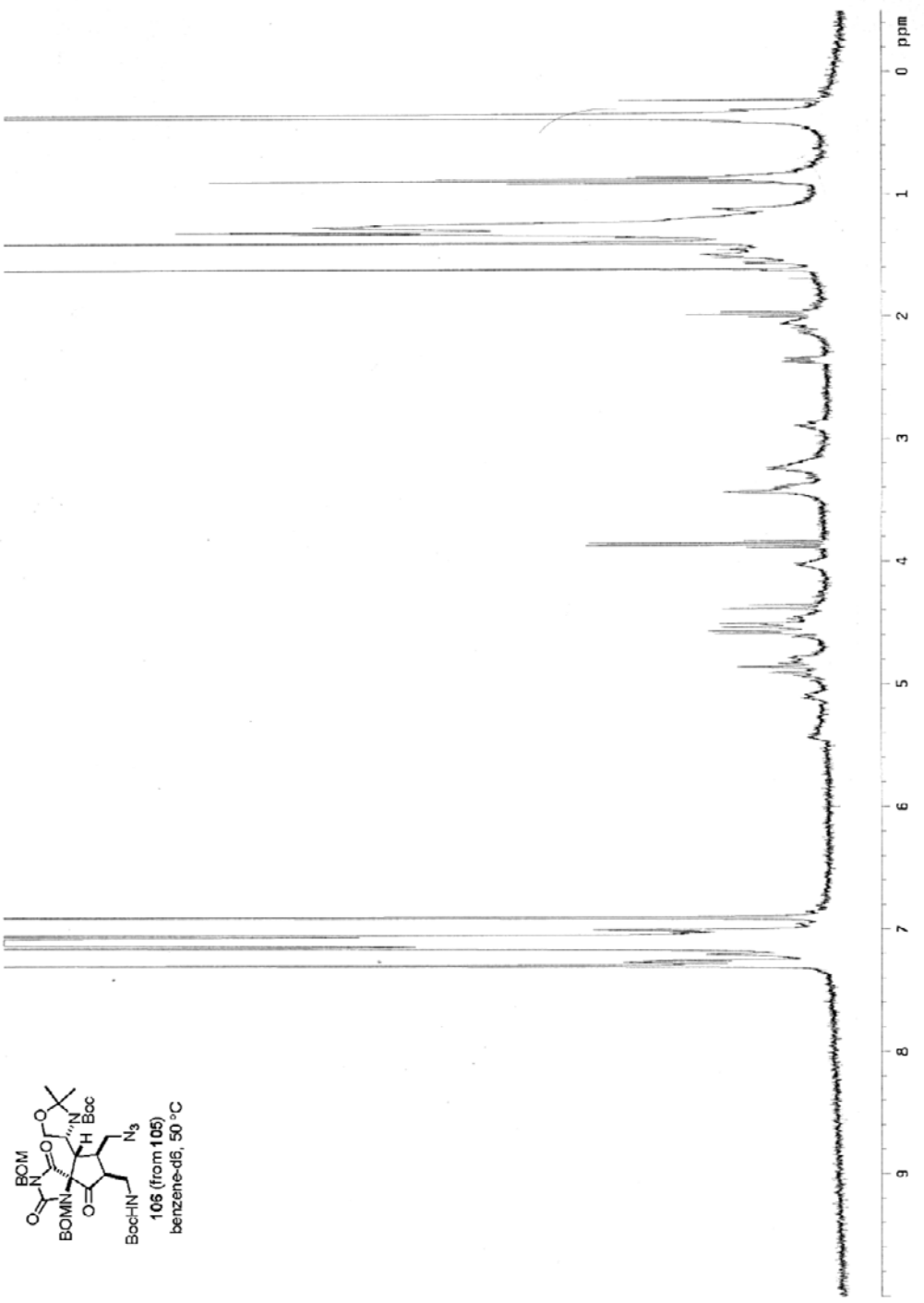


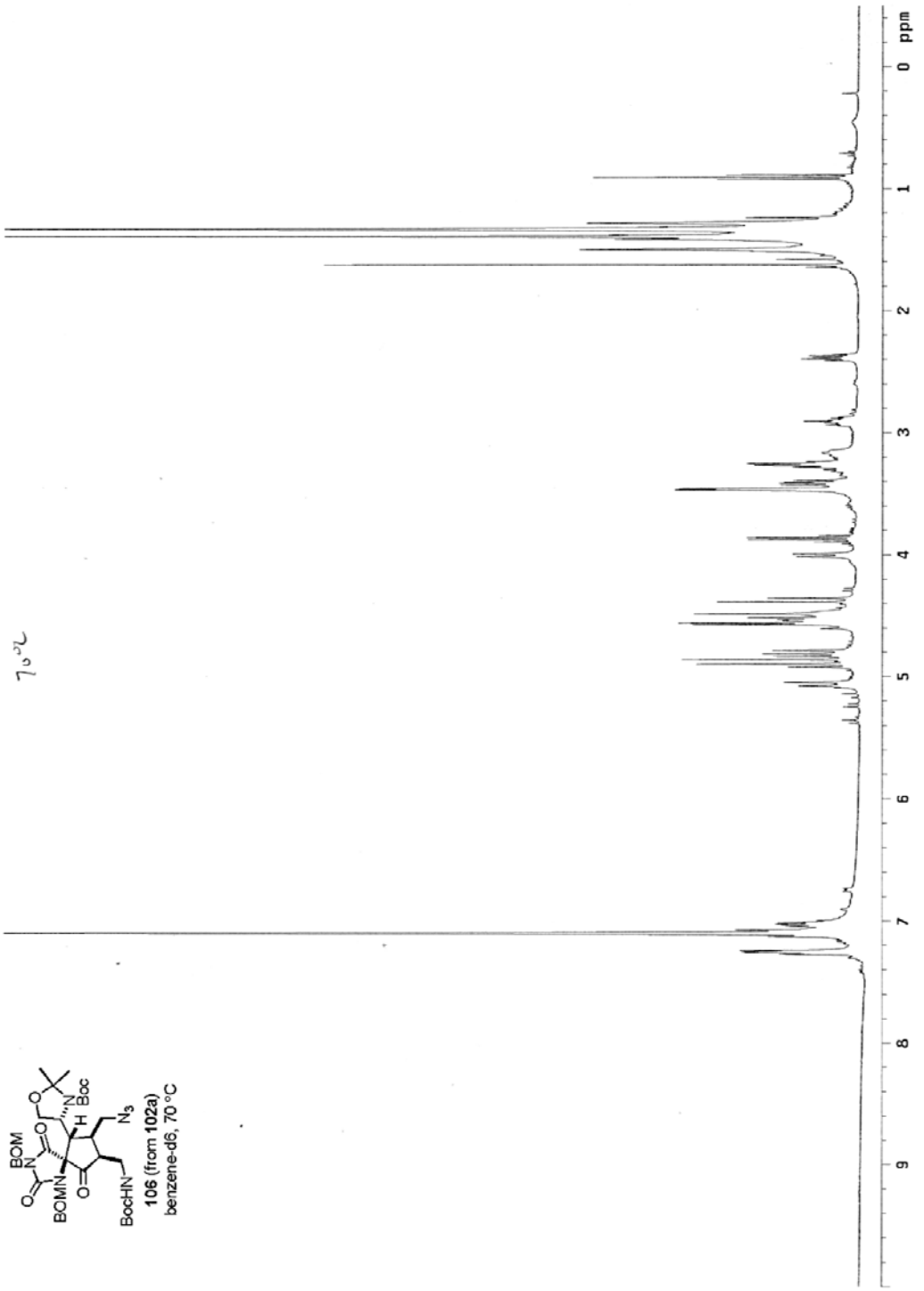
105

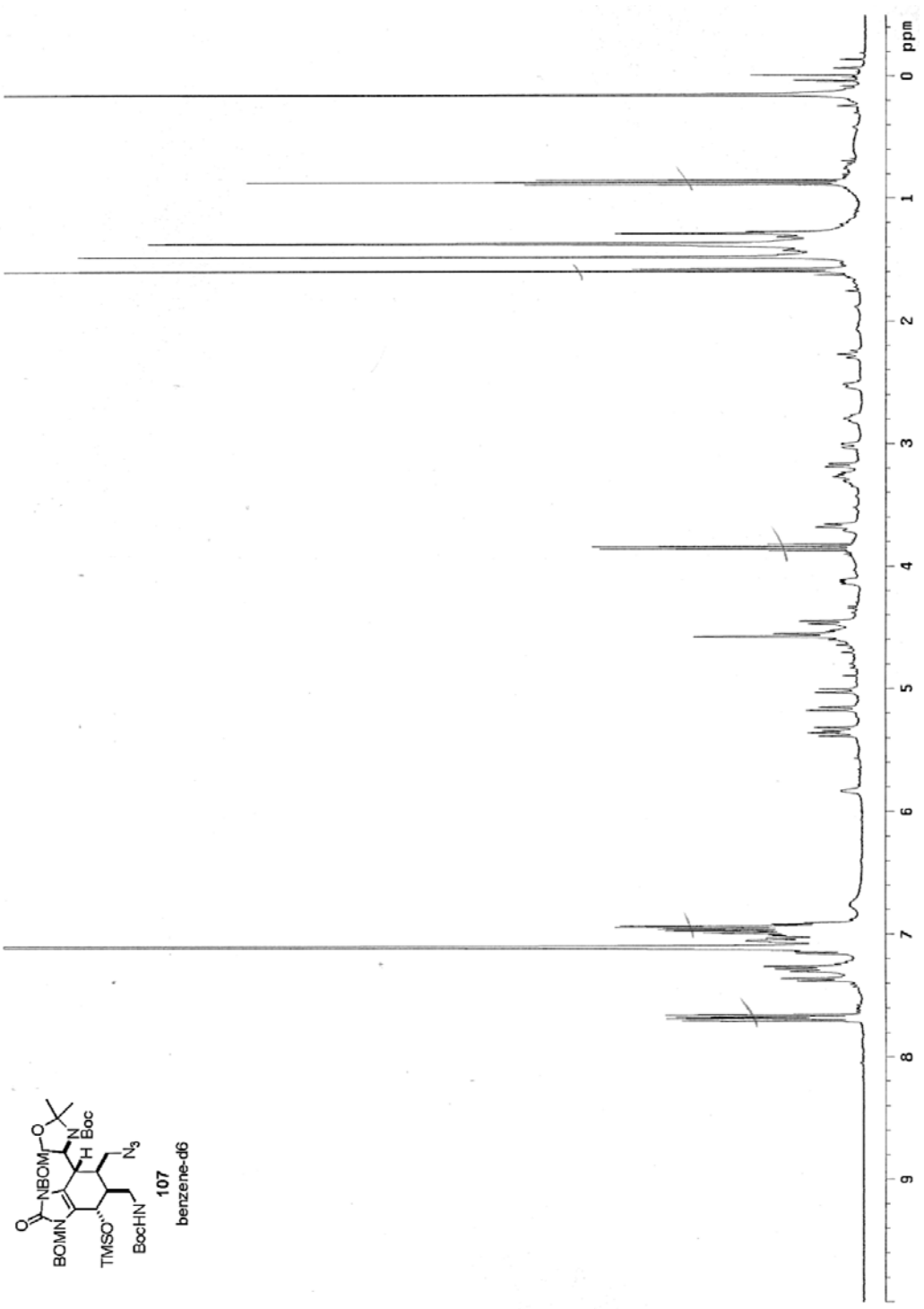
benzene-d_6, 50 °C

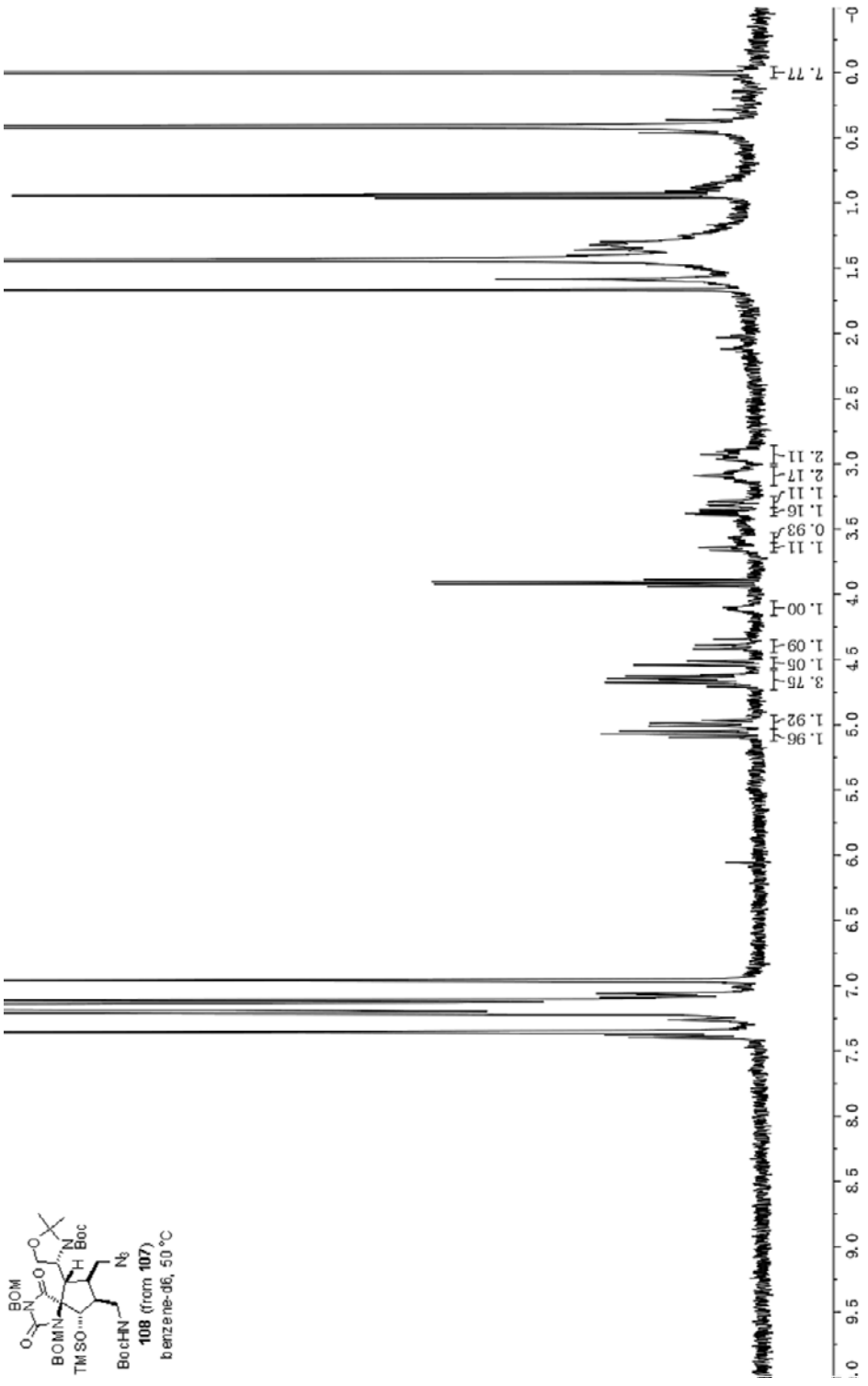


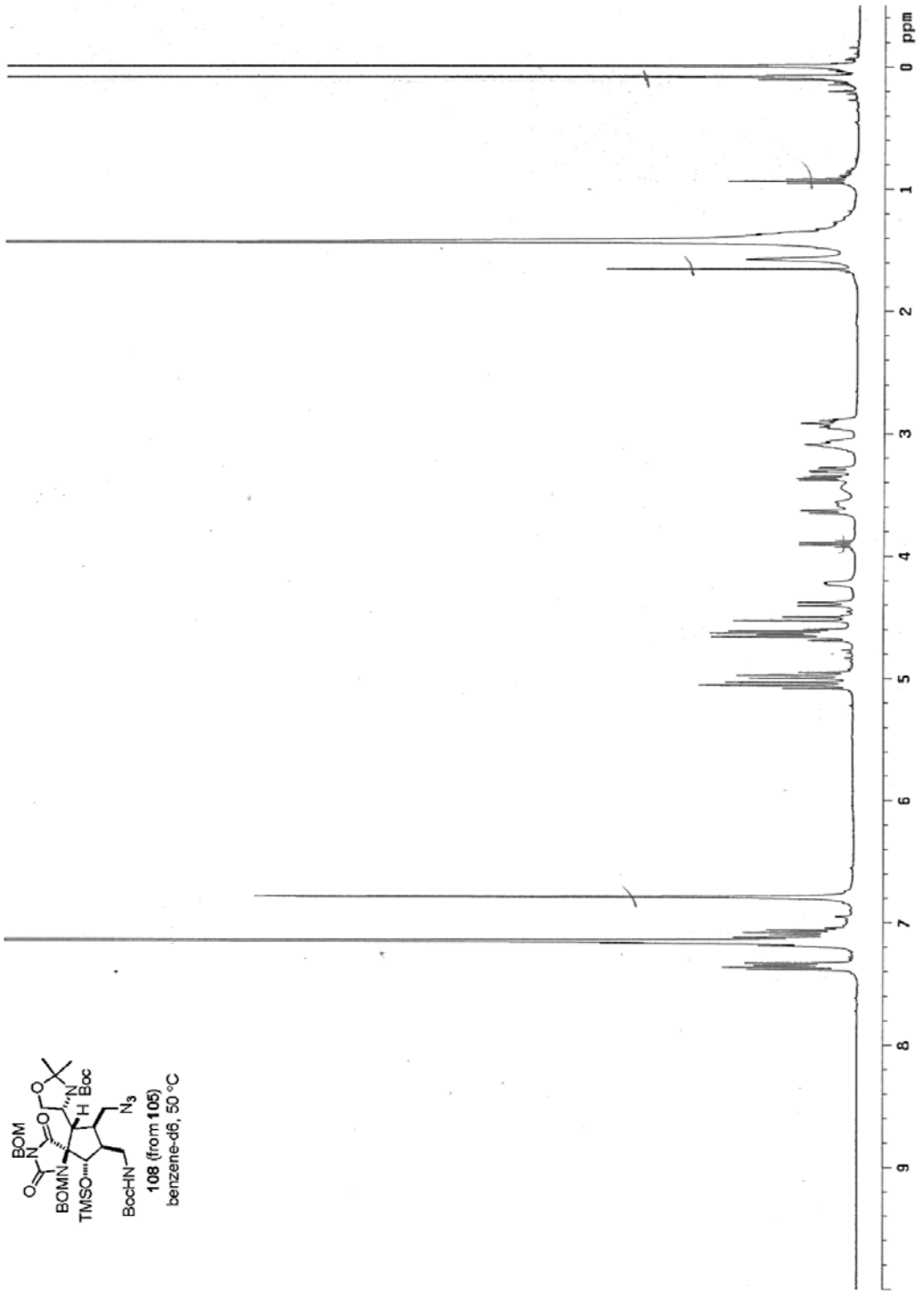

BOM
BOMN
HO
H
BocHN
N3
Boc
105
benzene-d6, 50 °C
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
ppm
-0.48
-100.00
17.49
-0.13

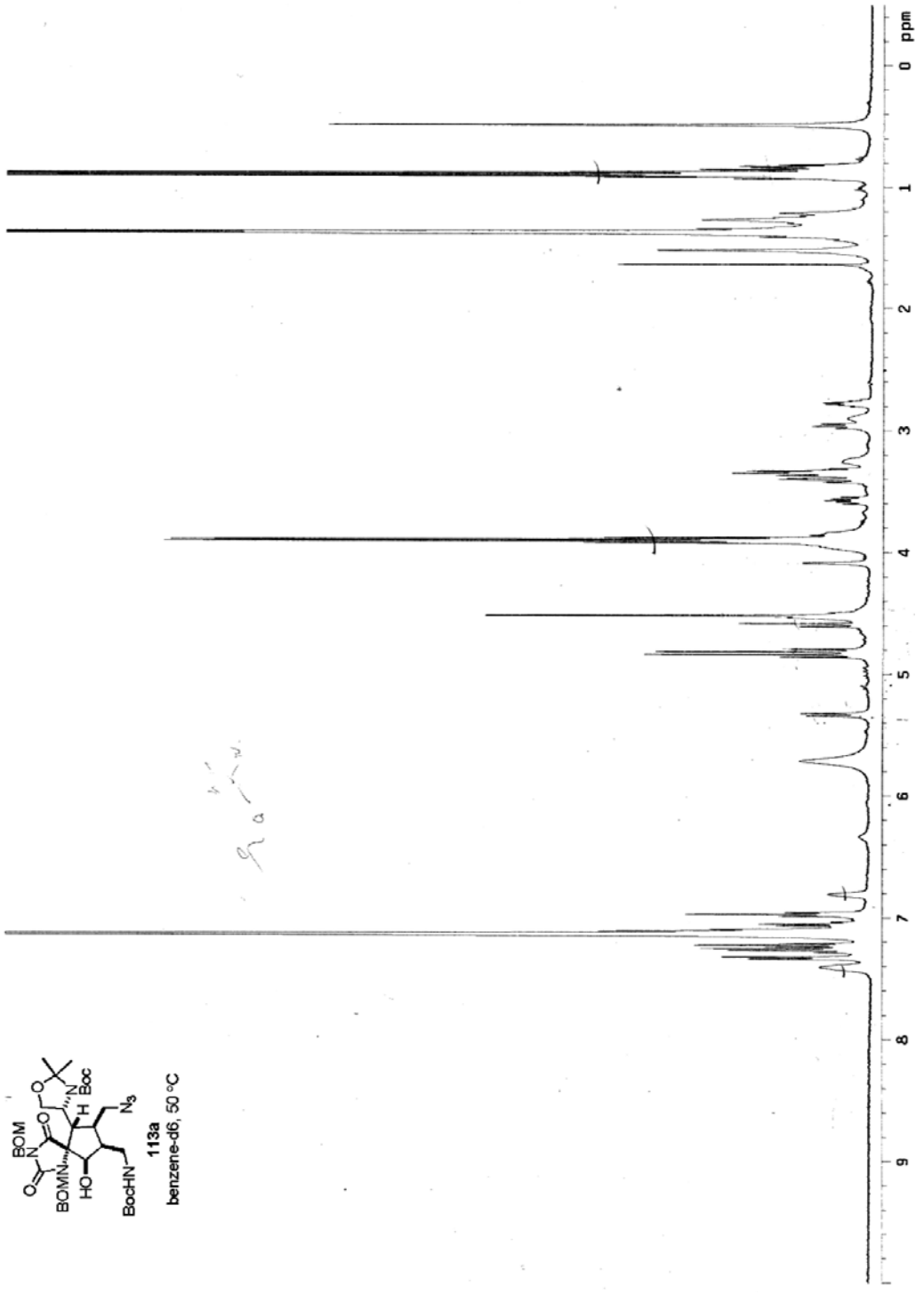

BOM
BOMN
Boc-HN
N3
Boc
H
O
O
O
O
N
N
106 (from 105)
benzene-d6, 50 °C
9
8
7
6
5
4
3
2
1
0 ppm

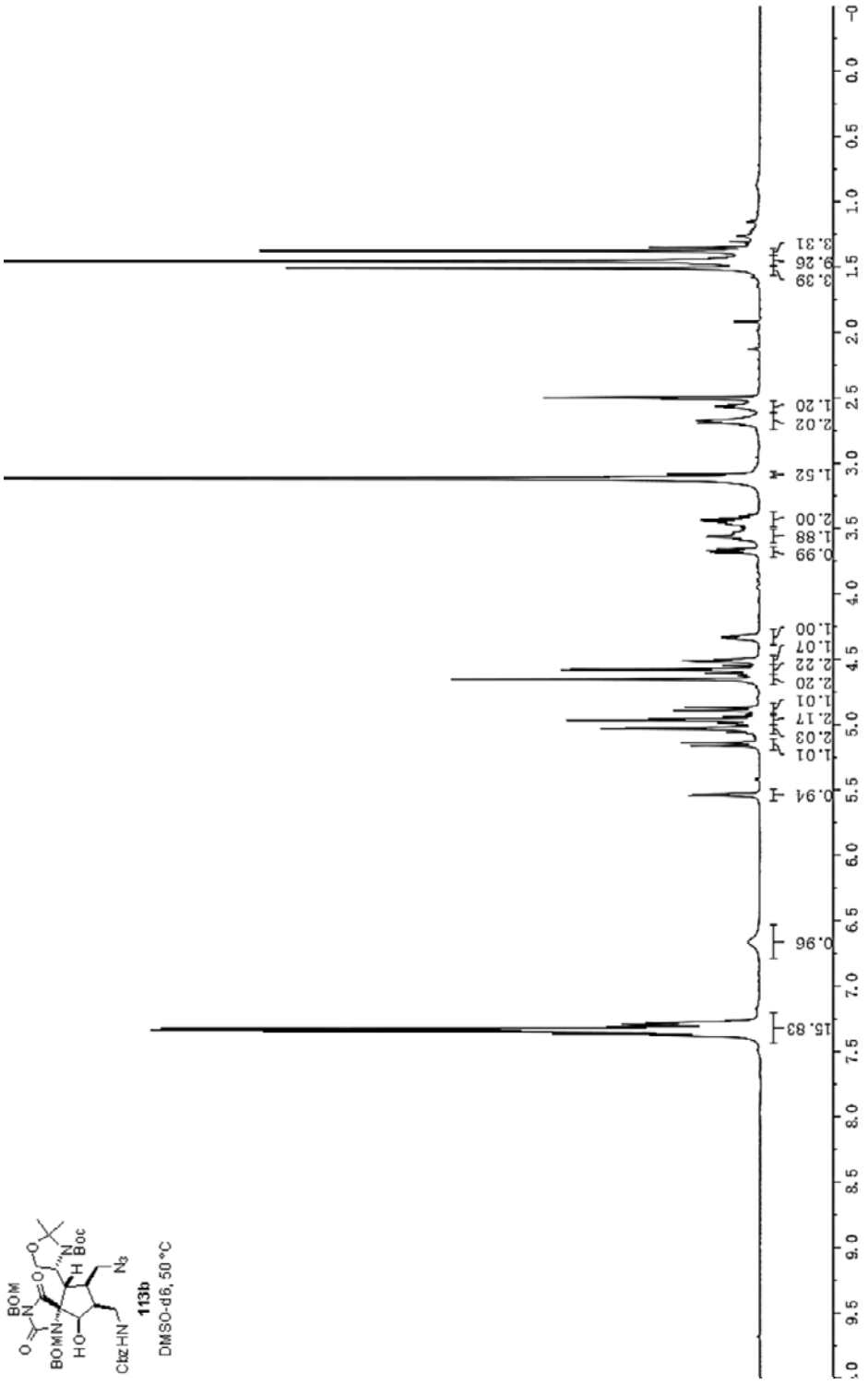

70°C
BOM
BOMN
BocHN
Boc
N_3
106 (from 102a)
benzene-d6, 70 °C
0 ppm
1
2
3
4
5
6
7
8
9

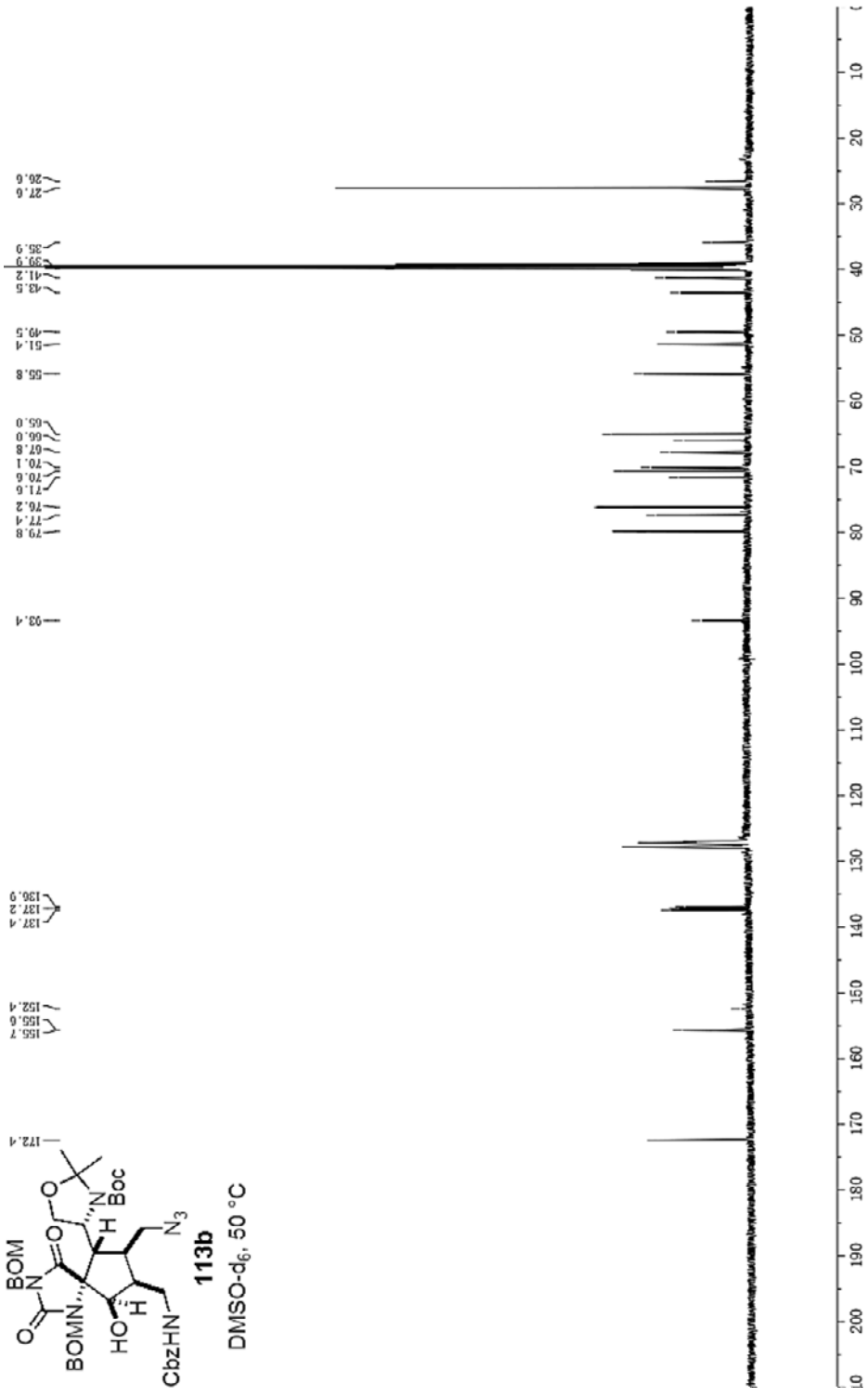

ppm
0
1
2
3
4
5
6
7
8
9
NBOM
BOMN
TMSO
BocHN
N3
Boc
107
benzene-d6

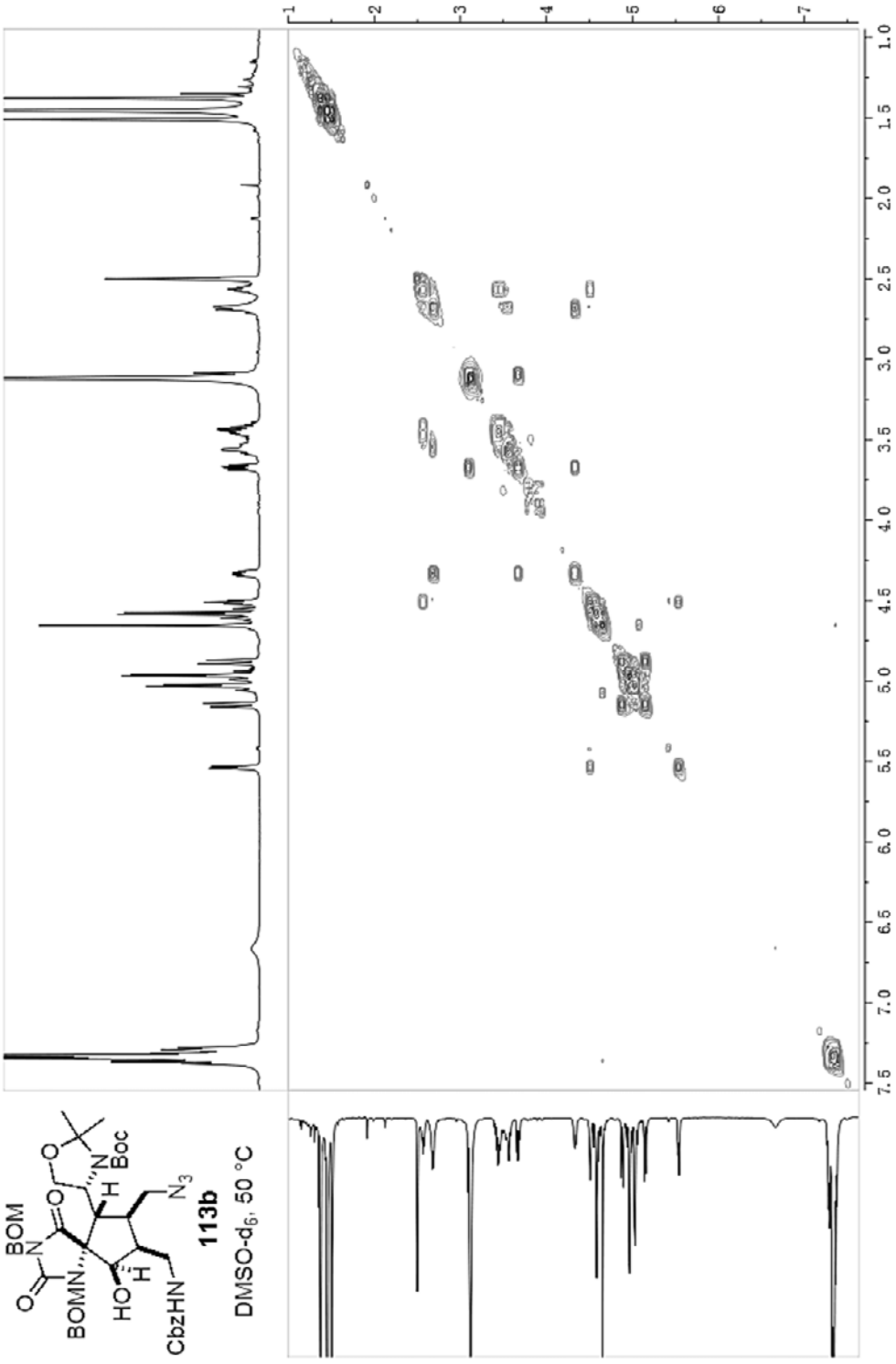

BOM
BOMN
TMSO
BocHN
N3
Boc
108 (from 107)
benzene-d6, 50 °C
7.77
1.96
1.92
3.76
1.06
1.09
1.00
1.11
0.93
1.16
1.11
2.17
2.11

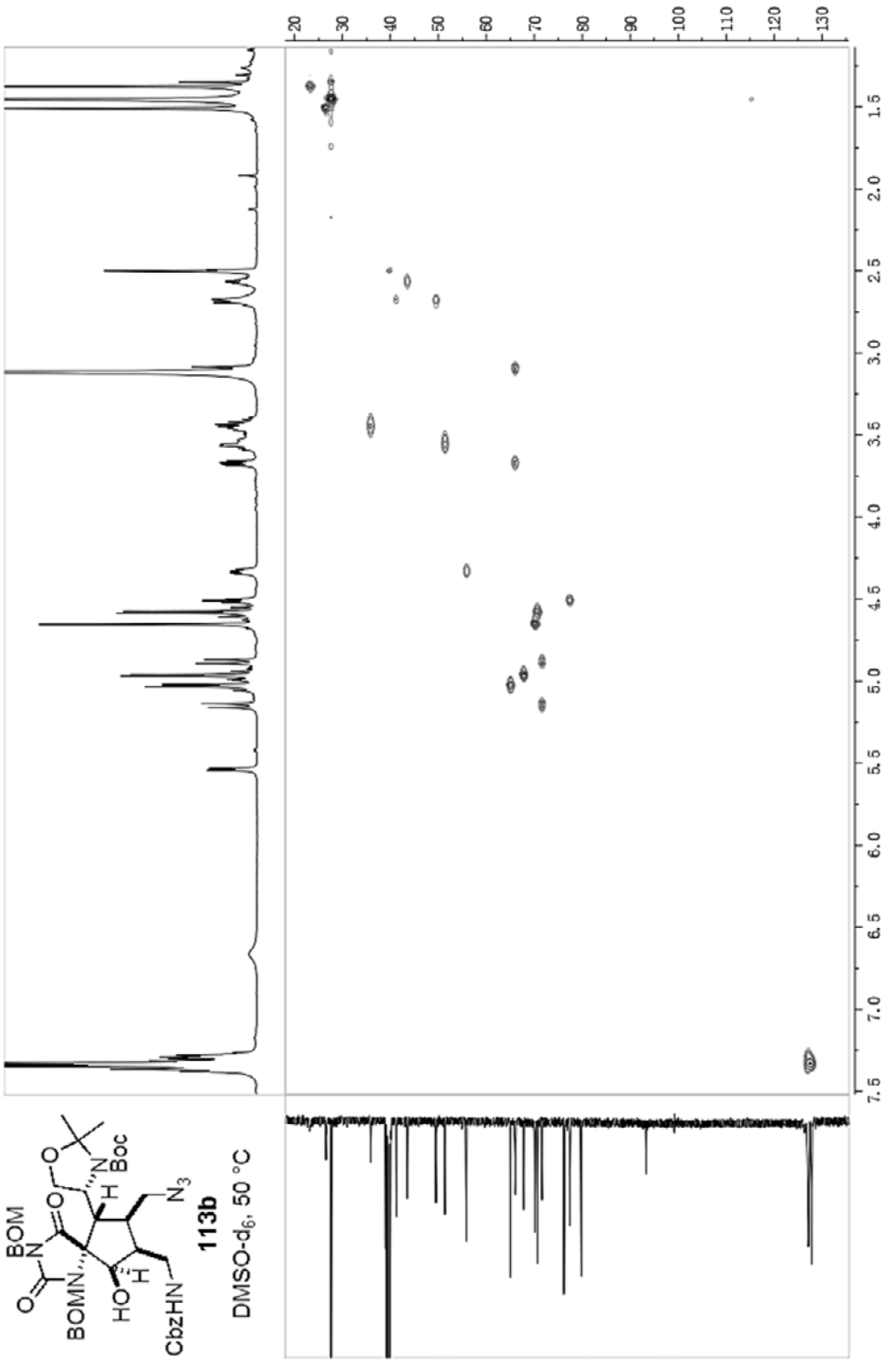

BOM
BOMN
TMSO
H Boc
N3
Boc-HN
108 (from 105)
benzene-d6, 50 °C
0 ppm
1
2
3
4
5
6
7
8
9

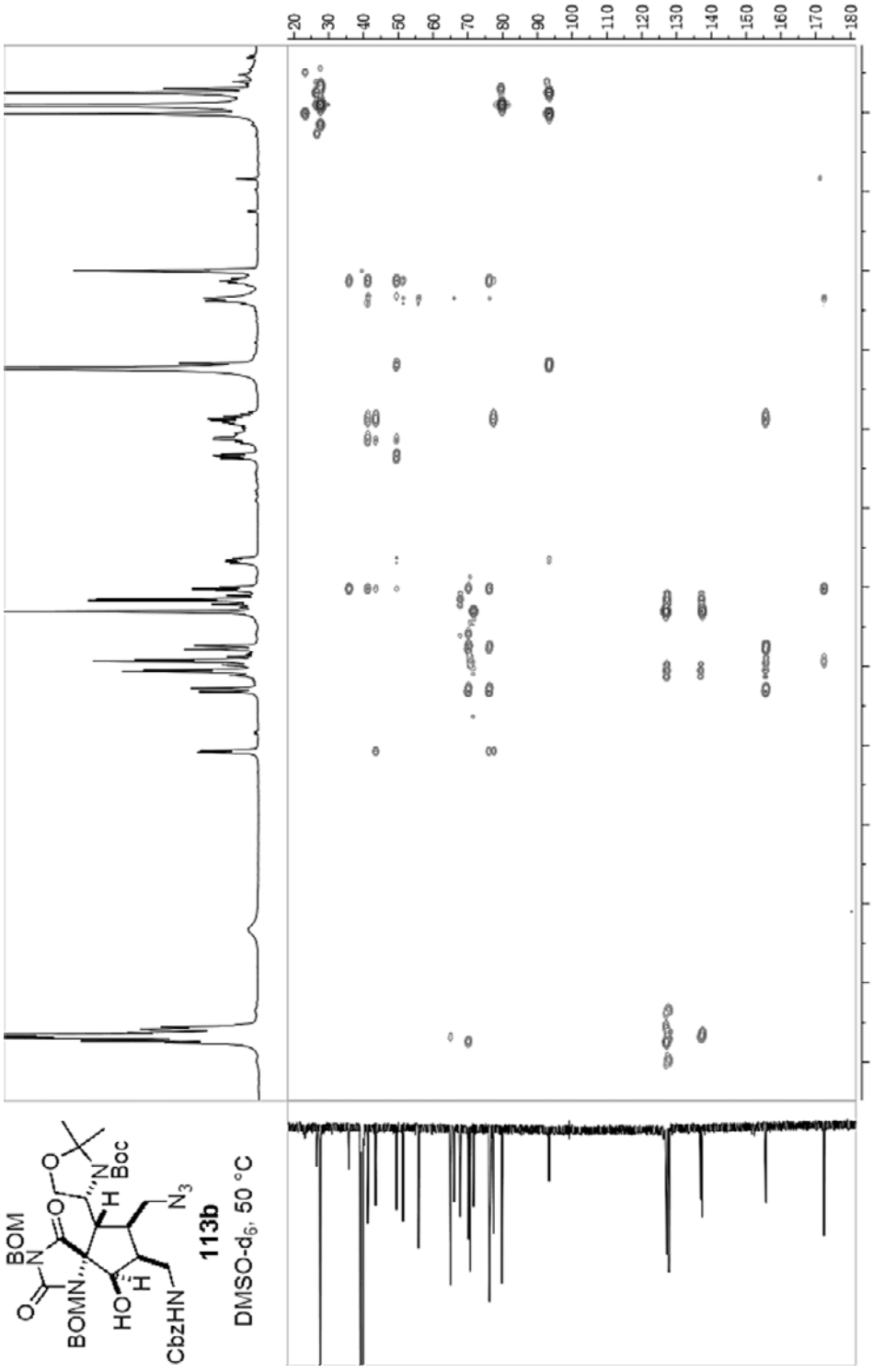

BOM
BOMN
HO
H Boc
N3
BocHN
113a
benzene-d6, 50 °C
0 ppm

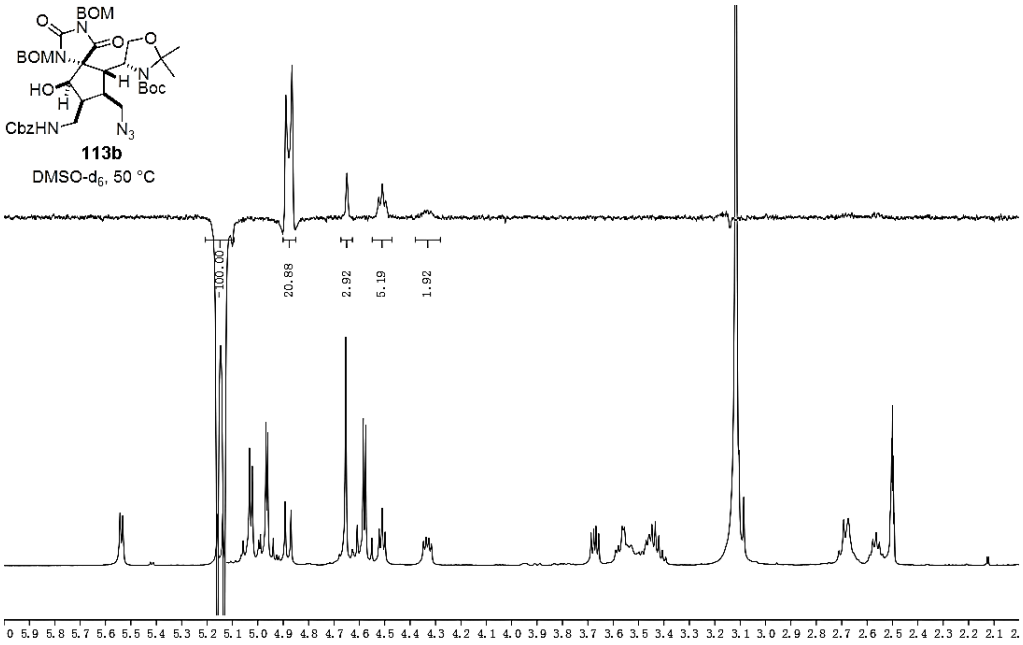

BOM
BOMN
HO
Boc
N3
CbzHN
113b
DMSO-d6, 50 °C

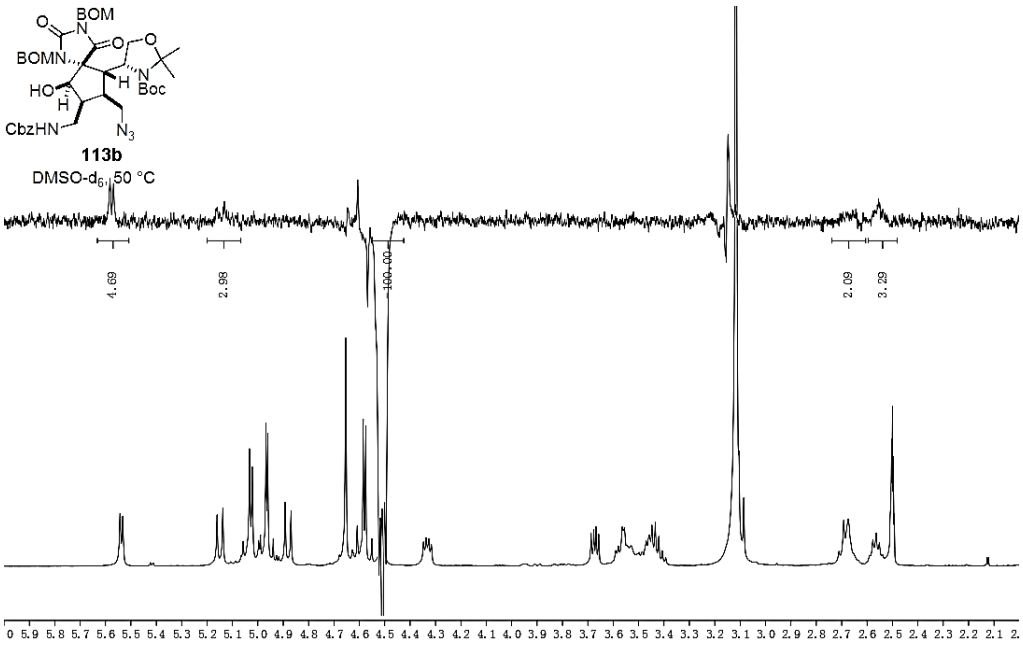

BOM
BOMN
HO
CbzHN
Boc
N_3
113b
DMSO-d_6, 50 °C

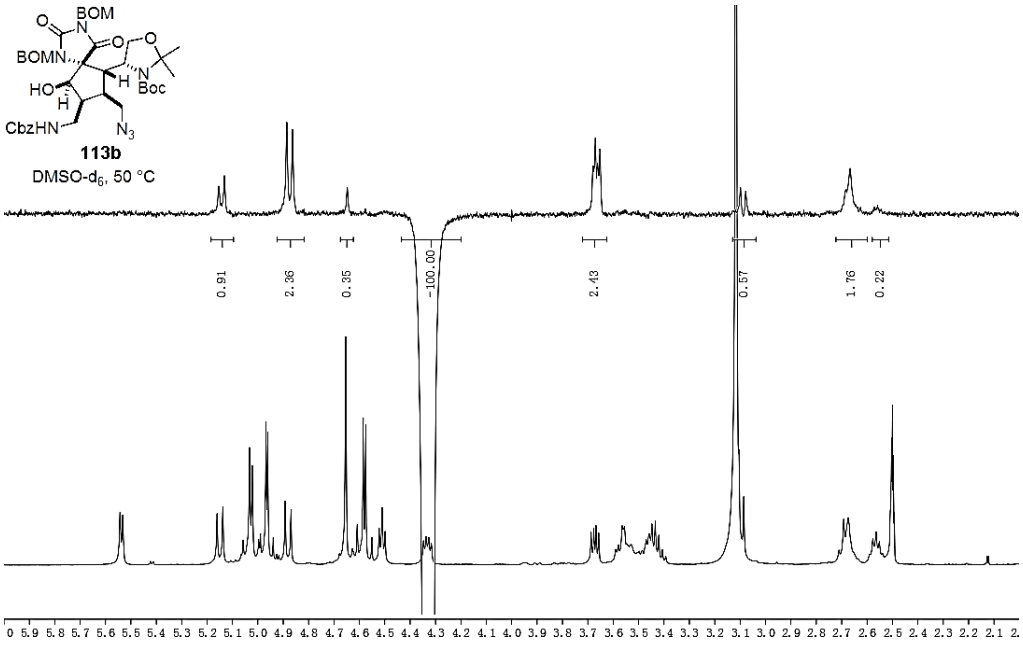

BOM
BOMN
HO
CbzHN
Boc
N_3
113b
DMSO-d_6, 50 °C

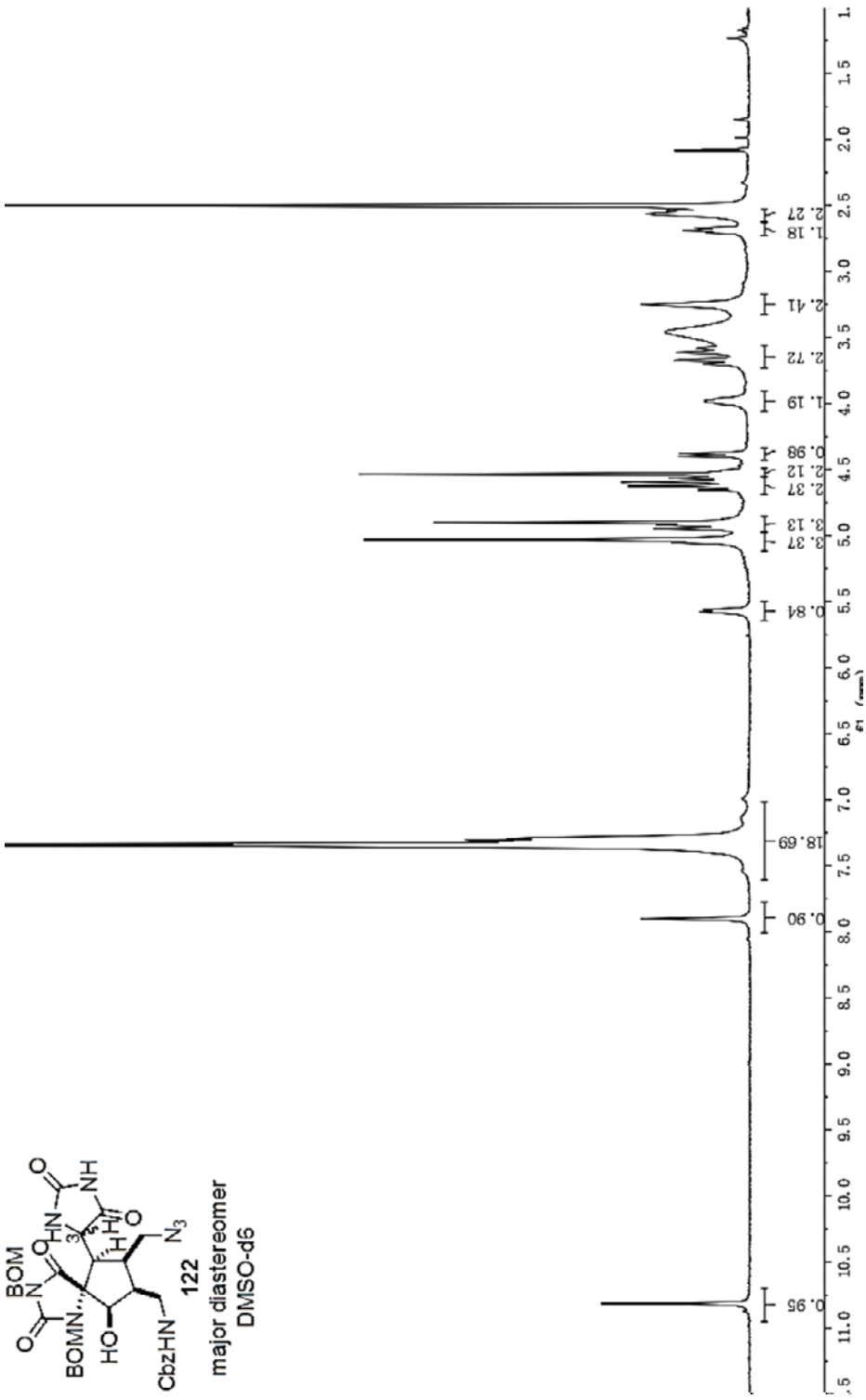

BOM
BOMN
HO
CbzHN
Boc
N_3
113b
DMSO-d_6, 50 °C

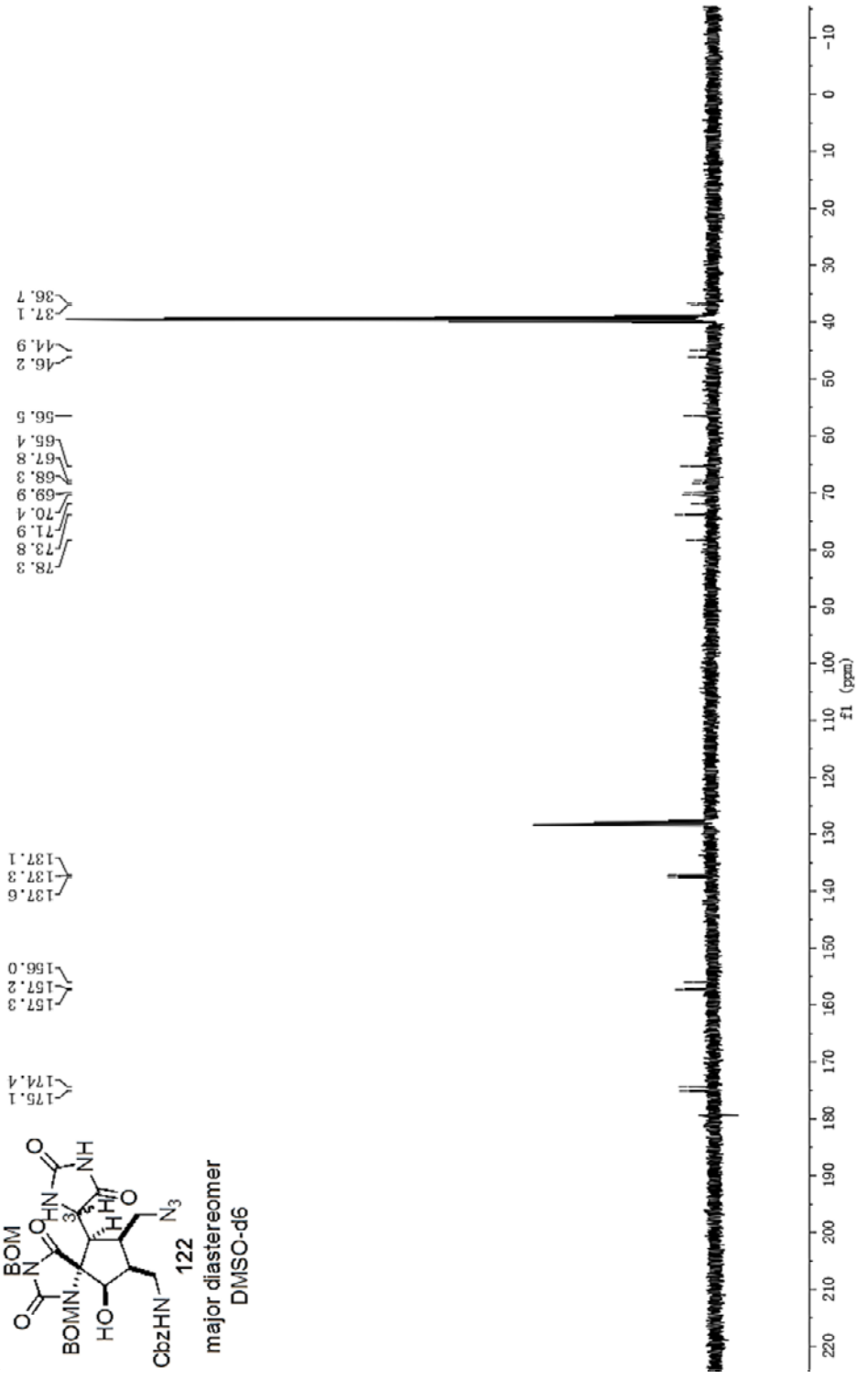

BOM
BOMN
HO
CbzHN
Boc
N_3
113b
DMSO-d_6, 50 °C

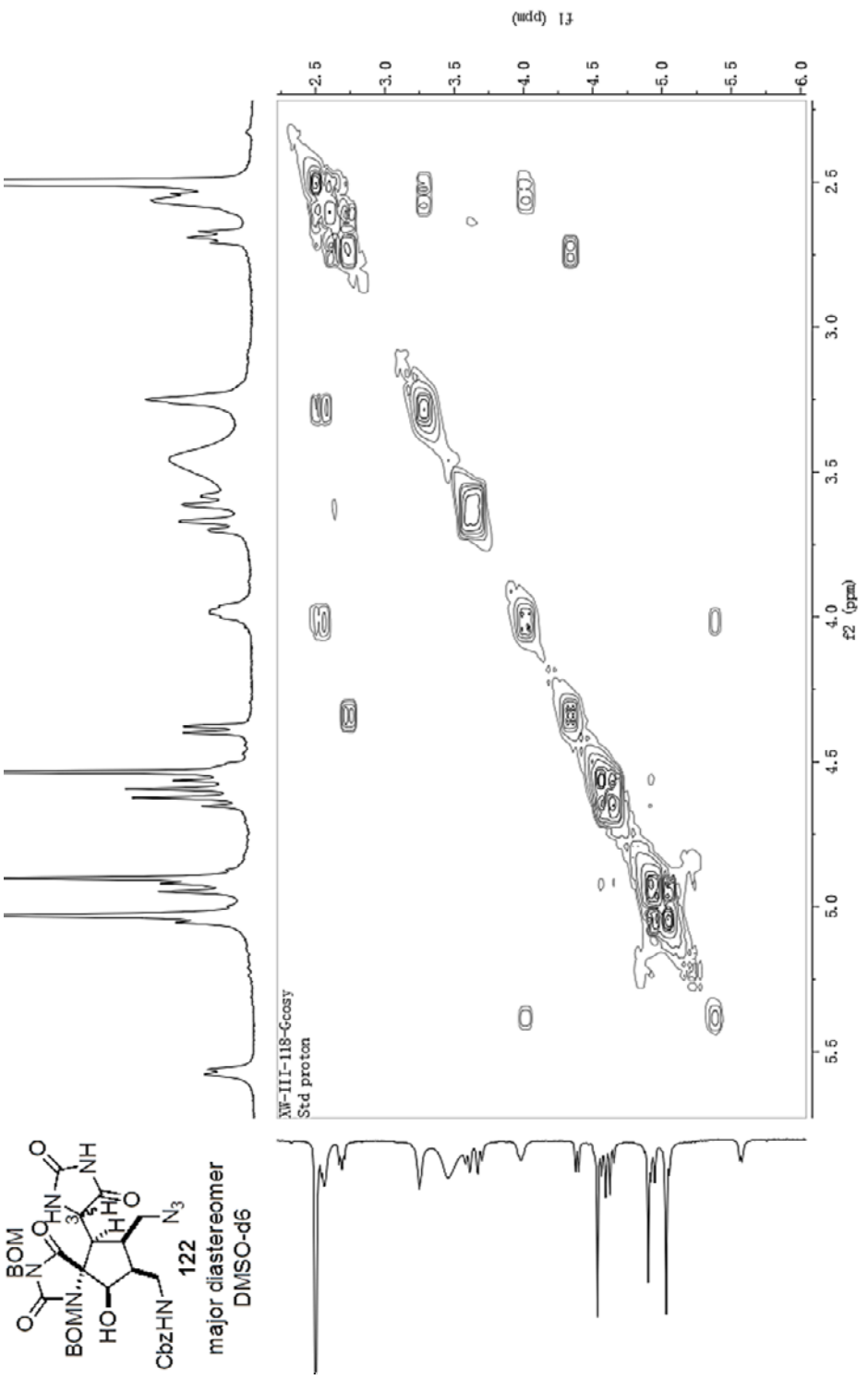

BOM
BOMN
HO
H
N
Boc
CbzHN
N3
113b
DMSO-d6, 50 °C
100.00
20.88
2.92
5.19
1.92

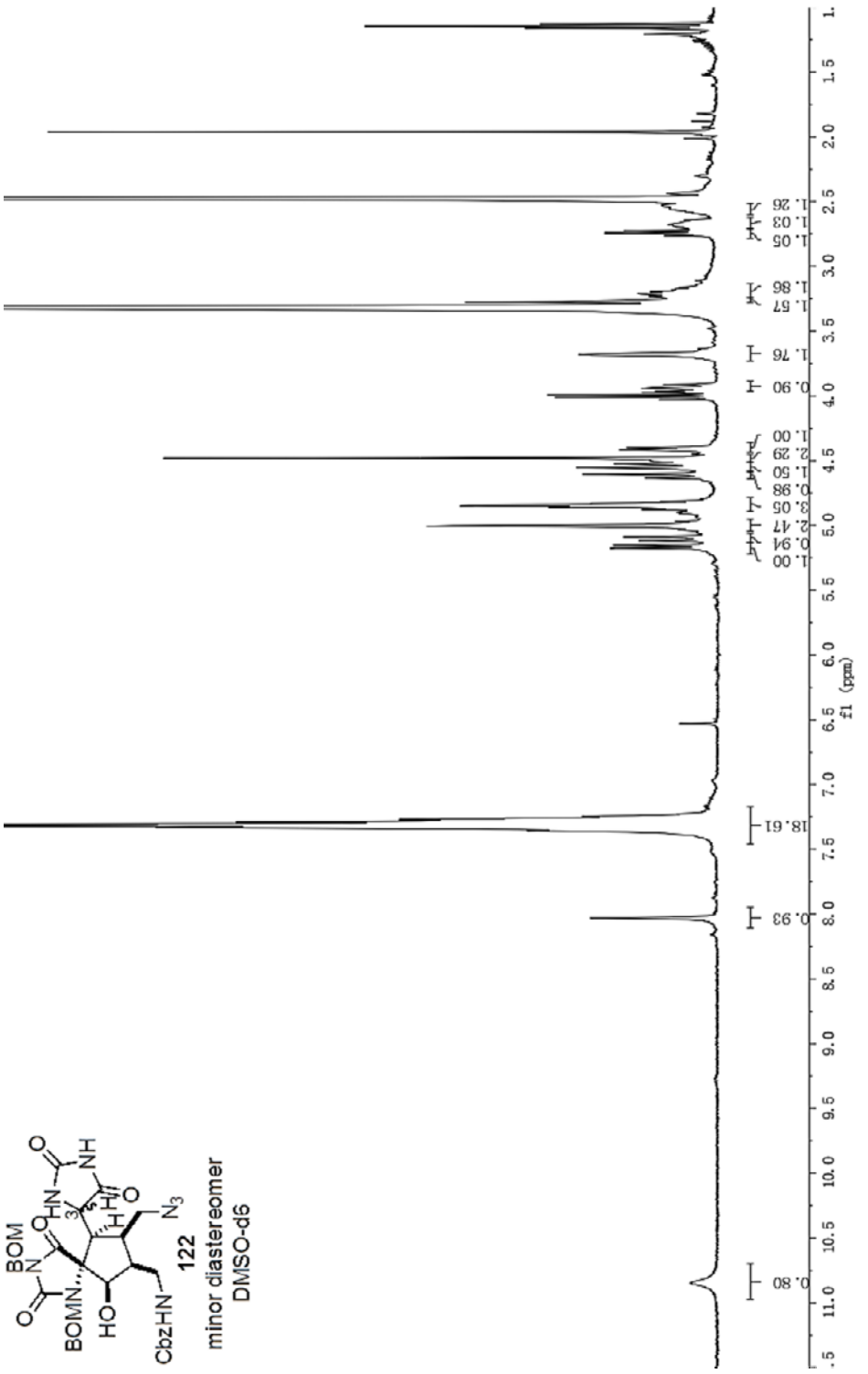

BOM
BOMN
HO
H
N
Boc
CbzHN
N3
113b
DMSO-d6, 50 °C
4.69
2.98
100.00
2.09
3.29

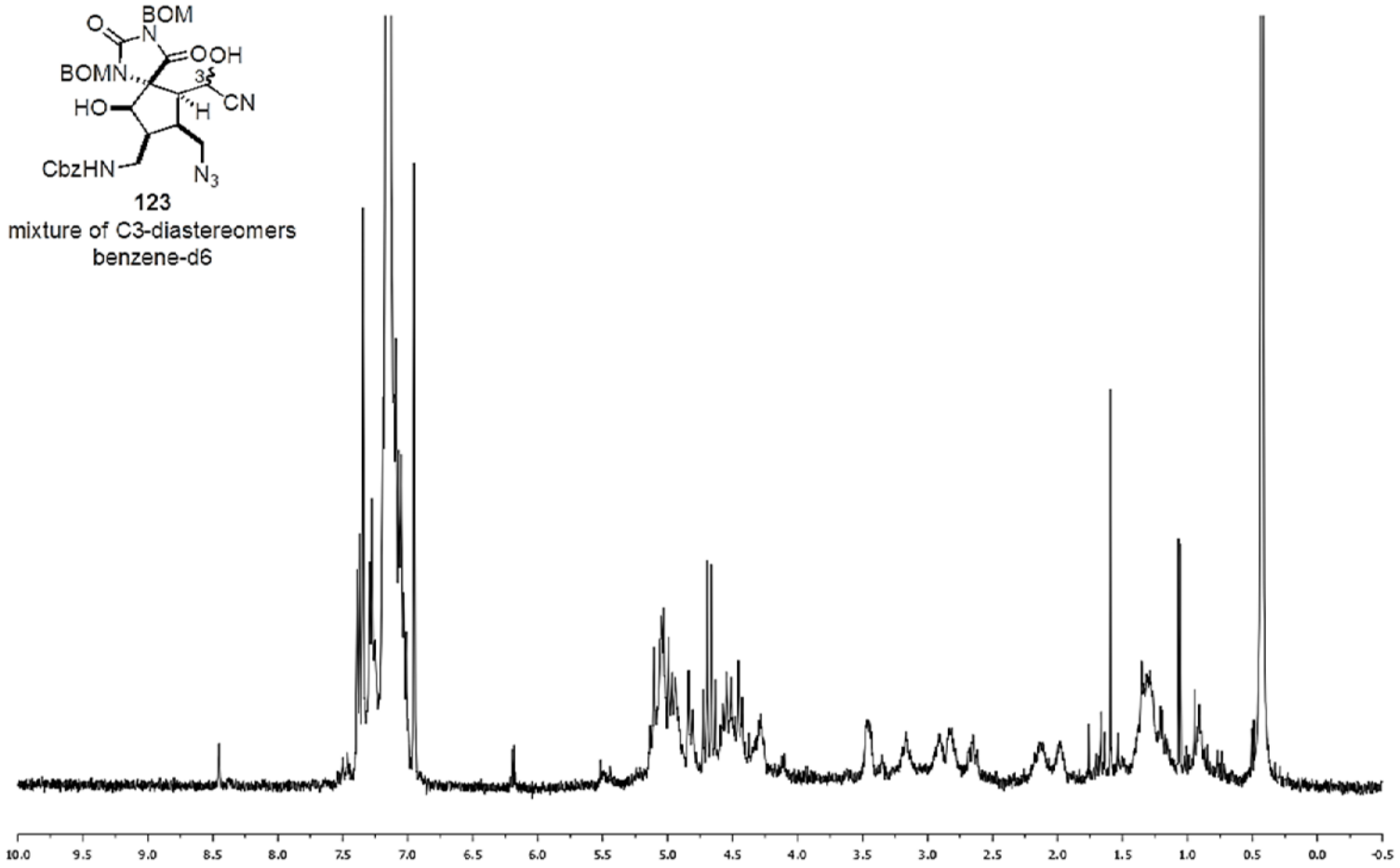

BOM
BOMN
HO
H
H
N
Boc
CbzHN
N3
113b
DMSO-d6, 50 °C
0.91
2.36
0.35
-100.00
2.43
0.57
1.76
0.22


BOM
BOMN
HO
CbzHN
N3
122
major diastereomer
DMSO-d6
0.95
18.69
0.90
0.84
3.37
3.13
2.37
2.12
0.98
1.19
2.72
2.41
1.18
2.27

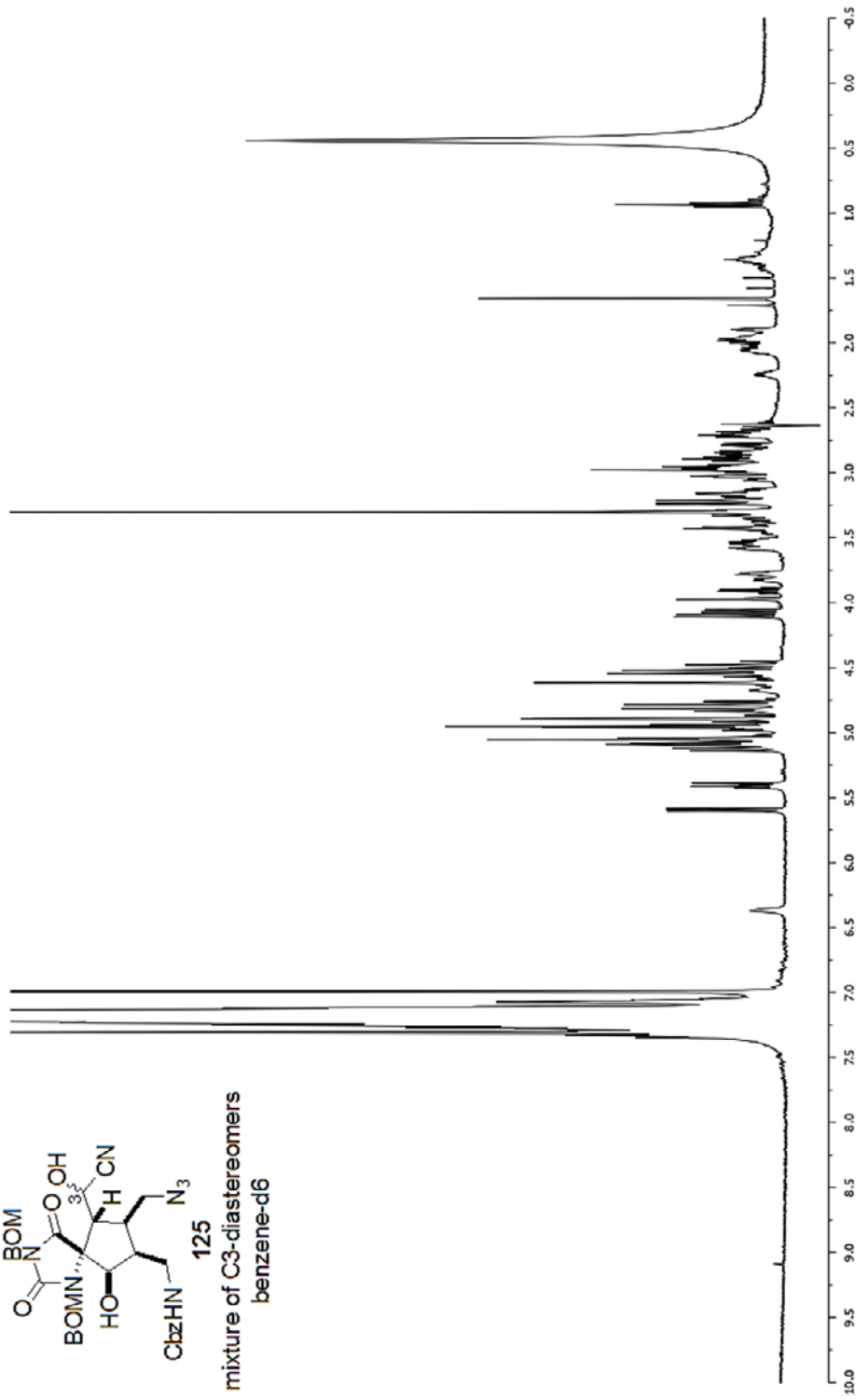

175.1
174.4
157.3
157.2
156.0
137.6
137.3
137.1
78.3
73.8
71.9
70.4
69.9
68.3
67.8
66.4
56.5
46.2
44.9
37.1
36.7
f1 (ppm)
BOM
BOMN
HO
CbzHN
N3
122
major diastereomer
DMSO-d6

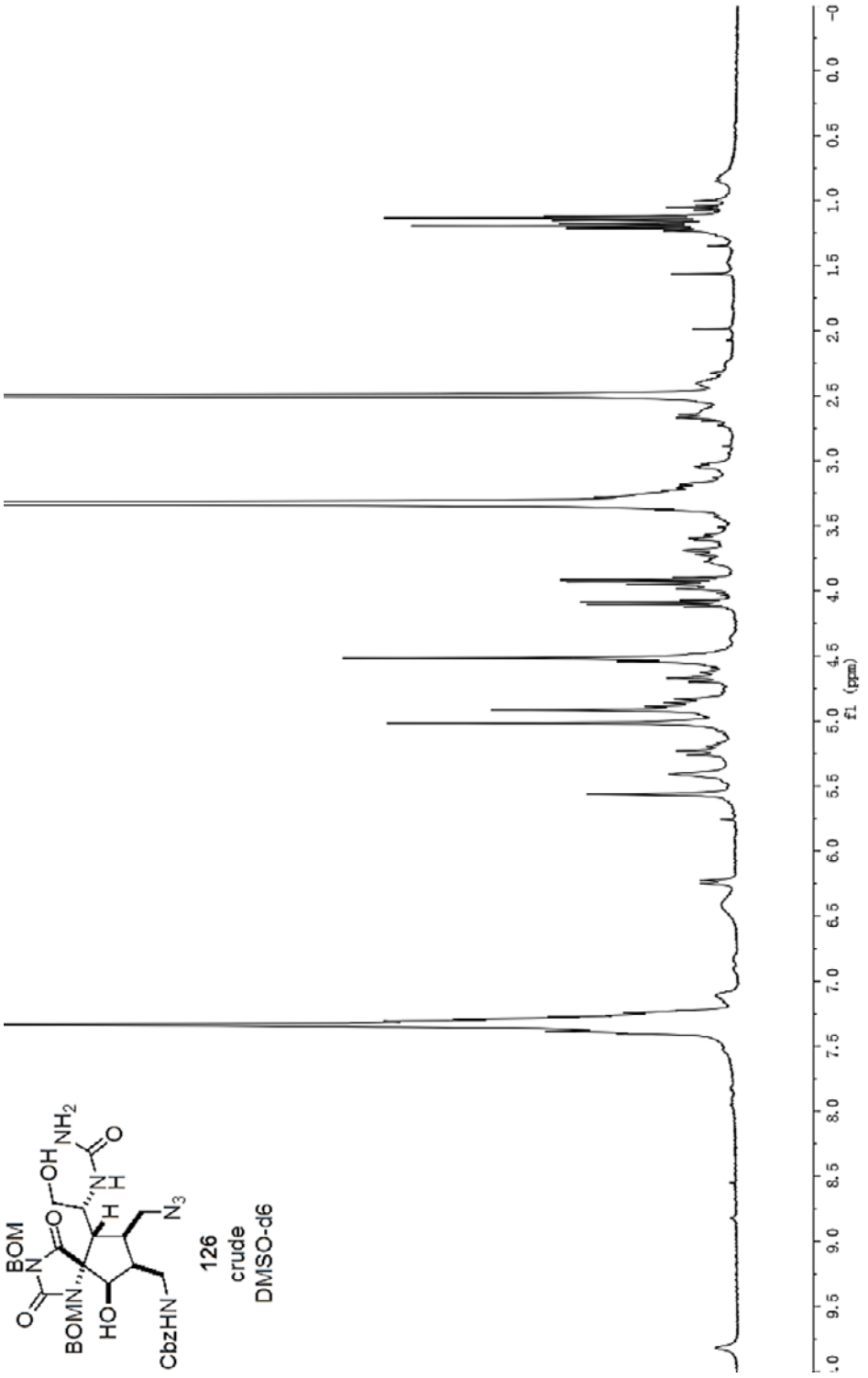

BOM
BOMN
HO
CbzHN
N3
122
major diastereomer
DMSO-d6
XW-III-118-Gcosy
Std proton
f1 (ppm)
f2 (ppm)
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0

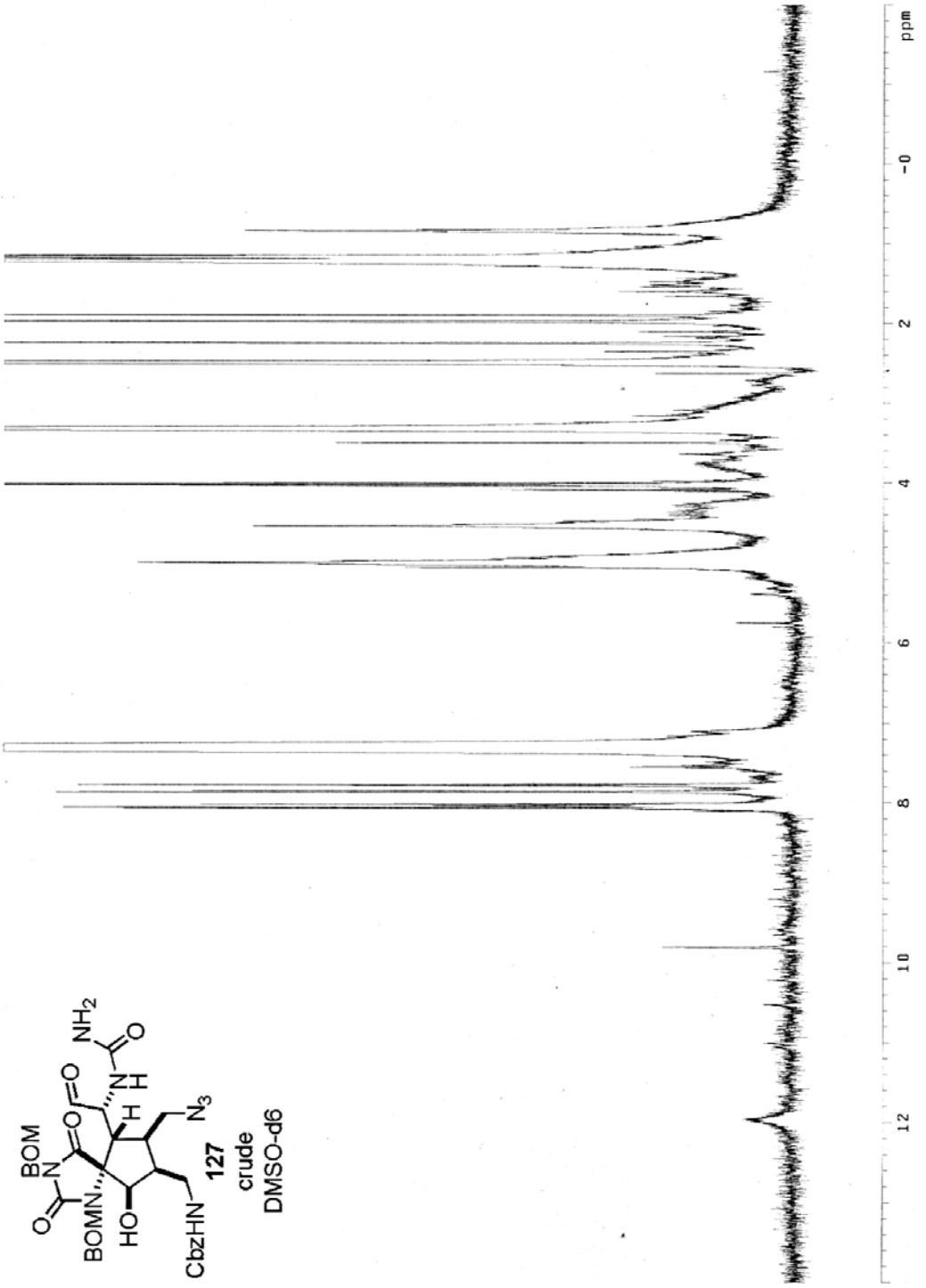

BOM
BOMN
HO
CbzHN
N_3
122
minor diastereomer
DMSO-d6
f1 (ppm)

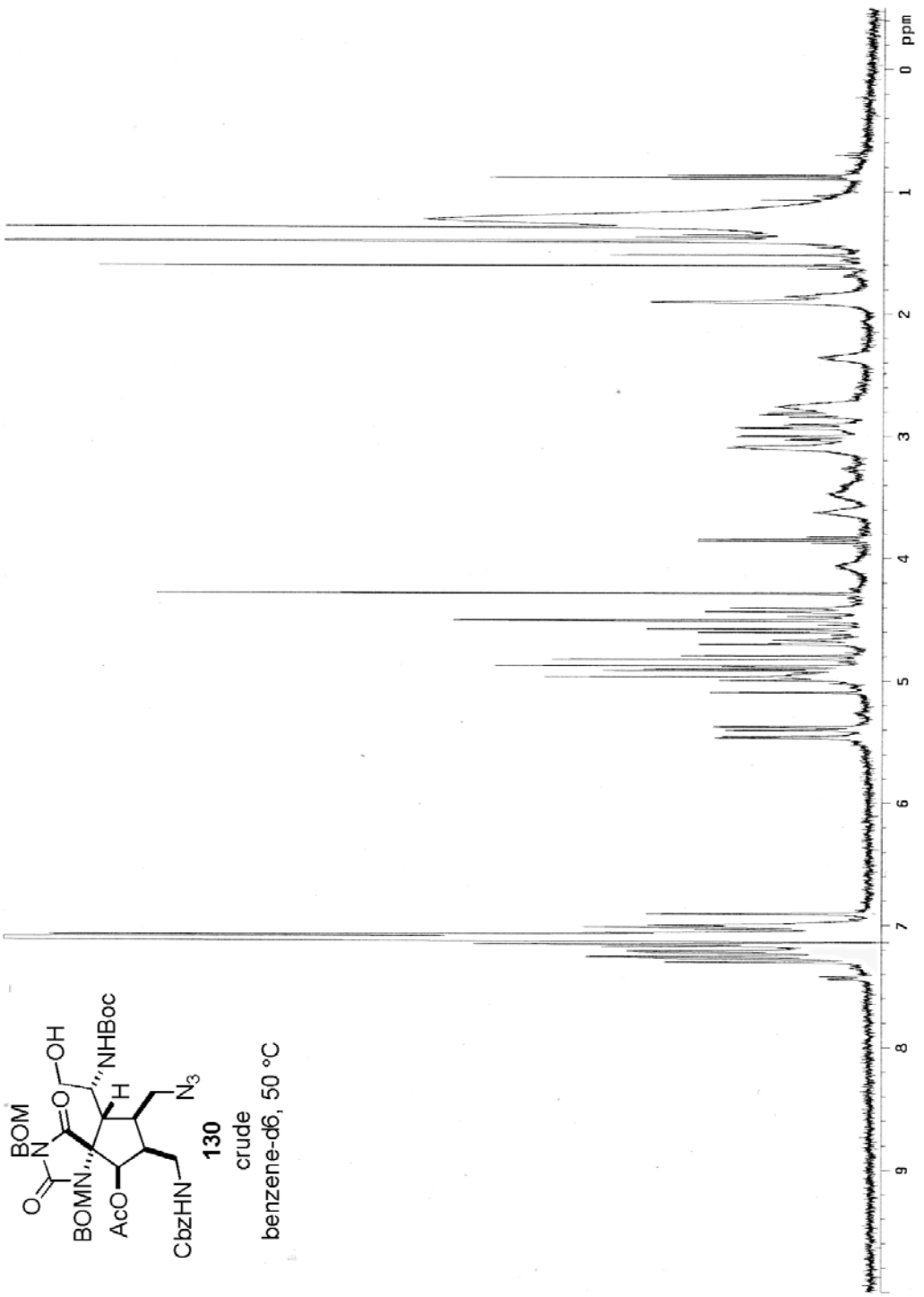


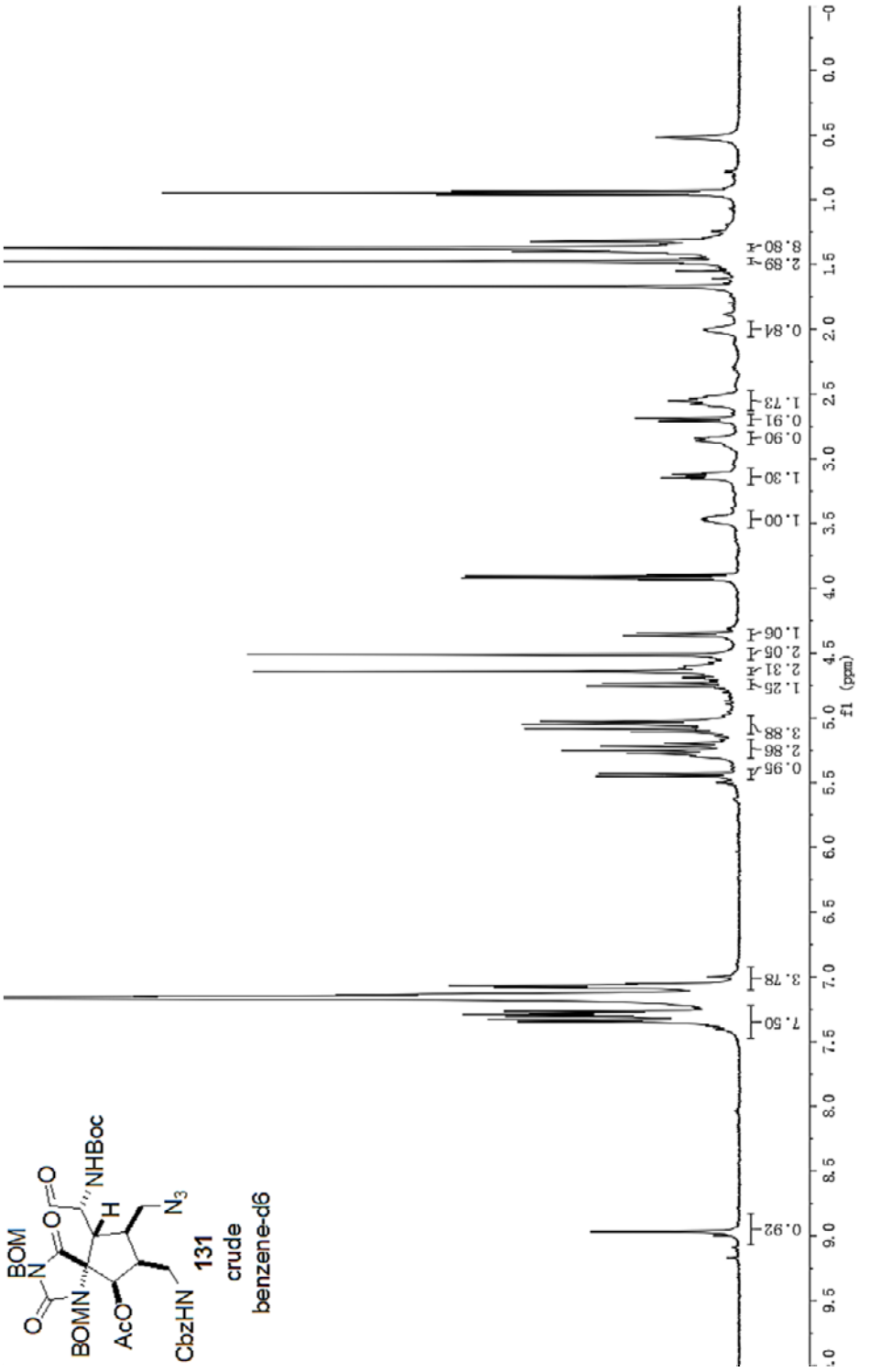
123
mixture of C3-diastereomers
benzene-d6

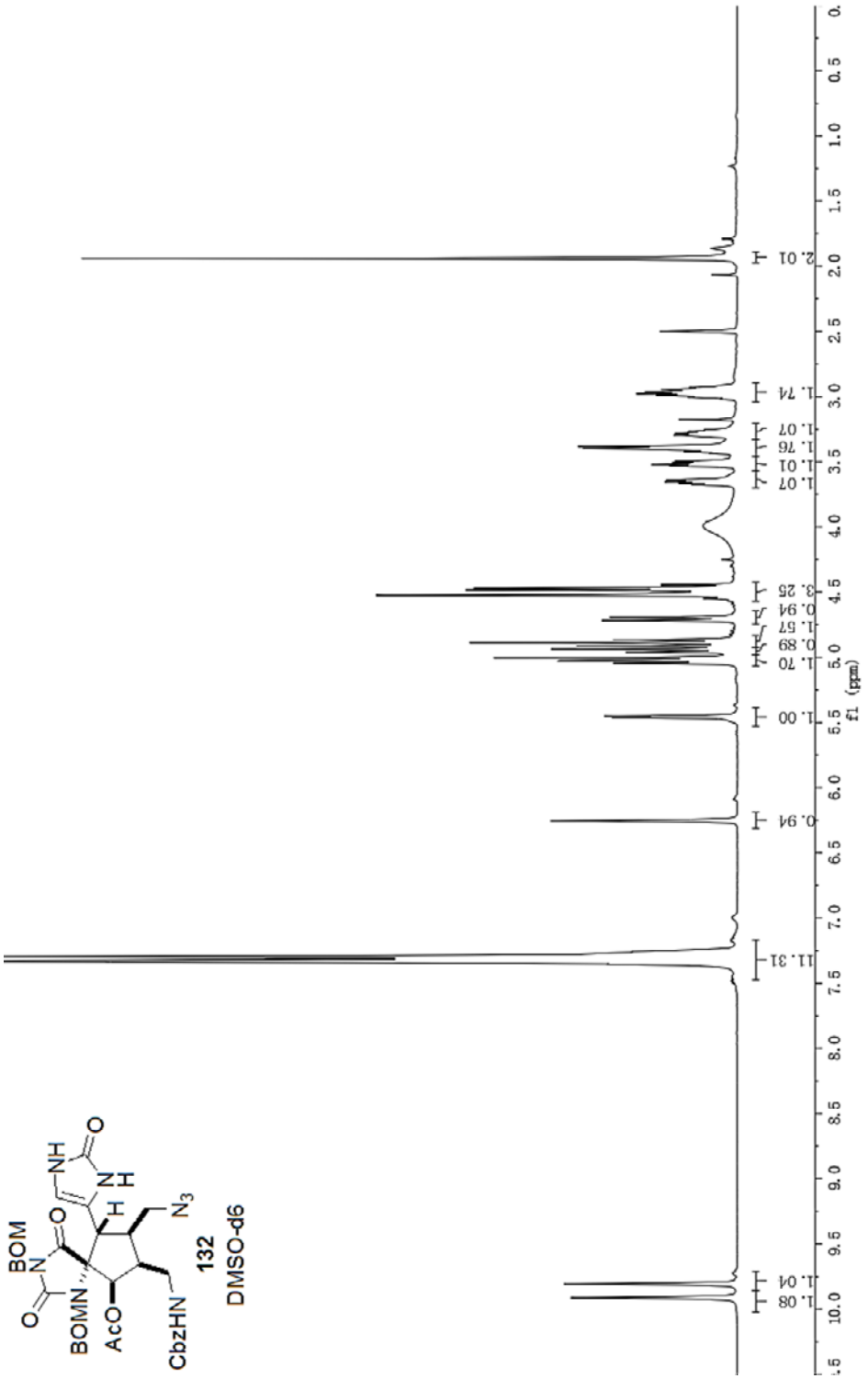

BOM
N
O
O
OH
3
H
CN
BOMN
HO
N3
CbzHN
125
mixture of C3-diastereomers
benzene-d6
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

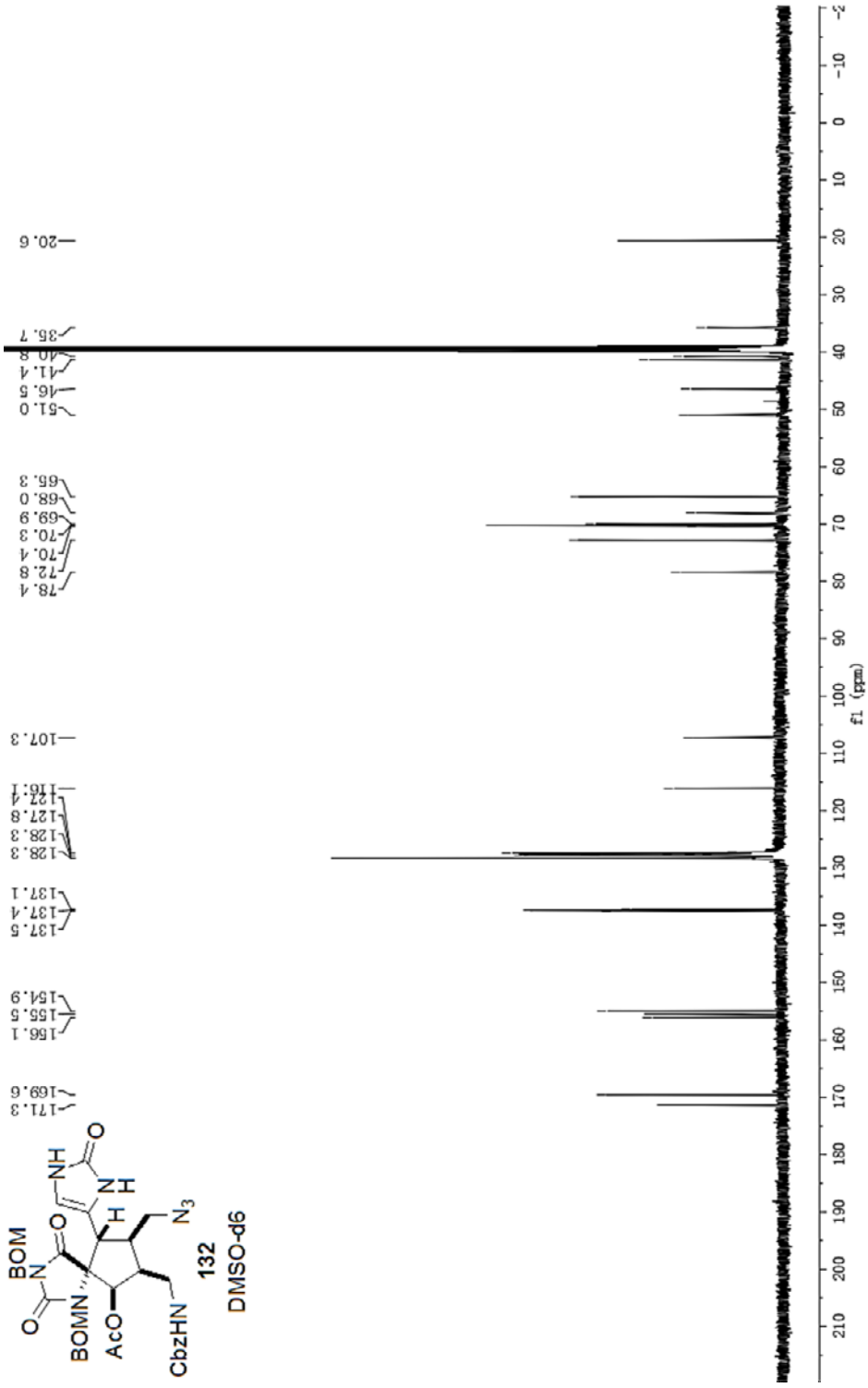

BOM
BOMN
HO
CbzHN
126
crude
DMSO-d6
f1 (ppm)

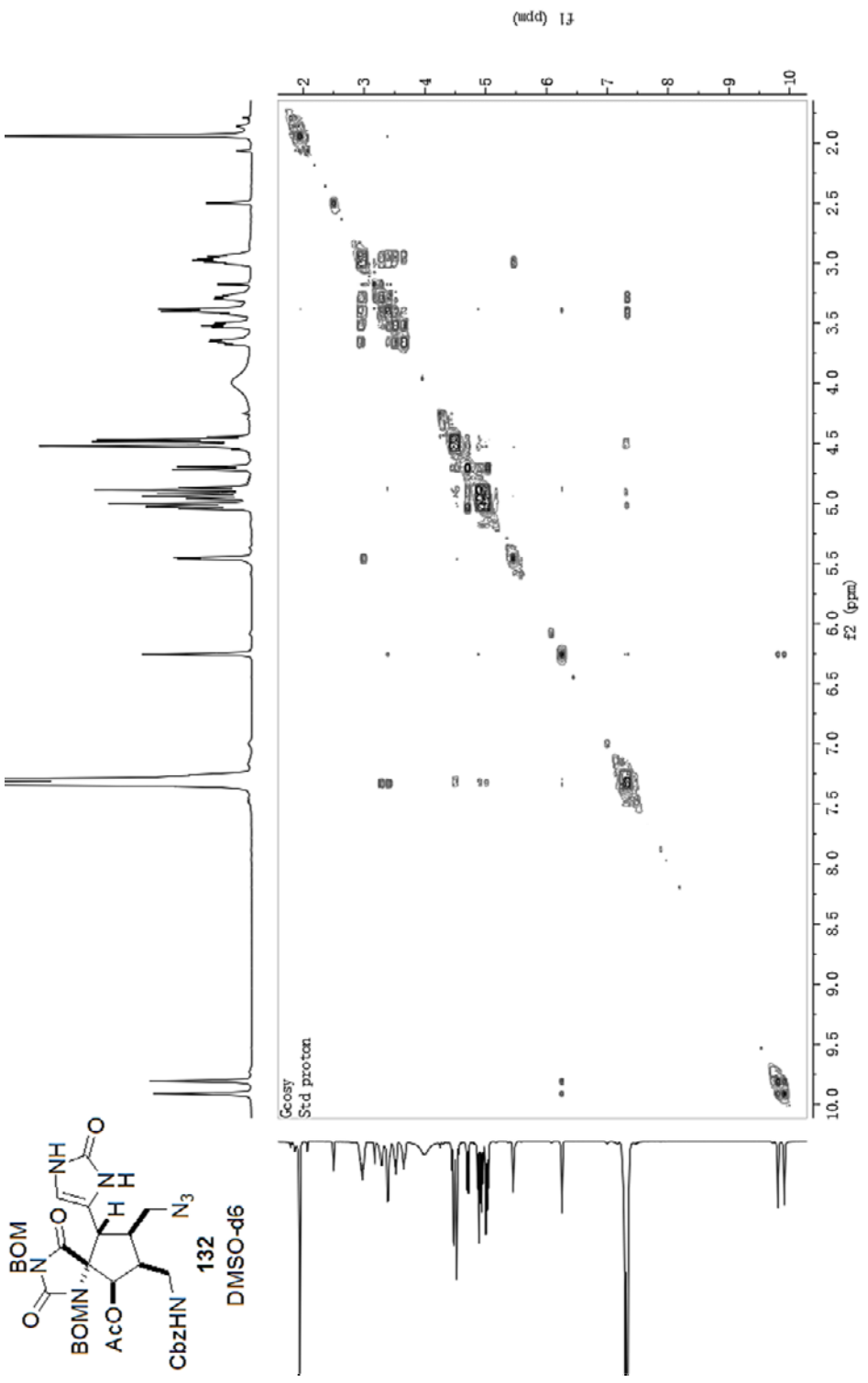

BOM
BOMN
HO
CbzHN
N3
NH2
127
crude
DMSO-d6
ppm
12
10
8
6
4
2
-0

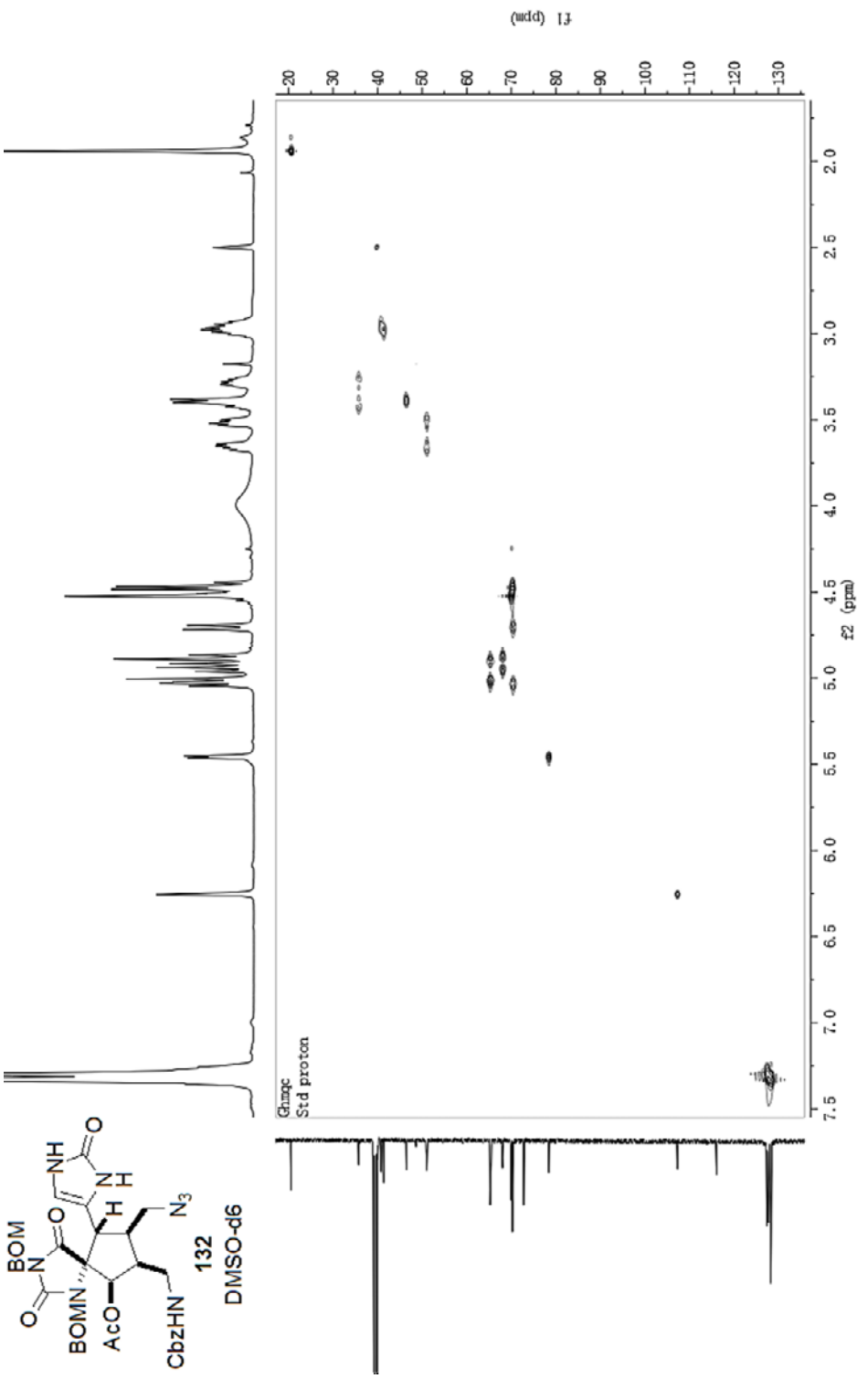

BOM
N
O
O
OH
NHBoc
H
N3
BOMN
AcO
CbzHN
130
crude
benzene-d6, 50 °C
9
8
7
6
5
4
3
2
1
0 ppm

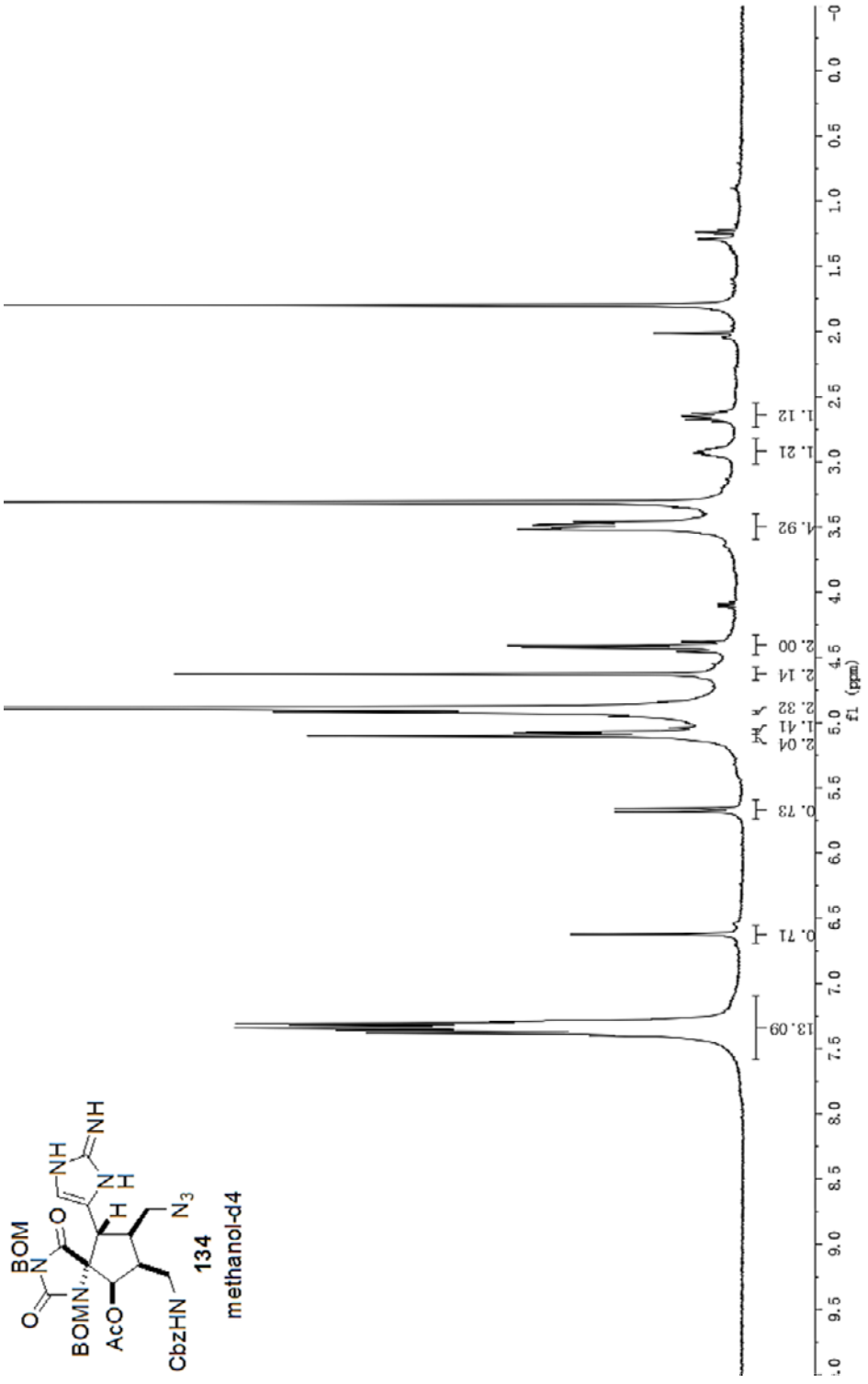

BOM
N
O
O
O
NHBoc
H
BOMN
AcO
N3
CbzHN
131
crude
benzene-d6
0.92
7.50
3.78
0.95
2.86
3.88
1.25
2.31
2.05
1.06
1.00
1.30
0.90
0.91
1.73
0.84
8.80
2.89
f1 (ppm)

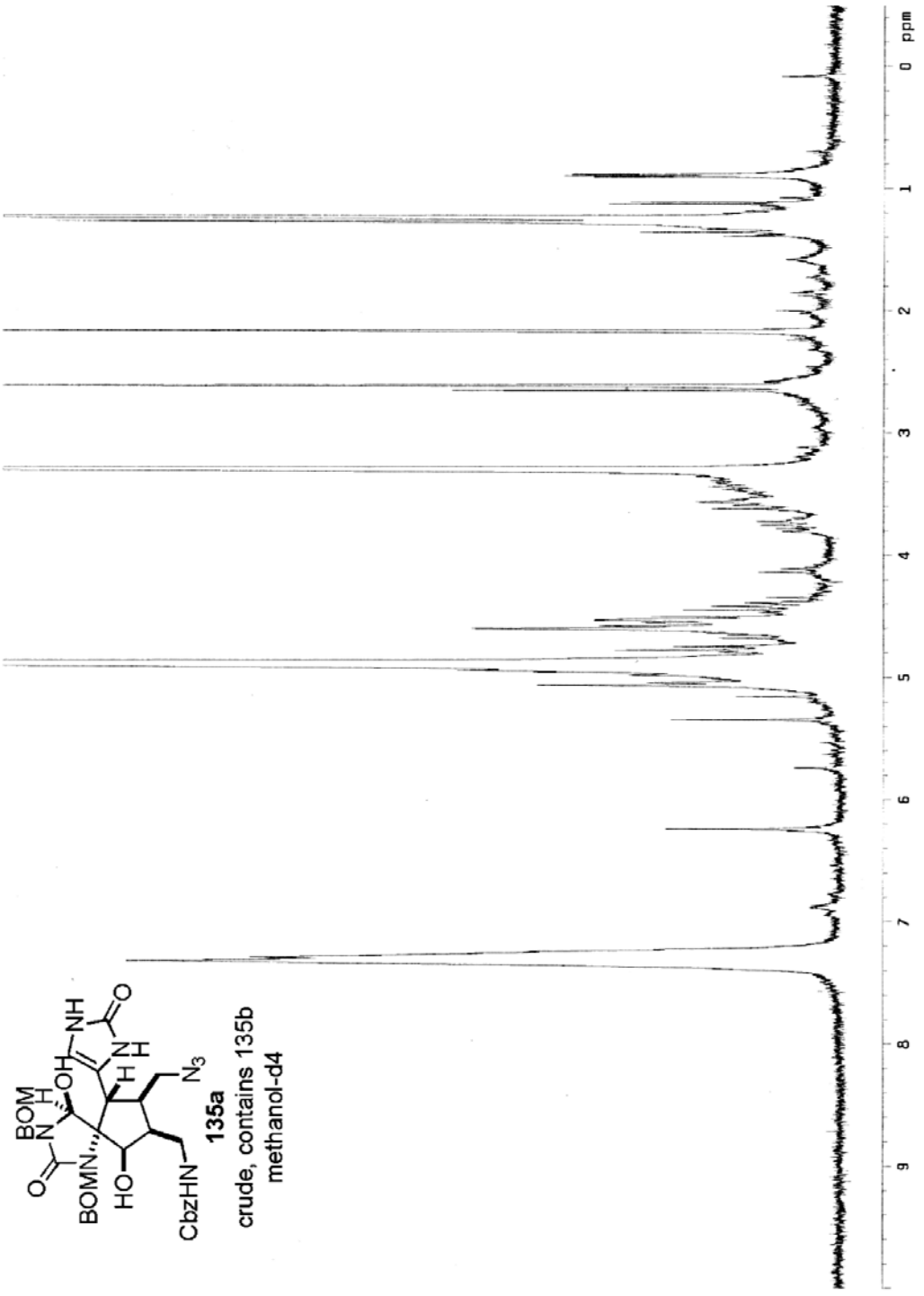

BOM
BOMN
AcO
CbzHN
N3
132
DMSO-d6
f1 (ppm)

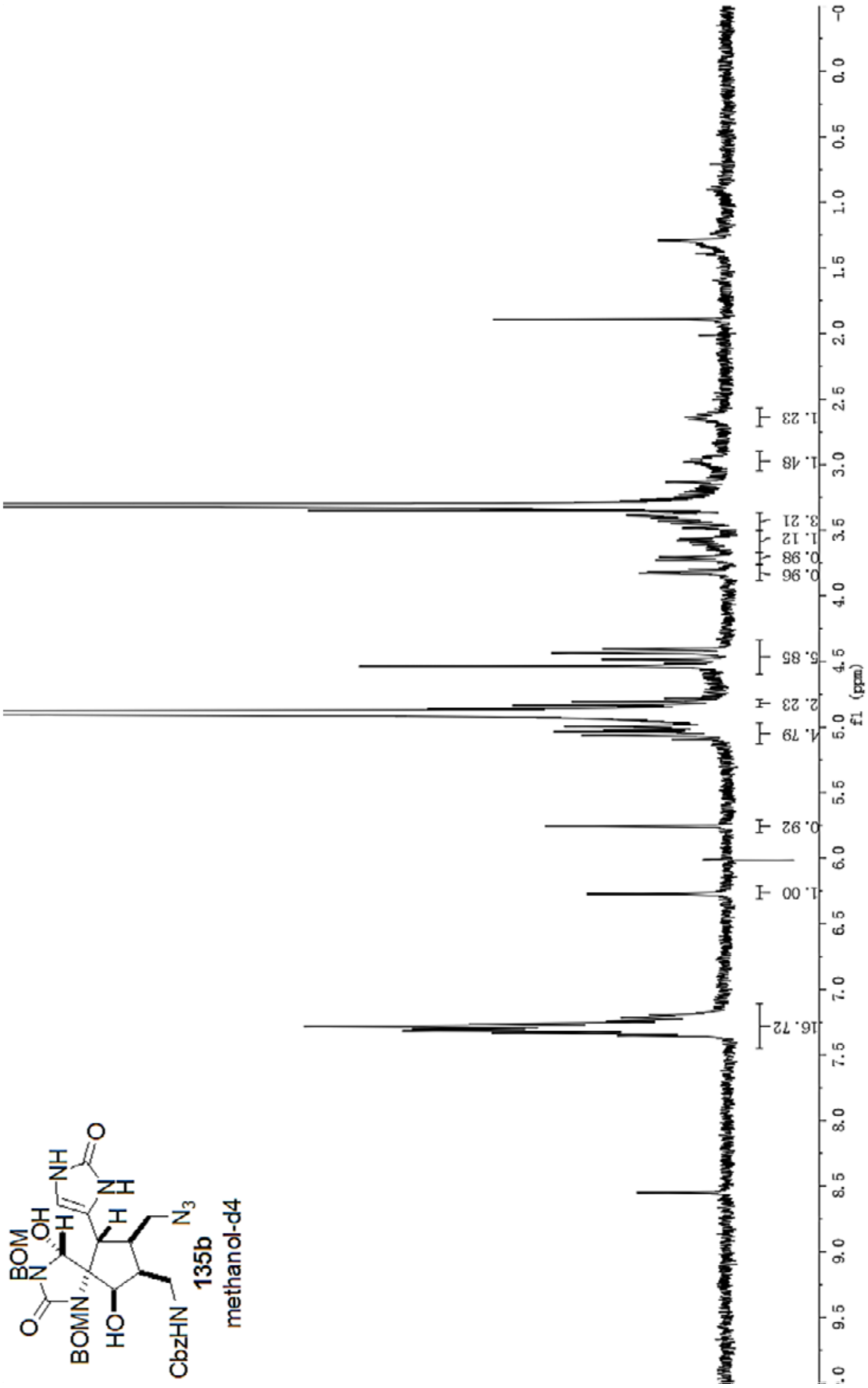

20.6
35.7
40.8
41.4
46.5
51.0
65.3
68.0
69.9
70.3
70.4
72.8
78.4
107.3
116.1
122.4
127.8
128.3
128.3
137.1
137.4
137.5
154.9
155.5
156.1
169.6
171.3
f1 (ppm)
BOM
BOMN
AcO
CbzHN
132
DMSO-d6

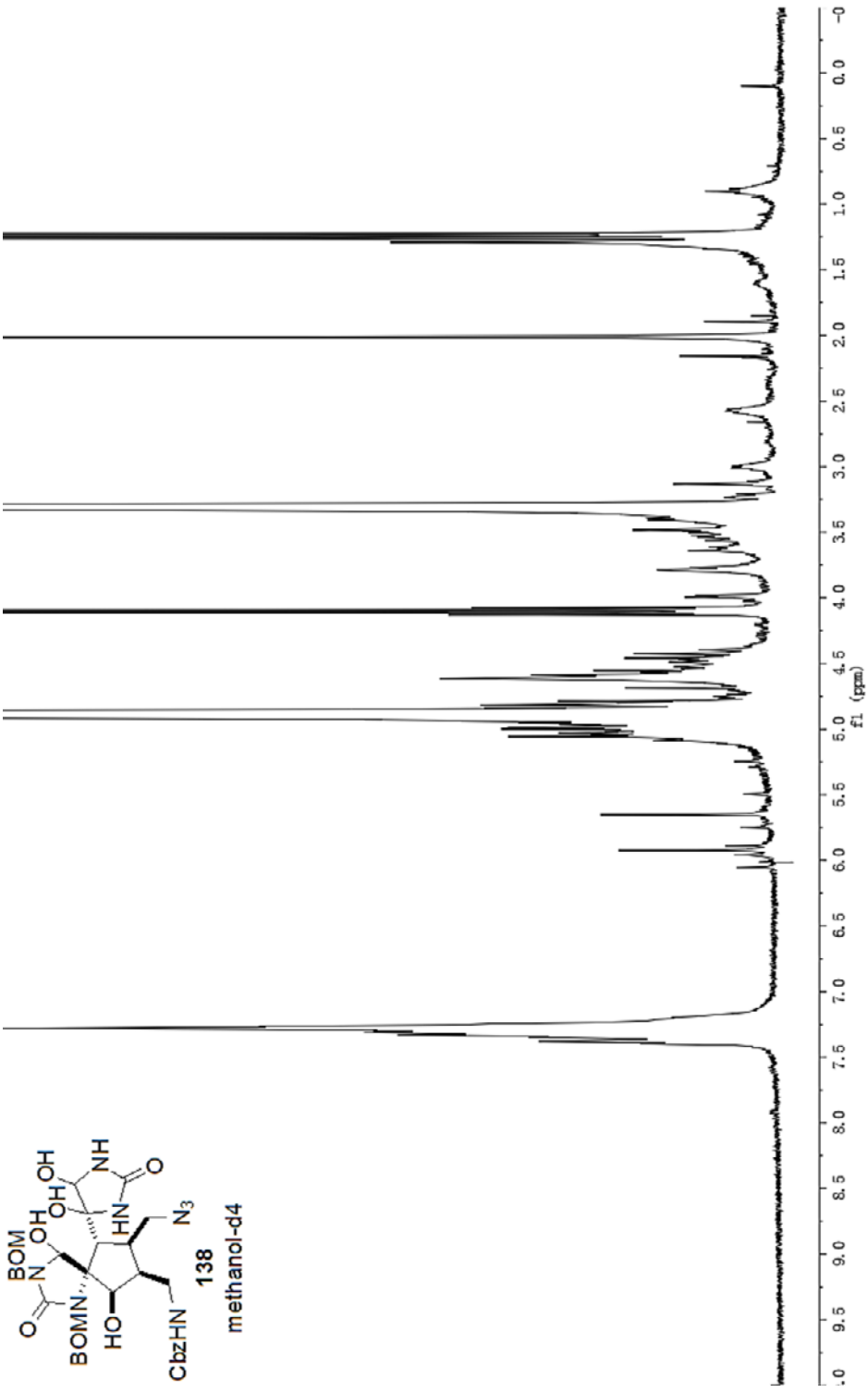

BOM
BOMN
AcO
CbzHN
132
DMSO-d6
Cosy
Std proton
f2 (ppm)
f1 (ppm)

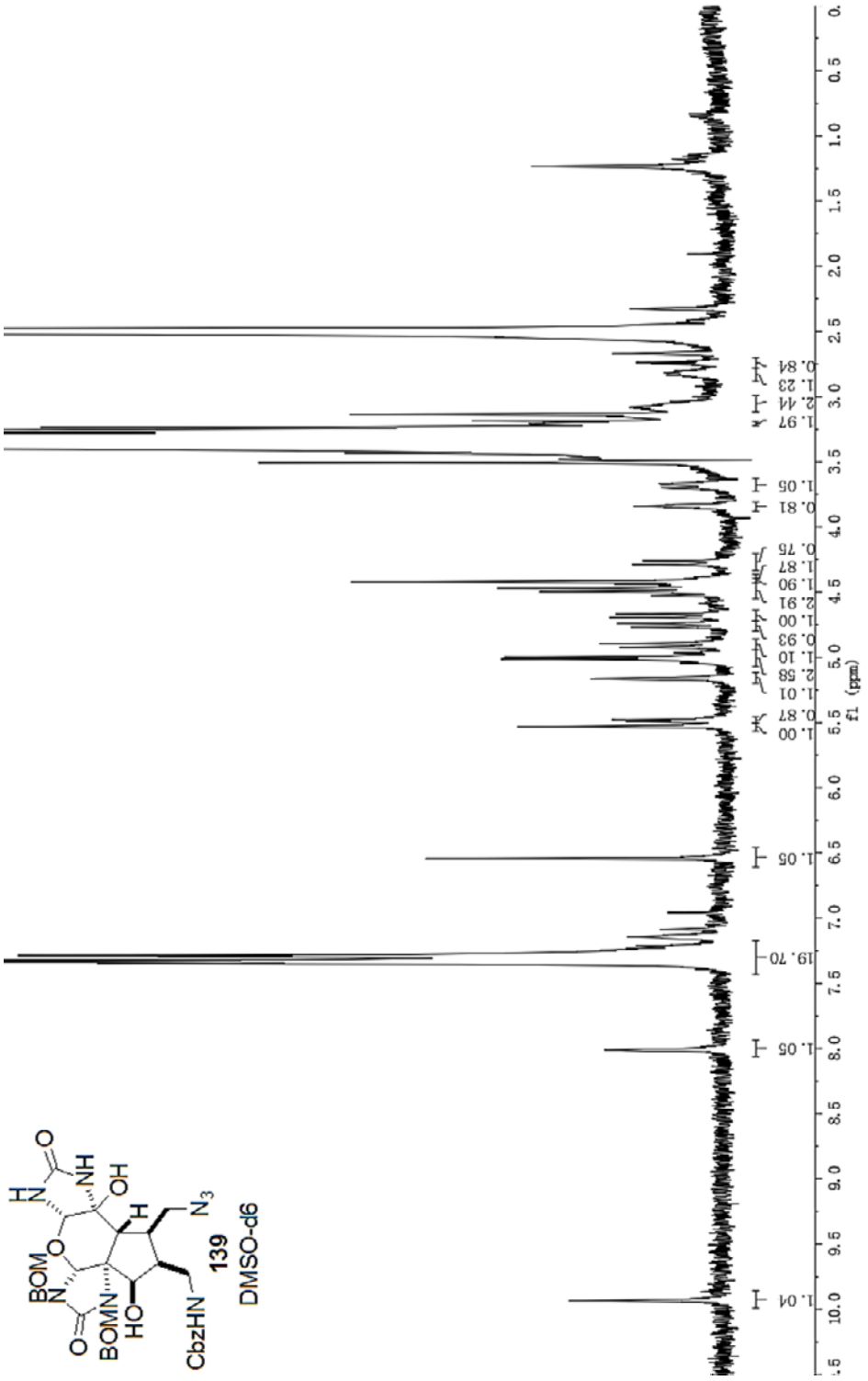

BOM
BOMN
AcO
CbzHN
N_3
132
DMSO-d6
Gmqc
Std proton
f1 (ppm)
f2 (ppm)

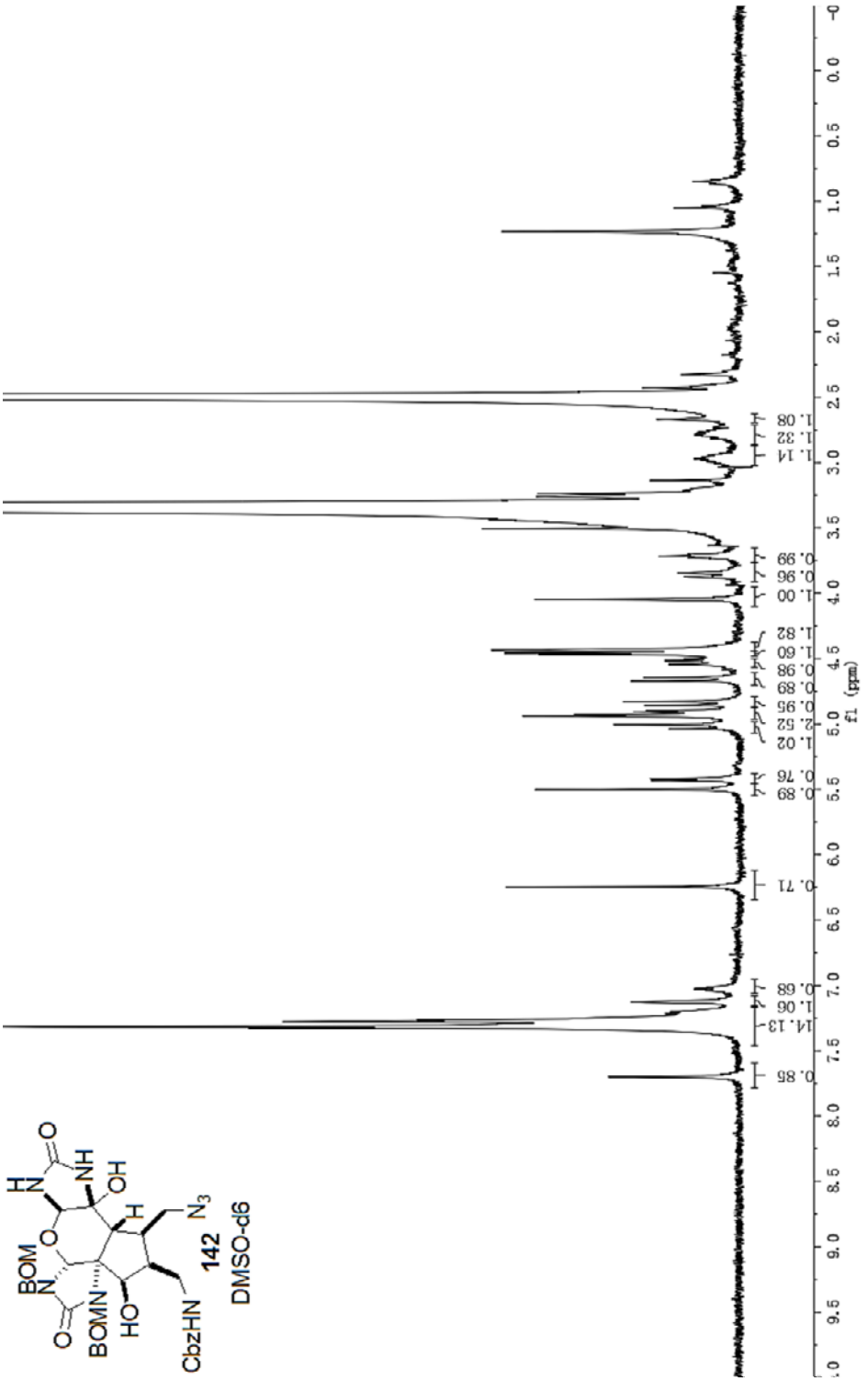

BOM
BOMN
AcO
CbzHN
N_3
134
methanol-d4
13.09
0.71
0.73
2.04
1.41
2.32
2.14
2.00
4.92
1.21
1.12
f1 (ppm)

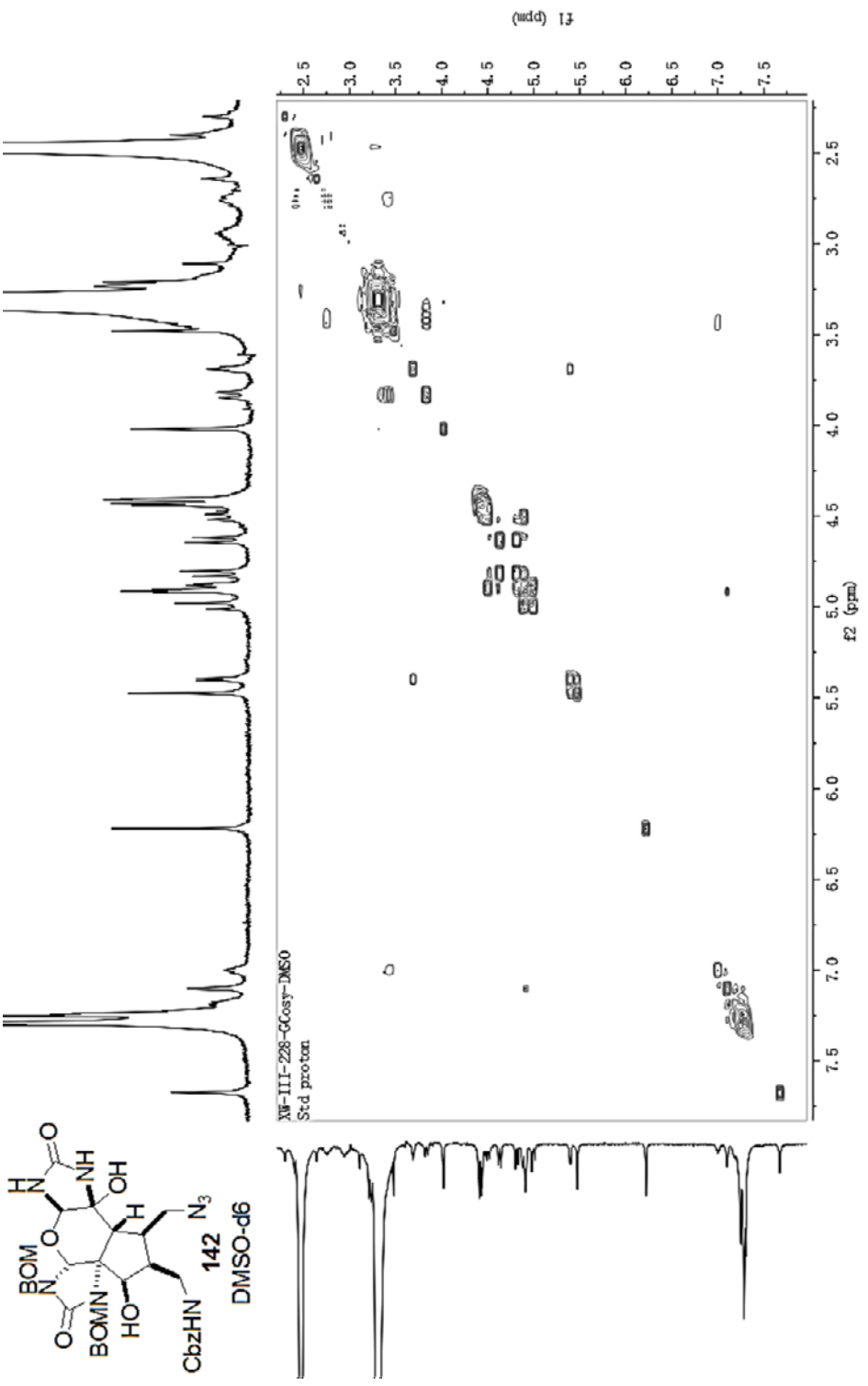

BOM
NH
O
OH
NH
H
N3
BOMN
HO
CbzHN
135a
crude, contains 135b
methanol-d4
9
8
7
6
5
4
3
2
1
0 ppm

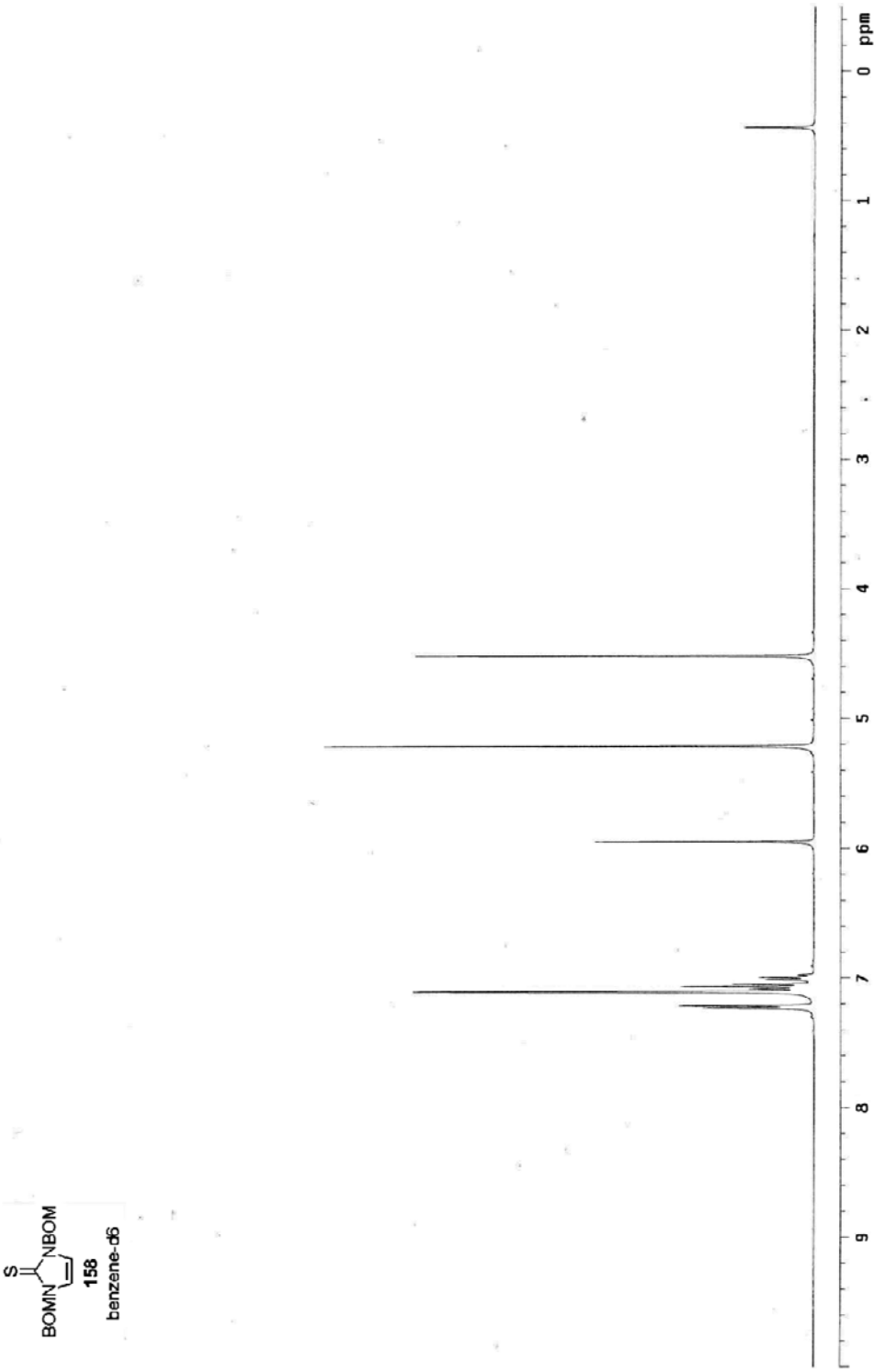

BOM
OH
H
NH
O
BOMN
HO
H
H
N3
CbzHN
135b
methanol-d4
f1 (ppm)

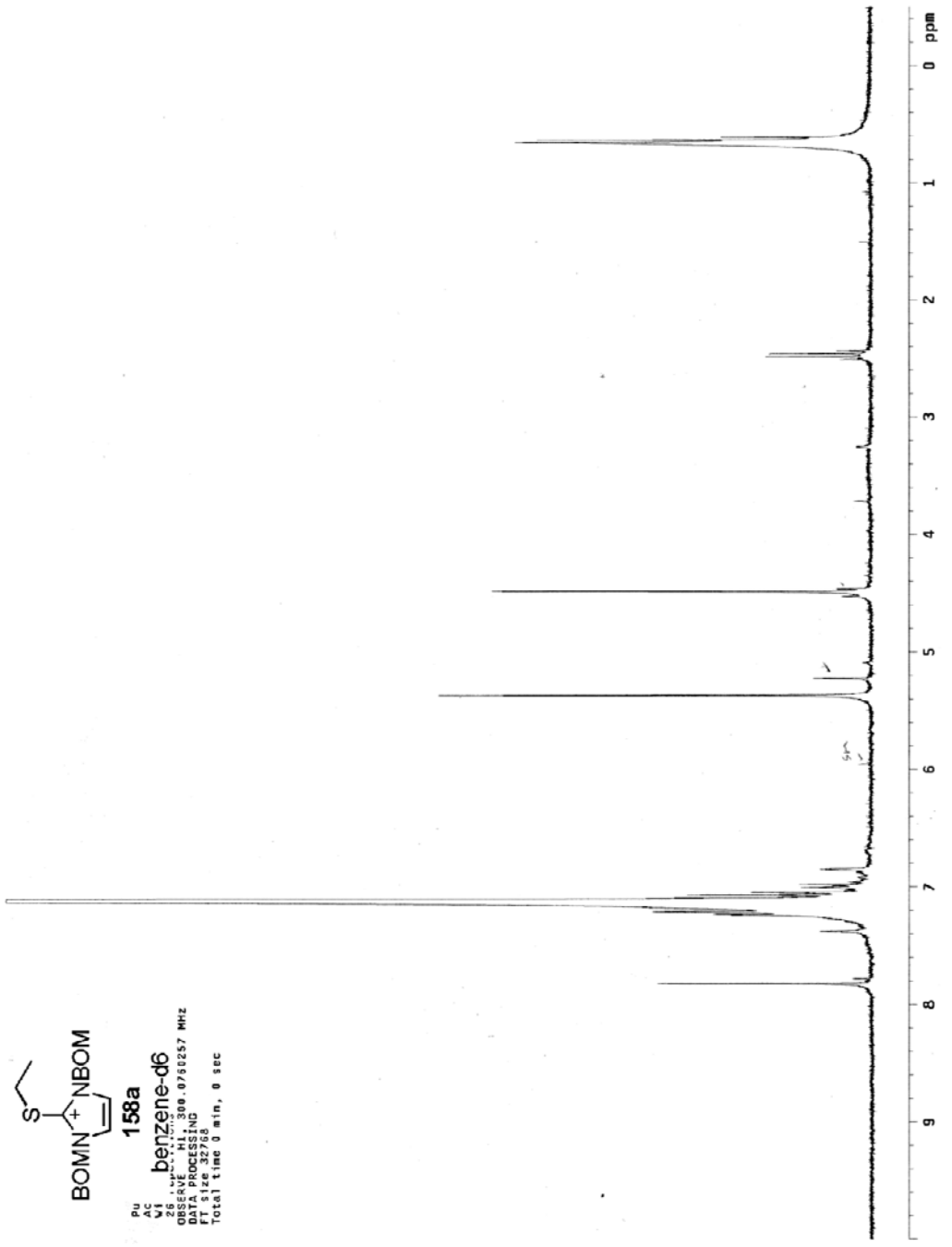

BOM
N
OH
OH
OH
NH
O
HN
N3
O
BOMN
HO
CbzHN
138
methanol-d4
f1 (ppm)

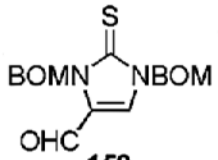

BOM
BOMN
CbzHN
139
DMSO-d6
f1 (ppm)


BOM
BOMN
CbzHN
142
DMSO-d6
f1 (ppm)


BOM
N
O
NH
OH
H
N3
BOMN
HO
CbzHN
142
DMSO-d6
XW-III-228-COcsy-DMSO
Std proton
f1 (ppm)
f2 (ppm)

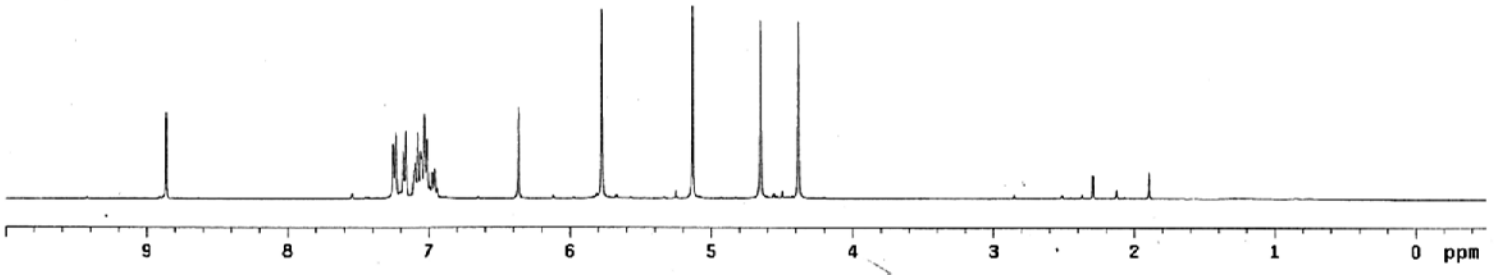

S
BOMN
NBOM
158
benzene-d6
9
8
7
6
5
4
3
2
1
0 ppm

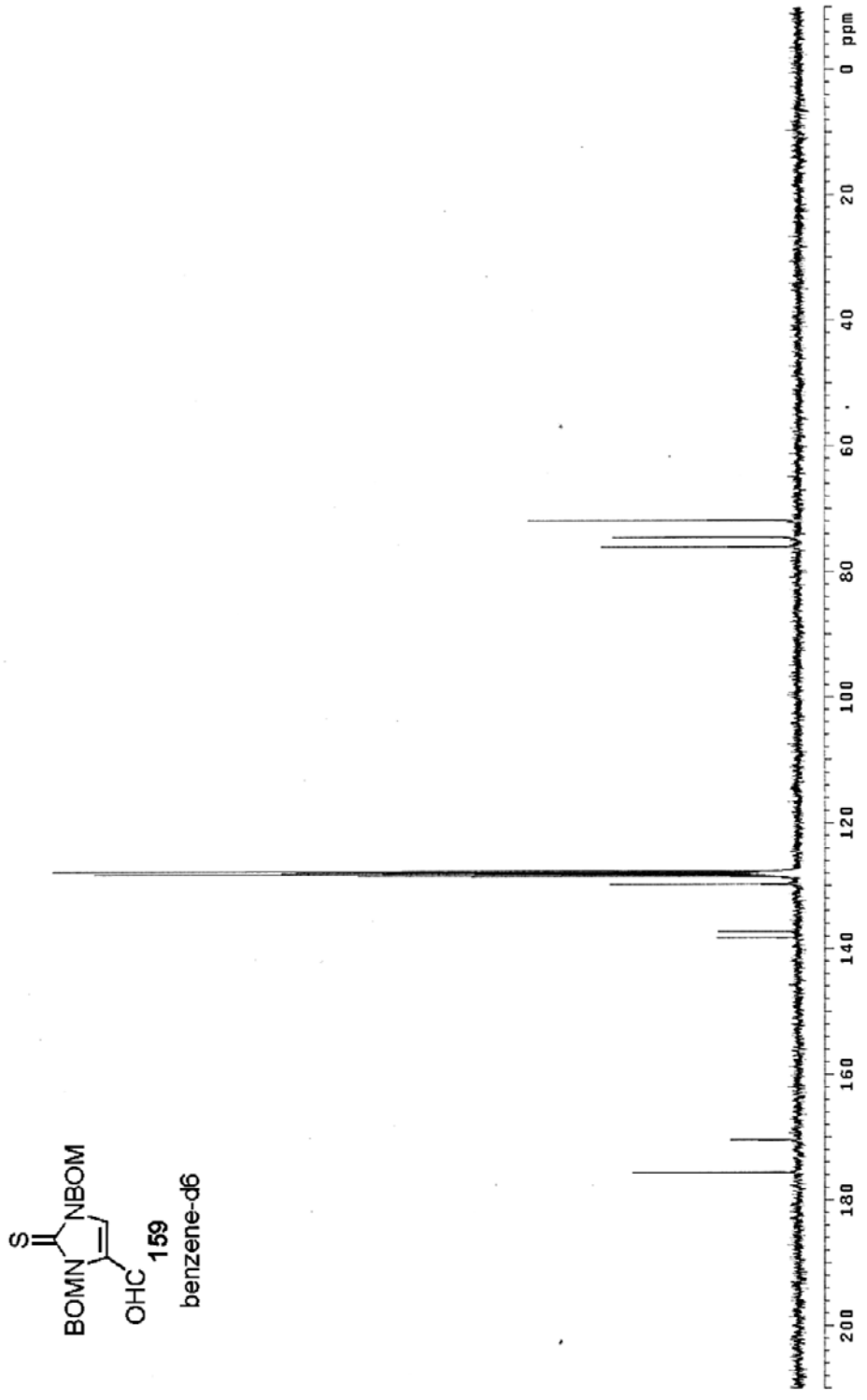

BOMN
NBOM
158a
benzene-d6
OBSERVE H1, 300.0760257 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 0 sec
9
8
7
6
5
4
3
2
1
0 ppm

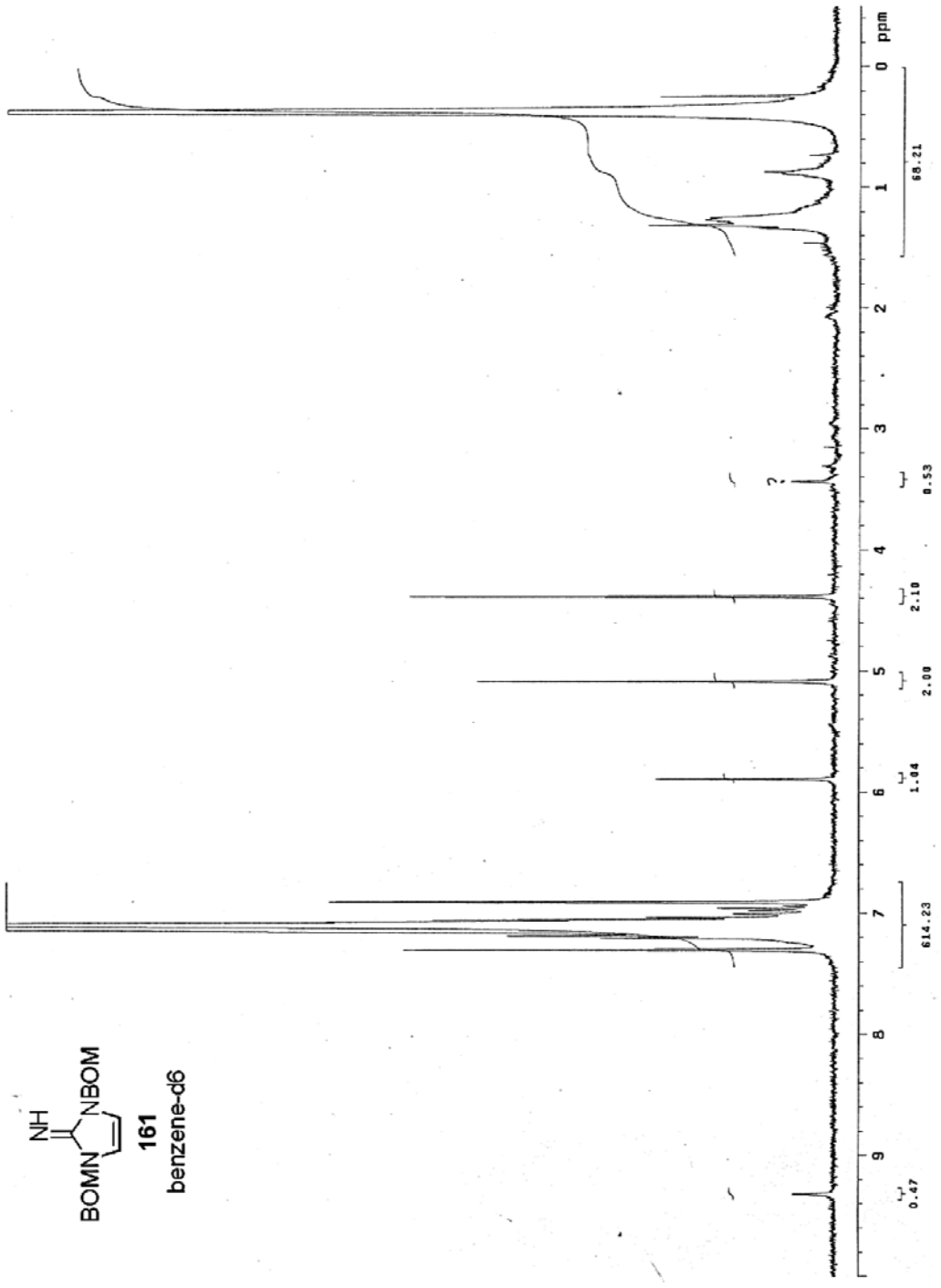


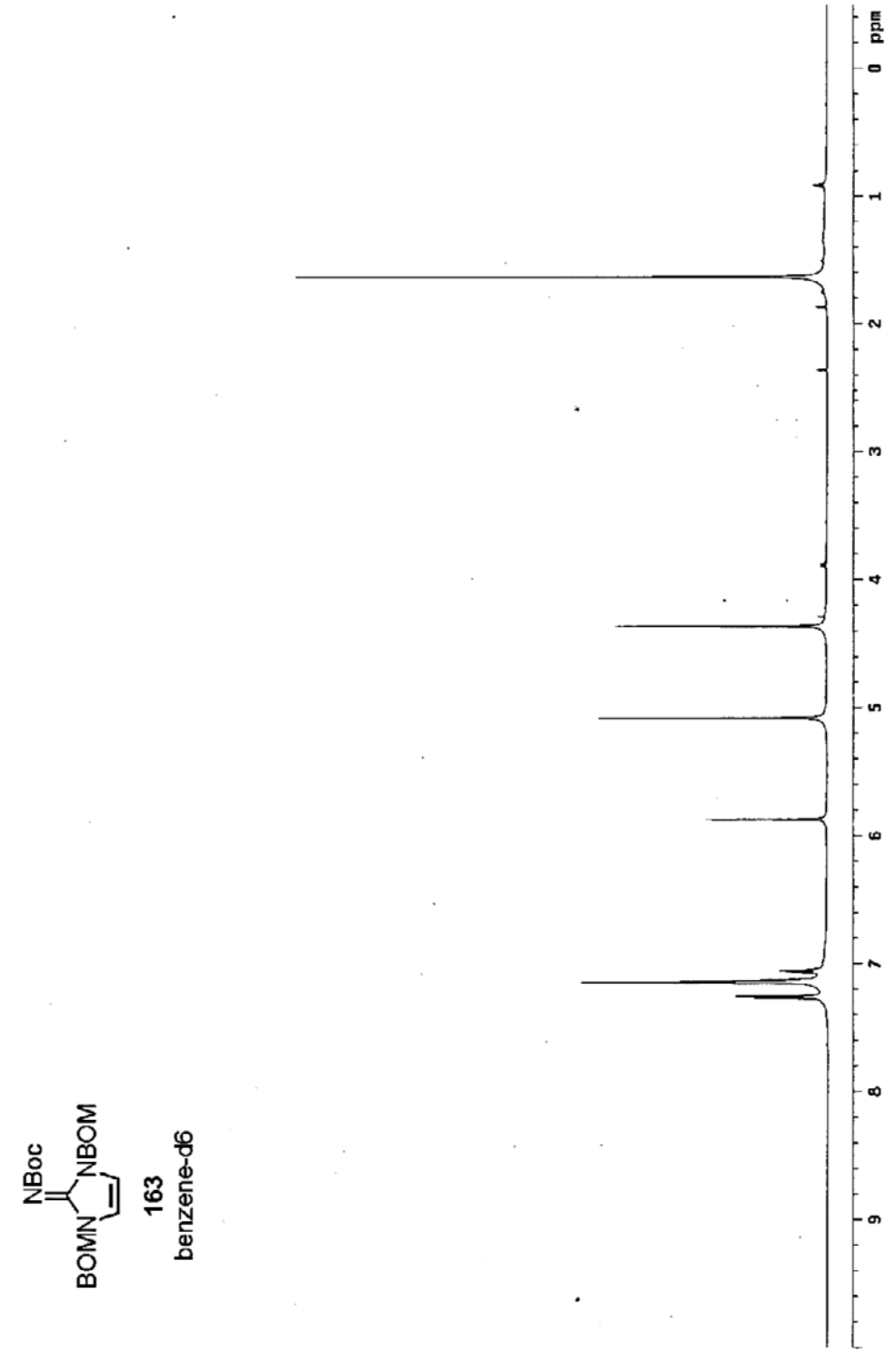
159

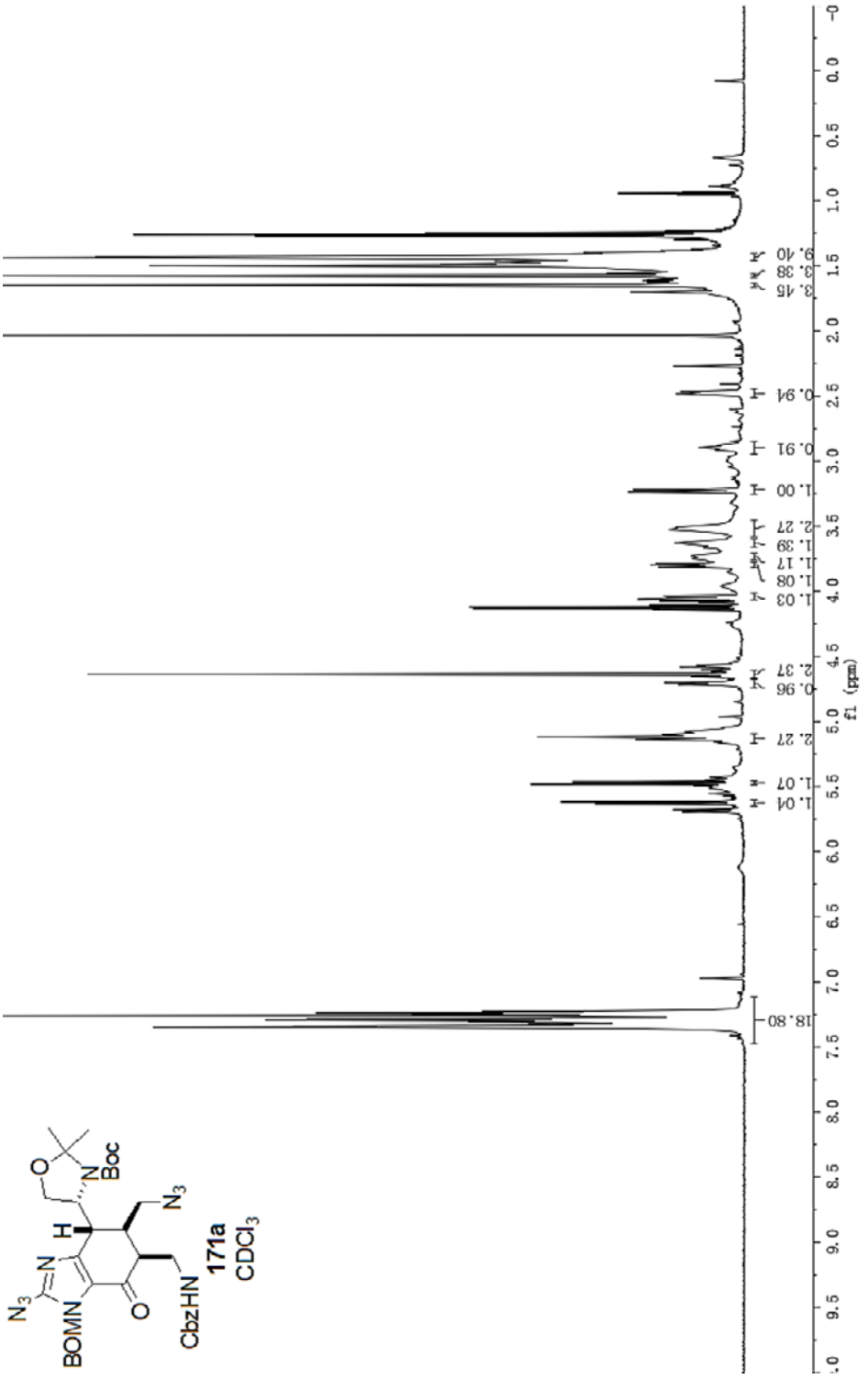
benzene-d6

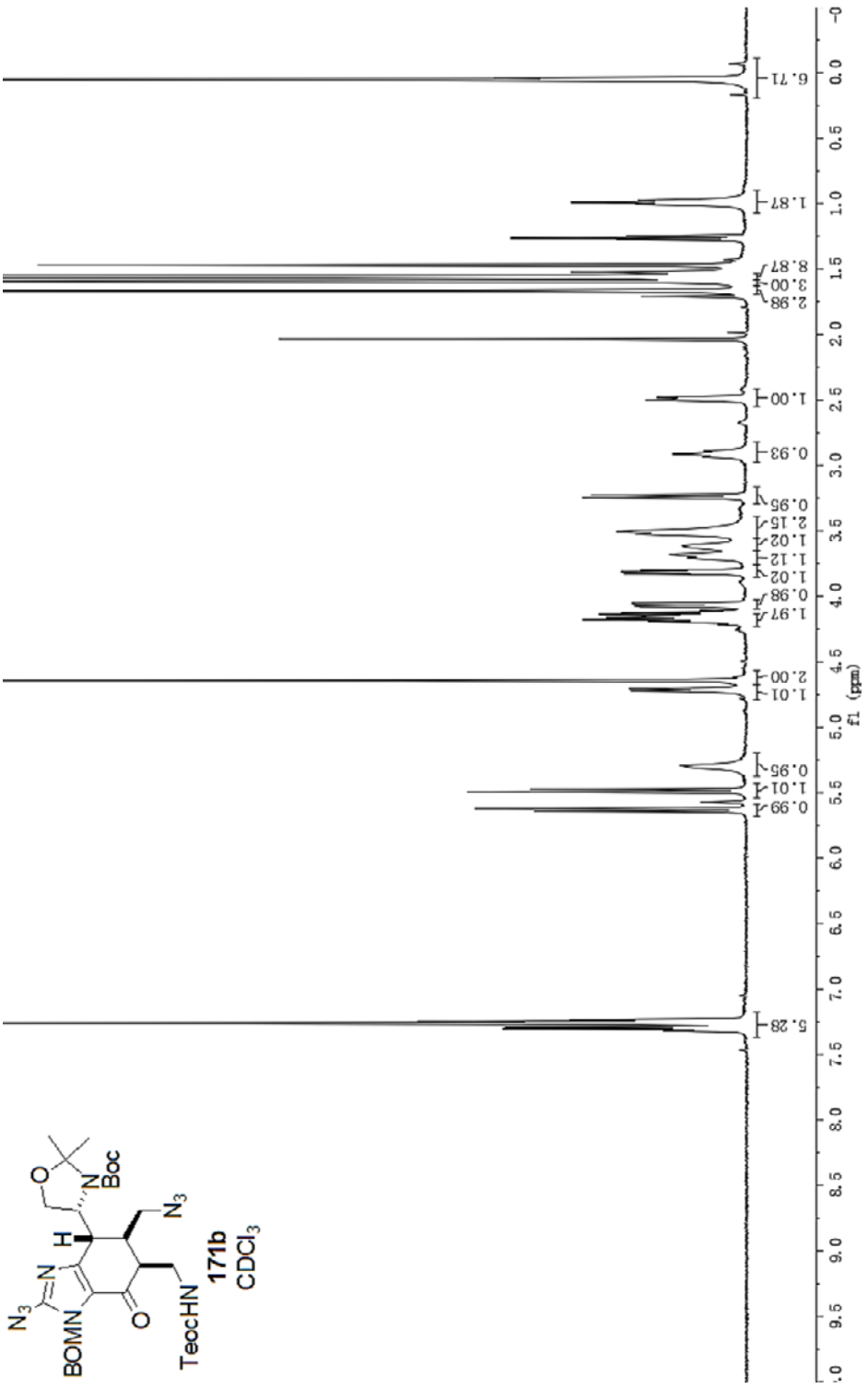


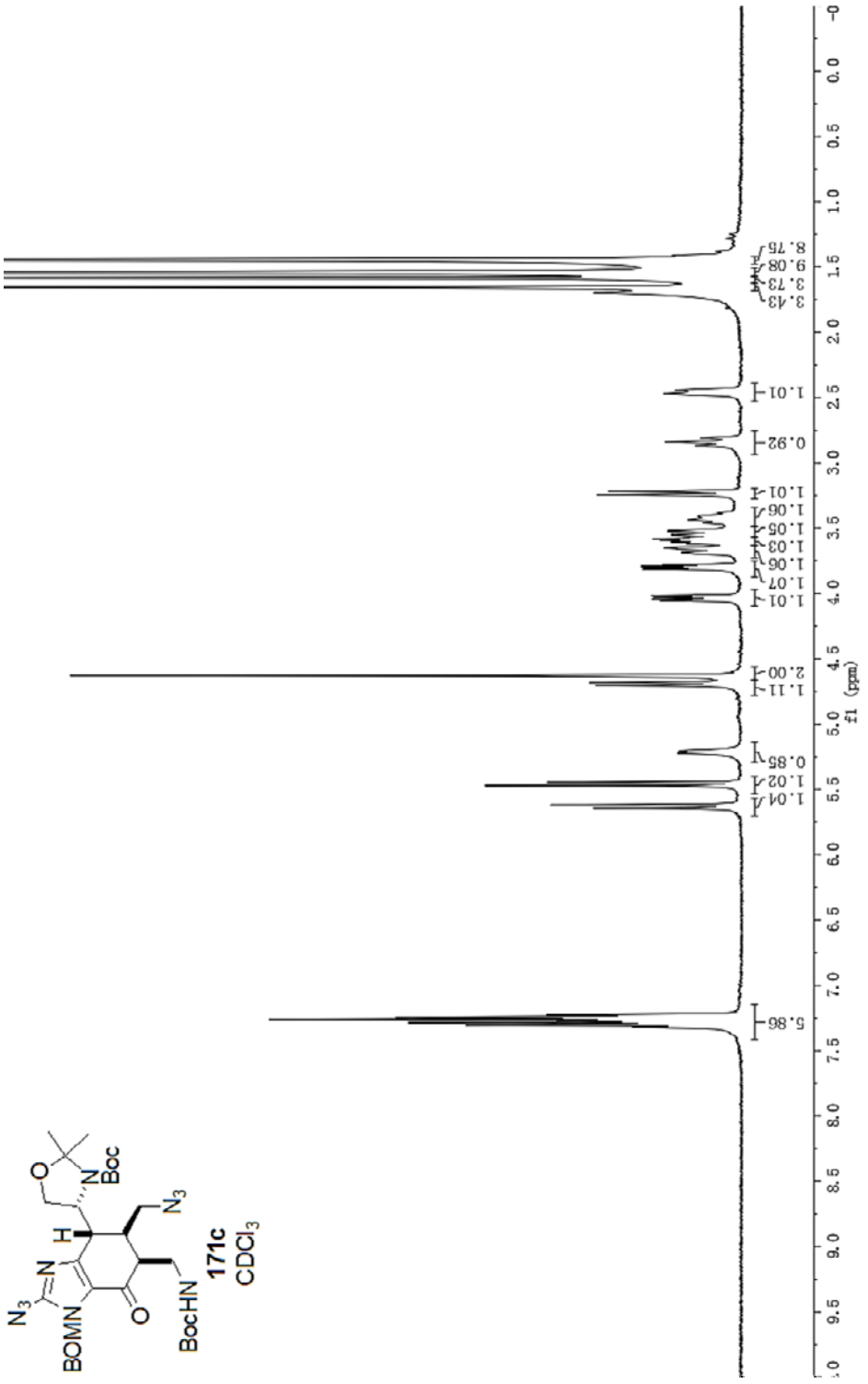

S
NBOM
BOMN
OHC
159
benzene-d6
200
180
160
140
120
100
80
60
40
20
0 ppm

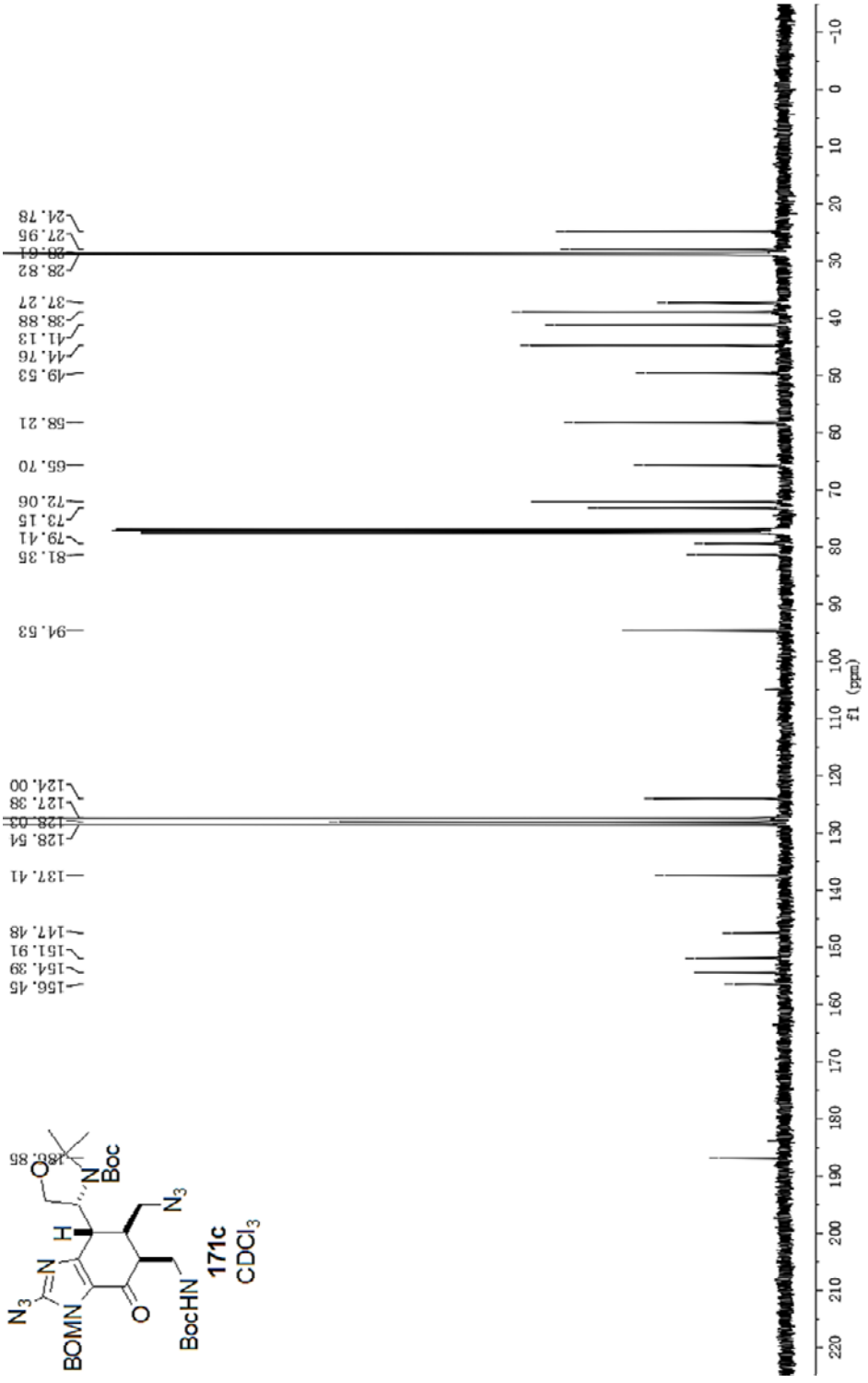

NH
BOMN
NBOM
161
benzene-d6
ppm
0
1
2
3
4
5
6
7
8
9
68.21
8.53
2.10
2.00
1.04
614.23
0.47

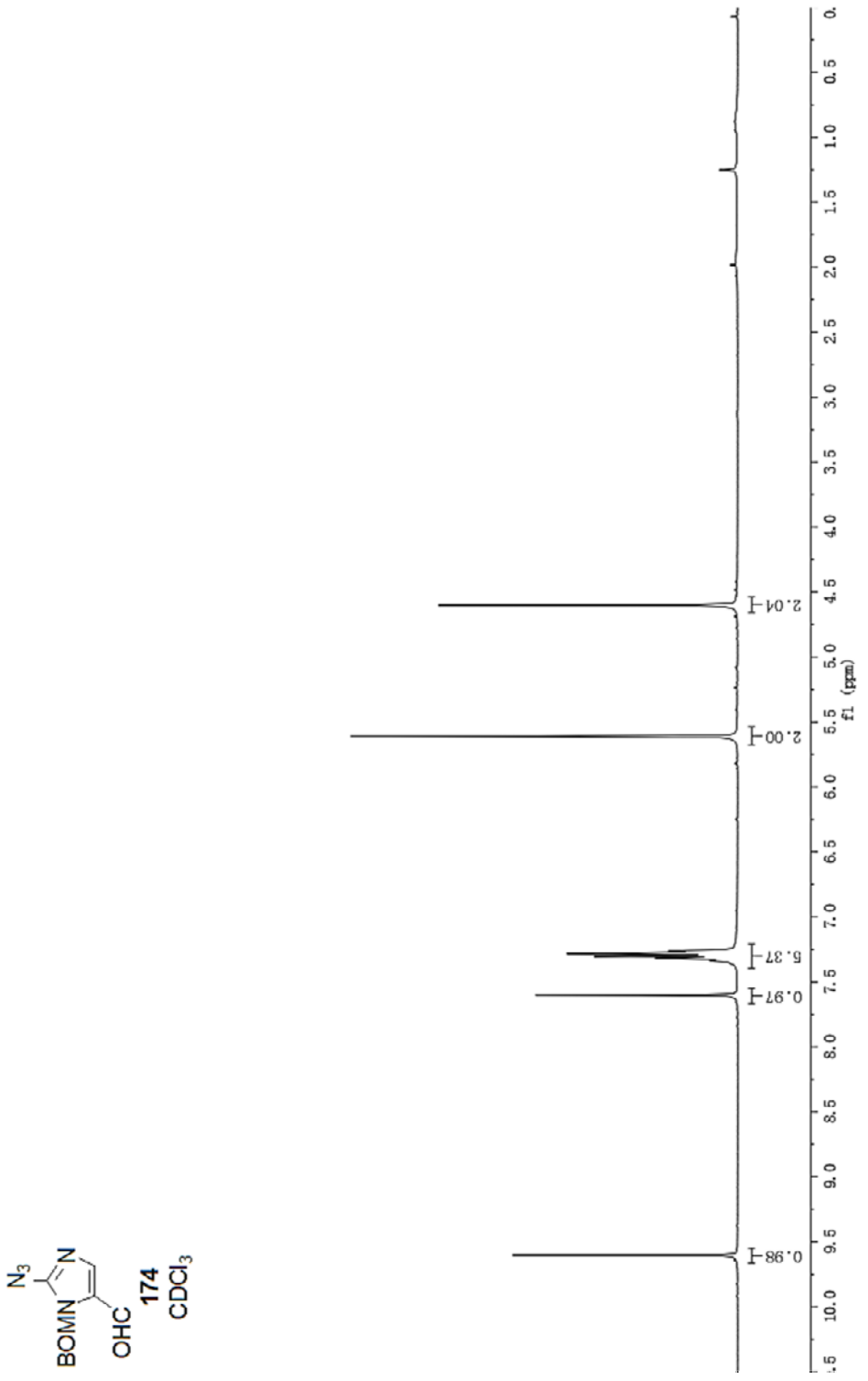

NBoc
BOMN
NBOM
163
benzene-d6
9
8
7
6
5
4
3
2
1
0 ppm

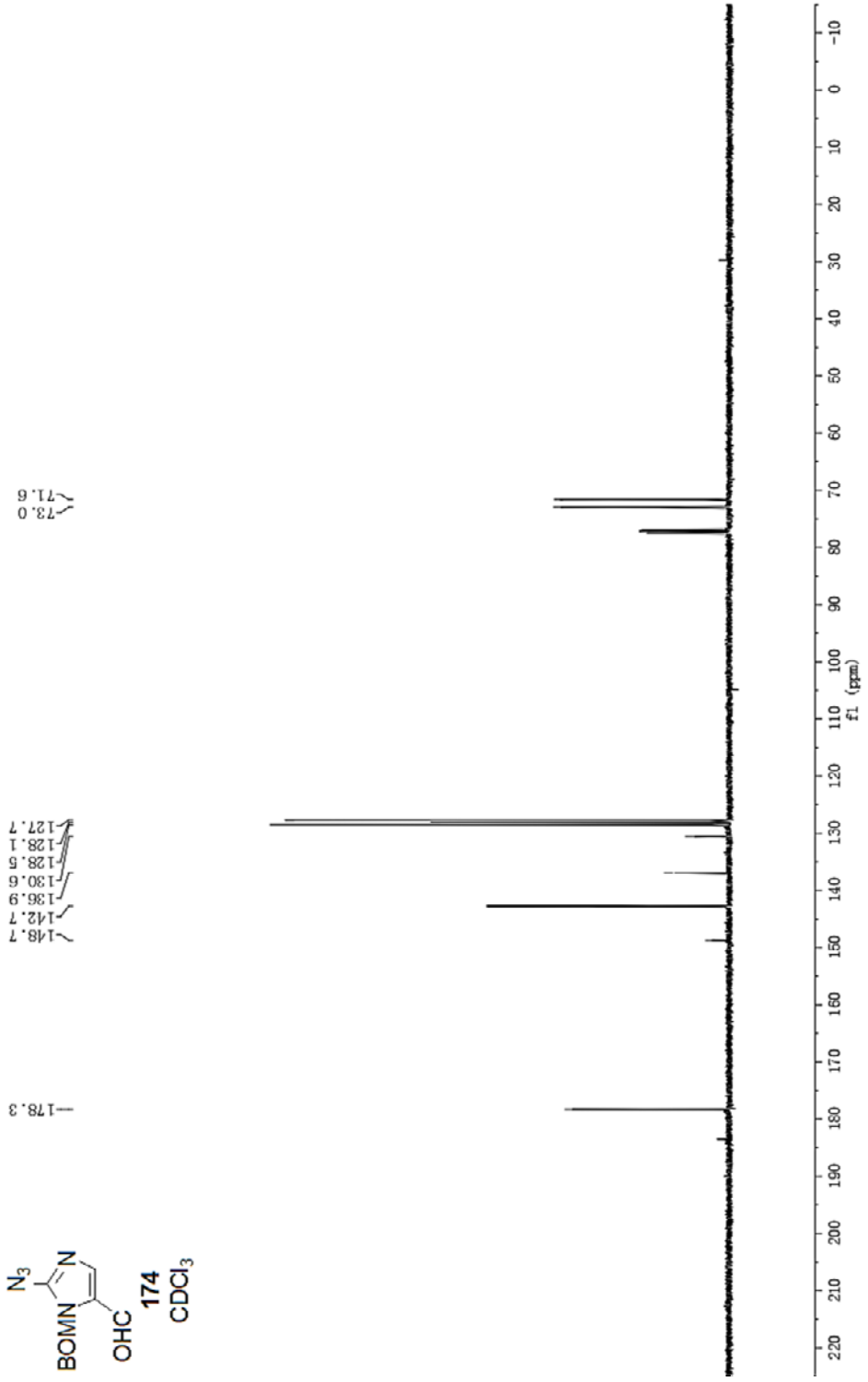

171a
CDCl3
BOMN
CbzHN
Boc
f1 (ppm)

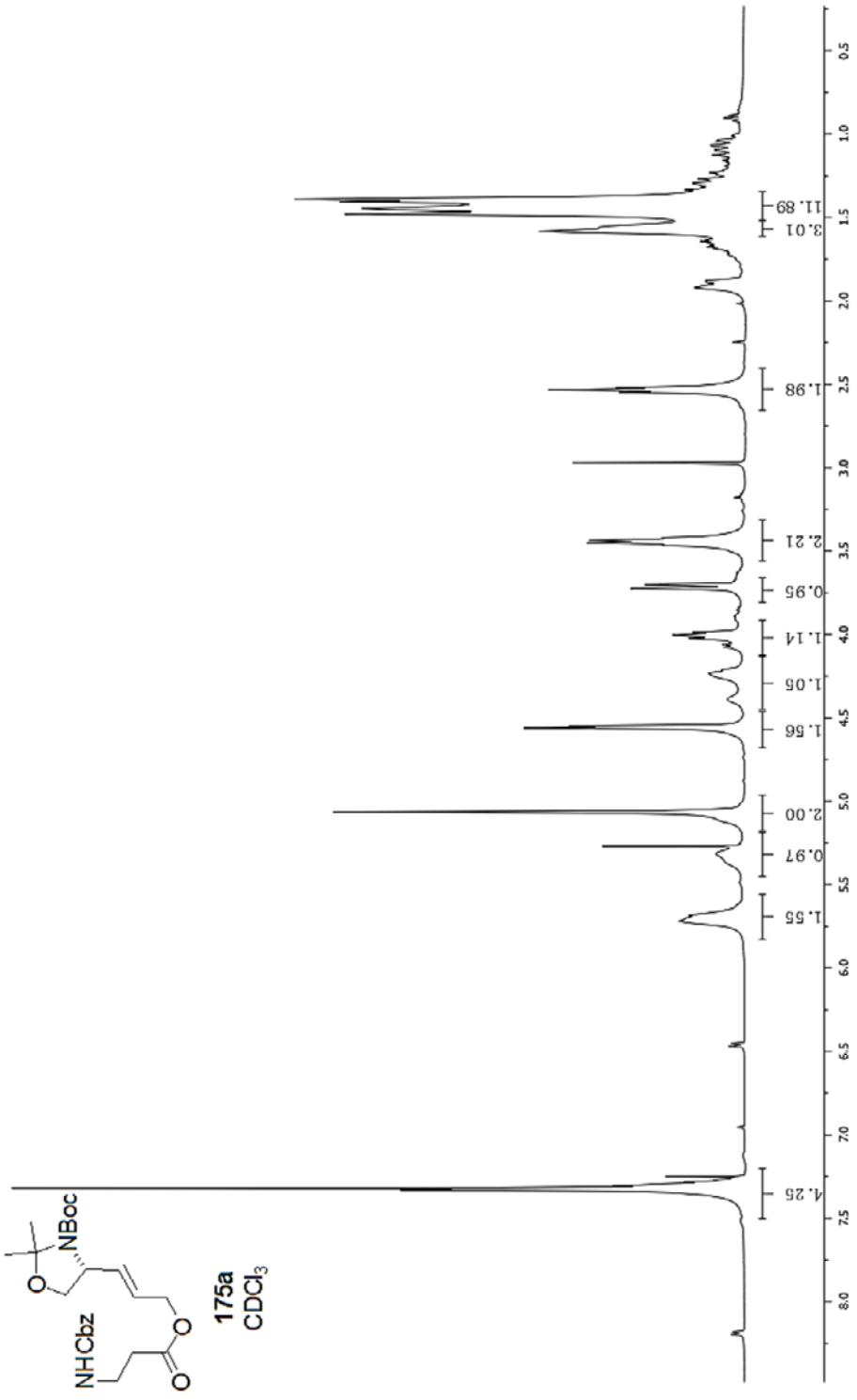

171b
$CDCl_3$
BOMN
TeocHN
Boc
N_3
6.71
1.87
8.87
3.00
2.98
1.00
0.93
0.95
2.15
1.02
1.12
1.02
0.98
1.97
2.00
1.01
0.95
0.99
1.01
5.28
f1 (ppm)

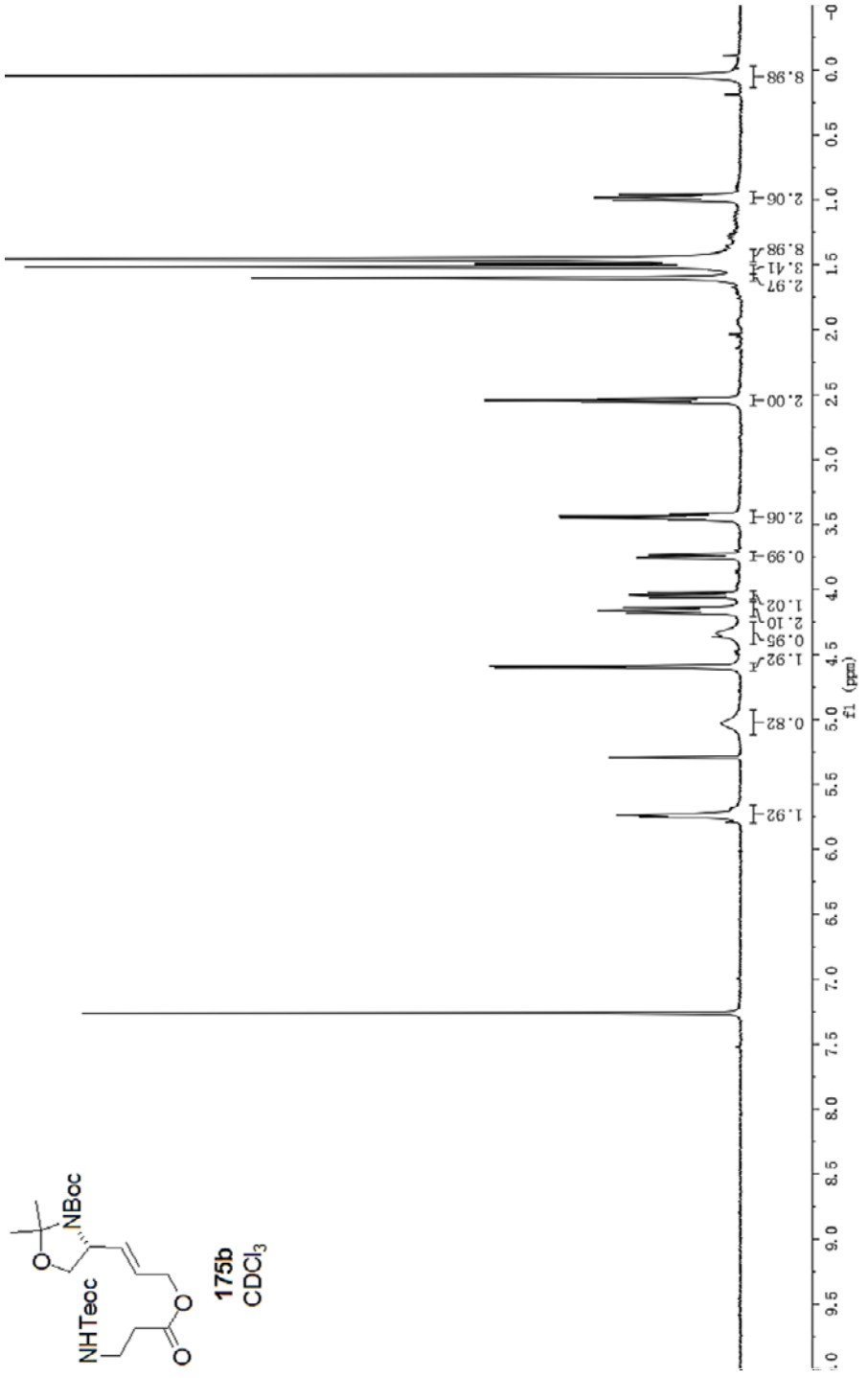

171c
$CDCl_3$
BOMN
BocHN
Boc
N_3
H
O
N
f1 (ppm)

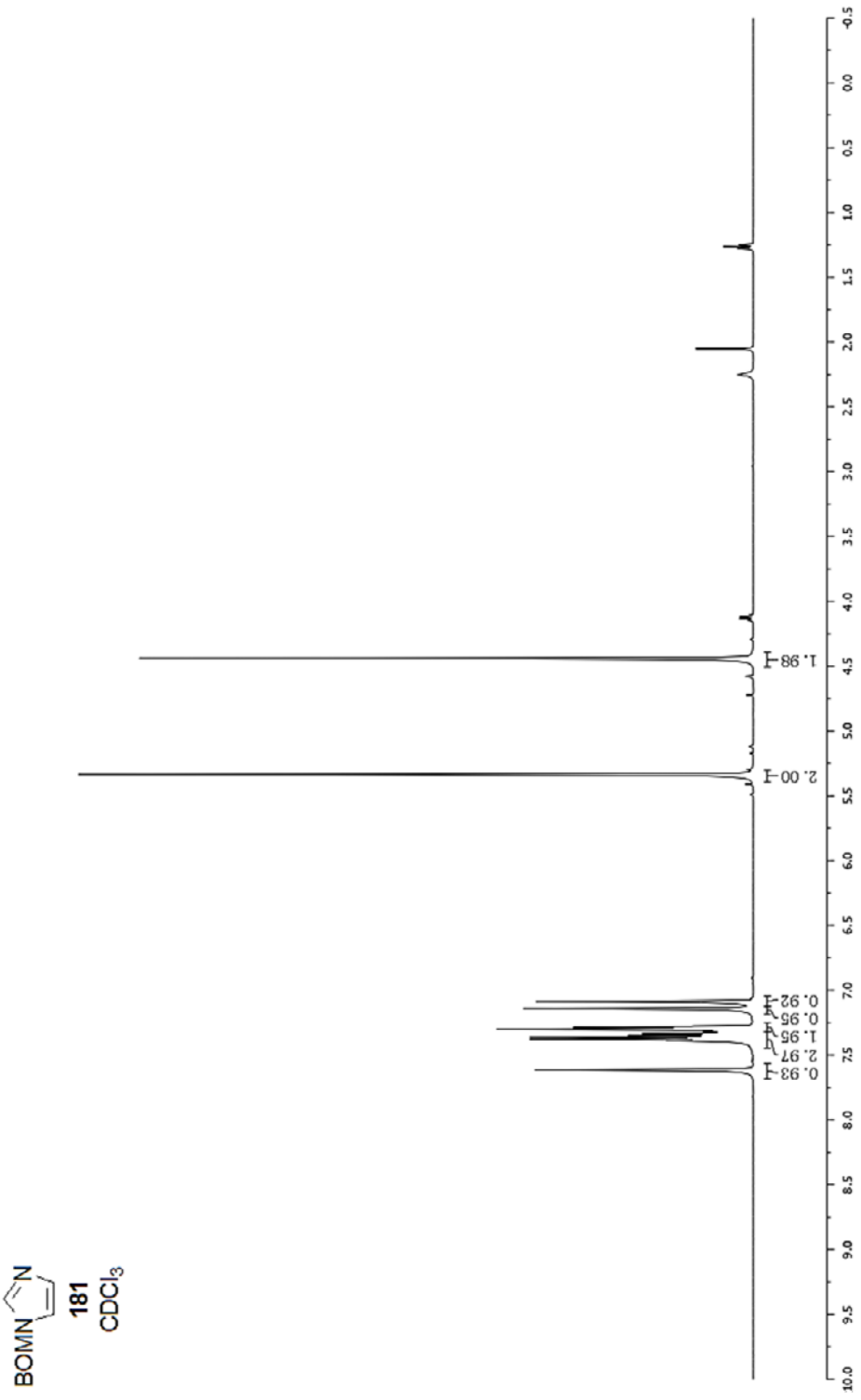

156.45
154.39
151.91
147.48
137.41
128.54
128.03
127.38
124.00
94.53
81.35
79.41
73.15
72.06
65.70
58.21
49.53
44.76
41.13
38.88
37.27
28.82
28.61
27.95
24.78
185.85
f1 (ppm)
171c
CDCl3
BOMN
BocHN
Boc

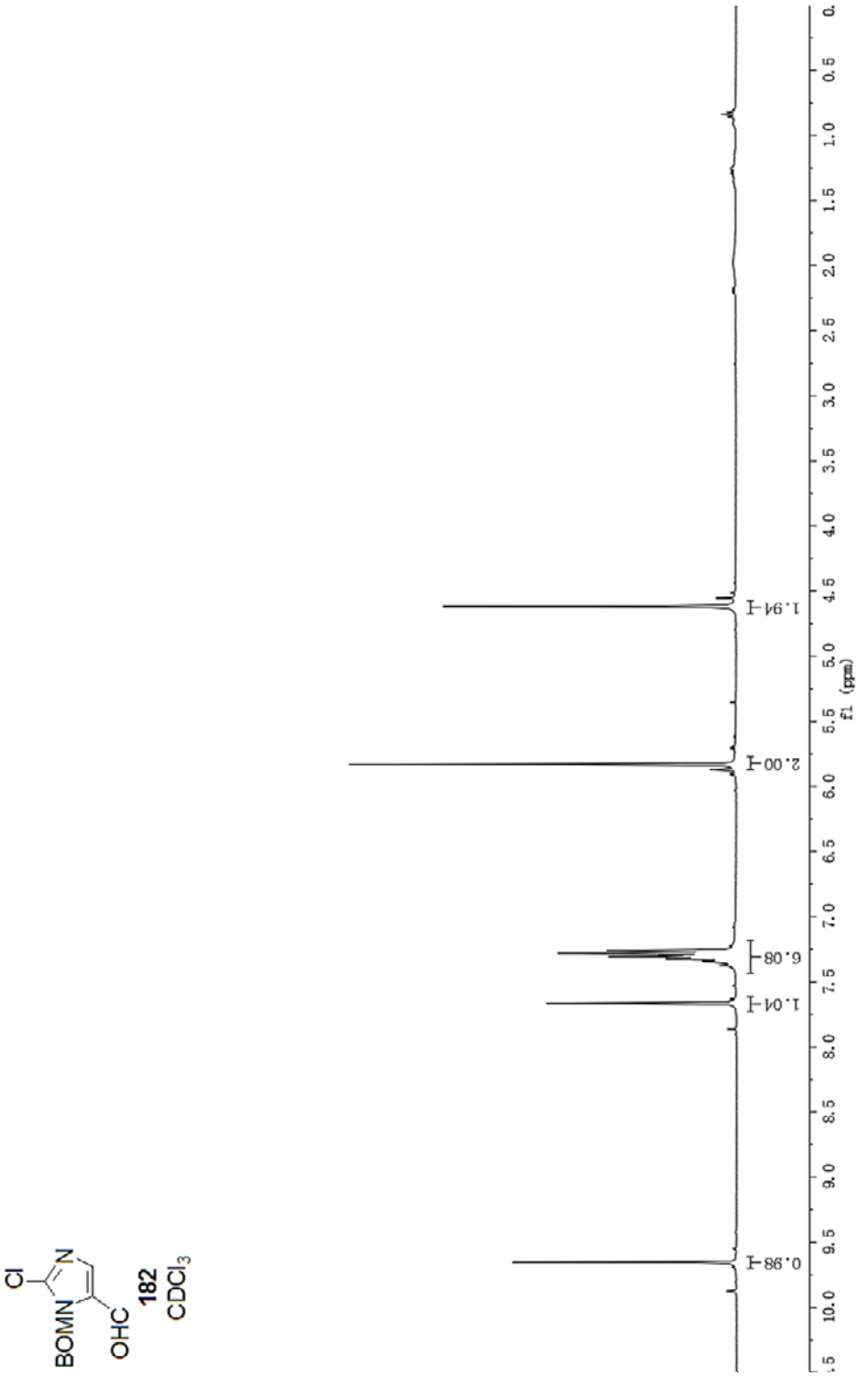

N3
N
BOMN
OHC
174
CDCl3
0.98
2.04
2.00
5.37
0.97
f1 (ppm)

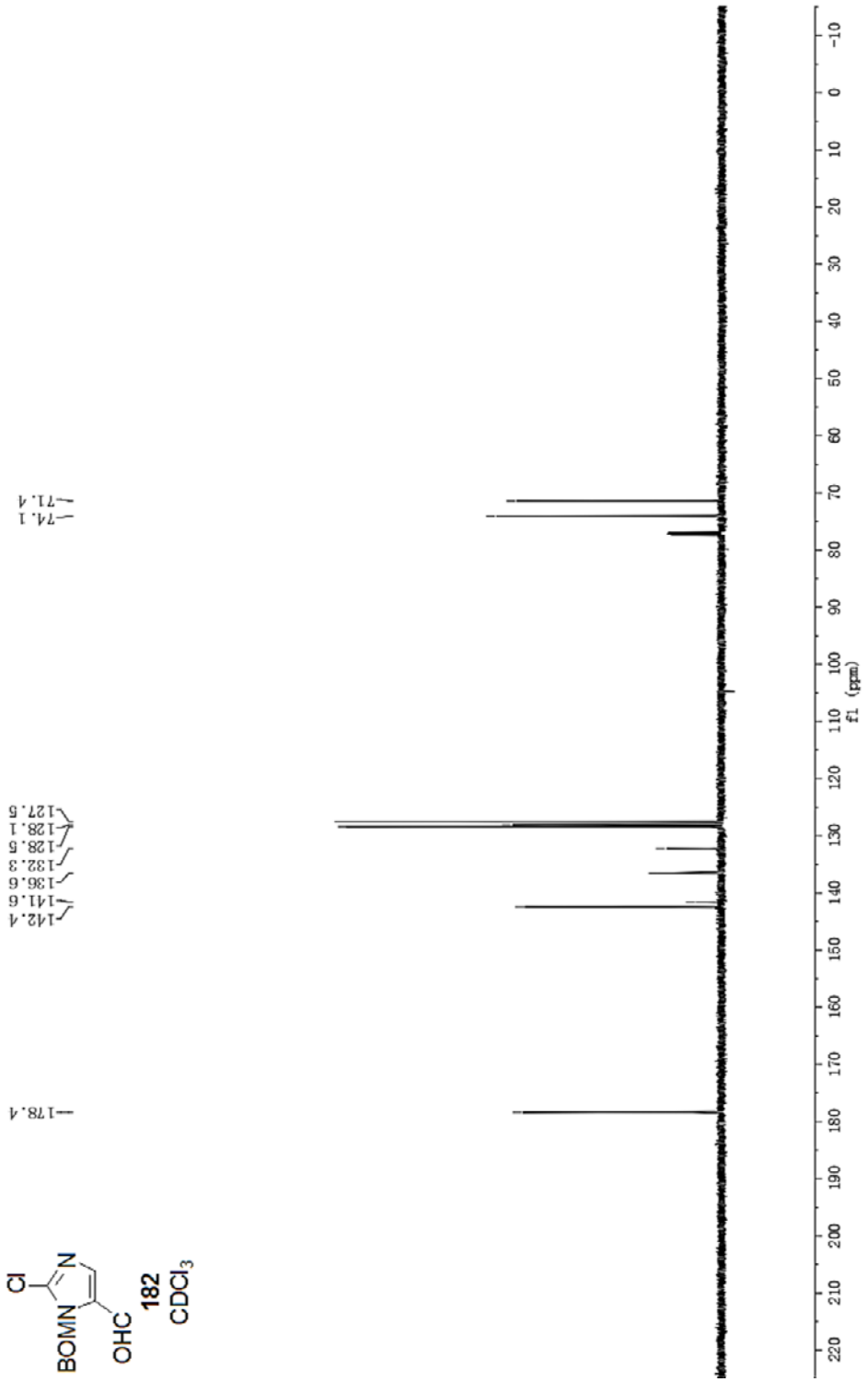

N3
N
BOMN
OHC
174
CDCl3
178.3
148.7
142.7
136.9
130.6
128.5
128.1
127.7
73.0
71.6
f1 (ppm)

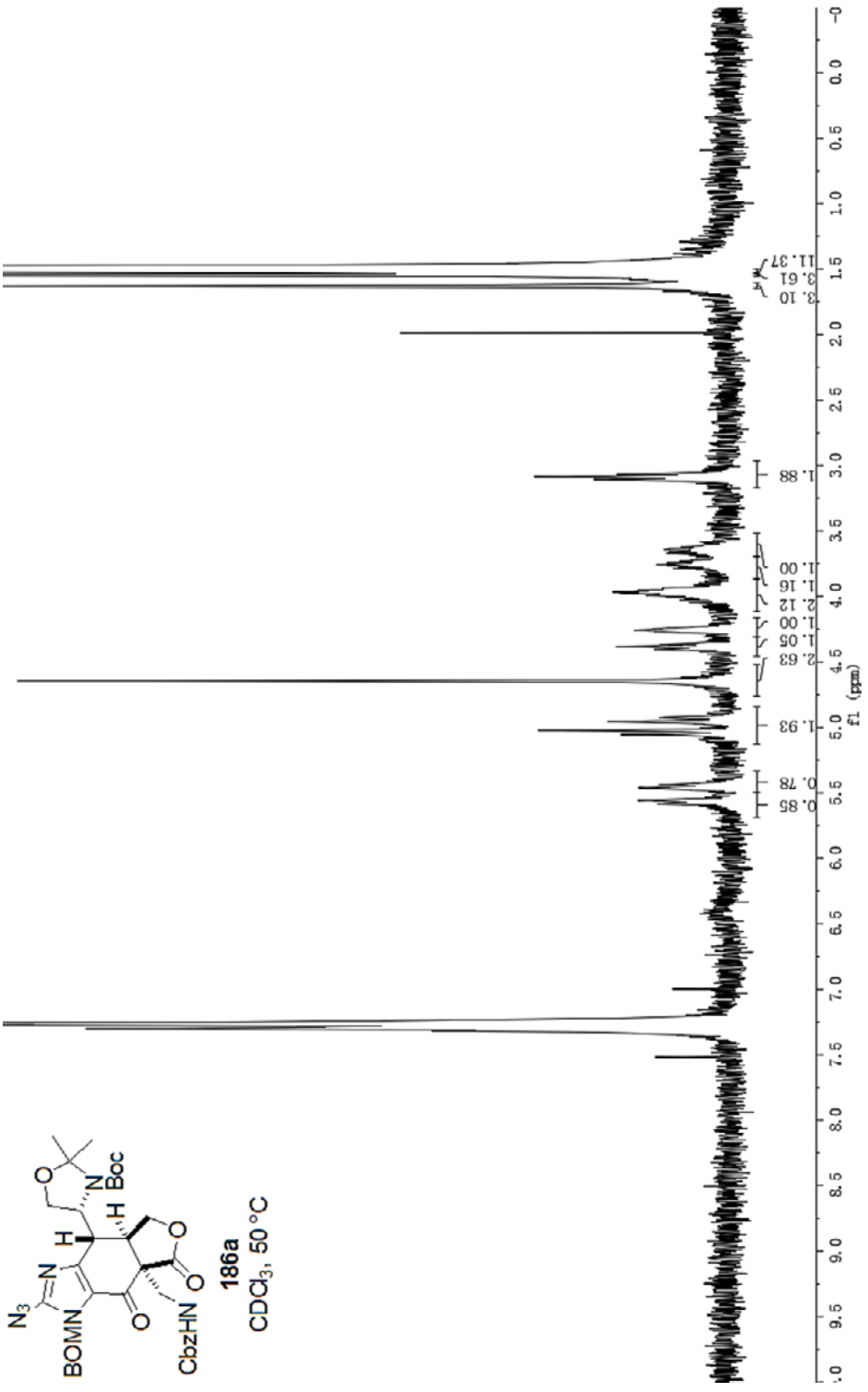

NBoc
O
O
NHCbz
O
O
175a
CDCl3
4.25
1.55
0.97
2.00
1.56
1.05
1.14
0.95
2.21
1.98
3.01
11.89

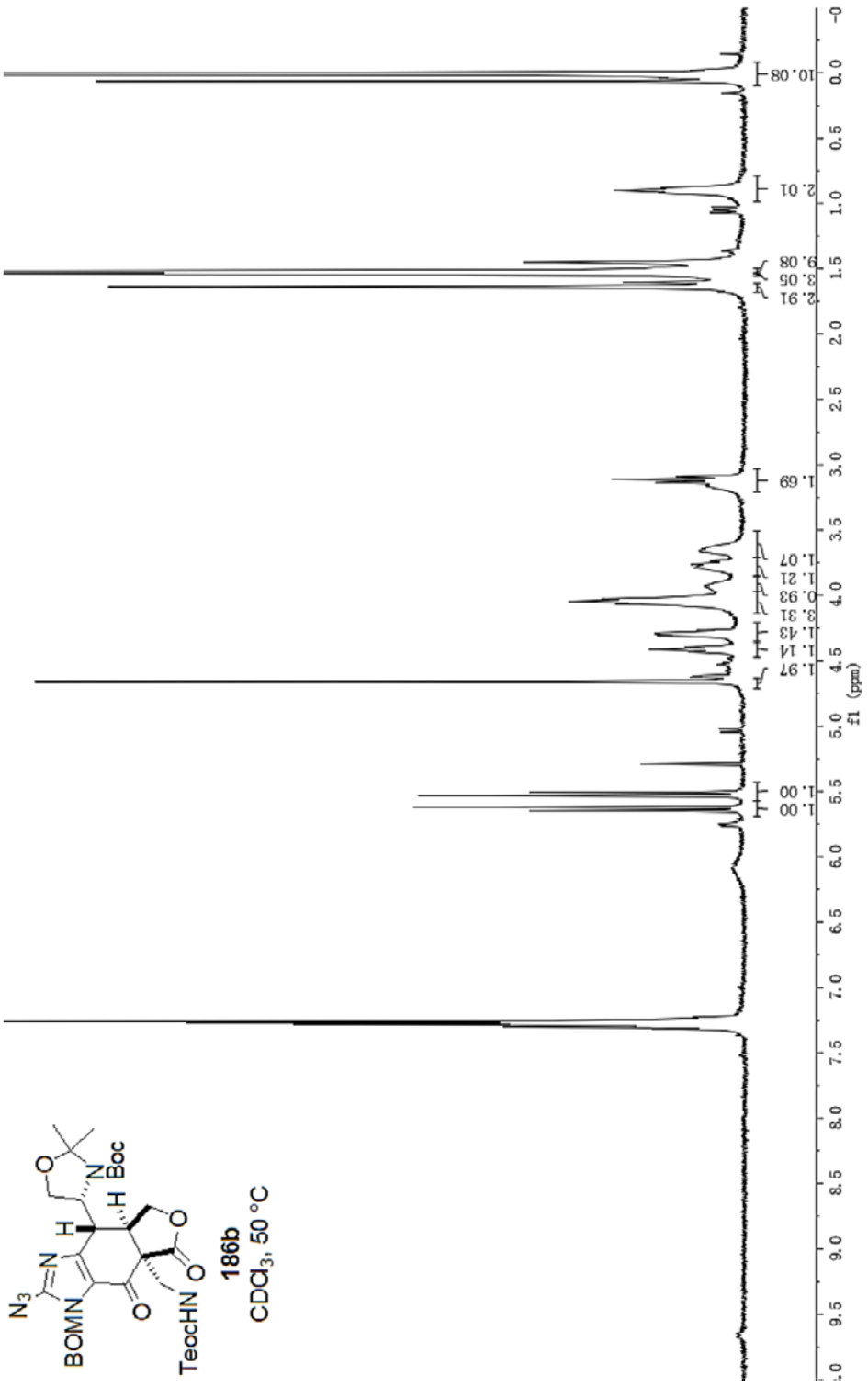

NBoc
NHTeoc
O
O
O
175b
$CDCl_3$
8.98
2.06
8.98
3.41
2.97
2.00
2.06
0.99
1.02
2.10
0.95
1.92
0.82
1.92
f1 (ppm)

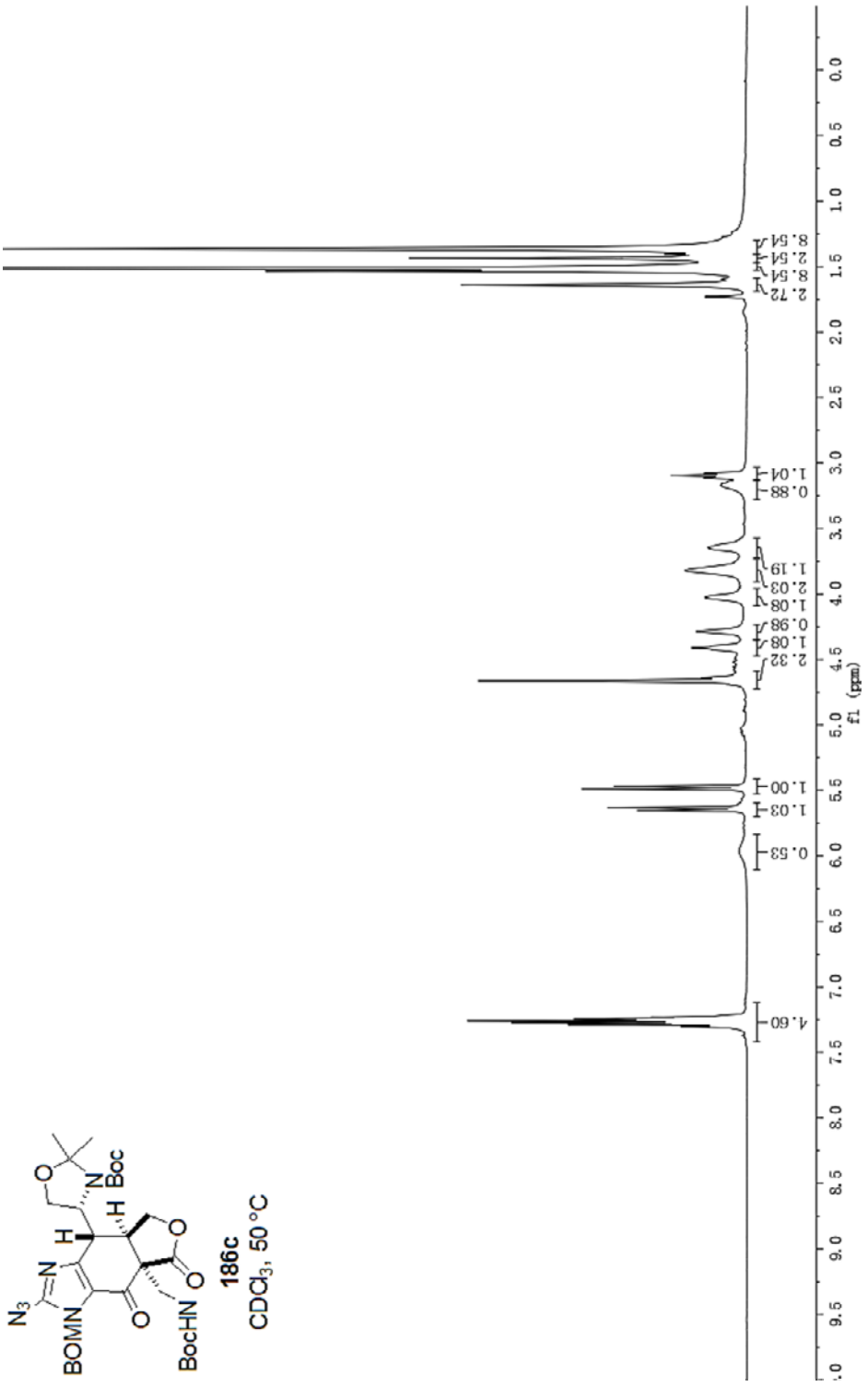

BOMN
N
181
CDCl3
1.98
2.00
0.93
2.97
1.95
0.95
0.92

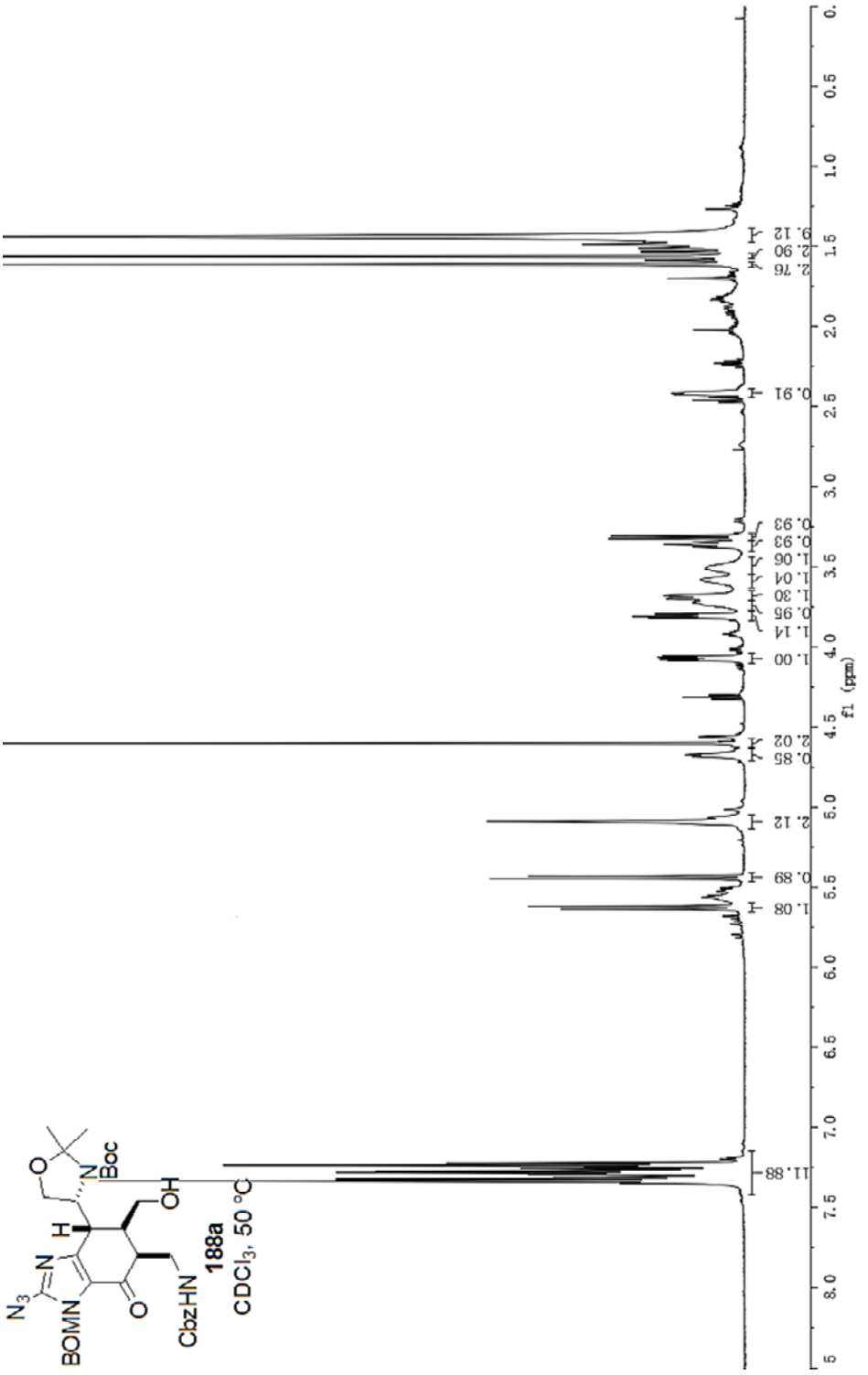

Cl
N
BOMN
OHC
182
$CDCl_3$
0.98
1.94
2.00
6.08
1.04
f1 (ppm)

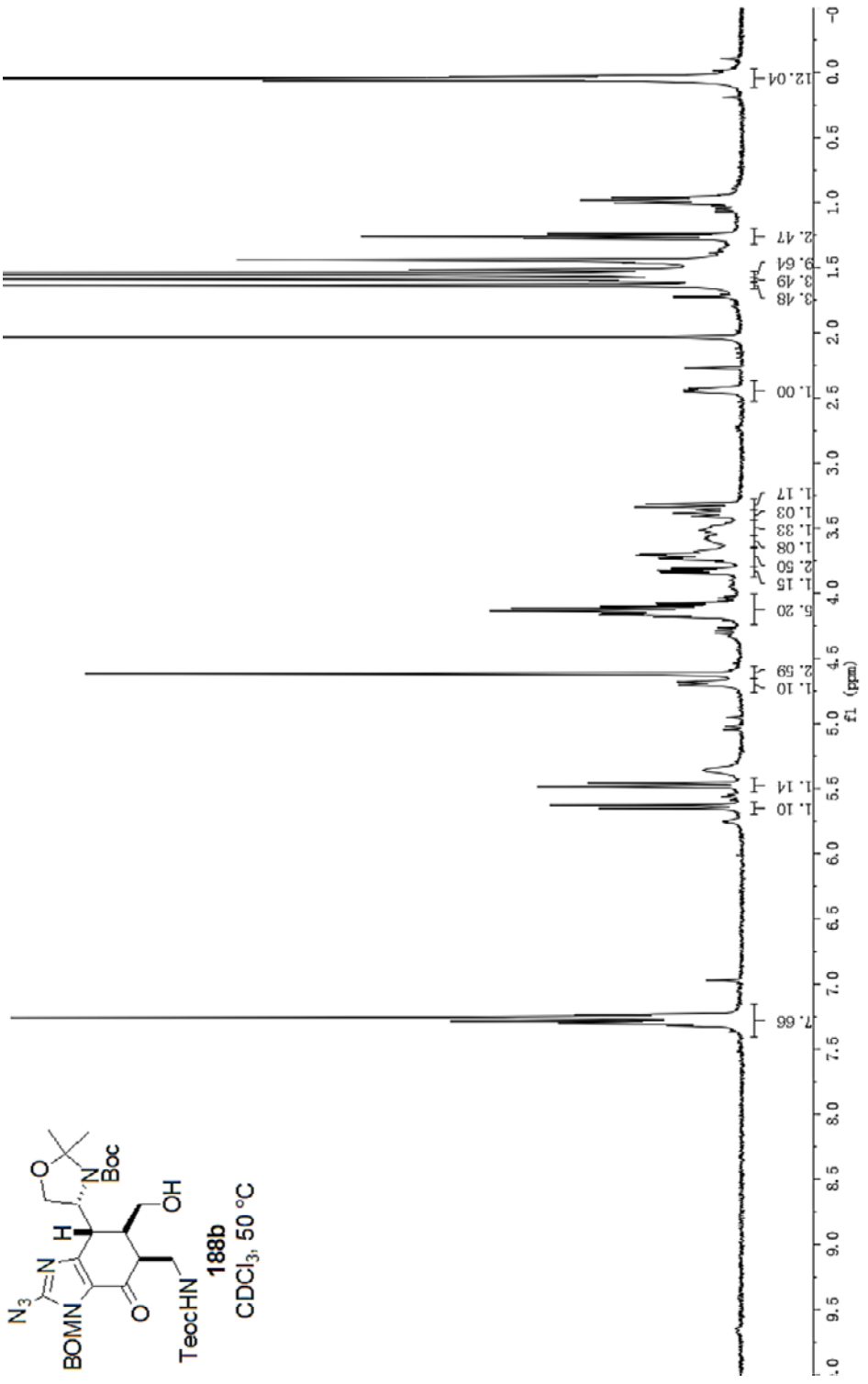

Cl
BOMN
N
OHC
182
$CDCl_3$
178.4
142.4
141.6
136.6
132.3
128.5
128.1
127.5
74.1
71.4
f1 (ppm)

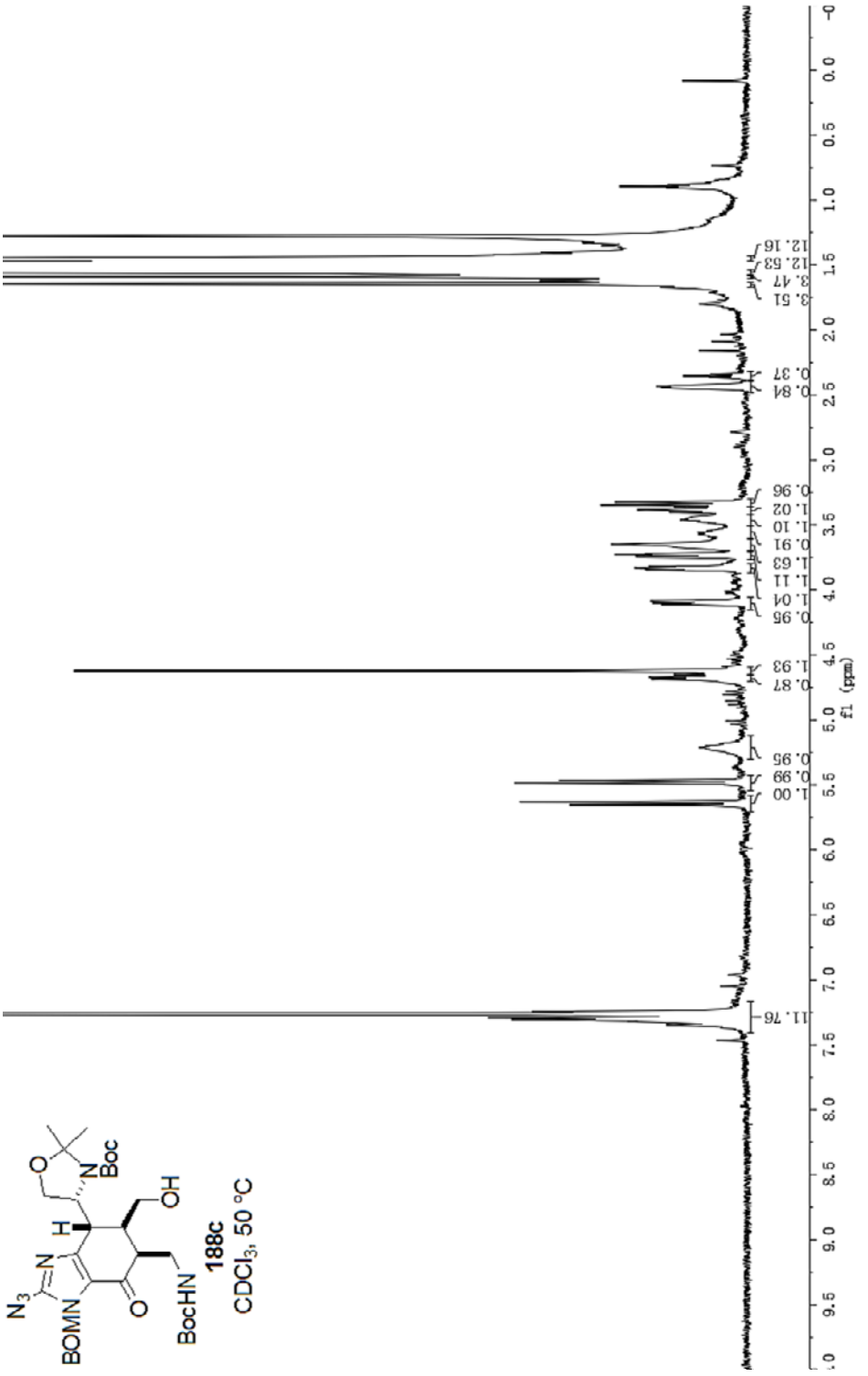

186a
CDCl3, 50 °C
BOMN
CbzHN
Boc
11.37
3.61
3.10
1.88
1.00
1.16
2.12
1.00
1.05
2.63
1.93
0.78
0.85
f1 (ppm)

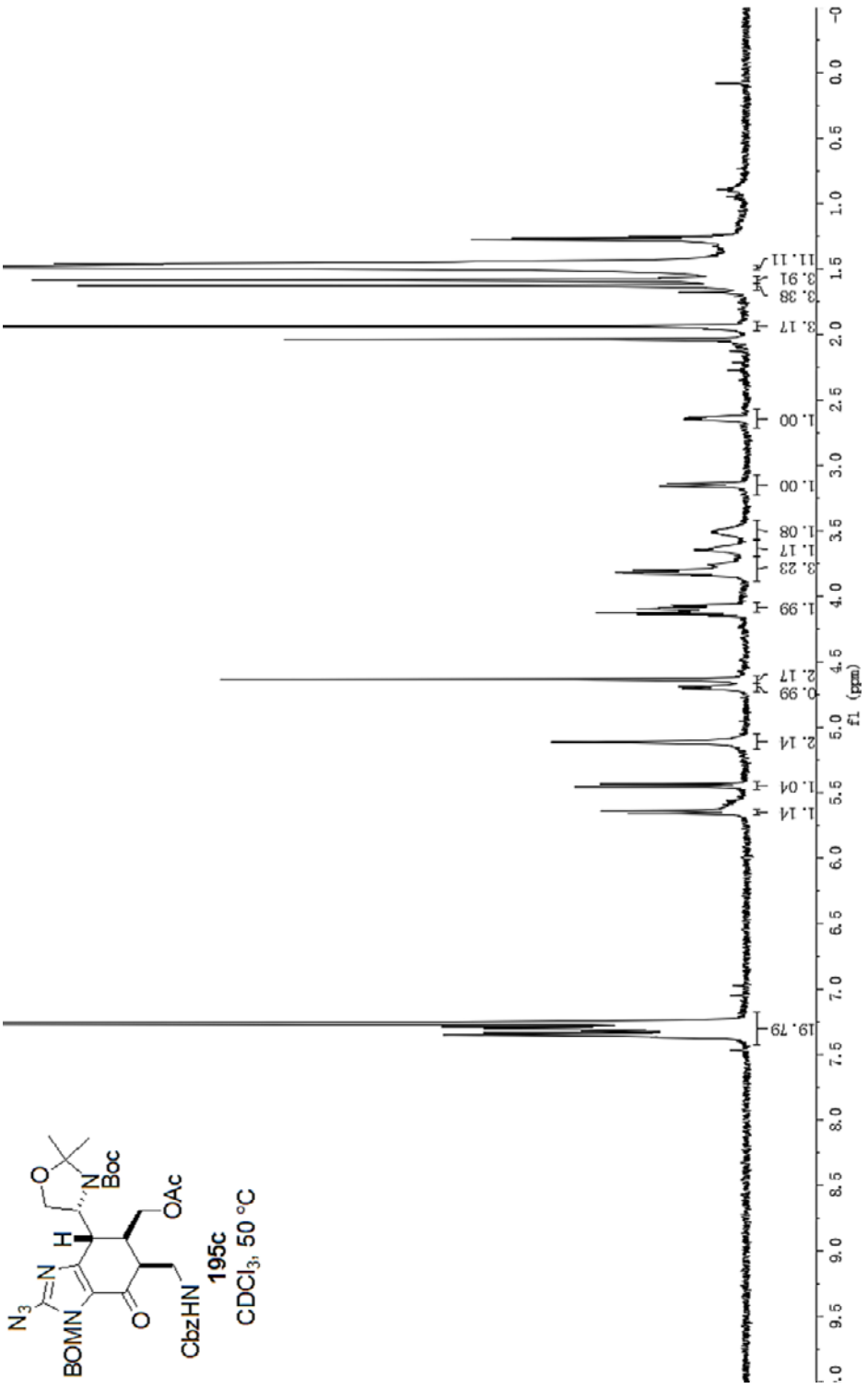

186b
CDCl3, 50 °C
BOMN
TeocHN
Boc
f1 (ppm)

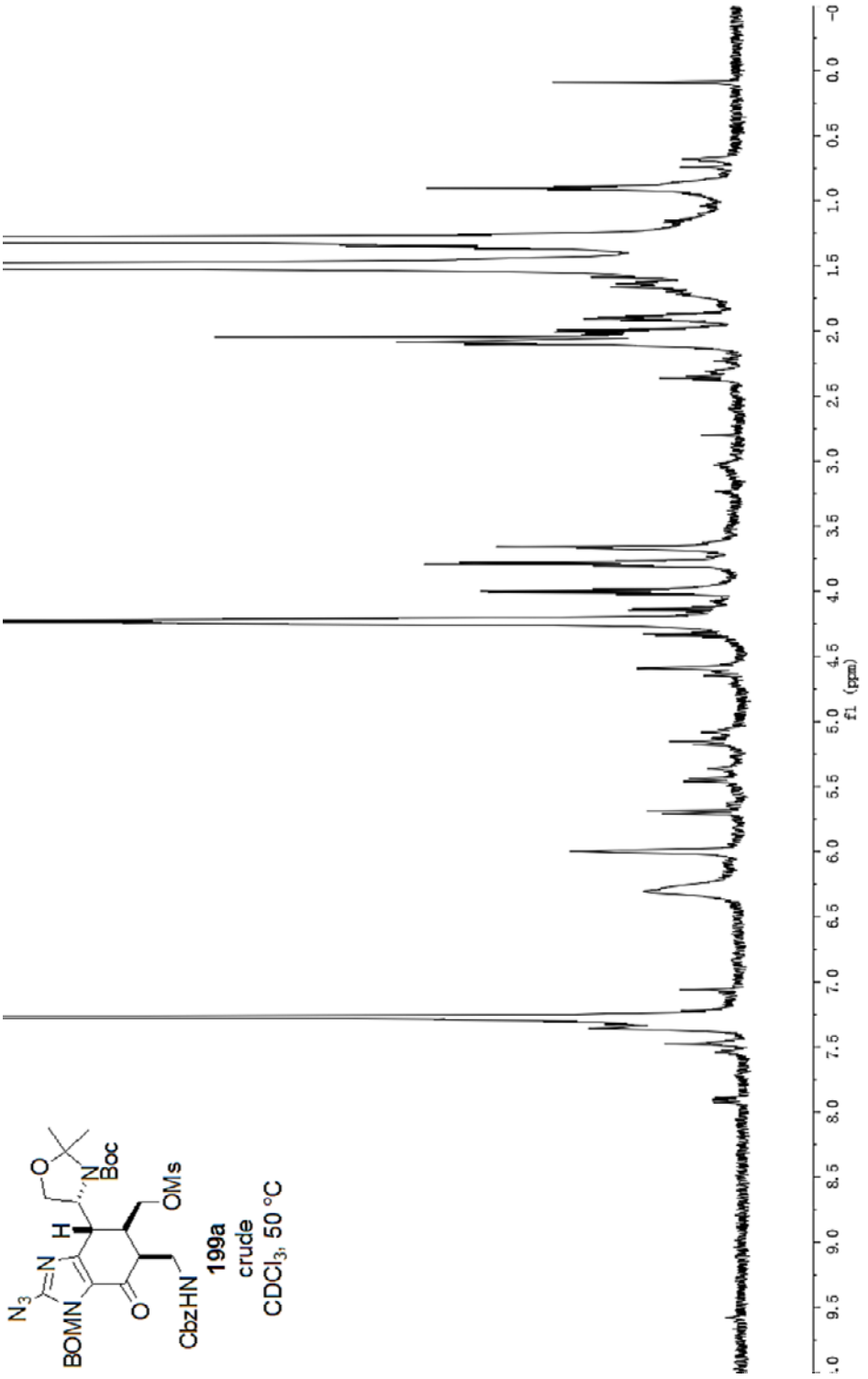

N3
BOMN
BocHN
Boc
186c
CDCl3, 50 °C
f1 (ppm)

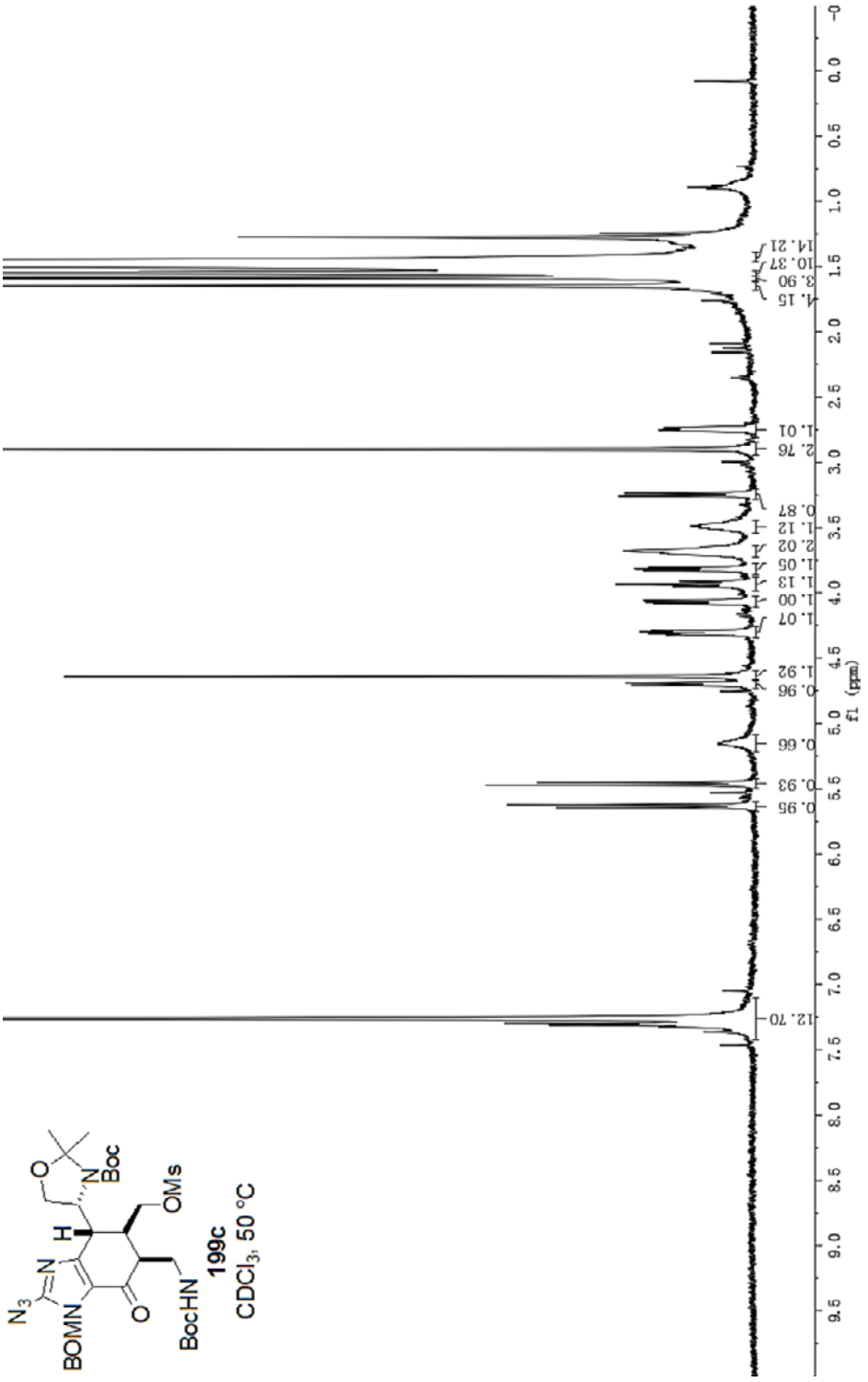

188a
CDCl3, 50 °C
f1 (ppm)

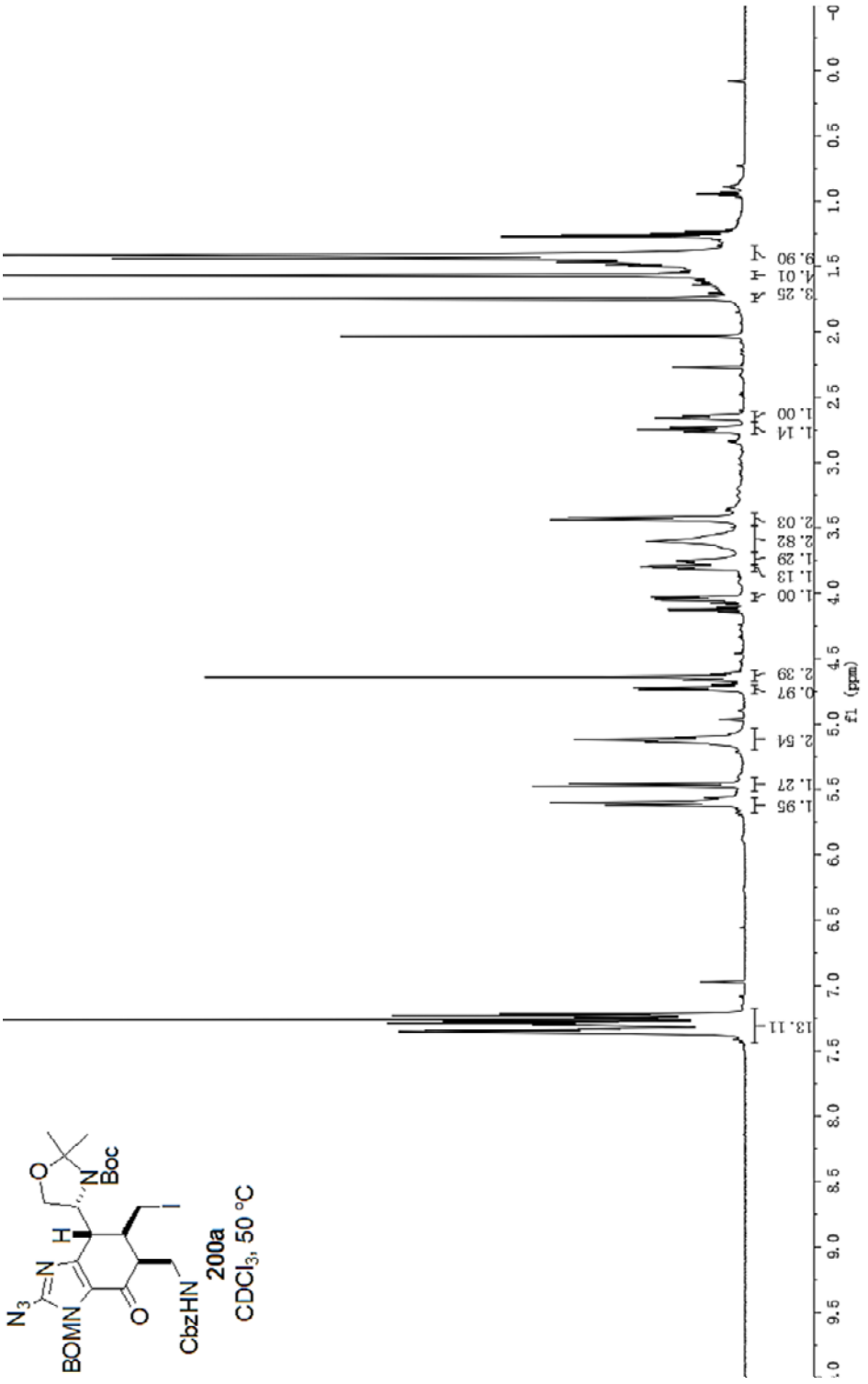

188b
CDCl3, 50 °C
f1 (ppm)

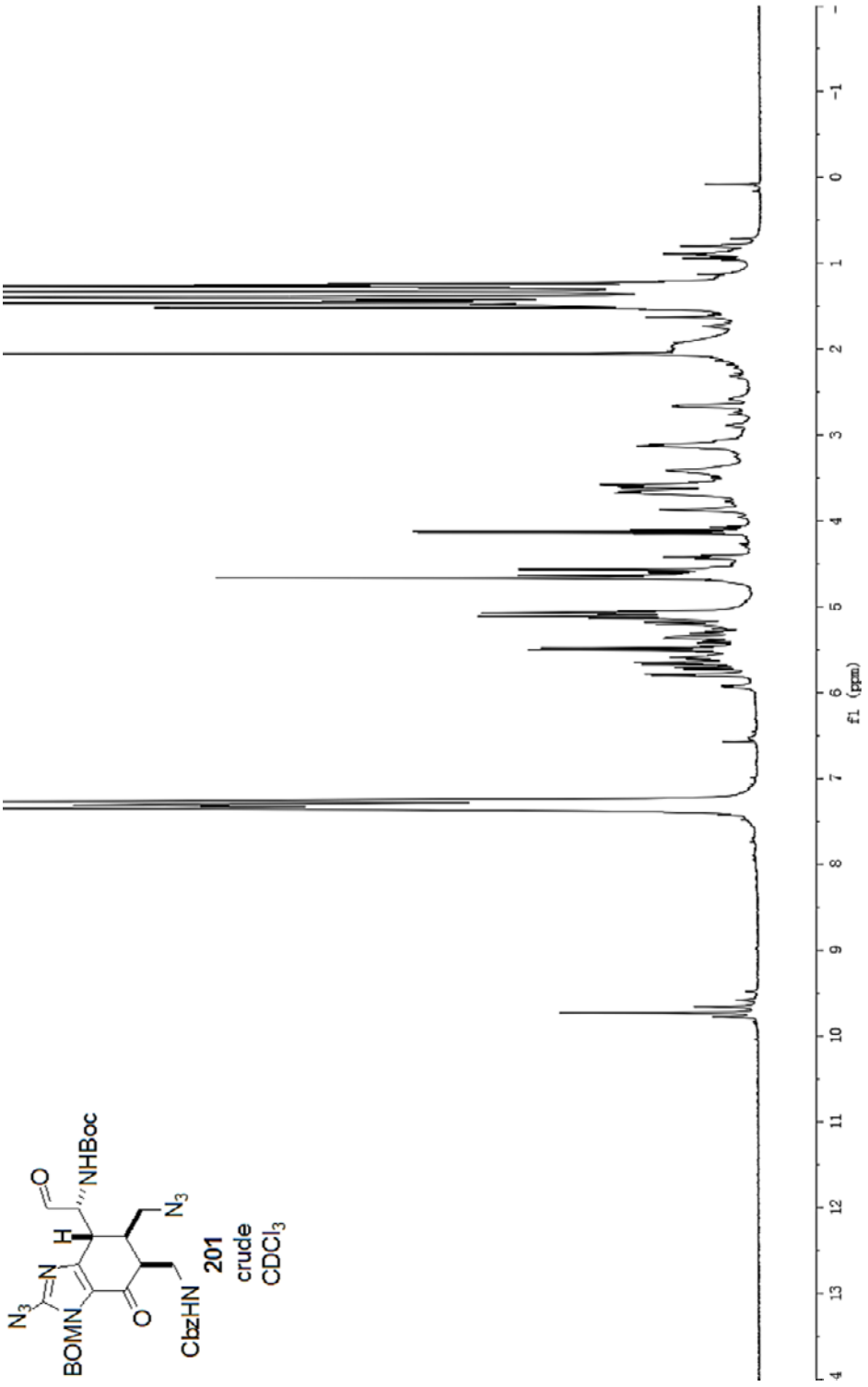

N3
BOMN
N
H
O
N
Boc
OH
BocHN
O
188c
CDCl3, 50 °C
11.76
1.00
0.99
0.95
0.87
1.93
0.95
1.04
1.11
1.63
0.91
1.10
1.02
0.96
0.84
0.37
3.51
3.47
12.53
12.16
f1 (ppm)

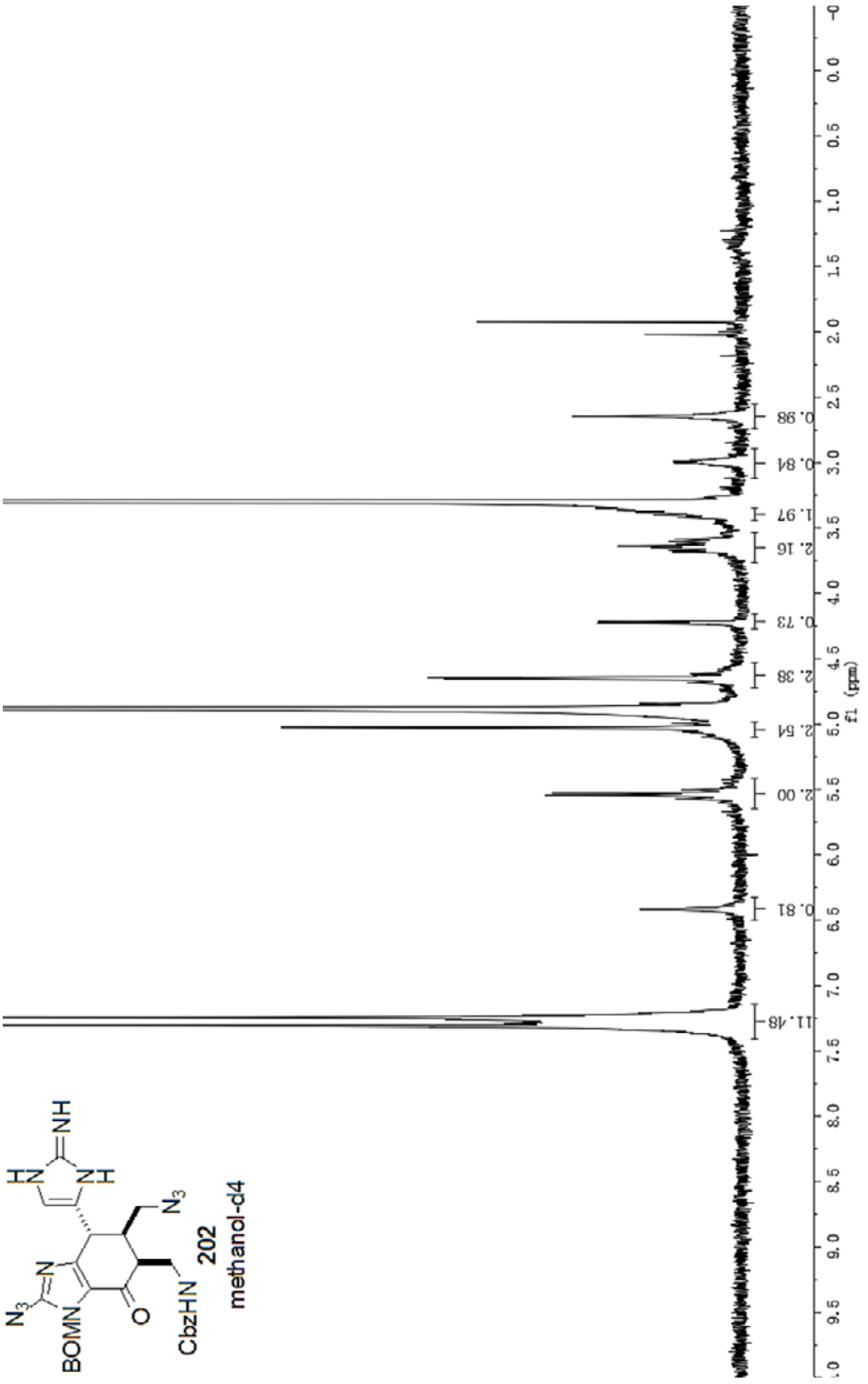

19.79
1.14
1.04
2.14
0.99
2.17
1.99
3.23
1.17
1.08
1.00
1.00
3.17
3.38
3.91
11.11
f1 (ppm)
N3
BOMN
N
H
O
N
Boc
OAc
O
CbzHN
195c
CDCl3, 50 °C

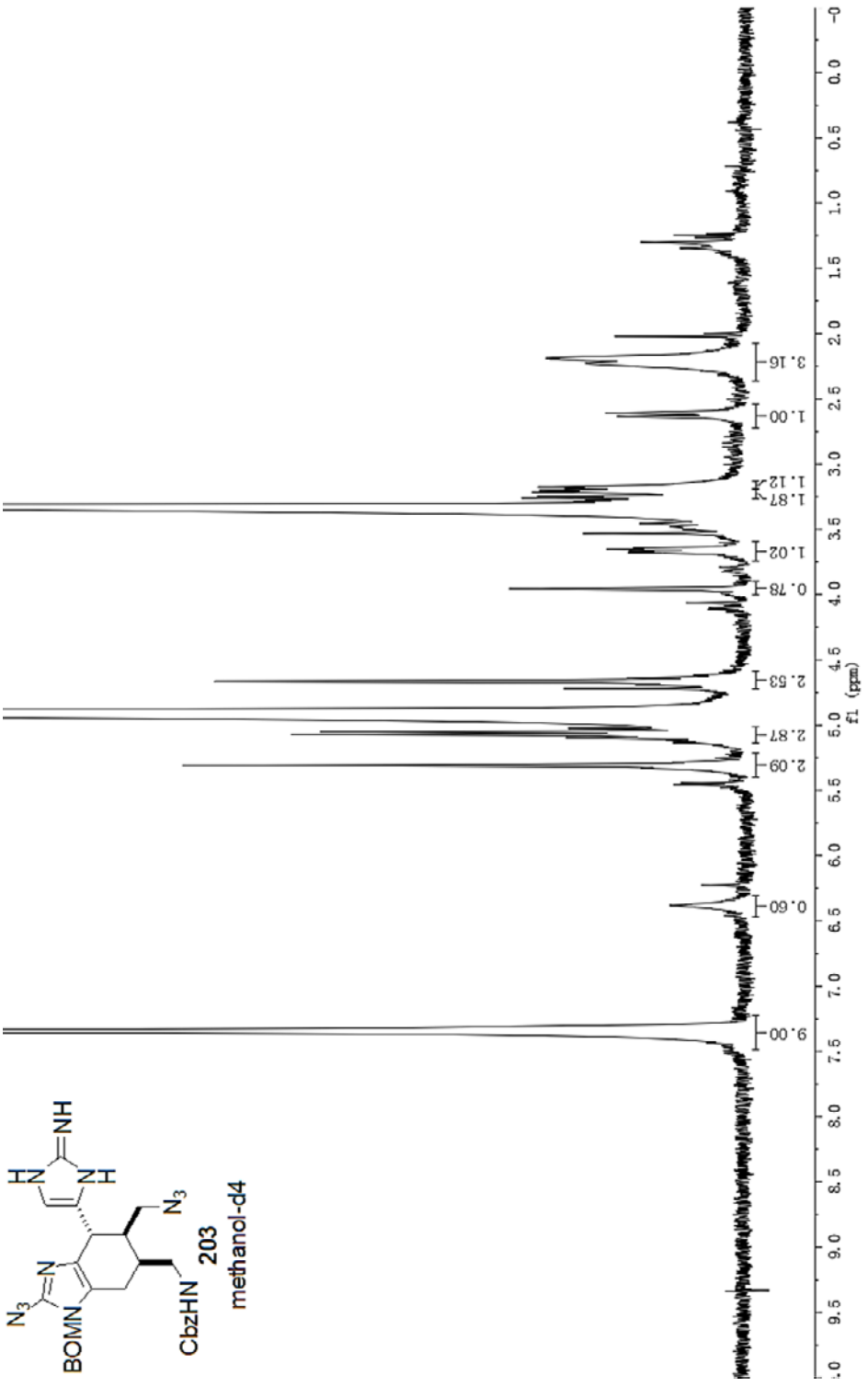

199a
crude
CDCl3, 50 °C
f1 (ppm)

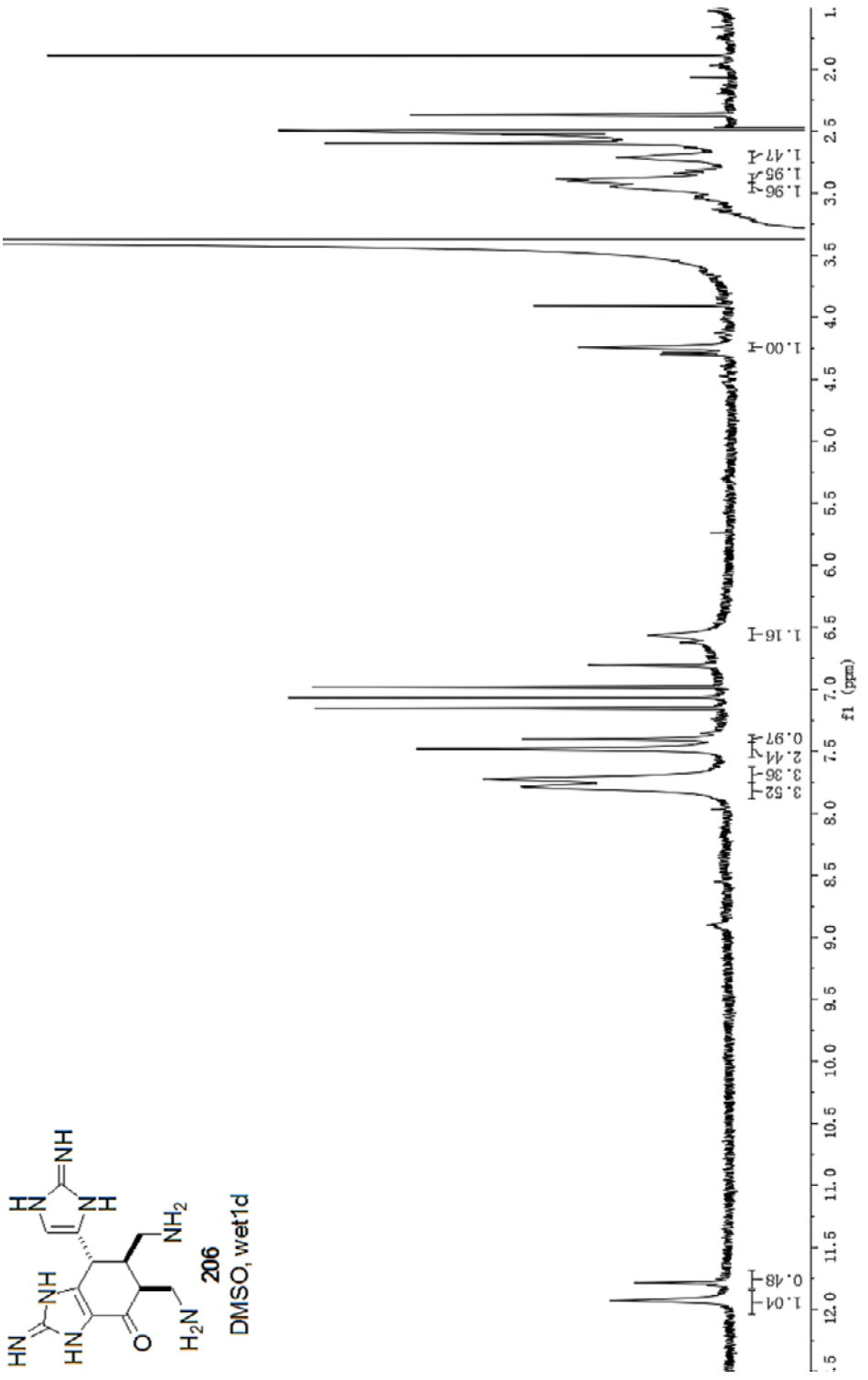

199c
CDCl3, 50 °C
f1 (ppm)

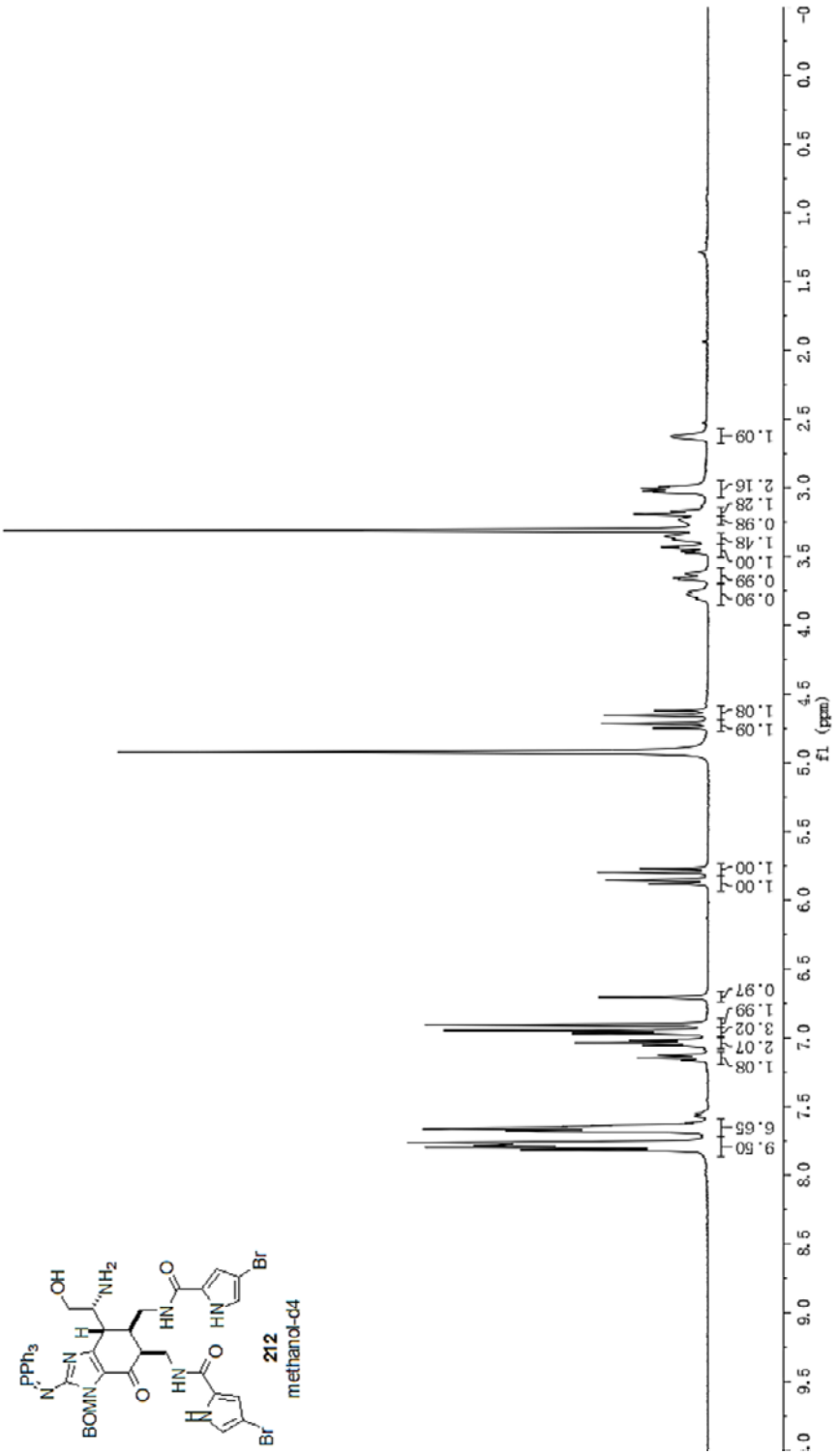

200a
CDCl3, 50 °C
BOMN
CbzHN
Boc
f1 (ppm)

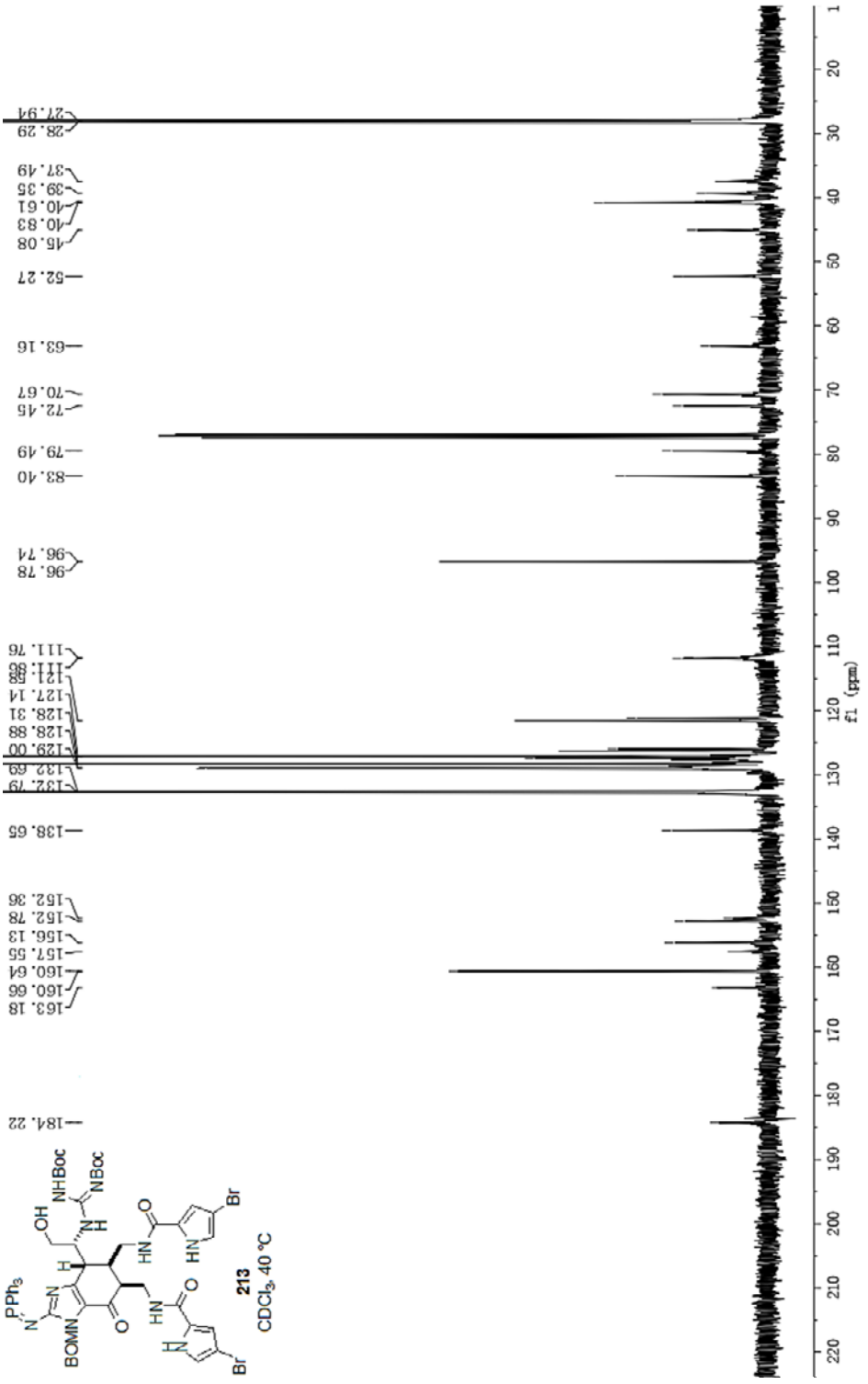

f1 (ppm)
201
crude
$CDCl_3$

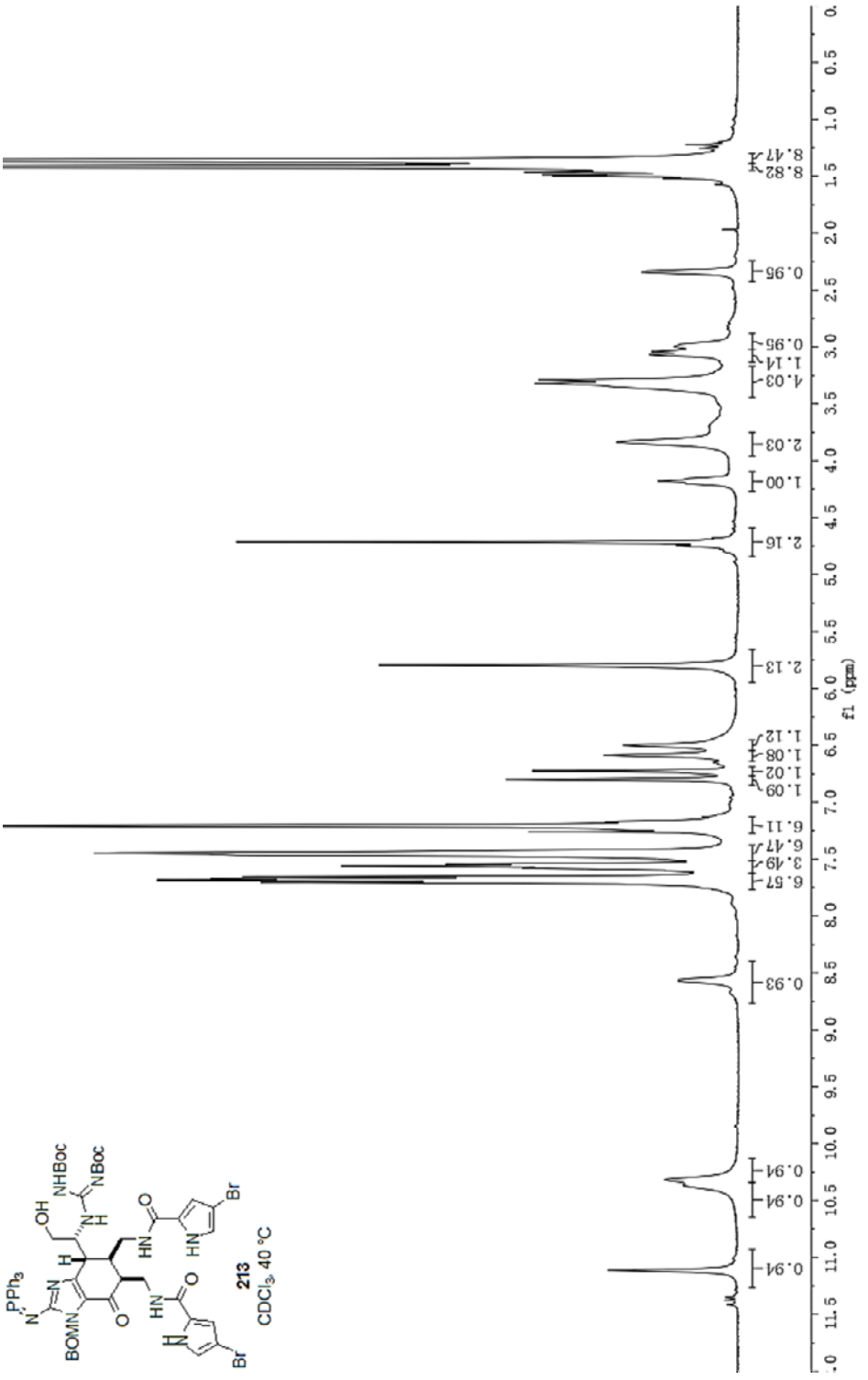

11.48
0.81
2.00
2.54
2.38
0.73
2.16
1.97
0.84
0.98
f1 (ppm)
BOMN
CbzHN
202
methanol-d4

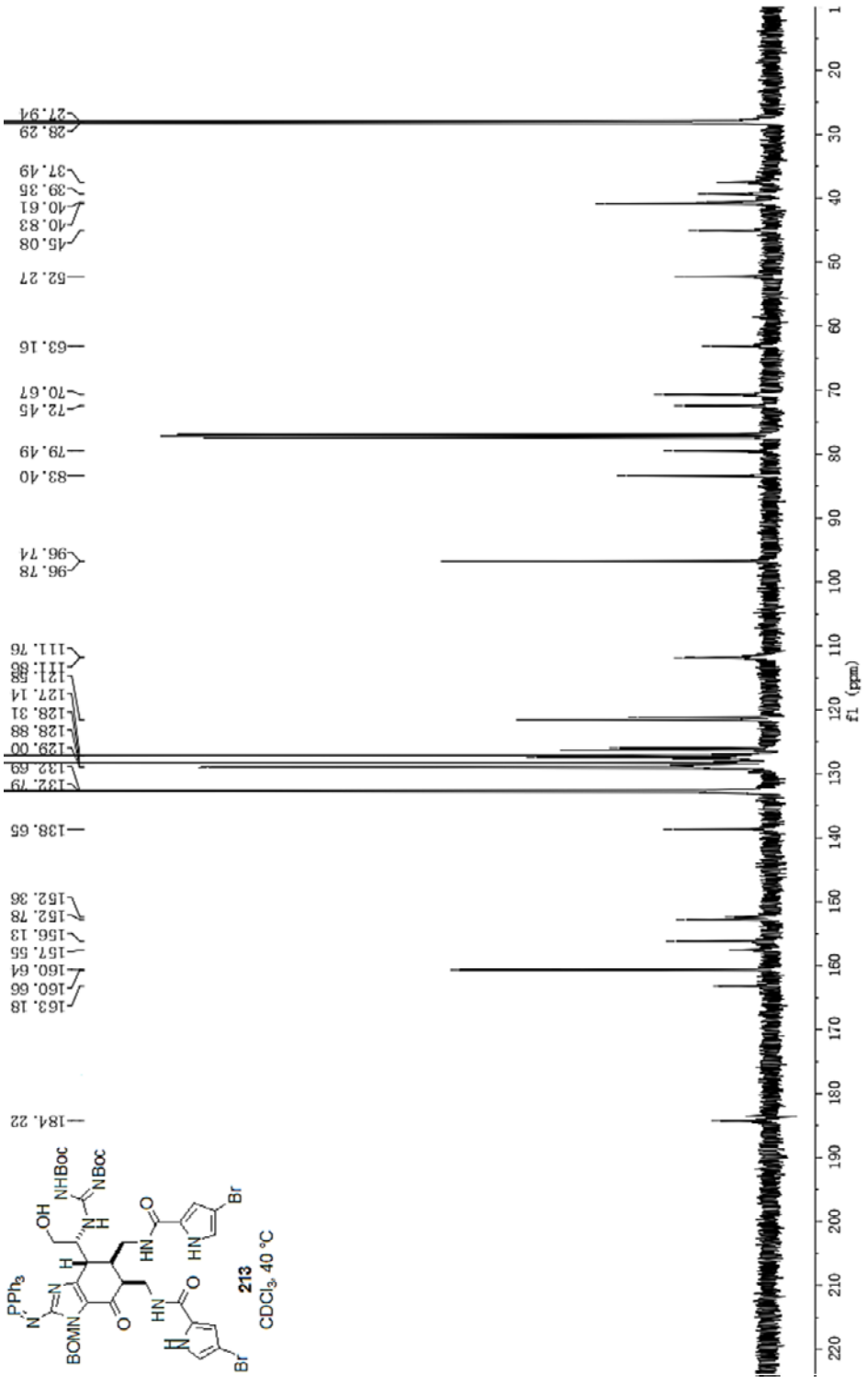

NH
HN
NH
N3
N
N3
BOMN
CbzHN
203
methanol-d4
9.00
0.60
2.09
2.87
2.53
0.78
1.02
1.87
1.12
1.00
3.16
f1 (ppm)

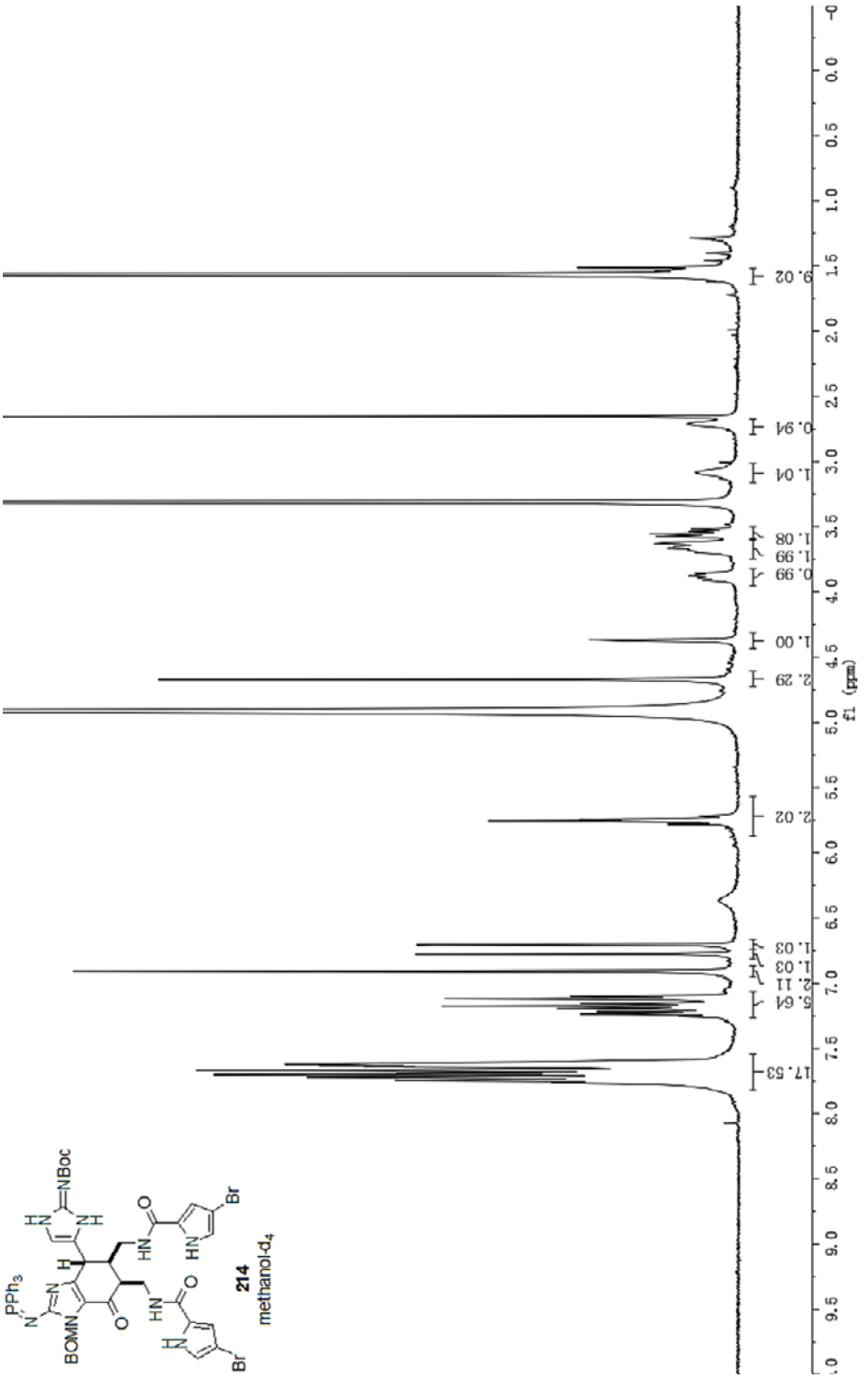

206
DMSO, wet1d
f1 (ppm)

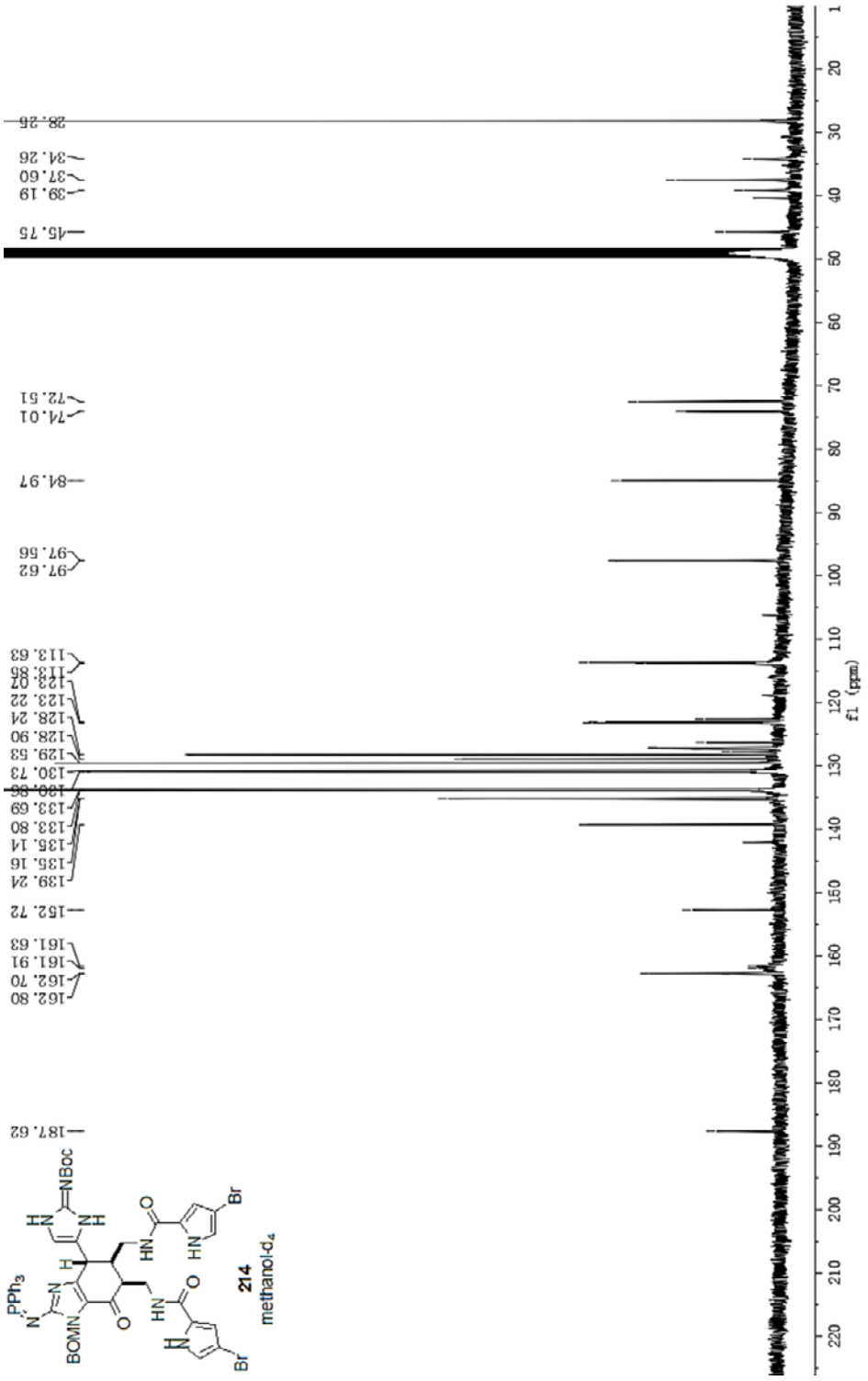

212
methanol-d4
f1 (ppm)

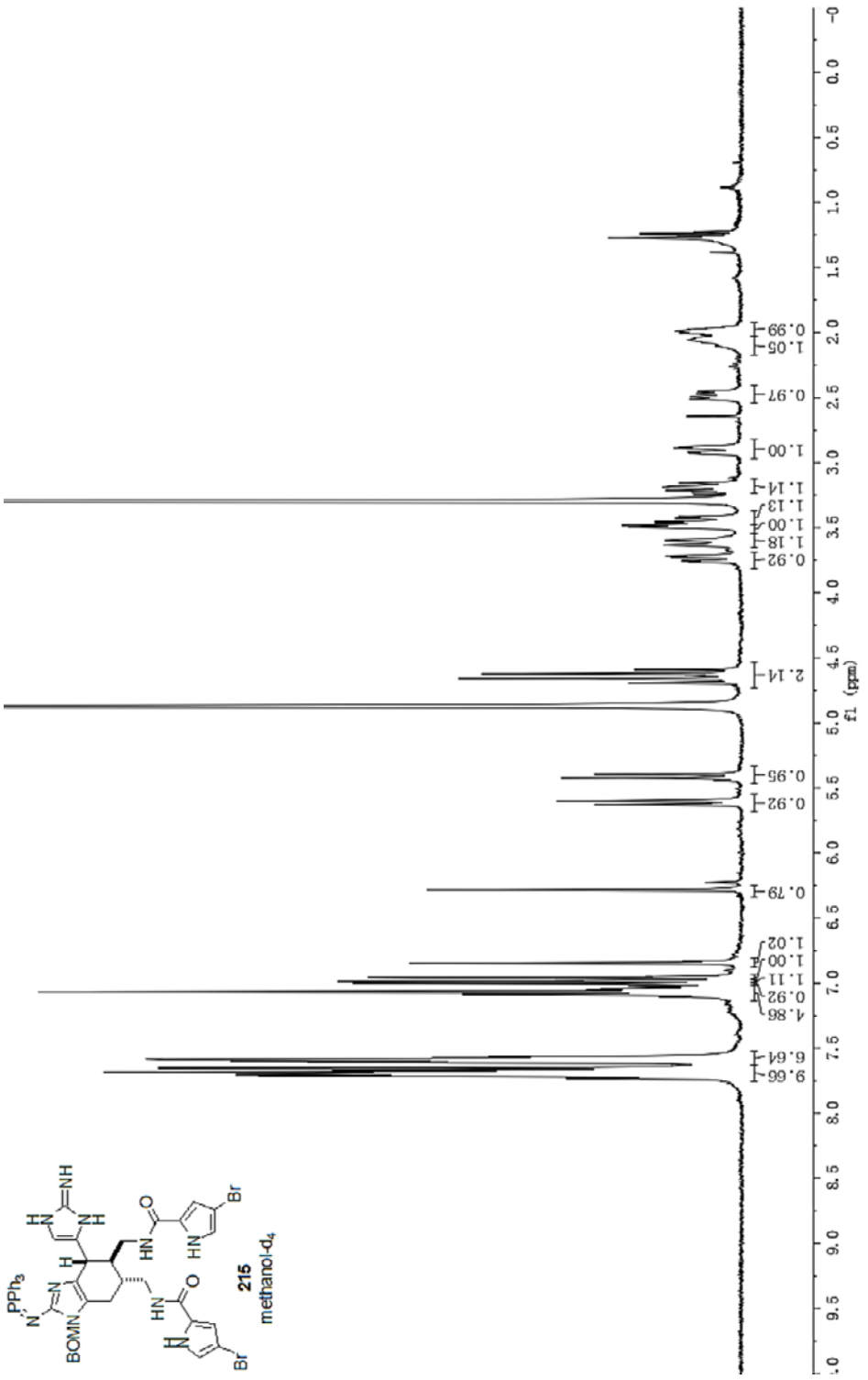

27.94
28.29
37.49
39.35
40.61
40.83
45.08
52.27
63.16
70.67
72.45
79.49
83.40
96.74
96.78
111.76
111.86
121.58
127.14
128.31
128.88
129.00
132.69
132.79
138.65
152.36
152.78
156.13
157.55
160.64
160.66
163.18
184.22
f1 (ppm)
213
CDCl3, 40 °C

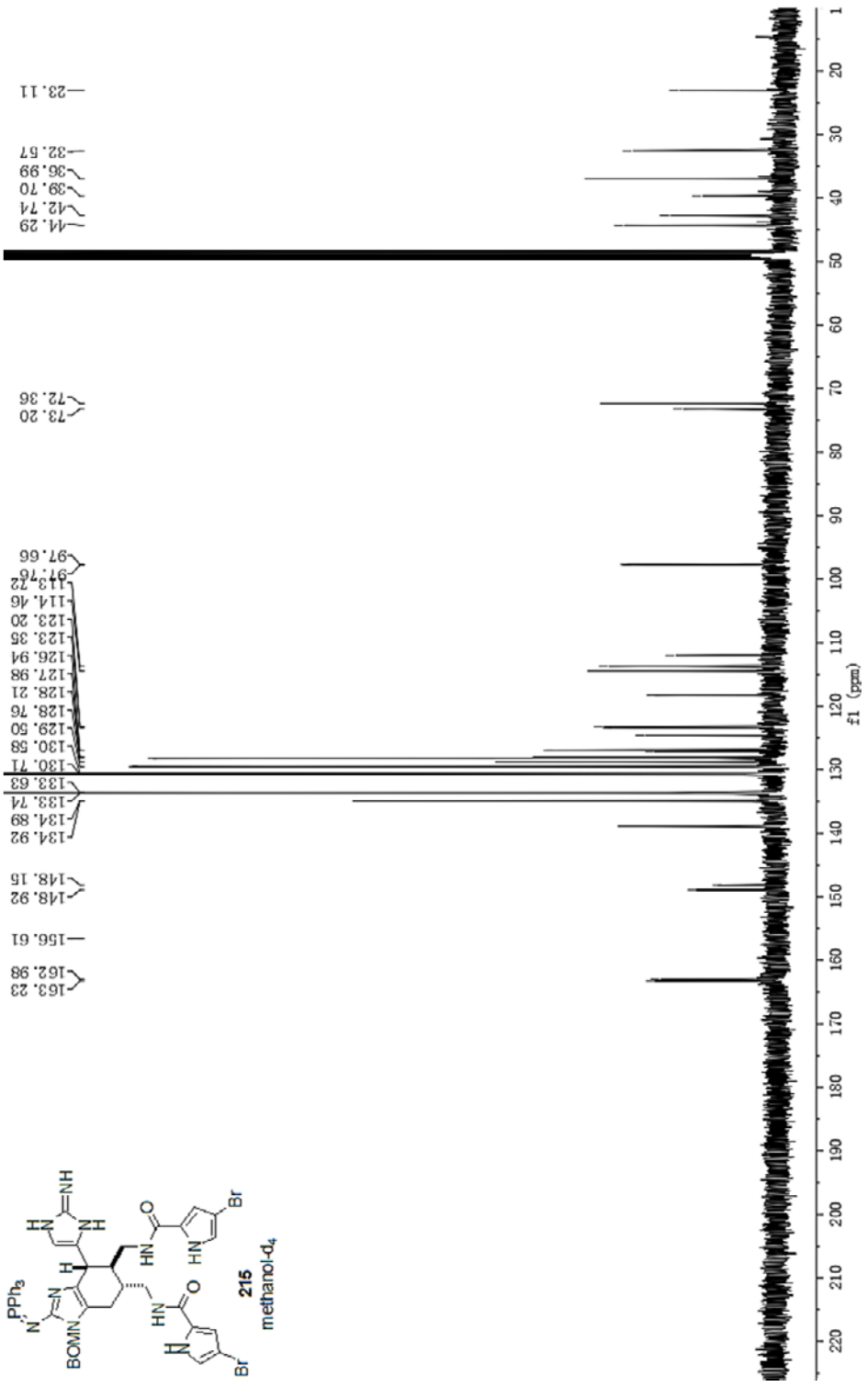

PPh3
BOMN
NHBoc
NBoc
OH
Br
Br
213
CDCl3, 40 °C
f1 (ppm)

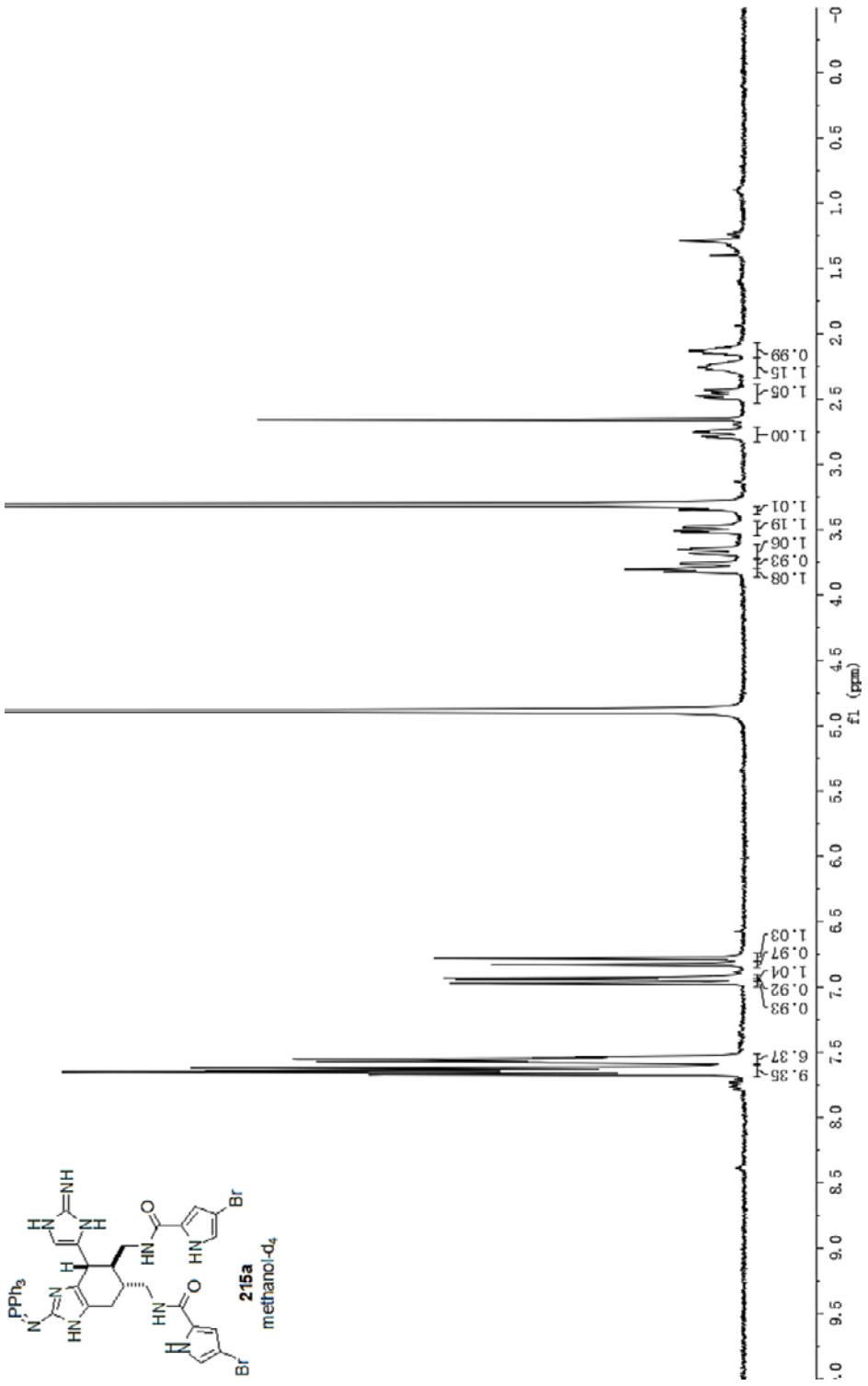

27.94
28.29
37.49
39.35
40.61
40.83
45.08
52.27
63.16
70.67
72.45
79.49
83.40
96.74
96.78
111.76
121.58
121.86
127.14
128.31
128.88
129.00
132.69
132.79
138.65
152.36
152.78
156.13
157.55
160.64
160.66
163.18
184.22
NHBoc
NBoc
OH
BOMN
PPh3
Br
Br
213
CDCl3, 40 °C
f1 (ppm)

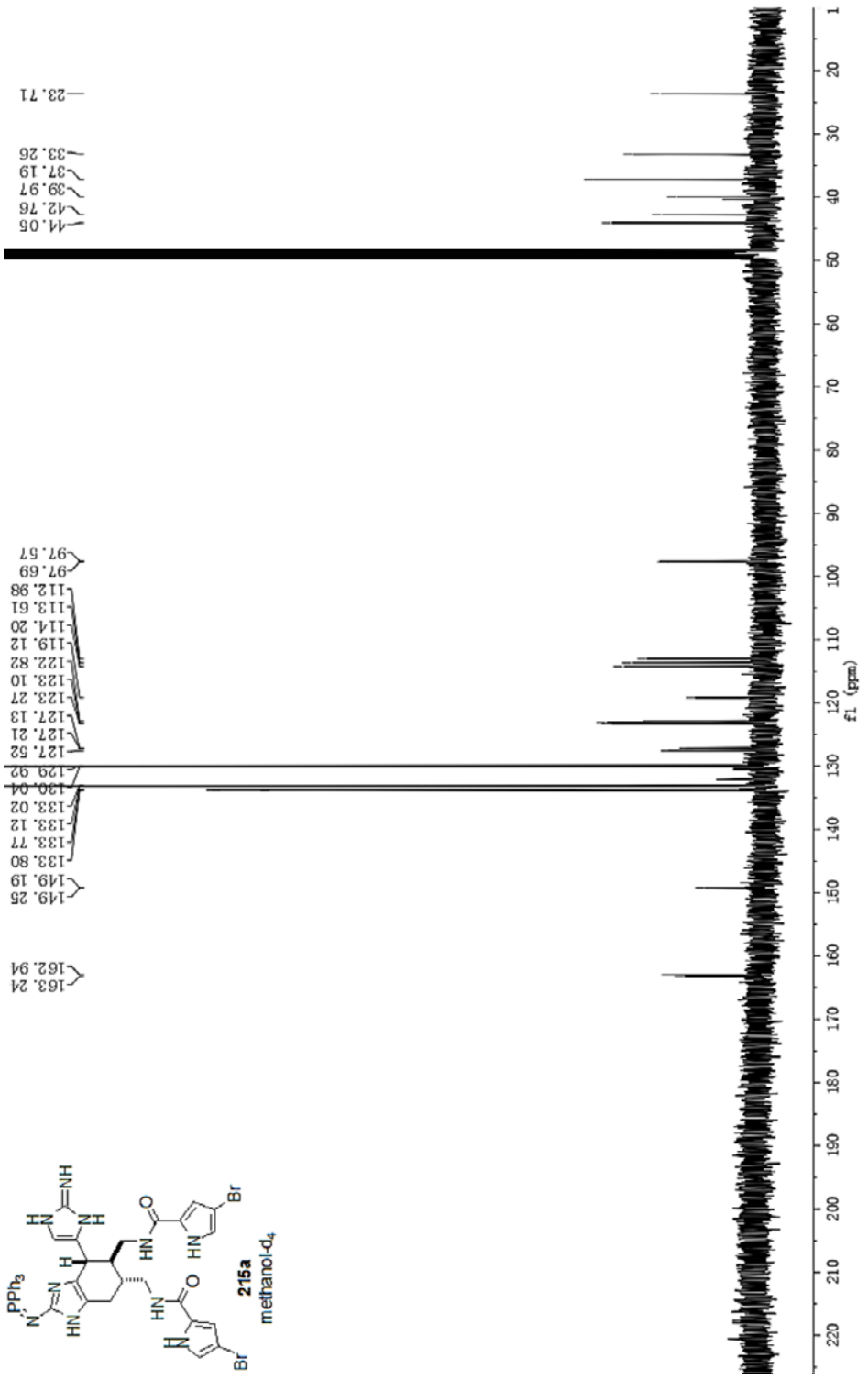

NBoc
PPh3
BOMN
Br
Br
214
methanol-d4
17.53
5.64
2.11
1.03
1.03
2.02
2.29
1.00
0.99
1.99
1.08
1.04
0.94
9.02
f1 (ppm)

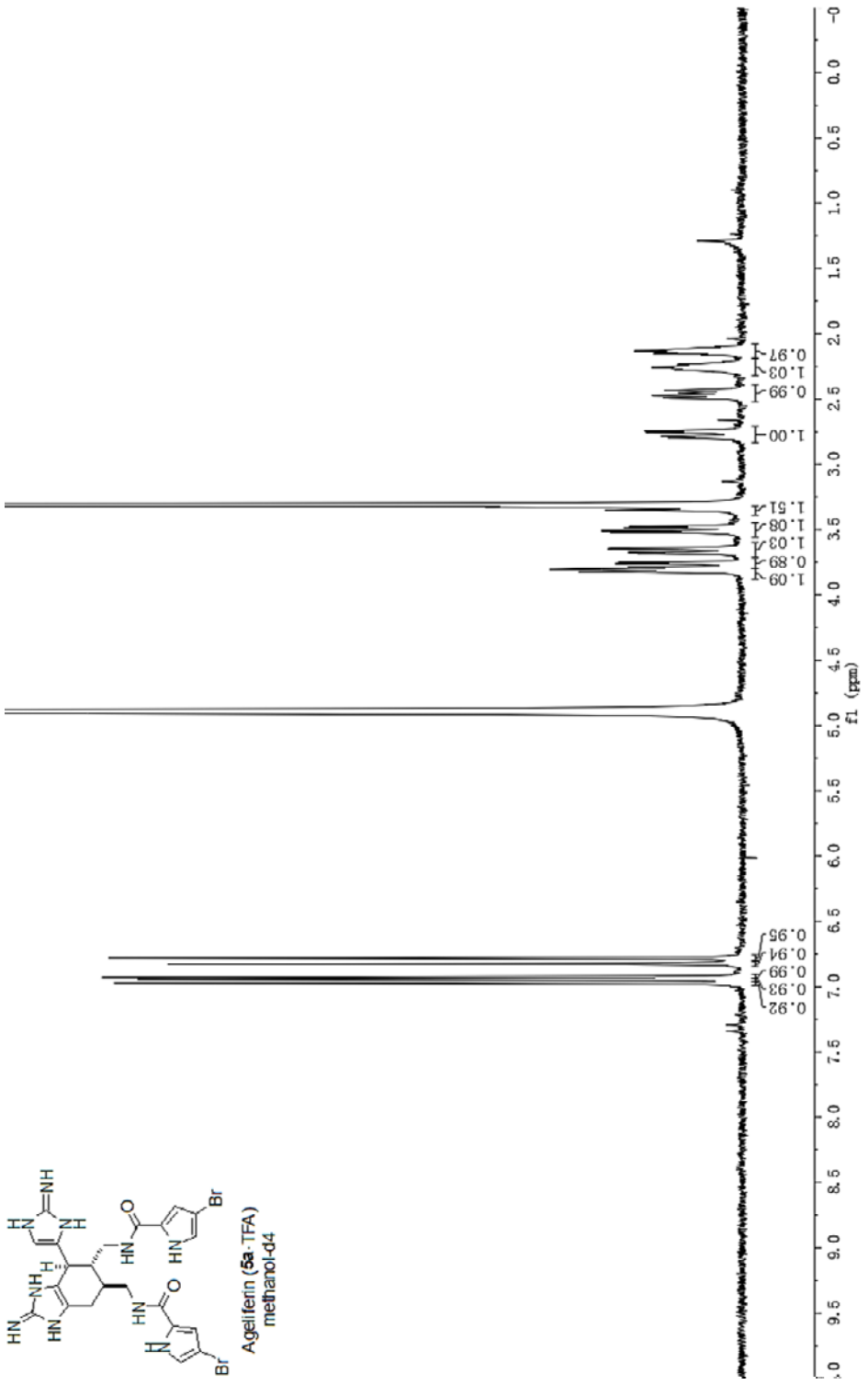

28.26
34.26
37.60
39.19
45.75
72.51
74.01
84.97
97.62
97.66
113.63
113.86
123.07
123.22
128.24
128.90
129.53
130.73
133.69
133.80
135.14
135.16
139.24
152.72
161.63
161.91
162.70
162.80
187.62
f1 (ppm)
214
methanol-d4

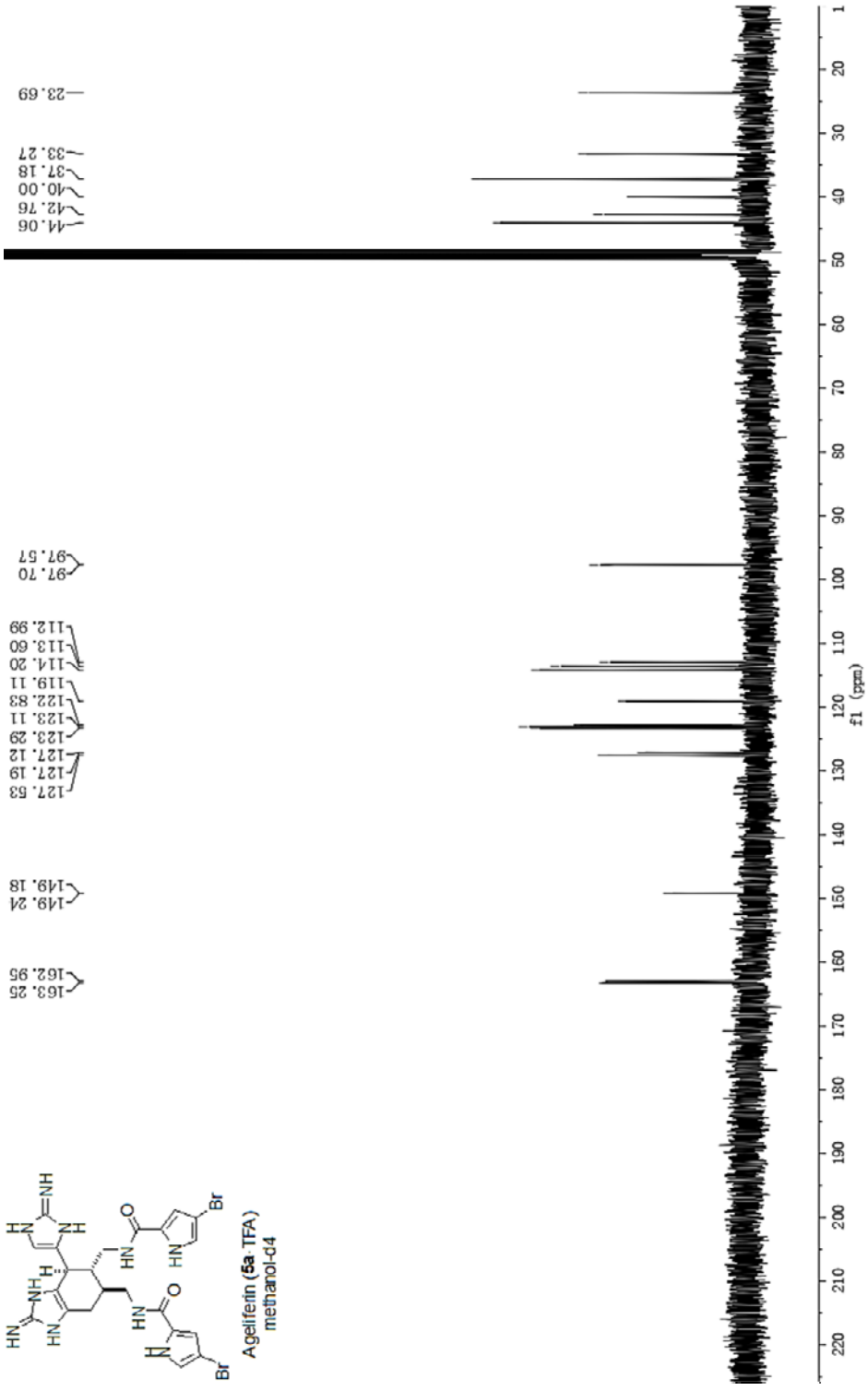

215
methanol-d4
f1 (ppm)

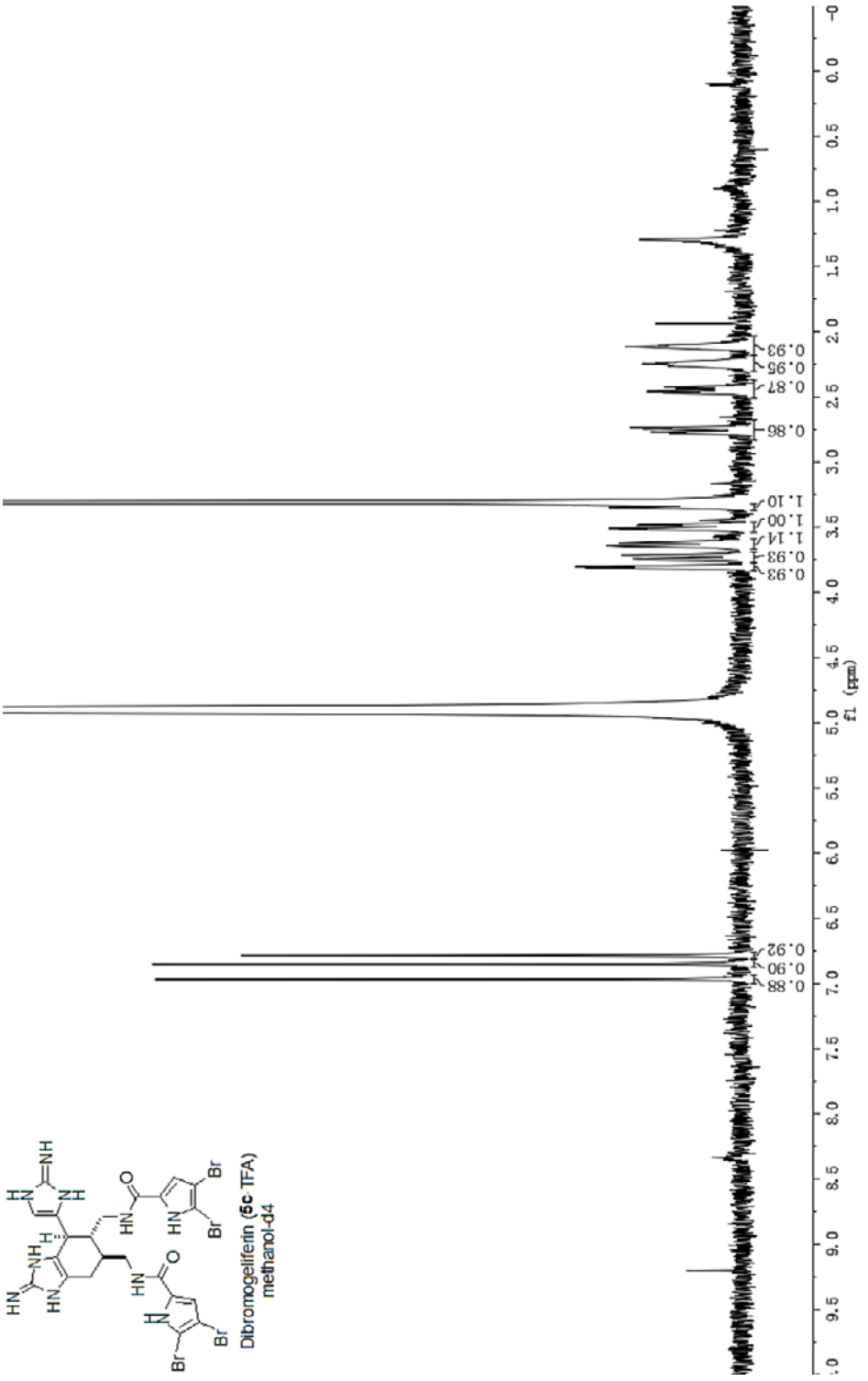

23.11
32.57
36.99
39.70
42.74
44.29
72.36
73.20
97.66
97.76
113.22
114.46
123.20
123.35
126.94
127.98
128.21
128.76
129.50
130.58
130.71
133.63
133.74
134.89
134.92
148.92
148.15
156.61
162.98
163.23
f1 (ppm)
PPh3
BOMN
215
methanol-d4
Br
Br

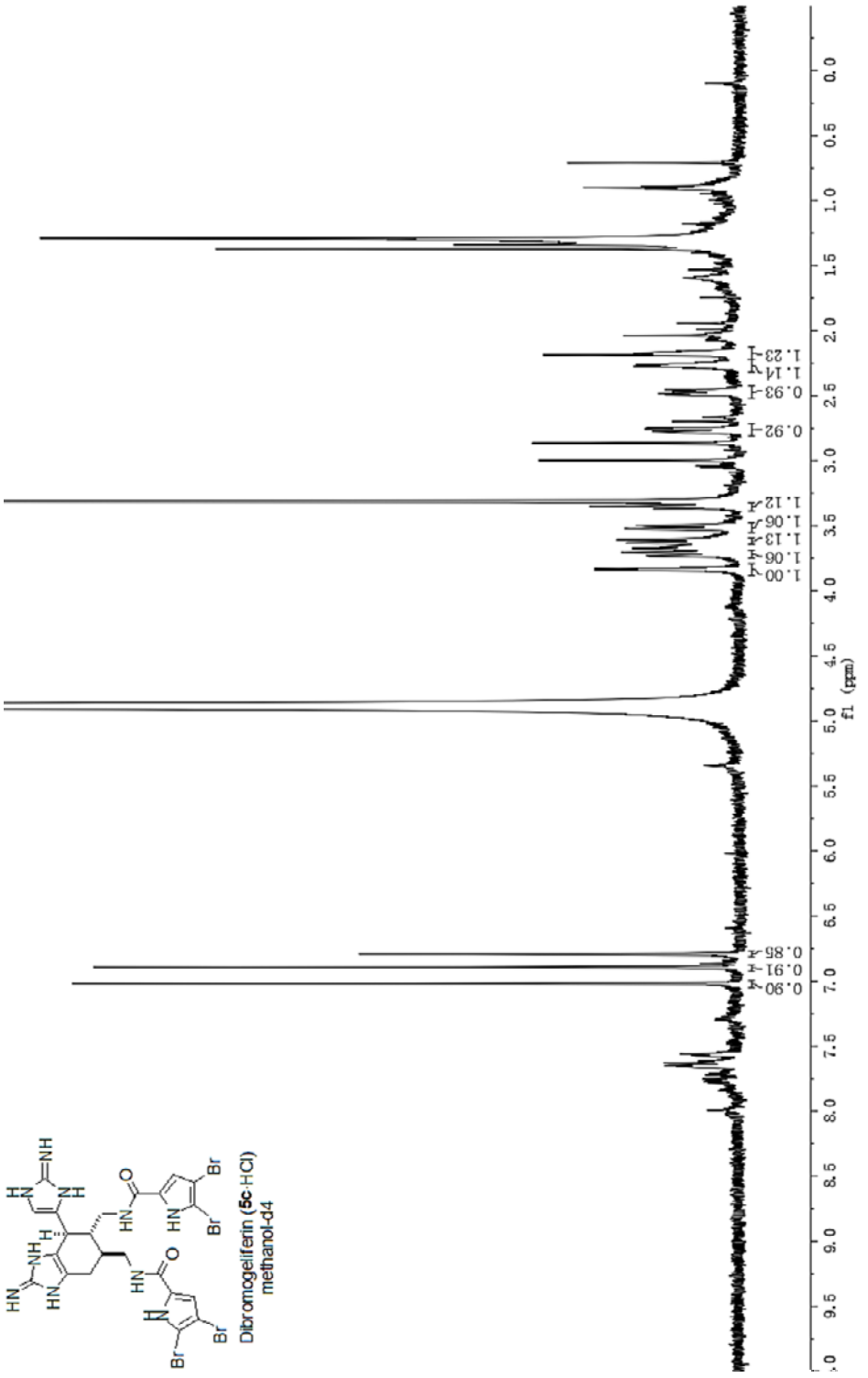

215a
methanol-d4
f1 (ppm)


23.71
33.26
37.19
39.97
42.76
44.05
97.57
97.69
112.98
113.61
114.20
119.12
122.82
123.10
123.27
127.13
127.21
127.52
129.92
130.04
133.02
133.12
133.77
133.80
149.19
149.25
162.94
163.24
f1 (ppm)
215a
methanol-d4


Agelliferin (5a · TFA)
methanol-d4
f1 (ppm)


Agelliferin (5a: TFA)
methanol-d4
Br
Br
f1 (ppm)


Dibromogeliferin (5c TFA)
methanol-d4
0.88
0.90
0.92
0.93
0.93
1.14
1.00
1.10
0.86
0.87
0.95
0.93
f1 (ppm)


Dibromogeliferin (5c·HCl)
methanol-d4
0.90
0.91
0.86
1.00
1.06
1.13
1.06
1.12
0.92
0.93
1.14
1.23
f1 (ppm)

BIBLIOGRAPHY

Al Mourabit, A.; Potier, P. *Eur. J. Org. Chem*. **2001**, 237–243.

Al-Mourabit, A.; Zancanella, M. A.; Tilvi, S.; Romo, D. *Nat. Prod. Rep*. **2011**, *28*, 1229–1260.

Arndt, H.-D.; Riedrich, M. *Angew. Chem., Int. Ed*. **2008**, *47*, 4785–4788.

Baran, B. S.; Zografos, A. L.; O'Malley, D. P. *J. Am. Chem. Soc*. **2004**, *126*, 3726–3727.

Baran, P. S.; Li, K.; O'Malley, D. P.; Mitsos, C. *Angew. Chem., Int. Ed*. **2006**, *45*, 249–252.

Baran, P. S.; O'Malley, D. P.; Zografos, A. L. *Angew. Chem., Int. Ed*. **2004**, *43*, 2674–2677.

Baran, P. S.; Zografos, A. L.; O'Malley, D. P. *J. Am. Chem. Soc*. **2004**, *126*, 3726–3727.

Belanger, G.; Hong, F.-T.; Overman, L. E.; Rogers, B. N.; Tellew, J. E.; Trenkle, W. C. *J. Org. Chem*. **2002**, *67*, 7880–7883.

Bhandari, M. R.; Yousufuddin, M.; Lovely, C. J. *Org. Lett*. **2011**, *13*, 1382–1385.

Birman, V. B.; Jiang, X. *Org. Lett.* **2004**, *6*, 2369–2371.

Breder, A.; Chinigo, G. M.; Waltman, A. W.; Carreira, E. M. *Angew. Chem., Int. Ed*. **2008**, *47*, 8514–8517.

Breder, A.; Chinigo, G. M.; Waltman, A. W.; Carreira, E. M. *Chem. Eur. J*. **2011**, *17*, 12405–12416.

Broeker, J. L.; Houk, K. N. *J. Org. Chem*. **1991**, *56*, 3651–3655.

Buchanan, M. S.; Carroll, A. R.; Addepalli, R.; Avery, V. M.; Hooper, J. N. A.; Quinn, R. J. *J. Org. Chem*. **2007**, *72*, 2309–2317.

Buchanan, M. S.; Carroll, A. R.; Quinn, R. J. *Tetrahedron Lett*. **2007**, *48*, 4573–4574.

Bucherer, H. T.; Fischbeck, H. T. *J. Prakt. Chem*. **1934**, *140*, 69–89.

Bucherer, H. T.; Steiner, W. *J. Prakt. Chem*. **1934**, *140*, 291–316.

Bultman, M. S.; Ma, J.; Gin, D. Y. *Angew. Chem., Int. Ed*. **2008**, *47*, 6821–6824.

Cernak, T. A.; Gleason, J. L. *J. Org. Chem*. **2008**, *73*, 102–110.

Chinigo, G. M.; Breder, A.; Carreira, E. M. *Org. Lett*. **2011**, *13*, 78–81.

Corey, E. J.; Kang, M.-C. *J. Am. Chem. Soc*. **l984**, *106*, 5384–5385.

Crimmins, M. T.; Ellis, J. M. *J. Org. Chem*. **2008**, *73*, 1649–1660.

Demir, A. S.; Emrullahoglu, M. *Curr. Org. Syn*. **2007**, *4*, 321–350.

Dilley, A. S.; Romo, D. *Org. Lett*. **2001**, *3*, 1535–1538.

Ding, H.; Roberts, A. G.; Harran, P. G. *Angew. Chem., Int. Ed*. **2012**, *51*, 1–5.

Dransfield, P. J.; Dilley, A. S.; Wang, S.; Romo, D. *Tetrahedron*. **2006**, *62*, 5223–5247.

Dransfield, P. J.; Wang, S.; Dilley, A.; Romo, D. *Org. Lett*. **2005**, *7*, 1679–1682.

Du, H.; He, Y.; Sivappa, R.; Lovely, C. J. *Synlett*. **2006**, 965–992.

Feldman, K. S.; Nuriye, A. Y.; Li, J. *J. Org. Chem*. **2011**, *76*, 5042–5060.

Feldman, K. S.; Nuriye, A. Y. *Org. Lett*. **2010**, *12*, 4532–4535.

Feldman, K. S.; Skoumbourdis, A. P.; Fodor, M. D. *J. Org. Chem*. **2007**, *72*, 8076–8086.

Foley, L. H.; Büchi, G. *J. Am. Chem. Soc*. **1982**, *104*, 1776–1777.

Forenza, S.; Minale, L.; Riccio, R. Fattorusso, E. *J. Chem. Soc., D. Chem. Commun*. **1971**, 1129–1130.

Forte, B.; Malgesini, B.; Piutti, C.; Quartieri, F.; Scolaro, A.; Papeo, G. *Mar. Drugs*. **2009**, *7*, 705–753.

Gaich, T.; Baran, P. S. *J. Org. Chem*. **2010**, *75*, 4657–4673.

Garcia, E. E.; Benjamin, L. E.; Fryer, R. I. *J. Chem. Soc., Chem. Commun*. **1973**, 78–79.

Garrido-Hernandez, H.; Nakadai, M.; Vimolratana, M.; Li, Q.; Doundoulakis, T.; Harran, P. G. *Angew. Chem., Int. Ed*. **2005**, *44*, 765–769.

Grube, A.; Köck, M. *Angew. Chem., Int. Ed*. **2007**, *46*, 2320–2324.

Grube, A.; Köck, M. *Org. Lett*. **2006**, *8*, 4675–4678.

Grube, A; Immel, S.; Baran, P. S.; and Köck, M. *Angew. Chem., Int. Ed*. **2007**, *46*, 6721–6724.

He, Y.; Chen, Y.; Wu, H.; Lovely, C. J. *Org. Lett*. **2003**, *5*, 3623–3626.

He, Y.; Krishnamoorthy, P.; Lima, H. M.; Chen, Y.; Wu, H.; Sivappa, R.; Dias, H. V. R.; Lovely C. J. *Org. Biomol. Chem*. **2011**, *9*, 2685–2701.

Heasley, B. *Eur. J. Org. Chem*. **2009**, 1477–1489.

Hoffmann, H.; Lindel, T. *Synthesis*. **2003**, 1753–1783.

Hoveyda, A.H.; Evans, D. A.; Fu, G. C. *Chem. Rev*., **1993**, *93*, 1307–1370.

Hudon, J.; Cernak, T. A.; Ashenhurst, J. A.; Gleason, J. L. *Angew. Chem., Int. Ed*. **2008**, *47*, 8885–8888.

Jacobi, N.; Lindel, T.; *Eur. J. Org. Chem*. **2010**, 5415–5425.

Jacquot, D. E. N.; Lindel, T. *Curr. Org. Chem*. **2005**, *9*, 1551–1565.

Katz, J. D.; Overman, L. E. *Tetrahedron*. **2004**, *60*, 9559–9568.

Kawasaki, I.; Sakaguchi, N.; Fukushima, N.; Fujioka, N.; Nikaido, F.; Yamashita, M.; Ohta, S. *Tetrahedron*. **2002**, *43*, 4377–4380.

Kawasaki, I.; Sakaguchi, N.; Khadeer, A.; Yamashita, M.; Ohta, S. *Tetrahedron*. **2006**, *62*, 10182–10192.

Keifer, P. A.; Schwartz, R. E.; Koker, M. E. S.; Hughes, R.G., Jr.; Rittschof, D.; Rinehart, K. L. *J. Org. Chem*. **1991**, *56*, 2965–2975.

Kinnel, R. B.; Gehrken, H. P.; Scheuer, P. J. *J. Am. Chem. Soc*. **1993**, *115*, 3376–3377.

Kinnel, R. B.; Gehrken, H.-P.; Swali, R.; Skoropowski, G.; Scheuer, P. J. *J. Org. Chem*. **1998**, *63*, 3281–3286.

Kobayashi, H.; Kitamura, K.; Nagai, K.; Nakao, Y.; Fusetani, N.; van Soest, R. W. M.; Matsunaga, S. *Tetrahedron Lett*. **2007**, *48*, 2127–2129.

Kobayashi, J.; Tsuda, M.; Murayama, T.; Nakamura, H.; Ohizumi, Y.; Ishibashi, M.; Iwamura, M.; Ohta, T.; Nozoe, S. *Tetrahedron*. **1990**, *46*, 5579–5586.

Köck, M.; Grube, A.; Seiple, I. B.; Baran, P. S. *Angew. Chem., Int. Ed*. **2007**, *46*, 6586–6594.

Koenig, S. G.; Miller, S. M.; Leonard, K. A.; Löwe, R. S.; Chen, B. C.; Austin, D. J. *Org. Lett*. **2003**, *5*, 2203–2206.

Kubik, S.; Meissner, R. S.; Rebek Jr., J. *Tetrahedron Lett.* **1994**, *35*, 6635–6638.

Lanman, B. A.; Overman, L. E. *Heterocycles*. **2006**, *70*, 557–570.

Lanman, B. A.; Overman, L. E.; Paulini, R.; White, N. S. *J. Am. Chem. Soc*. **2007**, *129*, 12896–12900.

Li, Q.; Hurley, P.; Ding, H.; Roberts, A. G.; Akella, R.; Harran, P. G. *J. Org. Chem*. **2009**, *74*, 5909–5919.

Lovely, C. J.; Du, H.; Dias, H. V. R. *Org. Lett.*, **2001**, *3*, 1319–1322.

Lovely, C. J.; Du, H.; He, Y.; Dias, H. V. R. *Org. Lett.*, **2004**, *6*, 735–738.

Lovely, C. J.; Du, H.; Sivappa, R.; Bhandari, M. R.; He, Y.; Dias, H. V. R. *J. Org. Chem*. **2007**, *72*, 3741–3749.

Lu, J.; Tan, X.; Chen, C. *J. Am. Chem. Soc.* 2007, *129*, 7768–7769.

Ma, Z.; Lu, J.; Wang, X.; Chen, C. *Chem. Commun*. **2011**, *47*, 427–429.

Melikyan, G. G. *Aldrichimica Acta*. **1998**, *31*, 50–64.

Melikyan, G. G. *Org. React*. **1997**, *49*, 427–675.

Myers, A. G.; Kung, D. W.; Zhong, B. *J. Am. Chem. Soc*. **2000**, *122*, 3236–3237.

Nakadai, M.; Harran, P. G. *Tetrahedron Lett*. **2006**, *47*, 3933–3935.

Namba, K.; Inai, M.; Sundermeier, U.; Greshock, T. J.; Williams, R. M. *Tetrahedron Lett*. **2010**, *51*, 6557–6559.

Namba, K.; Kaihara, Y.; Yamamoto, H.; Imagawa, H.;Tanino, K.; Williams, R. M.; Nishizawa, M. *Chem. Eur. J*. **2009**, *15*, 6560–6563.

Nishimura, S.; Matsunaga, S.; Shibazaki, M.; Suzuki, K.; Furihata, K.; van Soest, R. W. M.; Fusetani, N. *Org. Lett*. **2003**, *5*, 2255–2257.

Northrop, B. H.; O'Malley, D. P.; Zografos, A. L.; Baran, P. S.; Houk, K. N. *Angew.Chem., Int. Ed*. **2006**, *45*, 4126–4130.

O'Malley, D. P.; Li, K.; Maue, M.; Zografos, A. L.; Baran, P. S. *J. Am. Chem. Soc*. **2007**, *129*, 4762–4775.

O'Malley, D. P.; Yamaguchi, J.; Young, I. S.; Seiple, I. B.; Baran, P. S. *Angew. Chem., Int. Ed*. **2008**, *47*, 3581–3583.

Olofson, A.; Yakushijin, K.; Horne, D. A. *J. Org. Chem*. **1997**, *62*, 7918–7919.

Overman, L. E.; Rogers, B. N.; Tellew, J. E.; Trenkle, W. C. *J. Am. Chem. Soc*. **1997**, *119*, 7159–7160.

Poullennec, K. G.; Kelly, A. T.; Romo, D. *Org. Lett*. **2002**, *4*, 2645–2648.

Poullennec, K. G.; Romo, D. *J. Am. Chem. Soc*. **2003**, *125*, 6344–6345.

Pöverlein, C.; Breckle, G.; Lindel, T. *Org. Lett*. **2006**, *8*, 819–821.

Rinehart, K. L. *Pure Appl. Chem*. **1989**, *61*, 525–528.

Sarges, R.; Goldstein, S. W.; Welch, W. M. *J. Med. Chem*. **1990**, *33*, 1859–1865.

Seiple, I. B.; Su, S.; Young, I. S.; Lewis, C. A.; Yamaguchi, J.; Baran, P. S. *Angew. Chem., Int. Ed*. **2010**, *49*, 1095–1098.

Seiple, I. B.; Su, S.; Young, I. S.; Nakamura, A.; Yamaguchi, J.; Jørgensen, L.; Rodriguez, R. A.; O'Malley, D. P.; Gaich, T.; Köck, M.; Baran, P. S. *J. Am. Chem. Soc*. **2011**, *133*, 14710–14726.

Sivappa, R.; Hernandez, N. M.; He, Y.; Lovely, C. J. *Org. Lett.* **2007**, *9*, 3861–3864.

Sivappa, R.; Mukherjee, S.; Dias, H. V. R.; Lovely, C. J. *Org. Biomol. Chem.* **2009**, *7*, 3215–3218.

Snider, B. B. *Chem. Rev.* **1996**, *96*, 339–363.

Snider, B. B. *Tetrahedron*. **2009**, *65*, 10738–10744.

Starr, J. T.; Koch, G.; Carreira, E. M. *J. Am. Chem. Soc*. **2000**, *122*, 8793–8794.

Stout, E. P.; Wang, Y.; Romo, D.; Molinski, T. F. *Angew. Chem., Int. Ed*. **2012**, *51*, 1–6.

Su, S.; Rodriguez, R. A.; Baran. P. S. *J. Am. Chem. Soc*. **2011**, *133*, 13922–13925.

Su, S.; Seiple, I. B.; Young, I. S.; Baran, P. S. *J. Am. Chem. Soc*. **2008**, *130*, 16490–16491.

Tan, X.; Chen, C. *Angew. Chem., Int. Ed*. **2006**, *45*, 4345–4348.

Tang, L.; Romo, D. *Heterocycles*. **2007**, *74*, 999–1008.

Tanino, H.; Nakata, T.; Kaneko, T.; Kishi, Y. *J. Am. Chem. Soc*. **1977**, *99*, 2818–2819.

Travert, N.; Al-Moura, A. *J. Am. Chem. Soc*. **2004**, *126*, 10252–10253.

Trost, B. M.; Braslau, R. *J. Org. Chem*. **1988**, *53*, 532–537.

Urban, F. J.; Jasys, V. J. *Org. Proc. Res. Dev*. **2004**, *8*, 169–175.

Urban, S.; Leone, P. d. A.; Carroll, A. R.; Fechner, G. A.; Smith, J.; Hooper, J. N. A.; Quinn, R. J. *J. Org. Chem*. **1999**, *64*, 731–735.

Walker, R. P.; Faulkner, D. J.; Van Engen, D.; Clardy, J. *J. Am.Chem. Soc*. **1981**, *103*, 6772–6773.

Wang, S.; Dilley, A. S.; Poullennecz, K. G.; Romo, D. *Tetrahedron*. **2006**, *62*, 7155–7161.

Wang, S.; Romo, D. *Angew. Chem., Int. Ed*. **2008**, *47*, 1284–1286.

Wang, X.; Ma, Z.; Lu, J.; Tan, X.; Chen, C. *J. Am. Chem. Soc*. **2011**, *133*, 15350–15353.

Ware, E. *Chem. Rev*. **1950**, *46*, 403–470.

Weinreb, S. M. *Nat. Prod. Rep*. **2007**, *24*, 931–948.

Wiese, K. J.; Yakushijin, K.; Horne, D. A. *Tetrahedron Lett*. **2002**, *43*, 5135–5136.

Williams, D. H.; Faulkner, D. J. *Tetrahedron*. **1996**, *52*, 5381–5390.

Yamaguchi, J.; Seiple, I. B.; Young, I. S.; O'Malley, D. P.; Maue, M.; Baran, P. S. *Angew. Chem., Int. Ed*. **2008**, *47*, 3578–3580.

Zancanella, M. A.; Romo, D. *Org. Lett*. **2008**, *10*, 3685–3688.