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On the Synthesis of Breitfussins

Toward the total synthesis of Breitfussin A and analogues

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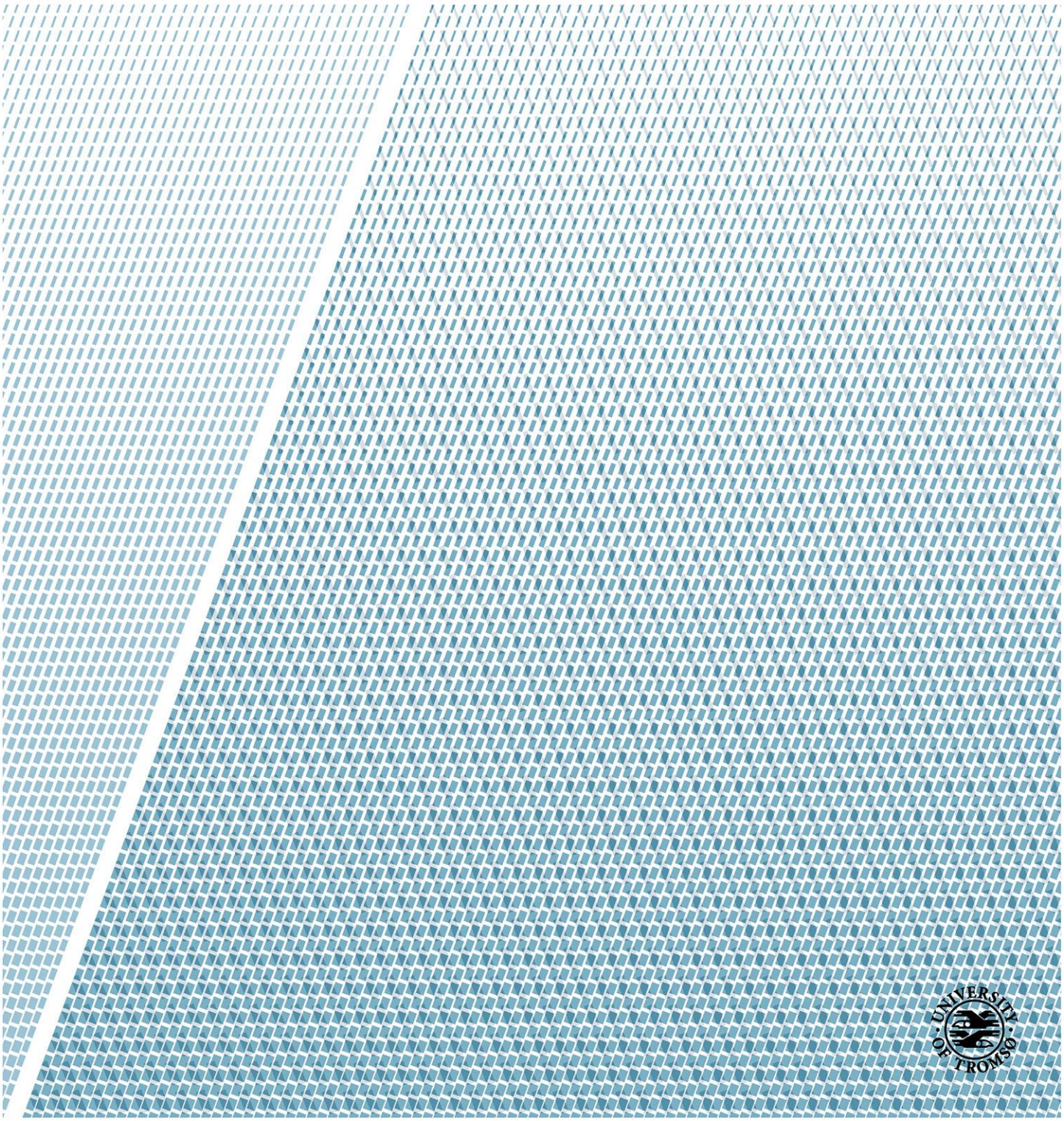

I ABSTRACT

The Breitfussins are a series of closely related heterocyclic compounds originated from the marine organism *Thelia Breitfussi*. The core is a 5(indol-3-yl)-2-(pyrrol-2-yl)oxazole, which has not been observed prior to its isolation in 2007. The divergence of the Breitfussins lies in the halogenation pattern and methoxy substitution. Breitfussin A is of synthetic interest because of its novel structural features, as a final proof of its structure (since it was determined using nonstandard techniques) and to provide material for biological testing.

In this thesis, efforts towards a synthesis of Breitfussin A are described as well as application of the synthetic strategy for making an analogue library. The synthesis features a Leimgruber-Batcho indole synthesis to prepare the correctly substituted indole. Two procedures were tested for introduction of the oxazole moiety: the Schöllkopf protocol and a Suzuki-Miyaura coupling. Development of iodination protocols are given much attention, and a novel regioselective oxazole iodination is presented.

The synthesis of a late stage intermediate of Breitfussin A was performed in a shortest sequence of 11 steps from the commercially available starting material 2,6-DNP, in 12 % total yield. The whole strategy was successfully tested on a model compound with an unsubstituted indole, with the exception of the final deprotection. A range of compounds (at different stages in the synthesis) were produced for an analogue library.

II ACKNOWLEDGEMENTS

There are many people without whom this thesis would not have been possible. First I would like to thank my Supervisor at the University of Tromsø Ass. Prof. Annette Bayer for giving me the opportunity to work on this challenging project. I am thankful for the constructive discussions we have had during the last years, both related to chemistry and to life in general. It has been a pleasure working under your supervision.

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I want to thank my wife Silje-Marie, who has supported me endlessly through the last few years (and thought me "social competence"). I want to thank my family, especially my brother and sisters Ørjan, Åshild, Astrid, Luise and Anna, and my grandparents Aase and Egil. Thank you for supporting me.

Lastly, I thank God for creating us all.

III ABBREVIATIONS

^{13}C-NMR	Carbon-13 nuclear magnetic resonance
^{1}H-NMR	Proton nuclear magnetic resonance
2,6-DNT	2,6-Dinitrotoluene
DAST	Diethylaminosulfur trifluoride
DBH	1,3-Dibromo-5,5-dimethyl hydantoin
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DME	Dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMFDMA	*N*,*N*-dimethylformamide dimethylacetal
DMP	Dess-Martin Periodinane
DMSO	Dimethylsulfoxide
EAS	Electrophilic aromatic substitution
ESI	Electrospray ionization
GC-MS	Gas Chromatography with Mass Spectrometry detector
HMTA	Hexamethylenetetramine
HPLC	High pressure/performance liquid chromatography
HRMS	High Resolution Mass Spectrometry
IR	Infrared (spectroscopy)
LiHMDS	Lithium hexamethyldisilazane
MIC	Minimum inhibitory concentration
MRSA	Methicillin resistant *Staphylococcus aureus*
MTBE	Methyl *tert*-butyl ether
MW	Microwave
NaHMDS	Sodium hexamethyldisilazane
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMR	Nuclear magnetic resonance
ppm	Parts per million
TBDMS-Cl	*tert*-butyldimethylsilyl chloride
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS-Cl	Triisopropylsilyl chloride
TIPS-OH	Triisopropylsilanol
TLC	Thin layer chromatography
TMSOTf	Trimethylsilyl triflate
TNT	Trinitrotoluene
TosMIC	Tosyl methyl isocyanide
SAR	Structure-activity relationship
S_N2	Bimolecular nucleophilic substitution

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1 AIMS OF THE THESIS

The Breitfussins are a series of closely related heterocyclic compounds originated from the marine organism *Thelia Breitfussi*. The core is a 5(indol-3-yl)-2-(pyrrol-2-yl)oxazole, which has not been observed prior to its isolation in 2007. The divergence of the Breitfussins lies in the halogenation pattern and methoxy substitution. Two compounds are published, Breitfussin A (**1**) and Breitfussin B (**2**).

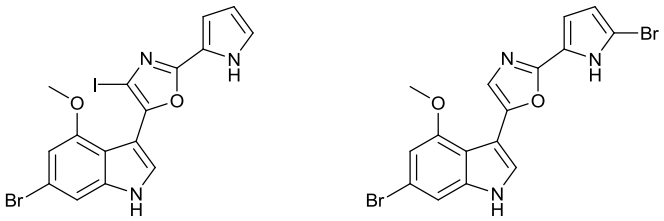


*Figure 1. Breitfussin A (**1**) and Breitfussin B (**2**)*

The Breitfussins are interesting targets for many reasons. From a purely synthetic organic chemistry perspective the synthesis is interesting. The structural core has many reactive positions and a synthetic plan needs to take this into account. In addition to this "synthesis for the sake of synthesis" argument, total syntheses are regarded a useful way of assessing the generality of reactions. The syntheses of complex molecules of natural origin often demands novel reactions or altered protocols for existing reactions, rendering total synthesis a useful tool for basic research.As non-traditional methods were used in the structure determination of **1** and **2**[1], the total synthesis will provide a final proof of the structure, as well as confirming the validity of the novel combination of analytical methods.

From a biochemical perspective the synthesis of Breitfussins has useful applications. The Breitfussins shows interesting biological activity[*]. However, the Breitfussins were isolated in only minute amounts and further biological testing requires more material. Moreover, development of a synthetic route to Breitfussin A will provide useful information for synthesis of Breitfussin analogues. Therefore emphasis will be put on development of a synthetic methodology that can be used in an efficient synthesis of a compound library based on the Breitfussin structural scaffold. Biological testing of Breitfussins and their analogues will give structure-activity relationship (SAR) information which will be useful in the development of Breitfussins for medicinal purposes. Ultimately, the goal is to produce a lead compound for the marine biodiscovery programme MabCent and its commercial partners.

In light of this, the aims of my work presented here were:

- To synthesize Breitfussin A.
- To synthesize a library of Breitfussin analogues.
- To develop methodology for transformations encountered during the syntheses.

[*] Unpublished and confidential information from MabCent-SFI.

2 BACKGROUND

2.1 BREITFUSSIN A

2.1.1 Isolation

In the marine biodiscovery programme MabCent a wide range of arctic marine species is collected and extracted with MeOH/dichloromethane (DCM) for subsequent screening. A diverse selection of assays is used in the screening process, among them the TNFα (immunostimulatory) and MTT (anticancer)[2]. In a fraction collected from Bjørnøya in 2007 from the arctic marine hydrozoan *Thuaria Breitfussi* (Figure 2) biological activity was found and two molecules were isolated by mass guided high pressure/performance liquid chromatography (HPLC) to yield two compounds, named Breitfussin A (**1**) and Breitfussin B (**2**) in 6.2 mg and 4.0 mg yields, respectively. High resolution mass spectrometry gave the molecular formulas $C_{16}H_{11}N_3O_2BrI$ for **1** and $C_{16}H_{11}N_3O_2Br_2$ for **2**.

Figure 2. Thuaria Breitfussi (Photo: Robert A. Johansen, Marbank)

2.1.2 Structure Determination

NMR spectroscopy revealed a 3,4,6-trisubstituted indole and 2-substituted pyrrole fragments (2,5-disubstituted for compound **2**). The connectivity of the fragments was not possible to determine unequivocally by NMR alone, due to the low amount of protons relative to the heavier atoms, with just 11 protons of 34 atoms in total. Computer Assisted Structure Elucidation (CASE), Atomic Force Microscopy (AFM) and calculation of ^{13}C-NMR chemical shift by density functional theory (DFT) were used to aid the determination of the structures given in Figure 1 for **1** and **2**[1].

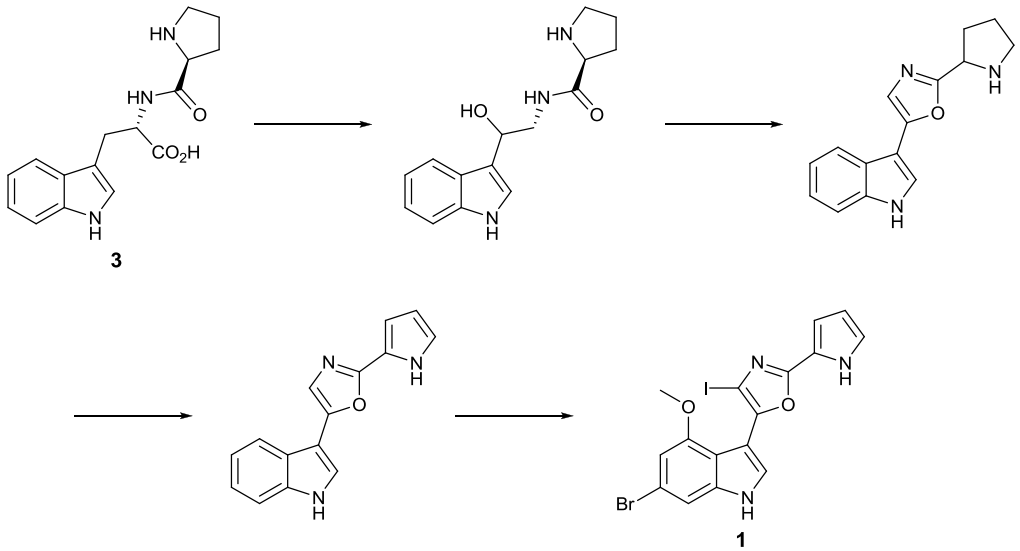
2.1.3 Biological Activity

While the isolated compounds have biological activity this is yet unpublished and will not be disclosed in this work.

2.1.4 Biosynthesis

The biological origin of the Breitfussins is unknown, but presumed to be the dipeptide proline-tyrosine (**3**). This dipeptide is cyclized and decarboxylated, the proline

aromatizitized and subsequently modified by halogenation, oxidation and methylation. This proposed process is described briefly in Scheme 1[1].



Scheme 1. An overview of the proposed biosynthetic origin of Breitfussin A

2.2 NATURAL PRODUCTS IN MEDICINE

Natural products are very useful for medicinal purposes. Throughout history, natural sources of molecules have been used for therapeutic purposes. This chapter will, through examples, show the use of natural products in medicine. Both natural products and compounds inspired by natural products will be discussed. Some principles of drug development will be discussed. A 2010 review of approved drugs in the period 1981-2010 shows that 27 % are natural products or compounds made directly from natural products. Another 24 % can be considered natural product inspired. For totally synthetic drugs the number is 29 %. The resulting 21 % are vaccines and macromolecules[3].

2.2.1 Erythromycin

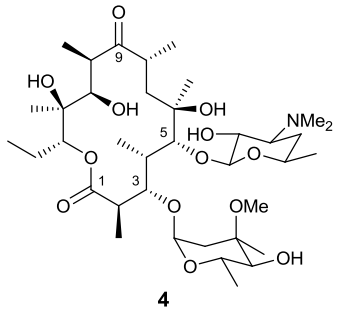


*Figure 3. Erythromycin A (**4**)*

Erythromycins are a series of related compounds of the macrolide subclass of the polyketide natural products. The polyketides can often be recognized by the characteristic placement of oxygen, with hydroxyl or keto groups (or occasionally double bonds) in 1,3-position which is derived from the use of acetate or propionate in the biosynthesis. Macrolides are macrocyclic esters (lactones) of polyketides. Erythromycins have two sugar units at the 3-

and 5- positions (the 1-position being the ester carbon), at least one of them being an amino sugar. These are enzymatically attached after the aglycone is synthesized.

Erythromycins have been used as antibiotics since the 1950s, after its isolation from the fungus *Streptomyces erythreus*[4]. It is mainly used against gram-positive bacteria. Erythromycin A (**4**) is the most used macrocycle antibiotic, but due to acidic instability and resistance problems modified erythromycins have also been used as drugs (Figure 1).

To improve the pharmacokinetics of the new erythromycins, chemical stability was desired. Clarithromycin (**5**) has a 6-methyl group that blocks hemiketal formation of the 6-hydroxyl and 9-carbonyl groups. Azithromycin (**6**) has altogether removed the carbonyl group, instead having an expanded aza-macrolide. Other erythromycins have been made which have sought to improve pharmacokinetic and pharmacodynamics properties to overcome resistance problems[5].

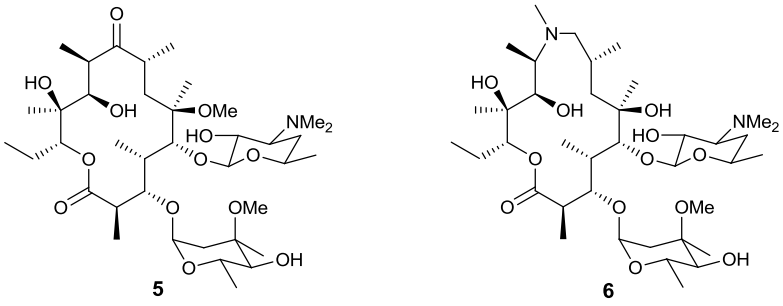


*Figure 4. Clarithromycin (**5**) and Azithromycin (**6**)*

2.2.2 Chloramphenicol

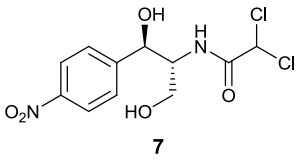


*Figure 5. Chloramphenicol (**7**)*

Chloramphenicol (**7**) is one of the earliest broad-spectrum antibiotics, isolated from *Streptomyces venezuelae*. It is produced in the Shikimate pathway via a *p*-aminophenylalanine. It works in a bacteriostatic manner by blocking the peptidyltransferase activity in bacteria. Its use has declined because of adverse effects and resistance problems.

2.2.3 Orlistat

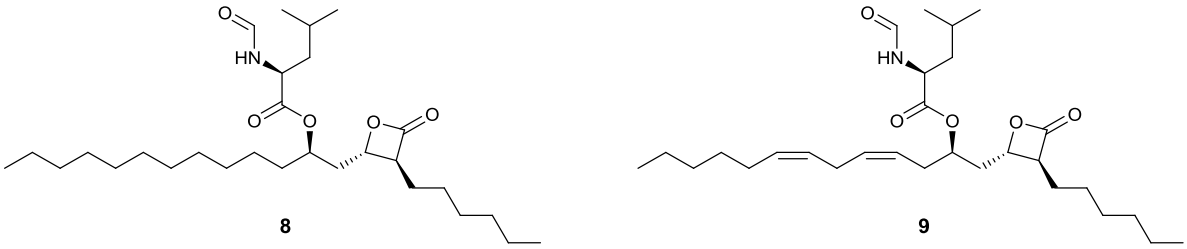


*Figure 6. Orlistat (**8**) and Lipstatin (**9**)*

The anti-obesity drug Orlistat (**8**) is a good example of using a natural product as a lead compound for development of drugs. Orlistat (**8**) is the tetrahydro-derivate of lipstatin (**9**) originally isolated from *Streptomyces toxytricini*[6]. The double bonds were not essential for activity and were removed to make a simpler compound, more accessible to chemical synthesis.

2.3 MARINE NATURAL PRODUCTS

Exploring marine environments as a source of natural products started in the second half of the 20th century, with the isolation of spongouridin (**10**) from the sponge *Cryptotethya crypta*[7] as a milestone. This discovery eventually gave lead compounds which were used in development for the drug Vidarabine (**11**) (9-β-D-arabinofuranosyladenine)[8]. Their structures are given in Figure 7.

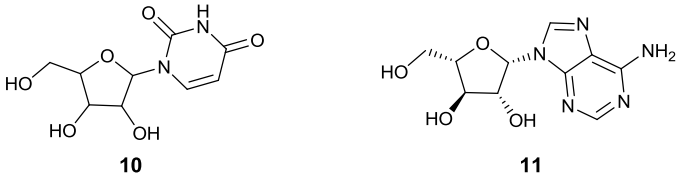


*Figure 7. Spongouridin (**10**) and Vidarabine (**11**)*

This chapter will describe a few marine natural products found in arctic marine waters and their biological activity to illustrate the marine environment as a source of compounds for use in medicine. Comprehensive annual reviews on discovery of marine natural products are written by John W. Blunt at the University of Canterbury, New Zealand, the latest ones covering 2013[9] and 2012[10].

2.3.1 Eusynstyelamides

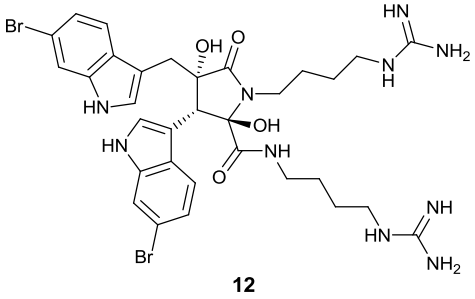


*Figure 8. Eusynstyelamide A (**12**)*

The Eusynstyelamides are a series of compounds that has been isolated from a variety of marine organisms including *Eusynstyela latericius*, the organism from which they have their name[11], *Eusynstyela misakiensis*[12] and *Tegella cf. spitzbergensis*[13]. Eusynstyelamide A (**12**), B and C have agmatine ((4-aminobutyl)guanidine) side chains (As shown in Figure 8 for **12**) and vary only in the stereochemistry of the core lactone while the eusynstyelamides D, E and F have one or two tetramethylene diamine side chains instead of agmatine. Biosynthetically, the eusynstyelamides are dimers of modified tryptophan-arginine peptides. A synthesis of racemic Eusynstyelamide A was published by Snider in 2010, using a double aldol dimerization to make the central dihydroxybutyrolactam[14].

Eusynstyelamides A-C inhibits neuronic nitric oxide synthase (nNOS) at low micromolar IC_{50} values and has slight antimicrobial activity[11]. Eusynstyelamides D-E has antibiotic activity with minimum inhibitory concentrations (MIC) as low as 8 micromolar against *Staphylococcus aureus*. Eusynstyelamides B and D have some activity against the human melanoma A 2058 cancer cell line[13].

A similar natural products is Barretin (**13**), which is a diketopiperazine derivate of a similar modified tryptophan-arginine peptide. Its structure is given in Figure 9[15].

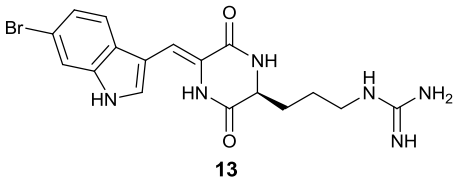


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*Figure 9. Barretin (**13**)*

2.3.2 Synoxazolidinones

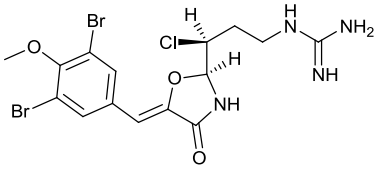

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*Figure 10. Synoxazolidinone A (**14**)*

The two synoxazolidinones A (**14**) and B were isolated from the sub-arctic ascidian *Synoicum pulmonaria*. Synoxazolidinone B is the non-chlorinated form of A. Biosynthetically, the synoxazolidinones are modified tyrosine-arginine dipeptides.

The synoxazolidinones has antibiotic effects in assays for the bacteria *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus* (MRSA) and *Corynebacterium glutamicum* with MIC values of 6.25-10 µg/ml for Synoxazolinone A and somewhat lower for B, showing the biological importance of the chlorine atom. Recently syntheses of the synoxazolinones has been published, along with SAR studies based on the core ring[16].

2.4 Structurally Related Natural Products

The Breitfussins contain a hitherto unprecedented structural scaffold containing a 5-(indol-3-yl)-2-(pyrrole-2-yl)oxazole. The 4-iodo oxazole is also a novel structural element in a natural product (though not in synthesis, as will be described in section 2.6).Oxazoles are not uncommon in natural products[17] and their biosynthetic origin is often assigned to amino acids.

2.4.1 Indolyl-oxazoles

5-(indol-3-yl)oxazoles exists in a variety of natural products ranging from the relatively simple pimprinine (**15**) [18] and streptochlorin (**16**)[19] to the complex diazonamide A (**17**)[20] shown in Figure 11. Pimprinine has a range of biological activities, from antibiotic and fungicidal effects to monoamide oxidase inhibition and anti-epilepsy[21]. Streptochlorin has a

broad fungicidal activity[19]. The diazonamides A and B have nanomolar activity against HCT-116 human carcinoma and B-16 murine melanoma cell lines[22].

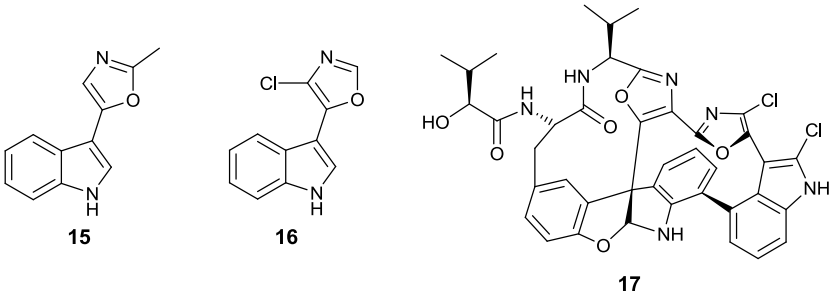


*Figure 11. Pimprinine (**15**), Streptochlorin (**16**) and Diazonamide A (**17**)*

2.4.2 Pyrrolyl-oxazoles

The only 2-(pyrrol-2-yl)oxazoles described in literature are the phorbaxoles A-D (**18a-d**), shown in Figure 12. The phorbazoles are tyrosine-proline dipeptide derivates which are chlorinated on the pyrrole and for Phorbazole A, on the 4-position of the oxazole, similar to the diazonamides[23].

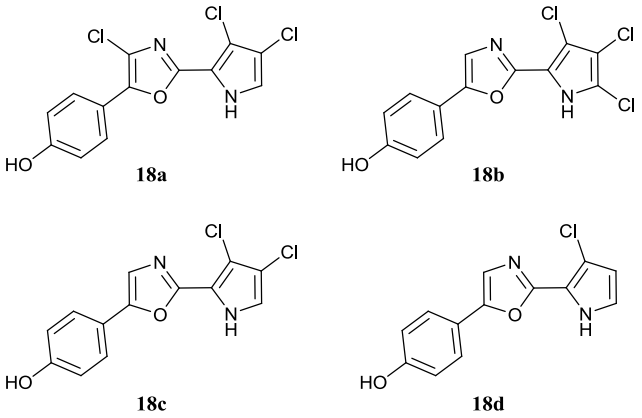


Figure 12. Phorbazoles A-D

2.5 Oxazole Synthesis in Natural Products

In this part, syntheses of the oxazole part of natural products will be described. While there are a plethora of methods for oxazole synthesis, only some of the common methods will be highlighted here with examples from total syntheses of natural products. These methods are of the most frequently used in total synthesis of oxazole containing natural products that were developed during the 1990s. A comprehensive review is written by Knight in the book *Heterocycles in Natural Product Synthesis*[24]. During the last 10 years an increasing effort has been put towards palladium based syntheses. These will be described briefly in section 2.6.3. An overview of disconnections for oxazole synthesis discussed here is given in Figure 13.

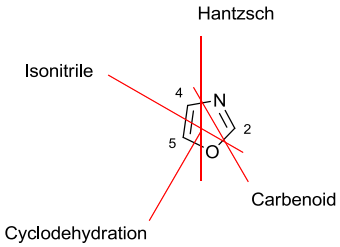


Figure 13. Overview of methods used for synthesis of oxazoles discussed in this chapter

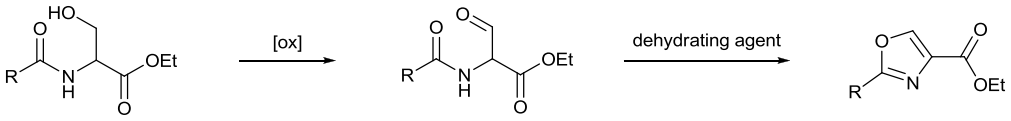
Most oxazole containing natural products has a 2,4-substitution pattern, which is not surprising given the biological origin of most oxazoles. Post-translational modifications of serine, threonine and cysteine containing peptides by enzymes capable of oxidative cyclisation yields 2,4-substituted oxazoles and thioxazoles[25]. For threonine a 5-methyl substituent will also be present. A range of these will be described below.

The biosynthesis of 2,5-substituted oxazoles is not described in literature and there are fewer examples of 2,5-substitution than 2,4-substitution. A few of the 2,5-substituted oxazole containing natural products are given in Figure 11.

2.5.1 Cyclodehydration based oxazole synthesis

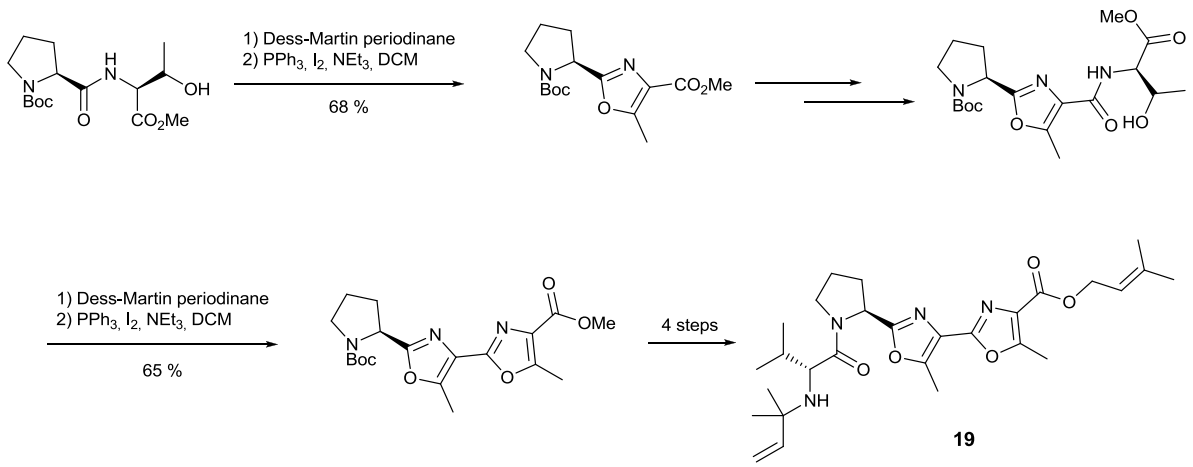
This method of making oxazoles in natural products is by far the most common. The synthesis of the serine- or serine –like precursors is relatively simple and the reaction conditions can be very mild. There are two processes that must be performed to make an oxazole by this method: oxidation and dehydration. Either process can be performed first.

The Robinson Gabriel cyclodehydration is the earliest example, which has been applied to synthesis of 2,4-substituted oxazoles following Scheme 2. An *N*-acyl substituted serine (or threonine, if 5-methyl is desired) is oxidized to its carbonyl counterpart and then dehydrated. The classical dehydrating agents are sulfuric acid and phosphoryl chloride ($POCl_3$), but these conditions would be too harsh for most complex substrates.



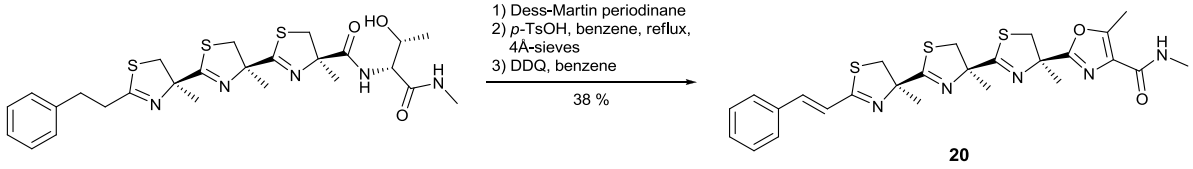
Scheme 2. Robinson Gabriel synthesis of oxazole from serine

A modern approach is used in the Wipf' 1996 total synthesis of (-)-Muscoride A (**19**)[26]. Dess-Martin Periodinane (DMP) oxidizes the serine before dehydration with triphenyl phosphine and iodine in mild base. This synthesis involves two successive, identical oxidation-dehydration sequences described in Scheme 3.



*Scheme 3. Oxazole formation in Wipf' total synthesis of (-)-Muscaride A (**19**)*

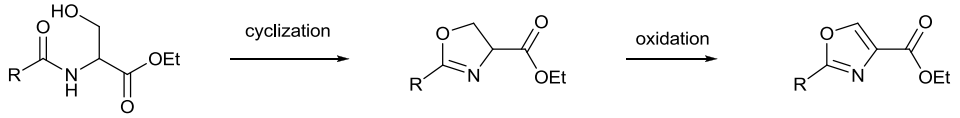
Alternative dehydration protocols have been used, for example in the Heatcock 1994 total synthesis of (-)-Thiangazole (**20**)[27], where the presence of the sulfides precludes use of triphenyl phosphine. Instead acid and molecular sieves are used. The synthesis is given in Scheme 4 (The last step is a benzylic oxidation to complete the synthesis).



*Scheme 4. Oxazole formation in Heatcocks total syntehsis of (-)-Thiangazole (**20**)*

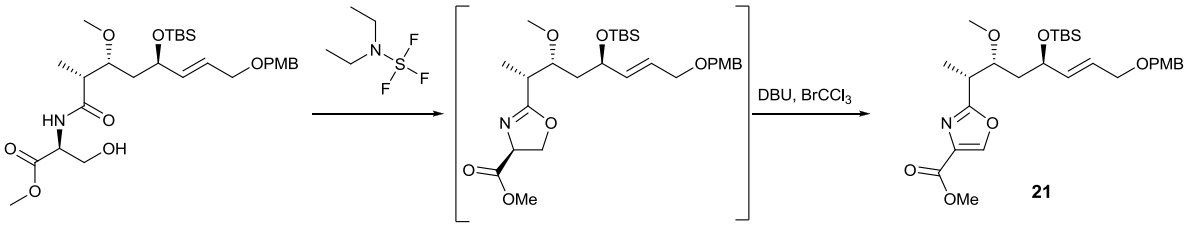
These methods are very mild and have even been performed in the endgame of a complex total synthesis of Phorboxazole A by Forsyth[28].

In the reversed sequence, cyclization is performed first and oxidation later. This proceeds through the sequence in Scheme 5 where an oxazoline is formed by cyclization followed by a formal oxidation to yield an oxazole.



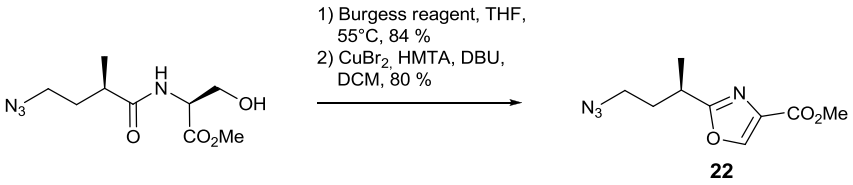
Scheme 5. Oxazole formation by cyclization followed by a formal oxidation

One of the most commonly used methods is the Wipf cyclodehydration using diethylaminosulfur fluoride (DAST) for cyclization followed by bromination-elimination by $BrCCl_3$/1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give the oxidized oxazole ring. This method is applied in Kalesses synthesis of the oxazole segment **21** of Chivosazole A[29] in Scheme 6. Other similar fluoride reagents have been used, for example bis(2-methoxyethyl)aminosulfur Trifluoride (Deoxo-Fluor)[30]. These procedures need neither harsh conditions like acid, base or high temperature nor extreme care, as they are robust to air and traces of water. The functional group tolerance of DAST and Deoxo-Fluor is high.



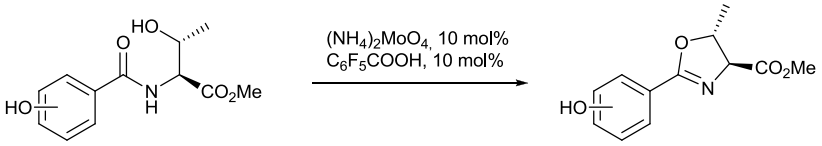
Scheme 6. Kalesses use of Wipf cyclodehydration in a segment synthesis of Chivasazole A

Another method involves the Burgess-reagent (methyl *N*-(triethylammoniumsulfonyl)carbamate) for cyclodehydration, which was used in Smiths synthesis of Calyculins[31] in tandem with the Barrish-Singh oxidation with cupper(II)bromide and hexamethylenetetramine (HMTA)[32].



*Scheme 7. Burgess-reagent and Barrish-Singh oxidation in Smiths synthesis of oxazole part **22** of Calyculins*

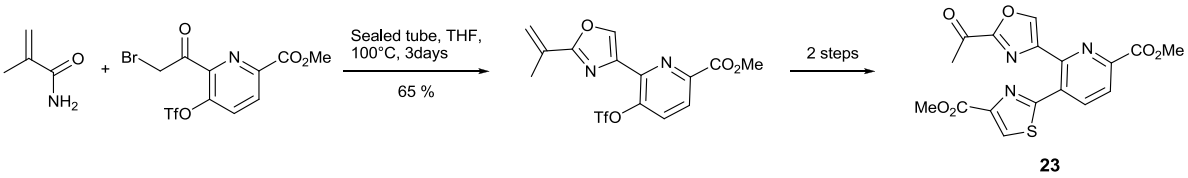
An interesting cyclodehydration of serine-like compounds is the Sakakura molybdenum oxide method in Scheme 9Scheme 8, which retains the stereochemistry of the 5-position of the oxazoline intermediate, which is important for threonine-based oxazolines, as retention of the stereochemistry is the natural state. It is also one of the only mild substochiometric methods for cyclization. Oxazole formation from this can be performed with any suitable oxidation procedure



Scheme 8. Molybdenum oxide oxazolidine formation

2.5.2 Hantzsch Oxazole Synthesis

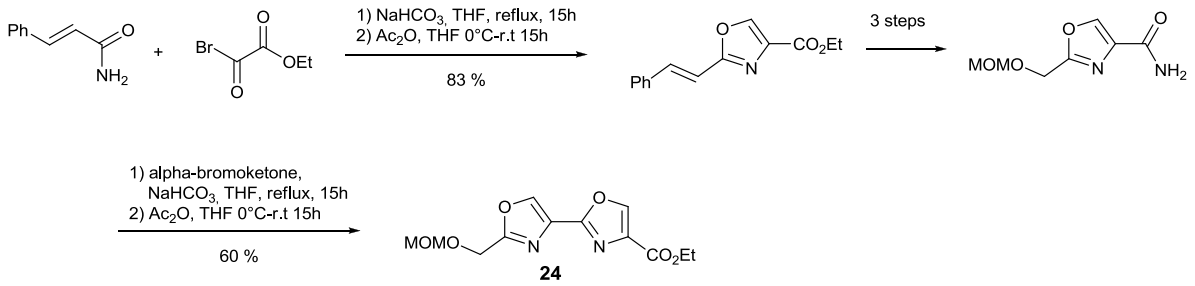
The Hantzsch oxazole synthesis is a method of making simple 2,4-substituted oxazoles which have applications in natural product synthesis. The necessary substrates are a primary amide and an alpha-halo ketone which results in a 2,4-substituted oxazole. An example is given in Scheme 9 for the synthesis of an early intermediate in a synthesis of dimethyl sulfomycinamate (**23**) by Kelly[33].



*Scheme 9. Hantzsch oxazole synthesis in a synthesis of dimethyl sulfomycinamate (**23**)*

A milder variant was used by Panek in a synthesis of the polyoxazole fragment **24** of Ulapualide A[34], where the dehydration was performed with acetic anhydride in Scheme 10.

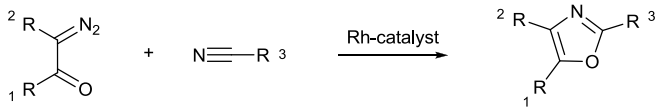
In this paper the Hantzsch procedure was performed twice. The Hantzsch synthesis is not suitable for late stage oxazole formation because of the relatively harsh conditions.



Scheme 10. Hantzsch oxazole synthesis applied to polyoxazole synthesis

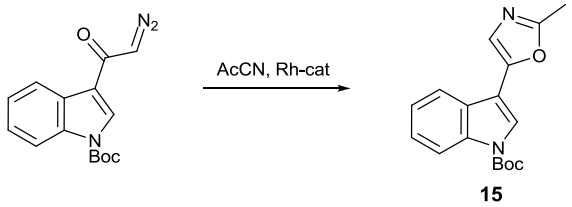
2.5.3 Carbenoid oxazole synthesis

The rhodium catalyzed oxazole synthesis utilizes a carbonyl stabilized diazocompound and a nitrile according to Scheme 11[35]. This method has been used to make both 2,4- and 2,5-substituted oxazoles.



Scheme 11. Rhodium catalyzed carbenoid oxazole synthesis

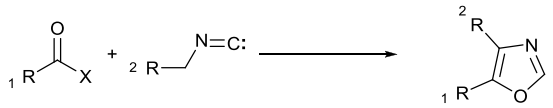
An example of application of this method is given in Scheme 12, where Moody[36] used this procedure to make Pimprinine (**15**) and related compounds.



*Scheme 12. Use of rhodium catalyzed Pimprinine (**15**) synthesis*

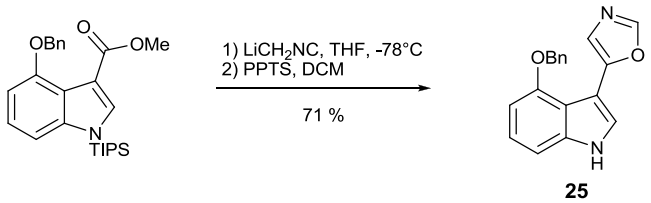
2.5.4 Methylisocyanide oxazole synthesis

The isocyanide synthon is used for making 5-substituted oxazoles, either with or without a 4-substituent, but always with the 2-position unsubstituted (Scheme 13).



Scheme 13. Metylisocyanide oxazole synthesis

Examples of isocyanide reagents used in natural product synthesis are scarce because the 5-position is rarely an important substituent in commonly occurring oxazole compounds. One example can be found in Vedejs synthesis of the indolyl-oxazole part **25** of Diazonamide A[37] using the Schöllkopf conditions given in Scheme 14 below.



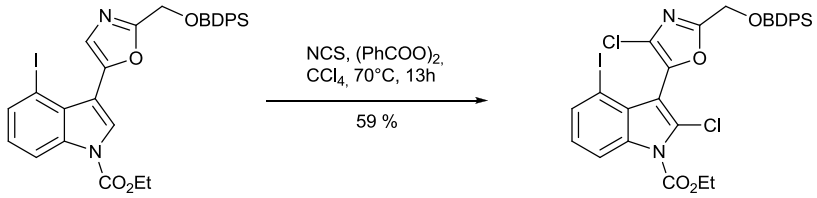
Scheme 14. Schöllkopf isocyanide approach in Vedejs approach to Diazonamide A

2.6 OXAZOLE FUNCTIONALIZATION

The reactivity of an already formed oxazole is important for the further substitution. Three topics will be covered here: electrophilic aromatic substitution (EAS), metalation and C-C bond forming cross coupling. Pericyclic reactions will not be discussed.

2.6.1 Electrophilic aromatic substitution

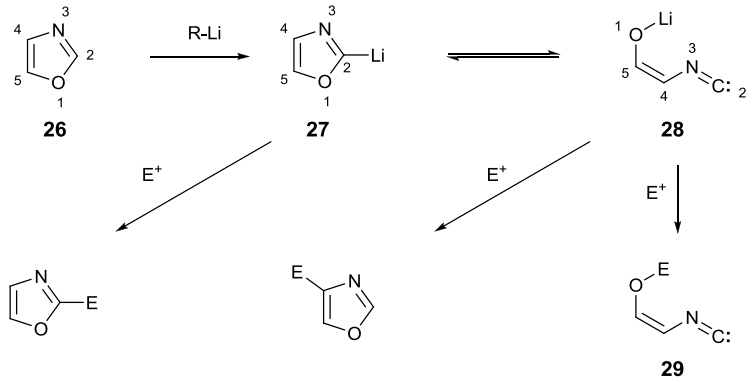
EAS is rarely used on oxazoles, but it is possible and a few examples exist. The most nucleophilic position is the 5-position, followed by the 4-position[38]. No example exist of a 2-substitution by EAS. Introduction of an electron-donating group increases the rate of the substitution. An example of EAS in natural product chemistry is the use of *N*-chlorosuccinimide (NCS) to introduce the 4-chloro substituent of an oxazole in Diazonamide A (**17**)[39] (Scheme 15). This particular example also highlights the use of EAS on the indole 2-position. A similar procedure was used in the last steps of the first total synthesis of Diazonamide A (**17**) by Nicolaou[40]. Other examples exist with substitution in the 5-position[41].



*Scheme 15. EAS on oxazole - an example on the synthesis towards Diazonamide A (**17**)*

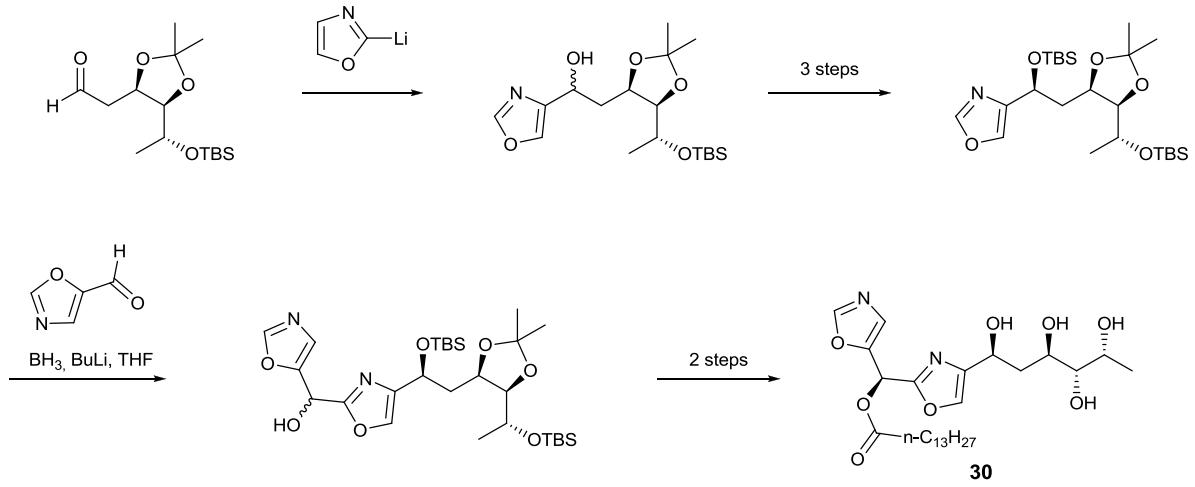
2.6.2 Metalation of oxazoles

The 2-proton of oxazole (**26**) is the most basic one, but upon treatment with base the 2-lithiated oxazole **27** is not observed. The only detected compound is the ring opened isomer **28** (see Scheme 16). As can be seen from the scheme three possible products can be formed upon treating the metalated oxazole with electrophiles. *O*-substituted vinylisocyanides **29** were observed using silyl chloride electrophiles[42] and acyl chloride electrophiles[43].



Scheme 16. Lithiation of oxazole followed by electrophile

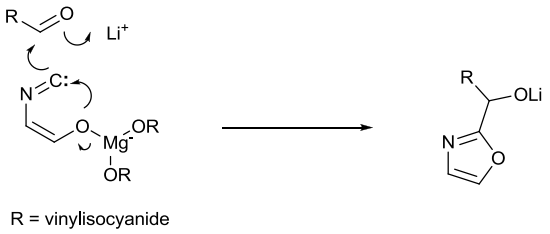
To differ between 2- and 4-position is fairly complex. There is a range of literature describing selective (and non-selective) 2- or 4-substitution of metalated oxazole. The position of the electrophile will depend on many factors: temperature[44], electrophile[42], additives[45,46] and counter ion. The equilibrium between **27** and **28** will mainly lie towards **28** and trapping of this metalated oxazole will lead to a 4-substituted oxazole by an enolate-like mechanism and ring closing. Trapping of aldehydes will give 4-substituted oxazoles, as described in the upper part of Scheme 17 for the total synthesis of Bengazole A (**30**) by Molinsky in 1999[47]. It is possible to complex the oxazole with borane to give the 2-substituted oxazole exclusively[46], as illustrated in the lower part of Scheme 17.



*Scheme 17. 4- and 2-substitution of oxazole by metalation illustrated in the total synthesis of Bengazole A (**30**)*

The dependence of temperature and reactivity of the electrophile has been described by Hodges [44]. At low temperatures (-78°C) the open form oxazole **28** reacts preferentially, but the electrophile must be reactive, like aldehydes. Less reactive electrophiles like ketones and DMF react at 2-position, but only on elevated temperature (0-25°C). Diiodoethane is described by Greaney to react at the 2-position[48], while iodine reacts at the 4-position as described by Vedejs[45]. In the same paper by Vedejs, additives like 1,3-Dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone (DMPU) seems to increase the 4-selectivity upon using iodine as an electrophile.

Other bases than the most commonly used n-BuLi and Lithium hexamethyldisilazane (LiHMDS) have been used. Tributyl lithium magnesate[49] and isopropyl magnesium chloride[50] has given 2-substituted oxazoles exclusively upon quenching with electrophiles. Use of these bases has led to speculations on the mechanism of 2-substitution. A Passerini-type mechanism has been proposed (Scheme 18)[49]. When the 2-position is substituted, the metalation will take place at the 5-position. With both 2- and 5-position substituted, metalation will take place at the 4-position.

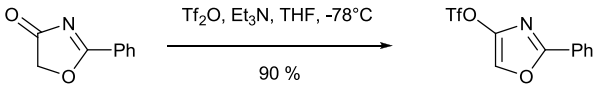


Scheme 18. Passerini like mechanism for 2-substitution of oxazole

2.6.3 Cross coupling reactions of oxazoles

The use of C-C bond forming reactions by cross coupling reactions depends mainly on the accessibility of the organometalic and electrophilic partner. Whether oxazole can be used as either partner depends on the synthesis of the respective partner. The synthesis of these follows the principles outlaid in the previous subchapter, and will not be discussed in depth. The Suzuki-Myiaura, Stille, Negishi and Sonogashira cross coupling reactions are known on oxazoles[51].

For synthesis of the electrophilic partner the electrophile must be a halogen or triflate. Another possibility is to react an oxazolinone with triflic anhydride in mild base as described in Scheme 19. It is possible to make triflates in the 2-, 4- and 5-positions, but only the 4-triflate is stable.



Scheme 19. Synthesis of 2-phenyl-4-triflate oxazole[52]

Using the oxazole as the organometalic partner depends on the synthesis of the metalated oxazole. Boronic acids for Suzuki-Myiaura reaction can be made by using boronic esters as electrophiles. Stannanes for Stille couplings can be made by using stannyl chlorides as electrophiles. Zinc halides for Negishi couplings can be made by transmetalating lithiated oxazoles to the zinc species.

3 TOTAL SYNTHESIS OF BREITFUSSIN A

3.1 THE SCOPE OF THE CHAPTER

This chapter describes my contributions to the synthesis of Breitfussin A (**1**) performed from September 2012 to October 2013. Initial studies were performed in Tromsø and the main part of the described work was done during a 3-month stay in the group of Dr. Christian Hedberg at MPI Dortmund. It was judged more appropriate to finish the total synthesis in his group after the stay in Dortmund.

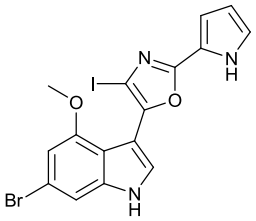
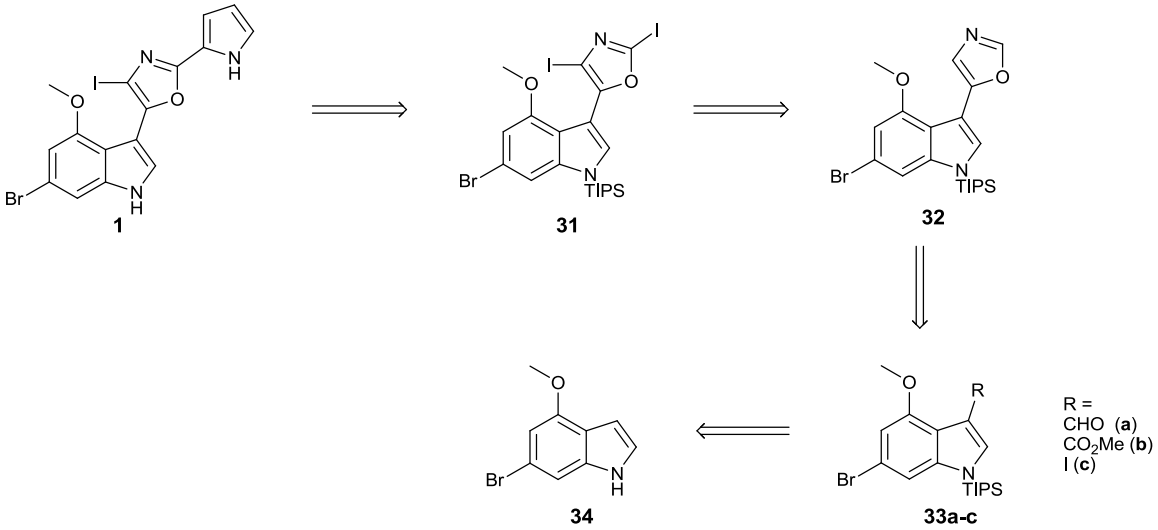


*Figure 14. Breitfussin A (**1**)*

3.2 STRATEGY AND RETROSYNTHESIS

The strategy for synthesis of Breitfussin A (**1**) is outlined in the retrosynthetic analysis in Scheme 20.



*Scheme 20. Retrosynthetic analysis of Breitfussin A (**1**)*

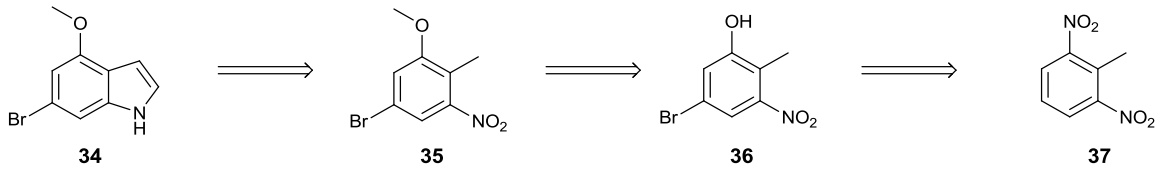
The first disconnection removes the pyrrole moiety revealing the diiodinated oxazole **31**. A crucial point in the synthesis is the diiodinated oxazole **31**. The 4-iodine must be present on the oxazole before the pyrrole is introduced, to avoid regioselectivity issues upon iodination. In the forward direction this is envisioned using the Suzuki-Miyaura cross coupling reaction. Literature is available showing that 2,4-diiodooxazoles react regioselectivly in palladium catalysed coupling reactions[48].

Further disconnection of diiodinated oxazole **31** gives the 5-substituted oxazole **32**. This transformation in the forward direction can be performed in two ways. The first method involves electrophilic aromatic substitution. Addition of iodine in the 4-position can be envisioned with *N*-iodosuccinimide (NIS), analogously to the previously reported NCS and *N*-Bromosuccinimide (NBS)[21]. To incorporate iodine in the 2-position metalation can be used. Alternatively both iodines can be introduced by the metalation-iodination sequence, either in two steps[45] or in one step[53].

Disconnection of the 5-substituted oxazole **32** reveals the 3-functionalized indoles **33a-c**. Two approaches to 5-substituted oxazoles were envisioned. The first one relies on the isocyanide synthon using the van Leusen tosylmethylisocyanide (TosMIC)[54] with indole **33a** or the Schöllkopf oxazole synthesis with methylisocyanide[55] with indole **33b**. The second approach relies on a Suzuki-Miyaura cross coupling on indole **33c** using a recently developed oxazole-5-boronic acid reagent[56].

Disconnecting the 3-functionalized indoles **33a-c** gives the unprotected indole **34**. In the forward direction, the indole **34** is reactive towards electrophiles in the 3-position and using the appropriate electrophile should give the desired 3-functionalized indoles **33a-c**.

Protection of the indole nitrogen with the triisopropylsilyl group protects the 2-position of the indole from metalation and electrophilic addition later in the synthesis[57].



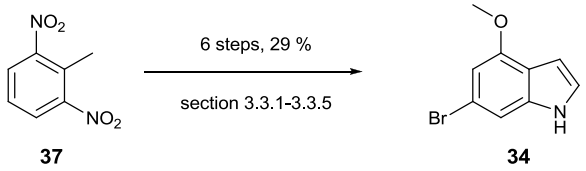
*Scheme 21. Retrosynthetic analysis of indole **34***

As indoles are not easily functionalized regioselectively at the carbocycle, the correctly substituted indole must be synthesized. The retrosynthesis of the indole **34** is shown in Scheme 21. The first disconnection reveals the indole precursor **35**. In the forward direction the Leimgruber Batcho indole synthesis is envisioned to give the indole **34**.

From the indole precursor **35** the *O*-methyl group is disconnected to give the phenol **36**. This phenol **36** is described in literature[58] and can be synthesized by bromination and functional group transformations from the commercially available 2,6-dinitrotoluene (2,6-DNT) **37**.

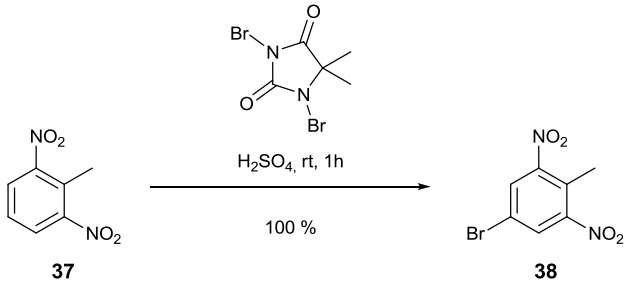
3.3 Synthesis of Indole Ring

This section describes the synthesis of the indole precursor **35** and the Leimgruber Batcho indole synthesis to yield indole **34** in 29 % total yield over 6 steps.



Scheme 22. Synthesis of indole fragment

Synthesis of 5-bromo-2-methyl-1,3-dinitrobenzene (38)



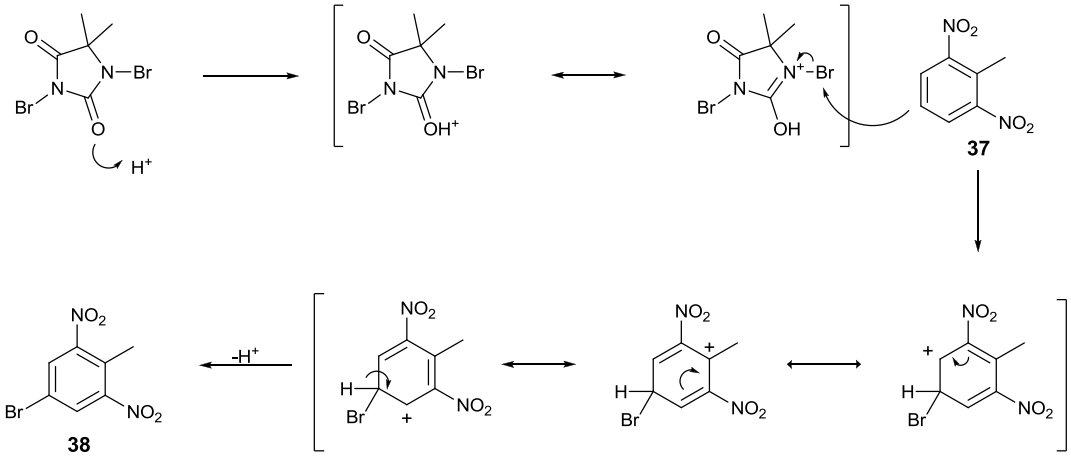
*Scheme 23. Synthesis of 5-bromo-2-methyl-1,3-dinitrobenzene **38***

The starting material for the synthesis 2,6-DNT **37**, is a byproduct from trinitrotoluene (TNT) synthesis and is commercially accessible.

The bromination was performed according to literature procedures[58] using 1,3-dibromo-5,5-dimethylhydantion (DBH) as the source of electrophilic bromine. The existing substituents direct the substitution to the 4-position, but the nitro groups are deactivating the substrate. Using concentrated sulfuric acid activates the DBH and dissolves the substrate. The reaction

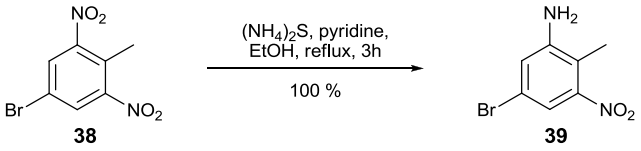
was performed on a 25 g scale and the bromo-DNT **38** product was obtained in quantitative yield after filtration. The reaction was repeated by an internship student in 98 % yield.

The mechanism is given in Scheme 24. Use of strong acid is necessary because the nitro groups are strongly deactivating the aromatic ring system for electrophilic aromatic substitution (EAS).



*Scheme 24. Mechanism for electrophilic aromatic substitution of 2,6-DNT (**37**)*

Synthesis of 5-bromo-2-methyl-3-nitroaniline (39)

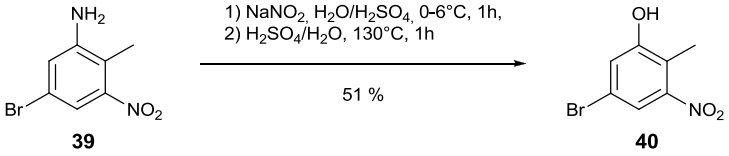


*Scheme 25. Synthesis of 5-bromo-2-methyl-3-nitroaniline **39***

Originally proposed by Nicolay Zinin in 1842[59], the use of sulfide in reduction of nitro compounds is an alternative to reductions with metals like Zinc or Iron and catalytic hydrogenations. The advantage of sulfide reductions is the ability to reduce dinitroaryls to nitroanilines even with excess sulfide[60]. The reason for this is that electron donating groups retard the reaction to a large extent[61]. An excess of sulfide is required as the oxidized sulfide can proceed to either elemental sulfur, polysulfides or thiosulfate. Use of basic conditions is important to keep the sulfide deprotonated, which will increase the rate of the reaction and reduce the amount of molecular sulfur formed[62]. The regioselectivity of the monoreduction in this case is irrelevant since starting material is symmetrical.

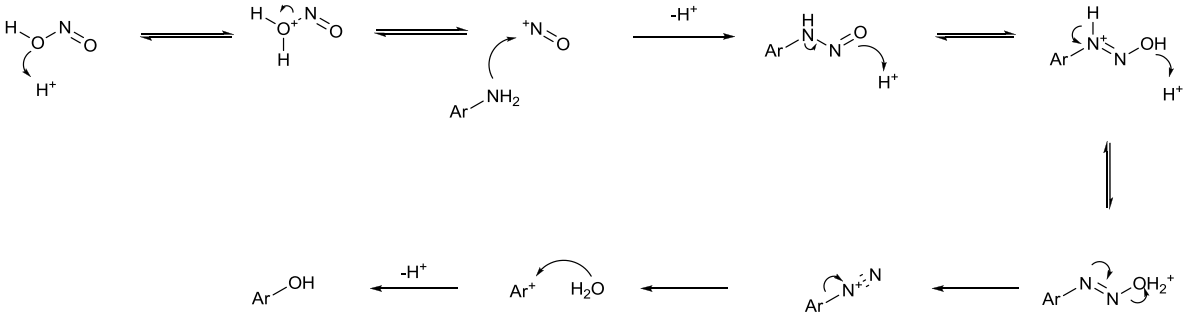
The monoreduction of bromo-DNT **38** was performed with ammonium sulfide according to literature procedure[58]. An excess of ammonium sulfide was added to a refluxing solution of bromo-DNT **38** and pyridine and reacted for a total of 3 hours. The reaction was performed on a 30 g scale and the resulting aniline **39** was obtained in quantitative yield after filtration, also when repeated by the internship student.

Synthesis of 5-bromo-2-methyl-3-nitrophenol (40)



*Scheme 26. Synthesis of 5-bromo-2-methyl-3-nitrophenol **40***

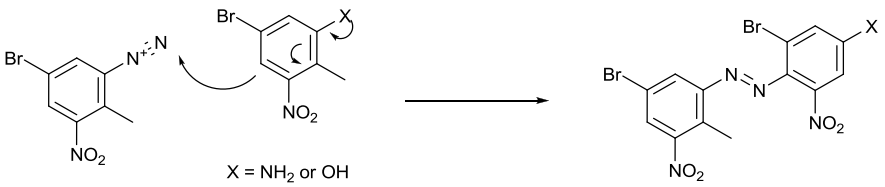
Diazotization is a method of making the ipso carbon of anilines electrophilic. Transforming the amino group to a very good leaving group, the diazonium group, makes it possible to substitute the amino group for a nucleophile. Possible nucleophiles are halogens, hydrides, cyanides, as well as water, which is used in this case. The mechanism of diazotization and phenol synthesis is outlined in Scheme 27. Acid is necessary to make the reactive nitrosyl cation and to dehydrate the nitrous amide.



Scheme 27. Mechanism for diazotation of anilines

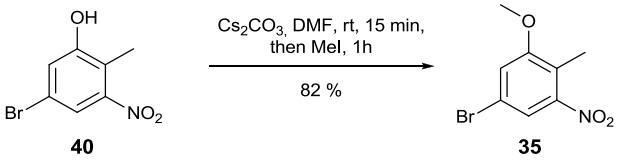
Diazotization of the aniline was performed according to standard procedures for diazotizations[63,58]. Aniline **39** was reacted with sodium nitrite in 30 % aqueous sulfuric acid at 0-6°C for one hour and transferred to a solution of 60 % sulfuric acid at 130°C and reacted for another hour. The reaction was performed in three 10 g scale batches with work up on the combined reactions. Column chromatography with DCM as eluent yielded 51 % phenol **40**) (46 % when repeated).

During the reaction an insoluble orange/yellow foamy solid was formed. It is suspected that this can be diarylazo byproducts that can be formed upon nucleophilic attack from the aniline starting material or newly formed phenol. A possible mechanism of the possible byproduct is given in Scheme 28. The rationale for carrying out the reaction in acid is that, in addition to the formation of the nitrosyl reactive intermediate, it also to suppress these side reactions. Possibly one could perform the reaction less concentrated.



Scheme 28. Possible mechanism for formation of azo byproduct

Synthesis of 5-bromo-1-methoxy-2-methyl-3-nitrobenzene (35)

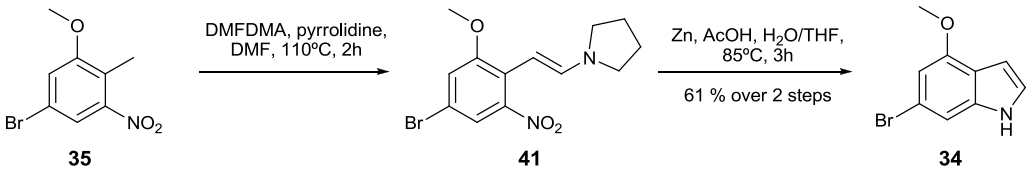


*Scheme 29. Synthesis of 5-bromo-1-methoxy-2-methyl-3-nitrobenzene **35***

The methylation of phenols is an S_N2 reaction with caesium phenolate as nucleophile. Carbonate is a weak base so the phenol is in equilibrium with the phenolate. The phenolate reacts with methyl iodide, which is a very good S_N2 electrophile because of the good leaving group and the lack of steric hindrance for backside attack. A common base for methylation is potassium carbonate, however, caesium carbonate is more soluble in organic solvents, effectively increasing the concentration of carbonate shifting the equilibrium towards phenolate and thus increasing the rate of reaction. It is therefore a better choice (though more expensive). Sodium hydride is another commonly used base for methylations, but for this particular substrate care should be taken to avoid a possible competing reaction on the methyl carbon, as the nitro group ortho to the methyl dramatically decreases its pKa.

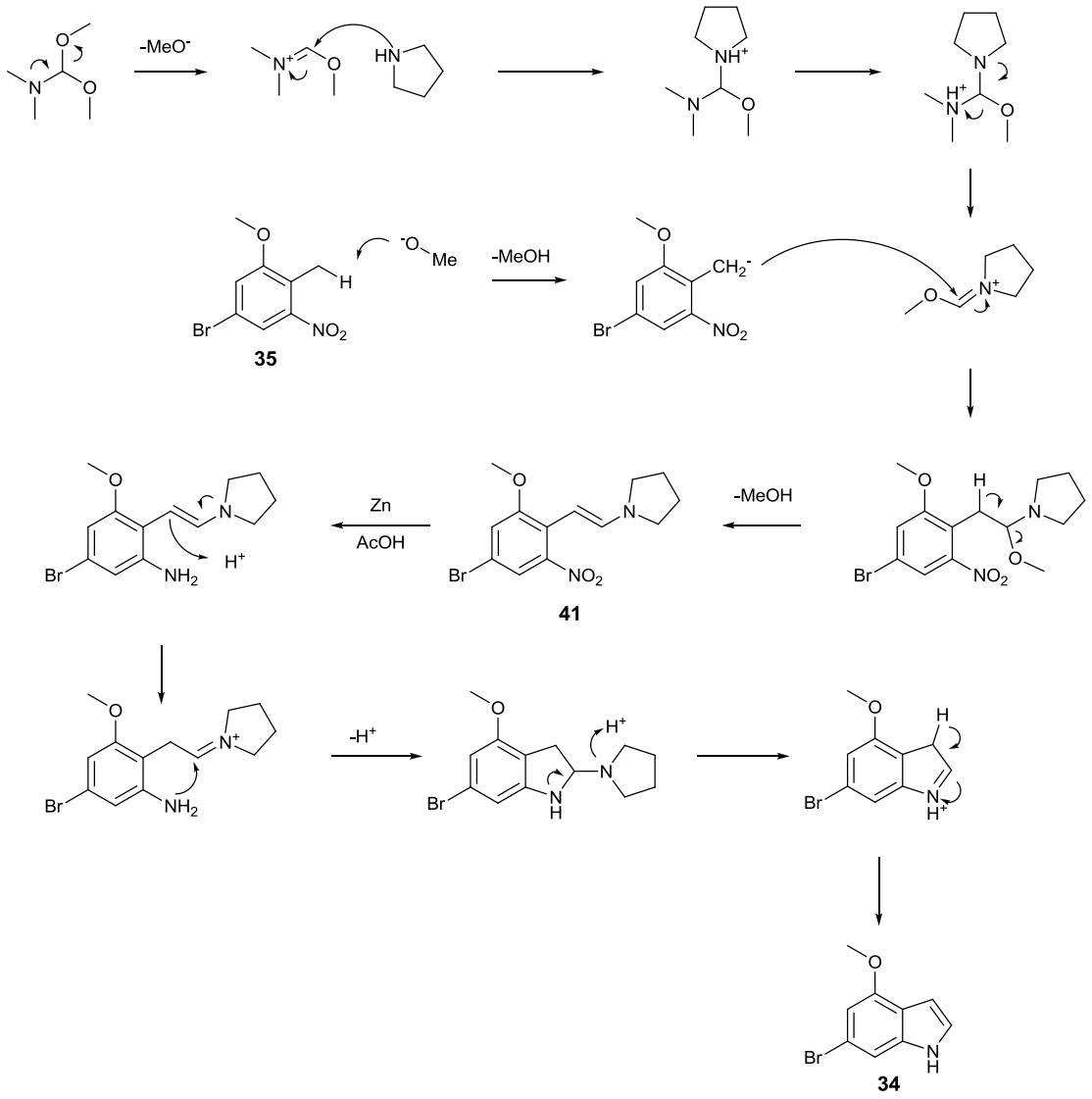
The phenol **40** and caesium carbonate were dissolved in *N*,*N*-dimethylformamide (DMF) and equilibrated for 15 minutes before drop-wise addition of methyl iodide under evolution of heat. The reaction was performed on a 15 g scale and the yield of indole precursor **35** after recrystallization in 90 % ethanol was 78 %. Column chromatography on the mother liquor gave additional 4 % yield.

Synthesis of 6-bromo-4-methoxy-1H-indole (34)



*Scheme 30. Synthesis of 6-bromo-4-methoxy-1H-indole **34***

The Leimgruber Batcho indole synthesis is a common protocol for synthesis of 2/3 unsubstituted indoles[64]. Using this process depends on having the correctly substituted *o*-nitrotoluene starting material. The mechanism for this reaction is given in Scheme 31. The rationale for using pyrrolidine is that the formylpyrrolidine acetal is more reactive than the dimethylformamide acetal[64]. Likely, a mixture of different acetals are present during the reaction.



*Scheme 31. Mechanism for Leimgruber Batcho synthesis of indole **34***

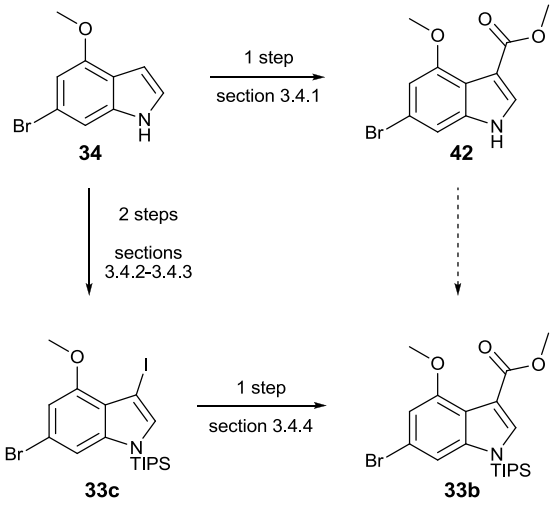
The indole precursor **35** was reacted with *N*,*N*-dimethylformamide dimethylacetal (DMFDMA) and pyrrolidine in DMF. An aqueous work up gave the enamine intermediate **41**. An examination of the original procedure by Leimgruber and Batcho led to an alternative work up procedure. The DMF and excess reagents were evaporated in a rotary evaporator connected to a high vacuum pump with a cold finger condenser at -78°C. A ^{1}H-NMR of the crude red oil confirmed the structure of the enamine intermediate **41** and the intermediate was used directly in the next step without purification.

4 equivalents of zinc were suspended in 80 % acetic acid and enamine intermediate **41** dissolved in tetrahydrofuran (THF) was added slowly. Another 4 equivalents of zinc were added and the reaction was heated to 85 °C for 3 hours. The reaction was performed on a 10 g scale and the indole **34** was purified by column chromatography in a 61 % yield in two steps from the indole precursor **35**. This sequence of reactions was repeated in 64 % yield.

3.4 FUNCTIONALIZATION OF INDOLE RING

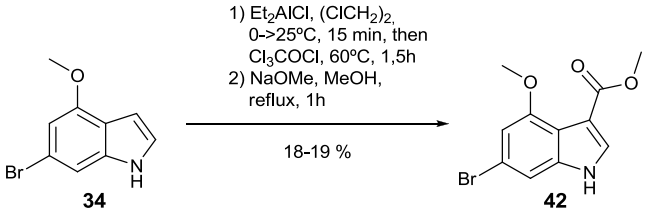
This section describes the functionalization of the indole **34** formed in section 3.3 in order to prepare the 3-functionalized indoles **33a-c** for the oxazole synthesis. At this point it was clear that the 3-carboxaldehyde indole **33a** was not necessary to prepare, as the van Leusen approach was deemed inferior to the Schöllkopf procedure (this is described in section 3.5.1.1).

An overview of the synthesis of **33b** and **33c** is given in Scheme 32. The direct formation of the methyl carboxylate **42** had too low yield and was abandoned. The iodinated indole **33c** was prepared in 81 % yield over two steps from indole **34** and the carboxylated indole **33b** was prepared in 73 % yield from the iodinated indole **33c**.



Scheme 32. Overview of indole functionalization

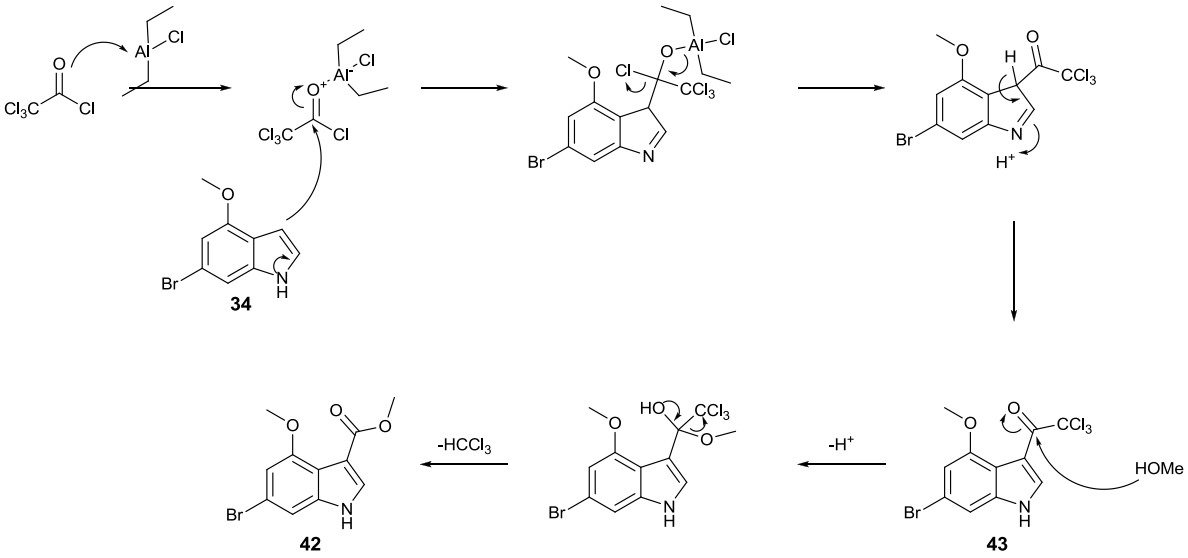
Synthesis of methyl 6-bromo-4-methoxy-indole-3-carboxylate (42)



*Scheme 33. Synthesis of methyl 6-bromo-4-methoxy-indole-3-carboxylate **43***

The heterocyclic positions (2- and 3-position) of an indole are easy to modify. The 3-position reacts directly with electrophiles 13 orders of magnitude better than benzene[65]. Metalation preferentially occurs at the 2-position. Reacting the 2-metallo indole with electrophiles gives 2-substituted indoles.

Carboxylation of the 3-position of indoles can be done by addition of trichloroacetyl chloride either with or without addition of Lewis acids [66]. Nucleophile attack on trichloroacetyl chloride will provide the trichloroacetyl derivate **43** which, upon treatment with methanol and catalytic amounts of base, will make the carboxylated indole **42** by loss of chloroform. A mechanism is given in Scheme 34.



*Scheme 34. Mechanism for synthesis of methyl carboxylate **42***

Although this reaction is frequently described in literature it did not yield any product upon reacting the indole **34** with trichloroacetyl chloride and pyridine in THF. Unreacted starting material **34** was recovered in 48 % yield. To increase the reactivity of the electrophile Lewis acids as catalyst to activate the trichloroacetyl chloride for nucleophilic attack was tested. A test reaction was performed on unsubstituted indole with diethyl aluminium chloride and trichloroacetyl chloride in DCM followed by reacting the trichloroacetylindole intermediate with sub stochiometric amounts of potassium hydroxide in methanol. After work up, the ^{1}H-NMR of the crude product seemed promising, with the methyl protons as a singlet with an integral of 3 at 3,79 ppm, the aromatic protons between 7.1 and 8.1 and an otherwise clean spectrum (except for solvents, Figure 15). A similar test with methyl chloroformate as the electrophilic partner was performed with similar results.

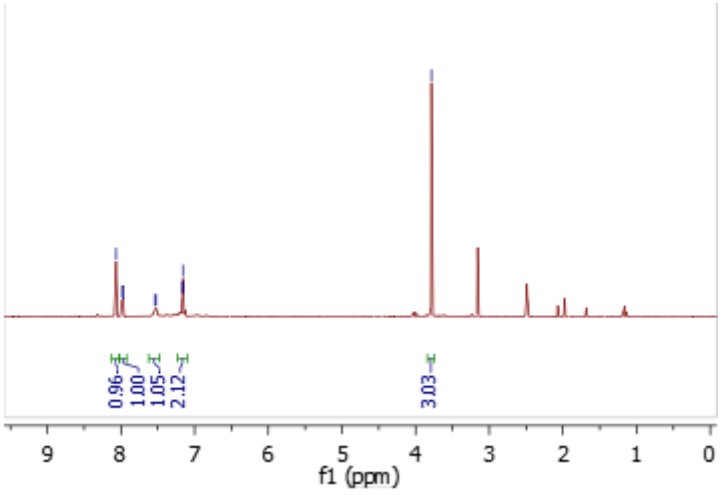
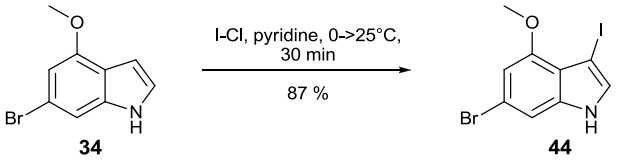


Figure 15. NMR of crude methyl indole-3-carboxylate

It was decided to perform the reaction with diethyl aluminium chloride as Lewis acid and trichloroacetyl chloride on the indole **34**. Purification by column chromatography yielded carboxylated indole **42** in 19 % yield as a black solid from a 300 mg scale reaction. It was thought that the low yield was due to problems with the column and the reaction was

repeated on a 1g scale with 18 % yield. The low yields led us to devise another route to the methyl carboxylate **33b** described below.

Synthesis of 6-bromo-3-iodo-4-methoxy-indole (44)

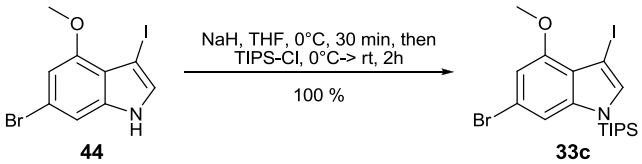


*Scheme 35. Synthesis of 6-bromo-3-iodo-4-methoxy-indole **44***

After the unsuccessful attempt to synthesize of the methyl carboxylate described above, a sequence with iodination and protection to yield 3-iodoindole **33c** from which the carboxylated indole **33b** can be made by metalation and reaction with a suitable electrophile. An electrophilic iodination would lead to the 3-iodinated indole with an EAS mechanism similar to Scheme 34. Iodine monochloride (I-Cl) was used as the source of electrophilic iodine. The advantage of iodine monochloride is that the chloride counterion does not react with the remaining reagent as molecular iodine would do, forming a less reactive I_3^- species.

To indole **34** in pyridine at 0°C, I-Cl was added. After 15 minutes at 0°C the reaction was heated to room temperature. In order to separate the starting material and the product on thin layer chromatography (TLC), a toluene based solvent system had to be used. A work up with aqueous thiosulfate was performed to remove excess I-Cl. The dark red solid was purified by elution from a short silica plug with ethyl acetate to yield 87 % 3-iodoindole **44**. It was decided to skip chromatography in subsequent reactions because the crude product was deemed sufficiently pure to use directly in the next step.

Synthesis of 6-bromo-3-iodo-4-methoxy-1-(triisopropylsilyl)-indole (33c)



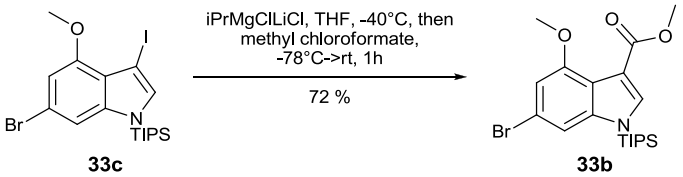
*Scheme 36. Synthesis of 6-bromo-3-iodo-4-methoxy-1-(triisopropylsilyl)-indole **33c***

Protection of the indole with TIPS-Cl has a double importance. As shown later, the TIPS group is essential for the Schöllkopf procedure to proceed. In addition to this, its steric bulk will protect the 2-position of the indole from electrophiles and metalation[57], which will be important steps later in the synthesis upon introducing the iodines. Standard procedures for TIPS protection involve TIPS-Cl and a base like triethylamine or sodium hydride in THF or DMF. The mechanism is an S_N2 mechanism with the deprotonated indole attacks the silicon, displacing the chloride.

A general procedure that was performed upon TIPS protection involves adding unprotected indole to NaH in THF at 0°C before addition of TIPS-Cl. The reaction is monitored by TLC and additional base and TIPS-Cl are added if starting material is left (usually 0,2-0,5 equivalents, depending on the relative intensity of spots on the TLC). After aqueous quenching and work up the product is purified by column chromatography.

The protection of 3-iodoindole **33c** in Scheme 36 was performed in quantitative yield after chromatography with 100 % cyclohexane. Protection of crude 3-iodoindole **44** without chromatography purification yielded 81 % 3-iodoindole **33c** over 2 steps on a 4 g scale. Repetition of this gave similar yield.

Synthesis of methyl 6-bromo-4-methoxy-1-(triisopropylsilyl)-indole-3-carboxylate (33b)



*Scheme 37. Synthesis of methyl 6-bromo-4-methoxy-1-(triisopropylsilyl)-indole-3-carboxylate **33b***

The Grignard reaction is an umpolung of an electrophilic carbon to form a carbon nucleophile. The C-X group is transformed to a C-MgX, dramatically increasing the electron density of the carbon atom. Addition of a Grignard compound to a carbon centered electrophile is a useful method for making carbon-carbon bonds. The classical method for making a Grignard compound is addition of metallic magnesium to the halogenated compound, which inserts into the carbon halide bond through single electron transfer[67].

Another method for making Grignard reagents is to use halogen-magnesium exchange[68]. This is normally much slower than halogen lithium exchange, which takes place at low temperature. Using traditional halogen magnesium exchange reagents like ethyl magnesium halogens are generally slow and have low conversion. by Knochel and co-workers used lithium chloride complexed isopropyl magnesium chloride (iPrMgCl·LiCl) to increase the rate of halogen magnesium exchange. The reason for the increased rate is possibly due to disruption of aggregates[69].

3-iodoindole **33c** was reacted with iPrMgCl·LiCl at -40°C to make the metalated intermediate. The quench with methyl chloroformate was performed at -78°C. The reaction was quenched in 0.1 M EDTA to complexate the magnesium. The resulting carboxylated indole **33b** was purified by column chromatography in a 72 % yield (71 % when repeated by the internship student).

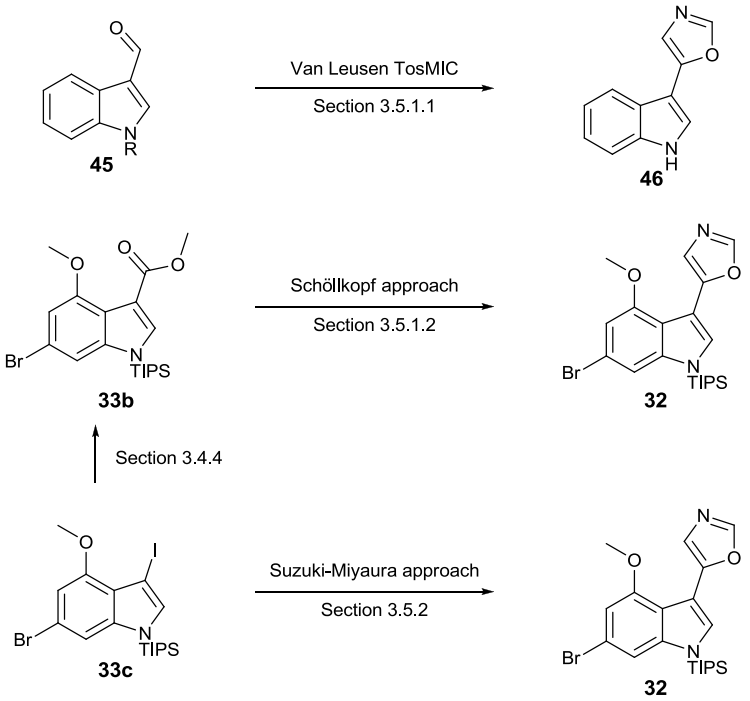
3.5 Oxazole Synthesis

Three different methods were explored in order to find a convenient synthesis of the 5-(indol-3-yl)oxazole **32**. Two of the methods relied on using a methyl isocyanide synthon. These use the van Leusen TosMIC reagent[54] or methyl isocyanide with the Schöllkopf procedure[55]. The last approach is a Suzuki-Miyaura cross coupling reaction. An overview is given in Scheme 38.

With the 3-iodoindole **33c** and carboxylated indole **33b** ready, the oxazole syntheses can be performed.

For the isocyanide approach extensive model studies were performed. The Van Leusen TosMIC reagent was shown to not work as well as the Schöllkopf procedure, which was used instead. The 5-substituted oxazole **32** was obtained in an overall yield of 38 % from

33c in 4 steps.The Suzuki-Miyaura approach was also successful. The 5-substituted oxazole **32** was obtained in an overall yield of 53 % from **33c** in 3 steps, even with a deprotection-reprotection sequence.

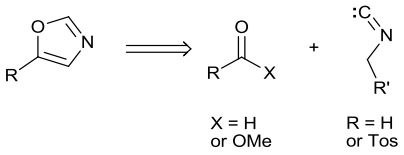


Scheme 38. Overview of oxazole syntheses

3.5.1 Isocyanide Approach

The methyl isocyanide synthon is useful for synthesizing a C-N-C part of a heterocycle (see Scheme 39). Schöllkopf used this method for synthesizing both oxazoles[55] and imidazoles[70]. The usefulness of this synthon comes from its nucleophilicity of the sp^3 carbon and electrophilicity of the isocyanide carbon towards the carbonyl oxygen.

We envisioned the use of either TosMIC or methyl isocyanide in the synthesis of the 5-(indol-3-yl)oxazole. The use of TosMIC has some advantages over methyl isocyanide. Isocyanide are toxic by skin exposure and inhalation. TosMIC is a white crystalline commercially available compound, while methyl isocyanide is a volatile liquid that must be premade. In addition to this, methyl isocyanide has a vile smell. A vivid account on its disagreeable odour is given in the personal recollection of Max Gergel[71] from a period before fume hoods were standard equipment in organic chemistry laboratories.



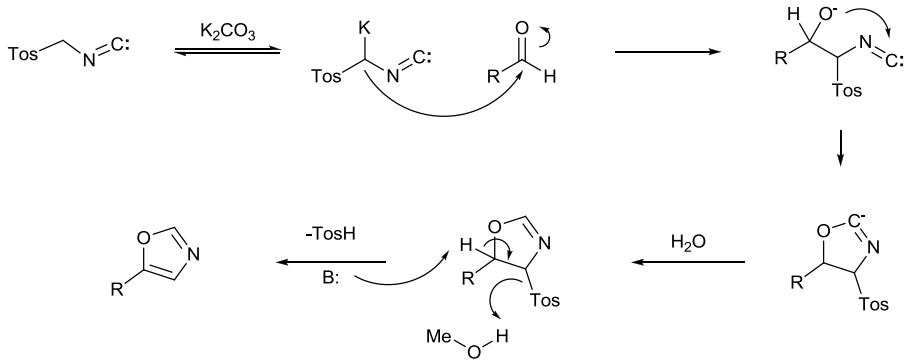
Scheme 39. Isocyanide for oxazole synthesis

The Van Leusen TosMIC reagent[54] has a much lower pKa than methyl isocyanide because it is in the alpha position of a sulfonyl group in addition to the isocyanide group, which allows for the use of a milder base. Carbonate bases are commonly used, but use of the resin bound base Ambersep 900OH is also reported[21]. Methyl isocyanide needs a strong base for

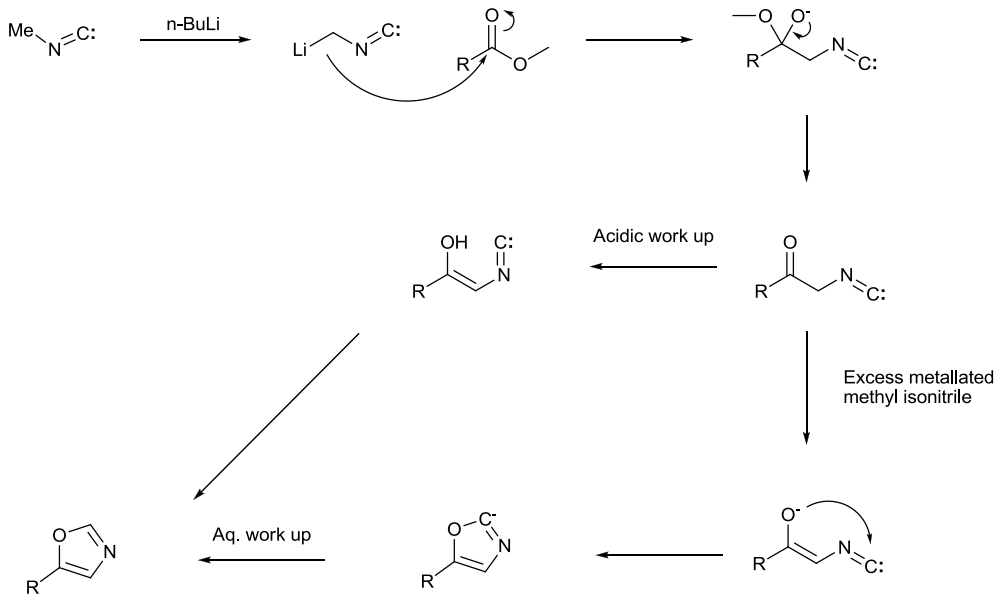
deprotonation, but it is also a better nucleophile. Commonly used bases are n-BuLi and lithium diisopropylamine (LDA).

A major difference between the TosMIC reagent and the Schöllkopf procedure is the leaving group as shown in the mechanisms in Scheme 40 and Scheme 41. The substrate for TosMIC is an aldehyde, which forms a 4-tosyloxazoline. The 4-tosyloxazoline is eliminated to give the oxazole product. Use of a carbonyl compound with a better leaving group like an ester or acid chloride will give a 4-tosyloxazole if the carbonyl leaving group is eliminated faster than the p-toluenesulfinate.

For the Schöllkopf reaction the methoxy group of the ester is eliminated (from what would be the 5-position) to form an α-isocyano ketone. The alpha isocyano ketone is then cyclized by deprotonation of yet another proton from the sp^3 methyl by the excess lithiated methyl isocyanide via an α-isocyano lithium enolate.

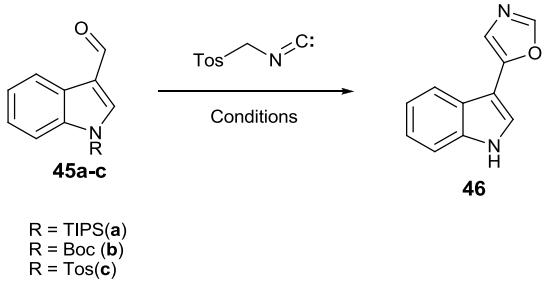


Scheme 40. Mechanism for the Van Leusen TosMIC reaction with an aldehyde



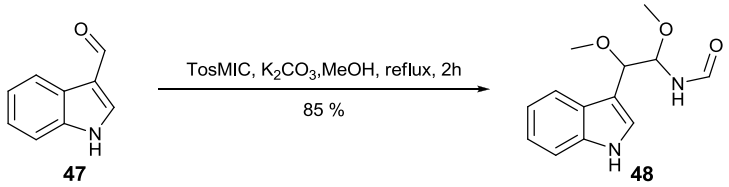
Scheme 41. Mechanism for the Schöllkopf oxazole synthesis of a methyl ester

3.5.1.1 Model studies of 5-(indol-3-yl)oxazole using TosMIC



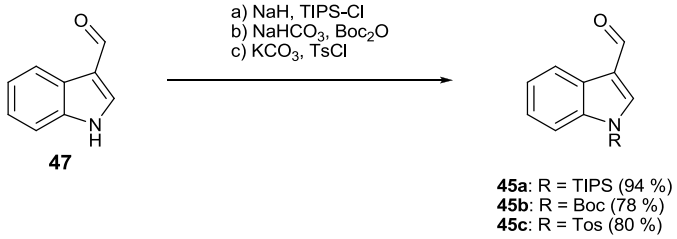
*Scheme 42. Attempted syntheses of 5-(indol-3-yl)oxazole **46** using TosMIC*

The initial studies towards a method for synthesis of the debromo demethoxy model compound of Breitfussin A were concentrated on the Van Leusen procedure for converting an indole-3-carboxaldehyde **47** to the corresponding 5-(indol-3-yl)oxazole. The need for a protecting group at the nitrogen was determined as the standard conditions yielded the dimethoxy ethylformamide **48** shown in Scheme 43 as previously described by Chakrabarty[72].



Scheme 43. Product from TosMIC reaction with unprotected indole

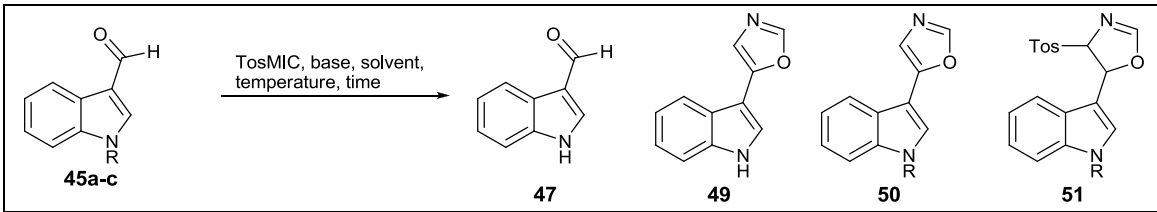
The *N*-protected indole-3-carboxaldehydes **45a-c** were made according to standard procedures as shown in Scheme 44.



*Scheme 44. Formation of protected indole-3-carboxaldehydes **45a-c***

The protected indoles were subjected to reaction with TosMIC under standard procedures[54] (potassium carbonate in refluxing methanol) or the modified procedure with basic resin in methanol and dimethoxyethane (DME)[21] complex mixtures of products were formed (entry a-j). The products consists of deprotected starting material **47**, deprotected 5-(indol-3-yl)oxazole **49**, 5-(*N*-protected indol-3-yl)oxazole **50** and 4-tosyl-oxazoline **51**. However, the oxazole product **49** were formed in low yields (0-42 %). An overview of the reactions are given in Table 1 (MW = microwave, DMSO = dimethylsulfoxide).

Table 1. TosMIC reactions.

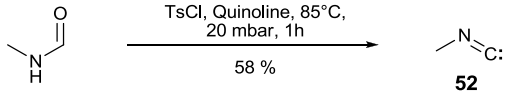


	R =	Base	Solvent	Temperature	Time	Product, yield
a	Boc	Ampersep	MeOH	60°C	2 h	**47, 50**
b	Boc	Ambersep	MeOH	100°C	15 min (MW)	-
c	Boc	Ambersep	MeOH	70°C	5 min (MW)	**47**
d	Boc	Ambersep	MeOH	70°C	15 min (MW)	**47**
e	Boc	Ambersep	MeOH	120°C	15 min (MW)	**47** (25 %)
f	Tos	Ambersep	MeOH	60°C	2h	**47**
g	Tos	K_2CO_3 (3 eq)	MeOH	60°C	2h	**47**
h	Tos	Ambersep	MeOH	60°C	2h	**49**
i	Tos	Ambersep	MeOH/DME	80°C	2h	**49** (36 %)
j	Tos	Ambersep	MeOH/DME	80°C	2h	**49** (42 %)
k	TIPS	Ambersep	MeOH	70°C	2h	-
l	Boc	DBU (2,5 eq)	DMSO	80°C	1,5h	-
m	Boc	DBU (2,5 eq)	DME	80°C	1,5h	-
n	Boc	DBU (2,5 eq)	DMF	80°C	1,5h	-
o	Boc	DBU (2,5 eq)	Et2O	40°C	1,5h	**51b** (98 %)
p	Boc	K_2CO_3 (3 eq)	DME	80°C	2h	-
q	Boc	K_2CO_3 (3 eq)	DCM	80°C	2h	-
r	Boc	0.8M NaOH	-	80°C	2h	-
s	Boc	DBU (2,5 eq)	DCM	80°C	2h	-
t	Boc	K_2CO_3 (3 eq)	DMSO	150°C	2h	-
u	Boc	K_2CO_3 (3 eq)	DMF	150°C	2h	-
v	TIPS	K_2CO_3 (3 eq)	DME	80°C	2h	-
w	TIPS	K_2CO_3 (3 eq)	DCM	80°C	2h	-
x	TIPS	0,8M NaOH	-	80°C	2h	-
y	TIPS	DBU (2,5 eq)	DME	80°C	2h	-
z	TIPS	DBU (2,5 eq)	DCM	80°C	2h	-
a’	TIPS	K_2CO_3 (3 eq)	DMSO	150°C	2h	-
b’	TIPS	K_2CO_3 (3 eq)	DMF	150°C	2h	-
c’	TIPS	DBU (2,5 eq)	DMSO	150°C	2h	-

Screening for different bases and solvents did not lead to any significant formation of products, but using DBU in diethyl ether lead to near quantitative formation of oxazoline **51b**, confirming that the oxazoline formation precedes the deprotection under these conditions. It is suspected that the electron density of the indole reduces the reactivity of the indole aldehyde. Tests were performed to eliminate the tosyl group in strong bases, but without success. It was decided to try the Schöllkopf oxazole formation instead.

3.5.1.2 Synthesis of 5-(indol-3-yl)oxazoles via the Schöllkopf method

Synthesis of methyl isocyanide



*Scheme 45. Synthesis of methyl isocyanide **52***

Isocyanides are cyanides bonded through the nitrogen rather than the carbon. This leads to compounds which have to resonance structures as shown in Figure 16. Curiously, the isocyanides are linear, as expected from a triple bond, but behave more like a carbenic structure[73]. In this thesis the latter will be used to emphasize the carbenic behaviour.

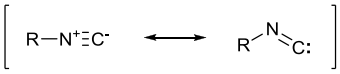
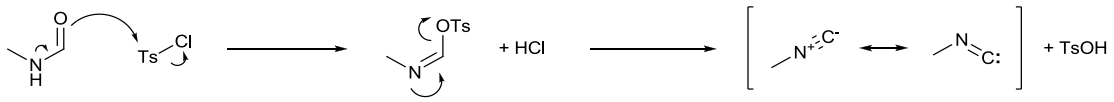


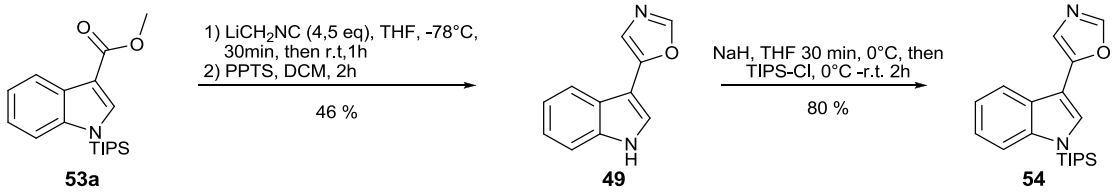
Figure 16. Isocyanide resonance forms

The first synthesis of isocyanides was reported by Gautier in 1868[74] using methyl iodide and silver cyanide. Our method for preparing methyl isocyanide **52** is described by Casanova in 1966[75]. *N*-methyl formamide is dehydrated using tosyl chloride (TsCl), eliminating hydrochloric acid and tosic acid which is scavenged by quinoline that is used both as base and solvent. The methyl isocyanide **52** is distilled off the reaction flask under reduced pressure at 85°C and collected in a liquid nitrogen cooled flask. The newly formed methyl isocyanide **52** is purified by distillation using a Vigreux-column. This reaction works best for larger scale preparations as less of the volatile isocyanide is lost in the headspace of glassware. One should at all times during the synthesis take care not to remove even traces of methyl isocyanide **52**, as its odour is repulsive. All glassware should be washed with acid after use to remove traces of isocyanide. Even when stored in a flask which is strictly air tight the smell is remarkable. The mechanism for this reaction is given in Scheme 46.



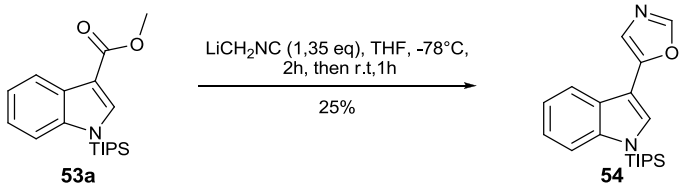
Scheme 46. Mechanism for the preparation of methyl isocyanide from N-methyl formamide

Model Studies Using the Schöllkopf Approach



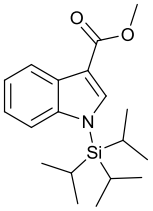
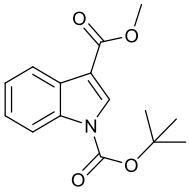
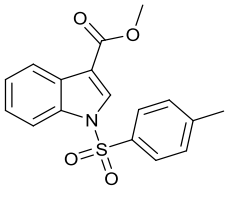
*Scheme 47. Synthesis of 5-(1-(triisopropylsilyl)indol-3-yl)oxazole **54**)*

After the low yields of the TosMIC reaction, testing was performed using methyl isocyanide **52** instead (Scheme 48). Dissolving methyl isocyanide **52** in THF, cooling to -78°C and adding n-butyl lithium (n-BuLi) yielded the metalated isocyanide into which a solution of methyl indole-3-carboxylate **53a** was added. Using the procedure of Rouch[76] with 1,5 equivalents of methyl isocyanide **52** and 1,35 equvalents of n-BuLi for 2 hours at -78°C before addition of indole yielded 25 % the expected oxazole **54** after aqueous work up and column chromatography (and about 35 % starting material determined by gas chromatography coupled to a mass spectrometer detector (GC-MS)). This is shown in Scheme 48. This yield was low and the same reaction was tested using other protecting groups without success. This is shown in Table 2.



*Scheme 48. Synthesis of 5(N-TIPS-indol-3-yl)oxazole **54***

Table 2. Schöllkopf reaction with differently protected methyl indole-3-carboxylates

Compound	 53a	 53b	 53c
Products and yields	25 % product (isolated) 35 % starting material	Only deprotected starting material observed by LCMS	Only deprotected starting material observed by LCMS

The Schöllkopf reaction has previously been performed on methyl indole-3-carboxylates by Vedejs in an approach towards Diazonamide A[37] wherein a 5-fold excess of lithiated methyl isocyanide was used yielding 71 % of deprotected indolyl oxazole. Upon increasing the amounts of methyl isocyanide **52** to 5 equivalents and n-BuLi to 4,5 equivalents using otherwise identical conditions we observed a mixture of 5-(indol-3-yl)oxazole **49** and its open form α-isocyano ketone isomer **55** (Figure 17). The methylene hydrogens have a very characteristic peak at 5,2 ppm in ^{1}H-NMR.

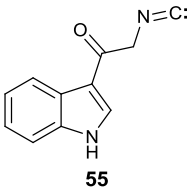
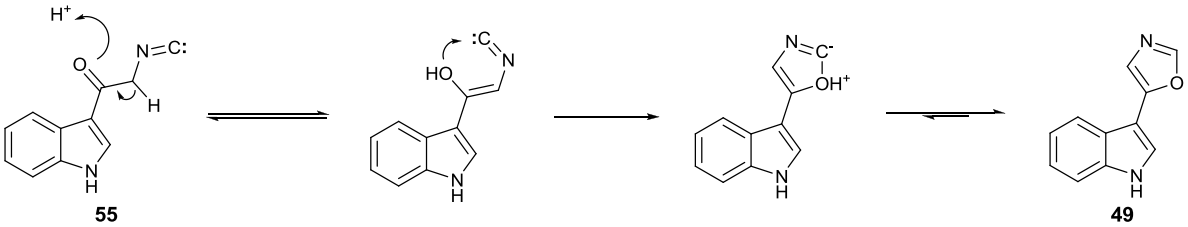


*Figure 17. 2-isocyano-1-(indol-3-yl)ethanone **55***

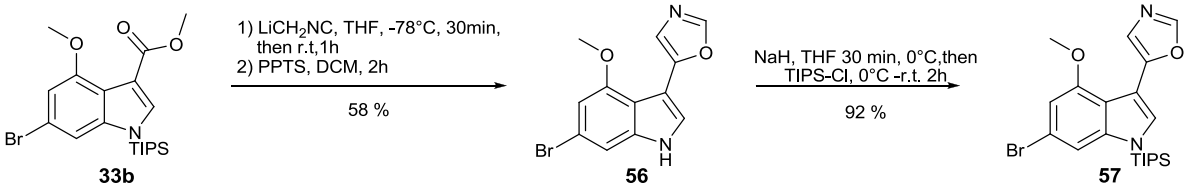
Using pyridinium *para*-toluene sulfonate (PPTS) in DCM on the crude mixture, the open form isomer **55** was converted completely to the closed ring oxazole **49**, similar to Vedejs procedure. A possible mechanism for this is given in Scheme 49. Upon purification it was apparent that the 5-substituted oxazole **49** was insoluble in many common solvents resulting in some loss of product on the silica column upon using ethyl acetate in cyclohexane. The yield for this procedure was 46 %, hardly better than for TosMIC, but it was decided to test this on the prepared carboxylated indole **33b**.



*Scheme 49. Possible mechanism for acidic cyclization of 2-isocyano-1-(indol-3-yl)ethanone **55***

As the Schöllkopf procedure removed the silyl protecting group of the indole nitrogen it was necessary to reprotect the indole before the next step. The TIPS protection was done using the same procedure as in section 3.5.1.2. Due to the low solubility of the 5-substituted oxazole **49**, it was added to the sodium hydride as a suspension in THF followed by 2 washes in which the rest of the solids were suspended. The protected 5-substituted oxazole **54** was synthesized in 80 % yield after column chromatography, as shown in Scheme 47 above.

Application of the Schöllkopf Approach in the Total Synthesis



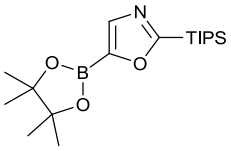
*Scheme 50. Synthesis of 5-(6-bromo-4-methoxy-1-(triisopropylsilyl)-indol-3-yl)oxazole **57**)*

The same procedure was used successfully in the total synthesis as for the model compound. 5 equivalents of methyl isocyanide **52** and 4,5 equivalents of n-BuLi was reacted at low temperature for 1 hour before drop-wise addition of the methyl carboxylate **33b**. After the acidic work up and treatment with PPTS in DCM, the 5-substituted oxazole **56** precipitated from the DCM solution. The precipitate was filtered and washed with DCM, removing all PPTS and triisopropylsilanol. Drying under vacuum yielded the pure **56** in 58 % yield. TIPS-protection of 5-substituted oxazole **56** gave protected 5-substituted oxazole **57** in 92 % yield. The total yield for the Schöllkopf procedure from iodoindole **33c** was 38 % in 4 steps.

3.5.2 Suzuki-Miyaura Approach

Not satisfied by the laborious Schöllkopf method we turned our attention cross coupling reactions to form the 5-3' C-C bond between the indole and the oxazole. Previous cross coupling reactions of the 5-position of the oxazole has been described in literature using the Stille cross coupling reaction with stannanes[77] or in one case direct C-5 arylation of the oxazole[78]. Organic tin compounds are not desirable to work with and direct C-5 arylation needs high temperatures and careful modulation of conditions to avoid C-2 arylation. Direct arylation of the 5 position is easier to perform on 2-substituted oxazoles[79].

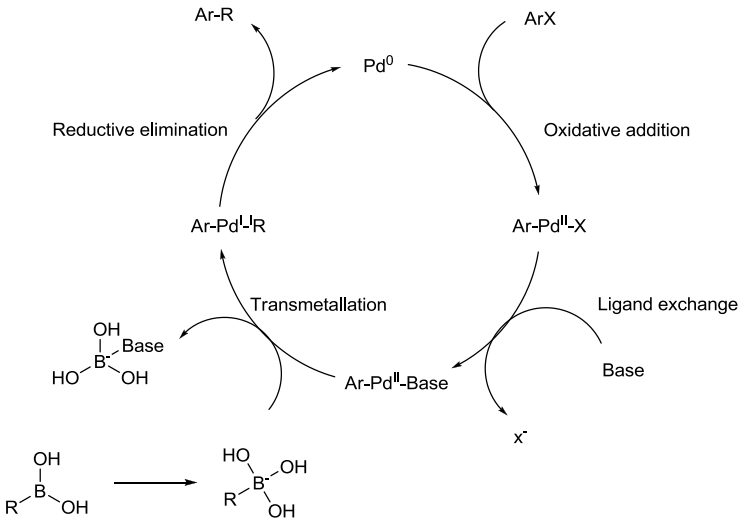
However, recently the developed of the 2-triisopropylsilyloxazole 5-boronic acid pinacol ester **58**[56] (Figure 18) has opened possibilities for using Suzuki-Miyaura cross coupling reactions to make oxazole C-5 bonds. According to Primas et al[56] the 2-TIPS protecting group falls off during work up after coupling, leading to the 5-monosubstituted oxazole in good to excellent yields.



58

*Figure 18. 2-triisopropylsilyloxazole 5-boronic acid pinacol ester **58***

An overview of the catalytic circle is given in Scheme 51. The reaction involves oxidative addition of Pd^0 into a C-X bond, where X is a halogen or a triflate, to form a Pd^{II} complex. The halogen is displaced by base, after which the transmetalating step can occur. For boronates the rate of transmetalation is increased when the boronate is negatively charged. The last step of the catalytic cycle is the reductive elimination forming the C-C coupled product and regenerating the active Pd^0. Ligands are omitted for clarity.

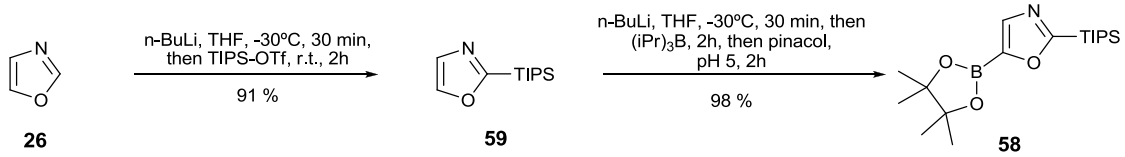


Scheme 51. Catalytic cycle for Suzuki-Miyaura cross coupling

The choice of halogen is important in this total synthesis. Using the 3,6-dibromoindole would preferentially insert the organometalic specie at the 6-bromo position since this is more reactive towards oxidative addition because it has a lower electron density[80]. Since

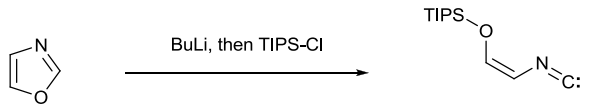
iodine is more reactive than bromine, an iodine in the 3-position of the indole is expected to give the desired 5-(indol-3-yl)oxazole, still conditions has to be chosen with care.

Synthesis Oxazole Boronic Acid (58)



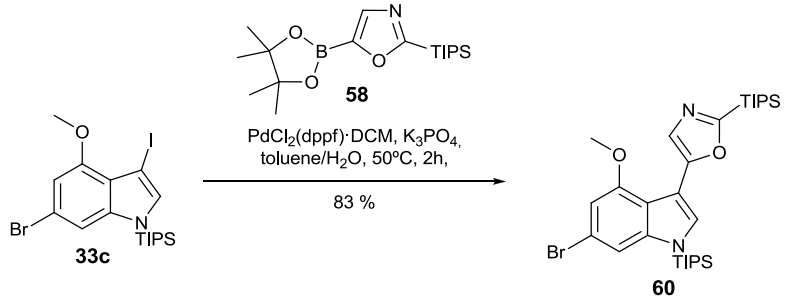
*Scheme 52. Synthesis of (2-(triisopropylsilyl)oxazol-5-yl)boronic acid pinacol ester **52***

The oxazole boronic acid ester **52** is prepared according to literature procedure[56]. Miller et al[17] demonstrated that upon changing from TIPS-Cl to TIPS-triflate (TIPS-OTf) the oxazole will be silylated at the C-2 carbon instead of the oxygen in the open ring form of the oxazole (as shown in Scheme 53). With the 2-position substituted another lithiation deprotonated the C-5 carbon. A quench with triisopropyl borate and subsequent acidic transesterification with acetic acid and pinacol gave boronic acid pinacol ester **58** in excellent yields for both steps.



Scheme 53. Silylation of oxazole with TIPS-Cl

Suzuki-Miyaura Cross Coupling used in the Total Synthesis



*Scheme 54. Synthesis of 5-(6-bromo-4-methoxy-1-(triisopropylsilyl)-indol-3-yl)-2-(triisopropylsilyl)oxazole **60***

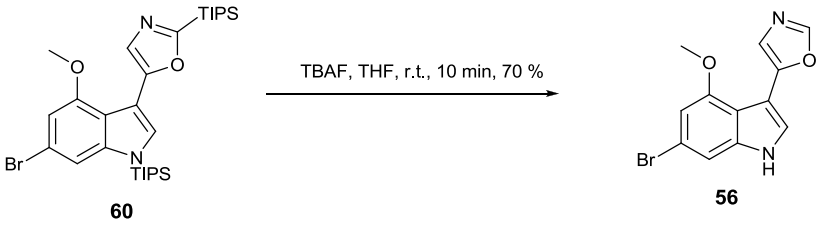
An initial attempt on coupling indole **33c** and boronic acid ester **58** using 1,3 equivalents of boronic acid ester at 80°C for 2 hours gave, after work up and column chromatography, 67 % of the coupling product **60** in addition to a 1:1 mixture of byproducts that coeluted using a cyclohexane based eluent. The exact structures of the products were not elucidated, but it is suspected that it might involve homocoupling and 5-(indol-6-yl)-oxazole formation. The products were separable in a toluene based eluent system, but no further attempt was made in separation and structure elucidation.

Using a lower temperature protocol at 50°C and 1,05 equivalents of boronic acid ester with otherwise identical conditions yielded 83 % coupling product **60** without significant amounts of by-products.

The good yields of the silylated coupling product were in contrast to the reported reaction where TIPS-deprotection was observed[56]. To remove the TIPS group it was decided not to spend time trying to selectively remove the 2-TIPS group, despite literature indication the

lability of the C-Si bond in 2-TIPS oxazoles. This selective desilylation has even been performed in the presence of a trimethylsilyl group[81]. This selective deprotection was later tested successfully in analogue synthesis described in chapter 4.

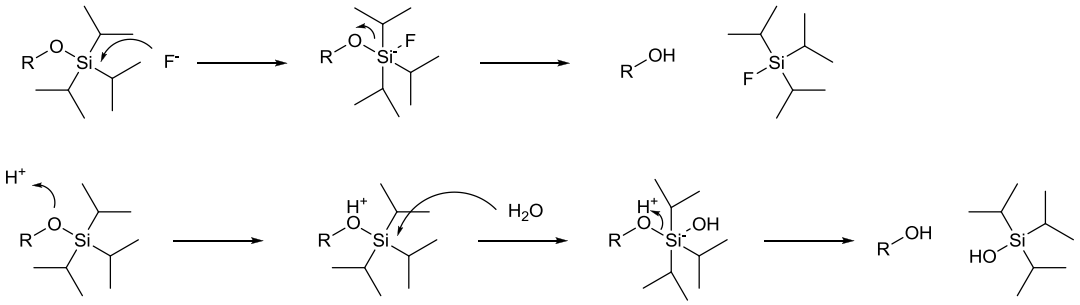
Deprotection of Suzuki-Miyaura Coupling Product (56)



60 **56**

*Scheme 55. Deprotection of disilylated coupling product **60***

To remove silyl protecting groups two general conditions are used, acid or fluoride. Both rely on the ability of silicon to form transient pentavalent compounds, as shown in Scheme 56.



Scheme 56. Mechanism for deprotection of silyl protection groups with fluoride (above) and acid (below)

Using 2 equivalents of tetraammoniumbutyl fluoride (TBAF) in THF removed both TIPS groups. Due to the previously described solubility issues with this compound (section 3.5.1.2) the eluent was changed from ethylacetate/cyclohexane to THF/cyclohexane. This resulted in a somewhat higher solubility and less tailing under purification by column chromatography. The yield 5-substituted oxazole **56** was 70 %. After reprotection identical to the previously described in a 92 % yield gave 5-substituted oxazole **57** in a total yield of 53 % from 3-iodoindole **33c**.

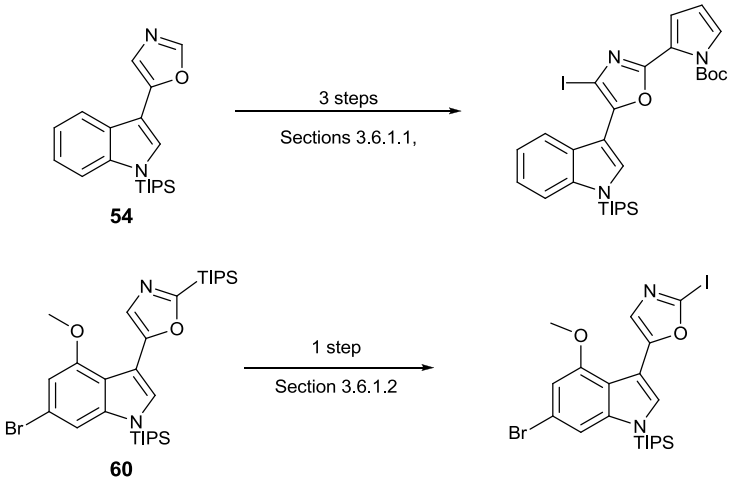
Summary of Oxazole Synthesis

Oxazole formation using the Schöllkopf procedure with methyl isocyanide **52** was performed in 38 % yield over 4 steps from the 3-iodoindole **33c**. This involved a halogen-magnesium exchange to prepare the methyl ester **33b** for the Schöllkopf reaction. After treating the methyl ester **33b** with the lithiated methyl isocyanide and PPTS, a step was needed to reintroduce the TIPS group. Oxazole formation using the van Leusen TosMIC reagent was not performed in the total synthesis.

The Suzuki-Miyaura approach gave a 53 % yield over 3 steps from 3-iodoindole **33c**. This is clearly a superior result to the Schöllkopf protocol, even including the inelegant deprotection-reprotection procedure. As will be described in the analogue synthesis chapter, using a selective deprotection, yields in the 70-80 % range can be obtained in one step.

3.6 IODINATION AND PYRROLE ASSEMBLY

With the indolyl-oxazole **57** in hand we concentrated on introducing the iodine in 4-position and pyrrol-2-yl in the 2-position of the oxazole. For the model substrate the synthesis up until the deprotection will be discussed, while for the natural product the attempts on iodination will be described. An overview is given in Scheme 57.

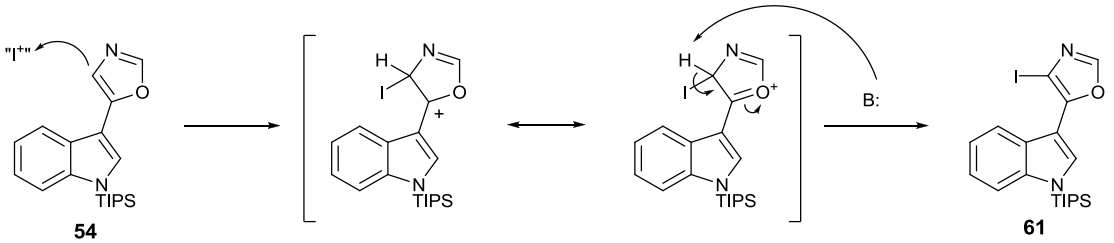


Scheme 57. Overview of iodination and pyrrole assembly

3.6.1 Oxazole iodination

Two possible strategies for introduction of the 2- and 4-iodo groups were considered. A metalation/iodination strategy could directly provide both iodine groups, however, due to the ring opened intermediates involved in metalation (Scheme 16) this method was considered less reliable. The alternative sequence was 4-iodination by EAS followed by a 2-iodination via a metalation/iodination reaction.

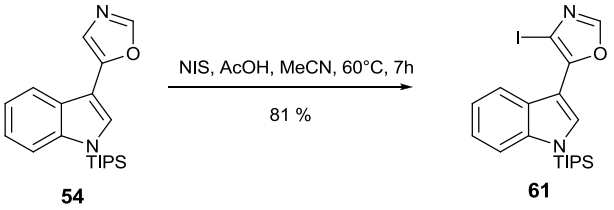
Iodination of oxazole can be done by electrophilic aromatic substitution, with a source of positive iodine. The mechanism is similar to the one shown for bromination in the first step of the synthesis (Scheme 23). The 4-position is the only position on the oxazole that are reactive enough for this purpose. All other electrophilic positions are already substituted (5-position of oxazole and 3-position of indole) or protected (2-position of indole). The mechanism for iodination is given in Scheme 58.



*Scheme 58. Mechanism for electrophilic iodination of 5-(1-(triisopropylsilyl)-indol-3-yl)oxazole **61***

3.6.1.1 Model Studies on iodination

Synthesis of 4-iodo-oxazole (61)

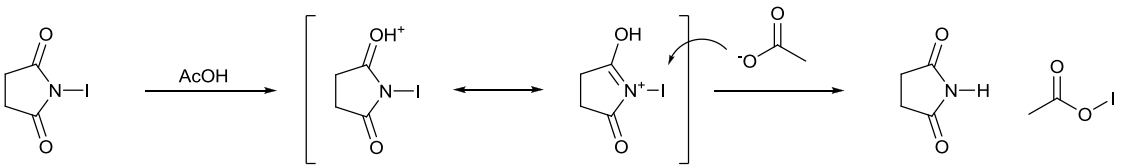


54 61

*Scheme 59. Synthesis of 4-iodo-5-(1-(triisopropylsilyl)-indol-3-yl)oxazole **61***

Iodination by EAS was tested with NIS in acetonitrile or 1:1 CCl_4:THF on the *N*-TIPS protected substrate **54** and the unprotected substrate **49**. The best results were obtained using acetonitrile as solvent on the *N*-TIPS protected substrate **54**. Iodination of the unprotected substrate **49** proceeded at least an order of magnitude slower than its protected counterpart, determined by LCMS.

Having determined appropriate reaction conditions, a half-gram scale reaction was performed, using the remaining indolyloxazole **54**. After 3 hours at 60°C, TLC analysis indicated a slow reaction. 0,3 equivalents of acetic acid was added to work as a catalyst giving the activated iodine shown in Scheme 60[82]. After additional 4 hours the reaction proceeded to completion and, after a reductive work up (to remove excess NIS) and column chromatography, an 81 % yield was obtained. In the ^{13}C-NMR there are 14 peaks, 3 more than the number of carbons, which indicates the presence of two rotamers (Figure 19).



Scheme 60. Activation of iodine with acetic acid

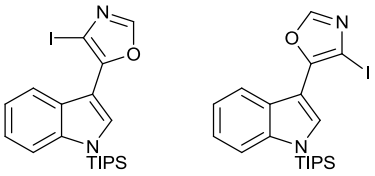
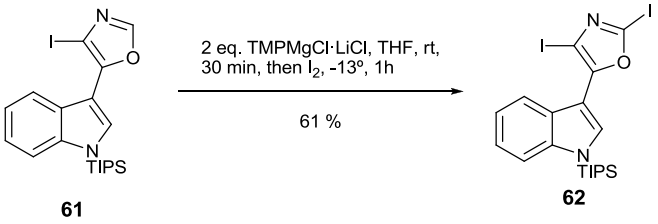


*Figure 19. Assumed rotamers of 4-iodo indolyl oxazole **61***

Synthesis of 2,4-diiodo-oxazole (62)



*Scheme 61. Synthesis of 2,4-diiodo-5-(1-(triisopropylsilyl)-indol-3-yl)oxazole **62***

For the 2-iodo substituent, a metalation/iodination sequence is necessary. The metalation is performed using 2,2,6,6-tetramethyl piperidinyl magnesium chloride lithium chloride complex (TMPMgCl·LiCl). This amide base developed by Knochel[83] is more selective than other bases and metalation can be performed in room temperature with a high functional group tolerance. The counter ion is a mixed magnesium lithium chloride complex that is used to break up the aggregated clusters that can form in solution (similar to the super Grignard reagent described in section 3.4).

The addition of TMPMgCl·LiCl to **61** was done at room temperature and equilibrated for 30 minutes before addition of iodine at -13°C. Using 1,1 equivalent base gave a 15 % yield of diiodinated indolyl oxazole **62** and a 34 % recovery of starting material. 1,2 equivalents of base gave 31 % product **62** and 45 % recovery of starting material. Given the 2-fold increase in yield upon increasing from 1,1 to 1,2 equivalents it was suspected that an excess of base was needed. Upon using 2,2 equivalents of base 61 % product **62** was isolated without traces of starting material indicating complete conversion. It is suspected that a TMP oxazole complex might be involved as shown in Figure 20. The second deprotonation would then occur on the 2-position followed by an iodine quench.The ^{13}C-NMR of **62** has 3 additional peaks, similar to **61** indicating the presence of rotamers.

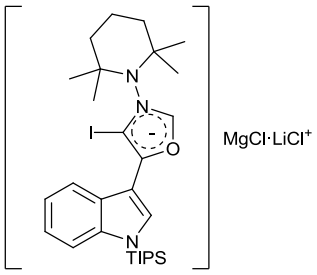
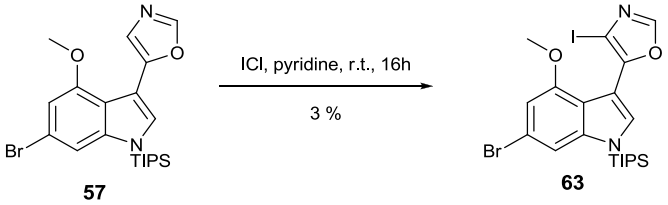


*Figure 20. Suspected TMP MgCl·LiCl complex of indolyl oxazole **61***

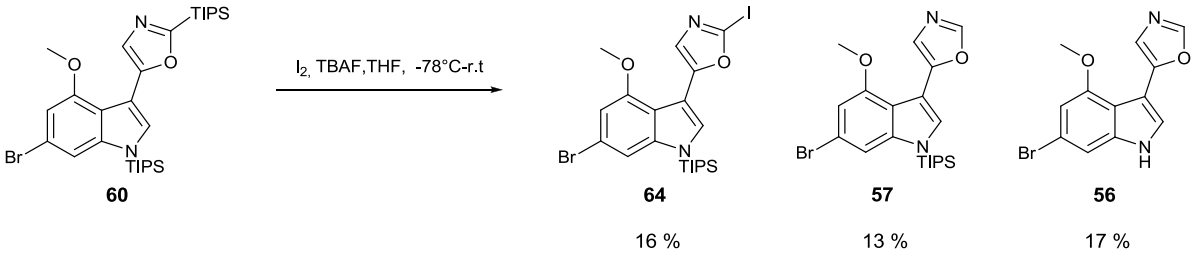
Attempted syntheses of iodinated oxazoles in total synthesis



*Scheme 62. Synthesis of iodinated 5-(6-bromo-4-methoxy-1-(triisopropylsilyl)-indol-3-yl)oxazoles **63***

Repeating the same procedure in section 3.6.1.1 with NIS and acetic acid gave no iodinated indolyl oxazole **63**. Using trimethylsilyltriflate (TMSOTf) to activate the iodine for

electrophilic attack did not seem to give better results. Using another electrophilic iodine (I-Cl) gave 3 % isolated yield of **63**. Further development of this method using the two step EAS then metalation sequence was performed in Germany after my stay. This tactic is feasible, but the yields of both reactions were moderate. Efforts will be directed towards metalation/iodination reactions to introduce the iodines in the total synthesis. The metalation/iodination approach will be described in the analogue synthesis in section 4.5.



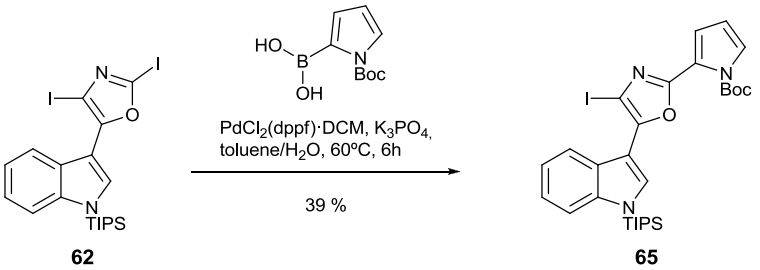
*Scheme 63. Synthesis of 5-(6-bromo-4-methoxy-1-(triisopropylsilyl)-indol-3-yl)-2-iodo-oxazole **64***

A one pot iododesilylation was also tested, using TBAF to remove the TIPS protecting group in the presence of iodine. Previous reports describes this reaction on vinyl-TIPS groups[84,85,85]and 2-TBDPS-oxazoles[86].

Using a 0.95 equivalents of TIPS-protected oxazole **60**, 1 equvalent of TBAF and 1.2 equivalents of iodine gave low yield of the expected 2-iodo oxazole **64**, some non-iodinated product **57** and some fully deprotected product **56**. With better control of conditions, this might be developed to a suitable way to prepare 2-iodinated oxazoles. This 2-iodinated oxazole **64** is an intermediate towards Breitfussin B (**2**).

3.6.2 Model Study on Suzuki-Miyaura Cross Coupling

For making the last C-C bond in the synthesis a Suzuki-Miyaura cross coupling was envisioned. Literature indicates that the 2-iodine of an oxazole should be more reactive towards oxidative insertion[48], which is not surprising given the proximity to two electronegative atoms for the 2-position versus one electronegative atom for the 4-position. A general mechanism for the Suzuki-Miyaura reaction is given in Scheme 51.



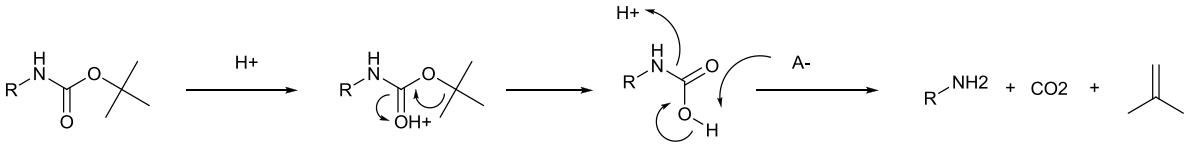
*Scheme 64. Synthesis of tert-butyl 2-(4-iodo-5-(1-(triisopropylsilyl)-indol-3-yl)oxazol-2-yl)-pyrrole-1-carboxylate **65***

Diiodo indolyl oxazole **62** was coupled to the *tert*-butyloxycarbonyl (Boc) protected 2-pyrrolyl boronic acid using the same conditions as in section 3.5.2, for the synthesis of **60**. The choice of boronic acid depends only on commercial availability. In addition to this boronic acid, the methyl iminodiacetic acid (MIDA) ester is commercially available. The MIDA ester is also more stable to air and temperature[87].

The reaction was prematurely stopped after 6 hours when some starting material was left. After purification by column chromatography protected pyrrolyl-indolyl oxazole **65** was obtained in 39 % yield (84 mg).

3.6.3 Model Study on Final Deprotection

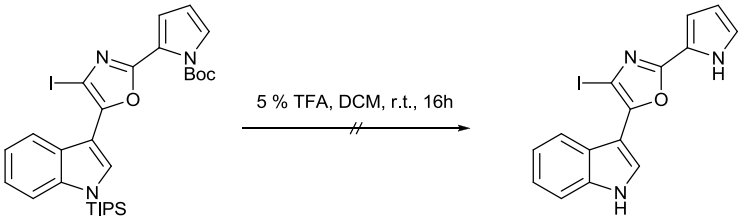
Deprotection of the Boc protecting group can be performed using acidic conditions, Lewis acids or by pyrolysis[88]. It is stable to basic conditions. The mechanism of deprotection is given in Scheme 65.



Scheme 65. Mechanism of deprotection of Boc groups

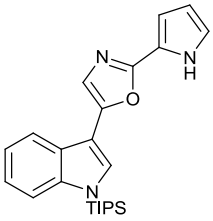
Deprotection of silyl protecting groups can be performed with acid or fluoride, as described in Scheme 56. The most frequently used reagent for introducing fluoride ions is TBAF.

Selective removal of either TIPS or Boc can be performed. Selective Boc removal has been reported using HCl in ethyl acetate[89] and TIPS can be removed by using TBAF. In this case, however, ortogonality of the protecting groups are not desired, as a one-step removal of both groups would be advantageous. This can be performed using acid, provided both are labile in the chosen acid. A common reagent for removal of Boc is trifluoroacetic acid TFA, and this acid is reported to remove TIPS and Boc groups, both on alcohols[90] and indoles[91].



*Scheme 66. Attempted synthesis of 2-(4-iodo-5-(indol-3-yl)oxazol-2-yl)-pyrrole **66***

Using modified conditions from Johnson[91] (50 % TFA in DCM), a 20 mg test scale reaction was performed with 5 % TFA in DCM. After 30 minutes, the TLC showed 3 spots, one for the remaining starting material **65** and two others with a lower r.f. value. After 2 hours the TLC was similar, but at 16 hours, the starting material had disappeared and the middle spot was very weak indicating that the reaction had gone almost to completion. An analysis on LCMS showed a mass of 405 for the main peak, as opposed to the expected 375 for the model Breitfussin **66**. This mass corresponds to the deiodinated product **67** in Figure 21.



67

*Figure 21. Deiodinated product **67** of TFA deprotection of **65***

This indicates that the *N*-TIPS group is fairly stable in acid. At this point there was no time for more testing, but further testing should be done using fluoride sources. A possible solution would be potassium fluoride in HCl, as that would provide both fluoride for TIPS deprotection and acid for Boc deprotection. As mild conditions as possible should be used to avoid the unexpected deiodination of the 4-iodine. Alternatively a two-step procedure can be performed.

4 SYNTHESIS OF BREITFUSSIN ANALOGUES

4.1 THE SCOPE OF THE CHAPTER

This chapter describes the initial efforts of making a library of Breitfussin analogues. The compounds in Figure 22 has currently been synthesized. **68-73** are at different stages in the synthesis.

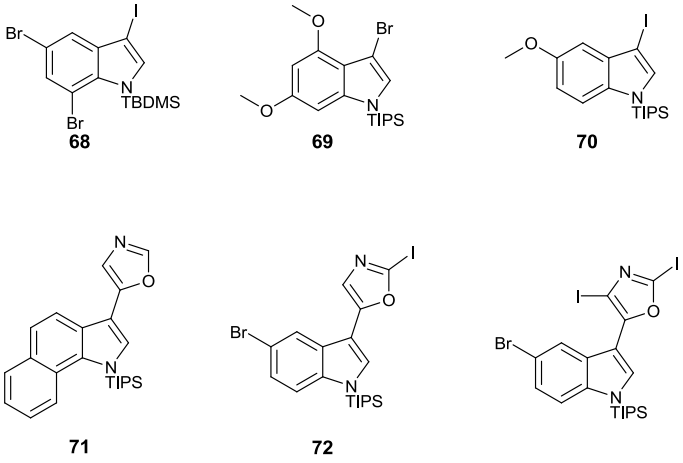


Figure 22. Compounds prepared for Breitfussin library

4.2 RATIONALE FOR ANALOGUE SYNTHESIS

In order to gather SAR information and possibly a lead compound it was decided to synthesize a library of Breitfussin analogues. This is done in cooperation with Sunil Pandey, a post-doctoral researcher at the University of Bergen. Here, my work will be described.

The library is focused on altering the pyrrole moiety and the substitution pattern of the indole, as shown in Figure 23. In the R_1 and R_2 positions bromine and methoxy groups are placed, spread over all the carbocycle-positions of the indole. A benzo[g]indole is also used to imitate the steric bulk of bromine.

A range of heterocycles is used in the R_3 position. This is mainly focused on changing the coordination properties of the "north-eastern" side of the molecule. Five five-membered rings with different heteroatoms (nitrogen, oxygen and sulfur), different position of the heteroatom (connected in 2- or 3-position) and methylation were chosen. In addition an indol-2-yl and 2-pyridyl R_3-group were chosen to expand further into a possible binding on the pyrrole side.

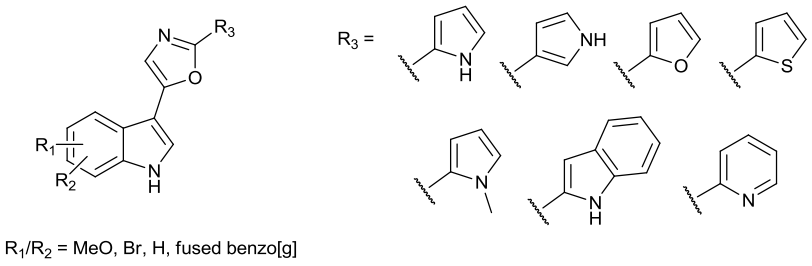
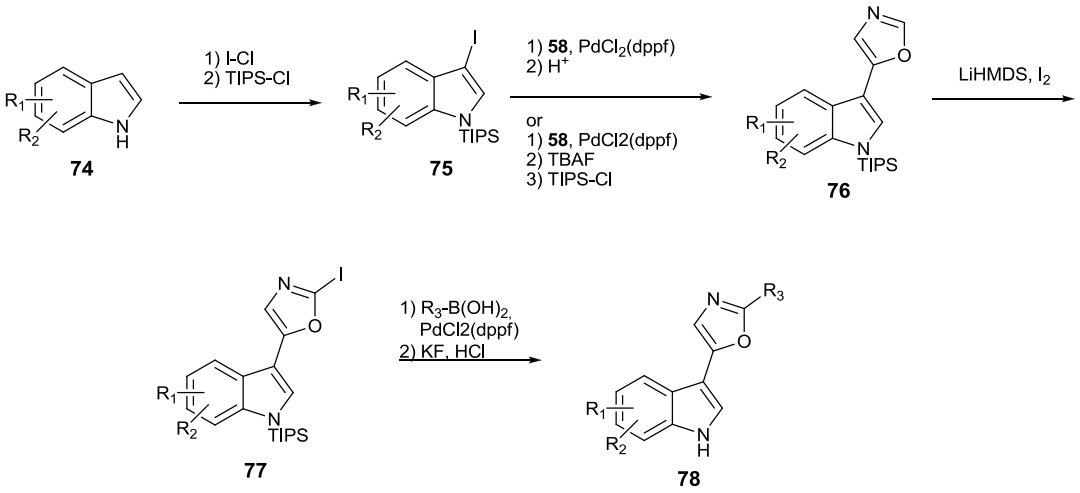


Figure 23. Overview of planned Breitfussin library

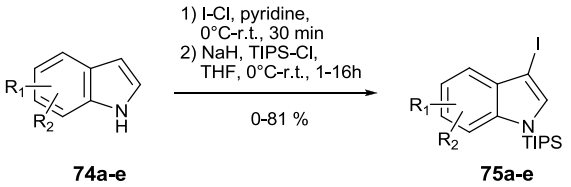
To most efficiently generate a library it was decided to use the same sequence of reaction as in the total synthesis of the natural product. If possible, a selective 2-TIPS-oxazole deprotection will be tested to reduce the sequence length by two steps. For an envisioned easier synthesis, the 4-iodo substituent on the oxazole will not be introduced.

An outline of the synthetic plan is shown in Scheme 67. The first step is protection and 3-iodination of the indoles **74** to yield 3-iodoindoles **75** for subsequent Suzuki coupling of the oxazole and removal of the 2-TIPS-oxazole protecting group, either by selective deprotection or a deprotection-reprotection sequence. Selective 2-iodination of oxazole **76** should give the iodinated oxazoles **77**. Coupling of the iodinated oxazoles **77** to different boronic acids before deprotection of TIPS and, if present, Boc groups to give the final analogues **78**.



Scheme 67. Overview of Breitfussin analogue synthesis

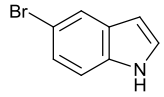
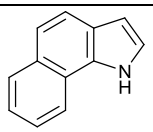
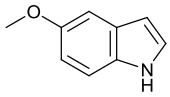
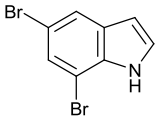
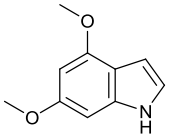
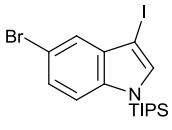
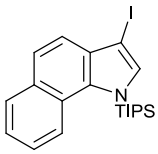
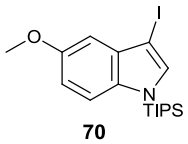
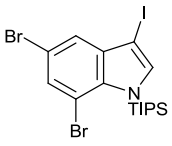
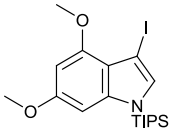
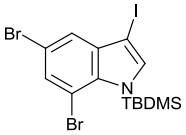
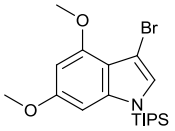
4.3 SYNTHESIS OF 3-HALO-*N*-TIPS-INDOLES



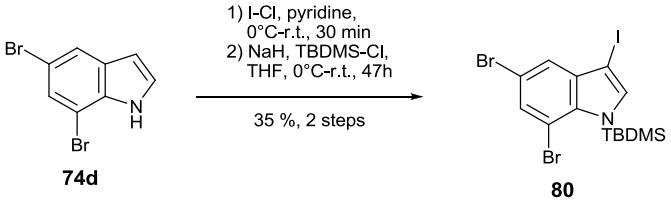
Scheme 68. Synthesis of 3-iodo-N-TIPS-indoles

On a range of commercially available indoles shown in Table 3, the procedure for successive iodination and TIPS-protection was followed identical to the corresponding steps in the total synthesis (Chapter 3). After 30 minute reaction time the samples were quenched and the identity of the 3-iodoindoles confirmed by high resolution MS and NMR on the crude sample. The results are shown in Table 3. The reaction sequence in Scheme 68 gave good results for 5-Bromo **74a**, benzo[g]indole **74b** and 5-methoxy **74c**. The reason for the low yield of benzo[g]indole **75b** is a poorly executed column that had to be repeated. The two last indoles **74d-e** will be discussed in the following two subchapters.

Table 3. List of indoles used in analogue synthesis

Indoles used in analogue synthesis	 **74a**	 **74b**	 **74c**	 **74d**	 **74e**
Product from reaction sequence (yield)	 **75a** 81 %	 **75b** 47 %	 **70** 81 %	 **75d** 0 %	 **75e** 0 %
Alternative product	-	-	-	 **80** 35 %	 **82b** 69 %

Synthesis of 5,7-dibromo-3-iodo-1-*tert*butyldimethylsilylindole



Scheme 69. Synthesis of 5,7-dibromo-3-iodo-1-tertbutyldimethylsilylindole

For 5,7-dibromoindole **74d** the iodination proceeded properly according to Scheme 68, but the reaction with TIPS-Cl did not show any trace of product on TLC, GC-MS and HRMS, even after several additions of more sodium hydride and TIPS-Cl. The reaction was quenched and the normal work-up procedure was performed. This gave an oily mixture of iodinated indole **79** (Figure 24) and TIPS-OH from which the TIPS-OH was washed out with pentane and the residue purified by column chromatography.

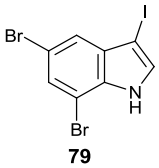
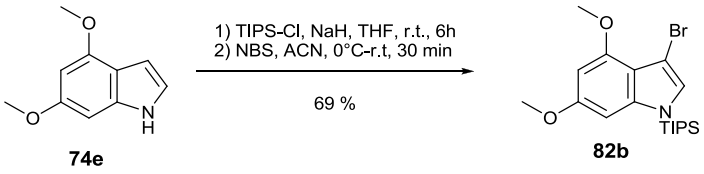

79

*Figure 24. Iodinated 5,7-dibromoindole intermediate in analogue synthesis **79***

A possible reason for the lack of reactivity is the steric interactions from the 7-bromo group which block access for the large TIPS group. A smaller silyl-protecting group was used with better results. The pure iodinated indole **79** was subjected to tert-butyl dimethyl silyl (TBDMS) protection according to the same procedure as for TIPS protection. TBDMS-Cl

yielded 61 % of protected iodoindole **80** after 47 hours reaction time and multiple additions of extra sodium hydride and TBDMS-Cl. The reaction was followed by TLC and showed no starting material left at 47 hours. However, 25 % starting material was recovered after column chromatography, possibly because the TLC sample was too dilute. The total yield over 2 steps was 35 %. This sequence is given in Scheme 69.

Synthesis of 3-Bromo-4,6-dimethoxy-1-triisopropylindole



Scheme 70. Synthesis of 3-Bromo-4,6-dimethoxy-1-triisopropylindole

Iodination of 4,6-dimethoxyindole **74e** with iodine monochloride gave a red/black insoluble material, both in the reaction flask and during work up. Only traces of iodinated product was detected by ^{1}H-NMR and HRMS. Performing the reaction at -45°C did not improve the results. Subjecting the combined crude products to the TIPS protection gave a small amount of non-iodinated *N*-TIPS-indole **81** (Figure 25).

It was decided to try the reversed order of reactions. The protection was preformed first and the iodination on the already protected indole. With *N*-TIPS-indole **81** available, several protocols for iodination were tested according to Table 4. For each test reaction, an aliquot from the reaction was quenched and analysed by TLC and GC-MS after 30 minutes.

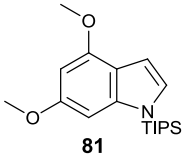
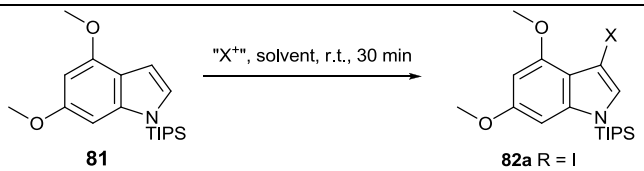


*Figure 25. 4,6-Dimethoxy-N-TIPS-indole **81***

*Table 4. Test scale reaction for iodination of **81***



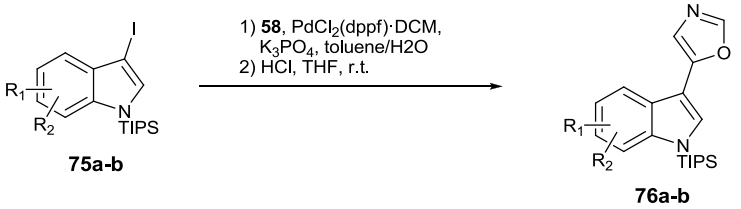
Entry	Halogen source	solvent	Product : s.m.
a	I-Cl (X = I)	Pyridine	1,7:1
b	I_2 (X = I)	Pyridine	1:1
c	1,3-diiodo-5,5-dimethylhydantoin (X = I)	Acetonitrile	-
d	1,3-diiodo-5,5-dimethylhydantoin (X = I)	Acetone	-
e	NBS (X = Br)	Acetonitrile	100 % **82b** (not isolated)

As can be seen from the table, electrophilic iodination can be performed on the *N*-protected dimethoxy indole **81**. I-Cl proceeds faster than I_2 (entry a,b), as could be suspected from the inability of the chloride counter ion to form complexes with the remaining iodine source. The results for 1,3-diiodo-5,5-dimethylhydantoin (DIH) were inconclusive (entry c,d), but deemed unimportant as iodination could be performed with I-Cl. Bromination with NBS was very successful (entry c).

A 200 mg scale iodination with I-Cl for 1 hour using conditions otherwise identical to Scheme 68 gave a crude product with no hydrogen in the 3-position determined by ^{1}H-NMR, but after column chromatography a 1:1 mixture of 3-iodo-*N*-TIPS-indole **82a** and starting material **81** indicating that decomposition of the iodinated species took place within hours.

It was decided to incorporate bromine instead, as it is assumed to be more stable. A test reaction using NBS gave promising results (Table 4, entry e). A 200 mg bromination yielded 69 % over 2 steps of the brominated *N*-TIPS-indole **82b**, which was stable during chromatography. The material was stored at -18^C and a ^{1}H-NMR was performed to assess decomposition after 10 days. The resulting spectrum indicated that 25 % of the material was debrominated. Brominated indole **82b** should therefore not be stored before coupling to the oxazole. The iodinated 5-methoxy indole **70** is also unstable upon storage, and should also be brominated directly before coupling.

4.4 SUZUKI-MIYAURA COUPLING AND SELECTIVE DEPROTECTION



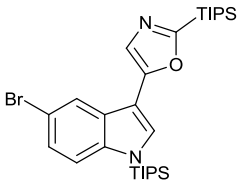
Scheme 71. Synthesis of 5-(N-TIPS-indol-3-yl)oxazoles

The Suzuki coupling of oxazole boronic acid **58** and 3-halo-indoles **75a-b**, **70**, **80** and **82** were, due to time limitations, only performed on the two substrates **75a** and **57b**. The coupling was performed according to the procedure in section 3.5.2, with minor changes. For the 5-bromoindole **75a**, the temperature was reduced to 40°C to minimize selectivity issues with the bromine, requiring a total of 4 hours for the starting material to disappear on TLC, while the temperature was elevated to 60°C for the benzo[g]indole-analogue **75b** requiring only 1 hour. The conditions are outlined in Table 5.

Instead of performing the non-selective deprotection followed by reprotection as described for the total synthesis in section 3.5.2, it was decided to try an acid-based selective deprotection of the 2-TIPS oxazole protective group[81]. This would require two fewer purification steps with column chromatography, one of which on a possibly poorly soluble compound (the completely deprotected indolyl oxazoles **49** and **56** seems to be poorly soluble in most common solvents).

Small scale test reactions from the crude product of the Suzuki-Miyaura coupling were performed trying to deprotect the 2-TIPS oxazole using acidic conditions. Testing were

performed on a two phase system with ethyl acetate and either 10 % citric acid, 1.2 M HCl or 3.2 M H_2SO_4. TLC of the organic phase showed an emerging peak below the peak of the diprotected intermediate **83** in Figure 26. This peak was confirmed by GC-MS to be the monoprotected compound. The same test was performed in a one-phase system with THF and 3M HCl, which ran to completion in 10 minutes. No deprotection of the *N*-TIPS group was observed.

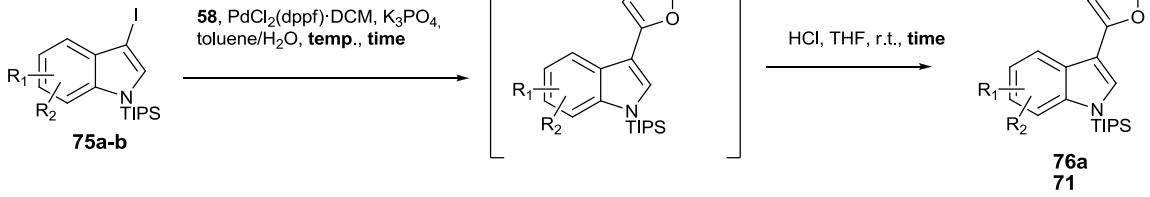


83

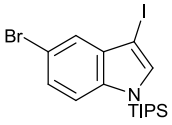
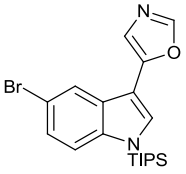
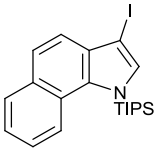
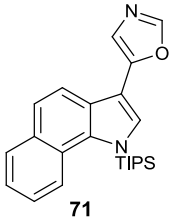
*Figure 26. Di-TIPS intermediate from Suzuki coupling of **75a** and **58***

For a large scale deprotection (4g scale), the crude coupling product **83** was dissolved in THF to a concentration of 0,25M and 2 ml 3M HCl added. Multiple additions of HCl were needed for the reaction to go to completion. Purification by column chromatography yielded 73 % of the monoprotected indolyl oxazole **76a** (Table 5). In addition to this, 11 % starting material **75a** was recovered. The benzo[g]indole **75b** needed less time and acid for the deprotection step to yield monoprotected benzo[g]indolyl oxazole **71** in 83 % yield.

Table 5. Suzuki-Miyaura cross coupling and selective deprotection of Breitfussin analogues



75a-b **76a** **71**

entry	Starting material	Temperature	Time(1)	Time(2)	Product
a	 **75a**	40°C	4h	1h	 **76a** 73 %
b	 **75b**	60°C	1h	10 min	 **71** 83 %

The procedure combining coupling and selective deprotection seems to be the most efficient route to indolyl-oxazoles. Overall yields from this concerted procedure were 73 and 83 %, compared to 52 % over 3 steps for the non-selective deprotection-reprotection procedure (3 column chromatography purifications) and 38 % over 4 steps for the Schöllkopf oxazole synthesis with reprotection (3 column chromatography purifications). Both the latter ones were performed in the total synthesis.

4.5 Synthesis of Iodinated Oxazoles

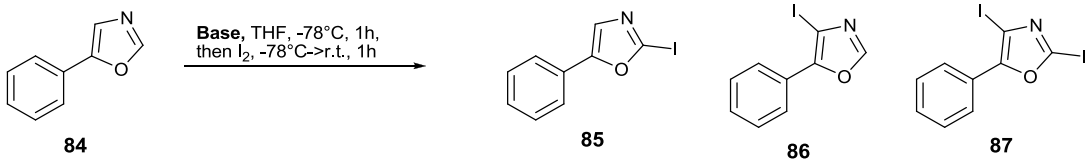
Discouraged by the results of electrophilic iodination of oxazoles in the total synthesis (section 3.6.1), our attention turned to metalation/iodination to introduce iodine on the oxazole in the analogue synthesis. Previous testing had already been performed on the simple substrate 5-phenyl oxazole **84**, trying to reproduce the results of Vedejs, where 4-iodination was archived by LiHMDS/I_2 in THF with DMPU as co-solvent and 2-iodination by LiHMDS/diiodoethane in THF.

4.5.1 Model Studies on 5-phenyl oxazole

Initial tests were performed with LiHMDS/I_2 in THF and gave surprisingly good regioselectivity, up to 15:1 favoring the 2-iodinated oxazole **85** over the 4-iodinated oxazole **86**, contrary to previously reported results (Table 6, entries a,b). Since these test reactions were performed before the total synthesis, the diiodo oxazole was also interesting. While Vedejs regarded the diiodo product undesirable, it would be useful for a one step introduction of two iodines in our project. Observation of the diiodo product **87** in the first reactions (entries a,b) spurred testing of two equivalents of base, which gave a 2:1 ratio of diiodinated product to the mono-iodinated product. The regioselectivity of the remaining mono-iodinated product increased compared to the use of 1 equivalent of base. This is expected since the 2-position is more reactive towards the next iodine, removing the remaining 4-monoiodinated oxazole **85**. Use of sodium hexamethyldisilazane (NaHMDS) reversed the regiochemistry, making the two bases complementary for regioselective iodination.

This provides a route to regioselectively 5-substituted oxazole monoiodination. A simple procedure for this transformation is unprecedented in literature. The diiodination is previously described in good yields, but the reaction requires a fortnight[53]. A study of scope and limitations should be performed to prepare a manuscript for publication.

*Table 6. Iodination of 5-phenyl oxazole **84***



84 **85** **86** **87**

Entry	Base	Isolated yields	ratio 2-I/4-I	ratio mono-I/di-I
a	LiHMDS (1,1 eq)	NA	4,8 : 1	3,9 : 1
b	LiHMDS (1,1 eq)	NA	15 : 1	6,5 : 1

c	LiHMDS (2,2 eq)	18 % **85**, 27 % **87**	37 : 1	1 : 2
d	NaHMDS (1,1 eq)	75 % **86**, 17 % **87**	1 : 28	11 : 1

The three different products were isolated from the reactions described in entry c and d (Table 6) and the regiochemistry was assigned. The relevant spectral regions of the monoiodinated oxazoles are given in Figure 27. The 2-H of 4-iodo oxazole **86** is found at 7.90 ppm, while the 4-H of 2-iodo oxazole **85** is found at 7.29 ppm. The phenyl peaks are shifted downfield for 4-iodo oxazole **86** compared to the 2-iodo regioisomer **85**. From either spectrum the minor isomer is observed.

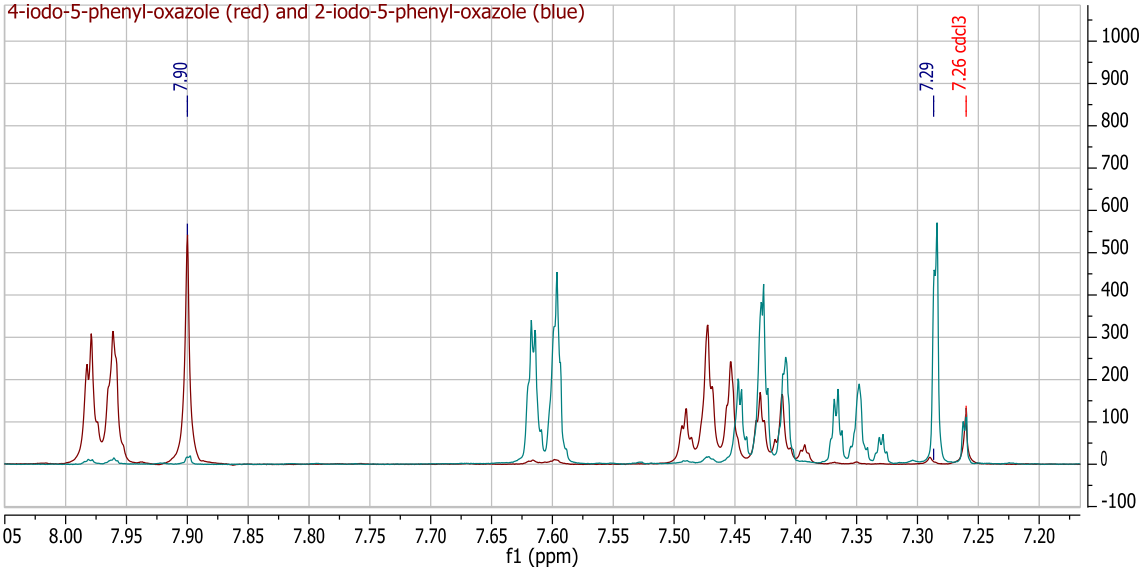


*Figure 27. 2-iodo oxazole **85** (blue) and 4-iodo oxazole **86** (red)*

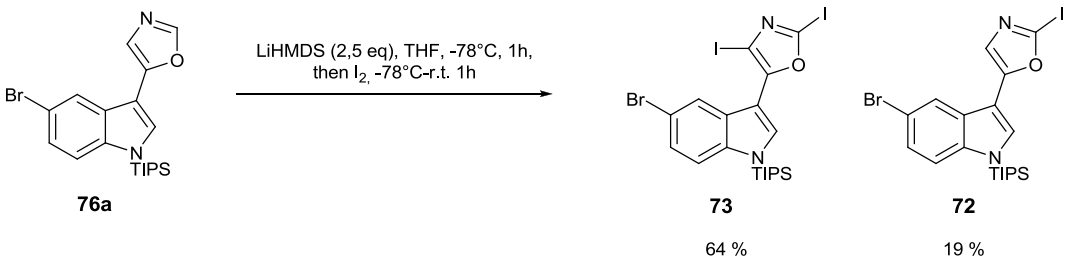
4.5.2 Application of metalation/iodination to indolyloxazole 76a

The initially planned library of Breitfussin analogues included only 4-unsubstituted oxazoles. A series of test reactions similar to those presented in Table 6 above were performed and analyzed by GC-MS. However, the method used for eluting the compounds used high temperatures that gave a heightened baseline because polysiloxanes leaked from the column. In addition the diiodinated product was too non-volatile to elute from the column within reasonable time and temperature. The regioselectivity information is therefore compromised and the ratios of diiodinated to monoiodinated product is nonexistent. It is still possible to ascertain that the main regioisomers of the monoiodinated products follow the same pattern as for the simple substrate 5-phenyl oxazole **84**, with LiHMDS giving 2-iodination and NaHMDS giving 4-iodination.

TLC analysis indicated presence of both starting material **76a**, monoiodinated product **72** and diiodinated product **73**. The exceptions to this are for reactions with more than 1,1 equivalents of base and iodine. In these cases no starting material was present. These studies will be repeated using HPLC analysis to yield correct ratios.

With the lack of information on regioselectivity a decision was made to make a large batch of diiodinated oxazole **73** to prepare some 4-iodinated compounds for the library. Deprotonation of oxazole **76a** with 2,5 equivalents of freshly prepared LiHMDS at -78°C

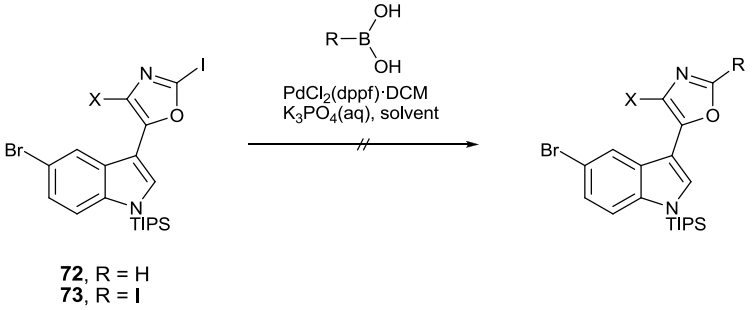
with iodine quench on a 0,8 g scale gave 64 % diiodinated oxazole **73** along with 19 % 2-iodinated oxazole **72** after separation by column chromatography.



*Scheme 72. Synthesis of 5-(5-bromo-indol-3-yl)-2,4-diiodooxazole **73***

An alternative way of making 2-iodinated oxazoles is the iododesilylation of disilylated compounds like **60** or **83** (see section 3.6.1), which would be selective for the 2-position. A reliable protocol is required for this.

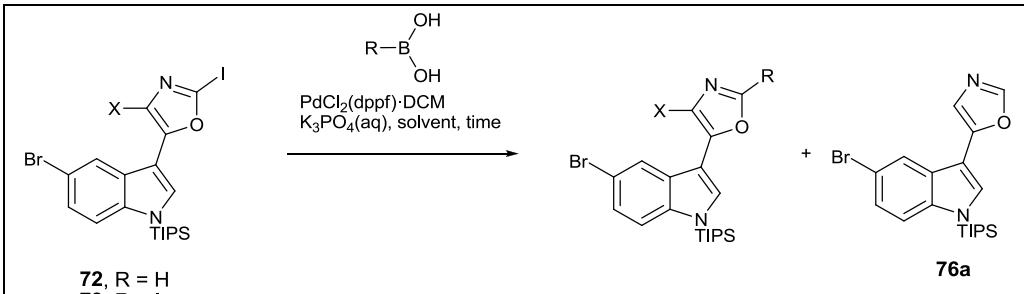
4.6 ATTEMPTED SUZUKI-MIYAURA REACTIONS



Scheme 73. Attempted Suzuki-Miyaura reactions

Due to limited time, only a few experiments were attempted on coupling boronic acids to the newly formed iodinated oxazoles **72** and **73**, using the same procedure as for the Suzuki-Miyaura coupling of the model substrate **62** of the total synthesis in section 3.6.2. The results are summarized in Table 7. A toluene/water two phase system was initially tested, but as no reaction was observed, THF was added (which immediately gave the characteristic black color of Pd^0). After 16 hours at 75°C no reaction was observed in entry b, but for entry a 55 % of deiodinated oxazole **76a** was isolated along with 34 % starting material. Using only THF/water gave no reaction (entry c). Due to solubility problems with 2-iodinated oxazole **72** in toluene, dioxane/water was used (entry d), but no reaction was observed. To find suitable conditions a solvent and ligand screen will be performed.

*Table 7. Attempts on Suzuki-Miyaura reactions on iodinated oxazoles **72** and **73***



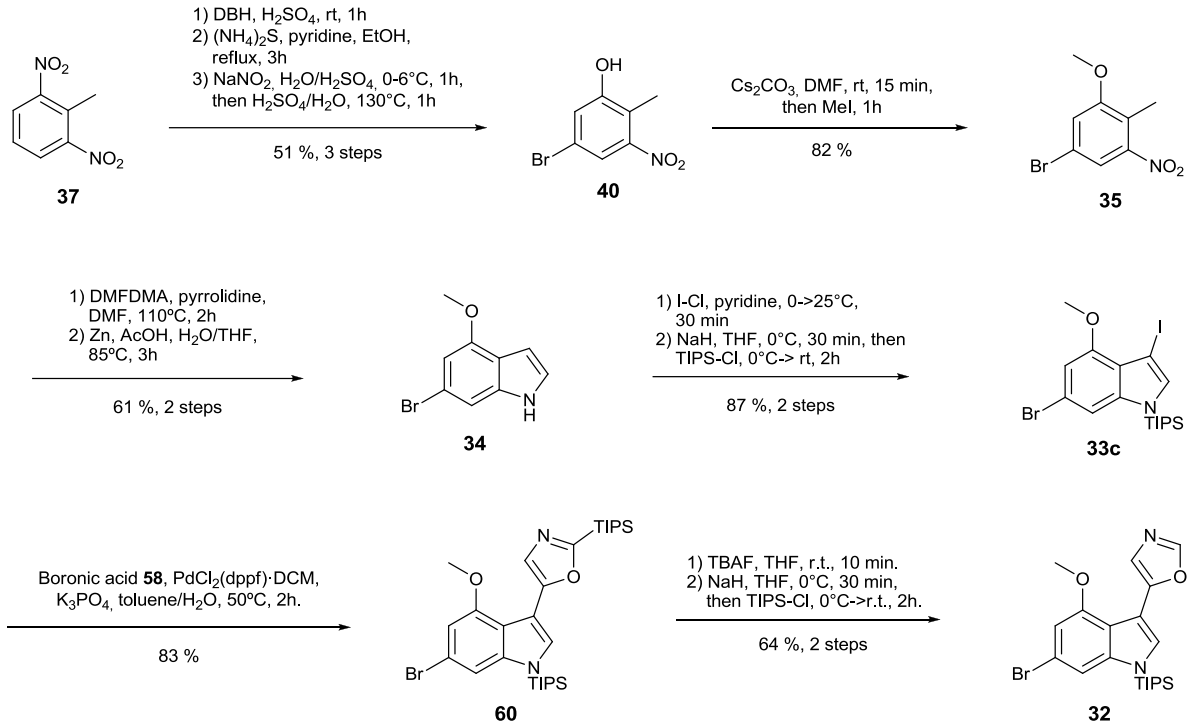
72, R = H
73, R = I

76a

Entry	Starting material	R	Temperature	Time	Solvent	Product
a	**73**	*N*-Boc-pyrrole (MIDA ester)	75°C	16h	Toluene/THF/H_2O	**76a** 55 %
b	**73**	2-thionyl	75°C	16h	Toluene/THF/H_2O	NR
c	**73**	2-furanyl	75°C	1h	THF/H_2O	NR
d	**72**	2-furanyl	75°C	16h	dioxane/H_2O	NR

5 CONCLUSION

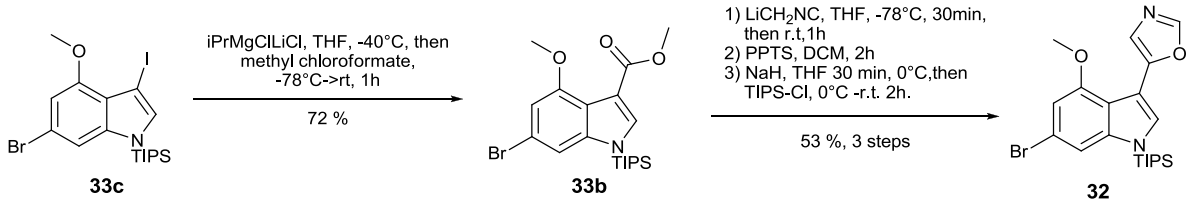
The first part of this thesis (Chapter 3) describes my efforts towards the total synthesis of Breitfussin A. The synthesis of the late stage intermediate indolyl-oxazole **32** was performed in 11 steps from the commercially available starting material 2,6-DNP **37** in 12 % total yield. The whole strategy was successfully tested on a model compound with an unsubstituted indole, except the final deprotection of the model compound, which is currently not successfully executed.



*Scheme 74. Summary of the synthesis of late stage intermediate **32** in the total synthesis of Breitfussin A (**1**)*

Synthesis of the indole **34** proceeded as planned using the Leimgruber-Batcho reaction. Further functionalization gave the iodinated indole **33c** which was used in a Suzuki-Miyaura cross coupling to introduce the oxazole of Breitfussin A. The coupling product **60** was deprotected and reprotected to give the 5-substituted oxazole **32**.

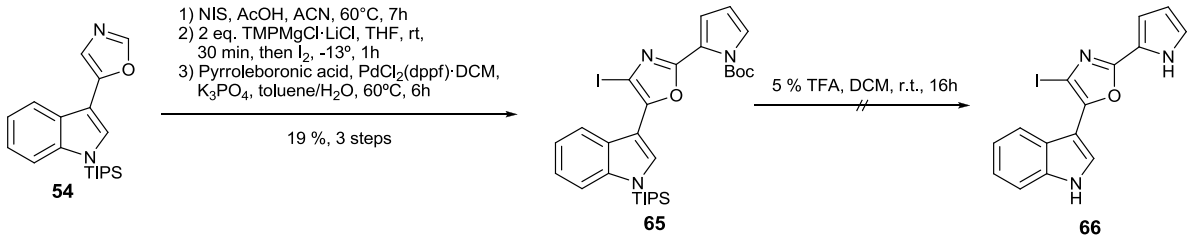
The iodinated indole **33c** was also used in the Schöllkopf approach for making the oxazole (Scheme 75). This approach was longer and the yields were lower than for the cross-coupling approach (53 % in 3 steps compared to 38 % in 4 steps).



Scheme 75. Summary of the Schöllkopf approach to oxazole 32

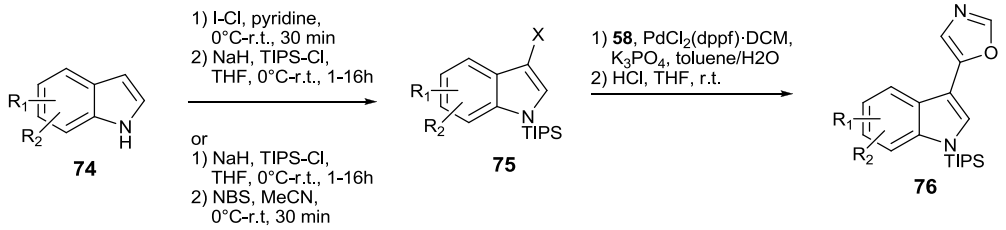
Iodination of model oxazole **54** proceeded smoothly via EAS to the 4-iodinated oxazole, then using TMPMgCl·LiCl to give the diiodinated oxazole. For the total synthesis this did

not perform to par, and the focus will be directed towards a metalation approach to introduce both iodines. Regioselective cross-coupling of the diiodinated oxazole model compound did work, but the final deprotection is not yet successfully executed.



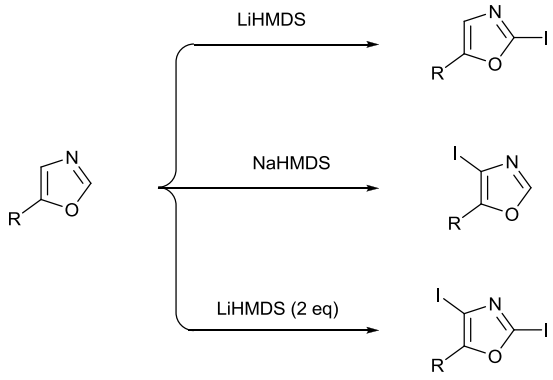
Scheme 76. Summary of model studies on late steps

The second part of the thesis (Chapter 4) describes the procedure of making a library of Breitfussin analogues using the general strategy of the total synthesis.



Scheme 77. Summary of Breitfussin analogue synthesis

Commercially available indoles with different substitution patterns **74** were subjected to the iodination-protection sequence or an alternative protection-bromination sequence (for electron rich indoles) to yield iodinated indoles **75** (5 compounds made). Introduction of the oxazole was done using the Suzuki-Miyaura approach. A procedure for selective desilylation to compounds **76** was developed and performed in higher yields, less steps and less chromatography than the deprotection-reprotection sequence of the total synthesis (2 compounds made). In this part is also described the discovery of a regioselective iodination procedure for oxazoles (Scheme 78) and its application to derivate synthesis (2 compounds made).



Scheme 78. Summary of regioselective iodination procedure

Further work on these projects are ongoing. Priority is given to complete the total synthesis. A procedure for metalation/iodination is developed for the analogue synthesis which will be tested on the total synthesis. A screen for different ligands and solvents for the last cross-

coupling will be performed on model compounds (intermediates in the analogue synthesis) to determine optimal conditions before applying it to the total synthesis. Optimized procedures and tactics developed during the analogue synthesis will be applied to the total synthesis.

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7 EXPERIMENTAL PROCEDURES

All reagents were purchased from Sigma Aldrich Co. and used as received. Dry THF was obtained from a sodium/benzophenone still or from water free bottles under inert gas. All glassware used under inert conditions were heated in oven at 130°C or with torch before use. Column chromatography was performed using silica gel 35-70 micron from Grace GmbH. Reactions monitored by TLC was run on 60 F254 silica gel plates and visualized with UV and stains.

NMR spectra were recorded on Varian Mercury-400 plus or Varian Mercury-400 Oxford NMR spectrometers. Chemical shift values (δ) are reported in parts per million (ppm) relative to tetramethylsilane. All NMR spectra were processed with MestReNova v7.1.1. Some ^{13}C-NMR spectra from the early model studies have noises in a repeating pattern originating from an unknown radio transmitter.

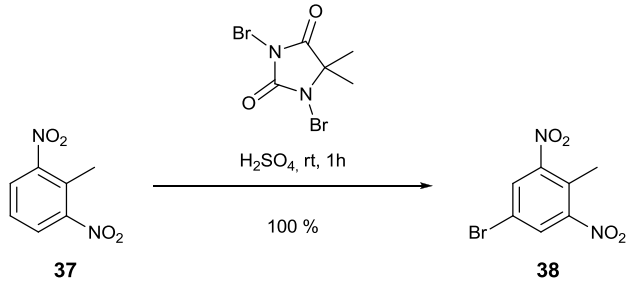
GC-MS chromatograms were recorded on a Thermo Scientifinc Trace GC Ultra with a Thermo Scientific ITQ 1100 detector. HPLC measurements were performed on an Agilent 1100 series. HRMS spectra were recorded LTQ Orbitrap XL in positive or negative electrospray ionization (ESI) mode. IR spectra were obtained on a Varian 7000e FT-IR spectrometer. Absorptions are given in reciprocal centimetres and the intensity and line shape is described (w = weak intensity, m = medium intensity, br = broad peak). Microwave irradiation was carried out in a Biotage initiator microwave synthesizer.

For the intermediates in the total synthesis, HPLC and HRMS analysis is performed for all compounds where HRMS data is given. These spectra are not included in the thesis, because they were not sent to Tromsø from MPI Dortmund in time for submission.

7.1 TOTAL SYNTHESIS OF BREITFUSSIN A (CHAPTER 3)

7.1.1 Synthesis of Indole Fragment (section 3.3)

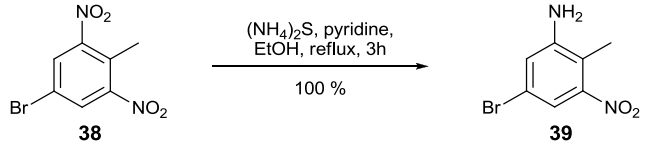
7.1.1.1 5-Bromo-2-methyl-1,3-dinitrobenzene



37 **38**

2,6-Dinitrotoluene **37** (20.5 g, 113 mmol) was suspended in concd. H_2SO_4 (80 mL) and 1,3,-dibromo-5,5-dimethylhydantoin (17.56 g, 60.8 mmol) was added portionwise to the mixture over 10 min. The reaction was initially exothermic leading to dissolution of the solid before the formation of a yellow precipitate. The heterogeneous mixture was stirred at RT for 1 h before it was poured onto 600 ml ice/water slurry. The pale yellow solid was collected and dried in vacuo to give 5-bromo-2-methyl-1,3-dinitro-benzene **38** (29.4 g, 100 %). **m.p.**: 85-86°C. **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 8.12 (s, 2H), 2.52 ppm (s, 3H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 152.09, 130.67, 126.38, 120.14, 14.89.

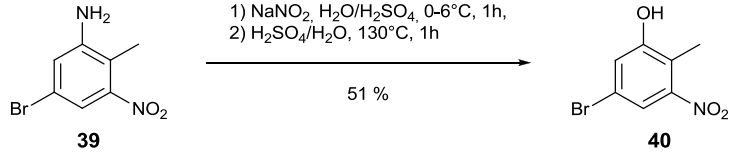
7.1.1.2 5-Bromo-2-methyl-3-nitroaniline



38 **39**

5-Bromo-2-methyl-1,3-dinitrobenzene **38** (29.38 g, 113 mmol) was dissolved in 2 equal batches each of 250 ml ethanol in 500 ml three necked flasks. 2x 22 ml (0.55 mol) pyridine was added and heated to reflux for 1h. 45 % aqueous Ammonium sulfide (2x 25 ml, 0.35 mol) diluted in 2x 75 ml water was added over 1h. The mixture was reacted at reflux for 2h before cooling to r.t. The reaction mixtures was poured into 500 ml ice slurry. The bright yellow precipitate was collected and dried in vacuo to yield 5-bromo-2-methyl-3-nitroaniline **39** (26.0 g, 100 %). **m.p.**: 118-119°C. **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 7.28 (d, 1H, J = 1.6), 6.99 (d, 1H, J = 1.5), 3.97 (bs, 2H), 2.18 (s, 3H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 147.6, 120.8, 119.7, 116.6, 115.1, 112.5, 12.6. **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_7H_8O_2N_2Br$ 230.97637; found 230.97658.

7.1.1.3 5-Bromo-2-methyl-3-nitrophenol

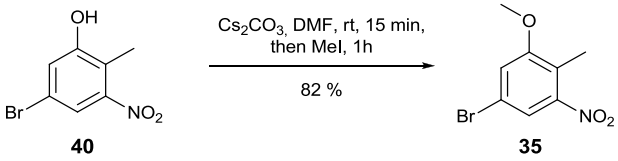


39 **40**

5-Bromo-2-methyl-3-nitroaniline **39** (32.14 g, 139 mmol) was suspended in 170 ml 30 % sulfuric acid and cooled to 0°C on ice bath. Sodium nitrite (10.7 g, 155 mmol) in 40 ml water was added via an addition funnel while keeping the temperature below 6°C. The

reaction was stirred at 0°C for 1h before being transferred via a plastic cannula to a solution of 60 % H_2SO_4 in water (225 mL) at 130°C. An initial drop in the internal temperature of the reaction was observed (110 °C) during the addition, heating was continued until the internal temperature returned to 130°C. The reaction was cooled, poured on ice (1L), and extracted with tert-butylmethyl ether. The organic phase was washed in water and brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The solid was purified by chromatography with DCM to give 5-bromo-2-methyl-3-nitro-phenol **40** as a dark orange-red solid (16.6 g, 51 %). **m.p.**: 133-135°C. **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 7.57 (d, 1H, J = 1.87) 7.17 (d, 1H, J = 2.00), 5.54 (s, 1H), 2.34 (s, 3H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 155.7, 122.3, 119.8, 116.5, 119.2, 11.6. (No peak observed for C-3).

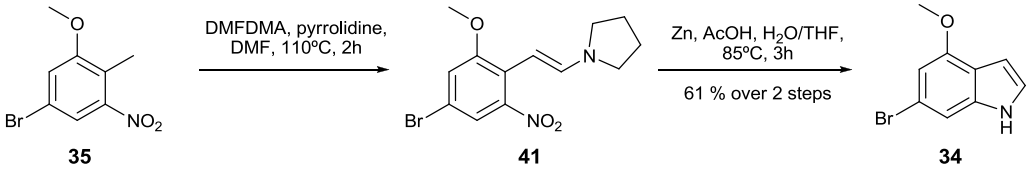
7.1.1.4 5-bromo-1-methoxy-2-methyl-3-nitrobenzene



40 **35**

5-Bromo-2-methyl-3-nitrophenol **40** (16.55 g 71.3 mmol) and Cs_2CO_3 (34.8 g, 107 mmol) were dissolved in 60 ml DMF. The reaction mixture was left for 15 min before drop-wise addition of methyl iodide (4.9 ml, 78.4 mmol) under evolution of heat. The reaction mixture was stirred for 1h before it was poured into an ice slurry (1L). The precipitate was filtered, dissolved in chloroform (250 ml) and extracted with water (100 ml) and brine (100 ml). The organic phase was dried with $MgSO_4$ and evaporated in vacuo. The solids (15.05 g) were recrystallized in 90 % ethanol in water to yield brown crystals (13.77 g). The mother liquor was evaporated and purified by chromatography (2 % EtOAc in pentane) to yield 0.69 g and a total of 15.46 g (82 %) of 5-bromo-1-methoxy-2-methyl-3-nitrobenzene **35**. **m.p.** 87.7-89.3°C. **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 7.55 (d, 1H, J = 1.8), 7.14 (d, 1H, J = 1.5), 3.89 (s, 3H), 2.29 (s, 3H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 159.2, 121.6, 119.6, 118.9, 117.4, 56.8, 11.6. (No peak observed for C-3).

7.1.1.5 6-Bromo-4-methoxy-1H-indole



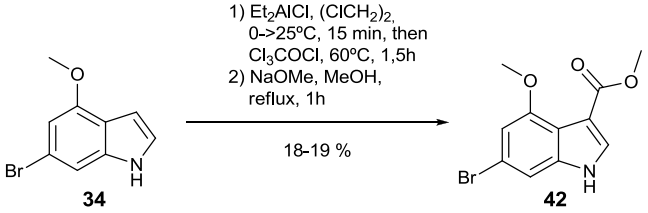
35 **41** **34**

5-bromo-1-methoxy-2-methyl-3-nitrobenzene **35** (4.54 g, 18,5 mmol) was dissolved in 40 ml DMF. DMFDMA (7.3 ml, 55.4 mmol) and pyrrolodine (2.4 ml, 29.5 mmol) were added by syringe. The mixture was stirred at 110°C for 2h then cooled to r.t, poured into ether and washed with water (3x 50 ml). The aqueous phase was extracted with ether (3x 50 ml). The combined organic phases were predried with brine and dried with Na_2SO_4 before evaporation in vacuo. The resulting deep red oil (intermediate **41**) was dissolved in 10 ml THF and added slowly to a suspension of zinc powder (9.7 g, 148 mmol) in 125 ml 80 % acetic acid in water at 75°C. The reaction mixture was stirred at 85°C for 3h before cooling to r.t. 200 ml water was added and extracted with EtOAc (3x 75 ml). The organic phase was washed with water (2x 50 ml), then added 200 ml water and Na_2CO_3 until gas evolution ceased. The phases were separated and the organic phase washed with brine and dried with

$MgSO_4$. The solvent was evaporated and the resulting brown solid was purified by chromatography (SiO_2, 10-16 % EtOAc in cyclohexane) to yield 2.54g (61 %) 6-Bromo-4-methoxy-1H-indole **34** as a light brown solid. **m.p.** 69-70°C. **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 8.13 (bs, 1H), 7.18 (t, 1H, J = 1.1 Hz), 7.06 (m, 1H), 6.65 (d, 1H, J = 1.31), 6.62 (m, 1H), 3.94 (s, 3H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 153.8, 137.6, 123.2, 117.9, 115.9, 107.7, 104.1, 100.4, 55.8. **HRMS** (ESI) m/z: $[M+H]^+$ calcd. for C_9H_9NOBr 225.98620 found: 225.98639.

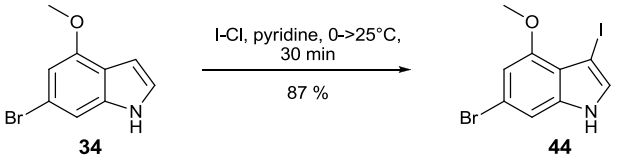
7.1.2 Functionalization of Indole (section 3.4)

7.1.2.1 Methyl 6-bromo-4-methoxy-indole-3-carboxylate



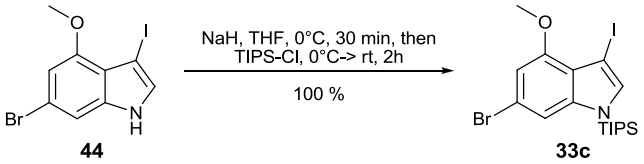
6-Bromo-4-methoxy-1H-indole **34** (1.00g, 4.42 mmol) was dissolved in 7 ml 1,2-dichloroetane. Diethyl aluminium chloride (1M in heptane, 4.64 ml, 4.64 mmol) was added drop-wise at 0°C and allowed to reach room temperature for 15 min before addition of trichloroacetyl chloride (0.59 ml, 5.31 mmol) in 3 ml 1,2-dichloroetane. The resulting black mixture was heated to 60°C for 1.5h, allowed to cool and quenched in a 100 ml mixture of 1M HCl and ice. The aqueous suspension was extracted with 3x50 ml ethyl acetate and the organic phase was washed with 50 ml saturated $NaHCO_3$, 50 ml brine, dried with $MgSO_4$ and evaporated. The residue was dissolved in methanol and added sodium methoxide (185 mg, 3.42 mmol). The solution was heated to reflux for 1h, cooled to room temperature, partitioned between chloroform and saturated sodium bicarbonate. The organic phase was dried with $MgSO_4$ and evaporated. The residue was purified by chromatography on silica with 20 % ethyl acetate in toluene to yield 230 mg (18 %) methyl 6-bromo-4-methoxy-indole-3-carboxylate **42** as a black solid. **m.p.**: 166-168. **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 8.97 (bs, 1H), 7.76 (d, 1H, J = 2.9), 7.17 (d, 1H, J = 1.4), 6.75 (d, 1H, J = 1.4), 3.93 (s, 3H), 3.87 (s, 3H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 164.7, 154.7, 138.8, 131.4, 117.4, 114.7, 109.5, 108.2, 107.0, 56.3, 51.7. **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{11}H_{11}O_3NBr$ 283.99168; found 283.99199.

7.1.2.2 6-bromo-3-iodo-4-methoxy-indole

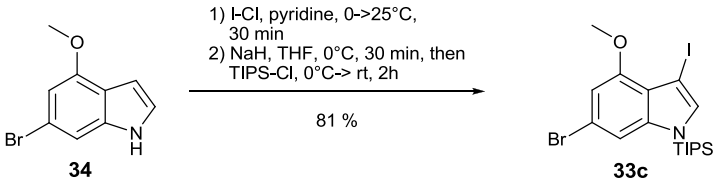


6-Bromo-4-methoxy-1H-indole **34** (2.00g, 8.85 mmol) was dissolved in 5 ml pyridine. Iodine monochloride (1M in DCM, 9.83 ml, 9.83 mmol) was added drop-wise at 0°C. The reaction mixture was stirred 15 min at 0°C then 1h at room temperature. The reaction was poured onto a mixture of water and ice and 1N HCl was added to pH 5. The aqueous suspension was extracted with ethyl acetate 3x50 ml, washed with 50 ml sodium thiosulfate, 50 ml water and 50 ml brine. The organic phase was dried with $MgSO_4$ and evaporated. The residue was dissolved in 4 ml ethyl acetate and filtered through a plug of silica (ethyl acetate eluent) to yield 2.72 g (87 %) 6-bromo-3-iodo-4-methoxy-indole **44** as a dark red solid. **m.p.**: 124°C (dec.). **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 8.26 (bs, 1H), 7.16 (d, 1H, J = 0.9), 7.14 (d, 1H, J = 2.3), 6.64 (d, 1H, J = 1.0), 3.92 (s, 3H). **^{13}C-NMR** ($CDCl_3$, 140 MHz): δ 154.1, 137.9, 128.8, 117.4, 116.8, 107.8, 105.2, 55.8, 51.2. **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for C_9H_8ONBrI 351.88285; found 351.88257.

7.1.2.3 6-bromo-3-iodo-4-methoxy-1-(triisopropylsilyl)-indole

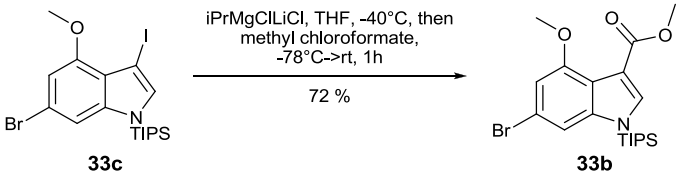


A: Sodium hydride (270 mg, 11.3 mmol) was added to a flame dried 100ml round bottom flask and suspended in 15 ml dry THF. 6-bromo-3-iodo-4-methoxy-indole **44** (2.64 g, 7.49 mmol) in 15 ml THF was added drop-wise over 5 min at 0°C and left for 30 min. Triisopropylsilyl chloride (2.4 ml, 11.3 mmol) was added drop-wise at 0°C. The reaction mixture was reacted for 1h at room temperature and quenched by slow addition of water before extraction with ethyl acetate 3x 50 ml. The organic phase was washed with brine, dried with $MgSO_4$ and evaporated. The residue was filtered through a plug of silica with cyclohexane to yield 3.95 g (100 %) of 6-bromo-3-iodo-4-methoxy-1-(triisopropylsilyl)-indole **33c** as a white solid.



B: 6-Bromo-4-methoxy-1H-indole **34** (3.89 g, 17.2 mmol) was dissolved in 10 ml pyridine. Iodine monochloride (1M in DCM, 18.9 ml, 18.9 mmol) was added drop-wise at 0°C. The reaction mixture was stirred 15 min at 0°C then 1h at room temperature. The reaction was poured onto a mixture of water and ice and 1N HCl was added to pH 2. The aqueous suspension was extracted with ethyl acetate 3x50 ml, washed with 50 ml sodium thiosulfate, 50 ml water and 50 ml brine. The organic phase was dried with $MgSO_4$ and evaporated to dryness and used directly in the next step. Sodium hydride (540 mg, 22.4 mmol) was added to a flame dried 100ml round bottom flask and suspended in 25 ml dry THF. The dried crude was dissolved in 20 ml THF and added drop-wise over 5 min at 0°C and left for 30 min. Triisopropylsilyl chloride (4.8 ml, 22.4 mmol) was added drop-wise at 0°C. The reaction mixture was reacted for 1h at room temperature and quenched by slow addition of water before extraction with ethyl acetate 3x 50 ml. The organic phase was washed with brine, dried with $MgSO_4$ and evaporated. The residue was filtered through a plug of silica with cyclohexane to yield 7.11 g (81 %) 6-bromo-3-iodo-4-methoxy-1-(triisopropylsilyl)-indole **33c** as a white solid. **m.p.**: 111-112°C. **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 7.24 (m, 1H), 7.13 (s, 1H), 6.65 (d, 1H, J = 1.2 Hz), 3.91 (s, 3H), 1.62 (sept, 3H, J = 7.5 Hz), 1.13 (d, 18H, J = 7.5 Hz). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 153.8, 142.8, 135.6, 120.3, 116.1, 110.4, 105.3, 55.7, 53.3, 18.2, 13.0. **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{18}H_{27}ONBrISi$ 507.00845; found 507.00852.

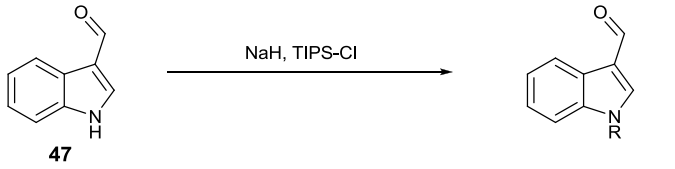
7.1.2.4 Methyl 6-bromo-4-methoxy-1-(triisopropylsilyl)-indole-3-carboxylate



6-bromo-3-iodo-4-methoxy-1-(triisopropylsilyl)-indole **33c** (1.07 g, 2.01 mmol) was dissolved in 8 ml dry THF and cooled to -40°C in an acetone/dry ice bath before drop-wise addition of isopropyl magnesium chloride lithium chloride complex (1.3 M in THF, 1.78 ml, 2.32 mmol). The reaction mixture was stirred 30 min at -40°C then cooled to -78°C. Methyl chloroformate (203 µl, 2.63 mmol) in 1 ml THF was added drop-wise and reacted at -78°C for 15 min. The reaction mixture was heated to room temperature and stirred for 1h before quenching be addition to 100 ml water with 2.7 g EDTA. The aqueous phase was extracted with 3x50 ml ethyl acetate and washed with 50 ml water and 50 ml brine. The organic phase was dried with $MgSO_4$ and evaporated. The residue was purified by flash chromatography on silica with 7-15 % ethyl acetate in cyclohexane to yield 661 mg (72 %) methyl 6-bromo-4-methoxy-1-(triisopropylsilyl)-indole-3-carboxylate **33b** as a yellow oil. **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 7.79 (s, 1H), 7.24 (d, 1H, J = 1.4), 6.78 (d, 1H, J = 1.3), 3.96 (s, 3H), 3.86 (s, 3H), 1.67 (sept., 3H, J = 7.5), 1.15 (d, 18H, J = 7.5). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 164.7, 154.6, 143.7, 138.4, 117.6, 116.8, 111.3, 110.5, 107.1, 56.3, 51.6, 18.2, 12.9. **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{20}H_{31}O_3NBrSi$ 440.12511; found 440.12525.

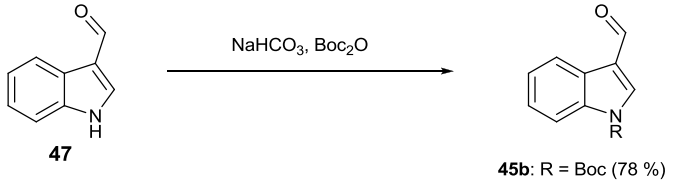
7.1.3 Oxazole Synthesis (section 3.5)

7.1.3.1 1-triisopropylsilyl-indole-3-carboxaldehyde



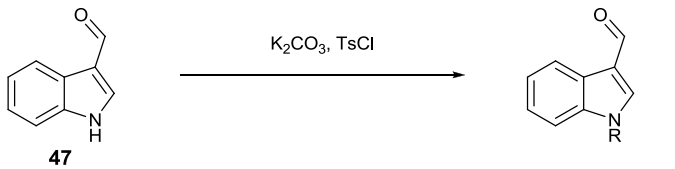
Indole-3-carboxaldehyde (0.50 g, 3.41 mmol, 1 eq) was dissolved in 12 ml dried THF. 60 % NaH (0.15 g, 3.76 mmol, 1.11 eq) was added to the solution at 0°C under evolution of gas. The colour changed to pale red. After 5 minutes TIPS-Cl (0.95 ml, 4.44 mmol, 1.3 eq) was added drop-wise. The colour changed gradually to yellow, then green. After 30 minutes the reaction was quenched with ice. The mixture was extracted with EtOAc (x3) and the combined organic phase was dried with Na_2SO_4. The solvent was evaporated and the resulting solid was filtered through a plug of silica to yield 1-triisopropylsilyl-indole-3-carboxaldehyde **45a** as a white solid in 94 % yield. **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 10.06 (s, 1H), 8.30 (dd, 1H, J = 1.8, 7.6 Hz), 7.87 (s, 1H), 7.50 (dd, 1H, J = 1.4, 8.0 Hz), 7.23-7.29 (m, 2H), 1.72 (sept., 3H, J = 7.5 Hz), 1.15 (d, 18H, J = 7.6 Hz), 1.04 (s, 11H, imp.). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 185.1, 143.2, 141.8, 127.5, 123.8, 122.8, 121.9, 121.5, 114.1, 18.0, 12.6. **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{18}H_{28}ONSi$ 302.1935, found 302.1940.

*7.1.3.2 1-(*tert*-butoxycarbonyl)-indole-3-carboxaldehyde*



Indole-3-carboxaldehyde (1.19 g, 8.16 mmol, 1 eq) and sodium bicarbonate (2.73 g, 32 mmol, 4 eq) was dissolved in 23 ml acetonitrile before addition of di-*tert*-butoxy-dicarbonate (1.97 g, 9.03 mmol, 1.1 eq). The solution was stirred at r.t. for 16 hours before additional di-*tert*-butoxy-dicarbonate (3.44 mmol, 0.75 g, 0.48 eq) was added and stirred for 4 additional hours. The solvent was evaporated under reduced pressure and the resulting residue was dissolved in ethyl acetate, washed with 1M HCl, 1M NaHSO4 and dried with brine. Purification on column (10 % EtOAc in pentane) yielded the pure 1-(*tert*-butoxycarbonyl)-indol-3-carboxaldehyde **45b** (1.56 g, 6.36 mmol, 78 %) as a white solid. **m.p.**: 124-125°C. **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 10.07 (s, 1H), 8.27 (dd, 1H, J = 1.5, 6.9 Hz), 8.20 (s, 1H), 8.13 (d, 1H, J = 8.4 Hz), 7.36 (m, 2H), 1.70 (s, 9H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 185.7, 148.8, 136.5, 135.9, 126.1, 126.0, 124.6, 122.1, 121.5, 115.1, 85.6, 28.1. **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{14}H_{16}NO_3$ 246.1125, found 246.1123.

7.1.3.3 1-tosyl-indole-3-carboxaldehyde

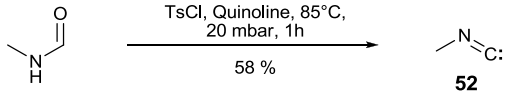


Indole-3-carboxaldehyde (6.89 mmol, 1.00 g, 1 eq) and *p*-tosyl chloride (7.58 mmol, 1.44 g, 1.1 eq) were suspended in 40 ml DCM containing potassium carbonate (19 mmol, 2.44 g, 2.76 eq) and stirred at room temperature for 5 days. The remaining carbonate was washed off with water (25 ml x2). The aqueous phase was extracted with ethyl acetate (25 ml x3). The combined organics were dried with Na_2SO_4 and evaporated under vacuum. Recrystallization from acetone/pentane yielded 1-tosyl-indole-3-carboxaldehyde **45c** as pale yellow crystals (5.49 mmol, 1.65 g, 80 %). **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 10.09 (s, 1H), 8.24 (m, 2H), 7.95 (d, 1H, J = 8.2 Hz), 7.85 (d, 2H, J = 8.1 Hz), 7.38 (m, 2H), 7.29 (d, 2H, J = 8.4 Hz), 2.37 (s, 3H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 185.3, 146.8, 146.1, 135.2, 134.3, 130.3, 127.2, 127.0, 126.3, 125.0, 122.6, 122.3, 113.2, 21.7. **HRMS** (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{16}H_{13}NO_3SNa$ 322.0508, found 322.0513.

7.1.3.4 General procedure for TosMIC reactions

The appropriate indole-3-carboxaldehyde (1 eq), TosMIC (1.2 eq) and base are dissolved in the appropriate solvent and heated at the designated temperature for the appropriate time. The reaction mixture is filtered and evaporated when ambersep is used as base. For K_2CO_3 the reaction mixture is partitioned between water and EtOAc and extracted with EtOAc (x2). The combined organic phases are dried with Na_2SO_4 and evaporated.

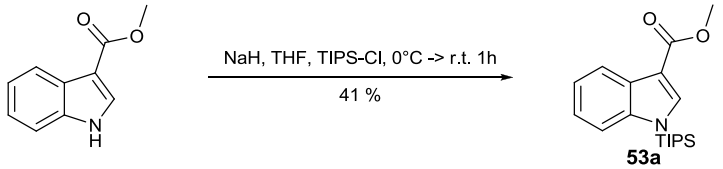
7.1.3.5 Methyl isocyanide



52

p-Tosyl chloride (98 g, 0.51 mol) was dissolved in Quinoline (162 ml, 1.37 mol) in a 500 ml three necked flask and heated to 85°C. A distillation head was connected and coupled to a membrane pump at 20 mbar before drop-wise addition of *N*-methyl formamide (20 ml, 0.34 mol) over 20 min. The distillate was collected in a liquid nitrogen bath in a heart shaped flask and an additional cooling trap. The combined yellow liquid was distilled in a vigreux column at atmospheric pressure. 8.04 g (58 %) of methyl isocyanide **52** as a colorless liquid was obtained at 61°C. **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 3.11 (t, J = 2.18). **^{13}C-NMR** ($CDCl_3$, 100 MHz): 157.0 (t, J = 6.31 Hz), 27.1, (t, J = 7.69 Hz) (Quadrupolar coupling to ^{14}N)

7.1.3.6 Methyl N-*triisopropylsilyl-indole-3-carboxylate*

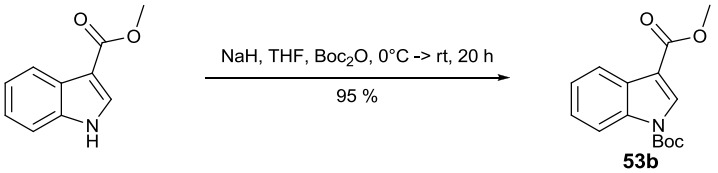


53a

Methyl indole-3-carboxylate (7.07 g, 40 mmol) was dissolved in 50 ml dry THF and cooled to 0°C. Sodium hydride (1.00 g, 42 mmol) was added portion wise over 15 min. The reaction mixture was stirred for 1h at 0°C before drop-wise addition of triisopropyl chloride (9.0 ml, 42 mmol). The reaction was stirred at 0°C for 3 hours then 1h at r.t. The reaction was quenched with100 ml water and extracted with 3x50 ml EtOAc, then washed with 50 ml water and 50 ml brine, dried with Na_2SO_4 and evaporated to dryness. The colorless oil was purified by chromatography on silica with 3 % EtOAc in pentane and recrystallized from methanol to yield 5.40 g (16.3 mmol, 41 %) methyl *N*-triisopropylsilyl-indole-3-

carboxylate **53a** as white crystals. **m.p.**: 175-179°C. **^{1}H-NMR** ($CDCl_3$, 400 Mhz): δ 8.19 (dd, 1H, J = 1.1, 8.6 Hz) 7.97 (s, 1H), 7.52 (d, 1H, J = 8.6 Hz), 7.26 (dt, 1H, J = 0.88, 8.28 Hz), 7.21 (dt, 1H, J = 1.20, 8.20 Hz), 3.92 (s, 3H), 1.74 (sept., 3H, J = 7.50 Hz), 1.16 (d, 18H, J = 7.52 Hz). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 165.8, 141.5, 138.7, 129.1, 122.8, 122.1, 121.7, 114.4, 110.8, 51.2, 18.2, 12.9. **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{19}H_{30}O_2NSi$ 332.2040; found 332.2044.

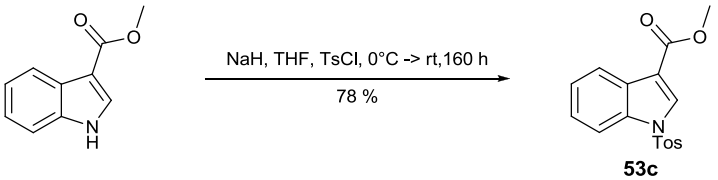
7.1.3.7 Methyl N-*tert-Butyl-indole-3-carboxylate*



53b

Sodium hydride (865 mg, 17.1 mmol) was dissolved in 20 ml dry THF in a 50 ml flame dried round bottom flask. Methyl indole-3-carboxylate (2.02 g, 11.5 mmol) in 8 ml dry THF was added drop-wise under argon over 5 min in ice bath. The reaction was stirred at 0°C for 30 min before drop-wise addition of di-tert-butyl dicarbonate (3.73 g, 17.1 mmol). The reaction was stirred at room temperature for 20h before drop-wise addition of aqueous saturated ammonium chloride until evolution of gas ceased. The resulting mixture was poured into 50 ml water and extracted with Diethyl ether (3x50 ml). The organic phase was washed with 50 ml water and 50 ml brine, dried with $MgSO_4$ and evaporated. The solid was purified by chromatography (SiO_2, 2-15% EtOAc in cyclohexane) to yield 3,01 g (10.9 mmol, 95 %) methyl *N-tert*-Butyl-indole-3-carboxylate **53b** as a light orange solid. **m.p.** 63.8-65.2°C. **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 8.27 (s, 1H), 8.17 (dt, 1H, J = 1.3, 8.3 Hz), 7.36 (m, 2H), 3.94 (s, 3H), 1.69 (s, 9H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 164.9, 149.2, 135.8, 132.3, 127.7, 125.3, 124.2, 121.9, 115.4, 112.4, 85.3, 51.7, 28.3. **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{15}H_{18}O_4N$ 276.12303; found 276.12321.

7.1.3.8 Methyl N-*tosyl-indole-3-carboxylate*

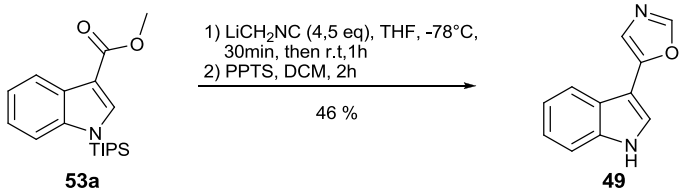


53c

Sodium hydride (301 mg, 12.5 mmol) was added to a flame dried 100 ml round bottom flask and dissolved in 5 ml dry THF. Methyl indole-3-carboxylate (2.03 g, 11.6 mmol) in 15 ml THF was added drop-wise over 5 min at 0°C and left for 30 min. Para-toluenesulfonyl chloride (2.61 g, 13.7 mmol) was added portion wise over 5 min. The reaction mixture was reacted for 16h and quenched by drop-wise addition of 3 ml saturated ammonium chloride before partitioning between water and methyl tert-butyl ether. A white precipitate was collected from the water phase and extracted with chloroform 3x30 ml). The chloroform phase was dried with $MgSO_4$ and evaporated to yield a white solid (2.13 g). The MTBE phase was evaporated and washed with 2x20 ml MTBE, dissolved in chloroform before the process was repeated to yield additional 0.80 g of methyl *N*-tosyl-indole-3-carboxylate **53c** as white solid for a total yield of 2.93 g (78 %). **m.p.**: 119.4-121.0°C. **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 8.27 (s, 1H), 8.13 (d, 1H, J = 8.4 Hz), 7.96 (d, 1H, J = 8.6 Hz), 7.82 (d, 2H, J = 8.5

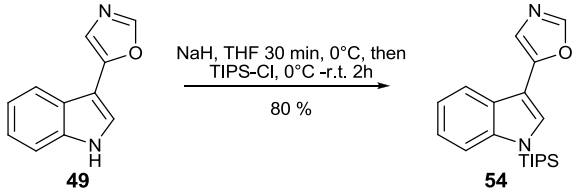
Hz), 7.35 (m, 2H), 7.25 (d, 2H, J = 8.4 Hz), 3.92 (s, 3H), 2.25 (s, 3H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 164.3, 146.0, 135.0, 134.9, 132.3, 130.4, 128.0, 127.3, 125.6, 124.6, 122.3, 113.7, 113.5, 51.8, 21.8. **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{17}H_{18}O_4NS$ 330.07946; found 330.07953.

7.1.3.9 5-(indol-3-yl)oxazole



To a solution of methyl isocyanide **52** (0.84 g, 20.4 mmol) in 13 ml THF at 0°C was added n-BuLi 2.5 M in hexanes (7.25 ml, 18.1 mmol) drop-wise at -78°C. The reaction mixture was left 1h at -78°C before drop-wise addition of methyl *N*-triisopropylsilyl-indole-3-carboxylate **53a** (1.50 g, 4.52 mmol) in 2 ml THF. The mixture left at -78°C for 1h, then room temperature 1h before siphoning it into a 100 ml mixture of saturated $NaHCO_3$ and ice. The suspension was extracted with ethyl acetate 3x50 ml. The organic phase was pre-dried with brine, dried with $MgSO_4$ and evaporated. The product was determined by NMR to be mainly the uncyclized 1-(indol-3-yl)-2-isocyanoethan-1-one and was therefore treated with PPTS (1.98 g, 7.88 mmol) in 5 ml DCM for 3h. The reaction was poured into saturated $NaHCO_3$ and extracted with ethyl acetate 3x50 ml. The organic phase was washed with brine, dried with $MgSO_4$ and evaporated. The brown oil was purified by chromatography on silica with ethyl acetate in DCM 1-10 % to yield 5-(indol-3-yl)oxazole **49** as a yellow solid (381 mg, 46 %). **m.p.**:167-169°C. **^{1}H-NMR** (Acetone-d6, 400 MHz): δ 8.11 (s, 1H), 7.90 (d, 1H, J = 7.6 Hz), 7.78 (s, 1H), 7.52 (d, 1H, J = 7.9 Hz), 7.37 (s, 1H), 7.21 (m, 2H). **^{13}C-NMR** (Acetone-d6, 100 MHz): δ 149.3, 148.5, 136.9, 124.4, 123.1, 122.6, 120.6, 119.8, 119.2, 112.1, 104.8. **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{11}H_9ON_2$ 185.07094; found 185.07084.

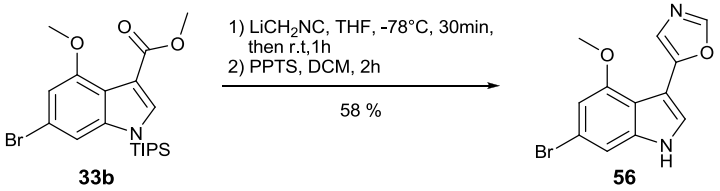
7.1.3.10 5-(1-(triisopropylsilyl)-indol-3-yl)oxazole



Sodium hydride (50 mg, 2.1 mmol) was added to a flame dried 50 ml round bottom flask and suspended in 5 ml dry THF. 5-(indol-3-yl)oxazol **49** (370 mg, 2.0 mmol) in 4 ml THF was added drop-wise over 5 min at 0°C and left for 30 min. triisopropylsilyl chloride (0.47 ml, 2.1 mmol) was added drop-wise. The reaction mixture was reacted for 1h and quenched by slow addition of water before extraction with ethyl acetate 3x 30 ml. The organic phase was washed with brine, dried with $MgSO_4$ and purified by chromatography on silica with 10 % ethyl acetate in cyclohexane to yield 544 mg (80 %) of 5-(1-(triisopropylsilyl)-indol-3-yl)oxazole **54** as a bright yellow oil. **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 8.00 (s, 1H), 7.83 (m, 1H), 7.63 (s, 1H), 7.55 (m, 1H), 7.32 (s, 1H), 7.25 (m, 2H), 1.73 (sept., 3H, J = 7.5 Hz), 1.17 (d, 18H, J = 7.5 Hz). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 149.0, 148.5, 141.6, 129.5, 127.5,

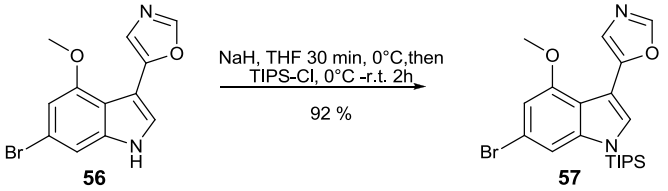
122.8, 121.3, 119.9, 119.0, 114.6, 107.3, 18.3, 13.0. **HRMS** (ESI) m/z: $[M+H]^+$ calcd. $C_{20}H_{29}ON_2Si$: 341.20437, found: 341.20478.

7.1.3.11 5-(6-bromo-4-methoxy-indol-3-yl)oxazole



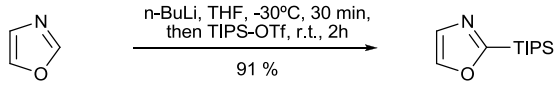
To a solution of methyl isocyanide **52** (368 µl, 7.05 mmol) in 4 ml THF at 0°C was added n-BuLi 2.5 M in hexanes (2.54 ml, 6.34 mmol) drop-wise at -78°C. The reaction mixture was left 1h at -78°C before drop-wise addition of methyl 6-bromo-4-methoxy-1-(triisopropylsilyl)-indole-3-carboxylate **33b** (621 mg, 1.41 mmol) in 1 ml THF. The mixture was left at -78°C for 1h, then 0°C for 1h before siphoning it into a 50 ml mixture of saturated $NaHCO_3$ and ice. The suspension was extracted with ethyl acetate 3x30 ml. The organic phase was washed with brine, dried with $MgSO_4$ and evaporated. The residue was treated with PPTS (0.78 g, 3.1 mmol) in 10 ml DCM for 2h. The solution was evaporated and the resulting red oil was purified by chromatography on silica with 1-1.5 % methanol in DCM to yield 5-(6-bromo-4-methoxy-indol-3-yl)oxazole **56** as a yellow solid (637 mg, 58 %). **m.p.**: 268.2-270.0°C (dec.). IR: 3222 (m, br), 3130 (m), 2926 (m), 2864 (w), 2080 (w), 1786 (w), 1735 (w). **^{1}H-NMR** (DMSO-d6, 400 MHz): δ 11.65 (bs, 1H), 8.24 (s, 1H), 7.62 (d, 1H, J = 2.7), 7.33 (s, 1H), 7.22 (d, 1H, J = 1.6), 6.71 (d, 1H, J = 1.4), 3.91 (s, 3H). **^{13}C-NMR** (DMSO-d6, 100 MHz): δ 154.3, 150.6, 148.0, 129.2, 124.4, 122.3, 116.0, 113.5, 108.7, 104.7, 104.4, 56.2. **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{12}H_{10}O_2N_2Br$ 292.9920; found 292.9924.

7.1.3.12 5-(6-bromo-4-methoxy-1-(triisopropylsilyl)-indol-3-yl)oxazole



Sodium hydride (123 mg, 5.13 mmol) was added to a flame dried 25 ml round bottom flask and suspended in 2 ml dry THF. 5-(6-bromo-4-methoxy-indol-3-yl)oxazole **56** (1.0 g, 3.41 mmol) suspended in 10 ml THF was added drop-wise over 5 min at 0°C and left for 30 min. Triisopropylsilyl chloride (1.09 ml, 5.12 mmol) was added drop-wise at 0°C. The reaction mixture was reacted for 30 min at room temperature and quenched by slow addition of water before extraction with ethyl acetate 3x 30 ml. The organic phase was washed with brine, dried with $MgSO_4$ and evaporated. The residue was filtered through a plug of silica with cyclohexane to yield 1.42 g (92 %) of 5-(6-bromo-4-methoxy-1-(triisopropylsilyl)-1H-indol-3-yl)oxazole **57** as a white solid. **m.p.**: 128.3-130.4°C. **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 7.82 (s, 1H), 7.46 (s, 1H), 7.44 (s, 1H), 7.26 (s, 1H), 6.72 (s, 1H), 3.95 (s, 3H), 1.68, (sept., 3H, J = 7.5 Hz), 1.16 (d, 18H, J = 7.5 Hz). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 154.1, 149.1, 148.0, 143.6, 129.4, 123.1, 116.7, 116.5, 110.7, 107.6, 105.5, 55.6, 18.3, 13.0. **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{21}H_{30}{}^{81}BrN_2O_2Si$ 451.1234; found 451.1233.

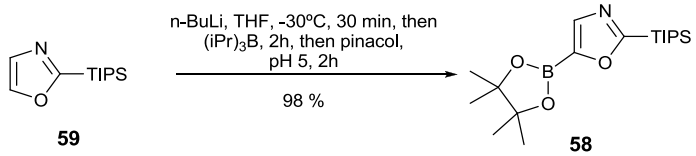
7.1.3.132-(triisopropylsilyl)oxazole



26 **59**

Oxazole (2.09 g, 31.1 mmol, 1 eq) was dissolved in 60 ml dry THF in a flame dried 250 ml round bottom flask and cooled to -30°C. BuLi (2.5M in hexanes, 7.04 ml, 32.6 mmol, 1.05) was added drop-wise and reacted for 30 minutes before drop-wise addition of Triisopropylsilyl triflate (10 g, 32.6 mmol). The solution was heated to room temperature and allowed to react for 2h before quench with water. The resulting solution was extracted with ethyl acetate 3x70 ml. The organic phase was washed with brine, dried with $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica with 3-5 % ethyl acetate in pentane to yield 2-(triisopropylsilyl)oxazole **59** (6.41 g, 91 %) as a colorless oil. **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 7.81 (d, 1H, J = 0.7 Hz), 7.21 (d, 1H, J = 0.5 Hz), 1.41 (sept., 3H, J = 7.5 Hz), 1.13 (d, 18H, J = 7.4 Hz). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 168.9, 140.7, 126.8, 18.6, 11.2. **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{12}H_{24}ONSi$ 226.1622; found 226.1615.

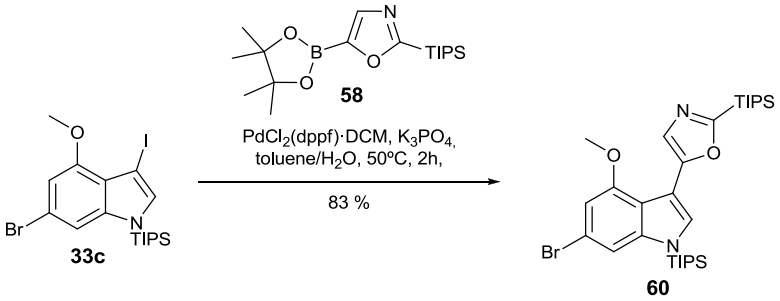
7.1.3.14(2-(triisopropylsilyl)oxazol-5-yl)boronic acid pinacol ester



59 **58**

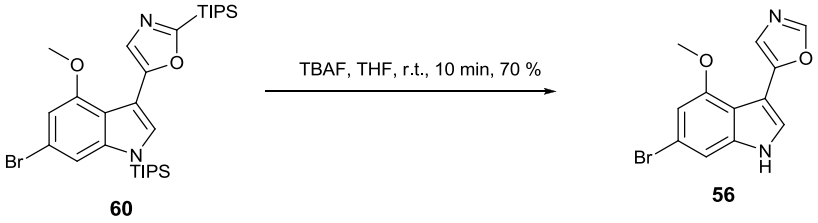
2-(triisopropylsilyl)oxazole **59** (6.32 g, 28.0 mmol, 1 eq) was dissolved in 120 ml THF in a 250 ml round bottom flask and cooled to -30°C. n-BuLi (2.5M in hexanes, 13.4 ml, 33.6 mmol, 1.2 eq) was added drop-wise and reacted for 30 minutes. Triisopropylborate (7.73 g, 33.6 mmol, 1.2 eq) was added drop-wise and the resulting solution was stirred for 2h at -30°C. The solution was heated to room temperature over a course of 1h. Pinacol (3.31 g, 28.0 mmol, 1 eq) was added in a single batch and the pH of the solution was adjusted to 5 by addition of approximately 5 ml glacial acetic acid. The solution was stirred 2h at room temperature before it was diluted with 150 ml diethyl ether, filtered and evaporated. The residue was purified by flash chromatography on silica with 30 % ethyl acetate in cyclohexane to yield 9.64 g (98 %) (2-(triisopropylsilyl)oxazol-5-yl)boronic acid pinacol ester **58** as a yellow oil that slowly crystallizes upon standing. **m.p.**: 39.3-41.0°C. **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 7.71 (s, 1H), 1.43 (sept., 3H, J = 7.5 Hz), 1.32 (s, 12H), 1.11 (d, 18H, J = 7.4 Hz). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 173.4, 139.6, 84.5, 24.9, 18.6, 11.3. (C-5 signal not observed in accordance with literature). **HRMS** (ESI) m/z: [M+H]+ Calcd for $C_{18}H_{25}O_3NBSi$ 352.2474, found 352.2473.

7.1.3.155-(6-bromo-4-methoxy-1-(triisopropylsilyl)-indol-3-yl)-2-(triisopropylsilyl)oxazole



6-bromo-3-iodo-4-methoxy-1-(triisopropylsilyl)-indole **33c** (1.00 g, 1.97 mmol) and (2-(triisopropylsilyl)oxazol-5-yl)boronic acid pinacol ester **58** (724 mg, 2.06 mmol) were dissolved in 3 ml toluene and added 1.5 ml water containing potassium phosphate (1.25 g, 5.90 mmol). The solution was degassed and $PdCl_2$(dppf)·DCM (81 mg, 0.10 mmol, 5 mol%) was added and reacted at 50°C for 2h. The mixture was partitioned between water and ethyl acetate and extracted with 2x50 ml ethyl acetate. The combined organic phase was washed with brine, dried with $MgSO_4$ and evaporated. The residue was purified by flash chromatography on silica with 5-15% EA in cyclohexane to yield disilylated compound **60** 996 mg (83 %) as a yellow oil. **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 7.53 (s, 1H), 7.48 (s, 1H), 7.24 (d, 1H, J = 1.4 Hz), 6.71 (d, 1h, J = 1.2 Hz), 3.93 (s, 3H), 1.66 (sept., 3H, J = 7.5 Hz), 1.44 (sept., 3H, J = 7.5 Hz), 1.19 (d, 18H, J = 7.5 Hz), 1.16 (d, 18H, J = 7.5). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 166.2, 145.2, 143.6, 140.9, 129.5, 123.5, 116.7, 116.3, 110.5, 108.2, 105.4, 55.5, 18.7, 18.3, 13.0, 11.3. **HRMS** (ESI) m/z: [M+H]+ Calcd for $C_{30}H_{50}{}^{81}BrN_2O_2Si_2$ 607.2568; found 607.2562

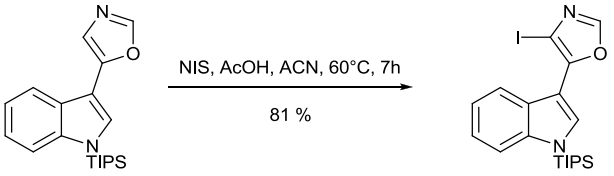
7.1.3.165-(6-bromo-4-methoxy-indol-3-yl)oxazole



Disilylated compound **60** (3.21 g, 5.30 mmol), was dissolved in 5 ml THF. TBAF·3H2O (3.60 g, 11.4 mmol) in 5 ml THF was added TLC showed no starting material after 10 minutes. The solvent was evaporated and the resulting oil was dissolved in 20 % THF in cyclohexane and applied on a 4 cm column. The compound was eluted with 20-100 % THF in cyclohexane. The fractions containing product was triturated with cyclohexane to remove BHT, yielding 5-(6-bromo-4-methoxy-indol-3-yl)oxazole **56** as a pale brown solid (1.08 g, 70 %). (For characterization see section 7.1.3.11)

7.1.4 Iodination and Pyrrole assembly (section 3.6)

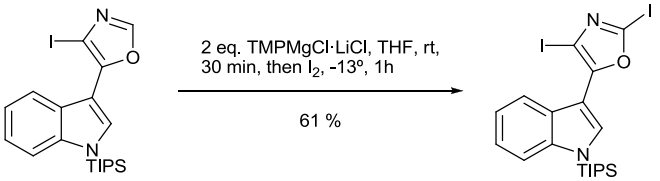
7.1.4.1 4-iodo-5-(1-(triisopropylsilyl)-indol-3-yl)oxazole



54 **61**

5-(1-(triisopropylsilyl)-indol-3-yl)oxazole **54** (519 mg, 1.52 mmol) was dissolved in 15 ml acetonitrile. *N*-iodosuccinimide (377 mg, 1.68 mmol) was added and the mixture was heated to 60°C for 4h. TLC showed a mixture of starting material and product and to the mixture was added acetic acid (87 µl, 1.5 mmol) and additional NIS (80 mg, 0.35 mmol). The reaction mixture was kept at 60°C for additional 3 hours until all trace of starting material vanished. The reaction was quenched with 5 % $Na_2S_2O_3$, extracted with ethyl acetate 3x50 ml, washed with brine, dried with $MgSO_4$ and evaporated. The residue was filtered through a silica plug with ethyl acetate in toluene to yield 457mg (81 %) 4-iodo-5-(1-(triisopropylsilyl)-indol-3-yl)oxazole **61** as a dark red oil. **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 8.14 (s, 1H), 8.05 (m, 1H), 7.95 (s, 1H), 7.55 (m, 1H), 7.24 (m, 2H), 1.74 (sept., 3H, J = 7.5), 1.19 (d, 18H, J = 7.5). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 150.4, 150.2, 141.0, 131.7, 130.2, 128.4, 122.9, 121.6, 121.4, 121.0, 118.1, 114.7, 114.4, 106.1, 18.3, 13.1. **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{20}H_{28}ON_2ISi$ 467.10101; found 467.10099.

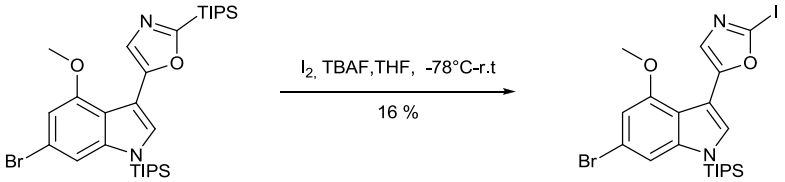
7.1.4.2 2,4-diiodo-5-(1-(triisopropylsilyl)-indol-3-yl)oxazole



61 **62**

TMPMgCl·LiCl (1 M in DCM, 076 ml, 0.76 mmol) was added to a flame dried round bottom flask. 4-iodo-5-(1-(triisopropylsilyl)-indol-3-yl)oxazole **61** (161 mg, 0.35 mmol) in 0.5 ml THF was added drop-wise at room temperature and stirred for 30 min. The reaction mixture was cooled to -13°C and iodine (201 mg, 0.79 mmol) in 1 ml THF was added drop-wise and stirred for 1h. The reaction mixture was added slowly to a stirred flask containing 5 % sodium thiosulfate and ice. Saturated NH_4Cl was added and the aqueous suspension was extracted with 3x30 ml chloroform. The organic phase was washed with brine, dried with $MgSO_4$ and evaporated. The residue was purified by chromatography on silica with 3-6 % ethyl acetate in cyclohexane to yield 127 mg (61 %) 2,4-diiodo-5-(1-(triisopropylsilyl)-indol-3-yl)oxazole **62** as a brown solid. **m.p.**: 154-155°C. **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 8.05 (s, 1H), 7.99 (m, 1H), 7.54 (m, 1H), 7.25 (m, 2H), 1.73 (sept., 3H, J = 7.5), 1.18 (d, 18H, J = 7.5). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 156.6, 141.0, 131.5, 128.7, 128.5, 128.2, 126.1, 123.0, 121.5, 120.9, 114.4, 112.7, 105.6, 97.8, 18.3, 13.0. **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{20}H_{27}ON_2I_2Si$ 592.99765; found 592.99747.

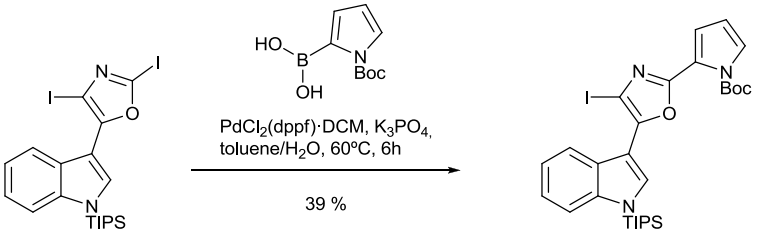
7.1.4.3 5-(6-bromo-4-methoxy-1-(triisopropylsilyl)-indol-3-yl)-2-iodooxazole



60 **64**

Disilylated compound **60** (136 mg, 0.22 mmol) and iodine (68 mg, 0.27 mmol, 1.2 eq) were dissolved in THF and cooled to -78°C. 0.2 M TBAF in THF (1.07 ml, 0.21 mmol, 0.95 eq) was added drop-wise during 15 minutes. TLC showed starting material left. The reaction mixture was heated to 0°C for 2 hours, then -18°C for 14 hours. No starting material was observed on TLC and the reaction was quenched with water and extracted with ethyl acetate (10 ml x3). The combined organic phase was washed with 10 % aqueous thiosulfate and brine, then dried with $MgSO_4$ and evaporated. Column chromatography (5-40 % ethyl acetate in pentane) gave iodinated oxazole **64** in 16 % yield (20 mg) as a colorless oil. IR: 2947 (m), 2867 (m), 2232 (w), 1800 (w), 1713 (w). **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 7.41 (s, 1H), 7.36 (s, 1H), 7.25 (d, 1H, J = 1.3 Hz), 6.71 (d, 1H, J = 1.3 Hz), 3.93 (s, 3H), 1.69 (sept., 3H, J = 7.5 Hz), 1.16 (d, 18H, J = 7.5 Hz). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 154.0, 153.7, 143.3, 129.4, 126.8, 116.4, 116.2, 110.4, 106.6, 105.4, 97.1, 55.4, 18.0, 12.7. **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{21}H_{29}{}^{81}BrIN_2O_2Si$ 577.0200; found 577.0204.

7.1.4.4 tert-*butyl 2-(4-iodo-5-(1-(triisopropylsilyl)-indol-3-yl)oxazol-2-yl)-pyrrole-1-carboxylate*



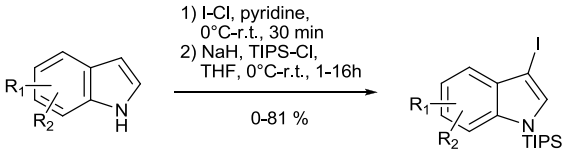
62 **65**

2,4-diiodo-5-(1-(triisopropylsilyl)-indol-3-yl)oxazole **62** (200 mg, 0.34 mmol) and (*N*-Boc-pyrrol-2-yl)boronic acid (100 mg, 0.44 mmol) were dissolved in 500 µl toluene and added 200 µl water containing potassium phosphate (215 mg, 1.01 mmol). The solution was degassed and $PdCl_2$(dppf)·DCM (13.8 mg, 16.9 µmol, 5 mol %) was added and reacted at 60°C for 6h. Additional 0.4 equivalents of boronic acid was added and stirred for 2h. The mixture was diluted with EA, filtered through a plug of celite and evaporated. The residue was purified by flash chromatography on silica with 50-100% toluene in cyclohexane to yield the protected model Breitfussin **65** 84 mg (39 %) as a yellow solid. **m.p.** 142.2-143.6°C. **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 8.16 (s, 1H), 8.07 (d, 1H, J = 7.8 Hz), 7.53 (d, 1H, J = 7.7 Hz), 7.46 (m, 1H), 7.22 (t, 1H, J = 6.9 Hz), 7.17 (t, 1H, J = 7.0 Hz), 6.78 (m, 1H), 6.30 (t, 1H, J = 3.4), 1.75 (sept, 3H, J = 7.5 Hz), 1.45 (s, 9H), 1.19 (d, 18H, J = 7.5 Hz). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ 155.2, 150.1, 148.5, 141.0, 131.5, 128.4, 124.8, 122.8, 121.4, 121.2, 120.7, 119.2, 114.3, 111.2, 106.4, 85.0, 76.2, 27.9, 18.3, 13.1. **HRMS** (ESI) m/z: $[M+H]^+$ Calcd. for $C_{29}H_{39}O_3N_3ISi$ 632.17999; found 632.18058.

7.2 SYNTHESIS OF BREITFUSSIN ANALOGUES (CHAPTER 4)

7.2.1 Synthesis of 3-halo-*N*-TIPS-indoles (section 4.3)

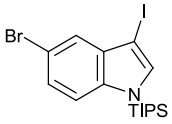
7.2.1.1 General procedure for synthesis of N-*triisopropylsilyl-3-iodoindoles*



74a-e **75a-e**

Indole (1 eq.) was dissolved in pyridine (3ml per gram indole) and cooled to 0°C. Iodine monochloride (1.05 eq., 1M in DCM) was added slowly by syringe. The reaction mixture was heated to room temperature after 15 minutes at 0°C. After additional 15 minutes at r.t. the mixture was poured onto a flask containing water and ethyl acetate. The organic layer was washed with water and brine, dried with Na_2SO_4 and dried under vacuum. The residues were used in the next step without purification. The crude 3-iodoindole was dissolved in 1.5 ml freshly prepared dry THF (Na/benzophenone) and added slowly to a suspension of 1.4 eq. Sodium hydride (1.4 eq., 95 % powder) in 1.5 ml dried THF at 0°C under argon. After 30 minutes at 0°C, triisopropylsilyl chloride (TIPS-Cl) (1.4eq.) was added by syringe. The mixture was allowed to react 30 minutes at 0°C, then 30 minutes at room temperature. The reaction progress was monitored by TLC, and additional sodium hydride and TIPS-Cl (0.2-0.5 eq) was added depending on the relative intensity of the permanganate stained TLC spots of the remaining starting material to the product. When no starting material was present the reaction was quenched with water and partitioned between water and ethyl acetate. The organic layer was washed with water and brine, dried with $MgSO_4$ and evaporated. The resulting crude materials were purified by column chromatography to yield the corresponding *N*-triisopropylsilyl-3-iodoindoles.

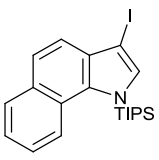
*7.2.1.2 5-Bromo-*N-*triisopropylsilyl-3-iodoindole*



75a

5-Bromo-*N*-triisopropylsilyl-3-iodoindole **75a** (8.48 g, 17.7 mmol, 81 %) was prepared from 5-bromoindole **74a** (21.8 mmol) as a white solid. **m.p.**: 71.2-72.2°C. IR: 2946 (m), 2866 (m), 1848 (w). **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ 7.59 (1H, d, J = 2.0 Hz), 7.33 (1H, d, J = 8.8 Hz), 7.25-7.28 (2H, m), 1.66 (3H, sept., J = 7.5 Hz), 1.12 (18H, d, J = 7.6 Hz). **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ 139.2, 136.2, 134.8, 125.4, 123.6, 115.3, 114.2, 59.1, 18.0, 12.7. **HRMS** calculated for $C_{17}H_{26}NSiBrI$ $[M+H]^+$ 479.0063, found 478.0057.

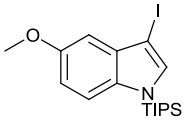
7.2.1.3 N-*triisopropylsilyl-3-iodobenzo[g]indole*



75b

N-triisopropylsilyl-3-iodobenzo[g]indole **75b** (1.39 g, 3.09 mmol, 47 %) was prepared from benzo[g]indole **74b** (6.52 mmol) as a white solid that darkens upon standing. **m.p.** 93.2-95.0°C. IR: 3144 (w), 3045 (w), 2946 (m), 2866 (m), 1742 (w), 1600 (w). **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ 8.27 (1H, d, J = 8.4 Hz), 7.97 (1H, dd, J = 2.9, 8.1 Hz), 7.65 (1H, d, J = 8.6 Hz), 7.59 (1H, d, J = 8.6 Hz), 7.54 (1H, t, J = 7.7 Hz), 7.49 (1H, s), 7.45 (1H, t, J = 4.4 Hz), 1.90 (3H, sept., J = 7.5 Hz), 1.21 (18H, d, J = 7.6 Hz). **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ 136.1, 135.5, 132.1, 130.7, 130.0, 125.1, 124.08, 124.06, 123.3, 122.4, 121.3, 62.4, 19.0, 15.1. **HRMS** calculated for $C_{21}H_{29}NSiI$ $[M+H]^+$ 450.1114, found 450.1108.

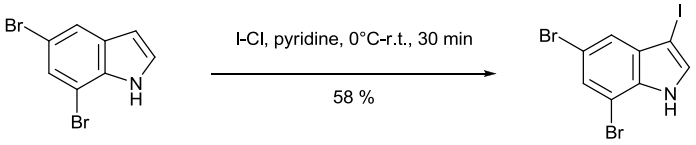
*7.2.1.4 5-methoxy-*N*-triisopropylsilyl-3-iodoindole*



70

5-methoxy-*N*-triisopropylsilyl-3-iodoindole **70** (3.08 g, 7.16 mmol, 81 %) was prepared from 5-methoxyindole **74c** (8.90 mmol) as a dark brown oil. **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ 7.35 (1H, d, J = 9.0 Hz), 7.26 (1H, s), 6.88 (1H, d, J = 2.5 Hz), 6.83 (1H, dd, J = 8.9, 2.6 Hz), 3.89 (3H, s), 1.66 (3H, sept., J = 7.5 Hz), 1.13 (18H, d, J = 7.6 Hz). **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ 155.0, 135.5, 135.2, 133.5, 114.8, 112.8, 59.7, 55.7, 18.0, 12.8. **HRMS** calculated for $C_{18}H_{29}NOSiI$ $[M+H]^+$ 430.1063, found 430.1058.

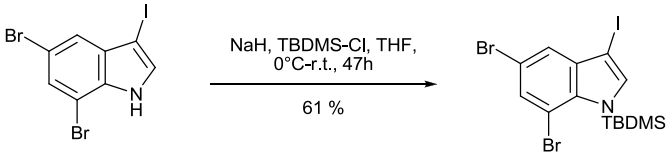
*7.2.1.5 5,7-dibromo-3-iodoindole (attempted synthesis of 5,7-dibromo-3-iodo-*N*-triisopropylsilylindole)*



74d **79**

The general procedure for *N*-triisopropylsilyl-3-iodoindoles was followed, but did not yield any *N*-TIPS product. The crude material was washed with pentane and purified by column chromatography to yield 5,7-dibromo-3-iodoindole **79** (0.76 g, 1.87 mmol, 57 %) as an orange solid. **m.p.**: 135.0-136.7°C. IR: 3406 (m, br), 2946 (w), 2864 (w), 2492 (w), 1993 (w), 1912 (w), 1737 (w). **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ 8.50 (1H, bs), 7.56 (1H, s), 7.53 (1H, d, J = 1.6 Hz), 7.35 (1H, d, J = 2.5 Hz). **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ 133.3, 131.9, 130.0, 127.8, 123.4, 113.8, 104.9, 57.4. **HRMS** calculated for $C_8H_3NBr_2I$ $[M-H]^+$ 397.7682, found 397.7682.

*7.2.1.6 5,7-dibromo-3-iodo-*N*-tertbutyldimethylsilylindole*

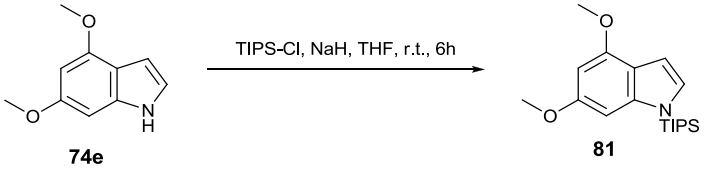


79 **80**

5,7-dibromo-3-iodoindole **79** (613 mg, 1.51 mmol) was dissolved in 1.5 ml freshly prepared dry THF (from a sodium/benzophenone still) and added slowly to a suspension of sodium

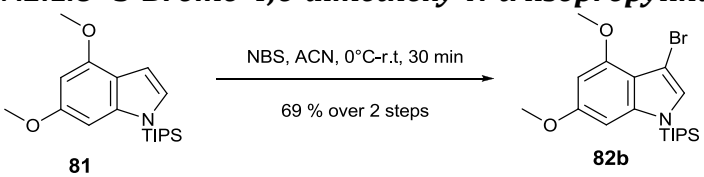
hydride (45 mg, 1.89 mmol) in 2 ml dried THF at 0°C under argon. After 30 minutes at 0°C, *tert*-butyl dimethyl chloride (296 mg, 1.96 mmol) was added by syringe. The mixture was allowed to react 30 minutes at 0°C, then 30 minutes at room temperature. The reaction progress was monitored by TLC, and aliquots of sodium hydride and TBDMS-Cl (0.5 eq) were added at 4h, 27h and 35 h. When no starting material was apparent by TLC (at 47h) the reaction was quenched with water and partitioned between water and ethyl acetate. The organic layer was washed with water and brine, dried with $MgSO_4$ and evaporated. The resulting crude material was purified by column chromatography to yield 25 % starting material and the title compound 5,7-dibromo-3-iodo-*N*-tertbutyldimethylsilylindole **80** (473 mg, 0.918 mmol, 61 % as a white solid. **m.p.**: 90.0-91.4°C. IR: 3147 (w), 2949 (w), 2932 (w), 2857 (w). **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ 7.59 (1H, d, J = 2.0 Hz), 7.56 (1H, d, J = 2.0 Hz), 7.42 (1H, s), 0.98 (9H, s), 0.72 (6H, s). **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ 139.1, 138.3, 137.0, 130.4, 123.3, 114.2, 106.0, 59.9, 27.2, 19.7, 1.6. **HRMS** calculated for $C_{14}H_{19}NSiBr_2I$ $[M+H]^+$ 513.8698, found 513.8693.

*7.2.1.7 4,6-dimethoxy-*N*-triisopropylsilylindole*



4,6-dimethoxyindole **74e** (1.098 g, 6.2 mmol) was dissolved in 1.5 ml freshly prepared dry THF (Na/benzophenone) and added slowly to a suspension of sodium hydride (179 mg, 7.44 mmol) in 2.5 ml dried THF at 0°C under argon. After 30 minutes at 0°C, triisopropylsilyl chloride (1.60 ml, 7.44 mmol) was added by syringe. The mixture was allowed to react 30 minutes at 0°C, then 30 minutes at room temperature. The reaction progress was monitored by TLC, and additional NaH and TIPS-Cl was added at 1h (0.6 eq.) and 5h (0.3 eq.). After 6 hours no starting material was present as determined by TLC and the reaction was quenched with water and partitioned between water and ethyl acetate. The organic layer was washed with water and brine, dried with $MgSO_4$ and evaporated. The resulting red oil is subject to use directly in 3-halogenation. The yield was not determined, but the NMR spectra of crude 4,6-dimethoxy-N-triisopropylsilylindole **81** were relatively pure, containing an impurity in the high field region. **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ 7.04 (1H, d, J = 3.2 Hz), 4.64 (2H, m), 6.26 (1H, d, J = 1.7 Hz), 3.92 (3H, s), 3.83 (3H, s), 1.67 (3H, sept., J = 7.5 Hz), 1.15 (18H, d, J = 7.6 Hz). (1.06, 14H, s. imp.) **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ 156.8, 153.2, 142.1, 128.3, 116.3, 101.5, 91.3, 90.7, 55.8, 55.2, 18.1, (17.7 imp.), 12.8, (12.3 imp.). **HRMS** calculated for $C_{19}H_{32}NO_2Si$ $[M+H]^+$ 334.2202, found 334.2196.

*7.2.1.8 3-Bromo-4,6-dimethoxy-*N*-triisopropylindole*

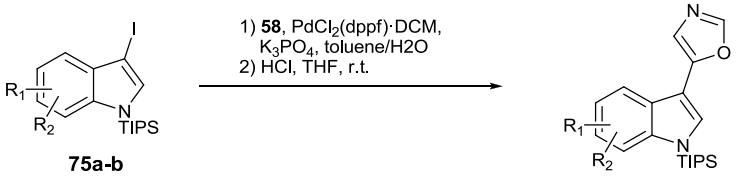


From the crude 4,6-dimethoxy-*N*-triisopropylsilylindole **81**, 312 mg (corresponding to 208 mg, 0.60 mmol) was dissolved in 2 ml acetonitrile and cooled to 0°C. *N*-Bromosuccinimide

(133 mg, 0.75 mmol) was added. The mixture was kept at 0°C 15 minutes, then room temperature 15 minutes, at which time GC-MS analysis showed no trace of starting material. The reaction mixture was partitioned between water and chloroform and extracted trice with chloroform. The organic phase was washed with brine, dried with $MgSO_4$, and evaporated. The residue was purified by column chromatography to yield 3-Bromo-4,6-dimethoxy-*N*-triisopropylindole **82b** (170 mg, 0.41 mmol, 69 %) as a white solid that quickly turns green. **m.p.**: 69.8-71.7°C (dec.). IR: 3198 (w, br), 2945 (m), 2866 (m). **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ 6.98 (1H, s), 6.56 (1H, d, J = 1.9 Hz), 6.25 (1H, d, J = 1.8 Hz), 3.91 (3H, s), 3.81 (3H, s), 1.62 (3H, sept., J = 7.6 Hz), 1.14 (18H, d, J = 7.5 Hz). **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ 157.3, 153.9, 142.1, 127.9, 113.6, 92.4, 90.5, 90.3, 55.6, 55.5, 18.1, 12.8. **HRMS** calculated for $C_{19}H_{32}NO_2Si$ $[M+H]^+$ 412.1307, found 312.1302.

7.2.2 Synthesis of 5-(*N*-TIPS-indol-3-yl)oxazoles (section 4.4)

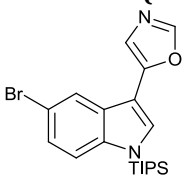
7.2.2.1 General method for synthesis of 5-(3'-indolyl)-oxazoles



75a-b **76a-b**

N-triisopropylsilyl-3-iodoindole, K_3PO_4 and 2-TIPS-oxazole-5-boronic acid pinacol ester were dissolved in water/toluene and degassed. $PdCl_2$(dppf)·DCM was added and the mixture was degassed and kept under argon. The mixture was heated and allowed to react until no trace of starting material was left as determined by TLC. The reaction was pulled through a short plug of celite and partitioned between water and ethyl acetate. The organic phase was washed with water and brine, dried with $MgSO_4$ and evaporated. The resulting crude mixture was dissolved in THF at room temperature and aliquots of 3M aqueous HCl were added every 15 minutes until no sign of the intermediate product was visible on TLC. The mixture was partitioned between water and ethyl acetate. The organic phase was washed with water and brine, dried with $MgSO_4$ and evaporated. The resulting crude materials were purified by column chromatography to yield the corresponding 5-(3-indolyl)-oxazoles.

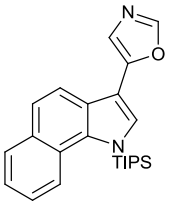
*7.2.2.2 5-(5-bromo-*N*-(triisopropylsilyl)-indol-3-yl)oxazole*



76a

5-(5-bromo-*N*-(triisopropylsilyl)-indol-3-yl)oxazole **76a** was prepared from 5-bromo-3-iodo-*N*-triisopropylsilyl-indole **75a** (7.0 g, 14.6 mmol), K_3PO_4 (9.2 g, 43.3 mmol), 2-TIPS-oxazole-5-boronic acid pinacol ester **58** (5.76 g, 16.4 mmol) and $PdCl_2$(dppf)·DCM (596 mg, 0.73 mmol) in 35 ml toluene and 15 ml water at 40°C. After 2, 2.5 and 3 hours 0.05 equivalents of 2-TIPS-oxazole-5-boronic acid pinacol ester **52** were added. A total of 8 ml 3M HCl over 1 hour was used for selective TIPS-deprotection in 30 ml THF. Column chromatography was performed using 100 % pentane to elute the remaining starting material in 11 % yield, 3-6 % ethyl acetate in pentane to elute TIPS-OH and 15-20 % ethyl acetate in pentane to elute 5-(5-bromo-*N*-(triisopropylsilyl)-indol-3-yl)oxazole **76a** as an orange solid in 73 % yield. **m.p.**: 113.0-115.3°C. IR: 2947 (m), 2867 (m). **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ 7.97 (1H, d, J = 2.0 Hz), 7.90 (1H, s), 7.56 (1H, s), 7.40 (1H, d, J = 8.8 Hz), 7.31 (1H, dd, J = 2.0, 8.8 Hz), 7.27 (1H, s), 1.71 (3H, sept., J = 7.5 Hz), 1.16 (18H, d, J = 7.5 Hz). **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ 149.0, 147.3, 140.0, 130.1, 129.2, 125.4, 122.5, 119.8, 115.6, 114.3, 107.1, 18.0, 12.7. **HRMS** calculated for $C_{20}H_{28}N_2OSiBr$ $[M+H]^+$ 419.1154, found 419.1149.

7.2.2.3 5-(1-(triisopropylsilyl)benzo[g]indol-3-yl)oxazole

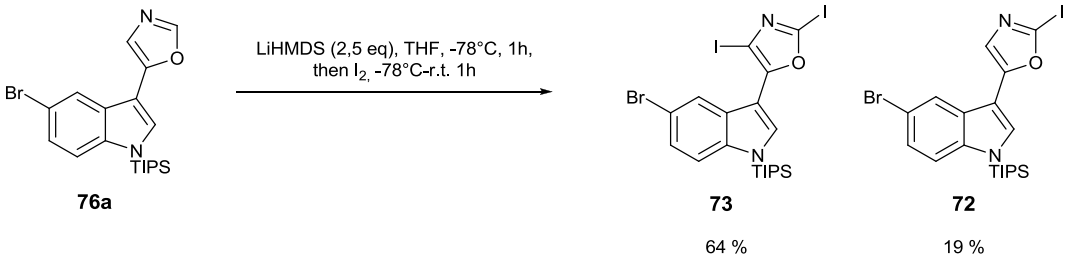


71

5-(1-(triisopropylsilyl)benzo[g]indol-3-yl)oxazole **71** was prepared from *N*-triisopropylsilyl-benzo[g]indole **75b** (1.32 g, 2.7 mmol), K_3PO_4 (1.72 g, 8.11 mmol), 2-TIPS-oxazole-5-boronic acid pinacol ester **58** (1.14 g, 3.24 mmol) and $PdCl_2$(dppf)·DCM (110 mg, 0.135 mmol) in 6 ml toluene and 3 ml water at 60°C. Total reaction time was 1 hour. 3 ml 3.6M HCl in one batch was used for selective TIPS-deprotection in 10 ml THF. The mixture was stirred 10 minutes before workup. Column chromatography was performed using 3-17 % ethyl acetate in pentane to elute 5-(1-(triisopropylsilyl)benzo[g]indol-3-yl)oxazole **71** as an orange oil in 83 % yield. IR: 3133 (w), 2949 (m), 2869 (m), 2732 (w). **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ 8.31 (1H, d, J = 8.4 Hz), 7.94-8.00 (3H, m), 7.77 (1H, s), 7.69 (1H, d, J = 8.6 Hz), 7.56 (1H, dt, 1.5, 7.6 Hz), 7.47 (1H, dt, J = 1.2, 7.5 Hz) 7.36 (1H, s), 1.93 (3H, sept., J = 7.5 Hz), 1.23 (18H, d, J = 7.5 Hz). **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ 149.0, 148.0, 136.4, 131.4, 129.5, 129.3, 124.8, 124.7, 123.8, 123.7, 122.9, 122.2, 119.9, 119.3, 108.3, 18.5, 14.6. **HRMS** calculated for $C_{24}H_{31}N_2OSi$ $[M+H]^+$ 391.2206, found 391.2201.

7.2.3 Synthesis of 5-(5-bromoindol-3-yl)-2,4-diiodooxazole (section 4.5)

7.2.3.1 5-(5-bromoindol-3-yl)-2,4-diiodooxazole



76a **73** 64 % **72** 19 %

5-(5-bromo-*N*-(triisopropylsilyl)-indol-3-yl)oxazole **76a** (0.80 g, 1.91 mmol) was dissolved in 15 ml THF and cooled to -78°C before drop-wise addition of freshly prepared LiHMDS (1M, 4.58 ml, 4.58 mmol, 2.5 eq). After 1h, iodine (1.16 g, 4.58 mmol, 2.5 eq) was added. The reaction was left for 1h at -78°C and heated to room temperature. The reaction was quenched with water and extracted with chloroform (3x). The combined organic phase was washed with brine, dried with $MgSO_4$ and evaporated. The resulting oil was purified by column chromatography on silica with 2 % EtOAc in pentane to yield 0.86 g (64 %) 5-(5-bromoindol-3-yl)-2,4-diiodooxazole **73** as a fluffy orange powder and 0.20 g (19 %) 5-(5-bromoindole-3-yl)-2-iodooxazole **72** as an orange solid.

5-(5-bromoindol-3-yl)-2,4-diiodooxazole **73**: **m.p.**: 60.5-65.5°C. IR: 2948 (w), 2866 (w), 2116 (w). **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ 8.10 (1H, d, J = 2.0 Hz), 8.04 (1H, s), 7.40 (1H, d, J = 9.4 Hz), 7.33 (1H, dd, J = 2.0, 9.7 Hz), 1.70 (3H, sept., J = 7.6 Hz), 1.16 (18H, d, J = 7.5 Hz). **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ 156.0, 139.9, 132.7, 130.1, 126.2, 123.7, 116.0, 115.2, 105.5, 98.5, 77.7, 18.5, 13.2. **HRMS** calculated for $C_{20}H_{26}BrI_2N_2OSi$ $[M+H]^+$ 670.9082, found 670.9087.

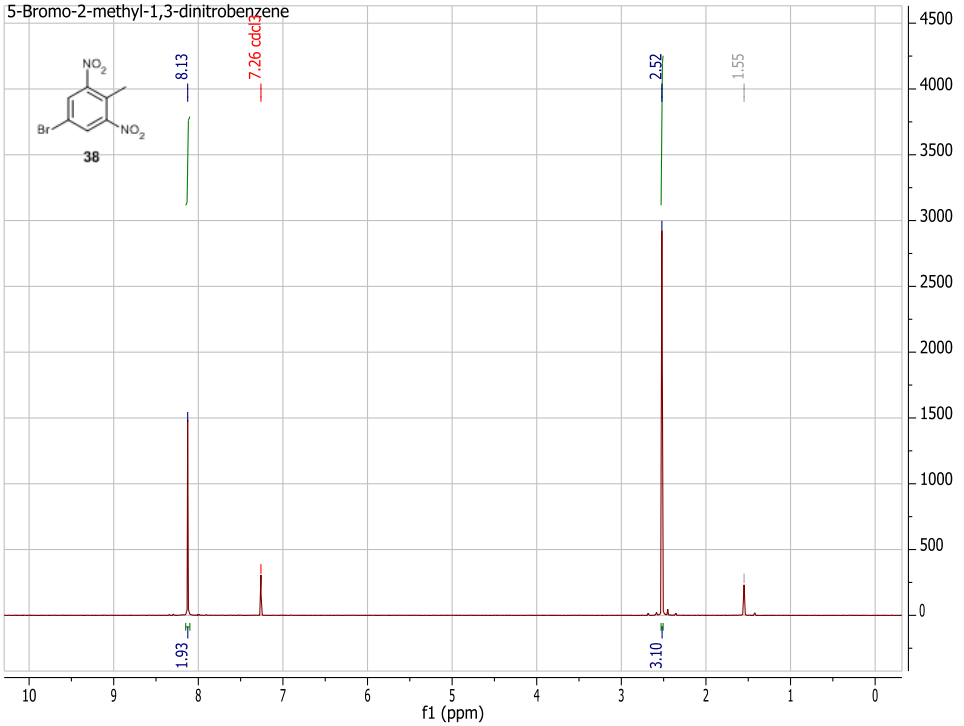
5-(5-bromoindole-3-yl)-2-iodooxazole **72**: **m.p.**: 160.7-161.9°C (dec.). IR: 2949 (m), 2869 (m). **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ 7.87 (1H, d, J = 2.0 Hz), 7.53 (1H, s), 7.39 (1H, d, J = 8.8 Hz), 7.32 (1H, dd, J = 2.0, 8.8 Hz), 7.21 (1H, s), 1.71 (3H, sept., J = 7.5 Hz), 1.16 (18H, d, J = 7.5 Hz). **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ 153.3, 139.9, 130.5, 128.8, 125.5, 123.7, 122.3, 115.7, 114.5, 106.4, 97.5, 18.0, 12.7. **HRMS** calculated for $C_{20}H_{27}BrIN_2OSi$ $[M+H]^+$ 545.0115, found 545.0017.

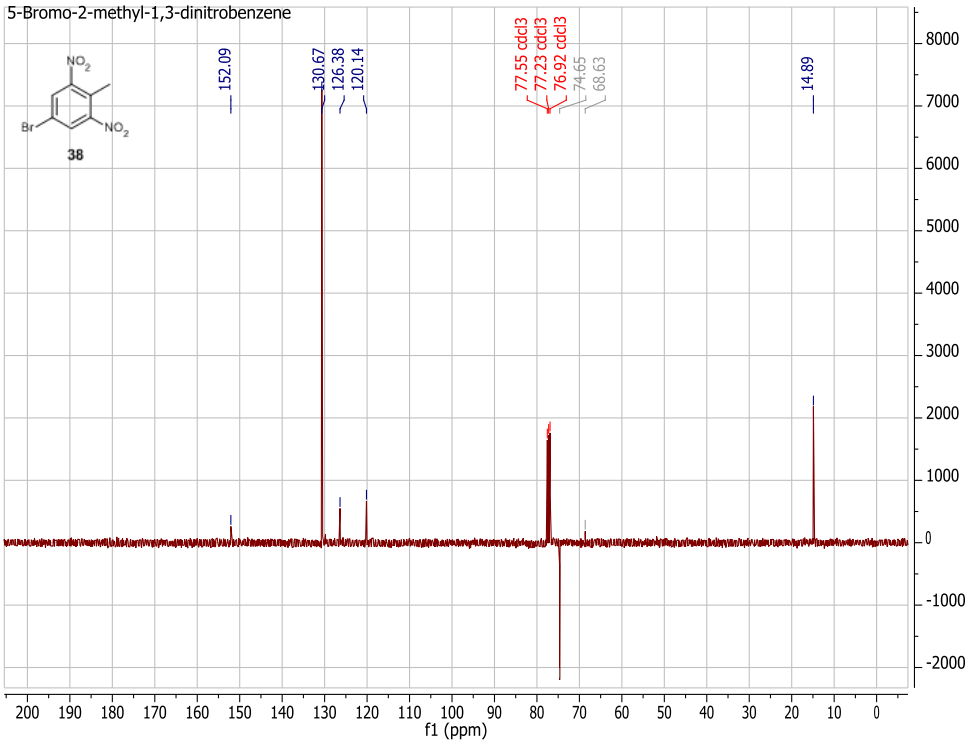
8 SPECTRA OF MOLECULES

8.1 TOTAL SYNTHESIS OF BREITFUSSIN A (CHAPTER 3)

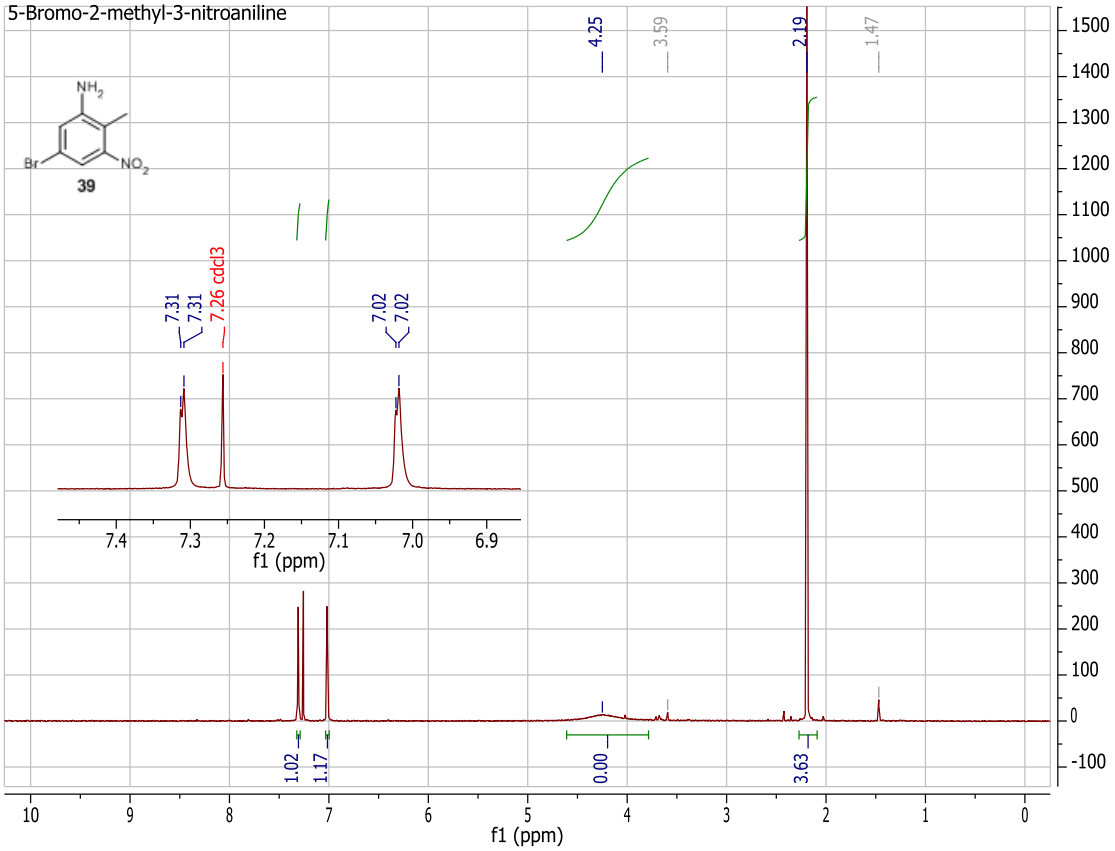
8.1.1 Synthesis of Indole Fragment (section 3.3)

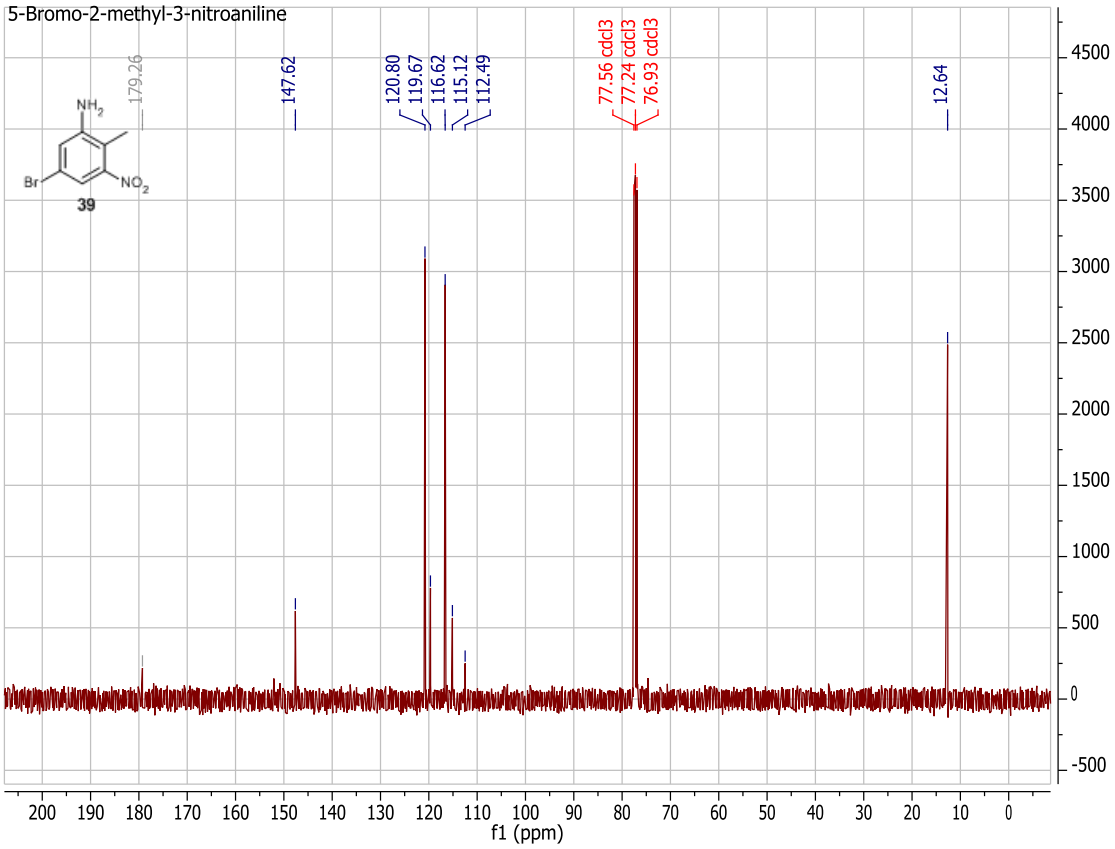
8.1.1.1 5-Bromo-2-methyl-1,3-dinitrobenzene (38)



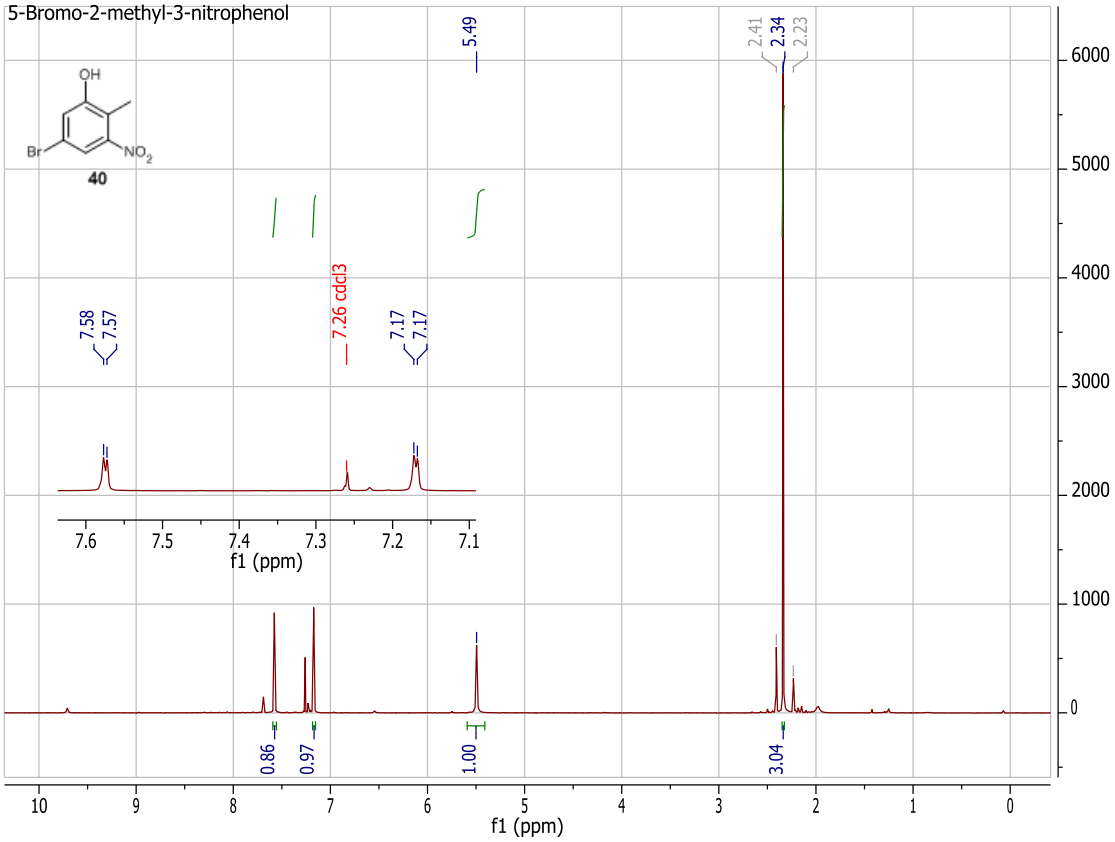


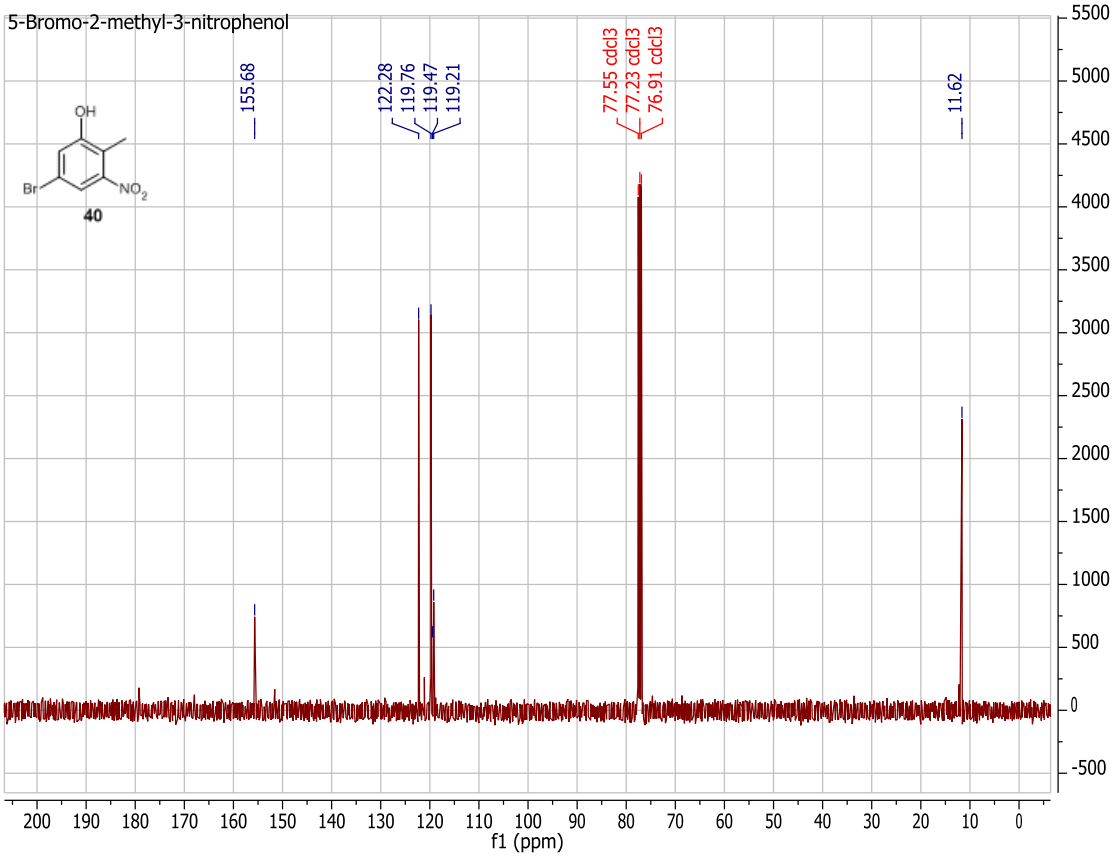
8.1.1.2 5-Bromo-2-methyl-3-nitroaniline (39)



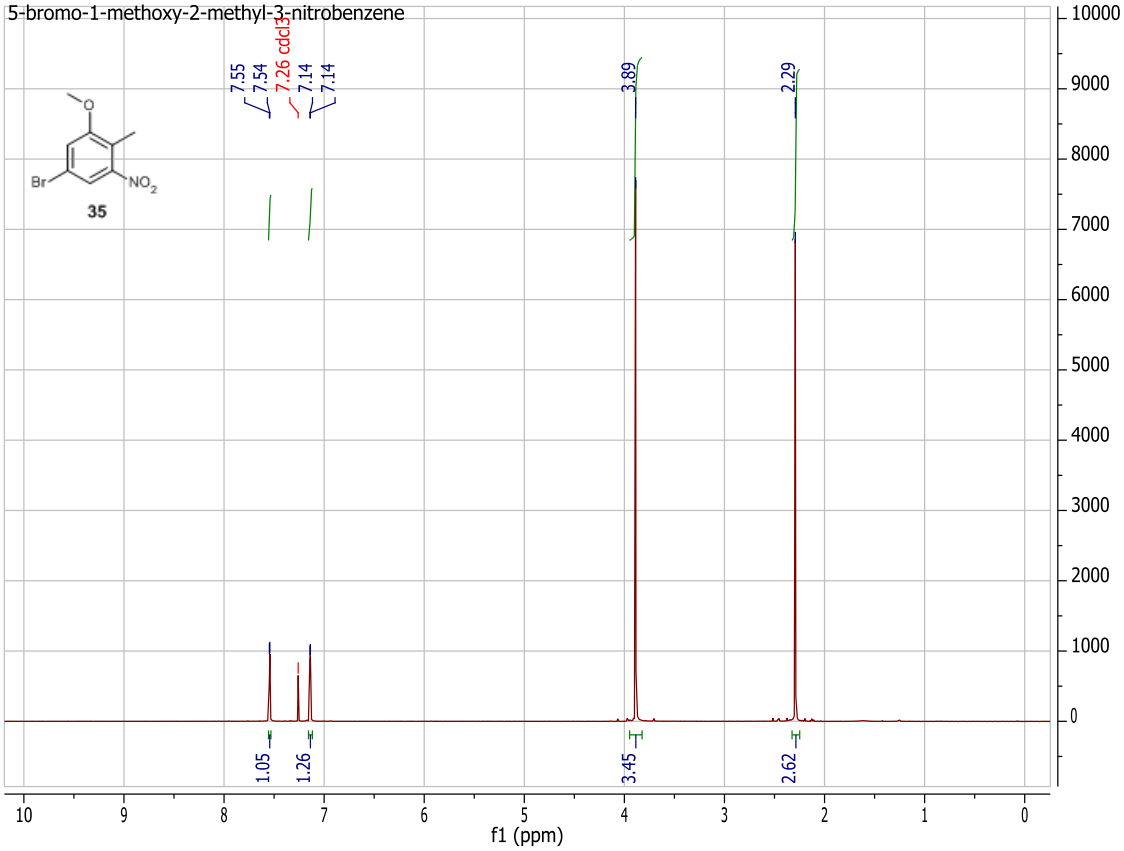


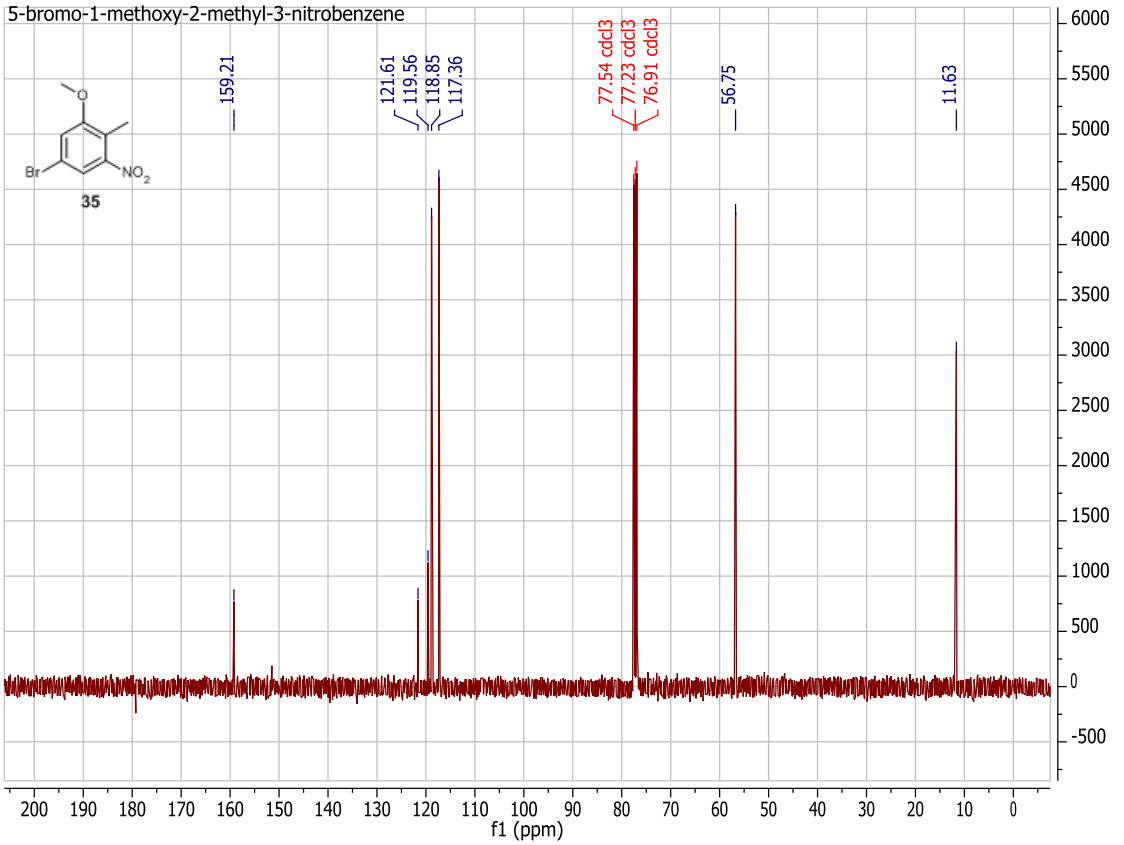
8.1.1.3 5-Bromo-2-methyl-3-nitrophenol (40)



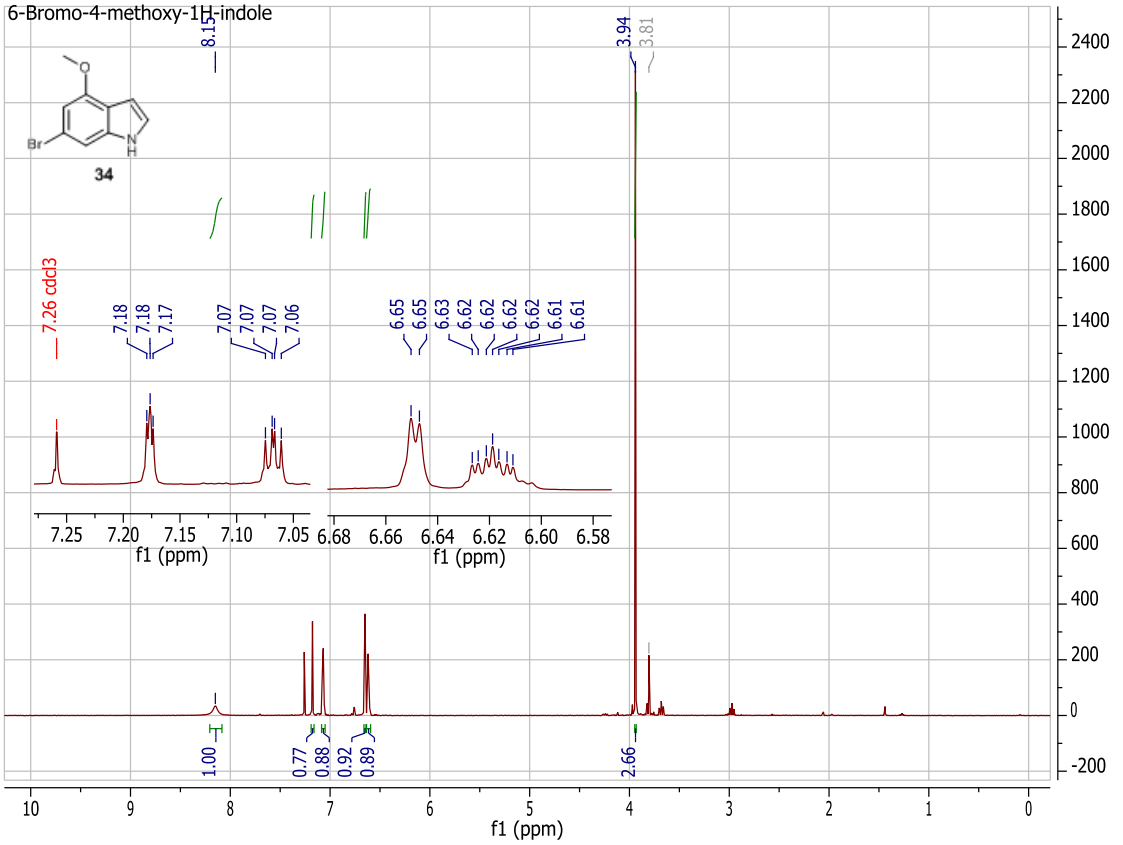


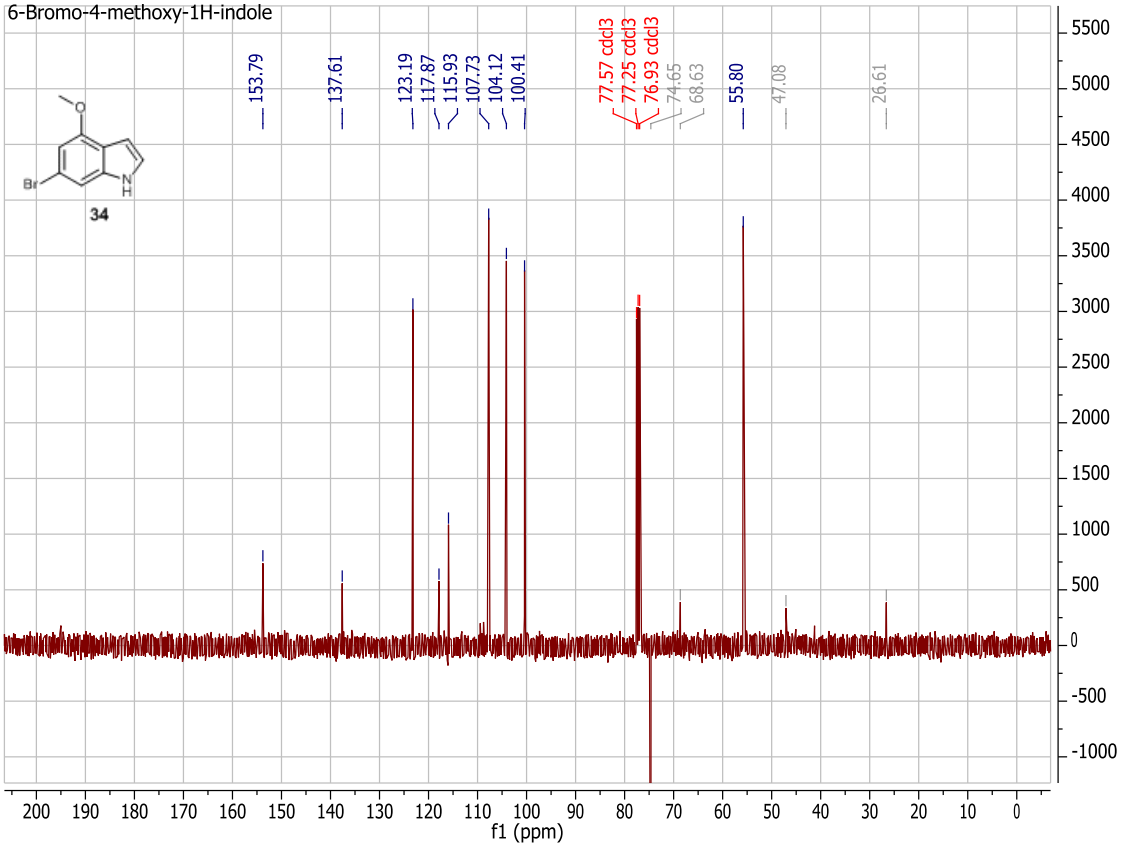
8.1.1.4 5-bromo-1-methoxy-2-methyl-3-nitrobenzene (35)





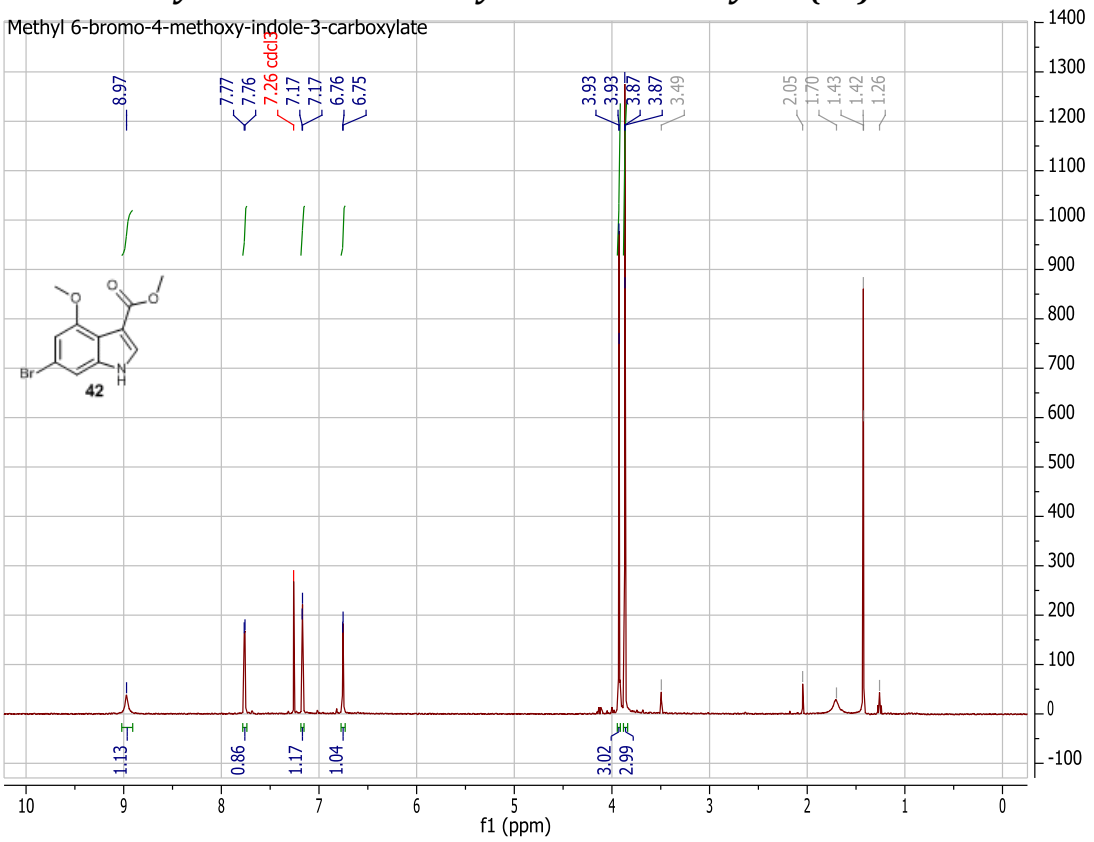
8.1.1.5 6-Bromo-4-methoxy-1H-indole (34)

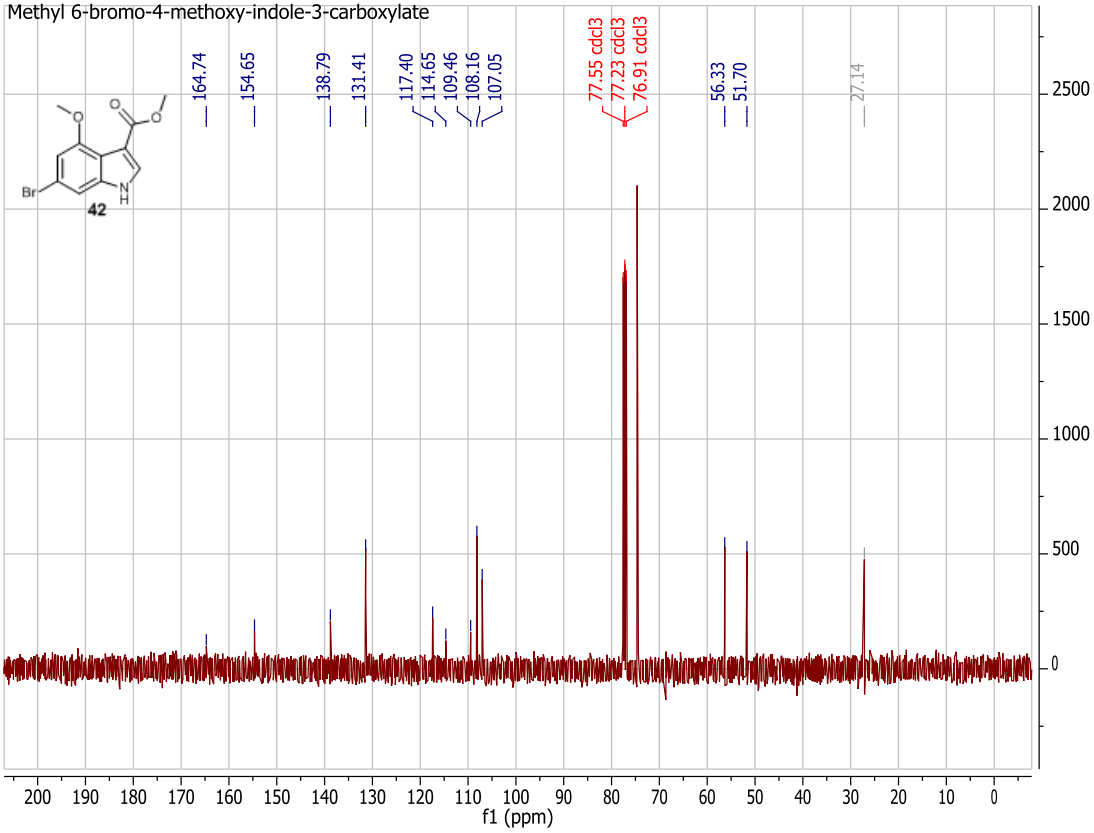




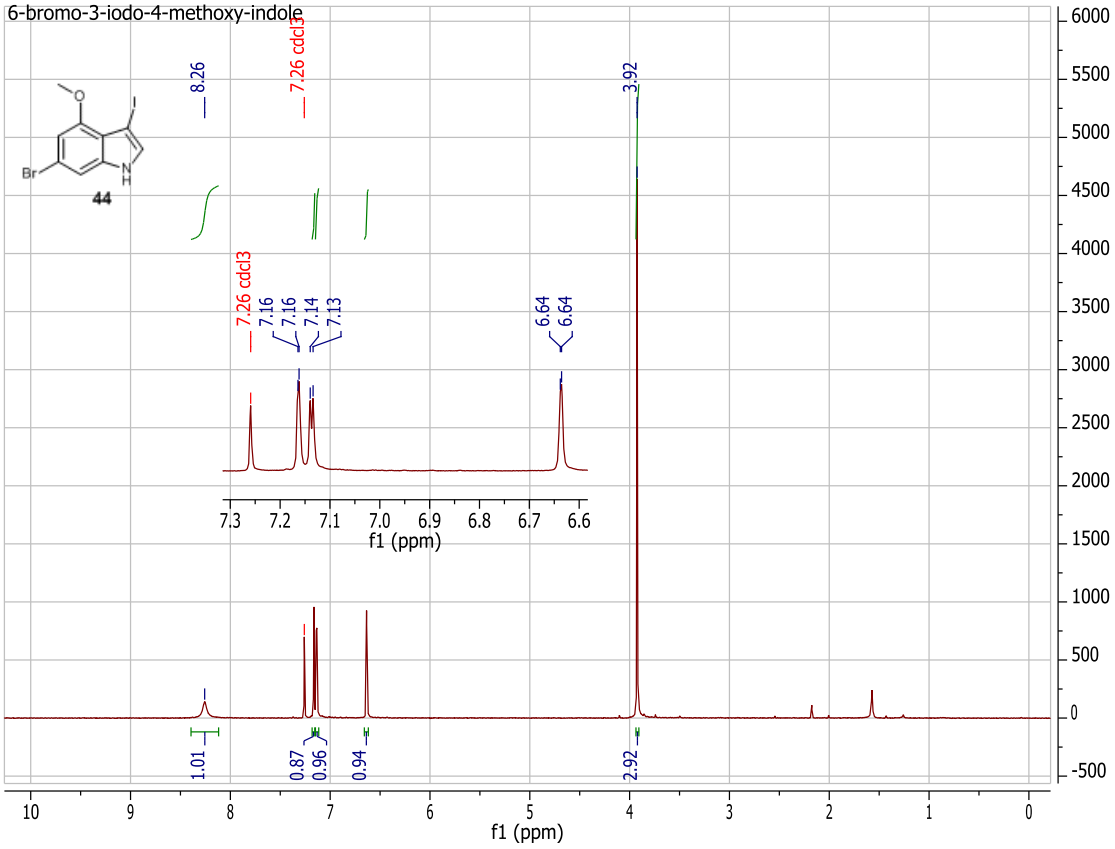
8.1.2 Functionalization of Indole (section 3.4)

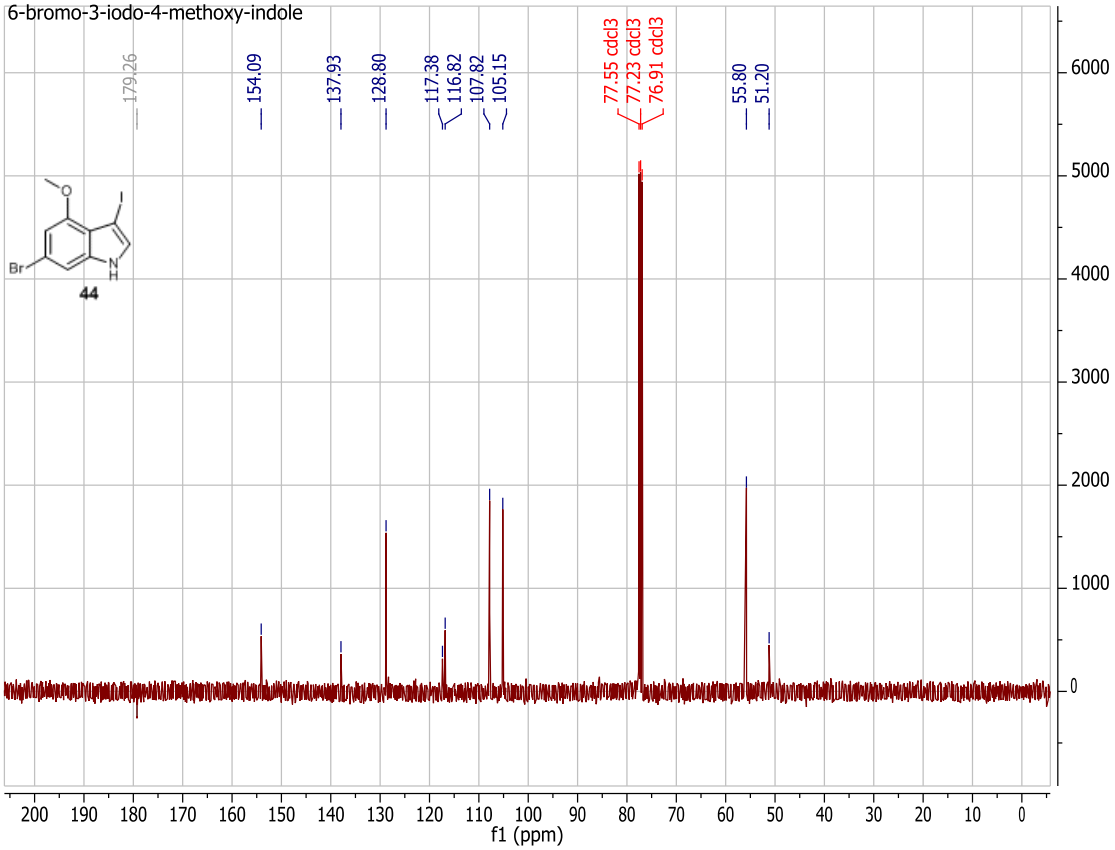
8.1.2.1 Methyl 6-bromo-4-methoxy-indole-3-carboxylate (42)



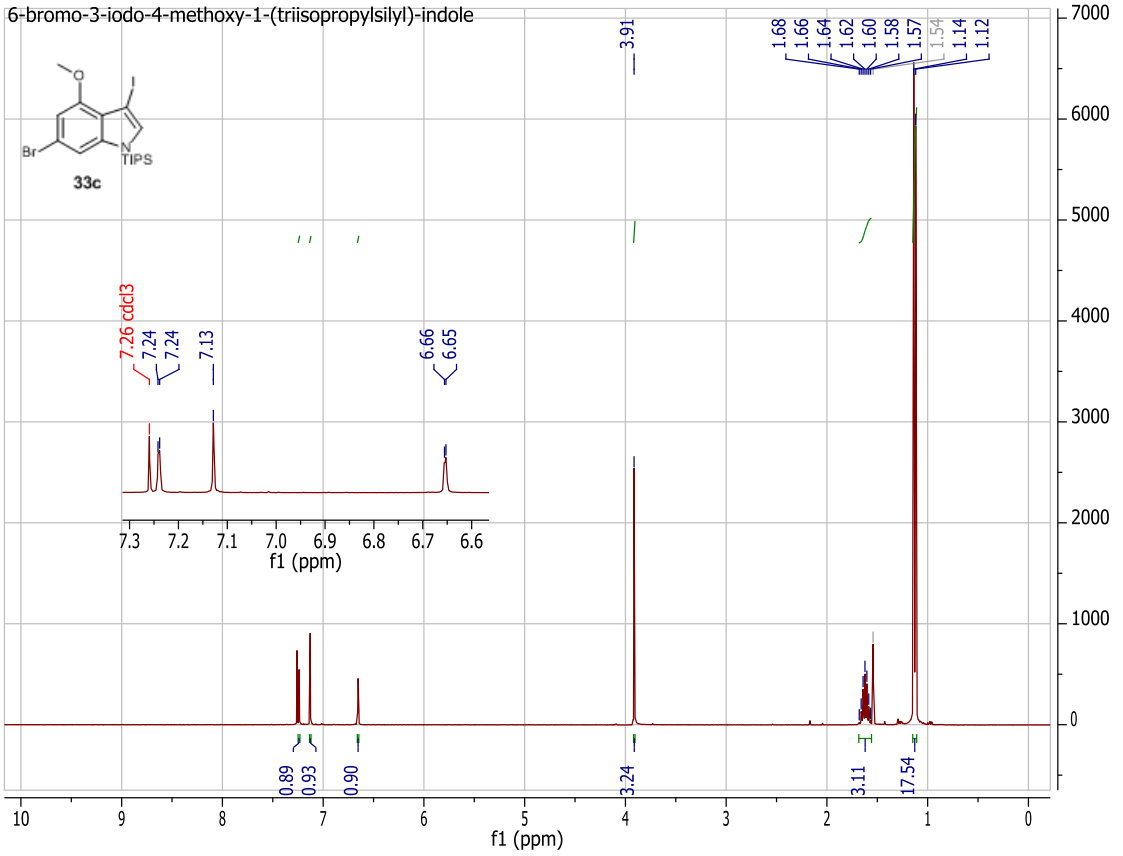


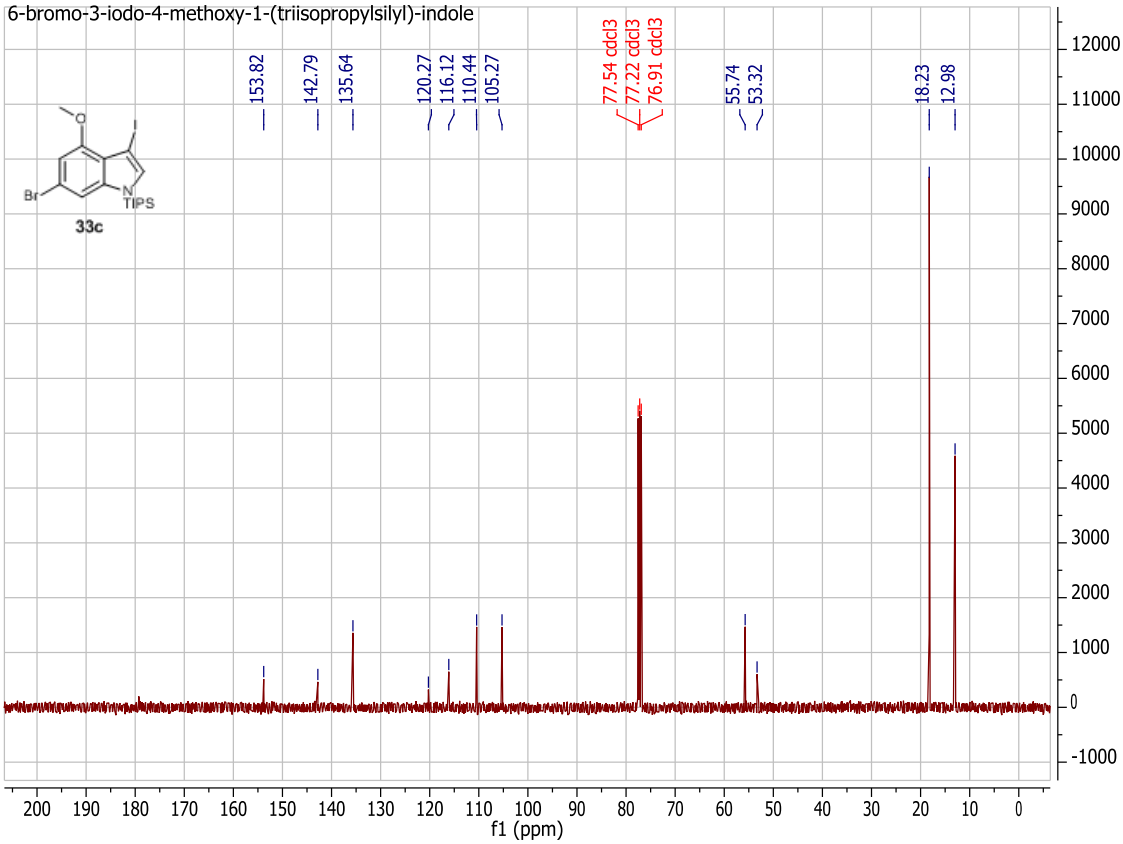
8.1.2.2 6-bromo-3-iodo-4-methoxy-indole (44)



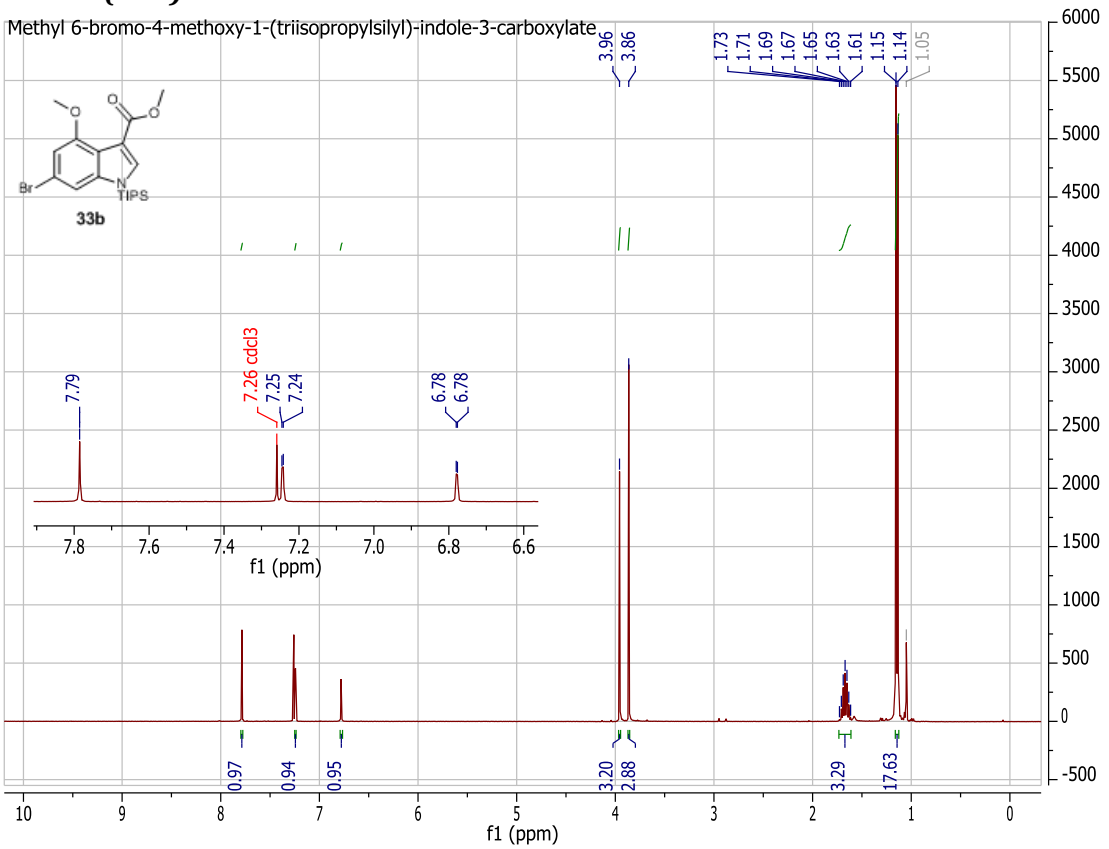


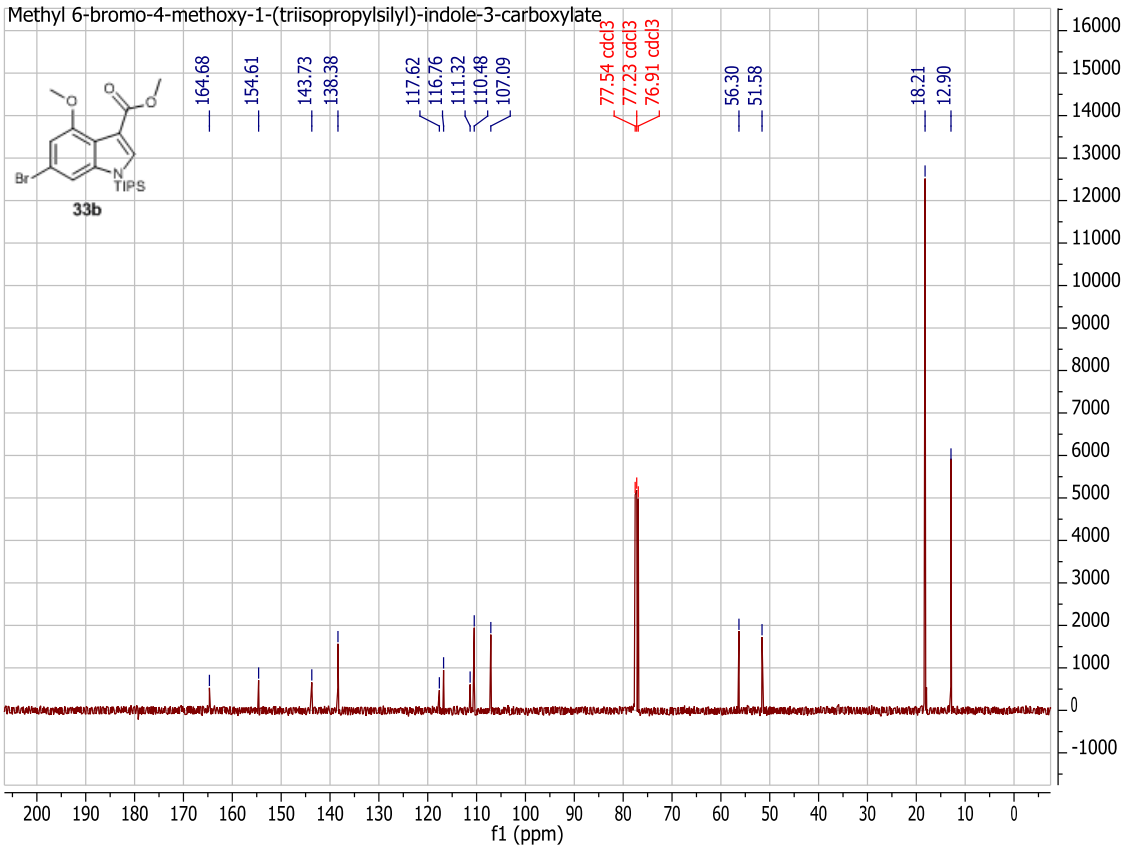
8.1.2.3 6-bromo-3-iodo-4-methoxy-1-(triisopropylsilyl)-indole (33c)





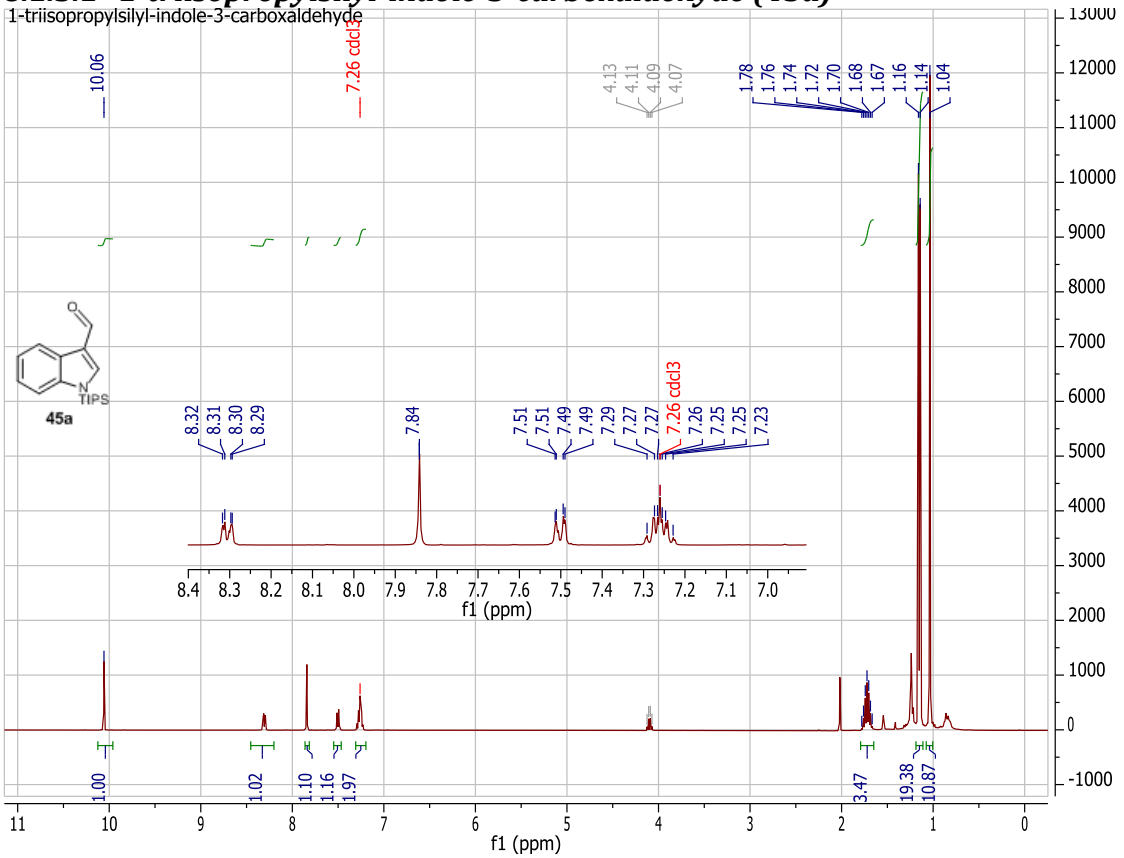
8.1.2.4 Methyl 6-bromo-4-methoxy-1-(triisopropylsilyl)-indole-3-carboxylate (33b)

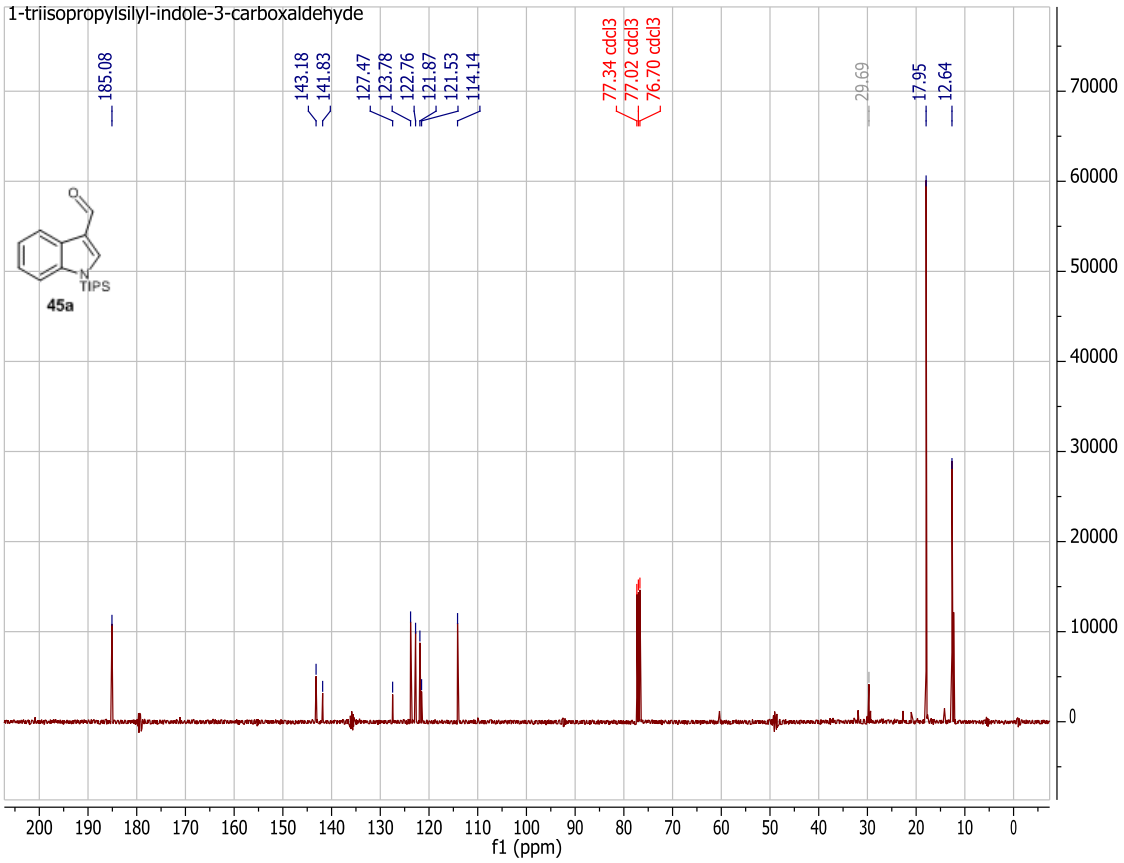


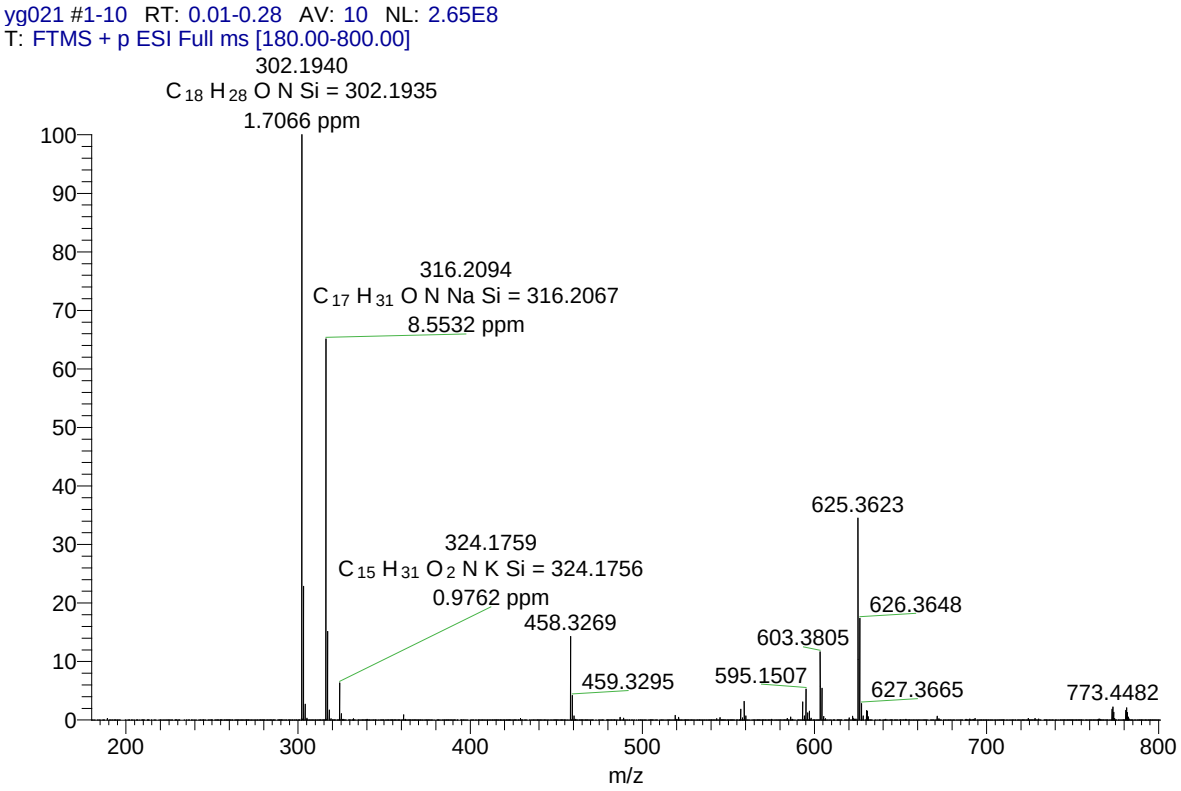


8.1.3 Oxazole Synthesis (section 3.5)

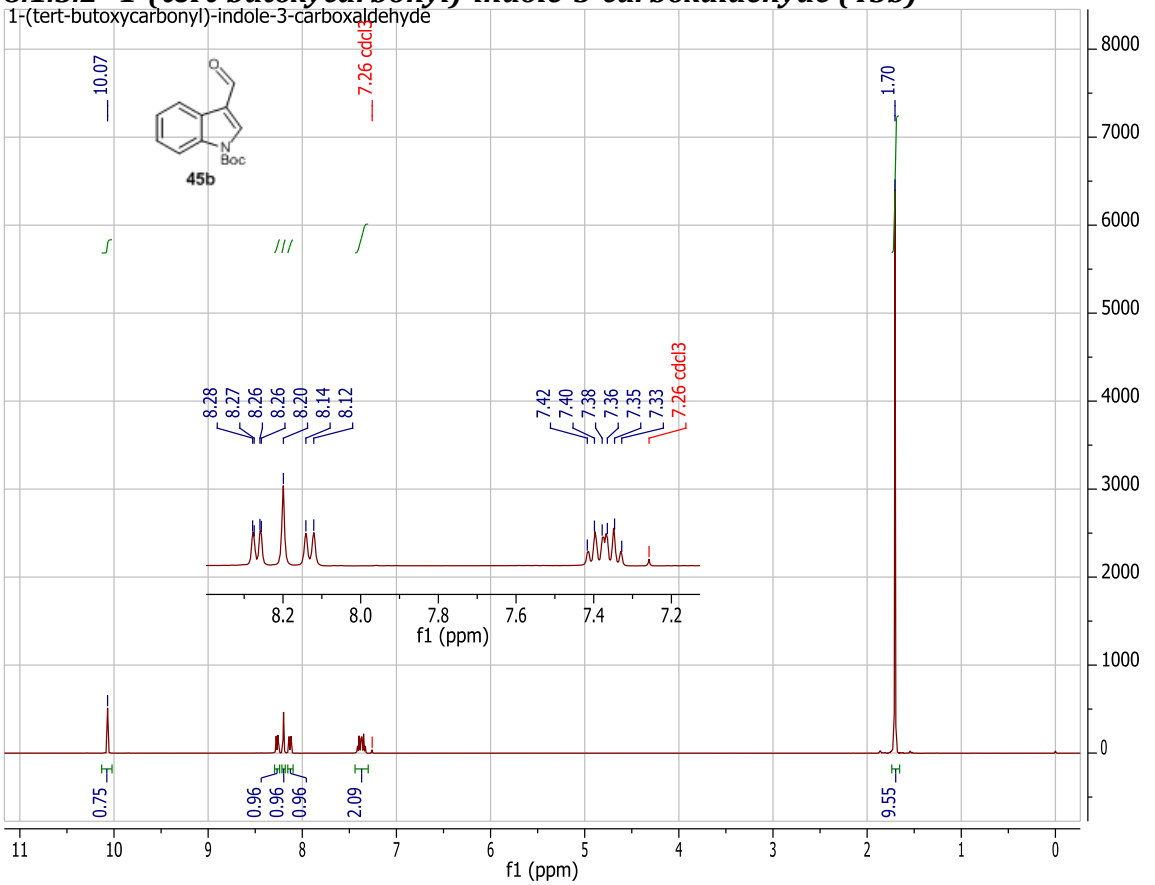
8.1.3.1 1-triisopropylsilyl-indole-3-carboxaldehyde (45a)

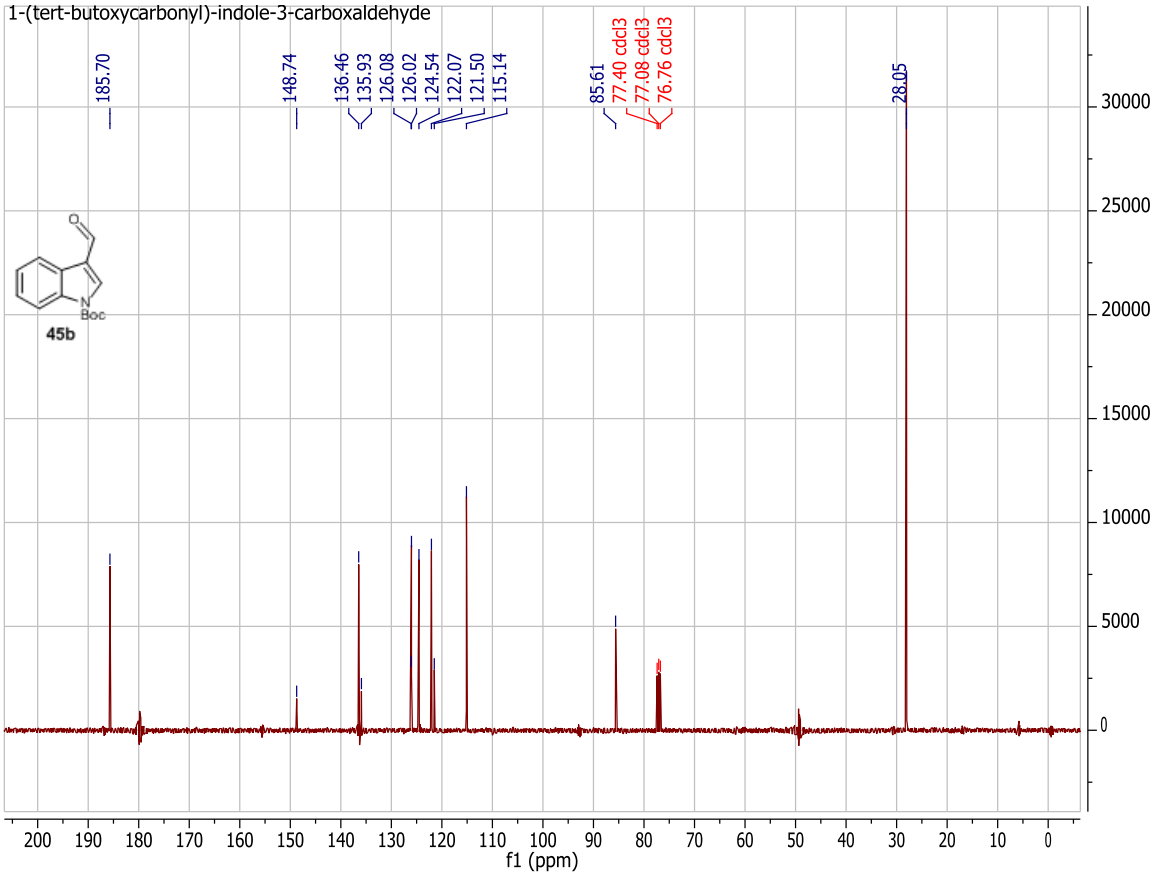




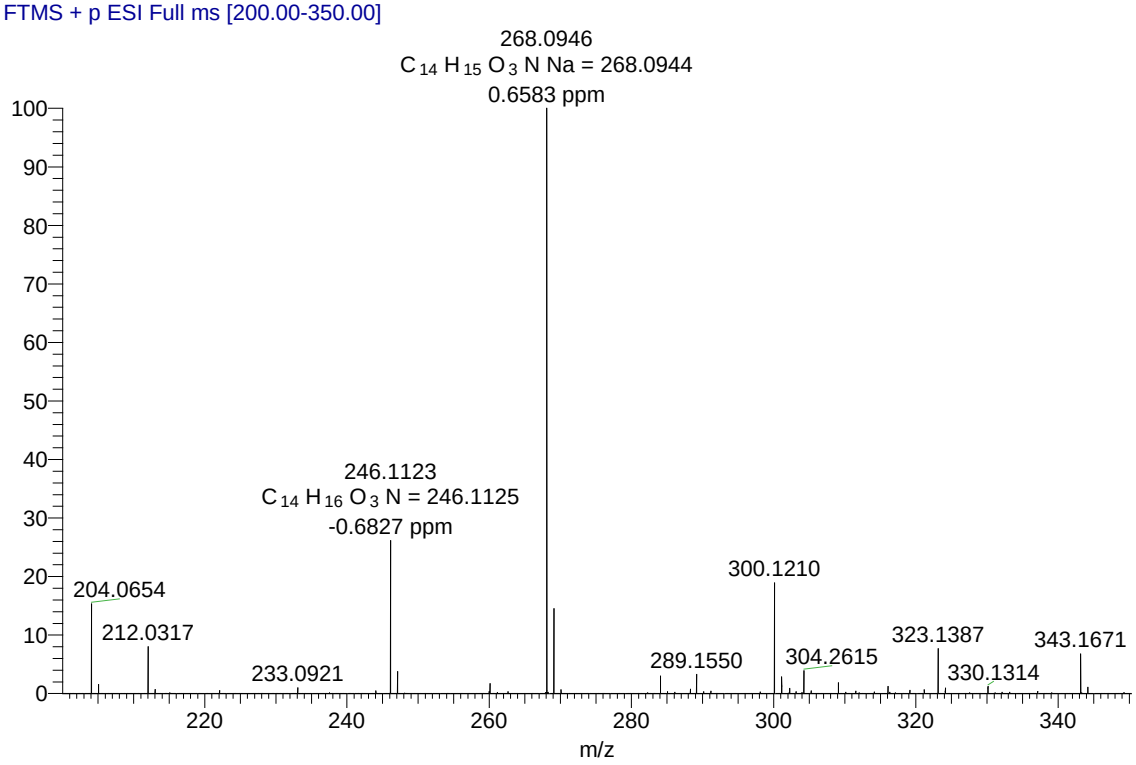

yg021 #1-10 RT: 0.01-0.28 AV: 10 NL: 2.65E8
T: FTMS + p ESI Full ms [180.00-800.00]
302.1940
C 18 H 28 O N Si = 302.1935
1.7066 ppm
316.2094
C 17 H 31 O N Na Si = 316.2067
8.5532 ppm
324.1759
C 15 H 31 O 2 N K Si = 324.1756
0.9762 ppm
458.3269
459.3295
595.1507
603.3805
625.3623
626.3648
627.3665
773.4482
100
90
80
70
60
50
40
30
20
10
0
200
300
400
500
600
700
800
m/z

8.1.3.2 1-(tert-butoxycarbonyl)-indole-3-carboxaldehyde (45b)

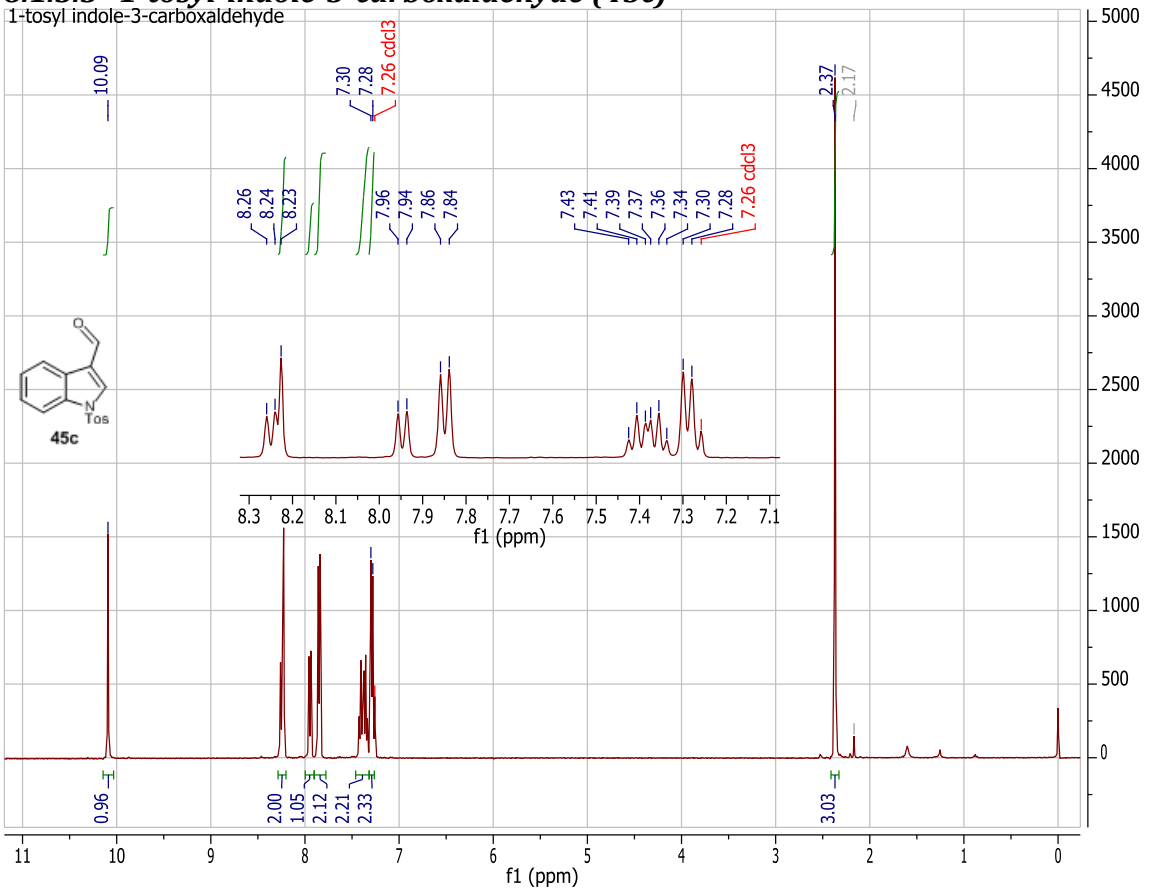


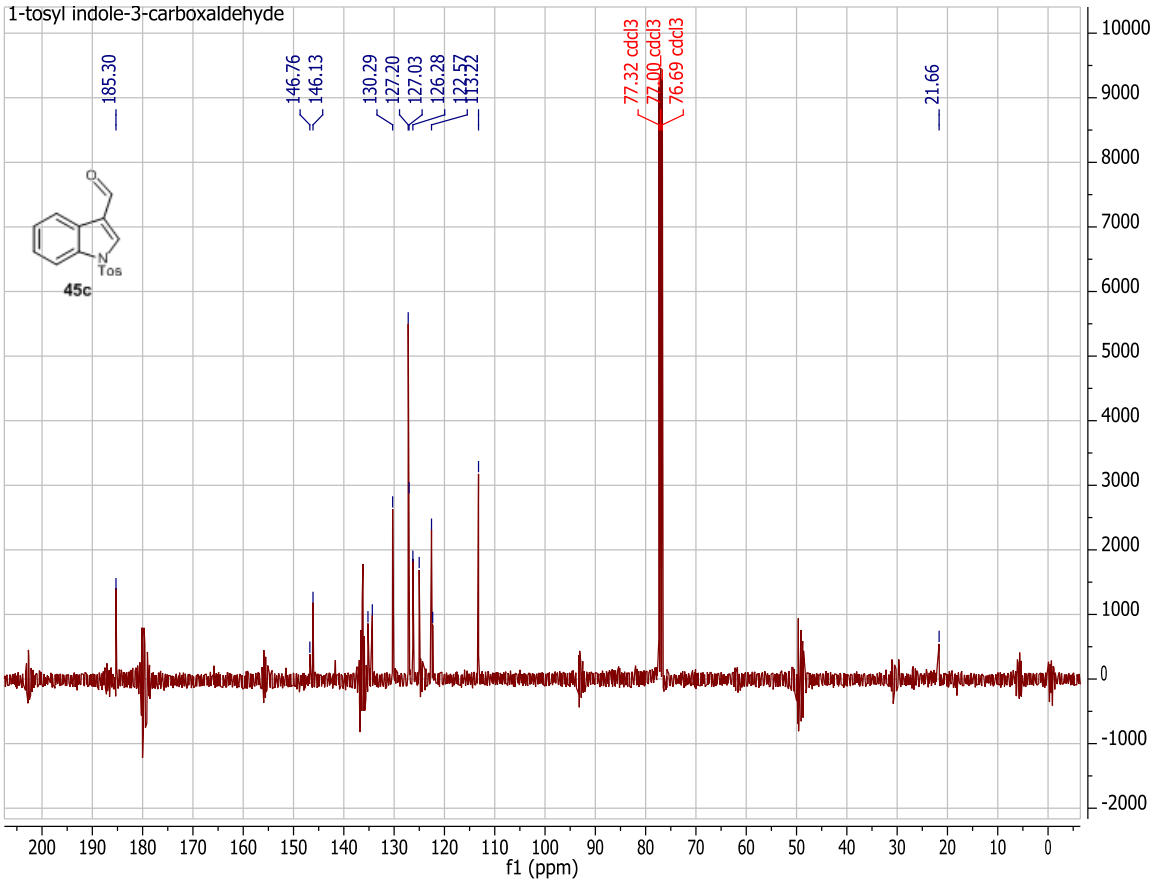


yg018 #1-5 RT: 0.02-0.13 AV: 5 NL: 8.08E7
T: FTMS + p ESI Full ms [200.00-350.00]

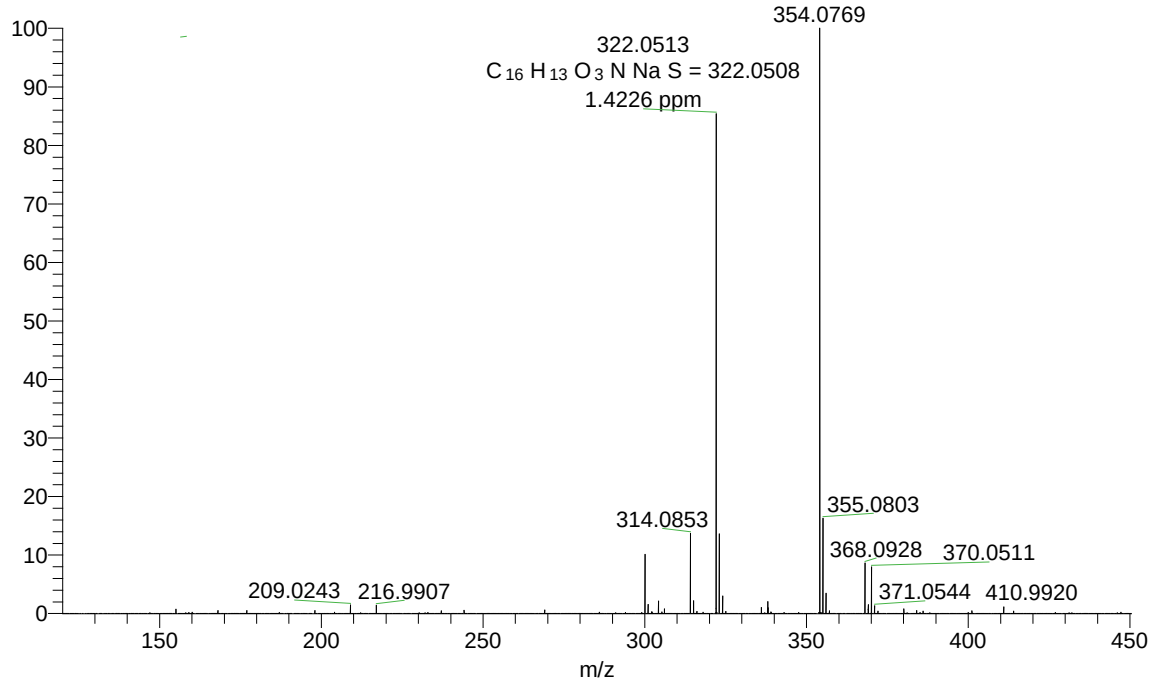


8.1.3.3 1-tosyl-indole-3-carboxaldehyde (45c)

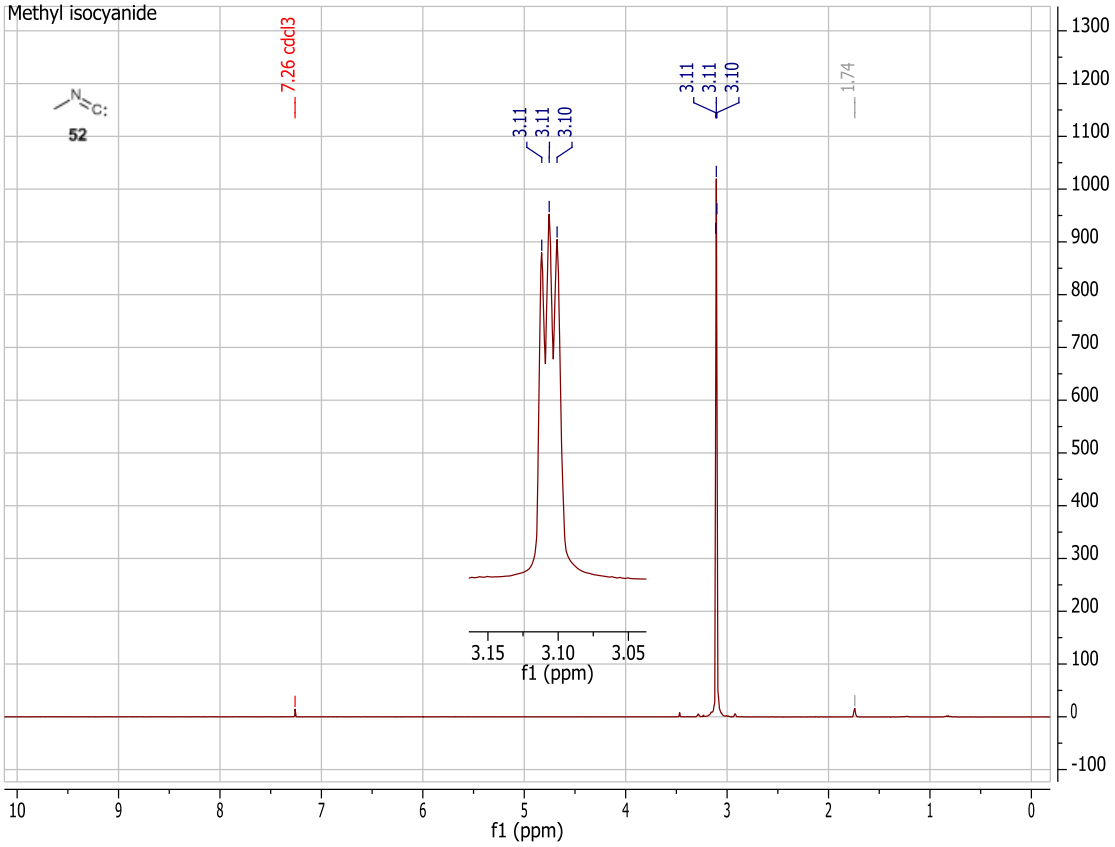


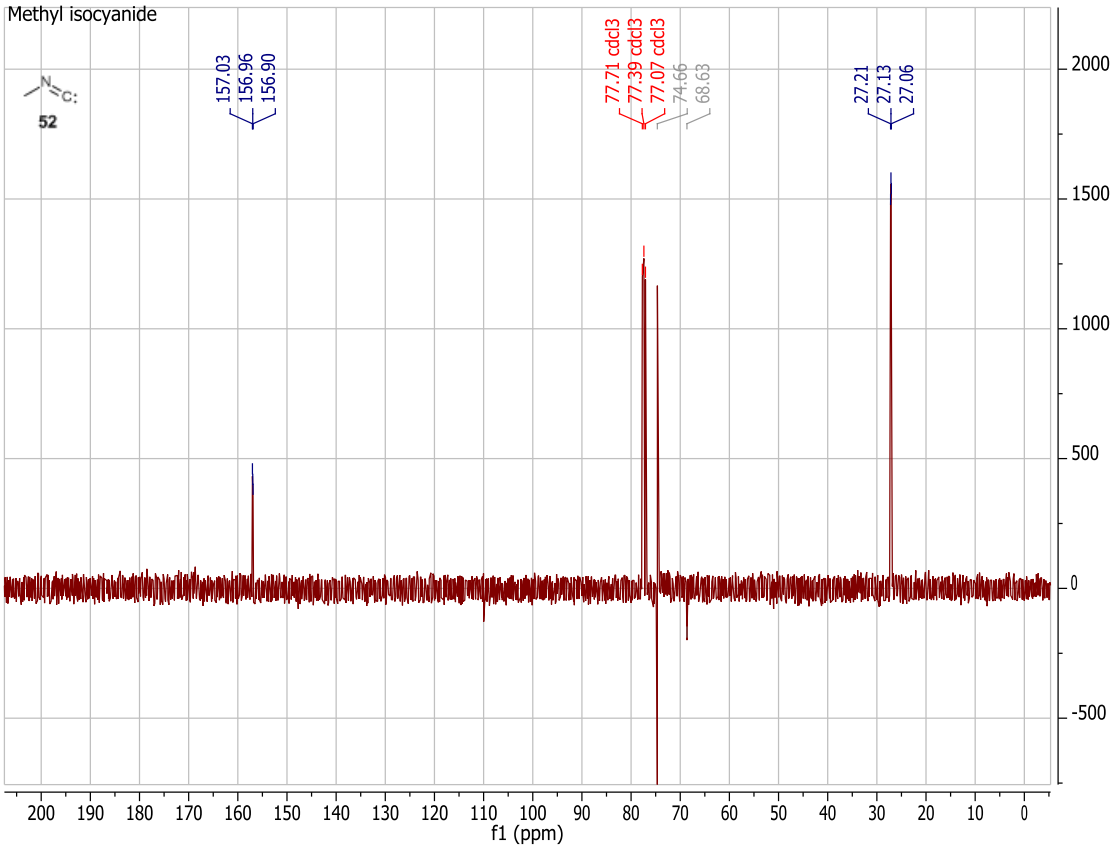


yg003c__ #1-10 RT: 0.02-0.27 AV: 10 NL: 1.11E8
T: FTMS + p ESI Full ms [120.00-450.00]

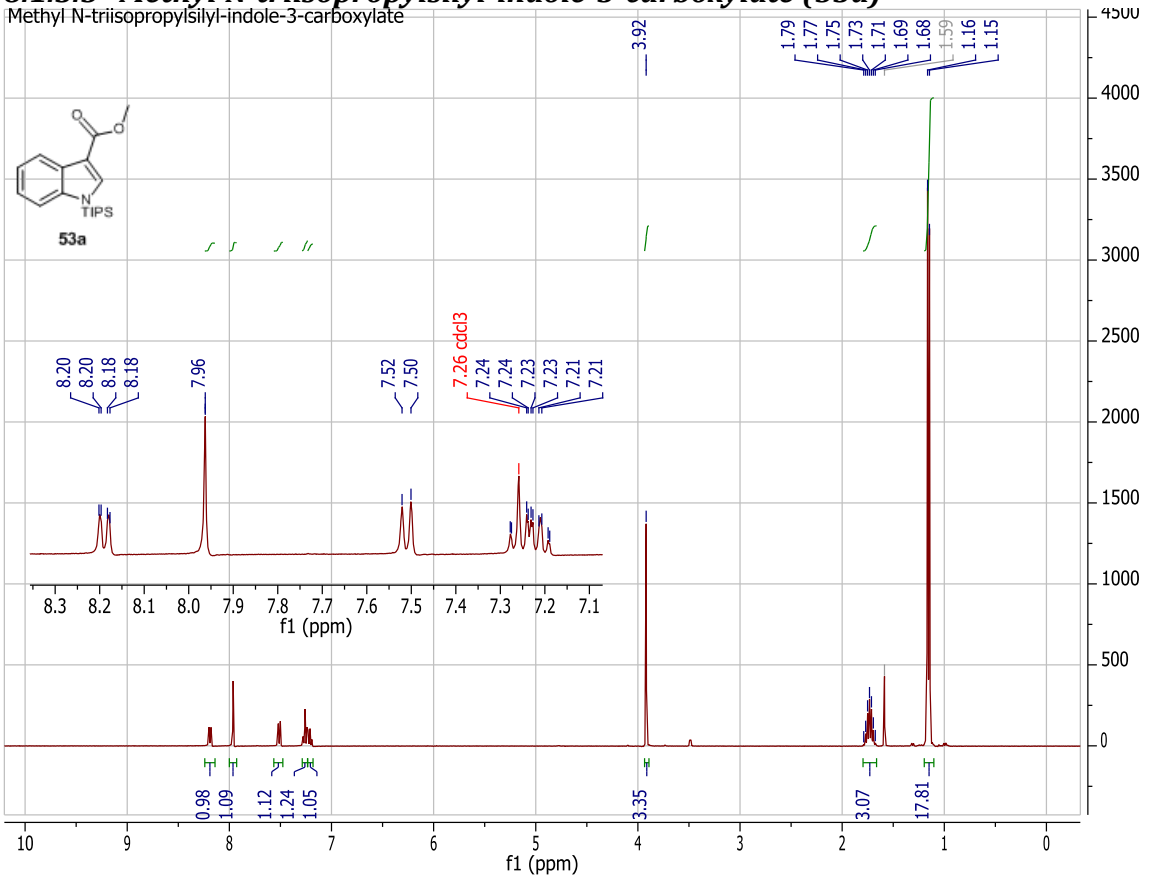


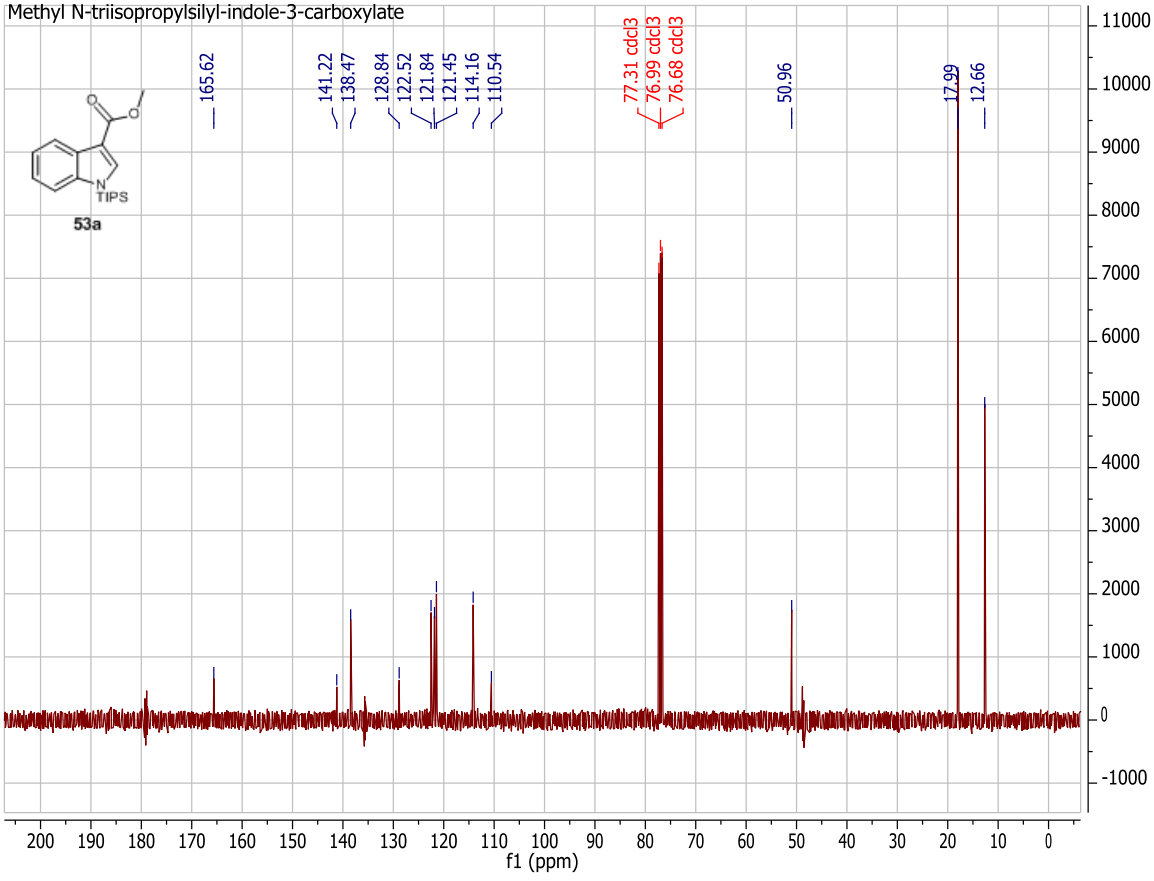
8.1.3.4 Methyl isocyanide (52)



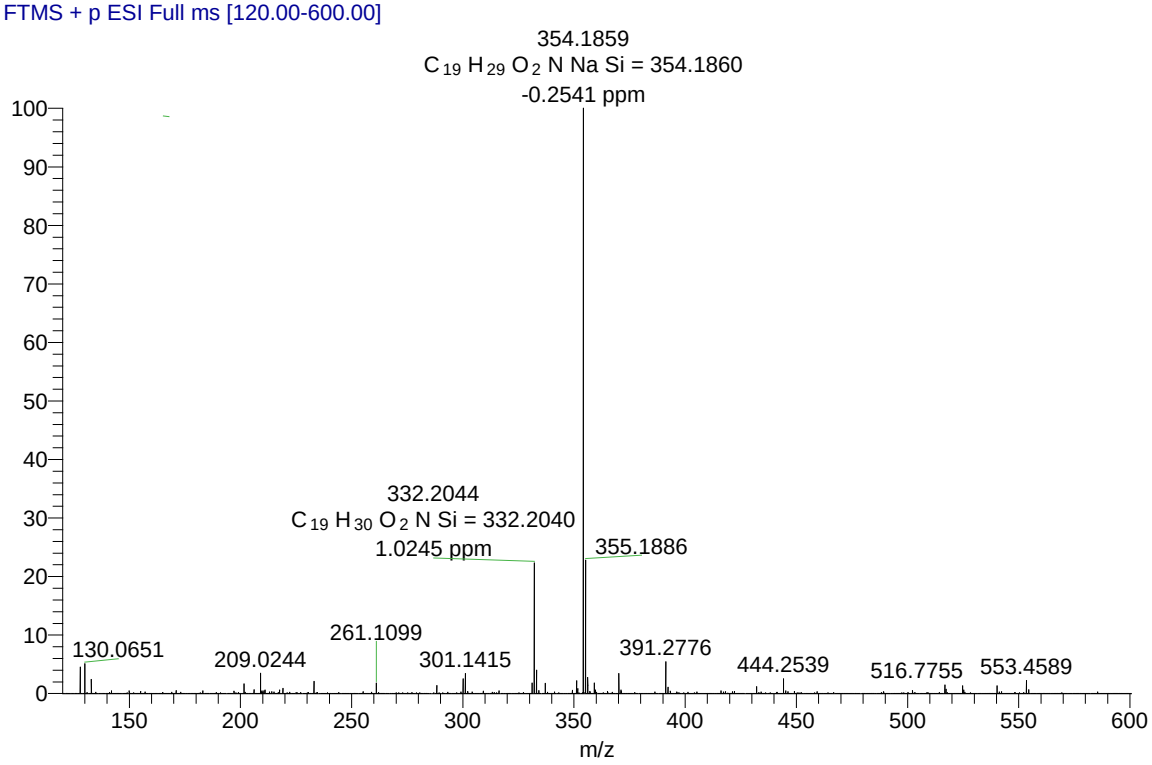


8.1.3.5 Methyl N*-triisopropylsilyl-indole-3-carboxylate (53a)*

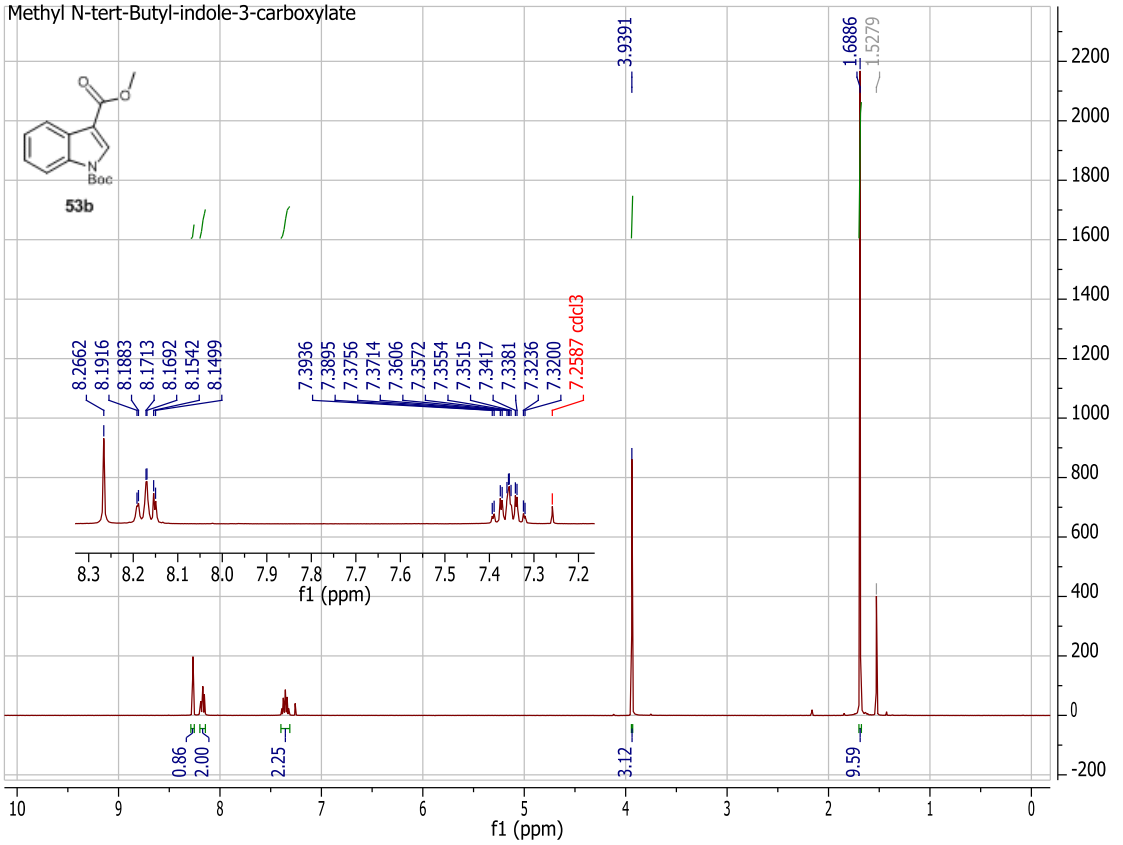


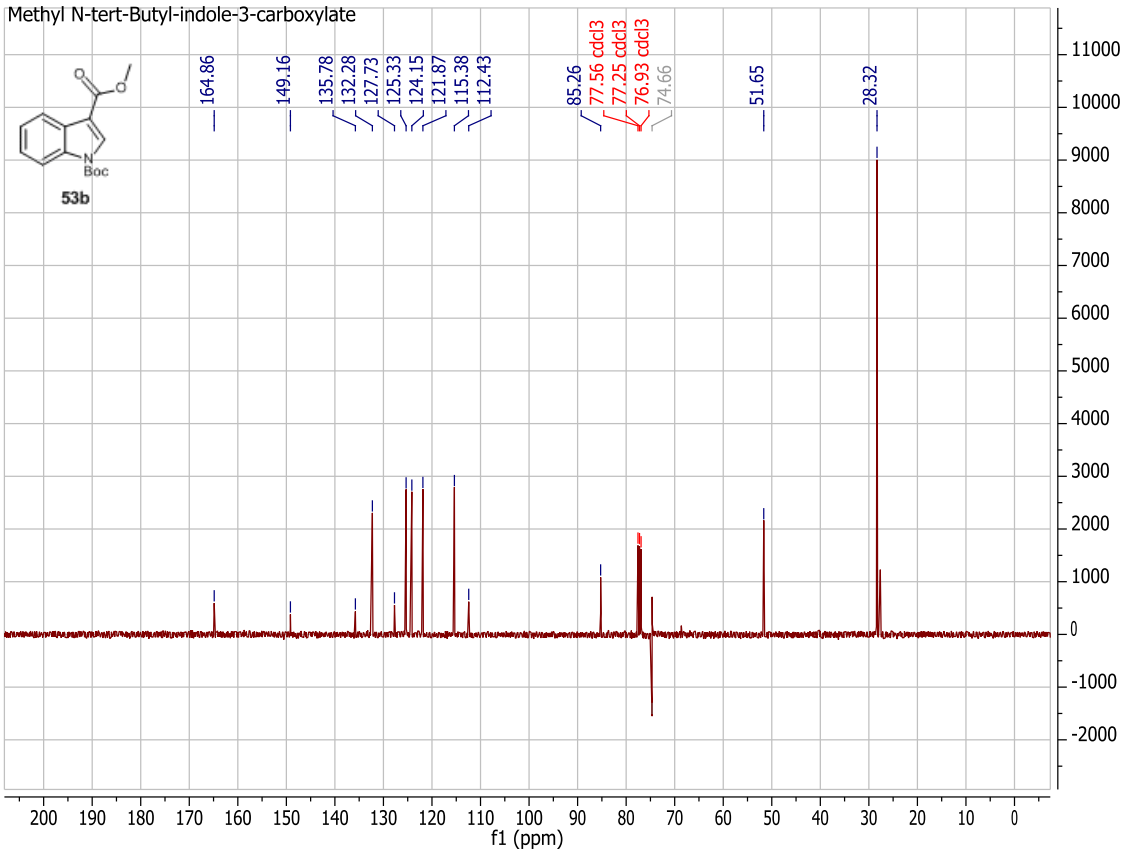


yg032_b #1-5 RT: 0.00-0.12 AV: 5 NL: 5.75E6
T: FTMS + p ESI Full ms [120.00-600.00]

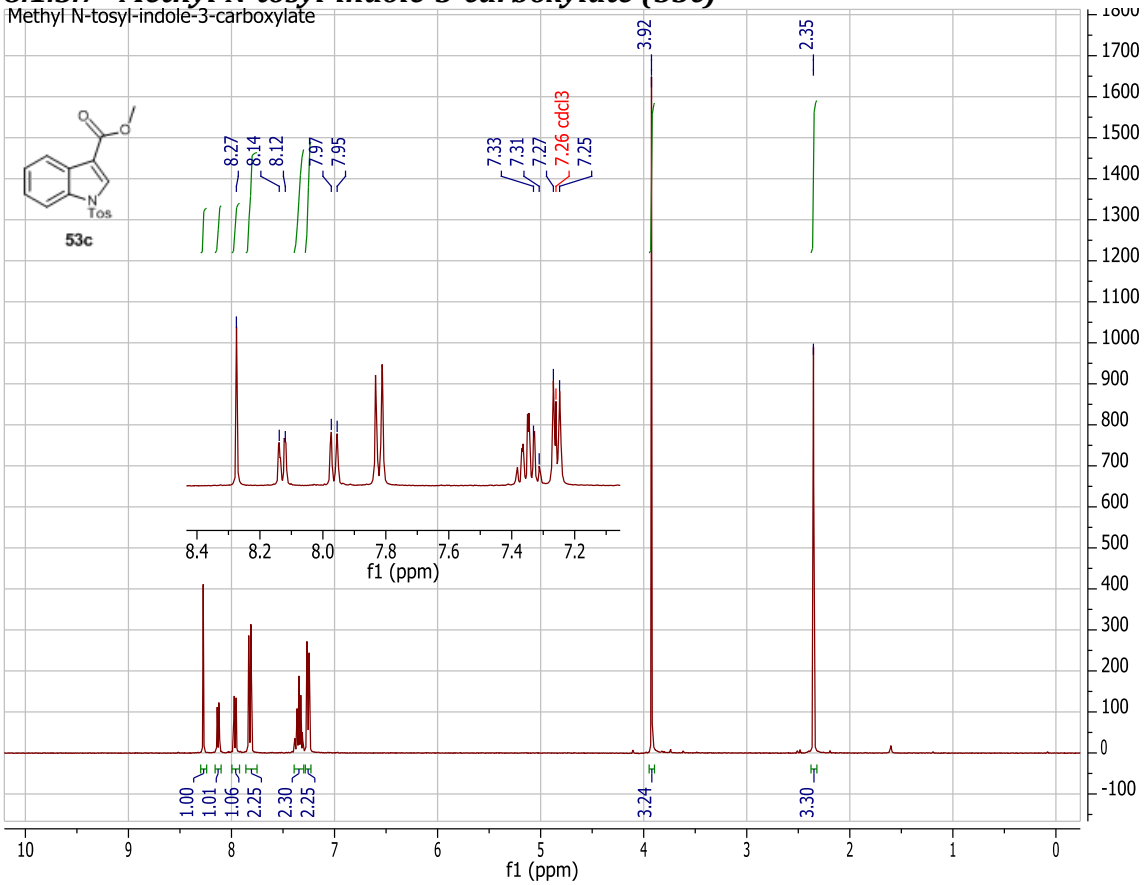


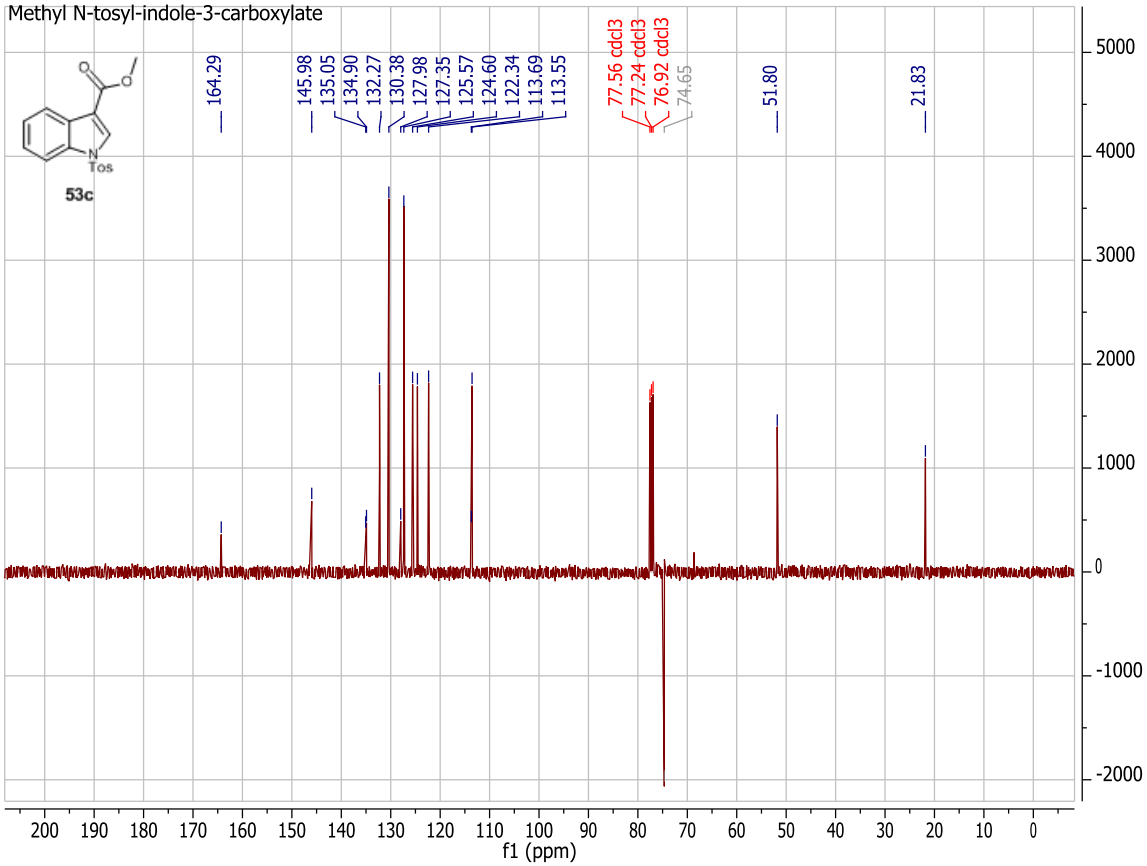
8.1.3.6 Methyl N*-tert-Butyl-indole-3-carboxylate (53b)*



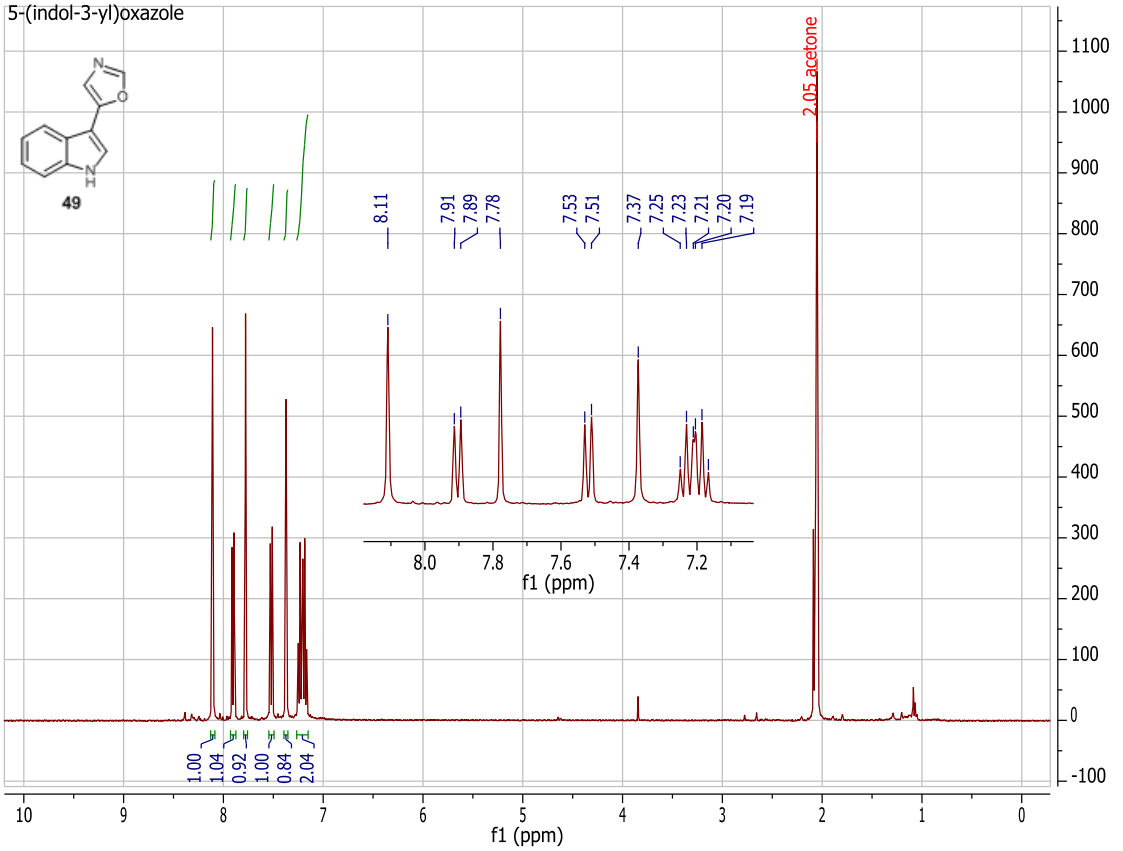


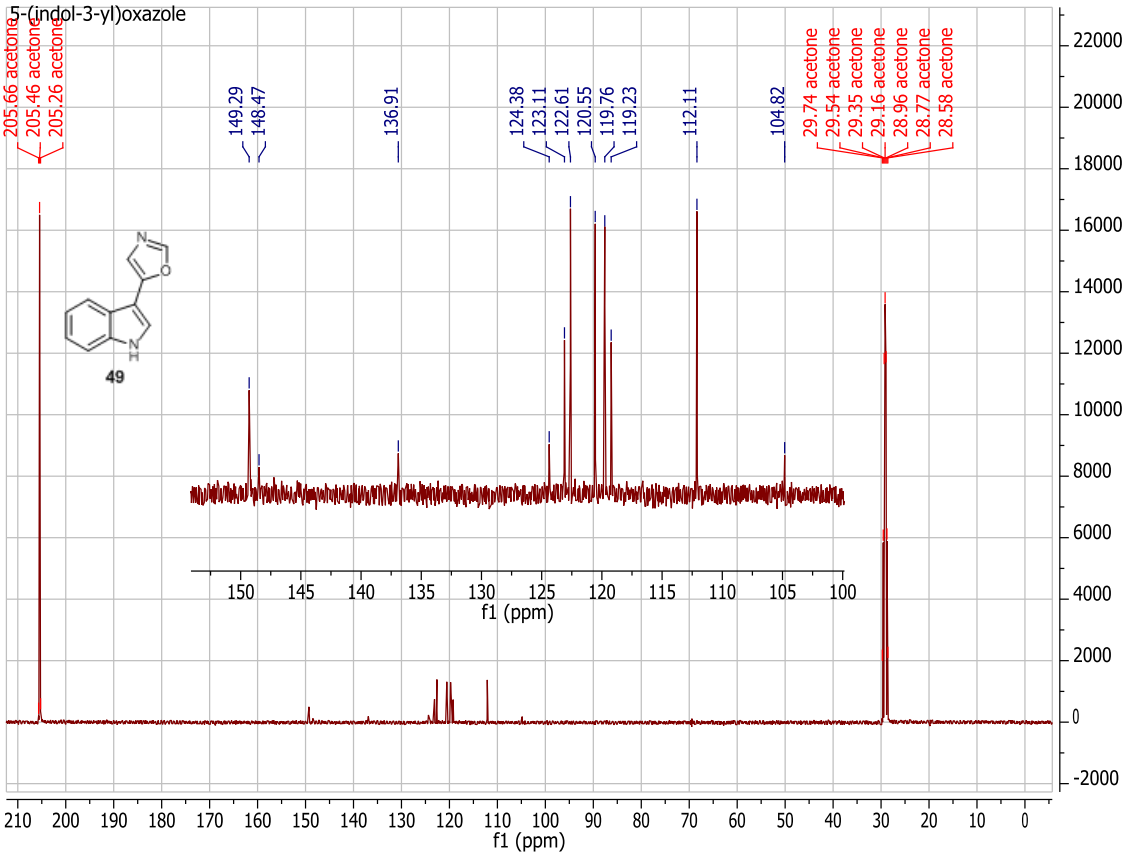
8.1.3.7 Methyl N-*tosyl-indole-3-carboxylate (53c)*



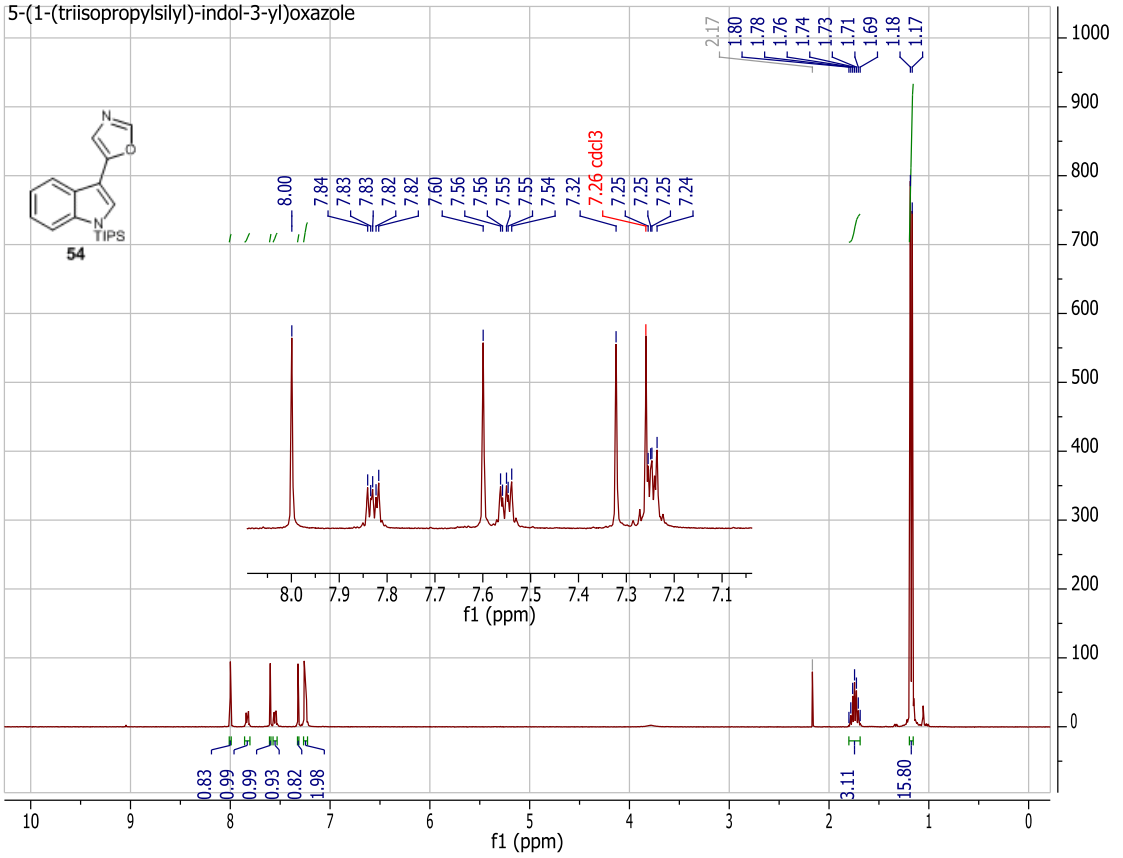


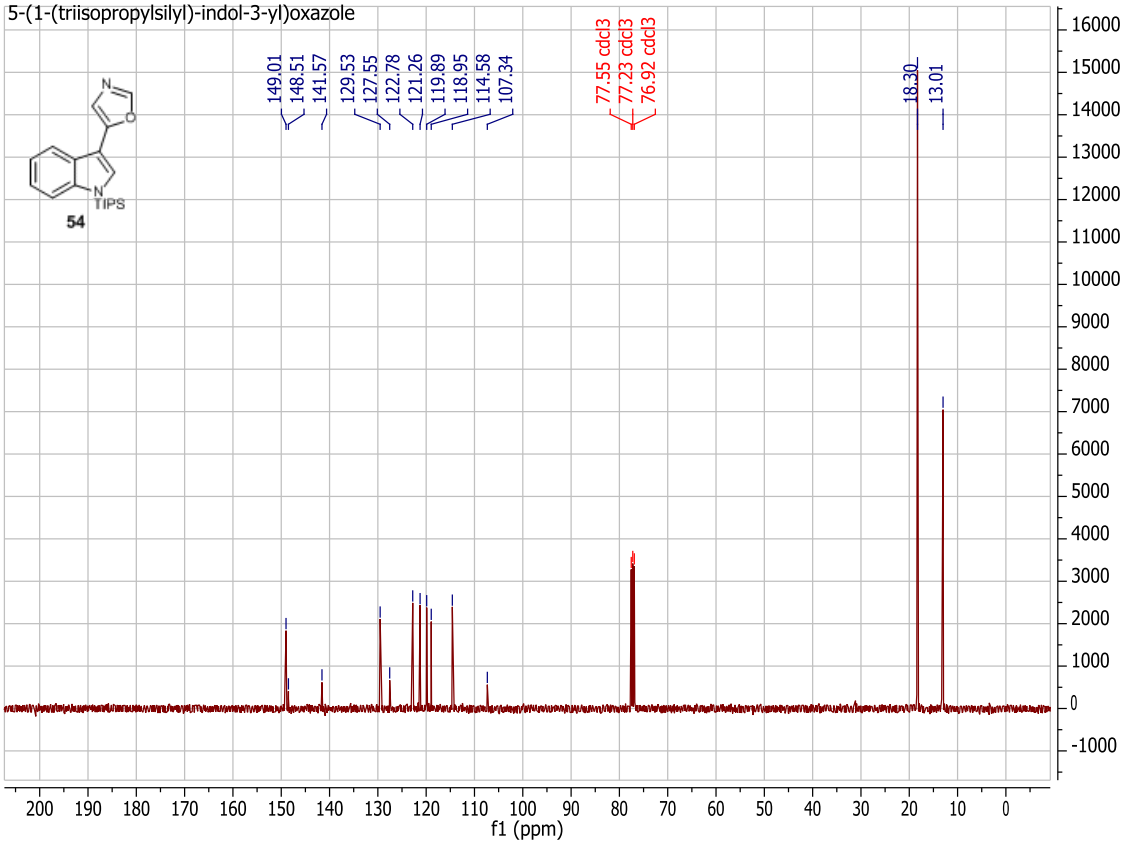
8.1.3.8 5-(indol-3-yl)oxazole (49)



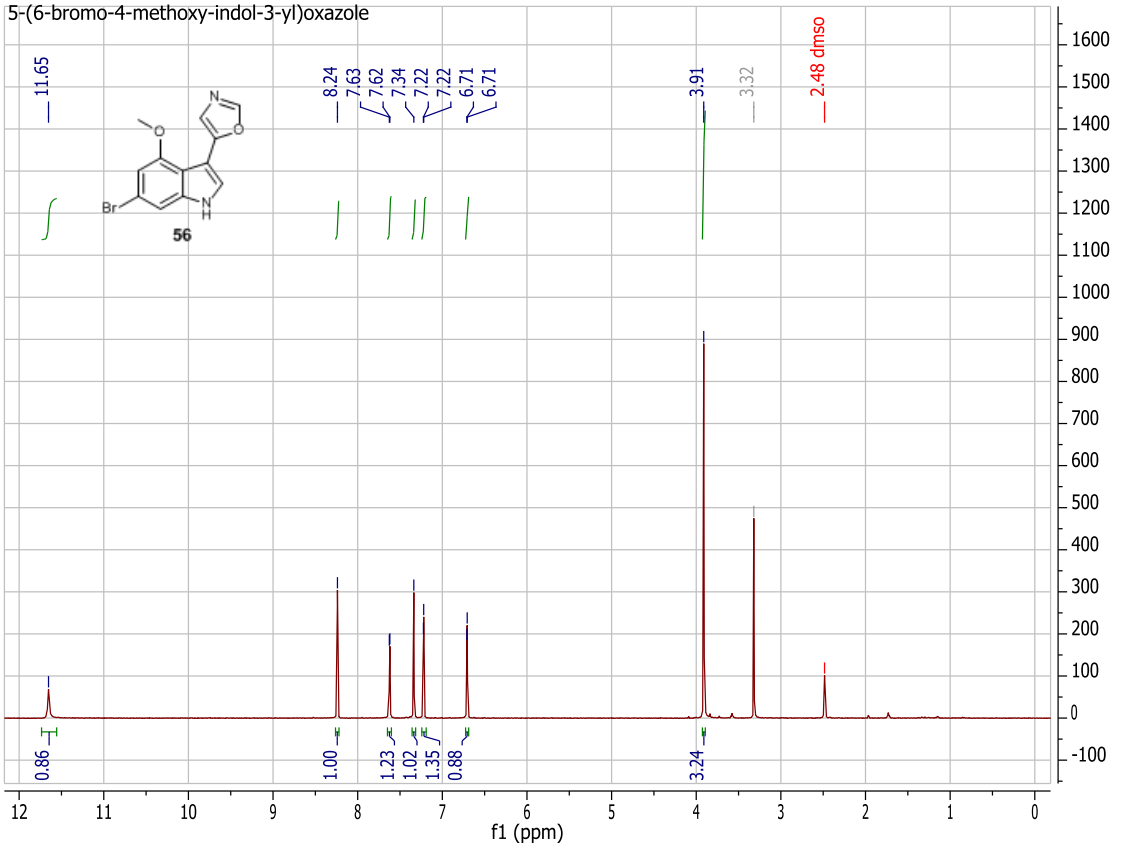


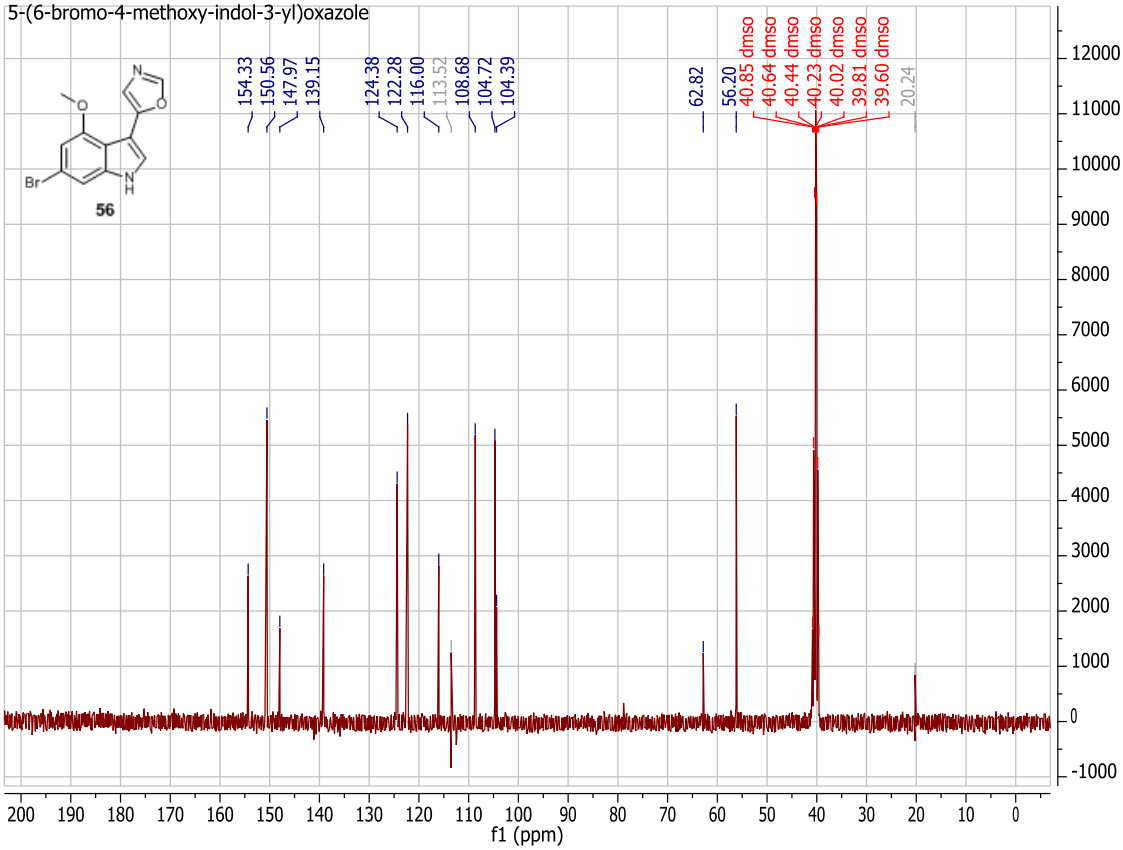
8.1.3.9 5-(1-(triisopropylsilyl)-indol-3-yl)oxazole (54)



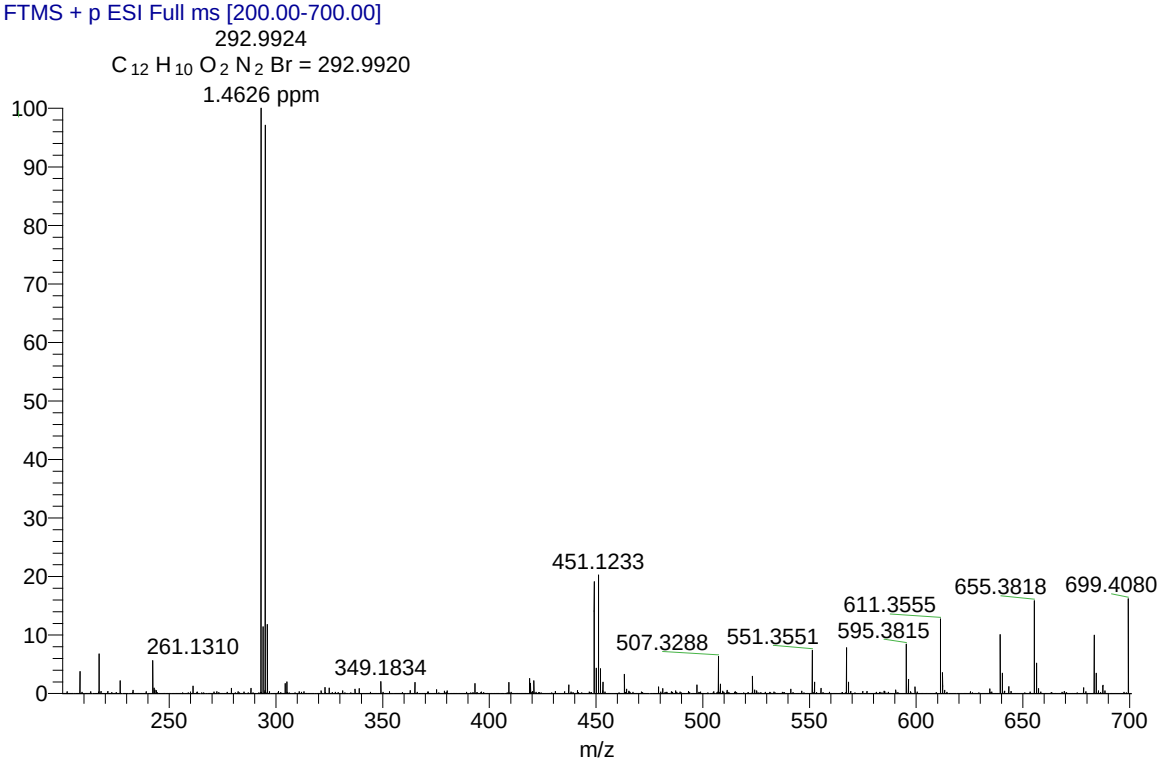


8.1.3.105-(6-bromo-4-methoxy-indol-3-yl)oxazole (56)

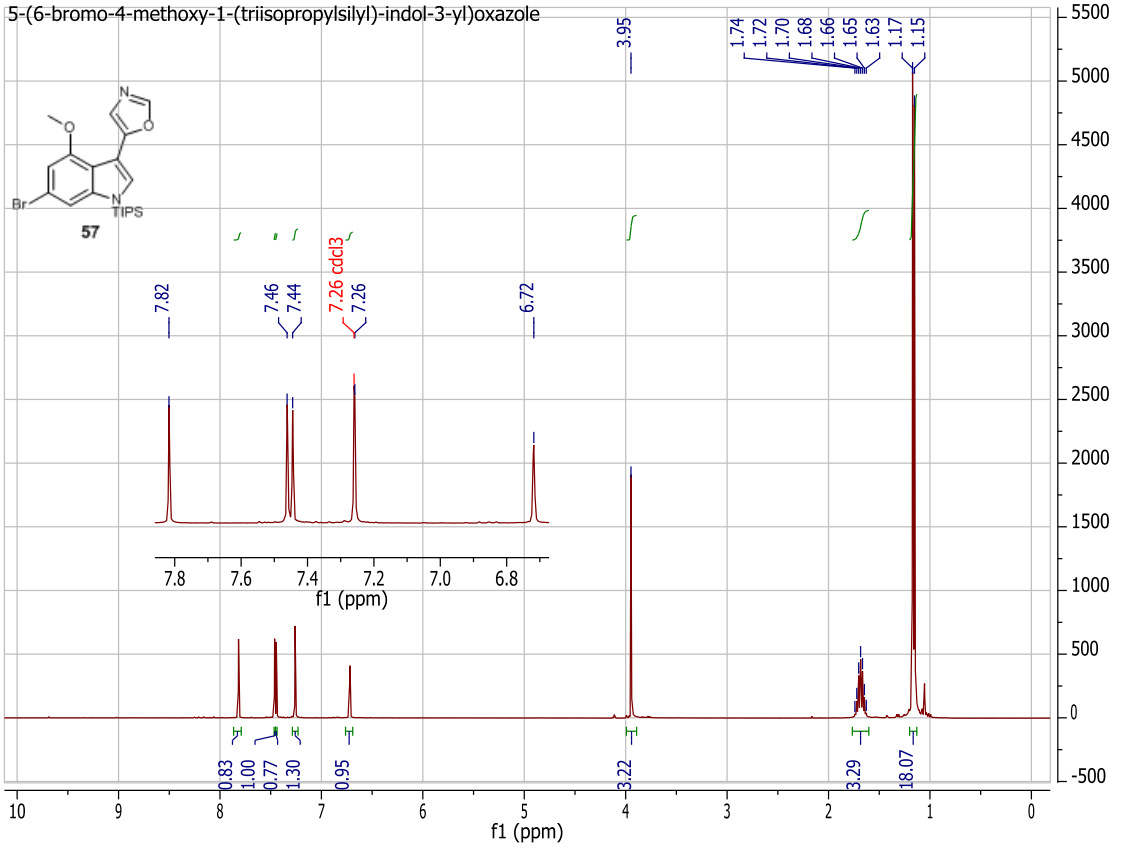


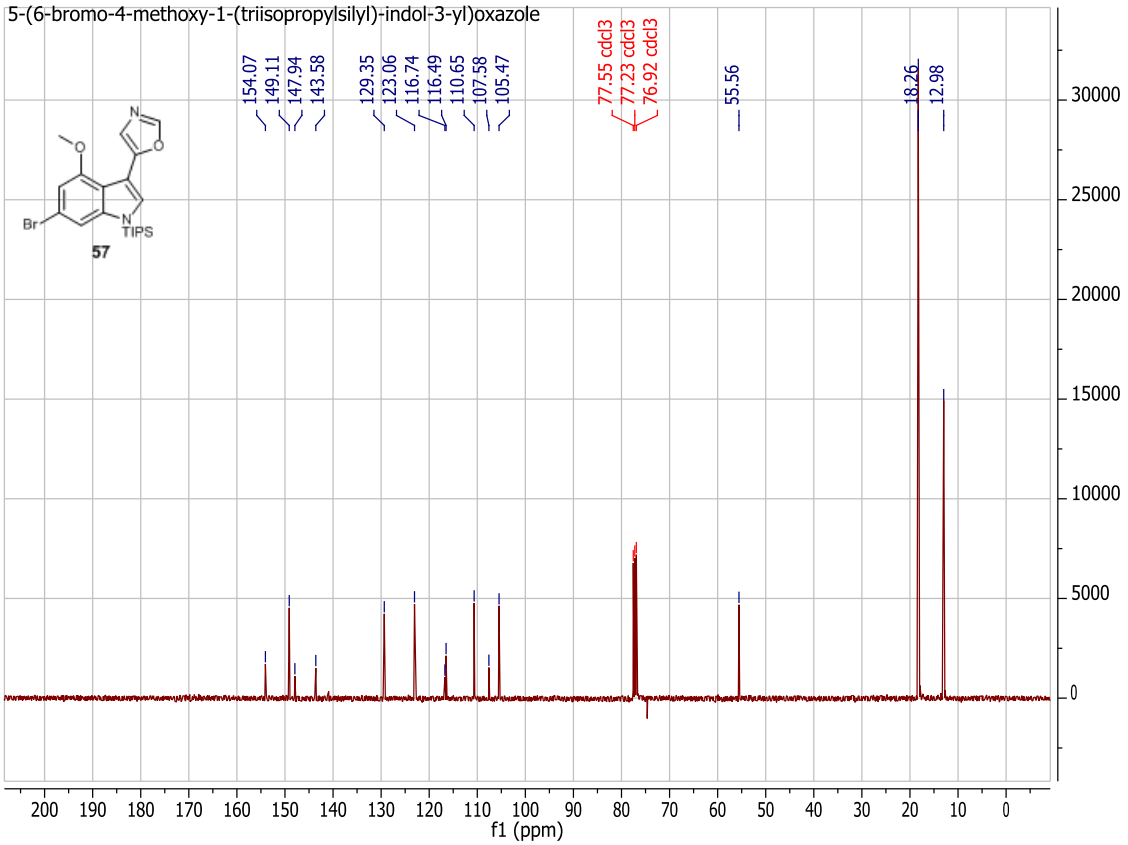


yg129-f22_Posb #1-5 RT: 0.02-0.16 AV: 5 NL: 7.95E5
T: FTMS + p ESI Full ms [200.00-700.00]

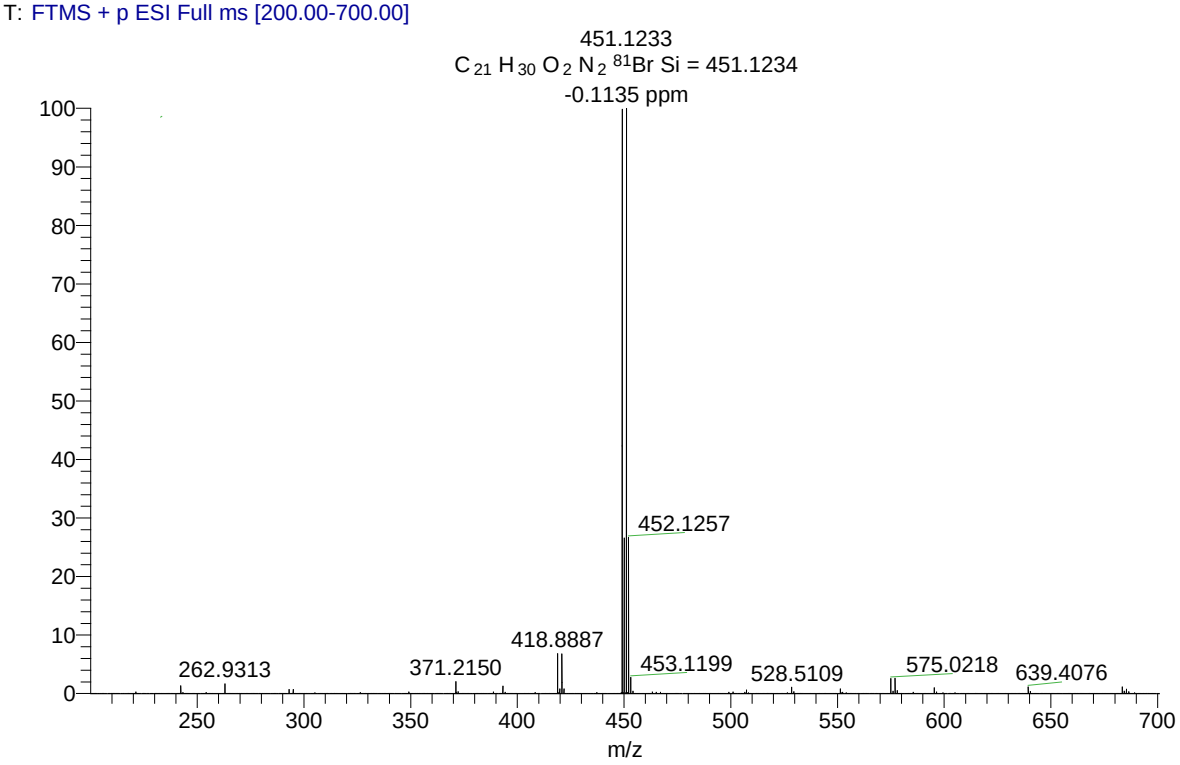


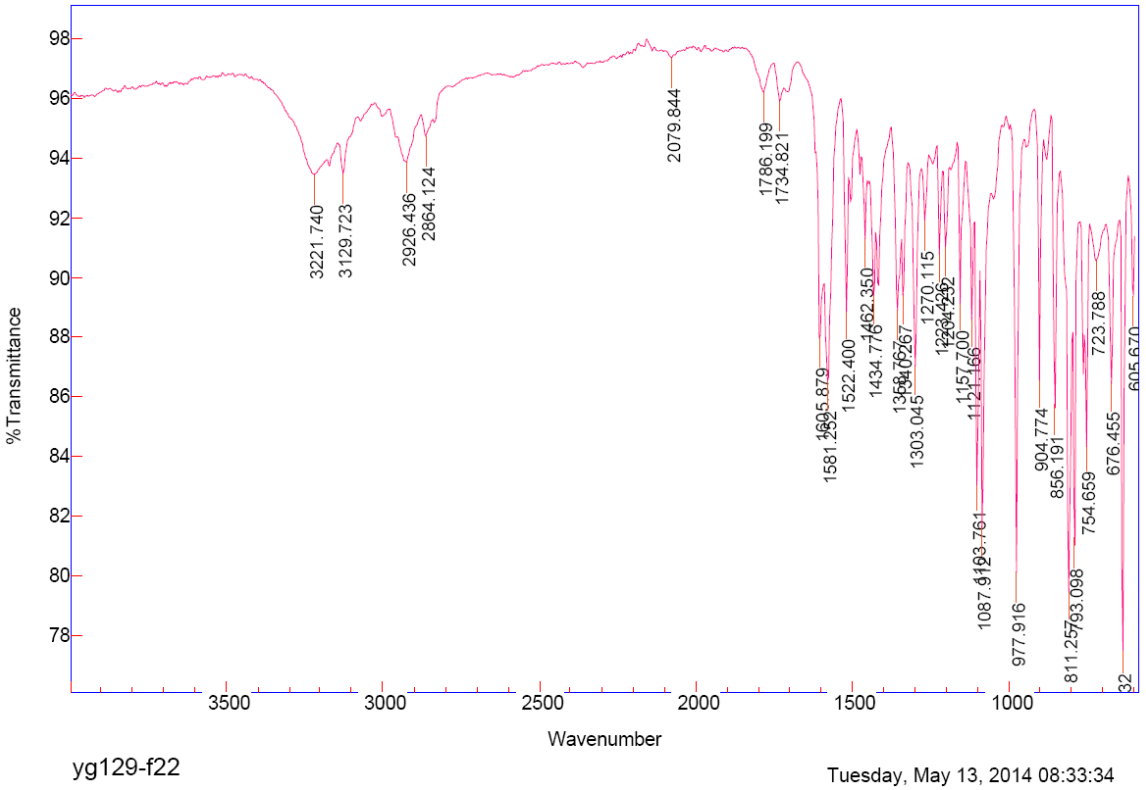
8.1.3.115-(6-bromo-4-methoxy-1-(triisopropylsilyl)-indol-3-yl)oxazole (57)



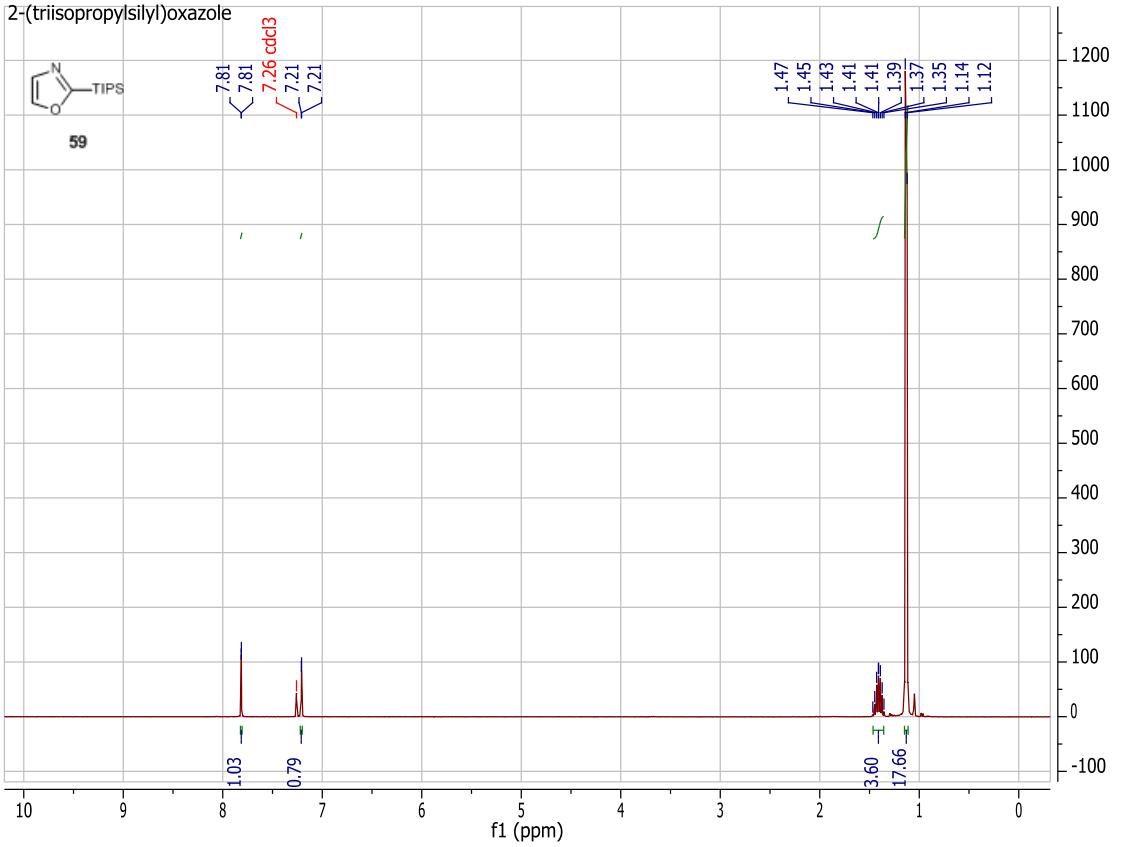


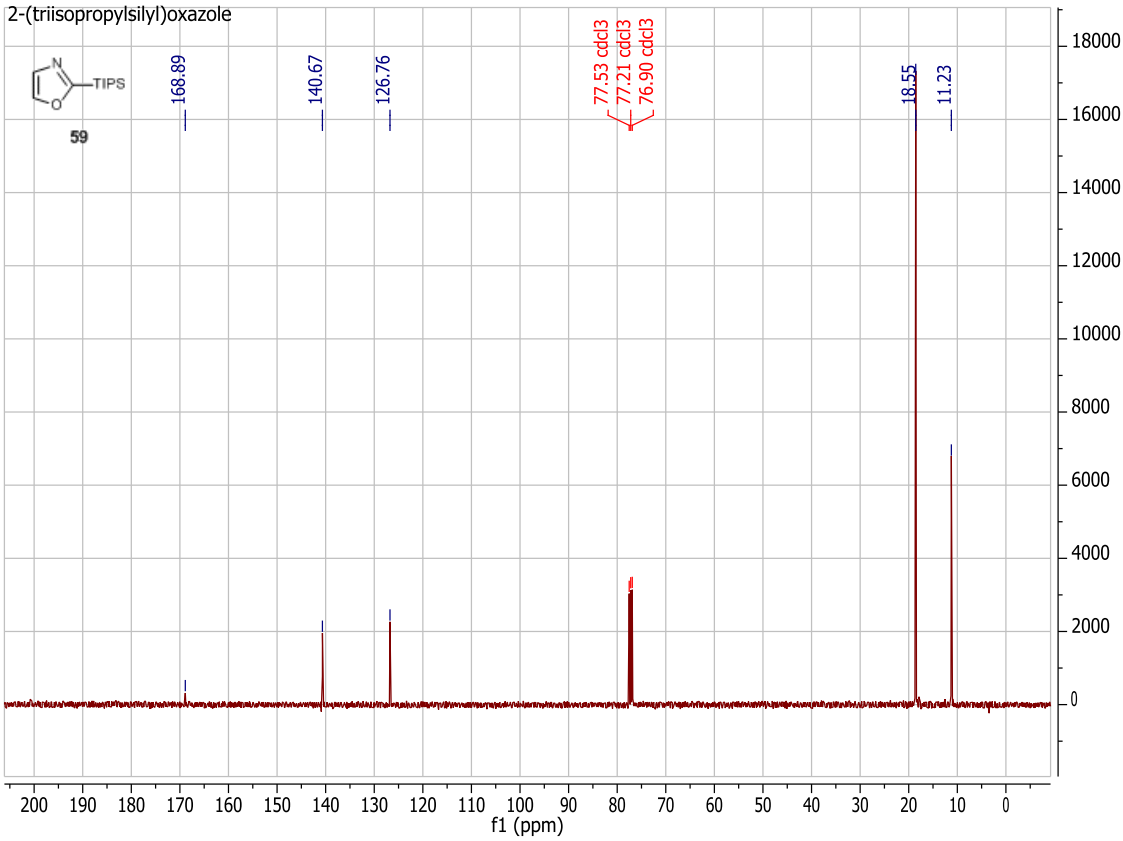
yg129-f15_Posb #1-5 RT: 0.01-0.12 AV: 5 NL: 1.66E7
T: FTMS + p ESI Full ms [200.00-700.00]

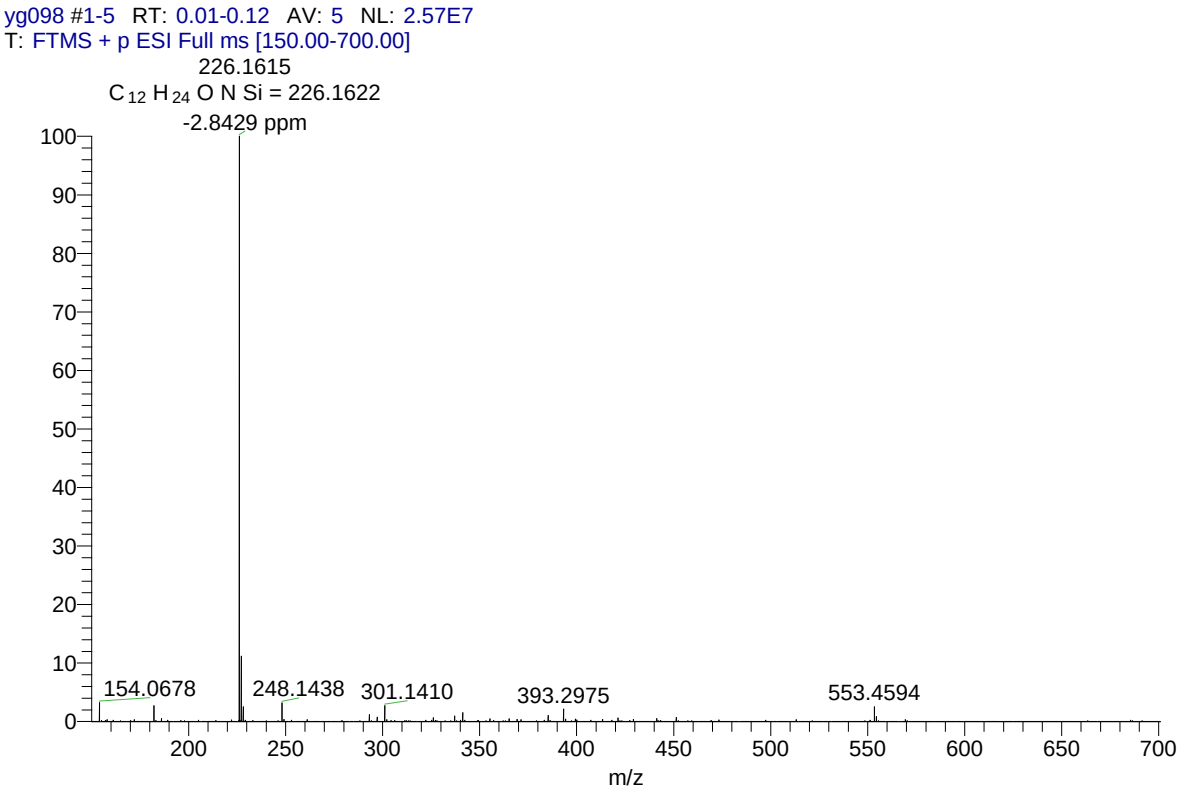




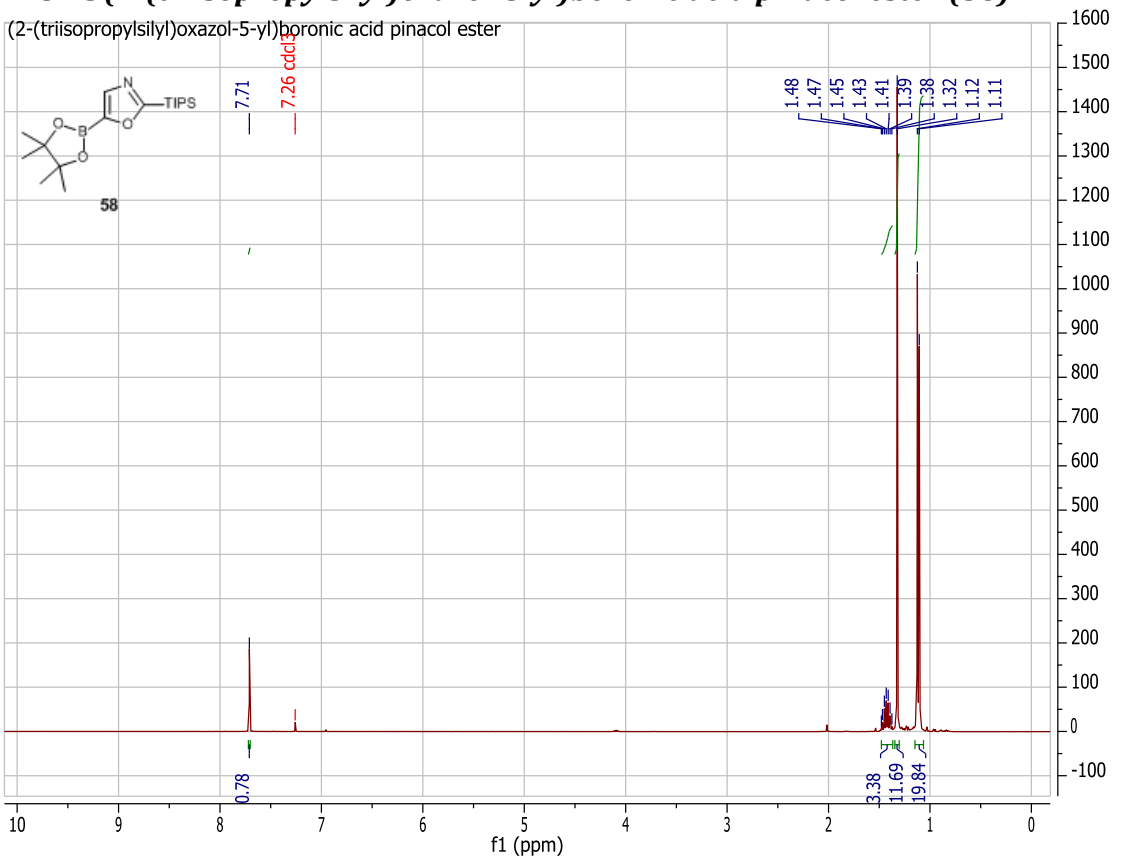
8.1.3.122-(triisopropylsilyl)oxazole (59)

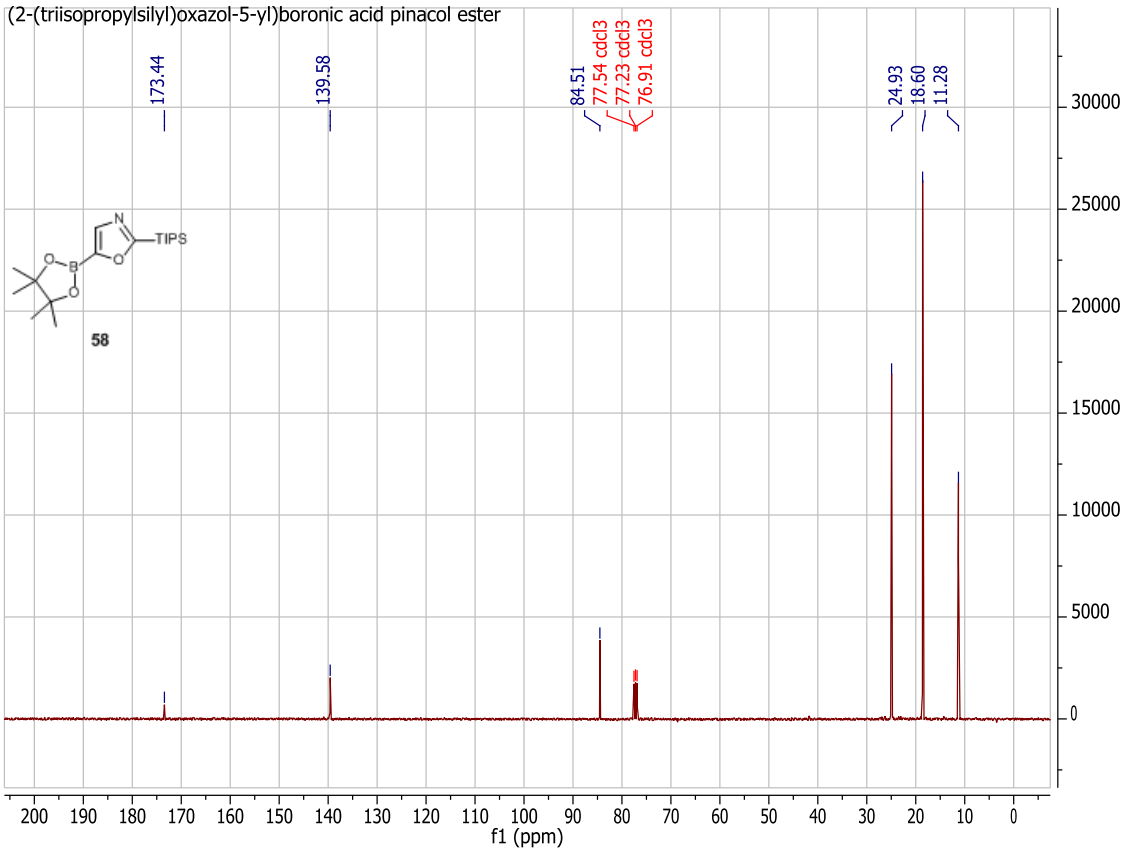




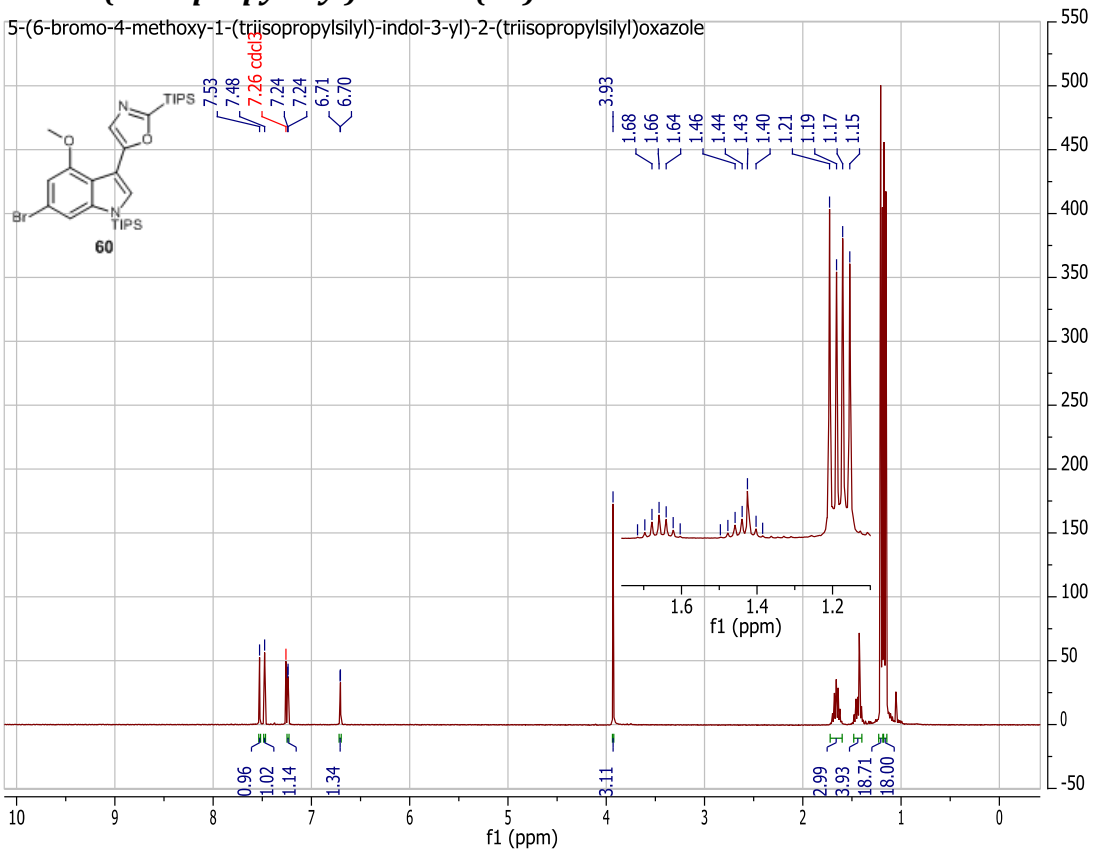

yg098 #1-5 RT: 0.01-0.12 AV: 5 NL: 2.57E7
T: FTMS + p ESI Full ms [150.00-700.00]
226.1615
C 12 H 24 O N Si = 226.1622
-2.8429 ppm
154.0678
248.1438
301.1410
393.2975
553.4594
m/z

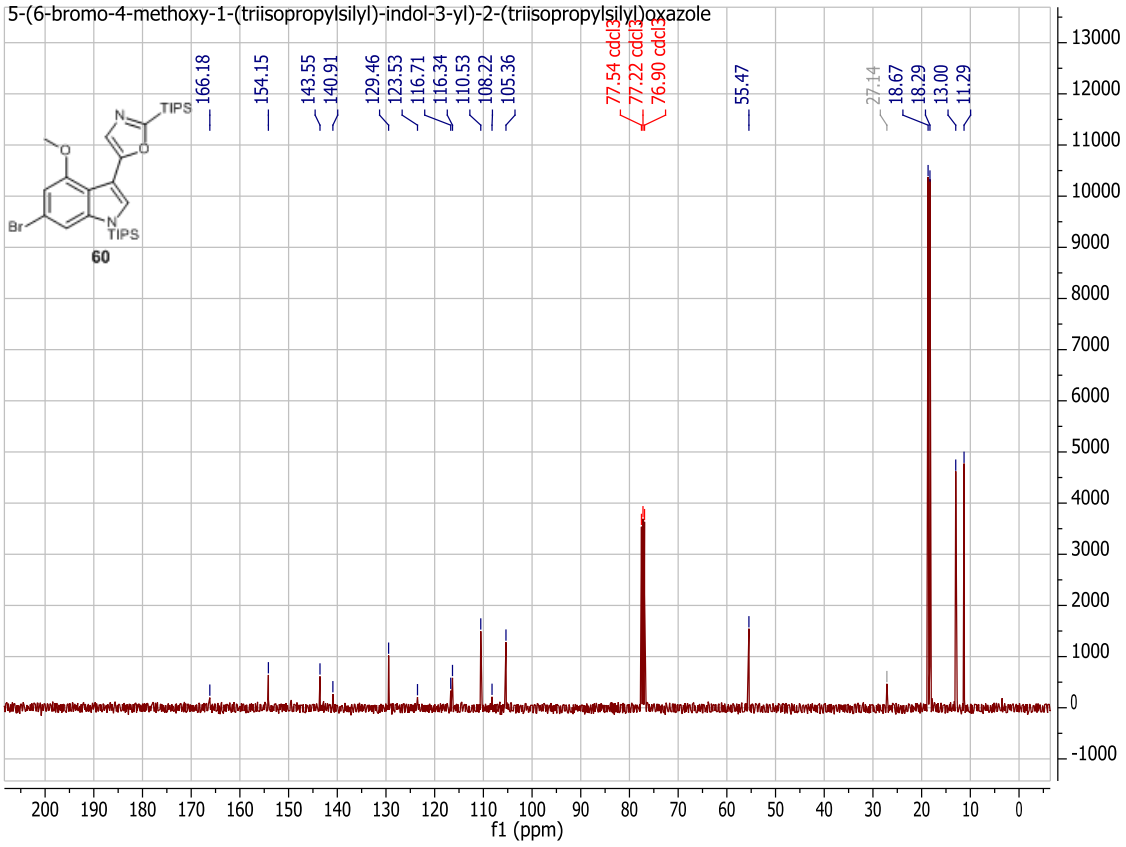
8.1.3.13 (2-(triisopropylsilyl)oxazol-5-yl)boronic acid pinacol ester (58)



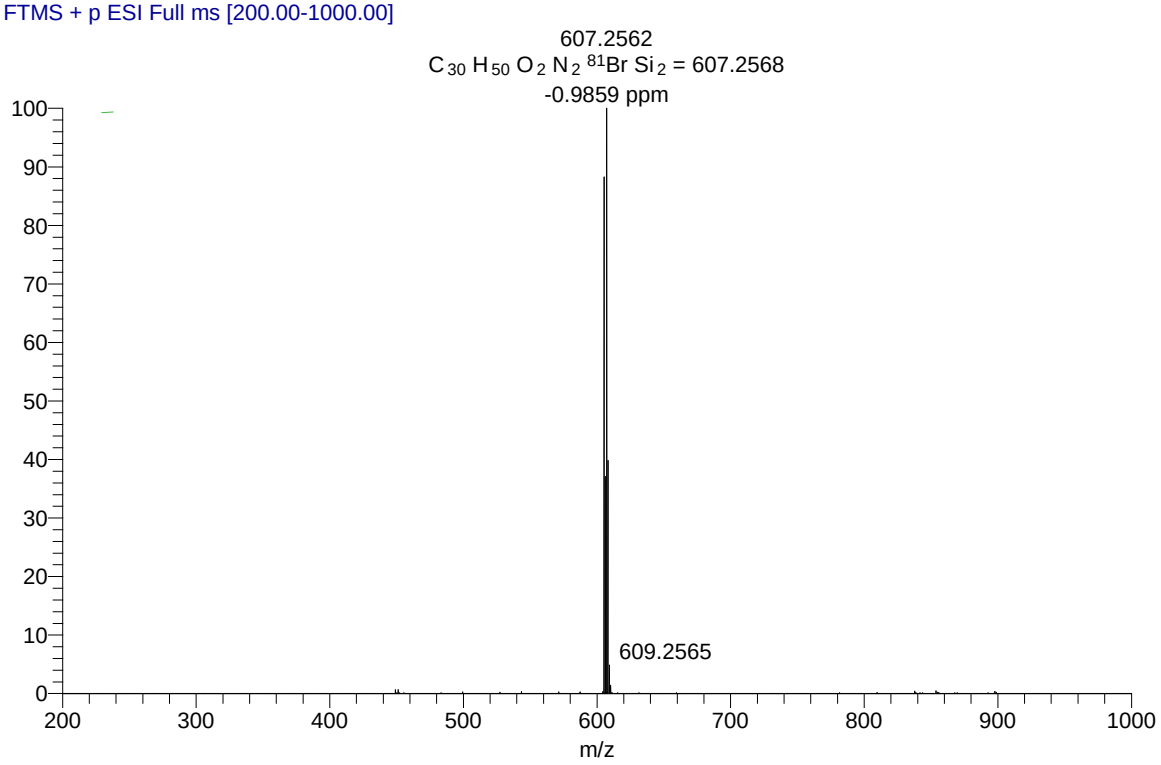


8.1.3.145-(6-bromo-4-methoxy-1-(triisopropylsilyl)-indol-3-yl)-2-(triisopropylsilyl)oxazole (60)



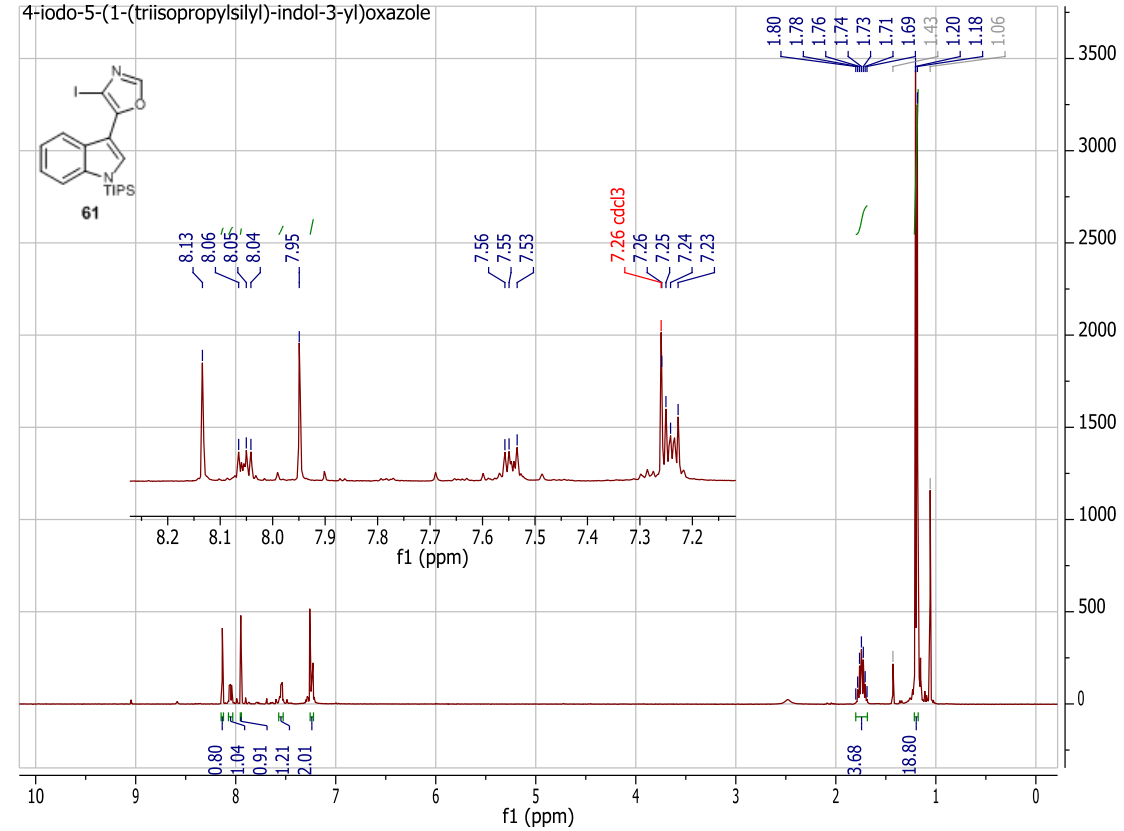


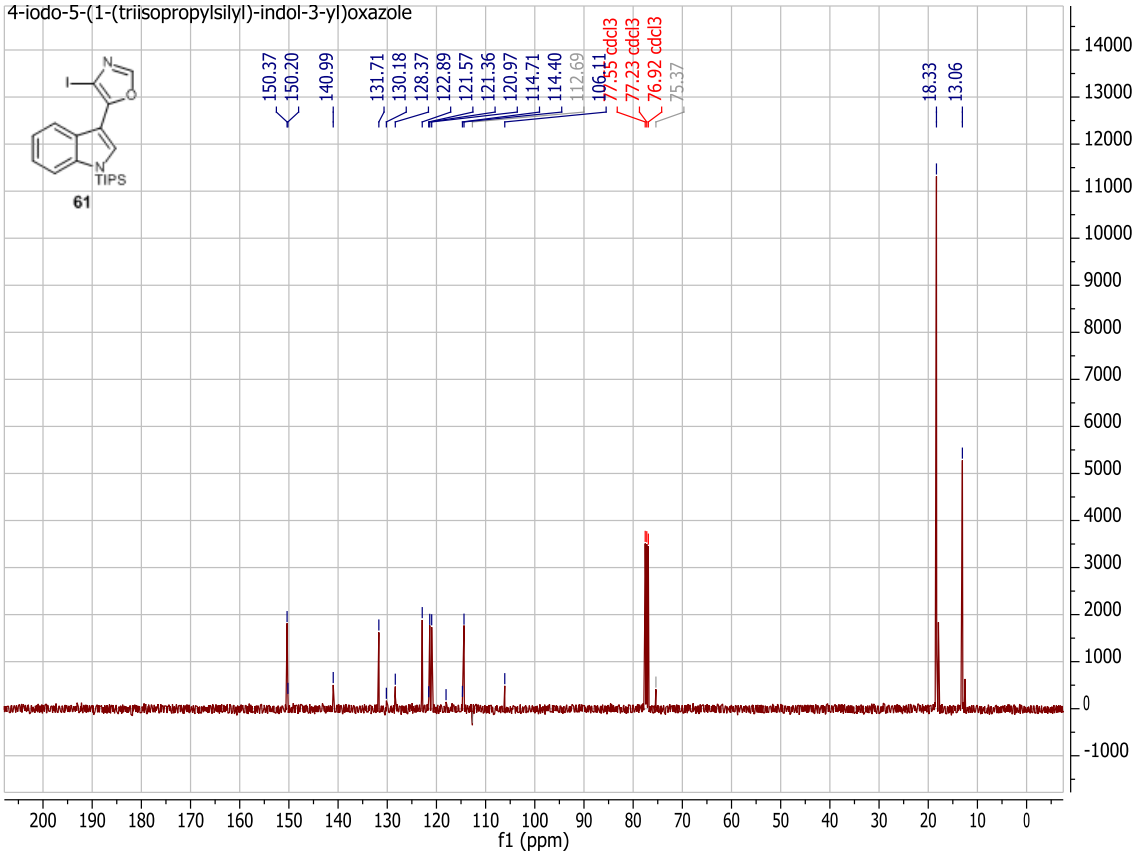
yg088-04b #695 RT: 10.34 AV: 1 NL: 5.88E8
T: FTMS + p ESI Full ms [200.00-1000.00]



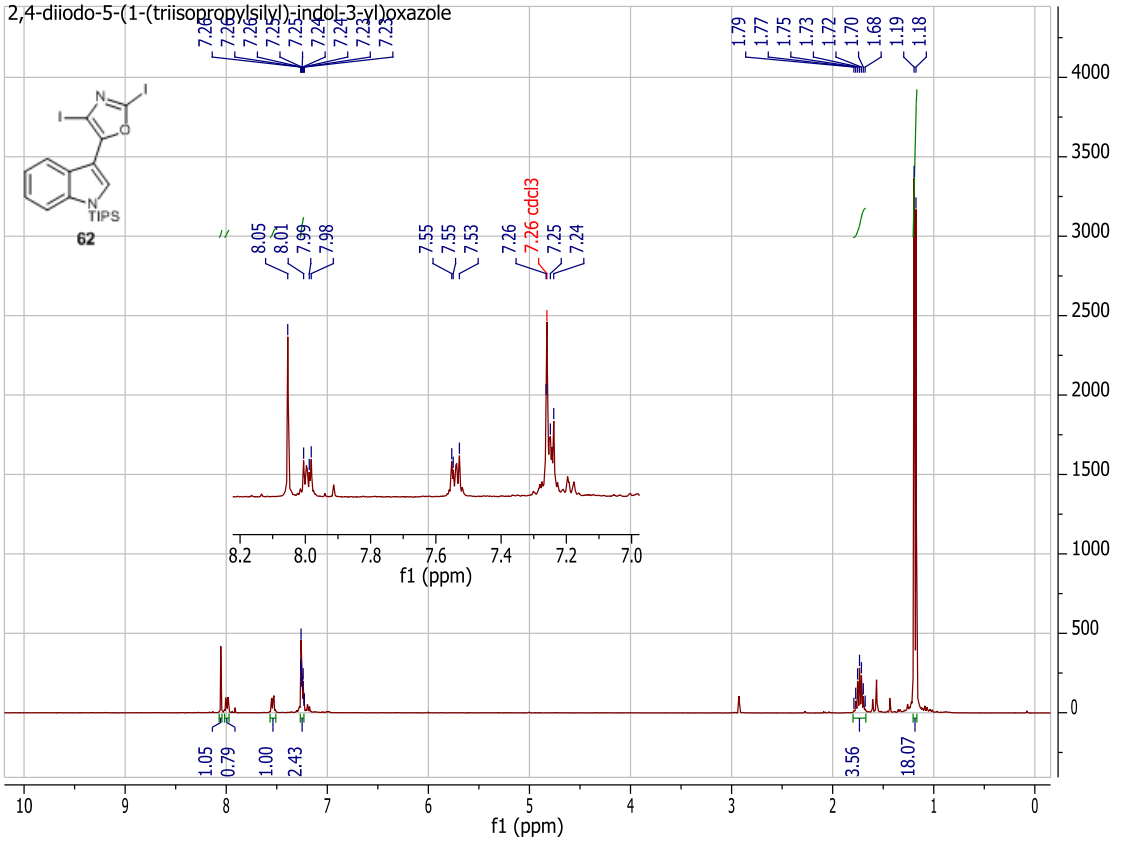
8.1.4 Iodination and Pyrrole assembly (section 3.6)

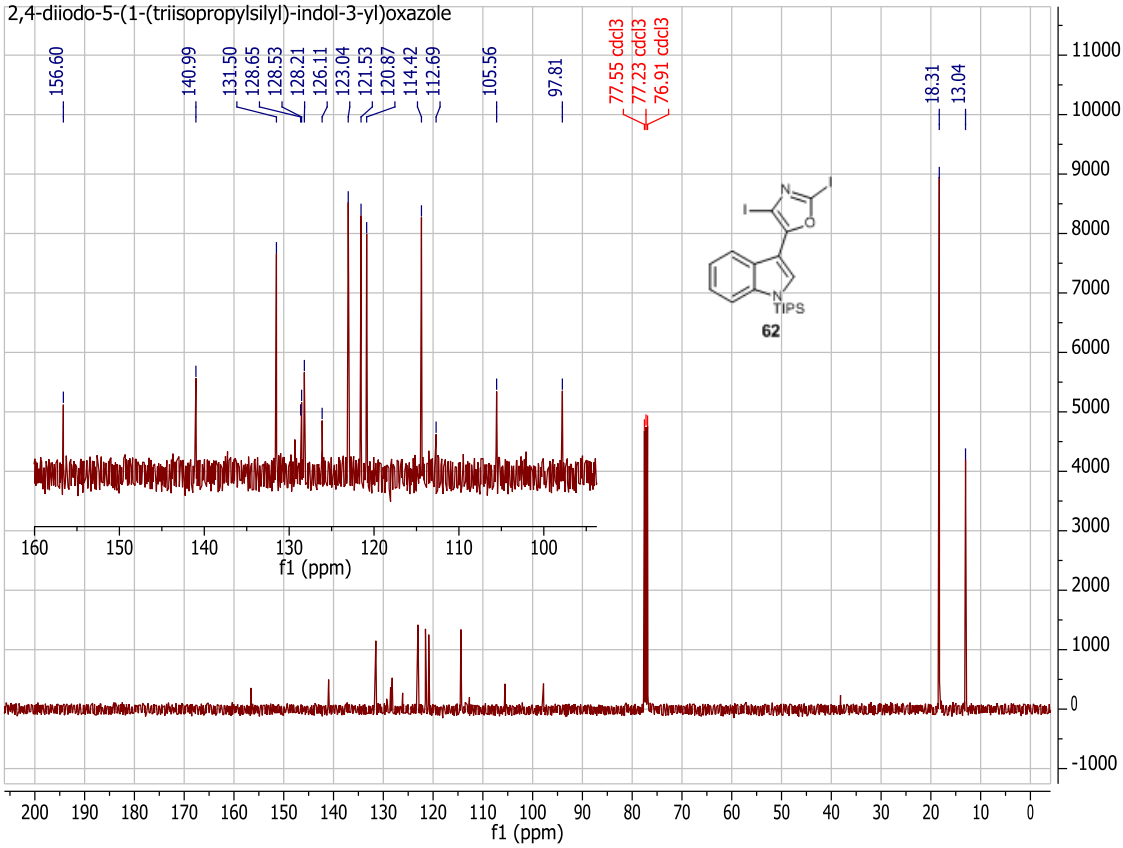
8.1.4.1 4-iodo-5-(1-(triisopropylsilyl)-indol-3-yl)oxazole (61)



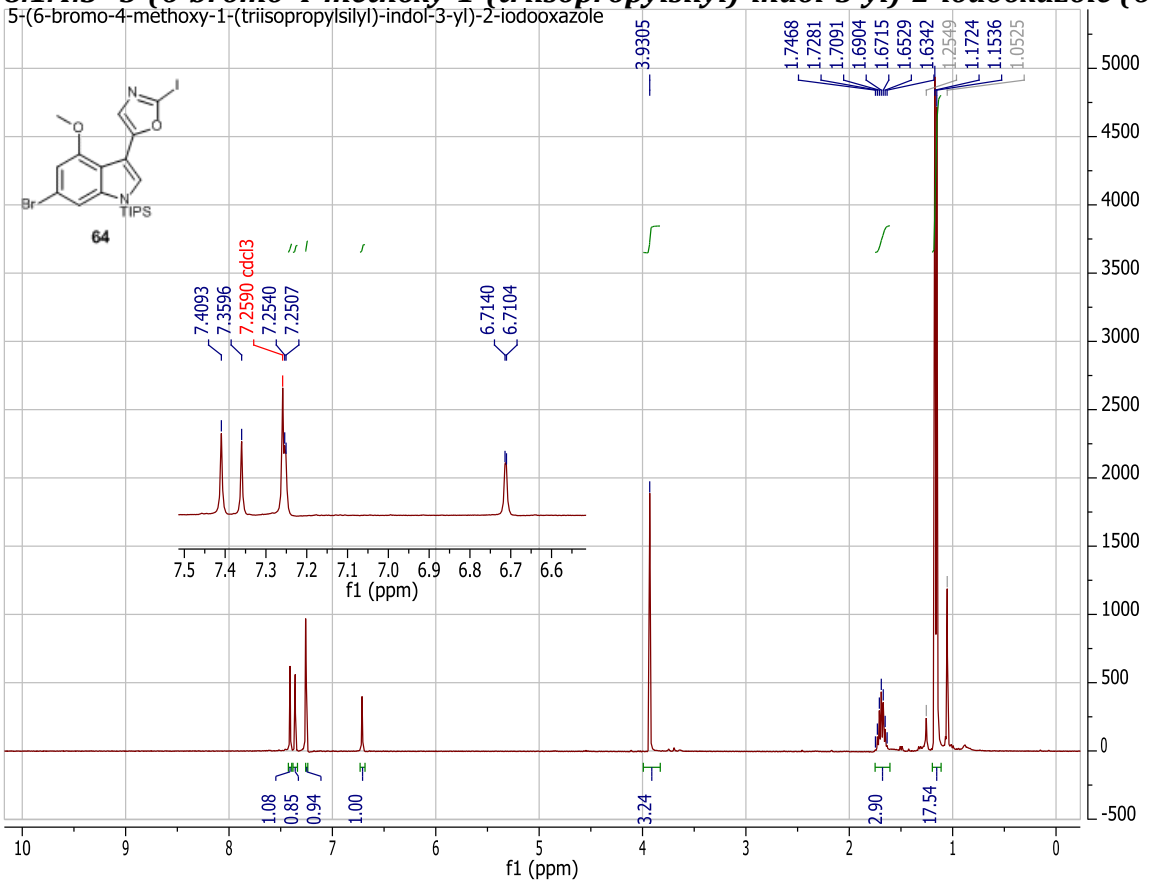


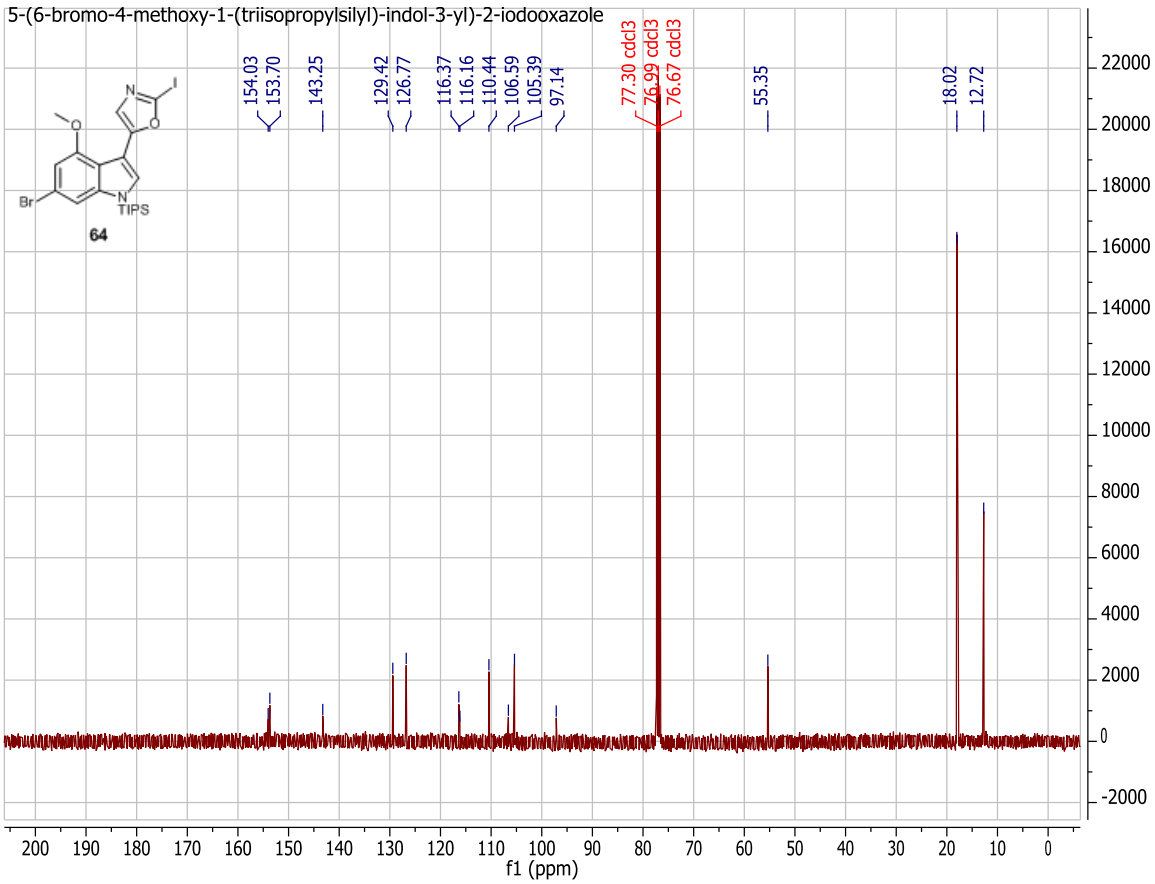
8.1.4.2 2,4-diiodo-5-(1-(triisopropylsilyl)-indol-3-yl)oxazole (62)



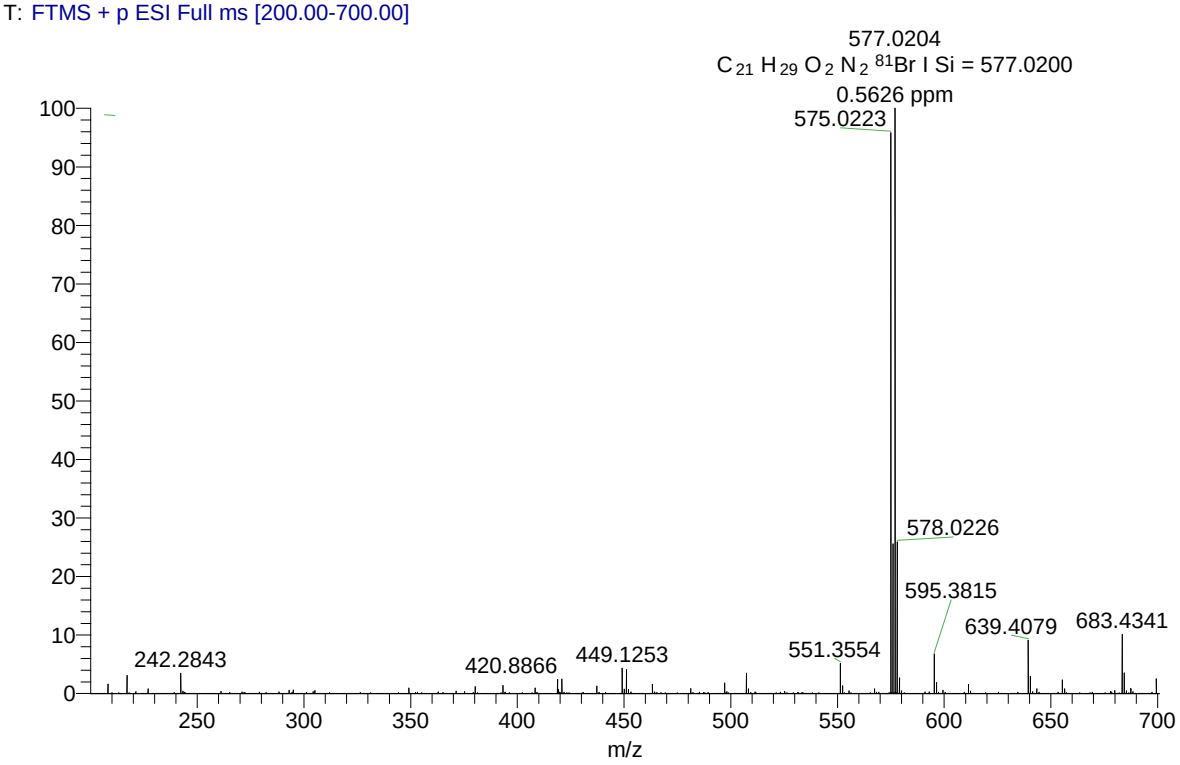


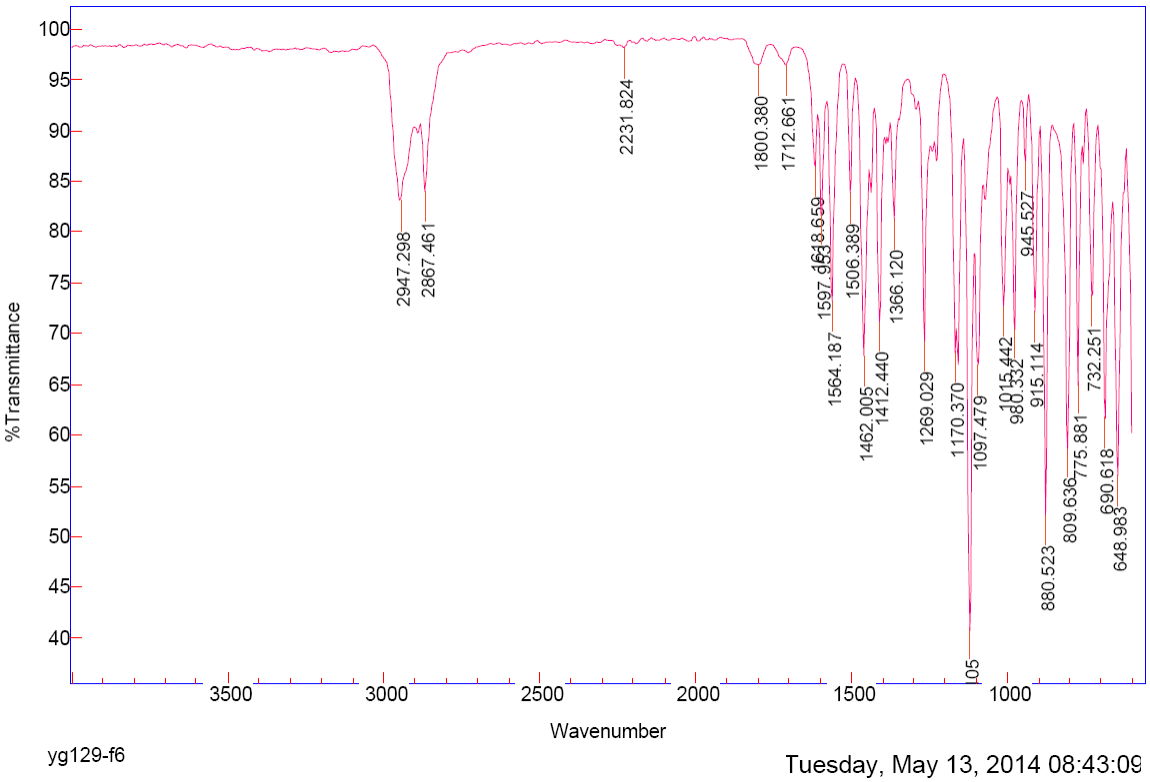
8.1.4.3 5-(6-bromo-4-methoxy-1-(triisopropylsilyl)-indol-3-yl)-2-iodooxazole (64)



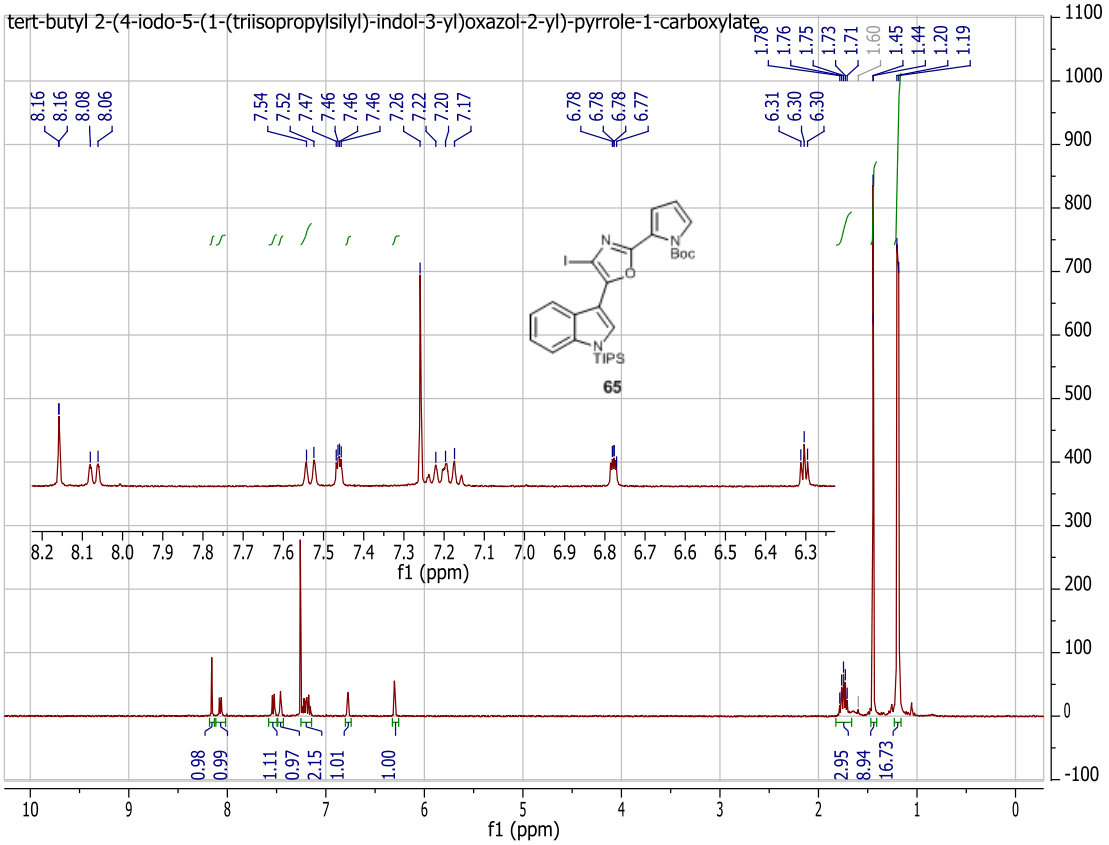


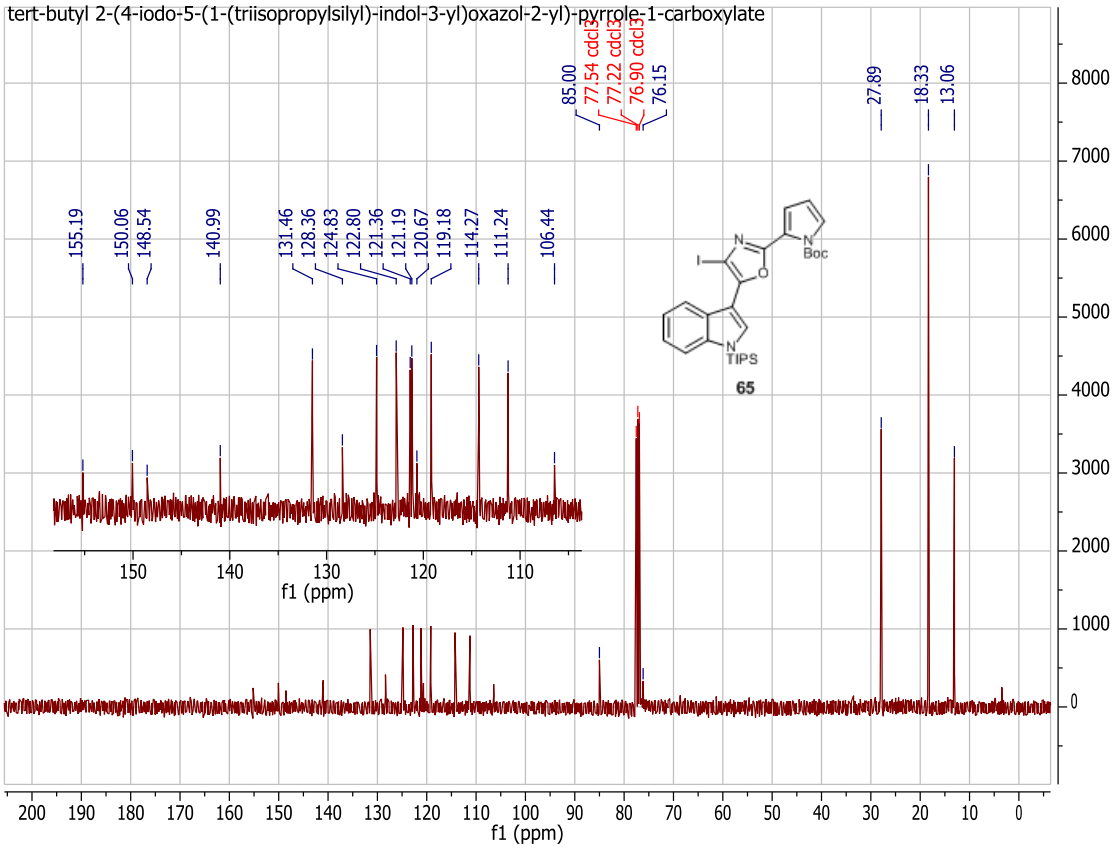
yg129-f6_Pos #1-5 RT: 0.02-0.15 AV: 5 NL: 1.22E6
T: FTMS + p ESI Full ms [200.00-700.00]





8.1.4.4 tert-*butyl 2-(4-iodo-5-(1-(triisopropylsilyl)-indol-3-yl)oxazol-2-yl)-pyrrole-1-carboxylate (65)*

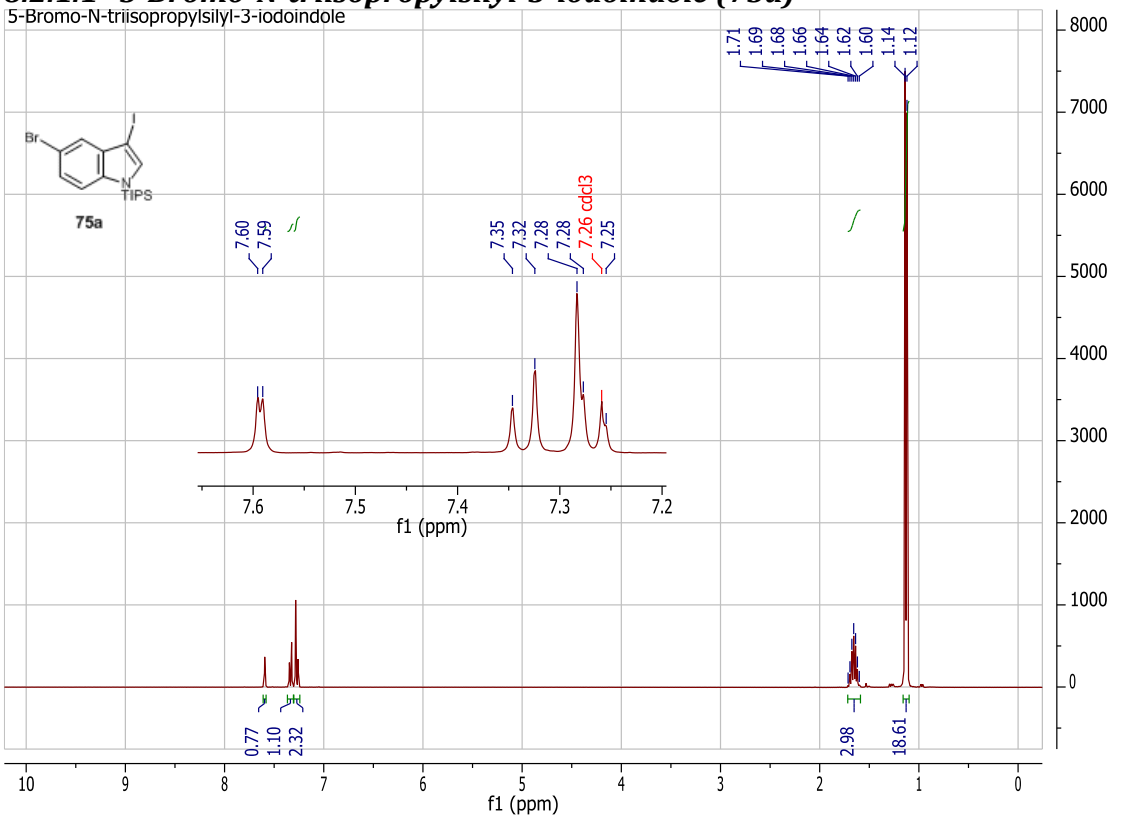


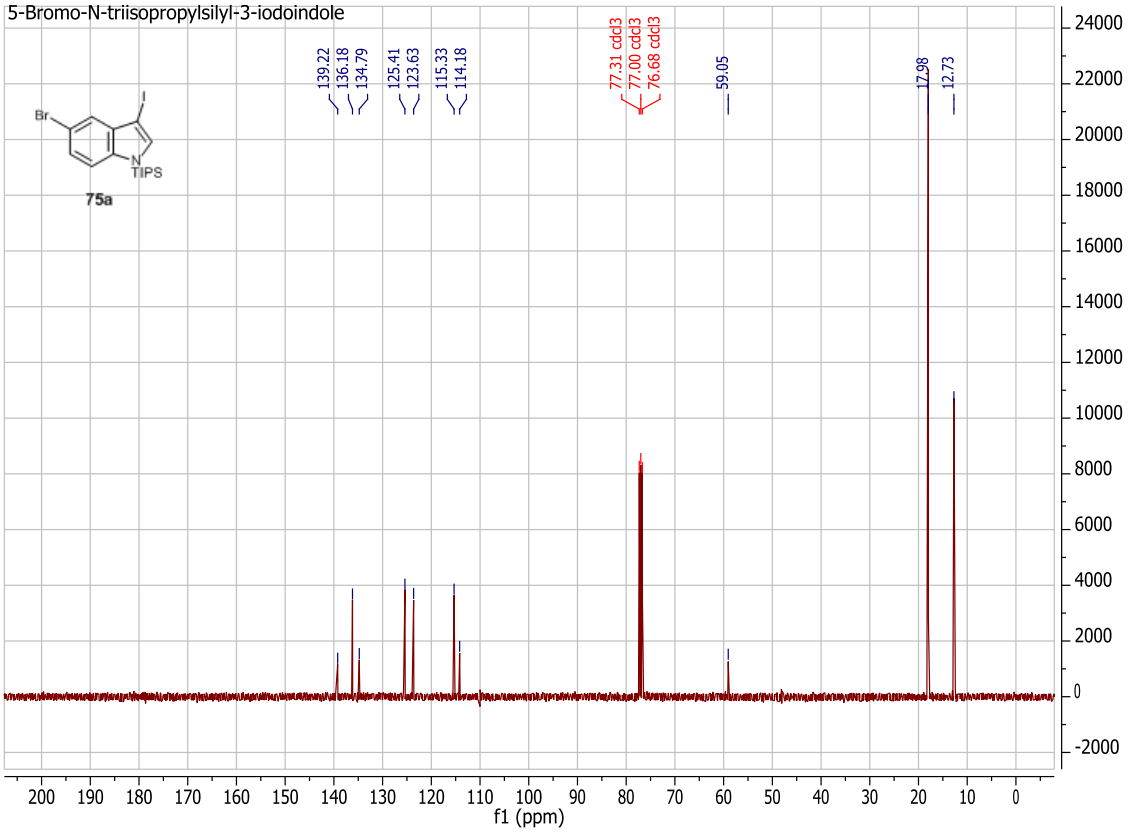


8.2 SYNTHESIS OF BREITFUSSIN ANALOGUES (CHAPTER 4)

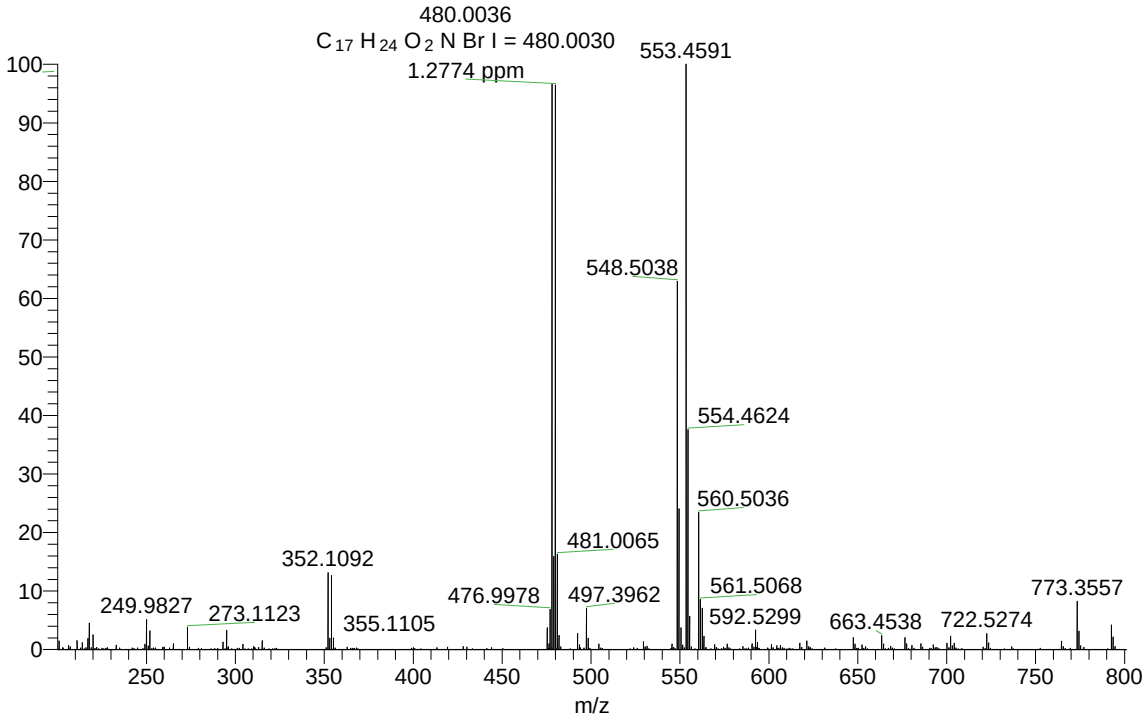
8.2.1 Synthesis of 3-halo-*N*-TIPS-indoles (section 4.3)

8.2.1.1 5-Bromo-N-triisopropylsilyl-3-iodoindole (75a)

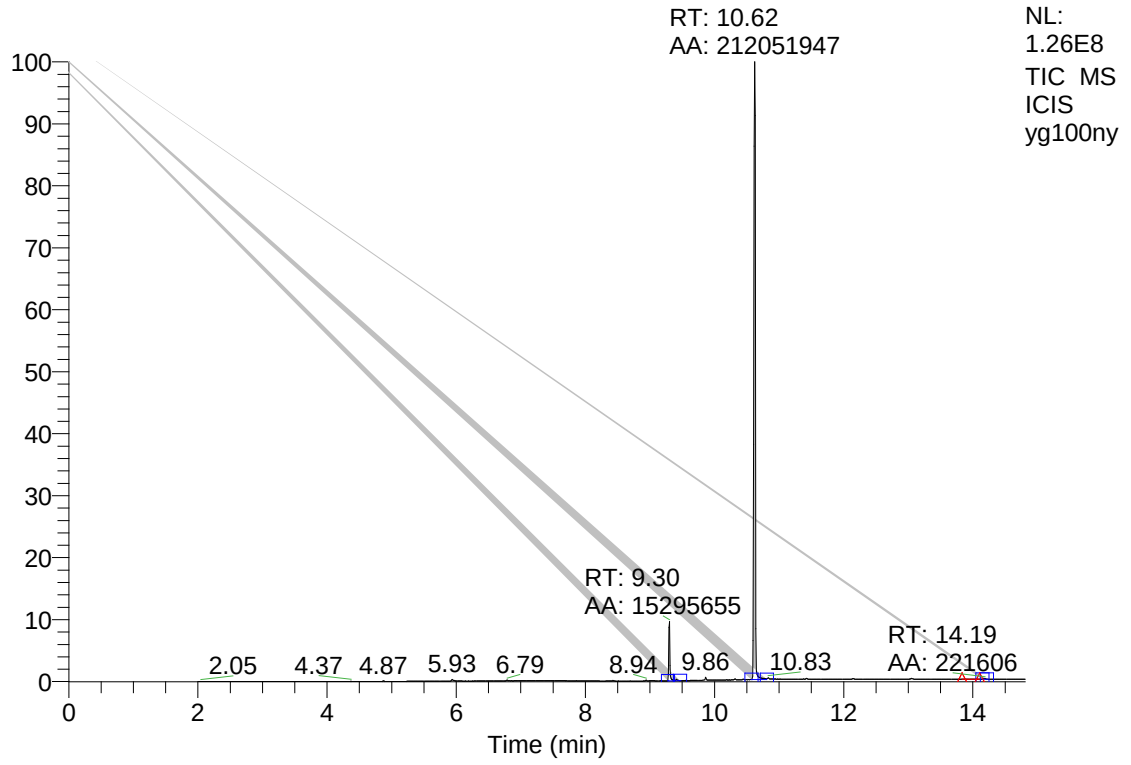


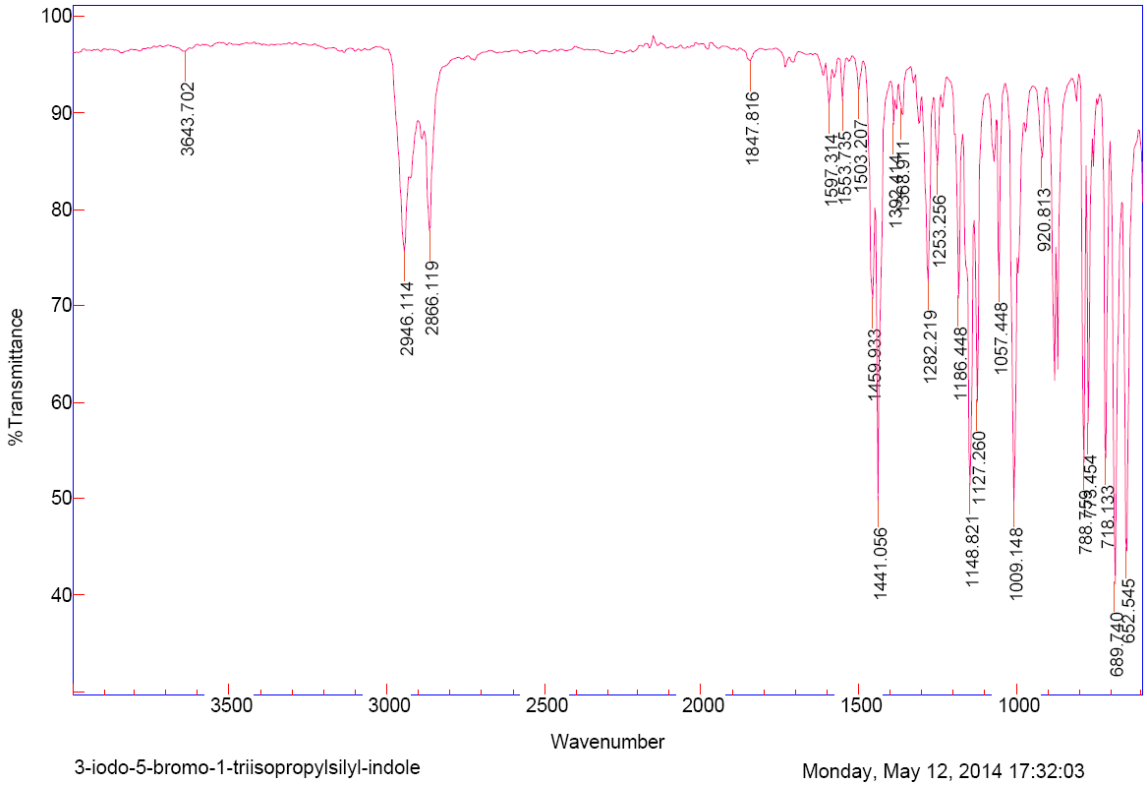


yg100-2-12_5 #1-5 RT: 0.02-0.13 AV: 5 NL: 6.98E6
T: FTMS + p ESI Full ms [200.00-800.00]

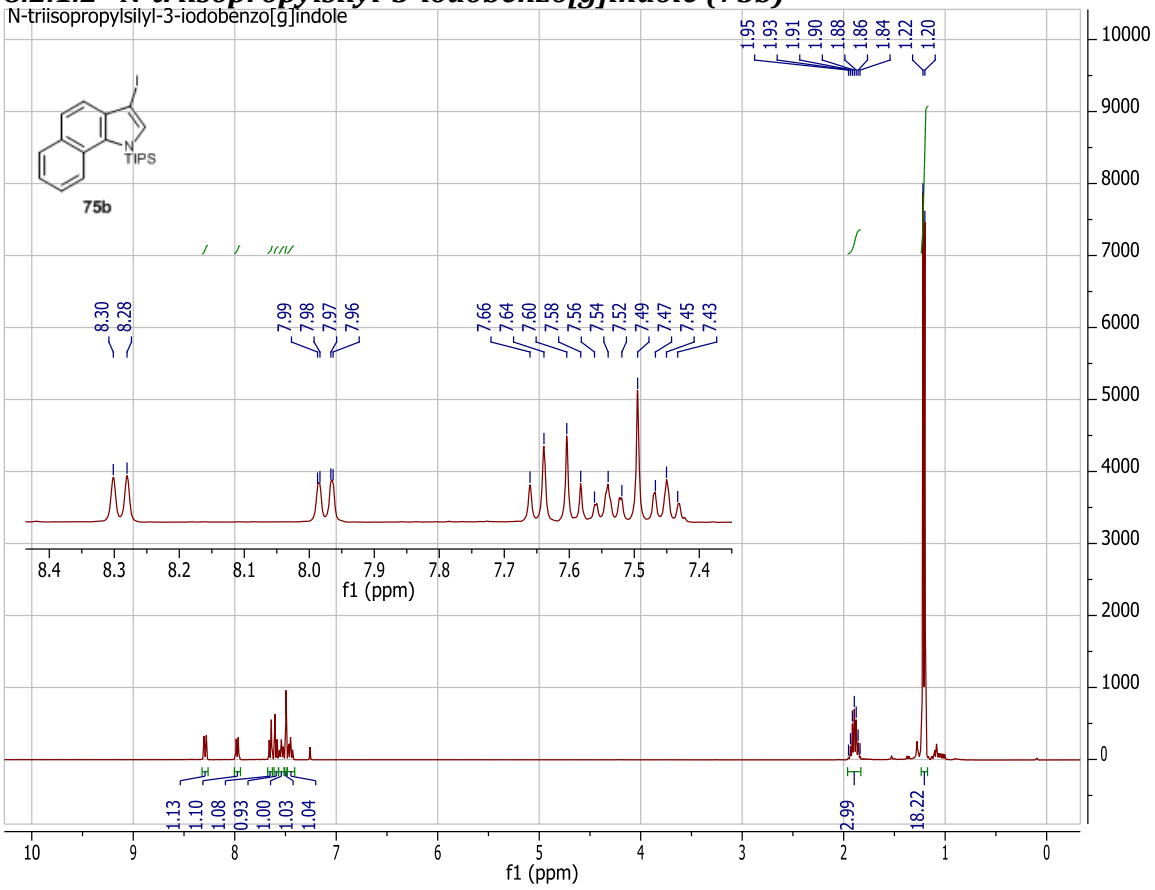


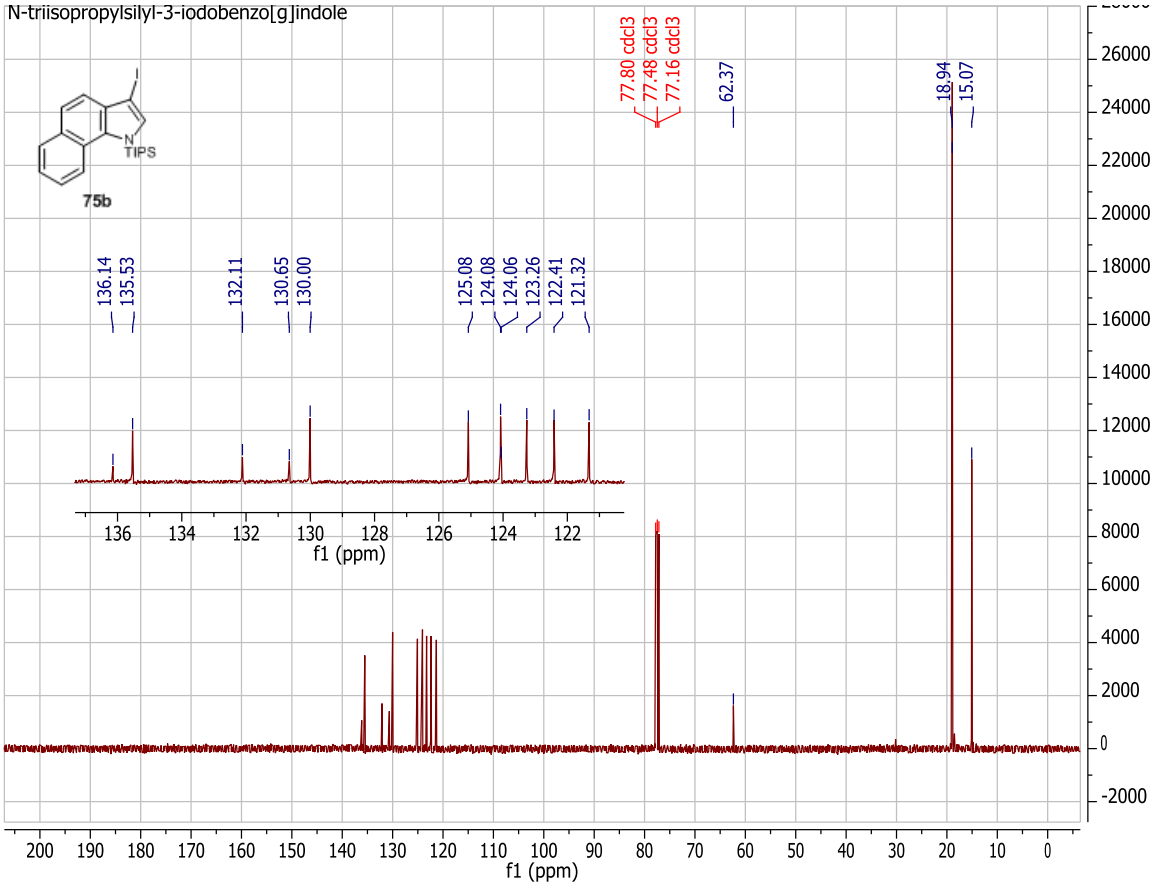
RT: 0.00 - 14.81



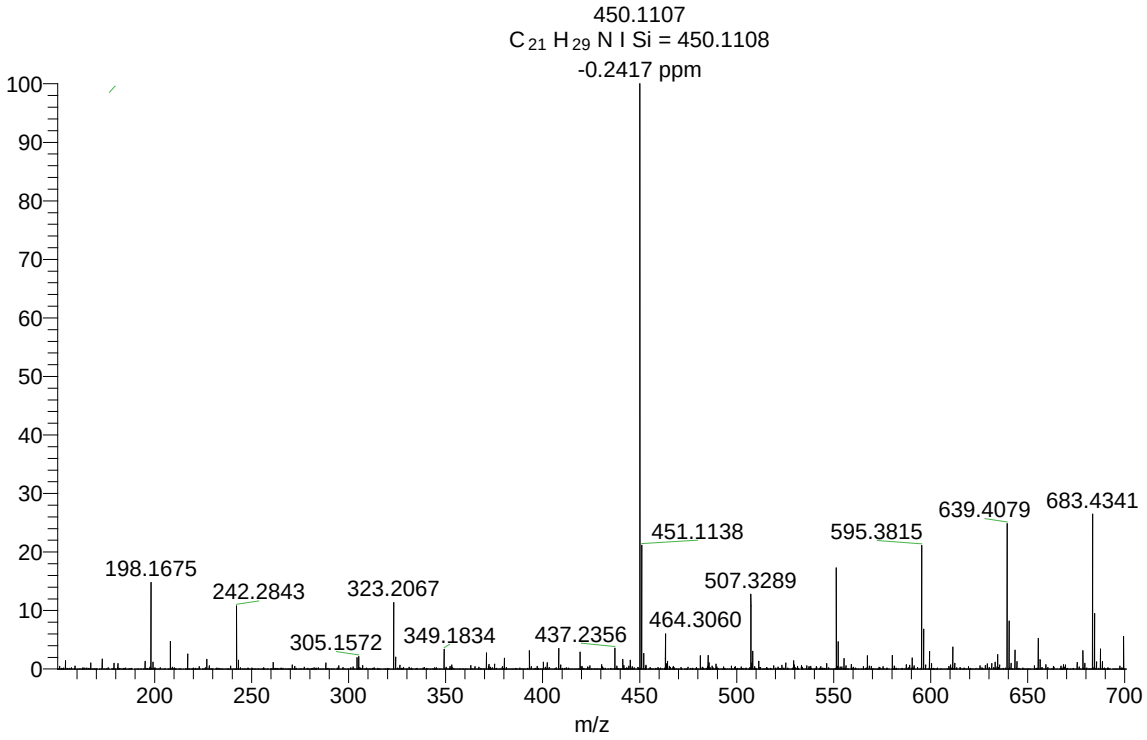

100
90
80
70
60
50
40
% Transmittance
3643.702
2946.114
2866.119
1847.816
1597.314
1553.735
1503.207
1459.933
1441.056
1282.219
1253.256
1186.448
1148.821
1127.260
1057.448
1009.148
920.813
788.759
718.133
689.740
652.545
3500
3000
2500
2000
1500
1000
Wavenumber
3-iodo-5-bromo-1-triisopropylsilyl-indole
Monday, May 12, 2014 17:32:03

8.2.1.2 N-*triisopropylsilyl-3-iodobenzo[g]indole (75b)*

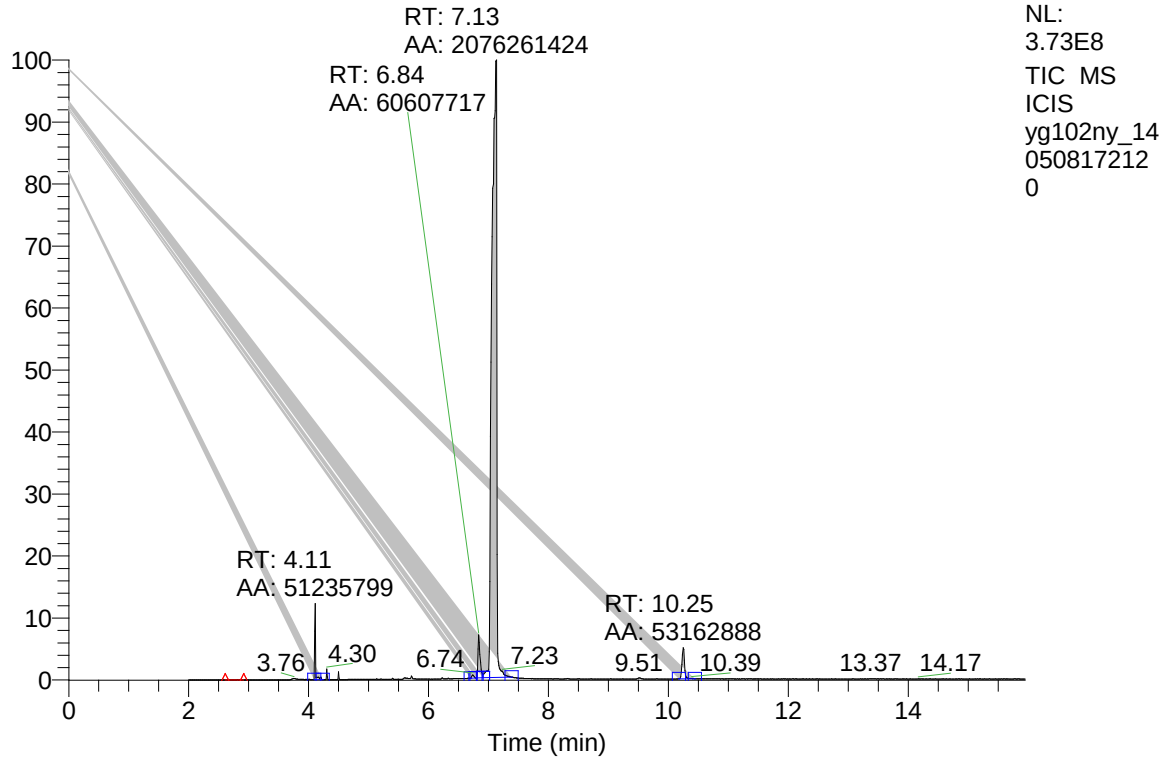


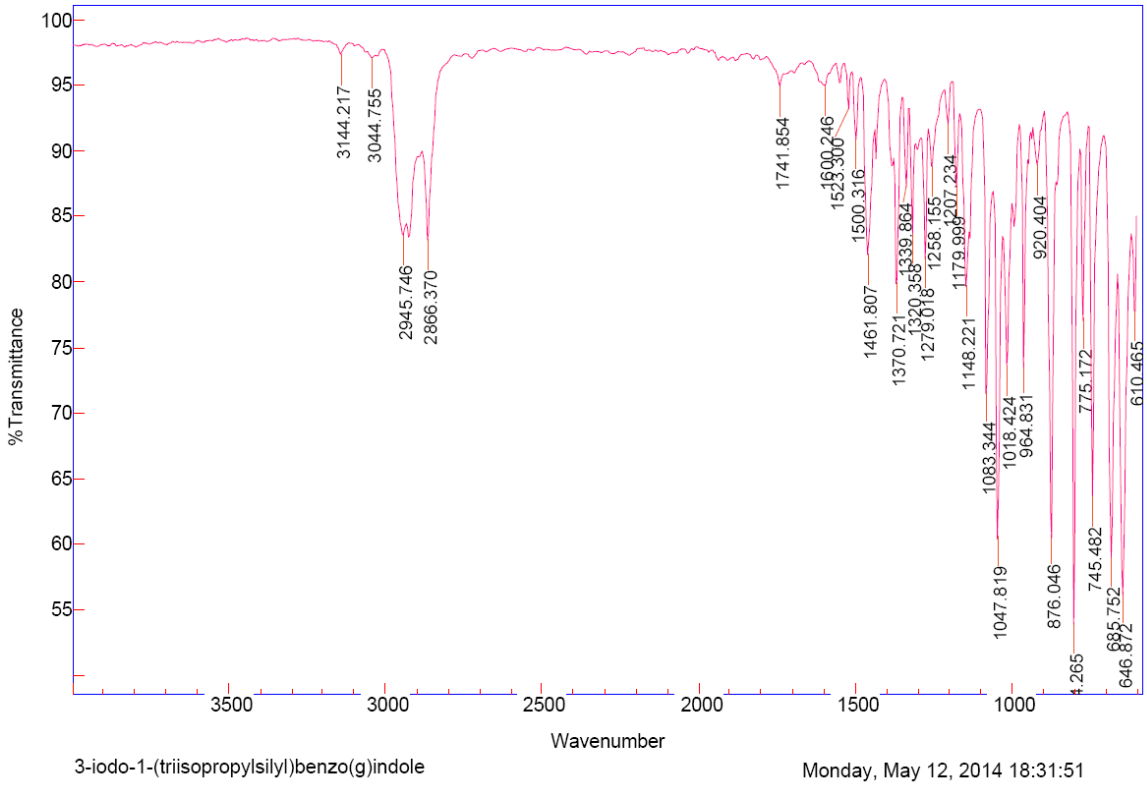


yg102-2-ny_Pos #1-5 RT: 0.02-0.16 AV: 5 NL: 8.37E5
T: FTMS + p ESI Full ms [150.00-700.00]

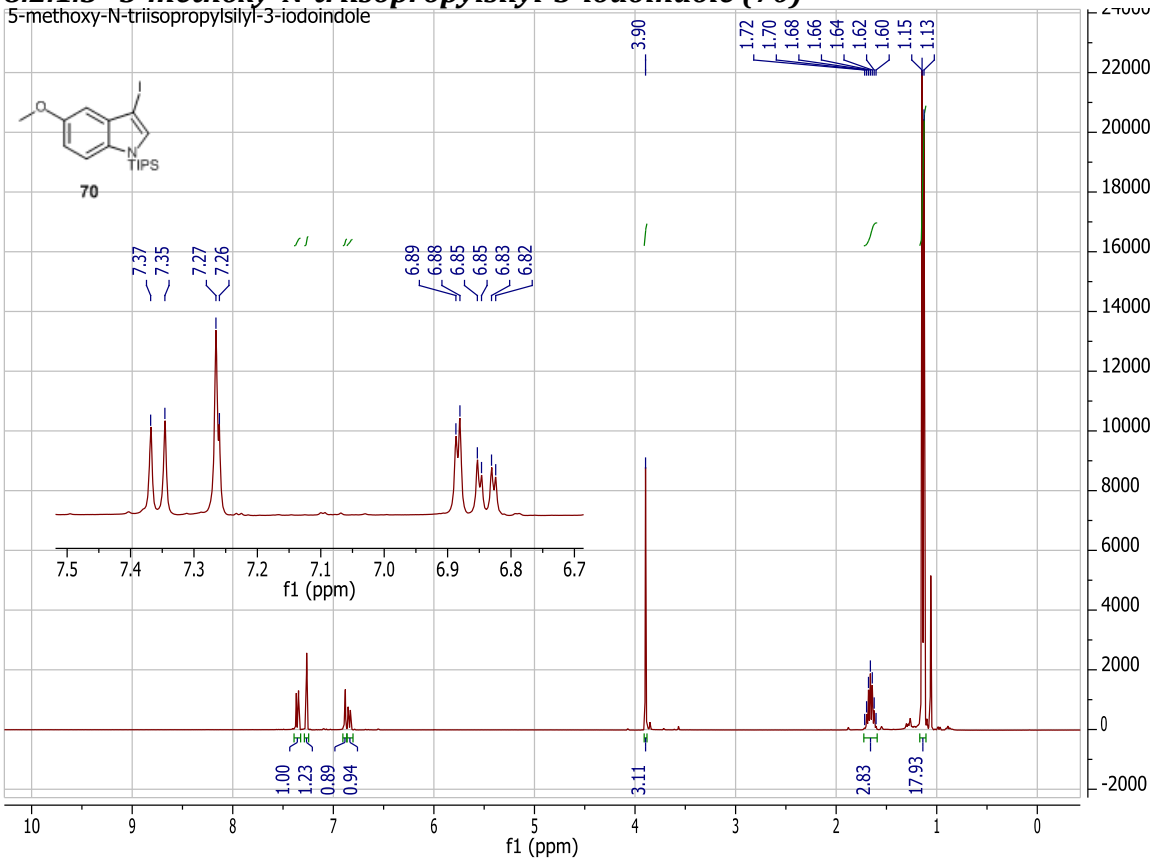


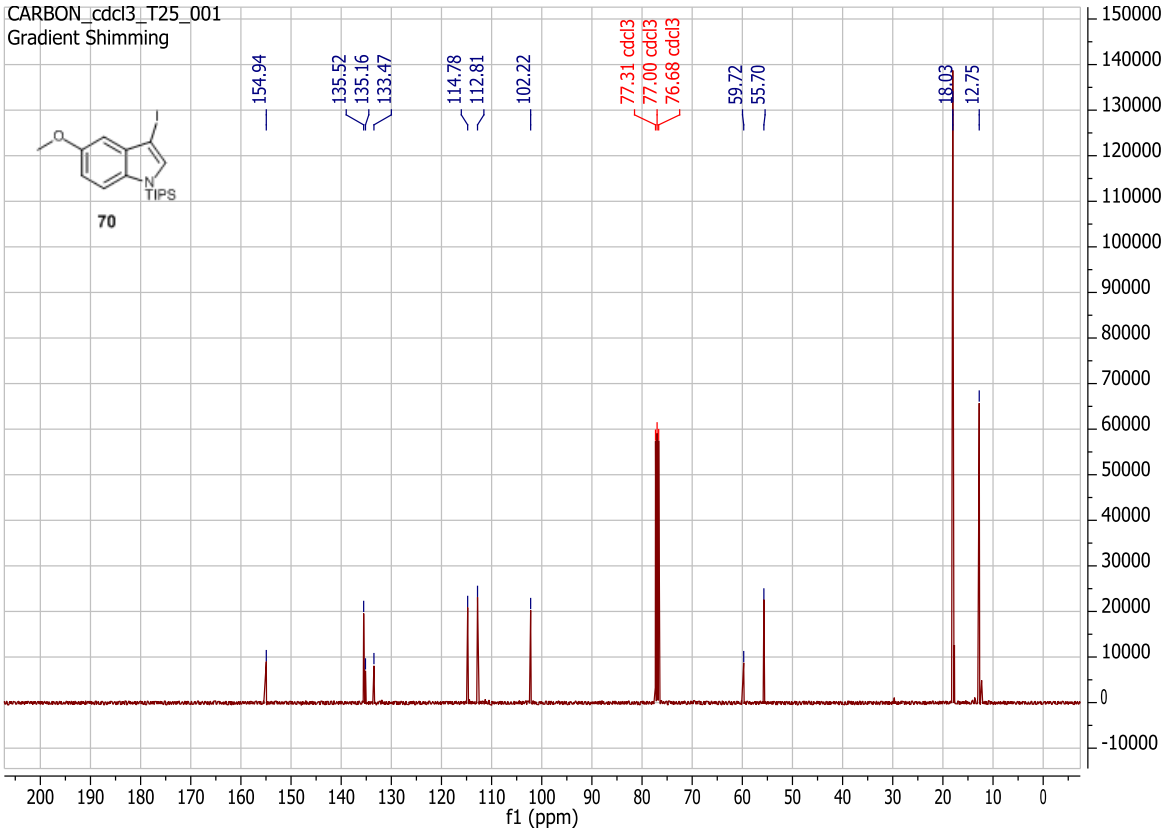
RT: 0.00 - 15.95



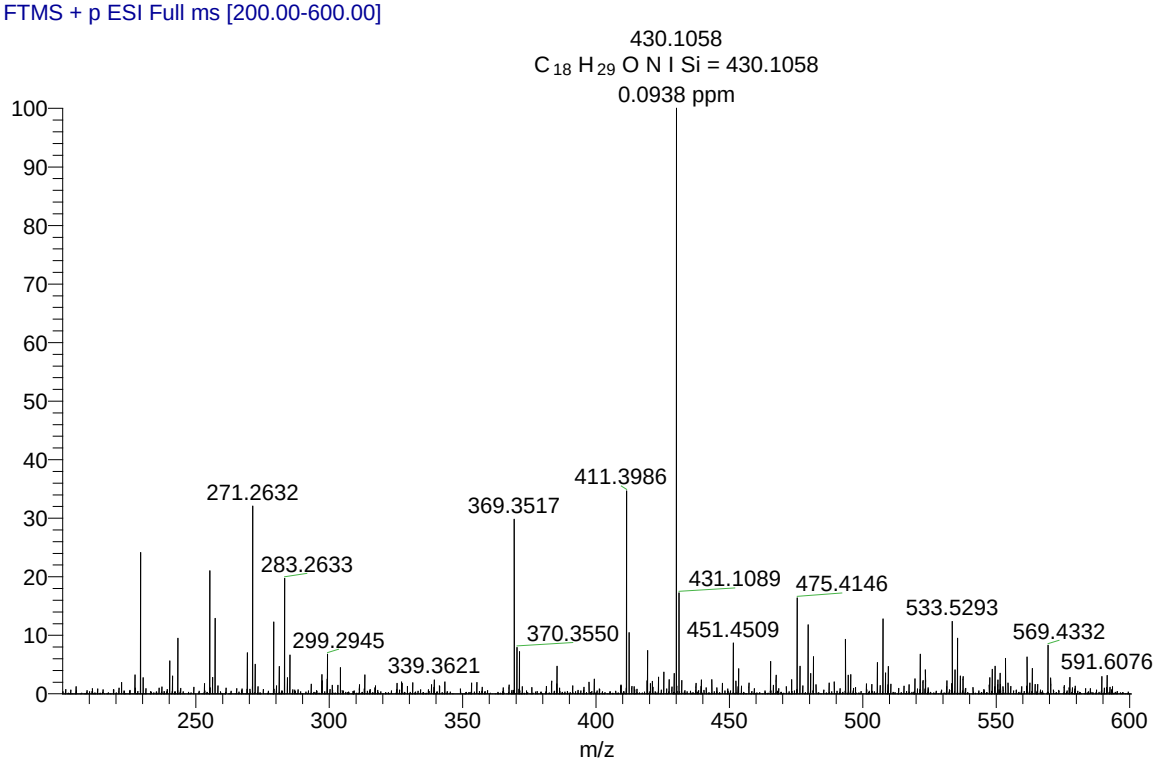

100
95
90
85
80
75
70
65
60
55
%Transmittance
3144.217
3044.755
2945.746
2866.370
1741.854
1600.246
1523.300
1500.316
1461.807
1370.721
1339.864
1320.358
1279.018
1258.155
1207.234
1179.999
1148.221
1083.344
1047.819
1018.424
964.831
920.404
876.046
775.172
745.482
685.752
646.872
610.465
3500
3000
2500
2000
1500
1000
Wavenumber
3-iodo-1-(triisopropylsilyl)benzo(g)indole
Monday, May 12, 2014 18:31:51

8.2.1.3 5-methoxy-N-triisopropylsilyl-3-iodoindole (70)

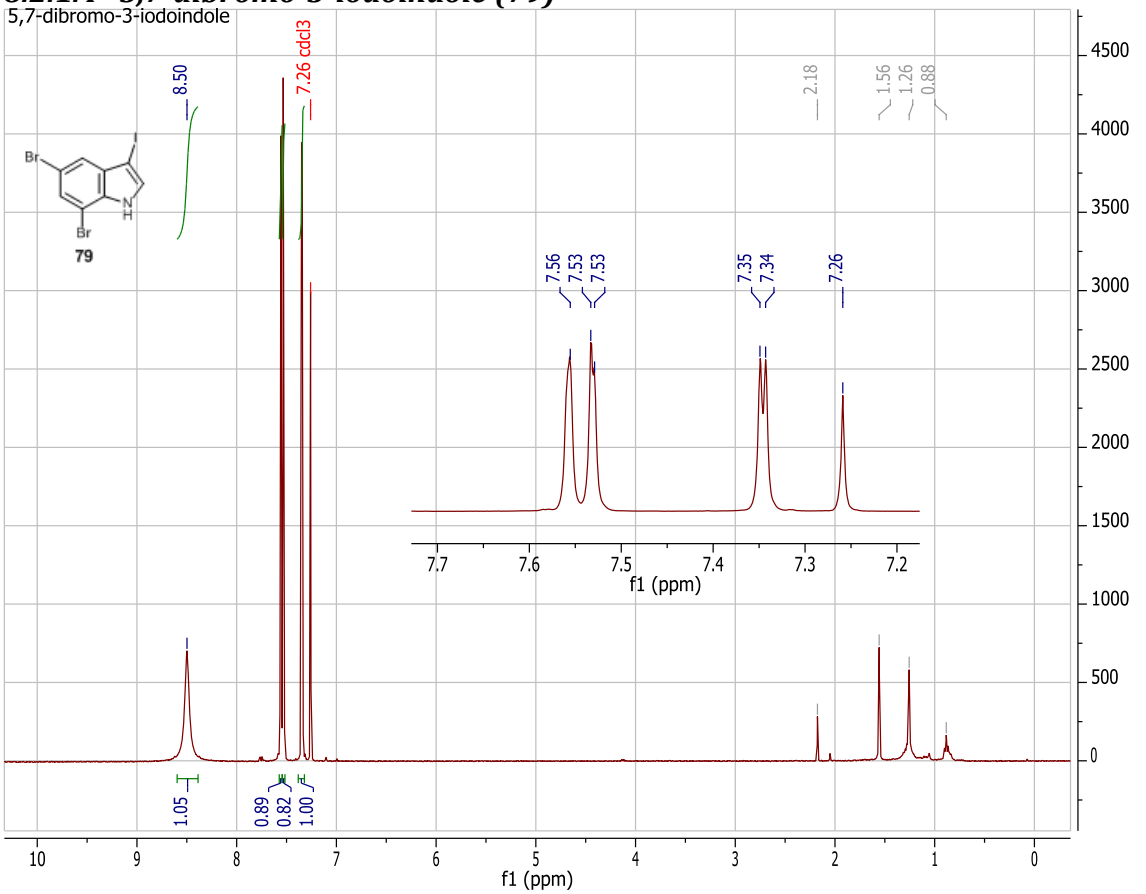


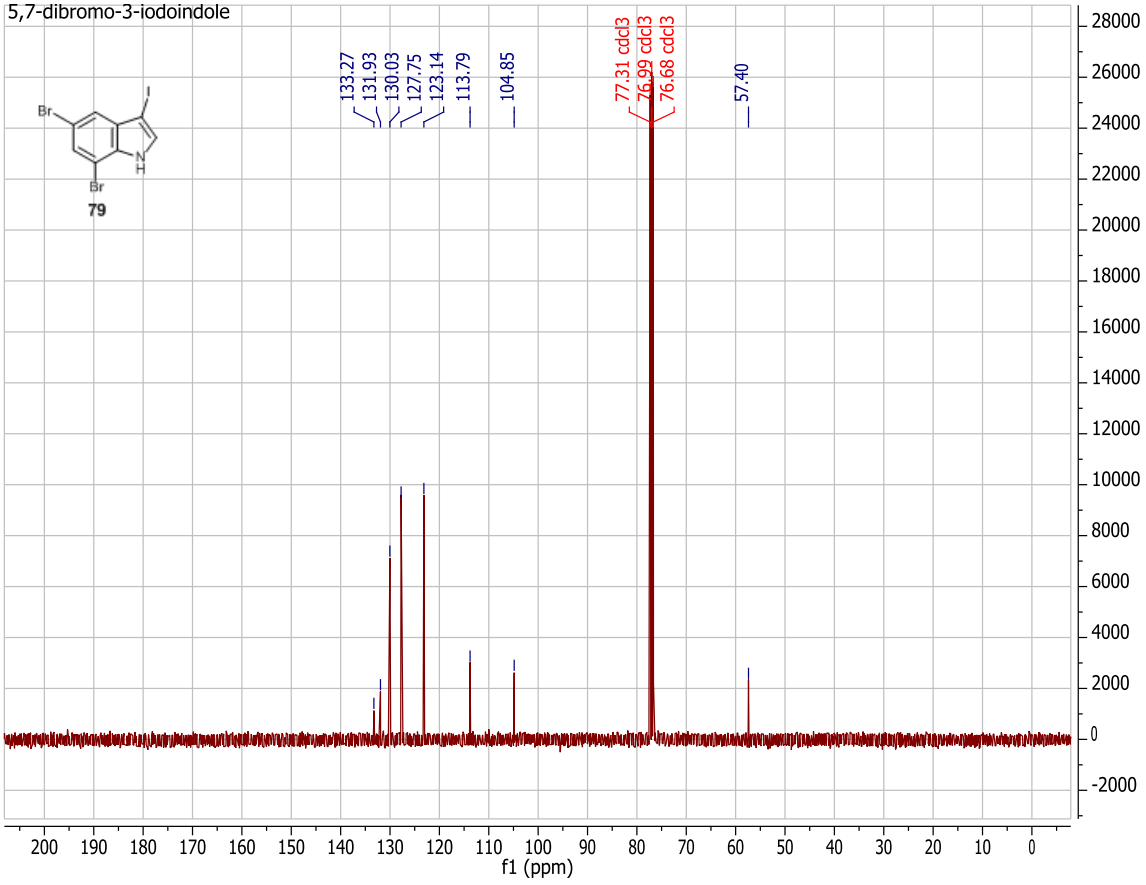


Yg103-2_b #1-5 RT: 0.02-0.14 AV: 5 NL: 7.36E5
T: FTMS + p ESI Full ms [200.00-600.00]

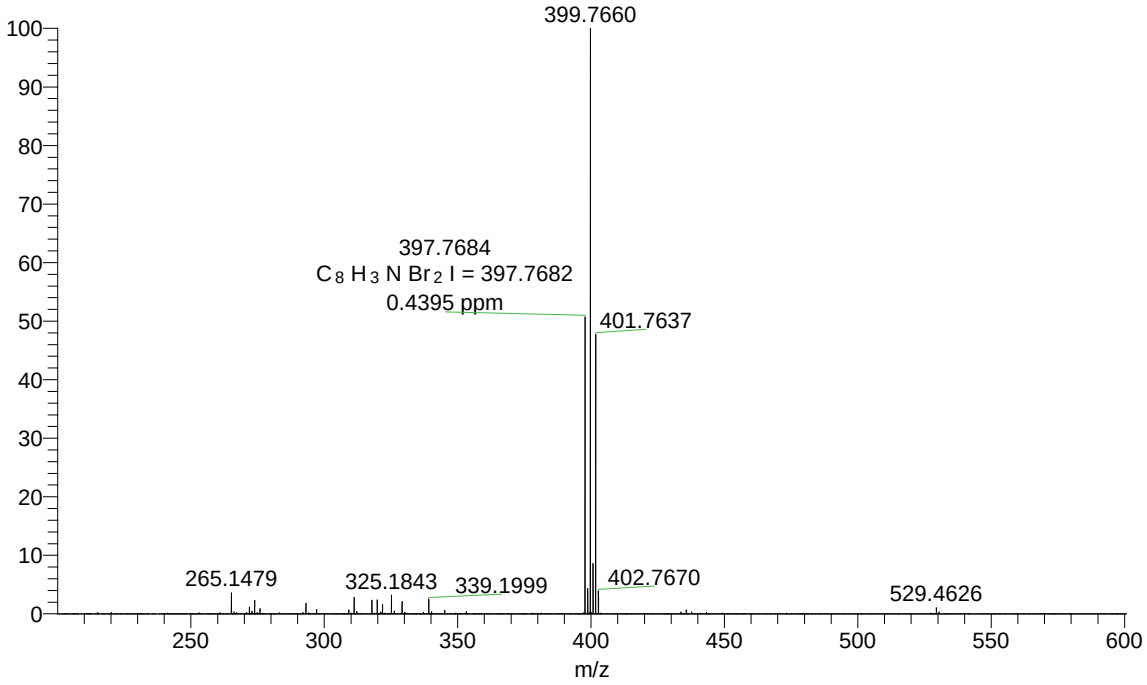


8.2.1.4 5,7-dibromo-3-iodoindole (79)

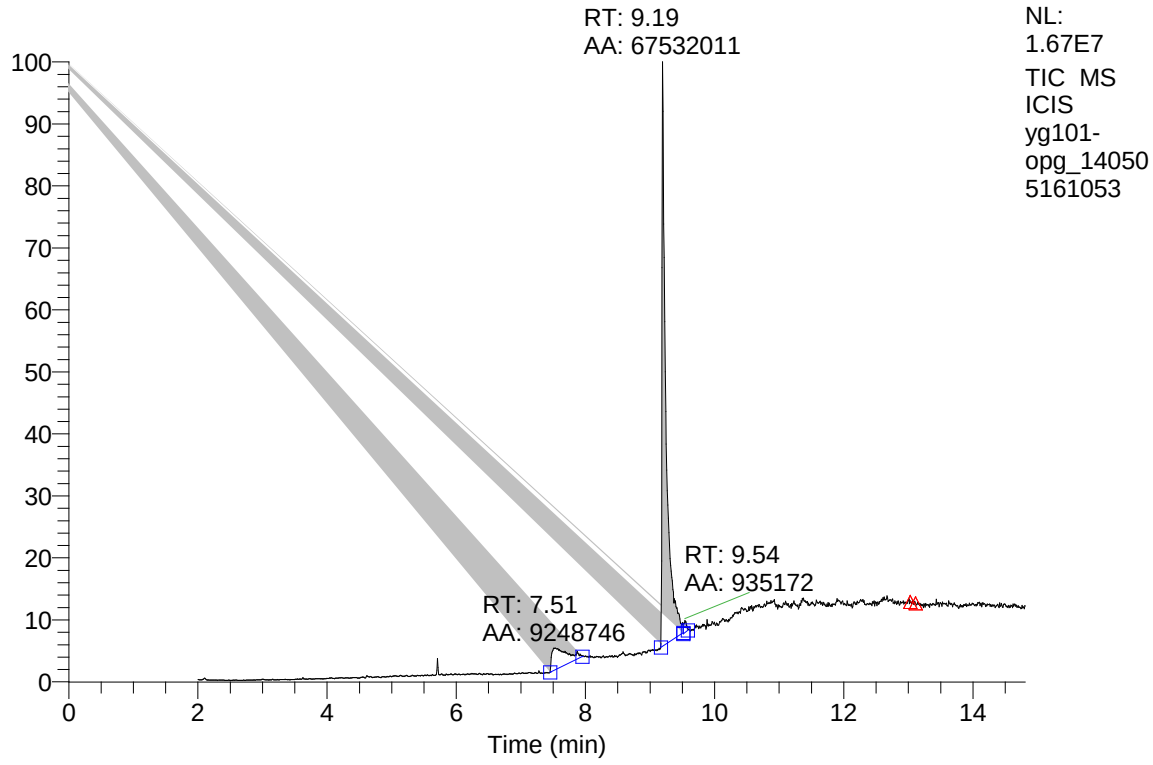


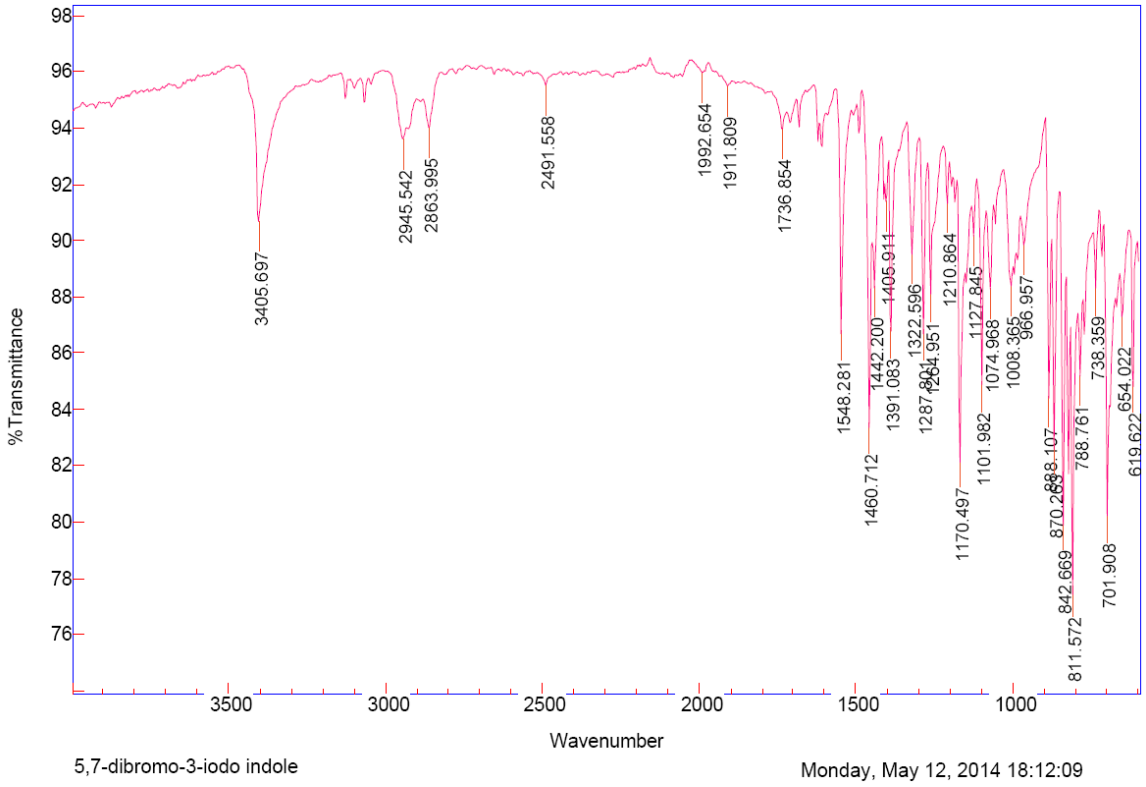


YG-101_neg-highres #1-5 RT: 0.01-0.15 AV: 5 NL: 9.37E5
T: FTMS - p ESI Full ms [200.00-600.00]

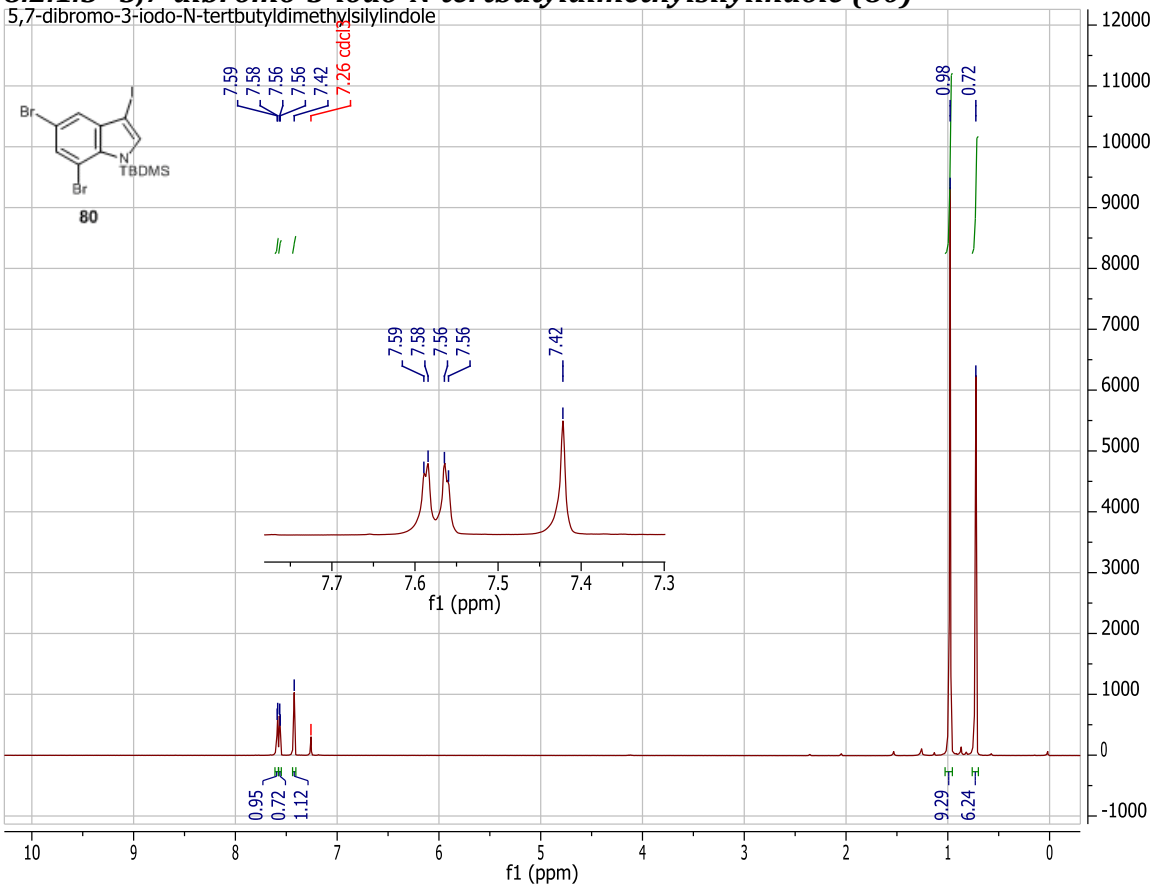


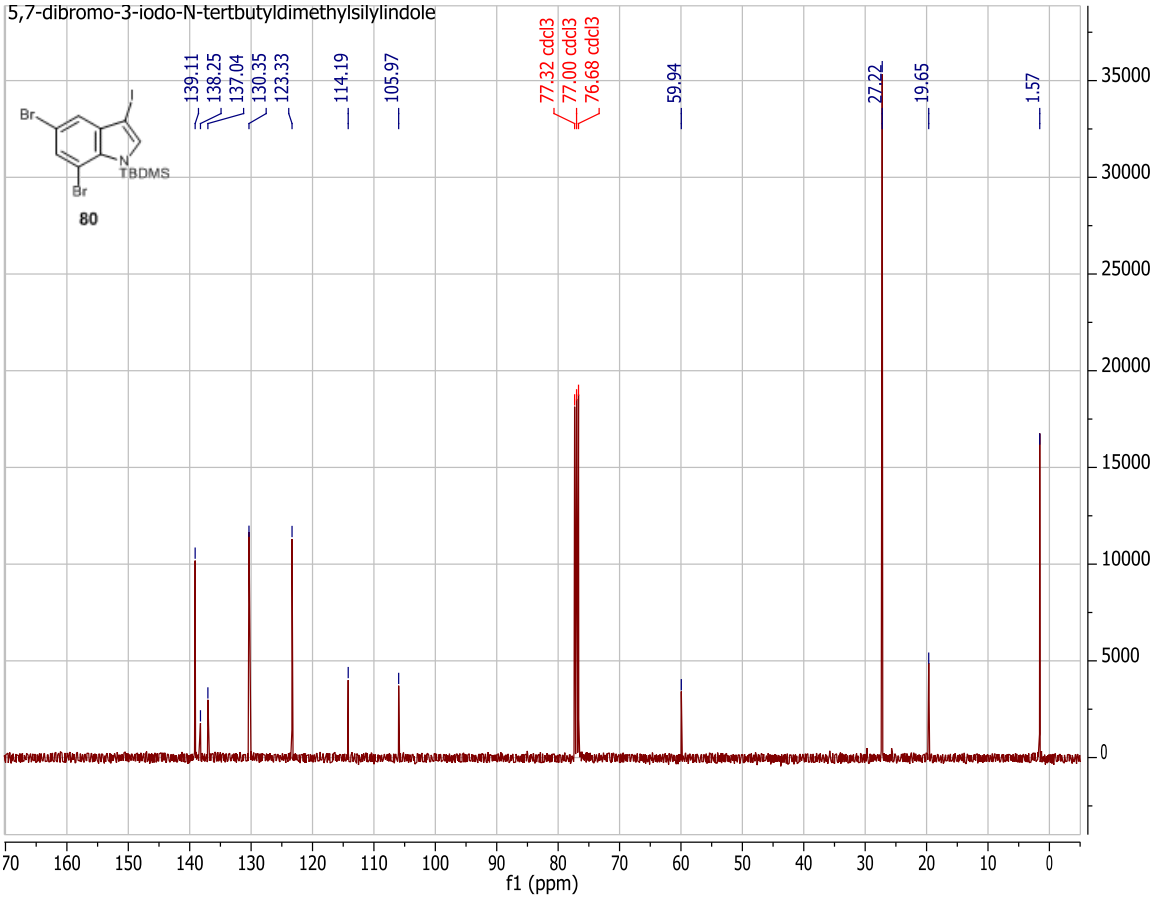
RT: 0.00 - 14.81



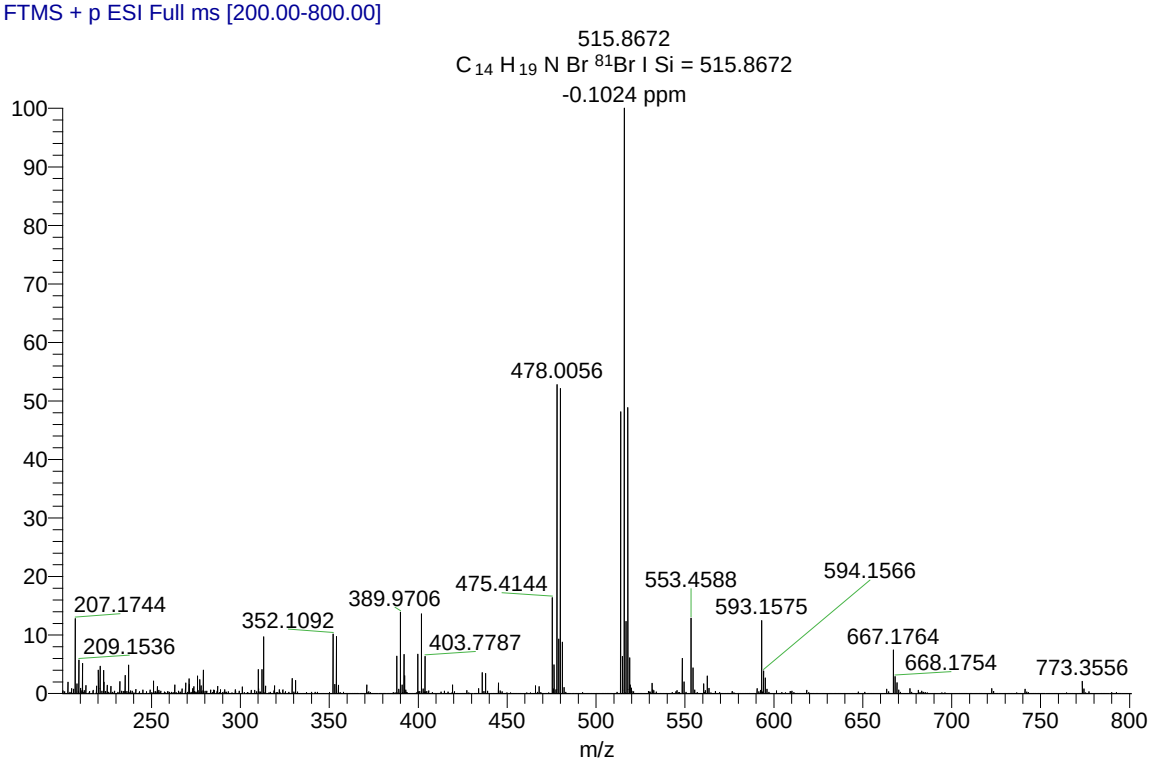

%Transmittance
Wavenumber
3405.697
2945.542
2863.995
2491.558
1992.654
1911.809
1736.854
1548.281
1460.712
1442.200
1405.911
1391.083
1322.596
1287.801
1264.951
1210.864
1170.497
1127.845
1101.982
1074.968
1008.365
966.957
888.107
870.283
842.669
811.572
788.761
738.359
701.908
654.022
619.622
5,7-dibromo-3-iodo indole
Monday, May 12, 2014 18:12:09

8.2.1.5 5,7-dibromo-3-iodo-N-tertbutyldimethylsilylindole (80)

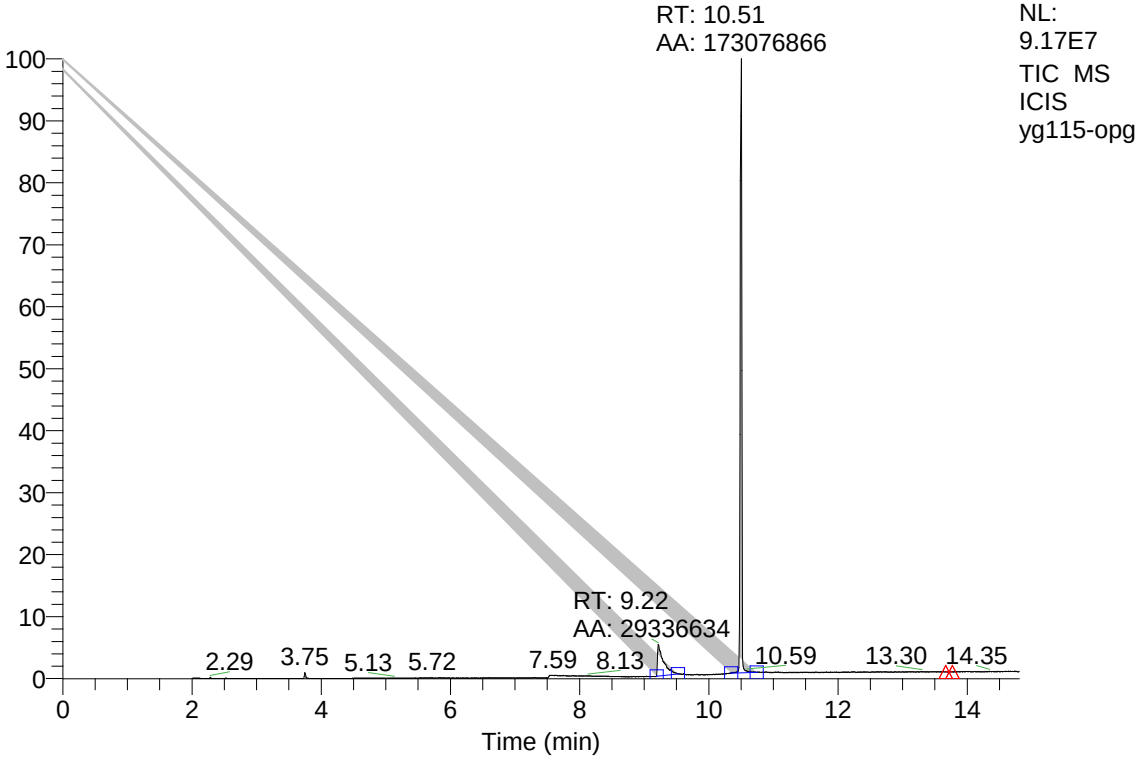


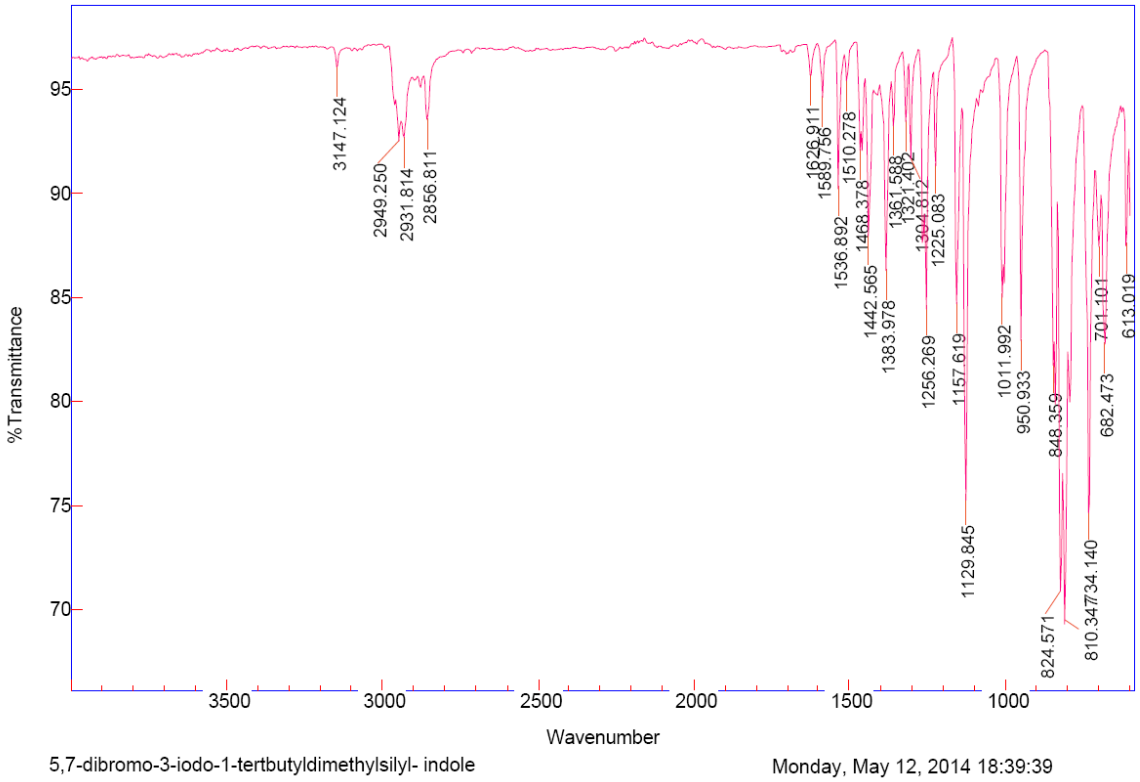


yg115-2-12_5 #1-5 RT: 0.01-0.15 AV: 5 NL: 2.96E5
T: FTMS + p ESI Full ms [200.00-800.00]

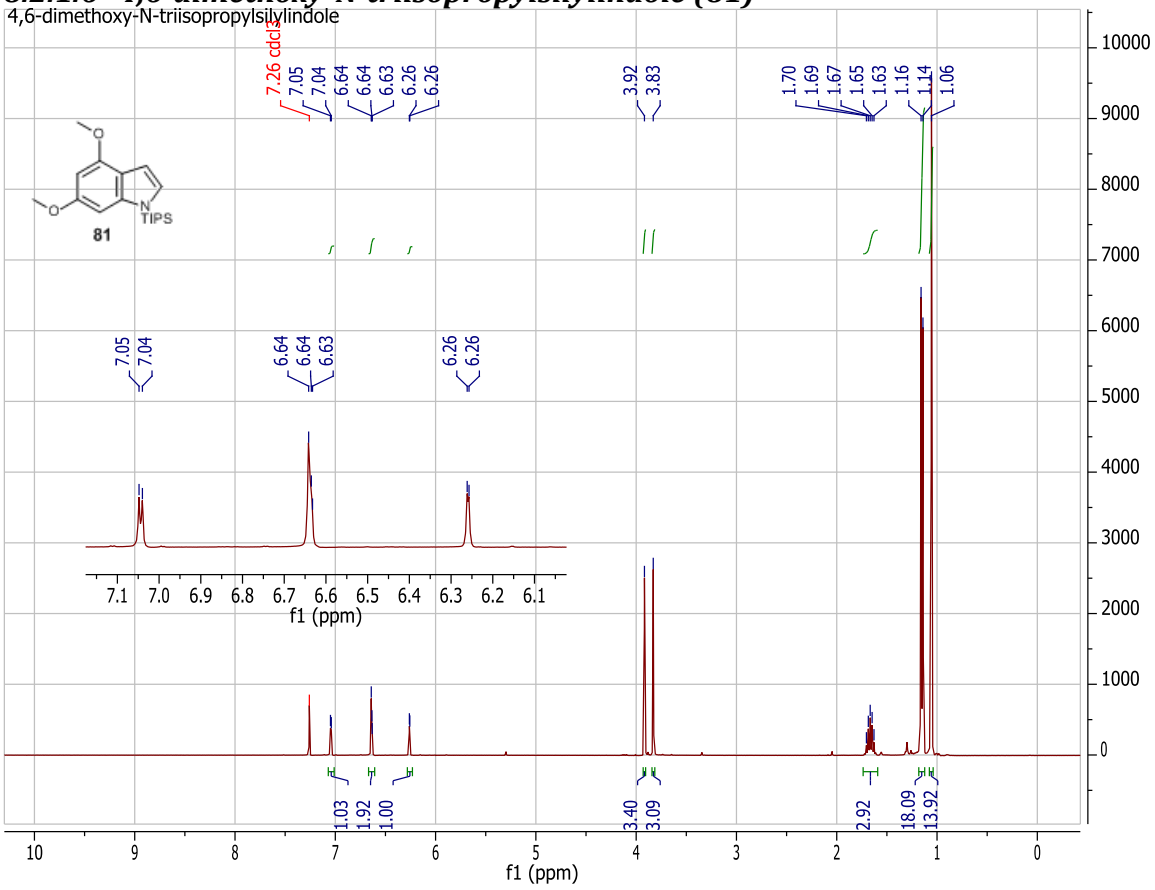


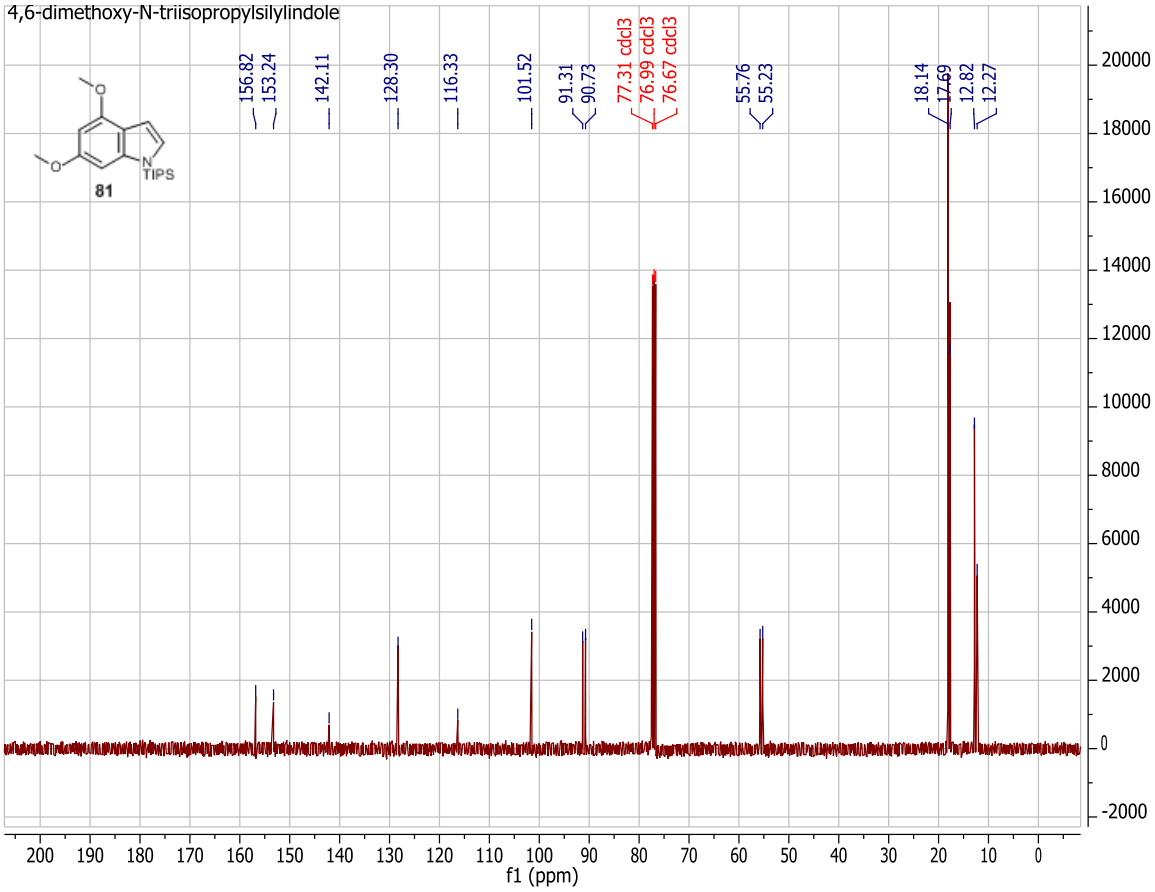
RT: 0.00 - 14.81



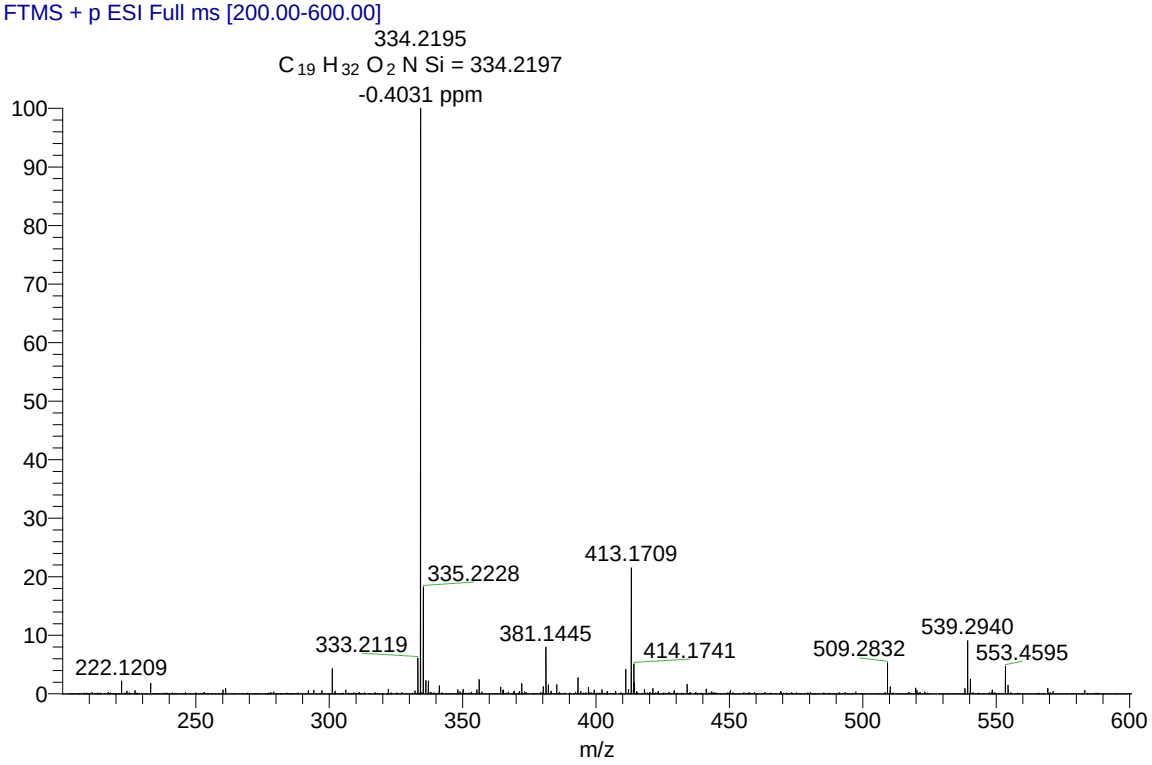

%Transmittance
95
90
85
80
75
70
3147.124
2949.250
2931.814
2856.811
1626.911
1589.756
1536.892
1510.278
1468.378
1442.565
1383.978
1361.588
1321.402
1304.812
1256.269
1225.083
1157.619
1129.845
1011.992
950.933
848.359
824.571
810.347
734.140
701.101
682.473
613.019
3500
3000
2500
2000
1500
1000
Wavenumber
5,7-dibromo-3-iodo-1-tertbutyldimethylsilyl- indole
Monday, May 12, 2014 18:39:39

*8.2.1.6 4,6-dimethoxy-*N*-triisopropylsilylindole (81)*

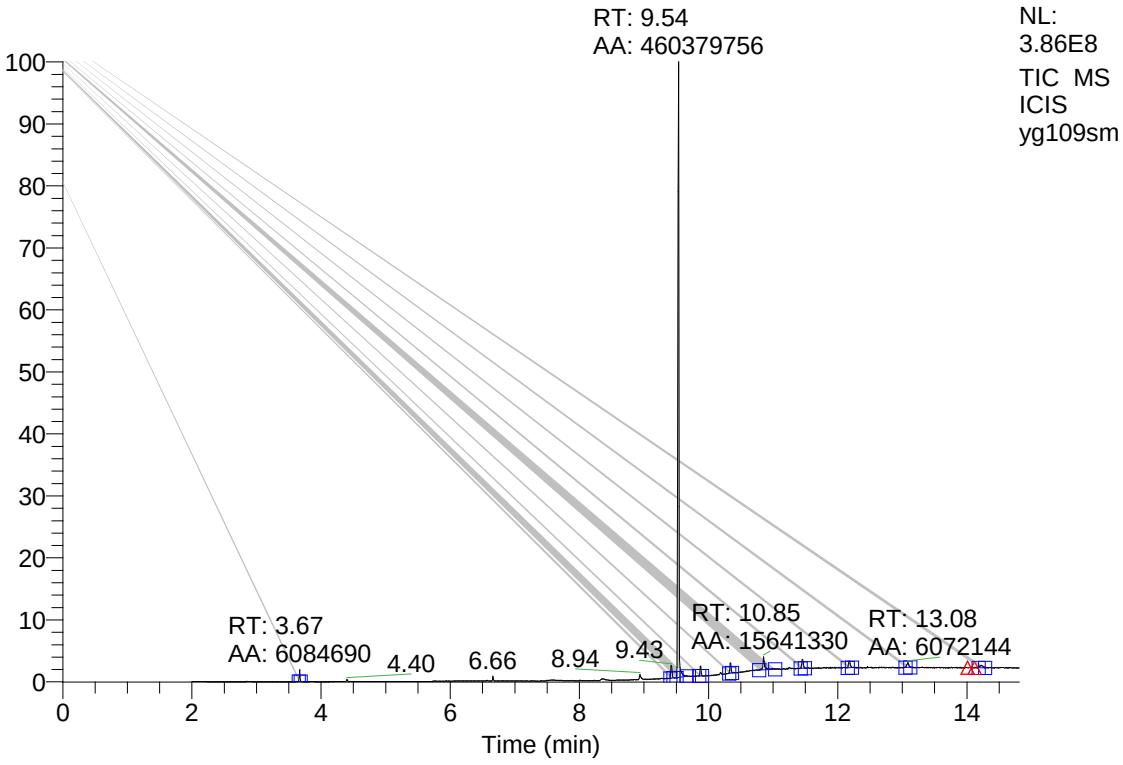




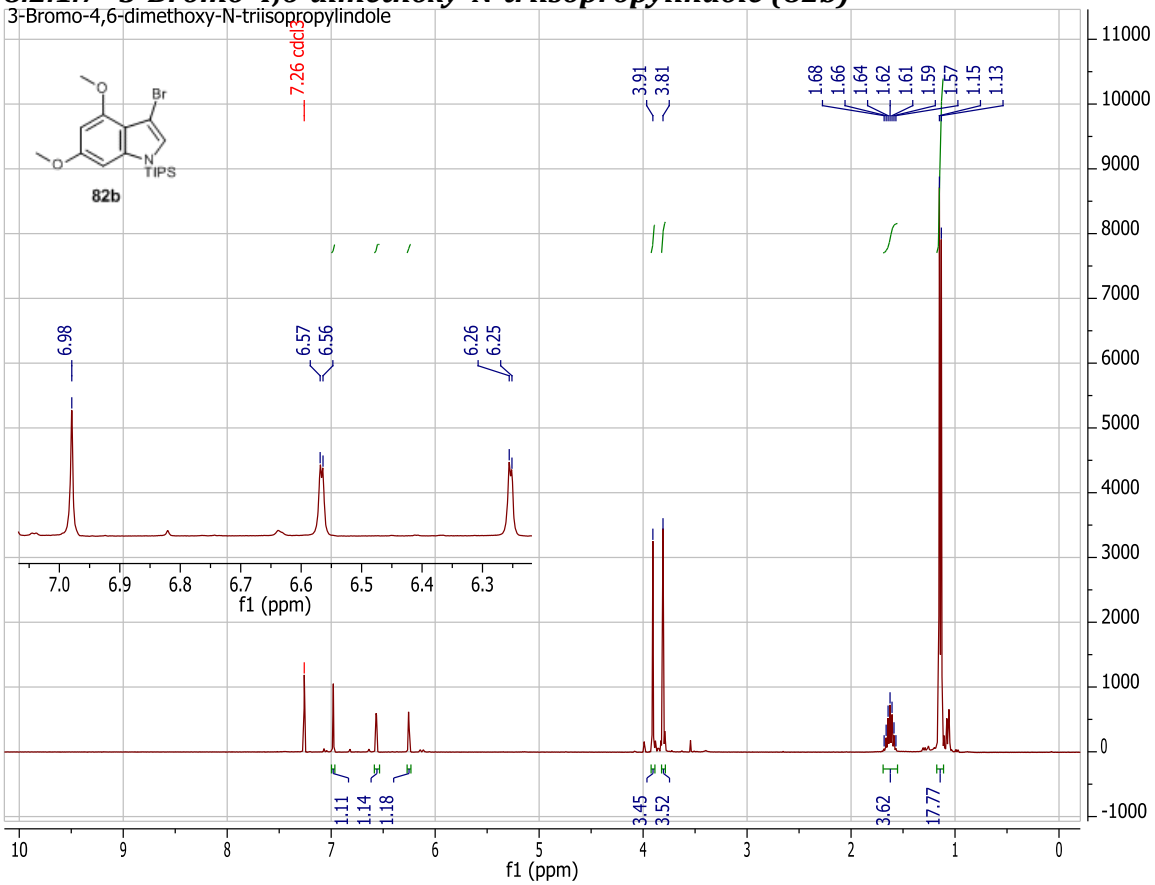
Yg107-2 #1-5 RT: 0.00-0.11 AV: 5 NL: 8.03E7
T: FTMS + p ESI Full ms [200.00-600.00]

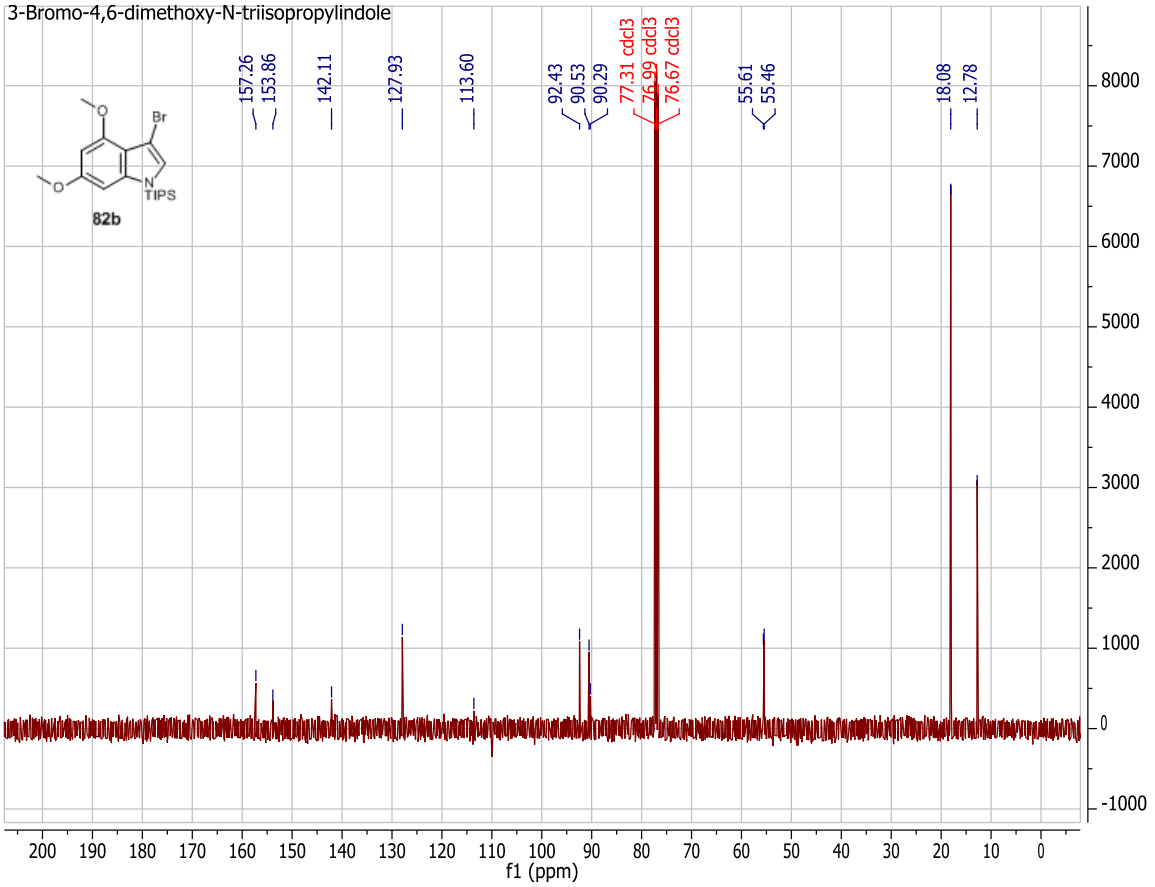


RT: 0.00 - 14.81

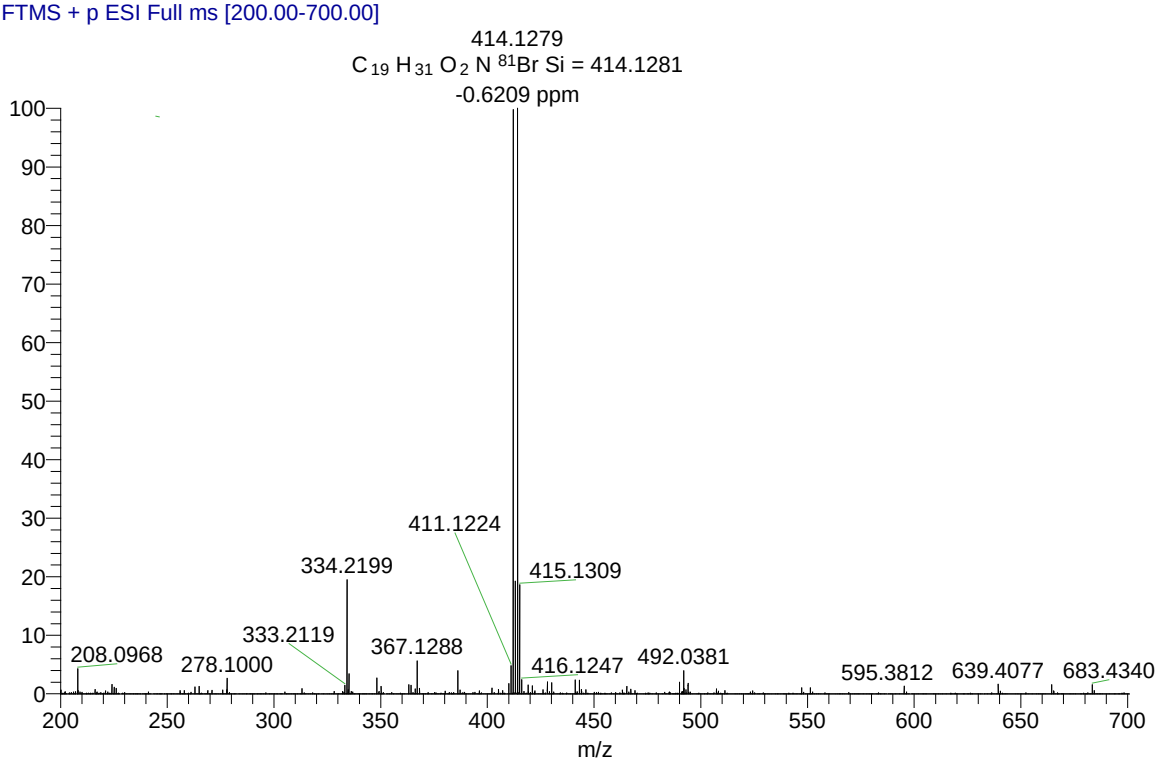


8.2.1.7 3-Bromo-4,6-dimethoxy-N-triisopropylindole (82b)

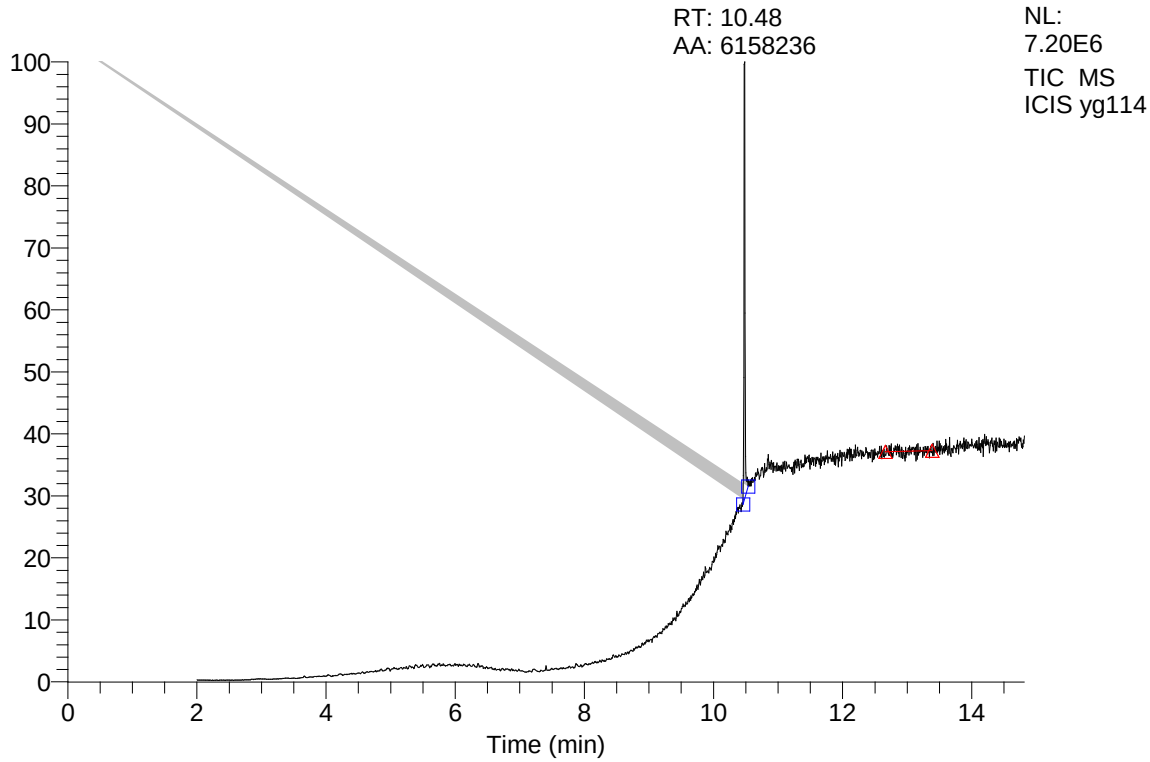


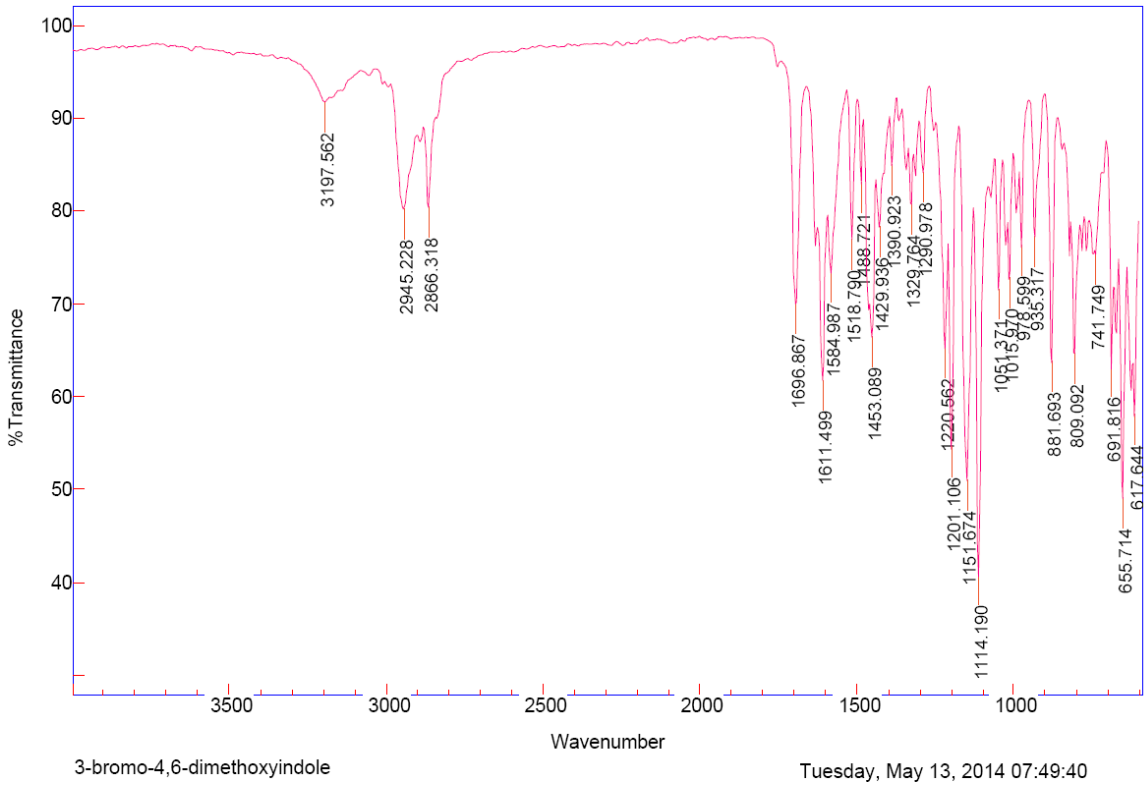


yg114ny #1-5 RT: 0.02-0.14 AV: 5 NL: 1.54E6
T: FTMS + p ESI Full ms [200.00-700.00]



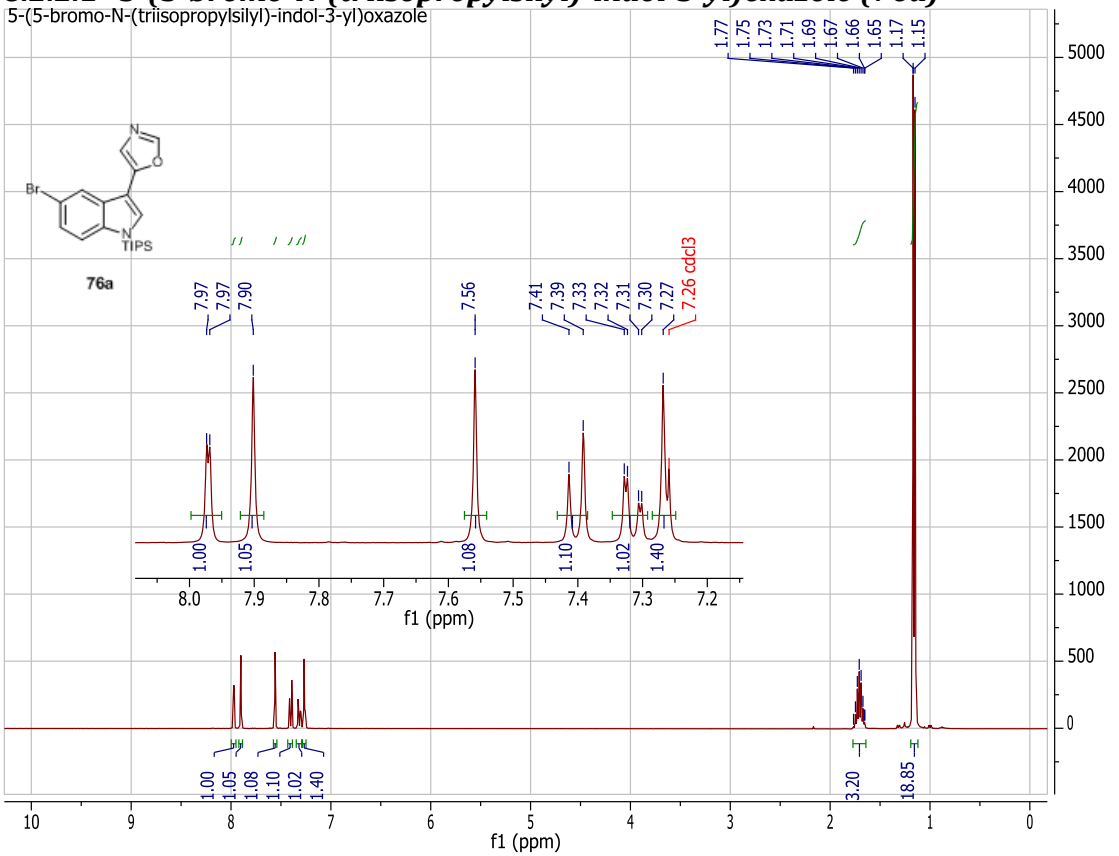
RT: 0.00 - 14.81

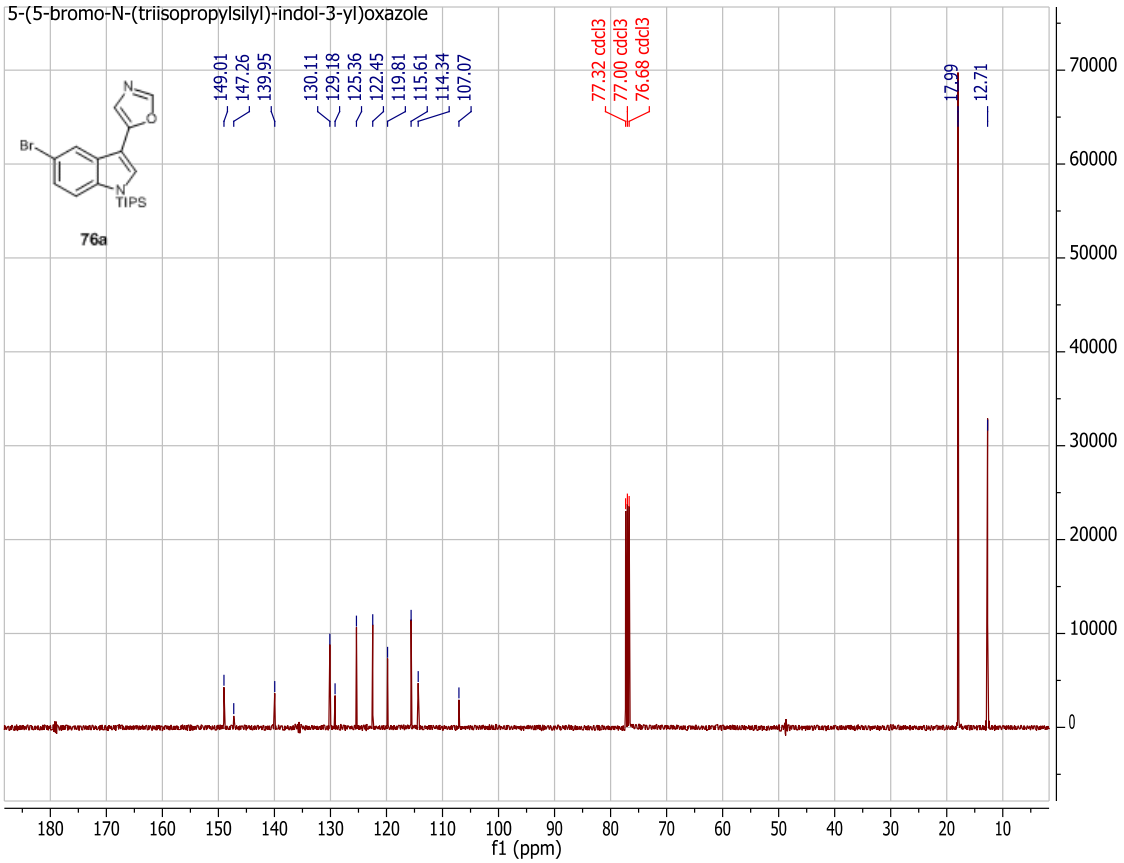



100
90
80
70
60
50
40
% Transmittance
3197.562
2945.228
2866.318
1696.867
1611.499
1584.987
1518.790
1488.721
1453.089
1429.936
1390.923
1329.764
1290.978
1220.562
1201.106
1151.674
1114.190
1051.371
1015.970
978.599
935.317
881.693
809.092
741.749
691.816
655.714
617.644
3500
3000
2500
2000
1500
1000
Wavenumber
3-bromo-4,6-dimethoxyindole
Tuesday, May 13, 2014 07:49:40

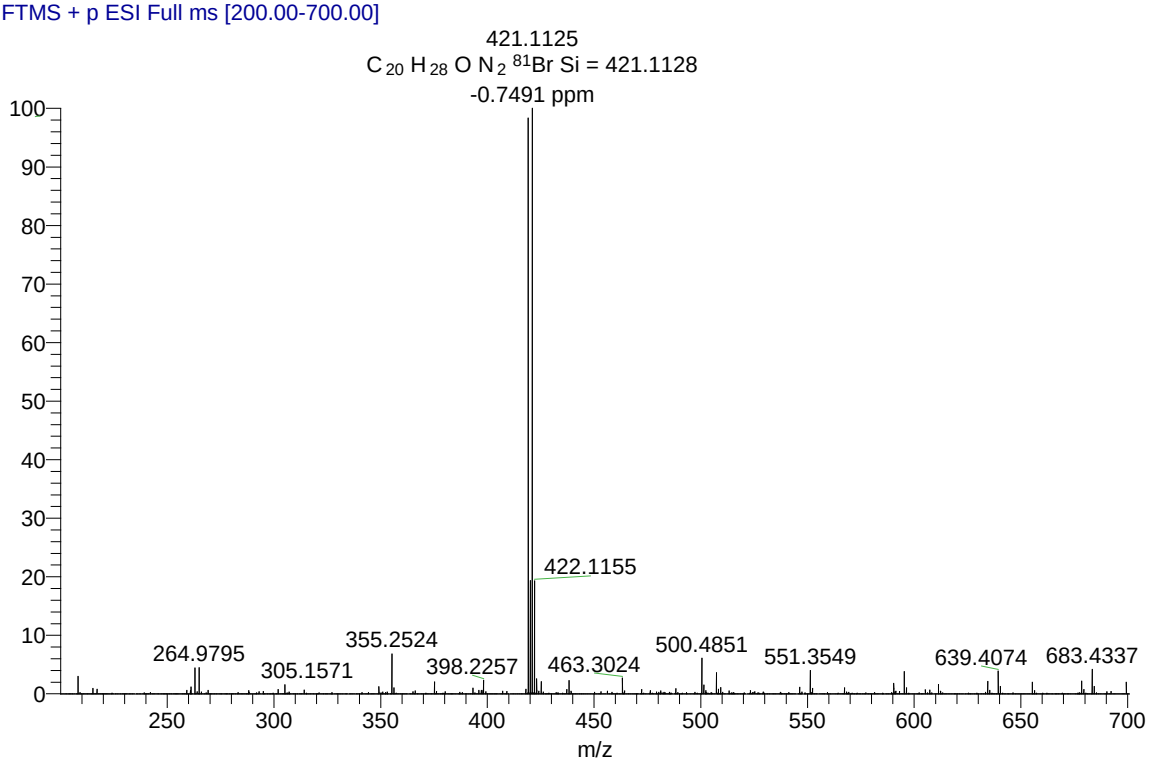
8.2.2 Synthesis of 5-(*N*-TIPS-indol-3-yl)oxazoles (section 4.4)

*8.2.2.1 5-(5-bromo-*N*-(triisopropylsilyl)-indol-3-yl)oxazole (76a)*

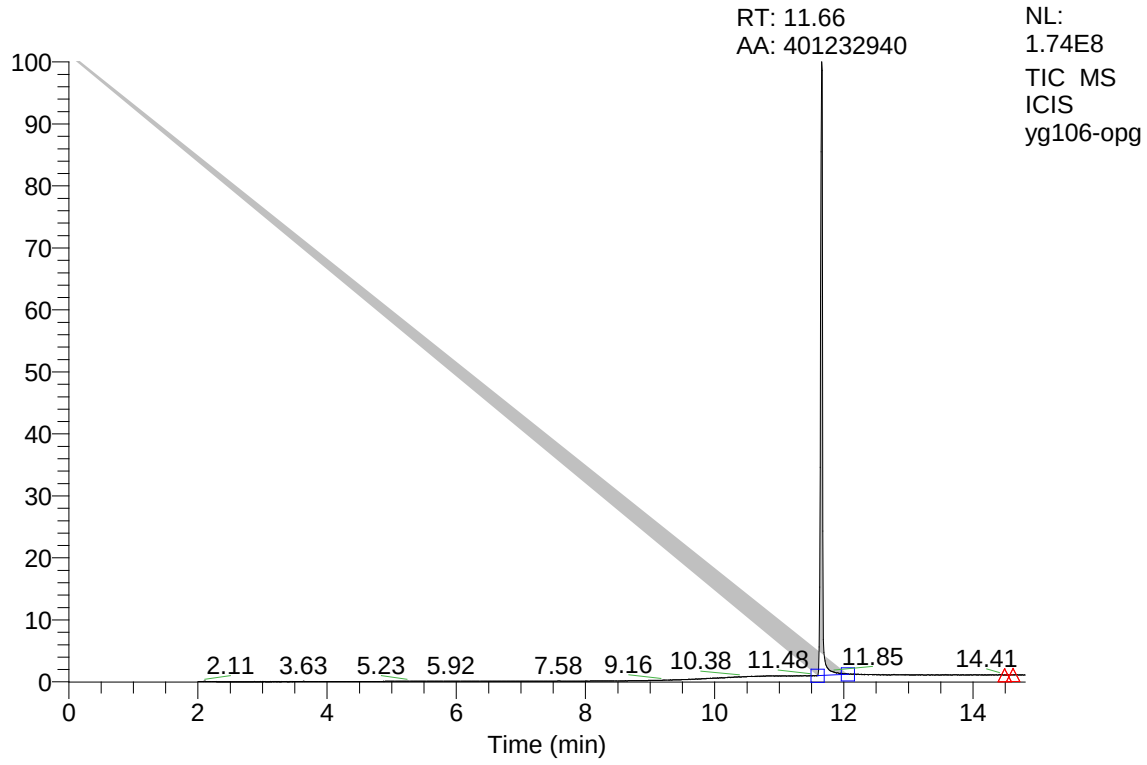


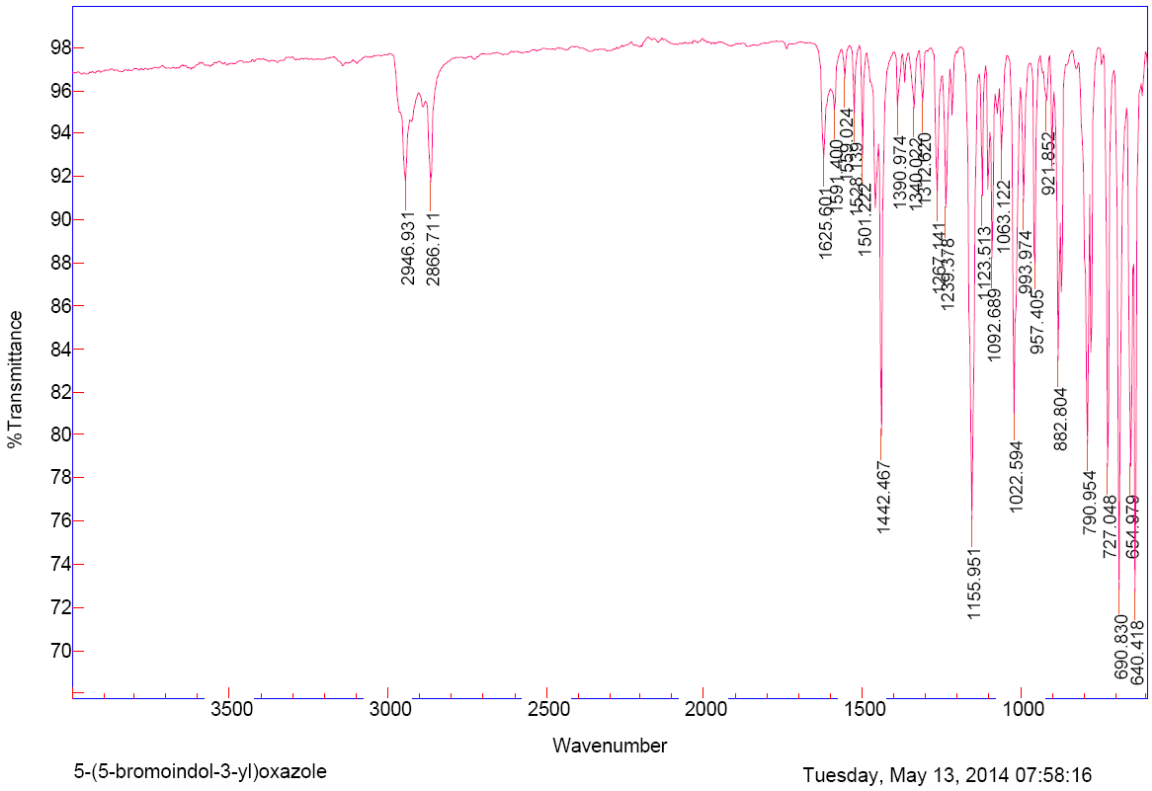


yg106ny #1-5 RT: 0.02-0.17 AV: 5 NL: 6.27E5
T: FTMS + p ESI Full ms [200.00-700.00]

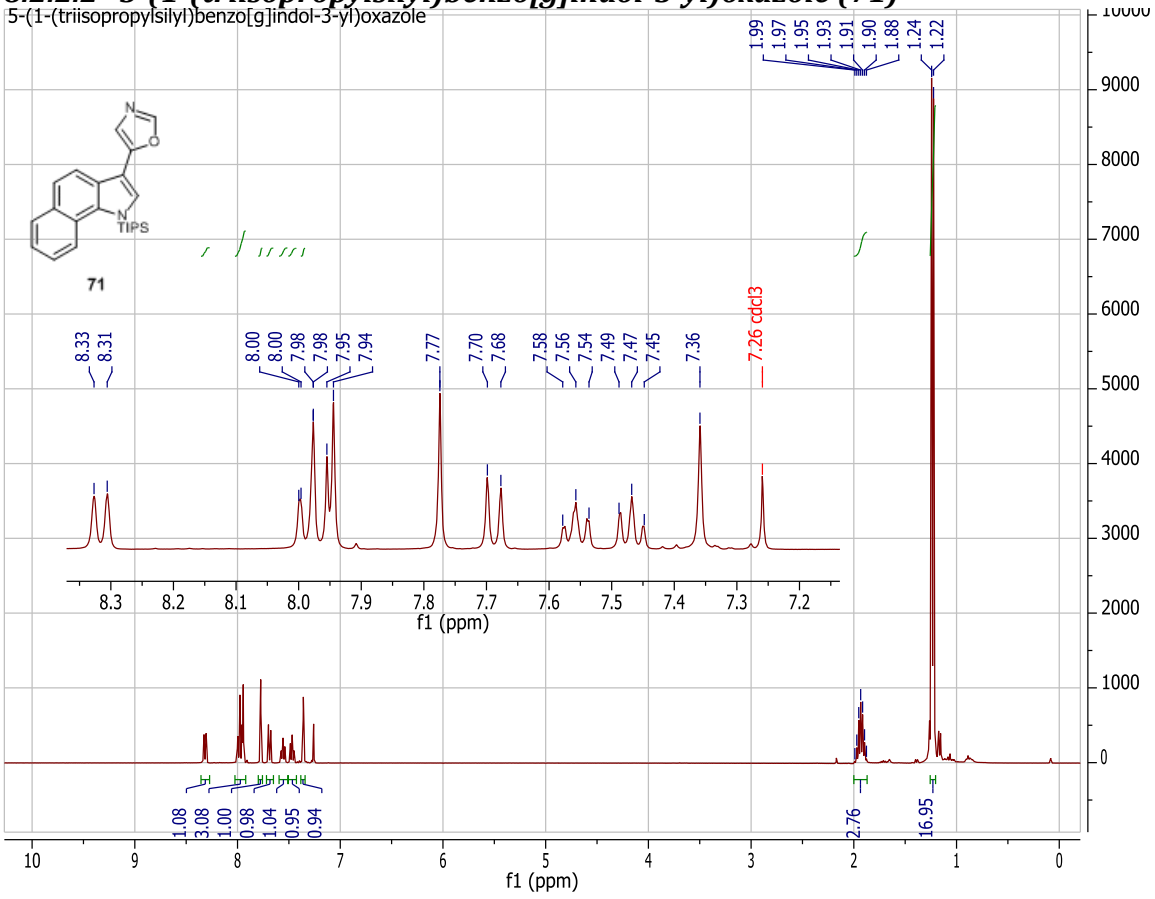


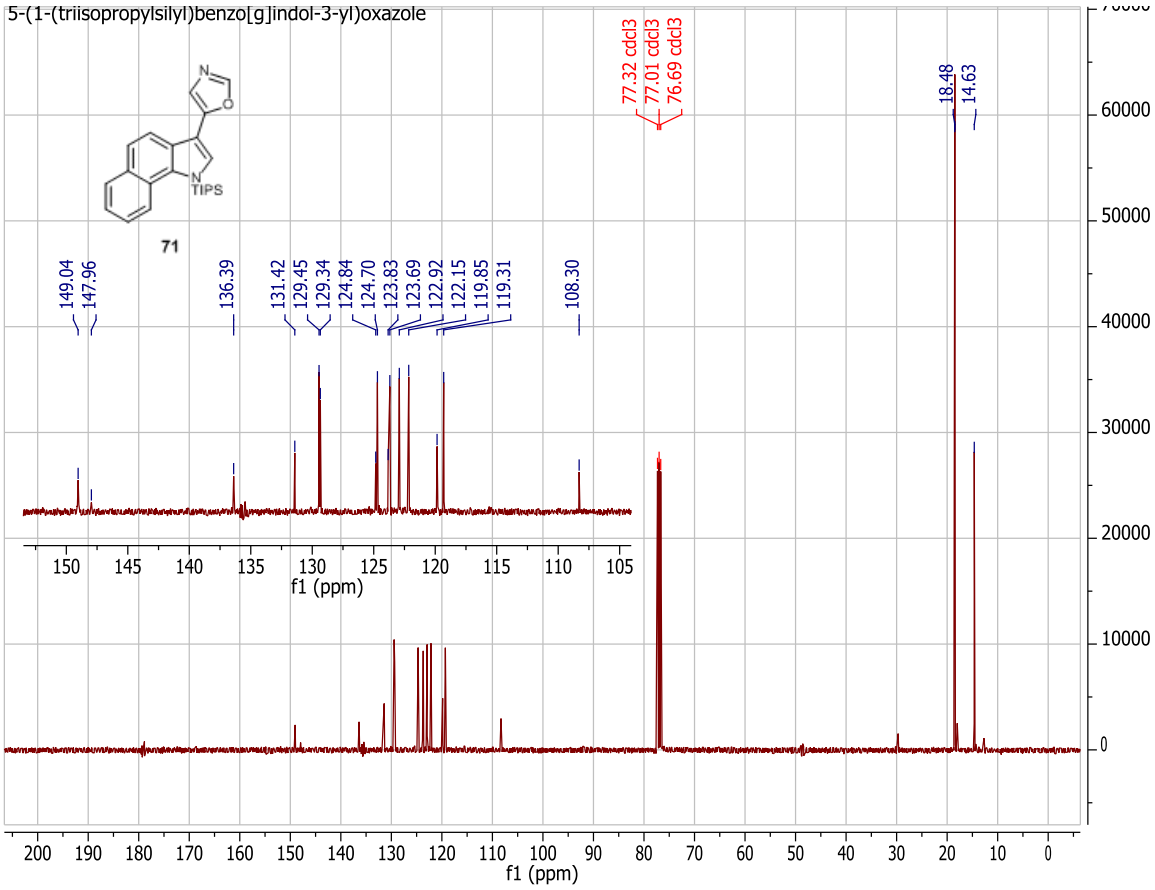
RT: 0.00 - 14.81



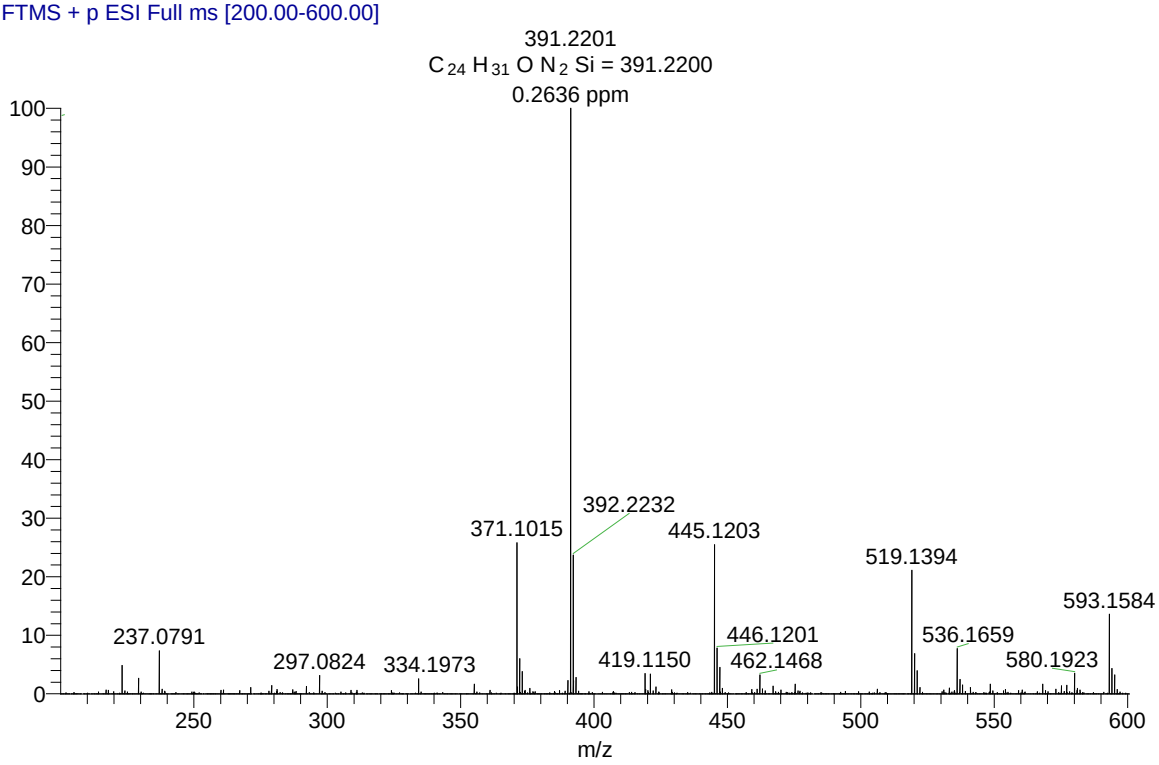

% Transmittance
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
2946.931
2866.711
1625.601
1591.400
1559.024
1538.139
1501.222
1442.467
1390.974
1340.022
1312.820
1267.141
1239.378
1155.951
1123.513
1092.689
1063.122
1022.594
993.974
957.405
921.852
882.804
790.954
727.048
690.830
654.979
640.418
3500
3000
2500
2000
1500
1000
Wavenumber
5-(5-bromoindol-3-yl)oxazole
Tuesday, May 13, 2014 07:58:16

8.2.2.2 5-(1-(triisopropylsilyl)benzo[g]indol-3-yl)oxazole (71)

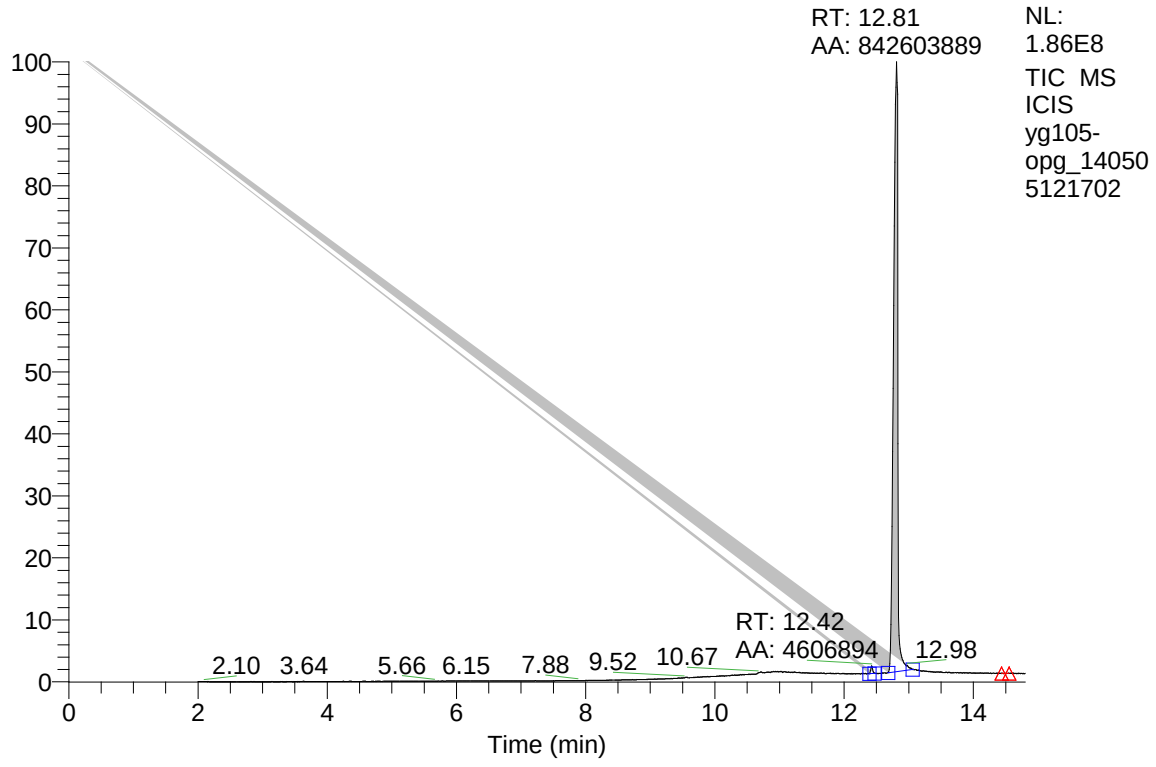


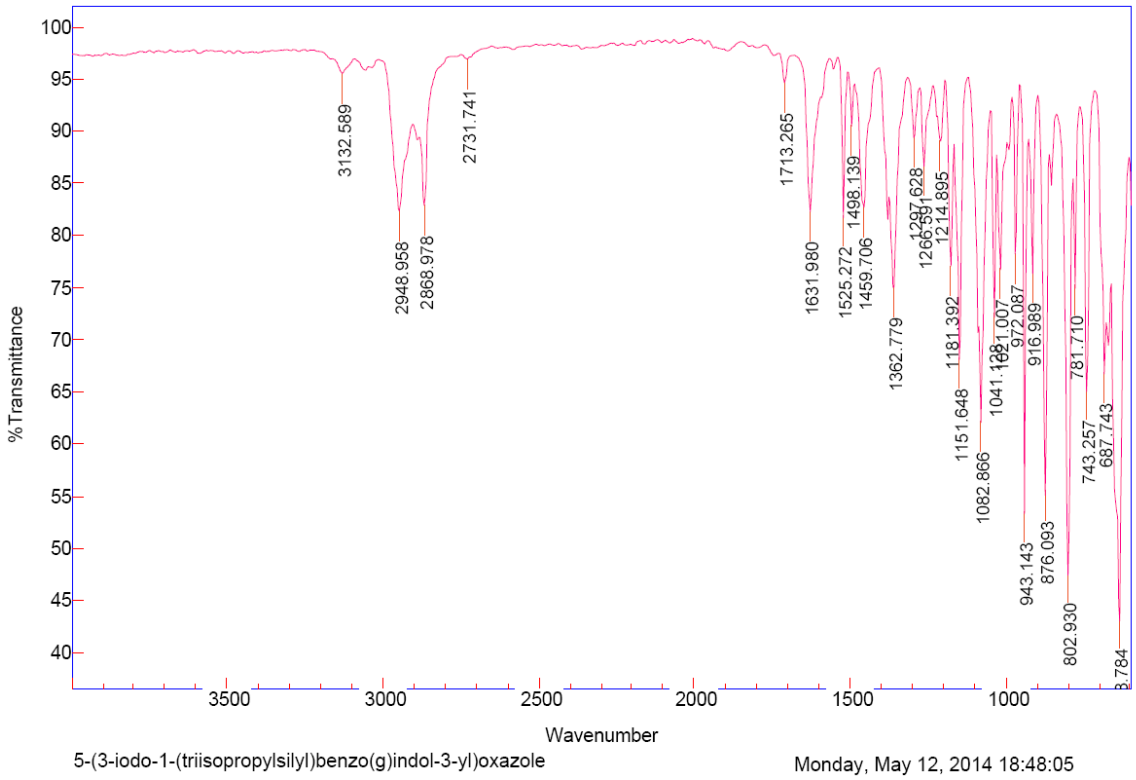


Yg105 #1-5 RT: 0.00-0.11 AV: 5 NL: 8.99E6
T: FTMS + p ESI Full ms [200.00-600.00]



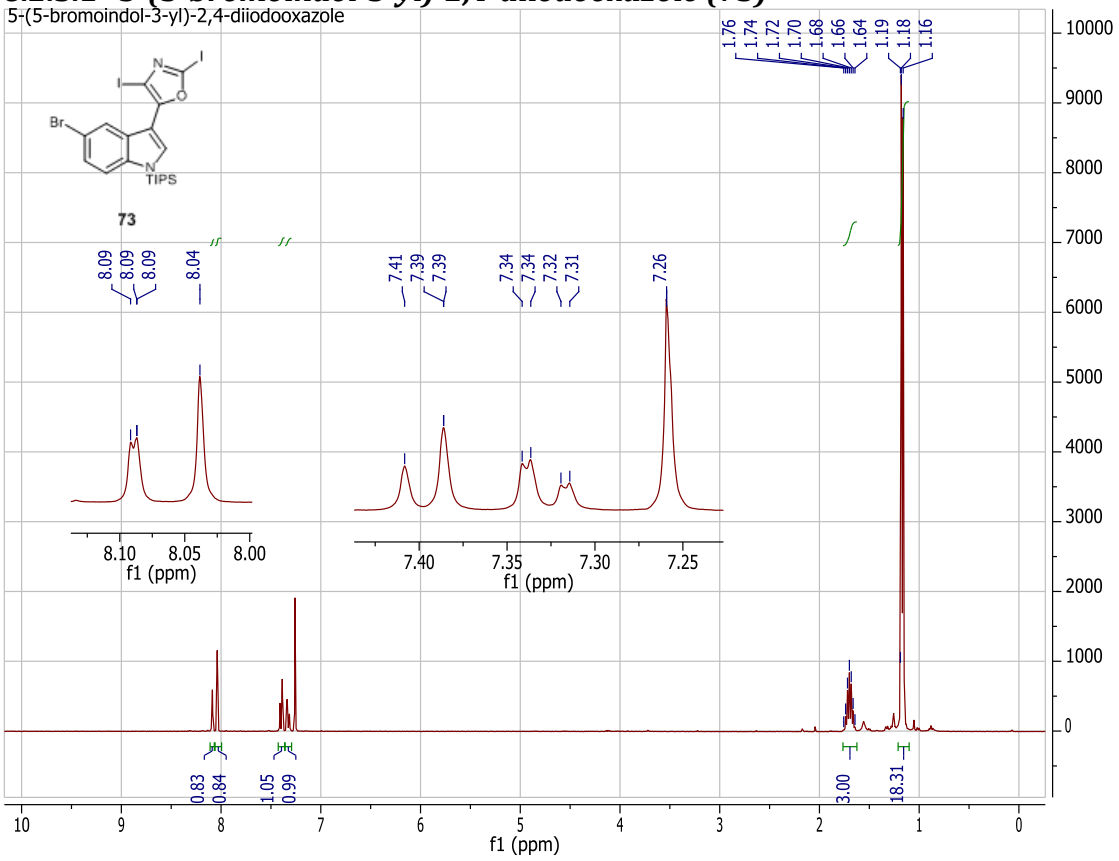
RT: 0.00 - 14.80

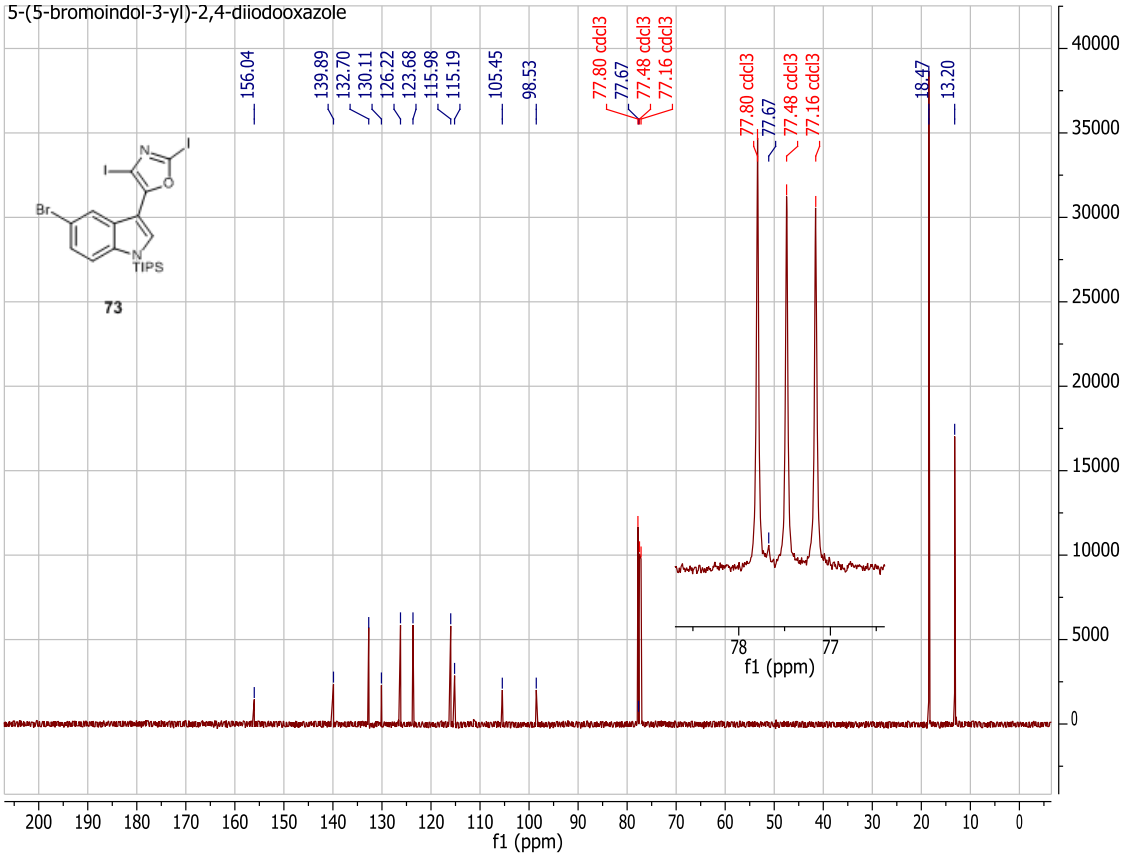



%Transmittance
100
95
90
85
80
75
70
65
60
55
50
45
40
3500
3000
2500
2000
1500
1000
Wavenumber
3132.589
2948.958
2868.978
2731.741
1713.265
1631.980
1525.272
1498.139
1459.706
1362.779
1297.628
1266.591
1214.895
1181.392
1151.648
1082.866
1041.128
1031.007
972.087
916.969
943.143
876.093
802.930
781.710
743.257
687.743
3.784
5-(3-iodo-1-(triisopropylsilyl)benzo(g)indol-3-yl)oxazole
Monday, May 12, 2014 18:48:05

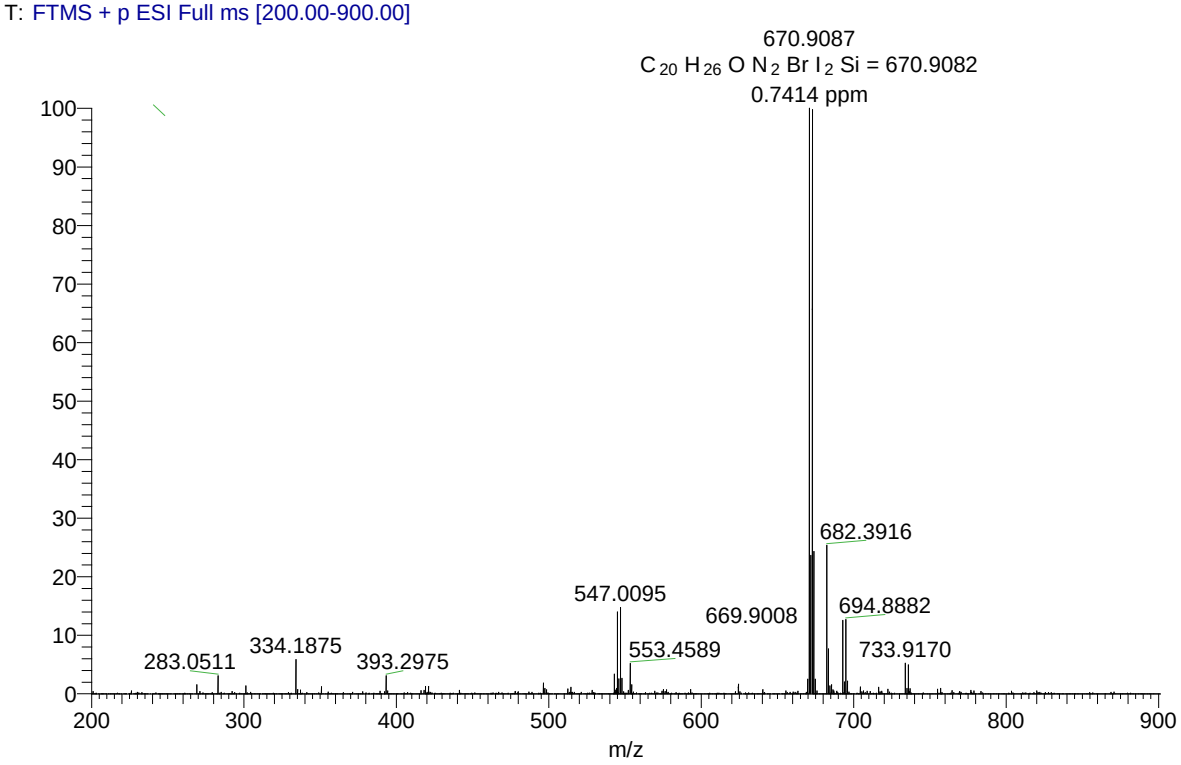
8.2.3 Synthesis of 5-(5-bromoindol-3-yl)-2,4-diiodooxazole (section 4.5)

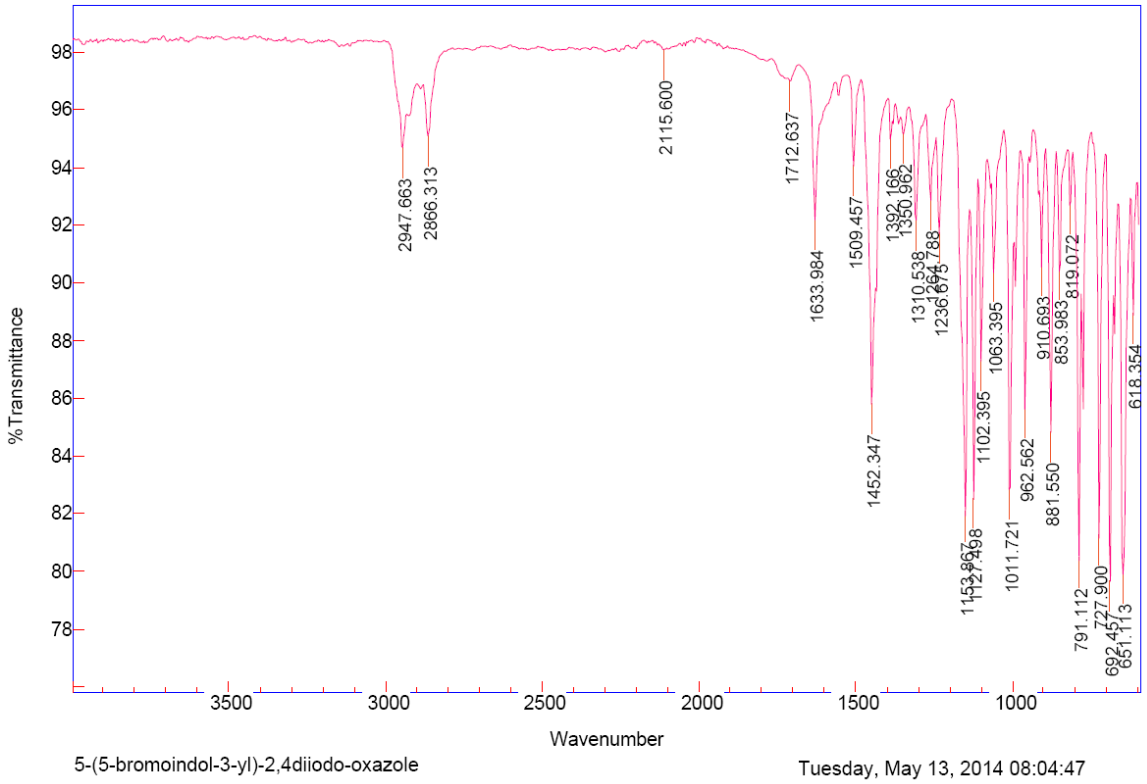
8.2.3.1 5-(5-bromoindol-3-yl)-2,4-diiodooxazole (73)



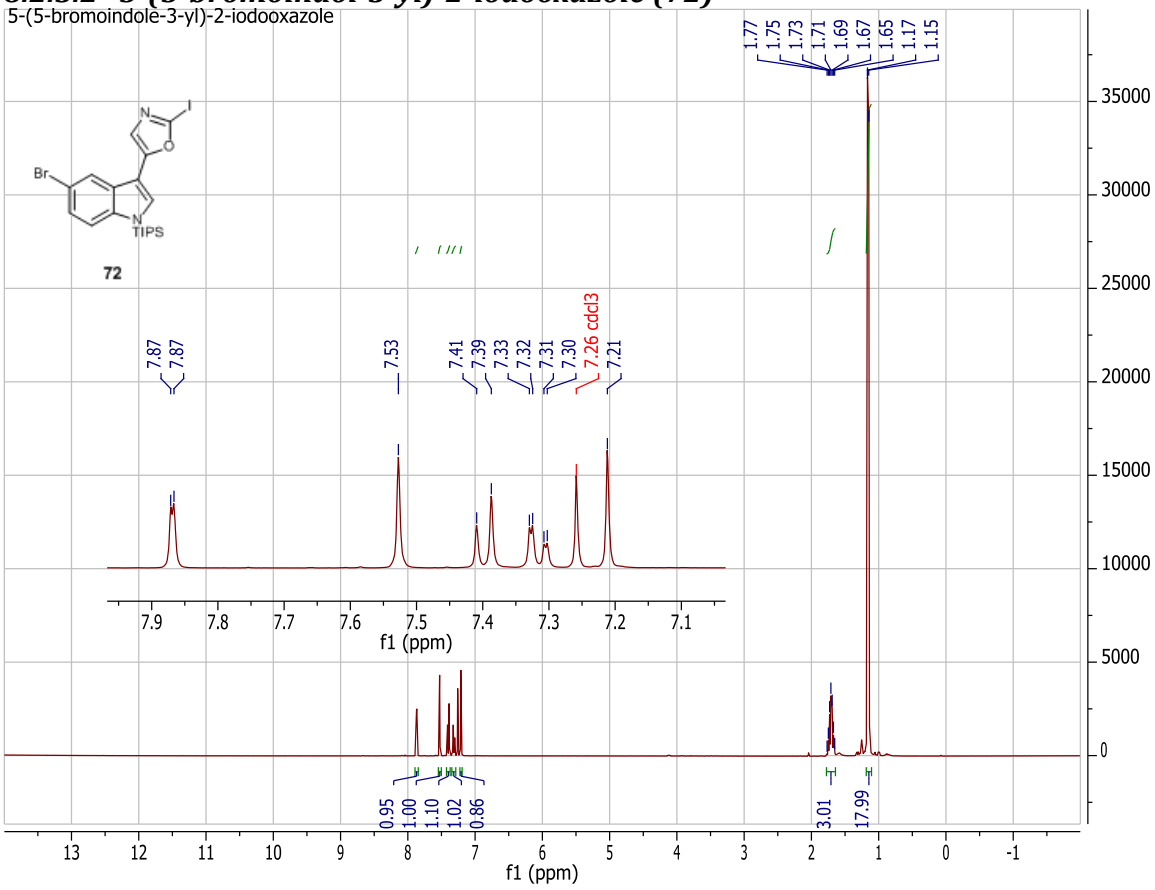


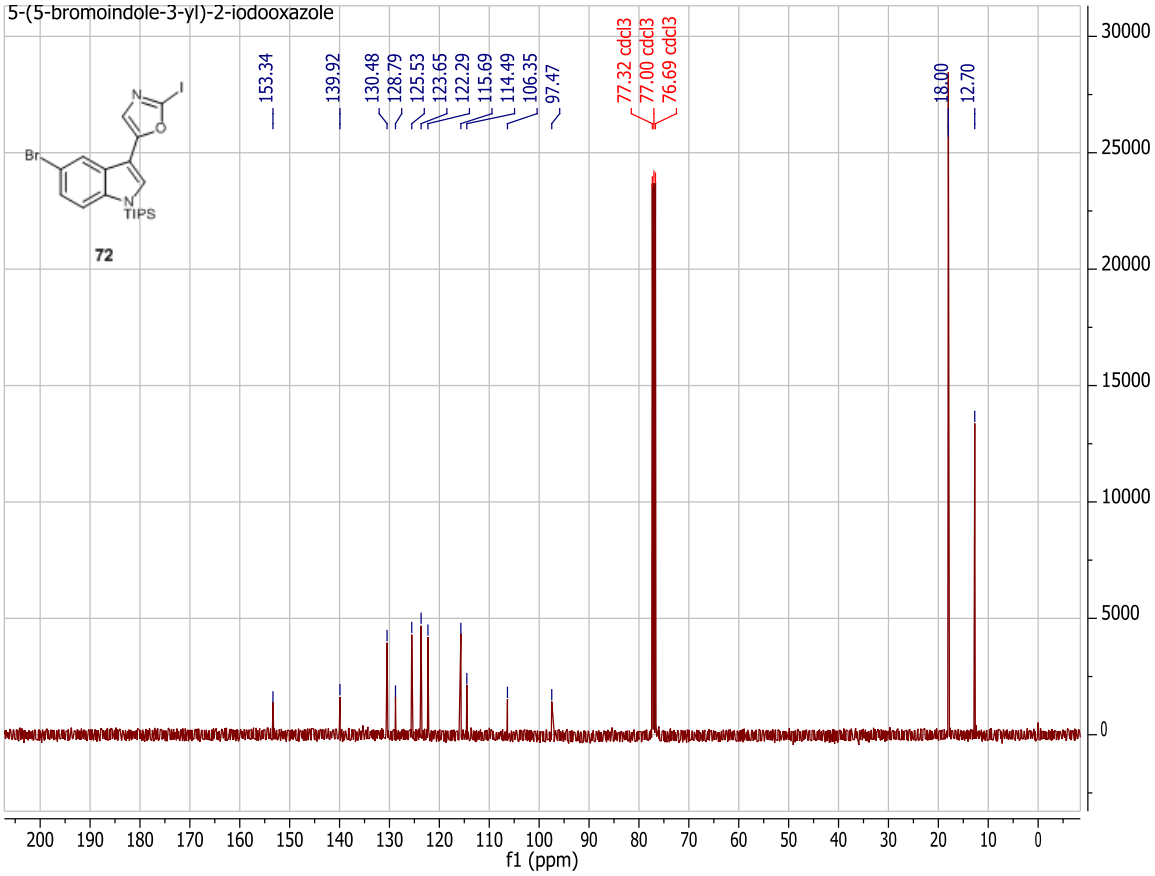
yg124f3 #1-5 RT: 0.00-0.11 AV: 5 NL: 3.54E7
T: FTMS + p ESI Full ms [200.00-900.00]



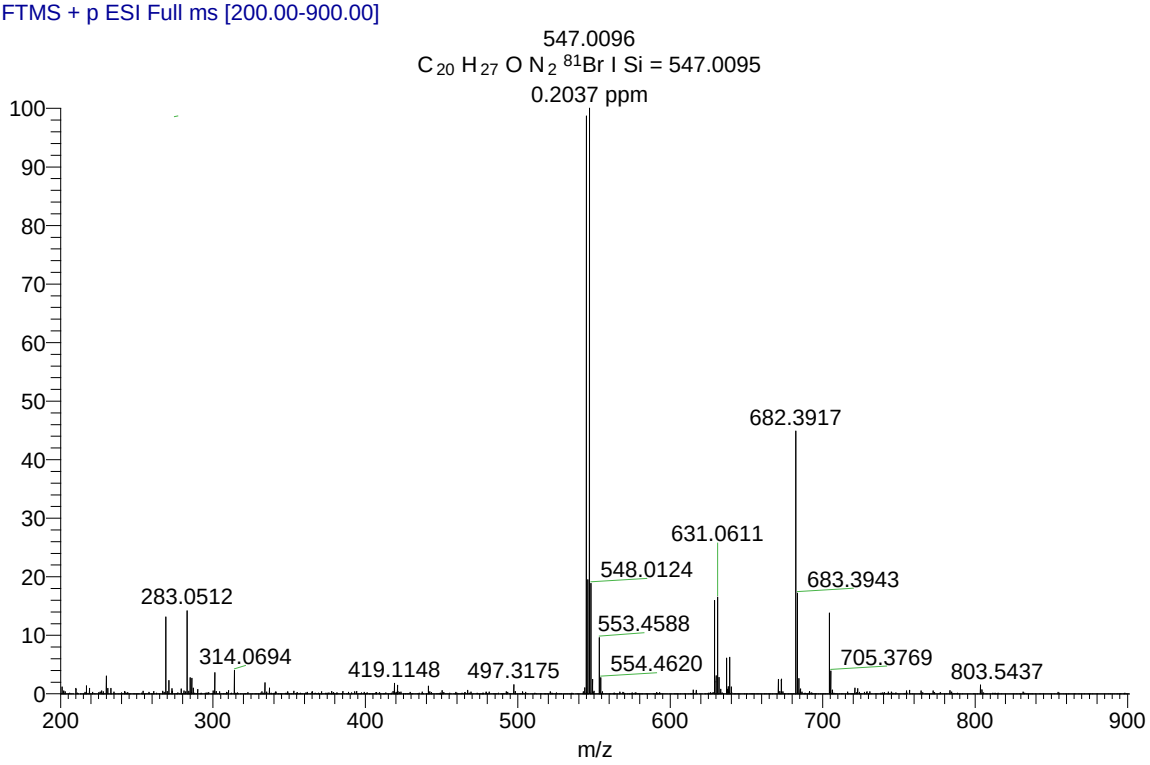


8.2.3.2 5-(5-bromoindol-3-yl)-2-iodooxazole (72)

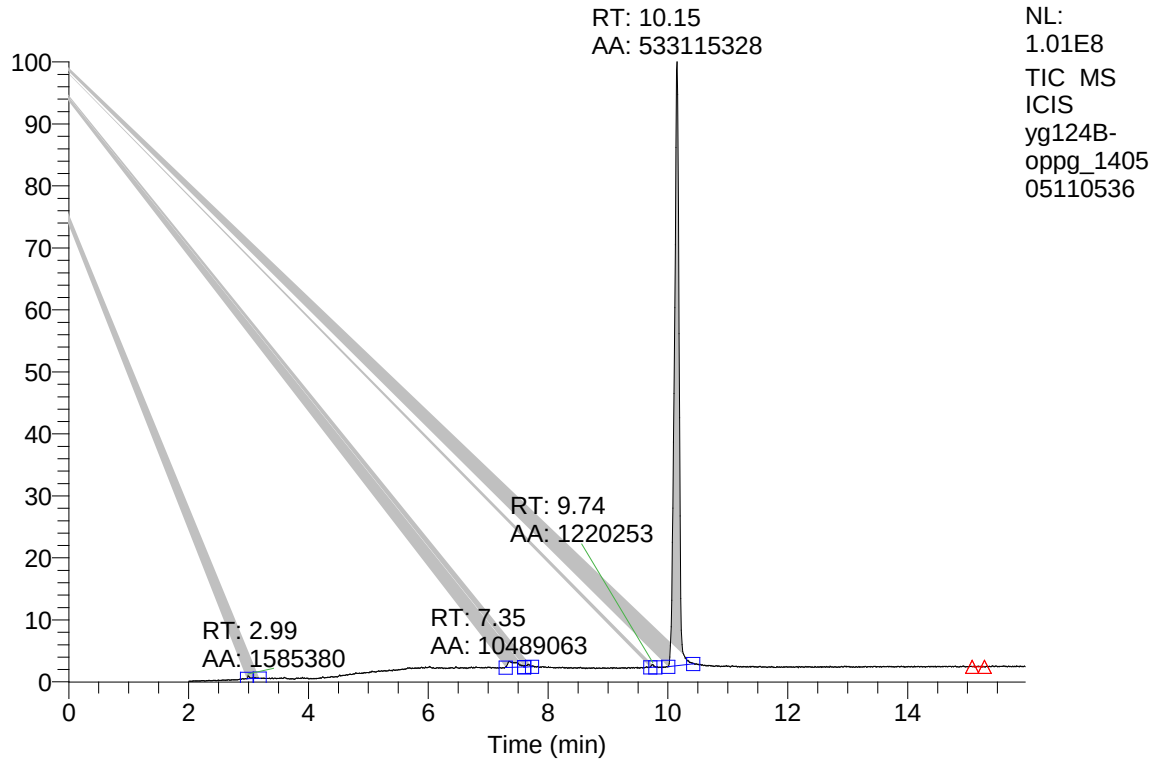


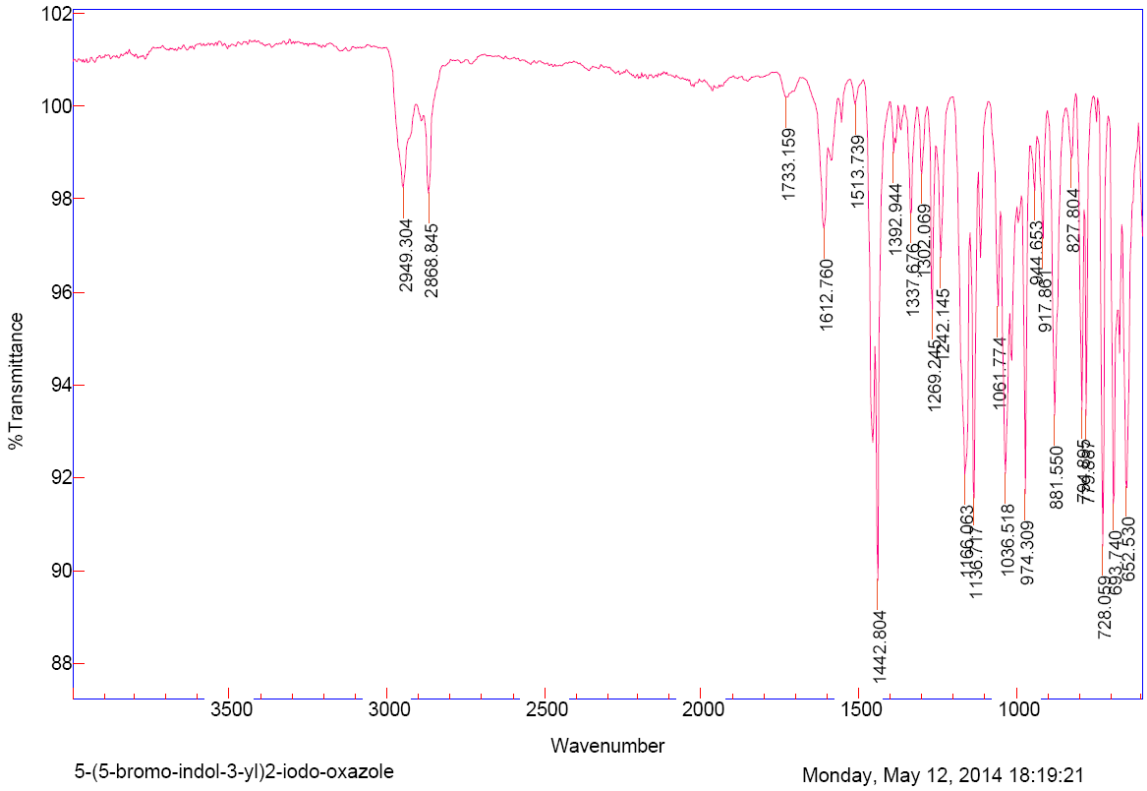


yg124f9 #1-5 RT: 0.01-0.12 AV: 5 NL: 1.47E7
T: FTMS + p ESI Full ms [200.00-900.00]



RT: 0.00 - 15.96




%Transmittance
Wavenumber
5-(5-bromo-indol-3-yl)2-iodo-oxazole
Monday, May 12, 2014 18:19:21
2949.304
2868.845
1733.159
1612.760
1513.739
1442.804
1392.944
1337.676
1302.069
1269.245
1242.145
1160.963
1136.717
1061.774
1036.518
974.309
917.881
881.550
827.804
794.885
728.059
683.740
652.530