

**Microwave Assisted Intramolecular Dehydrogenative Dehydro-Diels Alder Approach  
To Substituted Benzofused Heterocycles**

by

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# **Microwave Assisted Intramolecular Dehydrogenative Dehydro-Diels Alder Approach To Substituted Benzofused Heterocycles**

Justin T. Proto, M.S.

University of Pittsburgh, 2016

## **ABSTRACT**

The emergence of benzo[b]thiophenes and benzo[b]furans as biologically useful scaffolds is of growing attention in medicine as natural products and pharmaceutical drugs. The means to produce these synthetic cores quickly and from economic starting materials has garnered much attention. Much of the current methodology is focused on formation of the heterocyclic ring annulation from benzene derivatives. However, the mechanistic restraints of this chemistry narrows the substitutional scope of the resulting benzo-fused heterocycles. Presented here is a simple methodology to produce uniquely substituted benzo[b]thiophenes and benzo[b]furans via the intramolecular dehydro-Diels-Alder reaction induced by microwave heating. Starting from aromatic heterocycles and focusing on a strategy of benzene annulation from heterocyclic-diene alkynyl-dienophile pairs forming tricyclic fused heterocycles were readily synthesized. The allowance of major product selection was demonstrated by solvent choice during heating; fully aromatic heterocycles were favored when PhNO<sub>2</sub> was chosen, in as little as 10% by volume. The use of DMF favored the formation of dihydroheterocycles. The reaction showed a tolerance of terminal alkyne substitution and generally produced good yields.

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## ABBREVIATIONS

Glc – glucose

Ac – Acyl

Et – Ethyl

Bu – Butyl

Ph – Phenyl

Cy – Cyclohexyl

TMS – Trimethylsilyl

THF – Tetrahydrofuran

TEMPO – (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl

EDCI – 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide

DME – Dimethoxyethane

DMF – Dimethylformamide

IMDDA – Intramolecular Dehydro-Diels-Alder

*o*DCB – *ortho*-Dichlorobenzene

DCM – Dichloromethane

DCE – 1,2-Dichloroethane

PhNO<sub>2</sub> – Nitrobenzene

NMP – *N*-methyl-2-pyrrolidone

DMSO – Dimethyl Sulfoxide

PPA – Polyphosphoric Acid

LED – Light-emitting diode

TLC – Thin layer chromatography

## **PREFACE**

Thanks Aude, Mom, Dad, Karen, and Timothy for endless support and love. Frank, Gino, A. Levin, M. Rothbard to whom I owe a great deal; my family, friends, and colleagues past and present. All that is seen and all which is unseen. To the University of Pittsburgh, staff, and instructors who have given me this opportunity

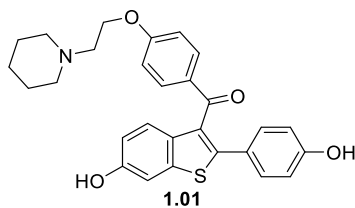
## 1.0 INTRODUCTION

The benzo[b]thiophene and benzo[b]furan core in recent decades has come to prominence as a promising lead functionality in natural products and pharmaceuticals. These heterocyclic aromatic bicycles are a component of coal tar; however, the imprecise nature of aromatic functionalization reactions implicates the demand for late stage annulation of the heterocycle moiety. To this end there has been considerable attention focused on both electrophilic induced cyclization and more recently transition metal catalyzed cyclization. However, these synthetic processes often impose substitutions on the heterocycle product due in part to stability of transition states arising from the particular synthetic technologies. Recently, methodological developments in the microwave-assisted intramolecular dehydro-Diels Alder reaction of styrene-yne substrates towards naphthalene derivatives has proven a successful approach toward aromatic annulation. As pursuant to the strategy of aromatic carbocycle annulation, it was thought that heterocyclic furan and thiophene could serve as a suitable substrate for the microwave-assisted intramolecular dehydro-Diels-Alder reaction towards the formation of substituted aromatic benzofused derivatives. The concerted reaction pathway of the [4+2] cycloaddition would allow for an orthogonal methodology versus the more traversed path of electrophilic and transition metal cyclizations of the heterocyclic ring.

## 1.1 BENZO[B]THIOPHENE APPLICATION IN DRUG LEADS AND NATURAL PRODUCTS

The benzo[b]thiophene heterocycle core has been shown as a promising lead core functionality to a diverse range of approved pharmaceuticals as well as small molecules under research development. These range in activity including antidepressive, anti-inflammatory, antifungal, antiviral, dopamine receptor antagonist, and recently recognized as a selective estrogen receptor modulator for post-menopausal treatments. Although the benzo[b]thiophene heterocycle functionality is promising as a pharmaceutical scaffold, mimicking the indole functionality, though benzo[b]thiophenes have infrequently been described in natural products.

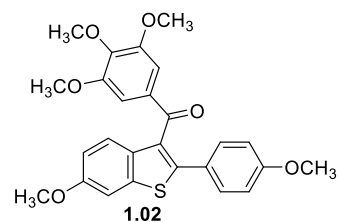
In 2007 the FDA approved the Eli Lilly Company drug, Raloxifene® **1.01**, for use in prevention of osteoporosis in post-menopausal woman as an orally active selective estrogen



**Figure 1** Raloxifene®

receptor modulator.<sup>1,2</sup> **1.01** may also reduce the risk of invasive breast cancer. The drug, however, does pose a risk to blood-clots and as a result, an increase in stroke, though this is not a common side-effect. For this reason, Eli Lilly went to develop Arizoxifene, a methoxy derivative of **1.01** at the C(2) of the benzo[b]thiophene as an alternative therapy.<sup>3</sup> However, Arizoxifene, failed to meet secondary guidelines in clinical studies and FDA approval was not sought.

A structurally similar compound, **1.02**, was found to exhibit antimetabolic effects.<sup>4</sup> **1.02**, was screened against a variety of cancer cell lines such as ovarian, central nervous system, renal, colon, and melanoma. **1.02**, showed sub-microliter per milliliter inhibitory



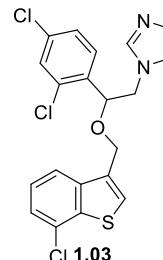
**Figure 2** Antimetabolic 2-(4'-methoxyphenyl)-3-(3',4',5'-trimethoxybenzoyl)-6-methoxybenzo[b]thiophene

effects on colon cancer cell line KM20L2 and breast cancer cell line MCF7. The mechanism of



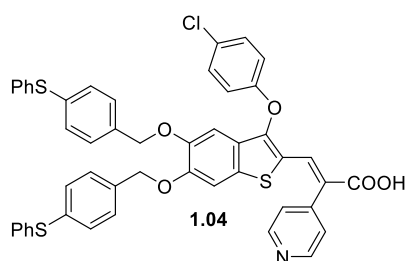
these effects was thought to involve binding to the colchicine binding site of tubulin. However, only modest binding to tubulin was demonstrated by **1.02** when compared to approved antimetabolites.<sup>4</sup>

Sertaconazole, **1.03**, is a FDA approved, benzo[b]thiophene containing antifungal drug developed by Mylan Lab Incorporated.<sup>5</sup> **1.03** is effective toward a wide range of common pathogenic fungi including *Candida albicans*, *Epidermophyton floccosum*, and *Trichophyton*.



Similar to other imidazole containing antifungal compounds, **1.03**, prevents the synthesis of ergosterol, a component of fungal cell membranes. The benzo[b]thiophene functionality mimics indole of tryptophan within the cell membrane proteins and allows a greater availability of **1.03** to form pores.<sup>5</sup> This mechanism will then cause cell death through cell leakage.

Compound **1.04** has been shown as an antithrombotic agent by De Nantenil *et al.*<sup>6</sup> The conversion of plasminogen to plasmin via the tissue type plasminogen activator, t-PA, induces a fibrinolytic mechanism and leads to de-clotting by plasmin. t-PA activity is inhibited by plasminogen activator inhibitor-1, PAI-1, in a stable 1:1 protein complex.

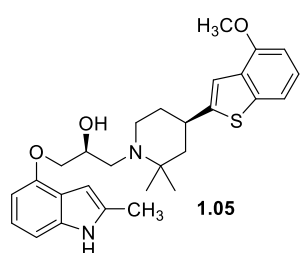


**Figure 4** Antithrombotic (*E*)-3-(3-(4-chlorophenoxy)-5,6-bis((4-(phenylthio)benzyl)oxy)benzo[b]thiophen-2-yl)-2-(pyridin-4-yl)acrylic acid

Elevated concentrations of PAI-1 have been correlated with various diseases such as diabetes, obesity, coronary artery disease and venous thromboembolism.

Although, a large benzo[b]thiophene library was synthesized, and said compounds were evaluated in a t-PA induced fibrin clot lysis assay for the prevention of the t-PA:PAI-1 complex. **1.04**, was the most effective inhibitor of the t-PA:PAI-1 complex, with an IC<sub>50</sub> of 39 nM.<sup>6</sup>

Selective 5-HT serotonin reuptake inhibitors, SSRIs, are used as antidepressant therapies.<sup>7,8</sup> These compounds, however, are not without issues of use such as slow onset of



effects, lack of consistent response, and other physiological side effects such as gastrointestinal intolerance, insomnia, and anxiety.

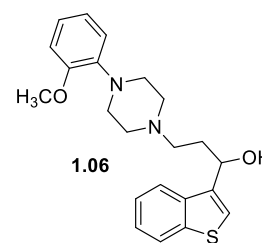
Due to these concerns the need for further development of antidepressant therapeutic compounds is ongoing. The activation of 5-

**Figure 5** SSRI (S)-1-((R)-4-(4-methoxybenzo[b]thiophen-2-yl)-2,2-dimethylpiperidin-1-yl)-3-((2-methyl-1H-indol-4-yl)oxy)propan-2-ol

HT<sub>1A</sub> is thought to play a role in the slow onset effects of the SSRI drugs. Therefore, Takeuchi *et al.* for Eli Lilly developed a library of benzo[b]thiophene compounds that would play an antagonistic role

to impede the 5-HT reuptake sites and 5-HT<sub>1A</sub> receptor.<sup>7</sup> Examination of structure activity relationships showed that all compounds examined showed antagonistic effects of both the 5-HT and 5-HT<sub>1A</sub> sites, with the indole functionality effective for the 5-HT<sub>1A</sub> sites and the benzo[b]thiophene functionality effective for the 5-HT reuptake site.<sup>7</sup> **1.05** showed good binding affinities to both the 5-HT and 5-HT<sub>1A</sub> receptor sites and represents a lead structural motif for further study for development of dual-action antidepressant compounds.

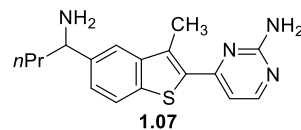
Maintaining the pharmacological theme of dual action SSRI compounds Esparza *et al.* focused on the development of novel piperazine based 5-HT reuptake inhibition and 5-HT<sub>1A</sub> receptor



antagonist for antidepressant therapies.<sup>8</sup> The synthetic design followed known compounds which induce serotonin reuptake inhibition. After employing a structure-activity relationship assay of 5-HT<sub>1A</sub> binding and 5-HT transporter binding found that **1.06** exhibited the desired pharmacological profile and represents a possible new compound class of dual action SSRI antidepressants.<sup>8</sup>

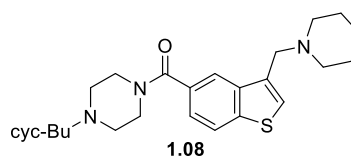
**Figure 6** SSRI 1-(benzo[b]thiophen-3-yl)-3-(4-(2-methoxyphenyl)piperazin-1-yl)propan-1-ol

Rho kinases are responsible for effecting intercellular signaling via a monomeric GTPase RhoA. The activation of RhoA enables binding to Rho kinases and activates their kinase activity. However, inhibitors of Rho kinases are known to induce many cellular events as cytoskeleton remodeling, and relax vascular smooth muscle tissue; Rho inhibitors have also been identified to decrease the intraocular pressure and therefore perhaps explore the use of Rho kinase inhibitors as a new class of compounds for the treatment of glaucoma.<sup>9</sup> A benzo[b]thiophene derivative was identified to be an inhibitor of Rho kinase 1 and Rho kinase 2. A structure-activity relationship study was put through multiple rounds of inhibitory activity of Rho kinase 1. **1.07** was found to inhibit Rho kinase 1 and Rho kinase 2 at sub-micromolar levels. These results prompted *in vivo* clinical study. **1.07** was found to have a statistically significant reduction of intraocular pressure in primates after an hour of topical eye dosing.<sup>9</sup>



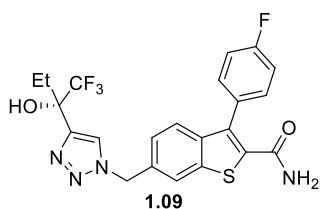
**Figure 7** Rho kinase inhibitor 4-(5-(1-aminobutyl)-3-methylbenzo[b]thiophen-2-yl)pyrimidin-2-amine

The histamine H<sub>3</sub> receptor is controlled with the synthesis and release of histamine in the body. The histamine H<sub>3</sub> receptor is thought to be a potential antagonistic target for a variety of ailments effecting sleeping, eating and memory. Disubstituted phenyl moieties have been identified to act as antagonists to the histamine H<sub>3</sub> receptor and for this reason the replacement of the phenyl core by disubstituted aromatic heterocycles as a means to further elucidate the structure-activity relationship of the histamine H<sub>3</sub> receptor.<sup>10</sup> A series of disubstituted benzo[b]thiophenes were synthesized and binding assay of the histamine H<sub>3</sub> receptor performed. **1.08** was found to be the most efficient and highest affinity as a histamine H<sub>3</sub> antagonist. However, *in vivo* trials were not performed and no further study completed.<sup>10</sup>



**Figure 8** Histamine H<sub>3</sub> antagonist (4-cyclobutylpiperazin-1-yl)(3-(piperidin-1-yl-methyl)benzo[b]thiophen-5-yl)methanone

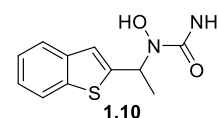
The benzo[b]thiophene core has seen use in anti-inflammatory drugs and in related compounds currently under development. Leukotrienes are locally acting hormones that are



**Figure 9** 5-LO inhibitor 3-(4-fluorophenyl)-6-((4-(1,1,1-trifluoro-2-hydroxybutan-2-yl)-1H-1,2,3-triazol-1-yl)methyl)benzo[b]thiophene-2-carboxamide

mediators in various inflammatory diseases. They are thought to play a role in arthrogenic disease, possibly cancer, and other oxidative related ailments. Leukotrienes are synthesized by 5-lipoxygenase enzymes, 5-LO, starting with an oxidative epoxidation of arachidonic acid.<sup>11</sup> Therefore compounds which inhibit 5-LO can lead to therapies that address these oxidative health issues. Li, *et al.* had previously identified a triazole containing benzo[b]thiophene scaffold which had an inhibitory effect on 5-LO. Therefore, a structure-activity relationship was explored by assessing the inhibition of recombinant human 5-lipoxygenase, H5-LO, and in the production of leukotriene B<sub>4</sub>, LTB<sub>4</sub>.<sup>11</sup> After multiple rounds of screening, compound **1.09** was found to be a potent and selective for H5-LO inhibition.<sup>11</sup> A key attribute to the inhibitory activity of **1.09** is its functional resistance to oxidative conditions. **1.09** showed good pharmacokinetic activity in pre-clinical species and was selected to advance to clinical studies.

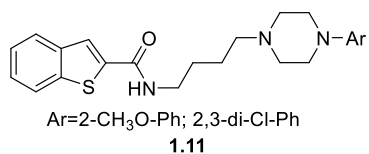
Introduced in 1996 by Abbott Laboratories, Zileuton **1.10**, is an orally active 5-LO inhibitor and suppresses the synthesis of



leukotrienes.<sup>12</sup> **1.10** is used as a maintenance drug for the treatment of chronic asthma, but is not used for treatment of acute asthma attacks.<sup>13</sup> The use of Zileuton can have negative side effects such as an increase in liver enzymes, also including sleep disturbances and behavioral changes.

The D3 dopamine receptor has been identified as a playing a role in reinforcing effects

of the stimulant cocaine. In recent studies involving curbing the use of cocaine a lead structural



motif was a pyrazole[1,5a]pyridine-aryl piperazine scaffold.<sup>14</sup>

This lead compound displayed a partial antagonism of the D3

receptor and was thought a logical start in developing a structure-activity relationship involve evaluation of similar

heterocyclic-aryl piperazine compounds. Compound **1.11** was found to have selective binding affinity ratios for D3 receptors versus other dopamine receptors: D2<sub>short</sub>, D2<sub>long</sub>, and D4

receptors.<sup>14</sup> **1.11** was also found to have a selective binding for the D3 receptor over the

serotonin receptors 5-HT-1<sub>A</sub> and 5-HT2. The *N*-aryl functionality played a crucial role in the

antagonistic effect of the D3 receptor. When the aryl functionality was 2-methoxy-phenyl only

partial antagonism was observed; while the 2,3-dichloro-phenyl derivative was a potent D3

receptor antagonist.<sup>14</sup> The high selectivity of **1.11** to the D3 receptor and ease of structural

modification regarding the antagonistic potency of the compounds offers potential scaffolds for

drug addiction therapies with the partial antagonist derivative and possible antipsychotic for the

more potent antagonist.<sup>14</sup>

Mitsumori *et al.* reported a prostaglandin D<sub>2</sub>, PGD<sub>2</sub>, receptor antagonist based off a novel bicyclo[2.2.1]heptane-phenyl sulfonamide structure.<sup>15</sup> The

PGD<sub>2</sub> receptor is associated with allergic inflammatory response

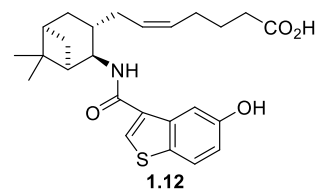
in such conditions as rhinitis, conjunctivitis and asthmas. These

compounds demonstrated PGD<sub>2</sub> receptor selective antagonism and

strong inhibitor and lower antagonism toward the PGI<sub>2</sub> and TXA<sub>2</sub>

receptors. It was thought that further development could lead to

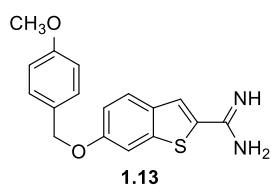
possible class of antiallergic drugs. The ensuing structure-activity relationship began with



**Figure 12** PGD<sub>2</sub> antagonist (Z)-7-((1R,2R,3S,5S)-2-(5-hydroxybenzo[b]thiophene-3-carboxamido)-6,6-dimethylbicyclo[3.1.1]heptan-3-yl)hept-5-enoic acid

modification of the bicycle-ring system; finding that bicyclo[3.1.1]heptane-amide system was a strong antagonist for the PGD<sub>2</sub> receptor.<sup>15</sup> Further structural modification identified **1.12** as an effective PGD<sub>2</sub> antagonist in sub-micromolar concentrations.<sup>15</sup> **1.12** was also an effective PGD<sub>2</sub> antagonist in conjunctive and asthma response in guinea pig models. These results prompted development of **1.12** as a viable compound for an antiallergic drug due to the over production of PGD<sub>2</sub>.<sup>15</sup>

Factor IX<sub>a</sub>, FIX<sub>a</sub>, is a vitamin K dependent blood coagulation factor that plays a crucial role in the cascade pathway which leads to thrombin formation.<sup>16</sup> Thrombin formation is accomplished by activation of FX<sub>a</sub> protease via FX activation; therefore selective inhibition of

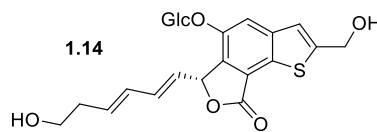


**Figure 13** Anticoagulant 6-((4-methoxybenzyl)oxy)benzo[b]thiophene-2-carboximidamide

FIX<sub>a</sub> from the initial activation of the coagulation factor was surmised as an approach to development of anticoagulation therapies. Wang *et al.*, starting with a lead 2-amidino-4-iodobenzo[b]thiophene compound along with active-site molecular modeling, began a structure-activity relationship study for the selective inhibition of FIX<sub>a</sub> versus the FX<sub>a</sub> enzyme.<sup>16</sup> Efficiency of the compounds were evaluated through binding assays with FIX<sub>a</sub> and FX<sub>a</sub>. After multiple synthetic iterations, altering the position and functionalities of the benzene ring component, **1.13** was found to be a strong inhibitor at sub-micromolar levels for FIX<sub>a</sub>.<sup>16</sup> However, most compounds analyzed including **1.13**, were also shown to be inhibitory toward FX<sub>a</sub>. Although, **1.13** was not the only compound with such low inhibition concentrations toward FIX<sub>a</sub>, **1.13** was the most selective toward FIX<sub>a</sub> inhibition versus FX<sub>a</sub> with over a fifty-fold selectivity.<sup>16</sup> Though **1.13** is a promising anticoagulant, further research is necessary to elucidate a greater selectivity toward inhibition of FIX<sub>a</sub>.

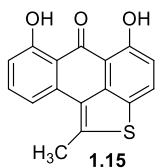
Though the benzo[b]thiophene is a promising pharmaceutical-core, the presence of

benzo[b]thiophene is scarce in natural products. Koike, *et al.*, have isolated a glycosylated benzo[b]thiophene-polycycle.<sup>17</sup> Echinothiophene, **1.14**, was isolated as yellow needles from the roots of *Echinops grijissi* through *n*-butyl alcohol extraction and methanol crystallization. The structure of **1.14** was confirmed through a combination of IR, HR-FAB MS and one and two dimensional NMR studies. **1.14** was observed as a mixture of epimers in methanol at room temperature; however, only a single epimer was observed upon recrystallization. Molecular mechanics and dynamics calculations concluded that the isolated epimer was the thermodynamically favorable structure.<sup>17</sup> The plant material from which **1.14** is isolated has been used in traditional Chinese medicine but further medical uses are not reported.



**Figure 14** Echinothiophene

Angiogenesis, the growth of blood vessels from existing blood vessels, is a crucial physiological process in tumor growth.<sup>18</sup> Compounds that inhibit angiogenic behavior may be valuable leads for antitumor proliferation. To this end, Miyamoto, *et al.*, screened acetone

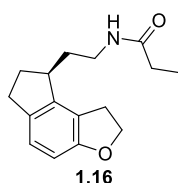


extracts from marine invertebrates.<sup>18</sup> The acetone extract of *Watersipora subtorquata* showed inhibitory effects on bovine aortic endothelial cell, BAEC, proliferation. Isolation of the mixture found bryoanthrathiophene, **1.15**, to

**Figure 15** possess inhibitory activity of BAEC proliferation in sub-micromolar concentrations. Although no further assays were performed, **1.15**, does represent a possible lead structure for further study in antitumor proliferation pathways from inhibition of vascular system growth.

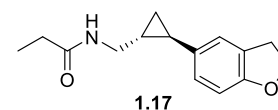
## 1.2 BENZO[B]FURAN APPLICATION IN DRUG LEADS AND NATURAL PRODUCTS

Melatonin is an indole based neurohormone that plays a key role in many physiological processes such as sleep/wake cycles, modulation of immune response, and cardiovascular system modulation. These physiological responses are due to antagonism of G-coupled protein receptors  $MT_1$  and  $MT_2$ . Melatonin is equally antagonistic to both receptor sites and is used as



**Figure 16** Ramelteon

**1.16**, approved by the FDA for use as treatment for insomnia.<sup>20</sup> **1.16** is a potent antagonist for  $MT_1$  and  $MT_2$  binding has half-life 2-3x that of melatonin.<sup>20</sup> **1.16** has low binding affinity for  $rGABA_A$ , which is associated with behavioral side effects of other insomnia drugs, and shows little potential of abuse.<sup>20</sup> Recently, tasimelteon, **1.17**, was developed by Vanda Pharmaceuticals and approved in 2014, as a drug for non-24 hour sleep/wake disorder and other insomnia associated disorders.<sup>21</sup> **1.17** is also a selective  $MT_1$  and  $MT_2$  antagonist. Certain

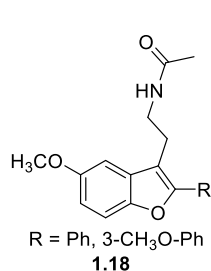


**Figure 17** Tasimelteon

serious side effects in rodents have been observed with the use of **1.17**.<sup>21</sup> In an effort to further the melatonin-like furan bioisosteres focusing on selective binding of  $MT_1$  and  $MT_2$ , Lesieur, *et al.*, carried out a structure-activity relationship study of benzo[b]furan derivatives of melatonin.<sup>22</sup> Binding assays were performed for both the  $MT_1$  and  $MT_2$  receptors from embryonic kidney cell line HEK260. The substitution at the C(2) of the benzo[b]furan with the



phenyl functionality **1.18** proved a nearly ten-fold more potent antagonist toward MT<sub>1</sub> and MT<sub>2</sub> receptors than melatonin; no selectivity was reported.<sup>22</sup> Alteration of the C(2) of the



**Figure 18** MT<sub>1</sub>/MT<sub>2</sub> antagonist *N*-(2-(5-methoxy-2-arylbenzofuran-3-yl)ethyl)acetamide

benzo[b]furan with the 3-methoxy-phenyl functionality in **1.18** led to excellent selectivity toward MT<sub>2</sub> receptor of 123-fold.<sup>22</sup> This selectivity is thought to arise from a secondary hydrophobic binding pocket. Deletion of

the 5-methoxy group caused a sharp decrease in MT<sub>1</sub> and MT<sub>2</sub>

receptor binding, and represents a crucial structural role in binding,

while alterations of the amide chain lowered MT<sub>1</sub> and MT<sub>2</sub> receptor

binding slightly.<sup>22</sup> It was postulated that amide alteration could tune the selective binding in future studies.

Developing continuous antiviral therapies is of foremost importance to medicinal chemists. Hepatitis C virus is the cause of chronic liver disorders and affects 200 million individuals worldwide. There are millions of new infections

each year and currently no vaccine exists, although, in recent years promising new therapies have emerged. The RNA-

dependent RNA polymerase NS5B is responsible for the synthesis of new viral RNA of the hepatitis C virus.

GlaxoSmithKline reported development of a boronic acid-

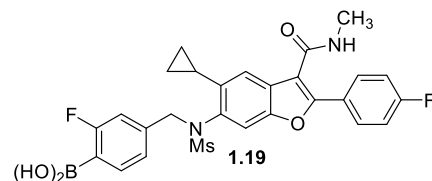
benzo[b]furan pharmacore to inhibit the NS5B activity via allosteric binding at the hydrophobic

palm II section of the polymerase.<sup>23</sup> The NS5B palm II site was chosen to allow the boronic acid

functionality close proximity to the catalytic-site and thought to affect incoming nucleotide

triphosphates or the ribose of the RNA strand. The starting structure was based on the

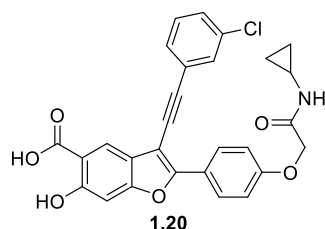
discontinued benzo[b]furan hepatitis C pharmaceutical nesbuvir. **1.19** was found to have



**Figure 19** Hepatitis C NS5B allosteric inhibitor (4-((*N*-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)methyl)-2-fluorophenyl)boronic acid

enzyme IC<sub>50</sub> activity of both the hepatitis C wild types 1a and 1b at nanomolar concentrations.<sup>23</sup> Additionally, **1.19** was found capable of blocking RNA replication, inhibiting NS5B at ten micromolar concentrations.<sup>23</sup> However, addition of further boronic acid functionalities did not improve the antiviral activity.

Protein tyrosine phosphorylation is a key cellular event involved in biological processes. Tyrosine phosphorylation is reciprocally regulated by protein tyrosine kinases, PTKs, and protein tyrosine phosphatases, PTPs.<sup>24</sup> Alterations to these two protein types have been associated with such illnesses as cancer, diabetes, obesity and autoimmune diseases. Though, the targeting of PTKs has led to many approved drugs, PTPs are relatively underexplored.<sup>24</sup> Of recent interest as an inhibitory target is the lymphoid-specific tyrosine phosphatase, LYP, a phosphatase found only in immune cells which functions as a negative regulator of T cell receptor signaling pathways.<sup>24</sup> Genetic mutations of LYP have shown to be a risk factor for a



**Figure 20** Protein Tyrosine Phosphatase inhibitor 3-((3-chlorophenyl)ethynyl)-2-(4-(2-(cyclopropylamino)-2-oxoethoxy)phenyl)-6-hydroxybenzofuran-5-carboxylic acid

number of serious autoimmune diseases such as type-I diabetes, rheumatoid arthritis, Graves disease, lupus erythematosus, etc.

Mutations of LYP that increase the phosphatase action of the enzyme

lead to increased inhibition of T/B cell signaling when compared to

the wild-type LYP. Further, inactivation or deletion of LYP in

mice has been shown to produce an immunosuppressive response

and render protection to type-I diabetes. Therefore selective

inhibition of LYP was thought to be viable strategy for addressing autoimmune syndromes. To

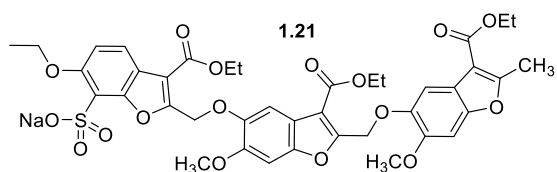
this end Zhang, *et al.*, began a structure-based lead optimization study to discover a small

molecule inhibitor of LYP.<sup>24</sup> A known issue with the PTP class is the active sites of these

enzymes are highly conserved with positively charge residues. Therefore, the task was to

identify a compound that would be selective for LYP with negatively charged functional component yet hydrophobic enough to allow membrane permeability. Starting with bicyclic salicylates as leads and after multiple rounds of LYP binding assays followed by structural modification the authors found **1.20** as the most potent LYP inhibitor. **1.20** was found to be a potent inhibitor toward LYP, needing only sub-micromolar concentrations.<sup>24</sup> Again, with the highly conserved active-sites of PTP enzymes, **1.20** was screened for binding potencies with a panel of over twenty other PTP enzymes and was nine-fold more selective toward LYP versus other PTPs.<sup>24</sup> Thus, **1.20** is a potent and selective inhibitor of LYP and serves as an excellent basis for further medicinal study in development of small molecule therapies for autoimmune related conditions.

In continuance with pursuing proteins for anticoagulation therapies, Desai *et al.*, targeted small molecule inhibition of factor XIa, fXIa.<sup>25</sup> Coagulation is induced through multiple protein cascades, eventually activating thrombin which leads to clot formation. fXIa is a homodimer serine protease with each sub-unit made up of four domains, A1-A4. Activation of fXIa converts fIX to fIXa and continues the cascade toward thrombosis.<sup>25</sup> The targeting of fXIa was of interest because fXIa deficient mice grew healthy and did not suffer from hemophiliac type diseases.



**Figure 21** fXIa allosteric inhibitor sodium 6-ethoxy-3-(ethoxycarbonyl)-2-(((3-(ethoxycarbonyl)-2-(((3-(ethoxycarbonyl)-6-methoxy-2-methylbenzofuran-5-yl)oxy)methyl)-6-methoxybenzofuran-5-yl)oxy)methyl)benzofuran-7-sulfonate

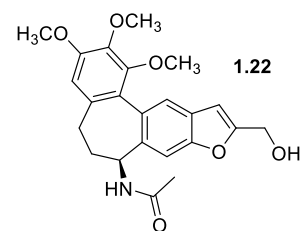
Additionally in hemophilia C, a natural deficiency of fXI induces benign bleeding. Therefore, it was surmised that inhibition of fXIa would safely induce

anticoagulation without severe hemophiliac risk. The use of small molecule sulfates was shown to induce allosteric inhibition of fXIa. The authors

screened 65 sulfonated small molecules as anticoagulation therapies at 300 micromolar

concentrations for reduction of fXIa activity and found that sulfonated benzo[b]furan dimers and trimers were the most potent inhibitors. Further inhibitory screening for fXIa inhibition found benzo[b]furan trimer **1.21** to be the most potent inhibitor, active at sub-micromolar concentrations.<sup>25</sup> It is thought that the allosteric interaction occurs at the A3 domain; more specifically at exposed basic lysine/arginine residues via sulfonate interaction which induces conformational disruption at the catalytic site.<sup>25</sup> Removal of the sulfonate from **1.21** greatly reduced the binding efficiency by over 450-fold.<sup>25</sup> Interestingly, additional sulfonates did not improve the potency of inhibition. Although no *in vivo* studies of **1.21** have been performed, it does serve as a basis for future structural design of allosteric inhibitors of fXIa as anticoagulation therapies.

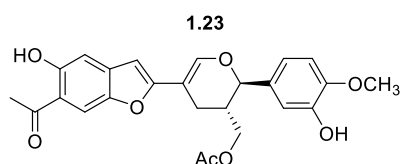
Microtubule assembly is essential in cell proliferation and maintenance. These processes are controlled by the protein tubulin via microtubule assembly/disassembly.<sup>4</sup> Microtubule assembly is also essential in the proliferation of cancer cells, and therefore the targeted inhibition of tubulin or microtubule disassembly is of ongoing interest.<sup>26</sup> The natural product colchicine is a known antimitotic agent acting through tubulin destabilization which blocks mitosis. However, the use of colchicine as an antitumor drug is limited due to severe cardiovascular and neurotoxic side effects. Colchicine derivatives have been studied as anticancer leads, yet drug development has not been pursued. Fedorov, *et al.*, have thus set out to synthesize and screen colchicine derivatives as antimitotic agents for cancer therapies.<sup>26</sup> Using molecular modeling, the authors found a key structural feature of colchicine and effective derivatives was a non-coplanar ring structure with the ability to form hydrogen bonds.<sup>26</sup> Multiple polycyclic colchicine derivatives were screened



**Figure 22** Antimitotic *N*-((7*S*)-10-(hydroxymethyl)-1,2,3-trimethoxy-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*f*]benzofuran-7-yl)acetamide

for cytotoxic effects via tubulin binding among HEK923, Jurkat, AsPC-1 cell lines, and **1.22** was found to be cytotoxic in sub-micromolar concentrations.<sup>26</sup> In a time-resolved turbidity study representative of microtubule assembly **1.22** was found to inhibit microtubule assembly at the 2.5 micromolar level inducing tubulin depolymerization activity. The *in vivo* activity of **1.22** was assessed by injecting 0.4mg/kg once every four weeks in mice inoculated with Wnt-1 breast tumor cells. **1.22** inhibited tumor growth while no weight loss, neurological, or behavioral changes were observed.<sup>26</sup> **1.22** shows high cytotoxicity through tubulin binding disrupting cell cycle proliferative activity. *In vivo* tumor inhibition was also observed in mice with few adverse side effects. Thus, **1.22** is a promising lead for further study as an antitumor therapy.

The benzo[b]furan structure is ubiquitously found in natural products due to the abundance of tyrosine and phenylalanine as synthetic feed stocks. Benzo[b]furans are continually discovered in natural materials and many show promise for further study both medicinally and in structural leads. Kadota, *et al.*, isolated novel benzo[b]furan derivatives from Brazilian propolis.<sup>27</sup> Propolis is a resinous hive substance produced by honeybees. Propolis has a

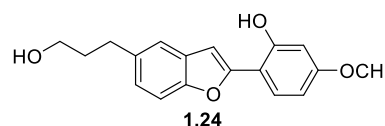


**Figure 23** Cytotoxic ((2R,3S)-5-(6-acetyl-5-hydroxybenzofuran-2-yl)-2-(3-hydroxy-4-methoxyphenyl)-3,4-dihydro-2H-pyran-3-yl)methyl acetate

known therapeutic use in traditional medicines and has been reported to possess properties such as anticancer, antioxidant, antifungal and antibiotic. Recently, propolis has gained popularity as a health food; ingesting the resin is purported to prevent inflammation, heart disease, and diabetes.<sup>27</sup> Extraction of the propolis with methanol showed cytotoxicity toward liver-metastatic murine colon 26-L5 carcinoma and human HT-1080 fibrosarcoma cells. These results prompted isolation of the constituents of the material. **1.23** was isolated from the methanol solutions of the Brazilian propolis and identified with IR, HR-FAB MS, and NMR experiments. **1.23** was found to exhibit moderate cytotoxicity toward liver-

metastatic murine colon 26-L5 carcinoma and human HT-1080 fibrosarcoma cells with and ED<sub>50</sub> values of 12.4 µg/mL and 13.9 µg/mL.<sup>27</sup> Though **1.23** is not as medicinally active as hoped, it serves as a pharmaceutical structural lead for further study.

The roots of the *Krameria lappacea* are used for oropharyngeal inflammation in traditional medicines from South America.<sup>28</sup> These roots have also been used in early-modern Europe as a remedy for stomachache, diarrhea, nose bleeds, and inflammation of the mouth. Previous studies show the constituents of *K. lappacea* have potential as anti-inflammatory therapies. Therefore, isolation

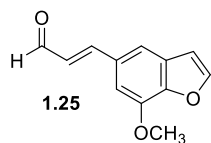


and identification of the root material constituent compounds was undertaken and examined for inflammatory properties by

**Figure 24** Anti-inflammatory 2-(5-(3-hydroxypropyl)benzofuran-2-yl)-5-methoxyphenol

Stuppner *et al.* **1.24** was isolated from dichloromethane extraction, and its structure elucidated by HR-FAB MS and NMR.<sup>28</sup> Activity of **1.24** as an anti-inflammatory agent was assessed through topological administration and binding assays of key intermediates of inflammation-inducing pathways. Topical administration of **1.24** at sub-micromolar concentrations reduced edema formation near completion after induced dermatitis in mice.<sup>28</sup> Microscopic analysis of the tissue showed a reduction of dermal swelling and reduced blood vessel dilation similar to that of the control tissue. To attempt to elucidate the direct mechanism of anti-inflammatory activity **1.24** was screened for binding activities for a number of known inflammation inducing enzymes. **1.24** was found to inhibit NF-κB activation at low micromolar concentrations.<sup>28</sup> **1.24** also showed significant inhibition of 5-lipoxygenase in leukotriene formation, active at low micromolar concentrations. **1.24** showed free radical scavenging activity at low micromolar concentrations. In a 2,2-diphenyl-1-picrylhydrazyl assay, **1.24** had equal scavenging potential to that of the standard, ascorbic acid.<sup>28</sup>

The *Zanthoxylum wutaiense* is an evergreen shrub native to Taiwan. Methanol extracts



of *Z. wutaiense* root wood were screened for antitubercular activity against

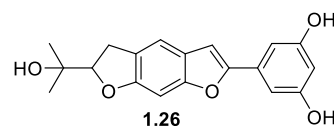
*Mycobacterium tuberculosis* H37Rv cell line which lead Chen *et al.*, to

**Figure 25** Antitubercular (*E*)-3-(7-methoxybenzofuran-5-yl)acrylaldehyde **1.25** isolate and elucidate the compounds in the methanol extract and verify their individual activities.<sup>29</sup> The authors were able to isolate

six benzo[b]furan natural products from the extracts. In a minimum inhibition concentration assay of *Mycobacterium tuberculosis*, H37Rv **1.25** was found to be the most potent inhibitor at 35 micrograms per milliliter.<sup>29</sup> Though this is five times higher than the control, ethambutol, it does represent a structural lead for further development of antitubercular drugs.

The ability for cells to respond to low cellular concentrations of oxygen is mediated by hypoxia-inducible factor 1, HIF-1.<sup>30</sup> The production of HIF-1 is coupled to the protein, vascular endothelial growth factor, VEGF, which induces vascular tissue growth in low oxygen tissues and is observed in hypoxia tumor cell proliferation.<sup>30</sup> HIF-1 is stabilized under low oxygen concentrations and overexpression is known to cause tumor cell proliferation and be a resistance factor in radio/chemotherapies. Lee *et al.*, in an effort to discover natural product HIF-1 inhibitors screened a series of plant extracts for inhibitory activity.<sup>30</sup> Chloroform extracts of the *Morus bombycis* showed inhibitory effects on HIF-1 due to low

oxygen concentrations. To identify the HIF-1 inhibitory activity of



the chloroform extract the authors isolated and identified the **Figure 26** HIF-1 inhibitor Moracin O individual small molecule constituents. Four benzo[b]furan compounds were isolated belonging to the moracin natural product family. **1.26**, moracin O, was found to be the most potent inhibitor of HIF-1 in human hepatocellular carcinoma Hep3B cells, inducing IC<sub>50</sub> inhibition in nanomolar concentrations.<sup>30</sup> Complete inhibition was observed at thirty micromolar

concentrations. Moracin P also showed similar concentration of inhibition. **1.26** measured effective in micromolar concentrations to limit the secretion of VEGF in the Hep3B cells in an ELISA assay. **1.26** represents a promising approach to HIF-1 inhibition and a lead molecule toward hypoxia tumor therapies.



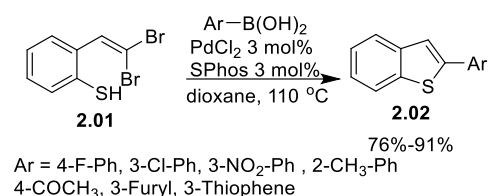
## **2.0 BENZO[B]THIOPHENE AND BENZO[B]FURAN SYNTHETIC CONSTRUCTION METHODS**

The construction of the benzo[b]thiophene and benzo[b]furan cores have seen much attention by synthetic chemists. Starting from pre-functionalized benzene derivatives and concentrating on heterocyclic ring formation has been the *lingua franca* of strategies employed to date. Heterocyclic annulation has equally employed both classical electrophilic cyclization mechanisms and, recently, transition metal catalysis. However, these reaction schemes, due to the mechanistic constraints, routinely yield highly substituted benzo[b]thiophenes and benzo[b]furans, namely at the C(2) and C(3) of the benzofused heterocycles.

### **2.1 BENZO[B]THIOPHENE SYNTHETIC CONSTRUCTION METHODS**

The tool kit of organic synthesis has an unrealizable debt owed to the utility and scope of transition metal carbon-carbon cross coupling reactions. Palladium catalyzed reactions have allowed access to products that traditional organic reactions could not achieve without penalty of low yields, mixtures or economically unsuitable conditions. The Pd-catalyzed C-S bond formation allows for simple thiophenol starting substrates which then limits deviation to unwanted byproduct formation.

Lautens, *et al.* developed a Pd catalyzed tandem C-S thiophene formation followed by Suzuki reaction for C(2) substitution.<sup>31</sup> Starting with simple *ortho gem*-dihalovinyl thiophenol, **2.01**, and 3% Pd SPhos catalyst formed first the intermediate 2-bromo-benzo[b]thiophene which was followed by *in situ* Suzuki arylation with a suitable boronic acid. The reaction required a



temperature of 110 °C in dioxane and multiple equivalents of base but proceeded in very good yields, 91%-82%, of aryl-2-benzothiophenes, **2.02**, from both

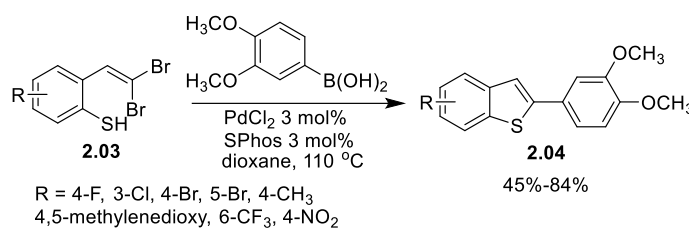
**Figure 27** Pd catalyzed tandem thiophene annulation/Suzuki coupling of *ortho geminal*-dihalovinyl thiophenols boronic acid variation

electron withdrawing and electron donating aryl boronic acids.<sup>31</sup> The authors found that the reaction

was compatible with boronic acids but also boronic esters, trifluoroborate salts, and alkyl boranes as Suzuki coupling agents; all proceeding to the benzo[b]thiophene products in good yields.

To widen the substrate scope of this Pd catalyzed tandem C-S bond formation followed by Suzuki reaction, examination of substitution effects on the *gem*-dihalovinyl thiophenol, **2.03**,

was undertaken. Substitutions of the thiophenol greatly impacted the outcome.<sup>31</sup> 4-Fluoro, 3-chloro and 4-



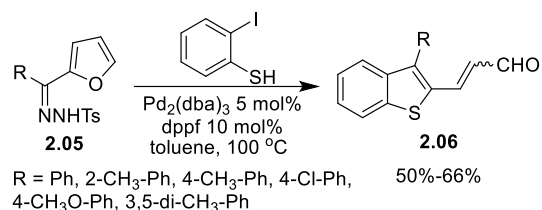
methyl substitutions to the thiophenol produced good yields of the corresponding benzo[b]thiophene product, **2.04**. Surprisingly, the 4-

**Figure 28** Pd catalyzed tandem thiophene annulation/Suzuki coupling of *ortho geminal*-dihalovinyl thiophenols variation

bromo and 5-bromo derivatives produced dual arylated benzo[b]thiophenes under reaction conditions, forming three bonds rather than two in good yields. 4,5-Methylenedioxy and 6-trifluoromethane both produced the C(2) arylated benzo[b]thiophene product in markedly lower yields. The 4-nitro thiophenol successfully underwent C-S bond formation but did not undergo

the subsequent Suzuki coupling. Finally, the authors showed that the Pd catalyzed C-S bond formation of the thiophenol substrate was also compatible with both Heck and Sonogashira tandem couplings.<sup>31</sup>

Transition metal carbenoids have been employed to achieve a number of highly chemoselective synthetic transformations including cyclopropanations, nucleophilic insertions and metathesis reactions; Yin, *et al.* set out to explore the use of palladium catalyzed metal



carbenoids in heterocyclic ring forming reactions

from simple 2-iodo thiophenols.<sup>32</sup> The highly reactive Pd carbenoid intermediate was thought

accessible through a 2-furyl diazoalkanes. However,

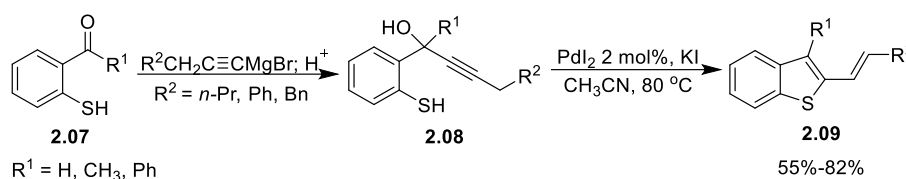
**Figure 29** Benzo[b]thiophene synthesis via Pd catalyzed cross-coupling of furfural tosylhydrazones and 2-iodo thiophenol

due to inherent instability and toxicity of these species, the 2-furyl diazoalkanes were best accessed

via deprotonation of the preceding stable furfural tosylhydrazone followed by decomposition to the diazo substrates.<sup>32</sup> After an extensive optimization screening the authors found that the ideal catalyst was five molar percent of 1,1'-bis(diphenylphosphino) ferrocene palladium in toluene at 100 °C with excess base. Using 2-iodo thiophenols and furfural aryl tosylhydrazone, **2.05**, the authors were able to achieve moderate yields of 2,3-substituted benzo[b]thiophenes, **2.06**. Jiang proposed the product formation proceeds through a number of key intermediates.<sup>32</sup> After the initial oxidative insertion of the 2-iodo thiophenol to the Pd center, the 2-furyl diazoalkane is complexed forming a Pd carbenoid species. An aryl migratory insertion at the carbenoid carbon affords a methylenepalladium halide. This is followed by allene formation via furan ring opening, the sulfur then nucleophilically attacks the sp carbon thus forming the heterocycle.<sup>32</sup> After Pd catalyst decomplexation, the benzo[b]thiophene, **2.06**, is formed.

Gabriele *et al.*, described a convenient and versatile method to convert simple 2-substituted thiophenols to 2,3-substituted benzo[b]thiophenes using a PdI<sub>2</sub> catalyst.<sup>33</sup> Starting with simple C(2) substituted aldehyde or ketone, thiophenols, **2.07**, are first converted to a propargylic alcohol via nucleophilic alkynyl Grignards. With the alkynyl moiety, **2.08**, installed it was found that as little of two molar percent of PdI<sub>2</sub> with KI co-catalyst at 80 °C in acetonitrile could initiate the nucleophilic 5-*exo-dig* attack of the sulfur and thus create the heterocycle.<sup>33</sup>

After dehydration, the product is decomplexed

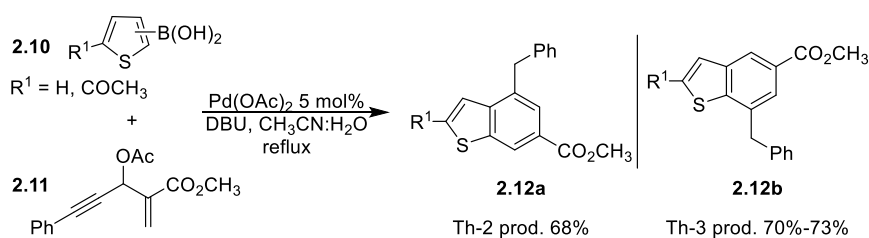


from the catalyst to generate 2,3-substituted

**Figure 30** Benzo[b]thiophene synthesis via Pd catalyzed heteroannulation and aromatic dehydration of 1-(2-mercaptophenyl)-2-yn-1-ol

benzo[b]thiophenes, **2.09**. The reaction showed tolerance for methyl and phenyl ketones, as well as aldehydes in the 2-carbonyl thiophenol starting materials, however, discrepancies were seen for the more sterically bulky alkynes.<sup>33</sup> Alkyl and phenyl alkynes produced moderately good yields of 70%-82%, however, when benzyl alkynes were employed the yields fell to 56%. This methodology employed a simple installment of alkynes to 2-carbonyl thiophenol and PdI<sub>2</sub> catalyzed heterocyclization.

Reddy, *et al.*, have developed a method of substituted benzo[b]thiophenes construction via benzene annulation via Suzuki coupling followed base promoted [4+2] cyclization.<sup>34</sup> The unsaturated **2.11** substrate

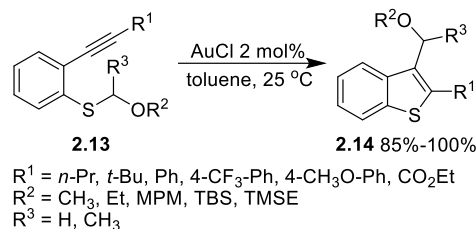


**Figure 31** Pd catalyzed Suzuki cross-coupling and base promoted benzene annulation to substituted benzo[b]thiophenes

is first coupled with an aryl heterocycle, **2.10**, via Suzuki reaction using five molar percent

Pd(OAc)<sub>2</sub> in refluxing acetonitrile. In the presence of nitrogenous base, the newly formed benzylic carbon is deprotonated and the resulting intermediate undergoes a 6-*exo-dig* annulation.<sup>34</sup> The newly formed carbocycle then undergoes a 1,7-proton shift and thus rearomatizes forming a benzo[b]thiophene core, **2.12a/b**. Using C(2) and C(3) thiophene boronic acid, **2.10**, led to comparable yields of 68% and 73% of benzo[b]thiophene product. Pushing the substrate scope further, when sterically bulky (5-acetylthiophen-3-yl)boronic acid as a Suzuki reagent, the benzo[b]thiophene adduct was isolated in 70% yield.<sup>34</sup>

Although many Pd catalyzed benzo[b]furan and indole methodologies exist starting from *ortho*-alkynyl phenols and anilines the same methodology is not applicable when attempting benzo[b]thiophene formation due to catalyst poisoning from the sulfur. Due to the simplicity of the starting material construction and the need for a reliable catalytic method of benzo[b]thiophene construction from said

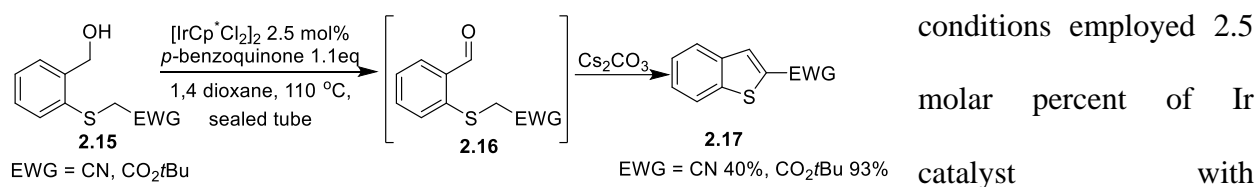


**Figure 32** Au catalyzed heteroannulation and sulfonium rearrangement to benzo[b]thiophenes

starting materials, Nakamura *et al.*, embarked on studies to cyclize *ortho*-alkynyl thiophenols, **2.13**, to the corresponding benzo[b]thiophenes, **2.14**.<sup>35</sup> After screening a number of transition metal catalysts it was found that as little as two molar percent of AuCl induced the cyclization of *o*-alkynyl sulfide **2.13** at room temperature to generate 2,3-substituted benzo[b]thiophene **2.14** in high yield.<sup>35</sup> The reaction showed compatibility with electron-withdrawing and electron-donating aryl alkynes, as well as alkyl alkynes. The authors suggested the gold catalyst first activates the alkyne to nucleophilic sulfur attack and heterocycle formation. The intermediate then undergoes an alkyl migration from the sulfonium ion to the C(3), which then decomplexes with the gold catalyst and forms the 2,3-substituted benzo[b]thiophenes.<sup>35</sup> This methodology is very

promising due to the ease of starting material construction, low catalyst load, mild reaction conditions and very high yields of 2,3-substituted benzo[b]thiophenes products.

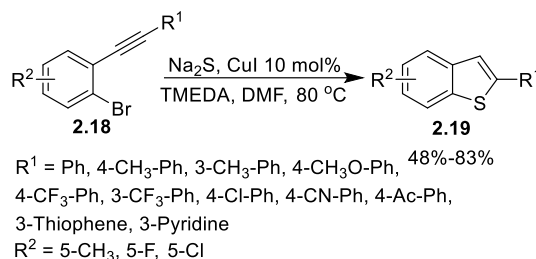
An iridium catalyzed hydrogen transfer of *ortho*-benzylic alcohol sulfides, **2.15**, has been developed which then undergoes heterocycle annulation under basic conditions.<sup>36</sup> It is known that iridium complexes are potent hydrogen transfer catalysts which could be employed to induce oxidation an aryl alcohol to the corresponding aldehyde, **2.15**. The screening of iridium complexes showed the  $[\text{IrCp}^*\text{Cl}_2]_2$  complex was most competent at hydrogen transfer.<sup>36</sup> However, a fully hydrogenated heterocycle byproduct was observed, therefore, the optimized



**Figure 33** Ir catalyzed benzylic alcohol oxidation and base promoted aromatic stoichiometric amount of dehydration to substituted benzo[b]thiophenes cesium carbonate base and *p*-benzoquinone as oxidizing agent for reduced iridium species.<sup>36</sup> Of note is the differentiation of yields with variation of electron withdrawing groups of the sulfide, **2.15**. When an alpha ester sulfide moiety was employed the thiophene cyclization proceeded in a high yield of 93%, **2.17**.<sup>36</sup> However, when an alpha nitrile sulfide moiety was employed the yield dropped dramatically to 40% product formation, **2.17**.<sup>36</sup> This can be rationalized by the lower acidity of the alpha proton of the nitrile functionality versus that of the carbonyl.

Recently, Zhang *et al.*, developed a copper catalyzed method of benzo[b]thiophene heterocycle annulation via tandem C-S bond formation from 2-bromo alkynylbenzenes, **2.18**, and sodium sulfide.<sup>37</sup> The methodology is significant due to the economical starting materials and catalyst. The thiophene annulation was preceded by Takimiya via heating at 180 °C in NMP using the 2-bromo alkynylbenzenes and sodium sulfide.<sup>37</sup> The need to improve this previous

methodology to lower reaction temperatures prompted interest in a catalytic means of accomplishing the hetero-annulation. Primary investigation of simply heating starting materials in DMF to 80 °C in the absence of catalyst produced low yield of the desired product, which concluded that high reaction temperatures were required to obtain benzo[b]thiophene products.<sup>37</sup> A thorough



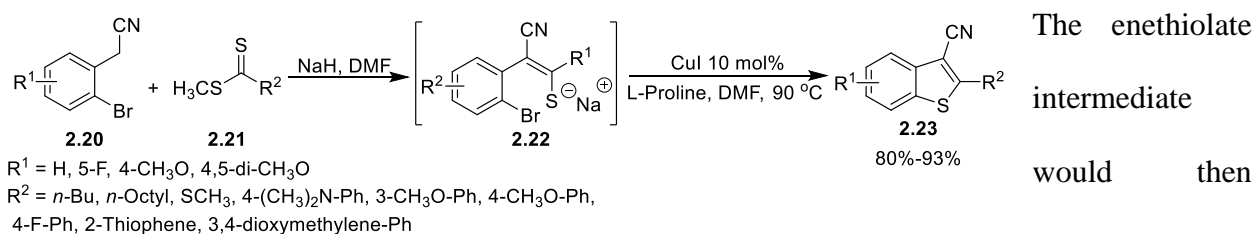
screen of copper salts, solvent, reaction temperatures, catalyst ligands and catalyst loading

**Figure 34** Cu catalyzed benzo[b]thiophene synthesis via dual C-S bond formation from 2-bromo alkynylbenzenes and sodium sulfide

found 10 molar percent CuI with tetramethyl ethylenediamine ligand while heating in DMF to 80 °C converted 1-bromo-2-(phenylethynyl)benzene, **2.18**, to 2-phenylbenzo[b]thiophene in 83%, **2.19**.<sup>37</sup> With optimized conditions in hand, a substrate screening was carried out to understand the tolerance of the reaction. Variations of the aryl functionality of the alkyne terminus commenced. Mildly electron donating phenyls: methyl, methoxy, and chloro, proved comparable to the model system; all producing good yields of 71%-82%, **2.19**. Heterocyclic thiophene and pyridine alkynyl substrates conveniently underwent the reaction in good yields of 73% and 70%. However, various electron poor aryls (trifluoromethyl, aceto, and nitrile) significantly lowered the product yields to 48%-54%. The reaction proved very sensitive to sterically demanding substrates; both isopropyl and biphenyl functionalities on the alkyne terminus gave no reaction in the first instance and only trace product in the second.<sup>37</sup> The reaction showed compatibility when multiple substituted 2-bromo-alkynylbenzenes were explored as substrates. 2-Bromo-4-methyl-1-(phenylethynyl)benzene derivatives proved successful in undergoing the annulation reaction. Of note is the use of 2-bromo-4-halo-1-

(phenylethynyl)benzene derivatives of fluorine and chlorine not only successfully underwent product formation but also maintained 6-halo substitution without incident.<sup>37</sup>

Building on catalytic copper C-S bond formation, Ila, *et al.*, focused on a strategy of C(7)-S(1) bond formation from a thioenolate intermediate, yielding 2,3-substituted benzo[b]thiophenes, **2.23**, in high yields.<sup>38</sup> The authors envisioned the thiophene ring could be formed in a tandem fashion, first, C(2)-C(3) bond formation by base induced condensation of dithioester, **2.21**, and 2-bromo-arylacetonitrile, **2.20**, resulting in intermediate enethiolate, **2.22**.



**Figure 35** Base promoted enethiolate formation from 2-bromo-arylacetonitriles and Cu catalyzed heteroannulation to substituted benzo[b]thiophenes

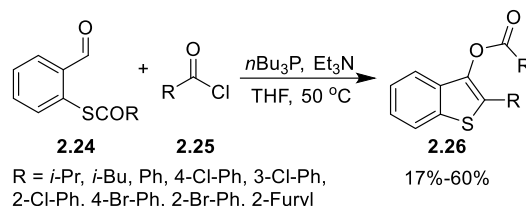
2-Bromo-5-methoxyphenylacetonitrile and 4-methoxyphenyl dithioester were used as model starting materials to explore optimized reaction conditions. After determining NaH was best suited for condensation to the sodium enethiolate intermediate, the screening of intramolecular C-S coupling conditions found the use of 10 molar percent of CuI and L-proline at 90 °C in DMF produced the 5-methoxy-3-nitrile-2-(4-methoxyphenyl)benzo[b]thiophene in 90% yield.<sup>38</sup> The subsequent substrate scope study displayed an extremely high tolerance to a plethora of aryl dithioesters, **2.21**, bearing electron donating/withdrawing, and sterically demanding aryl and heteroaryl moieties producing substituted benzo[b]thiophenes, **2.23**, in good yield.<sup>38</sup> The reaction conditions also proved compatible with dimethyl trithiocarbonate, dithiocarbonate, and isothiocyanate as the thiocarbonyl component producing the 3-nitrile-2-hetero-



benzo[b]thiophenes in excellent yields, 80%-93%. The above conditions show a high scope of substrate compatibility, high yielding product formation, economical reaction conditions in the formation of synthetically useful 2,3-benzo[b]thiophenes.<sup>38</sup>

Few synthetic transformations can compare to the reliability and functional tolerance of the Wittig reaction in construction of carbon-carbon double bonds. By virtue of these traits Lin *et al.*, studied the construction of 2,3-disubstituted

benzo[b]thiophenes, **2.26**, via intramolecular carbon double bond formation from 2-benzaldehyde thioesters, **2.24**.<sup>39</sup> The strategy

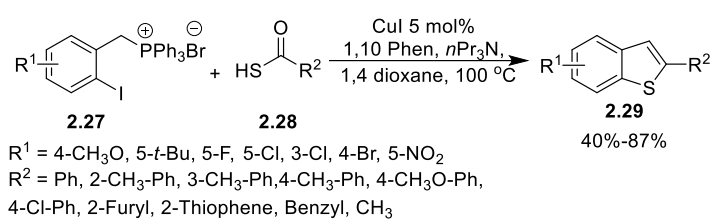


**Figure 36** Substituted benzo[b]thiophene synthesis via intramolecular Wittig olefination of 2-benzaldehyde thioesters

centered on 1,2 addition of phosphine to aryl aldehydes, **2.24**, followed by *in situ* trapping of the phosphonium oxide zwitterion intermediate via acylation. The trapped intermediate then undergoes base-induced Wittig reaction with the thioester sub-moiety, yielding the disubstituted benzo[b]thiophene product, **2.26**. The optimized conditions use tributylphosphine in slight stoichiometric excess, heating with *S*-(2-formylphenyl) benzothioate, **2.24**, in THF at 50 °C in the presence of triethyl amine and benzoyl chloride, **2.25**.<sup>39</sup> These conditions produced the desired 2-phenylbenzo[b]thiophen-3-yl benzoate in moderate 58% yield, **2.26**. Of note is the interesting C(3) oxy-substitution which in of itself is a unique functional pattern rarely observed in benzo[b]thiophene constructions. Moving to explore the substrate scope, the authors varied the thioester, **2.24**, as well as the acid chloride, **2.25**. 2-chloro, 3-chloro, and 4-chloro aryl groups produced comparable yields to that of the phenyl substrate. Note that the more sterically demanding 2-chloro aryl substrate produced the lowest conversion to the benzo[b]thiophene product, **2.26**.<sup>39</sup> When 4-bromo and 2-bromo aryl derivatives were employed the trend remained. The 4-bromo derivative, again, produced the

moderate yield of 51%. The steric effect of the larger bromine atom at the 2-position decreased the product yield to only 17%. Poor yields were also observed with the use of heterocyclic 2-furyl and alkyl *iso*-butyl derivatives only producing the benzo[*b*]thiophenes, **2.26**, in 23% and 42%.<sup>39</sup> The methodology here describes a straightforward manner in which to create uniquely substituted benzo[*b*]thiophenes, **2.26**, although in moderate yields and sees sterically demanding substrates diminish the product conversion.

Building on the use of the Wittig reaction as a reliable means to install the C(2)-C(3) double bond of the heterocycle, Yu *et al.*, employed a copper catalyzed C-S bond formation followed by Wittig reaction.<sup>40</sup> Although the reaction follows a parallel strategy of bond formation, the substrate employed is a 2-iodobenzyl phosphonium bromide salt, **2.27**, allowing



for simple and economic starting materials for the conversion of benzo[*b*]thiophenes products, **2.29**.

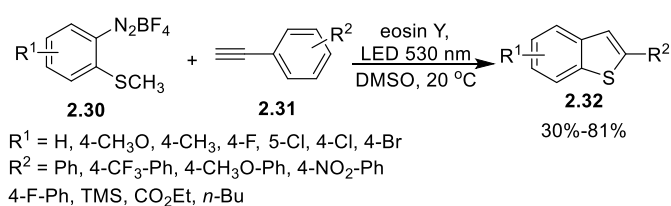
**Figure 37** Cu catalyzed C-S bond formation of thiocarboxylic acids to 2-iodobenzyl phosphonium salts and intramolecular Wittig olefination to substituted benzo[*b*]thiophenes

The critical installation of the sulfur atom was to be sourced from

thiobenzoic acid, **2.28**. Using (2-iodobenzyl) phosphonium bromide, **2.27**, and thiobenzoic acid, **2.28**, as model substrates, screening found optimized conditions of five molar percent of CuI, 1,10-phenanthroline as ligand and stoichiometric excess of tri-*n*-propyl amine in dioxane at 100 °C.<sup>40</sup> These conditions successfully produced 2-phenyl benzo[*b*]thiophene, **2.29**, in 87%. Using the optimized conditions, the scope of the reaction substrates were studied. Various substitutions of the phosphonium bromide salt, **2.27**, including electron donating and electron withdrawing groups showed little effect on the yield of the benzo[*b*]thiophene products, **2.29**.<sup>40</sup> Of note, the use of secondary alkyl phosphonium salt resulted in no desired heterocycle product. The

substitution of the thioaryl acids, **2.28**, resulted in good yields of benzo[b]thiophene products 67%-81%; with the lone exception of the electron withdrawing 4-chloro-thiobenzoic acid, which gave trace amount of product.<sup>40</sup> The use of 2-thiophene thiocarboxylic acid and of 2-furan thiocarboxylic acid produced the 2-heterocyclic-benzo[b]thiophenes in 63% and 74%. The reaction methodology was even compatible with the use of the aliphatic thiophenylacetic acid and thioacetic acid yielding 2-alkyl benzo[b]thiophenes in 60% and 40%.

In a divergence from metal catalyst methods for heterocycle annulation reactions benzo[b]thiophenes have been prepared through traditional electrophilic induced cyclization as well as newly reported radical induced cyclization. König, *et al.*, were the first to report a photocatalytic synthesis of benzo[b]thiophenes, **2.32**, from *ortho*-diazonium methyl sulfides,



**Figure 38** Visible light catalyzed benzo[b]thiophene synthesis from 2-(methylthio)benzene diazonium salts and phenyl acetylenes

**2.30**, through a radical annulation pathway.<sup>41</sup> The author previously report aryl substitution of benzo[b]thiophenes starting from aryl diazonium salts and benzo[b]thiophene via photocatalyst and

visible light.<sup>41</sup> Although the strategy conceptually proved successful, it was mired by poor yields and product mixtures of 2-aryl-benzo[b]thiophenes and 3-aryl-benzo[b]thiophenes.

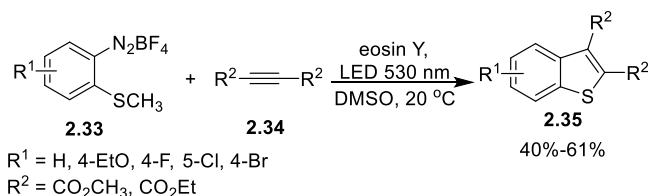
Building on this strategy, the authors surmised that photocatalytic heterocycle annulation via *ortho*-diazonium methyl sulfides, **2.30**, with alkynes, **2.31**, could potentially offer more reliable means to construct substituted benzo[b]thiophenes, **2.32**. To determine optimized reaction conditions phenyl acetylene, and 2-(methylthio)benzenediazonium were screened through various conditions. It was found the use of five molar percent of eosin Y as photoredox catalyst under 530 nm LED light in DMSO successfully induced the annulation, producing 2-phenyl-benzo[b]thiophene, **2.32**, in 75% and without any C(3) substituted isomer.<sup>41</sup> Proving the crucial

role of all reaction components, when the reaction was performed without light or eosin Y, only trace amounts of the product were isolated. With optimized conditions in hand, the breadth of the substrate scope was examined. Keeping phenyl acetylene, **2.31**, as the radical coupling partner, various aryl substitutions on the *ortho*-diazonium methyl sulfide, **2.30**, were explored.

Alkyl, halo, and alkyloxy functionalities at the C(4) or C(5) position of the *ortho*-diazonium methyl sulfide, **2.30**, proved

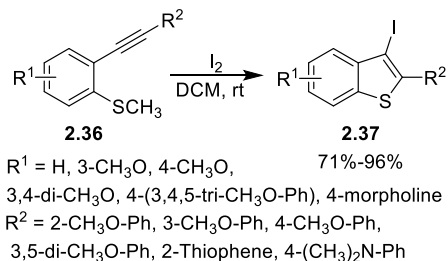
compatible to annulation conditions, producing the desired benzo[*b*]thiophenes

in good yields of 62%-76%.<sup>41</sup> Alternatively, substituting the alkyne, **2.31**, with a variety of electron withdrawing and electron donating phenyl derivatives yielded benzo[*b*]thiophenes, **2.32**, in comparable yields, 62%-81%.<sup>41</sup> Only when using *n*-butyl acetylene and trimethylsilyl acetylene did the reaction yield poor results, producing the 2-*n*-butyl-benzo[*b*]thiophene in 30% and the 2-trimethylsilyl-benzo[*b*]thiophene in slightly better 45%. Switching from terminal alkynes to 1,4-diester alkynes, **2.34**, gave moderate yields of 2,3-dicarboxylate benzo[*b*]thiophenes, **2.35**, 40%-61%.<sup>41</sup> The dimethyl esters proved slightly higher yielding than the diethyl esters, presumably due to the larger steric bulk of the ethyl component. In an effort to understand the mechanistic pathway, the authors doped the reaction of phenyl acetylene and 2-(methylthio)benzenediazonium with TEMPO to attempt the capture of radical intermediates. Two TEMPO adducts were found, the first indicating the radical disassociation of C-N<sub>2</sub><sup>+</sup> aryl bond, and the second, from a vinyl radical after the aryl radical alkyne coupling. It was proposed the vinyl radical then couples to the sulfur atom which undergoes oxidation via the redox catalyst and forms the benzo[*b*]thiophene product.<sup>41</sup>



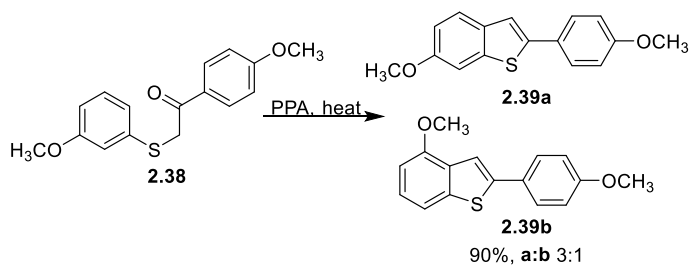
**Figure 39** Visible light catalyzed benzo[*b*]thiophene synthesis from 2-(methylthio)benzene diazonium salts and internal alkynes

Using simple means to construct synthetically useful and complex substrates are main motivations in synthetic chemistry. In an effort to build large libraries of small molecule of 2,3-disubstituted benzo[b]thiophenes, **2.37**, Larock, *et al.*, conducted simple electrophilic heterocyclization of 2-alkynyl-thioanisole, **2.36**, starting materials.<sup>42</sup> These aryl methyl sulfides, **2.36**, were previously made in good yields via Sonogashira coupling of 2-iodo-thioanisole. With a large library of 2-alkynyl-thioanisoles, the preparation of benzo[b]thiophenes with further synthetic utility commenced. The use of halogens as electrophilic species is well known. To this end Larock chose I<sub>2</sub> to induce electrophilic cyclization of the 2-iodo-thioanisole, **2.36**, which would produce 2-aryl-3-iodo-benzo[b]thiophenes, **2.37**, readily able to undergo further planned palladium catalyzed coupling.<sup>42</sup> Using a slight excess of I<sub>2</sub> in DCM at room temperature, the 2-alkynyl-thioanisole, **2.36**, derivatives readily cyclized to the 2-aryl-3-iodo-benzo[b]thiophenes, **2.37**, in excellent yields, 71%-96%.<sup>42</sup>



**Figure 40** Electrophilic alkylation of 2-alkynyl thioanisoles to substituted benzo[b]thiophenes

Heterocycle annulation is known to be accomplished through cation formation from proton-induced dehydration. This strategy was employed when designing 2,3-diaryl-benzo[b]thiophene, **2.39**, as a possible anti-tubulin agent by Pinney *et al.*<sup>4</sup> The straightforward strategy involved first nucleophilic attack of aryl thiols on  $\alpha$ -bromo-acetophenone, leading to 2-arylthio-acetophenones, **2.38**.<sup>4</sup> Heterocyclic annulation to 2-aryl-benzo[b]thiophenes was

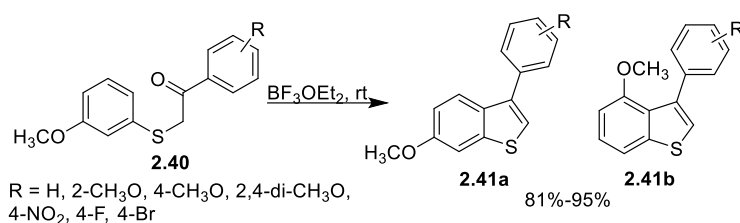


**Figure 41** Bronsted-Lowery acid promoted heterocyclization of 2-arylthio-acetophenones to substituted benzo[b]thiophenes

accomplished by heating the 2-arylthio-acetophenones, **2.38**, with polyphosphoric acid. Of significant note is the formation of C(2) substituted benzo[b]thiophenes, **2.39**, via a C(3)-C(2) aryl shift.<sup>4</sup> Further substitution at the C(3) was carried out by conventional Friedel-Craft acylation protocols.

Although straightforward and convenient, the proton mediated heterocyclization of 2-arylthio-acetophenones induced an aryl shift rendering a 2-aryl-benzo[b]thiophene. In an effort to maintain the starting 2-arylthio-acetophenones, **2.40**, without inducing the C(3)-C(2) aryl shift

during the annulation process, Kim *et al.*, set forth to developed mild conditions to prompt heteroannulation to yield 3-aryl-benzo[b]thiophenes, **2.41**.<sup>43</sup> It was



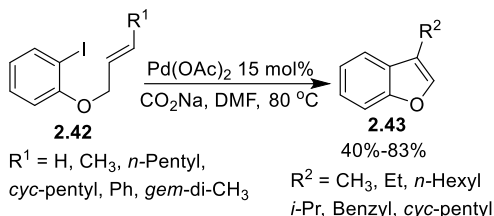
**Figure 42** Boron trifluoride-diethyletherate promoted heterocyclization of 2-arylthio-acetophenones to substituted benzo[b]thiophenes

found the use boron trifluoride-diethyletherate at room temperature induced 2-arylthio-acetophenones, **2.40**, to cyclize to the desired 3-aryl-benzo[b]thiophenes, **2.41**, in only 10%-15% after a day. To maintain these mild reaction conditions yet increase the efficiency of product formation, the authors used boron trifluoride-diethyletherate as a solvent.<sup>43</sup> This protocol increased the 3-aryl-benzo[b]thiophenes, **2.41**, yield to 81%-95%.<sup>43</sup> Both electron-withdrawing and electron-donating aryl derivatives were compatible with the use of boron trifluoride-diethyletherate to induce cyclization.

## 2.2 BENZO[B]FURAN SYNTHETIC CONSTRUCTION METHODS

Palladium based cross coupling in the formation of heterocyclic systems is well studied.

The wide commercial availability of halo-substituted aryl compounds allows simple construction



**Figure 43** Pd catalyzed Heck reaction toward the synthesis of substituted benzo[b]furans

of complex heterocyclic systems in few synthetic steps.

The coupling via Pd catalysis of an alkene to halo-alkyl or halo-aryl functionalities is known as the Heck reaction. This approach has been used in construction

of benzo[b]furans. Larock *et al.*, successfully

employed an intramolecular Heck cross coupling reaction to produce benzo[b]furans. Starting

from 2-iodo-phenol allylethers, **2.42**, the use of Pd(OAc)<sub>2</sub> catalyst in DMF at 80 °C formed the desired 3-substituted-benzo[b]furan, **2.43**, in moderate to good yields, 40%- 83%.<sup>44</sup> The authors

noted the importance of sodium formate which was

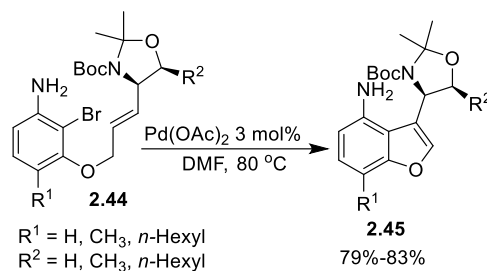
speculated to reduce the formation of  $\alpha$ -allyl palladium species within the reaction media. Using similar

reaction conditions as Larock, Kozikowski *et al.*,

demonstrated the intramolecular Heck reaction of a

highly complex 2-bromo-phenol allylether, **2.44**, to

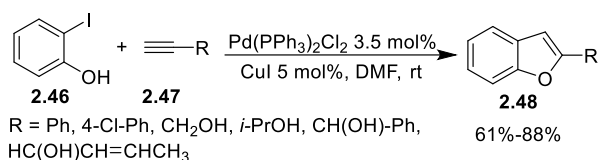
synthesize benzo[b]furan intermediate **2.45** in good yields, 79%-83%, to fabricate indolactam analogues.<sup>45</sup>



**Figure 44** Pd catalyzed Heck reaction for benzo[b]furan indolactam analogues

The Sonogashira reaction has been used in constructing benzo[b]furans by Kundu *et al.*<sup>46</sup> Using commercially available terminal alkynes, **2.47**, and 2-iodo-phenol, **2.46**, the authors developed methodology to perform a tandem aryl-alkyne coupling followed by nucleophilic heteroatom attack of an activated alkyne and heterocycle formation, forming 2-substituted-

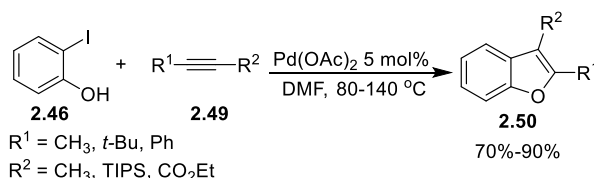
benzo[b]furans, **2.48**. Screening of reaction conditions found PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> and CuI the most



**Figure 45** Sonogishira coupling and tandem heteroannulation for the synthesis of substituted benzo[b]furan

benzo[b]furans in moderate to good yields, 61%-88%.

In a continuation of exploiting the reactivity of alkynes in heterocycle annulation, Larock *et al.*, developed conditions for the formation of 2,3-disubstituted benzo[b]furans from simple 2-iodo-phenols, **2.46**, and internal alkynes, **2.49**.<sup>47</sup> Using five molar percent of Pd(OAc)<sub>2</sub> at elevated temperatures and under basic conditions, the heteroannulation of 2-iodo-phenol, **2.46**, was readily accomplished. Sterically bulky 4,4-dimethylpent-2-yne produced the benzo[b]furan, **2.50**, in good yield of 86%, however, triisopropyl(prop-1-yn-1-yl)silane produced a synthetically useful 2-silyl-3-methyl-benzo[b]furan, **2.50**, in excellent 90%.<sup>47</sup> The electron withdrawing ethyl 3-phenylpropionate produced a mixture of substitution isomers, **2.50**, in 70%. In a



**Figure 46** Pd catalyzed heteroannulation of 2-iodo phenol and internal alkynes for benzo[b]furan synthesis

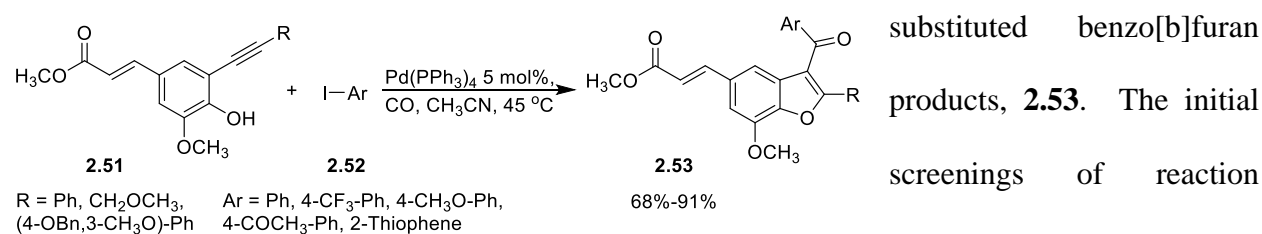
purposed mechanistic pathway the catalyst first undergoes oxidative insertion of the iodo-aryl bond. The Pd center then complexes with the

alkyne and followed by a 1,3-insertion, leading to a Pd-alkenyl intermediate.<sup>47</sup> The Pd then complexes to the oxygen and the catalyst undergoes a reductive elimination, yielding the original catalyst and the 2,3-disubstituted benzo[b]furan. This methodology represents a straightforward means to the highly substituted benzo[b]furan from simple and commercially available starting



materials and shows tolerance to sterically large starting alkynes, with the drawback of the need for elevated temperatures which may effect thermally unstable functionalities.

Yang *et al.*, developed useful methodology for multi-substituted benzo[b]furans via palladium catalysis under a carbon monoxide atmosphere from simple 2-alkynyl-phenols.<sup>48</sup> The strategy centered around the aryl carbonylation at the C(3) position after heterocycle annulation. The commercial availability of the 2-alkynyl phenol, **2.51**, starting materials and aryl iodide, **2.52**, coupling partner offers an economic and straight forward means to produce highly



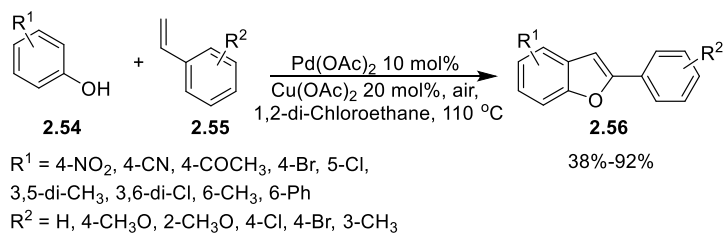
**Figure 47** Pd catalyzed carbonylative heteroannulation to substituted benzo[b]furans

substituted benzo[b]furan products, **2.53**. The initial screenings of reaction conditions with 2-(phenylethynyl)phenol and Pd(PPh<sub>3</sub>)<sub>4</sub> surprisingly produced 2-alkynyl phenolic esters and only trace amounts of the desired product.<sup>48</sup> To alleviate the unwanted product formation, an increase of Lewis acid character of the Pd catalyst was thought to better activate the alkyne, thus inducing nucleophilic attack and annulation. The addition of silver salts to the reaction was found to reverse the above reaction impasse, producing the 3-carbonyl-2-aryl benzo[b]furan in 30% and the unwanted 2-alkynyl phenolic ester in trace amounts. The substrate scope was evaluated next, using a highly substituted, methyl (*E*)-3-(4-hydroxy-3-methoxy-5-(phenylethynyl)phenyl)acrylate, **2.51**. Using a five molar percent Pd(PPh<sub>3</sub>)<sub>4</sub>, an atmosphere of carbon monoxide, and 4-methoxy phenyl iodide, **2.52**, at 50 °C successfully produced the benzo[b]furan product, **2.53**, in good yield of 86%.<sup>48</sup> Moving to screen the effects of other aryl iodides, **2.52**, phenyl iodide and thiophene-2-iodide again produced the substituted benzo[b]furans, **2.53**, in good yields, 91% and 68%. The

use of electron withdrawing 4-trifluoromethyl phenyl iodide and 4-acyl phenyl iodide produced the benzo[b]furan products, **2.53**, in moderate yields of 45% and 61%. This methodology shows high tolerance to highly substituted starting material variations and readily produces 3-carbonyl-2-aryl benzo[b]furans in good yields.<sup>48</sup>

The use of phenols as an economic and abundant starting material is a desirable means to produce the benzo[b]furan core by palladium catalyzed heteroannulation. Maiti *et al.*, developed a highly versatile method of heteroannulation by palladium catalyzed C-O/C-C bond formation between phenol, **2.54**, and alkenyl, **2.55**, starting materials producing C(2) substituted benzo[b]furans, **2.56**.<sup>49</sup> The authors found ten molar percent of Pd(OAc)<sub>2</sub> catalyst, 1,10-phenanthroline as ligand, Cu(OAc)<sub>2</sub> as oxidizing agent, and NaOAc as base in 1,2-dichloroethane at 110 °C the optimal conditions to transform the 4-nitro phenol, **2.54**, and styrene, **2.55**, to corresponding 5-nitro-2-phenylbenzofuran, **2.56**, in excellent 94% yield.<sup>49</sup> The substrate scope of the reaction was impressive.<sup>49</sup> The use

of 4-nitro-phenol, **2.54**, led to good conversion to the 5,2-substituted-benzo[b]furans, **2.56**, when either electron withdrawing or electron

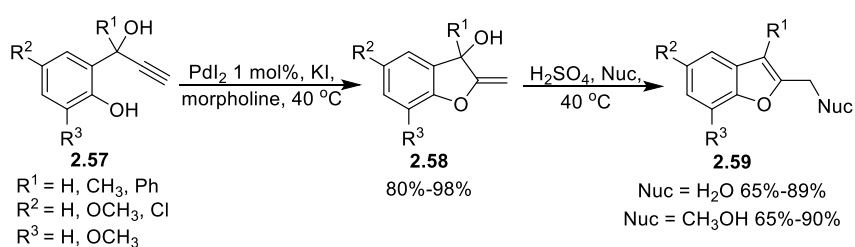


**Figure 48** Pd catalyzed synthesis of benzo[b]furans from phenols and styrenes

donating aryl styrenes, **2.55**, were employed as starting materials. The use of electron withdrawing 4-halo-phenol and 4-carbonyl-phenol with aryl styrenes produced the desired 2,5-substituted benzo[b]furans, **2.56**, albeit in moderate yields. Multisubstituted 2,5-dichloro-phenol and 3,5-dimethyl-phenol, **2.54**, were also able to convert to multisubstituted benzo[b]furans, **2.56**, in moderate yields. Use of 2-methyl-phenol and 2-phenyl-phenol under standard conditions also produced 6,2-substituted benzo[b]furans, **2.56**, in moderate yields

despite of the steric bulk of the starting materials. The standard reaction conditions also proved compatible with the use of aliphatic alkenes.<sup>49</sup> The heteroannulation was readily accomplished however the occurrence of a variety of substitutions was observed. The use of terminal alkenes provided 2-alkyl benzo[b]furans as well as 3-methyl-2-alkyl benzo[b]furans via allylic complexation of the alkene and palladium catalyst. The standard palladium conditions with phenols and aliphatic alkenes provided moderate yields of the benzo[b]furan products with complications of isomeric products.<sup>49</sup>

In a novel approach to 2,3-substituted benzo[b]furans Gabriele *et al.* developed a palladium catalyzed hetero-cyclization followed by acid-catalyzed dehydration and aromatization.<sup>50</sup> Starting from simple 2-carbonyl-phenols, the authors installed an alkynyl moiety creating 2-(1-hydroxyprop-2-yn-1-yl)phenols, **2.57**. The 2-(2-hydroxybut-3-yn-2-yl)phenol was selected as a model substrate and then screened with catalytic amounts of transition metal salts to induce heteroannulation to 3-methyl-2-methylene-2,3-dihydrobenzo[b]furan-3-ol, **2.58**. Using one molar percent PdI<sub>2</sub>, two equivalents of KI, and an equimolar amount of morpholine in



methanol at 40 °C efficiently caused the 5-*exo-dig* cyclization to the desired

dihydrobenzo[b]furan

**Figure 49** Pd catalyzed heteroannulation and acid catalyzed aromatization of via allylic isomerization

product, **2.58**, in 98%.<sup>50</sup> It

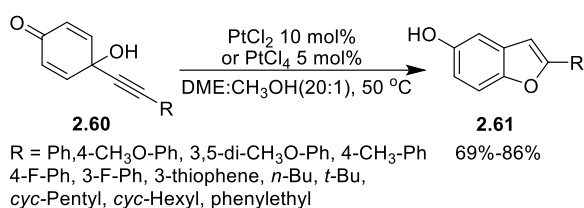
was also discovered that using one molar percent PdCl<sub>2</sub> under the same conditions accomplished the desired heteroannulation with only ten molar percent of morpholine to yield dihydrobenzo[b]furan product in 86%. The substrate scope of the cyclization step was assessed with functionalization at the benzylic carbon and substitution of the benzene ring. Under the

PdI<sub>2</sub> conditions, both hydrogen and phenyl substitutions of the benzylic carbon, **2.57**, were tolerated in the cyclization reaction. The addition of electron withdrawing chlorine at C(4) of the benzene ring, as well as electron donating methoxy at the C(4) and C(6) carbons all produced the dihydrombenzo[b]furan product in good yields, **2.58**, 82%-88%. With suitable conditions to implement the 5-*exo-dig* cyclization in good yields, the authors set out to induce aromatization of the furan via dehydration of the alcohol moiety. Envisioned was an acid catalyzed dehydration and allylic isomerization via a nucleophilic attack of water.<sup>50</sup> The mild heating of 3-methyl-2-methylene-2,3-dihydrobenzo[b]furan-3-ol, **2.58**, in 0.2 M H<sub>2</sub>SO<sub>4</sub> in dimethoxyethane successfully produced dehydrative-aromatization reaction, yielding the desired 2-hydroxymethyl-3-methyl-benzo[b]furan, **2.59**, in 83% yield. The use of methanol as a nucleophile was also assessed; using the same conditions as above with 3-methyl-2-methylene-2,3-dihydrobenzo[b]furan-3-ol and producing 2-(methoxymethyl)-3-methylbenzo[b]furan, **2.59**, in slightly lower 78%.<sup>50</sup> The use of the substituted derivatives described above in the PdI<sub>2</sub> annulation conditions under both acid catalyzed aromatizing conditions led to good yields of the 2-methyl-benzo[b]furan, **2.59**, products; under aqueous solvent 81%-90% and under alcohol solvent 70%-90%.<sup>50</sup> The lone exception to this trend was the use of 5-chloro-2-methylene-2,3-dihydrobenzofuran, which only produced the aromatized benzo[b]furan in 65% with the use of a water nucleophile and a poor yield of 15% when methanol was used as a nucleophile, the yield was increased to 65% with heating of the reaction medium.<sup>50</sup>

Kim, *et al.* studied the use of quinols in a platinum catalyzed rearrangement and cyclization to the formation of 2-substituted-5-hydroxybenzo[b]furans.<sup>51</sup> The authors envisioned that the starting quinol substrate would rearrange to a phenol derivative which then would proceed through a 5-*endo-dig* cyclization producing the heterocyclic 2-substituted-5-

hydroxybenzo[b]furan.<sup>51</sup> In a single step, the starting quinol, **2.60**, was made via nucleophilic addition of lithium acetylides on 1,4-benzoquinone. The screening of optimal reaction conditions and catalysts found that quinol **2.60** underwent the alkynyl rearrangement and cyclization with ten molar percent of PtCl<sub>2</sub> with a 20:1 DME:methanol solvent at 40 °C, yielding

2-phenyl-5-hydroxybenzo[b]furan, **2.61**, in 86%.<sup>51</sup> The use of PtCl<sub>4</sub> in only five molar percent in DME at room temperature gave a comparable yield of 78%. With reaction conditions understood, the breadth of substrate

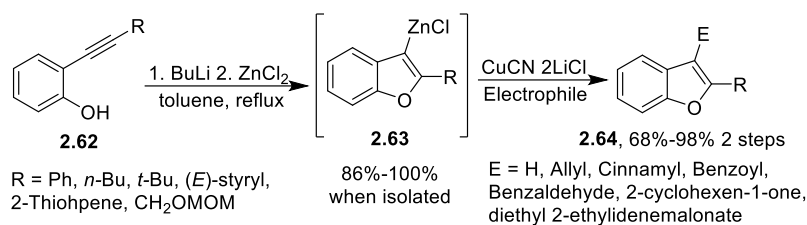


**Figure 50** Pt catalyzed tandem quinol rearrangement and heteroannulation for substituted benzo[b]furan synthesis

scope was assessed by variation of the terminus of the alkyne sub-moiety. Aryl, **2.60**, C(4) substitution of methoxy and methyl as well as C(3)/C(5) dimethoxy both produced the corresponding 2-aryl-5-hydroxybenzo[b]furans, **2.61**, in good yields 75%-81%. Reactions with electron withdrawing 4-fluoro, and 3-fluoro aryl moieties using PtCl<sub>4</sub> proceeded in 81% and 83%. The alkynyl thiophene-3-yl was able to produce the 2-thiophene-3-hydroxybenzo[b]furan in 86%. Moving to alkyl alkyne substitutions, phenylethyl, *t*-butyl, *n*-butyl, cyclohexenyl, and cyclopentyl all showed competency toward cyclization via PtCl<sub>2</sub> catalysis, producing 2-alkyl-5-hydroxybenzo[b]furans, **2.61**, in 69%-79%.<sup>51</sup> The facile method of starting material construction and substrate compatibility of the reaction conditions offers a broad prospect of utility in the formation of 2-substituted-5-hydroxybenzo[b]furans, **2.61**, via the platinum catalyzed quinol, **2.60**, rearrangement and intramolecular heterocyclization.

Nakamura *et al.*, focused on the electrophilic Zn<sup>II</sup> activation of *ortho*-phenol-ynes, **2.62**, as a means of benzo[b]furan construction.<sup>52</sup> Previously, diethylzinc reagents were used to achieve furan cyclization; however, the reaction was sluggish, and it was perceived that a stronger

Lewis acid could activate the substrate more readily. 2-(Phenylethynyl)phenol, **2.62**, as a model substrate was first deprotonated with an equivalent of *n*-BuLi followed by the addition of ZnCl<sub>2</sub>. The zinc intermediate, **2.63**, was then refluxed in toluene to induce the cyclization forming the 2-phenyl-benzo[*b*]furan product, **2.64**, in quantitative yield.<sup>52</sup> The reaction conditions tolerated variation of alkynyl terminus, **2.62**, and aryl, alkyl, heterocyclic, and benzylic functionalities



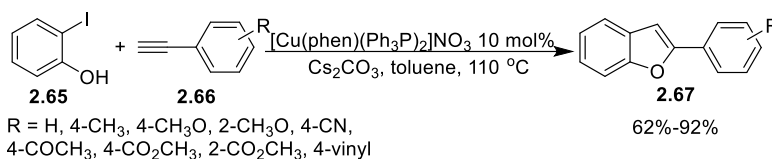
produced excellent yields of 86%-100%. Of note, when R=H, no desired benzo[*b*]furan was produced. Nakamura

**Figure 51** Zn induced heteroannulation of 2-alkynyl phenols to substituted benzo[*b*]furans

further elaborated the utility of this

chemistry by demonstrating that the organo-zinc intermediate, **2.63**, could be used for further bond formation. The addition of CuCN·2LiCl in the presence of zinc intermediate **2.63** induced trans-metalation and, in the presence of an electrophile, allowed nucleophilic attack of the copper species to yield 2,3-disubstituted benzo[*b*]furans, **2.64**.<sup>52</sup> The use of allyl bromide, cinnamyl bromide and benzoyl chloride as electrophiles produced 2-phenyl-3-substituted benzo[*b*]furans in 97%, 98% and 91%. Benzaldehyde as an electrophile produced the 2-phenyl-3-benzol benzo[*b*]furan, **2.64**, in good yield of 68%. Michael electrophiles 2-cyclohexen-1-one and diethyl 2-ethylidenemalonate successfully underwent the 1,4-addition producing the 2-phenyl-3-alkyl-benzo[*b*]furan, **2.64**, again, in good yields of 77% and 95%.<sup>52</sup> The ZnCl<sub>2</sub> mediated cyclization represents a useful method to form 2-substituted benzo[*b*]furans or further substitution via copper-3-benzo[*b*]furan nucleophiles producing 2,3-substituted benzo[*b*]furans. A drawback of this method is the need for equimolar amounts of the metallic reagents required for annulation chemistry.

Although the use of transition metals in benzo[b]furans formation from simple starting materials is well documented, the drive to use more inexpensive catalysts remains. To this end Venkaturaman *et al.*, have developed a high yielding copper catalyzed Sonogishira-type coupling of aryl acetylenes, **2.66**, and 2-iodo-phenols, **2.65**, followed by



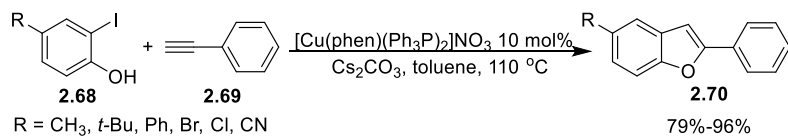
R = H, 4-CH<sub>3</sub>, 4-CH<sub>3</sub>O, 2-CH<sub>3</sub>O, 4-CN,  
4-COCH<sub>3</sub>, 4-CO<sub>2</sub>CH<sub>3</sub>, 2-CO<sub>2</sub>CH<sub>3</sub>, 4-vinyl

heterocycle annulation.<sup>53</sup> Using iodobenzene and phenyl acetylene

**Figure 52** Cu catalyzed tandem Sonogishira like coupling and heteroannulation of 2-iodo phenol and aryl acetylenes toward substituted benzo[b]furans

as a Sonogishira proxy reaction for catalyst efficiency, the authors found [Cu(1,10-phen)(Ph<sub>3</sub>P)<sub>2</sub>]NO<sub>3</sub> most effective and proceeded to identify conditions to generate the benzo[b]furan. Using 2-iodo-phenol, **2.65**, and phenyl acetylene, **2.66**, it was established that ten molar percent of [Cu(1,10-phen)(Ph<sub>3</sub>P)<sub>2</sub>]NO<sub>3</sub> with two equivalents of Cs<sub>2</sub>CO<sub>3</sub> in refluxing toluene produced 2-phenyl-benzo[b]furan, **2.67**, in an excellent 92%.<sup>53</sup> The substrate scope was then assessed. The aryl acetylenes, **2.66**, showed tolerance to electron withdrawing and electron donating functionalities as well as *ortho* and *para* substitutions producing the 2-aryl-benzo[b]furans, **2.67**, in yields 62%-91%. Of significance was the use of 4-vinyl-phenyl acetylene. No Heck type product was observed, only 2-(4-vinylphenyl)benzo[b]furan in 68%. The authors then moved to studying substitutions of the 2-iodo-phenols, **2.68**, at the C(4) under standard reaction conditions with phenyl acetylene, **2.69**. Without exception, the 2-iodo-phenols derivatives, **2.68**, were more robust in producing the desired 2,5-disubstituted-benzo[b]furans, **2.70**.<sup>53</sup> Substituting the C(4) 2-iodo-phenol with methyl, *t*-butyl, or phenyl functionalities produced the corresponding 2,5-disubstituted-benzo[b]furans, **2.70**, in good yields of 79%-85%.

When electron withdrawing phenol derivatives (bromo, chloro, and cyano) were placed at the C(4), even better yields of the 2,5-disubstituted-benzo[b]furans, **2.70**, were seen.<sup>53</sup> This reaction



**Figure 53** Cu catalyzed tandem Sonogishira like coupling and heteroannulation of 2-iodo phenols and phenyl acetylene toward substituted benzo[b]furans

high tolerance to functionalization of both the alkynyl and phenolic starting materials in excellent yields.

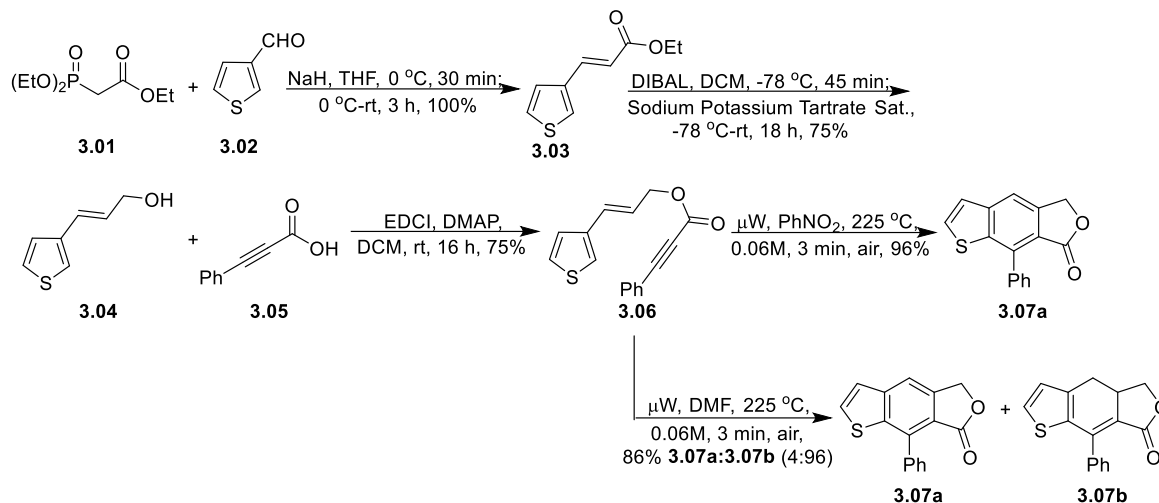
protocol represents an economic means with simple starting materials to achieve mono/poly-substituted benzo[b]furans with



### 3.0 MICROWAVE-ASSISTED DEHYDROGENATIVE DEHYDRO-DIELS-ALDER REACTION TO BENZOFUSED HETEROCYCLES.

Building on the successful selective conversion of styrene-alkynyl substrates to the cyclic naphthyl annulation products via microwave-assisted intramolecular dehydro-Diels-Alder (IMDDA) reaction, work commenced on exploring the aryl  $\pi$ -bond component of the diene with the hope to eventually produce benzofused heterocycles under the analogously selective solvent conditions as described previously.<sup>54</sup>

The IMDDA reaction was hypothesized to be a suitable means to form benzo[b]thiophene derivatives via benzene ring annulation, an orthogonal strategy to those commonly employed when starting from *ortho*-alkynyl benzenethiols. Envisioned was a thiophene-alkene diene that would undergo the [4+2] reaction in the presence of an activated alkynyl dienophile to yield the benzofused annulation product which could then be compared to findings of the styrene-yne substrates.<sup>54</sup> An ester tether was previously employed with the styrene-yne substrates. Due to the excellent product selectivities as well as the synthetically facile means of esterification, the same ester tether was deemed appropriate for preliminary thiophene substrates. Construction of the diene-dienophile substrate began first with alkene installation.<sup>55</sup>



**Figure 54** Synthetic scheme of thiophene(C3) diene-yne precursor and solvent based microwave Diels-Alder reaction

After surveying the literature it was determined exocyclic olefin installation could be accomplished with the use of thiophene-3-carbaldehyde, **3.02**, and triethyl phosphonoacetate, **3.01**, under Horner-Wadsworth-Emmons olefination conditions.<sup>56</sup> At 0 °C and with NaH as base, the reaction was completed in three hours to yield the product, **3.03**, in quantitative yield. The desired compound was confirmed via <sup>1</sup>H NMR with observance of the two resonances that appeared as doublets at 7.67 ppm and 6.26 ppm, each integrating to a single proton. Only the *trans* isomer was observed evidenced by a coupling constant of 15.9 Hz for both doublets. The next step in the diene-dienophile construction was conversion of the thiophene-3-acrylic ethyl ester, **3.03**, to the allylic alcohol, **3.04**.<sup>57</sup> The reduction of the ester to the desired alcohol was performed with use of three equivalents of diisobutyl aluminum hydride as a hydride source. A solution of thiophene-3-ethyl acrylate, **3.03**, was cooled to -78 °C and diisobutyl aluminum hydride added, keeping the temperature constant for forty five minutes. After quenching with an aqueous sodium potassium tartrate and purification, the thiophene-3-allylic alcohol, **3.04**, was collected in 75% yield. The penultimate synthetic manipulation was completion of the diene-dienophile substrate via tethering of an ester functionality. While there are many means to accomplish this transformation it was thought that the potentially reactive nature of the diene

and alkynyl substrates could complicate the step and, therefore, the mildest means available were chosen. Carbodiimide-mediated esterification showed capable of coupling cinnamyl alcohol and various alkynyl acids in previous work.<sup>55</sup> To accomplish the esterification of thiophene-3-allyl alcohol, **3.04**, and 3-phenyl propiolic acid, **3.05**, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide was chosen due to the advantageous purification ease when compared to the more commonly utilized *N,N'*-dicyclohexylcarbodiimide. Thiophene-3-allyl alcohol, **3.04**, and 3-phenyl propiolic, **3.05**, were dissolved in dichloromethane at room temperature and a catalytic amount of dimethylaminopyridine was added. When the solution was homogenous, an excess amount of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide was added in a single portion and the reaction stirred at room temperature overnight. After quenching the reaction, thiophene diene-yne, **3.06**, was isolated in 75% yield.

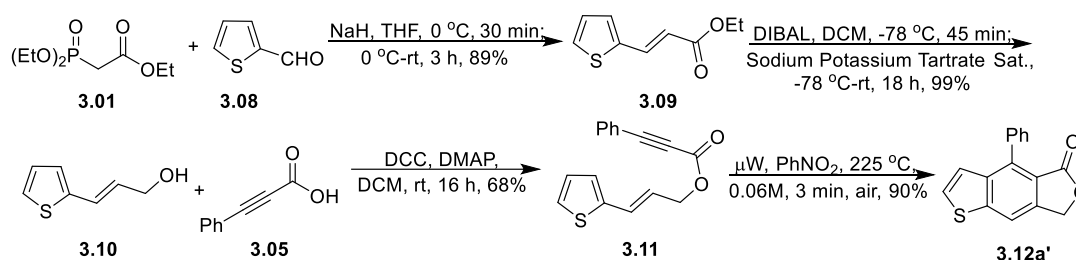
With the heterocyclic diene-yne substrate, (*E*)-3-(thiophen-3-yl) allyl 3-phenylpropiolate, **3.06**, in hand the solvent dependent IMDDA reaction of **3.06** was attempted. The use of nitrobenzene as solvent was first examined with the goal of forming the tricyclic aromatic benzo[b]thiophene lactone.<sup>55</sup> (*E*)-3-(Thiophen-3-yl) allyl 3-phenylpropiolate, **3.06**, was dissolved in nitrobenzene to a final concentration of 0.06 M and placed in an Anton Paar Monowave 300. The reaction solution was then heated to 225 °C for 3 minutes; during which time the solution changed from clear to an amber coloration. After purification, <sup>1</sup>H NMR analysis showed a singlet at 5.40 ppm integrating to two protons, belonging to the methylene of the lactone sub-moiety. All other <sup>1</sup>H NMR signals were within the aromatic region as expected; with the notable singlet from the single aromatic carbocycle at 7.93 ppm. Additional evidence for the product identity was obtained using HRMS (TOF MS ES+), and the *m/z* ratio found to be 266.0422. The IMDDA proved highly efficient, and the benzo[b]thiophene lactone, **3.07a**, was isolated in 96% yield.

With this promising result, the next iteration focused on elucidating conditions for the selective formation of the dihydrobenzo[b]thiophene. Dimethylformamide was chosen with the desire to form the tricyclic dihydrobenzo[b]thiophene lactone product **3.07b**. An Anton-Paar Monowave 300 was again used as the microwave source. (*E*)-3-(Thiophen-3-yl) allyl 3-phenylpropiolate, **3.06**, was dissolved in anhydrous DMF to a final concentration of 0.06 M. The reaction solution was then heated to 225 °C for 3 minutes, during which the solution changed from clear to an amber coloration. After purification and <sup>1</sup>H NMR analysis the annulation product, **3.07b** of the IMDDA reaction proved present. The product showed a substantially different NMR spectrum as compared to the benzo[b]thiophene lactone, **3.07a**. This was surmised based on five distinct signals in the <sup>1</sup>H NMR which are present in related dihydronaphthyl products previously identified: (1) two triplets belonging to the methylene lactone protons at 4.7 ppm and 4.03 ppm; (2) a multiplet belonging to the methine proton from 3.66-3.55 ppm; (3) a doublet of doublets at 3.13 ppm and a triplet at 2.66 ppm belonging to the methylene protons of the six-membered ring.<sup>55</sup> All signals integrate to a single proton, consistent with the above assignment.<sup>55</sup> This spectral data, along with HRMS (TOF MS ES+) mass which was found to be 268.0576 *m/z* ratio, offer compelling evidence that the IMDDA reaction was successful both with regard to utilizing the aromatic heterocycle thiophene, **3.06**, as a diene component and producing **3.07b** in 86% yield as 96:4 ratio of **3.07b**:**3.07a**, as the major product based on solvent selection. However, despite these promising initial results, a small amount of the fully aromatic benzo[b]thiophene lactone, **3.07a**, was observed. This side product is evidenced spectrally via <sup>1</sup>H NMR by a singlet at 5.40 ppm representing the aliphatic protons of the lactone moiety **3.07a**

Having established the viability of thiophene diene-yne **3.06** for use in the microwave-assisted IMDDA reaction and product selection based on solvent choice, the focus then shifted

to expand the substrate scope on two fronts: changing the position of the linear sub-segment to the C(2) carbon of the thiophene; and replacing the thiophene heterocycle with a furan moiety.

To construct the isomeric C(2) thiophene diene-yne, (*E*)-3-(thiophen-2-yl)allyl 3-phenylpropiolate, **3.11**, thiophene-2-carbaldehyde, **3.08**, was subjected to the same Horner-Wadsworth-Emmons olefination conditions which had successfully been employed for **3.02**.<sup>56</sup> At 0 °C triethyl phosphonoacetate, **3.01**, was deprotonated with NaH, thiophene-2-carbaldehyde, **3.08**, added dropwise, the reaction warmed to room temperature and stirred for three hours to yield the thiophen-2-ethyl acrylate, **3.09**, in 89% yield. Reduction to the allylic alcohol, **3.10**, was accomplished with diisobutyl aluminum hydride at -78 °C followed by quenching and vigorous stirring with half saturated aqueous solution of sodium potassium



**Figure 55** Synthetic scheme of thiophene(C2) diene-yne precursor and microwave Diels-Alder reaction

tartrate overnight.<sup>57</sup> After purification, the alcohol, **3.10**, was obtained in 99% yield. *N,N'*-dicyclohexylcarbodiimide mediated esterification with thiophene-2-allyl alcohol, **3.10**, and 3-phenyl propionic acid, **3.05**, with dimethylaminopyridine as activation catalyst successfully led to (*E*)-3-(thiophen-2-yl)allyl 3-phenylpropiolate, **3.11**, in 68% yield.

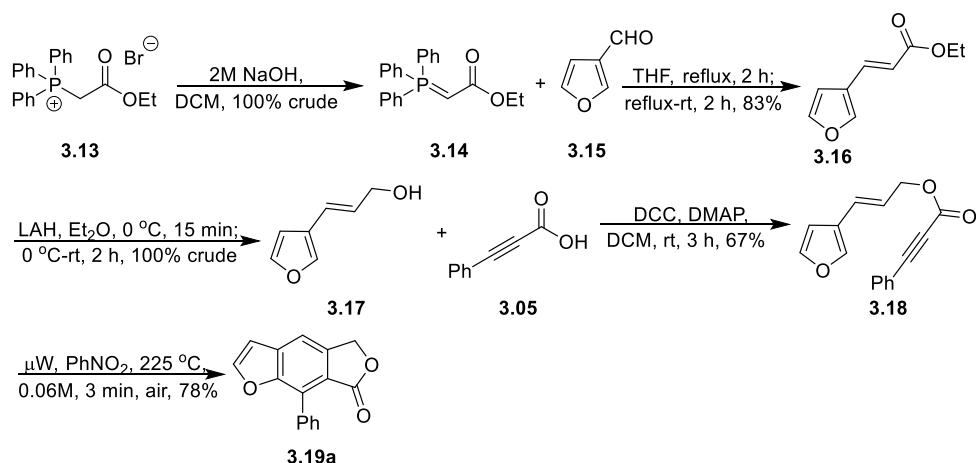
With the thiophene **3.11** in hand, the product selection in the microwave-assisted IMDDA reaction from solvent choice was evaluated. Performing the IMDDA reaction with (*E*)-3-(thiophen-2-yl)allyl 3-phenylpropiolate, **3.11**, in nitrobenzene, 0.06 M, heating with an Anton Paar Monowave 300 (225 °C) produced the fully aromatic benzo[b]thiophene lactone, **3.12a'**, in 90% yield. The observance of a singlet at 5.40 ppm with an integration value of two

as well as a singlet at 7.93 ppm corresponding to the lone aromatic carbocycle proton supported the desired product assignment. This was further corroborated with HRMS (TOF MS ES+).

Thiophene diene-yne isomers **3.06** and **3.11** proved successful in undergoing the microwave-assisted IMDDA reaction. Performing the IMDDA reaction of **3.06** and **3.11** in nitrobenzene yielded the fully aromatic benzo[b]thiophenes **3.07a**, 96% yield, and **3.12a'**, 90% yield, in short reaction times and as the only observed product.

We next opted to broaden the substrate of the IMDDA. Having shown that a single alkene belonging to the thiophene heterocycle could participate as a portion of the diene, furan heterocycle was considered to perhaps exhibit similar reactivity as part of a diene within the IMDDA. Hence, construction began to synthesize a furan diene-yne substrate with an ester tether linking diene and dienophile. The synthetic route employed in the construction of the previous thiophene examples was followed, however; when minor reaction differences were found within the literature these took precedent when applicable.

To begin the substrate synthesis, Wittig reaction conditions were employed. The phosphine Wittig reagent was generated by the reaction of triphenyl phosphine with ethyl 2-



bromoacetate in toluene at room temperature.<sup>58</sup>

Almost immediately a white precipitate

formed on the walls of the

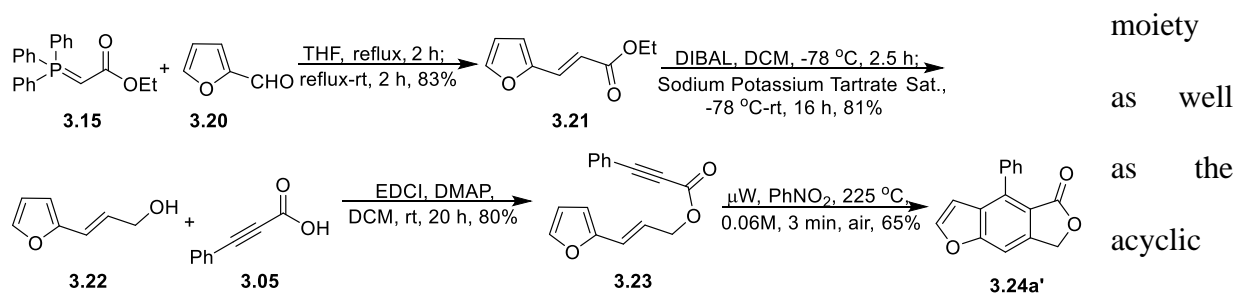
**Figure 56** Synthetic scheme of furan(C3) diene-yne precursor and microwave Diels-Alder reaction

flask. The reaction was stirred at room temperature overnight and analysis of the precipitate

was consistent with literature reports. The olefination reaction using Wittig conditions was then commenced.<sup>59</sup> First, deprotonation of the phosphonium bromide salt, **3.13**, to the nucleophilic ylide, **3.14**, was easily accomplished by washing the salt with 2 M sodium hydroxide, and extraction with dichloromethane. Upon solvent removal the beige solid Wittig reagent, **3.14**, was used in the next step without purification. The phosphorus ylide, **3.14**, was dissolved at room temperature in tetrahydrofuran and the solution warmed to reflux. Once at refluxing temperature, furan-3-carbaldehyde, **3.15**, was added dropwise into the solution and kept at the reflux temperature for two hours after which it was cooled to room temperature. After purification, ethyl (*E*)-3-(furan-3-yl)acrylate, **3.16**, was obtained in 83% yield. The *Z*-isomer was observed in 1% yield. Reduction to the allylic alcohol was accomplished with treatment of ethyl (*E*)-3-(furan-3-yl)acrylate, **3.16**, with lithium aluminum hydride at room temperature.<sup>59</sup> (*E*)-3-(Furan-3-yl)prop2-en-1-ol, **3.17**, was recovered in quantitative yield and the crude product proved very pure with no further purification carried out. With the allylic alcohol, **3.17**, in hand, installation of the alkynyl dienophile via ester linkage was required. The esterification was performed with addition of the allylic alcohol, **3.17**, 3-phenyl propiolic acid, **3.05**, and a catalytic amount of dimethylaminopyridine to a round bottom flask followed by solvation with dichloromethane. When the reaction solution was homogenous the esterifying reagent, *N,N'*-dicyclohexylcarbodiimide, was added in a single portion; changing the reaction solution from clear to dark brown. The reaction was stirred at room temperature for three hours after which the solution was poured directly onto a silica gel plug and the products eluted with diethyl ether. After purification, (*E*)-3-(furan-3-yl)allyl 3-phenylpropiolate, **3.18**, was collected as a white solid in 67% yield. The furan diene-yne substrate, (*E*)-3-(furan-3-yl)allyl 3-phenylpropiolate, **3.18**, was now primed to attempt the IMDDA reaction. The successful reaction conditions employed for annulation of the thiophene diene-yne were thought feasible for the furan

substrate. Motivated by the high rate of success in formation of fully aromatic fused cycles, the microwave-assisted IMDDA reaction in neat nitrobenzene furan diene-yne, **3.18**, was first assessed. **3.18** was added to a microwave vial and nitrobenzene added to the desired concentration of 0.06 M. The reaction solution was heated to 225 °C over 3 minutes and held at 225 °C for 3 minutes with an Anton Paar Monowave 300. This produced the fully aromatic benzo[b]furan lactone, **3.19a**, in a 78% yield. The observance of a singlet at 5.40 ppm with an integration value of two as well as a singlet at 7.93 ppm corresponding to the lone aromatic carbocycle proton supported the desired product presence. The formation of **3.19a** was further reinforced with HR MS (TOF MS ES+)  $m/z$  ratio found 250.0630.

With the moderate success of benzo[b]furan annulation product, **3.19a**, via the microwave-assisted IMDDA reaction, the variance of the position of the acyclic framework to the C(2) of the furan ring commenced. The same synthetic approach used in the previous example was done starting from furan-2-carbaldehyde, **3.20**, to yield ethyl (*E*)-3-(furan-2-yl)acrylate, **3.21** in 83% yield.<sup>59</sup> The transformation to the allylic alcohol was accomplished using lithium aluminum hydride as reductant, having the reaction completed in 1.5 h at room temperature. Analysis of the crude material showed conversion to (*E*)-3-(furan-2-yl)prop-2-en-1-ol, **3.22**. However, a significant amount of over reduction occurred reducing both the ester moiety



**Figure 57** Synthetic scheme of furan(C2) diene-yne precursor and microwave Diels-Alder reaction as well as the acyclic alkene to the fully saturated alcohol. In subsequent reductions, diisobutyl aluminum hydride was used as reductant alleviating the reduction of the acyclic olefin, recovering **3.22** in 81%. Purification

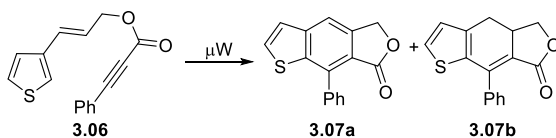


issues were encountered when performing previous esterification reactions with *N,N'*-dicyclohexylcarbodiimide, therefore, to obtain (*E*)-3-(furan-2-yl)allyl 3-phenylpropiolate, **3.23**, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide was supplemented for use. After charging a round bottom flask with **3.22** and **3.05** and dissolving the contents with dichloromethane, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide was added in a single portion and the reaction stirred for 20 hours at room temperature. Upon purification, **3.23** was obtained in 80% yield as a clear oil.

Performing the IMDDA reaction with (*E*)-3-(furan-2-yl)allyl 3-phenylpropiolate, **3.23**, in nitrobenzene, 0.06 M, with an Anton Paar Monowave 300 via ramping to 225 °C in 3 minutes and heating at 225 °C for 3 minutes produced the fully aromatic benzo[b]furan lactone, **3.24a'**, in 65% yield. The observance of a singlet at 5.38 ppm with an integration value of two as well as a singlet at 7.73 ppm corresponding to the lone aromatic carbocycle proton supported the presence of the desired product. This was further corroborated with HRMS (TOF MS ES+) *m/z* ratio found to be 250.0607.

The promising results of both the thiophene and furan substrates prompted further examination of solvent as to assess the role in the selective formation of the dihydro-annulation products versus the fully aromatic cycles in the microwave-assisted IMDDA reaction. Thiophene-3 substrate, **3.06**, was selected due to the higher degree of success in terms of yields from the previous experiments. Beginning, *ortho*-dichlorobenzene was selected, in part to the high boiling point as well as complete selectivity in formation of the naphthalene product with a full carbon tether.<sup>54</sup> The IMDDA reaction was performed with **3.06** varying both the temperature and the time of the reaction. All experiments gave mixtures of **3.07a:3.07b**, entries 1-5, **Table 1**. Some trends did emerge; lowering the temperature from 225 °C to 180 °C resulted in a lower ratio of **3.07a:3.07b**. Lowering the reaction temperature further to 150 °C

slowed the formation of product resulting in large amount of unreacted starting material, while still producing a similar 1:2 mixture of **3.07a**:**3.07b**. Upon lowering the reaction temperature to 120 °C, the reaction time was pushed to one hour in order for the products **3.07a** and **3.07b** to begin to eclipse the unreacted **3.06** as the major components in the experiment while still yielding sub-par selectivity. When changing the reaction solvent to 1,2-dichloroethane, similar



Entry <sup>a</sup>	[M]	Solvent	Conditions	3.06:3.07a:3.07b ratio <sup>b</sup>
1	[.06]	<i>o</i> -DCB	225 °C, 3 m	0:23:77
2	[.06]	<i>o</i> -DCB	180 °C, 3 m	0:34:66 <sup>c</sup>
3	[.06]	<i>o</i> -DCB	150 °C, 10 m	25:25:50
4	[.06]	<i>o</i> -DCB	120 °C, 10 m	83:5:12
5	[.06]	<i>o</i> -DCB	120 °C, 1 h	32:26:42
6	[.06]	1,2-DCE	120 °C, 1.5 h	27:33:41
7	[.06]	1,2-DCE	120 °C, 5 h	0:62:38
8	[.06]	20% PhNO <sub>2</sub> / <i>o</i> -DCB(v/v)	225 °C, 10 m	0:99:1
9	[.06]	10% PhNO <sub>2</sub> / <i>o</i> -DCB(v/v)	225 °C, 10 m	2:95:3
10	[.06]	10% PhNO <sub>2</sub> / <i>o</i> -DCB(v/v)	225 °C, 20 m	0:97:3
11	[.06]	5% PhNO <sub>2</sub> / <i>o</i> -DCB(v/v)	225 °C, 40 m	0:93:7

a) Reaction performed in Anton-Paar Monowave 300 microwave reactor

b) Ratios determined via integration of <sup>1</sup>H NMR of methylene lactone signals, pure yields not determined

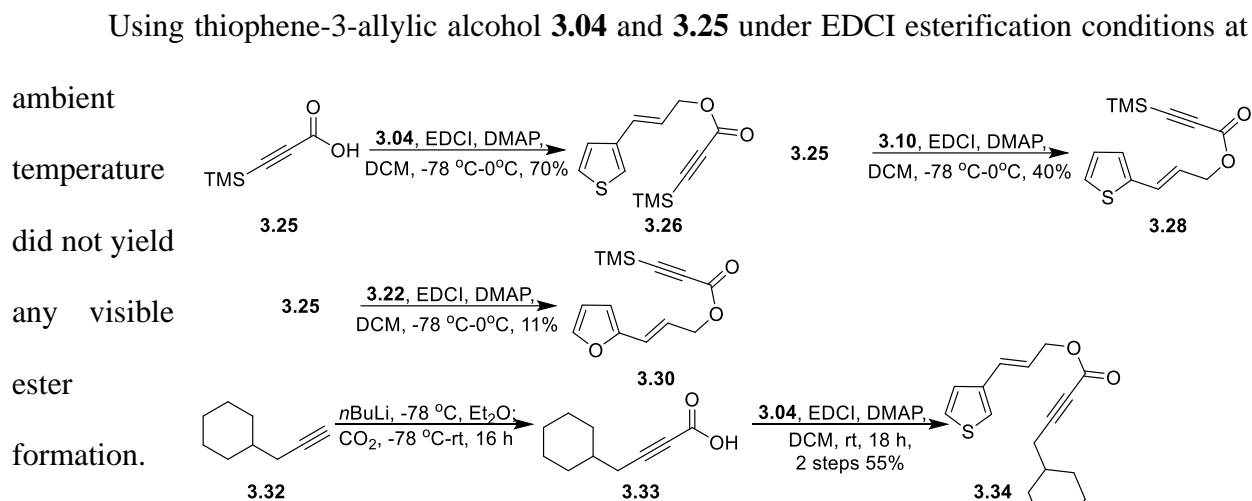
c) Average ratio of two experiments **3.07a**:**3.07b** (37:63), (31:69)

**Table 1** Exploration of solvent role in product determination on (*E*)-3-(thiophen-3-yl)allyl 3-phenylpropiolate

results were observed when attempting the IMDDA reaction of **3.06** at 120 °C, entry 6 **Table 1**. A strikingly similar ratio was observed when heating **3.06** at 120 °C in 1,2-DCE for 1.5 hours as to that of *o*-DCB for 1 hour; the distribution of **3.07b** remained the same while a slightly larger amount of **3.07a** observed. The IMDDA reaction took 5 hours to be fully consumed of **3.06**, entry 7 **Table 1**, favoring the formation of **3.07a**. Although the use of *o*-DCB and 1,2-DCE did not prove fruitful in allowing product selectivity for the microwave-assisted IMDDA, a desire to determine the lowest necessary amount of nitrobenzene while still allowing selective formation of the aromatic Diels-Alder products remained. An amount of 20% nitrobenzene/*o*-

dichlorobenzene solution was found suitable for selective formation of the naphthalene lactone.<sup>55</sup> Thiophene-3, **3.06**, was heated at 225 °C for ten minutes in a 20% nitrobenzene/*o*-dichlorobenzene solution and proved very promising in delivering the fully aromatic benzo[b]thiophene **3.07a** with near complete selectivity, entry 8 **Table 1**. Lowering nitrobenzene to 10% volume and heating at 225 °C for ten minutes led to a small amount of starting material remaining. Extending the reaction time to twenty minutes completed the reaction and only slightly reduced the selectivity of product distribution to **3.07a:3.07b**, 97:3 ratio, entries 9 and 10 **Table 1**. Further lowering the nitrobenzene to 5% volume solution and extending the reaction time to forty minutes produced a ratio of **3.07a:3.07b**, 93:7, entry 11 **Table 1**, which was thought to be less satisfactory than those previously done. Therefore, with all variables of the reaction conditions in mind, it was determined that a 10% nitrobenzene/*o*-dichlorobenzene solvent was the appropriate condition to further study the scope the IMDDA reaction. Thiophene-3, **3.06**, was heated at 225 °C in 10% nitrobenzene/*o*-dichlorobenzene for twenty minutes. Upon removal of solvent and purification with column chromatography, IMDDA product was obtained in an 86% yield with the fully aromatic benzo[b]thiophene the major compound as a 96:4 ratio of **3.07a:3.07b**, entry 1 **Table 2**.

Having established optimized conditions for the achievement of fully aromatic annulation product as well as a lower overall volume of nitrobenzene, efforts were then set forth to expand the substrate scope in two differing respects: (1) replacing the R- group on the terminus of the alkynyl dienophile and (2) alteration of heteroatom within the linker segment of the substrate. Having achieved good results with ester **3.06** to benzo[b]thiophene **3.07a** via  $\mu$ W heating at 225 °C for twenty minutes using a 10% nitrobenzene/*o*-dichlorobenzene (*v/v*) solution the construction of a trimethylsilane alkynyl terminus as well as an aliphatic alkynyl terminus commenced.

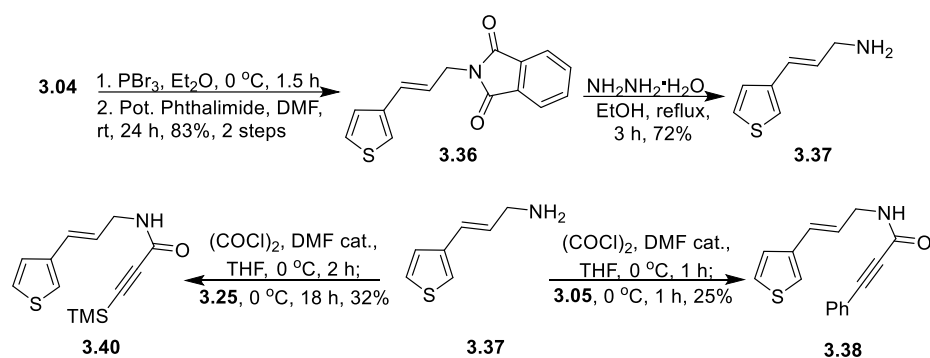


To

**Figure 58** Synthetic scheme toward functional variation of ester tether diene-yne Diels-Alder substrates accomplish

the esterification the entire flask contents were solvated in dichloromethane at room temperature then lowered to  $-78\text{ }^{\circ}\text{C}$ . Once the solution was sufficiently cooled the septa was removed and EDCI added in a single portion. The reaction solution was allowed to warm to  $0\text{ }^{\circ}\text{C}$  at which point the reaction was quenched. After purification the desired ester **3.26** was obtained in 70% yield. This synthetic procedure was repeated to produce C(2) analogs. The use of **3.10** and **3.25** produced **3.28** in moderate yield of 40%. The furan-2-allylic alcohol, **3.22**, proved less successful, producing **3.30** in only 11%. **3.30** proved highly unstable and decomposed rapidly at room temperature even upon immediate purification. The aliphatic ester **3.34** was obtained in three steps, starting from alkyne **3.32**. **3.32** was deprotonated with *n*-butyl lithium and carbon dioxide added, readily forming the alkynyl carboxylate.<sup>66</sup> Quenching with 1 M HCl produced **3.33** as a white solid. Esterification was achieved again with **3.04** and **3.33** using EDCI under ambient temperature. After purification the desired ester **3.34** was obtained in 55% yield over the two steps.

The installation of an amide tether linking the heterocyclic diene to the dienophile proved more exacting in terms of synthetic utility. Due to the facile approach to **3.04**, it was thought that the alcohol could be directly converted to the corresponding amine under Mitsunobu reaction conditions. However, after attempting the reaction and scrutinizing the products there was a peculiar new set of signals appeared in the  $^1\text{H}$  NMR. The new set of signals appeared to show terminal vinyl functionality. What is proposed to have occurred rather



than substitution at the carbinol carbon was in fact a  $\text{S}_{\text{N}}2'$  and rearrangement of the olefin. From this a more classic approach to nitrogen

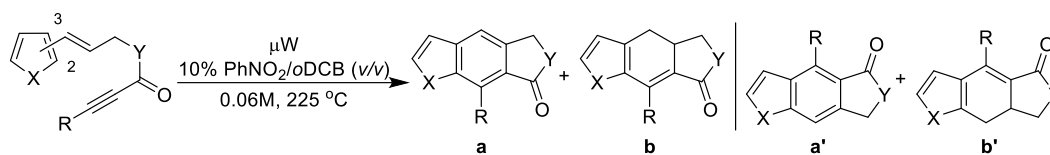
**Figure 59** Synthetic scheme toward functional variation of amide tether diene-yne Diels-Alder substrates

installation was attempted in the form of the Gabriel aniline synthesis.<sup>60</sup> To ready **3.04** for direct nucleophilic attack, the allylic alcohol was first converted to the corresponding allylic bromide with phosphorus tribromide at  $0^\circ\text{C}$ .<sup>60</sup> The bromination was monitored via TLC and proceeded without incident, however, the allylic bromide was not further purified after quenching rather proceeding with the crude product due to potential stability issues. Moving to nitrogen installation the crude thiophene-3-allylic bromide was solvated in anhydrous DMF and in a single portion potassium phthalimide added.<sup>60</sup> The reaction was stirred at room temperature for twenty four hours. The allylic phthalimide, **3.36**, was then purified and obtained in 83% yield over the two steps. Freeing the nitrogen was accomplished by refluxing **3.36** in ethanol with hydrazine for three hours.<sup>60</sup> The phthalazide by-product began to precipitate out of the refluxing solution after an hour and proved difficult to separate from the allylic amine **3.37**. It was found

that after solvating the reaction solution in a 1:1 water:methanol solution followed by multiple extractions with dichloromethane crude **3.37** could be obtained with very little phthalazide present. The last synthetic step prior to the IMDDA was linking the heterocyclic diene and the dienophile via amide functionality. The preferred approach of amidation was conversion the alkynyl carboxylic acid first to the acid chloride followed by the addition of **3.37**.<sup>61</sup> Conversion to the acid chloride was achieved by addition of **3.05** and oxalyl chloride with a catalytic amount of dimethylformamide at zero degrees. This was then followed by dropwise addition of **3.37** to the solution which caused the solution color to change from clear to yellow. After quenching and purification the desired amide, **3.38**, was obtained in a poor 25%. The same synthetic approach was taken with regard to the carboxylic acid **3.25** to obtain amide **3.40** in a 32% yield.

With the dienophile portion installed, the esters were ready for assessment in the microwave-assisted intramolecular Diels-Alder reaction. The substrates were solvated with 10% nitrobenzene/*o*-dichlorobenzene (*v/v*) solution to a 0.06 M concentration and heated at 225 °C. The reaction was monitored via TLC until completion, 20-80 minutes. All substrates underwent the intramolecular Diels-Alder reaction forming the fully aromatic benzo[b]thiophene lactone derivatives as major products in good yields. These exact reaction conditions and results are summarized in entries 1-5 **Table 2**.

Amides **3.39** and **3.40** were also examined in the microwave-assisted intramolecular Diels-Alder reaction. The amides were solvated with 10% nitrobenzene/*o*-dichlorobenzene (*v/v*) solution to a 0.06 M concentration and heated at 225 °C. The reactions were monitored via TLC until completion, 30 minutes. Both substrates underwent the intramolecular Diels-Alder reaction forming the fully aromatic benzo[b]thiophene lactam derivatives as major products in good yields. These exact reaction conditions and results are summarized in entries 6



Entry	Substrate	X	C(2/3)	Y	R	time	Yield	Proda:b ratio
1	<b>3.06</b>	S	3	O	Ph	20 m	86%	<b>3.07a:b</b> (96:4)
2	<b>3.26</b>	S	3	O	TMS	20 m	71%	<b>3.27a:b</b> (99:1)
3	<b>3.28</b>	S	2	O	TMS	20 m	86%	<b>3.29a':b'</b> (100:0)
4	<b>3.30</b>	O	2	O	TMS	20 m	42%	<b>3.31a':b'</b> (100:0)
5	<b>3.34</b>	S	3	O	CH <sub>2</sub> Cy	80 m	71%	<b>3.35a:b</b> (99:1)
6	<b>3.38</b>	S	3	N	Ph	30 m	82%	<b>3.39a:b</b> (95:5)
7	<b>3.40</b>	S	3	N	TMS	30 m	74%	<b>3.41a:b</b> (99:1)

a) reaction performed in Anton-Paar Monowave 300 microwave reactor

**Table 2** Summary of results in opt. aromatic annulation conditions

and **7 Table 2**. The microwave-assisted intramolecular dehydro-Diels-Alder reaction showed a high tolerance toward functional variation of the alkynyl terminus and heteroatom linker, albeit with varying time components associated with specific substrates. Both esters and amides offered compatible functional linkers to the heterocyclic diene-dienophile subcomponents. These ester/amide analogs also showed strikingly similar yields when the equivalent R- group functionalities present. One may conclude that the more demanding structural variable for the microwave-assisted IMDDA reaction is the functional group present on the alkyne terminus rather than the chosen heteroatom linker.

In continuation of studies focusing on conditions to allow for the selective formation of the dihydrobenzo[b]thiophene IMDDA products, attention was again focused on the use of DMF as a solvent. Having already demonstrated that the microwave-assisted IMDDA reaction will produce the dihydrobenzo[b]thiophene **3.07b**, entry 1 **Table 3**, as the major product in good yields from diene-yne **3.06**, the next step was varying the structural scope of the heterocyclic diene-dienophile. To start, (*E*)-3-(thiophen-2-yl)allyl 3-phenylpropiolate, **3.11**, was solvated in DMF to a final concentration of 0.06 M and heated to 225 °C. Upon removal of solvent and purification of the residue, it was determined by column chromatography that (*E*)-3-(thiophen-2-yl)allyl 3-phenylpropiolate, **3.11**, successfully underwent the IMDDA reaction

forming the dihydrobenzo[b]thiophene lactone, **3.12b'**, in a 58% yield, entry 2 **Table 3**. The <sup>1</sup>H NMR confirmed the formation of dihydrobenzo[b]thiophene lactone, **3.12b'**. Observed were two triplets belonging to the methylene lactone protons at 4.70 ppm and 4.03 ppm, a multiplet signal belonging to the methine proton from 3.70-3.60 ppm, and a doublet of doublets at 3.20 ppm and a triplet at 2.80 ppm belonging to the methylene protons of the six membered ring. Similarly, this reaction produced a mixture of dihydrobenzo[b]thiophene lactone, **3.12b'**, and benzo[b]thiophene lactone, **3.12a'**, in an improved 97:3 (**3.12b'**:**3.12a'**) ratio.

To assess the utility of (*E*)-3-(furan-3-yl)allyl 3-phenylpropiolate, **3.18**, to form the dihydrobenzo[b]furan product, dimethylformamide was again selected as solvent. **3.18** was dissolved to a final concentration of 0.06 M with dimethylformamide and heated; ramping to 225 °C in 3 minutes then holding at 225 °C for 3 minutes with an Anton Paar Monowave 300. Upon removal of solvent and purification of the reaction material it was determined that **3.18** successfully underwent the IMDDA reaction forming the dihydrobenzo[b]thiophene lactone **3.19b** in the low isolated yield of 36%, entry 3 **Table 3**. The structure of **3.19b** was confirmed to be the dihydrobenzo[b]furan lactone based on the distinguishable signature of the aliphatic protons as seen in previous reactions which produced similar dihydro-Diels-Alder adducts; two diastereomeric methylene protons of the lactone segment displayed as triplets at 4.70 ppm and 4.04 ppm, and a methine proton multiplet appeared at 3.72-3.60 ppm. The remaining protons of the six-membered ring showed as doublet of doublets at 2.96 ppm followed by a triplet at 2.63 ppm. All signals integrated to a single proton. Although the outcome of formation of the dihydrobenzo[b]furan lactone **3.19b** was poor, the results are further complicated by a high degree of formation of the fully aromatic benzo[b]furan lactone **3.19a**, which after removal of solvent was determined to be in a ratio of 88:12 (**3.19b**:**3.19a**) in the low yield of 36%. The

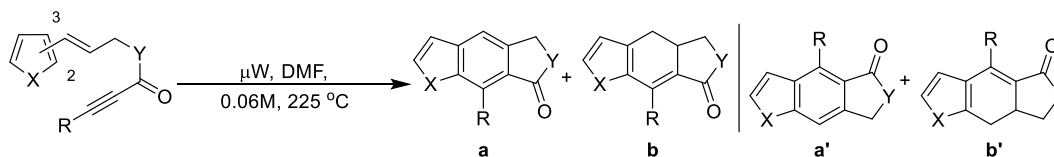


formation of **3.19b** was further reinforced with HR MS (TOF MS ES+)  $m/z$  ratio found 253.0888

(*E*)-3-(Furan-2-yl)allyl 3-phenylpropiolate, **3.23**, was now ready to undergo the microwave-assisted IMDDA reaction. To assess the viability of the IMDDA reaction with **3.23** to afford dihydrobenzo[*b*]furan lactone, **3.24b'**, dimethylformamide was chosen as solvent. **3.23**, was added to a microwave vial and solvated with dimethylformamide to a final concentration of 0.06 M. The reaction solution was heated at 225 °C for 3 minutes with an Anton Paar Monowave 300, ramp time 3 minutes. The IMDDA reaction proved successful with **3.23** as substrate to afford the dihydrobenzo[*b*]furan lactone **3.24b'** in a 41% yield, entry 4 **Table 3**. Like with previous dimethylformamide iterations the presence of the fully aromatic **3.24a'** was observed favoring dihydrobenzo[*b*]furan lactone; product in a 95:5 ratio of (**3.24b'**:**3.24a'**). The <sup>1</sup>H NMR exhibited the previously observed pattern of aliphatic protons indicating the dihydro-product, this was further reinforced with HR MS (TOF MS ES+) finding and  $m/z$  of 253.0892.

Diene-yne **3.34** was solvated in DMF to a final concentration of 0.06M. The solution was then heated at 225 °C for 3 minutes. Monitoring the reaction via TLC showed that a large amount of **3.34** remained, as a result the reaction was heated further, 15 minutes total, until all starting material was consumed. After purification, <sup>1</sup>H NMR showed that indeed the reaction conditions successfully produced the dihydrobenzo[*b*]thiophene product indicated by the familiar signal pattern encountered with previous dihydro-annulation products. The observed <sup>1</sup>H NMR signals were as follows: a one-H triplet at 4.63 ppm and a one-H triplet at 3.96 ppm (corresponding to the lactone protons) and a one-H multiplet at 3.39-3.29 ppm belonging to the tertiary carbon of the fused ring system. A two-hydrogen multiplet ranging from 3.09-3.01 ppm was observed and can be rationalized as the overlap of the axial hydrogen on the methylene

carbon of the newly formed ring and a hydrogen belonging to the acyclic methylene carbon of the aliphatic R- group. The next signal was a previously unobserved one hydrogen multiplet at 2.79-2.73 ppm; this signal belongs to the remaining hydrogen from the acyclic methylene carbon of the aliphatic R- group. A one hydrogen triplet was observed at 2.50 ppm and is part of the methylene carbon on the new six membered ring. The final signals belonging to the cyclohexyl protons of the aliphatic R- group, the first observed was a six hydrogen multiplet at 1.71-1.62 ppm and the second a five hydrogen multiplet at 1.28-1.14 ppm. The dihydrobenzo[b]thiophene product **3.35b** was isolated in a good yield of 71%, entry 5 **Table 3**, in a ratio of 93:7 (**3.35b**:**3.35a**).



Entry <sup>a</sup>	Substrate	X	C(2/3)	Y	R	time	Yield	Proda:b ratio
1	<b>3.06</b>	S	3	O	Ph	3 m	86%	<b>3.07a</b> : <b>b</b> (4:96)
2	<b>3.11</b>	S	2	O	Ph	3 m	58%	<b>3.12a'</b> : <b>b'</b> (3:97)
3	<b>3.18</b>	O	3	O	Ph	3 m	36%	<b>3.19a</b> : <b>b</b> (12:88)
4	<b>3.23</b>	O	2	O	Ph	3 m	41%	<b>3.24a'</b> : <b>b'</b> (5:95)
5	<b>3.26</b>	S	3	O	TMS	3 m	48%	<b>3.27a</b> : <b>b</b> (12:88) <sup>b</sup>
6	<b>3.34</b>	S	3	O	CH <sub>2</sub> Cy	15 m	71%	<b>3.35a</b> : <b>b</b> (7:93)

a) reaction performed in Anton-Paar Monowave 300 microwave reactor

b) Desilylated products

**Table 3** Summary of results with DMF as reaction solvent

Moving from the aliphatic R- group on the alkynyl terminus to the trimethyl silane of **3.26** preliminary reaction conditions were assessed to afford the silylated dihydrobenzo[b]thiophene annulation product. Following previously administered reaction parameters, **3.26** was solvated in DMF to a final concentration of 0.06 M. The reaction solution was then heated at 225 °C and the progress of the reaction monitored via TLC. After three minutes of microwave heating, complete consumption of starting materials was shown. After subsequent purification of presumed desired product, scrutiny of the <sup>1</sup>H NMR showed differently. The typically observed signals of the dihydroannulation skeleton were observed,

yet, there was no signal representative of the trimethylsilyl group. Instead a new signal was observed in the aromatic region of the  $^1\text{H}$  NMR at 7.44 ppm integrating to a single hydrogen. The yield for the product was low as well, and only 48% of the desilylated dihydrobenzo[b]thiophene product was recovered, entry 6 **Table 3**. A substantial amount of the fully aromatic desilylated benzo[b]thiophene product was observed though, favoring dihydro product in a 88:12 ratio, **3.27b:3.27a**. It was clear that the reaction conditions had caused desilylation of the substrate. A summation of the IMDDA reactions can be seen in **Table 3**.

## CONCLUSION

The above work has provided further applicable scope to the microwave-assisted dehydro-Diels-Alder reaction in attainment of several benzofused heterocyclic lactones and lactams. The reactions were completed in short times and in most cases high yields as when compared with conventional thermal heating methods. The major product selectivity of the resulting tricycles was based on solvent employed during the reaction. The reaction tolerated a range of terminal substitutions on the alkyne dienophile. The reaction proved successful when the diene-dienophile employed both ester and amide tethers forming the corresponding fused lactone/lactam in good yields. The microwave- assisted intramolecular dehydro-Diels-Alder reaction represents a simple means to access highly substituted benzo[b]thiophenes and benzo[b]furans.

## APPENDIX A

### SUPPORTING INFORMATION

#### A.1 CHEMICAL CHARACTERIZATION CHECKLIST

Compound, structure, or table-entry number	New	Known	Melting point range	IR	1H NMR	13C NMR	NMR	MS	HRMS	Copy of 1H/13C NMR spectrum in SI*
3.03		x			x	x				x
3.04		x			x	x				x
3.06	x			x	x	x			x	x
3.07a	x			x	x	x			x	x
3.07b	x			x	x	x			x	x
3.09		x			x	x				x
3.10		x			x	x				x
3.11	x			x	x	x			x	x
3.12a'	x			x	x	x			x	x
3.12b'	x			x	x	x			x	x
3.16		x			x	x				x
3.17		x			x	x				x
3.18	x			x	x	x			x	x
3.19a	x			x	x	x			x	x
3.19b	x			x	x	x			x	x

3.21		x			x	x				x
3.22		x			x	x				x
3.23	x			x	x	x			x	x
3.24a'	x			x	x	x			x	x
3.24b'	x			x	x	x			x	x
3.26	x			x	x	x			x	x
3.27a	x			x	x	x			x	x
3.27b	x			x	x	x			x	x
3.28	x			x	x	x			x	x
3.29a'	x			x	x	x			x	x
3.30	x			x	x	x			x	x
3.31a'	x			x	x	x			x	x
3.34	x			x	x	x			x	x
3.35a	x			x	x	x			x	x
3.35b	x			x	x	x			x	x
3.36	x			x	x	x			x	x
3.37	x			x	x	x			x	x
3.38	x			x	x	x			x	x
3.39a	x			x	x	x			x	x
3.40	x			x	x	x			x	x
3.41a	x			x	x	x			x	x

**Table 4** Chemical characterization checklist

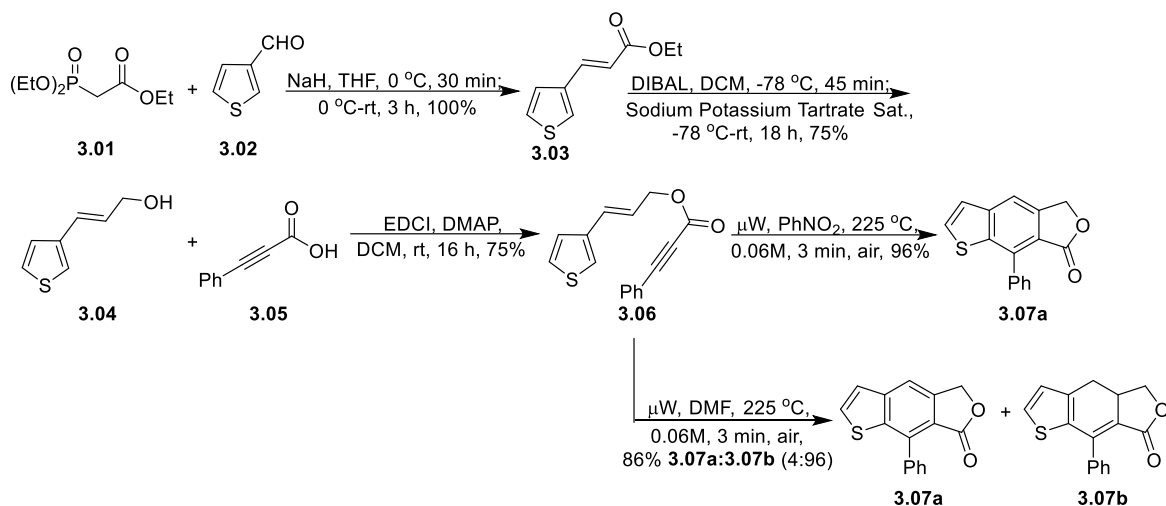
## A.2 GENERAL METHODS

Unless otherwise noted, all reactions were performed in flame-dried glassware sealed with rubber septa under a nitrogen atmosphere, and the reaction mixtures were stirred with a Teflon-coated magnetic stir bar. Liquid reagents and solvents were transferred via syringe and cannula using standard techniques. The reaction solvents tetrahydrofuran (THF), dichloromethane (DCM), and diethyl ether (Et<sub>2</sub>O) were dried by passage over a column of activated alumina using the Sol-Tek ST-002 solvent purification system; toluene was freshly distilled over calcium hydride prior to use. Chloroform and anhydrous *N,N*-dimethylformamide (DMF) were purchased from Aldrich Chemical Co and used as received. All other solvents and reagents were used as received unless otherwise noted. Reaction temperatures above 23 °C refer to oil bath temperature, which was controlled by an IKAmag temperature modulator. Reaction progress was monitored by thin layer chromatography (TLC) using EMD Chemicals Silica Gel 60 F254 glass plates (250 μm thickness) and visualized by UV irradiation (at 254 nm) and KMnO<sub>4</sub> staining. Purification of the compounds by flash column chromatography (FCC) was performed using silica gel (32-63 μm particle size, 60 Å pore size) purchased from Silicycle. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on Bruker Avance 300 MHz, 400 MHz, or 500 MHz spectrometers. <sup>1</sup>H and <sup>13</sup>C chemical shifts (δ) are reported relative to the solvent signal, CHCl<sub>3</sub> (δ = 7.26 for <sup>1</sup>H NMR and δ = 77.00 for <sup>13</sup>C NMR). Data are reported as follows: chemical shift (multiplicity, coupling constants where applicable, number of hydrogens). The following abbreviations are used to denote multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet; b, broad. Coupling constants, *J*, are reported in hertz (Hz). All NMR spectra were obtained at room temperature (RT) unless otherwise specified. IR spectra were recorded on a Nicolet Avatar E.S.P. 360 spectrometer and are reported in frequency of

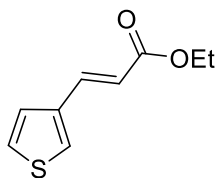
absorption ( $\text{cm}^{-1}$ ). Only selected IR peaks are reported. High-resolution mass spectral data were obtained from the University of Pittsburgh, Department of Chemistry Mass Spectral Facility. References located after compound names refer to literature protocols for the preparation of these or similar compounds by comparable methodology. All microwave heating was performed using an Anton Paar MonoWave 300 and heating monitored using an internal IR sensor.



### A.3 COMPOUND SYNTHESIS



**Figure 60** Synthetic scheme of thiophene(C3) dien-yne precursor and solvent based microwave Diels-Alder reaction



**Ethyl (E)-3-(thiophen-2-yl)acrylate (3.03).** In a manner entirely analogous to that previously reported,<sup>56</sup> a single-necked 250 mL round-bottomed flask equipped with a septum, magnetic stirring bar of dimension 150 mm by 100 mm, and nitrogen inlet was flame-dried and allowed to cool. The rubber septum was briefly removed, and the flask was charged with sodium hydride (960 mg of a 60% dispersion in mineral oil, 24 mmol) and tetrahydrofuran (80 mL). The mixture was cooled to 0 °C (bath temperature) in an ice bath, and triethyl phosphonoacetate (**3.01**, 4.4 mL, 22.2 mmol) was added drop wise via syringe (approximately 10 min). After the addition was complete, the reaction was stirred at 0 °C for an additional 30 min. Thiophene-3-carbaldehyde (**3.02**, 1.6 mL, 17.8 mmol) was added drop wise via syringe (approximately 10 min). During the course of the addition, the solution color became opaque-white. The reaction

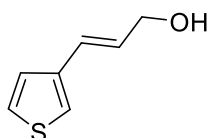
temperature was maintained at 0 °C for 15 min, then removed from the ice bath and allowed to warm to rt. The progress of the reaction was monitored by TLC. After 3 h, the reaction was transferred to a separatory funnel, diluted with diethyl ether (60 mL), and washed with deionized water (2 x 50 mL). The organic layer was transferred to an Erlenmeyer flask and dried over MgSO<sub>4</sub>, vacuum filtered, and concentrated under reduced pressure to yield compound **3.03** as an amber oil used without further purification (3.2 g, 100%). Notebook: 01-197, 01-143

Data for **3.03**<sup>62</sup>

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ = 7.67 (d, *J* = 15.9 Hz, 1 H), 7.49-7.48 (m, 1 H), 7.35-7.28 (m, 2 H), 6.26 (d, *J* = 15.9 Hz, 1 H), 4.25 (q, *J* = 7.2 Hz, 2 H), 1.31 (t, *J* = 7.2 Hz, 3 H).

<sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ = 167.2, 138.1, 137.6, 128.0, 127.0, 125.1, 117.9, 60.4, 14.3 ppm.

TLC (10% ethyl acetate/hexanes) R<sub>f</sub> = 0.4



**(E)-3-(Thiophen-3-yl)prop-2-en-1-ol (3.04)**. In a manner entirely analogous to that previously reported,<sup>57</sup> a single-necked 500 mL round-bottomed flask equipped with a septum, magnetic stirring bar of dimension 150 mm by 100 mm, and nitrogen inlet was flame-dried and allowed to cool. The flask was charged with (**3.03**, 3.2 g, 17.8 mmol) and dichloromethane (100 mL). The solution was cooled to -78 °C (bath temperature) in a dry ice/acetone bath, and diisobutylaluminum hydride (62.3 mL, 1 M solution in hexanes, 62.3 mmol) was added drop wise via syringe in three 20.8 mL portions (approximately 20 min). During the course of the

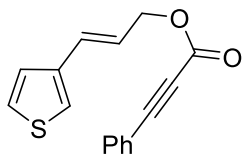
addition, the solution color became yellow. The reaction temperature was maintained at  $-78\text{ }^{\circ}\text{C}$  for an additional 45 min, after which time the solution was diluted with dichloromethane (50 mL) and immediately quenched with a half saturated solution of potassium sodium tartrate (200 mL), then removed from the dry ice/acetone bath and allowed to warm to rt while stirring vigorously. After 18 h, the reaction was transferred to a separatory funnel, and the organic phase was removed and transferred to an Erlenmeyer flask. The remaining aqueous phase was washed with diethyl ether (2 x 50 mL), and the organic layers were transferred to the said Erlenmeyer flask and dried over  $\text{MgSO}_4$ , vacuum filtered, and concentrated under reduced pressure. The off white solid was purified by silica gel column chromatography eluting with (20-30% diethyl ether/hexanes) to yield compound **3.04** as a white solid (1.9 g, 75%). Notebook: 01-200, 01-144

Data for **3.04**<sup>62</sup>

$^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.29-7.27 (m, 1 H), 7.23-7.21 (m, 1 H), 7.17-7.16 (m, 1 H), 6.63 (d,  $J$  = 15.9 Hz, 1 H), 6.23 (dt,  $J$  = 15.9 Hz, 5.7 Hz, 1 H), 4.29 (d,  $J$  = 5.7 Hz, 2 H), 1.37 (s, 1 H).

$^{13}\text{C NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 139.6, 128.7, 126.4, 125.8, 125.3, 122.6, 64.0 ppm

TLC (20% diethyl ether/hexanes)  $R_f$  = 0.08



**(E)-3-(Thiophen-3-yl)allyl 3-phenylpropiolate (3.06).** A single-necked 100 mL round bottomed flask equipped with a septum, magnetic stirring bar of dimension 2.5 cm by 1.25 cm, and nitrogen inlet was flame-dried and allowed to cool. The rubber septum was briefly removed,

and the flask was charged with (*E*)-3-(thiophen-3-yl)prop-2-en-1-ol (**3.04**, 402 mg, 2.9 mmol), 3-phenylpropionic acid (**3.05**, 420 mg, 2.9 mmol), dimethylaminopyridine (53 mg, 0.4 mmol) and dry dichloromethane (20 mL) at rt until homogeneous. The septa was briefly removed and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (825 mg, 4.3 mmol) added in a single portion; changing the solution to a clear yellow. The solution was then stirred at room temperature for 16 h. The solution was diluted with dichlorormethane (20 mL) and transferred to a separatory funnel. The organics were washed with deionized water (2 x 25 mL) then sat. brine (25 mL). The organic layer was transferred to an Erlenmeyer flask and dried over MgSO<sub>4</sub>, vacuum filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (25% diethyl ether/hexanes) to yield compound **3.06** as a white waxy solid (557 mg, 75%). Notebook: 01-203

#### Data for **3.06**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.60-7.58 (m, 2 H), 7.48-7.36 (m, 3 H), 7.29-7.28 (m, 1 H), 7.24-7.23 (m, 2 H), 6.74 (d, *J* = 15.6 Hz, 1 H), 6.19 (dt, *J* = 15.6 Hz, 6.8 Hz, 1 H), 4.86 (d, *J* = 6.8 Hz, 2 H).

<sup>13</sup>C NMR (500 MHz, CDCl<sub>3</sub>) δ = 153.9, 138.7, 133.0, 129.6, 128.6, 126.3, 125.0, 123.5, 121.8, 121.8, 119.6, 86.6, 80.5, 66.6 ppm.

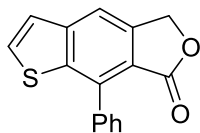
#### IR (thin film)

3102, 2947, 2213, 1710, 1659, 1275, 1163, 961, 756, 689 cm<sup>-1</sup>

#### HRMS (FTMS + p APCI)

[*M*] calcd for C<sub>16</sub>H<sub>11</sub>O<sub>2</sub>S: 267.0492; found, 267.0469

TLC (5% ethyl acetate/hexanes) R<sub>f</sub> = 0.4



**8-Phenylthieno[2,3-f]isobenzofuran-7(5H)-one (3.07a).** (entry 1 **Table 2**) To a 0.5-2 mL microwave vial and equipped with flea stir bar was added diene-yne (**3.06**, 30 mg, 0.1 mmol) in 10% nitrobenzene/*o*DCB (*v/v*) (1.85 mL) to a final concentration of 0.06 M. The solution was heated for 20 min at 225 °C and cooled to 55 °C. The reaction solution color changed from yellow to dark amber. The solution was poured directly onto silica plug, and solvent removed (10-30% ethyl acetate/hexanes), **3.07a** was isolated with (25% ethyl acetate/hexanes) to yield a yellow solid (25 mg, 86 %, as a 96:4 ratio of benzo[b]thiophene: dihydrobenzo[b]thiophene).  
Notebook: 02-044, 02-112, 02-117

Data for **3.07a**

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ = 7.84 (s, 1 H), 7.74 (d, *J* = 5.5 Hz, 1 H), 7.61-7.59 (m, 2 H), 7.55-7.50 (m, 3 H), 7.47 (d, *J* = 5.5 Hz, 1 H), 5.40 (s, 2 H).

<sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ = 169.8, 146.0, 142.1, 140.6, 138.6, 134.9, 130.1, 128.7, 128.2, 127.9, 124.3, 118.9, 114.9, 68.0 ppm

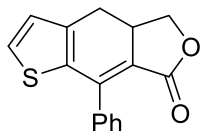
IR (thin film)

3081, 2924, 1759, 1593, 1496, 1356, 1089, 1026 cm<sup>-1</sup>

HRMS (TOF MS ES<sup>+</sup>)

[M] calcd for C<sub>16</sub>H<sub>10</sub>O<sub>2</sub>S: 266.0402; found 266.0422

TLC (25% ethyl acetate/hexanes) R<sub>f</sub> = 0.3



**8-Phenyl-4a,5-dihydrothieno[2,3-f]isobenzofuran-7(4H)-one (3.07b).** (entry 1 **Table 3**) To a 0.5-2 mL microwave vial and equipped with flea stir bar was added diene-yne (**3.06**, 22 mg, 0.8 mmol) in DMF (1.4 mL) to a final concentration of 0.06 M. The solution was heated for 3 min at 225 °C and cooled to 55 °C. The reaction solution color changed from clear to amber. The solution was diluted with 20 mL ethyl acetate and washed 3 x 20 mL deionized water. The organics were collected and dried with MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to yield brown oil. The residue was purified by silica gel column chromatography (20% ethyl acetate/hexanes), to yield compound **3.07b** as a yellow solid (19 mg, 86 %, as a 4:96 ratio of benzo[b]thiophene: dihydrobenzo[b]thiophene). Notebook: 01-149, 01-187

Data for **3.07b**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.59-7.44 (m, 5 H), 7.42 (d, *J* = 5.0 Hz, 1 H), 7.02 (d, *J* = 5.0 Hz, 1 H), 4.72 (t, *J* = 8.8 Hz, 1 H), 4.05 (t, *J* = 8.8 Hz, 1 H), 3.66-3.55 (m, 1 H), 3.16 (dd, *J* = 15.6 Hz, 8.0 Hz, 1 H), 2.70 (t, *J* = 16.4 Hz, 1 H).

Note: **3.07a** impurity (s, 7.84), (d, 7.73), (d, 7.59), (s, 5.40 ppm); H Grease impurity 1.26, 0.89 ppm; H<sub>2</sub>O impurity 1.58 ppm; unknown 1.69 ppm; dichloromethane 5.30 ppm

<sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ = 169.8, 146.0, 142.1, 140.6, 138.6, 134.9, 130.1, 128.7, 128.2, 127.9, 124.3, 118.9, 114.9, 68.0 ppm

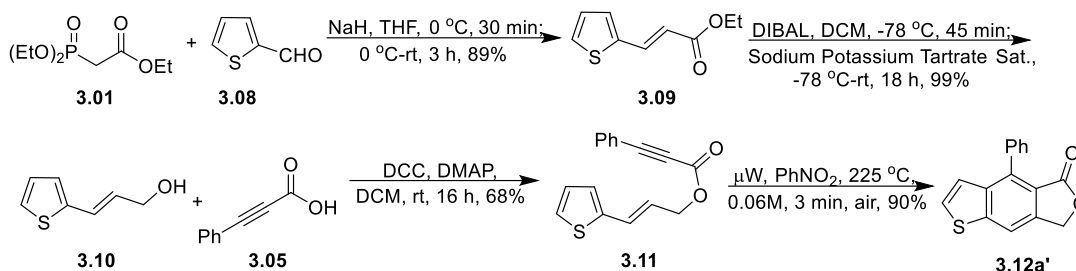
IR (thin film)

3081, 2924, 1759, 1593, 1496, 1356, 1089, 1026 cm<sup>-1</sup>

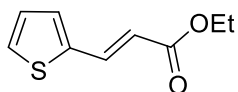
HRMS (TOF MS ES<sup>+</sup>)

[M] calcd for C<sub>16</sub>H<sub>12</sub>O<sub>2</sub>S: 268.0558; found 268.0576

TLC (25% ethyl acetate/hexanes) R<sub>f</sub> = 0.3



**Figure 61** Synthetic scheme of thiophene(C2) diene-yne precursor and microwave Diels-Alder reaction



**Ethyl (*E*)-3-(thiophen-2-yl)acrylate (3.09).** In a manner entirely analogous to that previously reported,<sup>56</sup> a single-necked 50 mL round-bottomed flask equipped with a septum, magnetic stirring bar of dimension 150 mm by 100 mm, and nitrogen inlet was flame-dried and allowed to cool. The rubber septum was briefly removed, and the flask was charged with sodium hydride (66 mg of a 60% dispersion in mineral oil, 2.75 mmol) and dry tetrahydrofuran (30 mL). The mixture was cooled to 0 °C (bath temperature) in an ice bath, and triethyl phosphonoacetate (**3.01**, 0.23 mL, 2.5 mmol) was added drop wise via syringe (approximately 5 min). After the addition was complete, the reaction was stirred at 0 °C for an additional 45 min. Thiophene-2-carbaldehyde (**3.08**, 0.5 mL, 2.5 mmol) was added drop wise via syringe (approximately 5 min). During the course of the addition, the solution color became opaque-white. The reaction temperature was maintained at 0 °C for 1.5 h, then removed from the ice bath and allowed to warm to rt. The progress of the reaction was monitored by TLC. After 17 h, the reaction was transferred to a separatory funnel, diluted with diethyl ether (20 mL), and washed with a saturated solution of ammonium chloride (2 x 25 mL) and brine (2 x 25 mL). The organic layer was transferred to an Erlenmeyer flask and dried over MgSO<sub>4</sub>, vacuum filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10–50%



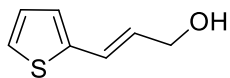
ethyl acetate/hexanes) to yield compound **3.09** as a colorless oil (216 mg, 89%). Notebook: 01-060, 01-173

Data for **3.09**<sup>56</sup>

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.45 (d,  $J$  = 15.6 Hz, 1 H), 7.34 (d,  $J$  = 5.1 Hz, 1 H), 7.22 (d,  $J$  = 3.3 Hz, 1 H), 7.01 (dd,  $J$  = 5.1 Hz, 3.6 Hz, 1 H), 6.20 (d,  $J$  = 15.9 Hz, 1 H), 4.20 (q,  $J$  = 7.2 Hz, 2 H), 1.29 (t,  $J$  = 7.2 Hz, 3 H).

<sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 167.0, 139.8, 137.2, 131.0, 128.5, 128.3, 117.3, 60.7, 14.5 ppm.

TLC (1% diethyl ether/hexanes)  $R_f$  = 0.25



**(E)-3-(Thiophen-2-yl)prop-2-en-1-ol (3.10)**. In a manner entirely analogous to that previously reported,<sup>57</sup> a single-necked 25 mL round-bottomed flask equipped with a septum, magnetic stirring bar of dimension 150 mm by 100 mm, and nitrogen inlet was flame-dried and allowed to cool. The flask was charged with (**3.09**, 216 mg, 1.19 mmol) and dichloromethane (10 mL). The solution was cooled to  $-78$  °C (bath temperature) in a dry ice/acetone bath, and diisobutylaluminum hydride (4.15 mL, 1 M solution in hexanes, 4.15 mmol) was added drop wise via syringe (approximately 5 min). During the course of the addition, the solution color became yellow. The reaction temperature was maintained at  $-78$  °C for an additional 45 min, after which time the solution was diluted with dichloromethane (10 mL) and immediately quenched with a half saturated solution of potassium sodium tartrate (15 mL), then removed from the dry ice/acetone bath and allowed to warm to rt while stirring vigorously. After 18 h,

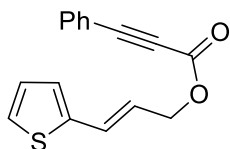
the reaction was transferred to a separatory funnel, and the organic phase was removed and transferred to an Erlenmeyer flask. The remaining aqueous phase was washed with diethyl ether (3 x 10 mL), and the organic layers were transferred to the said Erlenmeyer flask and dried over MgSO<sub>4</sub>, vacuum filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with (15% ethyl acetate/hexanes) to yield compound **3.10** as an opaque-white oil (165 mg, 99%). Notebook: 01-062, 01-174

Data for **3.10**<sup>63</sup>

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ = 7.15 (t, *J* = 3 Hz, 1 H), 6.96 (d, *J* = 3.3 Hz, 2 H), 6.73 (d, 15.6 Hz, 1 H), 6.16 (dt, *J* = 15.6 Hz, 5.7 Hz, 1 H), 4.27 (t, *J* = 5.1 Hz, 2H), 1.42 (t, *J* = 5.7 Hz, 1 H).

<sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub>) δ = 142.1, 128.5, 127.7, 126.1, 124.7, 124.6, 63.7 ppm

TLC (15% ethyl acetate/hexanes) R<sub>f</sub> = 0.15



**(E)-3-(Thiophen-2-yl)allyl 3-phenylpropiolate (3.11)**. A single-necked 10 mL round-bottomed flask equipped with a septum, magnetic stirring bar of dimension 150 mm by 100 mm, and nitrogen inlet was flame-dried and allowed to cool. The rubber septum was briefly removed, and the flask was charged with dimethylaminopyridine (8.7 mg, 0.07 mmol), 3-phenyl propiolic acid (**3.05**, 68.7 mg, 0.47 mmol), and dichloromethane (2 mL) at rt. (*E*)-3-(Thiophen-2-yl)prop-2-en-1-ol, (**3.10**, 66.5 mg, 0.47 mmol) was added to the solution via syringe in dichloromethane (2 mL). The rubber septum was briefly removed, and the flask was charged with dicyclohexylcarbodiimide (146 mg, 0.7 mmol) during which time the solution turned from

colorless to bright yellow. After 2 h, the solution was poured directly onto silica plug (25 mm diameter x 60 mm height) and eluted with diethyl ether. The residue was collected, concentrated, and purified by silica gel column chromatography (30% ethyl acetate/hexanes) to yield compound **3.11** as a white solid (86 mg, 68%). Notebook: 01-085

#### Data for **3.11**

$^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.57 (d,  $J$  = 7.2 Hz, 2 H), 7.36 (m,  $J$  = 7.2 Hz, 1 H), 7.34 (m,  $J$  = 6.9 Hz, 2 H), 7.18 (d,  $J$  = 5.1 Hz, 1 H), 7.00 (d,  $J$  = 3 Hz, 1 H), 6.95 (t,  $J$  = 4.8 Hz, 3.6 Hz, 1 H), 6.82 (d,  $J$  = 15.6 Hz, 1 H), 6.12 (dt,  $J$  = 15.6 Hz, 6.6 Hz, 1 H), 4.85 (d,  $J$  = 6.6 Hz, 2 H).

$^{13}\text{C NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 153.8, 140.9, 133.0, 130.7, 128.6, 128.5, 127.5, 126.9, 125.3, 121.4, 119.6, 86.7, 80.5, 66.2 ppm

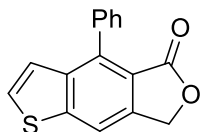
#### IR (thin film)

3067, 2938, 2219, 1708, 1650, 1280, 1185, 955, 758, 689  $\text{cm}^{-1}$

#### HRMS (FTMS + p ESI)

[ $M+1$ ] calcd for  $\text{C}_{16}\text{H}_{13}\text{O}_2\text{S}$ : 269.0630; found, 269.0630

TLC (10% diethyl ether/hexanes)  $R_f$  = 0.24



**4-Phenylthieno[2,3-f]isobenzofuran-5(7H)-one (3.12a')**. To a 0.5-2 mL microwave vial and equipped with flea stir bar was added diene-yne (**3.11**, 20 mg, 0.074 mmol) in nitrobenzene (1.2 mL) to a final concentration of 0.06 M. The solution was heated for 3 min at 225 °C and cooled to 55 °C. The reaction solution color changed from yellow to dark amber. The solution was

poured directly onto silica plug, and nitrobenzene was removed by eluting with (10–30% ethyl acetate/hexanes), **3.12a'** was isolated by eluting with (25% diethyl ether/hexanes) to yield a yellow solid (18 mg, 90 %). Notebook: 01-086, 01-141

Data for **3.12a'**

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.93 (s, 1 H), 7.51-7.47 (m, 6 H), 7.28 (d,  $J$  = 5.6 Hz, 1 H), 5.39 (s, 2 H).

Note Impurities: silicone grease (0.11-0.05); H Grease (s, 1.26), (b, 0.90-0.87);  $\text{H}_2\text{O}$  (s, 1.57)

$^{13}\text{C NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 169.8, 146.0, 142.1, 140.5, 138.5, 134.9, 130.1, 128.7, 128.2, 127.9, 124.3, 118.89, 114.9, 68.1 ppm.

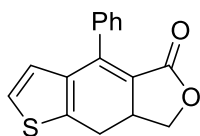
IR (thin film)

3108, 2923, 1759, 1593, 1496, 1450, 1356, 1088, 1025  $\text{cm}^{-1}$

(TOF MS ES+)

[M] calcd for  $\text{C}_{16}\text{H}_{10}\text{O}_2\text{S}$ : 266.0402; found 266.0423

TLC (25% diethyl ether/hexanes)  $R_f$  = 0.1



**4-Phenyl-7a,8-dihydrothieno[2,3-f]isobenzofuran-5(7H)-one (3.12b')**. (entry 2 **Table 3**) To a 0.5-2 mL microwave vial and equipped with flea stir bar was added diene-yne (**3.11**, 23.6 mg, 0.088 mmol) in dimethylformamide (1.5 mL) to a final concentration of 0.06 M. The solution was heated for 3 min at 225 °C and cooled to 55 °C. The reaction solution color changed from clear to amber. The reaction was diluted with ethyl acetate (10 mL) and washed with deionized

water (3 x 10 mL). The organic layer was transferred to an Erlenmeyer flask and dried over MgSO<sub>4</sub>, vacuum filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (25% diethyl ether/hexanes) to yield compound **3.12b'** as a white waxy solid (14 mg, 58 % as a 3:97 ratio of benzo[b]thiophene: dihydrobenzo[b]thiophene). Notebook: 01-084

Data for **3.12b'**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.42 (s, 3 H), 7.38 (d, *J* = 3.2 Hz, 2 H), 7.08 (d, *J* = 5.2 Hz, 1 H), 6.72 (d, *J* = 5.2 Hz, 1 H), 4.70 (t, *J* = 8.8 Hz, 1 H), 4.03 (t, *J* = 8.8 Hz, 1 H), 3.70-3.60 (m, *J* = 8.8 Hz, 1 H), 3.20 (dd, *J* = 15.6 Hz, 7.6 Hz, 1 H), 2.80 (t, *J* = 16.4 Hz, 1 H).

Note Impurities: silicone grease (.08); H Grease (s, 1.26), (b 0.88, 0.89); H<sub>2</sub>O (s, 1.57); dichloromethane (s, 5.30); **3.12a'** (s, 5.39)

<sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ = 168.1, 144.3, 139.3, 138.2, 134.4, 129.5, 128.9, 127.9, 126.9, 123.0, 117.7, 70.6, 37.6, 27.9 ppm

IR (thin film)

3120, 2898, 1746, 1631, 1506, 1220, 1094, 1008 cm<sup>-1</sup>

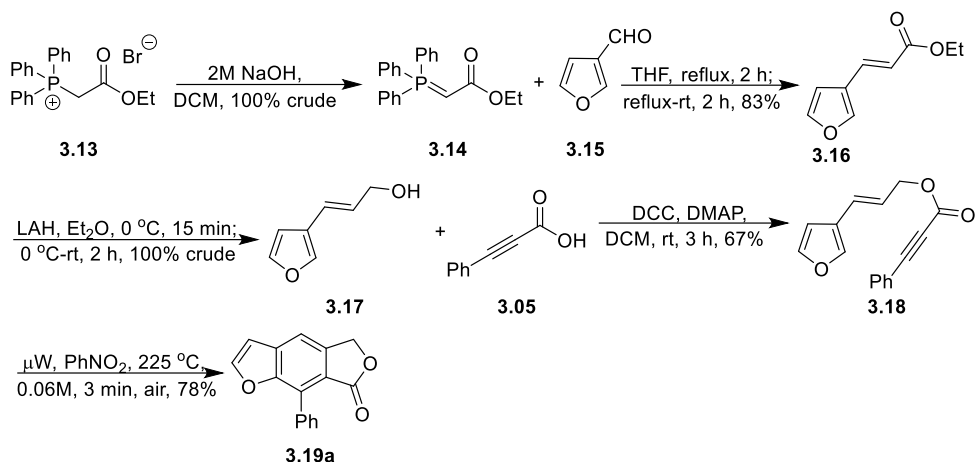
LRMS (TOF MS ES+)

*m/z* (%): 270 (29), 269 (100), 268 (48), 224 (15), 223 (58)

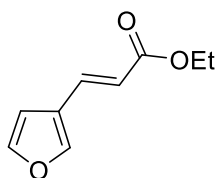
HRMS (TOF MS ES+)

[*M*+1] calcd for C<sub>16</sub>H<sub>13</sub>O<sub>2</sub>S: 269.0636; found, 269.0661

TLC (25% diethyl ether/hexanes) R<sub>f</sub> = 0.07



**Figure 62** Synthetic scheme of furan(C3) diene-yne precursor and microwave Diels-Alder reaction



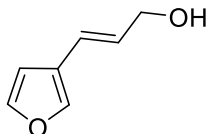
**Ethyl (*E*)-3-(furan-3-yl)acrylate (3.16).** In a manner entirely analogous to that previously reported,<sup>59</sup> a double-necked 50 mL round-bottom flask equipped with a septum, reflux condenser, magnetic stirring bar of dimension 300 mm by 150 mm, and nitrogen inlet was flame dried and allowed to cool. The flask was charged with ethyl 2-(triphenyl- $\lambda^5$ -phosphanylidene)acetate, (**3.14**, 1.54g, 4.4 mmol) and tetrahydrofuran (20 mL).<sup>58</sup> The solution was heated to reflux in an oil bath. Once the solution was at reflux, a solution of (**3.15**, 0.35 mL, 4.0 mmol) in tetrahydrofuran (0.35 mL) was added drop wise via syringe (approximately 5 min). After the addition was complete, the reflux was maintained for 2 h then removed from the oil bath and allowed to cool to rt. The solution was concentrated under reduced pressure to yield a tan solid. The residue was purified by silica gel column chromatography (50% dichloromethane/hexanes; 5%-10% diethyl ether/hexanes) to yield compound **3.16** as a white solid (549 mg, 83%). Notebook: 01-095

Data for **3.16**<sup>59</sup>

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.64 (d,  $J$  = 0.6 Hz, 1 H), 7.55 (d,  $J$  = 15.9 Hz, 1 H), 7.43-7.42 (m, 1 H), 6.58 (t,  $J$  = 1.2 Hz, 0.6 Hz, 1 H), 6.13 (d,  $J$  = 15.9 Hz, 1 H), 4.21 (q,  $J$  = 7.2 Hz, 6.9 Hz, 2 H), 1.30 (t,  $J$  = 7.2 Hz, 6.9 Hz, 3 H).

<sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 166.8, 144.2, 144.1, 134.3, 122.4, 117.9, 107.2, 60.2, 14.1 ppm.

TLC (10% diethyl ether/hexanes)  $R_f$  = 0.4



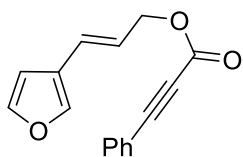
**(E)-3-(Furan-3-yl)prop-2-en-1-ol (3.17).** In a manner entirely analogous to that previously reported,<sup>59</sup> a single-necked 25 mL round-bottom flask equipped with a septum, magnetic stirring bar of dimension 300 mm by 100 mm, and nitrogen inlet was flame-dried and allowed to cool. The flask was charged with lithium aluminum hydride (114 mg, 3.0 mmol) and placed under vacuum for 20 min then flushed with nitrogen for 20 min. The flask was cooled to 0 °C (bath temperature) in water/ice bath, and diethyl ether (5 ml) was added to the flask. Once the solution was cooled, **(3.16)**, 166 mg, 1.0 mmol) was added drop wise via syringe (approximately 5 min) in a minimum volume of diethyl ether. During the course of the addition, gas evolution was observed. Once the addition of **3.16** was complete, the ice bath was removed and the reaction was allowed to warm to rt. After 1 h at rt, the reaction temperature was lowered to 0 °C, and the excess hydride was quenched via drop wise addition of water/tetrahydrofuran (10 mL, 7.5% v/v). During the course of the addition, gas evolution was observed. The resulting mixture was filtered over celite, and the filter cake was washed with diethyl ether. The resulting solution was

dried over MgSO<sub>4</sub>, vacuum filtered, and concentrated under reduce pressure to yield compound **3.17** (124 mg, 100% yield) as a clear oil. **3.17** was used in the next step without further purification. Notebook: 01-099, 01-168

Data for **3.17**<sup>59</sup>

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ = 7.36 (d, *J* = 4.2 Hz, 1 H), 7.33 (s, 1 H), 6.49 (t, *J* = 0.9 Hz, 0.6 Hz, 1 H), 6.40 (d, *J* = 15.6 Hz, 1 H), 6.00 (dt, *J* = 15.6 Hz, 5.7 Hz, 1 H), 4.19 (dd, *J* = 5.7 Hz, 1.2 Hz, 2 H), 2.85 (s, b, 1 H).

<sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ = 143.5, 140.5, 128.2, 123.7, 120.9, 107.6, 63.3 ppm.



**(E)-3-(Furan-3-yl)allyl 3-phenylpropiolate (3.18).** A single-necked 10 mL round-bottomed flask equipped with a septum, magnetic stirring bar of dimension 150 mm by 100 mm, and nitrogen inlet was flame-dried and allowed to cool. The rubber septum was briefly removed, and the flask was charged with dimethylaminopyridine (18.3 mg, 0.15 mmol), 3-phenyl propiolic acid (**3.05**, 146 mg, 1 mmol), and dichloromethane (2 mL) at rt. (*E*)-3-(Furan-2-yl)prop-2-en-1-ol (**3.17**, 124 mg, 1 mmol) was added to the solution via syringe in dichloromethane (2 mL). The rubber septum was briefly removed, and the flask was charged with dicyclohexylcarbodiimide (310 mg, 1.5 mmol) during which time the solution turned from colorless to brown. After 3 h, the solution was poured directly onto silica plug (25 mm diameter x 65 mm height) and eluted with diethyl ether. The residue was collected, concentrated, and purified by silica gel column



chromatography (5% diethyl ether/hexanes) to yield compound **3.18** as a white solid (169 mg, 67%). Notebook: 01-101, 01-172

Data for **3.18**

$^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.57 (d,  $J$  = 6.8 Hz, 2 H), 7.46-7.36 (m, 5 H), 6.58 (d,  $J$  = 15.9, 1H), 6.54 (d,  $J$  = 1.2 Hz, 1 H), 6.02 (dt,  $J$  = 15.9 Hz, 6.9 Hz, 1 H), 4.82 (dd,  $J$  = 6.9 Hz, 1.2Hz, 1 H).

$^{13}\text{C NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 153.8, 140.9, 133.0, 130.7, 128.6, 128.5, 127.5, 126.9, 125.3, 121.4, 119.6, 86.7, 80.5, 66.2 ppm

IR (thin film)

3143, 3059, 2951, 2220, 1704, 1667, 1283, 1170, 963, 758, 689  $\text{cm}^{-1}$

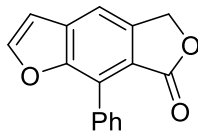
LRMS (TOF MS ES+)

$m/z$  (%): 253 (17), 252 (100), 251 (18), 225 (12), 223 (20), 213 (10), 208 (12), 207 (11)

HRMS (TOF MS ES+)

[M] calcd for  $\text{C}_{16}\text{H}_{12}\text{O}_3$ : 252.0786; found, 252.0785

TLC (5% diethyl ether/hexanes)  $R_f$  = 0.14



**8-Phenylbenzo[1,2-b:4,5-c']difuran-7(5H)-one (3.19a).** To a 0.5-2 mL microwave vial and equipped with flea stir bar was added diene-yne (**3.18**, 14 mg, 0.055 mmol) in nitrobenzene (0.9 mL) to a final concentration of 0.06 M. The solution was heated for 3 min at 225 °C and cooled to 55 °C. The reaction solution color changed from yellow to dark amber. The solution was

poured directly onto silica plug, and nitrobenzene was removed (10-30% ethyl acetate/hexanes), **3.19a** was isolated with (25% diethyl ether/hexanes) to yield an off-white solid (12 mg, 78 %).

Notebook: 01-105, 01-139, 01-181, 01-182

#### Data for **3.19a**

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.82 (d,  $J$  = 2.4 Hz, 1 H), 7.65 (dd,  $J$  = 8.1 Hz, 1.8 Hz, 2 H), 7.60 (s, 1 H), 7.56-7.48 (m, 3 H), 6.91 (d,  $J$  = 2.4 Hz, 1 H), 5.36 (s, 2 H).

Note Impurities: H Grease (t, 1.26); H<sub>2</sub>O (s, 1.54); acetone (s, 2.05); dichloromethane (s, 5.30)

<sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 170.1, 153.0, 149.6, 142.0, 133.9, 130.7, 130.5, 129.0, 128.1, 126.8, 118.3, 112.9, 107.11, 68.2 ppm

IR (thin film)

2914, 1751, 1610, 1476, 1348, 1260, 1132 cm<sup>-1</sup>

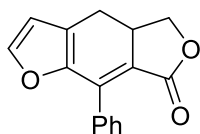
LRMS (TOF MS ES+)

$m/z$  (%): 251 (40), 250 (100), 249 (43), 221 (53)

HRMS (TOF MS ES+)

[M] calcd for C<sub>16</sub>H<sub>10</sub>O<sub>3</sub>: 250.0630; found 250.0608

TLC (25% diethyl ether/hexanes) R<sub>f</sub> = 0.08



**8-Phenyl-4a,5-dihydrobenzo[1,2-b:4,5-c']difuran-7(4H)-one (3.19b).** (entry 3 **Table 3**) To a 0.5-2 mL microwave vial and equipped with flea stir bar was added diene-yne (**3.18**, 14 mg, 0.055 mmol) in dimethylformamide (0.9 mL) to a final concentration of 0.06 M. The solution

was heated for 3 min at 225 °C and cooled to 55 °C. The reaction solution color changed from clear to amber. The reaction was diluted with ethyl acetate (10 mL) and washed with deionized water (3 x 10 mL). The organic layer was transferred to an Erlenmeyer flask and dried over MgSO<sub>4</sub>, vacuum filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (25% diethyl ether/hexanes) to yield compound **3.19b** as a white waxy solid (5 mg, 36 % as a 12:88 ratio of benzo[b]furan: dihydrobenzo[b]furan).  
Notebook: 01-104, 01-179, 01-180

Data for **3.19b**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.55-7.51 (m, 3 H), 7.49-7.43 (m, 3 H), 6.46 (d,  $J$  = 1.6 Hz, 1 H), 4.68 (t,  $J$  = 8.8 Hz, 1 H), 4.01 (t,  $J$  = 9.2 Hz, 1 H), 3.69-3.63 (m,  $J$  = 9.2 Hz, 1 H), 2.93 (dd,  $J$  = 16 Hz, 9.2 Hz, 1 H), 2.60 (t,  $J$  = 16 Hz, 1 H).

Note Impurities: H Grease (s, 1.26); H<sub>2</sub>O (b, 1.56); dichloromethane (s, 5.30); **3.19a** (d, 7.83), (d, 7.66), (s, 7.61), (d, 6.91), (s, 5.37)

<sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 168.7, 151.9, 146.0, 139.5, 131.2, 130.9, 130.6, 130.0, 128.5, 128.3, 124.4, 117.0, 112.0, 71.2, 38.6, 25.7 ppm.

IR (thin film)

2920, 1737, 1620, 1556, 1468, 1257, 1096 cm<sup>-1</sup>

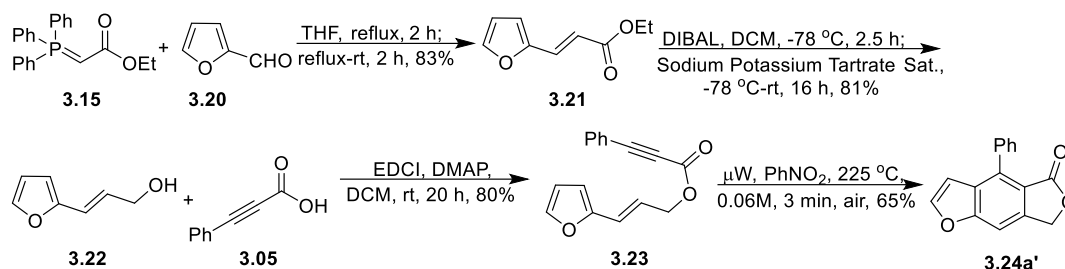
LRMS (TOF MS ES+)

$m/z$  (%): 268 (18), 253 (100), 252 (50), 251 (60), 250 (64), 221 (17), 208 (19), 207 (55)

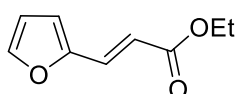
HRMS (TOF MS ES+)

[M+1] calcd for C<sub>16</sub>H<sub>13</sub>O<sub>3</sub>: 253.0865; found 253.0888

TLC (25% diethyl ether/hexanes) R<sub>f</sub> = 0.07



**Figure 63** Synthetic scheme of furan(C2) diene-yne precursor and microwave Diels-Alder reaction



**Ethyl (*E*)-3-(furan-2-yl)acrylate (3.21).** In a manner entirely analogous to that previously reported,<sup>59</sup> a double-necked 50 mL round-bottom flask equipped with a septum, reflux condenser, magnetic stirring bar of dimension 150 mm by 100 mm, and nitrogen inlet was flame-dried and allowed to cool. The flask was charged with ethyl 2-(triphenyl- $\lambda^5$ -phosphanylidene)acetate, (**3.15**, 1.54g, 4.4 mmol) and tetrahydrofuran (20 mL).<sup>58</sup> The solution was heated to reflux in an oil bath. Once the solution was at reflux, a solution of (**3.20**, 0.35 mL, 4 mmol) in tetrahydrofuran (0.35 mL) was added drop wise via syringe (approximately 5 min). After the addition was complete, the reflux was maintained for 2 h then removed from the oil bath and allowed to cool to rt. The solution was concentrated under reduced pressure to yield a tan solid. The residue was purified by silica gel column chromatography (50% dichloromethane/hexanes; 5%–10% diethyl ether/hexanes) to yield compound **3.21** as a clear liquid (552 mg, 83%).

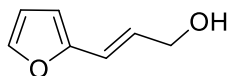
Notebook: 01-108

Data for **3.21**<sup>64</sup>

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.47 (t,  $J$  = 1.5 Hz, 0.9 Hz, 1 H), 7.40 (d,  $J$  = 15.6 Hz, 1 H), 6.59 (d,  $J$  = 3.3 Hz, 1 H), 6.45 (dd,  $J$  = 3.6 Hz, 1.8 Hz, 1 H), 6.28 (d,  $J$  = 15.6 Hz, 1 H), 4.20 (q,  $J$  = 7.2 Hz, 6.9 Hz, 2 H), 1.29 (t,  $J$  = 7.2 Hz, 6.9 Hz, 3 H).

<sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 167.3, 151.3, 145.0, 131.3, 116.3, 114.9, 112.5, 60.7, 14.6 ppm.

TLC (5% diethyl ether/hexanes)  $R_f$  = 0.38



**(E)-3-(Furan-2-yl)prop-2-en-1-ol (3.22).** In a manner entirely analogous to that previously reported,<sup>57</sup> a single-necked 250 mL round-bottomed flask equipped with a septum, magnetic stirring bar of dimension 150 mm by 100 mm, and nitrogen inlet was flame-dried and allowed to cool. The flask was charged with (**3.21**, 500 mg, 3.0 mmol) and dichloromethane (60 mL). The solution was cooled to  $-78$  °C (bath temperature) in a dry ice/acetone bath, and diisobutylaluminum hydride (7.5 mL, 1 M solution in hexanes, 7.5 mmol) was added drop wise via syringe (approximately 5 min). During the course of the addition, the solution color became yellow. The reaction temperature was maintained at  $-78$  °C for an additional 2.5 h, after which time the solution was diluted with dichloromethane (30 mL) and immediately quenched with a half saturated solution of potassium sodium tartrate (90 mL), then removed from the dry ice/acetone bath and allowed to warm to rt while stirring vigorously. After 16 h, the reaction was transferred to a separatory funnel, and the organic phase was removed and transferred to an Erlenmeyer flask. The remaining aqueous phase was washed with dichloromethane (3 x 25 mL), and the organic layers were transferred to the said Erlenmeyer flask and dried over MgSO<sub>4</sub>,

vacuum filtered, and concentrated under reduced pressure to yield a yellow oil. The oil was purified by silica gel column chromatography eluting with (30% ethyl acetate/hexanes) to yield **3.22** (303 mg, 81% yield) as a yellow oil. Notebook: 02-158

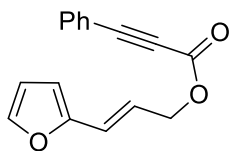
Data for **3.22**<sup>65</sup>

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.35 (s, 1 H), 6.48-6.24 (m, 4 H), 4.30 (s, 2 H), 1.47 (b, 1 H).

Note Impurities: H Grease (s, 1.26), (0.85)

<sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 152.6, 142.1, 127.5, 119.3, 111.4, 108.1, 63.2 ppm.

TLC (30% ethyl acetate/hexanes)  $R_f$  = 0.3



**(E)-3-(Furan-2-yl)allyl 3-phenylpropiolate (3.23).** A single-necked 25 mL round-bottomed flask equipped with a septum, magnetic stirring bar of dimension 150 mm by 100 mm, and nitrogen inlet was flame-dried and allowed to cool. The rubber septum was briefly removed, and the flask was charged with dimethylaminopyridine (9.4 mg, 0.08 mmol), 3-phenyl propiolic acid (**3.05**, 74.5 mg, 0.5 mmol), and dichloromethane (3 mL) at rt. (*E*)-3-(Furan-2-yl)prop-2-en-1-ol (**3.22**, 63 mg, 0.5 mmol) was added to the solution via syringe in dichloromethane (2 mL). The rubber septum was briefly removed, and the flask was charged with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (147 mg, 0.77 mmol). The solution turned from colorless to light brown. After 20 h, the reaction was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10-20% diethyl ether /hexanes) to yield compound **3.23** as a clear oil (103 mg, 80%). Notebook: 01-120, 01-185

Data for **3.23**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.60 (s, 1 H), 7.58 (d,  $J$  = 3.6 Hz, 1 H), 7.48-7.44 (m, 1H), 7.40-7.36 (m, 3 H), 6.52 (d,  $J$  = 16 Hz, 1 H), 6.38 (dd,  $J$  = 3.2, Hz,  $J$  = 1.6 Hz, 1 H), 6.32 (d,  $J$  = 3.2 Hz, 1 H), 6.22 (dt,  $J$  = 16 Hz, 6.4 Hz, 1 H), 4.85 (dd,  $J$  = 6.8 Hz, 1.2Hz, 1 H).

<sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 154.1, 152.0, 142.9, 133.4, 131.0, 128.9, 123.5, 120.9, 119.9, 111.7, 109.6, 87.0, 80.8, 66.4 ppm.

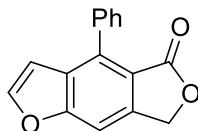
IR (thin film)

3059, 2960, 2922, 2217, 1706, 1260, 1167, 1100, 1016, 957, 755, 687 cm<sup>-1</sup>

HRMS (FTMS + pESI)

[M+1] calcd for C<sub>16</sub>H<sub>13</sub>O<sub>3</sub>: 253.08592; found 253.08588

TLC (20% diethyl ether/hexanes) R<sub>f</sub> = 0.45



**4-Phenylbenzo[1,2-b:4,5-c']difuran-5(7H)-one (3.24a')**. To a 0.5-2 mL microwave vial and equipped with flea stir bar was added diene-yne (**3.23**, 26 mg, 0.1 mmol) in nitrobenzene (1.7 mL) to a final concentration of 0.06 M. The solution was heated for 3 min at 225 °C and cooled to 55 °C. The reaction solution color changed from yellow to dark amber. The solution was poured directly onto silica plug, and nitrobenzene was removed (10-30% ethyl acetate/hexanes), **3.24a'** was isolated with (25% diethyl ether/hexanes) to yield an off-white solid (17 mg, 65 %).

Notebook: 01-134, 01-140

Data for **3.24a'**

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.72 (d,  $J$  = 2.4 Hz, 1 H), 7.57-7.45 (m, 6 H), 6.82 (d,  $J$  = 1.2 Hz, 1 H), 5.38 (s, 2 H).

Note Impurities: silicone grease (.08); H Grease (s, 1.26);  $\text{H}_2\text{O}$  (s, 1.59); dichloromethane (s, 5.30)

$^{13}\text{C NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 169.8, 158.1, 147.2, 144.3, 136.7, 134.1, 130.1, 129.5, 128.7, 128.2, 116.8, 107.0, 104.6, 68.1 ppm.

IR (thin film)

3121, 3059, 1753, 1593, 1539, 1477, 1293, 1104, 1026  $\text{cm}^{-1}$

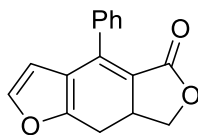
LRMS (TOF MS ES+)

$m/z$  (%): 251 (65), 250 (100), 249 (12), 222 (10), 221 (61)

HRMS (TOF MS ES+)

[M] calcd for  $\text{C}_{16}\text{H}_{10}\text{O}_3$ : 250.0630; found 250.0607

TLC (25% diethyl ether/hexanes)  $R_f$  = 0.12



**4-Phenyl-7a,8-dihydrobenzo[1,2-b:4,5-c']difuran-5(7H)-one (3.24b')**. (entry 4 **Table 3**) To

a 0.5-2 mL microwave vial and equipped with flea stir bar was added diene-yne (**3.23**, 23 mg, 0.09 mmol) in dimethylformamide (1.5 mL) to a final concentration of 0.06 M. The solution was heated for 3 min at 225 °C and cooled to 55 °C. The reaction solution color changed from clear to amber. The reaction was diluted with ethyl acetate (10 mL) and washed with deionized water (3 x 10 mL). The organic layer was transferred to an Erlenmeyer flask and dried over



MgSO<sub>4</sub>, vacuum filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (25% diethyl ether/hexanes) to yield compound **3.24b'** as a white waxy solid (9 mg, 41 % as a 5:95 ratio of benzo[b]furan: dihydrobenzo[b]furan).

Notebook: 01-133

Data for **3.24b'**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.45-7.41 (m, 5 H), 7.34 (s, 1 H), 6.27 (d,  $J$  = 1.6 Hz, 1 H), 4.70 (t,  $J$  = 8.8 Hz, 1 H), 4.03 (t,  $J$  = 9.2 Hz, 1 H), 3.82-3.71 (m,  $J$  = 9.2 Hz, 1 H), 3.10 (dd,  $J$  = 16.4 Hz, 9.6 Hz, 1 H), 2.76 (t,  $J$  = 16.8 Hz, 1 H).

Note Impurities: H Grease (s, 1.26), (b, 0.89-0.84); H<sub>2</sub>O (s, 1.56); dichloromethane (s, 5.30)

<sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 167.8, 154.4, 144.2, 142.9, 133.7, 129.4, 129.3, 127.9, 122.1, 114.6, 109.2, 70.6, 38.5, 26.5 ppm.

IR (thin film)

3124, 2936, 2860, 1741, 1633, 1568, 1251, 1091, 1015 cm<sup>-1</sup>

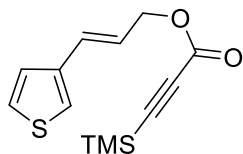
LRMS (TOF MS ES+)

$m/z$  (%): 268 (18), 253 (100), 252 (49), 251 (54), 250 (53), 221 (13), 208 (19), 207 (51)

HRMS (TOF MS ES+)

[M+1] calcd for C<sub>16</sub>H<sub>13</sub>O<sub>3</sub>: 253.0865; found 253.0892

TLC (25% diethyl ether/hexanes) R<sub>f</sub> = 0.08



**(E)-3-(Thiophen-3-yl)allyl 3-(trimethylsilyl)propiolate (3.26).** A single-necked 25 mL round-bottomed flask equipped with a septum, magnetic stirring bar of dimension 150 mm by 100 mm, and nitrogen inlet was flame-dried and allowed to cool. The rubber septum was briefly removed, and the flask was charged with (*E*)-3-(thiophen-3-yl)prop-2-en-1-ol (**3.04**, 140 mg, 1.0 mmol), 3-(trimethylsilyl)propionic acid (**3.25**, 213 mg, 1.5 mmol), dimethylaminopyridine (49 mg, 0.4 mmol) and dry dichloromethane (8 mL) at rt until homogeneous. The solution was then cooled to  $-78\text{ }^{\circ}\text{C}$  (bath temperature) in a dry ice/acetone bath. The septa was briefly removed and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (230 mg, 1.2 mmol) added in a single portion. The solution was slowly warmed to  $0\text{ }^{\circ}\text{C}$  over the course of 6 h. The solution was diluted with dichlorormethane (20 mL) and transferred to a separatory funnel. The organics were washed with deionized water (2 x 25 mL) then sat. brine (25 mL). The organic layer was transferred to an Erlenmeyer flask and dried over  $\text{MgSO}_4$ , vacuum filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5-10% ethyl acetate/hexanes) to yield compound **3.26** as a clear oil (192 mg, 70 %). Notebook: 02-062, 02-098

#### Data for **3.26**

**$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.34-7.31 (m, 1 H), 7.26-7.25 (m, 2 H), 6.74 (d,  $J$  = 15.6 Hz, 1 H), 6.18 (dt,  $J$  = 15.6 Hz, 6.8 Hz, 1 H), 4.83 (d,  $J$  = 6.8 Hz, 2 H), 0.30 (s, 9 H).

**$^{13}\text{C NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 153.1, 138.9, 130.0, 126.6, 125.2, 123.8, 122.0, 94.7, 94.6, 66.8, -0.6 ppm.

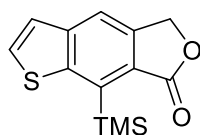
IR (thin film)

3101, 2961, 2176, 1710, 1658, 1451, 1252, 1216, 964, 848, 763  $\text{cm}^{-1}$

HRMS (FTMS + p ESI)

[M] calcd for  $\text{C}_{13}\text{H}_{15}\text{O}_2\text{SSi}$ : 263.0556; found, 263.0561

TLC (20% ethyl acetate/hexanes)  $R_f = 0.8$



**8-(Trimethylsilyl)-5,6-dihydro-7H-thieno[2,3-f]isoindol-7-one (3.27a).** (entry 2 Table 2) To a 0.5-2 mL microwave vial and equipped with flea stir bar was added diene-yne (**3.26**, 32 mg, 0.1 mmol) in 10% nitrobenzene/*o*DCB (*v/v*) (2.0 mL) to a final concentration of 0.06 M. The solution was heated for 20 min at 225 °C and cooled to 55 °C. The reaction solution color changed from yellow to dark amber. The solution was poured directly onto silica plug, and solvent removed (10-50% ethyl acetate/hexanes), **3.27a** was isolated with (10-20% ethyl acetate/hexanes) to yield a white solid (25 mg, 71 %, as a 99:1 ratio of benzo[b]thiophene: dihydrobenzo[b]thiophene). Notebook: 02-083, 02-092, 02-093

Data for **3.27a**

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta = 7.85$  (s, 1 H), 7.74 (d,  $J = 5.7$  Hz, 1 H), 7.41 (d,  $J = 5.7$  Hz, 1 H), 5.38 (s, 2 H), 0.61 (s, 9 H).

$\text{H}_2\text{O}$  impurity 1.57 ppm

$^{13}\text{C}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta = 172.4, 147.4, 143.3, 142.3, 137.6, 132.2, 127.2, 123.2, 117.5, 69.0, 1.7$  ppm

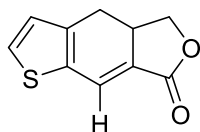
IR (thin film)

3094, 2954, 2898, 1756, 1591, 1455, 1354, 1304, 1245, 1190, 1154, 1088, 1067, 895, 844, 792, 741, 701, 629  $\text{cm}^{-1}$

HRMS (FTMS + p ESI)

[M+1] calcd for  $\text{C}_{13}\text{H}_{15}\text{O}_2\text{SSi}$ : 263.0556; found 263.0561

TLC (25% ethyl acetate/hexanes)  $R_f = 0.2$



**4a,5-Dihydrothieno[2,3-f]isobenzofuran-7(4H)-one (3.27b).** (entry 5 Table 3) To a 0.5-2 mL microwave vial and equipped with flea stir bar was added diene-yne (**3.26**, 31 mg, 0.1 mmol) in DMF (1.95 mL) to a final concentration of 0.06 M. The solution was heated for 3 min at 225 °C and cooled to 55 °C. The reaction solution color changed from clear to amber. The solution was diluted with 20 mL ethyl acetate and washed 3 x 20 mL deionized water. The organics were collected and dried with  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure to yield brown oil. The residue was purified by silica gel column chromatography (20% ethyl acetate/hexanes), to yield compound **3.27b** as a white waxy solid (11 mg, 48 %, as a 12:88 ratio of benzo[b]thiophene: dihydrobenzo[b]thiophene). Notebook: 02-137, 02-135

Data for **3.27b**

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta = 7.45\text{-}7.42$  (m, 2 H), 6.98 (d,  $J = 4.8$  Hz 1 H), 4.76 (t,  $J = 9.0$  Hz, 1 H), 4.05 (t,  $J = 9.0$  Hz, 1 H), 3.47-3.37 (m, 1 H), 3.16 (dd,  $J = 15.5$  Hz, 8.5 Hz, 1 H), 2.60 (t,  $J = 16.0$  Hz, 1 H).

Note: **Aromatic** impurity (s, 8.46), (s, 7.88), (d, 7.77), (s, 5.43 ppm); H Grease impurity 1.26, 0.89 ppm; H<sub>2</sub>O impurity 1.57 ppm; unknown 3.36, 2.36 ppm; dichloromethane 5.30 ppm

<sup>13</sup>C NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  = 169.5, 138.3, 134.2, 128.9, 127.6, 126.7, 124.4, 72.5, 36.1, 28.6 ppm

Note: **Aromatic** impurity 132.4, 123.8, 121.0, 116.8, 69.7, 30.0 ppm

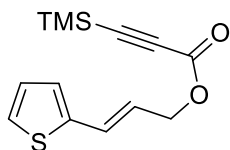
IR (thin film)

3122, 2997, 2921, 2895, 1741, 1637, 1506, 1472, 1377, 1290, 1268, 1238, 1173, 1073, 1043, 983, 939, 909, 731 cm<sup>-1</sup>

HRMS (FTMS + p ESI)

[M+1] calcd for C<sub>10</sub>H<sub>9</sub>O<sub>2</sub>S: 193.0318; found 193.0313

TLC (20% ethyl acetate/hexanes) R<sub>f</sub> = 0.3



**(E)-3-(Thiophen-2-yl)allyl 3-(trimethylsilyl)propiolate (3.28).** A single-necked 25 mL round-bottomed flask equipped with a septum, magnetic stirring bar of dimension 150 mm by 100 mm, and nitrogen inlet was flame-dried and allowed to cool. The rubber septum was briefly removed, and the flask was charged with (*E*)-3-(thiophen-2-yl)prop-2-en-1-ol (**3.10**, 205 mg, 1.5 mmol), 3-(trimethylsilyl)propionic acid (**3.25**, 213 mg, 1.5 mmol), dimethylaminopyridine (27 mg, 0.2 mmol) and dry dichloromethane (5 mL) at rt until homogeneous. The solution was then cooled to -78 °C (bath temperature) in a dry ice/acetone bath. The septa was briefly removed and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (420 mg, 2.2 mmol) added in a single portion. The solution was slowly warmed to 0 °C over the course of 6 h. The solution was diluted with

dichloromethane (15 mL) and transferred to a separatory funnel. The organics were washed with deionized water (2 x 20 mL) then sat. brine (20 mL). The organic layer was transferred to an Erlenmeyer flask and dried over MgSO<sub>4</sub>, vacuum filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20% dichloromethane/hexanes) to yield compound **3.28** as a clear oil (155 mg, 40 %). Notebook: 02-134

Data for **3.28**

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.20 (d,  $J$  = 5.0 Hz, 1 H), 7.01-7.00 (m, 1 H), 6.98-6.96 (m, 1 H), 6.82 (d,  $J$  = 15.7 Hz, 1 H), 6.12 (dt,  $J$  = 15.7 Hz, 6.5 Hz, 1 H), 4.78 (d,  $J$  = 6.5 Hz, 2 H), 0.25 (s, 9 H).

<sup>13</sup>C NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  = 153.1, 141.2, 128.9, 127.8, 127.2, 125.6, 121.6, 94.8, 94.7, 66.5, -0.6 ppm.

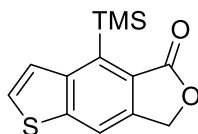
IR (thin film)

3104, 2960, 2175, 1710, 1657, 1449, 1252, 1216, 964, 848, 763 cm<sup>-1</sup>

HRMS (FTMS + p ESI)

[M+1] calcd for C<sub>13</sub>H<sub>17</sub>O<sub>2</sub>SSi: 265.0713; found, 265.0698

TLC (5% ethyl acetate/hexanes) R<sub>f</sub> = 0.2



**4-(Trimethylsilyl)thieno[2,3-f]isobenzofuran-5(7H)-one (3.29a')**. (entry 3 Table 2) To a 0.5-2 mL microwave vial and equipped with flea stir bar was added diene-yne (**3.28**, 31 mg, 0.12

mmol) in 10% nitrobenzene/*o*DCB (*v/v*) (1.9 mL) to a final concentration of 0.06 M. The solution was heated for 20 min at 225 °C and cooled to 55 °C. The reaction solution color changed from yellow to dark amber. The solution was poured directly onto silica plug, and solvent removed (10-50% ethyl acetate/hexanes), **3.29a'** was isolated with (10-15% ethyl acetate/hexanes) to yield a white solid (27 mg, 86 %, as a 100:0 ratio of benzo[b]thiophene: dihydrobenzo[b]thiophene). Notebook: 02-138, 02-139

Data for **3.29a'**

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ = 7.96 (s, 1 H), 7.89 (d, *J* = 6.0 Hz, 1 H), 7.58 (d, *J* = 6.0 Hz, 1 H), 5.38 (s, 2 H), 0.58 (s, 9 H).

H<sub>2</sub>O impurity 1.54 ppm

<sup>13</sup>C NMR (500 MHz, CDCl<sub>3</sub>) δ = 171.8, 145.6, 145.4, 141.6, 139.0, 128.2, 127.7, 126.3, 116.8, 68.8, 2.4 ppm

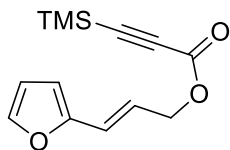
IR (thin film)

3110, 2944, 2897, 1756, 1586, 1443, 1417, 1360, 1240, 1164, 1089, 1023, 978, 886, 847, 771, 704, 689 cm<sup>-1</sup>

HRMS (FTMS + p ESI)

[*M*+1] calcd for C<sub>13</sub>H<sub>15</sub>O<sub>2</sub>SSi: 263.0556; found 263.0553

TLC (20% ethyl acetate/hexanes) R<sub>f</sub> = 0.2



**(E)-3-(Furan-2-yl)allyl 3-(trimethylsilyl)propiolate (3.30).** A single-necked 25 mL round-bottomed flask equipped with a septum, magnetic stirring bar of dimension 150 mm by 100 mm, and nitrogen inlet was flame-dried and allowed to cool. The rubber septum was briefly removed, and the flask was charged with (*E*)-3-(furan-2-yl)prop-2-en-1-ol (**3.22**, 150 mg, 1.2 mmol), 3-(trimethylsilyl)propionic acid (**3.25**, 172 mg, 1.2 mmol), dimethylaminopyridine (22 mg, 0.2 mmol) and dry dichloromethane (7 mL) at rt until homogeneous. The solution was then cooled to  $-78\text{ }^{\circ}\text{C}$  (bath temperature) in a dry ice/acetone bath. The septa was briefly removed and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (347 mg, 1.8 mmol) added in a single portion. The solution was slowly warmed to  $0\text{ }^{\circ}\text{C}$  over the course of 5 h. The solution was diluted with dichloromethane (15 mL) and transferred to a separatory funnel. The organics were washed with deionized water (2 x 20 mL) then sat. brine (20 mL). The organic layer was transferred to an Erlenmeyer flask and dried over  $\text{MgSO}_4$ , vacuum filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5% ethyl acetate/hexanes) to yield compound **3.30** as a clear oil (33 mg, 11 %). Notebook: 02-153, 02-157

Data for **3.30**

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.36 (s, 1 H), 6.50 (d,  $J$  = 16.0 Hz, 1 H), 6.38-6.37 (m, 1 H), 6.31-6.30 (m, 1 H), 6.21 (dt,  $J$  = 16.0 Hz, 6.8 Hz, 1 H), 4.79 (d,  $J$  = 6.8 Hz, 2 H), 0.25 (s, 9 H).

$^{13}\text{C NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  = 153.1, 152.0, 142.9, 123.6, 120.7, 111.7, 109.6, 94.7, 94.7, 66.3, -0.6 ppm.



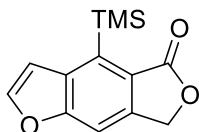
IR (thin film)

2961, 2175, 1712, 1657, 1489, 1253, 1216, 961, 848, 751, 705  $\text{cm}^{-1}$

HRMS (FTMS + p ESI)

[M] calcd for  $\text{C}_{13}\text{H}_{15}\text{O}_3\text{Si}$ : 247.0785; found, 247.0801

TLC (5% ethyl acetate/hexanes)  $R_f = 0.1$



**4-(Trimethylsilyl)benzo[1,2-b:4,5-c']difuran-5(7H)-one (3.31a')**. (entry 4 **Table 2**) To a 0.5-2 mL microwave vial and equipped with flea stir bar was added diene-yne (**3.30**, 33 mg, 0.13 mmol) in 10% nitrobenzene/*o*DCB (*v/v*) (2.2 mL) to a final concentration of 0.06 M. The solution was heated for 20 min at 225 °C and cooled to 55 °C. The reaction solution color changed from yellow to dark amber. The solution was poured directly onto silica plug, and solvent removed (5-20% ethyl acetate/hexanes), **3.31a'** was isolated with (10% ethyl acetate/hexanes) to yield a white solid (15 mg, 42 %, as a 100:0 ratio of benzo[b]furan: dihydrobenzo[b]furan). Notebook: 02-156, 02-164

Data for **3.31a'**

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta = 7.74$  (d,  $J = 2.5$  Hz, 1 H), 7.53 (s,  $J = 6.0$  Hz, 1 H), 7.17 (d,  $J = 2.5$  Hz, 1 H), 5.36 (s, 2 H), 0.54 (s, 9 H).

$^{13}\text{C}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta = 171.8, 157.4, 147.0, 143.7, 136.7, 134.8, 126.0, 109.0, 105.7, 69.0, 1.4$  ppm

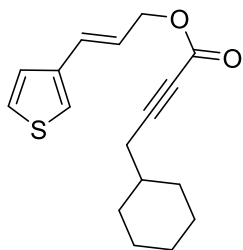
IR (thin film)

3076, 2944, 1748, 1544, 1451, 1375, 1340, 1278, 1245, 1140, 1110, 1021, 901, 874, 843, 769, 737 cm<sup>-1</sup>

HRMS (FTMS + p ESI)

[M+1] calcd for C<sub>13</sub>H<sub>15</sub>O<sub>3</sub>Si: 247.0785; found 247.0798

TLC (10% ethyl acetate/hexanes) R<sub>f</sub> = 0.2



**(E)-3-(Thiophen-3-yl)allyl 4-cyclohexylbut-2-ynoate (3.34).** A single-necked 25 mL round-bottomed flask equipped with a septum, magnetic stirring bar of dimension 150 mm by 100 mm, and nitrogen inlet was flame-dried and allowed to cool. The rubber septum was briefly removed, and the flask was charged with (*E*)-3-(thiophen-3-yl)prop-2-en-1-ol (**3.04**, 23 mg, 0.2 mmol), 4-cyclohexylbut-2-ynoic acid (**3.33**, 28 mg, 0.2 mmol), dimethylaminopyridine (3 mg, 0.02 mmol) and dry dichloromethane (3 mL) at rt until homogeneous.<sup>66</sup> The septa was briefly removed and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (48 mg, 0.25 mmol) added in a single portion. The solution was then stirred at room temperature for 16 h. The solution was diluted with dichlorormethane (15 mL) and transferred to a separatory funnel. The organics were washed with deionized water (2 x 20 mL) then sat. brine (20 mL). The organic layer was transferred to an Erlenmeyer flask and dried over MgSO<sub>4</sub>, vacuum filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (25% ethyl acetate/hexanes) to yield compound **3.34** as a clear oil (33 mg, 68 %). Notebook: 02-080, 02-096

Data for **3.34**

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ = 7.29-7.27 (m, 1 H), 7.22-7.21 (m, 2 H), 6.69 (d, *J* = 16.0 Hz, 1 H), 6.15 (dt, *J* = 16.0 Hz, 6.5 Hz, 1 H), 4.77 (d, *J* = 6.5 Hz, 2 H), 2.23 (d, *J* = 7.0 Hz, 2 H), 1.83-1.80 (m, 2 H), 1.74-1.71 (m, 2 H), 1.67-1.64 (m, 1 H), 1.59-1.54 (m, 1 H), 1.30-1.21 (m, 2 H), 1.19-1.13 (m, 1 H) 1.06-0.98 (m, 2 H).

<sup>13</sup>C NMR (500 MHz, CDCl<sub>3</sub>) δ = 154.0, 139.1, 129.7, 126.6, 125.3, 123.7, 122.4, 89.5, 66.6, 37.0, 33.0, 26.8, 26.4, 26.3 ppm.

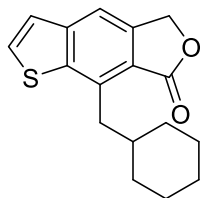
IR (thin film)

2924, 2851, 2231, 1709, 1448, 1365, 1243, 1072, 1058, 963, 831, 864, 770, 750 cm<sup>-1</sup>

HRMS (TOF MS ES+)

[M] calcd for C<sub>17</sub>H<sub>20</sub>O<sub>2</sub>S: 288.1184; found, 288.1187

TLC (25% ethyl acetate/hexanes) R<sub>f</sub> = 0.8



**8-(Cyclohexylmethyl)thieno[2,3-f]isobenzofuran-7(5H)-one (3.35a).** (entry 5 **Table 2**) To a 0.5-2 mL microwave vial and equipped with flea stir bar was added diene-yne (**3.33**, 32 mg, 0.1 mmol) in 10% nitrobenzene/*o*DCB (*v/v*) (1.8 mL) to a final concentration of 0.06 M. The solution was heated for 80 min at 225 °C and cooled to 55 °C. The reaction solution color changed from yellow to dark amber. The solution was poured directly onto silica plug, and solvent removed (10-50% ethyl acetate/hexanes), **3.35a** was isolated with (15-30% ethyl

acetate/hexane) to yield a clear solid (23 mg, 71%, as a 99:1 ratio of benzo[b]thiophene: dihydrobenzo[b]thiophene). Notebook: 02-101, 02-102, 02-103

Data for **3.35a**

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.71 (d,  $J$  = 5.5 Hz, 1 H), 7.69 (s, 1 H), 7.41 (d,  $J$  = 5.5 Hz, 1 H), 5.34 (s, 2 H), 3.31 (d,  $J$  = 7.5 Hz, 2 H), 1.94-1.89 (m, 1 H), 1.68-1.61 (m, 5 H), 1.24-1.14 (m, 5 H).

$\text{H}_2\text{O}$  impurity 1.55; Ethyl acetate impurity 4.12, 2.05, 1.2 ppm

$^{13}\text{C NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  = 171.2, 144.1, 142.8, 142.1, 139.2, 131.6, 124.3, 119.1, 114.4, 68.6, 39.4, 38.1, 33.7, 26.7, 26.6 ppm

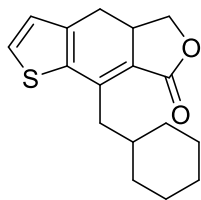
IR (thin film)

3103, 2922, 2849, 1746, 1606, 1499, 1447, 1344, 1322, 1263, 1209, 1161, 1092, 1064, 1013, 940, 892, 859, 828, 803, 737, 706  $\text{cm}^{-1}$

HRMS (FTMS + p ESI)

[ $M+1$ ] calcd for  $\text{C}_{17}\text{H}_{19}\text{O}_2\text{S}$ : 287.1100; found 287.1096

TLC (25% ethyl acetate/hexanes)  $R_f$  = 0.5



**4a,5-Dihydrothieno[2,3-f]isobenzofuran-7(4H)-one (3.35b).** (entry 6 **Table 3**) To a 0.5-2 mL microwave vial and equipped with flea stir bar was added diene-yne (**3.34**, 31 mg, 0.1 mmol) in DMF (1.76 mL) to a final concentration of 0.06 M. The solution was heated for 3 min at 225

°C and cooled to 55 °C. The reaction solution color changed from clear to amber. The solution was diluted with 20 mL ethyl acetate and washed 3 x 20 mL deionized water. The organics were collected and dried with MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to yield brown oil. The residue was purified by silica gel column chromatography (20% ethyl acetate/hexanes), to yield **3.35b** a white waxy solid (23 mg, 71%, as a 7:93 ratio of benzo[b]thiophene: dihydrobenzo[b]thiophene). Notebook: 02-130, 02-133

Data for **3.35b**

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ = 7.38 (d, *J* = 5.0 Hz, 1 H), 6.95 (d, *J* = 5.0 Hz, 1 H), 4.64 (t, *J* = 8.9 Hz, 1 H), 3.96 (t, *J* = 8.9 Hz, 1 H), 3.39-3.29 (m, 1 H), 3.09-3.01 (m, 2 H), 2.79-2.73 (m, 1 H), 2.50 (t, *J* = 15.9 Hz, 1 H), 2.04-1.62 (m, 6 H), 1.28-1.14 (m, 5 H).

Note: **3.35a** impurity (d, 7.71), (s, 7.69), (d, 7.41), (s, 5.34), (d, 3.31);

H<sub>2</sub>O impurity 1.56 ppm; H grease 1.26, 0.83 ppm; silicon grease 0.07 ppm

<sup>13</sup>C NMR (500 MHz, CDCl<sub>3</sub>) δ = 169.8, 144.6, 139.3, 138.7, 128.0, 127.8, 117.9, 71.3, 38.8, 37.2, 37.1, 33.7, 33.4, 28.8, 26.7, 26.7, 26.5 ppm

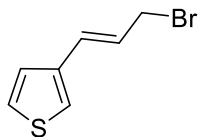
IR (thin film)

3098, 2922, 2849, 1732, 1626, 1512, 1447, 1420, 1372, 1339, 1270, 1225, 1170, 1073, 1045, 1008, 985, 936, 910, 838, 735 cm<sup>-1</sup>

HRMS (FTMS + p ESI)

[M+1] calcd for C<sub>17</sub>H<sub>21</sub>O<sub>2</sub>S: 289.1257; found 289.1251

TLC (25% ethyl acetate/hexanes) R<sub>f</sub> = 0.5



**(E)-3-(3-Bromoprop-1-en-1-yl)thiophene.** A single-necked 25 mL round-bottomed flask equipped with a septum, magnetic stirring bar of dimension 150 mm by 100 mm, and nitrogen inlet was flame-dried and allowed to cool. The rubber septum was briefly removed, and the flask was charged with (*E*)-3-(thiophen-3-yl)prop-2-en-1-ol (**3.04**, 201 mg, 1.4 mmol) and diethyl ether (11 mL) at rt. The solution was cooled to 0 °C (bath temperature) in an ice bath, and phosphorus tribromide (126 mg, 0.6 mmol) in diethyl ether (1 mL) was added drop wise via syringe (approximately 1 min). After 1.5 h at 0 °C, the reaction was poured to a separatory funnel, and washed with sat. sodium bicarbonate (15 mL). The organic layer was transferred to an Erlenmeyer flask and the aqueous layer extracted with diethyl ether (3 x 15 mL). The organics were combined and dried over MgSO<sub>4</sub>, vacuum filtered, and concentrated under reduced pressure to yield a yellow oil. The product was used directly without purification in the next step. Notebook: 02-068, 02-099

**Data for (*E*)-3-(3-Bromoprop-1-en-1-yl)thiophene**

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ = 7.30-7.28 (m, 1 H), 7.22-7.21 (m, 3.2 Hz, 2 H), 6.66 (d, *J* = 15.5 Hz, 1 H), 6.25 (dt, *J* = 15.5 Hz, 7.8 Hz, 1 H), 4.14 (d, *J* = 7.8 Hz, 2 H).

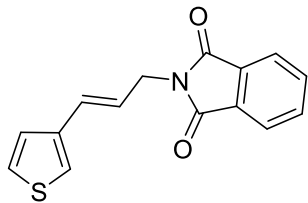
H<sub>2</sub>O impurity 1.54 ppm

<sup>13</sup>C NMR (500 MHz, CDCl<sub>3</sub>) δ = 138.8, 129.0, 126.7, 125.4, 125.3, 123.9, 33.9 ppm.

IR (thin film)

2150, 1642, 1454 cm<sup>-1</sup>

TLC (10% diethyl ether/hexanes) R<sub>f</sub> = 0.7



**(E)-2-(3-(Thiophen-3-yl)allyl)isoindoline-1,3-dione (3.36).** A single-necked 50 mL round-bottomed flask equipped with a septum, magnetic stirring bar of dimension 150 mm by 100 mm, and nitrogen inlet was flame-dried and allowed to cool. (*E*)-3-(3-Bromoprop-1-en-1-yl)thiophene (290 mg, 1.4 mmol) in dimethylformamide (1 mL) at rt was added to the flask. The rubber septum was briefly removed and potassium phthalimide (593 mg, 3.2 mmol) added in a single portion followed by dimethylformamide (9 mL).<sup>60</sup> The reaction was stirred at room temperature for 24 h. The solvent was removed under reduced pressure to yield a tan solid. The residue was solvated in ethyl acetate and passed through a silica gel plug (ethyl acetate). The resulting solution was concentrated under reduced pressure to yield compound **3.36** as a beige solid then recrystallized in ethyl acetate to yield white solid (320 mg, 83% yield over 2 steps). Notebook: 02-069, 02-082

Data for **3.36**

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.87-7.86 (m, 2 H), 7.73-7.72 (m, 2 H), 7.25-7.23 (m, 1 H), 7.17-7.16 (m, 2 H), 6.68 (d,  $J$  = 15.8 Hz, 1 H), 6.11 (dt,  $J$  = 15.8 Hz, 6.5 Hz, 1 H), 4.41 (d,  $J$  = 6.5 Hz, 2 H).

H<sub>2</sub>O impurity 1.54 ppm

<sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 168.3, 139.3, 134.4, 132.6, 128.5, 126.5, 125.3, 123.7, 123.2, 123.0, 40.0 ppm

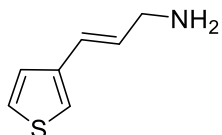
IR (thin film)

1703, 1469, 1427, 1397, 1108, 954, 861,830,800, 750, 717 cm<sup>-1</sup>

HRMS (FTMS + p ESI)

[M+1] calcd for C<sub>15</sub>H<sub>12</sub>O<sub>2</sub>NS: 270.0583; found, 270.0589

TLC (30% ethyl acetate/hexanes) R<sub>f</sub> = 0.45



**(E)-3-(Thiophen-3-yl)prop-2-en-1-amine (3.37).** A double-necked 100 mL round-bottomed flask equipped with a septum, magnetic stirring bar of dimension 150 mm by 100 mm, and nitrogen inlet was flame-dried and allowed to cool then attached to refluxing column. (*E*)-2-(3(thiophen-3-yl)allyl)isoindoline-1,3-dione (**3.36**, 320 mg, 1.2 mmol) in ethanol (10 mL) at rt was added to the flask through the side neck. Hydrazine monohydrate (0.3 mL, 5.9 mmol) was added dropwise through the side neck followed by ethanol (10 mL).<sup>60</sup> The solution was refluxed for 3 h and allowed to cool to rt. The contents were dissolved in a (1:1) H<sub>2</sub>O:CH<sub>3</sub>OH (60 mL) solution and the contents added to a separatory funnel. The product was then extracted with dichloromethane (5 x 20 mL). The organics were combined and dried over MgSO<sub>4</sub>, vacuum filtered, and concentrated under reduced pressure to yield a yellow oil. The resulting solution was concentrated under reduced pressure to yield compound **3.37** as a yellow oil (140 mg, 100% crude yield). The product was used without further purification in the next step.

Notebook: 02114, 02-121



Data for **3.37**

$^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.28-7.25 (m, 1 H), 7.21-7.19 (m, 1 H), 7.11 (s, 1 H) 6.52 (d,  $J$  = 15.9 Hz, 1 H), 6.18 (dt,  $J$  = 15.9 Hz, 5.8 Hz, 1 H), 3.45 (d,  $J$  = 5.8 Hz, 2 H)

$\text{H}_2\text{O}$  impurity 1.42 ppm, Grease impurity 1.26 ppm

$^{13}\text{C NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  = 140.1, 131.6, 126.3, 125.3, 124.1, 121.7 ppm

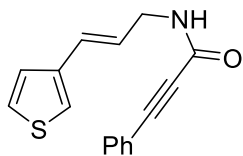
IR (thin film)

3369, 2254, 2127, 1658, 1474, 1376, 1322, 1025, 825, 764  $\text{cm}^{-1}$

HRMS (FTMS + p ESI)

[ $M+1$ ] calcd for  $\text{C}_7\text{H}_{10}\text{NS}$ : 140.0528; found 140.0532

TLC (Methanol)  $R_f$  = 0.01



**(*E*)-*N*-(3-(Thiophen-3-yl)allyl)-3-(trimethylsilyl)propiolamide (3.38).** A single-necked 10 mL round-bottomed flask equipped with a septum, magnetic stirring bar of dimension 150 mm by 100 mm, and nitrogen inlet was flame-dried and allowed to cool. The rubber septum was briefly removed, and the flask was charged with 3-phenylpropionic acid (**3.05**, 95 mg, 0.6 mmol), and tetrahydrofuran (4 mL) at rt. The solution was cooled to 0 °C (bath temperature) in an ice bath. Once cooled, dimethylformamide (4 drops, 21 gauge needle) was added dropwise. This was followed by dropwise addition of oxalyl chloride (60  $\mu\text{L}$ , 0.7 mmol) causing vigorous gas evolution.<sup>61</sup> The solution was stirred at 0 °C for 2 h then briefly removed from the ice bath and placed under vacuum to remove excess oxalyl chloride. The residue was dissolved in diethyl ether (1ml), cooled to 0 °C, and (*E*)-3-(thiophen-3-yl)prop-2-en-1-amine (**3.37**, 71 mg,

0.5 mmol) solvated in dichloromethane (0.5 mL) was added dropwise via syringe. After 2 h, the reaction was quenched with 5% hydrochloric acid (15 mL) and transferred to a separatory funnel. The aqueous layer washed with diethyl ether (3 x 20 mL). The organic layer was transferred to an Erlenmeyer flask and dried over MgSO<sub>4</sub>, vacuum filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10-30% ethyl acetate/hexanes) to yield compound **3.38** as a clear yellow solid (43 mg, 25%).

Notebook: 02-106

#### Data for **3.38**

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.55-7.52 (m, 2 H), 7.43-7.36 (m, 3 H), 7.28-7.27 (m, 1 H), 7.21-7.20 (m, 1 H), 7.18-7.17 (m, 1 H), 6.61 (d,  $J$  = 16.0 Hz, 1 H), 6.10 (dt,  $J$  = 16.0 Hz, 6.2 Hz, 1 H), 6.06 (b s, 1 H), 4.12 (t,  $J$  = 6.2 Hz, 2 H).

H<sub>2</sub>O impurity 1.56 ppm, Grease impurity 1.26 ppm, Unknown impurity 3.40, 2.73, 1.94 ppm

<sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 153.5, 139.2, 132.9, 132.8, 130.4, 128.9, 128.8, 127.4, 126.5, 125.2, 124.5, 122.8, 120.4, 42.2 ppm.

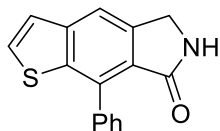
IR (thin film)

3269, 3056, 2920, 2219, 1629, 1537, 1300, 1216, 1085, 963, 757, 689 cm<sup>-1</sup>

HRMS (FTMS + p ESI)

[M+1] calcd for C<sub>16</sub>H<sub>14</sub>ONS: 268.0791; found, 268.0793

TLC (20% ethyl acetate/hexanes) R<sub>f</sub> = 0.3



**8-Phenyl-5,6-dihydro-7H-thieno[2,3-f]isoindol-7-one (3.39a).** (entry 6 **Table 2**) To a 0.5-2 mL microwave vial and equipped with flea stir bar was added diene-yne (**3.38**, 30 mg, 0.1 mmol) in 10% nitrobenzene/*o*DCB (*v/v*) (1.5 mL) to a final concentration of 0.06 M. The solution was heated for 30 min at 225 °C and cooled to 55 °C. The reaction solution color changed from yellow to dark amber. The solution was poured directly onto silica plug, and solvent removed (10-40% ethyl acetate/hexanes), **3.39a** was isolated with (50% ethyl acetate/hexanes) to yield a white solid (24 mg, 82 %, as a 95:5 ratio of benzo[b]thiophene: dihydrobenzo[b]thiophene). Notebook: 02-079, 02-108

Data for **3.39a**

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ = 7.85 (s, 1 H), 7.63-7.60 (m, 3 H), 7.52-7.44 (m, 4 H), 6.19 (b s, 1 H), 4.53 (s, 2 H).

H<sub>2</sub>O impurity 1.54 ppm; Ethyl Acetate 4.12, 2.05, 1.2 ppm

<sup>13</sup>C NMR (500 MHz, CDCl<sub>3</sub>) δ = 172.4, 146.7, 141.9, 139.9, 134.7, 133.8, 130.3, 123.2, 119.2, 45.0 ppm

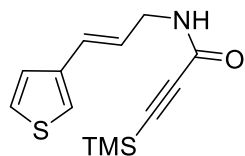
IR (thin film)

3225, 2985, 2926, 1742, 1691, 1607, 1554, 1464, 1374, 1243, 1047, 914, 745 cm<sup>-1</sup>

HRMS (FTMS + p ESI)

[M+1] calcd for C<sub>16</sub>H<sub>12</sub>ONS: 266.0634; found 266.0642

TLC (50% ethyl acetate/hexanes) R<sub>f</sub> = 0.4



**(E)-N-(3-(Thiophen-3-yl)allyl)-3-(trimethylsilyl)propiolamide (3.40).** A single-necked 25 mL round-bottomed flask equipped with a septum, magnetic stirring bar of dimension 150 mm by 100 mm, and nitrogen inlet was flame-dried and allowed to cool. The rubber septum was briefly removed, and the flask was charged with 3-(trimethylsilyl)propiolic acid (**3.25**, 126 mg, 0.9 mmol), and tetrahydrofuran (3 mL) at rt. The solution was cooled to 0 °C (bath temperature) in an ice bath. Once cooled, dimethylformamide (4 drops, 21 gauge needle) was added dropwise.<sup>61</sup> This was followed by dropwise addition of oxalyl chloride (80  $\mu$ L, 1.0 mmol) causing vigorous gas evolution. The solution was stirred at 0 °C for 2.5 hours then briefly removed from the ice bath and placed under vacuum to remove excess oxalyl chloride. The residue was placed back into the ice bath and (*E*)-3-(thiophen-3-yl)prop-2-en-1-amine (**3.37**, 139 mg, 1.0 mmol) solvated in dichloromethane (0.5 mL) was added dropwise via syringe and stirred overnight. The reaction was quenched with 5% hydrochloric acid (15 mL) and transferred to a separatory funnel. The aqueous layer washed with diethyl ether (3 x 20 mL). The organic layer was transferred to an Erlenmeyer flask and dried over MgSO<sub>4</sub>, vacuum filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10-30% ethyl acetate/hexanes) to yield compound **3.40** as a clear yellow oil (76 mg, 32%). Notebook: 02-075, 02-116

#### Data for **3.40**

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.28-7.27 (m, 1 H), 7.19-7.16 (m, 2 H), 6.56 (d,  $J$  = 16.0 Hz, 1 H), 6.03 (dt,  $J$  = 16.0 Hz, 6.5 Hz, 1 H), 5.93 (b s, 1 H), 4.04 (t,  $J$  = 6.5 Hz, 2 H), 0.23 (s, 9 H).

Z Amide Isomer 5.79 (b s), 4.18 (t), 0.25 (s)

$^{13}\text{C}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  = 152.9, 139.3, 127.6, 126.6, 125.3, 124.5, 122.9, 97.8, 92.1, 42.1, -0.3 ppm.

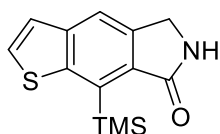
IR (thin film)

3101, 2959, 2170, 1707, 1635, 1536, 1251, 1083, 963, 848, 763  $\text{cm}^{-1}$

HRMS (FTMS + p ESI)

[M+1] calcd for  $\text{C}_{13}\text{H}_{18}\text{ONSSi}$ : 264.0873; found, 264.0879

TLC (20% ethyl acetate/hexanes)  $R_f$  = 0.4



**8-(Trimethylsilyl)-5,6-dihydro-7H-thieno[2,3-f]isoindol-7-one (3.41a).** (entry 7 Table 2) To a 0.5-2 mL microwave vial and equipped with flea stir bar was added diene-yne (**3.40**, 30 mg, 0.11 mmol) in 10% nitrobenzene/*o*DCB (*v/v*) (1.6 mL) to a final concentration of 0.06 M. The solution was heated for 30 min at 225 °C and cooled to 55 °C. The reaction solution color changed from yellow to dark amber. The solution was poured directly onto silica plug, and solvent removed (10-40% ethyl acetate/hexanes), **3.40a** was isolated with (30% ethyl acetate/hexanes) to yield a yellow solid (22.4 mg, 74 %, as a 99:1 ratio of benzo[b]thiophene: dihydrobenzo[b]thiophene). Notebook: 02-109, 02-120

Data for **3.41a**

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.87 (s, 1 H), 7.64 (d,  $J$  = 5.5 Hz, 1 H), 7.38 (d,  $J$  = 5.5 Hz, 1 H), 6.01 (b s, 1 H), 4.50 (s, 2 H), 0.61 (s, 9 H).

H<sub>2</sub>O impurity 1.54 ppm

<sup>13</sup>C NMR (500 MHz, CDCl<sub>3</sub>) δ = 172.5, 146.6, 141.8, 139.8, 134.5, 133.9, 130.1, 123.1, 119.1,

45.0, 2.5 ppm

IR (thin film)

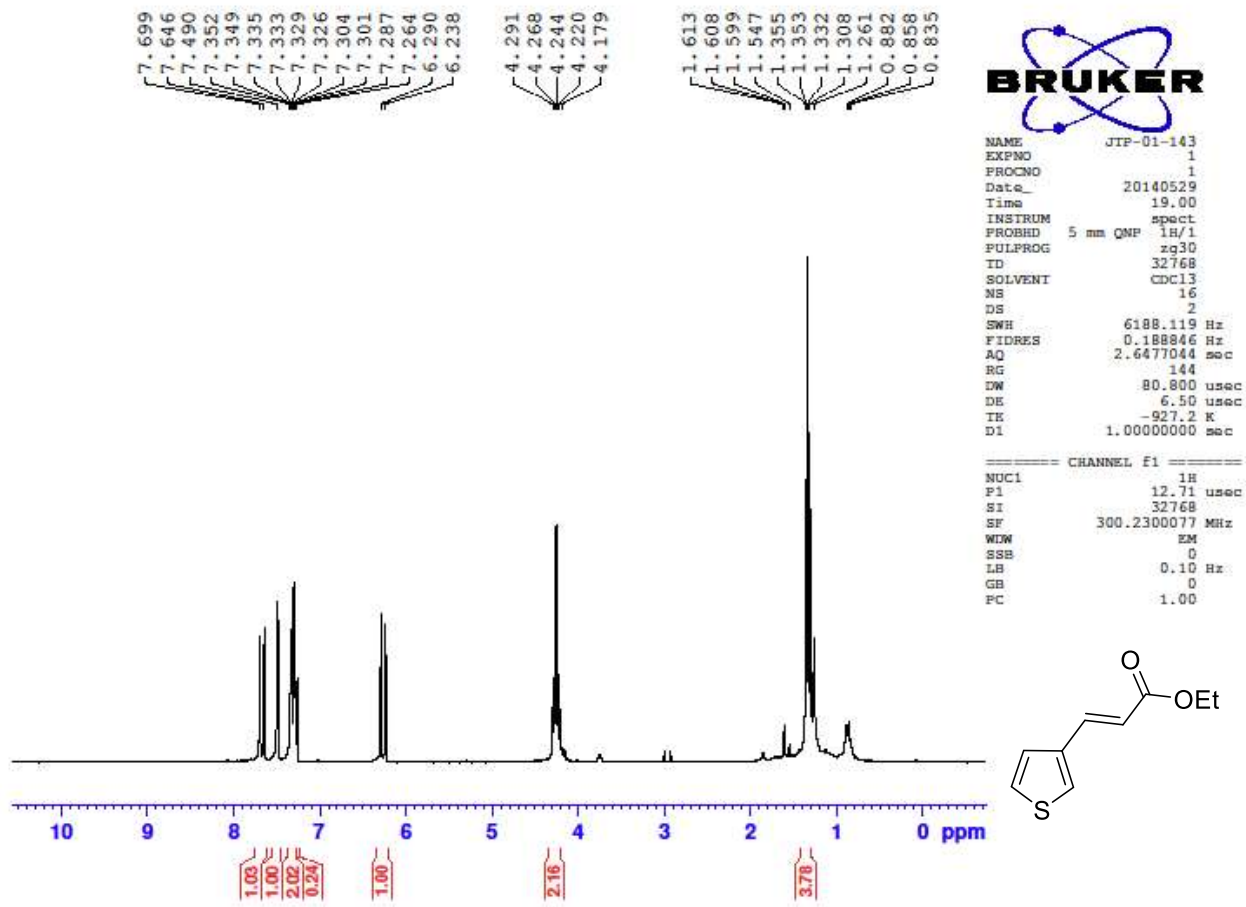
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cm<sup>-1</sup>

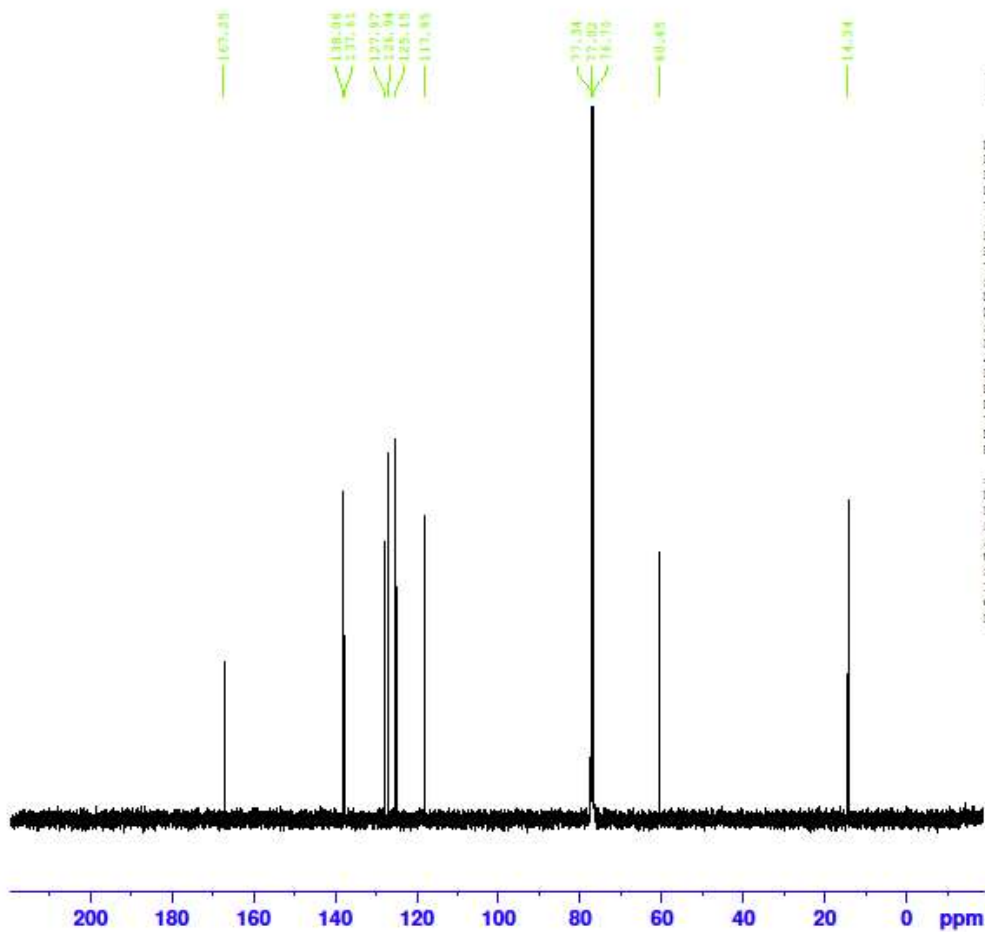
HRMS (FTMS + p ESI)

[M+1] calcd for C<sub>13</sub>H<sub>16</sub>ONSSi:262.0716; found 262.0721

TLC (30% ethyl acetate/hexanes) R<sub>f</sub> = 0.4

## A.4 COMPOUND <sup>1</sup>H AND <sup>13</sup>C NMR SPECTRA





```

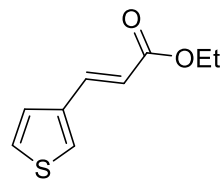
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NS         1024
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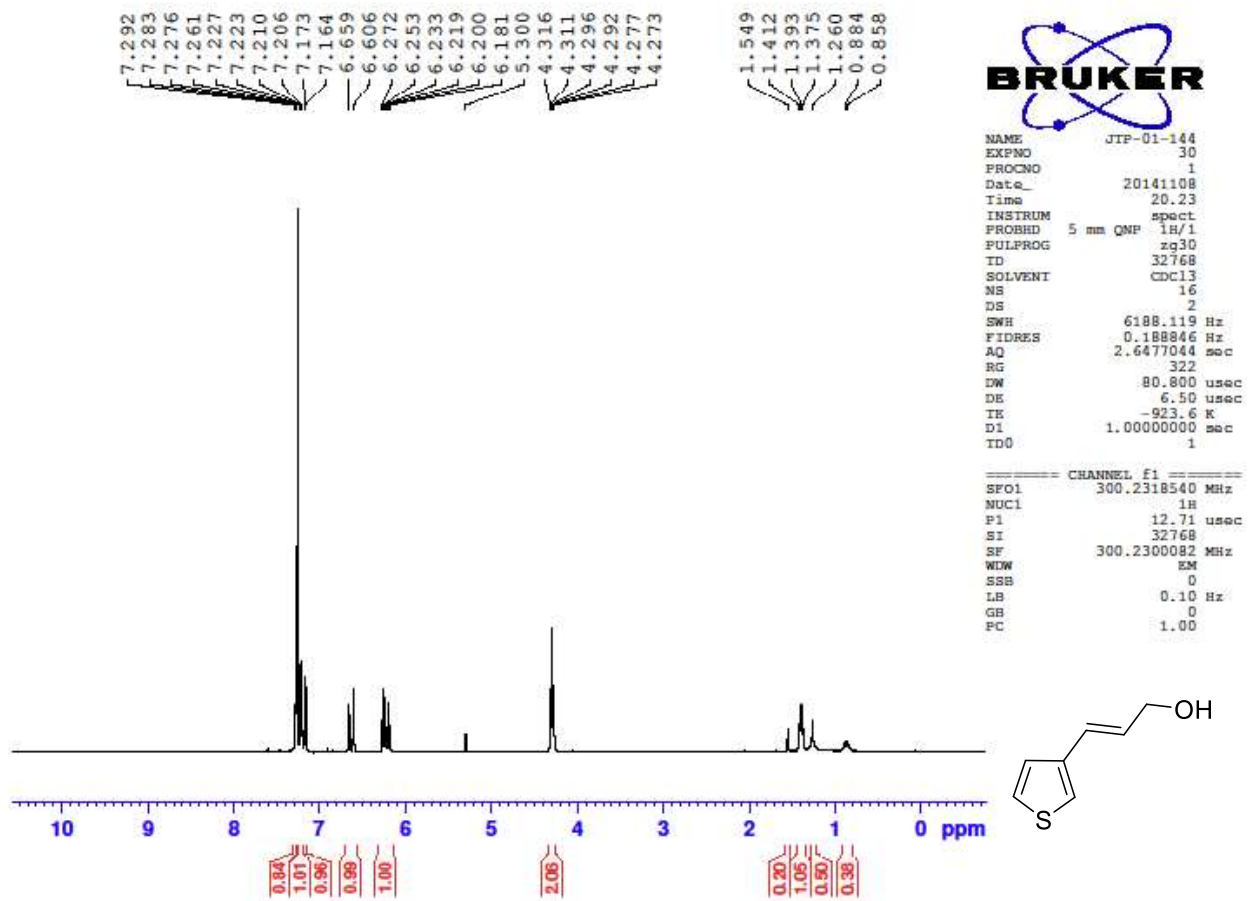
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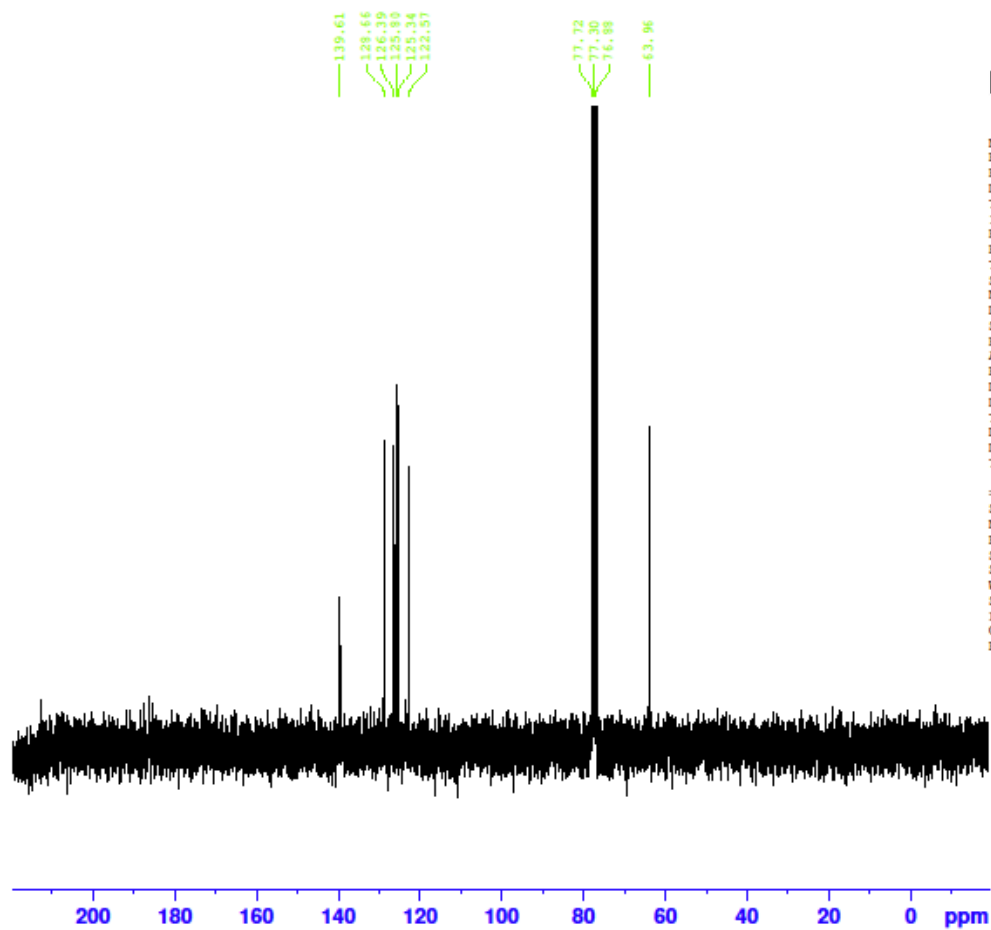
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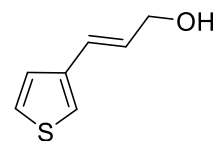


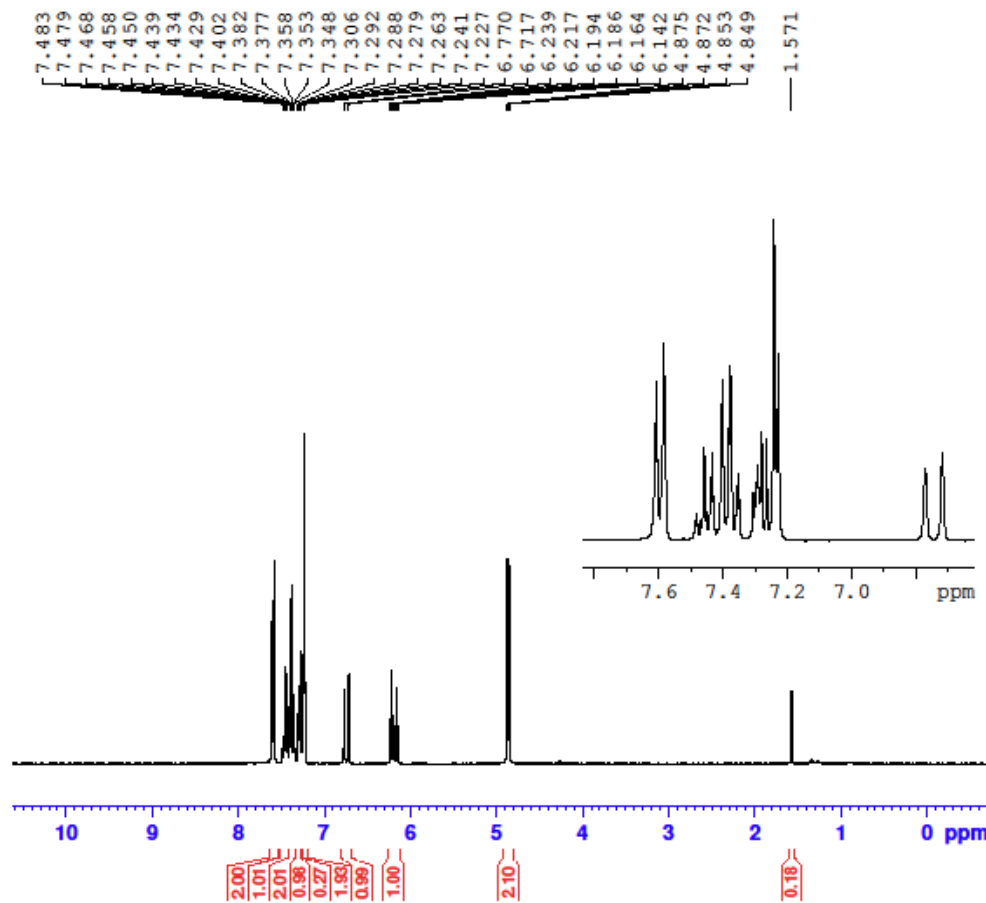
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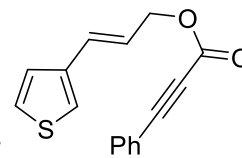
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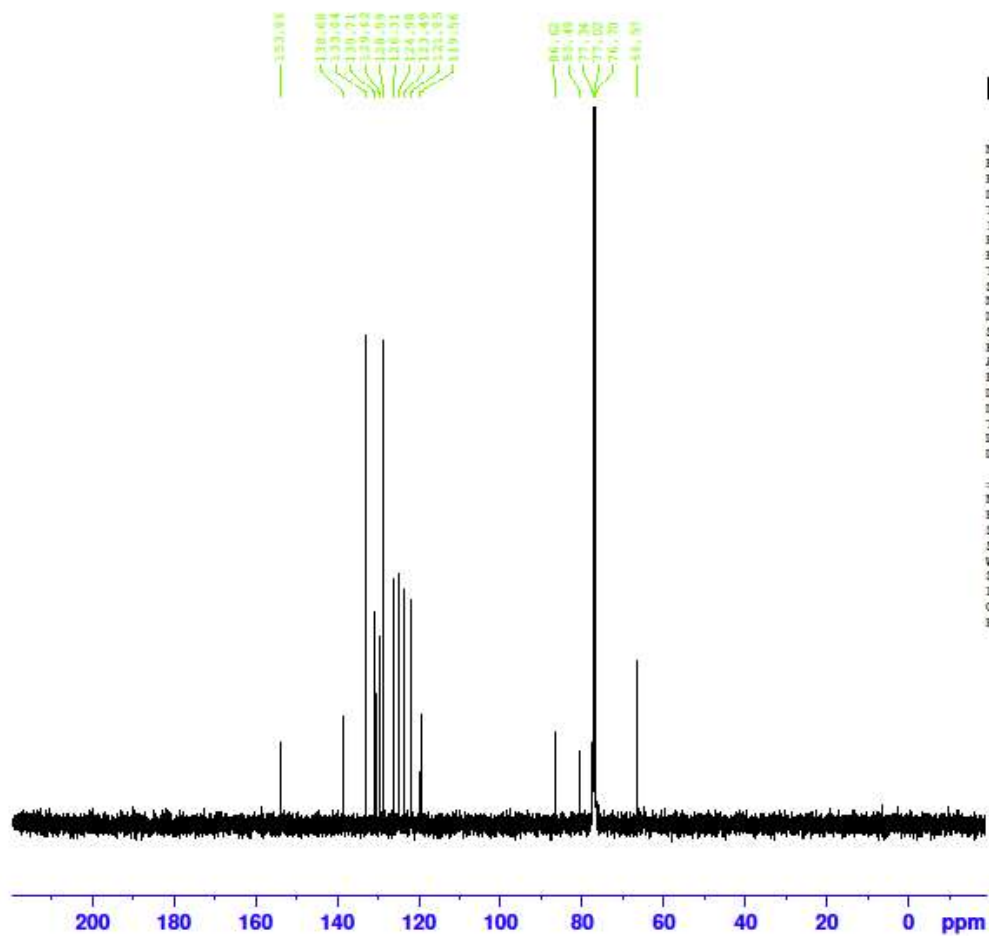




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 DS 2  
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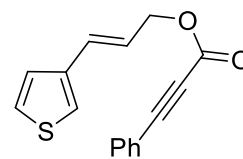
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PULPROG       zgpg30
TD            65536
SOLVENT       CDCl3
NS            1024
DS            4
SWH           24038.461 Hz
FIDRES        0.366798 Hz
AQ            1.3631988 sec
RG            203
EW           20.800 usec
DE            6.50 usec
TE            -1004.4 K
D1            2.00000000 sec
D11           0.03000000 sec

```

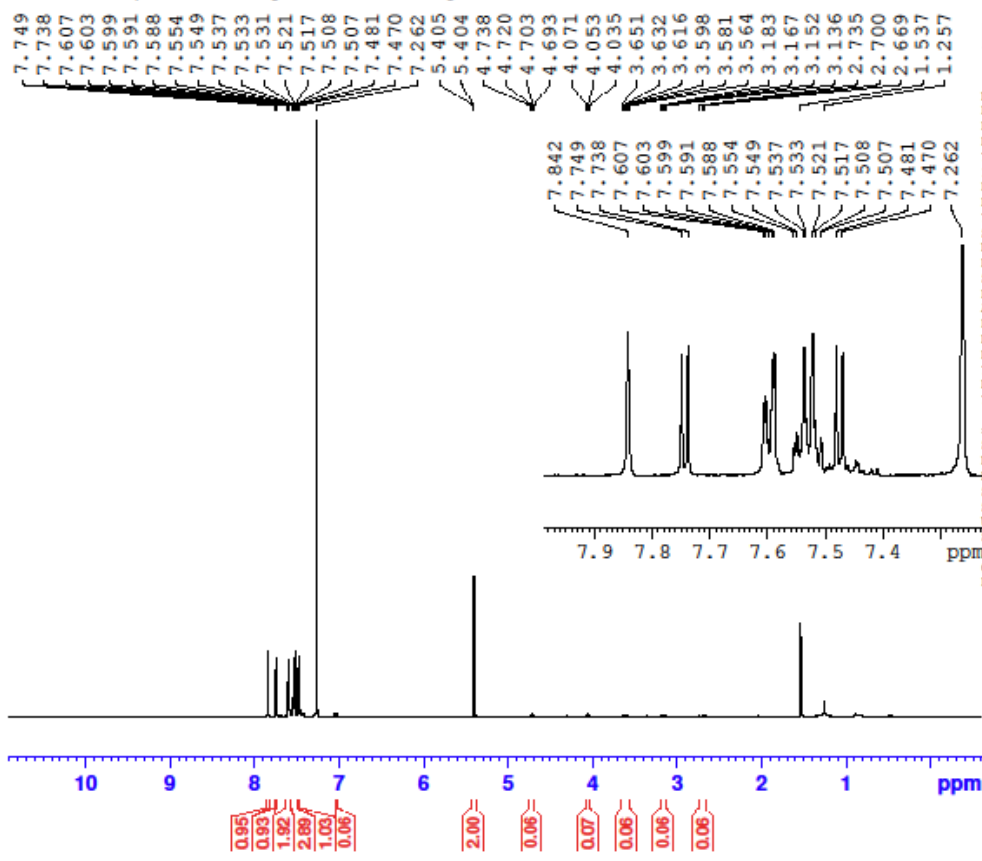
```

===== CHANNEL f1 =====
NUC1          13C
P1            10.00 usec
SI            32768
SF            100.6127690 MHz
WDW           EM
SSB           0
LB            1.00 Hz
GB            0
PC            1.40

```

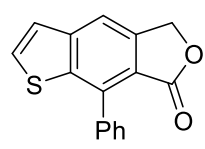


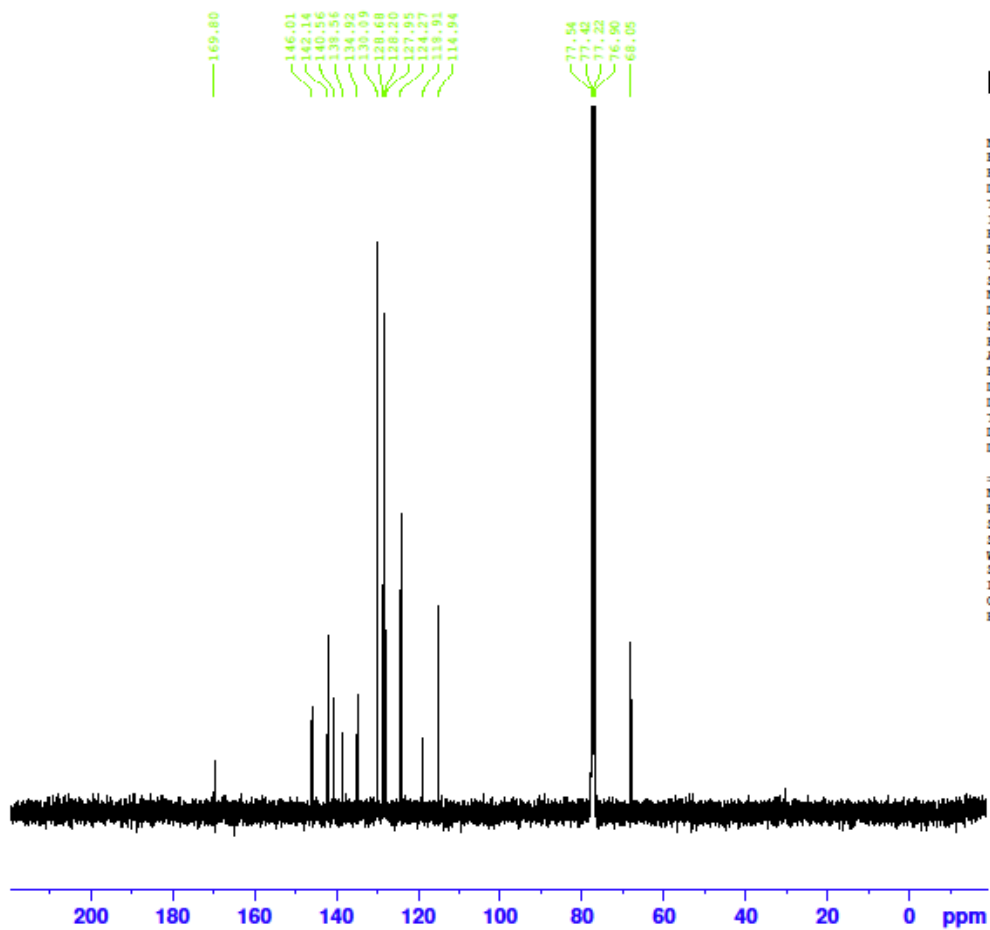
JTP-02-117, Benzothiophene Lactone pure



NAME JTP-02-117  
 EXPNO 20  
 PROCNO 1  
 Date\_ 20151015  
 Time 14.00  
 INSTRUM spect  
 PROBHD 5 mm PABBO BB/  
 PULPROG zg30  
 TD 65536  
 SOLVENT CDCl3  
 NS 16  
 DS 2  
 SWH 10000.000 Hz  
 FIDRES 0.152588 Hz  
 AQ 3.2768500 sec  
 RG 203  
 DW 50.000 usec  
 DE 6.50 usec  
 TE 297.7 K  
 D1 1.00000000 sec  
 TD0 1

==== CHANNEL f1 =====  
 SFO1 500.1630887 MHz  
 NUC1 1H  
 P1 11.45 usec  
 SI 65536  
 SF 500.1600119 MHz  
 MDW EM  
 SSB 0  
 GB 0.30 Hz  
 PC 1.00



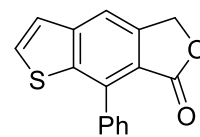


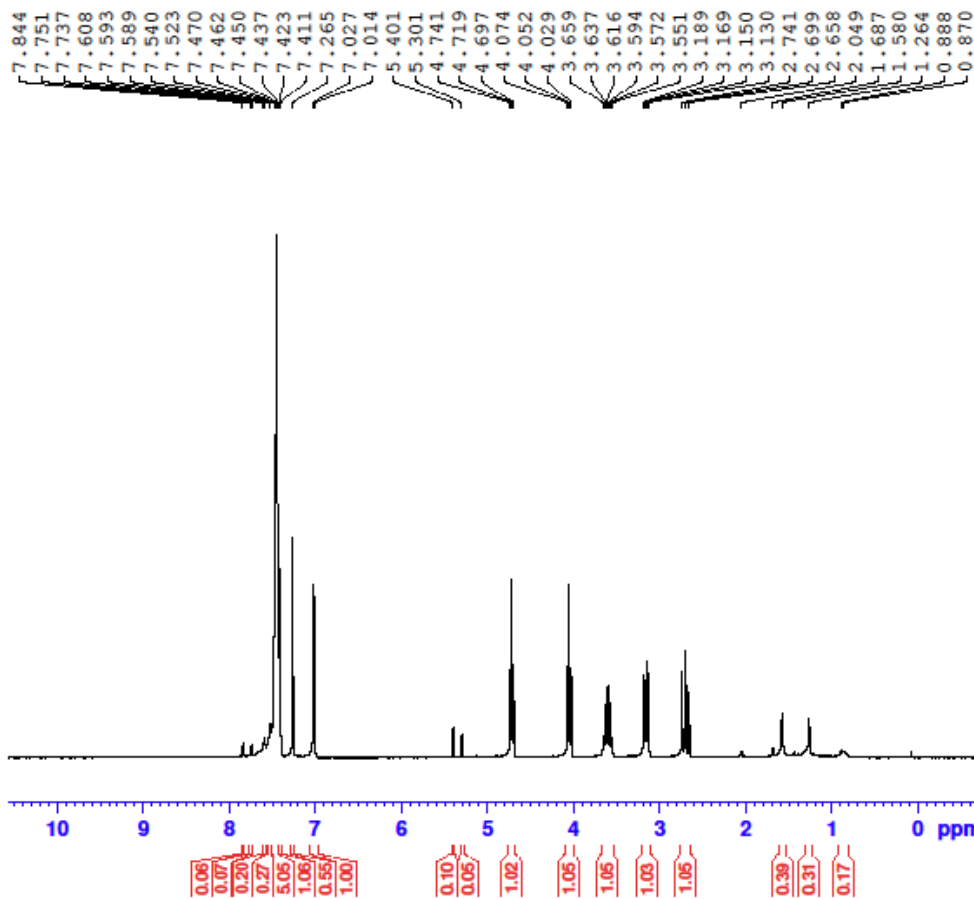
```

NAME      JTP-01-147
EXPNO     2
PROCNO    1
Date_     20140730
Time      23.04
INSTRUM   5 mm FAPBO BB-
PROBHD    spect
PULPROG   zgpg30
TD         65536
SOLVENT   cdcl3
NS         1024
DS         4
SWH        24038.461 Hz
FIDRES     0.366798 Hz
AQ         1.3631988 sec
RG         203
DW         20.800 usec
DE         6.50 usec
TE         93.8 K
D1         2.0000000 sec
D11        0.0300000 sec
  
```

```

===== CHANNEL f1 =====
NUC1      13C
P1        10.00 usec
SI        32768
SF        100.6127491 MHz
WDW       EM
SSB       0
LB        1.00 Hz
GB        0
PC        1.40
  
```



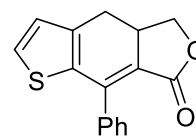


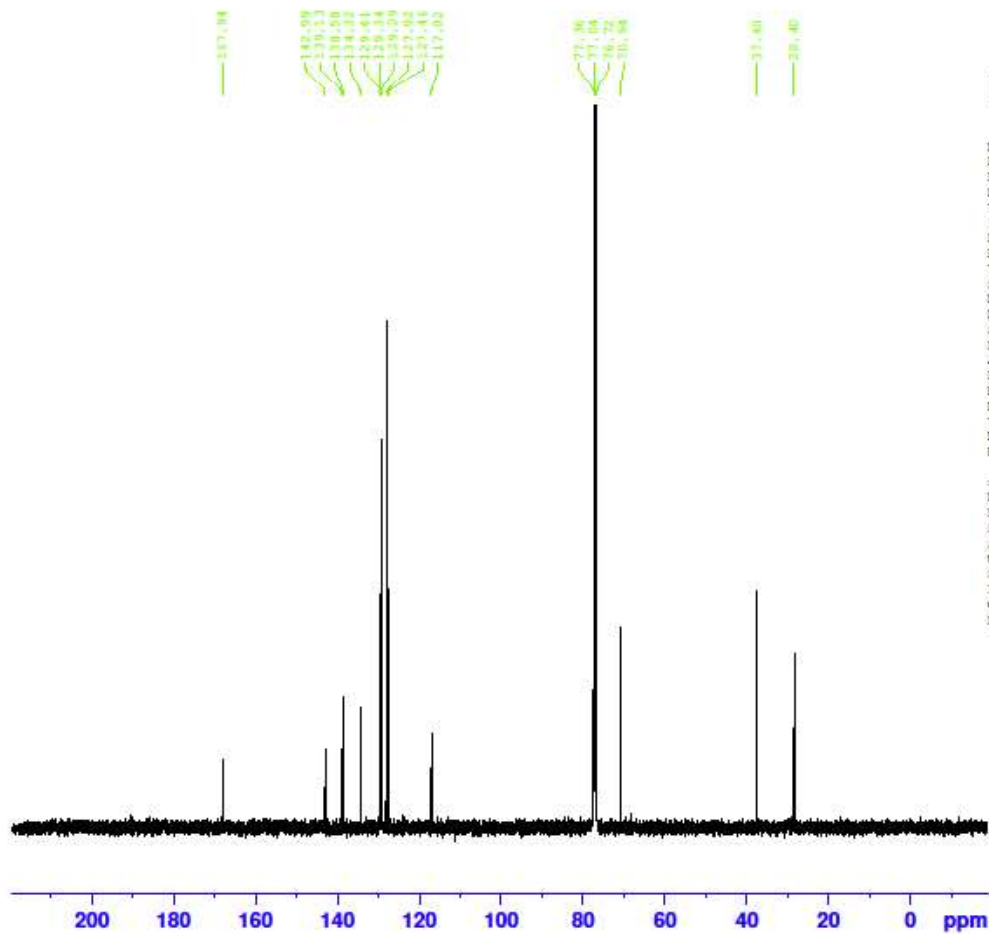
```

NAME          JTP-01-149
EXPNO         20
PROCNO        1
Date_         20140806
Time          18.57
INSTRUM       spect
PROBHD        5 mm PABBO BB-
PULPROG       zg30
TD            65536
SOLVENT       CDCl3
NS            16
DS            2
SWH           8223.685 Hz
FIDRES        0.125483 Hz
AQ            3.9846387 sec
RG            101
DW            60.800 usec
DE            6.50 usec
TE            92.9 K
D1            1.00000000 sec
  
```

```

===== CHANNEL f1 =====
NUC1          1H
P1            13.75 usec
SI            65536
SF            400.1300084 MHz
WDW           EM
SSB           0
LB            0.30 Hz
GB            0
PC            1.00
  
```





```

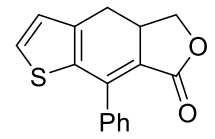
NAME      JTP-01-149
EXPNO     21
PROCNO    1
Date_     20140807
Time      4.08
INSTRUM   spect
PROBHD    5 mm PABBO BB-
PULPROG   zgpg30
TD        65536
SOLVENT   CDCl3
NS        1024
DS        4
SWH       24038.461 Hz
FIDRES    0.366798 Hz
AQ        1.3631988 sec
RG        203
EW        20.800 usec
DE        6.50 usec
TE        97.0 K
D1        2.00000000 sec
D11       0.03000000 sec

```

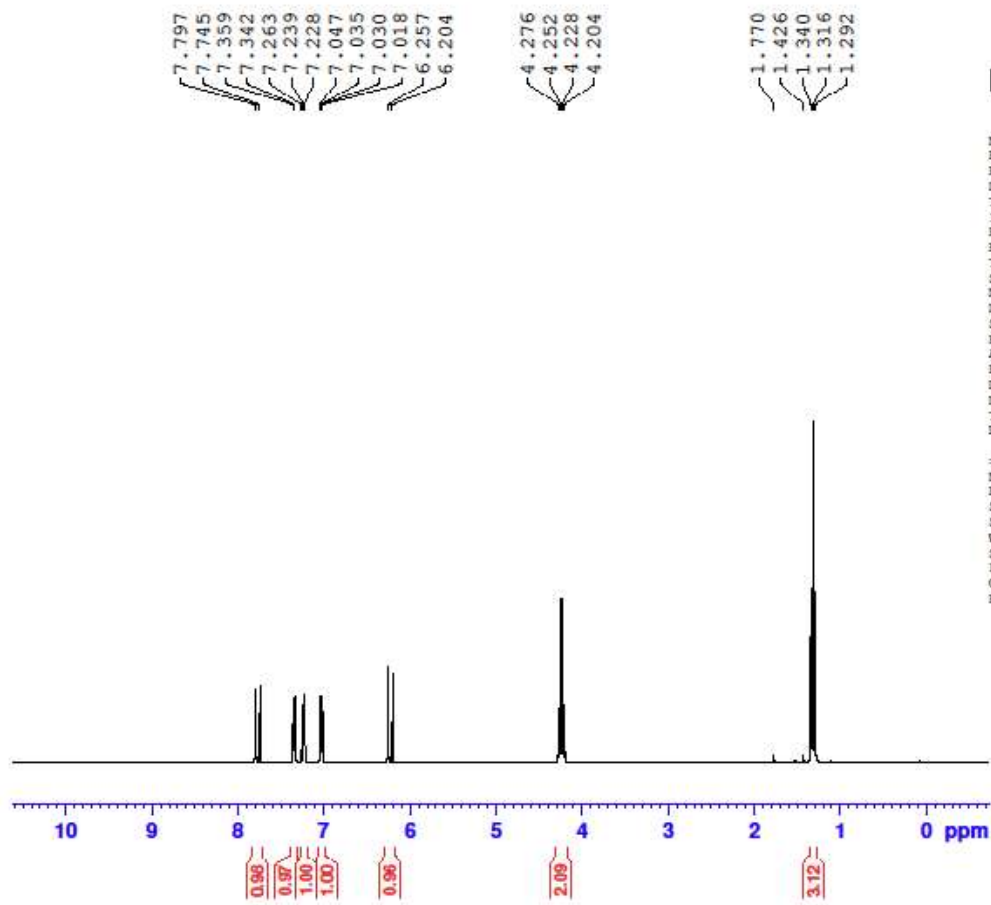
```

===== CHANNEL f1 =====
NUC1      13C
P1        10.00 usec
SI        32768
SF        100.6127690 MHz
WDW       EM
SSB       0
LB        1.00 Hz
GB        0
PC        1.40

```





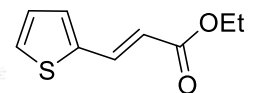


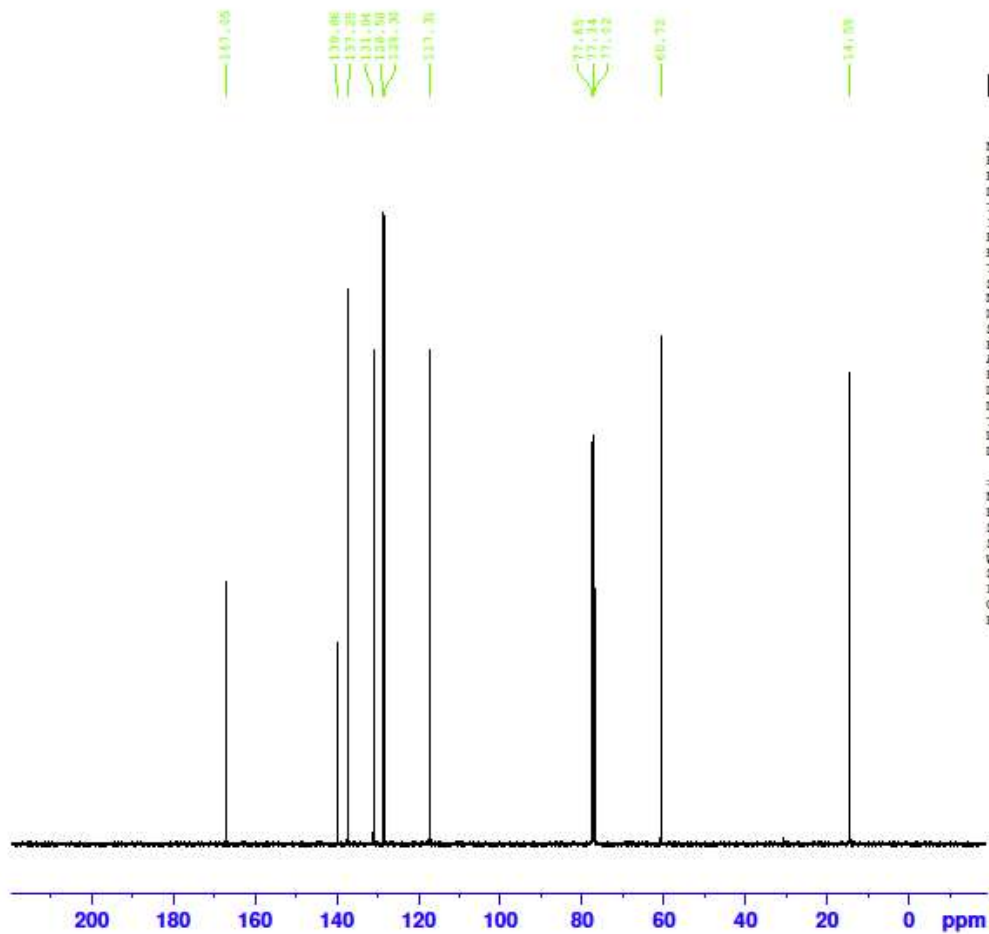
```

NAME      JTP-01-060
EXPNO     6
PROCNO    1
Date_     20140113
Time      13.10
INSTRUM   spect
PROBHD    5 mm QNP 1H/1
PULPROG   zg30
TD         32768
SOLVENT   cdcl3
NS         16
DS         2
SWH        6188.119 Hz
FIDRES     0.188846 Hz
AQ         2.6477044 sec
RG         57
DW         80.800 usec
DE         6.50 usec
TE         -929.4 K
D1         1.0000000 sec
  
```

```

===== CHANNEL F1 =====
NUC1      1H
P1        12.71 usec
SI        32768
SF        300.2300075 MHz
WDW       EM
SSB       0
LB        0.10 Hz
GB        0
PC        1.00
  
```



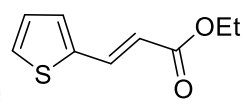


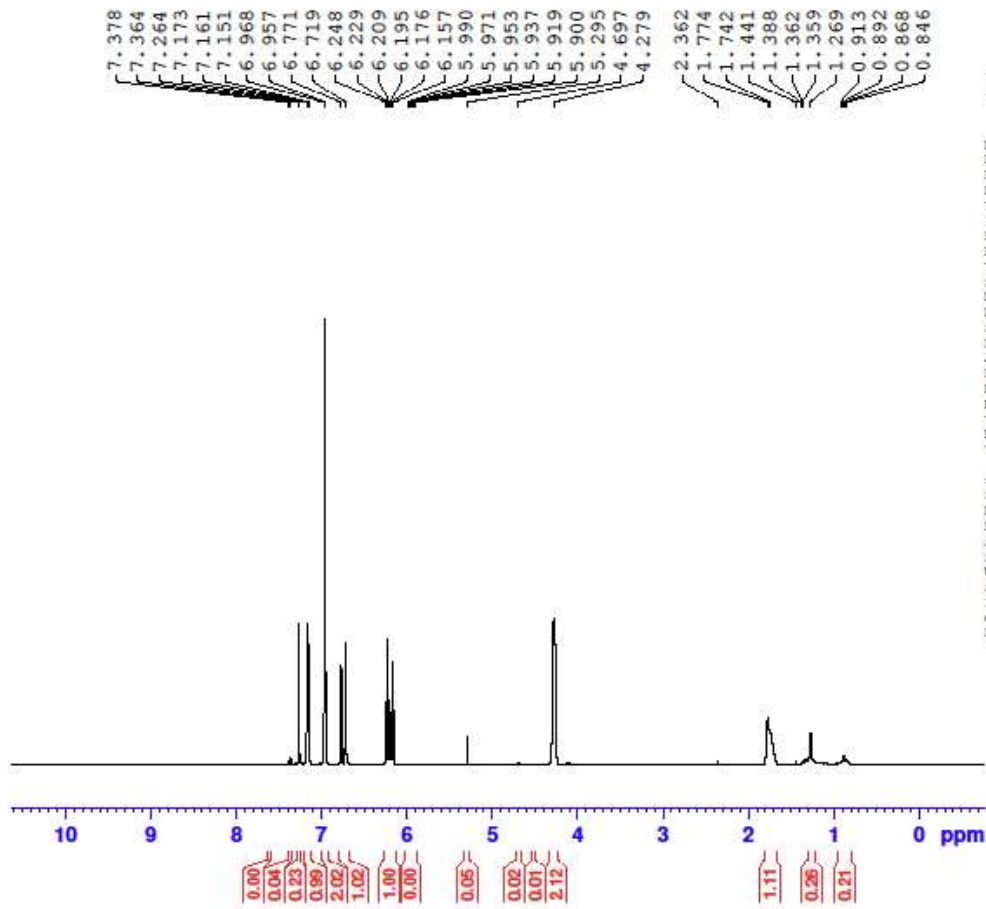
```

NAME      JTP-01-060
EXPNO     2
PROCNO    1
Date_     20140114
Time      2.15
INSTRUM   spect
PROBHD    5 mm PABBO BB-
PULPROG   zgpg30
TD         65536
SOLVENT   Cmc13
NS         1024
DS         4
SWH       24038.461 Hz
FIDRES    0.366798 Hz
AQ         1.3631988 sec
RG         203
DW         20.800 usec
DE         6.50 usec
TE         1625.8 K
D1         2.00000000 sec
D11        0.03000000 sec
  
```

```

===== CHANNEL f1 =====
NUC1      13C
P1         10.00 usec
SI         32768
SF        100.6127435 MHz
WDW        EM
SSB         0
LB         1.00 Hz
GB         0
PC         1.40
  
```



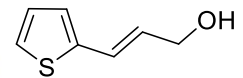


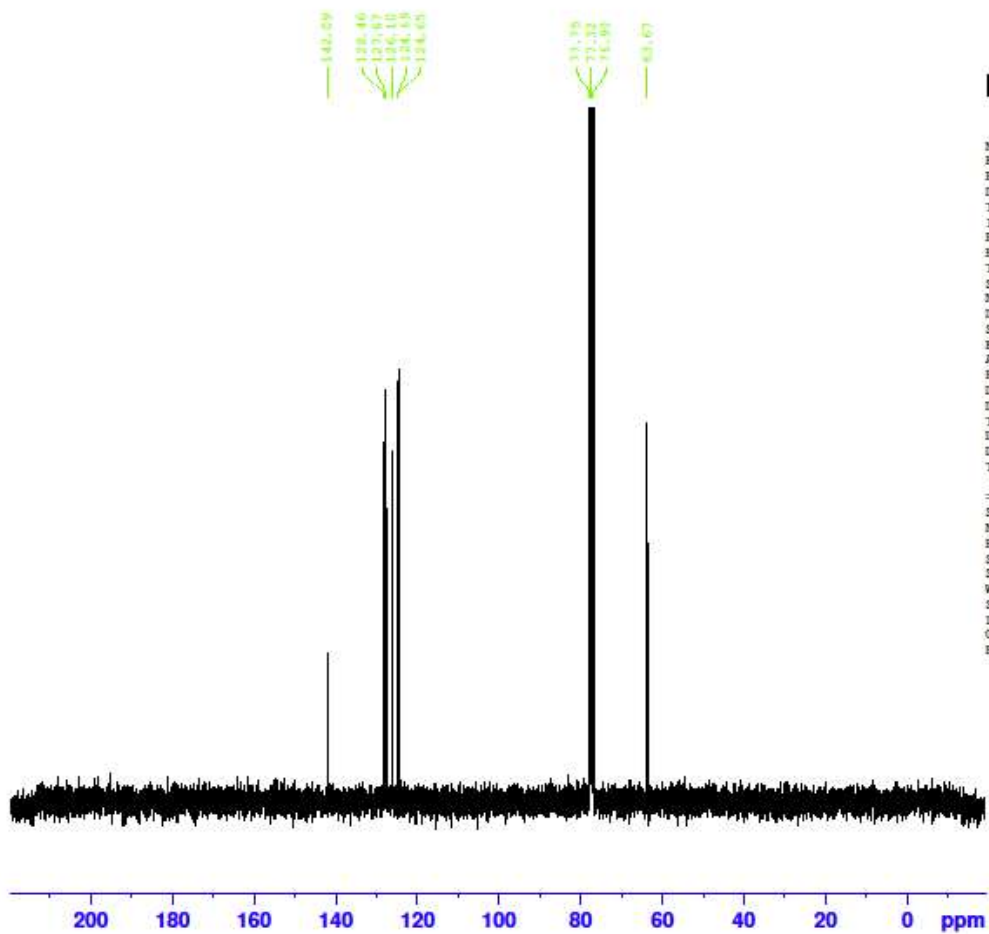
```

NAME      JTP-01-174
EXPNO     1
PROCNO    1
Date_     20141031
Time      15.07
INSTRUM   spect
PROBHD    5 mm QNP 1H/1
PULPROG   zg30
ID        32768
SOLVENT   cdcl3
NS        16
DS        2
SWH       6188.119 Hz
FIDRES    0.188846 Hz
AQ        2.6477044 sec
RG        101
DW        80.800 usec
DE        6.50 usec
TE        -923.3 K
D1        1.00000000 sec
TD0       1
  
```

```

===== CHANNEL f1 =====
SFO1     300.2318540 MHz
NUC1     1H
P1       12.71 usec
SI       32768
SF       300.2300079 MHz
WDW      EM
SSB      0
LB       0.10 Hz
GB       0
PC       1.00
  
```



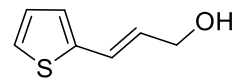


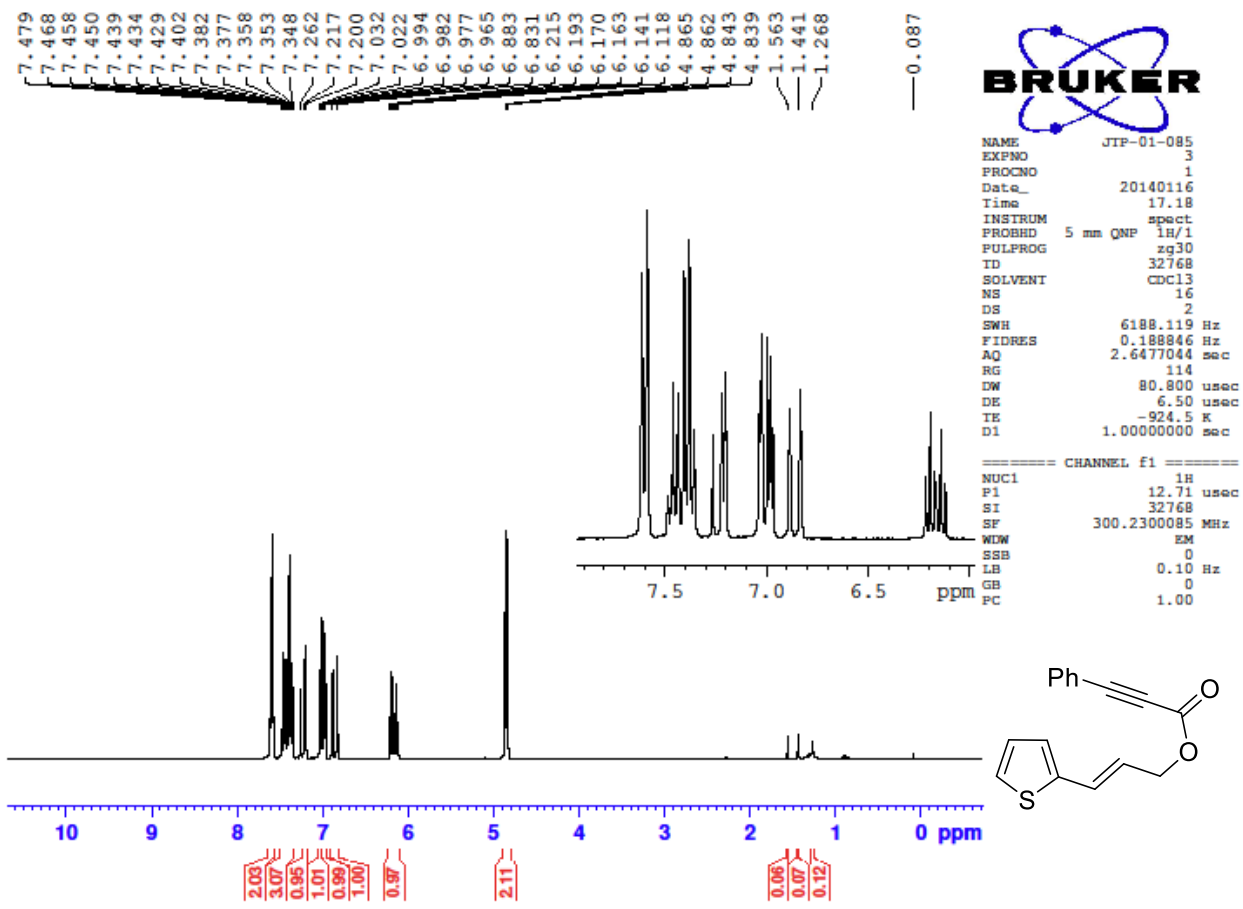
```

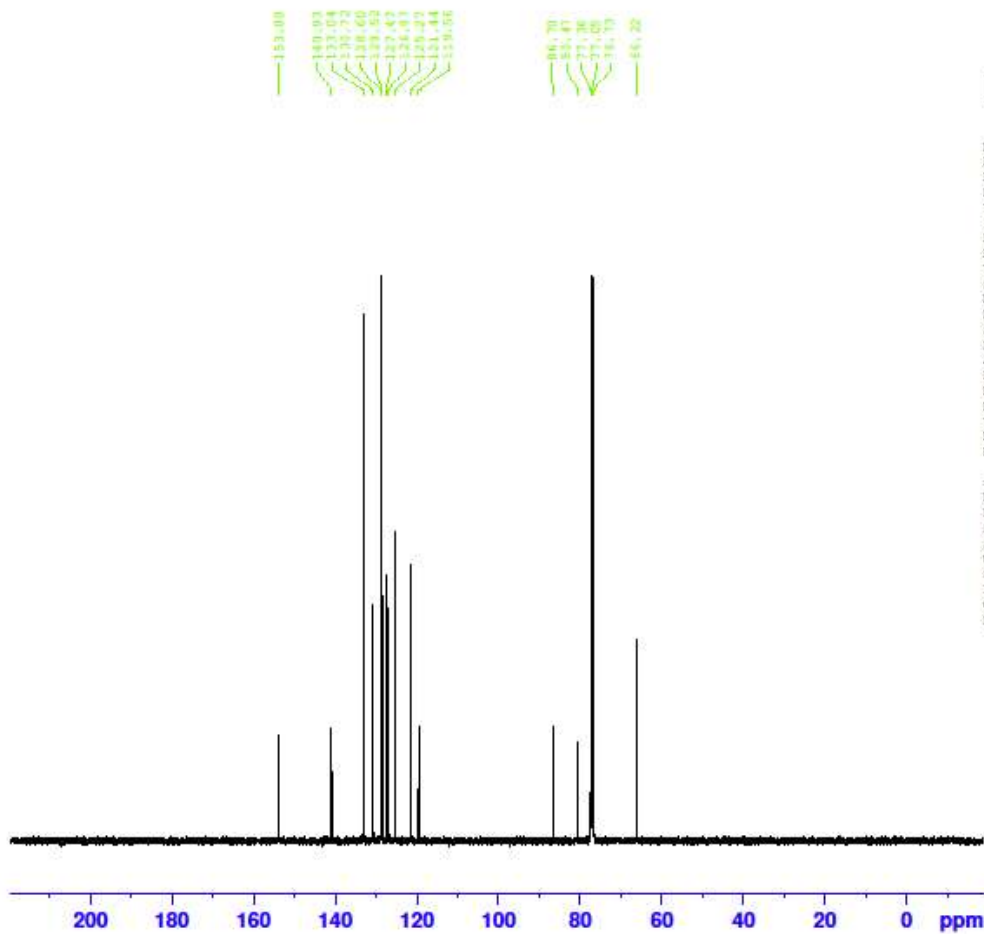
NAME      JTP-01-174
EXPNO     30
PROCNO    1
Date_     20141108
Time      17.38
INSTRUM   spect
PROBHD    5 mm QNP 1H/1
FULPROG   zgpg30
TD         65536
SOLVENT   CDCl3
NS         200
DS         4
SWH       18028.846 Hz
FIDRES    0.275098 Hz
AQ         1.8175818 sec
RG         228
DW         27.733 usec
DE         6.50 usec
TE         -923.5 K
D1         2.00000000 sec
D11        0.03000000 sec
TD0        1
  
```

```

===== CHANNEL f1 =====
SFO1     75.5004428 MHz
NUC1      13C
P1        12.00 usec
SI        32768
SF        75.4928714 MHz
WDW       EM
SSB       0
LB        1.00 Hz
GB         0
PC         1.40
  
```







```

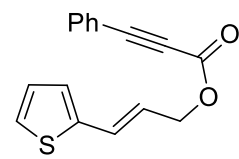
NAME      JTP-01-085
EXPNO     1
PROCNO    1
Date_     20140117
Time      6.38
INSTRUM   spect
PROBHD    5 mm PABBO BB-
PULPROG   zgpg30
TD         65536
SOLVENT   CDCl3
NS         1024
DS         4
SWH       24038.461 Hz
FIDRES    0.366798 Hz
AQ         1.3631988 sec
RG         203
EW         20.800 usec
DE         6.50 usec
TE         1287.7 K
D1         2.00000000 sec
D11        0.03000000 sec

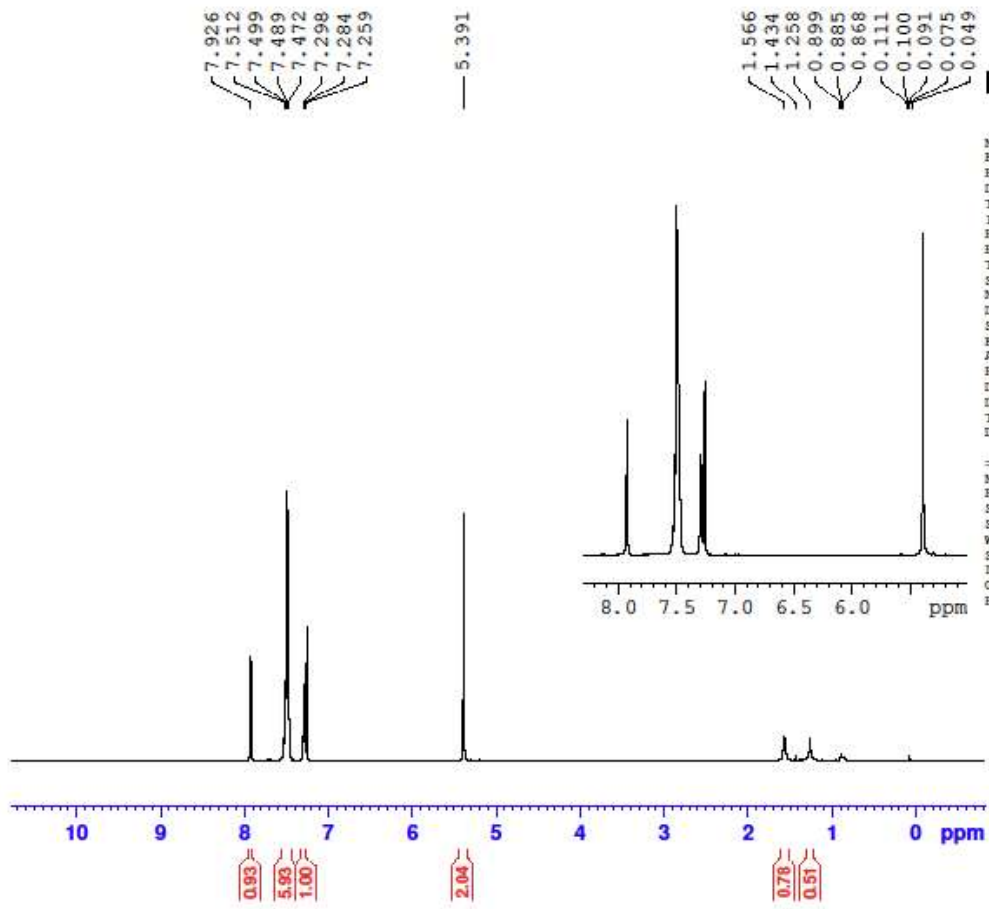
```

```

===== CHANNEL f1 =====
NUC1      13C
P1        10.00 usec
SI        32768
SF        100.6127690 MHz
WDW       EM
SSB       0
LB        1.00 Hz
GB        0
PC        1.40

```

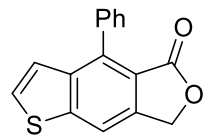


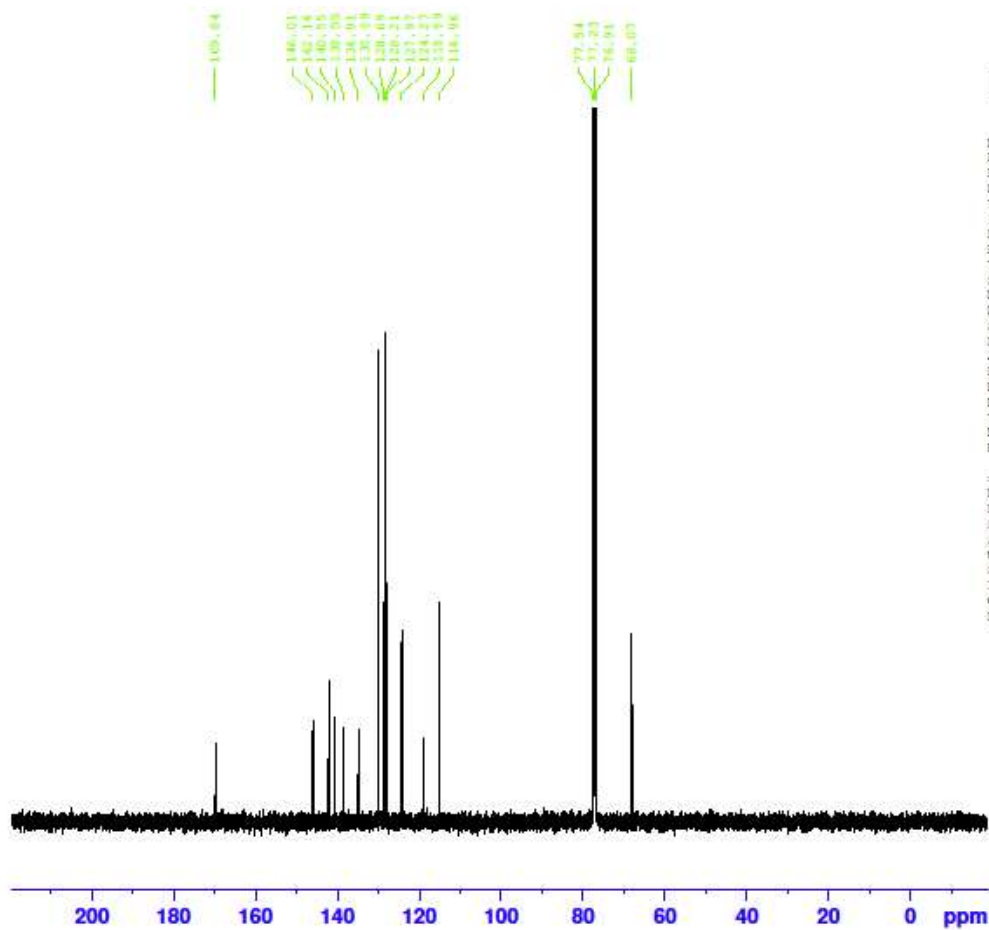


```

NAME      JTP-01-141
EXPNO     1
PROCNO    1
Date_     20140730
Time      16.15
INSTRUM   spect
PROBHD    5 mm PABBO BB-
PULPROG   zg30
TD         65536
SOLVENT   CDCl3
NS         16
DS         2
SWH       8223.685 Hz
FIDRES    0.125483 Hz
AQ         3.9846387 sec
RG         128
DW         60.800 usec
DE         6.50 usec
TE         95.9 K
D1         1.00000000 sec

===== CHANNEL f1 =====
NUC1       1H
P1         13.75 usec
SI         65536
SF         400.1300100 MHz
WDW        EM
SSB        0
LB         0.30 Hz
GB         0
PC         1.00
  
```





```

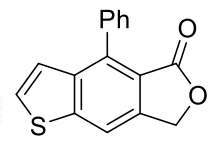
NAME      JTP-01-141
EXPNO     2
PROCNO    1
Date_     20140730
Time      22.02
INSTRUM   spect
PROBHD    5 mm PABBO BB-
PULPROG   zgpg30
TD         65536
SOLVENT   cdcl3
NS         1024
DS         4
SWH        24038.461 Hz
FIDRES     0.366798 Hz
AQ         1.3631988 sec
RG         203
EW         20.800 usec
DE         6.50 usec
TE         94.1 K
D1         2.00000000 sec
D11        0.03000000 sec

```

```

===== CHANNEL f1 =====
NUC1      13c
P1        10.00 usec
SI        32768
SF        100.6127491 MHz
WDW       EM
SSB       0
LB        1.00 Hz
GB        0
PC        1.40

```





7.417  
7.390  
7.382  
7.261  
7.091  
7.078  
6.737  
6.724  
5.393  
5.298  
4.747  
4.725  
4.703  
4.079  
4.056  
4.034  
3.703  
3.682  
3.660  
3.639  
3.618  
3.596  
3.262  
3.243  
3.223  
3.203  
2.879  
2.838  
2.797  
1.568  
1.436  
1.309  
1.291  
1.261  
0.885  
0.859

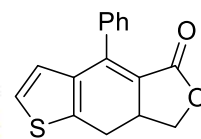
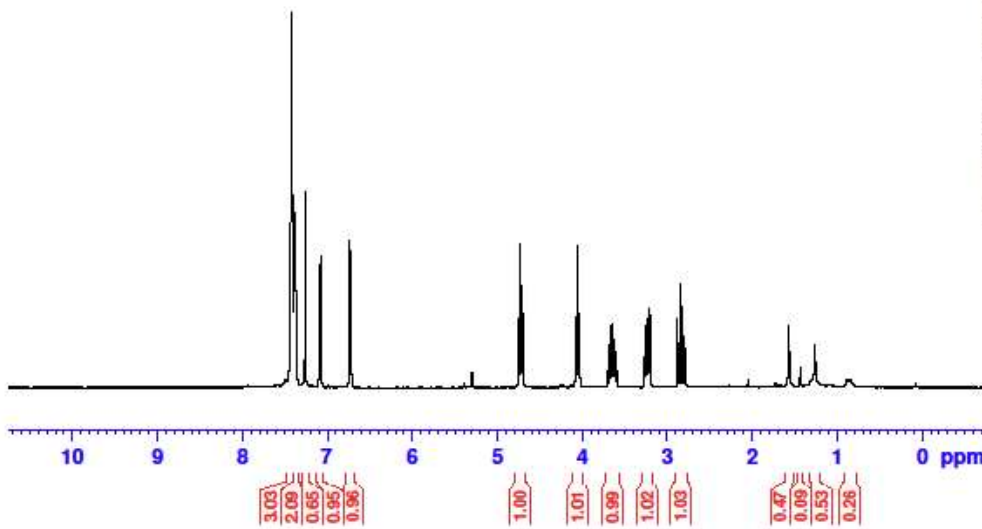


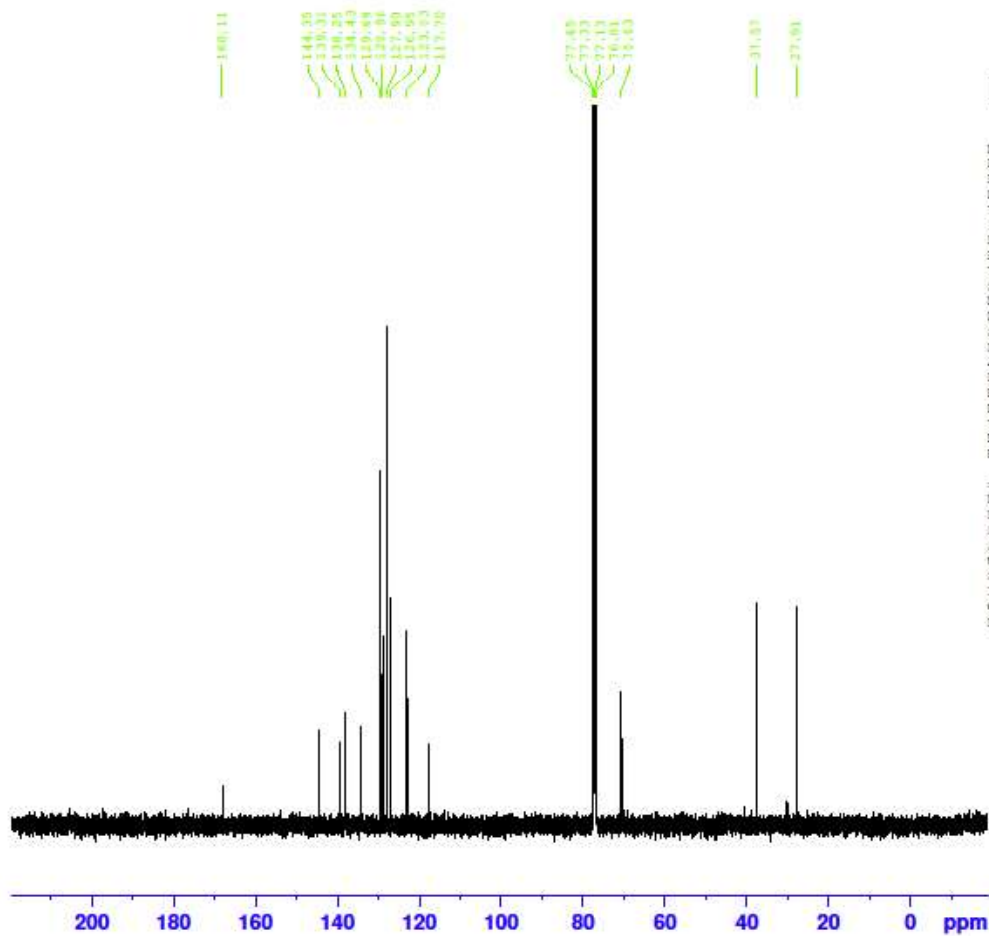
```

NAME      JTP-01-084
EXPNO     3
PROCNO    1
Date_     20140806
Time      11.52
INSTRUM   spect
PROBHD    5 mm PABBO BB-
PULPROG   zg30
TD         65536
SOLVENT   cdcl3
NS         16
DS         2
SWH       8223.685 Hz
FIDRES    0.125483 Hz
AQ         3.9846387 sec
RG         114
DW         60.800 usec
DE         6.50 usec
TE         93.8 K
D1         1.0000000 sec
  
```

```

===== CHANNEL F1 =====
NUC1      1H
P1        13.75 usec
SI        65536
SF        400.130094 MHz
WDW       EM
SSB       0
LB        0.30 Hz
GB        0
PC        1.00
  
```



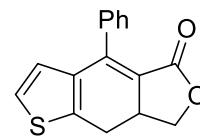


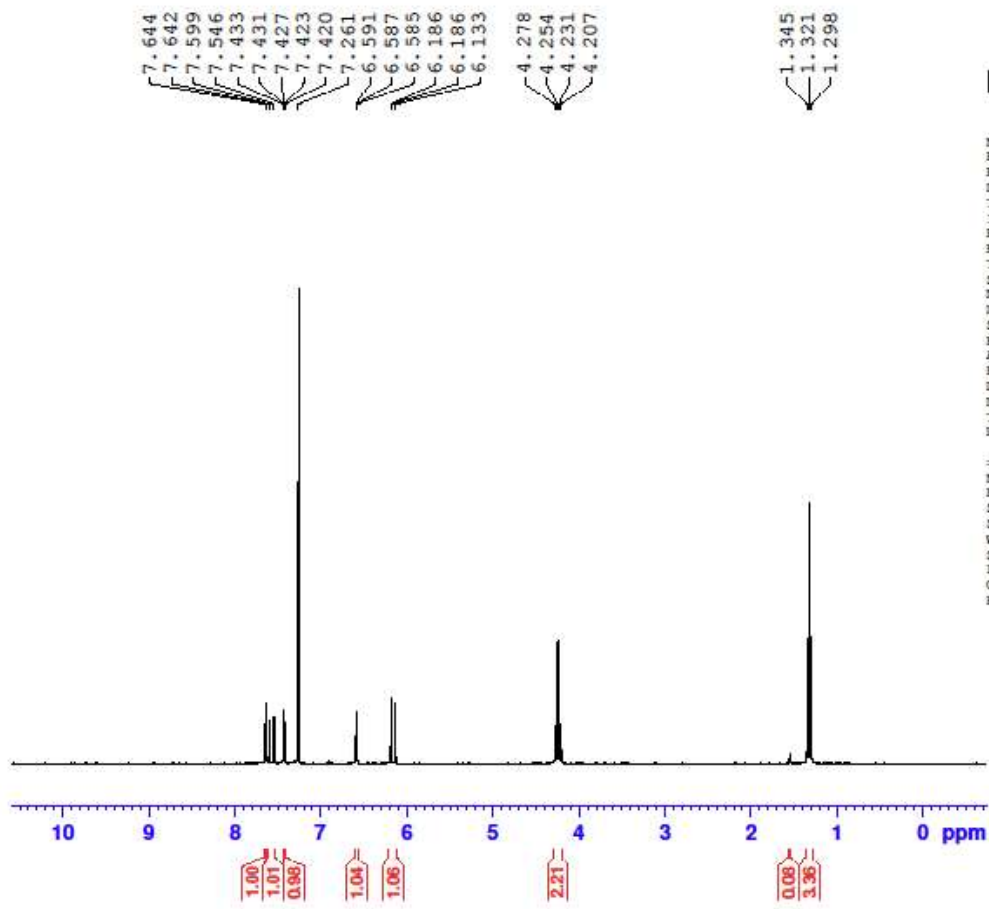
```

NAME      JTP-01-084
EXPNO     2
PROCNO    1
Date_     20140805
Time      2.52
INSTRUM   spect
PROBHD    5 mm PABBO BB-
PULPROG   zgpg30
TD         65536
SOLVENT   CDCl3
NS         1024
DS         4
SWH       24038.461 Hz
FIDRES    0.366798 Hz
AQ         1.3631988 sec
RG         203
EW         20.800 usec
DE         6.50 usec
TE         300.0 K
D1         2.00000000 sec
D11        0.03000000 sec
  
```

```

===== CHANNEL f1 =====
NUC1      13C
P1        10.00 usec
SI        32768
SF        100.6127580 MHz
WDW       EM
SSB       0
LB        1.00 Hz
GB        0
PC        1.40
  
```

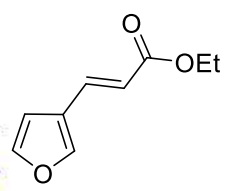


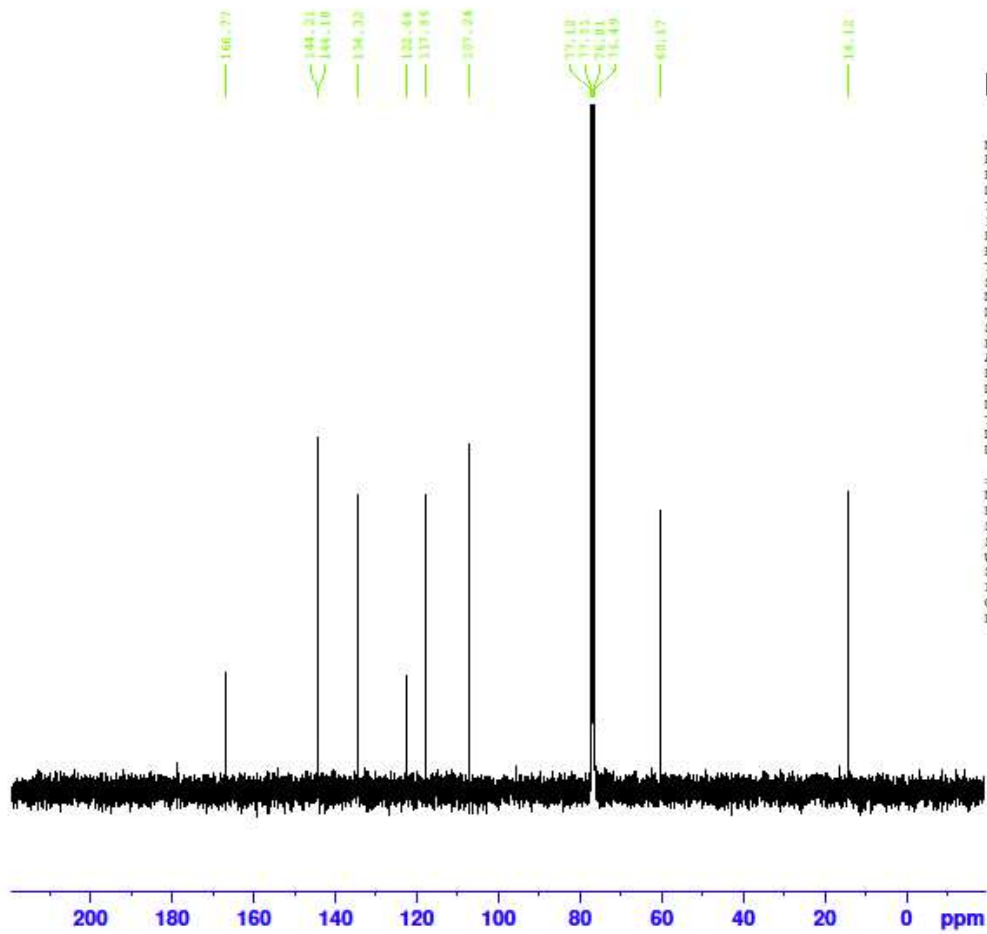


```

NAME      JTP-01-095
EXPNO     4
PROCNO    1
Date_     20131115
Time      12.27
INSTRUM   spect
PROBHD    5 mm QNP 1H/1
PULPROG   zg30
TD         32768
SOLVENT   CDCl3
NS         16
DS         2
SWH        6188.119 Hz
FIDRES     0.188846 Hz
AQ         2.6477044 sec
RG         322
DW         80.800 usec
DE         6.50 usec
TE         -926.5 K
D1         1.00000000 sec

===== CHANNEL f1 =====
NUC1       1H
P1         12.71 usec
SI         32768
SF         300.2300086 MHz
WDW        EM
SSB        0
LB         0.10 Hz
GB         0
PC         1.00
  
```





```

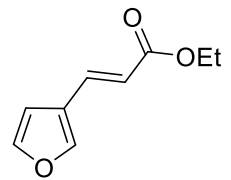
NAME      JTP-01-095
EXPNO     2
PROCNO    1
Date_     20140124
Time      0.02
INSTRUM   spect
PROBHD    5 mm FAPBO BB-
PULPROG   zgpg30
TD        65536
SOLVENT   CDCl3
NS        1024
DS        4
SWH       24038.461 Hz
FIDRES    0.366798 Hz
AQ        1.3631988 sec
RG        203
DW        20.800 usec
DE        6.50 usec
TE        1510.0 K
D1        2.0000000 sec
D11       0.03000000 sec

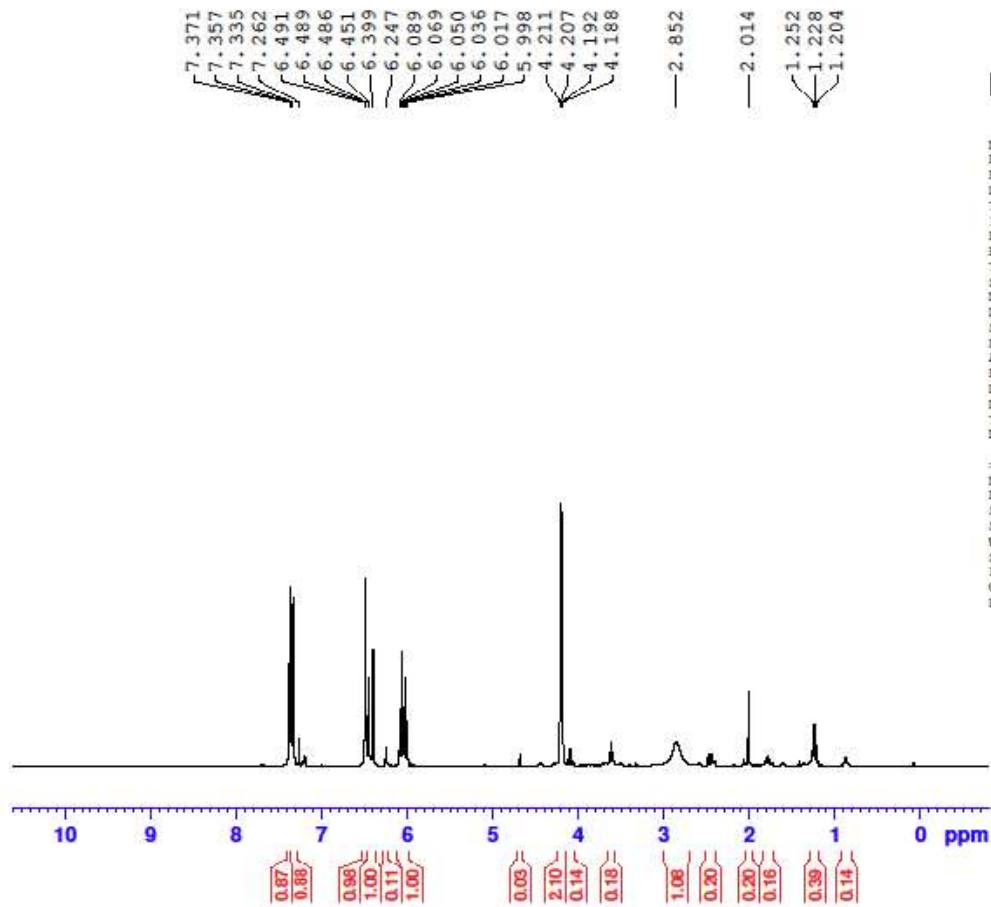
```

```

===== CHANNEL f1 =====
NUC1      13C
P1        10.00 usec
SI        32768
SF        100.6127893 MHz
WDW       EM
SSB       0
LB        1.00 Hz
GB        0
PC        1.40

```



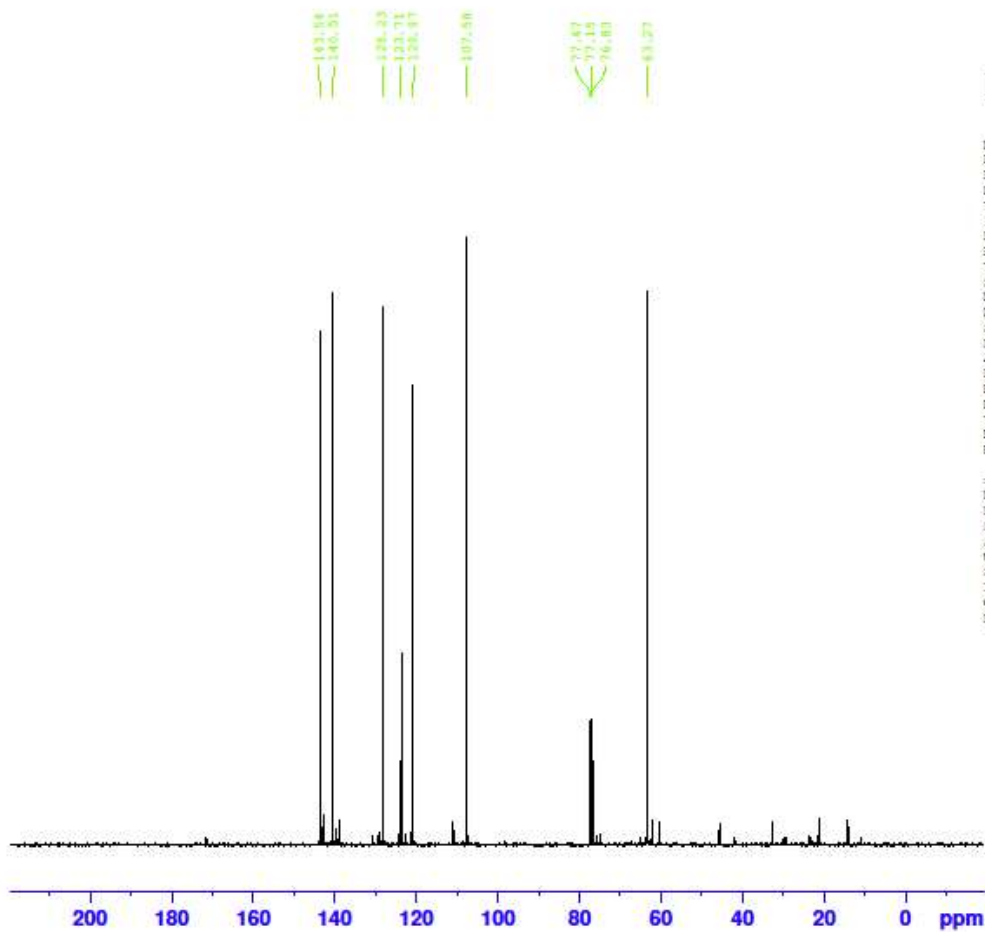


```

NAME      JTP-01-099
EXPNO     1
PROCNO    1
Date_     20131120
Time      17.29
INSTRUM   spect
PROBHD    5 mm QNP 1H/1
PULPROG   zg30
TD         32768
SOLVENT   cdcl3
NS         16
DS         2
SWH        6188.119 Hz
FIDRES     0.188846 Hz
AQ         2.6477044 sec
RG         36
DW         80.800 usec
DE         6.50 usec
TE         -925.9 K
D1         1.0000000 sec
  
```

```

===== CHANNEL F1 =====
NUC1      1H
P1        12.71 usec
SI        32768
SF        300.2300073 MHz
WDW       EM
SSB       0
LB        0.10 Hz
GB        0
PC        1.00
  
```



```

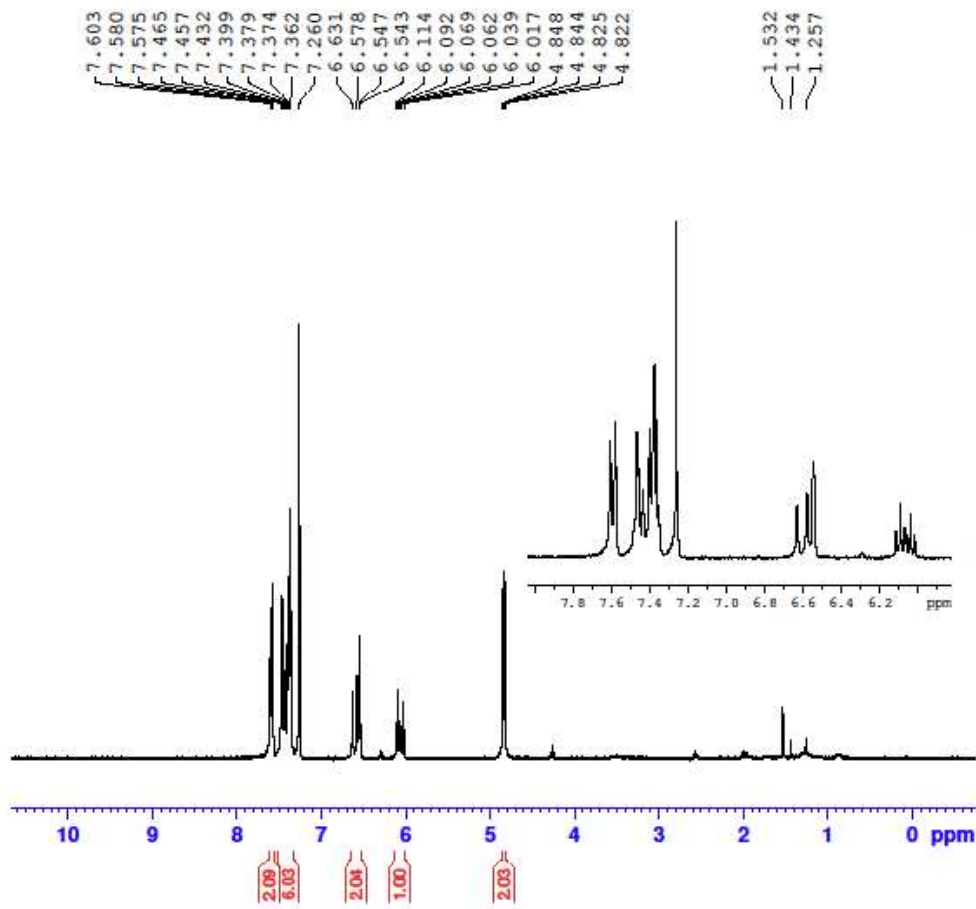
NAME          JTP-01-099
EXPNO         1
PROCNO        1
Date_         20131121
Time          3.52
INSTRUM       spect
PROBHD        5 mm PAHBO BB-
PULPROG       zgpg30
ID            65536
SOLVENT       CDCl3
NS            1024
DS            4
SWH           24038.461 Hz
FIDRES        0.366798 Hz
AQ            1.3631988 sec
RG            203
EW            20.800 usec
DE            6.50 usec
TE            298.9 K
D1            2.0000000 sec
D11           0.03000000 sec

```

```

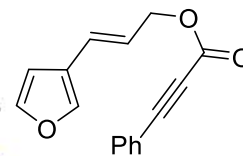
===== CHANNEL f1 =====
NUC1          13C
P1            10.00 usec
SI            32768
SF            100.6127690 MHz
WDW           EM
SSB           0
LB            1.00 Hz
GB            0
PC            1.40

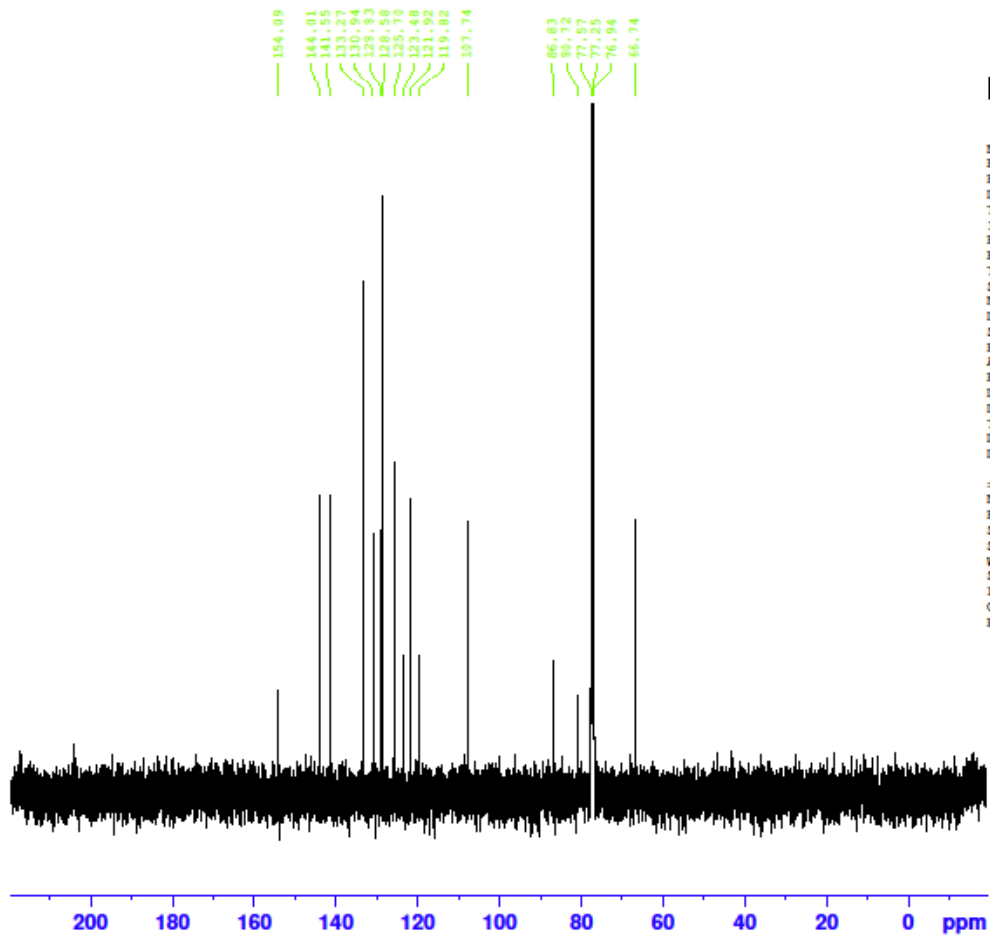
```



NAME JTP-01-101  
EXPNO 3  
PROCNO 1  
Date\_ 20131223  
Time 17.42  
INSTRUM spect  
PROBHD 5 mm QNP 1H/1  
PULPROG zg30  
TD 32768  
SOLVENT cdcl3  
NS 16  
DS 2  
SWH 6188.119 Hz  
FIDRES 0.188846 Hz  
AQ 2.6477044 sec  
RG 322  
DW 80.800 usec  
DE 6.50 usec  
TE -928.8 K  
D1 1.00000000 sec

==== CHANNEL f1 ====  
NUC1 1H  
P1 12.71 usec  
SI 32768  
SF 300.2300090 MHz  
WDW EM  
SSB 0  
LB 0.10 Hz  
GB 0  
PC 1.00





```

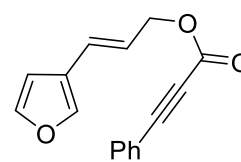
NAME      JTP-01-101
EXPNO     1
PROCNO    1
Date_     20131224
Time      1.07
INSTRUM   5 mm F400
PROBHD    spect
PULPROG   zgpg30
ID        65536
SOLVENT   CDCl3
NS        1024
DS        4
SWH       24038.461 Hz
FIDRES    0.366798 Hz
AQ        1.3631988 sec
RG        203
DW        20.800 usec
DE        6.50 usec
TE        90.7 K
D1        2.0000000 sec
D11       0.03000000 sec

```

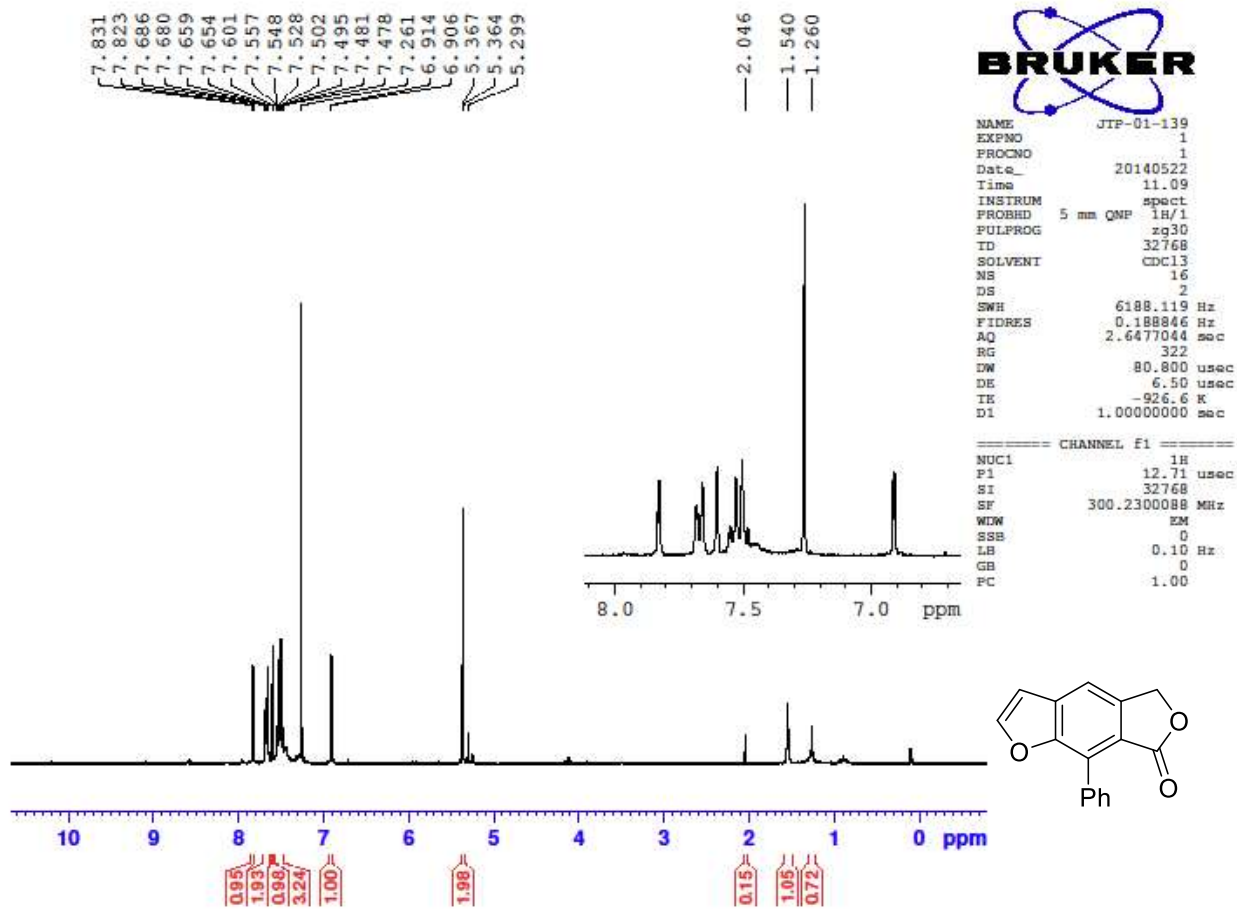
```

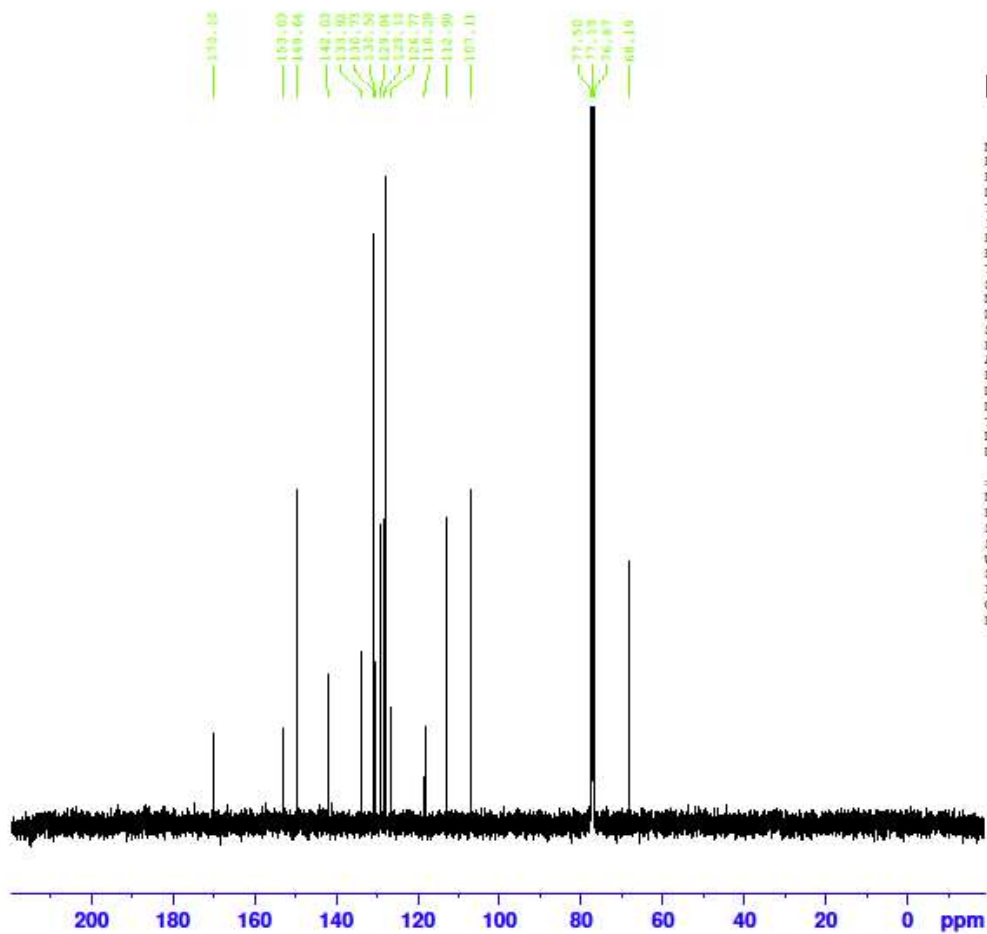
===== CHANNEL f1 =====
NUC1      13C
P1        10.00 usec
SI        32768
SF        100.6127445 MHz
WDW       EM
SSB       0
LB        1.00 Hz
GB        0
PC        1.40

```







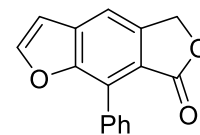


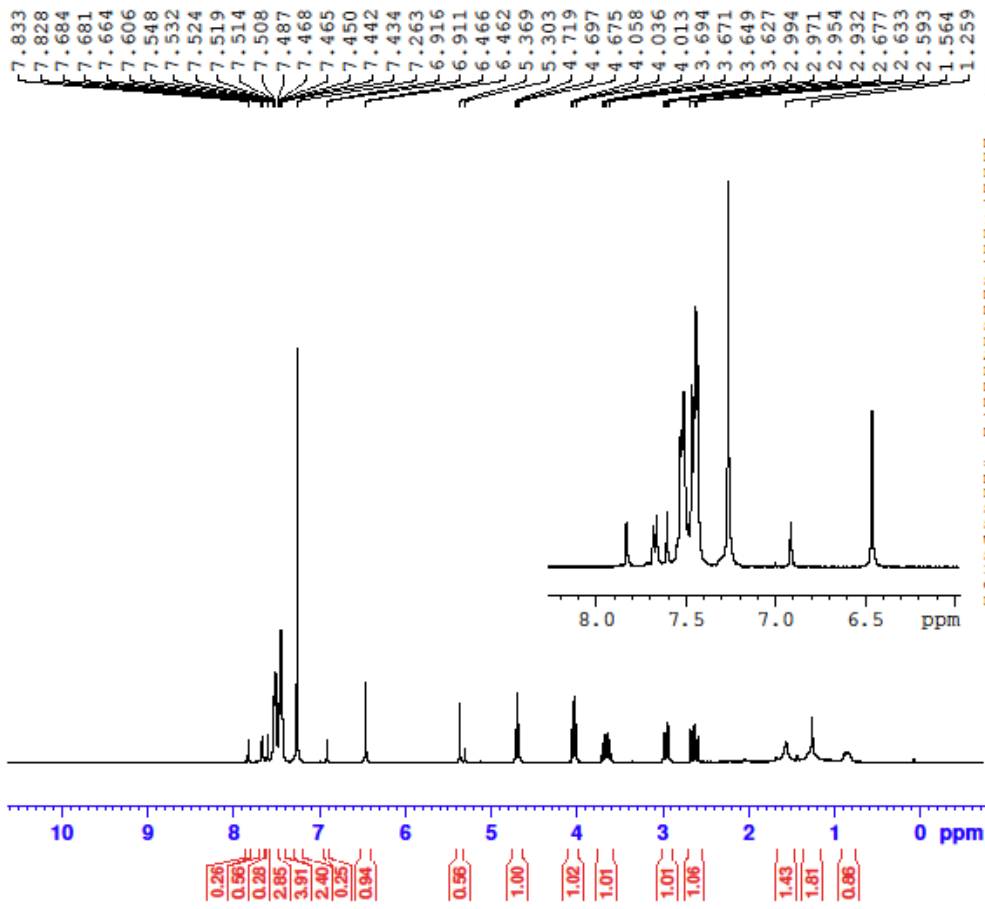
```

NAME      JTP-01-139
EXPNO     5
PROCNO    1
Date_     20140803
Time      0.32
INSTRUM   spect
PROBHD    5 mm PABBO BB-
PULPROG   zgpg30
TD        65536
SOLVENT   CDCl3
NS        1024
DS        4
SWH       24038.461 Hz
FIDRES    0.366798 Hz
AQ        1.3631988 sec
RG        203
DW        20.800 usec
DE        6.50 usec
TE        300.0 K
D1        2.0000000 sec
D11       0.0300000 sec
  
```

```

===== CHANNEL f1 =====
NUC1      13C
P1        10.00 usec
SI        32768
SF        100.6127534 MHz
WDW       EM
SSB       0
LB        1.00 Hz
GB        0
PC        1.40
  
```

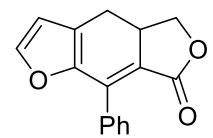


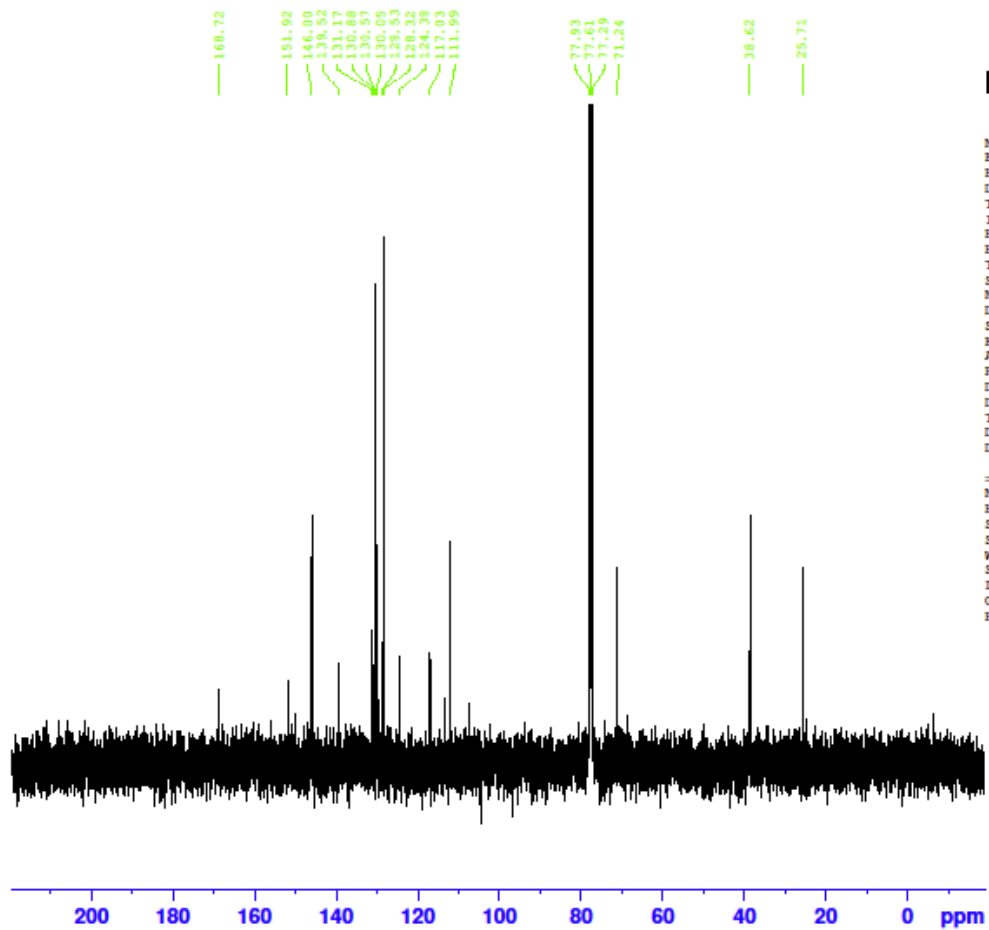


```

NAME      JTP-01-104
EXPNO     10
PROCNO    1
Date_     20140806
Time      18.51
INSTRUM   spect
PROBHD    5 mm PABBO BB-
PULPROG   zg30
TD         65536
SOLVENT   CDCl3
NS         16
DS         2
SWH       8223.685 Hz
FIDRES    0.125483 Hz
AQ         3.9846387 sec
RG         144
DW         60.800 usec
DE         6.50 usec
TE         92.9 K
D1         1.00000000 sec

===== CHANNEL f1 =====
NUC1       1H
P1         13.75 usec
SI         65536
SF         400.1300086 MHz
WDW        EM
SSB        0
LB         0.30 Hz
GB         0
PC         1.00
  
```





168.72  
 151.92  
 146.00  
 139.52  
 131.17  
 130.99  
 130.95  
 128.53  
 128.32  
 124.38  
 117.03  
 111.99  
 77.03  
 77.63  
 77.29  
 71.24  
 38.62  
 25.71

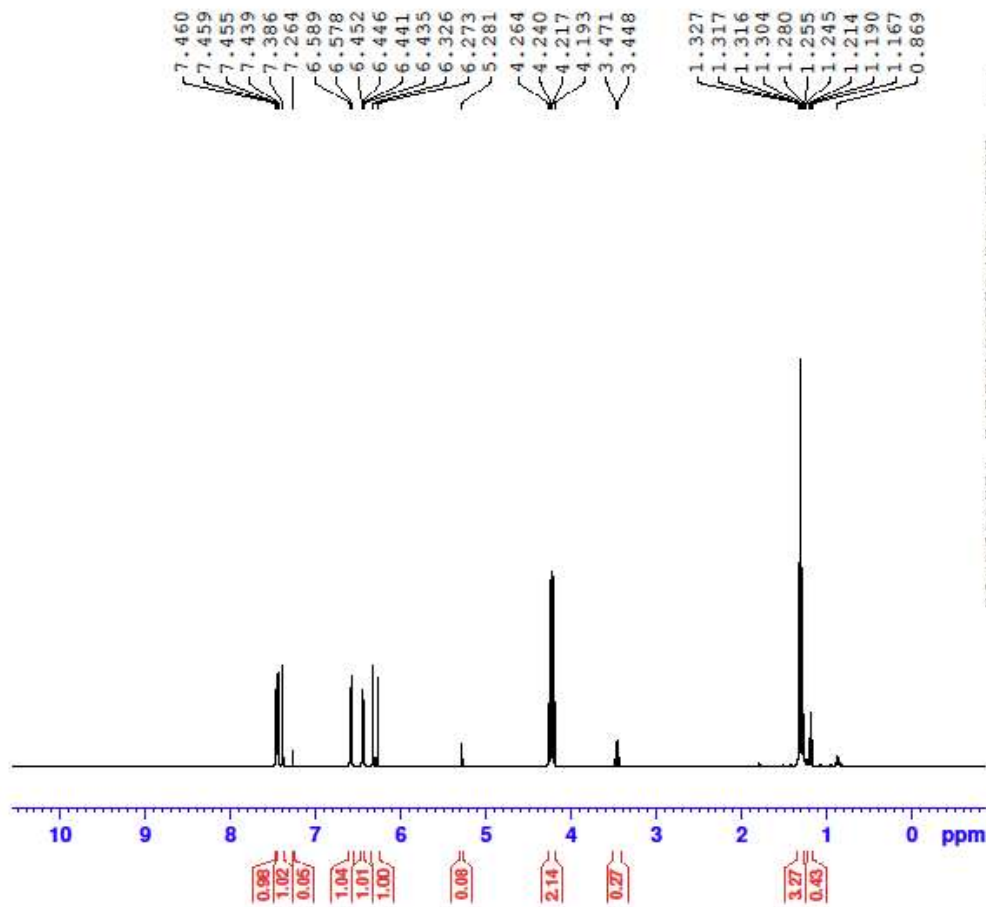


```

NAME      JTP-01-104
EXPNO     11
PROCNO    1
Date_     20140807
Time      3.04
INSTRUM   spect
PROBHD    5 mm FAPBO BB-
PULPROG   zgpg30
TD         65536
SOLVENT   cdcl3
NS         1024
DS         4
SWH       24038.461 Hz
FIDRES    0.366798 Hz
AQ         1.3631988 sec
RG         203
DW         20.800 usec
DE         6.50 usec
TE         97.6 K
D1         2.0000000 sec
D11        0.03000000 sec
  
```

```

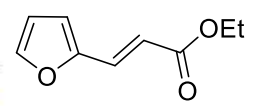
===== CHANNEL f1 =====
NUC1      13C
P1        10.00 usec
SI        32768
SF        100.6127094 MHz
WDW       EM
SSB       0
LB        1.00 Hz
GB        0
PC        1.40
  
```

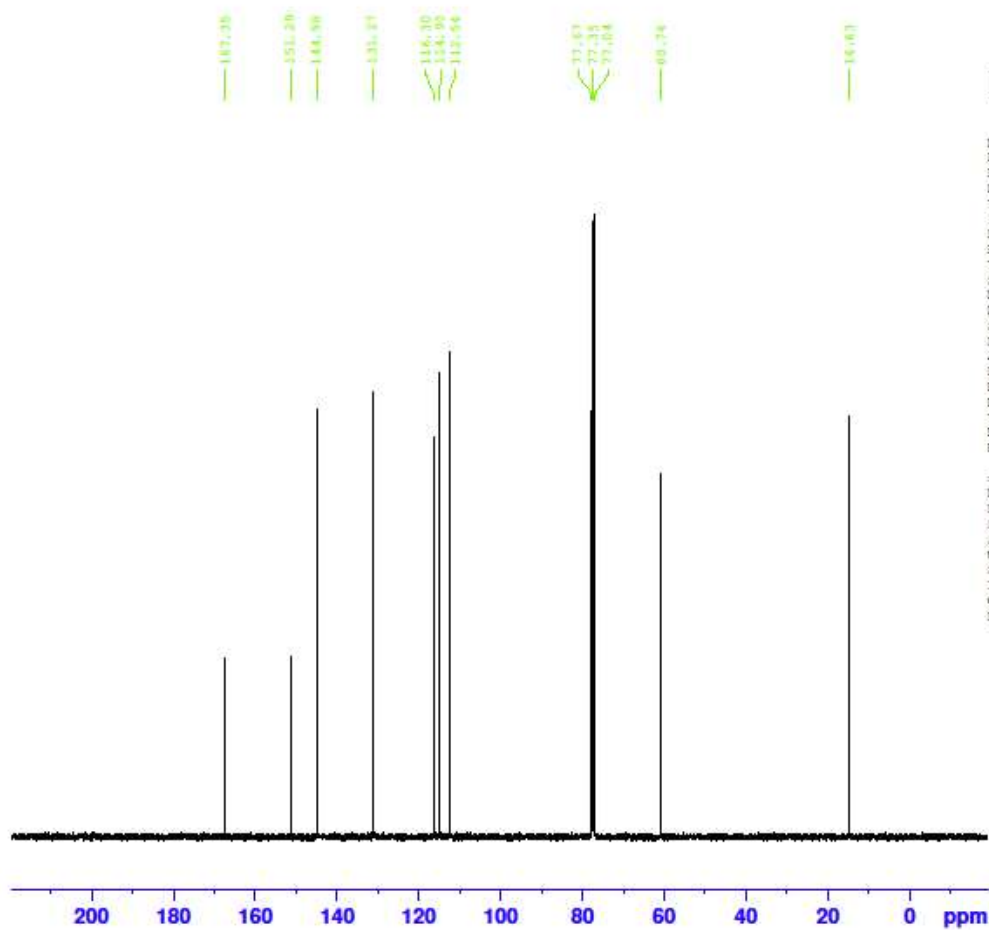


```

NAME          JTP-01-108
EXPNO         2
PROCNO        1
Date_         20140311
Time          13.44
INSTRUM       spect
PROBHD        5 mm QNP 1H/1
PULPROG       zg30
TD            32768
SOLVENT       CDCl3
NS            16
DS            2
SWH           6188.119 Hz
FIDRES        0.188846 Hz
AQ            2.6477044 sec
RG            57
EW            80.800 usec
DE            6.50 usec
TE            -931.3 K
D1            1.00000000 sec

===== CHANNEL f1 =====
NUC1          1H
P1            12.71 usec
SI            32768
SF            300.2300074 MHz
WDW           EM
SSB           0
LB            0.10 Hz
GB            0
PC            1.00
  
```



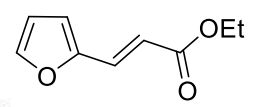


```

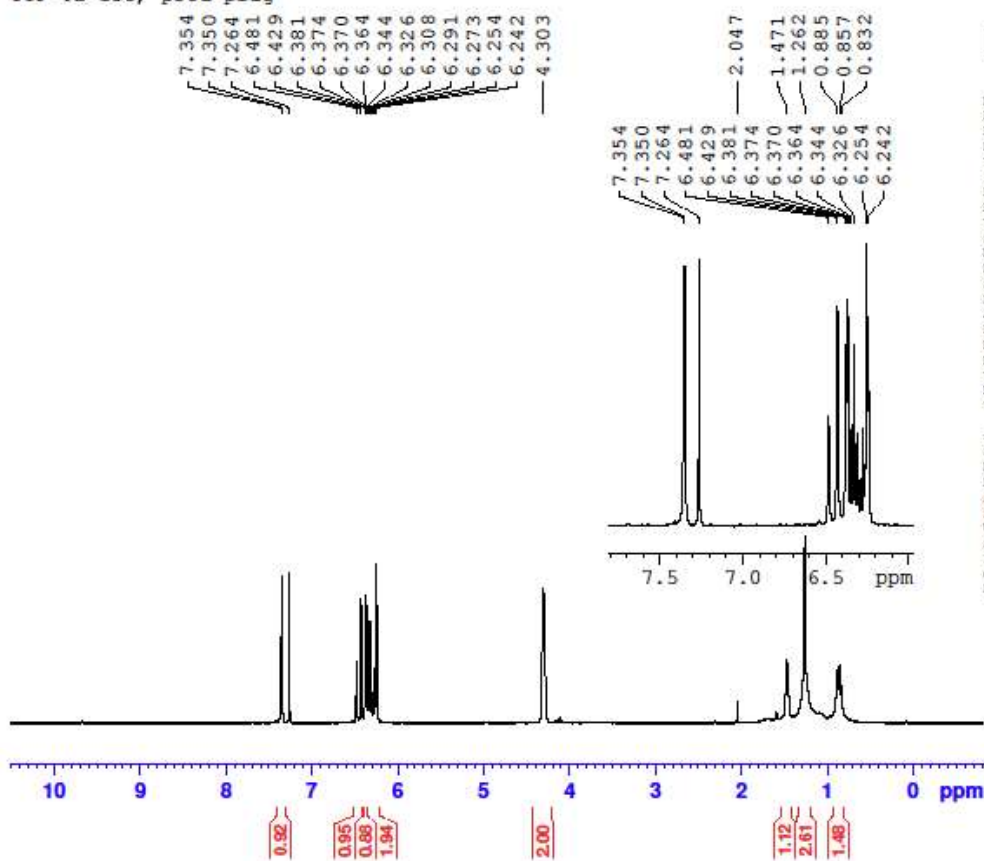
NAME      JTP-01-108
EXPNO     10
PROCNO    1
Date_     20140311
Time      23.03
INSTRUM   spect
PROBHD    5 mm PABBO BB-
PULPROG   zgpg30
TD         65536
SOLVENT   cdcl3
NS         1024
DS         4
SWH       24038.461 Hz
FIDRES    0.366798 Hz
AQ         1.3631988 sec
RG         203
EW         20.800 usec
DE         6.50 usec
TE         2080.2 K
D1         2.00000000 sec
D11        0.03000000 sec
  
```

```

===== CHANNEL f1 =====
NUC1      13C
P1        10.00 usec
SI        32768
SF        100.6127366 MHz
WDW       EM
SSB       0
LB        1.00 Hz
GB        0
PC        1.40
  
```



JTP-02-158, prod plug

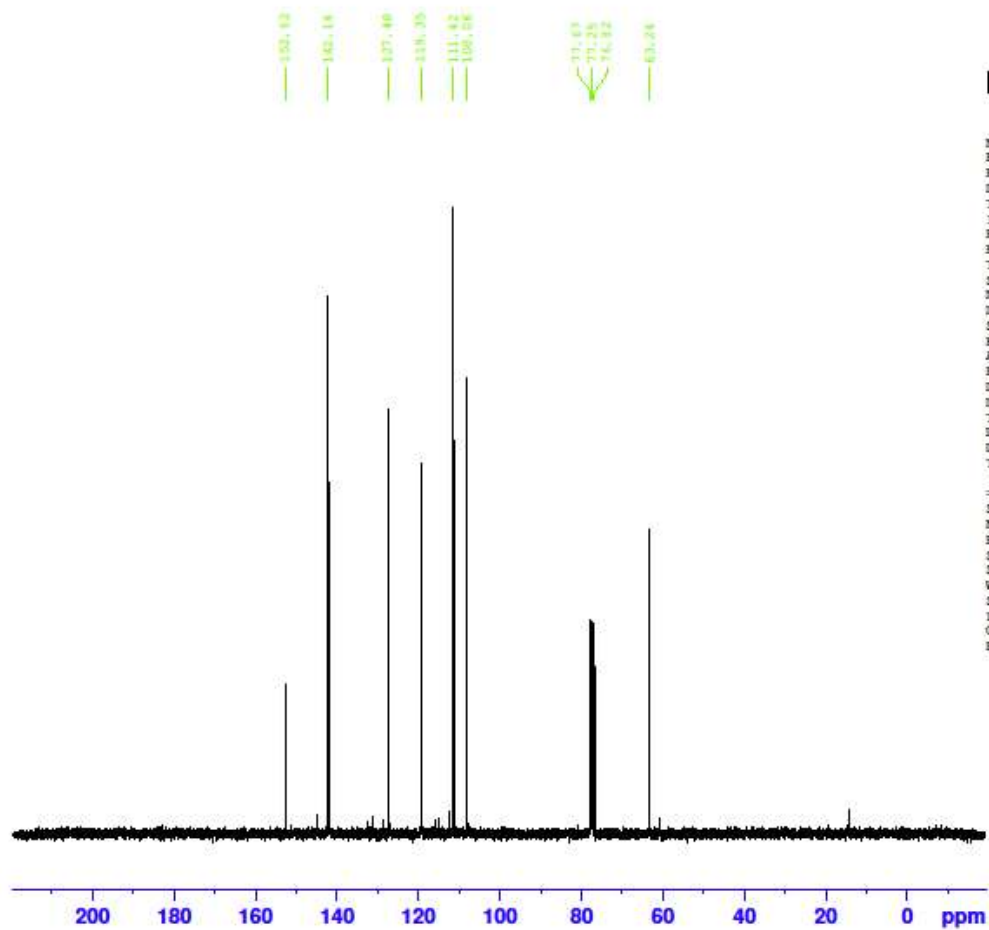


```

NAME      JTP-02-158
EXPNO    10
PROCNO   1
Date_    20160205
Time     12.47
INSTRUM  spect
PROBHD   5 mm QNP 1H/1
PULPROG  zg30
ID       32768
SOLVENT  CDCl3
NS       16
DS       2
SWH      6188.119 Hz
FIDRES   0.188846 Hz
AQ       2.6477044 sec
RG       128
EW       80.800 usec
DE       6.50 usec
TE       -927.8 K
D1       1.00000000 sec
TD0      1
  
```

```

===== CHANNEL f1 =====
SFO1    300.2318540 MHz
NUC1     1H
P1      12.71 usec
SI      32768
SF      300.2300078 MHz
WDW     EM
SSB     0
LB      0.10 Hz
GB      0
PC      1.00
  
```

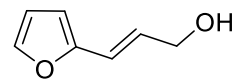


```

NAME          JTP-01-184
EXPNO         10
PROCNO        1
Date_         20141110
Time          19.23
INSTRUM       spect
PROBHD        5 mm QNP 1H/1
PULPROG       zgpg30
TD            65536
SOLVENT       CDCl3
NS            200
DS            4
SWH           18028.846 Hz
FIDRES        0.275098 Hz
AQ            1.8175818 sec
RG            256
DW            27.733 usec
DE            6.50 usec
TE            -928.4 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0           1
  
```

```

===== CHANNEL f1 =====
SFO1          75.5004428 MHz
NUC1          13C
P1            12.00 usec
SI            32768
SF            75.4928818 MHz
WDW           EM
SSB           0
LB            1.00 Hz
GB            0
PC            1.40
  
```





7.588  
7.584  
7.478  
7.465  
7.459  
7.453  
7.444  
7.440  
7.437  
7.399  
7.380  
7.366  
7.362  
7.264  
6.560  
6.520  
6.394  
6.390  
6.386  
6.382  
6.325  
6.317  
6.295  
6.279  
6.262  
6.256  
6.239  
6.223  
4.872  
4.869  
4.855  
4.853  
1.437  
1.343  
1.325  
1.308  
1.298  
1.289  
1.261

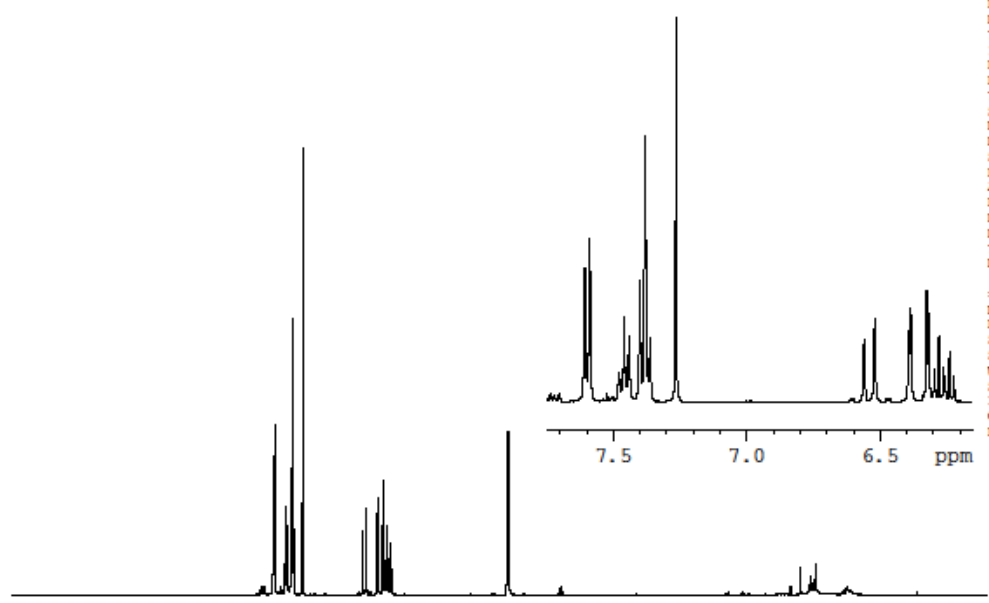


```

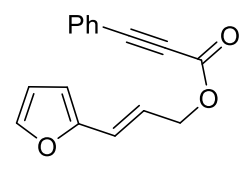
NAME      JTP-01-185
EXPNO     10
PROCNO    1
Date_     20141113
Time      18.50
INSTRUM   spect
PROBHD    5 mm PABBO BB-
PULPROG   zg30
TD         65536
SOLVENT   CDCl3
NS         16
DS         2
SWH       8223.685 Hz
FIDRES    0.125483 Hz
AQ         3.9846387 sec
RG         114
DW         60.800 usec
DE         6.50 usec
TE         1348.7 K
D1         1.00000000 sec
  
```

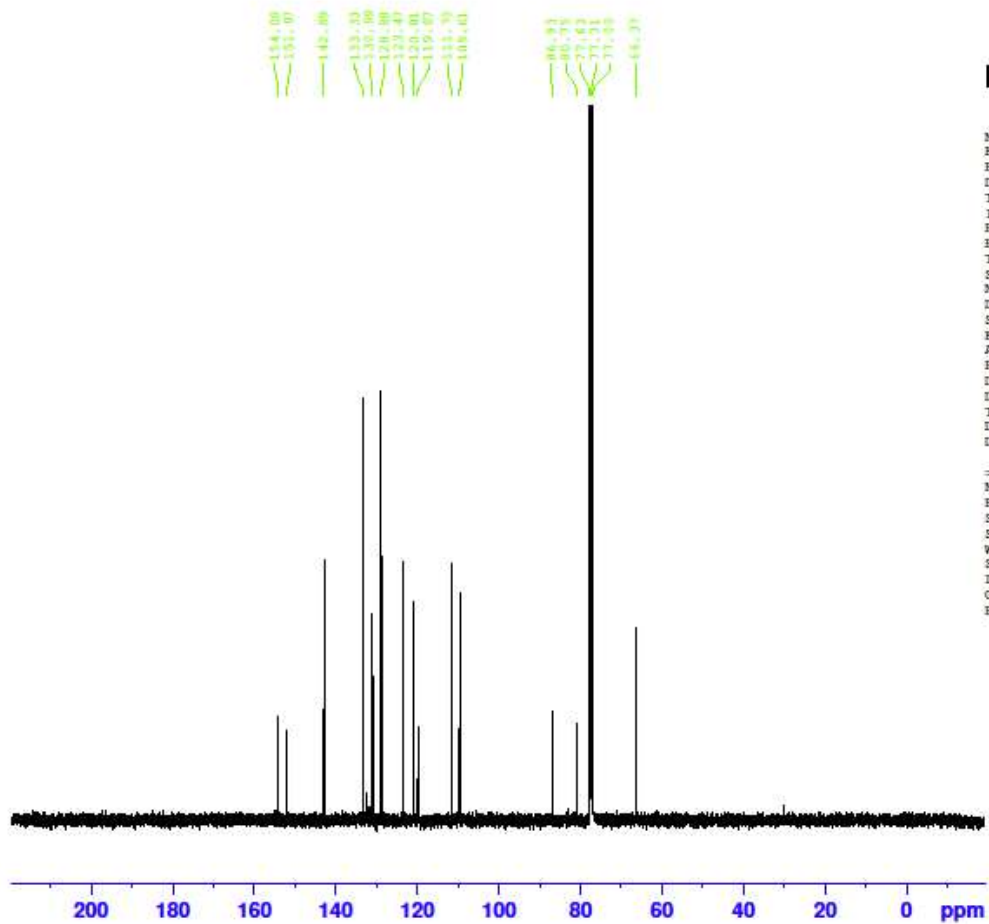
```

===== CHANNEL f1 =====
NUC1      1H
P1        13.75 usec
SI        65536
SF        400.1300085 MHz
WDW       EM
SSB       0
LB        0.30 Hz
GB        0
PC        1.00
  
```



2.06  
0.25  
1.07  
3.10  
1.00  
1.00  
1.02  
1.05  
2.11  
0.00  
0.13  
0.28  
0.51  
0.42



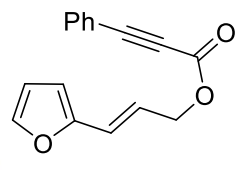


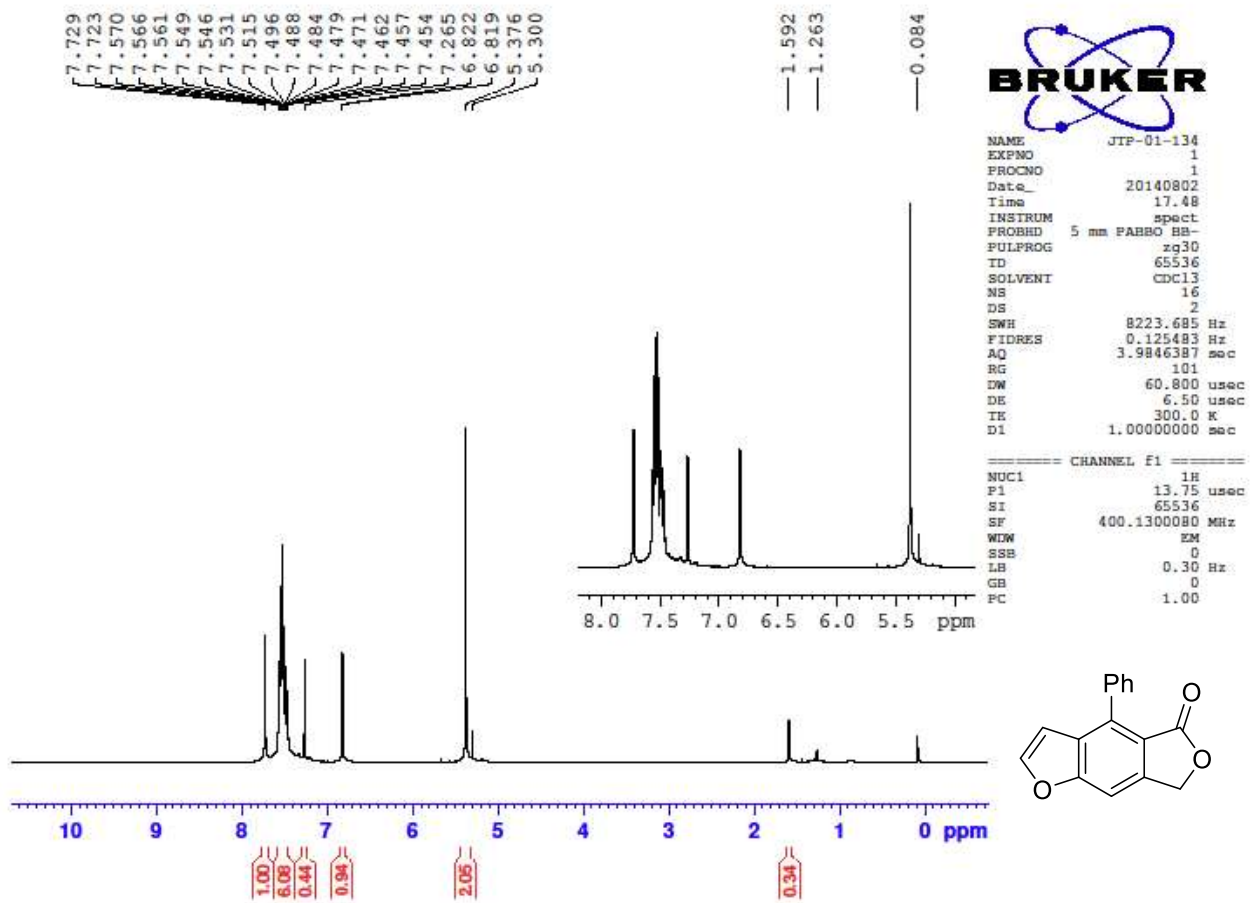
```

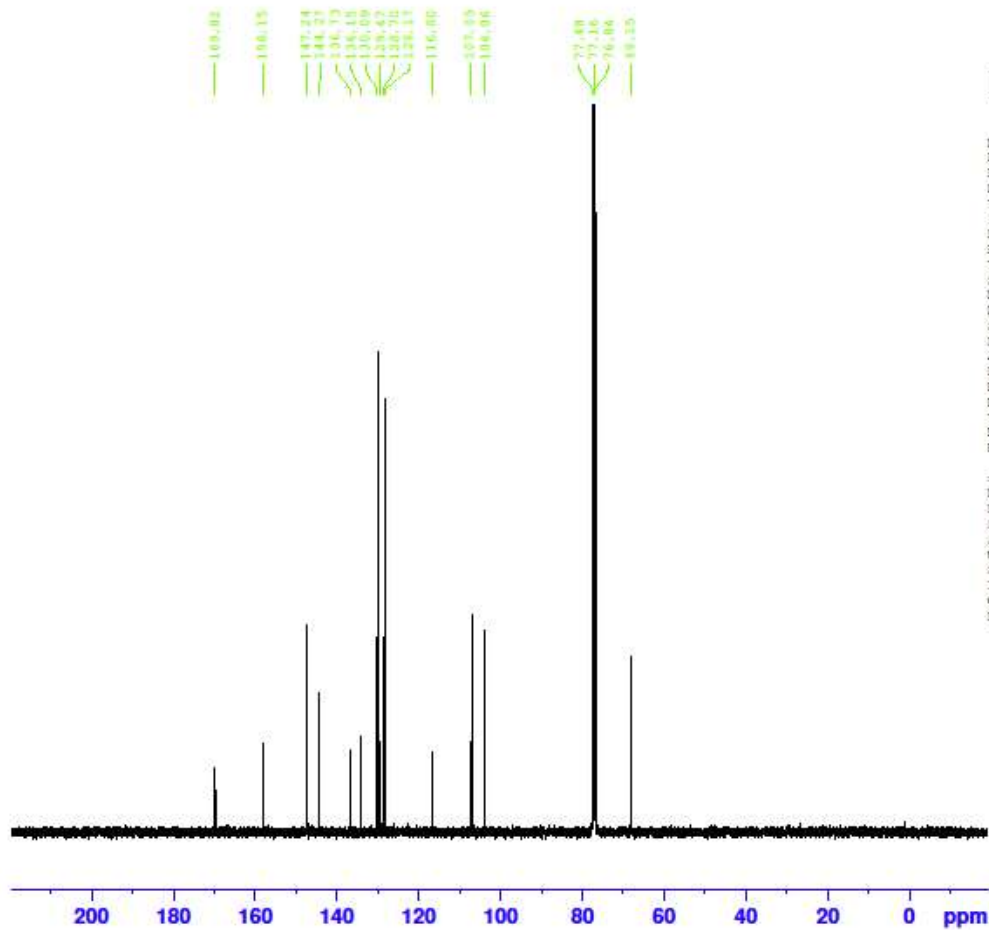
NAME      JTP-01-185
EXPNO     20
PROCNO    1
Date_     20141114
Time      6.02
INSTRUM   spect
PROBHD    5 mm PABBO BB-
PULPROG   zgpg30
TD        65536
SOLVENT   CDCl3
NS        1024
DS        4
SWH       24038.461 Hz
FIDRES    0.366798 Hz
AQ        1.3631988 sec
RG        181
DW        20.800 usec
DE        6.50 usec
TE        94.6 K
D1        2.0000000 sec
D11       0.03000000 sec
  
```

```

===== CHANNEL f1 =====
NUC1      13C
P1        10.00 usec
SI        32768
SF        100.6127392 MHz
WDW       EM
SSB       0
LB        1.00 Hz
GB        0
PC        1.40
  
```





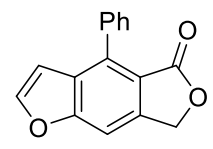


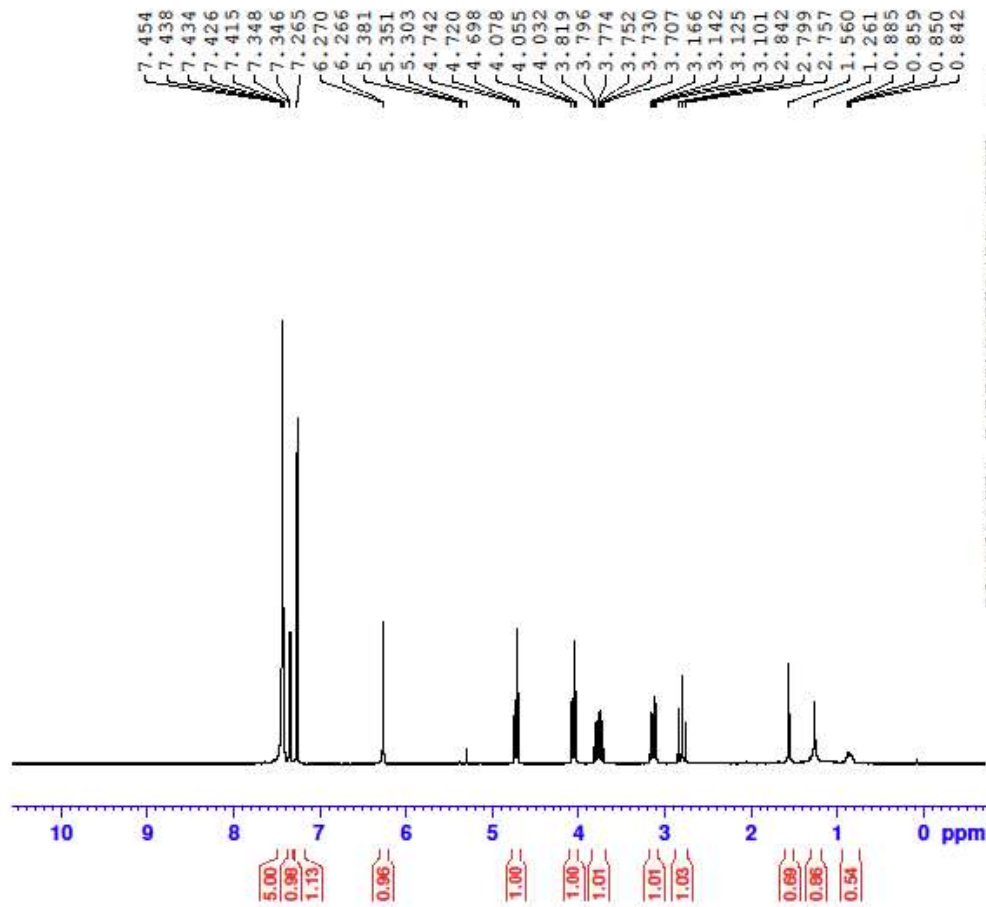
```

NAME      JTP-01-134
EXPNO     2
PROCNO    1
Date_     20140803
Time      1.48
INSTRUM   spect
PROBHD    5 mm PABBO BB-
PULPROG   zgpg30
TD         65536
SOLVENT   CDCl3
NS         1024
DS         4
SWH       24038.461 Hz
FIDRES    0.366798 Hz
AQ        1.3631988 sec
RG         203
EW        20.800 usec
DE         6.50 usec
TE         300.0 K
D1         2.00000000 sec
D11        0.03000000 sec
  
```

```

===== CHANNEL f1 =====
NUC1      13C
P1        10.00 usec
SI        32768
SF        100.6127572 MHz
WDW       EM
SSB       0
LB        1.00 Hz
GB        0
PC        1.40
  
```

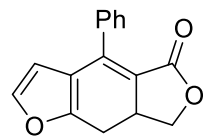


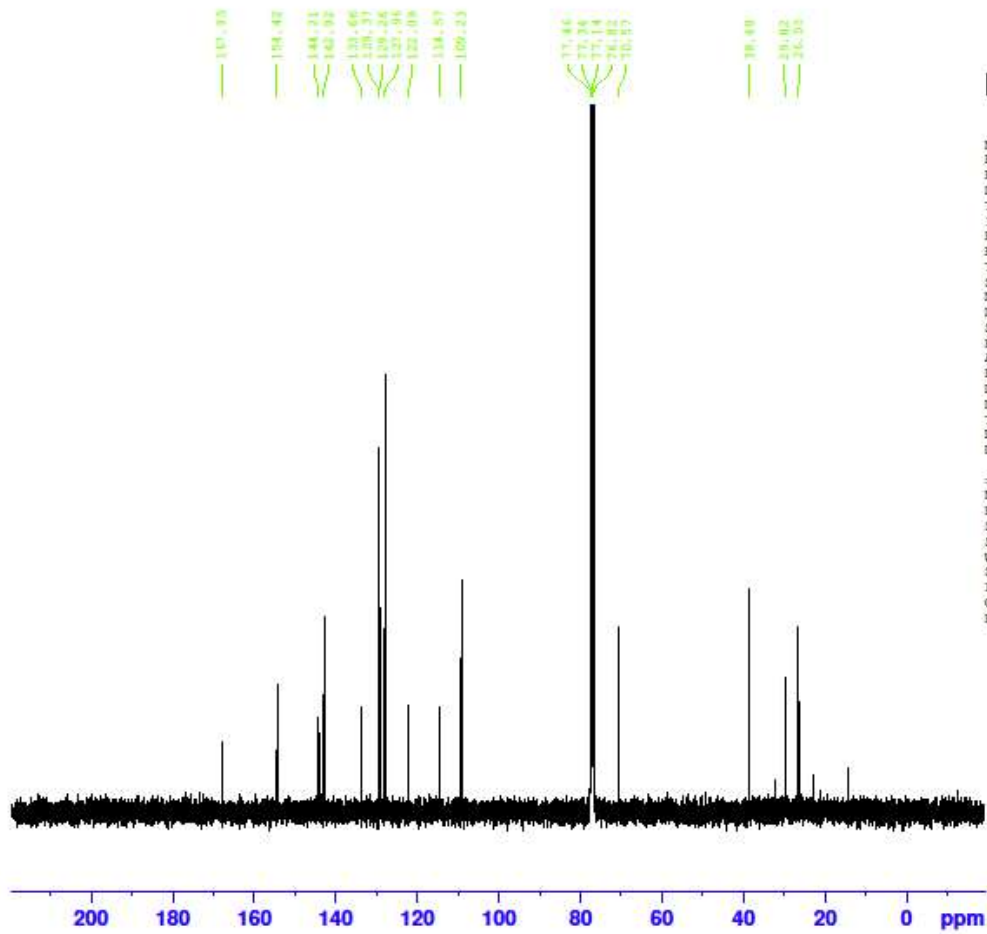


```

NAME          JTP-01-133
EXPNO         3
PROCNO        1
Date_         20140806
Time          11.46
INSTRUM       spect
PROBHD        5 mm PABBO BB-
PULPROG       zg30
TD            65536
SOLVENT       CDCl3
NS            16
DS            2
SWH           8223.685 Hz
FIDRES        0.125483 Hz
AQ            3.9846387 sec
RG            128
DW            60.800 usec
DE            6.50 usec
TE            93.7 K
D1            1.00000000 sec

===== CHANNEL f1 =====
NUC1          1H
P1            13.75 usec
SI            65536
SF            400.1300080 MHz
WDW           EM
SSB           0
LB            0.30 Hz
GB            0
PC            1.00
  
```





```

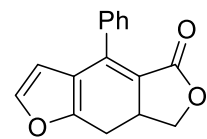
NAME      JTP-01-133
EXPNO     2
PROCNO    1
Date_     20140801
Time      21.02
INSTRUM   spect
PROBHD    5 mm PABBO BB-
PULPROG   zgpg30
TD        65536
SOLVENT   CDCl3
NS        1024
DS        4
SWH       24038.461 Hz
FIDRES    0.366798 Hz
AQ        1.3631988 sec
RG        203
DW        20.800 usec
DE        6.50 usec
TE        89.8 K
D1        2.0000000 sec
D11       0.0300000 sec

```

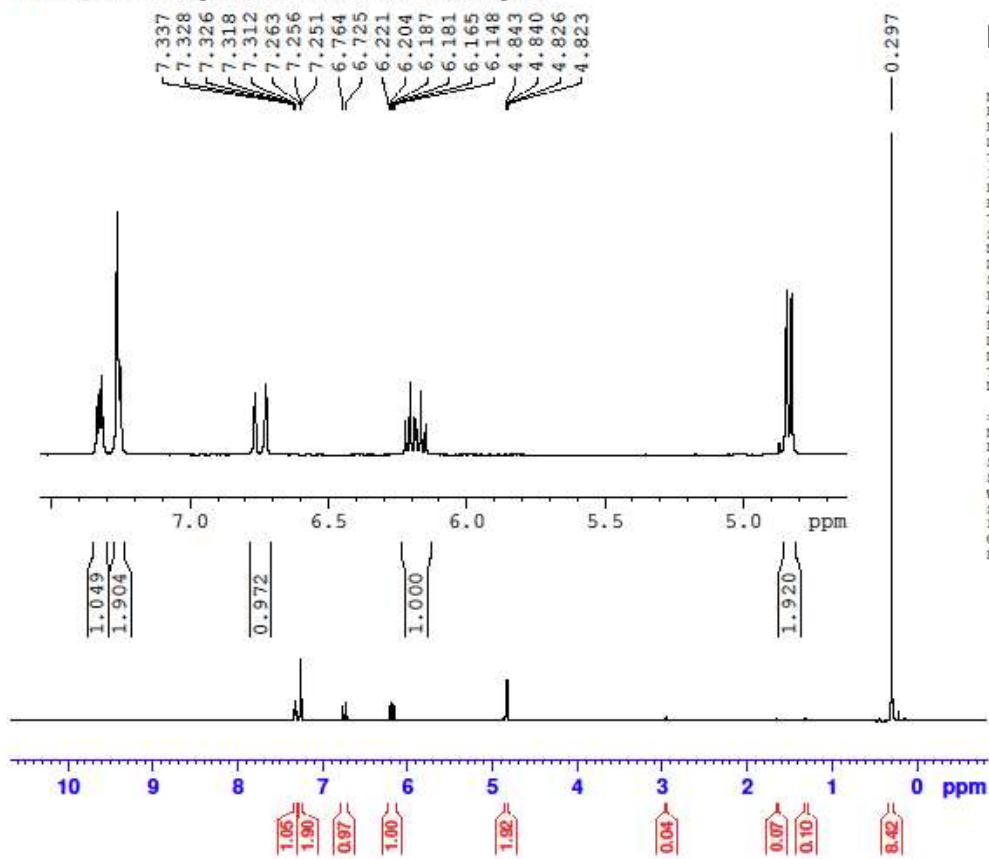
```

===== CHANNEL f1 =====
NUC1      13C
P1        10.00 usec
SI        32768
SF        100.6127572 MHz
WDW       EM
SSB       0
LB        1.00 Hz
GB        0
PC        1.40

```



JIP-02-062 Thiophene-3-TMS Final Ester pure

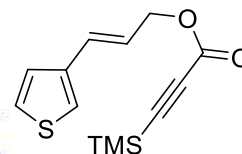


```

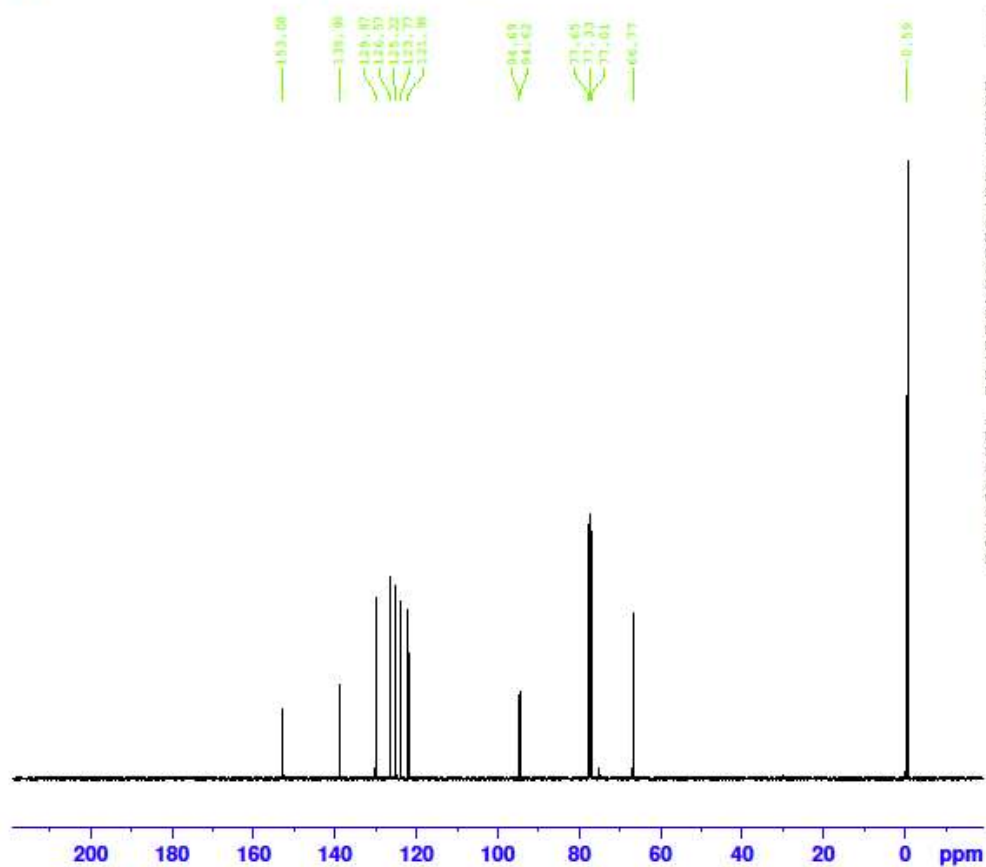
NAME      JIP-02-062
EXPNO     1
PROCNO    1
Date_     20150519
Time      16.07
INSTRUM   spect
PROBHD    5 mm PABBO BB-
PULPROG   zg30
TD         65536
SOLVENT   cdcl3
NS         16
DS         2
SWH        8223.685 Hz
FIDRES     0.125483 Hz
AQ         3.9846387 sec
RG         32
DW         60.800 usec
DE         6.50 usec
TE         -936.3 K
D1         1.0000000 sec
    
```

```

===== CHANNEL F1 =====
NUC1      1H
P1        13.75 usec
SI        65536
SF        400.1299895 MHz
WDW       EM
SSB       0
LB        0.30 Hz
GB        0
PC        1.00
    
```

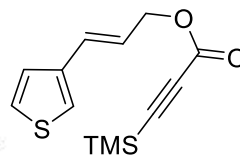


JIP-02-062, Thiophene-3-IMS Ester pure



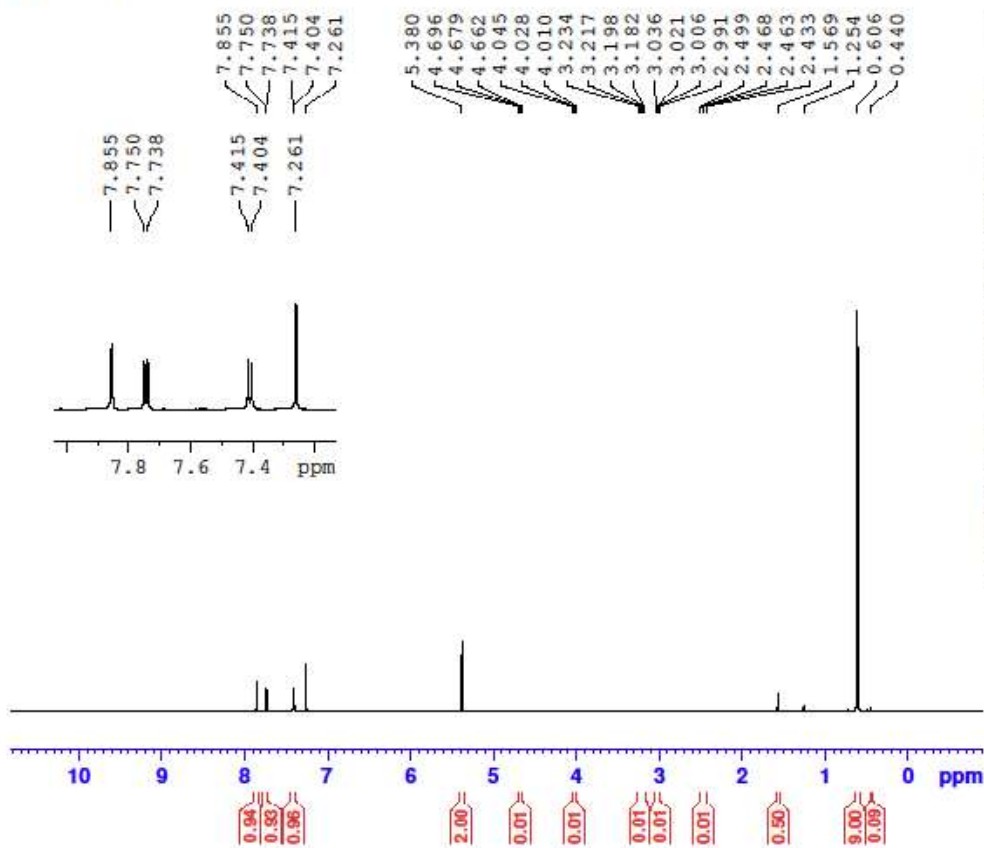
NAME JIP-02-062  
EXPNO 3  
PROCNO 1  
Date\_ 20150521  
Time 1.15  
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zgpg30  
TD 65536  
SOLVENT CDCl3  
NS 1024  
DS 4  
SWH 24038.461 Hz  
FIDRES 0.366798 Hz  
AQ 1.3631988 sec  
RG 114  
DW 20.800 usec  
DE 6.50 usec  
TE 94.6 K  
D1 2.00000000 sec  
D11 0.03000000 sec

==== CHANNEL f1 =====  
NUC1 13C  
P1 10.00 usec  
SI 32768  
SF 100.6127430 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40





JTP-02-083, Benzothiophene3 TMS Lactone, pure

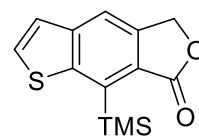


```

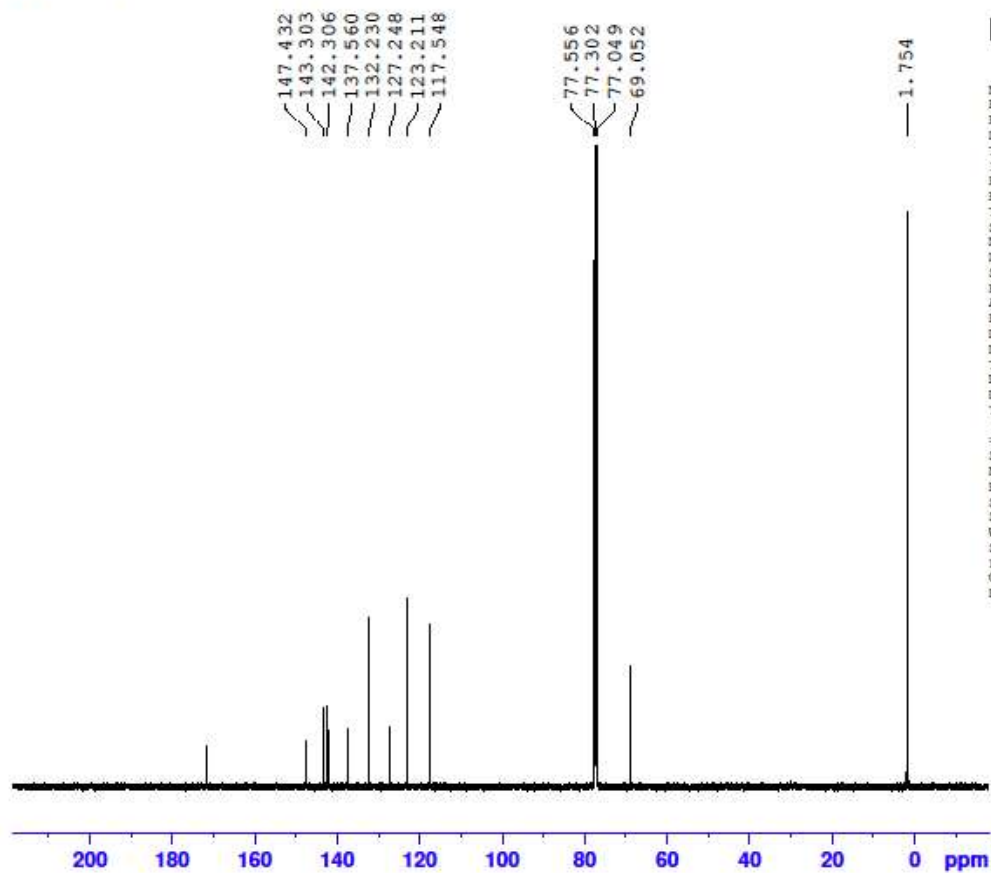
NAME      JTP-02-083
EXPNO    1
PROCNO   1
Date_    20150716
Time     21.03
INSTRUM  spect
PROBHD   5 mm PABBO BB/
PULPROG  zg30
TD       65536
SOLVENT  cdc13
NS       16
DS       2
SWH      10000.000 Hz
FIDRES   0.152588 Hz
AQ       3.2768500 sec
RG       114
DW       50.000 usec
DE       6.50 usec
TE       296.9 K
D1       1.0000000 sec
TD0      1
  
```

```

===== CHANNEL f1 =====
SFO1    500.1630887 MHz
NUC1     1H
P1      11.45 usec
SI      65536
SF      500.1600127 MHz
WDW     EM
SSB     0
LB      0.30 Hz
GB      0
PC      1.00
  
```

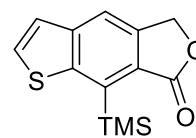


JTP-02-083, Benzothiophene3 TMS Lactone, pure

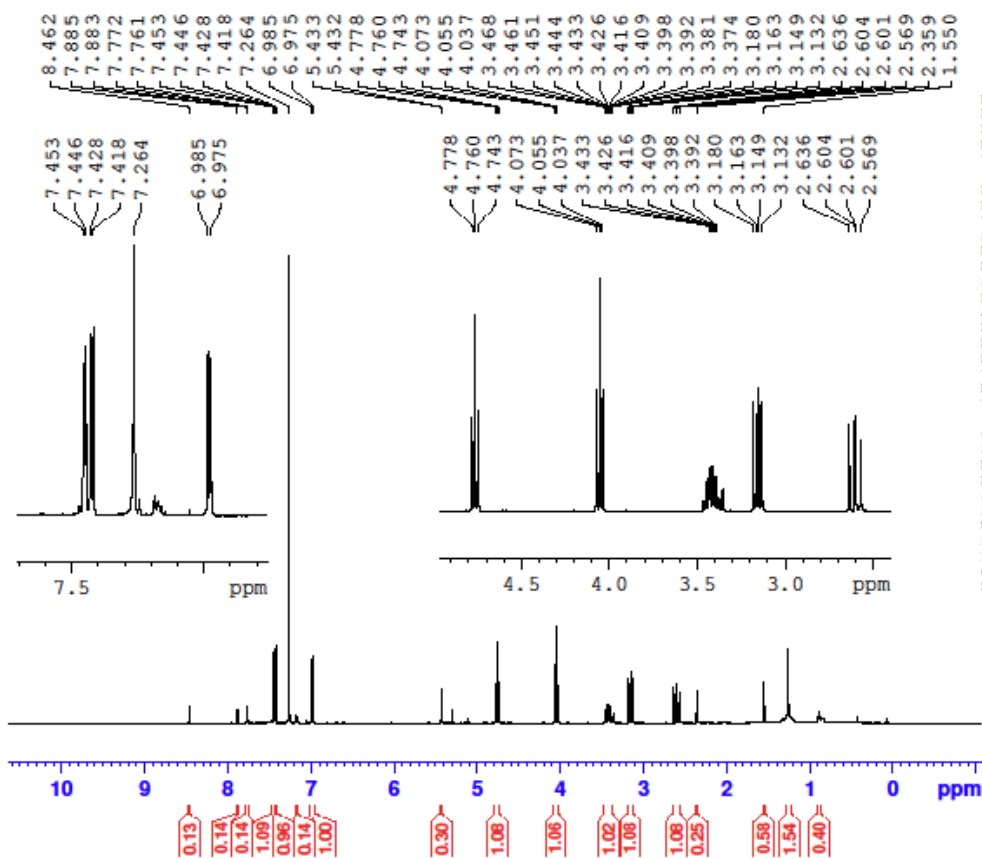


NAME JTP-02-083  
EXPNO 2  
PROCNO 1  
Date\_ 20150717  
Time 5.40  
INSTRUM spect  
PROBHD 5 mm FAPBO BB/  
PULPROG zgig30  
TD 65536  
SOLVENT cdcl3  
NS 2500  
DS 4  
SWH 29761.904 Hz  
FIDRES 0.454131 Hz  
AQ 1.1010548 sec  
RG 203  
DW 16.800 usec  
DE 6.50 usec  
TE 297.4 K  
D1 2.0000000 sec  
D11 0.0300000 sec  
TD0 1

==== CHANNEL f1 =====  
SF01 125.7779086 MHz  
NUC1 13C  
P1 10.50 usec  
SI 32768  
SF 125.7652971 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40



JTP-02-135

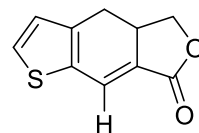


```

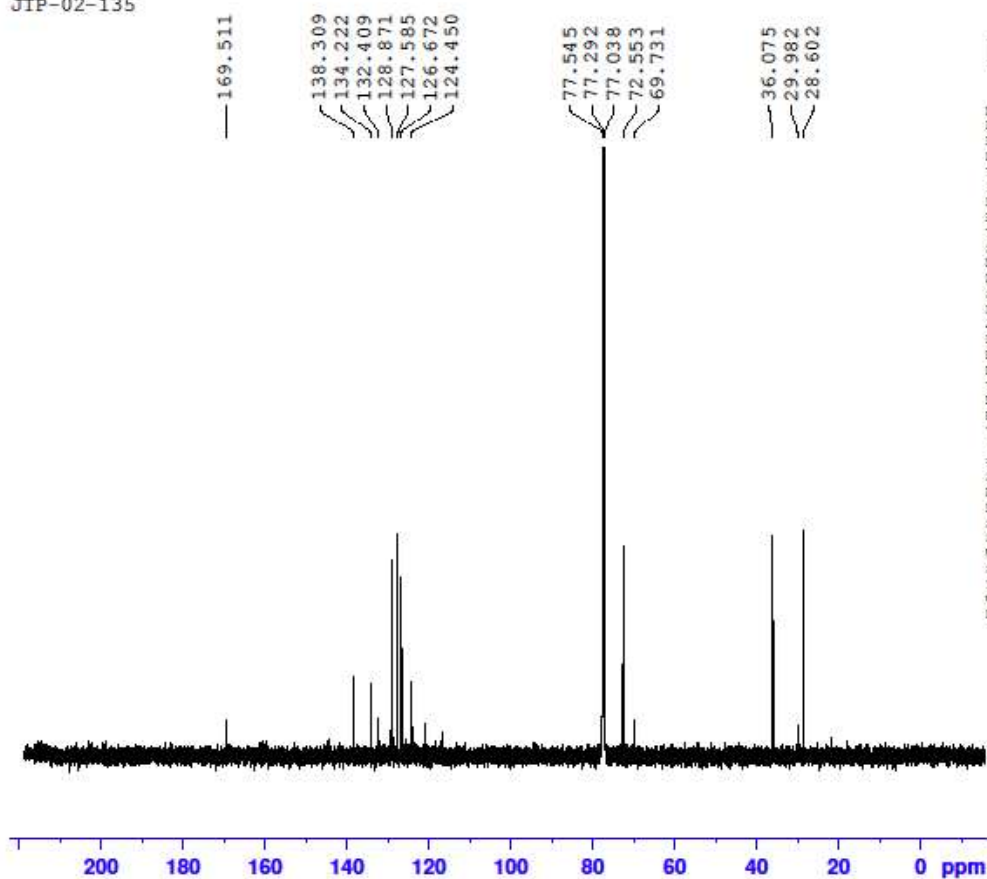
NAME          JTP-02-135
EXPNO         20
PROCNO        1
Date_         20160104
Time          18.40
INSTRUM       spect
PROBHD        5 mm PABBO BB/
PULPROG       zg30
TD            65536
SOLVENT       CDCl3
NS            16
DS            2
SWH           10000.000 Hz
FIDRES        0.152588 Hz
AQ            3.2768500 sec
RG            203
DW            50.000 usec
DE            6.50 usec
TE            298.7 K
D1            1.00000000 sec
TD0           1
  
```

```

===== CHANNEL f1 =====
SFO1          500.1630887 MHz
NUC1          1H
P1            11.45 usec
SI            65536
SF            500.1600103 MHz
WDW           EM
SSB           0
LB            0.30 Hz
GB            0
PC            1.00
  
```

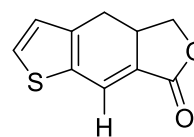


JTP-02-135

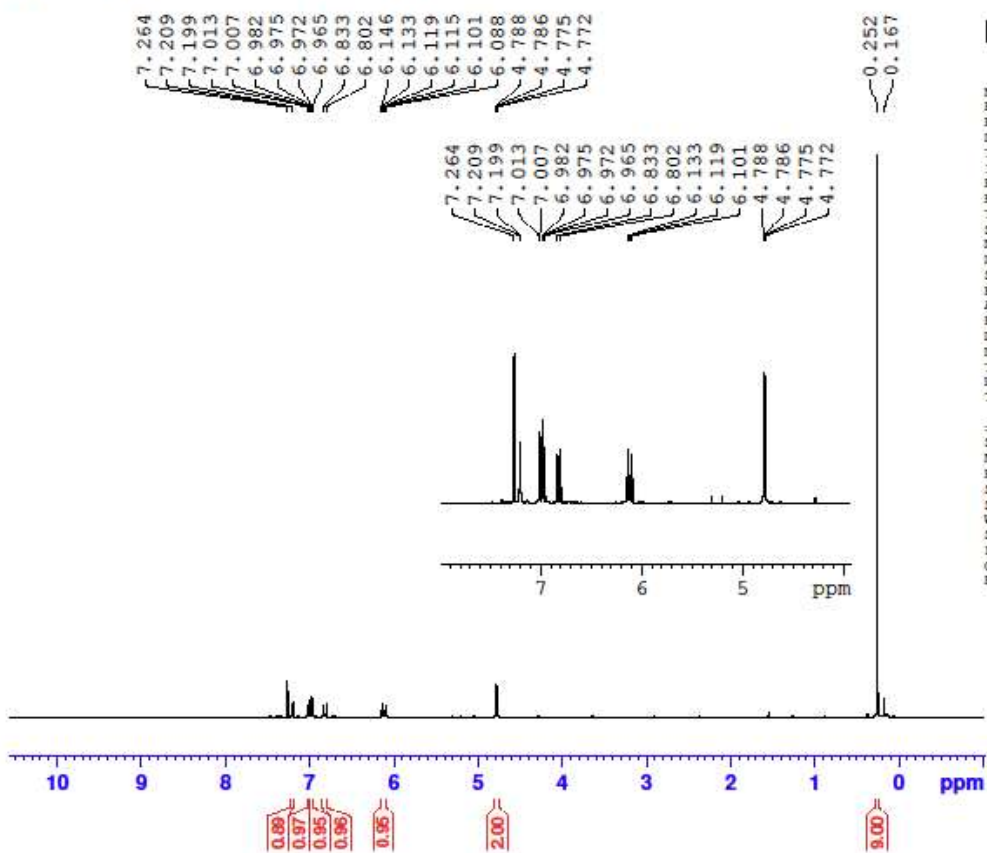


NAME JTP-02-135  
EXPNO 21  
PROCNO 1  
Date\_ 20160104  
Time 23.40  
INSTRUM spect  
PROBHD 5 mm PABBO BB/  
PULPROG zgpg30  
TD 65536  
SOLVENT CDCl3  
NS 3000  
DS 4  
SWH 29761.904 Hz  
FIDRES 0.454131 Hz  
AQ 1.1010548 sec  
RG 203  
DW 16.800 usec  
DE 6.50 usec  
TE 299.6 K  
D1 2.00000000 sec  
D11 0.03000000 sec  
TD0 1

==== CHANNEL f1 =====  
SFO1 125.7779086 MHz  
NUC1 13C  
P1 10.50 usec  
SI 32768  
SF 125.7652966 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40



JIP-02-134, Thiophene-2-IMS Ester pure



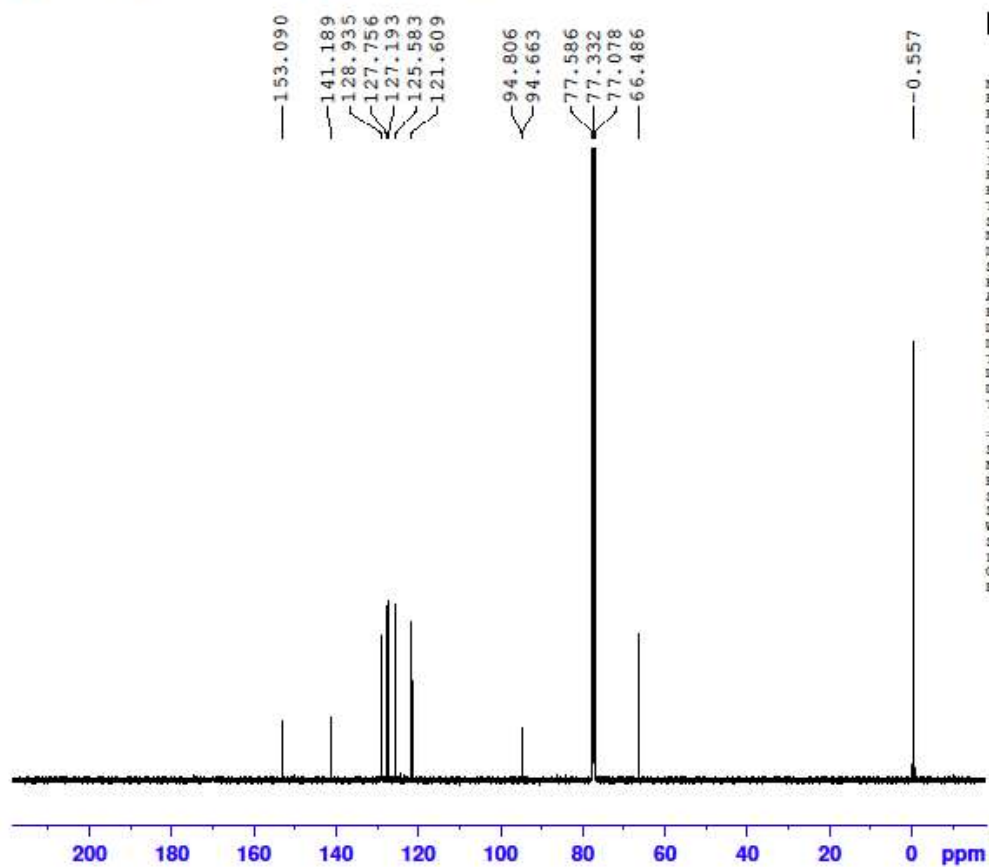
```

NAME      JIP-02-134
EXPNO    10
PROCNO   1
Date_    20151103
Time     17.01
INSTRUM  spect
PROBHD   5 mm PABBO BB/
PULPROG  zg30
TD       65536
SOLVENT  CDCl3
NS       16
DS       2
SWH      10000.000 Hz
FIDRES   0.152588 Hz
AQ       3.2768500 sec
RG       101
DW       50.000 usec
DE       6.50 usec
TE       297.0 K
D1       1.00000000 sec
TD0      1
    
```

```

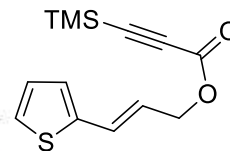
===== CHANNEL f1 =====
SFO1    500.1630887 MHz
NUC1     1H
P1      11.45 usec
SI      65536
SF      500.1600107 MHz
WDW     EM
SSB     0
LB      0.30 Hz
GB      0
PC      1.00
    
```

JTP-02-134, Thiophene-2-IMS Ester pure

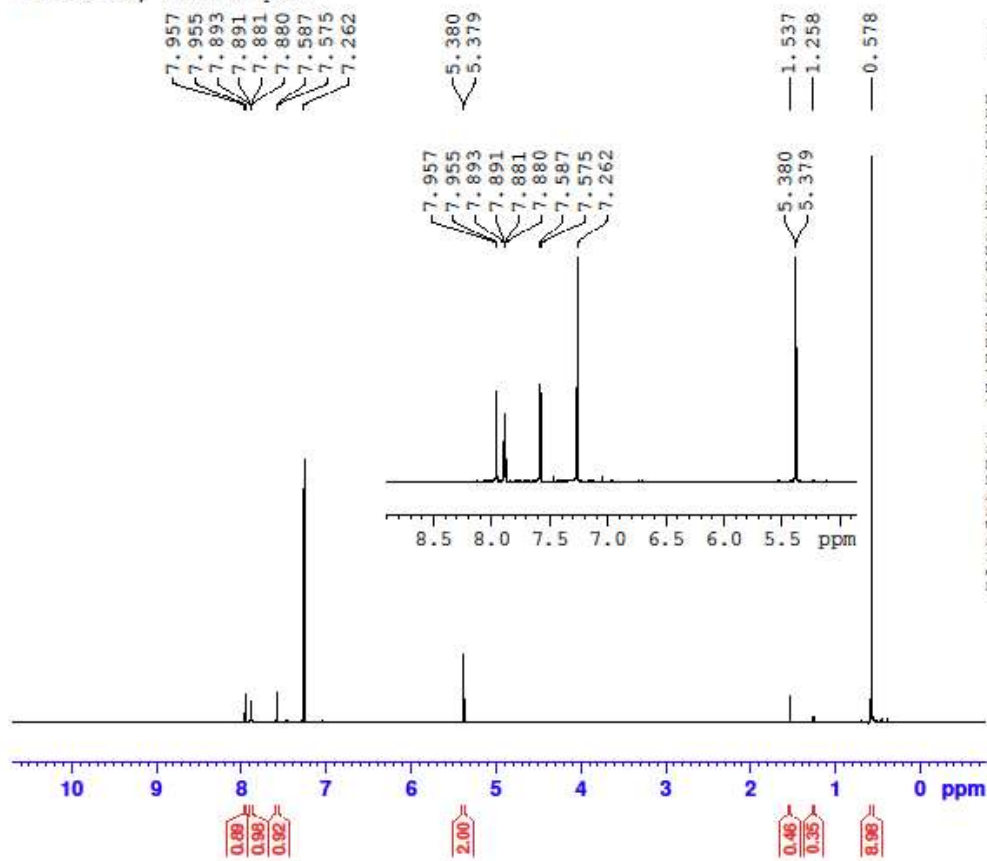


NAME JTP-02-134  
EXPNO 11  
PROCNO 1  
Date\_ 20151106  
Time 0.51  
INSTRUM spect  
PROBHD 5 mm PABBO BB/  
PULPROG zgig30  
TD 65536  
SOLVENT CDCl3  
NS 2000  
DS 4  
SWH 29761.904 Hz  
FIDRES 0.454131 Hz  
AQ 1.1010548 sec  
RG 203  
EW 16.800 usec  
DE 6.50 usec  
TK 297.7 K  
D1 2.00000000 sec  
D11 0.03000000 sec  
TD0 1

==== CHANNEL f1 =====  
SF01 125.7779086 MHz  
NUC1 13C  
P1 10.50 usec  
SI 32768  
SF 125.7652932 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40

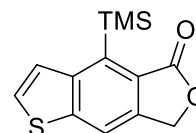


JIP-02-138, Product pure

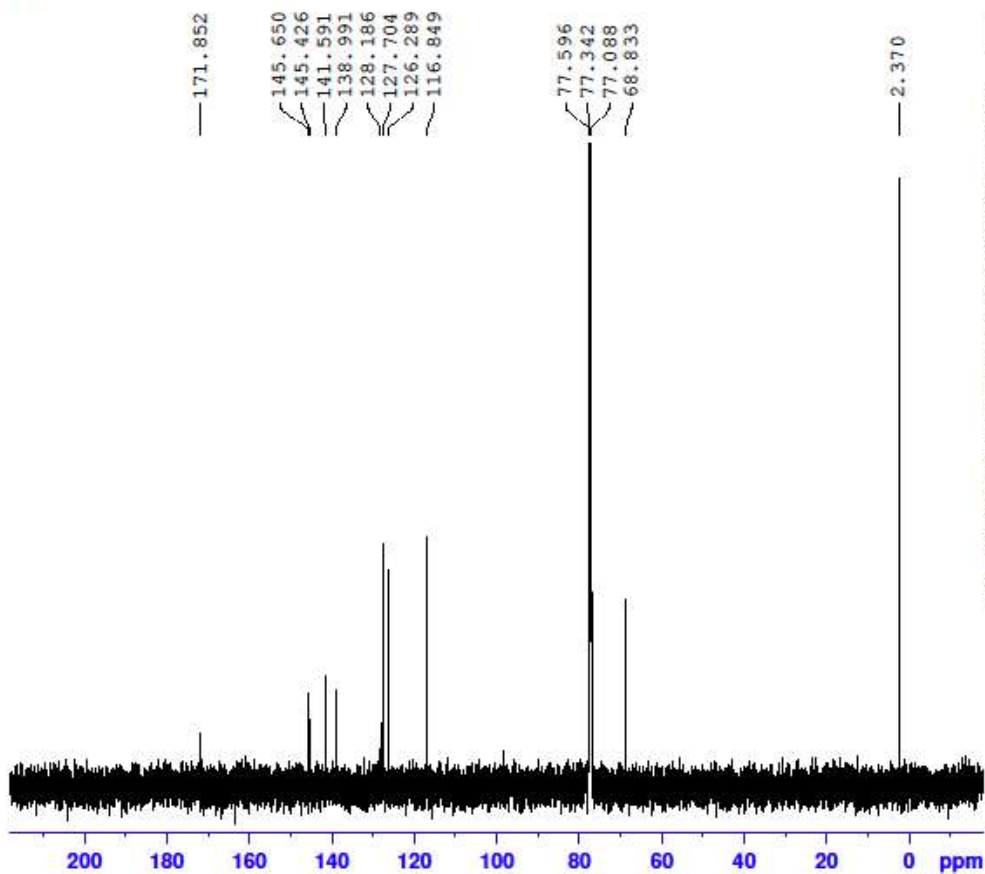


NAME JIP-02-138  
EXPNO 11  
PROCNO 1  
Date\_ 20160114  
Time 16.49  
INSTRUM spect  
PROBHD 5 mm PABBO BB/  
PULPROG zg30  
TD 65536  
SOLVENT CDCl3  
NS 16  
DS 2  
SWH 10000.000 Hz  
FIDRES 0.152588 Hz  
AQ 3.2768500 sec  
RG 203  
DW 50.000 usec  
DE 6.50 usec  
TK 298.5 K  
D1 1.00000000 sec  
TD0 1

==== CHANNEL f1 =====  
SFO1 500.1630887 MHz  
NUC1 1H  
P1 11.45 usec  
SI 65536  
SF 500.1600115 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00

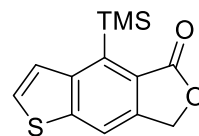


JIP-02-138, Product pure



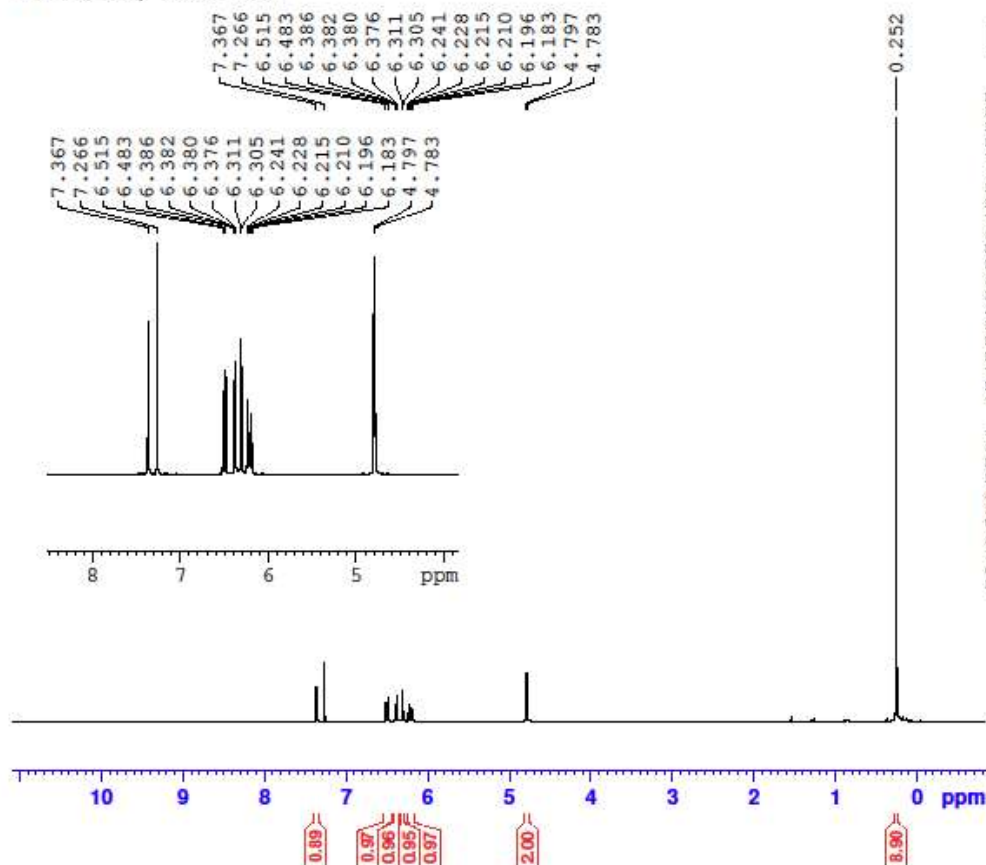
```
NAME JIP-02-138
EXPNO 12
PROCNO 1
Date_ 20160115
Time 2.31
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgig30
TD 65536
SOLVENT Cocl3
NS 3000
DS 4
SWH 29761.904 Hz
FIDRES 0.454131 Hz
AQ 1.1010548 sec
RG 203
EW 16.800 usec
DE 6.50 usec
TE 299.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
```

```
===== CHANNEL f1 =====
SFO1 125.7779086 MHz
NUC1 13C
P1 10.50 usec
SI 32768
SF 125.7652898 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
```



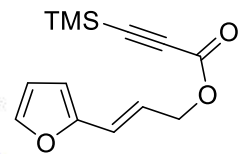


JIP-02-157, Prod. Pure

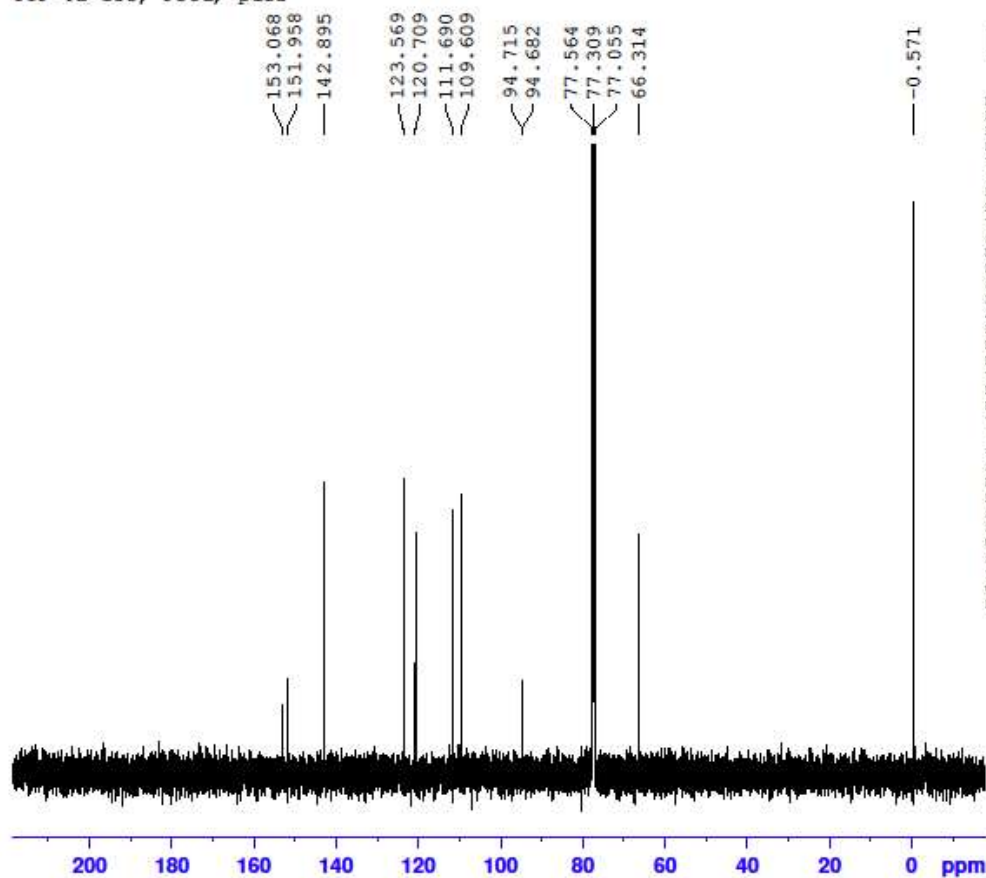


NAME JIP-02-157  
EXPNO 20  
PROCNO 1  
Date\_ 20160123  
Time 22.43  
INSTRUM spect  
PROBHD 5 mm PABBO BB/  
PULPROG zg30  
TD 65536  
SOLVENT CDCl3  
NS 16  
DS 2  
SWH 10000.000 Hz  
FIDRES 0.152588 Hz  
AQ 3.2768500 sec  
RG 114  
DW 50.000 usec  
DE 6.50 usec  
TE 299.4 K  
D1 1.00000000 sec  
TD0 1

==== CHANNEL f1 =====  
SFO1 500.1630887 MHz  
NUC1 1H  
P1 11.45 usec  
SI 65536  
SF 500.1600101 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00

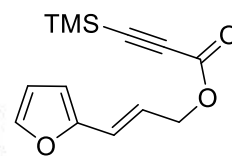


JIP-02-153, Prod, pure

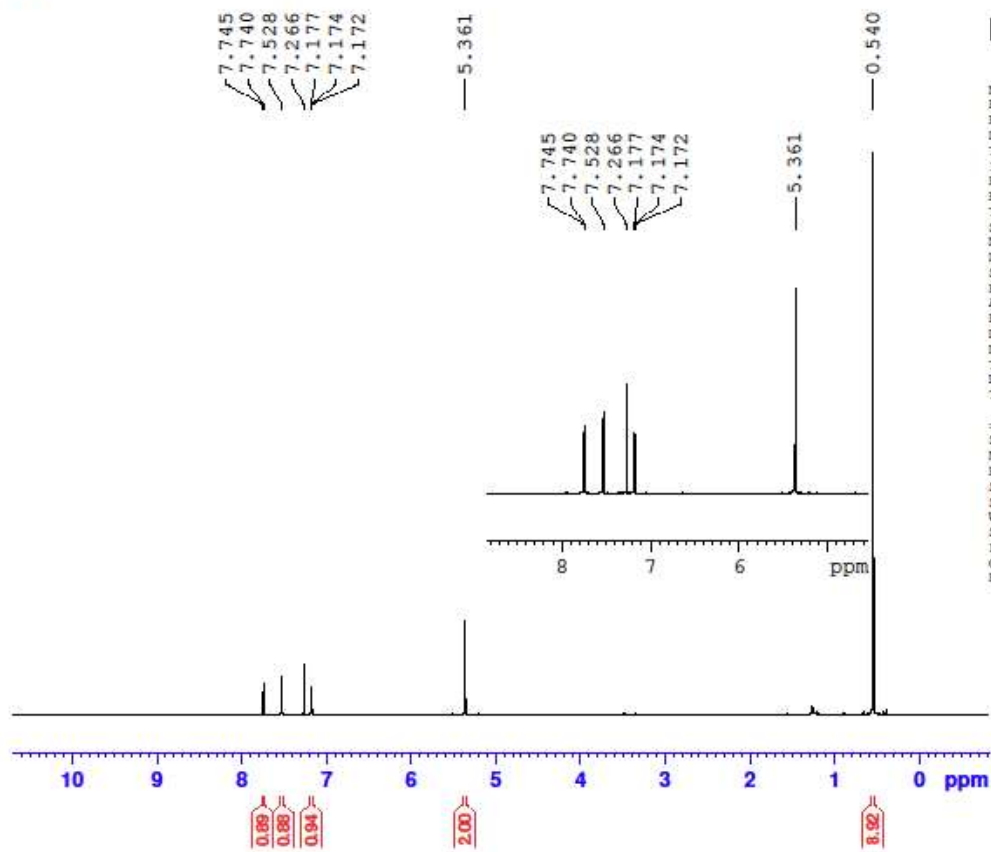


NAME JIP-02-153  
EXPNO 61  
PROCNO 1  
Date\_ 20160112  
Time 0.08  
INSTRUM spect  
PROBHD 5 mm PABBO BB/  
PULPROG zgig30  
TD 65536  
SOLVENT CDCl3  
NS 1024  
DS 4  
SWH 29761.904 Hz  
FIDRES 0.454131 Hz  
AQ 1.1010548 sec  
RG 203  
EW 16.800 usec  
DE 6.50 usec  
TK 299.0 K  
D1 2.00000000 sec  
D11 0.03000000 sec  
TD0 1

==== CHANNEL f1 =====  
SFO1 125.7779086 MHz  
NUC1 13C  
P1 10.50 usec  
SI 32768  
SF 125.7652939 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40

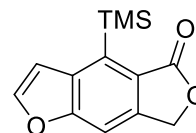


JTP-02-156, Prod. Pure

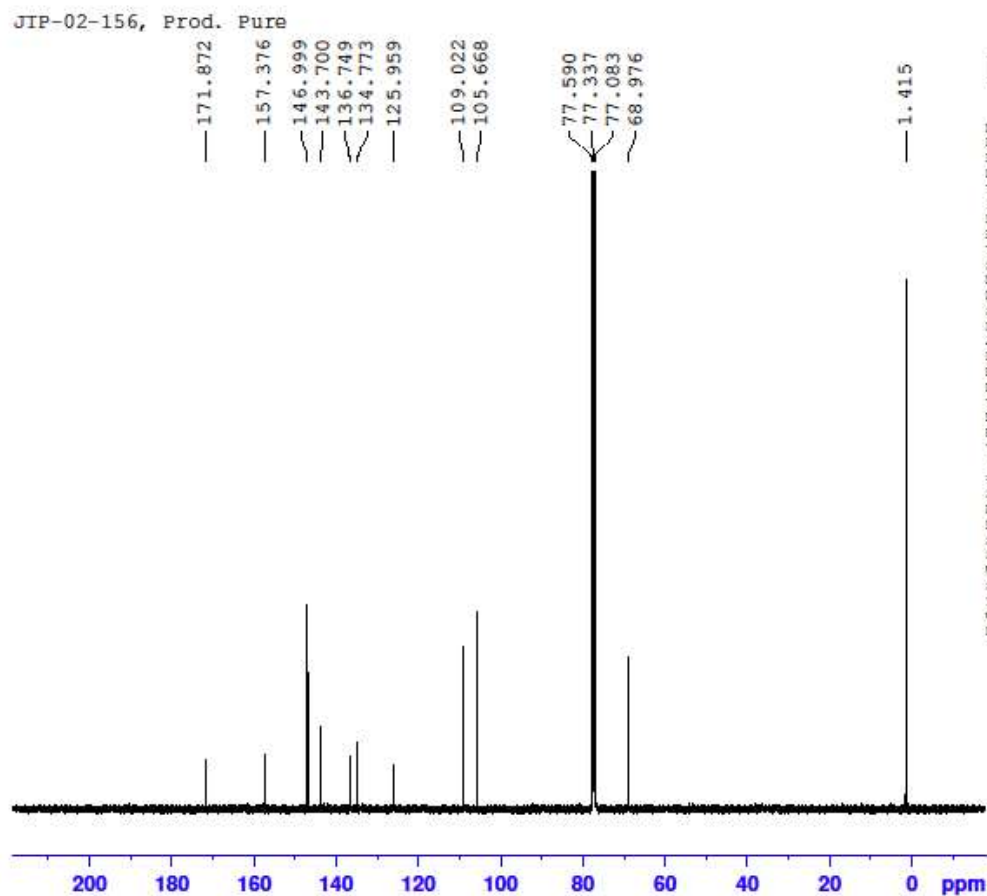


NAME JTP-02-156  
EXPNO 10  
PROCNO 1  
Date\_ 20160123  
Time 20.55  
INSTRUM spect  
PROBHD 5 mm PABBO BB/  
PULPROG zg30  
TD 65536  
SOLVENT cdc13  
NS 16  
DS 2  
SWH 10000.000 Hz  
FIDRES 0.152588 Hz  
AQ 3.2768500 sec  
RG 161  
DW 50.000 usec  
DE 6.50 usec  
TE 299.4 K  
D1 1.00000000 sec  
TD0 1

==== CHANNEL F1 =====  
SFO1 500.1630887 MHz  
NUC1 1H  
P1 11.45 usec  
SI 65536  
SF 500.1600097 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00

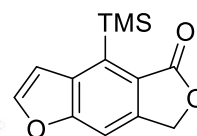


JIP-02-156, Prod. Pure

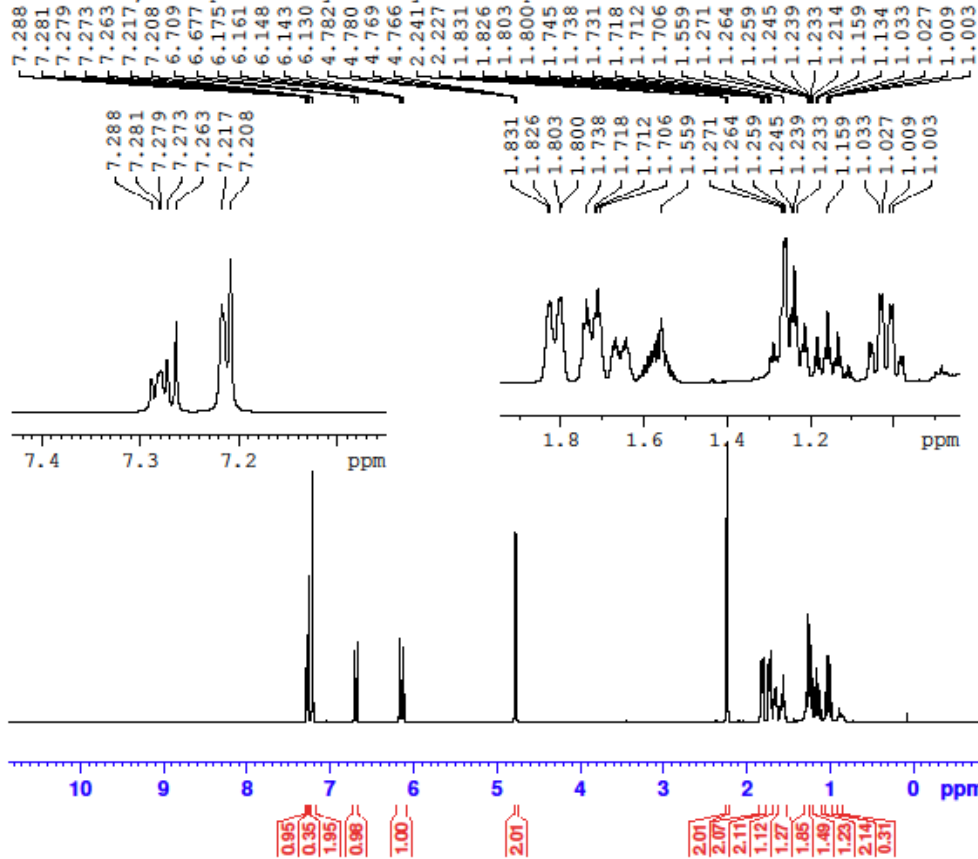


```
NAME JIP-02-156
EXPNO 11
PROCNO 1
Date_ 20160123
Time 22.35
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgig30
TD 65536
SOLVENT CDCl3
NS 180
DS 4
SWH 29761.904 Hz
FIDRES 0.454131 Hz
AQ 1.1010548 sec
RG 203
EW 16.800 usec
DE 6.50 usec
TE 299.8 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
```

```
===== CHANNEL f1 =====
SFO1 125.7779086 MHz
NUC1 13C
P1 10.50 usec
SI 32768
SF 125.7652908 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
```

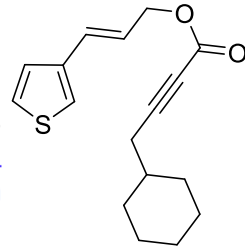


JTP-02-080, Thiophene-3-Cyclohexyl Ester pure

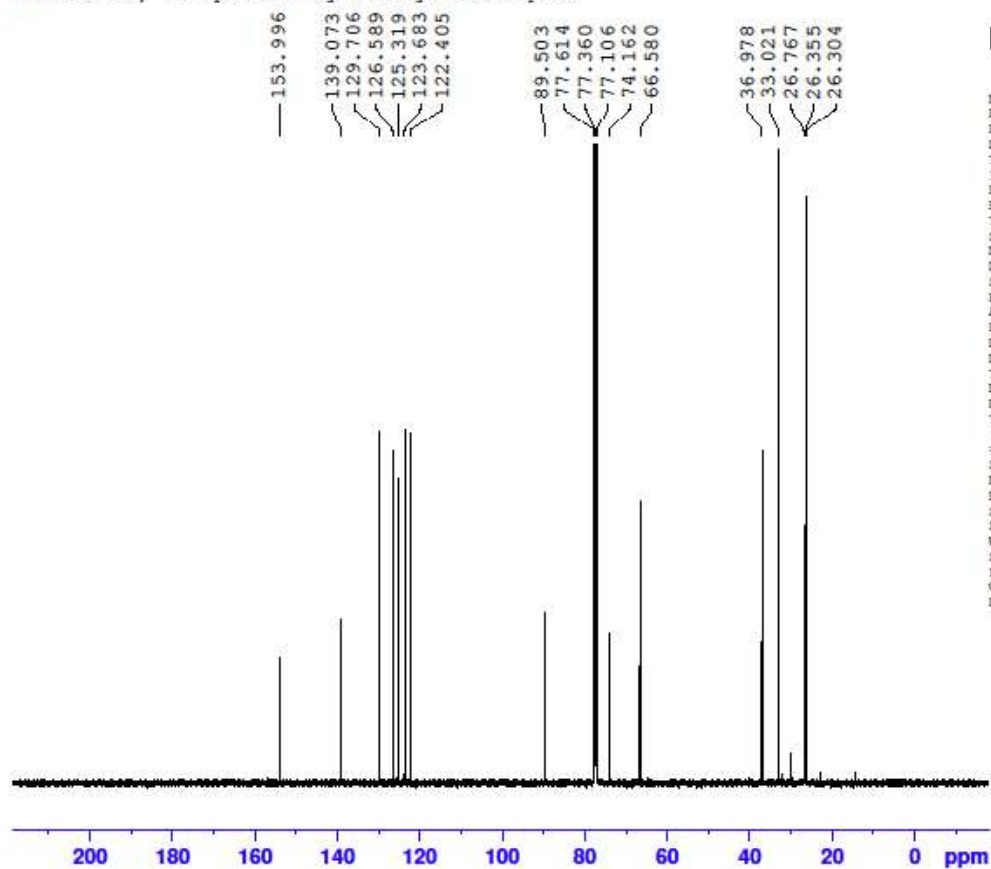


NAME JTP-02-080\_2  
 EXPNO 2  
 PROCNO 1  
 Date\_ 20150626  
 Time 14.21  
 INSTRUM spect  
 PROBHD 5 mm PABBO BB/  
 PULPROG zg30  
 TD 65536  
 SOLVENT CDCl3  
 NS 16  
 DS 2  
 SWH 10000.000 Hz  
 FIDRES 0.152588 Hz  
 AQ 3.2768500 sec  
 RG 80.6  
 DW 50.000 usec  
 DE 6.50 usec  
 TE 298.2 K  
 D1 1.00000000 sec  
 TD0 1

===== CHANNEL f1 =====  
 SFO1 500.1630887 MHz  
 NUC1 1H  
 P1 11.45 usec  
 SI 65536  
 SF 500.1600109 MHz  
 WDW EM  
 SSB 0  
 LB 0.30 Hz  
 GB 0  
 PC 1.00



JTP-02-080, Thiophene-3-Cyclohexyl Ester pure

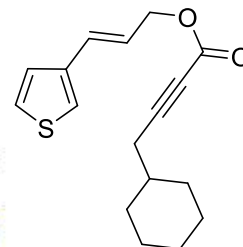


```

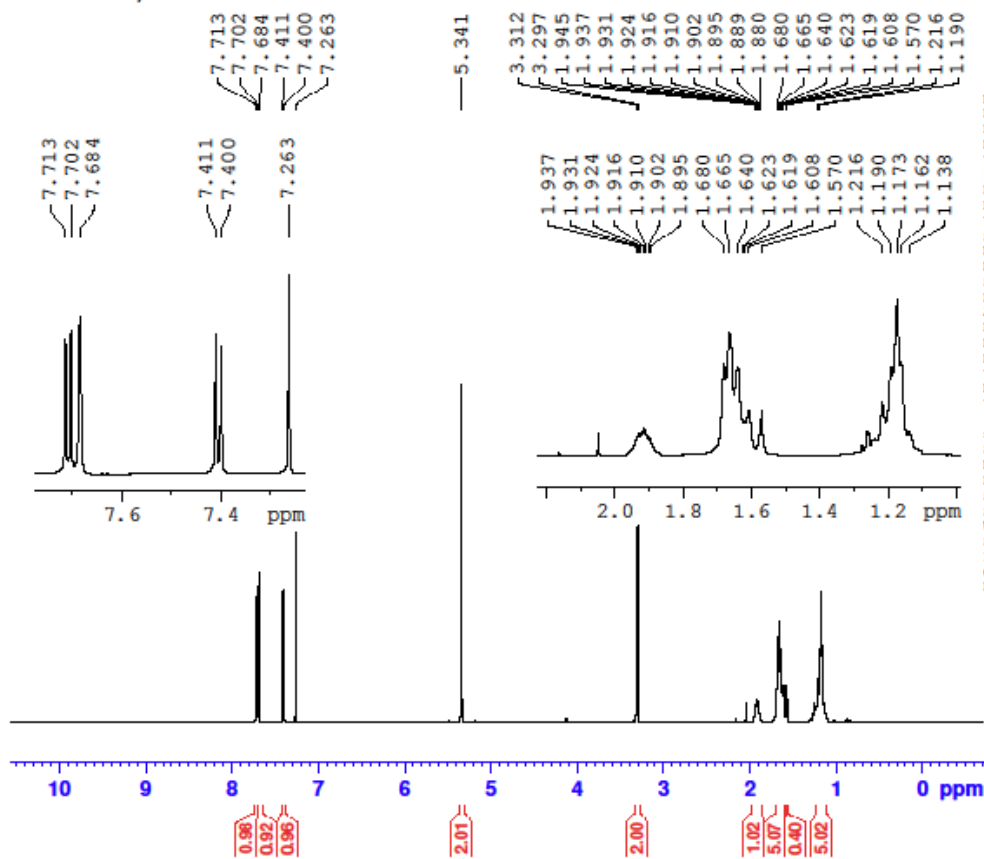
NAME      JTP-02-080
EXPNO     3
PROCNO    1
Date_     20150627
Time      3.43
INSTRUM   spect
PROBHD    5 mm FAPBO BB/
PULPROG   zgig30
TD        65536
SOLVENT   cdcl3
NS        3000
DS        4
SWH       29761.904 Hz
FIDRES    0.454131 Hz
AQ        1.1010548 sec
RG        203
DW        16.800 usec
DE        6.50 usec
TE        298.2 K
D1        2.0000000 sec
D11       0.0300000 sec
TD0       1
    
```

```

===== CHANNEL f1 =====
SF01     125.7779086 MHz
NUC1     13C
P1       10.50 usec
SI       32768
SF       125.7652903 MHz
WDW      EM
SSB      0
LB       1.00 Hz
GB       0
PC       1.40
    
```



JTP-02-089, Product

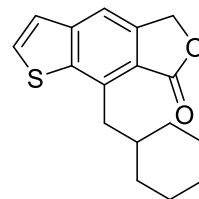


```

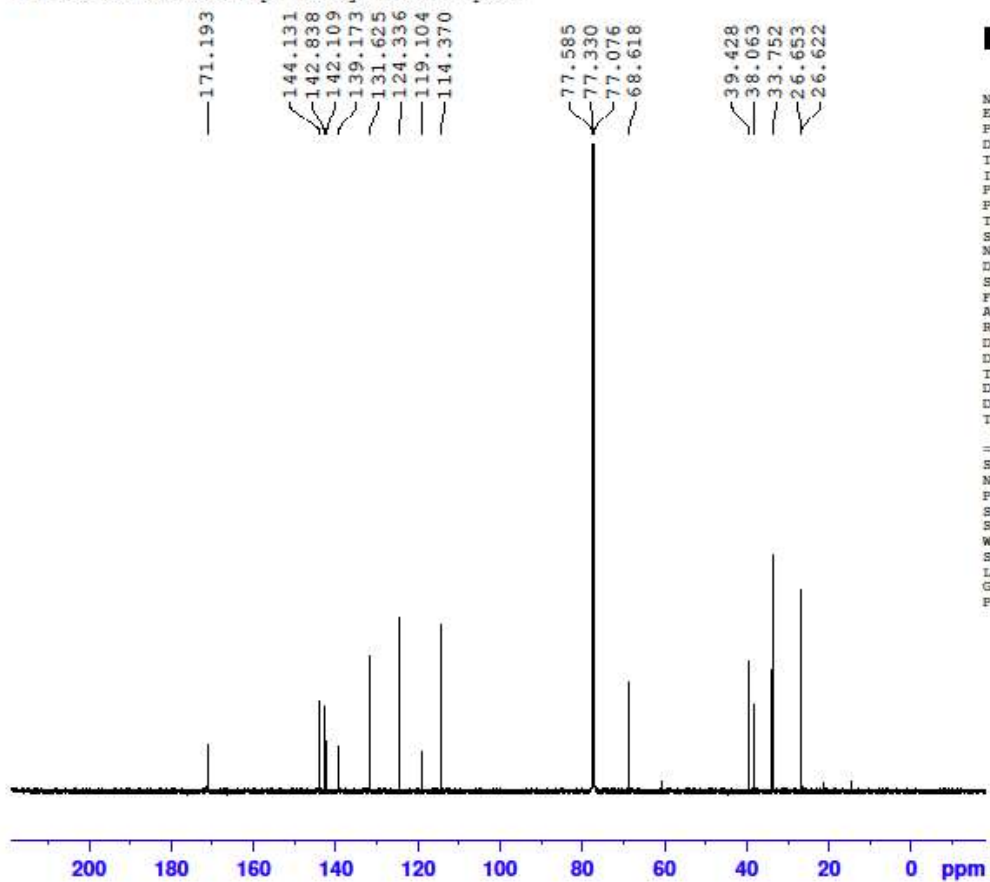
NAME      JTP-02-089
EXPNO    10
PROCNO   1
Date_    20150811
Time     18.25
INSTRUM  spect
PROBHD   5 mm PABBO BB/
PULPROG  zg30
TD       65536
SOLVENT  CDCl3
NS       16
DS       2
SWH      10000.000 Hz
FIDRES   0.152588 Hz
AQ       3.2768500 sec
RG       114
DW       50.000 usec
DE       6.50 usec
TE       296.8 K
D1       1.00000000 sec
TD0      1
  
```

```

===== CHANNEL f1 =====
SFO1    500.1630887 MHz
NUC1     1H
P1      11.45 usec
SI      65536
SF      500.1600111 MHz
WDW     EM
SSB     0
LB      0.30 Hz
GB      0
PC      1.00
  
```

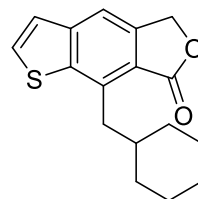


JIP-02-089 Benzothiophene Cy Product pure



NAME JIP-02-089  
EXPNO 3  
PROCNO 1  
Date\_ 20150703  
Time 4.45  
INSTRUM spect  
PROBHD 5 mm F4BBO BB/  
PULPROG zgpg30  
TD 65536  
SOLVENT cdcl3  
NS 2500  
DS 4  
SWH 29761.904 Hz  
FIDRES 0.454131 Hz  
AQ 1.1010548 sec  
RG 203  
DW 16.800 usec  
DE 6.50 usec  
TE 298.2 K  
D1 2.0000000 sec  
D11 0.0300000 sec  
TD0 1

==== CHANNEL f1 =====  
SF01 125.7779086 MHz  
NUC1 13C  
P1 10.50 usec  
SI 32768  
SF 125.7652937 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40





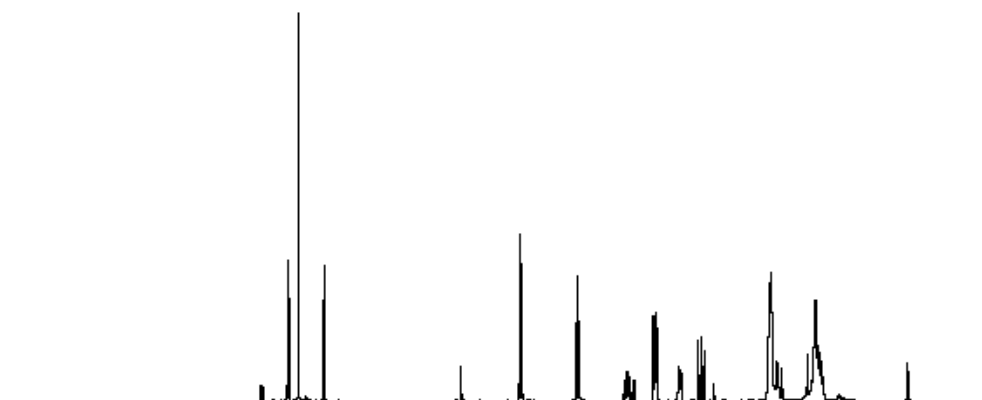
JIP-02-130, Product

7.388  
7.378  
7.263  
6.964  
6.954  
5.343  
5.341  
4.658  
4.640  
4.623  
3.982  
3.964  
3.946  
3.371  
3.075  
3.060  
3.054  
3.044  
3.039  
3.029  
2.784  
2.780  
2.771  
2.768  
2.759  
2.755  
2.542  
2.511  
2.508  
2.477  
1.695  
1.689  
1.681  
1.617  
1.609  
1.557  
1.257  
1.177  
1.173  
1.162  
1.136  
1.131  
1.127  
1.103



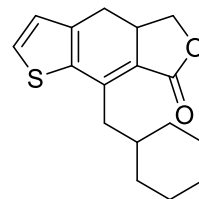
NAME JIP-02-130\_2  
EXPNO 10  
PROCNO 1  
Date\_ 20160103  
Time 17.22  
INSTRUM spect  
PROBHD 5 mm FAPBO BB/  
PULPROG zg30  
TD 65536  
SOLVENT cdc13  
NS 16  
DS 2  
SWH 10000.000 Hz  
FIDRES 0.152588 Hz  
AQ 3.2768500 sec  
RG 114  
DW 50.000 usec  
DE 6.50 usec  
TE 297.8 K  
D1 1.0000000 sec  
TD0 1

==== CHANNEL F1 =====  
SFO1 500.1630887 MHz  
NUC1 1H  
P1 11.45 usec  
SI 65536  
SF 500.1600105 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00

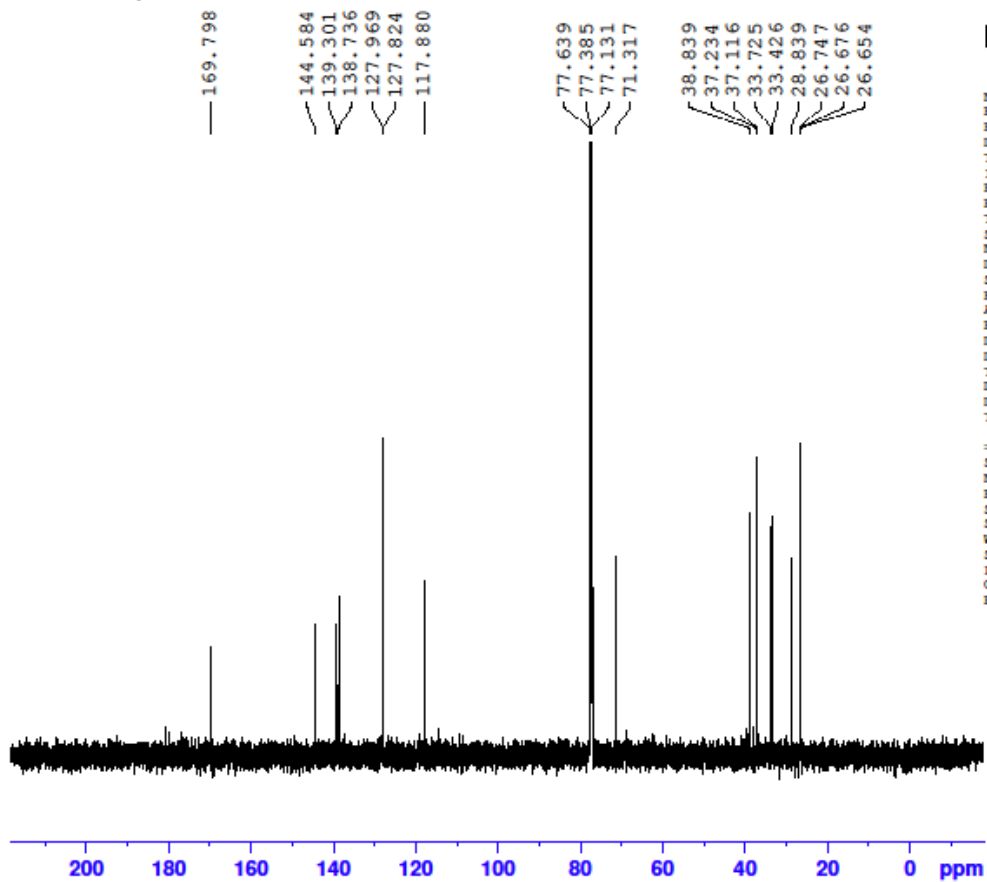


10 9 8 7 6 5 4 3 2 1 0 ppm

0.08  
0.08  
0.08  
0.92  
0.95  
0.16  
1.00  
1.00  
0.99  
0.16  
2.00  
1.00  
1.00  
6.71  
0.27  
0.48  
5.84

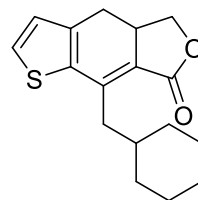


JTP-02-130, Product

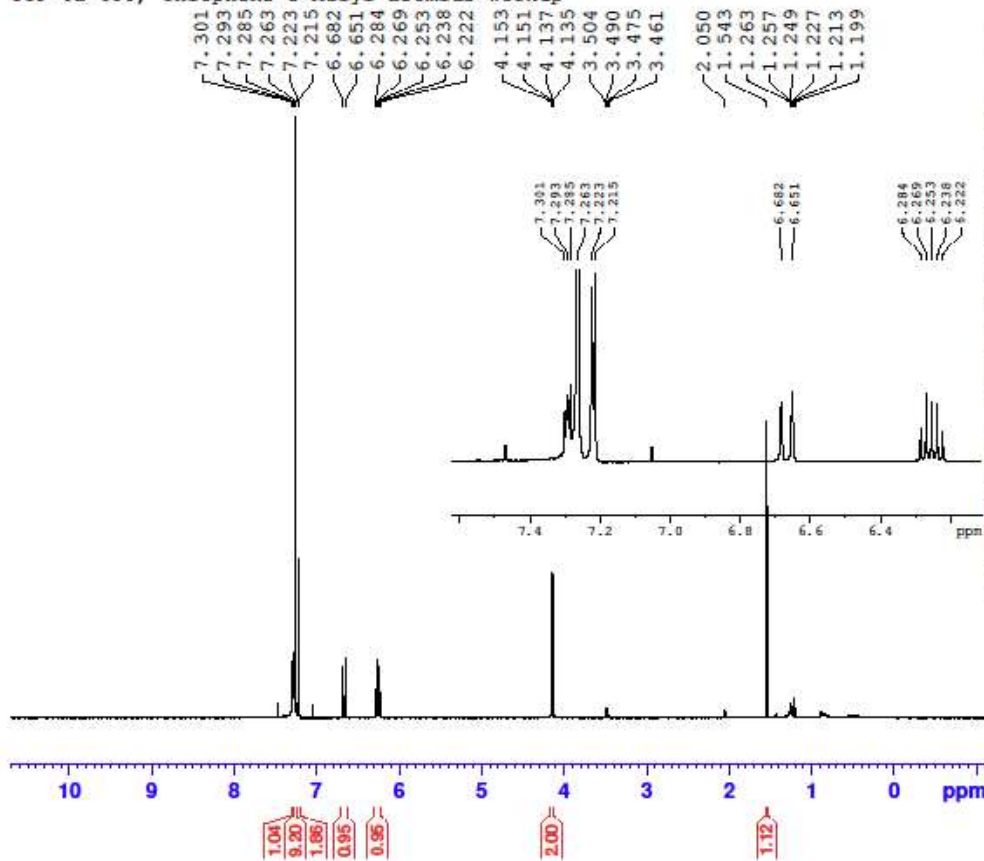


NAME JTP-02-130  
EXPNO 11  
PROCNO 1  
Date\_ 20160103  
Time 18.18  
INSTRUM spect  
PROBHD 5 mm PABBO BB/  
PULPROG zgig30  
TD 65536  
SOLVENT CDCl3  
NS 1024  
DS 4  
SWH 29761.904 Hz  
FIDRES 0.454131 Hz  
AQ 1.1010548 sec  
RG 203  
DW 16.800 usec  
DE 6.50 usec  
TE 298.3 K  
D1 2.00000000 sec  
D11 0.03000000 sec  
TD0 1

==== CHANNEL f1 =====  
SFO1 125.7779086 MHz  
NUC1 13C  
P1 10.50 usec  
SI 32768  
SF 125.7652854 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40



JTP-02-099, Thiophene-3-Allyl Bromide workup

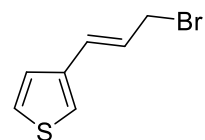


```

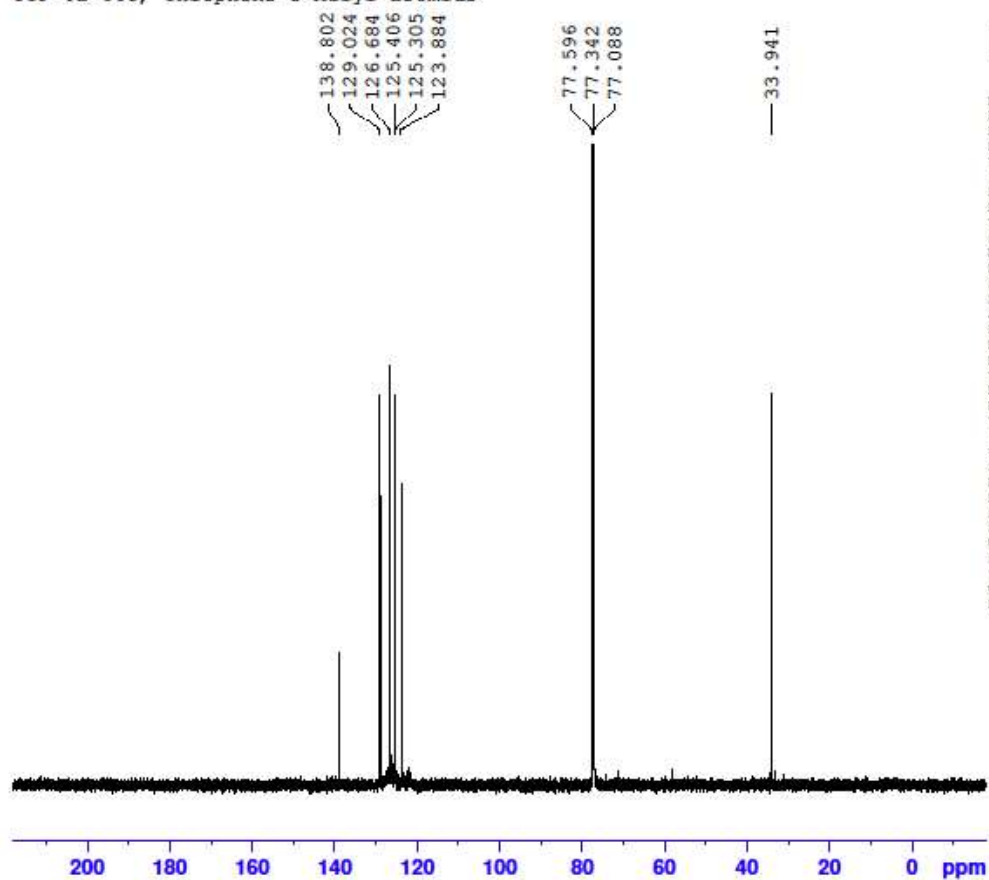
NAME      JTP-02-099
EXPNO     1
PROCNO    1
Date_     20150721
Time      19.16
INSTRUM   spect
PROBHD    5 mm PABBO BB/
PULPROG   zg30
TD         65536
SOLVENT   cdc13
NS         16
DS         2
SWH        10000.000 Hz
FIDRES     0.152588 Hz
AQ          3.2768500 sec
RG          203
DW          50.000 usec
DE          6.50 usec
TE          295.2 K
D1          1.00000000 sec
TD0         1
    
```

```

===== CHANNEL F1 =====
SFO1      500.1630887 MHz
NUC1       1H
P1         11.45 usec
SI         65536
SF         500.1600110 MHz
WUW        EM
SSB         0
LB          0.30 Hz
GB          0
PC          1.00
    
```



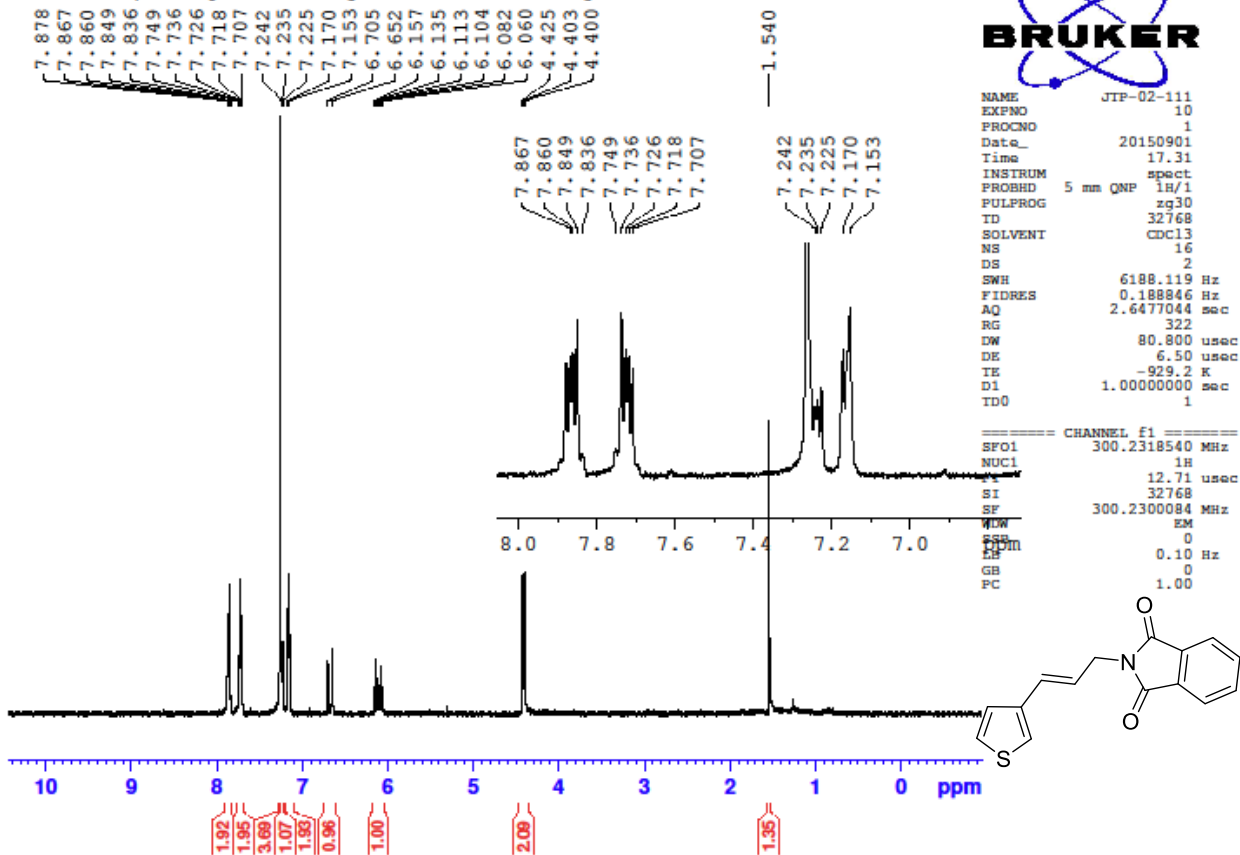
JTP-02-068, Thiophene-3-Allyl Bromide



NAME JTP-02-068  
EXPNO 2  
PROCNO 1  
Date\_ 20150527  
Time 0.55  
INSTRUM spect  
PROBHD 5 mm FAPBO BB/  
PULPROG zgig30  
TD 65536  
SOLVENT cdc13  
NS 1024  
DS 4  
SWH 29761.904 Hz  
FIDRES 0.454131 Hz  
AQ 1.1010548 sec  
RG 203  
DW 16.800 usec  
DE 6.50 usec  
TE 298.2 K  
D1 2.0000000 sec  
D11 0.0300000 sec  
TD0 1

==== CHANNEL f1 =====  
SF01 125.7779086 MHz  
NUC1 13C  
P1 10.50 usec  
SI 32768  
SF 125.7652935 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40

JIP-02-111, Thiophene-3-Allyl Phthalimide recryst. air dried

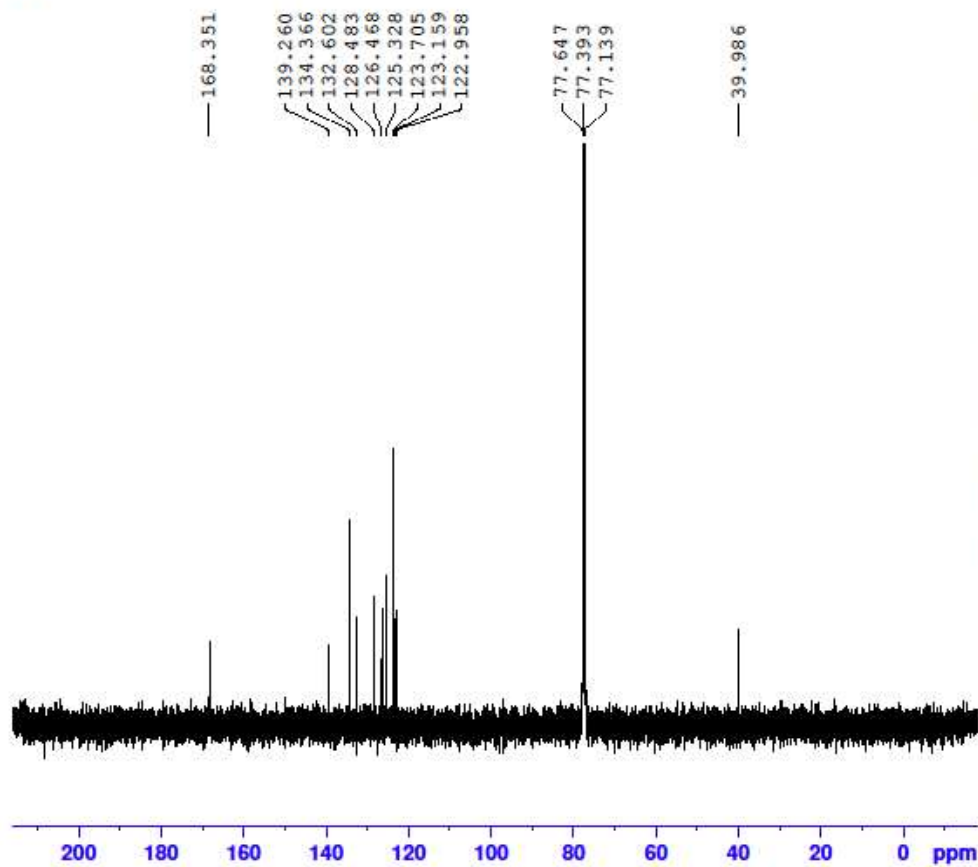


```

NAME      JIP-02-111
EXPNO     10
PROCNO    1
Date_     20150901
Time      17.31
INSTRUM   spect
PROBHD    5 mm QNP 1H/1
PULPROG   zg30
ID        32768
SOLVENT   CDCl3
NS        16
DS        2
SWH       6188.119 Hz
FIDRES    0.188846 Hz
AQ        2.6477044 sec
RG        322
DW        80.800 usec
DE        6.50 usec
TE        -929.2 K
D1        1.00000000 sec
TD0       1

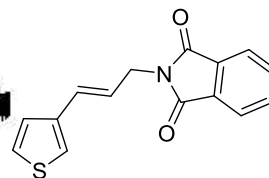
===== CHANNEL f1 =====
SFO1     300.2318540 MHz
NUC1     1H
SI       12.71 usec
SF       32768
WDW      EM
SSB      0
LB       0.10 Hz
GB       0
PC       1.00
    
```

JTP-02-111, Product pure

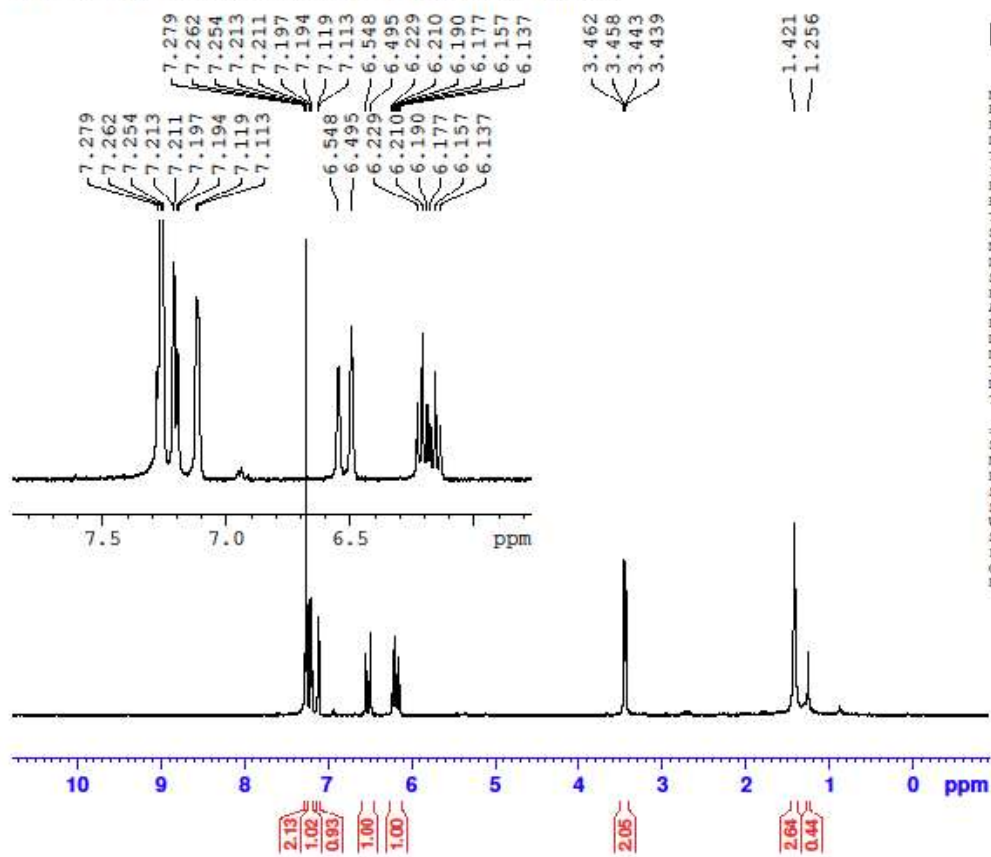


```
NAME      JTP-02-111
EXPNO     20
PROCNO    1
Date_     20160110
Time      0.42
INSTRUM   spect
PROBHD    5 mm FAPBO BB/
PULPROG   zgig30
TD        65536
SOLVENT   cdcl3
NS        2000
DS        4
SWH       29761.904 Hz
FIDRES    0.454131 Hz
AQ        1.1010548 sec
RG        203
DW        16.800 usec
DE        6.50 usec
TE        298.6 K
D1        2.0000000 sec
D11       0.03000000 sec
TD0       1
```

```
==== CHANNEL f1 =====
SFO1     125.7779086 MHz
NUC1     13C
P1       10.50 usec
SI       32768
SF       125.7652833 MHz
WDW      EM
SSB      0
LB       1.00 Hz
GB       0
PC       1.40
```



JTP-02-114, Thiophene-2-Allyl Amine After workup

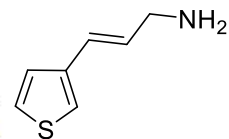


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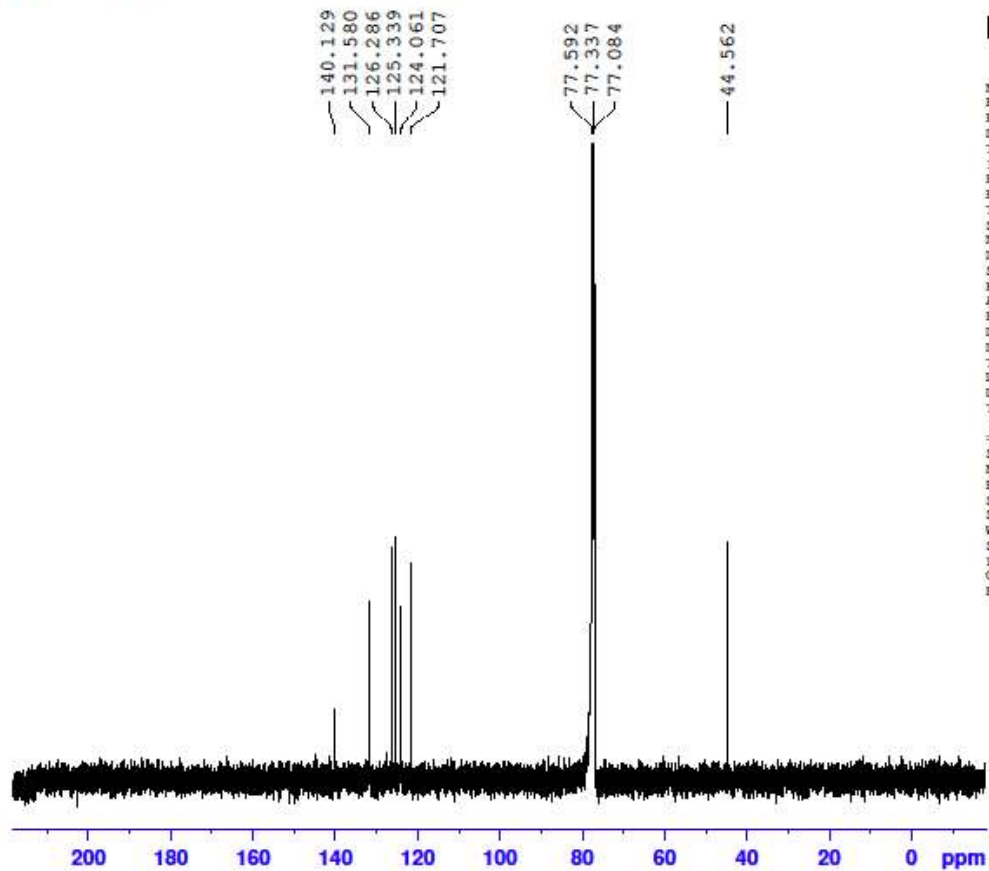
NAME      JTP-02-114
EXPNO    10
PROCNO   1
Date_    20150903
Time     18.12
INSTRUM  spect
PROBHD   5 mm QNP 1H/1
PULPROG  zg30
TD       32768
SOLVENT  CDCl3
NS       16
DS       2
SWH      6188.119 Hz
FIDRES   0.188846 Hz
AQ       2.6477044 sec
RG       322
DW       80.800 usec
DE       6.50 usec
TE       -928.6 K
D1       1.00000000 sec
TD0      1
  
```

```

===== CHANNEL f1 =====
SFO1    300.2318540 MHz
NUC1     1H
P1      12.71 usec
SI      32768
SF      300.2300078 MHz
WDW     EM
SSB     0
LB      0.10 Hz
GB      0
PC      1.00
  
```

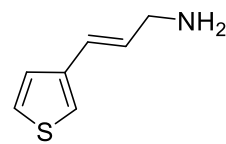


JTP-02-114, Thiophene-3-Allyl Amine, workup



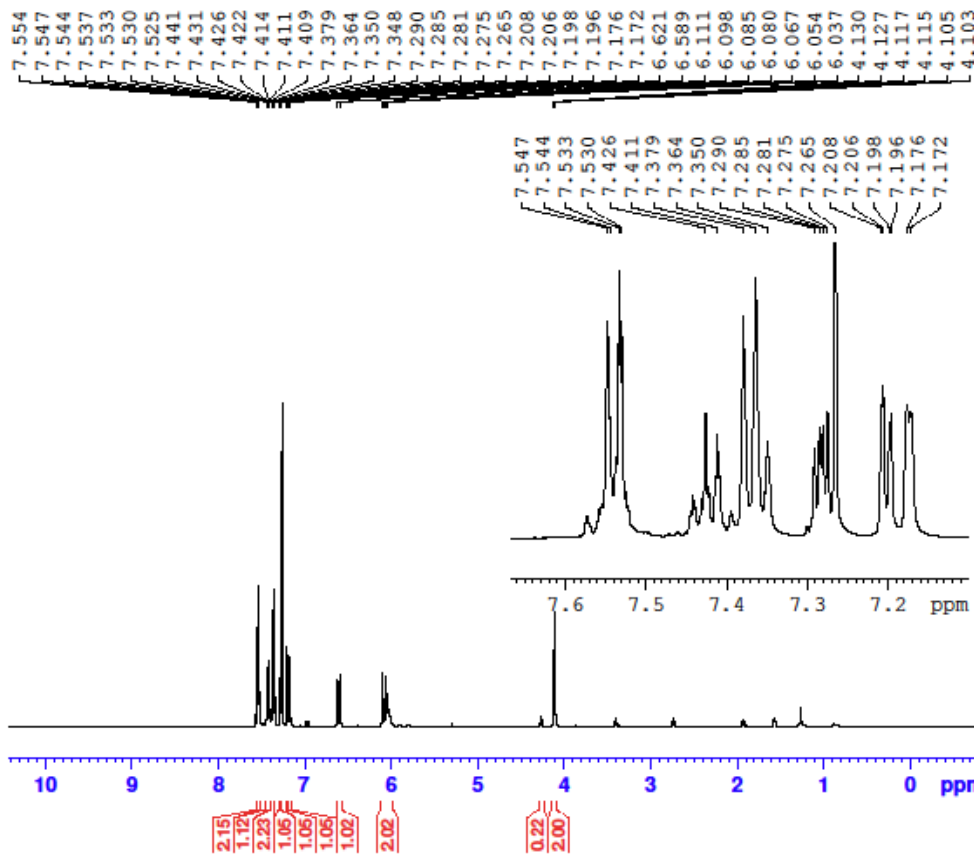
NAME JTP-02-114  
EXPNO 10  
PROCNO 1  
Date\_ 20150904  
Time 5.23  
INSTRUM spect  
PROBHD 5 mm PABBO BB/  
PULPROG zgig30  
TD 65536  
SOLVENT CDCl3  
NS 3000  
DS 4  
SWH 29761.904 Hz  
FIDRES 0.454131 Hz  
AQ 1.1010548 sec  
RG 203  
DW 16.800 usec  
DE 6.50 usec  
TE 297.8 K  
D1 2.00000000 sec  
D11 0.03000000 sec  
TD0 1

==== CHANNEL f1 =====  
SF01 125.7779086 MHz  
NUC1 13C  
P1 10.50 usec  
SI 32768  
SF 125.7652920 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40



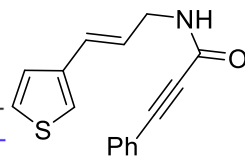


JIP-02-106

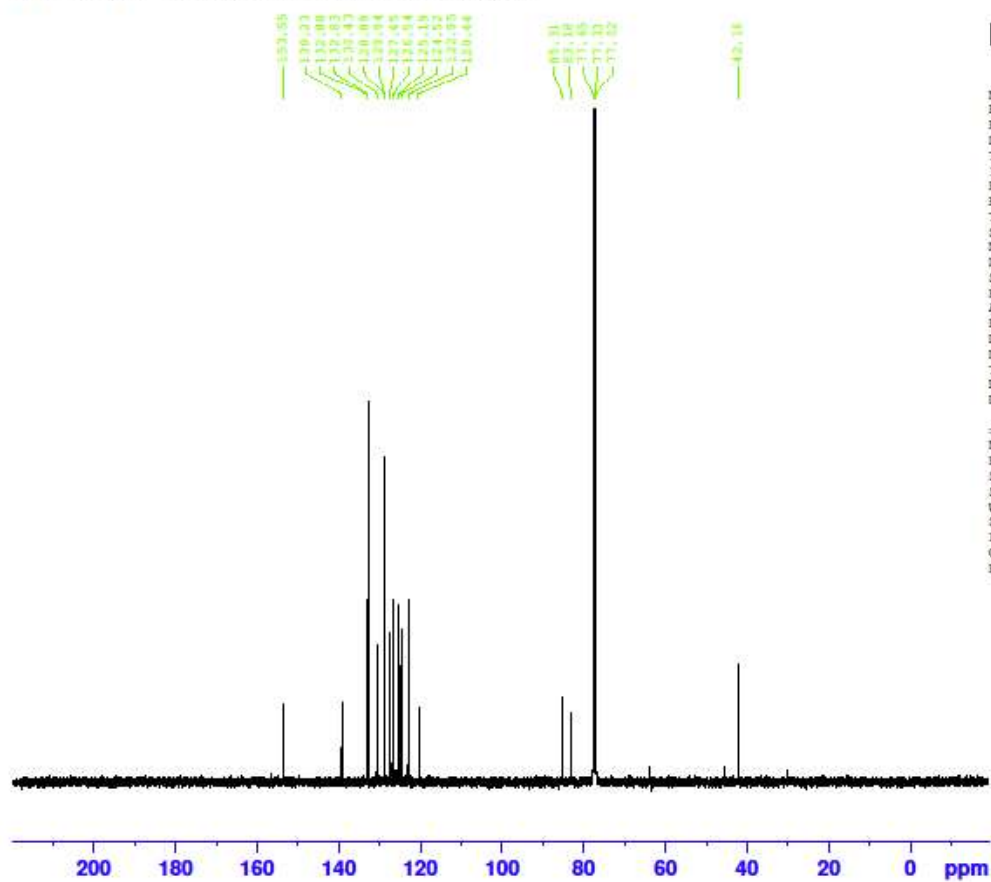


NAME JIP-02-106\_2  
EXPNO 20  
PROCNO 1  
Date\_ 20160104  
Time 18.32  
INSTRUM spect  
PROBHD 5 mm FAPBO BB/  
PULPROG zg30  
TD 65536  
SOLVENT cdc13  
NS 16  
DS 2  
SWH 10000.000 Hz  
FIDRES 0.152588 Hz  
AQ 3.2768500 sec  
RG 203  
DW 50.000 usec  
DE 6.50 usec  
TE 298.6 K  
D1 1.0000000 sec  
TD0 1

==== CHANNEL F1 =====  
SFO1 500.1630887 MHz  
NUC1 1H  
P1 11.45 usec  
SI 65536  
SF 500.1600091 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00

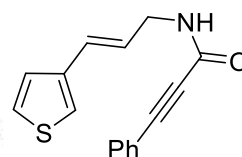


JTP-02-047, Thiophene-3-Phenyl Amide pure

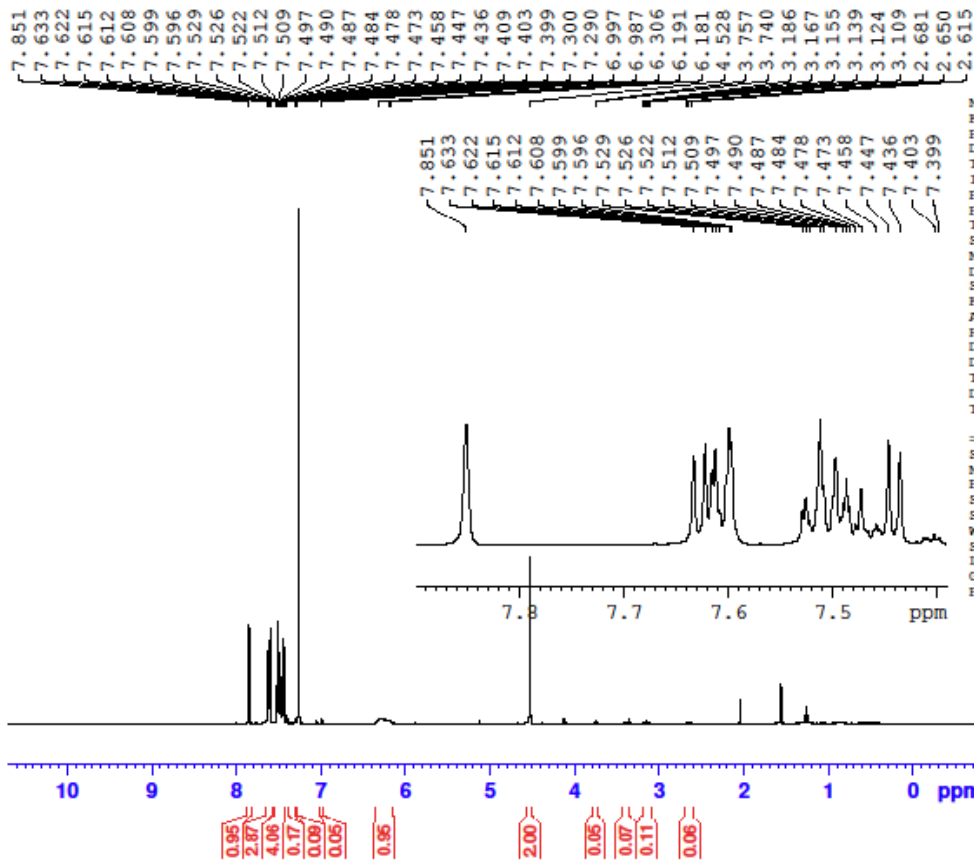


NAME JTP-02-047  
EXPNO 3  
PROCNO 1  
Date\_ 20150521  
Time 0.11  
INSTRUM spect  
PROBHD 5 mm FAPBO BB-  
PULPROG zgpg30  
TD 65536  
SOLVENT cdc13  
NS 1024  
DS 4  
SWH 24038.461 Hz  
FIDRES 0.366798 Hz  
AQ 1.3631988 sec  
RG 114  
DW 20.800 usec  
DE 6.50 usec  
TE 94.9 K  
D1 2.0000000 sec  
D11 0.0300000 sec

==== CHANNEL f1 =====  
NUC1 13C  
P1 10.00 usec  
SI 32768  
SF 100.6127401 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40

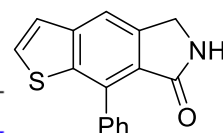


JTP-02-108, Product pure

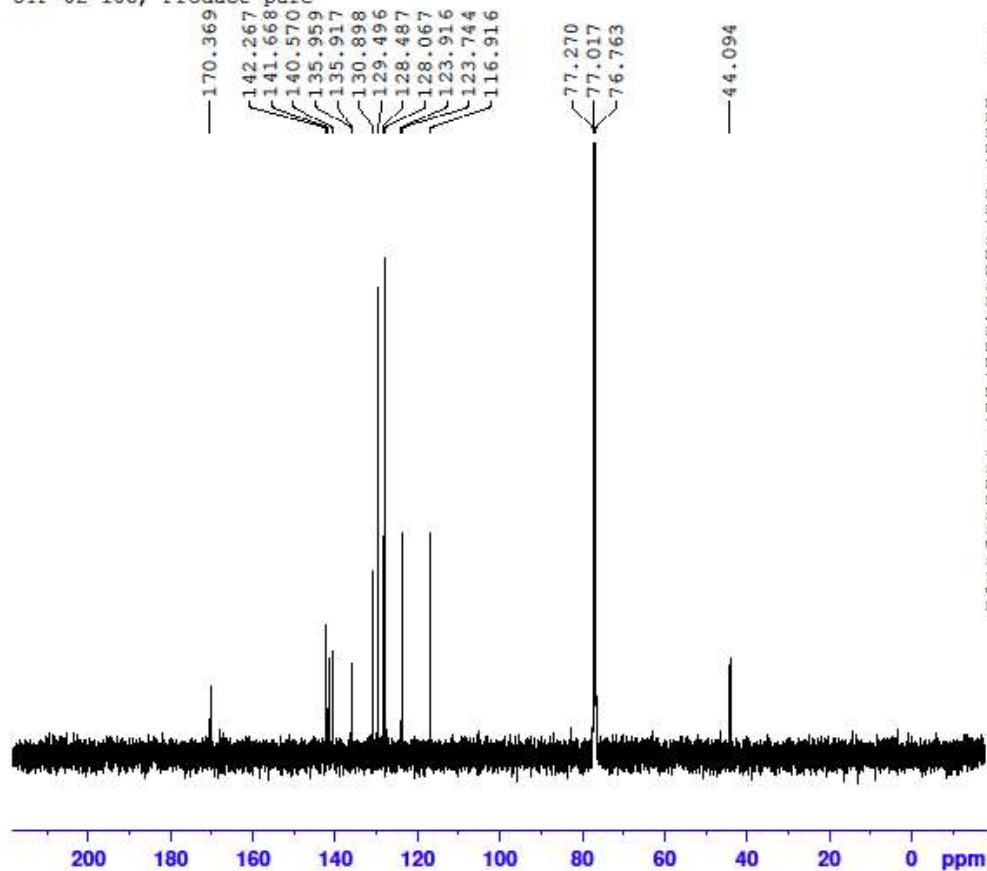


NAME JTP-02-108  
EXPNO 10  
PROCNO 1  
Date\_ 20150826  
Time 13.57  
INSTRUM spect  
PROBHD 5 mm PABBO BB/  
PULPROG zg30  
ID 65536  
SOLVENT CDCl3  
NS 16  
DS 2  
SWH 10000.000 Hz  
FIDRES 0.152588 Hz  
AQ 3.2768500 sec  
RG 203  
DW 50.000 usec  
DE 6.50 usec  
TE 297.3 K  
D1 1.00000000 sec  
TD0 1

==== CHANNEL f1 =====  
SFO1 500.1630887 MHz  
NUC1 1H  
P1 11.45 usec  
SI 65536  
SF 500.1600119 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00

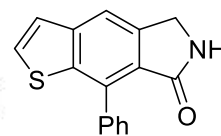


JIP-02-108, Product pure

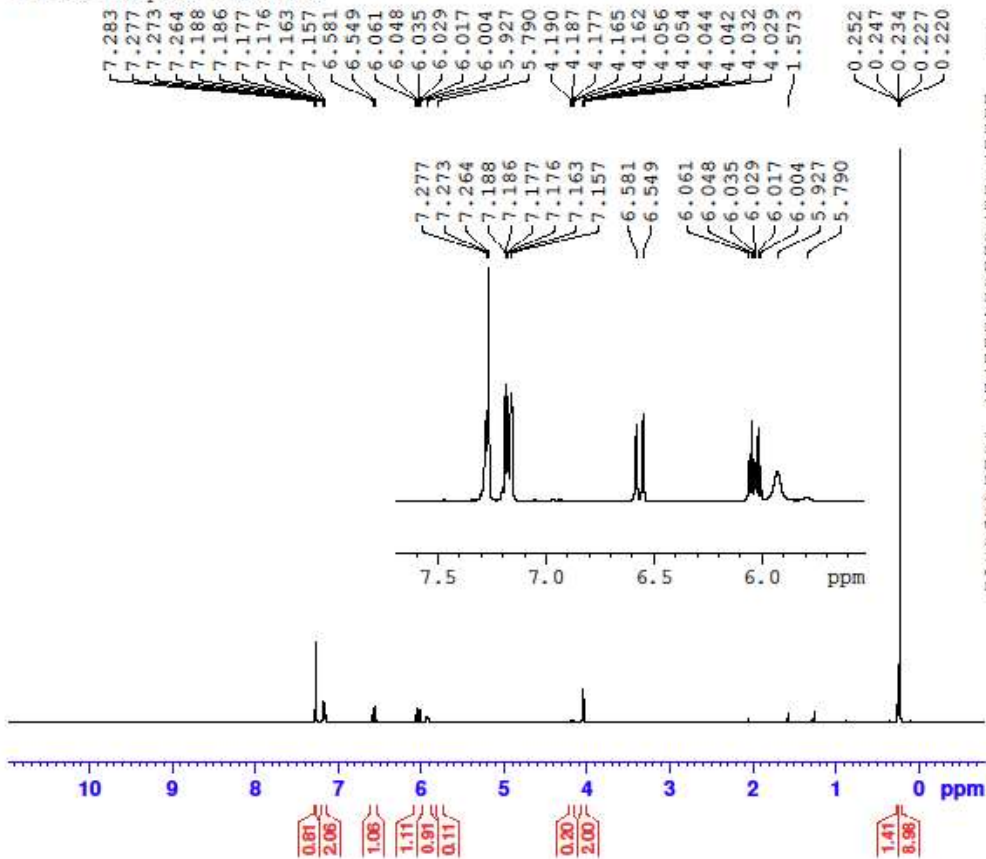


NAME JIP-02-108  
EXPNO 11  
PROCNO 1  
Date\_ 20150827  
Time 1.40  
INSTRUM spect  
PROBHD 5 mm PABBO BB/  
PULPROG zgig30  
TD 65536  
SOLVENT CDCl3  
NS 2500  
DS 4  
SWH 29761.904 Hz  
FIDRES 0.454131 Hz  
AQ 1.1010548 sec  
RG 203  
DW 16.800 usec  
DE 6.50 usec  
TE 297.7 K  
D1 2.00000000 sec  
D11 0.03000000 sec  
TD0 1

==== CHANNEL f1 =====  
SFO1 125.7779086 MHz  
NUC1 13C  
P1 10.50 usec  
SI 32768  
SF 125.7653320 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40



JIP-02-116 pure TMS amide

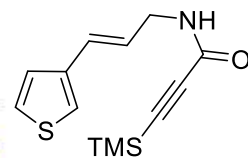


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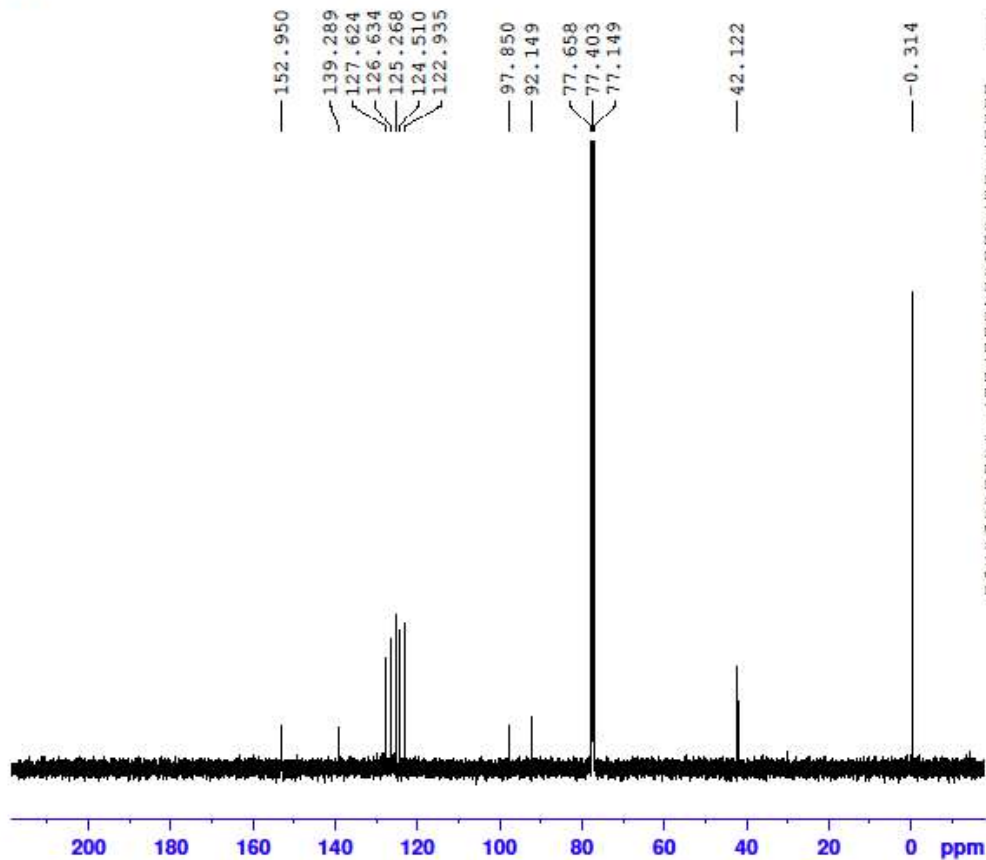
NAME      JIP-02-116
EXPNO    30
PROCNO   1
Date_    20150922
Time     15.01
INSTRUM  spect
PROBHD   5 mm PABBO BB/
PULPROG  zg30
TD       65536
SOLVENT  CDCl3
NS       16
DS       2
SWH      10000.000 Hz
FIDRES   0.152588 Hz
AQ       3.2768500 sec
RG       181
DW       50.000 usec
DE       6.50 usec
TE       297.3 K
D1       1.00000000 sec
TD0      1
  
```

```

===== CHANNEL f1 =====
SFO1    500.1630887 MHz
NUC1     1H
P1      11.45 usec
SI      65536
SF      500.1600106 MHz
WDW     EM
SSB     0
LB      0.30 Hz
GB      0
PC      1.00
  
```



JIP-02-075, Thiophene-3-Allyl TMS Amide

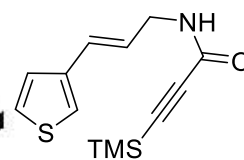


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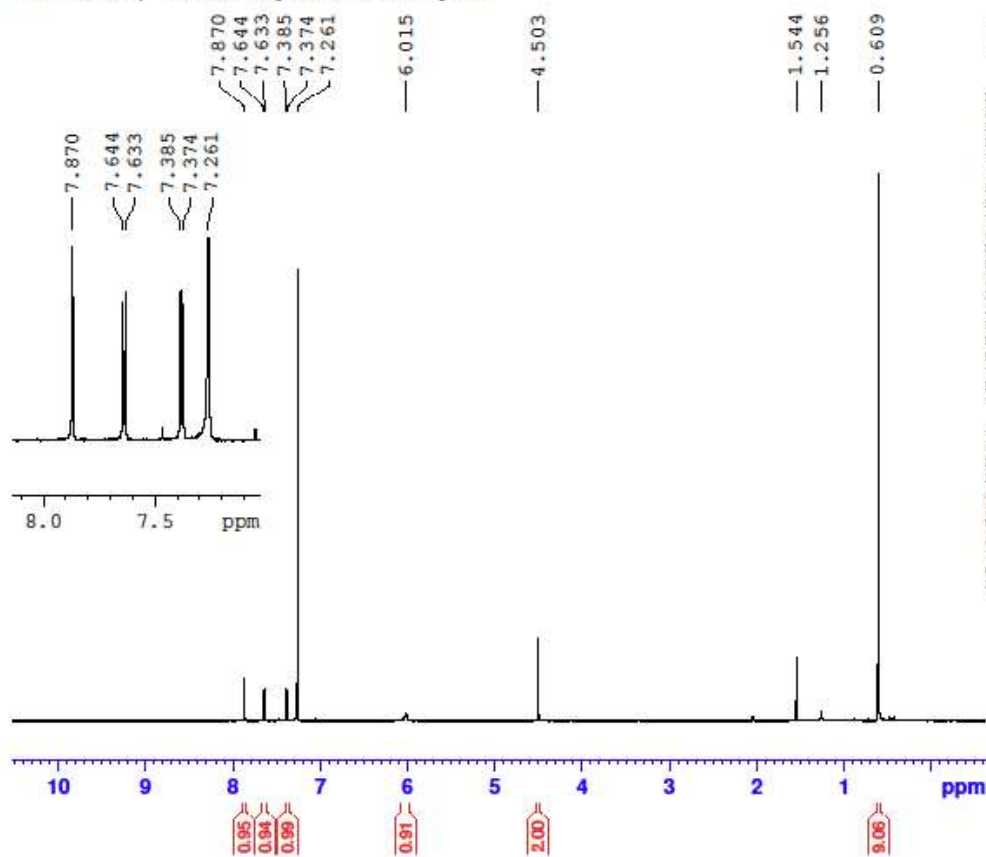
NAME      JIP-02-075
EXPNO     3
PROCNO    1
Date_     20150605
Time      21.58
INSTRUM   spect
PROBHD    5 mm F4BBO BB/
PULPROG   zgpg30
TD         65536
SOLVENT   CDCl3
NS         1024
DS         4
SWH        29761.904 Hz
FIDRES     0.454131 Hz
AQ         1.1010548 sec
RG         203
DW         16.800 usec
DE         6.50 usec
TE         298.2 K
D1         2.0000000 sec
D11        0.0300000 sec
TD0        1
    
```

```

===== CHANNEL f1 =====
SFO1      125.7779086 MHz
NUC1       13C
P1         10.50 usec
SI         32768
SF         125.7652837 MHz
WDW        EM
SSB        0
LB         1.00 Hz
GB         0
PC         1.40
    
```



JTP-02-120, Benzothiophene Lactam pure

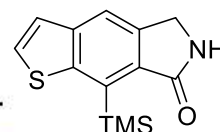


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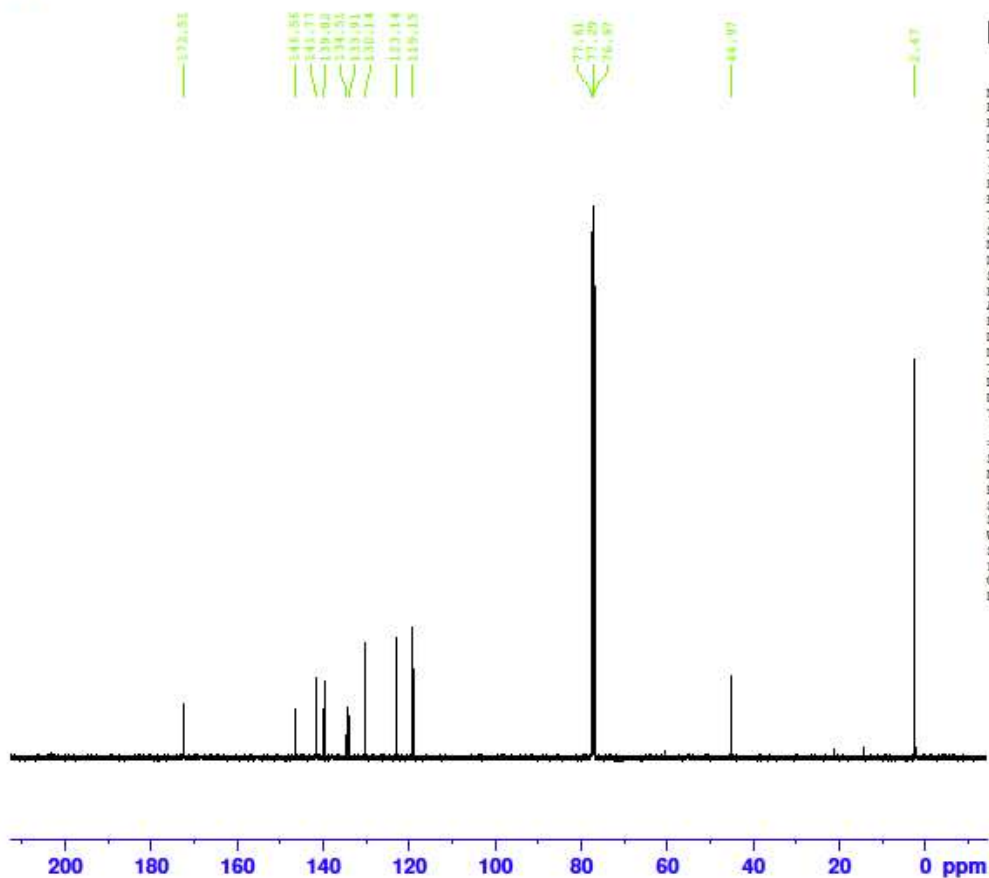
NAME      JTP-02-120
EXPNO    30
PROCNO   1
Date_    20151015
Time     14.27
INSTRUM  spect
PROBHD   5 mm PABBO BB/
PULPROG  zg30
TD       65536
SOLVENT  CDCl3
NS       16
DS       2
SWH      10000.000 Hz
FIDRES   0.152588 Hz
AQ       3.2768500 sec
RG       203
DN       50.000 usec
DE       6.50 usec
TE       297.6 K
D1       1.00000000 sec
TD0      1
  
```

```

===== CHANNEL f1 =====
SFO1    500.1630887 MHz
NUC1     1H
P1      11.45 usec
SI      65536
SF      500.1600119 MHz
WDW     EM
SSB     0
LB      0.30 Hz
GB      0
PC      1.00
  
```

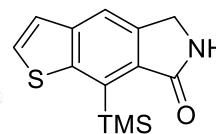


JTP-02-120



NAME JTP-02-120  
EXPNO 10  
PROCNO 1  
Date\_ 20160404  
Time 1.10  
INSTRUM spect  
PROBHD 5 mm FAPBO BB-  
PULPROG zgpg30  
TD 65536  
SOLVENT cdc13  
NS 1024  
DS 4  
SWH 24038.461 Hz  
FIDRES 0.366798 Hz  
AQ 1.3631988 sec  
RG 203  
DW 20.800 usec  
DE 6.50 usec  
TE 96.3 K  
D1 2.0000000 sec  
D11 0.0300000 sec  
TD0 1

==== CHANNEL F1 =====  
SF01 100.6228293 MHz  
NUC1 13C  
P1 10.00 usec  
SI 32768  
SF 100.6127440 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40





## BIBLIOGRAPHY

1. Bradley, D. A.; Godfrey, A. G.; Schmid, C. R., *Tet. Lett.* **1999**, *40*, 5155-5159.
2. Eun, J. J.; Liu, Y.; Lin, H.; Hu, M., *Drug Metabolism & Disposition*, **2005**, *33*, 785-794.
3. Schmid, C. R.; Sluka, J. P.; Duke, K. M., *Tet. Lett.* **1999**, *40*, 675-678.
4. Pinney, K. G.; Bounds, A. D.; Dingeman, K. M.; Mocharla, V. P.; Pettit, G. R.; Bai, R.; Hamel, E., *Bioorg. & Med. Chem. Lett.* **1999**, *9*, 1081-1086.
5. Croxtall, J. D.; Plosker, G. L., *Drugs*, **2009**, *69*, 339-359.
6. Nanteuil, G. D.; Lila-Ambroise, C.; Rupin, A.; Vallez, M. O.; Verbeuren, T. J., *Bioorg. & Med. Chem. Lett.* **2003**, *13*, 1705-1708.
7. Takeuchi, K.; Kohn, T. J.; Honigschmidt, N. A.; Rocco, V. P.; Spinazze, P. G.; Atkinson, S. T.; Hertel, L. W.; Nelson, D. L.; Wainscott, D. B.; Ahmad, L. J.; Shaw, J.; Threlkeld, P. G.; Wong, D. T., *Bioorg. & Med. Chem. Lett.* **2003**, *13*, 3939-3942.
8. Martínez-Esparza, J.; Oficialdegui, A. M.; Pérez-Silanes, S.; Heras, B.; Orús, L.; Palop, J.; Lasheras, B.; Roca, J.; Mourelle, M.; Bosch, A.; Del Castillo, J. C.; Tordera, R.; Del Río, J.; Monge, A., *J. Med. Chem.* **2001**, *44*, 418-428.
9. Davis, R. L.; Kahraman, M.; Prins, T. J.; Beaver, Y.; Cook, T. G.; Cramp, J.; Cayanan, C. S.; Gardiner, E. M. M.; McLaughlin, M. A.; Clark, A. F.; Hellberg, M. R.; Shiau, A. K.; Noble, S. A.; Borchardt, A. J., *Bioorg. & Med. Chem. Lett.* **2010**, *20*, 3361-3366.
10. Santillan, A. J.; McClure, K. J.; Allison, B. D.; Lord, B.; Boggs, J. D.; Morton, K. L.; Everson, A. M.; Nepomuceno, D.; Letavic, M. A.; Lee-Dutra, A.; Lovenberg, T. W.; Carruthers, N. I.; Grice, C. A., *Bioorg. & Med. Chem. Lett.* **2010**, *20*, 6226-6230.
11. Li, L.; Berthelette, C.; Chateauneuf, A.; Ouellet, M.; Sturino, C. F.; Wang, Z., *Bioorg. & Med. Chem. Lett.* **2010**, *20*, 7440-7443.
12. Hsiao, C. N.; Kolasa, T., *Tet. Lett.* **1992**, *33*, 2629-2632.

13. Lu, P.; Schrag, M. L.; Slaughter, D. E.; Raab, C. E.; Shou, M.; Rodrigues, A. D., *Drug Metabolism & Disposition*, **2005**, *31*, 1352-1360.
14. Bettinetti, L.; Schlotter, K.; Hubner, H.; Gmeiner, P., *J. Med. Chem.* **2002**, *45*, 4594-4597.
15. Mitsumori, S.; Tsuru, T.; Honma, T.; Hiramatsu, Y.; Okada, T.; Hashizume, H.; Kida, S.; Inagaki, M.; Arimura, A.; Yasui, K.; Asanuma, F.; Kishino, J.; Ohtani, M., *J. Med. Chem.* **2003**, *46*, 2446-2455.
16. Wang, S.; Beck, R.; Burd, A.; Blench, T.; Marlin, F.; Ayele, T.; Buxton, S.; Dagostin, C.; Malic, M.; Joshi, R.; Barry, J.; Sajad, M.; Cheung, C.; Shaikh, S.; Chahwala, S.; Chander, C.; Baumgartner, C.; Holthoff, H. P.; Murray, E.; Blackney, M.; Giddings, A., *J. Med. Chem.* **2010**, *53*, 1465-1472.
17. Koike, K.; Jia, Z.; Nikaido, T.; Liu, Y.; Zhao, Y.; Guo, D., *Org. Lett.* **1999**, *1*, 197-198.
18. Jeong, S. J.; Higuchi, R.; Miyamoto, T.; Ono, M.; Kuwano, M.; Mawatari, S. F., *J. Nat. Prod.* **2002**, *65*, 1344-1345.
19. Zlotos, D. P.; Jockers, R.; Cecon, E.; Rivara, S.; Witt-Enderby, P. A., *J. Med. Chem.* **2014**, *57*, 3161-3185.
20. Owen, R. T., *Drugs Today*, **2006**, *42*, 255-263.
21. Vachharajani, N. N.; Yeleswaram, K.; Boulton, D. W., *J. Pharm. Scien.* **2003**, *92*, 760-772.
22. Wallez, V.; Durieux-Poissonnier, S.; Chavatte, P.; Boutin, J. A.; Audinot, V.; Nicolas, J. P.; Bennejean, C.; Delagrange, P.; Renard, P.; Lesieur, D., *J. Med. Chem.* **2002**, *45*, 2788-2800.
23. Maynard, A.; Crosby, R. M.; Ellis, B.; Hamatake, R.; Hong, Z.; Johns, B. A.; Kahler, K. M.; Koble, C.; Leivers, A.; Leivers, M. R.; Mathis, A.; Peat, A. J.; Pouliot, J. J.; Roberts, C. D.; Samano, V.; Schmidt, R. M.; Smith, G. K.; Spaltenstein, A.; Stewart, E. L.; Thommes, P.; Turner, E. M.; Voitenleitner, C.; Walker, J. T.; Waitt, G.; Weatherhead, J.; Weaver, K.; Williams, S.; Wright, L.; Xiong, Z. Z.; Haigh, D.; Shotwell, J. B., *J. Med. Chem.* **2014**, *57*, 1902-1913.
24. He, Y.; Liu, S.; Menon, A.; Stanford, S.; Oppong, E.; Gunawan, A. M.; Wu, L.; Wu, D. J.; Barrios, A. M.; Bottine, N.; Cato, A. C. B.; Zhang, Z. Y., *J. Med. Chem.* **2013**, *55*, 4990-5008.
25. Argade, M. D.; Mehta, A. Y.; Sarkar, A.; Desai, U. R., *J. Med. Chem.* **2014**, *57*, 3559-3569.
26. Voitovich, Y. V.; Shegravina, E. S.; Sitnikov, N. S.; Faerman, V. I.; Fokin, V. V.; Schmalz, H. G.; Combes, S.; Allegro, D.; Barbier, P.; Beletskaya, I. P.; Svirshchevskaya, E. V.; Fedorov, A. Y., *J. Med. Chem.* **2015**, *58*, 692-704.

27. Banskota, A. H.; Tezuka, Y.; Midorikawa, K.; Matsushige, K.; Kadota, S., *J. Nat. Prod.* **2000**, *63*, 1277-1279.
28. Baumgartner, L.; Sosa, S.; Atanasov, A. G.; Bodensieck, A.; Fakhrudin, N.; Bauer, J.; Del Favero, G.; Ponti, C.; Heiss, E. H.; Schwaiger, S.; Ladurner, A.; Widowitz, U.; Loggia, R. D.; Rollinger, J. M.; Werz, O.; Bauer, R.; Dirsch, V. M.; Tubaro, A.; Stuppner, H., *J. Nat. Prod.* **2011**, *74*, 1779-1786.
29. Huang, H. Y.; Ishikawa, T.; Peng, C. F.; Tsai, I. L.; Chen, I. S., *J. Nat. Prod.* **2008**, *71*, 1146-1151.
30. Dat, N. T.; Jin, X.; Lee, K.; Hong, Y. S.; Kim, Y. H.; Lee, J. J., *J. Nat. Prod.* **2009**, *72*, 39-43.
31. Bryan, C. S.; Braunger, J. A.; Lautens, M., *Angew. Chem.* **2009**, *121*, 7198-7202.
32. Yin, B.; Zhang, X.; Zhang, X.; Peng, H.; Zhou, W.; Liu, B.; Jiang, H., *Chem. Commun.* **2015**, *51*, 6126-6129.
33. Gabriele, B.; Mancuso, R.; Lupinacci, E.; Veltri, L.; Salerno, G.; Carfagna C., *J. Org. Chem.* **2011**, *76*, 8277-8286.
34. Reddy, C. R.; Dilipkumar, U.; Reddy, M. D., *Org. Lett.* **2014**, *16*, 3792-3795.
35. Nakamura, I.; Sato, T.; Yamamoto, Y., *Angew. Chem. Int. Ed.* **2006**, *45*, 4473-4475.
36. Anxionnat, B.; Pardo, D. G.; Ricci, G.; Rossen, K.; Cossy, J., *Org. Lett.* **2013**, *15*, 3876-3879.
37. Sun, L. L.; Deng, C. L.; Tang, R. Y.; Zhang, X. G., *J. Org. Chem.* **2011**, *76*, 7546-7550.
38. Acharya, A.; Kumar, S. V.; Saraiyah, B.; Ila, H., *J. Org. Chem.* **2015**, *80*, 2884-2892.
39. Syu, S.; Lee, Y. T.; Jang, Y. J.; Lin, W., *Org. Lett.* **2011**, *13*, 2970-2973.
40. Yu, H.; Zhang, M.; Li, Y., *J. Org. Chem.* **2013**, *78*, 8898-8903.
41. Hari, D. P.; Hering, T.; Konig, B., *Org. Lett.* **2012**, *14*, 5334-5337.
42. Cho, C. H.; Neuenswander, B.; Lushington, G. H.; Larock, R. C., *J. Comb. Chem.* **2009**, *11*, 900-906.
43. Kim, S.; Yang, J.; DiNinno, F., *Tet. Lett.* **1999**, *40*, 2909-2912.
44. Larock, R. C.; Stinn, D. E., *Tet. Lett.* **1988**, *29*, 4687-4690.
45. Kozikowski, A. P.; Ma, D.; Du, L.; Lewin, N. E.; Blumberg, P. M., *J. Am. Chem. Soc.* **1995**, *117*, 6666-6672.

46. Kundu, N. G.; Pal, M.; Mahanty, J. S.; De, M., *J. Chem. Soc., Perkin Trans. 1*, **1997**, 2815-2820.
47. Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C., *J. Org. Chem.* **1995**, *60*, 3270-3271
48. Hu, Y.; Zhang, Y.; Yang, Z.; Fathi, R., *J. Org. Chem.* **2002**, *67*, 2365-2368.
49. Sharma, U.; Naveen, T.; Maji, A.; Manna, S.; Maiti, D., *Angew. Chem. Int. Ed.* **2013**, *52*, 12669-12673.
50. Gabriele, B.; Mancuso, R.; Salerno, G., *J. Org. Chem.* **2008**, *73*, 7336-7341.
51. Kim, I.; Kim, K.; Choi, J., *J. Org. Chem.* **2009**, *74*, 8492-8495.
52. Nakamura, M.; Ilies, L.; Otsubo, S.; Nakamura, E., *Org. Lett.* **2006**, *8*, 2803-2805.
53. Bates, C. G.; Saejueng, P.; Murphy, J. M.; Venkataraman, D., *Org. Lett.* **2002**, *4*, 4727-4729.
54. Kocsis, L. S.; Benedetti, E.; Brummond, K. M., *Org. Lett.* **2012**, *14*, 4430-4433.
55. Kocsis, L. S.; K. M., *Org. Lett.* **2014**, *16*, 4158-4161
56. Lapointe, D.; Makiewicz, T.; Whipp, C. J.; Toderian, A.; Fagnou, K., *J. Org. Chem.* **2011**, *76*, 749-759.
57. Roethle, P. A.; Chen, I. T.; Trauner, D., *J. Am. Chem. Soc.* **2007**, *129*, 8960-8961.
58. Werkhoven, T. M.; van Nispen, R.; Lugtenburg, J., *Eur. J. Org. Chem.* **1999**, 2909-2914.
59. Perez, M.; Perez, D. I.; Martinez, A.; Castro, A.; Gomez, G.; Fall, Y., *Chem. Commun.* **2009**, 3252-3254.
60. He, Y.; Chen, Y.; Wu, H.; Lovely, C. J., *Org. Lett.* **2003**, *5*, 3623-3626.
61. Medvedeva, A. S.; Andreev, M. V.; Safronova, L.P., *Russ. J. Org. Chem.* **2010**, *46*, 1466-1470.
62. Kotoku, N.; Fujioka, S.; Nakata, C.; Yamada, M.; Sumii, Y.; Kawachi, T.; Arai, M.; Kobayashi, M., *Tetrahedron* **2011**, *67*, 6673-6678.
63. Morrill, C.; Beutner, G. L.; Grubbs, R. H., *J. Org. Chem.* **2006**, *71*, 7813-7825.
64. Cristau, H. J.; Taillefer, M., *Tetrahedron* **1998**, *54*, 1507-1522.
65. Charette, A. B.; Molinaro, C.; Brochu, C., *J. Am. Chem. Soc.* **2001**, *123*, 12168-12175.
66. Zhang, X.; Zhang, W. Z.; Ren, X.; Zhang, L. L.; Lu, X. B., *Org. Lett.* **2011**, *13*, 2402-2405.