이학석사학위논문

Synthetic Studies toward (+)-Fendleridine Using a Metal-Catalyzed Cascade Cyclization Approach

연쇄 고리화 촉매반응 접근을 이용한 (+)-펜들러리딘 합성 연구

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지도교수 이철범

이 논문을 이학석사학위논문으로 제출함
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ABSTRACT

The (+)-fendleridine alkaloid natural product is a botanic natural product and has attracted much attentions from the synthetic community due to its characteristic core structure. Several synthetic efforts have been made toward fendleridine and its congener 1-acetyl-asipdoalbidine. However, these synthesis studies have not established a route either for an enantioselective synthesis or formation of the key N,O-ketal core structure. Taking these facts into account, our synthetic effort focuses on the construction of 5-6 fused bicycle by metal-catalyzed cascade cyclization which offers a reliable route to construct the key N,O-ketal moiety. Combined with an enantioselective oxindole synthesis, the synthetic approach we have developed here have provided a reliable and enantioselective route to (+)-fendleridine.

Keywords: (+)-Fendleridine, Total synthesis, Enantioselective acyl-migration, Metal catalysis, Cascade cyclization, Oxidative oxy-carbonylation, Relay-acylation

Student ID: 2012-20273

INTRODUCTION

(+)-Fendleridine, the botanic natural product isolated from the Venezuelan tree *Aspidosperma fendleri* WOODSON by Burnell in 1964, [1] is a hexaxyclic indole alkaloid which has an additional tetrahydrofuran ring with respect to the usual pentacyclic aspidosperma skeleton. Although no particular biological activity of the fendleridine has been known to date, several structural features make it an attractive objective of synthesis studies.[2] Structurally, fendleridine possesses a hexacyclic skeleton without any substituent outside fused-ring systems which is the simplest core itself of the related natural products. It has four continuous stereogenic centers, including two all-carbon quaternary centers and the N,O-mixed ketal, all lying on the central cyclohexane ring. In addition, fendleridine and its congener (+)-1-acetyl-aspidoalbidine[3] are regarded as parent members of the related natural product as exemplified by the ancient Azteks insecticide haplophytine and its right-half aspidophytine (Figure 1).

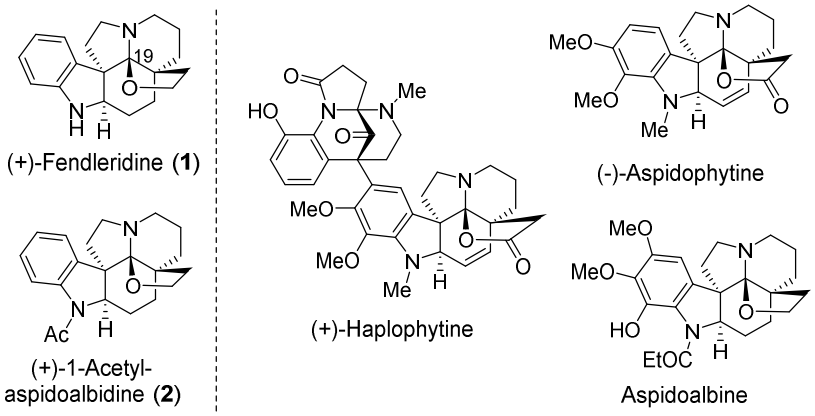
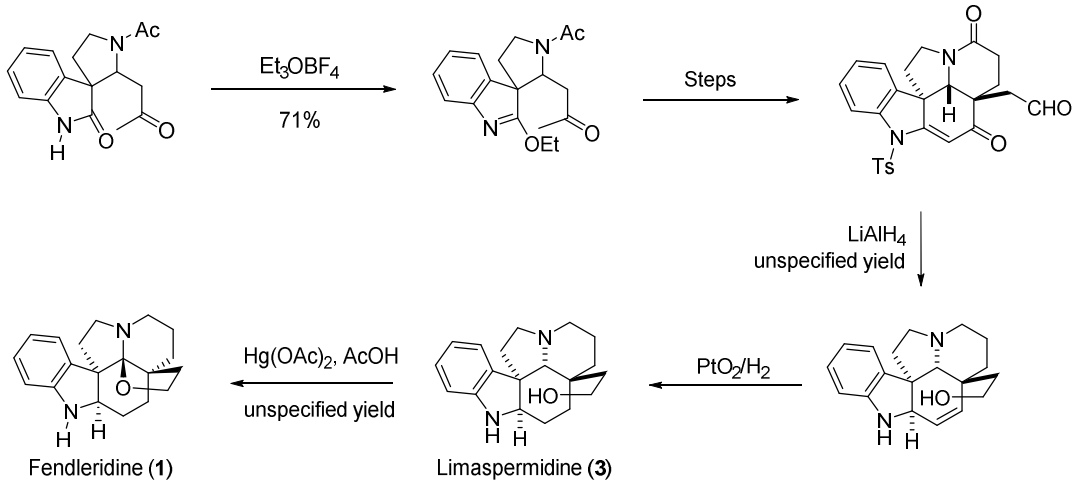


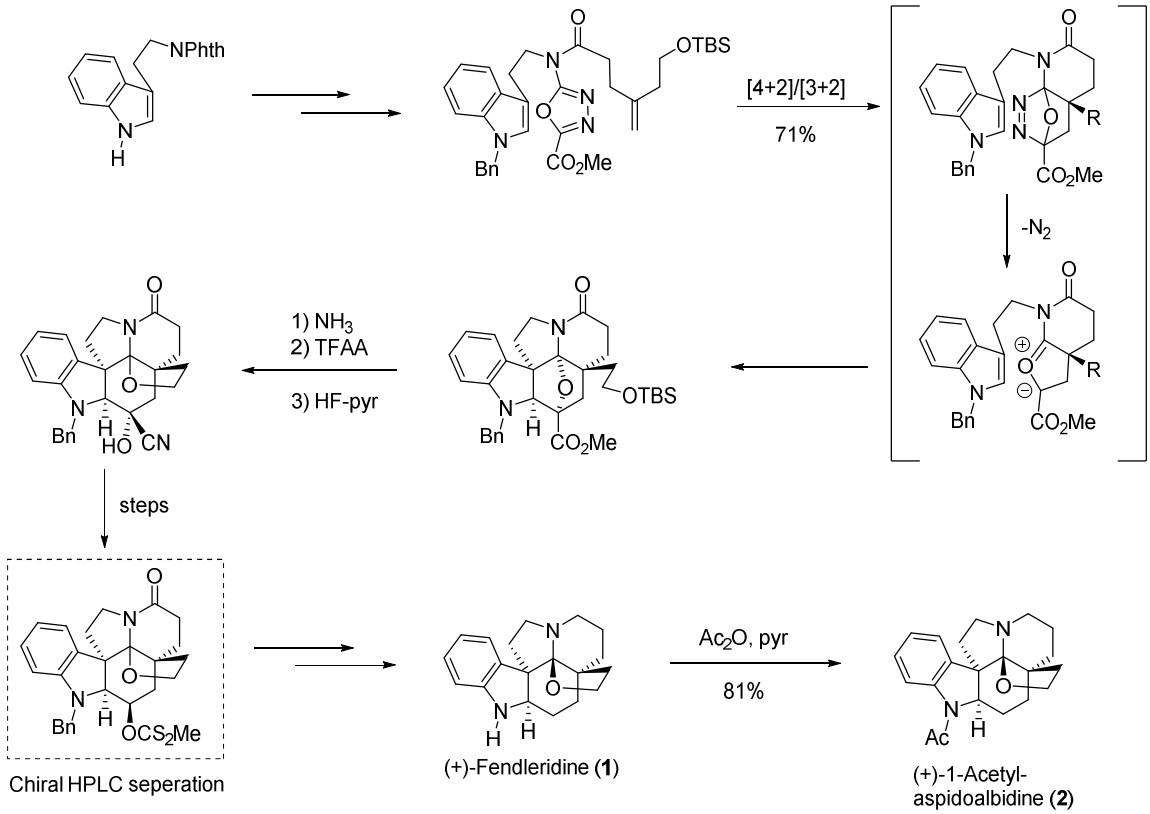
Figure 1. Fendleridine and related natural products

The first total synthesis of **1** was accomplished by Ban et al. in 1975.[2a] Ban and coworkers adopted amide activation strategies to make two 6-membered rings by using a Meerwein's salt. Noteworthy is the last stage oxidation of C19 C-H bond of limaspermidine **3** with stoichiometric mercury(II) acetate to form the N,O-ketal, however, the yield of this key step was unspecified (Scheme 1).



Scheme 1. Ban's synthesis of **1**

Recently, Boger and coworkers have described a landmark synthesis of fendleridine employing Boger's signature [4+2]/[3+2] tandem cycloaddition reaction.[2b] In this work, the N,O-ketal is formed in the middle, rather than the late stage of the synthesis. The absolute configuration of fendleridine was determined also in Boger's work by separating each enantiomer through semi-preparative ChiarlCel OD HPLC (Scheme 2).



Scheme 2. Boger's synthesis of **1** and **2**

Since Boger's elegant synthesis, the synthetic efforts toward fendleridine and 1-acetyl-aspidoalbidine have been active. However, there is no total or fomal synthesis of *fendleridine* reported after Boger's work in stark contrast to three formal synthesis of *1-acetyl-aspidoalbidine* that have been reported. Although these three syntheses subsequent to Boger's total synthesis of fendleridine and Overman's formal synthesis of 1-acetyl-aspidoalbidine all prepared limaspermidine, Ban's precursor of the fendleridine, all of them finished their synthesis at the stage of 1-acetyl-aspidoalbidine, not fendleridine (Figure 2). Moreover, Ban's seminal work did not specify the yield of the final step, and

Banwell commented that Ban's oxidative ketalization was not reproducible by their hands, suggesting that Ban's route might not be reliable.[2f]

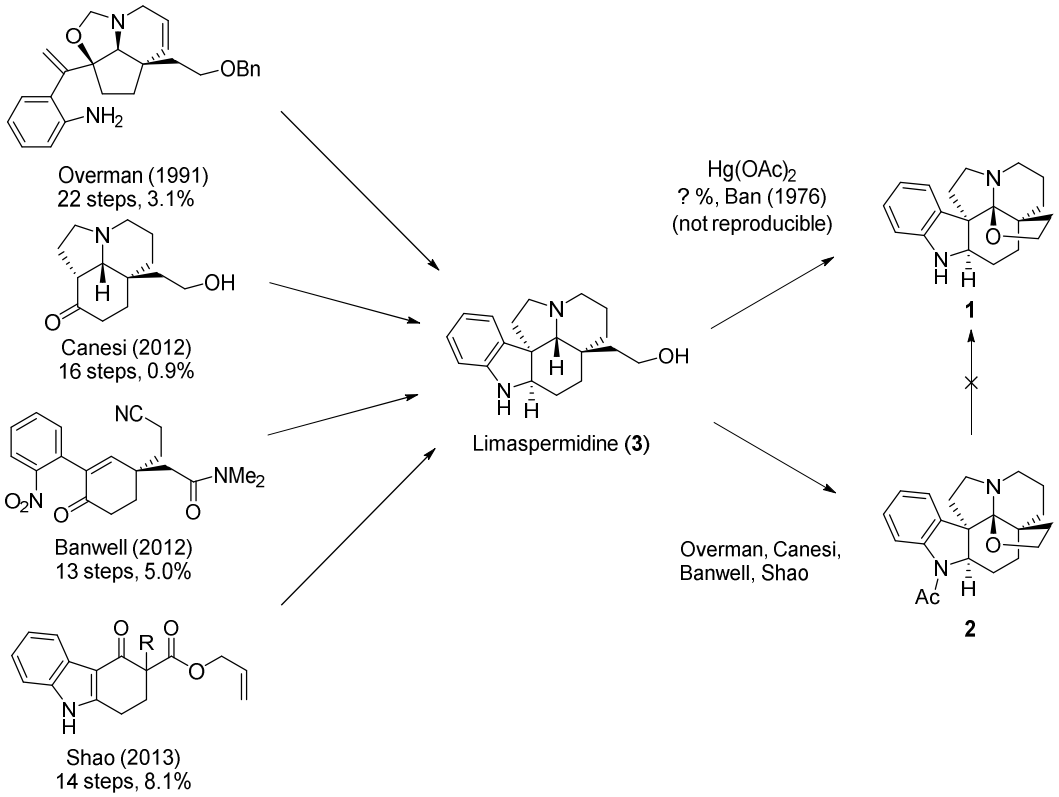


Figure 2. Total synthesis of limaspermidine and formal synthesis of **2**

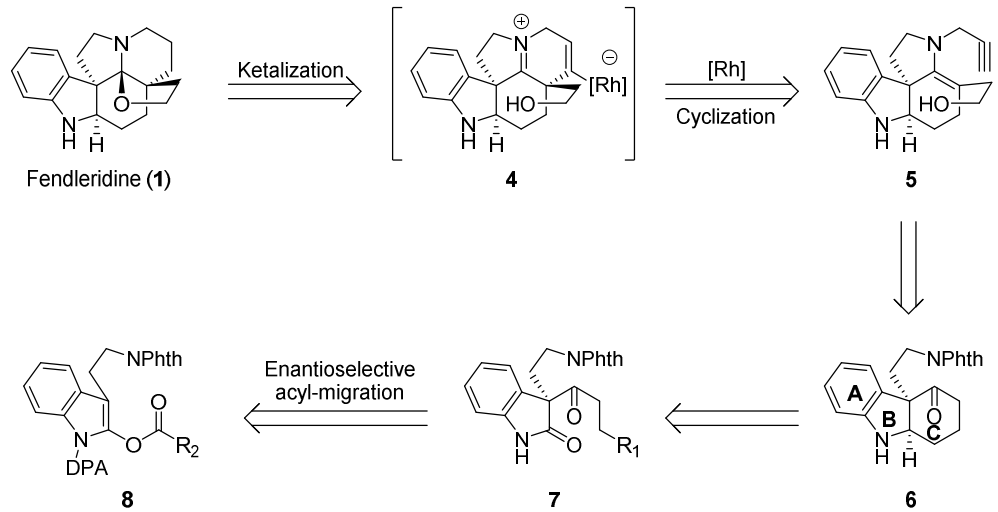
Most recently, Shao and coworkers reported the first enantioselective synthesis of (-)-1-acetyl-aspidoalbidine by using enantioselective decarboxylative allylation as a key step. However, the Shao synthesis also utilized Ban's method to make the N,O-ketal, and only reached 1-acetyl congener, not the fendleridine. In addition, Ban mentioned that deacetylation from 1-acetyl-aspidoalbidine was not successful, suggesting a reliable ketalization step to be more desired to access fendleridine. Thus, we embarked on our synthetic efforts toward an enantioselective synthesis of fendleridine using a trasition

metal-catalyzed cascade cyclization approach that aimed at the reliable construction of the C19 N,O-ketal and completion of an enantioselective synthesis.

RESULT AND DISCCUSION

1. Retrosynthetic Analysis

Our synthetic plan was based on the metal-catalalyzed cascade cyclization concept which would enable the formation of key tetrahydrofuran ring simply by quenching iminium intermediate **4.** It was envisioned that the intermediate would be generated by cycloisomerization of enyne **5** employing rhodium-catalyzed cyclization of propargyl enamines developed in our laboratory (Scheme 3).[4]



Scheme 3. Retrosynthesis of **1**

For the preparation of **5**, alkylation of ketone **6** followed by condensation to enamine **5** was deemed to the most straightforward and plausible. The tricyclic indolinocyclohaxane **6** could be prepared from the oxindole **7** by an intramolecular cyclization. Taking advantage of known enantioselective O- to C-acyl-migration chemistry, the first

stereogenic center at indole C3, stereo-controlling center, was expected to be installed starting from O-acyl oxindole **8**.

2. Preparation of the Oxindole

2.1 Oxidation of indoles

2.1.1 DMDO Oxidation of N-Boc indole

For the construction of indoline C3 quaternary stereocenter, there are two synthetically useful methods enabling enantioselective acyl-migration of oxindoles reported by Fu[5a] and Vedejs[5b] respectively (Figure 3). Although Fu's planar chiral DMAP can only transfer a one-carbon unit, trichloro-*tert*-butyloxycarbonyl group, it has been proven to be effective even for complex molecules as demonstrated in the Overman's total synthesis of gliocladine C.[6]

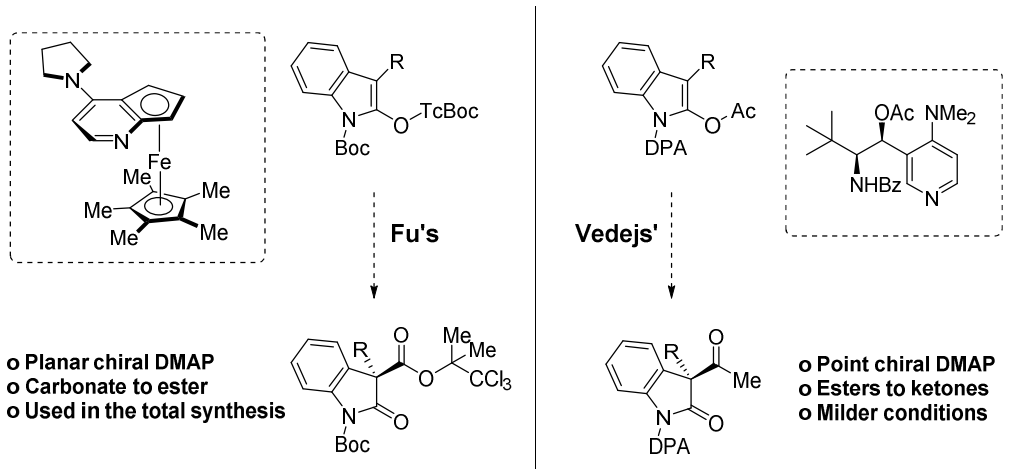
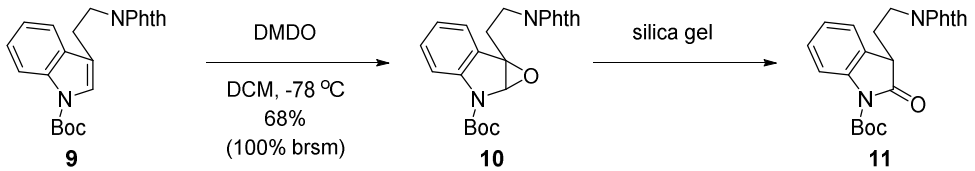


Figure 3. Fu's and Vedejs' acyl-migrations

Thus, we commenced our synthesis with preparation of oxindole **11**, precursor of the *O*-acyl oxindole. Starting from known compound **9**, trivial DMDO oxidation conditions furnished desired product **11** cleanly. A possible over-oxidation of the enolizable lactam was not detected. In this sequence, oxirane intermediate **10** was observed after a mild work-up process. However, column chromatographic purification of **10** on silica gel afforded rearranged product **11** (Scheme 4).



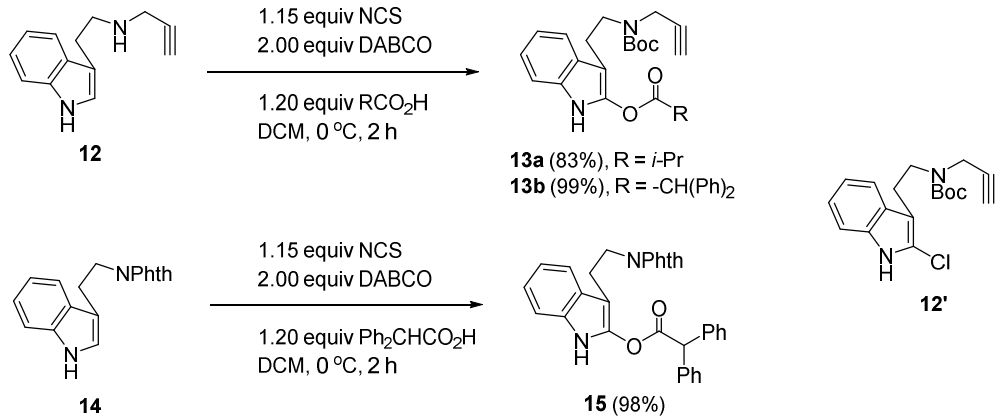
Scheme 4. DMDO oxidation of N-Boc indole **9**

The preliminary result was promising but with a few disadvantages. Firstly, the concentration of DMDO was difficult to control varying from 0.09 M to 0.11 M. Thus, the equivalency of the oxidant is not accurate for each operation. Secondly, preparation of DMDO for large scale reactions is difficult due to its low molar concentration and stability. Lastly and most importantly, simple adjustment of oxidation states without change in the molecular skeleton is not encouraged in modern organic synthesis, thus leaving a question if there is a more step-economical and redox-economical route.

2.1.2 Oxidative oxy-carbonylation

Along with the DMDO oxidation, we simultaneously tested oxidative oxy-carbonylation reactions. A few NCS-mediated oxidative C2 funtionalizations of indoles have been reported, [7] however, the scope of nucleophiles are not broad. Only a few examples have

been reported using allylic alcohols, imidazoles, phenols and thiophenols as nucleophiles. We surmised that if NCS-mediated oxy-carbonylation would be possible, we might be able to install the acyl-group concomitantly with the oxidation of indoles. Thus, the feasibility of the transformation was tested. Interestingly, a common amine base used in known methods, such as 1,4-dimethylpiperazine, led to only 2-chloroindole **12'** in the presence of acid. Instead, a bicyclic analogue DABCO smoothly resulted in 2-carboxylated indoles **13a, 13b** and **15** in excellent yields (Scheme 5).



Scheme 5. Oxidative Oxy-carbonylation of indoles

2.2 Anionic Relay Acylation

Next, we turned our intention to protection of the indole nitrogen. According to Vedejs' work, the most proper group is a diphenylacetyl group in terms of both reactivity and enantioselectivity.[5b] However, deprotonation of N-H proton with LiHMDS and addition of diphenylacetyl chloride resulted in the formation of mixture of two isomers which were identified as desired product **16** and acyl-switched compound **17** respectively. This

result indicated facile acyl migration happened from the O-acyl oxindole to the N-acyl oxindole upon treatment of a strong base (Figure 4).

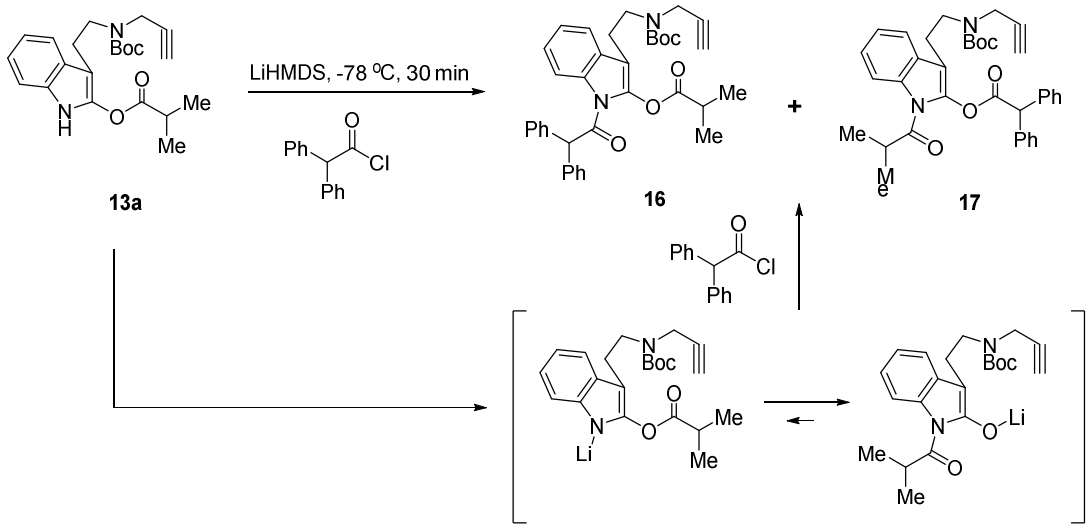


Figure 4. Scrambling of acyl groups

To circumvent the acyl scrambling, a reversed order of acylation was attempted. The oxy-carbonylation with diphenylacetic acid and subsequent anionic relay-acylation with isobutyric chloride gave rise to desired product **16**. In this process, deprotonation of acidic C-H bond of the alkynyl group was detrimental. With brief screening of bases, the use of soft KH base turned out to be the best for N-propargylic systems (Figure 5).

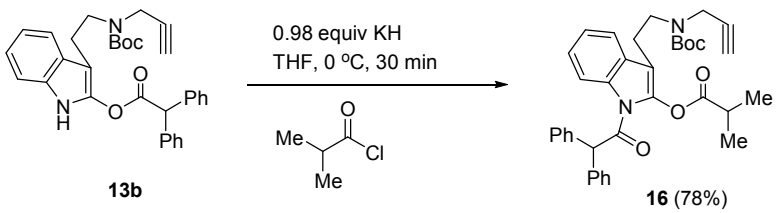
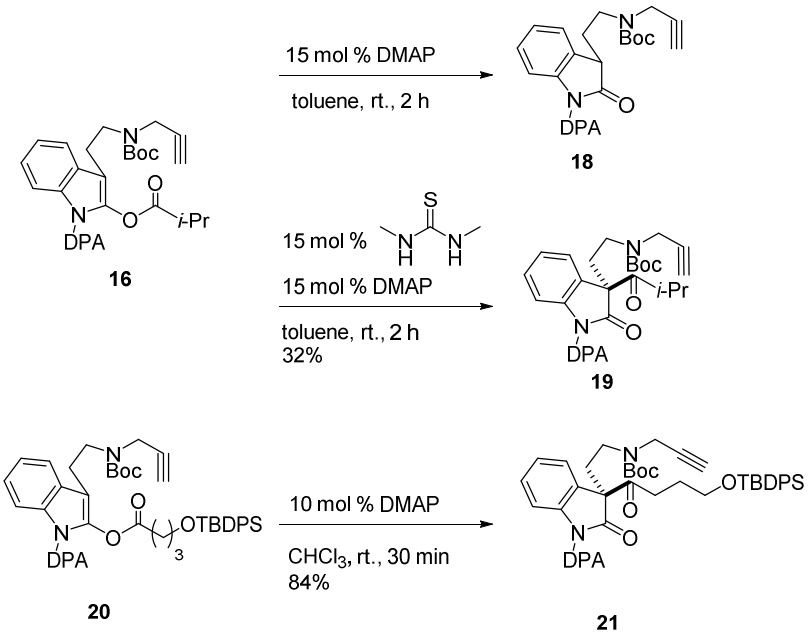


Figure 5. Optimized conditions for the anionic-relay acylation.

2.3 Nucleophilic Acyl-Migration

As a key enantio-determining step, Vedejs' acyl-migration chemistry serves as a decent starting point, however, only an acetyl group was reported to migrate. Migration of the acyl group bearing a secondary alkyl chain will be advantageous since carbon atoms constituting central cyclohexane ring (C ring) and tetrahydrofuran ring (F ring) can be introduced in early stage of the synthesis. As a model system, isobutyryl substrate **16** was subjected to DMAP-catalyzed migration conditions, however, the only observable product was deacylated oxindole **18** mostly with recovered starting material. The deacylation presumably occurred because of the slow reaction rate of nucleophilic acyl substitution.



Scheme 6. DMAP-catalyzed acyl migrations

Addition of a thiourea improved the reaction in terms of reactivity[8] giving desired product up to 32% yield, but attempts to optimize the process have met only limited success. In contrast, the acyl group with a primary alkyl chain migrated well in excellent yield while producing only a small amount of deacylated product (Scheme 6).

3. Attempted C Ring Formation

3.1 Michael Addition-Intramolecular Wittig Reactions

Failure to form secondary alkyl ketones via acyl migration required a two extra carbon unit for the formation of the C ring. In this regard, a top-to-bottom approach, which can utilize a plethora of enolate chemistry, is the most intuitive way. Thus, we designed tandem Michael addition-Wittig reactions by using triphenylvinylphosphonium bromide (Schweiser's reagent) as the two-carbon unit (Figure 6).[9]

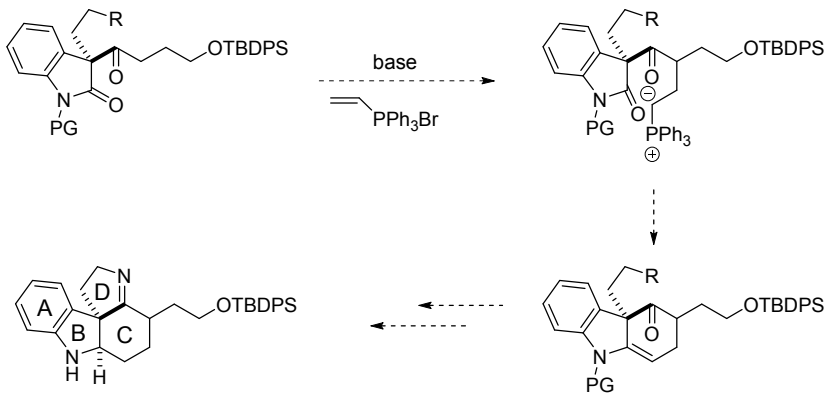
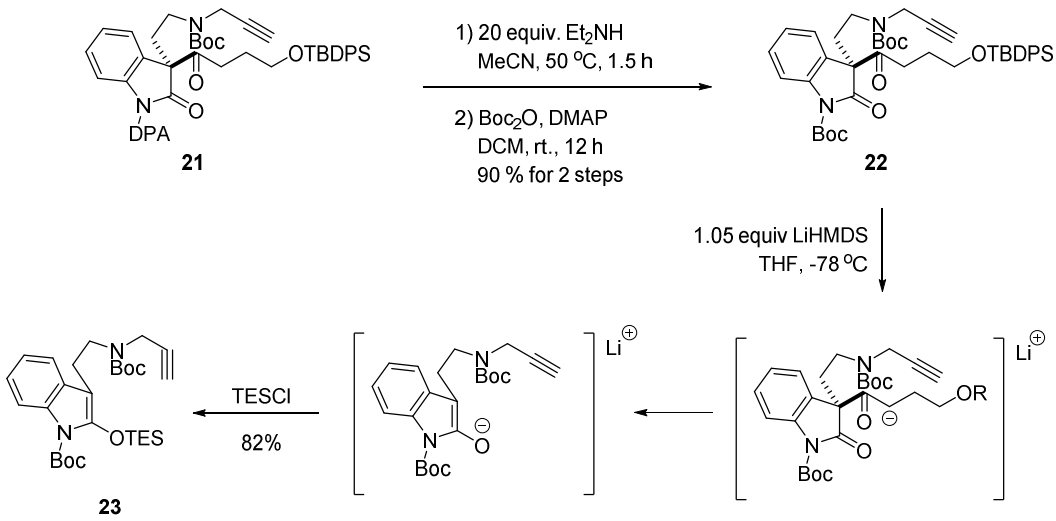


Figure 6. Tandem Michael addition/intramolecular Wittig approach

Initial studies with **21** resulted in deprotonation at the diphenylacetyl group in preference to the ketone, leading to complex mixtures. Thus, replacement of the diphenylacetyl group with a Boc or benzyl group was necessary. However, the generation of enolates from N-Boc substrate **22** led only to decomposition of the molecule giving deacylated products. The possible explanation for these observations is that high stability of the resulting oxindole anion, whose conjugate acid has pK_a value around 15,[10] drove the deacylation (Scheme 7). Even at a cryogenic temperature as low as -78 ^{o}C, the deacylation product was observed right after addition of the base. This anionic deacylation pathway was confirmed by a few quenching experiment. For example, an addition of chlorotriethylsilane afforded silylated oxindole **23**.[11]



Scheme 7. Deacylation of the 3-acyloxindole

3.2 Amide Activation-Cross Coupling

3.2.1 Ketone Functionalization

After failure of the top-to-bottom cyclization approach, we envisioned that cyclization in a reverse direction could be an alternative way. Activation of a secondary amide by triflic anhydride is known to give an imidoyl triflate which participate well in a variety of nucleophilic substitution and palladium-catalyzed cross coupling reactions.[12] Even though there are only few reports using imidoyl triflates in cross-coupling chemistry, analogous imidoyl chlorides have been used in cross-coupling reactions frequently.[13] It was anticipated that subsequent to the vinyl cross-coupling reaction, cyclization and condensation would give the desired tetracyclic intermediate (Figure 7).

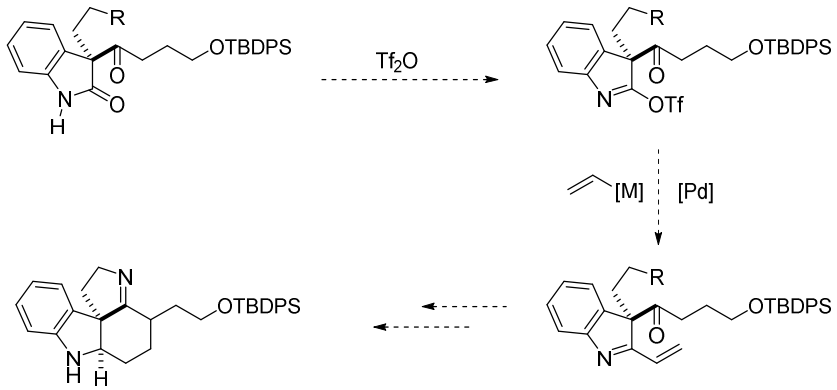
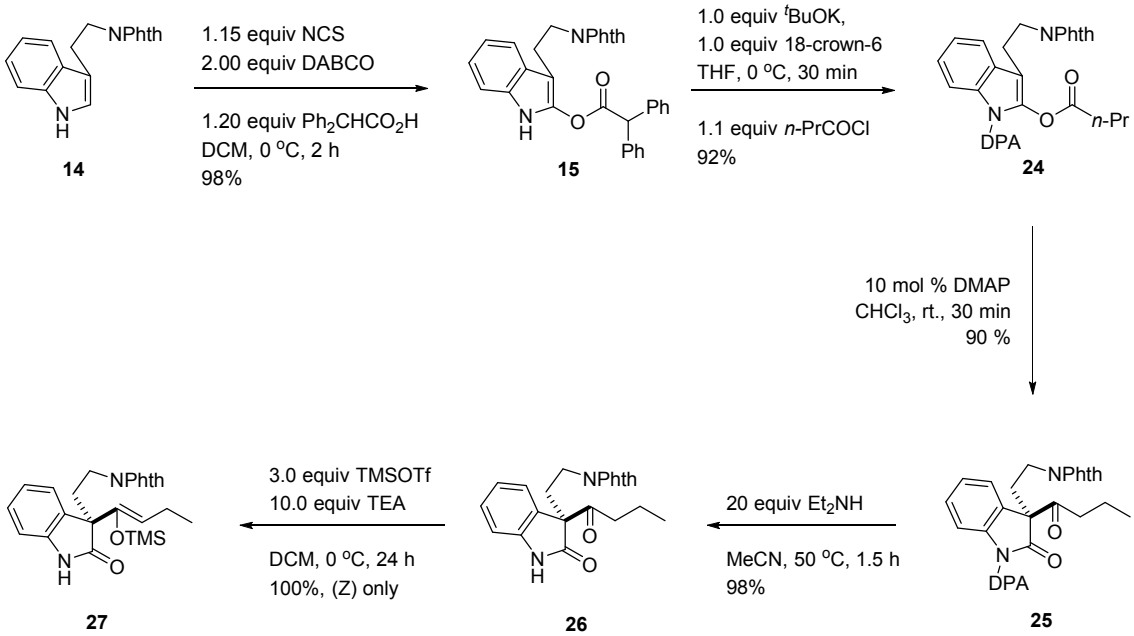


Figure 7. The bottom-to-top approach toward cyclohexane core

At this juncture, we first studied a model system (e.g. **25**) having a propyl sidechain in the ketone part instead of the propylsiliylether group because overlapped ^{1}H NMR peaks in 3-4 ppm region prohibited fine analysis of the reaction mixture (Scheme 8). Also, the amine protecting group was changed to a phthalimide from the Boc group since N-Boc

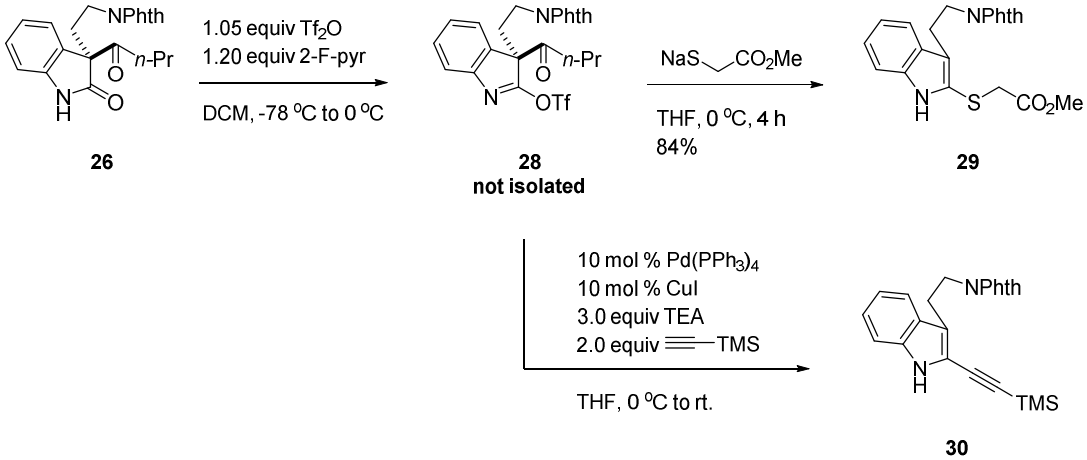
substrates all failed to afford desired imidoyl triflates upon exposure to the triflic anhydride.[14]



Scheme 8. Synthesis of silyl enol ether **22**

During the preparation of the model system, optimization of a few steps was also accomplished. Especially in the relay acyl migration step, use of potassium *tert*-butoxide together with a crown ether prohibited racemic C-acylation bypass affording clean O-acylation product **24** with excellent yield. At the end of this sequence, it was necessary to convert ketone **26** into silyl enol ether **27** in order to prevent deacylation, readily taking place due to the propensity for rearomatizaiton. For example, attempts to prepare an Eschenmoser contraction substrate[15] or mimic the coupling reaction of 3*H*-indole-2-yl-triflate with an acetylide reported by Iwabuchi's group,[16] resulted in formations of rearomatized indole product **29** and **30** respectively. This results indicated that although

the imidoyl triflate could participate either nucleophilic addition or palladium-catalyzed cross coupling reactions, deacylation aptitude was too high to deal with (Scheme 9).[17]

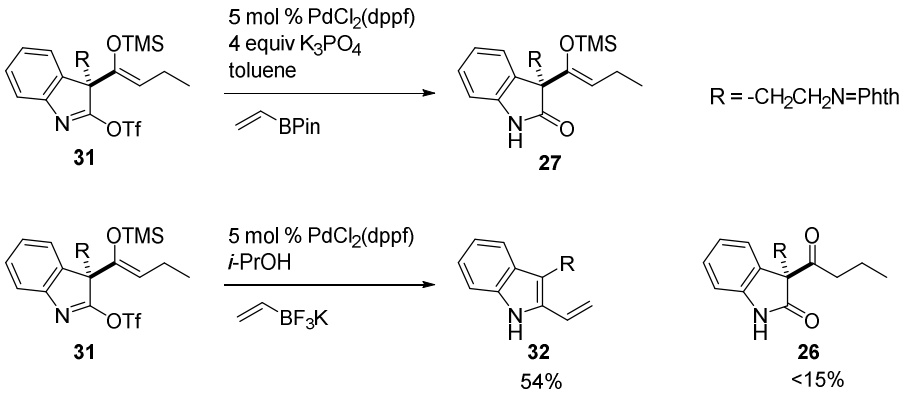


Scheme 9. Deacylations and rearomatizations of ketone **28**

3.2.2 The Suzuki Coupling

The Pd-catalyzed cross-coupling reactions are among the most powerful methods to make C-C bonds under mild conditions. Among the various methods using different transmetallation partners, the Suzuki coupling is regarded as benign, mild, and efficient. In conjunction with broad availability of vinyl boron species, the Suzuki coupling appeared as an amenable route to be employed. However, the reactions of imidoyl triflate **31** with vinylboronic acid pinacol ester under the standard Suzuki conditions gave only formal hydrolysis product **27**, implying the sensitive nature of the triflate toward hydroxide ions (Scheme 10). According to the Molander group, vinyltrifluoroborate coumplex can participate in the Suzuki reactions without using water co-solvent.[18] Efforts toward the vinyl coupling following the Molander method hinted at the feasibility

of the coupling reaction to some extent, but again, the propensity toward rearomatization made reactions only afford 2-vinylindole **32**.

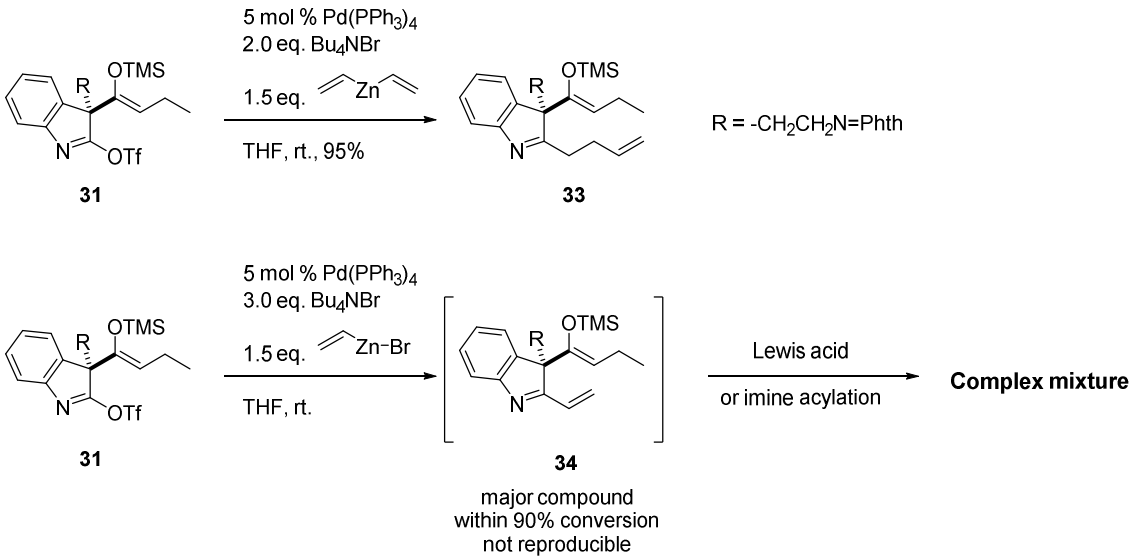


Scheme 10. The Suzuki reaction of imidoyl triflate **31**

3.2.3 The Negishi coupling

The problems encountered so far appeared to arise from the low reaction rate of the coupling reactions compared to that of desilylation leading to facile deacylation. We hypothesized that accelerating the turn-over limiting transmetallation step under anhydrous conditions might avoid the problematic deacylation. In order to assure faster transmetallation and anhydrous conditions, we turned our attentions to using more metallic partners. Preliminary results of the Kumada reactions were poor although the boundary conditions were satisfied.[19] Hence, it was hoped that divinyl zinc would not react toward the phthalimide or imidoyl triflate and undergo a Negishi reaction at room temperature. In the presence of a palladium catalyst and divinyl zinc, triflate **31** slowly disappeared as monitored by thin layer chromatography. Addition of tetrabutylammonium bromide into the mixture accelerated the reaction significantly.[20]

However, it was butenylated product **33**, not the desired vinylated product, that was isolated in 95% yield presumably through vinyl-coupling/Michael addition sequence (Scheme 11).



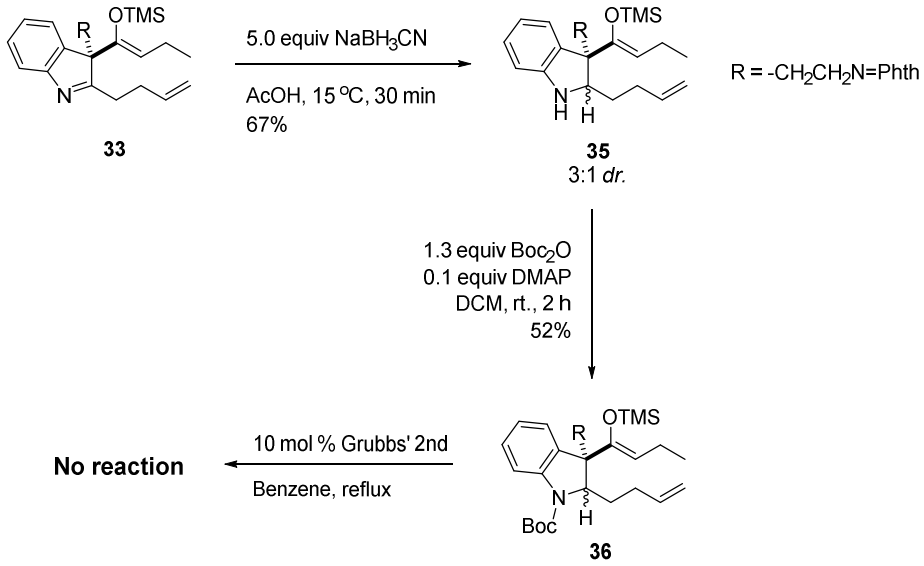
Scheme 11. Zincate Negishi reactions

With careful administration of vinyl/bromide ratio of zincate complex, monovinylation product **34** could be observed in ^{1}H NMR. However, vinyl imine **34** was so unstable that all the attempts to purify the product failed. In addition, this result was irreproducible and a few attempts to form 6-membered cycle using imine acylation or Lewis acid were not successful.

3.2.4 The Metathesis Reaction

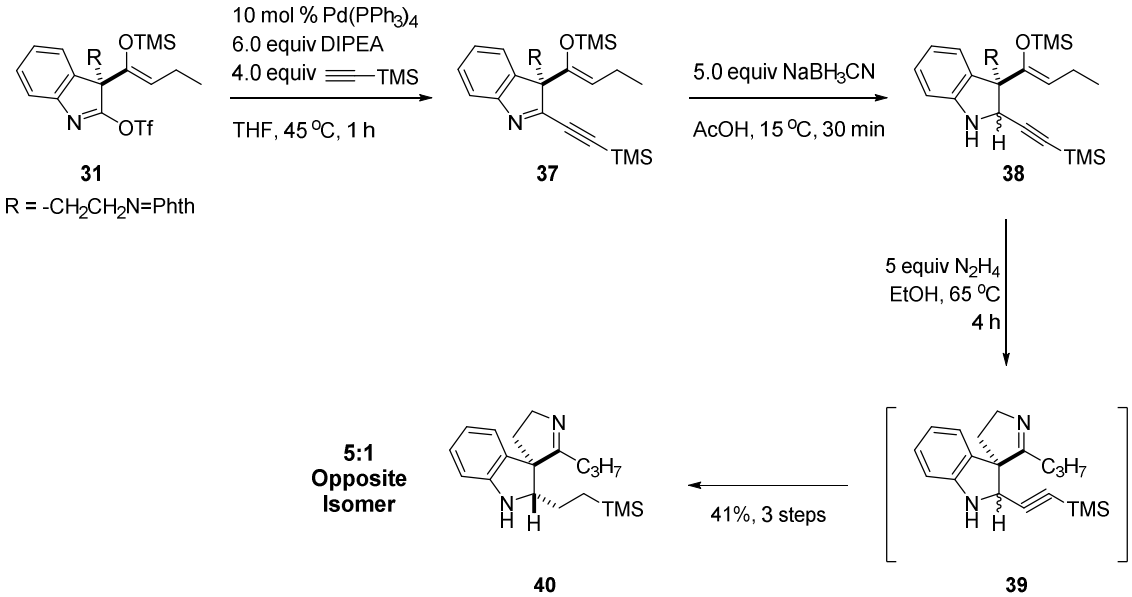
The amide-activation/cross-coupling strategy, the bottom-to-top approach, was only partially realized at the moment. The last hurdle is apparently the cyclization of C-ring,

which is challenging because of low stability of the vinyl imine and high aptitude of deacylation/rearomatization. We planned to avoid this problem by taking advantage of high stability of the Michael adduct **33**. To cut off two carbon surplus in the molecule, we tapped the metathesis chemistry into the construction of C ring. Silyl enol ethers are known to deactivate Grubbs' catalyst if the initiation take place on the enol ether while catalytic cycles are unperturbed if the enol ether participate later in the catalytic cycle.[21] The Michael adduct **33** was expected to be free from such a problem because of steric crowdedness around the silyl enol ether. When the Michael adduct **33** was subjected to a variety of metathesis conditions, unfortunately, only unproductive complexation of the substrate with ruthenium catalyst was observed. [21] In order to prevent complexation of the ruthenium catalyst with a basic nitrogen, the imine was reduced and the indoline nitrogen was protected with a Boc group to furnish **36** as a 3:1 diastereomeric mixture. However, the approach did not improve the reaction. In this case, the starting materials were intact hinting that either the stereochemistry on the C2 was inadequate for cyclization or the silyl enol ether was too congested to make a ruthanacyclobutane required in the catalytic cycle (Scheme 12).



Scheme 12. Metathesis routes toward C-ring cyclization

In order to confirm the stereochemistry of the reduction step, we designed a 2-alkynyl indoline compound (e.g. **39**) which would be expected to show a clear 2D-NOESY signal of C2-proton with either ethyl group or pyroline chain. The Sonogashira coupling of imidoyl triflate **33** in the presence of copper co-catalyst led to only deacylated products. In this case, a classic Heck alkynylation conditions worked well giving fairly detectable but not isolable imino-alkyne **37** which was reduced directly to indoline **38**. While subsequent deprotection of the phtalimide functionality led to condensation to imine as expectedly, unexpected reduction of the alkynyl moiety also occurred to give alkyl silane **40** (Scheme 13).



Scheme 13. Confirmation of stereochemical outcome of reduction of 3H-indole

The resulting methine proton at the indoline C2 position showed 3.4% correlations with the methylene protons of the propyl substituent outside pyroline ring, implying the reduction gave an undesired stereoisomer predominantly (Figure 8). The ongoing research will focus on the reversal of the stereochemical outcome.

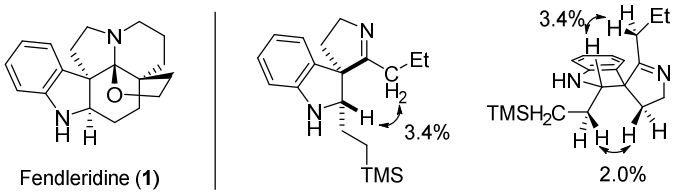


Figure 8. NOESY correlations of **40**

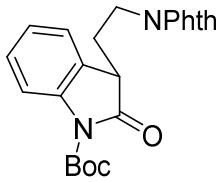
Conclusion

In summary, during our efforts toward total synthesis of (+)-fendleridine, we have developed a facile, gram-scale route to 3-keto-oxindoles. Oxidative oxy-carbonylation and anionic realy-acylation revealed unexplored reactivities of indoles. In conjunction with the known nucleophilic acyl-migration chemistry, this work provides highly effective, scalable, and facile route for the preparation of 3,3-disubstituted oxindoles. In addition to the oxindole preparation, we have also discovered intrinsic reactivity of the 3-acyl-oxindole core and explored the cross-coupling reactions of 3*H*-indole-2-triflate. Our ongoing efforts will be focused on correct stereochemistry at indoline C2 and finding an effective cyclization method for the C ring formation en route to (+)-fendleridine.

EXPERIMENTAL SECTION

General information. NMR spectra were obtained on an Agilent 400-MR DD2 Magnetic Resonance System (400 MHz) and a Varian/Oxford As-500 (500 MHz) spectrophotometer. Chemical shift values were recorded as parts per million relative to tetramethylsilane as an internal standard unless otherwise indicated, and coupling constants in Hertz. The following abbreviations (or combinations thereof) were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were measured on a Thermo Scientific Nicolet 6700 spectrometer. High resolution mass spectra were recorded on a JEOL JMS-600W or a JEOL JMS-700 spectrometer using electron impact (EI) or chemical ionization (CI) method. CHI650B potentiostat, and gas chromatography data were obtained on a Hewlett Packard HP 6890 Series GC systems.

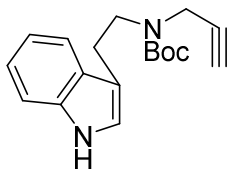
The progress of reaction was checked on thin layer chromatography (TLC) plates (Merck 5554 Kiesel gel 60 F254), and the spots were visualized under 254 nm UV light and/or charring after dipping the TLC plate into a vanillin solution (15.0 g of vanillin and 2.5 mL of concentrated sulfuric acid in 250 mL of ethanol), a $KMnO_4$ solution (3.0 g of $KMnO_4$, 20.0 g of K_2CO_3, and 5.0 mL of 5% NaOH solution in 300 mL of water), or a phosphomolybdic acid solution (250 mg phosphomolybdic acid in 50 mL ethanol). Column chromatography was performed on silica gel (Merck 9385 Kiesel gel 60) using hexanes-EtOAc (v/v). All solvents were obtained by passing through activated alumina columns of solvent purification systems from Glass Contour.



***tert*-butyl 3-(2-(1,3-dioxoisoindolin-2-yl)ethyl-2-oxindole-1-carboxylate (11)**

To a solution of indole **9**[22] (141.0 mg, 0.36 mmol) in anhydrous DCM (2.0 mL) was added freshly prepared DMDO solution[23] (3.6 mL, 0.104 M in acetone) dropwise at -78 ^{o}C under argon atmosphere through Teflon needle. After stirring for 1 h at – 78 ^{o}C, the mixture was allowed to warm to room temperature over 1 hour period. Removal of all the volatile gave yellow oil residue which was further purified by flash column chromatography on silica (Hexane:EA = 5:1) providing *N*-Boc oxindole **11** (90.7 mg, 62%) and recovered starting materials (54.7 mg, 38%).

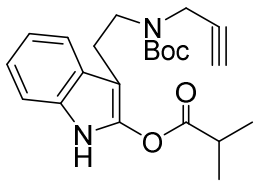
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70-7.78 (m, 3H), 7.65 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.28 (d, *J* = 7.3 Hz, 1H), 7.14 (t, *J* = 7.8 Hz, 1H), 6.99 (t, *J* = 7.5 Hz, 1H), 3.92 (dt, *J* = 14.6, 7.4 Hz, 1H), 3.77 (dt, *J* = 14.6, 9.0 Hz, 1H), 3.61 (t, *J* = 5.7 Hz, 1H), 2.45 (dt, *J* = 13.9, 7.2 Hz, 1H), 2.39 - 2.30 (m, 1H), 1.61 (s, 9H); ^{13}C (500 MHz, $CDCl_3$) δ 175.45, 168.30, 149.46, 140.43, 134.14, 132.28, 128.45, 127.10, 124.54, 123.72, 123.44, 115.42, 84.52, 4 4.27, 35.22, 29.26, 28.41



***tert*-butyl (2-(1*H*-indol-3-yl)ethyl)(prop-2-yn-1-yl)carbamate (12)**

To a solution of *N*-propargyl tryptamine (2.4559 g, 12.4 mmol) and DMAP (151.5 mg, 1.24 mmol) in anhydrous MeOH (27 mL) was slowly added Boc_2O (5.87 mL, 24.8 mmol) at room temperature under nitrogen atmosphere. The mixture was stirred for 4 hours until an evolution of gas was completely ceased. Evaporation of solvent followed by flash column chromatography gave **12** as a sticky yellow oil (3.5701 g, 97%).

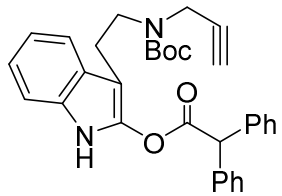
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (br, 1H), 7.70 (d, *J* = 7.3 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.23 (t, *J*= 7.2 Hz, 1H), 7.17 (m, 1H), 7.0 (s, 1H), 4.18-3.96 (br, 2H), 3.75-3.62 (br s, 2H), 3.16-3.02 (br s, 2H), 2.28 (s, 1H), 1.65-1.35 (br m, 9H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 136.45, 127.45, 122.23, 121.79, 119.12, 118.64, 112.76, 111.32, 80.24, 79.97, 71.67, 47.45, 36.09, 28.31, 24.15; IR (neat): ν_{max}3413, 3303, 3057, 2976, 2929, 1675, 1457, 1250, 1163, 731 cm^{-1}



3-(2-((tert-butoxycarbonyl)(prop-2-yn-1-yl)amino)ethyl)-1*H*-indole-2-yl isobutyrate (13a)

To a solution of indole **12**(539.3 mg, 1.8 mmol) and DABCO (728.4 mg, 4.0 mmol) in anhydrous DCM (24 mL) was added *N*-chlorosuccinimide (243.4 mg, 1.8 mmol) in three portions at -20 ^{o}C. After stirring for 10 min, the mixture was allowed to warm to 0 ^{o}C and isobutyric acid (0.18 mL, 2.1 mmol) was added slowly and the mixture was stirred for another 4 h. The solvent was evaporated to approximately one quarter of its original

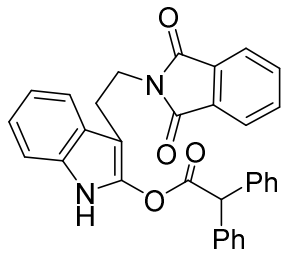
volume and poured into water (20 mL). The layers were separated and the aqueous layer was extracted with ethylacetate (20 mL X 3). Combined organic layers were washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Flash column chromatography of the residue on silica gel afforded compound **13a** as a sticky oil (573.0 mg, 83%); ^{1}H NMR(500 MHz, $CDCl_3$) δ 8.84-8.61 (br s, 1H), 7.55 (s, 1 H), 7.27 (m, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 7.12 (t, *J* = 7.4 Hz, 1H), 4.18-3.80 (br m, 2H), 3.57 (t, *J* = 7.4 Hz, 2H), 2.93 (t, J = 7.1 Hz, 2H), 2.87 (m, 1H), 2.18 (s, 1H), 1.54-1.40 (br m, 9H), 1.36 (d, *J* = 7.0 Hz, 6H); IR (neat): ν_{max}3294, 2977, 1769, 1673, 1459, 1367, 1166, 1085, 740 cm^{-1}



3-(2-((*tert*-butoxycarbonyl)(prop-2-yn-1-yl)amino)ethyl)-1*H*-indol-2-yl diphenylacetate (13b)

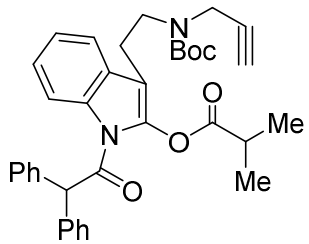
Analogous procedure as for preparation of the compound **13a**, but using diphenylacetic acid instead of isobutyric acid, afforded **13b** as a sticky oil (1.9885g, 99% from 1.1800g, 4.0 mmol of **12**); ^{1}H NMR (500 MHz, $CDCl_3$) δ9.14 (s, 1H), 7.71 (s, 1H), 7.54 (d, *J* = 7.5 Hz, 4H), 7.47 (t, *J* = 7.5 Hz, 4H), 7.40 (t, *J*= 7.5 Hz, 2H), 7.35-7.20 (m, 3H), 5.41 (s, 1H), 4.07-3.81 (br m, 2H), 3.62 (br s, 2H), 2.92 (br s, 2H), 2.24 (s, 1H), 1.71-1.36 (br m, 9H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 170.19, 137.54, 131.43, 128.80, 128.54, 127.68, 126.40,

121.66, 119.81, 111.09, 97.47, 80.02, 77.36, 56.70, 46.00, 28.17, 21.55; IR (neat): ν_{max} 3289, 2976, 2930, 1770, 1672, 1457, 1366, 1163, 1100, 742, 699 cm^{-1}



3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-1*H*-indol-2-yl diphenylacetate (15)

Strarting from indole **9** (5.2368 g, 18 mmol), same procedure as for preparation of the **13a** provided **14** as an yellow solid (7.7809 g, 88%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.99 (m, 1H), 7.77 (m, 2H), 7.67 (d, *J* = 6.7 Hz, 1H), 7.60 (m, 2H), 7.45 (d, *J* = 7.7 Hz, 4H), 7.37 (t, *J* = 7.5 Hz, 4H), 7.29 (t, *J* = 7.3 Hz, 2H), 7.21 (d, *J* =5.5 Hz, 1H), 7.31 (m, 2H), 5.32 (s, 1H), 3.90 (t, *J* = 7.5 Hz, 2H), 2.98 (t, *J* = 7.5 Hz, 2H), 2.14 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 170.27, 168.23, 140.11, 137.60, 133.80, 132.14, 131.41, 128.89, 128.75, 127.71, 126.28, 123.09, 121.87, 120.16, 118.50, 111.10, 96.77, 56.87, 37 .54, 22.09

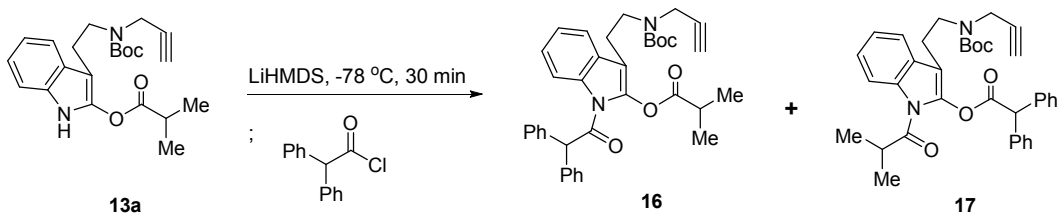


3-(2-((tert-butoxycarbonyl)(prop-2-yn-1-yl)amino)ethyl)-1-(2,2-diphenylacetyl)-1H-indol-2-yl isobutyrate (16)

To a solution of *O*-acyl oxindole **13b** (1.5296 g, 1.0 equiv) in THF (12 mL) was added KH (366.2 mg, 35 % wt, 1.05 equiv) at -78 ^{o}C under argon atmosphere and the mixture was slowly warmed to 0 ^{o}C with vigorous stirring. After the starting material was disappeared completely, isobutyryl chloride (0.62 mL, 2 equiv) and TEA (2.1 mL, 5 equiv) were added successively at the same temperature. After stirring at 0 ^{o}C for 10 h, the mixture was poured into water (20 mL) and extracted with ether (20 mL X 3).

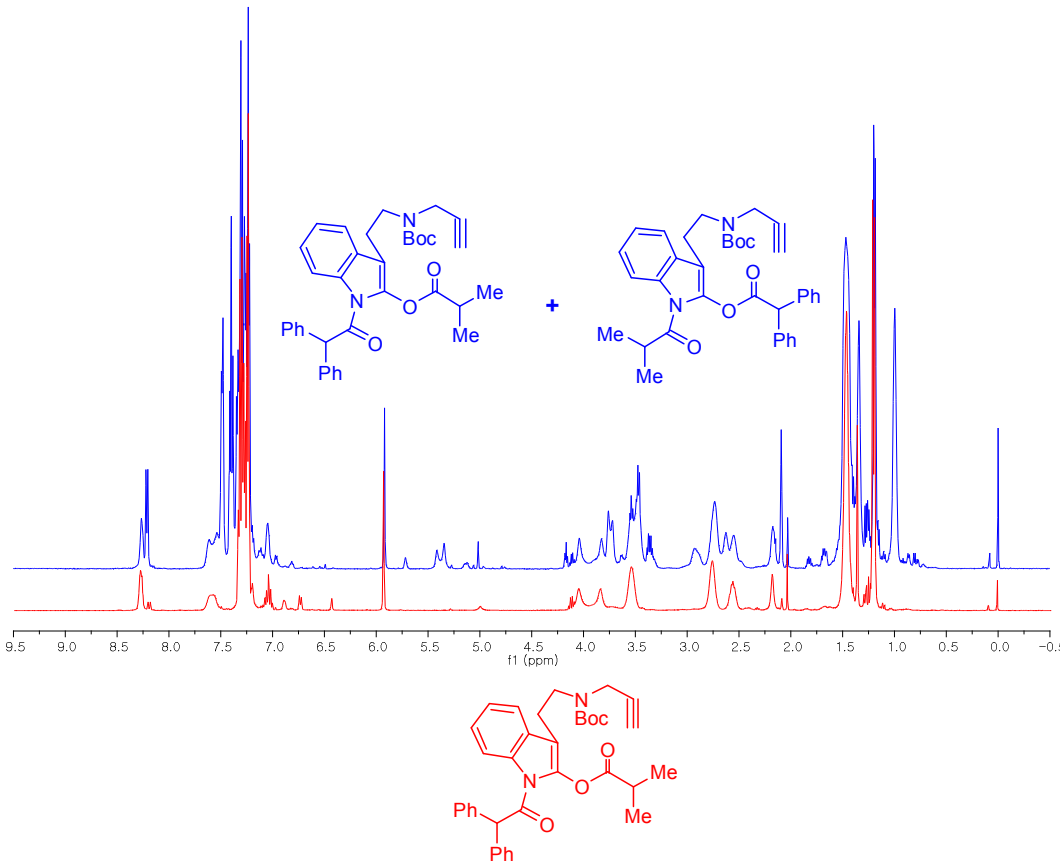
Combined organic layers were washed with sat. $NaHCO_{3(aq)}$, water, and brine, dried over $MgSO_{4(s)}$, concentrated under reduced pressure. The crude mixture was further purified by flash column chromatography on silica gel (Hexane:EA = 8:1 to 5:1) affording desired product **16** as a yellow oil (1.3209 g, 76%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.52 (br s, 1H), 7.17-7.34 (m, 11H), 7.04 (m, 1H), 5.94 (s, 1H), 3.76-4.10 (br m, 2H), 3.55 (br s, 2H), 2.76 (br s, 2H), 2.54 (m, 1H), 2.17 (s, 1H), 1.43 (s, 9H), 1.21 (d, *J* = 7.0 Hz, 6H)

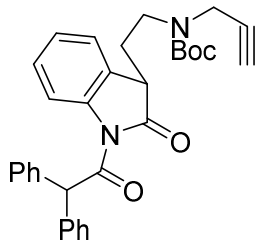
o Acyl-scrambling of the **13b**



To a solution of *O*-acyl oxindole **13a** (462.0mg, 1.0 equiv) in THF (12 mL) was added LiHMDS (1.3 mL, 1.0 M in THF, 1.1 equiv) at -78 ^{o}C. After the mixture was stirred for 30 min at -78 ^{o}C, diphenylacetyl chloride (2.4 mL, 1.0 M in THF, 2.4 equiv) was added

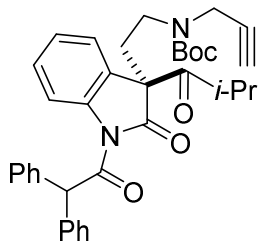
to the mixture. After stirring at 0 °C for 4 h, the mixture was poured into water (20 mL) and extracted with ether (20 mL X 3). Combined organic layers were washed with sat. $NaHCO_{3(aq)}$, water, and brine and dried over $MgSO_{4(s)}$, concentrated under reduced pressure. The crude mixture was further purified by flash column chromatography on silica gel (Hexane:EA = 8:1 to 5:1) affording an inseparable mixture of **16** and **17** (505.7mg, **16**:**17** = 1:1.2, ca. 70%)





***tert*-butyl (2-(1-(2,2-diphenylacetyl)-2-oxoindole-3-yl)ethyl)(prop-2-yn-1-yl)carbamate (18)**

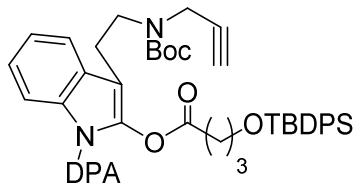
To a solution of *O*-acyl oxindole **16** (210 mg, 1,0 equiv) dissolved in toluene (6 mL) was added DMAP (6.84 mg, 15 mol %) at room temperature under nitrogen atmosphere. The mixture was stirred for 3 h at room temperature and concentrated *in vacuo*. Flash column chromatography on silica (Hexane:EA = 6:1) afforded deacylated oxindole **18** (75.7 mg, 41%).; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.27 (d, *J* = 7.9 Hz, 1H), 7.38-7.18 (m, 13H), 6.60 (s, 1H), 4.00-3.77 (br s, 2H), 3.58 (t, *J* = 5.5 Hz, 1H), 3.33-3.09 (br s, 2H), 2.19-2.08 (m, 3H), 1.42 (s, 9H)



***tert*-butyl (2-(1-(2,2-diphenylacetyl)-3-isobutyryl-2-oxoindole-3-yl)ethyl)(prop-2-yn-1-yl)carbamate (19)**

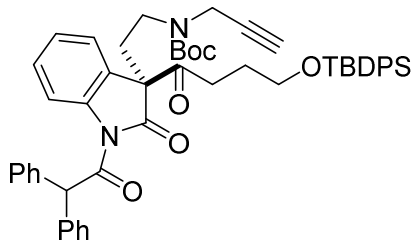
To a flame-dried round-bottom flask were added *O*-acyl oxindole **15** (210 mg, 1,0 equiv) and anhydrous toluene (6 mL). To the mixture was added DMAP (6.84 mg, 15 mol %)

and *N,N*'-dimethylthiourea (5.83 mg, 15 mol %) at room temperature under nitrogen atmosphere. The mixture was stirred for 3 h at room temperature and filtered through a short pad of silica flushing with ether. Concentration under reduced pressure and flash column chromatography on silica gel (Hexane:EA = 6:1) afforded acyl-migrated product **19** as a yellow oil (69.0 mg, 32%).; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.15 (d, *J* = 8.2 Hz, 1H), 7.44-7.16 (m, 10H), 7.15-7.08 (m, 1H), 7.05 (d, *J* = 7.9 Hz, 1H), 6.80 (d, *J* = 7.7 Hz, 1H), 5.28 (s, 1H), 4.05-3.68 (br s, 2H), 3.15-2.77 (br m, 2H),2.70 (m, 1H) 2.58-2.33 (br m, 2H),2.13 (t,*J* = 2.4 Hz,1H), 1.37 (d,*J* = 12.5 Hz,9H), 1.17 (d,*J* = 10.1 Hz,3H), 1.08 (d, *J* = 10.3 Hz, 3H)



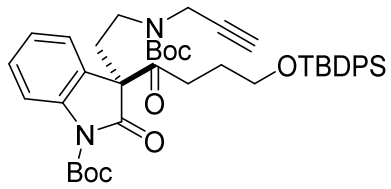
3-(2-((*tert*-butoxycarbonyl)(prop-2-yn-1-yl)amino)ethyl)-1-(2,2-diphenylacetyl)-1H-indol-2-yl 4-((*tert*-butyldiphenylsilyl)oxy)butanoate (20)

According to the procedure for the preparation of **16**, *O*-acyl oxindole **20** was prepared starting from **13b** and4-(*tert*-butyldiphenylsilyloxy)butanoyl chloride.[24] 792.9 mg of **13b** afforded 924.9 mg (74%) of **20** as a sticky oil.; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.35-8.30 (m, 1H), 7.69 (dd, J = 7.7, 1.4 Hz, 4H), 7.60-7.54 (m, 1H), 7.49-7.33 (m, 8H), 7.33-7.19 (m, 10H), 5.94 (s, 1H), 4.12-3.78 (br s, 2H), 3.67 (t, *J* = 5.7 Hz, 2H), 3.61-3.46 (br s, 2H), 2.88-2.74 (br s, 2H), 2.16 (m, 1H),1.89-2.74 (br s, 2H), 1.54-1.43 (br s, 9H), 1.10 (s, 9H)



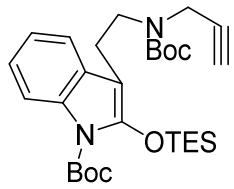
***tert*-butyl (2-(3-(4-(*tert*-butyldiphenylsilyloxy)butanoyl)-1-(2,2-diphenylacetyl)-2-oxindole-3-yl)ethyl)(prop-2-yn-1-yl)carbamate (21)**

To a flame-dried round-bottom flask was added *O*-acyl oxindole **20** (2.8877 g, 1.0 equiv), $CHCl_3$ (50 mL) and DMAP (42.7 mg, 10 mol %) at room temperature under nitrogen atmosphere. The mixture was stirred for 30 min at room temperature and concentrated *in vacuo*. Flash column chromatography on silica gel (Hexane:EA = 7:1) afforded acyl-migrated product **21** as a sticky oil (2.4331 mg, 84%).; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.35 (d, J = 8.2 Hz, 1H), 7.58-7.52 (m, 4H), 7.47-7.26 (m, 14H), 7.23-7.11 (m, 4H), 7.06 (t, J = 7.2 Hz, 1H), 6.56 (s, 1H), 3.89-3.68 (br s, 2H), 3.41-2.23 (m, 2H),2.87-2.72 (br m, 2H),2.13 (s, 1H), 1.95-1.76 (m, 2H), 1.58-1.42 (m, 2H), 1.40 (s, 9H), 0.95 (s, 9H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 200.62, 174.72, 172.85, 154.60, 140.96, 137.92, 137.51, 135.46, 133.77, 133.65, 129.78, 129.64, 129.41, 128.69, 128.54, 127.66, 127.41, 126.01, 123.27, 116.94, 85.54, 79.33, 65.36, 62.24, 58.14, 42.12, 34.28, 28.28, 26.91, 26.81, 26.71, 26.02, 19.12



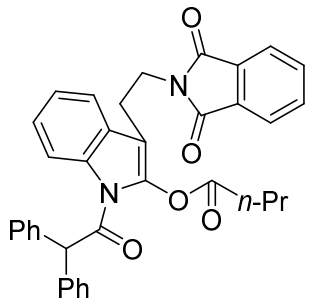
***tert*-butyl3-(2-((*tert*-butoxycarbonyl)(prop-2-yn-1-yl)amino)ethyl)-3-(4-(*tert*-butyldiphenylsilyloxy)butanoyl)-2-oxindole-1-carboxylate (22)**

To a solution of *C*-acyl oxindole **21** (416.6 mg, 1.0 equiv) dissolved in MeCN (2.5 mL) was added Et_2NH (1.1 mL, 20 equiv) at room temperature. The mixture was stirred for 90 min at 50 ^oC and diluted with $CHCl_3$ (10 mL) after the mixture was cooled down to room temperature, and then the mixture was concentrated *in vacuo*. To the crude mixture which was re-dissolved in DCM (3.5 mL) was asdded DMAP (4.3 mg, 0.1 equiv) and Boc_2O (85.5 mg, 1.1 equiv) sequentially under nitrogen atmosphere. After stirring for 12 h at room temperature, the mixture was concentrated under reduced pressure and directly subjected to flash column chromatography on silica gel (Hexane:EA = 9:1) affording N-Boc protected oxindole **22** as a clear oil. (331.6 mg, 90% for 2 steps); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.89 (br s, 1H), 7.54-7.48 (m, 4H), 7.41-7.28(m, 7H), 7.19-7.07 (m, 2H), 3.97-3.72 (br s, 2H), 3.47 (t, J = 6.1 Hz, 2H), 3.13-2.95 (br s, 2H), 2.60-2.39 (m, 3H),2.33 (ddd, J = 18.3, 8.2, 6.4 Hz, 1H), 2.11 (t, J = 2.4 Hz, 1H), 1.76-1.65 (m, 2H), 1.63 (s, 9H), 1.37 (s, 9H), 0.92 (s, 9H)



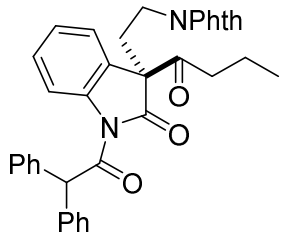
***tert*-butyl 3-(2-((*tert*-butoxycarbonyl)(prop-2-yn-1-yl)amino)ethyl)-2-((triethylsilyl)oxy)-1H-indole-1-carboxylate (23)**

To a flame-dried round-bottom flask was added Boc-protected oxindole **22** (370.2 mg, 1.0 equiv) and THF (5 mL). LiHMDS (0.5 mL, 1.0 M in THF, 1.0 equiv) was added dropwise to the mixture at -78 ^{o}C. After stirring for 20 min at -78^{o}C, all the starting materials disappeared. TESCl (0.13 mL, 1.5 equiv) were added and the mixture was stirred for another 2 hours at -78 ^{o}C and 30 min at room temperature before sat. $NH_4Cl_{(aq)}$ (5 mL) was added. The aqueous layer was extracted with ether (20 mL X 2) and combined organic layers were washed with brine, dried over $Na_2SO_{4(s)}$, and concentrated *in vacuo*. The crude mixture was further purified by flash column chromatography on a short pad of silica gel (Hexane:EA = 5:1) affording *O*-silylated oxindole **23** as a clear oil. (220.6 mg, 82%); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.80 (d, *J* = 7.7 Hz, 1H), 7.55-7.38 (br s, 1H), 7.20-7.09 (m, 2H), 4.22-3.86 (br s, 2H), 3.55 (t, *J* = 7.7 Hz, 2H), 2.26-2.18 (br s, 2H), 2.04 (s, 1H), 1.68 (s, 9H), 1.49 (s, 9H), 1.00 (t, *J* = 7.9 Hz, 9H), 0.84 (q, *J* = 7.8 Hz, 6H)



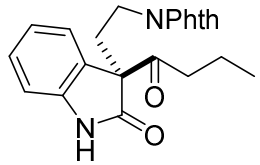
3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-1-(2,2-diphenylacetyl)-1H-indol-2-yl butyrate (24)

To a solution of **23** (1.8400 g, 1.0 equiv) and 18-crown-6 ether (987.9 g, 1.1 equiv) in THF (40 mL) was added ^{t}BuOK (3.9 mL, 1.0 M in THF, 1.1 equiv) slowly at 0 ^{o}C under nitrogen atmosphere. After stirring for 30 min, butyryl chloride (0.5 mL, 1.3 equiv) was added at 0 ^{o}C and the mixture was stirred for another 12 h before quenched with saturated aqueous NH_4Cl (20 mL). The organic layer was separated and the aqueous layer was extracted with ether (30 mL X 2). Combined organic layers were washed with brine, dried over $MgSO_{4(s)}$, and concentrated under reduced pressure. Flash column chromatography on silica gel (Hexane:EA = 4:1) provided desired relay-acylated product **24** as a sticky oil (1.9278 g, 92%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.25 (dd, J = 6.8, 1.9 Hz, 1H), 7.86-7.78 (m, 2H), 7.74-7.69 (m, 2H), 7.69-7.64 (m, 1H), 7.34-7.25 (m, 8H), 7.21-7.16 (m, 4H), 5.81 (s, 1H), 3.93-3.81 (m, 2H), 2.85-2.78 (m, 2H), 2.21 (t, J =7.5 Hz, 2H), 1.59-1.47 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H)



2-(2-(3-butyryl-1-(2,2-diphenylacetyl)-2-oxoindolin-3-yl)ethyl)isoindoline-1,3-dione(25)

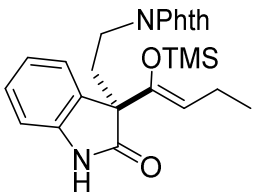
To a solution of **24** (2.6710 g, 1.0 equiv) in $CHCl_3$ (78 mL) was added DMAP (57.5 mg, 0.1 equiv) at room temperature. After stirring for 30 min, the mixture was concentrated to *ca.* 10 mL volume under reduced pressure. The mixture was filtered through a short pad of silica flushed with Et_2O:Hexane:$CHCl_3$ (2:2:1). The filtrate was concentrated and recrystallized from $CHCl_3$/Et_2O affording rearranged product **25** as a white solid (2.3897 g, 90%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.16 (d, J = 7.9 Hz, 1H), 7.68-7.59 (m, 4H), 7.38-7.20 (m, 10H), 7.10 (t, J = 8.2 Hz, 1H), 7.04 (d,J = 6.4 Hz, 1H), 7.01-6.96 (m, 1H), 6.57 (s, 1H), 3.86 (dt, J = 14.9 Hz, 9.7 Hz, 1H),3.41 (dt, J = 14.9 Hz, 9.7 Hz, 1H), 2.74 (dt, J = 14.9 Hz, 7.6 Hz, 1H), 2.55 (dt, J = 14.5 Hz, 6.0 Hz, 1H), 1.57 (dt, J = 18.1 Hz, 6.9 Hz, 1H), 1.44 (dt, J = 18.1 Hz, 7.0 Hz, 1H), 1.23-1.10 (m, 2H), 0.45 (t, J = 7.4 Hz, 3H)



2-(2-(3-butyryl-2-oxindole-3-yl)ethyl)isoindoline-1,3-dione(26)

To a solution of *C*-acyl oxindole **25** (537.6 mg, 1.0 equiv) dissolved in MeCN (5.0 mL) was added Et_2NH (2.0 mL, 20 equiv) at room temperature. The mixture was stirred for 4

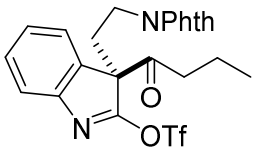
h at 50 ^{o}C and concentrated *in vacuo*. Flash column chromatography on silica gel afforded desired N-deprotected product **26** as colorless oil which turned to white solid upon standing at -20 ^{o}C (357.4 mg, 98%).; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.00 (s, 1H), 7.73-7.55 (m, 4H), 7.08-6.99 (m, 2H), 6.90 (d, *J* = 7.7 Hz, 1H), 6.80 (t, *J* = 7.5 Hz, 1H), 3.71-3.51 (m, 2H), 2.86-2.73 (m, 1H), 2.65-2.54 (m, 1H), 2.44 (dt, *J* = 17.7 Hz, 7.0 Hz, 1H),2.18-2.05 (m, 1H), 1.45 (qt, *J* = 14.0 Hz, 6.9 Hz, 2H), 0.69 (t, *J* = 7.4 Hz, 3H)



(Z)-2-(2-(3-(1-((trimethylsilyl)oxy)but-1-en-1-yl)-2-oxindole-3-yl)ethyl)isoindoline-1,3-dione (27)

To a flame-dried round-bottom flask was added solution of oxindole **26** (111.7 mg, 1.0 equiv) dissolved in DCM (3.0 mL), TEA (0.45 mL, 10 equiv) and TMSOTf (0.19 mL, 3.0 equiv) sequentially under argon atmosphere at 0 ^{o}C. The mixture was stirred for 24 h at 0 ^{o}C before quenched with saturated aqueous $NaHCO_3$ solution (5 mL). The biphasic mixture was diluted with ethyl acetate (20 mL) and the organic phase was washed with water (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography on a short pad of silica gel (Hexane:EA = 6:4) afforded desired TMS-enolether **27** as a colorless oil which was further purified by recrystallization ($CHCl_3$/Hexane). (white needle, 134.6 mg, 100%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ8.71-8.42 (br s, 1H), 7.74-7.67 (m, 2H), 7.17 (d, *J* = 7.4 Hz,

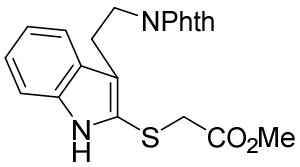
1H), 7.02 (td, J = 7.7, 1.2 Hz, 1H), 6.87-6.74 (m, 2H), 4.78 (t, J = 6.8 Hz, 1H), 3.65-3.55 (m, 2H), 2.55 (dt, J = 13.7, 7.8 Hz, 1H), 2.39-2.29 (m, 1H),2.07-1.83 (m, 2H), 0.94 (t, J = 7.5 Hz, 3H), -0.09 (s, 9H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 179.62, 167.90, 147.38, 141.88, 133.66, 131.90, 130.86, 128.21, 124.26, 122.94, 122.20, 111.23, 110.26, 77.25, 57.34, 34.13, 31.84, 19.46, 14.11, 0.41



3-butyryl-3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-3H-indol-2-yltrifluoromethanesulfonate (28)

To a flame-dried round-bottom flask was added a solution of oxindole **26** (37.4 mg, 1.0 equiv) dissolved in DCM (0.5 mL). 2-fluoropyridine (10 μL, 1.2 equiv) and trifluoromethanesulfonic anhydride (105 μL, 1.0 M in DCM, 1.05 equiv) were added to the mixture sequentially under argon atmosphere at -78 ^{o}C. After stirring for 20 min, the mixture was allowed to warm to 0 ^{o}C and stirred for 30 min at 0 ^{o}C before quenched with saturated aqueous $NaHCO_3$ solution (3 mL). The biphasic mixture was extracted twice with ether (5 mL each) and the combined organics were washed with water (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The resulting triflate was usually used directly in next steps without further purification. Flash column chromatography on silica gel (Hexane:EA = 3:1) afforded pure trilfate **28** albeit in lower yield due to its poor stability on silica gel. (26.8 mg, 53%); ^{1}H NMR ($CDCl_3$,

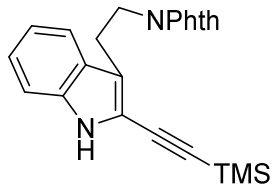
400 MHz) δ7.79-7.70 (m, 2H), 7.70-7.57 (m, 3H), 7.38 (t, *J* = 7.2 Hz, 1H), 7.32-7.20 (m, 2H), 3.43-3.22 (m, 2H), 2.88-2.76 (m, 1H), 2.59-2.47 (m, 1H), 2.12 (dt, *J* = 17.7, 6.8 Hz, 1H), 1.91 (dt, *J* = 17.8, 7.1 Hz, 1H),1.50-1.31 (m, 2H), 0.67 (t, *J* = 7.4 Hz, 3H)



methyl 2-((3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-1H-indol-2-yl)thio)acetate (28)

To a flame-dried round-bottom flask was added a solution of oxindole **26** (37.4 mg, 1.0 equiv) dissolved in DCM (0.5 mL). 2-fluoropyridine (10 μL, 1.2 equiv) and trifluoromethanesulfonic anhydride (105 μL, 1.0 M in DCM, 1.05 equiv) were added to the mixture sequentially under argon atmosphere at -78 ^{o}C. After stirring for 20 min, the mixture was allowed to warm to 0 ^{o}C and stirred for 30 min at 0 ^{o}C before quenched with saturated aqueous $NaHCO_3$ solution (3 mL). The biphasic mixture was extracted twice with ether (5 mL each) and the combined organics were washed with water (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The resulting triflate **28** was re-dissolved in THF (0.25 ml). To a solution of methyl thioglycolate (10 μl, 2.0 equiv) in THF (0.25 mL) was added NaH (4.0 mg, 60% wt. in mineral oil, 2.0 equiv) at 0 ^{o}C. After an evolution of gas was ceased, the solution of **28** was added slowly to the thioglycolate solution at 0 ^{o}C and stirred for 4 h. The mixture was quenched with saturated aqueous NH_4Cl (1 mL), and extracted with ether twice (5

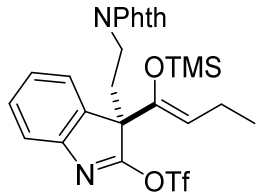
mL each). Combined organic layers were washed with water and brine and dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography on silica gel (Hexane:EA = 3:1) afforded pure 2-thio-indole **29** as a colorless oil. (16.5 mg, 84%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ8.99 (br s, 1H), 7.78 (dd, *J* = 5.2, 3.0 Hz,2H), 7.67-7.57 (m,3H), 7.29 (d, *J* = 8.1 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 3.93 (t, *J* = 7.4 Hz, 2H), 3.75 (s, 3H), 3.50 (s, 2H), 3.22 (t, *J* = 7.5 Hz, 1H)



2-(2-(2-((trimethylsilyl)ethynyl)-1H-indol-3-yl)ethyl)isoindoline-1,3-dione(30)

To a flame-dried round-bottom flask was added a solution of oxindole **26** (37.4 mg, 1.0 equiv) dissolved in DCM (0.5 mL). 2-fluoropyridine (10 μL, 1.2 equiv) and trifluoromethanesulfonic anhydride (105 μL, 1.0 M in DCM, 1.05 equiv) were added to the mixture sequentially under argon atmosphere at -78 ^{o}C. After stirring for 20 min, the mixture was allowed to warm to 0 ^{o}C and stirred for 30 min at 0 ^{o}C before quenched with saturated aqueous $NaHCO_3$ solution (3 mL). The biphasic mixture was extracted twice with ether (5 mL each) and the combined organics were washed with water (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Resulting triflate **28** was re-dissolved in THF (0.5 ml). To the solution of **28** was added $Pd(PPh_3)_4$ (6.12 mg, 0.1 equiv), CuI (3.01 mg, 0.3 equiv), TEA (73 μL, 10.0 equiv) and ethynyltrimethylsilane (15 μL, 2.0 equiv) sequentially under constant flow of argon gas.

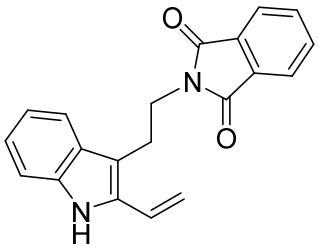
The mixture was stirred at room temperature for 3 h, and then filtered through a pad of silica eluting with diethyl ether. The mixture was concentrated under reduced pressure. ^{1}H NMR of the residual oil exhibited mainly 2-alkynylindole **30**; ^{1}H NMR ($CDCl_3$, 400 MHz) δ7.80 (br s, 1H), 7.77-7.58 (m, 4H), 7.50-7.39 (m, 3H), 7.18-7.11 (m, 1H), 4.97 (t, *J* = 7.5 Hz, 2H), 3.10 (t, *J* = 7.6 Hz, 1H), 0.17 (s, 9H)



(Z)-3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-3-(1-((trimethylsilyl)oxy)but-1-en-1-yl)-3H-indol-2-yl trifluoromethanesulfonate (31)

To a flame-dried round-bottom flask was added a solution of oxindole **27**(22.4 mg, 1.0 equiv) dissolved in DCM (0.5 mL). 2-fluoropyridine (5.2μL, 1.2 equiv) and trifluoromethanesulfonic anhydride (52μL, 1.0 M in DCM, 1.05 equiv) were added to the mixture sequentially under argon atmosphere at -78 ^{o}C. After stirring for 20 min, the mixture was allowed to warm to 0 ^{o}C and stirred for 30 min at 0 ^{o}C before quenched with saturated aqueous $NaHCO_3$solution (3 mL). The biphasic mixture was extracted twice with ether (5 mL each) and the combined organics were washed with water (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The resulting triflate was usually used directly in next steps without further purification.^{1}H NMR of the crude mixture showed full conversion of the oxindole into the corresponding triflate.; ^{1}H NMR ($CDCl_3$, 400 MHz) δ7.79-7.73 (m, 2H), 7.72-7.63 (m, 2H), 7.55 (d, *J* = 7.4 Hz, 1H), 7.36 (td, *J* = 7.2, 2.1 Hz, 1H), 7.29-7.20 (m, 2H), 4.85 (t, *J* = 6.8 Hz, 1H),

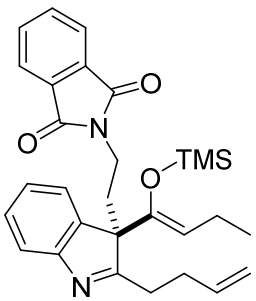
3.42-3.36 (m, 1H), 3.28-3.19 (m, 1H), 2.50-2.36 (m, 2H),2.12-1.89 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H), -0.50 (s, 9H)



2-(2-(2-vinyl-1H-indol-3-yl)ethyl)isoindoline-1,3-dione(32)

To a flame-dried round-bottom flask was added a solution of oxindole **27** (26.4 mg, 1.0 equiv) dissolved in DCM (0.6 mL). 2-fluoropyridine (6.2μL, 1.2 equiv) and trifluoromethanesulfonic anhydride (62μL, 1.0 M in DCM, 1.05 equiv) were added to the mixture sequentially under argon atmosphere at -78 ^{o}C. After stirring for 20 min, the mixture was allowed to warm to 0 ^{o}C and stirred for 30 min at 0 ^{o}C before quenched with saturated aqueous $NaHCO_3$solution (3 mL). The biphasic mixture was extracted twice with ether (5 mL each) and the combined organics were washed with water (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The resulting triflate was re-dissolved in *n*-PrOH (0.6 mL). To the solution of triflate **31** were added $PdCl_2$(dppf)-CH_2Cl_2 (4.9 mg, 0.1 equiv), potassium vinyltrifluoroborate[17b] (12.1 mg, 1.5 equiv), and DIPEA (21 μL, 2.0 equiv) sequentially under constant flow of argon gas. After stirring for 18 h at 65 ^{o}C, the reaction mixture was filtered through a short pad of celite flushed with ether. The mixture was concentrated *in vacuo* and directly subjected to a flash column chromatography on silica gel affording 2-vinyl indole **32** as an yellow

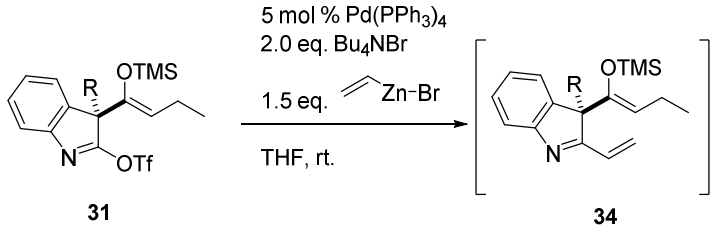
oil (9.8 mg, 54%). Remainder of the mixture were recovered starting material **27** and desilylated starting material **26**.; ^{1}H NMR ($CDCl_3$, 400 MHz) δ8.03 (br s, 1H), 7.83-7.78 (m, 2H), 7.73-7.59 (m, 3H), 7.27 (d, *J* = 7.8 Hz, 1H), 7.18 (t, *J* = 7.2 Hz, 1H), 7.09 (t, *J* = 7.4 Hz, 1H), 6.86 (dd, *J* = 18.4, 12.2 Hz, 1H), 5.42 (d, *J* = 18.2 Hz, 1H), 5.21 (d, *J* = 12.0 Hz, 1H), 3.89 (t, *J* = 7.0 Hz, 2H), 3.17 (t, *J* = 6.8 Hz, 2H)



(Z)-2-(2-(2-(but-3-en-1-yl)-3-(1-((trimethylsilyl)oxy)but-1-en-1-yl)-3H-indol-3-yl)ethyl)isoindoline-1,3-dione (33)

To a flame-dried round-bottom flask was added a solution of oxindole **27** (179.4 mg, 1.0 equiv) dissolved in DCM (4.0 mL). 2-fluoropyridine (41μL, 1.2 equiv) and trifluoromethanesulfonic anhydride (420μL, 1.0 M in DCM, 1.05 equiv) were added to the mixture sequentially under argon atmosphere at -78 ^{o}C. After stirring for 20 min, the mixture was allowed to warm to 0 ^{o}C and stirred for 30 min at 0 ^{o}C before quenched with saturated aqueous $NaHCO_3$solution (5 mL). The biphasic mixture was extracted twice with ether (10 mL each) and the combined organics were washed with water (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The resulting triflate was re-dissolved in a small amount of THF (1.0 mL). To the solution of triflate were added $Pd(PPh_3)_4$ (23.1 mg, 0.05 equiv), tetrabutylammonium bromide (386.8

mg, 3.0 equiv), and divinylzinc (3.2mL,0.25 M in THF, 2.0 equiv) sequentially under constant flow of argon gas. After stirring for 12 h at room temperature, the reaction mixture was filtered through a short pad of celite flushed with ether. The mixture was concentrated in vacuo, and directly subjected to a flash column chromatography on silica gel (Hexane:EA = 4:1) affording indole **33** as an yellow oil (191.2 mg, 99%).; ^{1}H NMR ($CDCl_3$, 400 MHz) δ7.84-7.80 (m, 2H), 7.79-7.73 (m, 2H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.40-7.28 (m, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 6.17-6.02 (m, 1H), 5.22 (d, *J* = 18.4 Hz, 1H), 5.10 (d, *J* = 11.2 Hz, 1H), 4.91 (t, *J* = 6.2 Hz, 1H)3.08-2.91 (m, 2H), 2.82-2.69 (m, 4H), 2.50-2.40 (m, 1H), 2.35-2.24 (m, 1H), 2.20-2.08 (m, 1H), 2.04-1.95 (m, 1H), 1.03 (t, *J* = 7.4 Hz, 3H), -0.52 (s, 9H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 186.70, 167.95, 156.47, 148.15, 139.78, 138.24, 134.01, 132.09, 128.69, 125.48, 123.24, 122.84, 120.45, 115.03, 111.15, 77.33, 66.25, 33.38, 31.16, 30.02, 28.97, 19.57, 14.40, 0.18

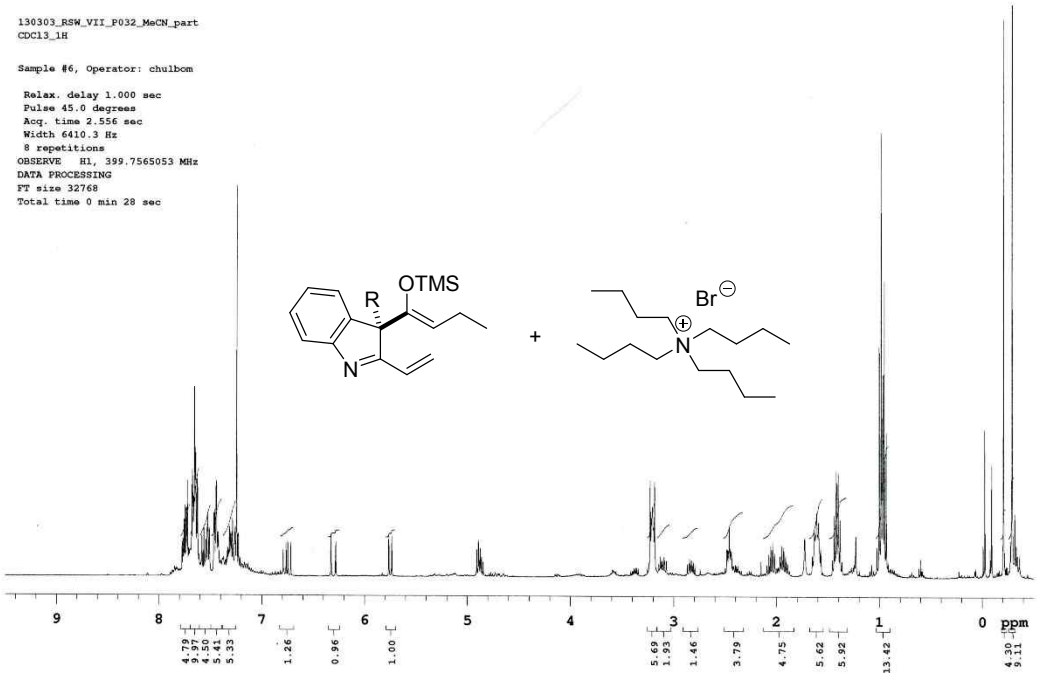


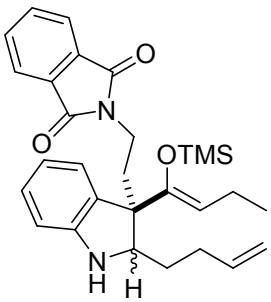
31 34

The Negishi coupling reaction of 31 with vinylzinc bromide-TBAB complex

To a solution of oxindole **27** (17.1 mg, 1.0 equiv) dissolved in DCM (0.4 mL) was added 2-fluoropyridine (4.1 μL, 1.2 equiv) and trifluoromethanesulfonic anhydride (42 μL, 1.0 M in DCM, 1.05 equiv) sequentially under argon atmosphere at -78 ^{o}C. After stirring for 20 min, the mixture was allowed to warm to 0 ^{o}C and stirred for 30 min at 0 ^{o}C before

quenched with saturated aqueous $NaHCO_3$ solution (3 mL). The biphasic mixture was extracted twice with ether (5 mL each) and the combined organics were washed with water (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The resulting triflate was re-dissolved in a small amount of THF (0.4 mL). To the solution of triflate were added $Pd(PPh_3)_4$ (2.31 mg, 0.05 equiv) and the solution was bubbled with argon gas for 10 min. To a solution of zinc bromide (16.2 mg, 1.80 equiv) in THF (0.7 mL) was added vinylmagnesium bromide (72 μL, 1.0 M in THF, 1.80 equiv) at 0 ^{o}C. After stirring for 10 min, tetrabutylammonium bromide (46.4 mg, 3.6 equiv) was added to the vinylzinc bromide solution in one portion. The resulting suspension was transferred to the THF solution of the triflate **31** over 1 h period under constant flow of argon gas at room temperature. After stirring for another 40 min at room temperature, the reaction mixture was filtered through a short pad of celite flushed with ether. The mixture was concentrated *in vacuo* and partitioned between MeCN and hexane (10 mL each). The MeCN layer was washed with hexane twice and concentrated under reduced pressure. The ^{1}H NMR of the crude mixture showed that satisfactory conversion of triflate **31** into vinyl 3H-indole **34** was achieved. Excess TBAB could be washed out with ether/water extraction.

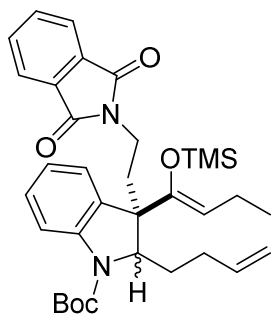




2-(2-(2-(but-3-en-1-yl)-3-((Z)-1-((trimethylsilyl)oxy)but-1-en-1-yl)indolin-3-yl)ethyl)isoindoline-1,3-dione (35)

To a solution of **33** (168.5 mg, 1.0 equiv) in AcOH (6 mL) was added sodium cyanoborohydride (110.8 mg, 5.0 equiv) at 15^{o}C. After stirring for 30 min, the mixture was poured into aqueous ammonia solution (10 mL). The aqueous layer was basified with

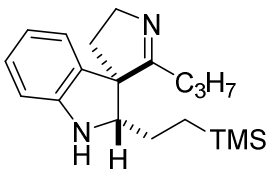
additional aqueous ammonia solution until pH became 8.0-8.5.The aqueous layer was extracted with DCM twice (20 mL) and combined organic layer were dried over $Na_2SO_{4(s)}$ and concentrated *in vacuo*. The resulting oil was further purified by flash column chromatography on silica gel (Hexane:EA = 4:1) affording inseperable diastereomeric mixture of desired indoline **35** as yellow oil (112.7 mg, 67%, 5:1 *dr.*).; ^{1}H NMR ($CDCl_3$, 400 MHz) δ7.88-7.73 (m, 2H), 7.73-7.61 (m, 2H), 7.61-7.41 (m, 1H), 7.13 (d, *J* = 7.6 Hz, minor 1H), 7.09 (d, *J* = 7.4 Hz, major 1H), 7.05 (t, *J* = 7.7 Hz, 1H), 6.85-6.80 (m, minor 1H), 6.80-6.76 (m, major 1H), 6.69 (d, *J* = 7.8Hz, 1H), 6.62 (d, *J*= 7.7 Hz, 1H), 5.97-5.79 (m, 1H), 5.14-5.06 (m, 1H), 5.05-4.97 (m, 1H), 4.83 (t, *J* = 6.8 Hz, major 1H), 4.59-4.54 (t, *J* = 5.6 Hz, minor 1H), 4.07-3.95 (m, 1H), 3.86-3.60 (m, 2H), 3.46-3.31 (m, 1H), 2.35-2.10 (m, 2H), 2.09-1.90 (m, 4H), 1.92-1.71 (m, 2H), 0.98 (t, *J* = 7.5 Hz, major 3H) 0.81 (t, *J* = 7.4 Hz, minor 3H), -0.06 (s, major 9H), -0.30 (s, minor 9H)



***tert*-butyl2-(but-3-en-1-yl)-3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-3-((Z)-1-((trimethylsilyl)oxy)but-1-en-1-yl)indoline-1-carboxylate (36)**

To a solution of **35** (68.4 mg, 1.0 equiv) in DCM (1.4 mL) was added DMAP (1.7 mg, 0.1 equiv) and Boc_2O (39.7 mg, 1.3 equiv) at room temperature under nitrogen

atmosphere. After stirring for 2 h at room temperature, the mixture was concentrated under reduced pressure and directly subjected to flash column chromatography on silica gel (Hexane:EA = 7:1) to afford Boc-protected indoline **36** as colorless oil. (43.0 mg, 52%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ7.82-7.79 (m, minor 2H), 7.78-7.75 (m, major 2H), 7.72-7.63 (m, 2H), 7.53-7.50 (m, minor 1H), 7.49-7.45 (m, major 1H), 7.31-7.23 (m, minor 1H), 7.18-7.00 (m, 2H), 6.81-6.73 (m, 1H), 6.85-6.80 (m, minor 1H), 6.80-6.76 (m, major 1H), 5.97-5.70 (m, 1H), 5.11 (d, *J* = 18.0 Hz, major 1H), 5.03-4.97 (m, 1H), 4.92(d, *J* = 10.8 Hz, minor 1H), 4.81 (t, *J* = 6.6 Hz, 1H), 4.03-3.92(m, 1H), 3.83-3.77 (m, 1H), 3.41-3.35 (m, 1H), 2.33-1.60 (m, 8H), 0.97 (t, *J* = 7.5 Hz, major 3H),0.63-0.20 (br s, 9H), 0.82 (t, *J* = 7.4 Hz, minor 3H), 0.12 (s, minor 9H), -0.09 (s, major 9H)



2'-propyl-2-(2-(trimethylsilyl)ethyl)-4',5'-dihydrospiro[indoline-3,3'-pyrrole] (40)

To a solution of oxindole **27** (22.4 mg, 1.0 equiv) dissolved in DCM (0.5 mL) was added 2-fluoropyridine (5.1 μL, 1.2 equiv) and trifluoromethanesulfonic anhydride (52 μL, 1.0 M in DCM, 1.05 equiv) sequentially under argon atmosphere at -78 ^{o}C. After stirring for 20 min, the mixture was allowed to warm to 0 ^{o}C and stirred for another 30 min at 0 ^{o}C before quenched with saturated aqueous $NaHCO_3$ solution(3 mL). The biphasic mixture was extracted twice with ether (5 mL each) and the combined organics were washed with

water (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The resulting triflate was re-dissolved in THF (0.5 mL). To the solution of triflate **31** were added $Pd(PPh_3)_4$ (5.8 mg, 0.1 equiv), ethynyltrimethylsilane (28 μl, 4.0 equiv), and DIPEA (52 μL, 6.0 equiv) sequentially under constant flow of argon gas. The mixture was warmed up to 45 ^oC with pre-heated oil bath and stirred for 1 h. Then, the reaction mixture was filtered through a short pad of celite flushed with ether. The mixture was concentrated under reduced pressure and re-dissolved in acetic acid (0.5 mL). To the mixture was added sodium cyanoborohydride (15.7 mg, 5.0 equiv) in one portion at 15 ^oC. After stirring for 30 min, the mixture was quenched with aqueous ammonia solution (1.0 mL) and further ammonia solution was added until pH was adjusted to 8-9. The aqueous layer was extracted with DCM (5 mL 3) and combined organic layer were dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was re-dissolved in ethanol (0.5 mL) and hydrazine hydrate (20 μl, 5.0 equiv) was added to the mixture. The mixture was stirred for 4 h at 65 ^oC and concentrated to dryness. The crude mixture was concentrated three times azeotropically with toluene. The resulting solid was filtered and the solid was washed with chloroform. The filtrate was concentrated under reduced pressure and subjected to a flash column chromatography on silica gel affording pyroline **40** as an yellow oil (6.3 mg, 41%). ; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.07 (td, *J* = 7.7, 1.2 Hz, 1H), 6.83-6.80 (m, 1H), 6.74-6.70 (m, 1H), 6.66 (d, *J* = 7.5 Hz, 1H), 4.00-3.90 (m, 1H), 3.86-3.77 (m, 1H), 3.73 (dt, *J* = 11.2, 5.6 Hz, 1H), 2.46 (ddd, *J* = 13.5, 8.2, 5.5 Hz, 1H), 2.33-2.16 (m, 2H), 1.83-1.76 (m, 1H), 1.74-1.53 (m, 3H), 1.49 (tt, *J* = 13.4, 4.3 Hz,1H), 0.91 (t, *J* = 7.4 Hz, 3H), 0.60 (td, *J* = 13.6, 4.6 Hz, 1H),

0.42-0.34 (m, 1H), 0.00 (s, 9H); IR (neat): ν_{max}3362, 2954, 2871, 1636, 1606, 1484, 1466, 1248, 862, 836, 742 cm^{-1}

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국문 초록

(+)-펜드러리딘은 식물로부터 유래된 알칼로이드 천연물로서 특징적인 중심 구조로 인하여 합성계로부터 많은 주목을 받아왔다. 펜드러리딘과 이의 유도체인 1-아세틸-아스피도알비딘에 대한 여러 합성이 보고 되었지만 이들은 비대칭 전합성과 재현성 있는 N,O-케탈의 형성을 동시에 수행하지는 못했다. 이러한 사실들에 비추어 연쇄적 고리화 촉매 반응을 통해 신뢰성 있는 N,O-케탈의 형성과 5각-6각 접합 이중고리를 만드는 접근을 통해 펜드러리딘의 합성을 시도하고자 한다. 이와 함께 비대칭적 옥신돌의 합성법을 이용, 우리의 합성 전략은 (+)-펜드러리딘에 대한 신뢰성 높은 거울상비대칭적 합성 경로를 제공할 것이다.

주요어: (+)-펜드러리딘, 전합성, 거울상 선택적 아실 옮김, 금속 촉매, 연쇄고리화 반응, 산화적 옥시카르보닐화 반응, 연속적 아실화 반응

학번: 2012-20273

감사의 글

정신 차릴 새 없이 지나갔던 지난 4 년여의 시간들을 도중에나마 짚어 볼 수 있는 이 시간에 감사하며, 짧더라도 정성을 담아 감사의 글을 남기고자 합니다.

항상 저를 비롯한 학생들에게 믿음을 가지며 학문적인 길을 지도해주시는 이철범 교수님께 가장 먼저 감사 드립니다. 자유롭지만 주도적이고, 열정적이면서도 책임감 있는 연구자세를 가르쳐 주시기 위해 항상 노력해주시고 세심하고 따뜻한 지도를 해주셨습니다.

지금까지 가장 가까이에서 저의 부족함 점을 지적해주며, 고인 물 마냥 머무르지 않도록 등 뒤를 받쳐주었던 성환, 태교, Caroline heesher, 경민에게 감사의 말을 전하고 싶습니다. 학부생으로서 실험실에 처음 발을 들여 놓았을 때부터 꾸준히 저의 거울이 되어준 진, 호윤, 그리고 희준이 에게도 감사의 말을 전합니다. 같이 동고동락했던 인수형,

동길형 어서 졸업하고 결혼하셨으면 좋겠습니다. 실험실이 시작할 때부터 어마어마한 프로젝트를 이끌어 나가고 있는 동석형, 승주누나, 은혜누나, 바쁜 와중에도 실험적으로, 정신적으로 챙겨주셔서 항상 감사합니다. 지금은 멀리 있지만 항상 서로의 소소한 일상을 공유할 수 있었던 재우, 모두들 항상 바쁜데도 불구하고 좋은 의견을 제시해 준 실험실 사람들 태훈, 성현형, 성미, 현정누나, 선우형, 혜진누나, 명수형, 지현누나, 희경이, 여울이 모두 감사드립니다. 정신없이 지내느라 충분한 지도를 해주지 못한 것 같은 호준, 영현, 인환, 도원, Brian 에게는 감사함과 동시에 미안하다는 말을 하고 싶습니다. 실험실 사람들 모두 진행하고 있는 연구가 잘 되었으면 좋겠고, 올해에는 모든 전합성 프로젝트가 마무리 되었으면 좋겠습니다.

마지막으로 항상 옆에서 물심양면 지원을 아끼지 않고 지켜봐 준 가족들에게 무한한 감사함을 전하고 싶습니다.

SPECTRA

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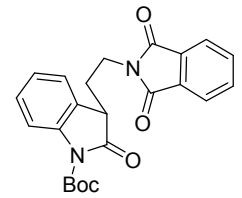

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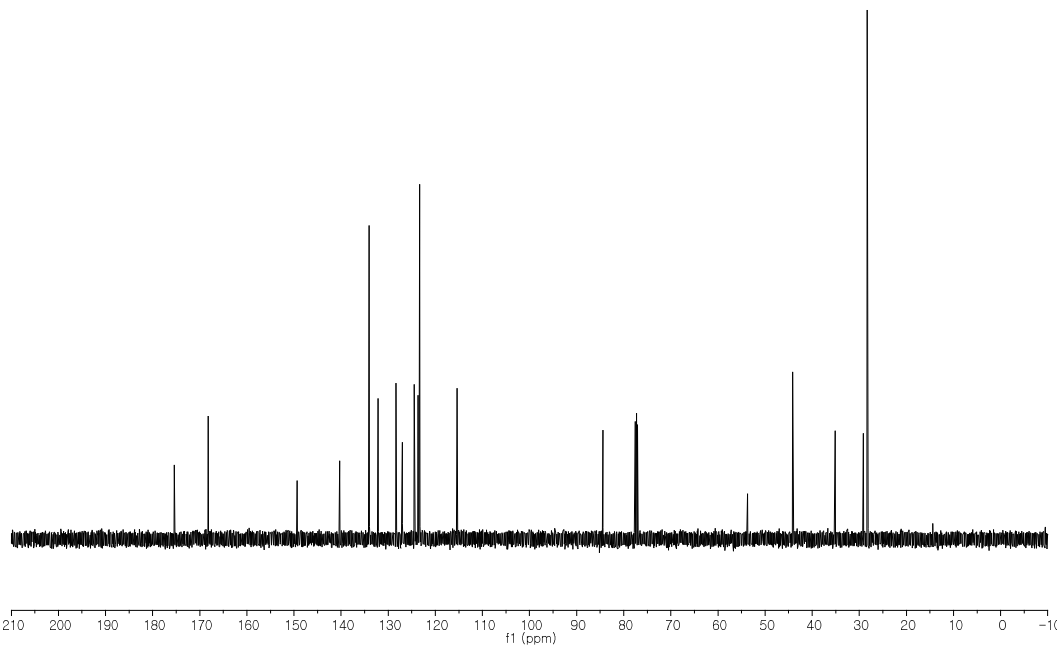

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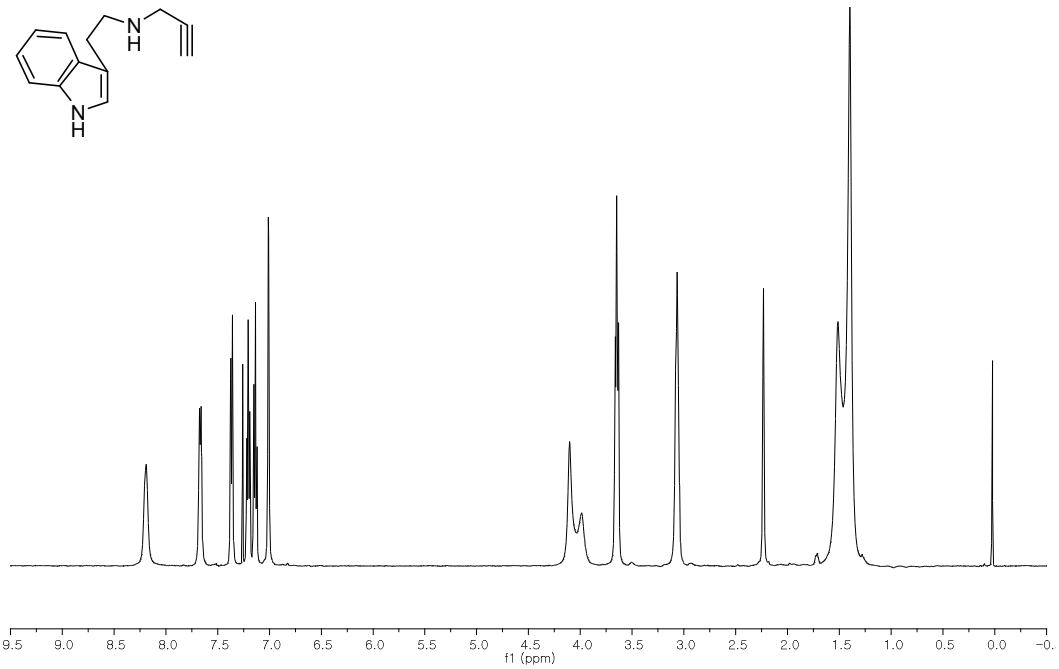
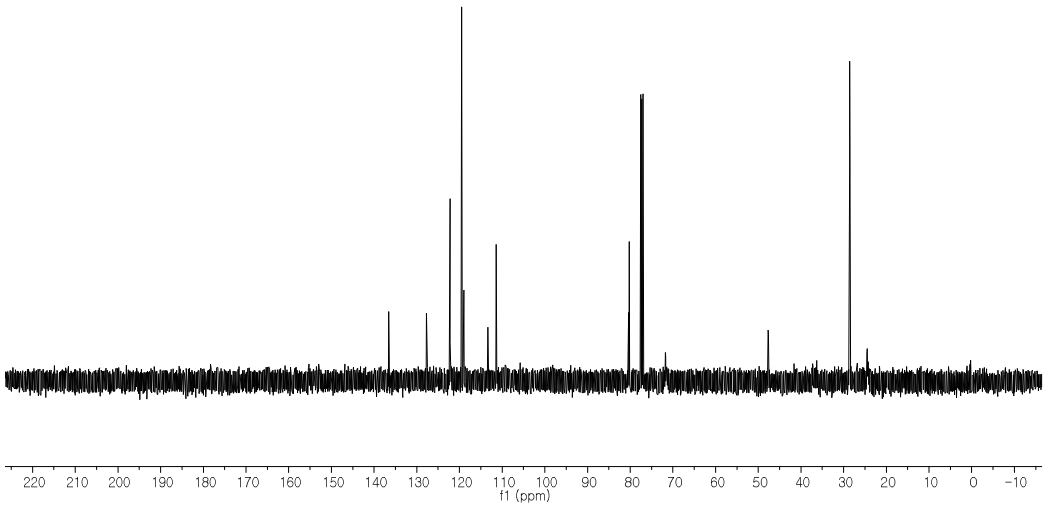
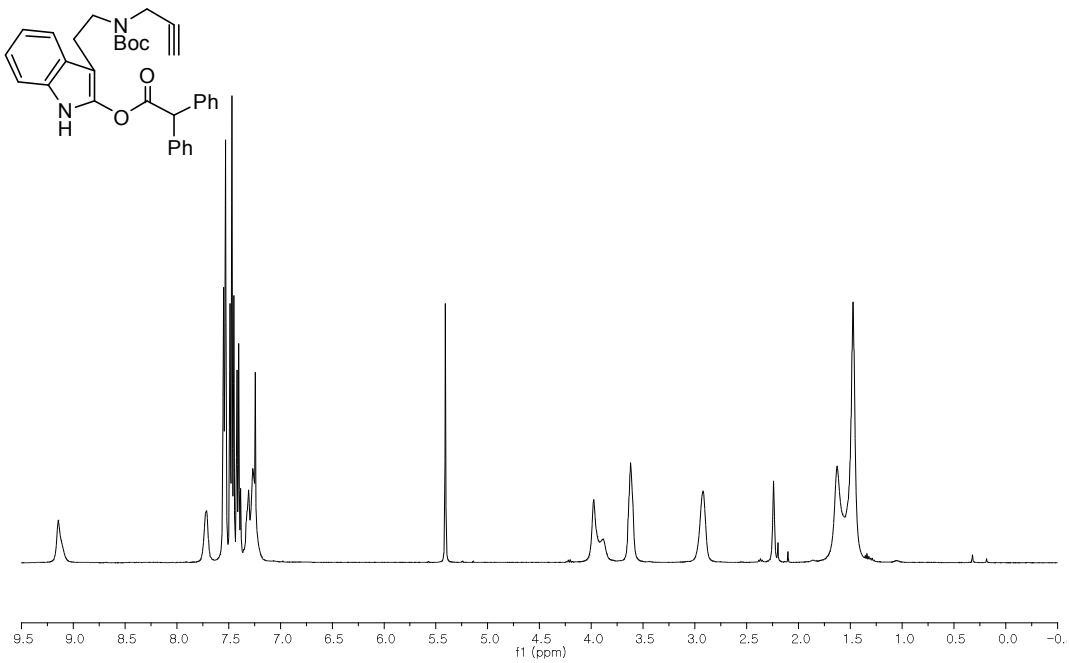
CDCl3_1H



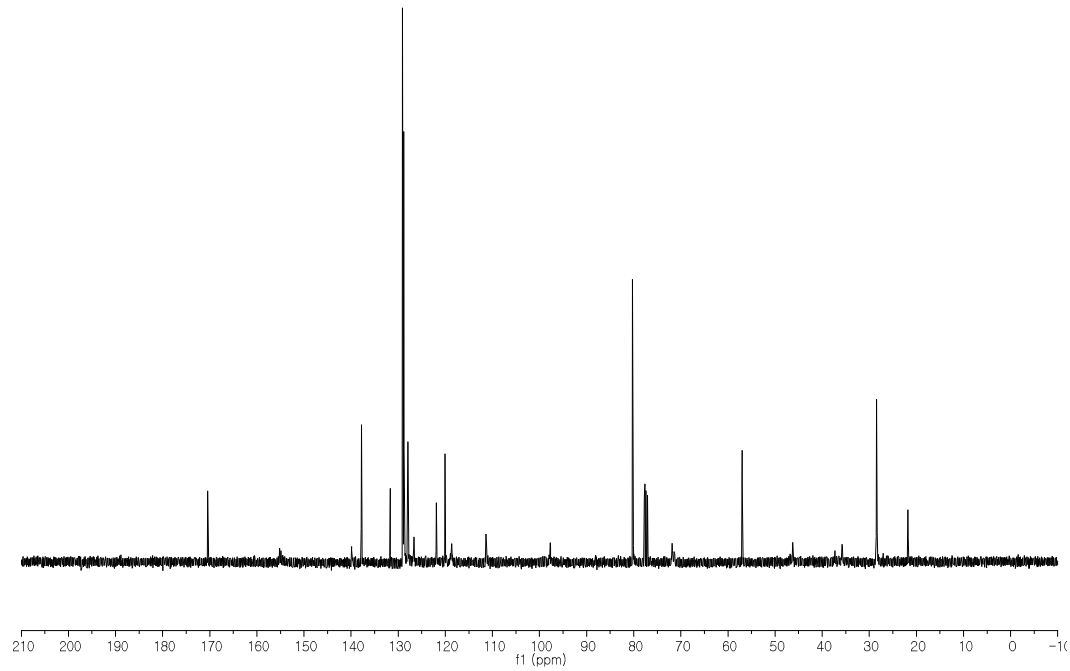
120707_RSW_IV_P058_Product_CDCl3_13C
120707_RSW_IV_P058_Product
CDCl3_13C



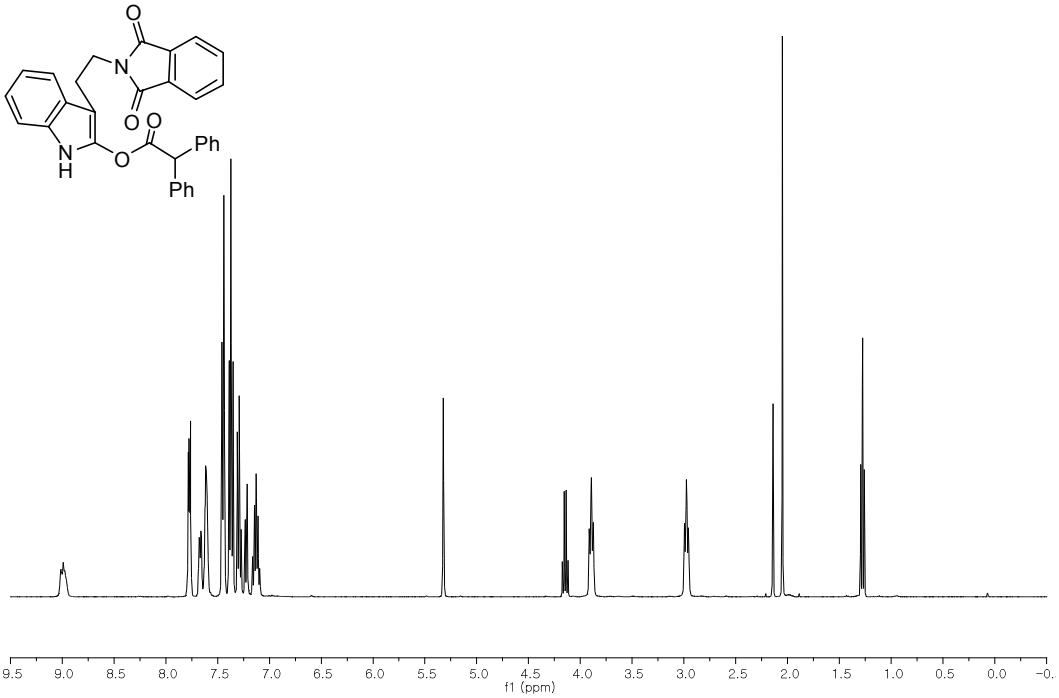
120722_RSW_IV_P071_Product_CDCl3_1H
120722_RSW_IV_P071_Product
CDCl3_1H



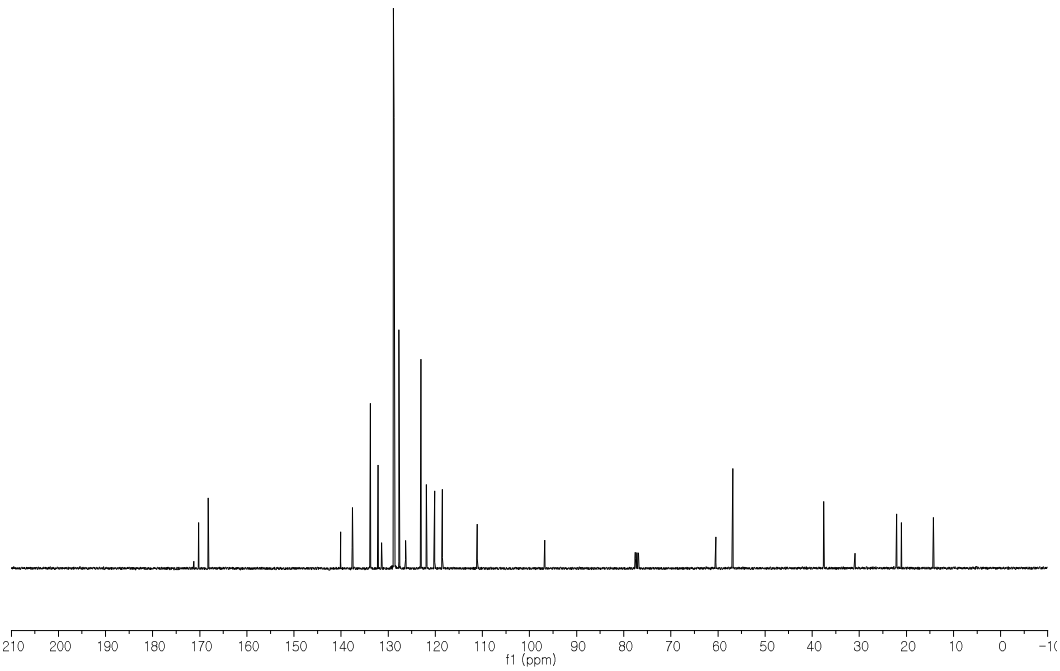
120722_RSW_IV_P071_Product_CDCl3_13C
120722_RSW_IV_P071_Product
CDCl3_13C



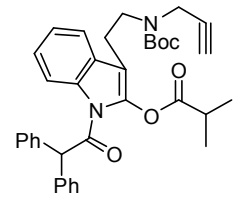
121019_RSW_V_P037_Product_CDCl3_1H

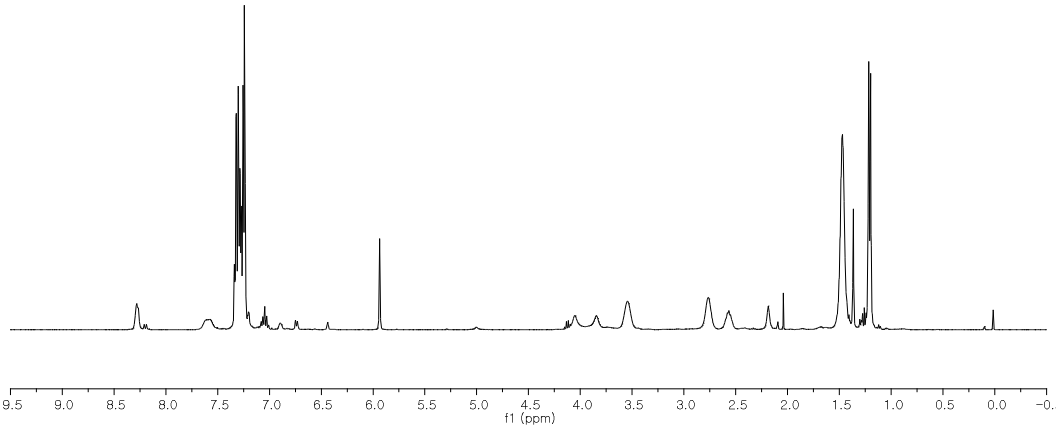


121019_RSW_V_P037_Product_CDCl3_13C

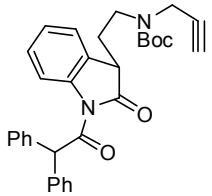


120718_RSW_IV_P069_Product_CDCl3_1H
120718_RSW_IV_P069_Product
CDCl3_1H

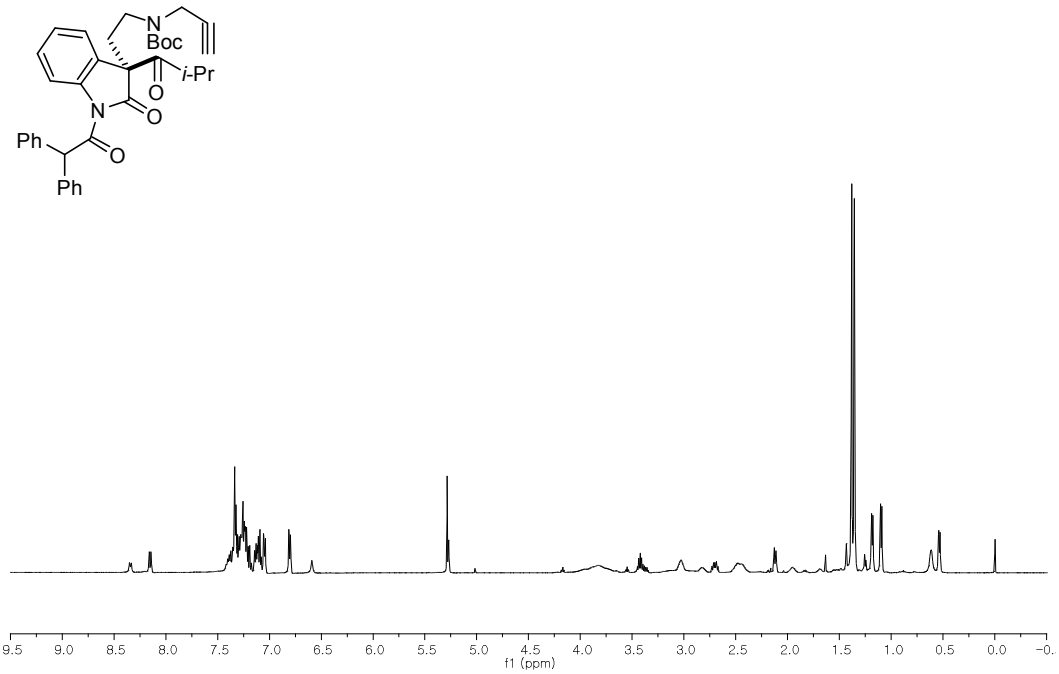




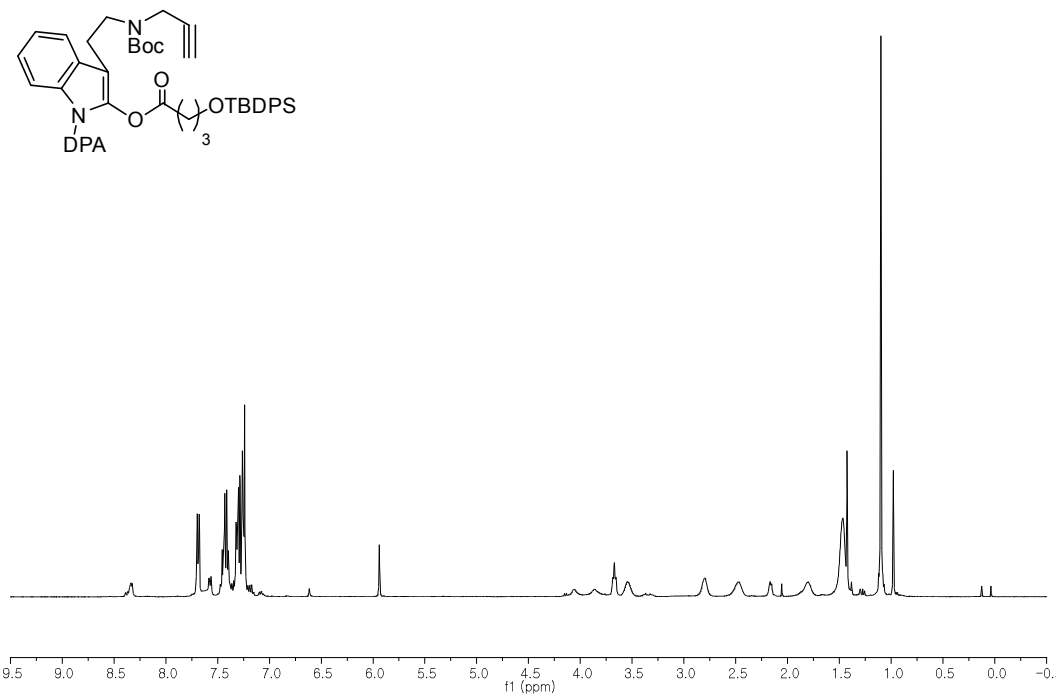
120621_RSW_IV_P049_tt_23_24_spot_C_CDCl3_1H
120621_RSW_IV_P049_tt_23_24_spot_C
CDCl3_1H



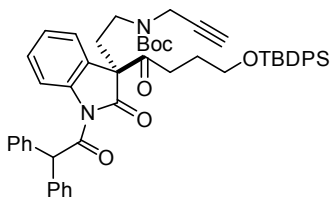
120621_RSW_IV_P049_tt_12_13_spot_A_CDCl3_1H
120621_RSW_IV_P049_tt_12_13_spot_A
CDCl3_1H



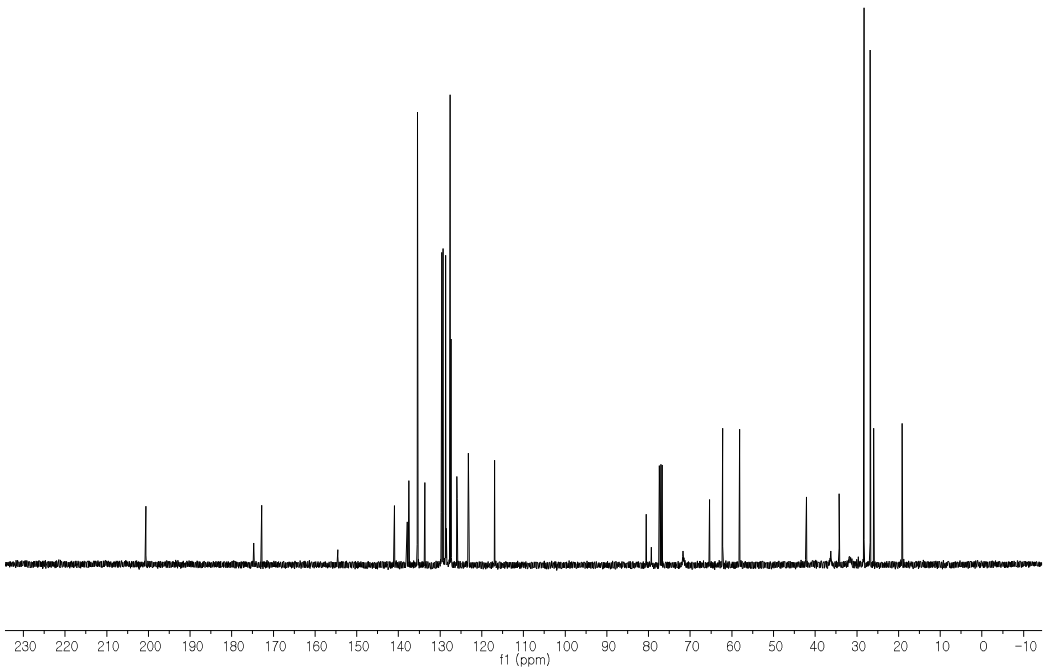
120731_RSW_IV_P074_Product_CDCl3_1H



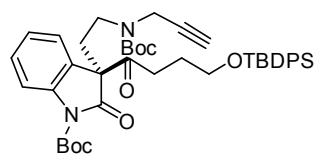
120801_RSW_IV_P077_Product_CDCl3_1H
Gradient Shimming



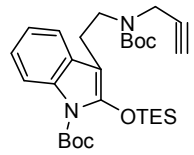
120801_RSW_IV_P077_Product_CDCl3_13C
Gradient Shimming



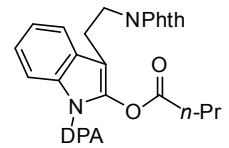
120910_RSW_V_P007_Product_CDCl3_1H
Gradient Shimming

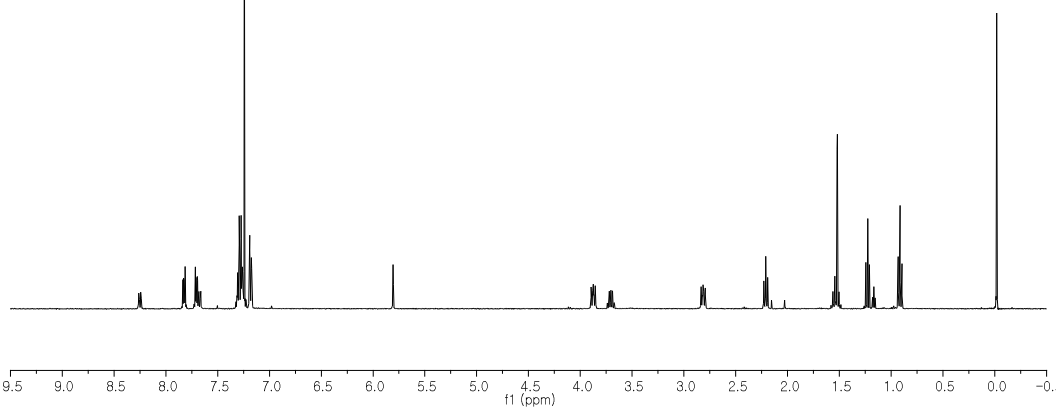


120923_RSW_V_P019_spot_A_with_decomposed_spot_CDCl3_1H
120922

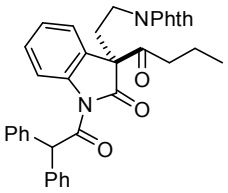


121020_RSW_V_P038_recrystallization_from_EtOH_CDCl3_1H

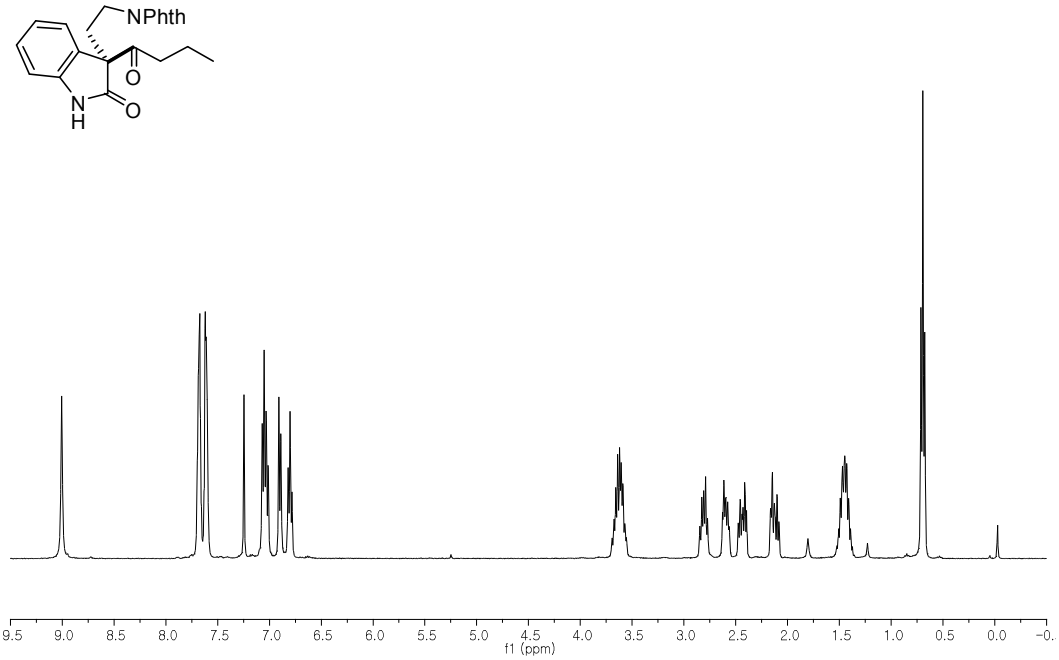


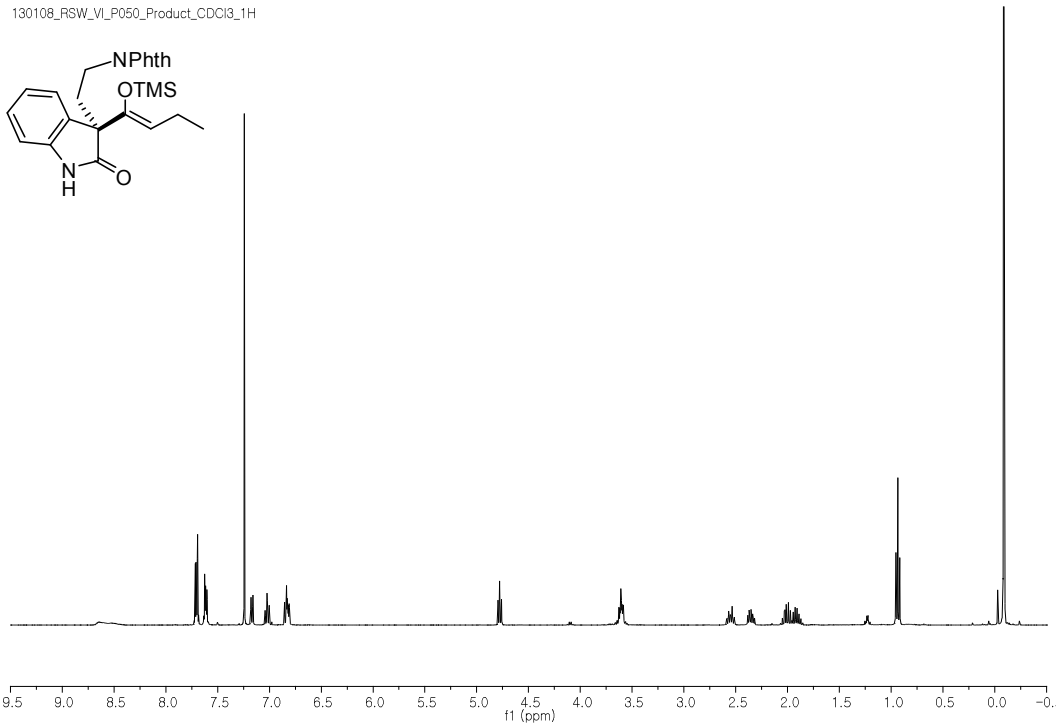


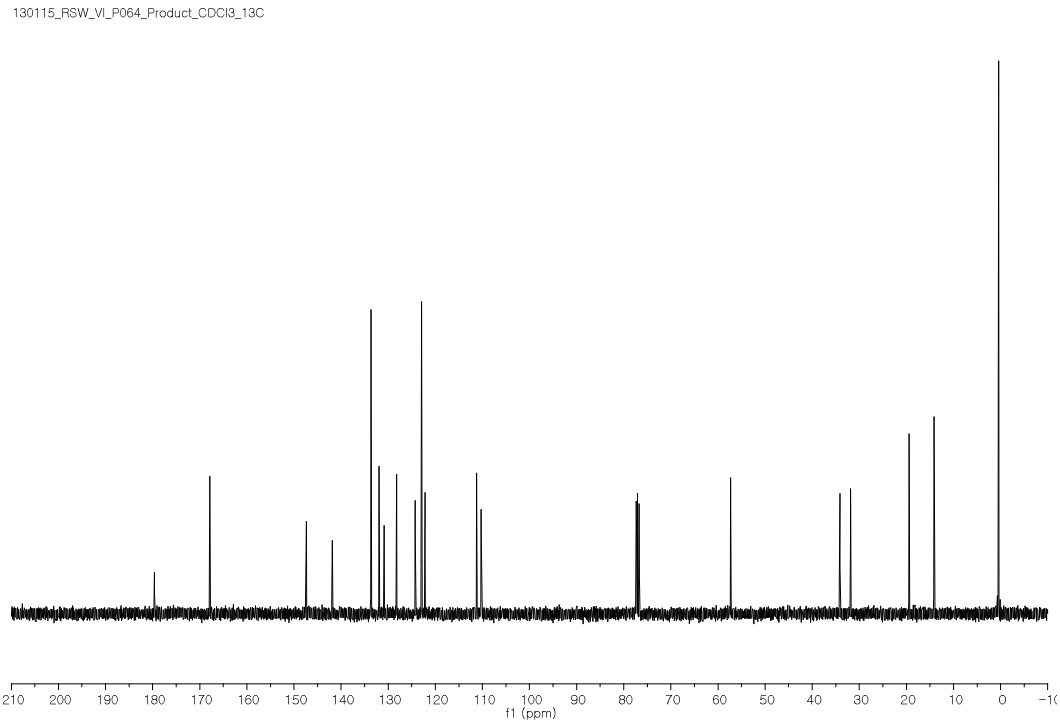
121021_RSW_V_P031_3rd_crop_CDCl3_1H
Gradient Shimming



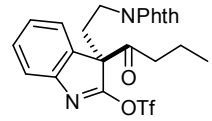
121226_RSW_VI_P040_Product_CDCl3_1H
121226_RSW_VI_P040_Product
CDCl3_1H



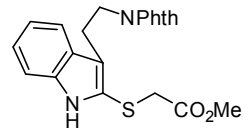

130108_RSW_VI_P050_Product_CDCl3_1H
NPhth
OTMS
N
H
O
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


130115_RSW_VI_P064_Product_CDCl3_13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

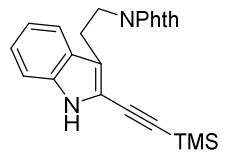
121023_RSW_V_P041_spot_A_CDCl3_1H

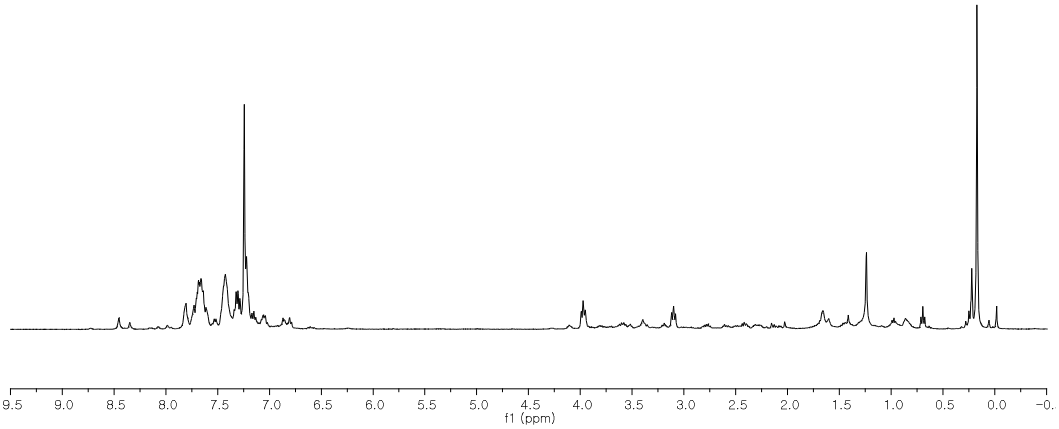


121227_RSW_VI_P041_spot_C_major_A_CDCl3_1H



121023_RSW_V_P042_Crude_CDCl3_1H

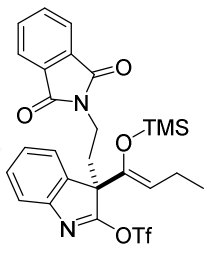


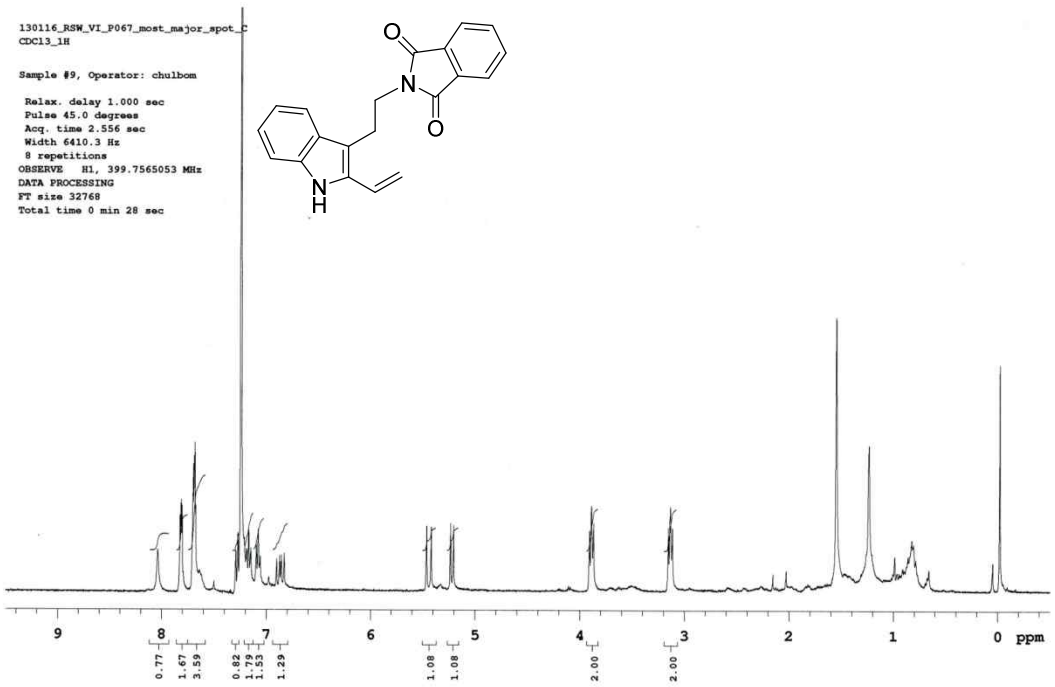


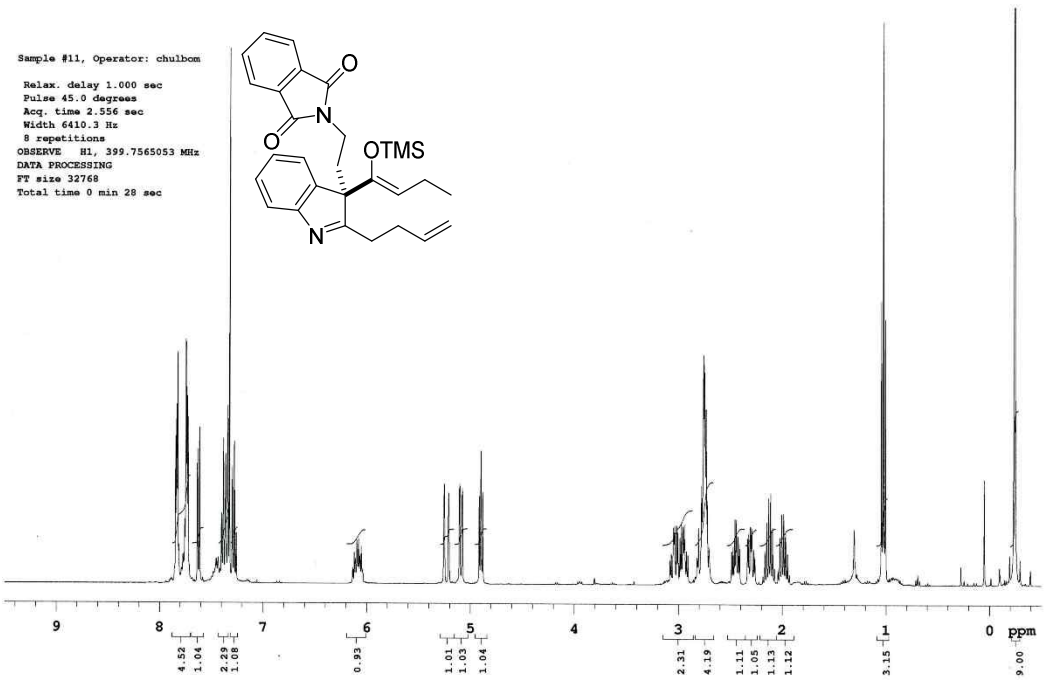
130107_RSW_VI_P051_Crude
CDCl3_1H

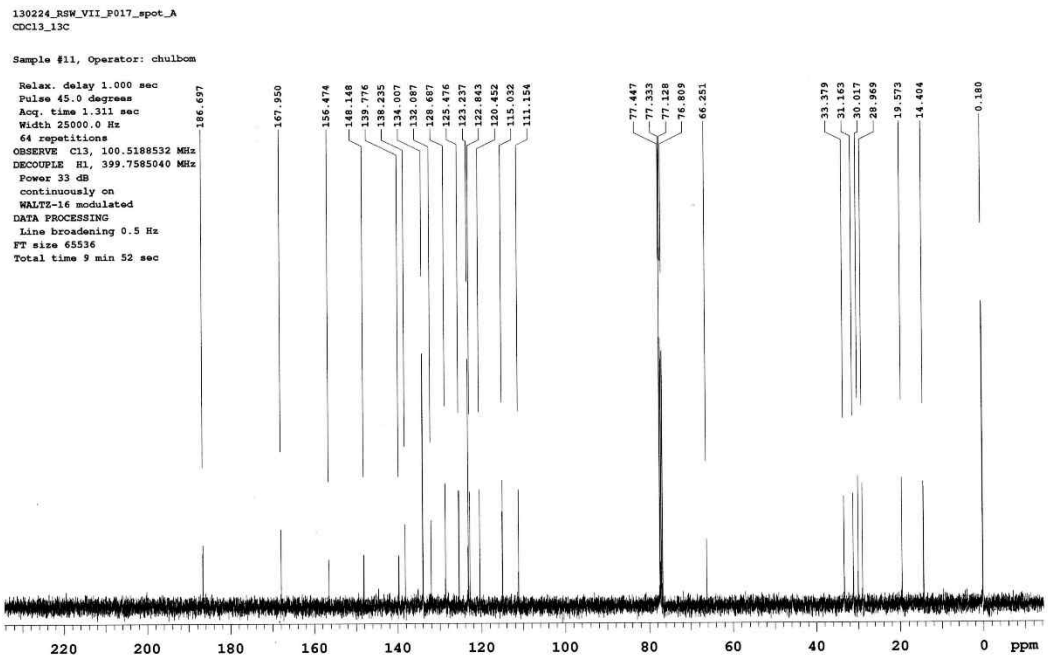
Operator: chulbom

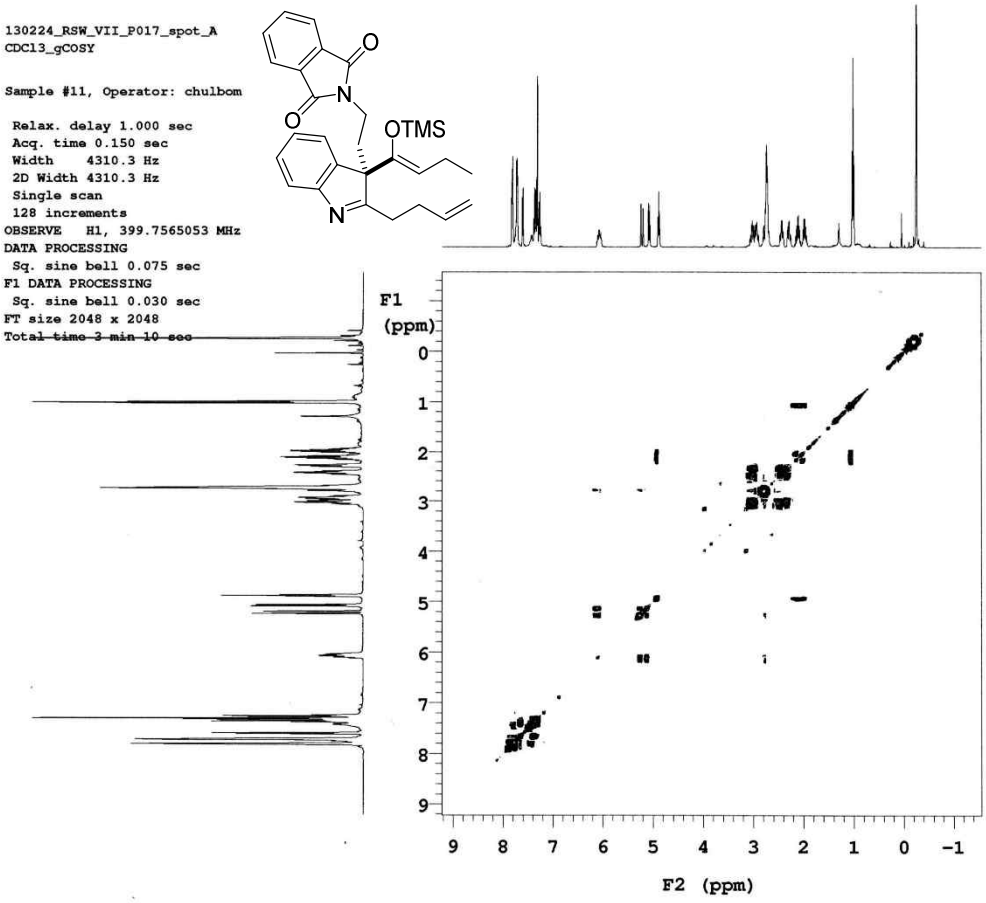
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
16 repetitions
OBSERVE H1, 399.7565053 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 57 sec

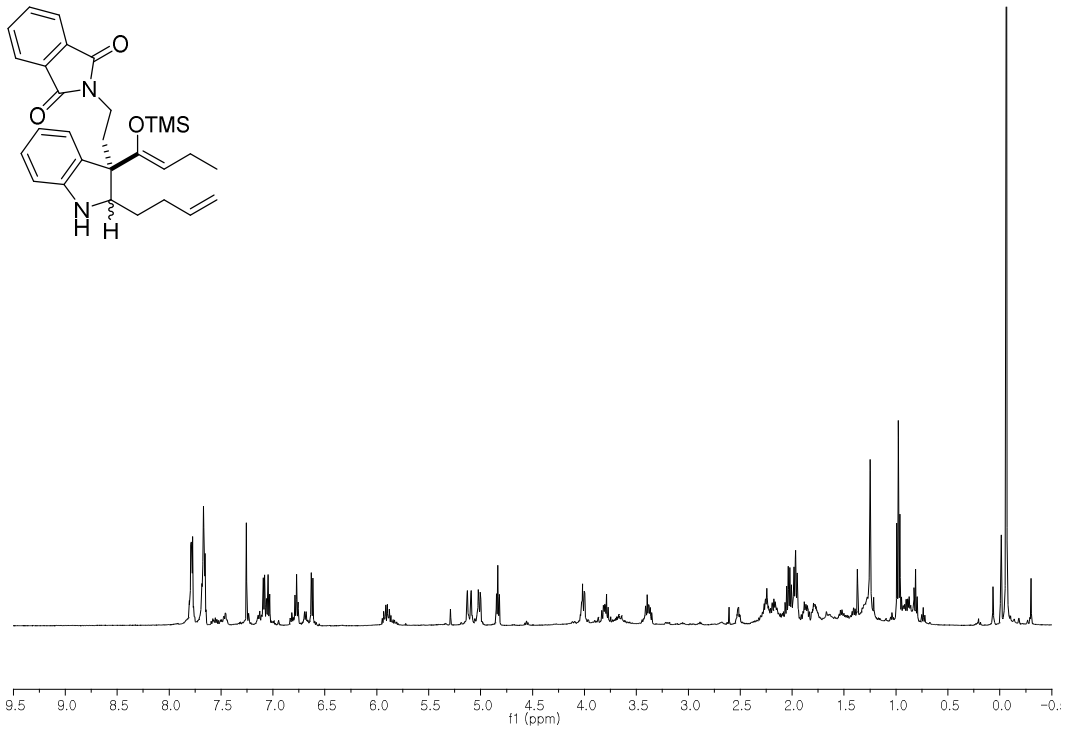


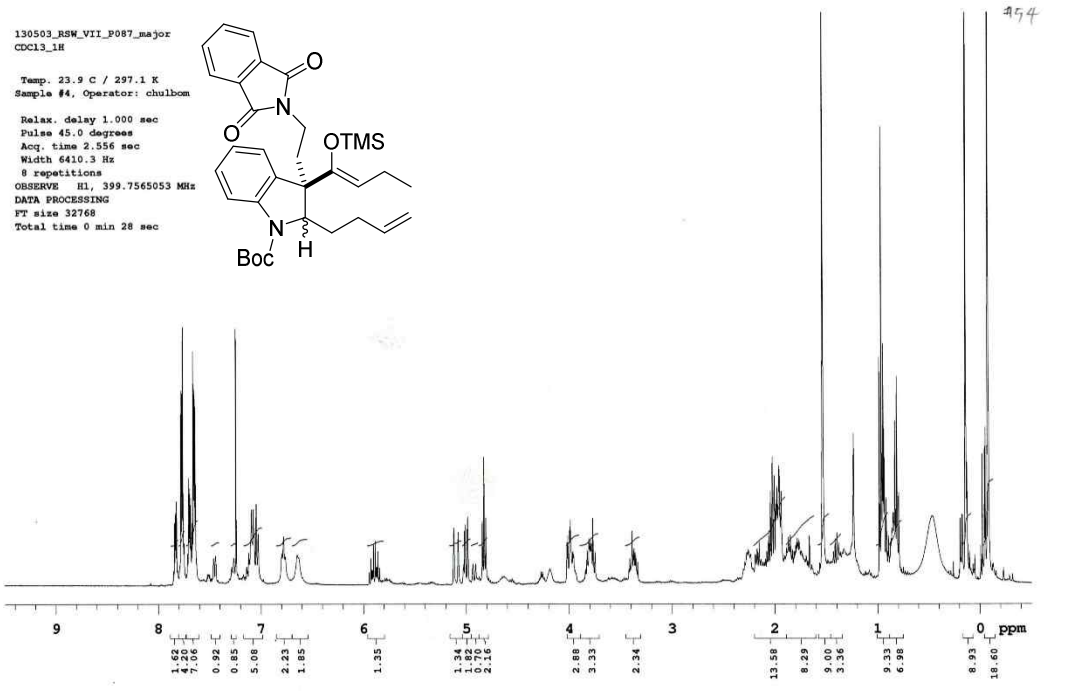

130116_RSW_VI_P067_most_major_spot_C
CDCl3_1H
Sample #9, Operator: chulbom
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7565053 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 28 sec
O
N
O
N
H
9
8
7
6
5
4
3
2
1
0 ppm
0.77
1.67
3.59
0.82
1.79
1.53
1.29
1.08
1.08
2.00
2.00


Sample #11, Operator: chulbom
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7565053 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 28 sec
O
N
O
OTMS
N
9
8
7
6
5
4
3
2
1
0 ppm
4.52
1.04
2.29
1.08
0.93
1.01
1.03
1.04
2.31
4.19
1.11
1.05
1.13
1.12
3.15
9.00

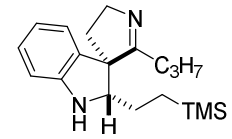

130224_RSW_VII_P017_spot_A
CDCl3_13C
Sample #11, Operator: chulbom
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.311 sec
Width 25000.0 Hz
64 repetitions
OBSERVE C13, 100.5188532 MHz
DECOUPLE H1, 399.7585040 MHz
Power 33 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 9 min 52 sec
186.697
167.950
156.474
148.148
139.776
138.235
134.007
132.087
128.697
125.476
123.237
122.843
120.452
115.032
111.154
77.447
77.333
77.128
76.809
66.251
33.379
31.163
30.017
28.969
19.573
14.404
0.180
220
200
180
160
140
120
100
80
60
40
20
0 ppm


130224_RSW_VII_P017_spot_A
CDCl3_gCOSY
Sample #11, Operator: chulbom
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 4310.3 Hz
2D Width 4310.3 Hz
Single scan
128 increments
OBSERVE H1, 399.7565053 MHz
DATA PROCESSING
Sq. sine bell 0.075 sec
F1 DATA PROCESSING
Sq. sine bell 0.030 sec
FT size 2048 x 2048
Total time 3 min 10 sec
O
N
O
OTMS
N
F1
(ppm)
0
1
2
3
4
5
6
7
8
9
9 8 7 6 5 4 3 2 1 0 -1
F2 (ppm)


O
N
O
OTMS
N
H
H
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


130503_RSW_VII_P087_major
CDCl3_1H
Temp. 23.9 C / 297.1 K
Sample #4, Operator: chulbom
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7565053 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 28 sec
O
N
O
OTMS
N
H
Boc
9 8 7 6 5 4 3 2 1 0 ppm

130813_RSW_VIII_P061_product_CDCl3_1H
KTH_IV_12_pr

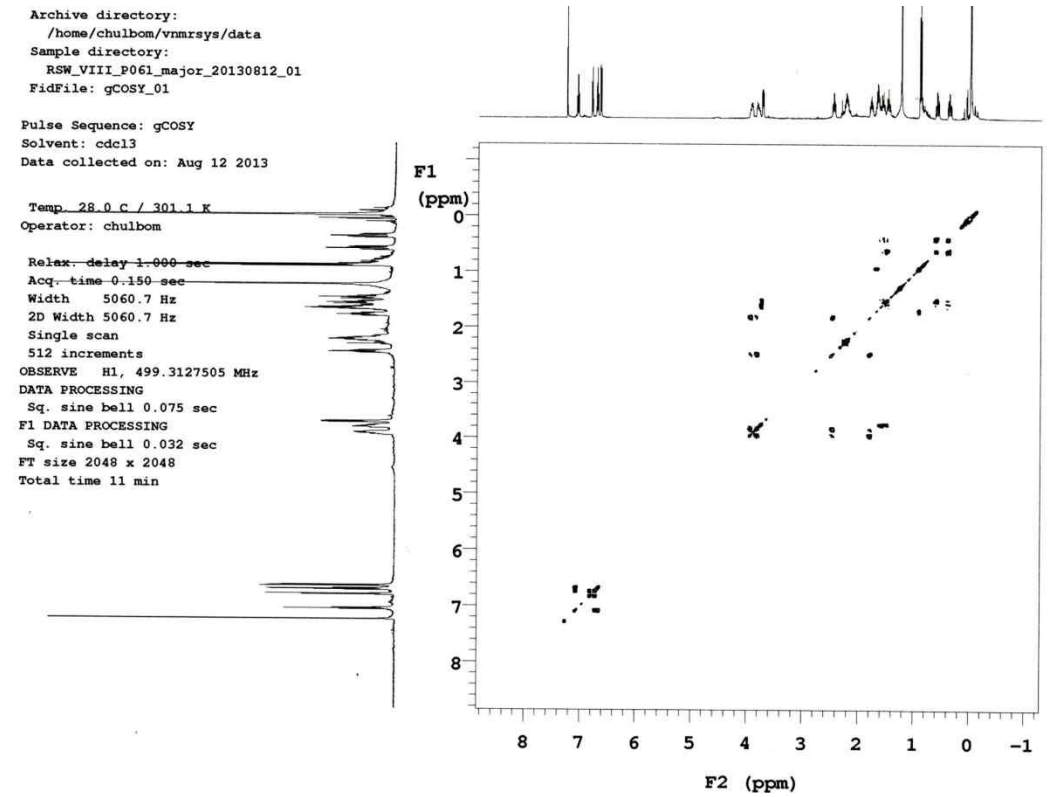


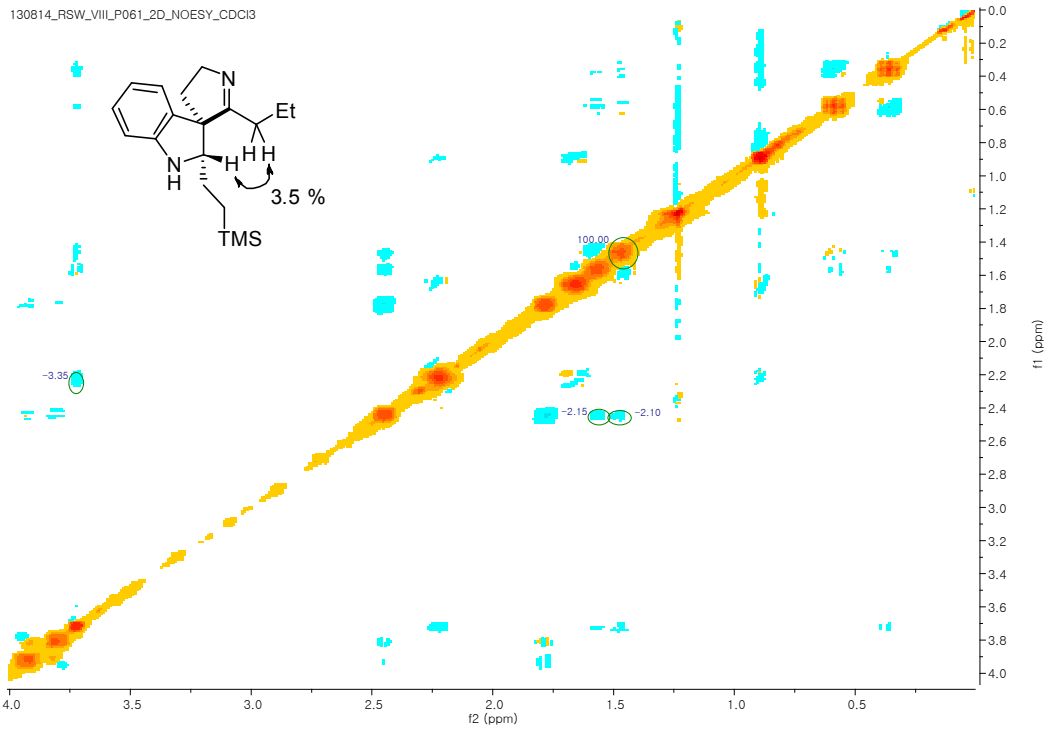
Archive directory:
/home/chulbom/vnmrsys/data
Sample directory:
RSW_VIII_P061_major_20130812_01
FidFile: gCOSY_01

Pulse Sequence: gCOSY
Solvent: cdcl3
Data collected on: Aug 12 2013

Temp. 28.0 C / 301.1 K
Operator: chulbom

Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 5060.7 Hz
2D Width 5060.7 Hz
Single scan
512 increments
OBSERVE H1, 499.3127505 MHz
DATA PROCESSING
Sq. sine bell 0.075 sec
F1 DATA PROCESSING
Sq. sine bell 0.032 sec
FT size 2048 x 2048
Total time 11 min




130814_RSW_VIII_P061_2D_NOESY_CDCl3
N
Et
H H
N
H
H
3.5 %
TMS
100.00
-3.35
-2.15
-2.10
f2 (ppm)
f1 (ppm)