Natural Product Synthesis via Indium Catalyzed Friedel-Crafts Alkylation

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Natural Product Synthesis via Indium Catalyzed Friedel-Crafts Alkylation

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Abstract

Natural products are becoming an increasingly valuable resource in the design and development of new drug candidates. Since 2009 natural products have grossed over $16 billion (U.S. dollars) producing 10 out of the top 20 best-selling drugs on the market. Flinderoles, natural products isolated from the Flindersia plant found in Papua New Guinea, are garnering interest in the synthetic organic community due to their antimalarial properties, especially against chloroquine-resistant strains. Malaria is an infectious disease caused by the parasite *Plasmodium falciparum* which in 2010 led to 216 million cases worldwide, claiming 655,000 victims. Based on previous research in synthesizing 1*H*-pyrrolo[1,2-*a*]indole frameworks via an indium catalyzed intramolecular Friedel-Crafts alkylation, we propose an efficient methodology for the synthesis of Flinderole C using a similar protocol. The compound will be synthesized in seven linear steps from tryptamine derivatives becoming shorter than previously reported synthesis (11 linear steps). If proven successful, this scheme will provide efficient alternatives to synthesizing large heteroaromatic-based natural products, aiding in the search for new drug candidates.

Introduction

A plethora of natural products serve as inspiration for many potent therapeutic and pharmaceutically relevant compounds. In the pharmaceutical industry, many discoveries of novel drugs and medical breakthrough have stemmed from the isolation of natural products. Assaying natural products is one of the most reliable strategies of drug discovery and development grossing over $16 billion (U.S. dollars) since 2009 and producing 10 of the top 20 best-selling drugs.[1] Indole tryptamines, along with their analogs, are recognized as potent 5-HT receptor antagonists[2] and are considered privileged structures due their binding properties and diverse

biological targeting.[3] In particular, the pyrrolo[1,2-*a*]indole and hydropyrido[1,2-*a*]indole frameworks have been recognized as key structural motifs in many anticancer, antimalarial, and psychoactive compounds. Mersicarpine and leuconoxine are hydropyrido[1,2-*a*]indoles that have cytotoxic effects against cancer while flinderole C and yuremamine are pyrrolo[1,2-*a*]indoles with antimalarial and psychoactive properties, respectively (Figure 1).

Due to their large *N*-fused heteroaromatic cores, these molecules are difficult to synthesize, thereby emphasizing the need to find less harsh and high-yielding routes to produce these compounds. The heart of our research is focused on using a Lewis acid-catalyzed intramolecular Friedel-Crafts alkylation to offer a modular approach to the synthesis of complex natural products. To test our methodology we started by cyclizing substituted alkenes and cyclopropyl rings into 2,3-dihydro-*1H*-pyrrolo[1,2-*a*]indole and hydropyrido[1,2-*a*]indole cores, respectively (Figure 1). A plethora of electron donating and withdrawing bearing compounds were constructed and readily cyclized, establishing the versatility of our protocol.[4] Our success with cyclizations of 3-methylindole warranted further exploration into using 2-methylindole to access the reactivity of the 7-position on the indole ring. By blocking the 2-position with a functional group, the Friedel-Crafts alkylation is forced to occur from the indole 7-position generating the pyrrolo[3,2,1-*ij*]quinoline core. This intramolecular cyclization efficiently

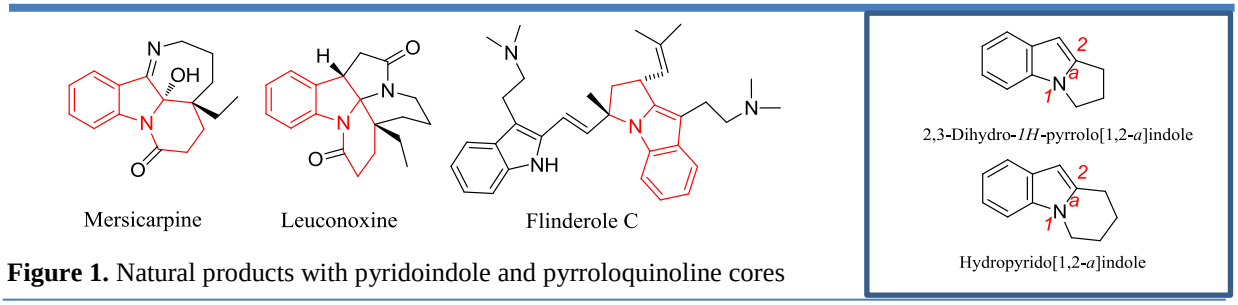


Figure 1. Natural products with pyridoindole and pyrroloquinoline cores

generated the 6-5-6 membered scaffold from a wide scope of substituted alkenes. Success with intramolecular Friedel-Craft alkylations inspired our novel retrosynthetic approach to

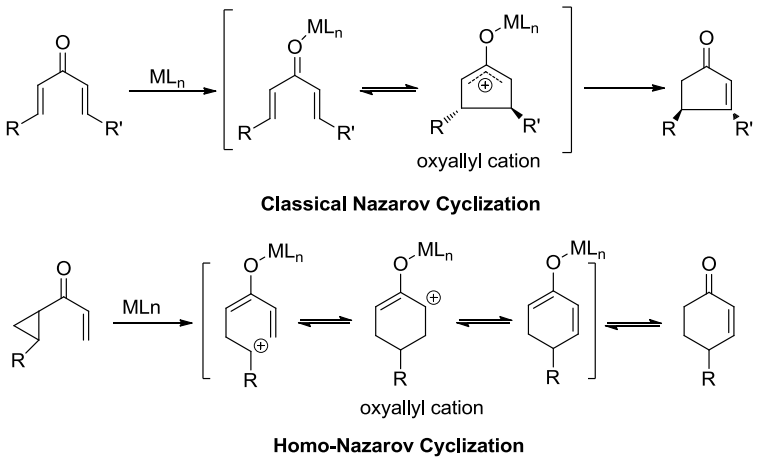
synthesizing flinderole C. In this new route, the two halves of flinderole C will be synthesized separately and coupled together via a copper-promoted conjugate addition. Dethe reported a biomimetic synthesis affording 17% yield using 11 linear steps.[5] The original synthesis by Toste et al. consisted of 4% yield over 18 total steps (longest linear sequence 14 steps).[6] Our methodology will drastically reduce the number of reactions and become the shortest linear sequence published, seven steps. Success with this synthesis will demonstrate the versatility of acid-catalyzed diastereoselective intramolecular Friedel-Crafts alkylation to synthesize large, substituted heteroaromatic compounds and serve as an effective tool for the synthesis of other complex natural products.

Synthesis of Hydropyrido[1,2-a]indole-6(7*H*)-ones

(In collaboration with Dadasaheb Patil and Marchello Cavitt)

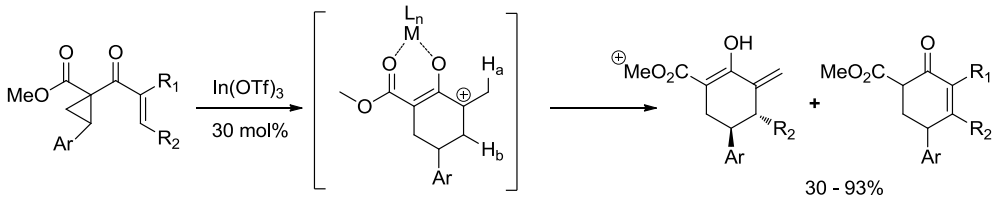
The hydropyrido[1,2-*a*]indole framework, in particular its C(6)-oxidized congeners, occur in an impressive number of natural indole alkaloids and therapeutic compounds.[4] Though the synthesis of these compounds is reported, many approaches require the use of harsh reaction conditions, toxic reactants, and inefficient multi-step mechanisms to synthesize N-fused 6-5-6 heteroaromatic rings.[7] By utilizing an electrocyclic ring closure via a Lewis acid-catalyzed intramolecular Friedel-Crafts alkylation of the indole core, we offer an efficient and modular approach to synthesizing hydropyrido[1,2-*a*]indole-6(7*H*)-ones from 3-methylindole; a relatively cheap, commercially available starting material.

Our new approach stems from our previous research with the Nazarov and homo-Nazarov cyclizations. The Nazarov cyclization utilizes a Lewis/Brønsted acid to catalyze electrocyclic ring closure of a divinyl ketone to afford cyclopentanones.[8] This concept has been further adapted into the homo-Nazarov cyclization which cyclizes vinyl-cyclopropyl ketones into cyclohexanones via a Lewis/Brønsted acid facilitated formation of an intermediate cyclic oxyallyl cation, followed by electrocyclic ring closure (Scheme 2).[9] Though the Nazarov



Scheme 1. Nazarov and homo-Nazarov cyclizations[8,9]

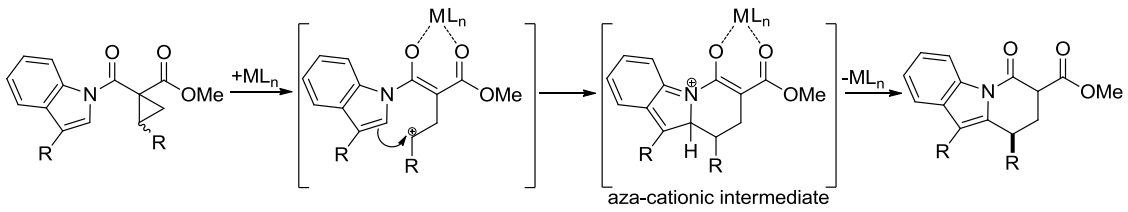
cyclization is well researched (over 500 publications), the homo-Nazarov mechanism is not (only five total publications) due to a lack of generality, poor yields (16-63%), and harsh reaction conditions.[9] To solve these shortcomings, we envisioned using donor-acceptor cyclopropyl vinyl ketones bearing an α'-positioned ester (another secondary acceptor) to facilitate cyclization through localizing the charge density on the cyclic oxyallyl cation intermediate (Scheme 2).[9] This scheme proved to be extremely successful, affording cyclized products of substituted



Scheme 2. Basic protocol of previous research with homo-Nazarov cyclization[9]

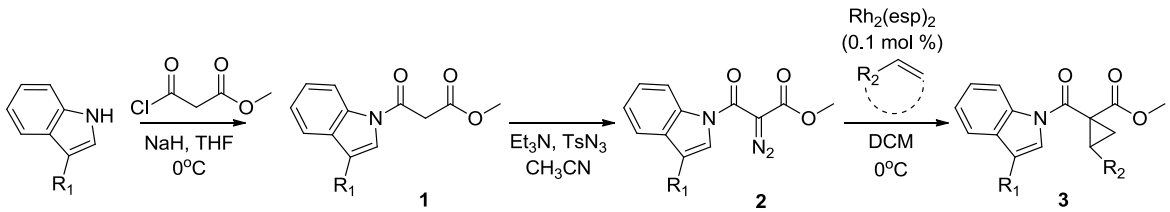
alkenes and cyclopropanes with yields ranging from 30-93%.[9] Our success with this methodology was an invaluable asset in our exploration of the synthesis of 3-substituted hydropyrido[1,2-*a*]indole-6(7*H*)-ones.

By utilizing a similar protocol, we explored the scope and limitations of synthesizing hydropyrido[1,2-*a*]indole-6(7*H*)-ones from *N*-acylindole β-keto esters. Our approach involved Lewis-acid catalyzed cyclopropane ring-opening to generate a carbocation followed by an intramolecular Friedel-Crafts alkylation of the indole, proceeding through an aza-cationic intermediate, to generate the newly formed *N*-fused 6-membered ring (Scheme 3).[4] To begin



Scheme 3. Intramolecular cyclopropane ring opening/Friedel-Craft alkylation[1]

our study, we developed a modular preparation of the various cyclization precursors. Starting from 3-methylindole an *N*-acylation with commercially-available methyl malonyl chloride was conducted affording the 1,3-dicarbonyl scaffold (**1**). A diazo transfer using triethylamine and tosyl azide provided the α-diazoester (**2**). Cyclopropanation with $Rh_2(esp)_2$



Scheme 4. Modular preparation of cyclopropyl precursors[1]

(bis[rhodium(α,α,α',α'-tetramethyl-1,3-benzenedipropionic acid)]) in the presence of a requisite alkene constructs the desired methyl 1-(1 *H*-indole-carbonyl)-1-cyclopropanecarboxylate (**3**) with yields up to 70% over the three steps (Scheme 4).[4] By changing the alkene during cyclopropanation, we were able to generate a wide variety of substrates with various electronic properties.

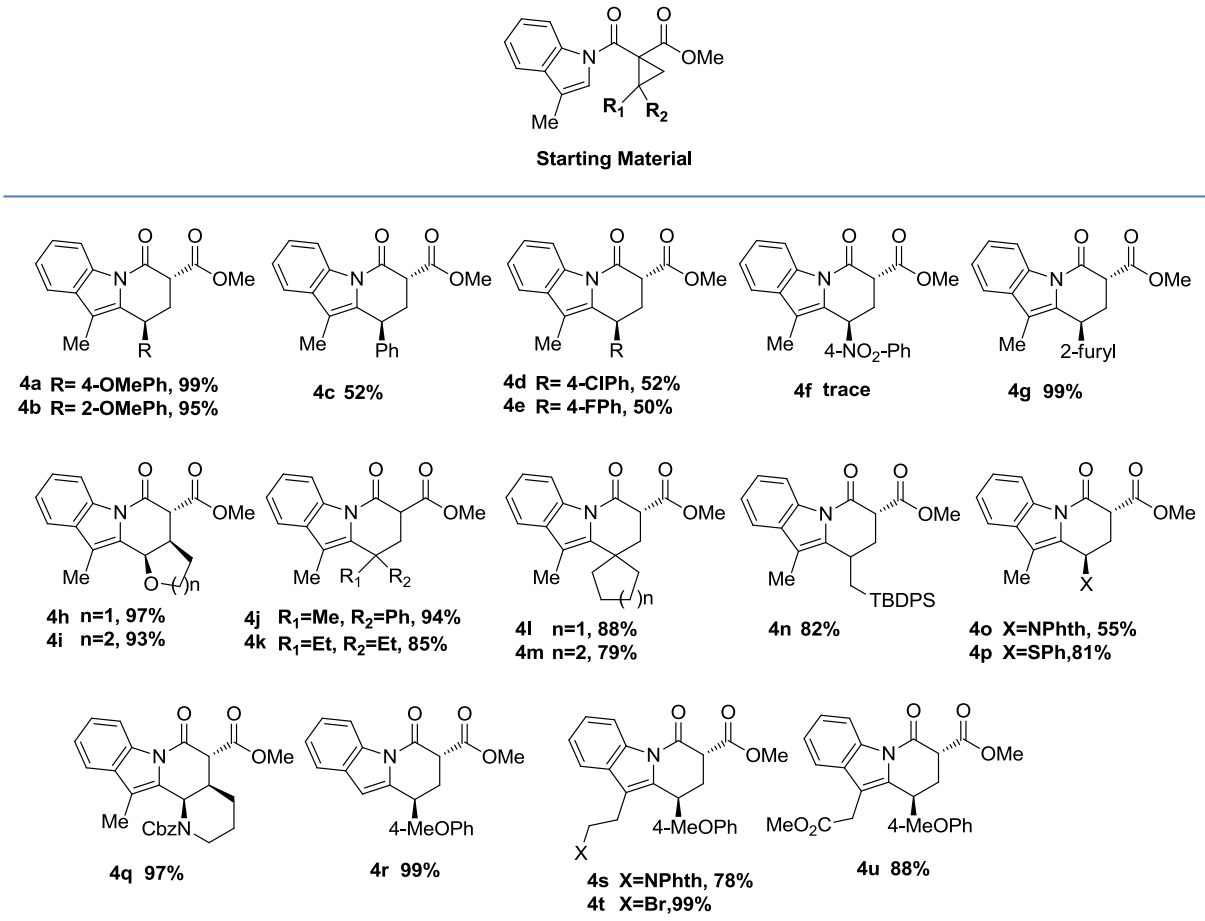


Figure 2. Substrate scope and yields of products[4]

Starting with donor substituted cyclopropanes, cyclizations were assayed using indium triflate (our prescreened catalyst). As seen in Figure 2, the hydropyrido[1,2-*a*]indole products were generated for 2 and 4-methoxy phenyl cyclopropane in near quantitative yields (**4a**, **4b**).

Next, electron withdrawing *para*-substituted phenyl, 4-fluorophenyl, 4-chlorophenyl, and 4-nitrophenyl cyclopropanes were cyclized (**4c, 4d, 4e**, and **4f**). Interestingly, room temperature cyclizations in DCM using 30 mol% $In(OTf)_3$ yielded no reaction (only starting material), while reflux in 1,2-dichloroethane afforded cyclization with yields ranging from 50% to 52%; though only trace amounts of cyclized 4-nitrophenyl was generated as identified in ^1H NMR spectrum of the crude product. A 2-furyl heteroaromatic donor group (**4g**) was also tested as the donor ligand resulting in 99% yield with a 4.5:1 diastereomeric ratio (trans:cis). Cyclopropanes of **4h** and **4i** (made from dihydropyran or dihydrofuran) were synthesized in yields of 97% and 93%, respectively. In all three cases of using the furan structure, the major diastereomer was the *cis*-conformer.[4]

The functionality of additional cation stabilizing donor substituents on the cyclopropane was then tested by cyclization of phenyl-methyl and diethyl cyclopropanes to **4j** and **4k** with yields of 94% and 85%, respectively. We noticed the phenyl-methyl species was reacted at room temperature while the diethyl species required refluxing in 1,2-dichloroethane. Next **4l** (derived from methylene cyclopentane) and **4m** (derived from methylene cyclohexane) were cyclized in DCE with $In(OTF)_3$ providing 88% and 79% yield, respectively. This is particularly notable since several hydropyrido[1,2-*a*]indole natural products have *gem*-dialkyl substituents at C(*9*) and these spirocyclic compounds can be easily accessed from 1,1-disubstituted alkenes.[4]

Cyclization of compounds bearing activating silyl substituents such as **4n** (a t-butyldiphenylsilyl group) afforded only one diastereomer with yields of 82%. This is important because the silyl group helps stabilize the carbocation (through β-silyl effect) and can be used for

further functionalization. Phthalimido and phenylthioether substituted cyclopropanes were also synthesized, producing **4o** and **4p** in 55 and 81% yields. The Cbz-protected ring-fused piperidinyl cyclopropane was synthesized to **4q** in 97% with 7.1:1 *dr*.[4]

To further demonstrate the versatility of this methodology we explored the cyclization of 4-methoxyphenyl cyclopropanes with various 3-substituted ligands. This was done to test the steric and electronic effects that various 3-substituents functionalities have on the Friedel-Crafts alkylation. Cyclization of **4r** readily occurred at room temperature in 99% yield with 1.1:1 *dr*. Then phthalimide-protected tryptamine and 3-(2-bromoethyl)-1*H*-indole cyclopropanes were synthesized into **4s** and **4t** producing 78 and 99% yield, respectively. The phthalimide product can be readily deprotected using standard conditions to provide the free amine. With **4t**, the bromine stayed intact through cyclization making it available for further functionalization. Lastly, the 3-methyl acetate indole derivative (**4u**) cyclized producing 88% yield with a 2.0:1 *dr*.[4]

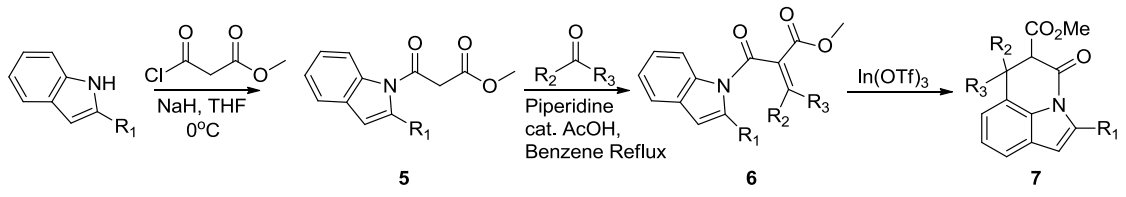
In summary, we provided an efficient and modular approach to constructing functionalized hydropyrido[1,2-*a*]indole-6(7*H*)-ones using an indium triflate facilitated catalytic ring-opening/Friedel-Crafts alkylation. The hydropyrido[1,2-*a*]indole products were synthesized in 4 linear steps with good to excellent yields (48%-99%), demonstrating the versatility of this methodology. Our success with this reaction sequence led to our investigation of construction pyrrolo[3,2,1-*ij*]quinoline cores from 2-methylindole using the same protocol.

Synthesis of Pyrrolo[3,2,1-*ij*]quinolines

(In collaboration with Dadasaheb Patil and Marchello Cavitt)

The pyrrolo[3,2,1-*ij*]quinoline core is a key fragment in many natural alkaloids and has shown bioactivity towards treatment of tuberculosis and cancer.[10] Though the synthesis of these molecules is already reported, an effective modular approach has yet to present itself. With our previous success in constructing pyrrolo[1,2-*a*]indoles and hydropyrido[1,2-*a*]indoles, we envisioned that blocking the 2-position of the indole would result in a Friedel-Crafts alkylation at the 7-position on the other side of the ring. This should quickly generate the pyrrolo[3,2,1-*ij*]quinoline structure in high yields, further substantiating the effectiveness of our methodology.

We began our exploration by synthesizing a wide range of substrate precursors that could be further cyclized. By treating 2-methylindole with methyl malonyl chloride the β-ester-amide (**5**) was afforded. Next a Knovenagel condensation of the *N*-acylated indole and an aldehyde/ketone yielded the desired acrylate (**6**) (Scheme 5). With our substrates in hand we began to cyclize them to afford the corresponding pyrrolo[3,2,1-*ij*]quinoline (**7**) structure using the catalyst indium triflate.



Scheme 5. Substrate synthesis and cyclization

Starting with *para*-substituted phenyl substituents 4-methoxyphenyl, 4-nitrophenyl, and 4-fluorophenyl were cyclized from their alkene substrates in 62.5%, 78%, and 94% yield (entries **7a**, **7b**, and **7c**). After establishing the effects of electron donating and withdrawing groups on cyclization, the effects of various indole 5-position, 3-position, and 2-position substituents were tested using the 4-methoxyphenyl substituted alkene as a standard (Figure 3). The addition of electron withdrawing groups such as fluorine and chlorine on the indole 5-position had no substantial effect, cyclizing to 88% and 90% yield, respectively (**7d**, **7e**). Next, compound **7f** was synthesized from 2,3-dimethylindole in 80% yield. This di-substituted system tests the effects of using additional stabilizing donor groups on the indole ring, showing that the addition indeed stabilizes the system increasing the yields from 62% to 80%. A heteroaromatic donating phenyl ligand was substituted at the 2-position cyclizing to 97% yield (**7g**). This was expected due to a *pi*-conjugated stabilizing effect contributed to the indole from the phenyl ring. Next, a cyclohexane attached to the indole 2 and 3 position cyclized to 82% yield and saturated 5 and 6 carbon indole rings were cyclized with yields of 81% and 83%, respectively (**7h**, **7i**, **7j**). Lastly, a vinyl-phenyl substituted alkene was cyclized to **7k** in 65% yield.

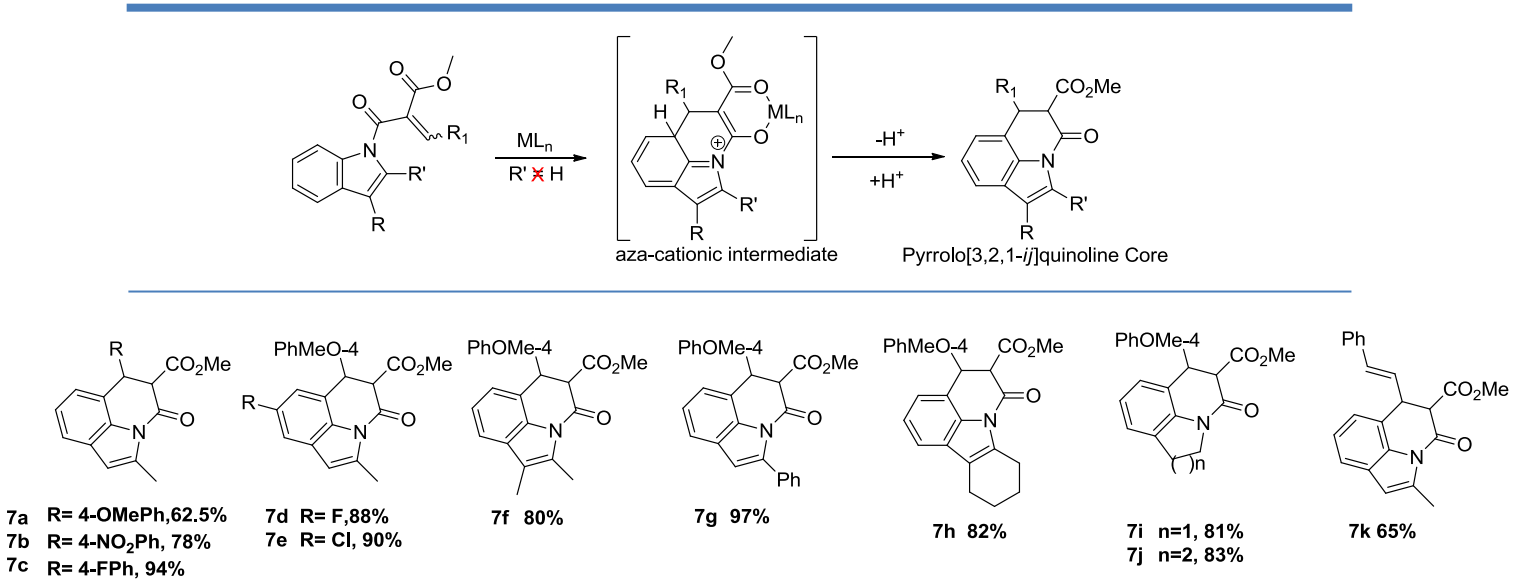


Figure 3. Cyclized Aromatic Acrylates

In conclusion, this protocol produces the pyrrolo[3,2,1-*ij*]quinoline framework via an indium triflate catalyzed Friedel-Crafts alkylation of the indole. The pyrrolo[3,2,1-*ij*]quinoline products were synthesized in 3 linear steps with good-to-excellent yields (62% to 97%) establishing the effectiveness of this mechanism to produce several types of unique indole frameworks. With an efficient, well understood methodology we began to apply our protocol to the synthesis of natural products such as flinderole C.

Synthesis of Flinderole C

In an effort to discover new anti-malarial drugs capable of inhibiting the multi-drug resistant malarial strains, natural products such as flinderoles A-C, borreverine, isoborreverine, and dimethylisoborreverine are being assayed as potential treatments (Figure 4).

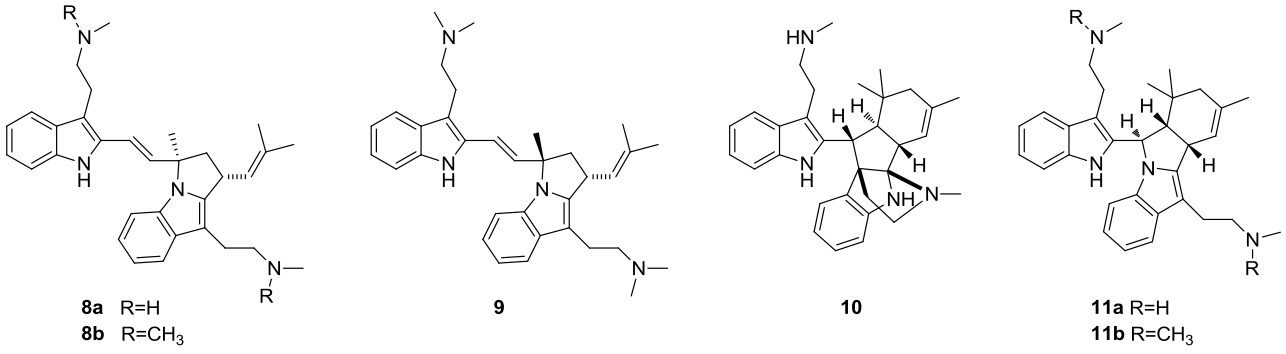


Figure 4. Structural configuration of flinderoles A-C (**8a**, **8b**, and **9**), borreverine (**10**), isoborreverine (**11a**), and dimethylisoborreverine (**11b**)

Flinderole A (**8a**) was discovered in the natural product library at the Eskitis Institute and isolated from the plant *Flindersia acuminate*.[11] The natural products flinderoles B and C (**8b**, **9**)

were isolated from HPLC bioassay-guided fractionation of *Flindersia amboinensis* extract and identified through product screening as potential anti-malarials.[11] Borreverine (**10**), isoborreverine (**11a**), and dimethylisoborreverine (**11b**) were discovered before the flinderoles and are a unique set of tryptamine-isoprenes isolated from the plant *Flindersia fournieri*.[11] When tested, the flinderoles and borreverine compounds showed inhibition of (chloroquine-resistant) *P. falciparum* growth with IC_{50} values ranging between 0.08 and 1.42 μM.[11] Though these compounds are effective inhibitors, their limited availability in nature and difficulty in isolation requires the use of synthetic strategies to generate enough material for therapeutic drug activity studies.

The synthesis of flinderole C has been reported using two completely different schemes. In the protocol by Toste et al., the synthesis of flinderole C took 18 steps (14 longest linear sequence) in 4% overall yield.[6] Their synthesis features a Horner-Wadsworth-Emmons olefination of a phosphate and ketone to join the two halves of the molecule together, followed by deprotection of *t*-butyldiphenylsilyl ether and some functional group manipulation to afford the N-dimethyl side chain. A retrosynthetic look at their protocol required the two pieces to be made separately before being fused together. A *N*-dimethyltryptamine piece would be constructed from a zinc-promoted Fisher indole reaction to create the protected 2-methyltryptophol structure followed by an Arbuzov/Radical bromination to give rise to the desired phosphonate ester. The pyrrolidine scaffold was constructed more strategically starting with an *N*-alkylation of tryptophol to introduce a methyl ester, which subsequently underwent an enolate alkylation followed by gold(I)-catalyzed hydroarylation to afford the pyrrolidine

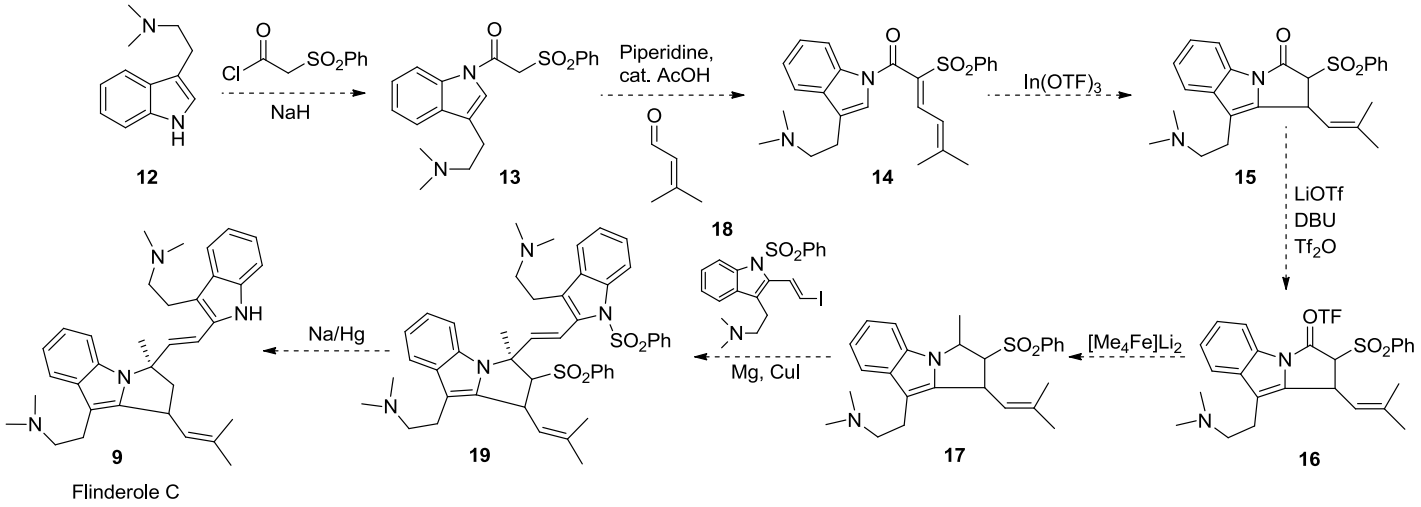
framework.[6] Though this was the first reported synthesis of flinderole C the scheme had several drawbacks including the use of strong bases and overall poor yields.

Later, Dethe et al. used a biomimetic pathway to synthesize Flinderole C in 17.2% overall yield using only 11 steps in the longest linear sequence.[5] Their methodology hinged on the use of a monomeric tryptamine diene as a precursor in the synthesis. The scheme began with a treatment of *N*-protected indole aldehyde with $Ph_3P{=}CHCO_2Et$ followed by an addition of MeMgBr to the generated ester, resulting in the creation of a 3-butene-2-ol tail on the indole.[5] This compound was the precursor to the *N*-unprotected and tryptamine diene compounds which were then cyclized using copper triflate. A treatment with 2-iodoxybenzoic acid followed by a reductive amination of the resulting bisaldehyde yielded flinderoles B and C in a 2 :3 ratio.[5] This route had higher overall yields compared to the previous methodology but still consisted of a long reaction sequence that hinged on a low yielding cyclization.

Our modular approach was inspired from previous reports and our research with synthesizing pyrrolo[1,2-*a*]indoles. We envisioned using our Friedel-Craft alkylation methodology to shorten the synthesis of flinderole C and increase the diastereoselectivity of the products (Scheme 6). Our forward synthetic analysis of flinderole C starts with the acylation of an *N*,*N*-dimethyltryptamine (**12**) with a α-sulfonyl acetyl chloride followed by a Knovenagel condensation with 3-methyl-2-butenal to afford the requisite cyclization precursor (**14**). The divinyl amide (**14**) could then be cyclized using our modular Lewis acid-catalyzed intramolecular Friedel-Crafts alkylation to afford the pyrrolo[1,2-*a*]indole-3(2*H*)one (**15**). Triflate formation (**16**) followed by iron promoted methylation will generate the α,β-unsaturated

sulfone (**17**) which will then be coupled by copper-promoted conjugate addition. The conjugate addition will require **17** to be converted to a Grignard reagent before being treated with **18** in the presence of copper iodide. Finally a dissolving metal reduction will deprotect the phenyl sulfonyl groups yielding flinderole C (**9**). This approach will provide the flinderoles from commercially available tryptamine derivatives using a longest linear sequence of 7 steps.

Thus far, we have successfully synthesized the pyrrolo[1,2-*a*]indole-3(2*H*)one (**22**) and the N-sulfonyl acetamide (**25**). The construction of the pyrrolo piece took several trials before using the methodology shown below (Figure 5). Our attempts with acylating *N*,*N*-dimethyltryptamine with the α-sulfonyl acetyl chloride lead to the loss of the dimethylamine while acylations with methyl malonyl chloride afforded extremely poor yields, requiring us to rethink our strategy. By using 3-(2-bromoethyl)-1*H*-indole, we envisioned an easier synthesis without the loss of functional groups during the subsequent reactions. Acylations with α-sulfonyl



Scheme 6. Forward Synthetic Analysis of Flinderole C

acetyl chloride and 3-(2-bromoethyl)-1*H*-indole were conducted successfully, but the Knovenagel condensation with 3-methylbut-2-enal led to a deprotection of the phenyl sulfonyl group. By returning to our original methodology the 3-(2-bromoethyl)-1*H*-indole was readily converted into the β-keto ester (**20**) in 48 % yield, followed by a Knovenagel condensation with 3-methylbut-2-enal to afford the desired acrylate (**21**) in 30 % yield. Though Friedel-Craft alkylation with $In(OTf)_3$ afforded the pyrrolo[1,2-*a*]indole core (**22**), $Sc(OTf)_3$ gave overall higher yields (66%) with fewer side products.

The construction of the N-sulfonyl acetamide (**24**) also required revamping due to the loss of the functional groups during various stages of its synthesis. Starting with 2-(1H-indol-3-yl)acetic acid, acylations with 4-methylbenzene-1-sulfonyl chloride afforded the N-protected indole acetic acid (**23**) in good yields, 57.8%. A formylation reaction was then conducted to yield

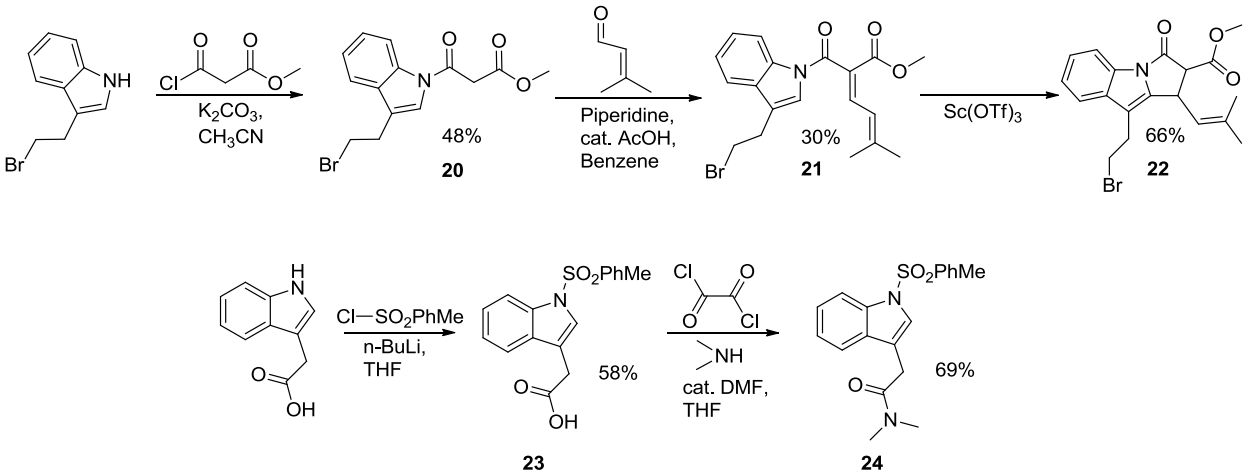


Figure 5. Progress towards Synthesis of Flinderole C

a 2-positioned aldehyde, but the chemistry failed most likely due to the reactivity of the carboxylic acid functionality. To bypass this discrepancy, treatment of the N-protected indole

acetic acid with oxalyl chloride, dimethyl amine, and catalytic amounts of DMF afforded the acetamide (**24**) which we hope will undergo formylation without any problems. Though the yields of these reactions are far from quantitative, further optimization using different solvents and reaction conditions should produce higher product ratios. An update on the synthesis of flinderole C will be reported in due course.

Conclusion

In summary, we report an efficient synthesis of hydropyrido[1,2-*a*]indole-6(7*H*)-ones and pyrrolo[3,2,1-*ij*]quinolines via an intramolecular $In(OTf)_3$ catalyzed Friedel-Craft alkylation, demonstrating the versatility of our methodology. Further application of this protocol has been demonstrated in the synthesis of precursors used in the total synthesis of flinderole C. Our sequence is currently being applied to preparing mersicarpine and yuremamine, two natural products which are not well reported. By exploring modular approaches to constructing polycyclic compounds, we envision that our methodology will aid the preparation of *N*-fused heteroaromatic natural products.

Materials and Methods

General Methods

All reactions were carried out in oven and flame-dried glassware. Each reaction was carried out under a nitrogen atmosphere using dry solvents, unless otherwise noted. The

tetrahydrofuran was distilled from sodium/benzophenone ketyl under nitrogen while the dichloromethane was purified by distillation from calcium hydride under nitrogen. All other reagents were purchased from Acros, Sigma-Aldrich, Fluka, VWR, Merck, Alfa Aesar, TCI or Strem (for metal catalysts).

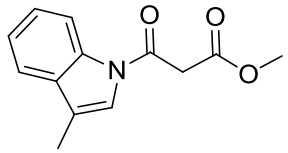
Purification was performed using flash chromatography with Silicycle silica gel (40-63 μm) and technical grade solvents indicated as eluent with 0.1-0.5 bar pressure. Thin-layer chromatography (TLC) was performed on EMD silica gel 60 F254 TLC glass plates to gauge reaction completion and chromatographic separation. Visualization of TLC's was accomplished via UV light, aqueous basic potassium permanganate ($KMnO_4$) solution, and iodine chips. The yield of each reaction refers to isolated analytically pure material.

Infrared (IR) spectra were obtained using a Nicolet 4700 FTIR with an ATR attachment from SmartOrbit Thermoelectronic Corp. The IR bands are characterized as broad (br), weak (w), medium (m), and strong (s). Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Varian Mercury Vx 300 spectrometer or a Varian Mercury Vx 400 spectrometer with solvent resonances as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, dd =doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, t = triplet, m = multiplet), coupling constants (Hz), and integration. Mass spectra were obtained using a VG-70SE instrument.

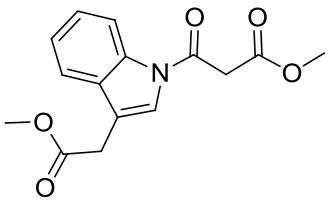
Experimental Procedure

A. N-Acylations of Indole Compounds

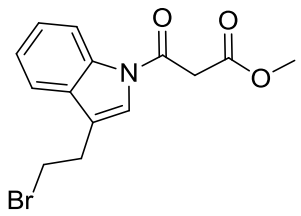
Sodium hydride (1.1 equiv.) was suspended in THF (20 mL), cooled to 0 °C. A solution of the desired indole (1.0 equiv.) dissolved in 30 mL THF was syringed into the reaction vessel. After 30 min, methyl-3-chloro-3-oxopropanoate (1.1 equiv.) was slowly added to the solution and allowed to react for 14 h at room temperature. The reaction mixture was quenched with water (100 mL), the organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine, dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography for product isolation.



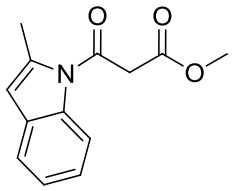
Methyl 3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (1a): A variation of the general procedure was followed using sodium hydride (1.90 g, 47.7 mmol), 3-methyl-1*H*-indole (5.00 g, 38.1 mmol), methyl-3-chloro-3-oxopropanoate (4.9 mL, 45.7 mmol), and THF (50 mL). After 14 h, the reaction was quenched, and column chromatography (20% EtOAc/Hex, Rf 0.26 and Rf 0.15 for keto and enol tautomers) afforded **1a** as a pale brown solid (6.44 g, 73%). [**m.p.** 49-51°C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.43 (d, J = 7.1 Hz, ^{1}H), 7.52 – 7.47 (m, 1H), 7.41 – 7.28 (m, 2H), 7.10 (s, 1H), 3.92 (s, 2H), 3.79 (s, 3H), 2.27 (s, J = 1.3 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.8, 163.4, 136.0, 131.5, 125.5, 124.0, 121.4, 119.7, 118.9, 116.7, 52.9, 43.6, 9.7. **IR:** 3051.9 (w), 2937.6 (w), 1747.0 (s), 1685.1 (s), 1604.1 (w), 1447.0 (s), 1375.5 (s), 1232.6 (m), 1070.7 (m), 913.5 (m), 732.6 (s) cm^{-1}. **HRMS (ESI)** M/Z Calc. 231.0895, Obs. 231.0895.



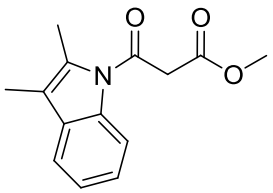
Methyl 3-(3-(2-methoxy-2-oxoethyl)-1*H*-indol-1-yl)-3-oxopropanoate (1u): The general procedure was followed using sodium hydride (0.702 g, 17.6 mmol), methyl 2-(1*H*-indol-3-yl)acetate (3.00 g, 15.9 mmol), methyl-3-chloro-3-oxopropanoate (2.0 mL, 18.6 mmol), and THF (60 mL). After 16 h, the reaction was quenched, and column chromatography (30% EtOAc/Hex, Rf 0.24) afforded **1u** as a dark brown oil (3.55 g, 77%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.43 (d, J = 8.0 Hz, 1H), 7.57 – 7.49 (m, 1H), 7.43 – 7.27 (m, 3H), 3.96 (s, 2H), 3.79 (s, 3H), 3.73 (s, 2H), 3.72 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.0, 166.6, 163.6, 135.8, 130.1, 125.8, 124.2, 123.1, 118.9, 116.8, 116.0, 52.8, 52.2, 43.4, 30.6. **IR:** 3009.3 (w), 2952.1 (w), 1737.4 (s), 1703.2 (s), 1595.1 (m), 1366.0 (s), 1265.7 (m), 1204.7 (s), 1148.4 (s), 1015.7 (m), 909.4 (m), 728.3 (s) cm^{-1}. **HRMS (ESI)** M/Z Calc. 289.0950, Obs. 289.0945.



Methyl 3-(3-(2-bromoethyl)-1*H*-indol-1-yl)-3-oxopropanate (20): A different method from the above methodology was utilized to synthesize this compound. A solution of 3-(2-bromoethyl)-1*H*-indole (6.69 g, 29.8 mmol) and potassium carbonate (2.71 g, 19.6 mmol) was heated in acetonitrile until reflux (60 mL) before the addition of methyl malonyl chloride (5.67 mL, 52.8 mmol). After allowing the reaction to stir all night the reaction was cooled, filtered, and dried *in vacuo*. The residue was extracted three times with EtOAc, separating the organic layer, dried with anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification via column chromatography using 10% EtoAc/Hex yielding **20** as a light yellow oil (4.65 g, 48 %).%). [**m.p.** 68-70°C] **^{1}H NMR** (300 MHz, CDCl3) δ 8.41 (d, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.40 – 7.24 (m, 2H),7.22 (s, 1H), 3.92 (s, 2H), 3.76 (s, 3H), 3.61 (t, *J* = 7.2 Hz, 2H), 3.22 (t, *J* = 7.2 Hz, 2H). **^{13}C NMR** (75MHz, CDCl3) δ 166.5, 163.5, 135.7, 129.8, 125.6, 123.9, 122.1, 120.4, 118.4, 116.7, 52.7, 43.3, 31.1,28.5. **IR**: 3091.7 (w), 2940.7 (w), 2878.8 (w), 1760.1 (s), 1657.8 (s), 1615.6 (s), 1535.5 (s), 1440.9 (s), 1239.4 (s), 1191.4 (s), 1040.8 (m), 820.8 (m), 777.4 (m) cm-1. **HRMS (ESI)** M/Z Calc. 323.0157, Obs.323.0162.



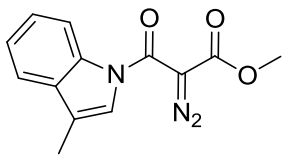
Methyl 3-(2-methyl-1*H*-indol-1-yl)-3-oxopropanoate (5a): The general procedure was followed using sodium hydride (1.90 g, 47.7 mmol), 2-methyl-1*H*-indole (5.00 g, 38.1 mmol), methyl-3-chloro-3-oxopropanoate (4.9 mL, 45.7 mmol), and THF (125 mL). After 14 h, the reaction was quenched, and column chromatography (30% EtOAc/Hex, R_f 0.40) afforded **5a** as a brick red solid (6.05 g, 68.7%). [**m.p.** 74 - 76°C]. **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.93-7.87 (m, 1H), 7.46-7.42 (m, 1H), 7.29-7.20 (m, 2H), 6.37 (t, *J* = 1.05 Hz, 1H), 4.05 (s, 2H), 3.81 (s, 3H), 2.59 (d, *J* = 1.20 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.9, 165.8, 136.9, 136.3, 129.7, 123.8, 123.5, 119.9, 114.9, 110.5, 52.6, 45.5, 17.2.



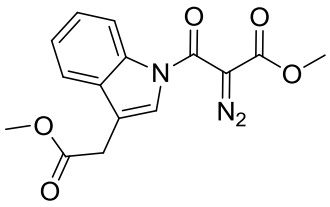
Methyl 3-(2,3-dimethyl-1*H*-indol-1-yl)-3-oxopropanoate (5f): The general procedure was followed using sodium hydride (0.330 g, 8.26 mmol), 2,3-dimethyl-1*H*-indole (1.00 g, 6.88 mmol), methyl-3-chloro-3-oxopropanoate (0.921 mL, 8.61 mmol), and THF (35 mL). After 14 h, the reaction was quenched, and column chromatography (20% EtOAc/Hex) afforded **5f** as a pale yellow solid (1.05 g, 62.2%). [**m.p.** 75-77°C]. **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.77-7.84 (m, 1H), 7.26-7.32 (m, 1H), 7.17 (m, 2H), 3.88 (s, 2H), 3.72 (s, 3H), 2.34 (s, 3H), 2.03 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 8.1, 13.4, 45.1, 52.1, 114.4, 115.7, 117.7, 122.8, 123.5, 130.7, 131.5, 135.0, 165.3, 166.7. **HRMS (ESI)** M/Z Calc. 245.1052, Obs. 245.1053.

B. Formation of Diazo Compounds

The β-amide ester (1.0 equiv.) was dissolved in acetonitrile and treated with triethylamine (1.2 equiv.). After stirring for 10 min, tosyl azide (1.2 equiv.) was placed in the reaction flask. The mixture was stirred at room temperature for 12 h and concentrated under reduced pressure. The resulting residue was purified by silica gel flash chromatography to afford the diazo compound.



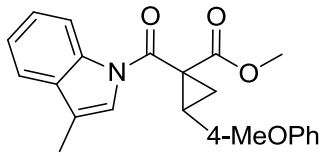
Methyl 2-diazo-3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (2a): The general procedure was followed using methyl 3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (2.71 g, 11.7 mmol), triethylamine (2.0 mL, 14.4 mmol), tosyl azide (2.81 g. 14.2 mmol), and acetonitrile (30 mL). After 12 h, the reaction mixture was concentrated, and column chromatography (20% EtOAc/Hex, Rf 0.41) afforded **2a** as a yellow solid (2.79 g, 93%). [**m.p.** 74-76°C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.17 (d, J = 8.6 Hz, 1H), 7.51 – 7.47 (m, 1H), 7.39 –7.26 (m, 2H), 7.11 (s, 1H), 3.85 (s, 3H), 2.28 (s, 3H). **^{13}C NMR** (75 MHz, CDCl3) δ 161.5, 158.9, 136.0, 131.7, 124.8, 123.7, 123.3, 118.9, 117.7, 115.7, 69.7, 52.6, 9.7. **IR:** 3047.1 (w), 2956.6 (w), 2918.5 (w), 2132.7 (s), 1708.9 (s), 1651.7 (s), 1601.0 (m), 1466.0 (s), 1349.6 (s), 1302.9 (s), 1254.3(s), 1127.9(s), 1046.9 (s), 865.9 (m), 732.7 (s) cm-1. **HRMS (ESI)** M/Z Calc. 257.0800, Obs. 257.0805.



Methyl 2-diazo-3-(3-(2-methoxy-2-oxoethyl)-1*H*-indol-1-yl)-3-oxopropanoate (2u): The general procedure was followed using methyl 3-(3-(2-methoxy-2-oxoethyl)-1*H*-indol-1-yl)-3-oxopropanoate (1.49 g, 5.16 mmol), triethylamine (880 µL, 6.31 mmol), tosyl azide (1.22 g, 6.19 mmol), and acetonitrile (20 mL). After 18 h, the reaction mixture was concentrated, and column chromatography (40% EtOAc/Hex, Rf 0.43) afforded **2u** as a brown solid (1.36 g, 83%). [**m.p.** 77-79°C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.17 (d, J = 7.8 Hz, 1H), 7.52 (d, J = 7.7 Hz, 1H), 7.41 – 7.26 (m, 3H), 3.84 (s, 3H), 3.73 (s, 2H), 3.72 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.1, 161.3, 159.2, 135.9, 130.3, 125.2, 125.1, 123.9, 118.9, 115.8, 114.1, 70.1, 52.7, 52.1, 30.7. **IR:** 2999.5 (w), 2961.4 (w), 2137.5 (s), 1721.8 (s), 1637.44 (s), 1599.3 (w), 1446.9 (s), 1364.2 (s), 1305.1 (s), 1253.8 (s), 1139.6 (s), 1051.6 (w), 870.7 (m), 747.9 (s) cm-1. **HRMS (ESI)** M/Z Calc. 315.0855, Obs. 315.0860.

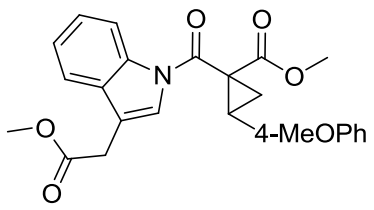
C. Synthesis of the Cyclopropanes

A round bottom flask was charged with $Rh_2(esp)_2$ (0.1 mol%) and 2.0 mL DCM was added to the flask. The reaction vessel was cooled to 0°C, and the corresponding alkene (1.0 equiv.) was added. After 10 min, the diazo reagent (1.3 equiv.) was dissolved in DCM (5 mL) and syringed into the reaction mixture. After 10 min, the ice bath was removed and the reaction proceeded at room temperature. Upon completion (monitored by TLC) or 12 h of reactivity, the solution was quenched with saturated thiourea and stirred for 30 min. The organic layer was separated, and the aqueous layer extracted three times with DCM. The combined organic layers were washed with brine, dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography.



Methyl 2-(4-methoxyphenyl)-1-(3-methyl-1*H*-indole-1-carbonyl) cyclopropane carboxylate (3a): The general procedure was followed using 4-methoxystyrene (0.201 g, 1.49 mmol), methyl 2-diazo-3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.500 g, 1.94 mmol), $Rh_2(esp)_2$ (1.5 mg, 1.98 μmol) and DCM (8 mL). After 12 h, the reaction was quenched, and column chromatography (20% EtOAc/Hex, R*f* 0.52) afforded **3a** as a pale yellow solid (0.328 g, 60%). [**m.p.** 110-112°C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.45 (d, *J* = 8.0 Hz, 1H), 7.61-7.45 (m, 1H), 7.44 – 7.26 (m, 5H), 6.90 – 6.83 (m, 2H), 3.81 (s, 3H), 3.41 (t, *J* = 4Hz, 1H), 3.41 (s, 3H), 2.40 (dd, *J* = 8.3, 5.2 Hz, 1H), 2.28 (s, 3H), 1.82 (dd, *J* = 9.3, 5.2 Hz, 1H). **^{13}CNMR** (75 MHz, $CDCl_3$) δ 168.0, 165.8, 158.9, 136.0, 131.5, 130.2, 126.1, 125.4, 123.8, 121.5, 119.2, 118.9,

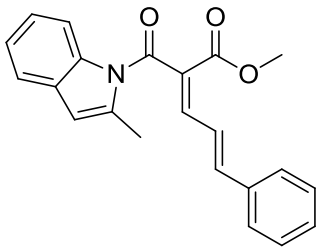
116.5, 113.6, 55.2, 52.8, 39.5, 31.1, 18.8, 9.8. **IR**: 3050.0 (w), 2914.3 (m), 1742.9 (m), 1681.0 (s), 1600.0 (m), 1514.29 (m), 1450.0 (s), 1346.3 (s), 1246.8 (s), 1176.5 (s), 1028.6 (s), 838.1 (s), 748.2 (s) cm^{-1}. **HRMS (ESI)** M/Z Calc. 363.1471, Obs. 363.1471.



Methyl 1-(3-(2-methoxy-2-oxoethyl)-1*H*-indole-1-carbonyl)-2-(4-methoxyphenyl) cyclopropanecarboxylate (3u): The general procedure was followed using 4-methoxystyrene (0.211 g, 1.57 mmol), methyl 2-diazo-3-(3-(2-methoxy-2-oxoethyl)-1*H*-indol-1-yl)-3-oxopropanoate (0.611 g, 1.94 mmol,), $Rh_2(esp)_2$ (1.5 mg, 1.98 µmol), and DCM (8 mL). After 14 h, the reaction was quenched, and column chromatography (20% EtOAc/Hex, Rf 0.21) afforded **3u** as a yellow solid (0.312 g, 47%). [**m.p.** 82 – 84°C]. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.46 (d, J = 8.1 Hz, 1H), 7.58 – 7.49 (m, 2H), 7.46 – 7.26 (m, 4H), 6.92 – 6.82 (m, 2H), 3.81 (s, 3H), 3.73 (s, 2H), 3.73 (s, 3H), 3.43 (s, 3H), 3.43 (t, J = 4.5 Hz, 1H), 2.42 (dd, J = 8.3, 5.3 Hz, 1H), 1.86 (dd, J = 9.4, 5.2 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.0, 167.8, 166.0, 158.9, 135.9, 130.2, 130.1, 125.9, 125.6, 124.0, 123.3, 119.0, 116.6, 115.7, 113.6, 55.2, 52.8, 52.2, 39.3, 31.3, 30.8, 18.9. **IR:** 3009.0 (w), 2947.1 (w), 1742.2 (s), 1694.6 (s), 1608.9 (m), 1504.1 (m), 1446.9 (s), 1356.5 (s), 1246.9 (s), 1032.6 (m), 827.8 (m), 732.8 (s) cm^{-1}. **HRMS (ESI)** M/Z Calc. 421.1525, Obs. 421.1519.

D. Knovenagel Condensation of β-Keto Ester

In a dry flask the requisite aldehyde (1.3 equiv.), piperidine (0.1 equiv.), and acetic acid (0.4 equiv.) were added to 25 mL of benzene. The solution was then brought to reflux using a Dean-Stark apparatus and allowed to react for 12 hours. The solution was then quenched using water and extracted using ethyl acetate. The organic layer was then washed with 1N HCl and sodium bicarbonate before being dried with magnesium sulfate and concentrated under vacuum. The residue was separated and purified via silica gel flash chromatography.



(2Z,4E)-Methyl 2-(2-methyl-1*H*-indole-1-carbonyl)-5-phenylpenta-2,4-dienoate (6k): The general procedure was followed using methyl 3-(2-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.300 g, 1.29 mmol), cinnamaldehyde (0.21 mL, 1.69 mmol), piperidine (13.9 μL, 0.129 mmol), and acetic acid (0.0357 g, 0.596 mmol) in 25 mL of benzene. After 20 h, the reaction was quenched and column chromatography (20% EtOAc/Hex) afforded **6k** as a reddish orande oil (0.256 g, 57.2 %). **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.78 (s, 1H), 7.43 (m, 4H), 7.29 (m, 5H), 7.15 (s, 1H), 6.88 (dd, *J* = 15.35, 11.74 Hz, 1H), 6.42 (s, 1H), 3.74 (s, 3H), 2.54 (d, *J* = 1.09 Hz, 3H).). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.1, 164.8, 145.4, 145.0, 136.7, 136.6, 135.1, 130.0, 129.7, 129.7, 129.0, 128.8, 128.5, 127.8, 123.9, 123.7, 122.2, 119.8, 115.3, 110.4, 52.6, 16.7. *dr* 1:1. **HRMS (ESI)** M/Z Calc. 345.1365, Obs. 345.1383.

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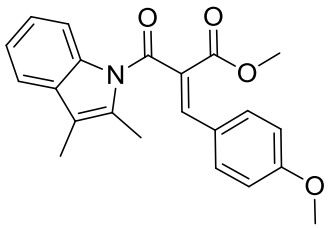
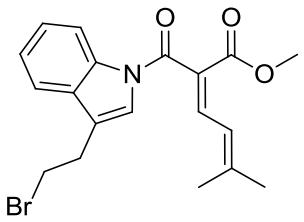


(Z)-methyl 2-(2,3-dimethyl-1*H*-indole-1-carbonyl)-3-(4-methoxyphenyl)acrylate (6f): The general procedure was followed using methyl 3-(2,3-dimethyl-1*H*-indol-1-yl)-3-oxopropanoate (1.00 g, 4.08 mmol), 4-methoxybenzaldehyde (0.617 mL, 5.09 mmol), piperidine (0.040 mL, 0.407 mmol), and acetic acid (0.112 g, 1.88 mmol) in 60 mL of benzene. After 18 h, the reaction was quenched and column chromatography (20% EtOAc/Hex) afforded **6f** as a yellow solid (1.08 g, 72.9 %). [**m.p.** 94-96°C]. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.63 (br. s, 1H), 7.87 (br. s., 1H), 7.33 - 7.48 (m, 3H), 7.28 (br. s., 2H), 6.73 (d, *J* = 8.50 Hz, 2H), 3.77 (s, 3H), 3.67 (d, *J* = 1.21 Hz, 3H), 2.25 - 2.53 (m, 3H), 2.15 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.9, 165.2, 161.9, 142.5, 136.1, 131.8, 131.5, 126.6, 125.3, 124.3, 123.6, 117.9, 116.5, 114.6, 55.2, 52.4, 13.4, 8.6. **HRMS (ESI)** M/Z Calc. 363.1471, Obs. 363.1470.

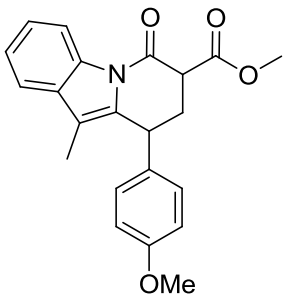


(Z)-methyl 2-(3-(2-bromoethyl)-1*H*-indole-1-carbonyl)-5-methylhexa-2,4-dienoate (21): The general procedure was followed using methyl 3-(3-(2-bromoethyl)-1*H*-indol-1-yl)-3-oxopropanate (1.25 g, 3.86 mmol), 3-methyl-2-butenal (0.421 g, 5.01 mmol), piperidine (32.8 mg, 0.386 mmol), and acetic acid (0.106 g, 1.77 mmol) in benzene (25 mL). After 12 hours the reaction was quenched and column chromatography (20 % EtOAc/Hex) yielding **21** as a dark red solid (0.411 g, 27.4 %).**^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 8.62 (s, 1H), 7.89 (d, *J* = 12.45 Hz, 1H), 7.56-7.30 (m, 3H), 7.06 (s, 1H), 5.96 (dd, *J* = 12.48, 1.14 Hz, 1H), 3.75 (s, 3H), 3.62 (t, *J* = 7.33, 7.33 Hz, 2H), 3.18 (td, *J* = 29.00, 7.18, 7.18 Hz, 2H), 1.99 (s, 3H), 1.83 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.8, 153.2, 140.4, 135.4, 130.5, 133.2, 125.4, 124.0, 120.2, 119.1, 118.4, 117.0, 52.4, 43.1, 31.1, 28.6, 26.9, 19.2.

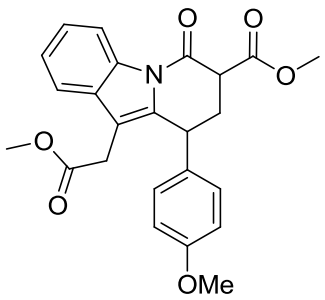
E. In(OTf)3 Catalyzed Friedel-Craft Alkylations

Cyclopropyl β-amide ester (1.0 equiv) was added to a solution of $In(OTf)_3$ (0.30 equiv) in anhydrous dichloromethane (2 mL) at room temperature. Upon completion, the reaction mixture was quenched with water and the product was extracted from the aqueous phase with dichloromethane. The combined organic layers were washed with brine and dried over $MgSO_4$. The organic layers were concentrated for silica gel flash column chromatography.

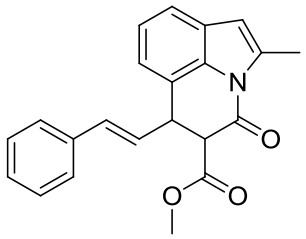
General Method B: To a mixture of $In(OTf)_3$ (0.30 equiv) in anhydrous 1,2-dichloroethane heated to a reflux, dissolved cyclopropyl β-amide ester (1.0 equiv) was syringed into the reaction vessel. The reaction was monitored by TLC and quenched with water. The phases were separated, and the product was extracted from the aqueous phase with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated for silica gel flash column chromatography.



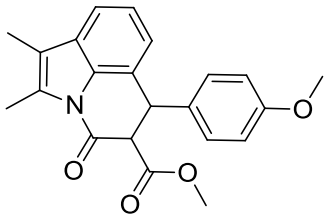
Methyl 9-(4-methoxyphenyl)-10-methyl-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-Carboxylate (4a): Methyl 2-(4-methoxyphenyl)-1-(3-methyl-1*H*-indole-1-carbonyl)cyclopropanecarboxylate (0.100 g, 0.275 mmol), $In(OTf)_3$ (0.046 g, 0.082 mmol) and DCM (4 mL) were combined according to general method A to afford **4a** as a pale brown oil (0.099 g, 99%) after 2 h. R*f* 0.35 (20% EtOAc/Hex). *dr.* (2.6:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.55 – 8.47 (m, 1.34), 7.50 – 7.28 (m, 4.53), 7.15 – 7.09 (m, 0.86), 7.01 – 6.95 (m, 2.09), 6.88 – 6.80 (m, 3.05), 4.59 (t, *J* = 4.3 Hz, 0.94), 4.34 (dd, *J* = 8.5, 5.1 Hz, 0.36), 3.81 – 3.78 (m, 8.28), 3.69 (d, *J* = 4.5 Hz, 0.56), 3.65 (d, *J* = 4.5 Hz, 0.56), 3.56 (d, *J* = 1.1 Hz, 1.37), 2.92 – 2.68 (m, 1.40), 2.59 – 2.34 (m, 1.39), 2.00 (s, 3.0), 1.75 (s, 1.26). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.6, 169.2, 165.0, 164.9, 158.5, 158.5, 134.5, 134.4, 133.7, 133.5, 132.8, 132.3, 131.3, 131.0, 128.9, 128.3, 124.8, 124.8, 124.1, 124.0, 118.1, 118.0, 116.5, 115.2, 114.8, 114.1, 113.9, 55.1, 52.5, 52.4, 49.7, 47.1, 43.4, 37.9, 35.2, 33.8, 33.0, 8.7, 8.3. **IR**: 3051.9 (w), 2932.8 (w), 1747.0 (s), 1685.1 (s), 1618.4 9 (w), 1451.7 (s), 1366.0 (s), 1242.2 (s), 1170.7 (s), 1156.4 (s), 1023.1 (s), 899.2 (m), 729.0 (s) cm^{-1}. **HRMS (ESI)** M/Z Calc. 363.1471, Obs. 363.1475.



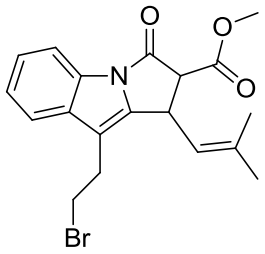
Methyl-10-(2-methoxy-2-oxoethyl)-9-(4-methoxyphenyl)-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (4u): Methyl 1-(3-(2-methoxy-2-oxoethyl)-1*H*-indole-1-carbonyl)-2-(4-methoxyphenyl) cyclopropanecarboxylate (0.070 g, 0.167 mmol), In(OTf)3 (0.028 g, 0.049 mmol) and DCM (3 mL) were combined according to general method A to afford **4u** as a brown oil (0.062 g, 88.0%) after 3 h. R_f 0.45 (40% EtOAc/Hex). iastereomeric ratio: (2.0:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.56 – 8.47 (m, 1.45), 7.56 – 7.48 (m, 1.05), 7.44 – 7.28 (m, 3.67), 7.18 – 7.11 (m, 1.06), 7.01 – 6.90 (m, 2.29), 6.88 – 6.78 (m, 3.02), 4.66 (t, J = 4.5 Hz, 1), 4.40 (dd, J = 9.7, 5.1 Hz, 0.48), 3.90 – 3.81 (m, 1.32), 3.81 – 3.78 (m, 7.54), 3.73 – 3.67 (m, 1.32), 3.64 (s, 1.44), 3.55 (s, 1.42), 3.53 (s, 2.98), 3.52 (s, 0.31), 3.43 (d, J = 17.3 Hz, 1.59), 3.32 (d, J = 17.7 Hz, 0.85), 3.02 – 2.69 (m, 2.34), 2.58 – 2.38 (m, 1.62). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.8, 170.6, 169.4, 169.1, 165.2, 158.9, 158.8, 136.3, 135.8, 134.6, 134.5, 132.3, 131.9, 130.3, 129.9, 129.2, 128.5, 125.2, 125.2, 124.5, 124.4, 118.4, 118.0, 116.7, 114.2, 114.1, 112.3, 112.0, 55.3, 52.7, 52.6, 52.0, 51.9, 50.1, 47.2, 38.5, 35.4, 34.0, 33.2, 29.7, 29.4. **IR:** 3013.8 (w), 2918.6 (w), 2832.8 (w), 1747.0 (s), 1737.7 (s), 1699.3 (s), 1613.6 (m), 1518.4 (m), 1456.5 (s), 1366.0 (s), 1245.6 (s), 1152.1 (s), 1032.6 (s), 837.3 (m), 731.8 (s) cm^{-1}. **HRMS (ESI)** M/Z Calc. 421.1525, Obs. 421.1522.



(E)-methyl-2-methyl-4-oxo-6-styryl-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinoline-5-carboxylate (7k): (2Z, 4E)-methyl 2-(2-methyl-1*H*-indole-1-carbonyl)-5-phenylpenta-2,4-dienoate (0.0700 g, 0.2028 mmol), $In(OTf)_3$ (0.0341 g, 0.0608 mmol) and toluene (4 mL) were combined according to the general procedure to afford **7k** as a pale yellow solid (0.0457 g, 65.32%) after 14 h. (20% EtOAc/Hex, R_f 0.35). [**m.p.** 98 - 100 °C]. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.15 - 7.44 (m, 7H), 7.08 (d, *J* = 7.40 Hz, 1H), 6.63 (d, *J* = 15.68 Hz, 1H), 6.40 (d, *J* = 1.14 Hz, 1H), 6.24 (dd, *J* = 8.65, 15.68 Hz, 1H), 4.58 (t, *J* = 9.44 Hz, 1H), 4.00 (d, *J* = 10.22 Hz, 1H), 3.78 (s, 3H), 2.64 - 2.74 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.0, 164.0, 137.2, 136.2, 134.6, 134.5, 128.6, 128.0, 127.6, 126.5, 126.4, 124.1, 121.0, 120.5, 118.8, 109.3, 56.7, 52.8, 43.9, 15.2.

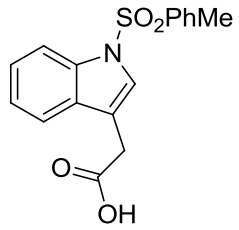


Methyl 6-(4-methoxyphenyl)-1,2-dimethyl-4-oxo-5,6-dihydro-4*H*-pyrrolo[3,2,1-ij]quinoline-5-carboxylate (7f): (Z)-Methyl 2-(2,3-dimethyl-1*H*-indole-1-carbonyl)-3-(4-methoxyphenyl)acrylate (0.0900 g, 0.2476 mmol), $In(OTf)_3$ (0.0208 g, 0.0371 mmol) and DCE (5 mL) were combined according to the general procedure to afford **7f** as a colorless oil (0.774 g, 86.0%) after 4 h. (20% EtOAc/Hex, R_f 0.40). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.73 Hz, 1H), 7.40 (s, 1H), 7.27 - 7.33 (m, 2H), 6.98 - 7.04 (m, 2H), 6.86 (d, *J* = 7.44 Hz, 1H), 5.08 (d, *J* = 10.66 Hz, 1H), 4.31 (d, *J* = 10.66 Hz, 1H), 3.93 - 3.97 (m, 3H), 3.82 (s, 3H), 2.78 (s, 3H), 2.35 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.2, 163.6, 159.0, 134.0, 132.3, 131.2, 129.5, 129.0, 123.8, 122.5, 121.1, 116.9, 116.6, 114.3, 58.9, 55.2, 52.6, 45.2, 12.4, 8.6. **HRMS (ESI)** M/Z+ Calc. 363.1471, Obs. 363.1465.

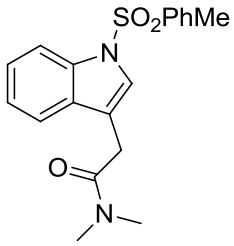


Methyl 9-(2-bromoethyl)-1-(2-methylprop-1-en-1-yl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-2-carboxylate (22): A varying synthesis route was used compared to the above general methodology. A solution of $Sc(OTf)_3$ (15 mol %) was refluxed in xylene before (*Z*)-methyl 2-(3-(2-bromoethyl)-1*H*-indole-1-carbonyl)-5-methylhexa-2,4-dienoate (500 mg, 1.21 mmol) was added to the solution. After two hours, the reaction was quenched with water, extracted with EtoAC, the organic layer was dried with magnesium sulfate, filtered, and concentrated *in vacuo* for column chromatography. The residue was columned (20% EtoAc/Hex) affording **22** as a dark red solid (0.311 g, 66 %). **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 8.01 (ddd, *J* = 6.15, 3.25, 0.74 Hz, 1H), 7.44 (dd, *J* = 5.76, 3.29 Hz, 1H), 7.29 (dd, *J* = 5.91, 3.20 Hz, 2H), 5.20 (d, *J* = 10.26 Hz, 1H), 4.74 (dd, *J* = 9.90, 5.29 Hz, 1H), 3.84 (s, 3H), 3.80 (d, *J* = 5.28 Hz, 1H), 3.70-3.63 (m, 1H), 3.52 (dt, *J* = 7.63, 7.30, 1.24 Hz, 1H), 3.09 (td, *J* = 30.75, 7.21, 7.21 Hz, 2H), 1.84 (dd, *J* = 3.50, 1.32 Hz, 3H), 1.80 (t, *J* = 1.54, 1.54 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.1, 165.1, 140.9, 137.1, 135.0, 130.17, 124.47, 121.4, 118.5, 114.1, 60.1, 53.2, 43.5, 36.6, 31.4, 27.4, 27.2, 25.6, 18.3

F. Acetamide Synthesis



2-(1-tosyl-1*H*-indol-3-yl)acetic acid (23): A solution of 2-(1*H*-indol-3-yl)acetic acid (5.25 g, 30.0 mmol) was cooled to -78°C and allowed to react with n-BuLi (4.10 g, 64.0 mmol) for one hour. Then a solution of $ClSO_2PhMe$ (7.41 g, 39 mmol) in THF (50 mL) was slowly added to the solution, warmed to room temperature, and allowed to react overnight. The reaction was concentrated *in vacuo*, dissolved in DCM, washed with brine then 1 N HCL, and the organic layer was concentrated for chromatography. The residue was purified using column chromatography (20% EtoAc/Hex) affording 5.71g of **23** as a brown solid in 57.8% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 11.78 (s, 1H), 8.01 (d, *J* = 7.81 Hz, 1H), 7.77 (d, *J* = 8.36 Hz, 2H), 7.62 (s, 1H), 7.50 (d, *J* = 7.88 Hz, 1H), 7.34 (m, 4H), 3.74 (s, 2H), 2.28 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 176.9, 144.9, 134.9, 134.8, 130.1, 129.8, 126.7, 124.8, 123.2, 119.4, 114.1, 113.5, 30.6, 21.4, 14.06.



N,N-dimethyl-2-(1-tosyl-1*H*-indol-3-yl)acetamide (24): 2-(1-tosyl-1*H*-indol-3-yl) acetic acid (500 mg, 1.51 mmol) was dissolved in dry DCM (12 mL) and cooled to 0°C before the addition of oxalyl chloride (250 mg, 1.97 mmol) and catalytic amounts of DMF (0.1 mL). The solution was allowed to react for 3 hours before being concentrated *in vacuo*, dissolving in dry THF (12 mL), and adding 40% dimethylamine in water (255 mg, 2.26 mmol). The reaction was extracted with EtOAc, washed with brine, and the organic layer was concentrated *in vacuo*. Using column chromatography (70% EtOAc/Hex) separated **24** as a brown oil yielding 0.210 g (69.1 %). **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.95 (d, *J* = 8.97 Hz, 1H), 7.72 (d, *J* = 7.94 Hz, 2H), 7.51 (d, 8.50 Hz 1H), 7.49 (s, 1H), 7.22 (m, 4H), 3.69 (s, 2H), 2.95 (dd, *J* = 7.79, 0.93 Hz, 6H), 2.26 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.6, 144.7, 134.8, 130.4, 129.6, 126.6, 124.7, 123.9, 123.1, 119.6, 116.2, 113.4, 37.6, 35.47, 30.8, 21.32.

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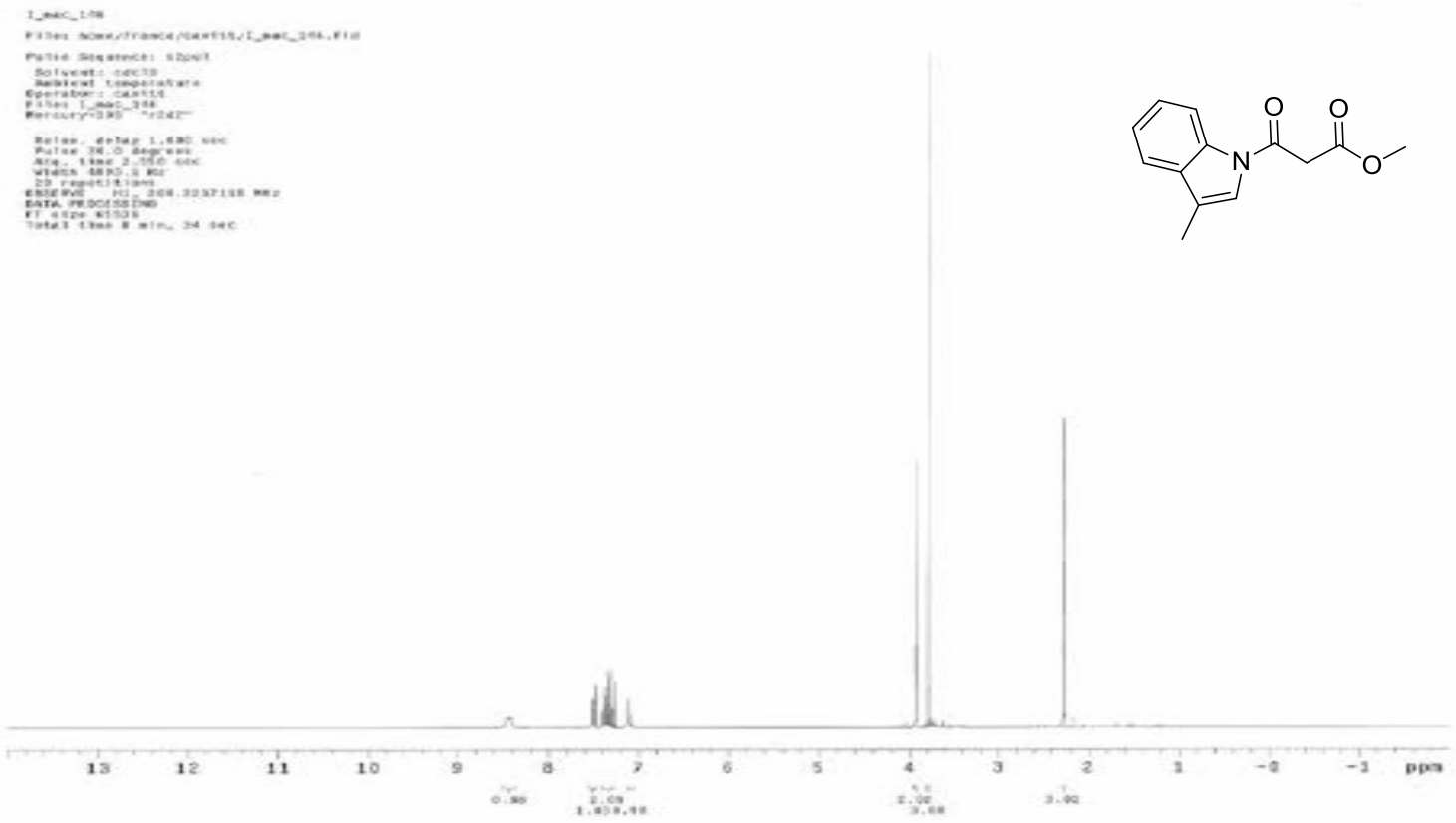
Appendix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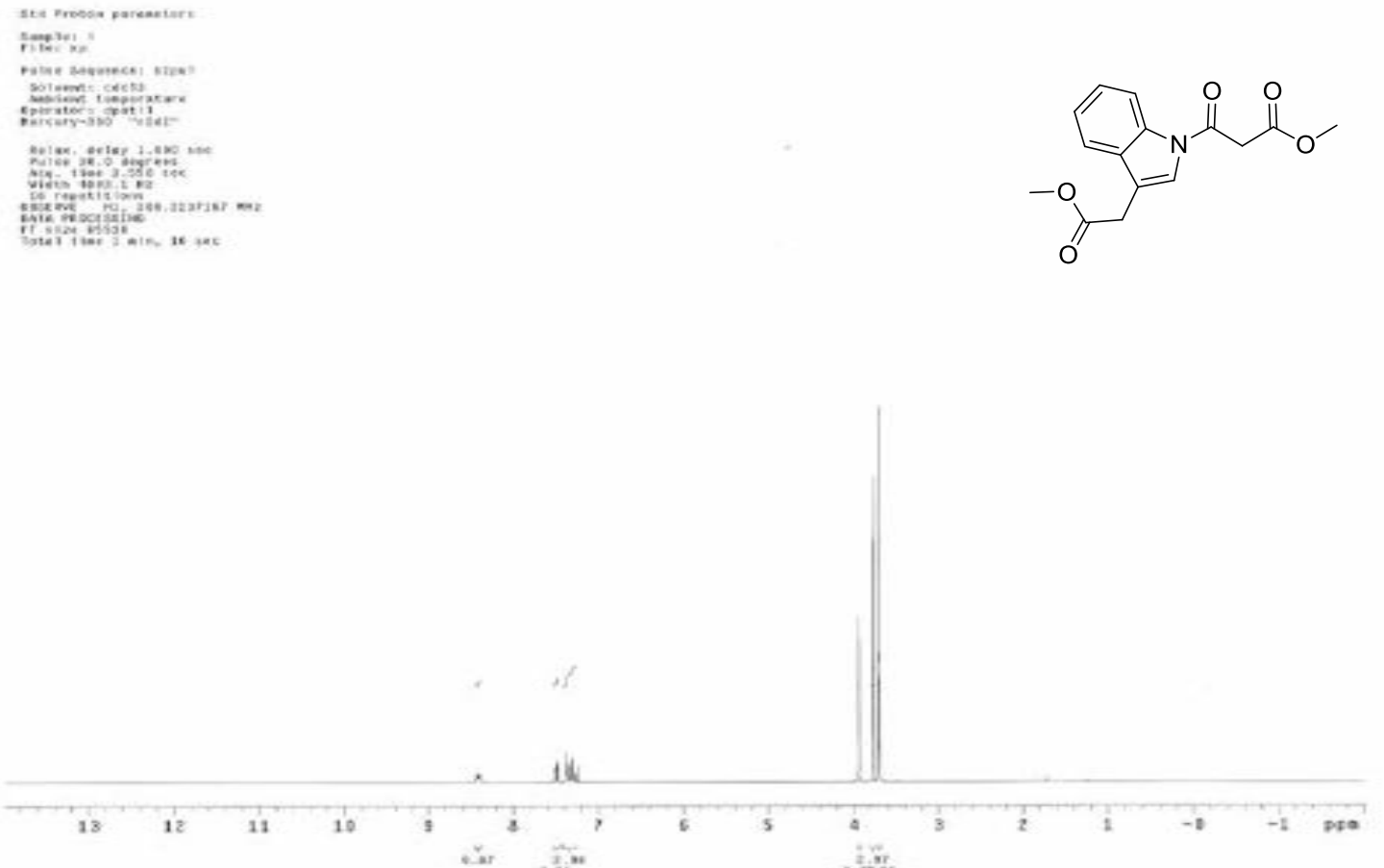
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II-MAC-36-H

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 Ambient temperature
Operator: cavitt
Mercury-400BB "amidala"

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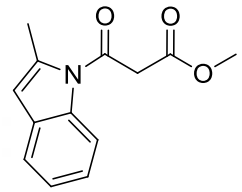

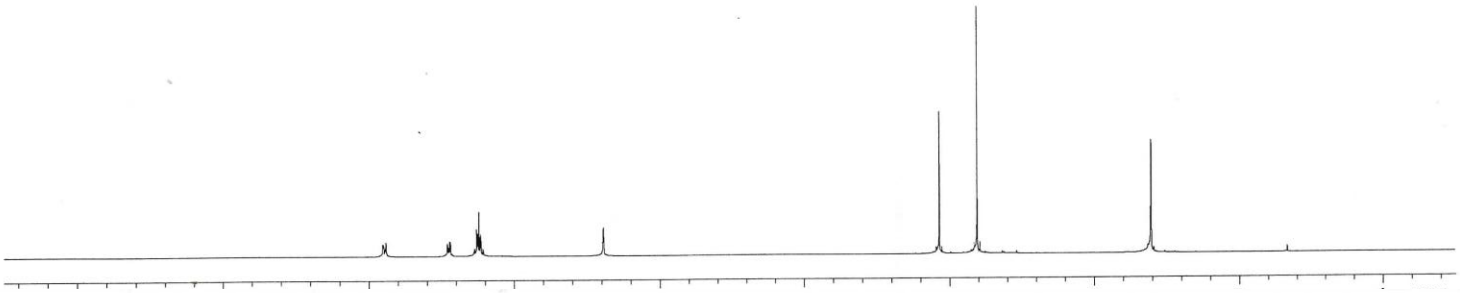

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 Ambient temperature
Operator: dpatil
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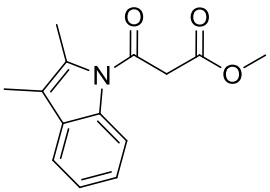

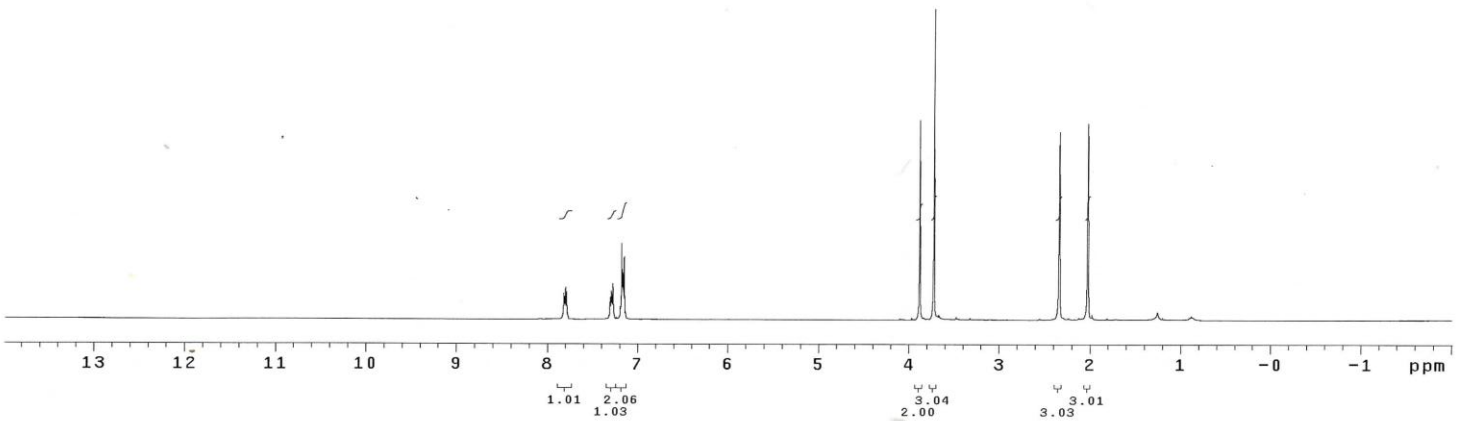

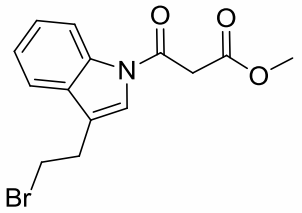
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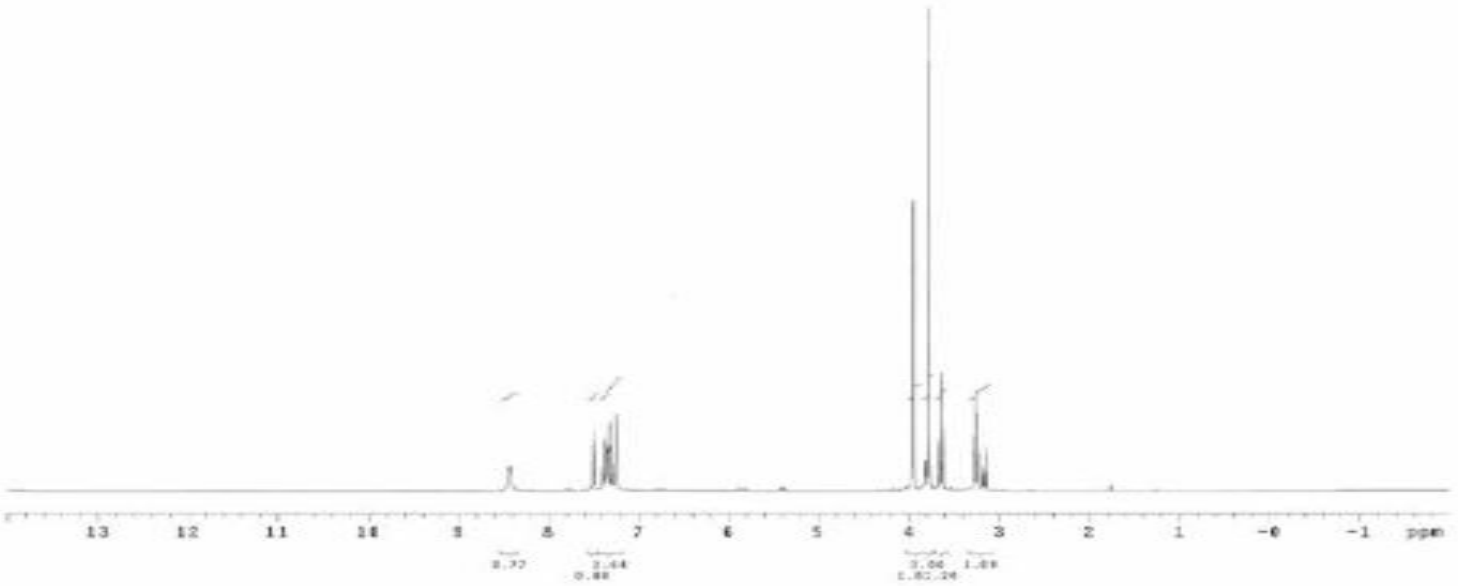
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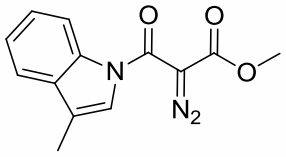
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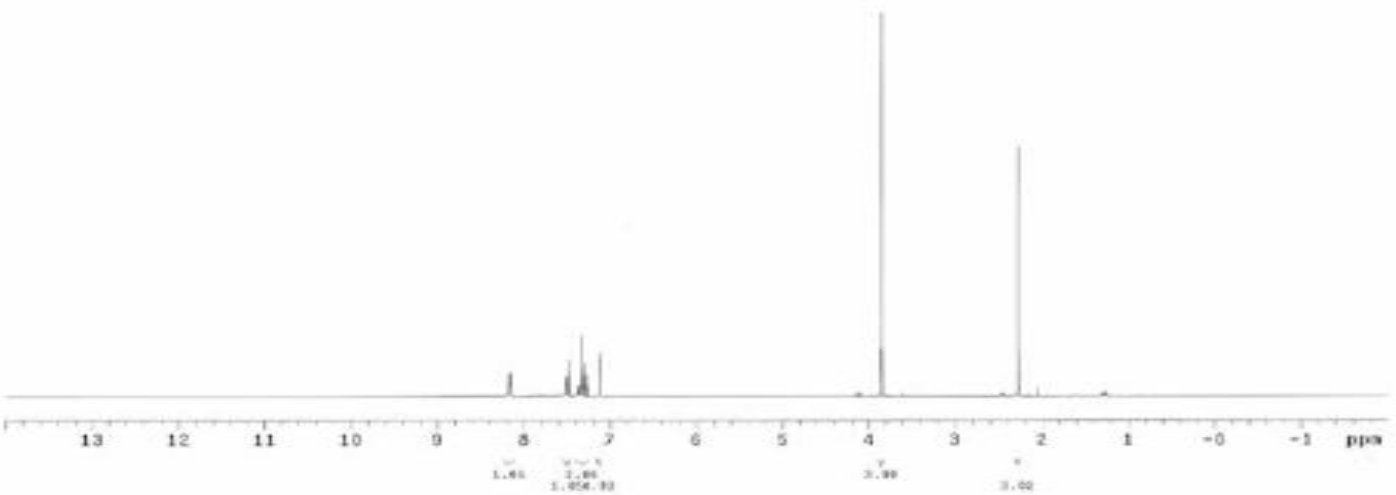
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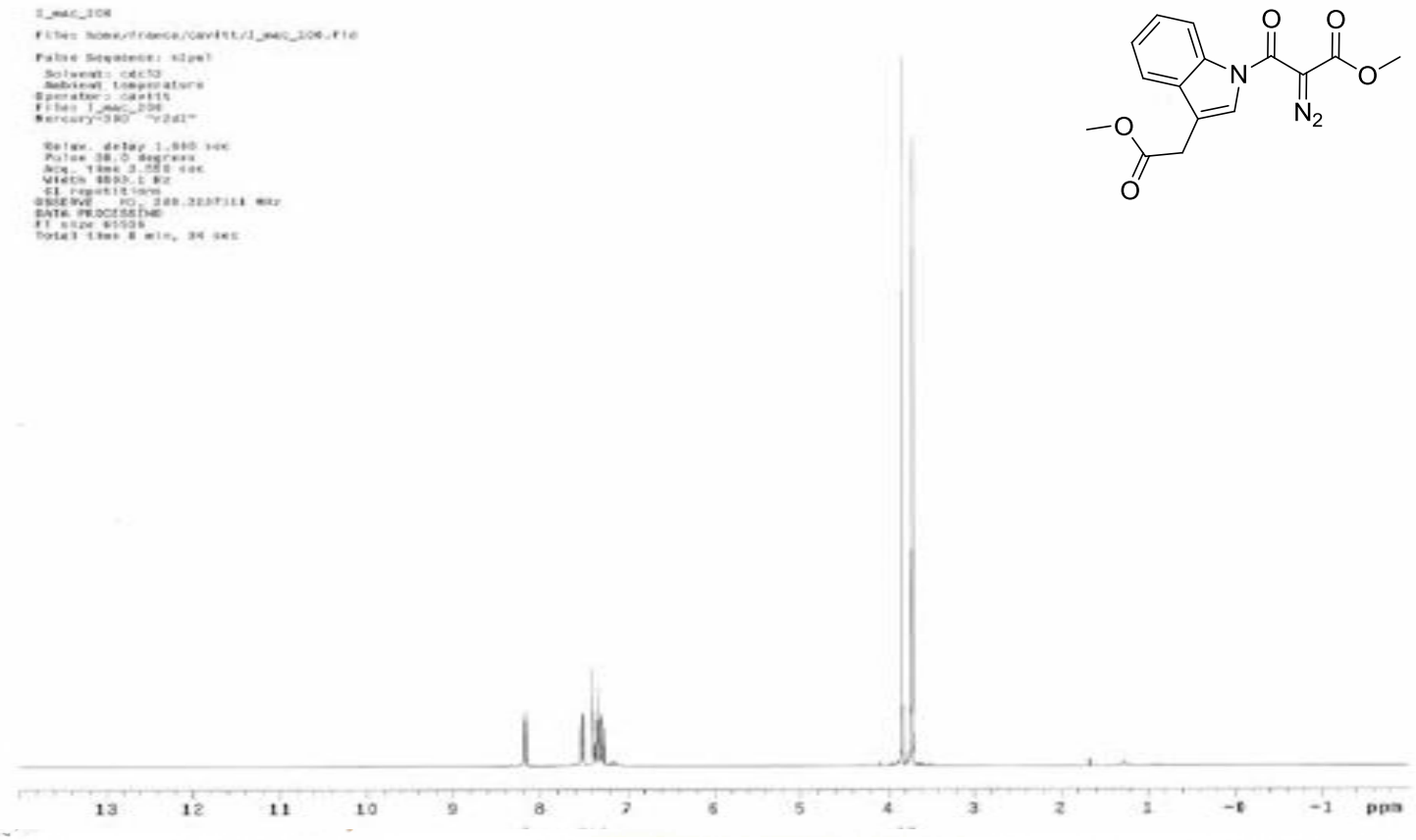

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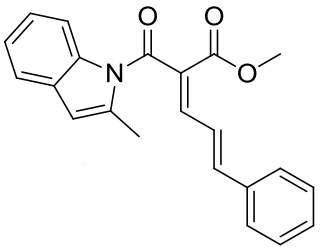
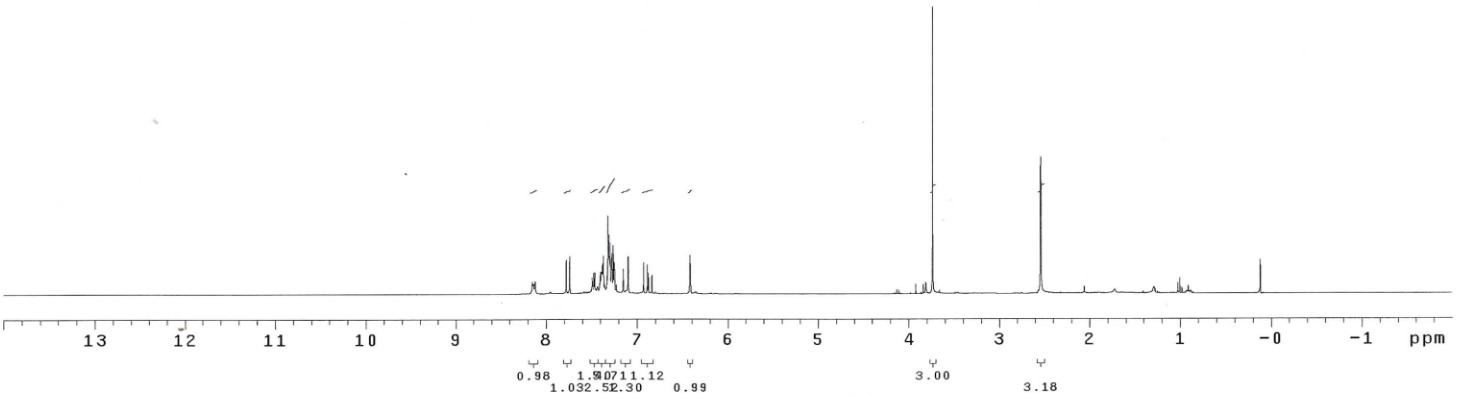
Ambient temperature
Operator: dpatil
Mercury-300 "r2d2"

Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 3.550 sec
Width 4803.1 Hz
16 repetitions
OBSERVE H1, 300.2185002 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 16 sec



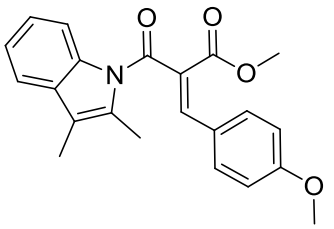


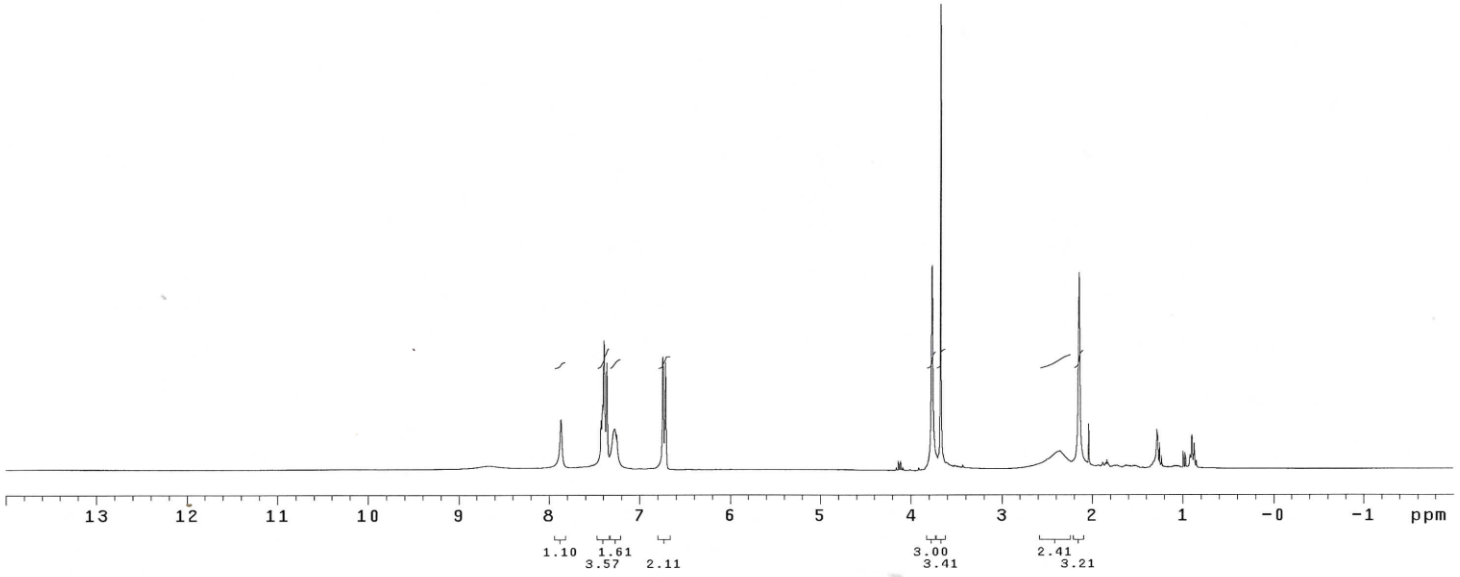
Std Proton parameters

Sample: NB-5-DVP-33-A-H
File: xp

Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Operator: dpatil
Mercury-300 "r2d2"

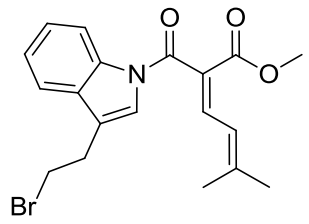
Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 3.550 sec
Width 4803.1 Hz
16 repetitions
OBSERVE H1, 300.2237117 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 16 sec

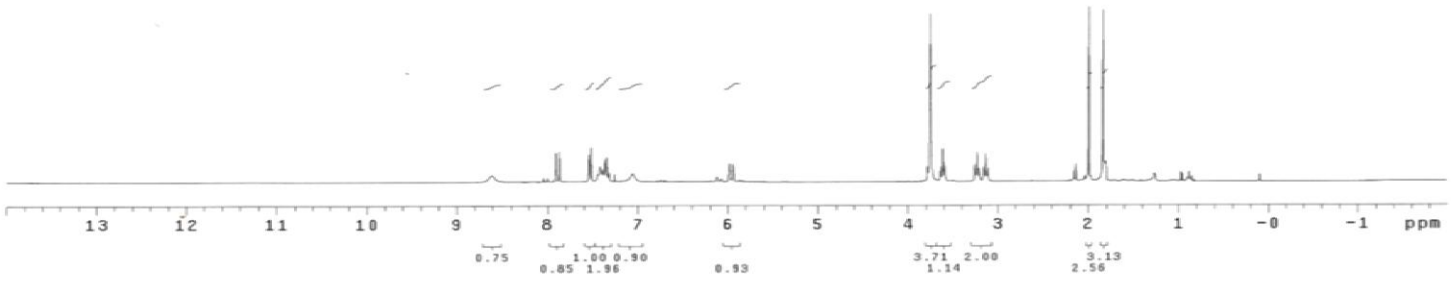


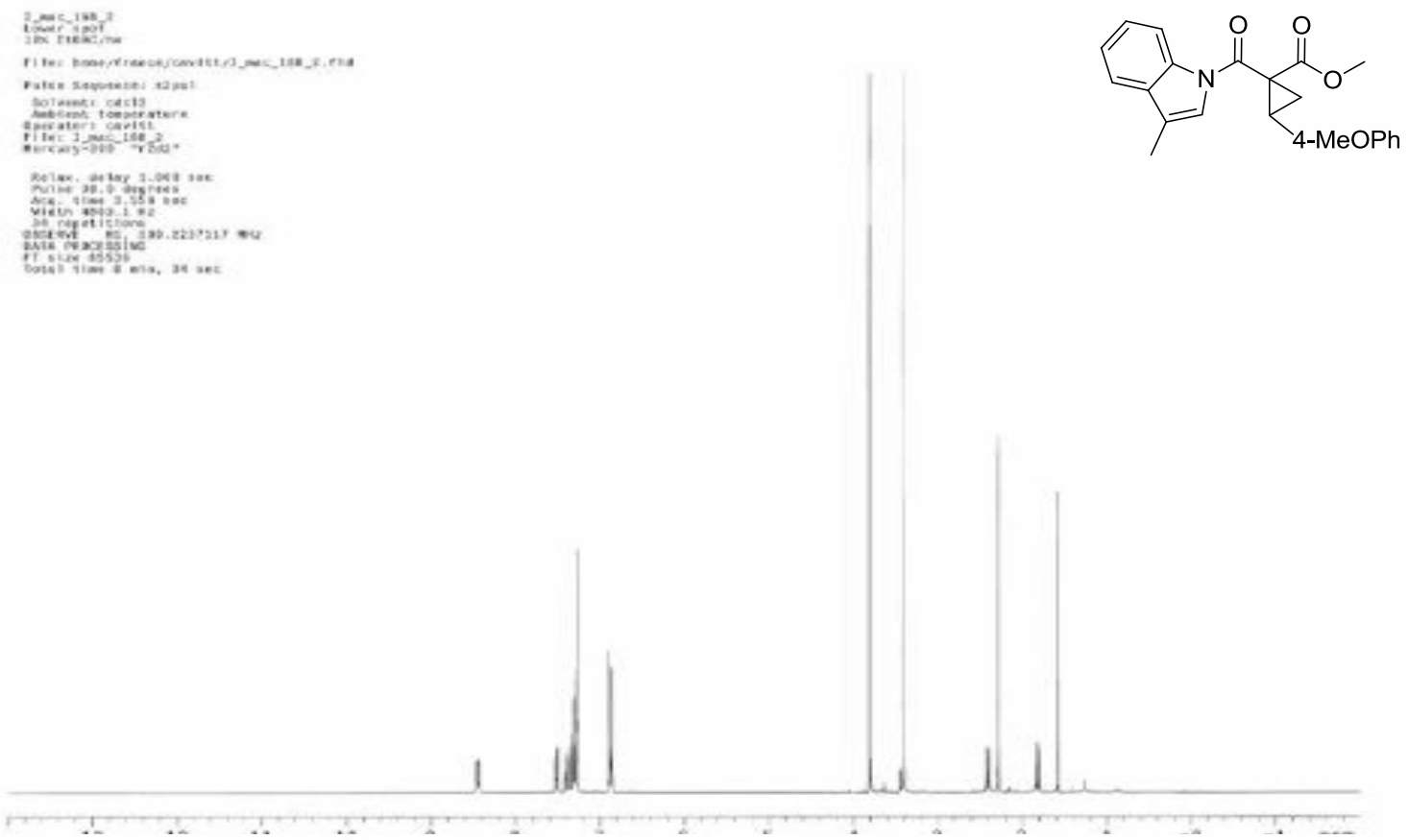


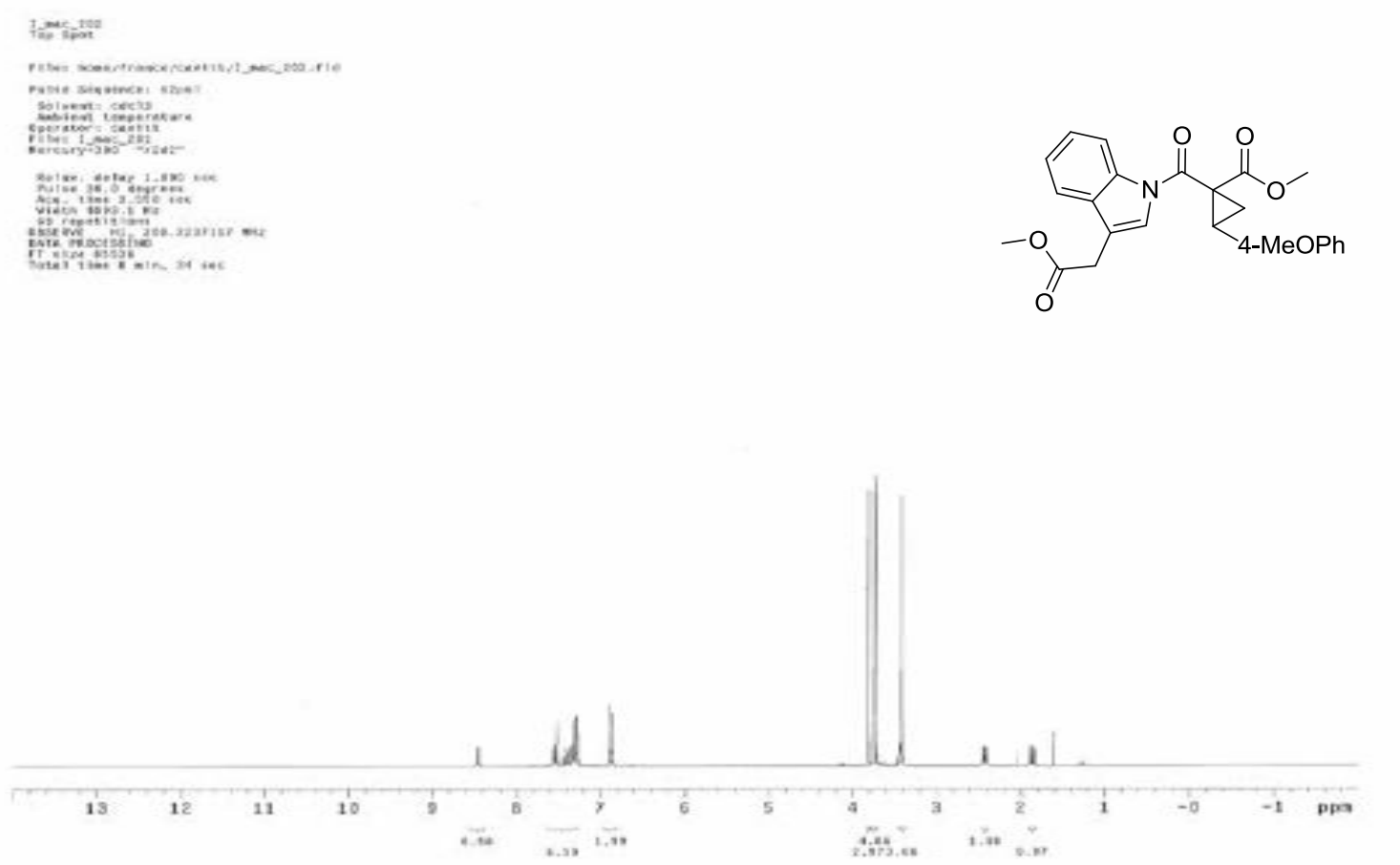
Solvent: cdcl3
Temp. 21.0 C / 294.1 K
Operator: dpatil
Mercury-300 "r2d2"

Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 3.550 sec
Width 4803.1 Hz
46 repetitions
OBSERVE H1, 300.2185002 MHz
DATA PROCESSING
FT size 65536
Total time 158 hr, 30 min, 28 sec






4-MeOPh


4-MeOPh
13
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm

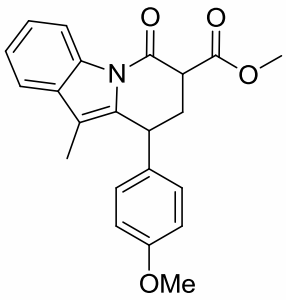
Std Proton parameters

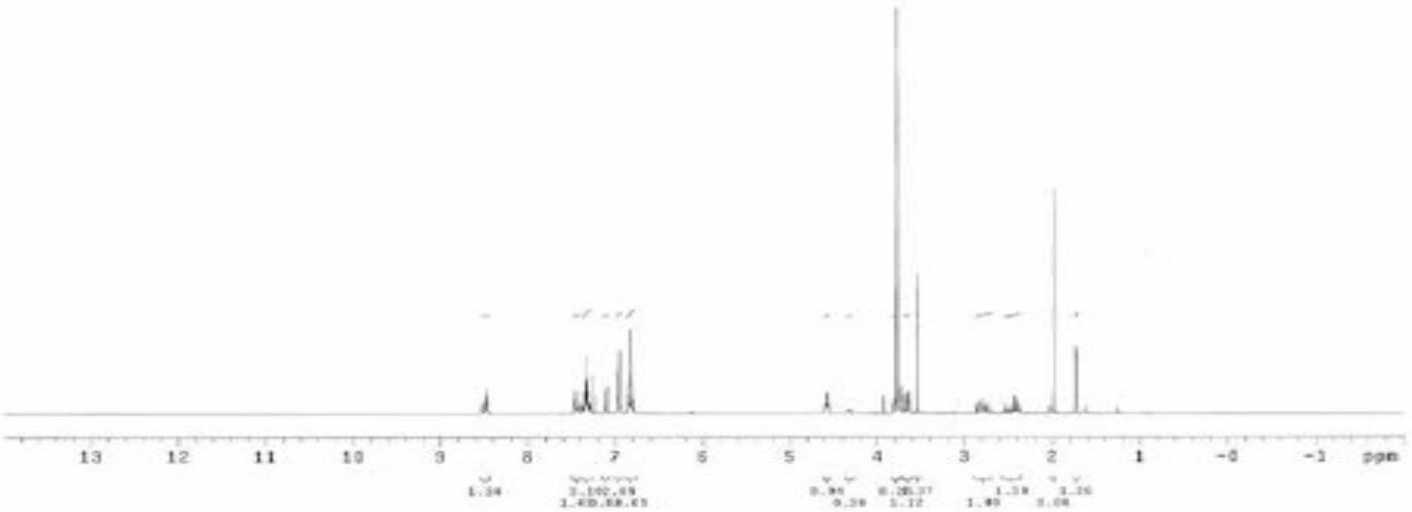
Sample: 6-Methyltryptamine-cyclo-H
File: mp

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 22.8 C / 295.1 K
Operator: apatil
Mercury-300 "r202"

Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 3.558 sec
Width 5600.1 Hz
16 repetitions
OBSERVE H1, 300.2180956 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 16 sec





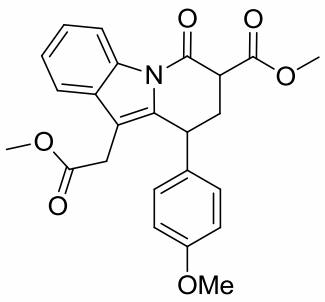
1_mec_105_b

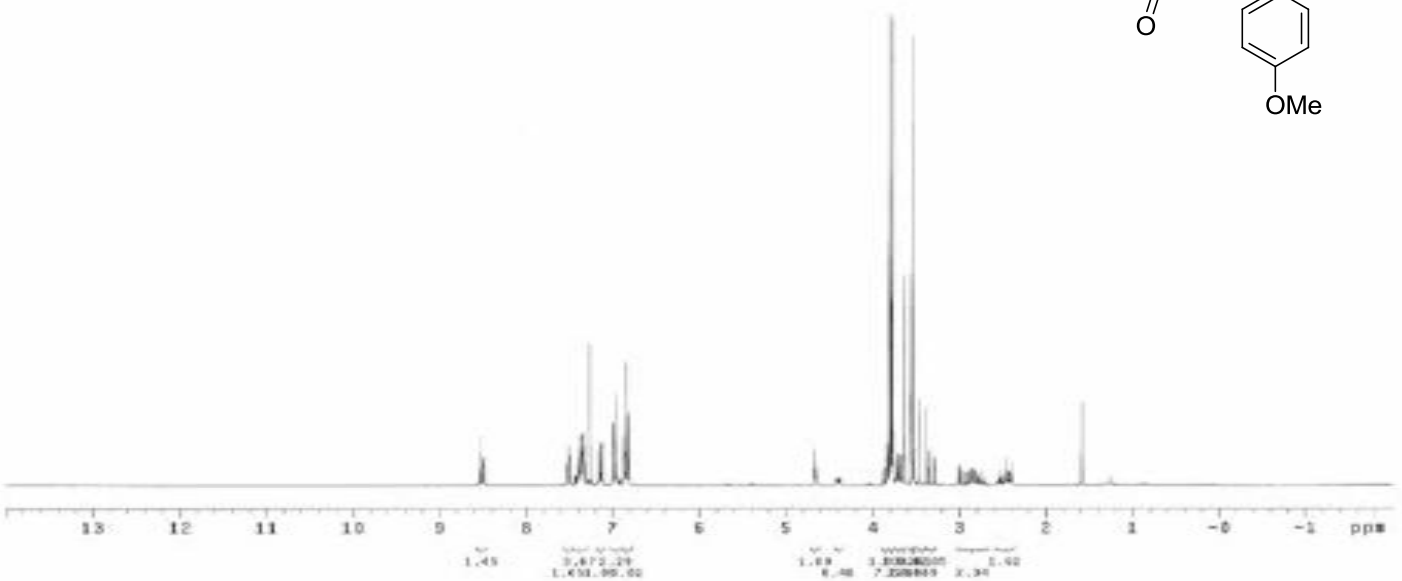
File: home/fdevos/cavitt/1_mec_105_b.fid

Pulse Sequence: s2pul

Solvent: cdcl3
Ambient temperature
Operator: cavitt
File: 1_mec_105_b
Mercury-300 "r2cl"

Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 3.558 sec
Width 4803.1 Hz
32 repetitions
OBSERVE H1, 299.9237180 MHz
DATA PROCESSING
FT size 65536
Total time 0 min, 34 sec



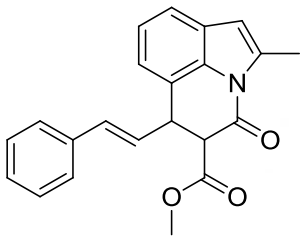


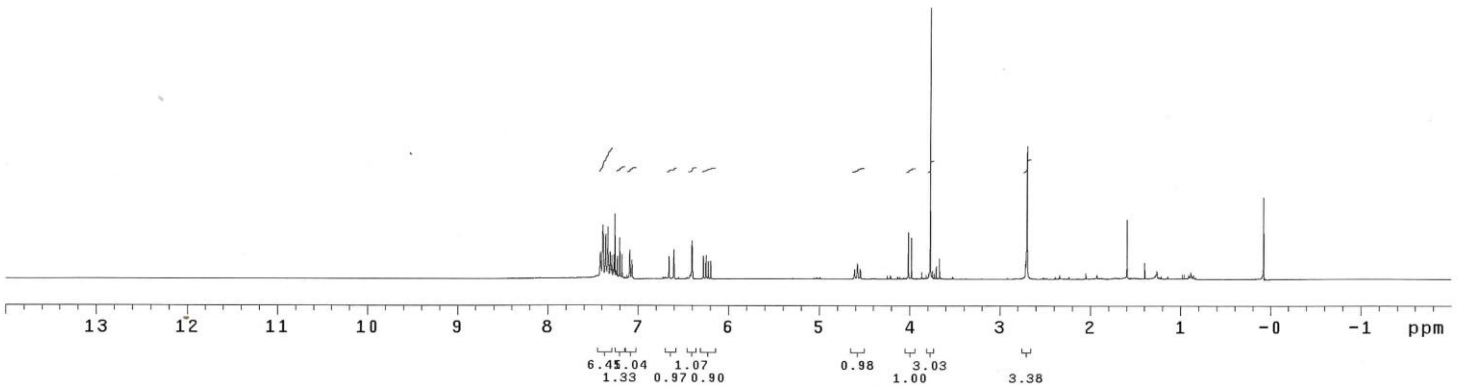
Std Proton parameters

Sample: NB-6-DVP-3-B-H
File: xp

Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Operator: dpatil
Mercury-300 "r2d2"

Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 3.550 sec
Width 4803.1 Hz
46 repetitions
OBSERVE H1, 300.2185002 MHz
DATA PROCESSING
FT size 65536
Total time 15 hr, 51 min, 3 sec



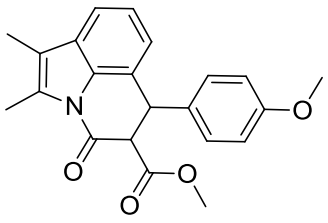


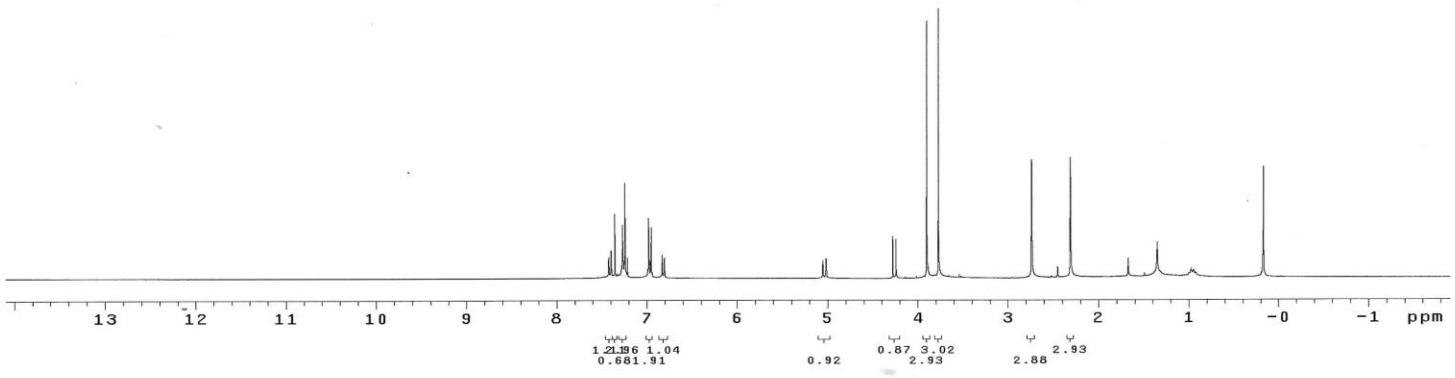
Std Proton parameters

Sample: NB-5-DVP-34-H
File: xp

Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 20.0 C / 293.1 K
Operator: dpatil
Mercury-300 "r2d2"

Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 3.550 sec
Width 4803.1 Hz
16 repetitions
OBSERVE H1, 300.2236825 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 16 sec





NB-1-PG-14-T_2-H

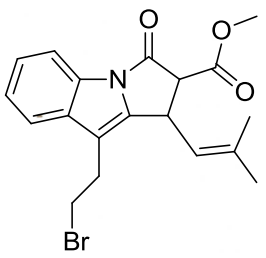
~~NB-1-DXP~~ -T_2-C

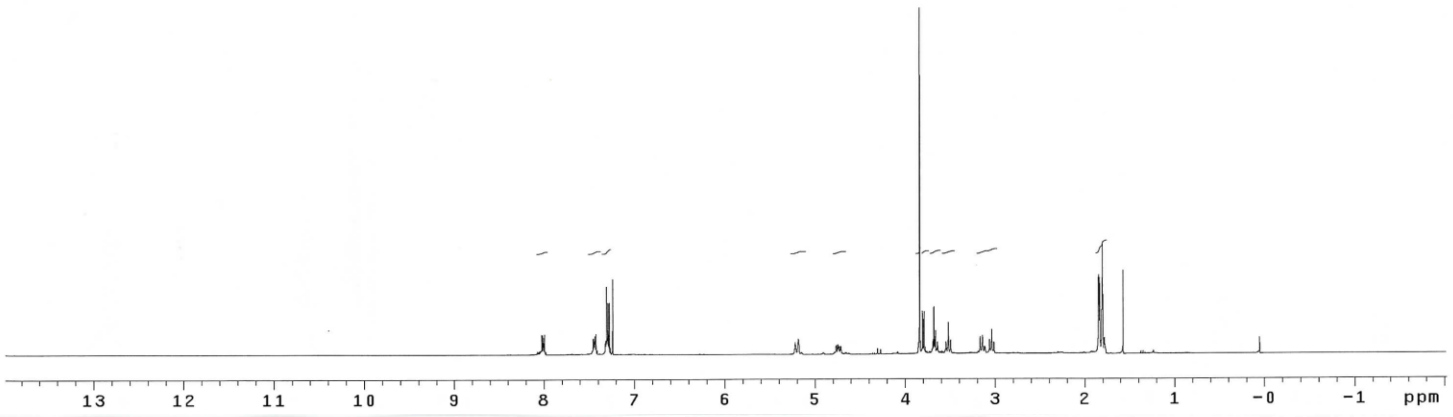
Std Proton parameters

Sample: ~~flinderole-cyclin~~
File: xp

Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 21.0 C / 294.1 K
Operator: dpatil
Mercury-300 "r2d2"

Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 3.550 sec
Width 4803.1 Hz
54 repetitions
OBSERVE H1, 300.2185070 MHz
DATA PROCESSING
FT size 65536
Total time 15 hr, 51 min, 3 sec



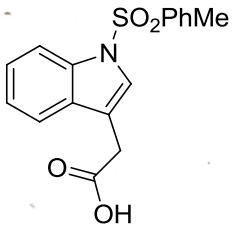


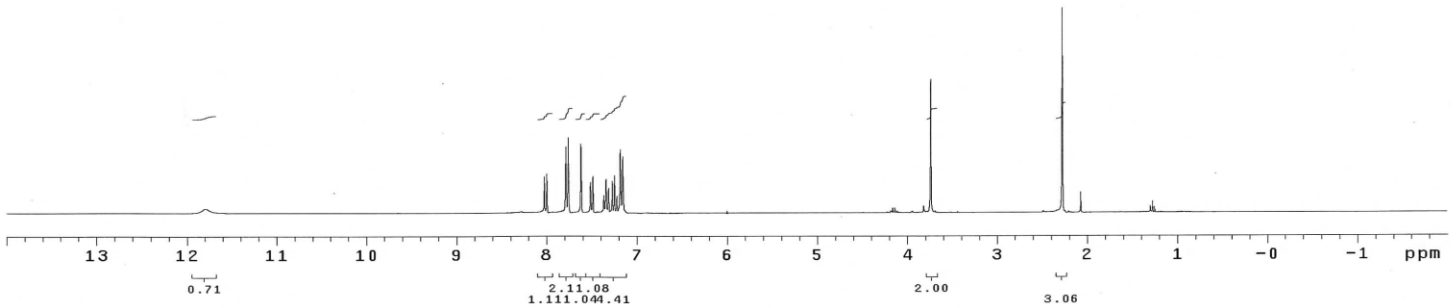
lower spot

Sample: NB-6-DVP-6-H
File: xp

Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Operator: dpatil
Mercury-300 "r2d2"

Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 3.550 sec
Width 4803.1 Hz
32 repetitions
OBSERVE H1, 300.2185002 MHz
DATA PROCESSING
FT size 65536
Total time 158 hr, 30 min, 28 sec





Saved as –

Std Proton parameters

Sample: ~~dimethylamide formation N-tosylindole~~
File: xp NB-1-PG-16-A-H.
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 20.0 C / 293.1 K
Operator: dpatil
Mercury-300 "r2d2"

Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 3.550 sec
Width 4803.1 Hz
34 repetitions
OBSERVE H1, 300.2185002 MHz
DATA PROCESSING
FT size 65536
Total time 158 hr, 30 min, 28 sec