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Racemization Studies and Absolute Stereochemistry Determination of Cannabichromene and Development of Cine Substitution of *N*-Phenylsulfonyl 3-Substituted Indoles

A Dissertation submitted in partial satisfaction
of the requirements for the degree of

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in

Chemistry

by

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December 2021

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University of California, Riverside

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ABSTRACT OF THE DISSERTATION

Racemization Studies and Absolute Stereochemistry Determination of Cannabichromene and Development of Cine Substitution of *N*-Phenylsulfonyl 3-Substituted Indoles

by

Alon Roy Llagas Agua

Doctor of Philosophy, Graduate Program in Chemistry
University of California, Riverside, December 2021
Dr. Michael C. Pirrung, Chairperson

Cannabichromene (CBC) is a cannabinoid of special interest because it has been reported as both scalemic and racemic from *Cannabis* plants with an unknown absolute stereochemistry. This observation can be explained by the (partial) racemization of the natural, or original, single CBC enantiomer produced through biosynthesis. CBC was resolved chromatographically, and the enantiomer matching the major enantiomer of scalemic CBC isolated from commercially available, naturally derived cannabinoid products was identified. It was determined that CBC racemized rather slowly under laboratory conditions. However, irradiation of CBC with sunlight can lead to facile racemization. Due to unsuccessful attempts of resolving CBC as well as to prevent its potential racemization, CBC was converted to its [2 + 2] cycloaddition product, cannabicyclol (CBL). Natural CBC was determined as the *R* absolute stereochemistry

based on chiroptical data for related natural products and the absolute configuration of a CBL analog determined by X-ray crystallography.

The derivatization of indoles is an important transformation because of the numerous biologically relevant indole-containing compounds. Due to their electron-rich nature, indoles typically behave as nucleophiles in a reaction. However, indoles containing a leaving group on the nitrogen and an electron-withdrawing group on the ring can undergo a cine substitution reaction allowing for C2-functionalization. Pioneering work of Somei showed the cine substitution of *N*-methoxy 3-formylindole with a variety of oxygen-, nitrogen-, and carbon-centered nucleophiles. However, due to the lack of availability of *N*-methoxy indoles and challenge of making them, *N*-sulfonyl indoles were chosen as ideal substrates for cine substitution. The cine substitution of *N*-phenylsulfonyl 3-substituted indoles with primary alkyl alcohol nucleophiles afforded the desired products in 67 to 88% yield. Formation of side products, for example, 3-substituted indole and sulfonylated nucleophile, can be greatly dependent on the reaction conditions.

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Chapter 1: Introduction on Cannabichromene and Related Cannabinoids

1.1 *Cannabis Sativa* L. and Cannabinoids

Cannabis sativa L. (Figure 1.1) has been an essential plant with numerous applications, such as food, fiber, medicine, and recreation, for over 5000 years.[1] Originating from Central and Northeast Asia, the cultivation and use of *Cannabis* have spread worldwide throughout the years with current usage mainly for its psychoactive as well as therapeutic properties, e.g., analgesic, sedative, anti-inflammatory, anti-spasmodic, and anti-convulsant.[1]

Figure 1.1 *Cannabis sativa* L. (Image copied from ref. 1b.)

A major deterrent on *Cannabis* has historically been its legality. Due to safety concerns on the psychoactive effects and long-term use of *Cannabis*, the United States made the medicinal use of *Cannabis* illegal in 1970 and any compounds isolated from *Cannabis* were restricted and classified as Schedule I drugs. Although *Cannabis* is still prohibited under U.S. federal regulations, its recreational use in many U.S. states has been decriminalized in 2020, resulting in increased demands of its consumption.

Cannabis is a flowering plant covered with crystal-like structures called trichomes, which are resin secreting glands (Figure 1.2).[1b,2] The resin contains bioactive compounds, such as cannabinoids, that give rise to the psychotropic and medicinal effects of *Cannabis*. There are more than 60 known cannabinoids, or terpenophenolic compounds found in *Cannabis*, many of which are chiral and optically active.[3]

Figure 1.2 Trichomes on *Cannabis*. (Image copied from ref. 2.)

1.2 Tetrahydrocannabinol and Cannabidiol

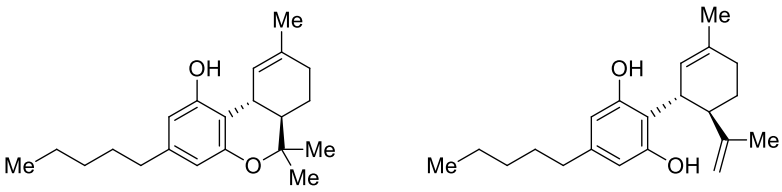


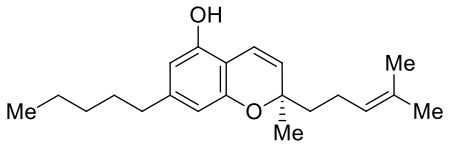
Figure 1.3 Structures of THC and CBD.

Tetrahydrocannabinol (THC) (Figure 1.3) is the most abundant cannabinoid in marijuana, which is *Cannabis* containing more than 0.3% THC, and well-known for its psychoactive effect.[4] In 1964, THC was isolated from *Cannabis* by Mechoulam with an optical rotation of -140° and its structure was elucidated.[5] In 1967, Mechoulam determined the absolute configuration of THC to be (*R,R*)-*trans*.[6] Natural THC ((–)-(*R,R*)-*trans*) was marketed as a drug (dronabinol) in 1985 for chemotherapy-induced nausea.[7] (–)-(*R,R*)-THC is 100 times more potent than (+)-(*S,S*)-THC in depressing schedule-controlled behavior in monkeys.[8] Meanwhile, (+)-*trans*-THC and (+)-*cis*-THC are less effective than (–)-*trans*-THC (their potency differed by at least tenfold) in the dog static-ataxia test.[8] Interestingly, (–)-*cis*-THC is able to elicit a full tetrad response (hypothermia, catalepsy, hypolocomotion, and analgesia) in mice while (+)-*cis*-THC is inactive.[9]

Cannabidiol (CBD) (Figure 1.3) is the most abundant cannabinoid in hemp, which is *Cannabis* containing 0.3% or less THC.[4] CBD was isolated in 1940 with an optical rotation of -119° by Adams and its (*R,R*)-*trans* absolute configuration was established in 1969 by Petrzilka.[10] It is a nonpsychotropic compound that possesses medicinal properties.

In 2018, Epidiolex, the first and only FDA-approved prescription plant-derived CBD, hit the market to help treat seizures. CBD is in over 100 clinical studies, which include pain, Parkinson disease, Crohn disease, traumatic brain injury, Prader-Willi syndrome, Rett syndrome, and mental health conditions (e.g. addiction disorders).[4b] Surprisingly, the unnatural enantiomer of CBD ((+)-(*S*,*S*)) is not completely inactive: both CBD *trans* enantiomers are essentially equipotent in anticonvulsant activity.[11] No bioactivity has been reported for *cis*-CBD isomers.

1.3 Cannabichromene



1

Figure 1.4 Structure of CBC **1**.

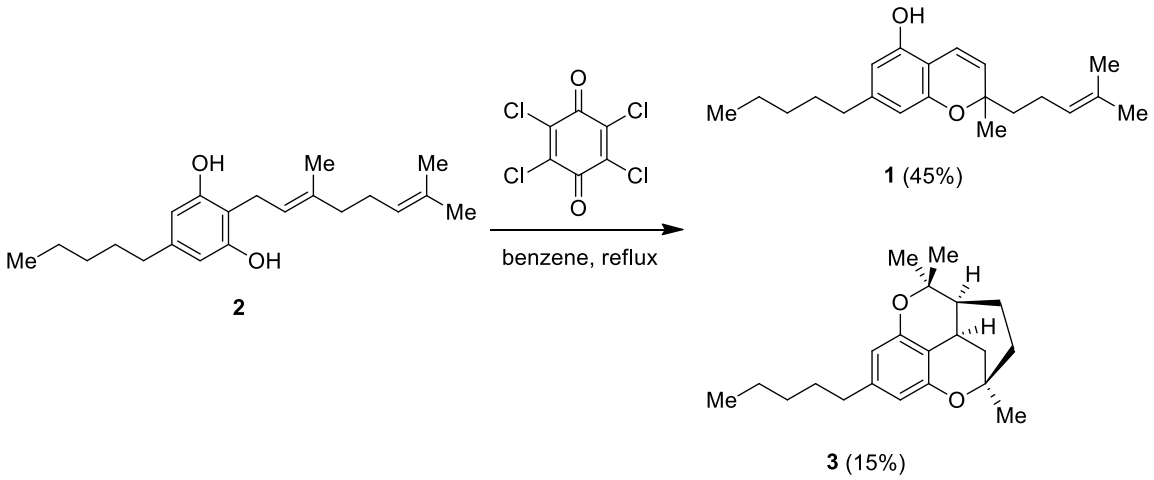
Cannabichromene (CBC) **1** (Figure 1.4) is the least studied and abundant cannabinoid in comparison to THC and CBD. As a nonpsychoactive cannabinoid, **1** displays important biological properties, such as anti-bacterial, anti-microbial, and anti-fungal.[12] It is also an agonist of transient receptor potential ankyrin 1 (TRPA1), which is a calcium ion channel that functions as a pain sensor.[13]

CBC **1** is of particular interest because it is a chiral molecule that has been described as both racemic[14] and scalemic[4a,15] in Nature. And unlike THC and CBD, which have well known absolute configurations, the stereochemistry of **1** has not been determined. In 1966,

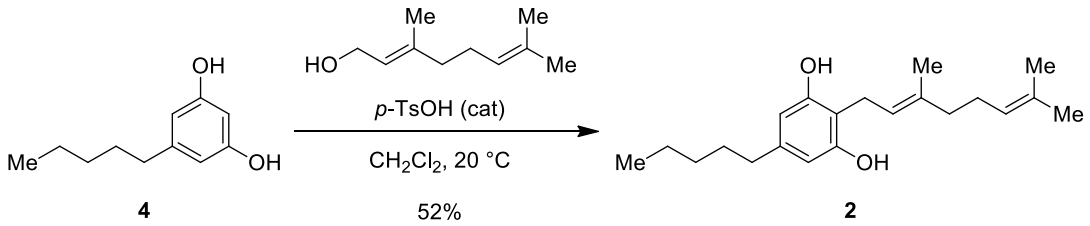
both Claussen[16] and Mechoulam[17] independently isolated **1** as a minor component from *Cannabis sativa* L. and reported optical rotation values of +3.4 and -9°, respectively. In 1971, Mechoulam reported that natural **1** has no optical activity and is a racemic mixture upon further purification.[18]

1.4 Chemical Syntheses of Cannabichromene

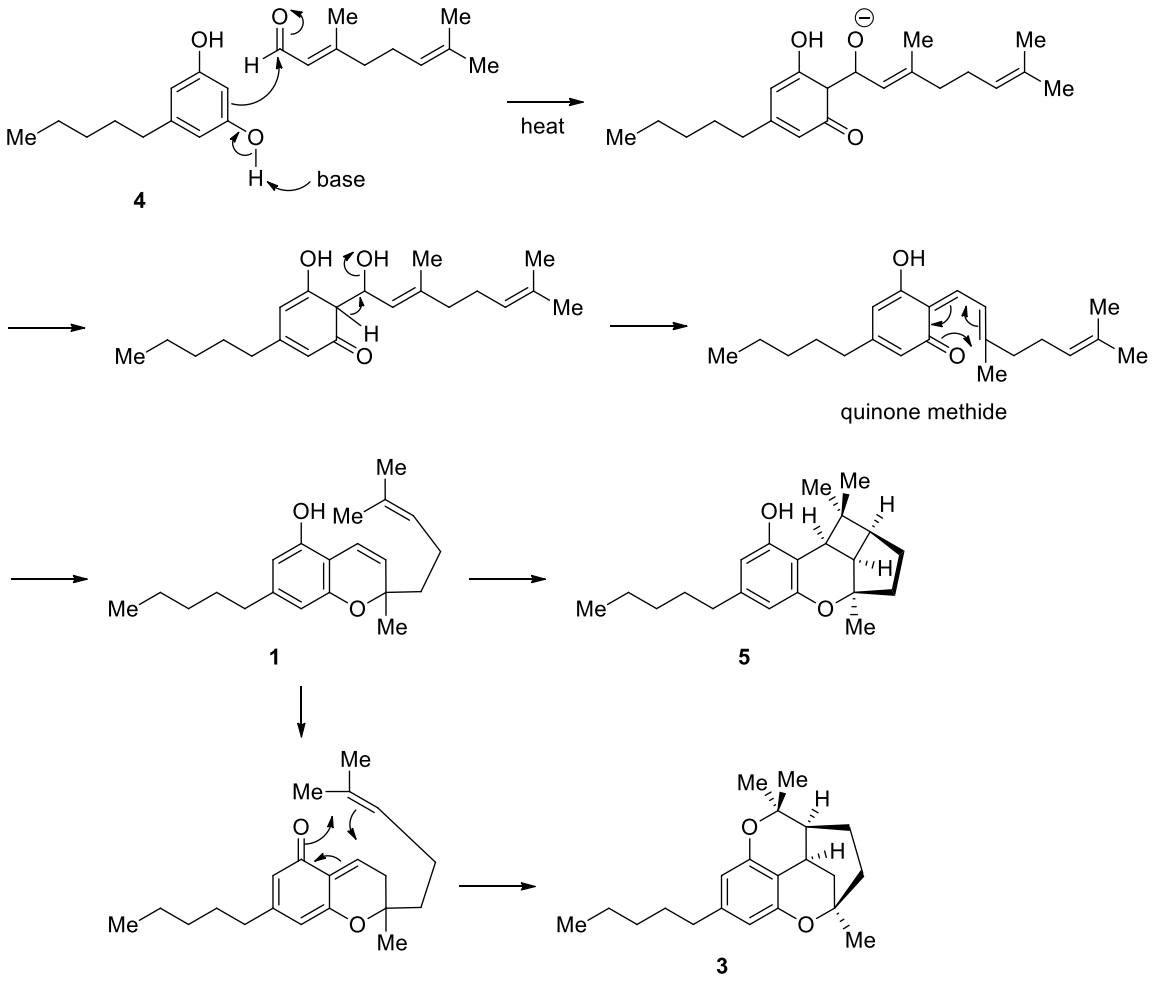
In 1968, the first total synthesis of racemic CBC **1** was reported by Mechoulam in 45% yield via chloranil dehydrogenation of cannabigerol (CBG) **2** in boiling benzene (Scheme 1.1).[19] Cannabicitran (CBT) **3** was also formed in a smaller amount. Mechoulam made **2** from 5-*n*-pentylresorcinol (olivetol) **4** and geraniol with catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH), in methylene chloride (CH_2Cl_2) (Scheme 1.2).[20]



Scheme 1.1 Chloranil dehydrogenation of CBG **2** by Mechoulam.



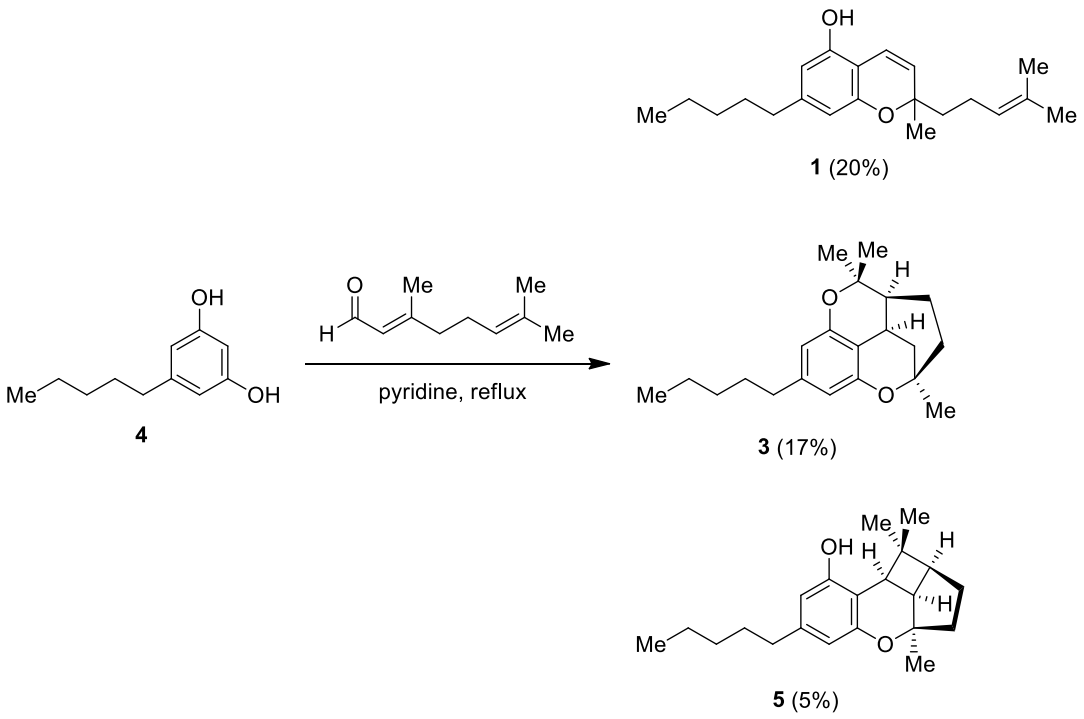
Scheme 1.2 Mechoulam's synthesis of CBG **2** from olivetol **4** and geraniol.



Scheme 1.3 Reaction of olivetol **4** and citral under basic conditions.

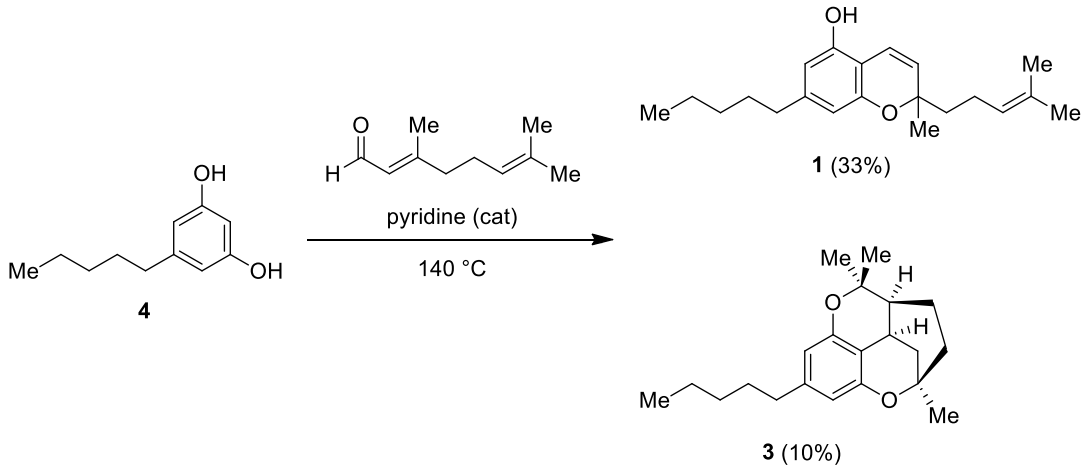
However, the classic formation of CBC **1** comes from the tandem Knoevenagel-electrocyclic reaction of olivetol **4** and citral under basic conditions via quinone methide intermediate (Scheme 1.3).[4a,21] Different reactions of **1** can occur to eventually form the intramolecular [2 + 2] and [4 + 2] cycloaddition byproducts, cannabicyclol (CBL) **5** and CBT **3**, respectively.

Later in 1968, Razdan made racemic CBC **1** in 20% yield by reacting olivetol **4** and citral in pyridine under reflux (Scheme 1.4).[21a] Racemic CBL **5** was obtained in 5% yield during the reaction; this was the first total synthesis of (±)-**5**. CBT **3** was also formed in 17% yield.



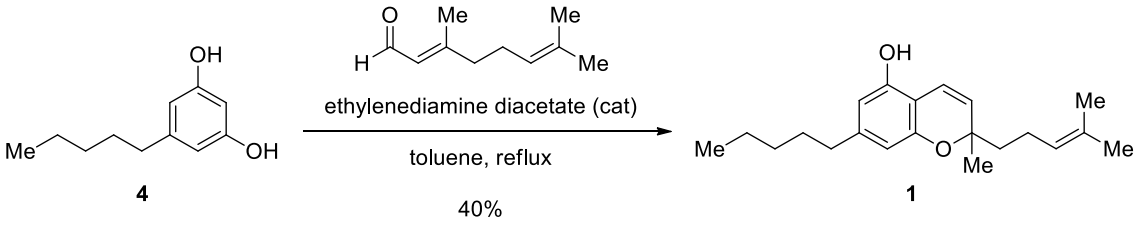
Scheme 1.4 Razdan's reaction of **4** and citral in refluxing pyridine.

Crombie performed the pyridine-catalyzed condensation of olivetol **4** and citral at 140 °C to make CBC **1** in 33% yield while forming CBT **3** in 10% yield (Scheme 1.5).[21b]



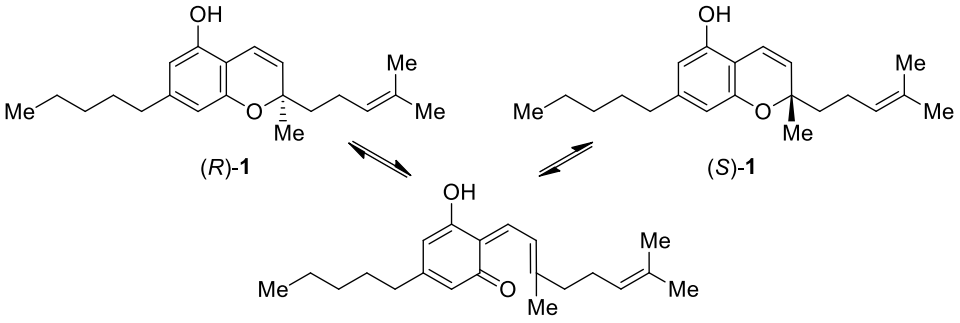
Scheme 1.5 Pyridine-catalyzed reaction of **4** and citral by Crombie.

Lee was able to synthesize CBC **1** in a slightly improved 40% yield from olivetol **4** and citral using catalytic amount of ethylenediamine diacetate in refluxing toluene (Scheme 1.6).[21c]



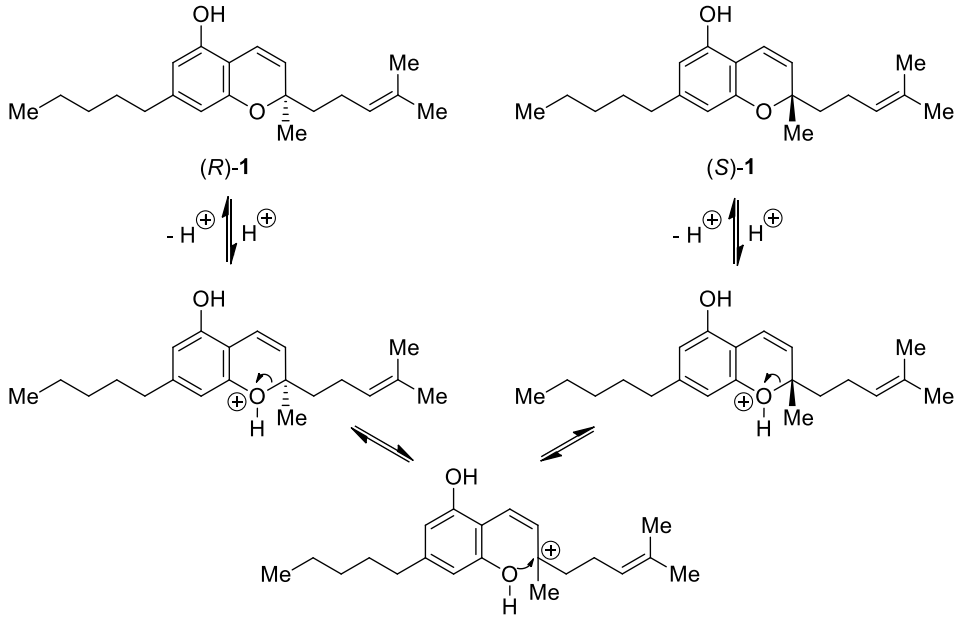
Scheme 1.6 Lee's reaction of **4** and citral with catalytic amount of ethylenediamine diacetate.

1.5 Proposed Racemization of Cannabichromene



Scheme 1.7 Proposed racemization of CBC **1** via electrocyclization.

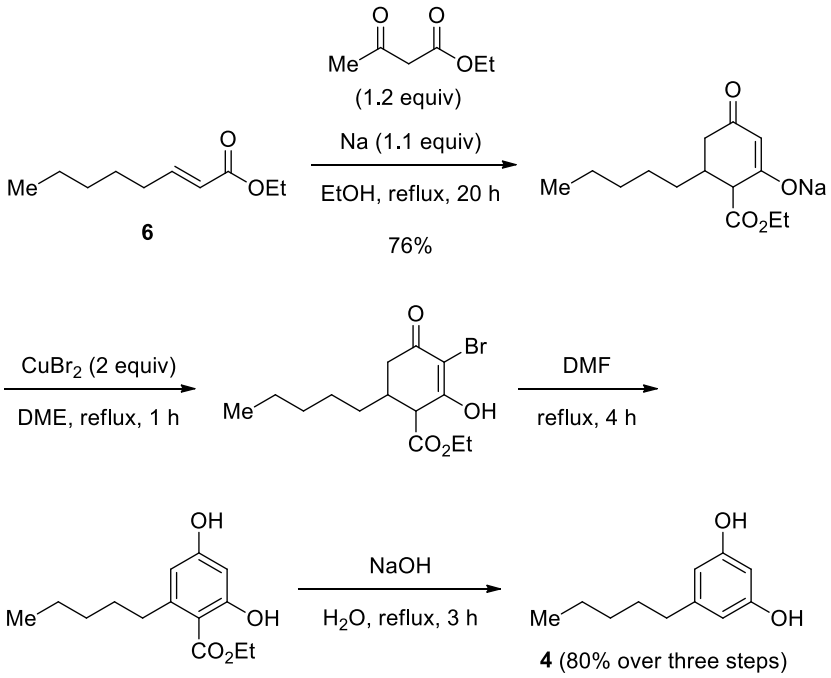
A plausible mechanism for the racemization of CBC **1** is via 6π-electrocyclic ring opening to form the achiral quinone methide intermediate (Scheme 1.7). The electrocyclic ring closing reaction has been proposed towards the synthesis of (±)-**1** from olivetol **4** and citral as shown in the previous section. Another possible racemization pathway of **1** is by ether protonation and tertiary allylic cation formation (Scheme 1.8).



Scheme 1.8 Proposed racemization of **1** via protonation of ether and formation of tertiary allylic cation.

1.6 Methods for Making 5-Alkylresorcinols

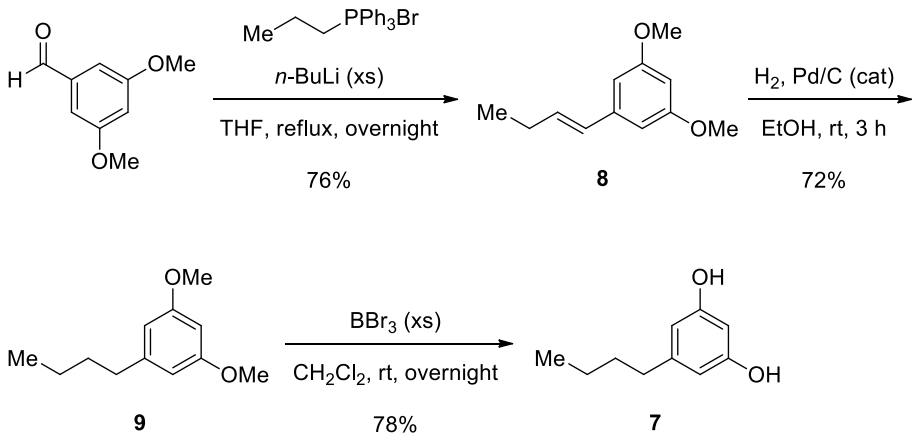
Since olivetol **4** is a precursor of CBC **1**, understanding the formation of 5-alkylresorcinols is important. Enolate chemistry has been applied towards the multistep synthesis of 5-alkylresorcinols.[22] For example, Marmor was able to prepare **4** via Michael addition-intramolecular Claisen condensation of an α,β-unsaturated ester **6** and ethyl acetoacetate followed by aromatization, hydrolysis, and decarboxylation (Scheme 1.9).[22b]



Scheme 1.9 Marmor's formation of olivetol **4** via Michael addition-intramolecular Claisen condensation.

Starting with the aromatic ring, concise syntheses of 5-alkylresorcinols have been done via the Wittig reaction of 3,5-dimethoxybenzaldehyde and alkylphosphonium salts.[23] For instance, 5-*n*-butylresorcinol **7** can be made by treating 3,5-dimethoxybenzaldehyde with *n*-propyltriphenylphosphonium bromide and *n*-butyllithium (*n*-BuLi) to form 5-(1-

butenyl)-1,3-dimethoxybenzene **8** followed by hydrogenation and demethylation (Scheme 1.10) as described by Wrasidlo.[23b]



Scheme 1.10 Wrasidlo's synthesis of 5-*n*-butylresorcinol **7** via Wittig olefination.

1.7 Cannabicyclol

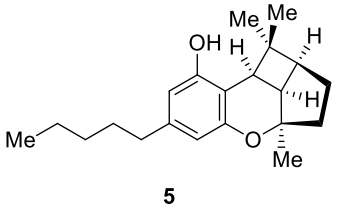
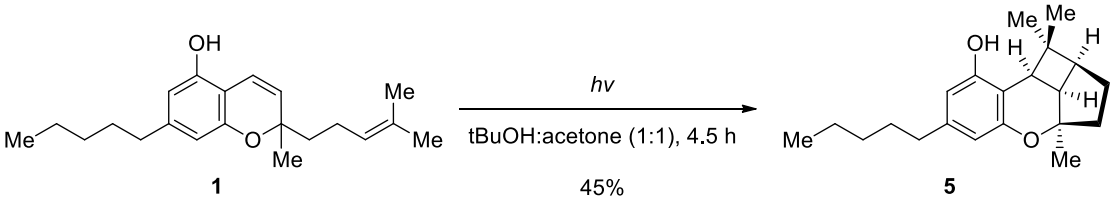


Figure 1.5 Structure of CBL **5**.

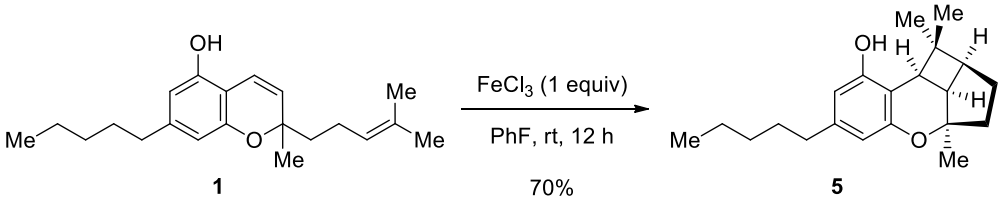
Cannabicyclol (CBL) **5** (Figure 1.5) is a cannabinoid isolated from *Cannibis* in 1968 by Mechoulam that showed an optical rotation of -3°.[24] The structure of **5** was confirmed in 1970 by Whiting using X-ray analysis.[25] However, in 1972, Shoyama isolated **5** from *Cannabis* and reported its optical rotation to be zero.[26] As a result, **5** has

been described as racemic.[14] And like CBC **1**, the natural absolute stereochemistry of **5** is unknown.

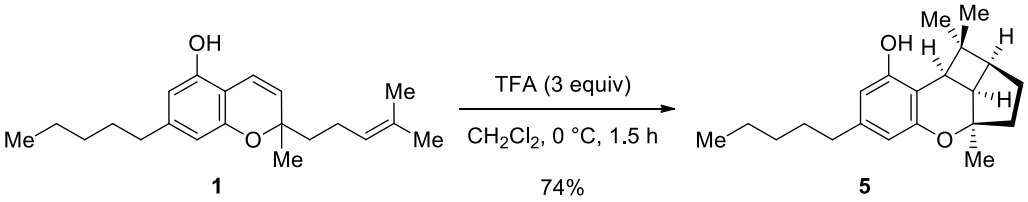
CBL **5** can be synthesized from **1** via intramolecular [2 + 2] cycloaddition. The photochemical [2 + 2] cycloaddition of **1** to **5** (Scheme 1.11) was conducted by Crombie using a 450 watt Hanovia lamp.[27] The [2 + 2] cycloaddition of **1** can also be performed in the presence of a Lewis acid. For instance, **1** can react with iron trichloride ($FeCl_3$) (Scheme 1.12) and trifluoroacetic acid (TFA) (Scheme 1.13) to form **5** as reported by Lee[28] and Hsung[29], respectively.



Scheme 1.11 Crombie's synthesis of CBL **5** via photochemical [2 + 2] cycloaddition of **1**.

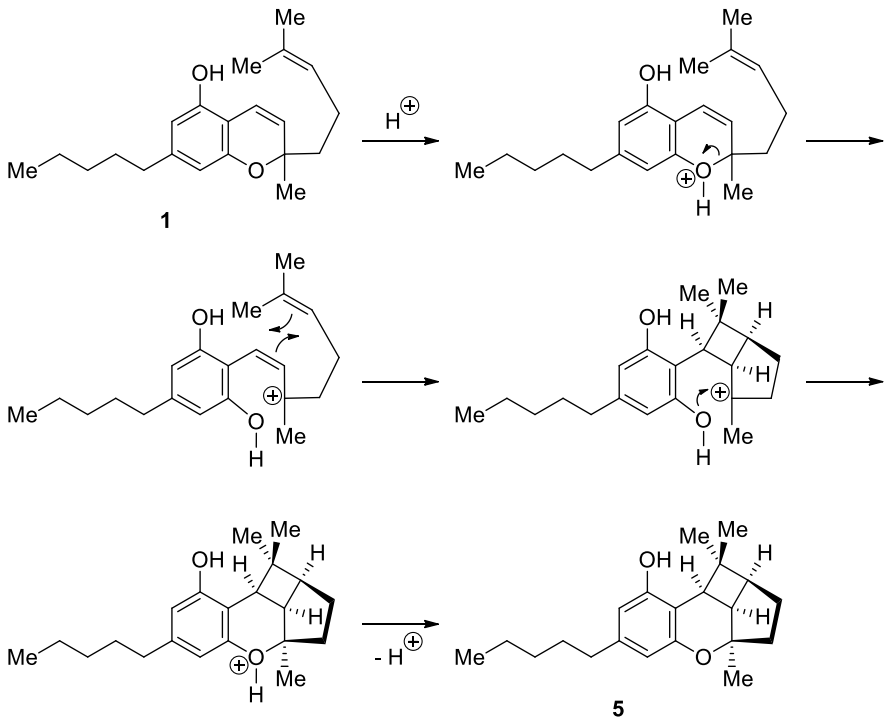


Scheme 1.12 Lee's synthesis of **5** via $FeCl_3$-promoted [2 + 2] cycloaddition of **1**.



Scheme 1.13 Hsung's synthesis of **5** via TFA-mediated [2 + 2] cycloaddition of **1**.

The [2 + 2] cycloaddition of **1** under acidic conditions to form CBL **5** was described as a stepwise, cationic process by Hsung. Earlier work by Gassman showed that allylic cations are excellent dienophiles for cycloaddition reactions.[30] Thus, the proposed mechanism for the formation of **5** via [2 + 2] cycloaddition of **1** in the presence of an acid begins with the protonation of the ether and formation of the tertiary cation (Scheme 1.14). The allylic cation intermediate then undergoes the [2 + 2] cycloaddition to form the cyclobutane moiety followed by cyclization of the benzopyran ring and deprotonation to afford **5**.



Scheme 1.14 Proposed mechanism of an acid-mediated [2 + 2] cycloaddition of **1**.

1.8 Cannabichromenic Acid

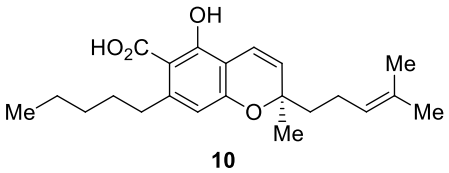
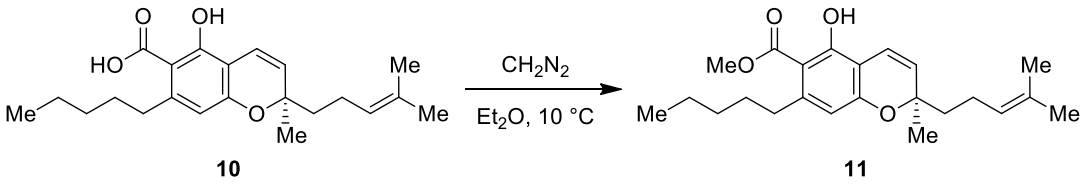
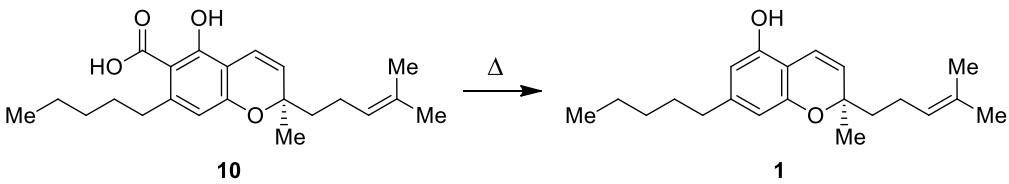


Figure 1.6 Structure of CBCA **10**.

Cannabichromenic acid (CBCA) **10** (Figure 1.6) is the acid precursor of CBC **1** during biosynthesis (as will be discussed in the next section). In the original isolation of **10** from *Cannabis* in 1968, Shoyama reported its optical rotation as +4.8°.[31] In order to determine the identity of **10**, its methyl ester variant **11** was synthesized using diazomethane (CH_2N_2) in ether at 10 °C (Scheme 1.15) and compared to **1** by proton nuclear magnetic resonance (^{1}H NMR). The methyl ester derivative of **10** showed an extra methyl peak and one less aromatic peak compared to **1**, as expected. In addition, **10** was heated to undergo decarboxylation and form **1** (Scheme 1.16), which was confirmed by spectral data.



Scheme 1.15 Shoyama's methylation of CBCA **10**.



Scheme 1.16 Shoyama's thermal decarboxylation of **10**.

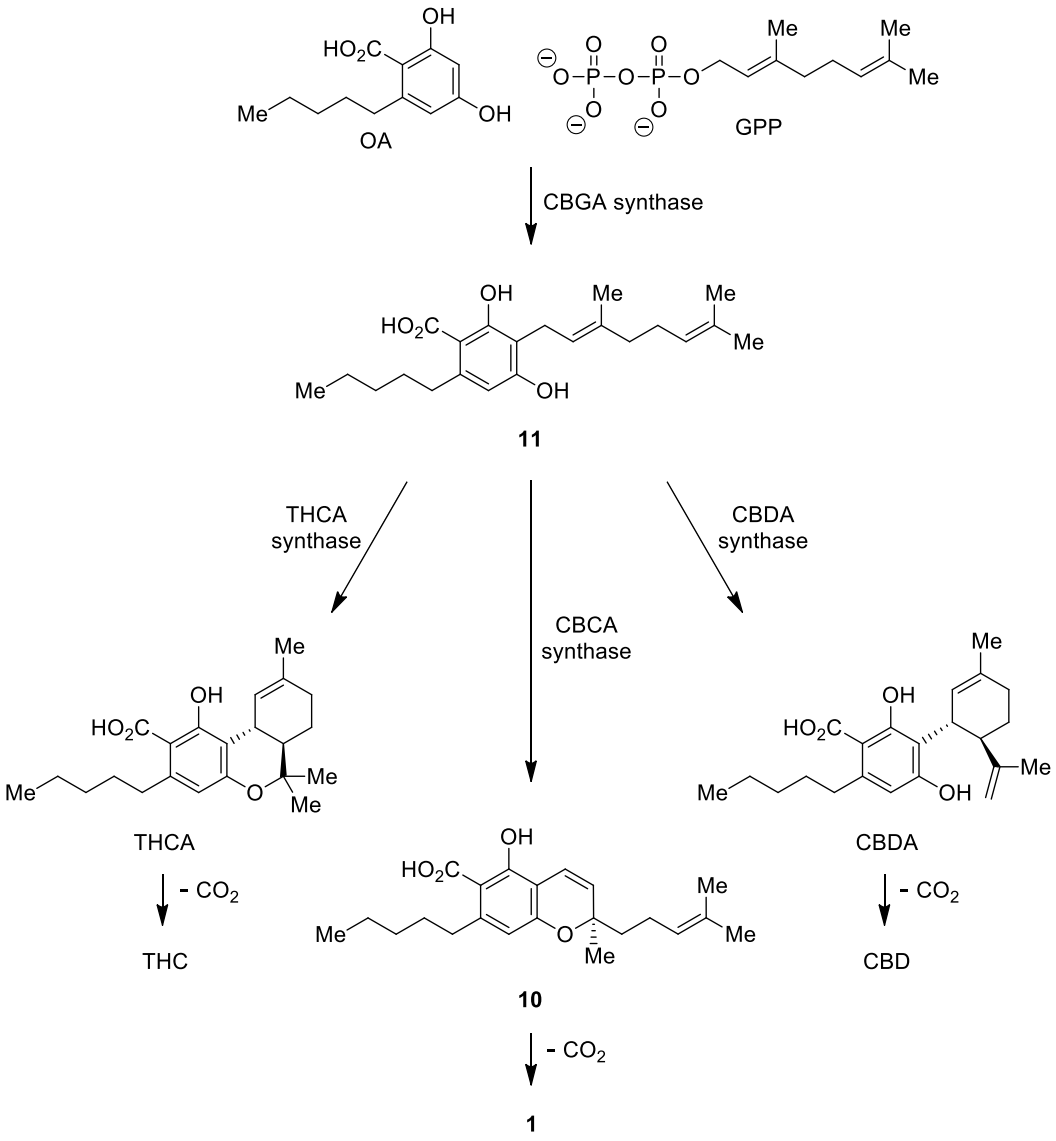
1.9 Biosynthesis of Cannabinoids

Cannabinoids, such as THC, CBD, and CBC **1**, are biosynthesized from monoterpenes and polyketides through the key cannabigerolic acid (CBGA) **11** intermediate (Scheme 1.17).[32] The formation of CBGA is catalyzed by CBGA synthase, which couples olivetolic acid (OA) and geranyl pyrophosphate (GPP). CBGA then has diverging pathways, albeit all through an oxidative cyclization, to form the different cannabinoids based on the enzyme acting upon it. CBGA is converted to:

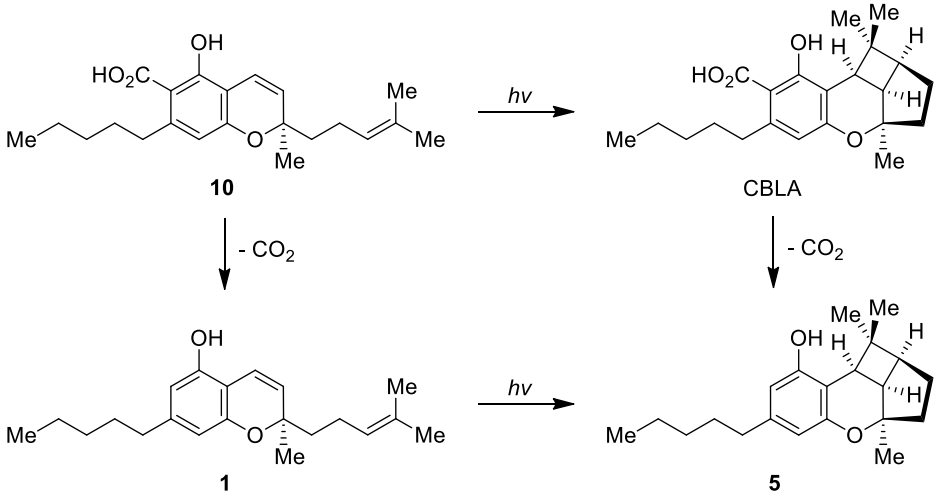
1. tetrahydrocannabinolic acid (THCA) by THCA synthase,
2. cannabidiolic acid (CBDA) by CBDA synthase, and
3. CBCA **10** by CBCA synthase.

CBCA **10** can undergo a photochemical [2 + 2] cycloaddition to synthesize cannabicyclolic acid (CBLA) by sunlight irradiation (Scheme 1.18).[14a,32b,33]

Like the chemical process of converting salicylic acid to phenol via thermal decarboxylation,[34] THCA, CBDA, CBCA **10**, and CBLA can decarboxylate in plants upon exposure to heat to form THC, CBD, CBC **1**, and CBL **5**, respectively (Schemes 1.17 and 1.18).[14,32,33] The thermal decarboxylation of cannabinoids containing the salicylic acid moiety can be achieved in the laboratory as well. For instance, as seen in Section 1.8 and as we will see in Section 1.11, **10** can be decarboxylated by applying heat to yield **1**.[31,35] Also, **5** can be made from **1** in plants via sunlight-induced [2 + 2] cycloaddition (Scheme 1.18).[14,32,33]



Scheme 1.17 Biosynthesis of cannabinoids.



Scheme 1.18 Biosynthesis of CBL **5**.

These chiral cannabinoids are likely formed as a single enantiomer because the enzymes that make them are also chiral. Therefore, if a cannabinoid is isolated as a scalemic mixture (as we will see later with **1**), the presumption is that the *major enantiomer is the natural, or original, single enantiomer formed during biosynthesis, which then partially racemized*.

Due to the ambiguity of solely relying on optical rotation to assert that a compound is racemic, other methods need to be used, such as chiral column chromatography and circular dichroism (CD).

1.10 Chiral Column Chromatography

Chiral column chromatography is an important method used to analyze the ratio of enantiomers and separate enantiomers on a preparative scale.[36] A pair of enantiomers,

isolated from *Cannabis* for instance, can form diastereomeric complexes with the chiral stationary phase (CSP) resulting in different retention time (R_t).

Examples of separation techniques by chiral chromatography are high performance liquid chromatography (HPLC) and supercritical fluid chromatography (SFC). HPLC uses liquid solvent as the mobile phase while SFC uses supercritical liquid (e.g., carbon dioxide). However, both use the same CSP. Therefore, determining the correct CSP is important in the separation of stereoisomers.

CSPs can be composed of either a chiral polymeric backbone, like a polysaccharide, or an achiral stationary support, e.g., silica-gel, coated with a chiral substance as seen in Pirkle-type CSPs. Similar to silica, sugar-based CSPs are fine granular material.

Naturally occurring polysaccharides, typically cellulose and amylose (Figure 1.7), have been used for chiral chromatography. Derivatives of cellulose and amylose as CSPs have different higher-order structures. The β-(1,4)-glucose linkage in cellulose-based CSPs result in a more rigid, linear structure while the α-(1,4)-glucose linkage in amylose-based CSPs lead to a helical one (Figure 1.8). Having two different higher-order structures can influence the ability of two sugar-based CSPs to participate in intermolecular interactions. It is important to note that CSPs with the same sugar backbone (e.g., either both cellulose or both amylose) might correlate in regards to which enantiomer has a faster or slower R_t. However, switching the sugar backbone (e.g., from amylose to cellulose) may result in a switch in elution order of the two enantiomers being resolved.

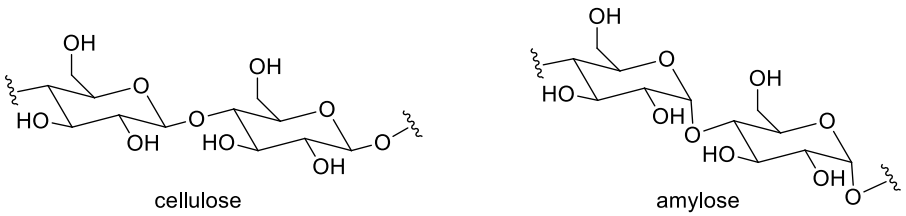


Figure 1.7 Structures of cellulose and amylose.

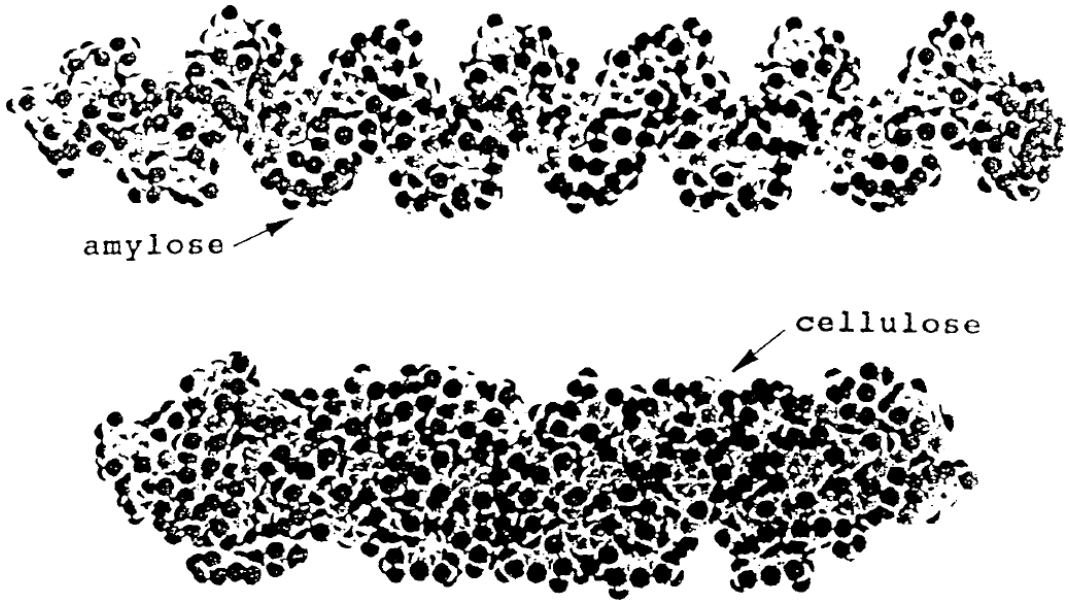


Figure 1.8 Three-dimensional structures of amylose and cellulose chiral columns. (Image copied from ref. 36b.)

The hydroxyl groups of these sugars have been derivatized into carbamates and esters for use as CSPs. Some intermolecular interactions that polysaccharide CSPs can participate in with compounds being resolved are hydrogen bonding, dipole-dipole, and π-π interactions. Examples of derivatized polysaccharide CSPs and their corresponding column trade names have been provided (Table 1.1).

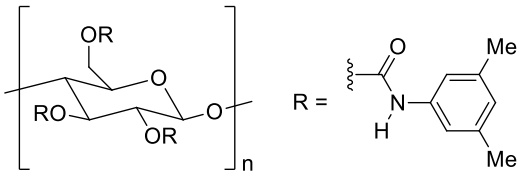
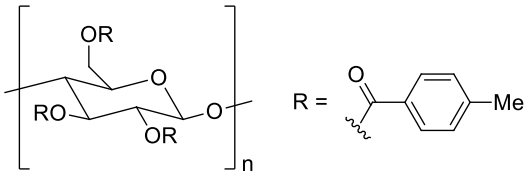
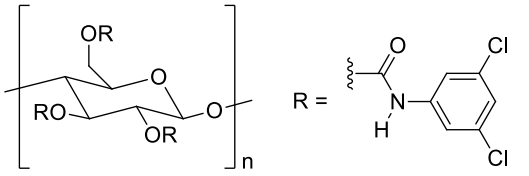
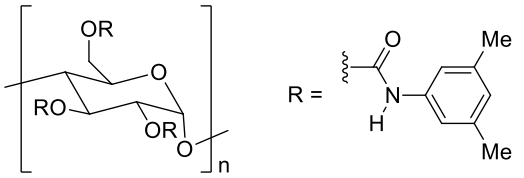
Column Trade Name	Polysaccharide CSP
Chiralcel OD, Lux Cellulose-1	 cellulose tris(3,5-dimethylphenylcarbamate)
Chiralcel OJ, Lux Cellulose-3	 cellulose tris(4-methylbenzoate)
Chiralpak IC, Lux Cellulose-5	 cellulose tris(3,5-dichlorophenylcarbamate)
Chiralpak AD, Lux Amylose-1	 amylose tris(3,5-dimethylphenylcarbamate)

Table 1.1 Examples of polysaccharide-based chiral columns.

Although Pirkle-type CSPs can participate in intermolecular interactions, such as hydrogen bonding and dipole-dipole, they are categorized by their ability to act as either a π-electron acceptor, π-electron donor, or both as a π-electron donor and acceptor.

A structural motif widely used in many Pirkle-type CSPs is the π-acceptor 3,5-dinitrobenzamido group. An example of this is the Whelk-O1 chiral column, which contains the π-electron withdrawing 3,5-dinitrobenzamido group as well as the π-electron donating naphthyl (Figure 1.9).

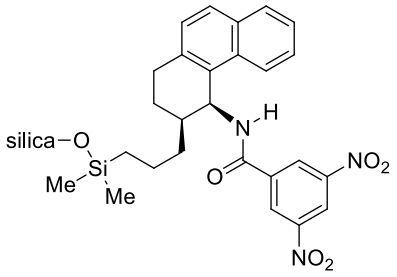
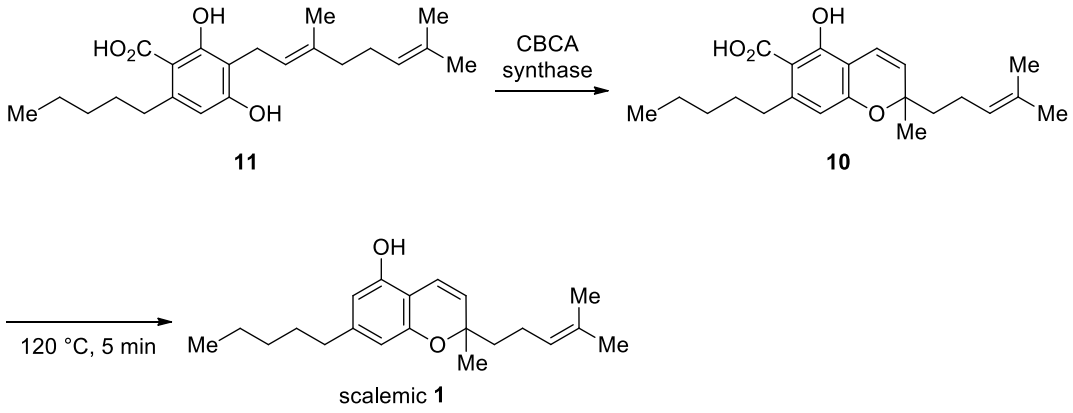


Figure 1.9 Chemical structure of Whelk-O1 chiral column.

1.11 Enzyme-Derived Scalemic Cannabichromene



Scheme 1.19 Synthesis of enzymatically derived CBC **1**.

Morimoto was able to make CBCA **10** from CBGA **11** using a partially purified CBCA synthase from *Cannabis* leaves (Scheme 1.19).[35] In order to determine if the enzyme-derived **10** was made in racemic form, chiroptical data was obtained. The

enzymatically produced **10** gave an optical rotation of almost zero, but it did exhibit a CD signal. Due to Morimoto's unsuccessful attempts to resolve a chemically synthesized racemic **10** under various HPLC conditions, the optical purity of the enzymatically derived **10** could not be analyzed by chromatographic means.

Morimoto then performed the thermal decarboxylation (120 °C, 5 min) of the enzymatically synthesized **10** to afford scalemic CBC **1** (Scheme 1.19). The resulting enantiomers of **1** were separated by chiral HPLC (Figure 1.10) using a Chiralcel OD-R column and their CD spectra (Figure 1.11) were obtained. The natural (or major, enzymatically produced) **1** is the slower eluting enantiomer and is favored by a five to one ratio based on the chiral HPLC. The natural **1** has a positive CD signal at ca. 280 nm. The unnatural **1**, or minor enantiomer formed from the racemization of the natural **1**, has a negative CD signal at the same wavelength. Interestingly, Morimoto shared unpublished information with us: that CD spectra were similar for natural **1** (presumably, from *Cannabis*) and the minor **1** formed from the racemization of the natural, enzymatically derived **1**. Therefore, Morimoto's conclusions about the sign of the CD signal of the natural **1** enantiomer are truly ambiguous.

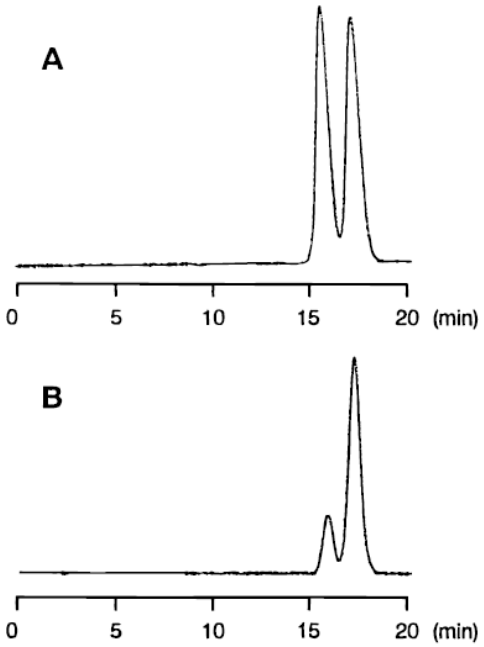


Figure 1.10 A. HPLC of racemic CBC **1** prepared via chemical synthesis. B. HPLC of scalemic **1** via decarboxylation of enzymatically produced CBCA **10**. (Image copied from ref. 35.)

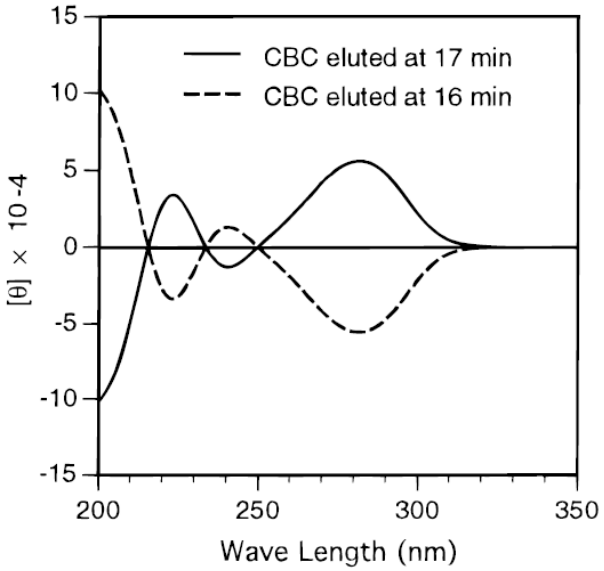


Figure 1.11 CD spectra of natural, enzymatically produced CBC **1** and minor, unnatural **1** formed via racemization. The solid line is the natural, enzymatically derived **1** and the dashed line is the minor, unnatural **1**. (Image copied from ref. 35.)

1.12 Scalemic Cannabichromene from a *Cannabis* Cultivar

A recent study in 2017 by Gasparrini and co-workers showed that CBC **1** from a medicinal *Cannabis* cultivar is scalemic.[15] Using chiral SFC with both (*R*,*R*)- and (*S*,*S*)-Whelk-O1 columns, they were able to resolve the isolated **1** and determine the enantiomeric excess (ee) of about 25% (Table 1.2). According to Gasparrini, the major, natural **1** has a positive CD signal at 280 nm while the minor, unnatural **1** has a negative CD signal at the same wavelength.

CSP config.	Peak name	Enantiomeric ratio	ee (%)
(*R*,*R*)	[CD(–)280]-CBC	37.42	25.16
	[CD(+)280]-CBC	62.58	
(*S*,*S*)	[CD(+)280]-CBC	62.81	25.62
	[CD(–)280]-CBC	37.19	

Table 1.2 Enantiomeric excess of CBC **1** in medicinal *Cannabis* cultivar.

Chapter 2: Cannabichromene Racemization and Absolute Stereochemistry Based on a Cannabicyclol Analog

2.1 Research Goals and Strategy

Establishing the stereochemistry of any bioactive molecule is essential to all its uses, including medicinal. Since enantiomers can have different biological activities, knowing which enantiomer is the active isomer will be important in its use as a therapeutic.

Unlike THC and CBD, which have well known absolute configurations, CBC **1** does not. Therefore, one of the goals of this work is to establish the absolute stereochemistry of **1**. The absolute configuration of CBL **5** will also be elucidated in the process.

Since **1** has been reported as both racemic and scalemic in *Cannabis* plants, understanding this observation is important. A reasonable explanation for this is that natural **1** is formed as a single enantiomer during biosynthesis and then (partially) racemizes. Thus, the other goal is to perform racemization studies of **1** under various conditions to determine how easily it occurs.

Understanding the ease of racemization of **1** as well as determining the absolute stereochemistry of the natural **1** were undertaken and achieved as described here.[37] The intended overall strategy to determine the absolute configuration of **1** is by the following:

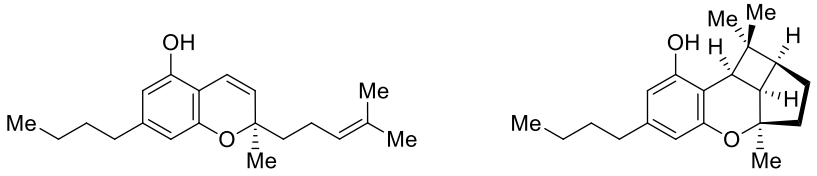
1. resolve racemic **1**,

2. identify which of those enantiomers is the natural, or major, isomer found in *Cannabis* plants, and
3. determine the absolute configuration of that enantiomer by some means.

Meanwhile, the racemization of **1** can be conducted by the following way:

1. obtain a pure enantiomer of **1** and allow it to react under different conditions, and
2. analyze the percent racemization at various time points.

However, since cannabinoids currently have ambiguous regulatory status in the United States with some being labeled as Schedule 1 drugs, *nor* analogs of CBC and CBL were used for the remainder of the work. *nor*-CBC **12** and *nor*-CBL **13** consist of a butyl group (Figure 2.1) instead of a pentyl present in CBC **1** and CBL **5**. Because only a subtle and minor change in the alkyl chain occurred, properties (e.g., chiroptical and biological) of *nor* analogs of CBC and CBL can be validly compared to those of CBC **1** and CBL **5**. These chiroptical properties will help determine the absolute stereochemistry of natural CBC.



12 **13**

Figure 2.1 Structures of *nor*-CBC **12** and *nor*-CBL **13**.

Racemic *nor*-CBC **12** was obtained by reacting 5-*n*-butylresorcinol **7** with citral. The resolution of (±)-**12** was attempted by coupling (±)-**12** to chiral molecules, but the separation of the resulting diastereomeric products was unsuccessful. Racemic **12** was therefore converted to (±)-*nor*-CBL **13** and derivatized, which allowed for its successful separation. In addition, the conversion of **12** to **13** became a strategy to lock in its stereochemistry and prevent the racemization of **12** during the determination of its absolute stereochemistry. Unlike CBC **1**, CBL **5** does not have an obvious pathway of racemization. The absolute stereochemistry of natural CBC **1** can then be elucidated based on a CBL analog of known absolute configuration via its X-ray crystal structure. During this process, the absolute configuration of natural CBL **5** can also be determined.

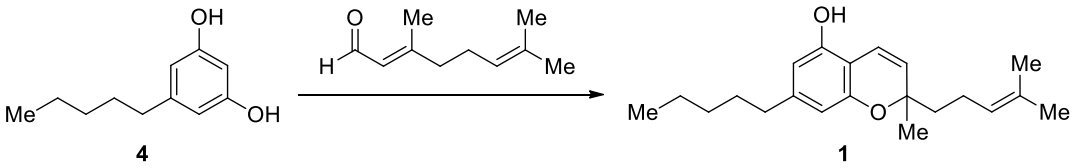
2.2 Identification of Natural Cannabichromene and Synthesis and Resolution of Racemic Cannabichromene

We established a collaboration with Dr. Charles Marlowe and Dr. Philip Barr from BayMedica, who obtained CBC **1** from commercially available, naturally derived cannabinoid products and identified the natural **1** by chiral HPLC using Lux Amylose-1 (Table 2.1). Based on this chromatographic method and enantiomeric ratio (*er*) of **1** with the enantiomers listed in elution order, natural **1** was identified as the slower eluting enantiomer.

Sources of CBC	***er***
cannabicitran tincture	44:56
Cannabis extract 1	29:71
Cannabis extract 2 ($scCO_2$)	21:79

Table 2.1 Enantiomeric ratio of CBC **1** from commercial, naturally derived *Cannabis* products.

Dr. Marlowe and Dr. Barr made racemic **1** from olivetol **4** and citral (Scheme 2.1) via literature procedures and provided it to Regis Technologies, which separated the two enantiomers by preparative chiral HPLC (Lux Amylose-1).



Scheme 2.1 Synthesis of (±)-**1**.

2.3 Chiroptical Properties of Natural and Unnatural Cannabichromene

Natural **1** showed a negative optical rotation (-96°) while unnatural **1** showed a positive optical rotation (+96°).

The CD spectra of the natural and unnatural enantiomers of **1** were obtained and displayed a mirror-image relationship (Figure 2.2).

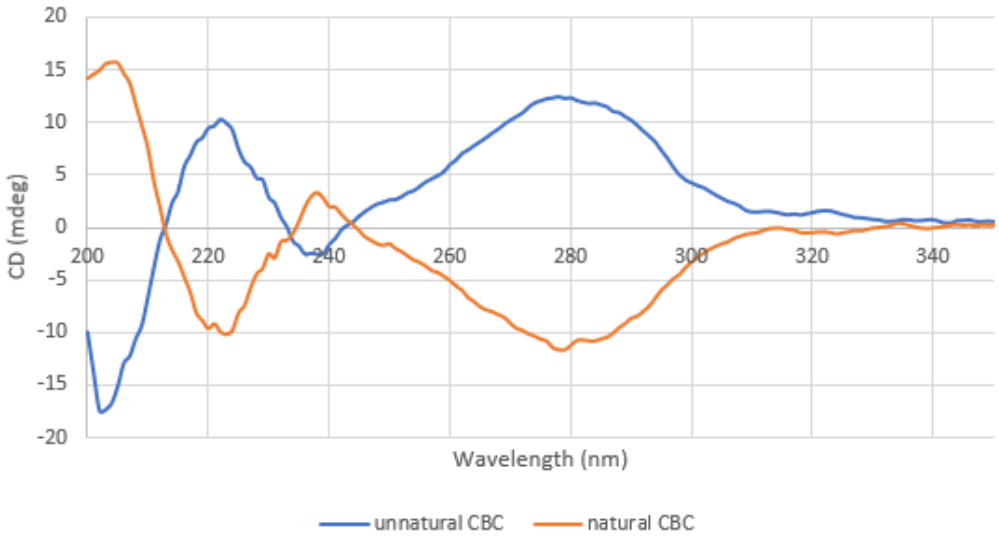


Figure 2.2 CD spectra of enantiomers of **1** in methanol. The gold line (negative at 280 nm) is the natural enantiomer and the blue line (positive at 280 nm) is the unnatural enantiomer.

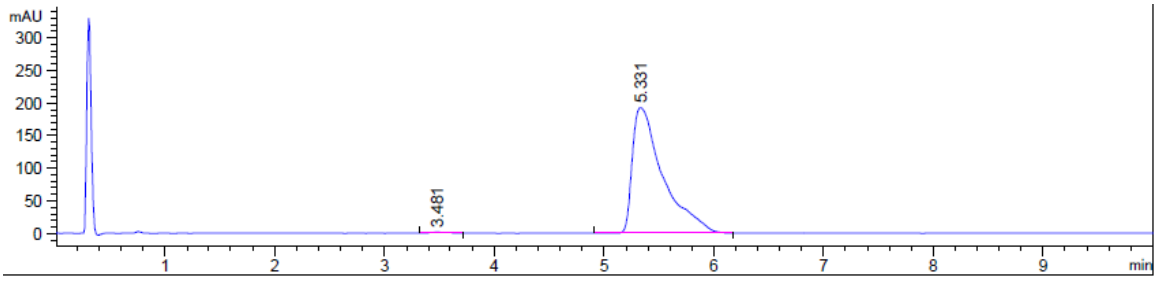
The CD spectra are similar to those in Morimoto's published work except Morimoto showed the natural (major), enzymatically produced **1** with a positive CD signal at 280 nm. However, Morimoto's unpublished data supports the findings reported here, which is that both Morimoto's natural **1** (presumably, from *Cannabis*) and the natural **1** in this work have a negative CD signal at 280 nm.

The CD data obtained for the natural **1** contradicts Gasparrini's work (discussed in Section 1.12), which showed that major **1** isolated from a *Cannabis* cultivar has a positive CD signal at 280 nm. A possible explanation for the inconsistency is that *Cannabis* cultivars from diverse geographies may produce different enantiomers of **1**. There are examples of natural products, closely related in structure to CBC, that have been isolated from plants belonging to the same genus but lie in different enantiomeric series (as will be further discussed in Section 2.13).

2.4 Racemization Studies of Cannabichromene

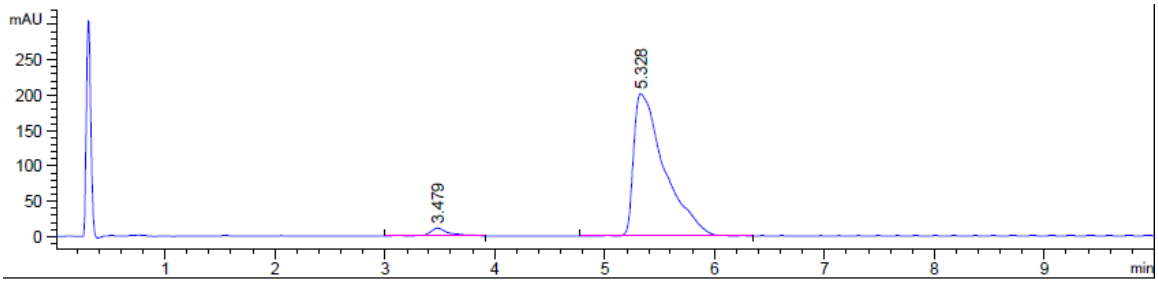
Thermal racemization study of CBC **1** was performed by heating (+)-**1** in toluene at different temperatures (80, 90, and 100 °C). Aliquots were taken at various time points, immediately cooled in ice water, and analyzed by chiral SFC using Lux Cellulose-5. The % racemization of each resulting sample was obtained; note that 100% racemization corresponds to a 50:50 ratio of the two enantiomers.

As a control, the chiral SFC of a sample of (+)-**1** prior to heating was obtained and displayed 0.9% racemization (Figure 2.3). After 24 hours at 80 °C, only 6.9% racemization occurred (Figure 2.4). After six hours at 90 °C, 7.0% racemization was observed (Figure 2.5). After six hours at 100 °C, 23.7% racemization was obtained (Figure 2.6). A table summarizing the % racemization of **1** at various temperatures and time points is provided (Table 2.2).



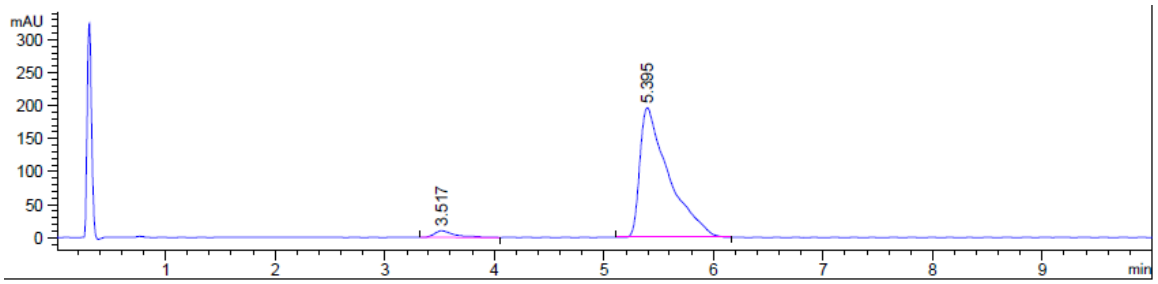
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.481	BV	0.1618	16.44279	1.52434	0.4384
2	5.331	VB R	0.2820	3733.84302	192.77504	99.5616

Figure 2.3 Chiral SFC of (+)-**1** prior to heating. R_t of (–)-**1** and (+)-**1** are 3.48 and 5.33 min, respectively.



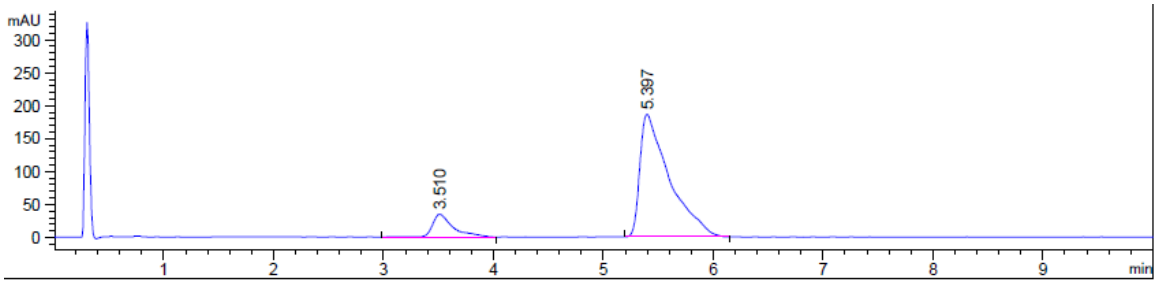
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.479	VB R	0.1821	138.84354	11.08848	3.4250
2	5.328	VV R	0.2840	3914.98047	202.13795	96.5750

Figure 2.4 Chiral SFC of (+)-**1** after 24 h at 80 °C. R_t of (–)-**1** and (+)-**1** are 3.48 and 5.33 min, respectively.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.517	BB	0.1878	131.41829	9.96696	3.5195
2	5.395	BB	0.2520	3602.63599	196.40854	96.4805

Figure 2.5 Chiral SFC of (+)-**1** after 6 h at 90 °C. R_t of (–)-**1** and (+)-**1** are 3.52 and 5.40 min, respectively.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.510	VB R	0.1970	465.55557	34.59278	11.8417
2	5.397	BB	0.2532	3465.94775	186.20926	88.1583

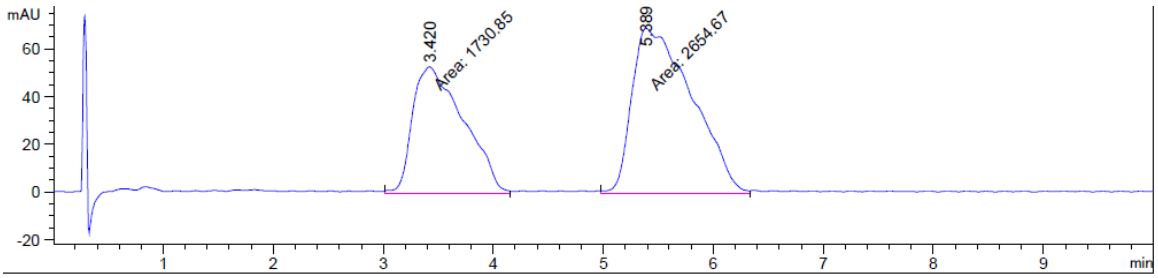
Figure 2.6 Chiral SFC of (+)-**1** after 6 h at 100 °C. R_t of (–)-**1** and (+)-**1** are 3.51 and 5.40 min, respectively.

Temperature	Time (h)	% Racemization
rt	0	0.9
80 °C	24	6.9
90 °C	6	7.0
100 °C	6	23.7

Table 2.2 Percent racemization of **1** at different temperatures and time points.

Acid-catalyzed racemization study of **1** was done by mixing (+)-**1** with 10 mol% tosic acid in acetonitrile at room temperature. Aliquots were removed at various time points and quenched with 10 mol% triethylamine. However, no detectable racemization occurred up to 24 hours.

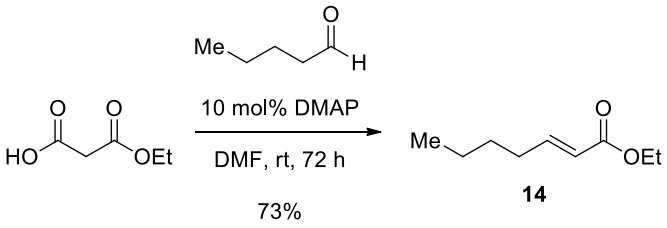
A solution of (+)-**1** in methanol was irradiated with sunlight for one hour, which resulted in 78.9% racemization by chiral SFC (Figure 2.7). ^{1}H NMR showed only the presence of **1** without any decomposition.



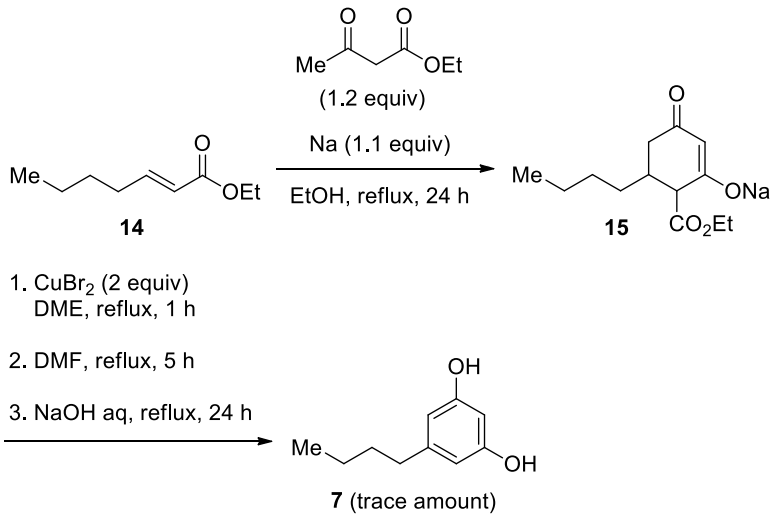
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.420	MM	0.5414	1730.84863	53.28441	39.4674
2	5.389	MM	0.6368	2654.66577	69.47813	60.5326

Figure 2.7 Chiral SFC of (+)-**1** after being irradiated with sunlight for 1 h. R_t of (–)-**1** and (+)-**1** are 3.42 and 5.39 min, respectively.

2.5 Synthesis of (±)-*nor*-Cannabichromene



Scheme 2.2 Synthesis of ethyl-2-heptenoate **14**.



Scheme 2.3 Synthesis of 5-*n*-butylresorcinol **7** via enolate chemistry.

Using Lee's method in the synthesis of (±)-CBC **1**,[21c] it was envisioned that (±)-*nor*-CBC **12** can also be formed by reacting 5-*n*-butylresorcinol **7** and citral with ethylenediamine diacetate. The initial attempt to make **7** was done through the Michael addition-intramolecular Claisen condensation route.[22b] Monoethyl malonate, prepared from the monohydrolysis of diethyl malonate,[38] and pentanal underwent a decarboxylative Knoevenagel reaction to form ethyl-2-heptenoate **14** (Scheme 2.2) using List's conditions.[39] The reaction of **14** with ethyl acetoacetate and sodium in ethanol under reflux conditions presumably afforded the salt intermediate **15** as a crude solid (Scheme 2.3). It was difficult to characterize the solid due to its inability to dissolve in deuterated solvents. Nonetheless, the solid was subjected to conditions that promote aromatization, hydrolysis, and decarboxylation to yield **7** in trace amount.

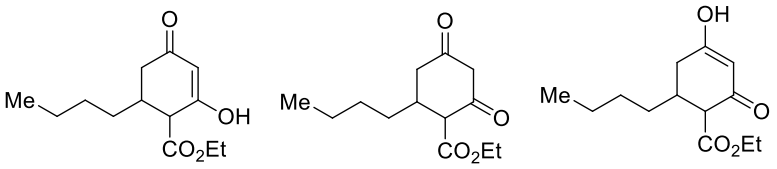
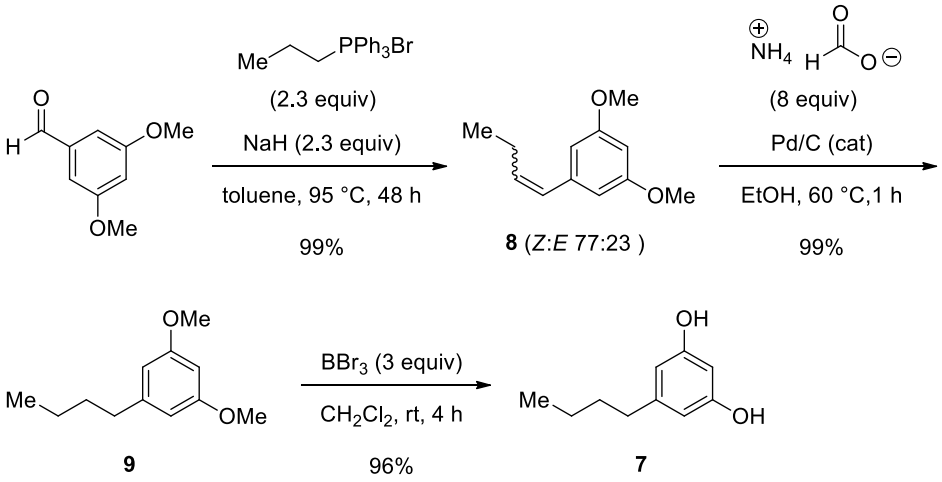


Figure 2.8 Structures of β-hydroxy unsaturated ketone and its isomers.

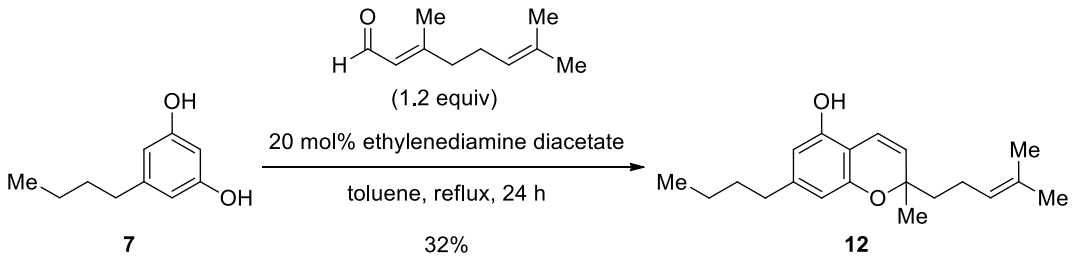
The Michael addition-intramolecular Claisen condensation of ethyl-2-heptenoate **14** and ethyl acetoacetate with sodium in refluxing ethanol was ran again, but with acidic workup. The resulting crude material showed unreacted starting material and a mixture of products resembling the β-hydroxy unsaturated ketone and its isomers (Figure 2.8).



Scheme 2.4 Formation of 5-*n*-butylresorcinol **7** via Wittig reaction route.

Because the target compound could not be easily formed, the Wittig olefination route became ideal for the synthesis of 5-*n*-butylresorcinol **7** since it used a benzaldehyde derivative as a starting reagent. Compound **7** was prepared in a three-step, high-yielding synthesis via the key Wittig reaction (Scheme 2.4). The formation of **7** began with the Wittig reaction between 3,5-dimethoxybenzaldehyde and *n*-propyltriphenylphosphonium

bromide with sodium hydride (NaH) as base to form a mixture of *cis* and *trans* alkene **8** isomers. The reduction of **8** was done via catalytic transfer hydrogenation using ammonium formate and palladium on carbon to afford 5-*n*-butyl-1,3-dimethoxybenzene **9**. Using Vanek's procedure for synthesizing olivetol **4** via demethylation by boron tribromide,[40] **9** was converted to **7**.



Scheme 2.5 Synthesis of (±)-*nor*-CBC **12**.

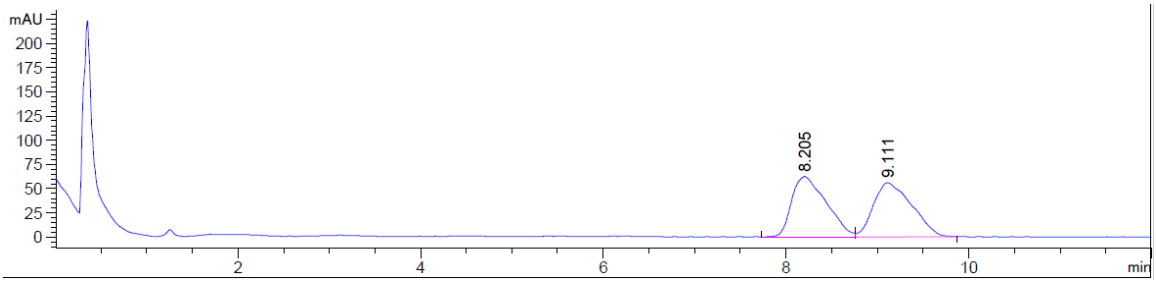


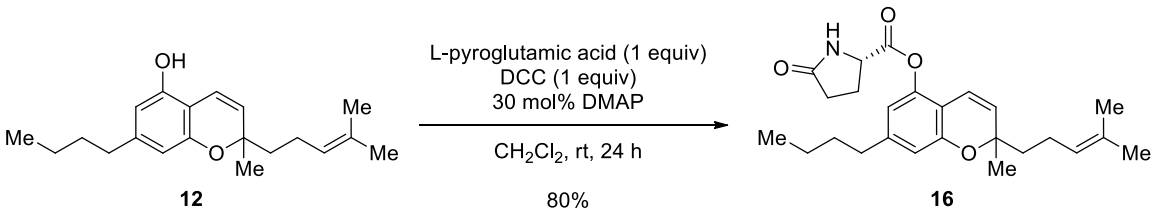
Figure 2.9 Chiral SFC of (±)-*nor*-CBC **12**.

With 5-*n*-butylresorcinol **7** at hand, Lee's procedure (described earlier) was applied towards the synthesis of (±)-*nor*-CBC **12** by treating **7** with citral and catalytic amount of ethylenediamine diacetate (Scheme 2.5). (±)-*nor*-CBC **12** was analyzed via chiral SFC using Lux Cellulose-1, and the two enantiomers were baseline separated (Figure 2.9). Now

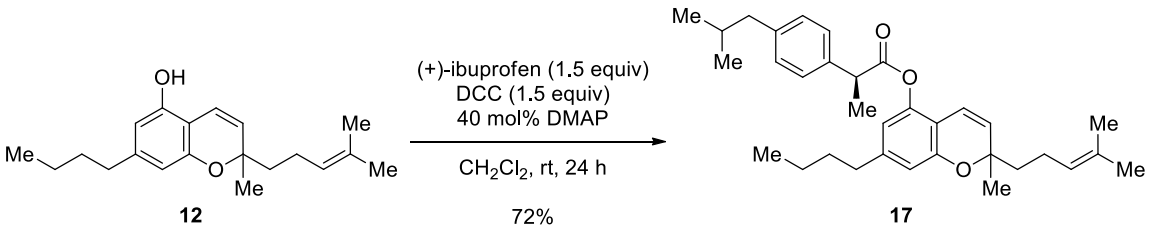
that conditions were successfully established to analyze the enantiopurity of **12**, its resolution was attempted.

2.6 Attempted Resolution of (±)-*nor*-Cannabichromene

By coupling the racemic *nor*-CBC **12** with a chiral molecule, it was hoped that the resulting diastereomeric products could be separated. If at least one of those diastereomers was crystalline, an X-ray crystal structure could be obtained, which would allow the absolute stereochemistry determination of not just the *nor*-CBC analog, but also the corresponding *nor*-CBC enantiomer. In the case where the separation of *nor*-CBC derivatives, acquirement of an X-ray structure, and conversion of a *nor*-CBC analog to a pure *nor*-CBC **12** enantiomer are possible, racemization studies of a single enantiomer of **12** can be performed.

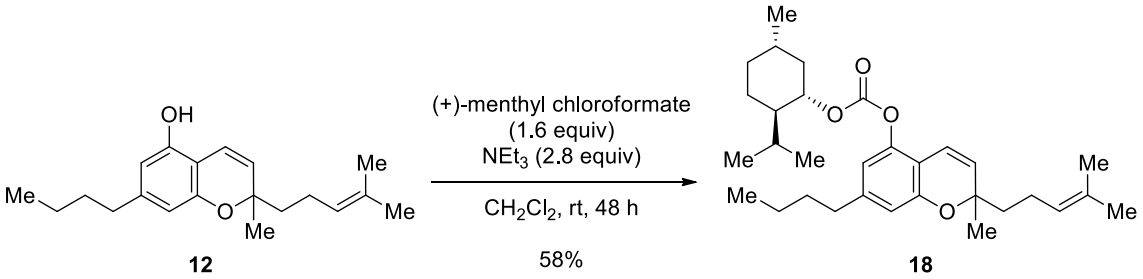


Scheme 2.6 Coupling of (±)-**12** and L-pyroglutamic acid.



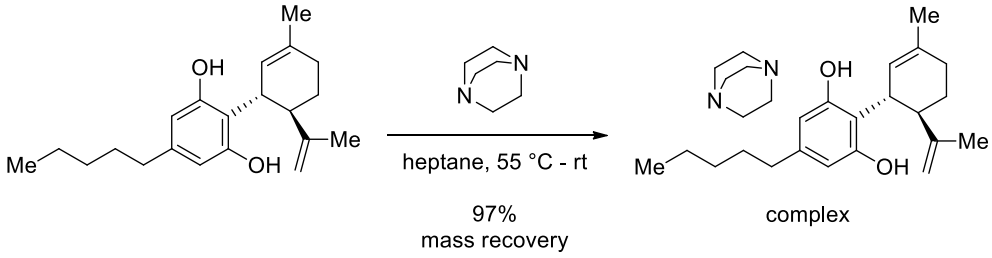
Scheme 2.7 Coupling of (±)-**12** and (+)-ibuprofen.

Utilizing Santi and Hamann's procedures,[41] (±)-*nor*-CBC **12** was reacted with chiral acids, such as L-pyroglutamic acid and (+)-ibuprofen, in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) and catalytic amount of 4-dimethylaminopyridine (DMAP) affording inseparable diastereomeric pyroglutamate **16** and ibuprofenate **17** esters (Schemes 2.6 and 2.7).



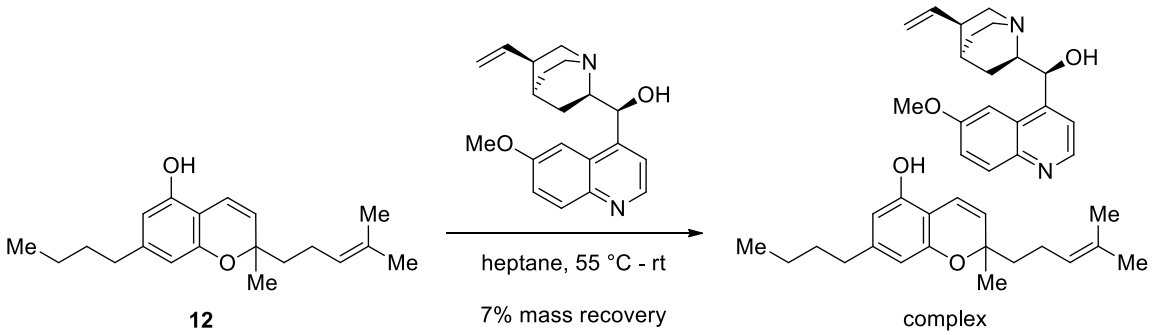
Scheme 2.8 Coupling of (±)-**12** and (+)-menthyl chloroformate.

Using conditions that couple phenols and (+)-menthyl chloroformate,[42] racemic *nor*-CBC **12** was reacted with (+)-menthyl chloroformate using triethylamine in methylene chloride to form carbonate ester diastereomers **18**, which also could not be separated (Scheme 2.8).



Scheme 2.9 Crystallization of CBD DABCO complex by Bencivenga.

Another method of possibly separating the enantiomers of *nor*-CBC **12** is through a chiral resolution by crystallization. This was inspired by Bencivenga's work, which showed that CBD can crystallize and form a complex with 1,4-diazabicyclo[2.2.2]octane (DABCO) through intermolecular forces (Scheme 2.9).[43]



Scheme 2.10 Formation of **12** quinidine complex.

It was hoped that treating racemic *nor*-CBC **12** with a chiral tertiary amine, analogous to DABCO, would lead to its resolution by crystallization. Racemic **12** was mixed with quinidine using Bencivenga's conditions, which afforded a small amount of solid precipitate (Scheme 2.10). However, when this solid was dissolved in an organic solvent and washed with aqueous acid, the resulting **12** was still racemic based on chiral SFC analysis.

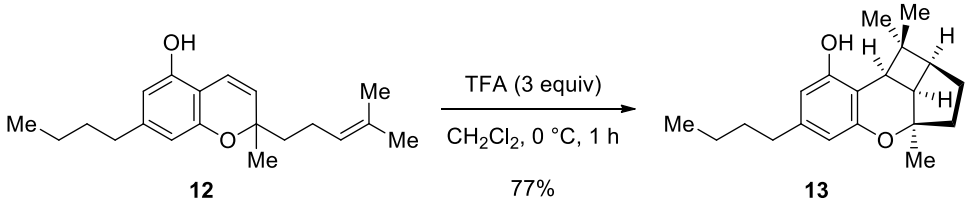
2.7 Conversion of (±)-*nor*-Cannabichromene to (±)-*nor*-Cannabicyclol

Due to the unsuccessful attempts of resolving (±)-*nor*-CBC **12**, it was converted to (±)-*nor*-CBL **13** in hopes that (±)-**13** can be resolved instead. Transformation of *nor*-CBC **12** to *nor*-CBL **13** helps to lock in its stereochemistry and prevent racemization since **13**

does not have an obvious pathway of racemization, unlike **12**. The resolution of *nor*-CBL analogs, formed from a chiral compound with known stereochemistry, could be achieved, and their absolute configuration could be determined. This would lead to the absolute stereochemistry elucidation of *nor*-CBL **13** and *nor*-CBC **12**, which could be validly compared to those of natural CBL **5** and CBC **1**, respectively.

Also, having a single enantiomer of *nor*-CBL **13** could possibly be converted back to *nor*-CBC **12** via retro [2 + 2] cycloaddition. The absolute stereochemistry of a *nor*-CBC derivative, prepared from a chiral molecule with a known configuration, could then be determined, which would help elucidate the absolute stereochemistry of natural CBC **1**.

Implementing Hsung's [2 + 2] cycloaddition reaction procedures that converted (±)-CBC **1** to (±)-CBL **5**,[29] (±)-*nor*-CBC **12** was reacted under acidic conditions to synthesize (±)-*nor*-CBL **13** (Scheme 2.11).



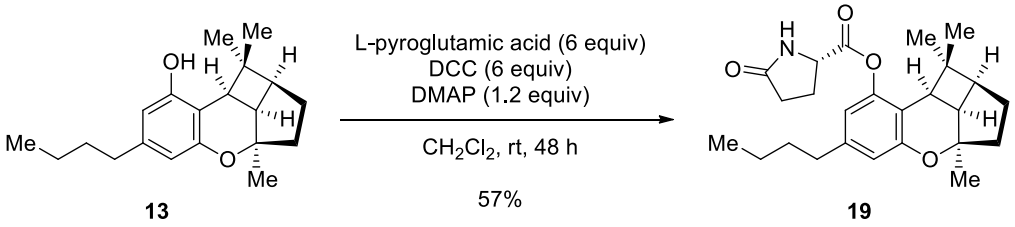
12 **13**

Scheme 2.11 Synthesis of (±)-*nor*-CBL **13**.

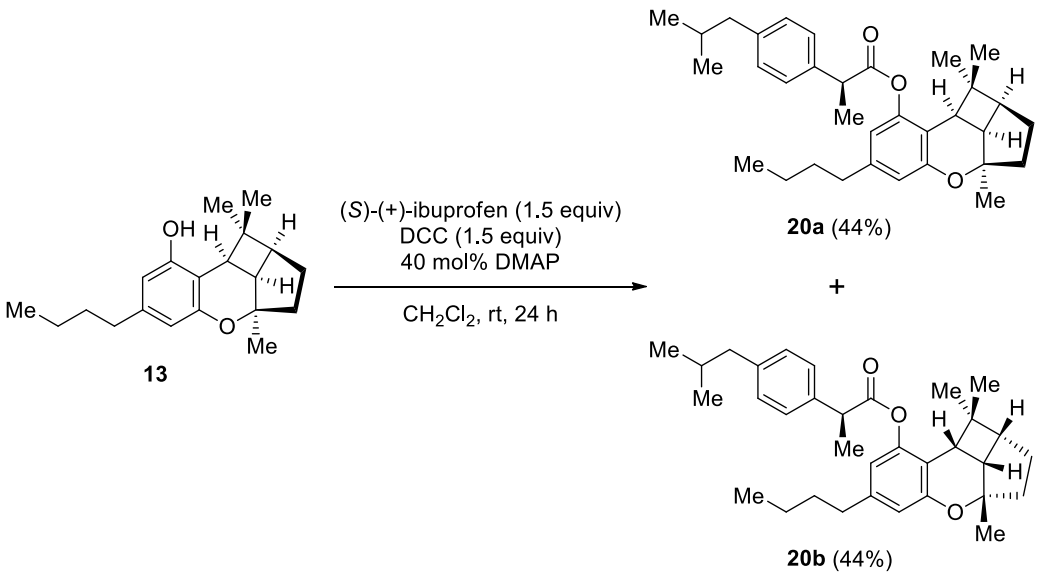
2.8 Chiral Acid Coupling of (±)-*nor*-Cannabicyclol

Implementing Santi and Hamann's procedures,[41] the coupling of (±)-*nor*-CBL **13** and L-pyroglutamic acid with DCC and DMAP afforded *nor*-cannabicyclyl glutamate

esters **19** that could not be separated (Scheme 2.12). On the other hand, using (+)-ibuprofen as the chiral acid led to the formation of *nor*-cannabicyclyl ibuprofenate diastereomers **20a** and **20b**, which were separable by column chromatography (Scheme 2.13).



Scheme 2.12 Synthesis of *nor*-cannabicyclyl glutamates **19**.



Scheme 2.13 Synthesis of *nor*-cannabicyclyl ibuprofenates **20a** and **20b**.

2.9 X-ray Crystal Structure of (1a*S*,1a^1*R*,3a*R*,8b*R*,2′S)-*nor*-Cannabicyclyl Ibuprofenate

One of the *nor*-cannabicyclyl ibuprofenate diastereomers, **20a**, was attained as a crystalline product. An X-ray crystal structure of the crystalline diastereomer **20a**, obtained by Dr. Charlene Tsay, revealed that it was (1a*S*,1a^1*R*,3a*R*,8b*R*,2′*S*)-*nor*-cannabicyclyl ibuprofenate (Figure 2.10).

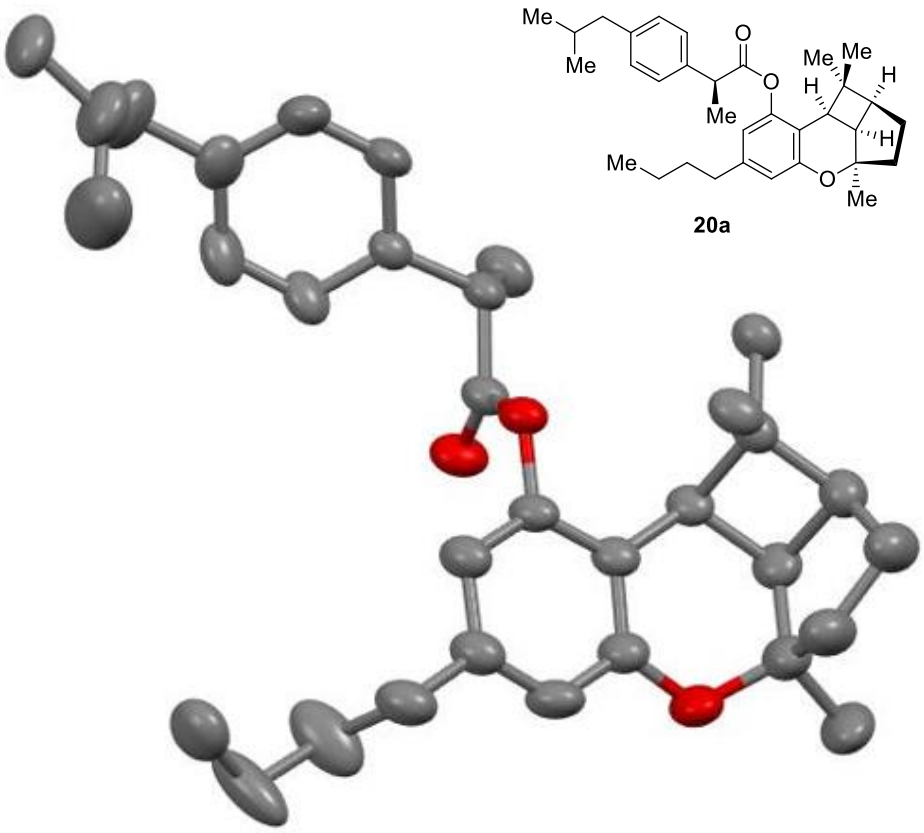
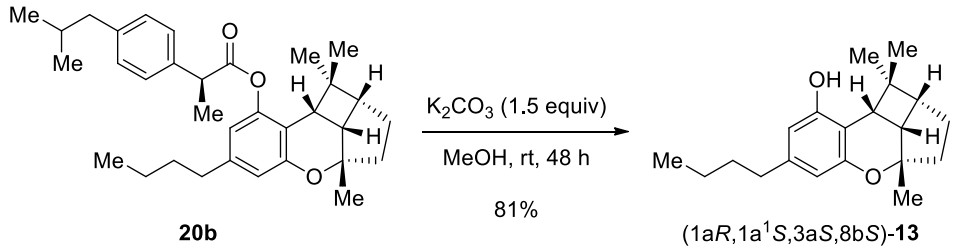


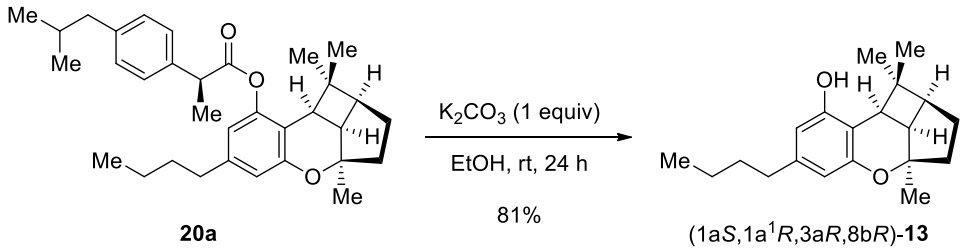
Figure 2.10 X-ray crystal structure of (1a*S*,1a^1*R*,3a*R*,8b*R*,2′*S*)-*nor*-cannabicyclyl ibuprofenate **20a**. H-atoms omitted, thermal ellipsoids for heavy atoms, probability level 50%.

2.10 Synthesis of (+)-*nor*-Cannabicyclol and (–)-*nor*-Cannabicyclol

The cleavage of the noncrystalline (1a*R*,1a^1*S*,3a*S*,8b*S*,2′*S*)-*nor*-cannabicyclyl ibuprofenate **20b** and crystalline (1a*S*,1a^1*R*,3a*R*,8b*R*,2′*S*)-*nor*-cannabicyclyl ibuprofenate **20a** was performed using potassium carbonate in an alcohol solvent to afford (1a*R*,1a^1*S*,3a*S*,8b*S*)-**13** (Scheme 2.14) and (1a*S*,1a^1*R*,3a*R*,8b*R*)-**13** (Scheme 2.15), respectively. A structure of *nor*-CBL **13** denoting the positions of its stereocenters is provided (Figure 2.11).



Scheme 2.14 Synthesis of (1a*R*,1a^1*S*,3a*S*,8b*S*)-**13**.



Scheme 2.15 Synthesis of (1a*S*,1a^1*R*,3a*R*,8b*R*)-**13**.

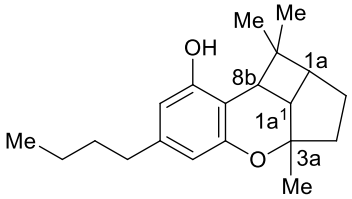


Figure 2.11 Structure of *nor*-CBL **13** with labeled stereocenters.

The optical rotation values obtained for (1a*R*,1a^1*S*,3a*S*,8b*S*)-**13** and (1a*S*,1a^1*R*,3a*R*,8b*R*)-**13** are +6° and -6°, respectively. Thus, (1a*R*,1a^1*S*,3a*S*,8b*S*)-**13** is (+)-**13** and (1a*S*,1a^1*R*,3a*R*,8b*R*)-**13** is (–)-**13** (Figure 2.12).

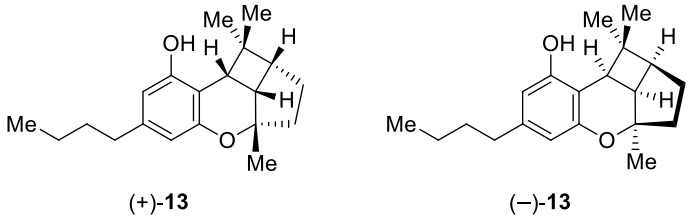


Figure 2.12 Structures of (+)-**13** and (–)-**13**.

The CD spectra of (+)-**13** and (–)-**13** in methanol were acquired (Figure 2.13).

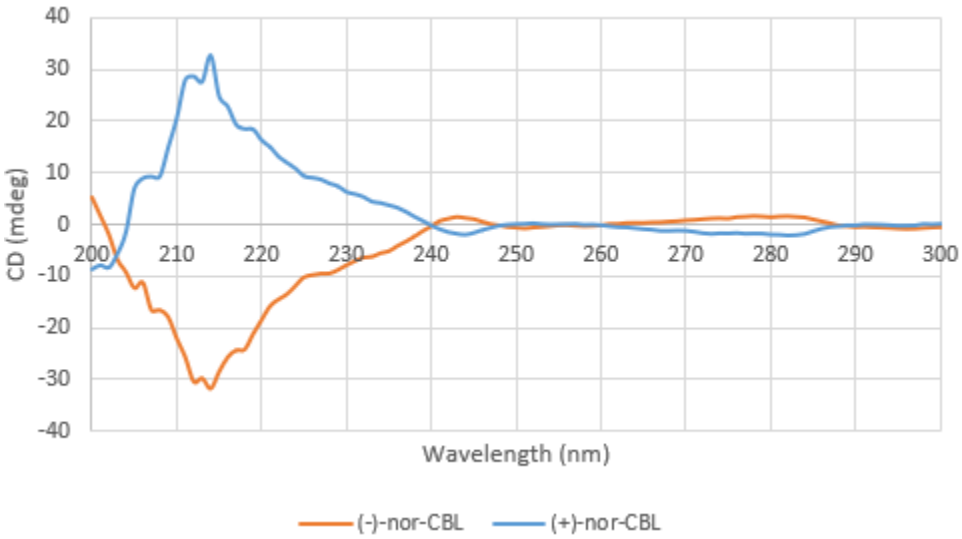
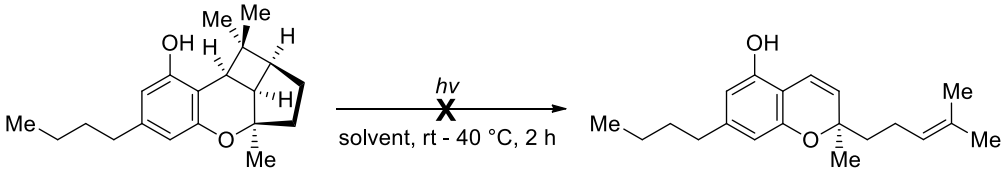


Figure 2.13 CD spectra of (+)-**13** and (–)-**13** in methanol. The blue line (positive at 215 nm) is (+)-**13** and the gold line (negative at 215 nm) is (–)-**13**.

2.11 Attempted Retro [2 + 2] Cycloaddition of *nor*-Cannabicyclol

Since the resolution of *nor*-CBL **13** has been achieved, converting one of its enantiomers to the corresponding *nor*-CBC **12** enantiomer via retro [2 + 2] cycloaddition would allow the absolute stereochemistry determination of the *nor*-CBC enantiomer, which could be validly compared to one of the enantiomers of CBC **1**. Also, obtaining a single enantiomer of *nor*-CBC **12** would allow the study of its racemization.

Attempts of the retro [2 + 2] cycloaddition of *nor*-CBL **13** were done by irradiating scalemic **13** with ultra-violet light (254 and 350 nm) in various solvents, but no desired product was formed, and only starting material was observed (Scheme 2.16). The addition of 50 mol% of benzophenone, to act as a photosensitizer, still resulted in no reaction.



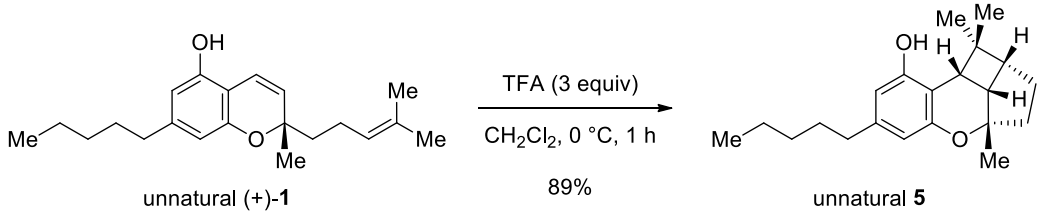
solvent = $CDCl_3$, acetone, EtOAc, toluene, MeCN, MeOH, THF

Scheme 2.16 Attempted retro [2 + 2] cycloaddition of scalemic **13**.

However, because of the collaboration formed with BayMedica, CBC **1** was available not only for racemization studies (as shown in Section 2.4), but also as a precursor for CBL **5**, which will be discussed in the next section. Comparing chiroptical properties of CBL **5** with those of *nor*-CBL **13**, which now has a known absolute configuration, will allow the elucidation of its absolute stereochemistry, as well as that of CBC **1**, by inference.

2.12 Formation of Unnatural (+)-Cannabicyclol

Using the reaction conditions developed by Hsung as described earlier, unnatural (+)-CBC **1** was treated with TFA to undergo a [2 + 2] cycloaddition to form unnatural CBL **5** (Scheme 2.17). The CD spectrum of the synthesized unnatural **5** was obtained (Figure 2.14). Unnatural **5** also showed a positive optical rotation value of +4°. As mentioned in Section 1.7, natural **5**, isolated from *Cannabis*, was reported to have an optical rotation of -3°.[24]



Scheme 2.17 Synthesis of unnatural CBL **5**.

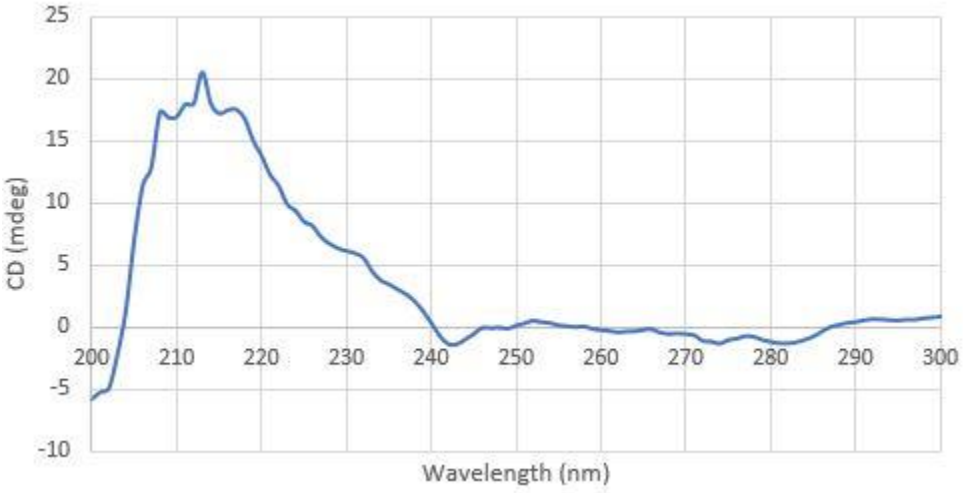


Figure 2.14 CD spectrum of unnatural CBL **5** in methanol.

2.13 Absolute Stereochemistry Determination of Natural (–)-Cannabicyclol and Natural (–)-Cannabichromene

Both (1a*R*,1a[1]*S*,3a*S*,8b*S*)-*nor*-CBL **13** and unnatural CBL **5** have positive optical rotation values; therefore, the two compounds share the same absolute stereochemistry, which has the *S* absolute configuration at the tertiary ether (Figure 2.15). Also, the CD data of (+)-**13** and unnatural (+)-**5** infer that the two lie in the same enantiomeric series since both have their major positive CD signals at ca. 215 nm.

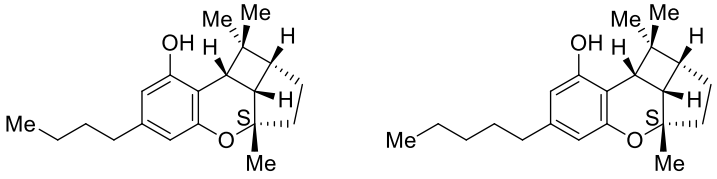


Figure 2.15 Structures of (+)-*nor*-CBL **13** and unnatural (+)-CBL **5**.

Therefore, (–)-*nor*-CBL **13** and natural (–)-CBL **5** must also have the same absolute stereochemistry, which contains the *R* configuration at the tertiary ether (Figure 2.16). And since the stereocenter at the tertiary ether is conserved during the [2 + 2] cycloaddition of CBC **1** to form CBL **5**, natural (–)-**1** must be the *R* enantiomer (Figure 2.17).

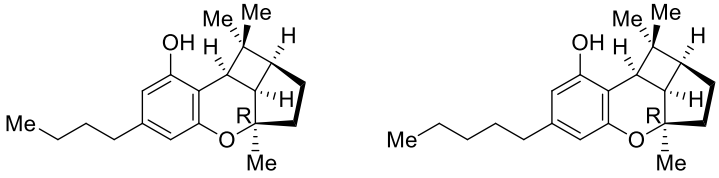
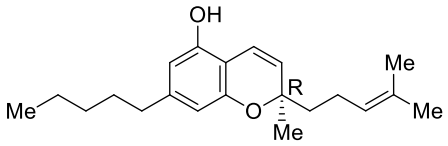


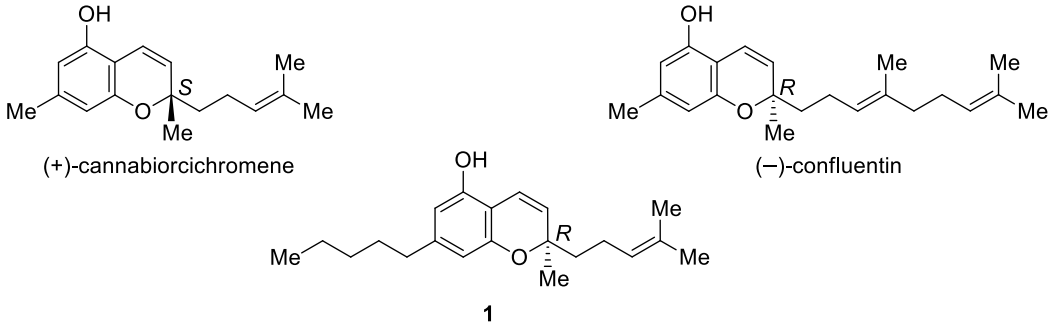
Figure 2.16 Structures of (–)-*nor*-CBL **13** and natural (–)-CBL **5**.



natural (–)-(*R*)-**1**

Figure 2.17 Structure of natural (–)-(*R*)-CBC **1**.

The absolute configuration assignment of CBC **1** can be further supported by looking at two classes of natural products that are closely related in structure to **1**: cannabiorcichromene[44] and confluentin[45] (Figure 2.18). Both are isolated from *Rhododendron* sp., but they lie in different enantiomeric series. Congeners of cannabiorcichromene are all *S* isomers with a positive CD signal at 280 nm and positive optical rotation values. On the other hand, congeners of confluentin are all *R* isomers with a negative CD signal at 280 nm and negative optical rotation values, which are also shared by natural **1**. A summary of chiroptical properties from these chromene natural products is shown (Table 2.3).



(+)-cannabiorcichromene (–)-confluentin

1

Figure 2.18 Structures of cannabiorcichromene, confluentin, and CBC **1**.

name	**source**	**CD signal at 280 nm**	**$[\alpha]_D$**	**assigned absolute config.**	**reference**
CBC	*Cannabis*	negative	negative	*R*	this work
cannabiorcichromene	*Rhododendron*	positive	NR	*S*	Kitanaka[44]
confluentin	*Rhododendron*	negative	negative	*R*	Kitanaka[45]

Table 2.3 Stereochemical measures of chromene natural products.

Chapter 3: Introduction on Indoles and Cine Substitution

3.1 Importance of Indoles

Indole **21** represents one of the most important structural motifs present in many bioactive compounds and natural products (Figure 3.1).[46] The indole scaffold is ubiquitous in Nature due to the indole-containing, amino acid tryptophan.

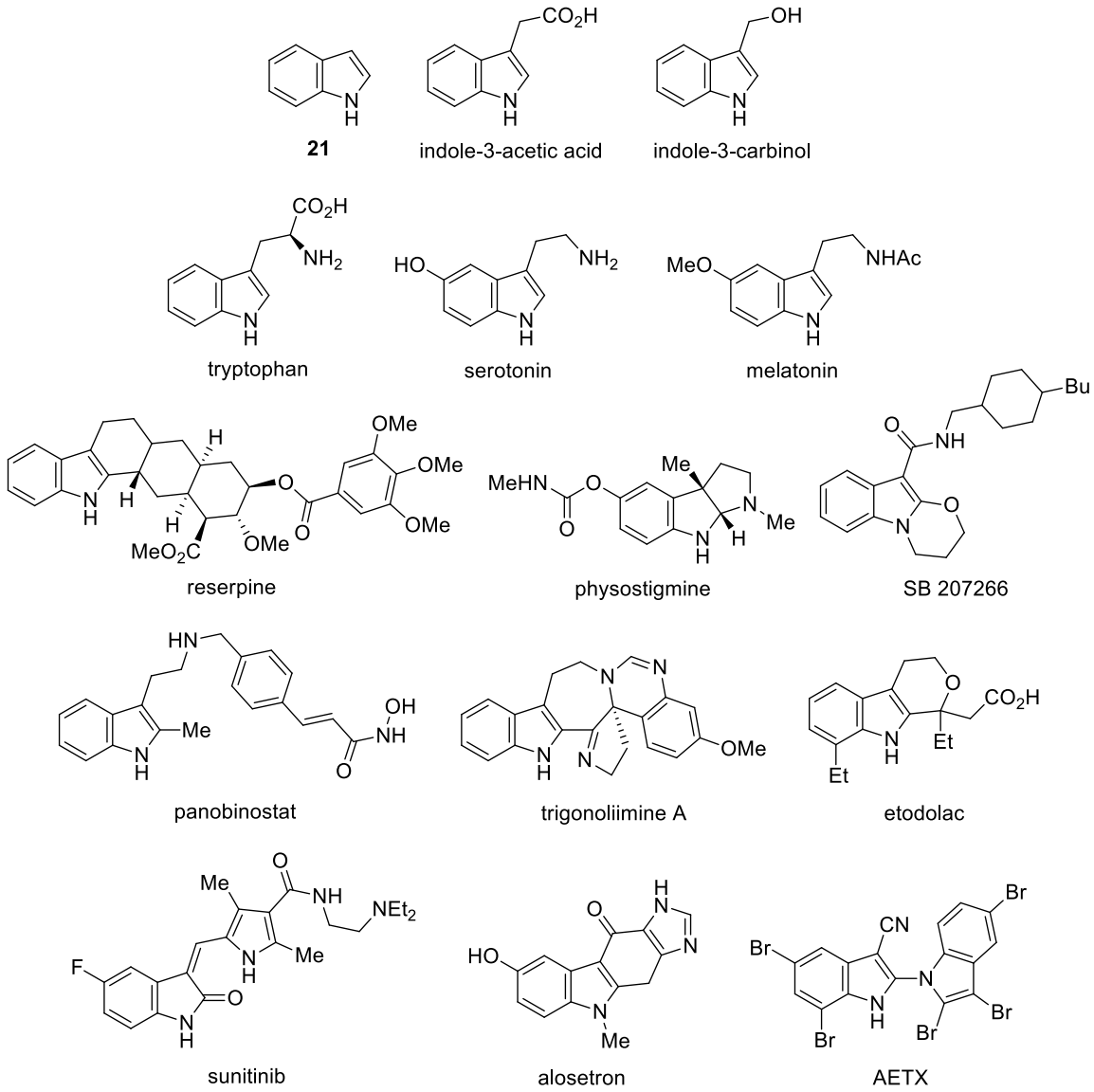


Figure 3.1 Structures of indole **21** and indole-containing biologically active compounds and natural products.

An example of an indole-containing natural product is indole-3-acetic acid, which is a plant hormone produced by the degradation of tryptophan. Serotonin, a tryptophan derivative, is a neurotransmitter present in animals. Melatonin, another analog of tryptophan, is a hormone present in animals, plants, and microbes; it is associated with control of the sleep-wake cycle in animals. Indole-3-carbinol, a natural product found in cruciferous vegetables, has anticancer, antioxidant, and antiatherogenic effects. Other examples of biologically active indole alkaloids and their synthetic analogs are:

1. reserpine, an indole-containing natural product used to treat high blood pressure and severe agitation with those suffering from mental disorders,
2. physostigmine, an alkaloid with anticholinergic activity used to help fight diseases, such as glaucoma, Alzheimer's disease, and bronchitis,
3. SB 207266, an antagonist of 5-hydroxytrptamine$_4$ (5-HT$_4$) receptor, which help modulate cholinergic nerve pathways promoting peristalsis, via *in vitro* and *in vivo* studies,
4. panobinostat, a drug synthesized by Novartis for the treatment of multiple myeloma and acquired immunodeficiency syndrome (AIDS),
5. trigonoliimine A, an alkaloid with activity against human immunodeficiency virus (HIV),
6. etodolac, a synthetic compound used as a nonsteroidal anti-inflammatory drug (NSAID),
7. sunitinib, a synthetic drug for treating renal cell carcinoma and gastrointestinal stromal tumor,

8. alosetron, a synthetic drug used for nausea and vomiting, and
9. aetokthonotoxin (AETX), a neurotoxin made by a cyanobacteria in plants resulting in death of eagles.

3.2 Chemistry of Indoles

Indole **21** is an electron-rich, aromatic, bicyclic heterocycle (Figure 3.2) that typically reacts with an electrophile (E) and participates in an electrophilic aromatic substitution (EAS) at the C2 and C3 sites (Schemes 3.1 and 3.2).[46d] However, the C3-position is preferred due to the stabilization resulting from the delocalization of positive charge by the adjacent nitrogen lone pair while keeping aromaticity intact in the intermediate. EAS at the C2-position forms a less favorable intermediate because delocalization of the positive charge disrupts aromaticity in the phenyl ring. Examples of EAS of indoles are Friedel-Crafts alkylation and Vilsmeier-Haack formylation.

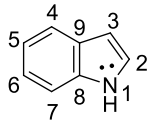
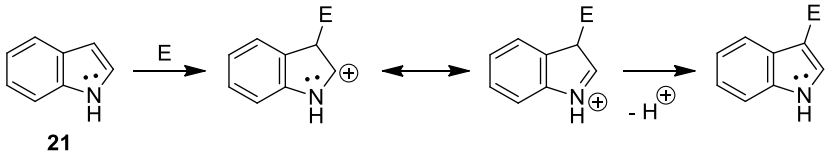
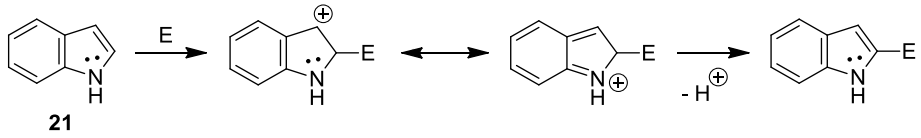


Figure 3.2 Structure of indole **21** with atom numbering.

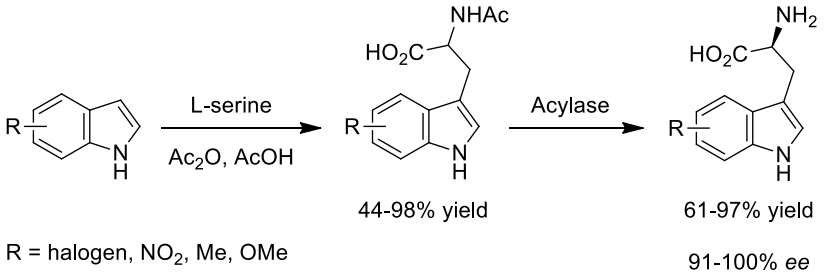


Scheme 3.1 EAS of indole **21** at C3-position.



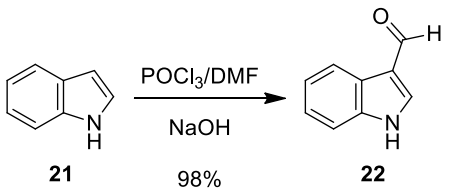
Scheme 3.2 EAS of **21** at C2-position.

Friedel-Crafts alkylation of different 5- and 6-substituted indoles with L-serine in the presence of acetic anhydride (Ac_2O) and acetic acid (AcOH) forms racemic *N*-acetyl tryptophan derivatives, which can be followed by enzymatic resolution to yield analogs of L-tryptophan (Scheme 3.3).[47]



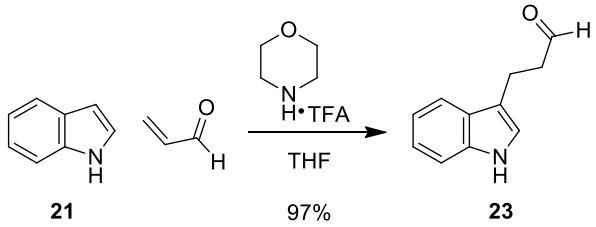
Scheme 3.3 Synthesis of L-tryptophan derivatives via Friedel-Crafts alkylation of 5- and 6-substituted indoles with L-serine followed by enzymatic resolution.

The Vilsmeier-Haack reaction is great way to formylate indoles. Treatment of indole **21** with phosphorus oxychloride ($POCl_3$) in DMF followed by addition of aqueous sodium hydroxide (NaOH) affords 3-formylindole **22** (Scheme 3.4).[48]

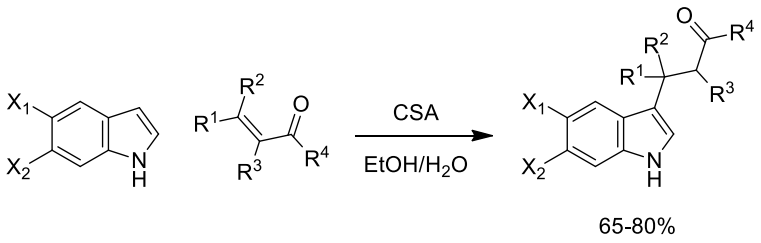


Scheme 3.4 Vilsmeier-Haack acylation of **21** to form 3-formylindole **22**.

Indoles can react with unsaturated carbonyls to undergo Michael addition as well. For instance, the Michael reaction of indole **21** with acrolein and a morpholine salt organocatalyst produces indole-3-propanal **23** (Scheme 3.5).[49] Also, **21** and mono and disubstituted indoles treated with methyl vinyl ketone and mono and disubstituted enones in the presence of catalytic amount of camphorsulfonic acid (CSA) form the Michael addition products (Scheme 3.6).[50]

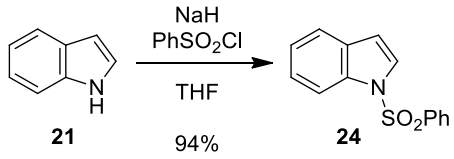


Scheme 3.5 Organocatalyzed Michael reaction of **21** with acrolein.



Scheme 3.6 Acid-catalyzed Michael addition of **21** and substituted indoles with a variety of enones.

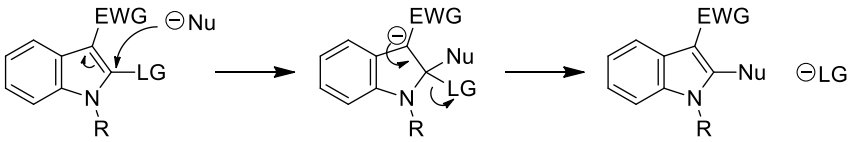
Reactions can also occur at the 1-position of indoles. For instance, the amine of indole **21** can get deprotonated with a strong base and sulfonylated in the presence of phenylsulfonyl chloride ($PhSO_2Cl$) to afford *N*-phenylsulfonyl indole **24** (Scheme 3.7).[51]



Scheme 3.7 Synthesis of *N*-phenylsulfonyl indole **24** via sulfonylation of **21**.

3.3 Nucleophilic Aromatic Substitution of Indoles

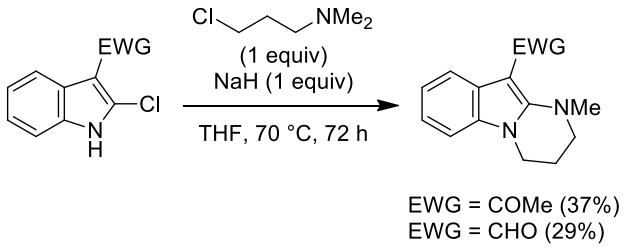
Indoles can behave as electrophiles and participate in nucleophilic aromatic substitution (SNAr) if they contain a leaving group (LG) and typically at least one electron-withdrawing group (EWG) (Scheme 3.8). Many of the indole SNAr reactions involve an anionic nucleophile, which can be formed under basic conditions from its conjugate acid (Nu-H).



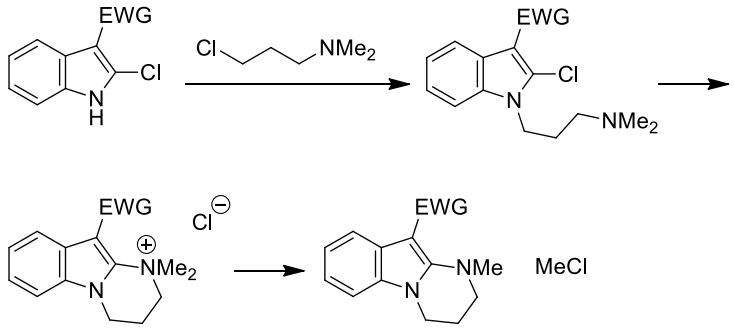
Scheme 3.8 Mechanism of an indole SNAr.

Early examples of indole SNAr were conducted in 1979 by Coppola in which 2-chloro-3-formylindole and 3-acetyl-2-choroindole were reacted with 3-chloro-*N*,*N*-dimethyl-1-propylamine in the presence of NaH to afford tricyclic indole products in 29 and 37% yield, respectively (Scheme 3.9).[52] Coppola proposed that the *N*-alkyl indole

intermediate, formed from the *N*-alkylation of the indole starting material, undergoes an intramolecular SNAr followed by the loss of methyl chloride to afford the tricylic indole (Scheme 3.10).

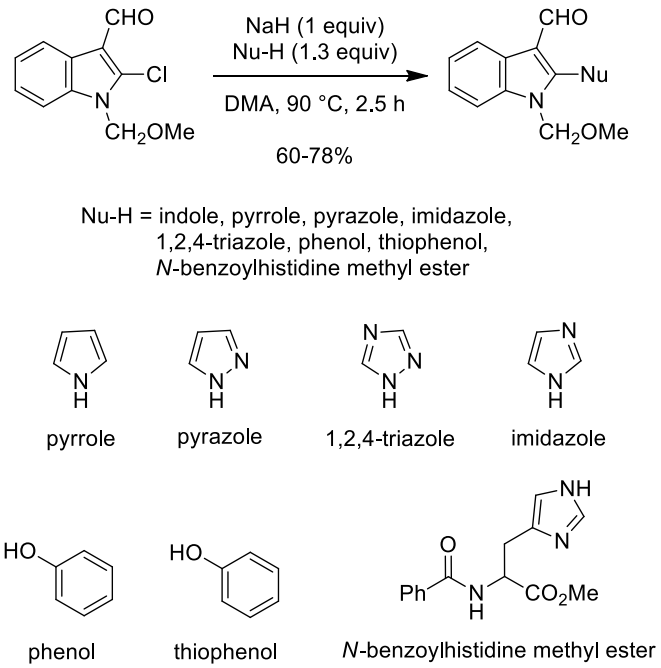


Scheme 3.9 Coppola's formation of tricyclic indoles via intramolecular SNAr.



Scheme 3.10 Coppola's proposed reaction pathway to the tricyclic indole via intramolecular SNAr of *N*-alkyl indole intermediate.

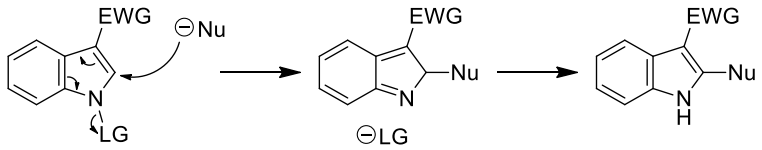
In 1992, Moody showed that 2-chloro-1-(methoxymethyl)indole-3-carboxaldehyde can undergo SNAr after being treated with different nucleophiles, such as phenol, thiophenol, and *N*-containing aromatic compounds, under basic conditions (Scheme 3.11).[53]



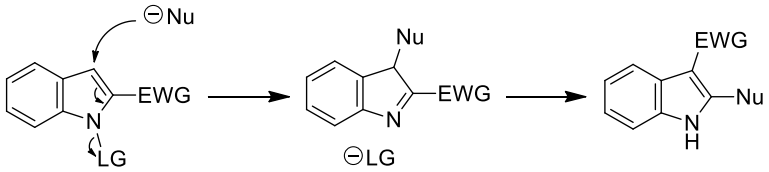
Scheme 3.11 Moody's SNAr of 2-chloro-1-(methoxymethyl)indole-3-carboxaldehyde.

3.4 Synthesis of *N*-Hydroxy Indoles and Their Analogs for Cine and Tele Substitutions

In the case where the LG is on the 1-position, cine and tele substitutions of indoles can occur. According to the International Union of Pure and Applied Chemistry (IUPAC), cine substitution is "a substitution reaction (generally aromatic) in which the entering group takes up a position adjacent to that occupied by the leaving group" (Scheme 3.12) while tele substitution is "a substitution reaction in which the entering group takes up a position more than one atom away from the atom to which the leaving group was attached" (Scheme 3.13).[54]



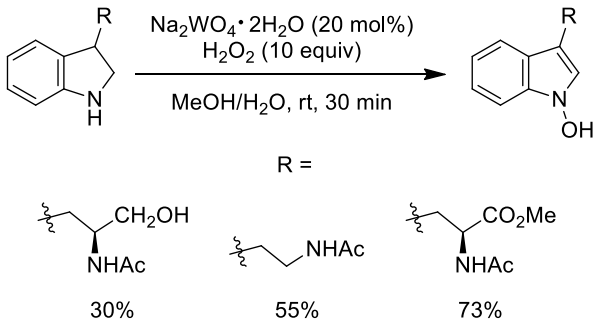
Scheme 3.12 Mechanism of an indole cine substitution.



Scheme 3.13 Mechanism of an indole tele substitution.

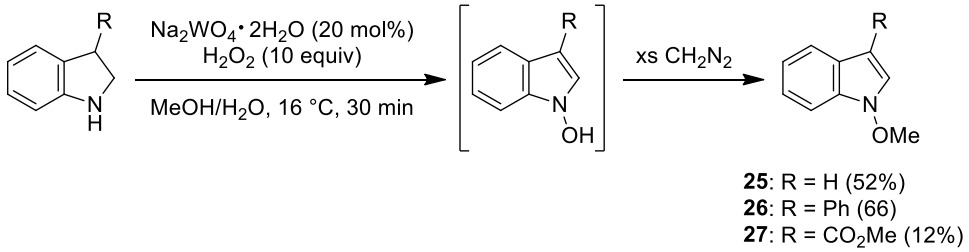
N-Hydroxy indoles and their analogs can undergo cine and tele substitutions. 1-Hydroyxindole itself is unstable and unisolable; however, its derivatives can be isolated in certain cases where the indole nucleus is substituted.[55] 1-Hydroxyindoles can also be converted to the more stable 1-methoxyindoles.

Somei synthesized 1-hydroxytryptophan derivatives by reacting 3-alkyl indolines, prepared from the sodium cyanoborohydride reduction of the corresponding tryptophan analog precursors, with catalytic amount of sodium tungstate dihydrate ($Na_2WO_4 \bullet 2H_2O$) and excess hydrogen peroxide (H_2O_2) (Scheme 3.14).[55a] Somei noted that the primary alkyl alcohol product formed in 30% yield gradually decomposed after one hour at room temperature.

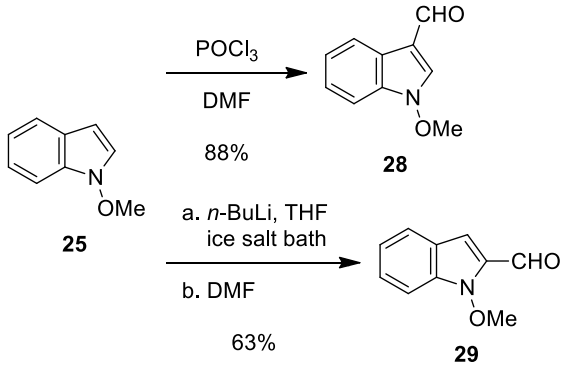


Scheme 3.14 Somei's synthesis of 1-hydroxytryptophan derivatives.

Somei also formed other 1-hydroxyindoles *in situ* by treating their indoline precursors with 20 mol% Na_2WO_4•$2H_2O$ and 10 equivalents of H_2O_2; addition of excess ethereal diazomethane afforded the 1-methoxyindoles **25**-**27** (Scheme 3.15).[55b] 3-Formyl-1-methoxyindole **28** and 2-formyl-1-methoxyindole **29** can be prepared via Vilsmeier-Haack reaction and lithiation of **25**, respectively (Scheme 3.16).[56]



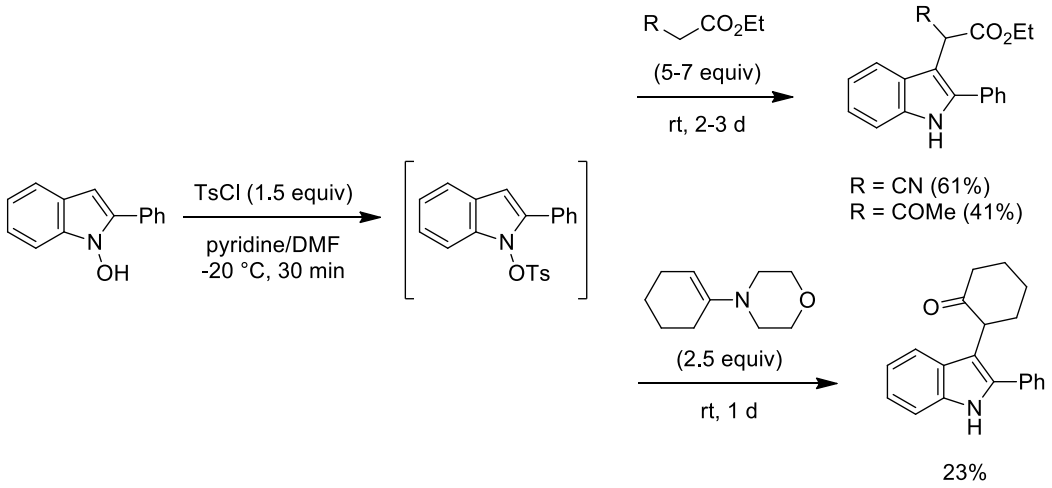
Scheme 3.15 Somei's synthesis of 1-methoxyindoles **25**-**27** via 1-hydroxyindole intermediates.



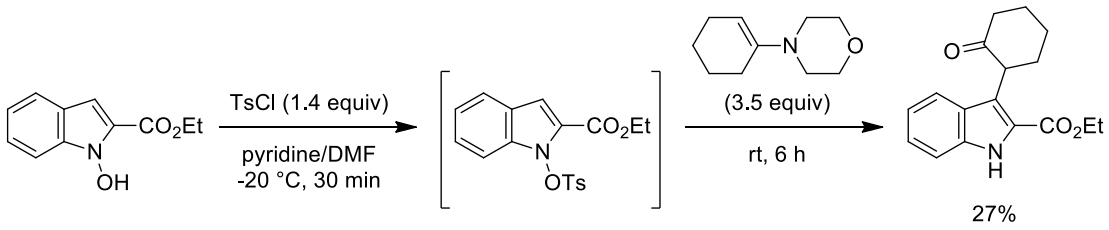
Scheme 3.16 Somei's synthesis of 3- and 2-formyl-1-methoxyindoles **28** and **29**.

3.5 Cine and Tele Substitutions of *N*-Hydroxy Indoles and Their Analogs

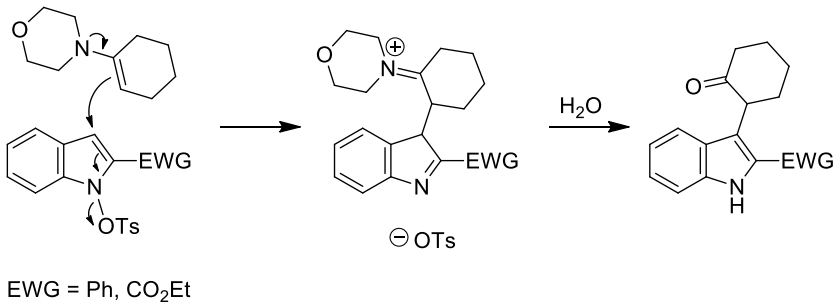
In 1981, Hamana treated 1-hydroxy-2-phenylindole with tosyl chloride (TsCl) to form the *N*-sulfonate ester intermediate *in situ*, which was reacted with ethyl cyanoacetate, ethyl acetoacetate, and 1-morpholinocyclohexene to give the tele substitution products in 61, 41, and 23% yield, respectively (Scheme 3.17).[57] In 1984, Hamana tosylated 2-(ethoxycarbonyl)-1-hydroxyindole, and then performed the tele substitution of the *N*-sulfonate intermediate by adding 1-morpholinocyclohexene to afford the disubstituted indole product in 27% yield (Scheme 3.18).[58] Hamana's results show that indoles with a LG on the nitrogen and an EWG at the 2-position can undergo a regioselective tele substitution at the 3-position. Hamana's proposed mechanism for the tele substitution of *N*-sulfonate indoles with the enamine is shown (Scheme 3.19).[57,58] Interestingly, when Hamana allowed 2-(ethoxycarbonyl)-1-hydroxyindole to react with TsCl at -20 °C for six hours, 3-chloro-2-(ethoxycarbonyl)indole was formed (Scheme 3.20), presumably from the tele substitution of the *N*-sulfonate indole intermediate with the chloride anion.[58]



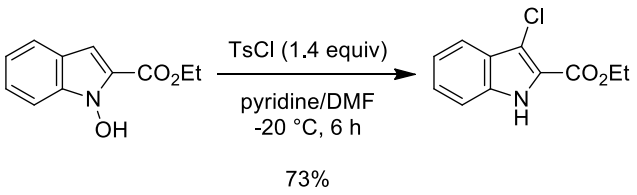
Scheme 3.17 Hamana's synthesis of 3-substituted 2-phenylindoles via tele substitution.



Scheme 3.18 Hamana's synthesis of 3-cyclohexanonyl-2-(ethoxycarbonyl)indole via tele substitution.



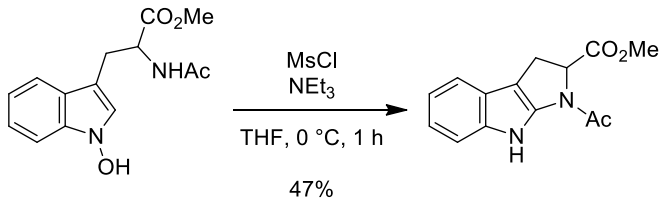
Scheme 3.19 Hamana's proposed mechanism of the tele substitution of *N*-sulfonate indoles with 1-morpholinocyclohexene.



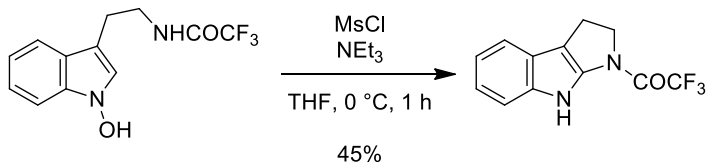
Scheme 3.20 Hamana's formation of 3-chloro-2-(ethoxycarbonyl)indole via tele substitution.

In 1992, Somei conducted the intramolecular cine substitution of (±)-*N*-acetyl-1-hydroxytryptophan and *N*-trifluoroacetyl-1-hydroxytryptophan using MsCl and NEt_3 to form tricyclic indoles (Schemes 3.21 and 3.22).[59] Somei also showed that the hydroxy group can act as a LG for SNAr; 1-hydroxyindole in aqueous methanol was treated with

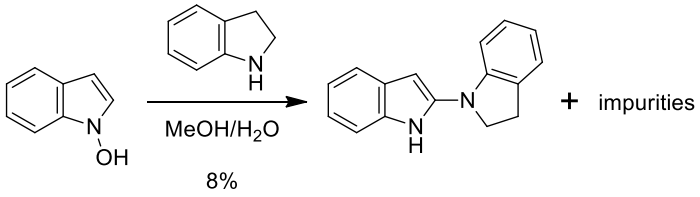
indoline to give the cine substitution product albeit in low yield and combined with unknown impurities. (Scheme 3.23).[59]



Scheme 3.21 Somei's synthesis of tricyclic acetylindole via intramolecular cine substitution.

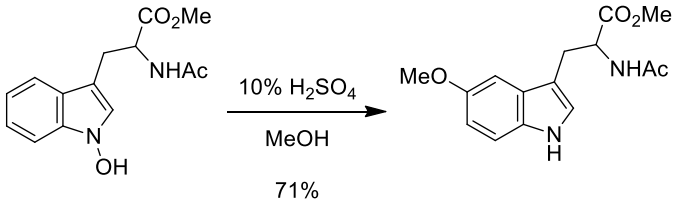


Scheme 3.22 Somei's synthesis of tricyclic trifluoroacetylindole via intramolecular cine substitution.



Scheme 3.23 Somei's cine substitution of 1-hydroxyindole with indoline.

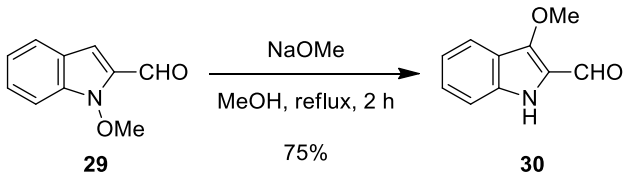
In 1993, Somei performed the regioselective tele substitution of (±)-*N*-acetyl-1-hydroxytryptophan at the 5-position using methanolic sulfuric acid (Scheme 3.24).[60] Presumably, acidic conditions facilitate the substitution by protonating the hydroxy group and converting it into a better leaving group as water. Steric hindrance about the 2-position may have been the cause for the lack of selectivity at that site.



Scheme 3.24 Somei's regioselective tele substitution of (±)-*N*-acetyl-1-hydroxytryptophan under acidic conditions.

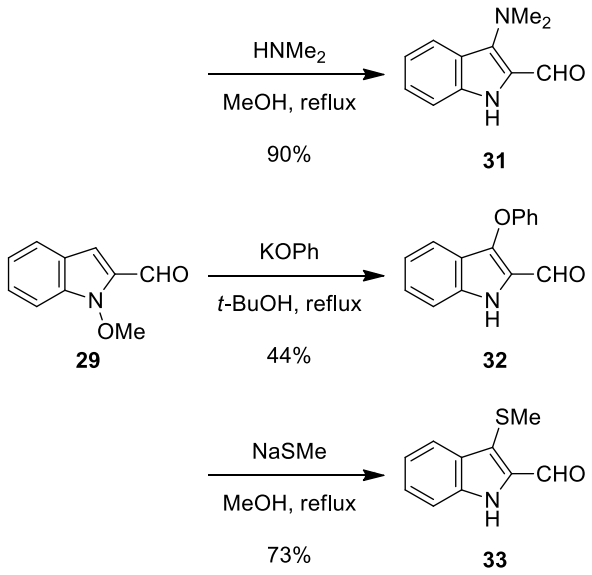
3.6 Tele Substitution of *N*-Methoxy 2-Formylindole

Somei demonstrated that *N*-methoxy 2-formylindole can undergo tele substitution. In 1992, Somei performed the tele substitution of 2-formyl-1-methoxyindole **29** with sodium methoxide to afford 2-formyl-3-methoxyindole **30** (Scheme 3.25).[59]



Scheme 3.25 Somei's tele substitution of 2-formyl-1-methoxyindole **29** with sodium methoxide.

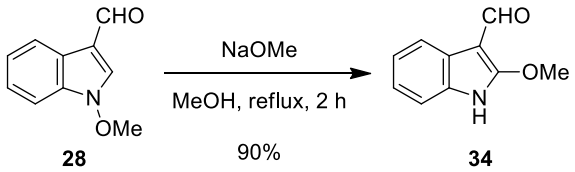
In 1993, Somei reacted 2-formyl-1-methoxyindole **29** with dimethylamine, potassium phenoxide, and sodium thiomethoxide (Scheme 3.26) to form tele substitution products **31**-**33**.[61]



Scheme 3.26 Somei's tele substitution of 2-formyl-1-methoxyindole **29** with dimethylamine, potassium phenolate, and sodium thiomethoxide.

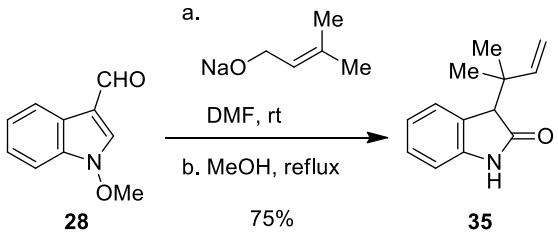
3.7 Cine Substitution of *N*-Methoxy 3-Formylindole

The cine substitution of *N*-methoxy 3-formylindole has been a major focus of Somei. In 1992, Somei showed that 3-formyl-1-methoxyindole **28** can undergo cine substitution with sodium methoxide to make 3-formyl-2-methoxyindole **34** (Scheme 3.27).[59] Also, when **28** was treated with sodium ethoxide and sodium thiomethoxide, their corresponding cine substitution products were formed in 95 and 94% yield, respectively.

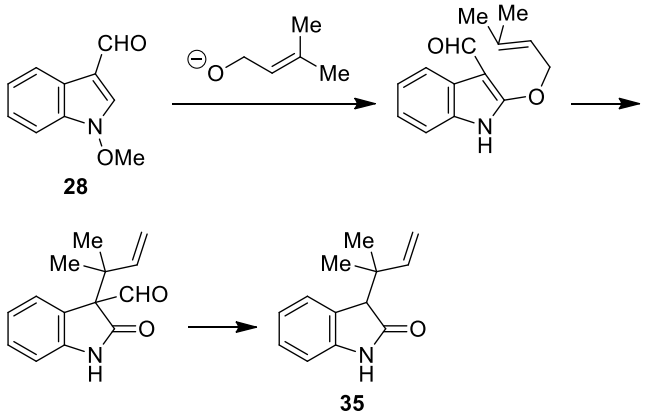


Scheme 3.27 Somei's cine substitution of 3-formyl-1-methoxyindole **28** with sodium methoxide.

In 1993, Somei synthesized 3-(1,1-dimethylallyl)-2-oxindole **35** in a one-pot reaction from 3-formyl-1-methoxyindole **28** and sodium 3-methyl-2-buten-1-olate (Scheme 3.28).[61] Somei proposed that **35** is formed from the cine substitution of **28** with the allyl alkoxide followed by Claisen rearrangement, loss of formyl group, and protonation (Scheme 3.29).



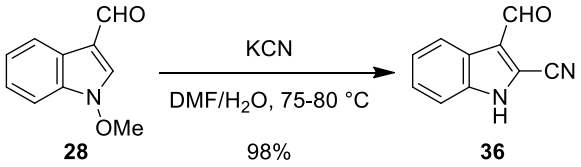
Scheme 3.28 Somei's conversion of 3-formyl-1-methoxyindole **28** to 3-(1,1-dimethylallyl)-2-oxindole **35**.



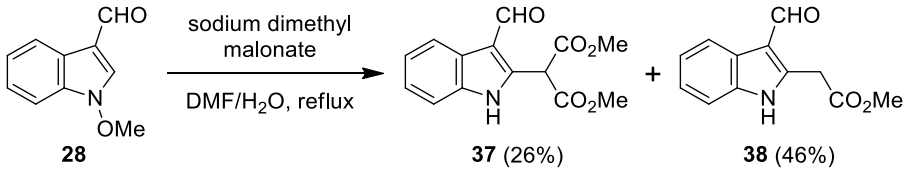
Scheme 3.29 Somei's proposed reaction pathway for the formation of **35** from **28**.

Somei also reacted 3-formyl-1-methoxyindole **28** with different carbon-centered nucleophiles to undergo cine substitution.[61] Using potassium cyanide (KCN) as the nucleophile afforded the desired disubstituted indole product **36** in excellent yield (Scheme

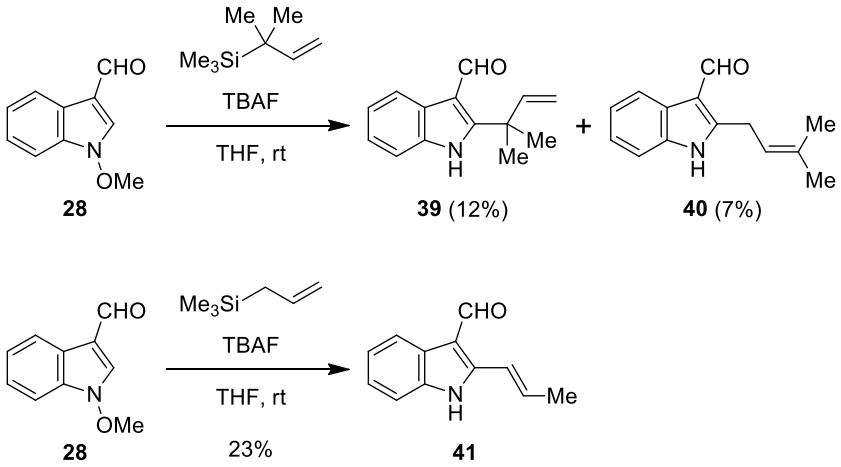
3.30). Sodium dimethyl malonate resulted in the formation of the cine substitution product **37** and its byproduct **38**, presumably formed via hydrolysis and decarboxylation of **37**, in 26% and 46% yield, respectively (Scheme 3.31). Lastly, when allyl silanes were used in the presence of tetrabutylammonium fluoride (TBAF), their corresponding cine substitution products **39**-**41** were isolated (Scheme 3.32).



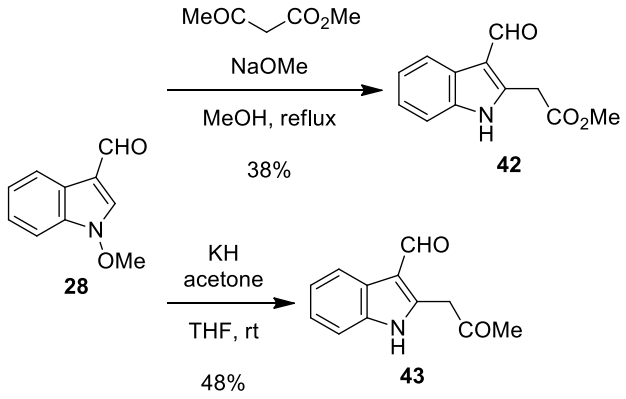
Scheme 3.30 Somei's cine substitution of **28** with potassium cyanide.



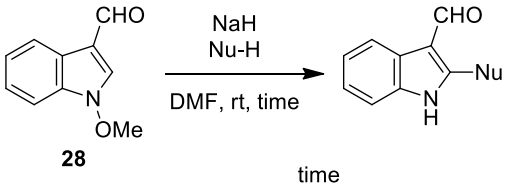
Scheme 3.31 Somei's cine substitution of **28** with sodium dimethyl malonate.



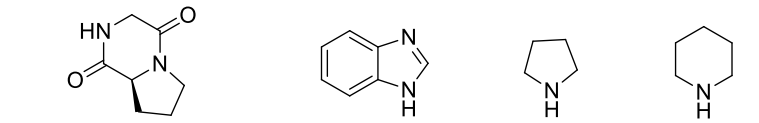
Scheme 3.32 Somei's cine substitution of **28** with allyl silanes.



Scheme 3.33 Somei's cine substitution of **28** with methyl acetoacetate and acetone under basic conditions.



Nu-H	time (h)	% yield
pyrrole	3	99
indole	24	95
imidazole	48	81
(8a*S*)-octahydropyrrolo [1,2-a]pyrazine-1,4-dione	6	63
benzimidazole	120	30
pyrrolidine	6	71
piperidine	6	26

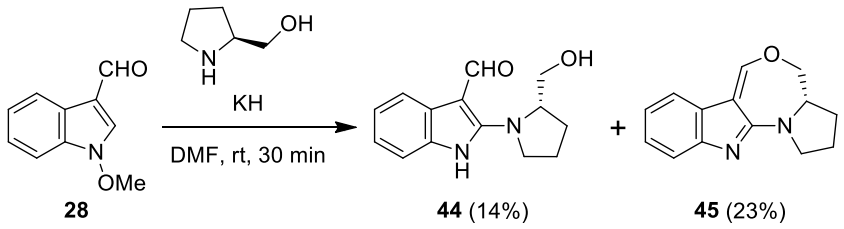


(8a*S*)-octahydropyrrolo [1,2-a]pyrazine-1,4-dione | benzimidazole | pyrrolidine | piperidine

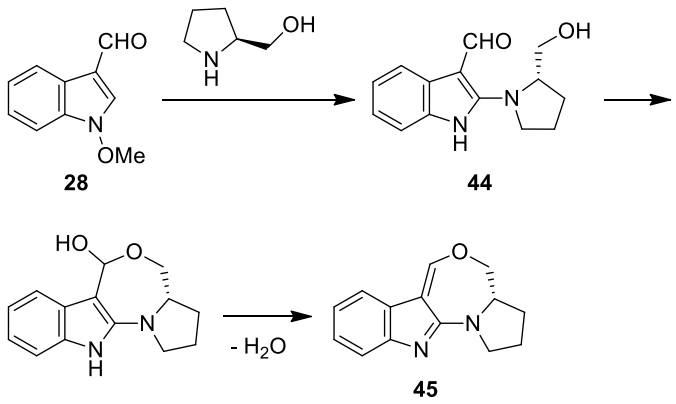
Scheme 3.34 Somei's cine substitution of **28** with *N*-centered nucleophiles.

Somei further used carbon-containing nucleophiles for cine substitution in 1994 by reacting 3-formyl-1-methoxyindole **28** with: 1. acetone and potassium hydride (KH) in THF at room temperature, and 2. methyl acetoacetate and sodium methoxide in refluxing methanol (Scheme 3.33).[62] Nitrogen-centered nucleophiles were also investigated by Somei for the cine substitution of **28** in DMF at room temperature to afford the desired products (Scheme 3.34).[62]

In 1999, Somei reacted 3-formyl-1-methoxyindole **28** with (*S*)-prolinol to give the disubstituted indole **44** and tetracyclic byproduct **45** (Scheme 3.35), presumably via cine substitution followed by intramolecular cyclization and dehydration (Scheme 3.36).[63] It is worth noting that the amine is the reactive functional group of the nucleophile, and not the hydroxy group.



Scheme 3.35 Somei's cine substitution of **28** with (*S*)-prolinol.



Scheme 3.36 Proposed reaction pathway for the formation of tetracyclic indole **45**.

Using Somei's 2012 paper, a summary of products formed from the cine substitution of 3-formyl-1-methoxyindole **28** with sulfur-, oxygen-, carbon-, and nitrogen-centered nucleophiles has been provided along with their respective yields (Figures 3.3, 3.4, and 3.5).[64] Somei's cine substitution method was utilized in the synthesis of the biindole-containing AETX, as seen in Section 3.1, by Ricardo in 2021.[65]

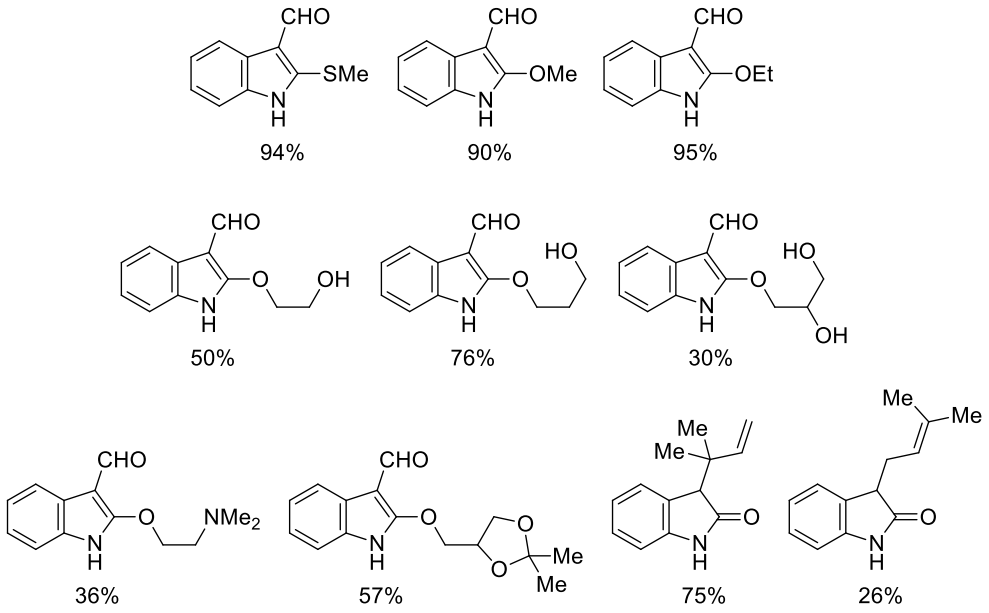


Figure 3.3 Product summary of Somei's cine substitution of 3-formyl-1-methoxyindole **28** with sulfur- and oxygen-centered nucleophiles.

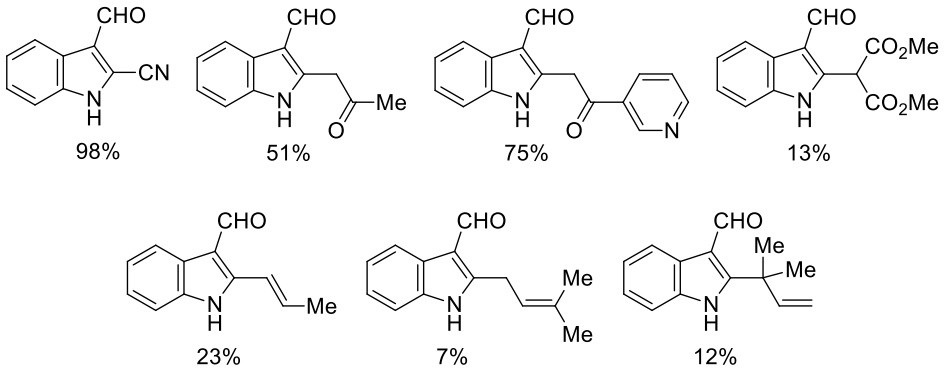


Figure 3.4 Product summary of Somei's cine substitution of **28** with carbon-centered nucleophiles.

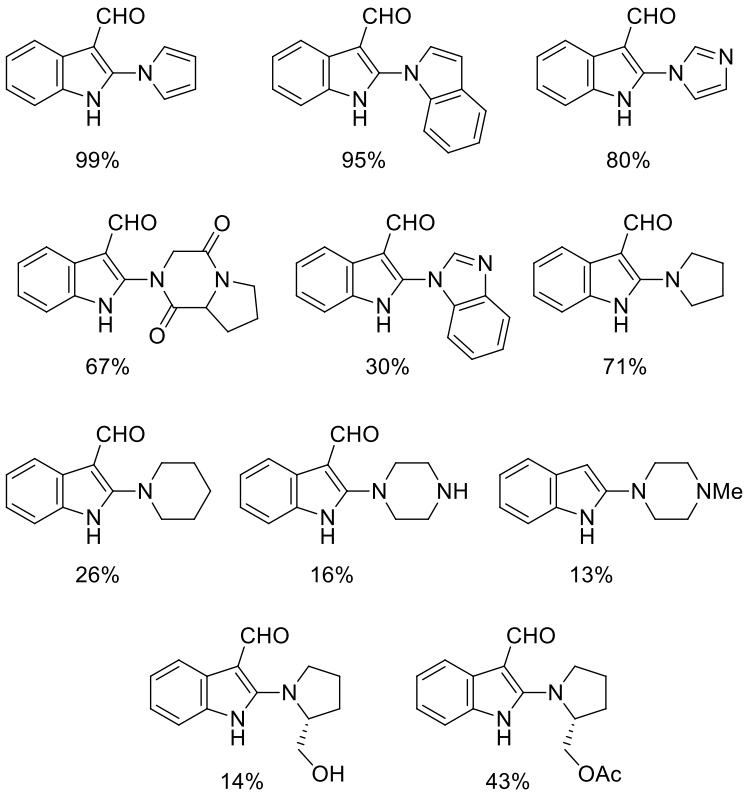
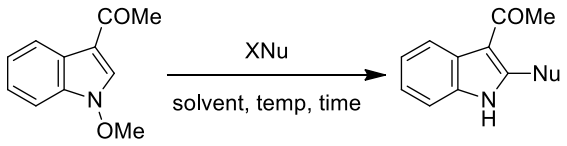


Figure 3.5 Product summary of Somei's cine substitution of **28** with nitrogen-centered nucleophiles.

3.8 Cine Substitution of *N*-Methoxy 3-Acetylindole

Somei also demonstrated that other EWGs at the 3-position of *N*-methoxy indole can facilitate cine substitution. In 1999, Somei showed that 3-acetyl-1-methoxyindole **46** can participate in cine substitution with sodium alkoxides, sodium thiomethoxide, and potassium dimethyl malonate nucleophiles (XNu) (Scheme 3.37).[66]



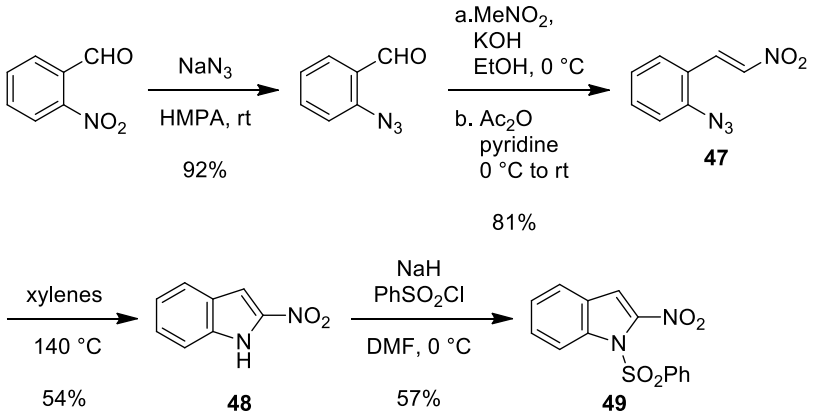
46

XNu	solvent	temp	time	% yield
NaOMe	MeOH	reflux	40 min	93
NaOEt	EtOH	reflux	40 min	94
NaSMe	MeOH	reflux	1 h	quant
$K(CH(CO_2Me)_2)$	DMF	120 °C	1 h	51

Scheme 3.37 Somei's cine substitution of 3-acetyl-1-methoxyindole **46**.

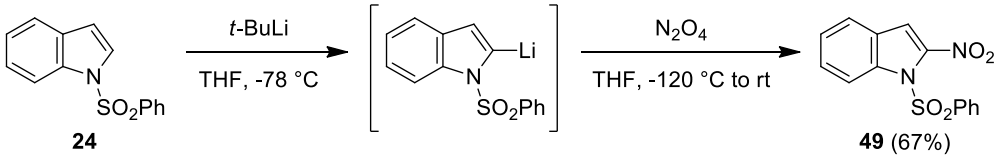
3.9 Cine and Tele Substitutions of *N*-Phenylsulfonyl Nitroindoles

Gribble determined that *N*-phenylsulfonyl nitroindoles can undergo SNAr as well. The initial synthesis of *N*-phenylsulfonyl 2-nitroindole **49** by Gribble was conducted via nucleophilic aromatic substitution of 2-nitrobenzaldehyde with sodium azide (NaN_3) to give 2-azidobenzaldehyde (Scheme 3.38).[67] Treatment of the aryl azide with nitromethane ($MeNO_2$) promoted the Henry reaction to afford the nitrostyrene **47**, which was heated to form 2-nitroindole **48** via Sundberg indole synthesis. Sulfonylation of **48** gave **49**.



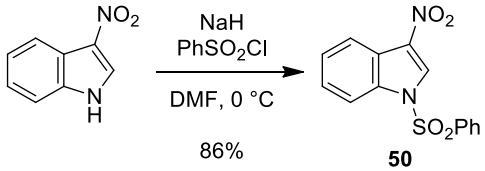
Scheme 3.38 Gribble's synthesis of *N*-phenylsulfonyl 2-nitroindole **49** via Sundberg reaction.

Gribble also formed *N*-phenylsulfonyl 2-nitroindole **49** via C2-lithiation of *N*-phenylsulfonyl indole **24** with *tert*-BuLi followed by nitration using dinitrogen tetraoxide (N_2O_4) (Scheme 3.39).[68]

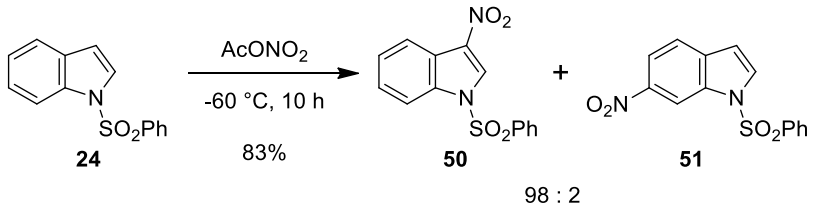


Scheme 3.39 Gribble's formation of **49** via lithiation.

On the other hand, Gribble synthesized *N*-phenylsulfonyl 3-nitroindole **50** by treating 3-nitroindole with $PhSO_2Cl$ under basic conditions in 86% yield (Scheme 3.40).[69] Also, the reaction of acetyl nitrate ($AcONO_2$), preformed from nitric acid (HNO_3) and acetic anhydride (Ac_2O), with *N*-phenylsulfonyl indole **24** afforded a 98:2 ratio of regioisomeric products **50** and **51** in 83% yield after column chromatography (Scheme 3.41); pure **50** was obtained after further purification by recrystallization.[70]

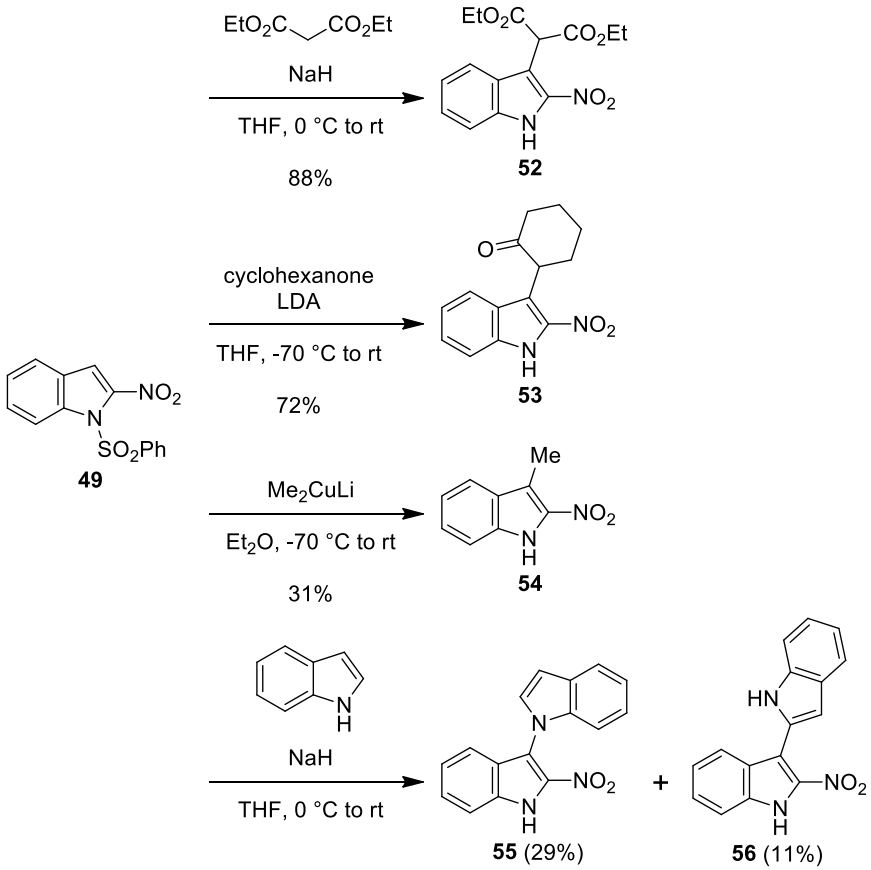


Scheme 3.40 Gribble's formation of *N*-phenylsulfonyl 3-nitroindole **50** via sulfonylation.

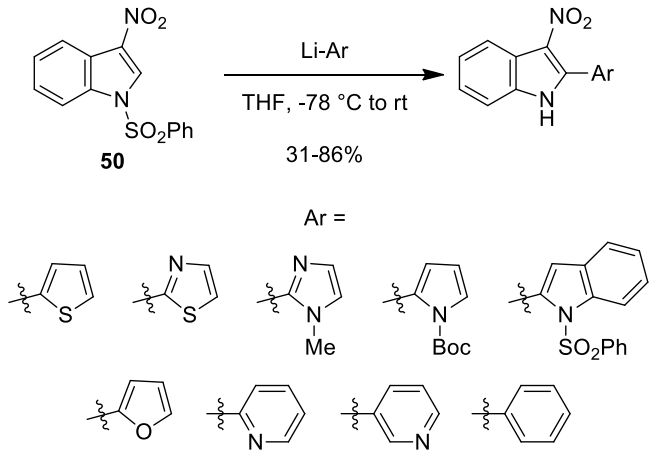


Scheme 3.41 Gribble's synthesis of **50** via nitration.

In 1999, Gribble showed the tele substitution of *N*-phenylsulfonyl 2-nitroindole **49** with different nucleophiles (Scheme 3.42).[71] In 2010, Gribble demonstrated that *N*-phenylsulfonyl 3-nitroindole **50** can participate in cine substitution with aryl lithiums (Scheme 3.43).[72] The aryl lithiums were prepared *in situ* by either direct lithiation with lithium diisopropylamide (LDA), lithium-bromine exchange with *tert*-BuLi, or lithium-iodine exchange with *tert*-BuLi.



Scheme 3.42 Gribble's tele substitution of **49** with various nucleophiles.

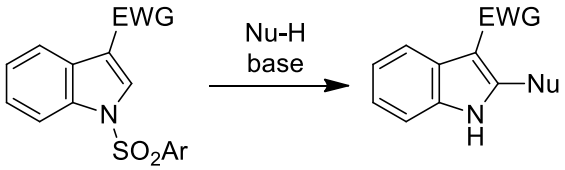


Scheme 3.43 Gribble's cine substitution of **50** with aryl lithiums.

Chapter 4: Development of Cine Substitution of *N*-Phenylsulfonyl 3-Substituted Indoles

4.1 Research Goal and Strategy

N-Methoxy indoles that do the known Somei chemistry are difficult to access. They are not readily available and need to be formed in multiple steps via unstable 1-hydroxyindole intermediates. Aiming to find substrates that could allow the same reaction pathway, but would be more accessible, is a driving force of this work. Due to the large availability of sulfonyl halides, with aryl and alkyl sulfonyl chlorides being the most commercially available sulfinate derivatives,[73] it is possible that an array of *N*-sulfonyl indoles can be efficiently prepared for cine substitution. In addition, *N*-sulfonyl indoles would be ideal electrophiles because sulfinates are theoretically better LGs than methoxide, as predicted by the pKa values of their conjugate acids (e.g., phenylsulfinic acid has a pKa of 2.1 while methanol has a pKa of 15.5).[74] And since *N*-phenylsulfonyl 3-nitroindole **50** has been shown to undergo cine substitution with aryl lithiums, as described by Gribble in Section 3.9, using other EWGs may lead to new reactivity and products.



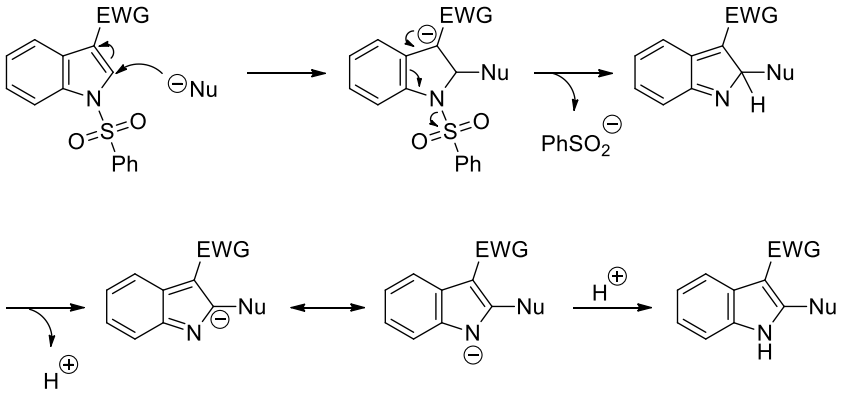
Scheme 4.1 Cine substitution of *N*-sulfonyl 3-substituted indoles.

The goal of this project is to develop a method to functionalize the 2-position of indoles via cine substitution of *N*-arylsulfonyl 3-substituted indoles (Scheme 4.1). The

overall strategy in developing the cine substitution of *N*-arylsulfonyl 3-substituted indoles is by examining different:

1. EWGs at the 3-position of the *N*-arylsulfonyl indole,
2. nucleophiles,
3. arylsulfonyls at the 1-position of the indole,
4. bases, and
5. reaction conditions, such as solvents, temperatures, and times.

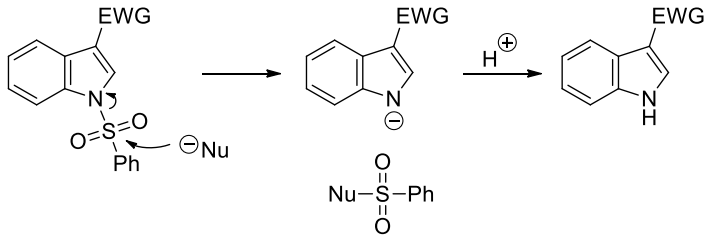
4.2 Proposed Mechanisms for the Cine Substitution of *N*-Sulfonyl 3-Substituted Indoles and its Competing Reactions



Scheme 4.2 Proposed mechanism for the cine substitution of *N*-sulfonyl 3-substituted indoles.

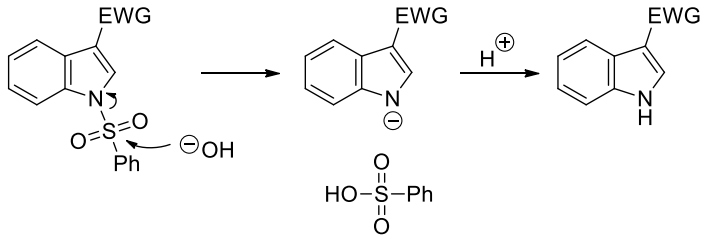
The cine substitution reaction begins with the negatively charged nucleophile attacking the 2-position of the *N*-sulfonyl 3-substituted indole (Scheme 4.2). An EWG at the 3-position of the sulfonyl indole stabilizes the formation of negative charge in the intermediate once the nucleophile adds, which is followed by the departure of the good

sulfinate leaving group. Consecutive deprotonation and protonation steps reform aromaticity and yield the desired product.



Scheme 4.3 Proposed mechanism for the trans-sulfonylation of *N*-sulfonyl 3-substituted indoles with the nucleophile.

A competing pathway to the cine substitution is the trans-sulfonylation, where the anionic nucleophile attacks the sulfur of the sulfonyl indole producing the sulfonylated nucleophile and conjugate base of 3-substituted indole (Scheme 4.3). If the substituent at the 3-position of the sulfonyl indole is an EWG, the negatively charged indole is stabilized. Protonation at the nitrogen forms the 3-substituted indole. The sulfonyl transfer reaction is also favored for sterically hindered alcohols, which appear to have a harder time approaching the 2-position of the sulfonyl indole.

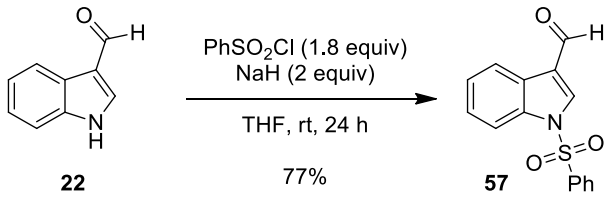


Scheme 4.4 Proposed mechanism for the hydrolysis of *N*-sulfonyl 3-substituted indoles.

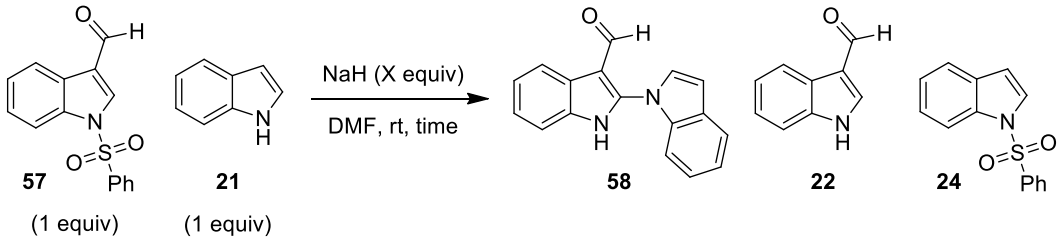
Lastly, if the reaction is not completely dry, hydroxide can form under the basic conditions and desulfonylate the *N*-sulfonyl 3-substituted indole (Scheme 4.4).

4.3 Attempted Cine Substitution of *N*-Phenylsulfonyl 3-Formylindole with Indole

We became interested in coupling C2 of indole with another indole N because that structure is present in AETX. Using Zhang's procedure,[48] 3-formylindole **22** was sulfonylated with excess phenylsulfonyl chloride and NaH to afford *N*-phenylsulfonyl 3-formylindole **57** (Scheme 4.5).



Scheme 4.5 Formation of *N*-phenylsulfonyl 3-formylindole **57**.



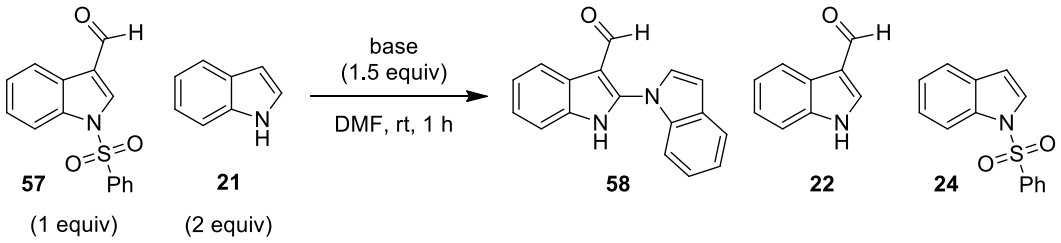
NaH (equiv)	time (h)	isolated yield of **58** (%)	isolated yield of **22** (%)	isolated yield of **24** (%)
1	48	0	37	36
1.5	1	0	46	31

Figure 4.1 Attempted cine substitution of *N*-phenylsulfonyl 3-formylindole **57** with indole **21** using different amounts of NaH.

The cine substitution of *N*-phenylsulfonyl 3-formylindole **57** with indole **21** using varying amounts of NaH as the base in anhydrous DMF was attempted (Figure 4.1). Monitoring by TLC, the reaction with excess NaH resulted in a shorter reaction time.

Although both reactants were consumed in the two reactions, the desired product **58** was not observed; rather, 3-formylindole **22** and *N*-phenylsulfonyl indole **24** were made. It is ideal to track the reaction with the disappearance of the sulfonyl indole starting material **57** since the indole nucleophile **21** partially overlaps with the *N*-phenylsulfonyl indole **24** on TLC. Based on the results, **57** is acting as a sulfonylating agent.

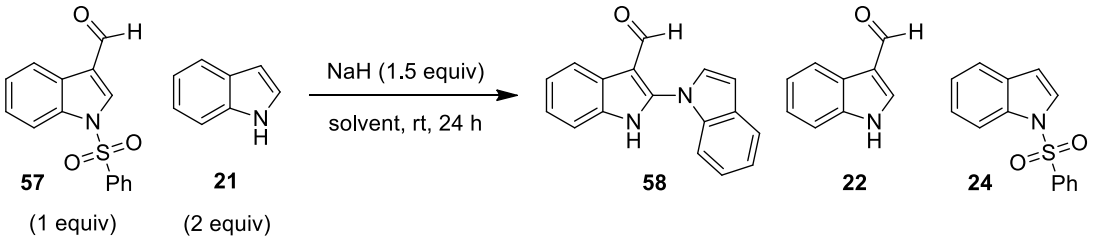
Lithium hexamethyldisilazide (LiHMDS) and potassium *tert*-butoxide (KOtBu) were also examined along with NaH (Figure 4.2). The use of 1.5 equivalents of base and 2 equivalents of indole **21** ensures excess indole conjugate base was present to act as a nucleophile. In all the reactions, the desired product **58** was not formed, and again, only 3-formylindole **22** and *N*-phenylsulfonyl indole **24** were isolated. The consumption of *N*-phenylsulfonyl 3-formylindole **57** occurred in these reactions, and any unreacted **21** was removed, along with DMF, via the acidic and aqueous washes during the work-up.



base	isolated yield of **58** (%)	isolated yield of **22** (%)	isolated yield of **24** (%)
NaH	0	96	78
LiHMDS	0	96	82
KOtBu	0	69	47

Figure 4.2 Attempted cine substitution of **57** with excess **21** using different bases.

To determine if solvent has an effect, the cine substitution of *N*-phenylsulfonyl 3-formylindole **57** with indole **21** was also performed in THF and MeCN (Figure 4.3). Unlike the reaction in DMF, where the consumption of **57** was done in one hour, the reactions in the other two polar, aprotic solvents were much slower. ^{1}H NMR of the crude from both reactions did not show desired product **58**; instead, the reaction in MeCN formed 3-formylindole **22** and *N*-phenylsulfonyl indole **24** while the reaction in THF only made **22**.



ratio of compounds
(based on ^{1}H NMR integrals of crude)

solvent	**57** : **58** : **22** : **24**
THF	0 : 0 : 100 : 0
MeCN	0 : 0 : 50 : 50

Figure 4.3 Attempted cine substitution of **57** with **21** in different solvents.

4.4 Attempted Cine Substitution of *N*-Phenylsulfonyl 3-Formylindole with Various Nucleophiles

The cine substitution of *N*-phenylsulfonyl 3-formylindole **57** with various nucleophiles **A**-**E** (Figure 4.4) in equimolar amounts was attempted (Figure 4.5). The reaction with 2-naphthol **B** had a clear consumption of starting materials by TLC, and therefore was stopped after three hours. The other reactions were stirred for 24 hours and still had small amount of unreacted sulfonyl indole **57**. Only the reaction with citronellol

A as the nucleophile resulted in the formation of any desired product, along with 3-formylindole **22**. The other reactions afforded a mixture of **22** and sulfonylated nucleophiles **60A-E**, or only **22**.

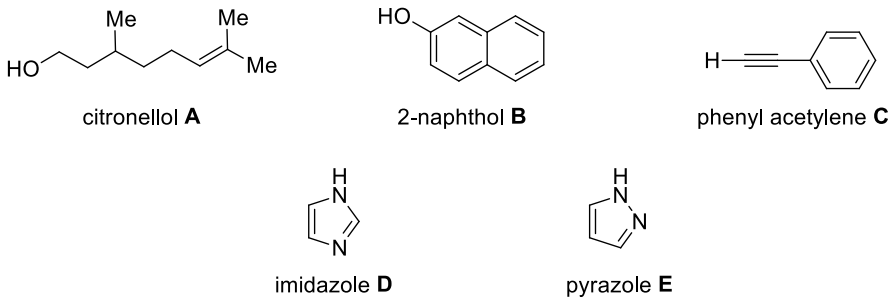
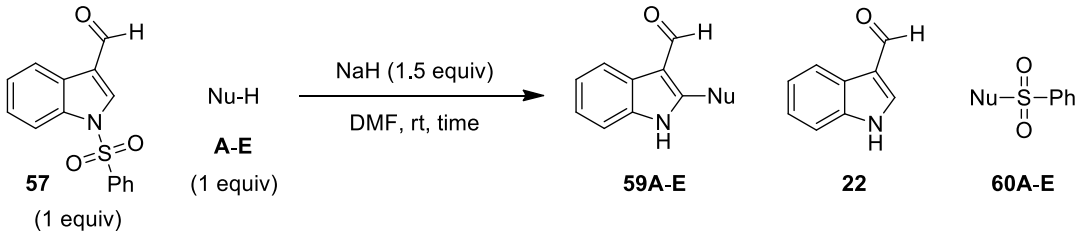


Figure 4.4 Structures of nucleophiles **A-E**.



Nu-H	time (h)	ratio of compounds (based on ^{1}H NMR integrals of crude) **57** : **59** : **22** : **60**
A	24	13 : 48 : 39 : 0
B	3	0 : 0 : 46 : 54
C	24	19 : 0 : 81 : 0
D	24	8 : 0 : 46 : 46
E	24	5 : 0 : 50 : 45

Figure 4.5 Attempted cine substitution of **57** with nucleophiles **A-E**.

4.5 Cine Substitution of *N*-Phenylsulfonyl 3-Formylindole with Citronellol

The cine substitution of *N*-phenylsulfonyl 3-formylindole **57** with two equivalents of citronellol **A** was conducted (Figure 4.6). Compared to the reaction consisting of equimolar amounts of **57** and citronellol **A** (as seen in Figure 4.5), using excess nucleophile **A** led to the consumption of **57** and more formation of the desired product **59A**; purification of **59A** resulted in an isolated yield of 57%. Unreacted nucleophile **A** was removed via the aqueous washes during the work-up.

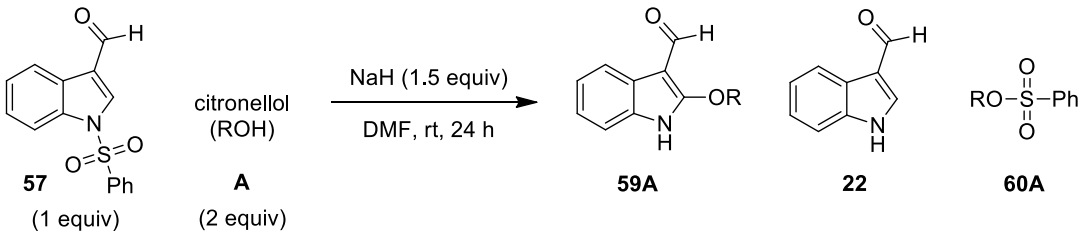
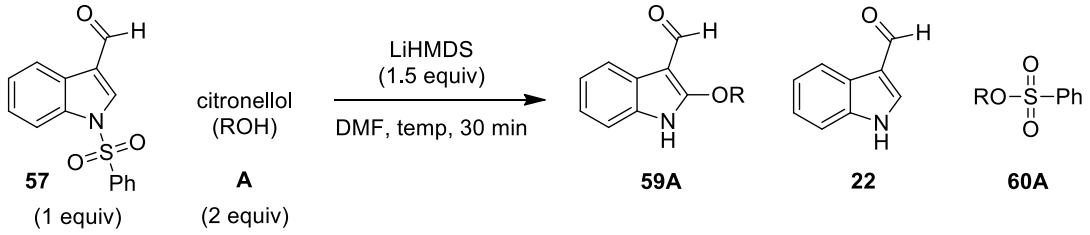


Figure 4.6 Cine substitution of **57** with excess citronellol **A**.

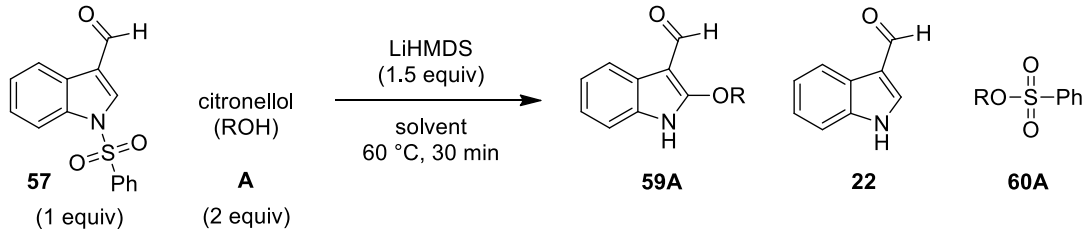
Switching base to LiHMDS, the cine substitution of *N*-phenylsulfonyl 3-formylindole **57** with citronellol **A** at different temperatures was performed (Figure 4.7). The reactions were performed at shorter reaction times, and sulfonyl indole starting material **57** was consumed in all cases. At room temperature, a mixture of the desired product **59A**, 3-formylindole **22**, and sulfonylated citronellol **60A** were obtained. Running the reaction at 60 °C resulted in the synthesis of **59A** and **22** with a ratio of 87 to 13, respectively. Formation of **59A** afforded an isolated yield of 80%. The product

distribution for the reaction at 90 °C was slightly less favorable towards the desired product in comparison to the reaction at 60 °C.



temp	ratio of compounds (based on ^{1}H NMR integrals of crude) **57** : **59A** : **22** : **60A**	isolated yield of **59A** (%)
rt	0 : 26 : 38 : 36	--
60 °C	0 : 87 : 13 : 0	80
90 °C	0 : 81 : 19 : 0	--

Figure 4.7 Cine substitution of **57** with citronellol **A** using LiHMDS at different temperatures.

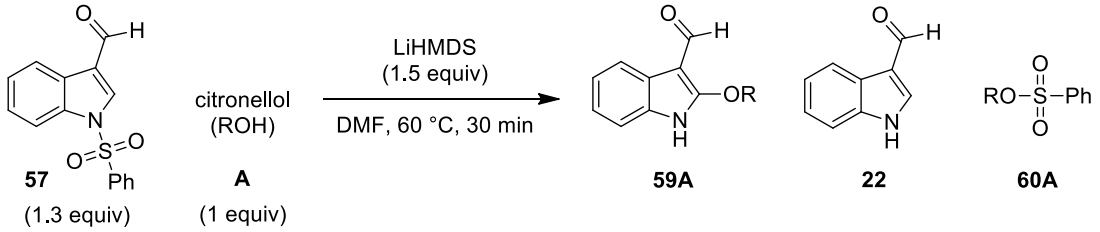


solvent	ratio of compounds (based on ^{1}H NMR integrals of crude) **57** : **59A** : **22** : **60A**
THF	0 : 13 : 43 : 44
MeCN	5 : 5 : 43 : 47

Figure 4.8 Cine substitution of **57** with citronellol **A** in different solvents.

A solvent screen was performed for the cine substitution of *N*-phenylsulfonyl 3-formylindole **57** with citronellol **A** using LiHMDS (Figure 4.8). The results show that DMF is the superior polar, aprotic solvent; THF and MeCN afforded a lower amount of desired product **59A** formed.

When citronellol **A** was used as the limiting reagent, the cine substitution of *N*-phenylsulfonyl 3-formylindole **57** resulted in the formation of the desired product **59A**, but the product ratio was slightly less favorable (Figure 4.9).



ratio of compounds
(based on ^{1}H NMR integrals of crude)

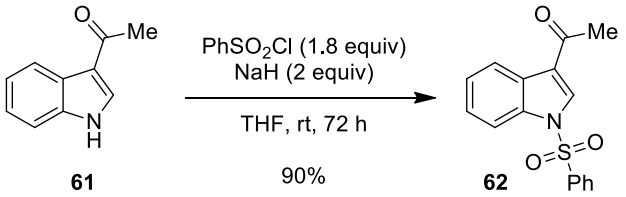
59A : **22** : **60A**

72 : 28 : 0

Figure 4.9 Cine substitution of **57** with citronellol **A** as the limiting reagent.

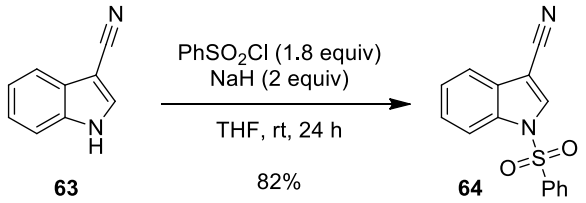
4.6 Cine Substitution of *N*-Phenylsulfonyl 3-Substituted Indoles with Different Alcohols

Using Zhang's conditions described earlier, *N*-phenylsulfonyl 3-acetylindole **62** was prepared by reacting 3-acetylindole **61** with excess phenylsulfonyl chloride and NaH in THF (Scheme 4.6).



Scheme 4.6 Formation of *N*-phenylsulfonyl 3-acetylindole **62**.

3-Cyanoindole **63**, synthesized from 3-formylindole and hydroxylammonium chloride using Kang's procedure,[75] was sulfonylated to form *N*-phenylsulfonyl 3-cyanoindole **64** (Scheme 4.7).



Scheme 4.7 Formation of *N*-phenylsulfonyl 3-cyanoindole **64**.

The cine substitution of *N*-phenylsulfonyl 3-formylindole **57**, *N*-phenylsulfonyl 3-acetylindole **62**, and *N*-phenylsulfonyl 3-cyanoindole **64** with various alcohols **A** and **F**-**J** (Figure 4.10) was performed (Figures 4.11, 4.12, and 4.13). The key factor influencing product distribution is the steric effect of the alcohol structure. There are small differences in the product ratios observed between the three EWGs on the indole starting material. In all cases, the indole starting material was consumed.

Primary alcohols (citronellol **A** and 4-penten-1-ol **F**) and primary allylic alcohol (crotyl alcohol **G**) resulted in the greatest amount of desired cine substitution product formed with the least amount of 3-substituted indole side product made. Secondary allylic

alcohol (1-buten-3-ol **H**) slightly favored the formation of the desired product over the 3-substituted indole. However, with primary β-branched alcohol (2-methyl-3-buten-1-ol **I**) and secondary alcohol (4-penten-2-ol **J**), the sulfonyl transfer reaction began to occur resulting in the synthesis of phenylsulfonylated alcohols, increased production of 3-substituted indoles, and decreased formation of desired products.

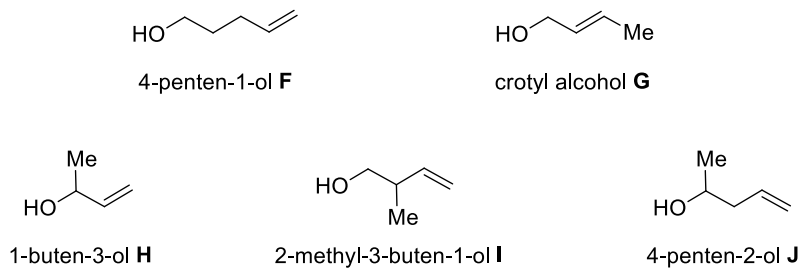
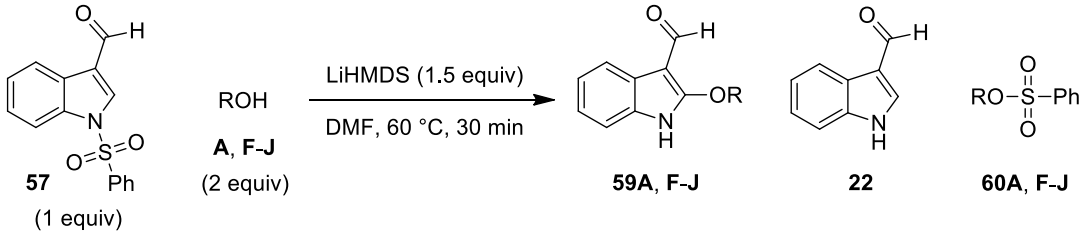
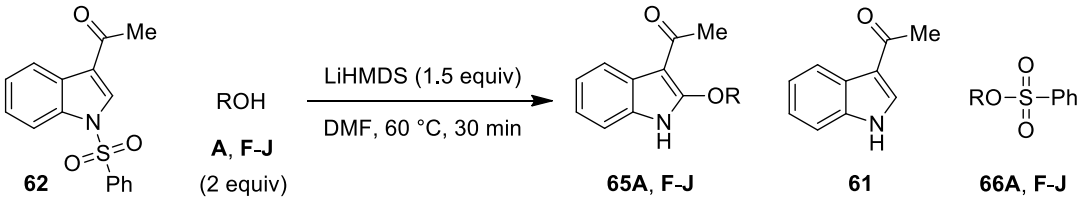


Figure 4.10 Structures of alcohols **F**-**J**.



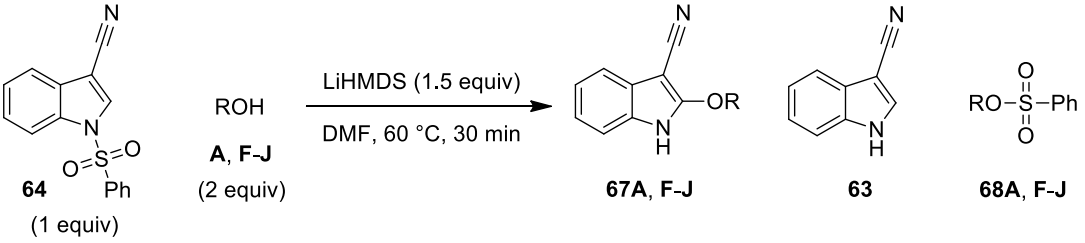
ROH	ratio of compounds (based on ^{1}H NMR integrals of crude) **59 : 22 : 60**	isolated yield of **59** (%)
A	87 : 13 : 0	80
F	87 : 13 : 0	83
G	84 : 16 : 0	81
H	56 : 44 : 0	--
I	26 : 44 : 30	--
J	20 : 51 : 29	--

Figure 4.11 Cine substitution of *N*-phenylsulfonyl 3-formylindole **57** with alcohols **A** and **F**-**J**.



ROH	ratio of compounds (based on ^{1}H NMR integrals of crude) **65** : **61** : **66**	isolated yield of **65** (%)
A	87 : 13 : 0	74
F	91 : 9 : 0	88
G	84 : 16 : 0	78
H	59 : 41 : 0	--
I	33 : 48 : 19	--
J	23 : 60 : 17	--

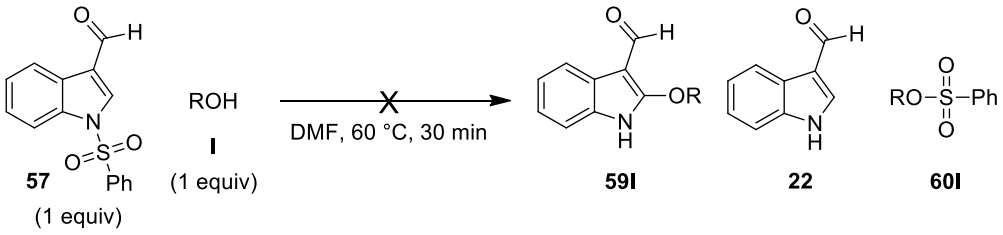
Figure 4.12 Cine substitution of *N*-phenylsulfonyl 3-acetylindole **62** with alcohols **A** and **F-J**.



ROH	ratio of compounds (based on ^{1}H NMR integrals of crude) **67 : 63 : 68**	isolated yield of **67** (%)
A	73 : 27 : 0	67
F	85 : 15 : 0	78
G	80 : 20 : 0	71
H	54 : 46 : 0	--
I	21 : 52 : 27	--
J	15 : 57 : 28	--

Figure 4.13 Cine substitution of *N*-phenylsulfonyl 3-cyanoindole **64** with alcohols **A** and **F-J**.

To ascertain that the half equivalent of excess alcohol is not participating in the reaction, e.g., as a nucleophile in the sulfonyl transfer, equimolar amounts of *N*-phenylsulfonyl 3-formylindole **57** and 2-methyl-3-buten-1-ol **I** were reacted without any base, which resulted in only unreacted starting material (Scheme 4.8)

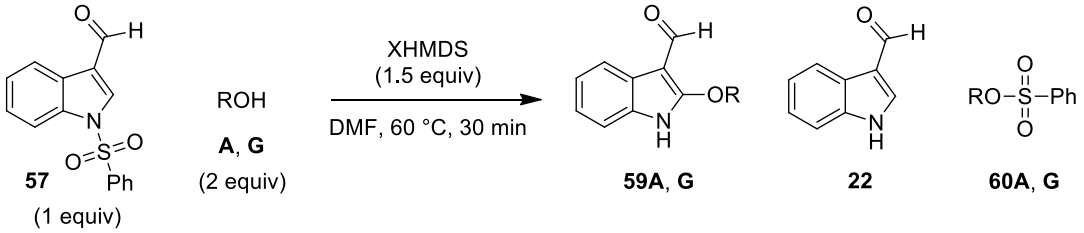


Scheme 4.8 Attempted reaction of **57** with 2-methyl-3-buten-1-ol **I** without base.

4.7 Hexamethyldisilazide with Different Countercations in Cine Substitution of *N*-Phenylsulfonyl 3-Formylindole

The countercation of the HMDS base was analyzed in the cine substitution of *N*-phenylsulfonyl 3-formylindole **57** with different alcohols (Figures 4.14 and 4.15). The results show that the cine substitution is less favored with sodium hexamethyldisilazide (NaHMDS) and potassium hexamethyldisilazide (KHMDS) when compared to LiHMDS (as seen in the previous section).

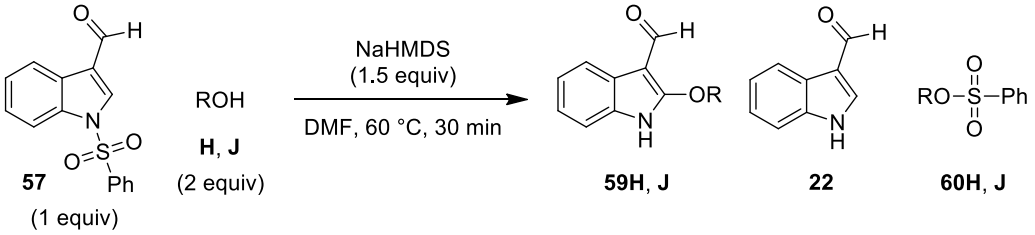
Using NaHMDS and KHMDS for the cine substitution of *N*-phenylsulfonyl 3-formylindole **57** with primary alcohols, citronellol **A** and crotyl alcohol **G** (Figure 4.14), resulted in unreacted sulfonyl indole **57** and less desired product formed and more 3-formylindole **22** made compared to the same reactions with LiHMDS as base (Figure 4.11).



ratio of compounds
(based on ^{1}H NMR integrals of crude)

X	ROH	**57** : **59** : **22** : **60**
K	**A**	36 : 12 : 52 : 0
Na	**A**	38 : 10 : 52 : 0
Na	**G**	28 : 13 : 59 : 0

Figure 4.14 Cine substitution of **57** with primary alcohols, citronellol **A** and crotyl alcohol **G**, using KHMDS and NaHMDS.



ratio of compounds
(based on ^{1}H NMR integrals of crude)

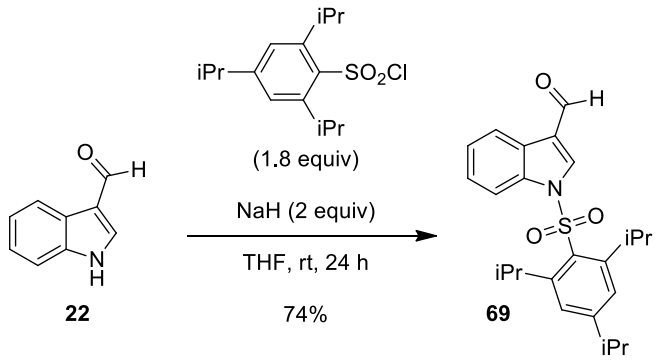
ROH	**57** : **59** : **22** : **60**
H	42 : 0 : 58 : 0
J	55 : 0 : 45 : 0

Figure 4.15 Cine substitution of **57** with secondary alcohols, 1-buten-3-ol **H** and 4-penten-2-ol **J**, using NaHMDS.

Unlike using LiHMDS for the cine substitution of **57** with 1-buten-3-ol **H** and 4-penten-2-ol **J** secondary alcohols, which afforded a combination of the desired product, 3-formylindole **22**, and sulfonylated alcohol (Figure 4.11), using NaHMDS only resulted in unreacted **57** and side product **22** (Figure 4.15).

4.8 Cine Substitution of *N*-Triisopropylbenzenesulfonyl 3-Formylindole with Various Nucleophiles

Using Zhang's sulfonylating conditions mentioned earlier, *N*-triisopropylbenzenesulfonyl 3-formylindole **69** was made by reacting 3-formylindole **22** with triisopropylbenzenesulfonyl chloride in the presence of NaH (Scheme 4.9).



Scheme 4.9 Formation of *N*-triisopropylbenzenesulfonyl 3-formylindole **69**.

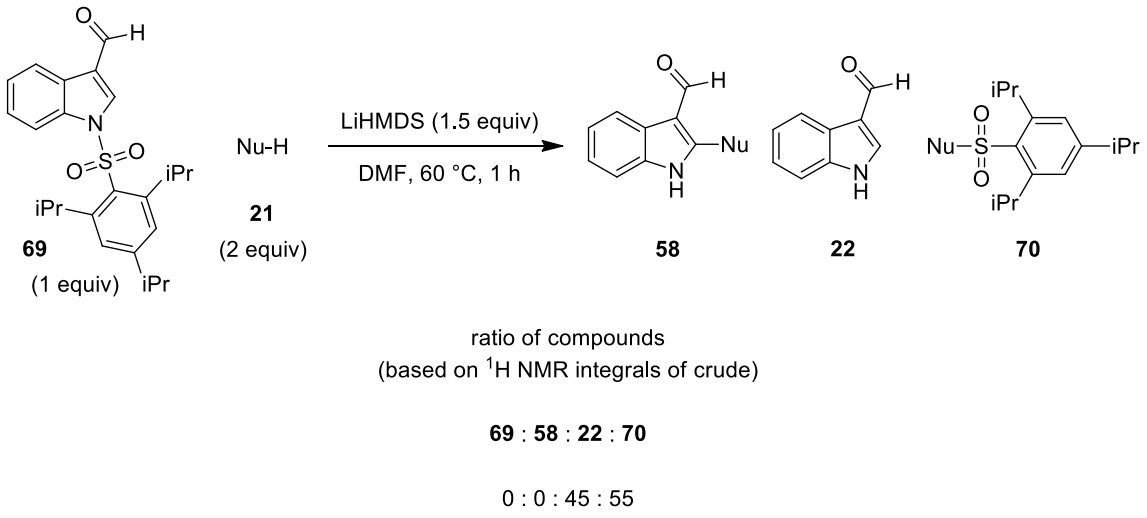
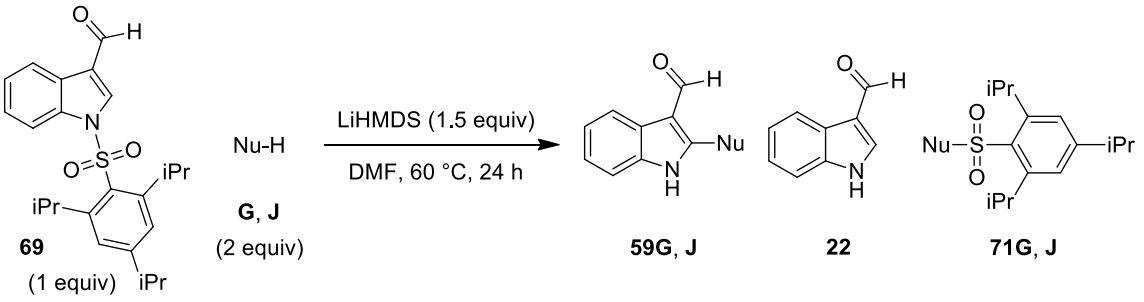


Figure 4.16 Attempted cine substitution of *N*-triisopropylbenzenesulfonyl 3-formylindole **69** with indole **21**.



ratio of compounds
(based on ^{1}H NMR integrals of crude)

Nu-H	**69** : **59** : **22** : **71**
G	0 : 77 : 23 : 0
J	0 : 33 : 67 : 0

Figure 4.17 Cine substitution of **69** with crotyl alcohol **G** and 4-penten-2-ol **J**.

In hopes to prevent any undesired sulfonyl transfer and sulfonamide hydrolysis, the cine substitution of the more sterically hindered sulfonyl indole **69** was attempted with indole **21** (Figure 4.16) and alcohols, crotyl alcohol **G** and 4-penten-2-ol **J** (Figure 4.17), as the nucleophiles.

The reaction of *N*-triisopropylbenzenesulfonyl 3-formylindole **69** with indole **21** at 60 °C after one hour resulted in the consumption of **69** without the formation of the desired product **58**. Instead, 3-formylindole **22** and *N*-triisopropylbenzenesulfonyl indole **70** (Figure 4.16) were made. These results are like those from the reaction of *N*-phenylsulfonyl 3-formylindole **57** with **21** at room temperature for one hour, which only formed **22** and *N*-phenylsulfonyl indole **24** (as shown in Section 4.3). The sterics on the sulfonyl group of **69** does not seem to have a major impact on the products formed when **21** is the nucleophile. However, higher temperature was used for the bulkier **69**.

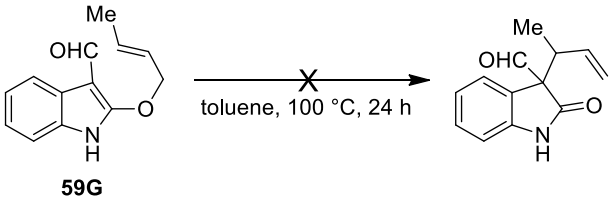
The cine substitution of **69** with crotyl alcohol **G** at 60 °C for 24 hours formed the desired product **59G** and 3-formylindole **22** in a ratio of 77 to 23, respectively (Figure 4.17). This is a less favorable product ratio compared to when *N*-phenylsulfonyl 3-formylindole **57** was treated with the primary allylic alcohol **G** at 60 °C for 30 minutes (as seen in Section 4.6). The bulkier sulfonyl indole **69** may block the 2-position and make it less accessible for alcohol **G** to approach and form the desired product **59G**.

The cine substitution of **69** with 4-penten-2-ol **J** at 60 °C (Figure 4.17) also took longer (24 hours) to consume the arylsulfonyl indole **69** compared to the reaction of *N*-phenylsulfonyl 3-formylindole **57** with the secondary alcohol **J**, which required only 30 minutes at the same temperature (as seen in Section 4.6). The reaction of alcohol **J** with the more sterically hindered sulfonyl indole **69** afforded the desired product **59J** and 3-formylindole **22** without any sulfonylated alcohol **71J**. However, as seen in Section 4.6, the reaction of *N*-phenylsulfonyl 3-formylindole **57** with alcohol **J** yielded a mixture of the desired product **59J**, side product **22**, and sulfonylated alcohol **60J**. Longer reaction time, absence of sulfonylated alcohol **71J**, and increased amount of desired product **59J** observed when using the bulkier sulfonyl indole **69** seem to suggest that steric hindrance about the sulfonyl group prevents trans-sulfonylation for sterically hindered alcohols, such as **J**.

4.9 Attempted Claisen Rearrangement of 3-Substituted Indolyl Crotyl Ethers

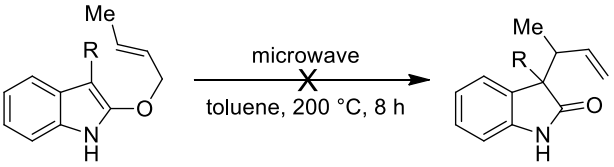
The Claisen rearrangement reaction of 3-substituted indolyl crotyl ethers, synthesized from the cine substitution reaction, was attempted. 3-Formylindolyl crotyl ether **59G** in toluene was allowed to react at 100 °C by conventional heating for 24 hours,

which afforded only unreacted starting material (Scheme 4.10). Using microwave conditions, **59G** and 3-cyanoindolyl crotyl ether **67G** were heated at 200 °C in toluene for eight hours, which resulted in only unreacted starting material as well (Scheme 4.11). Utilizing Somei's Claisen rearrangement conditions,[61] a solution of 3-formylindolyl crotyl ether **59G** in methanol was refluxed for 48 hours, which gave just unreacted starting material.



59G

Scheme 4.10 Attempted Claisen rearrangement of 3-formylindolyl crotyl ether **59G** at 100 °C.



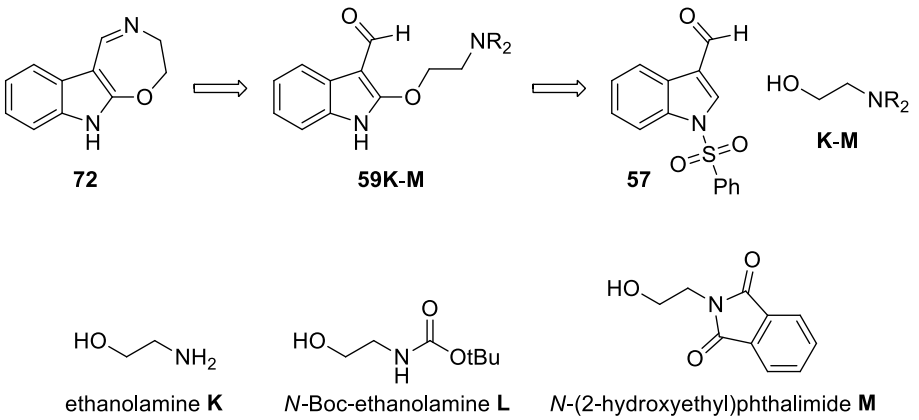
R = CHO (**59G**), CN (**67G**)

Scheme 4.11 Attempted Claisen rearrangement of **59G** and 3-cyanoindolyl crotyl ether **67G** at 200 °C.

4.10 Cine Substitution of *N*-Phenylsulfonyl 3-Formylindole with Ethanolamine and its Derivatives to Access a Novel Tricyclic Indole-Fused Seven-Membered Ring Scaffold

A novel tricyclic indole-fused seven-membered ring scaffold **72** can be hypothetically accessed via intramolecular imine condensation of compounds that come

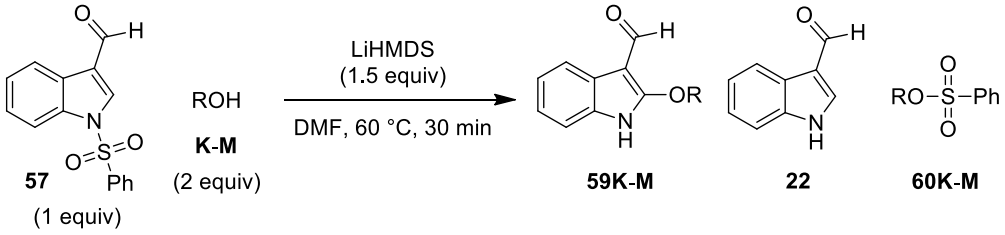
from the cine substitution of *N*-phenylsulfonyl 3-formylindole **57** and ethanolamine **K** and its derivatives, such as *N*-(*tert*-butoxycarbonyl)ethanolamine **L** (*N*-Boc-ethanolamine **L**) and *N*-2-(hydroxyethyl)phthalimide **M** (Scheme 4.12).



Scheme 4.12 Retrosynthesis of a novel tricyclic indole-fused seven-membered ring scaffold **72**.

The cine substitution of *N*-phenylsulfonyl 3-formylindole **57** with ethanolamine **K** and its analogs **L** and **M** was performed (Figure 4.18). In all cases, the sulfonyl indole starting material **57** was consumed based on ^{1}H NMR of the crude. The reaction with ethanolamine **K** resulted in only 3-formylindole **22**. On the other hand, Boc-protected ethanolamine **L**, prepared using Dreassi's method,[76] afforded the desired product **59L** and **22** as the minor and major products, respectively. *N*-2-(Hydroxyethyl)phthalimide **M** yielded a mixture of the desired product **59M**, **22**, and sulfonylated alcohol **60M**. A primary alcohol containing a free amine appears to be completely unreactive towards cine substitution (as well as trans-sulfonylation) as observed in the reaction using ethanolamine **K**. Although protecting the free amine with Boc and phthaloyl groups improved the

formation of the desired product, further work needs to be done to increase the desired product's selectivity and yield.

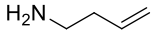


ratio of compounds
(based on ^{1}H NMR integrals of crude)

ROH	**57** : **59** : **22** : **60**
K	0 : 0 : 100 : 0
L	0 : 21 : 79 : 0
M	0 : 28 : 44 : 28

Figure 4.18 Attempted cine substitution of *N*-phenylsulfonyl 3-formylindole **57** with ethanolamine **K**, *N*-Boc-ethanolamine **L**, and *N*-2-(hydroxyethyl)phthalimide **M**.

To determine if a free amine by itself is a potential nucleophile for cine substitution, 3-buten-1-amine **N** (Figure 4.19) was reacted with *N*-phenylsulfonyl 3-formylindole **57** (Figure 4.20). Results show that the primary amine **N** can participate in sulfonyl transfer, but not in cine substitution. Unreacted indole starting material **57** and 3-formylindole **22** are also observed.



3-buten-1-amine **N**

Figure 4.19 Structure of 3-buten-1-amine **N**.

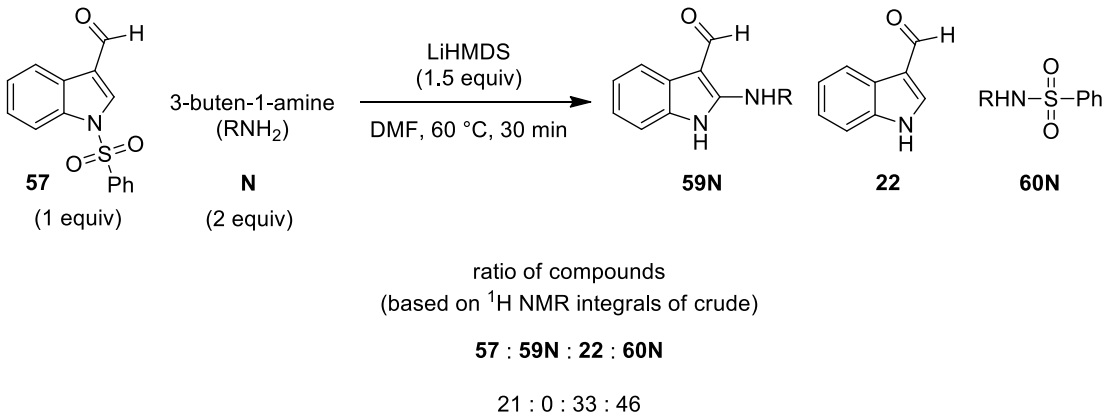


Figure 4.20 Attempted cine substitution of **57** with 3-buten-1-amine **N**.

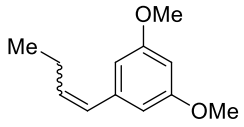
The reactivity of an alkyl amine (without a hydroxyl group), e.g., 3-buten-1-amine **N**, is comparable to that of *N*-containing aromatic compounds (as seen in Sections 4.2 and 4.3), in that both result in the formation of the 3-formylindole **22** and sulfonylated amines. The results also seem to suggest that a nucleophile containing both a hydroxyl and a free amine, as in the case of ethanolamine **K**, completely renders each functional group unreactive for cine substitution and trans-sulfonylation.

Chapter 5: Experimental

5.1 General Information

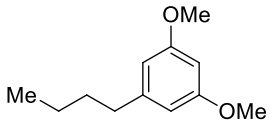
TLC was performed using Merck 60 F254 aluminum-backed plates. Flash column chromatography was performed using Silicycle silica gel (230-400 mesh). Melting points were determined using an automated Buchi B-545 melting point apparatus, which provides a specific melting point, not a range, and are corrected. ^{1}H NMR spectra were obtained on a Bruker Avance (500 MHz) spectrometer. ^{13}C NMR spectra were obtained on Bruker Avance NEO (100 MHz) and Bruker Avance (150 MHz) spectrometers. Chemical shifts are referenced to the residual solvent signal ($CDCl_3$: δ_H = 7.26, δ_C = 77.16). Infrared spectra were recorded on a Bruker Alpha spectrometer. High-resolution mass spectra were obtained using an Agilent 6545 LC/SFC Hybrid Q-TOF spectrometer. Optical rotations were taken on a Rudolph AutoPol IV polarimeter. Circular dichroism experiments were performed on a Jasco J-815 CD spectrometer.

5.2 Chapter 2 Experimental

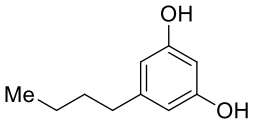


5-(1-Butenyl)-1,3-dimethoxybenzene (8). To a suspension of *n*-propyltriphenylphosphonium bromide (300 mg, 0.780 mmol) in toluene (10 mL) was added 60% NaH in oil (30 mg, 0.78 mmol). The mixture was stirred for 30 min at room temperature and then 3,5-dimethoxybenzaldehyde (100 mg, 0.600 mmol) was added. The reaction was stirred at 95 °C for 24 h under argon before cooling to room temperature. The

mixture was passed through a silica plug and eluted with 20% ethyl acetate in hexanes. The solvent was removed under reduced pressure to afford a mixture of alkene isomers (*Z*:*E* 77:23) as a pale-yellow oil (110 mg, 99%.). The spectroscopic properties matched those earlier reported.[23b]

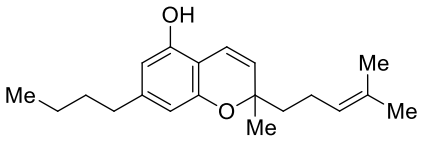


5-*n*-Butyl-1,3-dimethoxybenzene (9). A mixture of 5-(1-butenyl)-1,3-dimethoxybenzene isomers (1.22 g, 6.34 mmol), ammonium formate (3.20 g, 50.8 mmol), and 10% Pd/C (0.20 g, 0.19 mmol) in ethanol (80 mL) was stirred at 60 °C for 1 h. The resulting suspension was cooled to room temperature, passed through a silica plug, and eluted with ethyl acetate. The solvent was removed under reduced pressure to give a clear oil (1.22 g, 99%). The spectroscopic data of the product agreed with the reported literature.[23b,77]

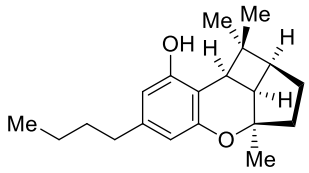


5-*n*-Butylresorcinol (7). Using the procedure of Vanek,[40] this compound was prepared by dropwise adding a 1 M solution of boron tribromide in methylene chloride (1.23 mL, 1.23 mmol) to a solution of 5-*n*-butyl-1,3-dimethoxybenzene (96 mg, 0.49 mmol) in methylene chloride (7 mL) in an ice bath. The reaction was stirred under argon with temperature rising to room temperature over 4 h. The reaction mixture was quenched with saturated $NaHCO_3$ aqueous solution and extracted with methylene chloride. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to afford an off-white solid (79 mg, 96%). The

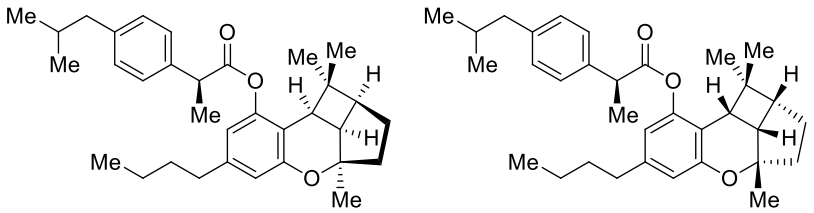
spectroscopic data for this compound were consistent with the structure and information available from the literature.[23b,77,78]



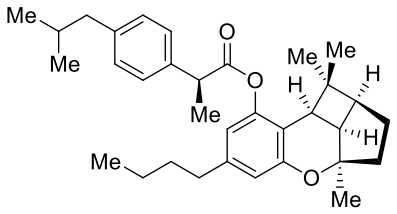
(±)-*nor*-Cannabichromene (12). Using the procedure of Lee,[21c] this compound was synthesized by adding ethylenediamine diacetate (13 mg, 0.072 mmol) to a solution of 5-*n*-butylresorcinol (60 mg, 0.36 mmol) and citral (66 mg, 0.43 mmol) in toluene (5 mL) at room temperature. The mixture was heated under reflux and argon for 24 h and then cooled to room temperature. Removal of solvent at reduced pressure left a viscous oily solid residue. The residue was purified by flash column chromatography (5% ethyl acetate in hexanes) to give an orange oil (35 mg, 32%). R_f (10% ethyl acetate in hexanes) 0.28. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.61 (d, J = 10 Hz, 1H), 6.25 (s, 1H), 6.12 (s, 1H), 5.49 (d, J = 10 Hz, 1H), 5.09 (t, J = 7.1 Hz, 1H), 4.77 (s, 1H), 2.45 (t, J = 7.7 Hz, 2H), 2.10 (m, 2H), 1.75 – 1.67 (m, 2H) 1.66 (s, 3H), 1.57 (s, 3H), 1.54 (m, 2H), 1.38 (s, 3H), 1.32 (m, 2H), 0.90 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.2, 151.1, 144.8, 131.8, 127.4, 124.3, 116.9, 109.3, 107.8, 107.1, 78.3, 41.2, 35.7, 33.2, 26.4, 25.8, 22.8, 22.4, 17.7, 14.1. IR (neat) 3397, 3045, 2960, 2926, 2857, 1622, 1575 cm^{-1}. HRMS (ESI) m/z $[M - H]^-$ Calcd for $C_{20}H_{27}O_2$: 299.2011. Found: 299.2023. SFC (Lux Cellulose-1; 35 °C; CO_2/MeOH 98:2; 2.75 mL/min; 1 mg/mL in MeOH) R_t 8.205 and 9.111 min.



(±)-*nor*-Cannabicyclol (13). Using the procedure of Hsung,[29] this compound was made by dropwise adding a solution of trifluoroacetic acid (40 mg, 0.35 mmol) in methylene chloride (1 mL) to a solution of (±)-*nor*-cannabichromene (35 mg, 0.12 mmol) in methylene chloride (1 mL) in an ice bath. The reaction mixture was stirred for 1 h in an ice bath and then quenched by pouring it into a saturated $NaHCO_3$ aqueous solution. The organic phase was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (2% ethyl acetate in hexanes) to afford a white solid (27 mg, 77%). R_f (10% ethyl acetate in hexanes) 0.45. Mp 138.6 °C (petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.33 (s, 1H), 6.18 (s, 1H), 4.53 (s, 1H), 3.07 (d, J = 9.6 Hz, 1H), 2.58 (m, 1H), 2.46 (m, 2H), 2.40 (t, J = 7.2 Hz, 1H), 1.98 (s, 1H), 1.72 – 1.65 (m, 1H), 1.65 – 1.50 (m, 4H), 1.38 (s, 3H), 1.38 (s, 3H), 1.32 (m, 2H), 0.90 (t, J = 7.3 Hz, 3H), 0.80 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 154.2, 154.1, 142.7, 110.5, 108.7, 107.4, 83.3, 46.4, 39.1, 37.9, 37.8, 36.2, 35.5, 34.1, 33.3, 27.8, 25.8, 22.5, 18.1, 14.1. IR (neat) 3353, 2950, 2929, 2861, 1620, 1582 cm^{-1}. HRMS (ESI) m/z [M + H]$^+$ Calcd for $C_{20}H_{29}O_2$: 301.2168. Found: 301.2175.

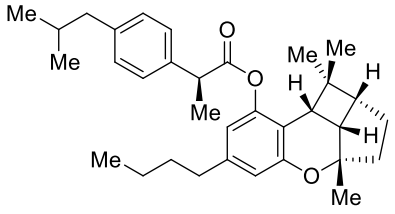


***nor*-Cannabicyclyl Ibuprofenate (20).** To a solution of (±)-*nor*-cannabicyclol (87 mg, 0.29 mmol) in methylene chloride (5 mL) was added *N*,*N*′-dicyclohexylcarbodiimide (90 mg, 0.43 mmol) and 4-dimethylaminopyridine (21 mg, 0.17 mmol). (*S*)-(+)-Ibuprofen (90 mg, 0.43 mmol) was then added, and the solution was stirred at room temperature under nitrogen for 24 h. The precipitate was filtered off and the filtrate was evaporated *in vacuo*. The residue was dissolved in ethyl acetate and washed with water. The organic phase was dried with Na_2SO_4 and concentrated via rotary evaporation to give an oily solid. The oily solid was purified by flash column chromatography (20% methylene chloride in hexanes) to afford the two diastereomeric products separately: one as an oil (62 mg, 44%) and the other as a solid (62 mg, 44%).

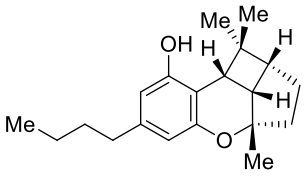


(1a*S*,1a^1*R*,3a*R*,8b*R*,2′*S*)-*nor*-Cannabicyclyl Ibuprofenate (20a): White solid (62 mg, 44%). R_f (40% methylene chloride in hexanes) 0.30. Mp 69.2 °C (ethanol/water). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 6.58 (s, 1H), 6.27 (s, 1H), 3.91 (q, J = 7.1 Hz, 1H), 2.94 (d, J = 9.6 Hz, 1H), 2.55 – 2.45 (m, 5H), 2.36 (m, 1H), 2.00 – 1.80 (m, 2H), 1.74 – 1.65 (m, 1H), 1.60 (d, J = 7.1 Hz, 3H), 1.53 (m, 4H), 1.34

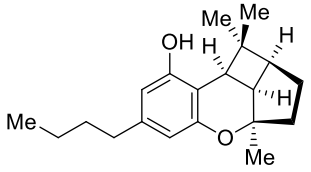
(s, 3H), 1.30 (m, 2H), 1.22 (s, 3H), 0.93 – 0.87 (m, 9H), 0.66 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 173.0, 154.3, 149.6, 142.4, 140.9, 137.3, 129.6, 127.5, 115.7, 114.7, 113.9, 83.7, 46.5, 45.6, 45.2, 39.6, 38.7, 38.4, 36.3, 35.3, 34.2, 33.1, 30.4, 29.9, 27.1, 25.6, 22.5, 18.8, 18.3, 14.1. IR (neat) 2952, 2925, 2855, 1754, 1624, 1568 cm^{-1}. HRMS (ESI) m/z [M + H]$^+$ Calcd for $C_{33}H_{45}O_3$: 489.3369. Found: 489.3352. $[\alpha]_D^{23}$ +60° (*c* 0.2, $CHCl_3$). The stereostructure was established by X-ray crystallography.



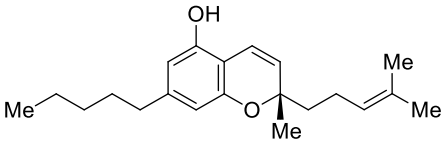
(1a*R*,1a^1*S*,3a*S*,8b*S*,2′*S*)-*nor*-Cannabicyclyl Ibuprofenate (20b): Pale yellow oil (62 mg, 44%). R_f (40% methylene chloride in hexanes) 0.23. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.58 (s, 1H), 6.42 (s, 1H), 3.90 (q, *J* = 7.1 Hz, 1H), 2.86 (d, *J* = 9.6 Hz, 1H), 2.46 (m, 5H), 2.31 (m, 1H), 1.97 (m, 1H), 1.86 (m, 1H), 1.68 (m, 1H), 1.61 (d, *J* = 7.2 Hz, 3H), 1.55 (m, 4H), 1.35 – 1.27 (m, 5H), 1.03 (s, 3H), 0.94 – 0.85 (m, 9H), 0.63 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 173.2, 154.4, 149.4, 142.3, 140.9, 137.4, 129.6, 127.5, 115.6, 115.0, 114.2, 83.9, 46.5, 45.6, 45.2, 39.6, 39.4, 38.8, 35.8, 35.4, 33.9, 33.2, 30.4, 29.9, 26.6, 25.5, 22.5, 19.5, 18.6, 14.1. IR (neat) 2952, 2926, 2857, 1755, 1624, 1573 cm^{-1}. HRMS (ESI) m/z [M + H]$^+$ Calcd for $C_{33}H_{45}O_3$: 489.3369. Found: 489.3358. $[\alpha]_D^{23}$ +13° (*c* 0.2, $CHCl_3$).



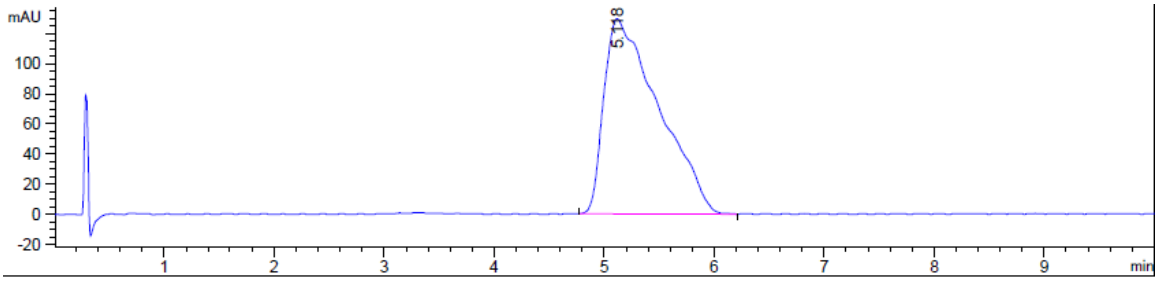
(+)-(1a*R*,1a^1*S*,3a*S*,8b*S*)-*nor*-Cannabicyclol (13). To a solution of noncrystalline (1a*R*,1a^1*S*,3a*S*,8b*S*,2′*S*)-*nor*-cannabicyclyl ibuprofenate (62 mg, 0.13 mmol) in methanol (2 mL) was added potassium carbonate (27 mg, 0.19 mmol) and the solution was stirred at room temperature for 48 h. The solvent was removed under reduced pressure to afford a yellow oily solid. It was purified by flash column chromatography (1% ethyl acetate in hexanes) to give a white solid (31 mg, 81%). Mp 107.4 °C (petroleum ether). $[\alpha]_D^{21}$ +6° (*c* 0.8, $CHCl_3$).

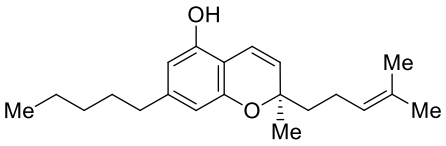


(–)-(1a*S*,1a^1*R*,3a*R*,8b*R*)-*nor*-Cannabicyclol (13). Crystalline (2^1*S*,1a*S*,1a^1*R*,3a*R*,8b*R*)-*nor*-cannabicyclyl ibuprofenate (43 mg, 0.09 mmol) was dissolved in ethanol (2 mL) at 50 °C. The solution remained homogenous upon cooling to room temperature. To the solution was added potassium carbonate (12 mg, 0.09 mmol) and the mixture was stirred at room temperature for 24 h. The mixture was passed through a silica plug and eluted with ethyl acetate. The collected pale-yellow solution was concentrated under reduced pressure into a yellow oily solid. The solid was purified by flash column chromatography (1% ethyl acetate in hexanes) to afford a white solid (21 mg, 81%). Mp 107.7 °C (petroleum ether). $[\alpha]_D^{21}$ -6° (*c* 0.6, $CHCl_3$).

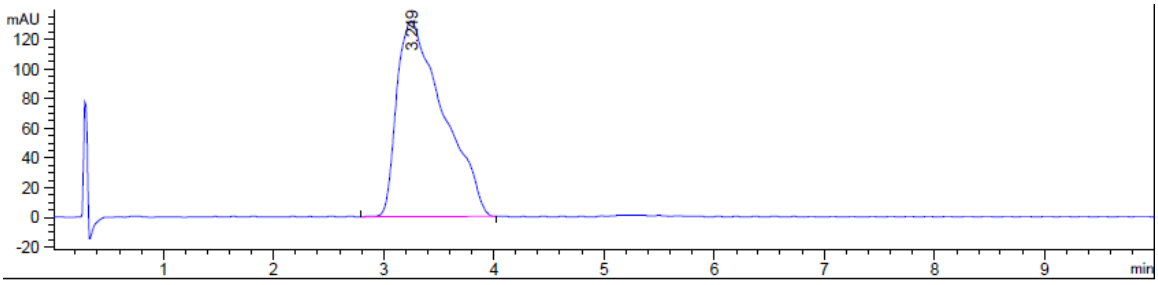


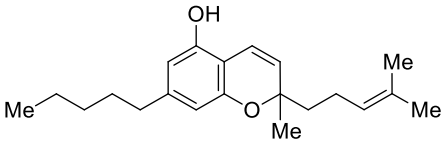
(+)-Cannabichromene (1). This sample was obtained from BayMedica. $[\alpha]_D^{22}$ +96° (*c* 1.1, $CHCl_3$). SFC (Lux Cellulose-5; 35 °C; CO_2:MeOH 98:2; 2.75 mL/min; 1 mg/mL in MeOH) R_t 5.12 min.



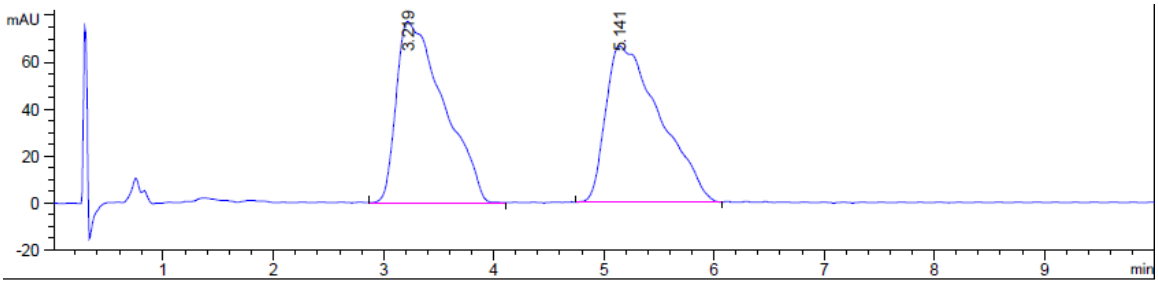


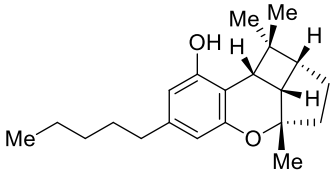
(–)-Cannabichromene (1). This sample was obtained from BayMedica. $[\alpha]_D^{22}$ -96° (*c* 1.1, $CHCl_3$). SFC (Lux Cellulose-5; 35 °C; CO_2:MeOH 98:2; 2.75 mL/min; 1 mg/mL in MeOH) R_t 3.25 min.





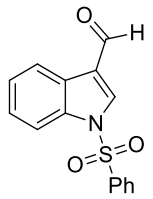
(±)-Cannabichromene (1). This sample was obtained from BayMedica. SFC (Lux Cellulose-5; 35 °C; CO_2:MeOH 98:2; 2.75 mL/min; 1 mg/mL in MeOH) R_t 3.22 and 5.14 min.



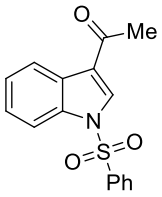


(+)-Cannabicyclol (5). Using Hsung's procedure,[29] the compound was made by dropwise adding a solution of trifluoroacetic acid (38 mg, 0.33 mmol) in methylene chloride (1 mL) to a solution of (+)-cannabichromene (35 mg, 0.11 mmol) in methylene chloride (1 mL) in an ice bath. The reaction mixture was stirred for 1 h in an ice bath and then quenched by the addition of saturated $NaHCO_3$ aqueous solution. The organic phase was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (1% ethyl acetate in hexanes) to afford a white solid (31 mg, 89%). Mp 87.7 °C (pentane). $[\alpha]_D^{23}$ +4° (*c* 0.7, $CHCl_3$). Its spectroscopic properties matched those earlier reported.[79]

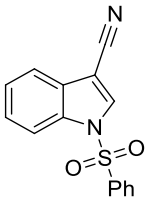
5.3 Chapter 4 Experimental



***N*-Phenylsulfonyl 3-Formylindole (57).** Using the procedure of Zhang,[48] 60% NaH (400 mg, 9.00 mmol) was portionwise added to a stirred solution of 3-formylindole (726 mg, 5.00 mmol) in tetrahydrofuran (12 mL) cooled in an ice bath and then the reaction was slowly warmed to room temperature. After stirring at room temperature for 30 min, phenylsulfonyl chloride (1.50 g, 9.00 mmol) was added dropwise. The reaction was stirred for 24 h at room temperature. The resulting heterogenous mixture was concentrated under reduced pressure into a crude solid. The solid was dissolved in a mixture of water and methylene chloride. The aqueous layer was separated and extracted three times with methylene chloride. The combined organic layer was dried with sodium sulfate and concentrated *in vacuo*. The resulting solid was dissolved in minimum amount of hot methylene chloride/hexanes mixture and allowed to cool slowly to room temperature to afford off-white crystals (1.10 g, 77%). The spectroscopic data of the product agreed with the reported literature.[51]

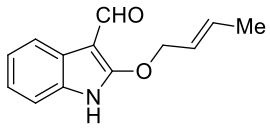


***N*-Phenylsulfonyl 3-Acetylindole (62).** Using the procedure of Zhang,[48] 60% NaH (160 mg, 4.00 mmol) was portionwise added to a stirred solution of 3-acetylindole (318 mg, 2.00 mmol) in tetrahydrofuran (5 mL) cooled in an ice bath and then the reaction was slowly warmed to room temperature. After stirring at room temperature for 30 min, phenylsulfonyl chloride (636 mg, 3.60 mmol) was added dropwise. The reaction was stirred for 72 h at room temperature. The resulting heterogenous mixture was concentrated under reduced pressure into a crude solid. The solid was dissolved in a mixture of water and methylene chloride. The aqueous layer was separated and extracted three times with methylene chloride. The combined organic layer was dried with sodium sulfate and solvent removed *in vacuo*. The resulting solid was dissolved in minimum amount of hot methylene chloride/hexanes mixture and allowed to cool slowly to room temperature to afford off-white crystals (540 mg, 90%). The spectroscopic data of the product agreed with the reported literature.[80]



***N*-Phenylsulfonyl 3-Cyanoindole (64).** Using the procedure of Zhang,[48] 60% NaH (154 mg, 3.84 mmol) was portionwise added to a stirred solution of 3-cyanoindole (273 mg, 1.92 mmol) in tetrahydrofuran (5 mL) cooled in an ice bath and then the reaction was

slowly warmed to room temperature. After stirring at room temperature for 30 min, phenylsulfonyl chloride (610 mg, 3.45 mmol) was added dropwise. The reaction was stirred for 24 h at room temperature. The resulting heterogenous mixture was concentrated under reduced pressure into a crude solid. The solid was dissolved in a mixture of water and methylene chloride. The aqueous layer was separated and extracted three times with methylene chloride. The combined organic layer was dried with sodium sulfate and solvent removed *in vacuo*. The resulting solid was dissolved in minimum amount of hot methylene chloride/hexanes mixture and allowed to cool slowly to room temperature to afford off-white crystals (441 mg, 82%). The spectroscopic data of the product agreed with the reported literature.[81]

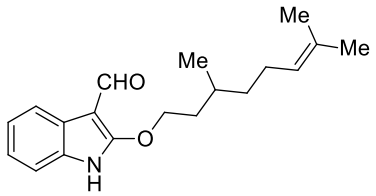


2-(But-2-en-1-yloxy)-1H-indole-3-carbaldehyde (59G). To a solution of crotyl alcohol (72 mg, 1.0 mmol) in dimethylformamide (5 mL) was added a solution of 1 M LiHMDS (0.75 mL, 0.75 mmol) and stirred at room temperature for 30 min. *N*-Phenylsulfonyl 3-formylindole (143 mg, 0.500 mmol) was added and the reaction was stirred at 60 °C for 30 min. The reaction was quenched with saturated ammonium chloride aqueous solution (5 mL) and diluted with ethyl acetate (25 mL). The organic layer was washed twice with water (5 mL), once with brine (5 mL), and dried with sodium sulfate. The organic solution was concentrated under reduced pressure and the crude material was purified by flash column chromatography (10-20% ethyl acetate in hexanes) to afford a white solid. (83 mg, 77%).

R_f (40% ethyl acetate in hexanes) 0.53. Mp 128.3 °C (methylene chloride/hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.99 (s, 1H), 8.31 (d, J = 7.2 Hz, 1H), 7.73 (s, 1H), 7.41 – 7.29 (m, 3H), 5.83 – 5.59 (m, 2H), 4.70 (d, J = 6.0 Hz, 2H), 1.75 (d, J = 6.4 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 184.7, 138.2, 137.4, 131.4, 125.6, 124.6, 124.0, 123.0, 122.2, 118.2, 110.4, 49.1, 17.8. IR (neat) 3119, 3024, 2952, 2915, 2850, 1650, 1610, 1575, 1527 cm^{-1}. HRMS (ESI) m/z [M – H]$^-$ Calcd for $C_{13}H_{12}NO_2$: 214.0868. Found: 214.0885.

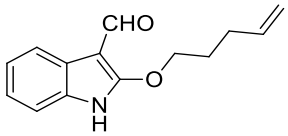
General procedure of cine substitution of *N*-phenylsulfonyl 3-substituted indoles with alcohols

To a solution of alcohol (0.20 mmol) in dimethylformamide (1 mL) was added a solution of 1 M LiHMDS (0.15 mmol) and stirred at room temperature for 30 min. The *N*-phenylsulfonyl 3-substituted indole (0.10 mmol) was added and the reaction was stirred at 60 °C for 30 min. The reaction was quenched with saturated ammonium chloride aqueous solution (1 mL) and diluted with ethyl acetate (5 mL). The organic layer was washed twice with water (1 mL), once with brine (1 mL), and dried with sodium sulfate. The organic solution was concentrated under reduced pressure and the crude material was purified by flash column chromatography (ethyl acetate/hexanes) to afford the desired product.

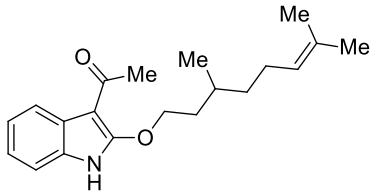


2-((3,7-Dimethyloct-6-en-1-yl)oxy)-1H-indole-3-carbaldehyde (59A). Pale yellow oil. 24 mg (80%). R_f (40% ethyl acetate in hexanes) 0.62. ^{1}H NMR (500 MHz, $CDCl_3$): δ

10.00 (s, 1H), 8.31 (d, J = 7.3 Hz, 1H), 7.73 (s, 1H), 7.42 – 7.28 (m, 3H), 5.10 – 5.00 (m, 1H), 4.28 – 4.10 (m, 2H), 2.08 – 1.86 (m, 3H), 1.76 – 1.69 (m, 1H), 1.67 (s, 3H), 1.57 (s, 3H), 1.55 – 1.46 (m, 1H), 1.46 – 1.36 (m, 1H), 1.40 – 1.20 (m, 1H), 1.01 (d, J = 6.5 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 184.5, 138.4, 137.3, 131.9, 125.6, 124.2, 124.1, 123.1, 122.3, 118.2, 110.2, 45.5, 36.9, 36.8, 30.2, 25.9, 25.4, 19.5, 17.8. IR (neat) 3105, 3046, 2957, 2921, 2853, 1656, 1614, 1577, 1531 cm^{-1}. HRMS (ESI) m/z [M – H]$^-$ Calcd for $C_{19}H_{24}NO_2$: 298.1807. Found: 298.1821.

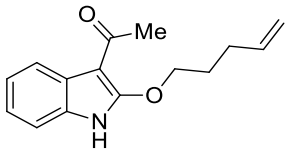


2-(Pent-4-en-1-yloxy)-1H-indole-3-carbaldehyde (59F). Clear viscous oil. 19 mg (83%). R_f (40% ethyl acetate in hexanes) 0.48. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.00 (s, 1H), 8.35 – 8.28 (m, 1H), 7.71 (s, 1H), 7.41 – 7.28 (m, 3H), 5.87 – 5.73 (m, 1H), 5.12 – 5.03 (m, 2H), 4.19 (t, J = 7.0 Hz, 2H), 2.16 – 2.06 (m, 2H), 2.06 – 1.95 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.6, 138.4, 137.3, 136.7, 125.6, 124.0, 123.0, 122.3, 118.2, 116.4, 110.2, 46.5, 30.7, 28.8. IR (neat) 3103, 3050, 2922, 2850, 2808, 2751, 1654, 1613, 1577, 1530 cm^{-1}. HRMS (ESI) m/z [M – H]$^-$ Calcd for $C_{14}H_{14}NO_2$: 228.1025. Found: 228.1032.

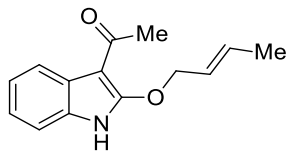


1-(2-((3,7-Dimethyloct-6-en-1-yl)oxy)-1H-indol-3-yl)ethenone (65A). Pale yellow oil. 23 mg (74%). R_f (40% ethyl acetate in hexanes) 0.64. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41

– 8.35 (m, 1H), 7.74 (s, 1H), 7.42 – 7.27 (m, 3H), 5.13 – 4.99 (m, 1H), 4.26 – 4.08 (m, 2H), 2.53 (s, 3H), 2.09 – 1.85 (m, 3H), 1.76 – 1.69 (m, 1H), 1.68 (s, 3H), 1.58 (s, 3H), 1.56 – 1.47 (m, 1H), 1.47 – 1.36 (m, 1H), 1.31 – 1.20 (m, 1H), 1.01 (d, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.0, 136.9, 134.7, 131.9, 126.5, 124.3, 123.3, 122.8, 122.6, 117.1, 109.9, 45.3, 37.0, 36.9, 30.3, 27.8, 25.8, 25.4, 19.6, 17.8. IR (neat) 3105, 3050, 2960, 2918, 2854, 1642, 1613, 1575, 1525 cm^{-1}. HRMS (ESI) m/z [M – H]$^-$ Calcd for $C_{20}H_{26}NO_2$: 312.1964. Found: 312.1920.

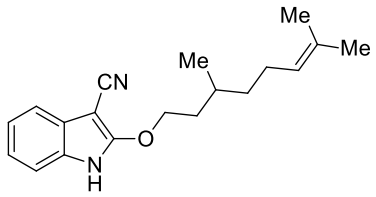


1-(2-(Pent-4-en-1-yloxy)-1H-indol-3-yl)ethenone (65F). Clear viscous oil. 21 mg (88%). R_f (40% ethyl acetate in hexanes) 0.51. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 – 8.35 (m, 1H), 7.73 (s, 1H), 7.39 – 7.27 (m, 3H), 5.89 – 5.72 (m, 1H), 5.12 – 5.03 (m, 2H), 4.16 (t, J = 7.1 Hz, 2H), 2.53 (s, 3H), 2.16 – 2.06 (m, 2H), 2.06 – 1.93 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.1, 136.9, 136.8, 134.9, 126.5, 123.3, 122.8, 122.6, 117.1, 116.3, 109.9, 46.4, 30.8, 28.9, 27.7. IR (neat) 3105, 3076, 3054, 2973, 2929, 2858, 1638, 1613, 1574, 1524 cm^{-1}. HRMS (ESI) m/z [M – H]$^-$ Calcd for $C_{15}H_{16}NO_2$: 242.1181. Found: 242.1185.

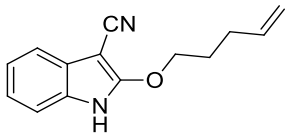


1-(2-(But-2-en-1-yloxy)-1H-indol-3-yl)ethenone (65G). White solid. 18 mg (78%). R_f (40% ethyl acetate in hexanes) 0.55. Mp 70.2 °C (methylene chloride/hexanes). ^{1}H NMR

(400 MHz, $CDCl_3$): δ 8.42 – 8.34 (m, 1H), 7.74 (s, 1H), 7.38 – 7.27 (m, 3H), 5.80 – 5.60 (m, 2H), 4.68 (d, J = 5.7 Hz, 2H), 2.53 (s, 3H), 1.74 (dd, J = 6.1, 1.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.1, 137.0, 134.6, 130.8, 126.5, 125.0, 123.3, 122.7, 122.6, 117.2, 110.1, 48.9, 27.8, 17.8. IR (neat) 3048, 2956, 2917, 2850, 1630, 1575, 1519 cm^{-1}. HRMS (ESI) m/z [M – H]$^-$ Calcd for $C_{14}H_{14}NO_2$: 288.1025. Found: 228.1029.

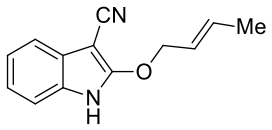


2-((3,7-Dimethyloct-6-en-1-yl)oxy)-1H-indole-3-carbonitrile (67A). Pale yellow oil. 20 mg (67%). R_f (40% ethyl acetate in hexanes) 0.68. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 – 7.74 (m, 1H), 7.59 (s, 1H), 7.43 – 7.27 (m, 3H), 5.08 – 5.00 (m, 1H), 4.25 – 4.09 (m, 2H), 2.07 – 1.82 (m, 3H), 1.73 – 1.63 (m, 4H), 1.57 (s, 3H), 1.52 – 1.34 (m, 2H), 1.29 – 1.19 (m, 1H), 0.99 (d, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.4, 134.6, 132.0, 128.1, 124.2, 123.8, 122.2, 120.1, 116.2, 110.6, 85.7, 45.4, 36.9, 36.8, 30.1, 25.8, 25.4, 19.5, 17.8. IR (neat) 3117, 3053, 2960, 2917, 2852, 2217, 1615, 1531 cm^{-1}. HRMS (ESI) m/z [M – H]$^-$ Calcd for $C_{19}H_{23}N_2O$: 295.1810. Found: 295.1832.



2-(Pent-4-en-1-yloxy)-1H-indole-3-carbonitrile (67F). Clear viscous oil. 18 mg (78%). R_f (40% ethyl acetate in hexanes) 0.78. ^{1}H NMR (400 MHz, $CDCl_3$): δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.74 (m, 1H), 7.59 (s, 1H), 7.45 – 7.27 (m, 3H), 5.85 – 5.72 (m,

1H), 5.11 – 5.03 (m, 2H), 4.17 (t, J = 7.0 Hz, 2H), 2.14 – 2.03 (m, 2H), 2.03 – 1.02 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.6, 135.4, 134.8, 128.1, 123.9, 122.2, 120.1, 116.5, 116.1, 110.6, 85.7, 46.5, 30.6, 28.8. IR (neat) 3116, 3077, 3063, 2918, 2849, 2215, 1641, 1615, 1530 cm^{-1}. HRMS (ESI) m/z $[M - H]^-$ Calcd for $C_{14}H_{13}N_2O$: 225.1028. Found: 225.1039.



2-(But-2-en-1-yloxy)-1H-indole-3-carbonitrile (67G). Clear viscous oil. 15 mg (71%). R_f (40% ethyl acetate in hexanes) 0.65. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 7.2 Hz, 1H), 7.61 (s, 1H), 7.44 – 7.27 (m, 3H), 5.82 – 5.54 (m, 2H), 4.69 (d, J = 5.9 Hz, 2H), 1.74 (dd, J = 6.3, 1.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.5, 134.6, 131.4, 128.1, 124.6, 123.8, 122.2, 120.0, 116.1, 110.9, 85.8, 49.1, 17.8. IR (neat) 3117, 3055, 3037, 2918, 2853, 2214, 1673, 1614, 1529 cm^{-1}. HRMS (ESI) m/z $[M - H]^-$ Calcd for $C_{13}H_{11}N_2O$: 211.0871. Found: 211.0875.

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