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The Asymmetric Phase-Transfer Catalyzed Alkylation of Imidazolyl Ketones and Aryl Acetates and Their Applications to Total Synthesis

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By

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A dissertation submitted to the faculty of
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ABSTRACT

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Phase-transfer catalysts derived from the cinchona alkaloids cinchonine and cinchonidine are widely used in the asymmetric alkylation of substrates bearing moieties that resonance-stabilize their enolates. The investigation of α-oxygenated esters revealed decreased α-proton acidity, indicating the oxygen's overall destabilizing effect on enolates by electron-pair repulsion. Alkylation of α-oxygenated aryl ketones with various alkyl halides proved successful with a cinchonidine catalyst, giving products with high yield and enantioselectivity. The resulting compounds were converted to esters through modified Baeyer-Villiger oxidation.

Alkylation with indolyl electrophiles gave products that underwent decomposition under Baeyer-Villiger conditions. Alternative *N*-methylimidazolyl ketones were explored. Alkylated imidazolyl ketones, obtained in high yield and enantioselectivity, could be converted to esters through treatment with methyl triflate and basic methanol. This technique has the advantage of not requiring stoichiometric addition of chiral reagents, which is requisite when employing traditional chiral auxiliaries. This method's utility is demonstrated in the total asymmetric syntheses of (+)-kurasoin B and analogs, and 12-*(S)*-HETE.

Kurasoin B is a fungal-derived natural compound possessing moderate farnesyl transfer (FTase) inhibitive activity (IC_{50} = 58.7 μM). FTase catalyzes post-translation modifications of membrane-bound Ras proteins, which function in signal cell transduction that stimulates cell growth and division. The oncogenic nature of mutated Ras proteins is demonstrated by their commonality in human tumors. Thus, FTase inhibitors like (+)-kurasoin B possess potential as cancer chemotherapy leads. Derivatization may enable structure-activity-relationship studies and greater FTase inhibition activity to be found.

12-*(S)*-HETE, a metabolite from a 12-lipoxygenase pathway from arachidonic acid, has been found to participate in a large number of physiological processes. Its transient presence in natural tissues makes total synthesis an attractive avenue for obtaining sufficient quantities for further study. Five asymmetric syntheses of 12-*(S)*-HETE have been reported. Three require chiral resolutions of racemates, with the undesired enantiomers being discarded or used for other applications.

Asymmetric PTC alkylation is also described for aryl acetates, whose products were enantioenriched through recrystallization. This technique is applied to a total synthesis of the anti-inflammatory drug *(S)*-Naproxen.

Keywords: phase-transfer catalysis, asymmetric alkylation, kurasoin, 12-*(S)*-HETE, farnesyl transferase, acyl imidazole, aryl acetate, *(S)*-Naproxen

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List of Abbreviations

2-NPM	2-naphthalenemethyl
AIBN	azobisisobutyronitrile
Bn	benzyl
Boc	*tert*-butoxylcarbonyl
Cd	cinchonidine or cinchonidinium
Cn	cinchonine or cinchoninium
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DPM	diphenylmethyl
EDCI	*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride
ee	enantiomeric excess
HPLC	high-pressure liquid chromatography
HWE	Horner-Wadsworth-Emmons
IC_{50}	Half maximal inhibitory concentration

KHMDS	potassium hexamethyldisilazide
LiHMDS	Lithium Hexamethyldisilazide
NBS	*N*-bromosuccinimide
NHC	*N*-heterocyclic carbenoid
Np	naphthyl
OTf	triflate (trifluoromethane sulfonate)
OTs	tosylate (*p*-toluenesulfonate)
PCC	pyridinium chlorochromate
PhH	Benzene
Piv	pivaloyl
PMB	*p*-methoxybenzyl
PTC	phase-transfer catalysis or phase-transfer catalyzed
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyl dimethylsilyl
TES	triethylsilyl

Chapter 1. Background

1.1. (+)-Kurasoin B

1.1.1. Ras Proteins and Farnesyl Transferase

Ras proteins are G-proteins that play central roles in various cell functions, including signal transduction and cell proliferation.[1] The Ras super family includes over 100 proteins originating from three functional *RAS* genes: H-*RAS*, N-*RAS*, and K-*RAS*.[1,2] *RAS* genes encode four cytoplasmic precursor proteins (H-Ras, N-Ras, and the alternatively spliced K-RasA and K-RasB), which are functionalized and diversified through various post-translational modifications.[1] The first of these modifications is prenylation, followed by proteolysis, carboxymethylation, and palmitoylation.[3-7]

Ras protein prenylation begins in the cytosol with farnesylation, which occurs at the cysteine residue of the protein's CAAX (C, cysteine; A, aliphatic amino acid; X, any amino acid), CC, or CXC carboxy-terminal consensus sequences.[8-11] Farnesylation is catalyzed by the 93 kDa enzyme farnesyl transferase (FTase), which binds the protein's carboxy terminus in proximity to farnesyl pyrophosphate (FPP) and forms a thioether link with the 15-carbon farnesyl moiety. Further modifications then produce fully functional, membrane-bound proteins. Ras proteins that are modified so as to *not* undergo farnesylation fail to functionalize, despite further post-translational modifications.[12]

RAS gene mutations are present in 20-30% of all human tumors, with higher frequencies observed in adenocarcinomas of the pancreas (90%), colon (50%), and lung (30%).[1,13] *RAS* mutations have also been found in neoplasms of the small intestine, prostate, liver, skin, and thyroid, as well as in multiple myeloma and a number of leukemias, making them among the most frequently observed in human cancer.[1,14] The more common mutations at codons 12, 13,

and 61 produce Ras mutants that fail to interact properly with GTPase activating proteins (GAPs).[1,15] This inhibits the GTP hydrolysis necessary to turn Ras proteins "off", thereby contributing to uncontrolled cell growth and cancer.

Oncogenic Ras activities might be subdued by inhibiting post-translational modification. This idea has led to great interest in FTase inhibitors as potential anti-cancer therapeutics.[14,16-19] Various candidates have been explored, including FPP analogues, CAAX derivatives, and "bisubstrate" molecules bearing both FPP and CAAX moieties.[1] Several of these drug leads have been explored in Phase I and Phase II clinical trials.[1,20]

FTase inhibitors have been found to act synergistically with other anticancer therapeutics, including paclitaxel and the epothilones, in halting tumor cell growth.[21] Advantageously, FTase inhibitors exhibit minimal toxicity to healthy cells. This is thought to occur because cancerous activity is more frequently observed with mutations in N-Ras proteins. K-Ras proteins, which contribute less often to cancer and have a 10- to 50-fold higher affinity for FTase, may possess redundant functionality with N-Ras proteins.[1] Thus, cancers caused by N-Ras mutations are selectively impeded by FTase inhibitors, whereas the more active K-Ras proteins continue to contribute to normal cell growth. Unfortunately, the higher affinity of K-Ras for FTase makes cancers caused by K-Ras mutation more resistant to FTase inhibition.[1,22-24]

1.1.2. Isolation, Syntheses, and Characterization

While searching for natural FTase inhibitors, Ōmura and coworkers[25] prepared 20 liters of broth from the cultured mycelia of the Japanese soil fungus *Paecilomyces* species FO-3684. Extensive extractions yielded a heavy brown oil that was purified by HPLC to provide two unknown white powders in 2.1- and 4.5-milligram amounts. HR-FAB-MS (High-Resolution-

Fast-Atom-Bombardment-Mass-Spectrometry) analysis revealed their molecular weights to be 256 and 279, respectively, and later HMQC experiments uncovered their structures to be **1** and **2** (Figure 1.1). These compounds were named kurasoins A and B.

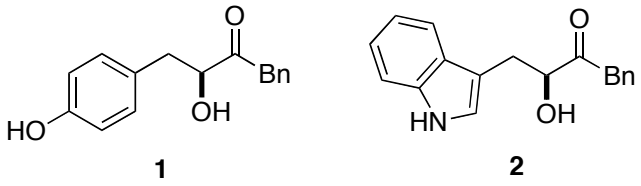
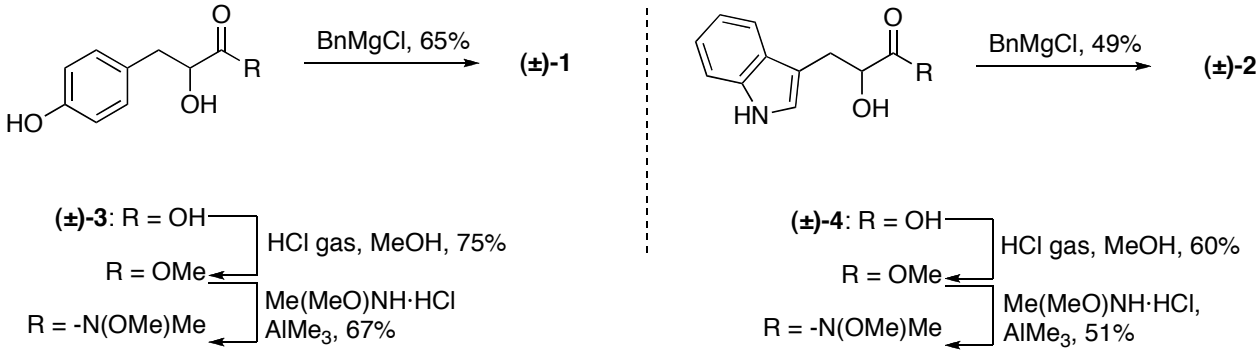
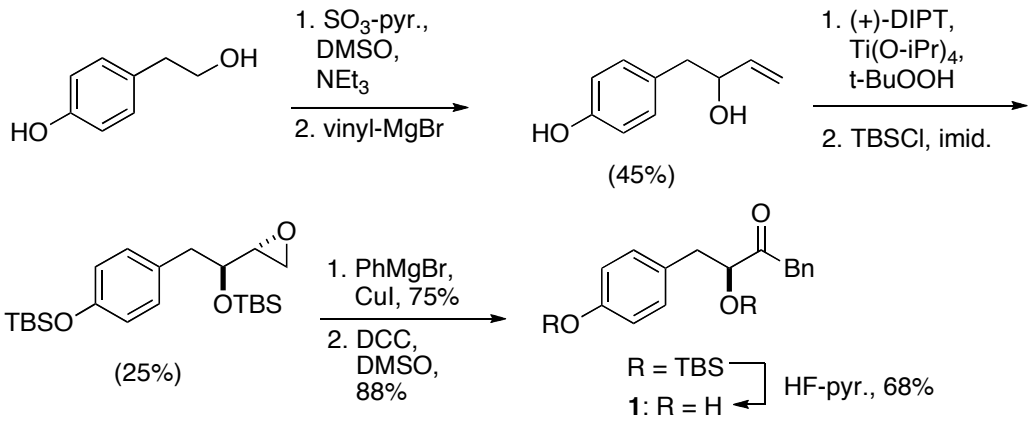


Figure 1.1. Kurasoins A (**1**) and B (**2**).

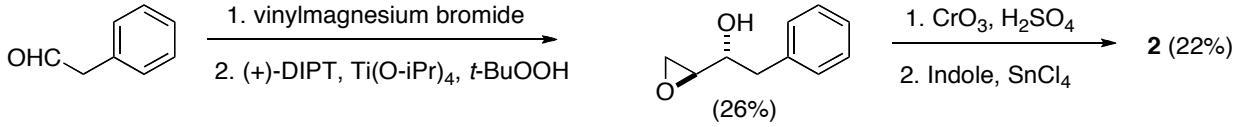
·In concert with this discovery, Ōmura's group reported racemic syntheses of **1** and **2** from commercially available lactic acids (±)-**3** and (±)-**4**, illustrated in Scheme 1.1.[25] Ōmura later determined the kurasoins' absolute stereochemical configurations through asymmetric total syntheses (Schemes 1.2 and 1.3).[26] These routes provided **1** and **2** with respective yields of 5.0 and 5.7%.



Scheme 1.1. Ōmura's racemic syntheses of **1** and **2** from lactic acids **3** and **4**.[25]



Scheme 1.2. Ōmura's asymmetric synthesis of **1**.[26]



Scheme 1.3. Ōmura's asymmetric synthesis of **2**.[26]

1.1.3. Biological Activity

When employed in an FTase inhibition assay,[27] kurasoins A and B were found to possess respective IC_{50} values of 59.0 μM and 58.7 μM, respectively.[25] Later investigations revealed that the *S* configuration was essential to the molecules' bioactivities, with the *S* enantiomers being >6 times more potent than their *R* counterparts.[26] Though micromolar potency is not sufficient for practical pharmaceutical application, derivatization of the kurasoins might provide increased efficacy and insight into their mode of action on FTase.

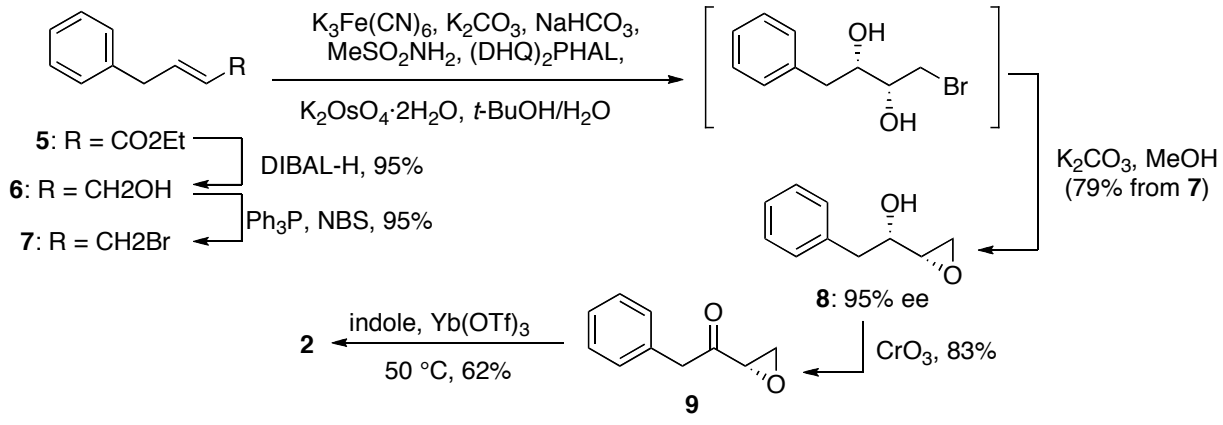
Independent model work by Pang et al.[20] revealed more about the mode of interaction of kurasoin B with FTase. The calculated lowest energy complex of kurasoin B showed that its

carbonyl carbon interacts electrostatically with the divalent zinc cation present in FTase's active site. Kurasoin B's phenyl ring was found to π-stack with a tyrosine moiety in the enzyme's active site, whereas its indolyl appendage interacts with four adjacent lysines. Kurasoin B's free hydroxyl group then complexes with an approaching FPP molecule, inhibiting pro-Ras proteins' abilities to be farnesylated at FTase's active site.

1.1.4. Additional Synthetic Efforts

Since Ōmura's asymmetric syntheses of the kurasoins were disclosed, previous members of our group successfully completed the only other asymmetric total synthesis of (+)-kurasoin A, achieved in 29% yield over 10 steps.[28] Later efforts were undertaken in unsuccessful attempts to prepare (+)-kurasoin B, which will be addressed later on.

More recently, an asymmetric synthesis of **2** was disclosed by Fernandes.[29] This route began by reducing commercial ester **5** to alcohol **6**, which was then converted to bromide **7** (Scheme 1.4). Sharpless asymmetric dihydroxylation, followed by nucleophilic displacement of the terminal bromide, furnished epoxide **8** with a 95% ee in a two-step, one-pot procedure. Jones



Scheme 1.4. Fernandes' synthesis of **2**.[29]

oxidation gave **9**, which was subjected to ytterbium-catalyzed ring opening with nucleophilic indole. This route provided **2** in 37% yield over six steps from **5**.

1.2. 12-*(S)*-HETE

1.2.1. Background and Isolation

When triggered by various stimuli, phospholipase A_2, which is present in most mammalian cells, releases arachidonic acid **10** from glycerol moieties embedded in the cell's phospholipid membrane (Figure 1.2).[30-31] Arachidonic acid then serves as a synthetic precursor for a class of paracrine hormones called eicosanoids.

Three types of eicosanoids exist: prostaglandins, thromboxanes [formed from **10** through cyclooxygenase (COX) activity], and leukotrienes (produced from **10** by lipoxygenase enzymes).[31-32]

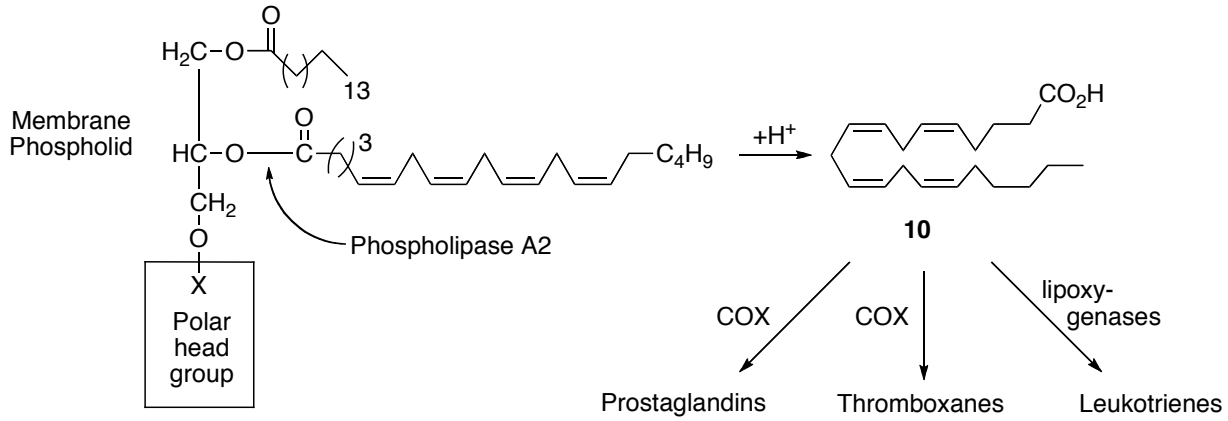
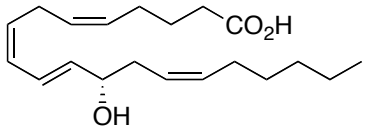


Figure 1.2. Formation of eicosanoids from arachidonic acid (**10**).

In 1974, Hamberg and Samuelsson isolated three metabolites from aggregating platelet cells suspended in medium containing ^{14}C-labeled arachidonic acid.[33] One of these was a novel compound named 12(*S*)-hydroxy-5(*E*),8(*Z*),10(*E*),14(*Z*)-eicosatetraenoic acid (**11**), later known

as 12-*(S)*-HETE (Figure 1.3). Lacking the conjugated triene core characteristic of traditional leukotrienes formed from 5-lipoxygenase, 12-*(S)*-HETE's discovery confirmed the existence of a previously unknown 12-lipoxygenase pathway from arachidonic acid.[34] Compound **11** was later found in keratinocytes[35] and psoriatic lesions.[36]



11

Figure 1.3. 12-*(S)*-HETE.

1.2.2. Biological Activity

Though its precise functions remain largely unknown, 12-*(S)*-HETE has been implicated in many physiological processes, including inflammation,[34,37] stimulation of neutrophils[38] and smooth muscle cells,[39] hypertension,[40] COX attenuation,[41] cellular response to epidermal growth factor and insulin,[42] human pancreatic cancer cell proliferation,[43] endothelial cell retraction,[44] angiogenesis,[45] tumor cell metastasis,[46] atherogenesis,[47] coronary thrombosis,[48] type I diabetes induction,[49] psoriasis,[34,50] and inhibition of apoptosis.[51]

In light of 12-*(S)*-HETE's biological relevance, it would be very desirable to understand its specific functions. Unfortunately, the compound's transience in biological tissues makes large-scale isolation impractical.[34] Efficient total synthesis, therefore, has become an attractive goal, opening possible avenues for increased testing.

1.2.3. Synthetic Overview

Since its discovery, five syntheses of optically pure 12-*(S)*-HETE have been reported.[52-56] Though thorough coverage is beyond the scope of this introduction, critical details will be addressed later on. As Table 1.1 summarizes, overall yields and route lengths vary. It is noteworthy that the more recent approaches by Sato, Spur, and Suh were all achieved through the use of different chiral resolutions of racemates, with the undesired enantiomers being unused in the total synthesis of **11**.

Group	Number of steps	Overall yield (%)	Ref.
Corey	11	Unreported (>12.8)	52
Just	12	4.1	53
Sato	12	15.3	54
Spur	10	11.5	55
Suh	13	9.0	56

Table 1.1. Summary of the five published routes to optically active 12-*(S)*-HETE.

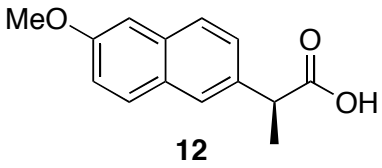
Interestingly, it has been found that 12-*(R)*-HETE (the enantiomer of **11**) also possesses important bioactivity, being the more prominent enantiomer in psoriatic lesions and having greater potency than 12-*(S)*-HETE in attracting human leukocytes.[31]

Twenty-two years after publishing his 12-*(S)*-HETE synthesis,[52] E. J. Corey reported a route to 12-*(R)*-HETE[34] that employs a complimentary chiral antipode as reagent in its key step. This total synthesis will be addressed later on in this work.

1.3. *(S)*-Naproxen

1.3.1. Discovery

In consequence of a search for nitrogen-free, nonsteroidal antiinflammatory drugs (NSAIDs), the Syntex research group released a 1970 disclosure of several bioactive naphthylacetic acid derivatives.[57] The most potent of these was the *S* enantiomer of 2-(6-methoxynaphthalen-2-yl)propanoic acid **12**, which came to be known as *(S)*-Naproxen (Figure 1.4).



12

Figure 1.4. *(S)*-Naproxen.

Since its inception as an antiinflammatory drug in 1976, *(S)*-Naproxen has become one of the most profitable optically pure pharmaceuticals in the world.[58] *(S)*-Naproxen and its sodium salt have been made available under various trade names, including Naprosyn, Anaprox, Midol Extended Relief, and Aleve.

1.3.2. Biological Activity

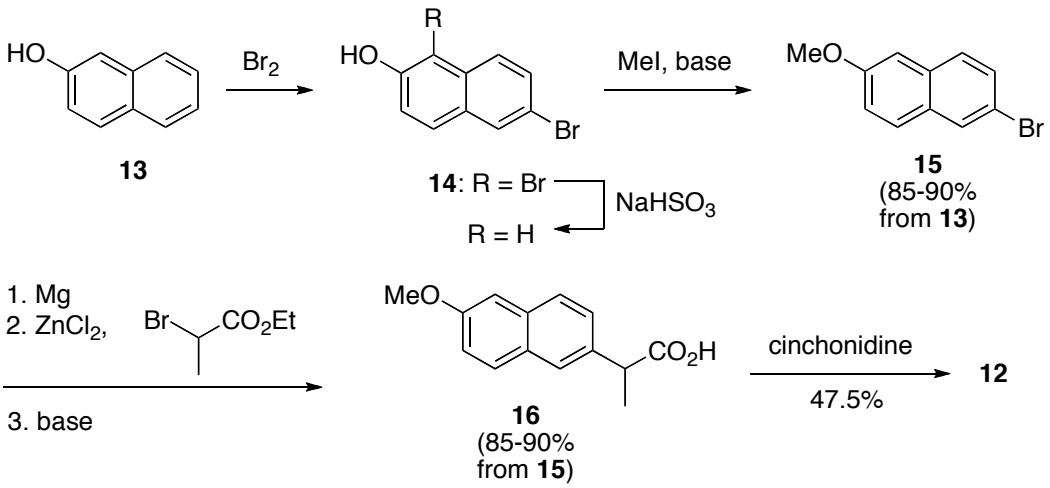
COX-1, being constitutively expressed in most tissues, participates in various homeostatic functions that include gastric cytoprotection. COX-2, which contributes more actively to pain and inflammation, is an inducible enzyme typically present in low levels. Indiscriminate attenuation of both COX enzymes would logically subdue the protective activities of COX-1, thereby causing adverse gastrointestinal side effects.[59]

Many common NSAIDs inhibit both COX enzymes, and *(S)*-Naproxen is no exception, attenuating COX activity by blocking the active site that binds arachidonic acid (**10**).[59] This obstructs prostaglandin and thromboxane syntheses, thereby reducing inflammation, fever, pain, and swelling.[60] Unsurprisingly, *(S)*-Naproxen's COX-1 inhibition damages the gastrointestinal tract among chronic users. Furthermore, regular *(S)*-Naproxen use can also cause cardiovascular problems like myocardial infarction and stroke.

(S)-Naproxen's exact binding mode still remains unclear; however, studies suggest that the molecule's acid moiety associates with an arginine residue in the COX isozymes' active sites.[61] *(S)*-Naproxen's in vivo IC_{50} values have not been reported, though in vitro numbers range from 1.7 to 17 μM (for COX-1) and 14 to 50 μM (for COX-2).[62] Enantiopurity is crucial for potency: the *R* enantiomer of **12** is virtually devoid of any COX-attenuating activity.[63]

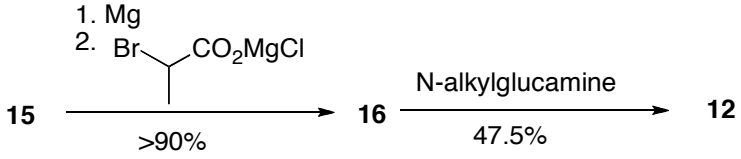
1.3.3. Synthetic Overview

Thorough coverage of the vast number of *(S)*-Naproxen syntheses is well beyond the scope of this introduction. The first industrial-scale approach began by converting β-naphthol **13** to dibromide **14**, as Scheme 1.5 illustrates.[58] Treatment with bisulfite removed the more labile bromine at the 1-position, providing ether **15** after methylation. This intermediate was then converted to a Grignard reagent. Transmetalation with zinc (II) chloride and treatment with bromo ethylpriopionate, followed by basic hydrolysis, then furnished racemic Naproxen **16** with a 50-60% yield over three steps. Recrystallization with cinchonidine gave two diastereomeric salts; the more potent enantiomer of **12** was obtainable from the less soluble salt in 47.5% yield (95% of the theoretical). This ultimately provided optically pure *(S)*-Naproxen in 20-25% yield over seven steps from β-naphthol.



Scheme 1.5. The first industrial-scale approach to optically-pure **12**.[58]

Synthetic streamlining uncovered a more expeditious route to *(S)*-Naproxen, which circumvented the need for undesirable zinc byproducts.[58] Shown in Scheme 1.6, intermediate **15** (obtained as per Scheme 1.5) was again converted to a Grignard reagent and then treated with a magnesium salt of bromo ethylpriopionate, furnishing racemic **16** in >90%. A less-expensive resolution, achieved through recrystallization from *N*-alkylglucamine, then gave optically pure **12** in 47.5% yield (95% of the theoretical). This alternative synthesis provided *(S)*-Naproxen in 36-38% yield over six steps from β-naphthol.



Scheme 1.6. The second industrial-scale route to optically-pure **12**.[58]

Ongoing research continues to provide new routes to **12** that circumvent the need for wasteful resolutions of racemates, which account for two-thirds of the compound's total

production cost. Such approaches include using materials from the chiral pool,[58,64] asymmetric catalytic hydrogenation,[65] and asymmetric hydroformylation,[66] among others.[58] As new technologies arise, more efficient means to this useful anti-inflammatory drug, as well as related compounds possessing other biologically valuable properties, are anticipated.

1.4. References and Notes

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Chapter 2. Asymmetric Phase-Transfer Catalyzed Alkylation

2.1. Background

Enantioselective carbon-carbon bond formation is a central objective of synthetic chemistry. One way of achieving this goal is by asymmetrically alkylating substrates with sp^3-hybridized electrophiles. Most examples depend heavily on the use of chiral auxiliaries, which have to be added in stoichiometric amounts.[1]

General, catalytic means of asymmetric alkylation are often limited to a narrow substrate scope.[2-4] Within this field, asymmetric phase-transfer catalyzed (PTC) alkylation continues to broaden as a useful means of forming enantio-enriched C-C bonds.

Phase-transfer catalysts typically possess polar, charged centers and non-polar, hydrocarbon appendages, giving them partial dual solubility in both polar and non-polar media. Chiral quaternary ammonium salts are the catalysts of choice, since many are known or easily synthesized.

PTC alkylation of carbonyl-bearing substrates **17** (Figure 2.1) occurs under biphasic conditions (organic/aqueous or organic/solid), where deprotonation at the interphase (path A) gives achiral enolate complex **18**.[5] Alkylation with halide R_3X (path B) would then produce racemic product **(±)-19**. Divergently, cation exchange with an asymmetric ammonium catalyst $X^- N^+(alk)_4$* (path C) would give non-racemic complex **20**. Alkylation of this complex would form asymmetric product **19** and regenerate the catalyst.

Stereoselective outcome depends heavily on the relative rates of cation exchange (k_1) from **18** to **20** and their individual reactivities with R_3X (k_2 vs. k_3). When k_1 is slow and k_2 is

fast, racemic **(±)-19** is favored. When k_1 is fast, the structure of **20** and its mode of interaction with the electrophile, as well as reaction conditions, contribute significantly to outcome.

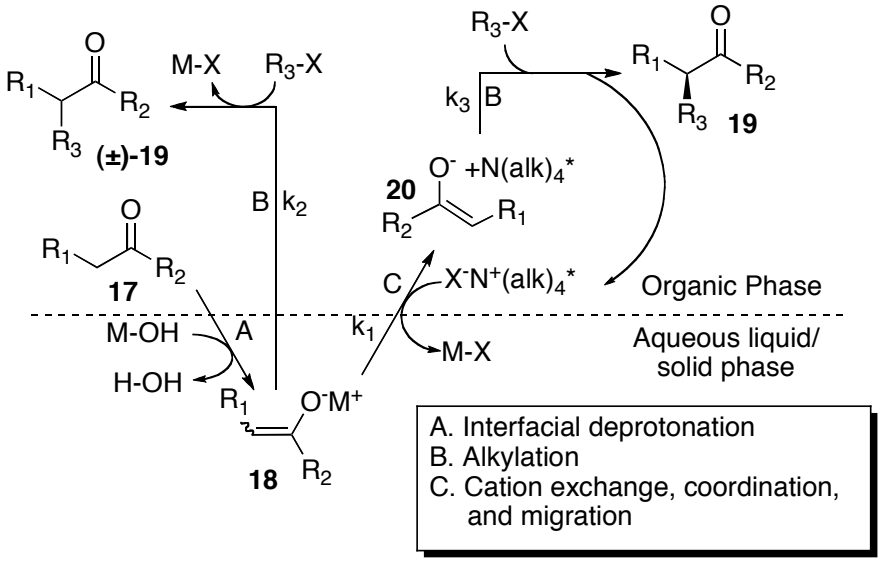
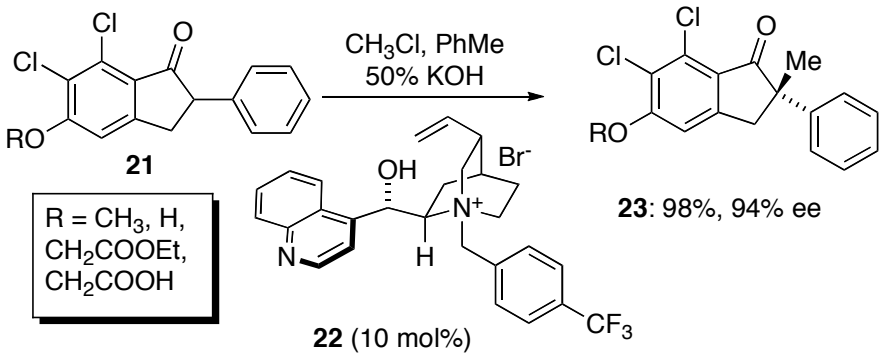


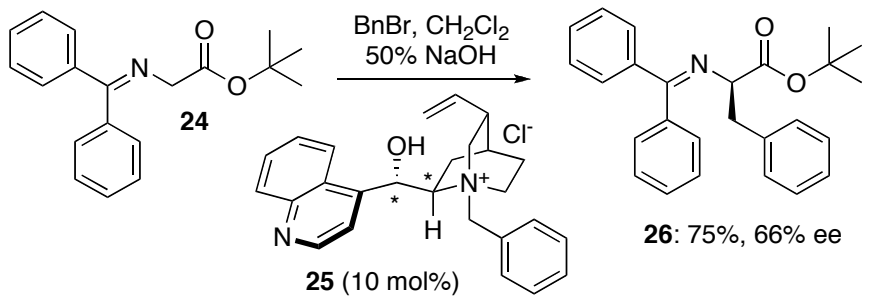
Figure 2.1. The mechanism of asymmetric phase-transfer catalyzed alkylation.[5]

Asymmetric PTC alkylation was pioneered by researchers at Merck,[6-7] who treated substrates **21** with methyl chloride and catalyst **22** to give products **23** with high selectivity and yield (Scheme 2.1).



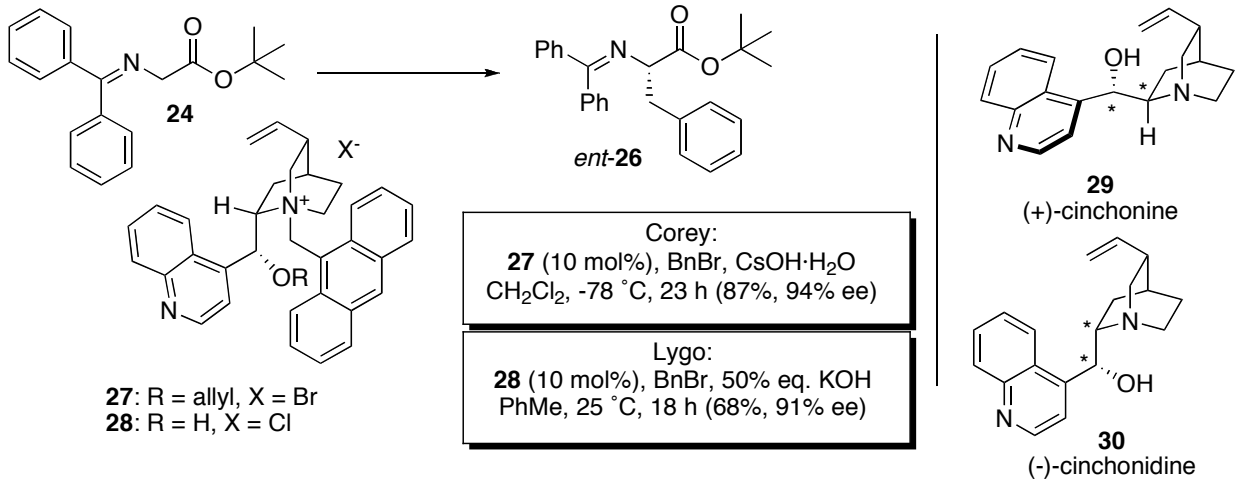
Scheme 2.1. PTC methylation of **21** by Merck.[6-7]

O'Donnell extended the field by benzylating glycine derivative **24** through use of (+)-cinchonine catalyst **25**, giving rise to phenylalanine derivative **26** (Figure 2.3).[8]



Scheme 2.2. O'Donnell's benzylation of **24** with cinchonine-derived catalyst **25**.[8]

Corey and Lygo independently benzylated **24** with (-)-cinchonidine anthracenylmethyl catalysts **27** and **28** to give *ent*-**26** (Figure 2.4), thus demonstrating the enantio-complementarity of catalysts derived from (+)-cinchonine (**29**) and (-)-cinchonidine (**30**).[9-10] These two diastereomeric cinchona antipodes are epimeric at the asterisked carbon stereocenters.



Scheme 2.3. Corey and Lygo's benzylation of **24** with cinchonidine catalysts **27** and **28**.[9-10]

Numerous cinchona catalysts have been reported since these groundbreaking findings, as portrayed generally in Figure 2.2. These may be easily modified at positions R_1, R_2, and Ar and are typically accessible in just a few linear steps from naturally occurring cinchona alkaloids.

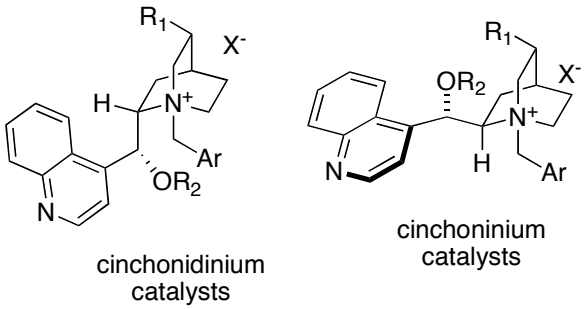
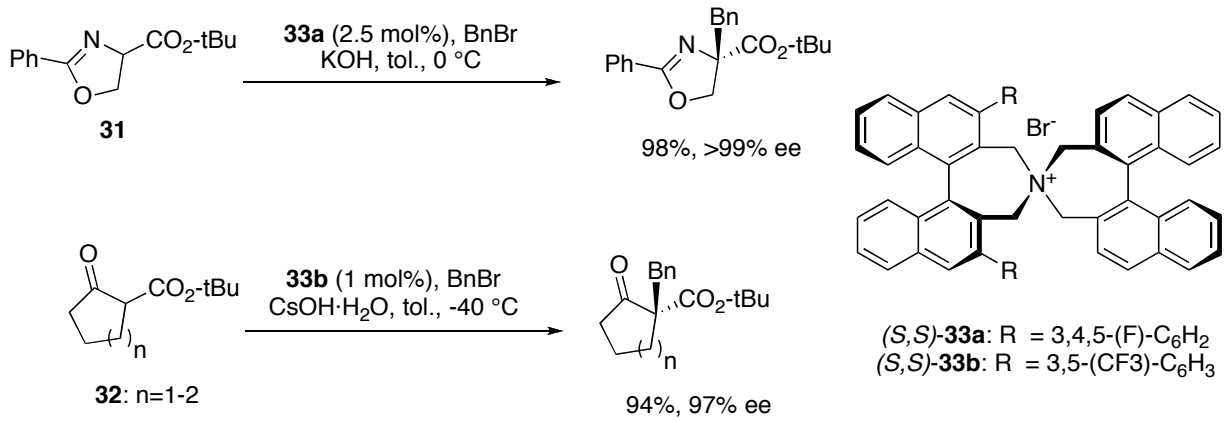


Figure 2.2. General depiction of cinchonidinium (Cd) and cinchoninium (Cn) phase-transfer catalysts.

Additional PTC catalysts have also been developed by Maruoka from complimentary *(S)*- or *(R)*-biphenolic cores.[11] These generally require lower catalyst loadings, but take more steps to synthesize.[12-14] Two representative examples are seen in the benzylation of compounds **31** and **32** (Scheme 2.4).[11]



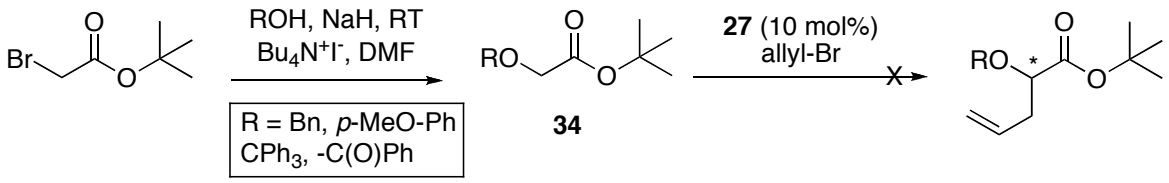
Scheme 2.4. Asymmetric PTC benzylations of **31** and **32** by Maruoka.[11]

2.2. PTC Alkylations of α-Oxygenated Substrates

Despite a diversity of catalysts, until recently asymmetric PTC alkylations were limited to glycine derivatives such as **24** and **31**, or cyclic β-keto esters like **32**, all of which possess moieties that resonance-stabilize their respective enolates. To expand the field's scope, members of the Andrus group examined replacing the nitrogen of **24** with an oxygen.

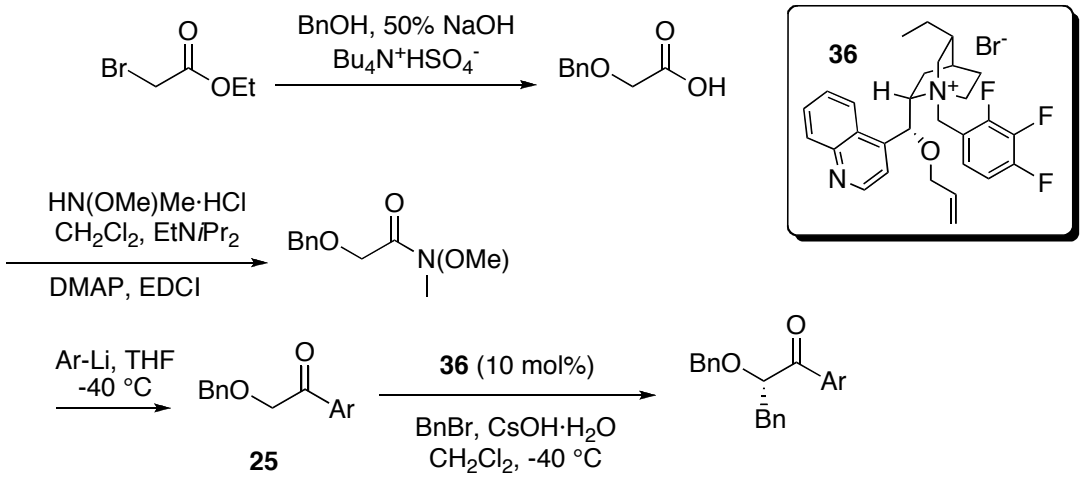
It was initially unclear how this modification might affect reactivity. α-Proton pKa values are about 19.7 for **24**,[15] stabilized by delocalization into the unsaturated diphenylketimine moiety. The pKa for an oxygenated surrogate was less obvious. Though an oxygen's higher electronegativity could inductively stabilize the enolate and decrease pKa, its additional lone electron pair and lack of resonance delocalization might have the opposite effect.

To address this question, compounds **34** were prepared and tested with Corey catalyst **27** (Scheme 2.5). Various conditions were screened, but failed to produce observable reactivity. Apparently, oxygen's destabilizing effects predominate, decreasing α-proton acidity.



Scheme 2.5. Previous group members' attempts at PTC allylation of substrates **34**.

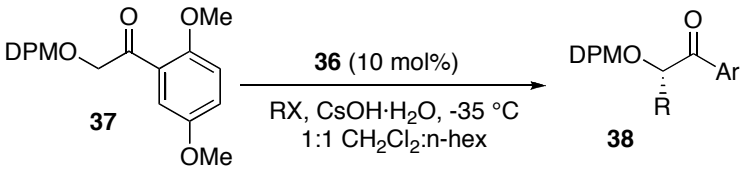
Because a ketone's α-protons are more acidic than an ester's, it was reasoned that a ketone surrogate for **34** might improve reactivity. Hence, aryl ketones **35** were prepared and benzylated with catalyst **36** at -40 °C (Table 2.1).[16-17] Reactivity was markedly improved, with the 2,5-dimethoxy-appended ester giving the best enantioselectivity (entry 11).



entry	Ar	time (h)	yield (%)	ee (%)
1	phenyl	26	74	25
2	p-anisyl	6	82	54
3	o-anisyl	8	78	66
4	m-anisyl	16	50	50
5	N,N-dimethylaniline	13	87	17
6	o-toluyl	12	72	62
7	2,4-xylyl	8	70	66
8	5-methyl-2-anisyl	11	83	60
9	1-naphthyl	8	78	55
10	2,4-dimethoxy	13	90	54
11	2,5-dimethoxy	7	83	71

Table 2.1. Preparation and PTC benzylations of substrate **25**.[16]

A screen of oxygen-protecting groups revealed that the diphenylmethyl (DPM) group gave ideal reactivity, and substrate **37** (Table 2.2) was subsequently studied. Alkylations with allyl, benzyl, and propargyl electrophiles provided compounds **38** in high yields and excellent enantioselectivities.[16] Aliphatic halides failed to give positive results. Products **38** could be converted to aryl esters by exposure to non-epoxidizing Baeyer-Villiger conditions developed by Shibasaki.[18]



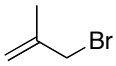
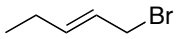
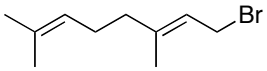
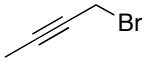
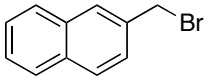
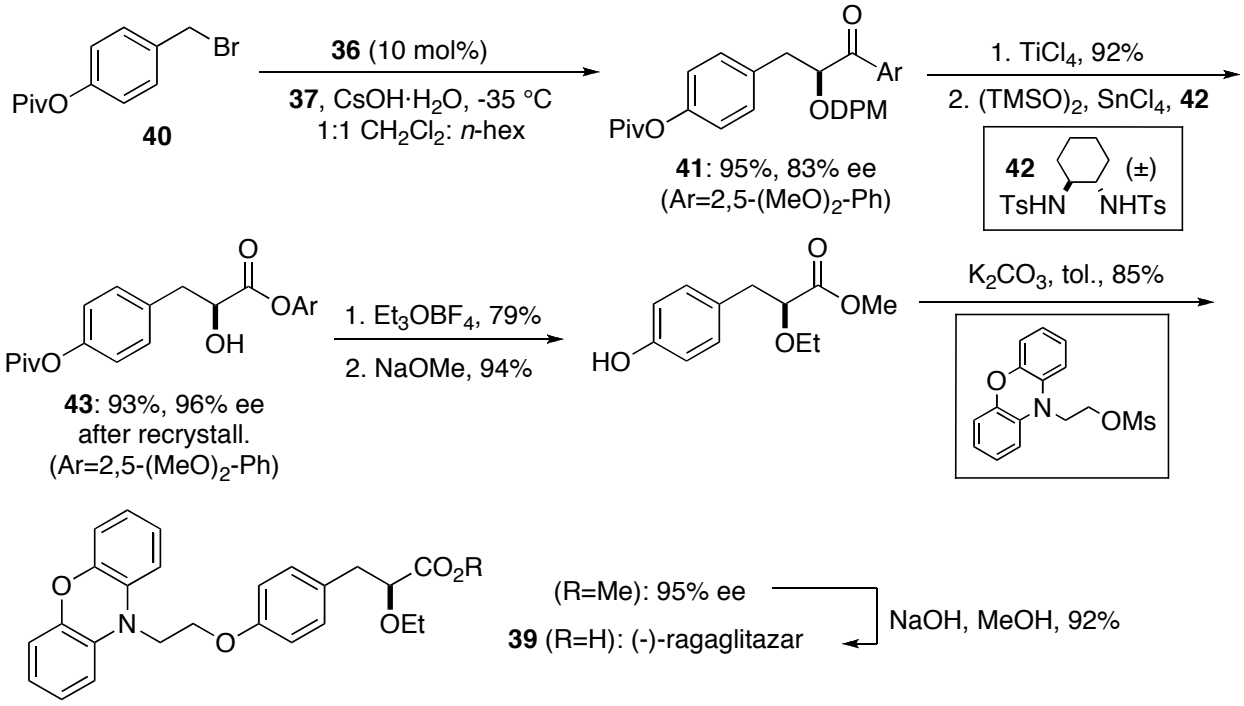
entry	RX	time (h)	yield (%)	ee (%)
1	allyl-Br	5	83	84
2	allyl-I	3	81	70
3		5	78	88
4		4	85	82
5		8	80	84
6		4	89	80
7		24	91	88
8		8	70	66
9	BnBr	13	94	86
10	4-*t*-Bu-BnBr	5	96	84
11	2-Ph-BnBr	5	96	84
12	2-MeO-5-NO_2-BnBr	5	96	84

Table 2.2. PTC alkylations of **37**.[16]

2.3. Total Syntheses of (–)-Ragaglitazar and (+)-Kurasoin A

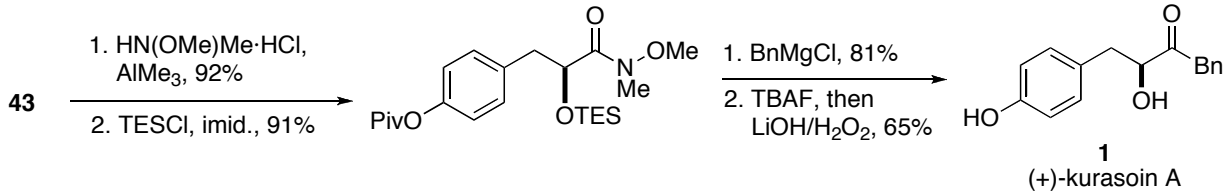
The now-developed methodology was next applied to an asymmetric total synthesis of the diabetes drug (–)-ragaglitazar **39** (Scheme 2.6).[17] This synthesis featured the asymmetric PTC alkylation of **37** with electrophile **40** in its key step, arriving at **41** in 95% yield and 83% ee. DPM removal was accomplished by treating **41** with titanium (IV) chloride; subjection to the aforementioned Shibasaki Baeyer-Villiger conditions (TMS-peroxide, $SnCl_4$, and sulfonamide

42) then provided aryl ester **43**, whose ee was boosted to 95% after recrystallization from 1:1 Et_2O/hexanes. Subsequent transformations then led to the final target **39** in 38% yield over 10 steps.



Scheme 2.6. The total synthesis of (–)-ragaglitazar.[17]

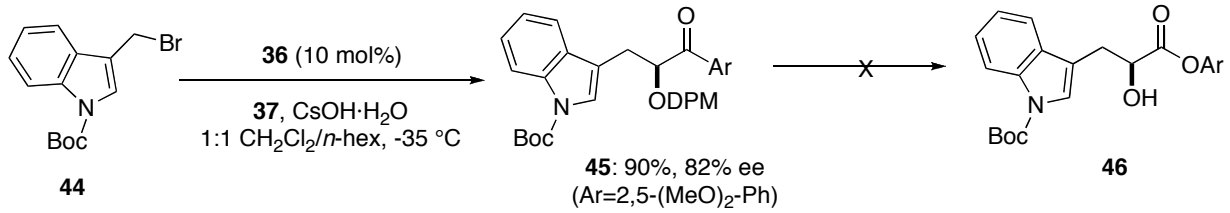
A later synthesis of (+)-kurasoin A **1** was realized from **43** (Scheme 2.7).[19] As with (–)-ragaglitazar, asymmetric PTC alkylation and Baeyer-Villiger oxidation were employed as key steps in the synthesis.



Scheme 2.7. Andrus group total synthesis of (+)-kurasoin A (**1**).[19]

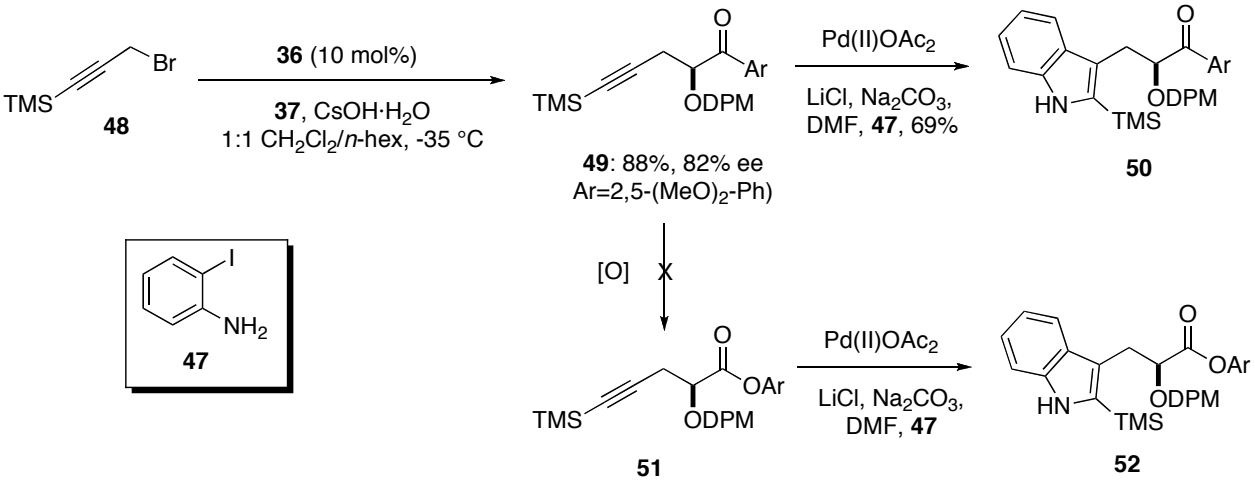
2.4. Limits of the Methodology: Attempted Synthesis of (+)-Kurasoin B

A total synthesis of (+)-kurasoin B **2** began with the PTC alkylation of substrate **37** with electrophile **44** (Scheme 2.8).[5] This provided **45** in 90% yield and 82% ee. Unfortunately, all attempts to convert to ester **46** only resulted in substrate decomposition, even when alternative *N*- and *O*-protecting groups were employed.



Scheme 2.8. Attempted synthesis of **46** en route to (+)-kurasoin B (**2**).[5]

A different route was investigated, based on Larock's indole syntheses from 2-iodoaniline **47** and various internal alkynes.[20-21] PTC alkylation of **37** with electrophile **48** gave intermediate **49** with high yield and enantioselectivity (Scheme 2.9).[5] Exposure to catalytic palladium (II) acetate, 2-iodoaniline **47**, LiCl, and Na_2CO_3 in DMF at 90 °C then produced **50**. As with **45**, all attempts to convert **50** to its aryl ester derivative failed. It was hoped, then, that **49** might be esterified *prior* to indole formation, giving **51** as a synthetic precursor to compound **52** and, ultimately, (+)-kurasoin B. Unfortunately, all conditions failed to give **51**, effectively ending work toward **2** through alkylation of **37**.



Scheme 2.9. Synthesis of **50** and attempted route to **51** and **52**.[5]

The indole moiety's sensitivity to Baeyer-Villiger oxidation demonstrated the limits of the new PTC methodology. An alternative PTC alkylation methodology that did not require Baeyer-Villiger oxidation was consequently desired.

2.5. References and Notes

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16. Andrus, M. B.; Hicken, E. J.; Stephens, J. C. *Org. Lett.* **2004**, *6*, 2289–2292.

17. Andrus, M. B.; Hicken, E. J.; Stephens, J. C.; Bedke, D. K. *J. Org. Chem.* **2005**, *70*, 9470–9479.

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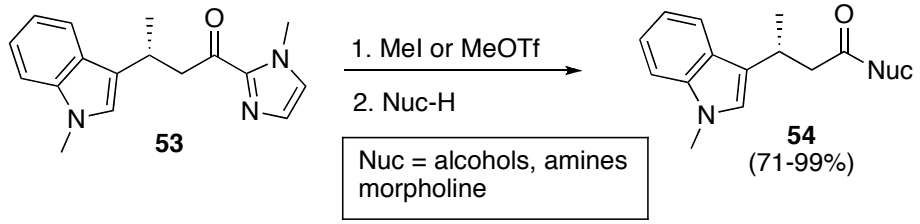
Chapter 3. Phase-Transfer-Catalyzed Asymmetric Acylimidazole Alkylation

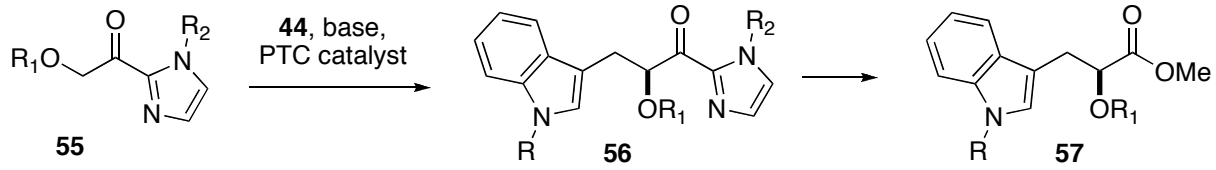
3.1. Bypassing the Baeyer-Villiger Oxidation Step

As explained in chapter 2, it became desirable to create a PTC methodology that provided α-oxy, α-alkylated esters without requiring harsh Baeyer-Villiger conditions. A potential alternative was inspired by a report from Evans' group at Harvard, in which the imidazole appendages of ketones **53** were activated with iodomethane or methyl triflate and then displaced by various nucleophiles.[1-3] This one-pot, two-step transformation converted ketones **53** to esters, acids, or amides **54** in high yield without disturbing their indole moieties.



Sheme 3.1. Nucleophilic displacement of the imidazole moiety in **53**.[1-3]

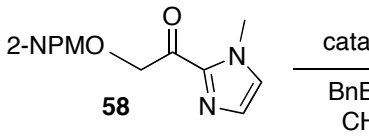
We reasoned that if imidazolyl ketones of type **55** underwent expeditious alkylation with electrophile **44**, then the resulting products **56** might be converted to methyl esters **57**. This route would circumvent Baeyer-Villiger oxidation and provide a new PTC methodology ideal for an alternate route to (+)-kurasoin B.

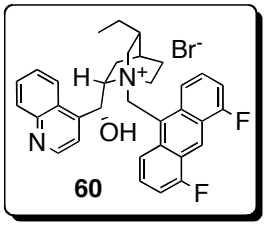


Scheme 3.2. Envisioned synthesis of indole-appended compounds **57**.

3.2. Substrate, Catalyst, and Reaction Condition Development

To test this plan, 2-naphthalenemethyl (2-NPM) protected substrate **58** was prepared and screened with four catalysts to form product **59** (Table 3.1).[4] Though Andrus catalyst **60**[5] gave 86% ee, its accompanying 58% yield was modest. By comparison, cinchonidinium (Cd) dimer catalyst **61**[6] provided **59** in 82% yield and 86% ee (ee's measured by comparison with racemic samples via chiral HPLC).





catalyst	time (h)	yield (%)	ee (%)
36	6	77	74
27	6	58	71
60	16	58	86
61	4.5	82	86

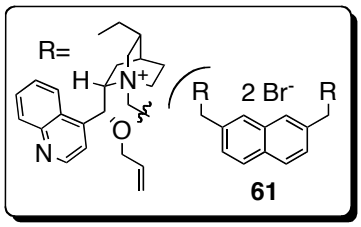
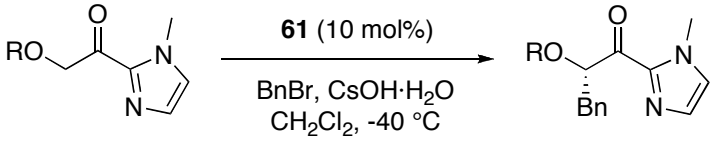


Table 3.1. Catalyst screen in the PTC benzylation of **58**.[4]

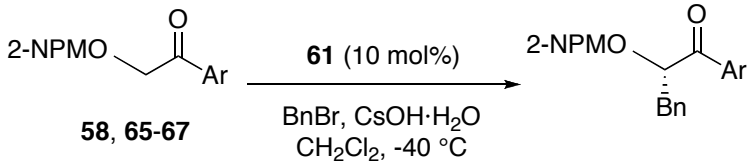
An *O*-protecting group screen was done next, which showed the 2-NPM group to be ideal in terms of overall yield and enantioselectivity (Table 3.2, entry 1). Surprisingly, DPM protection, which had been optimal for substrate **37**, gave comparably modest results (entry 2).



entry	substrate	time (h)	yield (%)	ee (%)
1	**58**: R = 2-NPM	4.5	82	86
2	**62**: R = DPM	5.5	70	58
3	**63**: R = Bn	7	75	82
4	**64**: R = PMB	5	78	81

Table 3.2. *O*-protecting group screen.

Imidazolyl variation was next explored, which revealed the modest performances of *N*-phenyl and *N*-benzyl imidazole-appended substrates **65** and **66** (Table 3.3, entries 2–3). By comparison, *N*-methylbenzimidazolyl ketone **67** gave 76% yield and 93% ee (entry 4).



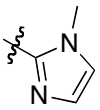
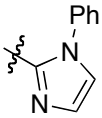
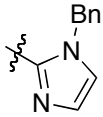
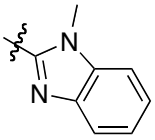
entry	compound	Ar	time (h)	yield (%)	ee (%)
1	**58**		4.5	82	86
2	**65**		18	31	0
3	**66**		16	99	69
4	**67**		4	76	93

Table 3.3. Imidazole variation screen.

Because substrates **58** and **67** both performed so well, neither was abandoned at this juncture. Instead, an in-depth study of reaction conditions was conducted. Ultimately, ideal results were obtained by employing $CsOH·H_2O$ as the base at -40 °C in either dichloromethane or 1:1 CH_2Cl_2/*n*-hexane. These conditions provided benzylated products with yields and enantiomeric excesses above 90% in many cases.

When investigations with *allyl* bromide began, substrate **67** gave surprisingly modest yields of 41–54% and ee's of less than 72% at best. Surprisingly, other electrophiles performed

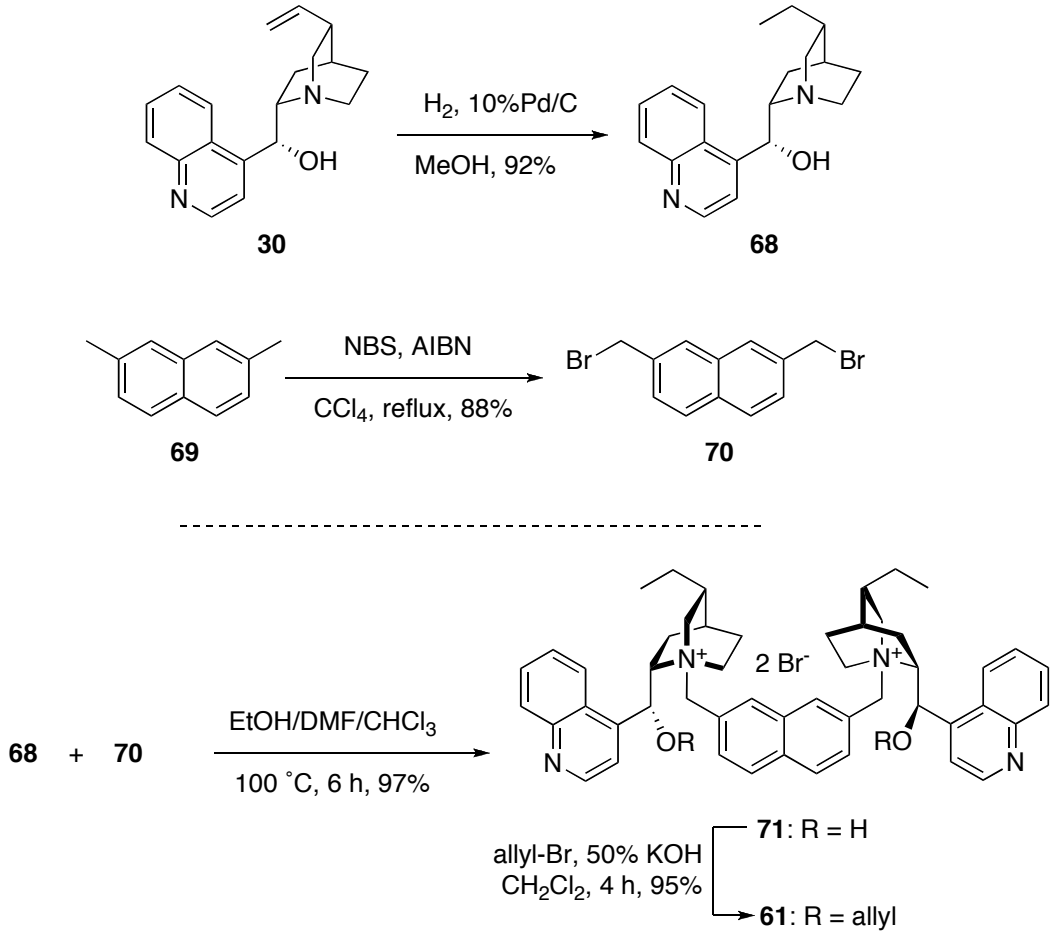
even worse, showing the excellent performance of the **67**/benzylbromide system to be somewhat atypical. The exact cause of this outcome remains unclear, but focus naturally shifted to allylating **58**, which occurred with a satisfactory 70% yield and 80% ee during initial trials.

When the preliminary batch of catalyst **61** ran out after introductory investigations, efforts to repeat its synthesis according to Park's original report[6] and previous group members' notes resulted in discoveries crucial to the catalyst's improvement and the project's ultimate success.

3.3. A Modified and Improved Synthesis of the Catalyst

Catalyst **61** was originally synthesized by Park and coworkers,[6] who used it in the asymmetric alkylation of **24** with various allyl, benzyl, and propargyl electrophiles. Park's route began with the palladium-catalyzed reduction of (–)-cinchonidine **30** to (–)-hydrocinchonidine **68**, achieved in 92% yield as Scheme 3.3 depicts (*vide infra*). Separate treatment of 2,7-dimethylnaphthalene **69** with NBS and AIBN then produced intermediate **70** with an 88% yield. When combined at high temperature, **68** and **69** furnished a reportedly light-pink di-ammonium salt **71** in 97% yield, which was subsequently allylated to give catalyst **61**.

To synthesize the new batch of catalyst, we followed Park's procedure, seamlessly providing compounds **68** and **70**. However, when these were combined to produce **71**, a dark-purple syrup formed in which no product was detectable by HRMS. (No further characterization of this mixture was performed.)



Scheme 3.3. Park's original synthesis of catalyst **61**.[6]

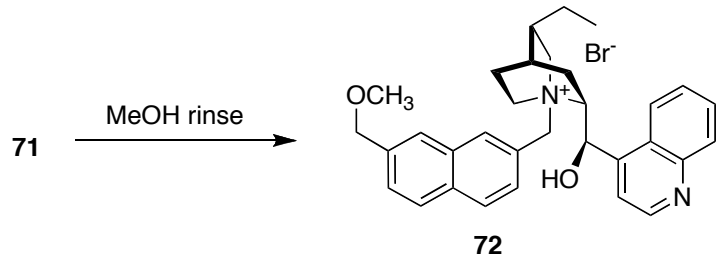
A second attempt on smaller scale formed the light-pink solid desired, but scale-up once again yielded a dark-purple syrup. Presuming that intermediates **68** and **70** were somehow impure, these were newly synthesized and submitted freshly on large scale to form **71**. Strangely, a *yellow* solid was now obtained, which eventually gave catalyst **61** in 60% yield after chromatographic purification. Unfortunately, PTC allylation of substrate **58** with this batch of catalyst provided product with a modest 44% yield and 53% ee. Formation of **71** was clearly a problematic step in the catalyst's synthesis, though the cause for this difficulty remained as yet enigmatic.

The purity of **68** and **70** was carefully determined by developing new conditions for monitoring reaction progression via TLC. Great attention was also paid to spectroscopic characterization of products. By increasing the number of Fourier transforms, our first clear NMR spectra for **68** and **70** were obtained. Despite our growing confidence in the purity of these compounds, a renewed attempt to prepare **71** once again gave a dark-purple mixture.

It was hypothesized that one of four factors might be causing failure in the formation of the catalyst: (1) trace Pd/C left in **68** was causing detrimental effects; (2) syringes or needles were contaminated; (3) solvents were not sufficiently dry; or (4) reaction temperature was too high.

These questions were eventually addressed by intentionally adding trace amounts of Pd/C and water in separate formations of **71**. It was found that Pd/C caused formation of the dark-purple syrup, whereas water resulted in yellow discoloration. Hence, great effort was taken thereafter to thoroughly dry solvents and to completely filter Pd/C from **68**, which was ultimately isolated in 67% yield as an off-white solid (free from any gray discoloration).

With reagents and conditions now optimized, large-scale reaction of **68** with **70** at lower temperature (50 °C) gave **71** as the desired, light-pink solid. Surprisingly, rinsing the crude product with dichloromethane and methanol during flask transfer converted it to a dark-*red* solid, in which the presence of byproduct **72** (Scheme 3.4) was confirmed by HRMS (481.2827 $[M+H]^+$ found; calcd 481.28 for $[C_{32}H_{37}N_2O_2]^+$). Compound **72** is likely produced through a solvation/substitution reaction of methanol for one of the two hydrocinchonidinium moieties. Catalyst formed from this batch of **72** gave poor enantioselectivity and yield in PTC alkylations.



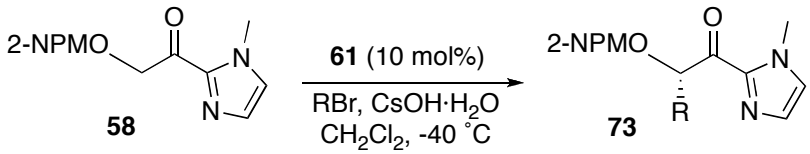
Scheme 3.4. Formation of **72** during methanolic rinse of **71**.

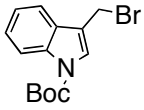
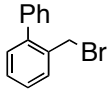
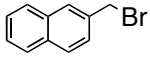
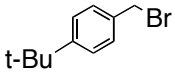
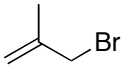
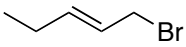
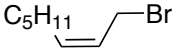
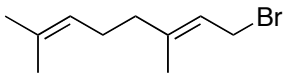
With these observations now made after many optimization experiments, **68** was synthesized again and filtered thoroughly to ensure removal of Pd/C. Dry solvents were employed, which ultimately furnished **71** cleanly as a light-pink solid on 500 mg scale. **71** was not rinsed with methanol, and subsequent allylation then furnished catalyst **61**.

Catalyst purification was now addressed. Earlier cinchona catalysts synthesized by our group were being tediously purified by column chromatography in 5% methanol-dichloromethane. The reason for this was that recrystallization from dichloromethane-hexane, as described by Park,[6] had repeatedly failed in our lab, resulting in the crude catalyst remaining completely dissolved in solution.

Recrystallization was now explored. In time it was found that the crude catalyst could be dissolved in a minimal amount of warm dichloromethane and then precipitated instantly by copious addition of hexanes. When filtered immediately, **61** was obtained cleanly as a light-yellow solid in 96% yield. If left in solution, crystalline **61** redissolved.

Previous batches of **61** had failed to give acceptable results with any electrophiles other than benzyl bromide. In contrast, our latest batch, which was prepared according to the modifications just described, showed dramatic improvement, giving products **73** with high yields and excellent enantioselectivities (Table 3.4).



entry	RBr	time (h)	yield	ee (%)
1		60	91	>99
2		22	92	>99
3		22	88	>99
4		22	88	>99
5		49	82	85
6	BnBr	26	85	83
7	Allyl-Br	49	59	73
[a]8	Allyl-Br	8	90	88
[b]9		7	80	91
[b]10		8	77	79
[b]11		6	75	75

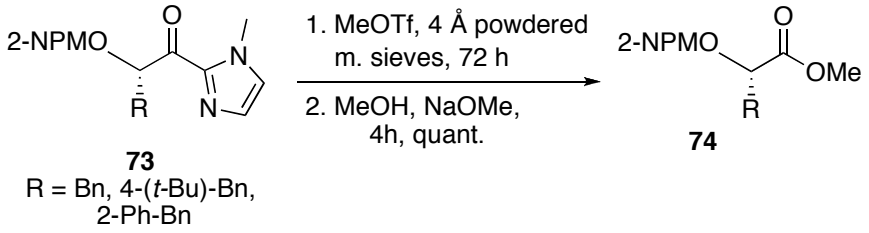
[a]obtained with a later batch of **61** in 1:1 CH_2Cl_2/*n*-hex.

[b]obtained in 1:1 CH_2Cl_2/*n*-hex.

Table 3.4. PTC alkylations of substrate **58** with optimized batch of catalyst **61**.

3.4. Finishing the Methodology

The next step in developing the methodology was to displace the *N*-methylimidazole appendages of the alkylated products. After screening many conditions, we found that stirring compounds **73** with methyl triflate for three days facilitated imidazolium formation. Addition of sodium methoxide/methanol then provided methyl esters **74** with quantitative yield and no measurable epimerization. Alternative nucleophiles (ethanol, isopropanol, morpholine, and hydrogen peroxide) were ineffective.

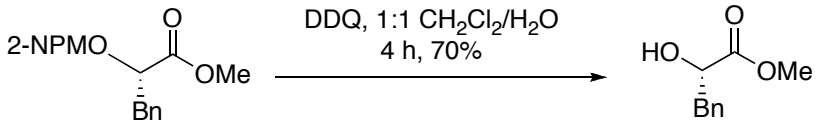


73
R = Bn, 4-(*t*-Bu)-Bn,
2-Ph-Bn

74

Scheme 3.5. Converting ketones **73** to esters **74**.

With imidazole displacement now optimized, product **74** (where R = Bn) was treated with DDQ to remove the 2-NPM protecting group (Scheme 3.6). These conditions afforded optically active **75** in 70% yield. Optical rotation comparison with known **75**[7] confirmed the absolute stereoconfiguration as *S*.



74

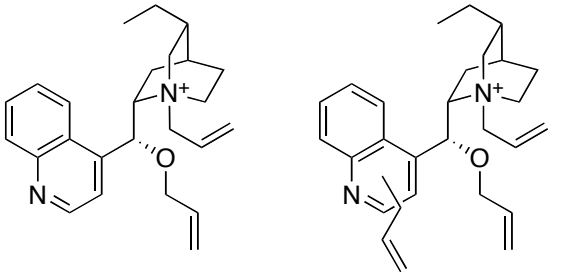
75
$[a]_D$ –6.25°
Lit. $[a]_D$ –6.8°

Scheme 3.6. Converting product **74** to known hydroxy ester **75**.

These final developments represent a new PTC route to asymmetric α-oxy, α-alkylated esters that does not require Baeyer-Villiger oxidation. This work culminated in a published summary of our most important findings.[8]

3.5. Further Optimization of the Catalyst

Further discoveries relating to the catalyst's synthesis have been made since generating the data featured in Table 3.4. These came about when HRMS examination of in-house batches of catalyst showed the presence of two unexpected ions at 377 and 417, respectively. Candidate structures **76** and **77**, shown in Figure 3.1, were proposed.

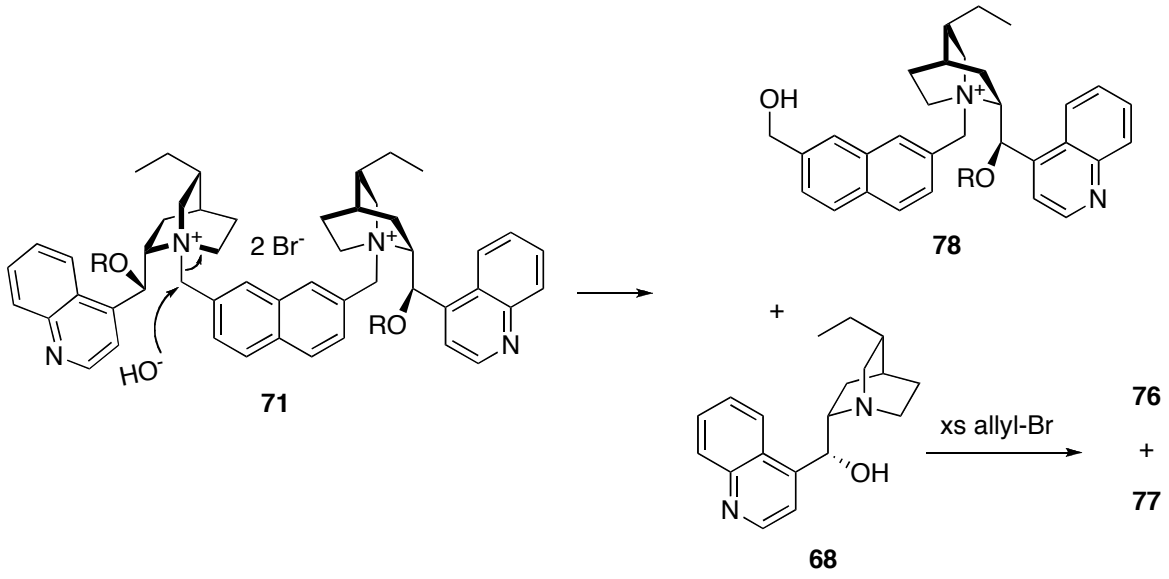


76
$C_{25}H_{33}N_2O^+$
Exact Mass: 377.26

77
$C_{28}H_{37}N_2O^+$
Exact Mass: 417.29

Figure 3.1. Structures **76** and **77**.

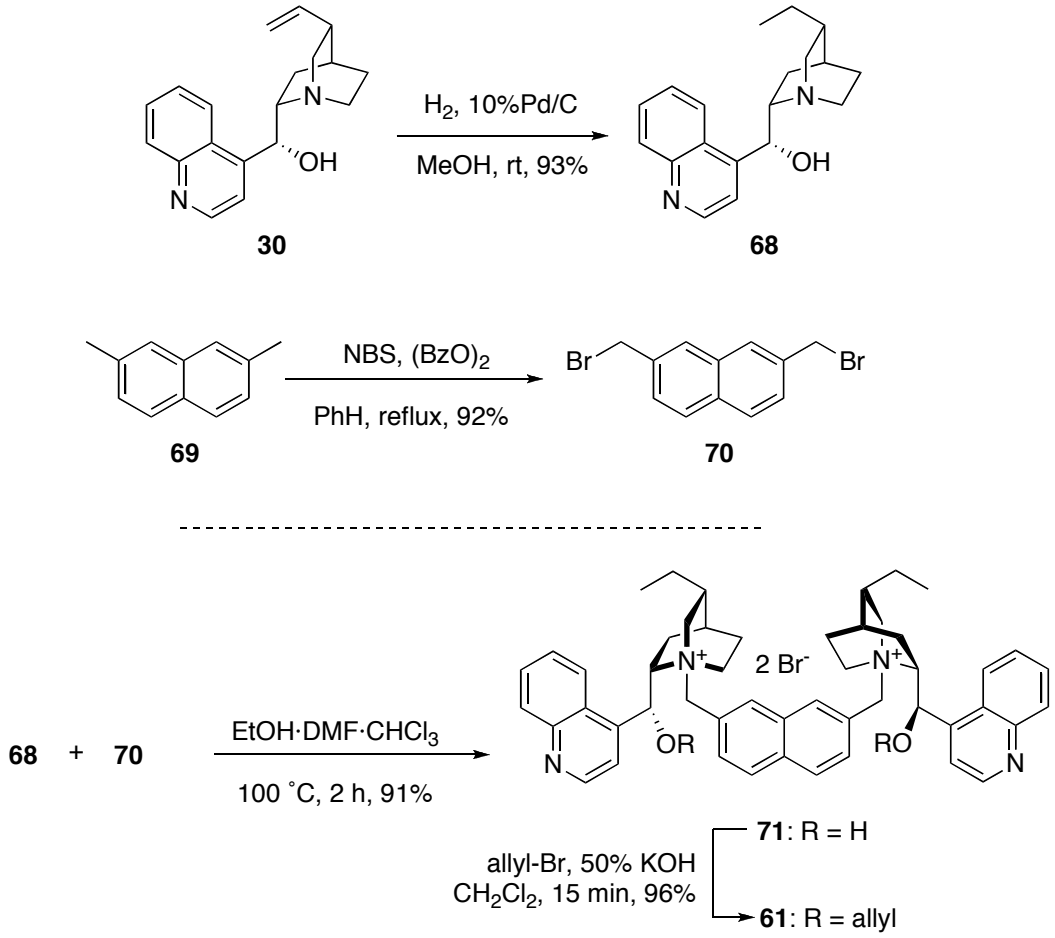
Potential origins of **76** and **77** are somewhat straightforward. During catalyst formation from **71**, hydroxyl attack might occur, liberating free hydrocinchonidine **68** and forming byproduct **78** (Scheme 3.7). Subsequent allylation of **68**, expected in the presence of excess allyl bromide, could then produce inseparable contaminants **76** and **77**. These might behave as competitive, non-selective catalysts, explaining the poor results sporadically obtained with some catalyst batches.



Scheme 3.7. Proposed origin of byproducts **76** and **77**.

When allylating **71** during the final step of the catalyst's synthesis, excessive reaction time might presumably exacerbate this effect and increase the amounts of **76** and **77**. Monitoring the reaction in situ by HRMS revealed that starting material **71** was completely consumed after only 15 minutes. This contrasts sharply with Park's original procedure, which calls for stirring the reaction at room temperature for four hours.

To avoid these contaminants and thereby improve catalyst performance, modifications to the synthesis of the catalyst were developed (Scheme 3.8). The most meaningful advance of this improved procedure lies in the thoroughness of its experimental details, which now make the catalyst's preparation comparatively straightforward and reproducible. A researcher with minimal lab experience can now reproducibly synthesize **61** with high yield in only a few days.



Scheme 3.8. Modified synthesis of catalyst **61**.

Through this process, several improvements to the catalyst's synthesis have been made. First, TLC conditions are now reported for monitoring reaction completion during the formation of intermediates **68** and **70**.[8] Next, higher-yielding conditions (benzoyl peroxide in refluxing benzene) are now used as an alternative means to **70**. The yellow, dark-red, or dark-purple contaminants, which give rise to unsuitable catalyst, are now reported as byproducts to the synthesis of **71** under certain conditions. Likely causes of these contaminants are also confirmed. Additionally, formation of byproduct **72** is reported; avoiding exposure of **71** to methanol is critically noted. Byproducts **76** and **77** are duly noted, resulting in optimal catalyst

formation by running the final step for only 15 minutes. Lastly, the mode of catalyst purification by recrystallization is now reported with sufficient detail to allow its reproducible application, and printed NMR spectra for the catalyst and each intermediate in its synthesis are published.[8]

3.6. Comparisons with Commercial Catalyst

Since this work began, catalyst **61** was made commercially available by Aldrich. For comparison's sake, commercial **61** was purchased and used to benzylate **58** under the same conditions shown in Table 3.4, entry 6. This reaction ran 19 hours and gave product **73** in 86% yield and 76% ee. When commercial catalyst was tested by HRMS for the presence of contaminants **76** and **77**, only **76** was observed [found 377.2592 $(M)^+$ and 378.2724 $(M+H)^+$, calcd 377.26 for $(C_{25}H_{33}N_2O)^+$ and 378.27 for $(C_{25}H_{34}N_2O)^+$].

3.7. References and Notes

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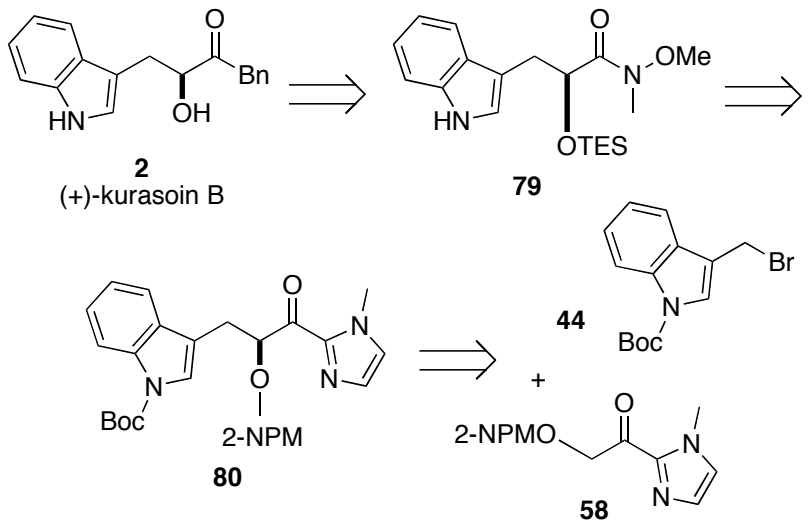
Chapter 4. The Total Synthesis of (+)-Kurasoin B

4.1. Synthetic Analysis

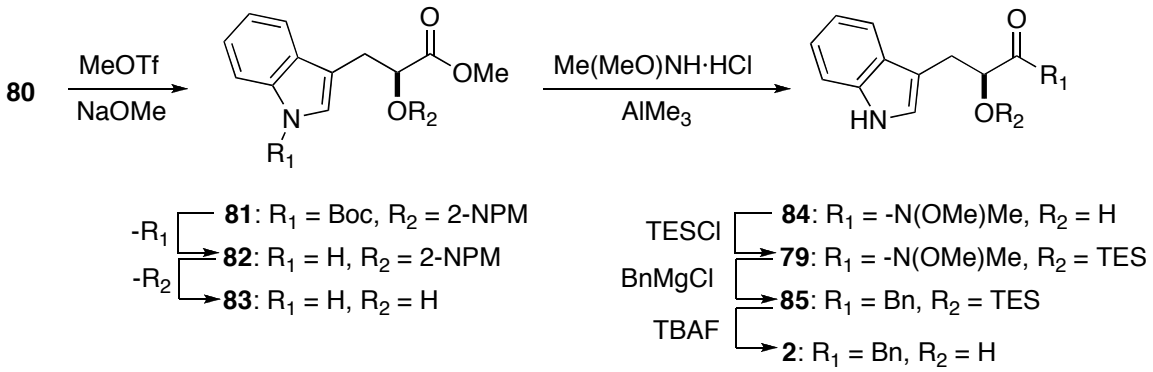
With the new methodology now developed, the stage was set to complete the total synthesis of (+)-kurasoin B. This was envisioned retrosynthetically through benzyl Grignard addition and deprotection of **79** (Scheme 4.1). Compound **79**, in turn, would originate from straightforward manipulations of **80**, which would be obtained from an asymmetric PTC alkylation of **58** with electrophile **44**.



Scheme 4.1. Retroanalysis of **2**.

In the forward sense, it was envisioned that compound **80** could be converted to **79** via the approach illustrated in Scheme 4.2. Formation of methyl ester **81** could be accomplished via treatment of **80** with methyl triflate and sodium methoxide. Boc removal would give **82**, and deprotection of the 2-NPM group would furnish **83**; this could then be converted to Weinreb amide **84**. Protecting this intermediate's free hydroxyl group as a TES ether would then provide

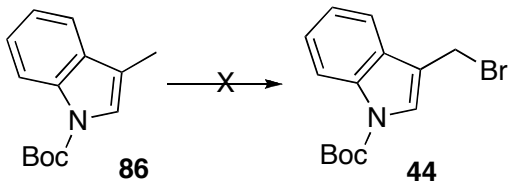
79. Although this deprotection/reprotection sequence might appear inefficient, previous work with (+)-kurasoin A had shown it necessary to prevent undesired byproduct formation and low overall yield during benzyl Grignard addition.[1] Treatment of **79** with BnMgCl would give **85**, and reaction with TBAF would then unveil the final target.



Scheme 4.2. Planned synthesis of (+)-kurasoin B **2** from **80**.

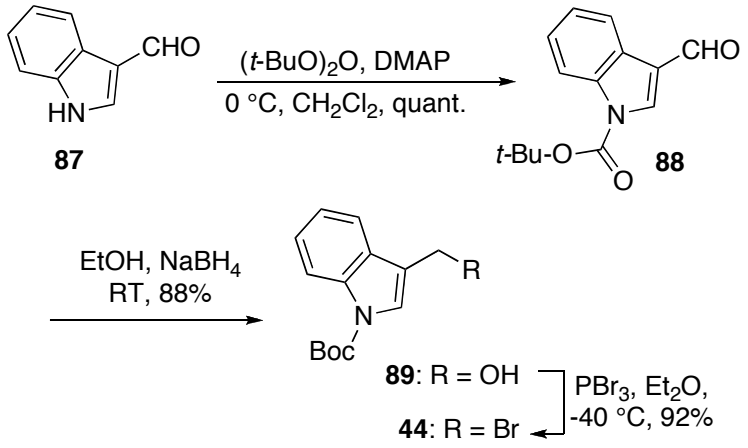
4.2. Making the Electrophile

Despite its commercial availability, a synthetic route to electrophile **44** was sought, due to the compound's high cost ($356 per gram). Attempted brominations of **86** (accessible in one step from 3-methylindole) failed, even after applying numerous conditions suggested by literature precedent (Scheme 4.3).[2-3]



Scheme 4.3. Bromide **44** was inaccessible from **86**.

An alternative route, shown in Scheme 4.4, was pursued from indole-3-carboxaldehyde **87**. Following published conditions,[4] *N*-Boc protection of **87** provided **88** in quantitative yield, and sodium borohydride reduction of **88** gave **89**. At this stage, different bromination conditions were explored. Treatment with $Br_2/Ph_3P/Et_3N$ failed, giving only a complex mixture. By comparison, an alternative procedure with mesyl chloride and lithium bromide[5] gave spectroscopically pure **44** in quantitative yield. This product was a deep-purple solid that became more darkly colored over time. All alkylations with this electrophile gave modest selectivity (<50% ee), so an improved procedure was sought. This led to the treatment of **89** with PBr_3 at low temperature, giving electrophile **44** as a white solid in 92% yield. The first alkylation of **58** with this electrophile provided **80** in 83% yield and 95% ee.

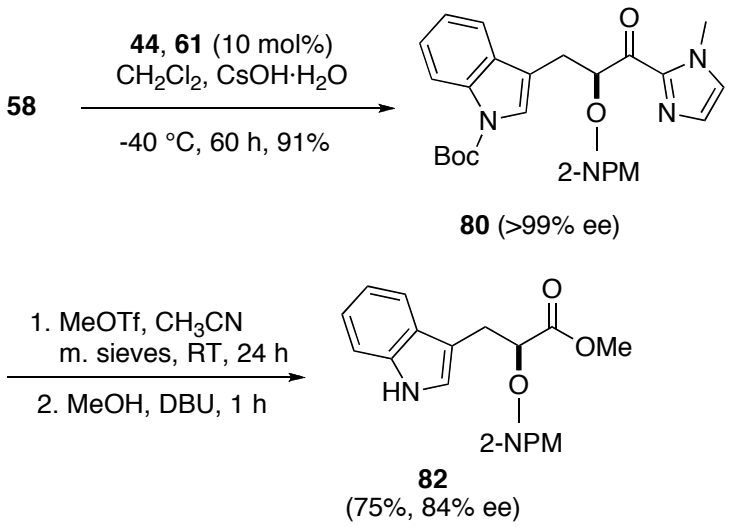


Scheme 4.4. Completed synthesis of electrophile **44**.

4.3. First-Generation Synthesis

When the synthesis of compound **80** was attempted again (this time on two-gram scale) with the now-optimized catalyst, product **80** was obtained in 91% yield and ~100% enantiomeric purity (Scheme 4.5). With **80** now in hand, displacement of the *N*-methylimidazole group was

explored. Eventually, conditions were found that provided **82** in 75% yield, with some epimerization (84% ee). Fortuitously, cleavage of the Boc group also occurred, thereby increasing the simplicity of the overall synthesis.

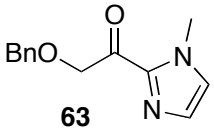


Scheme 4.5. Synthesis of **82** from **58**.

With **82** in hand, removal of the 2-naphthalenemethyl protecting group was explored.[7] Unfortunately, every condition examined—including high-pressure hydrogenation and treatment with boron trichloride or DDQ—failed, producing only complex mixtures or no reaction. Attempts to remove the 2-NPM protecting group during later stages of the synthesis were also unsuccessful.

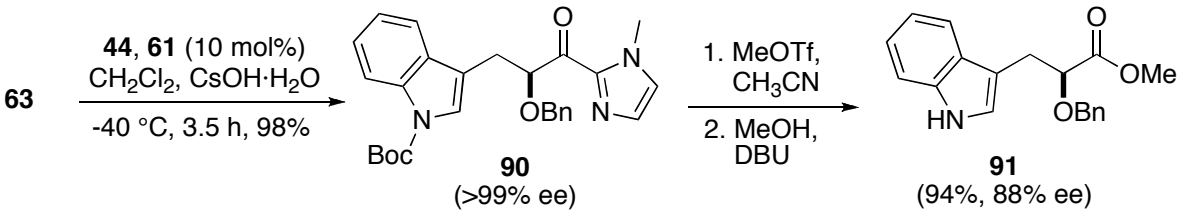
4.4. Second-Generation Synthesis

At this stage, benzyl-protected substrate **63** was reconsidered. This compound had performed satisfactorily in earlier studies (see Table 3.2, entry



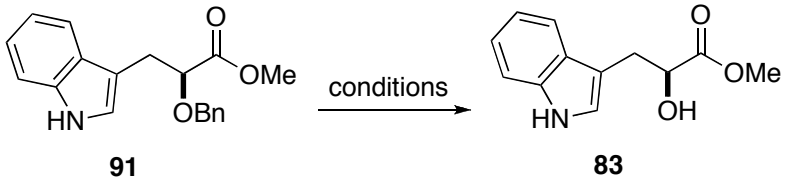
3) and seemed a better alterative to **58**, given the difficulty we encountered in trying to remove the 2-NPM protection from **82**.

Gratifyingly, PTC alkylation of **63** with electrophile **44** gave product **90** in 98% yield and ~100% enantiomeric purity (Scheme 4.6). Besides providing a slightly higher yield than **58** in this alkylation (compare Scheme 4.5), substrate **63** also required less reaction time (3.5 hours versus 60 hours for **58**). With product **90** now in hand, treatment with methyl triflate and basic methanol provided ester **91** in 94% yield, with some epimerization (88% ee).



Scheme 4.6. Synthesis of **91** from **63**.

Conditions were now screened to remove **91**'s benzyl protecting group (Table 4.1). Complex mixtures resulted from treatment of **91** with DDQ and $Pd(OH)_2/H_2$ (entries 1-2), while 10% Pd/C gave incomplete reactivity (entry 3). Boron trichloride eventually proved suitable,



entry	conditions	results
1	DDQ, 1:1 CH_2Cl_2/H_2O	complex mixture
2	20% $Pd(OH)_2/C$, H_2, MeOH	complex mixture
3	10% Pd/C, H_2, EtOH	no rxn.
4	BCl_3, CH_2Cl_2, -78 °C	**83** formed (56%)
5	BCl_3, CH_2Cl_2, -78 °C → -20 °C	**83** formed (quant.)

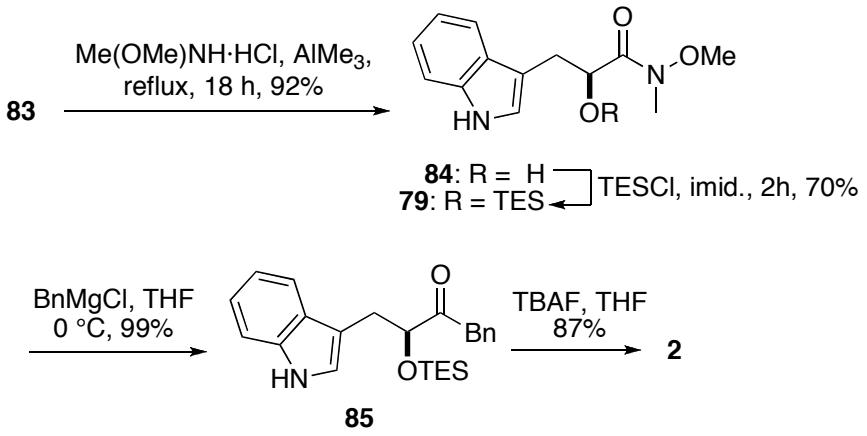
DDQ = 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

Table 4.1. Benzyl deprotection screen of **91**.

giving ester **83** cleanly in 56% yield at -78 °C (entry 4). When the temperature was increased to -20 °C as the reaction proceeded, quantitative product formation ensued (entry 5).

Besides having the more easily-cleaved benzyl protecting group, substrate **63** is less expensive to make than **58**. This is because **63** is formed from benzyl alcohol (20¢ per gram), while **58** is made from costlier 2-naphthalene methanol ($15.66 per gram). The efficiency of compound **63** in asymmetric PTC alkylation, coupled with its relatively low cost, proved doubly advantageous to the attractiveness of this method.

With enantioenriched **83** now formed on large scale, seamless manipulations thereafter completed the total synthesis of (+)-kurasoin B. As Scheme 4.7 illustrates, treatment with *N,O*-dimethylhydroxylamine·HCl and trimethyl aluminum provided Weinreb amide **84** in 92% yield. TES protection then gave **79**, and benzyl Grignard addition gave **85**. Final deprotection with TBAF then provided (+)-kurasoin B (**2**) in 43% yield over ten steps from benzyl alcohol. Data obtained from our synthetic sample, including optical rotation, matched those of the natural compound, culminating in a published summary of the total synthesis.[7]

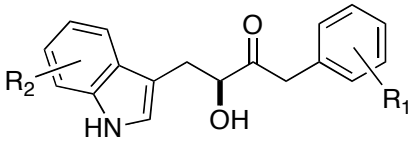


Scheme 4.7. Final steps to (+)-kurasoin B (**2**) from **83**.

4.5. Analog Syntheses

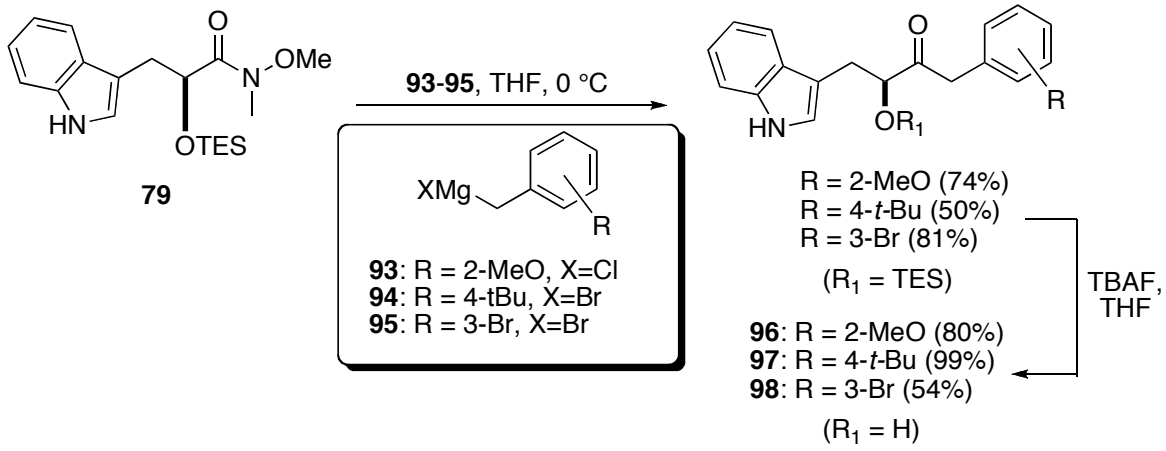
4.5.1. First-Generation Analogs

In hopes of conducting structure-activity relationship studies and possibly discovering (+)-kurasoin B derivatives with higher FTase-inhibitory activity, analogs of type **92** were desired (Figure 4.1). To this end, intermediate **79** was reacted with commercial Grignard reagents **93-95** to give **96-98** after TBAF deprotection (Scheme 4.8).



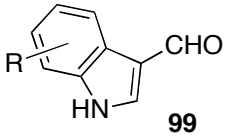
92

Figure 4.1. General (+)-kurasoin B analog structures.



Scheme 4.8. Syntheses of analogs **96-98** from **79**.

Indole variation proved more challenging. Despite the existence of substituted indoles of type **99** (Figure 4.2), their commercial availability is often limited and cost-prohibitive.



99

Figure 4.2. General representation of 3-formylindole variants.

One exception is 5-bromoindole **100**. Based on literature precedent,[8-11] it was envisioned that coupling reactions with **100** might produce various substituted indoles that could eventually lead to an expanded library of (+)-kurasoin B analogs.

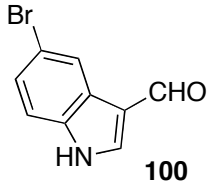
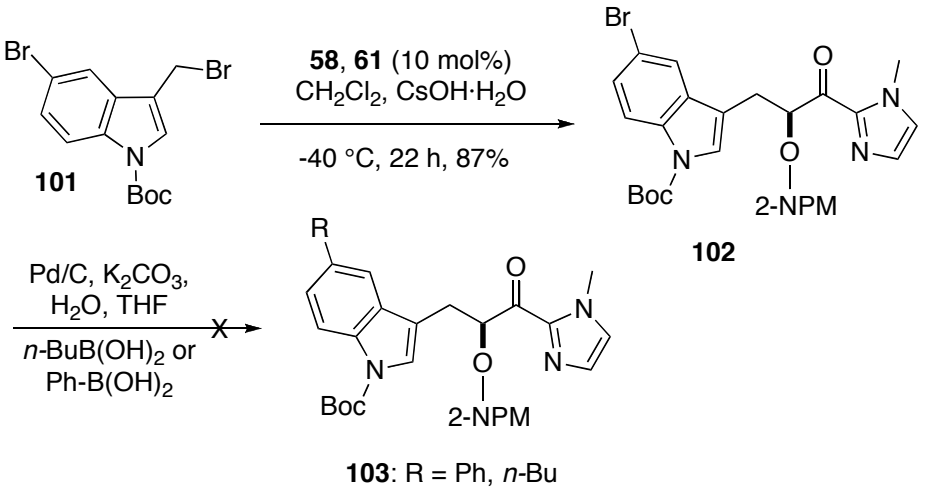


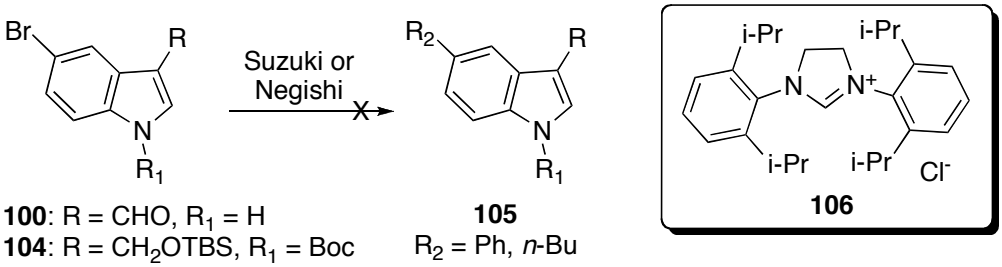
Figure 4.3. Bromoindole **100**.

To this end, electrophile **101** was prepared from **100** in a sequence analogous to the one used to prepare **44** (Scheme 4.4). This electrophile was then used in the PTC alkylation of substrate **58**, giving **102** in 87% yield (Scheme 4.9). Compound **102**, for which no enantiomeric excess was measured, was then examined as a substrate for Suzuki couplings to form analogs **103**. A variety of attempts were unsuccessful, but exhaustive optimization was not pursued.



Scheme 4.9. Attempted Suzuki couplings of **102** to form **103**.

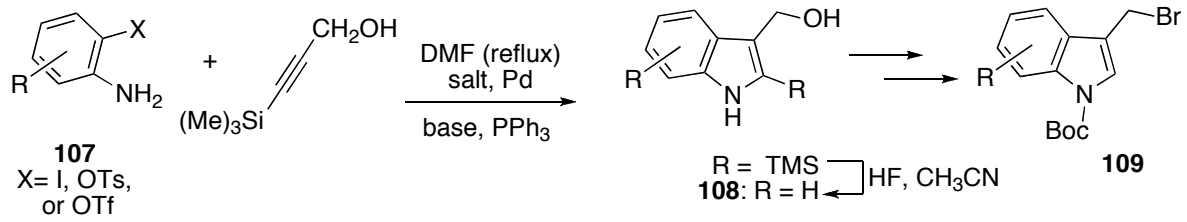
An alternative route to indole variation was envisioned from *N*-Boc-protected TBS ether **104**, as well as from aldehyde **100** itself (Scheme 4.10). Multiple Suzuki conditions (not shown) with various coupling partners failed to give products **105** in significant quantities, despite the use of reactive NHC ligand **106**[12] during many attempts. Alternative Negishi conditions, for which some literature precedent was known,[8] were also unsuccessful, due to the apparent stability of indoles **100** and **104**.



Scheme 4.10. Attempted Suzuki couplings of **100** and **104** to form **105**.

4.5.2. Indole Variation Through Modified Larock Chemistry

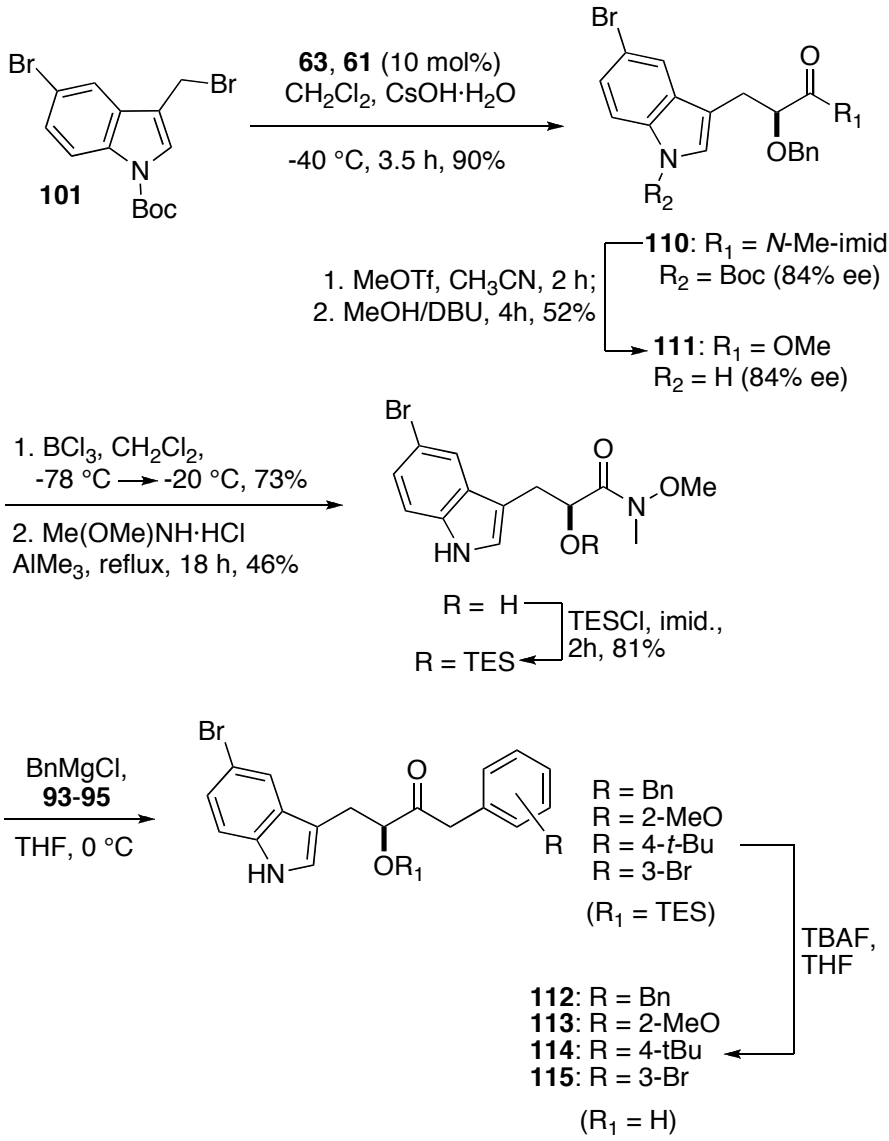
At this stage modification of Larock's indole chemistry[13-14] was considered. It was reasoned that available iodoanilines or accessible amino tosylates or triflates **107** might provide indoles **108** after TMS removal. These could then be transformed into electrophiles **109** as an alternative means to (+)-kurasoin B analogs. Unfortunately, all attempts at indole formation from arenes **107**[15-17] failed, effectively halting our work toward indole variation.



Scheme 4.11. Envisioned syntheses of **109** from **107**.

4.5.3. Second-Generation Analogs

Despite these setbacks, PTC alkylation of **63** was done with **101** to give **110** in 90% yield and 84% ee on large scale (Scheme 4.12). This was then converted to **111**. Work currently advances toward bromoindolyl analogs **112-115**, with the reaction conditions and unoptimized yields indicated. Once their preparations are completed, these analogs will be tested alongside compounds **96-98** for FTase-inhibitory activity.



Scheme 4.12. Current progress toward analogs **112-115**.

4.6. References and Notes

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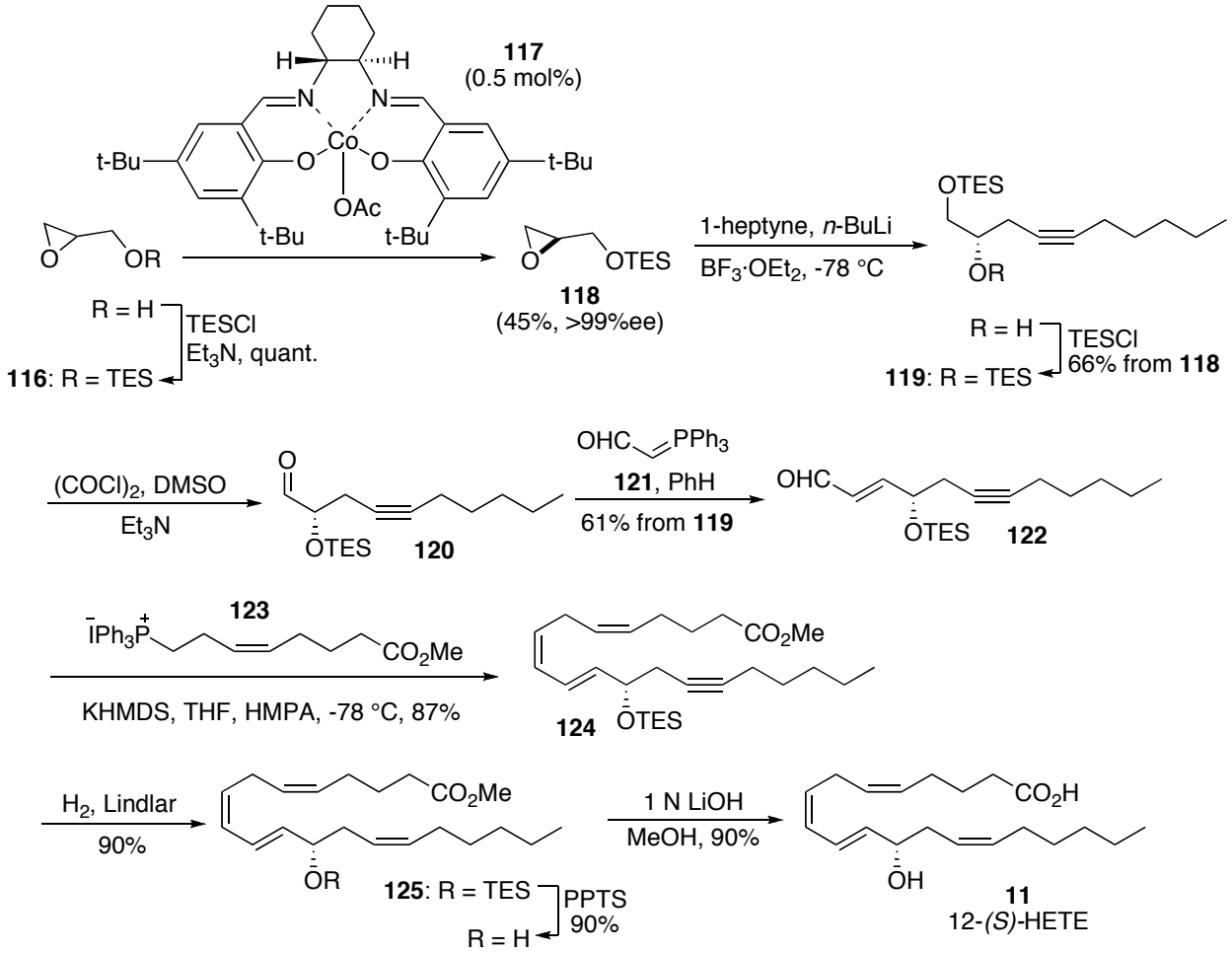
Chapter 5. The Total Synthesis of 12-*(S)*-HETE

5.1. Previous Synthetic Efforts

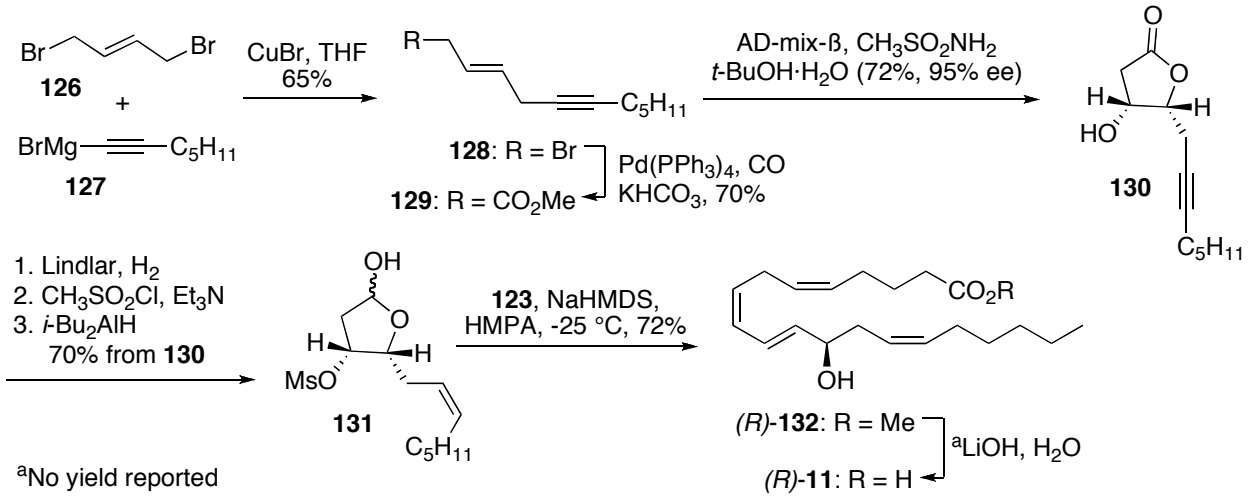
Of the various routes to 12-HETE mentioned in chapter 1, two bear particular relevance to our work. The first, reported by Spur et al.,[1] began by chiral resolution of epoxide **116** with catalyst **117**, which gave enantiopure **118** in 45% yield (Scheme 5.1). Treatment of **118** with lithiated 1-heptyne, followed by TES protection, then gave **119**. Swern oxidation of **119** selectively affected the primary TES ether, directly affording aldehyde **120**. This was then reacted with stabilized Wittig reagent **121** to produce compound **122**. Exposure to Wittig salt **123**



Scheme 5.1. Spur and coworkers' synthesis of 12-*(S)*-HETE (**11**).[1]

(addressed later on) provided **124**, which was hydrogenated with Lindlar catalyst to access **125**. Deprotection and hydrolysis then furnished the final product with an 11.5% yield over 10 steps from **116**.

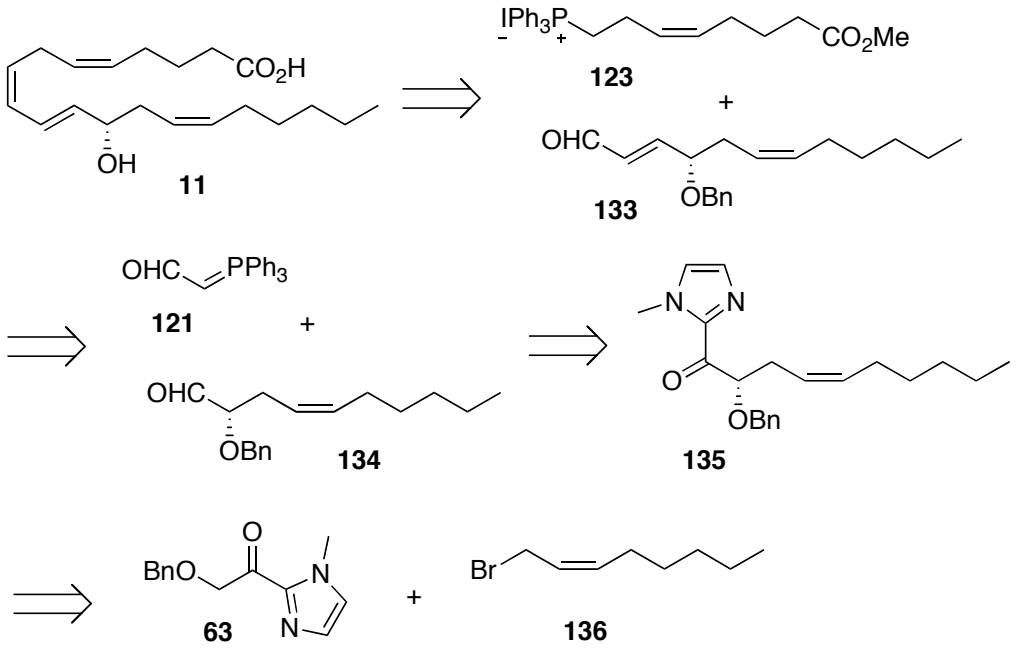
Corey's route to 12-*(R)*-HETE[2] began by coupling **126** with **127** to form allyl bromide **128**, which was then converted to ester **129** (Scheme 5.2). Asymmetric dihydroxylation with AD-mix-β occurred with concomitant lactonization, producing intermediate **130** in 95% ee. Lindlar reduction provided the *Z*-olefinic moiety; the free alcohol was converted thereafter to a mesylate, and the lactone reduced to a lactol, giving **131**. Reaction with **123** (shown above) then provided *(R)*-**132**, which was hydrolyzed to the final target (no yield reported). The synthesis was reported as embarking eight total steps from **126**. However, formation of **123** was lower-yielding and required the same number of steps as **131**. Hence, the total synthesis was actually done over eight steps from hex-5-ynenitrile (the precursor to **123**) with <12.8% yield (no yield reported for the last step). Its advantage lies in its amenability to 12-*(S)*-HETE **11** by using complimentary AD-mix-α in the key step.



Scheme 5.2. Corey and coworkers' synthesis of 12-*(R)*-HETE.[2]

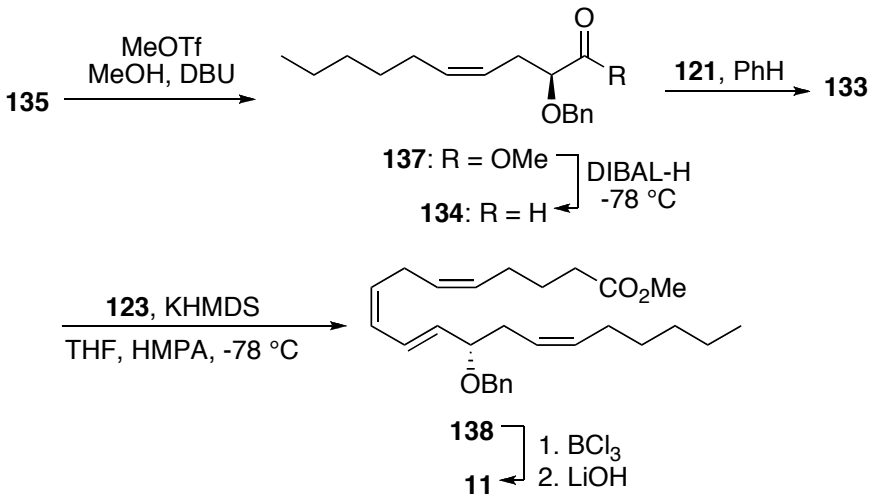
5.2. Synthetic Analysis

To further showcase the utility of our PTC alkylation methodology, a route to 12-*(S)*-HETE **11** was devised, as depicted in Scheme 5.3. Retrosynthetically, **11** was envisioned as arising from **123** and **133**. Compound **133**, in turn, could come from reacting aldehyde **134** with Wittig reagent **121**. Compound **134** could be derived from **135**, which could originate from the asymmetric PTC alkylation of **63** with electrophile **136**.



Scheme 5.3. Retroanalysis of **11**.

In the forward direction, treating **135** with methyl triflate and basic methanol would yield ester **137**, and careful reduction of **137** would give aldehyde **134** (Scheme 5.4). Reaction with **121** would then produce **133**. Noting **133**'s structural similarity to **122** above, coupling with Wittig reagent **123** would be anticipated to provide **138**. Deprotection and hydrolysis would then give the final target, formed over 10 steps from the benzyl alcohol used to make **63**.



Scheme 5.4. Planned synthesis of **11** from **135**.

5.3. First-Generation Synthesis

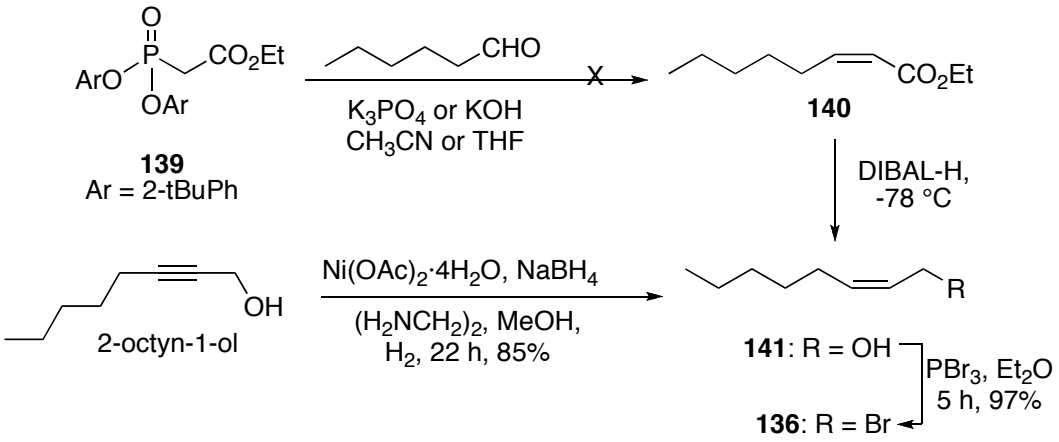
5.3.1. Making the Electrophile

The synthesis began by examining PTC alkylation with electrophile **136**. This had been done earlier on substrate **58** (see Table 3.4, entry 10) to give product with an acceptable 77% yield and 79% ee. Unfortunately, the reaction suffered from irreproducibility. Typical alkylations with electrophile **136** resulted in 45-65% yields and ee's below 75%.

Our earlier syntheses of **136** had been done by reducing 2-octyn-1-ol to *Z*-2-octen-1-ol and then converting the alcohol to its bromide derivative.[3-4] However, this bromide had never been properly characterized. As modest alkylations of **58** and **63** continued, our electrophile's purity was questioned. Alternative routes to purer electrophile were consequently examined.

The first was envisioned by coupling **139**[5-6] with hexanal to produce ester **140**, which could undergo reduction to alcohol **141** and subsequent conversion to bromide **138** (Scheme 5.5). Despite clean formation of **139**, all coupling reactions with hexanal failed. Hence, attention was turned back to reducing 2-octyn-1-ol. After exploring several conditions, use of catalytic nickel

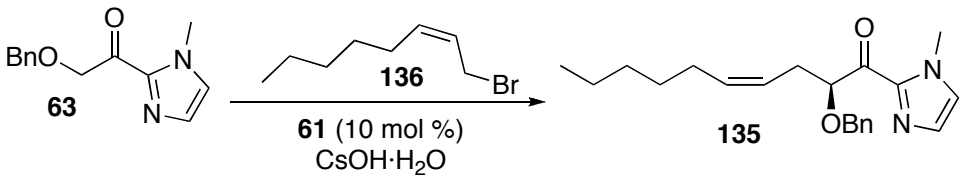
(II) acetate proved successful, providing pure **141** (no *E* isomer detected) in 85% yield.[7] This reaction had to be monitored by taking an aliquot from the reaction mixture in situ and analyzing it by ^{1}H NMR spectroscopy prior to quench and workup. Successful bromination of **141** was eventually achieved with PBr_3, providing spectroscopically pure **136** in 97% yield. Low vacuum was necessary when concentrating **136** and its precursors, due to their high volatility.



Scheme 5.5. Investigated routes to electrophile **136**.

5.3.2. Alkylation Screen

Initial alkylations of **63** with **136** were conducted without purification (Table 5.1). Instead, ee's were measured quickly by chiral HPLC after flushing the crude product through a short silica pad. Decreasing to 2.0 equivalents of electrophile caused unacceptably sluggish reactivity (entry 1), while 4.0 equivalents gave product in 65% ee (entry 2). Solvent screens showed modest improvement when a 2:1 mixture of dichloromethane/*n*-hexane was employed (entry 3). Decreased base equivalency also caused unacceptably slow reactivity (entry 4), while lowered temperature (-60 °C) provided **135** after 23 hours in 80% ee (entry 5).



entry	solvent/temperature	modifications	time (h)	ee (%)
1	CH_2Cl_2, -40 °C	2.0 equiv **136**	>48	--
2	CH_2Cl_2, -40 °C	4.0 equiv **136**	28	65
3	2:1 CH_2Cl_2/*n*-hex, -40 °C	4.0 equiv **136**	25	70
4	2:1 CH_2Cl_2/*n*-hex, -40 °C	2.0 equiv $CsOH·H_2O$ used	>48	--
5	2:1 CH_2Cl_2/*n*-hex, -60 °C	4.0 equiv $CsOH·H_2O$ used	23	80

Table 5.1. Condition screens in alkylating **63** with electrophile **136**.

Catalysts depicted in Figure 5.1 were used in a broad alkylation screen under now-optimized conditions, producing the data shown in Table 5.2. Novel catalyst **142**, developed from the fairly inexpensive 2,6-dimethylnaphthalene, only gave product with a 54% ee (entry 2). Commercial Maruoka catalysts **143** and **144** (added in 1 mol percent) resulted in excessive reaction times (entries 3-4). Catalyst **60** gave a complex mixture (entry 5), while **145** and **146** caused unacceptable reaction times (entries 6-7). Pleasingly, catalysts **36** and **147** produced ee's of 86-87% (entries 8-9). Furthermore, novel catalyst **148** furnished product with a superior 88% ee, which was reproducible on large scale.

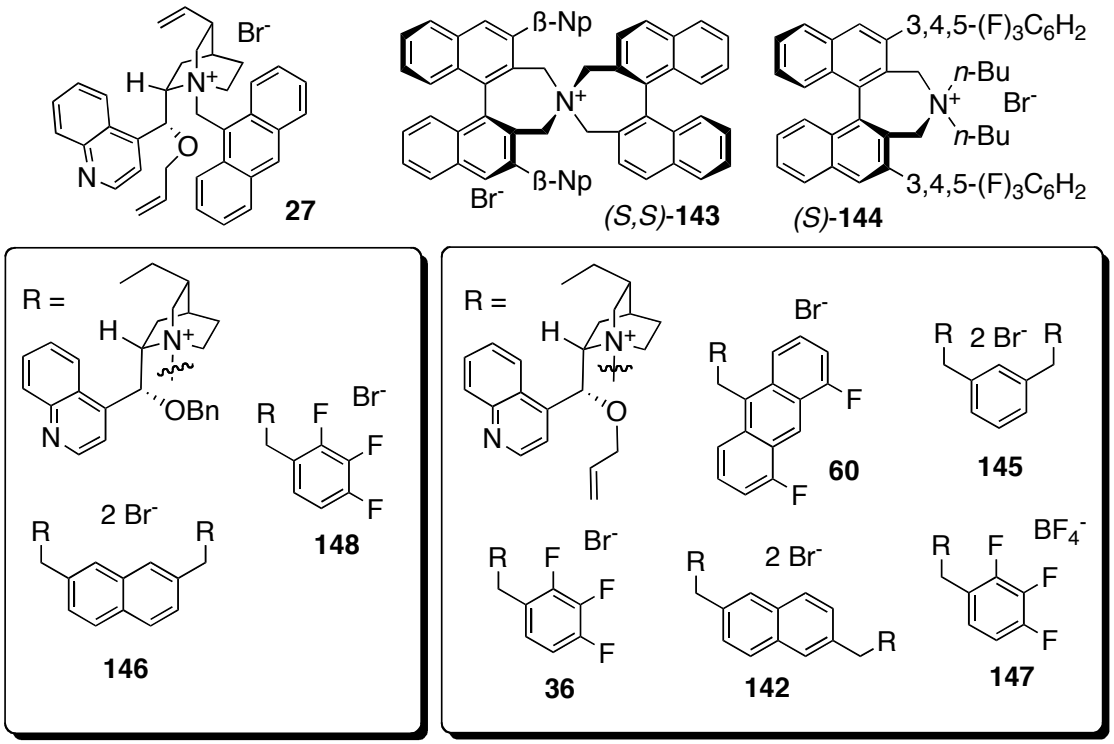
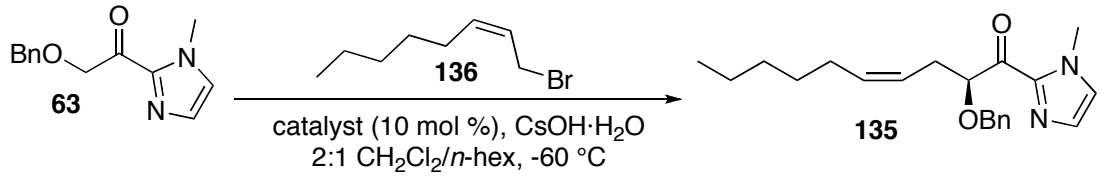


Figure 5.1. Catalysts used in Table 5.2.



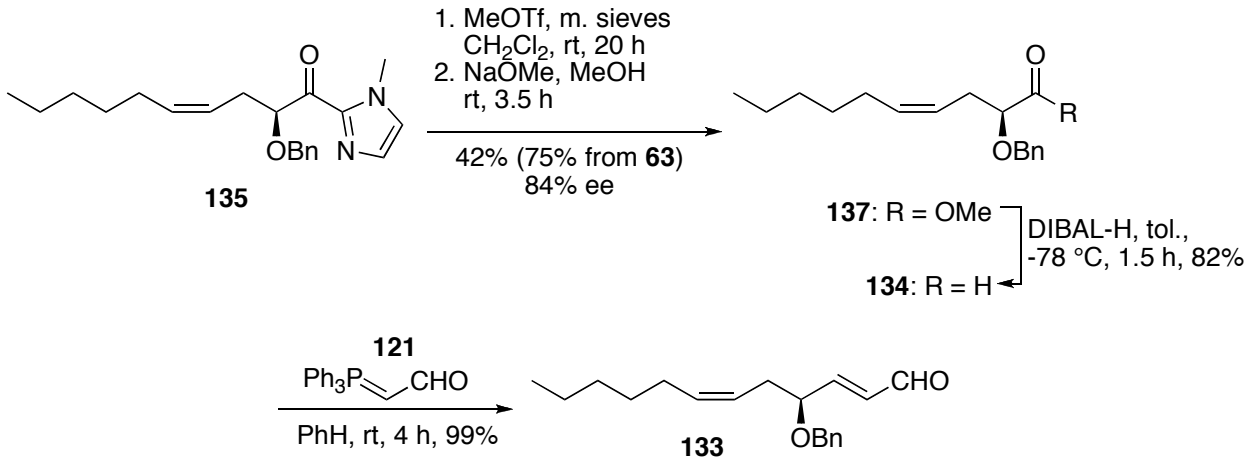
entry	catalyst	time (h)	ee (%)
1	**27**	>48	[a]--
2	**142**	25	54
3	**143** (1 mol%)	>48	[a]--
4	**144** (1 mol%)	>48	[a]--
5	**60**	16	complex mixture
6	**145**	>48	[a]--
7	**146**	>48	[a]--
8	**36**	23	86
9	**147**	18	87
10	**148**	22	88

[a]ee not measured

Table 5.2. Catalyst screen.

5.3.3. To Aldehyde 133

Product **135** was next reacted in crude form with methyl triflate and sodium methoxide/methanol to give **137** in 75% yield over two steps from **63** (Scheme 5.6). Slight epimerization was observed, with **137** being isolated in 84% ee. Conversion to aldehyde **134** proceeded smoothly in 82% yield by employing DIBAL-H at -78 °C,[8-13] and treatment with commercial reagent **121** in benzene gave α,β-unsaturated aldehyde **133** in 99% yield. With this key intermediate now in hand, attention turned to Wittig salt **123**.

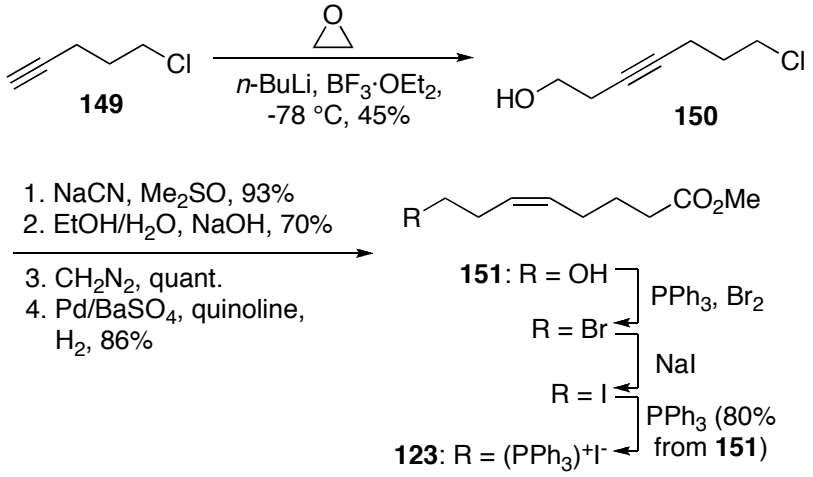


Scheme 5.6. Formation of α,β-unsaturated aldehyde **133** from **135**.

5.3.4. Making Wittig Salts 123 and 158

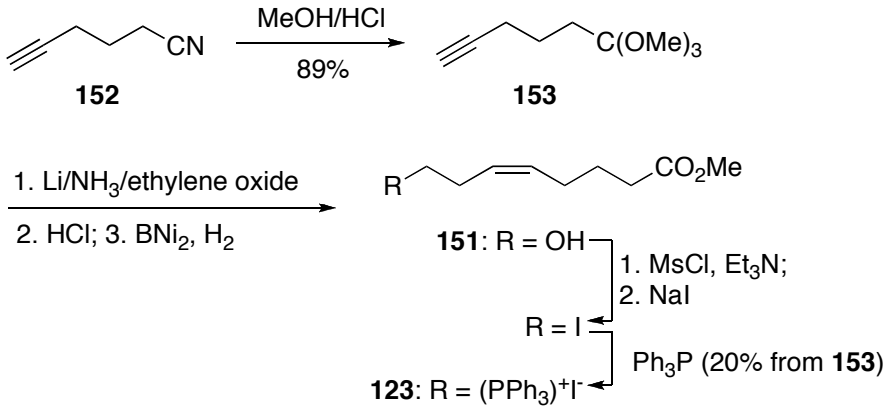
Three different routes to **123** are known. In their racemic synthesis of 12-HETE,[14] Gunn and Brooks began by lithiating chloropentyne **149** and adding ethylene oxide to access alcohol **150** (Scheme 5.7).[15] Nitrile substitution, acidification, and methyl esterification with diazomethane, followed by palladium-catalyzed reduction, then provided alcohol **151**.

Straightforward transformations continued thereafter to **123** in 20% yield over eight steps from **149**.



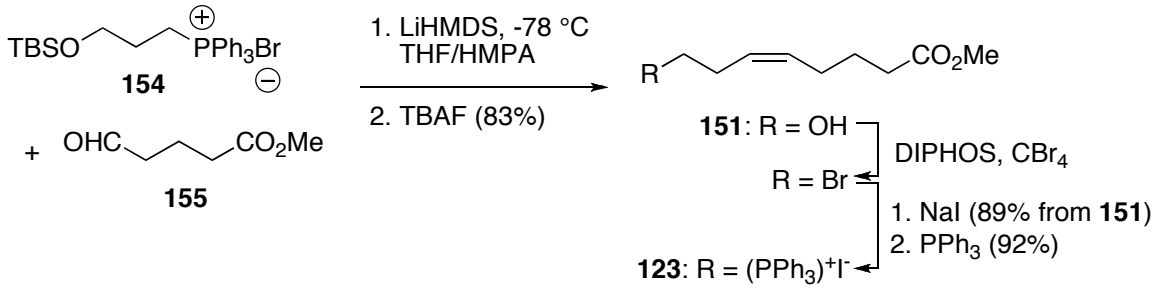
Scheme 5.7. Gunn synthesis of **123**.[14-15]

Just and coworkers, who published a synthesis of 12-*(S)*-HETE in 1986,[16] formed **123** by the same route used in Corey's 12-*(R)*-HETE synthesis.[2,17] This began by converting nitrile **152** to orthoester **153** in 89% yield. Lithiation and treatment with ethylene oxide,[18] followed by acidification and reduction, then gave alcohol **151**. Sequential manipulations thereafter provided **123** in 18% yield over six steps from **152**.



Scheme 5.8. Route to **123** used independently by Just and Corey.[16-18]

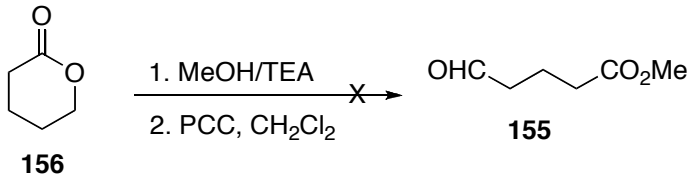
A more expeditious route to **123** by Rokach et al. began by employing LiHMDS to couple Wittig salt **154** (made quantitatively from 3-bromopropanol)[19] with aldehyde **155**. The crude product was then deprotected to provide alcohol **151**. Bromination, iodination, and reaction with triphenylphosphine then afforded **123** in 68% yield over seven steps from 3-bromopropanol.



Scheme 5.9. Rokach's route to **123**.[19]

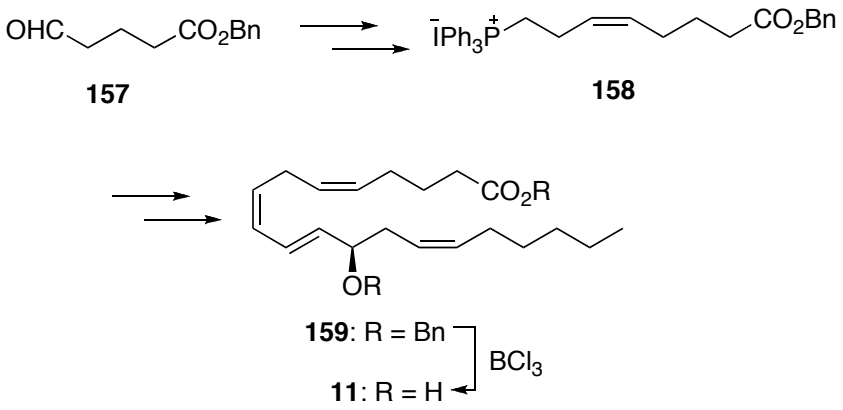
Incomplete experimental details made these procedures all potentially challenging. It was eventually opted to follow Rokach's route, however, since it gave product in higher yield and included the greatest amount of procedural information.

We followed Rokash's conditions to seamlessly obtain compound **154** in quantitative yield from 3-bromopropanol.[20-21] However, attempts to prepare **155** from δ-valerolactone **156** gave product that was heavily contaminated by an unidentified aromatic compound.[22-23] Purification by chromatography and distillation failed.



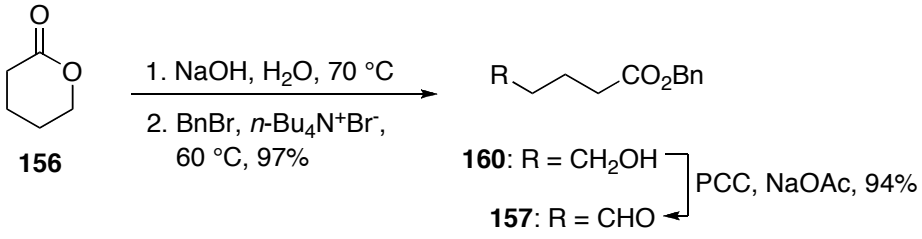
Scheme 5.10. Attempted formation of **155** from **156**.[22-23]

An alternative approach was envisioned in which benzyl ester **157** could serve as a surrogate for **155** (Scheme 5.11). Compound **157** is UV-active, a desirable property that would enable easier chromatographic purification and monitoring of reaction progress via TLC. One potential synthetic advantage of **158** over **123** would be the possibility of doubly deprotecting intermediate **159** with boron trichloride in a *single* step, instead of the two steps required by synthon **138**.



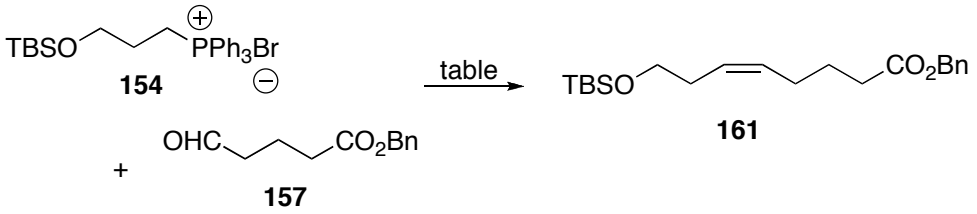
Scheme 5.11. Envisioned formation of **158** en route to 12-*(S)*-HETE **11**.

According to plan, **156** was converted smoothly to alcohol **160** in 97% yield.[23] As anticipated, compound **160** was UV-active and easily purified by column chromatography. Oxidation with PCC then provided **157** cleanly after column purification.



Scheme 5.12. Preparation of **157** from **156**.

As Table 5.3 illustrates, coupling screens proved lithium and sodium hexamethyl-disilazides ineffective at producing **161** (entries 1-2). These only gave dark mixtures of unidentifiable byproducts. Screens with *n*-butyllithium and sodium hydride gave modest yields initially (entries 3-4), but *n*-butyllithium's performance improved as temperatures were varied (entries 5-7), ultimately providing **161** in 97% yield. As with compounds **136** and **141** above, concentration of **161** had to be done cautiously under low vacuum to prevent product loss.

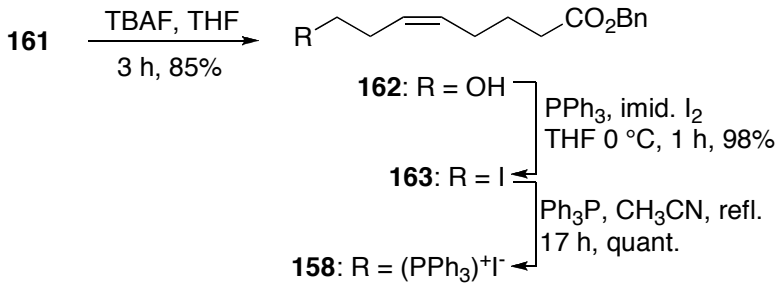


entry	conditions	yield (%)
1	LiHMDS, THF, HMPA, -78 °C	--
2	NaHMDS, THF, HMPA, -78 °C	--
3	n-BuLi, THF, -30 °C	7.7
4	NaH, THF, RT	11
5	n-BuLi, THF, -90 °C	22
6	n-BuLi, THF, RT	50
7	[a]n-BuLi, THF, -30 °C	97

[a]Low vaccum used during concentration

Table 5.3. Condition screen in forming **161**.

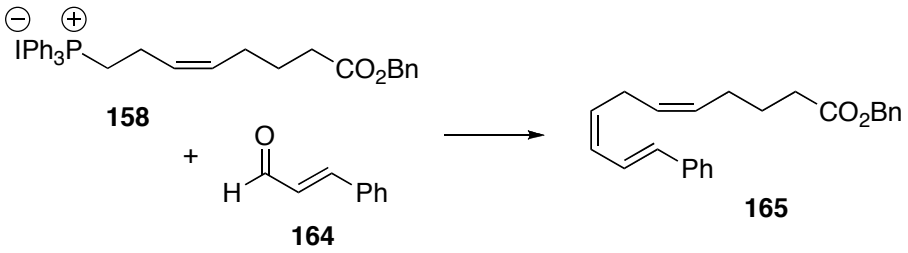
Deprotection of **161** unveiled alcohol **162** in 85% yield (Scheme 5.13). Direct conversion to iodide **163** was then facilitated through use of triphenylphosphine, imidazole, and iodine (98% yield), and overnight treatment with triphenylphosphine in refluxing acetonitrile gave **158** quantitatively as desired. As anticipated, each of these intermediates was UV-active, which facilitated chromatographic purification. Once optimized, this route provided **158** efficiently from δ-valerolactone (**156**) in 74% yield over six steps.



Scheme 5.13. Formation of **158** from **161**.

5.3.5. Coupling with Aldehyde 133

Initial couplings of Wittig salt **158** with aldehyde **133** gave product **159** in only 19% yield. To conserve precious **133**, cinnamaldehyde **164** was used as a test substrate to optimize conditions (Table 5.4). When a first trial gave no product (entry 1), **158** was purified by column chromatography in 5% MeOH/CH_2Cl_2. This salt, isolated as a dark yellow syrup, was found to



entry	conditions	yield (%)
1	[a]n-BuLi, m. sieves, THF -30 °C	--
2	KHMDS, m. sieves, THF, HMPA, -30 °C	7
3	*t*-BuLi, m. sieves, THF, HMPA, -30 °C	35
4	*n*-BuLi, m. sieves, THF, HMPA, -30 °C	44
5	*n*-BuLi, m. sieves, THF, HMPA, -40 °C	33
6	*n*-BuLi, m. sieves, THF, HMPA, -78 °C	15
7	[b]MeLi, m. sieves, THF, HMPA, -78 °C	84

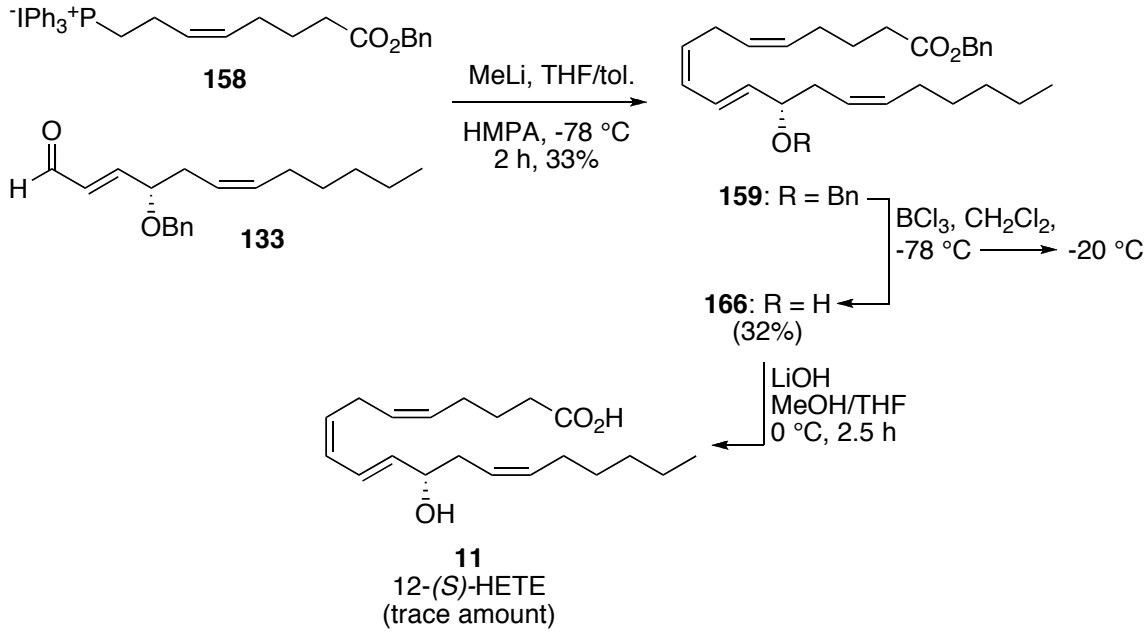
[a]**158** used without purification or P_2O_5 drying
[b]**158** used after purification and P_2O_5 drying

Table 5.4. Condition screen for coupling **158** with cinnamaldehyde (**164**).

be extremely water sensitive and only functioned well when subjected to overnight concentration in vacuo with phosphorous pentoxide (P_2O_5). In time, screening of the base revealed *n*-butyllithium's superiority (entries 2-4), though decreased temperature limited reactivity (entries 5-6). Vigorous drying by azeotropic distillation with THF/toluene, followed by in vacuo concentration overnight in the presence of P_2O_5, provided **158** in its driest form. Renewed reactivity with methyllithium then produced **165** cleanly in 85% yield.

5.3.6. Completing the Synthesis

Salt **158** was found to decompose slowly over time. Consequently, its ability to provide positive results gradually ceased, eventually necessitating preparation of a new batch. Once prepared and properly dried, fresh **158** was coupled with **133** (200 mg scale) under optimized conditions to furnish **159** (Scheme 5.14). Disappointingly, this proceeded with only a 33% yield after purification. Cleavage of both the benzyl ether and ester of **159** in a single step proved

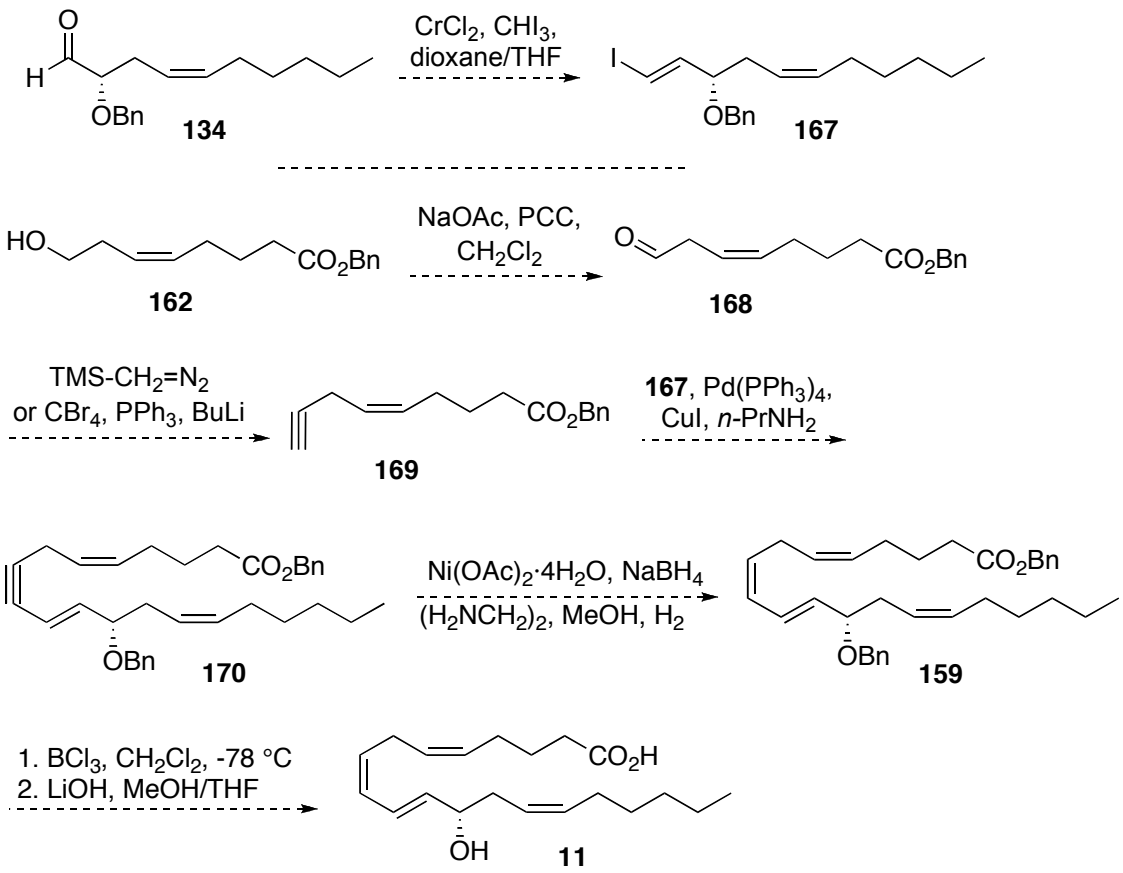


Scheme 5.14. Final steps to 12-*(S)*-HETE **11** from aldehyde **133**.

unsuccessful. Instead, treatment with boron trichloride at low temperature furnished intermediate **166**, in which only the benzyl ether was cleaved (32% yield). LiOH-mediated hydrolysis of the ester was then performed following Corey's procedure,[2] but the amount of compound **11** isolated was too small to characterize spectroscopically. We were able to detect product **11** in the crude reaction mixture by HRMS after quench and workup.

5.4. Second-Generation Synthesis

In light of the coupling failures with Wittig salt **158**, a second-generation synthesis of 12-*(S)*-HETE is currently in development. This is projected to unfold as Scheme 5.15 depicts, by converting aldehyde **134** (prepared as per Scheme 5.6) to vinyl iodide **167**.[24-25] Separate



Scheme 5.15. Second-Generation route to 12-*(S)*-HETE **11** currently underway.

oxidation of alcohol **162** (prepared as per Scheme 5.13) should yield aldehyde **168**. Treatment with TMS-diazomethane[26] or CBr_4, PPh_3 and *n*-butyllithium[27] should then provide terminal acetylene **169**. Sonagashira coupling with **167**, for which similar conditions were reported in a 12-*(S)*-HETE synthesis by Sato and coworkers,[28] should then produce intermediate **170**. Half reduction of the internal alkyne should proceed without disturbing the olefinic moieties,[28] giving compound **159**. Benzyl deprotection and hydrolysis should then give 12-*(S)*-HETE **11**, obtained over seven steps in the longest linear sequence from benzyl alcohol (the precursor to **134**).

5.5. References and Notes

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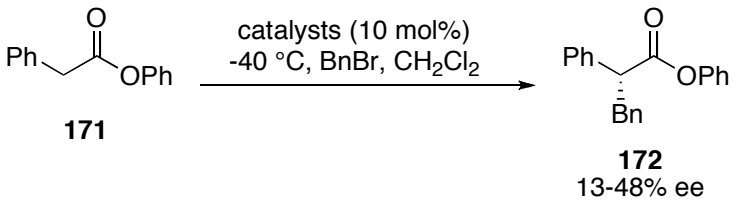
Chapter 6. Phase-Transfer Catalyzed Asymmetric Arylacetate Alkylation

6.1. PTC Alkylation of α-Aryl Esters

Attention turned next to the asymmetric PTC alkylation of esters lacking α-oxygenation, beginning with test substrate **171**, which was benzylated with various catalysts and a multitude of conditions (not shown) to provide **172** with modest enantioselectivities (Scheme 6.1).

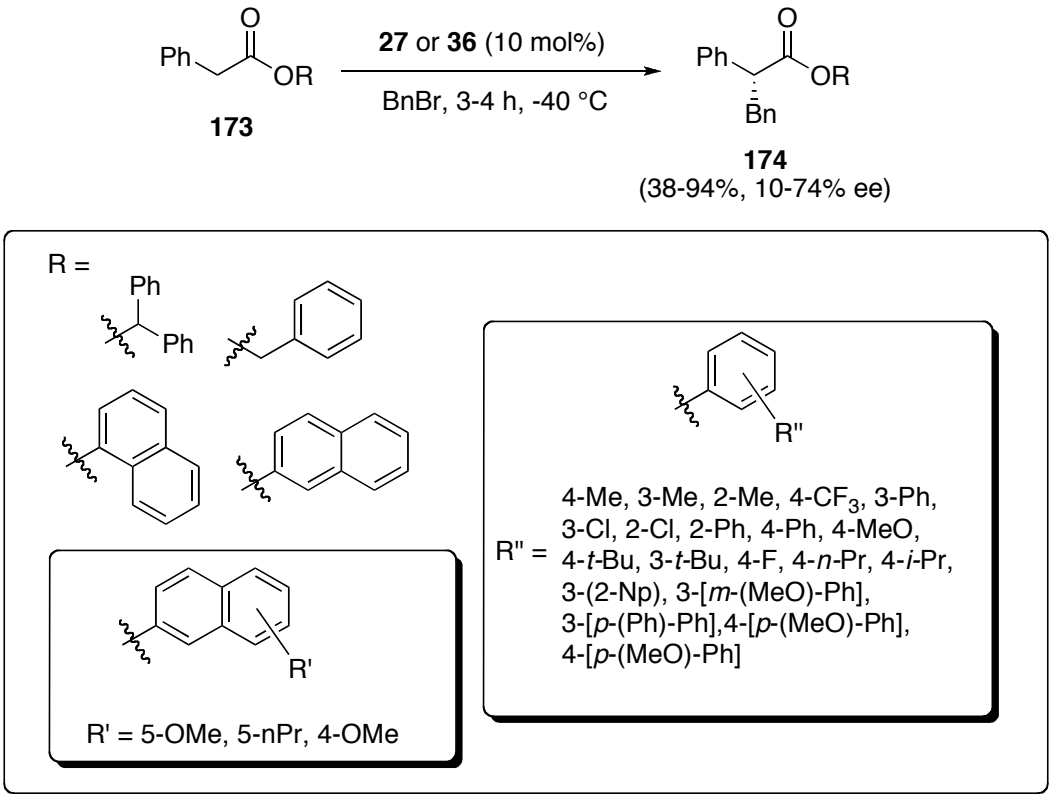


Scheme 6.1. Asymmetric PTC benzylations of **171**.

Ester variation was explored by preparing an extensive library of substrates **173** (Scheme 6.2, vide infra). These were asymmetrically benzylated under a vast array of conditions (not shown) with catalysts **27** and **36**. Dimer catalyst **61**, whose synthesis had not yet been optimized by this time, performed quite poorly with these substrates. The highest ee's obtained (60-74%) were not reproducible. Typical enantiomeric excesses ranged from 40–55%.

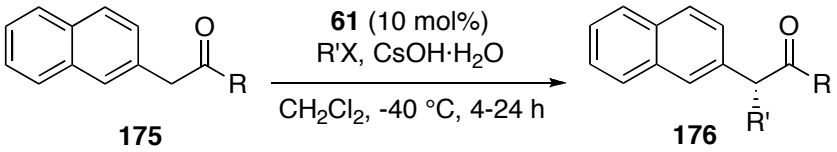
When the synthesis of catalyst **61** had finally been optimized, esters and ketones **175** (shown in Table 6.1 below) were explored in anticipation of a new methodology applicable to *(S)*-Naproxen **12**. Surprisingly, the *N*-methylimidazolyl variant gave no observable enantioselectivity (entry 1). Slight improvements were obtained with various aryl esters and amides (entries 2-5 and 7), though selectivities were still modest. The phenethyl variants, in

contrast, gave marked enhancement (entries 10-12), with the phenethyl ester featured in entry 10 providing **176** in near-quantitative yield.

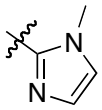
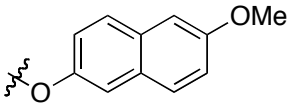
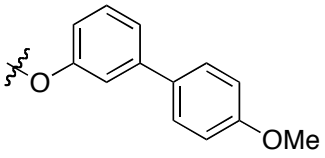
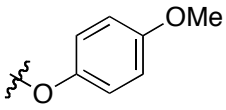
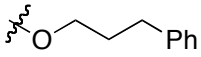
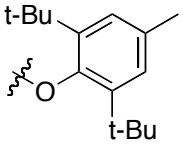
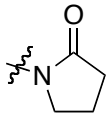
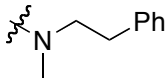
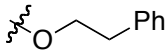
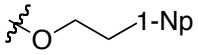
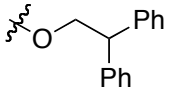


Scheme 6.2. Asymmetric PTC benzylation of esters **173**.

As Table 6.2 illustrates (*vide infra*), no selectivity enhancements were observed when various catalysts were screened in the allylation of phenethyl ester **177**. Not surprisingly, higher temperature decreased reaction time (entry 5), while lower temperature had the opposite effect (entry 6); however, enantioselectivity remained a modest 56% ee at best.

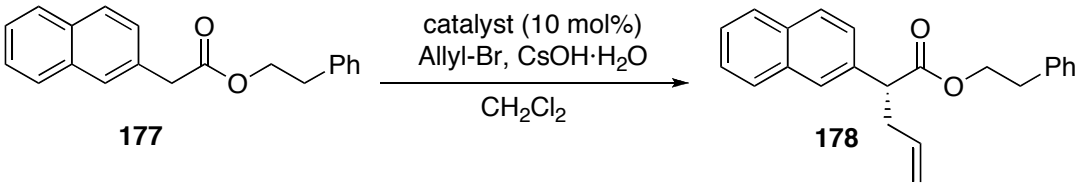


175 **176**

entry	R	R'X	yield (%)	ee (%)
[a]1		BnBr	73	0
2		BnBr	83	8
3		BnBr	67	4
4		BnBr	86	0
5	-O-PMB	BnBr	98	24
6		allyl-Br	67	28
7		allyl-Br	54	8
8		allyl-Br	48	8
9		allyl-Br	92	34
10		allyl-Br	99	56
11		allyl-Br	78	59
12		allyl-Br	78	54

[a]6-MeO-naphthyl acetate used as substrate

Table 6.1. Alkylation screen of β-naphthyl esters and ketones **175**.



177 **178**

entry	catalyst	temp (°C)	time (h)	yield (%)	ee (%)
1	**61**	-40	8	99	56
2	**36**	-40	8	72	48
3	**143** (1 mol%)	-40	8	81	44
4	**144** (1 mol%)	-40	8	52	46
5	**61**	-20	4	84	22
6	**61**	-60	50	76	49

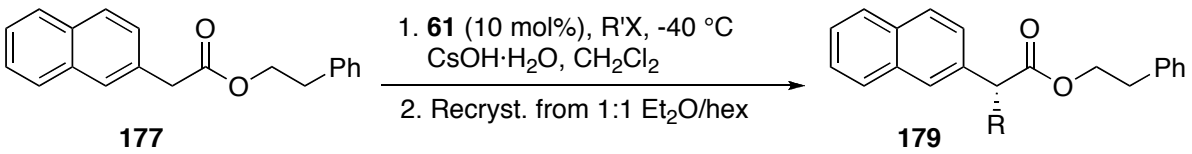
Table 6.2. Catalyst allylation screen with substrate **177**.

As additional attempts at optimization continued to give modest improvements, abandonment of the project was considered. However, it was fortuitously discovered that product **178** could be recrystallized overnight from 1:1 ether/hexanes to produce an enantio-enriched product. This gave pure **178** in 63% yield and 93% ee, all without any chromatographic purification.

This technique was successfully applied to alkylations with other electrophiles, generating enantio-enriched products **179** (Table 6.3). Thus a new route to asymmetrically α-alkylated naphthyl acetates had been devised.

6.2. PTC Alkylation of 6-Methoxynaphthyl Acyl Esters

While engaged in this research we discovered a recent report by Kumar and Ramachandran[1] that featured the asymmetric methylation of *tert*-butyl ester **180**, catalyzed by cinchonine catalyst **181** (Scheme 6.3, vide infra). This technique generated product **182** in 74%



177 179

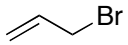
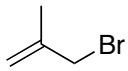
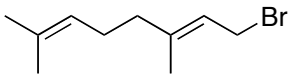
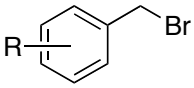
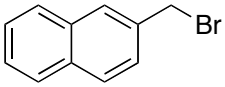
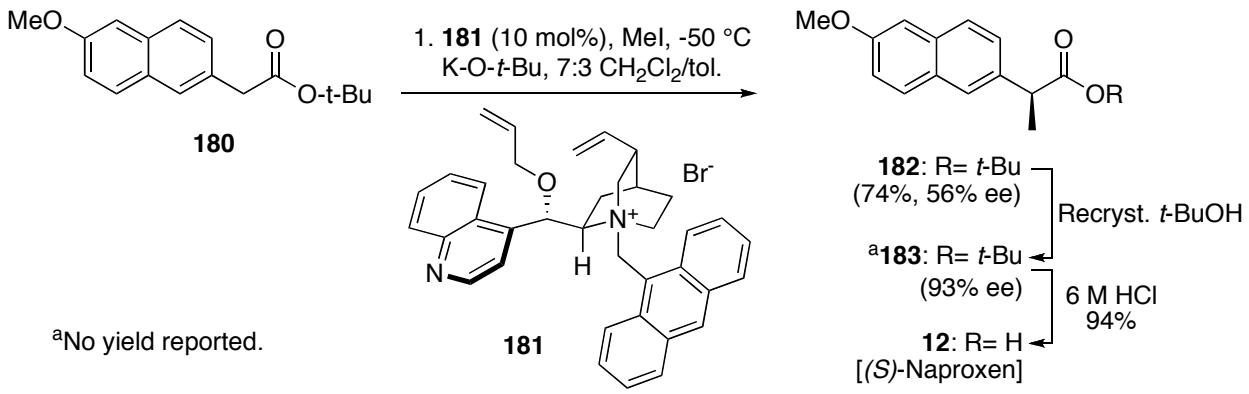
entry	R'X	time (h)	crude ee (%)	after recrystallization yield (%)	ee (%)
1		8	56	63	93
2		26	57	68	86
3		28	59	68	70
4	 R = 4-Br	28	48	67	97
5	R = 4-t-Bu	23	71	72	99
6	R = 2-Ph	28	89	81	92
7		27	63	73	94
8	MeI	18	55	71	92

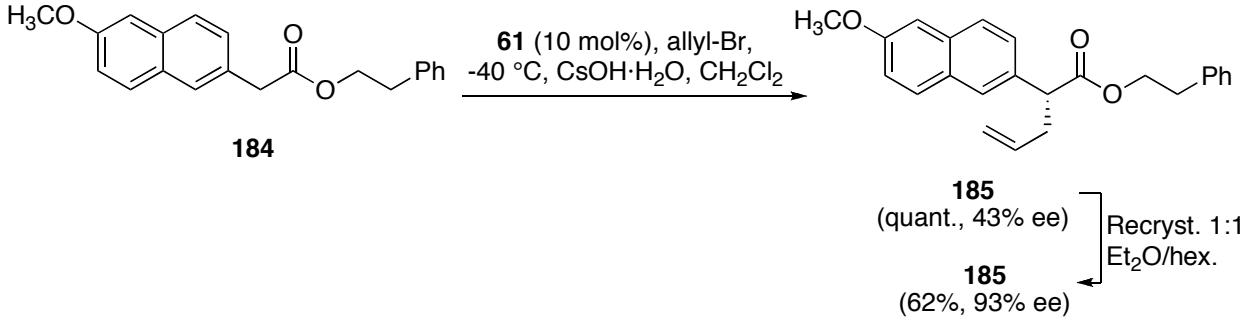
Table 6.3. PTC alkylations of **177** and enantio-enriching kinetic resolutions of **179**.

yield and 56% ee. Recrystallization from *tert*-butyl alcohol then gave enantioenriched **183** in 93% ee, though no isolated yield was reported. Hydrolysis then provided *(S)*-Naproxen **12** in 94% yield.

For the sake of comparison, substrate **180** was prepared by our group and treated with catalyst **61** and methyl iodide under our conditions. Surprisingly, no measurable product was formed, even after 48 hours. 2-Phenethyl ester **184**, by comparison, underwent complete allylation after only 18 hours with catalyst **61** (Scheme 6.4). (Methylation was not attempted.) This quantitatively provided **185** in 43% ee. Recrystallization from 1:1 ether/hexanes then furnished enantioenriched product in 93% ee and 62% yield.



Scheme 6.3. Kumar and Ramachandran's synthesis of *(S)*-Naproxen (**12**).[1]



Scheme 6.4. Allylation of **184** and enantio-enriching recrystallization of **185**.

6.3. Total Synthesis of *(S)*-Naproxen

Absolute configurations of products thus far were presumed to be *R* based on previous alkylations with cinchonidine catalysts. This was corroborated by Ramachandran's production of *S*-product **182** using complimentary cinchonine catalyst **181**. A total synthesis of *(S)*-Naproxen from **184** was therefore reasoned to similarly require a cinchonine catalyst. Consequently, novel bis-cinchoninium catalyst **186** was prepared (Figure 6.1).

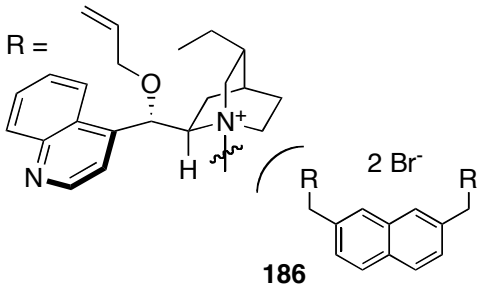
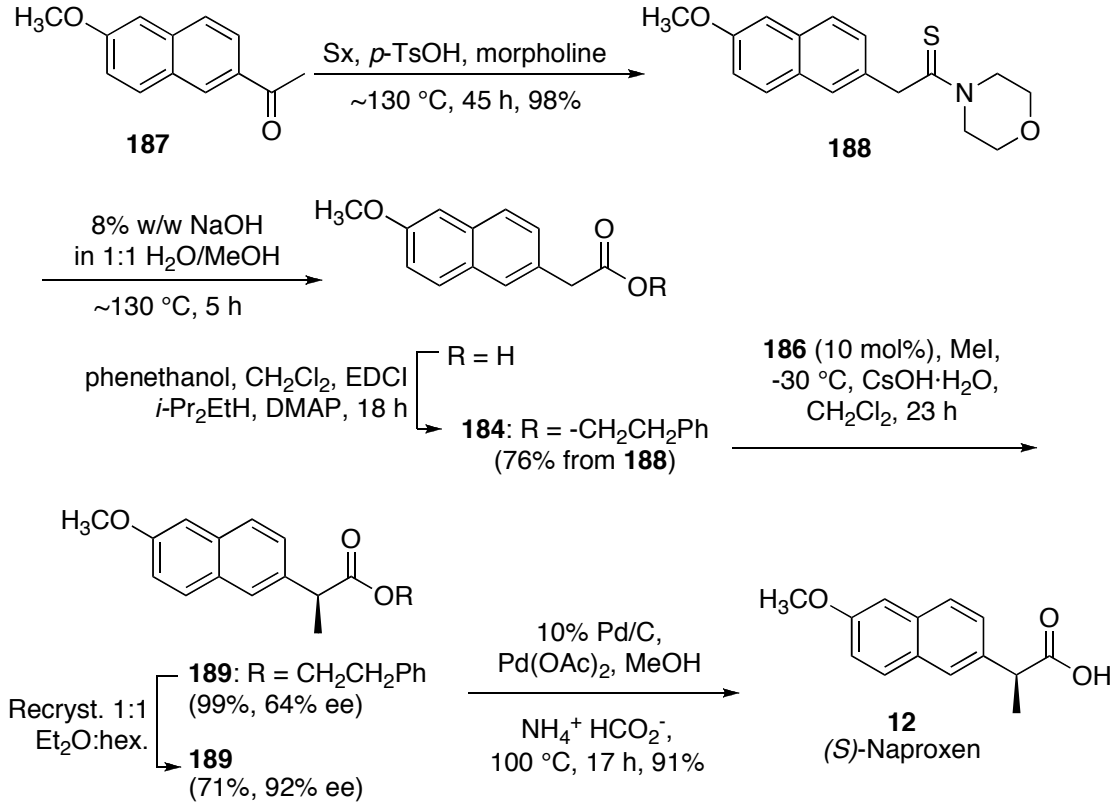


Figure 6.1. Cn catalyst **186**.

The total synthesis began with Willgerodt-Kindler[2] conversion of acetyl naphthalene **187** to morpholine thioamide **188** in 98% yield (Scheme 6.5). Hydrolysis and EDCI coupling with phenethanol then gave ester **184** in 76% yield. PTC methylation of **184** with catalyst **186** proceeded smoothly at -30 °C to give **189** in 71% yield and 92% ee after recrystallization from



Scheme 6.5. Total synthesis of *(S)*-Naproxen **12** from **187**.[3-4]

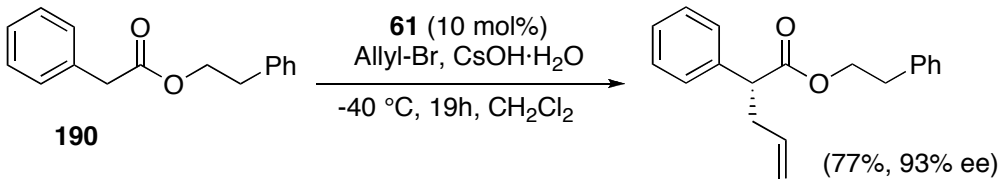
1:1 ether/hexanes. This intermediate's optical rotation and HPLC data matched those of a separate sample of **187** made from commercial *(S)*-Naproxen, thereby confirming its absolute configuration as *S*.[3-4]

Hydrolysis was facilitated smoothly in 91% yield with non-epimerizing conditions reported by Carpino and Tunga.[5] Our synthetic **12** matched a commercial sample by HRMS, NMR spectroscopy, and optical rotation. This new method furnished *(S)*-Naproxen in 48% yield over six steps from 6-methoxy-2-naphthalene **187**.

The elegance of this approach lies in the fact that only two intermediates (**184** and **188**) require chromatographic purification, and the key step generates **189** in 71% yield and 92% ee with no requisite chromatography. This is potentially advantageous over traditional routes to *(S)*-Naproxen that necessitate costly chiral resolutions and recycling of racemates[6-9] or chiral auxiliaries that have to be recovered.[10-12]

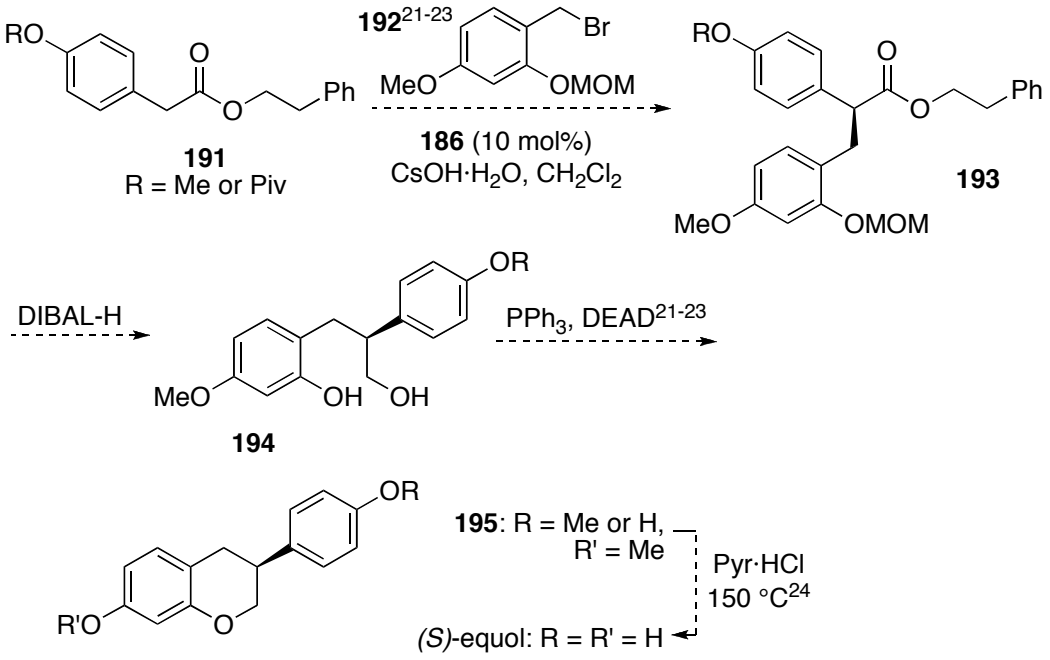
6.4. Asymmetric PTC Alkylation of Phenyl Phenylacetates

As the arylacetate alkylation methodology progressed, a single allylation of substrate **190** was found to give product in 77% yield and 93% ee without any enantio-enriching recrystallization (Scheme 6.6).[3]



Scheme 6.6. PTC allylation of substrate **190**.[3]

This finding might be logically extended to 4-oxygenated derivatives of type **191** in an anticipated route to the isoflavanoid *S*-equol (Scheme 6.7).[13-20] Synthetically, PTC alkylation of **191** with electrophile **192**[21-23] would be anticipated to generate product **193**. The requisite *S*-configuration would be expected through use of cinchonine catalyst **186**. Reduction of **193** would then give diol **194** with concomitant pivalate removal, and ring-closing Mitsunobu chemistry could provide **195**.[21-23] Di-demethylation of **195** would then unveil the final target over four steps from **191**. Work toward this end is currently underway.



Scheme 6.7. Planned total synthesis of the isoflavonoid *(S)*-equol.

6.5. References and Notes

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Chapter 7. Experimental Details and Data

7.1. General Methods and Materials

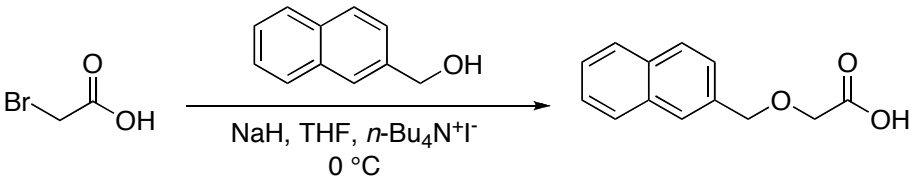
Air and water sensitive reactions were performed in flame-dried glassware under nitrogen atmosphere. Air and moisture sensitive reagents were introduced via dry syringe or cannula. THF, methylene chloride, acetonitrile, DMF, triethylamine, DMSO, benzene, methanol, toluene, and diethyl ether were drawn from a pressurized dry solvent system, which maintains solvent dryness by flushing HPLC (or comparable) grade solvents through activated alumina casks stored under argon. (Freshly distilled solvents would serve as adequate substitutes.) HPLC grade chloroform, ethanol, and hexanes were dried over 4 Å molecular sieves before use. Flash chromatography was carried out using 230 x 400 mesh silica gel purchased from Sorbent Technologies (catalog #30930M). Analytical thin-layer chromatography (TLC) was performed with silica gel 60 F_{254}, 0.255 mm pre-coated TLC plates, purchased from Merck. TLC plates were visualized using UV_{254} and a cerium molybdate stain with charring (see procedure below). All ^{1}H NMR spectra were obtained with 300 or 500 MHz Varian spectrometers using TMS (0.0 ppm) or chloroform (7.27 ppm) as an internal reference. Signals are reported as m (multiplet), s (singlet), d (doublet), t (triplet), q (quartet), bs (broad singlet), dd (doublet of doublets), or dq (doublet of quartets); the coupling constants are reported in hertz (Hz). ^{13}C NMR spectra (75 or 125 MHz) were acquired with chloroform (77.2 ppm) as the internal standard. Mass spectral data (HRMS) were obtained using an Agilent multi-mode source mass spectrometer. Optical rotations were acquired with a Bellingham and Stanley Limited ADP220 polarimeter using the sodium D line at ambient temperature. Low temperatures were maintained using a Neslab CC100 immersion cooler with a cooling probe placed in an acetone bath.

7.2. Cerium Molybdate Stain

A solution of cerium molybdate stain was prepared by dissolving 0.5 g ceric ammonium nitrate, 24 g ammonium molybdate tetrahydrate, and 28 mL concentrated sulfuric acid in 500 mL distilled water, stirred for three hours at room temperature to form a clear, yellow solution. TLC plates, once developed, were dipped in this solution and then charred, glass side down, on a hot plate, until spot visualization occurred.

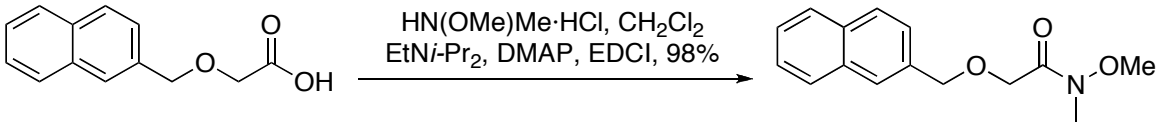
7.3. Procedures from Chapter 3

7.3.1. Acyl Imidazole Substrate Preparations



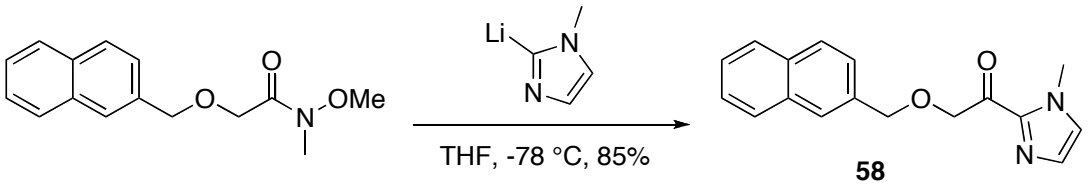
2-(naphthalen-2-ylmethoxy) acetic acid. To a flame-dried 100 mL round bottom flask (flask A) was added bromoacetic acid (2.054 g, 1.0 equiv) and THF (42 mL, 0.35 M). Sodium hydride (886 mg, 2.5 equiv) was then added carefully. This suspension was stirred at room temperature until hydrogen gas stopped evolving, monitored by attaching an outlet tube from the flask to a bubbler. Once this occurred, flask A was cooled to 0 °C. To a separate flask 100 mL round bottom flask (flask B) was added naphthalene methanol (1.59 g, 0.68 equiv) and THF (42 mL, 0.35 M). This was also cooled to 0 °C. The contents of flask B were then added to flask A at 0 °C, and the combined solution was warmed to room temperature with vigorous stirring. *n*-tetrabutyl ammonium iodide (55 mg, 0.05 equiv) was then added, and the resulting mixture was

fitted with a water condenser and brought to reflux, which continued with vigorous stirring for 4 hours. The reaction flask was then cooled to 0 °C and ethanol (10 mL) was added. This crude mixture was concentrated by rotary evaporator, and the solid material was diluted with ethyl ether (40 mL) and was extracted with saturated aqueous sodium bicarbonate (3 x 50 mL). The aqueous layer was then carefully acidified to pH 2 with 1 N aqueous HCl, and was extracted with CH_2Cl_2 (5 x 50 mL). The acid product was then dried over magnesium sulfate, filtered, and concentrated in vacuo to give an off-white solid, isolated in a quantitative yield of the crude product (2.44 g).



***N*-methoxy-*N*-methyl-2-(naphthalen-2-ylmethoxy)acetamide.** To a flame-dried 50 mL round-bottom flask, 2-(naphthalen-2-ylmethoxy) acetic acid (2.24 g, 10.34 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (41 mL) and cooled, while stirring, to 0 °C under N_2. To this were added *N,O*-dimethylhydroxylamine hydrochloride (1.51 g, 97.55 mmol, 1.5 equiv), 4-(dimethylamino)pyridine (316 mg, 122.17 mmol, 0.25 equiv), diisopropylethylamine (2.88 mL, 129.25 mmol, 16.5 equiv), and *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDCI, 1.982 g, 191.71 mmol, 10.34 equiv). This mixture was then stired, warming gradually overnight to room temperature, for 25 hours. The reaction was then quenched by adding H_2O (50 mL) and $CHCl_3$ (50 mL). The layers were separated, and the aqueous layer was extracted with $CHCl_3$ (3 x 50 mL). The combined organic layers were then washed sequentially with 3M aqueous H_3PO_4 (1 x 10 mL), saturated aqueous $NaHCO_3$ (1 x 10 mL), and brine (1 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated by rotary

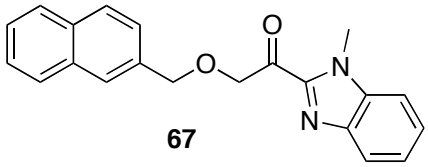
evaporator. The crude product was isolated without purification as an off-white solid (2.63 g, 98% yield). Data are: TLC R_f= 0.55 (50% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.84-7.83 (m, 4H), 7.55 (d, *J* = 4. 2 Hz, 1H), 7.48-7.45 (m, 2H), 4.84 (s, 2H), 4.33 (s, 2H), 4.56 (s, 3H), 3.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.4, 133.5, 133.3, 128.5, 128.2, 128.0, 127.1, 126.4, 126.2, 73.5, 67.4, 61.6.



58

1-(1-methyl-1H-imidazol-2-yl)-2-(naphthalen-2-ylmethoxy) ethanone (58). To a flame-dried 25 mL round-bottom flask (flask A), *N*-methylimidazole (1.08 mL, 13.57 mmol) was dissolved in THF (4.0 mL). This was cooled, while stirring, to 0 °C. *n*-butyl lithium (1.6 M in hexanes) was then added dropwise (8.15 mL), and the resulting orange solution was stirred at 0 °C for 1 hour. As flask A neared one hour of stirring, 1-morpholino-2-(naphthalen-2-ylmethoxy) ethanone (1.55 g, 5.43 mmol) was dissolved in THF (5.43 mL) in a separate, flame-dried 25 mL pear-shaped flask (flask B), cooled to -78 °C. Once flask A had stirred for 1 hour, it was also cooled to -78 °C and was added to flask B by cannula, giving a dark-green solution. This combined solution was then warmed to -40 °C and stirred for 1 hour, during which time it warmed further to -15 °C. The reaction was quenched by the addition of a 1 N aqueous HCl (20 mL), stirred for 5 minutes, and then diluted with a saturated solution of aqueous NaCl (10 mL) and saturated aqueous sodium bicarbonate (10 mL). This suspension was then transferred to a separatory funnel and was extracted with EtOAc (3 x 50 mL) and CH_2Cl_2 (1 x 50 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by rotary

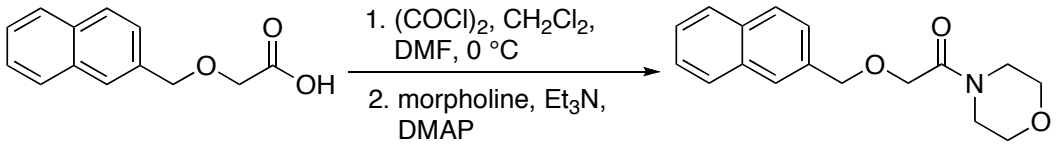
evaporator. The crude product was then purified by column chromatography in 50% EtOAc/hexanes to afford 1.29 g (85%) of the desired compound as an off-white solid. Data are: TLC R_f= 0.35 (50% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.84-7.80 (m, 4H), 7.54 (d, *J* = 2.5 Hz, 1H), 7.45-7.43 (m, 2H), 7.04 (s, 1H), 6.95 (s, 1H), 4.98 (s, 2H), 4.85 (s, 2H), 3.93, (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 188.3, 141.2, 135.3, 133.5, 133.3, 129.5, 129.2, 128.5, 128.2, 127.9, 127.2, 127.1, 126.3, 126.2, 72.8, 72.4, 36.0; HRMS found 281.1285 $[M+H]^+$, calcd 280.1212 for $C_{17}H_{16}N_2O_2^+$.



67

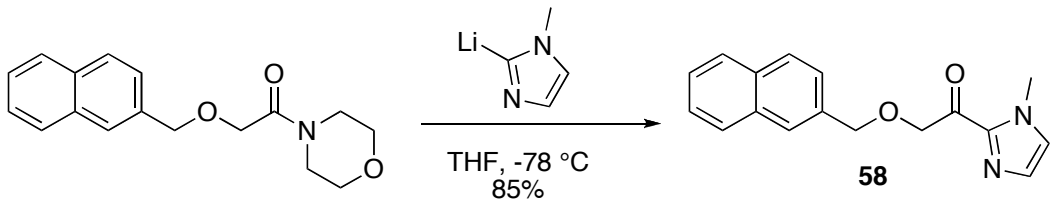
1-(1-methyl-1*H*-benzo[d]imidazol-2-yl)-2-(naphthalen-2-ylmethoxy)ethanone (67). Following the same technique used described for **58**, where *N*-methylbenzimidazole was used in place of *N*-methylimidazole, **67** was obtained in 71% yield (455 mg) as an off-white solid. Data are: TLC R_f= 0.80 (50% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.86-7.82 (m, 4H), 7.59 (d, *J* = 4.2 Hz, 1H), 7.47-7.29 (m, 6H), 5.18 (s, 2H), 4.90 (s, 2H), 4.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.2, 144.1, 141.8, 136.8, 135.2, 133.5, 133.4, 128.6, 128.2, 128.0, 127.1, 126.4, 126.3, 126.2, 126.2, 124.2, 122.0, 110.8, 73.8, 73.2, 32.2; HRMS found 330.1368 $[M]^+$, calcd 330.1368 for $C_{21}H_{18}N_2O_2^+$.

7.3.2. Alternative Route to Acyl Imidazole Substrates (EDCI-Free)



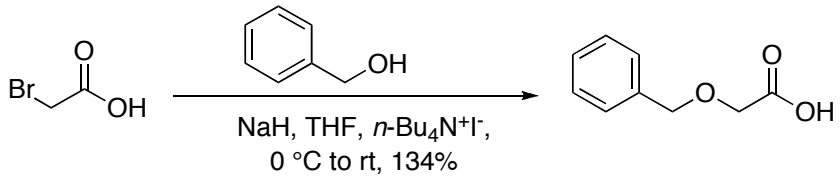
1-morpholino-2-(naphthalen-2-ylmethoxy) ethanone. To a flame-dried 50 mL round bottom flask was added 2-(naphthalen-2-ylmethoxy) acetic acid (1.53g, 7.08 mmol) and CH_2Cl_2 (14.15 mL). This solution was cooled with stirring to 0 °C. Oxalyl chloride (1.54 mL, 17.69 mmol) was then added, with vigorous stirring. This was followed by careful addition of 3 drops of DMF, added very slowly to avoid uncontrolled bubbling over. This mixture was then stirred at 0 °C, warming to room temperature overnight, for 18.5 hours. Benzene (14.15 mL) was then added, and the solvent was evaporated off using a rotary evaporator. More benzene (14.15 mL) was then added and then evaporated off once again rotary evaporator. This addition of benzene, followed by its removal via evaporation, was repeated one more time to remove excess oxalyl chloride. More CH_2Cl_2 (14.15 mL) was then introduced, and the solution was cooled with stirring once again to 0 °C. Triethyl amine (2.96 mL), morpholine (1.85 mL, 21.23 mmol), and dimethylamino pyridine (0.86 g, 0.71 mmol) were then added, whereupon the reaction was stirred for 6.5 hours. The reaction was then quenched by addition of a 1N aqueous HCl (20 mL) and added to a separatory funnel. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL), dried over $MgSO_4$, filtered, and purified by column chromatography (100% EtOAc) to afford 1.55 g (77%) of the desired compound as a yellow oil. Data are: TLC R_f= 0.4 (2 x 50% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.87-7.80 (m, 4 H), 7.51-7.48 (m, 3H), 4.77 (s, 2H), 4.21 (s, 2H), 3.65-3.60 (m, 6H), 3.47-3.45 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.0,

134.9, 133.5, 133.4, 128.6, 128.2, 127.1, 127.20, 126.5, 126.4, 126.1, 73.6, 69.5, 67.0, 45.8, 42.34; HRMS found 286.1438 $[M+H]^+$, calcd 286.1438 for $C_{17}H_{20}NO_3^+$.



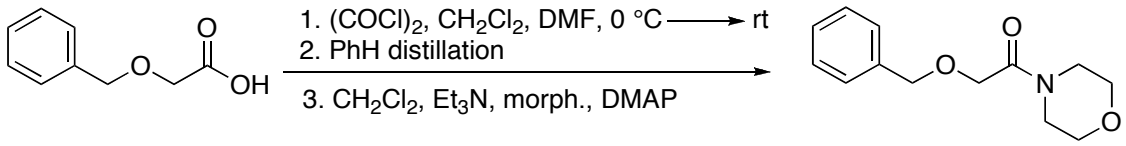
1-(1-methyl-1*H*-imidazol-2-yl)-2-(naphthalen-2-ylmethoxy) ethanone (58). To a flame-dried 25 mL round-bottom flask (flask A), *N*-methylimidazole (1.08 mL, 13.57 mmol) was dissolved in THF (4.0 mL). This was cooled, while stirring, to 0 °C. *n*-butyl lithium (1.6 M in hexanes) was then added dropwise (8.15 mL), and the resulting orange solution was stirred at 0 °C for 1 hour. As flask A neared one hour of stirring, 1-morpholino-2-(naphthalen-2-ylmethoxy) ethanone (1.55 g, 5.43 mmol) was dissolved in THF (5.43 mL) in a separate, flame-dried 25 mL pear-shaped flask (flask B), cooled to -78 °C. Once flask A had stirred for 1 hour, it was also cooled to -78 °C and was added to flask B by cannula, giving a dark-green solution. This combined solution was then warmed to -40 °C and stirred for 1 hour, during which time it warmed further to -15 °C. The reaction was quenched by the addition of a 1 N aqueous HCl (20 mL), stirred for 5 minutes, and then diluted with a saturated solution of aqueous NaCl (10 mL) and saturated aqueous sodium bicarbonate (10 mL). This suspension was then transferred to a separatory funnel and was extracted with EtOAc (3 x 50 mL) and CH_2Cl_2 (1 x 50 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by rotary evaporator. The crude product was then purified by column chromatography in 50% EtOAc/hexanes to afford 1.29 g (85%, 73% from naphthalene methanol) of the desired compound as an off-white solid. Substrates shown from table 1 (where Ar = *N*-

methylbenzimidazole, *N*-phenylimidazole, and *N*-benzylimidazole) were prepared in the same manner, substituting the parent heterocycles for *N*-methylimidazole as shown in this procedure. Data are: TLC R_f= 0.35 (50% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.84-7.80 (m, 4H), 7.54 (d, *J* = 2.5 Hz, 1H), 7.45-7.43 (m, 2H), 7.04 (s, 1H), 6.95 (s, 1H), 4.98 (s, 2H), 4.85 (s, 2H), 3.93, (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 188.3, 141.2, 135.3, 133.5, 133.3, 129.5, 129.2, 128.5, 128.2, 127.9, 127.2, 127.1, 126.3, 126.2, 72.8, 72.4, 36.0; HRMS found 281.1285 $[M+H]^+$, calcd 280.1212 for $C_{17}H_{16}N_2O_2^+$.



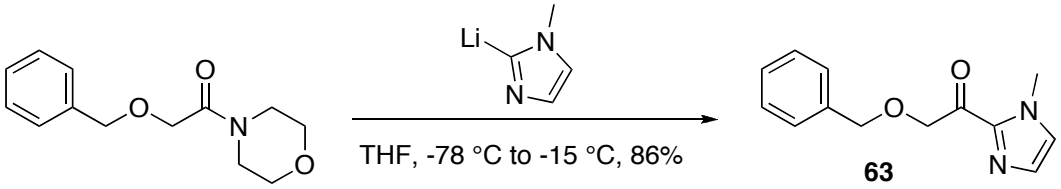
2-(benzyloxy)acetic acid. Bromoacetic acid (18.89 g, 135.93 mmol, 1.0 equiv) was dissolved in THF (387 mL, 0.239 M with respect to the alcohol) in a flame-dried 1000 mL round bottom flask with a stir bar (flask A). Sodium hydride (8.167 g, 340.28 mmol, 3.68 equiv) was then added carefully. This suspension was stirred at room temperature until hydrogen gas stopped evolving, monitored by attaching an outlet tube from the flask to a bubbler. Once this occurred, flask A was cooled to 0 °C under N_2. To a separate, flame-dried 500 mL round bottom flask with a stir bar (flask B), benzyl alcohol (9.57 mL, 92.47 mmol, 1.0 equiv) was dissolved in THF (387 mL, 0.239 M). This was also cooled, with stirring under N_2, to 0 °C. The contents of flask B were then transferred to flask A at 0 °C, and the combined solution was warmed to room temperature with vigorous stirring. *N*-tetrabutyl ammonium iodide (2.527 g, 0.074 equiv) was added, and the resulting mixture was fitted with a water condenser and brought to reflux, which continued with vigorous stirring for 19 hours. The reaction flask was then cooled gradually to 0 °C and ethanol (93 mL) was added. This crude mixture was concentrated by rotary evaporator,

and the solid material was diluted with Et_2O (200 mL) and transferred to a separatory funnel. The resulting suspension was extracted with saturated aqueous sodium bicarbonate (3 x 100 mL). The combined aqueous layers were then carefully acidified to pH 2 with 1 N aqueous HCl and were then transferred to another large separatory funnel. This suspension was then extracted with CH_2Cl_2 (5 x 100 mL). These combined CH_2Cl_2 organic layers were now dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude acid quantitatively as an off-white solid (20.59 g), which was used without further purification.



2-(benzyloxy)-1-morpholinoethanone. 2-(benzyloxy) acetic acid (8.16 g, 49.13 mmol, 1 equiv) was dissolved in CH_2Cl_2 (98 mL, 0.5 M) in a flame-dried 1000 mL round bottom flask with a stir bar. This solution was cooled, while stirring, to 0 °C under N_2. Oxalyl chloride (10.7 mL, 122.8 mmol, 2.5 equiv) was then added, followed by CAREFUL AND SLOW addition of DMF (1 mL), done very slowly to avoid uncontrolled bubbling over. This was then stirred at 0 °C, warming to room temperature overnight, for 16 hours. Benzene (98 mL, 0.5 M) was then added, and the solvent was carefully evaporated off using a rotary evaporator. More benzene (98 mL, 0.5 M) was then added and evaporated off once again using the rotary evaporator. A third addition of benzene (98 mL, 0.5 M), followed by its evaporation, was then done. These three benzene distillations were done to remove excess oxalyl chloride. More CH_2Cl_2 (98 mL, 0.5 M) was then added, and the solution was cooled, with stirring under N_2, to 0 °C. Triethyl amine (20.54 mL, 147.4 mmol, 3 equiv), morpholine (12.85 mL, 147.4 mmol, 3 equiv), and dimethylamino pyridine (0.6 g, 4.91 mmol, 0.1 equiv) were then added, and the reaction was

stirred for 6.5 hours. The reaction was then quenched by addition of 1N aqueous HCl (20 mL) and was transferred to a separatory funnel. The layers were mixed and then separated, and the aqueous layer was extracted with CH_2Cl_2 (5 x 30 mL). The combined organic layers were then dried over $MgSO_4$, filtered, and purified by column chromatography (50% EtOAc/hexanes, then 100% EtOAc) to afford 8.391 g (73% yield, 98% from benzyl alcohol) of the title compound as a yellow oil. (Note: Once done with the benzene distillations, it is important to clean out the rotary evaporator by aspirating distilled water and acetone directly into the catch trap in alternating fashion, three times each, to remove excess oxalyl chloride condensed at this stage.) Data are: TLC R_f= 0.38 (100% EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.29 -7.23 (m, 5 H), 4.52 (t, *J* = 3.5, 2H), 4.09 (t, *J* = 4, 2H), 3.58 (bs, 2H), 3.54 (bs, 4H), 3.39 (d, *J* = 1.75, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.9, 137.4, 128.7, 128.2, 73.4, 69.6, 67.0, 45.8, 42.3; HRMS found 236.1281 $[M+H]^+$, calcd 236.1281 for $C_{13}H_{18}NO_3^+$.

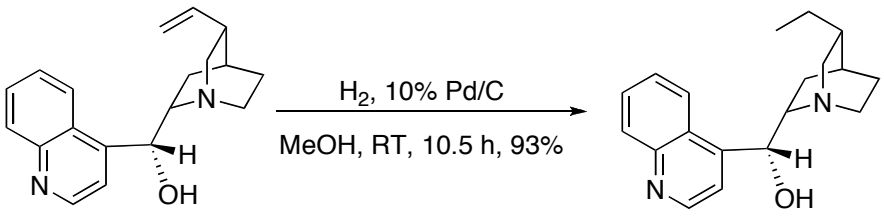


63

2-(benzyloxy)-1-(1-methyl-1H-imidazol-2-yl)ethanone (63). 1-methylimidazole (0.774 mL, 9.75 mmol, 2.5 equiv) was dissolved in THF (2.9 mL, 1.33 M) in a flame-dried 25 mL round-bottom flask (flask A) and was cooled under N_2 to 0 °C. *N*-butyl lithium (1.6 M in hexanes, 5.36 mL, 8.58 mmol, 2.2 equiv) was then added dropwise, and the resulting yellow solution was stirred at 0 °C for 1 hour. As flask A neared its one hour of stirring, 2-(benzyloxy)-1-morpholinoethanone (0.917 g, 3.9 mmol) was dissolved in THF (3.9 mL, 1 M) in a separate, flame-dried 50 mL round-bottom flask (flask B) with a spin vane. This was cooled, while

stirring under N_2, to -78 °C. Once flask A had been stirred for 1 hour, it was also cooled to -78 °C and was transferred to flask B by cannula, giving a dark brown solution. This mixture was then warmed to -40 °C and stirred for 1 hour, during which time it warmed further to -15 °C. The reaction was quenched by the addition of 1 N aqueous HCl (5 mL), was stirred for 5 minutes, and was then diluted with a saturated solution of aqueous NaCl (10 mL) and saturated aqueous sodium bicarbonate (10 mL). This suspension was then transferred to a separatory funnel and was extracted with CH_2Cl_2 (5 x 50 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by rotary evaporator. The crude product was then purified by column chromatography (50% EtOAc/hexanes, then 100% EtOAc) to afford 0.775 g (86%, 84% from benzyl alcohol) of the desired compound as an off-white solid. Data are: TLC R_f= 0.54 (100% EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.43 – 7.4 (m, 2H), 7.37 – 7.28 (m, 3H), 7.08 (s, 1H), 7.03 (s, 1H), 4.94 (s, 2H), 4.69 (s, 2H), 4.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 188.3, 137.8, 129.5, 128.7, 128.3, 128.1, 127.2, 73.7, 72.3, 36.1; HRMS found 231.1302 $[M+H]^+$, calcd 231.1128 for $C_{13}H_{15}N_2O_2^+$.

7.3.3. Catalyst Synthesis

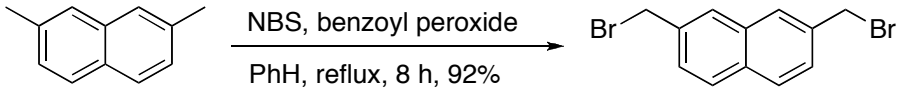


30 **68**

Hydrocinchonidine (68). To a flame-dried, 3-neck round bottom flask with a stir bar was added (-)-cinchonidine **30** (5 g, 16.98 mmol, 1 equiv), followed by anhydrous MeOH (154 mL, 0.11

M). 10% Pd/C was then added carefully (1 g, 1 g Pd/C for every 5 g (-)-cinchonidine). H_2 gas (1 large balloon) was afterward introduced by evacuating the flask 3 times and flushing it under H_2 atmosphere. The reaction was then stirred at room temperature under H_2 balloon pressure for 10.5 h. The crude reaction mixture was afterward filtered through celite thusly: a 500 mL, 25-50 micron filter cup filled with celite 545 was placed over a 1 L filter flask and was bathed in CH_2Cl_2. The crude reaction mixture was then added to the top of the celite and vacuum-filtered through the celite, with CH_2Cl_2 used as the eluent solvent (added frequently enough to prevent air from introducing bubbles in the celite). Periodic swabs with capillary tubes were taken from the drip off the filter cup as the liquid passed through. Each swab was monitored under UV light for luminescence, indicating the presence of the hydro-cinchonidine product. When the luminescent color had dissipated under UV, the filtration was stopped. The resulting filtered liquid was then concentrated in a 500 mL round bottom flask to give an off-white solid. (Note: If this solid bears any black or gray color, it may be indicative of the presence of either unfiltered Pd/C or contaminating celite. Under such circumstance, the product should be re-filtered through celite prior to its suspension in hexanes.) This solid was suspended in hexanes (200 mL, 0.085 M) and was stirred at RT for 1 h. The resulting precipitate, hydrocinchonidine, was then filtered, concentrated by rotary evaporator, and collected as an off-white solid (4.7 g, 93% yield). (Note: The final product can be compared by TLC to the starting material, to ensure reaction completion. Starting material, R_f = 0.275 (100% MeOH); product, R_f = 0.15 (100% MeOH).) When running the ^{1}H NMR, an increased number of Fourier transfer scans were necessary. Data are: TLC R_f = 0.15 (100% MeOH); ^{1}H NMR ($CHCl_3$-d_1, 500 MHz): δ 8.90 (d, J = 2.3 Hz, 1H), 8.13 (d, J = 4 Hz, 1H), 8.05 (d, J = 4 Hz, 1H), 7.71 (t, J = 8 Hz, 1H), 7.59 (d, J = 2.3 Hz, 1H), 7.53 (t, J = 8 Hz, 1H), 5.64 (bs, 1H), 3.39 – 3.38 (m, 1H), 3.16 – 3.13 (m, 1H), 3.09 – 3.04 (dd,

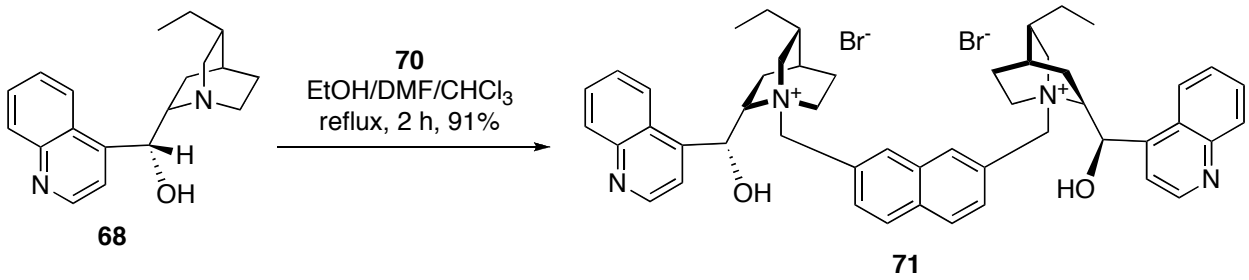
1H), 2.87 (bs, 1H), 2.66 – 2.62 (m, 1H), 2.42 – 2.38 (m, 1H), 1.782 (d, J = 1.2 Hz, 1H), 1.73 – 1.66 (m, 2H), 1.56 – 1.54 (m, 1H), 1.45 -1.40 (m, 2H), 1.28 – 1.24 (m, 2H), 0.82 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CHCl_3$-d_1, 125 MHz): δ 150.25, 149.1, 148.3, 130.4, 129.0, 126.6, 123.1, 118.1, 72.4, 60.2, 58.7, 43.3, 37.6, 28.4, 27.6, 25.5, 21.7, 12.1; HRMS found 297.1961 $[M+H]^+$, calcd 297.1961 for $[C_{19}H_{25}N_2O]^+$.



69 **70**

2,7-bis(bromomethyl) naphthalene (70). To a flame-dried 250 mL round bottom flask with a stir bar was added 2,7-dimethylnaphthalene **69** (1.48 g, 9.47 mmol, 1 equiv), followed by PhH (190 mL, 0.05 M). *N*-bromosuccinimide was then added (3.75 g, 21.05 mmol, 2.223 equiv), followed by benzoyl peroxide (123 mg, 0.509 mmol, 0.0538 equiv). This suspension was then heated and stirred vigorously at reflux (~120 °C) for 8 h. The reaction was monitored by TLC for consumption of starting material (R_f = 0.7; product, R_f = 0.345, 5% EtOAc/Hexanes). Once this stirring was done, the reaction mixture was cooled slowly to 0 °C and was filtered through a 25-50 micron filter cup. (All solid collected in the filter cup is precipitate succinimide; the final product remains in the mother liqueur.) The mother liqueur was concentrated by rotary evaporator and the residue was recrystallized from $CHCl_3$/hexanes thusly: warm $CHCl_3$ was added until the crude solid dissolved; then a generous amount of hexanes at RT was added until precipitation occurred. The suspension was capped and cooled in the freezer overnight. The next morning it was filtered to give 2,7-Bis(bromomethyl)naphthalene **70** as an off-white solid (2.73 g, 92% yield). Data are: TLC R_f = 0.345 (5% EtOAc/Hexanes); ^{1}H NMR ($CHCl_3$-d_1, 500

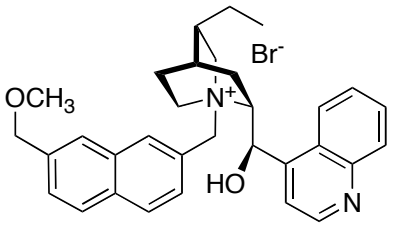
MHz): δ 7.85 (d, *J* = 7.5 Hz, 2H), 7.55 (d, *J* = 8.5 Hz, 2H), 7.29 (s, 2H), 4.69 (s, 4H); ^{13}C NMR ($CHCl_3$-d_1, 125 MHz): δ 128.8, 128.1, 127.7, 33.9.



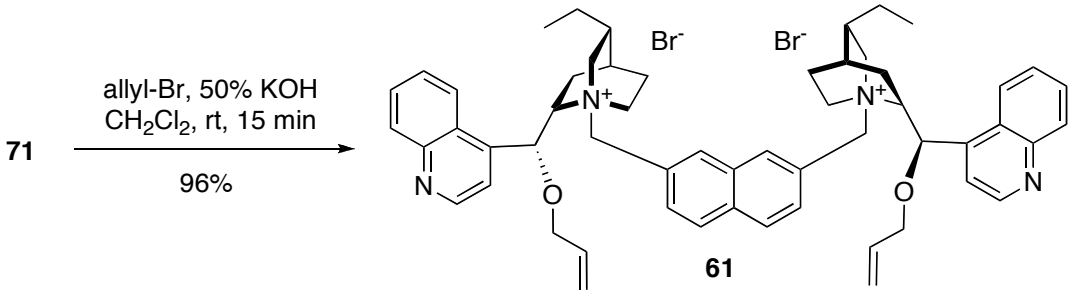
68 71

2,7-bis(hydrocinchonidinium-*N*-methyl) naphthalene dibromide (71). To a pre-weighed 250 mL round bottom flask with a stir bar were dissolved 2,7-Bis(bromomethyl)naphthalene **70** (1.5 g, 4.77 mmol, 1 equiv) and hydrocinchonidine **68** (2.88 g, 9.73 mmol, 2.04 equiv) in EtOH (7.2 mL, 0.662 M), DMF (8.6 mL, 0.552 M), and $CHCl_3$ (2.9 mL, 1.655 M). This suspension was heated to reflux (100-120ºC) and stirred vigorously for 2 H. The reaction was monitored for the consumption of 2,7-Bis(bromomethyl) naphthalene by TLC (R_f = 0.345, 5% EtOAc/Hexanes). The reaction was then cooled to room temperature and diluted with MeOH (29 mL, 0.1655 M) and Et_2O (87 mL, 0.055 M). This suspension was stirred at room temperature for 1 H. The crude, light-pink precipitate was afterward filtered through a 25-50 micron filter cup and was rinsed with Et_2O (3x25 mL). It was scraped out of the filter cup using a spatula and was placed back in the original pre-weighed reaction flask, isolated as a pink solid (3.94 g, 4.34 mmol, 91% yield). Data are: ^{1}H NMR (DMSO-d_6, 500 MHz, with increased Fourier transfers): δ 9.00 (d, *J* = 2.3 Hz, 2H), 8.33 (d, *J* = 4 Hz, 2H), 8.22 (d, *J* = 4 Hz, 2H), 8.14 (d, *J* = 4 Hz, 2H), 7.92 (d, *J* = 4.2 Hz, 2H), 7.88 – 7.84 (m, 4H), 7.75 (t, *J* = 7.5 Hz, 2H), 6.78 (d, *J* = 2 Hz, 2H), 6.63 (s, 2H), 5.31 (d, *J* = 6.5 Hz, 2H), 5.12 (d, *J* = 6 Hz, 2H), 4.36 (bs, 2H), 3.98 (t, *J* = 8 Hz, 2H), 3.53 (m, 2H), 2.18-2.08 (m, 4H), 1.98 (bs, 2H), 1.77 – 1.72 (m, 4H), 1.41 – 1.39 (m, 2H), 1.28 – 1.61 (m,

4H), 0.72 (t, J = 7 Hz, 4H); large extraneous peaks: δ 3.36 (H_2O in DMSO-d_6), 2.5 (DMSO-H_x in DMSO-d_6). HRMS: 746.4560 [$C_{50}H_{58}N_4O_2$] and 374.2353 $[C_{50}H_{58}N_4O_2]^{2+}$/2 found; calcd 746.4549 for $[C_{50}H_{58}N_4O_2]^{2+}$. (Note: If the initial reaction suspension turns dark purple or red soon after reflux, this indicates Pd/C contamination. The resulting product will not form good catalyst. Crude **71** should not be rinsed with MeOH, or byproduct **72** will result, turning the light-pink solid product to a dark red. Compound **72** confirmed by HRMS: 481.2827 $[M+H]^+$ found; calcd 481.2850 $[C_{32}H_{37}N_2O_2]^+$. Contamination with **72** will result in poor catalyst.



72

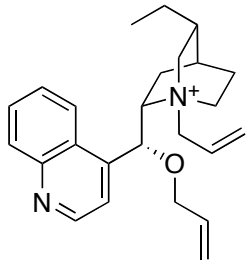


61

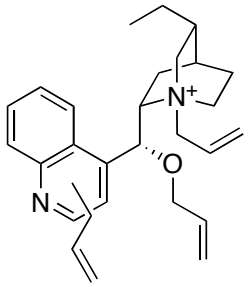
2,7-bis[*O*(9)-allylhydrocinchonidinium-*N*-methyl]naphthalene dibromide (61). To a 100 mL round bottom flask with a stir bar was added 2,7-bis(hydro-cinchonidinium-*N*-methyl) naphthalene dibromide **71** (4.258 g, 4.695 mmol, 1 equiv) and CH_2Cl_2 (13.5 mL, 0.35 M). Allyl bromide (2.38 mL, 28.17 mmol, 6 equiv) was then added, followed by 50% aqueous KOH (47 mL, 0.1 M), forming a yellow-brown solution. This was stirred at room temperature for 15 minutes, during which time the solution turned yellow-orange. At this stage a small amount of the reaction solvent was removed with a pipet, diluted with CH_2Cl_2, and rushed to the mass spec lab for analysis, which revealed complete consumption of the starting material ($[M+2H]^{2+}$/2 =

373.2207 for $[C_{50}H_{58}N_4O_2]^{2+}/2$). The reaction was afterward quenched by addition of 30 mL H_2O and was transferred to a separatory funnel. The layers were mixed and then separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 75 mL). The combined organic layers were dried over $MgSO_4$, filtered thoroughly, concentrated by rota-evaporation, and then purified by recrystallization as follows: the crude solid was dissolved in a minimal amount of warm CH_2Cl_2; then hexane at ambient temperature was added generously, causing swift precipitation. The precipitate was filtered immediately through a 25-50 micron filter cup. (Note: the crude product should be filtered immediately after recrystallization. If left in the recrystallization solvent, it will dissolves.) The filtered product, 2,7-bis[*O*(9)-allylhydrocinchonidinium-*N*-methyl] naphthalene dibromide **61**, was isolated as a light-orange solid (4.44 g, 4.50 mmol, 96%). Data are: ^{1}H NMR (DMSO-d_6, 500 MHz, with increased Fourier transfers): δ 9.03 (s, 1H), 8.39 (s, 2H), 8.27 – 8.23 (m, 4H), 8.15 (d, J = 8.5 Hz, 2H), 7.94-7.88 (m, 4H), 7.81-7.78 (m, 2H), 7.72 (t, J = 5 Hz, 2H), 6.50 (s, 2H), 6.23-6.16 (m, 2H), 5.50 (d, J = 8.7 Hz, 2H), 5.33-5.32 (m, 4H), 5.06 (d, J = 6.25 Hz, 2H), 4.41 – 4.38 (m, 2H), 4.14 – 4.09 (m, 2H), 4.04 – 3.99 (m, 4H), 2.32 – 2.29 (m, 2H), 2.11 – 2.07 (m, 2H), 2.00 (bs, 2H), 1.76 (bs, 4H), 1.52 (t, J = 13.5, 2H), 1.23 – 1.16 (m, 6H), 0.70 (t, J = 7 Hz, 6 H); large extraneous peaks: δ 5.75 (CH_2Cl_2 in DMSO-d_6), 3.33 (H_2O in DMSO-d_6), 2.49 (DMSO-H_x in DMSO-d_6). HRMS found 413.2587 $[M+2H]^{2+}/2$; calcd 413.2588 for $[C_{56}H_{66}N_4O_2]^{2+}/2$. (Note: Allylation of unreacted hydrocinchonidine gives byproducts **76** and **77**, which are inseparable from catalyst **61** and may behave as competitive catalysts. Improved catalyst is made if the hydrocinchonidine is completely consumed during the formation of intermediate **71**. If allylation of **71** is run too long, increased formation of **76** and **77** will result. The presence of byproducts **76** and **77** was confirmed by HRMS. For **76**: found 377.2587 $[M^+]$; calcd 377.2587 for $[C_{25}H_{33}N_2O]^+$. For **77**: found 417.2904 $[M^+]$; calcd

417.2900 for $[C_{28}H_{37}N_2O]^+$. Trace amounts of **76** seem unavoidable, confirmed by HRMS in the purest batches of catalyst.

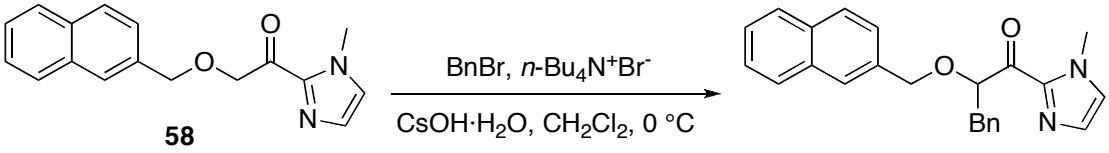


76
$C_{25}H_{33}N_2O^+$
Exact Mass: 377.26



77
$C_{28}H_{37}N_2O^+$
Exact Mass: 417.29

7.3.4. General Procedure for Racemic Alkylations

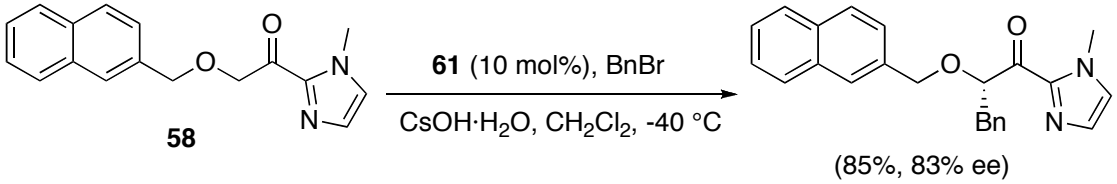


58

(±)-1-(1-methyl-1*H*-imidazol-2-yl)-2-(naphthalen-2-ylmethoxy)-3-phenylpropan-1-one (Table 3.4). To a flame-dried round bottom flask was added 1-(1-methyl-1H-imidazol-2-yl)-2-(naphthalen-2-ylmethoxy)-ethanone **58** (50 mg, 0.178 mmol), *n*-$Bu_4N^+Br^-$ (6.5 mg, 0.021 mmol) and CH_2Cl_2 (1.78 mL). The solution was cooled to 0 °C and then $CsOH{\cdot}H_2O$ (0.120 g, 0.712 mmol) was added in one portion. The mixture stirred at 0 °C for 10 min, at which time benzyl bromide (0.106 mL, 0.89 mmol) was added. The mixture then stirred at 0 °C, allowing to warm to room temperature overnight, for 17 h, at which time the reaction was diluted with Et_2O (30 mL) and H_2O (10 mL). The layers were mixed and then separated and the organic layer was washed with a saturated aqueous solution of aqueous NaCl (1 x 10 mL) and then dried over $MgSO_4$. The mixture was filtered, the solvent was removed by rotary evaporator, and the crude

residue was purified by column chromatography (40% EtOAc/hexanes) to afford 0.031 g (47%) of the desired compound as an off-white solid. Data are: TLC R_f= 0.4 (40% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.81-7.79 (m, 1H), 7.73-7.67 (m, 2H), 7.56 (s, 1H), 7.46-7.42 (m, 3H), 7.38-7.25 (m, 5H), 7.17 (s, 1H), 7.02 (s, 1H), 5.51 (dd, 1H), 4.70 (dd, 2H), 3.93 (s, 3H), 3.36-3.02 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.3, 142.1, 138.2, 135.7, 133.3, 133.0, 129.9, 129.7, 128.4, 128.1, 128.0, 127.7, 127.3, 126.6, 126.0, 126, 125.9, 81.6, 72.7, 39.7, 36.1; HRMS found 370.1681 M^+, calcd 370.1681 for $C_{24}H_{22}N_2O_2$; the enantiomers' retention times were determined by chiral HPLC (DAICEL Chiralpack AD-H column, 5% EtOH/hexane, 1.0 mL/min, 23 °C, λ = 254 nm, retention times: *S* 21.2 min, *R* 47.2 min, 50.7 : 49.2 er).

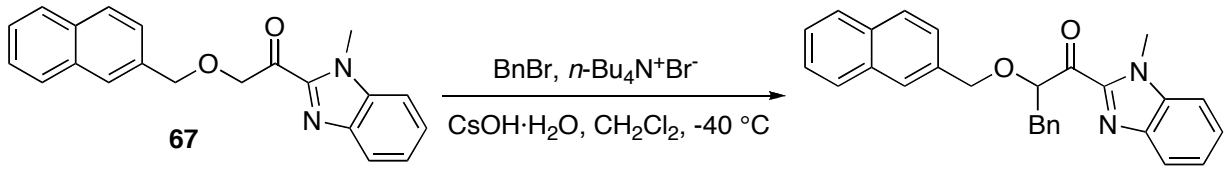
7.3.5. General Procedure for Asymmetric Alkylations



***(S)*-1-(1-methyl-1H-imidazol-2-yl)-2-(naphthalen-2-ylmethoxy)-3-phenylpropan-1-one (Table 3.4, entry 6).** To a flame-dried round bottom flask was added **58** (50 mg, 0.178 mmol), catalyst **61** (17 mg, 0.017 mmol) and CH_2Cl_2 (1.8 mL). The solution was cooled to -40 °C and then $CsOH·H_2O$ (0.120 g, 0.712 mmol) was added in one portion. The mixture stirred at -40 °C for 10 min, at which time benzyl bromide (0.106 mL, 0.89 mmol) was added. The mixture then stirred at -40 °C for 5 h (monitored by TLC for consumption of starting material), at which time the reaction was diluted with Et_2O (30 mL) and H_2O (10 mL). The layers were mixed and then separated and the organic layer was washed with a saturated aqueous solution of aqueous NaCl

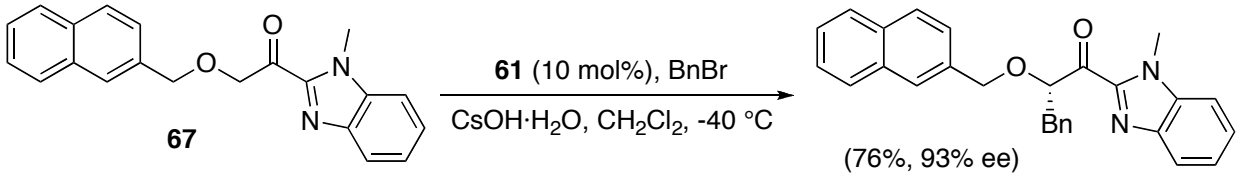
(1 x 10 mL) and then dried over $MgSO_4$. The mixture was filtered and concentrated, and the crude residue was purified by column chromatography (40% EtOAc/hexanes) to afford 0.057 g (85%) of product as an off-white solid. Data are: TLC R_f= 0.45 (50% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.81-7.79 (m, 1H), 7.73-7.67 (m, 2H), 7.56 (s, 1H), 7.46-7.42 (m, 3H), 7.38-7.25 (m, 5H), 7.17 (s, 1H), 7.02 (s, 1H), 5.51 (dd, *J* = 2.7 Hz, 1H), 4.70 (dd, 2H), 3.93 (s, 3H), 3.36-3.02 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.3, 142.1, 138.2, 135.7, 133.3, 133.0, 129.9, 129.7, 128.4, 128.1, 128.0, 127.7, 127.3, 126.6, 126.0, 126, 125.9, 81.6, 72.7, 39.7, 36.1; HRMS found 370.1681 M^+, calcd 370.1681 for $C_{24}H_{22}N_2O_2$; the enantiomers' retention times were determined by chiral HPLC and compared to the racemic samples listed above (DAICEL Chiralpack AD-H column, 5% EtOH/hexane, 1.0 mL/min, 23 °C, λ = 254 nm, retention times: *S* (major) 20.9 min, *R* (minor) 46.7 min, 91.5 : 8.5 er).

7.3.6. Selected Alkylation Data

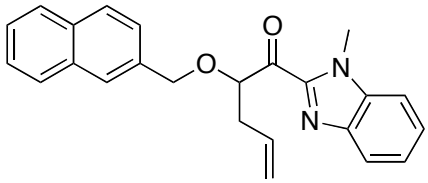


(±)-1-(1-methyl-1H-benzo[d]imidazol-2-yl)-2-(naphthalen-2-ylmethoxy)-3-phenylpropan-1-one (Table 3.3, entry 4). Following the general procedure for racemic alkylations above on 50 mg scale, 0.029 g (38%) of product were isolated as an off-white solid. Data are: TLC R_f= 0.44 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.94 (d, *J* = 3.75 Hz, 1H), 7.81 (d, *J* = 3.75 Hz, 1H), 7.73 (d, *J* = 4.2 Hz, 1H), 7.66 (d, *J* = 3.6 Hz, 1H), 7.6 (s, 1H), 7.49-7.30 (m, 11H), 5.74 (dd, *J1* = 2.56 Hz, *J2* = 1.8 Hz, 1H), 4.89 (d, *J* =6.2 Hz, 1H), 4.66 (d, *J* =*6* Hz, 1H), 4.03 (s, 3H), 3.46-3.11 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.6, 130.0, 128.5, 128.2, 127.8,

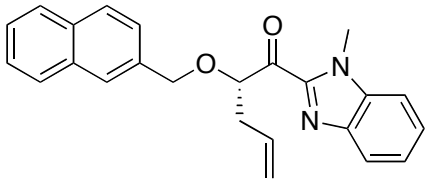
126.9, 126.8, 126.4, 126.2, 126.0, 124.1, 122.4, 110.8, 82.3, 73.0, 39.6, 32.2; HRMS found 420.1838 (M^+), calcd 420.1838 for $C_{28}H_{24}N_2O_2$; the enantiomers' retention times were determined by chiral HPLC (DAICEL Chiralpack AD-H column, 5% EtOH/hexane, 1.0 mL/min, 23 °C, λ = 254 nm, retention times: *S* 18.4 min, *R* 58.1 min, 53.9 : 46.1 er).



***(S)*-1-(1-methyl-1H-benzo[d]imidazol-2-yl)-2-(naphthalen-2-ylmethoxy)-3-phenylpropan-1-one (Table 3.3, entry 4).** Following the general procedure for asymmetric alkylations above on 50 mg scale, 0.048 g (76%) of product were isolated as an off-white solid. Data are: TLC R_f= 0.44 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.94 (d, *J* = 3.75 Hz, 1H), 7.81 (d, *J* = 3.75 Hz, 1H), 7.73 (d, *J* = 4.2 Hz, 1H), 7.66 (d, *J* = 3.6 Hz, 1H), 7.6 (s, 1H), 7.49-7.30 (m, 11H), 5.74 (dd, *J1* = 2.56 Hz, *J2* = 1.8 Hz, 1H), 4.89 (d, *J* =6.2 Hz, 1H), 4.66 (d, *J* =*6* Hz, 1H), 4.03 (s, 3H), 3.46-3.11 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.6, 130.0, 128.5, 128.2, 127.8, 126.9, 126.8, 126.4, 126.2, 126.0, 124.1, 122.4, 110.8, 82.3, 73.0, 39.6, 32.2; HRMS found 420.1838 (M^+), calcd 420.1838 for $C_{28}H_{24}N_2O_2$; the enantiomers' retention times were determined by chiral HPLC (DAICEL Chiralpack AD-H column, 5% EtOH/hexane, 1.0 mL/min, 23 °C, λ = 254 nm, retention times: *S* 18.4 min, *R* 58.1 min, 96.4 : 3.6 er).

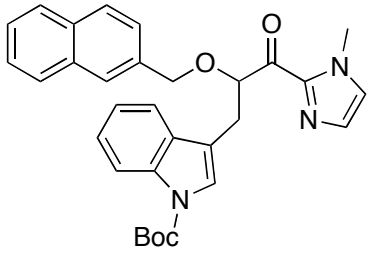


(±)-1-(1-methyl-1H-benzo[d]imidazol-2-yl)-2-(naphthalen-2-ylmethoxy)pent-4-en-1-one. Following the general procedure for racemic alkylations above on 50 mg scale, where allyl bromide was substituted for benzyl bromide, 0.024g (43%) of the desired compound were isolated as an off-white solid. Data are: TLC R_f= 0.53 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.96-7.30 (m, 11H), 5.63-5.59 (m, 1H), 5.15-5.09 (m, 1H), 4.94-4.90 (m, 2H), 4.79 (d, *J* = 6Hz, 1H), 4.65 (d, *J* = 5.5 Hz, 1H), 4.0 (s, 3H), 2.90-2.68 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.6, 133.7, 128.5, 128.3, 128.2, 127.8, 127.3, 126.4, 126.2, 124.1, 122.3, 118.1, 110.8, 80.6, 73.0, 39.5, 37.8, 32.2; HRMS found 370.1681 (M^+), calcd 370.1681 for $C_{24}H_{22}N_2O_2$; the enantiomers' retention times were determined by chiral HPLC (DAICEL Chiralpack AD-H column, 5% EtOH/hexane, 1.0 mL/min, 23 °C, λ = 254 nm, retention times: *S* 13.4 min, *R* 27.5 min, 51 : 49 er).

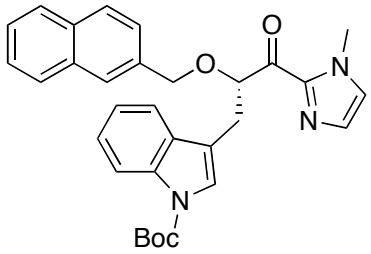


***(S)*-1-(1-methyl-1H-benzo[d]imidazol-2-yl)-2-(naphthalen-2-ylmethoxy)pent-4-en-1-one.** Following the general procedure for asymmetric alkylations above on 50 mg scale, where allyl bromide was substituted for benzyl bromide, 0.024g (54%) of the desired compound were isolated as an off-white solid. Data are: TLC R_f= 0.53 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.96-7.30 (m, 11H), 5.63-5.59 (m, 1H), 5.15-5.09 (m, 1H), 4.94-4.90 (m, 2H), 4.79

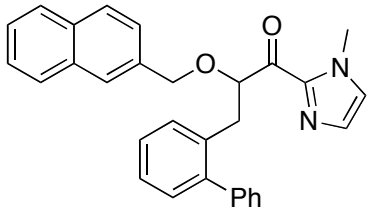
(d, *J* = 6Hz, 1H), 4.65 (d, *J* = 5.5 Hz, 1H), 4.0 (s, 3H), 2.90-2.68 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.6, 133.7, 128.5, 128.3, 128.2, 127.8, 127.3, 126.4, 126.2, 124.1, 122.3, 118.1, 110.8, 80.6, 73.0, 39.5, 37.8, 32.2; HRMS found 370.1681 (M^+), calcd 370.1681 for $C_{24}H_{22}N_2O_2$; the enantiomers' retention times were determined by chiral HPLC (DAICEL Chiralpack AD-H column, 5% EtOH/hexane, 1.0 mL/min, 23 °C, λ = 254 nm, retention times: *S* 13.4 min, *R* 27.5 min, 86.2 : 13.8 er).



(±)-*Tert*-butyl 3-(3-(1-methyl-1*H*-imidazol-2-yl)-2-(naphthalen-2-ylmethoxy)-3-oxopropyl)-1*H*-indole-1-carboxylate (Table 3.4, entry 1). Following the general procedure for racemic alkylations above on 50 mg scale, where electrophile **44** (described in section 7.4.1 below) was substituted for benzyl bromide, 0.055 g (61%) of product were isolated as an off-white solid. Data are: TLC R_f= 0.5 (40% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.13 (bs, 1H), 7.77-7.76 (m, 1H), 7.68-7.54 (m, 4H), 7.45-7.42 (m, 3H), 7.32-7.27 (m, 3H), 7.21 (d, *J*= 2.25 Hz, 1H), 7.16 (t, *J*= 7.5 Hz, 1H), 7.03 (s, 1H), 5.58 (dd, *J1*=2.25 Hz, *J2*=1.5 Hz, 1H), 4.83 (d, *J* =5.75 Hz, 1H), 4.60 (d, *J* = 6 Hz, 1H), 3.88 (s, 3H), 3.43-3.17 (m, 2H), 1.66 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 191.2, 150.0, 142.2, 135.6, 133.4, 133.1, 131.0, 129.8, 128.2, 128.1, 127.8, 127.5, 126.9, 126.2, 126.1, 126.0, 124.8, 124.4, 122.6, 119.8, 116.7, 115.3, 83.5, 80.2, 72.8, 36.1, 29.4, 28.5; HRMS found 509.2315 (M^+), calcd 509.2315 for $C_{31}H_{31}N_3O_4$; the enantiomers' retention times were determined by chiral HPLC (DAICEL Chiralpack AD-H column, 10% EtOH/hexane, 1.0 mL/min, 23 °C, λ = 254 nm, retention times: *S* 12.7 min, *R* 118.3 min, 50.1 : 49.8 er).

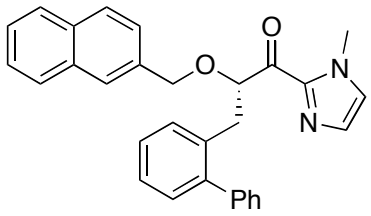


***(S)-Tert*-butyl 3-(3-(1-methyl-1*H*-imidazol-2-yl)-2-(naphthalen-2-ylmethoxy)-3-oxopropyl)-1*H*-indole-1-carboxylate (Table 3.4, entry 1).** Following the general procedure for asymmetric alkylations above on 2.33 g scale, where electrophile **44** was substituted for benzyl bromide, 3.85 g (91%) of product were isolated as an off-white solid. Data are: TLC R_f= 0.5 (40% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.13 (bs, 1H), 7.77-7.76 (m, 1H), 7.68-7.54 (m, 4H), 7.45-7.42 (m, 3H), 7.32-7.27 (m, 3H), 7.21 (d, *J*= 2.25 Hz, 1H), 7.16 (t, *J*= 7.5 Hz, 1H), 7.03 (s, 1H), 5.58 (dd, *J1*=2.25 Hz, *J2*=1.5 Hz, 1H), 4.83 (d, *J* =5.75 Hz, 1H), 4.60 (d, *J* = 6 Hz, 1H), 3.88 (s, 3H), 3.43-3.17 (m, 2H), 1.66 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 191.2, 150.0, 142.2, 135.6, 133.4, 133.1, 131.0, 129.8, 128.2, 128.1, 127.8, 127.5, 126.9, 126.2, 126.1, 126.0, 124.8, 124.4, 122.6, 119.8, 116.7, 115.3, 83.5, 80.2, 72.8, 36.1, 29.4, 28.5; HRMS found 509.2315 (M^+), calcd 509.2315 for $C_{31}H_{31}N_3O_4$; the enantiomers' retention times were determined by chiral HPLC (DAICEL Chiralpack AD-H column, 10% EtOH/hexane, 1.0 mL/min, 23 °C, λ = 254 nm, retention times: *S* 12.7 min, *R* 118.3 min, >99.0 : <1.0 er).



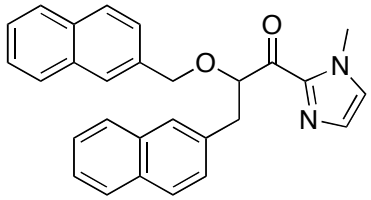
(±)-3-(biphenyl-2-yl)-1-(1-methyl-1*H*-imidazol-2-yl)-2-(naphthalen-2-ylmethoxy) propan-1-one (Table 3.4, entry 2). Following the general procedure for racemic alkylations above on 50

mg scale, where 2-phenylbenzyl bromide was substituted for benzyl bromide, 41 mg of product (52%) were isolated as an off-white solid. Data are: TLC R_f= 0.76 (50% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.82 (bs, 2H), 7.75 (d, *J* = 4 Hz, 2H), 7.59 (s, 2H), 7.48 (q, *J* = 1.5 Hz, 2H), 7.37-7.26 (m, 8H), 7.09 (s, 1H), 6.97 (s, 1H), 5.50 (dd, *J* = 6.5 Hz, 1H), 4.66 (dd, 2H), 3.90 (s, 3H), 3.35-3.15 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.5, 143.0, 141.8, 135.8, 135.5, 133.4, 133.2, 130.7, 130.4, 129.9, 129.7, 128.3, 128.1, 127.8, 127.4, 127.3, 126.9, 126.7, 126.6, 126.1, 126.1, 126.0, 81.2, 72.7, 36.1; HRMS found 446.1994 M^+, calcd 446.1994 for $C_{30}H_{26}N_2O_2$; the enantiomers' retention times were determined by chiral HPLC (DAICEL Chiralpack AD-H column, 5% EtOH/hexane, 1.0 mL/min, 23 °C, λ = 254 nm, retention times: *S* 22.84 min, *R* 38.9 min, 50.4 : 49.6 er).

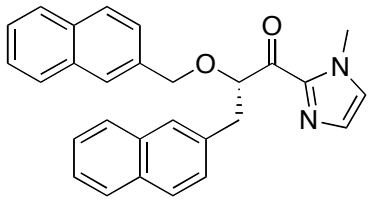


***(S)*-3-(biphenyl-2-yl)-1-(1-methyl-1*H*-imidazol-2-yl)-2-(naphthalen-2-ylmethoxy) propan-1-one (Table 3.4, entry 2).** Following the general procedure for racemic alkylations above on 50 mg scale, where 2-phenylbenzyl bromide was substituted for benzyl bromide, 73 mg of product (92%) were isolated as an off-white solid. Data are: TLC R_f= 0.5 (40% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.82 (bs, 2H), 7.75 (d, *J* = 4 Hz, 2H), 7.59 (s, 2H), 7.48 (q, *J* = 1.5 Hz, 2H), 7.37-7.26 (m, 8H), 7.09 (s, 1H), 6.97 (s, 1H), 5.50 (q, *J* = 6.5 Hz, 1H), 4.66 (dd, 2H), 3.90 (s, 3H), 3.35-3.15 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.5, 143.0, 141.8, 135.8, 135.5, 133.4, 133.2, 130.7, 130.4, 129.9, 129.7, 128.3, 128.1, 127.8, 127.4, 127.3, 126.9, 126.7, 126.6, 126.1, 126.1, 126.0, 81.2, 72.7, 36.1; HRMS found 446.1994 M^+, calcd 446.1994 for

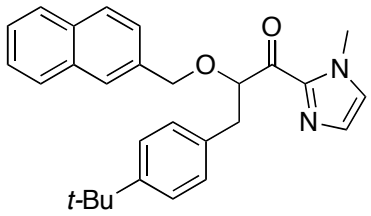
$C_{30}H_{26}N_2O_2$; the enantiomers' retention times were determined by chiral HPLC and compared to the racemic samples listed above (DAICEL Chiralpack AD-H column, 5% EtOH/hexane, 1.0 mL/min, 23 °C, λ = 254 nm, retention times: *S* (major) 22.5 min, *R* (minor) 37.4 min, > 99 : < 1 er).



(±)-1-(1-methyl-1*H*-imidazol-2-yl)-3-(naphthalen-2-yl)-2-(naphthalen-2-ylmethoxy)propan-1-one (Table 3.4, entry 3). Following the general procedure for racemic alkylations above on 50 mg scale, where 2-bromomethylnaphthalene was substituted for benzyl bromide, 33 mg of product (44%) were isolated as an off-white solid. Data are: TLC R_f= 0.35 (40% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.90-7.87 (m 2H), 7.82-7.76 (m, 4H), 7.64-7.39 (m, 8H), 7.72 (s, 1H), 7.02 (s, 1H), 5.62 (dd, 1H), 4.72 (dd, 2H), 3.94 (s, 3H), 3.56-3.20 (m, 2H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 191.4, 135.9, 135.6, 133.8, 133.4, 133.1, 132.7, 129.9, 128.6, 128.5, 128.2, 128.0, 128.0, 127.9, 127.8, 127.5, 126.8, 126.1, 126.0, 126.0, 125.6, 81.7, 72.8, 40.0, 36.2; HRMS found 420.1838 [M^+], calcd 420.1838 for $C_{28}H_{24}N_2O_2$; the enantiomers' retention times were determined by chiral HPLC (DAICEL Chiralpack AD-H column, 10% EtOH/hexane, 1.0 mL/min, 23 °C, λ = 254 nm, retention times: *S* 25 min, *R* 56.3 min, 48.8 : 51.2 er).

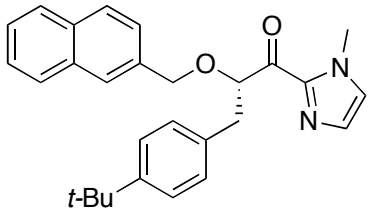


***(S)*-1-(1-methyl-1*H*-imidazol-2-yl)-3-(naphthalen-2-yl)-2-(naphthalen-2-ylmethoxy) propan-1-one (Table 3.4, entry 3).** Following the general procedure for asymmetric alkylations above on 50 mg scale, where 2-bromomethylnaphthalene was substituted for benzyl bromide, 66 mg of product (88%) were isolated as an off-white solid. Data are: TLC R_f= 0.38 (40% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.90-7.87 (m 2H), 7.82-7.76 (m, 4H), 7.64-7.39 (m, 8H), 7.72 (s, 1H), 7.02 (s, 1H), 5.62 (dd, 1H), 4.72 (dd, 2H), 3.94 (s, 3H), 3.56-3.20 (m, 2H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 191.4, 135.9, 135.6, 133.8, 133.4, 133.1, 132.7, 129.9, 128.6, 128.5, 128.2, 128.0, 128.0, 127.9, 127.8, 127.5, 126.8, 126.1, 126.0, 126.0, 125.6, 81.7, 72.8, 40.0, 36.2; HRMS found 420.1838 [M^+], calcd 420.1838 for $C_{28}H_{24}N_2O_2$; the enantiomers' retention times were determined by chiral HPLC and compared to the racemic samples listed above (DAICEL Chiralpack AD-H column, 10% EtOH/hexane, 1.0 mL/min, 23 °C, λ = 254 nm, retention times: *S* (major) 24.6 min, *R* (minor) no measurable signal, > 99 : < 1 er).



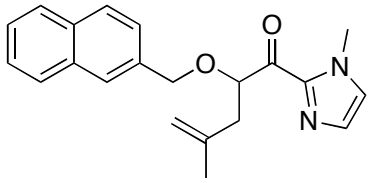
(±)-3-(4-tert-butylphenyl)-1-(1-methyl-1*H*-imidazol-2-yl)-2-(naphthalen-2-ylmethoxy) propan-1-one (Table 3.4, entry 4). Following the general procedure for racemic alkylations above on 50 mg scale, where 4-*tert*butylbenzyl bromide was substituted for benzyl bromide, 23 mg of product (30%) were isolated as an off-white solid. Data are: TLC R_f= 0.45 (40%

EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.81-7.78 (m, 2H), 7.72-7.69 (m, 2H), 7.56 (bs, 2H), 7.44 (t, *J* = 4.5 Hz, 2H), 7.35-7.25 (m, 3H), 7.17 (s, 1H), 7.02 (s, 1H), 5.50 (dd, *J* = 4.8 Hz, 1H), 4.72 (dd, 2H), 3.93 (s, 3H), 3.31-3.01 (m, 2H), 1.36 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.6, 149.4, 142.3, 135.8, 135.1, 133.1, 129.8, 129.6, 128.2, 128.0, 127.8, 127.3, 126.7, 126.1, 126.0, 125.9, 125.4, 81.7, 75.4, 72.6, 39.2, 36.2, 34.7, 31.7; HRMS found 426.2307 M^+, calcd 426.2307 for $C_{28}H_{30}N_2O_2$; the enantiomers' retention times were determined by chiral HPLC (DAICEL Chiralpack AD-H column, 5% EtOH/hexane, 1.0 mL/min, 23 °C, λ = 254 nm, retention times: *S* 10.1 min, *R* 40.5 min, 49.9 : 50.1 er).

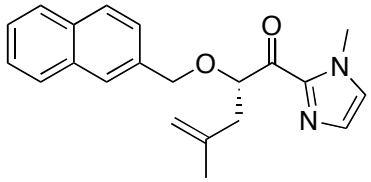


***(S)*-3-(4-tert-butylphenyl)-1-(1-methyl-1*H*-imidazol-2-yl)-2-(naphthalen-2-ylmethoxy) propan-1-one (Table 3.4, entry 4).** Following the general procedure for asymmetric alkylations above on 50 mg scale, where 4-*tert*butylbenzyl bromide was substituted for benzyl bromide, 67 mg of product (88%) were isolated as an off-white solid. Data are: TLC R_f = 0.5 (40% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.81-7.78 (m, 2H), 7.72-7.69 (m, 2H), 7.56 (bs, 2H), 7.44 (t, *J* = 4.5 Hz, 2H), 7.35-7.25 (m, 3H), 7.17 (s, 1H), 7.02 (s, 1H), 5.50 (dd, *J* = 4.8 Hz, 1H), 4.72 (dd, 2H), 3.93 (s, 3H), 3.31-3.01 (m, 2H), 1.36 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.6, 149.4, 142.3, 135.8, 135.1, 133.1, 129.8, 129.6, 128.2, 128.0, 127.8, 127.3, 126.7, 126.1, 126.0, 125.9, 125.4, 81.7, 75.4, 72.6, 39.2, 36.2, 34.7, 31.7; HRMS found 426.2307 M^+, calcd 426.2307 for $C_{28}H_{30}N_2O_2$; the enantiomers' retention times were determined by chiral HPLC and compared to the racemic samples listed above (DAICEL Chiralpack AD-H column, 5%

EtOH/hexane, 1.0 mL/min, 23 °C, λ = 254 nm, retention times: *S* (major) 11.7 min, *R* (minor) 40.7 min, >99 : < 1 er).

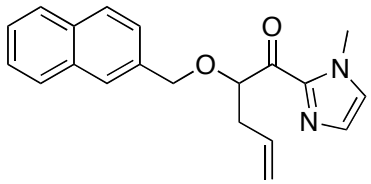


(±)-4-methyl-1-(1-methyl-1*H*-imidazol-2-yl)-2-(naphthalen-2-ylmethoxy) pent-4-en-1-one (Table 3.4, entry 5). Following the general procedure for racemic alkylations above on 50 mg scale, where 3-bromo-2-methylpropene was substituted for benzyl bromide, 16 mg of product (27%) were isolated as an off-white solid. Data are: TLC R_f= 0.75 (50% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.89-7.79 (m, 4H), 7.54-7.46 (m, 3H), 7.17, (d, *J* = 2.5 Hz, 1H), 7.02 (d, *J* = 2.5 Hz, 1H) 5.50 (dd, *J* = 2 Hz, 1H), 4.90-4.69 (m, 4H), 3.92 (s, 3H), 2.72-2.53 (m, 2H), 1.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.5, 131.0, 130.8, 129.2, 128.9, 128.7, 128.6, 128.4, 128.3, 128.1, 128.1, 127.7, 127.6, 127.0, 127.7, 66.7, 54.0, 42.0, 41.5, 40.1; HRMS found 334.1681 M^+, calcd 334.1681 for $C_{21}H_{22}N_2O_2$; the enantiomers' retention times were determined by chiral HPLC (DAICEL Chiralpack AD-H column, 5% EtOH/hexane, 1.0 mL/min, 23 °C, λ = 254 nm, retention times: *S* 11.9 min, *R* 16.9 min, 50.5 : 40.5 er).



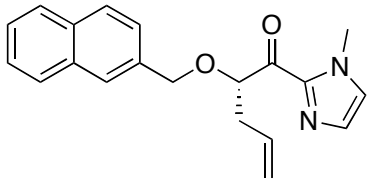
***(S)*-4-methyl-1-(1-methyl-1*H*-imidazol-2-yl)-2-(naphthalen-2-ylmethoxy) pent-4-en-1-one (Table 3.4, entry 5).** Following the general procedure for asymmetric alkylations above on 50 mg scale, where 3-bromo-2-methylpropene was substituted for benzyl bromide, 49 mg of

product (82%) were isolated as an off-white solid. Data are: TLC R_f= 0.44 (50% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.89-7.79 (m, 4H), 7.54-7.46 (m, 3H), 7.17, (d, *J* = 2.5 Hz, 1H), 7.02 (d, *J* = 2.5 Hz, 1H) 5.50 (dd, *J* = 2 Hz, 1H), 4.90-4.69 (m, 4H), 3.92 (s, 3H), 2.72-2.53 (m, 2H), 1.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.5, 131.0, 130.8, 129.2, 128.9, 128.7, 128.6, 128.4, 128.3, 128.1, 128.1, 127.7, 127.6, 127.0, 127.7, 66.7, 54.0, 42.0, 41.5, 40.1; HRMS found 334.1681 M^+, calcd 334.1681 for $C_{21}H_{22}N_2O_2$; the enantiomers' retention times were determined by chiral HPLC and compared to the racemic samples listed above (DAICEL Chiralpack AD-H column, 5% EtOH/hexane, 1.0 mL/min, 23 °C, λ = 254 nm, retention times: *S* (major) 12.6 min, *R* (minor) 18.3 min, 92.7 : 7.3 er).

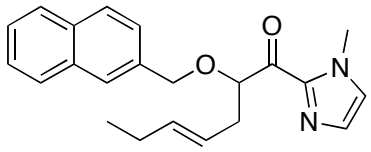


(±)-1-(1-methyl-1*H*-imidazol-2-yl)-2-(naphthalen-2-ylmethoxy)pent-4-en-1-one (Table 3.4, entry 7). Following the general procedure for racemic alkylations above on 50 mg scale, where allyl bromide was substituted for benzyl bromide, 34 mg of product (68%) were isolated as an off-white solid. Data are: TLC R_f= 0.63 (50% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.85-7.79 (m, 4H), 7.55-7.46 (m, 3H), 7.18 (s, 1H), 7.04 (s 1H), 6.03-5.90 (m, 1H), 5.40-5.34 (m, 1H), 5.15-5.08 (m, 2H), 4.78 (dd, 2H), 3.94 (s, 3H), 2.81-2.60, (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.46, 131.0, 130.8, 129.2, 128.9, 128.7, 128.6, 128.4, 128.3, 128.1, 128.1, 127.7, 127.6, 127.0, 126.7, 66.7, 54.0, 42.0, 41.5, 40.1; HRMS found 320.1525 M^+, calcd 320.1525 for $C_{20}H_{20}N_2O_2$; the enantiomers' retention times were determined by chiral HPLC (DAICEL

Chiralpack AD-H column, 5% EtOH/hexane, 1.0 mL/min, 23 °C, λ = 254 nm, retention times: *S* 20.5 min, *R* 32.8 min, 51 : 49 er).

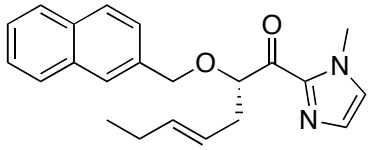


***(S)*-1-(1-methyl-1*H*-imidazol-2-yl)-2-(naphthalen-2-ylmethoxy) pent-4-en-1-one (table 3.6, entry 8).** Following the general procedure for racemic alkylations above on 50 mg scale, where allyl bromide was substituted for benzyl bromide, 51 mg of product (90%) were isolated as an off-white solid. Data are: TLC R_f = 0.50 (50% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.85-7.79 (m, 4H), 7.55-7.46 (m, 3H), 7.18 (s, 1H), 7.04 (s 1H), 6.03-5.90 (m, 1H), 5.40-5.34 (m, 1H), 5.15-5.08 (m, 2H), 4.78 (dd, 2H), 3.94 (s, 3H), 2.81-2.60, (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.46, 131.0, 130.8, 129.2, 128.9, 128.7, 128.6, 128.4, 128.3, 128.1, 128.1, 127.7, 127.6, 127.0, 126.7, 66.7, 54.0, 42.0, 41.5, 40.1; HRMS found 320.1525 M^+, calcd 320.1525 for $C_{20}H_{20}N_2O_2$; the enantiomers' retention times were determined by chiral HPLC and compared to the racemic samples listed above (DAICEL Chiralpack AD-H column, 5% EtOH/hexane, 0.75 mL/min, 23 °C, λ = 254 nm, retention times: *S* (major) 25 min, *R* (minor) 35 min, 94 : 6 er).

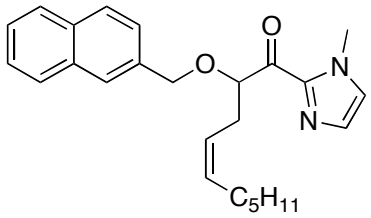


(±)-(*E*)-1-(1-methyl-1*H*-imidazol-2-yl)-2-(naphthalen-2-ylmethoxy) hept-4-en-1-one (Table 3.4, entry 9). Following the general procedure for racemic alkylations above on 50 mg scale, where *(E)*-1-bromo-2-pentene was substituted for benzyl bromide, 17 mg of product (27%) were

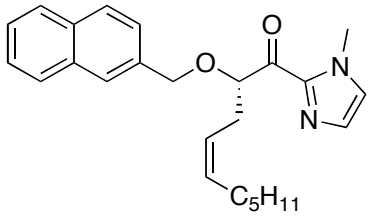
isolated as an off-white solid. Data are: TLC R_f= 0.27 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.83-7.79 (m, 4H), 7.52-7.44 (m, 3H), 7.15 (s, 1H), 7.01 (s, 1H), 5.54-5.51 (m, 2H), 5.33-5.29 (m, 1H), 4.76 (dd, 2H), 3.92 (s, 3H), 2.76-2.53 (m, 2H), 1.99 (q, *J* = 2 Hz, 2H), 0.92 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.8, 135.9, 135.5, 133.4, 133.2, 129.5, 128.1, 127.8, 127.2, 126.9, 126.3, 126.1, 126.0, 124.1, 100.2, 80.5, 72.6, 36.7, 36.1, 29.9, 25.8, 13.9; HRMS found 348.1838 M^+, calcd 348.1838 for $C_{22}H_{24}N_2O_2$; the enantiomers' retention times were determined by chiral HPLC (DAICEL Chiralpack AD-H column, 5% EtOH/hexane, 1.0 mL/min, 23 °C, λ = 254 nm, retention times: *S* 15.3 min, *R* 32.9 min, 53.8 : 46.2 er).



***(S)*-(*E*)-1-(1-methyl-1H-imidazol-2-yl)-2-(naphthalen-2-ylmethoxy) hept-4-en-1-one (Table 3.4, entry 9).** Following the general procedure for racemic alkylations above on 50 mg scale, where *(E)*-1-bromo-2-pentene was substituted for benzyl bromide, 50 mg of product (80%) were isolated as an off-white solid. Data are: TLC R_f= 0.34 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.83-7.79 (m, 4H), 7.52-7.44 (m, 3H), 7.15 (s, 1H), 7.01 (s, 1H), 5.54-5.51 (m, 2H), 5.33-5.29 (m, 1H), 4.76 (dd, 2H), 3.92 (s, 3H), 2.76-2.53 (m, 2H), 1.99 (q, *J* = 2 Hz, 2H), 0.92 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.8, 135.9, 135.5, 133.4, 133.2, 129.5, 128.1, 127.8, 127.2, 126.9, 126.3, 126.1, 126.0, 124.1, 100.2, 80.5, 72.6, 36.7, 36.1, 29.9, 25.8, 13.9; HRMS found 348.1838 M^+, calcd 348.1838 for $C_{22}H_{24}N_2O_2$; the enantiomers' retention times were determined by chiral HPLC and compared to the racemic samples listed above (DAICEL Chiralpack AD-H column, 5% EtOH/hexane, 1.0 mL/min, 23 °C, λ = 254 nm, retention times: *S* (major) 17.6 min, *R* (minor) 34.2 min, 95.8 : 4.2 er).

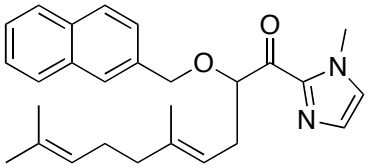


(±)-(*Z*)-1-(1-methyl-1*H*-imidazol-2-yl)-2-(naphthalen-2-ylmethoxy) dec-4-en-1-one (Table 3.4, entry 10). Following the general procedure for racemic alkylations above on 50 mg scale, where *(Z)*-1-bromo-2-octene (described in chapter 5's experimental section) was substituted for benzyl bromide, 14 mg of product (20%) were isolated as an off-white solid. Data are: TLC R_f= 0.27 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.85-7.79 (m, 4H), 7.3-7.44 (m, 3H), 7.15 (s, 1H), 7.01 (s, 1H), 5.54-5.45 (m, 2H), 5.32 (t, *J* = 5.4 Hz, 1H), 4.76 (dd, 2H), 3.92 (s, 3H), 2.74-2.68 (m, 2H), 1.95-1.91 (m, 2H), 1.27-1.22 (m, 6H), 0.85 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.6, 135.9, 133.5, 133.2, 133.0, 129.6, 128.5, 128.1, 127.8, 127.2, 126.9, 126.3, 126.1, 125.9, 125.6, 125.4, 124.2, 80.5, 72.7, 36.1, 31.5, 29.4, 27.5, 22.7, 14.2; HRMS found 390.2307 M^+, calcd 390.2307 for $C_{25}H_{30}N_2O_2$; the enantiomers' retention times were determined by chiral HPLC (DAICEL Chiralpack AD-H column, 5% EtOH/hexane, 1.0 mL/min, 23 °C, λ = 254 nm, retention times: *S* 12.1 min, *R* 16.6 min, 51.3 : 48.7 er).



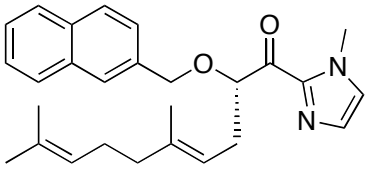
***(S)*-(*Z*)-1-(1-methyl-1H-imidazol-2-yl)-2-(naphthalen-2-ylmethoxy) dec-4-en-1-one (Table 3.4, entry 10).** Following the general procedure for racemic alkylations above on 50 mg scale, where *(Z)*-1-bromo-2-octene (described in chapter 5's experimental section) was substituted for benzyl bromide, 53.5 mg of product (77%) were isolated as an off-white solid. Data are: TLC R_f

= 0.27 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.85-7.79 (m, 4H), 7.3-7.44 (m, 3H), 7.15 (s, 1H), 7.01 (s, 1H), 5.54-5.45 (m, 2H), 5.32 (t, *J* = 5.4 Hz, 1H), 4.76 (dd, 2H), 3.92 (s, 3H), 2.74-2.68 (m, 2H), 1.95-1.91 (m, 2H), 1.27-1.22 (m, 6H), 0.85 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.6, 135.9, 133.5, 133.2, 133.0, 129.6, 128.5, 128.1, 127.8, 127.2, 126.9, 126.3, 126.1, 125.9, 125.6, 125.4, 124.2, 80.5, 72.7, 36.1, 31.5, 29.4, 27.5, 22.7, 14.2; HRMS found 390.2307 M^+, calcd 390.2307 for $C_{25}H_{30}N_2O_2$; the enantiomers' retention times were determined by chiral HPLC and compared to the racemic samples listed above (DAICEL Chiralpack AD-H column, 5% EtOH/hexane, 1.0 mL/min, 23 °C, λ = 254 nm, retention times: *S* 11.2 min, *R* 13.5 min, 89.5 : 10.5 er).



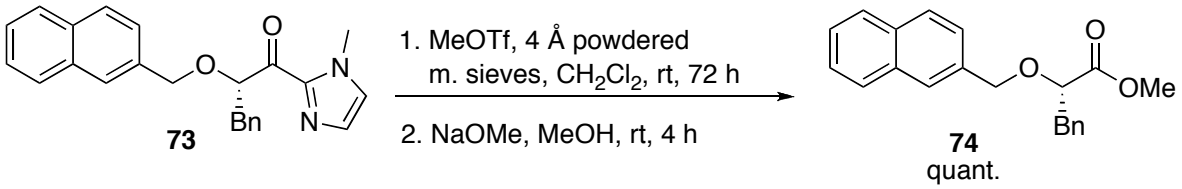
(±)-(*E*)-5,9-dimethyl-1-(1-methyl-1H-imidazol-2-yl)-2-(naphthalen-2-ylmethoxy) deca-4,8-dien-1-one (Table 3.4, entry 11). Following the general procedure for racemic alkylations above on 50 mg scale, where geranyl bromide was substituted for benzyl bromide, 34.8 mg of product (47%) were isolated as an off-white solid. Data are: TLC R_f= 0.64 (50% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.85-7.77 (m, 4H), 7.55-7.44 (m, 3H), 7.16 (s, 1H), 7.02 (s, 1H), 5.35-5.29 (m, 2H), 5.19-5.05 (m, 1H), 4.78 (dd, 2H), 3.93 (s, 3H), 2.73-2.51, (m, 2H), 2.0 (bs, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.56 (s, 3H), 1.29-1.23 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.9, 142.3, 138.2, 135.9, 131.6, 130.7, 129.9, 128.2, 127.8, 127.4, 126.9, 126.5, 126.4, 126.1, 126.0, 125.1, 124.5, 119.2, 80.6, 72.7, 40.0, 32.3 30.0, 26.9, 25.6, 18.7, 16.5; HRMS found 416.2464 M^+, calcd 416.2464 for $C_{27}H_{32}N_2O_2$; the enantiomers' retention

times were determined by chiral HPLC (DAICEL Chiralpack AD-H column, 10% EtOH/hexane, 1.0 mL/min, 23 °C, λ = 254 nm, retention times: *S* 7.9 min, *R* 12.1 min, 50.5 : 48.5 er).



***(S)*-(*E*)-5,9-dimethyl-1-(1-methyl-1H-imidazol-2-yl)-2-(naphthalen-2-ylmethoxy) deca-4,8-dien-1-one (Table 3.4, entry 11).** Following the general procedure for racemic alkylations above on 50 mg scale, where geranyl bromide was substituted for benzyl bromide, 74 mg of product (75%) were isolated as an off-white solid. Data are: TLC R_f= 0.64 (50% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.85-7.77 (m, 4H), 7.55-7.44 (m, 3H), 7.16 (s, 1H), 7.02 (s, 1H), 5.35-5.29 (m, 2H), 5.19-5.05 (m, 1H), 4.78 (dd, 2H), 3.93 (s, 3H), 2.73-2.51, (m, 2H), 2.0 (bs, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.56 (s, 3H), 1.29-1.23 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12341234; HRMS found 416.2464 M^+, calcd 416.2464 for $C_{27}H_{32}N_2O_2$; the enantiomers' retention times were determined by chiral HPLC and compared to the racemic samples listed above (DAICEL Chiralpack AD-H column, 10% EtOH/hexane, 1.0 mL/min, 23 °C, λ = 254 nm, retention times: *S* (major) 7.9 min, *R* (minor) 12.1 min, 87.5 : 12.5 er).

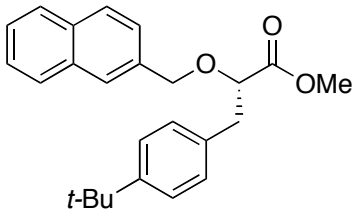
7.3.7. General Procedure for Converting Imidazole Products to Methyl Esters



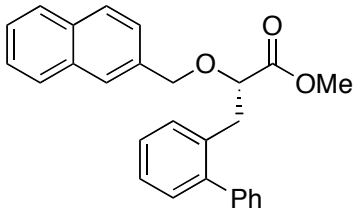
73 **74** quant.

***(S)*-Methyl 2-(naphthalen-2-ylmethoxy)-3-phenylpropanoate (74).** To a flame-dried 10 mL round bottom flask was added 1-(1-methyl-1*H*-imidazol-2-yl)-2-(naphthalen-2-ylmethoxy)-3-

phenylpropan-1-one **73** (0.058 g, 0.156 mmol), powdered 4 Å molecular sieves (0.039 g), and CH_2Cl_2 (3.12 mL). These were stirred vigorously at room temperature for 5 minutes. Methyl triflate (0.177 mL, 1.56 mmol) was then added in one portion. This mixture was stirred at room temperature for 72 hours, monitored by TLC for the consumption of starting material (R_f = 0.33, 30% EtOAc/Hexanes). Anhydrous methanol (3.12 mL) was then added, followed by dry sodium methoxide (0.064 g, 1.19 mmol). The mixture was then stirred for 4 hours at room temperature. It was afterward diluted with H_2O (10 mL) and CH_2Cl_2 (20 mL). The layers were mixed and then separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated by rotary evaporator. The crude residue was purified by column chromatography (10% EtOAc/hexanes) to afford 0.050 g (quant.) of the desired compound as an off-white solid. Data are: TLC R_f= 0.75 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.82-7.80 (m, 1H), 7.74-7.72 (m, 2H), 7.56 (s, 1H), 7.48-7.46 (m, 3H), 7.33-7.23 (m, 5H), 4.70 (dd, 2H), 4.20 (q, *J* = 2 Hz, 1H), 3.75 (s, 3H), 3.14-3.04 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.0, 137.3, 135.0, 133.4, 133.2, 129.8, 128.6, 128.3, 128.2, 127.8, 127.0, 126.8, 126.3, 126.1, 125.9, 79.3, 72.7, 52.2, 39.8; HRMS found 338.1751 $[M+NH_4]^+$, calcd 338.1751 for $[C_{21}H_{20}O_3 \cdot NH_4]+$. The enantiomers' retention times were determined by chiral HPLC and compared to samples prepared from racemic **74**. The data revealed that no racemization had occurred. (DAICEL Chiralpack AD-H column, 5% EtOH/hexane, 0.75 mL/min, 23 °C, λ = 254 nm, retention times: *S* (major) 15.2 min, *R* (minor) 18.8 min, 95.5 : 4.5 er). Racemic **74** HPLC data (same column/conditions): *S* (major) 17.6, *R* (minor) 20.9 min, 54 : 46 er.



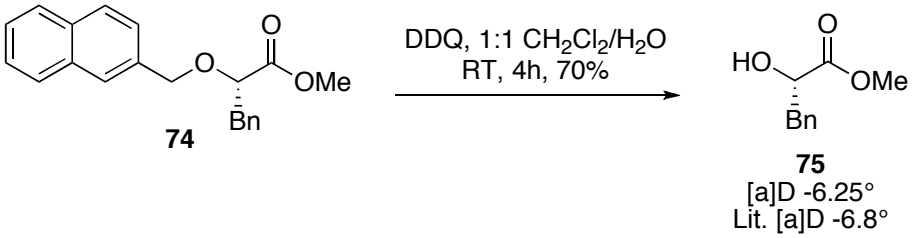
***(S)*-methyl 3-(4-tert-butylphenyl)-2-(naphthalen-2-ylmethoxy)propanoate.** Following the general procedure for converting imidazole products to methyl esters above, the product was obtained in quantitative yield as an off-white solid. Data are: TLC R_f= 0.72 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.85-7.82 (m, 2H), 7.76-7.74 (m, 2H), 7.61 (s, 2H), 7.51-7.46 (m, 2H), 7.38-7.20 (m, 3H), 4.74 (dd, 2H), 4.23 (dd, *J* = 1.5 Hz, 1H), 3.78 (s, 3H), 3.11-3.07 (m, 2H), 1.38 (s, 9 H), ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.1, 135.1, 134.3, 133.2, 129.5, 128.3, 128.2, 127.9, 126.8, 126.2, 126.1, 125.9, 125.5, 79.4, 72.6, 52.2, 39.2, 34.7, 31.7; HRMS found 376.2039 $[M]^+$, calcd 376.2039 for $C_{25}H_{28}O_3^+$. The data revealed that no racemization had occurred. (DAICEL Chiralpack AD-H column, 5% EtOH/hexane, 0.75 mL/min, 23 °C, λ = 254 nm, retention times: *S* (major) 9.0 min, *R* (minor) 10.0 min, 96 : 4 er.) Racemic data (same column/conditions): *S* (major) 5.9 min, *R* (minor) 6.5 min, 54 : 46 er.



***(S)*-methyl 3-(biphenyl-2-yl)-2-(naphthalen-2-ylmethoxy)propanoate.** Following the general procedure for converting imidazole products to methyl esters above, the product was obtained in quantitative yield as an off-white solid. Data are: TLC R_f= 0.63 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.87-7.85 (m, 2H), 7.83-7.73 (m, 2H), 7.53-7.50 (m, 2H), 7.41-7.29 (m, 2H), 7.25-7.15 (m, 8H), 4.60 (dd, 2H), 3.99 (dd, *J* = 1.6 Hz, 1H), 3.67 (s, 3H), 3.24-3.08 (m,

2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.9, 142.8, 141.5, 135.0, 134.6, 133.4, 133.3, 130.9, 130.5, 129.5, 128.4, 128.3, 128.2, 127.9, 127.6, 127.2, 127.0, 126.9, 126.3, 126.1, 126.0, 78.4, 72.6, 52.1, 36.4; HRMS found 396.1725 $[M]^+$, calcd 396.1725 for $C_{27}H_{24}O_3^+$. The data revealed that no racemization had occurred. (DAICEL Chiralpack AD-H column, 1% EtOH/hexane, 0.75 mL/min, 23 °C, λ = 254 nm, retention times: *S* (major) 20.3 min, *R* (minor) 22.1 min, 90 : 10 er.) Racemic data (same column/conditions): *S* (major) 20.05 min, *R* (minor) 21.72 min, 53 : 47 er.

7.3.8. 2-NPM Removal with DDQ

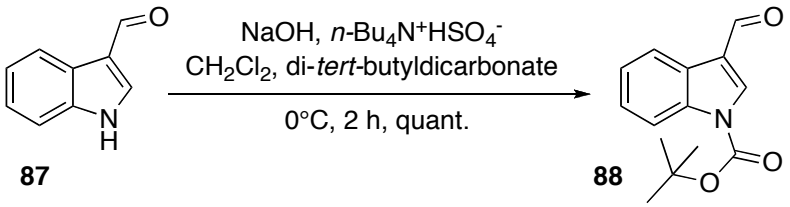


***(S)*-methyl 2-hydroxy-3-phenylpropanoate (75).** To a flame-dried 10 mL round bottom flask was added (*S*)-methyl 2-(naphthalen-2-ylmethoxy)-3-phenylpropanoate (0.075 g, 0.234 mmol), CH_2Cl_2 (9.36 mL), and H_2O (1.87 mL), and the mixture was stirred for 5 minutes a room temperature. DDQ (0.106 g, 0.468 mmol) was then added, turning the solution a black-brown color, and the reaction was stirred at room temperature for 4 hours. It was quenched by the addition of a saturated aqueous solution of sodium thiosulfate (30 mL) and was then diluted with EtOAc (50 mL) and saturated aqueous sodium bicarbonate (20 mL). The layers were mixed and then separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated by rotary evaporator. The crude residue was purified by column chromatography (10% EtOAc/hexanes) to afford 0.030 g (70%) of the desired compound as an off-white solid. (Note: when dilute, this product is only

faintly UV-visible, but stains well if spotted heavily on the TLC plate.) Data are: TLC R_f= 0.18 (20% EtOAc/hexanes); $[\alpha]_D^{26}$ = -6.25° (c 0.48, $CHCl_3$), lit. $[\alpha]_D^{24}$ =-6.8° (c 1.39, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36-7.24 (m, 5H), 4.51-4.47 (m, 1H), 3.81 (s, 3H), 3.20-2.97 (m, 2H), 2.78-2.76 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.8, 136.5, 129.7, 128.7, 127.2, 71.5, 52.7, 40.8; HRMS found 180.0786 $[M]^+$, calcd 180.0786 for $[C_{10}H_{12}O_3]$+. Product verification and absolute configuration were obtained by optical rotation comparison with Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168-4178.

7.4. Procedures from Chapter 4

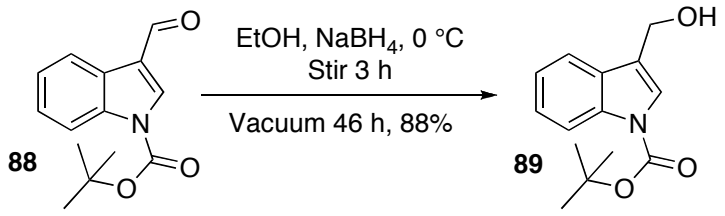
7.4.1. Synthesis of Electrophile 44



87 **88**

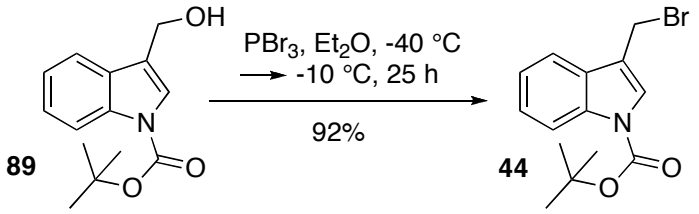
***N*-(*tert*-butoxycarbonyl)-3-formyl indole (88).** To a flame-dried 250 mL round bottom flask with a stir bar were added powdered NaOH (7.58 g, 189.44 mmol, 2.75 equiv) and tetra-*n*-butylammonium hydrogensulfate (470 mg, 1.378 mmol, 0.02 equiv). These were dissolved in anhydrous CH_2Cl_2 (92 mL, 0.75 M with respect to the indole), and the resulting suspension was cooled, under N_2 atmosphere, to 0°C. Indole-3-carboxyaldehyde (**87**) was then added in one portion (10 g, 68.889 mmol, 1 equiv), and the resulting suspension was stirred at 0°C for 10 minutes. At this stage, a solution of di-tertbutyldicarbonate (16.54 g, 75.78 mmol, 1.1 equiv) in CH_2Cl_2 (pre-chilled to 0 °C, 46 mL, 1.5 M) was added. This suspension was stirred at 0°C for 20 minutes, after which time more CH_2Cl_2 (46 mL, 1.5 M) was added. The combined mixture was

then stirred at 0°C for 2 h. The reaction was quenched by adding a saturated solution of aqueous $NaHCO_3$ (50 mL). The layers were mixed and then separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 150 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated by rotary evaporation, and left under high vacuum for 1 h to give 16.9 g (quant. yield) of **88** as an off-white, crystalline solid, used without further purification. Data are: TLC R*f* = 0.85 (40% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.12 (d, *J* = 1.4 Hz, 1 H), 8.32 (d, *J* = 3.6 Hz, 1H), 8.25 (d, *J* = 1.2 Hz, 1H), 8.18 (d, *J* = 3.9 Hz, 1H), 7.45 – 7.40 (m, 2H), 1.75 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 186.0, 136.8, 126.3, 124.8, 122.3, 121.7, 115.4, 85.9, 28.3.



***Tert*-butyl 3-(hydroxymethyl)-1*H*-indole-1-carboxylate (89).** To a flame-dried 250 mL round bottom flask with a stir bar, *N*-(*tert*-butoxycarbonyl)-3-formyl indole **88** (16.9 g, 69.28 mmol, 1 equiv) was dissolved in anhydrous EtOH (92 mL, 0.75 M) and was cooled under N_2 to 0 °C. $NaBH_4$ was then added (5.241 g, 138.56 mmol, 2 equiv). The resulting suspension was stirred for 30 minutes at 0 °C and then allowed to warm to RT and stir for 2.5 h, monitored for consumption of the starting material by TLC. The EtOH was then evaporated off using a rotary evaporator, and the crude product was diluted in 1.0 N aqueous NaOH (50 mL). The aqueous layer was extracted with Et_2O (3 x 150 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated by rotary evaporator to give a yellow, viscous oil, which was left under high vacuum for 46 h to remove the triethoxy borane byproduct. This gave 15.08 g

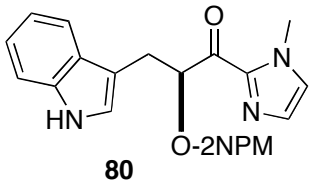
(88%) of the final product as a viscous, clear, colorless oil, which eventually crystallized as an off-white solid after refrigeration. Data are: TLC R*f* = 0.48 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.14 (bs, 1 H), 7.62 (d, *J* = 4 Hz, 1H), 7.56 (s, 1H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.25 (t, *J* = 7.5 Hz, 1H), 4.79 (s, 2H), 1.67 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 150.0, 135.9, 129.4, 124.8, 123.9, 122.9, 120.8, 119.6, 115.5, 84.0, 57.2, 28.4.



***Tert*-butyl 3-(bromomethyl)-1*H*-indole-1-carboxylate (44).** Phosphorous tribromide (0.683 mL, 7.27 mmol, 0.4 equiv) was carefully dissolved in Et_2O (11.4 mL, 1.6 M with respect to the indole) in a flame-dried 100 mL round bottom flask (flask A) with a stir bar. This solution was then cooled under N_2 to -40 °C. In a separate flame-dried, 25 mL pear-bottomed flask with a spin vane (flask B), *tert*-butyl 3-(hydroxymethyl)-1*H*-indole-1-carboxylate **83** (4.5 g, 18.197 mmol, 1.0 equiv) was dissolved in Et_2O (11.4 mL, 1.6 M). This solution was also cooled under N_2 to -40 °C. Once both flasks were cooled and stirring homogeneously, the contents of flask B were transferred dropwise, via syringe, to flask A. Flask B was then rinsed twice with 11.4 mL of Et_2O at ambient temperature, with each rinse being transferred into flask B, bringing the total Et_2O volume to 45.6 mL. This reaction suspension was then raised to -10 °C and became a yellow-pink solution. It was afterward stirred at -10 °C for 25 h, until the starting material had been consumed (as visualized by TLC). The reaction was quenched by adding ice water (100 mL) and Et_2O (150 mL). The layers were mixed and then separated, and the aqueous layer was extracted with Et_2O (3 x 75 mL). The combined organic layers were washed with brine (50 mL),

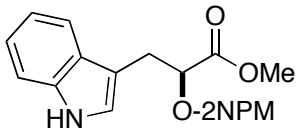
dried over $MgSO_4$, filtered, concentrated by rotary evaporator, and left under high vacuum for 1 h to give 5.15 g (92% yield) of as an off-white crystalline solid, used without further purification. Data are: TLC R*f* = 0.82 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.15 (bs, 1 H), 7.7 (q, *J* = 3.5 Hz, 2H), 7.39 – 7.31 (m, 2H), 4.70 (s, 2H), 1.68 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.6, 135.9, 128.9, 125.3, 125.2, 123.1, 119.6, 117.4, 115.7, 84.4, 28.4, 24.8. Note: this compound should be stored at -20 °C under argon or nitrogen. This compound gradually decomposes within about two to three weeks –even when properly stored—to form a dark purple, crystalline solid. Once it has this appearance, it will no longer give good asymmetric results as an alkylation electrophile.

7.4.2. Alkylating Substrate 58 with Indole Electrophile 44



80

***(S)-Tert*-butyl 3-(3-(1-methyl-1*H*-imidazol-2-yl)-2-(naphthalen-2-ylmethoxy)-3-oxopropyl)-1*H*-indole-1-carboxylate (80).** Preparation of this compound is detailed above under section 7.3.6.

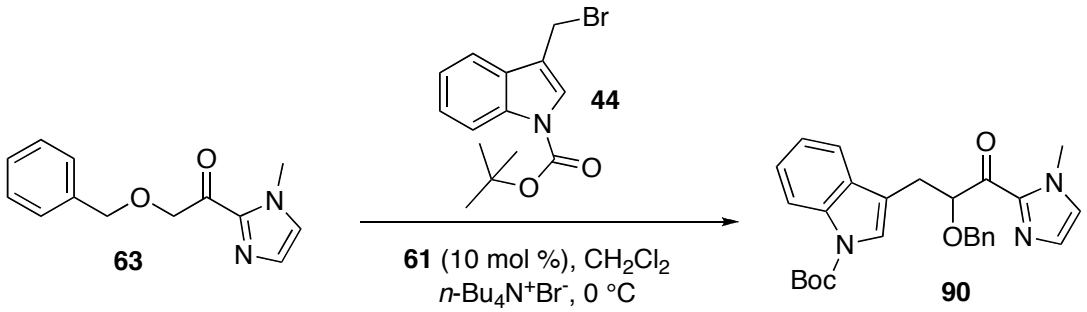


82
75%, 84% ee

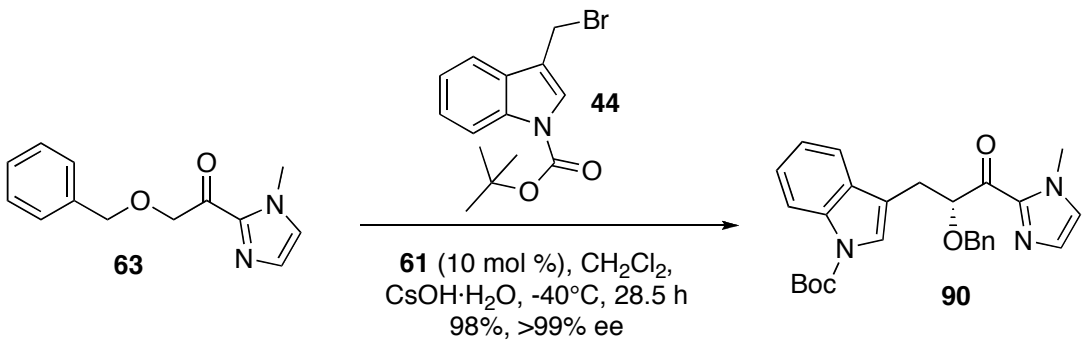
***(S)*-methyl 3-(1*H*-indol-3-yl)-2-(naphthalen-2-ylmethoxy)propanoate (82).** To a flame-dried 50 mL round bottom flask was added **80** (0.5 g, 0.98 mmol), powdered 4 Å molecular sieves

(0.098 g), and CH_3CN (5.8 mL). These were stirred vigorously at room temperature for 5 minutes. Methyl triflate (0.245 mL, 2.16 mmol) was then added in one portion. This mixture was stirred at room temperature for 24 hours, monitored by TLC for the consumption of starting material (R_f = 0.78, 50% EtOAc/Hexanes). Anhydrous methanol (5.8 mL) was then added, followed by DBU (1.4 mL). The mixture was then stirred for 1 hour at room temperature. It was afterward diluted with H_2O (50 mL) and CH_2Cl_2 (100 mL). The layers were mixed and then separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 75 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by column chromatography (20% EtOAc/hexanes) to afford 0.264 g (75%) of the desired compound as an off-white solid. Data are: TLC R_f= 0.75 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.13 (bs, 1H), 7.79 (d, *J*=2.5 Hz, 1H), 7.71-7.68 (m, 2H), 7.60 (s, 1H), 7.50-7.46 (m, 4H), 7.30-7.27 (m, 4H), 7.16 (t, *J*=7.5 Hz, 1H), 4.87 (d, *J* = 6 Hz, 1H), 4.58 (d, *J* = 5.75 Hz, 1H), 4.29-4.28 (m, 1H), 3.74 (s, 3H), 3.23-3.14 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.3, 136.3, 135.1, 133.4, 128.3, 128.2, 127.9, 126.9, 126.2, 126.1, 126.0, 123.4, 122.2, 120.0, 119.1, 111.3, 78.9, 72.8, 52.2, 30.0, 29.3; HRMS found 359.1521 $[M]^+$, calcd 359.1521 for $[C_{23}H_{21}NO_3]^+$. The enantiomers' retention times were determined by chiral HPLC and compared to samples prepared from racemic **75**. The data revealed slight racemization, with **75** being obtained in 84% ee. (DAICEL Chiralpack AD-H column, 5% EtOH/hexane, 0.75 mL/min, 23 °C, λ = 254 nm, retention times: *S* (major) 30.4 min, *R* (minor) 43.7 min, 92 : 8.0 er). Racemic **67** HPLC data (same column/conditions): *S* (major) 31.2, *R* (minor) 44.1 min, 52 : 48 er.

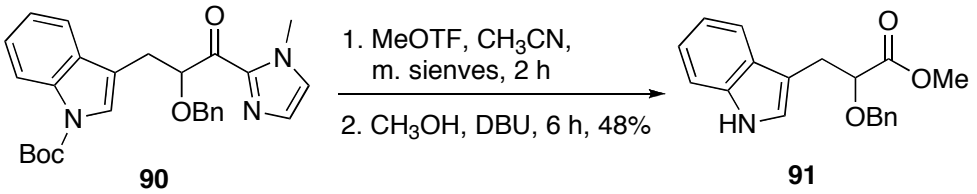
7.4.3. Total Synthesis of (+)-Kurasoin B



(±)-*Tert*-butyl 3-(2-(benzyloxy)-3-(1-methyl-1*H*-imidazol-2-yl)-3-oxopropyl)-1*H*-indole-1-carboxylate (90). Following the general procedure for racemic alkylations (section 7.3.4 above) on 50 mg scale, where electrophile **44** (section 7.4.1 above) was substituted for benzyl bromide, 0.085 g (85%) of **90** were isolated as an off-white solid. Data are: TLC R_f= 0.74 (40% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.13 (bs, 1H), 7.55 (d, *J* = 3.75 Hz, 1H), 7.50 (s, 1H), 7.29 (t, *J* = 9.5 Hz, 2H), 7.22 – 7.17 (m, 6 H), 7.06 (s, 1H), 5.52 (dd, *J* = 2 Hz, 1H), 4.67 (d, *J* = 6 Hz, 1H), 4.43 (d, *J* = 5.75 Hz, 1H), 3.91 (s, 3H), 3.40-3.37 (m, 1H), 3.20-3.15 (m, 1H), 1.67 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 191.14, 142.21, 138.1, 129.8, 128.4, 128.1, 127.8, 127.4, 124.8, 124.3, 122.5, 119.6, 116.5, 115.2, 83.5, 80.1, 72.7, 36.2, 29.3, 28.5; HRMS found 459.2153 M^+, calcd 459.2158 for $C_{27}H_{29}N_3O_4$; the enantiomers' retention times were determined by chiral HPLC (DAICEL Chiralpack AD-H column): 10% EtOH/hexane, 0.75 mL/min, 23 °C, λ = 254 nm, retention times: *S* 7.11 min, *R* 93.10 min, 50.8 : 49.2 er).

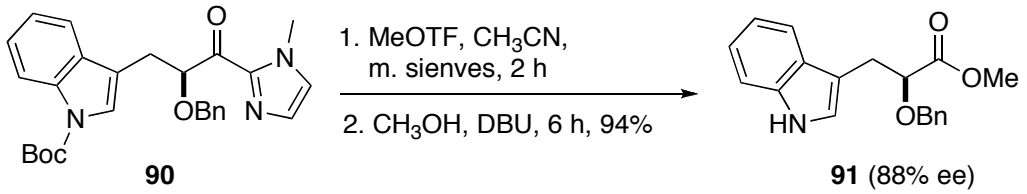


***(S)-tert*-butyl 3-(2-(benzyloxy)-3-(1-methyl-1*H*-imidazol-2-yl)-3-oxopropyl)-1*H*-indole-1-carboxylate (84).** Following the general procedure for asymmetric alkylations (section 7.3.5 above) on 4.66 g scale, where electrophile **44** (section 7.4.1 above) was substituted for benzyl bromide, 9.12 g (98%) of **90** were isolated as an off-white solid. Data are: TLC R_f = 0.56 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.14 (bs, 1H), 7.55 (d, *J* = 3.75 Hz, 1H), 7.50 (s, 1H), 7.29 (t, *J* = 9.5 Hz, 2H), 7.22 – 7.17 (m, 6 H), 7.06 (s, 1H), 5.52 (dd, *J* = 2 Hz, 1H), 4.67 (d, *J* = 6 Hz, 1H), 4.43 (d, *J* = 5.75 Hz, 1H), 3.91 (s, 3H), 3.40-3.37 (m, 1H), 3.20-3.15 (m, 1H), 1.67 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 191.14, 149.9, 142.2, 138.1, 131.0, 129.8, 128.4, 128.1, 127.8, 127.4, 124.8, 124.3, 122.5, 119.6, 116.5, 115.2, 83.5, 80.1, 72.7, 36.2, 29.3, 28.5; HRMS found 459.2153 M^+, calcd 459.2158 for $C_{27}H_{29}N_3O_4$; the enantiomers' retention times were determined by chiral HPLC (DAICEL Chiralpack AD-H column): 10% EtOH/hexane, 0.75 mL/min, 23 °C, λ = 254 nm, retention times: *S* (major) 9.99 min, *R* (minor) >99 : <1 er). $[\alpha]_D^{24}$ = +16.75° (c 5.55, $CHCl_3$).



90 **91**

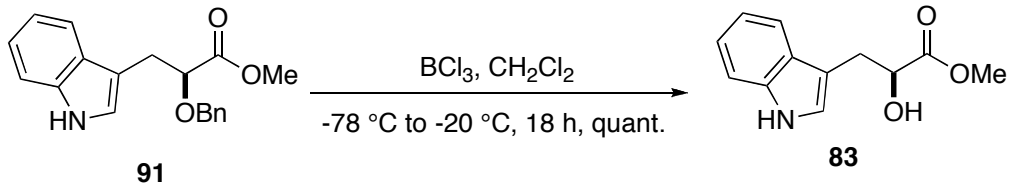
(±)-Methyl-2-(benzyloxy)-3-(1*H*-indol-3-yl) propanoate (91). Following the general procedure for compound **74** (section 7.3.7 above) on 84 mg scale, 0.027 g (48%) of **91** were isolated as a yellow oil. TLC showed formation of two products: **91** (R_f= 0.75 in 30% EtOAc/hexanes) and Boc-deprotected **90** (R_f= 0.31 in 30% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.057 (bs, 1H), 7.61 (d, *J* = 3.9 Hz, 1H), 7.38 (d, *J* = 4 Hz, 1H), 7.28 – 7.10 (m, 8H), 4.73 (d, *J* = 5.75 Hz, 1H), 4.48 (d, *J* = 5.75 Hz, 1H), 4.28 (dd, *J1* = 1 Hz, *J2* = 5 Hz, 1H), 3.72 (s, 3 H), 3.35 – 3.26 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 128.5, 128.2, 127.9, 123.4, 122.2, 119.6, 119.1, 111.3, 78.9, 72.7, 52.1, 29.2; HRMS found 310.1434 $[M+H]^+$, calcd 310.1438 for $[C_{19}H_{20}NO_3]$+; the enantiomers' retention times were determined by chiral HPLC (DAICEL Chiralpack AD-H column): 10% EtOH/hexane, 0.75 mL/min, 23 °C, λ = 254 nm, retention times: *S* (major) 17.05 min, *R* (minor) 21.38 min, 50.2 : 49.8 er).



90 **91** (88% ee)

***(S)*-methyl 2-(benzyloxy)-3-(1*H*-indol-3-yl)propanoate (91).** To a flame-dried 100 mL round bottom flask was added *(S)-tert*-butyl 3-(2-(benzyloxy)-3-(1-methyl-1H-imidazol-2-yl)-3-oxopropyl)-1*H*-indole-1-carboxylate **90** (5.5 g, 11.976 mmol, 1 equiv), powdered 4 Å molecular sieves (1.2 g), and CH_3CN (70 mL, 0.17 M). These were stirred vigorously at room temperature for 5 minutes. Methyl triflate (6.78 mL, 59.88 mmol, 5.0 equiv) was then added in one portion,

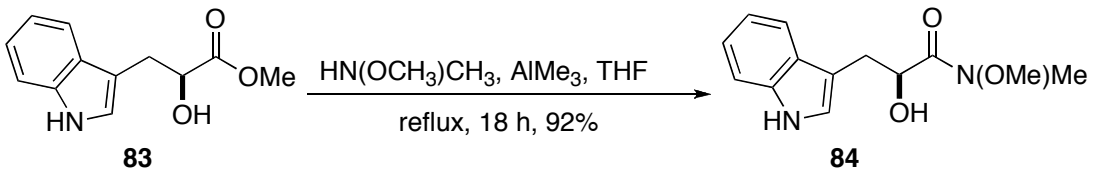
and the mixture was stirred at room temperature for 2 hours, after which time the starting material was completely consumed, giving only methylated baseline intermediate (TLC). Anhydrous methanol (70 mL, 0.17 M) was then added, followed by DBU (4.48 mL, 29.94 mmol, 2.5 equiv), and the mixture was stirred for 6 hours at room temperature. The reaction was then quenched by adding H_2O (60 mL) and CH_2Cl_2 (125 mL) and was transferred to a separatory funnel. The layers were mixed and then separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 70 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated by rotary evaporator. TLC showed that two products were formed: the desired product (R_f= 0.69 in 30% EtOAc/hexanes) and deprotected starting material (R_f = 0.33 in 30% EtOAc/hexanes). The crude residue was purified by column chromatography (20% EtOAc/hexanes) to afford 3.48 g (94%) of the target compound as a yellow oil. Data are: TLC R_f= 0.69 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.305 (d, *J* = 4.5 Hz, 1H), 7.62 (d, *J* = 4 Hz, 1H), 7.33 – 7.18 (m, 7H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.00 (s, 1H), 4.73 (d, *J* = 5.75 Hz, 1H), 4.48 (d, *J* = 5.75 Hz, 1H), 4.32 (dd, *J1* = 1 Hz, *J2* = 5 Hz, 1H), 3.72 (s, 3 H), 3.35 – 3.26 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.4, 137.7, 136.3, 128.6, 128.5, 128.2, 127.7, 123.7, 122.1, 119.5, 119.0, 111.5, 110.7, 79.0, 72.8, 52.2, 29.3; HRMS found 310.1434 $[M+H]^+$, calcd 310.1438 for $[C_{19}H_{20}NO_3]$+; the enantiomers' retention times were determined by chiral HPLC (DAICEL Chiralpack AD-H column): 10% EtOH/hexane, 0.75 mL/min, 23 °C, λ = 254 nm, retention times: *S* (major) 16.99 min, *R* (minor) 21.69 min, 94.1 : 5.9 er). $[\alpha]_D^{24}$ = +34.68° (c 2.508, $CHCl_3$).



91 **83**

***(S)*-methyl 2-hydroxy-3-(1*H*-indol-3-yl)propanoate (83).** *(S)*-methyl 2-(benzyloxy)-3-(1H-indol-3-yl)propanoate **91** (2.5 g, 8.087 mmol, 1 equiv) was dissolved in CH_2Cl_2 (45 mL, 0.18 M) in a flame-dried 100 mL round bottom flask and was cooled, while stirring under N_2, to -78 °C. A solution of BCl_3 (1.0 M in CH_2Cl_2, 20.22 mL, 20.22 mmol, 2.5 equiv) was then added slowly over 45 minutes, and the entire reaction was stirred for 1 h at -78 °C under N_2. The reaction mixture was then warmed to -20 °C and was kept stirring at -20 °C for 18 h. Once the starting material had been consumed (as observed by TLC), the reaction was diluted with 50 mL of a 1:1 MeOH : CH_2Cl_2 solution that had been pre-chilled to -40 °C prior to its addition. The resulting mixture was then warmed to RT, and the solvent was removed under reduced pressure using a rotary evaporator. More 1:1 MeOH : CH_2Cl_2 (50 mL at ambient temperature) was added and was subsequently removed using the rotary evaporator. Then an additional amount of 1:1 MeOH/CH_2Cl_2 (50 mL at ambient temperature) was added, and was also removed using the rotary evaporator. The crude material was afterward diluted using a saturated solution of aqueous sodium bicarbonate (20 mL) and was transferred to a separatory funnel. The aqueous suspension was extracted with CH_2Cl_2 (3 x 75 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated by rotary evaporator. The crude material was purified by column chromatography (20% EtOAc/hexanes) to afford 1.77 g (quant.) of the target compound as a brown, crystalline solid. Data are: TLC R_f= 0.49 (40% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.17 (bs, 1H), 7.62 (d, J = 4 Hz, 1H), 7.34 (d, J = 3.75, 1H), 7.20 (t, J = 8 Hz, 1H), 7.14 (t, J = 7 Hz, 1H), 7.06 (bs, 1H), 4.55 (q, J = 2.5 Hz, 1H), 3.73 (s, 3H), 3.32-3.28 (m, 1H),

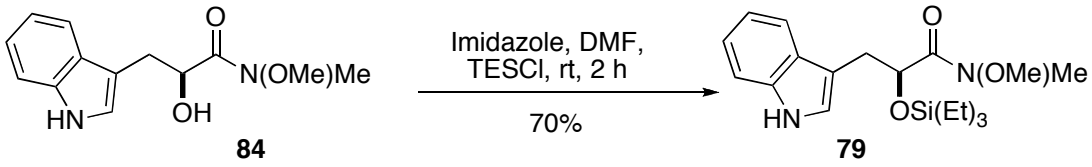
3.22-3.17 (m, 1H), 2.86 (d, J = 3.25 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.0, 136.4, 127.8, 123.5, 122.3, 119.7, 119.1, 111.5, 110.2, 71.0, 52.7, 30.5; HRMS found 220.0968 $[M+H]^+$, calcd 220.0968 for $[C_{12}H_{14}NO_3]$; $[\alpha]_D^{24}$ = +17.72° (c 1.69, $CHCl_3$).



83 **84**

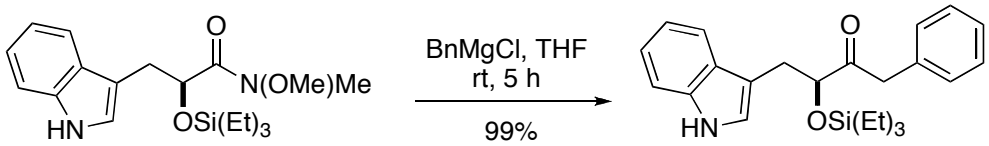
***(S)*-2-hydroxy-3-(1*H*-indol-3-yl)-*N*-methoxy-*N*-methylpropanamide (84).** *N,O*-dimethylhydroxylamine·HCl (0.111 g, 1.141 mmol, 5 equiv) was dissolved in THF (4.6 mL, 0.05 M with respect to ester substrate) in a flame-dried 10 mL round bottom flask with a stir bar. This was cooled, while stirring under N_2, to 0 °C. A solution of $AlMe_3$ (2.0 M in toluene, 0.57 mL, 1.14 mmol, 5.0 equiv) was then added, and the resulting suspension was warmed to RT and stirred for 30 minutes. This mixture was then transferred by cannula to a 25 mL round bottom flask (with stir bar) containing a solution of *(S)*-methyl 2-hydroxy-3-(1*H*-indol-3-yl)propanoate (**83**) (50 mg, 0.228 mmol, 1 equiv) in THF (2.28 mL, 0.1 M). At this stage the resulting suspension was warmed and stirred at reflux for 18 h. Once the starting material had been consumed (as observed by TLC), the reaction was cooled to RT and the crude material was transferred to a 100 mL round bottom flask containing Rochelle salts (23 mL) and CH_2Cl_2 (23 mL). The original reaction flask was then rinsed several times with additional CH_2Cl_2, and each rinse was added to the flask containing the Rochelle salts (this was to ensure complete transfer of the crude product). When it had been completely transferred to the 100 mL RB flask with the Rochelle salts, the mixture was stirred at RT for 1 hour, until clean separation of layers was observed. Once this occurred, the solution was transferred to a separatory funnel, and the layers were separated. The aqueous layer was then extracted with CH_2Cl_2 (3 x 30 mL). The combined

organic layers were washed with 1 N HCl (30 mL), and were also washed with a saturated solution of aqueous sodium bicarbonate (30 mL). The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated by rotary evaporator. The crude material was purified by column chromatography (40% EtOAc/hexanes), with the aliquots coming off the column being tested by TLC and HRMS for the presence of product. 52 mg (92%) of the target compound were isolated as a yellow, crystalline solid. Data are: TLC R_f= 0.41 (100% EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.12 (bs, 1H), 7.60 (d, *J* = 4 Hz, 1H), 7.35 (d, *J* = 3.5, 1H), 7.19 (t, *J* = 10 Hz, 1H), 7.13 – 7.10 (m, 2H), 4.70 (bs, 1H), 3.75 (s, 3H), 3.39 (d, *J* = 3.75 Hz, 1H), 3.28 – 3.05 (m, 2H), 3.22 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.5, 136.3, 127.9, 123.4, 122.1, 119.6, 118.8, 111.4, 111.3, 69.2, 61.7, 32.7, 30.8, 30.0; HRMS found 249.1234 $[M+H]^+$, calcd 249.1234 for $[C_{13}H_{17}N_2O_3]$; $[\alpha]_D^{24}$ = -2.4995° (c 0.52, $CHCl_3$).



***(S)*-3-(1*H*-indol-3-yl)-*N*-methoxy-*N*-methyl-2-(triethylsilyloxy)propanamide (79).** *(S)*-2-hydroxy-3-(1*H*-indol-3-yl)-*N*-methoxy-*N*-methylpropanamide **84** (49 mg, 0.197 mmol, 1 equiv) was dissolved in DMF (1.97 mL, 0.1 M) in a flame-dried 10 mL round bottom flask with a stir bar. Imidazole (54 mg, 0.79 mmol, 4 equiv) was then added, followed by chlorotriethylsilane (0.067 mL, 0.395 mmol, 2 equiv). This mixture was then stirred at RT for 2 hours. Once the starting material had been consumed (as observed by TLC), the reaction was diluted with distilled water (5 mL) and EtOAc (20 mL) and was transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporator. The

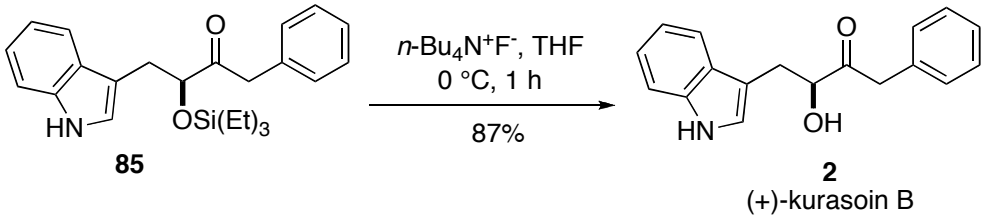
crude material was purified by column chromatography (30% EtOAc/hexanes), with the aliquots coming off the column being tested by TLC and HRMS for the presence of product. 49 mg (70%) of the target compound were isolated as a yellow, crystalline solid. Data are: TLC R_f= 0.56 (40% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.18 (bs, 1H), 7.63 (d, *J* = 3.75 Hz, 1H), 7.36 (d, *J* = 4, 1H), 7.18 (t, *J* = 7 Hz, 1H), 7.13 – 7.08 (m, 2H), 4.85 (bs, 1H), 3.30-3.27 (m, 1H), 3.16 (s, 3H), 3.08-3.04 (m, 1H), 0.85 (t, *J* = 7.5 Hz, 9H), 0.50 (q, *J* = 2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 136.4, 127.9, 123.8, 122.0, 119.5, 118.8, 111.6, 111.4, 69.4, 61.4, 32.6, 31.2, 30.0, 6.8, 4.8; HRMS found 363.2099 $[M+H]^+$, calcd 363.2098 for $[C_{19}H_{31}N_2O_3Si]$; $[\alpha]_D^{24}$ = +8.16° (c 0.49, $CHCl_3$).



79 **85**

***(S)*-4-(1*H*-indol-3-yl)-1-phenyl-3-(triethylsilyloxy)butan-2-one (85).** *(S)*-3-(1*H*-indol-3-yl)-*N*-methoxy-*N*-methyl-2-(triethylsilyloxy)propanamide **79** (91 mg, 0.357 mmol, 1 equiv) was dissolved in THF (4.25 mL, 0.059 M) in a flame-dried 10 mL round bottom flask with a stir bar. This solution was then cooled, while stirring under N_2, to 0 °C. A solution of benzylmagnesium chloride (2.0 M in THF, 0.628 mL, 1.255 mmol, 5.0 equiv) was then added slowly over 5 minutes, and the mixture was warmed to RT. It was then stirred at RT for 5 h, until the starting material had been consumed (as observed by TLC). The reaction was afterward diluted with distilled water (7 mL) and CH_2Cl_2 (20 mL) and was transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated by rotary evaporator.

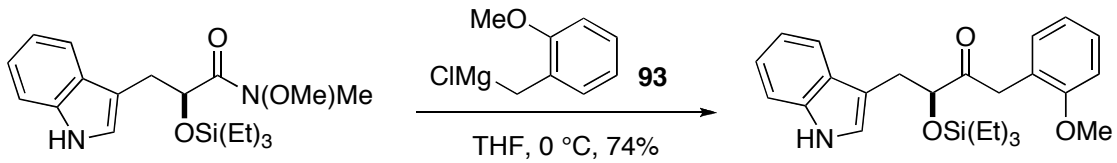
The crude material was purified by column chromatography (15% EtOAc/hexanes), with the aliquots coming off the column being tested by TLC and HRMS for the presence of product. 98 mg (99%) of the target compound were isolated as a clear, colorless oil. Data are: TLC R_f= 0.43 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.00 (bs, 1H), 7.60 (d, *J* = 3.75 Hz, 1H), 7.35 (d, *J* = 4.25, 1H), 7.26 – 7.18 (m, 4H), 7.12 (t, *J* = 7.5 Hz, 1H), 6.99 (bs, 1H), 6.94 (d, *J* = 3.5 Hz, 2H), 4.49 (t, *J* = 5.5 Hz, 1H), 3.75 (d, *J* = 8.25 Hz, 1H), 3.61 (d, *J* = 8.25 Hz, 1H), 3.13 (d, *J* = 2.75 Hz, 2H), 0.90 (t, *J* = 8 Hz, 9H), 0.52 (q, *J* = 4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 210.7, 136.0, 134.0, 129.7, 128.3, 127.7, 126.6, 123.2, 122.0, 119.5, 119.2, 111.0, 110.8, 78.6, 44.9, 31.4, 6.7, 4.7; HRMS found 394.2197 $[M+H]^+$, calcd 394.2197 for $[C_{24}H_{32}NO_2Si]$; $[\alpha]_D^{24}$ = -13.79° (c 0.29, $CHCl_3$).



(+)-Kurasoin B (2). *(S)*-4-(1*H*-indol-3-yl)-1-phenyl-3-(triethylsilyloxy)butan-2-one **85** (86 mg, 0.2187 mmol, 1 equiv) was dissolved in THF (1.57 mL, 0.042 M) in a flame-dried 10 mL round bottom flask with a stir bar. This solution was then cooled, while stirring under N_2, to 0 °C. A solution of tetra-*n*-butyl ammonium fluoride (1.0 M in THF, 0.235 mL, 0.23424 mmol, 1.071 equiv) was then added, and the reaction was stirred at 0 °C for 1 h, until the starting material had been consumed (as observed by TLC). The reaction was afterward diluted with a saturated solution of aqueous NH_4Cl (10 mL) and CH_2Cl_2 (30 mL) and was transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated by rotary

evaporator. The crude material was purified by column chromatography (30% EtOAc/hexanes), with the aliquots coming off the column being tested by TLC and HRMS for the presence of product. 53 mg (87%) of (+)-kurasoin B (**2**) were thereby isolated as an off-white crystalline solid. Synthetic data matched those of the natural product. Data are: TLC R_f= 0.38 (30% EtOAc/hexanes); ^{1}H NMR (CD_3OD, 500 MHz) δ 7.54 (d, *J* = 3.75 Hz, 1H), 7.35 (d, *J* = 4 Hz, 1H), 7.23 – 7.18 (m, 3H), 7.12 – 7.09 (m, 2H), 7.01 (t, *J* = 7 Hz, 2H), 6.96 (d, *J* = 3.75 Hz, 2H), 4.52 (t, *J* = 5.5 Hz, 1H), 3.70 (q, *J* = 7.25 Hz, 2H), 3.62-3.32 (m, 1H), 3.20-3.16 (m, 1H); ^{13}C NMR (CD_3OD, 125 MHz) δ 211.3, 136.6, 134.0, 129.4, 127.9, 127.4, 126.3, 123.3, 121.0, 118.4, 118.2, 110.8, 109.5, 76.4, 45.4, 29.7; HRMS found 280.1332 $[M+H]^+$, calcd 280.1332 for $[C_{18}H_{18}NO_2]$; $[\alpha]_D^{24}$ = +45° (c 0.83, $CHCl_3$).

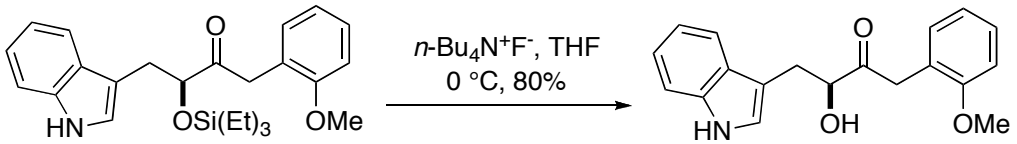
7.4.4. First-Generation Analogs



79

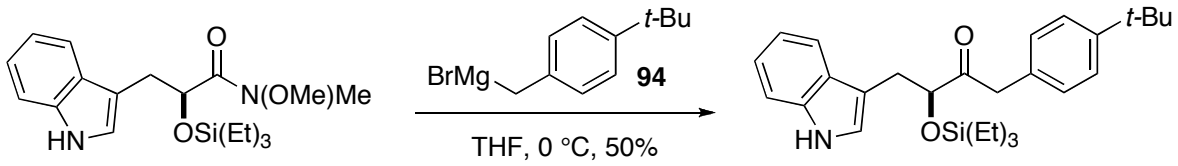
***(S)*-4-(1*H*-indol-3-yl)-1-(2-methoxyphenyl)-3-(triethylsilyloxy)butan-2-one.** Following the procedure for compound **85** above on 95 mg scale, where reagent **93** (0.25 M in THF, 5.0 equiv.) was substituted for benzylmagnesium chloride, 0.082 g (74%) of the target compound were isolated. Data are: TLC R_f= 0.73 (20% EtOAc/hexanes x 2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.0 (bs, 1H), 7.61 (d, *J*=4 Hz, 1H), 7.36 (d, *J*=4 Hz, 1H), 7.27-7.18 (m, 2 H), 7.12 (t, *J*=7.5 Hz, 1H), 7.04 (d, *J*=1 Hz, 1H), 6.90-6.84 (m, 3 H), 4.517 (dd, *J1*=1H, *J2*=2.5 Hz, 1H), 3.85 (d, *J* = 8.75 Hz, 1H), 3.71 (d, *J* = 9 Hz, 1H), 3.72 (s, 3H), 0.88 (t, *J*=7.5 Hz, 9H), 0.52-0.47 (m, 6H); ^{13}C

NMR ($CDCl_3$, 125 MHz) δ 210.7, 157.6, 136.3, 131.7, 128.5, 128.0, 123.6, 123.5, 122.1, 120.7, 119.6, 119.4, 111.4, 111.3, 110.5, 78.8, 55.4, 40.5, 31.4, 7.0, 4.8; HRMS found 423.2230 (M^+), calcd 423.2230 for [$C_{25}H_{33}NO_3Si$]; $[\alpha]_D^{23}$ = -21° (c 0.23, $CHCl_3$).



96

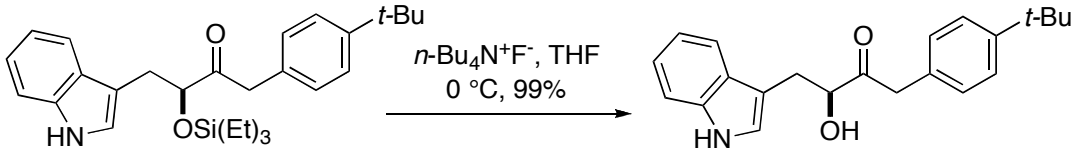
***(S)*-3-hydroxy-4-(1*H*-indol-3-yl)-1-(2-methoxyphenyl)butan-2-one (96).** Following the procedure for compound **2** above on 58 mg scale provided 34 g (80%) of the target compound. Data are: TLC R_f= 0.22 (30% EtOAc/hexanes x 2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.10 (bs, 1H), 7.58 (d, *J*=4 Hz, 1H), 7.37 (d, *J*=4 Hz, 1H), 7.31-7.27 (m, 2H), 7.22 (t, *J*=8 Hz, 1H), 7.15-7.08 (m, 2H), 6.94 (t, *J*=7.5 Hz, 1H), 6.88 (d, *J*=4 Hz, 1H), 4.64 (m, 1H), 3.87 (d, *J* = 8 Hz, 1H), 3.74 (d, *J* = 8 Hz, 1H), 3.77 (s, 3H), 3.48 (d, *J*=2.75 Hz, 1H), 3.38 (dd, *J1*=5.25 Hz, *J2*=2 Hz, 1H), 3.13 (dd, *J1*=4.25 Hz, *J2*=3.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) 210.0, 157.1, 136.1, 131.4, 128.8, 127.5, 123.0, 122.5, 122.1, 120.8, 119.5, 118.8, 111.2, 110.8, 110.5, 76.2, 55.3, 40.6, 29.7; HRMS found 309.1365 (M^+), calcd 309.1365 for [$C_{19}H_{19}NO_3$].



79

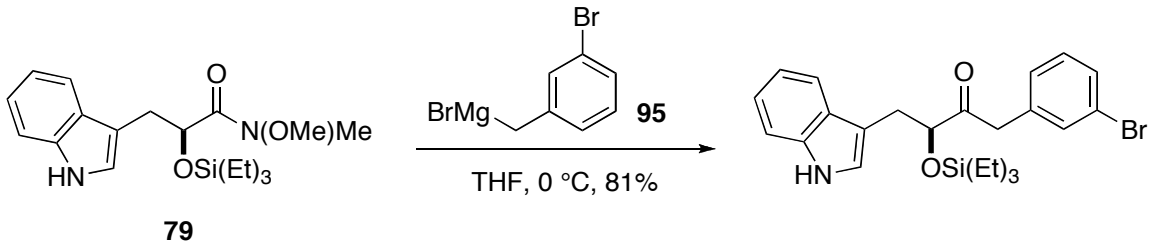
***(S)*-1-(4-tert-butylphenyl)-4-(1*H*-indol-3-yl)-3-(triethylsilyloxy)butan-2-one.** Following the procedure for compound **85** above on 96 mg scale, where reagent **94** (0.25 M in THF, 5.0 equiv.) was substituted for benzylmagnesium chloride, 0.060 g (50%) of the target compound were

isolated. Data are: TLC R_f= 0.67 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.0 (bs, 1H), 7.61 (d, *J*=4 Hz, 1H), 7.36 (d, *J*=4 Hz, 1H), 7.28 (t, *J*=7.5 Hz, 1H), 7.20 (t, *J*=7.5 Hz, 2H), 7.13 (t, *J*=7.5 Hz, 1H), 6.99 (s, 1H), 6.92 (d, *J*=4 Hz, 2H), 4.50 (t, *J*=6 Hz, 1H), 3.75 (d, *J* = 8.5 Hz, 1H), 3.6 (d, *J* = 8.5 Hz, 1H), 3.72 (d, *J*=2.75 Hz, 2H), 1.30 (s, 9H), 0.89 (t, *J*=8 Hz, 9H), 0.51 (q, *J1*=4 Hz, *J2*=4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 210.9, 149.5, 136.1, 130.9, 129.4, 127.7, 125.3, 123.4, 122.0, 119.5, 119.1, 111.0, 110.8, 78.5, 44.6, 34.4, 31.3, 6.7, 4.6; HRMS found 449.2750 (M^+), calcd 449.2750 for [$C_{28}H_{39}NO_2Si$]; $[\alpha]_D^{23}$ = -8.42° (c 0.95, $CHCl_3$).

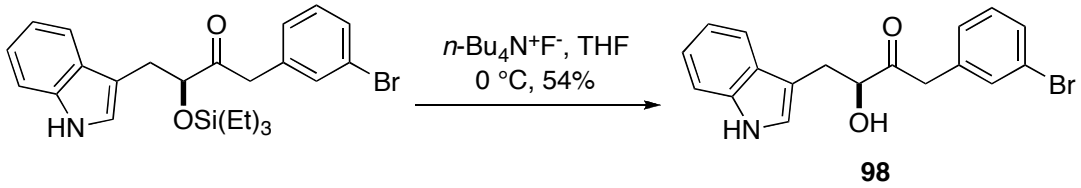


97

***(S)*-1-(4-tert-butylphenyl)-3-hydroxy-4-(1*H*-indol-3-yl)butan-2-one (97).** Following the procedure for compound **2** above on 0.057 mg scale provided 0.054 g (99%) of the target compound as a yellow solid. Data are: TLC R_f= 0.29 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.08 (bs, 1H), 7.59 (d, *J*=4 Hz, 1H), 7.37-7.32 (m, 3 H), 7.22 (t, *J*=7.5 Hz, 1H), 7.14 (t, *J*=7 Hz, 1H), 7.06-7.04 (m, 3H), 4.61 (d, *J*=2.25 Hz, 1H), 3.76 (d, *J*=5.5 Hz, 2H), 3.32 (bs, 2H), 3.17-3.13 (m, 1H), 1.32 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) 209.9, 150.1, 136.1, 130.0, 129.2, 127.4, 125.7, 123.0, 122.3, 119.7, 118.7, 111.3, 110.4, 76.0, 45.2, 34.5, 31.3, 29.9, 29.7; HRMS found 355.1885 (M^+), calcd 335.1885 for [$C_{22}H_{25}NO_2$]; $[\alpha]_D^{23}$ = +33.3° (c 0.9, $CHCl_3$).



***(S)*-1-(3-bromophenyl)-4-(1*H*-indol-3-yl)-3-(triethylsilyloxy)butan-2-one.** Following the procedure for compound **85** above on 92 mg scale, where reagent **95** (0.25 M in Et_2O, 5.0 equiv.) was substituted for benzylmagnesium chloride, 0.097 g (81%) of the target compound were isolated. Data are: TLC R_f= 0.63 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.1 (bs, 1H), 7.61 (d, *J*=4 Hz, 1H), 7.38-6.94 (m, 7H), 6.79 (d, *J*=3.75 Hz, 1H), 4.50 (t, *J*=5.5 Hz, 1H), 3.66 (d, *J* = 8.75 Hz, 1H), 3.49 (d, *J* = 8.5 Hz, 1H), 3.22-3.09 (m, 2H), 0.89 (t, *J*=8 Hz, 9H), 0.59 (q, *J1*=4 Hz, *J2*=4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 210.5, 136.2, 136.0, 132.7, 129.7, 129.7, 128.4, 127.6, 123.3, 122.2, 122.2, 119.6, 119.2, 111.1, 110.4, 78.5, 44.6, 31.5, 14.2, 6.6, 4.7; HRMS was negative; $[\alpha]_D^{23}$ = -11.6° (c 1.47, $CHCl_3$).

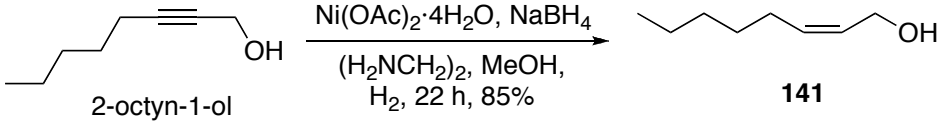


***(S)*-1-(3-bromophenyl)-3-hydroxy-4-(1*H*-indol-3-yl)butan-2-one (98).** Following the procedure for compound **2** above on 0.088 mg scale provided 0.036 g (54%) of the target compound as a yellow solid. Data are: TLC R_f= 0.18 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.11 (bs, 1H), 7.62 (d, *J*=4 Hz, 1H), 7.38 (d, *J*=4 Hz, 2H), 7.26-7.22 (m, 1H), 7.18-7.12 (m, 3H), 7.06 (s, 1H), 6.97 (d, *J*=3.75 Hz, 1H), 4.59 (d, *J*=2.75 Hz, 1H), 3.70 (dd, *J1*=12.25 Hz, *J2*=8 Hz, 2H), 3.32-3.17 (m, 2 H), 3.21 (d, *J*=2.75 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) 209.1, 136.2, 1335.3, 132.6, 130.3, 130.0, 128.2, 127.3, 123.1, 122.6, 122.5, 119.9, 118.7, 111.4,

110.1, 76.4, 45.0, 30.0, 29.7; HRMS found 357.0364 (M^+), calcd 357.0364 for [$C_{18}H_{16}BrNO_2$]; $[\alpha]_D^{23}$ = +33.3° (c 0.9, $CHCl_3$).

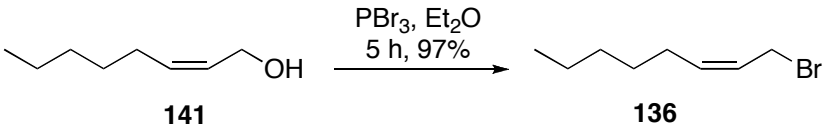
7.5. Procedures from Chapter 5

7.5.1. Synthesizing Electrophile 136



***(Z)*-oct-2-en-1-ol (141).** $Ni(OAc)_2 \cdot H_2O$ (0.87 g, 3.49 mmol) was dissolved in anhydrous MeOH (18 mL) in a two-neck flask and stirred under N_2 at room temperature, forming a blue-green solution. This was cooled to 0 °C, and sodium borohydride (132 mg, 3.49 mmoL) was added in one portion, causing gaseous evolution and turning the solution black. This suspension was warmed to room temperature and stirred 5 min. Ethylenediamine (0.437 mL, 6.98 mmoL) was then added; the solution stirred 5 min longer. A solution of oct-2-yn-1-ol (2.0 mL, 13.96 mmoL) in anhydrous MeOH (6 mL) was then added. An H_2 balloon was attached, and the flask was purged 3x with H_2. It was then stirred under H_2 atmosphere at RT for 22 hours (a lesser time of 5 hours has also been successful). A small aliquot was removed from the mixture and subjected to a mini workup, concentrated, and analyzed by NMR to ensure consumption of starting matierla and formation of product. Once complete, the reaction mixture was filtered through celite with copious amounts of CH_2Cl_2, being careful to keep the pyrophoric Nickel (II) immersed in solution. The purple mother liqueur was then carefully concentrated, re-diluted in Et_2O, and transferred to a separatory funnel. It was washed 1x with water (which removed the dark color), and the organic layer was then dried ($MgSO_4$), filtered through a short silica pad

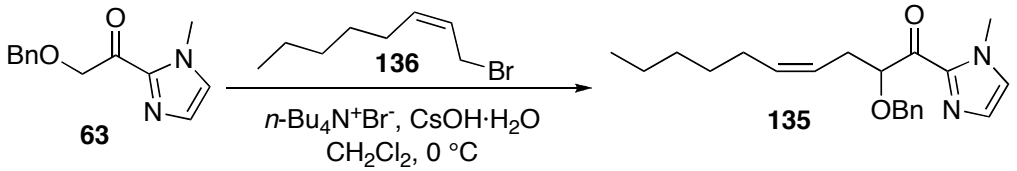
with copious amounts of Et_2O, and carefully concentrated under low vacuum to afford 1.51 g (85%) of **141** as a clear, yellow oil. Data are: TLC R_f= 0.52 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.60-5.56 (m, 2H), 4.20 (d, *J*=3 Hz, 2H), 2.07 (q, *J1*=3.5 Hz, *J2*=3.75 Hz, 2H), 1.38-1.26 (m, 7H), 0.89 (t, *J*=7.5 Hz, 3H) ; ^{13}C NMR ($CDCl_3$, 125 MHz) 133.3,128.3, 58.6, 31.4, 29.3, 27.4, 22.5, 14.0; HRMS found 128.1201 (M^+), calcd 128.1201 for [$C_8H_{16}O$].



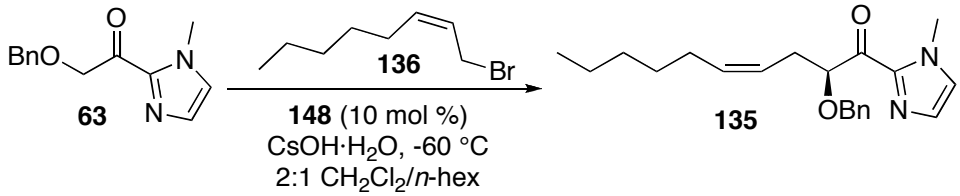
141 **136**

(Z)-1-bromooct-2-ene (136). *(Z)*-oct-2-en-1-ol **141** (1.63 g, 12.7 mmol) was dissolved in Et_2O (32 mL) and cooled to 0 °C under N_2. PBr_3 (1M in CH_2Cl_2, 5.232 mL, 5.23 mmol) was then added dropwise, and the solution stirred at 0 °C for three hours. A small aliquot was removed from the mixture and subjected to a mini workup, concentrated, and analyzed by NMR to ensure consumption of **141** and formation of **136**. Once complete, the reaction was carefully diluted with ice water and extracted with Et_2O (5 x 30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and carefully concentrated under low vacuum to afford 2.36 g (97%) of **146** as a clear, off-white oil. Data are: TLC R_f= 0.90 (15% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.77-5.56 (m, 2H), 4.00 (d, *J*=4.2 Hz, 2H), 2.17-2.09 (m, 2H), 1.45-1.19 (m, 6H), 0.90 (t, *J*=2.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 136.4, 125.4, 31.7, 29.1, 27.7, 27.2, 22.8, 14.3; HRMS was negative.

7.5.2. PTC Alkylations

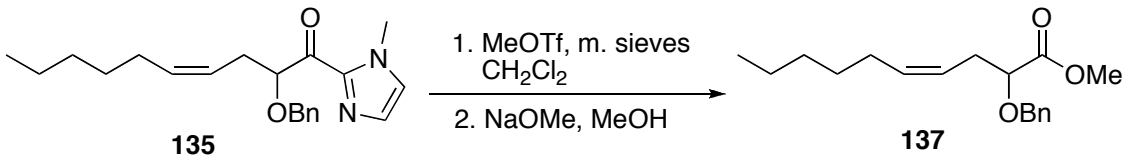


(±)-(*Z*)-2-(benzyloxy)-1-(1-methyl-1*H*-imidazol-2-yl)dec-4-en-1-one (135). Substrate **63** (52 mg, 0.225 mmol), *n*-$Bu_4N^+Br^-$ (8.2 mg, 0.027 mmol), and electrophile **136** (0.086 g, 0.45 mmol) were diluted in CH_2Cl_2 (2.25 mL) and cooled to 0 °C. After 10 minutes, $CsOH·H_2O$ (0.151 g, 0.9 mmol) was added in one portion. The mixture then stirred at 0 °C, warming to room temperature overnight, for 18 h, at which time the reaction was diluted with Et_2O (30 mL) and H_2O (10 mL). The layers were mixed and separated, and the organic layer was washed with a saturated aqueous solution of aqueous NaCl (1 x 10 mL) and then dried over $MgSO_4$. The crude product was then purified by column chromatography (20% EtOAc/hexanes) to afford 0.065 g (85%) of the desired compound as a clear yellow oil. Data are: TLC R_f= 0.69 (40% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36 (d, *J*=3.5 Hz, 2H), 7.3 (t, *J*=7. Hz, 2H), 7.26-7.23 (m, 1H), 7.15 (s, 1H), 7.03 (s, 1H), 5.52-5.43 (m, 2H), 5.26 (dd, *J1*=0.75 Hz, *J2*=5Hz, 1H), 4.68 (d, *J* = 6 Hz, 1H), 4.49 (d, *J* = 5.75 Hz, 1H), 3.98 (s, 3H), 2.73-2.62 (m, 2H), 1.93-1.90 (m, 2H), 1.30-1.15 (6H), 0.85 (t, *J*=7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.4, 142.0, 138.2, 132.7, 129.3, 128.2, 127.9, 127.5, 127.0, 123.9, 80.2, 72.2, 36.0, 31.4, 31.2, 29.2, 27.2, 22.5, 14.0; HRMS found 340.2151 (M^+), calcd 340.2151 for [$C_{21}H_{28}N_2O_2$]; the enantiomers' retention times were determined by chiral HPLC (DAICEL Chiralpack AD-H column, 5% EtOH/hexane, 0.75 mL/min, 23 °C, λ = 254 nm, retention times: *S* 10.16 min, *R* 13.46 min, 51.4 : 48.6 er).



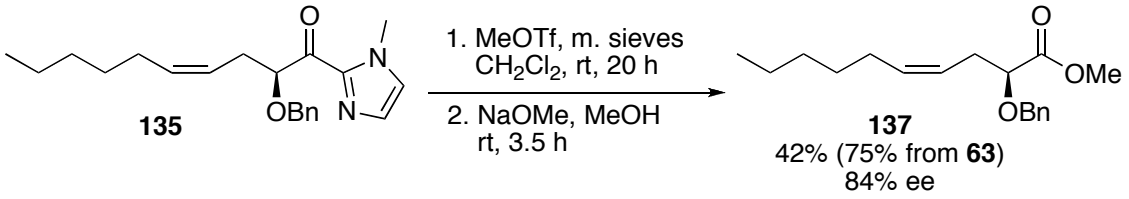
(*S*,*Z*)-2-(benzyloxy)-1-(1-methyl-1H-imidazol-2-yl)dec-4-en-1-one (135). Substrate **63** (1.88 g, 8.18 mmol), catalyst **148** (0.5 g, 0.82 mmol), and electrophile **136** (4.334 g, 22.68 mmol) were diluted in CH_2Cl_2 (55 mL) and *n*-hexanes (27 mL) and cooled to -60 °C. After 10 minutes, $CsOH{\cdot}H_2O$ (5.49 g, 32.70 mmol) was added in one portion. The reaction then stirred at –60 °C for 23 h, at which time it was found completed done (TLC). It was subsequently diluted with Et_2O (250 mL) and H_2O (100 mL). The layers were mixed and separated, and the organic layer was washed with a saturated aqueous solution of aqueous NaCl (1 x 100 mL) and then dried over $MgSO_4$. The crude product was then flushed through a short silica pad using copious amounts of Et_2O. It was concentrated to furnish 4.95 g of a clear yellow oil (178% crude yield) and was analyzed, in crude form, by chiral HPLC. Data are: TLC R_f= 0.69 (40% EtOAc/hexanes); HRMS found 340.2151 (M^+), calcd 340.2151 for [$C_{21}H_{28}N_2O_2$]; the enantiomers' retention times were determined by chiral HPLC (DAICEL Chiralpack AD-H column, 5% EtOH/hexane, 0.75 mL/min, 23 °C, λ = 254 nm, retention times: *S* 9.7 min, *R* 12.9 min, 94.2 : 5.8 er). A small amount was purified to provide optical rotation data: $[\alpha]_D^{23}$ = -17.14° (c 0.7, $CHCl_3$).

7.5.3. To Aldehyde 133



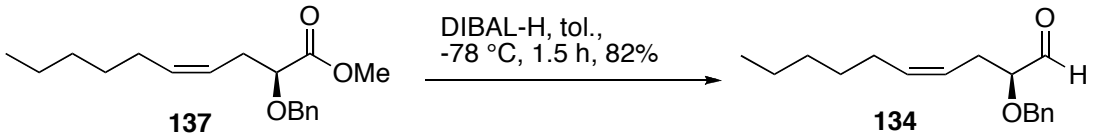
(±)-*(Z)*-methyl 2-(benzyloxy)dec-4-enoate (137). To a flame-dried 10 mL round bottom flask was added **(±)-135** (0.061 g, 0.179 mmol), powdered 4 Å molecular sieves (0.045 g), and CH_2Cl_2

(1.05 mL). These were stirred vigorously at room temperature for 5 minutes. Methyl triflate (0.102 mL, 0.896 mmol) was then added in one portion. This mixture was stirred at room temperature for 24 hours, monitored by TLC for the consumption of starting material (R_f = 0.67, 40% EtOAc/Hexanes). Anhydrous methanol (1.05 mL) was then added, followed by dry sodium methoxide (0.074 g, 1.36 mmol). The mixture was then stirred for 4.5 hours at room temperature. It was afterward diluted with H_2O (10 mL) and CH_2Cl_2 (20 mL). The layers were mixed and then separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by column chromatography (10% EtOAc/hexanes) to afford 8 mg (15%) of the desired compound as clear yellow oil. Data are: TLC R_f= 0.53 (100% hexanes → 5% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37-7.27 58.75, *J2*=5.75 Hz, 2H), 3.99 (t, *J*=6.5 Hz, 1H), 3.75 (s, 3H), 2.55 (t, *J*=6.5 Hz, 2H), 2.02 (q, *J1*=3.75 Hz, *J2*=3.5 Hz, 2H), 1.35-1.25 (m, 6H), 0.89 (t, *J*=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.8, 137.5, 133.3, 128.4, 127.9, 127.8, 123.3, 78.1, 72.3, 51.8, 31.5, 31.0, 29.2, 27.3, 22.5, 14.0; HRMS found 290.1882 $[M]^+$, calcd 290.1882 for $[C_{18}H_{26}O_3]^+$. The enantiomers' retention times were determined by chiral HPLC (DAICEL Chiralpack OD-H column, 1.5 *i*PrOH/heptane, 0.5 mL/min, 23 °C, λ = 254 nm, retention times: *S* (major) 14.91 min, *R* (minor) 21.02 min, 50.04 : 49.96 er).



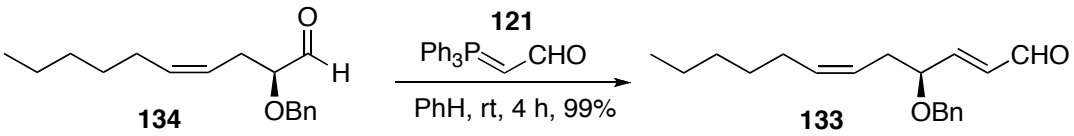
(*S*,*Z*)-methyl 2-(benzyloxy)dec-4-enoate (137). To a flame-dried 10 mL round bottom flask was added crude **135** (3.04 g, 8.92 mmol), powdered 4 Å molecular sieves (2.23 g), and CH_2Cl_2

(178 mL). These were stirred vigorously at room temperature for 5 minutes. Methyl triflate (5.05 mL, 44.59 mmol) was then added in one portion. This mixture was stirred at room temperature for 20 hours, monitored by TLC for the consumption of starting material (R_f = 0.28, 30% EtOAc/Hexanes). Anhydrous methanol (178 mL) was then added, followed by dry sodium methoxide (3.66 g, 67.78 mmol). The mixture was then stirred for 3.5 hours at room temperature. It was afterward diluted with H_2O (75 mL) and CH_2Cl_2 (200 mL). The layers were mixed and then separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 150 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by column chromatography (100% hexanes → 5% EtOAc/hexanes) to afford 1.09 g (42%, 75% from **63**) of **137** as clear yellow oil. Data are: TLC R_f = 0.53 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37-7.27 58.75, *J2*=5.75 Hz, 2H), 3.99 (t, *J*=6.5 Hz, 1H), 3.75 (s, 3H), 2.55 (t, *J*=6.5 Hz, 2H), 2.02 (q, *J1*=3.75 Hz, *J2*=3.5 Hz, 2H), 1.35-1.25 (m, 6H), 0.89 (t, *J*=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.8, 137.5, 133.3, 128.4, 127.9, 127.8, 123.3, 78.1, 72.3, 51.8, 31.5, 31.0, 29.2, 27.3, 22.5, 14.0; HRMS found 290.1882 $[M]^+$, calcd 290.1882 for $[C_{18}H_{26}O_3]^+$. The enantiomers' retention times were determined by chiral HPLC (DAICEL Chiralpack OD-H column, 1.5 *i*PrOH/heptane, 0.5 mL/min, 23 °C, λ = 254 nm, retention times: *S* (major) 14.90 min, *R* (minor) 21.41 min, 91.8 : 8.2 er). $[\alpha]_D^{26}$ = -35.03° (c 2.85, $CHCl_3$). Optical rotation data: $[\alpha]_D^{23}$ = -17.14° (c 0.7, $CHCl_3$).



(*S,Z*)-2-(benzyloxy)dec-4-enal (134). Compound **137** (299 mg, 1.03 mmol) was dispensed into a dry, empty flask and purged for 10 minutes with N_2. Dry toluene (21 mL) was then added, and

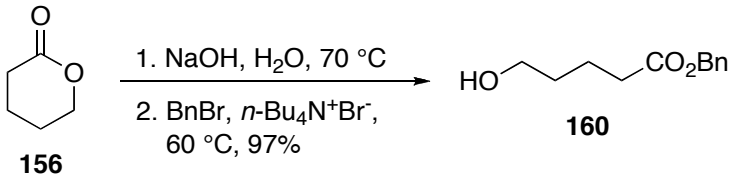
the solution was cooled to –78 °C. DIBAL-H (1M in toluene, 2.06 mL, 2.06 mmol) was then added slowly, and the reaction stirred 1.5 hours. The reaction was then diluted with MeOH (26 mL, pre-chilled to –78 °C), warmed gradually to room temperature, and stirred for 1 hour. It was quenched with Rochelle salts and extracted 3 x with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, concentrated, and purified by column (10% EtOAc/hexanes) to afford 220 mg (84%) of **134** as a clear, yellow oil. Data are: TLC R_f= 0.45 (10% EtOAc/hexanes x 2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.65 (d, *J*=1 Hz, 1H), 7.36-7.26 (m, 5H), 5.55-5.38 (m, 2H), 4.67 (d, *J* = 6 Hz, 1H), 4.59 (d, *J* = 6 Hz, 1H), 3.79 (t, *J*=7.5 Hz, 1H), 2.50 (t, *J*=6 Hz, 1H), 2.02 (dd, *J1*=3.5 Hz, *J2*=7Hz), 1.37-1.22 (m, 6H), 0.86 (t, *J*=2.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 203.3, 137.3, 133.7, 128.5, 128.1, 127.9, 122.6, 83.2, 72.5, 31.5, 20.7, 20.1, 28.3, 27.4, 22.6, 14.0; HRMS found 260.1814 $[M]^+$, calcd 260.1776 for $[C_{17}H_{24}O_2]^+$. $[\alpha]_D^{23}$ = -33.7° (c 0.24, $CHCl_3$). Optical rotation data: $[\alpha]_D^{23}$ = -33.7° (c 4.0, $CHCl_3$).



(*S*,2*E*,6*Z*)-4-(benzyloxy)dodeca-2,6-dienal (133). Aldehyde **134** (630 mg, 2.42 mmol) was dissolved in dry benzene (36 mL). Triphenylphosphorilidene acetaldehyde **121** was then added, and the reaction was warmed and stirred at 60 °C for 4 hours. Once **134** was consumed (TLC), the reaction was concentrated and purified by column chromatography (5% EtOAc/hexanes) to afford 685 mg of **133** (99%) as a clear yellow oil. Data are: TLC R_f= 0.26 (10% EtOAc/hexanes x 1, then 5% EtOAc/hexanes x 1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.58 (d, *J*=4 Hz, 1H), 7.37-7.26 (m, 5H), 6.75 (dd, *J1*=5 Hz, *J2*=2.75 Hz, 1H), 6.32-6.27 (m, 1H), 5.55-5.34 (m, 2H), 4.59 (d, *J* = 5.75 Hz, 1H), 4.47 (d, *J* = 5.75 Hz, 1H), 4.13-4.09 (m, 1H), 2.51-2.40 (m, 2H), 2.00 (dd,

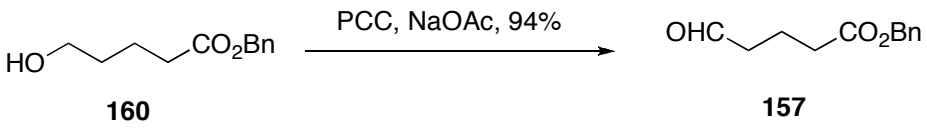
J1=3.5 Hz, *J2*=3.75 Hz, 2H), 1.36=1.22 (m, 6H), 0.88 (t, *J*=7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 193.4, 156.7, 137.8, 13.4, 132.5, 128.5, 127.8127.7, 123.2, 77.8, 71.3, 32.6, 31.5, 29.1, 27.4, 22.5, 14.0; HRMS found 286.1932 $[M]^+$, calcd 286.1933 for $[C_{18}H_{26}O_2]^+$. $[\alpha]_D^{23} = -33.7°$ (c 0.24, $CHCl_3$). Optical rotation data: $[\alpha]_D^{23} = -11.37°$ (c 4.48, $CHCl_3$).

7.5.4. To Wittig Salt 158



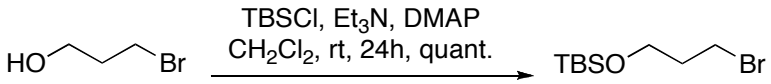
156 **160**

Benzyl 5-hydroxypentanoate (160). Following the procedure detailed in Weber, A. E.; Halgren, T. A.; Doyle, J. J.; Lynch, R. J.; Siegl, P. K. S.; Parsons, W. H.; Greenlee, W. J.; Patchett, A. A. *J. Med. Chem.* **1991**, *34*, 2692-2701, 5.0 grams (49.94 mmol) of δ-valerolactone (**156**) were converted to crude **160**, which was purified by column chromatography (20% EtOAc) to provide 10.06 g (97%) of product as a clear, colorless oil. This compound was concentrated carefully at low vacuum due to its volatility. Data are: TLC R_f= 0.09 (10% EtOAc/hexanes x 1, then 20% EtOAc/hexanes x 1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37 (m, 5H), 5.12 (s, 2H), 3.63 (dd, *J1*=1.5 Hz, *J2*=3.25 Hz, 2H), 2.4 (q, *J1*=2.5 Hz, *J2*=1.25 Hz, 2H), 1.85 (bs, 1H), 1.77-1.71 (m, 2H), 1.62-1.56 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.8, 136.2, 128.8, 128.4, 66.5, 62.4, 34.1, 32.6, 21.3; HRMS found 208.1099 $[M]^+$, calcd 208.1099 for $[C_{12}H_{16}O_3]^+$.

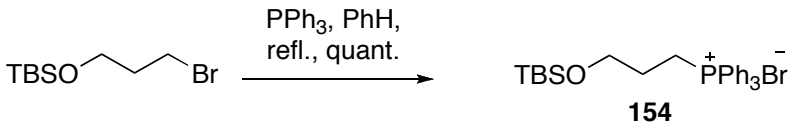


160 **157**

Benzyl 5-oxopentanoate (157). Following the procedure detailed in Gannett, P. M.; Nagel, D. L.; Reilly, P. J.; Lawson, T.; Sharpe, J.; Toth, B. *J. Org. Chem.* **1987**, *53*, 1064-1071, 1.32 grams (6.34 mmol) of **160** were oxidized to crude **157**, which was purified by column chromatography (10 % EtOAc) to afford 1.23 g (94%) of product as a clear, colorless oil. This compound was concentrated carefully at low vacuum due to its volatility. Data are: TLC R_f= 0.63 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.75 (s, 1H), 7.38-7.31 (m, 5h), 5.11 (s, 2H), 2.51 (t, *J*=7.5 Hz, 2H), 2.42 (t, *J*=7.5 Hz, 2 H), 1.99-1.93 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.5, 172.7, 135.8, 128.6, 128.5, 128.3, 128.2, 66.3, 42.9, 33.1, 17.3; HRMS found 206.0943 $[M]^+$, calcd 206.0943 for $[C_{12}H_{14}O_3]^+$.



(3-bromopropoxy)(*tert*-butyl)dimethylsilane. Following the procedure detailed in Boutellier, M.; Wallach, D.; Tamm, C. *Helv. Chim. Acta.* **1993**, *76*, 2515-2527, 3.52 grams (25.34 mmol) of 3-bromopropanol were converted crude product, which was flushed through a short silica pad with copious amounts of Et_2O to afford 6.4 g (quant.) of (3-bromopropoxy)-(*tert*-butyl) dimethylsilane as a dark yellow oil. Data are: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.77 (t, *J*=5.7 Hz, 2H), 3.55 (t, *J*=6.3 Hz, 2H), 2.11-1.96 (m, 2H), 0.93 (s, 9H), 0.1 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 60.7, 35.8, 31.0, 26.2, 18.6, -5.1.



154

(3-(tert-butyldimethylsilyloxy)propyl)triphenylphosphonium bromide (154). (3-bromopropoxy)(*tert*-butyl)dimethylsilane (6.23 g, 24.59 mmol) was diluted in dry benzene (17.6 mL). Triphenylphosphine (7.09 g, 27.05 mmol) was then added. The reaction was fitted with a water condenser and brought to reflux for 72 hours. It was then concentrated to give a hygroscopic foam, which was dried under high vacuum for three days using the apparatus shown (fig. 7.1). This cleanly provided 12.6 g (quant.) of **154** as a white solid. Data are: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.82-7.79 (m, 9H), 7.72-7.69 (m, 6H), 3.83 (bs, 2H), 3.76-3.71 (m, 2H), 1.89 (d, *J*=2.5 Hz, 2H), 0.83 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 135.0, 133.4, 133.3, 130.4, 130.3, 118.4, 117.7, 61.6 (d, *J*=8.31 Hz), 25.7, 18.97 (d, *J*=26.25 Hz), 17.9, -5.5. HRMS found 435.2273 $[M]^+$, calcd 435.2268 for $[C_{27}H_{36}OPSi]^+$.

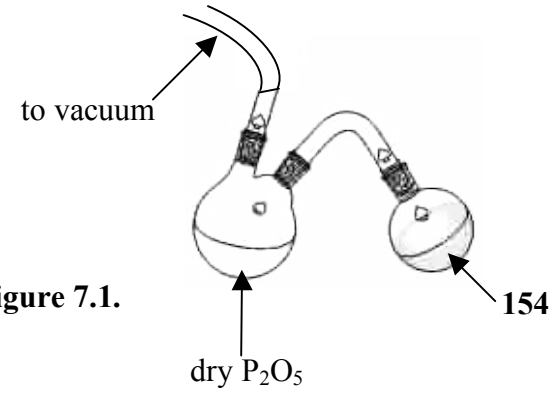
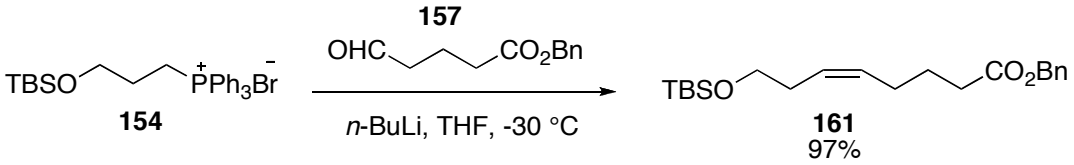
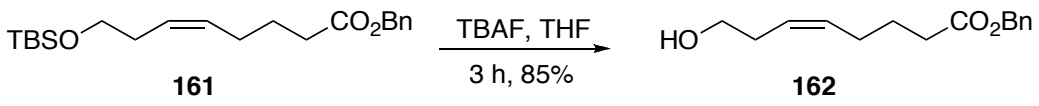


Figure 7.1.

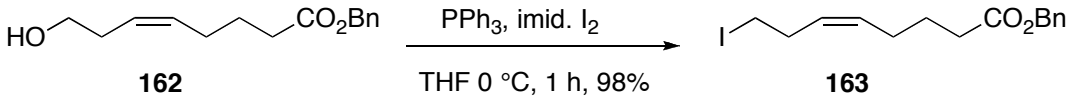


(*Z*)-benzyl 8-(*tert*-butyldimethylsilyloxy)oct-5-enoate (161). Phosphonium salt **154** (8.56 g, 16.61 mmol) was dissolved in dry THF (166 mL) and cooled under N_2 to –30 °C. *n*-Butyllithium (1.6 M/hexanes, 11.42 mL, 18.27 mmol) was then added, turning the solution bright orange. This was warmed and stirred at room temperature for 10 minutes. Then a solution of aldehyde **157** (4.11 g, 19.93 mmol) in THF (33 mL) was added by cannula. The reaction mixture was next cooled down to –30 °C and stirred for three hours. It was then quenched by addition of water (100 mL) and dichloromethane (200 mL). The layers were mixed and separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 200 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by column chromatography (5% EtOAc/hexanes) to afford 5.85 g (97%) of clean **161** as a clear yellow oil. This compound was concentrated carefully at low vacuum due to its volatility. Data are: TLC R_f = 0.1 (5% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) 7.35-7.25 (m, 5H), 5.41 (t, *J* = 5.5 Hz, 2H), 5.11 (s, 2H), 3.59 (q, *J1* = 4 Hz, *J2* = 3.5 Hz, 2H), 2.37 (t, *J* = 8 Hz, 2H), 2.26=2.24 (m, 2H), 2.10-2.09 (m, 2H), 1.74-1.71 (m, 2H), 0.9 (s, 9H), 0.06 (s, 6H); δ ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.6, 130.5, 128.8, 128.4, 127.2, 66.3, 63.1, 53.6, 33.9, 31.3, 26.9, 26.2, 25.1, 18.6, -5.0. HRMS found 362.2277 $[M]^+$, calcd 362.2277 for $[C_{21}H_{34}O_3Si]^+$.



***(Z)*-benzyl 8-hydroxyoct-5-enoate (162).** Ester **161** (1.36 g, 3.75 mmol) was dissolved in dry THF (89 mL) and cooled under N_2 to 0 °C. Tetra-*n*-butylammonium fluoride (1.0 M/THF, 4.5

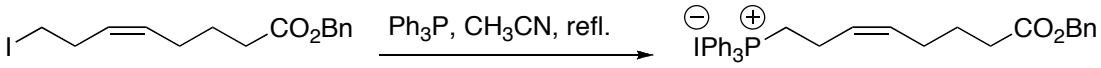
mL, 4.5 mmol) was then added, and the solution stirred at 0 °C for 3 hours. Once starting material was consumed (TLC), the reaction was quenched with saturated aqueous NH_4Cl (90 mL) and transferred to a separatory funnel. It was sequentially extracted with CH_2Cl_2 (2 x 50 mL) and EtOAc (3 x 75 mL). The combined organize layers were dried ($MgSO_4$), filtered, concentrated, and purified by column (20% EtOAc/hexanes → 50% EtOAc/hexanes) to afford 0.795 g (85%) of **162** as a yellow oil. This compound was concentrated carefully at low vacuum due to its volatility. Data are: TLC R_f= 0.08 (15% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36-7.27 (m, 5H), 5.51-5.40 (m, 2H), 5.30 (s, 2H), 3.62 (t, *J*=6.5 Hz, 2H), 2.37 (t, *J*=7.5 Hz, 2H), 2.27 (q, *J1*=3.25 Hz, *J2*=3.5 Hz, 2H), 2.13-2.09 (m, 2H), 1.76-1.70 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.5, 136.0, 131.6, 128.5, 128.2, 128.2, 126.5, 66.1, 62.2, 33.5, 30.7, 26.5, 24.7, 14.1. HRMS found 248.1436 $[M]^+$, calcd 248.1436 for $[C_{15}H_{20}O_3]^+$.



162 **163**

***(Z)*-benzyl 8-iodooct-5-enoate (163)**. Alcohol **162** (370 mg, 1.49 mmol) was dissolved in dry THF (22 mL) and cooled to 0 °C. Triphenylphosphine (586 mg, 2.23 mmol), imidazole (304 mg, 4.47 mmol), and iodine (567 mg, 2.23 mmol) were then added, and the reaction stirred at 0 °C for 1 hour. Once the starting material was consumed (TLC), the reaction was diluted with saturated aqueous sodium bisulfate (25 mL) and Et_2O (75 mL). The layers were mixed and separated, and the aqueous layer was extracted with Et_2O (2 x 75 mL). The combined organic layers were then washed with brine (25 mL), dried ($MgSO_4$), filtered, and concentrated. The crude product was then purified by chromatography (2.5 % EtOAc/hexanes) to afford 526 mg (98%) of **163** as a clear yellow oil. This compound was concentrated carefully at low vacuum due to its volatility. It was also concentrated and handled in darkness to prevent potential

decomposition. Data are: TLC R_f= 0.13 (2.5% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36 (bs, 5H), 5.51-5.34 (m, 2H), 5.13 (s, 2H), 3.11 (t, *J*=6.5 Hz, 2H), 2.59 (q, *J1*=3.5 Hz, *J2*=4.75 Hz, 2H), 2.38 (t, *J*=7.5 Hz, 2H), 2.81-2.06 (m, 2H), 1.76-1.72 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.5, 136.3, 129.0, 128.8, 128.7, 128.5, 128.4, 66.4, 33.9, 31.6, 27.0, 24.9, 5.6.

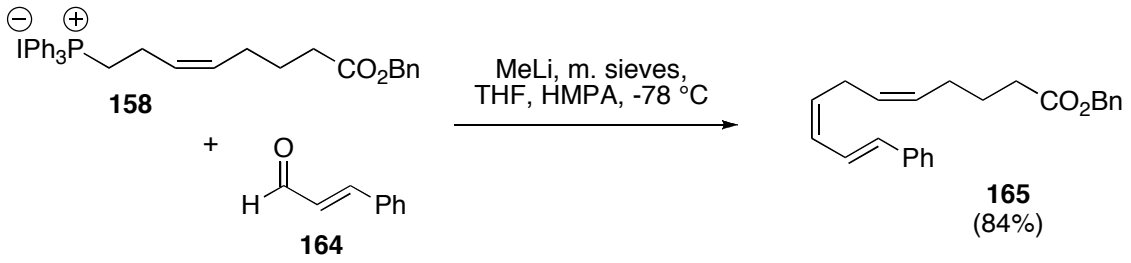


163 **158**

(*Z*)-(8-(benzyloxy)-8-oxooct-3-enyl)triphenylphosphonium iodide (158). Iodide **163** (509 mg, 1.42 mmol) was dissolved in acetonitrile (21 mL). Triphenylphosphine (745 mg, 2.84 mmol) was then added, and the solution was brought and stirred at reflux for 20 hours. Once **163** had been consumed (TLC), the crude material was cooled and diluted further with 150 mL of acetonitrile. This material was then extracted with hexanes (12 x 25 mL), transferred to a tared flask, and concentrated to produce 878 mg (quant.) of **158** as a deep yellow syrup. To react adequately with coupling aldehydes, **158** must also be dried overnight using the apparatus shown in Figure 7.1 above. Even when stored under argon atmosphere at low temperature, this salt decomposes slowly to unidentified products over two to three weeks. This material can also be purified chromatographically (10% MeOH/CH_2Cl_2), though it still remains unclear whether doing so inhibits later coupling reactivity. Data are: TLC R_f= 0.73 (10% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.85-7.79 (m, 9H), 7.73-7.65 (m, 6H), 7.36-7.28 (m, 5H), 5.67-5.62 (m, 1H), 5.41-5.36 (m, 1H), 5.05 (s, 2H), 3.77-3.72 (m, 2H), 2.46-2.39 (m, 2H), 2.26 (t, *J*=7.5 Hz, 2H), 1.90-1.86 (m, 2H), 1.62-1.58 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.2, 135.3,

135.6, 130.7, 128.6, 128.5, 128.1, 126.8, 126.7, 118.0, 117.4, 66.0, 33.4, 26.7, 24.3, 22.9, 20.2, 14.2. HRMS was negative.

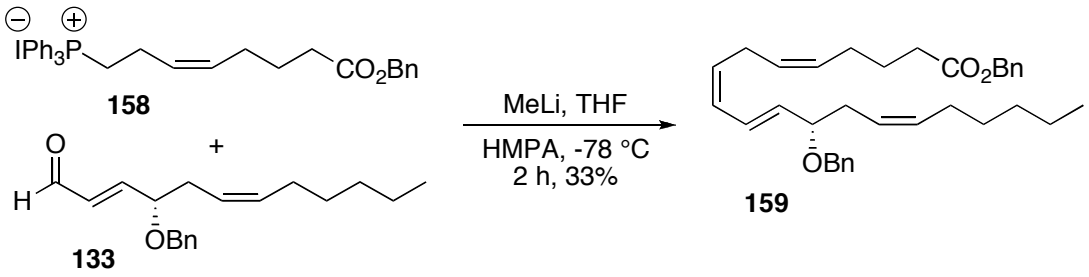
7.5.5. Coupling with Trans-Cinnamaldehyde



(5*Z*,8*Z*,10*E*)-benzyl 11-phenylundeca-5,8,10-trienoate (165). Prior to reaction, Wittig salt **158** was thoroughly dried by repeated dilution/re-concentration in dry 1:1 THF: toluene, followed by overnight subjection to the apparatus depicted in figure 7.1 above. **158** (189 mg, 0.30 mmol) was then dissolved in dry THF (2.03 mL) and cooled under N_2 to –78 °C. Methyllithium was them added, which turned the solution dark yellow. The reaction was stirred 5 minutes at –78 °C, then warmed and stirred at –25 °C for 30 minutes. Toluene (2.03 mL) was then added, and the solution was re-cooled to –78 °C. *Trans*-cinnamaldehyde **164** (0.025 mL, 0.203 mmol) was then added, and the solution stirred at –78 °C for 5 minutes. It was then warmed to –40 °C and stirred for 1 minute, at which time HMPA (0.331 mL) was added. The reaction continued stirring, warming gradually to –10 °C over two hours, until cinnamaldehyde consumption was observed (TLC). The reaction was subsequently quenched by addition of 25% aqueous ammonium acetate (10 mL), followed by water (10 mL). The suspension was transferred to a separatory funnel, and Et_2O (30 mL) was added. The layers were mixed and separated, and the aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic layers were washed

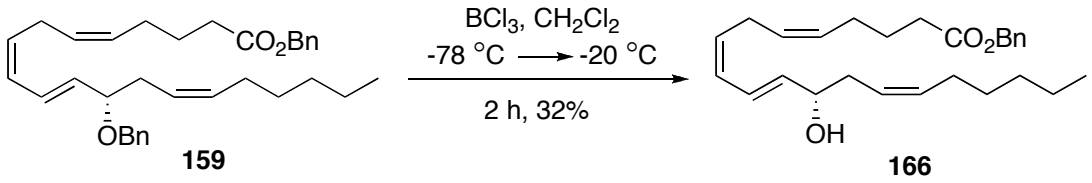
with brine (10 mL), dried ($MgSO_4$), filtered, concentrated, and then purified by chromatography (20% EtOAc/hexanes). This afforded 59 mg of clean **165** (84%) as a yellow oil. Data are: TLC R_f= 0.6 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.42 (d, *J*=4 Hz 2H), 7.37-7.28 (m, 6H), 7.26 (s, 1H), 7.22 (t, *J*=7 Hz, 1 H), 7.09-7.04 (m, 1H), 6.54 (d, *J*=7.75 Hz, 1H), 6.16 (t, *J*=11 Hz, 1H), 5.48-5.38 (m, 3H), 5.12 (s, 2H), 3.00 (t, *J*=7 Hz, 2H), 2.39 (t, *J*=7 Hz, 2H), 2.16 (dd, *J1*=3.75 Hz, *J2*=3.5 Hz, 2H), 1.78-1.71 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.8, 134.9, 133.5, 130.0, 128.0, 126.8, 126.4, 126.0, 126.0, 125.9, 125.6, 125.6, 124.9, 123.8, 121.5, 63.6, 31.1, 24.0, 23.9, 23.7, 22.2. HRMS found 346.1932 $[M]^+$, calcd 346.1932 for $[C_{24}H_{26}O_2]^+$.

7.5.6. Completing the Synthesis



(*S*,5*Z*,8*Z*,10*E*,14*Z*)-benzyl 12-(benzyloxy)icosa-5,8,10,14-tetraenoate (159). Prior to reaction, Wittig salt **158** was thoroughly dried by azeotropic distillation with 1:1 THF/toluene (3x) and then overnight subjection to the apparatus depicted in Figure 7.1 above. **158** (684 mg, 1.10 mmol) was then dissolved in dry THF (4.9 mL) and cooled under N_2 to –78 °C. Methyllithium (1.6 M/Et_2O, 0.92 mL, 1.47 mmol) was then added, which turned the solution dark yellow. The reaction was stirred 5 minutes at –78 °C, then warmed to -40 °C and stirred 30 minutes. Dry toluene (4.9 mL) was then added, and then stirring solution was cooled back down to -78 °C. At this stage, a solution of aldehyde **133** (210 mg, 0.735 mmol, 1.0 equiv) in dry THF (4.9 mL) was

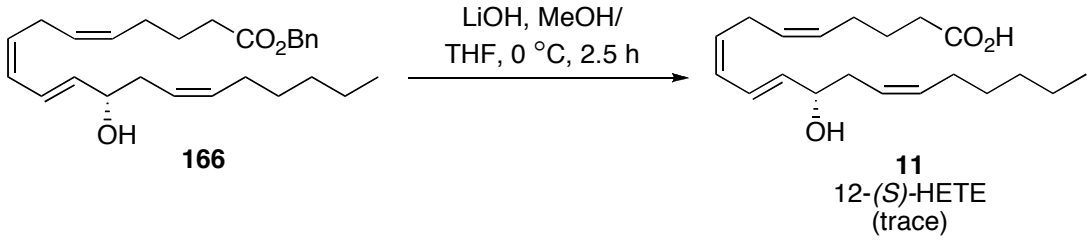
added by cannula. The resulting mixture was then stirred at -78 °C for 5 minutes, then warmed to -40 °C and stirred 1 minute. HMPA was then added, and the entire solution was stirred at -40 °C, warming gradually to -10 °C over two hours. Complete consumption of **133** did not occur (TLC); nevertheless, the reaction was quenched by adding 25% aqueous ammonium acetate (15 mL) and water (10 mL). The suspension was then extracted with dichlormethane (3 x 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by column (100% hexanes → 2.5% EtOAc/hexanes). This afforded 123 mg of **159** (33%) as a yellow oil. Data are: TLC R_f= 0.38 (5% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37-7.32 (m, 6H), 7.26-7.25 (m, 4h), 6.50-6.44 (m, 1H), 6.03-5.98 (m, 1H), 5.60 (dd, *J1*=3.75 Hz, *J2*=4 Hz, 1H), 5.48-5.37 (m, 5H), 5.10 (s, 2H), 4.59 (d, *J* = 6 Hz, 1H), 4.38 (d, *J* = 5.75 Hz), 3.84 (q, *J1*=3.75 Hz, *J2*=3Hz, 1H), 2.93-2.2.88 (m, 2H), 2.47-2.41 (m, 1H), 2.38-2.29 (m, 3H), 2.11 (q, *J1*=3.25 Hz, *J2*=3.75 Hz, 2H), 2.03-1.99 (m, 2H), 1.76-1.67 (m, 2H), 1.35-1.26 (m, 6H), 0.89 (t, *J*=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.4, 138.8, 136.1, 134.1, 134.0, 132.1, 130.3, 130.1, 130.0, 129.3, 129.9, 128.7, 128.6, 128.4, 128.3, 128.2, 128.2, 128.0, 124.8, 79.7, 70.1, 66.1, 33.7, 33.6, 31.9, 30.9, 29.2, 27.5, 26.6, 24.7, 24.6, 22.6, 14.1. HRMS found 500.3291 $[M]^+$, calcd 500.3290 for $[C_{34}H_{44}O_3]^+$. Optical rotation data: $[\alpha]_D^{23}$ = -17.54° (c 2.17, $CHCl_3$).



159 **166**

(*S*,5*Z*,8*Z*,10*E*,14*Z*)-benzyl 12-hydroxyicosa-5,8,10,14-tetraenoate (166). Compound **159** (57 mg, 0.114 mmol, 1 equiv) was dissolved in dry dichloromethane (1.14 mL) and cooled under N_2 to -78 °C. Boron trichloride (1 M/toluene, 0.137 mL, 0.137 mmol, 1.2 equiv) was then added

dropwise, and the solution stirred at -78 °C for 1 hour. It was then warmed to -20 °C and stirred for an additional hour. The reaction never completely consumed **159** (TLC); nevertheless, it was quenched by adding brine (2 mL) and dichloromethane (10 mL). The layers were mixed and separated, and the aqueous layer was then extracted with dichlormethane (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by column (100% hexanes → 2.5% EtOAc/hexanes). This afforded 15 mg of **166** (32%) as a yellow oil. Data are: TLC R_f= 0.22 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38-7.32 (m, 3H), 7.32-7.26 (m, 2H), 6.16-6.11 (m, 1H), 6.06-6.01 (m, 1H), 5.67-5.61 (m, 1H), 5.48-5.33 (m, 4H), 5.12 (s, 2H), 3.56 (q, *J1*=3.75 Hz, *J2*=7 Hz, 1H), 2.79 (t, *J*=6 Hz, 2H), 2.38-2.34 (m, 2H), 2.27-2.21 (m, 1H), 2.10 (q, *J1*=3.75 Hz, *J2*=2.75 Hz, 2H), 2.03-1.99 (m, 3H), 1.75-1.69 (m, 2H), 1.36-1.26 (m, 8H), 0.88 (t, *J*=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.4, 136.1, 133.0, 132.1, 128.6, 128.2, 127.7, 124.8, 82.0, 33.7, 33.5, 31.9, 29.7, 27.4, 24.7, 24.7, 22.5, 14.1; HRMS found 410.2821 $[M]^+$, calcd 410.2821 for $[C_{27}H_{38}O_3]^+$. Optical rotation data: $[\alpha]_D^{23}$ = -1.33° (c 0.75, $CHCl_3$).

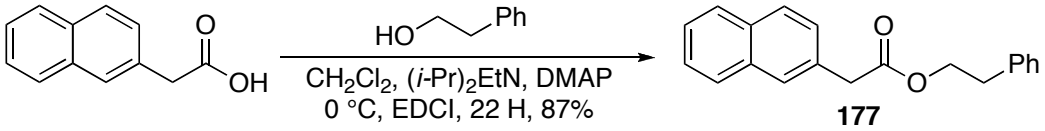


12-*(S)*-HETE (11). Compound **166** (15 mg, 0.037 mmol, 1 equiv) was dissolved in dry THF (2.6 mL) and cooled under N_2 to 0 °C. 1 N LiOH (0.73 mL, 0.73 mmol, 20 equiv) was then added, followed by methanol (0.313 mL, 0.117 M). The solution was stirred 2.5 hours. It was then quenched with dry ice, concentrated, and diluted with EtOAc (10 mL) and a pH 5.0 buffer solution. The layers were mixed and separated. The aqueous layer was then extracted with

EtOAc (3 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Efforts to purify by column chromatography were unsuccessful. However, the crude material did test positive by HRMS: found 320.2351 $[M]^+$, calcd 320.2351 for $[C_{20}H_{32}O_3]^+$.

7.6. Procedures from Chapter 6

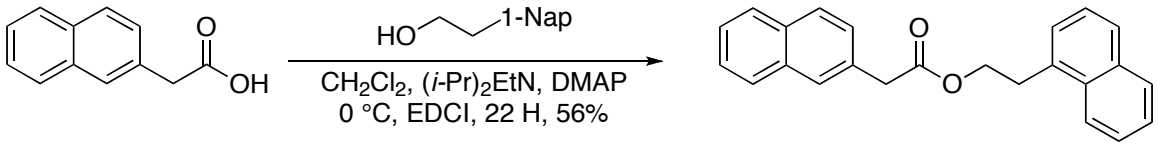
7.6.1. Selected Substrate Preparations



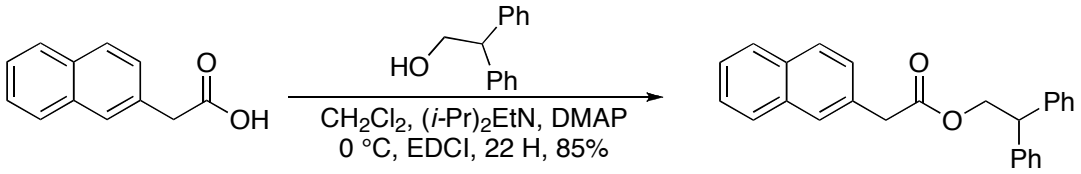
177

Phenethyl 2-(naphthalen-2-yl)acetate (177). 2-napthaleneacetic acid (2.0 g, 10.74 mmol, 1.2 equiv) was dissolved in CH_2Cl_2 (26.85 mL, 0.4M) and was cooled, stirring under N_2, to 0 °C. Once the acid had dissolved, phenethanol (1.07 mL, 8.95 mmol, 1.0 equiv), diisopropylethylamine (2.34 mL, 13.43 mmol, 1.5 equiv), and *N,N*-dimethylaminopyridine (164 mg, 1.34 mmol, 0.15 equiv) were added. This suspension was stirred five minutes, at which time was added 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDCI, 2.57 g, 13.43 mmol, 1.5 equiv). The reaction stirred 22.5 hours, warming from 0 °C to RT. Once the phenethanol was consumed (TLC), the reaction crude was diluted with water (20 mL) and $CHCl_3$ (120 mL). The layers were mixed and separated, and the aqueous layer was extracted with $CHCl_3$ (3 x 10mL). The organic layers were combined and were washed sequentially with 3M H_3PO_4 (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and saturated aqueous NaCl (30 mL). The organic layers were then dried ($MgSO_4$), filtered, and concentrated. The crude material was purified by column chromatography (7% EtOAc/hexanes) to afford 2.26 g (87%) of product **177** as a white solid. Data are: TLC R_f= 0.8 (30% EtOAc/hexanes); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.85 – 7.80 (m, 3H), 7.71 (s, 1H), 7.50

– 7.48 (m, 2H), 7.40 – 7.37 (m, 1H), 7.24 – 7.22 (m, 3H), 7.15 – 7.13 (m, 2H), 4.34 (t, J =7.0 Hz, 2H), 3.78 (s, 2H), 2.93 (t, J =7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.5, 137.7, 133.5, 132.5, 131.5, 128.9, 128.4, 128.2, 128.0, 127.7, 127.7, 127.4, 126.5, 126.1, 125.8, 65.4, 41.7, 35.0; HRMS found 291.1318 $[M+H]^+$, calcd 291.1307 for $[C_{20}H_{19}O_2]^+$.



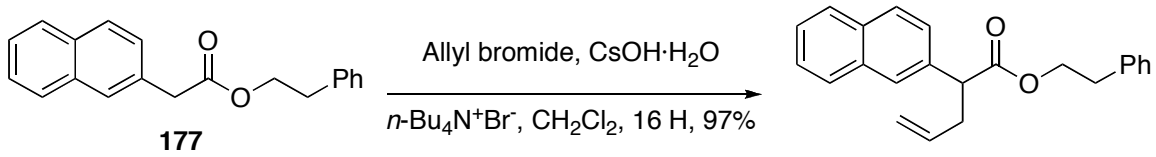
2-(naphthalen-1-yl)ethyl 2-(naphthalen-2-yl)acetate (Table 6.1, entry 11). Following the above procedure for **177**, substituting 2-(naphthalen-1-yl)ethanol (obtained by reducing 1-naphthylacetic acid with DIBAL-H) for phenethanol, the crude material was purified by column chromatography (10% EtOAc/hexanes) to give the product with a 56% yield. Data are: TLC R_f= 0.8 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.13 (d, J = 4 Hz, 1H), 7.90 – 7.78 (m, 6H), 7.76 – 7.30 (m, 7H), 4.52 (t, J = 7.5 Hz, 2H), 3.83 (s, 2H), 3.45 (t, J = 7.5 Hz, 2H), ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.9, 134.2, 133.9, 133.8, 132.9, 132.4, 131.8, 129.2, 128.6, 128.4, 128.1, 128.0, 127.8, 127.4, 126.5, 126.2, 126.0, 125.8, 123.9, 65.3, 41.9, 32.5.



2,2-diphenylethyl 2-(naphthalen-2-yl)acetate (Table 6.1, entry 12). Following the above procedure for **177**, substituting 2,2-diphenylethanol for phenethanol, the crude material was purified by column chromatography (10% EtOAc/hexanes) to give the product with an 85% yield. Data are: TLC R_f= 0.68 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.93 – 7.91

(m, 1H), 7.84 – 7.83 (m, 2H), 7.70 (s, 1H), 7.58 – 7.56 (m, 2H), 7.347.28 (m, 11H), 4.79 (d, J = 3.75 Hz, 2H), 4.46 (t, J = 7.5 Hz, 1H), 3.79 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.7, 141.3, 133.8, 132.8, 131.7, 128.9, 128.6, 128.5, 128.4, 128.1, 128.0, 127.7, 127.1, 126.4, 126.2, 67.5, 50.2, 41.9.

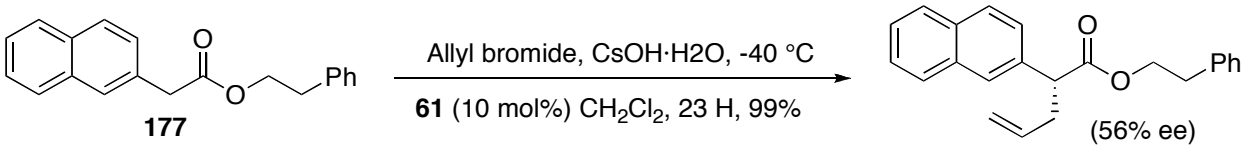
7.6.2. General Procedure for Racemic Aryl Acetate Alkylations



(±)-Phenethyl 2-(naphthalen-2-yl)pent-4-enoate (Table 6.1, entry 10). Phenethyl 2-(naphthalen-2-yl)acetate **177** (50 mg, 0.172 mmol, 1.0 equiv) and tetra-*n*-butylammonium bromide (6.5 mg, 0.02 mmol, 0.12 equiv) were dissolved in CH_2Cl_2 (1.75 mL, 0.1 M). This solution was cooled, while stirring under N_2, to 0 °C. Allyl bromide (73μL, 0.86 mmol, 5.0 equiv) was then added, and the solution continued stirring for an additional 10 minutes, whereupon $CsOH{\cdot}H_2O$ (116 mg, 0.689 mmol, 4.0 equiv) was added. The reaction vessel was sealed under N_2 and continued stirring for 16 hours, warming from 0 °C to RT. Once compound **177** was consumed (TLC), the reaction crude was diluted with water (10 mL) and diethyl ether (30 mL). The layers were mixed and then separated, and the organic layer was washed with saturated aqueous NaCl (1x10 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by column chromatography (5% EtOAc/hexanes) to afford 58 mg (97%) of the product as a yellow oil. Data are: TLC R_f= 0.42 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.82 – 7.78 (m, 3H), 7.73 (s, 1H), 7.49 – 7.42 (m, 3H), 7.16 – 7.15 (m, 3H), 7.07 – 7.06 (m, 2H), 4.70 (d, J = 9.5 Hz, 2H), 4.28 (t, J = 6.5 Hz, 2H), 3.95 (t, J = 7.5 Hz, 1H), 2.93 – 2.84 (m, 3H), 2.52 (dd, $J1$ =

4 Hz, *J2* = 11 Hz, 1H), 1.72 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.5, 142.6, 137.7, 136.2, 133.1, 132.7, 128.8, 128.4, 128.3, 127.9, 127.6, 126.8, 126.4, 126.1, 125.9, 125.9, 112.3, 65.3, 50.2, 41.1, 35.0, 22.7; HRMS found 345.1864 $[M+H]^+$, calcd 345.1849 for $[C_{24}H_{24}O_2]+$; enantiomers' retention times were determined by chiral HPLC (DAICEL Chiralpak AD-H column): 5% EtOH/hexane, 0.5 mL/min, 23 °C, λ = 254 nm, retention times: *S* 12.16 min, *R* 12.78 min, 48.96 : 51.04 er.

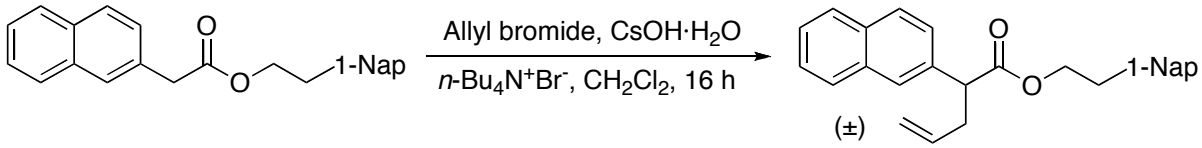
7.6.3. General Procedure for Asymmetric Aryl Acetate Alkylations



***(R)*-phenethyl 2-(naphthalen-2-yl)pent-4-enoate (Table 6.1, entry 10).** Phenethyl 2-(naphthalen-2-yl)acetate **177** (50 mg, 0.172 mmol, 1.0 equiv) and catalyst **61** (17 mg, 0.0172 mmol, 0.1 equiv) were dissolved in CH_2Cl_2 (pre-chilled to -40 °C, 1.75 mL, 0.1 M). This solution was then stirred at -40 °C under N_2. Allyl bromide (73μL, 0.86 mmol, 5.0 equiv) was added, and the solution continued stirring for an additional 10 minutes, whereupon $CsOH·H_2O$ (116 mg, 0.689 mmol, 4.0 equiv) was added. The reaction vessel was then sealed with a rubber stopper under N_2, and the mixture continued stirring for 23 hours at -40 °C. When compound **177** was consumed (TLC), the reaction crude was diluted with water (10 mL) and diethyl ether (30 mL). The layers were mixed and separated, and the organic layer was washed with saturated aqueous NaCl (10 mL). The combined organic layers were dried ($MgSO_4$) and then passed through 20 mL of silica gel packed into a 30M filter cup that was fitted onto an evacuated filter flask (eluent: Et_2O, 250 mL). The filtrate was transferred to a pre-weighed RB flask, concentrated, and then left under high vacuum for 3 h, giving 56 mg (99%) of product as a yellow oil. Data are: TLC R_f= 0.53 (2 x 5%

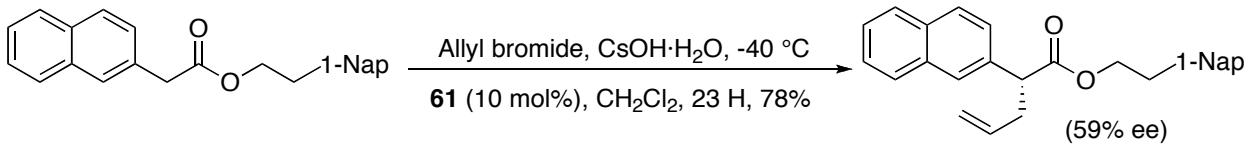
EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.85 – 7.78 (m, 3H), 7.73 (s, 1H), 7.52 – 7.47 (m, 2H), 7.43 (dd, *J1* = 3.5 Hz, *J2* = 1.5 Hz, 1H), 7.18 – 7.16 (m, 2H), 7.08 – 7.06 (m, 2H), 5.77 – 5.69 (m, 1H), 5.10 – 4.99 (m, 2H), 4.34 – 4.27 (m, 2H), 3.80 (t, *J* = 8.0 Hz, 1H), 2.94 – 2.82 (m, 3H), 2.65 – 2.59 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.3, 137.7, 135.9, 135.2, 133.4, 132.7, 128.9, 128.4, 128.4, 127.9, 127.6, 126.9, 126.4, 126.2, 125.9, 125.9, 117.1, 65.3, 51.6, 27.3, 35.0; HRMS found 331.1692 $[M+H]^+$, calcd 331.1620 for $[C_{23}H_{23}O_2]^+$; the enantiomers' retention times were determined by chiral HPLC (DAICEL Chiralpak AD-H column): 5% EtOH/hexane, 0.5 mL/min, 23 °C, λ = 254 nm, retention times: *S* (minor) 12.89 min, *R* (major) 13.41 min, 22.23 : 77.78 er, 56% ee.

7.6.4. Selected Alkylations



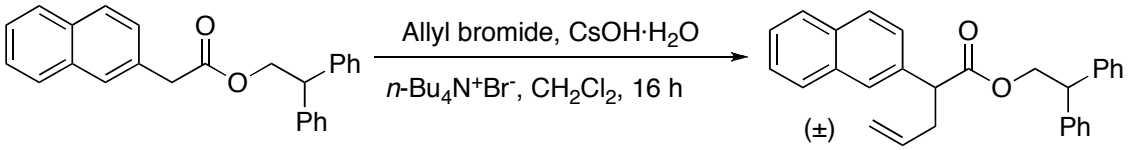
(±)-2-(naphthalen-1-yl)ethyl 2-(naphthalen-2-yl)pent-4-enoate (Table 6.1, entry 11). Following the general procedure for racemic aryl acetate alkylations (section 7.6.2 above), the crude material was purified by column chromatography (20% EtOAc/hexanes) to give the product as a white solid. Data are: TLC R_f= 0.77 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.03 (d, *J* = 4.5 Hz, 1H), 7.83 – 7.78 (m, 4H), 7.71 – 7.68 (m, 2H), 7.51 – 7.40 (m, 5H), 7.23 (d, *J* = 1 Hz, 1H), 7.16 (d, *J* = 3 Hz, 1H), 5.75 – 5.67 (m, 1H), 5.08 – 4.96 (m, 2H), 4.44 – 4.39 (m, 2H), 3.78 (t, *J* = 3.75 Hz, 1H), 3.36 – 3.29 (m, 2H), 2.92 – 3.29 (m, 1H), 2.63 – 2.57 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.4, 135.9, 135.2, 133.8, 133.5, 133.4, 132.7, 132.0, 128.8, 128.4, 127.9, 127.7, 127.4, 127.1, 127.0, 126.2, 126.2, 125.9, 125.6, 125.4, 123.6, 117.1,

64.8, 51.7, 37.4, 32.1; HRMS found 381.1701 $[M+H]^+$, calcd 381.1849 for $[C_{27}H_{24}O_2]^+$; enantiomers' retention times were determined by chiral HPLC (DAICEL Chiralpak AD-H column): 5% EtOH/hexane, 0.5 mL/min, 23 °C, λ = 254 nm, retention times: *S* 15.53 min, *R* 16.19 min, 48.76 : 51.24 er.

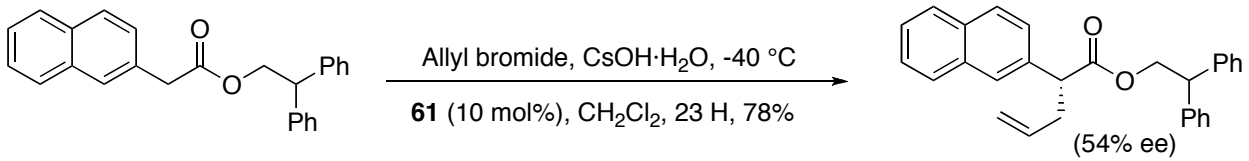


***(R)*-2-(naphthalen-1-yl)ethyl 2-(naphthalen-2-yl)pent-4-enoate (Table 6.1, entry 11).**

Following general procedure for asymmetric aryl acetate alkylations (section 7.6.3 above), the crude material was purified by column chromatography (5% EtOAc/hexanes) to give the product as a white solid with a 78% yield. Data are: TLC R_f = 0.78 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.03 (d, *J* = 4.5 Hz, 1H), 7.83 – 7.78 (m, 4H), 7.71 – 7.68 (m, 2H), 7.51 – 7.40 (m, 5H), 7.23 (d, *J* = 1 Hz, 1H), 7.16 (d, *J* = 3 Hz, 1H), 5.75 – 5.67 (m,1H), 5.08 – 4.96 (m, 2H), 4.44 – 4.39 (m, 2H), 3.78 (t, *J* = 3.75 Hz, 1H), 3.36 – 3.29 (m, 2H), 2.92 – 3.29 (m, 1H), 2.63 – 2.57 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.4, 135.9, 135.2, 133.8, 133.5, 133.4, 132.7, 132.0, 128.8, 128.4, 127.9, 127.7, 127.4, 127.1, 127.0, 126.2, 126.2, 125.9, 125.6, 125.4, 123.6, 117.1, 64.8, 51.7, 37.4, 32.1; HRMS found 381.1701 $[M+H]^+$, calcd 381.1849 for $[C_{27}H_{24}O_2]^+$; the enantiomers' retention times were determined by chiral HPLC (DAICEL Chiralpak AD-H column): 5% EtOH/hexane, 0.5 mL/min, 23 °C, λ = 254 nm, retention times: *S* (minor) 13.79 min, *R* (major) 14.47 min, 20.05 : 79.05, 59% ee.

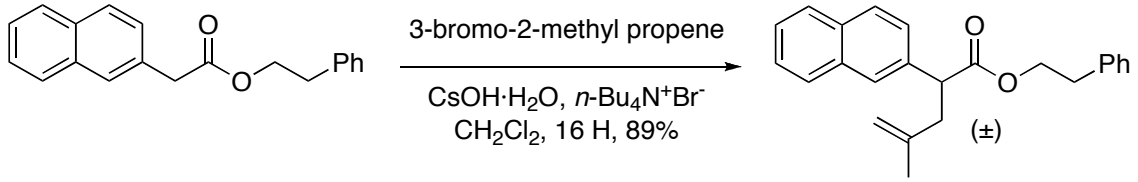


(±)-2,2-diphenylethyl 2-(naphthalen-2-yl)pent-4-enoate (table 6.1, entry 12). Following the general procedure for racemic aryl acetate alkylations (section 7.6.2 above), the crude material was purified by column chromatography (20% EtOAc/hexanes) to give the product as a white solid. Data are: TLC R_f= 0.82 (20% EtOAc/hexanes); enantiomers' retention times were determined by chiral HPLC (DAICEL Chiralpak AD-H column): 5% EtOH/hexane, 0.5 mL/min, 23 °C, λ = 254 nm, retention times: *S* 20.79 min, *R* 21.52 min, 42.98 : 57.02 er.

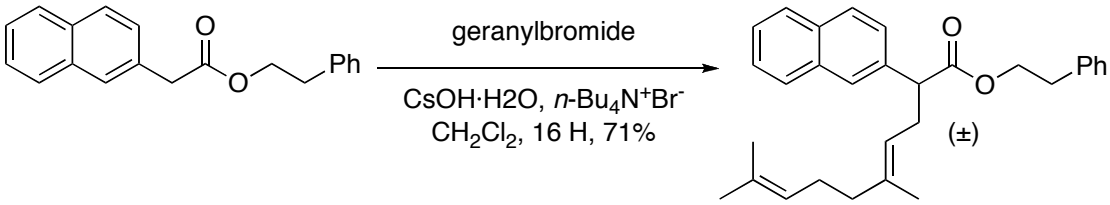


***(R)*-2,2-diphenylethyl 2-(naphthalen-2-yl)pent-4-enoate (Table 6.1, entry 12).** Following the general procedure for asymmetric aryl acetate alkylations (section 7.6.3 above), the crude material was purified by column chromatography (5% EtOAc/hexanes) to give the product as a white solid with a 78% yield. Data are: TLC R_f= 0.78 (20% EtOAc/hexanes); retention times were determined by chiral HPLC (DAICEL Chiralpak AD-H column): 2.5% EtOH/hexane, 0.5 mL/min, 23 °C, λ = 254 nm, retention times: *S* (minor) 20.65 min, *R* (major) 21.31 min, 23.2 : 76.8, 54% ee.

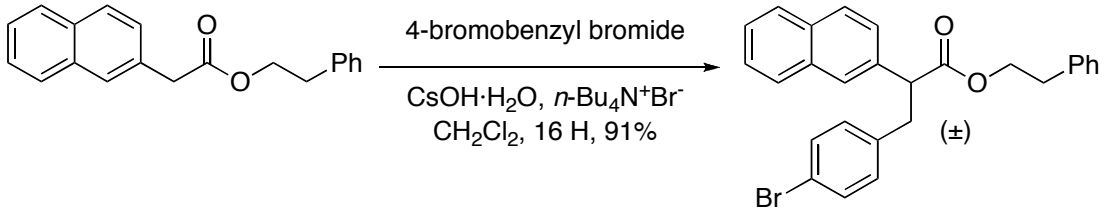
7.6.5. Racemic Alkylation Products From Table 6.3



(±)-phenethyl 4-methyl-2-(naphthalen-2-yl)pent-4-enoate (Table 6.3, entry 2). Following the general procedure for racemic aryl acetate alkylations (section 7.6.2 above), substituting 3-bromo-2-methyl propene for allyl bromide, the crude material was purified by column chromatography (10% EtOAc/hexanes) to give the product as a white solid with an 89% yield. Data are: TLC R_f = 0.45 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.83 – 7.78 (m, 3H), 7.73 (s, 1H), 7.49 – 7.42 (m, 3H), 7.16 – 7.15 (m, 3H), 7.07 – 7.06 (m, 2H), 4.70 (d, *J* = 9.5 Hz, 2H), 4.28 (t, *J* = 6.5 Hz, 2H), 3.95 (t, *J* = 7.5 Hz, 1H), 2.93 – 2.84 (m, 3H), 2.52 (dd, *J1* = 4 Hz, *J2* = 11 Hz, 1H), 1.72 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.5, 142.6, 137.7, 136.2, 133.1, 132.7, 128.8, 128.4, 128.3, 127.9, 127.6, 126.8, 126.4, 126.1, 125.9, 125.9, 112.3, 65.3, 50.2, 41.1, 35.0, 22.7; HRMS found 345.1864 $[M+H]^+$, calcd 345.1849 for $[C_{24}H_{24}O_2]^+$; the enantiomers' retention times were determined by chiral HPLC (DAICEL Chiralpak AD-H column): 5% EtOH/hexane, 0.5 mL/min, 23 °C, λ = 254 nm, retention times: *S* 13.89 min, *R* 14.83 min, 48.89 : 51.11 er.

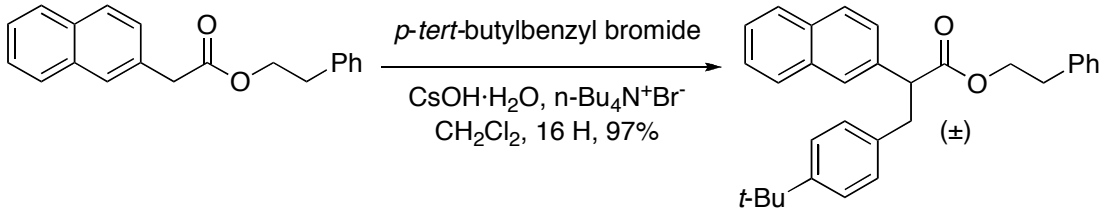


(±)-*(E)*-phenethyl 5,9-dimethyl-2-(naphthalen-2-yl)deca-4,8-dienoate (Table 6.3, entry 3). Following the general procedure for racemic aryl acetate alkylations (section 7.6.2 above), substituting geranylbromide for allyl bromide, the crude material was purified by column chromatography (5% EtOAc/hexanes) to give the target compound as a clear colorless oil with a 71% yield. Data are: TLC R_f= 0.54 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.83 – 7.77 (m, 3H), 7.71 (s, 1H), 7.49 – 7.40 (m, 3H), 7.16 – 7.14 (m, 3H), 7.06 – 7.05 (m, 2H), 5.05 (t, *J* = 6.5 Hz, 1H), 5.00 (t, *J* = 5.5 Hz, 1H), 4.32 – 4.24 (m, 2H), 3.70 (t, *J* = 8 Hz, 1H), 2.89 – 2.81 (m, 3H), 2.58 – 2.52 (m, 1H), 2.04 – 1.90 (m, 4H), 1.63 (s, 3H), 1.57 (s, 3H), 1.55 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.9, 137.9, 137.9, 136.6, 133.6, 132.8, 131.6, 129.1, 128.6, 128.4, 128.5, 127.8, 127.9, 126.6, 126.3, 126.0, 124.3, 121.0, 65.4, 52.3, 39.9, 35.2, 32.1, 26.8, 25.9, 17.9, 16.4; HRMS found 427.2636 $[M+H]^+$, calcd 427.2631 for $[C_{30}H_{34}O_2]^+$; the enantiomers' retention times were determined by chiral HPLC (DAICEL Chiralpak AD-H column): 2.5% EtOH/hexane, 0.5 mL/min, 23 °C, λ = 254 nm, retention times: *S* 9.38 min, *R* 9.68 min, 49.58 : 50.42 er.



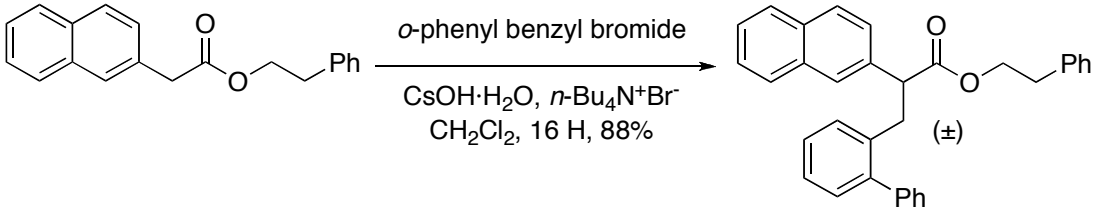
(±)-phenethyl 3-(4-bromophenyl)-2-(naphthalen-2-yl)propanoate (Table 6.3, entry 4). Following the general procedure for racemic aryl acetate alkylations (section 7.6.2 above),

substituting 4-bromobenzyl bromide for allyl bromide, the crude material was purified by column chromatography (5% EtOAc/hexanes) to give the target compound as a white solid with a 91% yield. Data are: TLC R_f= 0.46 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) 7.81 – 7.78 (m, 3H), 7.68 (s, 1H), 7.48 – 7.48 (m, 2H), 7.39 (d, *J* = 4 Hz,1H), 7.32 (d, *J* = 3.75 Hz, 2H), 7.14 (bs,3H), 6.98 (m, 4H), 4.24 (t, *J* = 6.5 Hz, 2H), 3.93 (t, *J* = 7.5 Hz, 1H), 3.42 (t, *J* = 11 Hz, 1H), 3.05 (dd, *J1* = 3.5 Hz, *J2* = 9.5 Hz, 1H), 2.79 (t, *J* = 6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.2, 138.2, 137.8, 135.8, 133.6, 132.9, 131.6, 130.9, 129.0, 128.7, 128.6, 128.1, 127.8, 127.2, 126.7, 126.5, 126.2, 126.0, 120.6, 96.4, 65.6, 53.8, 39.1, 35.1; HRMS found 459.0905 $[M+H]^+$, calcd 459.0954 for $[C_{27}H_{23}BrO_2]^+$; the enantiomers' retention times were determined by chiral HPLC (DAICEL Chiralpak AD-H column): 2.5% EtOH/hexane, 0.5 mL/min, 23 °C, λ = 254 nm, retention times: *S* 26.5 min, *R* 27.3 min, 51.81: 48.19 er.



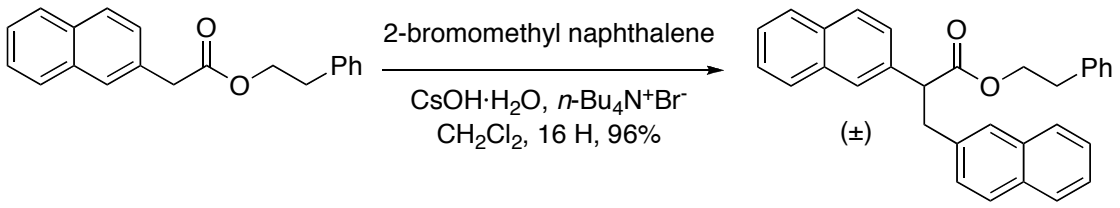
(±)-phenethyl 3-(4-*tert*-butylphenyl)-2-(naphthalen-2-yl)propanoate (Table 6.3, entry 5). Following the general procedure for racemic aryl acetate alkylations (section 7.6.2 above), substituting *p*-tertbutylbenzyl bromide for allyl bromide, the crude material was purified by column chromatography (5% EtOAc/hexanes) to give the target compound as a white solid with a 97% yield. Data are: TLC R_f= 0.49 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.83 – 7.78 (m, 3H), 7.73 (s, 1H), 7.48 – 7.45 (m, 3H), 7.25 (d, *J* = 3.75 Hz, 2H), 7.13 – 7.07 (m, 5H), 6.98 (d, *J* = 1.75 Hz, 2H), 4.28 – 4.18 (m, 2H), 4.00 (t, *J* = 7.5 Hz, 2H), 3.47 (dd, *J1* = 2 Hz, *J2* = 11.5 Hz, 1H), 3.08 (dd, *J1* = 3.5 Hz, *J2* = 10 Hz, 1H), 2.76 (t, *J* = 6.5 Hz, 2H), 1.27 (s, 9H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.3, 149.2, 137.7, 136.3, 136.0, 133.4, 132.7, 128.8, 128.6, 128.4, 128.4, 127.9, 127.6, 126.9, 126.4, 126.1, 126.0, 125.9, 125.3, 65.3, 53.8, 39.0, 35.0, 34.4, 31.4; HRMS found 437.2471 $[M+H]^+$, calcd 437.2475 for $[C_{31}H_{32}O_2]^+$; the enantiomers' retention times were determined by chiral HPLC (DAICEL Chiralpak AD-H column): 5% EtOH/hexane, 0.5 mL/min, 23 °C, λ = 254 nm, retention times: *S* 14.85 min, *R* 15.65 min, 47.17 : 52.83 er.

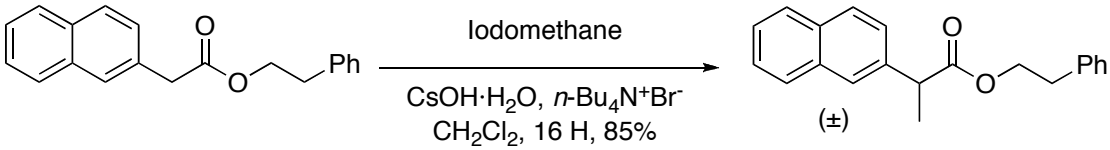


(±)-phenethyl 3-(biphenyl-2-yl)-2-(naphthalen-2-yl)propanoate (Table 6.3, entry 6). Following the general procedure for racemic aryl acetate alkylations (section 7.6.2 above), substituting *o*-phenyl benzyl bromide for allyl bromide, the crude material was purified by column chromatography (5% EtOAc/hexanes) to give the target compound as a white solid with an 88% yield. Data are: TLC R_f = 0.46 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.76 – 7.74 (m, 1H), 7.67 – 7.63 (m, 2H), 7.45 – 7.34 (m, 6H), 7.22 – 7.12 (m, 9H) 7.02 (d, *J* = 4 Hz, 1H), 6.93 – 6.92 (m, 2H), 4.20 – 4.13 (m, 2H), 3.71 (t, *J* = 7.75 Hz, 1H), 3.40 (dd, *J1* = 2.5 Hz, *J2* = 11.5 Hz, 1H), 3.20 (dd, *J1* = 1 Hz, *J2* = 7.5 Hz, 1H), 2.72 (t, *J* = 7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.3, 142.6, 141.7, 137.9, 136.5, 136.3, 133.5, 132.7, 130.4, 130.2, 129.4, 129.2, 129.0, 128.5, 128.5, 128.3, 128.0, 127.7, 127.6, 127.2, 126.7, 126.6, 126.2, 126.0, 125.9, 65.4, 52.7, 37.5, 35.1; HRMS found 457.2188 $[M+H]^+$, calcd 457.2162 for $[C_{33}H_{28}O_2]^+$; the enantiomers' retention times were determined by chiral HPLC (DAICEL Chiralpak AD-H

column): 5% EtOH/hexane, 0.5 mL/min, 23 °C, λ = 254 nm, retention times: *S* 13.03 min, *R* 14.17 min, 50.1 : 49.9 er.

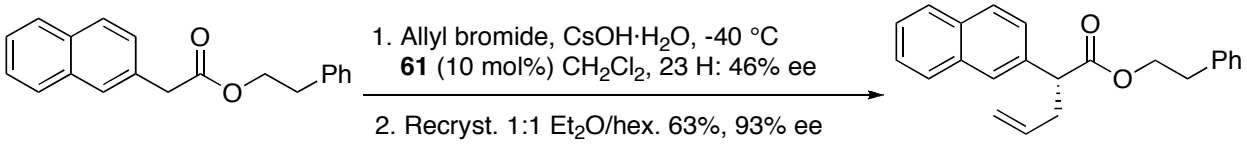


(±)-phenethyl 2,3-di(naphthalen-2-yl)propanoate (Table 6.3, entry 7). Following the general procedure for racemic aryl acetate alkylations (section 7.6.2 above), substituting 2-bromomethyl naphthalene for allyl bromide, the crude material was purified by column chromatography (10% EtOAc/hexanes) to give the target compound as a white solid with a 96% yield. Data are: TLC R_f = 0.77 (4 x 5% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.83 – 7.76 (m, 5H), 7.73 – 7.70 (m, 2H), 7.61 (s, 1H), 7.48 – 7.40 (m, 5H), 7.27 (d, *J* = 4.5 Hz, 1H), 7.12 – 7.05 (m, 3H), 6.92 (d, *J* = 3.5 Hz, 2H), 4.21 (t, *J* = 7 Hz, 2H), 4.11 (t, *J* = 7.5 Hz, 1H), 3.66 (dd, *J1* = 2.25 Hz, *J2* = 11.75 Hz, 1H), 3.27 (dd, *J1* = 3.5 Hz, *J2* = 10 Hz, 2H), 2.75 (t, *J* = 2.75 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz*)* δ 172.7, 137.1, 136.1, 135.5, 132.9, 132.9, 132.2, 131.7, 128.2, 127.9, 127.8, 127.4, 127.3, 127.1, 127.1, 127.1, 126.9, 126.9, 126.4, 125.8, 125.6, 125.4, 124.9, 64.8, 53.3, 39.2, 34.4; HRMS found 431.2005 $[M+H]^+$, calcd 431.2005 for $[C_{31}H_{26}O_2]^+$; the enantiomers' retention times were determined by chiral HPLC (DAICEL Chiralpak AD-H column): 5% EtOH/hexane, 0.5 mL/min, 23 °C, λ = 254 nm, retention times: *S* 26.575 min, *R* 29.543 min, 50.4 : 49.6 er.



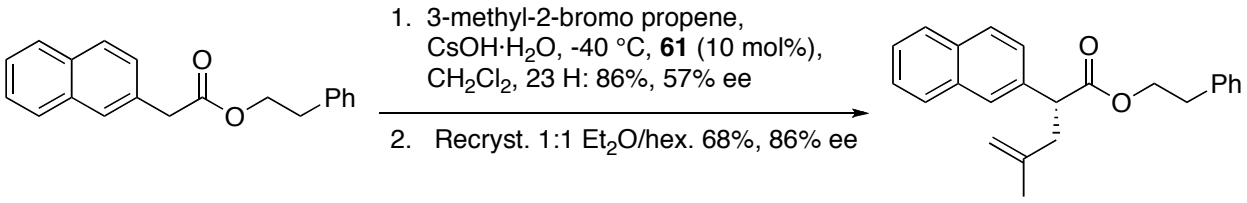
(±)-phenethyl 2-(naphthalen-2-yl)propanoate (Table 6.3, entry 8). Following the general procedure for racemic aryl acetate alkylations (section 7.6.2 above), substituting iodomethane for allyl bromide, the crude material was purified by column chromatography (10% EtOAc/hexanes) to give the target compound as a white solid with an 85% yield. Data are: TLC R_f= 0.46 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.85 – 7.80 (m, 3H), 7.73 (s, 1H), 7.51 – 7.47 (m, 2H), 7.41 (dd, *J1* = 3.5 Hz, *J2* = 5 Hz, 1H), 7.17 – 7.16 (m, 3H), 7.07 – 7.05 (m, 2H), 4.36 – 4.27 (m, 2H), 3.88 (q, *J* = 3.5 Hz, 1H), 2.89 – 2.86 (m, 2H), 1.59 (d, *J* = 3.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.6, 138.1, 137.9, 133.7, 132.8, 129.1, 128.6, 128.5, 128.0, 127.8, 126.6, 126.4, 126.3, 126.0, 126.0, 65.5, 45.9, 35.2, 18.6; HRMS found 305.1559 $[M+H]^+$, calcd 305.1536 for $[C_{21}H_{20}O_2]^+$; the enantiomers' retention times were determined by chiral HPLC (DAICEL Chiralpak AD-H column): 5% EtOH/hexane, 0.5 mL/min, 23 °C, λ = 254 nm, retention times: *S* 16.74 min, *R* 19.09 min, 50.39 : 49.67 er.

7.6.6. Recrystallization Data from Table 6.3



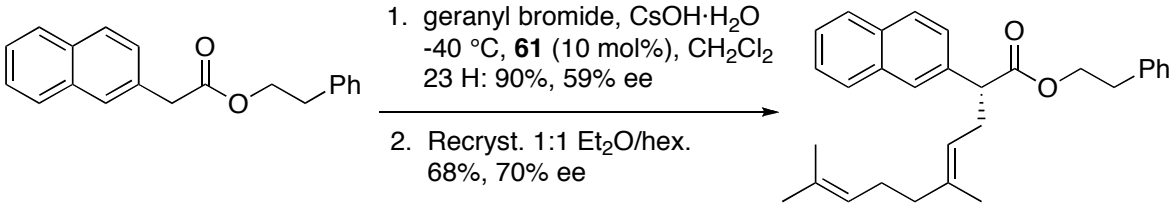
***(R)*-phenethyl 2-(naphthalen-2-yl)pent-4-enoate (Table 6.3, entry 1).** Following the general procedure for asymmetric aryl acetate alkylations (section 7.6.3 above), the product was isolated after filtration and was analyzed (without further purification) by chiral HPLC (DAICEL

Chiralpak AD-H column, 5% EtOH/hexanes, 0.5 mL/min, 23 °C, λ = 254 nm), giving the following retention times: *S* 12.64 min, *R* 13.20 min, 26.98 : 73.02 er, 46% ee. The product was then reconcentrated *in vacuo* and dissolved in a minimal amount of warm 1:1 Et_2O/hexanes. It was capped under argon and cooled in solution overnight in the freezer, giving precipitated product by the next day. This was filtered to afford 36 mg (63%) of the title compound as a white, crystalline solid. The material was deemed pure by NMR and was reanalyzed by chiral HPLC. Data are: TLC R_f= 0.53 (5% EtOAc/hexanes 2x); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.85 – 7.78 (m, 3H), 7.73 (s, 1H), 7.52 – 7.47 (m, 2H), 7.43 (dd, *J1* = 3.5 Hz, *J2* = 1.5 Hz, 1H), 7.18 – 7.16 (m, 2H), 7.08 – 7.06 (m, 2H), 5.77 – 5.69 (m, 1H), 5.10 – 4.99 (m, 2H), 4.34 – 4.27 (m, 2H), 3.80 (t, *J* = 8.0 Hz, 1H), 2.94 – 2.82 (m, 3H), 2.65 – 2.59 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.3, 137.7, 135.9, 135.2, 133.4, 132.7, 128.9, 128.4, 128.4, 127.9, 127.6, 126.9, 126.4, 126.2, 125.9, 125.9, 117.1, 65.3, 51.6, 27.3, 35.0; HRMS found 331.1692 $[M+H]^+$, calcd 331.1620 for $[C_{23}H_{23}O_2]$+; the enantiomers' retention times were determined by chiral HPLC (DAICEL Chiralpak AD-H column): 5% EtOH/hexane, 0.5 mL/min, 23 °C, λ = 254 nm, retention times: *S* 12.10 min, *R* 12.59 min, 3.77 : 96.23 er, 93% ee. $[\alpha]_D^{25}$ = -41° (c 0.267, $CHCl_3$). The absolute configuration of the major enantiomer was deduced as *R* based on evidences presented below.



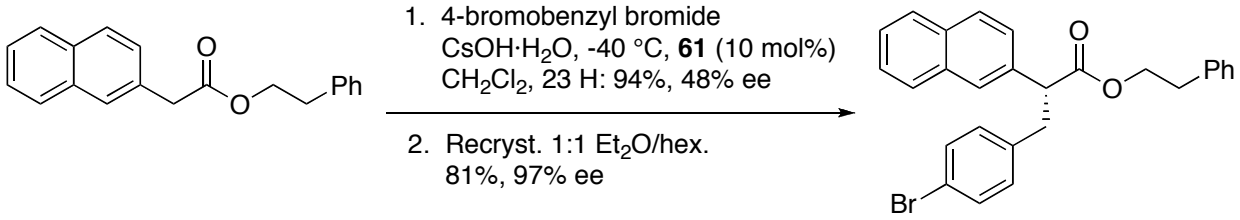
***(R)*-phenethyl 4-methyl-2-(naphthalen-2-yl)pent-4-enoate (Table 6.3, entry 2).** Following the general procedure for asymmetric aryl acetate alkylations (section 7.6.3 above), substituting

3-methyl-2-bromo propene for allyl bromide, the crude product was obtained as a yellow oil (86%) with the following chiral HPLC data (DAICEL Chiralpak AD-H column, 5%EtOH/hexanes, 0.5 mL/min, 23 °C, λ = 254 nm): *S* (minor) 12.80 min, *R* (major) 13.64 min, 21.49 : 78.51 er, 57% ee. After recrystallization in 1:1 Et_2O/hexanes, as described above, the product was obtained as a white, crystalline solid (68%) giving the following chiral HPLC data (same column/conditions): *S* (minor) 11.27 min, *R* (major) 12.01 min, 7.22 : 92.78, 85.6% ee. Data are: TLC R_f= 0.45 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.83 – 7.78 (m, 3H), 7.73 (s, 1H), 7.49 – 7.42 (m, 3H), 7.16 – 7.15 (m, 3H), 7.07 – 7.06 (m, 2H), 4.70 (d, *J* = 9.5 Hz, 2H), 4.28 (t, *J* = 6.5 Hz, 2H), 3.95 (t, *J* = 7.5 Hz, 1H), 2.93 – 2.84 (m, 3H), 2.52 (dd, *J1* = 4 Hz, *J2* = 11 Hz, 1H), 1.72 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.5, 142.6, 137.7, 136.2, 133.1, 132.7, 128.8, 128.4, 128.3, 127.9, 127.6, 126.8, 126.4, 126.1, 125.9, 125.9, 112.3, 65.3, 50.2, 41.0, 35.0, 22.7; HRMS found 345.1864 $[M+H]^+$, calcd 345.1849 for $[C_{24}H_{24}O_2]^+$; $[\alpha]_D^{24}$ = -38° (c 0.183, $CHCl_3$).



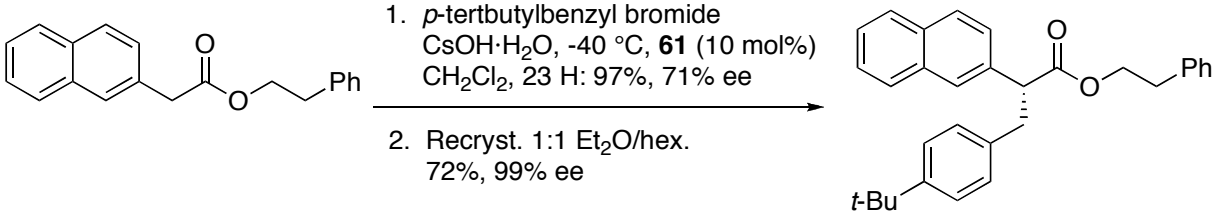
***(R,E)*-phenethyl 5,9-dimethyl-2-(naphthalen-2-yl)deca-4,8-dienoate (Table 6.3, entry 3).** Following the general procedure for asymmetric aryl acetate alkylations (section 7.6.3 above), substituting geranyl bromide for allyl bromide, the crude product was obtained as a yellow oil (90%) with the following chiral HPLC data (DAICEL Chiralpak AD-H column, 2.5% EtOH/hexanes, 0.5 mL/min, 23 °C, λ = 254 nm): *S* (minor) 10.52 min, *R* (major) 11.08 min, 20.55 : 79.45 er, 59% ee. After recrystallization in pure hexanes at -78 °C, the product was obtained as

a white, crystalline solid (68%) and gave the following chiral HPLC data (same column/conditions): *S* (minor) 11.4 min, *R* (major) 11.95 min, 15.16 : 84.84, 70% ee. Data are: TLC R_f = 0.54 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.83 – 7.77 (m, 3H), 7.71 (s, 1H), 7.49 – 7.40 (m, 3H), 7.16 – 7.14 (m, 3H), 7.06 – 7.05 (m, 2H), 5.05 (t, *J* = 6.5 Hz, 1H), 5.00 (t, *J* = 5.5 Hz, 1H), 4.32 – 4.24 (m, 2H), 3.70 (t, *J* = 8 Hz, 1H), 2.89 – 2.81 (m, 3H), 2.58 – 2.52 (m, 1H), 2.04 – 1.90 (m, 4H), 1.63 (s, 3H), 1.57 (s, 3H), 1.55 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.9, 137.9, 137.9, 136.6, 133.6, 132.8, 131.6, 129.1, 128.6, 128.4, 128.5, 127.8, 127.9, 126.6, 126.3, 126.0, 124.3, 121.0, 65.4, 52.3, 39.9, 35.2, 32.1, 26.8, 25.9, 17.9, 16.4; HRMS found 427.2636 $[M+H]^+$, calcd 427.2631 for $[C_{30}H_{34}O_2]^+$; $[\alpha]_D^{24}$ = -54° (c 0.167, $CHCl_3$).

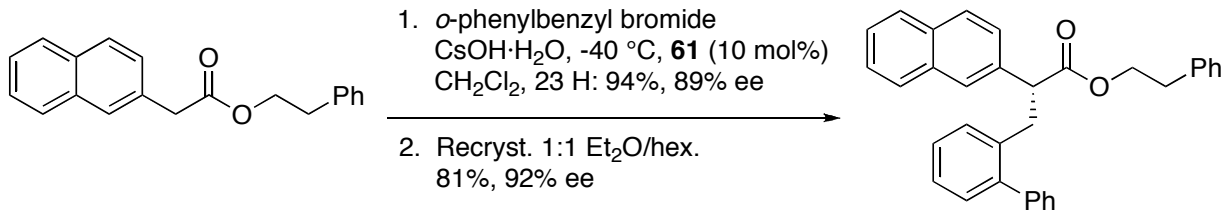


***(R)*-phenethyl 3-(4-bromophenyl)-2-(naphthalen-2-yl)propanoate (Table 6.3, entry 4).** Following the general procedure for asymmetric aryl acetate alkylations (section 7.6.3 above), substituting 4-bromobenzyl bromide for allyl bromide, the crude product was obtained as a yellow oil (94%) with the following chiral HPLC data (DAICEL Chiralpak AD-H column, 2.5% EtOH/hexanes, 0.5 mL/min, 23 °C, λ = 254 nm): *S* (minor) 26.39 min, *R* (major) 27.12 min, 26.27 : 73.73 er, 47.5% ee. After recrystallization in 1:1 Et_2O/hexanes, as described above, the product was obtained as a white, crystalline solid (67%) giving the following chiral HPLC data (same column/conditions): *S* (minor) 28.84 min, *R* (major) 29.65 min, 1.32 : 98.68, 97% ee. Data are: TLC R_f = 0.46 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) 7.81 – 7.78 (m, 3H), 7.68 (s, 1H), 7.48 – 7.48 (m, 2H), 7.39 (d, *J* = 4 Hz,1H), 7.32 (d, *J* = 3.75 Hz, 2H), 7.14 (bs, 3H), 6.98

(m, 4H), 4.24 (t, *J* = 6.5 Hz, 2H), 3.93 (t, *J* = 7.5 Hz, 1H), 3.42 (t, *J* = 11 Hz, 1H), 3.05 (dd, *J1* = 3.5 Hz, *J2* = 9.5 Hz, 1H), 2.79 (t, *J* = 6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.3, 138.2, 137.8, 135.8, 133.6, 132.9, 131.6, 130.9, 129.0, 128.7, 128.6, 128.1, 127.8, 127.2, 126.7, 126.5, 126.2, 126.0, 120.5, 96.4, 65.6, 53.8, 39.1, 35.1; HRMS found 459.0905 $[M+H]^+$, calcd 459.0954 for $[C_{27}H_{23}BrO_2]^+$; $[\alpha]_D^{24}$ = -71° (c 0.65, $CHCl_3$).

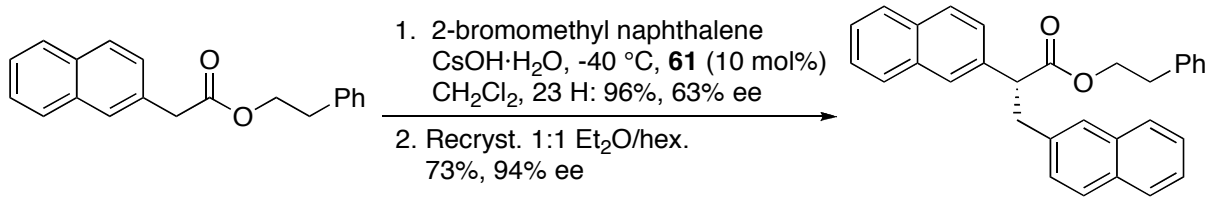


***(R)*-phenethyl 3-(4-tert-butylphenyl)-2-(naphthalen-2-yl)propanoate (Table 6.3, entry 5)**. Following the general procedure for asymmetric aryl acetate alkylations (section 7.6.3 above), substituting *p*-tertbutylbenzyl bromide for allyl bromide, the crude product was obtained as a yellow oil (96.5%) with the following chiral HPLC data (DAICEL Chiralpak AD-H column, 5% EtOH/hexanes, 0.5 mL/min, 23 °C, λ = 254 nm): *S* (minor) 14.83 min, *R* (major) 15.57 min, 14.73 : 85.27 er, 71% ee. After recrystallization in 1:1 Et_2O/hexanes, as described above, the product was obtained as a white, crystalline solid (72%) giving the following chiral HPLC data (same column/conditions): *S* (minor) 15.29 min, *R* (major) 16.10 min, 0.08 er : 99.02, 99% ee. Data are: TLC R_f = 0.49 (10% EtOAc/hexanes); ^{1}H NMR (CDCl3, 500 MHz) δ 7.83 - 7.78 (m, 3H), 7.73 (s, 1H), 7.48 - 7.45 (m, 3H), 7.25 (d, *J* = 3.75 Hz, 2H), 7.13 - 7.07 (m, 5H), 6.98 (d, *J* = 1.75 Hz, 2H), 4.28 - 4.18 (m, 2H), 4.00 (t, *J* = 7.5 Hz, 2H), 3.47 (dd, *J1* = 2 Hz, *J2* = 11.5 Hz, 1H), 3.08 (dd, *J1* = 3.5 Hz, *J2* = 10 Hz, 1H), 2.76 (t, *J* = 6.5 Hz, 2H), 1.27 (s, 9H); ^{13}C NMR (CDCl3, 125 MHz) δ 173.3, 149.2, 137.7, 136.3, 136.0, 133.4, 132.7, 128.8, 128.6, 128.4, 128.4, 127.9, 127.6, 126.9, 126.4, 126.1, 126.0, 125.9, 125.3, 65.3, 53.8, 39.0, 35.0, 34.4, 31.4; HRMS found 437.2471 [M+H]+, calcd 437.2475 for $[C_{31}H_{32}O_2]^+$; $[\alpha]_D^{24}$ = -61° (c 0.0983, $CHCl_3$).

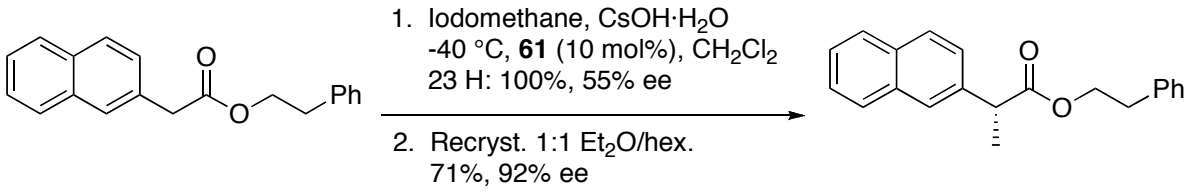


***(R)*-phenethyl 3-(biphenyl-2-yl)-2-(naphthalen-2-yl)propanoate (Table 6.3, entry 6).**

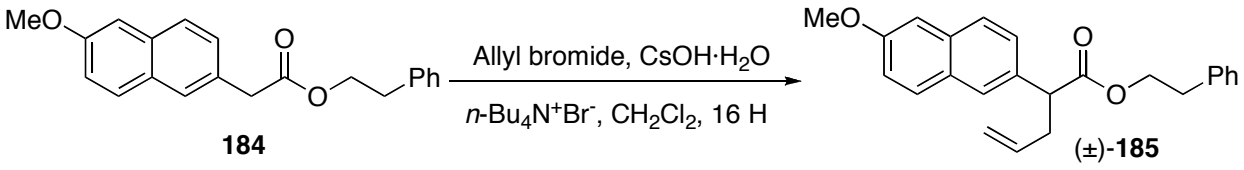
Following the general procedure for asymmetric aryl acetate alkylations (section 7.6.3 above), substituting *o*-phenylbenzyl bromide for allyl bromide, the crude product was obtained as a yellow oil (94%) with the following chiral HPLC data (DAICEL Chiralpak AD-H column, 5% EtOH/hexanes, 0.5 mL/min, 23 °C, λ = 254 nm): *S* (minor) 12.81 min, *R* (major) 13.87 min, 5.62 : 94.38 er, 89% ee. After recrystallization in 1:1 Et_2O/hexanes, as described above, the product was obtained as a white, crystalline solid (81%) giving the following chiral HPLC data (same column/conditions): *S* (minor) 12.34 min, *R* (major) 13.72 min, 3.87 : 96.13, 92% ee. Data are: TLC R_f= 0.46 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.76 – 7.74 (m, 1H), 7.67 – 7.63 (m, 2H), 7.45 – 7.34 (m, 6H), 7.23 – 7.12 (m, 9H) 7.02 (d, *J* = 4 Hz, 1H), 6.93 – 6.92 (m, 2H), 4.20 – 4.13 (m, 2H), 3.71 (t, *J* = 7.75 Hz, 1H), 3.40 (dd, *J1* = 2.5 Hz, *J2* = 11.5 Hz, 1H), 3.20 (dd, *J1* = 1 Hz, *J2* = 7.5 Hz, 1H), 2.72 (t, *J* = 7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.3, 142.6, 141.7, 137.9, 136.5, 136.3, 133.5, 132.7, 130.4, 130.2, 129.4, 129.2, 129.0, 128.5, 128.5, 128.3, 128.0, 127.7, 127.6, 127.2, 126.7, 126.6, 126.2, 126.0, 125.9, 65.4, 52.7, 37.5, 35.1; HRMS found 457.2188 $[M+H]^+$, calcd 457.2162 for $[C_{33}H_{28}O_2]^+$; $[\alpha]_D^{24}$ = -35° (c 0.716, $CHCl_3$).



***(R)*-phenethyl 2,3-di(naphthalen-2-yl)propanoate (Table 6.3, entry 7).** Following the general procedure for asymmetric aryl acetate alkylations (section 7.6.3 above), substituting 2-bromomethyl naphthalene for allyl bromide, the crude product was obtained as a yellow oil (96%) with the following chiral HPLC data (DAICEL Chiralpak AD-H column, 5% EtOH/hexanes, 0.5 mL/min, 23 °C, λ = 254 nm): *S* (minor) 29.49 min, *R* (major) 31.82 min, 18.62 : 81.38 er, 63% ee. After recrystallization in 1:1 Et_2O/hexanes, as described above, the product was obtained as a white, crystalline solid (73%) giving the following chiral HPLC data (same column/conditions): *S* (minor) 34.59 min, *R* (major) 37.63 min, 2.86 : 97.14, 94% ee. Data are: TLC R_f = 0.77 (4 x 5% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.83 – 7.76 (m, 5H), 7.73 – 7.70 (m, 2H), 7.61 (s, 1H), 7.48 – 7.40 (m, 5H), 7.27 (d, *J* = 4.5 Hz, 1H), 7.12 – 7.05 (m, 3H), 6.92 (d, *J* = 3.5 Hz, 2H), 4.21 (t, *J* = 7 Hz, 2H), 4.11 (t, *J* = 7.5 Hz, 1H), 3.66 (dd, *J1* = 2.25 Hz, *J2* = 11.75 Hz, 1H), 3.27 (dd, *J1* = 3.5 Hz, *J2* = 10 Hz, 1H), 2.746 (t, *J* = 2.74 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.7, 137.1, 136.1, 135.5, 132.9, 132.9, 132.2, 131.7, 128.2, 127.9, 127.8, 127.4, 127.3, 127.1, 127.1, 127.1, 126.9, 126.9, 126.4, 125.8, 125.6, 125.4, 124.9, 64.8, 53.3, 39.2, 34.4; HRMS found 431.2005 $[M+H]^+$, calcd 431.2005 for $[C_{31}H_{26}O_2]^+$; $[\alpha]_D^{24}$ = -64° (c 0.11, $CHCl_3$).

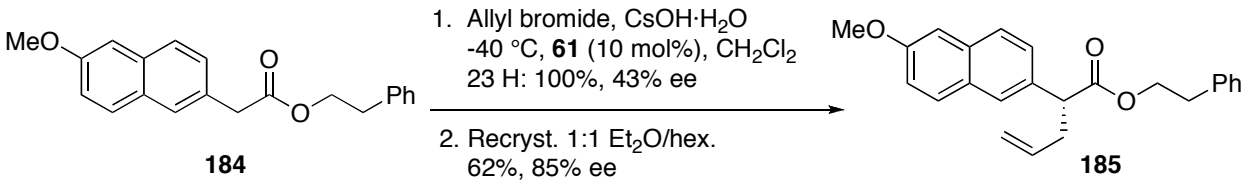


***(R)*-phenethyl 2-(naphthalen-2-yl)propanoate (Table 6.3, entry 8).** Following the general procedure for asymmetric aryl acetate alkylations (section 7.6.3 above), substituting iodomethane for allyl bromide, the crude product was obtained as a yellow oil (100%) with the following chiral HPLC data (DAICEL Chiralpak AD-H column, 5% EtOH/hexanes, 0.5 mL/min, 23 °C, λ = 254 nm): *S* (minor) 15.39 min, *R* (major) 17.48 min, 22.38 : 77.62 er, 55% ee. After recrystallization in 1:1 Et_2O/hexanes, as described above, the product was obtained as a white, crystalline solid (71%) giving the following chiral HPLC data (same column/conditions): *S* (minor) 15.62 min, *R* (major) 17.76 min, 4.08 : 95.92, 92% ee. Data are: TLC R_f= 0.46 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.85 – 7.80 (m, 3H), 7.73 (s, 1H), 7.51 – 7.47 (m, 2H), 7.41 (dd, *J1* = 3.5 Hz, *J2* = 5 Hz, 1H), 7.17 – 7.16 (m, 3H), 7.07 – 7.05 (m, 2H), 4.36 – 4.27 (m, 2H), 3.88 (q, *J* = 3.5 Hz, 1H), 2.89 – 2.86 (m, 2H), 1.59 (d, *J* = 3.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.6, 138.1, 137.9, 133.7, 132.8, 129.1, 128.6, 128.5, 128.0, 127.8, 126.6, 126.4, 126.3, 126.0, 125.9, 65.5, 45.9, 35.2, 18.6; HRMS found 305.1559 $[M+H]^+$, calcd 305.1536 for $[C_{21}H_{20}O_2]^+$; $[\alpha]_D^{24}$ = -25° (c .1666, $CHCl_3$).



(±)-phenethyl 2-(6-methoxynaphthalen-2-yl)pent-4-enoate (185). Following the general procedure for racemic aryl acetate alkylations (section 7.6.2 above), substituting substrate **184** (described in section 7.6.7 below) for **177**, the crude material was purified by column

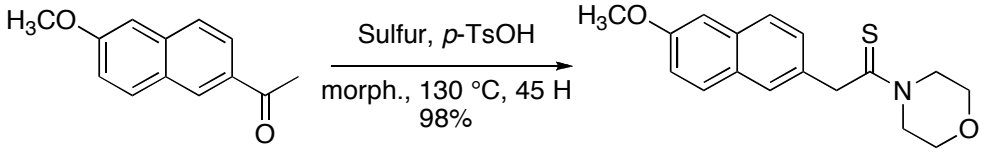
chromatography (20% EtOAc/hexanes) to give the product as a white solid. Data are: TLC R_f= 0.57 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.71 (dd, *J1* = 4.5 Hz, *J2* = 8.5 Hz, 2H), 7.66 (s, 1H), 7.39 (d, *J* = 4.25 Hz, 1H), 7.19 – 7.16 (m, 4H), 7.14 (bs, 2H), 7.09 – 7.07 (m, 2H), 5.77 – 5.69 (m, 1H), 5.10 – 4.99 (m, 2H), 4.35 – 4.27 (m, 2H), 3.95 (s, 3H), 3.77 (t, *J* = 8 Hz, 1H), 2.94 – 2.82 (m, 3H), 2.63 – 2.57 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.5, 157.7, 137.7, 135.3, 133.8, 133.6, 129.4, 128.9, 128.9, 128.4, 127.2, 126.7, 126.4, 126.4, 119.0, 117.0, 105.5, 65.3, 55.3, 51.4, 37.4, 35.0; HRMS found 360.1725 $[M+H]^+$, calcd 360.1725 for $[C_{24}H_{24}O_3]$+; enantiomers' retention times were determined by chiral HPLC (DAICEL Chiralpak AD-H column): 3% EtOH/hexanes, 0.5 mL/min, 23 °C, λ = 254 nm, retention times: *S* 29.35 min, *R* 32.03 min, 50.1 : 49.9 er.



***(R)*-Phenethyl 2-(6-methoxynaphthalen-2-yl)pent-4-enoate (185).** Following the general procedure for racemic aryl acetate alkylations (section 7.6.3 above), substituting substrate **184** (described in section 7.6.7 below) for **177**, the crude product was obtained as a yellow oil (100%) with the following chiral HPLC data (DAICEL Chiralpak AD-H column, 5% EtOH/hexanes, 0.5 mL/min, 23 °C, λ = 254 nm): *S* (minor) 29.34 min, *R* (major) 32.34 min, 28.57 : 71.43 er, 43% ee. After recrystallization in 1:1 Et_2O/hexanes, as described above, the product was obtained as a white, crystalline solid (62%) giving the following chiral HPLC data (same column/conditions): *S* (minor) 29.17 min, *R* (major) 32.07 min, 7.57 : 92.43, 85% ee. Data are: TLC R_f= 0.37 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.71 (dd, *J1* = 4.5 Hz, *J2* =

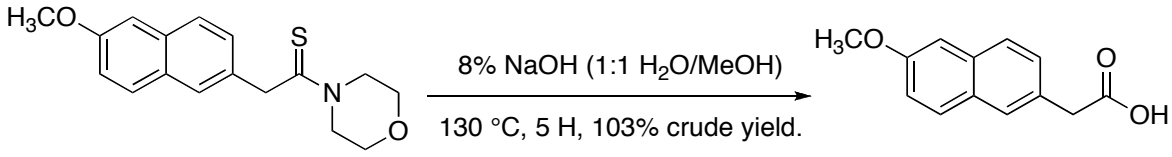
8.5 Hz, 2H), 7.66 (s, 1H), 7.39 (d, *J* = 4.25 Hz, 1 H), 7.19 – 7.16 (m, 4H), 7.14 (bs, 2 H), 7.09 – 7.07 (m, 2 H), 5.77 – 5.69 (m, 1 H), 5.10 – 4.99 (m, 2 H), 4.35 – 4.27 (m, 2 H), 3.95 (s, 3 H), 3.77 (t, *J* = 8 Hz, 1 H), 2.94 – 2.82 (m, 3 H), 2.63 – 2.57 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.5, 157.7, 137.7, 135.3, 133.8, 133.6, 129.4, 128.9, 128.9, 128.4, 127.2, 126.7, 126.4, 126.4, 119.0, 117.0, 105.5, 65.3, 55.3, 51.4, 37.4, 35.0; HRMS found 360.1725 $[M+H]^+$, calcd 360.1725 for $[C_{24}H_{24}O_3]^+$.

7.6.7. Total Synthesis of *(S)*-Naproxen



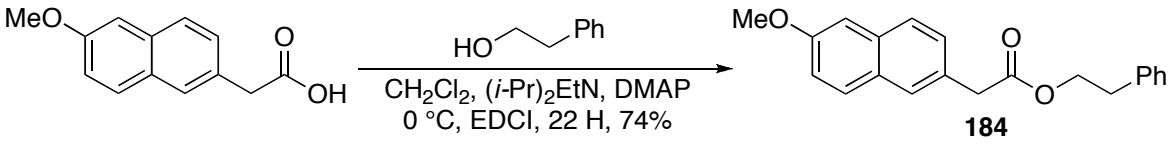
2-(6-methoxynaphthalen-2-yl)-1-morpholinoethanethione. 6-methoxy-2-acetylnaphthalene (1.0 g, 4.99 mmol, 1.0 equiv), sulfur (precipitated USP, 319 mg, 9.99 mmol, 2.0 equiv), and *p*-toluenesulfonic acid (15 mg, 0.074 mmol, 0.015 equiv) were dissolved in morpholine (1.3 mL, 14.98 mmol, 3.0 equiv) and stirred at reflux (~130 °C) to form a deep red mixture, which continued for ~45 hours. Once the starting material was consumed (TLC), the reaction mixture was cooled to RT, diluted with CH_2Cl_2 (10 mL), and wash sequentially with saturated aqueous $NaHCO_3$ (1x10 mL) and saturated aqueous NaCl (1x10 mL). The organic layer was concentrated and purified by column chromatography (20% EtOAc/hexanes) to afford 1.47 g (98%) of the target compound as a yellow/gray solid. Data are: TLC R_f= 0.36 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.74 – 7.66 (m, 3H), 7.45 (d, *J* = 3.5 Hz, 1H), 7.18 – 7.14 (m, 2H), 4.49 (s, 1H), 4.41 – 4.33 (m, 2H), 3.98 – 3.91 (m, 2H), 3.79 – 3.66 (m, 6H), 3.37 (t, *J* = 4.5 Hz, 1H), 2.68 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.8, 133.7, 130.9, 129.2, 129.1, 127.6, 126.5, 126.2, 119.3, 105.8, 66.5, 66.2, 55.4, 50.9, 50.7, 50.3; HRMS found 302.1258 $[M+H]^+$, calcd 302.1209 for

$[C_{17}H_{19}NO_2S]^+$. [Note: An alternative procedure for this compound was successfully employed using 1.2 equivalents of sulfur (precipitated USP) and 3.28 equivalents of morpholine, with no *p*-toluenesulfonic acid added. Otherwise following the same conditions (including temperature, time, and workup) the crude product was taken on to the next step without any purification. The crude yield was 123% (1.855 g).

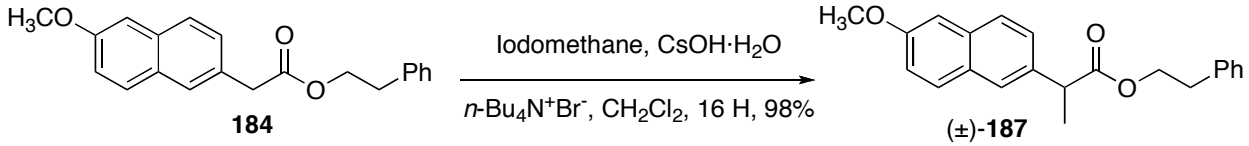


2-(6-methoxynaphthalen-2-yl)acetic acid. 2-(6-methoxynaphthalen-2-yl)-1-morpholino-ethanethione (283 mg, 0.939 mmol, 1.0 equiv) was diluted with 8% w/w NaOH in 1:1 H_2O/MeOH (187 mL, 0.005 M) and was stirred at reflux (~130 °C), gradually forming a yellow solution. After 5 hours, the reaction mixture was cooled to RT, was diluted with CH_2Cl_2 (1 x 50 mL) and transferred to a separatory funnel. The layers were mixed and separated (the organic layer being discarded), and the aqueous layer was transferred to a 1 L beaker, where it was lowered to pH 4 with 50% aqueous AcOH. Once it had reached pH 4, the solution was concentrated, transferred again to a separatory funnel, and was diluted with CH_2Cl_2 (50 mL). The layers were mixed and separated, and the aqueous layer was extracted with CH_2Cl_2 (5 x 50mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated, giving 209 mg (103% crude yield) of the target compound as a light-tan solid. The material was rinsed with hexanes and taken on to the next step without further purification. Data are: TLC R_f= 0.00 (20% EtOAc/hexanes); ^{1}H NMR (Acetone d_6/$CDCl_3$, 500 MHz) δ 7.69 (d, J = 7 Hz, 2H), 7.66 (s, 1H), 7.37 (d, J = 4.25 Hz, 1H), 7.17 (s, 1H), 7.08 (d, J = 4.5 Hz, 1H), 3.87 (s, 3H), 3.71 (s, 2H); ^{13}C NMR (Acetone d_6/$CDCl_3$, 125 MHz) δ 171.6, 156.8, 132.9, 129.1, 128.2, 128.2, 127.3, 126.9, 126.1, 118.1, 104.8, 54.1, 39.9; HRMS found 216.0786 $[M]^+$; calcd 216.0786 for $[C_{13}H_{12}O_2]^+$. [Note: An alternative procedure for this compound was successfully employed using the same conditions, except that

acidification was done with 1 N HCl to pH 2.0. This gave the final product as a yellow solid with an 88% yield (0.951 g).]

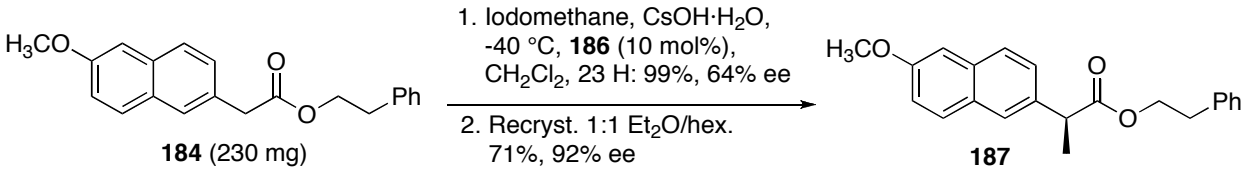


Phenethyl 2-(6-methoxynaphthalen-2-yl)acetate (184). Following procedure for **177** (section 7.6.1 above), 250 mg (1.16 mmol) of 2-(6-methoxynaphthalen-2-yl)acetic acid was converted to ester **184**. Following column purification (10% EtOAc/hexanes), 274 mg of **184** (74%) were obtained as a white solid. Data are: TLC R_f = 0.51 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.66 (dd, *J1* = 1.25 Hz, *J2* = 4.75 Hz, 2H), 7.59 (s, 1H), 7.31 (d, *J* = 4.25 Hz, 1H), 7.20 – 7.17 (m, 3H), 7.14 – 7.71 (m, 4H), 4.29 (t, *J* = 7 Hz, 2H), 3.87 (s, 3H), 3.70 (s, 2H), 2.88 (t, *J* = 7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.7, 157.7, 137.8, 133.7, 129.3, 129.2, 129.0, 128.5, 128.0, 127.9, 127.1, 126.6, 119.0, 105.6, 65.4, 55.3, 41.5, 35.1; HRMS found 321.1481 $[M+H]^+$, calcd 321.1485 for $[C_{21}H_{20}O_3]^+$.



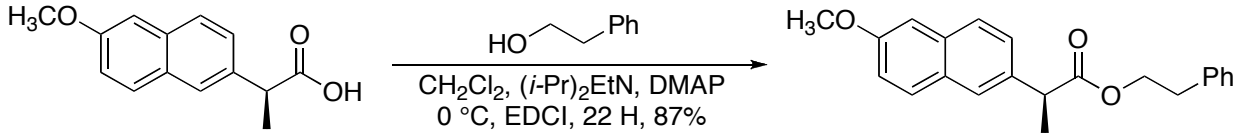
(±)-phenethyl 2-(6-methoxynaphthalen-2-yl)propanoate (187). Following the general procedure for racemic aryl acetate alkylations (section 7.6.2 above), substituting iodomethane for allyl bromide, 51 mg of product **(±)-187** (98%) were obtained as a white solid. Data are: TLC R_f = 0.62 (20% EtOAc/hexanes); ^{1}H NMR δ 7.69 – 7.67 (m, 2H), 7.62 (s, 1H), 7.35 (dd, *J1* = 3.5 Hz, *J2* = 5 Hz, 1H), 7.15 – 7.11 (m, 5H), 7.05 – 7.03 (m, 2H), 4.33 – 4.23 (m, 2H), 3.91 (s, 3H), 3.82 (q, *J* = 7 Hz, 1H), 2.86 – 2.82 (m, 2H), 1.55 (d, *J* = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz)

δ174.8, 157.8, 137.9, 135.8, 133.9, 129.5, 129.1, 129.7, 128.5, 127.3, 126.6, 126.5, 126.2, 119.1, 105.7, 65.4, 55.5, 45.7, 35.2, 18.6; HRMS found 335.1318 $[M+H]^+$, calcd 335.1641 for $[C_{22}H_{22}O_3]^+$; the enantiomers' retention times were determined by chiral HPLC (DAICEL Chiralpak AD-H column): 5% EtOH/hexane, 0.5 mL/min, 23 °C, λ = 254 nm, retention times: *S* 19.89 min, *R* 23.70 min, 49.65 : 50.35 er.



***(S)*-phenethyl 2-(6-methoxynaphthalen-2-yl)propanoate (187).** Following the general procedure for asymmetric aryl acetate alkylations (section 7.6.3 above), substituting iodomethane for allyl bromide and catalyst **186** (described in section 7.6.8 below) for catalyst **61**, the crude product was obtained as a yellow oil (99%) with the following chiral HPLC data (DAICEL Chiralpak AD-H column, 5% EtOH/hexanes, 0.5 mL/min, 23 °C, λ = 254 nm): *S* (major) 18.06 min, *R* (minor) 22.05 min, 81.93 : 18.07 er, 64% ee. After recrystallization in 1:1 Et_2O/hexanes, as described above in section 7.6.6, the product was obtained as a white, crystalline solid (71%) giving the following chiral HPLC data (same column/conditions): *S* (major) 17.94 min, *R* (minor) 22.07 min, 96.18 : 3.82, 92% ee. Data are: TLC R_f= 0.62 (20% EtOAc/hexanes); ^{1}H NMR δ 7.69 – 7.67 (m, 2H), 7.62 (s, 1H), 7.35 (dd, *J1* = 3.5 Hz, *J2* = 5 Hz, 1H), 7.15 – 7.11 (m, 5H), 7.05 – 7.03 (m, 2H), 4.33 – 4.23 (m, 2H), 3.91 (s, 3H), 3.82 (q, *J* = 7 Hz, 1H), 2.86 – 2.82 (m, 2H), 1.55 (d, *J* = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ174.8, 157.8, 137.9, 135.8, 133.9, 129.5, 129.1, 129.7, 128.5, 127.3, 126.6, 126.5, 126.2, 119.1, 105.7, 65.4, 55.5, 45.7, 35.2, 18.6; HRMS found 335.1318 $[M+H]^+$, calcd 335.1641 for $[C_{22}H_{22}O_3]^+$; $[\alpha]_D^{24}$ = +29° (c 0.550, $CHCl_3$). [Note: The absolute configuration of the major enantiomer was deduced as *S* based on

the following: (1) commercial *(S)*-Naproxen was converted to **187** (see below) and gave the same optical rotation and spectral data; (2) *(S)*-Naproxen made from synthetic **187** gave the same optical rotation and spectral data as a commercial sample (see below); (3) The major *S* enantiomer of **187** has a lower retention time than its *R* counterpart by chiral HPLC. Alkylation reactions run with catalyst **61**, therefore, were presumed to give *R*-enriched products because their major enantiomers had higher retention times (chiral HPLC). *S*-product **187** gave positive optical rotation, while alkylation products from **61** gave negative.

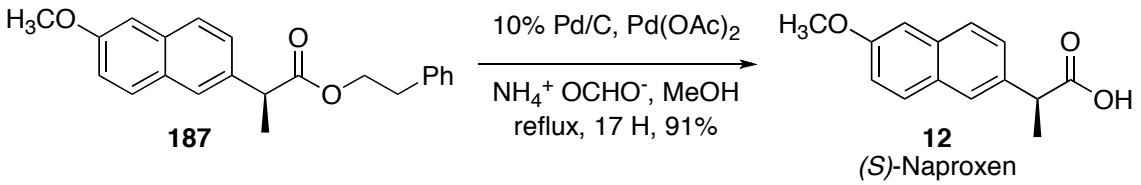


12
(commercial sample)

187

***(S)*-phenethyl 2-(6-methoxynaphthalen-2-yl)propanoate (187).** Following procedure for **177** (section 7.6.1 above), 1.5 g (6.51 mmol) of commercial *(S)*-Naproxen **12** [*(S)*-(+)-6-methoxy-α-methyl-2-naphthaleneacetic acid] was converted to **187**. After purification by column chromatography (10% EtOAc/hexanes), 1.69 g of **187** (93%) was isolated as a white crystalline solid. Data are: TLC R_f = 0.62 (20% EtOAc/hexanes); ^{1}H NMR δ 7.76 (d, *J* = 4.25 Hz, 2H), 7.71 (s, 1H), 7.45 (d, *J* = 4.25 Hz, 1H), 7.23 – 7.19 (m, 5H), 7.12 (bs, 2H), 4.41 – 4.31 (m, 2H), 3.94 (s, 3H), 3.90 (q, *J* = 3.5 Hz, 1H), 2.92 (bs, 2H), 1.64 (d, *J* = 3.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.6, 157.7, 137.8, 135.7, 133.8, 129.4, 129.1, 129.0, 128.4, 127.2, 126.5, 126.3, 126.1, 119.0, 105.6, 65.3, 55.3, 45.6, 35.1, 18.5; HRMS found 334.1569 $[M]^+$, calcd 334.1569 for $[C_{22}H_{22}O_3]^+$; $[\alpha]_D^{24}$ = +27.5° (c 1.018, $CHCl_3$); the enantiomers' retention times were determined by chiral HPLC (DAICEL Chiralpak AD-H column, 5% EtOH/hexanes, 0.5 mL/min,

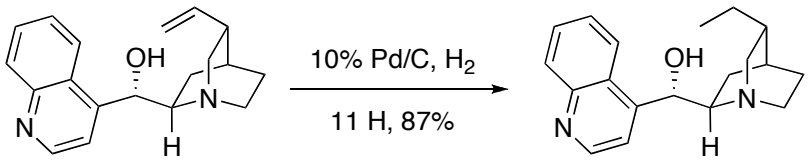
23 °C, λ = 254 nm): *S* (major) 18.67 min, *R* (minor) 22.22 min, 99.47 : 0.53 er, >98% ee. These data match those of **187** made from **184** (above).



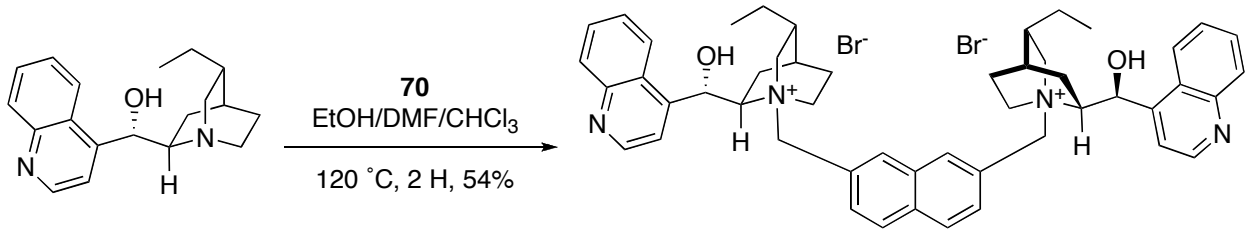
***(S)*-Naproxen (12).** *(S)*-phenethyl 2-(6-methoxynaphthalen-2-yl)propanoate **187** (96 mg, 0.287 mmol, 1.0 equiv), 10% Pd/C (64 mg, 0.667 grams of Pd/C per gram of **187**), palladium acetate (71 mg, 0.316 mmol, 1.1 equiv), and ammonium formate (86 mg, 1.36 mmol, 4.76 equiv) were dissolved in methanol (6.5 mL, 0.0442 M). The mixture was then stirred at reflux (~65°C) for 17 hours. Once **187** was consumed (TLC), the reaction flask was cooled to RT. The crude suspension was filtered, and the filtrate was concentrated to form a white solid. This material was dissolved in chloroform (50 mL), and the organic layer was washed with 1N aqueous HCl (10 mL). The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated. It was then diluted and passed through 20 mL of silica gel packed into a 30M filter cup that was fitted onto an evacuated filter flask (eluent: 50% EtOAc/hexanes, 250 mL + ~5 drops AcOH). The filtrate was transferred to a pre-weighed flask and was concentrated by rotary evaporator. (Note: diluting and then evaporating this concentrated product a few times with cyclohexane azeotropically removes excess AcOH.) This gave 60 mg (91%) of *(S)*-Naproxen (**12**) as a white, crystalline solid. Data are: TLC R_f= 0.10 (20% EtOAc/hexanes); ^{1}H NMR δ 11.12 (bs, 1H), 7.71 (d, *J* = 5 Hz, 3H), 7.43 (d, *J* = 4.25, 1H), 7.17 – 7.12 (m, 2H), 3.92 (s, 3H), 3.89 (q, *J1* = 3.5 Hz, *J2* = 7 Hz, 1H), 1.61 (d, *J* = 3.75 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 180.9, 157.7, 134.9, 133.8, 129.3, 128.9, 127.3, 126.2, 126.1, 119.0, 105.6, 55.3, 45.3, 18.1; $[\alpha]_D^{24}$ = +56° (c 0.767, $CHCl_3$). Data for commercial *(S)*-Naproxen (**12**): ^{1}H NMR δ 11.29 (bs, 1H), 7.72 – 7.70 (m, 3H), 7.42 (d, *J* = 4.25, 1H), 7.16 – 7.12 (m, 2H), 3.92 (s, 3H), 3.88 (q, *J1* = 3.75 Hz, *J2* = 7 Hz, 1H), 1.60 (d, *J* = 3.5

Hz, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 180.1, 157.7, 134.8, 133.8, 129.3, 128.9, 127.3, 126.2, 126.1, 119.1, 105.5, 55.3, 45.2, 18.2; $[\alpha]_D^{24}$ = +64° (c 0.7667, $CHCl_3$).

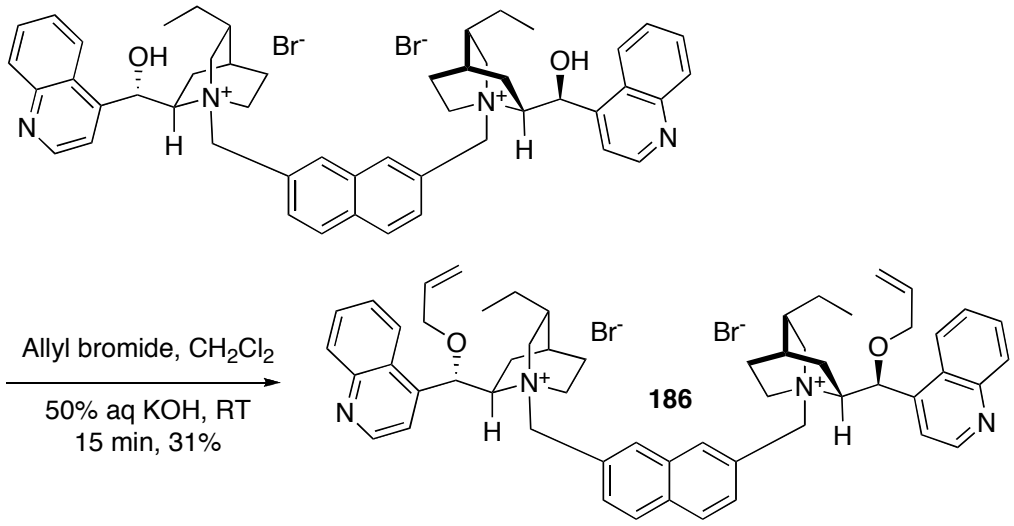
7.6.8. Synthesis of Catalyst 186



Hydrocinchonine. Following the procedure for hydrocinchonidine **68** (section 7.3.3 above), substituting (+)-cinchonine for (-)-cinchonidine, 1.73 g (87%) of product were isolated as an off-white solid.

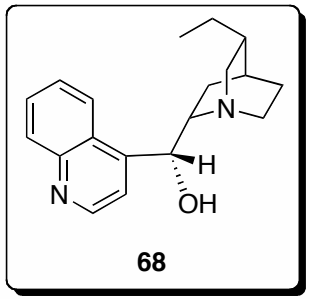


2,7-bis(hydrocinchoninium-*N*-methyl) naphthalene dibromide. Following the procedure described for compound **71** (section 7.3.3 above), substituting hydrocinchonine for hydrocinchonidine, 0.885 g (54%) of product were isolated as a light red solid.

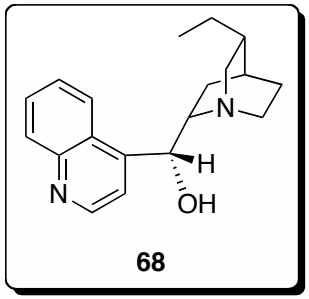


2,7-bis[*O*(9)-allylhydrocinchoninium-*N*-methyl]naphthalene dibromide (186). Following the procedure for catalyst **61** (section 7.3.3 above), substituting 2,7-bis(hydrocinchoninium-*N*-methyl) naphthalene dibromide for **71**, 0.297 g (31%) of product **186** were isolated as an orange-cream solid. Data are: ^{1}H NMR (DMSO-d_6, 500 MHz, with increased Fourier transfers): δ 9.03 (s, 1H), 8.45 (s, 2H), 8.34 – 8.27 (m, 2H), 8.27 – 8.23 (m, 2H), 8.16 – 8.14 (m, 2H), 7.99 – 7.95 (m, 2H), 7.87 – 7.87 (m, 2H), 7.76 – 7.74 (m, 4H), 7.65 – 7.63 (m, 1H), 6.44 (bs, 2H), 6.22 – 6.16 (m, 2H), 5.50 (d, J = 8.75 Hz, 2H), 5.36 – 5.13 (m, 4H), 4.83 (d, J = 6 Hz, 2H), 4.34 (d, J = 6.5 Hz, 2H), 4.02 – 3.91 (m, 8H), 3.74 – 3.58 (m, 3H), 2.97 (m, 3H), 1.89 – 1.68 (m, 6H), 1.53 (bs, 4H), 1.22 (bs, 4H), 0.85 (t, J = 7 Hz, 6H); large extraneous peaks: δ 3.33 (H_2O in DMSO-d_6), 2.49 (DMSO-H_x in DMSO-d_6). HRMS found 413.2587 $[M+2H]^{2+}/2$; calcd 413.26 for $[C_{56}H_{66}N_4O_2]^{2+}/2$.

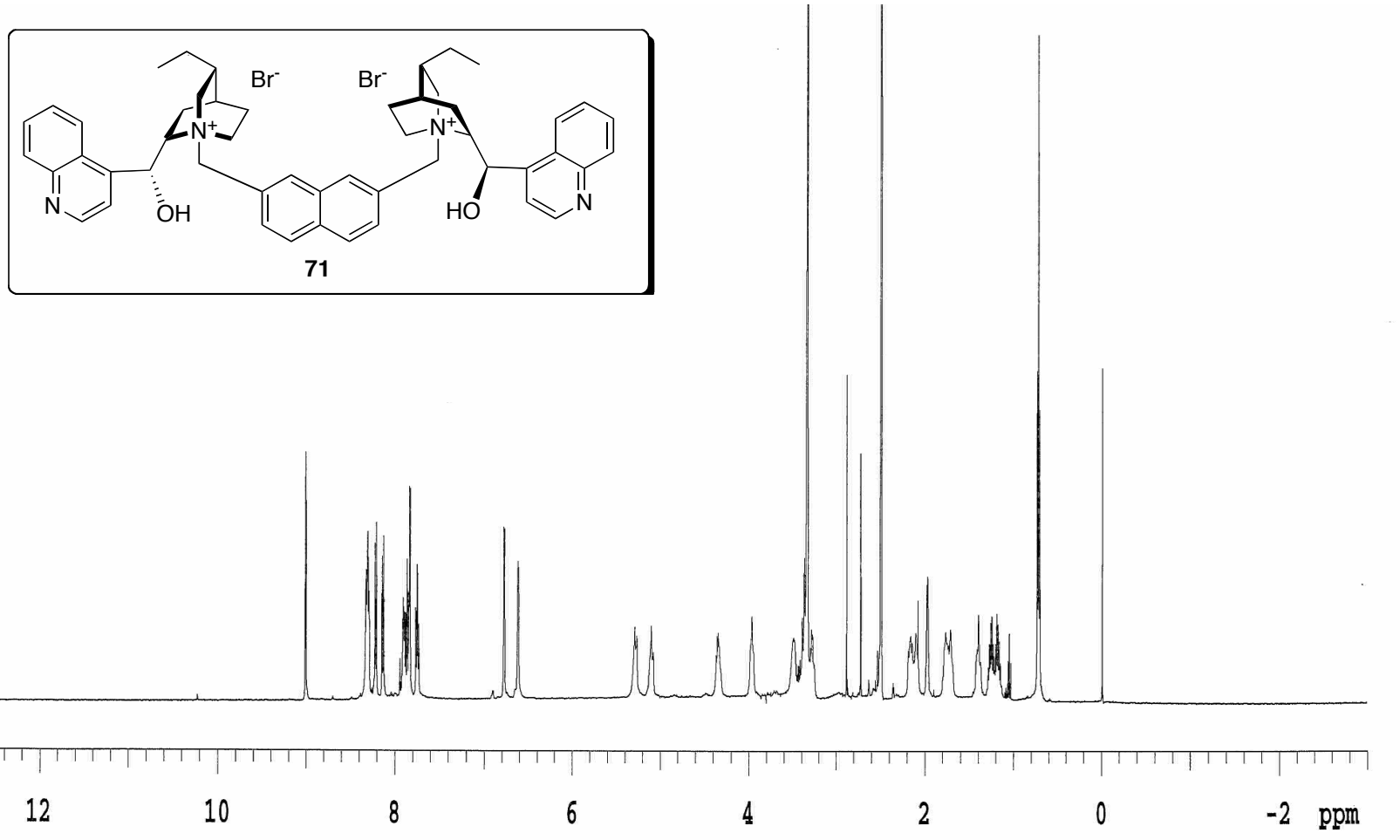
Selected NMR Spectra

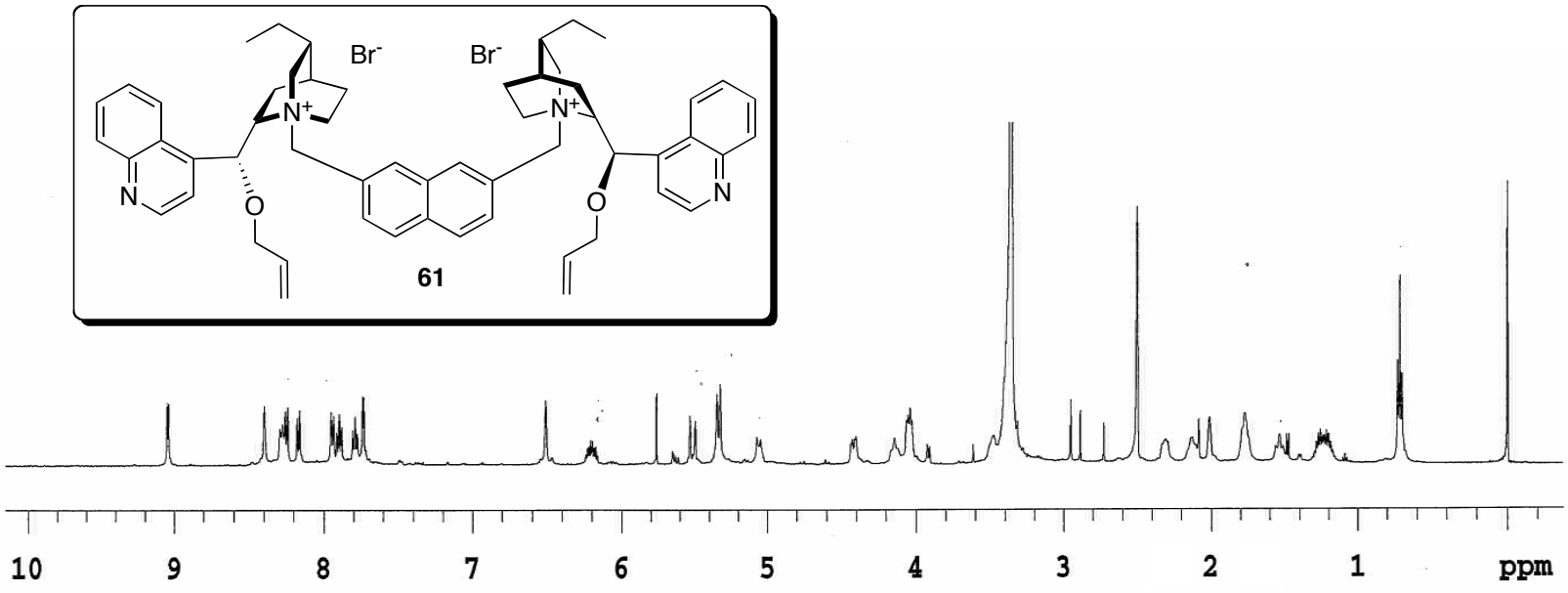


68



68


Br-
Br-
N+
N+
N
OH
HO
N
71
12
10
8
6
4
2
0
-2
ppm


Br-
Br-
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N+
N
N
O
O
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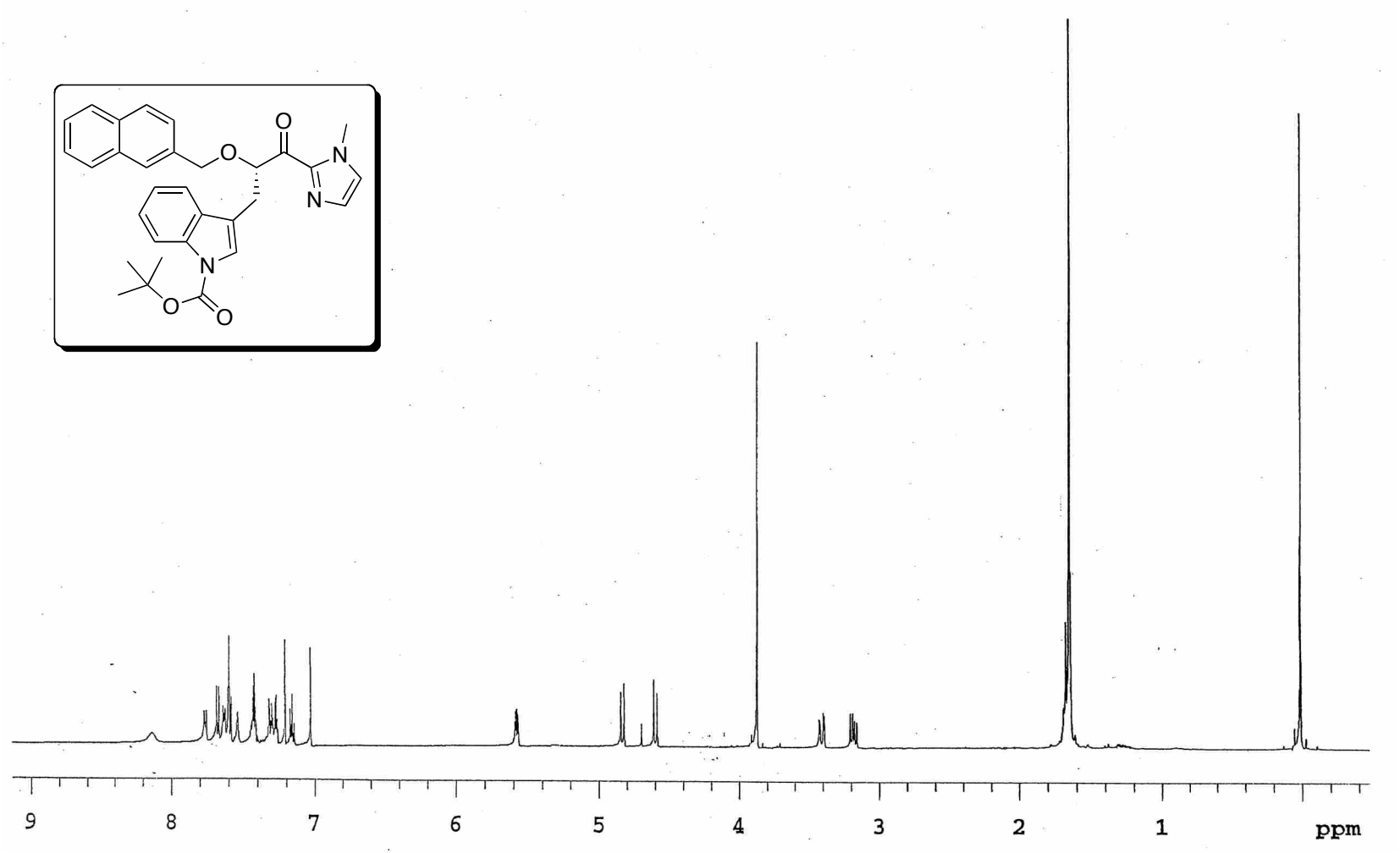
1
ppm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N
O
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3
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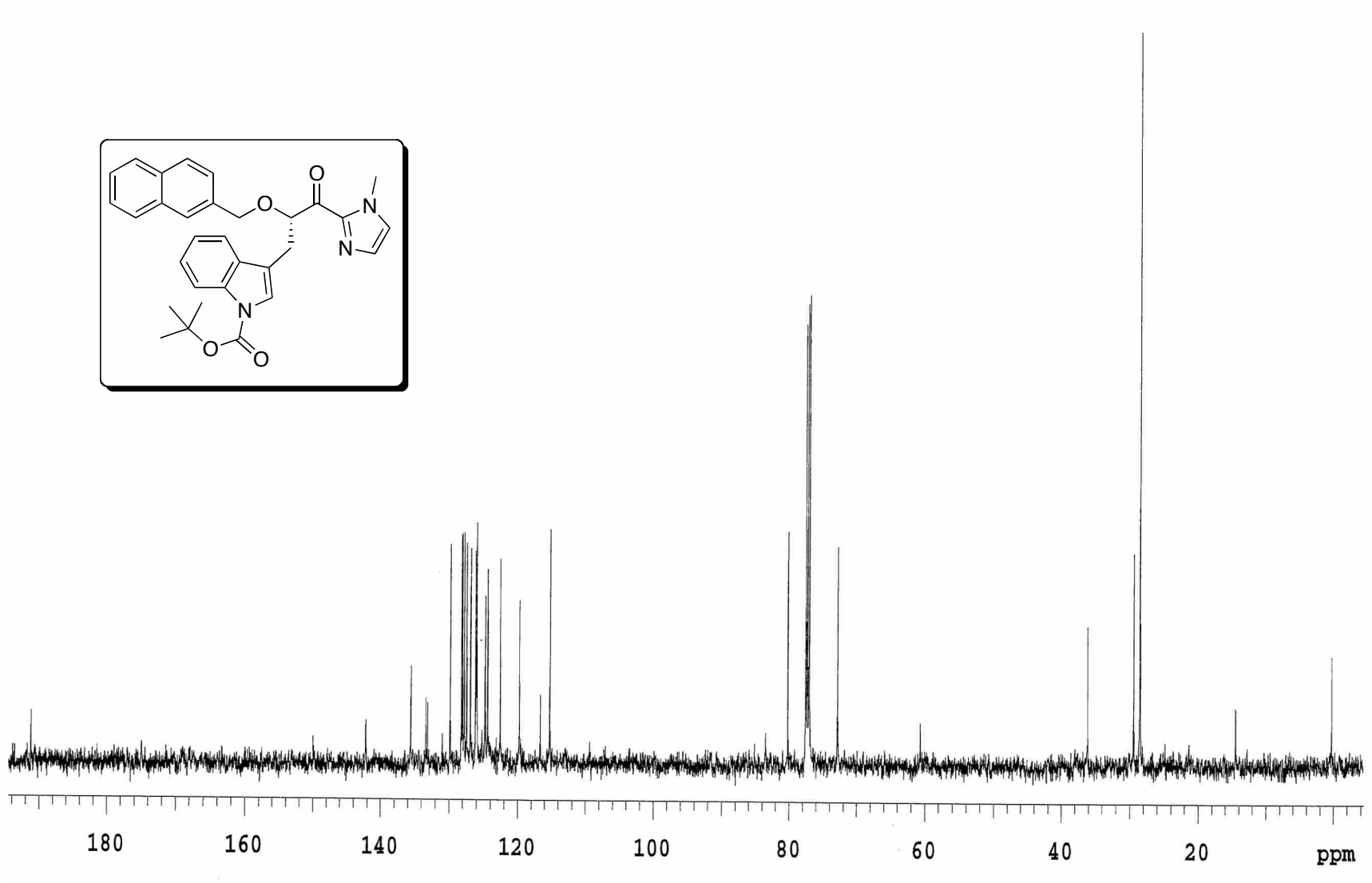
ppm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O
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N
N
O
O
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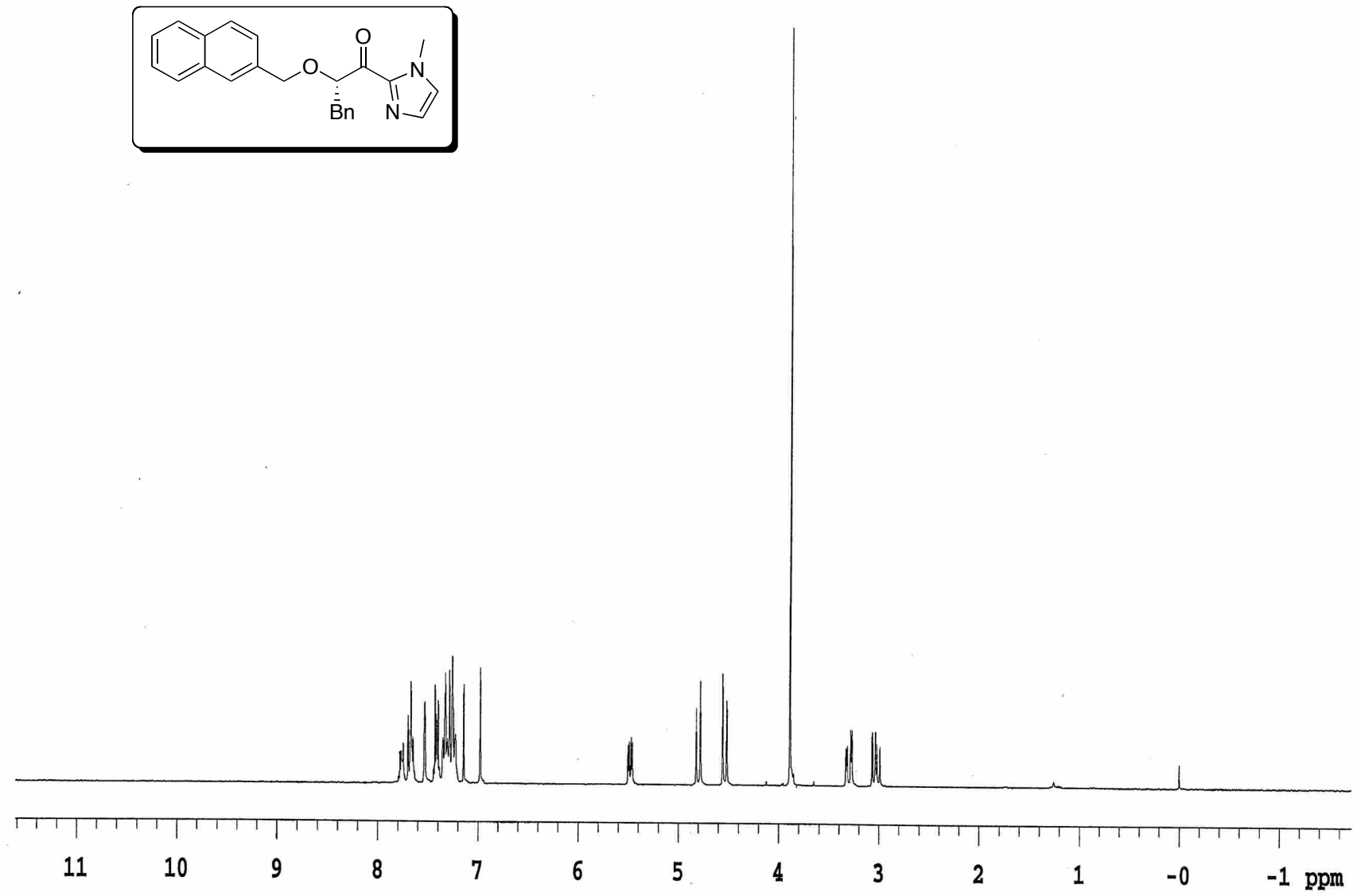
20
ppm


O
O
N
Bn
N
11
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9
8
7
6
5
4
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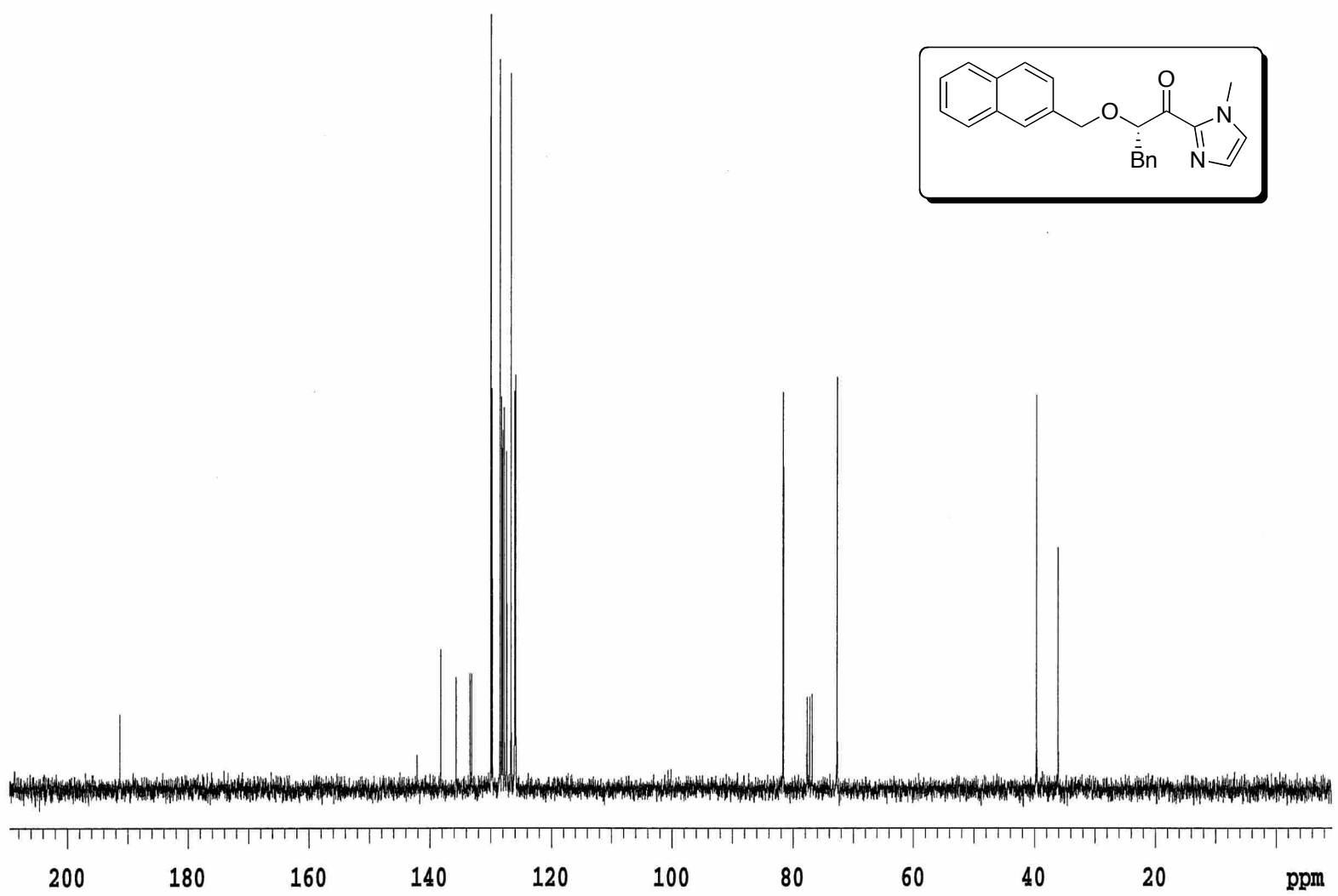
2
1
-0
-1 ppm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O
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Bn
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60
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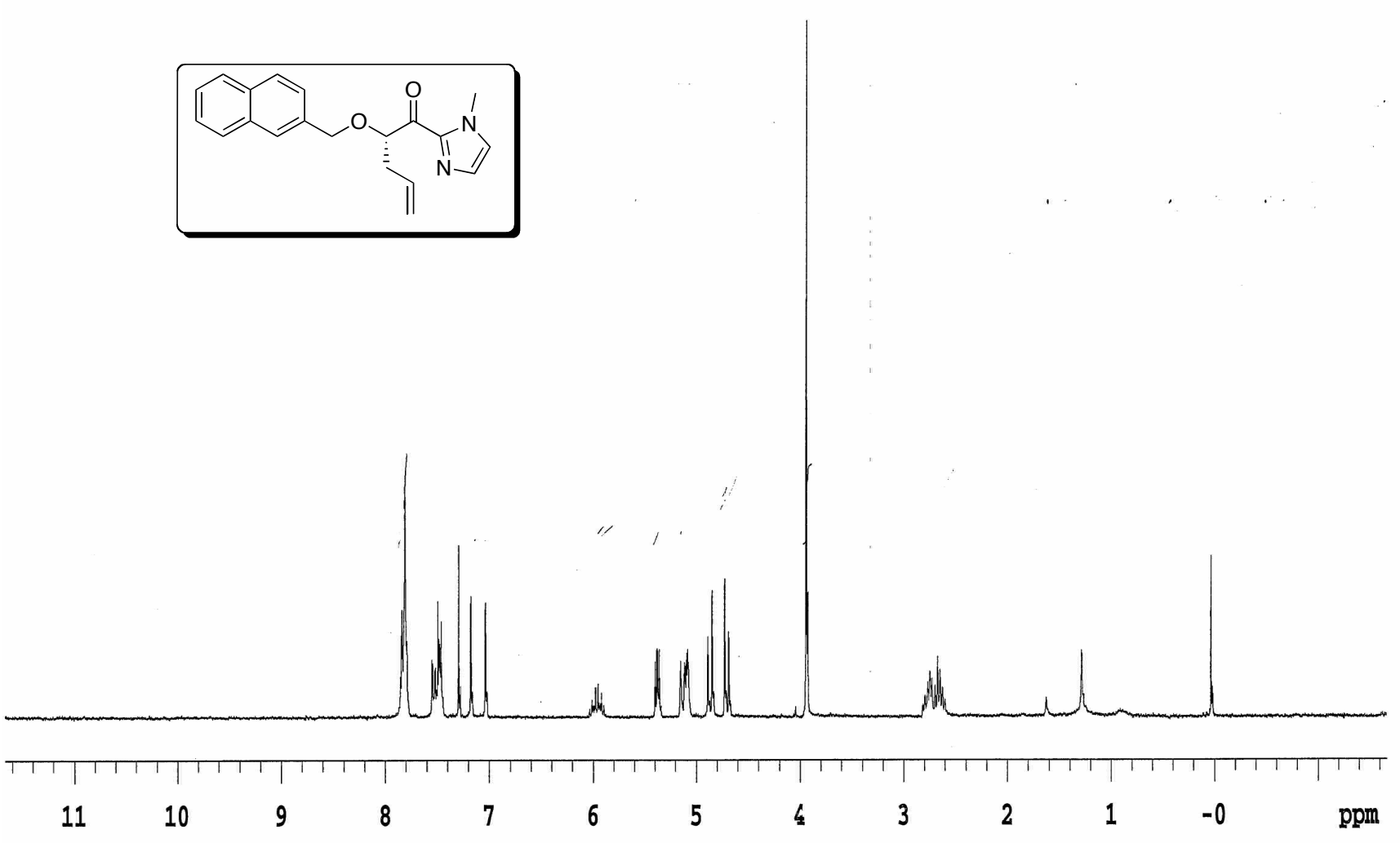
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O
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10
9
8
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6
5
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2
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-0
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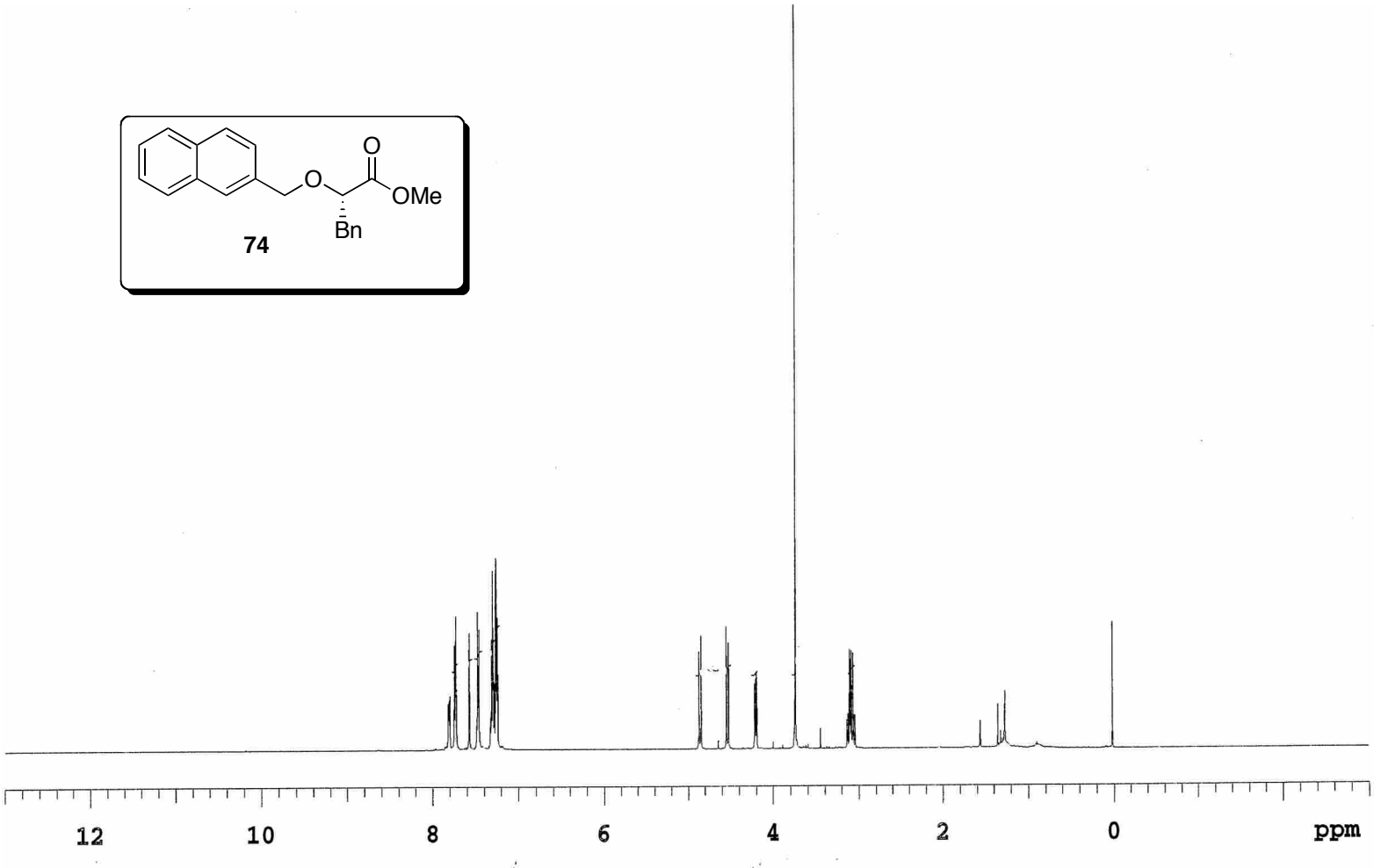
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O
OMe
Bn
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4
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0
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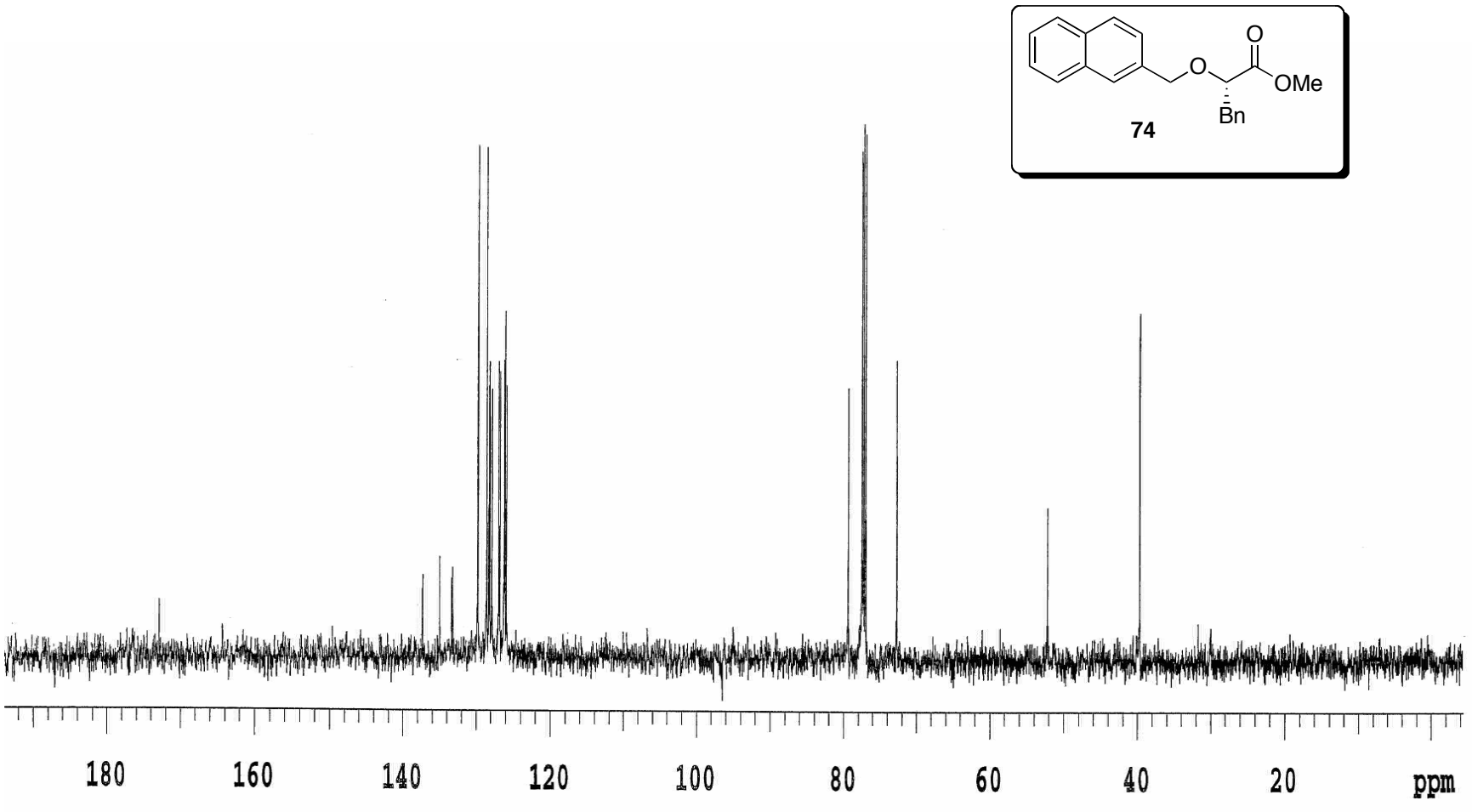
O
O
OMe
Bn
74
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140
120
100
80
60
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20
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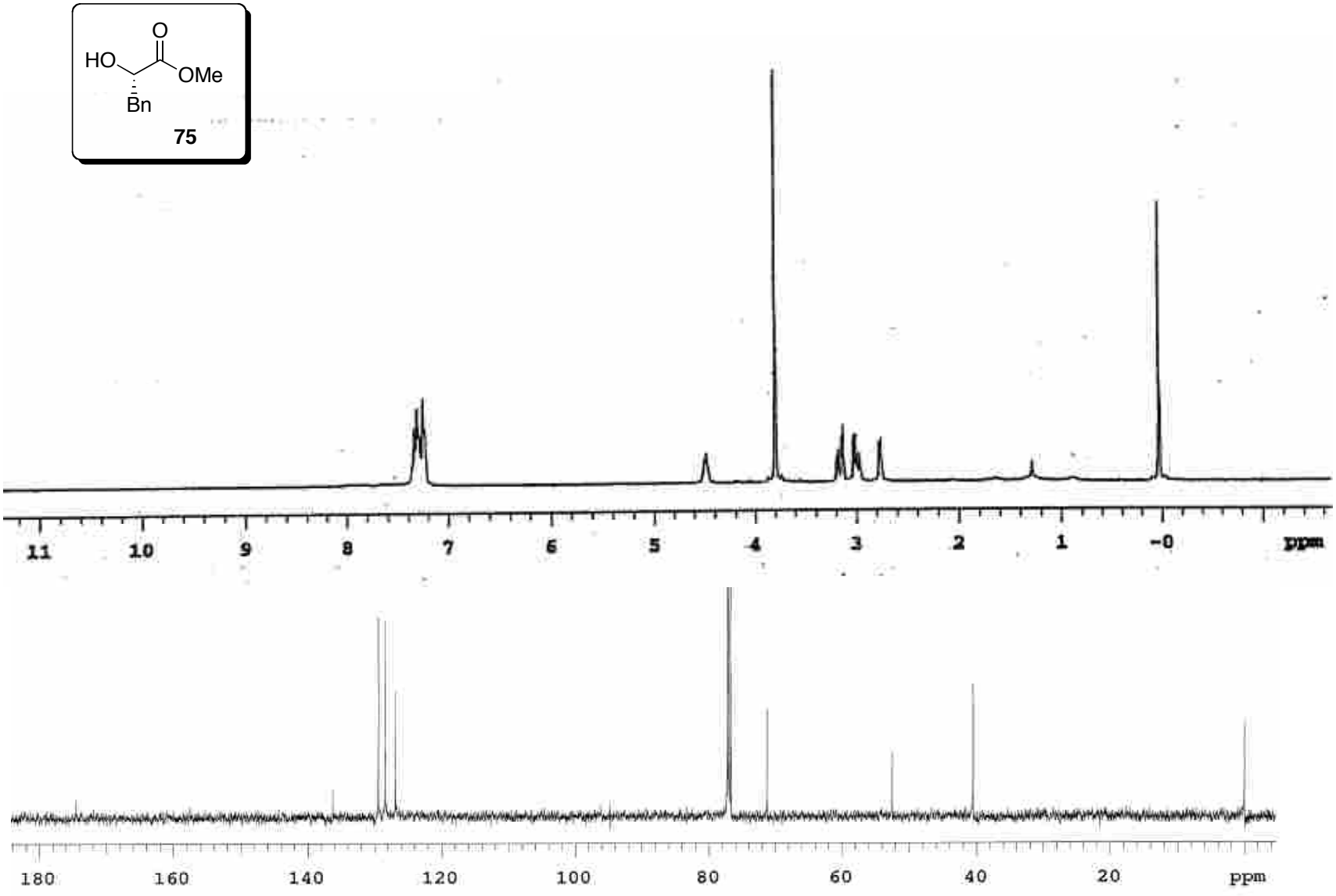
HO
O
OMe
Bn
75
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9
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2
1
-0
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60
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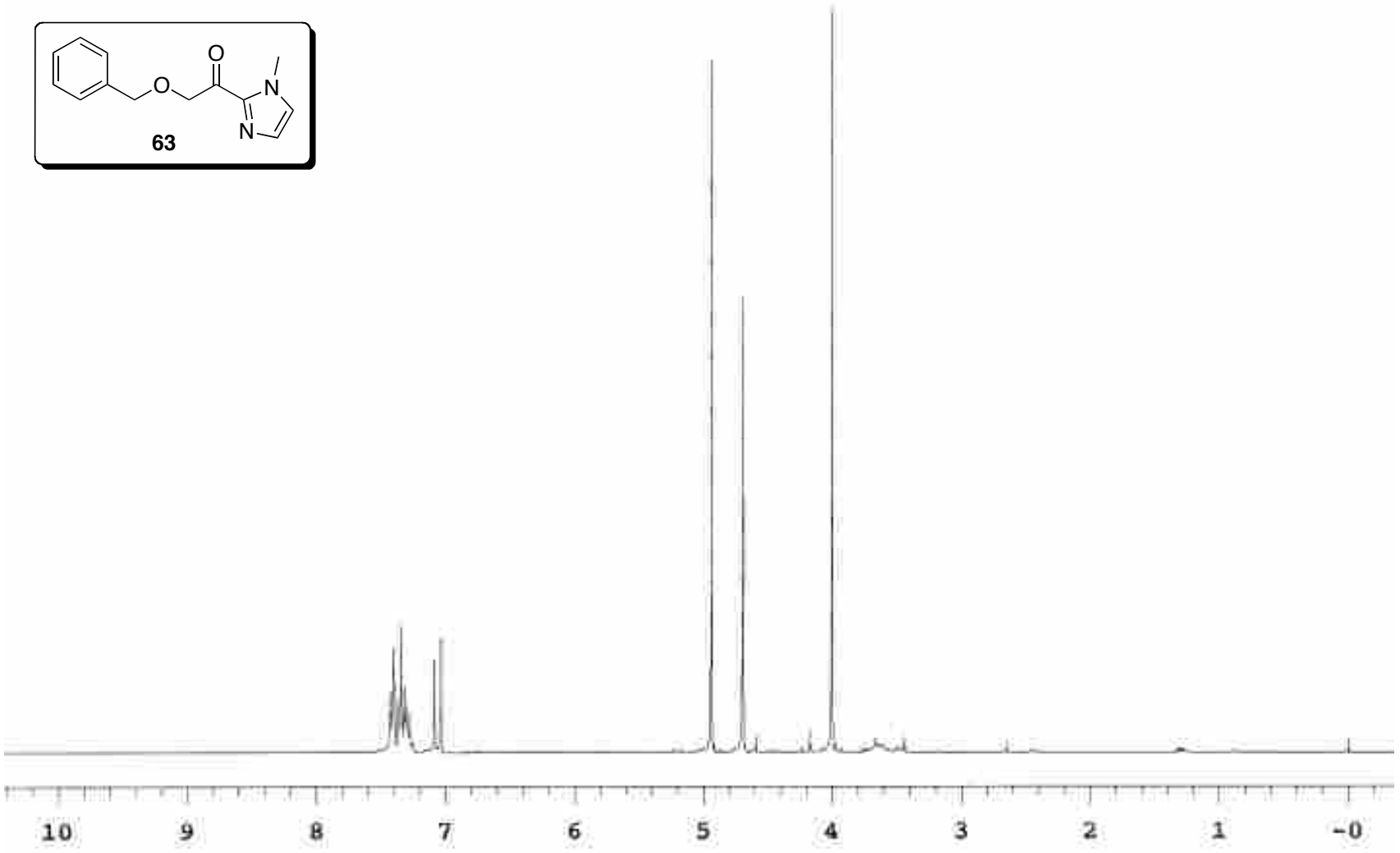
20
ppm


O
O
N
N
63
10
9
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7
6
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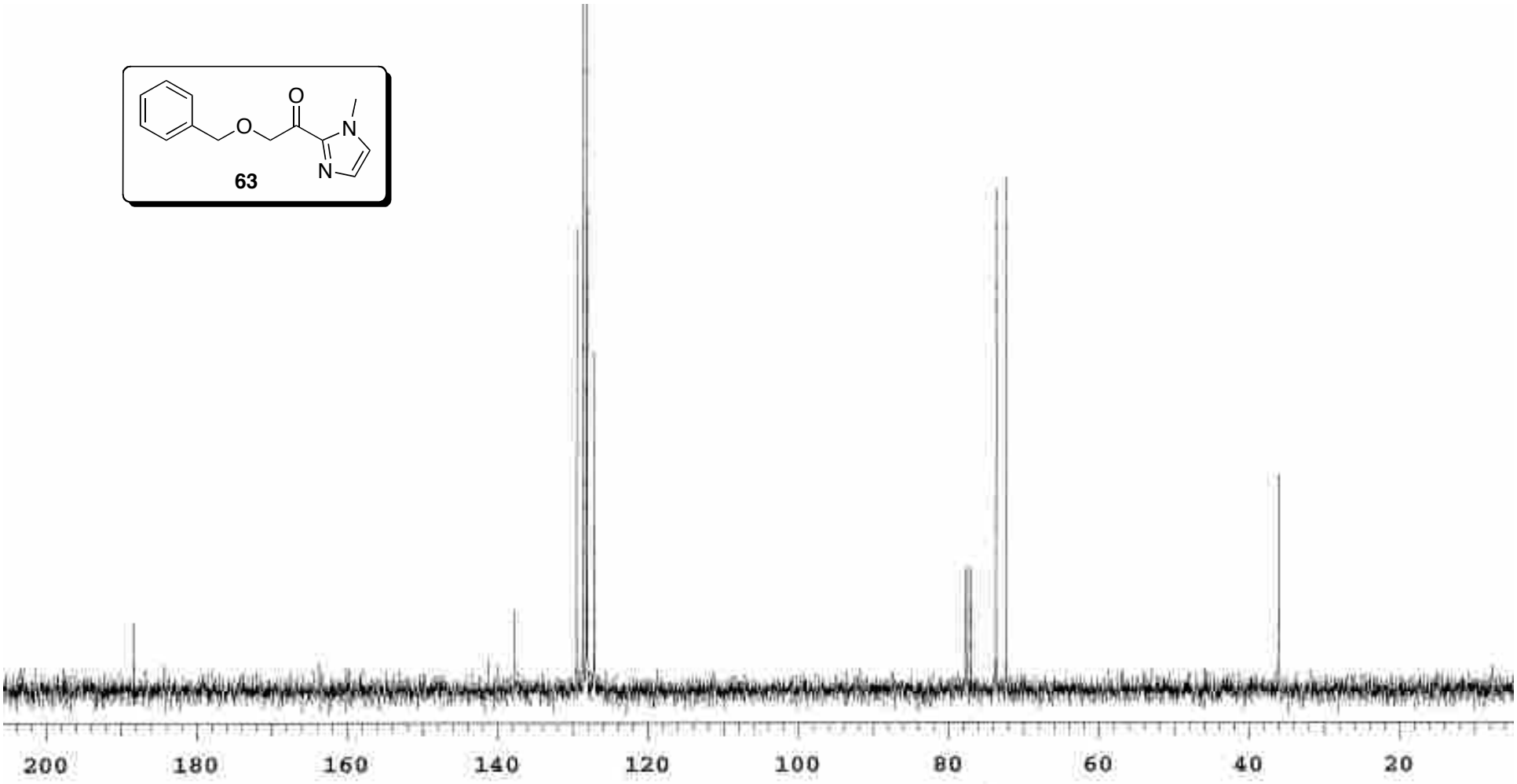
4
3
2
1
-0


O
O
N
N
63
200
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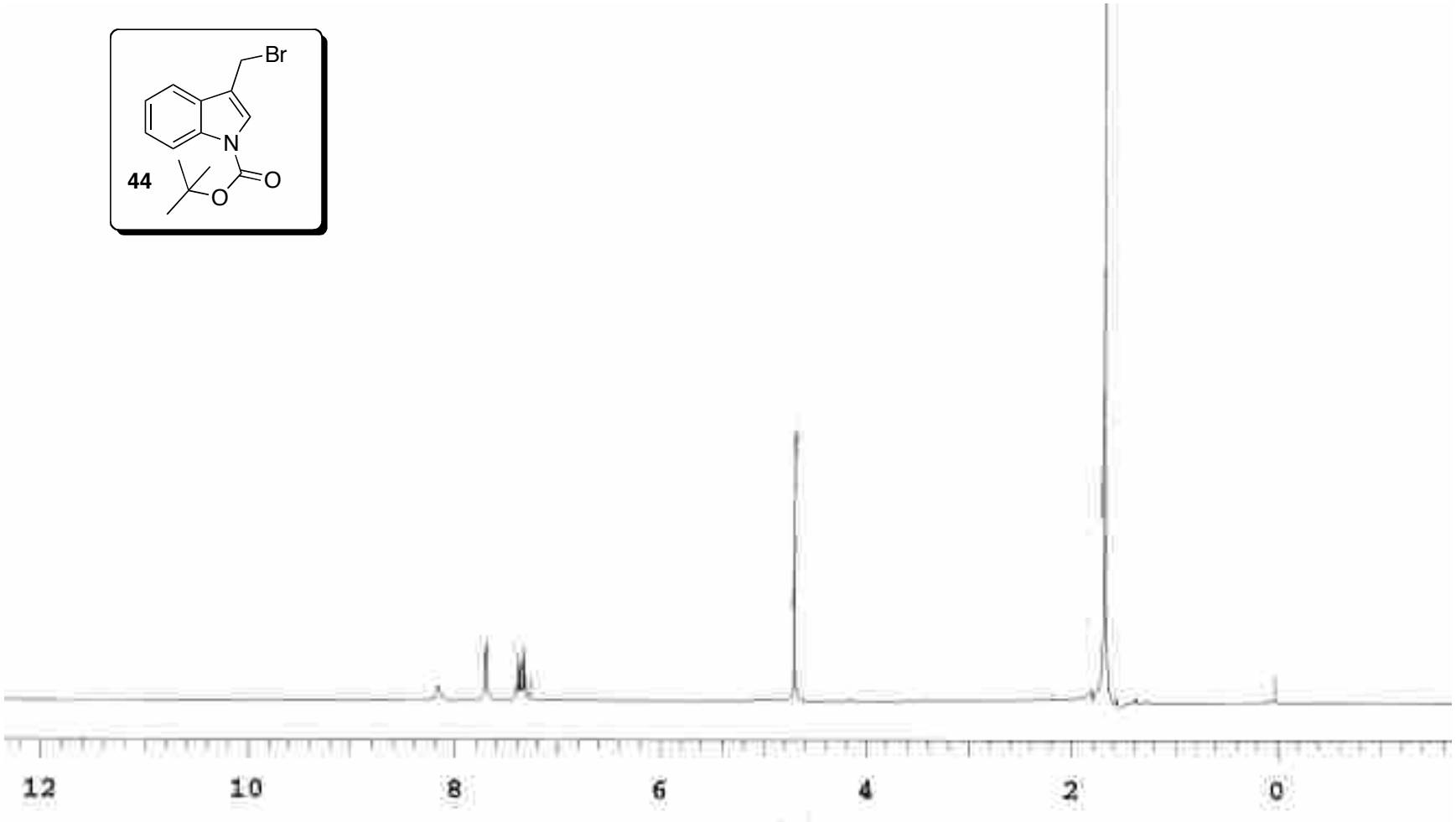
160
140
120
100
80
60
40
20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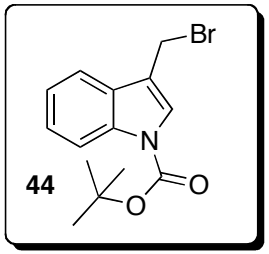
N
O
O
44
12
10
8
6
4
2
0



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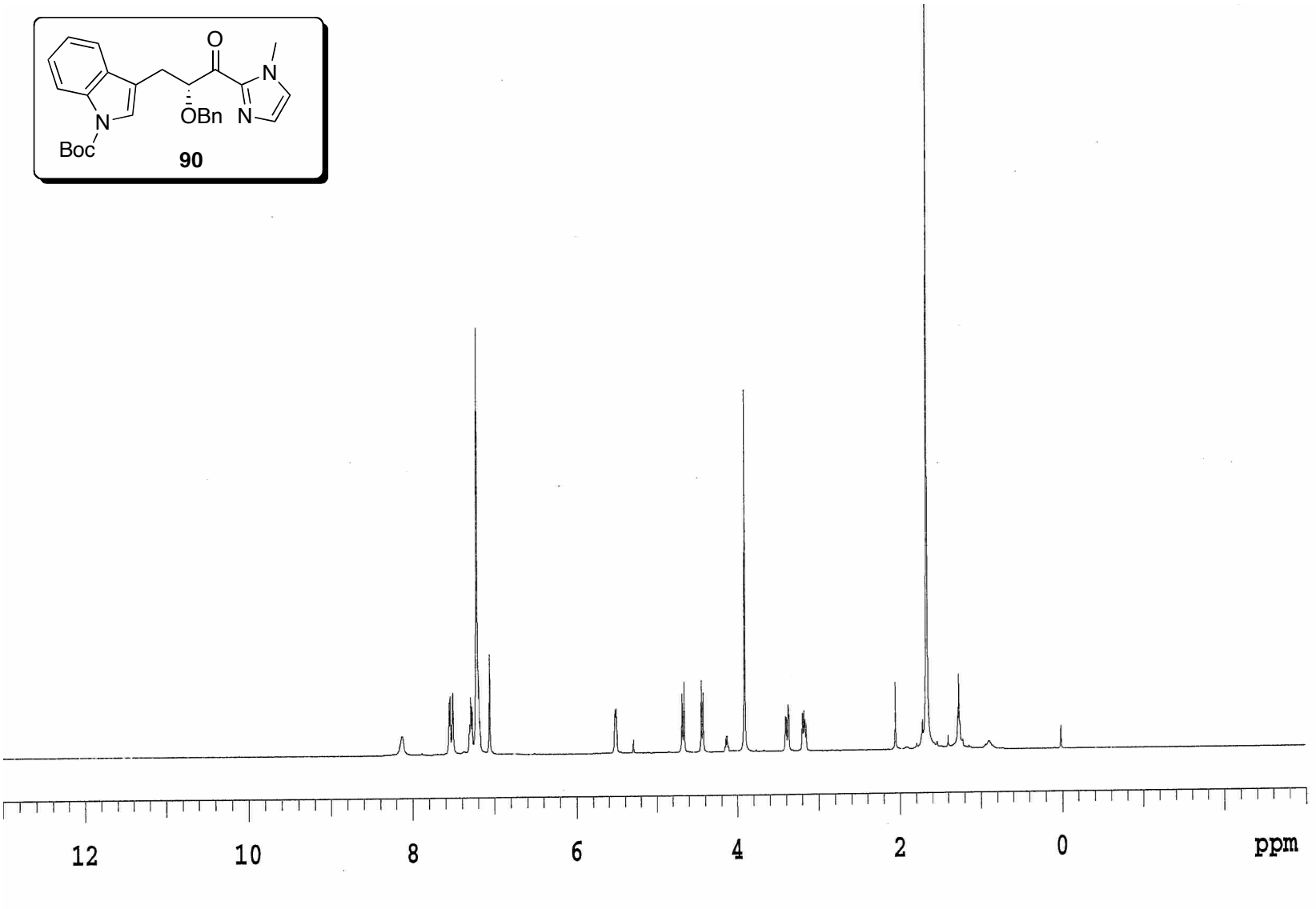
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N
OBn
N
N
Boc
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12
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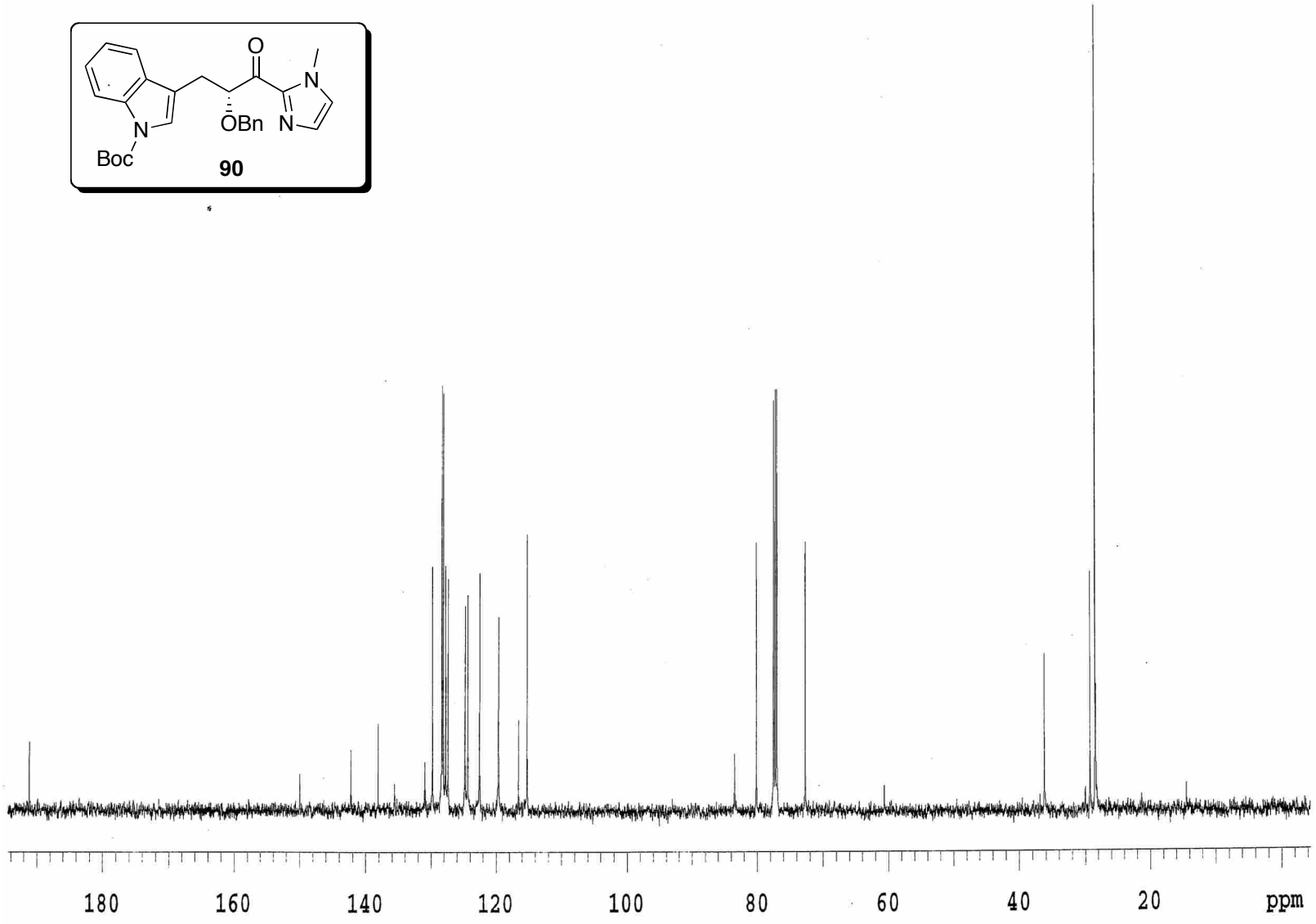
8
6
4
2
0
ppm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OBn
N
N
Boc
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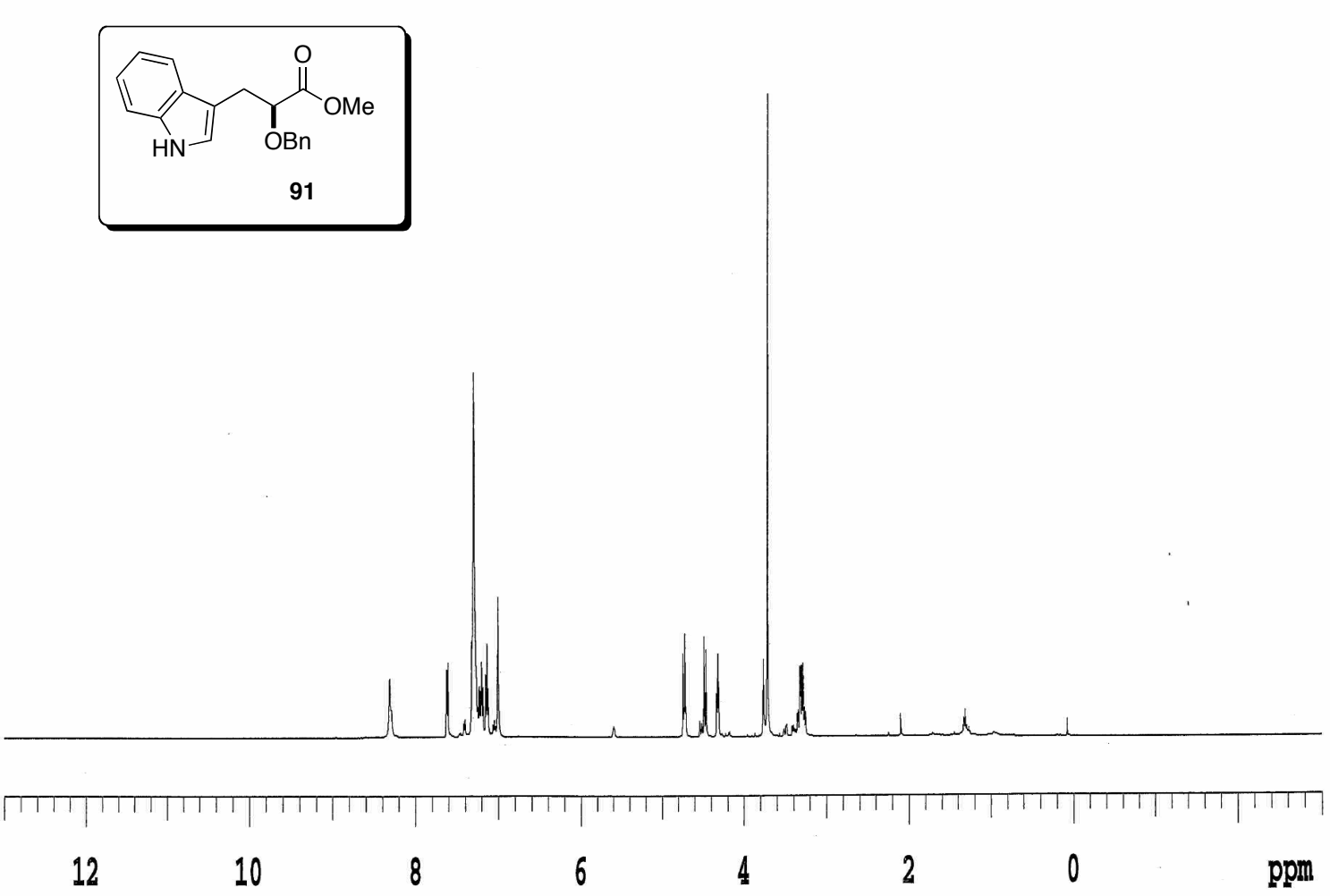
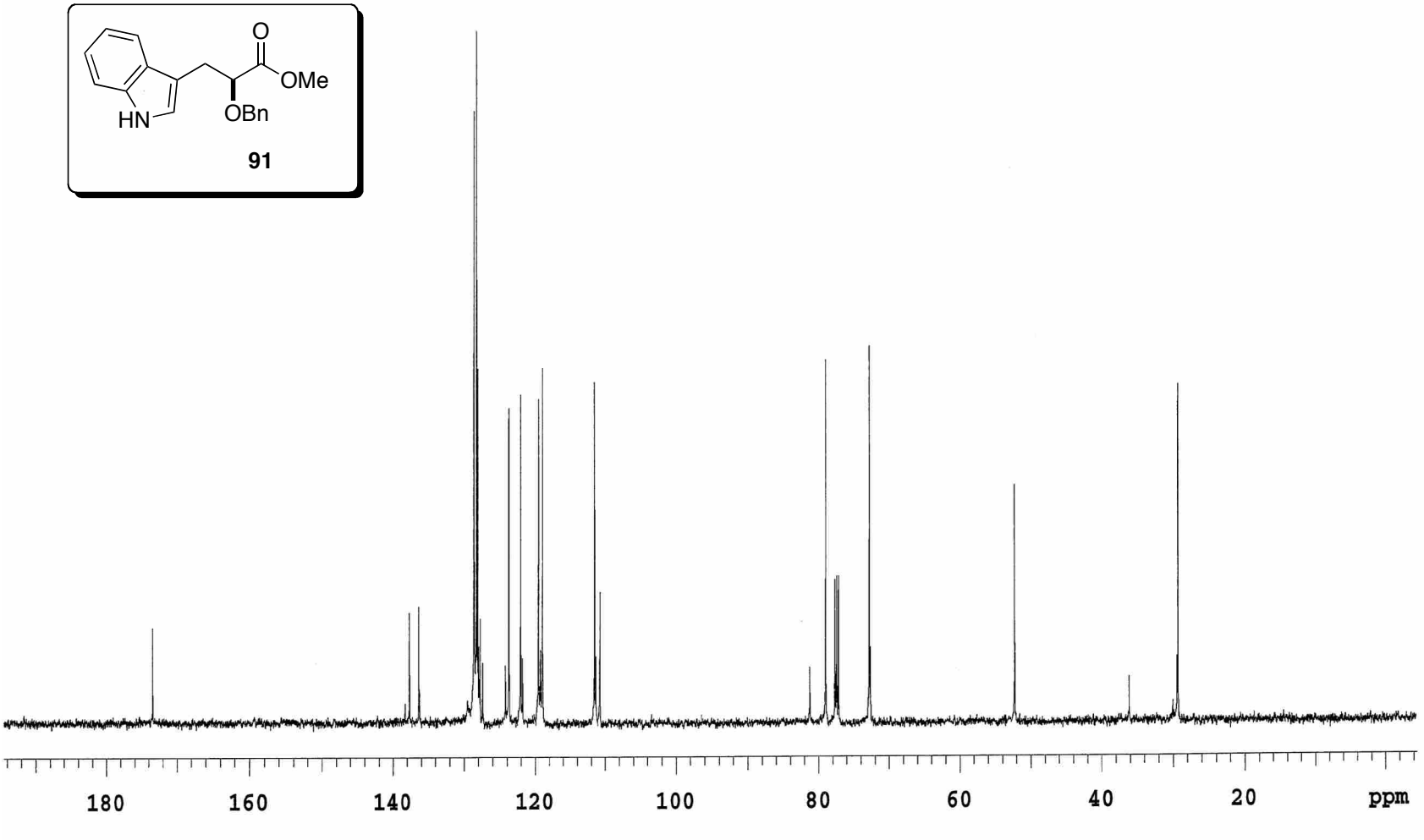
20
ppm


O
OMe
HN
OBn
91
12
10
8
6
4
2
0
ppm


O
OMe
HN
OBn
91
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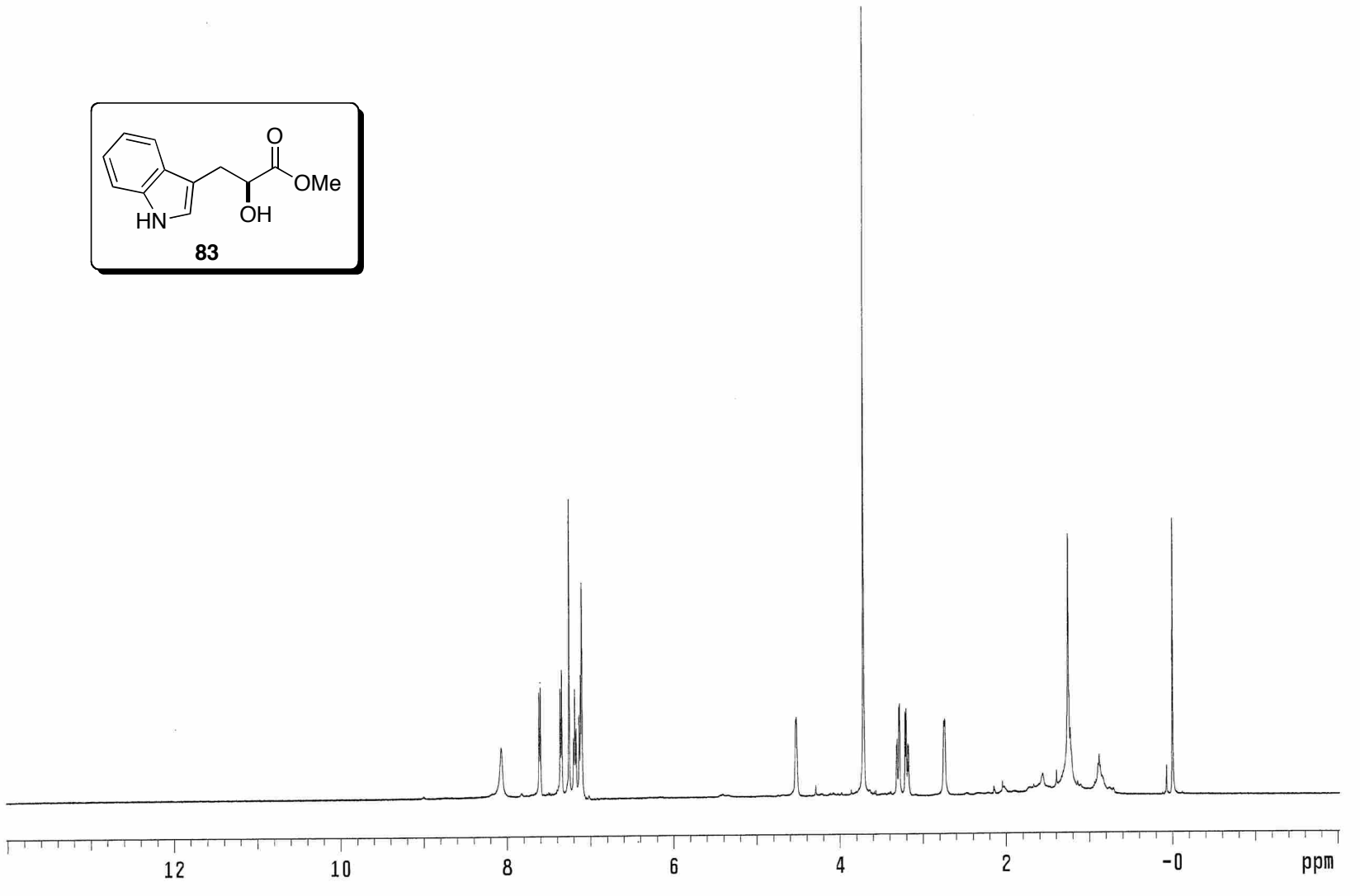
60
40
20
ppm


O
OMe
HN
OH
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10
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6
4
2
-0
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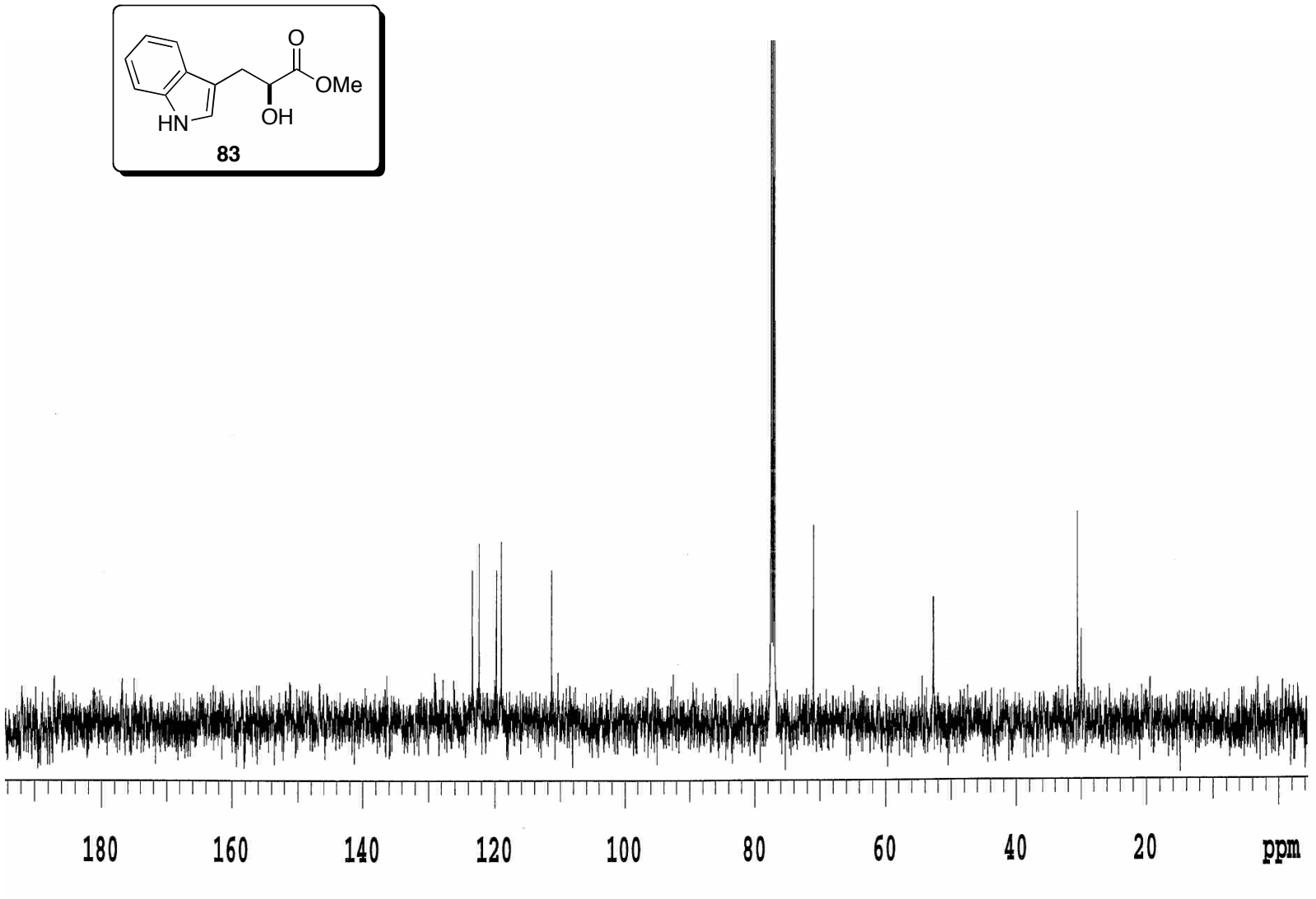
O
OMe
HN
OH
83
180
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20
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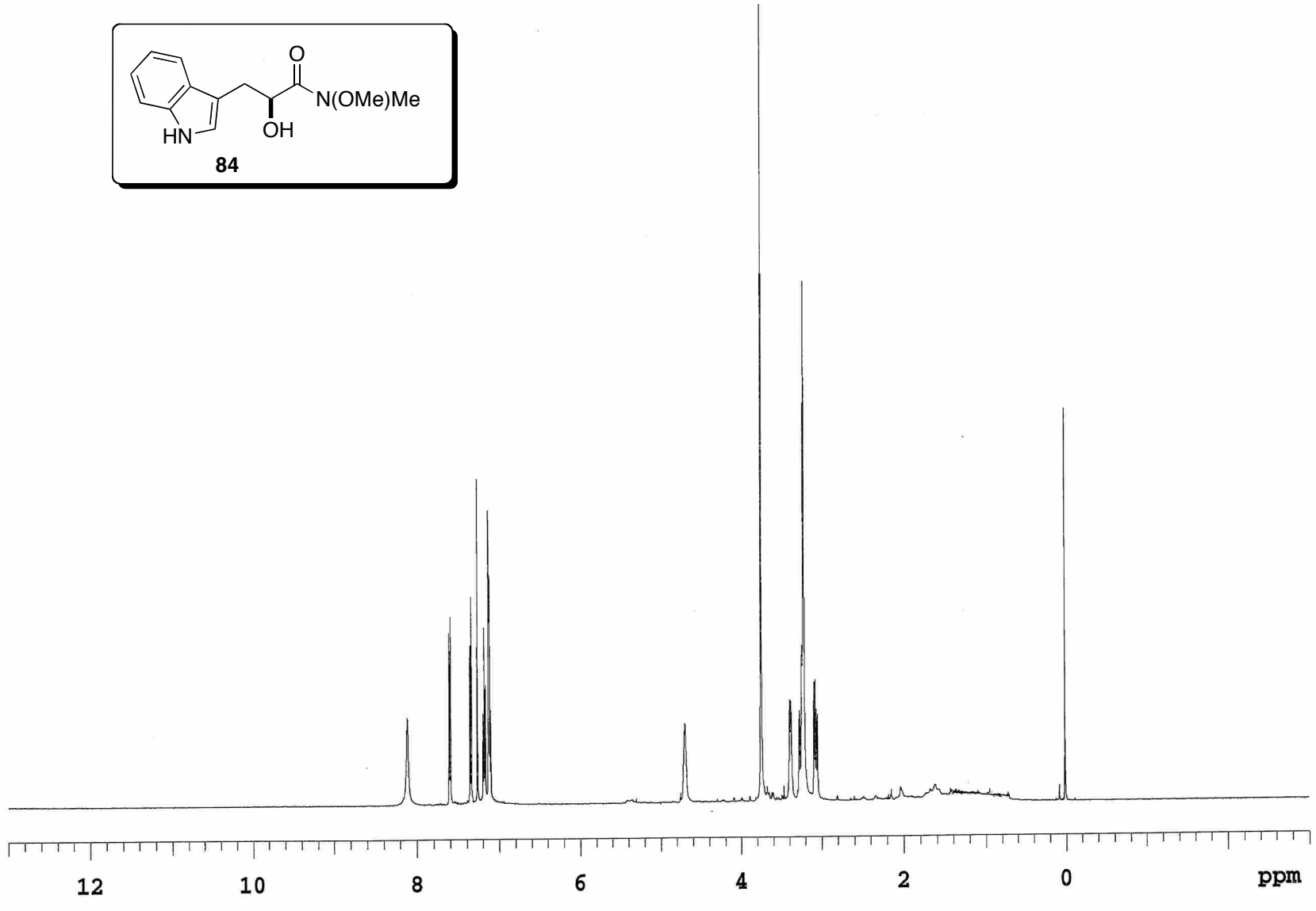
O
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HN
OH
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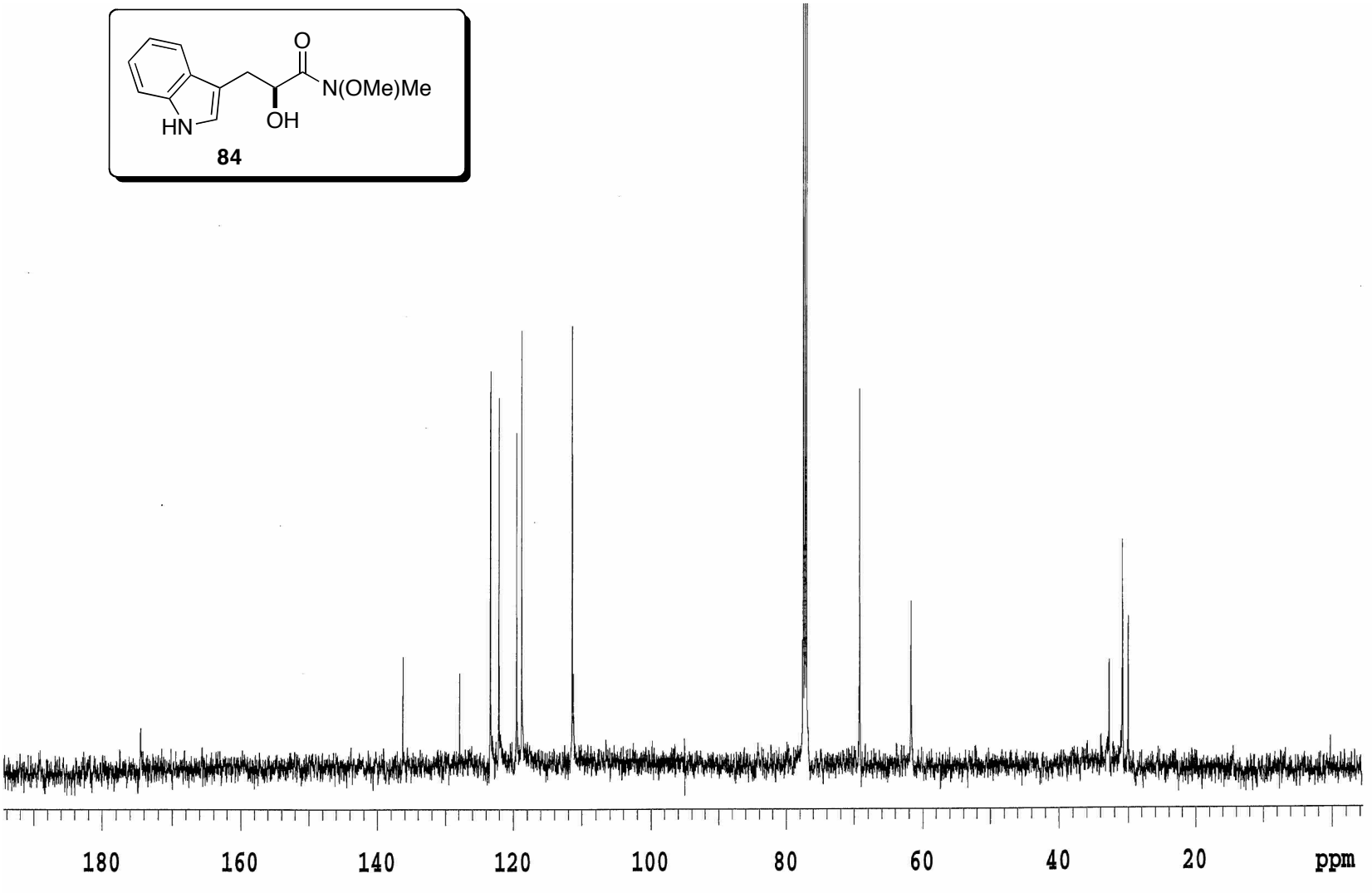
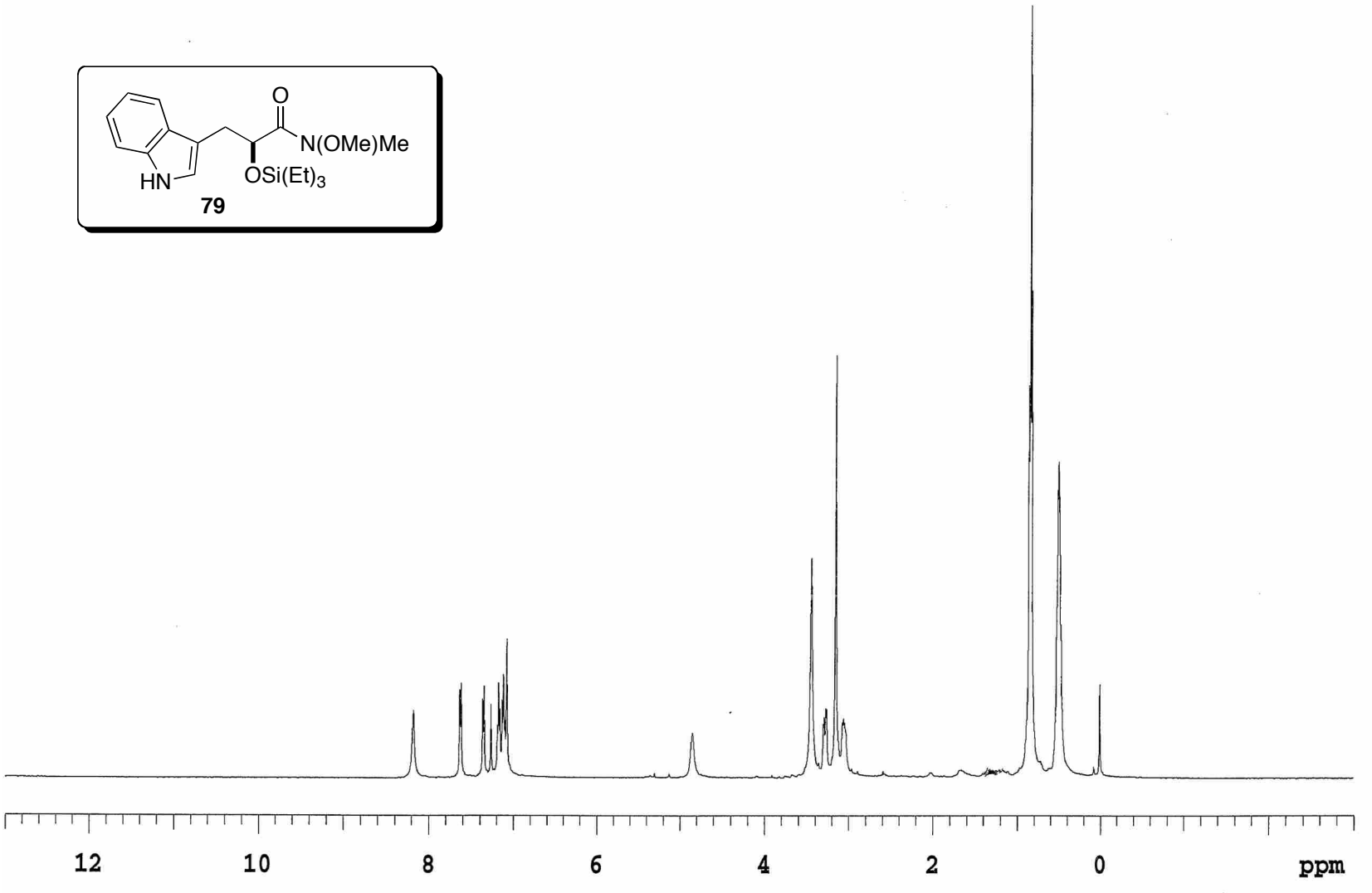
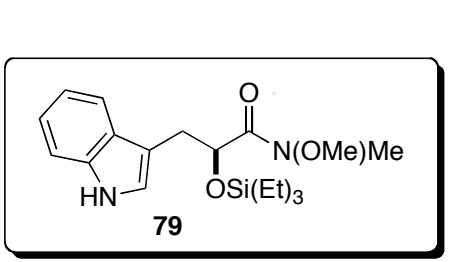
10
8
6
4
2
0
ppm


O
N(OMe)Me
OH
HN
84
180
160
140
120
100
80
60
40
20
ppm


O
N(OMe)Me
HN
OSi(Et)3
79
12
10
8
6
4
2
0
ppm



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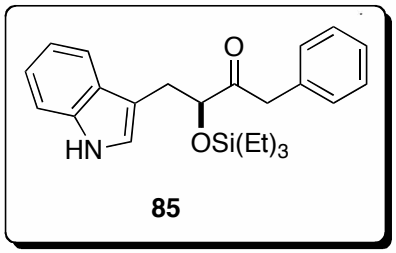

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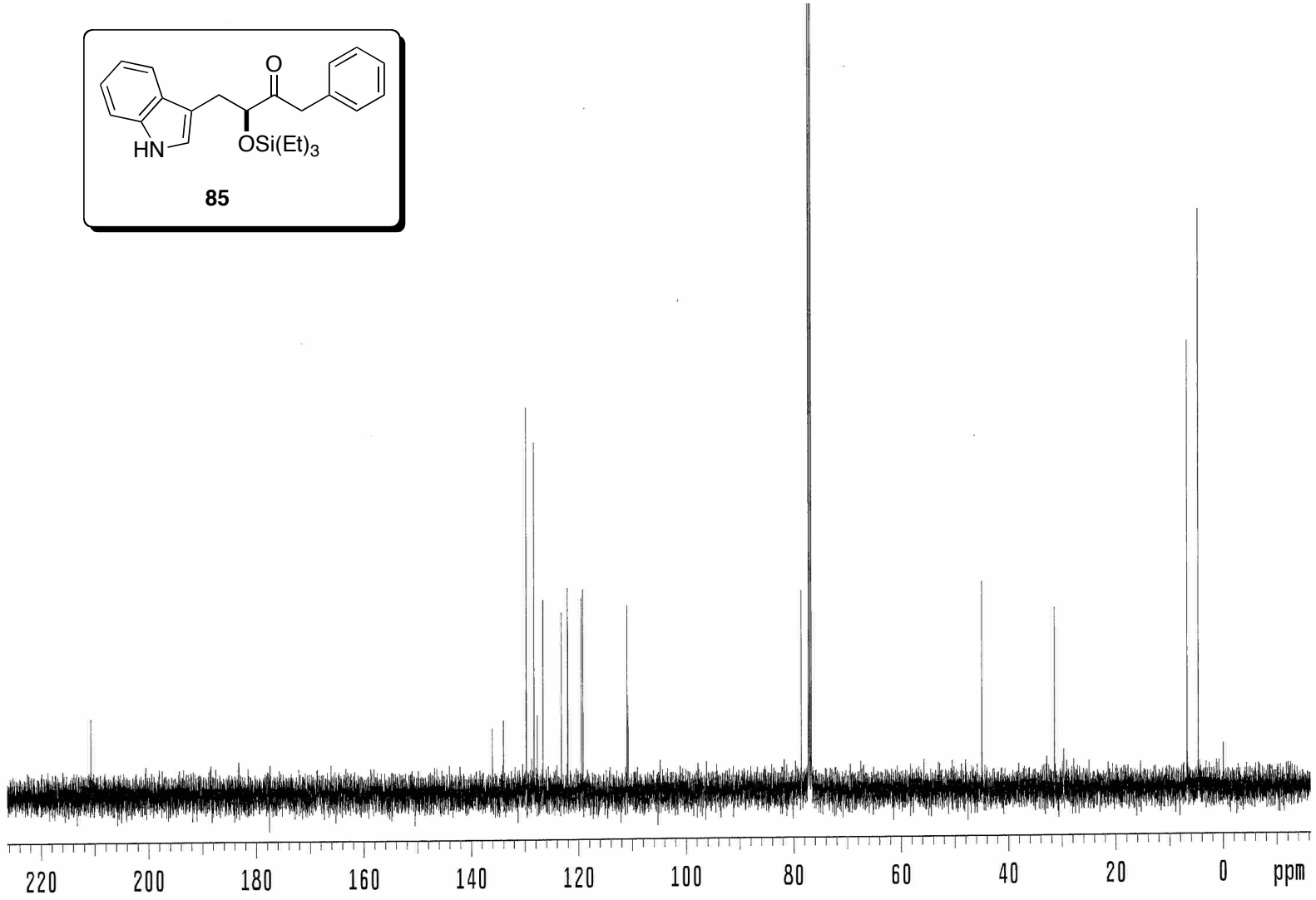
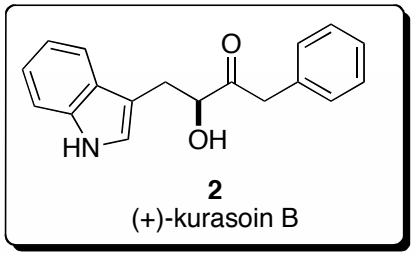
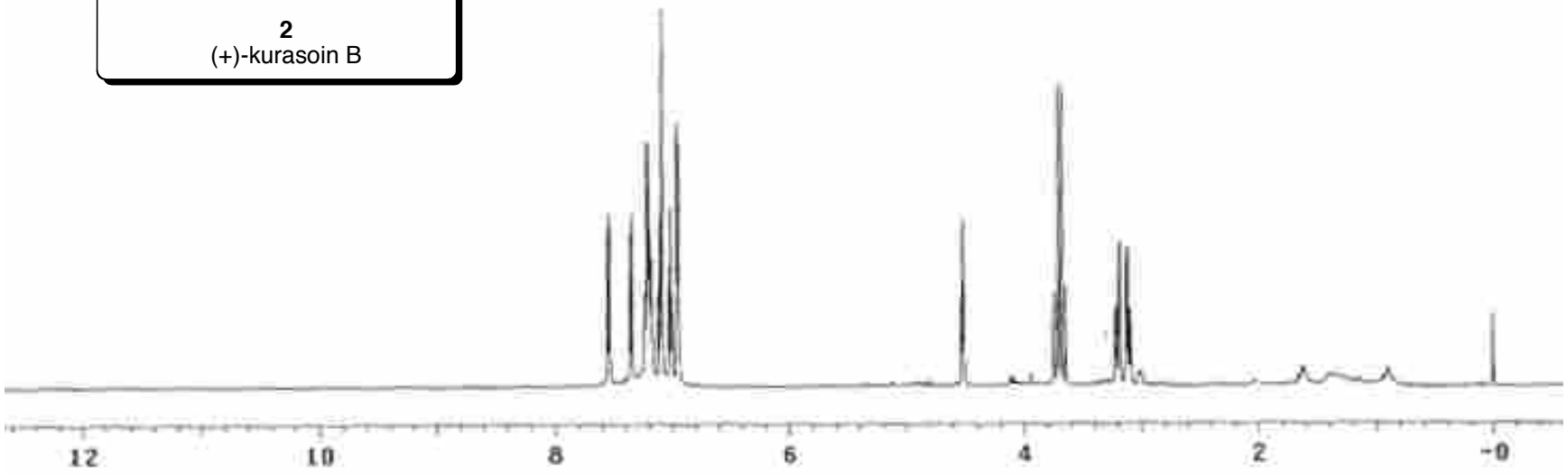
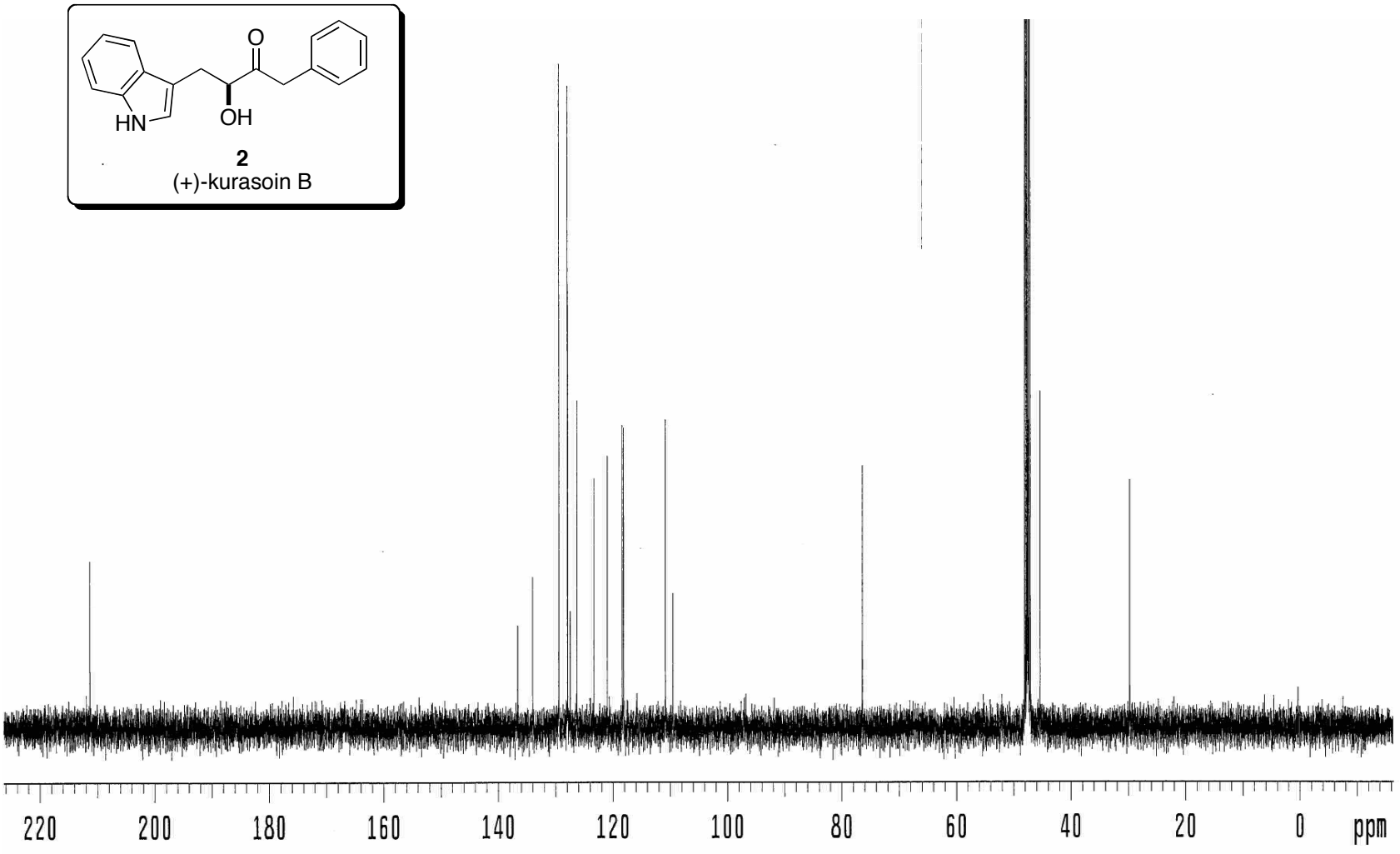
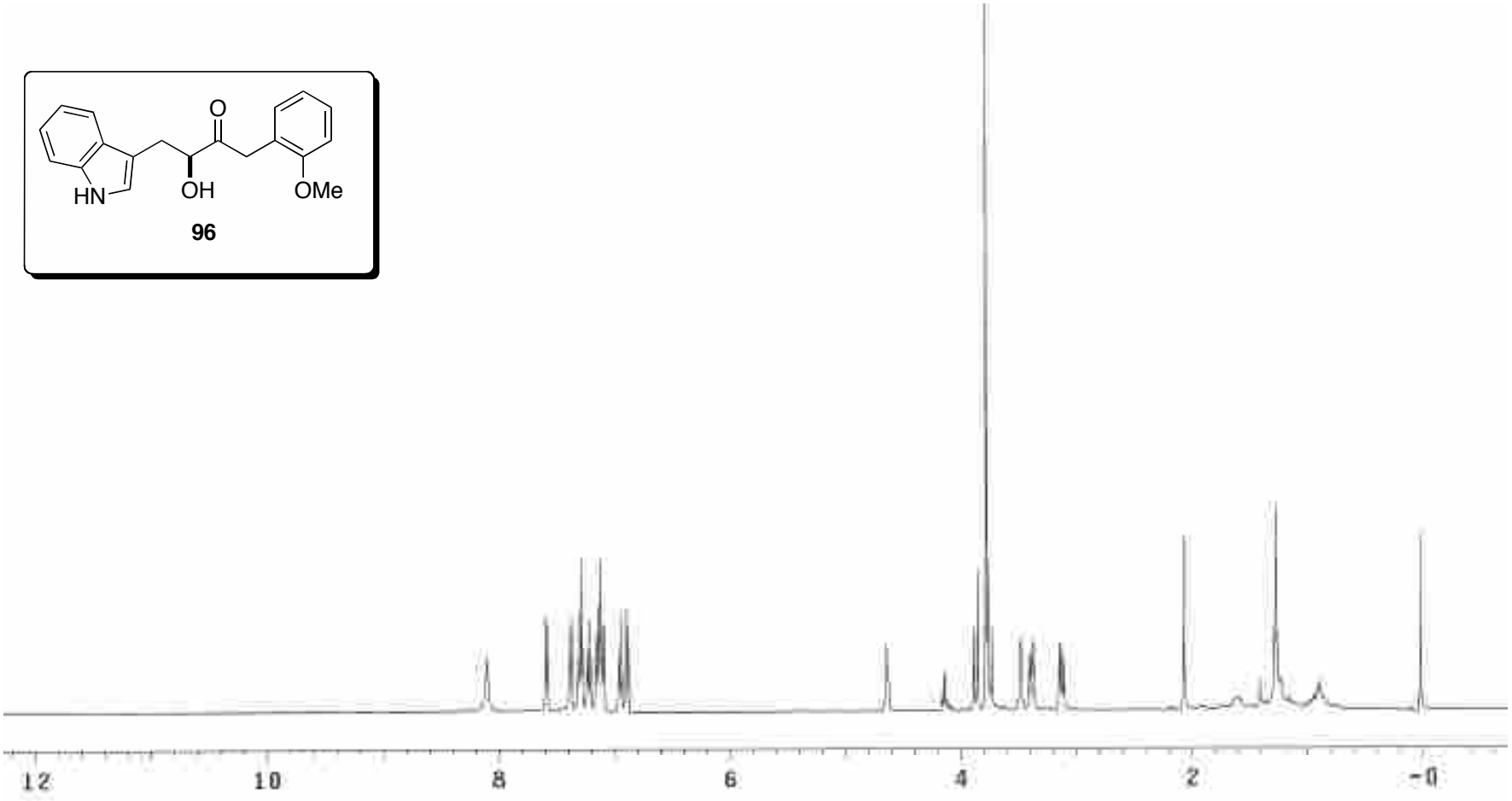

O
HN
OSi(Et)3
85
220
200
180
160
140
120
100
80
60
40
20
0
ppm

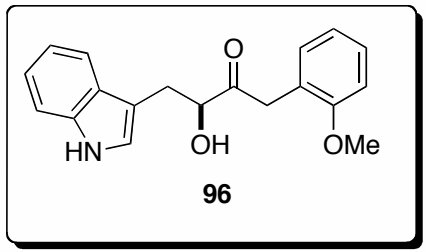


2
(+)-kurasoin B




O
HN
OH
2
(+)-kurasoin B
220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
HN
OH
OMe
96
12
10
8
6
4
2
-0



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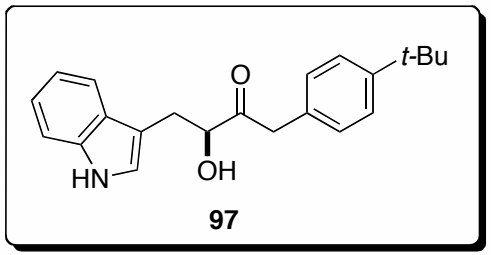

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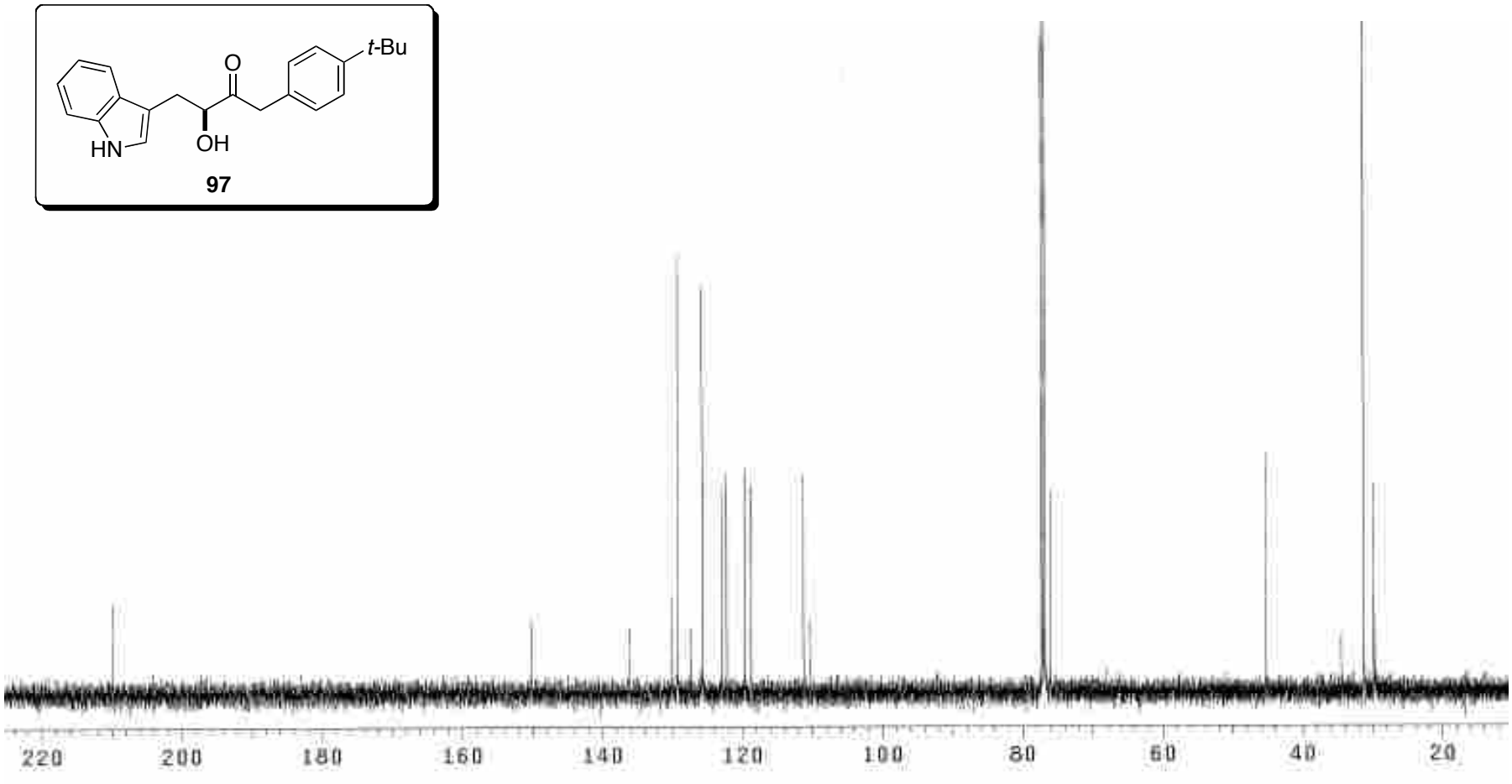
t-Bu
O
HN
OH
97
220
200
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140
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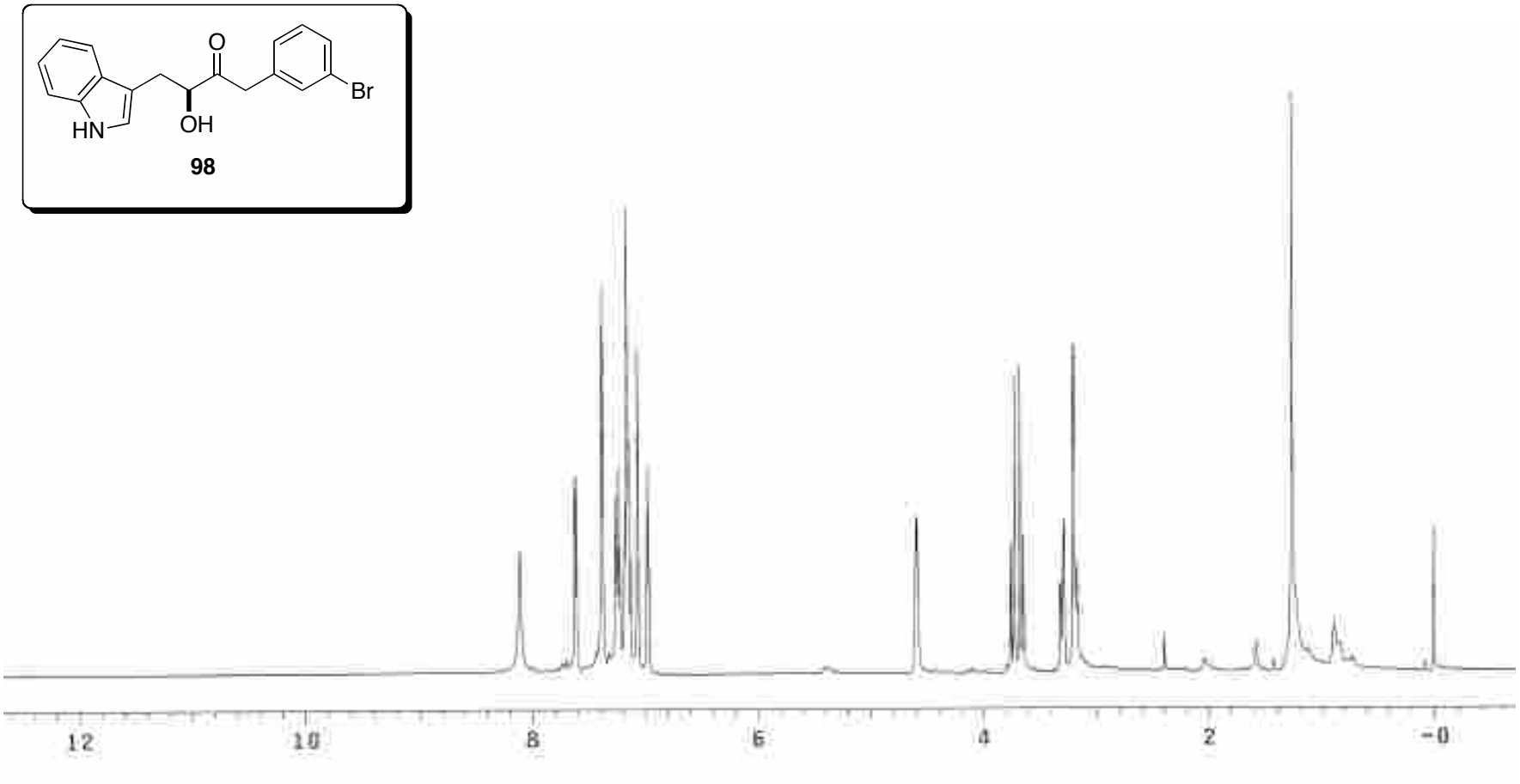
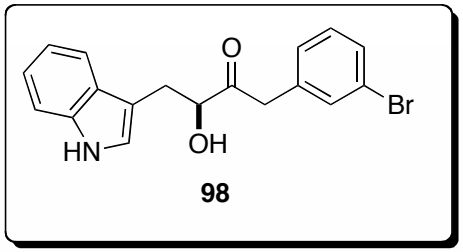
100
80
60
40
20


O
Br
HN
OH
98
12
10
8
6
4
2
-0



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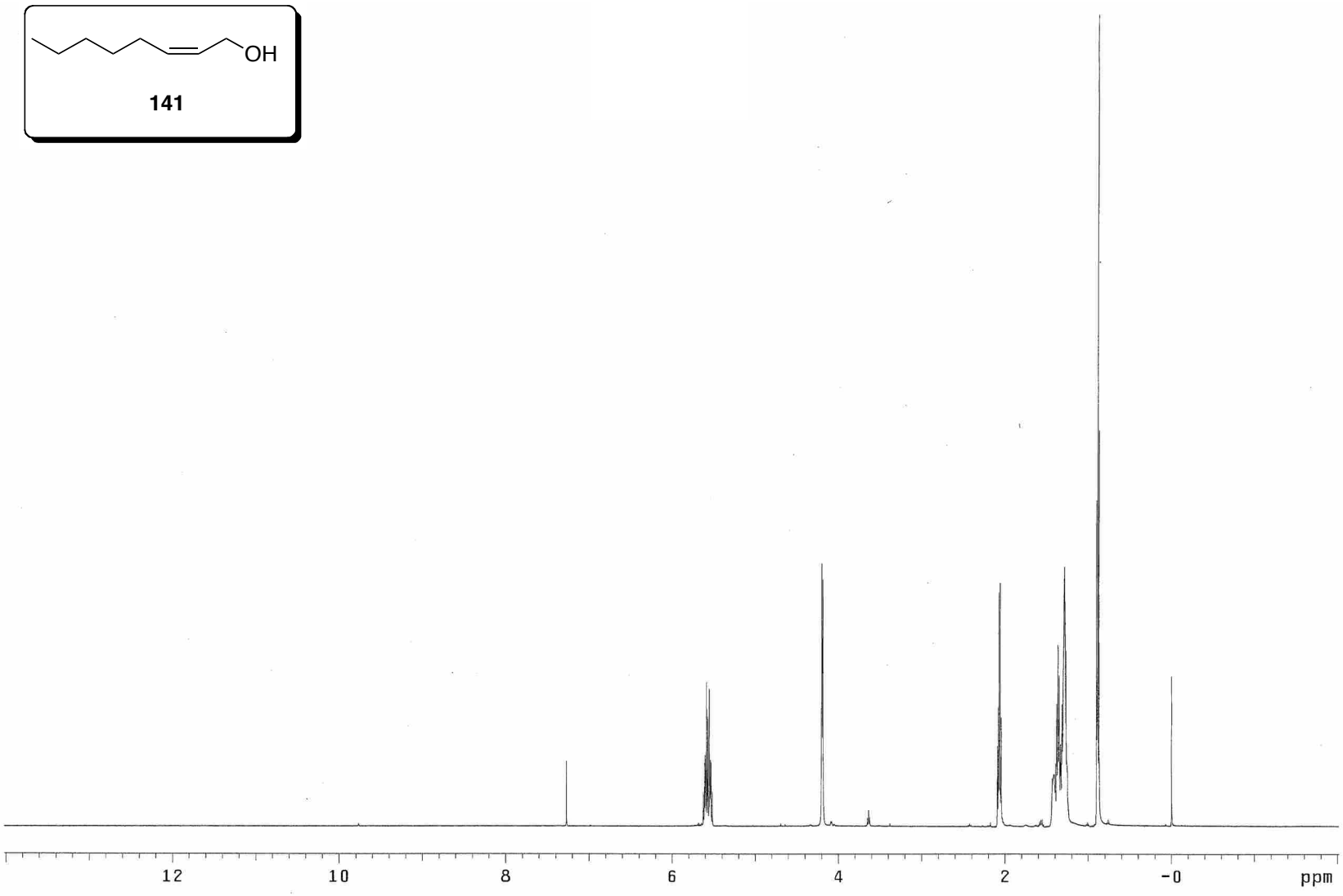
OH
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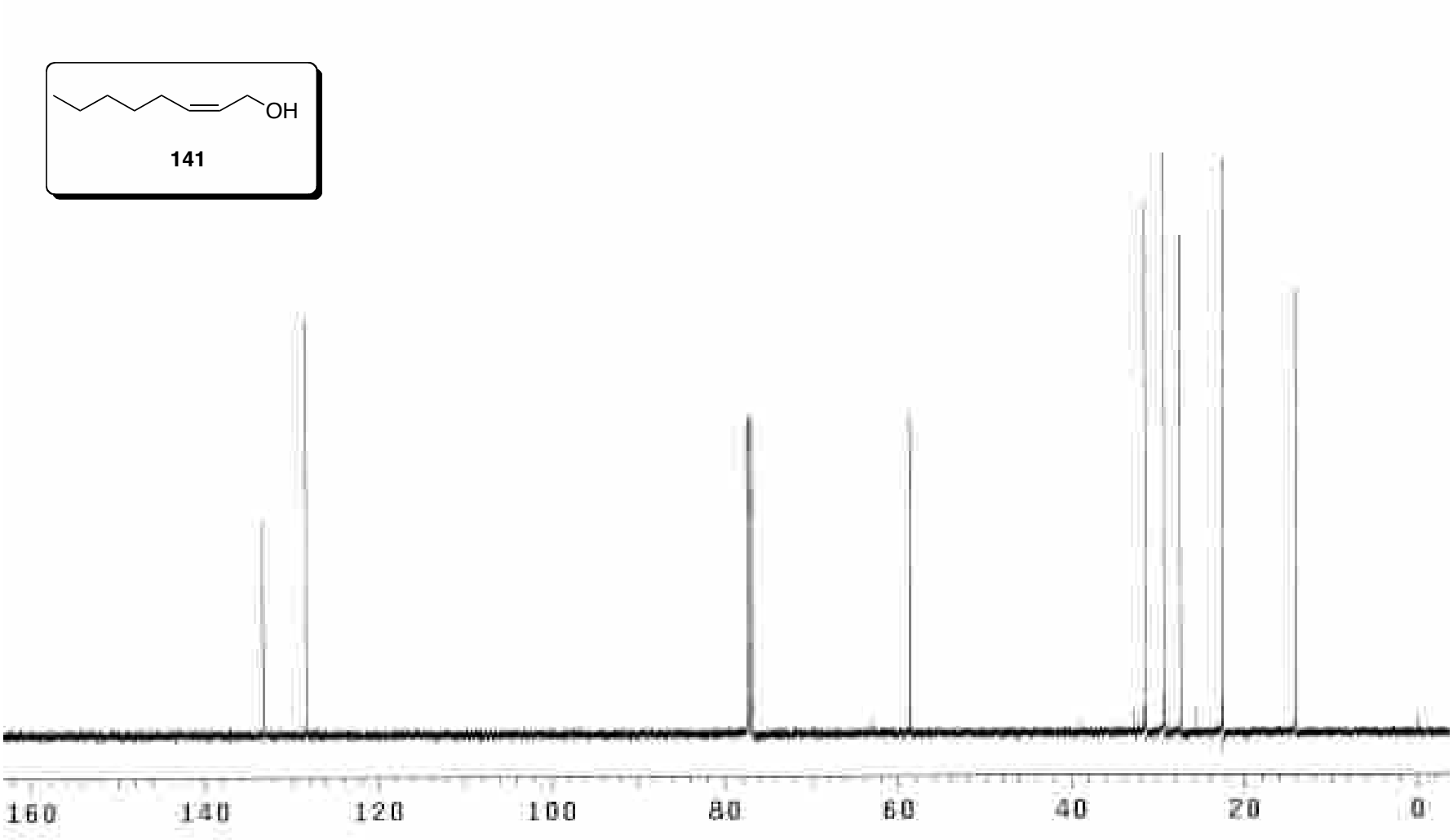
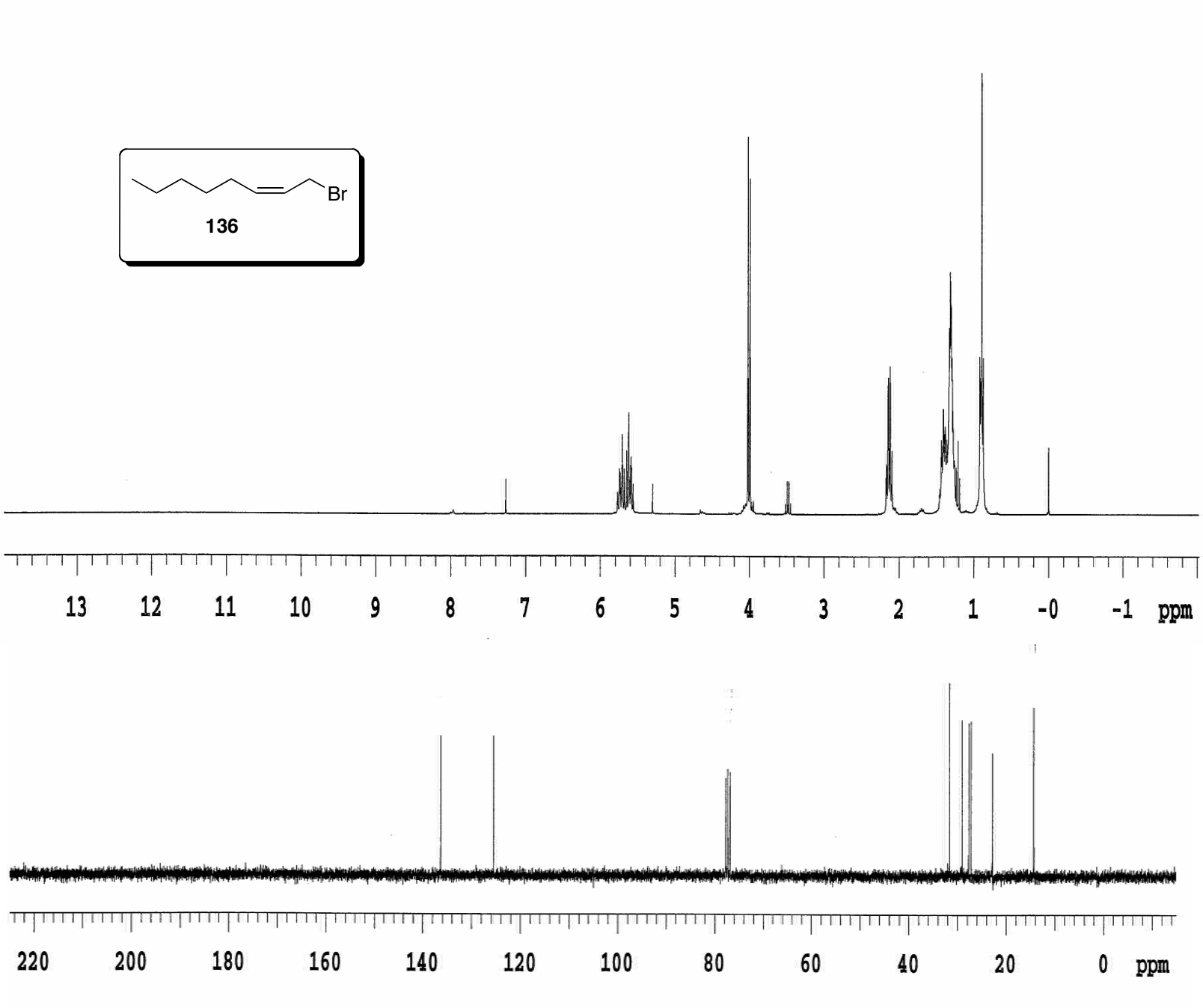
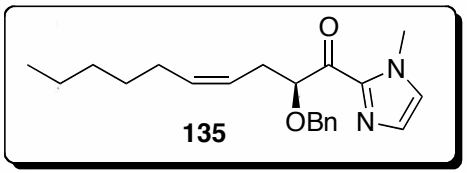
12
10
8
6
4
2
-0
ppm


OH
141
160
140
120
100
80
60
40
20
0


Br
136
13 12 11 10 9 8 7 6 5 4 3 2 1 -0 -1 ppm
220 200 180 160 140 120 100 80 60 40 20 0 ppm



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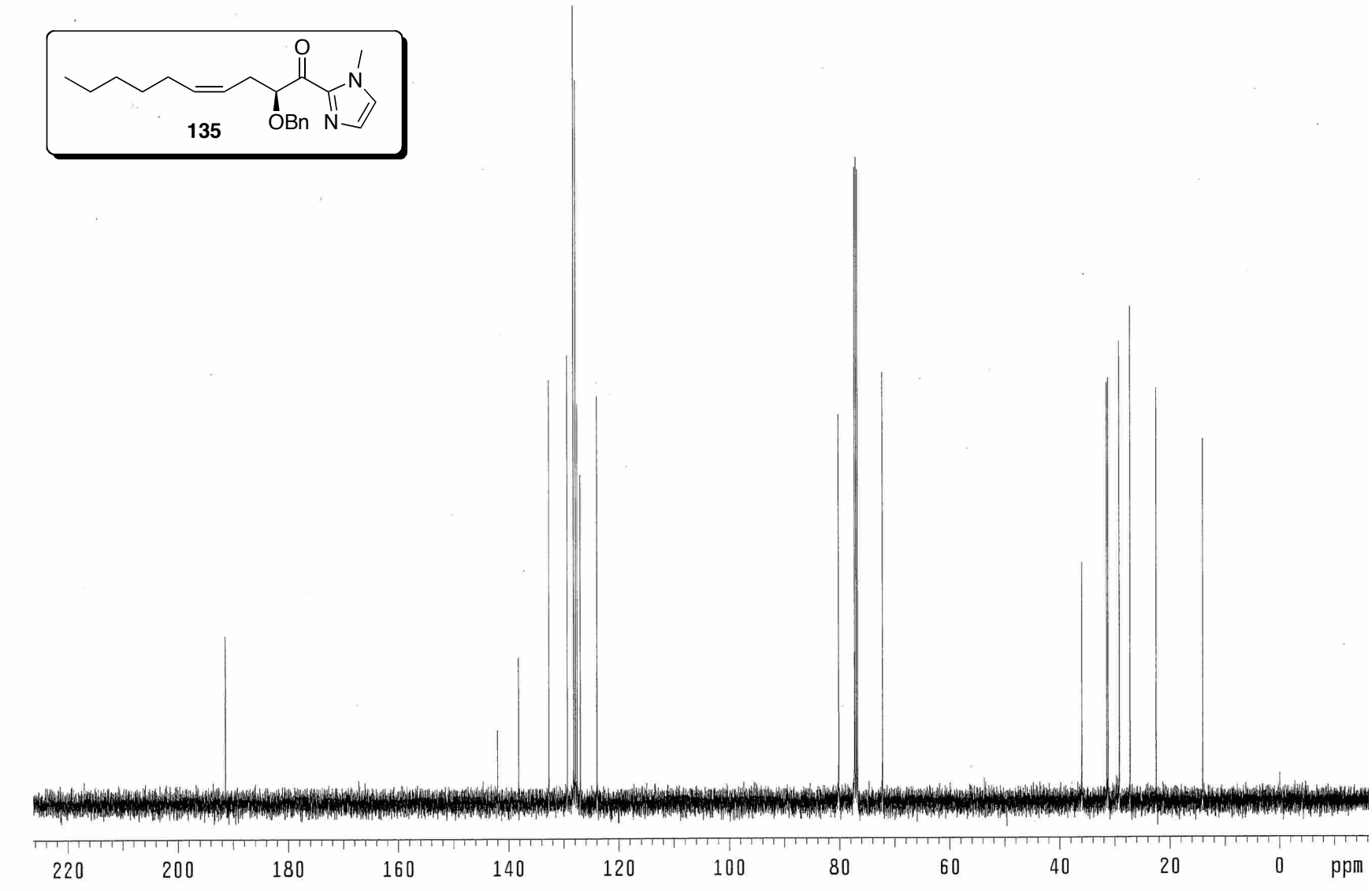
O
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OBn
N
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220
200
180
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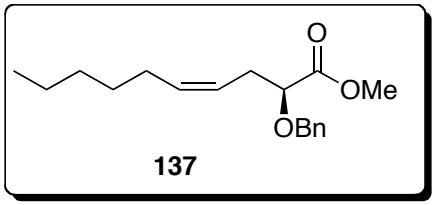
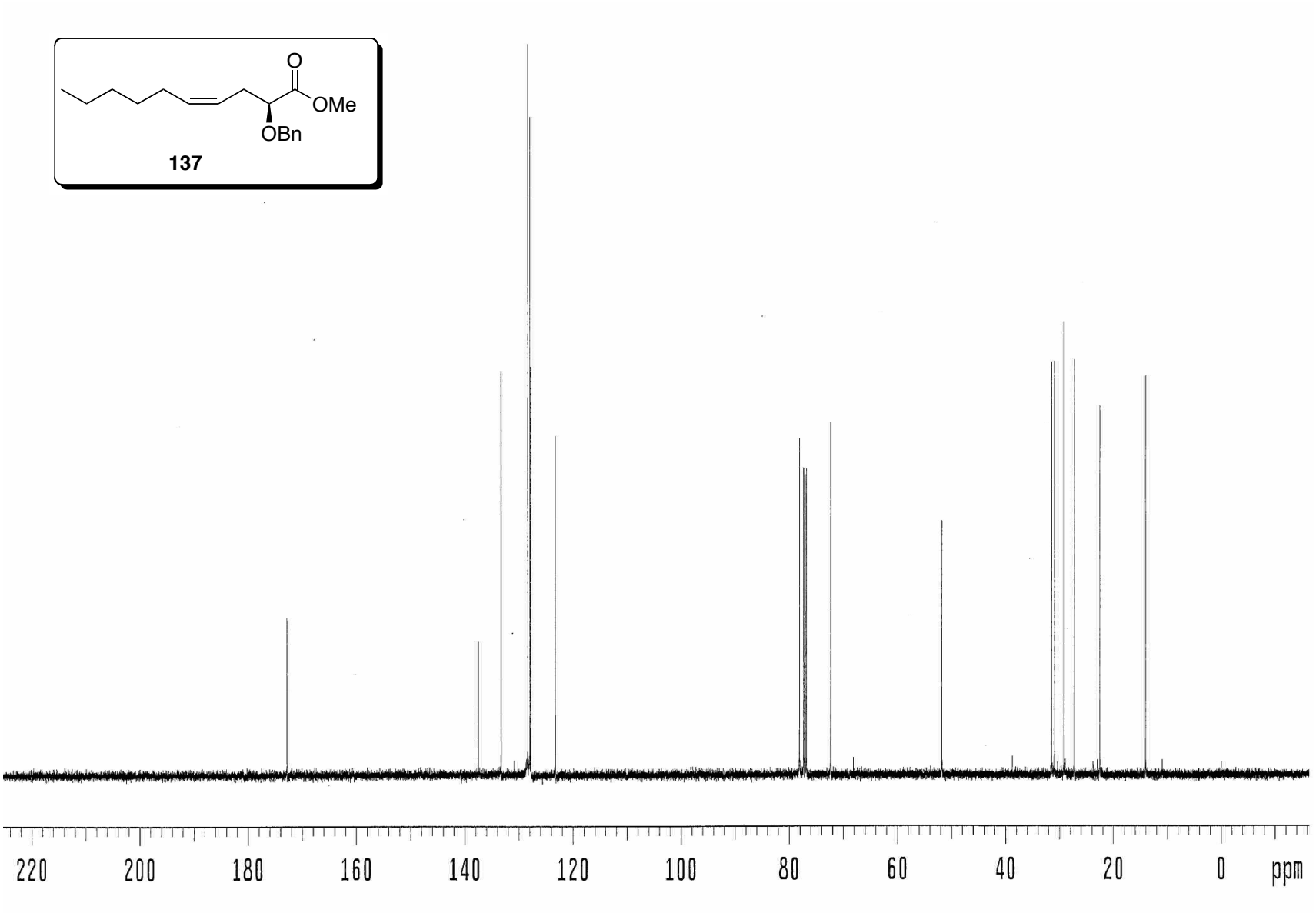
140
120
100
80
60
40
20
0
ppm



137


O
OMe
OBn
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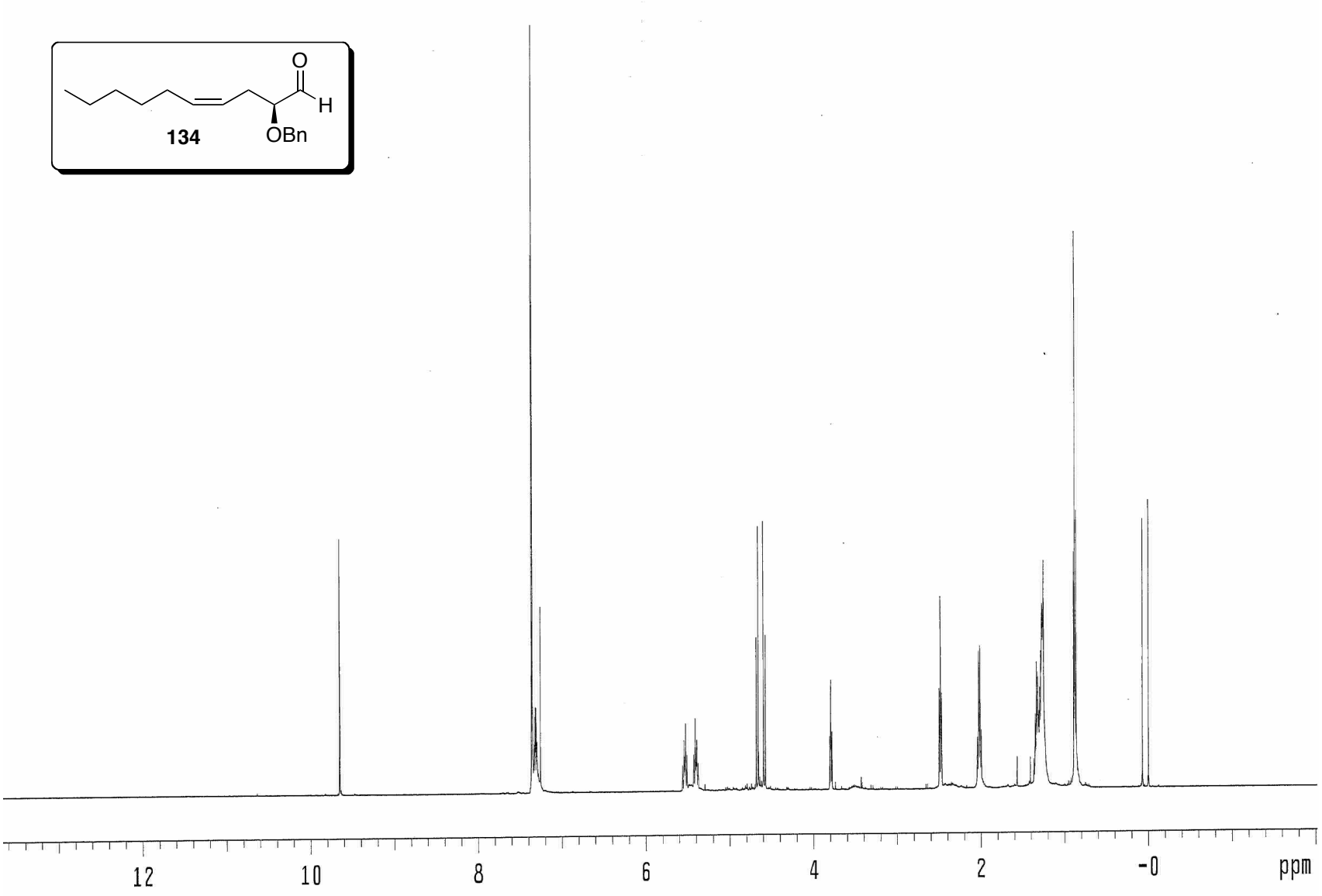
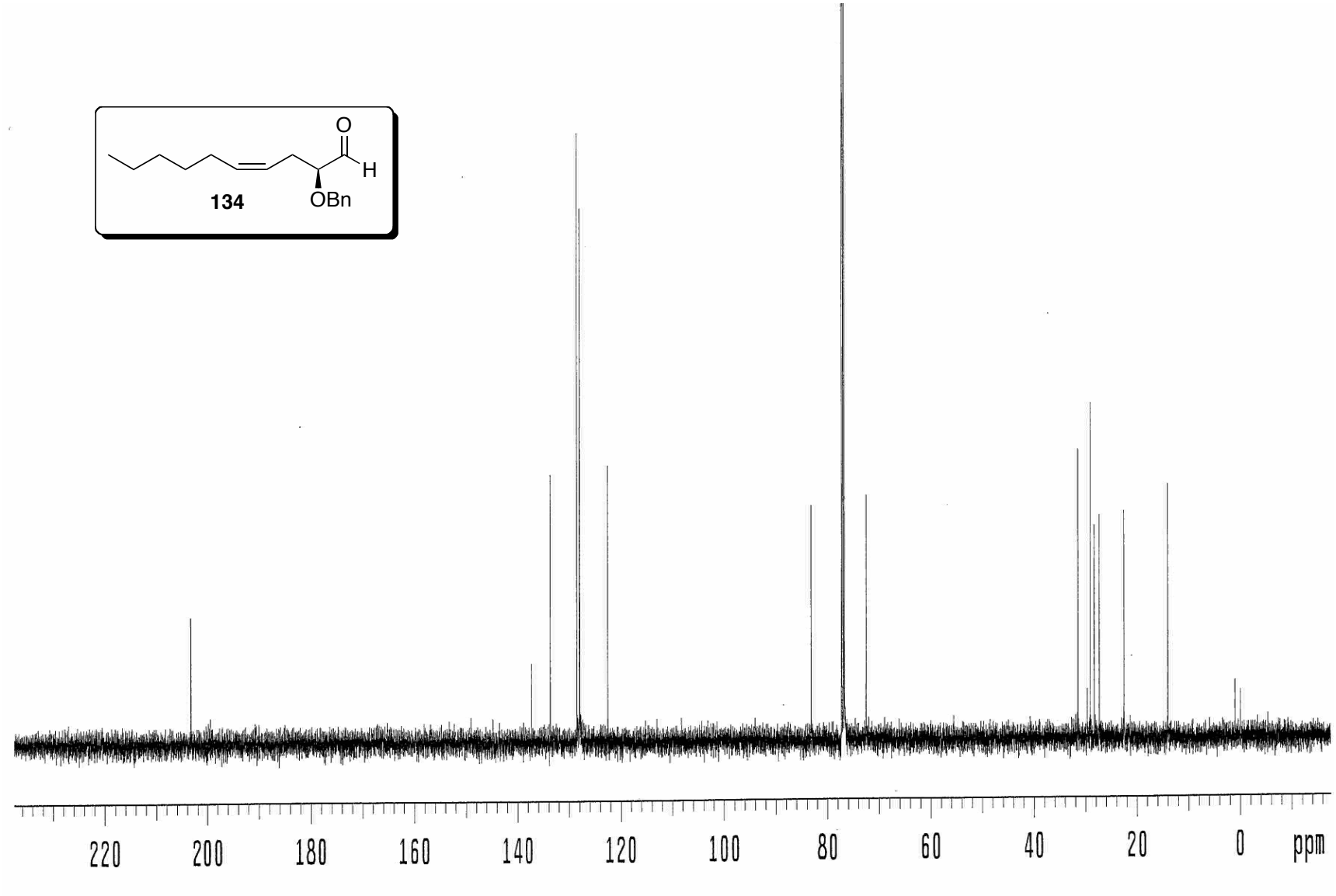
220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
H
134
OBn
12
10
8
6
4
2
-0
ppm


O
H
134
OBn
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180
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40
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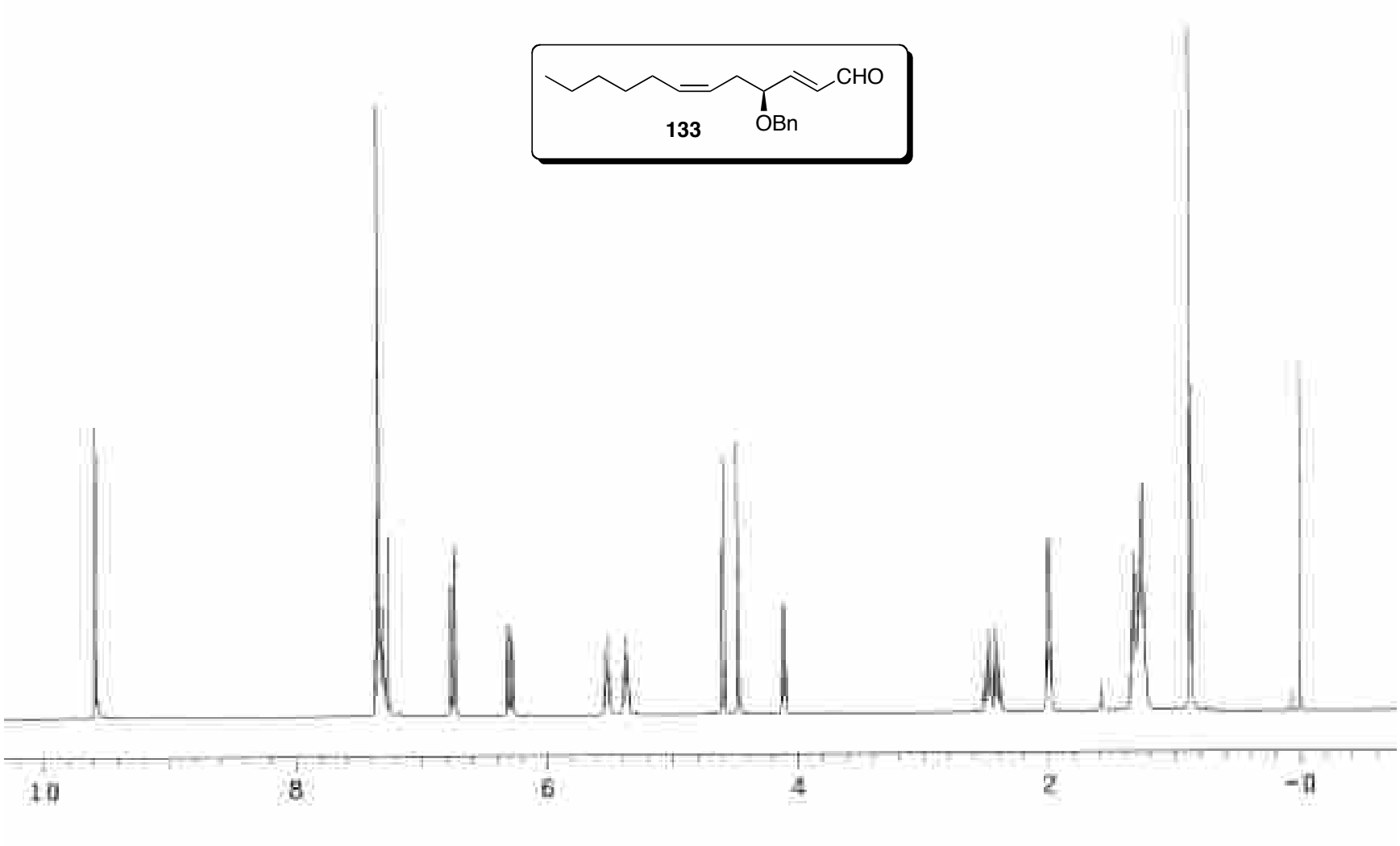
0
ppm


CHO
OBn
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4
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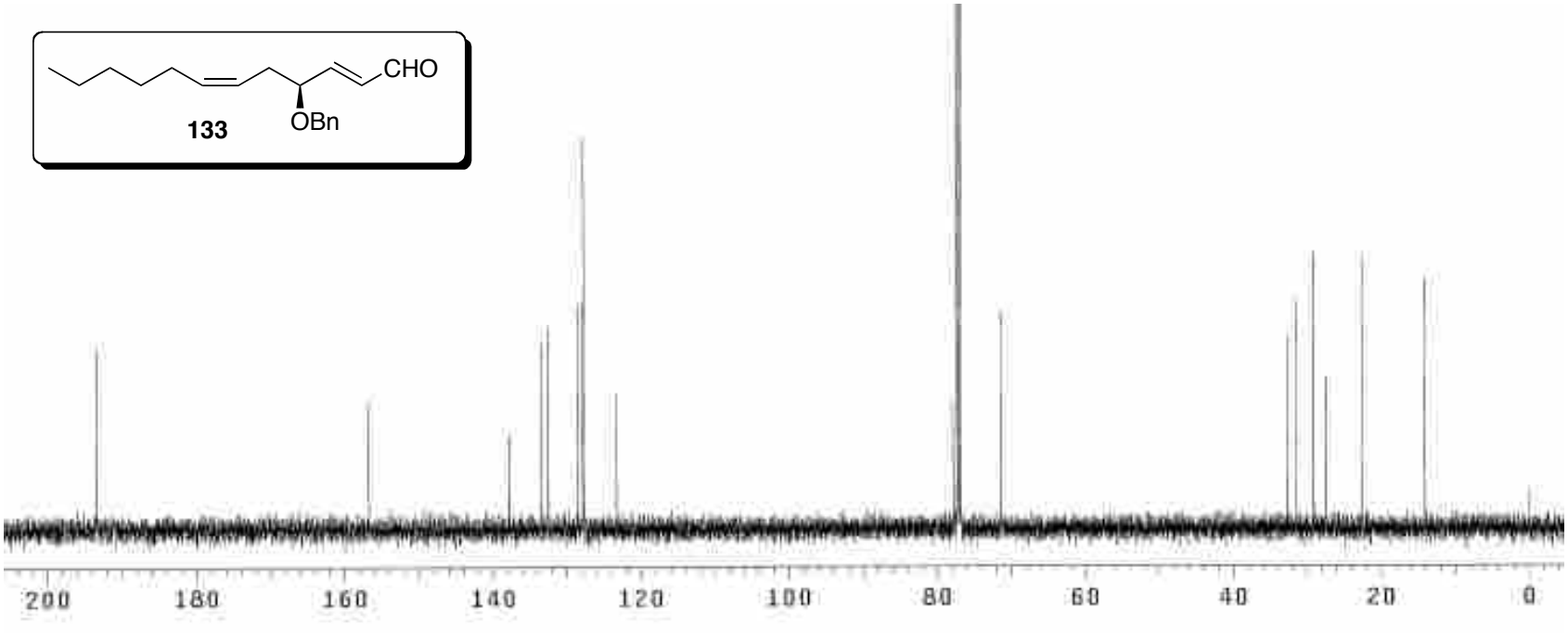
CHO
OBn
133
200
180
160
140
120
100
80
60
40
20
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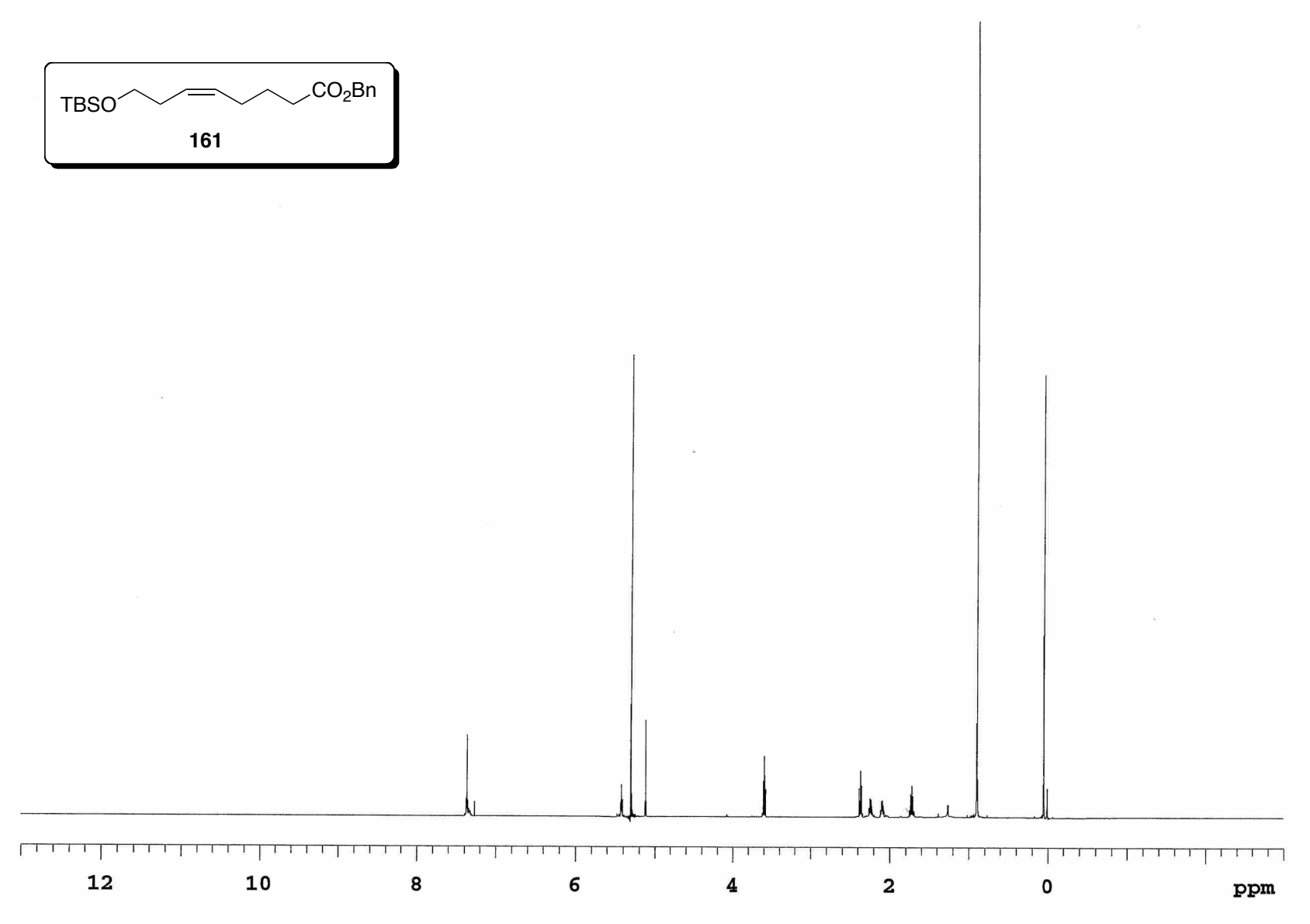
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CO2Bn
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4
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0
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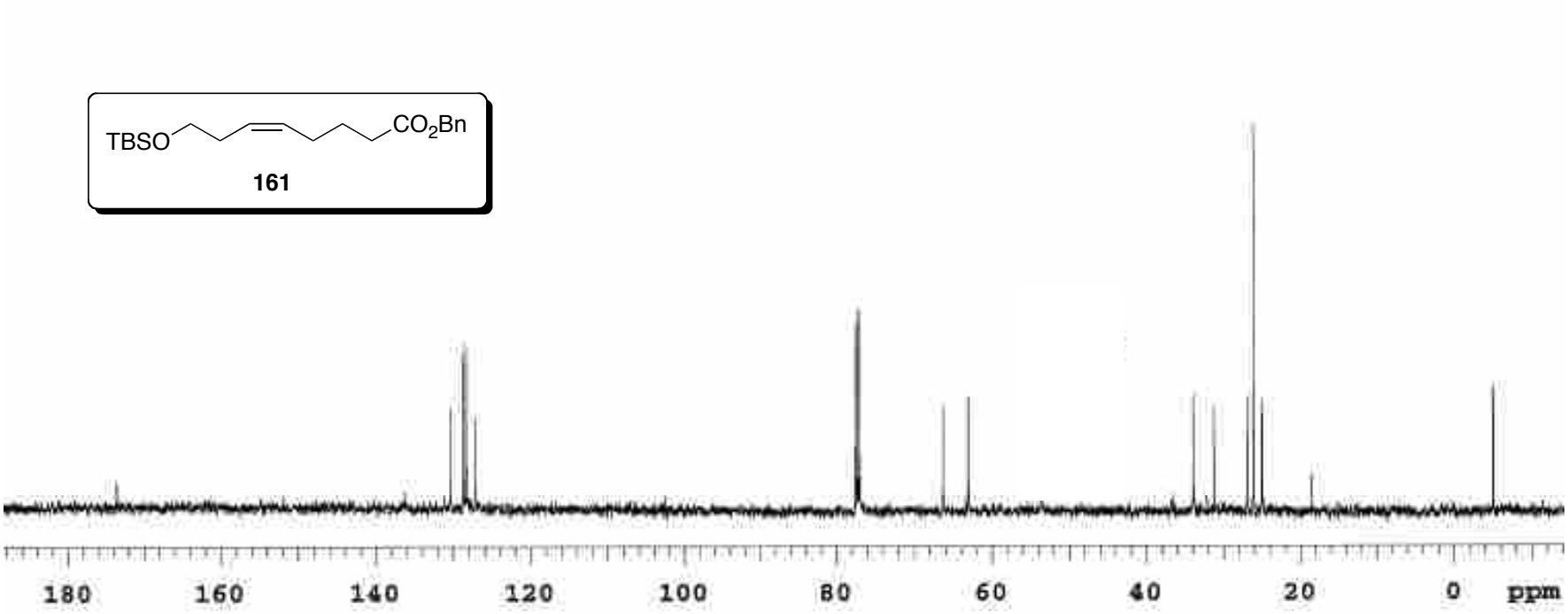
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CO2Bn
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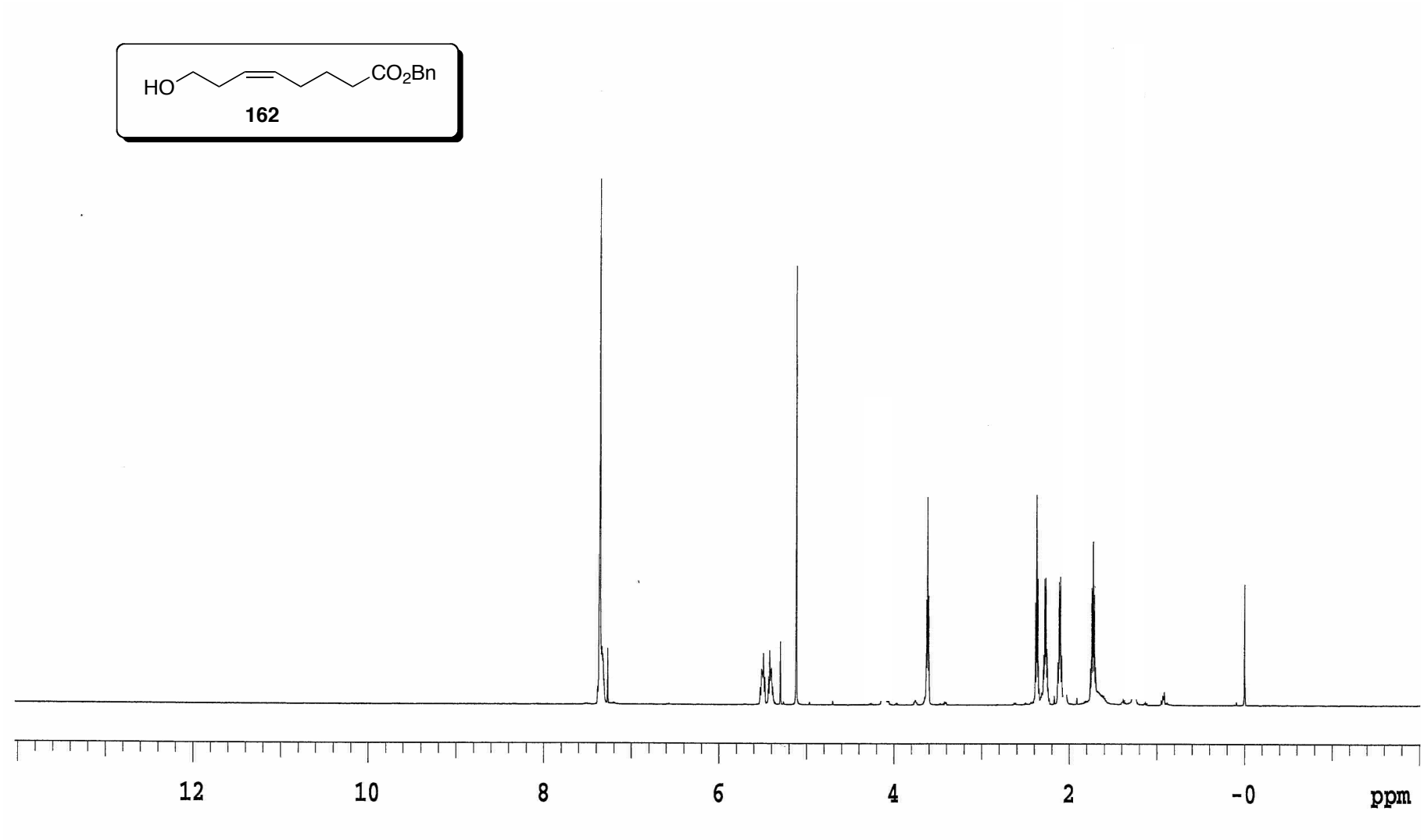
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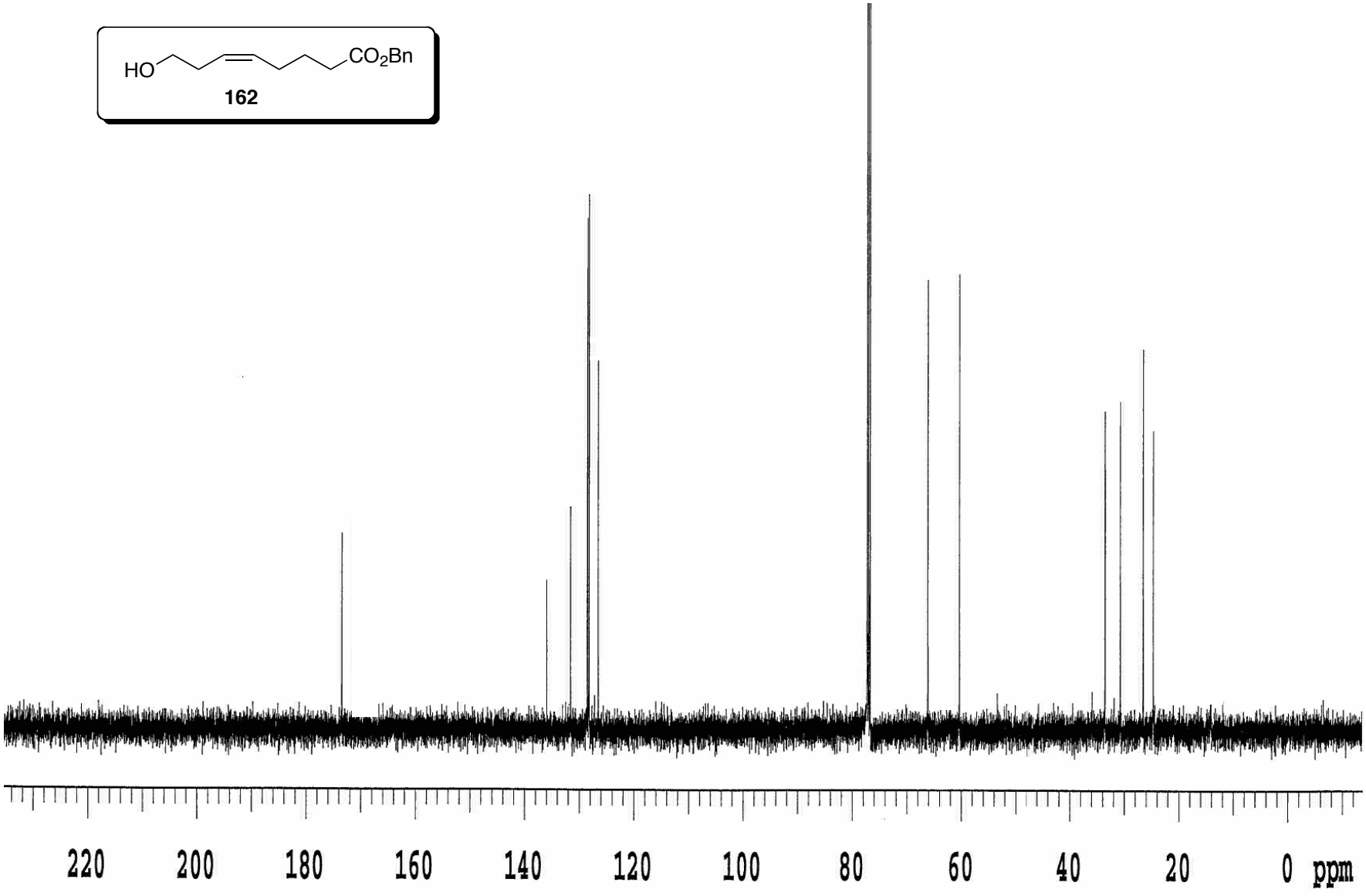
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CO2Bn
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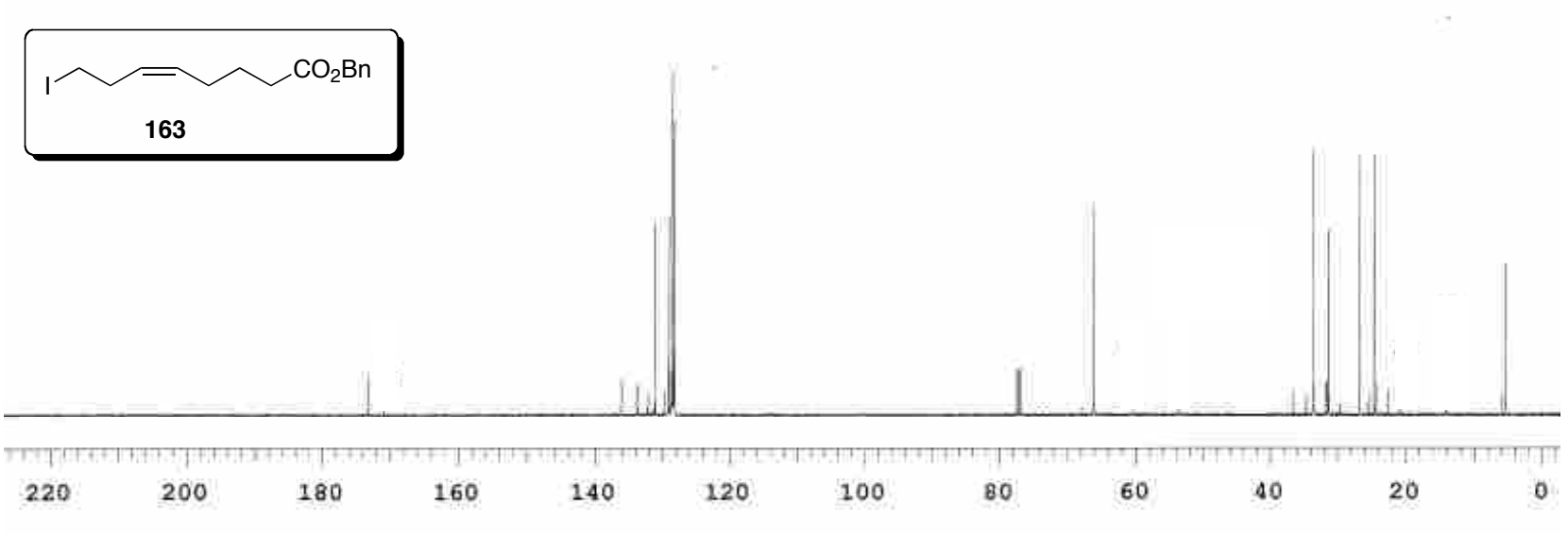
I
CO2Bn
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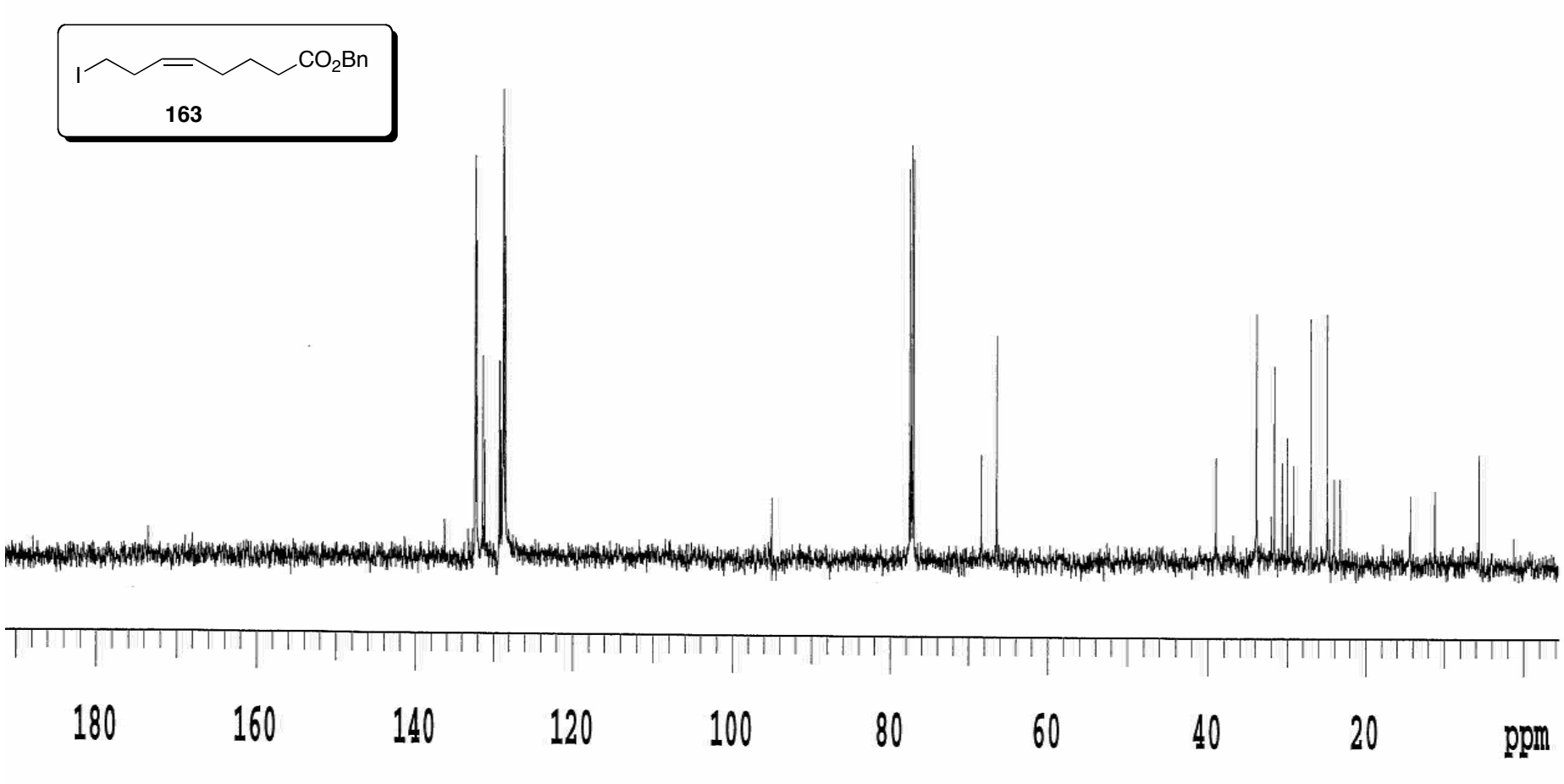
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CO2Bn
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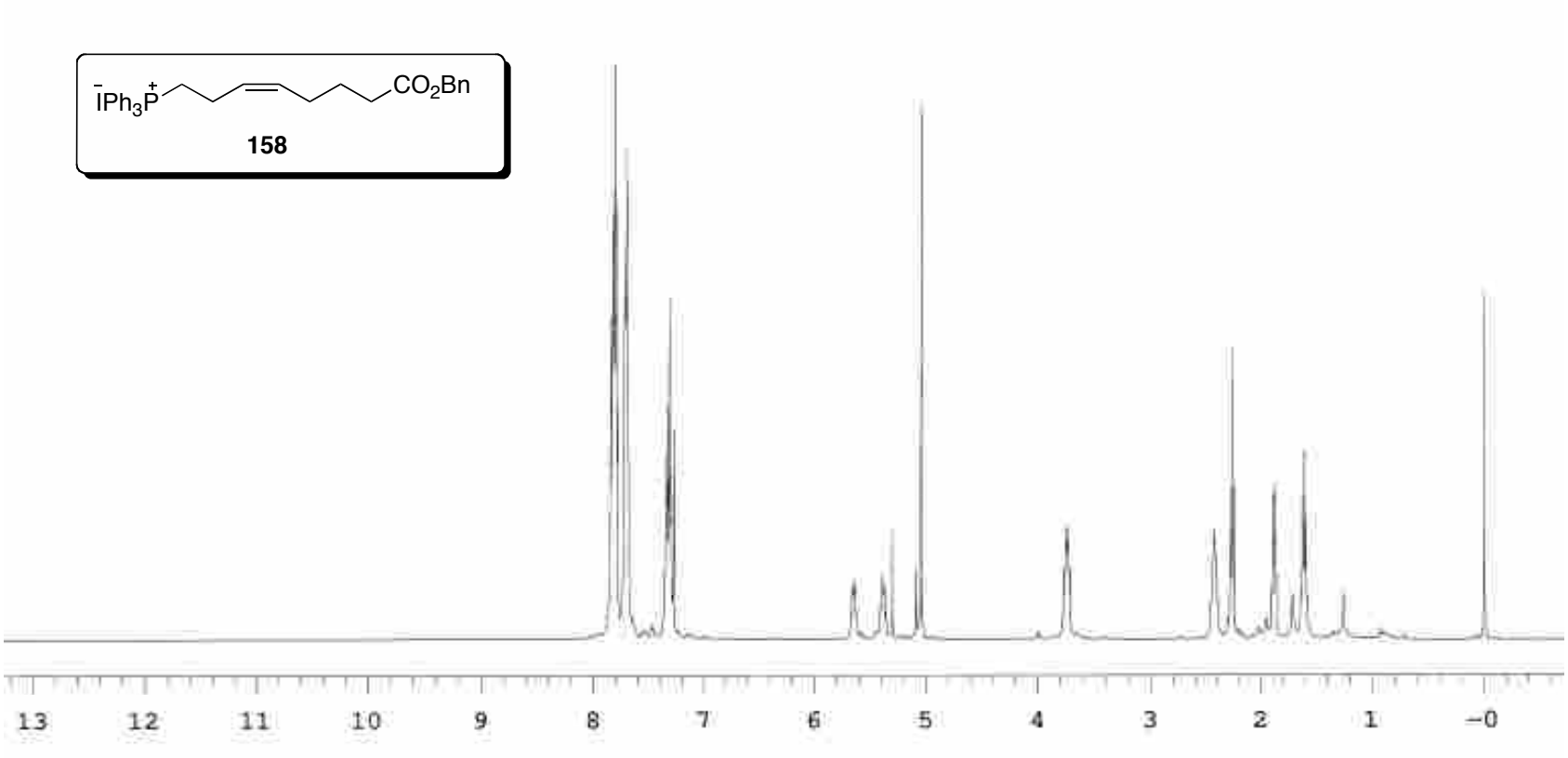
ppm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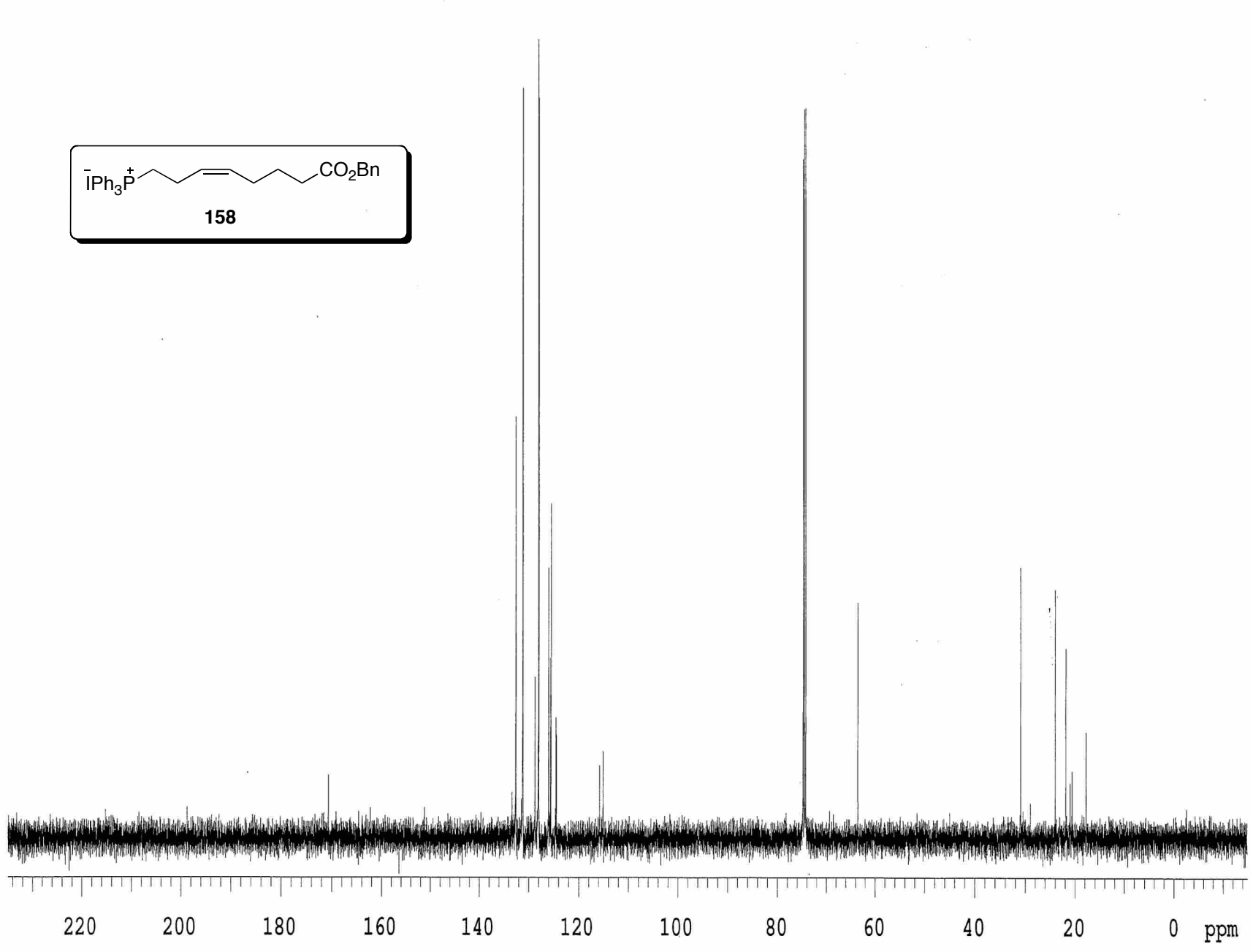
$^{-}IPh_3P^{+}$
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120
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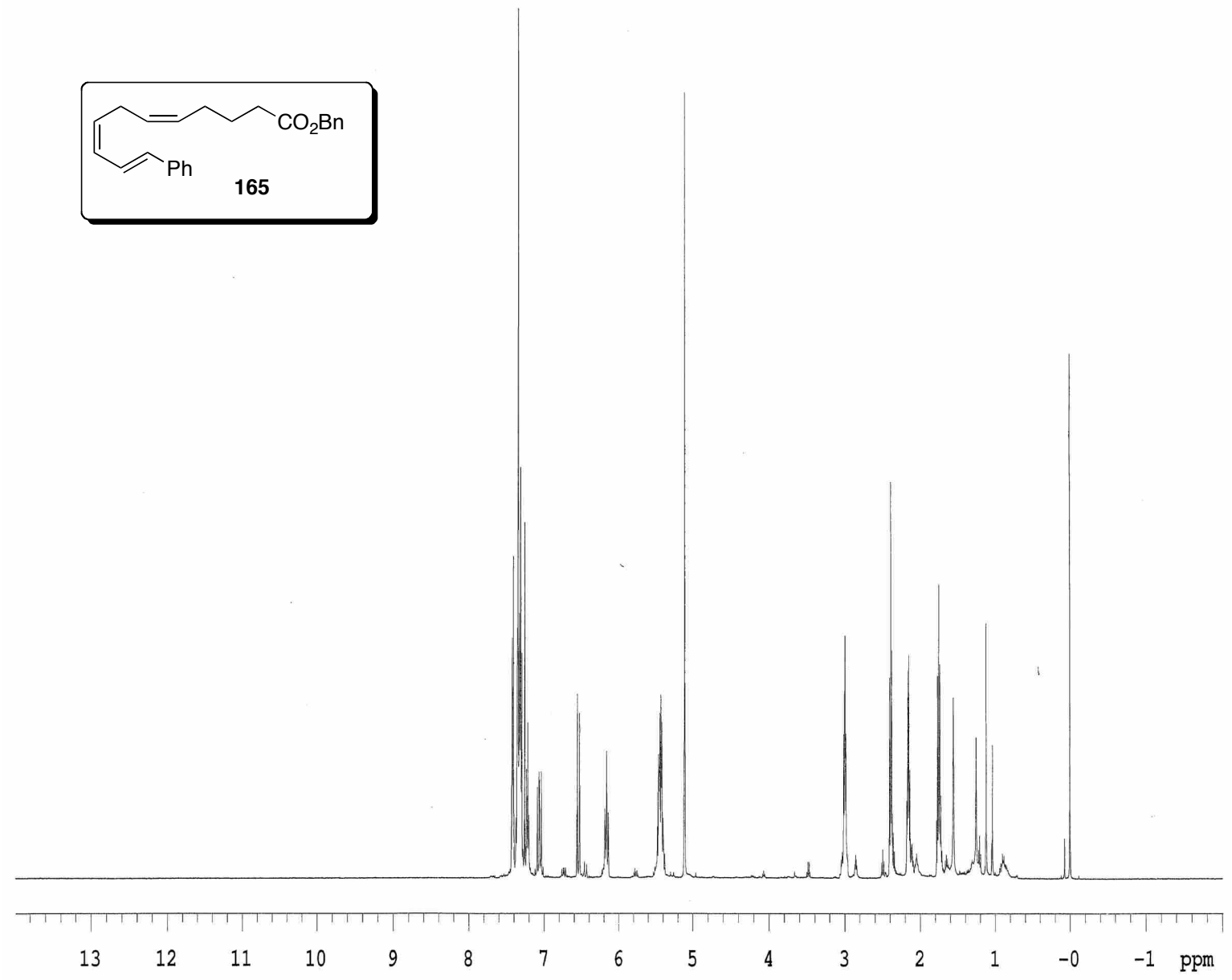
CO2Bn
Ph
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11
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6
5
4
3
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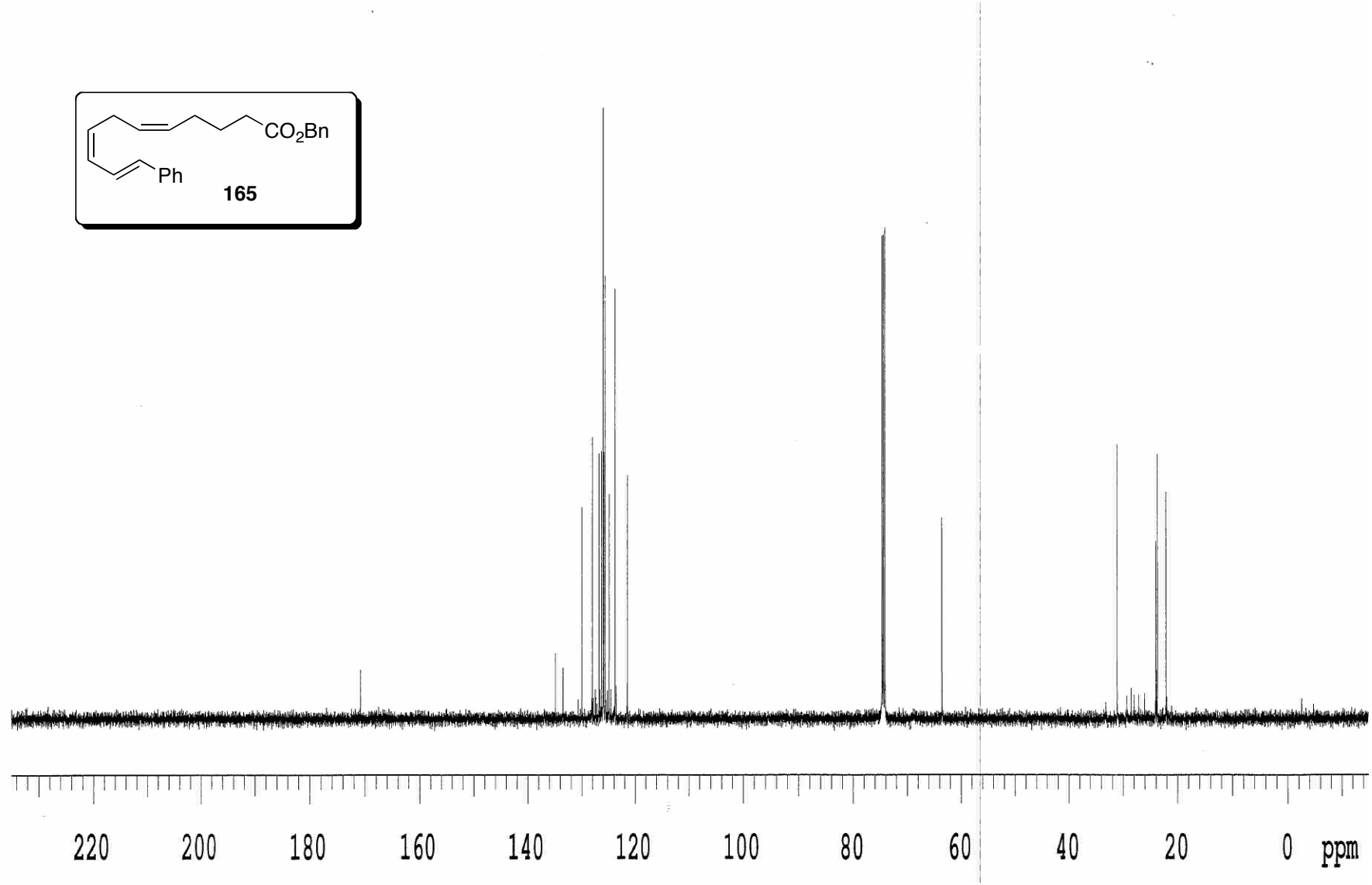
1
-0
-1
ppm


CO2Bn
Ph
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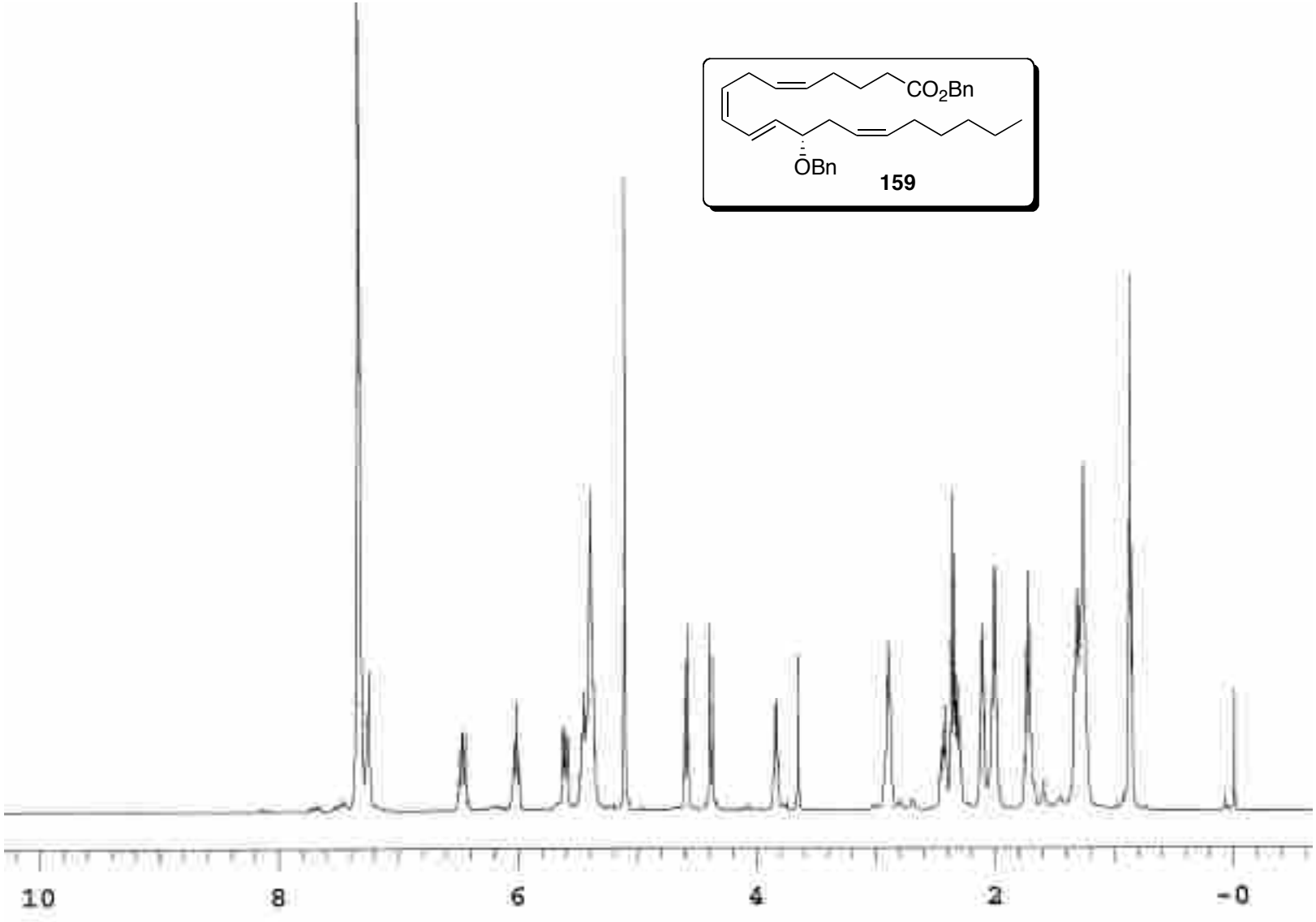
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OBn
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6
4
2
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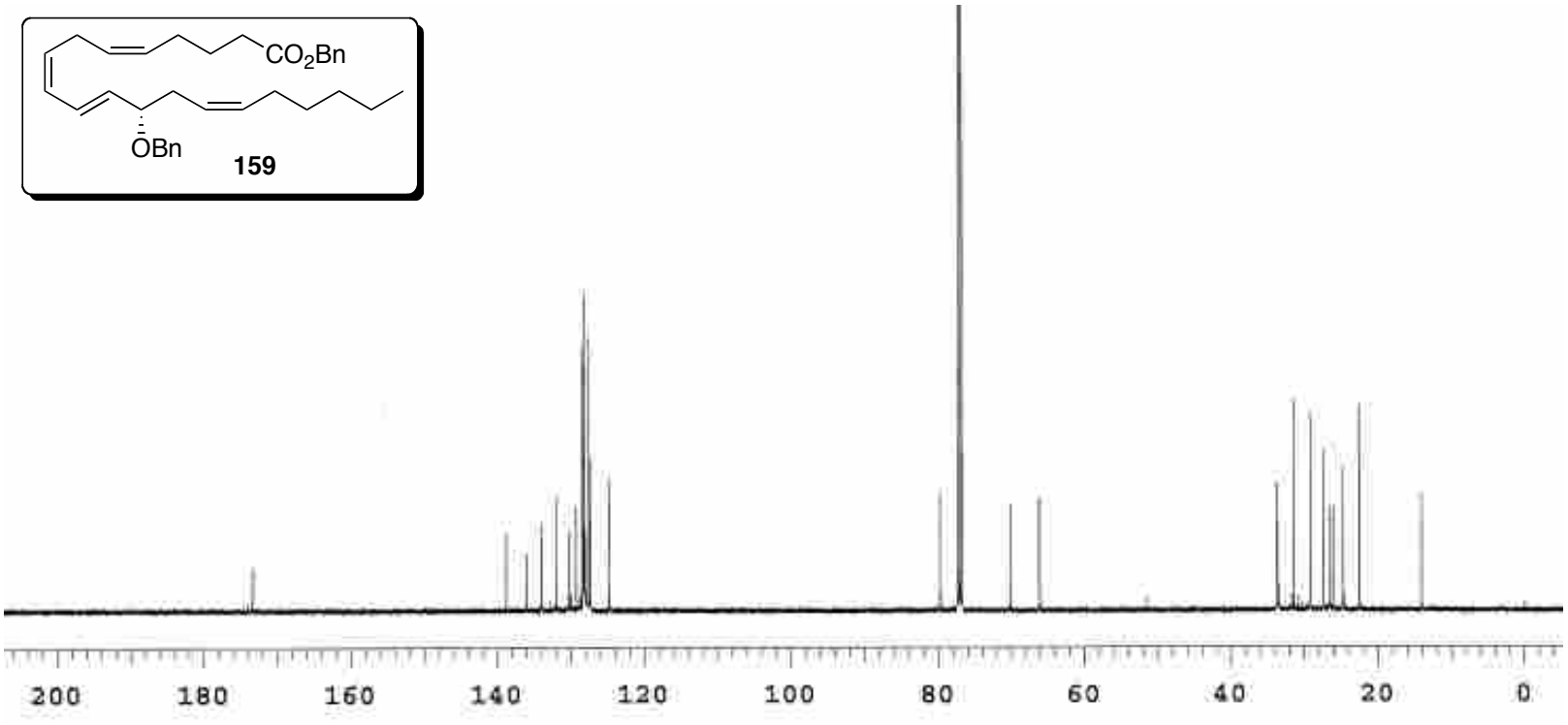
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OBn
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200
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120
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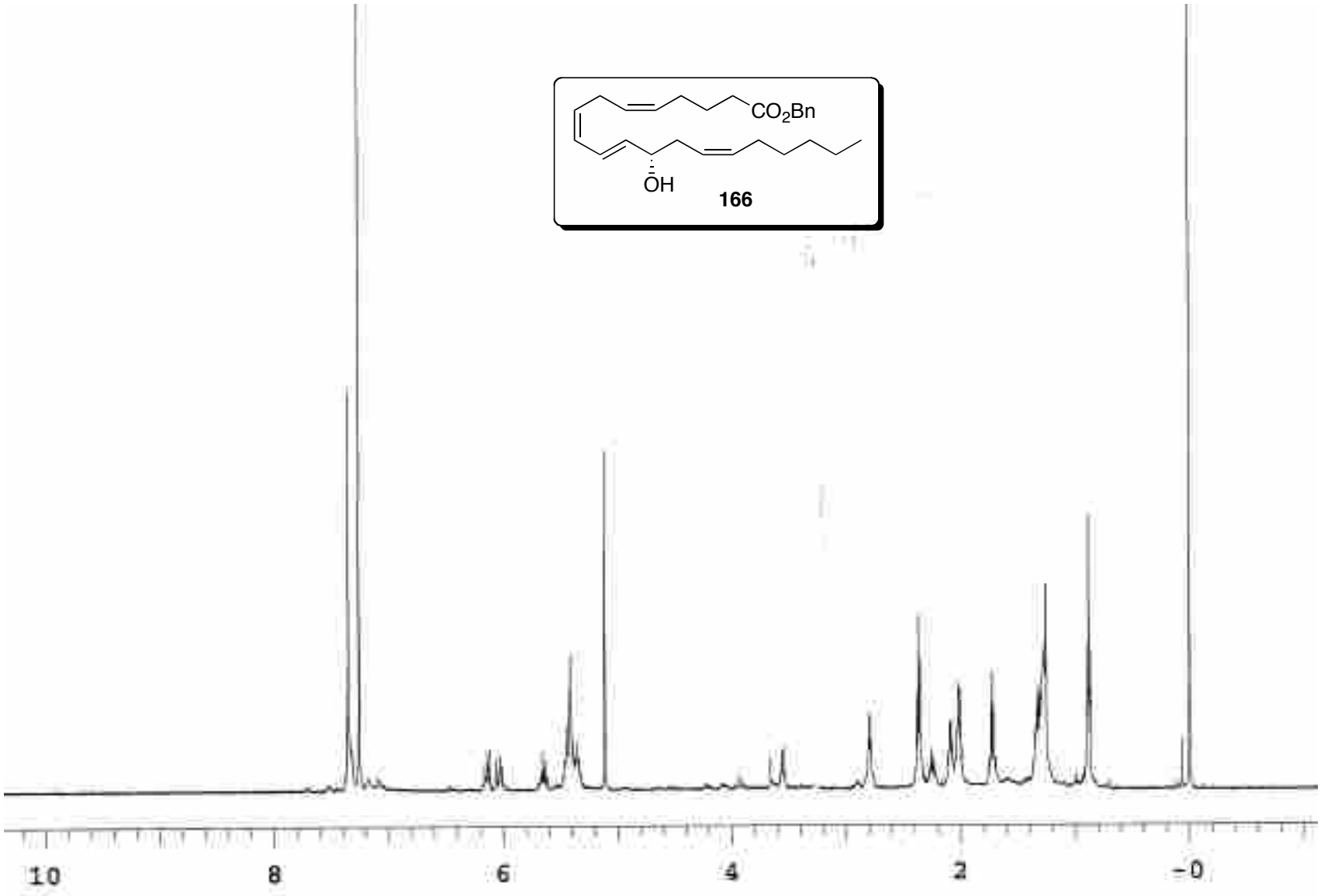
60
40
20
0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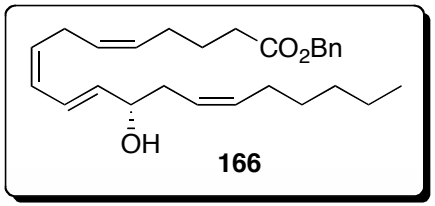
6
4
2
-0



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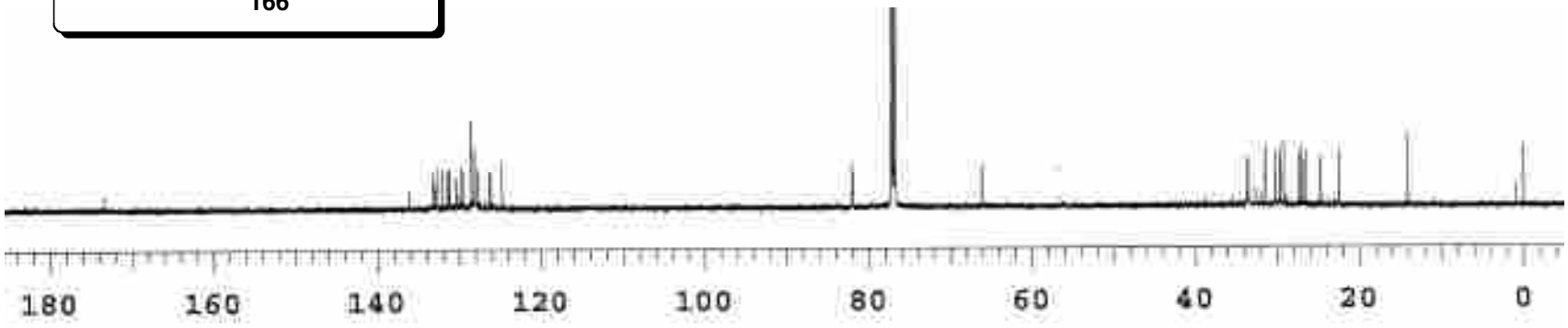

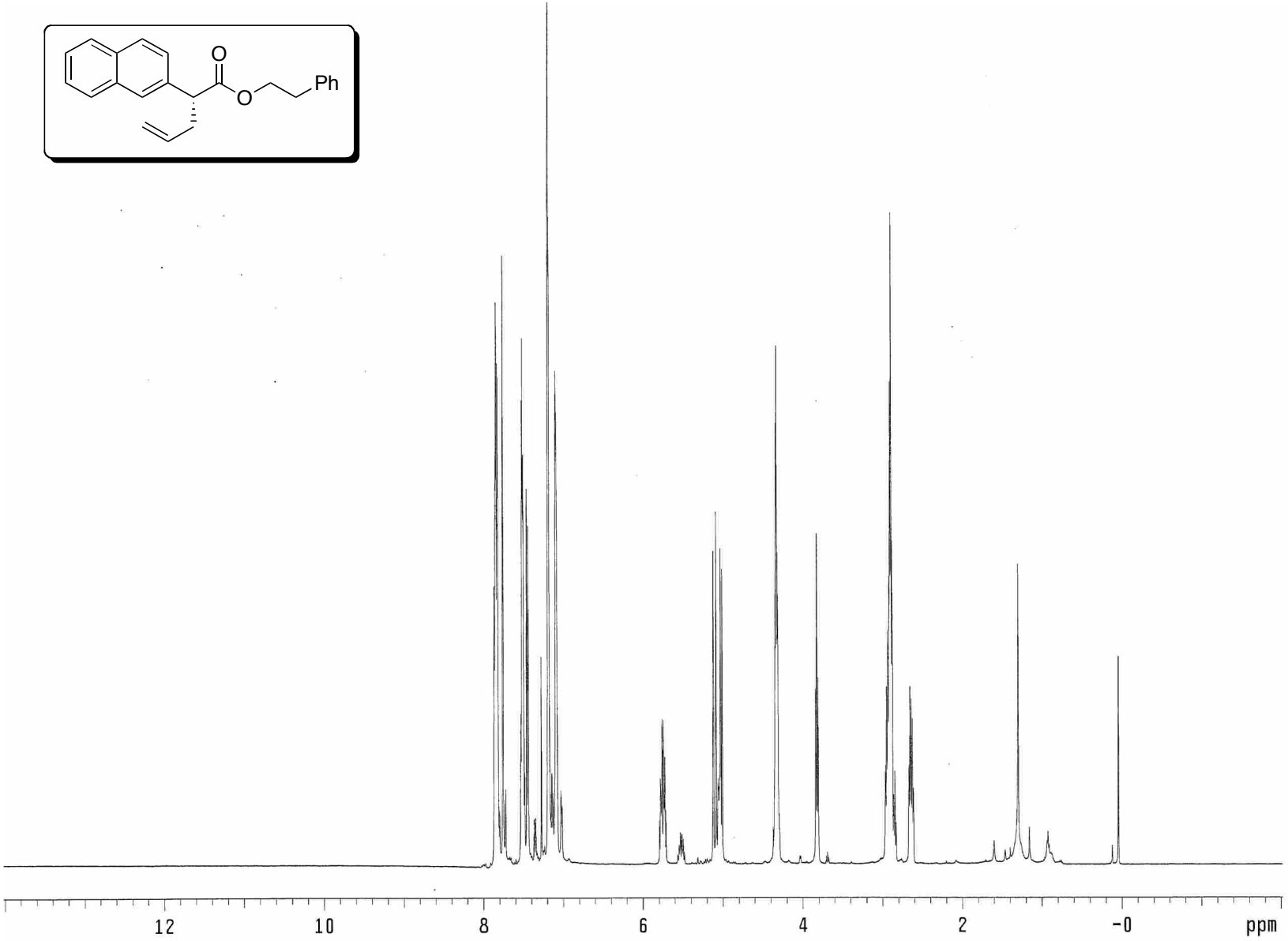
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O
Ph
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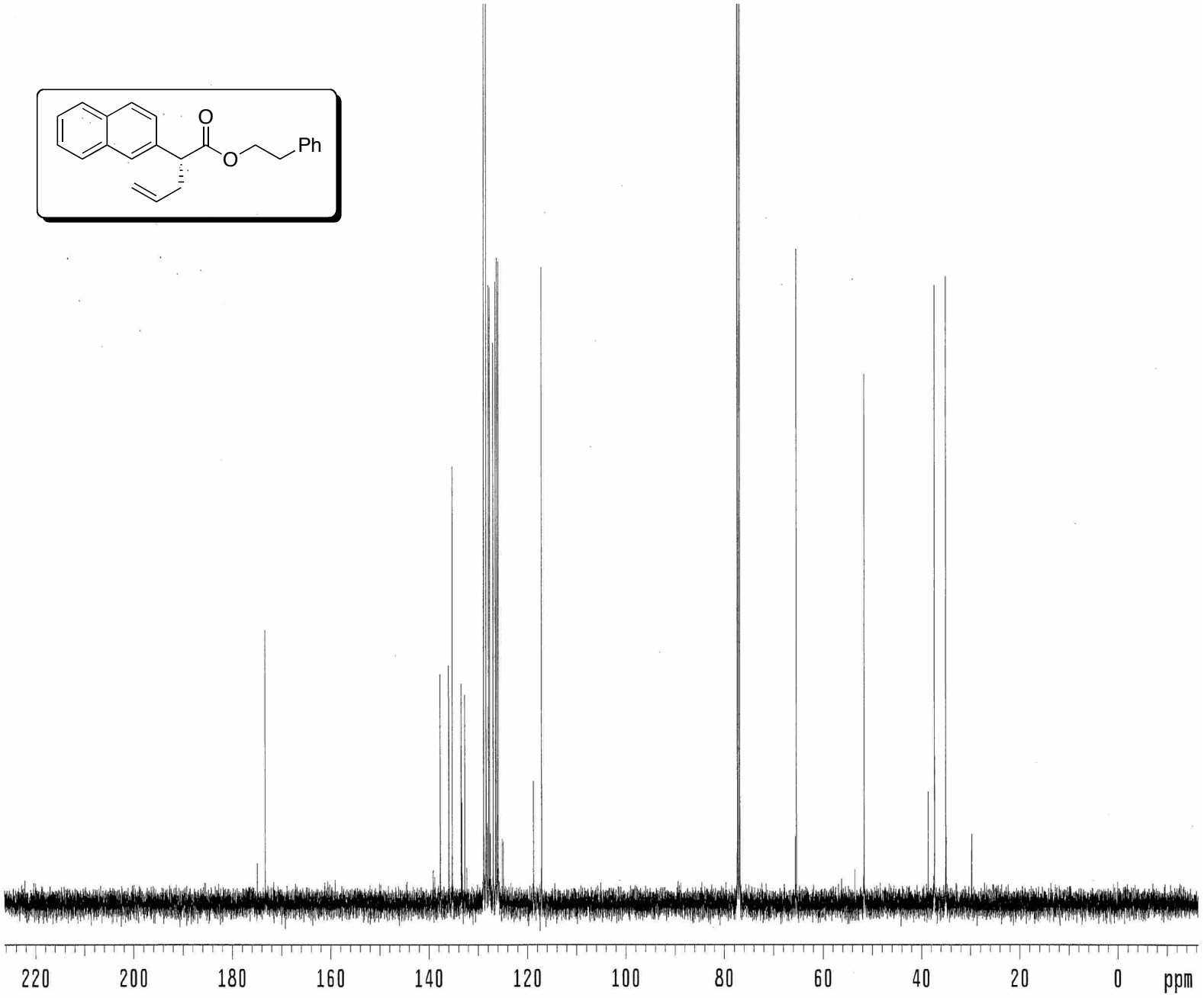
10
8
6
4
2
-0
ppm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O
Ph
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200
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100
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40
20
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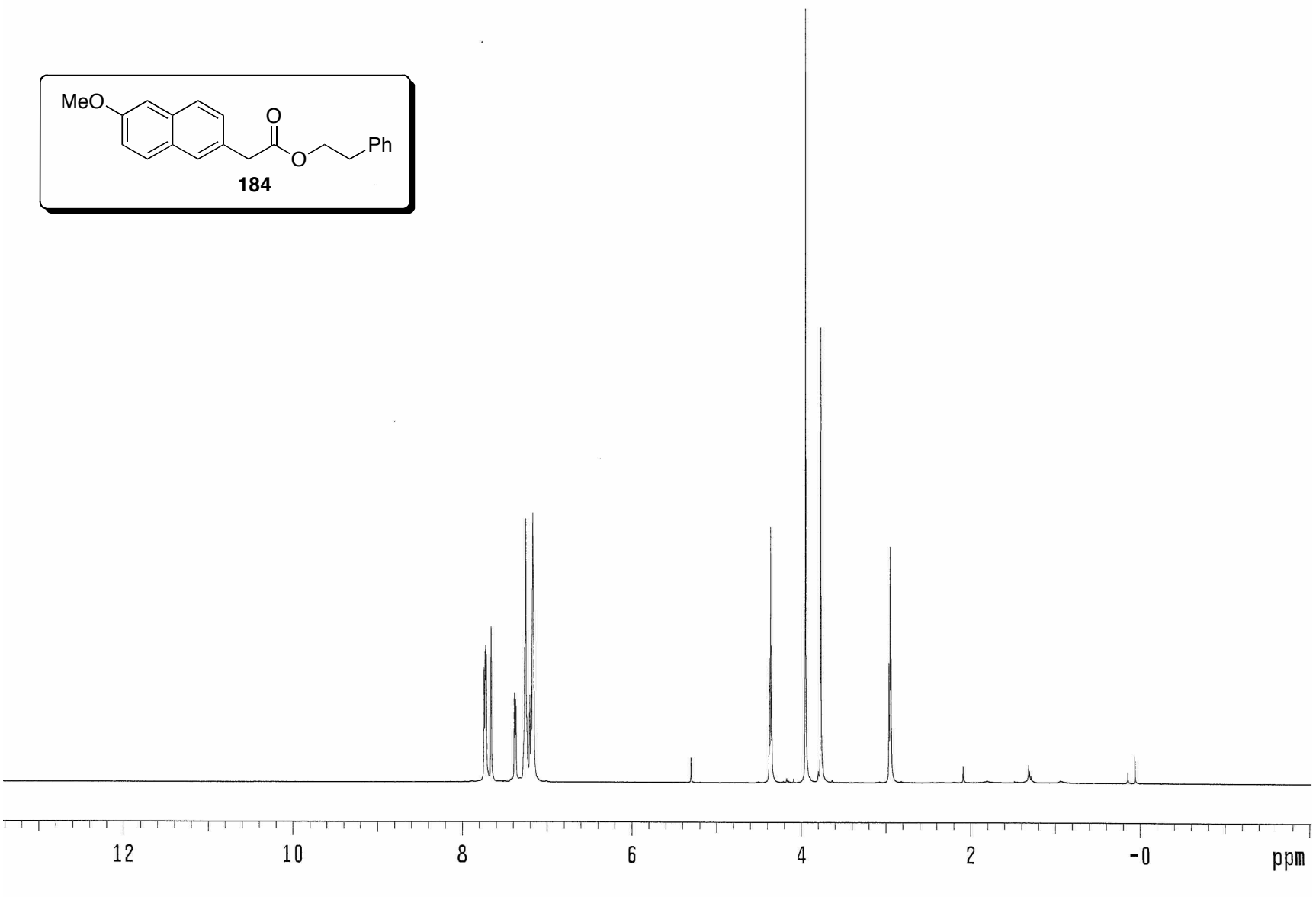
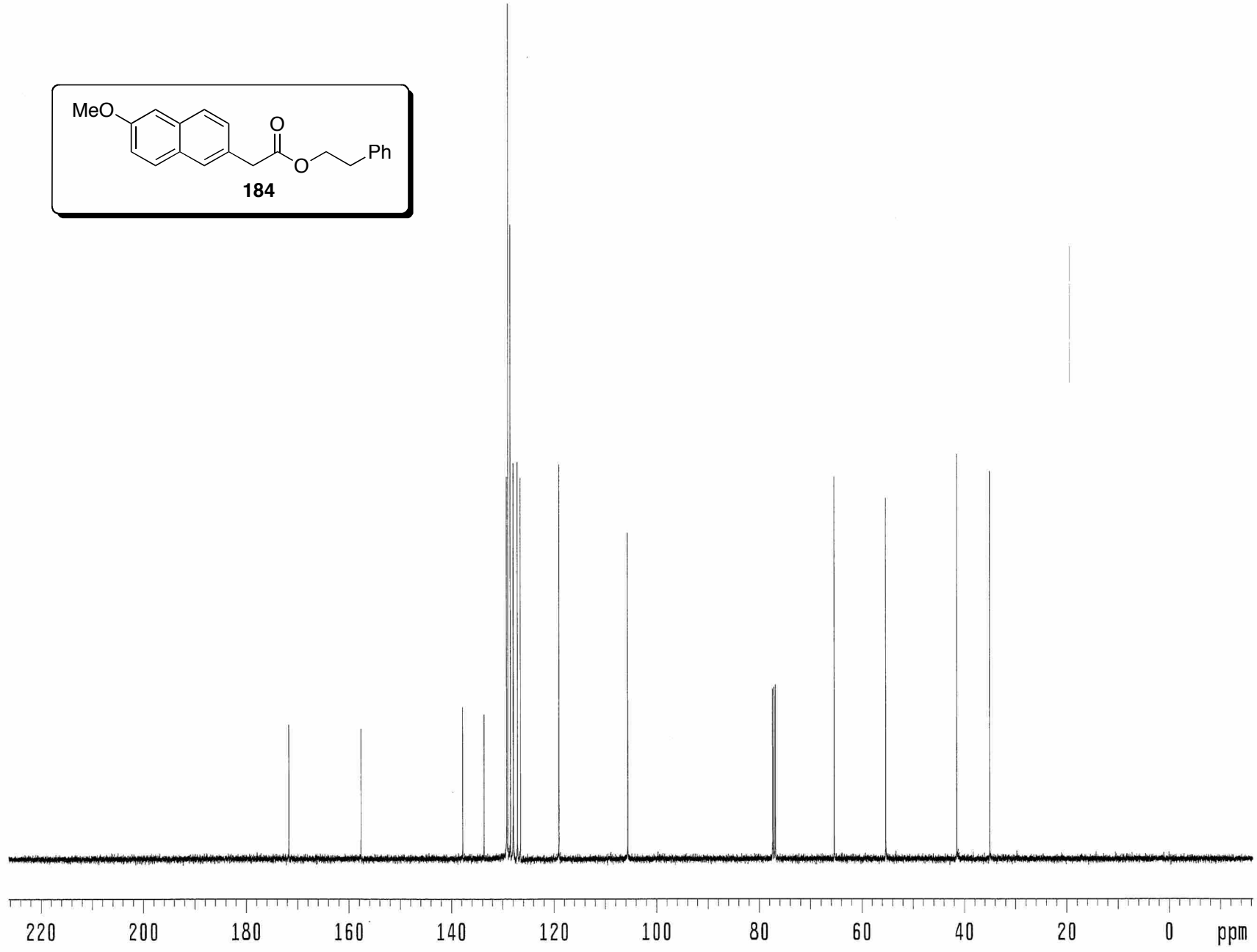
ppm


MeO
O
O
Ph
184
12
10
8
6
4
2
-0
ppm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Ph
184
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200
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160
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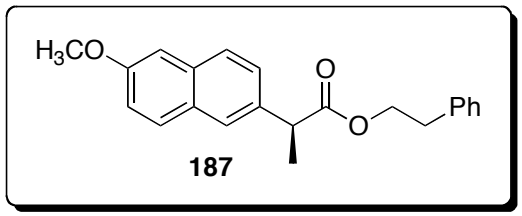
ppm



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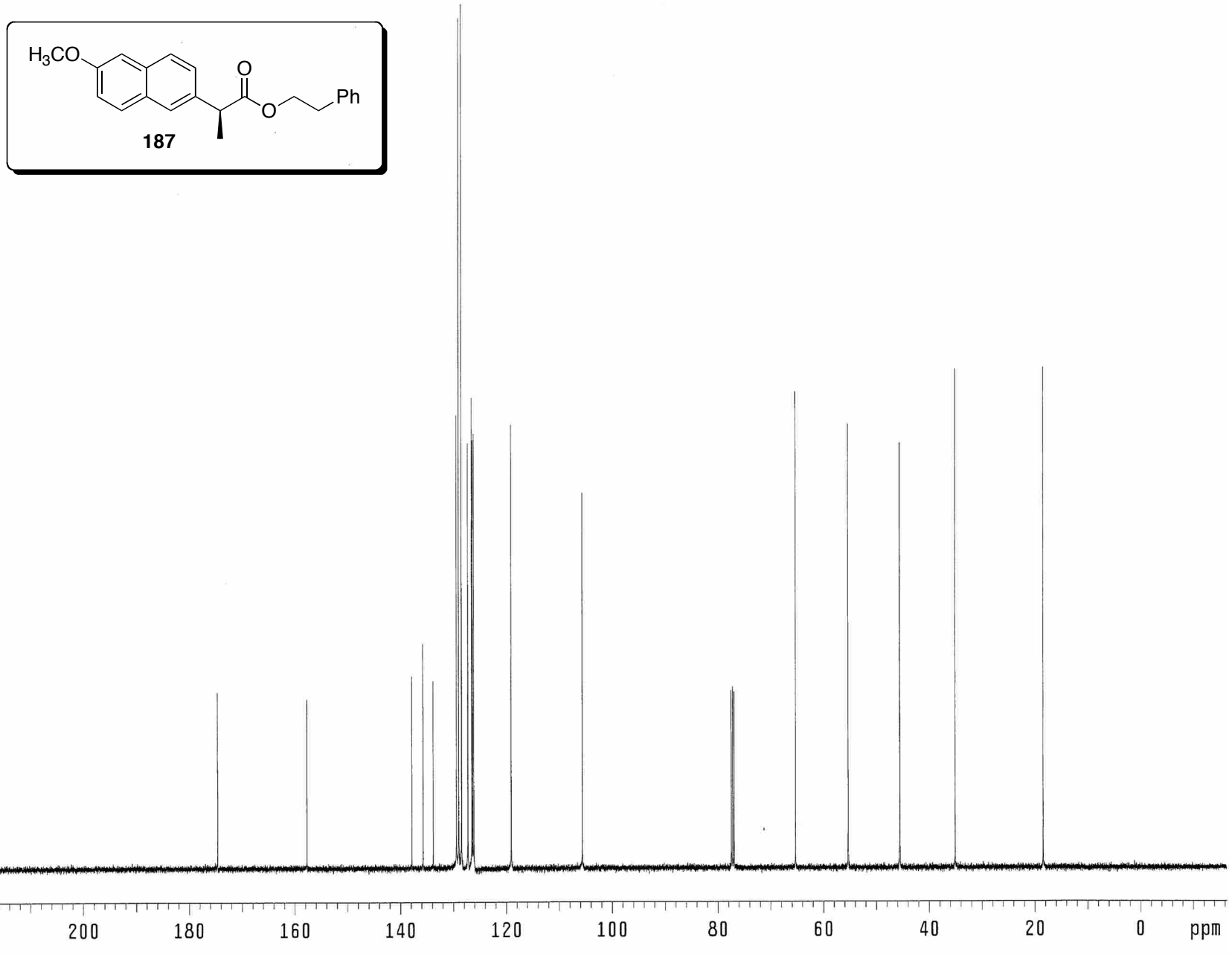
H3CO
O
O
Ph
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200
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120
100
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40
20
0
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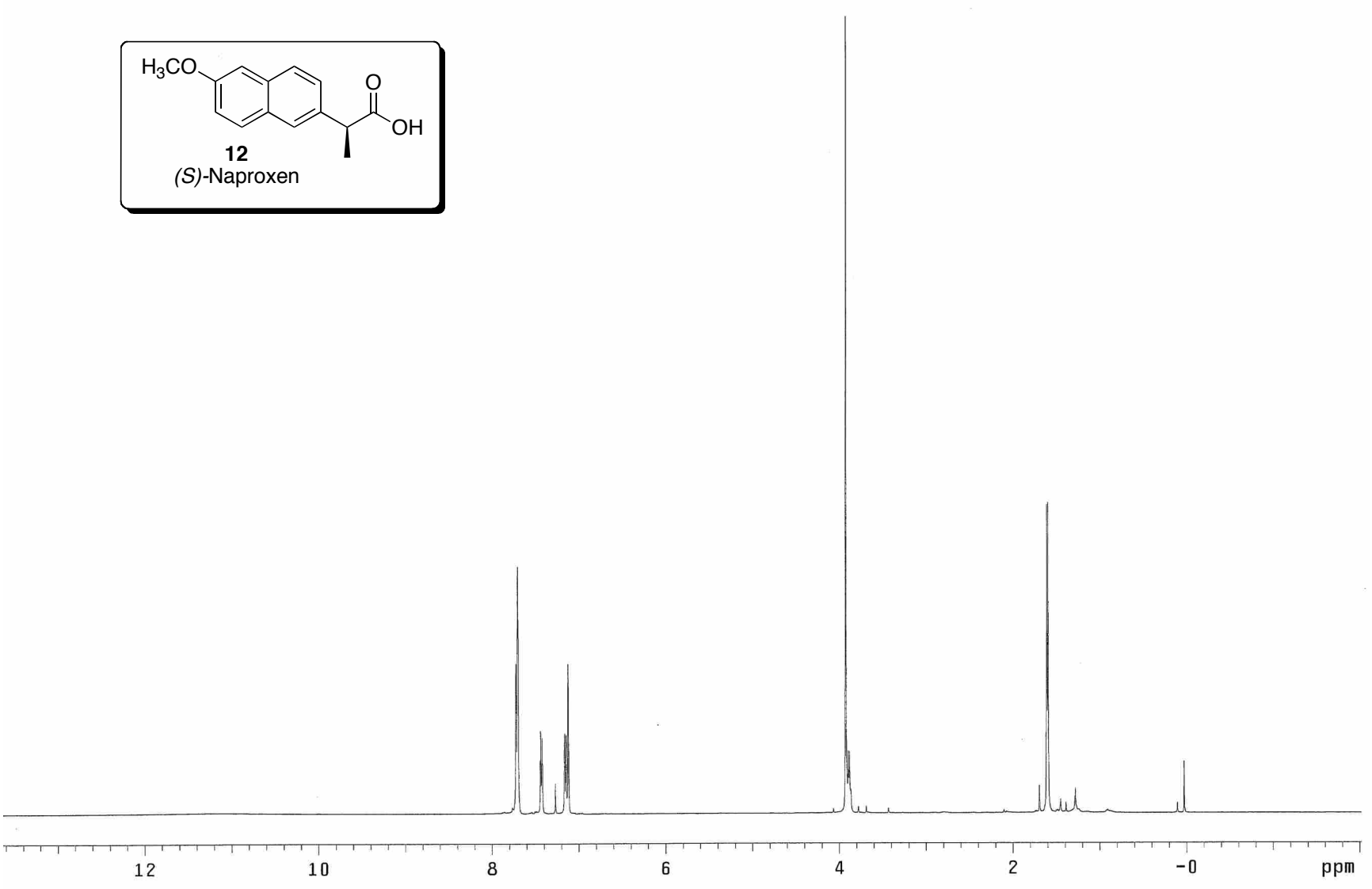
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O
OH
12
(S)-Naproxen
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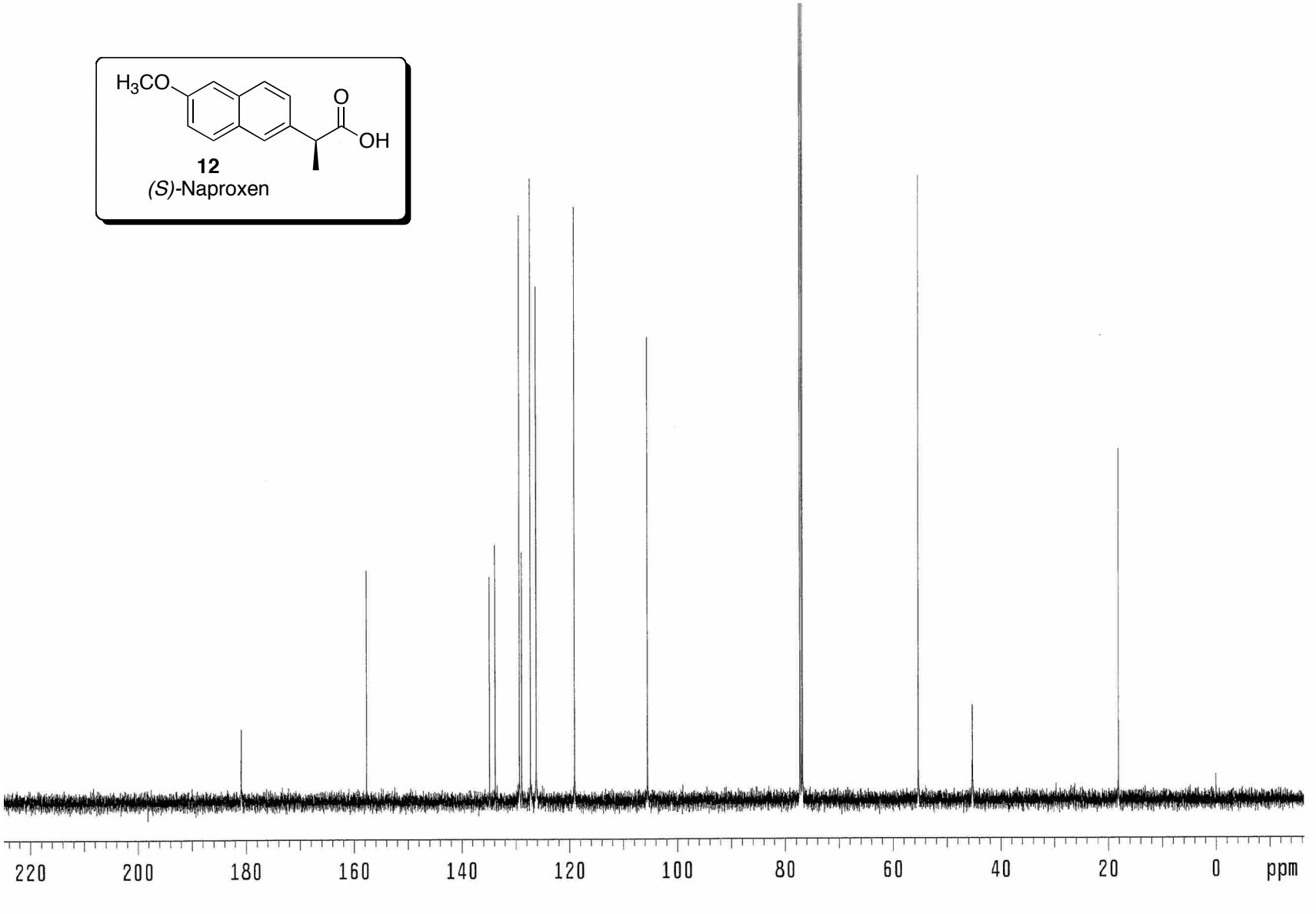
8
6
4
2
-0
ppm


H3CO
O
OH
12
(S)-Naproxen
220
200
180
160
140
120
100
80
60
40
20
0
ppm