SEQUENTIAL DOMINO ONE-POT PROCESSES: SYNTHESIS OF HETEROCYCLIC COMPOUNDS

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Department of Chemistry

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ii

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Dedicated to

My Parents

Abstract

One-pot synthetic processes are considered as convenient methods to synthesize organic molecules with high degree of complexity, without isolating intermediates. Such one-pot processes could be made possible by using one metal complex to catalyze a multiple reactions sequence or by adding various metal catalysts in a sequential manner to achieve multiple reaction sequence. These processes have proven to have several advantages over step-wise operations, as they avoid the isolation of intermediate species, thereby considerably reducing waste generation, increasing efficiency, minimizing the use of solvents, reagents, time and energy. Moreover, it was also found that in most cases the overall yields in one-pot processes are usually higher than those obtained from the corresponding step-wise operations. Herein, one-pot synthetic strategies have been developed for tetrahydroisoquinolines, cinnamate diesters, isochromenes, 2-benzoxepinones and aryl-indenoindoles.

Synthesis of Tetrahydroisoquinolines:

The 1,2,3,4-tetrahydroisoquinoline **1** core is a ubiquitous structural entity existing in numerous plant based isoquinoline alkaloid natural products exhibiting a broad spectrum of biological activities such as antitumor, anti-microbial, anti-inflammatory, anti-HIV, anti-analgesic, neurotoxins and psychoactive properties. Representative examples are salsolidine, salsolinol, arizonine, O-methylpeyoxylic acid, cherylline, latifine, Dopamine moieties include 6,7-DHBnTIQ, 3′,4′-DHBnTIQ, canadine, stepharinine, pronuciferine, erythrocarine (Figure 1).

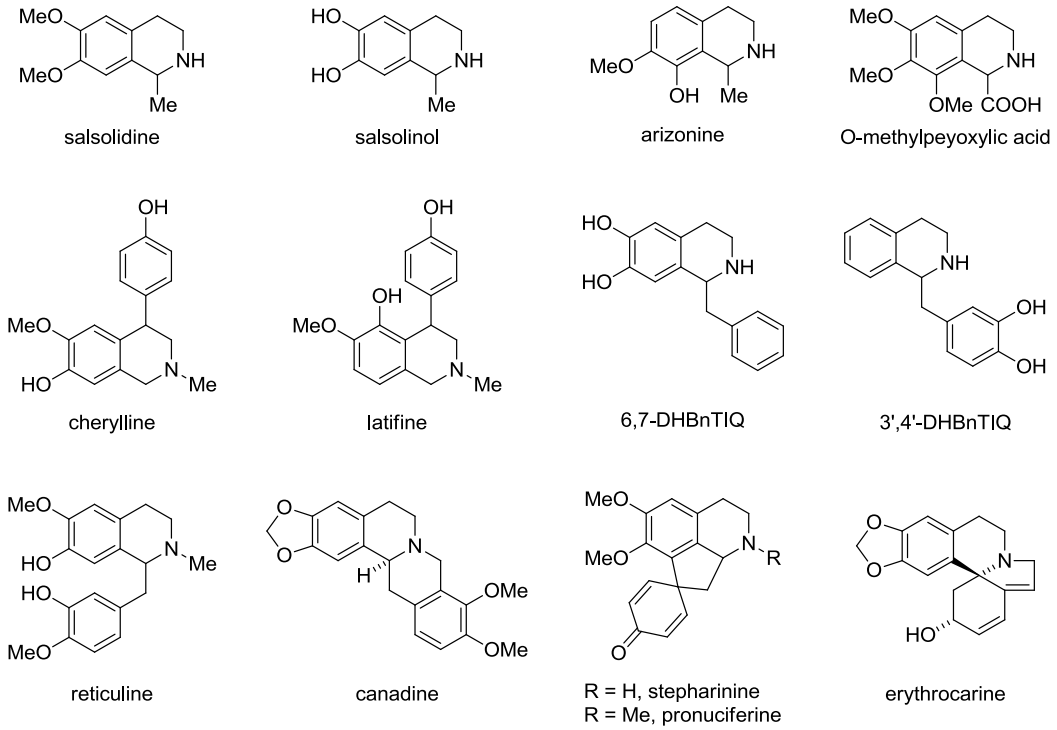
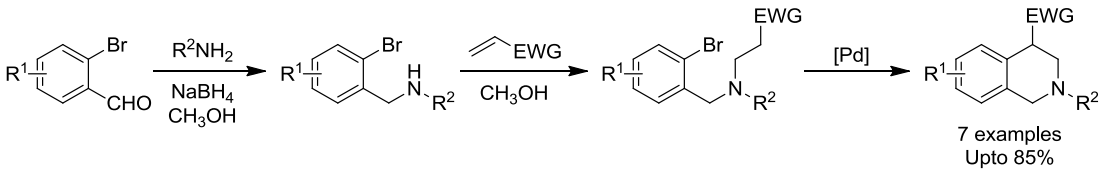


Figure 1

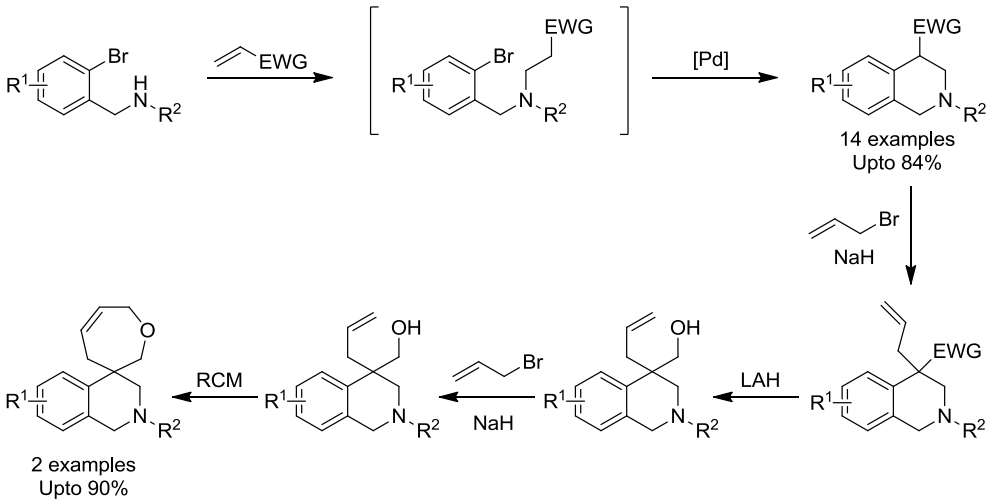
The tetrahydroisoquinoline existence in natural products having interesting biological activities made synthetic chemists pay attention to their synthesis and numerous methods were developed by different research groups. These methods include the classical Pictet-Spengler condensation, Pomeranz-Fritsch-Bobbit cyclization, Friedel-Crafts reaction, cyclization of quaternary ammonium salts and metal mediated (or metal complex catalyzed) reductions of isoquinoline derivatives. Buchwald-Hartwig α-arylation and norbornene mediated domino reactions are the recent methods reported in the literature, for the synthesis of tetrahydroisoquinolines using palladium catalysis.

With the interest to develop synthetic techniques based on transition metal catalysis, we have accomplished the concise stepwise synthesis of tetrahydroisoquinolines in good yields by using palladium catalyzed intramolecular Buchwald-Hartwig α-arylation of β-amino esters as the key step. The β-amino esters which were required for the α-arylation were achieved by simple aza-Michael addition of 2-bromobenzyl amines, which in turn were accomplished from readily available 2-bromobenzaldehydes (Scheme 1).



Scheme 1

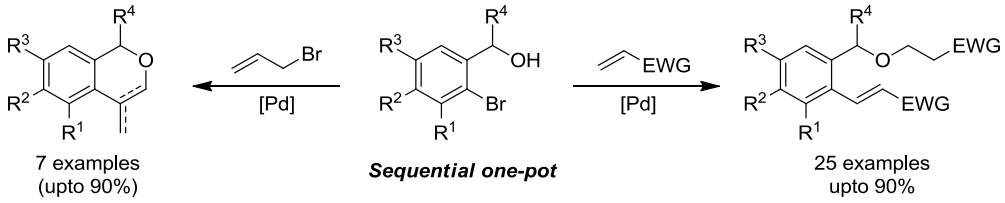
After step-wise accomplishment of tetrahydroisoquinolines, we made the method more efficient by employing a domino sequential one-pot neat aza-Michael addition followed by Buchwald-Hartwig α-arylation on secondary amines without isolating the intermediate β-amino ester. Overall, this method resulted in tetrahydroisoquinolines with yields comparable with stepwise syntheses of tetrahydroisoquinolines, where the final cyclization was conducted on the isolated β-amino ester (Scheme 2). Moreover, this method was successfully applied for the synthesis of novel aza-spirotricyclic ethers (Scheme 2). The results are explained in the chapter 1.



Scheme 2

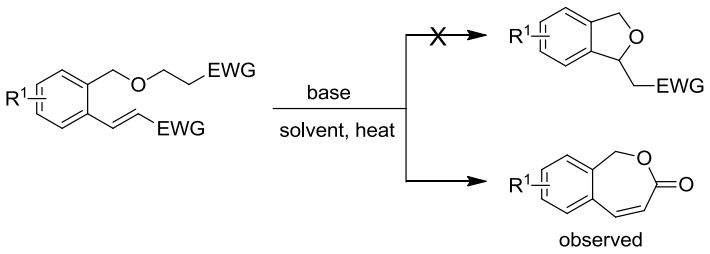
Synthesis of Cinnamate diesters, Isochromenes and 2-Benzoxepinones:

The successful one-pot accomplishment of tetrahydroisoquinoline syntheses encouraged us to develop one-pot protocols. In this regard we have developed the efficient sequential one-pot intermolecular oxy-Michael addition and intermolecular Heck coupling for the synthesis of functionalized cinnamates. Bulky *tert*-butyl acrylate was identified as a more suitable Michael acceptor for initial oxy-Michael addition as it precludes the formation of undesired cross condensed ester over simple methyl or ethyl acrylate and acrylo nitrile (where acrylo nitrile interfers with the Pd-species during the reaction and decreases it's activity). Most importantly, the current method was further extended to the sequential one-pot *o*-allylation with subsequent intramolecular Heck cyclization and successfully achieved the synthesis of isochromenes (Scheme 3).



Scheme 3

After the success of cinnamate diesters and isochromenes, the method was applied to the synthesis of 2-benzoxepinones via sequential intermolecular Heck reaction, oxy-Michael addition and intramolecular degradation. When the cinnamate was subjected to the retro-Michael addition followed by intramolecular Michael addition to form iso-benzofuran we were surprised to obtain 2-benzoxepinone as the major product (Scheme 4).



Scheme 4

Interestingly these kinds of skeletons were found to be core structures in antibiotics such as xylarinol A and xylarinol B, and in natural products like ulocladol and alterlactone which have interesting biological activities (Figure 2).

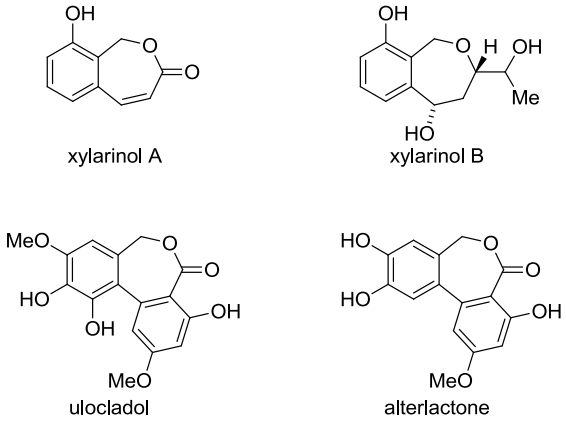
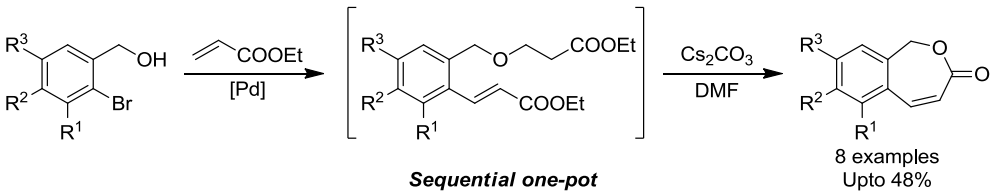


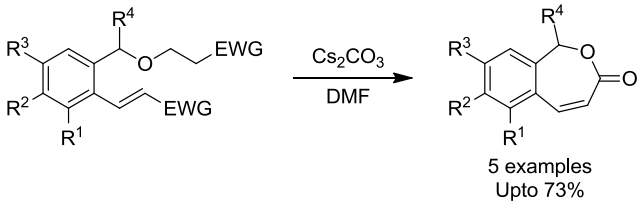
Figure 2

This observation lead us to develop the new one-pot strategy for the formation of 2-benzoxepinone derivatives directly from *ortho*-bromo benzyl alcohols involving sequential one-pot oxy-Michael addition and Heck reactions followed by degradation. This one-pot protocol for 2-benzoxepinones directly from primary *ortho*-bromo benzyl alcohols was successful only with ethyl acrylate as Michael acceptor (Scheme 5).



Scheme 5

In the case of secondary alcohols with either ethyl acrylate or tert-butyl acrylate as and primary alcohols with tert-butyl acrylate Michael acceptors, the step wise degradation protocol from the corresponding diesters was followed in order to yield respective 2-benzoxepinones (Scheme 6). The results are detailed in the chapter 2.



Scheme 6

Synthesis of Aryl-indenoindoles:

In addition to the one-pot protocols developed for tetrahydroisoquinolines and 2-benzoxepinones, we have also developed one-pot superacid mediated synthesis of novel 10-phenyl-5,10-dihydroindeno[1,2-*b*]-indoles, ubiquitous core structures of alkaloid natural products like yuechukene and borreverine. Significantly, such tetracyclic analogues were found to exhibit very good biological activities such as radical scavenging activity and anticancer activities (Figure 3).

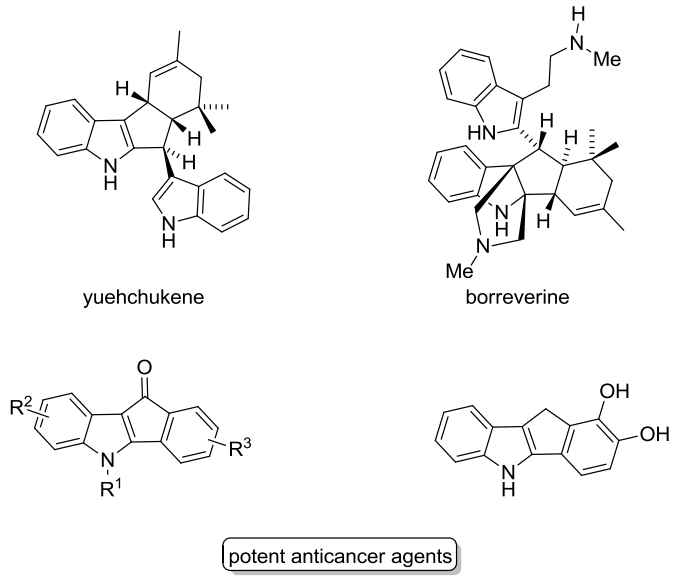
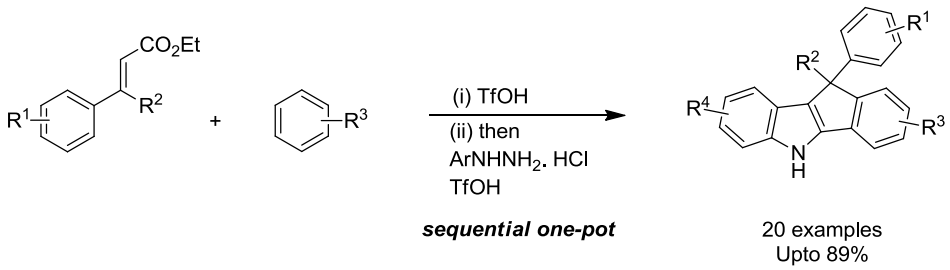


Figure 3

The entire sequential process involved a domino intermolecular Friedel-Crafts alkylation and intramolecular acylation of simple and easily accessible ethyl cinnamates to furnish the indanones, followed by a Fischer indole reaction. Interestingly, this method enabled the synthesis of various dihydroindeno[1,2-*b*]-indoles possessing tertiary and quaternary centers at the 10th position (Scheme 7). The results are explicated in the chapter 3.



Scheme 7

LIST OF ABBREVIATIONS

Ac	:	acetyl
Anal	:	analysis
Anhy	:	anhydrous
APCI	:	atmospheric pressure chemical ionization
Ar	:	aryl
aq	:	aqueous
Bn	:	benzyl
br. s	:	broad singlet
calcd	:	calculated
cm	:	centi meter
CPD	:	carbon protan decoupling
DCE	:	dichloro ethane
DCM	:	dichloro methane
dd	:	doublet of doublet
ddd	:	doublet of doublet of doublet
dt	:	doublet of triplet
DIPA	:	N,N-diisopropyl amine
DMF	:	N,N-dimethyl formamide
DMSO	:	dimethyl sulfoxide
equiv	:	equivalents
Et	:	ethyl
ESI	:	electron spray ionization
Fig.	:	figure
g	:	gram(s)
h	:	hour(s)
HR-MS	:	high resolution mass spectrum
Hz	:	Hertz

^{i}pr	:	iso propyl
IR	:	infrared
Liq	:	liquid
Lit.	:	literature
m	:	multiplet
Me	:	methyl
mg	:	milli gram(s)
MHz	:	mega hertz
min	:	minute(s)
mL	:	milli liter(s)
mmol	:	milli mole(s)
M.P	:	melting point
MS	:	molecular seives
NMR	:	Nuclear Magnetic Resonance
ph	:	phenyl
q	:	quartet
R_f	:	Retention factor
rt	:	room temperature
sept	:	septet
t	:	triplet
TEBAC	:	triethylbenzylammonium chloride
TEPA	:	triethyl phospano acetate
^{t}Bu	:	tertiary butyl
tert	:	tertiary
TFA	:	trifluroacetic acid
TfOH	:	trifluoromethanesulfonic acid
THF	:	tetrahydrofuran
TLC	:	thin layer chromatography
UV	:	ultra violet

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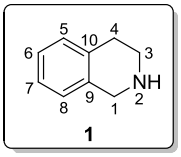
CHAPTER I

SYNTHESIS OF TETRAHYDROISOQUINOLINES

I.1 INTRODUCTION:



1

The 1,2,3,4-tetrahydroisoquinoline **1** core is a ubiquitous structural entity existing in numerous plant based isoquinoline alkaloid natural products exhibiting a broad spectrum of biological activities such as antitumor,[1] anti-microbial,[1,2] anti-inflammatory,[3] anti-HIV[4] and anti-analgesic[5] activities. Representative examples of such structures include salsolidine **2**, isolated from plants of the genus *Salsola*, an inhibitor of monoamine oxidase,[6] which upon enzymatic transformation in the presence of N-methyl-transferase furnishes N-methyl salsolidine **3**. Salsolinol **4**, a catechol isoquinoline, was detected in rat and human brain tissue samples. [7] While N-methyl salsolinol **5**, which was obtained from **4** upon the action of enzyme N-methyl-transferase, acts as neurotoxin.[7,8] Further, the natural product corypalline **6** from the plant *Papaver bracteatum* (Iranian poppy) is considered as the biosynthetic precursor of N-methylcorydaldine,[9] an alkaloid isolated from the plant *Thalictrum fendleri* and methylcorypalline **7**, isolated from the embryo of loti (*Nelumbo nucifera Gaertn*).[10] On a similar basis, arizonine **8** was obtained by chromatographic separation of *Carnegiea gigantean* extract,[11] while, isoanhaloidine **9**, isoanhalidine **10** and isoanhalamine **11** were obtained from North

American cactus *Lophophora williamsii*,[12] these compounds have been recognized as the carriers of the core structure of isoquinoline.

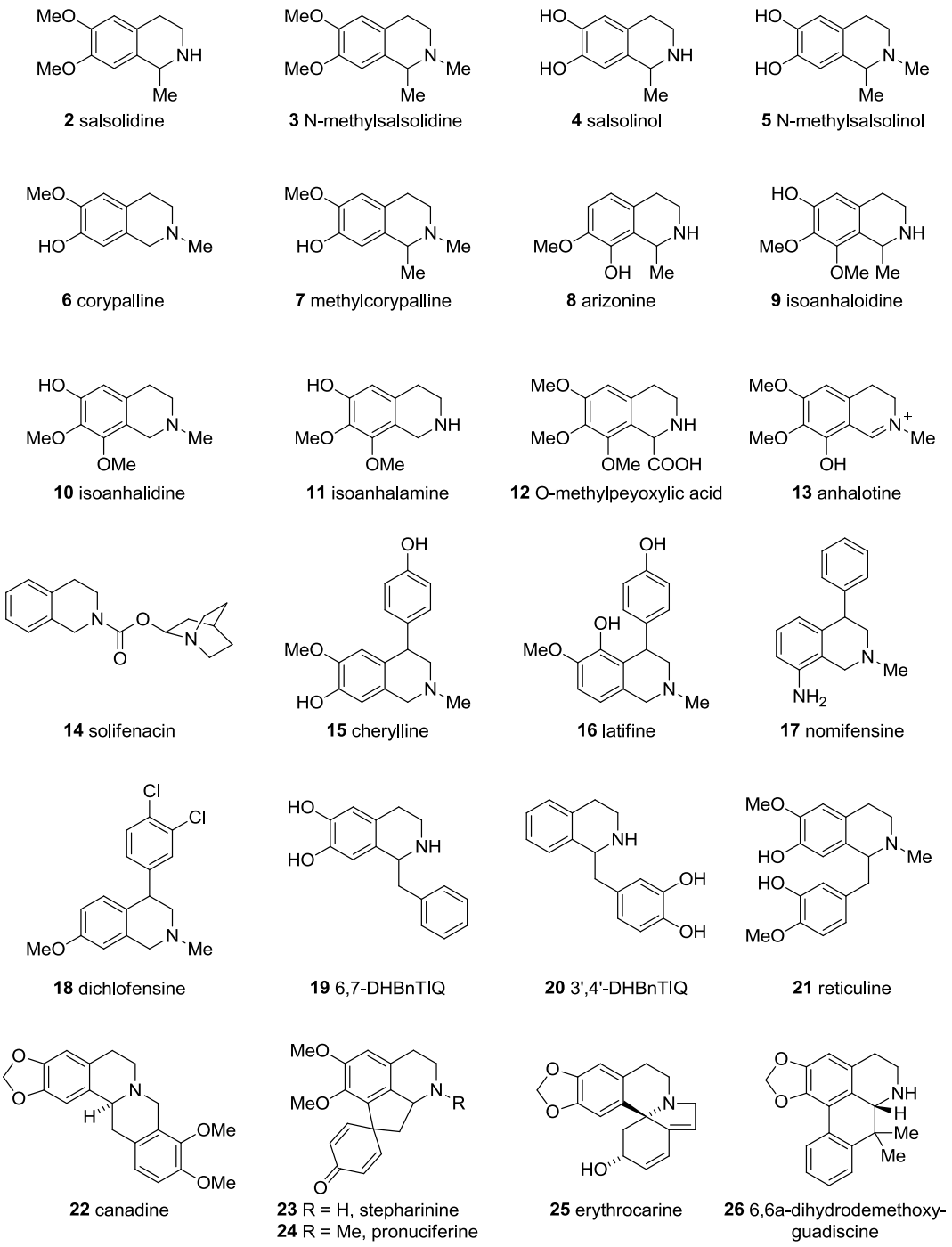


Figure I.1

The methylated form of peyoxylic acid, O-methylpeyoxylic acid **12**, was identified as a constituent of *Peyote* seeds and used as psychoactive North American entheogen.[13] Anhalotine **13** is a quaternary nitrogen containing alkaloid in *Lophophora williamsii*,[14] whereas, solifenacin **14** is a competitive cholinergic receptor antagonist and plays a critical role in the contraction of smooth muscle, thus controlling the urinary bladder smooth muscle tone.[15] Substituted saturated isoquinolines such as cherylline **15** and latifine **16**,[16,17] are phenolic Amaryllidaceae plant alkaloids isolated from several *Crinum species*, namely *Crinum latifolium* and *Crinum powelli*.[18] The similar structures namely nomifensine **17**[19] and dichlofensine **18**[20] control the central nervous system activity and reduce serotonin and dopamine up-take mechanisms. Dopamine derivatized moieties like 6,7-DHBnTIQ **19** and 3′,4′-DHBnTIQ **20** are detected in mouse brain of which **20** induces parkinsonism in mice.[21] Reticuline **21**, an opium alkaloid found in various plants such as like *Lindera aggregata*, *Annona squamosa* and *Ocotea fasciculata*,[22,23,24] possesses potent central nervous system depressing effects. The naturally occurring canadine **22** is a protoberberine class of alkaloid which blocks the calcium channel,[25] while, stepharinine **23** and pronuciferine **24** belonging to proaporphine alkaloids, have been identified as the biosynthetic precursors of aporphine,[26] a partial agonist of 5-HT1a. Erythrocarine **25** belongs to the family of widely distributed *Erythrina* plant alkaloids with interesting biological activities[27,28,29] whereas, 6,6a-dihydrodemethoxygaudiscine **26** was obtained from the extract of the stem of *Guatteriopsis friesiana*[30] (Figure I.1).

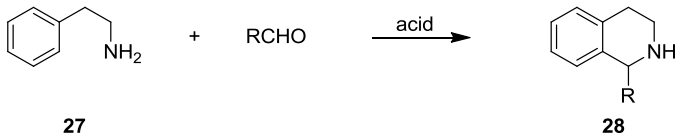
***I.2 BACKGROUND*:**

Due to the relative abundance of the tetrahydroisoquinoline core in natural products having interesting biological activities, numerous methods were reported in the literature by different research groups. Some of the notable methods include classical Pictet-Spengler condensation promoted by acid,[31] Pomeranz-Fritsch-Bobbit cyclization,[32] Friedel-Crafts reaction[33] and cyclization of quaternary ammonium salts.[34] On the other hand, reductions of isoquinoline derivatives with metals like lithium,[35] indium,[36] zinc borohydride,[37] were employed for the construction of tetrahydroisoquinolines. In addition, a reasonably good number of

methods were developed based on catalytic reductions using metal complexes of rhodium, iridium,[38] molybdenum,[39] osmium.[38] Moreover, reductions catalyzed by nickel,[40] platinum (Adam's catalyst: PtO_2),[41] and Pd-C[42] catalysts were also used for the tetrahydroisoquinoline synthesis. Also, processes like thermal cyclization,[43] biomimetic synthesis[44] and photo cyclization[45] were used to prepare tetrahydroisoquinolines. Recently, the synthesis of tetrahydroisoquinolines was accomplished using palladium catalyzed intramolecular Buchwald-Hartwig α-arylation[46] and norbornene mediated domino reactions.[47]

I.2.1 Pictet-Spengler condensation:

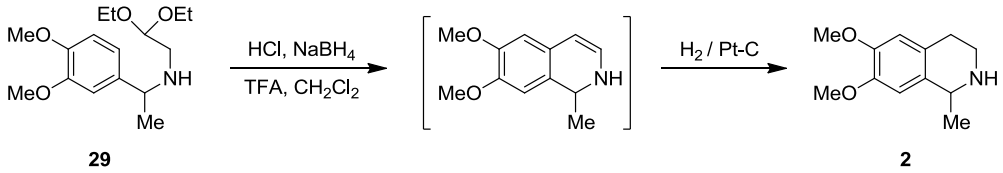
A classical and transformation was discovered by Pictet and Spengler in 1911, in which the reaction of β-aryl ethyl amine **27** with carbonyl compounds under acidic conditions leading to the formation of tetrhyadroisoquinolines **28** (Scheme I.1).



Scheme I.1

I.2.2 Pomeranz-Fritsch-Bobbit condensation:

The Pomeranz-Fritsch cyclization affords an efficient synthesis of isoquinolines, later modified by Bobbit, involving an acid catalyzed condensation of benzaldehyde with α-aminoethylacetal followed by catalytic reduction with H_2/Pt-C, which became a remarkable approach to achieve tetrahydroisoquinolines. Later, Rozwadowska et al successfully achieved the synthesis of salsolidine **2** from the diethyl acetal precursor **29** by using this Bobbit modification (Scheme I.2).

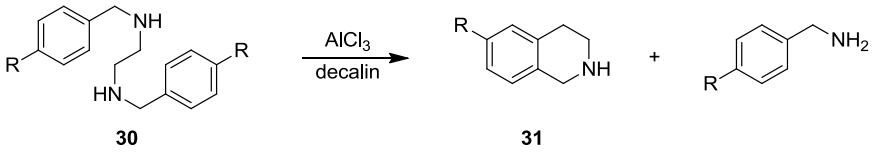


29 **2**

Scheme I.2

I.2.3 Friedel-Crafts reaction:

Yet another efficient synthesis of various tetrahydroisoquinolines **31** was proposed by Peerzada in 1997 by the Friedel-Crafts alkylation of N,N-dibenzylethylenediamines **30** in presence of the Lewis acid $AlCl_3$ (Scheme I.3).

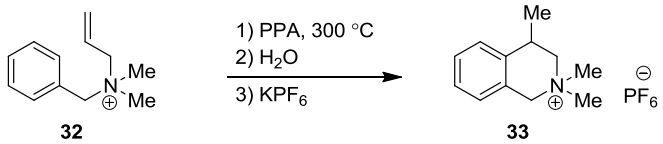


30 **31**

Scheme I.3

I.2.4 Cyclization of quaternary ammonium salts:

Allyl benzyl dimethyl quaternary ammonium salt **32** underwent *exo-trig* cyclization upon treatment with polyphosphoric acid to furnish tetrahydroisoquinoline salt **33** in good yield (Scheme I.4).

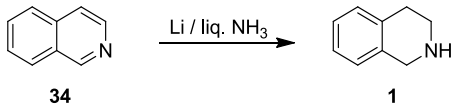


32 **33**

Scheme I.4

I.2.5 Reduction by lithium metal:

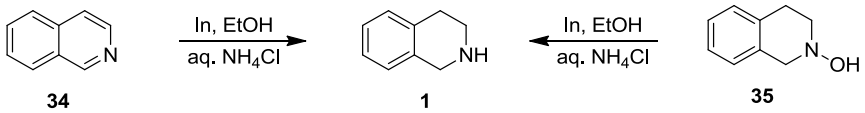
The research groups of Costanzo and Remers reported the reduction of isoquinoline **34** with lithium in liquid ammonia to furnish the tetrahydroisoquinoline **1**, albeit in poor yields (Scheme I.5).



Scheme I.5

I.2.6 Indium metal mediated reduction:

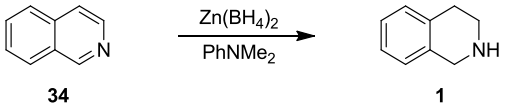
The co-workers of Moody[36a] and Goti[36b] developed indium metal mediated reductions of isoquinoline **34** and isoquinoline hydroxylamine **35** to tetrahydroisoquinoline **1**, in the presence of aqueous ammonium chloride and ethanol as solvent (Scheme I.6).



Scheme I.6

I.2.7 Reduction with zinc borohydride:

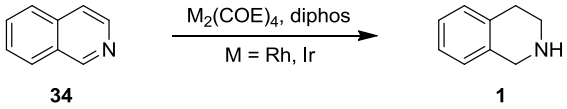
Ranu et al in 1998 developed a convenient and simple protocol for the reduction of isoquinoline **34** to 1,2,3,4-tetrahydroisoquinoline **1** in the presence of a catalytic amount of N,N-dimethyl aniline under sonication conditions (Scheme I.7).



Scheme I.7

I.2.8 Reduction with complexes of rhodium and iridium:

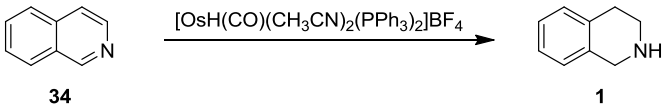
The research group of Rosales applied rhodium and iridium catalysis for regioselective isoquinoline **34** to tetrahydroisoquinoline **1** (Scheme I.8).



Scheme I.8

I.2.9 Reduction with osmium complex:

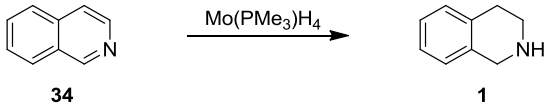
Rosales group yet again developed another reduction protocol to form tetrahydroisoquinoline **1** from isoquinoline **34** by osmium metal complex (Scheme I.9)



Scheme I.9

I.2.10 Reduction with tris-trimethylphosphinomolybdenumhydride:

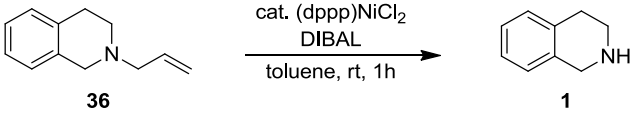
Parkin et al in 2008 reported the novel molybdenum catalysis for the conversion of isoquinoline **34** to tetrahydroisoquinoline **1** by means of co-ordination of the metal with isoquinoline followed by the reduction to tetrahydroisoquinoline **1** (Scheme I.10).



Scheme I.10

I.2.11 Nickel catalyzed deallylation:

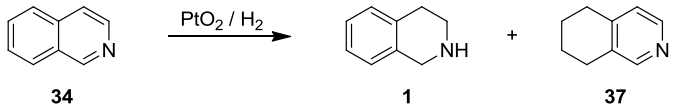
N-allyl tetrahydroisoquinoline **36** was subjected to undergo N-deallylation by nickel catalyst in the presence of DIBAL-H as reducing agent to result in another effective method to produce the tetrahydroisoquinoline **1** (Scheme I.11).



Scheme I.11

I.2.12 Reduction with Adams catalyst:

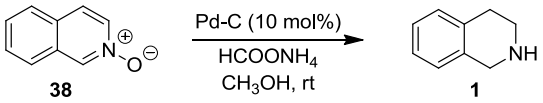
Reduction of isoquinoline **34** in the presence of PtO_2 was non selective and led to the formation of 5,6,7,8-tetrahydroisoquinoline **37** along with the 1,2,3,4-tetrahydroisoquinoline **1** (Scheme I.12).



Scheme I.12

I.2.13 Reduction of isoquinoline-N-oxide:

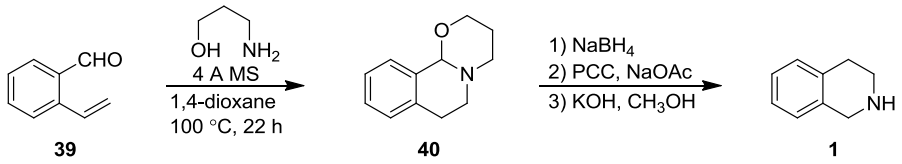
Zacharie et al reported a mild reduction procedure for the formation of tetrahydroisoquinoline **1** from quinolinium-N-oxide **38** by using palladium along with ammonium formate (Scheme I.13).



Scheme I.13

I.2.14 Thermal cyclization:

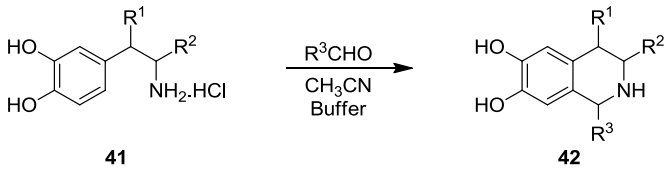
2-vinylbenzaldehyde **39** and 3-aminopropanol underwent double cyclization reaction thermally and furnished the tetrahydroisoquinoline **1** via the intermediate **40** (Scheme I.14). The research group of Asao applied this concept in 2008, towards the synthesis of natural product cryptostylline **II**.



Scheme I.14

I.2.15 Biomimetic synthesis from β-aryl ethylamines:

Hailes et al recently reported a novel phosphate buffer mediated one-pot synthesis of tetrahydroisoquinolines **42** under mild reaction conditions starting from dopamine derivatives **41** (Scheme I.15).

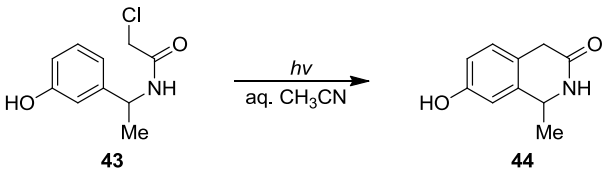


41 **42**

Scheme I.15

I.2.16 Photo-cyclization:

Under photo chemical conditions N-chloroacetylbenzylamine **43** in aqueous acetonitrile transformed into the corresponding cyclic amide **44** (Scheme I.16).

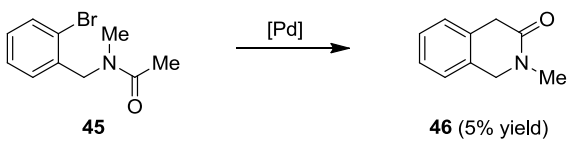


43 **44**

Scheme I.16

I.2.17 Intramolecular Buchwald-Hartwig α-arylation:

Intramolecular α-arylation of acyclic amide **45** to the cyclic amide **46**, was achieved by Hartwig and group in 1998, albeit in poor yield. This might be due to the weak acidic methyl proton of an acetamide group (Scheme I.17).

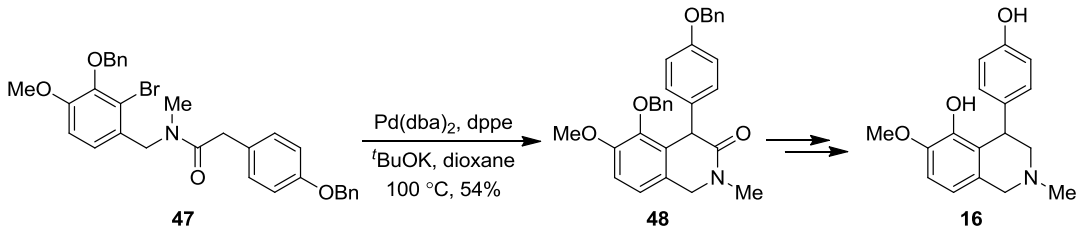


45 **46** (5% yield)

Scheme I.17

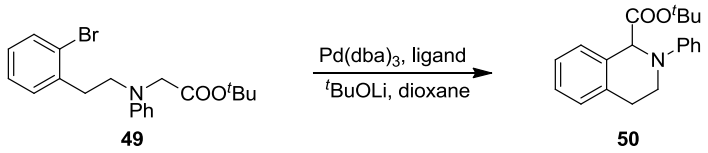
In the sequence of designing strategies using palladium, Honda et al in 2001 reported the synthesis of 4-arylisoquinoline **48** via Pd-catalyzed intramolecular α-

arylation as key transformation from a relatively more acidic methylene amide precursor **47** (Scheme I.18). The advanced intermediate **48** was used for the total synthesis of alkaloid natural product latifine **16**.



Scheme I.18

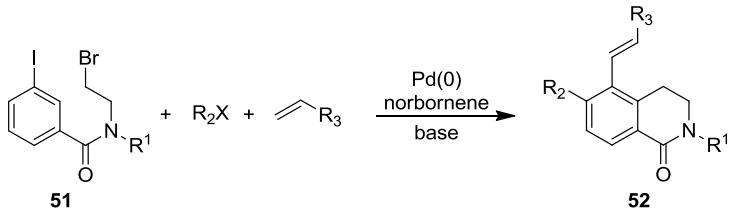
Buchwald et al in 2002 reported a similar type of palladium catalyzed α-arylation on α-amino ester precursor **49** and achieved the corresponding tetrahydroisoquinoline derivative **50** in very good yield (Scheme I.19).



Scheme I.19

I.2.18 Norbornene mediated approach:

The research group of Mark Lautens in 2008, reported the palladium catalyzed norbornene mediated domino *ortho*-alkylation/alkenylation on the amide precursors **51** to form the functionalized tetrahydroisoquinolines **52** in excellent yields (Scheme I.20).



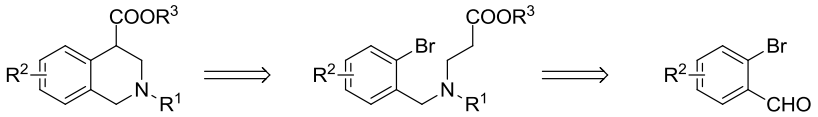
Scheme I.20

With the understanding of the science of synthesis of tetrahydroisoquinolines, and interest to develop synthetic methods based on transition metal catalysis, we have aimed at the synthesis of tetrahydroisoquinolines using palladium catalyzed intramolecular Buchwald-Hartwig α-arylation[48] as the key step. The strategy proposed involved a step-wise as well as the sequential domino one-pot method for the efficient synthesis of tetrahydroisoquinolines and the details are presented in the results and discussion section of this chapter.

I.3 RESULTS AND DISCUSSION:

I.3.1 Synthesis of Tetrahydroisoquinolines (Stepwise Approach):

In the designed retro synthetic analysis, we envisioned that the targeted 1,2,3,4-tetrahydrisoquinolines **56** could be achieved by Pd-mediated intramolecular α-arylation of β-amino esters **55**. The β-amino esters **55**, which in turn could be easily prepared from the readily available 2-bromobenzaldehydes **53** via reductive amination and aza-Michael addition **54** protocol (Scheme I.21).

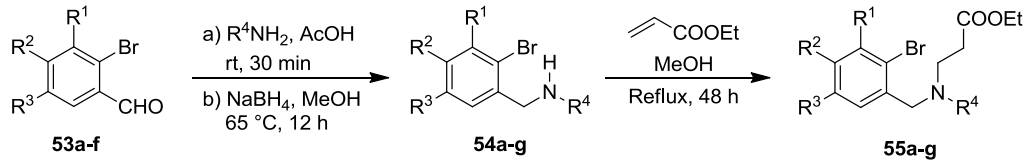


56 **55** **53**

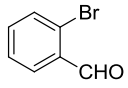
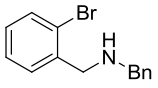
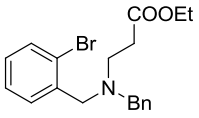
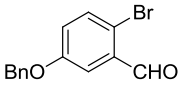
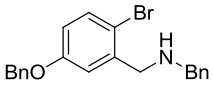
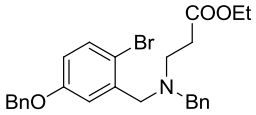
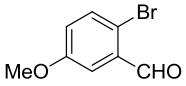
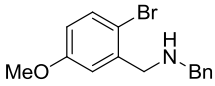
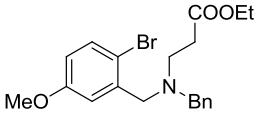
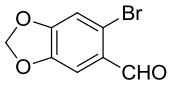
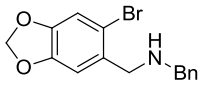
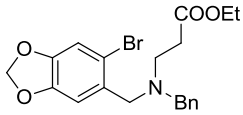
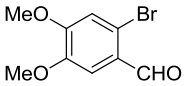
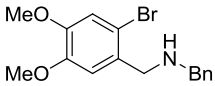
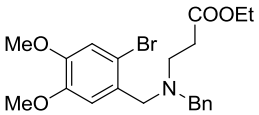
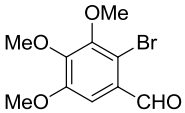
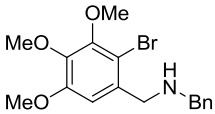
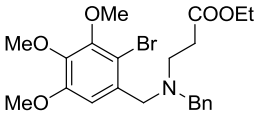
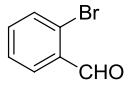
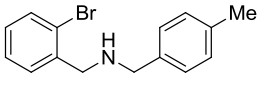
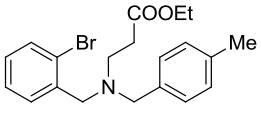
Scheme I.21

Thus, the synthetic sequence began with the preparation of 2-bromobenzaldehydes. Except for the 2-bromobenzaldehyde **53a**, all the other *ortho*-bromobenzaldehydes **53b–53f** were prepared using the literature reported standard bromination conditions.[49]

Table I.1: Synthesis of β-aminoesters **55a–55g** via secondary amines **54a–54g**.[a]



53a-f **54a-g** **55a-g**

 **53a**	 **54a** (94%)	 **55a** (88%)
 **53b**	 **54b** (74%)	 **55b** (90%)
 **53c**	 **54c** (93%)	 **55c** (86%)
 **53d**	 **54d** (93%)	 **55d** (93%)
 **53e**	 **54e** (91%)	 **55e** (95%)
 **53f**	 **54f** (91%)	 **55f** (92%)
 **53a**	 **54g** (87%)	 **55g** (84%)

[a] isolated yields of the chromatographically pure products

The 2-bromobenzaldehydes **53a–53f** were subjected for reductive amination with benzylamine/4-methylbenzylamine, in refluxing methanol and in the presence of a catalytic amount of acetic acid followed by portioned addition of sodium borohydride, furnished the secondary amines **54a–54g** in good to excellent yields

(74–94%, Table I.1). The formation and structure of the reductive amine **54** was evident from the spectral data of **54a**. The absence of an absorption band due to carbonyl stretching of aldehyde group and the presence of a broad absorption band at 3334 cm^{-1} due to the N–H stretching in the IR spectrum indicated the formation of the secondary amine **54a**. Aza-Michael addition reaction of secondary amines **54a–54g** with the Michael acceptor ethyl acrylate in refluxing methanol furnished the corresponding β-aminoesters **55a–55g** in excellent yields (84–95%, Table I.1).[50]

In the ^{1}H-NMR spectrum (Figure I.2.1), the absence of the aldehydic proton resonance, the presence of a doublet at δ 7.58 resulting from one aromatic proton, a multiplet in the region δ 7.48–7.24 due to seven aromatic protons, a doublet of doublet at δ 7.16 due to one aromatic proton, two singlets at δ 3.93 and 3.84 for the two benzylic methylene groups and one broad singlet at δ 1.91 ppm for one proton attached to the nitrogen elucidated the structure of the secondary amine **54a**. In addition, the 12 lines in ^{13}C-NMR spectrum (Figure I.2.2), showing the presence of three quaternary carbon resonances at δ 140.0, 139.1 and 124.0 due to three aromatic carbons, nine aromatic methine carbons at δ 132.8, 130.4, 128.6, 128.4, 128.2, 127.4 and 127.0 & two methylenes at 53.1 and 53.0 ppm confirmed the structure of the secondary amine **54a**.

Aza-Michael addition of secondary amines **54a–54g** with the Michael acceptor ethyl acrylate in refluxing methanol furnished the corresponding β-aminoesters **55a–55g** in excellent yields (84–95%, Table 1).[51] The β-aminoesters **55** were confirmed from the spectral data analysis of **55a**. The absence of the stretching absorption band due to N–H group and presence of the strong absorption band at 1731 cm^{-1} due to the C=O stretching frequency of the ester group, in the IR spectrum indicated the formation of the β-aminoester **55a**. In the ^{1}H-NMR spectrum (Figure I.3.1), absence of the N–H proton resonance, the presence of two doublet of doublets at δ 7.48 and 7.40 due to two aromatic protons, a multiplet in the region δ 7.30–7.08 account for the six aromatic protons, a doublet of doublet of doublet at δ

6.99 due to one aromatic proton, a quartet at δ 3.99 due to two protons of O-methylene, two singlets at δ 3.61 and 3.54 for two N-methylene

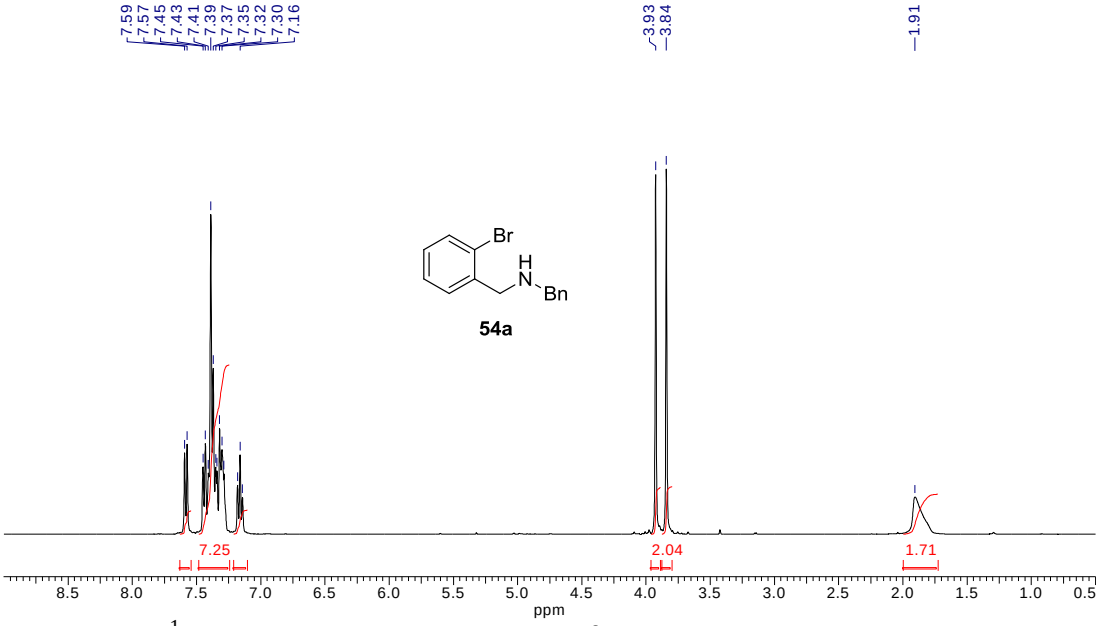


Figure I.2.1: ^{1}H-NMR (400 MHz) spectrum of **54a** in $CDCl_3$

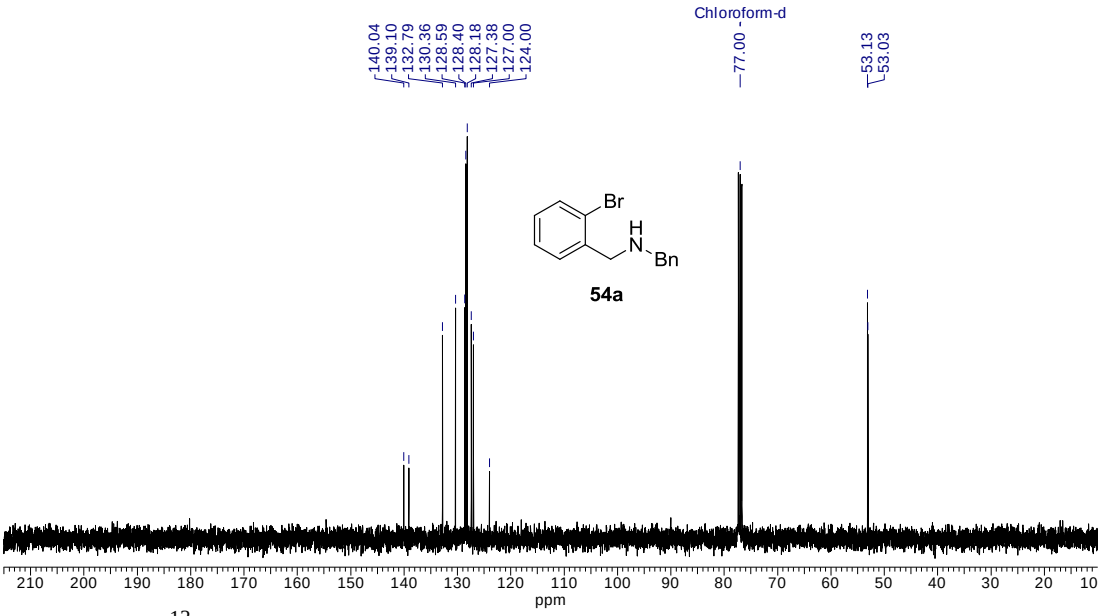


Figure I.2.2: ^{13}C NMR (100 MHz) spectrum of **54a** in $CDCl_3$

groups, two triplets at δ 2.76 and 2.43 for two methylene groups, and one triplet at δ 1.11 ppm for three protons of the methyl group illustrated the structure of the β-aminoester **55a**. In the 17 lines ^{13}C-NMR spectrum (Figure I.3.2), the presence of

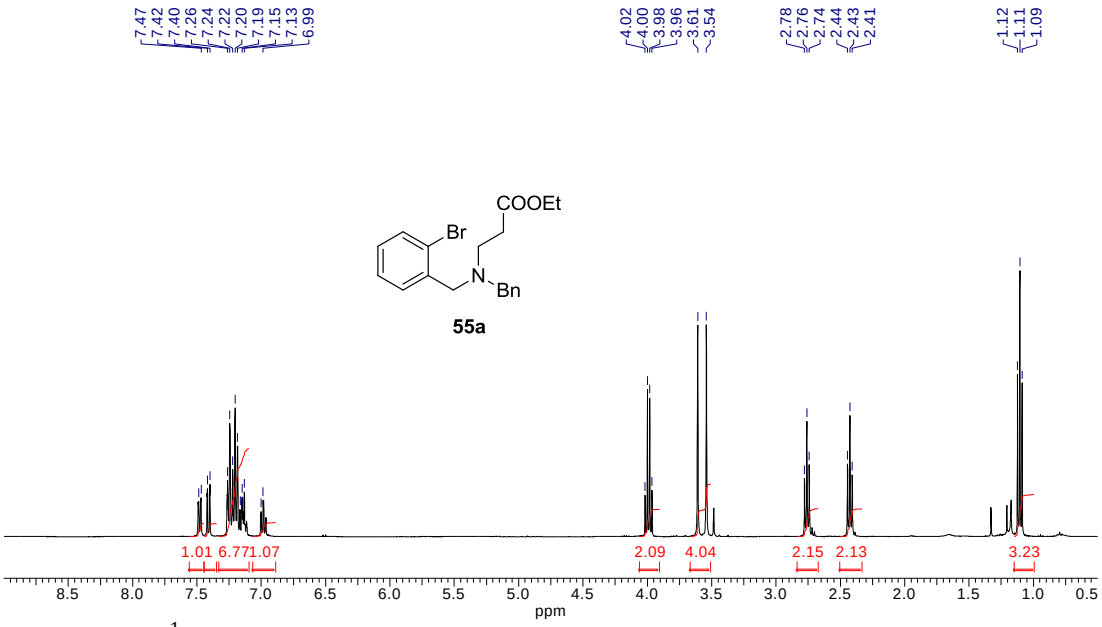


Figure I.3.1: ^{1}H-NMR (400 MHz) spectrum of **55a** in $CDCl_3$

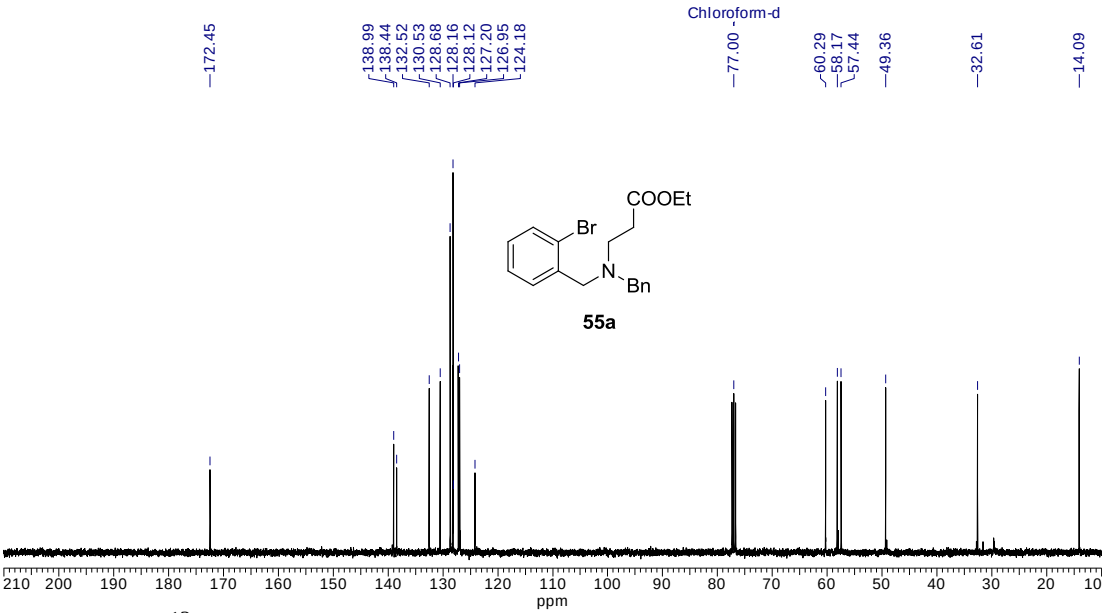


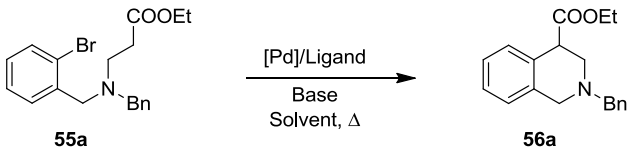
Figure I.3.2: ^{13}C NMR (100 MHz) spectrum of **55a** in $CDCl_3$

one quaternary carbon resonance at δ 172.4 due to one ester carbonyl, and three quaternary carbon resonances at 139.0, 138.4 and 124.2 and the three aromatic carbons, respectively, nine aromatic methane carbon atoms at δ 132.5, 130.5, 128.7, 128.2, 128.1, 127.2 & 126.9 and five methylenes at δ 60.3, 58.2, 57.4, 49.4 and 32.6 and a methyl at δ 14.1 ppm confirmed the structure of β-aminoester **55a**.

The β-aminoesters **55a–55g**, the key intramolecular Buchwald-Hartwig α-arylation of the ester **55a** was explored under different set of reaction conditions and the results are summarized in Table I.2. Therefore the treatment of the aminoester **55a** with $Pd(dba)_2$ (5 mol%) in the presence of N-[2'-(dicyclohexylphosphino)-1,1'-biphenyl-2-yl]-N,N-dimethylamine ligand (10 mol%) with NaHMDS (4 equiv) as base in refluxing THF, failed to furnish the product **56a**, and led to the recovery of starting material **55a** (entry 1, Table I.2). Upon replacing the base NaHMDS with ^{t}BuOK (4 equiv) and without altering the catalyst, ligand and solvent parameters, led to the isolation of starting material **55a** (entry 2, Table I.2). On the other hand, changing the ligand to PPh_3 (10 mol% or 20 mol%), use of different bases such as ^{t}BuOK (4 equiv) and Cs_2CO_3 (2 equiv), in DMF at 80 °C for a prolonged duration of 24 h, identical outcome was observed (entries 3–5, Table I.2). The reaction under microwave irradiation using toluene as solvent at 70 °C for 1 h also failed to furnish the product (entry 6, Table I.2). Interestingly, increasing the temperature and time to 110 °C and 3 h, respectively, afforded the expected product **56a** in a moderate yield of 40% (entry 7, Table I.2). The use of K_2CO_3 in toluene at 70 °C for 24 h yielded no product (entry 8, Table I.2), however, at an elevated temperature and increased time gave the isoquinoline product **56a**, albeit, in moderate yield 43% (entry 9, Table I.2). Interestingly, the reaction with K_3PO_4 as the base in hot toluene afforded the isoquinoline product **56a** in 35% yield along with acid resulting from the hydrolysis of the ester, (entry 10, Table I.2). On the other hand, use of $Pd(OAc)_2$/BINAP as a catalyst in combination with ^{t}BuOK in anhydrous toluene and use of $Pd(OAc)_2/PPh_3$ with ^{t}BuOK/NaHMDS in anhydrous THF were unsuccessful and produced the corresponding acid, which might have resulted from the saponification of the ester **55c** (entries 11–13, Table I.2). The generation of the

acid was however not clear as it was unlikely to form during neutral workup. Significant improvement in the yield of product **56a** was observed, when the reaction was performed with Cs_2CO_3 in toluene at 120 °C (entry 14, Table I.2). Gratifyingly, 10 mol% of the catalyst $Pd(OAc)_2$ and 20 mol% of the ligand PPh_3, in the presence of Cs_2CO_3 at 80 °C for 24 h, furnished the intramolecular α-arylated tetrahydroisoquinoline product **56a** in very good yield 82% (entry 15, Table I.2). Furthermore, the use of 10 mol% of $Pd[PPh_3]_4$, Cs_2CO_3 (2 equiv) in toluene at 80 °C for 24 h, afforded the product **56a** in good yield 68% (entry 16, Table I.2).

Table I.2: Optimization of reaction conditions for the synthesis of 1,2,3,4-tetrahydroisoquinoline **56a**.



Entry[a]	[Pd] (mol%)	Ligand (mol%)	Solvent	Base (equiv)	Temp (°C)	Time (h)	yield **56a** (%)[b]
1	$Pd(dba)_2$ (5)	L[c] (10)	THF	NaHMDS (4)	65	12	0
2	$Pd(dba)_2$ (5)	L[c] (10)	THF	^{t}BuOK (4)	65	12	0
3	$Pd(dba)_2$ (5)	PPh_3 (10)	DMF	^{t}BuOK (4)	80	24	0
4	$Pd(dba)_2$ (5)	PPh_3 (10)	DMF	Cs_2CO_3 (2)	80	24	0
5	$Pd(dba)_2$ (5)	PPh_3 (20)	DMF	Cs_2CO_3 (2)	80	24	0
6	$Pd(OAc)_2$ (5)	PPh_3 (10)	toluene	Cs_2CO_3 (3)	70 (μw)	1	0
7	$Pd(OAc)_2$ (5)	PPh_3 (10)	toluene	Cs_2CO_3 (3)	110 (μw)	3	40

8	$Pd(OAc)_2$ (5)	PPh_3 (10)	toluene	K_2CO_3 (4)	70	24	0
9	$Pd(OAc)_2$ (5)	PPh_3 (10)	toluene	K_2CO_3 (4)	110	48	43
10	$Pd(OAc)_2$ (5)	PPh_3 (20)	toluene	K_3PO_4 (2)	80	24	35[d]
11	$Pd(OAc)_2$ (5)	BINAP (10)	toluene	^{t}BuOK (3)	120	24	–[d]
12	$Pd(OAc)_2$ (5)	PPh_3 (10)	THF	^{t}BuOK (4)	65	24	–[d]
13	$Pd(OAc)_2$ (5)	PPh_3 (10)	THF	NaHMDS (4)	65	24	–[d]
14	$Pd(OAc)_2$ (5)	PPh_3 (10)	toluene	Cs_2CO_3 (2)	120	32	61
15	**$Pd(OAc)_2$ (10)**	**PPh_3 (20)**	**toluene**	**Cs_2CO_3 (2)**	**80**	**24**	**82**
16	$Pd[PPh_3]_4$ (10)	No ligand	toluene	Cs_2CO_3 (2)	80	24	68

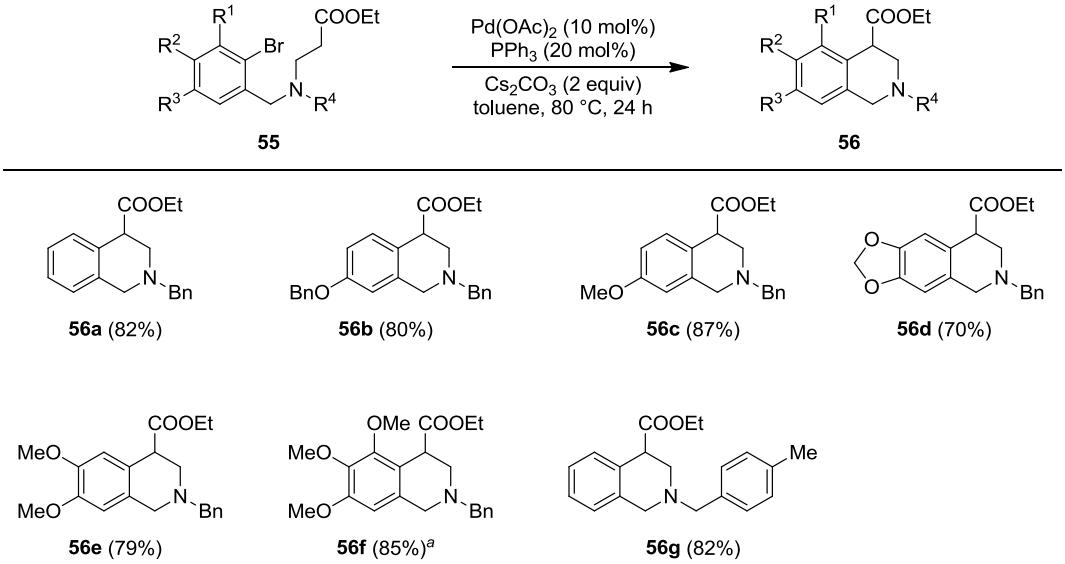
[a] Unless otherwise noted all the reactions were carried out under anhydrous and inert atmospheric conditions. [b] Isolated yields of chromatographically pure products. [c] N-[2'-(Dicyclohexylphosphino)-1,1'-biphenyl-2-yl]-N,N-dimethylamine was used as the ligand. [d] Corresponding acid resulting from the hydrolysis of the ester is isolated.

Out of all conditions from the Table I.2, the conditions of entry 15 were the best; therefore, these conditions were applied on other β-aminoesters **55b–55g** to check the scope and generality of the method. The method was found to be successful on all the esters **55** and yielded the products **56b–56g** containing simple to electron rich bromoaryl moieties, in very good yields (70–87%), as summarized in the Table I.3.

The presence of the strong absorption band at 1730 cm^{-1} due to the C=O stretch of the ester group in the IR spectrum indicated the formation of the 1,2,3,4–tetrahydroisoquinoline **56a**. In the ^{1}H-NMR spectrum (Figure I.4.1), the

presence of a multiplet in the region δ 7.31–7.05 due to eight aromatic protons, one doublet of doublet at δ 6.95 due to one aromatic proton, a multiplet in the region δ 4.15–3.98 due to two protons of the O-methylene group, one doublet of doublet at δ 3.77 due to one methine proton attached to carboxylic ester, four doublets at δ 3.70, 3.64, 3.58 and 3.53 for four protons of two N-methylene groups, two doublet of

Table I.3: Scope and applicability of Buchwald-Hartwig α-arylation on β-amino esters **55b–55g**.



[a] yield is based on the recovery of the starting material

doublets at δ 3.09 and 2.77 for two protons of methylene group and one triplet at δ 1.12 ppm due to three protons of the methyl group elucidated the structure of 1,2,3,4-tetrahydroisoquinoline **56a**. In the 17 lines from the ^{13}C-NMR spectrum (Figure I.4.2), the presence of a quaternary carbon resonance at δ 173.1 due to the ester carbonyl, three quaternary carbon resonances at 138.0, 135.1 and 131.5 for the three aromatic carbons, respectively, ten aromatic methines at δ 129.2, 129.0, 128.2, 127.2, 126.8, 126.6, 126.2 and 45.4, four methylene carbons at δ 62.2, 60.8, 56.0 and 52.9 and a methyl at δ 14.1 ppm confirmed the structure of 1,2,3,4-tetrahydroisoquinoline **56a**.

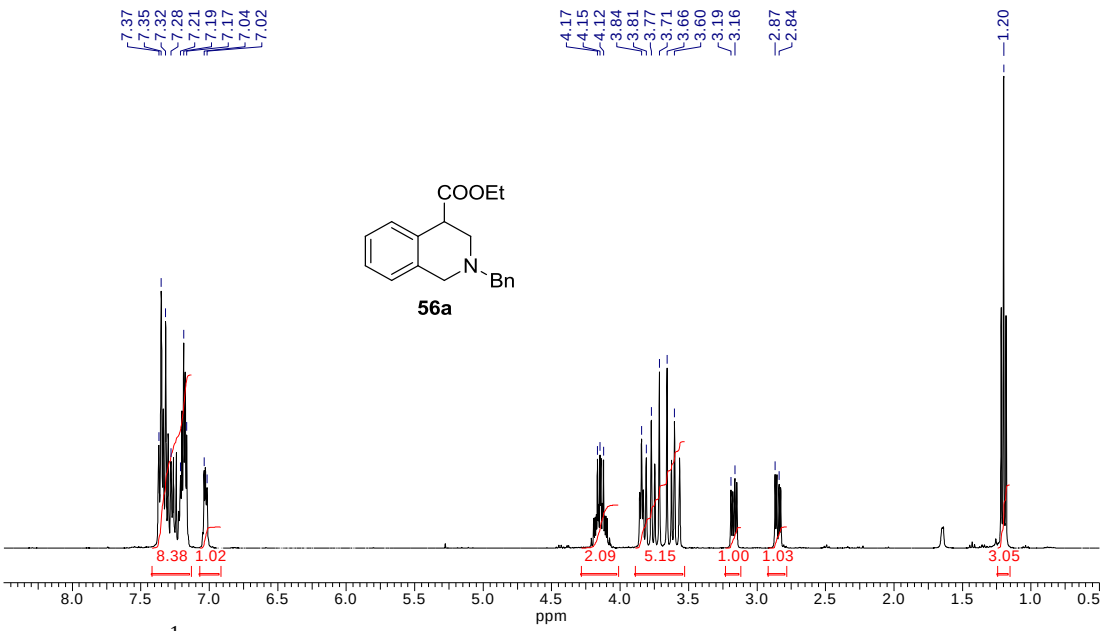


Figure I.4.1: ^{1}H-NMR (400 MHz) spectrum of **56a** in $CDCl_3$

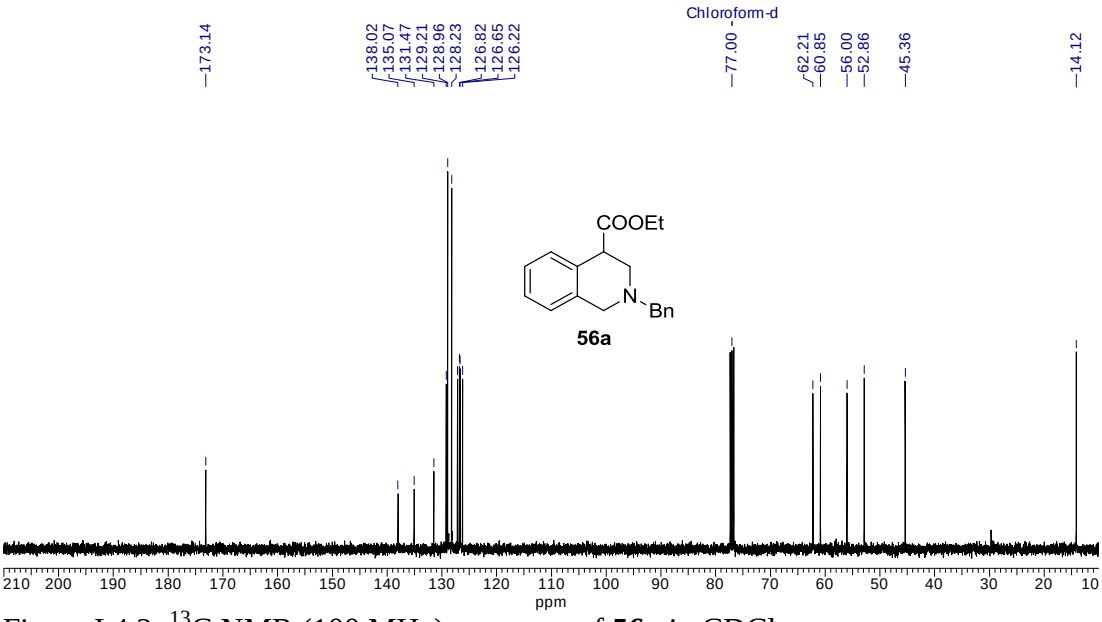
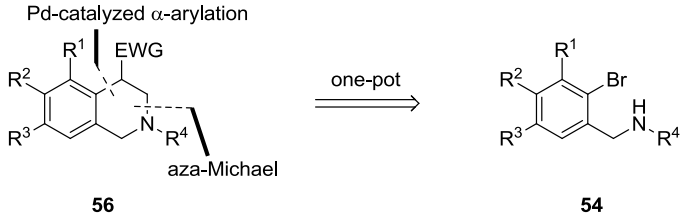


Figure I.4.2: ^{13}C NMR (100 MHz) spectrum of **56a** in $CDCl_3$

I.3.2 Synthesis of Tetrahydroisoquinolines (Sequential One-Pot Approach):

Certainly, sequential/domino one-pot methods hold advantages over step-wise methods. For example, such transformations, avoids the isolation of intermediates, minimizes the amount of waste generation, improves strategic

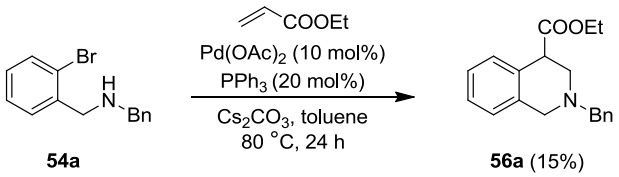
efficiency, requires less amount of time, and diminishes the use of number of solvents and reagents.[52] In this regard, after accomplishment of tetrahydroisoquinolines **56a–56g** in a step-wise strategy, we became interested in making the method more efficient by employing a domino one-pot aza-Michael addition followed by Buchwald-Hartwig α-arylation on secondary amines **54** without isolating the intermediate Michael addition product **55** (Scheme I.22).



56 **54**

Scheme I.22

The secondary amine **54a** was chosen as a model for this study of domino one-pot aza-Michael addition followed by Pd-catalyzed intramolecular Buchwald-Hartwig α-arylation method. The reaction of secondary amine **54a** with the Michael acceptor ethyl acrylate, Pd-catalyst [$Pd(OAc)_2/PPh_3$], and Cs_2CO_3, in toluene at 80 °C for 24 h gave the final product **56a**, albeit in poor yield 15% (Scheme I.23). The poor yield of **56a** might be due to the formation of aryl palladium species through insertion into the C-Br bond of the aryl bromide in competition to aza-Michael addition of ethyl acrylate.



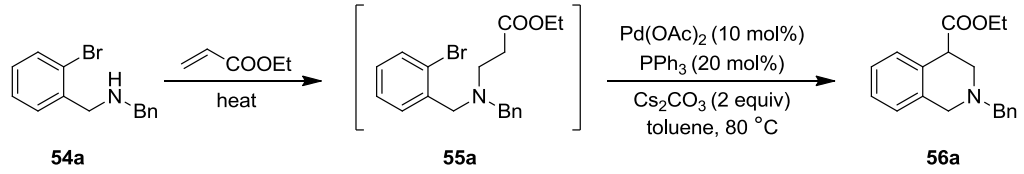
54a **56a** (15%)

Scheme I.23

Since, the above direct domino one-pot method was found inferior to step wise method, we thought that an alternative aza-Michael addition followed by in-

situ treatment of the β-amino ester intermediate **55a** for subsequent Pd-catalysed α-arylation may help to improve the yield of the end product **56a**. The overall idea is to allow the smooth and complete formation of the initial Michael addition intermediate product **55a** in an uninterrupted fashion, so that the overall yield of target product **56a** would be increased by eliminating possible competitive reactions. Hence, it was important to identify the suitable reaction conditions for the aza-Michael reaction that would also be amenable for subsequent intramolecular palladium catalyzed α-arylation. Since, the Pd-catalyzed intramolecular α-arylation was smooth in toluene, the aza-Michael addition was explored with the secondary amine **54a** using varying amounts of ethyl acrylate and the Cs_2CO_3, in hot toluene (50 °C and 80 °C). However, these trials furnished the β-aminoester **55a** in poor to moderate yields (entries 1 to 4, Table I.4). Similar results were obtained by conducting the reaction at increased temperature (100 °C) in toluene without Cs_2CO_3 (entries 5 & 6, Table I.4). Interestingly, there was an improvement in the yield to (60%) upon using xylene as the solvent at high temperature 130 °C (entry 7, Table I.4). Alternatively, the reaction of amine **54a** with ethyl acrylate without using any solvent (neat conditions) under microwave irradiation was also found to be less progressive (entry 8, Table I.4). Similarly, conventional heating of the secondary amine **54a** and ethyl acrylate (1.5 equiv) without the base and xylene at 110 °C for 48 h, furnished the β-amino ester **55a** in poor yield (entry 9, Table I.4). A low yield of the intermediate β-amino ester **56a** might be attributed due to low boiling point of ethyl acrylate (100 °C), as it may escape from the reaction vessel. Therefore, it was envisioned that excess equivalents of the Michael acceptor ethyl acrylate might help to improve the yield of **55a**. As expected, the reaction with excess (5 equiv) of ethyl acrylate at 110 °C for 48 h, showed 100% conversion to the intermediate β-amino ester **55a**, which was on in-situ intramolecular Pd-catalyzed α-arylation, resulted the tetrahydroisoquinoline product **56a**, albeit in moderate yield 43% (entry 10, Table I.4). Moderate yield of the tetrahydroisoquinoline **56a**, was probably due to the intermolecular intrusion of excess Michael acceptor ethyl acrylate with the

Table I.4: Optimization of the one-pot reaction conditions for the synthesis of 1,2,3,4-tetrahydroisoquinoline **56a**.



54a **55a** **56a**

Reaction conditions for aza-Michael addition							Reaction conditions for Pd-catalyzed α-arylation		
Entry	Ethyl acrylate (equiv)	Base (equiv)	Solvent	Temp (°C)	Time (h)	Yield of **55a** (%)	Toluene (mL)	Time (h)	Yield of **56a** (%)[h]
1[a]	1.5	Cs_2CO_3	toluene	80	48	10	–	–	–
2[a]	5	Cs_2CO_3	toluene	50	24	18	–	–	–
3[a]	5	Cs_2CO_3	toluene	50	48	30	–	–	–
4[a]	5	Cs_2CO_3	toluene	100	48	45	–	–	–
5[a]	1.5	–[c]	toluene	100	48	10	–	–	–
6[a]	5	–[c]	toluene	100	48	40	–	–	–
7[a]	5	–[c]	xylene	130	48	60	–	–	–
8[a]	5	–[d]	–	80	1 (μw)	25	–	–	–
9[a]	1.5	–[d]	–	110	48	30	–	–	–
10[b]	5	–[d]	–	110	48	100[e]	4	24	43
11[b]	5	–[d]	–	110	48	100[e]	8	48	48
12[b]	**5**	–[d]	–	**110**	**24**	**100[f,g]**	**3**	**24**	**77**

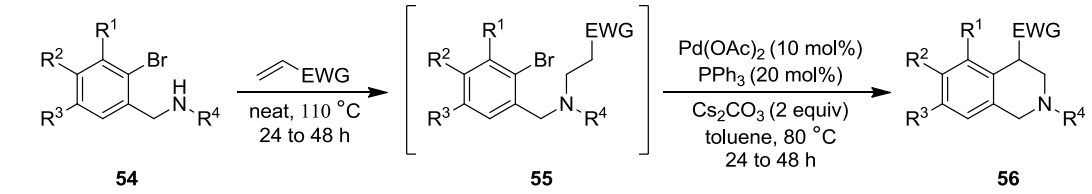
[a] Isolated yields of chromatographically pure product **55a** and not subjected to the subsequent Pd-catalyzed α-arylation. [b] The product **55a** was not isolated and the complete conversion of secondary amine **54a** to product **55a** was confirmed by TLC. [c] Base omitted in these attempts. [d] Both base and solvent omitted in these entries, only neat reaction conditions were employed. [e] Reaction was performed on 100 mg scale of secondary amine **54a**. [f] Reaction performed on one mmol scale of secondary amine **54a**. [g] Excess ethyl acrylate was removed under vacuum (10^{-2} mbar) just before the addition of Pd-catalyst, base and solvent, for subsequent Pd-catalyzed α-arylation. [h] Isolated yields of chromatographically pure product **56a**.

intermediate aryl Pd-species of β-amino ester during the cyclization. Upon dilution of the reaction mixture with excess of solvent, after the complete formation of the β-amino ester **55a**, and subjecting it for further cyclization, slightly improved the yield of tetrahydroisoquinoline product **56a** (entry 11, Table I.4), but still concluded the interference of excess ethyl acrylate, which was still present in the reaction mixture. Finally, it was decided to eliminate of excess ethyl acrylate in order to avoid its interruption with aryl Pd-species of β-amino ester **55a**. Therefore, after formation of β-amino ester **55a**, excess of ethyl acrylate was removed under mild vacuum (10^{-2} mbar) and then subjected for subsequent intramolecular Buchwald-Hartwig α-arylation. These conditions were quite successful and furnished the tetrahydroisoquinoline product **56a** in good yield 77%. These results have been detailed in the entry 12, Table I.4, wherein, the amine was used on a 1 mmol scale with 5 equivalents of ethyl acrylate for 24 h. The overall yield of the **56a** (77%) was found to be as good as in stepwise formation of **56a** (72%), which was calculated from the 82% of intramolecular α-arylation and 88% Michael addition reactions, respectively.

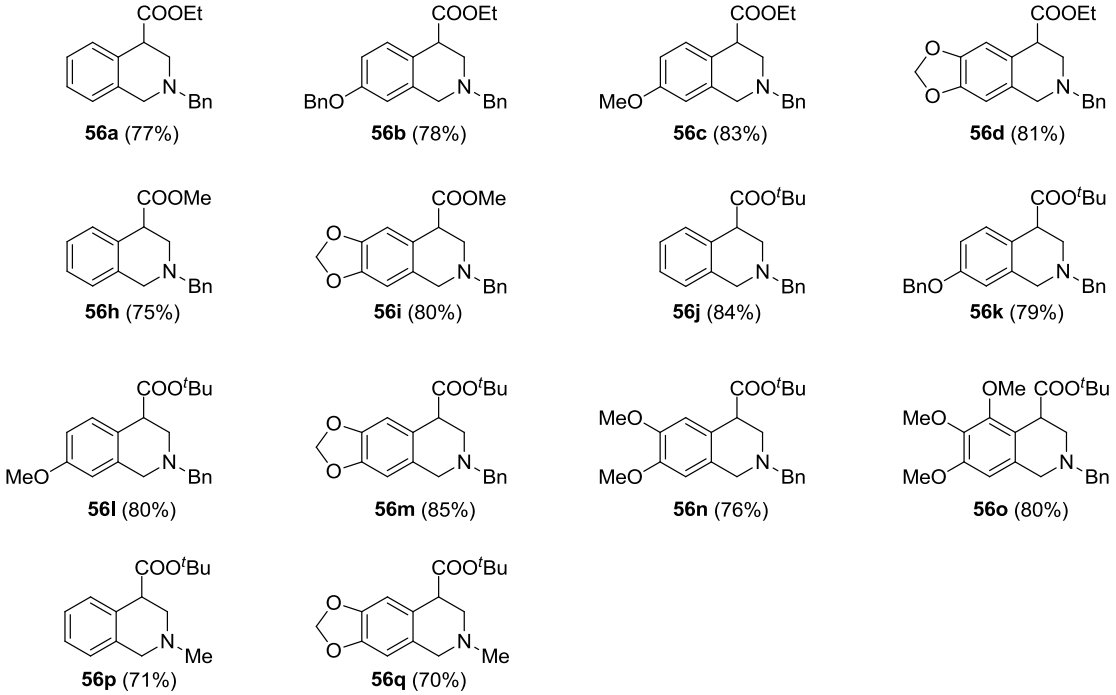
The optimized conditions (entry 12, Table I.4) were thus applied to the other secondary amines **54b–54i** with various other Michael acceptors (methyl, ethyl, *tert*-butyl acrylates) were also tried. In general, these results were quite similar to that obtained for **54a**, and furnished the tetrahydroisoquinolines **56** having simple to electron donating functionalities on aromatic rings, in very good yields (Table I.5). It was observed that in case of ethyl and methyl acrylates the aza-Michael reaction was completed in 24 h, whereas, in case of *tert*-butyl acrylate it took up to 48 h and succeeding Pd-catalyzed α-arylation was completed in 24 to 48 h.

Following the successful synthesis of tetrahydroisoquinolines **56** using the sequential one-pot method, attempts were made for the synthesis of novel 2-benzyl-2,3,4',7'-tetrahydro-1*H*-spiro[isoquinoline-4,3'-oxepine] systems. Notably, it was documented that the spiro-cyclic systems are useful molecules for drug discovery and show a good range of biological properties. Moreover, spiro-cyclic systems are

Table I.5: Sequential domino one-pot aza-Michael-Pd-catalyzed α-arylation for the synthesis of 1,2,3,4-tetrahydroisoquinolines **56a–56q** from secondary amines **54a–54i**.

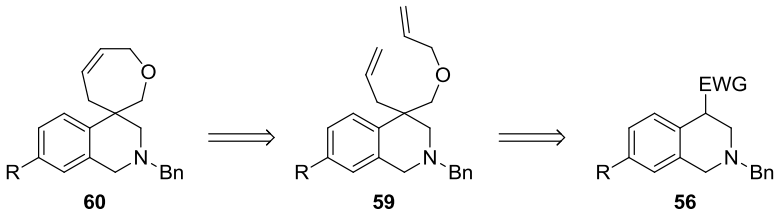


54 **55** **56**



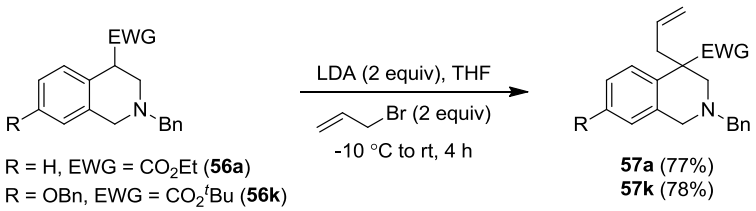
[a] Isolated yields of chromatographically pure products.

explained as privileged scaffolds, since they have been successfully engaged as ligands for a wide variety of targets.[53] According to our retrosynthetic analysis, it was envisioned that the targeted spiro-system **60** can be obtained from the diene **59** using a ring closing metathesis (RCM) reaction. The diene system **59** in turn could be synthesized from tetrahydroisoquinolines **56**, via the LDA mediated α-allylation of **56**, reduction of ester functionality followed by O-allylation sequence (Scheme I.24).



Scheme I.24

The synthetic sequence began for the synthesis of spiro tricyclics **60a** and **60k** with the C-allylation of α-carbon of cyclic esters **56a** & **56k**. The in-situ C-allylation with allyl bromide on the enolate generated by treatment of the cyclic esters **56a** & **56k** with lithium di-isopropyl amide (LDA), gave the products **57a** & **57k** (Scheme I.25).



Scheme I.25

The chemical structure of **57a** was confirmed from the spectral data. The presence of the strong absorption band at 1722 and 1638 cm^{-1} due to the C=O and C=C group in the IR spectrum indicated the formation of the allyl tetrahydroisoquinoline **57a**. In the ^{1}H-NMR (Figure I.5.1) spectrum, the presence of three doublets at δ 7.35, δ 7.29 and δ 6.91 due to four aromatic protons, two doublet of doublets at δ 7.24 and δ 7.18 due to three aromatic protons, a multiplet in the region of δ 7.15–7.01 due to two aromatic protons, three multiplets in the region δ 5.70–5.31, δ 4.99–4.85 and δ 4.18–3.95 due to the three olefinic protons and two O-methylene protons, two singlets at δ 3.58 and 3.54 due to four protons two N-CH_2

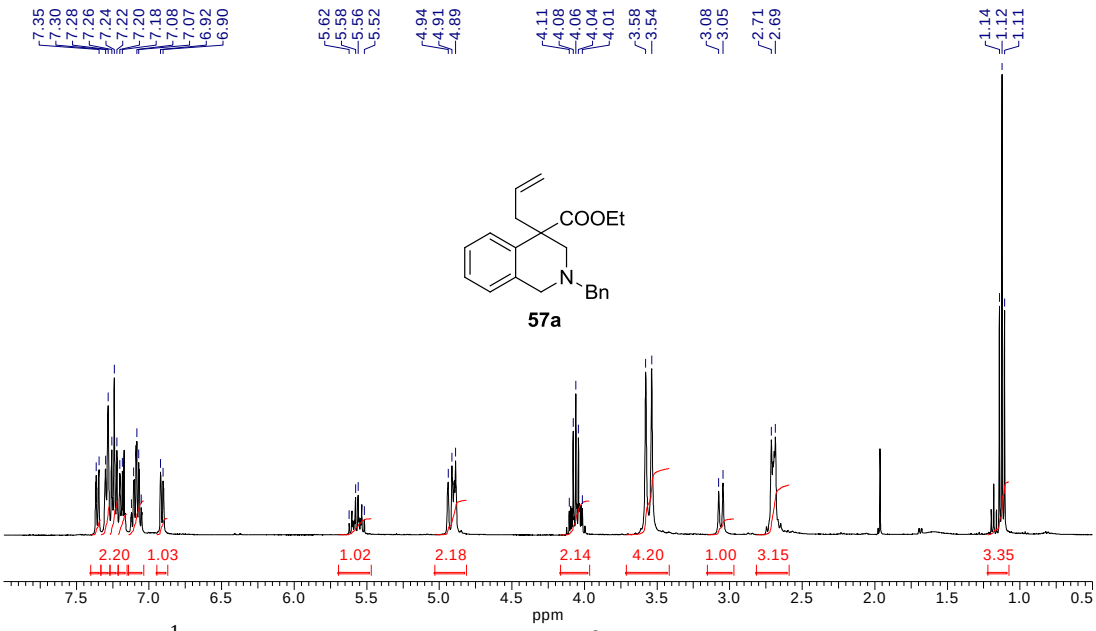


Figure I.5.1: ^{1}H-NMR (400 MHz) spectrum of **57a** in $CDCl_3$

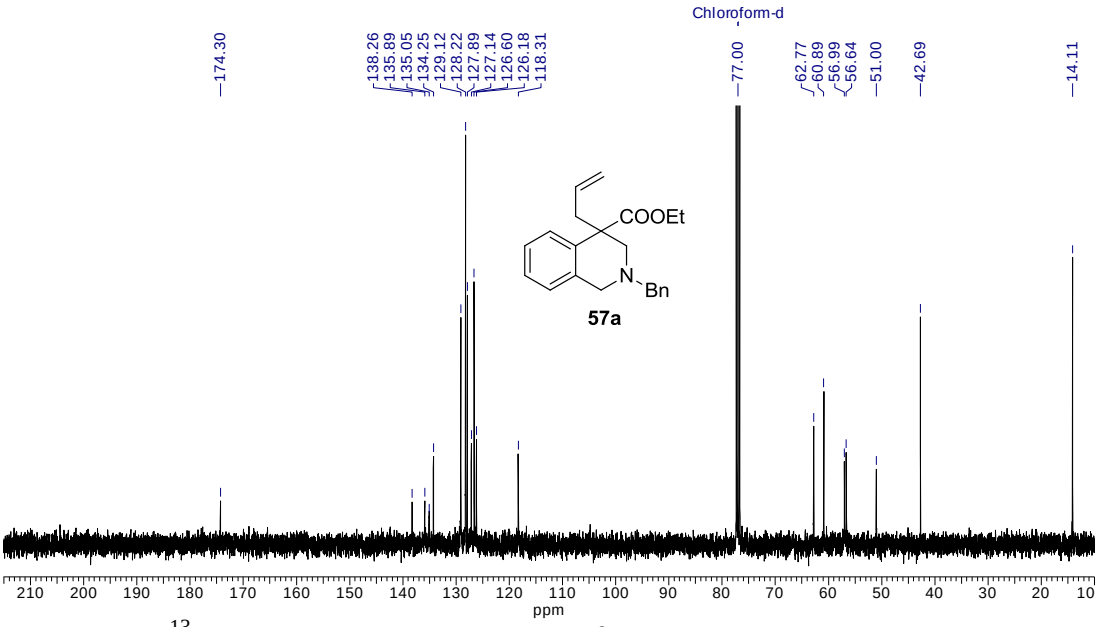
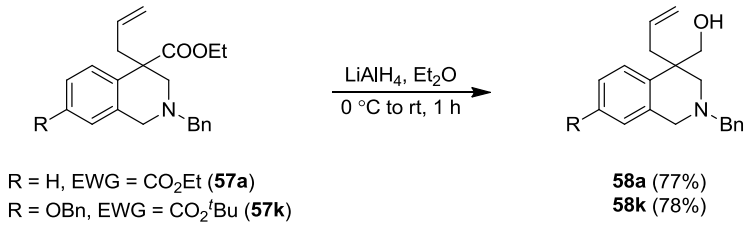


Figure I.5.2: ^{13}C NMR (100 MHz) spectrum of **57a** in $CDCl_3$

methylene groups, doublet at δ 3.06 and one multiplet in the region δ 2.75–2.60 due to four protons of two methylene groups attached to nitrogen and olefin and a triplet at δ 1.12 ppm due to three protons of a methyl group elucidated the structure of allyl 1,2,3,4-tetrahydroisoquinoline **57a**. Among the 20 lines seen in ^{13}C NMR (Figure

I.5.2) spectrum, existence of five quaternary carbon resonances at δ 174.3 as a result of one ester carbonyl, 138.3, 135.9 & 135.1 due to three aromatic carbons and 51.0 due to one aliphatic carbon, respectively, ten methines at δ 134.2, 129.1, 128.2, 127.9, 127.1, 126.6, 126.5 and 126.2 due to one olefinic and nine aromatic carbons, six methylenes at δ 118.3, 62.8, 60.9, 57.0, 56.7 and 42.7 and a methyl at δ 14.1 ppm confirmed the structure of allyl tetrahydroisoquinoline **57a**. Presence of the $[M+H]^+$ ion peak at m/z 336.1942 $[C_{22}H_{26}NO_2]^+$ in the HR-MS spectrum concluded **57a** formation.

Reduction of the esters **57a** & **57k** with lithium aluminum hydride ($LiAlH_4$) in dry ether as solvent at 0 °C to room temperature for 1 h, afforded the primary alcohols **58a** & **58k** in excellent yields (Scheme I.26).



Scheme I.26

The presence of the absorption band at 3396 cm^{-1} because of O–H stretching and disappearance of the 1722 cm^{-1} band (due to the C=O stretching) in the IR spectrum indicated the formation of the alcohol **58a**, which was further proved by the existence of band at 1638 cm^{-1} due to C=C stretching absorption band of the terminal olefin. In the ^1H NMR (Figure I.6.1) spectrum, the presence of a multiplet in the region δ 7.15–7.01 due to seven aromatic protons, one doublet of doublet at δ 7.05 and one doublet at δ 6.89 due to two aromatic protons, three multiplets were observed in the region δ 5.50–5.35 due to one olefinic proton, δ 3.78–3.65 for one methylene of CH_2OH group and one N-methylene, a broad singlet at δ 5.33 due to OH group, two doublets at δ 5.02 and δ 4.97 due to two protons of olefin methylene, two doublets at δ 3.51 and δ 3.23 due to two protons of N-methylene and four doublet of doublets at 2.87, 2.53, 2.42 and 2.11 for four protons of olefin

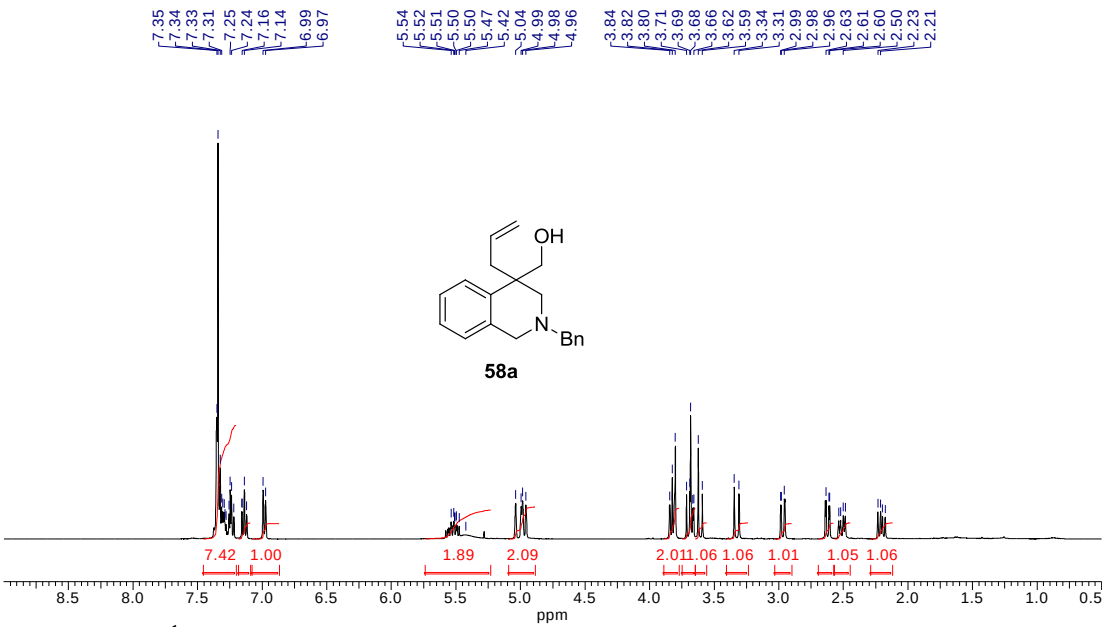


Figure I.6.1: ^{1}H-NMR (400 MHz) spectrum of **58a** in $CDCl_3$

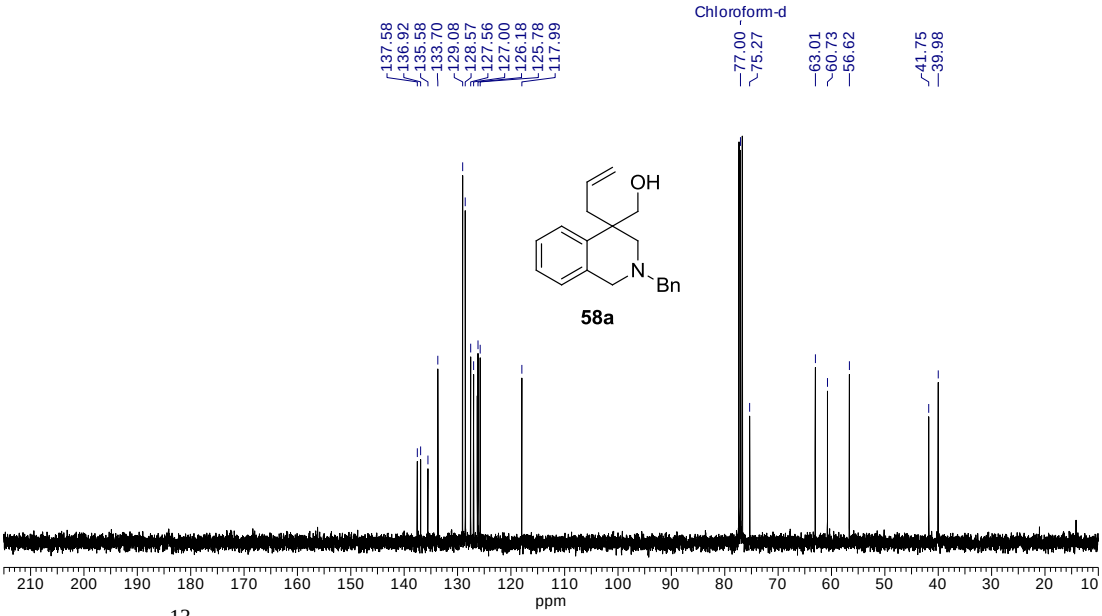
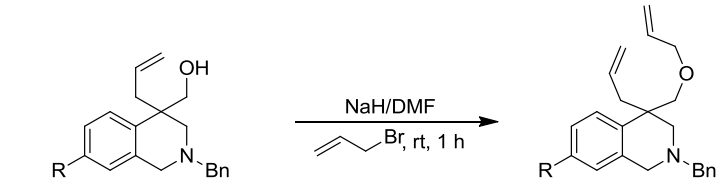


Figure I.6.2: ^{13}C NMR (100 MHz) spectrum of **58a** in $CDCl_3$

methylene and N- methylene clarified the structure of alcohol **58a**. Of the 18 lines ^{13}C NMR (Figure I.6.2) spectrum, existence of four quaternary carbon resonances at δ 137.6, 136.9, 135.6 and 41.7 was noticed due to three aromatic carbons, and one

aliphatic carbon, respectively, ten methines at δ 133.7, 129.1, 128.6, 127.6, 127.0, 126.3, 126.2 and 125.8 due to one olefinic and nine aromatic carbons and six methylenes at δ 118.0, 75.3, 63.0, 60.7, 56.6 and 40.0 confirmed the structure of alcohol **58a**. Presence of the $[M+H]^+$ ion peak at m/z 294.1845 $[C_{20}H_{24}NO]^+$ in the HR-MS spectrum concluded **58a** formation.

Now, O-allylation of the hydroxyl group of alcohols **58a** & **58k** with allyl bromide in the presence of base NaH, furnished the corresponding allyl ethers **59a** & **59k** in very good yields (Scheme I.27).



R = H, EWG = CO_2Et (**58a**)
R = OBn, EWG = $CO_2{}^tBu$ (**58k**)

59a (83%)
59k (90%)

Scheme I.27

The lack of the absorption band at 3396 cm^{-1} and occurrence of a band at 1639 cm^{-1} due to C=C in the IR spectrum showed the formation of the ether **59a**. In the ^1H NMR (Figure I.7.1) spectrum, presence of five multiplets in the regions δ 7.45–7.20 due to six aromatic protons, δ 5.95–5.75, 5.65–5.50 for two methine protons of olefin & δ 3.95–3.84 and δ 3.72–3.56 because of 6 protons of three methylene groups, five doublet of doublets at δ 7.15 and δ 7.15 due to two aromatic protons & δ 3.45, 2.62 and δ 2.53 due to four methylene protons of olefin methylene and seven doublets at δ 6.96 due to one aromatic proton, δ 5.19, 5.10, 4.96, 4.91, 2.82 and 2.46 for four geminal protons of two olefin methylene groups and two protons of a methylene clarified the structure of ether **59a**. Amongst the 18 lines ^{13}C NMR (Figure I.7.2) spectrum, presence of four quaternary carbon resonances at δ 138.8, 138.5 & 135.8 found due to three aromatic carbons, and 42.9 is because of one aliphatic carbon, respectively, eleven methines at δ 135.3, 135.2,

128.9, 128.2, 127.2, 127.0, 126.5, 126.0 and 125.9 due to two olefinic and nine aromatic carbons,

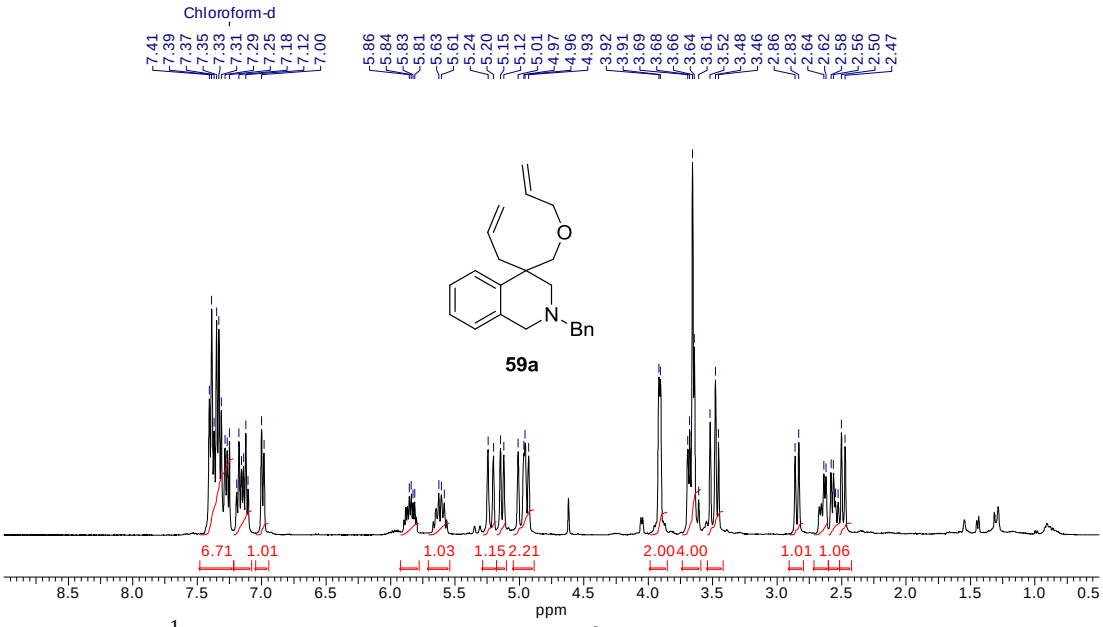


Figure I.7.1: ^{1}H-NMR (400 MHz) spectrum of **59a** in $CDCl_3$

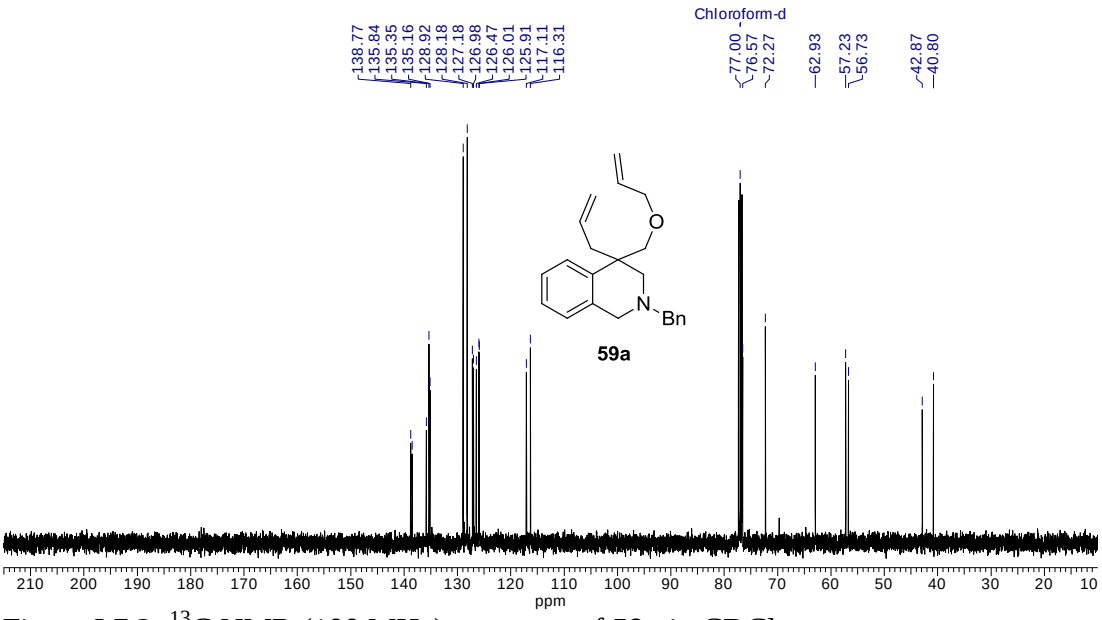
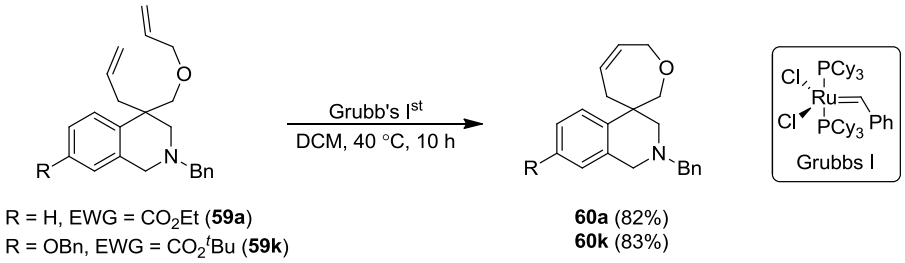


Figure I.7.2: ^{13}C NMR (100 MHz) spectrum of **59a** in $CDCl_3$

eight methylenes at δ 117.1, 116.3, 76.6, 72.3, 62.9, 57.2, 56.7 and 40.8 confirmed the structure of ether **59a**. Presence of the $[M+H]^+$ ion peak at m/z 334.2150 for $[C_{23}H_{28}NO]^+$ in the HR-MS spectrum concluded **59a** formation.

Finally, ring closing metathesis (RCM) of the dienes **59a** and **59k** with 5 mol% of the first generation Grubb's catalyst in dichloromethane at room temperature afforded the target spiro-tricyclic system **60a** & **60k**, in very good yields, respectively (Scheme I.28).



Scheme I.28

The presence of a stretching frequency at 1603 cm^{-1} due to C=C in the IR spectrum showed the formation of the spiro-oxepine **60a**. In the ^1H NMR (Figure I.8.1) spectrum, presence of three doublet of doublets at δ 7.47, 7.31 and 7.16 due to four aromatic protons, nine doublets at δ 7.38, 6.95 (for three aromatic protons), 4.00, 3.77, 3.76, 3.56, 3.55, 3.50 and 2.69 (due to six methylene protons), a triplet at δ 7.25 and a doublet of doublet of doublet at δ 7.10 due to two aromatic protons and four multiplets in the regions δ 5.77–5.64, 5.63–5.50 (for two protons of olefin), δ 4.38–4.20 and δ 2.63–2.44 (of four methylene protons) clarified the structure of ether **60a**. In the 18 lines ^{13}C NMR (Figure I.8.2) spectrum, presence of four quaternary carbon resonances at δ 141.4, 138.6 & 134.7 found due to three aromatic carbons, and 44.9 due to one aliphatic carbon, respectively, eleven methine carbons at δ 129.4, 128.9, 128.2, 128.0, 126.7, 126.6, 126.3 and 126.0 due to two olefinic and nine aromatic carbons and six methylene carbons at δ 78.9, 71.7, 62.8, 58.7, 56.7 and 37.1 confirmed the structure of spiro-oxepine **60a**. The presence of the

$[M+Na]^+$ ion peak at m/z 328.1686 $[C_{21}H_{23}NNaO]^+$ in the HR-MS spectrum concluded **60a** formation.

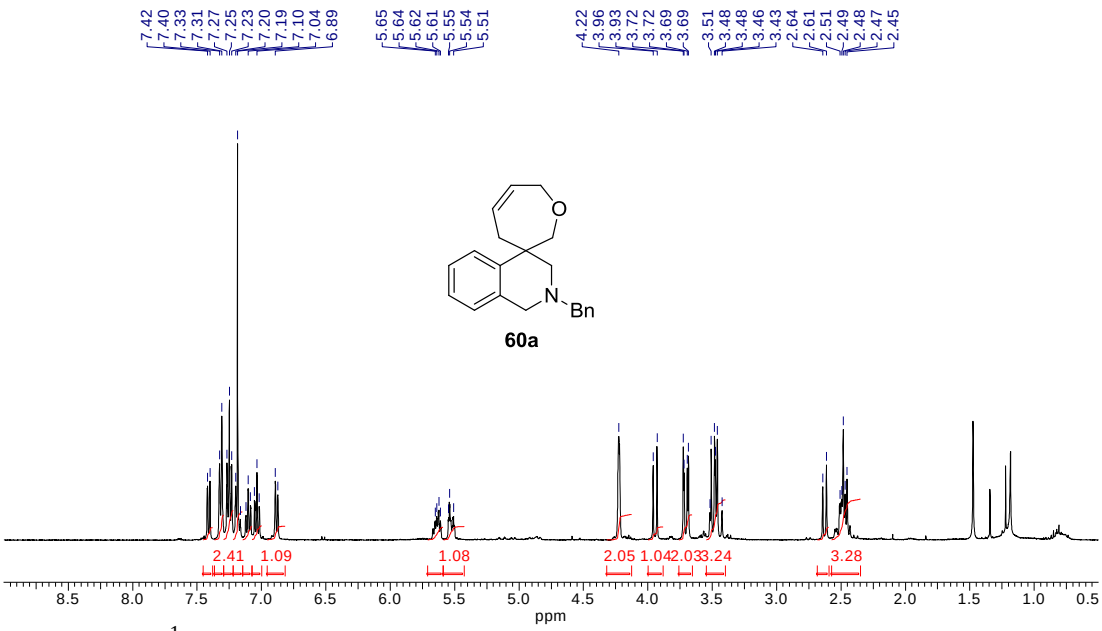


Figure I.8.1: ^{1}H-NMR (400 MHz) spectrum of **60a** in $CDCl_3$

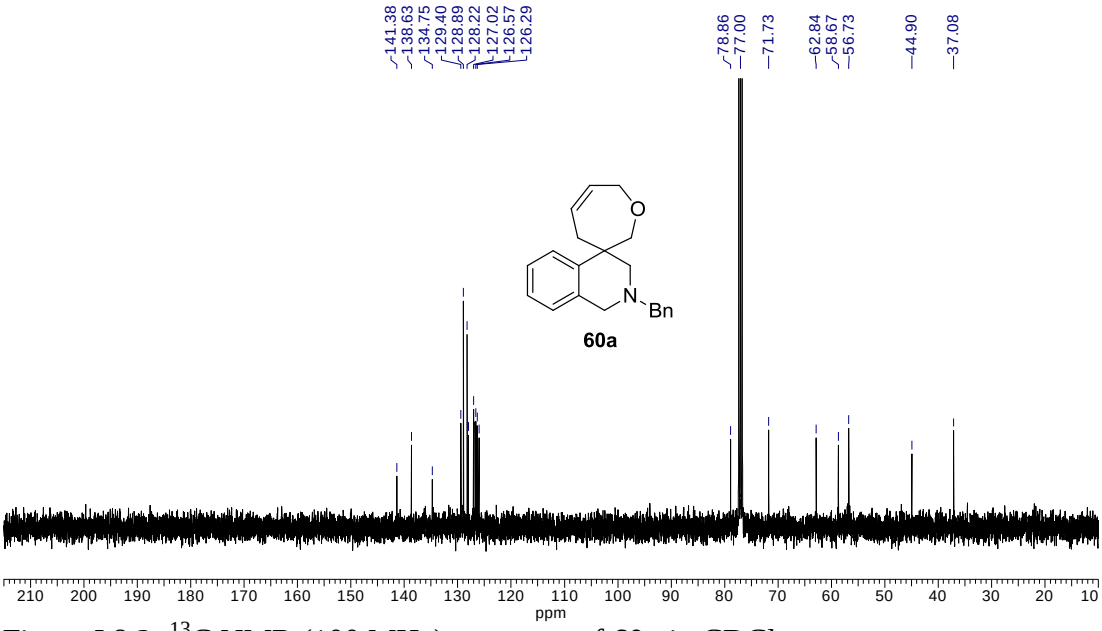
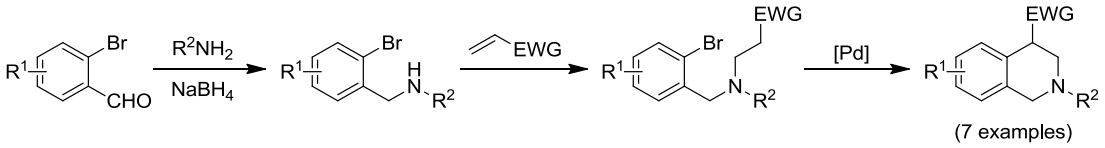


Figure I.8.2: ^{13}C NMR (100 MHz) spectrum of **60a** in $CDCl_3$

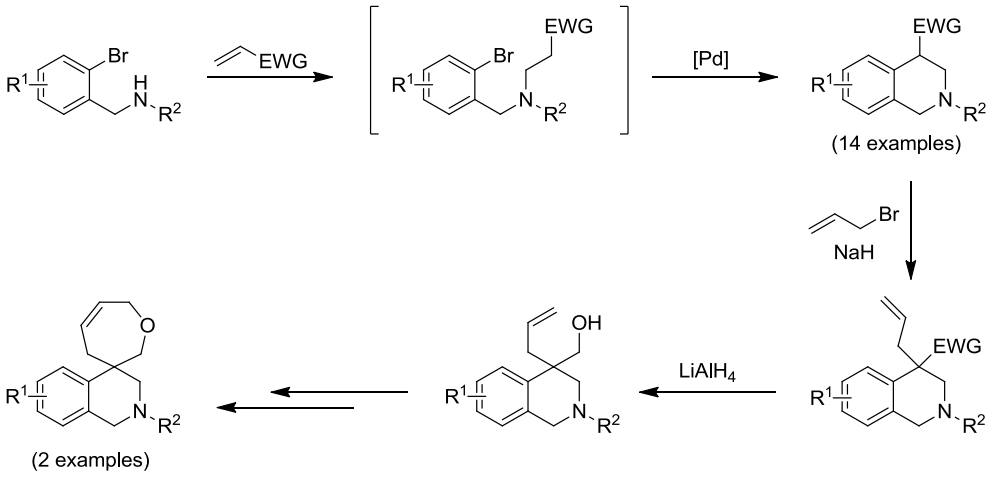
I.4 CONCLUSIONS:

In summary, an efficient step-wise synthetic strategy for the synthesis of functionalized 1,2,3,4-tetrahydroisoquinolines was developed based on a Buchwald-Hartwig α-arylation as the key step starting from 2-bromobenzaldehydes. The method was improvised by conducting a sequential one-pot intermolecular aza-Michael addition and Pd-catalyzed intermolecular Buchwald-Hartwig α-arylation of secondary amines. An optimized neat method (only with amine & acrylate and with out any base or solvent) was established for an intermolcular aza-Michael addition to generate β-aminoesters, which were directly subjected for further intramolecular Buchwald-Hartwig α-arylation. The strategy was very efficient and amenable for the synthesis of a number of tetrahydroisoquinoline derivatives, a struct ural unit present in many tetrahydroisoquinoline based biologically active alkaloid natural products. Moreover, the sequential domino one-pot protocol was successfully applied for the synthesis of novel 2-benzyl-2,3,4',7'-tetrahydro-1*H*-spiro[isoquinoline-4,3'-oxepine] systems.

Step wise synthesis of tetrahydroisoquinolines



Domino sequential one-pot synthesis of tetrahydroisoquinolines and application to the spiro-tricyclic systems



I.5 EXPERIMENTAL SECTION:

IR spectra were recorded on Bruker Tensor 37 (FTIR) and Bruker ALPHA (FTIR) spectrophotometers. ^{1}H-NMR spectra were recorded on Bruker Avance 400 (400 MH_Z) spectrometer at 295 K in $CDCl_3$; chemical shifts (δ ppm) and coupling constants (Hz) are reported in standard fashion with reference to either internal standard tetramethylsilane (TMS) (δ_H = 0.00 ppm) or $CHCl_3$ (δ_H = 7.25 ppm). ^{13}C-NMR spectra were recorded on Bruker Avance 400 (100 MH_Z) spectrometer at RT in $CDCl_3$; chemical shifts (δ ppm) are reported relative to $CHCl_3$ [δ_C = 77.00 ppm (central line of triplet)]. In the ^{13}C-NMR, the nature of carbons (C, CH, CH_2 and CH_3) was determined by recording the DEPT-135 spectra, and is given in parentheses and noted as s = singlet (for C), d = doublet (for CH), t = triplet (for CH_2) and q = quartet (for CH_3). In the ^{1}H-NMR, the following abbreviations were used throughout: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, m = multiplet and br. s = broad singlet. The assignment of signals was confirmed by ^{1}H, ^{13}C CPD (Carbon Proton Decoupling) and DEPT spectra. High-resolution mass spectra (HR-MS) were recorded using Agilent 6538 UHD Q-TOF using multimode [electron spray ionization (ESI^+) and atmospheric pressure chemical ionization ($APCI^+$)] source. All small scale dry reactions were carried out using Schlenk tube

and standard syringe-septum technique. Reactions were monitored by TLC on silica gel using a combination of petroleum ether and ethyl acetate as eluents. Reactions were generally run under inert (argon or a nitrogen) atmosphere. Solvents such as toluene, tetrahydrofuran (THF) and diethyl ether were dried over sodium metal wire, whereas dimethylformamide (DMF) and dichloromethane (DCM) were dried over calcium hydride prior to use. Solvents like petroleum ether, ethyl acetate, dichloromethane, and methanol were distilled prior to use; petroleum ether with a boiling range of 60 to 80 °C was used. Methylamine was used as 25% CH_3NH_2 in methanol. Benzylamine (with purity 98%) and ethyl acrylate (with purity 99.5%) were purchased from Sigma-Aldrich, whereas methyl acrylate (with purity 99%) and *tert*-butyl acrylate (with purity 98%) were purchased from other commercial sources and used as received. All benzaldehydes (with purity 98%) in order to make corresponding 2-bromobenzaldehydes [except 2-bromobenzaldehyde, which was commercially available (with purity 98%)] were purchased from commercial sources and used as received. Acme's silica gel (60–120 mesh) was used for column chromatography (approximately 20 g per one gram of crude material).

I.5.1 Synthesis of tetrahydroisoquinolines using step-wise strategy:

General Procedure for the Reductive Amination with Benzyl Amine, for the Preparation of Secondary Amines 54a–54g (GP-1):

To an ice cold round bottomed flask containing 2-bromobenzaldehyde **53** (1 mmol), were added methanol (15 mL) followed by benzylamine (2 mmol) and acetic acid (0.3 mL). The reaction mixture was allowed to stir at room temperature for 1 h. To this reaction mixture, was added sodium borohydride (1.5 mmol) and then the reaction mixture was stirred at 65 °C for an additional 12 h. Solvent was removed under reduced pressure, treated with aqueous NH_4Cl solution and extracted with ethyl acetate (3 × 20 mL). The organic layers were washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the filtrate under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate) furnished the secondary amine **54** (74–93%).

General Procedure for Reductive Amination with Methyl Amine, for the Preparation of Amines 54h–54i (GP-2):

To an ice cold round bottomed flask containing 2-bromobenzaldehyde **53** (1 mmol), were added methanol (15 mL) followed by methylamine (3 mmol) [25% in methanol]. The reaction mixture was allowed to stir at that ice temperature for 1 h. To this ice cold reaction mixture, was added sodium borohydride (1.5 mmol) and then the reaction mixture was allowed to attain room temperature and stirred for an additional 3 h. Solvent was removed under reduced pressure, treated with aqueous NH_4Cl solution and extracted with ethyl acetate (3 × 20 mL). The organic layers were washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the filtrate under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate) furnished the secondary amine **54** (74–83%).

General Procedure for aza-Michael Addition (GP-3):

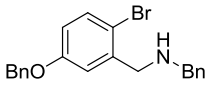
To the solution of secondary amine **54** (1 mmol) in methanol (4 mL), was added ethyl acrylate (2 mmol) and the reaction mixture was refluxed for 48 h and monitored by TLC. After complete conversion of starting material to the Michael addition product **55**, methanol was evaporated in vacuo. Purification of the residue on a silica gel column using petroleum ether/ethyl acetate as eluent furnished pure aza-Michael addition product **55** (84–95%).

General Procedure for Buchwald–Hartwig Cyclization (GP-4):

In an oven-dried Schlenk tube under nitrogen atmosphere were taken $Pd(OAc)_2$ (10 mol%), Ph_3P (20 mol%), and Cs_2CO_3 (2 mmol) in toluene (1.0 mL), and the mixture was stirred for 5 min. To this mixture was added β-amino ester **55** (1 mmol) in toluene (3.0 mL), and the reaction mixture was stirred for 24 h at 80 °C and monitored by TLC. After completion of the reaction, the reaction mixture was quenched by the addition of aqueous NH_4Cl and extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced

pressure. Purification of the residue by column chromatography (petroleum ether/ethyl acetate) furnished the tetrahydroisoquinoline **56** (70–87%).

The secondary amines **54a**, **54c**, **54d** and **54e** are already reported in the literature.[54]



54b

N-Benzyl-N-[5-(benzyloxy)-2-bromobenzyl]amine 54b:

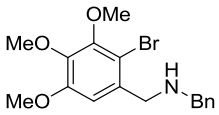
GP-1 was carried out with 2-bromo-5-benzyloxybenzaldehyde **53b** (1.5 g, 5.15 mmol), benzyl amine (828 mg, 10.3 mmol), acetic acid (0.3 mL) and $NaBH_4$ (300 mg, 7.72 mmol) in methanol (25 mL). Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to petroleum ether/ethyl acetate, 70:30) furnished the secondary amine **54b** (1.46 g, 74%) as yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 90:10), R_f(**53b**)=0.70, R_f(**54b**)=0.15, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3330, 2868, 1580, 1463, 1376, 1289, 1236, 1166, 1015, 807 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.52–7.28 (m, 11H, Ar-H), 7.13 (d, 1H, J=2.6 Hz, Ar-H), 6.80 (dd, 1H, J=8.7 and 2.9 Hz, Ar-H), 5.09 (s, 2H, OCH_2Ph), 3.89 (s, 2H, NCH_2), 3.84 (s, 2H, NCH_2), 2.02 (br. s, 1H, NH) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=158.2 (s, Ar-C), 140.3 (s, Ar-C), 140.1 (s, Ar-C), 136.7 (s, Ar-C), 133.4 (d, Ar-CH), 128.7 (d, 2C, 2 × Ar-CH), 128.5 (d, 2C, 2 × Ar-CH), 128.2 (d, 2C, 2 × Ar-CH), 128.1 (d, Ar-CH), 127.5 (d, 2C, 2 × Ar-CH), 127.1 (d, Ar-CH), 116.8 (d, Ar-CH), 115.2 (d, Ar-CH), 114.5 (s, Ar-C), 70.2 (t, OCH_2Ph), 53.2 (t, NCH_2), 53.1 (t, NCH_2) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{21}H_{20}BrNNaO]^+$=$[M+Na]^+$: 404.0620; found 404.0621.



54f

N-Benzyl-N-(2-bromo-3,4,5-triemthoxybenzyl)amine (54f):

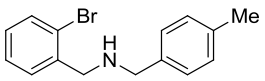
GP-1 was carried out with 2-bromo-3,4,5-trimethoxybenzaldehyde **53f** (1.0 g, 3.63 mmol), benzyl amine (779 mg, 7.26 mmol), acetic acid (0.4 mL) and $NaBH_4$ (206.9 mg, 5.44 mmol) in methanol (25 mL). Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 90:10 to petroleum ether/ethyl acetate, 70:30) furnished the secondary amine **54f** (1.21 g, 91%) as yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 70:30), R_f(**53f**)=0.60, R_f(**54f**)=0.30, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3341, 2935, 1567, 1478, 1452, 1394, 1327, 1161, 1104, 1007, 974, 923, 737, 698 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.42–7.30 (m, 4H, Ar-H), 7.30–7.23 (m, 1H, Ar-H), 6.84 (s, 1H, Ar-H), 3.91 (s, 3H, Ar-OCH_3), 3.89 (s, 3H, Ar-OCH_3), 3.86 (s, 3H, Ar-OCH_3), 3.86 (s, 2H, NCH_2), 3.83 (s, 2H, NCH_2), 1.96 (br. s, 1H, NH) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=152.6 (s, Ar-C), 150.9 (s, Ar-C), 142.1 (s, Ar-C), 140.1 (s, Ar-C), 134.9 (s, Ar-C), 128.4 (d, 2C, 2 × Ar-CH), 128.2 (d, 2C, 2 × Ar-CH), 127.1 (d, Ar-CH), 109.9 (s, Ar-C), 109.1 (d, Ar-CH), 61.1 (q, Ar-OCH_3), 61.0 (q, Ar-OCH_3), 56.1 (q, Ar-OCH_3), 53.4 (t, NCH_2), 53.2 (t, NCH_2) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{17}H_{20}BrNNaO_3]^+$=$[M+Na]^+$: 388.0519; found 388.0528.



54g

N-(2-bromobenzyl)-N-(4-methylbenzyl)amine (54g):

GP-1 was carried out with 2-bromobenzaldehyde **53a** (1.0 g, 5.40 mmol), 4-methylbenzylamine (1.31 g, 8.10 mmol), acetic acid (0.4 mL) and $NaBH_4$ (308.4 mg, 8.10 mmol) in methanol (25 mL). Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate 95:5 to 70:30) furnished the

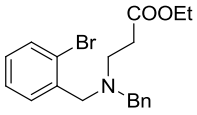
product secondary amine **54g** (1.38 g, 87%) as colorless viscous liquid [TLC control (petroleum ether/ethylacetate 8:2, R_f(**53a**)=0.70, R_f(**54g**)=0.25, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3019, 2827, 1514, 1440, 1358, 1101, 1043, 1023, 802, 747, 656 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.57 (d, 1H, *J*=7.9 Hz, Ar-H), 7.43 (d, 1H, *J*=7.6 Hz, Ar-H), 7.33–7.20 (m, 3H, Ar-H), 7.17–7.07 (m, 3H, Ar-H), 3.90 (s, 2H, NCH_2), 3.79 (s, 2H, NCH_2), 2.37 (s, 3H, $ArCH_3$), 1.96 (br. s, 1H, NH) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=139.2 (s, Ar-C), 137.0 (s, Ar-C), 136.6 (s, Ar-C), 132.8 (d, Ar-CH), 130.4 (d, Ar-CH), 129.1 (d, 2C, 2 × Ar-CH), 128.6 (d, Ar-CH), 128.2 (d, 2C, 2 × Ar-CH), 127.4 (d, Ar-CH), 124.1 (s, Ar-C), 53.1 (t, NCH_2), 52.8 (t, NCH_2), 21.16 (q, $ArCH_3$) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{15}H_{17}BrN]^+$=$[M+H]^+$: 290.0539; found 290.0553.



55a

Ethyl N-benzyl-N-(2-bromobenzyl)-β-alaninate (55a):

GP-3 was carried out with the secondary amine **54a** (1.1 g, 3.98 mmol) and ethyl acrylate (797.9 g, 7.97 mmol) in methanol (25 mL). After completion, the reaction mixture was concentrated on the rotary evaporator and purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 99:1 to 96:4) furnished the Michael addition product ester **55a** (1.32 g, 88%) as colorless liquid [TLC control (petroleum ether/ethyl acetate 9:1, R_f(**54a**)=0.25, R_f(**55a**)=0.55, UV detection)].

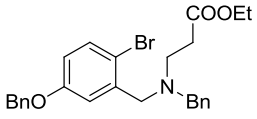
IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2980, 2805, 1731, 1444, 1368, 1244, 1182, 1129, 1024, 749, 698 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.57 (d, 1H, *J*=7.6 Hz, Ar-H), 7.51 (d, 1H, *J*=8.0 Hz, Ar-H), 7.40–7.20 (m, 6H, Ar-H), 7.09 (dd, 1H, *J*=7.8 and 7.6 Hz, Ar-H), 4.09 (q, 2H, *J*=7.2 Hz, O*CH*$_2$$CH_3$), 3.71 (s, 2H, NCH_2), 3.64 (s, 2H, NCH_2), 2.86 (t,

2H, *J*=7.2 Hz, NCH_2CH$_2$COOEt), 2.53 (t, 2H, *J*=7.2 Hz, CH_2COOEt), 1.21 (t, 3H, *J*=7.2 Hz, OCH$_2$CH_3) ppm.

^{13}C NMR (CDCl$_3$, 100 MHz): δ=172.5 (s, O–C=O), 139.1 (s, Ar-C), 138.5 (s, Ar-C), 132.6 (d, Ar-CH), 130.6 (d, Ar-CH), 128.8 (d, 2C, 2 × Ar-CH), 128.3 (d, Ar-CH), 128.2 (d, 2C, 2 × Ar-CH), 127.3 (d, Ar-CH), 127.0 (d, Ar-CH), 124.3 (s, Ar-C), 60.4 (t, O*C*H$_2$CH$_3$), 58.3 (t, NCH$_2$), 57.5 (t, NCH$_2$), 49.4 (t, N*C*H$_2$CH$_2$COOEt), 32.7 (t, *C*H$_2$COOEt), 14.2 (q, OCH$_2$*C*H$_3$) ppm.

HR-MS (ESI$^+$): m/z calculated for [C$_{19}$H$_{22}$BrNNaO$_2$]$^+$=[M+Na]$^+$: 398.0726; found 398.0729.



55b

Ethyl N-benzyl-N-[5-(benzyloxy)-2-bromobenzyl)-β-alaninate (55b):

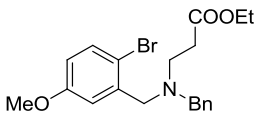
GP-3 was carried out with the secondary amine **54b** (1.4 g, 3.66 mmol), ethylacrylate (733 mg, 7.3 mmol) in methanol (10 mL). Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 98:2 to 85:15) furnished the β-amino ester **55b** (1.6 g, 90%) as a liquid [TLC control (petroleum ether/ethyl acetate 8:2, R_f(**54b**)=0.20, R_f(**55b**)=0.55, UV detection)].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2980, 2933, 2815, 1732, 1591, 1463, 1373, 1275, 1237, 1183, 1018, 808 cm^{-1}.

^{1}H NMR (CDCl$_3$, 400 MHz): δ=7.50–7.23 (m, 12H, Ar-H), 6.75 (dd, 1H, *J*=8.7 and 2.8 Hz, Ar-H), 5.08 (s, 2H, OCH$_2$Ph), 4.12 (q, 2H, *J*=7.1 Hz, OCH_2CH$_3$), 3.68 (s, 2H, NCH$_2$), 3.67 (s, 2H, NCH$_2$), 2.88 (t, 2H, *J*=7.2 Hz, NCH_2CH$_2$COOEt), 2.53 (t, 2H, *J*=7.2 Hz, NCH$_2$CH_2COOEt), 1.23 (t, 3H, *J*=7.1 Hz, OCH$_2$CH_3) ppm.

^{13}C NMR (CDCl$_3$, 100 MHz): δ=172.5 (s, O–C=O), 158.2 (s, Ar-C), 139.7 (s, Ar-C), 139.1 (s, Ar-C), 136.8 (s, Ar-C), 133.1 (d, Ar-CH), 128.7 (d, 2C, 2 × Ar-CH), 128.6 (d, 2C, 2 × Ar-CH), 128.3 (d, 2C, 2 × Ar-CH), 128.1 (d, Ar-CH), 127.5 (d, 2C, 2 × Ar-CH), 127.1 (d, Ar-CH), 116.6 (d, Ar-CH), 115.3 (d, Ar-CH), 114.7 (s, Ar-C), 70.1 (t, OCH$_2$Ph), 60.4 (t, O*C*H$_2$CH$_3$), 58.3 (t, NCH$_2$), 57.5 (t, NCH$_2$), 49.6 (t, N*C*H$_2$CH$_2$COOEt), 32.7 (t, NCH$_2$*C*H$_2$COOEt), 14.2 (q, O*C*H$_2$CH$_3$) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{26}H_{28}BrNNaO_3]^+$=$[M+Na]^+$: 504.1145; found 504.1150.



55c

Ethyl N-benzyl-N-(2-bromo-5-methxybenzyl)-β-alaninate (55c):

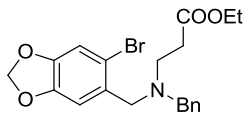
GP-3 was carried out with the secondary amine **54c** (4.0 g, 13.1 mmol), ethyl acrylate (2.62 g, 26.2 mmol) in methanol (40 mL) and the reaction mixture was refluxed for 2 days. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 95:5 to 80:20) yielded bromoester **55c** (5.2 g, 98%) as a viscous liquid [TLC control (petroleum ether/ethyl acetate 6:4, R_f(**54c**)=0.45, R_f(**55c**)=0.70, UV detection)].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2935, 2836, 1733, 1595, 1468, 1370, 1272, 1186, 1048, 1021, 809 cm^{-1}.

^{1}H NMR (CDCl$_3$, 400 MHz): δ=7.45–7.18 (m, 7H, Ar-H), 6.68 (dd, 1H, J=8.7 and 3.0 Hz, Ar-H), 4.11 (q, 2H, J=7.1 Hz, OCH_2CH$_3$), 3.81 (s, 3H, ArOCH_3), 3.68 (s, 2H, NCH$_2$), 3.66 (s, 2H, NCH$_2$), 2.89 (t, 2H, J=7.2 Hz, NCH_2CH$_2$COOEt), 2.54 (t, 2H, J=7.2 Hz, NCH$_2$CH_2COOEt), 1.22 (t, 3H, J=7.1 Hz, OCH$_2$CH_3) ppm.

^{13}C NMR (CDCl$_3$, 100 MHz): δ=172.5 (s, O–C=O), 159.0 (s, Ar-C), 139.6 (s, Ar-C), 139.1 (s, Ar-C), 133.0 (d, Ar-CH), 128.7 (d, 2C, 2 × Ar-CH), 128.3 (d, 2C, 2 × Ar-CH), 127.0 (d, Ar-CH), 115.8 (d, Ar-CH), 114.4 (s, Ar-C), 114.2 (d, Ar-CH), 60.4 (t, OCH$_2$CH$_3$), 58.3 (t, NCH$_2$), 57.5 (t, NCH$_2$), 55.4 (q, Ar-OCH$_3$), 49.6 (t, NCH$_2$CH$_2$COOEt), 32.8 (t, NCH$_2$$CH_2$COOEt), 14.2 (q, OCH$_2$$CH_3$) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{20}H_{24}BrNNaO_3]^+$=$[M+Na]^+$: 428.0832; found 428.0833.



55d

Ethyl N-benzyl-N-[(6-bromo-1,3-benzodioxol-5-yl)methyl]-β-alaninate (55d):

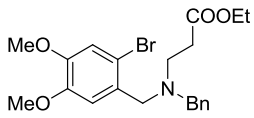
GP-3 was carried out with the secondary amine **54d** (500 mg, 1.56 mmol), ethyl acrylate (312 mg, 3.13 mmol) in methanol (20 mL). Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 95:5 to 80:20) furnished the product ester **55d** (613 mg, 93%) as a viscous liquid [TLC control (petroleum ether/ethyl acetate 7:3, R_f (**54d**)=0.30, R_f (**55d**)=0.55, UV detection)].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2978, 2903, 1732, 1473, 1236, 1185, 1115, 1038, 934, 838 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.37–7.27 (m, 4H, Ar-H), 7.25 (dd, 1H, *J*=7.8 and 7.3 Hz, Ar-H), 7.10 (s, 1H, Ar-H), 6.97 (s, 1H, Ar-H), 5.96 (s, 2H, OCH_2O), 4.13 (q, 2H, *J*=7.1 Hz, OCH_2CH3), 3.64 (s, 2H, NCH_2), 3.62 (s, 2H, NCH_2), 2.85 (t, 2H, *J*=7.1 Hz, NCH_2CH_2COOEt), 2.53 (t, 2H, *J*=7.1 Hz, NCH_2CH_2COOEt), 1.24 (t, 3H, *J*=7.1 Hz, OCH_2CH_3) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=172.5 (s, O–C=O), 147.4 (s, Ar-C), 147.2 (s, Ar-C), 139.1 (s, Ar-C), 131.8 (s, Ar-C), 128.8 (d, 2C, 2 × Ar-CH), 128.3 (d, 2C, 2 × Ar-CH), 127.1 (d, Ar-CH), 114.2 (s, Ar-C), 112.4 (d, Ar-CH), 110.2 (d, Ar-CH), 101.6 (t, OCH_2O), 60.4 (t, OCH_2CH_3), 58.2 (t, NCH_2), 57.2 (t, NCH_2), 49.4 (t, NCH_2CH_2COOEt), 32.7 (t, NCH_2CH_2COOEt), 14.2 (q, OCH_2CH_3) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{20}H_{22}BrNNaO_4]^+$=$[M+Na]^+$: 442.0624; found 442.0638.



55e

Ethyl N-benzyl-N-(2-bromo-4,5-dimethxybenzyl)-β-alaninate (55e):

GP-3 was carried out with the secondary amine **54e** (510 mg, 1.52 mmol), ethyl acrylate (304 mg, 3.03 mmol) in methanol (15 mL). Purification of the residue

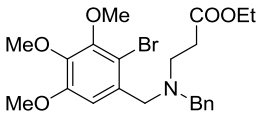
on a silica gel column chromatography (petroleum ether/ethyl acetate 95:5 to 80:20) furnished the product β-aminoester **55e** (629 mg, 95%) as a light brownish viscous liquid [TLC control (petroleum ether/ethyl acetate 7:3, R_f (**54e**)=0.20, R_f (**55e**)=0.50, UV detection)].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2977, 2838, 1730, 1502, 1443, 1374, 1252, 1184, 1157, 1032, 799, 739, 699 cm^{-1}.

^{1}H NMR (CDCl$_3$, 400 MHz): δ=7.38–7.26 (m, 4H, Ar-H), 7.25–7.20 (m, 1H, Ar-H), 7.13 (s, 1H, Ar-H), 6.97 (s, 1H, Ar-H), 4.07 (q, 2H, J=7.1 Hz, OCH_2CH$_3$), 3.89 (s, 3H, ArOCH$_3$), 3.86 (s, 3H, ArOCH$_3$), 3.65 (s, 2H, NCH$_2$), 3.62 (s, 2H, NCH$_2$), 2.87 (t, 2H, J=7.1 Hz, NCH_2CH$_2$COOEt), 2.52 (t, 2H, J=7.1 Hz, CH_2COOEt), 1.19 (t, 3H, J=7.1 Hz, OCH$_2$CH_3) ppm.

^{13}C NMR (CDCl$_3$, 100 MHz): δ=172.5 (s, O–C=O), 148.4 (s, ArOCH$_3$), 148.3 (s, ArOCH$_3$), 139.2 (s, Ar-C), 130.6 (s, Ar-C), 128.7 (d, 2C, 2 × Ar-CH), 128.2 (d, 2C, 2 × Ar-CH), 127.0 (d, Ar-CH), 115.0 (d, Ar-CH), 113.8 (s, Ar-C), 113.1 (d, Ar-CH), 60.3 (t, OCH$_2$CH$_3$), 58.2 (t, NCH$_2$), 57.0 (t, NCH$_2$), 56.1 (q, ArOCH$_3$), 56.0 (q, ArOCH$_3$), 49.5 (t, NCH$_2$CH$_2$COOEt), 32.8 (t, CH$_2$COOEt), 14.1 (q, OCH$_2$$CH_3$) ppm.

HR-MS (ESI$^+$): m/z calculated for [C$_{21}$H$_{26}$BrNNaO$_4$]$^+$=[M+Na]$^+$: 458.0937; found 458.0937.



55f

Ethyl N-benzyl-N-(2-bromo-3,4,5-trimethxybenzyl)-β-alaninate (55f):

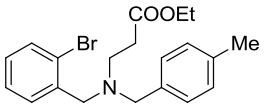
GP-3 was carried out with the secondary amine **54f** (1.1 g, 3.27 mmol), ethyl acrylate (656 mg, 6.55 mmol) in methanol (15 mL). Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 97:3 to 85:15) gave the product β-amino ester **55f** (1.29 g, 92%) as a yellowish viscous liquid [TLC control (petroleum ether/ethyl acetate 7:3, R_f(**54f**)=0.30, R_f(**55f**)=0.60, UV detection)].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2938, 1731, 1570, 1474, 1388, 1330, 1241, 1185, 1105, 1011, 740, 698 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.37–7.26 (m, 4H, Ar-H), 7.26–7.21 (m, 1H, Ar-H), 7.06 (s, 1H, Ar-H), 4.09 (q, 2H, *J*=7.1 Hz, OC*H*$_2$CH$_3$), 3.89 (s, 3H, Ar-OCH$_3$), 3.88 (s, 6H, 2 × Ar-OCH$_3$), 3.69 (s, 2H, NCH$_2$), 3. 65 (s, 2H, NCH$_2$), 2.89 (t, 2H, *J*=7.1 Hz, NC*H*$_2$CH$_2$COOEt), 2.54 (t, 2H, *J*=7.1 Hz, C*H*$_2$COOEt), 1.20 (t, 3H, *J* =7.1 Hz, OCH$_2$C*H*$_3$) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=172.5 (s, O–C=O), 152.6 (s, Ar-C), 150.5 (s, Ar-C), 141.8 (s, Ar-C), 139.1 (s, Ar-C), 134.3 (s, Ar-C), 128.6 (d, 2C, 2 × Ar-CH), 128.3 (d, 2C, 2 × Ar-CH), 127.1 (s, Ar-C), 110.0 (s, Ar-C), 108.9 (d, Ar-CH), 61.1 (q, Ar-OCH$_3$), 60.9 (q, Ar-OCH$_3$), 60.4 (t, O*C*H$_2$CH$_3$), 58.4 (t, NCH$_2$), 57.5 (t, NCH$_2$), 56.1 (q, ArOCH$_3$), 49.7 (t, N*C*H$_2$CH$_2$COOEt), 32.8 (t, *C*H$_2$COOEt), 14.2 (q, OCH$_2$*C*H$_3$) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{22}H_{28}BrNNaO_5]^+$=$[M+Na]^+$: 488.1043; found 488.1045.



55g

Ethyl N-(2-bromobenzyl)-N-(4-methylbenzyl)-β-alaninate (55g):

GP-3 was carried out with the secondary amine **54g** (600 mg, 2.07 mmol), ethyl acrylate (414 mg, 4.14 mmol) in methanol (15 mL). Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 99:1 to 95:5) furnished the product β-amino ester **55g** (679 mg, 84%) as colorless liquid [TLC control (petroleum ether/ethyl acetate 8:2, R_f(**54g**)=0.25, R_f(**55g**)=0.60, UV detection)].

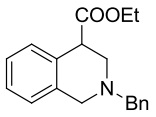
IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2980, 2814, 1732, 1513, 1440, 1367, 1242, 1181, 1130, 1042, 1023, 797, 749, 662 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.60 (d, 1H, *J*=7.3 Hz, Ar-H), 7.50 (d, 1H, *J*=7.8 Hz, Ar-H), 7.27 (dd, 1H, *J*=7.8 and 7.8 Hz, Ar-H), 7.26 (d, 2H, *J*=8.3 Hz, Ar-H), 7.08 (dd, 1H, *J*=7.8 and 7.3 Hz, Ar-H), 7.06 (d, 2H, *J*=8.3 Hz, Ar-H), 4.14 (q,

2H, *J*=7.1 Hz, OC*H*$_2$CH$_3$), 3.71 (s, 2H, NCH$_2$), 3.62 (s, 2H, NCH$_2$), 2.87 (t, 2H, *J*=7.2 Hz, NC*H*$_2$CH$_2$COOEt), 2.54 (t, 2H, *J*=7.2 Hz, C*H*$_2$COOEt), 2.34 (s, 3H, ArCH$_3$), 1.19 (t, 3H, *J*=7.1 Hz, OCH$_2$C*H*$_3$) ppm.

^{13}C NMR (CDCl$_3$, 100 MHz): δ=172.6 (s, O–C=O), 138.6 (s, Ar-C), 136.6 (s, Ar-C), 135.9 (d, Ar-CH), 132.6 (d, Ar-CH), 130.6 (d, Ar-CH), 129.0 (d, 2C, 2 × Ar-CH), 128.8 (d, 2C, 2 × Ar-CH), 128.3 (d, Ar-CH), 127.3 (d, Ar-CH), 124.3 (s, Ar-C), 60.4 (t, O*C*H$_2$CH$_3$), 58.0 (t, NCH$_2$), 57.4 (t, NCH$_2$), 49.4 (t, N*C*H$_2$CH$_2$COOEt), 32.7 (t, *C*H$_2$COOEt), 21.1 (q, ArCH$_3$), 14.2 (q, OCH$_2$*C*H$_3$) ppm.

HR-MS (ESI$^+$): m/z calculated for [C$_{20}$H$_{24}$BrNNaO$_2$]$^+$=[M+Na]$^+$: 412.0883; found 412.0875.



56a

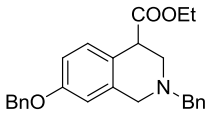
Ethyl 2-benzyl-1,2,3,4-tetrahydroisoquinolidine-4-carboxylate (56a):

GP-4 was carried out with the ester **55a** (100 mg, 0.28 mmol), Pd(OAc)$_2$ (6 mg, 10 mol%), PPh$_3$(15 mg, 20 mol%) and Cs$_2$CO$_3$ (182 mg, 0.56 mmol) in toluene (1.5 mL) under nitrogen atmosphere at 80 °C for 24 h. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 98:2 to 95:5) furnished the tetrahydroisoquinoline **56a** (64.4 mg, 82%) as a colorless viscous liquid [TLC control (petroleum ether/ethyl acetate 9:1, R$_f$(**55a**)=0.55, R$_f$(**56a**)=0.45, UV detection)].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2926, 2806, 1732, 1452, 1369, 1242, 1166, 1034, 741, 699 cm^{-1}.

^{1}H NMR (CDCl$_3$, 400 MHz): δ=7.36–7.10 (m, 8H, Ar-H), 7.06–6.98 (m, 1H, Ar-H), 4.20–4.10 (m, 2H, OC*H*$_2$CH$_3$), 3.85 (dd, 1H, *J*=5.6 and 4.8 Hz, CHCOOEt), 3.80 [d, 1H, *J*=14.9 Hz, NCH$_2$(a, b)], 3.74 [d, 1H, *J*=13.2 Hz, NCH$_2$(a’,b’)], 3.65 [d, 1H, *J*=13.2 Hz, NCH$_2$(a’,b’)], 3.59 [d, 1H, *J*=14.9 Hz, NCH$_2$(a, b)], 3.18 (dd, 1H, *J*=11.5 and 5.6 Hz, NC*H*$_{2a}$CHCOOEt), 2.85 (dd, 1H, *J*=11.5 and 4.8 Hz, NC*H*$_{2b}$CHCOOEt), 1.23 (t, 3H, *J*=7.2 Hz, OCH$_2$C*H*$_3$) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz): δ=173.2 (s, O–C=O), 138.1 (s, Ar-C), 135.2 (s, Ar-C), 131.6 (s, Ar-C), 129.3 (d, Ar-CH), 129.0 (d, 2C, 2 × Ar-CH), 128.3 (d, 2C, 2 × Ar-CH), 127.2 (d, Ar-CH), 126.9 (d, Ar-CH), 126.7 (d, Ar-CH), 126.3 (d, Ar-CH), 62.3 (t, NCH_2), 60.9 (t, OCH_2CH_3), 56.1 (t, NCH_2), 52.9 (t, $NCH_2CHCOOEt$), 45.5 (d, *C*HCOOEt), 14.2 (q, OCH_2CH_3) ppm. HR-MS (ESI^+) m/z calculated for $[C_{19}H_{22}NO_2]^+$=$[M+H]^+$: 296.1645; found 296.1656.



56b

Ethyl 2-benzyl-7-(benzyloxy)-1,2,3,4-tetrahydroisoquinolidine-4-carboxylate (56b):

GP-4 was carried out with the ester **55b** (156 mg, 0.33 mmol), $Pd(OAc)_2$ (7.2 mg, 10 mol%), PPh_3 (16.9 mg, 20 mol%) and Cs_2CO_3 (210 mg, 0.65 mmol) in toluene at 80 °C for 24 h. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 95:5 to 85:15) furnished the tetrahydroisoquinoline **56b** (105 mg, 80%) as colorless solid, m. p. 102–105 °C, recrystallized from petroleum ether and dichloromethane [TLC control (petroleum ether/ethyl acetate 8:2, R_f(**55b**)=0.60, R_f(**56b**)=0.40, UV detection)].

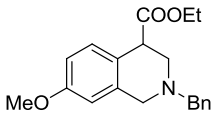
IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3060, 2983, 1732, 1612, 1504, 1454, 1265, 1173, 1096, 1027, 736, 700 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.50–7.25 (m, 10H, Ar-H), 7.18 (d, 1H, *J*=8.0 Hz, Ar-H), 6.87 (dd, 1H, *J*=8.0 and 2.4 Hz, Ar-H), 6.68 (d, 1H, *J*=2.4 Hz, Ar-H), 5.05 (s, 2H, OCH_2Ph), 4.22–4.13 (m, 2H, OCH_2CH_3), 3.88–3.53 (m, 1H, CHCOOEt), 3.83 [d, 1H, *J*=14.6 Hz, NCH_2(a, b)], 3.79 [d, 1H, *J*=14.6 Hz, NCH_2(a, b)], 3.74 [d, 1H, *J*=13.8 Hz, NCH_2(a', b')], 3.65 [d, 1H, *J*=13.8 Hz, NCH_2(a', b')], 3.21 (dd, 1H, *J*=11.4 and 5.6 Hz, $NCH_{2a}CHCOOEt$), 2.90 (dd, 1H, 1H, *J*=11.4 and 4.2 Hz, $NCH_{2b}CHCOOEt$), 1.24 (t, 3H, *J*=7.2 Hz, OCH_2CH_3) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=173.5 (s, O–C=O), 157.7 (s, Ar-C), 138.1 (s, Ar-C), 137.1 (s, Ar-C), 136.4 (s, Ar-C), 130.4 (d, Ar-CH), 129.0 (d, 2C, 2 × Ar-CH), 128.6 (d, 2C, 2 × Ar-CH), 128.3 (d, 2C, 2 × Ar-CH), 128.0 (d, Ar-CH), 127.5

(d, 2C, 2 × Ar-CH) 127.2 (d, Ar-CH), 124.1 (s, Ar-C), 113.6 (d, Ar-CH), 112.2 (d, Ar-CH), 70.0 (t, OCH_2Ph), 62.2 (t, OCH_2CH_3), 60.9 (t, NCH_2), 56.2 (t, NCH_2), 53.1 (t, $NCH_2CHCOOEt$), 44.7 (d, $NCH_2CHCOOEt$), 14.2 (q, OCH_2CH_3) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{26}H_{27}NNaO_3]^+$=$[M+Na]^+$: 424.1883; found 424.1887.



56c

Ethyl 2-benzyl-7-methoxy-1,2,3,4-tetrahydroisoquinolidine-4-carboxylate (56c):

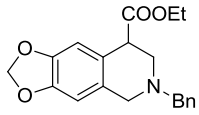
GP-4 was carried out with the amino ester **55c** (109 mg, 0.27 mmol), $Pd(OAc)_2$ (6 mg, 10 mol%), PPh_3 (14 mg, 20 mol%) and Cs_2CO_3 (174 mg, 0.54 mmol) in toluene (1.5 mL) at 80 °C for 24 h. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 95:5 to 80:20) furnished the tetrhydroisoquinoline **56c** (76 mg, 87%) as a viscous liquid [TLC control (Petroleum ether/ethyl acetate 8:2, R_f (**55c**)=0.55, R_f(**56c**)=0.45, UV detection)].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2931, 2802, 1732, 1613, 1503, 1458, 1324, 1250, 1168, 1035, 854 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.40–7.25 (m, 5H, Ar-H), 7.16 (d, 1H, J=8.4 Hz, Ar-H), 6.79 (dd, 1H, J=8.4 and 2.2 Hz, Ar-H), 6.58 (d, 1H, J=1.6 Hz, Ar-H), 4.24–4.10 (m, 2H, OCH_2CH_3), 3.83–3.79 (m, 1H, CHCOOEt), 3.78 (s, 3H, Ar–OCH_3), 3.77 [d, 1H, J=15.0 Hz, NCH_2(a', b')], 3.74 [d, 1H, J=13.2 Hz, NCH_2(a, b)], 3.68 [d, 1H, J=13.2 Hz, NCH_2(a, b)], 3.60 [d, 1H, J=15.0 Hz, NCH_2(a, b)], 3.19 (dd, 1H, J=11.4 and 5.7 Hz, $NCH_{2a}CHCOOEt$), 2.87 (dd, 1H, J=11.5 and 4.8 Hz, $NCH_{2b}CHCOOEt$), 1.23 (t, 3H, J=7.1 Hz, OCH_2CH_3) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=173.5 (s, O–C=O), 158.4 (s, Ar-C), 138.1 (s, Ar-C), 136.3 (s, Ar-C), 130.3 (d, Ar-CH), 129.0 (d, 2C, 2 × Ar-CH), 128.3 (d, 2C, 2 × Ar-CH), 127.2 (d, Ar-CH), 123.7 (s, Ar-C), 112.8 (d, Ar-CH), 111.2 (d, Ar-CH), 62.2 (t, OCH_2CH_3), 60.9 (t, NCH_2), 56.2 (t, $NCH_2CHCOOEt$), 55.2 (q, $ArOCH_3$), 53.1 (t, NCH_2), 44.6 (d, $NCH_2CHCOOEt$), 14.2 (q, OCH_2CH_3) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{20}H_{23}NNaO_3]^+$=$[M+Na]^+$: 348.1570; found 348.1575.



56d

Ethyl 6-benzyl-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinolidine-8-carboxylate (56d):

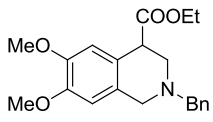
GP-4 was carried out with the β-aminoester **55d** (148 mg, 0.35 mmol), $Pd(OAc)_2$ (7.9 mg, 10 mol%), PPh_3 (18.4 mg, 20 mol%) and Cs_2CO_3 (229 mg, 0.71 mmol) in toluene (1.5 mL) at 80 °C for 24 h. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 95:5 to 80:20) furnished the tetrahydroisoquinoline **56d** (83 mg, 70%) as a viscous liquid [TLC control (petroleum ether/ethyl acetate 8:2, R_f(**55d**)=0.50, R_f(**56d**)=0.40, UV detection)].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2918, 1728, 1488, 1454, 1238, 1213, 1179, 1119, 1029, 925, 730, 693 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.39–7.26 (m, 5H, Ar-H), 6.70 (s, 1H, Ar-H), 6.50 (s, 1H, Ar-H), 5.91 (d, 2H, *J*=5.0 Hz, OCH_2O), 4.18–4.15 (m, 2H, OCH_2CH_3), 3.76–3.65 (m, 1H, CHCOOEt), 3.75 [d, 1H, *J*=13.0 Hz, NCH_2(a,b)], 3.73 [d, 1H, *J*=14.6 Hz, NCH_2(a',b')], 3.65 [d, 1H, *J*=13.0 Hz, NCH_2(a,b)], 3.51 [d, 1H, *J*=14.6 Hz, NCH_2(a', b')], 3.16 (dd, 1H, *J*=11.3 and 5.3 Hz, NCH_{2a}CHCOOEt), 2.82 (dd, 1H, *J*=11.3 and 4.1 Hz, NCH_{2b}CHCOOEt), 1.23 (t, *J*=7.1 Hz, 3H, OCH_2CH_3) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=173.3 (s, O–C=O), 146.7 (s, Ar-C), 146.2 (s, Ar-C), 138.1 (s, Ar-C), 129.0 (d, 2C, 2 × Ar-CH), 128.6 (s, Ar-C), 128.3 (d, 2C, 2 × Ar-CH), 127.2 (d, Ar-CH), 124.4 (s, Ar-C), 109.0 (d, Ar-CH), 106.5 (d, Ar-CH), 100.9 (t, OCH_2O), 62.1 (t, OCH_2CH_3), 61.0 (t, NCH_2), 56.1 (t, $NCH_2CHCOOEt$), 52.8 (t, NCH_2), 45.3 (d, $NCH_2CHCOOEt$), 14.2 (q, OCH_2CH_3) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{20}H_{21}NNaO_4]^+$=$[M+Na]^+$: 362.1363; found 362.1367.



56e

Ethyl 2-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolidine-4-carboxylate (56e):

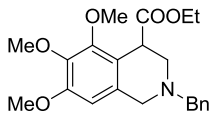
GP-4 was carried out with the bromoester **55e** (100 mg, 0.23 mmol), $Pd(OAc)_2$ (5.2 mg, 10 mol%), PPh_3 (12.1 mg, 20 mol%) and Cs_2CO_3 (150 mg, 0.46 mmol) in toluene (1.5 mL) at 80 °C for 24 h. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 98:2 to 80:20) furnished the tetrahydroisoquinoline **56e** (64.5 mg, 79%) as a viscous liquid [TLC control (petroleum ether/ethyl acetate 7:3, R_f(**55e**)=0.50, R_f(**56e**)=0.40, UV detection)].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2931, 1729, 1514, 1455, 1366, 1252, 1134, 1032, 741, 697 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.41–7.24 (m, 5H, Ar-H), 6.74 (s, 1H, Ar-H), 6.52 (s, 1H, Ar-H), 4.26–4.06 (m, 2H, OCH_2CH$_3$), 3.85 (s, 3H, Ar-OCH$_3$), 3.83 (s, 3H, Ar-OCH$_3$), 3.78 (dd, 1H, *J*=5.5 and 4.8 Hz, CHCOOEt), 3.74 [d, 1H, *J*=13.1 Hz, NCH$_2$(a',b')], 3.67 [d, 1H, *J*=14.5 Hz, NCH$_2$(a,b)], 3.65 [d, 1H, *J*=13.1 Hz, NCH$_2$(a',b')], 3.52 [d, 1H, *J*=14.5 Hz, NCH$_2$(a,b)], 3.17 (dd, 1H, *J*=11.4 and 5.5 Hz, NCH_{2a}CHCOOEt), 2.85 (dd, 1H, *J*=11.4 and 4.8 Hz, NCH_{2b}CHCOOEt), 1.22 (t, 3H, *J*=7.1 Hz, OCH$_2$CH_3) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=173.3 (s, O–C=O), 148.1 (s, Ar-C), 147.5 (s, Ar-C), 138.1 (s, Ar-C), 129.0 (d, 2C, 2 × Ar-CH), 128.3 (d, 2C, 2 × Ar-CH), 127.4 (s, Ar-C), 127.2 (d, Ar-CH), 123.3 (s, Ar-C), 111.8 (d, Ar-CH), 109.2 (d, Ar-CH), 62.2 (t, NCH$_2$), 60.9 (t, O*C*H$_2$CH$_3$), 55.9 (q, Ar-OCH$_3$), 55.8 (q, Ar-OCH$_3$), 55.7 (t, NCH$_2$), 53.0 (t, N*C*H$_2$CHCOOEt), 44.9 (d, *C*HCOOEt), 14.2 (q, OCH$_2$*C*H$_3$) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{21}H_{25}NNaO_4]^+$=$[M+Na]^+$: 378.1676; found 378.1685.



56f

Ethyl 2-benzyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinolidine-4-carboxylate (56f):

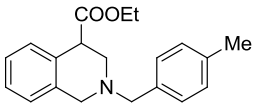
GP-4 was carried out with the β-aminoester **55f** (100 mg, 0.22 mmol), $Pd(OAc)_2$ (5 mg, 10 mol%), PPh_3(11.3 mg, 20 mol%) and Cs_2CO_3 (140 mg, 0.43 mmol) in toluene (1.5 mL) at 80 °C for 24 h. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 95:5 to 85:15) furnished the tetrahydroisoquinoline **56f** (56.9 mg, 85%) as a viscous liquid [TLC control (petroleum ether/ethyl acetate 7:3, R_f(**55f**)=0.55, R_f(**56f**)=0.45, UV detection)] based on the recovery of starting material **55f** (19 mg, 19%).

IR (neat; MIR-ATR, 4000–600 cm^{-1}): 2937, 1732, 1598, 1458, 1357, 1238, 1171, 1118, 1020, 741, 698 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.42–7.20 (m, 5H, Ar-H), 6.35 (s, 1H, Ar-H), 4.25–4.00 (m, 2H, O*C*H_2CH$_3$), 3.87 (s, 3H, Ar-OCH$_3$), 3.83 (s, 3H, Ar-OCH$_3$), 3.81 (s, 3H, Ar-OCH$_3$), 3.80–3.67 (m, 1H, CHCOOEt), 3.74 [d, 1H, *J*=14.8 Hz, NCH$_2$(a,b)], 3.72 [d, 1H, *J*=13.2 Hz, NCH$_2$(a',b')], 3.70 [d, 1H, *J*=14.8 Hz, NCH$_2$(a,b)], 3.60 [d, 1H, *J*=13.2 Hz, NCH$_2$(a',b')], 3.08 (dd, 1H, *J*=11.5 and 5.1 Hz, NCH_{2a}CHCOOEt), 2.81 (dd, 1H, *J*=11.5 and 4.8 Hz, NCH_{2b}CHCOOEt), 1.20 (t, 3H, *J*=7.2 Hz, OCH$_2$CH_3) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=173.9 (s, O–C=O), 152.8 (s, Ar-C), 151.5 (s, Ar-C), 140.0 (s, Ar-C), 138.0 (s, Ar-C), 130.7 (s, Ar-C), 128. 9 (d, 2C, 2 × Ar-CH), 128.3 (d, 2C, 2 × Ar-CH), 127.2 (d, Ar-CH), 118.4 (s, Ar-C), 104.8 (d, Ar-CH), 62.0 (t, O*C*H$_2$CH$_3$), 60.7 (q, Ar-OCH$_3$), 60.7 (t, NCH$_2$), 60.3 (q, Ar-OCH$_3$), 55.9 (t and q, 2C, NCH$_2$ & ArOCH$_3$), 53.5 (t, N*C*H$_2$CHCOOEt), 41.3 (d, NCH$_2$*C*HCOOEt), 14.2 (q, OCH$_2$*C*H$_3$) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{22}H_{27}NNaO_5]^+$=$[M+Na]^+$: 408.1781; found 408.1781.



56g

Ethyl 2-(4-methylbenzyl)-1,2,3,4-tetrahydroisoquinolidine-4-carboxylate (56g):

GP-4 was carried out with the β-aminoester **55g** (100 mg, 0.26 mmol), $Pd(OAc)_2$ (5.7 mg, 10 mol%), PPh_3 (13.4 mg, 20 mol%) and Cs_2CO_3 (167 mg, 0.52 mmol) in toluene (1.5 mL) at 80 °C for 24 h. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 98:2 to 95:5) furnished the cyclic ester **56g** (58.6 mg, 74%) as a colorless viscous liquid [TLC control (petroleum ether/ethyl acetate 9:1, R_f(**55g**)=0.55, R_f(**56g**)=0.45, UV detection)].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): 2979, 2798, 1731, 1514, 1453, 1366, 1238, 1193, 1158, 1092, 1023, 803, 745, 725 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.34–7.10 (m, 7H, Ar-H), 7.06 (dd, 1H, *J*=8.6 and 2.8 Hz, Ar-H), 4.30–4.05 (m, 2H, OC*H*$_2$CH$_3$), 3.88 (dd, 1H, *J*=5.8 and 4.9 Hz, CHCOOEt), 3.78 [d, 1H, *J*=15.0 Hz, NCH_2(a,b)], 3.71 [d, 1H, *J*=13.0 Hz, NCH_2(a',b')], 3.65 [d, 1H, *J*=13.0 Hz, NCH_2(a',b')], 3.60 [d, 1H, *J*=15.0 Hz, NCH_2(a,b)], 3.18 (dd, 1H, *J*=11.4 and 5.8 Hz, NC*H*$_{2a}$CHCOOEt), 2.88 (dd, 1H, *J*=11.5 and 4.9 Hz, NC*H*$_{2b}$CHCOOEt), 2.37 (s, 3H, $ArCH_3$), 1.24 (t, 3H, *J*=7.1 Hz, OCH_2CH_3) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=173.2 (s, O–C=O), 136.8 (s, Ar-C), 135.2 (s, Ar-C), 135.0 (s, Ar-C), 131.6 (s, Ar-C), 129.2 (d, Ar-CH), 129.0 (d, 4C, 4 × Ar-CH), 126.9 (d, Ar-CH), 126.7 (d, Ar-CH),126.3 (d, Ar-CH), 62.0 (t, O*C*H$_2$CH$_3$), 60.9 (t, NCH_2), 56.1 (t, NCH_2), 52.9 (t, N*C*H$_2$CHCOOEt), 45.5 (d, *C*HCOOEt), 21.2 (s, $ArCH_3$), 14.2 (q, OCH_2CH_3) ppm.

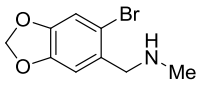
HR-MS (ESI$^+$): m/z calculated for $[C_{20}H_{23}NNaO_2]^+$=$[M+Na]^+$: 332.1621; found 332.1628.

I.5.2 Synthesis of tetrahydroisoquinolines using sequential domino one-pot method from the secondary amines:

The secondary amines **54a**, **54c**, **54d**, **54e** and **54h** are reported in the literature.[52]

General Procedure for Sequential One-pot Reaction, for the Synthesis of Tetrahydroisoquinoline 56 (GP- 1):

To an oven dried Schlenk tube, were added secondary amine **54** (1 mmol) and alkyl (ethyl, or methyl and or *tert*-butyl) acrylate (5 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at 110 °C in an oil bath, for 24 h (for methyl and ethyl acrylates) and for 48 h (for *tert*-butyl acrylate). Progress of the Michael addition was monitored by TLC till the reaction is completed. The reaction mixture was allowed to attain room temperature and excess of alkyl acrylate was removed under vacuum (10^{-2} mbar). To the resultant reaction mixture at room temperature, were added $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%) and Cs_2CO_3 (2 mmol) followed by toluene (3 mL) under nitrogen atmosphere. The reaction mixture was then allowed to stir at 80 °C for 24 h (in case of **56h**, **56i**, **56a** and **56d**), 36 h (in case of **56b**, **56c**, **56j**, **56l**, **56m**, **56n**, **56p** and **56q**) and 48 h (in case of **56k** and **56o**) in an oil bath and the progress was monitored by TLC. The mixture was cooled to room temperature, treated with aqueous NH_4Cl solution and then extracted with ethyl acetate (3 × 15 mL). The organic layers were washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate) furnished the tetrahydroisoquinoline **56** (70–85%).



54i

N-[(6-bromo-1,3-benzodioxol-5-yl)methyl]-N-methylamine (54i):

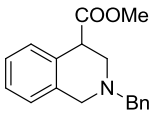
GP-2 was followed for the 2-bromopiperanal **53d** (1.5 g, 6.55 mmol) with methyl amine (609 mg, 19.65 mmol) and $NaBH_4$ (374 mg, 9.82 mmol) in methanol (25 mL). Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 60:40 to ethyl acetate/methanol, 90:10) furnished the secondary amine **54i** (1.18 g, 74%) as viscous liquid. [TLC control (ethyl acetate/methanol 90:10, R_f(**53d**)=0.90, R_f(**54i**)=0.35, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3291, 2893, 1501, 1473, 1408, 1389, 1369, 1230, 1114, 1033, 929, 859, 830, 786, 719, 673, 650 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=6.96 (s, 1H, Ar-H), 6.86 (s, 1H, Ar-H), 5.93 (s, 2H, OCH_2O), 3.71 [s, 2H, Ar-CH_2N(H)Me], 2.50 (br. s, 1H, NH), 2.40 (s, 3H, NCH_3) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=147.3 (s, Ar-C), 147.3 (s, Ar-C), 131.7 (s, Ar-C), 114.2 (s, Ar-C), 112.6 (d, Ar-CH), 110.1 (d, Ar-CH), 101.6 (t, OCH_2O), 55.2 [t, $ArCH_2N$(H)Me], 35.4 (q, NCH_3) ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_9H_9BrNO_2]^+$=$[M–H]^+$: 241.9811; found 241.9802.



56a

Methyl 2-benzyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (56h):

GP-1 was followed to the secondary amine **54a** (276 mg, 1 mmol) with methyl acrylate (430 mg, 5 mmol) at 110 °C for 24 h. After removal of excess methyl acrylate, to the resultant reaction mixture at room temperature, were added $Pd(OAc)_2$ (22.4 mg, 10 mol%), PPh_3 (52.4 mg, 20 mol%) and Cs_2CO_3 (651.6 mg, 2 mmol) followed by toluene (3 mL) under nitrogen atmosphere, at room temperature and stirred at 80 °C in an oil bath, for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 90:10) furnished the tetrahydroisoquinoline **56h** (211 mg, 75%) as colorless viscous liquid. [TLC control (petroleum ether/ethyl acetate 85:15), R_f(**54a**)=0.40, R_f(**56h**)=0.55, UV detection].

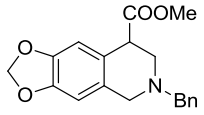
IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3026, 2949, 2803, 1732, 1495, 1453, 1433, 1239, 1197, 1163, 1094, 1028, 922, 740, 699 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.36–7.05 (m, 8H, Ar-H), 6.96 (dd, 1H, *J*=8.0 and 3.5 Hz, Ar-H), 3.79 (dd, 1H, *J*=5.5 and 4.8 Hz, CHCOOMe), 3.72 [d, 1H, *J*=15.0 Hz, NCH_2(a,b)], 3.66 [d, 1H, *J*=13.2 Hz, NCH_2(a',b')], 3.60 (s, 3H, $COOCH_3$), 3.58 [d, 1H, *J*=13.2 Hz, NCH_2(a',b')], 3.51 [d, 1H, *J*=15.0 Hz,

NCH_2(a,b)], 3.10 (dd, 1H, *J*=11.5 and 5.5 Hz, NCH_{2a}CHCOOMe), 2.77 (dd, 1H, *J*=11.5 and 4.8 Hz, NCH_{2b}CHCOOMe) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=173.6 (s, O–C=O), 137.9 (s, Ar-C), 135.1 (s, Ar-C), 131.4 (s, Ar-C), 129.3 (d, Ar-CH), 129.0 (d, 2C, 2 × Ar-CH), 128.2 (d, 2C, 2 × Ar-CH), 127.2 (d, Ar-CH), 126.9 (d, Ar-CH), 126.7 (d, Ar-CH), 126.3 (d, Ar-CH), 62.1 (t, NCH_2), 55.9 (t, NCH_2), 52.8 (t, NCH_2), 52.0 (q, COO*C*H_3), 45.4 (d, *C*HCOOMe) ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{18}H_{20}NO_2]^+$=$[M+H]^+$: 282.1489; found 282.1498.



56i

Methyl 6-benzyl-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinoline-8-carboxylate (56i):

GP-1 was followed to the secondary amine **54d** (320 mg, 1 mmol) with methyl acrylate (430 mg, 5 mmol) at 110 °C for 24 h. After removal of excess methyl acrylate, to the resultant reaction mixture at room temperature, were added $Pd(OAc)_2$ (22.4 mg, 10 mol%), PPh_3 (52.4 mg, 20 mol%) and Cs_2CO_3 (651.6 mg, 2 mmol) followed by toluene (3 mL) under nitrogen atmosphere and stirred at 80 °C in an oil bath, for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 80:20) furnished the tetrahydroisoquinoline **56i** (260 mg, 80%) as pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 80:20), R_f(**54d**)=0.35, R_f(**56i**)=0.45, UV detection].

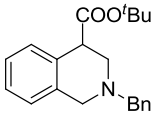
IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2950, 2922, 1736, 1503, 1485, 1454, 1391, 1240, 1206, 1163, 1118, 1039, 938, 863, 742, 700 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.45–7.25 (m, 5H, Ar-H), 6.70 (s, 1H, Ar-H), 6.51 (s, 1H, Ar-H), 5.92 (d, 2H, *J*=4.8 Hz, OCH_2O), 3.77 (dd, 1H, *J*=5.5 and 4.8 Hz, CHCOOMe), 3.74 [d, 1H, *J*=13.2 Hz, NCH_2(a,b)], 3.73 [d, 1H, *J*=14.7 Hz, NCH_2(a',b')], 3.71 (s, 3H, $COOCH_3$), 3.65 [d, 1H, *J*=13.2 Hz, NCH_2(a,b)], 3.51 [d,

1H, *J*=14.7 Hz, NCH_2(a',b')], 3.16 (dd, 1H, *J*=11.5 and 5.5 Hz, $NCH_{2a}CHCOOMe$), 2.81 (dd, 1H, *J*=11.5 and 4.8 Hz, $NCH_{2b}CHCOOMe$) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=173.6 (s, O–C=O), 146.7 (s, Ar-C), 146.1 (s, Ar-C), 137.9 (s, Ar-C), 128.9 (d, 2C, 2 × Ar-CH), 128.5 (s, Ar-C), 128.3 (d, 2C, 2 × Ar-CH), 127.3 (d, Ar-CH), 124.3 (s, Ar-C), 109.0 (d, Ar-CH), 106.4 (d, Ar-CH), 100.8 (t, OCH_2O), 62.0 (t, NCH_2), 56.0 (t, NCH_2), 52.7 (t, NCH_2), 52.1 (q, $COOCH_3$), 45.2 (d, *C*HCOOMe) ppm.

HR-MS (mixed APCI$^+$ and ESI$^+$): m/z calculated for $[C_{19}H_{20}NO_4]^+=[M+H]^+$: 326.1387; found 326.1373.



56j

***Tert*-butyl 2-benzyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (56j):**

GP-5 was followed to the secondary amine **54a** (276 mg, 1 mmol) with *tert*-butyl acrylate (640 mg, 5 mmol) at 110 °C for 48 h. After removal of excess *tert*-butyl acrylate, to the resultant reaction mixture at room temperature, were added $Pd(OAc)_2$ (22.4 mg, 10 mol%), PPh_3 (52.4 mg, 20 mol%) and Cs_2CO_3 (651.6 mg, 2 mmol) followed by toluene (3 mL) under nitrogen atmosphere and stirred at 80 °C in an oil bath, for 36 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 98:2 to 85:15) furnished the tetrahydroisoquinoline **56j** (271 mg, 84%) as colorless viscous liquid. [TLC control (petroleum ether/ethyl acetate 90:10), R_f(**54a**)=0.35, R_f(**56j**)=0.60, UV detection].

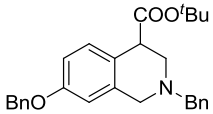
IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2976, 2930, 2803, 1725, 1453, 1366, 1254, 1156, 1131, 1025, 977, 846, 750, 698 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.30 (d, 2H, *J*=7.3 Hz, Ar-H), 7.24 (dd, 2H, *J*=7.5 and 7.5 Hz, Ar-H), 7.21–7.03 (m, 4H, Ar-H), 6.93 (dd, 1H, *J*=5.0 and 5.0 Hz, Ar-H), 3.68 (dd, 1H, *J*=5.8 and 4.9 Hz, CHCOO^{t}Bu), 3.67 [d, 1H, *J*=14.9 Hz, NCH_2(a,b)], 3.62 [d, 1H, *J*=13.2 Hz, NCH_2(a',b')], 3.56 [d, 1H, *J*=13.2 Hz, NCH_2(a',b')], 3.47 [d, 1H, *J*=14.9 Hz, NCH_2(a,b)], 3.08 (dd, 1H, *J*=11.5 and 5.8 Hz,

NCH_{2a}CHCOO^{t}Bu), 2.78 (dd, 1H, *J*=11.5 and 4.9 Hz, NCH_{2b}CHCOO^{t}Bu), 1.34 [s, 9H, C(CH_3)$_3$] ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=172.3 (s, O–C=O), 138.1 (s, Ar-C), 135.0 (s, Ar-C), 131.9 (s, Ar-C), 129.2 (d, Ar-CH), 129.1 (d, 2C, 2 × Ar-CH), 128.3 (d, 2C, 2 × Ar-CH), 127.1 (d, Ar-CH), 126.7 (d, Ar-CH), 126.6 (d, Ar-CH), 126.1 (d, Ar-CH), 80.8 [s, COO*C*(CH_3)$_3$], 62.5 (t, NCH_2), 56.1 (t, NCH_2), 53.3 (t, NCH_2), 46.1 (d, *C*HCOO^{t}Bu), 28.0 [q, 3C, C(*C*H_3)$_3$] ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{21}H_{26}NO_2]^+$=$[M+H]^+$: 324.1958; found 324.1968.



56k

***Tert*-butyl 2-benzyl-7-(benzyloxy)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (56k)**:

GP-5 was followed to the secondary amine **54b** (382 mg, 1 mmol) with *tert*-butyl acrylate (640 mg, 5 mmol) at 110 °C for 48 h. After removal of excess *tert*-butyl acrylate, to the resultant reaction mixture at room temperature, were added $Pd(OAc)_2$ (22.4 mg, 10 mol%), PPh_3 (52.4 mg, 20 mol%) and Cs_2CO_3 (651.6 mg, 2 mmol) followed by toluene (3 mL) under nitrogen atmosphere and stirred at 80 °C in an oil bath, for 48 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 96:4 to 80:20) furnished the tetrahydroisoquinoline **56k** (339 mg, 79%) as pale yellow semi-solid. [TLC control (petroleum ether/ethyl acetate 85:15), R_f(**54b**)=0.35, R_f(**56k**)=0.55, UV detection].

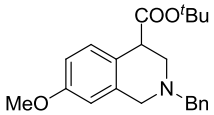
IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2976, 2798, 1724, 1611, 1502, 1454, 1366, 1272, 1242, 1132, 1094, 1026, 849, 734, 697 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.45–7.20 (m, 10H, Ar-H), 7.13 (d, 1H, *J*=8.5 Hz, Ar-H), 6.82 (dd, 1H, *J*=8.5 and 2.6 Hz, Ar-H), 6.61 (d, 1H, *J*=2.6 Hz, Ar-H), 4.99 (s, 2H, OCH_2Ph), 3.71 [d, 1H, *J*=14.9 Hz, NCH_2(a,b)], 3.68 (dd, 1H, *J*=5.8 and 5.0 Hz, CHCOO^{t}Bu), 3.67 [d, 1H, *J*=13.2 Hz, NCH_2(a',b')], 3.62 [d, 1H, *J*=13.2 Hz, NCH_2(a',b')], 3.49 [d, 1H, *J*=14.9 Hz, NCH_2(a,b)], 3.14 (dd, 1H, *J*=11.5 and 5.8

Hz, NCH_{2a}CHCOO^{t}Bu), 2.83 (dd, 1H, *J*=11.5 and 5.0 Hz, NCH_{2b}CHCOO^{t}Bu), 1.41 [s, 9H, C(CH_3)$_3$] ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=172.5 (s, O=C-O), 157.5 (s, Ar-C), 138.1 (s, Ar-C), 137.0 (s, Ar-C), 136.3 (s, Ar-C), 130.2 (d, Ar-CH), 129.0 (d, 2C, Ar-CH), 128.5 (d, 2C, Ar-CH), 128.2 (d, 2C, Ar-CH), 127.8 (d, Ar-CH), 127.3 (d, 2C, Ar-CH), 127.1 (d, Ar-CH), 124.4 (s, Ar-C), 113.5 (d, Ar-CH), 112.1 (d, Ar-CH), 80.7 [s, COO*C*(CH_3)$_3$], 69.9 (t, OCH_2Ph), 62.3 (t, NCH_2), 56.2 (t, NCH_2), 53.4 (t, NCH_2), 45.3 (d, *C*HCOO^{t}Bu), 28.0 [q, 3C, C(*C*H_3)$_3$] ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{28}H_{32}NO_3]^+$=$[M+H]^+$: 430.2377; found 430.2370.



56l

***Tert*-butyl 2-benzyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (56l)**:

GP-5 was followed to the secondary amine **54c** (306 mg, 1 mmol) with *tert*-butyl acrylate (640 mg, 5 mmol) at 110 °C for 48 h. After removal of excess *tert*-butyl acrylate, to the resultant reaction mixture at room temperature, were added $Pd(OAc)_2$ (22.4 mg, 10 mol%), PPh_3 (52.4 mg, 20 mol%) and Cs_2CO_3 (651.6 mg, 2 mmol) followed by toluene (3 mL) under nitrogen atmosphere and stirred at 80 °C in an oil bath, for 36 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 80:20) furnished the tetrahydroisoquinoline **56l** (282 mg, 80%) as yellowish brown solid, M. P. 91–93 °C (recrystallized from DCM/Hexane). [TLC control (petroleum ether/ethyl acetate 85:15), R_f(**54c**)=0.30, R_f(**56l**)=0.55, UV detection].

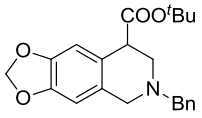
IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2975, 2926, 1727, 1613, 1504, 1454, 1366, 1274, 1245, 1146, 1095, 1030, 850, 739, 699 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.29 (d, 2H, *J*=7.1 Hz, Ar-H), 7.24 (dd, 2H, *J*=7.1 and 7.1 Hz, Ar-H), 7.18 (t, 1H, *J*=7.1 Hz, Ar-H), 7.06 (d, 1H, *J*=8.5 Hz, Ar-H), 6.67 (dd, 1H, *J*=8.5 and 2.6 Hz, Ar-H), 6.45 (d, 1H, *J*=2.6 Hz, Ar-H), 3.66 (s,

3H, Ar-OCH_3), 3.64 [d, 1H, *J*=14.8 Hz, NCH_2(a,b)], 3.61 (dd, 1H, *J*=5.9 and 4.9 Hz, $CHCOO^tBu$), 3.59 [d, 1H, *J*=13.2 Hz, NCH_2(a',b')], 3.55 [d, 1H, *J*=13.2 Hz, NCH_2(a',b')], 3.42 [d, 1H, *J*=14.8 Hz, NCH_2(a,b)], 3.06 (dd, 1H, *J*=11.5 and 5.9 Hz, $NCH_{2a}CHCOO^tBu$), 2.76 (dd, 1H, *J*=11.5 and 4.9 Hz, $NCH_{2b}CHCOO^tBu$), 1.33 [s, 9H, $C(CH_3)_3$] ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=172.6 (s, O–C=O), 158.2 (s, Ar-C), 138.1 (s, Ar-C), 136.2 (s, Ar-C), 130.2 (d, Ar-CH), 129.0 (d, 2C, Ar-CH), 128.2 (d, 2C, Ar-CH), 127.1 (d, Ar-CH), 124.1 (s, Ar-C), 112.7 (d, Ar-CH), 111.1 (d, Ar-CH), 80.7 [s, $COOC(CH_3)_3$], 62.4 (t, NCH_2), 56.2 (t, NCH_2), 55.2 (q, Ar-OCH_3), 53.5 (t, NCH_2), 45.3 (d, $CHCOO^tBu$), 28.0 [q, 3C, $C(CH_3)_3$] ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{22}H_{28}NO_3]^+=[M+H]^+$: 354.2064; found 354.2074.



56m

***Tert*-butyl 6-benzyl-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinoline-8-carboxylate (56m)**:

GP-5 was followed to the secondary amine **54d** (320 mg, 1 mmol) with *tert*-butyl acrylate (640 mg, 5 mmol) at 110 °C for 48 h. After removal of excess *tert*-butyl acrylate, to the resultant reaction mixture at room temperature, were added $Pd(OAc)_2$ (22.4 mg, 10 mol%), PPh_3 (52.4 mg, 20 mol%) and Cs_2CO_3 (651.6 mg, 2 mmol) followed by toluene (3 mL) under nitrogen atmosphere and stirred at 80 °C in an oil bath, for 36 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetrahydroisoquinoline **56m** (312 mg, 85%) as colorless viscous liquid. [TLC control (petroleum ether/ethyl acetate 85:15), R_f(**54d**)=0.30, R_f(**56m**)=0.60, UV detection].

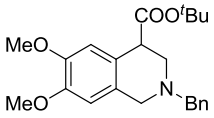
IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2976, 2899, 1725, 1503, 1484, 1454, 1391, 1366, 1238, 1147, 1116, 1038, 939, 849, 734, 699 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.40 (d, 2H, *J*=7.1 Hz, Ar-H), 7.36 (dd, 2H, *J*=7.1 and 7.1 Hz, Ar-H), 7.30 (t, 1H, *J*=7.1 Hz, Ar-H), 6.72 (s, 1H, Ar-H), 6.50 (s,

1H, Ar-H), 5.91 (d, 2H, *J*=6.9 Hz, OCH_2O), 3.73 [d, 1H, *J*=13.0 Hz, NCH_2(a,b)], 3.72 (dd, 1H, *J*=5.8 and 4.9 Hz, $CHCOO^tBu$), 3.68 [d, 1H, *J*=14.6 Hz, NCH_2(a',b')], 3.65 [d, 1H, *J*=13.0 Hz, NCH_2(a,b)], 3.47 [d, 1H, *J*=14.6 Hz, NCH_2(a',b')], 3.15 (dd, 1H, *J*=11.5 and 5.8 Hz, $NCH_{2a}CHCOO^tBu$), 2.84 (dd, 1H, *J*=11.5 and 4.9 Hz, $NCH_{2b}CHCOO^tBu$), 1.46 [s, 9H, $C(CH_3)_3$] ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=172.4 (s, O–C=O), 146.5 (s, Ar-C), 146.0 (s, Ar-C), 138.0 (s, Ar-C), 129.0 (d, 2C, Ar-CH), 128.4 (s, Ar-C), 128.2 (d, 2C, Ar-CH), 127.1 (d, Ar-CH), 124.8 (s, Ar-C), 108.9 (d, Ar-CH), 106.3 (d, Ar-CH), 100.7 (t, OCH_2O), 80.8 [s, $COOC(CH_3)_3$], 62.3 (t, NCH_2), 56.1 (t, NCH_2), 53.2 (t, NCH_2), 46.0 (d, $CHCOO^tBu$), 28.0 [q, 3C, $C(CH_3)_3$] ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{22}H_{26}NO_4]^+$=$[M+H]^+$: 368.1856; found 368.1849.



56n

***Tert*-butyl 2-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (56n)**:

GP-5 was followed to the secondary amine **54e** (336 mg, 1 mmol) with *tert*-butyl acrylate (640 mg, 5 mmol) at 110 °C for 48 h. After removal of excess *tert*-butyl acrylate, to the resultant reaction mixture at room temperature, were added $Pd(OAc)_2$ (22.4 mg, 10 mol%), PPh_3 (52.4 mg, 20 mol%) and Cs_2CO_3 (651.6 mg, 2 mmol) followed by toluene (3 mL) under nitrogen atmosphere and stirred at 80 °C in an oil bath, for 48 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 90:10 to 70:30) furnished the tetrahydroisoquinoline **56n** (291 mg, 76%) as brown viscous liquid. [TLC control (petroleum ether/ethyl acetate 70:30), R_f(**54e**)=0.30, R_f(**56n**)=0.60, UV detection].

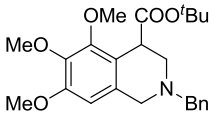
IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2974, 2933, 1724, 1612, 1517, 1463, 1453, 1365, 1254, 1225, 1132, 1028, 992, 851, 732, 698 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.34 (d, 2H, *J*=7.1 Hz, Ar-H), 7.29 (dd, 2H, *J*=7.1 and 7.1 Hz, Ar-H), 7.22 (t, 1H, *J*=7.1 Hz, Ar-H), 6.72 (s, 1H, Ar-H), 6.46 (s,

1H, Ar-H), 3.81 (s, 3H, Ar-OCH_3), 3.77 (s, 3H, Ar-OCH_3), 3.68 [d, 1H, *J*=13.2 Hz, NCH_2(a,b)], 3.66 (dd, 1H, *J*=6.1 and 5.0 Hz, $CHCOO^tBu$), 3.64 [d, 1H, *J*=14.4 Hz, NCH_2(a',b')], 3.62 [d, 1H, *J*=13.2 Hz, NCH_2(a,b)], 3.47 [d, 1H, *J*=14.4 Hz, NCH_2(a',b')], 3.15 (dd, 1H, *J*=11.4 and 6.1 Hz, $NCH_{2a}CHCOO^tBu$), 2.84 (dd, 1H, *J*=11.4 and 5.0 Hz, $NCH_{2b}CHCOO^tBu$), 1.40 [s, 9H, $C(CH_3)_3$] ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=172.3 (s, O–C=O), 147.9 (s, Ar-C), 147.4 (s, Ar-C), 138.1 (s, Ar-C), 129.0 (d, 2C, Ar-CH), 128.2 (d, 2C, Ar-CH), 127.2 (s, Ar-C), 127.1 (d, Ar-CH), 123.7 (s, Ar-C), 111.7 (d, Ar-CH), 109.2 (d, Ar-CH), 80.7 [s, $COOC(CH_3)_3$], 62.4 (t, NCH_2), 55.8 (q, Ar-OCH_3), 55.7 (q, Ar-OCH_3), 55.6 (t, NCH_2), 53.3 (t, NCH_2), 45.6 (d, $CHCOO^tBu$), 28.0 [q, 3C, $C(CH_3)_3$] ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{23}H_{30}NO_4]^+$=$[M+H]^+$: 384.2169; found 384.2182.



56o

***Tert*-butyl 2-benzyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (56o)**:

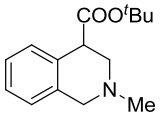
GP-5 was followed to the secondary amine **54f** (366 mg, 1 mmol) with *tert*-butyl acrylate (22.4 mg, 5 mmol) at 110 °C for 48 h. After removal of excess *tert*-butyl acrylate, to the resultant reaction mixture at room temperature, were added $Pd(OAc)_2$ (22.4 mg, 10 mol%), PPh_3 (52.4 mg, 20 mol%) and Cs_2CO_3 (651.6 mg, 2 mmol) followed by toluene (3 mL) under nitrogen atmosphere and stirred at 80 °C in an oil bath, for 36 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 80:20) furnished the tetrahydroisoquinoline **56o** (330 mg, 80%) as pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 80:20), R_f(**54f**)=0.30, R_f(**56o**)=0.50, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2974, 2935, 1730, 1599, 1495, 1457, 1364, 1275, 1240, 1142, 1078, 1020, 990, 743, 698, 632 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.38 (d, 2H, *J*=7.2 Hz, Ar-H), 7.34 (dd, 2H, *J*=7.2 and 7.2 Hz, Ar-H), 7.28 (t, 1H, *J*=7.2 Hz, Ar-H), 6.34 (s, 1H, Ar-H), 3.90 (s, 3H, Ar-OCH_3), 3.85 (s, 3H, Ar-OCH_3), 3.81 (s, 3H, Ar-OCH_3), 3.78 [d, 1H, *J*=14.8 Hz, NCH_2(a,b)], 3.76 (dd, 1H, *J*=5.0 and 4.3 Hz, CHCOO^{t}Bu), 3.73 [d, 1H, *J*=13.0 Hz, NCH_2(a',b')], 3.60 [d, 1H, *J*=13.0 Hz, NCH_2(a,b)], 3.40 [d, 1H, *J*=14.8 Hz, NCH_2(a',b')], 3.18 (dd, 1H, *J*=11.5 and 4.3 Hz, NCH_{2a}CHCOO^{t}Bu), 2.75 (dd, 1H, *J*=11.5 and 4.3 Hz, NCH_{2b}CHCOO^{t}Bu), 1.43 [s, 9H, C(CH_3)$_3$] ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=172.8 (s, O–C=O), 152.6 (s, Ar-C), 151.6 (s, Ar-C), 140.1 (s, Ar-C), 138.2 (s, Ar-C), 130.6 (s, Ar-C), 129.0 (d, 2C, Ar-CH), 128.3 (d, 2C, Ar-CH), 127.1 (d, Ar-CH), 118.7 (s, Ar-C), 104.8 (d, Ar-CH), 80.0 [s, COO*C*(CH_3)$_3$], 62.3 (t, NCH_2), 60.6 (q, Ar-OCH_3), 60.3 (q, Ar-OCH_3), 56.0 (t, NCH_2), 55.9 (q, Ar-OCH_3), 53.8 (t, NCH_2), 41.9 (d, *C*HCOO^{t}Bu), 28.0 [q, 3C, C(*C*H_3)$_3$] ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{24}H_{32}NO_5]^+$=$[M+H]^+$: 414.2276; found 414.2256.



56p

***Tert*-butyl 2-methyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (56p)**:

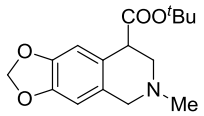
GP-2 was followed to the secondary amine **54h** (200 mg, 1 mmol) with *tert*-butyl acrylate (640 mg, 5 mmol) at 110 °C for 36 h. After removal of excess *tert*-butyl acrylate, to the resultant reaction mixture at room temperature, were added $Pd(OAc)_2$ (22.4 mg, 10 mol%), PPh_3 (52.4 mg, 20 mol%) and Cs_2CO_3 (651.6 mg, 2 mmol) followed by toluene (3 mL) under nitrogen atmosphere and stirred at 80 °C in an oil bath, for 36 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 80:20 to 60:40) furnished the isoquinoline **56p** (175 mg, 71%) as colorless viscous liquid. [TLC control (petroleum ether/ethyl acetate 20:80), R_f(**54h**)=0.15, R_f(**56p**)=0.45, I_2 chamber detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2974, 2934, 2773, 1724, 1453, 1367, 1274, 1246, 1138, 1101, 1033, 969, 850, 745 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.19 (dd, 1H, *J*=4.9 and 3.4 Hz, Ar-H), 7.10 (d, 1H, *J*=3.4 Hz, Ar-H), 7.08 (d, 1H, *J*=3.4 Hz, Ar-H), 6.96 (dd, 1H, *J*=4.9 and 3.4 Hz, Ar-H), 3.74 (dd, 1H, *J*=6.5 and 5.9 Hz, CHCOO^{t}Bu), 3.58 [d, 1H, *J*=14.9 Hz, NCH_2(a,b)], 3.44 [d, 1H, *J*=14.9 Hz, NCH_2(a,b)], 2.91 (dd, 1H, *J*=11.5 and 6.5 Hz, NCH_{2a}CHCOO^{t}Bu), 2.76 (dd, 1H, *J*=11.5 and 5.3 Hz, NCH_{2b}CHCOO^{t}Bu), 2.37 (s, 3H, NCH_3), 1.40 [s, 9H, $C(CH_3)_3$] ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=172.3 (s, O–C=O), 134.9 (s, Ar-C), 131.3 (s, Ar-C), 128.9 (d, Ar-CH), 126.6 (d, Ar-CH), 126.5 (d, Ar-CH), 126.2 (d, Ar-CH), 80.9 [s, COO*C*$(CH_3)_3$], 57.9 (t, NCH_2), 55.4 (t, NCH_2), 45.9 (q, NCH_3), 45.8 (d, *C*HCOO^{t}Bu), 28.0 [q, 3C, C(*C*$H_3)_3$] ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{15}H_{22}NO_2]^+$=$[M+H]^+$: 248.1645; found 248.1646.



56q

***Tert*-butyl 6-methyl-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinoline-8-carboxylate (56q)**:

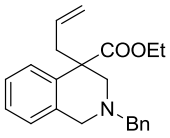
GP-2 was followed to the secondary amine **54i** (244 mg, 1 mmol) with *tert*-butyl acrylate (640 mg, 5 mmol) at 110 °C for 48 h. After removal of excess *tert*-butyl acrylate, to the resultant reaction mixture at room temperature, were added $Pd(OAc)_2$ (22.4 mg, 10 mol%), PPh_3 (52.4 mg, 20 mol%) and Cs_2CO_3 (651.6 mg, 2 mmol) followed by toluene (3 mL) under nitrogen atmosphere and stirred at 80 °C in an oil bath, for 36 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 80:20 to 55:45) furnished the isoquinoline **56q** (204 mg, 70%) as pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 20:80), R_f(**54i**)=0.12, R_f(**56q**)=0.43, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2974, 2935, 2789, 1725, 1504, 1483, 1390, 1367, 1250, 1238, 1145, 1125, 1035, 938, 850 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=6.71 (s, 1H, Ar-H), 6.48 (s, 1H, Ar-H), 5.89 (d, 1H, J=1.4 Hz, $OCH_{2a}O$), 5.87 (d, 1H, J=1.4 Hz, $OCH_{2b}O$), 3.68 (dd, 1H, J=6.4 and 5.0 Hz, $CHCOO^tBu$), 3.55 [d, 1H, J=14.7 Hz, NCH_2(a,b)], 3.38 [d, 1H, J=14.7 Hz, NCH_2(a,b)], 2.91 (dd, 1H, J=11.4 and 6.4 Hz, $NCH_{2a}CHCOO^tBu$), 2.76 (dd, 1H, J=11.4 and 5.0 Hz, $NCH_{2b}CHCOO^tBu$), 2.41 (s, 3H, NCH_3), 1.46 [s, 9H, $C(CH_3)_3$] ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=172.4 (s, O–C=O), 146.4 (s, Ar-C), 146.1 (s, Ar-C), 128.4 (s, Ar-C), 124.2 (s, Ar-C), 108.7 (d, Ar-CH), 106.2 (d, Ar-CH), 100.8 (t, OCH_2O), 81.0 [s, $COOC(CH_3)_3$], 57.9 (t, NCH_2), 55.4 (t, NCH_2), 45.8 (q, NCH_3), 45.7 (d, $CHCOO^tBu$), 28.1 [q, 3C, $C(CH_3)_3$] ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{16}H_{22}NO_4]^+=[M+H]^+$: 292.1543; found 248.1538.



57a

Ethyl 4-allyl-2-benzyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (57a):

To a cold (–10 °C) magnetically stirred solution of diisopropylethylamine (0.10 mL, 1.35 mmol) in dry THF (1 mL) was slowly added a solution of ^{n}BuLi (2.5 M in hexane, 0.43 mL, 1.08 mmol) and the reaction mixture was stirred for 5 min at the same temperature. To the LDA thus formed, was added drop-wise, a solution of tetrahydroisoquinoline **56a** (160 mg, 0.54 mmol) in dry THF (2 mL) and the reaction mixture was stirred for 30 min., at the same temperature. The enolate was then treated with allyl bromide (0.09 mL, 1.08 mmol) and stirred at room temperature for 4 h. The progress of the reaction was monitored by TLC. The reaction mixture was treated with aqueous NH_4Cl solution and then extracted with ethyl acetate (3 × 15 mL). The organic layers were washed with saturated NaCl solution, dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 98:2 to 95:5) furnished the allylated ester **57a** (140.3 mg, 77%) as a pale yellow

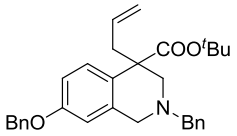
viscous liquid. [TLC control (petroleum ether/ethyl acetate 90:10), R_f(**56a**)=0.50, R_f(**57a**)=0.60, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3027, 2978, 2805, 1722, 1638, 1493, 1452, 1367, 1205, 1145, 1093, 1027, 918, 736, 699 cm^{-1}.

^{1}H NMR (CDCl$_3$, 400 MHz): δ=7.35 (d, 1H, *J*=7.3 Hz, Ar-H), 7.29 (d, 2H, *J*=7.0 Hz, Ar-H), 7.24 (dd, 2H, *J*=7.0 and 7.0 Hz, Ar-H), 7.18 (dd, 1H, *J*=7.3 and 7.3 Hz, Ar-H), 7.15–7.01 (m, 2H, Ar-H), 6.91 (d, 1H, *J*=7.0 Hz, Ar-H), 5.70–5.31 (m, 1H, CH_2CH=CH_2), 4.99–4.85 (m, 2H, CH_2CH=CH_2), 4.18–3.95 (m, 2H, OCH_2CH_3), 3.58 (s, 2H, NCH_2), 3.54 (s, 2H, NCH_2), 3.06 (d, 1H, *J*=11.5 Hz, NCH_{2a}CHCOOEt), 2.75–2.60 (m, 3H, CH_2CH=CH_2 and NCH_{2b}CHCOOEt), 1.12 (t, 3H, *J*=7.1 Hz, OCH_2CH_3) ppm.

^{13}C NMR (CDCl$_3$, 100 MHz): δ=174.3 (s, O–C=O), 138.3 (s, Ar-C), 135.9 (s, Ar-C), 135.1 (s, Ar-C), 134.2 (d, CH_2CH=CH_2), 129.1 (d, Ar-CH), 128.2 (d, 2C, Ar-CH), 127.9 (d, 2C, Ar-CH), 127.1 (d, Ar-CH), 126.6 (d, Ar-CH), 126.5 (d, Ar-CH), 126.2 (d, Ar-CH), 118.3 (t, CH_2CH=CH_2), 62.8 (t, NCH_2), 60.9 (t, OCH_2CH_3), 57.0 (t, NCH_2), 56.7 (t, NCH_2), 51.0 [s, *C*(COOEt)CH_2CH=CH_2], 42.7 (t, *C*H_2CH=CH_2) 14.1 (q, OCH_2CH_3) ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{22}H_{26}NO_2]^+$=$[M+H]^+$: 336.1958; found 336.1942.



57k

***Tert*-butyl 4-allyl-2-benzyl-7-(benzyloxy)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (57k)**:

To a cold (–15 °C) magnetically stirred solution of diisopropylethylamine (0.16 mL, 1.51 mmol) in dry THF (1 mL) was slowly added a solution of ^{n}BuLi (2.5 M in hexane, 0.50 mL, 1.21 mmol) and the reaction mixture was stirred for 5 min., at the same temperature. To the LDA thus formed, was added drop-wise, a solution of tetrahydroisoquinoline **56k** (260 mg, 0.61 mmol) in dry THF (2 mL) and the reaction mixture was stirred for 30 min at the same temperature. The enolate was

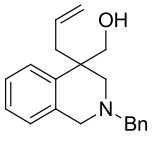
treated with allyl bromide (0.10 mL, 1.21 mmol) and stirred at room temperature for 4 h. The progress was monitored by TLC. The reaction mixture was treated with aqueous NH_4Cl solution and then extracted with ethyl acetate (3 × 15 mL). The organic layers were washed with saturated NaCl solution, dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 97:3 to 90:10) furnished the allylated ester **57k** (221.6 mg, 78%) as a colorless viscous liquid. [TLC control (petroleum ether/ethyl acetate 90:10), R_f(**56k**)=0.45, R_f(**57k**)=0.55, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3064, 2976, 1718, 1638, 1609, 1499, 1454, 1366, 1240, 1161, 1135, 1094, 1027, 915, 847, 734, 697 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.45–7.20 (m, 11H, Ar-H), 6.82 (dd, 1H, J=8.8 and 2.9 Hz, Ar-H), 6.57 (d, 1H, J=2.9 Hz, Ar-H), 5.75–5.55 (m, 1H, CH_2CH=CH_2), 5.10–4.90 (m, 4H, CH_2CH=CH_2 and OCH_2Ph), 3.70–3.55 (m, 2H, NCH_2), 3.53 (s, 2H, NCH_2), 3.09 (d, 1H, J=11.2 Hz, $NCH_{2a}CHCOO^tBu$), 2.77–2.66 (m, 3H, CH_2CH=CH_2 and $NCH_{2b}CHCOO^tBu$), 1.41 [s, 9H, $OC(CH_3)_3$] ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=173.5 (s, O–C=O), 157.2 (s, Ar-C), 138.4 (s, Ar-C), 137.1 (s, Ar-C), 136.4 (s, Ar-C), 134.5 (d, CH_2CH=CH_2), 129.2 (d, Ar-CH), 129.1 (d, 2C, Ar-CH), 128.8 (s, Ar-C), 128.5 (d, 2C, Ar-CH), 128.2 (d, 2C, Ar-CH), 127.9 (d, Ar-CH), 127.4 (d, 2C, Ar-CH), 127.1 (d, Ar-CH), 118.0 (t, CH_2CH=CH_2), 113.3 (d, Ar-CH), 111.9 (d, Ar-CH), 80.8 [s, $C(CH_3)_3$], 69.9 (t, OCH_2Ph), 62.9 (t, NCH_2), 57.5 (t, NCH_2), 56.8 (t, NCH_2), 50.8 [s, $C(COO^tBu)CH_2CH$=CH_2], 42.8 (t, CH_2CH=CH_2), 28.0 [q, 3C, $C(CH_3)_3$] ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{31}H_{36}NO_3]^+$=$[M+H]^+$: 470.2690; found 470.2698.



58a

(4-Allyl-2-benzyl-1,2,3,4-tetrahydroisoquinolin-4-yl)methanol (58a):

To a cold (–10 °C), magnetically stirred solution of the ester **57a** (100 mg, 0.30 mmol) in dry diethyl ether (10 mL), was added $LiAlH_4$ (34 mg, 0.89 mmol).

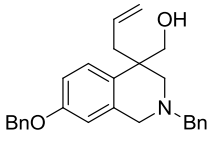
Then the reaction mixture stirred at the same temperature for 1 h. The reaction mixture was quenched with drop wise addition of ethyl acetate then treatment with aqueous NH_4Cl solution and extracted with ethyl acetate (3 × 15 mL). The organic layers were washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the filtrate under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate) furnished the alcohol **58a** (73.3 mg, 84%) as colorless viscous liquid. [TLC control (petroleum ether/ethyl acetate 90:10), R_f(**57a**)=0.60, R_f(**58a**)=0.30, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3396, 3065, 3028, 2915, 2813, 1638, 1493, 1451, 1368, 1094, 1072, 1034, 916, 755, 734, 700 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.30–7.10 (m, 7H, Ar-H), 7.05 (dd, 1H, *J*=7.5 and 7.5 Hz, Ar-H), 6.89 (d, 1H, *J*=7.5 Hz, Ar-H), 5.50–5.35 (m, 1H, CH_2CH=CH_2), 5.33 (br. s, 1H, OH), 4.92 (d, 1H, *J*=17.1 Hz, CH_2CH=CH_{2trans}), 4.88 (d, 1H, *J*=10.2 Hz, CH_2CH=CH_{2cis}), 3.78–3.65 (m, 2H, CH_2OH), 3.66–3.55 (m, 2H, NCH_2Ar), 3.51 (d, 1H, *J*=12.8 Hz, $NCH_{2a}Ph$), 3.23 (d, 1H, *J*=12.8 Hz, $NCH_{2b}Ph$), 2.87 [dd, 1H, *J*=11.5 and 1.6 Hz, $NCH_{2a}C(CH_2OH)CH_2CH=CH_2$], 2.53 [dd, 1H, *J*=11.5 and 2.5 Hz, $NCH_{2b}C(CH_2OH)CH_2CH=CH_2$], 2.42 (dd, 1H, *J*=14.4 and 6.0 Hz, $CH_{2a}CH=CH_2$), 2.11 (dd, 1H, *J*=14.4 and 8.4 Hz, $CH_{2b}CH=CH_2$) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=137.6 (s, Ar-C), 136.9 (s, Ar-C), 135.6 (s, Ar-C), 133.7 (d, $CH_2CH=CH_2$), 129.1 (d, 2C, Ar-CH), 128.6 (d, 2C, Ar-CH), 127.6 (d, Ar-CH), 127.0 (d, Ar-CH), 126.3 (d, Ar-CH), 126.2 (d, Ar-CH), 125.8 (d, Ar-CH), 118.0 (t, $CH_2CH=CH_2$), 75.3 (t, CH_2OH), 63.0 (t, NCH_2), 60.7 (t, NCH_2), 56.6 (t, NCH_2), 41.7 [s, $C(CH_2OH)CH_2CH=CH_2$], 40.0 (t, $CH_2CH=CH_2$) ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{20}H_{24}NO]^+$=$[M+H]^+$: 294.1852; found 294.1845.



58k

[4-Allyl-2-benzyl-7-(benzyloxy)-1,2,3,4-tetrahydroisoquinolin-4-yl]methanol (58k):

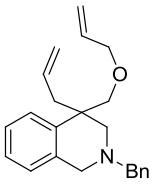
To a cold (–10 °C), magnetically stirred solution of the ester **57k** (191 mg, 0.41 mmol) in dry diethyl ether (10 mL), was added $LiAlH_4$ (46.4 mg, 1.22 mmol). Then the reaction mixture stirred at the same temperature for 1 h. The reaction mixture was quenched with drop-wise addition of ethyl acetate then treatment with aqueous NH_4Cl solution and extracted with ethyl acetate (3 × 15 mL). The organic layers were washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the filtrate under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate) furnished the alcohol **58k** (158.5 mg, 97%) as colorless viscous liquid. [TLC control (petroleum ether/ethyl acetate 75:25), R_f(**57k**)=0.65, R_f(**58k**)=0.30, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3295, 3029, 2912, 2824, 1637, 1609, 1500, 1453, 1382, 1319, 1278, 1241, 1091, 1073, 1026, 909, 731, 697 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.45–7.20 (m, 11H, Ar-H), 6.88 (dd, 1H, *J*=8.8 and 2.9 Hz, Ar-H), 6.59 (d, 1H, *J*=2.9 Hz, Ar-H), 5.65–5.40 (m, 1H, CH_2CH=CH_2), 5.38 (br. s, 1H, OH), 5.10–4.91 (m, 4H, OCH_2Ph and CH_2CH=CH_2), 3.85–3.55 (m, 5H, CH_2OH, NCH_2Ar and $NCH_{2a}Ph$), 3.29 (d, 1H, *J*=14.7 Hz, $NCH_{2b}Ph$), 2.94 [dd, 1H, *J*=11.7 and 2.0 Hz, $NCH_{2a}C(CH_2OH)CH_2CH$=CH_2], 2.53 [dd, 1H, *J*=11.7 and 2.5 Hz, $NCH_{2b}C(CH_2OH)CH_2CH$=CH_2], 2.42 (dd, 1H, *J*=14.7 and 6.3 Hz, $CH_{2a}CH$=CH_2), 2.11 (dd, 1H, *J*=14.7 and 8.8 Hz, $CH_{2b}CH$=CH_2) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=157.1 (s, Ar-C), 136.9 (s, Ar-C), 137.0 (s, Ar-C), 136.9 (s, Ar-C), 136.8 (s, Ar-C), 133.8 (d, CH_2CH=CH_2), 129.9 (s, Ar-C), 129.1 (d, 2C, Ar-CH), 128.6 (d, 2C, Ar-CH), 128.5 (d, 2C, Ar-CH), 127.9 (d, Ar-CH), 127.6 (d, Ar-CH), 127.4 (d, 2C, Ar-CH), 126.9 (d, Ar-CH), 117.9 (t, CH_2CH=CH_2), 114.3 (d, Ar-CH), 111.7 (d, Ar-CH), 75.2 (t, OCH_2Ph), 69.9 (t, CH_2OH), 63.0 (t, NCH_2), 60.9 (t, NCH_2), 56.8 (t, NCH_2), 41.2 [s, $C(CH_2OH)CH_2CH$=CH_2], 40.0 (t, CH_2CH=CH_2) ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{27}H_{28}NO_2]^+$=$[M–H]^+$: 398.2115; found 398.2104.



59a

4-Allyl-4-[(allyloxy)methyl]-2-benzyl-1,2,3,4-tetrahydroisoquinoline (59a):

To an oven dried round bottomed flask, were added the alcohol **58a** (47 mg, 0.16 mmol), sodium hydride (19 mg, 0.48 mmol) in dry DMF (3 mL) followed by addition of allyl bromide (58.2 mg, 0.48 mmol) under nitrogen atmosphere at room temperature. The reaction mixture was allowed to stir at room temperature for 1 h and then the reaction mixture was treated with aqueous NH_4Cl solution and extracted with ethyl acetate (3 × 10 mL). The organic layer was washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the filtrate under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate) furnished the allyl ether **59a** (44.2 mg, 83%) as colorless liquid. [TLC control (petroleum ether/ethyl acetate 85:15), R_f(**58a**)=0.35, R_f(**59a**)=0.75, UV detection].

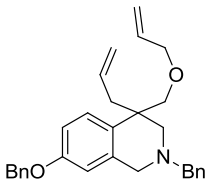
IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3064, 3027, 2924, 2853, 1639, 1493, 1452, 1368, 1345, 1145, 1090, 1027, 996, 916, 757, 730, 698 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.45–7.20 (m, 6H, Ar-H), 7.15 (dd, 1H, *J*=7.2 and 7.2 Hz, Ar-H), 7.10 (dd, 1H, *J*=7.4 and 7.4 Hz, Ar-H), 6.96 (d, 1H, *J*=7.4 Hz, Ar-H), 5.95–5.75 (m, 1H, CH_2CH=CH_2), 5.65–5.50 (m, 1H, CH_2CH=CH_2), 5.19 (d, 1H, *J*=17.2 Hz, CH_2CH=CH_{2trans}), 5.10 (d, 1H, *J*=10.4 Hz, CH_2CH=CH_{2cis}), 4.96 (d, 1H, *J*=17.4 Hz, CH_2CH=CH_{2trans}), 4.91 (d, 1H, *J*=10.4 Hz, CH_2CH=CH_{2cis}), 3.95–3.84 (m, 2H, CH_2OCH_2CH=CH_2), 3.72–3.56 (m, 4H, CH_2OCH_2CH=CH_2 and NCH_2Ar), 3.45 (dd, 2H, *J*=16.6 and 9.4 Hz, NCH_2Ph), 2.82 (d, 1H, *J*=11.4 Hz, $CH_{2a}CH$=CH_2), 2.62 [dd, 1H, *J*=14.3 and 6.4 Hz, $NCH_{2a}C(CH_2OCH_2CH$=$CH_2)CH_2CH$=CH_2], 2.53 [dd, 1H, *J*=14.3 and 7.9 Hz, $NCH_{2a}C(CH_2OCH_2CH$=$CH_2)CH_2CH$=CH_2], 2.46 (d, 1H, *J*=11.5 Hz, $CH_{2b}CH$=CH_2) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=138.8 (s, Ar-C), 138.5 (s, Ar-C), 135.8 (s, Ar-C), 135.3 (d, CH_2CH=CH_2), 135.2 (d, CH_2CH=CH_2), 128.9 (d, 2C, Ar-CH),

128.2 (d, 2C, Ar-CH), 127.2 (d, Ar-CH), 127.0 (d, Ar-CH), 126.5 (d, Ar-CH), 126.0 (d, Ar-CH), 125.9 (d, Ar-CH), 117.1 (t, $CH_2CH=CH_2$), 116.3 (t, $CH_2CH=CH_2$), 76.6 (t, $OCH_2CH=CH_2$), 72.3 (t, $CH_2OCH_2CH=CH_2$), 62.9 (t, NCH_2), 57.2 (t, NCH_2), 56.7 (t, NCH_2), 42.9 [s, $C(CH_2OCH_2CH=CH_2)CH_2CH=CH_2$], 40.8 (t, $CH_2CH=CH_2$) ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{23}H_{28}NO]^+=[M+H]^+$: 334.2165; found 334.2150.



59k

4-Allyl-4-[(allyloxy)methyl]-2-benzyl-7-(benzyloxy)-1,2,3,4-tetrahydroisoquinoline (59k):

To an oven dried round bottomed flask, were added the alcohol **58k** (132.0 mg, 0.33 mmol), sodium hydride (23.8 mg, 0.99 mmol) in dry DMF (3 mL) followed by addition of allyl bromide (120.1 mg, 0.99 mmol) under nitrogen atmosphere at room temperature. The reaction mixture was allowed to stir at room temperature for 1 h and then the reaction mixture was treated with aqueous NH_4Cl solution and extracted with ethyl acetate (3 × 15 mL). The organic layer was washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the filtrate under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate) furnished the allyl ether **59k** (130.8 mg, 90%) as colorless liquid. [TLC control (petroleum ether/ethyl acetate 75:25), R_f(**58k**)=0.30, R_f(**59k**)=0.75, I_2 chamber detection].

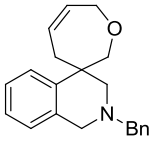
IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3064, 3029, 2851, 1637, 1609, 1578, 1499, 1453, 1342, 1278, 1240, 1139, 1091, 1019, 915, 843, 735, 697 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.50–7.20 (m, 11H, Ar-H), 6.80 (dd, 1H, *J*=8.8 and 2.4 Hz, Ar-H), 6.59 (d, 1H, *J*=2.4 Hz, Ar-H), 5.90–5.75 (m, 1H, $CH_2CH=CH_2$), 5.70–5.50 (m, 1H, $CH_2CH=CH_2$), 5.20 (d, 1H, *J*=17.2 Hz,

$CH_2CH=CH_{2trans}$), 5.11 (d, 1H, *J*=10.4 Hz, $CH_2CH=CH_{2cis}$), 4.98 (s, 2H, OCH_2Ph), 5.00–4.90 (m, 2H, $CH_2CH=CH_2$), 3.95–3.84 (m, 2H, $CH_2OCH_2CH=CH_2$), 3.70–3.55 (m, 4H, $CH_2OCH_2CH=CH_2$ and NCH_2Ar), 3.41 (dd, 2H, *J*=16.6 and 9.3 Hz, NCH_2Ph), 2.79 (d, 1H, *J*=11.7 Hz, $CH_{2a}CH=CH_2$), 2.59 [dd, 1H, *J*=14.2 and 6.4 Hz, $NCH_{2a}C(CH_2OCH_2CH=CH_2)CH_2CH=CH_2$], 2.50 [dd, 1H, *J*=14.2 and 7.8 Hz, $NCH_{2a}C(CH_2OCH_2CH=CH_2)CH_2CH=CH_2$], 2.46 (d, 1H, *J*=11.2 Hz, $CH_{2b}CH=CH_2$) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=156.9 (s, Ar-C), 138.8 (s, Ar-C), 137.2 (s, Ar-C), 137.1 (s, Ar-C), 135.4 (d, $CH_2CH=CH_2$), 135.2 (d, $CH_2CH=CH_2$), 130.9 (s, Ar-C), 128.9 (d, 2C, Ar-CH), 128.5 (d, 2C, Ar-CH), 128.3 (d, Ar-CH), 128.2 (d, 2C, Ar-CH), 127.9 (d, Ar-CH), 127.4 (d, 2C, Ar-CH), 127.0 (d, Ar-CH), 117.1 (t, $CH_2CH=CH_2$), 116.3 (t, $CH_2CH=CH_2$), 113.2 (d, Ar-CH), 111.9 (d, Ar-CH), 76.6 (t, $OCH_2CH=CH_2$), 72.2 (t, $CH_2OCH_2CH=CH_2$), 69.9 (t, OCH_2Ph), 62.8 (t, NCH_2), 57.4 (t, NCH_2), 56.8 (t, NCH_2), 42.3 [s, $C(CH_2OCH_2CH=CH_2)CH_2CH=CH_2$], 40.8 (t, $CH_2CH=CH_2$) ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{30}H_{34}NO_2]^+=[M+H]^+$: 440.2584; found 440.2581.



60a

2-Benzyl-2,3,4',7'-tetrahydro-1*H*-spiro[isoquinoline-4,3'-oxepine] (60a):

To an oven dried round bottomed flask, were added the allyl ether **59a** (29 mg, 0.09 mmol), Grubb's Ist generation catalyst (3.6 mg, 5 mol%), followed by addition of DCM (7 mL) under nitrogen atmosphere at room temperature (room temperature usually is in the range of 35 to 40 °C for the hot summer, in India), stirred at room temperature for 10 h and progress was monitored by TLC. Then the reaction mixture was treated with aqueous NH_4Cl solution and extracted with DCM (3 × 10 mL). The organic layer was washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the filtrate under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum

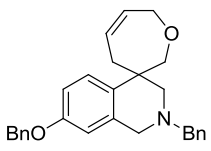
ether/ethyl acetate) furnished the oxepine **60a** (22 mg, 82%) as colorless liquid. [TLC control (petroleum ether/ethyl acetate 95:5), R_f(**59a**)=0.50, R_f(**60a**)=0.45, I_2 chamber detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3061, 3023, 2926, 2753, 1603, 1492, 1452, 1368, 1264, 1247, 1138, 1099, 1074, 1026, 922, 755, 732, 699 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.47 (dd, 1H, *J*=7.8 and 1.0 Hz, Ar-H), 7.38 (d, 2H, *J*=7.3 Hz, Ar-H), 7.31 (dd, 2H, *J*=7.3 and 7.3 Hz, Ar-H), 7.25 (t, 1H, *J*=7.3 Hz, Ar-H), 7.18 (dd, 1H, *J*=7.8 and 7.8 Hz, Ar-H), 7.10 (ddd, 1H, *J*=7.8, 7.8 and 1.0 Hz, Ar-H), 6.95 (d, 1H, *J*=7.8 Hz, Ar-H), 5.77–5.64 (m, 1H, CH_a=CH_b), 5.63–5.50 (m, 1H, CH_a=CH_b), 4.38–4.20 (m, 2H, CH_2OCH_2CH=CH), 4.00 (d, 1H, *J*=12.2 Hz, C$H_{2a}OCH_2CH$=CH), 3.77 (d, 1H, *J*=12.2 Hz, C$H_{2b}OCH_2CH$=CH), 3.76 (d, 1H, *J*=13.2 Hz, NCH_{2a}Ar), 3.56 (d, 1H, *J*=14.7 Hz, NCH_{2a}Ph), 3.55 (d, 1H, *J*=13.2 Hz, NCH_{2b}Ar), 3.50 (d, 1H, *J*=14.7 Hz, NCH_{2b}Ph), 2.69 [d, 1H, *J*=11.7 Hz, NCH_{2a}C(CH_2OCH_2)CH_2CH=CH], 2.63–2.44 [m, 3H, NCH_{2b}C(CH_2OCH_2)CH_2CH=CH and CH_2CH=CH] ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=141.4 (s, Ar-C), 138.6 (s, Ar-C), 134.7 (s, Ar-C), 129.4 (d, *C*H_a=CH_b), 128.9 (d, 2C, Ar-CH), 128.2 (d, 2C, Ar-CH), 128.0 (d, Ar-CH), 127.0 (d, Ar-CH), 126.7 (d, Ar-CH), 126.6 (d, Ar-CH), 126.3 (d, Ar-CH), 126.0 (d, CH_a=*C*H_b), 78.9 (t, O*C*H_2CH=CH), 71.7 (t, *C*H_2OCH_2CH=CH), 62.8 (t, NCH_2), 58.7 (t, NCH_2), 56.7 (t, NCH_2), 44.9 [s, *C*(CH_2OCH_2)CH_2CH=CH], 37.1 (t, *C*H_2CH=CH) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{21}H_{23}NNaO]^+$=$[M+Na]^+$: 328.1672; found 328.1686.



60k

2-Benzyl-7-(benzyloxy)-2,3,4',7'-tetrahydro-1*H*-spiro[isoquinoline-4,3'-oxepine] (60k):

To an oven dried round bottomed flask, were added the allyl ether **59k** (37 mg, 0.08 mmol), Grubb's Ist generation catalyst (3.5 mg, 5 mol%), followed by

addition of DCM (6 mL) under nitrogen atmosphere at room temperature (room temperature usually is in the range of 35 to 40 °C for the hot summer, in India), stirred at room temperature for 10 h and progress was monitored by TLC. Then the reaction mixture was treated with aqueous NH_4Cl solution and extracted with DCM (3 × 15 mL). The organic layer was washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the filtrate under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate) furnished the oxepine **60k** (29.0 mg, 83%) as colorless viscous liquid. [TLC control (petroleum ether/ethyl acetate 90:10), R_f(**59k**)=0.55, R_f(**60k**)=0.45, I_2 chamber detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3062, 3026, 2926, 1609, 1580, 1499, 1454, 1318, 1239, 1134, 1097, 1021, 908, 732, 697 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.40–7.10 (m, 11H, Ar-H), 6.74 (dd, 1H, *J*=8.8 and 2.9 Hz, Ar-H), 6.49 (d, 1H, *J*=2.9 Hz, Ar-H), 5.70–5.57 (m, 1H, CH_a=CH_b), 5.55–5.45 (m, 1H, CH_a=CH_b), 4.25–4.18 (m, 2H, CH_2OCH_2CH=CH), 3.93 (d, 1H, *J*=12.2 Hz, C$H_{2a}OCH_2CH$=CH), 3.68 (d, 1H, *J*=13.2 Hz, NCH_{2a}Ar), 3.65 (d, 1H, *J*=12.2 Hz, C$H_{2b}OCH_2CH$=CH), 3.47 (d, 1H, *J*=13.2 Hz, NCH_{2b}Ar), 3.42 (d, 1H, *J*=14.7 Hz, NCH_{2a}Ph), 3.38 (d, 1H, *J*=14.7 Hz, NCH_{2b}Ph), 2.62 [d, 1H, *J*=11.2 Hz, NCH_{2a}C(CH_2OCH_2)CH_2CH=CH], 2.52–2.35 [m, 3H, NCH_{2b}C(CH_2OCH_2)CH_2CH=CH and CH_2CH=CH] ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=156.9 (s, Ar-C), 138.6 (s, Ar-C), 137.1 (s, Ar-C), 136.1 (s, Ar-C), 133.8 (s, Ar-C), 129.4 (d, *C*H_a=CH_b), 128.8 (d, 2C, Ar-CH), 128.5 (d, 2C, Ar-CH), 128.2 (d, 2C, Ar-CH), 128.0 (d, Ar-CH), 127.9 (d, Ar-CH), 127.8 (d, CH_a=*C*H_b), 127.4 (d, 2C, Ar-CH), 127.0 (d, Ar-CH), 113.8 (d, Ar-CH), 111.6 (d, Ar-CH), 78.9 (t, O*C*H_2CH=CH), 71.6 (t, *C*H_2OCH_2CH=CH), 69.9 (t, OCH_2Ph), 62.8 (t, NCH_2), 58.8 (t, NCH_2), 56.8 (t, NCH_2), 44.2 [s, *C*(CH_2OCH_2)CH_2CH=CH], 37.2 (t, *C*H_2CH=CH) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{28}H_{30}NO_2]^+$=$[M+H]^+$: 412.2271; found 412.2279.

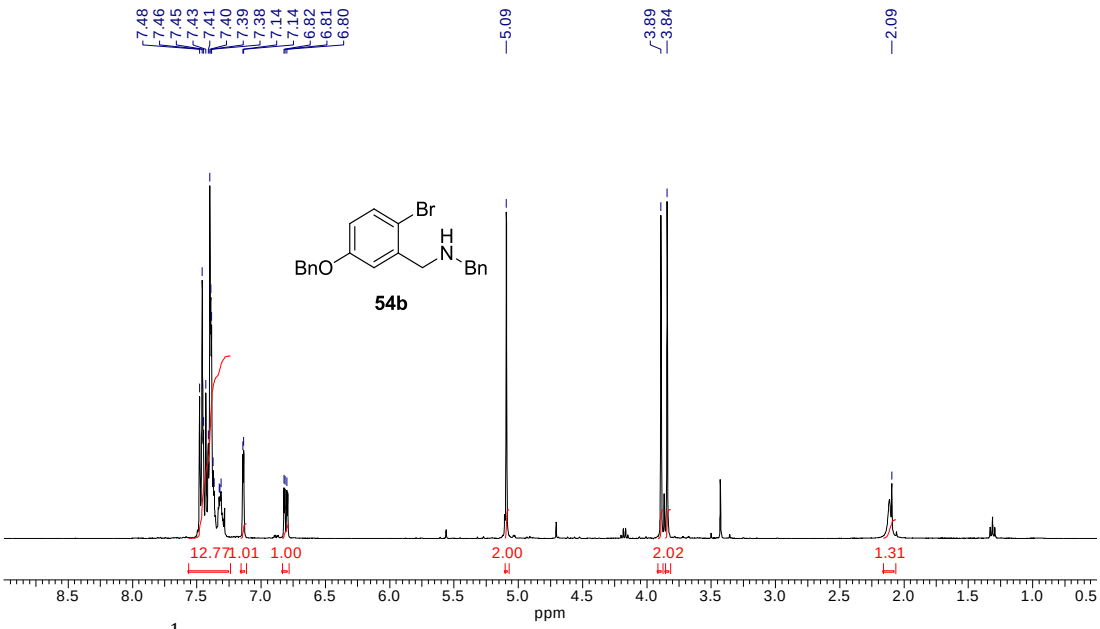


Figure I.9.1: ^{1}H NMR (400 MHz) spectrum of **54b** in $CDCl_3$

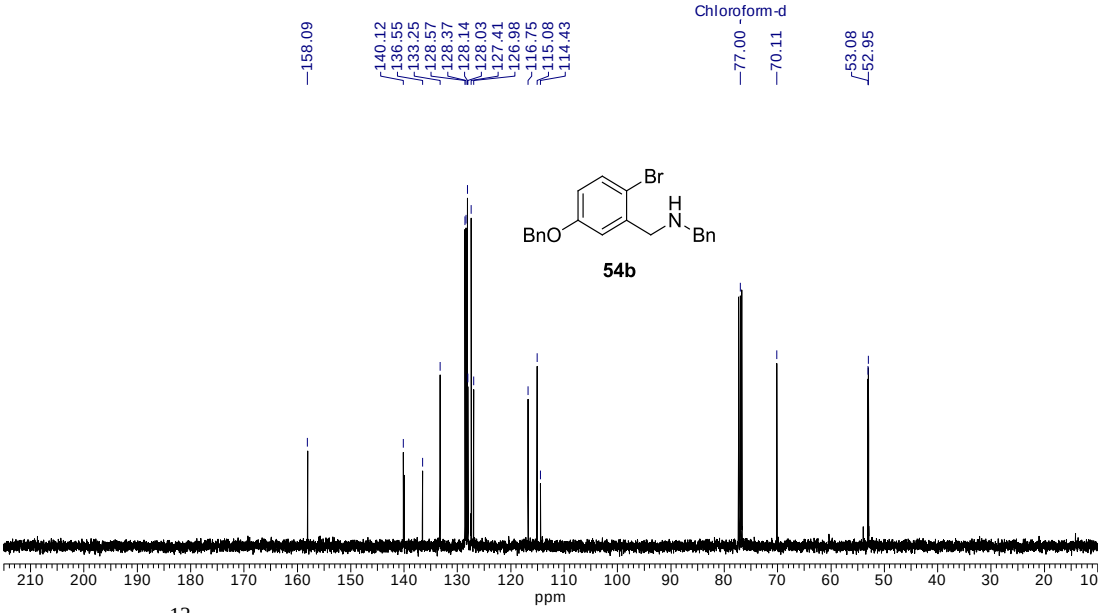


Figure I.9.2: ^{13}C NMR (100 MHz) spectrum of **54b** in $CDCl_3$

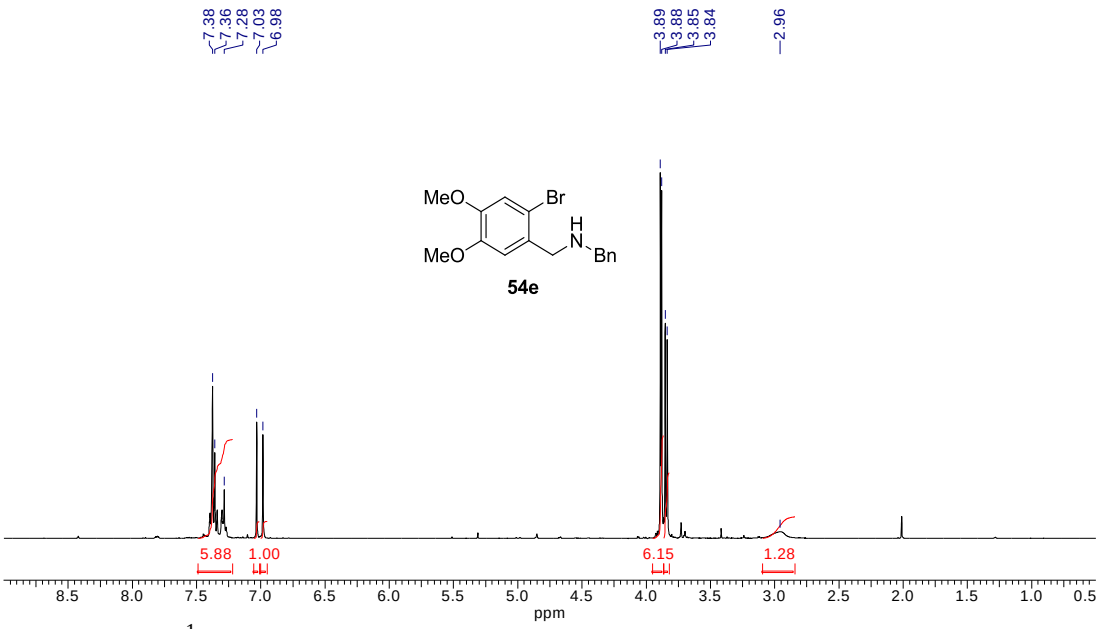


Figure I.10.1: ^{1}H NMR (400 MHz) spectrum of **54e** in $CDCl_3$

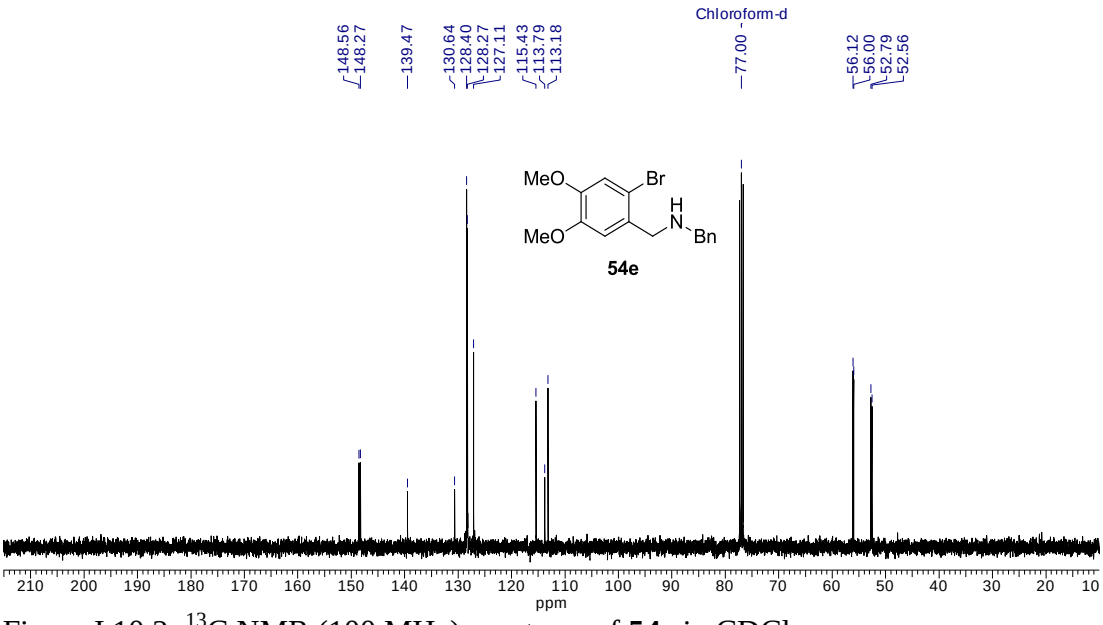


Figure I.10.2: ^{13}C NMR (100 MHz) spectrum of **54e** in $CDCl_3$

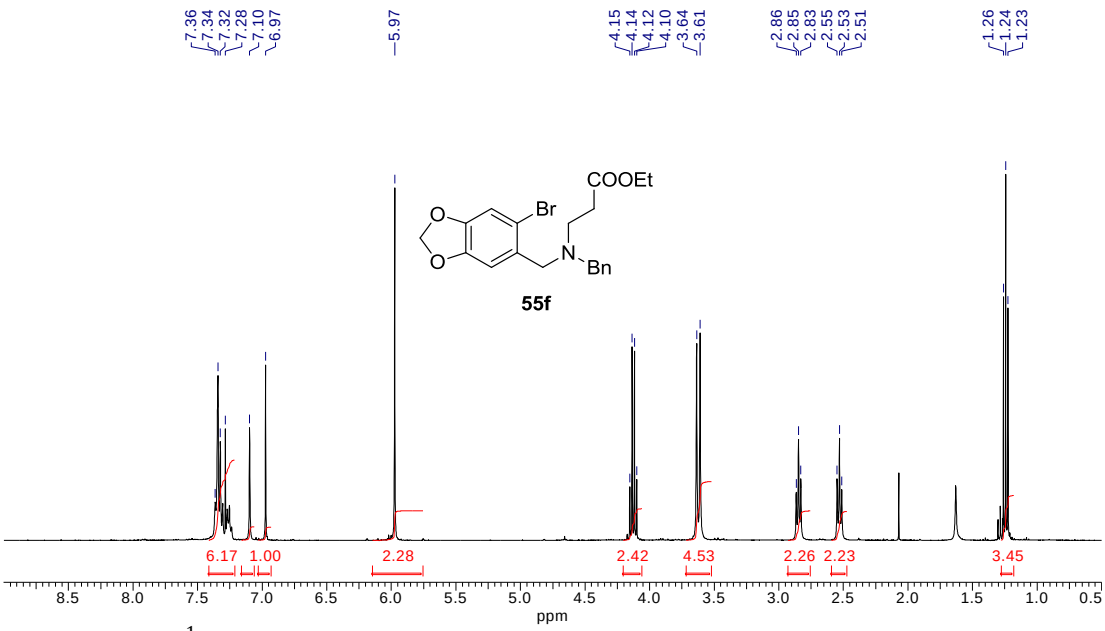


Figure I.11.1: ^{1}H NMR (400 MHz) spectrum of **55f** in $CDCl_3$

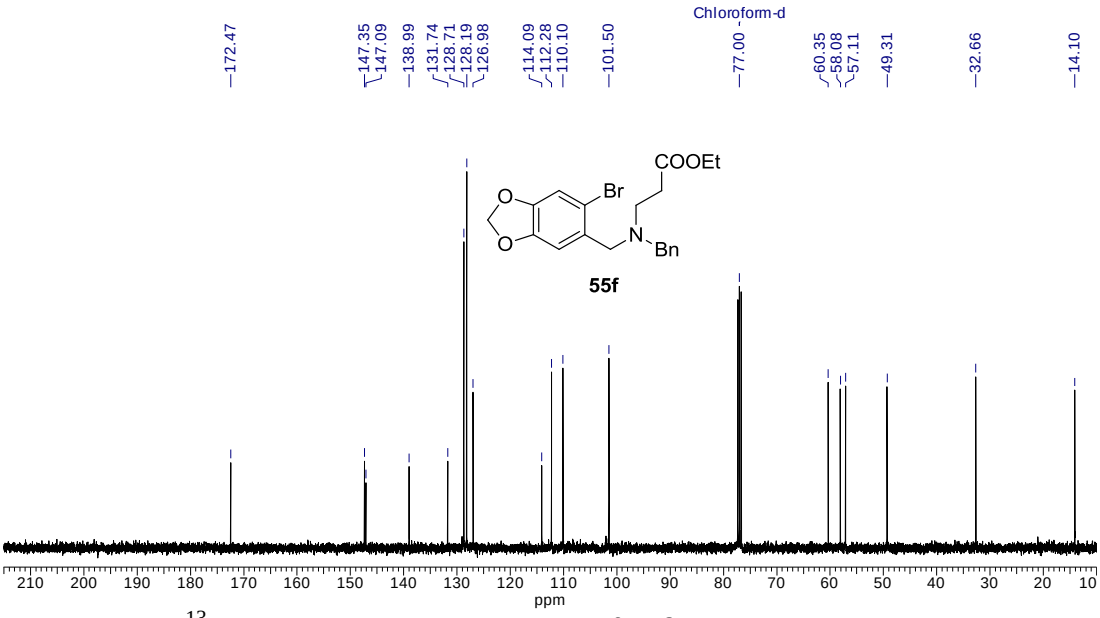


Figure I.11.2: ^{13}C NMR (100 MHz) spectrum of **55f** in $CDCl_3$

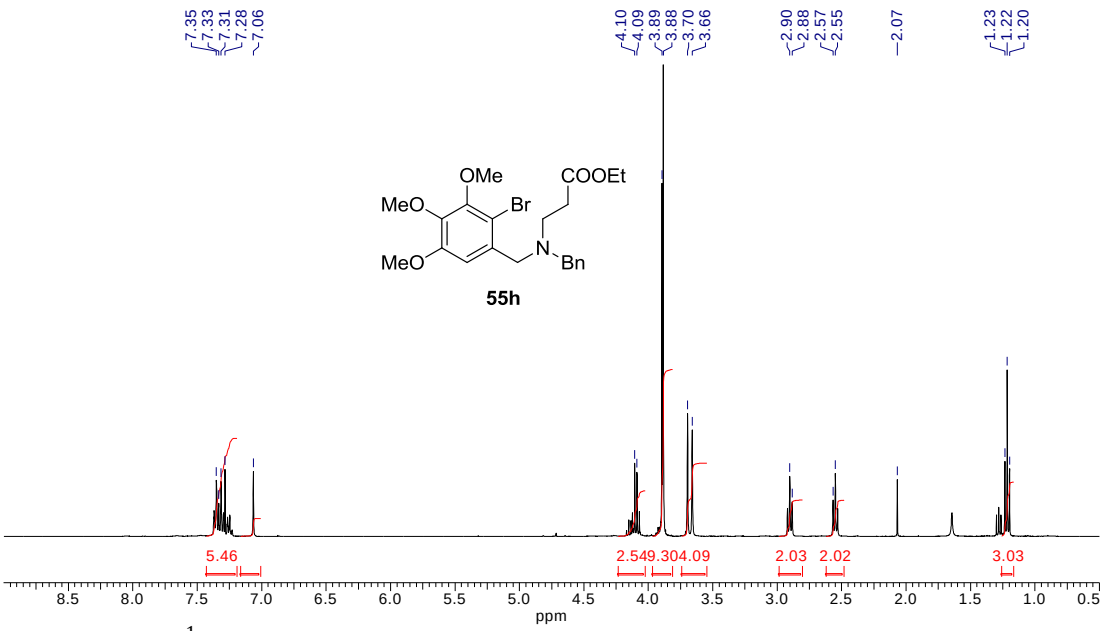


Figure I.12.1: ^{1}H NMR (400 MHz) spectrum of **55h** in $CDCl_3$

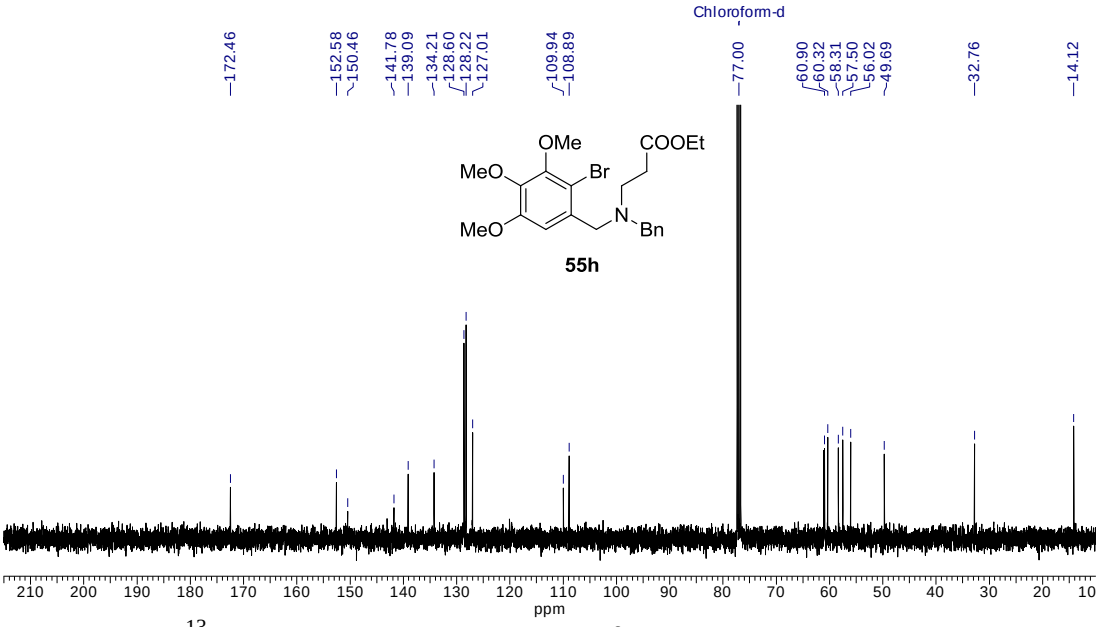


Figure I.12.2: ^{13}C NMR (100 MHz) spectrum of **55h** in $CDCl_3$

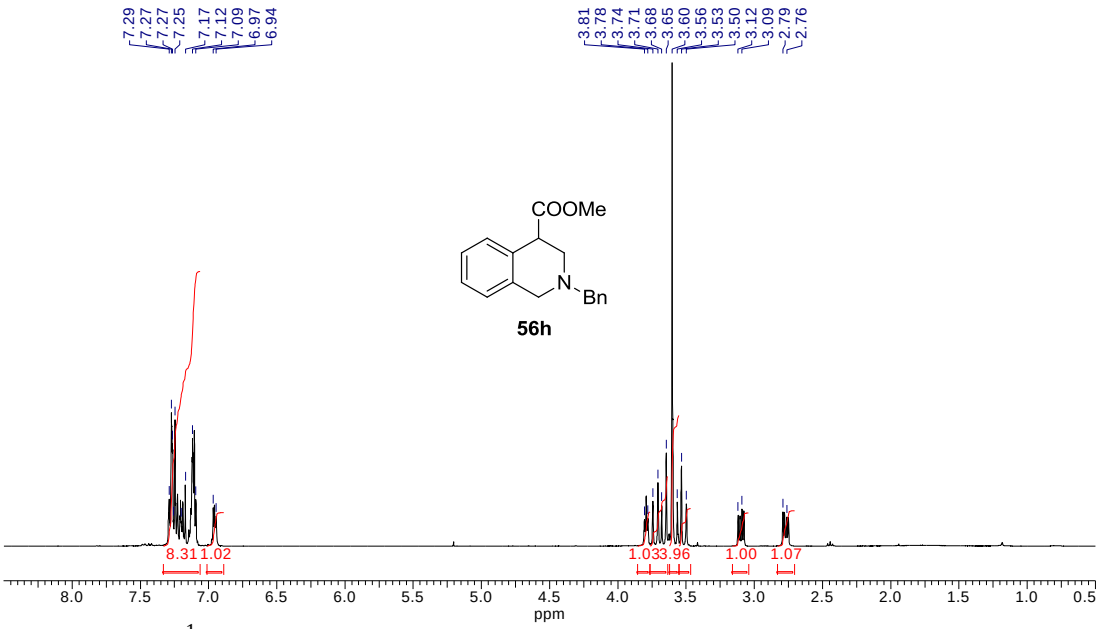


Figure I.13.1: ^{1}H NMR (400 MHz) spectrum of **56h** in $CDCl_3$

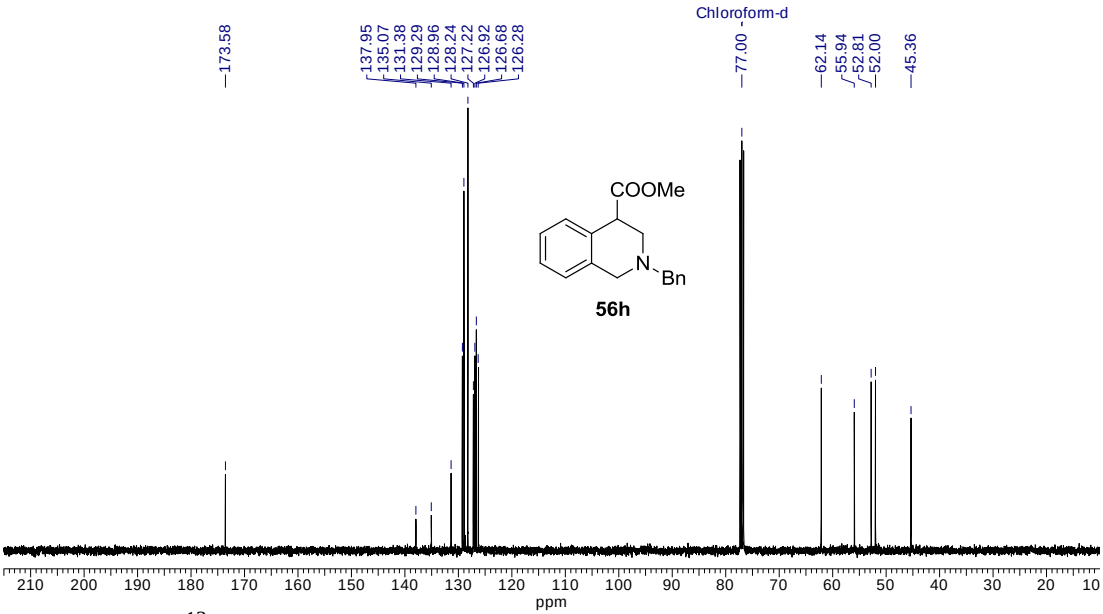


Figure I.13.2: ^{13}C NMR (100 MHz) spectrum of **56h** in $CDCl_3$

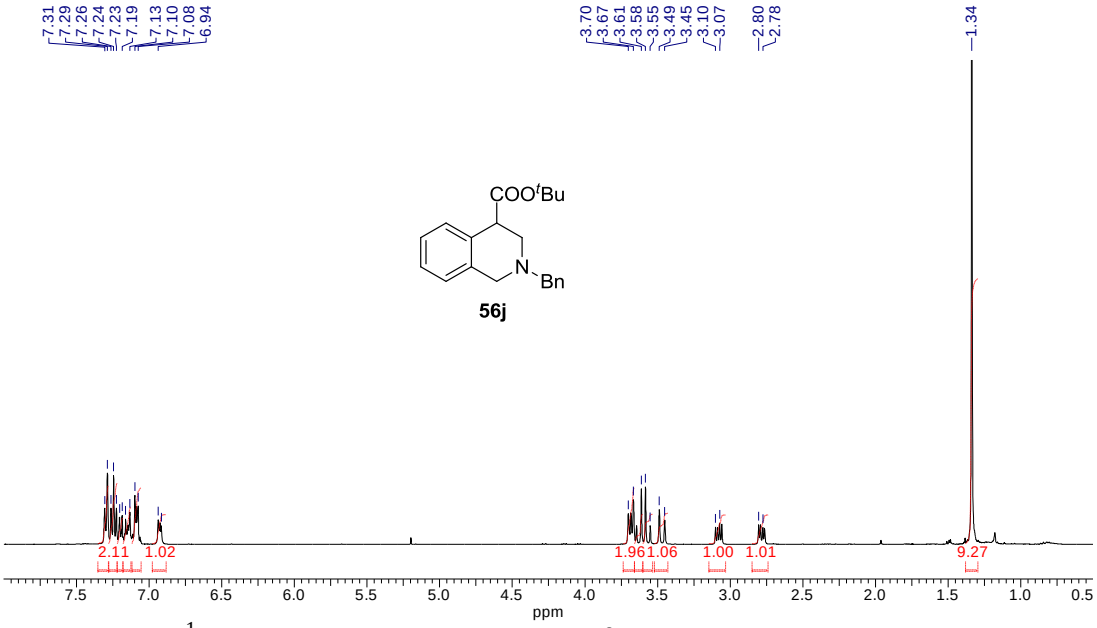


Figure I.14.1: ^{1}H NMR (400 MHz) spectrum of **56j** in $CDCl_3$

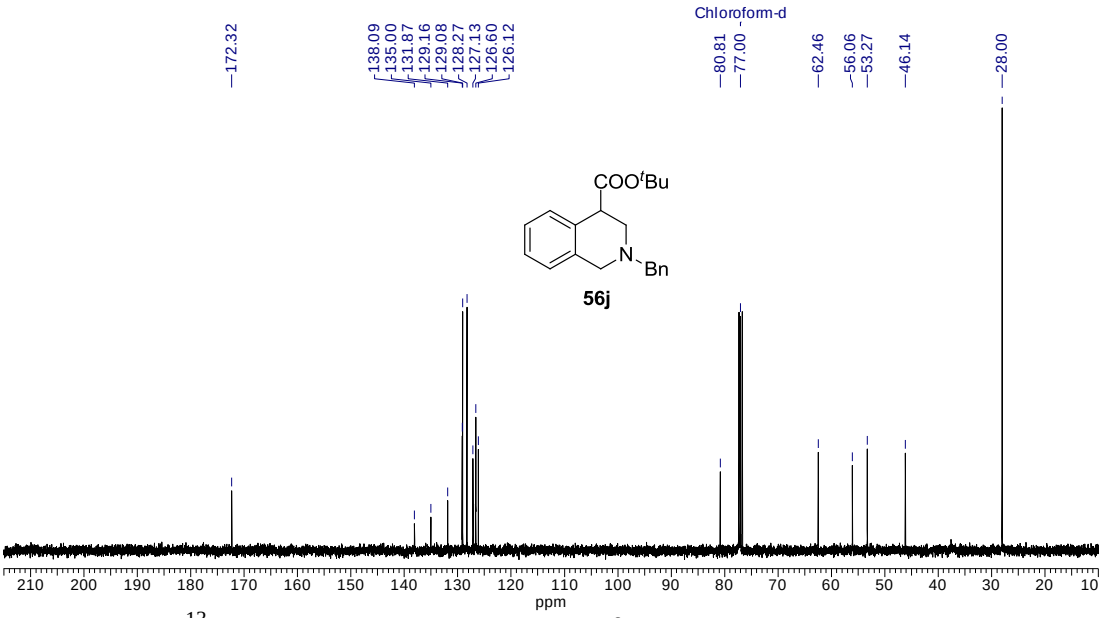


Figure I.14.2: ^{13}C NMR (100 MHz) spectrum of **56j** in $CDCl_3$

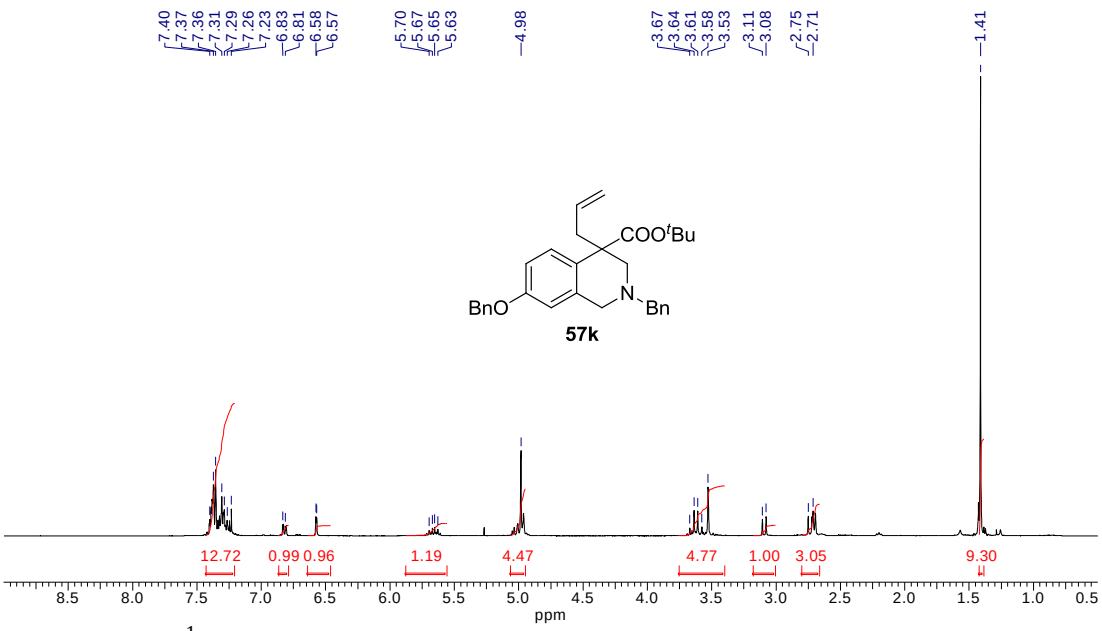


Figure I.15.1: ^{1}H NMR (400 MHz) spectrum of **57k** in $CDCl_3$

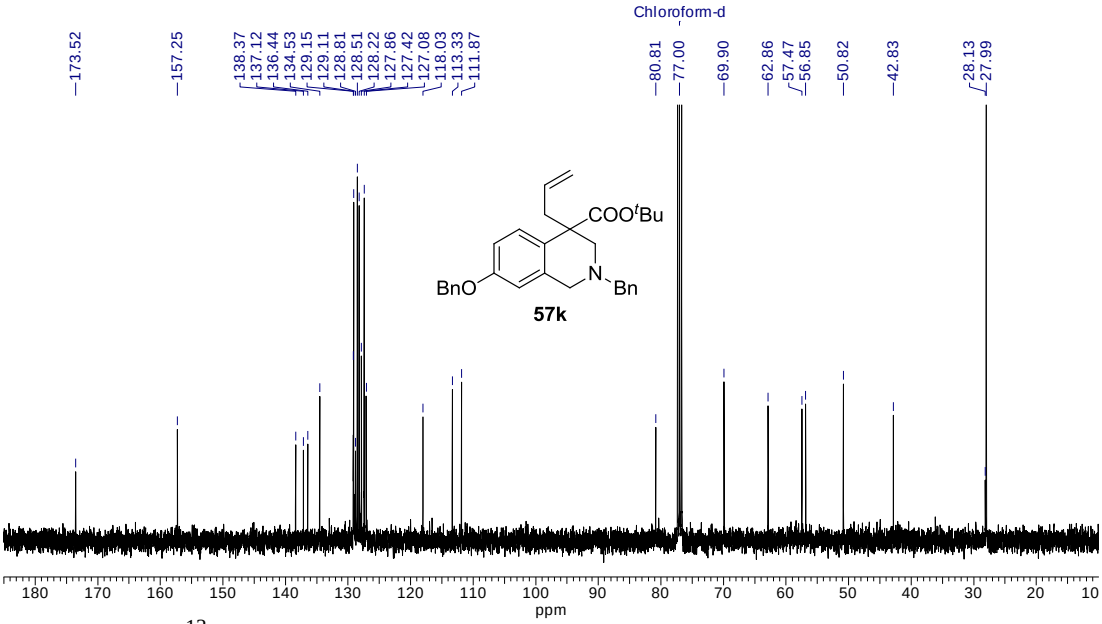


Figure I.15.2: ^{13}C NMR (100 MHz) spectrum of **57k** in $CDCl_3$

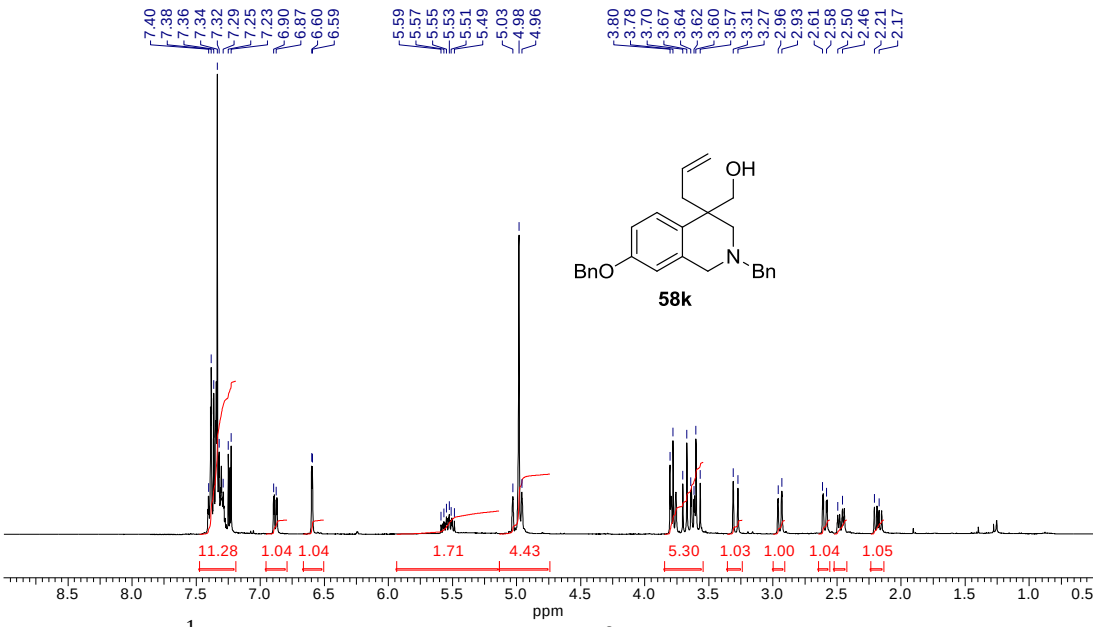


Figure I.16.1: ^{1}H NMR (400 MHz) spectrum of **58k** in $CDCl_3$

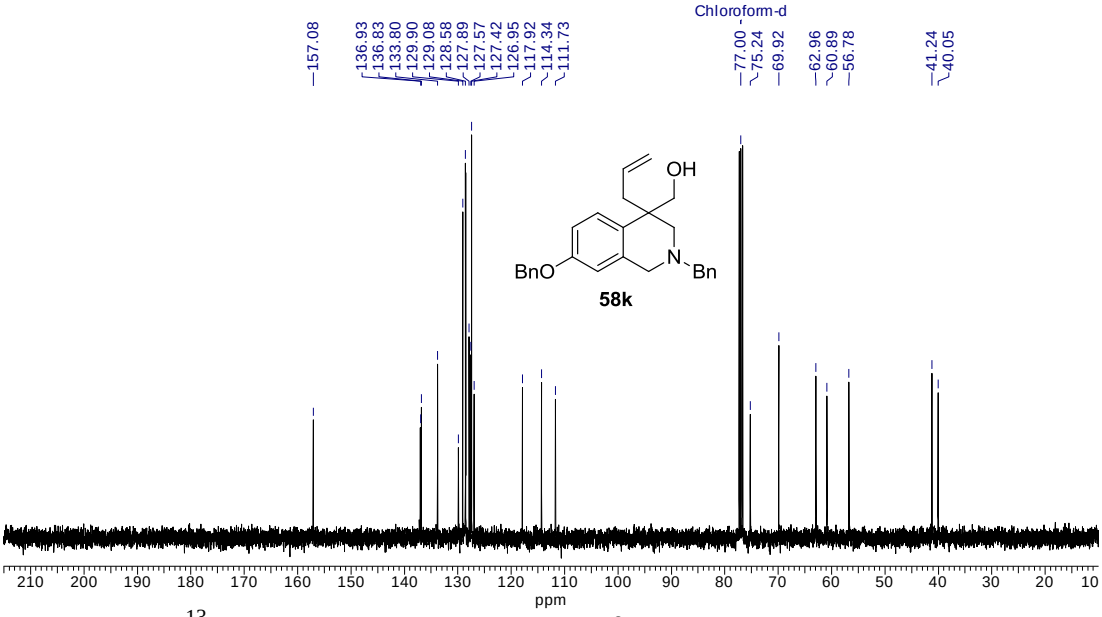


Figure I.16.2: ^{13}C NMR (100 MHz) spectrum of **58k** in $CDCl_3$

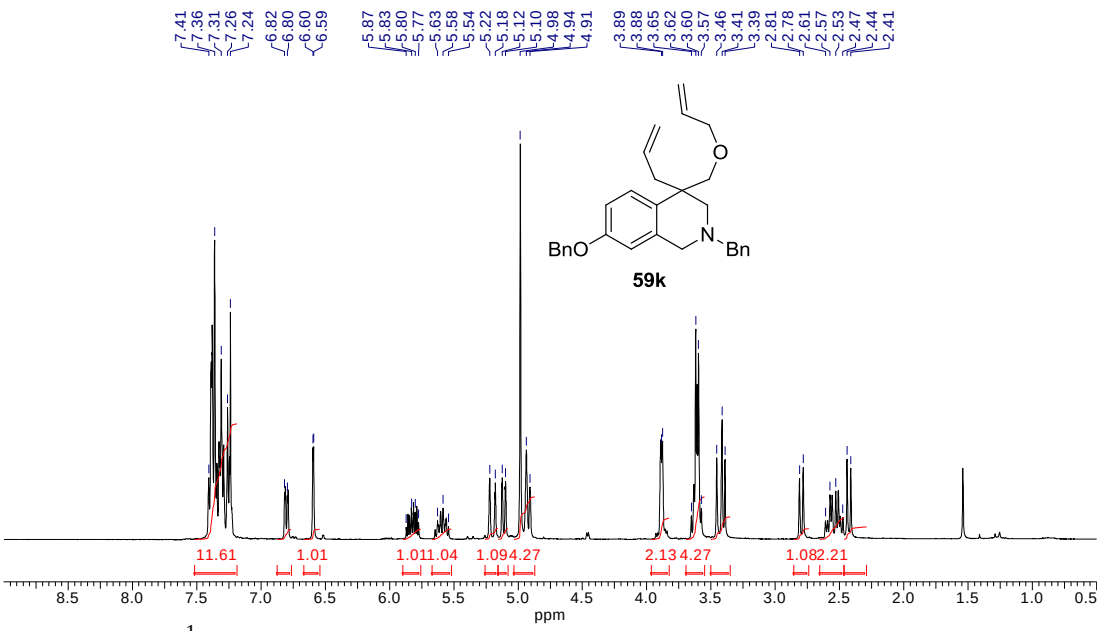


Figure I.17.1: ^{1}H NMR (400 MHz) spectrum of **59k** in $CDCl_3$

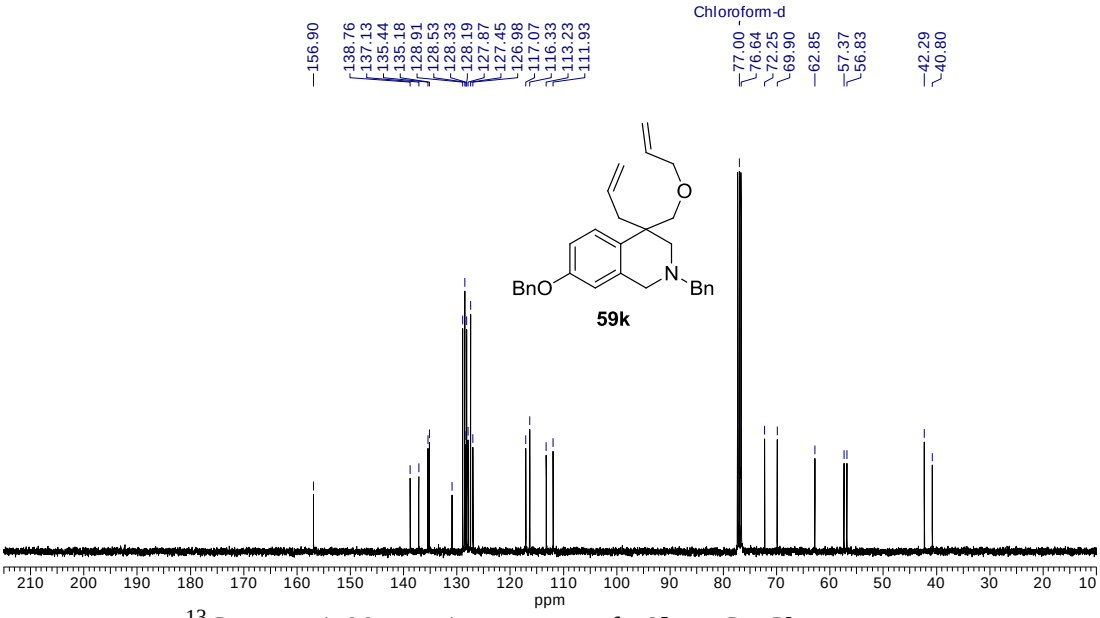


Figure I.17.2: ^{13}C NMR (100 MHz) spectrum of **59k** in $CDCl_3$

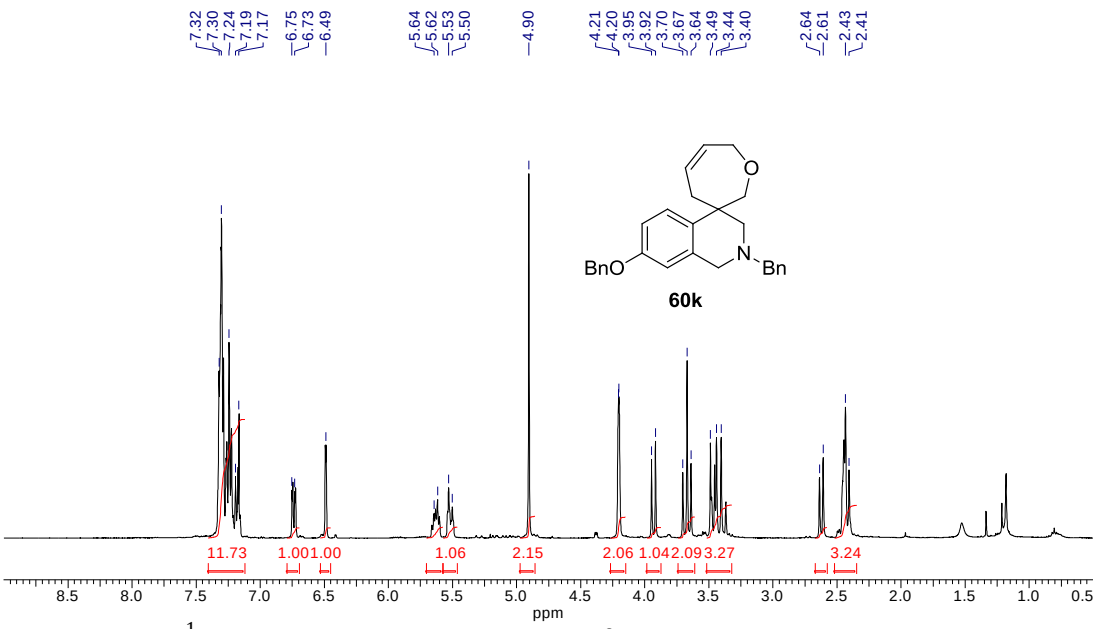


Figure I.18.1: ^{1}H NMR (400 MHz) spectrum of **60k** in $CDCl_3$

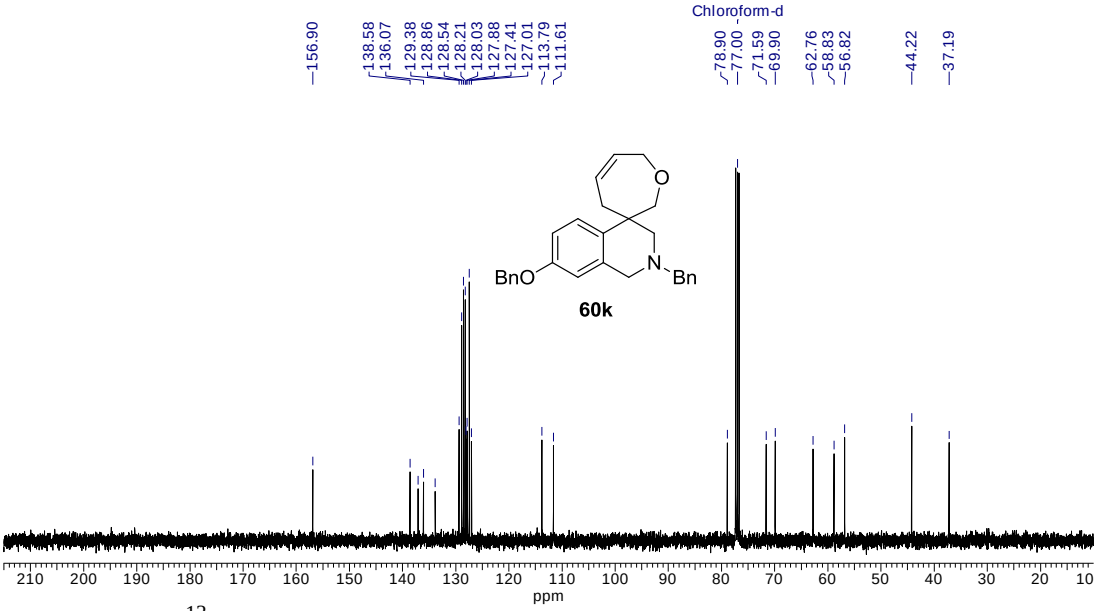


Figure I.18.2: ^{13}C NMR (100 MHz) spectrum of **60k** in $CDCl_3$

CHAPTER II

SYNTHESIS OF CINNAMATE DIESTERS, ISOCHROMENES AND 2-BENZOXEPINONES

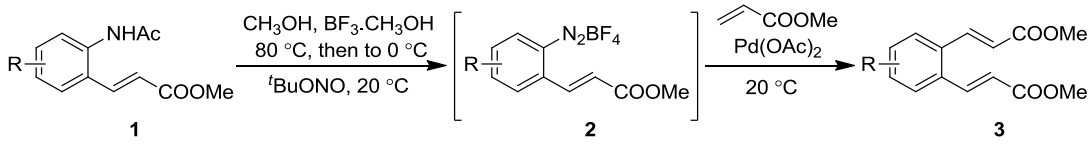
II.1 INTRODUCTION:

Organic chemistry has always demanded more efficient and economical synthetic strategies in the course of building this vast subject. Synthetic strategies involving fewer steps have been of great significance in recent times. In this regard, one-pot procedures are considered helpful for the synthesis of a variety of complex organic molecules, with no intermediate isolation.[55] This kind of one-pot transformation is possible by using a single metal complex to catalyze a sequence of multiple reactions,[56] or by the sequential addition of various metal/non-metal catalysts to achieve a multiple reaction series.[57] These types of reactions are known as multi-catalytic domino cascades, pseudo domino strategies, sequential domino one-pot protocol, telescoping synthesis and tandem reactions. These processes are of immense advantage to synthetic organic chemists, as they are recognized to have numerous benefits over normal step-wise operations, like they avoid intermediate species isolation, thereby considerably reducing waste generation, increasing strategic efficiency, using solvents and reagents minimally, and most importantly,

saving time.[50] In addition, it was also observed that in most cases, overall yields from one-pot processes were usually greater than those obtained from corresponding step-wise methods. Thus, one-pot syntheses that form multiple C–C bonds and complex cyclic structures are of immense interest and are desirable, as these complex cyclic structures constitute the core of many natural products with interesting biological activities.

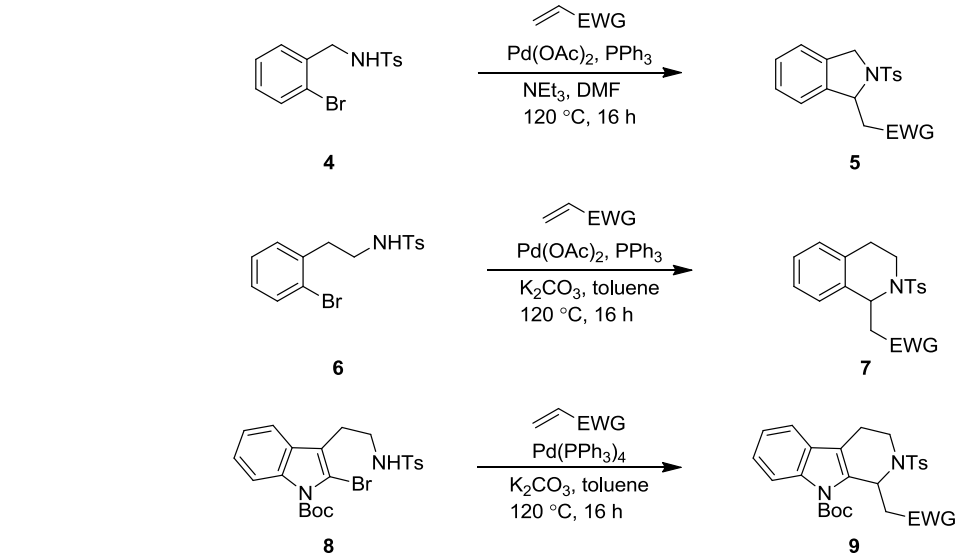
In recent times, one-pot processes catalyzed by transition metals and their development have gained much attention from synthetic organic chemists due to their practical advantages and unexpected novel reactions.[58],[59] Among a variety of these reactions, protocols involving palladium catalyzed Heck reactions were found to be the most useful and well documented.[60],[61],[62] A few examples of this kind of reaction and other associated transformations reported by different research groups involved oxidative-Heck reaction, Michael addition, electrocyclic ring closure and C–H activation.

Very recently, Schmidt and Elizarov reported a novel sequential one-pot deacetylative diazotization followed by Heck coupling on acetanilide esters **1** leading to the cimmamate diesters **3** via the intermediate **2** (Scheme II.1).[63]



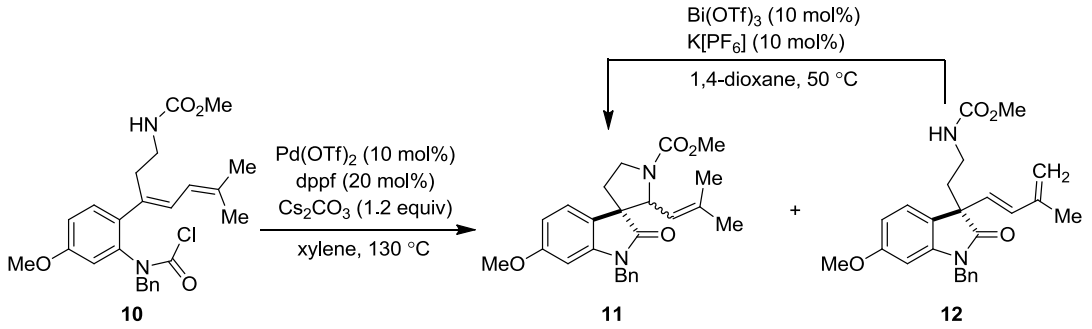
Scheme II.1

Pfeffer et al developed the palladium-catalyzed domino Heck followed by aza-Michael addition reactions,[64] for the synthesis of a series of isoindolines **5**, tetrahydroisoquinolines **7** and tetrahydro-β-carbolines **9** from the corresponding precursors **4**, **6** and **8**. The domino process involved the intermolecular Heck reaction of a haloarene with a Michael acceptor followed by an intramolecular aza-cyclization (intramolecular aza-Michael addition) reaction (Scheme II.2).



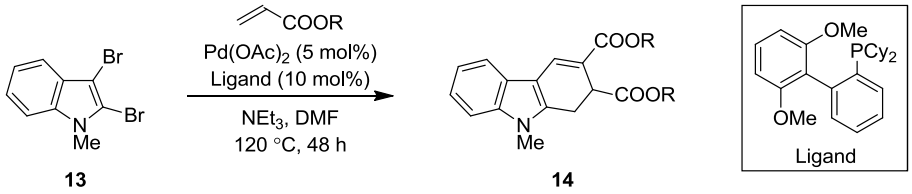
Scheme II.2

The research group of Takemoto established a domino palladium catalyzed Heck cyclization, for the formation of the spiro-tricyclic indole derivative **11** as a major product. Whereas, the Lewis acid (bismuth triflate) catalyzed hydroamination of the simple Heck cyclized product **12** gave the same spiro-tricyclic system **11**, which represents the skeleton of elacomine and isoealcomine (Scheme II.3).[65]



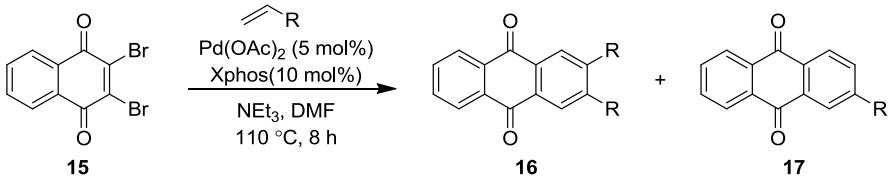
Scheme II.3

A novel domino reaction carried out by Langer et al involving a tandem double Heck reaction followed by eletrocyclic ring closure of 2,3-dibromo-N-methylindole **13**, using $Pd(OAc)_2$ as the catalyst and a selective biaryl monophosphine ligand, resulted in dihydrocarbazoles **14** (Scheme II.4).[66]



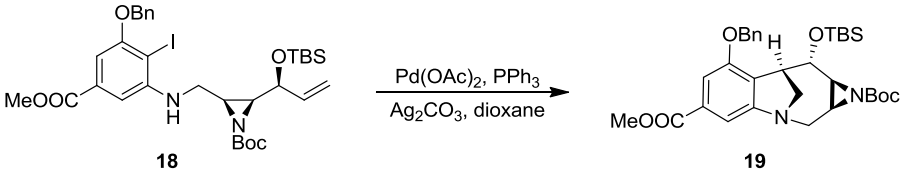
Scheme II.4

The same research group disclosed the synthesis of anthraquinones **16** and **17** from dibromonaphthaquinone **15** (Scheme II.5).[67]



Scheme II.5

The efforts of Trost and his co-workers[68] to synthesize FR900482, an epimer of anti-cancer, along with the 8-exo-trig Heck reaction to afford the benzazacine core from the precursor **18**, led to domino intramolecular C–H activation and furnished **19** (Scheme II.6).



Scheme II.6

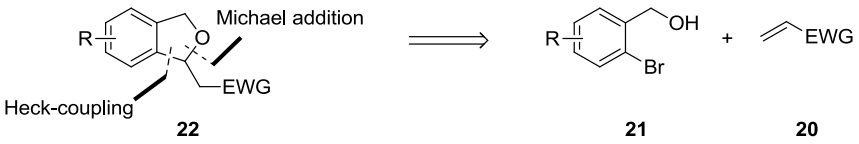
In spite of its wide applications, the popularity and reports of the Heck reaction, in combination with a succeeding cyclization step (for example, intramolecular Michael addition), are limited. It might be ideal to choose a base that would be suitable to promote both the Heck coupling as well as cyclization addition, as most of the palladium catalyzed transformations were base controlled

reactions.[69],[70] Remarkably, there were fewer approaches documented on Pd-catalyzed Heck-Michael,[17] and Heck-aza-Michael[71] one-pot processes.

II.2 RESULTS AND DISCUSSION:

II.2.1 Sequential one-pot synthesis of cinnamate diesters and isochromenes:

After successfully obtaining functionalized 1,2,3,4-tetrahydroisoquinolines by palladium catalysis and their extension to spiro-tricyclic oxepines (Chapter I) and based on the research literature initially, the synthesis of isobenzofurans **22** was targeted from *ortho*-bromobenzyl alcohols **20** through the palladium catalyzed intermolecular Heck reaction followed by an intramolecular Michael addition reaction with Michael acceptors **21**. It was envisioned that the use of a single base would be capable of promoting both Pd-catalysis as well as oxy-Michael addition. The requisite precursors, 2-bromobenzyl alcohols were readily obtained by simple reduction from sodium borohydride (Scheme II.7).



Scheme II.7

Thus, the synthetic study was initiated with the preparation of 2-bromobenzaldehydes. The required *ortho*-bromobenzyl alcohols **21a**–**21h** were synthesized by the standard reduction reaction of 2-bromobenzaldehydes **35a**–**35h**. Thus, treatment of 2-bromobenzaldehydes **35a**–**35h** with the sodium borohydride (fractional addition for about 10 minutes to avoid vigorous effervescence) at ice-cold temperature in methanol, followed by stirring the reaction

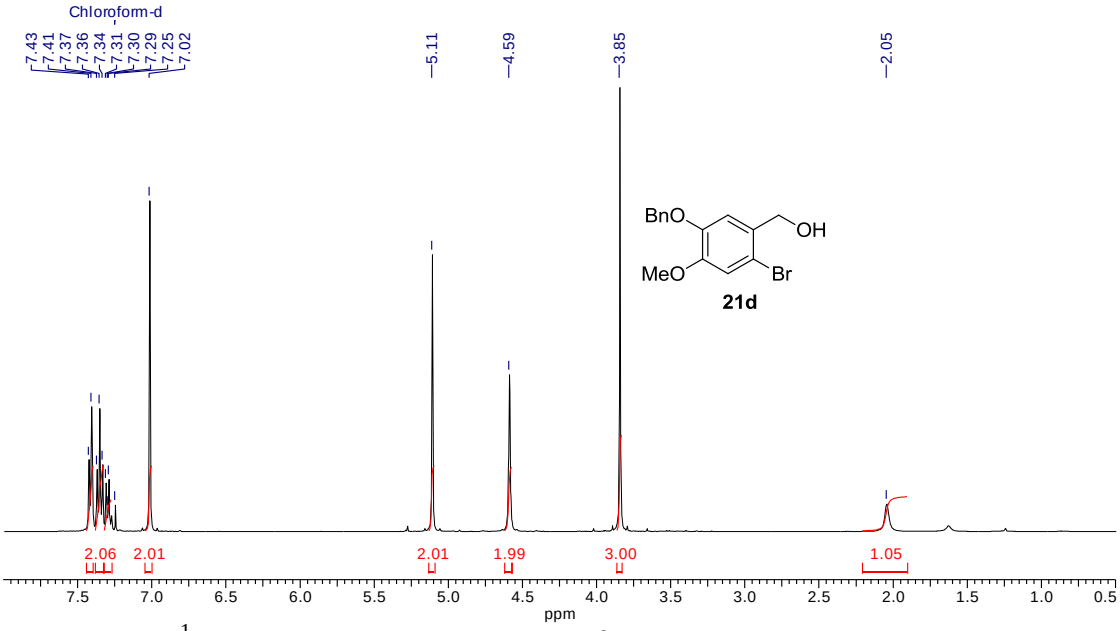


Figure II.1.1: ^{1}H NMR (400 MHz) spectrum of **21d** in $CDCl_3$

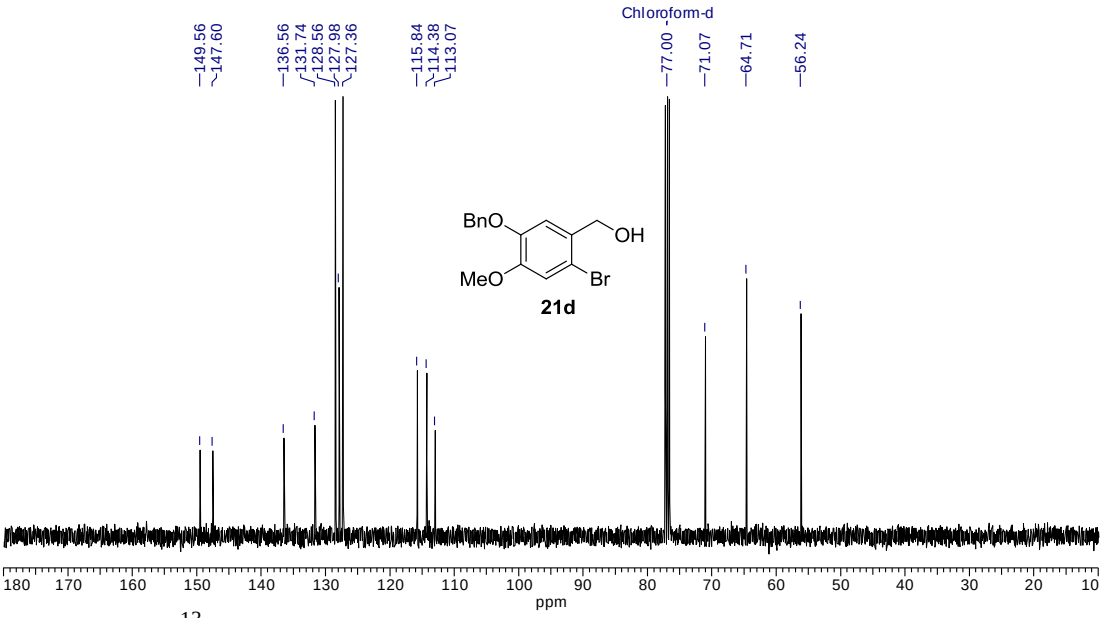


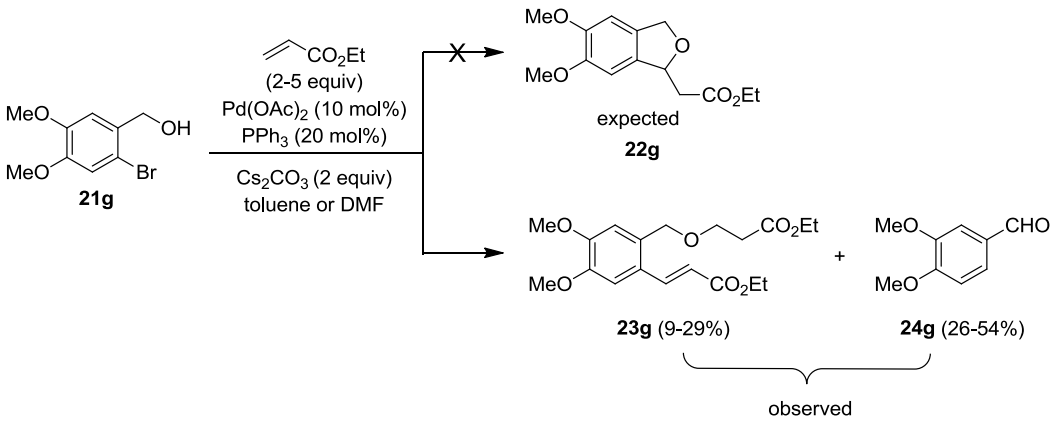
Figure II.1.2: ^{13}C NMR (100 MHz) spectrum of **21d** in $CDCl_3$

mixture at room temperature for one hour, furnished the 2-bromobenzylprimary alcohols **21a**–**21h**. The chemical structure of the 2-bromobenzyl alcohol **21d** was confirmed from the spectral data of **21d**. The lack of an absorption band due to carbonyl stretching of aldehyde group and the existence of the broad absorption

band at 3372 cm^{-1} due to the O–H stretching in the IR spectrum, indicated the formation of the 2-bromobenzyl alcohol **21d**. In the ^{1}H-NMR spectrum, the absence of aldehyde proton resonance, the presence of three doublets at δ 7.42, 7.36 and 7.35 due to four aromatic protons, a triplet at δ 7.29 due to one aromatic proton, two singlets at δ 7.02 due to two aromatic protons, three singlets at δ 5.11 and 4.59 due to four protons of two methylenes and 3.85 for one O-methyl proton and one broad singlet at δ 2.05 ppm for the proton of hydroxyl group elucidated the structure of the 2-bromobenzyl alcohol **21d** (Figure II.1.1). In addition, the appearance of five quaternary carbon resonances at δ 149.6, 147.6, 136.6, 131.7 and 113.1 due to five aromatic carbons, seven methine carbons at δ 128.6, 128.0, 127.4, 115.8 and 114.4, two methylenes at 71.1 and 64.7 and one quartet at 56.2 ppm in the 13 lines of ^{13}C-NMR spectrum confirmed the structure of 2-bromobenzyl alcohol **35a** (Figure II.1.2). On the other hand, the requisite secondary alcohols **21k**–**21o** were achieved by the standard methyl Grignard reaction on the corresponding 2-bromobenzaldehydes **35**. The reagent methylmagnesium iodide, which was used for the Grignard reaction, was prepared by the activation of a catalytic amount of magnesium by molecular iodine, followed by drop wise addition of methyl iodide to the magnesium metal in dry ether under an inert atmosphere.

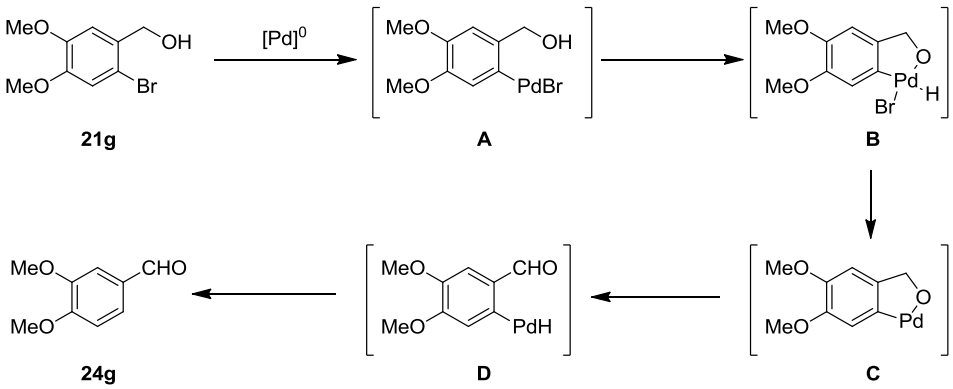
To initiate the synthetic study, 2-bromobenzyl alcohol **21g** was chosen as the model for the synthesis of expected isobenzofurans **22g** via palladium catalyzed domino one-pot Heck followed oxy-Michael addition sequence. Thus, initially, 2-bromobenzyl alcohol **21g** was treated with varying amounts of ethyl acrylate (2–5 equiv) in the presence of palladium catalyst [10 mol% of $Pd(OAc)_2$, 20 mol% of PPh_3] with the base Cs_2CO_3 (2 equiv) in hot toluene (or DMF) for 24 h (Scheme II.8). Unexpectedly, the result was the formation of a cinnamate derivative **23g**, albeit in very poor yield (9% by using 2 euivivalents of ethyl acrylate and 29% with 5 euivivalents of ethyl acrylate) along with a reasonable amount of simple veratraldehyde **24g** (54% by using 2 euivivalents of ethyl acrylate and 26% with 5 euivivalents of ethyl acrylate). The formation of **23g** took place via initial intermolecular oxy-Michael addition and succeeding intermolecular Heck coupling

instead of the expected cyclic ether **22g** through initial intermolecular Heck coupling followed by intramolecular oxy-Michael addition. This might be due to preferential nucleophilicity of the benzyl alcohol moiety **21g** towards the Michael acceptor ethyl acrylate over the intermolecular Heck reaction (Scheme II.8).



Scheme II.8

However, the latter one **24g** was formed by reductive debromination and oxidative cleavage. This can be explained by a competing formation of aryl-palladium(II) species **A**, which upon intramolecular coordination with neighbouring free benzylic OH group would lead to a five-membered palladacycle **B**. Then, subsequent cycloreversion of the pallacycle due to β-hydrogen atom transfer would lead to the benzaldehydes **24g** (scheme II.9).[72]



Scheme II.9

The formation and structure of the diester **23g** was apparent from the spectral data. The absence of a broad absorption band due to O–H stretching and the existence

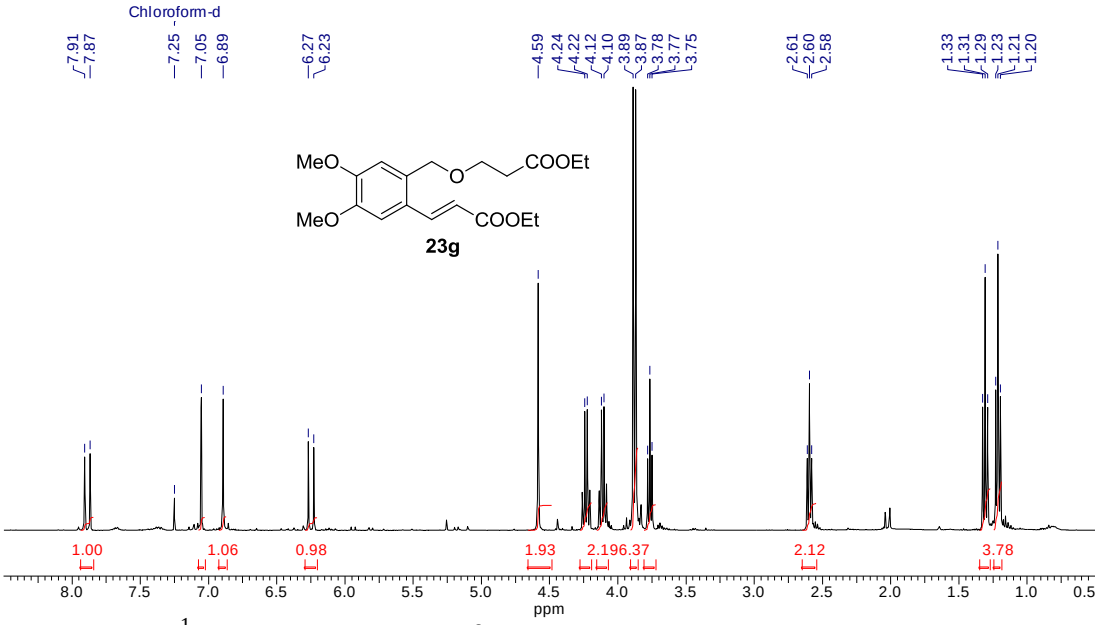


Figure II.2.1: ^{1}H NMR (400 MHz) of compound **23g** in $CDCl_3$

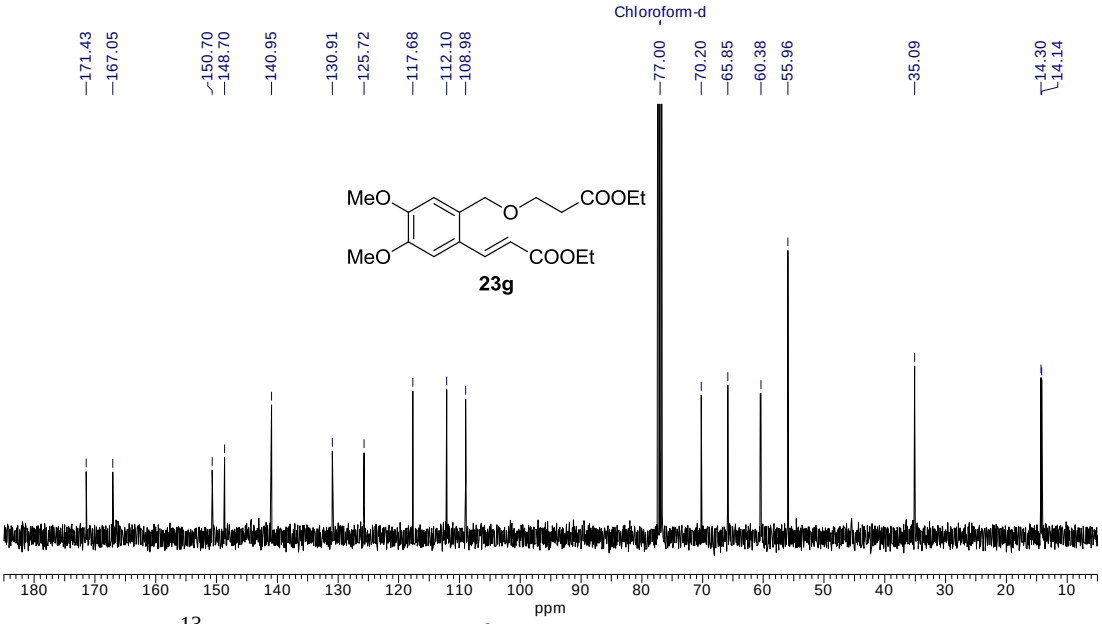
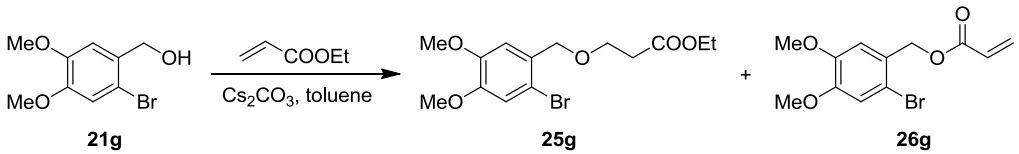


Figure II.2.2: ^{13}C NMR (100 MHz) of compound **23g** in $CDCl_3$

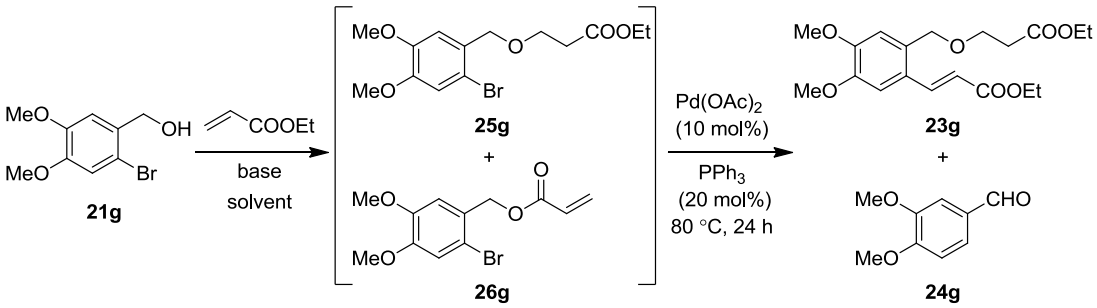
of the absorption band at 3372 cm^{-1} due to the carbonyl stretching of ester group in the IR spectrum showed the formation of diester **23g**. In the ^{1}H-NMR spectrum (Figure II.2.1), absence of O–H proton resonance, the presence of two doublets at δ 7.89 and 6.25 due to two olefinic protons, two singlets at δ 7.05 and 6.89 due to two aromatic protons, three singlets in the aliphatic region at δ 4.59 due to one benzylic methylene, 3.89 and 3.87 for two O-methyl groups, two quartets at δ 4.23 and 4.11 due to four protons of two O-methylene protons and four triplets at δ 3.77, 2.60, 1.31 and 1.25 ppm for 10 protons of two methylenes and two methyl moieties established the structure of diester **23g**. Additionally, the detection of six quaternary carbon resonances at δ 171.4 and 167.0 for two ester carbonyl carbons, signals at δ 150.7, 148.7, 130.9 and 125.7 for the four aromatic carbons, four methine carbons at δ 140.9 and 109.0 due to two olefinic carbons, 117.7 and 112.1 of two aromatic carbons, five methylenes at 70.2, 65.8, 60.5, 60.4 and 35.1 and four quartets at 56.0, 14.3 and 14.1 ppm from 18 lines of ^{13}C-NMR spectrum (Figure II.2.2) concluded the structure of diester **23g**.

Since the yield of product **23g** was very poor when the reaction was performed by direct addition of both the Michael acceptor and catalyst together with the 2-bromobenzyl alcohol **21g**, expected the sequential addition of the Michael acceptor (i.e. for the initial oxy-Michael addition in selective fashion) and loading of the palladium catalyst would help achieve **23g** in improved yields due to the high selectivity of each individual step of the reaction sequence. Thus oxy-Michael addition was administered for optimization. The treatment of **21g** with excess ethyl acrylate (5 equiv) in hot toluene (80 °C) for 48 h, furnished the expected oxy-Michael addition product, the bromoester **25g**, in fair yield (58%) along with the undesired condensed ester by-product **26g** in 22% yield (entry 1, Table II.1; Scheme II.10).



Scheme II.10

Table II.1: Optimization with various screening reaction conditions, for one-pot synthesis of **23g**.



	oxy-Michael addition						Heck coupling[d]	
Entry	Base (2 equiv)	Solvent	Temp (°C)	Time (h)	Yield **25g** (%)	Yield **26g** (%)	Yield **23g** (%)	Yield **24g** (%)
1[a]	Cs_2CO_3	toluene	80	24	58	22	-	-
2[b]	Cs_2CO_3	toluene	RT	72	73	14	-	-
3[a]	**Cs_2CO_3**	**toluene**	**50**	**48**	**78**	**16**	-	-
4[c]	**Cs_2CO_3**	**toluene**	**50**	**48**	-	-	**53**	-
5[c]	K_3PO_4	toluene	50	48	-	-	22	-
6[c]	Cs_2CO_3	THF	65	24	-	-	-	10
7[c]	Cs_2CO_3	CH_3CN	80	20	-	-	5	23
8[c]	K_3PO_4	CH_3CN	50	48	-	-	-	-
9[c]	Cs_2CO_3	DMF	80	20	-	-	5	30
10[c]	K_3PO_4	DMF	50	48	-	-	10	-

[a] Isolated yields of chromatographically pure products (**25g** and **26g**) and hence subsequent palladium catalyzed Heck coupling was not performed. [b] Isolated yields of products (**25g** and **26g**) based on starting material recovery and hence subsequent palladium catalyzed Heck coupling was not performed. [c] No oxy-Michael addition product was isolated and

subjected to in situ palladium catalyzed Heck coupling. [d] Isolated yields of chromatographically pure products (**23g** and **24g**).

We presumed that the decrease in temperature might prevent the formation of by-product **26g** and may improve the selectivity for the formation of bromoester **25g**. Quite interestingly, the reaction at ambient temperature showed a promising incremental effect in yield (73%) of **25g** at the expense of **26g** (14%) based on the recovery of starting material **21g** (entry 2, Table II.1). Gratifyingly, the product **25g** was furnished in very good yield (78%) along with **26g** (16%) at 50 °C for 48 h (entry 3, Table II.1).

The formation and structure of ester **25g** was obvious from the spectral data of **25g**. Absence of the broad absorption band due to O–H group and presence of absorption band at 1732 cm^{-1} for the ester carbonyl stretching in the IR spectrum indicated the formation of ester **25g**. In the ^{1}H-NMR spectrum (Figure II.3.1), the absence of O–H proton resonance, the presence of four singlets at δ 6.98 (due to two aromatic protons), 4.52 (due to two protons of benzylic methylene group), 3.86 and 3.84 (due to six protons of two O-methyl groups), a quartet at δ 4.14 (due to two protons of O-methylene group) and three triplets at δ 3.79, 2.62 and 1.24 ppm (due to four protons of two methylene groups and for three protons of one methyl group) elucidated the structure of ester **25g**. In addition, in 14 lines ^{13}C-NMR spectrum (Figure II.3.2), presence of five quaternary carbon resonances at δ 171.5 (due to ester carbonyl), 148.8, 148.5, 129.4 and 112.7 (due to four aromatic carbons), two aromatic methine carbons at δ 115.2 and 111.9, four methylenes at 72.0, 65.9, 60.5 and 35.1, three methyls at 56.1, 56.0 and 14.2 ppm confirmed the structure of ester **25g**.

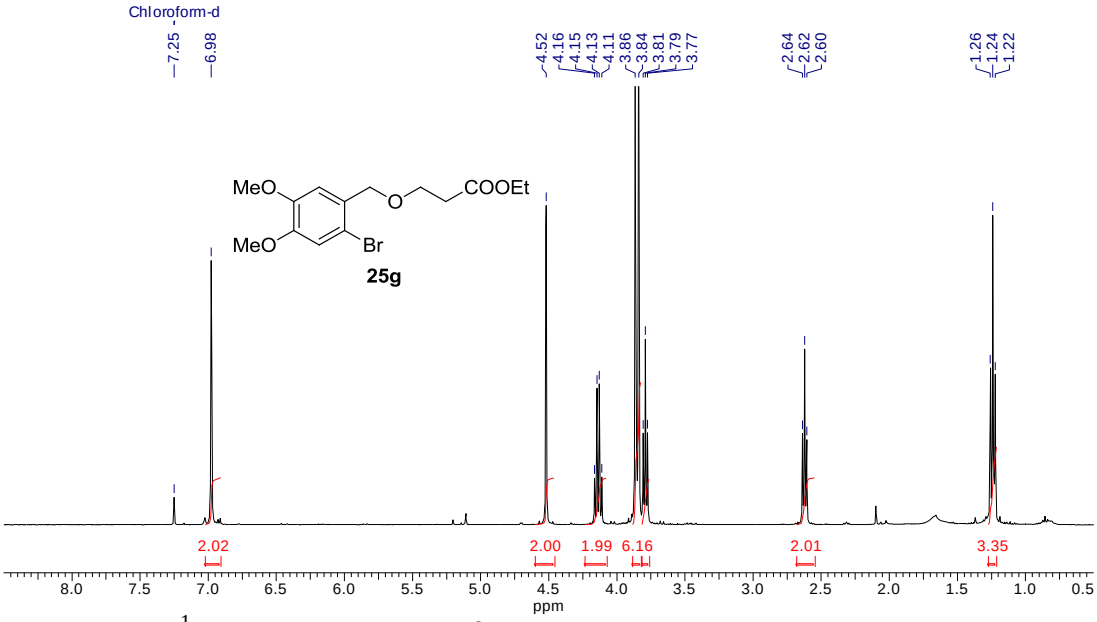


Figure II.3.1: ^{1}H NMR (400 MHz) of compound **25g** in $CDCl_3$

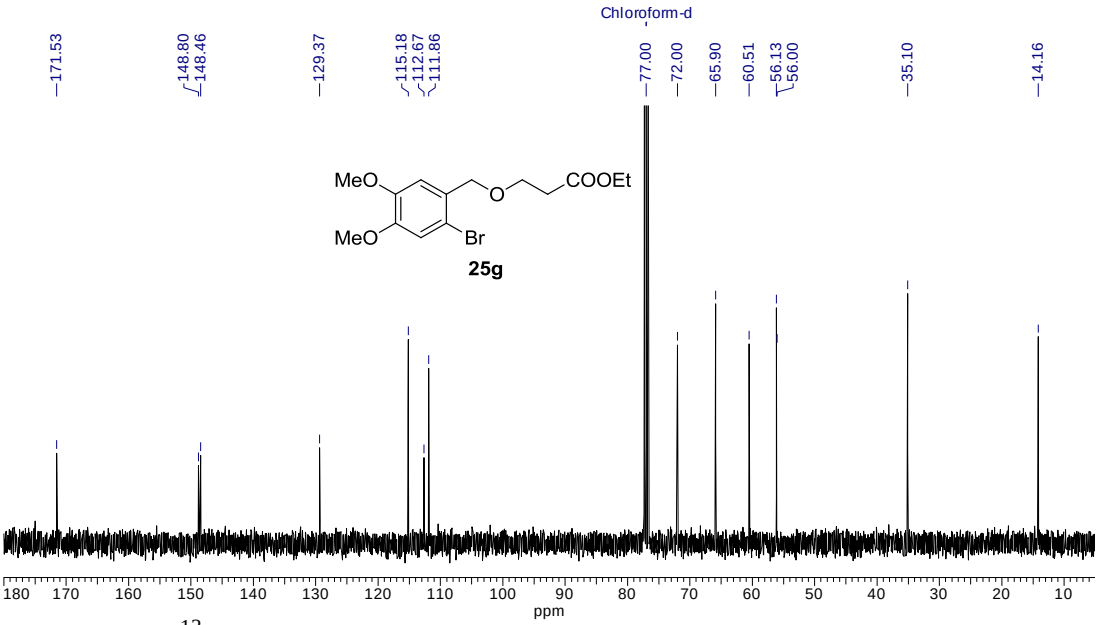


Figure II.3.2: ^{13}C NMR (100 MHz) of compound **25g** in $CDCl_3$

In a similar way, the structure and formation of ester **26g** was obvious from the spectral data of **26g**. The disappearance of a broad absorption band due to O–H

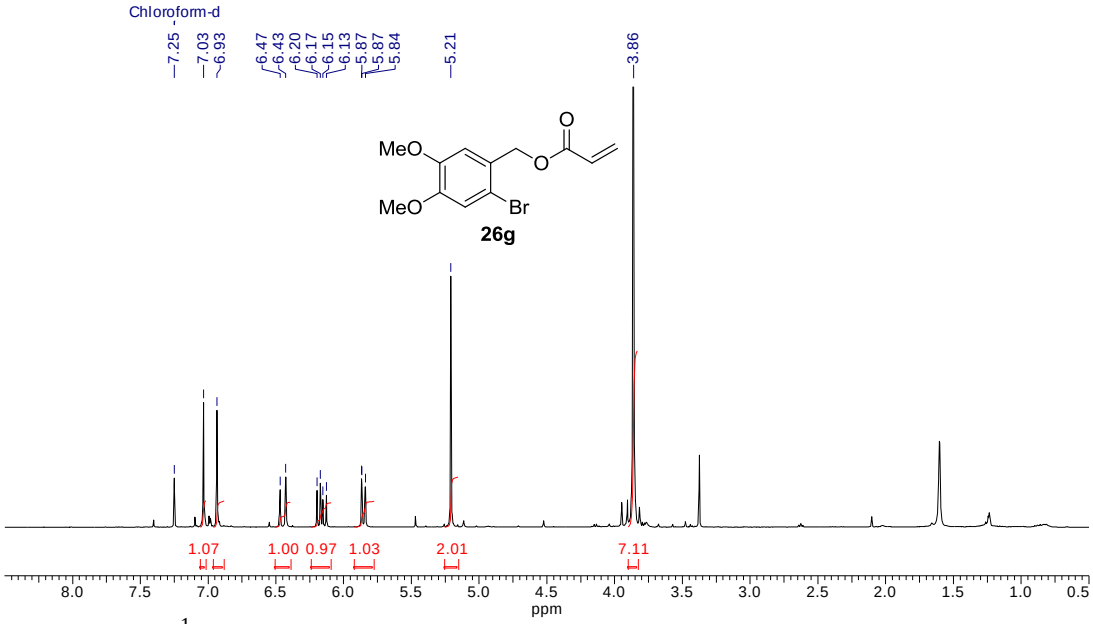


Figure II.4.1: ^{1}H NMR (400 MHz) of compound **26g** in $CDCl_3$

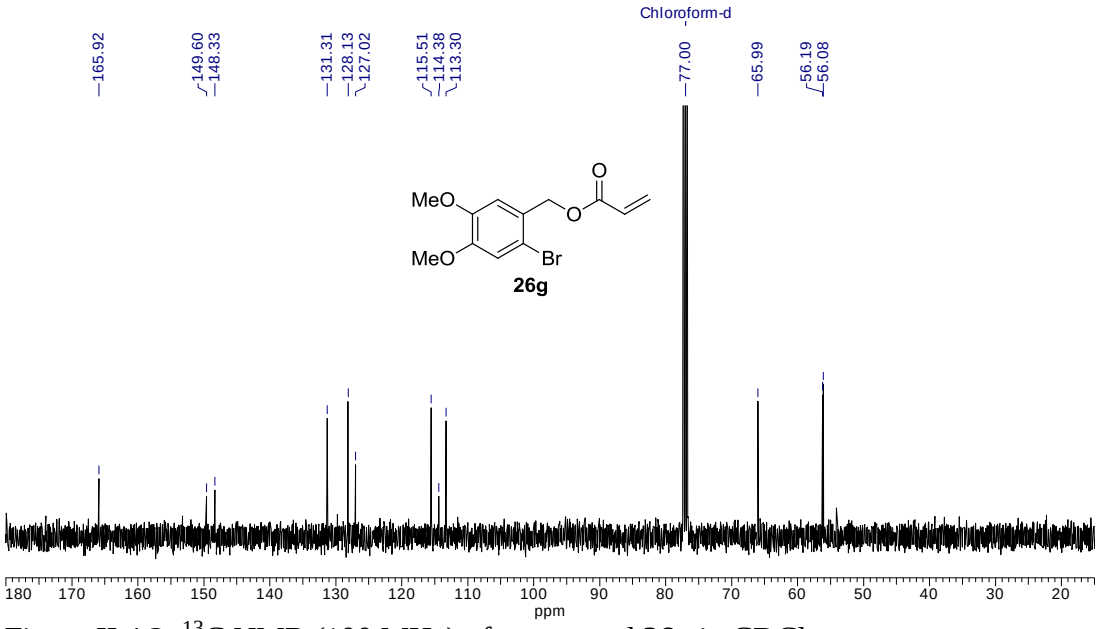
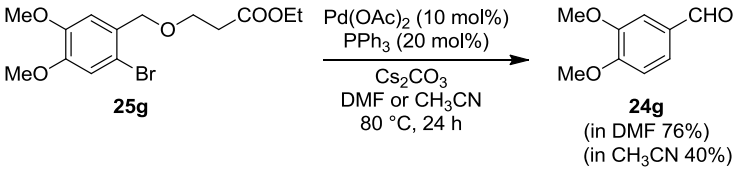


Figure II.4.2: ^{13}C NMR (100 MHz) of compound **26g** in $CDCl_3$

group and existence of absorption band at 1722 cm^{-1} due to ester carbonyl stretching in the IR spectrum signified the formation of ester **26g**. In the ^{1}H-NMR spectrum

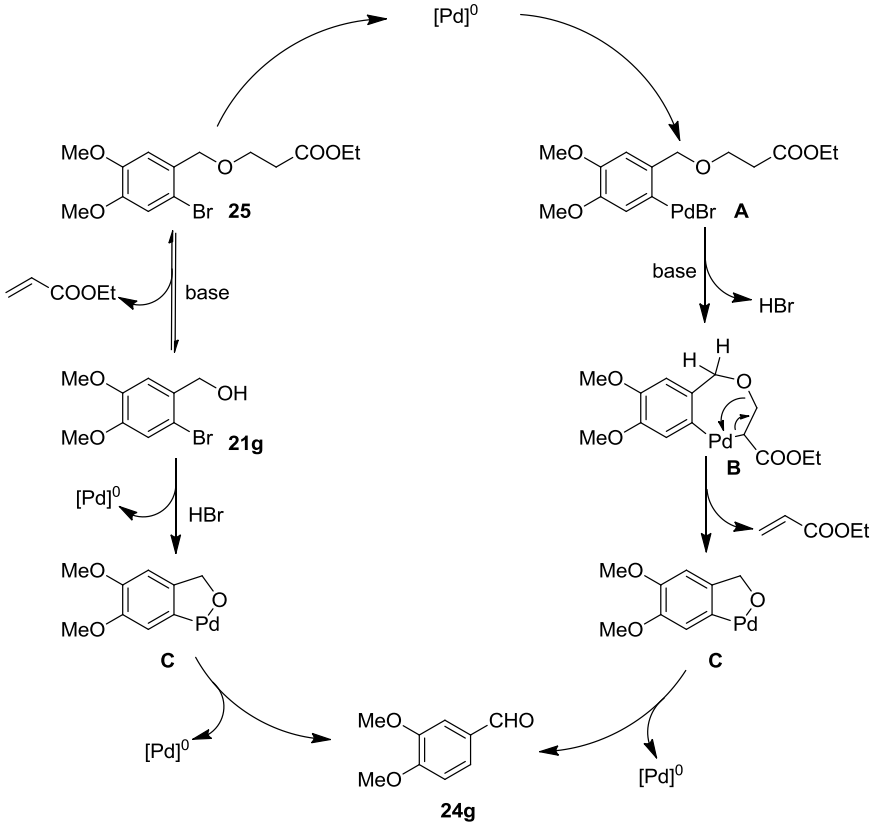
(Figure II.4.1), the presence of five singlets at δ 7.03 and 6.93 (due to two aromatic protons), 5.21 (because of two protons of benzylic methylene group), 3.86 and 3.85 (for six protons of two methoxy groups), and three doublet of doublets at δ 6.45, 6.16 and 5.85 ppm (due to three protons of vinyl group) established the structure of the condensed ester **26g**. To support it the 14 lines in ^{13}C-NMR spectrum (Figure II.4.2), showed the presence of five quaternary carbon resonances at δ 165.9 (due to ester carbonyl), δ 149.6, 148.3, 127.0 and 114.4 (due to four aromatic carbons), one vinylic methylene at δ 128.1, two aromatic methine carbons at δ 115.5 and 113.3, two methylenes at 131.3 and 66.0, two methoxy groups at 56.2 and 56.1 ppm concluded the confirmation of structure of ester **26g**.

With the above optimized reaction conditions for oxy-Michael addition (entry 3, Table II.1), the subsequent Heck coupling step was attempted. Thus, one-pot oxy-Michael addition at 50 °C for 48 h and subsequent treatment with the palladium catalyst at 80 °C for 24 h, furnished the product **23g**, in moderate yield 53% (entry 4, Table II.1). Optimization was also explored for this one-pot process with other solvents and bases at varying temperatures. However, the reaction with different solvents such as THF, CH_3CN and DMF failed, and by-product **24g** was found to be dominant (entries 6 to 10, Table II.1). It was quite surprising to see the formation of **24g** from the intermediate oxy-Michael addition product **25g**. This can be explained via C-H activation, which led to a 7-membered palladacycle, which upon β-carbon cleavage would generate the cyclic palladium intermediate and resulted in aldehyde **24g**. Alternately, it might also trigger a backward reaction to yield the starting material **24g** via *retro*-oxy-Michael addition under the basic (Cs_2CO_3) and at hot temperature (80 °C), which, in the presence of the palladium catalyst unambiguously led to the formation of **24g**.[72] The formation of **24g** was further confirmed by the reaction of bromoester **25g** with the palladium catalyst under similar reaction conditions. This interesting reaction in backward direction was successful, particularly with polar solvents such as DMF and CH_3CN (Scheme II.11).



Scheme II.11

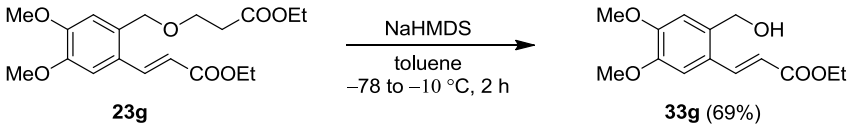
The formation of **24g** can be justified via base triggering *retro*-oxy-Michael addition on bromoester **25g** to set up an equilibration with the starting *ortho*-bromobenzyl alcohol **21g** (Scheme II.12). Alcohol **21g** reacts with the palladium catalyst and leads to the veratraldehyde **24g**.



Scheme II.12

In an alternative route, the presence of a base, seven-membered palladacycle **B**, which may have ultimately collapsed, could give the simple benzaldehyde **24g** via the palladacycle **C** (Scheme II.12).[72]

Of these two plausible mechanisms, the one with the formation of benzyl alcohol **21g** as an intermediate followed by palladium catalyzed transformation to **24g** would be justified based on the reaction of a strong base with the diester **23g** in dry THF at low temperature −78 °C, on treatment with NaHMDS in toluene followed by stirring at −10 °C for 2 h, yielding the alcohol enoate **33g** (Scheme II.13).



23g **33g** (69%)

Scheme II.13

The formation and structural pattern of the alcoholic ester **33g** was evident from the spectral data of **33g**. The presence of a broad absorption band at 3485 cm^{-1} due to O–H group and one strong absorption band at 1703 cm^{-1} for the ester carbonyl stretching in the IR spectrum indicated the formation of the alcoholic ester **33g**. In the ^{1}H-NMR spectrum (Figure II.5.1), presence of two doublets at δ 7.95 and 6.29 (for two aromatic protons), five singlets at δ 7.07, 6.95 (due to two aromatic protons), δ 4.78 (for two protons of benzylic methylene group), δ 3.90 and 3.89 (due to six protons of two methoxy groups), a quartet at δ 4.24 (due to two protons of O-methylene group), one broad singlet at δ 1.89 (because of hydroxyl group) and a triplet at 1.32 ppm (for three protons of a methyl group) explained the structure of the alcoholic ester **33g**. Additionally, the 13 lines of ^{13}C-NMR spectrum (Figure II.5.2) showed the presence of five quaternary carbon resonances at δ 167.2 (due to ester carbonyl) and δ 150.8, 148.6, 133.5 and 125.1 (due to four aromatic carbons), two olefinic methines at δ 140.8 and 108.9, two aromatic methine carbons at δ 117.6 and 115.5, two aliphatic methylenes at δ 62.3 and 60.5 and of the three methyl groups, two at 55.9 (due to two methoxy groups) and one at 14.2 ppm, which confirmed the structure of ester **33g**.

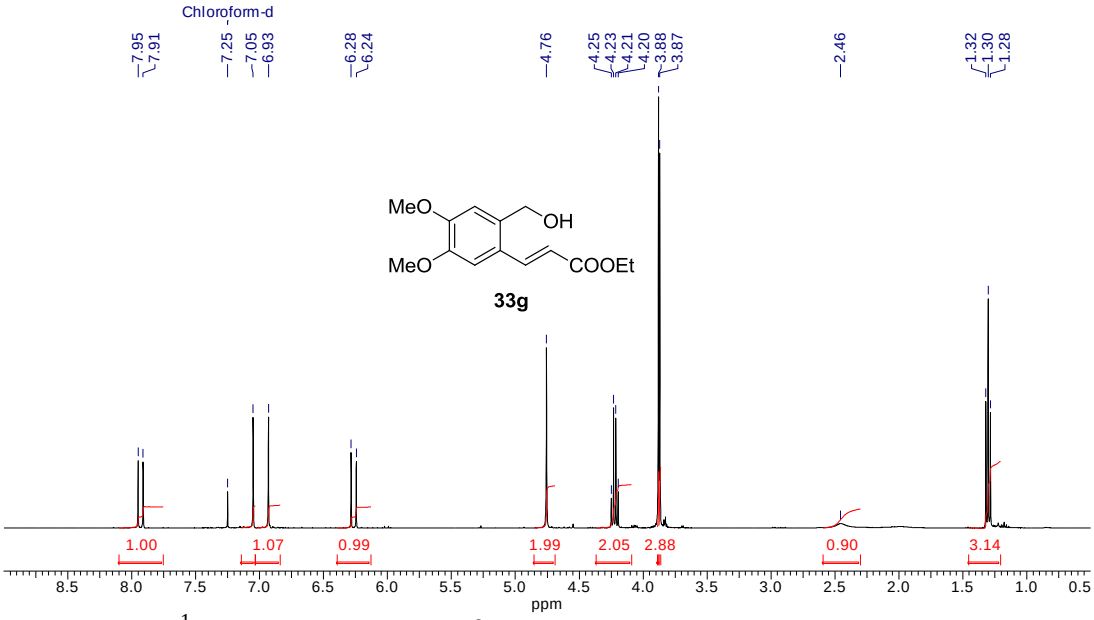


Figure II.5.1: ^{1}H NMR (400 MHz) of compound **33g** in $CDCl_3$

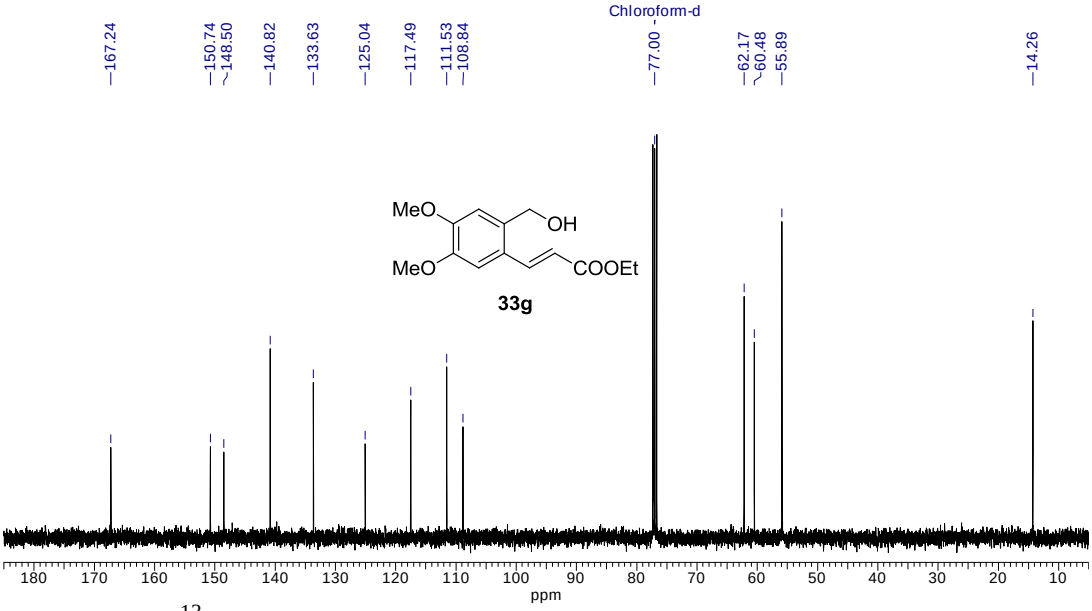
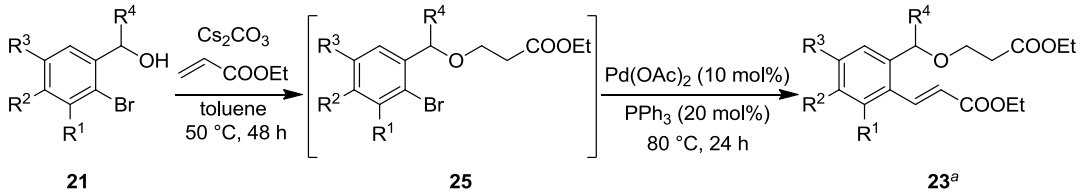


Figure II.5.2: ^{13}C NMR (100 MHz) of compound **33g** in $CDCl_3$

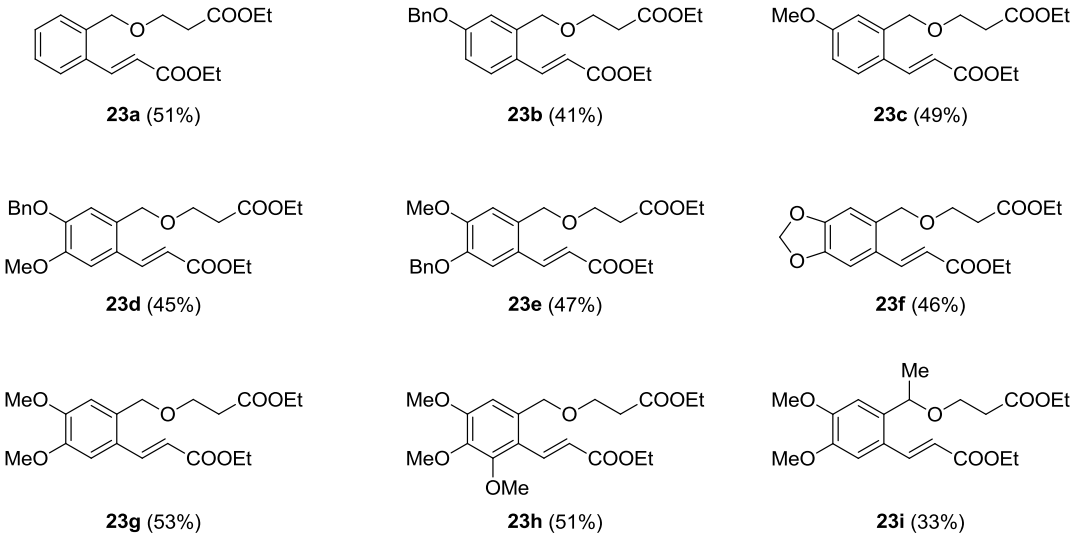
Even though, of all the screening conditions listed in Table II.1, product **23g** was obtained in moderate yield (entry 4, Table II.1), it turned out to be the best optimized condition. Hence, these reaction conditions were employed for other

benzylic alcohols **21** and the results summarized in Table II.2. As anticipated, the products **23a**–**23h** were generated in comparable to moderate yields. However, the reaction with secondary alcohol **21o** furnished product **23i** in inferior yield (33%). This might be due to the greater nucleophilicity of the secondary hydroxyl group that may prefer the formation of an undesired condensed by-product **26i** (Table II.2).

Table II.2: Scope of the sequential one-pot reaction on various benzyl alcohols **21** with ethylacrylate.



21 **25** **23**[a]



23a (51%) **23b** (41%) **23c** (49%)

23d (45%) **23e** (47%) **23f** (46%)

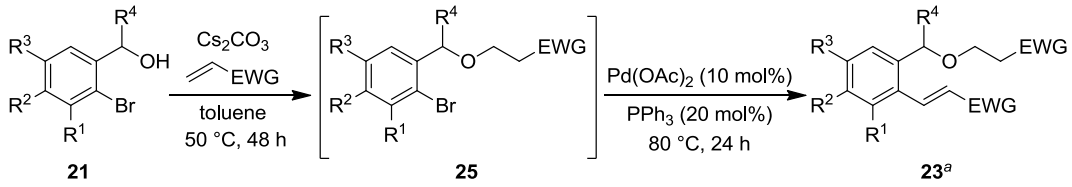
23g (53%) **23h** (51%) **23i** (33%)

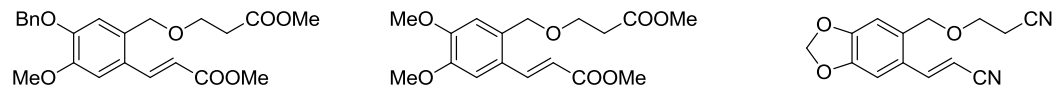
[a] Isolated yields of pure products.

After obtaining the ethyl cinnamate derivatives **23a**–**23i**, to check the scope and generality of the method, we also attempted this sequential one-pot reaction with other Michael acceptors such as methyl acrylate and acrylonitrile. Similar results were observed even with methyl acrylate, and the products **23w** and **23x** were obtained in inferior yields (Table II.3). This can be ascribed to the sterically less hindered nature of methoxy group of the acrylate that may further facilitate the increased formation of the undesired by-product **26**. Also, the same sort of reactivity

was noticed in case of acrylonitrile as Michael acceptor by the further dropping of yield (25%) of the corresponding product **23y** (Table II.3). This low yield is could be due to the interference of the cyano group with the hydroxyl functionality.

Table II.3: Scope of the sequential one-pot reaction on various benzyl alcohols **21** with methylacrylate and acrylonitrile.





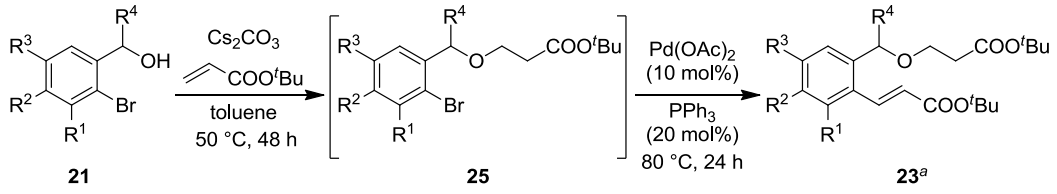
23w (26%) **23x** (32%) **23y** (32%)

[a] Isolated yields of pure products.

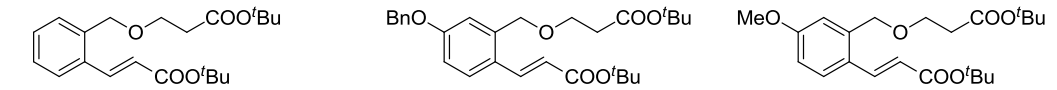
After obtaining cinnamate derivatives **23a**–**23i**, **23w**, **23x** and **23y**, in moderate yields, we envisioned that by inhibiting the cross-condensation of the Michael acceptor with the hydroxyl group of **21**, it would be possible to restrict the formation of undesired by-product **26** (Table II.1). The formation of this by-product **26** could be due to the less sterically hindered ethoxy (or methoxy) group of Michael acceptor that allowed the formation of cross-condensed undesired ester **26**. Hence, it was assumed that the use of a bulky alkoxy acrylate such as *tert*-butyl acrylate, might preclude the formation of by-product **26**, and consequently the yield of product **23** would improve. Therefore, *ortho*-bromobenzyl alcohols **21a**–**21o** possessing electron-deficient as well electron-rich aromatic substituents, were treated with *tert*-butyl acrylate as Michael acceptor, using optimized conditions. Gratifyingly, as expected, a dramatic improvement in yield was observed and the products **23j**–**23v** were isolated, in good to excellent yields (Table II.4).

After achieving the cinnamate derivatives 23a–23y, to further check the scope and applicability of the present method, we envisioned a divergent application

Table II.4: Scope of the sequential one-pot reaction on various benzyl alcohols **21** with *tert*-butyl acrylate.



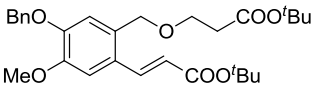
21 **25** **23**[a]



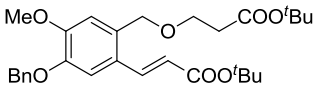
23j (71%)

23k (84 %)

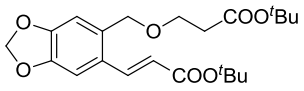
23l (78%)



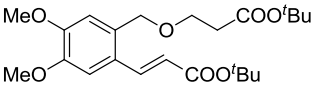
23m (71 %)



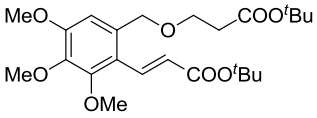
23n (90%)



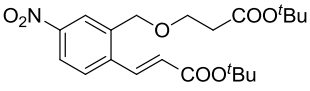
23o (87%)



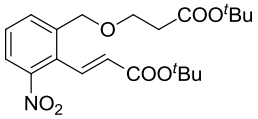
23p (72 %)



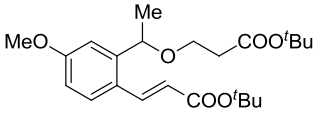
23q (79%)



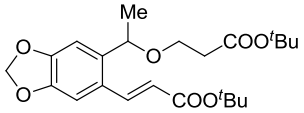
23r (74%)



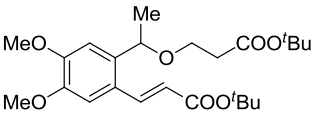
23s (75%)



23t (74%)



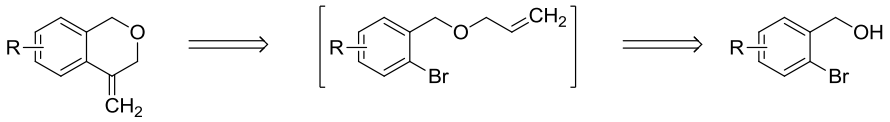
23u (85%)



23v (67%)

[a] Isolated yields of pure products.

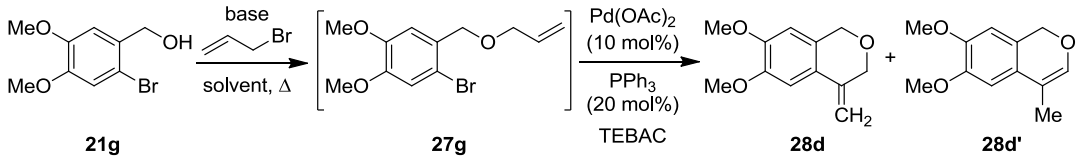
of this one-pot process for O-allylation and subsequent intramolecular Heck coupling to afford 4-methylene-3,4-dihydro-1*H*-isochromenes **28** directly from 2-bromobenzyl alcohols **21** (Scheme II.14). Palladium-catalyzed intramolecular Heck reaction is an efficient tool to achieve heterocyclic structures.[73] This method has also been successfully employed for the synthesis of many natural products.[74] Usually, these kind of systems were achieved only by a step-wise *o*-allylation and intramolecular Heck cyclization strategy.[75]



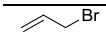
Scheme II.14

Thus, synthetic trials were initiated on 2-bromobenzyl alcohol **21g** using the above optimized conditions (entry 4, Table II.1). However, there was not much progress and most of the starting material of **21g** was recovered (entries 1 to 4, Table II.5). Hence, we thought that the use of a stronger base would be suitable to promote the O-allylation. Therefore, alcohol **21** was treated with allyl bromide in the presence of a base NaH, in DMF. The formation of a less polar spot on TLC was indicative of the formation of O-allylation product **27g** and hence, it was subjected to in-situ Heck cyclization by loading the palladium catalyst at 80 °C. It is worth mentioning after 12 h, the reaction led to the isolation of a mixture of three compounds as a regioisomeric mixture of required cyclic ethers (**28** and **28′**) and the intermediate O-allyl ether **27g**. However, increasing the reaction time of the Heck cyclization step to 24 h, furnished a regioisomeric mixture of cyclic ethers **28** and **28′** in 85% yield. Of the two cyclic ethers, *exo*-cyclic ether **28d** was formed as a major product, whereas the *endo*-isomer **28d′** was the minor one with respect to the double bond (entry 6, Table II.5). Interestingly, both the isomers were separated by column chromatography and fully characterized. It is noteworthy that the use of quaternary ammonium salts was found to be crucial for Heck cyclization [in the present case, we used triethylbenzylammonium chloride (TEBAC)].[23e] Since, it was established that the prolonged reaction time in the presence of palladium catalyst would favour the isomerization of the exo-olefin to the thermodynamically more stable *endo*-olefin, we decided to decrease the reaction time of Heck cyclization to control the formation of *exo*-olefin. However, the conversion of intermediate **27g** to the final products (**28** and **28′**) was incomplete, even after 12 h (entry 5, Table II.5).

Table II.5: Optimization of reaction conditions for sequential one-pot allylation and Heck reaction.



21g **27g** **28d** **28d'**

Entry	*o*-allylation						Heck cyclization			
	 [equiv]	Base [equiv]	Solvent	Temp [°C]	Time [h]	Yield **7** [%]	Temp [°C]	Time [h]	Yield [%] **28d**	**28d′**
1[a]	3	Cs_2CO_3 [2]	toluene	50	24	13	-	-	-	-
2[a]	3	Cs_2CO_3 [2]	DMF	80	48	20	-	-	-	-
3[a]	3	Cs_2CO_3 [2]	DMF	100	24	16	-	-	-	-
4	5	Cs_2CO_3 [2]	Neat	80	48	-	-	-	-	-
5	2	NaH [4]	DMF	RT	1	100[b]	80	12	-[c]	-[c]
6	2	NaH [4]	DMF	RT	1	100[b]	80	24	61[d]	24[d]

[a] Isolated yields of chromatographically pure product (**27g**). [b] 100% conversion based TLC and subjected to subsequent Heck cyclization. [c] Products (**28d** and **28d′**) formation was observed along with the recovery of intermediate (**27g**). [d] Isolated yields of chromatographically pure products (**28d** and **28d′**).

The structure and formation of isochromene **28d** was illustrated from its spectral data. The absence of a broad absorption band due to O–H group and presence of an absorption band at 1604 cm^{-1} for the stretching of olefin in the IR spectrum predicted the formation of isochromene **28d**. In the ^{1}H-NMR spectrum (Figure II.6.1), the absence of O–H proton resonance, the existence of eight singlets at δ 7.12, 6.48 (due to two aromatic protons), 5.42, 4.90 (because of two protons of olefinic methylene group), 4.73 (of benzylic methylene protons), 4.40 (for two

allylic methylene protons), 3.86 and 3.84 ppm (due to six protons of two O-methyl groups) elucidated the structure of isochromene **28d**. Additionally, in 12 lines ^{13}C-NMR spectrum (Figure II.6.2), the presence of five quaternary carbon resonances at δ 149.6, 148.2, 138.1, 127.6 and 123.5 (due to four aromatic carbons and one olefinic carbon), two aromatic methine carbons at δ 106.9 and 106.0, three methylenes at 104.6 (for olefin methylene), 70.8 (benzylic methylene group) and 68.7 (due to allylic methylene), two methyls at 56.0 and 55.9 ppm concluded the structure of isochromene **28d**.

Similarly, the structure of the ester **28d′** was obvious from the spectral data. The absence of O–H group broad absorption band and the existence of olefinic absorption band at 1637 cm^{-1} in the IR spectrum indicated the formation of isochromene **28d′**. In the ^{1}H-NMR spectrum (Figure II.7.1), the absence of O–H proton resonance, the presence of five singlets at δ 6.58, 6.51 (due to two aromatic protons), 4.85 (because of two protons of benzylic methylene group), 3.82 and 3.79 (due to six protons of two methoxy groups), one olefinic methine quartet at δ 6.33 and one doublet at δ 1.83 ppm due to three protons of the methyl group, established the structure of isochromene **28d′**. Furthermore, in 11 lines ^{13}C-NMR spectrum (Figure II.7.2), the presence of five quaternary carbon resonances at δ 148.8, 147.8, 121.0, 111.1 (due to four aromatic carbons) and 125.6 (for olefinic methine), respectively, one vinylic methine at δ 140.7, two aromatic methines at δ 108.0 and 104.9 one methylenes at 67.9, two methoxy groups at 56.1 and one methyl at 13.2 ppm confirmed the structure of isochromene **28d′**.

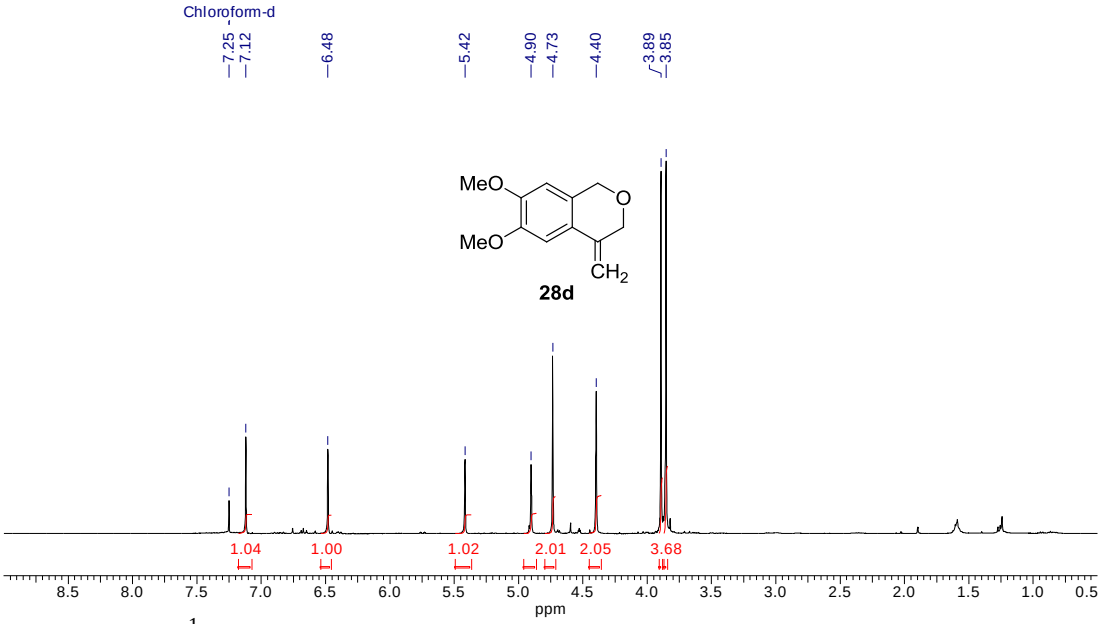


Figure II.6.1: ^{1}H NMR (400 MHz) of compound **28d** in $CDCl_3$

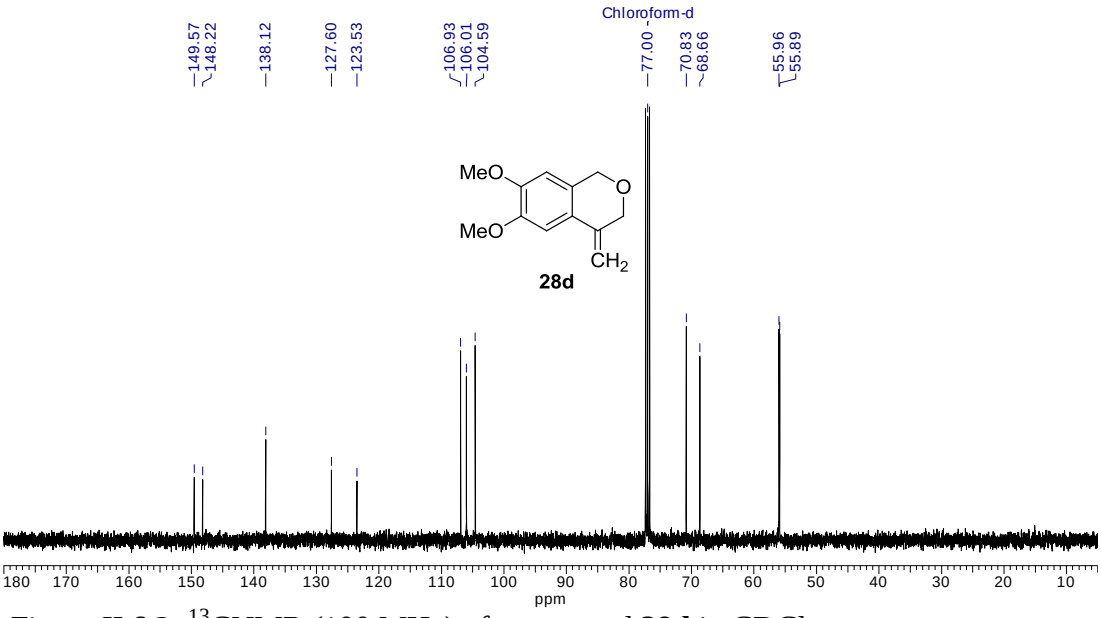


Figure II.6.2: ^{13}CNMR (100 MHz) of compound **28d** in $CDCl_3$

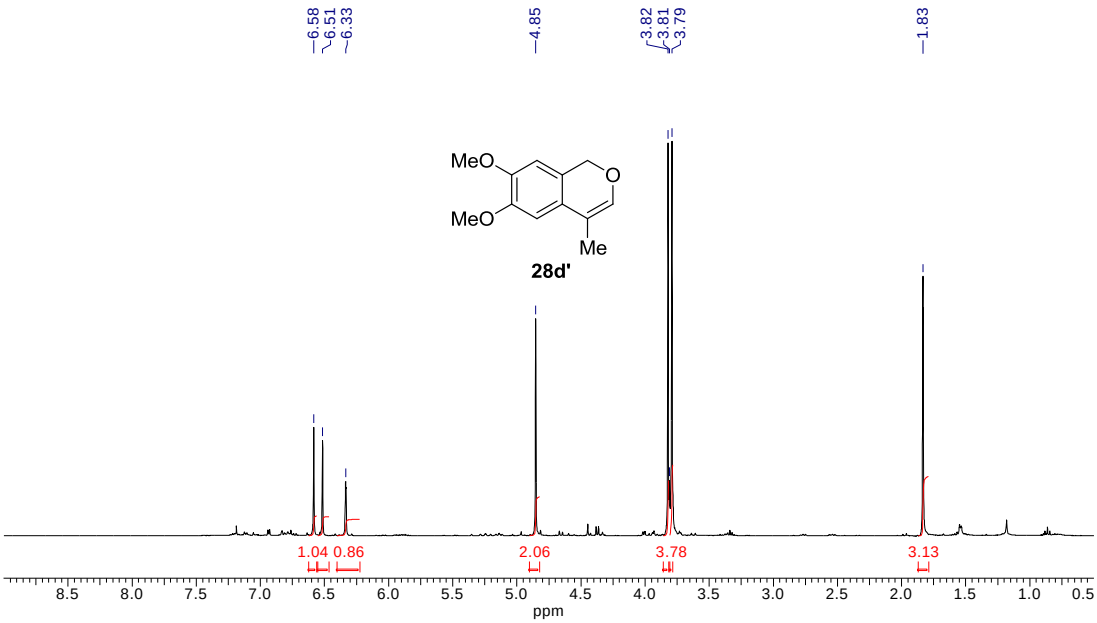


Figure II.7.1: ^{1}H NMR (400 MHz) of compound **28d′** in $CDCl_3$

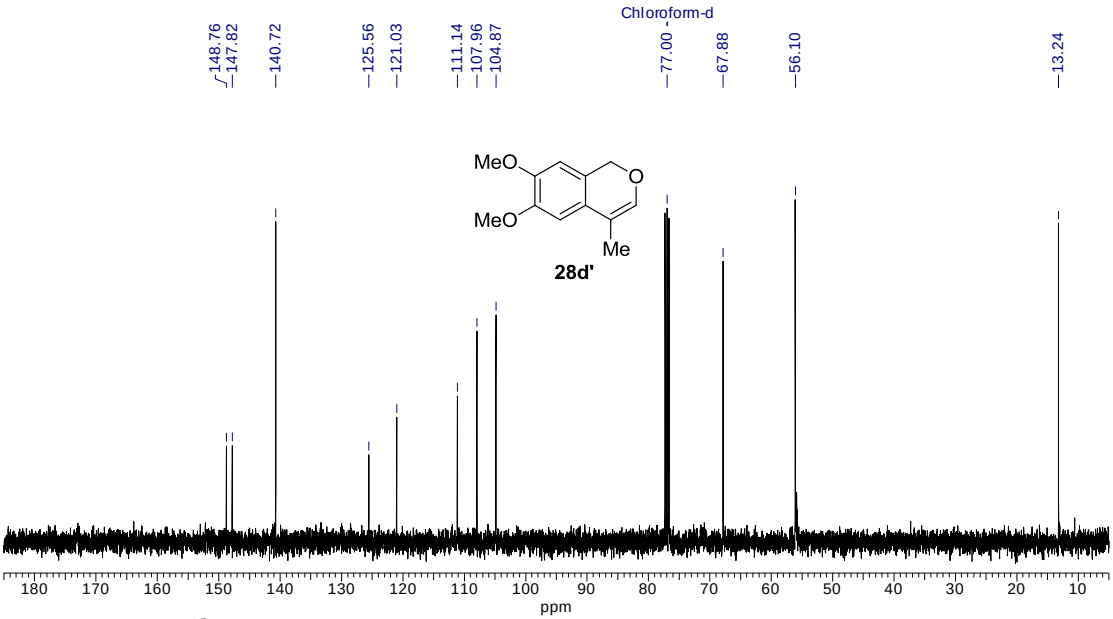
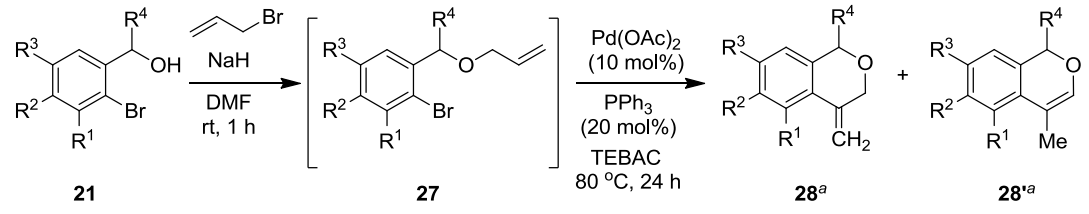


Figure II.7.2: ^{13}CNMR (100 MHz) of compound **28d′** in $CDCl_3$

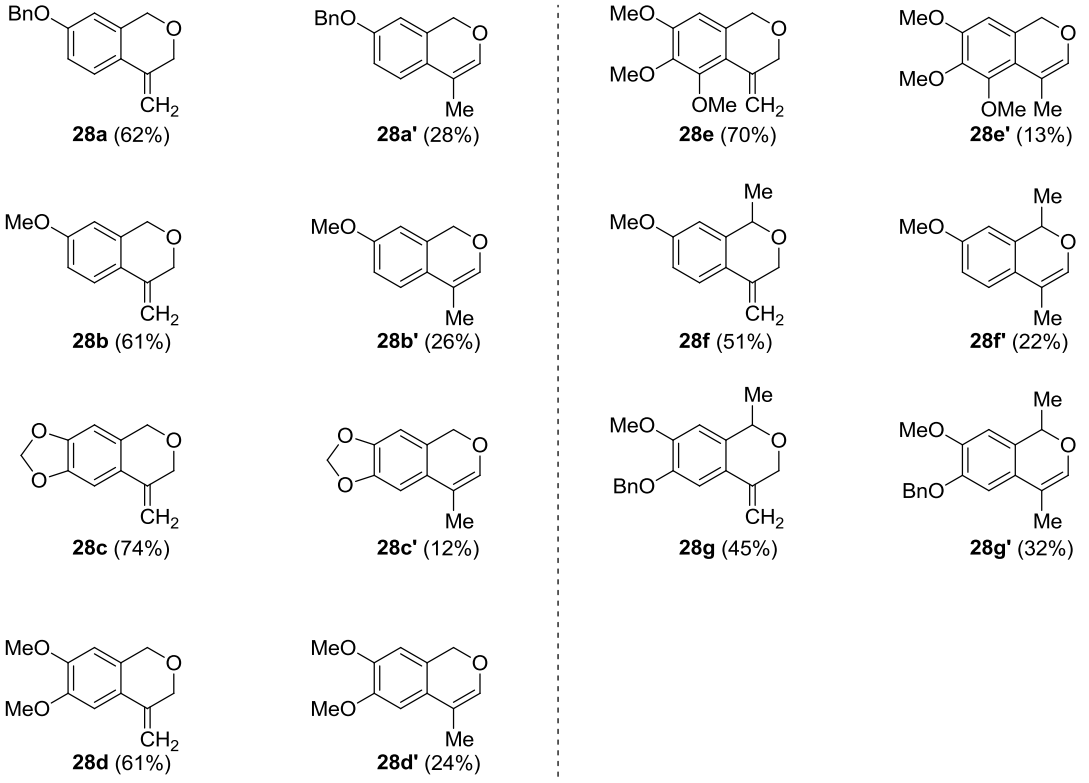
In order to check the generality and feasibility of the method, optimized reaction conditions were employed on various systems possessing the simple to electron-rich functionalities on the aromatic rings. The results were quite

satisfactory and furnished the corresponding isomeric products (**28a**–**28g** and **28a′**–**28g′**) in very good yield (Table II.6).

Table II.6: Scope of the sequential one-pot O-allylation and Heck reaction on various benzyl alcohols **21**.



21 **27** **28**[a] **28'**[a]



[a] Isolated yields of pure products.

II.2.2 Synthesis of 2-Benzoxepinones:

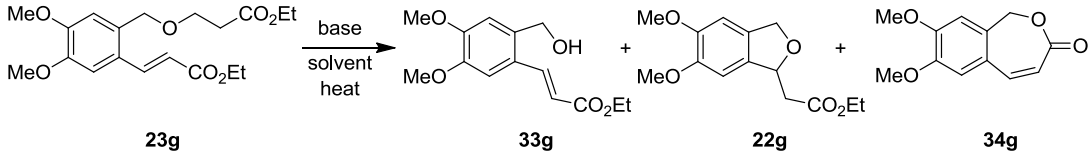
After successfully obtaining diesters **23** and isochromens **28** and **28'**, we turned our attention to extend this strategy for the concise synthesis of cyclic systems. Particularly, the retro-Michael addition of ester **23g** to alcohol **33g** (Scheme II.12) inspired us to investigate different base promoted cyclizations,

through the retro-Michael addition followed by a possible intramolecular oxy-Michael addition of diesters **23**, for the formation of isobenzofuran systems.[76] Since the alcohol enoate **33g** was the exclusive product of retro-Michael addition of **23g**, in the presence of strong base NaHMDS at the low temperature range (entry 1, Table II.7; Scheme II.13), the diester **23g** was subjected to the formation of initially aimed isobenzofuran **22g** through an intramolecular oxy-Michael addition, in the presence of the same strong base (NaHMDS) but at 50 °C. However, the reaction under these conditions was found to be unclear and did not lead to the isolation of either the starting material **23g** or any significant product (entry 2, Table II.7). Then the diester **23g** was subjected to the same type of degradation under established conditions of the diester **23g** formation without the palladium catalyst, with base Cs_2CO_3 at 80 °C in toluene in order to ensure the stability of the diester **23g**. As expected, the reaction showed no progress under these conditions and confirmed the inertness of esters (entry 3, Table II.7). We anticipated that the rise in temperature might activate the diester **23g** towards degradation (*retro*-oxy-Michael addition) followed by intramolecular cyclization. As expected, at 120 °C after 24 h, in toluene, the reaction yielded the isobenzofuran **22g**, albeit in poor yield along with an unexpected seven-membered lactenone **33g** (entry 4, Table II.7). As the retro-Michel addition was favoured in polar solvents, the solvent was changed from toluene to DMF and subjected the reaction at both 80 °C and 120 °C. Interestingly, switching to polar solvent proved to be beneficial and furnished the lactenone product **34g** exclusively, in good yield (entries 5 and 6, Table II.7). Moreover, the reaction in DMF at 120 °C was completed within 12 h, whereas, at 80 °C, it took up to 24 h.

The structure and formation of the isobenzofuran **22g** was apparent from the spectral data of **22g**. The presence of strong absorption band at 1728 cm^{-1} for the ester carbonyl in the IR spectrum predicted the formation of the isobenzofuran **22g**. In the ^{1}H-NMR spectrum (Figure II.8.1), the absence of O–H proton resonance, the presence of four singlets at δ 6.72, 6.70 (due to two aromatic protons), 3.86 and 3.84 ppm (due to six protons of two methoxy groups), a multiplet in the region δ 5.65–

5.55 due to methine of furan ring, three doublet of doublets at 5.08, 5.00 (due to two benzylic methylene protons) and 2.72 (due to two protons of methylene moiety), one quartet at δ 4.18 (for two protons of O-methylene) and a triplet at 1.25 ppm for the methyl clarified the structure of the isobenzofuran **22g**. Moreover, in 14 lines of ^{13}C-NMR spectrum (Figure II.8.2), five quaternary carbon resonances at δ 170.9 (due to ester carbonyl), 149.3, 148.9, 132.2 and 130.6 (due to four aromatic carbons), three methine carbons at δ 104.2, 103.9 (for two aromatic carbons) and 80.6 (of aliphatic methane), three methylenes at 72.8 (benzylic methylene group), 60.6 and 41.8 (for two aliphatic methylenes), a methyl at 14.2 ppm confirmed the structure of isobenzofuran **22g**.

Table II.7: Screening reaction conditions for the synthesis of **34g** starting from **23g**.



Entry	Base [2 equiv]	Solvent [2 mL]	Temp [°C]	Time [h]	Yield **33g** [%][a]	Yield **22g** [%][a]	Yield **34g** [%][a]
1	NaHMDS	toluene	–78 to –10	12	69	0	0
2	NaHMDS	toluene	50	12	0	0	0
3	Cs_2CO_3	toluene	80	48	0	0	0
4	Cs_2CO_3	toluene	120	24	0	16	23
5	**Cs_2CO_3**	**DMF**	**120**	**12**	**0**	**0**	**77**
6	Cs_2CO_3	DMF	80	24	0	0	78

[a] Yields of chromatographically isolated pure products.

In the same way the structure of lactenone **34g** was obvious from the spectral data of **34g**. The existence of a strong absorption band at 1693 cm^{-1} for the

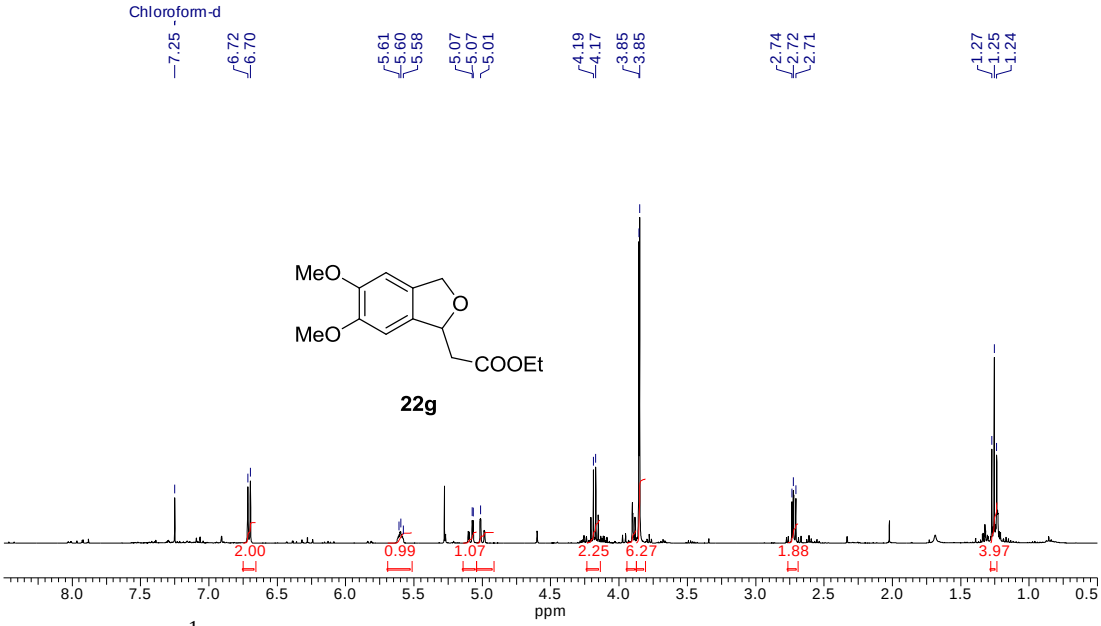


Figure II.8.1: ^{1}H NMR (400 MHz) spectrum of **22g** in $CDCl_3$

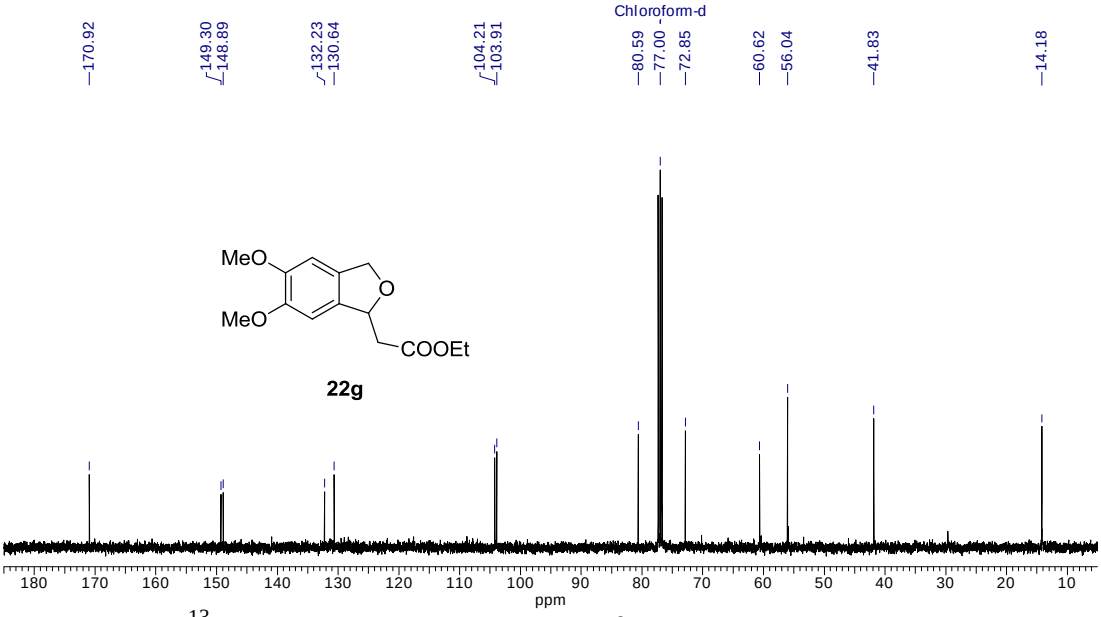


Figure II.8.2: ^{13}C NMR (100 MHz) spectrum of **22g** in $CDCl_3$

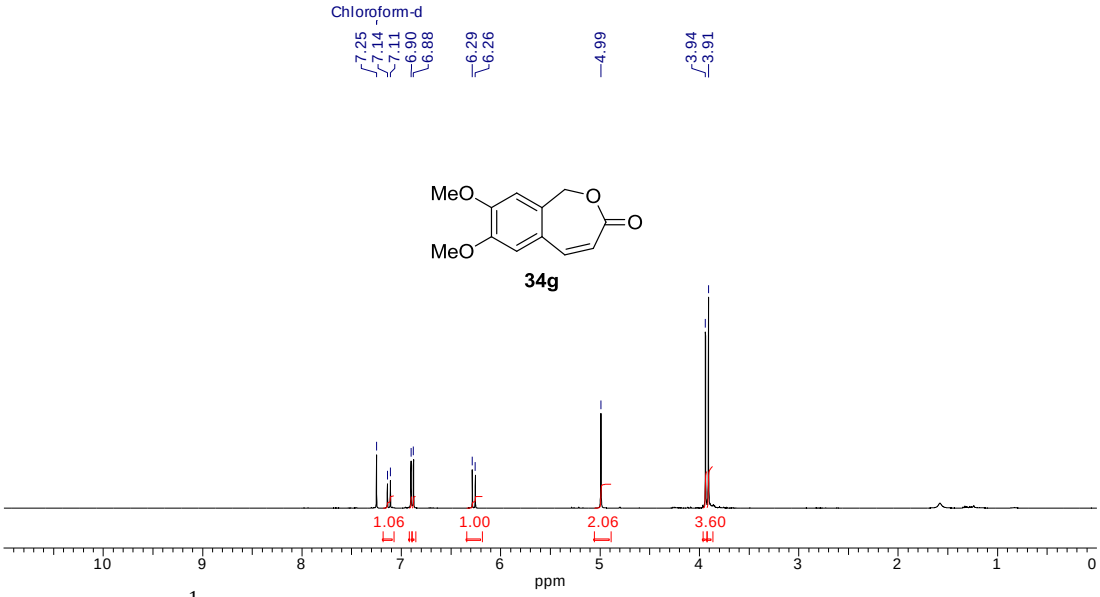


Figure II.9.1: ^{1}H NMR (400 MHz) spectrum of **34g** in $CDCl_3$

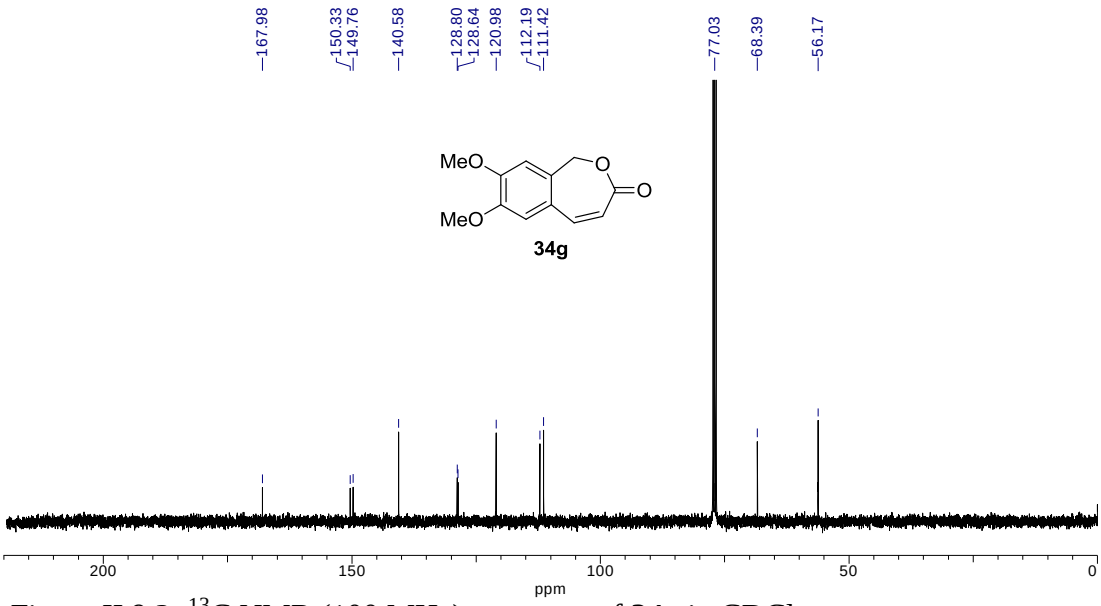


Figure II.9.2: ^{13}C NMR (100 MHz) spectrum of **34g** in $CDCl_3$

carbonyl of ester and olefinic absorption band at 1603 cm^{-1} in the IR spectrum indicated the formation of the lactenone **34g**. In the ^{1}H-NMR spectrum (Figure II.9.1), the presence of two doublets at δ 7.12 and 6.26 due to olefinic protons, five singlets at δ 6.90, 6.87 (due to two aromatic protons), 4.98 (because of two protons

of benzylic methylene group), 3.93 and 3.90 ppm (due to six protons methoxy groups) established the structure lactenone **34g**. Furthermore, in 12 lines ^{13}C-NMR spectrum (Figure II.9.2), presence of five quaternary carbon resonances at δ 168.0 (due to the ester cabonyl), 150.3, 149.7, 128.7 and 128.6 (due to four aromatic carbons), four methines at δ 140.6, 120.9 (for two olefinic methines), 112.1 and 111.3 (because of two aromatic methines), respectively. One methylene at 68.3, two methoxy groups at 56.2 and 56.1 ppm proved the structure of lactenone **34g**.

Quite interestingly, it was found in the literature that this lactenone **34** skeleton formed the core of a few natural products and biologically active compounds with this lactenone **34** skeleton. For example, these lactenones or 2-benzoxepin-3(1*H*)-ones **34** exist as the core structure in antibiotics xylarinol (A) **29** and xylarinol (B) **30**,[77] and as part of the structure in new tyrosine kinase (p56lck) inhibitor ulocladol **31**[78] and cytotoxic alterlactone **32**[79] (Figure II.10). Moreover, analogues of these 2-benzoxepin-3(1*H*)-ones **34** have been recognized to display good analgesic activities.[80]

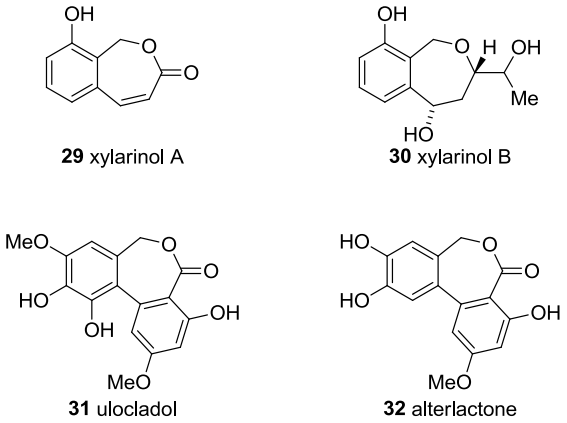
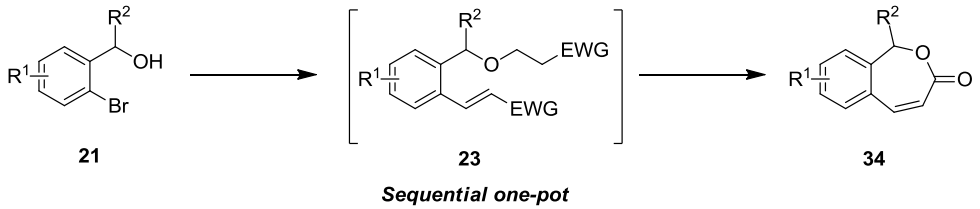


Figure II.10

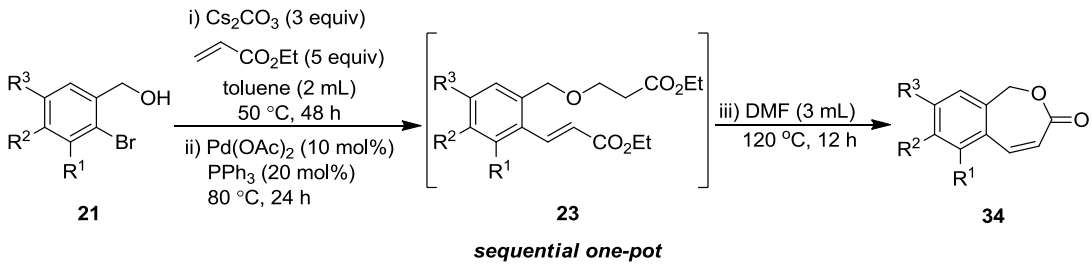
The interesting structure of lactenone **34g** present in naturally occurring compounds and the promising biological activities of their analogues made us synthesize more functionalized 2-bezoxepinones. After successfully obtaining lactenone **34g** by performing the reaction on an isolated diester **23g**, in order to make the method more efficient, we decided to perform the reaction in a domino

sequential one-pot manner by starting directly from *ortho*-bromobenzyl alcohols **21** (Scheme II.15).



Scheme II.15

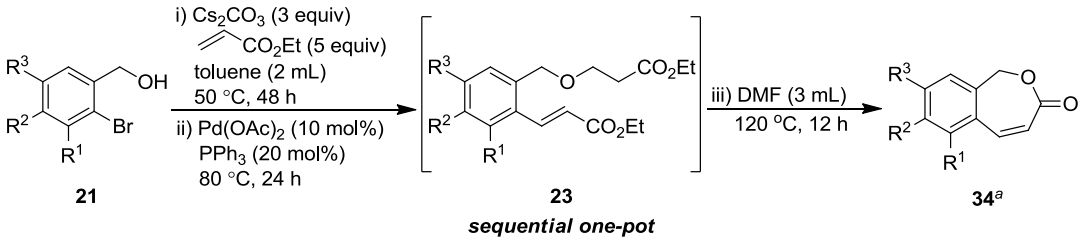
It is very evident that the established method yields the diesters **23** via sequential one-pot intermolecular oxy-Michael addition followed by an intermolecular Heck reaction of 2-bromobenzyl alcohols **21**. The present study was sketched to extend the so formed diesters **23** to lactenones **34** by in-situ intramolecular degradation (*retro*-oxy-Michael addition) and subsequent condensation promoted by base. However, there is a challenge that limits the use of a single solvent system to conduct all these reaction steps in a sequential one-pot method. For example, toluene was identified as the solvent suitable for oxy-Michael addition and succeeding Heck coupling, but not an appropriate solvent for the final retro-Michael addition and condensation; on the other hand, DMF was found to be an ideal solvent for the final cyclization to yield lactenone **34g** but not suitable for the formation of the diester **23g**. Hence, the choice of solvent was crucial and it was decided to implement toluene as the first solvent until the formation of the diester **23g** and then DMF as the second solvent system in order to promote the final cyclization from the diester **23g** to yield the lactenone **34g**. Since the formation of lactenone **34g** formation was at 120 °C in toluene (entry 4, Table II.7), the final cyclization was conducted at the same temperature after addition of DMF to the reaction mixture soon after the formation of diesters **23** (Scheme II.16).

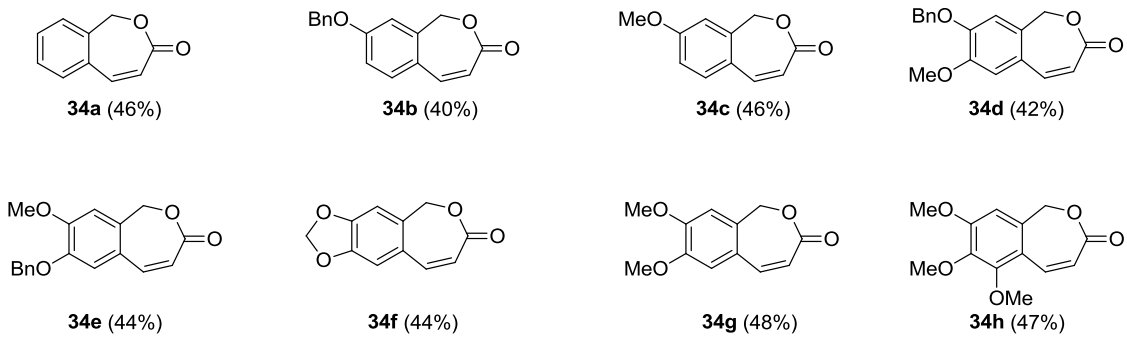


Scheme II.16

Based on the above knowledge, we proceeded as planned for the sequential one-pot synthesis of functionalized lactenones **34** by starting reaction between different benzyl alcohols **21** and ethyl acrylate. Agreeably, the reaction was quite successful and furnished cyclic lactenones **34a–34h** in moderate yields (Table II.8). Though moderate, the yields were still in an acceptable range, because it was the overall yield of the sequence after three individual reaction steps (i.e. every individual step approximately accounts for 75%), since this kind of systems were achieved in not less than three individual reactions.

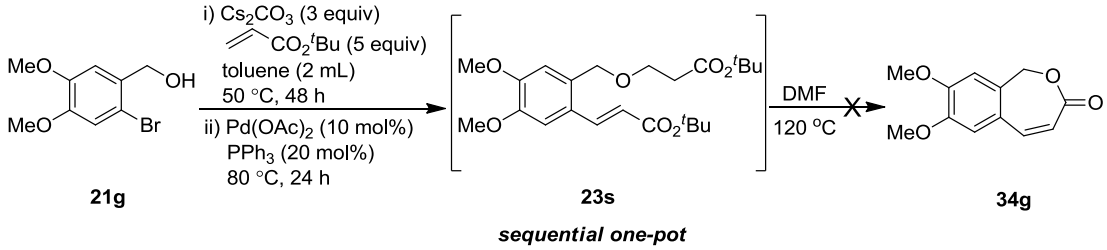
Table II.8: Scope of the sequential one-pot Michael addition, Heck reaction, degradation and condensation from various benzyl alcohols **21**.





[a] Yields of chromatographically isolated pure products.

After achieving 2-benzoxepinones **34a**–**34h** from ethyl diesters **23a**–**23h** we turned our interest towards the synthesis of lactenones **34** from *tert*-butyl diesters **23** and the esters of secondary alcohols **23**. Since it is well established that the sequential one-pot synthesis of diesters **23** is quite successful and yields excellent results with the bulkier *tert*-butyl acrylate as the Michael acceptor, we also expected the subsequent intramolecular cyclization in a sequential one-pot synthesis would be amenable to give the lactenones **34** in the manner similar to that used in case of ethyl acrylate. Hence, the 2-bromobezyl alcohol **21g** was subjected for direct sequential one-pot formation of lactenone **34g**, under optimized conditions by using *tert*-butyl acrylate as Michael acceptor. However, the sequential one-pot reaction between

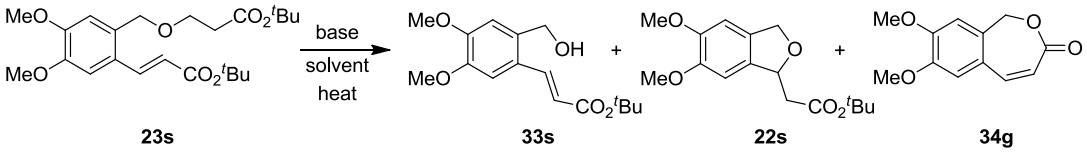


Scheme II.17

2-bromobenzyl alcohol **21g** and *tert*-butyl acrylate, under standard reaction conditions, was impeded after the formation of the diester **23s** (Scheme II.17).

On the other hand, the reaction with isolated diester **23s**, in the polar solvent, DMF, was also unable to produce the lactenone **34g** as an exclusive product; rather unexpectedly furnishing three products (entry 3, Table II.9). This might be due to the release of strong base CsO^tBu at the end of the lactenone **34g** formation, and might have reverted the 2-benzoxepinone **34g** to the acyclic alcohol enoate **33s** and the isobenzofuran **22s**. In another way, the bulky tertiary butyl group might have impeded final cyclization, after the initial cyclization (isobenzofuran ring formation) and induced ring opening through double bond isomerization. The reaction, when performed at higher temperature, also failed to produce any corresponding product (entry 7 and 8, Table II.9). The use of a much stronger base such as NaHMDS did

Table II.9: Screening of reaction conditions, for the synthesis of 2-benzoxepinone **34g** from the tertiary butyl diester **23s**.



23s **33s** **22s** **34g**

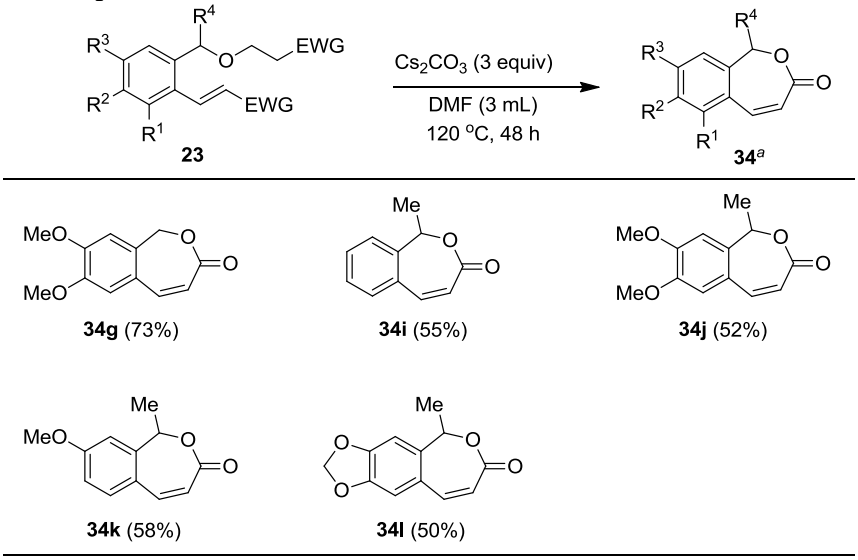
Entry	Base (equiv)	Solvent (mL)	Temp (°C)	Time (h)	Recovery of **23s** (%)	Yield **33s** (%)[a]	Yield **22s** (%)[a]	Yield **34g** (%)[a]
1	Cs_2CO_3 (2)	toluene (2)	80	48	93	0	0	0
2	Cs_2CO_3 (2)	toluene (2)	100	48	83	0	0	0
3	Cs_2CO_3 (3)	DMF (2)	80	24	-	9[b]	28	18[b]
4	Cs_2CO_3 (3)	CH_3CN (3)	80	24	-	0	20	16
5	Cs_2CO_3 (3)	DMF (2)	140	3	-	15[b]	23	40[b]
6	Cs_2CO_3 (1.5)	xylene (2)	130	48	30	0	24	10
7[c]	Cs_2CO_3 (3)	DMA (2)	160	12	-[d]	0	0	0
8	Cs_2CO_3 (3)	DMSO (2)	160	12	-[d]	0	0	0
9	NaHMDS (4)	toluene (2)	50	12	-[d]	0	0	0
10	**Cs_2CO_3 (3)**	**DMF (2)**	**120**	**48**	-	-	-	**73**

[a] Yields of chromatographically isolated pure products. [b] Yields of the products based on ^1H NMR. [c] Yields based on the recovery of the starting material (30%). [d] Reaction was not clean.

not yield anything fruitful (entry 9, Table II.9). However, the reaction under the usual conditions for a prolonged time in DMF facilitated the 2-benzoxepinone **34g** as an exclusive product in good yield (entry 10, Table II.9).

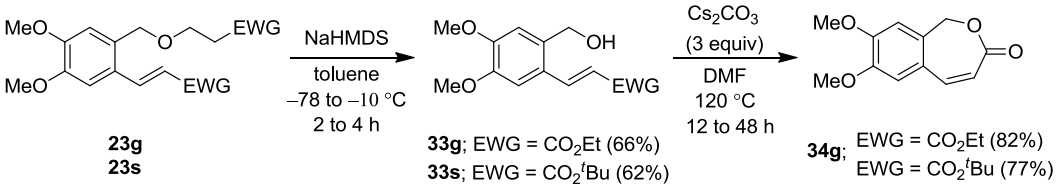
A similar problem was encountered with the diethyl/di-*tert*-butyl esters of secondary alcohols **23v**, **23z**, **23aa** and **2ab**. Hence, in these cases the separate base induced cyclization was applied to these diesters **23v**, **23z**, **23aa** and **2ab** (entry 6, Table II.3). As a result, the corresponding lactenones **34** were obtained in moderate to good yields (Table II.10).

Table II.10: Step-wise formation of lactenones **34**[a] from the diesters **23**.



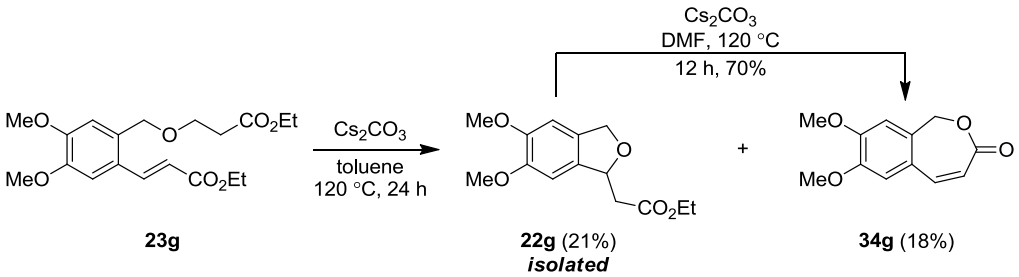
[a] Yields of chromatographically isolated pure products.

After successfully obtainig lactenones **34** starting from primary and secondary alcohols **21**, we were interested in studying the mechanistic aspects of the formation of lactenones **34**. In order to understand the reaction mechanism for their formation, we separately subjected the isolated alcohol esters **23g** and **23s** to condensation. According to our expectation, the process afforded the lactenone **34g** in good yield in both cases (Scheme II.18).



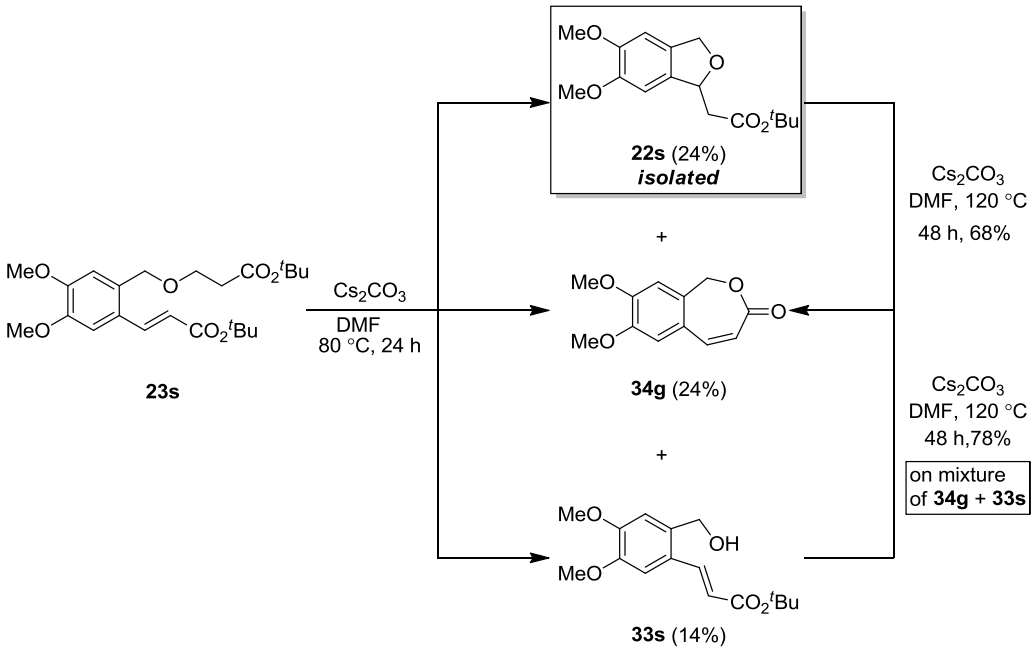
Scheme II.18

To further confirm the mechanism of the reaction, chromatographically isolated pure cyclic ether **22g**, which was prepared by the conditions of entry 4 in Table II.7, was also subjected to lactenone **34g** formation. In support of our hypothesis, the reaction furnished the expected lactenone **34g** (Scheme II.19).



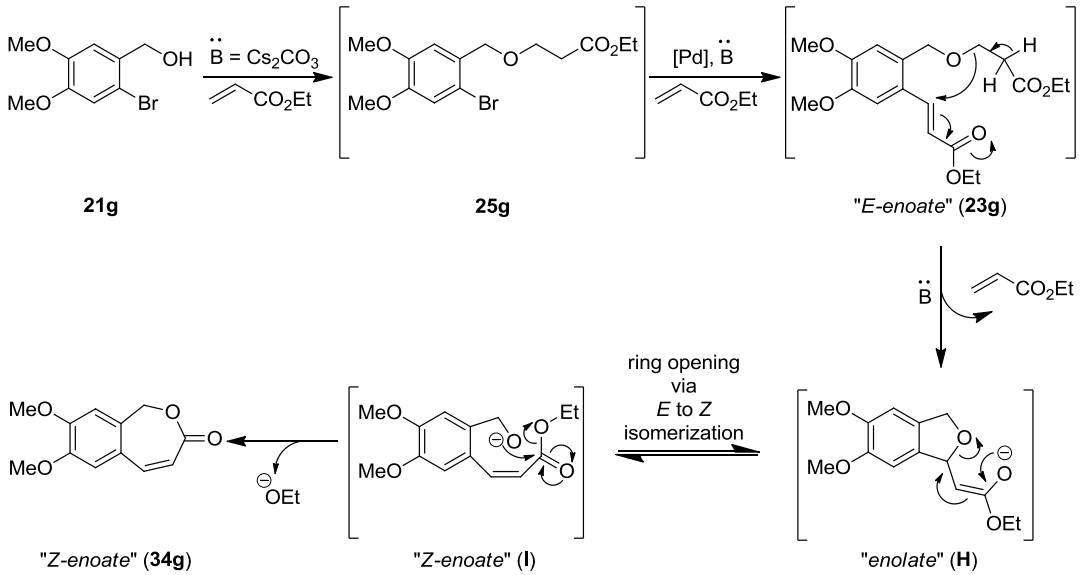
Scheme II.19

In addition, the products obtained by the degradation of diester **23s** on treatment with Cs_2CO_3 in DMF at 80 °C for 24 h (entry 3, Table II.9), i.e., isolated cyclic ether **22s** and the inseparable mixture of alcohol **33s** and lactenone **34g** were treated separately again with Cs_2CO_3 in DMF at 120 °C for 48 h (entry 10, Table II.9), to give the lactenone **34g** as expected (Scheme II.20).



Scheme II.20

Based on the above experimental studies, the possible reaction mechanism for the formation of **34g** from **23g** is as depicted in Scheme II.21. After the formation of oxy-Michael product **25g**, and subsequent Heck coupling gives **23g**. At this stage, the base may trigger *retro*-oxy-Michael addition (E_2-elimination) of **23g** and an intramolecular oxy-Michael addition of the resulted alkoxide would lead to cyclic enolate **H**. Now, the cycloreversion of the enolate **H** intermediate can set up an equilibration with its acyclic alkoxide **I** through possible E- to Z-isomerization of the cinnamate double bond. Finally, intramolecular condensation of the intermediate product **I** produces the lactenone **34g**.



Scheme II.21

In addition to NMR and other spectroscopic studies for structural elucidation, the structure of lactenone **34** was further unambiguously confirmed by single-crystal X-ray diffraction analysis of **34c** (Figure II.11).

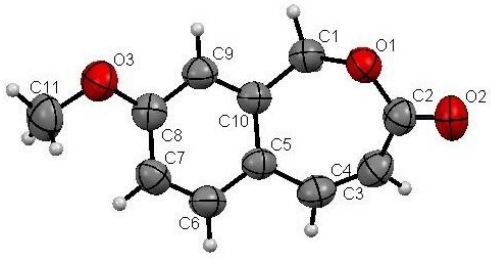


Figure II.11

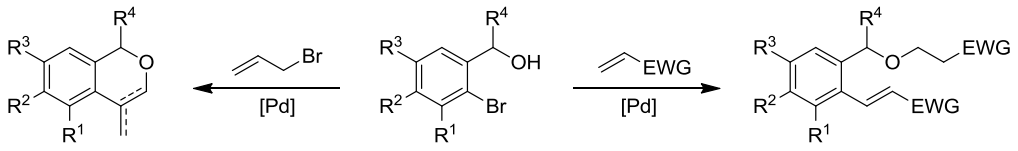
Figure II.11: X-ray crystal structure of **34c**. Thermal ellipsoids are drawn at 50% probability level.

II.3. CONCLUSIONS:

To conclude, an efficient domino sequential one-pot C–O and C–C bond formation via an intermolecular base mediated oxy-Michael addition/O-allylation

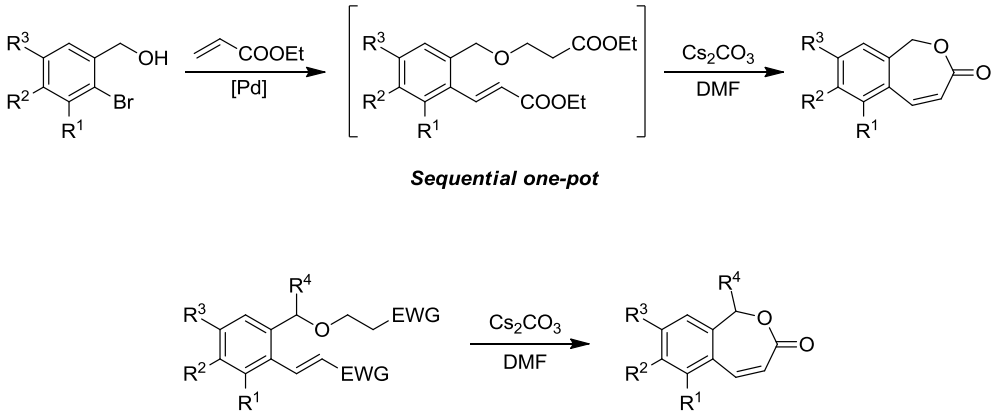
and subsequent inter/intra-molecular Heck reaction for the synthesis of functionalized cinnamates from simple 2-bromobenzyl alcohols was developed. Notably, for the preparation of cinnamate diesters, sterically hindered *tert*-butyl acrylate was identified as the ideal Michael acceptor. On the other hand, the reaction with less sterically hindered ethyl/methyl acrylates or acrylonitrile gave the product in moderate yield, which can be justified due to their less steric nature, allowing them to participate in the condensation as a competing reaction. This method was also applied to the efficient synthesis of isochromenes via sequential O-allylation and intramolecular Heck coupling. Furthermore, this method was successfully applied to the synthesis of functionalized 2-benzoxepin-3(1*H*)-ones in a novel domino reaction sequence, via an intermolecular oxy-Michael addition, intermolecular Heck coupling and intramolecular degradation (*retro*-oxy-Michael addition) followed by condensation. Quite interestingly, the 2-benzoxepin-3(1*H*)-ones are present as the major structural core of naturally occurring as well as analogous compounds, exhibiting interesting biological properties. Notably, a remarkable solvent effect was observed in-order to promote the final intramolecular degradation followed by condensation, for the synthesis of 2-benzoxepin-3(1*H*)-ones. The initial two steps involved a straight forward construction of C–O and C–C bonds for formation of the diesters, whereas the final cyclization involved a novel mechanistic path, a base promoted intramolecular degradation, double bond isomerization and condensation.

Synthesis of cinnamtes and isochromenes



Sequential one-pot

Synthesis of 2-benzoxepinones



II.4 EXPERIMENTAL SECTION:

General:

IR spectra were recorded on a Bruker Tensor 37 (FTIR) spectrophotometer. ^{1}H-NMR spectra were recorded on Bruker Avance 400 (400 MHz) spectrometer at 295 K in $CDCl_3$; chemical shifts (δ in ppm) and coupling constants (J in Hz) are reported in standard fashion with reference to either internal standard tetramethylsilane (TMS) (δ_H = 0.00 ppm) or $CHCl_3$ (δ_H = 7.25 ppm). ^{13}C-NMR spectra were recorded on Bruker Avance 400 (100 MHz) spectrometer at room temperature in $CDCl_3$; chemical shifts (δ in ppm) are reported relative to $CHCl_3$ [δ_C = 77.00 ppm (central line of triplet)]. In the ^{13}C-NMR, the nature of carbons (C, CH, CH_2 and CH_3) was determined by recording the DEPT-135 spectra, and is given in parentheses and noted as s = singlet (for C), d = doublet (for CH), t = triplet (for CH_2) and q = quartet (for CH_3). In the ^{1}H-NMR, the following abbreviations were used throughout: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, m = multiplet and br. s = broad singlet. The assignment of signals was confirmed by ^{1}H, ^{13}C CPD (Carbon Proton Decoupling) and DEPT spectra. High-resolution mass spectra (HR-MS) were recorded on an Agilent 6538 UHD Q-TOF using multimode source. All small scale dry reactions were carried out using Schlenk tube technique. Reactions were monitored by TLC on silica gel using a mixture of petroleum ether and ethyl acetate as eluents. Reactions were generally run under an argon or nitrogen

atmosphere. Solvents such as petroleum ether, ethyl acetate and dichloromethane were distilled prior use. petroleum ether with a boiling range of 60 to 80 °C was used. Diethyl ether and toluene were dried over benzophenone/sodium. DMF was dried over calcium hydride. 2-Bromobenzaldehyde and other aromatic aldehydes were purchased from local commercial sources and used as received. Acme's silica gel (60–120 mesh) was used for column chromatography (approximately 20 g per one gram of crude material).

II.4.1 SYNTHESIS OF DIESTERS AND ISOCHROMENES:

General Procedure for the Preparation of Alcohols (GP-1):

To an ice cold, magnetically stirred solution of a 2-bromobenzaldehyde **35** (500 mg, 1.56–2.70 mmol) in methanol (15–20 mL), was added sodium borohydride (2.73–4.05 mmol). Then the reaction mixture was allowed to attain room temperature and stirred for 1 h. Solvent was removed under reduced pressure, treated with aqueous NH_4Cl solution and extracted with ethyl acetate (3 × 15 mL). The organic layers were washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the filtrate under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate) furnished the alcohol **21** (77–98%).

General Procedure for Intermolecular Oxy-Michael Addition followed by an Intermolecular Heck reaction (GP-2):

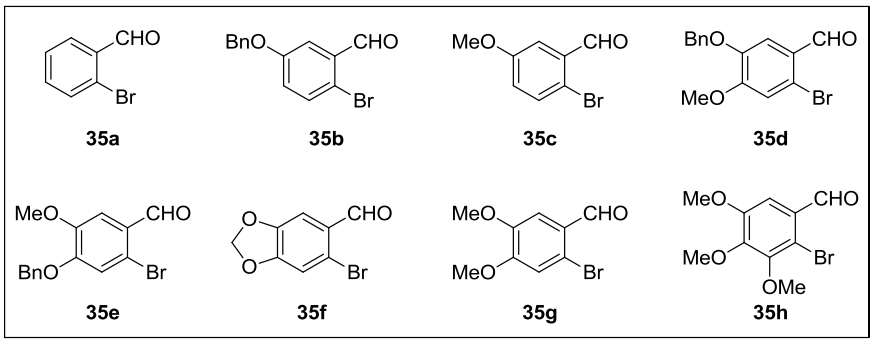
In an oven dried round bottomed flask fitted with a rubber septum, were added alcohol **21** (100 mg, 0.31–0.53 mmol), alkyl acrylate (methyl, ethyl and tertiary butyl acrylate, or acrylo–nitrile) (1.55–2.67 mmol) and Cs_2CO_3 (0.62–1.07 mmol) followed by addition of toluene (2 mL) at room temperature under a nitrogen atmosphere. The stirred reaction mixture was heated in an oil bath at 50 °C for 48 h. Progress of the Michael addition was monitored by TLC till the reaction is completed. To the cooled reaction mixture at room temperature, were added $Pd(OAc)_2$ (10 mol%) and PPh_3 (20 mol%) under nitrogen atmosphere. The stirred

reaction mixture was then heated in an oil bath at 80 °C for 24 h and monitored by TLC. Then, the mixture was cooled to room temperature, treated with aqueous NH_4Cl solution and then extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate) furnished the product **23** (25–90%).

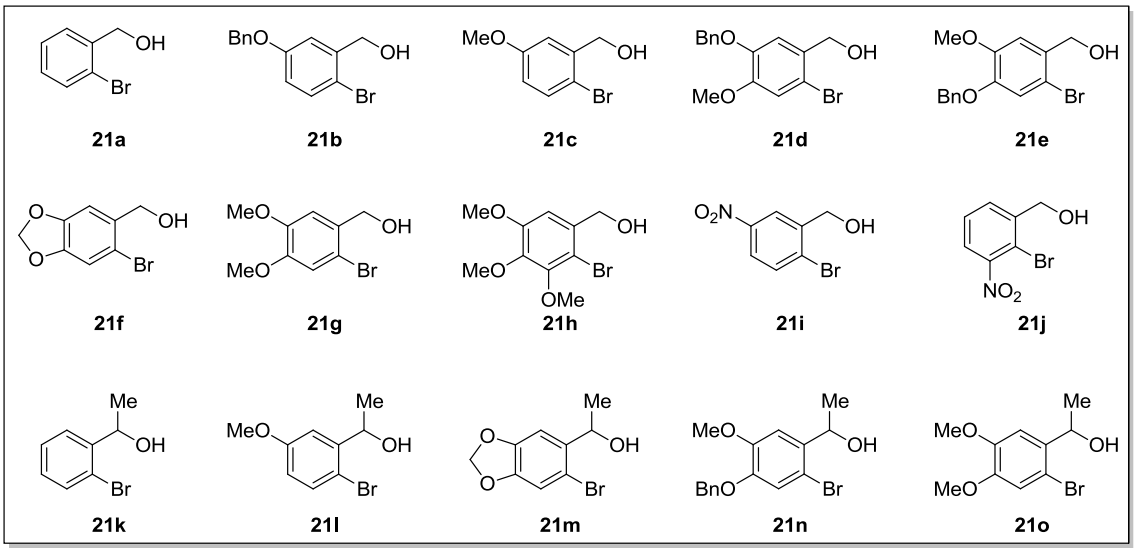
General Procedure for Intermolecular O-allylation followed by an Intramolecular Heck reaction (GP-3):

In an oven dried round bottomed flask fitted with a rubber septum, were added alcohol **21** (100 mg, 0.30–0.46 mmol), NaH (1.20–1.84 mmol) and DMF (3 mL) followed by addition of allylbromide (0.60–0.92 mmol) at room temperature under a nitrogen atmosphere. The suspension was allowed to stir at the same temperature for 1 h. Progress of the allylation was monitored by TLC till the reaction is completed. To the reaction mixture, cooled at room temperature, were added $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%) triethylbenzylammonium chloride (0.30–0.46 mmol) under a nitrogen atmosphere. The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h and monitored by TLC. The mixture was cooled to room temperature, treated with aqueous NH_4Cl solution and then extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate) furnished the isochromenes **28′** (12–32%) as a viscous liquid or a semi-solid. Further elution of crude material by silica gel column chromatography (petroleum ether/ethyl acetate) yielded isochromenes **28** (45–78%) as a viscous liquid or a semi-solid.

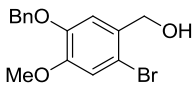
The following bromobenzaldehydes **35b–35h** from table were synthesized using literature reported bromination of corresponding benzaldehydes.[81]



Primary alcohols *ortho*-bromobenzyl alcohols **21a–21o** required as precursors for this study, were synthesized using reduction reaction on corresponding 2-bromobenzaldehydes **35a–35h** with the reducing agent $NaBH_4$. The secondary alcohols **21k–21o**, were obtained using standard methyl Grignard addition to the 2-bromobenzaldehydes (**35a**, **35c**, **35e**, **35f** & **35g**).



Compounds **21a**[82], **21b**[83], **21c**[84], **21f**[85], **21g**[86], **21h**[87], **21i**[88], **21j**[89] and **21k**–**21o**[90] are known in the literature.



21d

[5-(Benzyloxy)-2-bromo-4-methoxyphenyl]methanol (21d):

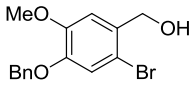
GP-1 was carried out with the 2-bromobenzaldehyde **35d** (500 mg, 1.56 mmol), $NaBH_4$ (117 mg, 3.12 mmol) in methanol (15 mL). The resulted ice cold mixture was allowed to attain room temperature and stirred for 1 h. Purification of the crude material by silica gel column (petroleum ether/ethyl acetate, 90:10 to 70:30) furnished the alcohol **21d** (440 mg, 87%) as a white solid, recrystallized from dichloromethane/hexane (m. p. 112–115 °C). [TLC control (petroleum ether/ethyl acetate 70:30), R_f(**35d**)=0.65, R_f(**21d**)=0.40, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3372, 2926, 1601, 1501, 1456, 1439, 1381, 1259, 1209, 1156, 1054, 1028, 855, 798, 738, 697 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.42 (d, 2H, *J*=7.3 Hz, Ar-H), 7.36 (d, 1H, *J*=7.3 Hz, Ar-H), 7.35 (d, 1H, *J*=7.3 Hz, Ar-H), 7.29 (t, 1H, *J*=7.3 Hz, Ar-H), 7.02 (s, 2H, Ar-H), 5.11 (s, 2H, Ar-CH_2OPh), 4.59 (s, 2H, Ar-C*H*$_2$OH), 3.85 (s, 3H, Ar-OCH_3), 2.05 (br. s, 1H, OH) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=149.6 (s, Ar-C), 147.6 (s, Ar-C), 136.6 (s, Ar-C), 131.7 (s, Ar-C), 128.6 (d, 2C, Ar-CH), 128.0 (d, Ar-CH), 127.4 (d, 2C, Ar-CH), 115.8 (d, Ar-CH), 114.4 (d, Ar-CH), 113.1 (s, Ar-C), 71.1 (t, Ar-CH_2OPh), 64.7 (t, Ar-CH_2OH), 56.2 (q, Ar-OCH_3) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{15}H_{14}BrO_2]^+$=$[(M+H)–H_2O]^+$: 305.0172; found 305.0173.



21e

[4-(Benzyloxy)-2-bromo-5-methoxyphenyl]methanol (21e):

GP-1 was carried out with the 2-bromobenzaldehyde **35e** (500 mg, 1.56 mmol), $NaBH_4$ (117 mg, 3.12 mmol) in methanol (15 mL). The resulted ice cold mixture was allowed to attain room temperature and stirred for 1 h. Purification of the crude material by silica gel column (petroleum ether/ethyl acetate, 90:10 to

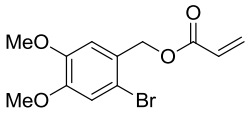
70:30) furnished the alcohol **21e** (470 mg, 93%) as a white solid, recrystallized from dichloromethane/ hexane (m. p. 102–108 °C). [TLC control (petroleum ether/ethyl acetate 70:30), R_f(**35e**)=0.65, R_f(**21e**)=0.40, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3392, 2934, 1600, 1501, 1459, 1385, 1260, 1159, 1050, 1011, 859, 744, 698 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.42 (d, 2H, *J*=7.0 Hz, Ar-H), 7.37 (d, 1H, *J*=7.0 Hz, Ar-H), 7.36 (d, 1H, *J*=7.0 Hz, Ar-H), 7.31 (t, 1H, *J*=7.0 Hz, Ar-H), 7.04 (s, 1H, Ar-H), 7.01 (s, 1H, Ar-H), 5.09 (s, 2H, Ar-CH_2OPh), 4.64 (s, 2H, Ar-CH_2OH), 3.86 (s, 3H, Ar-OCH_3), 2.14 (br. s, 1H, OH) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=149.2 (s, Ar-C), 148.0 (s, Ar-C), 136.3 (s, Ar-C), 132.4 (s, Ar-C), 128.6 (d, 2C, Ar-CH), 128.0 (d, Ar-CH), 127.4 (d, 2C, Ar-CH), 117.9 (d, Ar-CH), 112.3 (d, Ar-CH), 112.2 (s, Ar-C), 71.2 (t, Ar-CH_2OPh), 64.8 (t, Ar-*C*H_2OH), 56.1 (q, Ar-OCH_3) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{15}H_{14}BrO_2]^+$=$[(M+H)–H_2O]^+$: 305.0172; found 305.0175.



26g

2-Bromo-4,5-dimethoxybenzyl but-3-enoate (26g):

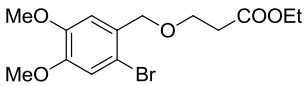
In an oven dried round bottomed flask fitted with a rubber septum, were added alcohol **21g** (100 mg, 0.40 mmol), ethyl acrylate (203 mg, 2.02 mmol) and Cs_2CO_3 (264 mg, 0.81 mmol) followed by addition of toluene (2 mL) at room temperature under a nitrogen atmosphere. The stirred reaction mixture was heated in an oil bath at 50 °C for 48 h. Progress of the Michael addition was monitored by TLC till it is completed. The reaction mixture was cooled to room temperature, treated with aqueous NH_4Cl and extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were washed with saturated NaCl solution, dried (Na_2SO_4) and filtered. Evaporation of the filtrate under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 89:11) furnished the condensed ester product **26g** (19.5 mg, 16%) as minor product,

as semi-solid. [TLC control (petroleum ether/ethyl acetate 70:30), R_f(**21g**)=0.40, R_f(**26g**)=0.62, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2934, 2843, 1722, 1680, 1601, 1504, 1461, 1439, 1383, 1260, 1211, 1163, 1030, 801 cm^{-1}.

^{1}H-NMR (CDCl$_3$, 400 MHz): δ=7.03 (s, 1H, Ar-H), 6.93 (s, 1H, Ar-H), 6.45 (dd, 1H, *J*=17.3 and 1.2 Hz, O=C-CH=C*H*$_{2A(trans)}$], 6.16 [dd, 1H, *J*=17.3 and 10.3 Hz, O=C-C*H*=CH$_2$], 5.85 [dd, 1H, *J*=10.3 and 1.2 Hz, O=C-CH=C*H*$_{2B(cis)}$], 5.21 (s, 2H, Ar-C*H*$_2$OC=O), 3.86 (s, 3H, Ar-OCH$_3$), 3.86 (s, 3H, Ar-OCH$_3$) ppm.

^{13}C-NMR (CDCl$_3$, 100 MHz): δ=165.9 (s, O=C–O), 149.6 (s, Ar-C), 148.3 (s, Ar-C), 131.3 (t, O=C-OCH=*C*H$_2$), 128.1 (d, O=C-O*C*H=CH$_2$), 127.0 (s, Ar-C), 115.5 (d, Ar-CH), 114.4 (s, Ar-C), 113.3 (d, Ar-CH), 66.0 (t, Ar-*C*H$_2$OC=O), 56.2 (q, Ar-OCH$_3$), 56.1 (q, Ar-OCH$_3$) ppm.



25g

Ethyl 3-[(2-bromo-4,5-dimethoxybenzyl)oxy]propanoate (25g):

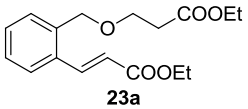
Further elution of crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 89:11 to 80:20) yielded Michael addition product **25g** (110 mg, 78%) as major product, as pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 70:30), R_f(**21g**)=0.40, R_f(**25g**)=0.60, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2933, 2848, 1732, 1602, 1505, 1463, 1440, 1381, 1260, 1185, 1161, 1107, 1030, 860, 800 cm^{-1}.

^{1}H-NMR (CDCl$_3$, 400 MHz): δ=6.98 (s, 2H, Ar-H), 4.52 (s, 2H, Ar-C*H*$_2$OCH$_2$), 4.14 (q, 2H, *J*=7.2 Hz, OC*H*$_2$CH$_3$), 3.86 (s, 3H, Ar-OCH$_3$), 3.84 (s, 3H, Ar-OCH$_3$), 3.79 (t, 2H, *J*=6.3 Hz, OC*H*$_2$CH$_2$COOEt), 2.62 (t, 2H, *J*=6.3 Hz, OCH$_2$C*H*$_2$COOEt), 1.24 (t, 3H, *J*=7.2 Hz, OCH$_2$C*H*$_3$) ppm.

^{13}C-NMR (CDCl$_3$, 100 MHz): δ=171.5 (s, O=C–O), 148.8 (s, Ar-C), 148.5 (s, Ar-C), 129.4 (s, Ar-C), 115.2 (d, Ar-CH), 112.7 (s, Ar-C), 111.9 (d, Ar-CH), 72.0 (t, Ar-*C*H$_2$OCH$_2$), 65.9 (t, O*C*H$_2$CH$_2$COOEt), 60.5 (t, O*C*H$_2$CH$_3$), 56.1 (q, Ar-OCH$_3$), 56.0 (q, Ar-OCH$_3$), 35.1 (t, OCH$_2$*C*H$_2$COOEt), 14.2 (q, OCH$_2$*C*H$_3$) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{14}H_{19}BrNaO_5]^+$=[M+Na]$^+$: 369.0308; found 369.0307.



23a

Ethyl (2*E*)-3-{2-[1-(3-ethoxy-3-oxopropoxy)methyl]phenyl}acrylate (23a):

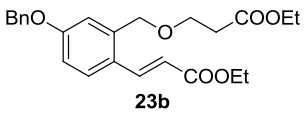
GP-2 was carried out with the 2-bromobenzyl alcohol **21a** (100 mg, 0.53 mmol), ethyl acrylate (268 mg, 2.67 mmol) and Cs_2CO_3 (349 mg, 1.07 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added $Pd(OAc)_2$ (12.0 mg, 10 mol%) and PPh_3 (28.1 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 80:20) furnished the diester **23a** (84.0 mg, 51%) as a colorless viscous oil. [TLC control (petroleum ether/ethyl acetate 85:15), R_f(**21a**)=0.45, R_f(**23a**)=0.44, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2980, 2935, 2872, 1731, 1711, 1634, 1602, 1368, 1313, 1268, 1176, 1095, 1031, 766 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.96 (d, 1H, *J*=15.9 Hz, C*H*=CHCOOEt), 7.57 (dd, 1H, *J*=7.4 and 1.6 Hz, Ar-H), 7.42–7.26 (m, 3H, Ar-H), 6.35 (d, 1H, *J*=15.9 Hz, CH=C*H*COOEt), 4.63 (s, 2H, Ar-CH_2OCH$_2$), 4.25 (q, 2H, *J*=7.1 Hz, OCH_2CH$_3$), 4.13 (q, 2H, *J*=7.1 Hz, OCH_2CH$_3$), 3.78 (t, 2H, *J*=6.5 Hz, OCH_2CH$_2$COOEt), 2.61 (t, 2H, *J*=6.5 Hz, OCH$_2$CH_2COOEt), 1.33 (t, 3H, *J*=7.1 Hz, OCH$_2$CH_3), 1.23 (t, 3H, *J*=7.1 Hz, OCH$_2$CH_3) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=171.4 (s, O=C–O), 166.8 (s, O=C–O), 141.5 (d, *C*H=CHCOOEt), 136.8 (s, Ar-C), 133.5 (s, Ar-C), 129.8 (d, CH=*C*HCOOEt), 129.3 (d, Ar-CH), 128.3 (d, Ar-CH), 126.7 (d, Ar-CH), 120.1 (d, Ar-CH), 70.8 (t, Ar-*C*H_2OCH$_2$), 65.9 (t, O*C*H$_2$CH$_2$COOEt), 60.5 (2 × t, 2C, O*C*H$_2$CH$_3$), 35.1 (t, OCH$_2$*C*H$_2$COOEt), 14.3 (q, OCH$_2$*C*H$_3$), 14.2 (q, OCH$_2$*C*H$_3$) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{17}H_{22}NaO_5]^+=[M+Na]^+$: 329.1359; found 329.1354.



23b

Ethyl (2*E*)-3-{4-(benzyloxy)-2-[1-(3-ethoxy-3-oxopropoxy)methyl]phenyl}acrylate (23b):

GP-2 was carried out with the 2-bromobenzyl alcohol **21b** (100 mg, 0.36 mmol), ethyl acrylate (179 mg, 1.79 mmol) and Cs_2CO_3 (234 mg, 0.72 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added $Pd(OAc)_2$ (8.0 mg, 10 mol%) and PPh_3 (18.8 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 96:4 to 80:20) furnished the diester **23b** (58 mg, 41%) as a yellow viscous oil. [TLC control (petroleum ether/ethyl acetate 80:20), R_f(**21b**)=0.45, R_f(**23b**)=0.45, UV detection].

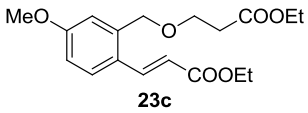
IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2980, 2930, 1730, 1714, 1634, 1602, 1311, 1257, 1176, 1096, 1029, 763 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.88 (d, 1H, *J*=15.8 Hz, C*H*=CHCOOEt), 7.54 (d, 1H, *J*=8.5 Hz, Ar-H), 7.46–7.26 (m, 5H, Ar-H), 7.05 (d, 1H, *J*=2.5 Hz, Ar-H), 6.89 (dd, 1H, *J*=8.5 Hz and 2.5 Hz, Ar-H), 6.26 (d, 1H, *J*=15.8 Hz, CH=C*H*COOEt), 5.09 (s, 2H, PhOCH_2Ar), 4.63 (s, 2H, Ar-CH_2OCH_2), 4.25 (q, 2H, *J*=7.2 Hz, OCH_2CH$_3$), 4.14 (q, 2H, *J*=7.2 Hz, OCH_2CH$_3$), 3.78 (t, 2H, *J*=6.5 Hz, OCH_2CH$_2$COOEt), 2.61 (t, 2H, *J*=6.5 Hz, OCH$_2$CH_2COOEt), 1.33 (t, 3H, *J*=7.2 Hz, OCH$_2$CH_3), 1.24 (t, 3H, *J*=7.2 Hz, OCH$_2$CH_3) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=171.4 (s, O=C–O), 167.1 (s, O=C–O), 160.2 (s, Ar-C), 140.8 (d, *C*H=CHCOOEt), 139.0 (s, Ar-C), 136.5 (s, Ar-C), 128.6 (d, 2C, Ar-CH), 128.3 (d, Ar-CH), 128.0 (d, Ar-CH), 127.4 (d, 2C, Ar-CH), 125.8 (s, Ar-C), 117.7 (d, CH=CHCOOEt), 114.9 (d, Ar-CH), 114.5 (d, Ar-CH), 70.5 (t, PhCH$_2$OAr), 70.0 (t, Ar-*C*H$_2$OCH$_2$), 66.0 (t, O*C*H$_2$CH$_2$COOEt), 60.5 (t, O*C*H$_2$CH$_3$),

60.3 (t, O*C*H_2CH_3), 35.0 (t, OCH_2*C*H_2COOEt), 14.3 (q, OCH_2*C*H_3), 14.1 (q, OCH_2*C*H_3) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{24}H_{28}NaO_6]^+$=$[M+Na]^+$: 435.1778; found 435.1781.



23c

Ethyl (2*E*)-3-{2-[1-(3-ethoxy-3-oxopropoxy)methyl]-4-methoxyphenyl}acrylate (23c):

GP-2 was carried out with the 2-bromobenzyl **21c** (100 mg, 0.46 mmol), ethyl acrylate (231 mg, 2.30 mmol) and Cs_2CO_3 (300 mg, 0.92 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added $Pd(OAc)_2$ (10.3 mg, 10 mol%) and PPh_3 (24.2 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 80:20) furnished the diester **23c** (76.2 mg, 49%) as a colorless viscous oil. [TLC control (petroleum ether/ethyl acetate 80:20), R_f(**21c**)=0.43, R_f(**23c**)=0.43, UV detection].

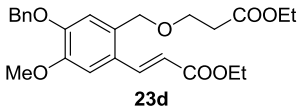
IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2980, 2930, 1732, 1710, 1632, 1604, 1499, 1259, 1179, 1161, 1096, 1034, 861 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.86 (d, 1H, *J*=15.8 Hz, C*H*=CHCOOEt), 7.53 (d, 1H, *J*=8.5 Hz, Ar-H), 6.94 (d, 1H, *J*=2.5 Hz, Ar-H), 6.81 (dd, 1H, *J*=8.5 Hz and 2.5 Hz, Ar-H), 6.24 (d, 1H, *J*=15.8 Hz, CH=C*H*COOEt), 4.62 (s, 2H, Ar-CH_2OCH_2), 4.23 (q, 2H, *J*=7.3 Hz, OCH_2CH_3), 4.13 (q, 2H, *J*=7.3 Hz, OCH_2CH_3), 3.81 (s, 3H, Ar-OCH_3), 3.79 (t, 2H, *J*=6.5 Hz, OCH_2CH_2COOEt), 2.61 (t, 2H, *J*=6.5 Hz, OCH_2CH_2COOEt), 1.31 (t, 3H, *J*=7.3 Hz, OCH_2CH_3), 1.23 (t, 3H, *J*=7.3 Hz, OCH_2CH_3) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=171.4 (s, O=C–O), 167.1 (s, O=C–O), 161.0 (s, Ar-C), 140.8 (d, *C*H=CHCOOEt), 139.0 (s, Ar-C), 128.3 (d, Ar-CH), 125.6 (s, Ar-C), 117.5 (d, CH=*C*HCOOEt), 114.0 (d, Ar-CH), 113.7 (d, Ar-CH), 70.6 (t,

Ar-*C*H_2OCH_2), 66.0 (t, O*C*$H_2$$CH_2$COOEt), 60.5 (t, O*C*$H_2$$CH_3$), 60.3 (t, O*C*$H_2$$CH_3$), 55.3 (q, Ar-O$CH_3$), 35.1 (t, O$CH_2$*C*$H_2$COOEt), 14.3 (q, O$CH_2$*C*$H_3$), 14.2 (q, O$CH_2$*C*$H_3$) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{18}H_{24}NaO_6]^+$=$[M+Na]^+$: 359.1465; found 359.1464.



23d

Ethyl (2*E*)-3-{4-(benzyloxy)-2-[(3-ethoxy-3-oxopropoxy)methyl]-5-methoxyphenyl}acrylate (23d):

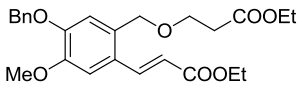
GP-2 was carried out with the 2-bromobenzyl alcohol **21d** (100 mg, 0.31 mmol), ethyl acrylate (155 mg, 1.55 mmol) and Cs_2CO_3 (202 mg, 0.62 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added $Pd(OAc)_2$ (6.8 mg, 10 mol%) and PPh_3 (16.4 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 85:15 to 75:25) furnished the diester **23d** (62 mg, 45%) as a white solid, recrystallized from dichloromethane/hexane (m. p. 64–68 °C). [TLC control (petroleum ether/ethyl acetate 70:30), R_f(**1d**)=0.44, R_f(**3ad**)=0.44, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2929, 2871, 1732, 1708, 1631, 1600, 1513, 1456, 1371, 1273, 1169, 1110, 1028, 858, 740, 698 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.88 (d, 1H, *J*=15.8 Hz, C*H*=CHCOOEt), 7.43 (d, 2H, *J*=7.2 Hz, Ar-H), 7.36 (d, 1H, *J*=7.2 Hz, Ar-H), 7.35 (d, 1H, *J*=7.2 Hz, Ar-H), 7.29 (t, 1H, *J*=7.2 Hz, Ar-H), 7.09 (s, 1H, Ar-H), 6.94 (s, 1H, Ar-H), 6.26 (d, 1H, *J*=15.8 Hz, Ar-C*H*=CHCOOEt), 5.18 (s, 2H, PhOCH_2Ar), 4.55 (s, 2H, ArC*H*$_2$OCH_2), 4.25 (q, 2H, *J*=7.2 Hz, OC*H*$_2$$CH_3$), 4.13 (q, 2H, *J*=7.2 Hz, OC*H*$_2$$CH_3$), 3.89 (s, 3H, Ar-O$CH_3$), 3.70 (t, 2H, *J*=6.5 Hz, OC*H*$_2$$CH_2$COOEt), 2.56 (t, 2H, *J*=6.5 Hz, OCH_2C*H*$_2$COOEt), 1.33 (t, 3H, *J*=7.2 Hz, OCH_2C*H*$_3$), 1.23 (t, 3H, *J*=7.2 Hz, OCH_2C*H*$_3$) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=171.4 (s, O=C–O), 167.0 (s, O=C–O), 149.8 (s, Ar-C), 149.2 (s, Ar-C), 140.9 (d, *C*H=CHCOOEt), 136.6 (s, Ar-C), 130.7 (s, Ar-C), 128.6 (d, 2C, Ar-C), 128.0 (d, Ar-CH), 127.3 (d, 2C, Ar-CH), 126.1 (s, Ar-C), 117.8 (d, Ar-CH), 114.3 (d, Ar-CH), 109.5 (d, CH=*C*HCOOEt), 70.8 (t, $PhCH_2OAr$), 70.1 (t, Ar-CH_2OCH_2), 65.7 (t, O*C*H_2CH_2COOEt), 60.5 (t, O*C*H_2CH_3), 60.4 (t, O*C*H_2CH_3), 56.1 (q, Ar-OCH_3), 35.0 (t, OCH_2*C*H_2COOEt), 14.3 (q, OCH_2*C*H_3), 14.2 (q, OCH_2*C*H_3) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{25}H_{30}NaO_7]^+$=$[M+Na]^+$: 465.1884; found 465.1853.



23e

Ethyl (2*E*)-3-{5-(benzyloxy)-2-[(3-ethoxy-3-oxopropoxy)methyl]-4-methoxyphenyl}acrylate (23e):

GP-2 was carried out with the 2-bromobenzyl alcohol **21e** (100 mg, 0.31 mmol), ethyl acrylate (155 mg, 1.55 mmol) and Cs_2CO_3 (202 mg, 0.62 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added $Pd(OAc)_2$ (6.8 mg, 10 mol%) and PPh_3 (16.4 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 85:15 to 75:25) furnished the diester **23e** (64.6 mg, 47%) as a white solid, recrystallized from dichloromethane/hexane (m. p. 64–66 °C). [TLC control (petroleum ether/ethyl acetate 70:30), R_f(**21e**)=0.44, R_f(**23e**)=0.44, UV detection].

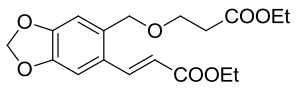
IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2978, 2930, 2870, 1731, 1706, 1630, 1600, 1513, 1460, 1264, 1169, 1110, 1028, 859, 742, 698 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.86 (d, 1H, *J*=15.8 Hz, C*H*=CHCOOEt), 7.43 (d, 2H, *J*=7.3, Ar-H), 7.36 (d, 1H, *J*=7.3 Hz, Ar-H), 7.35 (d, 1H, *J*=7.3 Hz, Ar-H), 7.32 (t, 1H, *J*=7.3 Hz, Ar-H), 7.11 (s, 1H, Ar-H), 6.93 (s, 1H, Ar-H), 6.14 (d, 1H, *J*=15.8 Hz, Ar-CH=C*H*COOEt), 5.14 (s, 2H, $PhOCH_2Ar$), 4.59 (s, 2H,

ArC*H*$_2$OCH$_2$), 4.24 (q, 2H, *J*=7.3 Hz, OC*H*$_2$CH$_3$), 4.13 (q, 2H, *J*=7.3 Hz, OC*H*$_2$CH$_3$), 3.91 (s, 3H, Ar-OCH$_3$), 3.78 (t, 2H, *J*=6.5 Hz, OC*H*$_2$CH$_2$COOEt), 2.61 (t, 2H, *J*=6.5 Hz, OCH$_2$C*H*$_2$COOEt), 1.32 (t, 3H, *J*=7.3 Hz, OCH$_2$C*H*$_3$), 1.23 (t, 3H, *J*=7.3 Hz, OCH$_2$C*H*$_3$) ppm.

^{13}C-NMR (CDCl$_3$, 100 MHz): δ=171.4 (s, O=C–O), 167.1 (s, O=C–O), 151.3 (s, Ar-C), 147.7 (s, Ar-C), 140.9 (d, *C*H=CHCOOEt), 136.6 (s, Ar-C), 131.3 (s, Ar-C), 128.6 (d, 2C, Ar-CH), 128.0 (d, Ar-CH), 127.3 (d, 2C, Ar-CH), 125.6 (s, Ar-C), 117.6 (d, Ar-CH), 112.4 (d, Ar-CH), 111.7 (d, CH=*C*HCOOEt), 71.1 (t, PhCH$_2$OAr), 70.2 (t, Ar-*C*H$_2$OCH$_2$), 65.9 (t, O*C*H$_2$CH$_2$COOEt), 60.5 (t, O*C*H$_2$CH$_3$), 60.4 (t, O*C*H$_2$CH$_3$), 56.0 (q, Ar-OCH$_3$), 35.0 (t, OCH$_2$*C*H$_2$COOEt), 14.3 (q, OCH$_2$*C*H$_3$), 14.1 (q, OCH$_2$*C*H$_3$) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{25}H_{30}NaO_7]^+$=$[M+Na]^+$: 465.1884; found 465.1881.



23f

Ethyl (2*E*)-3-{6-[1-(3-ethoxy-3-oxopropoxy)methyl]-1,3-benzodioxol-5-yl}acrylate (23f):

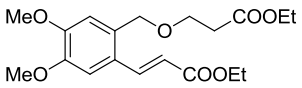
GP-2 was carried out with the 2-bromobenzyl alcohol **21f** (100 mg, 0.43 mmol), ethyl acrylate (217 mg, 2.16 mmol) and Cs_2CO_3 (282 mg, 0.86 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added $Pd(OAc)_2$ (9.7 mg, 10 mol%) and PPh_3 (23 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 80:20) furnished the diester **23f** (70.5 mg, 46%) as a colourless semi-solid. [TLC control (petroleum ether/ethyl acetate 80:20), R_f(**21f**)=0.45, R_f(**23f**)=0.45, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2981, 2904, 1731, 1709, 1632, 1612, 1504, 1485, 1372, 1293, 1259, 1178, 1037, 931, 858 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.87 (d, 1H, *J*=15.7 Hz, C*H*=CHCOOEt), 7.05 (s, 1H, Ar-H), 6.88 (s, 1H, Ar-H), 6.22 (d, 1H, *J*=15.7 Hz, CH=C*H*COOEt), 5.98 (s, 2H, O-CH_2-O), 4.56 (s, 2H, Ar-CH_2OCH_2), 4.24 (q, 2H, *J*=7.2 Hz, OC$H_2$$CH_3$), 4.14 (q, 2H, *J*=7.2 Hz, OC$H_2$$CH_3$), 3.77 (t, 2H, *J*=6.5 Hz, OC$H_2$$CH_2$COOEt), 2.61 (t, 2H, *J*=6.5 Hz, OCH_2CH_2COOEt), 1.32 (t, 3H, *J*=7.2 Hz, OCH_2CH_3), 1.24 (t, 3H, *J*=7.2 Hz, OCH_2CH_3) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=171.4 (s, O=C–O), 167.0 (s, O=C–O), 149.2 (s, Ar-C), 147.7 (s, Ar-C), 140.7 (d, *C*H=CHCOOEt), 132.4 (s, Ar-C), 127.2 (s, Ar-C), 118.0 (d, CH=*C*HCOOEt), 109.4 (d, Ar-CH), 105.9 (d, Ar-CH), 101.5 (t, O-CH_2-O), 70.2 (t, Ar-*C*H_2OCH_2), 65.8 (t, O*C*$H_2$$CH_2$COOEt), 60.5 (t, O*C*$H_2$$CH_3$), 60.4 (t, O*C*$H_2$$CH_3$), 35.0 (t, O$CH_2$*C*$H_2$COOEt), 14.3 (q, O$CH_2$*C*$H_3$), 14.1 (q, O$CH_2$*C*$H_3$) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{18}H_{22}NaO_7]^+$=$[M+Na]^+$: 373.1258; found 373.1243.



23g

Ethyl (2*E*)-3-{2-[(3-ethoxy-3-oxopropoxy)methyl]-4,5-dimethoxyphenyl}acrylate (23g):

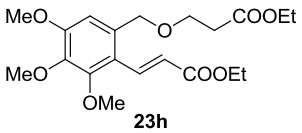
GP-2 was carried out with the 2-bromobenzyl alcohol **21g** (100 mg, 0.40 mmol), ethyl acrylate (203 mg, 2.02 mmol) and Cs_2CO_3 (264 mg, 0.81 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added $Pd(OAc)_2$ (9.1 mg, 10 mol%) and PPh_3 (21.2 mg, 0.81 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 90:10 to 80:20) furnished the diester **23g** (79 mg, 53%) as a pale brown viscous oil. [TLC control (petroleum ether/ethyl acetate 70:30), R_f(**21g**)=0.40, R_f(**23g**)=0.40, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2979, 2937, 2868, 1730, 1705, 1630, 1600, 1514, 1464, 1369, 1270, 1165, 1107, 1030, 856 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.89 (d, 1H, *J*=15.8 Hz, C*H*=CHCOOEt), 7.05 (s, 1H, Ar-H), 6.89 (s, 1H, Ar-H), 6.25 (d, 1H, *J*=15.8 Hz, CH=C*H*COOEt), 4.59 (s, 2H, Ar-CH_2OCH_2), 4.23 (q, 2H, *J*=7.1 Hz, OCH_2CH$_3$), 4.11 (q, 2H, *J*=7.1 Hz, OCH_2CH$_3$), 3.89 (s, 3H, Ar-OCH$_3$), 3.87 (s, 3H, Ar-OCH$_3$), 3.77 (t, 2H, *J*=6.4 Hz, OCH_2CH$_2$COOEt), 2.60 (t, 2H, *J*=6.4 Hz, OCH$_2$CH_2COOEt), 1.31 (t, 3H, *J*=7.1 Hz, OCH$_2$CH_3), 1.25 (t, 3H, *J*=7.1 Hz, OCH$_2$CH_3) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=171.4 (s, O=C–O), 167.0 (s, O=C–O), 150.7 (s, Ar-C), 148.7 (s, Ar-C), 140.9 (d, *C*H=CHCOOEt), 130.9 (s, Ar-C), 125.7 (s, Ar-C), 117.7 (d, Ar-CH), 112.1 (d, Ar-CH), 109.0 (d, CH=*C*HCOOEt), 70.2 (t, Ar-*C*H_2OCH_2), 65.8 (t, O*C*H_2CH$_2$COOEt), 60.5 (t, O*C*H_2CH$_3$), 60.4 (t, O*C*H_2CH$_3$), 56.0 (q, 2C, 2 × Ar-OCH$_3$), 35.1 (t, OCH$_2$*C*H$_2$COOEt), 14.3 (q, OCH$_2$*C*H$_3$), 14.1 (q, OCH$_2$*C*H$_3$) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{19}H_{27}O_7]^+$=$[M+H]^+$: 367.1751; found 367.1748.



23h

Ethyl (2*E*)-3-{6-[(3-ethoxy-3-oxopropoxy)methyl]-2,3,4-trimethoxyphenyl}acrylate (23h):

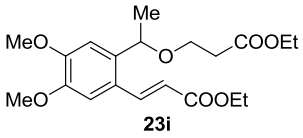
GP-2 was carried out with the 2-bromobenzyl alcohol **21h** (100 mg, 0.36 mmol), ethyl acrylate (180.7 mg, 1.80 mmol) and Cs_2CO_3 (235 mg, 0.72 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added $Pd(OAc)_2$ (8.1 mg, 10 mol%) and PPh_3 (19.0 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 80:20) furnished the diester **23h** (77 mg, 51%) as a colorless viscous oil. [TLC control (petroleum ether/ethyl acetate 80:25), R_f(**21h**)=0.45, R_f(**23h**)=0.45, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2980, 2938, 1734, 1711, 1630, 1591, 1461, 1300, 1176, 1129, 1031, 987 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.76 (d, 1H, *J*=16.2 Hz, C*H*=CH_2COOEt), 6.81 (s, 1H, Ar-H), 6.50 (d, 1H, *J*=16.2 Hz, CH=C*H*COOEt), 4.54 (s, 2H, Ar-CH_2OCH_2), 4.25 (q, 2H, *J*=7.1 Hz, OC$H_2$$CH_3$), 4.14 (q, 2H, *J*=7.1 Hz, OC$H_2$$CH_3$), 3.89 (s, 3H, Ar-O$CH_3$), 3.85 (s, 6H, 2 × Ar-O$CH_3$), 3.81 (t, 2H, *J*=6.4 Hz, OC$H_2$$CH_2$COOEt), 2.64 (t, 2H, *J*=6.4 Hz, OCH_2CH_2COOEt), 1.32 (t, 3H, *J*=7.1 Hz, OCH_2CH_3), 1.24 (t, 3H, *J*=7.1 Hz, OCH_2CH_3) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=171.5 (s, O=C–O), 167.8 (s, O=C–O), 154.2 (s, Ar-C), 153.6 (s, Ar-C), 141.8 (s, Ar-C), 137.6 (d, *C*H=CHCOOEt), 133.6 (s, Ar-C), 121.5 (d, Ar-CH), 120.4 (s, Ar-C), 108.3 (d, CH=*C*HCOOEt), 71.1 (t, Ar-*C*H_2OCH_2), 66.0 (t, O*C*$H_2$$CH_2$COOEt), 60.9 (q, Ar-O$CH_3$), 60.7 (q, Ar-O$CH_3$), 60.5 (t, O*C*$H_2$$CH_3$), 60.3 (t, O*C*$H_2$$CH_3$), 56.0 (q, Ar-O$CH_3$), 35.0 (t, O$CH_2$*C*$H_2$COOEt), 14.3 (q, O$CH_2$*C*$H_3$), 14.2 (q, O$CH_2$*C*$H_3$) ppm.

HR-MS (ESI^{+}): m/z calculated for $[C_{20}H_{28}NaO_8]^+$=$[M+Na]^+$: 419.1676; found 419.1676.



23i

Ethyl (2*E*)-3-{2-[1-(3-ethoxy-3-oxopropoxy)ethyl]-4,5-dimethoxyphenyl}acrylate (23i):

GP-2 was carried out with the 2-bromobenzyl alcohol **21o** (100 mg, 0.38 mmol), ethyl acrylate (192 mg, 1.91 mmol) and Cs_2CO_3 (250 mg, 0.77 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added $Pd(OAc)_2$ (8.6 mg, 10 mol%) and PPh_3 (20.1 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 90:10 to 80:20) furnished the diester **23i** (48 mg,

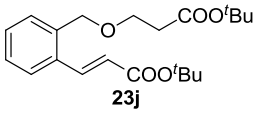
33%) as a pale yellow viscous oil. [TLC control (petroleum ether/ethyl acetate 70:30), R_f(**21o**)=0.45, R_f(**23i**)=0.45, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2977, 2934, 1732, 1708, 1601, 1510, 1464, 1263, 1168, 1098, 1028, 862 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.97 (d, 1H, *J*=15.7 Hz, C*H*=CHCOOEt), 7.01 (s, 1H, Ar-H), 7.01 (s, 1H, Ar-H), 6.25 (d, 1H, *J*=15.7 Hz, CH=C*H*COOEt), 4.83 [q, 1H, *J*=6.4 Hz, Ar-C*H*(CH_3)OCH_2], 4.26 (q, 2H, *J*=7.1 Hz, OCH_2CH_3), 4.13 (dq, 2H, *J*=7.1 and 2.4 Hz OCH_2CH_3), 3.93 (s, 3H, Ar-OCH_3), 3.89 (s, 3H, Ar-OCH_3), 3.59 (ddd, 1H, *J*=12.9, 9.4 and 6.1 Hz, O$CH_{2a}CH_2$COOEt), 3.56 (ddd, 1H, *J*=12.9, 9.4 and 6.1 Hz, O$CH_{2b}CH_2$COOEt), 2.56 (dd, 1H, *J*=6.1 and 2.7 Hz, OCH_2CH_{2a}COOEt), 2.55 (dd, 1H, *J*=6.1 and 2.7 Hz, OCH_2CH_{2b}COOEt), 1.38 [d, 3H, *J*=6.4, Ar-CH(CH_3)OCH_2],1.34 (t, 3H, *J*=7.1 Hz, OCH_2CH_3), 1.24 (t, 3H, *J*=7.1 Hz, OCH_2CH_3) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=171.5 (s, O=C–O), 167.1 (s, O=C–O), 151.4 (s, Ar-C), 148.2 (s, Ar-C), 140.4 (d, *C*H=CHCOOEt), 137.0 (s, Ar-C), 124.3 (s, Ar-C), 117.7 (d, CH=*C*HCOOEt), 108.5 (d, Ar-CH), 108.4 (d, Ar-CH), 74.1 [d, Ar-*C*H(CH_3)OCH_2], 64.2 (t, O*C*H_2CH_2COOEt), 60.5 (t, O*C*H_2CH_3), 60.4 (t, O*C*H_2CH_3), 56.0 (q, Ar-OCH_3), 55.9 (q, Ar-OCH_3), 35.2 (t, OCH_2*C*H_2COOEt), 24.2 [q, Ar-CH(*C*H_3)OCH_2], 14.3 (q, OCH_2*C*H_3), 14.2 (q, OCH_2*C*H_3) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{20}H_{29}O_7]^+$=$[M+H]^+$: 381.1908; found 381.1900.



23j

***Tert*-butyl (2*E*)-3-{2-[(3-*tert*-butoxy-3-oxopropoxy)methyl]phenyl}acrylate (23j):**

GP-2 was carried out with the 2-bromobenzyl alcohol **21a** (100 mg, 0.53 mmol), tertiarybutyl acrylate (342 mg, 2.67 mmol) and Cs_2CO_3 (348.5 mg, 1.07 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added $Pd(OAc)_2$ (12 mg, 10 mol%) and PPh_3 (28

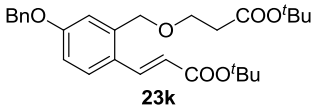
mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 98:2 to 90:10) furnished the diester **23j** (138.3 mg, 71%) as a colourless viscous oil. [TLC control (petroleum ether/ethyl acetate 90:10), R_f(**21a**)=0.40, R_f(**23j**)=0.55, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2977, 1726, 1709, 1633, 1602, 1367, 1150, 912, 846, 732 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.86 (d, 1H, *J*=15.8 Hz, C*H*=CHCOO^{t}Bu), 7.56 (dd, 1H, *J*=7.3 and 1.1 Hz, Ar-H), 7.39 (dd, 1H, *J*=7.4 and 1.5 Hz, Ar-H), 7.31 (ddd, 1H, *J*=8.5, 7.4 and 1.5 Hz, Ar-H), 7.29 (ddd, 1H, *J*=8.5, 7.3 and 1.1 Hz, Ar-H), 6.29 (d, 1H, *J*=15.8 Hz, CH=C*H*COO^{t}Bu), 4.62 (s, 2H, Ar-CH_2OCH$_2$), 3.75 (t, 2H, *J*=6.6 Hz, OCH_2CH$_2$COO^{t}Bu), 2.54 (t, 2H, *J*=6.6 Hz, OCH$_2$CH_2COO^{t}Bu), 1.53 [s, 9H, OC(CH$_3$)$_3$], 1.43 [s, 9H, OC(CH$_3$)$_3$] ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=170.8 (s, O=C–O), 166.2 (s, O=C–O), 140.4 (d, *C*H=CHCOO^{t}Bu), 136.9 (s, Ar-C), 133.6 (s, Ar-C), 129.6 (d, Ar-CH), 129.1 (d, Ar-CH), 128.1 (d, Ar-CH), 126.6 (d, Ar-CH), 122.0 (d, CH=*C*HCOO^{t}Bu), 80.6 [s, O*C*(CH$_3$)$_3$], 80.5 [s, O*C*(CH$_3$)$_3$], 70.7 (t, Ar-*C*H$_2$OCH$_2$), 66.3 (t, OCH$_2$CH$_2$COO^{t}Bu), 36.3 (t, CH$_2$*C*H$_2$COO^{t}Bu), 28.2 [q, 3C, OC(*C*H$_3$)$_3$], 28.1 [q, 3C, OC(*C*H$_3$)$_3$] ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{21}H_{30}NaO_5]^+$=$[M+Na]^+$: 385.1985; found 385.1984.



23k

***Tert*-butyl (2*E*)-3-{4-(benzyloxy)-2-[(3-*tert*-butoxy-3-oxopropoxy)methyl]phenyl}acrylate (23k):**

GP-2 was carried out with the 2-bromobenzyl alcohol **21b** (100 mg, 0.36 mmol), tertiarybutyl acrylate (229.4 mg, 1.79 mmol) and Cs_2CO_3 (234 mg, 0.72 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added $Pd(OAc)_2$ (8 mg, 10 mol%) and PPh_3 (19

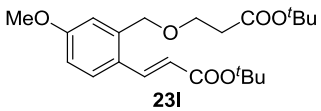
mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 97:3 to 85:15) furnished the diester **23k** (136.4 mg, 84%) as a pale yellow viscous oil. [TLC control (petroleum ether/ethyl acetate 80:20), R_f(**21b**)=0.45, R_f(**23k**)=0.60, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2975, 2926, 1728, 1705, 1628, 1590, 1458, 1366, 1304, 1243, 1153, 1130, 986, 848 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.78 (d, 1H, *J*=15.8 Hz, *C*H=CHCOO^{t}Bu), 7.53 (d, 1H, *J*=8.5 Hz, Ar-H), 7.46–7.26 (m, 5H, Ar-H), 7.07 (d, 1H, *J*=2.6 Hz, Ar-H), 6.87 (dd, 1H, *J*=8.5 and 2.6 Hz, Ar-H), 6.19 (d, 1H, *J*=15.8 Hz, CH=C*H*COO^{t}Bu), 5.08 (s, 2H, Ar-OCH$_2$Ph), 4.62 (s, 2H, Ar-C*H*$_2$OCH$_2$), 3.75 (t, 2H, *J*=6.5 Hz, OC*H*$_2$CH$_2$COO^{t}Bu), 2.54 (t, 2H, *J*=6.5 Hz, OCH$_2$C*H*$_2$COO^{t}Bu), 1.52 [s, 9H, OC(CH$_3$)$_3$], 1.44 [s, 9H, OC(CH$_3$)$_3$] ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=170.7 (s, O=C–O), 166.5 (s, O=C–O), 160.1 (s, Ar-C), 139.7 (d, *C*H=CHCOO^{t}Bu), 139.0 (s, Ar-C), 136.6 (s, Ar-C), 128.6 (d, 2C, Ar-CH), 128.2 (d, Ar-CH), 128.0 (d, Ar-CH), 127.5 (d, 2C, Ar-CH), 125.8 (s, Ar-C), 119.6 (d, CH=*C*HCOO^{t}Bu), 114.6 (d, Ar-CH), 114.5 (d, Ar-CH), 80.6 [s, O*C*(CH$_3$)$_3$], 80.3 [s, O*C*(CH$_3$)$_3$], 70.4 (t, Ar-OCH$_2$Ph), 70.0 (t, Ar-*C*H$_2$OCH$_2$), 66.3 (t, O*C*H$_2$CH$_2$COO^{t}Bu), 36.2 (t, OCH$_2$*C*H$_2$COO^{t}Bu), 28.2 [q, 3C, OC(*C*H$_3$)$_3$], 28.1 [q, 3C, OC(*C*H$_3$)$_3$] ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{28}H_{36}NaO_6]^+$=$[M+Na]^+$: 491.2404; found 491.2395.



23l

***Tert*-butyl (2*E*)-3-{2-[(3-*tert*-butoxy-3-oxopropoxy)methyl]-4-methoxyphenyl}acrylate (23l):**

GP-2 was carried out with the 2-bromobenzyl alcohol **21c** (100 mg, 0.46 mmol), tertiarybutyl acrylate (295 mg, 2.30 mmol) and Cs_2CO_3 (300 mg, 0.92 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction

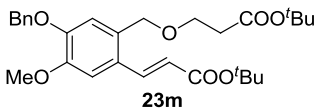
mixture at room temperature, were added $Pd(OAc)_2$ (10.3 mg, 10 mol%) and PPh_3 (24.2 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 96:4 to 80:20) furnished the diester **23l** (140.2 mg, 78%) as a colorless viscous oil. [TLC control (petroleum ether/ethyl acetate 80:20), R_f(**21c**)=0.43, R_f(**23l**)=0.58, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2976, 2933, 1727, 1704, 1630, 1603, 1497, 1366, 1255, 1145, 980, 864 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.77 (d, 1H, *J*=15.8 Hz, C*H*=CHCOO^{t}Bu), 7.52 (d, 1H, *J*=8.6 Hz, Ar-H), 6.96 (d, 1H, *J*=2.6 Hz, Ar-H), 6.80 (dd, 1H, *J*=8.6 and 2.6 Hz, Ar-H), 6.19 (d, 1H, *J*=15.8 Hz, CH=C*H*COO^{t}Bu), 4.61 (s, 2H, Ar-CH_2OCH$_2$), 3.82 (s, 3H, Ar-OCH$_3$), 3.76 (t, 2H, *J*=6.5 Hz, OCH_2CH$_2$COO^{t}Bu), 2.55 (t, 2H, *J*=6.5 Hz, OCH$_2$CH_2COO^{t}Bu), 1.52 [s, 9H, OC(CH$_3$)$_3$], 1.43 [s, 9H, OC(CH$_3$)$_3$] ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=170.7 (s, O=C–O), 166.5 (s, O=C–O), 160.9 (s, Ar-C), 139.8 (d, *C*H=CHCOO^{t}Bu), 139.0 (s, Ar-C), 128.1 (d, Ar-CH), 125.6 (s, Ar-C), 119.4 (d, CH=*C*HCOO^{t}Bu), 113.8 (d, Ar-CH), 113.7 (d, Ar-CH), 80.6 [s, O*C*(CH$_3$)$_3$], 80.2 [s, O*C*(CH$_3$)$_3$], 70.5 (t, Ar-*C*H$_2$OCH$_2$), 66.3 (t, OCH$_2$CH$_2$COO^{t}Bu), 55.3 (q, Ar-OCH$_3$), 36.2 (t, OCH$_2$*C*H$_2$COO^{t}Bu), 28.2 [q, 3C, OC(*C*H$_3$)$_3$], 28.1 [q, 3C, OC(*C*H$_3$)$_3$] ppm.

HR-MS (ESI$^+$) m/z calculated for $[C_{22}H_{32}NaO_6]^+$=$[M+Na]^+$: 415.2091; found 415.2082.



23m

***Tert*-butyl (2*E*)-3-{4-(benzyloxy)-2-[(3-*tert*-butoxy-3-oxopropoxy)methyl]-5-methoxyphenyl}acrylate (23m):**

GP-2 was carried out with the 2-bromobenzyl alcohol **21d** (100 mg, 0.31 mmol), tertiarybutyl acrylate (199 mg, 1.55 mmol) and Cs_2CO_3 (202 mg, 0.62 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction

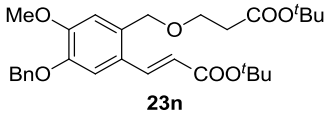
mixture at room temperature, were added $Pd(OAc)_2$ (6.8 mg, 10 mol%) and PPh_3 (16.4 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 90:10 to 75:25) furnished the diester **23m** (110 mg, 71%) as a white solid, recrystallized from dichloromethane/hexane (m. p. 76–80 °C). [TLC control (petroleum ether/ethyl acetate 70:30), R_f(**21d**)=0.44, R_f(**23m**)=0.60, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2978, 2930, 2871, 1729, 1703, 1632, 1600, 1516, 1384, 1367, 1277, 1152, 1110, 1028, 855, 741 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.80 (d, 1H, *J*=15.8 Hz, C*H*=CHCOO^{t}Bu), 7.43 (d, 2H, *J*=7.2 Hz, Ar-H), 7.35 (d, 1H, *J*=7.2 Hz, Ar-H), 7.34 (d, 1H, *J*=7.2 Hz, Ar-H), 7.29 (t, 1H, *J*=7.2 Hz, Ar-H), 7.08 (s, 1H, Ar-H), 6.97 (s, 1H, Ar-H), 6.20 (d, 1H, *J*=15.8 Hz, Ar-C*H*=CHCOO^{t}Bu), 5.16 (s, 2H, $PhCH_2OAr$), 4.54 (s, 2H, $ArCH_2OCH_2$), 3.88 (s, 3H, Ar-OCH_3), 3.67 (t, 2H, *J*=6.5 Hz, $OCH_2CH_2COO^tBu$), 2.49 (t, 2H, *J*=6.5 Hz, $OCH_2CH_2COO^tBu$), 1.53 [s, 9H, $OC(CH_3)_3$], 1.43 [s, 9H, $OC(CH_3)_3$] ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=170.7 (s, O=C–O), 166.3 (s, O=C–O), 149.6 (s, Ar-C), 149.0 (s, Ar-C), 139.9 (d, *C*H=CHCOO^{t}Bu), 136.6 (s, Ar-C), 130.7 (s, Ar-C), 128.5 (d, 2C, Ar-CH), 127.9 (d, Ar-CH), 127.3 (d, 2C, 2 × Ar-CH), 126.1 (s, Ar-C), 119.5 (d, Ar-CH), 114.1 (d, Ar-CH), 109.4 (d, CH=*C*HCOO^{t}Bu), 80.5 [s, O*C*$(CH_3)_3$], 80.3 [s, O*C*$(CH_3)_3$], 70.8 (t, $PhCH_2OAr$), 70.0 (t, Ar-C*H*$_2$OCH$_2$), 66.0 (t, $OCH_2CH_2COO^tBu$), 56.0 (q, Ar-OCH_3), 36.1 (t, $OCH_2CH_2COO^tBu$), 28.2 [q, 3C, $OC(CH_3)_3$], 28.0 [q, 3C, $OC(CH_3)_3$] ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{29}H_{38}NaO_7]^+$=$[M+Na]^+$: 525.2510; found 521.2506.



23n

***Tert*-butyl (2*E*)-3-{5-(benzyloxy)-2-[(3-*tert*-butoxy-3-oxopropoxy)methyl]-4-methoxyphenyl}acrylate (23n):**

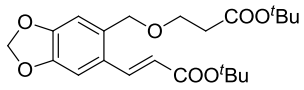
GP-2 was carried out with the 2-bromobenzyl alcohol **21e** (100 mg, 0.31 mmol), tertiarybutyl acrylate (199 mg, 1.55 mmol) and Cs_2CO_3 (202 mg, 0.62 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added $Pd(OAc)_2$ (6.8 mg, 10 mol%) and PPh_3 (16.4 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 90:10 to 75:25) furnished the diester **23n** (140 mg, 90%) as a white solid, recrystallized from dichloromethane/hexane (m. p. 77–79 °C). [TLC control (petroleum ether/ethyl acetate 70:30), R_f(**21e**)=0.44, R_f(**23n**)=0.60, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2975, 2927, 2869, 1727, 1704, 1630, 1600, 1513, 1366, 1278, 1150, 1112, 979, 851 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.77 (d, 1H, *J*=15.8 Hz, C*H*=CHCOO^{t}Bu), 7.43 (d, 2H, *J*=7.2 Hz, Ar-H), 7.37 (d, 1H, *J*=7.2 Hz, Ar-H), 7.35 (d, 1H, *J*=7.2 Hz, Ar-H), 7.30 (t, 1H, *J*=7.2 Hz, Ar-H), 7.11 (s, 1H, Ar-H), 6.95 (s, 1H, Ar-H), 6.08 (d, 1H, *J*=15.8 Hz, Ar-C*H*=CHCOO^{t}Bu), 5.13 (s, 2H, $PhCH_2OAr$), 4.58 (s, 2H, $ArCH_2OCH_2$), 3.90 (s, 3H, Ar-OCH_3), 3.75 (t, 2H, *J*=6.5 Hz, $OCH_2CH_2COO^tBu$), 2.54 (t, 2H, *J*=6.5 Hz, $OCH_2CH_2COO^tBu$), 1.52 [s, 9H, $OC(CH_3)_3$], 1.43 [s, 9H, $OC(CH_3)_3$] ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=170.7 (s, O=C–O), 166.4 (s, O=C–O), 151.2 (s, Ar-C), 147.7 (s, Ar-C), 139.8 (d, *C*H=CHCOO^{t}Bu), 136.7 (s, Ar-C), 131.3 (s, Ar-C), 128.6 (d, 2C, Ar-CH), 128.0 (d, Ar-CH), 127.4 (d, 2C, Ar-CH), 125.6 (s, Ar-C), 119.5 (d, Ar-CH), 112.3 (d, Ar-CH), 111.8 (d, CH=*C*HCOO^{t}Bu), 80.5 [s, O*C*$(CH_3)_3$], 80.3 [s, O*C*$(CH_3)_3$], 71.2 (t, $PhCH_2OAr$), 70.1 (t, Ar-C*H*$_2$$OCH_2$), 66.2 (t, $OCH_2CH_2COO^tBu$), 56.0 (q, Ar-OCH_3), 36.2 (t, $OCH_2CH_2{}^tBu$), 28.2 [q, 3C, OC(*C*$H_3)_3$], 28.1 [q, 3C,OC(*C*$H_3)_3$] ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{29}H_{38}NaO_7]^+$=$[M+Na]^+$: 521.2510; found 521.2500.



23o

***Tert*-butyl (2*E*)-3-{6-[(3-*tert*-butoxy-3-oxopropoxy)methyl]-1,3-benzodioxol-5-yl}acrylate (23o):**

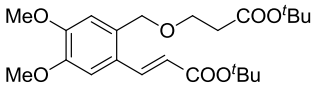
GP-2 was carried out with the 2-bromobenzyl alcohol **21f** (100 mg, 0.43 mmol), tertiarybutyl acrylate (277 mg, 2.16 mmol) and Cs_2CO_3 (282 mg, 0.86 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added $Pd(OAc)_2$ (9.7 mg, 10 mol%) and PPh_3 (23 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 96:4 to 80:20) furnished the diester **23o** (144.4 mg, 87%) as a pale yellow viscous oil. [TLC control (petroleum ether/ethyl acetate 80:20), R_f(**21f**)=0.45, R_f(**23o**)=0.60, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2976, 1728, 1705, 1630, 1602, 1483, 1366, 1293, 1256, 1151, 1039, 849 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.77 (d, 1H, *J*=15.7 Hz, C*H*=CHCOO^{t}Bu), 7.03 (s, 1H, Ar-H), 6.88 (s, 1H, Ar-H), 6.14 (d, 1H, *J*=15.7 Hz, CH=C*H*COO^{t}Bu), 5.96 (s, 2H, O-CH_2-O), 4.54 (s, 2H, Ar-CH_2OCH_2), 3.73 (t, 2H, *J*=6.5 Hz, OC$H_2$$CH_2$COO^{t}Bu), 2.52 (t, 2H, *J*=6.5 Hz, OCH_2CH_2COO^{t}Bu), 1.51 [s, 9H, OC(CH_3)$_3$], 1.43 [s, 9H, OC(CH_3)$_3$] ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=170.7 (s, O=C-O), 166.4 (s, O=C-O), 149.1 (s, Ar-C), 147.6 (s, Ar-C), 139.7 (d, *C*H=CHCOO^{t}Bu), 132.4 (s, Ar-C), 127.2 (s, Ar-C), 119.8 (d, CH=*C*HCOO^{t}Bu), 109.3 (d, Ar-CH), 105.8 (d, Ar-CH), 101.4 (t, O-CH_2-O), 80.6 [s, O*C*(CH_3)$_3$], 80.4 [s, O*C*(CH_3)$_3$], 70.1 (t, Ar-*C*H_2OCH_2), 66.2 (t, O*C*$H_2$$CH_2$COO^{t}Bu), 36.2 (t, O$CH_2$*C*$H_2$COO^{t}Bu), 28.2 [q, 3C, OC(*C*H_3)$_3$], 28.0 [q, 3C, OC(*C*H_3)$_3$] ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{22}H_{30}NaO_7]^+$=$[M+Na]^+$: 429.1884; found 429.1882.



23p

***Tert*-butyl (2*E*)-3-{2-[(3-*tert*-butoxy-3-oxopropoxy)methyl]-4,5-dimethoxyphenyl}acrylate (23p):**

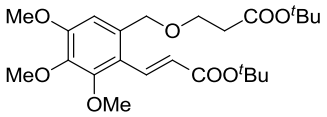
GP-2 was carried out with the 2-bromobenzyl alcohol **21g** (100 mg, 0.40 mmol), tertiarybutyl acrylate (260 mg, 2.02 mmol) and Cs_2CO_3 (264 mg, 0.81 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added $Pd(OAc)_2$ (9.1 mg, 10 mol%) and PPh_3 (21.2 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 80:20) furnished the diester **23p** (122.4 mg, 72%) as a pale brown viscous oil. [TLC control (petroleum ether/ethyl acetate 70:30), R_f(**21g**)=0.40, R_f(**23p**)=0.58, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2976, 2933, 1728, 1704, 1602, 1515, 1366, 1277, 1148, 1110, 849 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.82 (d, 1H, *J*=15.7 Hz, C*H*=CHCOO^{t}Bu), 7.06 (s, 1H, Ar-H), 6.93 (s, 1H, Ar-H), 6.19 (d, 1H, *J*=15.7 Hz, CH=C*H*COO^{t}Bu), 4.59 (s, 2H, Ar-CH_2OCH$_2$), 3.90 (s, 3H, Ar-OCH$_3$), 3.89 (s, 3H, Ar-OCH$_3$), 3.75 (t, 2H, *J*=6.5 Hz, OCH_2CH$_2$COO^{t}Bu), 2.54 (t, 2H, *J*=6.5 Hz, OCH$_2$CH_2COO^{t}Bu), 1.53 [s, 9H, OC(CH$_3$)$_3$], 1.43 [s, 9H, OC(CH$_3$)$_3$] ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=170.8 (s, O=C–O), 166.4 (s, O=C–O), 150.5 (s, Ar-C), 148.5 (s, Ar-C), 139.9 (d, *C*H=CHCOO^{t}Bu), 130.9 (s, Ar-C), 125.7 (s, Ar-C), 119.4 (d, CH=*C*HCOO^{t}Bu), 111.8 (d, Ar-CH), 108.7 (d, Ar-CH), 80.6 [s, O*C*(CH$_3$)$_3$], 80.4 [s, O*C*(CH$_3$)$_3$], 70.1 (t, Ar-*C*H$_2$OCH$_2$), 66.2 (t, O*C*H$_2$CH$_2$COO^{t}Bu), 55.9 (2 × q, 2C, 2 × Ar-OCH$_3$), 36.2 (t, OCH$_2$*C*H$_2$COO^{t}Bu), 28.2 [q, 3C, OC(*C*H$_3$)$_3$], 28.1 [q, 3C, OC(*C*H$_3$)$_3$] ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{23}H_{34}NaO_7]^+$=$[M+Na]^+$: 445.2197; found 445.2191.



23q

***Tert*-butyl (2*E*)-3-{6-[(3-*tert*-butoxy-3-oxopropoxy)methyl]-2,3,4-trimethoxyphenyl}acrylate (23q):**

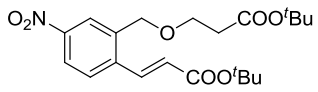
GP-2 was carried out with the 2-bromobenzyl alcohol **21h** (100 mg, 0.36 mmol), tertiarybutyl acrylate (231 mg, 1.80 mmol) and Cs_2CO_3 (235 mg, 0.72 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added $Pd(OAc)_2$ (8.1 mg, 10 mol%) and PPh_3 (19 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 96:4 to 80:20) furnished the diester **23q** (129.4 mg, 79%) as a pale yellow viscous oil. [TLC control (petroleum ether/ethyl acetate 80:20), R_f(**21h**)=0.45, R_f(**23q**)=0.60, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2974, 2921, 2851, 1728, 1705, 1591, 1458, 1366, 1330, 1304, 1243, 1152, 1128, 986, 848 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.67 (d, 1H, *J*=16.2 Hz, C*H*=CHCOO^{t}Bu), 6.83 (s, 1H, Ar-H), 6.40 (d, 1H, *J*=16.2 Hz, CH=C*H*COO^{t}Bu), 4.54 (s, 2H, Ar-CH_2OCH$_2$), 3.88 (s, 3H, Ar-OCH$_3$), 3.85 (s, 6H, 2 × Ar-OCH$_3$), 3.77 (t, 2H, *J*=6.5 Hz, OCH_2CH$_2$COO^{t}Bu), 2.56 (t, 2H, *J*=6.5 Hz, OCH$_2$CH_2COO^{t}Bu), 1.52 [s, 9H, OC(CH$_3$)$_3$], 1.43 [s, 9H, OC(CH$_3$)$_3$] ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=170.8 (s, O=C–O), 167.1 (s, O=C–O), 154.0 (s, Ar-C), 153.4 (s, Ar-C), 141.7 (s, Ar-C), 136.5 (d, *C*H=CHCOO^{t}Bu), 133.6 (s, Ar-C), 123.4 (d, CH=*C*HCOO^{t}Bu), 120.4 (s, Ar-C), 108.1 (d, Ar-CH), 80.6 [s, O*C*(CH$_3$)$_3$], 80.1 [s, O*C*(CH$_3$)$_3$], 71.0 (t, Ar-*C*H$_2$OCH$_2$), 66.3 (t, O*C*H$_2$CH$_2$COO^{t}Bu), 60.8 (q, Ar-OCH$_3$), 60.7 (q, Ar-OCH$_3$), 55.9 (q, Ar-OCH$_3$), 36.2 (t, OCH$_2$*C*H$_2$COO^{t}Bu), 28.2 [q, 3C, OC(*C*H$_3$)$_3$], 28.1 [q, 3C, OC(*C*H$_3$)$_3$] ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{24}H_{36}NaO_8]^+$=$[M+Na]^+$: 475.2302; found 475.2285.



23r

***Tert*-butyl (2*E*)-3-{2-[(3-*tert*-butoxy-3-oxopropoxy)methyl]-4-nitrophenyl}acrylate (23r):**

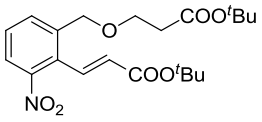
GP-2 was carried out with the 2-bromobenzyl alcohol **21i** (100 mg, 0.43 mmol), tertiarybutyl acrylate (276 mg, 2.15 mmol) and Cs_2CO_3 (281 mg, 0.86 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added $Pd(OAc)_2$ (9.6 mg, 10 mol%) and PPh_3 (22.6 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 96:4 to 80:20) furnished the diester **23r** (129.8 mg, 74%) as a pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 80:20), R_f(**21i**)=0.30, R_f(**23r**)=0.65, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2978, 1714, 1524, 1367, 1347, 1324, 1256, 1154, 1070, 980, 846 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=8.30 (d, 1H, *J*=2.3 Hz, Ar-H), 8.12 (dd, 1H, *J*=8.5 and 2.3 Hz, Ar-H), 7.77 (d, 1H, *J*=15.8 Hz, C*H*=CHCOO^{t}Bu), 7.66 (d, 1H, *J*=8.5 Hz, Ar-H), 6.38 (d, 1H, *J*=15.8 Hz, CH=C*H*COO^{t}Bu), 4.67 (s, 2H, Ar-CH_2OCH$_2$), 3.82 (t, 2H, *J*=6.3 Hz, OCH_2CH$_2$COO^{t}Bu), 2.57 (t, 2H, *J*=6.3 Hz, OCH$_2$CH_2COO^{t}Bu), 1.53 [s, 9H, OC(CH$_3$)$_3$], 1.44 [s, 9H, OC(CH$_3$)$_3$] ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=170.5 (s, O=C-O), 165.1 (s, O=C-O), 148.2 (s, Ar-C), 139.3 (s, Ar-C), 138.8 (s, Ar-C), 137.8 (d, *C*H=CHCOO^{t}Bu), 127.5 (d, Ar-CH), 125.9 (d, Ar-CH), 123.4 (d, CH=*C*HCOO^{t}Bu), 122.8 (d, Ar-CH), 81.3 [s, O*C*(CH$_3$)$_3$], 80.8 [s, O*C*(CH$_3$)$_3$], 69.7 (t, Ar-*C*H$_2$OCH$_2$), 66.8 (t, OCH$_2$CH$_2$COO^{t}Bu), 36.1 (t, OCH$_2$*C*H$_2$COO^{t}Bu), 28.1 [q, 3C, OC(*C*H$_3$)$_3$], 28.0 [q, 3C, OC(*C*H$_3$)$_3$] ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{21}H_{29}NNaO_7]^+$=$[M+Na]^+$: 430.1836; found 430.1827.



23s

***Tert*-butyl (2*E*)-3-{2-[(3-*tert*-butoxy-3-oxopropoxy)methyl]-6-nitrophenyl}acrylate (23s):**

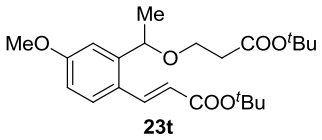
GP-2 was carried out with the 2-bromobenzyl alcohol **21j** (100 mg, 0.43 mmol), tertiarybutyl acrylate (276 mg, 2.15 mmol) and Cs_2CO_3 (281 mg, 0.86 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added $Pd(OAc)_2$ (9.6 mg, 10 mol%) and PPh_3 (22.6 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 75:25) furnished the diester **23s** (132.1 mg, 75%) as a colorless viscous liquid. [TLC control (petroleum ether/ethyl acetate 80:20), R_f(**21j**)=0.25, R_f(**23s**)=0.62, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2978, 1712, 1645, 1529, 1366, 1317, 1148, 1110, 976, 844, 745 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.85 (d, 1H, *J*=7.9 Hz, Ar-H), 7.76 (d, 1H, *J*=16.2 Hz, C*H*=CHCOO^{t}Bu), 7.75 (d, 1H, *J*=7.9 Hz, Ar-H), 7.45 (t, 1H, *J*=7.9 Hz, Ar-H), 5.90 (d, 1H, *J*=16.2 Hz, CH=C*H*COO^{t}Bu), 4.50 (s, 2H, Ar-CH_2OCH$_2$), 3.74 (t, 2H, *J*=6.4 Hz, OCH_2CH$_2$COO^{t}Bu), 2.53 (t, 2H, *J*=6.4 Hz, OCH$_2$CH_2COO^{t}Bu), 1.51 [s, 9H, OC(CH$_3$)$_3$], 1.43 [s, 9H, OC(CH$_3$)$_3$] ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=170.6 (s, O=C–O), 164.6 (s, O=C–O), 148.8 (s, Ar-C), 138.8 (s, Ar-C), 137.3 (d, *C*H=CHCOO^{t}Bu), 132.8 (d, Ar-CH), 129.9 (s, Ar-C), 128.7 (d, Ar-CH), 127.0 (d, CH=*C*HCOO^{t}Bu), 123.4 (d, Ar-CH), 81.2 [s, O*C*(CH$_3$)$_3$], 80.7 [s, O*C*(CH$_3$)$_3$], 70.0 (t, Ar-*C*H$_2$OCH$_2$), 66.6 (t, OCH$_2$CH$_2$COO^{t}Bu), 36.1 (t, OCH$_2$*C*H$_2$COO^{t}Bu), 28.1 [q, 3C, OC(*C*H$_3$)$_3$], 28.0 [q, 3C, OC(*C*H$_3$)$_3$] ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{21}H_{29}NNaO_7]^+$=$[M+Na]^+$: 430.1836; found 430.1851.



23t

***Tert*-butyl (2*E*)-3-{2-[1-(3-*tert*-butoxy-3-oxopropoxy)ethyl]-4-methoxyphenyl}acrylate (23t):**

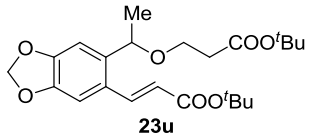
GP-2 was carried out with the 2-bromobenzyl alcohol **21l** (100 mg, 0.43 mmol), tertiarybutyl acrylate (277 mg, 2.16 mmol) and Cs_2CO_3 (282 mg, 0.87 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added $Pd(OAc)_2$ (9.7 mg, 10 mol%) and PPh_3 (22.7 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 98:2 to 80:20) furnished the diester **23t** (129.8 mg, 74%) as a pale pink viscous liquid. [TLC control (petroleum ether/ethyl acetate 80:20), R_f(**21l**)=0.45, R_f(**23t**)=0.66, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2976, 2932, 1729, 1704, 1629, 1602, 1492, 1366, 1291, 1250, 1143, 1104, 979, 849 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.86 (d, 1H, *J*=15.7 Hz, C*H*=CHCOO^{t}Bu), 7.49 (d, 1H, *J*=8.7 Hz, Ar-H), 7.03 (d, 1H, *J*=2.8 Hz, Ar-H), 6.78 (dd, 1H, *J*=8.7 and 2.8 Hz, Ar-H), 6.17 (d, 1H, *J*=15.7 Hz, CH=C*H*COO^{t}Bu), 4.79 (q, 1H, *J*=6.5 Hz, Ar-C*H*CH_3), 3.83 (s, 3H, Ar-OCH_3), 3.56 (ddd, 1H, *J*=12.9, 9.3 and 6.5 Hz, OC$H_{2a}$$CH_2$COO^{t}Bu), 3.53 (ddd, 1H, *J*=12.9, 9.3 and 6.5 Hz, OC$H_{2b}$$CH_2$COO^{t}Bu), 2.48 (t, 2H, *J*=6.5 Hz, OCH_2CH_2COO^{t}Bu), 1.52 [s, 9H, $OC(CH_3)_3$], 1.43 [s, 9H, $OC(CH_3)_3$], 1.37 (d, 3H, *J*=6.5 Hz, Ar-CHCH_3) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=170.8 (s, O=C–O), 166.5 (s, O=C–O), 161.4 (s, Ar-C), 145.1 (s, Ar-C), 139.6 (d, *C*H=CHCOO^{t}Bu), 128.1 (d, Ar-CH), 124.7 (s, Ar-C), 119.5 (d, CH=*C*HCOO^{t}Bu), 113.6 (d, Ar-CH), 110.6 (d, Ar-CH), 80.5 [s, O*C*$(CH_3)_3$], 80.3 [s, O*C*$(CH_3)_3$], 74.5 (d, Ar-*C*HCH_3), 64.7 (t, O*C*$H_2$$CH_2$COO^{t}Bu), 55.3 (q, Ar-$OCH_3$), 36.4 (t, OCH_2*C*H_2COO^{t}Bu), 28.2 [q, 3C, $OC(CH_3)_3$], 28.1 [q, 3C, $OC(CH_3)_3$], 23.9 (q, Ar-CH*C*H_3) ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{23}H_{34}NaO_6]^+$=$[M+Na]^+$: 429.2248; found 429.2256.



23u

***Tert*-Butyl (2*E*)-3-{6-[1-(3-*tert*-butoxy-3-oxopropoxy)ethyl]-1,3-benzodioxol-5-yl}acrylate (23u):**

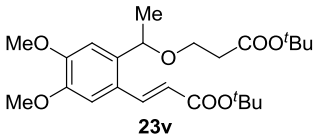
GP-2 was carried out with the 2-bromobenzyl alcohol **21m** (100 mg, 0.41 mmol), tertiarybutyl acrylate (261.2 mg, 2.04 mmol) and Cs_2CO_3 (266 mg, 0.82 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added $Pd(OAc)_2$ (9.1 mg, 10 mol%) and PPh_3 (21.4 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (Petroleum ether/ethyl acetate, 98:2 to 85:15) furnished the diester **23u** (145.9 mg, 85%) as a pale yellow viscous oil. [TLC control (petroleum ether/ethyl acetate 80:20), R_f(**1l**)=0.47, R_f(**3dl**)=0.65, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2976, 1730, 1707, 1628, 1617, 1482, 1367, 1288, 1253, 1153, 1104, 1040, 849 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.83 (d, 1H, *J*=15.6 Hz, C*H*=CHCOO^{t}Bu), 6.98 (s, 1H, Ar-H), 6.96 (s, 1H, Ar-H), 6.13 (d, 1H, *J*=15.6 Hz, CH=C*H*COO^{t}Bu), 5.97 (d, 1H, *J*=1.2 Hz, O-CH_{2A}-O), 5.95 (d, 1H, *J*=1.2 Hz, O-CH_{2B}-O), 4.77 (q, 1H, *J*=6.4 Hz, Ar-C*H*CH_3), 3.53 (ddd, 1H, *J*=12.0, 9.3 and 6.5 Hz, OC$H_{2a}$$CH_2$COO^{t}Bu), 3.50 (ddd, 1H, *J*=12.0, 9.3 and 6.5 Hz, OC$H_{2b}$$CH_2$COO^{t}Bu), 2.46 (t, 2H, *J*=6.5 Hz, OCH_2CH_2COO^{t}Bu), 1.52 [s, 9H, OC$(CH_3)_3$], 1.44 [s, 9H, OC$(CH_3)_3$], 1.33 (d, 3H, *J*=6.4 Hz, Ar-CHCH_3) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=170.8 (s, O=C–O), 166.4 (s, O=C–O), 149.7 (s, Ar-C), 147.1 (s, Ar-C), 139.4 (d, *C*H=CHCOO^{t}Bu), 138.8 (s, Ar-C), 125.9 (s, Ar-C), 120.0 (d, Ar-CH), 120.1 (d, CH=*C*HCOO^{t}Bu), 106.0 (d, Ar-CH), 105.6 (d, Ar-CH), 101.4 (t, O-CH_2-O), 80.5 [s, O*C*$(CH_3)_3$], 80.4 [s, O*C*$(CH_3)_3$], 74.0 (d, Ar-*C*HCH_3), 64.6 (t, O*C*H_2CH_2COO^{t}Bu), 36.5 (t, OCH_2*C*H_2COO^{t}Bu), 28.2 [q, 3C, OC(*C*$H_3)_3$], 28.1 [q, 3C, OC(*C*$H_3)_3$], 24.0 (d, Ar-CH*C*H_3) ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{23}H_{32}NaO_7]^+$=$[M+Na]^+$: 443.2040; found 443.2042.



23v

***Tert*-Butyl (2*E*)-3-{2-[1-(3-*tert*-butoxy-3-oxopropoxy)ethyl]-4,5-dimethoxyphenyl}acrylate (23v):**

GP-2 was carried out with the 2-bromobenzyl alcohol **21o** (100 mg, 0.38 mmol), tertiarybutyl acrylate (245 mg, 1.91 mmol) and Cs_2CO_3 (250 mg, 0.76 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added $Pd(OAc)_2$ (8.6 mg, 10 mol%) and PPh_3 (20.1 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 80:20) furnished the diester **23v** (112.3 mg, 67%) as a colorless semi-solid. [TLC control (petroleum ether/ethyl acetate 70:30), R_f(**21o**)=0.45, R_f(**23v**)=0.60, UV detection].

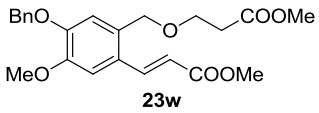
IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2976, 2932, 1729, 1705, 1601, 1511, 1367, 1287, 1267, 1152, 1105, 847 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.88 (d, 1H, *J*=15.7 Hz, C*H*=CHCOO^{t}Bu), 7.02 (s, 1H, Ar-H), 7.00 (s, 1H, Ar-H), 6.18 (d, 1H, *J*=15.7 Hz, CH=C*H*COO^{t}Bu), 4.81 [q, 1H, *J*=6.4 Hz, Ar-C*H*(CH_3)OCH_2], 3.92 (s, 3H, Ar-OCH_3), 3.88 (s, 3H, Ar-OCH_3), 3.55 (ddd, 1H, *J*=13.3, 9.3 and 6.8 Hz, OC$H_{2a}$$CH_2$COO^{t}Bu), 3.55 (ddd, 1H, *J*=13.3, 9.3 and 6.8 Hz, OC$H_{2b}$$CH_2$COO^{t}Bu), 2.47 (t, 2H, *J*=6.8 Hz, OCH_2CH_2COO^{t}Bu), 1.53 [s, 9H, OC(CH_3)$_3$], 1.43 [s, 9H, OC(CH_3)$_3$], 1.37 [d, 3H, *J*=6.4 Hz, Ar-CH(CH_3)OCH_2] ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=170.8 (s, O=C-O), 166.5 (s, O=C-O), 151.2 (s, Ar-C), 148.1 (s, Ar-C), 139.5 (d, *C*H=CHCOO^{t}Bu), 137.0 (s, Ar-C), 124.4 (s, Ar-C), 119.5 (d, CH=*C*HCOO^{t}Bu), 108.5 (d, Ar-CH), 108.4 (d, Ar-CH), 80.5 [s, 2C, 2 × O*C*(CH_3)$_3$], 74.0 [d, Ar-*C*H(CH_3)OCH_2], 64.5 (t, O*C*$H_2$$CH_2$COO^{t}Bu), 56.0

(q, Ar-OCH_3), 55.9 (q, Ar-OCH_3), 36.4 (t, $OCH_2CH_2COO^tBu$), 28.2 [q, 3C, $OC(CH_3)_3$], 28.1 [q, 3C, $OC(CH_3)_3$], 24.2 [q, Ar-$CH(CH_3)OCH_2$] ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{24}H_{36}NaO_7]^+=[M+Na]^+$: 459.2353; found 459.2324.



23w

Methyl (2*E*)-3-{4-(benzyloxy)-5-methoxy-2-[(3-methoxy-3-oxopropoxy)methyl]phenyl}acrylate (23w):

GP-2 was carried out with the 2-bromobenzyl alcohol **21d** (100 mg, 0.31 mmol), methyl acrylate (134 mg, 1.55 mmol) and Cs_2CO_3 (202 mg, 0.62 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added $Pd(OAc)_2$ (6.8 mg, 10 mol%) and PPh_3 (16.4 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 85:15 to 75:25) furnished the diester **23w** (34 mg, 26%) as a pale yellow viscous liquid. [TLC control (benzene/ethyl acetate 80:20), R_f(**21d**)=0.50, R_f(**23w**)=0.30, UV detection].

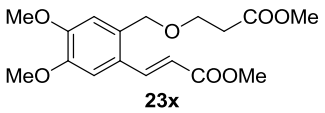
IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2951, 2927, 2870, 1737, 1716, 1631, 1601, 1514, 1454, 1384, 1276, 1170, 1111, 1026, 859, 739, 699 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.89 (d, 1H, *J*=15.8 Hz, C*H*=CHCOOMe), 7.43 (d, 2H, *J*=7.2 Hz, Ar-H), 7.36 (dd, 2H, *J*=7.2 and 7.2 Hz, Ar-H), 7.29 (t, 1H, *J*=7.2 Hz, Ar-H), 7.09 (s, 1H, Ar-H), 6.93 (s, 1H, Ar-H), 6.27 (d, 1H, *J*=15.8 Hz, C*H*=CHCOOMe), 5.18 (s, 2H, $PhCH_2OAr$), 4.55 (s, 2H, $ArCH_2OCH_2$), 3.89 (s, 3H, Ar-OCH_3), 3.79 (s, 3H, O=C-OCH_3), 3.69 (t, 2H, 6.4 Hz, OCH_2CH_2COOMe), 3.67 (s, 3H, O=C-OCH_3), 2.57 (t, 2H, *J*=6.4 Hz, OCH_2CH_2COOMe) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=171.9 (s, O=C–O), 167.5 (s, O=C–O), 149.8 (s, Ar-C), 149.2 (s, Ar-C), 141.2 (d, *C*H=CHCOOMe), 136.5 (s, Ar-C), 130.7 (s, Ar-C), 128.6 (d, 2C, Ar-CH), 128.0 (d, Ar-CH), 127.3 (d, 2C, Ar-CH), 126.0 (s, Ar-C), 117.3 (d, Ar-CH), 114.3 (d, Ar-CH), 109.5 (d, CH=*C*HCOOMe), 70.8 (t,

$PhCH_2OAr$), 70.2 (t, Ar-C*H*$_2$OCH$_2$), 65.6 (t, OC*H*$_2$CH$_2$COOMe), 56.1 (q, Ar-OCH_3), 51.7 (q, O=C-OCH_3), 51.6 (q, O=C-OCH_3), 34.8 (t, OCH_2CH_2COOMe) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{23}H_{25}O_6]^+$=[(M+H)–H_2O]$^+$: 397.1645; found 397.1664.



23x

Methyl (2*E*)-3-{4,5-dimethoxy-2-[(3-methoxy-3-oxopropoxy)methyl]phenyl}acrylate (23x):

GP-2 was carried out with the 2-bromobenzyl alcohol **21g** (100 mg, 0.40 mmol), methyl acrylate (174 mg, 2.02 mmol) and Cs_2CO_3 (264 mg, 0.81 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added $Pd(OAc)_2$ (9.1 mg, 10 mol%) and PPh_3 (21.2 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 85:15 to 70:30) furnished the diester **23x** (44 mg, 32%) as a yellow viscous oil. [TLC control (petroleum ether/ethyl acetate 30:20), R_f(**21g**)=0.40, R_f(**23x**)=0.35, UV detection].

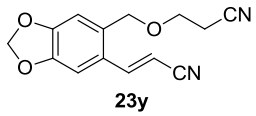
IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2951, 2868, 1736, 1714, 1631, 1601, 1516, 1438, 1271, 1170, 1111, 1029, 860 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.91 (d, 1H, *J*=15.8 Hz, C*H*=CHCOOMe), 7.07 (s, 1H, Ar-H), 6.91 (s, 1H, Ar-H), 6.27 (d, 1H, *J*=15.8 Hz, CH=C*H*COOMe), 4.60 (s, 2H, Ar-C*H*$_2$OCH$_2$), 3.91 (s, 3H, Ar-OCH_3), 3.89 (s, 3H, Ar-OCH_3), 3.80 (s, 3H, O=C-OCH_3), 3.78 (t, 2H, *J*=6.4 Hz, OC*H*$_2$CH$_2$COOMe), 3.68 (s, 3H, O=C-OCH_3), 2.63 (t, 2H, *J*=6.4 Hz, OCH_2C*H*$_2$COOMe) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=171.9 (s, O=C-O), 167.5 (s, O=C-O), 150.7 (s, Ar-C), 148.7 (s, Ar-C), 141.2 (d, *C*H=CHCOOMe), 130.9 (s, Ar-C), 125.7 (s, Ar-C), 117.3 (d, CH=*C*HCOOMe), 112.2 (d, Ar-CH), 109.0 (d, Ar-CH), 70.3 (t,

Ar-*C*H_2OCH_2), 65.8 (t, O*C*$H_2$$CH_2COOCH_3$), 56.0 (q, 2C, 2 × Ar-O$CH_3$), 51.7 (q, O=C-O*C*$H_3$), 51.6 (q, O=C-O*C*$H_3$), 34.9 (t, O$CH_2$*C*$H_2$COOMe) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{17}H_{22}NaO_7]^+$=$[M+Na]^+$: 361.1258; found 361.1271.



23y

(2*E*)-3-{6-[(2-Cyanoethoxy)methyl]-1,3-benzodioxol-5-yl}acrylonitrile (23y):

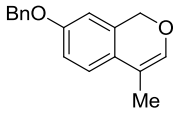
GP-2 was carried out with the 2-bromobenzyl alcohol **21f** (100 mg, 0.43 mmol), acrylonitrile (115 mg, 2.16 mmol) and Cs_2CO_3 (282 mg, 0.86 mmol) in toluene (2 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was heated in an oil bath at 50 °C for 48 h. To the cooled reaction mixture at room temperature, were added $Pd(OAc)_2$ (9.7 mg, 10 mol%) and PPh_3 (23 mg, 20 mol%). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ ethyl acetate 85:15 to 65:35) furnished the diester **23y** (28.2 mg, 25%) as a yellow semi-solid. [TLC control (petroleum ether/ethyl acetate 60:40), R_f(**21f**)=0.55, R_f(**23y**)=0.30, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2907, 2215, 1600, 1504, 1484, 1273, 1254, 1100, 1038, 930 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.62 (d, 1H, *J*=16.4 Hz, C*H*=CHCN), 6.97 (s, 1H, Ar-H), 6.86 (s, 1H, Ar-H), 6.02 (s, 2H, O-CH_2-O), 5.68 (d, 1H, *J*=16.4 Hz, CH=C*H*CN), 4.55 (s, 2H, Ar-C*H*$_2$OCH_2), 3.68 (t, 2H, *J*=6.4 Hz, OC*H*$_2$$CH_2$CN), 2.62 (t, 2H, *J*=6.4 Hz, OCH_2C*H*$_2$CN) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=150.1 (s, Ar-C), 148.4 (s, Ar-C), 146.7 (d, *C*H=CHCN), 131.2 (s, Ar-C), 126.9 (s, Ar-C), 118.3 (s, $CH_2$$CH_2$*C*N), 117.4 (s, CH=CH*C*N), 110.1 (d, Ar-CH), 105.3 (d, Ar-CH), 102.0 (t, O-CH_2-O), 96.1 (d, *C*H=CHCN), 70.7 (t, Ar-*C*H_2OCH_2), 64.8 (t, O*C*$H_2$$CH_2$CN), 18.9 (t, O$CH_2$*C*$H_2$CN) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{14}H_{12}N_2O_3]^+$=$[M]^+$: 256.0842; found 256.0849.



28a'

7-(Benzyloxy)-4-methyl-1*H*-isochromene (28a′):

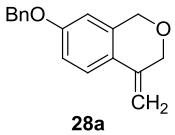
GP-3 was carried out with the 2-bromobenzyl alcohol **21b** (100 mg, 0.34 mmol), allyl bromide (82.6 mg, 0.68 mmol) and NaH (32.8 mg, 1.36 mmol) in DMF (3 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was stirred at the same temperature for 1 h. To the resultant reaction mixture at room temperature, were added $Pd(OAc)_2$ (7.6 mg, 10 mol%), PPh_3 (18.0 mg, 20 mol%) and triethylbenzylammonium chloride (78 mg, 0.34 mmol). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 99:1 to 98:2) furnished the isochromene **28a′** (24.1 mg, 28%) as a pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 90:10), R_f(**21b**)=0.15, R_f(**28a′**)=0.74, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2963, 2859, 1639, 1608, 1572, 1498, 1454, 1381, 1301, 1281, 1246, 1168, 1129, 1081, 1022, 926, 839, 807, 734, 695 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.46–7.26 (m, 5H, Ar-H), 7.03 (d, 1H, *J*=8.3 Hz, Ar-H), 6.88 (dd, 1H, *J*=8.3 and 2.4 Hz, Ar-H), 6.68 (d, 1H, *J*=2.4 Hz, Ar-H), 6.39 [d, 1H, *J*=1.5 Hz, ArC(Me)=C*H*OCH_2], 5.06 (s, 2H, $PhCH_2O$), 4.95 (s, 2H, $ArCH_2O$), 1.89 (d, 3H, *J*=1.5 Hz, CH=CCH_3) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=157.8 (s, Ar-C), 140.4 (d, *C*H=CCH_3), 136.9 (s, Ar-C), 130.5 (s, Ar-C), 128.6 (d, 2C, Ar-CH), 127.9 (d, Ar-CH), 127.4 (d, 2C, Ar-CH), 125.6 (s, CH=*C*CH_3), 121.6 (d, Ar-CH), 113.6 (d, Ar-CH), 111.2 (s, Ar-C), 111.1 (d, Ar-CH), 70.1 (t, $PhCH_2O$), 68.2 (t, $ArCH_2O$), 13.1 (q, CH=C*C*H_3) ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{17}H_{17}O_2]^+$=$[M+H]^+$: 253.1223; found 253.1225.



28a

7-(Benzyloxy)-4-methylene-3,4-dihydro-1*H*-isochromene (28a):

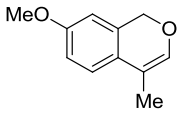
Further elution of the column (petroleum ether/ethyl acetate, 98:2 to 95:5) yielded the isochromene **28a** (53.3 mg, 62%) as a pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 90:10), R_f(**21b**)=0.15, R_f(**28a**)=0.65, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2954, 2825, 1634, 1606, 1571, 1496, 1453, 1310, 1276, 1231, 1168, 1110, 1085, 1023, 925, 880, 737, 696 cm^{-1}.

^{1}H-NMR (CDCl$_3$, 400 MHz): δ=7.61 (d, 1H, *J*=8.8 Hz, Ar-H), 7.46–7.27 (m, 5H, Ar-H), 6.87 (dd, 1H, *J*=8.8 and 2.6 Hz, Ar-H), 6.61 (d, 1H, *J*=2.6 Hz, Ar-H), 5.46 (s, 1H, ArC=CH_{2A}), 5.06 (s, 2H, PhCH_2O), 4.89 (s, 1H,ArC=CH_{2B}), 4.76 (s, 2H, ArCH_2OCH_2), 4.42 (s, 2H, ArCH_2OCH_2) ppm.

^{13}C-NMR (CDCl$_3$, 100 MHz): δ=158.6 (s, Ar-C), 137.9 (s, Ar-C), 136.7 (s, Ar-C), 136.0 (s, Ar-C), 128.6 (d, 2C, Ar-CH), 128.0 (d, Ar-CH), 127.4 (d, 2C, Ar-CH), 125.0 (d, Ar-CH), 124.2 (s, Ar*C*=CH$_2$), 114.4 (d, Ar-CH), 109.9 (d, Ar-CH), 104.7 (t, ArC=*C*H$_2$), 71.1 (t, PhCH$_2$O), 70.3 (t, Ar*C*H$_2$OCH$_2$), 69.1 (t, ArCH$_2$O*C*H$_2$) ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{17}H_{17}O_2]^+$=$[M+H]^+$: 253.1223; found 253.1224.



28b'

7-(Methoxy)-4-methyl-1*H*-isochromene (28b′):

GP-3 was carried out with the 2-bromobenzyl alcohol **21c** (100 mg, 0.46 mmol), allyl bromide (111.5 mg, 0.92 mmol) and NaH (44.2 mg, 1.84 mmol) in DMF (3 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was stirred at the same temperature for 1 h. To the resultant reaction mixture at room temperature, were added Pd(OAc)$_2$ (10.3 mg, 10 mol%), PPh$_3$ (24.2

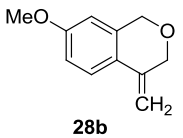
mg, 20 mol%) and triethylbenzylammonium chloride (105 mg, 0.46 mmol). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 99:1 to 98:2) furnished the isochromene **28b′** (21.2 mg, 26%) as a colorless viscous liquid. [TLC control (petroleum ether/ethyl acetate 90:10), R_f(**21c**)=0.14, R_f(**28b′**)=0.70, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2961, 2935, 2834, 1639, 1610, 1573, 1501, 1464, 1431, 1307, 1282, 1250, 1163, 1130, 1074, 1034, 946, 917, 838, 811, 781 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.02 (d, 1H, *J*=8.8 Hz, Ar-H), 6.80 (dd, 1H, *J*=8.8 and 2.9 Hz, Ar-H), 6.59 (d, 1H, *J*=2.9 Hz, Ar-H), 6.38 [q, 1H, *J*=1.5 Hz, ArC(Me)=C*H*OCH$_2$], 4.95 (s, 2H, ArCH$_2$O), 3.79 (s, 3H, Ar-OCH$_3$), 1.89 (d, 3H, *J*=1.5 Hz, CH=CC*H*$_3$) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=158.7 (s, Ar-C), 140.3 (d, *C*H=CCH$_3$), 130.5 (s, Ar-C), 125.4 (s, Ar-C), 121.6 (d, Ar-CH), 112.6 (d, Ar-CH), 111.2 (s, CH=*C*CH$_3$), 110.1 (d, Ar-CH), 68.2 (t, ArCH$_2$O), 55.3 (q, Ar-OCH$_3$), 13.1 (q, CH=C*C*H$_3$) ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{11}H_{13}O_2]^+$=$[M+H]^+$: 177.0910; found 177.0905.



28b

7-(Methoxy)-4-methylene-3,4-dihydro-1*H*-isochromene (28b):

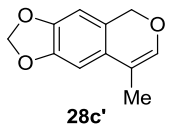
Further elution of the column (petroleum ether/ethyl acetate, 98:2 to 93:7) yielded the isochromene **28b** (49.3 mg, 61%) as a pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 90:10), R_f(**21c**)=0.14, R_f(**28b**)=0.60, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2955, 2833, 1632, 1605, 1497, 1452, 1310, 1278, 1269, 1234, 1110, 1086, 1031, 961, 881, 819, 768 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.61 (d, 1H, *J*=8.8 Hz, Ar-H), 6.80 (dd, 1H, *J*=8.8 and 2.9 Hz, Ar-H), 6.53 (d, 1H, *J*=2.9 Hz, Ar-H), 5.46 (s, 1H, $ArC=CH_{2A}$), 4.89 (s, 1H, $ArC=CH_{2B}$), 4.77 (s, 2H, $ArCH_2OCH_2$), 4.41 (s, 2H, $ArCH_2OCH_2$), 3.80 (s, 3H, $Ar\text{-}OCH_3$) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=159.4 (s, Ar-C), 137.9 (s, Ar-C), 136.0 (s, Ar-C), 125.0 (d, Ar-CH), 123.9 (s, $ArC=CH_2$), 113.6 (d, Ar-CH), 108.7 (d, Ar-CH), 104.6 (t, $ArC=CH_2$), 71.1 (t, $ArCH_2OCH_2$), 69.1 (t, $ArCH_2OCH_2$), 55.3 (q, $Ar\text{-}OCH_3$) ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{11}H_{13}O_2]^+=[M+H]^+$: 177.0910; found 177.0903.



28c'

8-Methyl-5*H*-[1,3]dioxolo[4,5-*g*]isochromene (28c′):

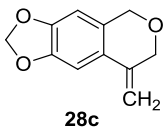
GP-3 was carried out with the 2-bromobenzyl alcohol **21f** (100 mg, 0.43 mmol), allyl bromide (104.8 mg, 0.86 mmol) and NaH (42 mg, 1.73 mmol) in DMF (3 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was stirred at the same temperature for 1 h. To the resultant reaction mixture at room temperature, were added $Pd(OAc)_2$ (9.7 mg, 10 mol%), PPh_3 (22.7 mg, 20 mol%) and triethylbenzylammonium chloride (99 mg, 0.43 mmol). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 99:1 to 98:2) furnished the isochromene **28c′** (10.2 mg, 12%) as a colorless viscous liquid. [TLC control (petroleum ether/ethyl acetate 90:10), R_f(**21f**)=0.15, R_f(**28c′**)=0.71, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2962, 2892, 1644, 1502, 1482, 1444, 1379, 1272, 1239, 1172, 1138, 1108, 1037, 1026, 980, 933, 856, 840, 790 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=6.64 (s, 1H, Ar-H), 6.55 (s, 1H, Ar-H), 6.40 [q, 1H, *J*=1.5 Hz, ArC(Me)=C*H*OCH_2], 5.92 (s, 2H, OCH_2O), 4.87 (s, 2H, $ArCH_2O$), 1.88 (d, 3H, *J*=1.5 Hz, CH=CCH_3) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=147.4 (s, Ar-C), 145.9 (s, Ar-C), 140.9 (d, *C*H=CCH_3), 127.0 (s, Ar-C), 122.2 (s, Ar-C), 111.5 (s, CH=*C*CH_3), 105.1 (d, Ar-CH), 101.9 (d, Ar-CH), 100.9 (t, OCH_2O), 68.2 (t, $ArCH_2O$), 13.4 (q, CH=C*C*H_3) ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{11}H_{11}O_3]^+$=$[M+H]^+$: 191.0703; found 191.0694.



28c

8-Methylene-7,8-dihydro-5*H*-[1,3]dioxolo[4,5-*g*]isochromene (28c):

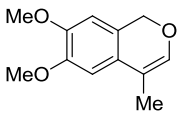
Further elution of the column (petroleum ether/ethyl acetate, 98:2 to 94:6) yielded the isochromene **28c** (64.3 mg, 78%) as a colorless viscous liquid. [TLC control (petroleum ether/ethyl acetate 90:10), R_f(**21f**)=0.15, R_f(**28c**)=0.60, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2893, 2827, 1622, 1502, 1479, 1442, 1357, 1341, 1289, 1238, 1217, 1176, 1099, 1035, 936, 921, 879, 859, 835, 779 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.10 (s, 1H, Ar-H), 6.46 (s, 1H, Ar-H), 5.93 (s, 2H, OCH_2O), 5.38 (s, 1H, ArC=CH_{2A}), 4.88 (s, 1H, ArC=CH_{2B}), 4.69 (s, 2H, Ar*C*H_2OCH_2), 4.38 (s, 2H, $ArCH_2OC$*H*$_2$) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=147.7 (s, Ar-C), 147.0 (s, Ar-C), 138.1 (s, Ar-C), 128.8 (s, Ar-C), 124.9 (s, Ar*C*=CH_2), 105.1 (t, ArC=*C*H_2), 104.4 (d, Ar-CH), 103.2 (d, Ar-CH), 101.0 (t, OCH_2O), 70.7 (t, Ar*C*H_2OCH_2), 68.9 (t, $ArCH_2OCH_2$) ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{11}H_{11}O_3]^+$=$[M+H]^+$: 191.0703; found 191.0697.



28d'

6,7-Dimethoxy-4-methyl-1*H*-isochromene (28d′):

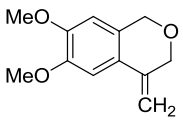
GP-3 was carried out with the 2-bromobenzyl alcohol **21g** (100 mg, 0.40 mmol) with allyl bromide (98 mg, 0.81 mmol) and NaH (39 mg, 1.62 mmol) in DMF (3 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was stirred at the same temperature for 1 h. To the resultant reaction mixture at room temperature, were added $Pd(OAc)_2$ (9.1 mg, 10 mol%), PPh_3 (21.3 mg, 20 mol%) and triethylbenzylammonium chloride (92.2 mg, 0.40 mmol). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 97:3 to 94:6) furnished the isochromene **28d′** (20.0 mg, 24%) as a pale yellow semi-solid. [TLC control (petroleum ether/ethyl acetate 85:15), R_f(**21g**)=0.15, R_f(**28d′**)=0.70, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2963, 2936, 2834, 1637, 1604, 1508, 1460, 1449, 1379, 1351, 1261, 1244, 1155, 1130, 1061, 1004, 860, 764 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=6.58 (s, 1H, Ar-H), 6.51 (s, 1H, Ar-H), 6.33 [q, 1H, *J*=1.3 Hz, ArC(Me)=C*H*OCH_2], 4.85 (s, 2H, ArCH_2O), 3.82 (s, 3H, Ar-OCH_3), 3.79 (s, 3H, Ar-OCH_3), 1.83 (d, 3H, *J*=1.3 Hz, CH=CC*H*$_3$) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=148.8 (s, Ar-C), 147.8 (s, Ar-C), 140.7 (d, *C*H=CCH_3), 125.6 (s, CH=*C*CH_3), 121.0 (s, Ar-C), 111.1 (s, Ar-C), 108.0 (d, Ar-CH), 104.9 (d, Ar-CH), 67.9 (t, ArCH_2O), 56.1 (2 × q, 2C, 2 × Ar-OCH_3), 13.2 (q, CH=C*C*H_3) ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{12}H_{15}O_3]^+$=$[M+H]^+$: 207.1016; found 207.1015.



28d

6,7-Dimethoxy-4-methylene-3,4-dihydro-1*H*-isochromene(28d):

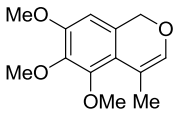
Further elution of the column (petroleum ether/ethyl acetate, 94:6 to 90:10) yielded the isochromene **28d** (50.9 mg, 61%) as a white semi-solid. [TLC control (petroleum ether/ethyl acetate 85:15), R_f(**21g**)=0.15, R_f(**28d**)=0.62, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2960, 2826, 1604, 1509, 1461, 1342, 1289, 1265, 1244, 1225, 1161, 1070, 1034, 991, 940, 881, 857, 768 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.12 (s, 1H, Ar-H), 6.48 (s, 1H, Ar-H), 5.42 (s, 1H, ArC=CH_{2A}), 4.90 (s, 1H, ArC=CH_{2B}), 4.73 (s, 2H, ArCH_2OCH_2), 4.40 (s, 2H, ArCH_2OCH_2), 3.89 (s, 3H, Ar-OCH_3), 3.85 (s, 3H, Ar-OCH_3) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=149.6 (s, Ar-C), 148.2 (s, Ar-C), 138.1 (s, Ar-C), 127.6 (s, Ar-C), 123.5 (s, Ar*C*=CH_2), 106.9 (d, Ar-CH), 106.0 (d, Ar-CH), 104.6 (t, ArC=*C*H_2), 70.8 (t, Ar*C*H_2OCH_2), 68.7 (t, ArCH_2O*C*H_2), 56.0 (q, Ar-OCH_3), 55.9 (q, Ar-OCH_3) ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{12}H_{15}O_3]^+$=$[M+H]^+$: 207.1016; found 207.1013.



28e'

5,6,7-Trimethoxy-4-methyl-1*H*-isochromene (28e′):

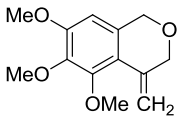
GP-3 was carried out with the 2-bromobenzyl alcohol **21h** (100 mg, 0.36 mmol), allyl bromide (87.4 mg, 0.72 mmol) and NaH (34.7 mg, 1.44 mmol) in DMF (3 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was stirred at the same temperature for 1 h. To the resultant reaction mixture at room temperature, were added $Pd(OAc)_2$ (8.1 mg, 10 mol%), PPh_3 (18.9 mg, 20 mol%) and triethylbenzylammonium chloride (82.2 mg, 0.36 mmol). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 97:3 to 95:5) furnished the isochromene **28e′** (10.9 mg, 13%) as a pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 85:15), R_f(**21h**)=0.15, R_f(**28e′**)=0.65, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2936, 2836, 1628, 1598, 1486, 1455, 1406, 1377, 1328, 1232, 1195, 1134, 1105, 1016, 951, 830 cm^{-1}.

^{1}H-NMR (CDCl$_3$, 400 MHz): δ=6.40 (s, 1H, Ar-H), 6.35 [q, 1H, *J*=1.4 Hz, ArC(Me)=C*H*OCH$_2$], 4.78 (s, 2H, ArCH$_2$O), 3.84 (s, 3H, Ar-OCH$_3$), 3.83 (s, 3H, Ar-OCH$_3$), 3.81 (s, 3H, Ar-OCH$_3$), 2.06 (d, 3H, *J*=1.4 Hz, CH=CC*H*$_3$) ppm.

^{13}C-NMR (CDCl$_3$, 100 MHz): δ=152.0 (s, Ar-C), 149.8 (s, Ar-C), 142.6 (s, Ar-C), 141.5 (d, *C*H=CCH$_3$), 126.0 (s, Ar-C), 118.8 (s, CH=*C*CH$_3$), 111.9 (s, Ar-C), 104.2 (d, Ar-CH), 68.6 (t, ArCH$_2$O), 61.1 (q, Ar-OCH$_3$), 60.8 (q, Ar-OCH$_3$), 56.1 (q, Ar-OCH$_3$), 16.1 (q, CH=C*C*H$_3$) ppm.

HR-MS (APCI$^+$): m/z calculated for [C$_{13}$H$_{16}$NaO$_4$]$^+$=[M+Na]$^+$: 259.0941; found 259.0929.



28e

5,6,7-Trimethoxy-4-methylene-3,4-dihydro-1*H*-isochromene (28e):

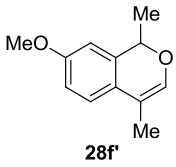
Further elution of the column (petroleum ether/ethyl acetate, 95:5 to 90:10) yielded cyclic ether **28e** (59.6 mg, 70%) as a pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 85:15), R_f(**21h**)=0.15, R_f(**28e**)=0.50, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2937, 2834, 1630, 1595, 1489, 1454, 1333, 1289, 1235, 1107, 1039, 1022, 930 cm^{-1}.

^{1}H-NMR (CDCl$_3$, 400 MHz): δ=6.32 (s, 1H, Ar-H), 6.06 (s, 1H, ArC=CH$_{2A}$), 5.12 (s, 1H, ArC=CH$_{2B}$), 4.73 (s, 2H, ArC*H*$_2$OCH$_2$), 4.32 (s, 2H, ArCH$_2$OC*H*$_2$), 3.85 (s, 3H, Ar-OCH$_3$), 3.84 (s, 3H, Ar-OCH$_3$), 3.83 (s, 3H, Ar-OCH$_3$) ppm.

^{13}C-NMR (CDCl$_3$, 100 MHz): δ=153.0 (s, 2C, Ar-C), 141.5 (s, Ar-C), 135.1 (s, Ar-C), 131.4 (s, Ar-C), 118.0 (s, Ar*C*=CH$_2$), 111.5 (t, ArC=*C*H$_2$), 103.1 (d, Ar-CH), 72.7 (t, Ar*C*H$_2$OCH$_2$), 69.1 (t, ArCH$_2$O*C*H$_2$), 60.9 (q, Ar-OCH$_3$), 59.8 (q, Ar-OCH$_3$), 55.9 (q, Ar-OCH$_3$) ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{13}H_{17}O_4]^+$=$[M+H]^+$: 237.1121; found 237.1125.



28f'

7-Methoxy-1,4-dimethyl-1*H*-isochromene (28f′):

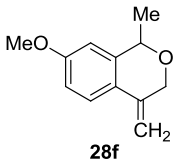
GP-3 was carried out with the 2-bromobenzyl alcohol **21l** (100 mg, 0.43 mmol), allyl bromide (104.8 mg, 0.87 mmol) and NaH (41.6 mg, 1.73 mmol) in DMF (3 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was stirred at the same temperature for 1 h. To the resultant reaction mixture at room temperature, were added $Pd(OAc)_2$ (9.7 mg, 10 mol%), PPh_3 (22.7 mg, 20 mol%) and triethylbenzylammonium chloride (98.6 mg, 0.43 mmol). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 99:1 to 98:2) furnished the isochromene **28f′** (18.0 mg, 22%) as a yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 90:10), R_f(**21l**)=0.15, R_f(**28f′**)=0.70, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2976, 2924, 2851, 1608, 1571, 1498, 1468, 1374, 1273, 1234, 1170, 1096, 1053, 927, 849, 816 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.03 (d, 1H, *J*=8.8 Hz, Ar-H), 6.78 (dd, 1H, *J*=8.8 and 2.4 Hz, Ar-H), 6.61 (d, 1H, *J*=2.4 Hz, Ar-H), 6.31 [q, 1H, *J*=1.5 Hz, ArC(Me)=C*H*OCH_2], 5.09 [q, 1H, *J*=6.4 Hz, ArCH(Me)O], 3.80 (s, 3H, Ar-OCH_3), 1.88 (d, 3H, *J*=1.5 Hz, CH=CC*H*$_3$), 1.56 [d, 3H, *J*=6.4 Hz, ArCHO(C*H*$_3$)] ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=158.7 (s, ArC), 138.9 (d, *C*H=CCH_3), 134.9 (s, ArC), 124.8 (s, ArC), 121.7 (d, ArCH), 111.9 (d, ArCH), 110.2 [s, Ar*C*(CH_3)=$COCH_3$], 109.9 (d, ArCH), 73.2 [d, Ar*C*H(CH_3)], 55.3 (q, $ArOCH_3$), 19.6 [q, ArCO(*C*H_3)], 13.2 (q, CH=C*C*H_3) ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{12}H_{15}O_2]^+$=$[M+H]^+$: 191.1067; found 191.1063.



28f

7-methoxy-1-methyl-4-methylene-3,4-dihydro-1*H*-isochromene (28f):

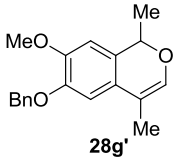
Further elution of the column (petroleum ether/ethyl acetate, 98:2 to 90:10) yielded the isochromene **28f** (42 mg, 51%) as a colorless oil. [TLC control (petroleum ether/ethyl acetate 90:10), R_f(**21l**)=0.15, R_f(**28f**)=0.61, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2957, 2923, 2850, 1607, 1493, 1463, 1302, 1276, 1119, 1089, 1067, 1036, 876, 850, 818 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.60 (d, 1H, J=8.8 Hz, Ar-H), 6.80 (dd, 1H, J=8.8 and 2.4 Hz, Ar-H), 6.61 (d, 1H, J=2.4 Hz, Ar-H), 5.44 (s, 1H, ArC=CH_{2A}), 4.87 (s, 1H, ArC=CH_{2B}), 4.85 [q, 1H, J=6.4 Hz, ArC*H*(CH_3)OCH_2], 4.50 [d, 1H, J=13.2 Hz, ArCH(Me)OCH_{2A}], 4.32 [d, 1H, J=13.2 Hz, ArCH(Me)OCH_{2B}], 3.81 (s, 3H, Ar-OCH_3), 1.55 [d, 3H, J=6.4 Hz, ArCH(CH_3)O] ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=159.5 (s, Ar-C), 140.5 (s, Ar-C), 138.4 (s, Ar-C), 125.0 (d, Ar-CH), 124.0 (s, Ar-*C*=CH_2), 112.8 (d, Ar-CH), 109.6 (d, Ar-CH), 104.5 (t, Ar-C=*C*H_2), 73.1 [d, Ar*C*H(CH_3)O], 69.1 [t, ArCH(CH_3)O*C*H_2], 55.3 (q, Ar-OCH_3), 21.0 [q, ArCH(*C*H_3)O] ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{12}H_{14}O_2]^+$=$[M]^+$: 190.0988; found 190.0980.



28g'

6-(Benzyloxy)-7-methoxy-1,4-dimethyl-1*H*-isochromene (28g′):

GP-3 was carried out with the 2-bromobenzyl alcohol **21n** (100 mg, 0.30 mmol), allyl bromide (72.2 mg, 0.60 mmol) and NaH (28.8 mg, 1.20 mmol) in DMF (3 mL) at room temperature under a nitrogen atmosphere. Then the reaction mixture was stirred at the same temperature for 1 h. To the resultant reaction mixture at room

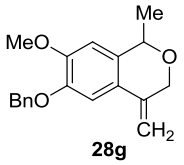
temperature, were added $Pd(OAc)_2$ (6.7 mg, 10 mol%), PPh_3 (15.6 mg, 20 mol%) and triethylbenzylammonium chloride (67 mg, 0.30 mmol). The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 98:2 to 97:3) furnished the isochromene **28g′** (28.0 mg, 32%) as a pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 85:15), R_f(**21n**)=0.15, R_f(**28g′**)=0.65, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2959, 2922, 2851, 1643, 1604, 1510, 1454, 1383, 1362, 1256, 1203, 1165, 1100, 1056, 1016, 856, 809, 738, 697 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.45 (d, 2H, *J*=7.3 Hz, Ar-H), 7.37 (d, 1H, *J*=7.3 Hz, Ar-H), 7.35 (d, 1H, *J*=7.3 Hz, Ar-H), 7.29 (t, 1H, *J*=7.3 Hz, Ar-H), 6.68 (s, 1H, Ar-H), 6.60 (s, 1H, Ar-H), 6.30 [q, 1H, *J*=1.5 Hz, ArC(Me)=C*H*OCH$_2$], 5.14 (s, 2H, ArC*H*$_2$), 5.07 [q, 1H, *J*=6.4 Hz, Ar-C*H*(CH_3)], 3.87 (s, 3H, Ar-OCH$_3$), 1.80 (d, 3H, *J*=1.5 Hz, CH=CC*H*$_3$), 1.54 [d, 3H, *J*=6.4 Hz, Ar-CH(C*H*$_3$)] ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=148.6 (s, Ar-C), 147.7 (s, Ar-C), 139.4 [d, Ar(CH_3)C=*C*H], 137.3 (s, Ar-C), 128.5 (d, 2C, Ar-CH), 127.9 (d, Ar-CH), 127.4 (d, 2C, Ar-CH), 126.3 (s, Ar-C), 125.0 (s, Ar-C), 110.1 (s, Ar*C*=CH$_2$), 108.2 (d, Ar-CH), 108.0 (d, Ar-CH), 73.1 [d, ArCH(CH_3)], 71.5 (t, Ar-CH$_2$), 56.4 (q, Ar-OCH$_3$), 19.7 [q, Ar(*C*H$_3$)C=CH], 13.2 [q, Ar(*C*H$_3$)CHO] ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{19}H_{21}O_3]^+$=$[M+H]^+$: 297.1485; found 297.1477.



28g

6-(Benzyloxy)-7-methoxy-1-methyl-4-methylene-3,4-dihydro-1*H*-isochromene (**28g**):

Further elution of the column (petroleum ether/ethyl acetate, 97:3 to 90:10) yielded the isochromene **28g** (40 mg, 45%). [TLC control (petroleum ether/ethyl acetate 85:15), R_f(**21n**)=0.15, R_f(**28g**)=0.55, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2922, 2851, 1600, 1510, 1455, 1320, 1280, 1260, 1168, 1076, 1052, 851, 747, 697 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.46 (d, 2H, *J*=7.3 Hz, Ar-H), 7.38 (d, 1H, *J*=7.3 Hz, Ar-H), 7.36 (d, 1H, *J*=7.3 Hz, Ar-H), 7.31 (t, 1H, *J*=7.3 Hz, Ar-H), 7.15 (s, 1H, Ar-H), 6.58 (s, 1H, Ar-H), 5.28 (s, 1H, ArC=CH_{2A}), 5.16 (s, 2H, Ar-CH_2), 4.85 (s, 1H, ArC=CH_{2B}), 4.85 [q, 1H, *J*=6.4 Hz, ArC*H*(CH_3)OCH_2], 4.48 [d, 1H, *J*=13.2 Hz, ArCH(Me)OCH_{2A}], 4.30 [d, 1H, *J*=13.2 Hz, ArCH(Me)OCH_{2B}], 3.88 (s, 3H, Ar-OCH_3), 1.53 [d, 3H, *J*=6.4 Hz, ArCH(CH_3)O] ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=150.1 (s, Ar-C), 147.2 (s, Ar-C), 138.5 (s, Ar-C), 137.0 (s, Ar-C), 132.7 (s, Ar-C), 128.5 (d, 2C, Ar-CH), 127.9 (d, Ar-CH), 127.4 (d, 2C, Ar-CH), 123.6 (s, Ar*C*=CH_2), 108.9 (d, Ar-CH), 107.7 (d, Ar-CH), 104.6 (t, ArC=*C*H_2), 72.8 [d, Ar*C*H(CH_3)OCH_2], 71.2 (t, ArCH_2O), 68.9 [t, ArCH(Me)O*C*H_2], 56.0 (q, Ar-OCH_3), 21.2 [q, ArCH(*C*H_3)O] ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{19}H_{20}NaO_3]^+$=$[M+Na]^+$: 319.1305; found 319.1305.

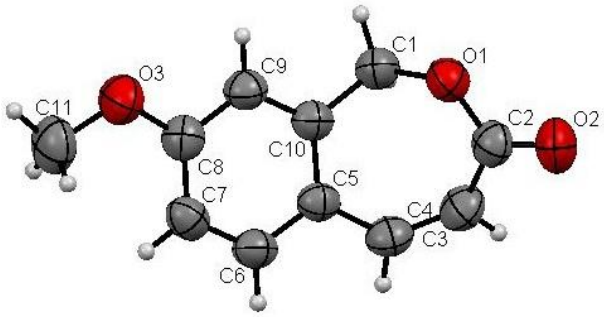
II.4.2 SYNTHESIS OF 2-BENZOXEPINONES:

General Procedure for the Sequential One-pot formation of Benzoxepinones (GP-1):

In an oven dried Schlenk tube, were added the 2-bromobenzyl alcohol **21** (100.0 mg, 0.31–0.53 mmol), ethyl acrylate [155.1–265.3 mg (i.e., 1.55–2.65 mmol)] and Cs_2CO_3 [303.0–518.0 mg (i.e., 0.93–1.59mmol)] followed by the addition of toluene (2 mL) at room temperature under nitrogen atmosphere. The resulted reaction mixture was stirred at 50 °C in an oil bath for 48 h. After the completion of Michael addition (monitored by TLC) and to the cooled reaction mixture at room temperature, were added $Pd(OAc)_2$ (6.9–11.9 mg, 10 mol%) and PPh_3 (16.3–27.8 mg, 20 mol%) under nitrogen atmosphere. The reaction mixture was then heated at 80 °C in an oil bath for 24 h. Once after formation intermolecular Heck coupling product, (monitored by TLC) and then to the cooled reaction mixture at room temperature, was added DMF (3 mL) and heated to 120 °C, in an oil bath

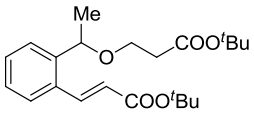
for 12 h (monitored by TLC). The reaction mixture at room temperature was quenched by the addition of aqueous NH_4Cl and extracted with DCM (3 × 15 mL). The organic layers were washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate) furnished the lactenones **34** (40–48%).

X-ray crystal structure data for the 8-methoxy-2-benzoxepin-3(1*H*)-one (34c): CCDC 930424



Operator	**K. Ravikumar**
Instrument	**Oxford SuperNova**
Empirical formula	$C_{11}H_{10}O_3$
Formula weight	190.19
Temperature/K	293(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	19.5629(10)
b/Å	10.2933(5)
c/Å	9.4042(5)
α/°	90.00
β/°	102.263(6)
γ/°	90.00

Volume/Å^3	1850.49(17)
Z	7
ρ_{calc}mg/mm^3	1.195
m/mm^{-1}	0.722
F(000)	700.0
Crystal size/mm^3	25 × 19 × 13
2Θ range for data collection	9.26 to 141.62°
Index ranges	-21 ≤ h ≤ 23, -12 ≤ k ≤ 12, -10 ≤ l ≤ 11
Reflections collected	7134
Independent reflections	3498[R(int) = 0.0232]
Data/restraints/parameters	3498/0/255
Goodness-of-fit on F^2	1.873
Final R indexes [I>=2σ (I)]	R_1 = 0.0869, wR_2 = 0.2741
Final R indexes [all data]	R_1 = 0.0967, wR_2 = 0.2819
Largest diff. peak/hole / e Å^{-3}	0.31/-0.28



23z

***Tert*-butyl (2*E*)-3-{2-[1-(3-*tert*-butoxy-3-oxopropoxy)ethyl]phenyl}acrylate (23z):**

In an oven dried Schlenk tube, were added the 2-bromobenzyl alcohol **21k** (200.0 mg, 0.99 mmol), tertiarybutyl acrylate (637.0 mg, 4.97 mmol) and Cs_2CO_3 (972.0 mg, 2.98 mmol) followed by addition of toluene (4 mL) at room temperature under nitrogen atmosphere. The stirred reaction mixture was heated in an oil bath at 50 °C for 48 h. Progress of the Michael addition was monitored by TLC till the reaction is completed. To the cooled reaction mixture at room temperature, were added $Pd(OAc)_2$ (22.0 mg, 10 mol%) and PPh_3 (52.0 mg, 20 mol%) under nitrogen

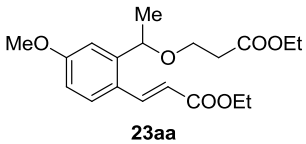
atmosphere. The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h and monitored by TLC. Then, the mixture was cooled to room temperature, treated with aqueous NH_4Cl solution and then extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 90:10) furnished the diester **23z** (220.0 mg, 59%) as yellow viscous oil. [TLC control (petroleum ether/ethyl acetate 90:10), R_f(**21k**)=0.35, R_f(**23z**)=0.45, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2922, 1730, 1709, 1632, 1367, 1319, 1149, 1105, 954, 762 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.98 (d, 1H, *J*=15.6 Hz, C*H*=CHCOO^{t}Bu), 7.52 (d, 1H, *J*=7.3 Hz, Ar-H), 7.48 (d, 1H, *J*=7.8 Hz, Ar-H), 7.38 (dd, 1H, *J*=7.8 and 7.3 Hz, Ar-H), 7.25 (dd, 1H, *J*=7.8 and 7.8 Hz, Ar-H), 6.27 (d, 1H, *J*=15.6 Hz, CH=C*H*COO^{t}Bu), 4.81 (q, 1H, *J*=6.4 Hz, Ar-C*H*CH_3), 3.55 (t, 2H, *J*=6.4 Hz, OC*H*$_2$$CH_2$COO^{t}Bu), 2.48 (td, 2H, *J*=6.4 and 1.5 Hz, OCH_2C*H*$_2$COO^{t}Bu), 1.55 [s, 9H, OC(CH_3)$_3$], 1.45 [s, 9H, OC(CH_3)$_3$], 1.40 (d, 3H, *J*=6.4 Hz, Ar-CHC*H*$_3$) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=170.8 (s, O=C–O), 166.1 (s, O=C–O), 142.8 (s, Ar-C), 140.3 (d, *C*H=CHCOO^{t}Bu), 132.4 (s, Ar-C), 130.0 (d, Ar-CH), 127.3 (d, Ar-CH), 126.6 (d, Ar-CH), 126.0 (d, Ar-CH), 122.0 (d, CH=*C*HCOO^{t}Bu), 80.5 [s, O*C*(CH_3)$_3$], 80.4 [s, O*C*(CH_3)$_3$], 74.7 (d, Ar-*C*HCH_3), 64.5 (t, O*C*$H_2$$CH_2$COO^{t}Bu), 36.4 (t, CH_2*C*H_2COO^{t}Bu), 28.1 [q, 3C, OC(*C*H_3)$_3$], 28.0 [q, 3C, OC(*C*H_3)$_3$], 23.7 (q, Ar-CH*C*H_3) ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{22}H_{31}O_5]^+$=$[M–H]^+$: 375.2166; found 375.2171.



23aa

Ethyl (2*E*)-3-{2-[1-(3-ethoxy-3-oxopropoxy)ethyl]-4-methoxyphenyl}acrylate (23aa):

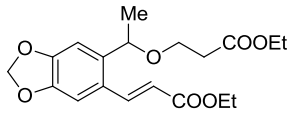
In an oven dried Schlenk tube, were added the 2-bromobenzyl alcohol **21l** (200.0 mg, 0.86 mmol), ethyl acrylate (433.0 mg, 4.32 mmol) and Cs_2CO_3 (846.0 mg, 2.58 mmol) followed by addition of toluene (4 mL) at room temperature under a nitrogen atmosphere. The stirred reaction mixture was heated in an oil bath at 50 °C for 48 h. Progress of the Michael addition was monitored by TLC till the reaction is completed. To the cooled reaction mixture at room temperature, were added $Pd(OAc)_2$ (19.4 mg, 10 mol%) and PPh_3 (45.0 mg, 20 mol%) under nitrogen atmosphere. The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h and monitored by TLC. Then, the mixture was cooled to room temperature, treated with aqueous NH_4Cl solution and then extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 90:10 to 85:15) furnished the diester **23aa** (200.0 mg, 57%) as a yellow viscous oil. [TLC control (petroleum ether/ethyl acetate 80:20), R_f(**21l**)=0.45, R_f(**23aa**)=0.45, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2923, 1735, 1712, 1631, 1603, 1493, 1252, 1179, 1162, 1107, 1034, 731 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.94 (d, 1H, *J*=15.6 Hz, C*H*=CHCOOEt), 7.50 (d, 1H, *J*=8.3 Hz, Ar-H), 7.02 (d, 1H, *J*=2.4 Hz, Ar-H), 6.79 (dd, 1H, *J*=8.3 Hz and 2.4 Hz, Ar-H), 6.23 (d, 1H, *J*=15.6 Hz, CH=C*H*COOEt), 4.80 (q, 1H, *J*=6.4 Hz, Ar-C*H*CH_3), 4.24 (q, 2H, *J*=7.3 Hz, OC*H*$_2CH_3$), 4.12 (qd, 2H, *J*=7.3 and 1.9 Hz, OC*H*$_2CH_3$), 3.83 (s, 3H, Ar-OCH_3), 3.70–3.45 (m, 2H, OC*H*$_2CH_2$COOEt), 2.56 (t, 2H, *J*=6.8 Hz, OCH_2C*H*$_2$COOEt), 1.37 (d, 3H, *J*=6.4 Hz, Ar-CHC*H*$_3$), 1.31 (t, 3H, *J*=7.3 Hz, OCH_2C*H*$_3$), 1.23 (t, 3H, *J*=7.3 Hz, OCH_2C*H*$_3$) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=171.4 (s, O=C–O), 167.1 (s, O=C–O), 161.5 (s, Ar-C), 145.0 (s, Ar-C), 140.5 (d, *C*H=CHCOOEt), 128.2 (d, Ar-CH), 124.6 (s, Ar-C), 117.7 (d, CH=*C*HCOOEt), 113.6 (d, Ar-CH), 110.7 (d, Ar-CH), 74.7 (d, Ar*C*HCH_3), 64.3 (t, O*C*H$_2CH_2$COOEt), 60.4 (t, O*C*H$_2CH_3$), 60.3 (t, O*C*H$_2CH_3$), 55.3 (q, Ar-OCH_3), 35.2 (t, OCH_2*C*H$_2$COOEt), 23.9 (q, ArCH*C*H$_3$), 14.3 (q, OCH_2*C*H$_3$), 14.1 (q, OCH_2*C*H$_3$) ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{19}H_{26}NaO_6]^+$=$[M+Na]^+$: 373.1622; found 373.1630.



23ab

Ethyl (2*E*)-3-{6-[1-(3-ethoxy-3-oxopropoxy)ethyl]-1,3-benzodioxol-5-yl}acrylate (23ab):

In an oven dried Schlenk tube, were added the 2-bromobenzyl alcohol **21m** (200.0 mg, 0.82 mmol), ethyl acrylate (408.0 mg, 4.10 mmol) and Cs_2CO_3 (798.0 mg, 2.46 mmol) followed by addition of toluene (4 mL) at room temperature under a nitrogen atmosphere. The stirred reaction mixture was heated in an oil bath at 50 °C for 48 h. Progress of the Michael addition was monitored by TLC till the reaction is completed. To the cooled reaction mixture at room temperature, were added $Pd(OAc)_2$ (18.0 mg, 10 mol%) and PPh_3 (42.0 mg, 20 mol%) under nitrogen atmosphere. The stirred reaction mixture was then heated in an oil bath at 80 °C for 24 h and monitored by TLC. Then, the mixture was cooled to room temperature, treated with aqueous NH_4Cl solution and then extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 90:10 to 85:15) furnished the diester **23ab** (178.0 mg, 60%) as a yellow viscous oil. [TLC control (petroleum ether/ethyl acetate 80:20), R_f(**21m**)=0.50, R_f(**23ab**)=0.50, UV detection].

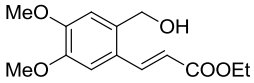
IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2958, 2921, 2852, 1732, 1618, 1482, 1285, 1254, 1180, 1103, 1038, 934 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.92 (d, 1H, *J*=15.6 Hz, C*H*=CHCOOEt), 6.99 (s, 1H, Ar-H), 6.97 (s, 1H, Ar-H), 6.20 (d, 1H, *J*=15.6 Hz, CH=C*H*COOEt), 5.98 (d, 1H, *J*=6.4 Hz, OCH_2O), 5.97 (d, 1H, *J*=6.4 Hz, Ar-H), 4.79 (q, 1H, *J*=6.8 Hz, Ar-C*H*CH_3), 4.24 (q, 2H, *J*=7.3 Hz, O*C*H_2CH_3), 4.14 (q, 2H, *J*=7.3 Hz, O*C*H_2CH_3), 3.65–3.50 (m, 2H, O*C*H_2CH_2COOEt), 2.55 (t, 2H, *J*=6.4 Hz,

OCH_2CH_2COOEt), 1.34 (d, 3H, *J*=6.8 Hz, Ar-$CHCH_3$), 1.32 (t, 3H, *J*=7.3 Hz, OCH_2CH_3), 1.25 (t, 3H, *J*=7.3 Hz, OCH_2CH_3) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=171.5 (s, O=C–O), 167.0 (s, O=C–O), 149.9 (s, Ar-C), 147.2 (s, Ar-C), 140.3 (d, *C*H=CHCOOEt), 138.9 (s, Ar-C), 125.8 (s, Ar-C), 118.2 (d, CH=*C*HCOOEt), 106.1 (d, Ar-CH), 105.6 (d, Ar-CH), 101.4 (t, OCH_2O), 74.1 (d, Ar*C*HCH_3), 64.2 (t, O*C*H_2CH_2COOEt), 60.5 (t, O*C*H_2CH_3), 60.4 (t, O*C*H_2CH_3), 35.3 (t, OCH_2CH_2COOEt), 24.0 (q, ArCH*C*H_3), 14.3 (q, OCH_2CH_3), 14.2 (q, OCH_2CH_3) ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{19}H_{25}O_7]^+$=$[M+H]^+$: 365.1595; found 365.1603.



33g

Ethyl (2*E*)-3-[2-(hydroxymethyl)-4,5-dimethoxyphenyl]acrylate (33g):

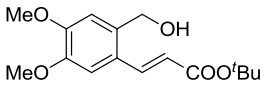
To a cold (–78 °C), magnetically stirred solution of the diester **23g** (80 mg, 0.22 mmol), under argon atmosphere, in dry toluene (2.5 mL), was added 1M solution of NaHMDS (1.1 mL, 1.1 mmol) in toluene. Then the reaction mixture was allowed to stir at –78 °C for 1.5 h followed by at –10 °C for 0.5 h. The reaction mixture was quenched with aqueous NH_4Cl solution and extracted with ethyl acetate (3 × 15 mL). The organic layers were washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the filtrate under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate 70:30 to 50:50) furnished the hydroxy ester (39.6 mg, 69%) as a pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 70:30), R_f(**23g**)=0.40, R_f(**33g**)=0.25, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3485, 2937, 1703, 1629, 1600, 1513, 1464, 1270, 1171, 1103, 1033, 859 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.95 (d, 1H, *J*=15.6 Hz, C*H*=CHCOOEt), 7.07 (s, 1H, Ar-H), 6.95 (s, 1H, Ar-H), 6.29 (d, 1H, *J*=15.6 Hz, CH=C*H*COOEt), 4.78 (s, 2H, Ar-CH_2OH), 4.24 (q, 2H, *J*=7.3 Hz, O*C*H_2CH_3), 3.90 (s, 3H, Ar-OCH_3), 3.89 (s, 3H, Ar-OCH_3), 1.89 (br. s, OH), 1.32 (t, 3H, *J*=7.3 Hz, OCH_2CH_3) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=167.2 (s, O=C–O), 150.8 (s, Ar-C), 148.6 (s, Ar-C), 140.8 (d, *C*H=CHCOOEt), 133.5 (s, Ar-C), 125.1 (s, Ar-C), 117.6 (d, Ar-CH), 111.5 (d, Ar-CH), 108.9 (d, CH=*C*HCOOEt), 62.3 (t, Ar-CH_2OH), 60.5 (t, O*C*H_2CH_3), 55.9 (q, 2C, 2 × Ar-OCH_3), 14.3 (q, OCH_2CH_3) ppm.

HR-MS (ESI^+): m/z calculated for $[C_{14}H_{18}NaO_5]^+$=$[M+Na]^+$: 289.1046; found 289.1057.



33s

***Tert*-butyl (2*E*)-3-[2-(hydroxymethyl)-4,5-dimethoxyphenyl]acrylate (33s):**

To a cold (–78 °C), magnetically stirred solution of the diester **23s** (100 mg, 0.24 mmol), under argon atmosphere, in dry toluene (2 mL), was added 1M solution of NaHMDS (0.96 mL, 0.96 mmol) in toluene. Then the reaction mixture was allowed to stir at –78 °C for 1 h and allowed to –10 °C for 3h. The reaction mixture was quenched with aqueous NH_4Cl solution and extracted with ethyl acetate (3 × 15 mL). The organic layers were washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the filtrate under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate 70:30 to 50:50) furnished the hydroxy ester **33s** (43.4 mg, 62%) as a pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 70:30), R_f(**23s**)=0.50, R_f(**33s**)=0.30, UV detection].

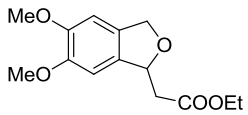
IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3432, 2975, 1702, 1629, 1601, 1514, 1457, 1274, 1146, 1104, 977, 845 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.87 (d, 1H, *J*=15.6 Hz, C*H*=CHCOO^{t}Bu), 7.07 (s, 1H, Ar-H), 6.94 (s, 1H, Ar-H), 6.22 (d, 1H, *J*=15.6 Hz, CH=C*H*COO^{t}Bu), 4.78 (s, 2H, Ar-CH_2OH), 3.90 (s, 3H, Ar-OCH_3), 3.89 (s, 3H, Ar-OCH_3), 1.89 (br. s, OH), 1.52 [(s, 9H, $C(CH_3)_3$] ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=166.6 (s, O=C-O), 150.6 (s, Ar-C), 148.6 (s, Ar-C), 139.8 (d, *C*H=CHCOO^{t}Bu), 133.4 (s, Ar-C), 125.3 (s, Ar-C), 119.6 (d,

Ar-CH), 111.6 (d, Ar-CH), 109.0 (d, CH=*C*HCOO^{t}Bu), 80.5 [(s, *C*$(CH_3)_3$] 62.3 (t, Ar-CH_2OH), 56.0 (q, Ar-OCH_3), 55.9 (q, Ar-OCH_3), 28.2 [(q, 3C, C(*C*$H_3)_3$] ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{16}H_{22}NaO_5]^+$=[(M+Na)]$^+$: 317.1359; found 317.1364.



22g

Ethyl (5,6-dimethoxy-1,3-dihydro-2-benzofuran-1-yl)acetate (22g):

In an oven dried Schlenk tube, were added the diester **23g** (50.0 mg, 0.14 mmol) and Cs_2CO_3 (133.5 mg, 0.72 mmol) followed by the addition of toluene (2 mL) at room temperature under nitrogen atmosphere. The resulted reaction mixture was stirred at 120 °C in an oil bath for 24 h. Progress of the reaction was monitored by TLC. The reaction mixture at room temperature was quenched by the addition of aqueous NH_4Cl and extracted with DCM (3 × 15 mL). The organic layers were washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 90:10 to 85:15) furnished the cyclic ether **22g** (5.6 mg, 16%), as a pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 75:25), R_f(**23g**)=0.45, R_f(**22g**)=0.46, UV detection].

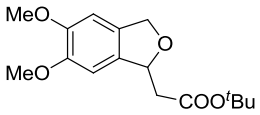
IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2917, 1728, 1602, 1505, 1464, 1266, 1220, 1163, 1107, 1037, 855, 729 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=6.72 (s, 1H, Ar-H), 6.70 (s, 1H, Ar-H), 5.65–5.55 (m, 1H, ArC*H*CH_2COOEt), 5.08 (dd, 1H, *J*=11.7 and 2.9 Hz, ArC$H_a$$H_b$O), 5.00 (dd, 1H, *J*=11.7 and 1.5 Hz, ArC$H_a$$H_b$O), 4.18 (q, 2H, *J*=7.3 Hz, OC$H_2$$CH_3$), 3.86 (s, 3H, $ArOCH_3$), 3.85 (s, 3H, $ArOCH_3$), 2.72 (dd, 2H, *J*=7.3 and 6.4 Hz, ArCHCH_2COOEt), 1.25 (t, 3H, *J*=7.3 Hz, OCH_2CH_3) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=170.9 (s, O=C–O), 149.3 (s, Ar-C), 148.9 (s, Ar-C), 132.2 (s, Ar-C), 130.6 (s, Ar-C), 104.2 (d, Ar-CH), 103.9 (d, Ar-CH), 80.6

(d, Ar*C*HCH$_2$COOEt), 72.8 (t, ArCH$_2$O), 60.6 (t, O*C*H$_2$CH$_3$), 56.1 (q, Ar-OCH$_3$), 56.0 (q, Ar-OCH$_3$), 41.8 (t, ArCH*C*H$_2$COOEt), 14.2 (q, OCH$_2$*C*H$_3$) ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{14}H_{18}NaO_5]^+$=[M+Na]$^+$: 289.1046; found 289.1052.



22s

***Tert*-butyl (5,6-dimethoxy-1,3-dihydro-2-benzofuran-1-yl)acetate (22s):**

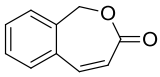
In an oven dried Schlenk tube, were added the diester **23s** (50.0 mg, 0.12 mmol) and Cs_2CO_3 (117.3 mg, 0.36 mmol) followed by the addition of CH_3CN (3 mL) at room temperature under nitrogen atmosphere. The resulted reaction mixture was stirred at 80 °C in an oil bath for 24 h. Progress of the reaction was monitored by TLC. The reaction mixture at room temperature was quenched by the addition of aqueous NH_4Cl and extracted with DCM (3 × 15 mL). The organic layers were washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate) furnished the cyclic ether **22s** (5.9 mg, 16%) as pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 80:20), R_f(**23s**)=0.45, R_f(**22s**)=0.47, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2975, 1723, 1603, 1503, 1464, 1391, 1274, 1220, 1146, 1108, 1036, 844, 766 cm^{-1}.

^{1}H-NMR (CDCl$_3$, 400 MHz): δ=6.71 (2 × s, 2H, Ar-H), 5.60–5.48 (m, 1H, ArC*H*CH$_2$COO^{t}Bu), 5.06 (dd, 1H, *J*=11.7 and 2.9 Hz, ArC*H*$_a$H$_b$O), 4.98 (dd, 1H, *J*=11.7 and 1.5 Hz, ArCH$_a$*H*$_b$O), 3.85 (s, 3H, ArOCH$_3$), 3.84 (s, 3H, ArOCH$_3$), 2.65 (dd, 2H, *J*=6.8 and 1.5 Hz, ArCHC*H*$_2$COOEt), 1.44 [s, 9H, OC(CH$_3$)$_3$] ppm.

^{13}C-NMR (CDCl$_3$, 100 MHz): δ=170.2 (s, O=C–O), 149.2 (s, Ar-C), 148.8 (s, Ar-C), 132.6 (s, Ar-C), 130.7 (s, Ar-C), 104.3 (d, Ar-CH), 103.9 (d, Ar-CH), 80.8 [s, O*C*(CH$_3$)$_3$], 80.7 (d, Ar*C*HCH$_2$COO^{t}Bu), 72.8 (t, ArCH$_2$O), 56.1 (q, Ar-OCH$_3$), 56.0 (q, Ar-OCH$_3$), 42.9 (t, ArCH*C*H$_2$COOEt), 28.0 [q, 3C, OC(*C*H$_3$)$_3$] ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{16}H_{20}O_4]^+$=[M–(H_2O)]$^+$: 276.1356; found 276.1352.



34a

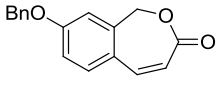
2-Benzoxepin-3(1*H*)-one (34a):

GP-1 was carried out with the 2-bromobenzyl alcohol **21a** (100.0 mg, 0.53 mmol), ethyl acrylate (265.3 mg, 2.65 mmol), Cs_2CO_3 (518.0 mg, 1.59 mmol), toluene (2 mL) for Michael addition at 50 °C for 48 h, then with $Pd(OAc)_2$ (11.9 mg, 10 mol%), PPh_3 (27.8 mg, 20 mol%) for Heck coupling at 80 °C for 24 h and finally with DMF (3 mL) at 120 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the lactenone **34a** (39.5 mg, 46%) as a pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 90:10), R_f(**21a**)=0.50, R_f(**34a**)=0.38, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2921, 1707, 1602, 1457, 1273, 1209, 1157, 1106, 1034, 818, 741 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.55–7.30 (m, 4H, Ar-H), 7.21 (d, 1H, *J*=11.7 Hz, C*H*=CHCO), 6.35 (d, 1H, *J*=11.7 Hz, CH=C*H*CO), 5.06 (s, 2H, $ArCH_2O$) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=167.6 (s, O=C–O), 140.6 (d, *C*H=CHCO), 135.4 (s, Ar-C), 135.1 (s, Ar-C), 130.2 (d, Ar-CH), 129.8 (d, Ar-CH), 129.7 (d, Ar-CH), 128.6 (d, Ar-CH), 122.7 (d, CH=*C*HCO), 68.6 (t, $ArCH_2O$) ppm. HR-MS (APCI+) m/z calculated for $[C_{10}H_7O]^+$=[(M+H)–H_2O]$^+$: 143.0491; found 143.0496.



34b

8-(Benzyloxy)-2-benzoxepin-3(1*H*)-one (34b):

GP-1 was carried out with the 2-bromobenzyl alcohol **21b** (100.0 mg, 0.34 mmol), ethyl acrylate (170.2 mg, 0.17 mmol), Cs_2CO_3 (332.3 mg, 1.03 mmol), toluene (2 mL) for Michael addition at 50 °C for 48 h, then with $Pd(OAc)_2$ (7.6 mg,

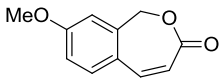
10 mol%), PPh_3 (17.8 mg, 20 mol%) for Heck coupling at 80 °C for 24 h and finally with DMF (3 mL) at 120 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 90:10 to 85:15) furnished the lactenone **34b** (36.2 mg, 40%) as a pale yellow semi-solid. [TLC control (petroleum ether/ethyl acetate 80:20), R_f(**21b**)=0.48, R_f(**34b**)=0.41, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2925, 1701, 1605, 1501, 1283, 1178, 1040, 835, 737 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.46–7.30 (m, 6H, Ar-H), 7.14 (d, 1H, *J*=12.2 Hz, C*H*=CHCO), 7.03 (dd, 1H, *J*=8.3 and 2.4 Hz, Ar-H), 7.01 (d, 1H, *J*=2.4 Hz, Ar-H), 6.22 (d, 1H, *J*=12.2 Hz, CH=C*H*CO), 5.12 (s, 2H, $PhCH_2O$), 5.00 (s, 2H, $ArCH_2O$) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=168.0 (s, O=C–O), 160.1 (s, Ar-C), 140.6 (d, *C*H=CHCO), 137.1 (s, Ar-C), 136.0 (s, Ar-C), 131.7 (d, Ar-CH), 128.7 (d, 2C, Ar-CH), 128.5 (s, Ar-C), 128.3 (d, Ar-CH), 127.4 (d, 2C, Ar-CH), 120.2 (d, CH=*C*HCO), 115.7 (d, Ar-CH), 115.1 (d, Ar-CH), 70.3 (t, $PhCH_2O$), 68.7 (t, $ArCH_2O$) ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{17}H_{15}O_3]^+$=$[M+H]^+$: 267.1016; found 267.1020.



34c

8-Methoxy-2-benzoxepin-3(1*H*)-one (34c):

GP-1 was carried out with the 2-bromobenzyl alcohol **21c** (100.0 mg, 0.46 mmol), ethyl acrylate (230.3 mg, 2.30 mmol), Cs_2CO_3 (449.6 mg, 1.38 mmol), toluene (2 mL) for Michael addition at 50 °C for 48 h, then with $Pd(OAc)_2$ (10.3 mg, 10 mol%), PPh_3 (24.1 mg, 20 mol%) for Heck coupling at 80 °C for 24 h and finally with DMF (3 mL) at 120 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 90:10 to 80:20) furnished the lactenone **34c** (40.4 mg, 46%) as a pale brown solid, recrystallized from

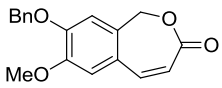
dichloromethane/hexane (m. p. 96–98 °C). [TLC control (petroleum ether/ethyl acetate 80:20), R_f(**21c**)=0.45, R_f(**34c**)=0.40, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2926, 1699, 1605, 1503, 1453, 1284, 1251, 1160, 1034, 909, 805, 727 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.34 (d, 1H, *J*=8.3 Hz, Ar-H), 7.14 (d, 1H, *J*=12.2 Hz, C*H*=CHCO), 6.96 (dd, 1H, *J*=8.3 and 2.4 Hz, Ar-H), 6.92 (d, 1H, *J*=2.4 Hz, Ar-H), 6.21 (d, 1H, *J*=12.2 Hz, CH=C*H*CO), 5.01 (s, 2H, $ArCH_2O$), 3.85 (s, 3H, Ar-OCH_3) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=168.1 (s, O=C–O), 161.0 (s, Ar-C), 140.7 (d, *C*H=CHCO), 137.0 (s, Ar-C), 131.7 (d, Ar-CH), 128.3 (s, Ar-C), 120.0 (d, CH=*C*HCO), 114.8 (d, Ar-CH), 114.2 (d, Ar-CH), 68.7 (t, $ArCH_2O$), 55.5 (q, Ar-OCH_3) ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{11}H_{11}O_3]^+$=$[M+H]^+$: 191.0703; found 191.0704.



34d

8-(Benzyloxy)-7-methoxy-2-benzoxepin-3(1*H*)-one (34d):

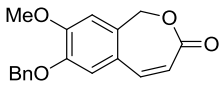
GP-1 was carried out with the 2-bromobenzyl alcohol **34d** (100.0 mg, 0.31 mmol), ethyl acrylate (155.2 mg, 1.55 mmol), Cs_2CO_3 (303.0 mg, 0.93 mmol), toluene (2 mL) for Michael addition at 50 °C for 48 h, then with $Pd(OAc)_2$ (6.9 mg, 10 mol%), PPh_3 (16.3 mg, 20 mol%) for Heck coupling at 80 °C for 24 h and finally with DMF (3 mL) at 120 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 85:15 to 75:25) furnished the lactenone **34d** (38.6 mg, 42%) as white solid, recrystallized from dichloromethane/hexane (m. p. 159–160 °C). [TLC control (petroleum ether/ethyl acetate 75:25), R_f(**21d**)=0.45, R_f(**34d**)=0.38, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2924, 1702, 1603, 1519, 1368, 1275, 1165, 1025, 740 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.42 (d, 2H, *J*=7.8 Hz, Ar-H), 7.38 (dd, 2H, *J*=7.8 and 7.3 Hz, Ar-H), 7.32 (t, 1H, *J*=7.3 Hz, Ar-H), 7.11 (d, 1H, *J*=12.2 Hz, C*H*=CHCO), 6.91 (s, 1H, Ar-H), 6.89 (s, 1H, Ar-H), 6.25 (d, 1H, *J*=12.2 Hz, CH=C*H*CO), 5.20 (s, 2H, $PhCH_2O$), 4.92 (s, 2H, $ArCH_2O$), 3.91 (s, 3H, Ar-OCH_3) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=167.9 (s, O=C–O), 150.3 (s, Ar-C), 149.5 (s, Ar-C), 140.5 (d, *C*H=CHCO), 136.2 (s, Ar-C), 129.0 (s, Ar-C), 128.7 (d, 2C, Ar-CH), 128.6 (s, Ar-C), 128.2 (d, Ar-CH), 127.2 (d, 2C, Ar-CH), 121.0 (d, CH=*C*HCO), 113.7 (d, Ar-CH), 112.7 (d, Ar-CH), 71.1 (t, $PhCH_2O$), 68.3 (t, $ArCH_2O$), 56.2 (q, Ar-OCH_3) ppm.

HR-MS (APCI^{+}): m/z calculated for $[C_{18}H_{17}O_4]^{+}$=$[M+H]^{+}$: 297.1121; found 297.1121.



34e

7-(Benzyloxy)-8-methoxy-2-benzoxepin-3(1*H*)-one (34e):

GP-1 was carried out with the 2-bromobenzyl alcohol **21e** (100.0 mg, 0.31 mmol), ethyl acrylate (155.2 mg, 1.55 mmol), Cs_2CO_3 (303.0 mg, 0.93 mmol), toluene (2 mL) for Michael addition at 50 °C for 48 h, then with $Pd(OAc)_2$ (6.9 mg, 10 mol%), PPh_3 (16.3 mg, 20 mol%) for Heck coupling at 80 °C for 24 h and finally with DMF (3 mL) at 120 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 85:15 to 75:25) furnished the lactenone **34e** (40.5 mg, 44%) as colorless solid, recrystallized from dichloromethane/petroleum ether (m. p. 160–161 °C). [TLC control (petroleum ether/ethyl acetate 75:25), R_f(**21e**)=0.45, R_f(**34e**)=0.38, UV detection].

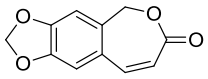
IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2925, 1694, 1602, 1517, 1453, 1354, 1275, 1164, 1106, 1031, 987, 864, 733, 698 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.42 (d, 2H, *J*=7.8 Hz, Ar-H), 7.37 (dd, 2H, *J*=7.8 and 7.3 Hz, Ar-H), 7.31 (t, 1H, *J*=7.3 Hz, Ar-H), 7.04 (d, 1H, *J*=12.2 Hz, C*H*=CHCO), 6.91 (s, 1H, Ar-H), 6.89 (s, 1H, Ar-H), 6.22 (d, 1H, *J*=12.2 Hz,

CH=C*H*CO), 5.16 (s, 2H, $PhCH_2O$), 4.97 (s, 2H, $ArCH_2O$), 3.93 (s, 3H, Ar-OCH_3) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=168.0 (s, O=C–O), 150.9 (s, Ar-C), 148.7 (s, Ar-C), 140.6 (d, *C*H=CHCO), 136.3 (s, Ar-C), 129.2 (s, Ar-C), 128.6 (d, 2C, Ar-CH), 128.4 (s, Ar-C), 128.1 (d, Ar-CH), 127.2 (d, 2C, Ar-CH), 120.7 (d, CH=*C*HCO), 114.7 (d, Ar-CH), 111.7 (d, Ar-CH), 71.1 (t, $PhCH_2O$), 68.3 (t, $ArCH_2O$), 56.2 (q, Ar-OCH_3) ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{18}H_{17}O_4]^+$=$[M+H]^+$: 297.1121; found 297.1120.



34f

[1,3]Dioxolo[4,5-*h*][2]benzoxepin-7(5*H*)-one (34f):

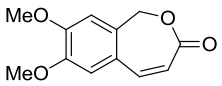
GP-1 was carried out with the 2-bromobenzyl alcohol **21f** (100.0 mg, 0.43 mmol), ethyl acrylate (215.2 mg, 2.15 mmol), Cs_2CO_3 (423.0 mg, 1.30 mmol), toluene (2 mL) for Michael addition at 50 °C for 48 h, then with $Pd(OAc)_2$ (9.6 mg, 10 mol%), PPh_3 (22.5 mg, 20 mol%) for Heck coupling at 80 °C for 24 h and finally with DMF (3 mL) at 120 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 90:10 to 80:20) furnished the lactenone **34f** (38.6 mg, 44%) as colorless solid, recrystallized from dichloromethane/petroleum ether (m. p. 149–150 °C). [TLC control (petroleum ether/ethyl acetate 80:20), R_f(**21f**)=0.45, R_f(**34f**)=0.40, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2921, 1698, 1617, 1504, 1490, 1387, 1267, 1238, 1147, 1023, 928, 879 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.06 (d, 1H, *J*=12.2 Hz, C*H*=CHCO), 6.86 (s, 1H, Ar-H), 6.83 (s, 1H, Ar-H), 6.24 (d, 1H, *J*=12.2 Hz, CH=C*H*CO), 6.03 (s, 2H, O-CH_2-O), 4.93 (s, 2H, $ArCH_2O$) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=167.8 (s, O=C–O), 149.0 (s, Ar-C), 148.7 (s, Ar-C), 140.3 (d, *C*H=CHCO), 130.2 (s, Ar-C), 130.0 (s, Ar-C), 121.0 (d, CH=*C*HCO), 109.3 (d, Ar-CH), 109.0 (d, Ar-CH), 101.9 (t, O-CH_2-O), 68.2 (t, $ArCH_2O$) ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{11}H_9O_4]^+=[M+H]^+$: 205.0495; found 205.0493.



34g

7,8-Dimethoxy-2-benzoxepin-3(1*H*)-one (34g):

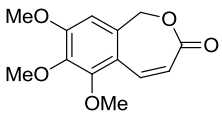
GP-1 was carried out with the 2-bromobenzyl alcohol **21g** (100.0 mg, 0.40 mmol), ethyl acrylate (202.6 mg, 2.02 mmol), Cs_2CO_3 (395.6 mg, 1.21 mmol), toluene (2 mL) for Michael addition at 50 °C for 48 h, then with $Pd(OAc)_2$ (9.1 mg, 10 mol%), PPh_3 (21.0 mg, 20 mol%) for Heck coupling at 80 °C for 24 h and finally with DMF (3 mL) at 120 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 85:15 to 70:30) furnished the lactenone **34g** (42.8 mg, 48%) as yellow semi-solid. [TLC control (petroleum ether/ethyl acetate 75:25), R_f(**21g**)=0.45, R_f(**34g**)=0.30, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2924, 1693, 1603, 1519, 1463, 1356, 1274, 1247, 1164, 1107, 1029, 988, 840, 731 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.12 (d, 1H, *J*=12.2 Hz, C*H*=CHCO), 6.90 (s, 1H, Ar-H), 6.87 (s, 1H, Ar-H), 6.26 (d, 1H, *J*=12.2 Hz, CH=C*H*CO), 4.98 (s, 2H, $ArCH_2O$), 3.93 (s, 3H, $ArOCH_3$), 3.90 (s, 3H, $ArOCH_3$) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=168.0 (s, O=C–O), 150.3 (s, Ar-C), 149.7 (s, Ar-C), 140.6 (d, *C*H=CHCO), 128.7 (s, Ar-C), 128.6 (s, Ar-C), 120.9 (d, CH=*C*HCO), 112.1 (d, Ar-CH), 111.3 (d, Ar-CH), 68.3 (t, $ArCH_2O$), 56.2 (q, Ar-OCH_3), 56.1 (q, Ar-OCH_3) ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{12}H_{13}O_4]^+=[M+H]^+$: 221.0808; found 221.0804.



34h

6,7,8-Trimethoxy-2-benzoxepin-3(1*H*)-one (34h):

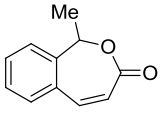
GP-1 was carried out with the 2-bromobenzyl alcohol **21h** (100.0 mg, 0.36 mmol), ethyl acrylate (180.7 mg, 1.80 mmol), Cs_2CO_3 (351.9 mg, 1.08 mmol), toluene (2 mL) for Michael addition at 50 °C for 48 h, then with $Pd(OAc)_2$ (8.1 mg, 10 mol%), PPh_3 (18.9 mg, 20 mol%) for Heck coupling at 80 °C for 24 h and finally with DMF (3 mL) at 120 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 85:15 to 75:25) furnished the lactenone **34h** (42.3 mg, 47%) as yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 80:20), R_f(**21h**)=0.45, R_f(**34h**)=0.38, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2925, 1703, 1595, 1498, 1458, 1375, 1338, 1249, 1123, 1089, 1031, 822 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.43 (d, 1H, *J*=12.2 Hz, C*H*=CHCO), 6.71 (s, 1H, Ar-H), 6.24 (d, 1H, *J*=12.2 Hz, CH=C*H*CO), 4.94 (s, 2H, $ArCH_2O$), 3.91 (s, 3H, $ArOCH_3$), 3.90 (s, 3H, $ArOCH_3$), 3.87 (s, 3H, $ArOCH_3$) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=168.2 (s, O=C–O), 155.0 (s, Ar-C), 152.2 (s, Ar-C), 142.5 (s, Ar-C), 135.6 (d, *C*H=CHCO), 131.9 (s, Ar-C), 122.6 (s, Ar-C), 120.2 (d, CH=*C*HCO), 107.4 (d, Ar-CH), 68.7 (t, $ArCH_2O$), 61.7 (q, Ar-OCH_3), 61.0 (q, Ar-OCH_3), 56.2 (q, Ar-OCH_3) ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{13}H_{15}O_5]^+$=$[M+H]^+$: 251.0914; found 251.0913.



34i

1-Methyl-2-benzoxepin-3(1*H*)-one (**34i**):

In an oven dried Schlenk tube, were added the diester **23z** (200.0 mg, 0.53 mmol) and Cs_2CO_3 (520.0 mg, 1.59 mmol) followed by the addition of DMF (4 mL) at room temperature under nitrogen atmosphere. The resulted reaction mixture was

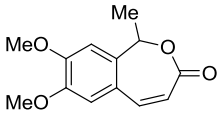
stirred at 120 °C in an oil bath for 12 h. Progress of the reaction was monitored by TLC. The reaction mixture at room temperature was quenched by the addition of aqueous NH_4Cl and extracted with DCM (3 × 15 mL). The organic layers were washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 90:10 to 80:20) furnished the lactenone **34i** (50.8 mg, 55%) as yellow oil. [TLC control (petroleum ether/ethyl acetate 80:20), R_f(**23z**)=0.50, R_f(**34i**)=0.25, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2923, 2852, 1701, 1617, 1455, 1398, 1269, 1215, 1152, 1068, 1044, 1018, 972, 823, 808, 777, 731cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.60–7.30 (m, 4H, Ar-C), 7.21 (d, 1H, *J*=12.2 Hz, C*H*=CHCO), 6.39 (d, 1H, *J*=12.2 Hz, CH=C*H*CO), 5.31 [q, 1H, *J*=6.8 Hz, ArC*H*(CH_3)O], 1.85 [d, 3H, *J*=6.8 Hz, ArCH(CH_3)O] ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=167.4 (s, O=C–O), 140.4 (d, *C*H=CHCO), 138.2 (s, Ar-C), 135.1 (s, Ar-C), 130.1 (d, Ar-CH), 129.9 (d, Ar-CH), 129.1 (d, Ar-CH), 124.9 (d, Ar-CH), 123.0 (d, CH=*C*HCO), 72.7 [d, Ar*C*H(CH_3)O], 17.3 [q, ArCH(*C*H_3)O] ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{10}H_9O]^+$=$[(M+H)–H_2O]^+$: 157.0648; found 157.0644.



34j

7,8-Dimethoxy-1-methyl-2-benzoxepin-3(1*H*)-one (**34j**):

In an oven dried Schlenk tube, were added the diester **23v** (220.0 mg, 0.50 mmol) and Cs_2CO_3 (493.0 mg, 1.50 mmol) followed by the addition of DMF (4 mL) at room temperature under nitrogen atmosphere. The resulted reaction mixture was stirred at 120 °C in an oil bath for 12 h. Progress of the reaction was monitored by TLC. The reaction mixture at room temperature was quenched by the addition of aqueous NH_4Cl and extracted with DCM (3 × 15 mL). The organic layers were washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of

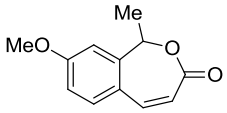
the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 70:30 to 60:40) furnished the lactenone **34j** (62.5 mg, 52%) as yellow oil. [TLC control (petroleum ether/ethyl acetate 60:40), R_f(**23v**)=0.75, R_f(**34j**)=0.20, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2925, 2852, 1695, 1604, 1518, 1462, 1362, 1335, 1199, 1177, 1151, 1068, 1025, 957, 863, 812, 729, 612cm^{-1}.

^{1}H-NMR (CDCl$_3$, 400 MHz): δ=7.11 (d, 1H, *J*=12.2 Hz, C*H*=CHCO), 6.96 (s, 1H, Ar-H), 6.86 (s, 1H, Ar-H), 6.30 (d, 1H, *J*=12.2 Hz, CH=C*H*CO), 5.25 [q, 1H, *J*=6.4 Hz, ArC*H*(CH$_3$)O], 3.95 (s, 3H, Ar-OCH$_3$), 3.90 (s, 3H, Ar-OCH$_3$) 1.83 [d, 3H, *J*=6.4 Hz, ArCH(C*H*$_3$)O] ppm.

^{13}C-NMR (CDCl$_3$, 100 MHz): δ=167.7 (s, O=C–O), 150.3 (s, Ar-C), 149.2 (s, Ar-C), 140.2 (d, *C*H=CHCO), 131.9 (s, Ar-C), 128.3 (s, Ar-C), 121.4 (d, CH=*C*HCO), 112.3 (d, Ar-CH), 107.9 (d, Ar-CH), 72.4 [d, Ar*C*H(CH$_3$)O], 56.1 (q, Ar-OCH$_3$), 56.0 (q, Ar-OCH$_3$), 17.5 [q, ArCH(*C*H$_3$)O] ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{13}H_{15}O_4]^+$=$[M+H]^+$: 235.0695; found 235.0694.



34k

8-Methoxy-1-methyl-2-benzoxepin-3(1*H*)-one (34k):

In an oven dried Schlenk tube, were added the diester **23aa** (150.0 mg, 0.43 mmol) and Cs_2CO_3 (419.0 mg, 1.29 mmol) followed by the addition of DMF (3 mL) at room temperature under nitrogen atmosphere. The resulted reaction mixture was stirred at 120 °C in an oil bath for 12 h. Progress of the reaction was monitored by TLC. The reaction mixture at room temperature was quenched by the addition of aqueous NH_4Cl and extracted with DCM (3 × 15 mL). The organic layers were washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 85:15 to 80:20)

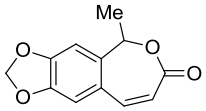
furnished the lactenone **34k** (50.8 mg, 58%) as yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 80:20), R_f(**23aa**)=0.60, R_f(**34k**)=0.30, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2923, 2852, 1697, 1605, 1562, 1501, 1460, 1399, 1382, 1236, 1218, 1178, 1073, 1035, 975, 876, 859 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.33 (d, 1H, *J*=8.3 Hz, Ar-H), 7.14 (d, 1H, *J*=11.7 Hz, C*H*=CHCO), 7.00 (d, 1H, *J*=2.4 Hz, Ar-H), 6.94 (dd, 1H, *J*=8.3 and 2.4 Hz, Ar-H), 6.25 (d, 1H, *J*=11.7 Hz, CH=C*H*CO), 5.26 [q, 1H, *J*=6.8 Hz, ArC*H*(CH_3)O], 3.87 (s, 3H, Ar-OCH_3) 1.82 [d, 3H, *J*=6.8 Hz, ArCH(C*H*$_3$)O] ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=167.8 (s, O=C–O), 161.1 (s, Ar-C), 140.5 (d, *C*H=CHCO), 140.2 (s, Ar-C), 131.8 (d, Ar-CH), 128.0 (s, Ar-C), 120.5 (d, CH=*C*HCO), 113.6 (d, Ar-CH), 111.4 (d, Ar-CH), 72.5 [d, Ar*C*H(CH_3)O], 55.5 (q, Ar-OCH_3), 17.3 [q, ArCH(*C*H_3)O] ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{12}H_{13}O_3]^+$=$[M+H]^+$: 205.0859; found 205.0862.



34l

8,9-Dihydro[1,3]dioxolo[4,5-*h*][2]benzoxepin-7(5*H*)-one (**34l**):

In an oven dried Schlenk tube, were added the diester **23ab** (80.0 mg, 0.22 mmol) and Cs_2CO_3 (214.0 mg, 0.66 mmol) followed by the addition of DMF (2 mL) at room temperature under nitrogen atmosphere. The resulted reaction mixture was stirred at 120 °C in an oil bath for 12 h. Progress of the reaction was monitored by TLC. The reaction mixture at room temperature was quenched by the addition of aqueous NH_4Cl and extracted with DCM (3 × 15 mL). The organic layers were washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 85:15 to 75:25) furnished the lactenone **34l** (24.0 mg, 50%) as yellow oil. [TLC control (petroleum ether/ethyl acetate 80:20), R_f(**23ab**)=0.50, R_f(**34l**)=0.20, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2921, 2851, 1694, 1505, 1489, 1385, 1261, 1156, 1036, 932 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=7.06 (d, 1H, *J*=12.2 Hz, C*H*=CHCO), 6.98 (s, 1H, Ar-H), 6.83 (s, 1H, Ar-H), 6.30 (d, 1H, *J*=12.2 Hz, CH=C*H*CO), 6.04 (d, 1H, *J*=6.3 Hz, OCH_aH_bO), 6.03 (d, 1H, *J*=6.3 Hz, OCH_aH_bO), 5.20 [q, 1H, *J*=6.3 Hz, $ArCH(CH_3)O$], 1.79 [d, 3H, *J*=6.3 Hz, $ArCH(CH_3)O$] ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=167.6 (s, O=C–O), 149.3 (s, Ar-C), 148.1 (s, Ar-C), 140.0 (d, *C*H=CHCO), 133.7 (s, Ar-C), 129.7 (s, Ar-C), 121.6 (d, CH=*C*HCO), 109.3 (d, Ar-CH), 105.6 (d, Ar-CH), 101.9 (t, OCH_2O), 72.3 (d, $ArCHCH_3$), 17.6 (q, $ArCHCH_3$) ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{12}H_{11}O_4]^+=[(M+H)]^+$: 219.0652; found 219.0657.

CHAPTER III

SYNTHESIS

OF

ARYL-DIHYDRO-INDENOINDOLES

III. 1 INTRODUCTION:

One-pot synthetic trials have gained significance in synthetic organic chemistry, as they involve constructing more than one bond using a single operation[53] and avoid intermediate isolation. Enhancement of such one-pot practices, which are useful in forming multiple C-C as well as C-heteroatom bonds, in particular, to construct complex molecular frame works and elegant biologically active natural products, are of immense interest. In this aspect, several synthetic methods based on a domino/sequential domino one-pot have been reported. For example, the use of multiple catalysts in one step either sequentially or together, a single catalytic system to catalyze multiple steps in a domino/sequential domino/tandem fashion and even an initial reaction mediated by the catalyst followed by in-situ treatment of a functionality which is generated in the first step by the addition of other reagents in stoichiometric quantities or vice versa, to promote subsequent simple and effective reactions.[54,55] Most of these one-pot techniques were carried out in same medium for all transformations with respect to solvent, reagents, acid and/or base. In case of a few sequential one-pot processes, prior work-up was required in situations where complications occurred before the next reaction could be conducted. Domino sequential one-pot reactions without isolation of the intermediate are said to be telescoping syntheses. Since these one-pot techniques avoid the isolation of intermediate species, there is a substantial decrease in waste generation, in terms of minimal use of solvents and reagents, leading to

improvement of strategic efficiency. Most importantly, they save time over conventional step-wise operations, which has caused chemists to pay greater attention to the development of such procedures.[91] Friedel-Crafts reaction and Fischer-indole synthesis are well-known classical and effective processes introduced by Friedel and Crafts in 1877[92] and Fischer in 1883,[93] respectively. The Fischer-indole synthesis lead to bio-active indole core commonly encountered in indole alkaloid natural products and in a few useful pharmaceuticals.[94] For example, indole alkaloids like yuehchukene **1** a polycyclic bis-indole alkaloid, acts as a potential fertility-regulating agent,[95] borreverine **2** shows antibacterial activity,[96] paspaline **3** displays a potent tremorgenic activity[97] and compounds **4** and **5** exhibit prostaglandin D_2 receptor antagonist activity (Figure III.1).[98]

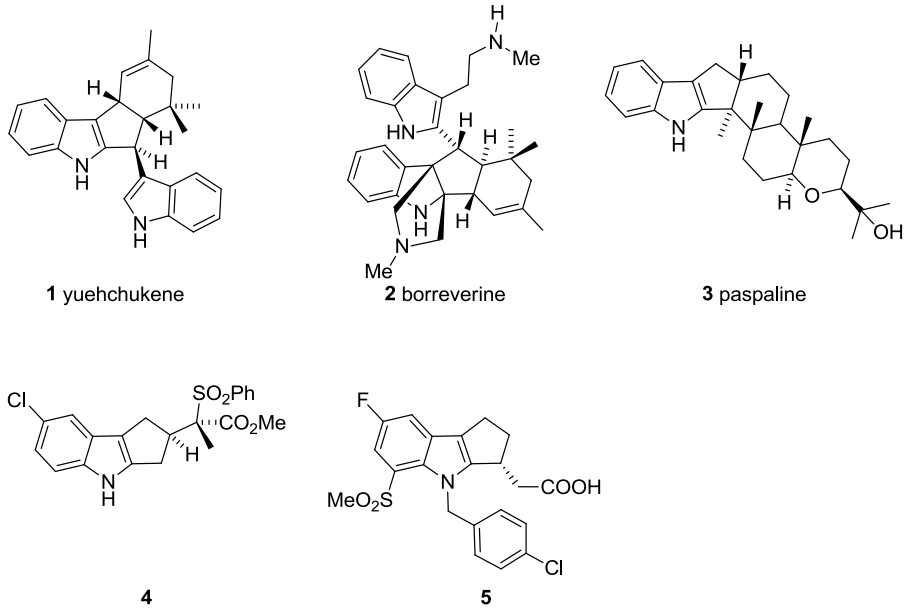


Figure III.1

Indole scaffolds, in particular, the indeno[1,2-*b*]indole system, has received extraordinary importance in the area of biological and pharmacologically active agents during the past decades.[99] For example, 5,10-dihydroindeno[1,2-*b*]indole is a key intermediate for the synthesis of the BARAC-Fluor reagent, used for cell labelling,[100] compounds **6**, **7** and **8** act as potential topoisomerase II–inhibiting anticancer agents[101] and compounds **9** and **10** show high anti-cancer[102] and

effective antioxidant activities, as well as radical scavenging activities (Figure III.2).[103]

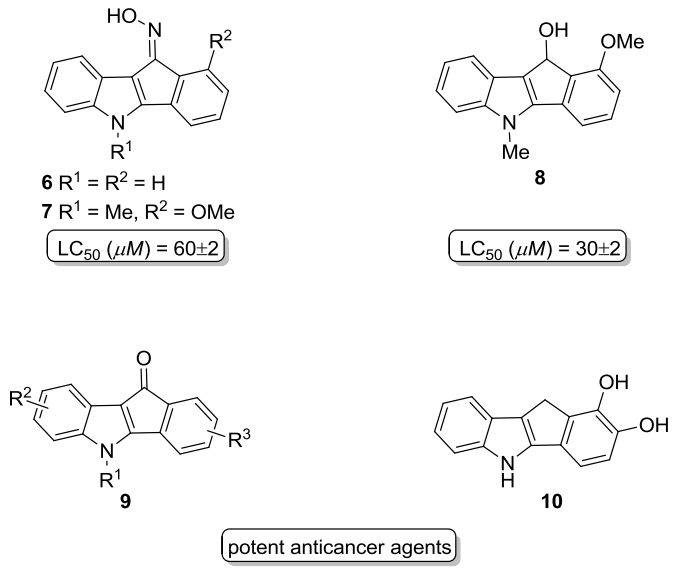
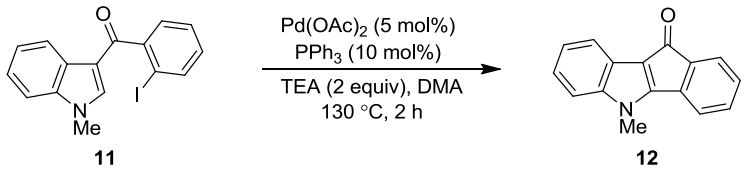


Figure III.2

***III.2 BACKGROUND*:**

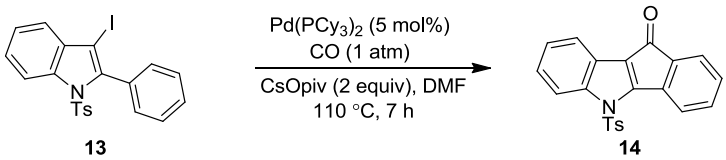
Due to their interesting structural features and wide range of biological activities, there are few reports on the synthesis of fused tricyclic indoles.[104] Notably, along with palladium catalyzed intramolecular Heck reactions and radical cyclizations, acid mediated domino strategies were employed to achieve indole based fused tetracyclic systems.[105]

The research group of Gevorgyan reported the palladium catalyzed intramolecular annulations of N-substituted benzoylindoles **11** to the corresponding fused heterocyclic system **12**. The reaction triggered a five membered ring formation, only in presence of triethylamine as base (Scheme III.1).[106]



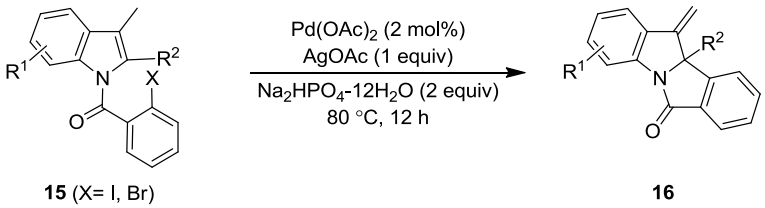
Scheme III.1

Larock and Campo developed cyclocarbonyl insertion followed by cyclization, using which they synthesized the fused tetracyclic ketone **14** from corresponding haloindole biaryl **13** (Scheme III.2).[107]



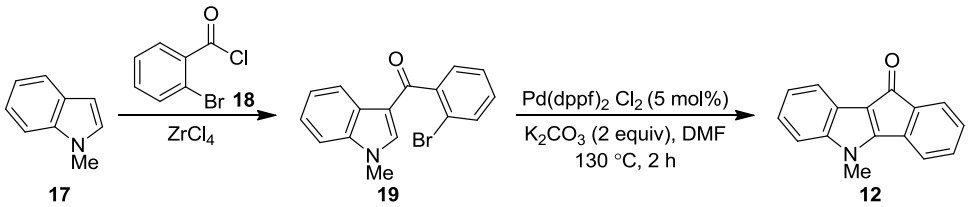
Scheme III.2

Wu and his co-workers established the synthesis of fused indole tetracyclics **16** by an intramolecular Heck reaction of N-(2-halo)-benzoyl indoles **15** (Scheme III.3).[108]



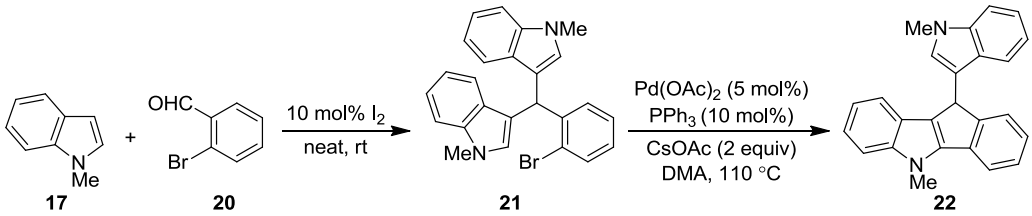
Scheme III.3

Guchhait and Kashyap disclosed an efficient two-step process involving 3-acylation of N-methyl indole **17** with 2-bromobenzoylchloride **18** followed by palladium catalyzed intramolecular annulation of **19**, leading to the fused indole tetracyclic ketone **12** (Scheme III.4).[109]



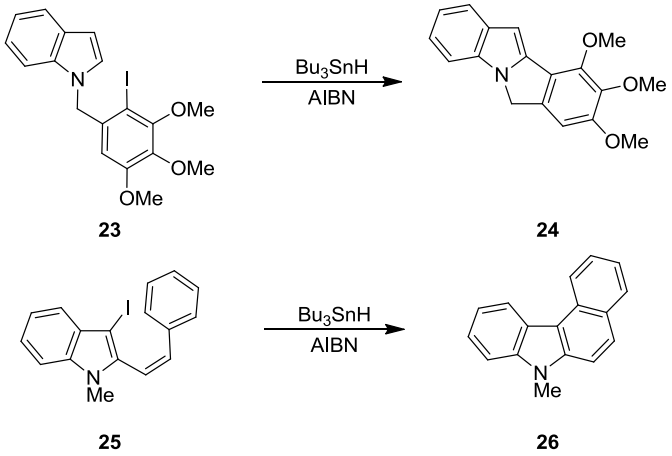
Scheme III.4

Similarly, the research group of Wang illustrated the synthesis of fused tetracyclic bis-indole alkaloids **22** in two steps from N-methyl indole **17** and bromo aldehydes **20** by a palladium catalyzed intramolecular Heck reaction of **21** as a key step (Scheme III.5).[110]



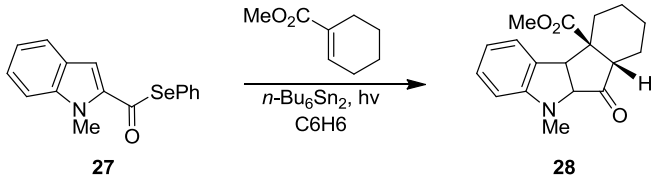
Scheme III.5

Harrowven's research group disclosed radical cyclization reactions on the derivatives of indoles, which led to novel five-membered fused tetracyclics **24** from the acyclic indole iodoarene derivative **23** and six-membered fused tetracyclics **26** from **25** (Scheme III.6).[111]



Scheme III.6

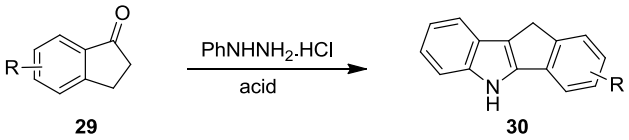
Bennasar and his co-workers developed a new selenium based free radical cyclization, which lead to the fused tetracylic **28** from the precursor **27** (Scheme III.7).[112]



27 **28**

Scheme III.7

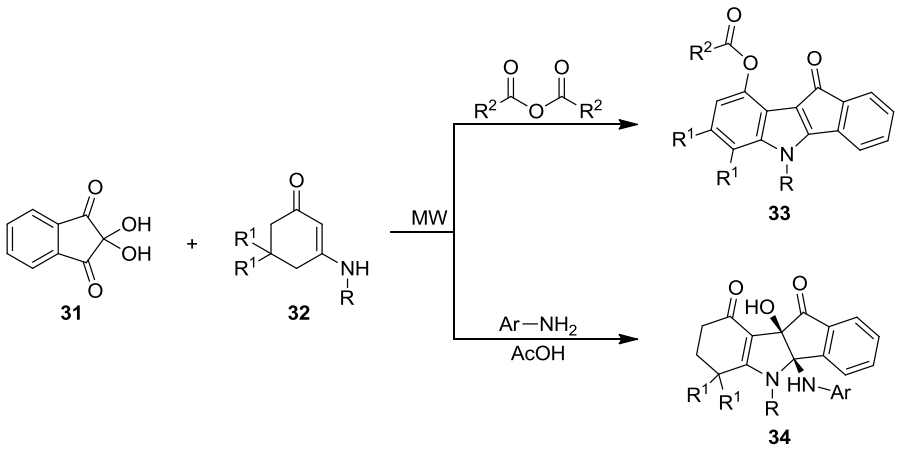
Direct Fischer indolization of indanones **29** with phenyl hydrazines furnished indenoindole fused tetracyclics **30** (Scheme III.8).[113]



29 **30**

Scheme III.8

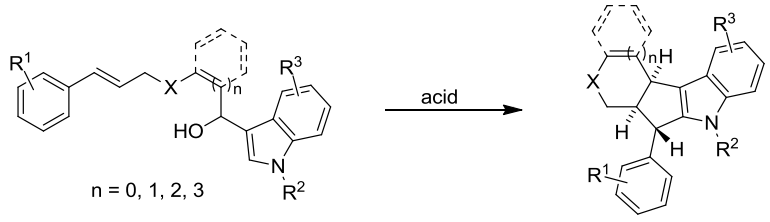
The research group of Tu reported a novel a three component domino method for the synthesis of novel tetracyclic systems **33** and **34** from ninhydrin **31** and enone **32** precursors (Scheme III.9). [18a]



31 **32** **33** **34**

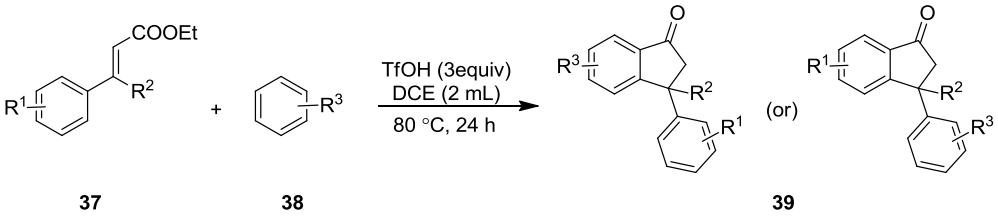
Scheme III.9

Hamada et al disclosed an expedient method for the synthesis of **36** using an acid promoted domino cyclization of indole based enol system **36** via a dual C–C bond formation [18b] (Scheme III.10).



Scheme III.10

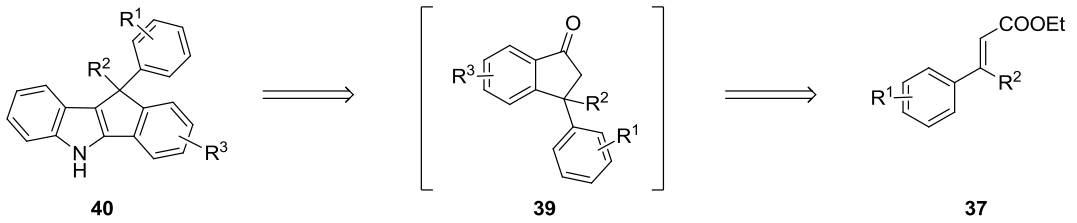
Very recently, we developed superacid mediated dual C-C bond formation, for the efficient synthesis of indanones **39** by employing a reaction between simple ethyl cinnamates **37** and an external arene **38** (Scheme III.11).[114]



Scheme III.11

III.3 RESULTS AND DISCUSSION:

With this background, the formation of novel tetracyclic fused systems was planned using a sequential domino one-pot process. Since both Friedel-Crafts and Fischer-indole reactions are feasible under acidic conditions, superacid (triflic acid) mediated Friedel-Crafts alkylation and acylation followed by Fischer-indole sequence was planned (Scheme III.12).



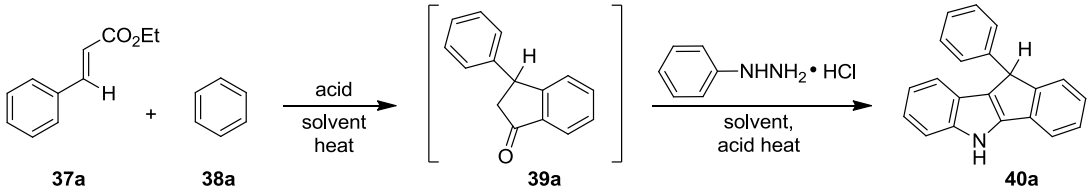
40 39 37

Scheme III.12

To the best of our knowledge, there have been no reports for Fischer-indole synthesis as a key step in either one-pot or sequential one-pot on the carbonyls that were generated in-situ.

The synthetic study began by choosing readily available simple ethyl cinnamate **37a** as a model. Ethyl cinnamate **37a** was treated under different acidic reaction conditions and the results are as summarized in Table III.1. Initially, the reaction of **37a** with benzene **38a** in the presence of triflic acid (TfOH) in hot DCE for 24 h, (i.e., initial formation of indanone **39a** followed by in-situ Fischer indole synthesis with phenylhydrazine), furnished the tetracylic cyclic system **40a**, albeit in very poor yield (entry 1, Table III.1). However, the reaction was not clean with Lewis acids such as $FeCl_3$ and $AlCl_3$ (entries 2 to 4, Table III.1), where, neither recovery of starting material **37a** nor the product **40a** product were observed. In a similar fashion, addition of different Brøwnsted acids or Lewis acids and solvents after the formation of indanone **39a**, in order to promote the subsequent Fischer-indole synthesis, was also found unproductive (entries 5 to 10, Table III.1). As most of the Fischer-indole syntheses were successful in the presence of protic solvents, addition of protic solvent EtOH as the second solvent at Fischer-indole stage, improved the yield to 22% along with the recovery of indanone **39a** (entry 11, Table III.1). Interestingly, the reaction was promoted by the additional amount of TfOH (3 equiv) along with EtOH in the Fischer indole stage by improvement in the yield, although, the intermediate product **39a** still prevailed and was recovered (entry 12, Table III.1). Further increase in the amount of triflic acid from 3 to 6 equiv, furnished the tetracyclic product **40a** in the best yield 74% (entry 13, Table III.1). The requirement of excess TfOH is justified based on the fact that the

Table III.1: Optimization conditions for the formation of **40a**.



37a 38a 39a 40a

Entry	Indanone **39a** formation				Subsequent tetracyclic fused system **40a** formation by Fischer-indole synthesis				
	Acid (equiv)	Solvent	Temp (°C)	Time (h)	Acid (equiv)	Solvent	Temp (°C)	Time (h)	Yield **40a** (%)[d]
1[a]	TfOH (3)	DCE	80	24	-	-	80	24	10
2[a]	$FeCl_3$ (3)	DCE	80	24	-	-	80	24	-[e]
3[b]	$AlCl_3$ (3)	DCE	50	12	-	-	-	-	-
4[c]	-	TFA	80	24	-	-	-	-	-
5[a]	TfOH (3)	DCE	80	24	H_2SO_4 (5)	EtOH	80	24	-[e]
6[a]	TfOH (3)	DCE	80	24	AcOH (3)	-	80	24	-[e]
7[a]	TfOH (3)	DCE	80	24	$AlCl_3$ (3)	-	80	24	-[e]
8[a]	TfOH (3)	DCE	80	24	$BF_3.Et_2O$ (20)	-	80	24	-[e]
9[a]	TfOH (3)	DCE	80	24	$AuCl_3$ (5 %)	-	80	24	-[f]
10[a]	TfOH (3)	DCE	80	24	AcOH (20)	EtOH	80	24	-[f]
11[a]	TfOH (3)	DCE	80	24	-	EtOH	80	24	22
12[a]	TfOH (3)	DCE	80	24	TfOH (3)	EtOH	80	24	55
13[a]	**TfOH (3)**	**DCE**	**80**	**24**	**TfOH (6)**	**EtOH**	**80**	**12**	**74**

[a] Proceeded for the sequential one-pot formation of the tetracyclic fused systems based on the complete conversion of cinnamate by TLC. [b] Reaction was not clean by TLC. [c] No conversion of ethyl cinnamate. [d] Isolated yields of chromatographically pure product (**40a)**. [e] Reaction was not clean by TLC. [f] No progress for Fischer-indole synthesis.

protic solvent EtOH and phenylhydrazine hydrochloride are good proton acceptors and hence, might reduce the acidity of triflic acid. Therefore, the conditions

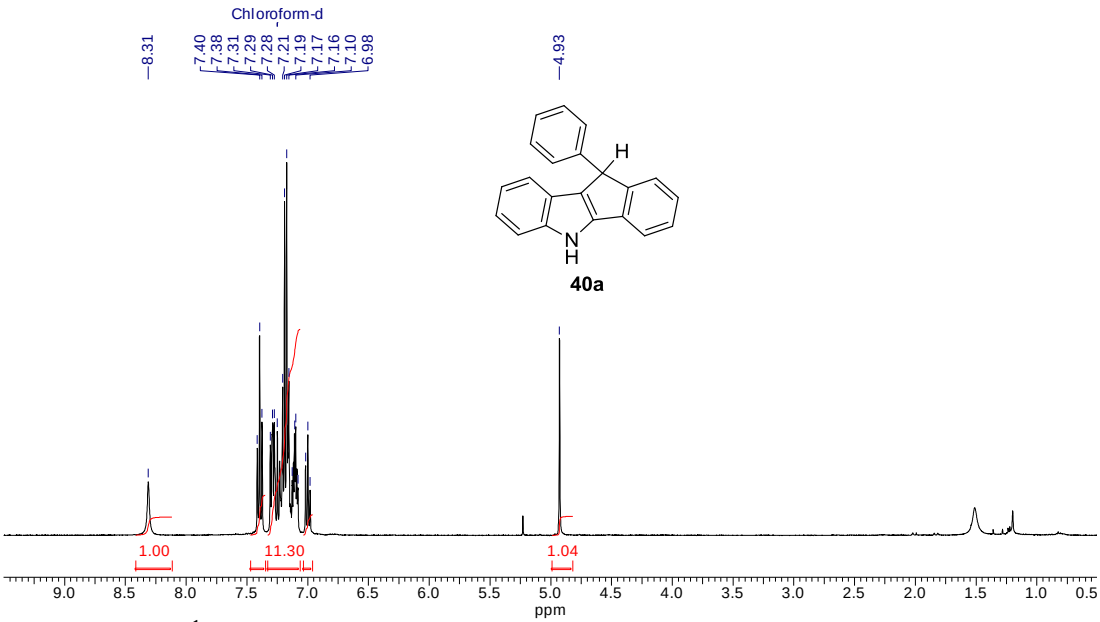


Figure III.3.1: ^{1}H NMR (400 MHz) spectrum of **40a** in $CDCl_3$

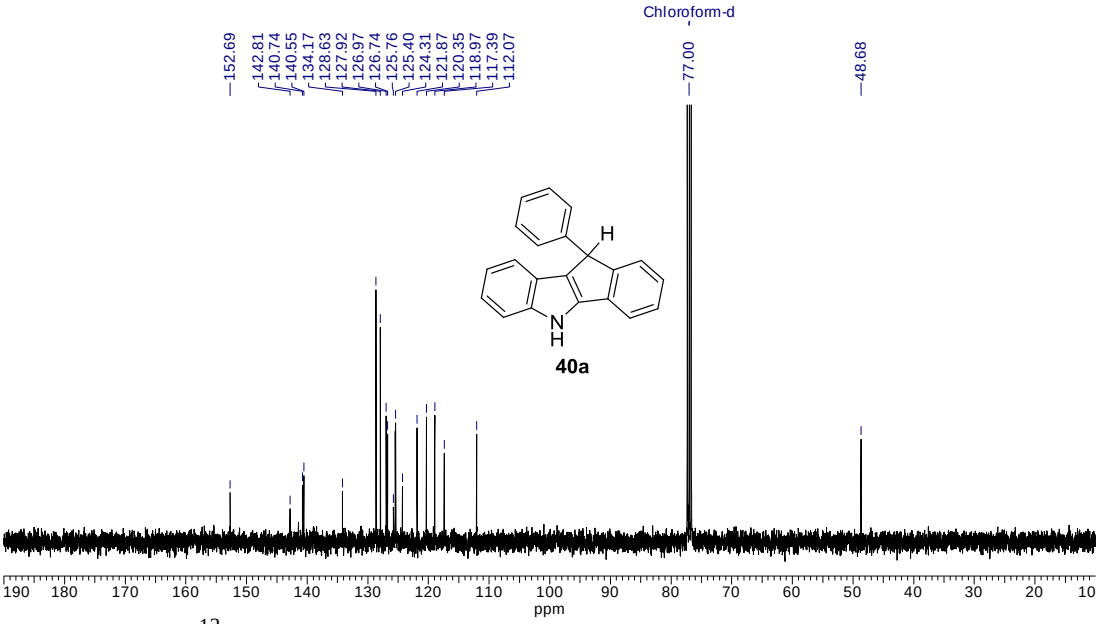


Figure III.3.2: ^{13}C NMR (100 MHz) spectrum of **40a** in $CDCl_3$

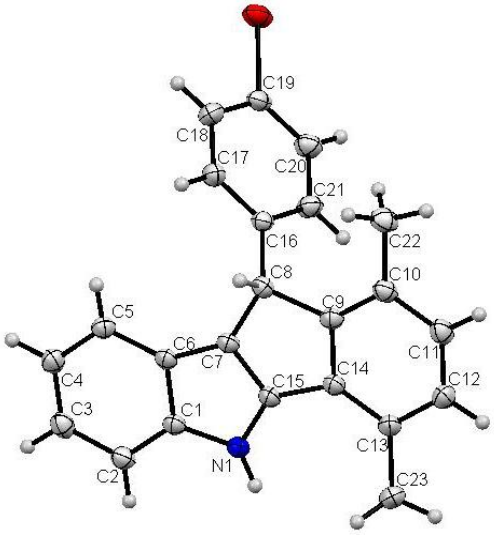
of entry 13 in Table III.1 turned out to be the best conditions and were applied to the other cinnamates **37** in order to check the scope and feasibility of the method.

The formation and structure of the tetracyclic compound **40a** was evident from spectral data. The absence of the absorption band due to carbonyl stretching of aldehyde group and the presence of the broad absorption band at 3334 cm^{-1} due to N–H stretching in the IR spectrum indicated the formation of **40a**. It was further proved from the ^{1}H-NMR spectrum (Figure III.3.1), by the presence of a broad singlet at δ 8.31 due to N–H proton, a doublet of doublet at 7.40 due to two aromatic protons, a multiplet in the region δ 7.30–7.04 because of 11 aromatic protons, a doublet of doublet at δ 7.00 for one aromatic proton, and one singlet at δ 4.93 ppm for one aliphatic proton elucidated the structure of the tetracyclic compound **40a**. In addition, in 18 lines of ^{13}C-NMR spectrum (Figure III.3.2), the presence of six quaternary carbon resonances at δ 152.7, 142.8, 140.7, 140.5, 134.2 and 124.3 due to six aromatic carbons and 11 aromatic methine carbons at δ 128.6, 127.9, 127.0, 126.7, 125.5, 125.4, 121.9, 120.3, 119.0, 117.4 and 112.1 resulting from 13 aromatic protons and one aliphatic methane at 48.7 ppm confirmed the structure of **40a**.

With the optimized reaction conditions in hand (entry 13, Table III.1), we further investigated the scope and limitations of the method using different ethyl cinnamates **37a–37i**, and the results are summarized in the Table III.2. Delightfully, this method proved to be efficient and amenable for a broad range of substrates with various substituents on the aromatic rings and furnished the corresponding fused tetracyclic products **40a–40o** containing a tertiary carbon atom at the 10th-position, in moderate to very good yields (Table III.2). Moreover, this protocol was also successfully applied to products **40p–40t** possessing a quaternary carbon center at the 10th-position (Table III.2). The method was found applicable to different aryl hydrazines and furnished the corresponding tetracyclic products **40c** and **40l** as shown in Table III.2. The regiochemistry of compound **40t** can be justified on the less sterically crowded methoxy group over the bromo substituent of **38e** that facilitates the initial Friedel-Crafts alkylation *ortho* to the methoxy group, which is

further confirmed by the 2D-NMR analysis. It is worth mentioning that among the two aromatic moieties, one from cinnamate **37** and the other from external arene **38**, for the initial indanone **39** formation, an aromatic ring that was relatively more rich in electrons selectively participated in the formation of intramolecular acylation (intramolecular condensation), after the Friedel-Crafts alkylation (Michael addition type).

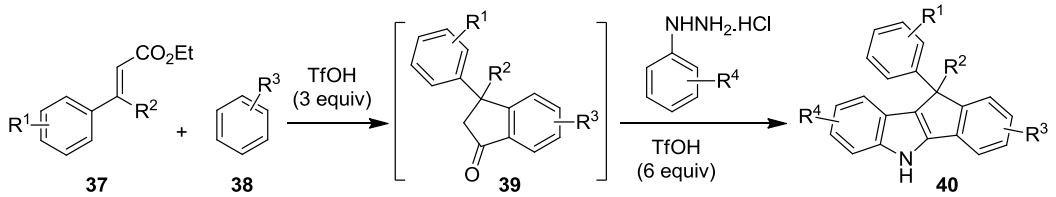
Other than spectroscopic evidence that confirmed the structure of compounds **40**, their complete structures were unambiguously confirmed by single crystal X-ray diffraction analysis of **40m** (Figure III.4).



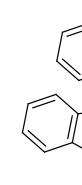
40m

(Figure III.4)

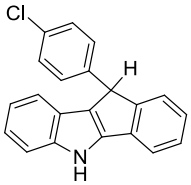
Table III.2: Synthesis of fused tetracyclic systems **40a–40t**.[a]



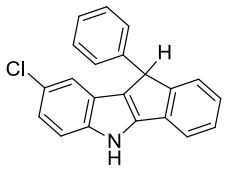
37 38 39 40



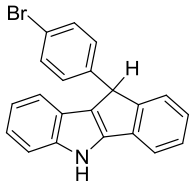
40a (74%)



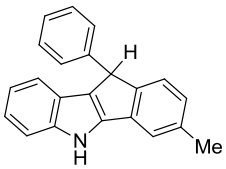
40b (72%)



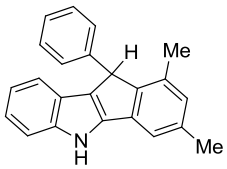
40c (68%)



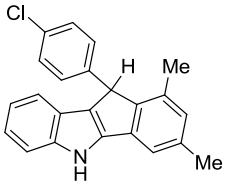
40d (70%)



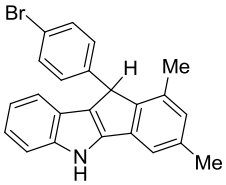
40e (61%)



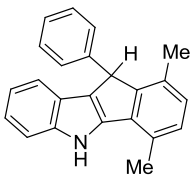
40f (76%)



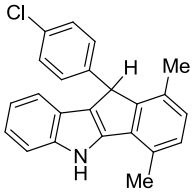
40g (61%)



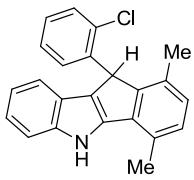
40h (55%)



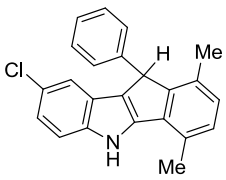
40i (84%)



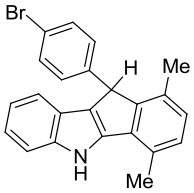
40j (72%)



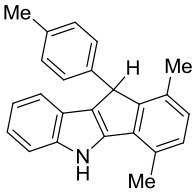
40k (74%)



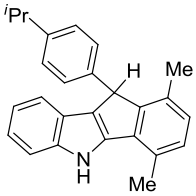
40l (76%)



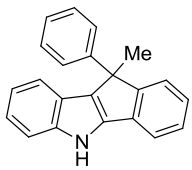
40m (89%)



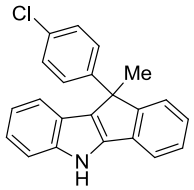
40n (62%)



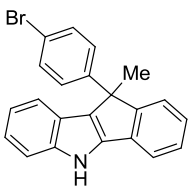
40o (60%)



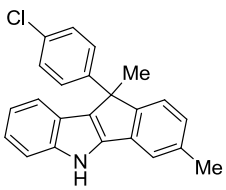
40p (63%)



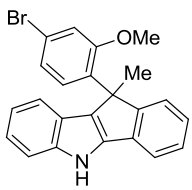
40q (63%)



40r (55%)



40s (60%)

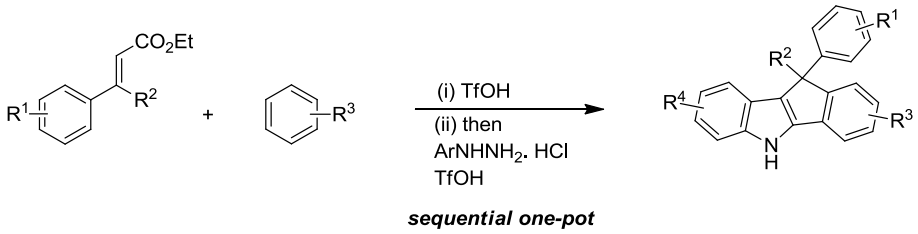


40t (51%)

[a] Yields in the parenthesis are the isolated yields of chromatographically pure products.

III.4. CONCLUSIONS:

In summary, an efficient sequential domino one-pot method was developed for the synthesis of novel fused tetracyclic indole systems via Friedel-Crafts alkylation and acylation followed by Fischer-indole reaction. These ubiquitous fused tetracyclic systems are found to be present in various biologically active alkaloid natural products. Additionally, such systems represent many biologically active scaffolds. Overall, this protocol illustrates the potential of sequential domino one-pot reactions in the field of organic chemistry.



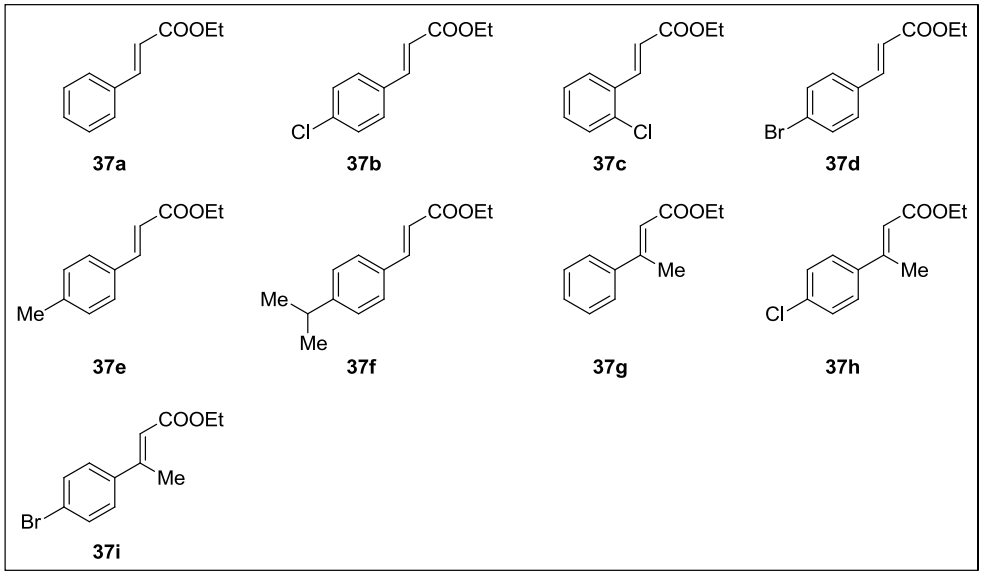
III.5 EXPERIMENTAL SECTION

General:

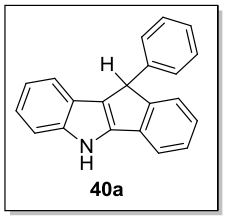
IR spectra were recorded on a Bruker Tensor 37 (FTIR) spectrophotometer. ^{1}H-NMR spectra were recorded on Bruker Avance 400 (400 MHz) spectrometer at 295 K in $CDCl_3$; chemical shifts (δ ppm) and coupling constants (Hz) are reported in standard fashion with reference to either internal standard tetramethylsilane (TMS) (δ_H =0.00 ppm) or $CHCl_3$ (δ_H = 7.25 ppm). ^{13}C-NMR spectra were recorded on Bruker Avance 400 (100 MHz) spectrometer at RT in $CDCl_3$; chemical shifts (δ ppm) are reported relative to $CHCl_3$ [δ_C = 77.00 ppm (central line of triplet)]. In the ^{13}C-NMR, the nature of carbons (C, CH, CH_2 and CH_3) was determined by recording the DEPT-135 spectra, and is given in parentheses and noted as s = singlet (for C), d = doublet (for CH), t = triplet (for CH_2) and q = quartet (for CH_3). In the ^{1}H-NMR, the following abbreviations were used throughout: s = singlet, d = doublet, t = triplet, q = quartet, qui =quintet, sept = septet, dd = doublet of doublet, m = multiplet and br. s = broad singlet. The assignment of signals was confirmed by

^{1}H, ^{13}C carbon proton decoupled (CPD) and distortionless enhancement polarization transfer (DEPT) spectra. High-resolution mass spectra (HR-MS) were recorded on an Agilent 6538 UHD Q-TOF electron spray ionization (ESI) mode and atmospheric pressure chemical ionization (APCI) modes. All small scale dry reactions were carried out using Schlenk tubes under inert atmosphere. Reactions were monitored by TLC on silica gel using a combination of hexane and ethyl acetate as eluents. Reactions were generally run under argon or a nitrogen atmosphere. Solvents were distilled prior to use; petroleum ether with a boiling range of 60 to 80 °C was used. Dichloroethane (DCE) was dried over CaH_2 and absolute ethanol was purchased from local sources, used as received. Trifluoromethanesulfonic acid (triflic acid) was purchased from Spectrochem pvt. Ltd. And used as received. Acme's silica gel (60–120 mesh) was used for column chromatography (approximately 20 g per one gram of crude material).

Ethyl cinnamate **37a** is commercially available, and other ethyl cinnamates **37b**,[115] **37c**,[116] **37d**,[117] **37e**,[118] **37f**,[119] **37g**,[120] **37h**,[121] and **37i**[122] are known in the literature.

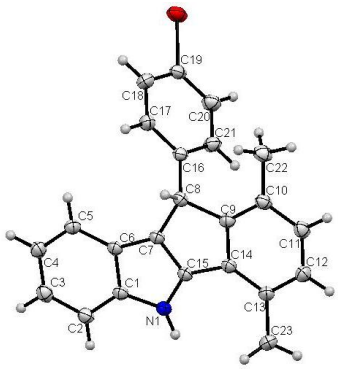


Compound **40a**[123] is also known in the literature



40a

X-ray crystal structure data for 10-(4-bromophenyl)-1,4-dimethyl-5,10-dihydroindeno[1,2-*b*]indole (40m): CCDC 990792



40m

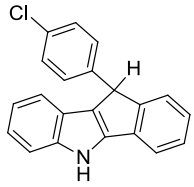
Operator	**K. Ravikumar**
Instrument	**Oxford SuperNova**
Empirical formula	$C_{23}H_{18}BrN$
Formula weight	388.29
Temperature/K	566(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	15.3751(5)
b/Å	5.2210(2)
c/Å	22.8112(7)

α/°	90.00
β/°	103.036(3)
γ/°	90.00
Volume/Å^3	1783.95(11)
Z	4
ρ_{calc}mg/mm^3	1.446
m/mm^{-1}	3.151
F(000)	792.0
Crystal size/mm^3	0.19 × 0.17 × 0.15
2Θ range for data collection	5.9 to 141.3°
Index ranges	-18 ≤ h ≤ 11, -6 ≤ k ≤ 3, -26 ≤ l ≤ 27
Reflections collected	6233
Independent reflections	3327[R(int) = 0.0228]
Data/restraints/parameters	3327/0/228
Goodness-of-fit on F^2	1.257
Final R indexes [I>=2σ (I)]	R_1 = 0.0499, wR_2 = 0.1642
Final R indexes [all data]	R_1 = 0.0622, wR_2 = 0.1824
Largest diff. peak/hole / e Å^{-3}	0.36/-0.88

General Procedure for the Preparation of 10-Phenyl-5,10-dihydroindeno[1,2-*b*]-indoles (GP-1):

In an oven dried Schlenk tube, were added cinnamate **37** (88.0–134.0 mg, 0.50 mmol), arene **38** [468.0–636 mg, 6.0 mmol (139.4 mg, 0.75 mmol in case of 3-bromoanisole)] and dichloroethane (1.5 mL) followed by triflic acid (0.13 mL, 1.5 mmol) at room temperature under nitrogen atmosphere and allowed the reaction mixture to stir at 80 °C for 24 h. Progress of the indanone **39** formation was

monitored by TLC till the reaction is completed. To the cooled reaction mixture at room temperature, were added aryl hydrazine hydrochloride (144.6–178.0 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 6.0 mmol) under nitrogen atmosphere. The stirred reaction mixture was then heated in an oil bath at 80 °C for 12 h and monitored by TLC. Then, the mixture was quenched by the addition of aqueous $NaHCO_3$ solution and extracted with ethyl acetate (3 × 15 mL). The organic layers were washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate) furnished the tetracyclic system **40** (102.8–159.7 mg, 51–89%) as viscous liquid/solid.



40b

10-(4-Chlorophenyl)-5,10-dihydroindeno[1,2-*b*]indole (40b):

GP-1 was carried out with cinnamate **37b** (105.0 mg, 0.50 mmol), benzene (468.0 mg, 6.0 mmol), triflic acid (0.13 mL, 1.5 mmol), dichoroethane (1.5 mL) at 80 °C for 24 h for the indanone **39b** formation, and then with phenylhydrazine hydrochloride (144.6 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system **40b** (113.4 mg, 72%) as a brown solid, was recrystallized the solid with dichloromethane/hexane. [TLC control (petroleum ether/ethyl acetate 95:5), R_f(**37b**)=0.51, R_f(**40b**)=0.37, UV detection].

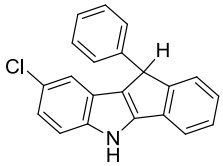
M.p.: 180–184 °C.

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3402, 2923, 1605, 1487, 1440, 1385, 1303, 1088, 1014, 814, 738 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=8.35 (br. s, 1H, NH), 7.46 (dd, 2H, *J*=7.3 and 7.3 Hz, Ar-H), 7.33 (dd, 2H, *J*=7.8 and 7.8 Hz, Ar-H), 7.31 (d, 1H, *J*=7.8 Hz, Ar-H), 7.24 (d, 2H, *J*=8.8 Hz, Ar-H), 7.22–7.15 (m, 2H, Ar-H), 7.15 (d, 2H, *J*=8.8 Hz, Ar-H), 7.08 (ddd, 1H, *J*=8.3, 7.8 and 1.0 Hz, Ar-H), 4.94 (s, 1H, CH) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=152.3 (s, Ar-C), 142.9 (s, Ar-C), 140.7 (s, Ar-C), 139.2 (s, 2C, 2 × Ar-C), 134.1 (s, Ar-C), 132.4 (s, Ar-C), 129.3 (d, 2C, Ar-CH), 128.8 (d, 2C, Ar-CH), 127.2 (d, Ar-CH), 125.6 (d, Ar-CH), 125.3 (d, Ar-CH), 124.1 (s, Ar-C), 122.0 (d, Ar-CH), 120.5 (d, Ar-CH), 118.8 (d, Ar-CH), 117.5 (d, Ar-CH), 112.2 (d, Ar-CH), 47.9 (d, CH) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{21}H_{14}ClNNa]^+$=$[M+Na]^+$: 338.0707; found 338.0708.



40c

8-Chloro-10-phenyl-5,10-dihydroindeno[1,2-*b*]indole (40c):

GP-1 was carried out with cinnamate **37a** (88.0 mg, 0.50 mmol), benzene (468.0 mg, 6.0 mmol), triflic acid (0.13 mL, 1.5 mmol), dichoroethane (1.5 mL) at 80 °C for 24 h for the indanone **39c** formation, and then with *para*-chlorophenylhydrazine hydrochloride (178.0 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system **40c** (107.1 mg, 68%) as a pale brown solid, which was recrystallized from dichloromethane/hexane. [TLC control (petroleum ether/ethyl acetate 95:5), R_f(**37a**)=0.50, R_f(**40c**)=0.36, UV detection].

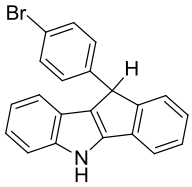
M.p.: 198–200 °C.

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3343, 2925, 1599, 1491, 1449, 1292, 1069, 937, 761, 701 cm^{-1}.

^{1}H-NMR [($CDCl_3$ + DMSO-D_6), 400 MHz]: δ=10.90 (br. s, 1H, NH), 6.90 (d, 1H, *J*=7.3 Hz, Ar-H), 6.70 (d, 1H, *J*=8.8 Hz, Ar-H), 6.65–6.38 (m, 9H, Ar-H), 6.29 (dd, 1H, *J*=8.8 and 2.0 Hz, Ar-H), 4.24 (s, 1H, CH) ppm.

^{13}C-NMR [($CDCl_3$ + DMSO-D_6), 100 MHz]: δ=150.9 (s, Ar-C), 143.4 (s, Ar-C), 139.2 (s, Ar-C), 137.9 (s, Ar-C), 132.6 (s, Ar-C), 127.1 (d, 2C, Ar-CH), 126.1 (d, 2C, Ar-CH), 125.5 (d, Ar-CH), 125.2 (d, Ar-CH), 124.1 (d, Ar-CH), 123.7 (d, Ar-CH), 123.2 (s, Ar-C), 123.0 (s, Ar-C), 121.9 (s, Ar-C), 119.3 (d, Ar-CH), 116.8 (d, Ar-CH), 115.8 (d, Ar-CH), 112.1 (d, Ar-CH), 46.5 (d, CH) ppm.

HR-MS (ESI^{+}): m/z calculated for $[C_{21}H_{14}ClNNa]^{+}$=$[M+Na]^{+}$: 338.0707; found 338.0691.



40d

10-(4-Bromophenyl)-5,10-dihydroindeno[1,2-*b*]indole (40d):

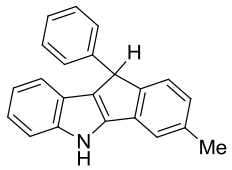
GP-1 was carried out with cinnamate **37d** (127.0 mg, 0.50 mmol), benzene (468.0 mg, 6.0 mmol), triflic acid (0.13 mL, 1.5 mmol), dichoroethane (1.5 mL) at 80 °C for 24 h for the indanone **39d** formation, and then with phenylhydrazine hydrochloride (144.6 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system **40d** (126.1 mg, 70%) as a brown semi-solid. [TLC control (petroleum ether/ethyl acetate 95:5), R_f(**37d**)=0.53, R_f(**40d**)=0.38, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3410, 3056, 1611, 1485, 1444, 1386, 1305, 1069, 1011, 740 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=8.41 (br. s, 1H, NH), 7.46 (dd, 2H, *J*=8.3 and 7.8 Hz, Ar-H), 7.38 (d, 2H, *J*=8.3 Hz, Ar-H), 7.35–7.28 (m, 3H, Ar-H), 7.13–7.22 (m, 2H, Ar-H), 7.09 (d, 2H, *J*=8.3 Hz, Ar-H), 7.10–7.04 (m, 1H, Ar-H), 4.92 (s, 1H, CH) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=152.1 (s, Ar-C), 142.9 (s, Ar-C), 140.7 (s, Ar-C), 139.7 (s, 2C, 2 × Ar-C), 134.1 (s, Ar-C), 131.7 (d, 2C, Ar-CH), 129.6 (d, 2C, Ar-CH), 127.2 (d, Ar-CH), 125.6 (d, Ar-CH), 125.3 (d, Ar-CH), 125.2 (s, Ar-C), 124.1 (s, Ar-C), 122.0 (d, Ar-CH), 120.5 (d, Ar-CH), 118.8 (d, Ar-CH), 117.5 (d, Ar-CH), 112.2 (d, Ar-CH), 48.0 (d, CH) ppm.

HR-MS (APCI^{+}): m/z calculated for $[C_{21}H_{15}{}^{81}BrN]^{+}$=$[M+H]^{+}$: 362.0382; found 362.0360.



40e

3-Methyl-10-phenyl-5,10-dihydroindeno[1,2-*b*]indole (40e):

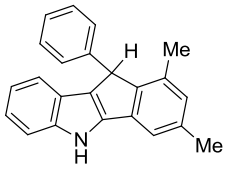
GP-1 was carried out with cinnamate **37a** (88.0 mg, 0.50 mmol), toluene (552.0 mg, 6.0 mmol), triflic acid (0.13 mL, 1.5 mmol), dichoroethane (1.5 mL) at 80 °C for 24 h for the indanone **39e** formation, and then with phenylhydrazine hydrochloride (144.6 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system **40e** (90.1 mg, 61%) as a brown semi-solid. [TLC control (petroleum ether/ethyl acetate 95:5), R_f(**37a**)=0.50, R_f(**40e**)=0.36, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3409, 2920, 1599, 1491, 1451, 1248, 907, 730 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=8.27 (br. s, 1H, NH), 7.33 (d, 1H, *J*=7.8 Hz, Ar-H), 7.26 (d, 2H, *J*=7.8 Hz, Ar-H), 7.20–6.90 (m, 8H, Ar-H), 6.88 (d, 1H, *J*=7.3 Hz, Ar-H), 4.86 (s, 1H, CH), 2.31 (s, 3H, Ar-CH_3) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=149.9 (s, Ar-C), 142.8 (s, Ar-C), 140.9 (s, Ar-C), 136.7 (s, Ar-C), 134.3 (s, Ar-C), 129.3 (s, Ar-C), 128.6 (d, 2C, Ar-CH), 128.5 (s, Ar-C), 127.9 (d, 2C, Ar-CH), 126.6 (d, Ar-CH), 126.2 (d, Ar-CH), 125.0 (d, Ar-CH), 124.4 (s, Ar-C), 121.7 (d, Ar-CH), 120.3 (d, Ar-CH), 118.9 (d, Ar-CH), 118.3 (d, Ar-CH), 112.1 (d, Ar-CH), 48.3 (d, CH), 21.5 (q, Ar-CH_3) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{22}H_{17}KN]^+$=$[M+K]^+$: 334.0993; found 334.0986.



40f

1,3-Dimethyl-10-phenyl-5,10-dihydroindeno[1,2-*b*]indole (40f):

GP-1 was carried out with cinnamate **37a** (88.0 mg, 0.50 mmol), *m*-xylene (636.0 mg, 6.0 mmol), triflic acid (0.13 mL, 1.5 mmol), dichoroethane (1.5 mL) at 80 °C for 24 h for the indanone **39f** formation, and then with phenylhydrazine hydrochloride (144.6 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system **40f** (117.6 mg, 76%) as a brown solid, which was recrystallized from dichloromethane/hexane. [TLC control (petroleum ether/ethyl acetate 95:5), R_f(**37a**)=0.50, R_f(**40f**)=0.36, UV detection].

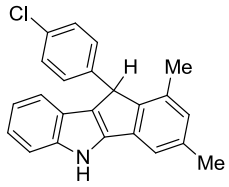
M.p.: 194–198 °C.

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3387, 2921, 1600, 1493, 1450, 1304, 1253, 907, 730 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=8.28 (br. s, 1H, NH), 7.38 (d, 1H, *J*=8.3 Hz, Ar-H), 7.34 (d, 1H, *J*=7.8 Hz, Ar-H), 7.24–7.13 (m, 6H, Ar-H), 7.10 (ddd, 1H, *J*=8.3, 7.8 and 1.0 Hz, Ar-H), 7.01 (ddd, 1H, *J*=7.8, 7.8 and 1.0 Hz, Ar-H), 6.81 (s, 1H, Ar-H), 4.92 (s, 1H, CH), 2.42 (s, 3H, Ar-CH_3), 2.04 (s, 3H, Ar-CH_3) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=147.5 (s, Ar-C), 142.0 (s, Ar-C), 140.5 (s, Ar-C), 140.4 (s, Ar-C), 137.2 (s, Ar-C), 135.1 (s, Ar-C), 135.0 (s, Ar-C), 128.5 (d, 2C, Ar-CH), 128.2 (d, Ar-CH), 127.9 (d, 2C, Ar-CH), 127.7 (s, ArC), 126.3 (d, Ar-CH), 124.1 (s, Ar-C), 121.6 (d, Ar-CH), 120.2 (d, Ar-CH), 118.4 (d, Ar-CH), 116.0 (d, Ar-CH), 111.9 (d, Ar-CH), 48.2 (d, CH), 21.4 (q, Ar-CH_3), 18.7 (q, Ar-CH_3) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{23}H_{23}N_2]^+=[M+NH_4]^+$: 327.1856; found 327.1841.



40g

10-(4-Chlorophenyl)-1,3-dimethyl-5,10-dihydroindeno[1,2-*b*]indole (40g):

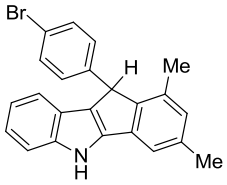
GP-1 was carried out with cinnamate **37b** (105.0 mg, 0.50 mmol), *m*-xylene (636.0 mg, 6.0 mmol), triflic acid (0.13 mL, 1.5 mmol), dichoroethane (1.5 mL) at 80 °C for 24 h for the indanone **39g** formation, and then with phenylhydrazine hydrochloride (144.6 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system **40g** (104.8 mg, 61%) as a brown viscous liquid. [TLC control (petroleum ether/ethyl acetate 95:5), R_f(**37b**)=0.51, R_f(**40g**)=0.36, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3406, 2921, 1615, 1488, 1454, 1305, 1014, 845, 742 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=8.28 (br. s, 1H, NH), 7.39 (d, 1H, *J*=7.8 Hz, Ar-H), 7.30 (d, 1H, *J*=7.8 Hz, Ar-H), 7.22–7.14 (m, 3H, Ar-H), 7.11 (ddd, 1H, *J*=7.8, 7.8 and 1.0 Hz, Ar-H), 7.07 (d, 2H, *J*=8.3 Hz, Ar-H), 7.01 (ddd, 1H, *J*=7.8, 7.3 and 1.0 Hz, Ar-H), 6.80 (s, 1H, Ar-H), 4.89 (s, 1H, CH), 2.41 (s, 3H, Ar-CH_3), 2.03 (s, 3H, Ar-CH_3) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=147.1 (s, Ar-C), 142.0 (s, Ar-C), 140.5 (s, Ar-C), 139.2 (s, Ar-C), 137.5 (s, Ar-C), 135.0 (s, Ar-C), 134.9 (s, Ar-C), 131.9 (s, Ar-C), 129.3 (d, 2C, Ar-CH), 128.7 (d, 2C, Ar-CH), 128.3 (d, Ar-CH), 127.3 (s, ArC), 124.0 (s, Ar-C), 121.8 (d, Ar-CH), 120.3 (d, Ar-CH), 118.3 (d, Ar-CH), 116.1 (d, Ar-CH), 112.0 (d, Ar-CH), 47.4 (d, CH), 21.4 (q, Ar-CH_3), 18.7 (q, Ar-CH_3) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{23}H_{19}ClN]^+$=$[M+H]^+$: 344.1201; found 344.1197.



40h

10-(4-Bromophenyl)-1,3-dimethyl-5,10-dihydroindeno[1,2-*b*]indole (40h):

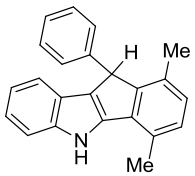
GP-1 was carried out with cinnamate **37d** (127.0 mg, 0.50 mmol), *m*-xylene (636.0 mg, 6.0 mmol), triflic acid (0.13 mL, 1.5 mmol), dichoroethane (1.5 mL) at 80 °C for 24 h for the indanone **39h** formation, and then with phenylhydrazine hydrochloride (144.6 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system **40h** (106.8 mg, 55%) as a brown semi-solid. [TLC control (petroleum ether/ethyl acetate 95:5), R_f(**37d**)=0.53, R_f(**40h**)=0.37, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3356, 2921, 1588, 1484, 1451, 1262, 1246, 1070, 1010, 739 cm^{-1}.

^{1}H-NMR (CDCl$_3$, 400 MHz): δ=8.27 (br. s, 1H, NH), 7.39 (d, 1H, *J*=8.3 Hz, Ar-H), 7.33 (d, 2H, *J*=8.3 Hz, Ar-H), 7.32 (d, 1H, *J*=8.3 Hz, Ar-H), 7.17 (s, 1H, Ar-H), 7.12 (ddd, 1H, *J*=8.3, 7.8 and 1.0 Hz, Ar-H), 7.03 (d, 2H, *J*=8.3 Hz, Ar-H), 7.02 (ddd, 1H, *J*=8.3, 7.8 and 1.0 Hz, Ar-H), 6.81 (s, 1H, Ar-H), 4.87 (s, 1H, CH), 2.41 (s, 3H, Ar-CH$_3$), 2.03 (s, 3H, Ar-CH$_3$) ppm.

^{13}C-NMR (CDCl$_3$, 100 MHz): δ=147.0 (s, Ar-C), 142.0 (s, Ar-C), 140.5 (s, Ar-C), 139.7 (s, Ar-C), 137.5 (s, Ar-C), 135.0 (s, Ar-C), 134.9 (s, Ar-C), 131.6 (d, 2C, Ar-CH), 129.7 (d, 2C, Ar-CH), 128.3 (d, Ar-CH), 127.1 (s, ArC), 123.9 (s, Ar-C), 121.8 (d, Ar-CH), 120.3 (d, Ar-CH), 119.9 (s, Ar-C), 118.3 (d, Ar-CH), 116.1 (d, Ar-CH), 112.0 (d, Ar-CH), 47.5 (d, CH), 21.4 (q, Ar-CH$_3$), 18.7 (q, Ar-CH$_3$) ppm.

HR-MS (ESI$^-$): m/z calculated for $[C_{23}H_{17}BrN]^-$=$[M–H]^-$: 386.0550; found 386.0558.



40i

1,4-Dimethyl-10-phenyl-5,10-dihydroindeno[1,2-*b*]indole (40i):

GP-1 was carried out with cinnamate **37a** (88.0 mg, 0.50 mmol), *p*-xylene (636.0 mg, 6.0 mmol), triflic acid (0.13 mL, 1.5 mmol), dichoroethane (1.5 mL) at 80 °C for 24 h for the indanone **39i** formation, and then with phenylhydrazine hydrochloride (144.6 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system **40i** (129.9 mg, 84%) as a pale yellow solid, which was recrystallized from dichloromethane/hexane. [TLC control (petroleum ether/ethyl acetate 95:5), R_f(**37a**)=0.50, R_f(**40i**)=0.35, UV detection].

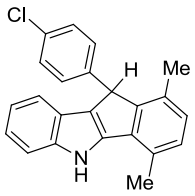
M. p.: 198–200 °C.

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3445, 3023, 1598, 1478, 1444, 1296, 1243, 1078, 1029, 907, 733 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=8.33 (br. s, 1H, NH), 7.42 (d, 1H, *J*=8.3 Hz, Ar-H), 7.36 (d, 1H, *J*=7.8 Hz, Ar-H), 7.25–7.09 (m, 6H, Ar-H), 7.07 (d, 1H, *J*=7.8 Hz, Ar-H), 7.02 (ddd, 1H, *J*=8.3, 7.8 and 1.0 Hz, Ar-H), 6.89 (d, 1H, *J*=7.8 Hz, Ar-H), 4.93 (s, 1H, CH), 2.67 (s, 3H, Ar-CH_3), 2.04 (s, 3H, Ar-CH_3) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=150.1 (s, Ar-C), 142.4 (s, Ar-C), 140.8 (s, Ar-C), 140.4 (s, Ar-C), 134.2 (s, Ar-C), 132.8 (s, Ar-C), 128.9 (d, Ar-CH), 128.5 (d, 2C, Ar-CH), 127.9 (d, 2C, Ar-CH), 127.5 (d, Ar-CH), 127.1 (s, ArC), 126.3 (d, Ar-CH), 125.5 (s, Ar-C), 123.9 (s, Ar-C), 121.5 (d, Ar-CH), 120.2 (d, Ar-CH), 118.4 (d, Ar-CH), 111.9 (d, Ar-CH), 48.4 (d, CH), 19.1 (q, Ar-CH_3), 18.5 (q, Ar-CH_3) ppm.

HR-MS (ESI^{-}): m/z calculated for $[C_{23}H_{19}NNa]^+$=$[M+Na]^+$: 332.1410; found 332.1404.



40j

10-(4-Chlorophenyl)-1,4-dimethyl-5,10-dihydroindeno[1,2-*b*]indole (40j):

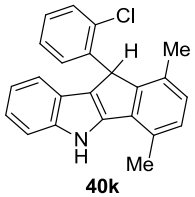
GP-1 was carried out with cinnamate **37b** (105.0 mg, 0.50 mmol), *p*-xylene (636.0 mg, 6.0 mmol), triflic acid (0.13 mL, 1.5 mmol), dichoroethane (1.5 mL) at 80 °C for 24 h for the indanone **39j** formation, and then with phenylhydrazine hydrochloride (144.6 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system **40j** (123.7 mg, 72%) as a brown semi-solid. [TLC control (petroleum ether/ethyl acetate 95:5), R_f(**37b**)=0.51, R_f(**40j**)=0.36, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3454, 2922, 1592, 1488, 1444, 1298, 1087, 1014, 803, 741 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=8.33 (br. s, 1H, NH), 7.43 (d, 1H, *J*=7.8 Hz, Ar-H), 7.32 (d, 1H, *J*=7.8 Hz, Ar-H), 7.18 (d, 2H, *J*=8.3 Hz, Ar-H), 7.12 (dd, 1H, *J*=7.8 and 7.3 Hz, Ar-H), 7.07 (d, 2H, *J*=8.3 Hz, Ar-H), 7.06 (d, 1H, *J*=7.8 Hz, Ar-H), 7.03 (dd, 1H, *J*=7.8 and 7.3 Hz, Ar-H), 6.88 (d, 1H, *J*=7.8 Hz, Ar-H), 4.89 (s, 1H, CH), 2.66 (s, 3H, Ar-CH_3), 2.03 (s, 3H, Ar-CH_3) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=149.6 (s, Ar-C), 142.4 (s, Ar-C), 140.8 (s, Ar-C), 139.1 (s, Ar-C), 134.1 (s, Ar-C), 132.7 (s, Ar-C), 131.9 (s, Ar-C), 129.3 (d, 2C, Ar-CH), 129.1 (d, Ar-CH), 128.7 (d, 2C, Ar-CH), 127.6 (d, Ar-CH), 126.6 (s, Ar-C), 125.7 (s, Ar-C), 123.7 (s, Ar-C), 121.6 (d, Ar-CH), 120.4 (d, Ar-CH), 118.2 (d, Ar-CH), 112.0 (d, Ar-CH), 47.6 (d, CH), 19.1 (q, Ar-CH_3), 18.5 (q, Ar-CH_3) ppm.

HR-MS (ESI^{+}): m/z calculated for $[C_{23}H_{19}ClN]^{+}$=$[M+H]^{+}$: 344.1201; found 344.1193.



40k

10-(2-Chlorophenyl)-1,4-dimethyl-5,10-dihydroindeno[1,2-*b*]indole (40k):

GP-1 was carried out with cinnamate **37c** (105.0 mg, 0.50 mmol), *p*-xylene (636.0 mg, 6.0 mmol), triflic acid (0.13 mL, 1.5 mmol), dichoroethane (1.5 mL) at 80 °C for 24 h for the indanone **39k** formation, and then with phenylhydrazine hydrochloride (144.6 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system **40k** (127.2 mg, 74%) as a pale brown solid, which was recrystallized from dichloromethane/hexane. [TLC control (petroleum ether/ethyl acetate 95:5), R_f(**37c**)=0.51, R_f(**40k**)=0.36, UV detection].

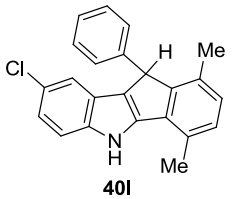
M.p.: 208–210 °C.

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3375, 2923, 1593, 1489, 1443, 1299, 1151, 1130, 1038, 820, 746 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=8.30 (br. s, 1H, NH), 7.51 (d, 1H, *J*=7.8 Hz, Ar-H), 7.50 (dd, 1H, *J*=7.8 and 1.0 Hz, Ar-H), 7.42 (d, 1H, *J*=7.8 Hz, Ar-H), 7.14 (ddd, 1H, *J*=8.3, 7.8 and 1.0 Hz, Ar-H), 7.12–7.02 (m, 3H, Ar-H), 6.92 (d, 1H, *J*=8.3 Hz, Ar-H), 6.89 (d, 1H, *J*=8.3 Hz, Ar-H), 6.44 (dd, 1H, *J*=7.8 and 1.5 Hz, Ar-H), 5.53 (s, 1H, CH), 2.67 (s, 3H, Ar-CH_3), 2.00 (s, 3H, Ar-CH_3) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=150.1 (s, Ar-C), 142.6 (s, Ar-C), 140.7 (s, Ar-C), 138.0 (s, Ar-C), 134.3 (s, Ar-C), 134.2 (s, Ar-C), 132.5 (s, Ar-C), 129.3 (d, Ar-CH), 129.0 (d, Ar-CH), 128.1 (d, Ar-CH), 127.6 (d, Ar-CH), 127.5 (d, Ar-CH), 127.2 (d, Ar-CH), 126.7 (s, Ar-C), 125.6 (s, Ar-C), 123.6 (s, Ar-C), 121.6 (d, Ar-CH), 120.4 (d, Ar-CH), 119.0 (d, Ar-CH), 111.8 (d, Ar-CH), 43.8 (d, CH), 19.1 (q, Ar-CH_3), 18.0 (q, Ar-CH_3) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{23}H_{18}ClN]^+$=$[M]^+$: 343.1122; found 343.1129.



40l

8-Chloro-1,4-dimethyl-10-phenyl-5,10-dihydroindeno[1,2-*b*]indole (40l):

GP-1 was carried out with cinnamate **37a** (88.0 mg, 0.50 mmol), *p*-xylene (636.0 mg, 6.0 mmol), triflic acid (0.13 mL, 1.5 mmol), dichoroethane (1.5 mL) at 80 °C for 24 h for the indanone **39l** formation, and then with *p*-chlorophenyl hydrazine hydrochloride (178.0 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system **40l** (130.6 mg,

76%) as a pale brown solid, which was recrystallized from dichloromethane/hexane [TLC control (petroleum ether/ethyl acetate 95:5), R_f(**37a**)=0.50, R_f(**40l**)=0.36, UV detection].

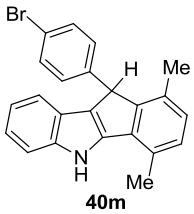
M.p.: 224–226 °C.

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3444, 2922, 1600, 1452, 1289, 1057, 797 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=8.31 (br. s, 1H, NH), 7.30 (d, 1H, *J*=8.8 Hz, Ar-H), 7.28 (d, 1H, *J*=1.9 Hz, Ar-H), 7.21 (d, 2H, *J*=7.8 Hz, Ar-H), 7.17 (t, 1H, *J*=7.3 Hz, Ar-H), 7.13–7.00 (m, 4H, Ar-H), 6.90 (d, 1H, *J*=7.8 Hz, Ar-H), 4.85 (s, 1H, CH), 2.64 (s, 3H, Ar-CH_3), 2.01 (s, 3H, Ar-CH_3) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=150.1 (s, Ar-C), 143.8 (s, Ar-C), 139.9 (s, Ar-C), 139.0 (s, Ar-C), 133.6 (s, Ar-C), 132.9 (s, Ar-C), 129.0 (d, Ar-CH), 128.7 (d, 2C, Ar-CH), 128.0 (d, Ar-CH), 127.8 (d, 2C, Ar-CH), 126.5 (s, Ar-C), 126.4 (s, Ar-C), 125.9 (s, Ar-C), 125.8 (s, Ar-C), 124.8 (s, Ar-C), 121.5 (d, Ar-CH), 117.7 (d, Ar-CH), 112.7 (d, Ar-CH), 48.2 (d, CH), 19.1 (q, Ar-CH_3), 18.4 (q, Ar-CH_3) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{23}H_{19}ClN]^+$=$[M+H]^+$: 344.1201; found 344.1199.



40m

10-(4-Bromophenyl)-1,4-dimethyl-5,10-dihydroindeno[1,2-*b*]indole (40m):

GP-1 was carried out with cinnamate **37d** (127.0 mg, 0.50 mmol), *p*-xylene (636.0 mg, 6.0 mmol), triflic acid (0.13 mL, 1.5 mmol), dichoroethane (1.5 mL) at 80 °C for 24 h for the indanone **39m** formation, and then with phenylhydrazine hydrochloride (144.6 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 °C for 12 h. Purification of the

crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system **40m** (172.0 mg, 89%) as a brown solid, which was recrystallized from dichloromethane/hexane. [TLC control (petroleum ether/ethyl acetate 95:5), R_f(**37d**)=0.53, R_f(**40m**)=0.37, UV detection].

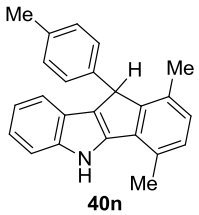
M.p.: 228–230 °C

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3443, 2918, 1591, 1485, 1444, 1298, 1070, 1010, 908, 803, 731 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=8.32 (br. s, 1H, NH), 7.43 (d, 1H, *J*=7.8 Hz, Ar-H), 7.35–7.28 (m, 1H, Ar-H), 7.33 (d, 2H, *J*=8.3 Hz, Ar-H), 7.13 (ddd, 1H, *J*=8.3, 7.3 and 1.0 Hz, Ar-H), 7.08 (d, 1H, *J*=7.8 Hz, Ar-H), 7.05 (d, 1H, *J*=7.8 Hz, Ar-H), 7.01 (d, 2H, *J*=8.3 Hz, Ar-H), 6.89 (d, 1H, *J*=7.3 Hz, Ar-H), 4.86 (s, 1H, CH), 2.65 (s, 3H, Ar-CH_3), 2.03 (s, 3H, Ar-CH_3) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=149.6 (s, Ar-C), 142.4 (s, Ar-C), 140.7 (s, Ar-C), 139.7 (s, Ar-C), 134.1 (s, Ar-C), 132.7 (s, Ar-C), 131.6 (d, 2C, Ar-CH), 129.7 (d, 2C, Ar-CH), 129.1 (d, Ar-CH), 127.6 (d, Ar-CH), 126.4 (s, ArC), 125.7 (s, Ar-C), 123.7 (s, Ar-C), 121.6 (d, Ar-CH), 120.4 (d, Ar-CH), 119.9 (s, Ar-C), 118.2 (d, Ar-CH), 112.0 (d, Ar-CH), 47.6 (d, CH), 19.1 (q, Ar-CH_3), 18.5 (q, Ar-CH_3) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{23}H_{18}BrN]^+$=$[M]^+$: 387.0623; found 387.0605.



40n

1,4-Dimethyl-10-(4-methylphenyl)-5,10-dihydroindeno[1,2-*b*]indole (40n):

GP-1 was carried out with cinnamate **37e** (95.0 mg, 0.50 mmol), *p*-xylene (636.0 mg, 6.0 mmol), triflic acid (0.13 mL, 1.5 mmol), dichoroethane (1.5 mL) at

80 °C for 24 h for the indanone **39n** formation, and then with phenylhydrazine hydrochloride (144.6 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system **40n** (100.2 mg, 62%) as a pale brown solid, which was recrystallized from dichloromethane/hexane. [TLC control (petroleum ether/ethyl acetate 95:5), R_f(**37e**)=0.52, R_f(**40n**)=0.37, UV detection].

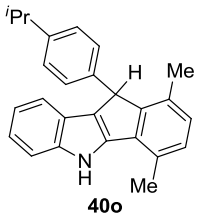
M.p.: 204–208 °C

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3440, 2917, 1589, 1510, 1479, 1443, 1298, 1244, 906, 801, 728 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=8.29 (br. s, 1H, NH), 7.42 (d, 1H, *J*=7.8 Hz, Ar-H), 7.42 (d, 1H, *J*=7.8 Hz, Ar-H), 7.39 (d, 1H, *J*=7.8 Hz, Ar-H), 7.13 (ddd, 1H, *J*=8.3, 7.8 and 1.0 Hz, Ar-H), 7.08 (d, 1H, *J*=7.3 Hz, Ar-H), 7.07–6.98 (m, 4H, Ar-H), 6.90 (d, 1H, *J*=7.8 Hz, Ar-H), 4.89 (s, 1H, CH), 2.66 (s, 3H, Ar-CH_3), 2.28 (s, 3H, Ar-CH_3), 2.06 (s, 3H, Ar-CH_3) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=150.2 (s, Ar-C), 142.3 (s, Ar-C), 140.8 (s, Ar-C), 137.1 (s, Ar-C), 135.7 (s, Ar-C), 134.1 (s, Ar-C), 132.8 (s, Ar-C), 129.2 (d, 2C, Ar-CH), 128.8 (d, Ar-CH), 127.7 (d, 2C, Ar-CH), 127.4 (d, Ar-CH), 127.2 (s, Ar-C), 125.5 (s, ArC), 123.9 (s, Ar-C), 121.4 (d, Ar-CH), 120.2 (d, Ar-CH), 118.4 (d, Ar-CH), 111.9 (d, Ar-CH), 48.0 (d, CH), 21.0 (q, Ar-CH_3), 19.1 (q, Ar-CH_3), 18.5 (q, Ar-CH_3) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{24}H_{22}N]^+$=$[M+H]^+$: 324.1747; found 324.1745.



40o

10-(4-Isopropylphenyl)-1,4-dimethyl-5,10-dihydroindeno[1,2-*b*]indole (40o):

GP-1 was carried out with cinnamate **37f** (109.0 mg, 0.50 mmol), *p*-xylene (636.0 mg, 6.0 mmol), triflic acid (0.13 mL, 1.5 mmol), dichoroethane (1.5 mL) at 80 °C for 24 h for the indanone **39o** formation, and then with phenylhydrazine hydrochloride (144.6 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system **40o** (105.4 mg, 60%) as a pale orange solid, which was recrystallized from dichloromethane/hexane. [TLC control (petroleum ether/ethyl acetate 95:5), R_f(**37f**)=0.53, R_f(**40o**)=0.38, UV detection].

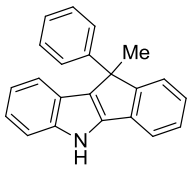
M.p.: 182–184 °C

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3379, 2959, 1602, 1485, 1454, 1298, 1245, 1053, 804, 743 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=8.29 (br. s, 1H, NH), 7.42 (d, 1H, *J*=8.3 Hz, Ar-H), 7.41 (d, 1H, *J*=7.8 Hz, Ar-H), 7.13 (dd, 1H, *J*=7.8 and 7.3 Hz, Ar-H), 7.09–6.96 (m, 6H, Ar-H), 6.89 (d, 1H, *J*=8.3 Hz, Ar-H), 4.90 (s, 1H, CH), 2.84 [sept, 1H, *J*=6.8 Hz, -C*H*$(CH_3)_2$], 2.66 (s, 3H, Ar-CH_3), 2.05 (s, 3H, Ar-CH_3), 1.20 [d, 6H, *J*=6.8 Hz, -CH(C*H*$_3)_2$] ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=150.2 (s, Ar-C), 146.6 (s, Ar-C), 142.3 (s, Ar-C), 140.8 (s, Ar-C), 137.3 (s, Ar-C), 134.1 (s, Ar-C), 132.8 (s, Ar-C), 128.8 (d, Ar-CH), 127.7 (d, 2C, Ar-CH), 127.4 (d, Ar-CH), 127.2 (s, Ar-C), 126.5 (d, 2C, Ar-CH), 125.4 (s, Ar-C), 123.9 (s, Ar-C), 121.4 (d, Ar-CH), 120.1 (d, Ar-CH), 118.5 (d, Ar-CH), 111.9 (d, Ar-CH), 48.0 (d, CH), 33.6 [d, -*C*H$(CH_3)_2$], 24.0 [q, -CH(*C*$H_3)_{2a}$], 23.9 [q, -CH(*C*$H_3)_{2b}$], 19.1 (q, Ar-CH_3), 18.5 (q, Ar-CH_3) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{26}H_{26}N]^+$=$[M+H]^+$: 352.2060; found 352.2045.



40p

10-Methyl-10-phenyl-5,10-dihydroindeno[1,2-*b*]indole (40p):

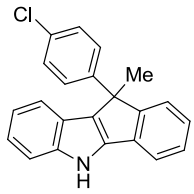
GP-1 was carried out with cinnamate **37g** (95.0 mg, 0.50 mmol), benzene (468.0 mg, 6.0 mmol), triflic acid (0.13 mL, 1.5 mmol), dichoroethane (1.5 mL) at 80 °C for 24 h for the indanone **39p** formation, and then with phenylhydrazine hydrochloride (144.6 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system **40p** (93.0 mg, 63%) as a brown viscous liquid. [TLC control (petroleum ether/ethyl acetate 95:5), R_f(**37b**)=0.51, R_f(**40b**)=0.36, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3412, 2925, 1599, 1495, 1441, 1315, 1247, 1018, 741 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=8.35 (br. s, 1H, NH), 7.44 (d, 1H, *J*=7.9 Hz, Ar-H), 7.43–7.36 (m, 5H, Ar-H), 7.27 (d, 1H, *J*=7.9 Hz, Ar-H), 7.25–7.13 (m, 5H, Ar-H), 7.07 (dd, 1H, *J*=7.5 and 7.4 Hz, Ar-H), 1.96 (s, 3H, Ar-C-CH_3) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=158.6 (s, Ar-C), 144.2 (s, Ar-C), 140.9 (s, Ar-C), 133.2 (s, Ar-C), 129.6 (s, Ar-C), 128.3 (d, 2C, Ar-CH), 126.8 (d, Ar-CH), 126.4 (d, Ar-CH), 126.3 (d, 2C, Ar-CH), 125.8 (d, Ar-CH), 124.0 (d, Ar-CH), 121.8 (s, Ar-C), 120.7 (s, Ar-C), 120.3 (d, Ar-CH), 118.8 (d, Ar-CH), 117.6 (d, Ar-CH), 115.3 (d, Ar-CH), 112.1 (d, Ar-CH), 50.6 (s, Ar-*C*-CH_3), 24.4 (q, Ar-C-*C*H_3) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{22}H_{18}N]^+=[M+H]^+$: 296.1434; found 296.1422.



40q

10-(4-Chlorophenyl)-10-methyl-5,10-dihydroindeno[1,2-*b*]indole (40q):

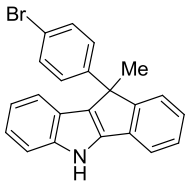
GP-1 was carried out with cinnamate **37h** (112.0 mg, 0.50 mmol), benzene (468.0 mg, 6.0 mmol), triflic acid (0.13 mL, 1.5 mmol), dichoroethane (1.5 mL) at 80 °C for 24 h for the indanone **39q** formation, and then with phenylhydrazine hydrochloride (144.6 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system **40q** (103.9 mg, 63%) as a brown viscous liquid. [TLC control (petroleum ether/ethyl acetate 95:5), R_f(**37h**)=0.52, R_f(**40q**)=0.36, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3406, 2925, 1604, 1489, 1441, 1310, 1246, 1094, 1012, 819, 741 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=8.37 (br. s, 1H, NH), 7.45 (dd, 2H, *J*=7.8 and 7.3 Hz, Ar-H), 7.35 (d, 1H, *J*=7.8 Hz, Ar-H), 7.35–7.24 (m, 4H, Ar-H), 7.22–7.12 (m, 4H, Ar-H), 7.08 (dd, 1H, *J*=7.8 and 7.3 Hz, Ar-H), 1.94 (s, 3H, Ar-C-CH_3) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=158.2 (s, Ar-C), 142.8 (s, Ar-C), 141.0 (s, Ar-C), 140.8 (s, Ar-C), 133.1 (s, Ar-C), 132.1 (s, Ar-C), 130.9 (s, Ar-C), 128.4 (d, 2C, Ar-CH), 127.8 (d, 2C, Ar-CH), 127.0 (d, Ar-CH), 125.9 (d, Ar-CH), 123.9 (d, Ar-CH), 123.4 (s, Ar-C), 122.0 (d, Ar-CH), 120.4 (d, Ar-CH), 118.6 (d, Ar-CH), 117.8 (d, Ar-CH), 112.2 (d, Ar-CH), 50.1 (s, Ar-*C*-CH_3), 24.2 (q, Ar-C-*C*H_3) ppm.

HR-MS (APCI$^+$): m/z calculated for $[C_{22}H_{17}ClN]^+$=$[M+H]^+$: 330.1044; found 330.1034.



40r

10-(4-Bromophenyl)-10-methyl-5,10-dihydroindeno[1,2-*b*]indole (40r):

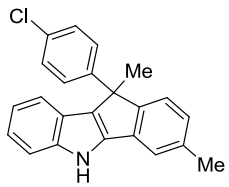
GP-1 was carried out with cinnamate **37i** (134.0 mg, 0.50 mmol), benzene (468.0 mg, 6.0 mmol), triflic acid (0.13 mL, 1.5 mmol), dichoroethane (1.5 mL) at 80 °C for 24 h for the indanone **39r** formation, and then with phenylhydrazine hydrochloride (144.6 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system **40r** (102.9 mg, 55%) as a brown viscous liquid. [TLC control (petroleum ether/ethyl acetate 95:5), R_f(**37i**)=0.54, R_f(**40r**)=0.38, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3401, 2925, 1599, 1487, 1444, 1390, 1315, 1078, 1008, 745 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=8.42 (br. s, 1H, NH), 7.45 (ddd, 2H, *J*=7.8, 7.3 and 1.0 Hz, Ar-H), 7.39–7.26 (m, 5H, Ar-H), 7.24–7.12 (m, 4H, Ar-H), 7.09 (ddd, 1H, *J*=8.3, 7.8 and 1.0 Hz, Ar-H), 1.94 (s, 3H, Ar-C-CH_3) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=158.1 (s, Ar-C), 143.4 (s, Ar-C), 141.0 (s, Ar-C), 140.8 (s, Ar-C), 133.1 (s, Ar-C), 131.4 (d, 2C, Ar-CH), 130.8 (s, Ar-C), 129.6 (s, Ar-C), 128.2 (d, 2C, Ar-CH), 127.0 (d, Ar-CH), 125.9 (d, Ar-CH), 123.9 (d, Ar-CH), 122.0 (d, Ar-CH), 120.4 (d, Ar-CH), 118.6 (d, Ar-CH), 117.8 (d, Ar-CH), 115.3 (s, Ar-C), 112.2 (d, Ar-CH), 50.1 (s, Ar-*C*-CH_3), 24.2 (q, Ar-C-*C*H_3) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{22}H_{16}BrN]^+$=$[M]^+$: 373.0466; found 373.0454.



40s

10-(4-Chlorophenyl)-3,10-dimethyl-5,10-dihydroindeno[1,2-*b*]indole (40s):

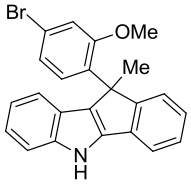
GP-1 was carried out with cinnamate **37h** (112.0 mg, 0.50 mmol), toluene (552.0 mg, 6.0 mmol), triflic acid (0.13 mL, 1.5 mmol), dichoroethane (1.5 mL) at 80 °C for 24 h for the indanone **39s** formation, and then with phenylhydrazine hydrochloride (144.6 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system **40s** (103.1 mg, 60%) as a brown viscous liquid. [TLC control (petroleum ether/ethyl acetate 95:5), R_f(**37h**)=0.52, R_f(**40s**)=0.37, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3409, 2924, 1607, 1489, 1441, 1312, 1094, 1013, 744 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ=8.35 (br. s, 1H, NH), 7.45 (d, 1H, *J*=8.3 Hz, Ar-H), 7.35 (d, 1H, *J*=7.8 Hz, Ar-H), 7.28–7.24 (m, 3H, Ar-H), 7.22–7.14 (m, 4H, Ar-H), 7.08 (ddd, 1H, *J*=7.8, 7.3 and 1.0 Hz, Ar-H), 6.99 (d, 1H, *J*=7.8 Hz, Ar-H), 2.40 (s, 3H, Ar-CH_3), 1.93 (s, 3H, Ar-C-CH_3) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=155.4 (s, Ar-C), 143.1 (s, Ar-C), 140.9 (s, Ar-C), 140.8 (s, Ar-C), 136.8 (s, Ar-C), 133.2 (s, Ar-C), 132.0 (s, Ar-C), 131.2 (s, Ar-C), 128.4 (d, 2C, Ar-CH), 127.7 (d, 2C, Ar-CH), 126.6 (d, Ar-CH), 123.6 (d, Ar-CH), 123.4 (d, Ar-CH), 121.9 (d, Ar-CH), 120.4 (d, Ar-CH), 118.6 (d, Ar-CH), 118.5 (d, Ar-CH), 112.2 (d, Ar-CH), 49.8 (s, Ar-*C*-CH_3), 24.2 (q, Ar-C-*C*H_3), 24.2 (q, Ar-CH_3) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{23}H_{18}ClN]^+$=$[M]^+$: 343.1128; found 343.1121.



40t

10-(4-Bromo-2-methoxyphenyl)-10-methyl-5,10-dihydroindeno[1,2-*b*]indole (40t):

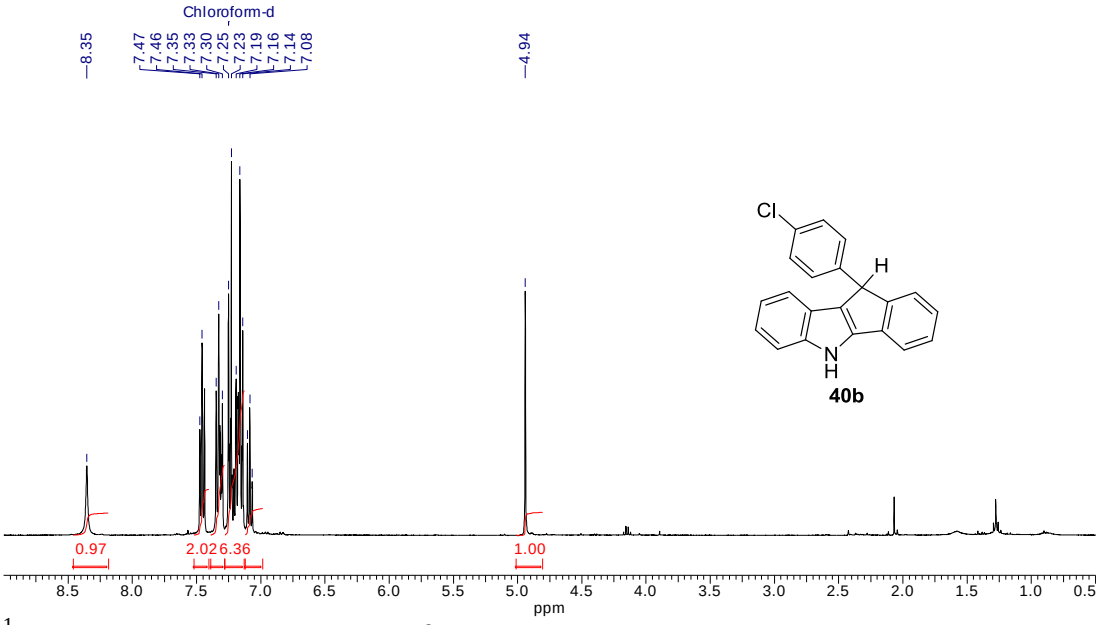
GP-1 was carried out with cinnamate **37g** (95.0 mg, 0.50 mmol), 3-bromoanisole (139.4 mg, 0.75 mmol), triflic acid (0.13 mL, 1.5 mmol), dichoroethane (1.5 mL) at 80 °C for 24 h for the indanone **39t** formation, and then with phenylhydrazine hydrochloride (144.6 mg, 1 mmol) and ethanol (1 mL) followed by triflic acid (0.26 mL, 3.0 mmol) for the Fischer-indole synthesis at 80 °C for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 85:15) furnished the tetracyclic system **40t** (110.0 mg, 59%) as a brown viscous liquid. [TLC control (petroleum ether/ethyl acetate 90:10), R_f(**37g**)=0.65, R_f(**40t**)=0.30, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3410, 2964, 1602, 1485, 1458, 1441, 1390, 1242, 1023, 908, 866, 738 cm^{-1}.

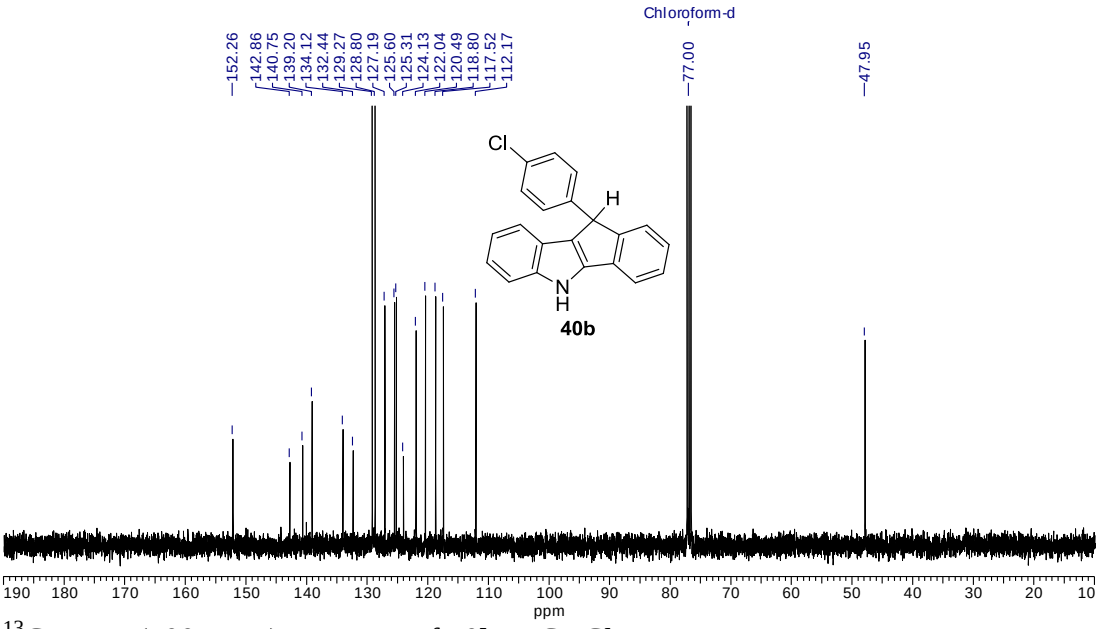
^{1}H-NMR ($CDCl_3$, 400 MHz): δ=8.35 (br. s, 1H, NH), 7.46 (d, 1H, *J*=7.3 Hz, Ar-H), 7.40 (d, 1H, *J*=8.3 Hz, Ar-H), 7.39 (d, 1H, *J*=7.3 Hz, Ar-H), 7.33–7.22 (m, 3H, Ar-H), 7.14 (d, 1H, *J*=7.3 Hz, Ar-H), 7.12 (d, 1H, *J*=7.3 Hz, Ar-H), 7.05 (dd, 1H, *J*=7.8 and 7.3 Hz, Ar-H), 6.97 (dd, 1H, *J*=8.3 and 2.0 Hz, Ar-H), 6.89 (d, 1H, *J*=2.0 Hz, Ar-H), 3.45 (s, 3H, $ArOCH_3$), 1.93 (s, 3H, Ar-C-CH_3) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ=159.2 (s, Ar-C), 158.4 (s, Ar-C), 140.9 (s, Ar-C), 140.6 (s, Ar-C), 133.3 (s, Ar-C), 131.7 (s, Ar-C), 130.4 (s, Ar-C), 129.7 (d, Ar-CH), 126.6 (d, Ar-CH), 125.5 (d, Ar-CH), 123.6 (s, Ar-C), 123.5 (d, Ar-CH), 123.4 (d, Ar-CH), 121.5 (d, Ar-CH), 121.0 (s, Ar-C), 120.1 (d, Ar-CH), 118.7 (d, Ar-CH), 117.4 (d, Ar-CH), 115.8 (d, Ar-CH), 112.1 (d, Ar-CH), 55.6 (q, Ar-OCH_3), 49.5 (s, Ar-*C*-CH_3), 24.7 (q, Ar-C-*C*H_3) ppm.

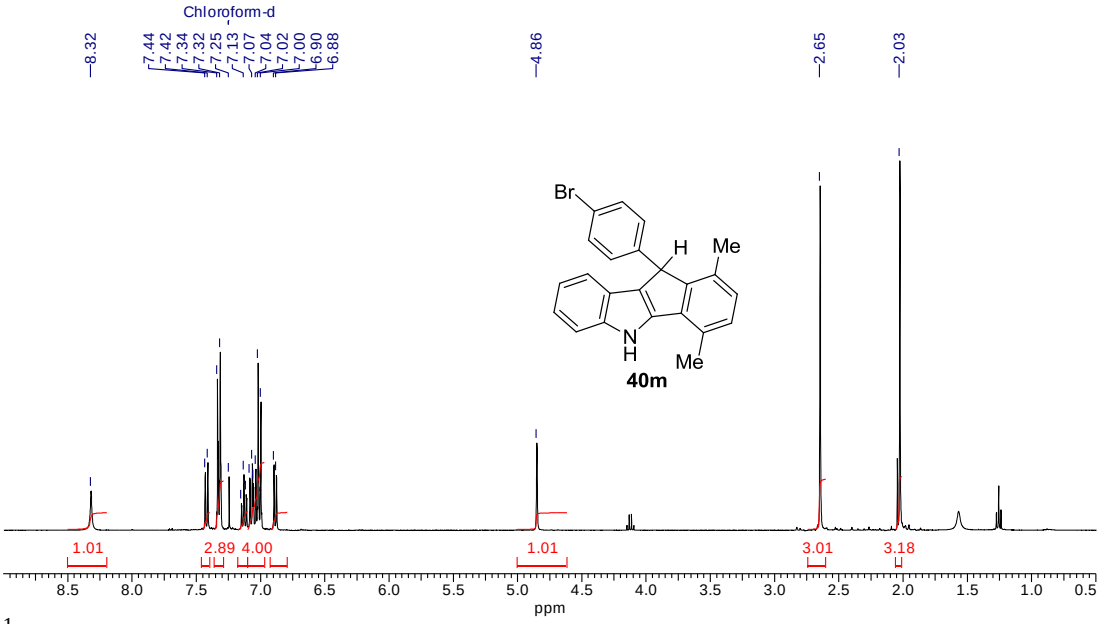
HR-MS (ESI$^+$): m/z calculated for $[C_{23}H_{22}{}^{81}BrN_2O]^+=[M+NH_4]^+$: 423.0890; found 423.0912.



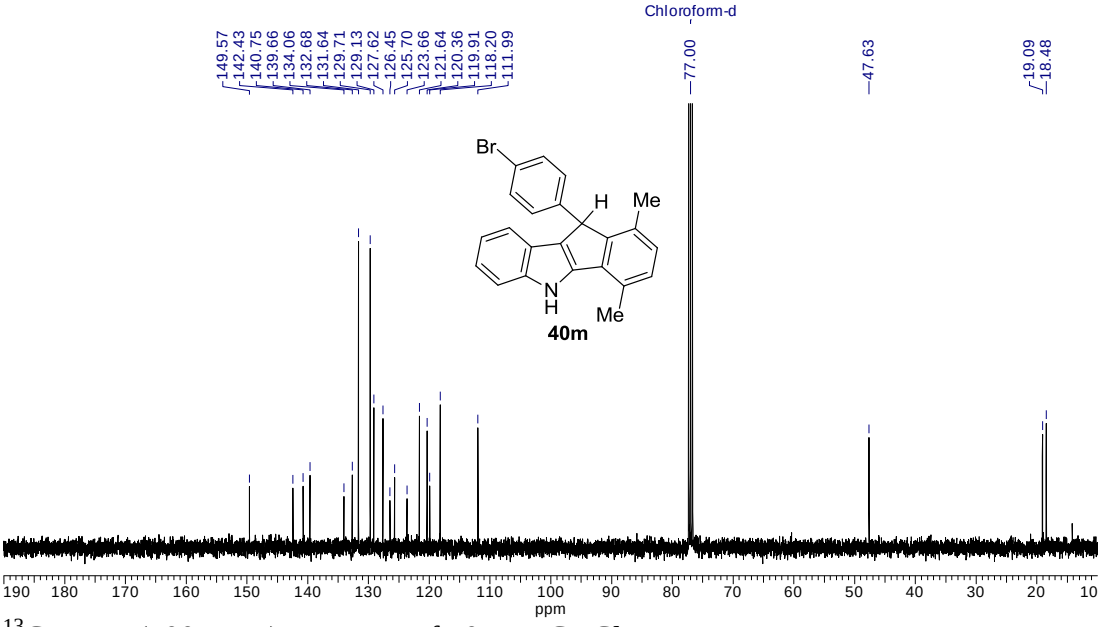
^{1}H-NMR (400 MHz) spectrum of **40b** in $CDCl_3$



^{13}C-NMR (100 MHz) spectrum of **40b** in $CDCl_3$



^{1}H-NMR (400 MHz) spectrum of **40m** in $CDCl_3$



^{13}C-NMR (100 MHz) spectrum of **40m** in $CDCl_3$

ABOUT THE AUTHOR

The author, Mr. Alavala Gopi Krishna Reddy, was born on 20th June, 1985 at Tedlem, Andhra Pradesh, India. He had his early education (SSC) in 2001 at Andhra Pradesh Residential School, Appala Raju Gudem, Andhra Pradesh. He completed his intermediate education (IPE) from Vidyavikas Residential college, Eluru, Andhra Pradesh in 2003 and obtained B.Sc. (Chemistry) degree in 2006 from Sir. C.R.R. College, Eluru, Andhra Pradesh. He obtained his M.Sc. degree (Organic Chemistry) in 2008 from D.L.R.P.G. College, G. Mamidada, Andhra Pradesh. In December 2009, he joined the Department of Chemistry for the Ph.D. program at Indian Institute of Technology Hyderabad, under the supervision of Dr. G. Satynarayana. He passed the comprehensive examination in May 2011. Presently he is continuing as a Senior Research Fellow of Council of Scientific Industrial Research, New Delhi, in the department.

LIST OF PUBLICATIONS

1. Palladium mediated intramolecular Buchwald-Hartwig α-arylation of β-amino esters: Synthesis of functionalized tetrahydroisoquinolines, **A. G. K. Reddy**, J. Krishna, and G. Satyanarayana, Synlett, (2011) 1756.

2. A simple efficient sequential one-pot intermolecular aza-Michael addition and intramolecular Buchwald-Hartwig α-arylation of amines: synthesis of functionalized tetrahydroisoquinolines, **A. G. K. Reddy** and G. Satyanarayana, Tetrahedron, 68, (2012) 8003.

3. An efficient sequential one-pot base mediated C–O and Pd-mediated C–C bond formation: synthesis of functionalized cinnamates and isochromenes, **A. G. K. Reddy**, J. Krishna, and G. Satyanarayana, Tetrahedron Lett., 53, (2012) 5635.

4. Sequential one-pot method for oxy-Michael addition, Heck coupling, and degradation followed by condensation: facile synthesis of 2-benzoxepin-3(1*H*)-ones, **A. G. K. Reddy**, J. Krishna, and G. Satyanarayana, Tetrahedron, 69, (2013) 10098.

5. Simple, copper(I)-catalyzed oxidation of benzylic/allylic alcohols to carbonyl compounds: Synthesis of functionalized cinnamates in one pot, **A. G. K. Reddy**, L. Mahendar and G. Satyanarayana, Synth. Commun., 44, (2014) 2076.

6. A facile, superacid promoted sequential domino one-pot dual c-c bond formation and fischer indole synthesis: Rapid access to 10-phenyl-5,10-dihydroindeno[1,2-*b*]-indoles, **A. G. K. Reddy** and G. Satyanarayana (manuscript submitted).

7. Palladium-mediated highly regio- and stereoselective intermolecular β-arylation on allylic alcohols: Synthesis of functionalized allylic alcohols, J. Krishna, **A. G. K. Reddy**, B. V. Ramulu, L. Mahendar and G. Satyanarayana, Synlett, 23, (2012) 375.

8. A domino palladium catalysis: Synthesis of 7-methyl-5H-dibenzo[a,c][7]annulen-5-ones, J. Krishna, **A. G. K. Reddy** and G. Satyanarayana, Synlett, 24, (2013) 967.

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10. Formation of bi-aryls via a domino palladium catalysis, J. Krishna, **A. G. K. Reddy** and G. Satyanarayana, Tetrahedron Lett., 55, (2014) 861.

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12. An efficient synthesis of highly substituted indanones and chalcones promoted by superacid, A. Das, **A. G. K. Reddy**, J. Krishna and G. Satyanarayana, RSC. Adv., 4, (2014) 26662.

13. [Cu]-Catalyzed domino Sonogashira coupling followed by intramolecular 5-exo-dig cyclization: Synthesis of 1,3-dihydro-2-benzofurans, L. Mahendar, **A. G. K. Reddy**, J. Krishna and G. Satyanarayana, (manuscript accepted).

14. A domino palladium-catalyzed C-C and C-O bonds formation via dual O-H bond activation: Synthesis of 6,6-dialkyl-6H-benzo[c]chromenes, L. Mahendar, J. Krishna, **A. G. K. Reddy** and G. Satyanarayana, Org. Lett., 14, (2012) 628.

15. Transition metals catalyzed C-C and C-O bonds formation: Facile synthesis of flavans and benzoxepines, B.V. Ramulu, L. Mahendar, J. Krishna, **A. G. K. Reddy** and G. Satyanarayana, Tetrahedron, 69, (2013) 8305.

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