NOVEL IODINE MEDIATED CARBOCYCLISATIONS AND HYPERVALENT IODINE(III) REAGENTS

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Ph.D. Thesis Summer, 2010

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FOR

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BY

ZULFIQAR ALI KHAN

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CARDIFF UNIVERSITY

Declaration

This work has not been accepted in substance for any degree and is not being concurrently submitted in candidature for any degree.

Signed .....(Z. A. Khan)

Date.....October 01, 2010.....

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Thesis is the result of my own investigations, except where stated otherwise. Other sources are acknowledged by endnotes giving explicit references. A bibliography is appended.

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Date.....October 01, 2010.....

Dedicated

To

My Father M. Nawaz Khan (Late) and My Mother

My Wife Salma Habib & My Daughter Sabeha Noor

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It is a matter of great pleasure to express my obligations and sincere thanks to my research supervisor Professor Thomas Wirth for giving me this research topic and research facilities related to my project. I wish to acknowledge invaluable suggestions and corrections offered by my research supervisor, who read entire manuscript of my thesis. I would like to convey my grateful thanks to Professor Michio Iwaoka (visiting professor from Tokai University, Kitakaname, Hiratsuka-shi, Kanagawa 259-1292, Japan) for performing *ab-initio* calculations mentioned in chapter 3. I am thankful to Dr. Robert David Richardson (post doctoral scholar in Wirth group) for his co-operation in the laboratory work. Thanks to all teachers at School of Chemistry for being a source of inspiration and enlightenment for me during my stay at Cardiff University. I am very thankful to my mentor Dr. James Redman and my examiner Professor Rudolf Allemann for their encouragement and suggestions during my six month reports viva.

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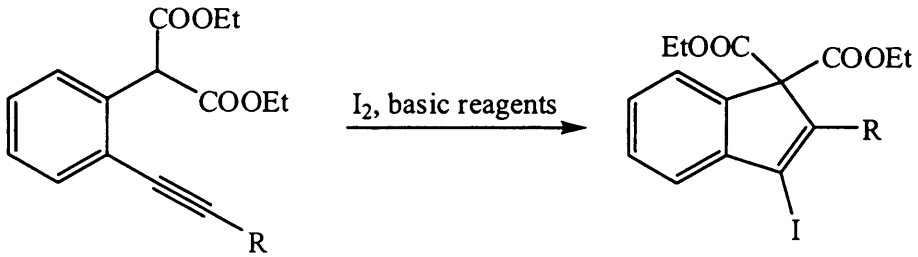
Zulfiqar Ali Khan

Abstract

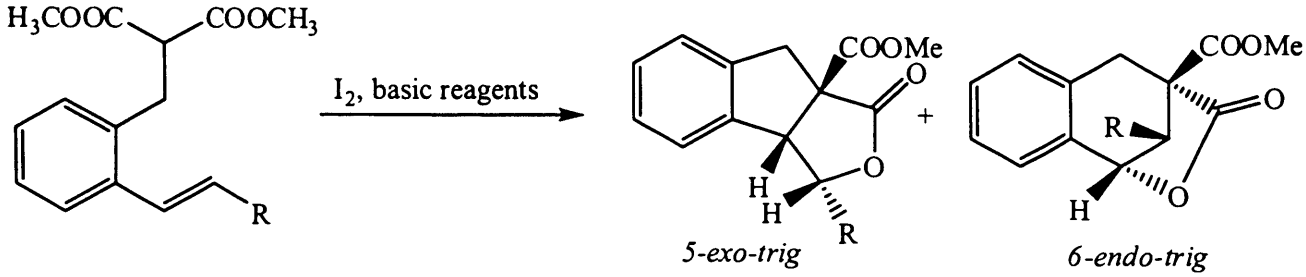
The first chapter focuses on the introduction of iodine mediated carbocyclisations and their applications continue to present a stimulating challenge in target- and diversity-oriented syntheses. Literature overview of more than past two decades about this area of research has been highlighted by including key examples along with their mechanistic aspects.

The second chapter discusses applications and literature synopsis about classical approaches towards the syntheses of indene derivatives. Herein the syntheses of 3-iodo-1*H*-indene derivatives by way of iodonium-promoted 5-*endo-dig* carbocyclisation of 2-substituted ethynylmalonates as a key starting material are described. The Sonogashira cross-coupling reaction is utilised as a key step in order to access 2- substituted ethynylmalonates as a starting material. A range of terminal acetylenes bearing aromatic, aliphatic and propargylic moieties can be employed to boost the scope of reaction. Further 3-iodo-1*H*-indene derivatives elaborated on using the Mizoroki-Heck reaction to form new C-C bond for further structural diversity. Within this study, we were able to show for the first time that the 3-iodo-1*H*-indene can be used as a synthetic platform not only for the palladium chemistry but also as a catalyst for the *in situ* generation of λ^3-hypervalent iodine reagent. Additionally, 3-iodo-1*H*-indene derivatives have the potential to perform asymmetric syntheses.

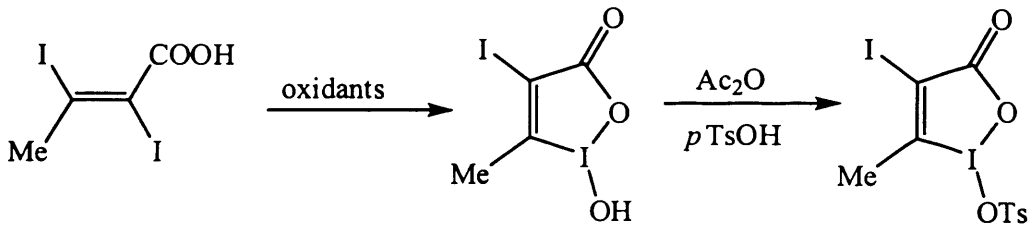


The third chapter demonstrates tandem iodine mediated carboannulation of the stilbene malonate derivatives via either 5-*exo*- or 6-*endo-trig* mode under basic reagents with subsequent lactonisation to structurally complex indanes and tetrahydronaphthalenes with three new stereogenic centres. The overall transformation entails the associated formation of one strategic carbon-carbon and one carbon-oxygen bonds leading to a tricyclic indane and tetrahydronaphthalene compounds from acyclic precursors in one synthetic operation. In the present study, a unique stereochemistry was observed in the case of tetrahydroindenofuranones and confirmed by single crystal X-ray analysis. While the stereochemistry of tetrahydronaphthalene derivatives is established by the

spectroscopic techniques. Both the compounds formed as a single diastereomers as judged from their ^{1}H and ^{13}C NMR spectra. A literature overview of synthetic methodologies and applications of the indane and tetrahydronaphthalene derivatives is also incorporated in the third chapter.



In the fourth chapter the syntheses of novel simplified analogues of **IBA** by oxidation of α,β-diiodoacrylic acids are described. The oxidation of (*E*)-2,3-diiodobut-2-enoic acid with various oxidants resulted in the successful formation of λ^3-iodane analogue. Additionally, λ^3-iodane derivative is transformed to its respective tosylate derivative by the reaction of *p*TsOH. These new reagents have been utilized in a variety of well established oxidative transformations as mild oxidants with elevated or comparable reactivity as conventional hypervalent iodine(III) reagents.



Finally, the experimental procedures detail and characterization data of the compounds is given in the fifth chapter.

Table of Contents

List of Abbreviations

Ar	aryl
°C	celsius (centigrade)
*m*CPBA	*meta*-choroperbenzoic acid
δ	chemical shift
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DMP	2,6-Dimethoxypyridine
dr or d.r.	diastereomeric ratio
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DMSO	dimethylsulfoxide
DMDO	Dimethyldioxirane
Ed.	Edition
equiv.	equivalent(s)
ee	enantiomeric excess
F-IBX	tetrafluoro-2-iodoxybenzoic acid
h	hour(s)
Hz	Hertz
IBA	2-iodosobenzoic acid
IBX	2-iodoxybenzoic acid
hν	irradiation
IFC	intramolecular Friedel-Crafts reaction
J	coupling constants
LiNaph.	lithium naphthalenide
Ln or L	ligands
LDA	lithium diisopropyl amide
M	Molarity
min	minute(s)
m.p.	melting point
Ms	methanesulfonyl
mol	mole
MHz	megahertz
m/z	mass over charge ratio

NOE	nuclear overhauser effect
NHC	N-heterocyclic carbene(s)
Nu	nucleophile(s)
ppm	parts per million
Py	pyridine
Pin	pinacol
r.t.	room temperature
rel.	relative
S_N2	nucleophilic substitution bimolecular
S_N1	nucleophilic substitution unimolecular
t	triplet
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TBDPS	*tertiary*-butyldimethylsilyl
t or tert.	tertiary
vol.	volume
$Ti(TADDOLate)_2$	titanium bis-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanol

Chapter 1

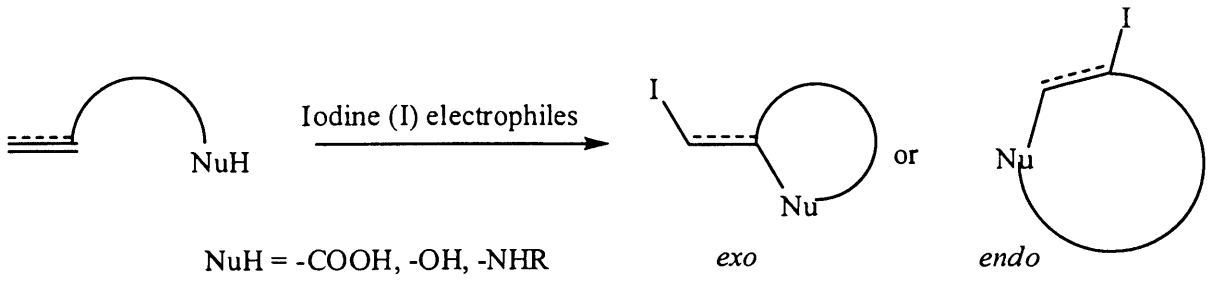
Introduction to Iodocarbocyclisations

The prior survey of the applications of iodine reagents in organic synthesis reflects an active current interest in the chemistry of carbon carbon bond forming reactions. The chapter 1 consists of a brief introduction of iodine mediated cyclisation of unsaturated substrates with special emphasis on the carbon as internal nucleophiles to build up carbocycles. A literature overview of more than past two decades in relation to this area of research has been enclosed by including vital examples.

1.1 Iodocyclisation reactions

The regiocontrolled functionalisation of unsaturated carbon carbon bonds by iodine containing electrophilic reagents is carrying enormous prospective in organic synthesis. This area of research has been comprehensively explored and reviewed in the literature as an important synthetic handle for an organic chemist [1]. The iodocyclisation is a reaction whereby the intramolecular nucleophilic species (or group) attacks the carbon-carbon unsaturated bond activated by iodine containing electrophilic reagents to give cyclic compounds depending on stereochemistry and ring size formed, either in *exo* or *endo* fashion (Scheme 1). This concept was extensively exercised in the synthesis of heterocyclic compounds and functionalisation of alkenes [1].

The old report on iodolactonisation reaction was acknowledged a century ago; Bougault treated the substrate with aqueous sodium carbonate solution, elemental iodine and potassium iodide [2]. However, there was almost no difference regarding the reagents and the reaction conditions used in modern times from those reported a century ago. The importance of new cyclisation reaction is located in the originality and exhibition of high selectivity as well as easy procurement and the synthesis of cyclisation precursors [1]. The primary and most well known nucleophiles used in iodocyclisations were carboxylic acids as well as alcohols and amines (Scheme 1) [1].

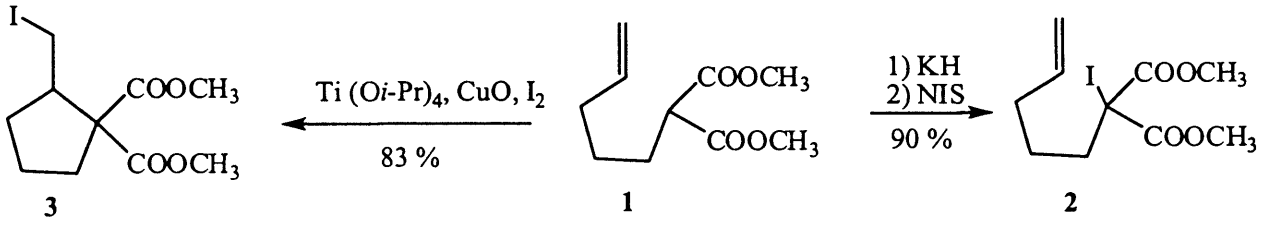


Scheme 1. General representation of iodocyclisation reactions.

1.2 Iodocarbocyclisation reactions

The iodocarbocyclisation reactions implicate an intramolecular attack of a carbon nucleophile on an unsaturated carbon bond activated by an electrophilic reagent was a known subject of research for more than past two decades. Iodocarbocyclisation reactions have emerged as a powerful tool for the formation of new C-C bonds and a handy method for stereoselcetive synthesis of functionalised carbocycles. Taguchi and co-workers have revealed that unsaturated malonates such as 4-pentenylmalonate can act as excellent nucleophiles in iodocarbocyclisation reactions [3]. The deprotonation of 4-pentenylmalonate (**1**) with potassium hydride gave no iodocarbocyclised product but only α-iodomalonate **2** was formed exclusively (Scheme 2) [4].

When the reaction between 4-pentenylmalonate (**1**) and iodine was conducted in the presence of titanium alkoxide and copper(II) oxide, α-iodomalonate **2** was not generated whereas iodocarbocyclised product **3** was obtained in high yields. In the absence of copper(II) oxide, a decrease in the yields of carbocyclised product **3** to 74% was observed (Scheme 2) [3].

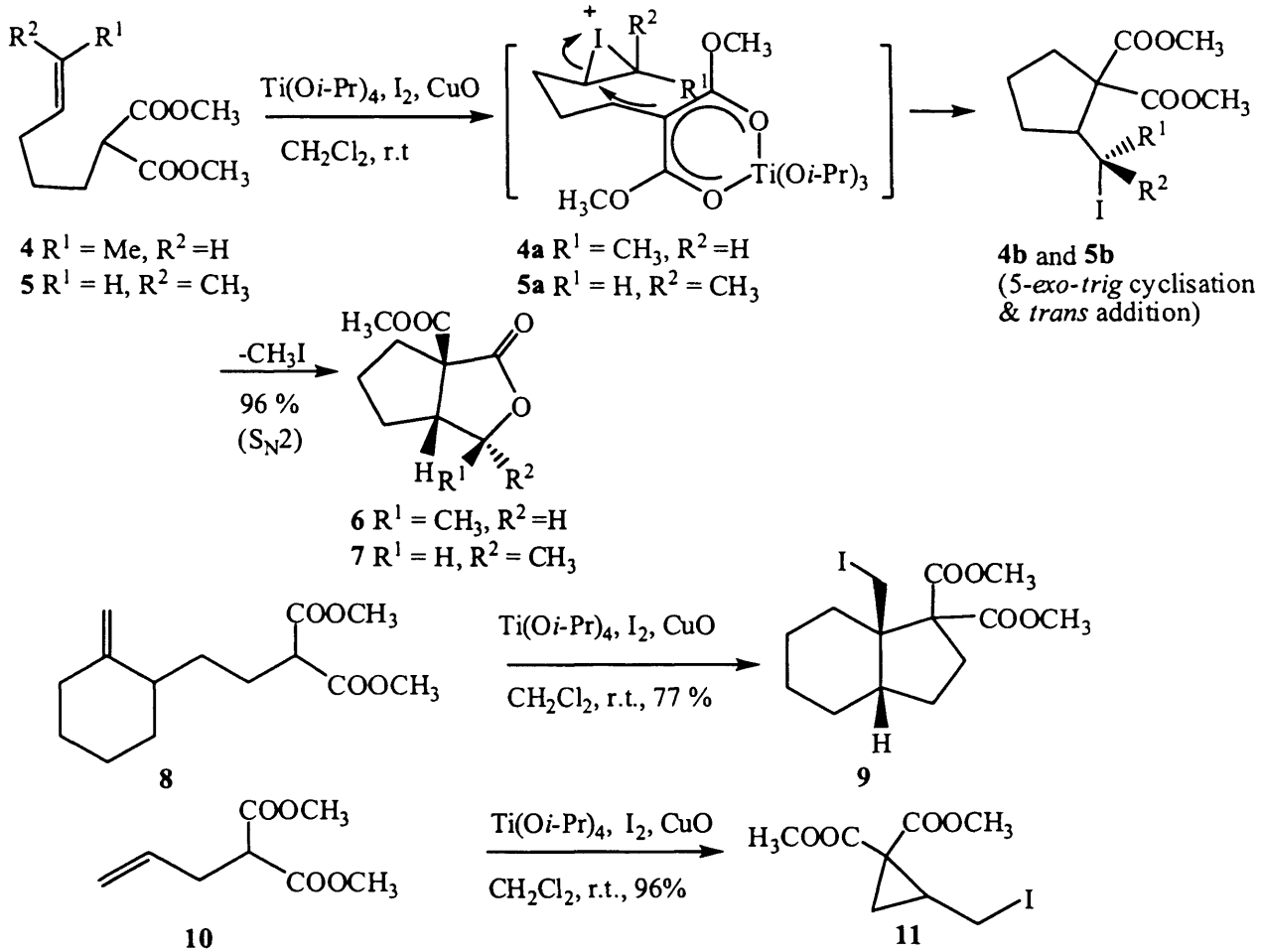


3 1 2

Scheme 2. Iodocarbocyclisation and direct iodination.

Further extension of similar reaction conditions towards (*E*) and (*Z*)-4-hexenylmalonate **4** and **5** gave bicyclic lactones **6** and **7** having three consecutive chiral centres produced in a highly stereospecific manner through substitution reaction of primarily produced secondary iodide **4b** and **5b** with free ester moieties. In this reaction, iodine is a good electrophile to activate the C-C π-bond, whereas Ti(O*i*-Pr)$_4$ acts as a basic reagent to enhance the nucleophilicity of malonate moiety through the formation of titanium enolate (a stable carbanion formed due to mesomeric effect). The reaction proceeded by a nucleophilic attack of titanium enolate on a three membered iodonium ion in 5-*exo-trig trans* addition manner (Scheme 3, **4a/5a**) [3]. The secondary iodides (**4b** and **5b**) formed by iodocarbocyclisations underwent lactonisation with inversion of configuration (S_N2) leading to the products **6** and **7** (Scheme 3).

Furthermore, the malonate **8** and **10** reacted with complete selectivity (5-*exo*-cyclisation and *trans*-addition) to produce the bicyclic compounds **9** and cyclopropane derivative **11** in excellent yields (Scheme 3).

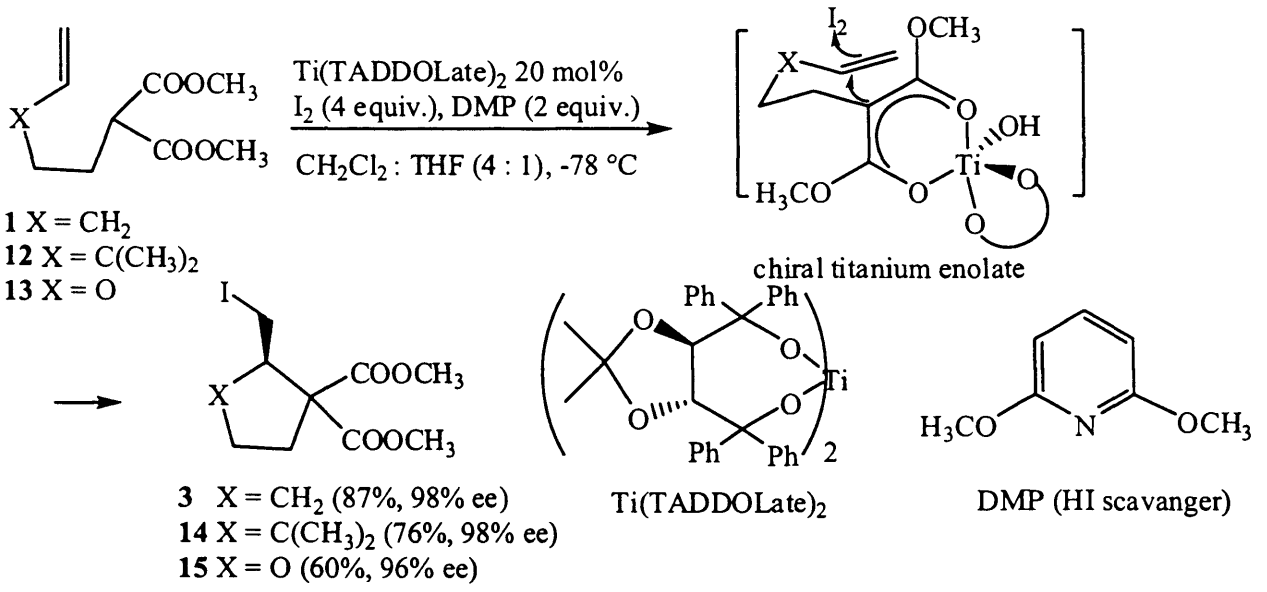


Scheme 3. Ti(O*i*-Pr)$_4$ mediated iodocarbocyclisation of various alkenylmalonates.

1.2.1 Catalytic asymmetric iodocarbocyclisations

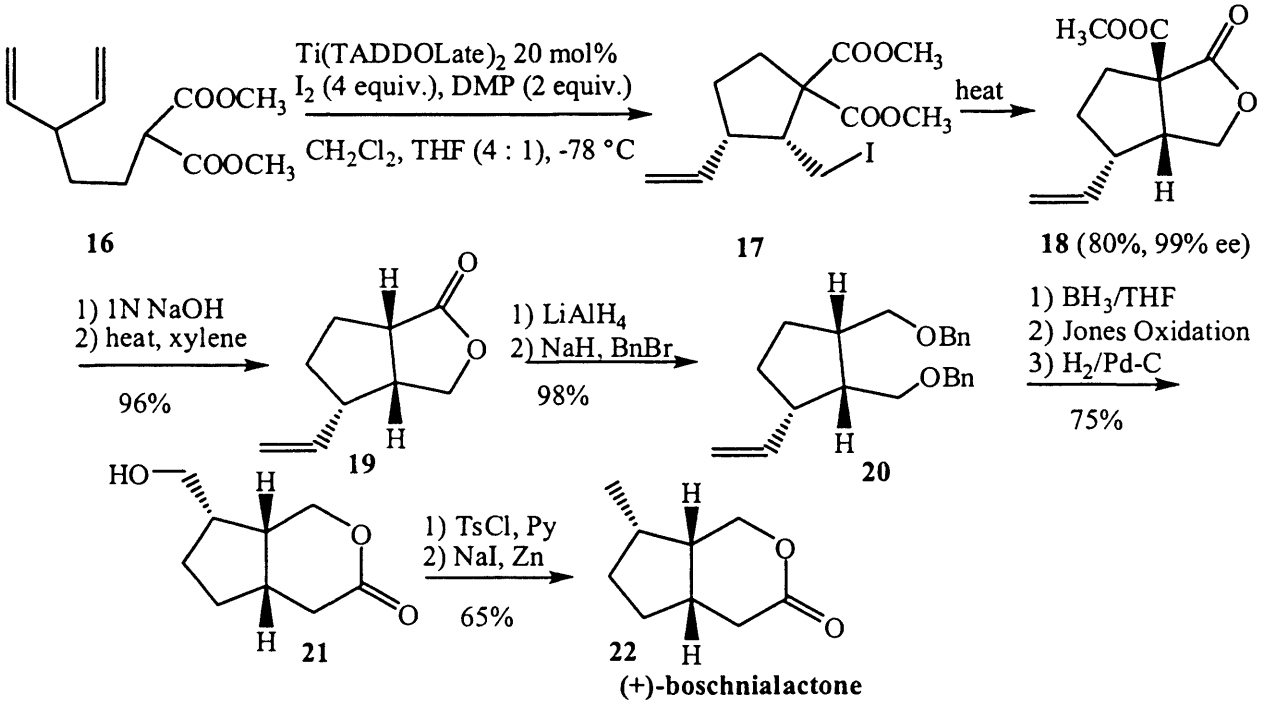
Based on these reactivities of titanium enolates, Taguchi *et al.* further investigated this concept in enantioselective iodocarbocyclisation reactions mediated by variety of chiral titanium reagents. The chiral titanium enolate intermediate was generated to study the enantiofacial differentiation of the alkene moiety at the cyclisation step.

Consequently, in the presence of a Ti(TADDOLate)$_2$ complex the iodocarbocyclisation of various alkenylmalontes **1**, **12** and **13** proceeded with high enantioselectivity (up to 98% ee) to gave the products **3**, **14** and **15** [5]. The use of 2,6-dimethoxypyridine (DMP) as a scavenger for hydrogen iodide (HI) gave high enantioselectivity (>96% ee) even with catalytic amount (20 mol%) of Ti(TADDOLate)$_2$ complex [6]. The absence of DMP would result in the decomposition of the Ti(TADDOLate)$_2$ complex by hydrogen iodide, resulting in decreased yields and optical purities of the products (Scheme 4).



Scheme 4. The enantiofacial selective reaction (catalytic asymmetric iodocarbocyclisations).

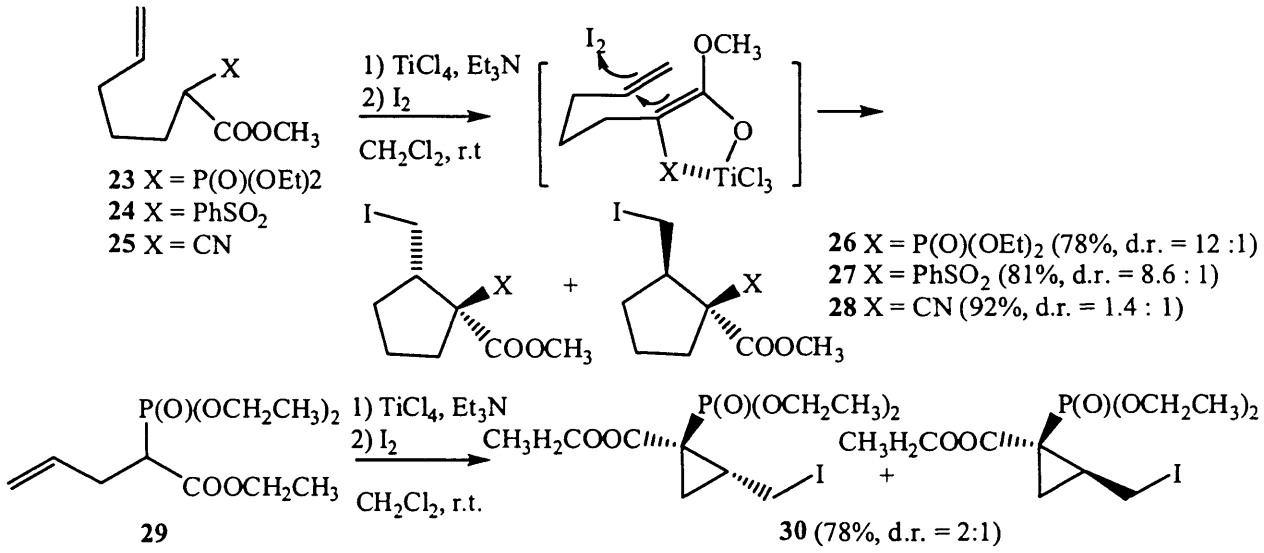
The iodocarbocyclisation of bisalkenylmalonate **16** was performed under the above mentioned conditions, only one of the prochiral alkene in malonate **16** reacted, giving rise to the trisubstituted cyclopentane derivative **17** thermally transformed to bicyclic lactone **18** with high enantiomeric excess (99%). The cyclised product can be transformed to boschnialactone **22**, an iridoid natural product, in high yields via a sequence of reactions described in Scheme 5. These were first examples of catalytic asymmetric iodocarbocyclisation reactions [6].



Scheme 5. Enaniotopic group selective reactions and their applications to synthesis of (+)-boschnialactone.

1.2.2 Iodocarbocyclisations of various alkenyl active methines

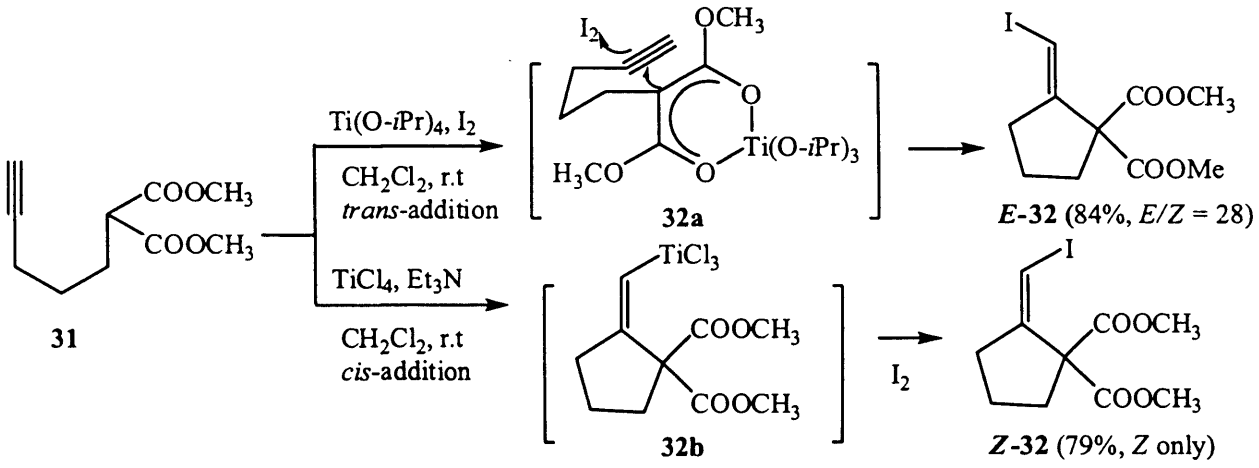
There were no cyclised products generated in the case of 4-pentenyl 2-phosphonoacetate **23**, sulfonylacetate **24** and cyanoacetate **25** in the presence of titanium alkoxide and iodine. The titanium enolate was effectively produced when titanium tetrachloride and triethylamine used in the case of alkenylated active methine compounds and that by subsequent addition of iodine to cyclised products **26**, **27** and **28** in very good yields [7] (Scheme 6). In another example, under similar reaction condition cyclopropane derivative **30** formed as a mixture of diastereomer in good yield from precursor molecule **29** (Scheme 6).



Scheme 6. $TiCl_4$-mediated iodocarbocyclisations of various alkenylated active methine compounds.

1.2.3 Iodocarbocyclisations of alkynyl malonates

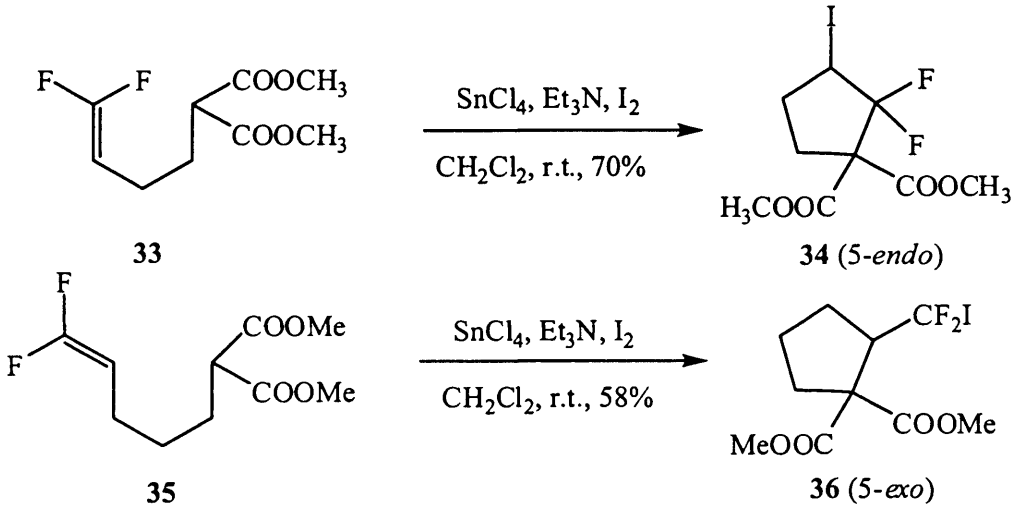
Surprisingly, when the iodocarbocyclisation conditions were applied to alkynyl malonate **31**, different stereoselectivity was observed depending on the titanium reagents. The compound **31** was treated with titanium alkoxide and iodine gave product *E*-**32** with high selectivity (*trans*-addition). When compound **31** reacted with titanium tetrachloride, triethylamine, and iodine, the reaction proceeded through an intramolecular carbotitanation of titanium enolate to the alkyne (*cis*-addition) to generate (Z)-vinyl titanium intermediate **32b** which on subsequently iodination (iodonolysis) gives Z-**32** with complete stereoselectivity (Scheme 7) [7].



Scheme 7. Iodocarbocyclisation and intermolecular carbotitanation of alkynylated malonates.

1.2.4 Iodocarbocyclisations of difluoroalkenylated malonates

Furthermore, the iodocarbocyclisation of difluoroalkenylated malonates gave satisfactory results by using tin tetrachloride and triethylamine. The 5-*endo-trig* cyclised product **34** was obtained from the reaction of 4,4-difluoro-3-butenyl malonate **33** and the 5-*exo-trig* cyclised product **36** was obtained from reaction of 5,5-difluoro-4-pentenyl malonate **35** (Scheme 8) [8]. The cyclisation product **34** was only observed in the case of 4,4-difluoro-3-butenyl malonate **33**, there was no cyclisation for simple 3-butenyl malonate without fluorine atoms [4].

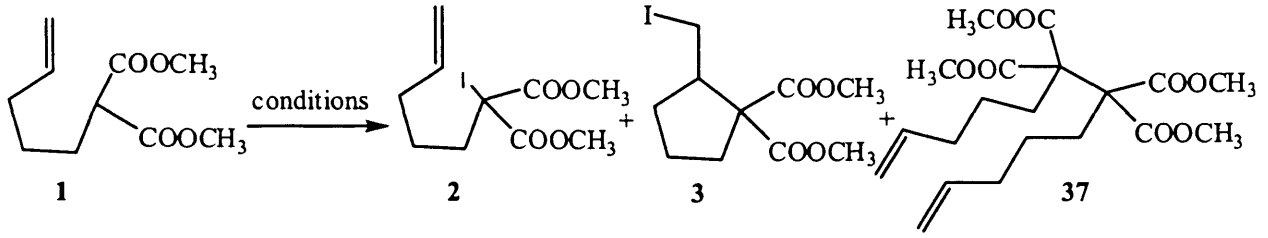


Scheme 8. Iodocarbocyclisation of difluoroalkenylated malonates.

1.2.5 Atom transfer cyclisations

The α-iodomalonates were a known class of compounds before 1989 and there were various methods developed for the iodination of malonate anions [4, 9].

Table 1. The products for iodination of 4-pentenyl malonate **1** under basic conditions.



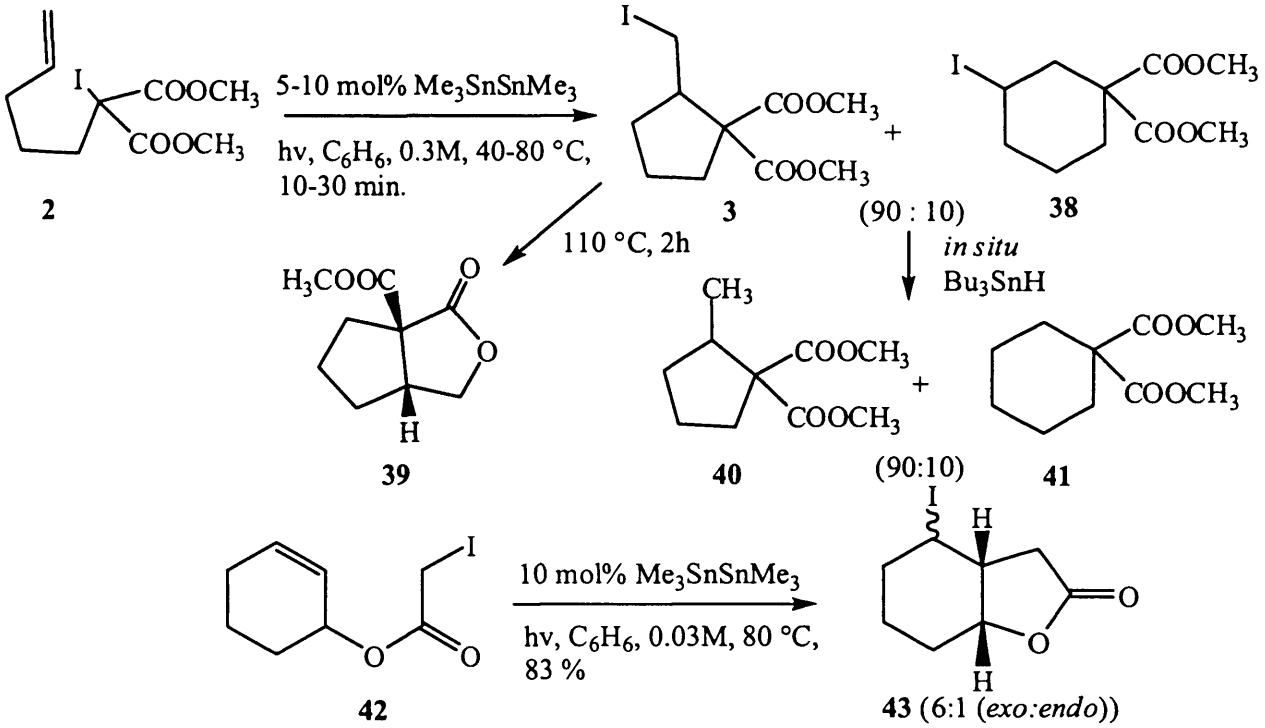
1 **2** **3** **37**

Entry	Conditions	Temperature [°C]	Product 2 (% Yield)	Product 3 (% Yield)	Product 37 (% Yield)
1	LDA/I_2	-78	-	68	28
2	NaH/I_2	r.t.	20	16	50
3	KH/NIS	r.t.	90	-	-

The deprotonation of **1** with LDA in THF gave the cyclic product **3** and the oxidatively coupled product **37** without the formation of desired compound α-iodomalonate **2** (Table 1, entry 1).The use of NaH as a base gave a small amount of α-iodomalonate **1** along with **3** and **37**. In contrast, deprotonation of **1** with KH and addition of NIS gave α-iodomalonates **1** as sole detectable product in 90% yield (Table 1, entry 3). The mechanistic origin of cyclised product **3** was not known. The free radicals would be formed by the oxidation of anions since oxidative coupling of anions with molecular iodine was a known reaction [10]. An ionic mechanism could be envisioned for such cyclisation reactions [4].

The growing applications of free radical reactions as a solution to the problems in organic syntheses were certification to the assorted type of transformations that can be accomplished. The intramolecular atom transfer addition of C-X bond (where X is a univalent halogen atom) was an essential reaction of organic free radicals; the capacity and fundamental philosophy were pioneered by D. P. Curran. Curran *et al.* whom investigated the atom transfer cyclisation of α-iodo ester, ketones, amides and malonates to form lactones, cyclic ketone, lactams, and carbocycles in high yields [4, 11]. The standard atom transfer conditions involved sunlamp irradiation of iodide with 10 mol % hexabutylditin in benzene [4]. As a typical example, compound **2** was irradiated under the standard atom transfer conditions, rapidly consumed (10 min), and an inseparable mixture of 5-*exo-trig* product **3** and 6-*endo-trig* product **38** was isolated in 86% yield. The ratio of products **3** and **38** in the crude mixture were 90:10. The

structures were easily assigned by *in situ* tin hydride reduction to give a 90:10 mixture of **40**:**41**. In addition, heating of the mixture transformed the major component **3** to lactone **39**. Additionally, the cyclisation of **42** by standard ditin procedure gave 83% yield of cyclised product **43** when sunlamp was very close (<6 cm) to reaction vessel (Scheme 9) [11].

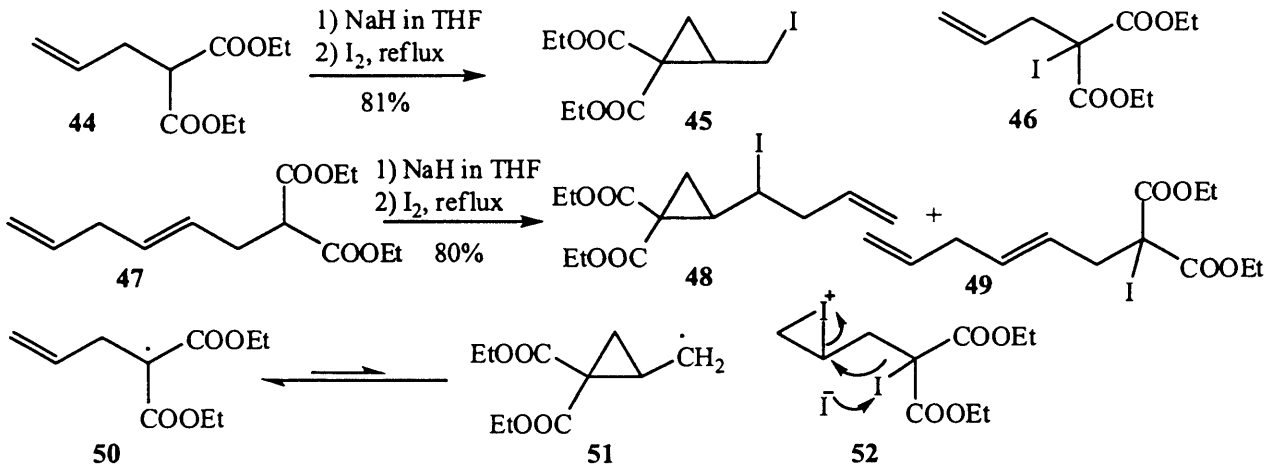


Scheme 9. Various examples of atom transfer cyclisations.

Beckwith *et al.* described an alternative approach in which the successive treatment of allylmalonate **44** with sodium hydride and iodine at reflux in THF, the cyclopropyl iodide **45** was isolated in 81%. The α-iodomalonate **46** could be a possible intermediate under the reaction conditions (Scheme 10). The isolated treatment of wholesome α-iodomalonate **46** with sodium iodide in THF followed by reflux gave a cyclised product **45**. In the absence of iodide ion α-iodomalonate **46** was an unstable compound and underwent slow fractional degeneration to parent malonate **44** [12]. The iodomalonate **46** gave a complex and intractable mixture of products when subjected to the standard conditions for radical atom transfer described by Curran (irradiation at 60 °C in a benzene solution with 10 mol% hexabutylditin) [4].

In another example, the treatment of compound **47** with NaH and iodine gave mixture of cyclised product **48** and α-iodomalonate **49** in good yields. A straightforward radical mechanism for the reactions described here appears unlikely since equilibrium between **50** and **51** lies highly in the favour of acyclic free radical form **50** (a tertiary radical, stable due to

mesomeric effect) [12]. The primary radical **51** is highly unstable. The existing evidence favoured the observation that the mechanism did not engage free radicals. The high stereoselectivity of the reaction gave only one diastereomer look like inconsistent with a free radical mechanism but consistent with an ionic mechanism [13]. The experimental evidences in this transformation trustworthy with the view that the reaction required both iodine electrophile and iodide anion to promote the cyclisation of an iodonium species **52** (Scheme 10).



Scheme 10. The reaction of alkenylmalonates with NaH/I_2.

1.3 Acidic strength of active methylene compounds

The aspect of acid-base chemistry that can be widely applied to understanding organic reactions was the strength of Brønsted acids and bases. The strength of a Brønsted acid is determined by how well it transfers a proton to a Brønsted base. The standard base traditionally used for comparison is water. The transfer of a proton from a general acid, HA, to a base H_2O is indicated by following equilibrium as shown in equation 1.

$$HA + H_2O \rightleftharpoons A^{-}: + H_3O^{+} \qquad \text{(equation 1)}$$

The equilibrium constant for this reaction was given by

$$K_{eq} = \frac{[A^{-}:]\ [H_3O^{+}]}{[HA][H_2O]} \qquad \text{(equation 2)}$$

The quantities in brackets are molar concentrations at equilibrium. Because water is solvent and its concentration remains effectively constant (55.55 m/L), regardless of the concentration of other species in the equilibrium, thus we multiply the equation 2 through by $[H_2O]$ and thus define another constant K_a called the dissociation constant.

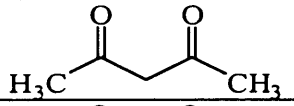
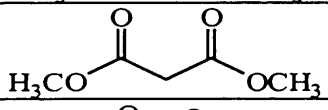
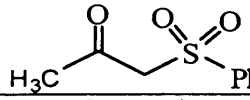
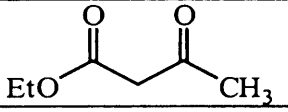
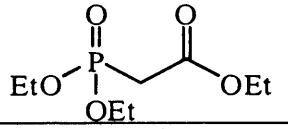
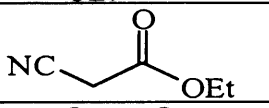
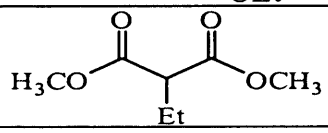
$$K_a = K_{eq}[H_2O] = \frac{[A:^-]\ [H_3O^+]}{[HA]} \qquad \text{(equation 3)}$$

Each acid has its own unique dissociation constant. The larger the dissociation constant of an acid, more H_3O^+ ions are formed when acid is dissolved in a solvent such as water at a given concentration. Thus, the strength of a Brønsted acid is measured by the magnitude of its dissociation constant (K_a). Because the dissociation constant of different Brønsted acids covered a range of many powers of 10, it is useful to express the acid strength in a logarthithmic manner. Using *p* as an abbreviation for negative logarithm, we can write the following definition:

$$pK_a = -\log K_a \qquad \text{(equation 4)}$$

Because stronger acids have larger K_a values, it follows from equation 4 that stronger acids have smaller pK_a values. The important organic reactions are carried out in non-aqueous solvents. In non-aqueous solvents, pK_a values typically differ substantially from pK_a values of same acids determined in water. However in some of these solvents the relative pK_a values are roughly the same as they are in water. The strength of some organic compounds as a measure of pK_a values are given in Table 2 [14].

Table 2. pK_a values of active methylene compounds.

Entry	Substrate	*pKa* H_2O (DMSO)
1		9 (13.3)
2		13 (15.7)
3		(12.5)
4		11 (14.2)
5		(18.6)
6		(13.1)
7		(18.5)

1.4 Research Plan

Despite of synthetic progress of various iodocarbocylisation conditions, potential lies in the simplicity, easily accessibility, and rational design of starting material to construct medicinally important carbocycles. These reactions can be conducted using precursors which can be readily synthesised in short steps, followed by their reaction under appropriate conditions to gave carbocyclic products with high regio- and stereoselectivity. We focussed our attention on fact that treatment of appropriate substrates with iodine in the presence of basic reagents resulted in the successful development of iodocarbocyclisation reactions possessing good selectivity. Further, sensitive organic functionalities could be tolerated under mild and efficient iodocarbocyclisation conditions. As a result, we have synthesised 2-substituted alkynylmalonate and stilbene malonate derivatives as precursor molecules for iodocarbocyclisation reactions. The detail of these reactions will be discussed in chapter **2** and **3**.

1.5 References

[1] French, A. N.; Bissmire, S.; Wirth, T. *Chem. Soc. Rev.* **2004**, *33*, 354.

[2] Bougault, J. *Acad. Sci.* **1904**, *139*, 864.

[3] (a) Kitagawa, O.; Inoue, T.; Taguchi, T. *Tetrahedron Lett.* **1992**, *33*, 2167.
(b) Kitagawa, O.; Inoue, T.; Hirano, K.; Taguchi, T. *J. Org. Chem.* **1993**, *58*, 3106.
(c) Inoue, T.; Kitagawa, O.; Oda, Y.; Taguchi, T. *J. Org. Chem.* **1996**, *61*, 8256.

[4] Curran, D. P.; Chang, C. T. *J. Org. Chem.* **1989**, *54*, 3140.

[5] Inoue, T.; Kitagawa, O.; Kurumizawa, S.; Ochiai, O.; Taguchi, T. *Tetrahedron Lett.* **1995**, *36*, 1479.

[6] Inoue, T.; Kitagawa, O.; Saito, A.; Taguchi, T. *J. Org. Chem.* **1997**, *62*, 7384.

[7] Kitagawa, O.; Suzuki, T.; Inoue, T.; Watanabe, Y.; Taguchi, T. *J. Org. Chem.* **1998**, *63*, 9470.

[8] Saito, A.; Okada, M.; Nakamura, Y.; Kitagawa, O.; Horikawa, H.; Taguchi, T. *J. Fluorine Chem.* **2003**, *123*, 75.

[9] Curran, D. P.; Chen, M. H.; Spletzer, E.; Seong, C. M.; Chang, C. T. *J. Am. Chem. Soc.* **1989**, *111*, 8872.

[10] Belletire, J. L.; Spletzer, E. G. *Tetrahedron Lett.* **1986**, *27*, 131.

[11] Curran, D. P.; Tamine, J. *J. Org. Chem.* **1991**, *56*, 2746.

[12] Beckwith, A. L. J.; Tozer, M. J. *Tetrahedron Lett.* **1992**, *33*, 4975.

[13] Beckwith, A. L. J.; Bowry, V. W. *J. Org. Chem.* **1989**, *54*, 2681.

[14] (a) March, J. "Advanced Organic Chemistry" fourth Ed., John Wiley and Sons Inc., © **1992**. (b) Bordwell, F.G. *Acc. Chem. Res.* **1988**, *21*, 456. (c) Bordwell, F.G.; Fried, H. E. *J. Org. Chem.* **1981**, 46, 4327.

Chapter 2

Syntheses of 3-Iodo-1*H*-indene Derivatives

The chapter 2 starts with concise detail of wide-ranging applications of indene derivatives. A brief literature overview of the various synthetically useful methods for the preparation of multisubstituted indene derivatives is discussed. In addition, special approaches of mechanistic interest are also briefly mentioned. Herein a facile synthesis of 3-iodo-1*H*-indene derivatives via iodonium-promoted 5-*endo-dig* carbocyclisation of 2-substituted ethynylmalonates as a key starting material is described. Their use as a catalyst for the *in situ* generation of hypervalent iodine(III) reagent and as a substrate for the Mizoroki-Heck reaction is demonstrated.

2.1 Applications of indene derivatives

The indene nucleus is prevalent in a wide variety of drug candidates possessing interesting biological activities. The estrogen receptors (ER) control the transcription of genes important for the developmental, reproductive, neural, skeletal, and cardiovascular processes. The indene derivatives have been used as therapeutic agents to selectively modulate the ER transcriptional activity for the treatment of diseases and normal human development [1]. The indene scaffolds display high affinities for the dopamine D1 and D2 receptors [2]. Major side effects, such as gastrointestinal (GI) haemorrhaging and ulceration have greatly limited the therapeutic potential of all the non-steroidal anti-inflammatory drugs (NSAIDs) [3]. The indene analogues are potent and selective COX-2 inhibitors to protect against GI haemorrhaging [3]. Indene-1-acetamide compounds inhibit human nonpancreatic secretory phospholipase A2 (sPLA2) mediated release of fatty acids and are useful for treatment of conditions such as septic shock [4].

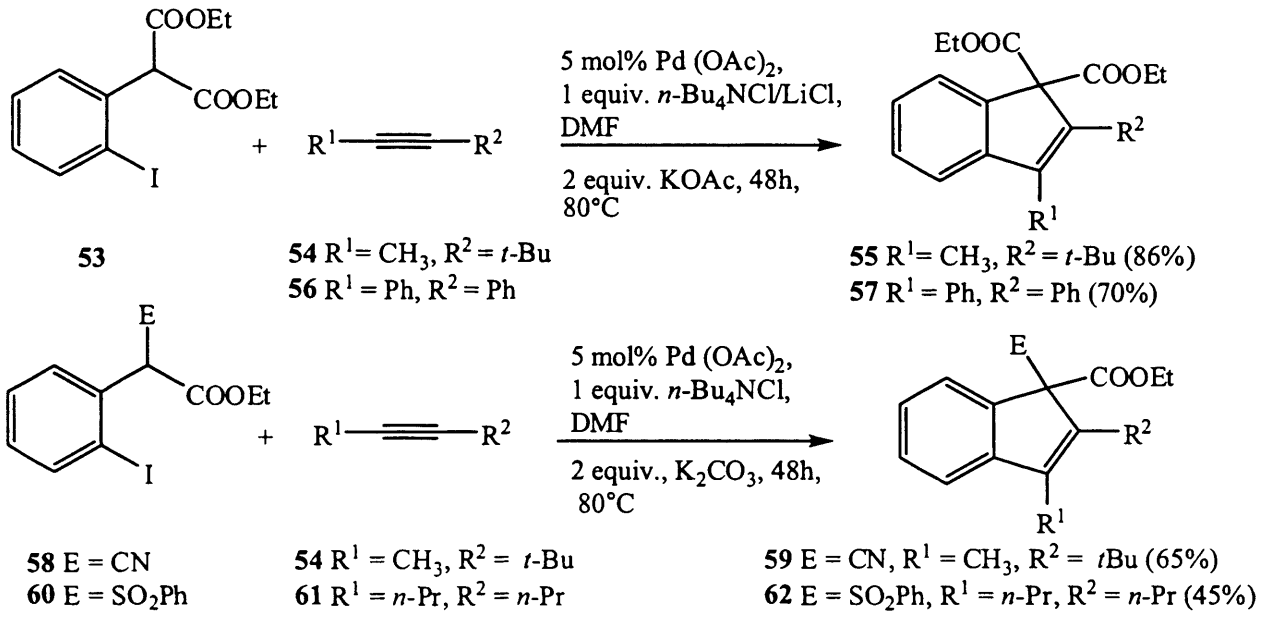
Apoptosis is an essential cellular process for the normal human development and homeostasis of multicellular organisms, to eliminate unwanted or damaged cells. Deregulated apoptosis plays a major role in many human diseases including cancer. The 2,3-dihydro-1*H*-indene derivatives provided methods for treating and preventing various diseases by regulating apoptosis [5]. Recently, the indenenylsulfonamides act as 5-HT_6 serotonin receptor agonists. This has helped to elucidate the role of 5-HT_6 receptor in cognition and learning as well as certain types of neuropsychological and neuropsychiatric diseases such as eating disorders, Schizophrenia and Alzheimers disease [6]. Additionally, indene derivatives were also used as ligands in metallocene complexes especially group IV metals in the catalysis of olefin polymerization to produce stereospecific polymers [7].

2.2 Literature overview to construct indene frameworks

Due to diverse applications of compounds containing indene ring system, a number of synthetic approaches have been developed to construct indene scaffolds and some of these classical approaches are discussed in detail.

2.2.1 Transition metal mediated carboannulation of terminal and internal alkynes

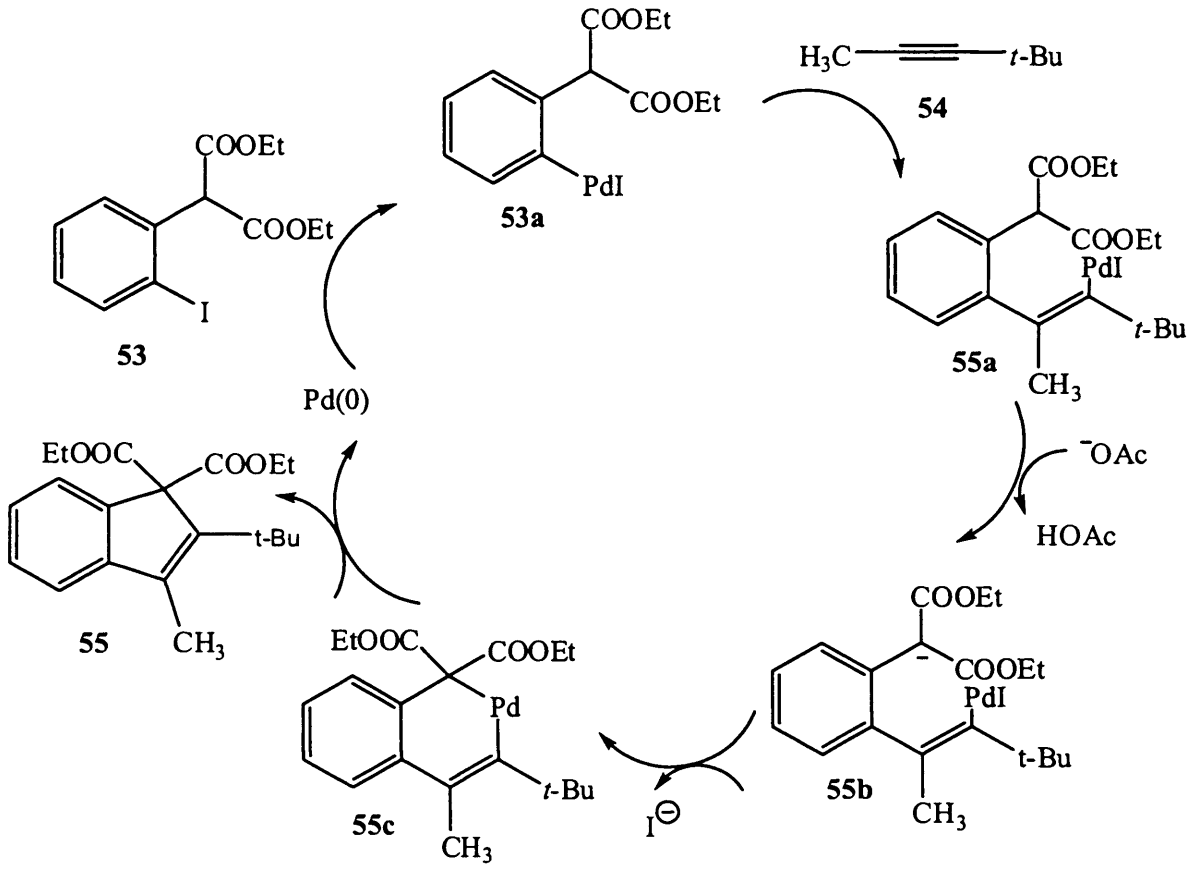
Larock *et al.* developed transition metal-mediated syntheses of highly substituted indene derivatives [8]. The foremost strategy involved the intermolecular palladium-catalysed carboannulation of internal alkynes by appropriately functionalised aryliodides. The reaction of diethyl (2-iodophenyl) malonate **53** with unsymmetrical alkyne **54** gave good yield of indene **55** as a single regioisomer. This approach was also quite effective for symmetrical alkyne **56** (Scheme 1). The aryl iodide having electron withdrawing goups like -CN, $-SO_2Ph$ in the case of compounds **58** and **60**, react with internal alkynes **54** and **61** to gave moderate yields of the corresponding indenes **59** and **62** (Scheme 1).



Scheme 1. Palladium-catalysed carboannulation of alkynes by aryliodides.

The high regioselectivity for unsymmetrical alkynes was probably due to steric hindrance present in developing carbon-carbon bond. As a result the unsymmetrical alkynes insertion occurs to generate the least steric strain in the vicinity of the developing carbon-carbon bond. Sensitive fuctional groups like –COOEt, -CN, $-SO_2Ph$ were readily accommodated under

reaction conditions [9] (Scheme 1). The proposed mechanism for the synthesis of compound **55** was shown in Scheme 2.

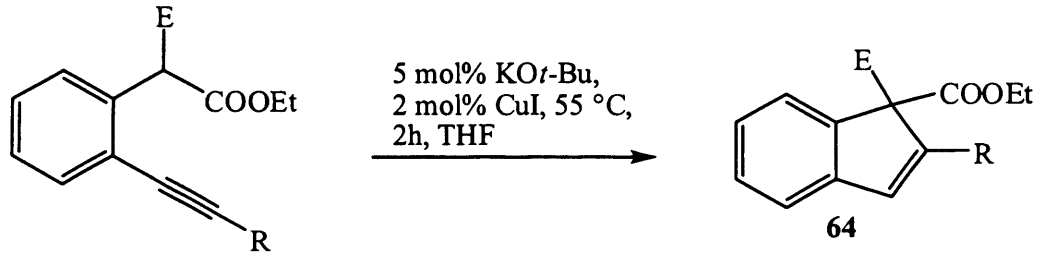


Scheme 2. Proposed mechanistic route for the synthesis of compound **55**.

First step was the oxidative addition of the aryl iodide to the Pd(0) catalyst. Further, the arylpalladium coordination to the alkyne and insertion of the alkyne to form a vinylic palladium intermediate **55a**. The deprotonation of compound **55a** by a base to gave a carbanion **55b** followed by the intramolecular nucleophilic attack of the carbanion on the vinylic palladium intermediate afforded a palladacycle intermediate **55c**. Finally, palladacycle intermediate **55c** underwent reductive elimination furnished indene **55** and regenerated Pd(0) catalyst.

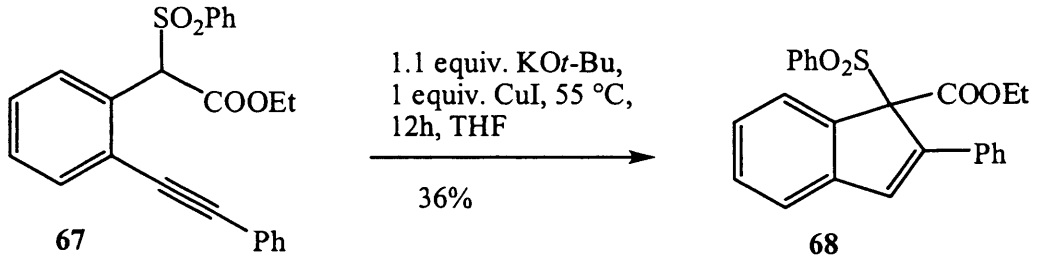
The next method involves the Sonogashira coupling of terminal alkynes with appropriately functionalised aryl iodides, followed by copper mediated intramolecular cyclisation (Scheme 3). In this approach, a variety of indene derivatives have been synthesised and this method also tolerates a variety of functional groups like ester, sulfone, and cyano groups [9].

The cyclisation of compound **63** with catalytic amount of KO*t*-Bu and CuI gave an excellent yield of indene **64** (Scheme 3). The cyclisation of compound **65** bearing an aliphatic chain afforded good yields of the desired product **66**. In the case of substrate **67**, even the use of stoichiometric amounts of both KO*t*-Bu and CuI and an elevated temperature afforded only a modest 36% yield of indene **68**.



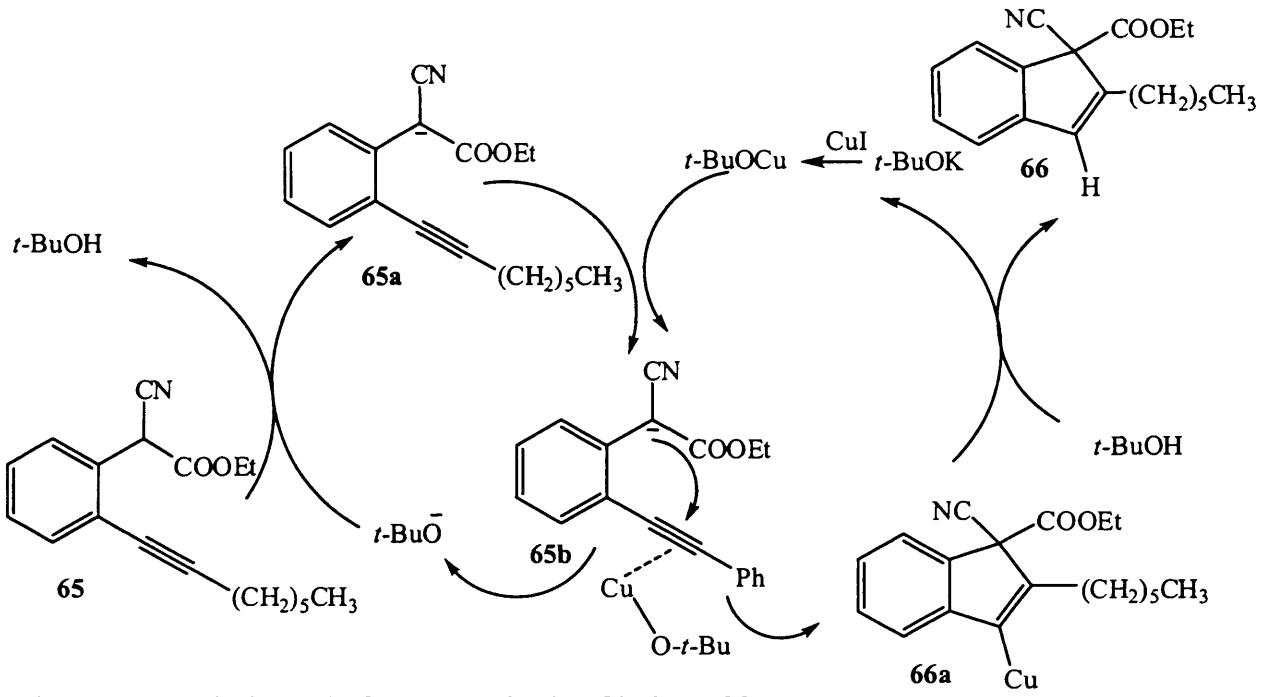
63 E = COOEt, R = *p*-methoxyphenyl
65 E = CN, R = n-hexanyl

64 E = COOEt, R = p-methoxyphenyl (96%)
66 E = CN, R = n-hexanyl (83%)



Scheme 3. Synthesis of indenes by copper(I) mediated carboannulation of internal alkynes.

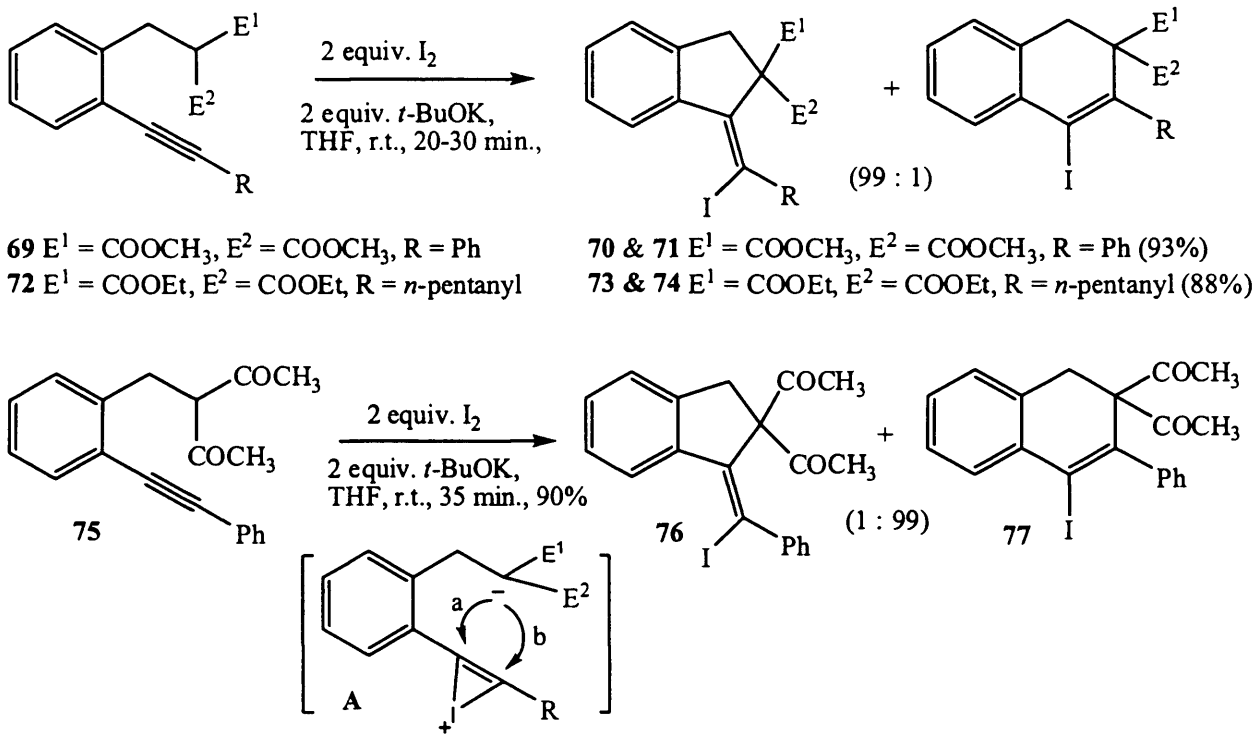
The proposed mechanism route for the synthesis of cyclised compound **66** was shown in Scheme 4. Presumably, the copper catalysed intramolecular cyclisation proceed via the generation of a carbanion **65a** by the *t*-butoxide. The activation of carbon carbon triple bond of intermediate **65a** by coordination of copper *t*-butoxide towards the intramolecular nucleophilic attack of the carbanion resulted in the formation of vinylic copper intermediate **66a**. The vinylic copper intermediate **66a** might accept proton from *t*-BuOH to furnish the indene **66** and regenerate the copper catalyst and copper *t*-butoxide (Scheme 4).



Scheme 4. Catalytic cycle for the synthesis of indene **66**.

2.2.2 Electrophilic cyclisation of acetylenic malonates and ketones

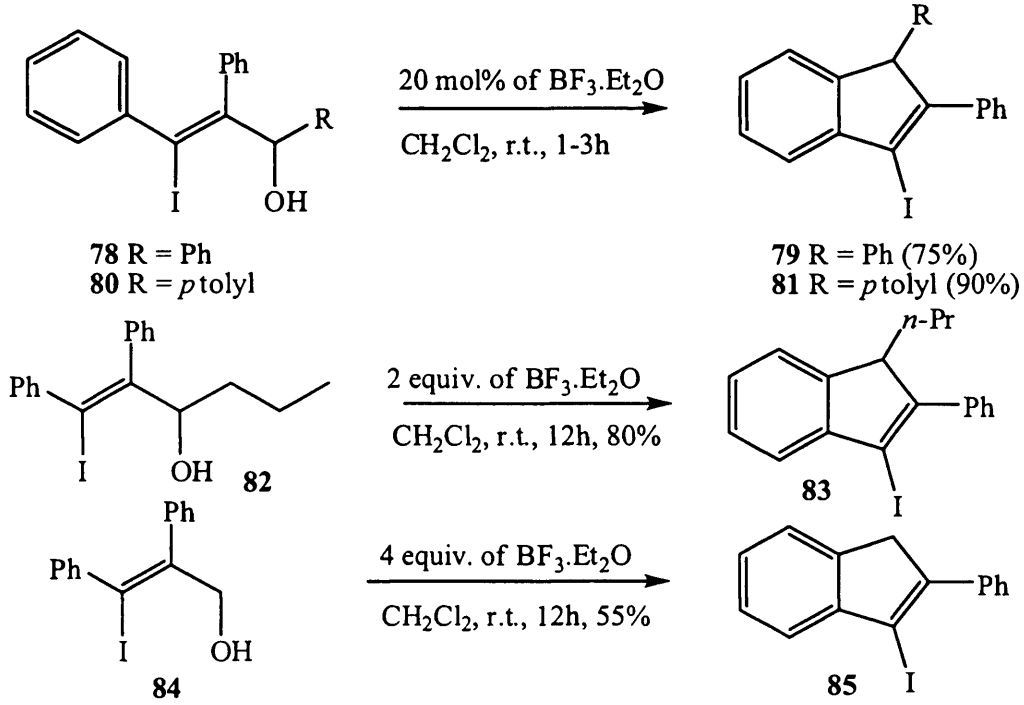
The highly regioselective syntheses of indene and dihydronaphthalene derivatives of acetylenic malonates and ketones with iodine electrophiles in excellent yields was described by Liang *and* co-workers [10]. The reaction of compound **69** with 2 equiv. of base and iodine in THF at r.t. gave high ratio of 5-*exo-dig* indene product **70** when compare to the 6-*endo-dig* dihydronaphthalene product **71** (99:1 respectively). Similar ratios of the carbocyclised products **73** and **74** (99:1) were observed for substrate **72** under the similar reaction conditions in good yield. Surprisingly, the ratio was reversed in the case of acetylenic ketone **75** to give 1:99 ratio of dihydronaphthalene **76** and indene derivative **77** (Scheme 5). The reaction occurs via an iodonium intermediate **A** formed from activation of carbon-carbon triple bond by iodine electrophile. This is followed by the attack of carbanion generated by base on the activated triple bond to afford the *5-exo-dig* (path a) and *6-endo-dig* (path b) cyclised products.



Scheme 5. Electrophilic cyclization of acetylenic malonates and ketones.

2.2.3 Lewis acid mediated Friedel-Crafts cyclisation of iodinated allylic alcohols

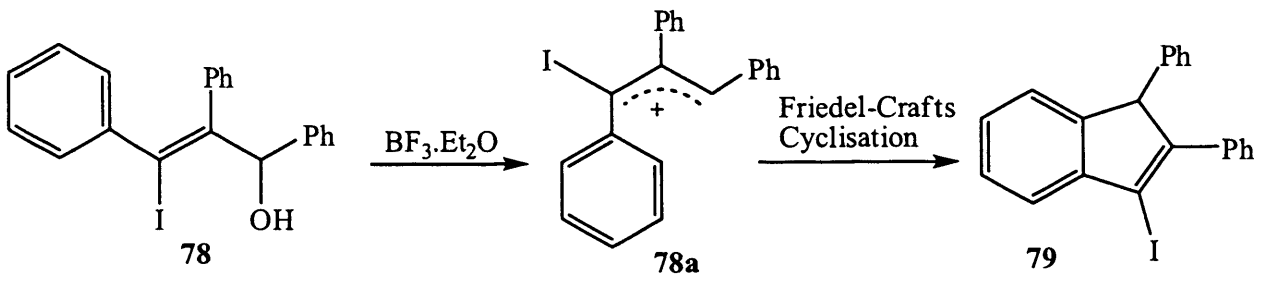
Recently, Li *et al.* reported the syntheses of multisubstituted 3-iodo-1*H*-indene derivatives via $BF_3.Et_2O$-catalysed Friedel-Crafts cyclisation of iodinated allylic alcohols [11].



Scheme 6. Lewis acid mediated synthesis of 3-iodo-1*H*-indene derivatives.

The yields were lower when reaction was catalysed by mineral acids such as HCl and H_2SO_4. A variety of allylic alcohols bearing a phenyl ring moiety were subjected to the Lewis acid ($BF_3.Et_2O$) conditions to define reaction scope. The substitution on the α-carbon of the allylic alcohols has a big influence on the cyclisation reaction. The secondary allylic alcohol (**78** and **80**) bearing an aromatic ring at the α-carbon cyclised very well to generate respective indenes (**79** and **81**) in good yields (Scheme 6).

However, when a secondary alcohol with alkyl substituent **82** or primary alcohol **84** was used, the desired products (**83** and **85** respectively) were obtained in 31% and 15% yields when catalytic amount of Lewis acid was used. The adequate to good yields of cyclised products for substrate **82** and **84** were obtained when the reaction was performed with 2 equiv. and 4 equiv. of Lewis acid (Scheme 6) [11].

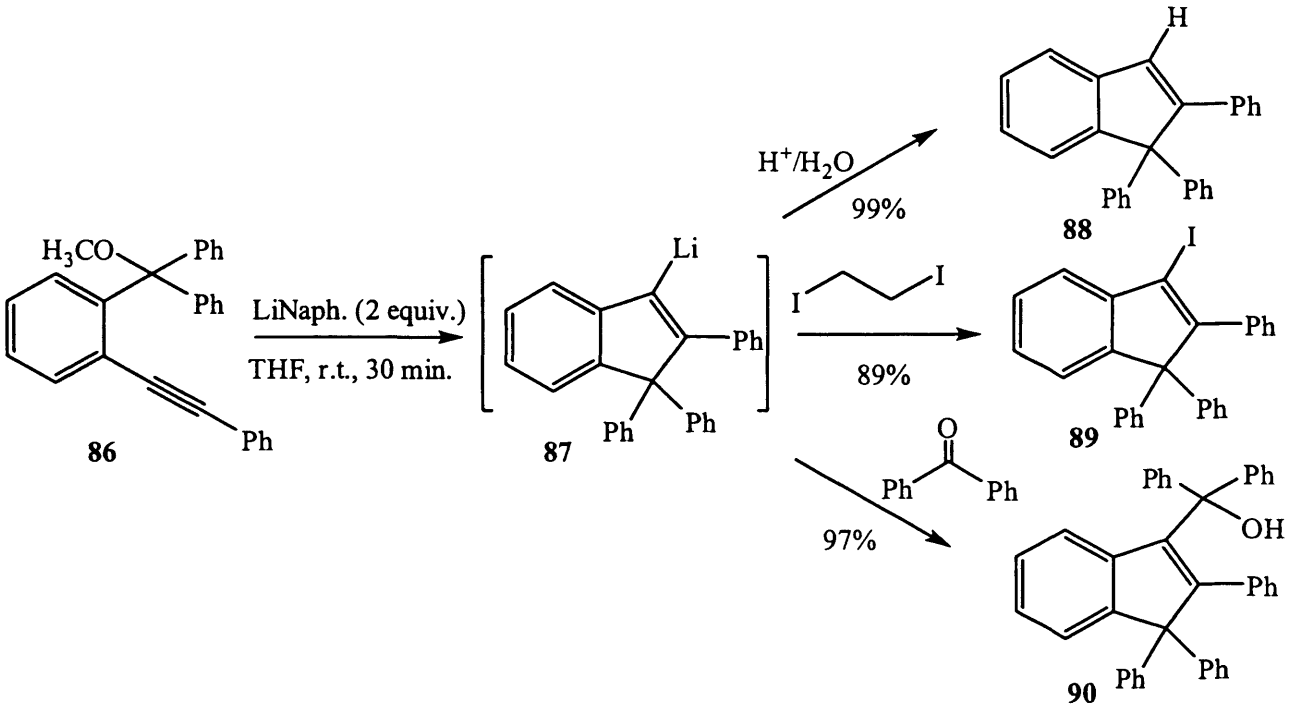


Scheme 7. Proposed mechanism for the cyclisation of compound **78**.

The proposed mechanism for the formation of 3-iodo-1*H*-indene derivative **79** was outlined in Scheme 7. Initial formation of an allyl cation **78a** generated *in situ* by cleavage of the carbon-oxygen bond in the presence of Lewis acid. Then allyl cation **78a** underwent an intramolecular Friedel-Crafts reaction to form indene **79**.

2.2.4 Modular syntheses of 1*H*-indenes

Nakamura *et al.* have developed a modular approach for the syntheses of substituted 1*H*-indenes via reductive cyclisation of 1-alkynyl-2-diphenyl(methoxy)methylbenzene [12].



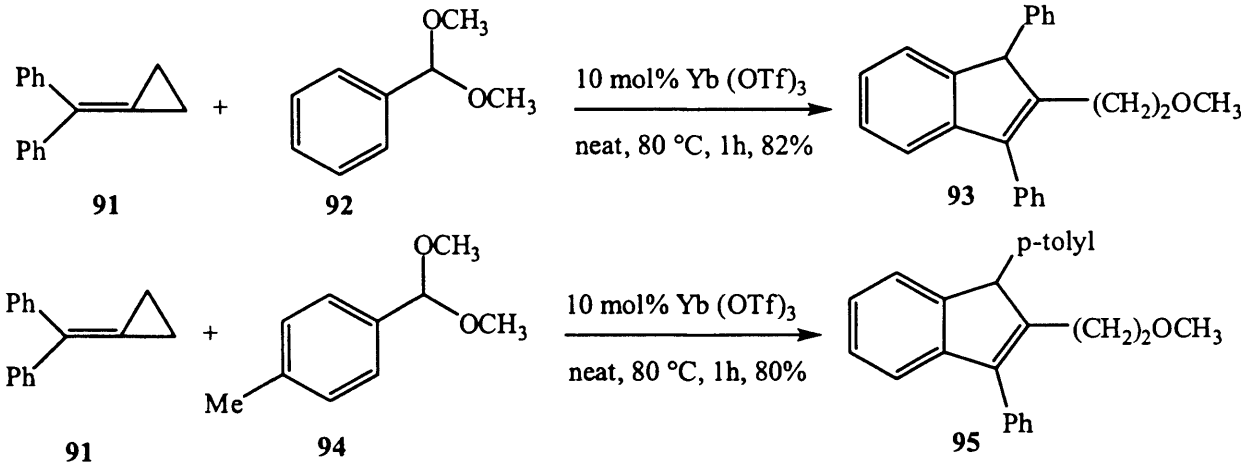
Scheme 8. Modular syntheses of substituted 1*H*-indene derivatives via reductive cyclisation.

The treatment of compound **86** with lithium naphthalenide (LiNaph.) at room temperature in THF resulted in the loss of the methoxy group and smooth formation of the desired indene **88** in 99% yield upon quenching with water, demonstrating the quantative formation of 3-lithioindene intermediate **87**. Iodination of synthetic module **87** with 1,2-diiodoethane gave 3-iodo-1*H*-indenes **89** in 89% yields [12]. The 3-lithioindene **87** added to benzophenone to give the expected tertiary alcohol **90** in 97% yield (Scheme 8).

2.2.5 Lewis acid catalysed reaction of arylidenecyclopropanes

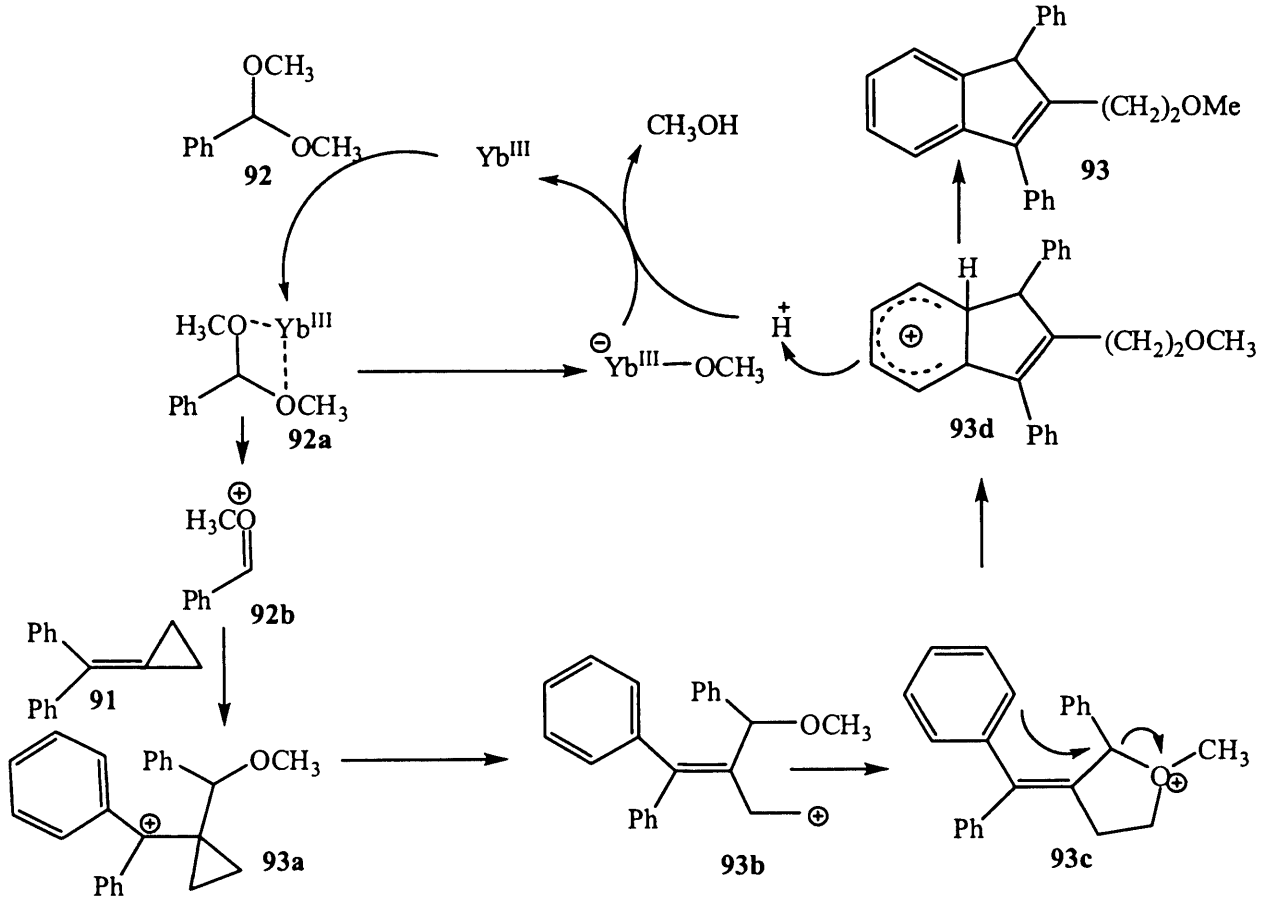
Yamamoto *et al.* have shown that the ytterbium catalysed tandem carboalkoxylation / Friedel-Crafts reaction of arylidenecyclopropanes with acetals afforded indene derivatives in good yields [13]. In the presence of 10 mol% of $Yb(OTf)_3$, the reaction of 1-phenylbenzylidene cyclopropane **91** with 2 equiv. of benzaldehyde dimethyl acetal **92** proceeded at 80 °C without solvent for 1h and afforded polysubstituted indene **93** in 82% yield. The reaction of *p*-

tolylaldehyde dimethyl acetal **94** with 1-phenylbenzylidene cyclopropane **91** proceeded under identical reaction conditions gave the corresponding indene **95** in 80% yield (Scheme 9) [13].



Scheme 9. $Yb(OTf)_3$ catalysed tandem carboalkoxylation / Friedel-Crafts reaction of aryldenecyclopropanes with acetals.

A plausible mechanism for this transformation was described in Scheme 10.

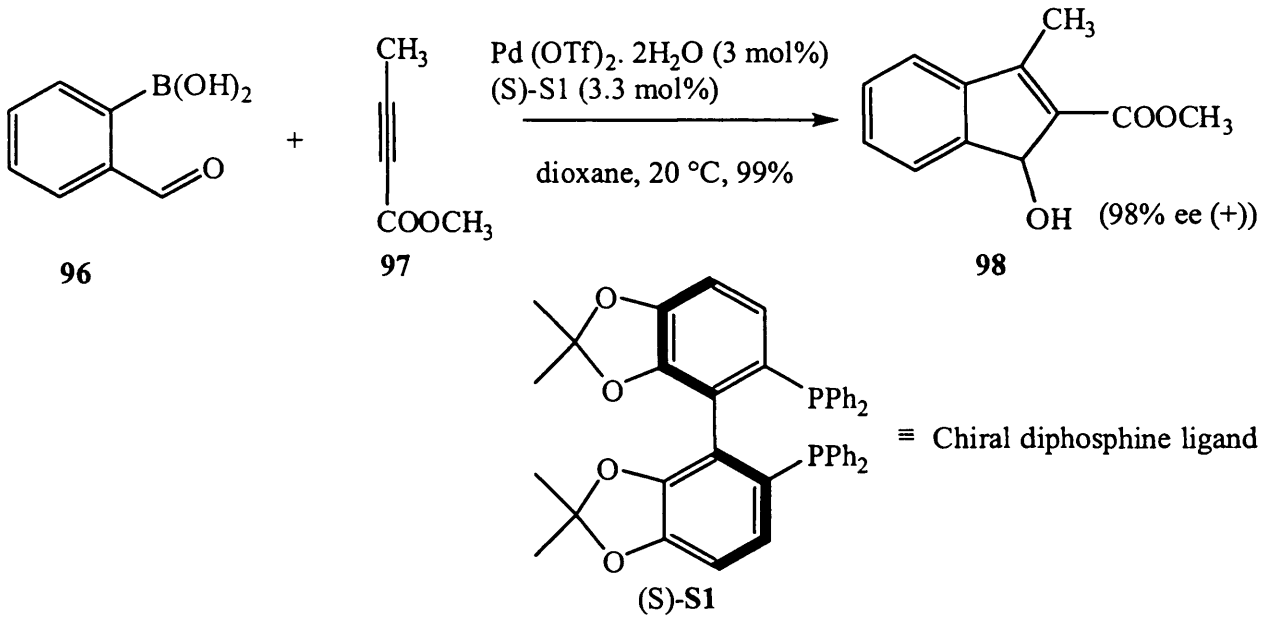


Scheme 10. The proposed mechanism for the synthesis of indene **93**.

The acetal group of compound **92** would co-ordinate to ytterbium as shown in the intermediate **92a** and elimination of ytterbium alkoxide from **92a** would give the oxonium cation **92b**. The nucleophilic attack of olefinic double bond of arylidene cyclopropane **91** to **92b** would lead to the cyclopropylcarbinyl cation **93a**. Cylopropylcarbinyl-homoallyl rearrangement would take place and subsequently intramolecular electrophilic attack of the resulting homoallyl cation **93b** to alkoxy group would lead to the cyclic oxonium intermediate **93c**. Friedel-Crafts type cyclisation would then give the product **93**.

2.2.6 Enantioselective syntheses of optically active 1-indenol

Lu *et al.* demonstrated a cationic palladium(II) catalysed enantioselective syntheses of optically active 1-indenol by using 2-acylboronic acid and substituted alkynes as precursor molecules in the presence of catalytic amount of chiral phosphine ligands.

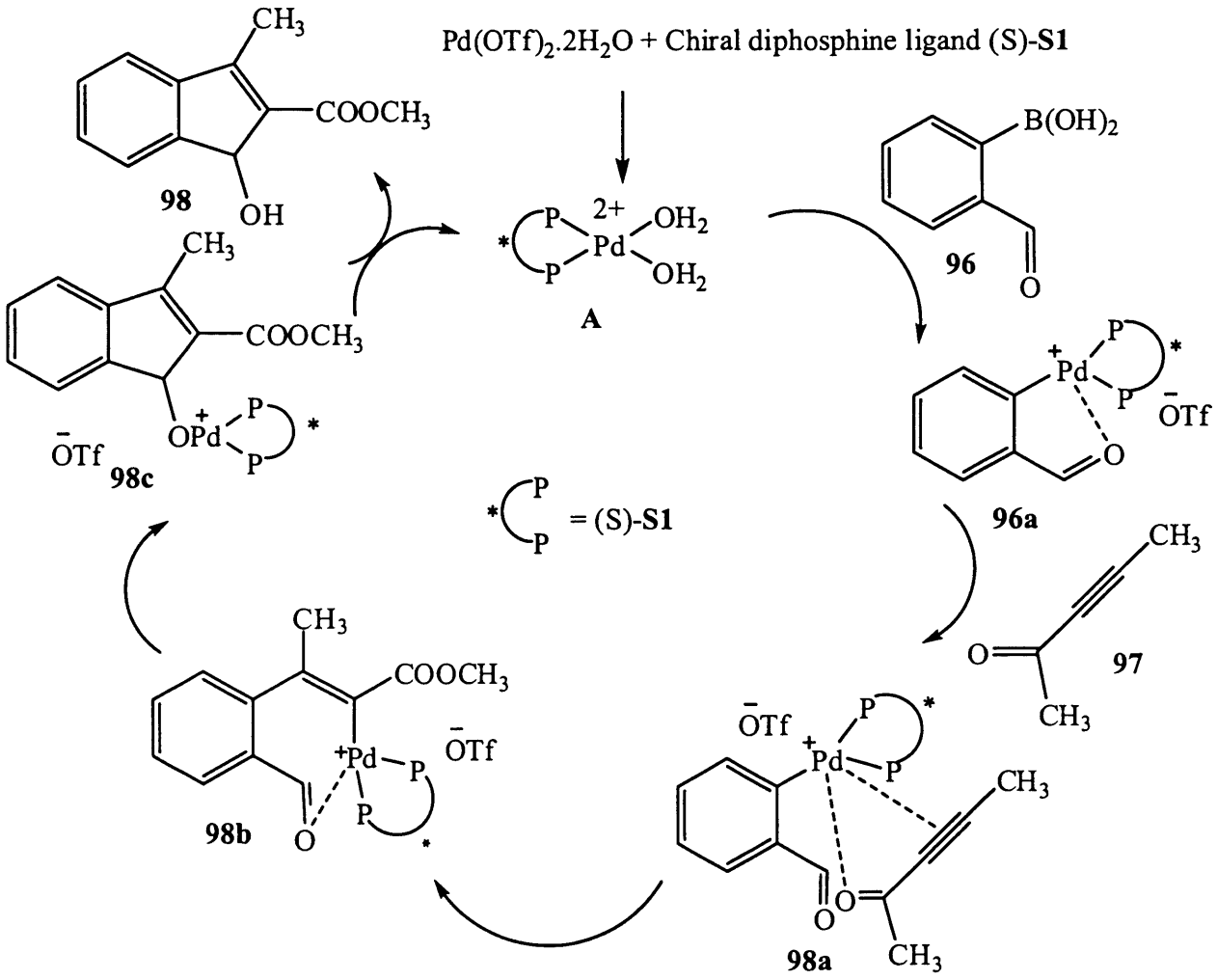


Scheme 11. Cationic Pd(II)-catalysed asymmetric annulations.

In a classic example of this strategy, the tandem [3+2] annulation of 2-acylboronic acid **96** with methyl-2-butynoate **97** in the presence of catalytic amount of chiral phosphine ligand (*S*)-**S1** to yield optically active 1-indenol **98** in almost quantative amounts and 98% enantiomeric excess (Scheme 11) [14].

A plausible mechanism for the asymmetric annulation was shown in Scheme 12. Initially the $Pd(OTf)_2.2H_2O$ and the chiral diphosphine ligand form cationic Pd(II) catalyst **A**. The

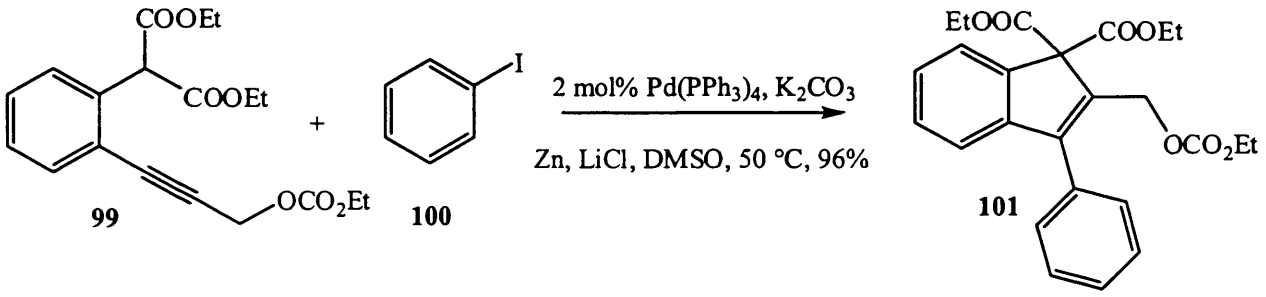
cationic nature of the transition metal species made transmetallation of catalyst with substrate **96** to give intermediate **96a,** in which σ-coordination of the carbonyl group with palladium centre may stabilize the intermediate and made the transmetallation easier. Next, π-coordination of carbon carbon triple bond of the alkyne **97** or σ-coordination of the oxygen in the alkynoates to the palladium centre would occur to form the intermediate **98a**. Then carbon carbon triple inserts into the carbon palladium bond to furnish vinyl palladium intermediate **98b**, which undergoes nucleophilic addition to the carbonyl group at *ortho* position resulting in the formation of five membered carbocycle **98c** with alkoxypalladium species. Finally protonlysis occured to form the product **98** and regenerated the cationic palladium species **A** (Scheme 12).



Scheme 12. Proposed catalytic cycle for the synthesis of compound **98**.

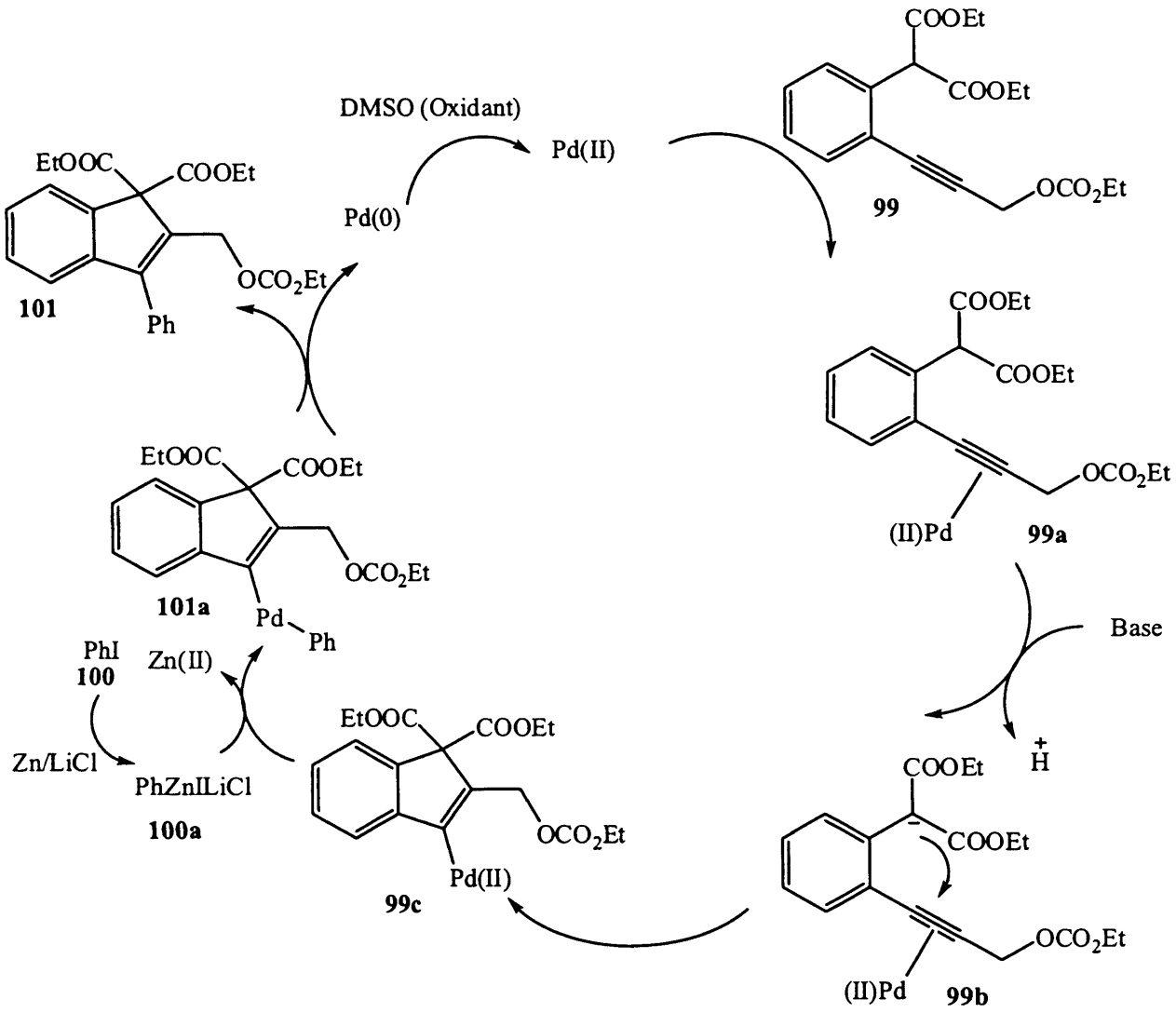
2.2.7 Palladium catalysed synthesis of indenes via propargylic carbonates

Liang *et al.* reported the synthesis of polysubstituted indene derivatives by palladium catalysed carboannulation and arylation of propargylic carbonates with *in situ* generated organozinc compounds [15]. On the basis of optimization efforts, the reaction of propargylic carbonate **99** (0.1 mmol), aryl iodide **100** (0.15 mmol) with zinc, LiCl, 2 mol% $Pd(PPh_3)_4$, and K_2CO_3 in 2mL of DMSO at 50 °C gave the best result for the synthesis of corresponding indene derivatives **101** (Scheme 13).



Scheme 13. Palladium catalysed annulations and arylation of propargylic carbonate.

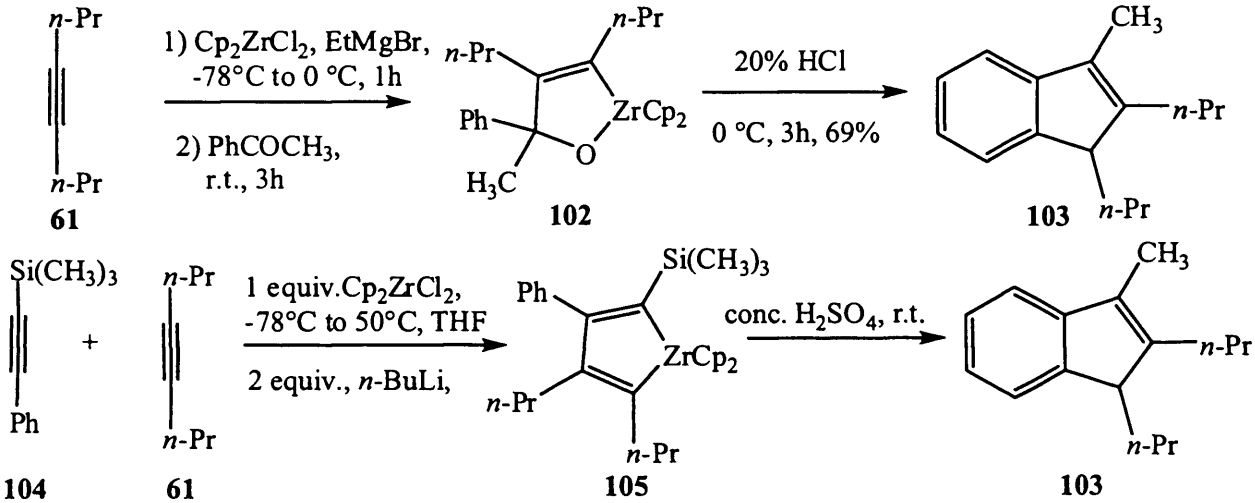
The proposed mechanistic route for compound **101** was shown in Scheme 14. The first step in the mechanism was the oxidation of Pd(0) to Pd(II) by DMSO and then π-co-ordination of Pd(II) to the carbon carbon triple bond of propargylic carbonate to give complex **99a**. The use of DMSO as a solvent was crucial since Pd(0) promotes decarboxylation of propargylic carbonate **99**. The second step is the intramolecular nucleophilic attack of carbanion on the activated carbon-carbon triple bond to afford a vinylic palladium intermediate **99c**. Then, transmetallation of **99c** with *in situ* generated organozinc compound afforded **101a**. The reductive elimination of the intermediate **101a** furnished the indene **101** and regenerated the Pd(0) catalyst (Scheme 14).



Scheme 14. The proposed mechanistic route for synthesis of indene derivative **101**.

2.2.8 Hydrolysis of oxazirconacyclopentenes and zirconacyclopentadienes

Another important strategy for the syntheses of polysubstituted indene derivatives was reported by Takahashi *et al.* In a representative example, the intermolecular coupling of an aromatic ketone with alkyne **61** resulted in the formation of oxazirconacyclopentene **102**, which upon quenching in 20% HCl resulted in the formation of indene derivative **103** (Scheme 15). In the second strategy, two different alkynes **104** & **61** can easily undergo cyclo-oxidative addition reaction with a low valent zirconacene species to afford zirconacyclopentadiene **105** which undergoes hydrolysis with concentrated H_2SO_4 to form indene derivative **103**. This strategy was also quite effective for two similar alkynes (Scheme 15) [16].

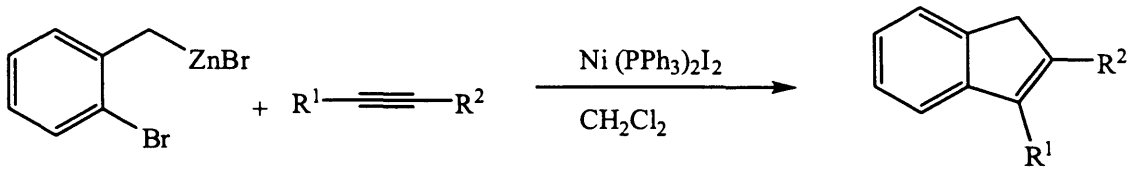


Scheme 15. Indene derivatives by hydrolysis of zirconocene-mediated intermolecular product of aromatic ketones and alkynes.

The generated zirconacyclopentadienes need to bear a phenyl group at the β-position for the formation of indene derivative. The silyl substituted alkynes were known to afford α-silylzirconacyclopentadienes selectively by above mentioned method. When $SiMe_3$ was one of the substituent, the desilylation take place in the concentrated acidic media afforded 3-methylindene derivative **103**.

2.2.9 Nickel catalysed carboannulation of *o*-bromobenzyl zinc bromide with alkynes

Sun *et al.* reported synthesis of indene derivatives by treating *o*-bromobenzyl zinc bromide with various terminal and internal alkynes in the presence of a nickel catalyst in good yields. [17]. This approach was quite effective for internal as well as terminal alkynes **56** & **108** respectively to afford respective indene derivatives **107** and **109** in good yields (Scheme 16).

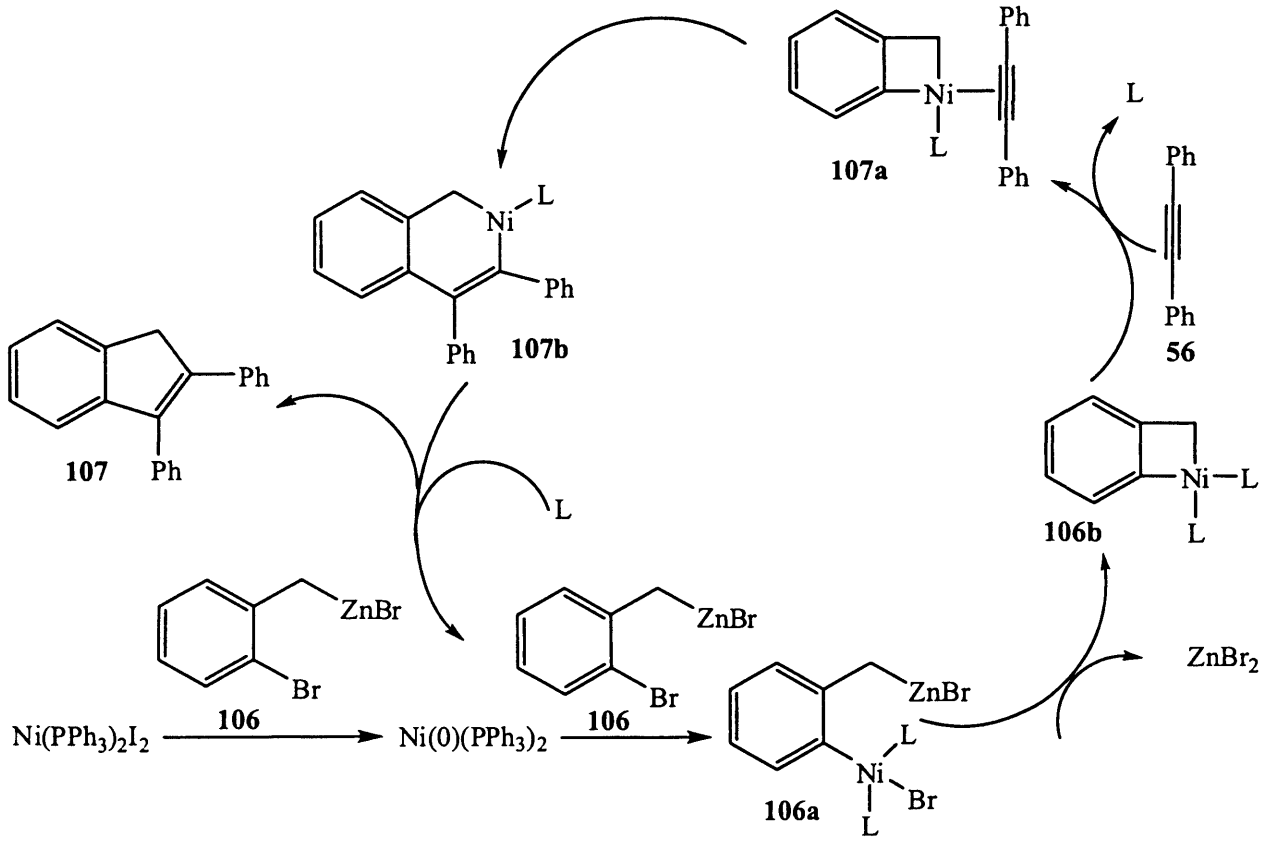


106 **56** R^1 = Ph, R^2 = Ph
108 R^1 = H, R^2 = *p*-methoxyphenyl

107 R^1 = Ph, R^2 = Ph (76%)
109 R^1 = H, R^2 = p-methoxyphenyl (76%)

Scheme 16. Nickel catalysed carboannulation of *o*-bromobenzyl zinc bromide with alkynes.

The exact mechanism for synthesis of indene derivative **107** was not clear.



Scheme 17. Catalytic cycle for the synthesis of indene derivative **107**.

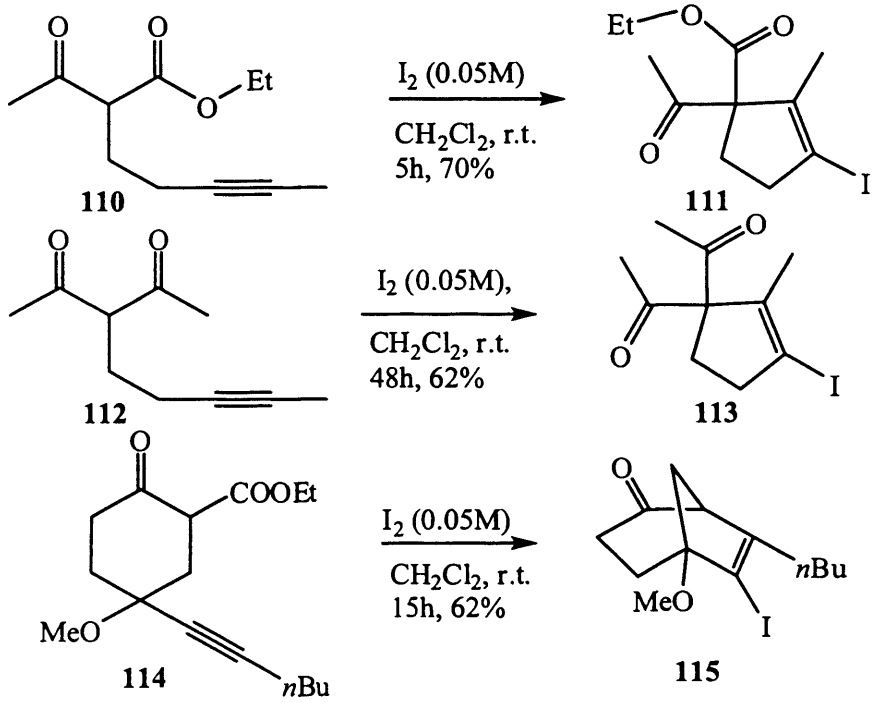
As indicated in Scheme 17, reduction of Ni(II) to Ni(0) by **106** initiated the catalysis. After the formation of **106b** from **106** and Ni(0) via path described in scheme 15, the co-ordination of alkyne **56** to **106b** via ligand exchange formed a nickel-alkyne complex **107a**. The intermediate **107a** underwent regioselective insertion of the alkyne into Ni-C_{sp2} bond to form intermediate **107b**. Reductive elimination from intermediate **107b** gave Ni(0) and indene product **107**.

2.3 Examples of 5-*endo-dig* cyclisations

There were various examples in the literature explaining the concept of intramolecular 5-*endo-dig* cyclisations. Some of these examples will be discussed in detail.

2.3.1 Synthesis of iodocyclopentenes

Barluenga *et al.* reported the syntheses of iodocyclopentenes via 5-*endo-dig* carbocyclisation of δ-alkynyl-β-ketoesters at room temperature with I_2 for several hours stirring in CH_2Cl_2.

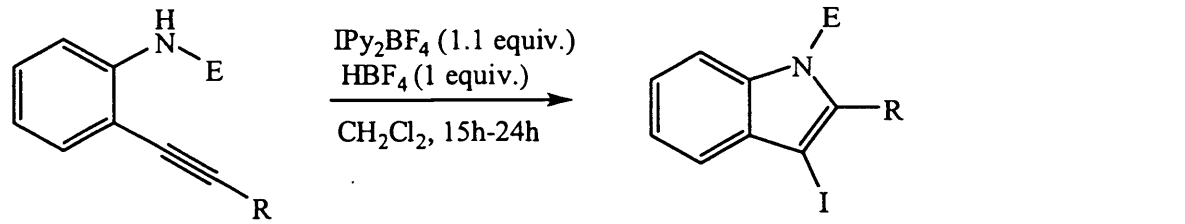


Scheme 18. Iodonium promoted *5-endo dig* mode of carbocyclization of δ-alkynyl-β-ketoesters.

Under refined condition, the target synthesis of carbocycle **111** from substrate **110** gave 70% yield by using stoichiometric amount I_2 (with respect to **110**) and CH_2Cl_2 as solvent. This methodology extended to 1,3-diketone **112** as a substrate to give cyclised product **113** in 62% yield. The formation of bicyclic skeleton **115** was possible in similar yields (Scheme 18) [18]. The major competing reaction pathway was the 1,2-addition of I_2 across the alkyne. Its impact was minimized by increasing the dilution from 0.3 to 0.05 M solution of iodine.

2.3.2 Synthesis of 3-iodoindole by iodocyclisation

Barluenga *et al.* reported the classical approach toward the syntheses of 2-substituted-3-iodoindoles from *N*-protected *o*-(alkynyl) anilines in the presence of IPy_2BF_4 as an iodinating agent [19]. The C-N bond formation reaction needed only simple activation of the iodinating agent by HBF_4 (1 equiv.). The substrate **116** having a phenyl substituent along with an *N*-Boc protecting group gave satisfactory results under the reaction conditions to form indole **117** in good yield. However, compound **118** having 1-cyclohexenyl gave poor yields of the respective indole derivative **119** due to formation of an allene structure as the major product. Alternatively, the related methanesulfonate derivative **120** furnished indole derivative **121** in 84% yields (Scheme 19).

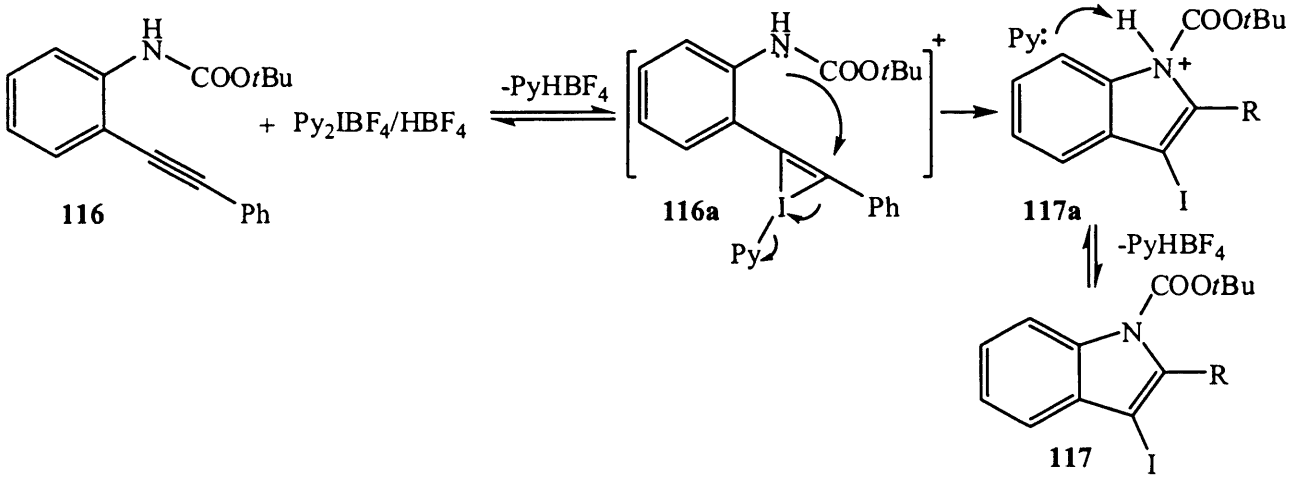


116 E = COO*t*Bu, R = Ph
118 E = COO*t*Bu, R = 1-cyclohexenyl
120 E = SO_2CH_3, R = *n*Bu

117 E = COO*t*Bu, R = Ph (68%)
119 E = COO*t*Bu, R = 1-cyclohexenyl (17%)
121 E = SO_2CH_3, R = *n*Bu (84%)

Scheme 19. The synthesis of indoles from o-alkynyl aniline derivatives promoted by IPy_2BF_4.

The proposed mechanistic route for the synthesis of compound **117** was given in Scheme 20.



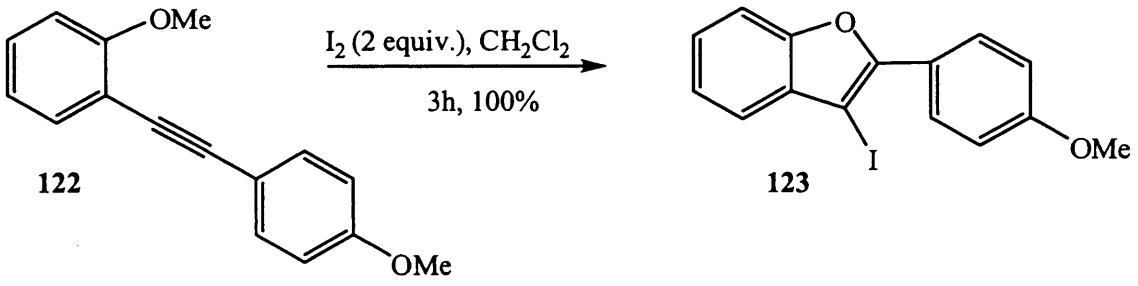
116 **116a** **117a** **117**

Scheme 20. Proposed reaction mechanism for the formation of compound **117**.

The initial interaction of electrophilic iodine with alkyne residue resulted in the formation of intermediate **116a**. The subsequent attack of nitrogen would lead to ring closure. One equivalent of acid (HBF_4) used to activate the reagent (Py_2IBF_4) in this reaction; therefore second pyridine might help to remove a proton from nitrogen atom (Scheme 20).

2.3.3 Synthesis of 2,3-disubstituted benzo[b]furan by electrophilic cyclisation

Larock *et al.* reported the synthesis of 2,3-disubstituted benzo[b]furan under very mild reaction conditions starting from 2-(arylethynyl)anisole. A range of readily available electrophiles (I_2, ICl, *p*-$O_2NC_6H_4SCl$ and PhSeCl) can be employed successfully in the cyclisation reactions [21].



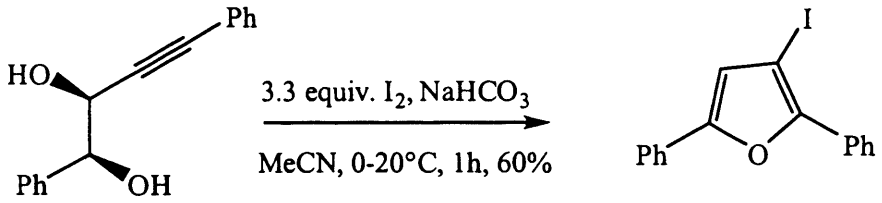
122 **123**

Scheme 21. The synthesis of benzo[b]furan **123** via *5-endo-dig* electrophilic cyclisation.

To form a furan moiety, the oxygen of the methoxy group has to undergo a *5-endo-dig* attack on the carbon-carbon triple bond (Scheme 21). The substrate **122** reacted with iodine at r.t. to afford 3-iodo-2-*para*-methoxyphenylbenzo[b]furan (**123**) in quantative yield [20].

2.3.4 Synthesis of β-iodofuran and 3-isoxazolines

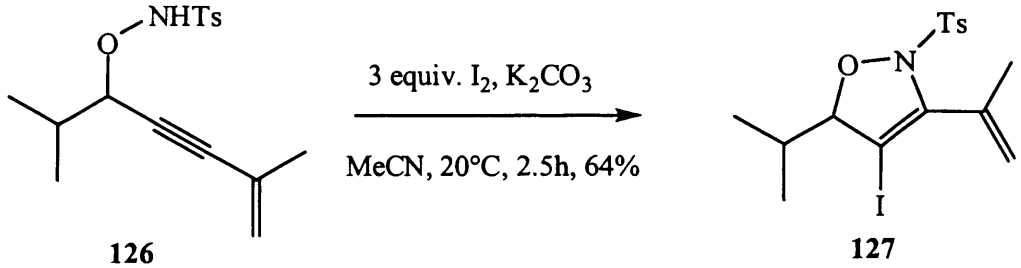
In 2007, the David Knight and co-workers reported the 5-*endo-dig* cyclisation of 3-alkyne-1,2-diol using iodine as the electrophile proceed smoothly to deliver β-iodofurans. In a typical example of this strategy the precursor molecule **124** gave clean conversion of β-iodofuran **125** in good yield under mild reaction conditions (Scheme 22) [21a].



124 **125**

Scheme 22. Synthetic route of β-iodofurans **125**.

Further extension of almost identical reaction conditions have been applied for the synthesis 4-iodo-2,5-dihydroisoxazole **127** via *5-endo-dig* cyclisation in good yields from alkynyl hydroxylamine **126** as a precursor molecule (Scheme 23) [21b].



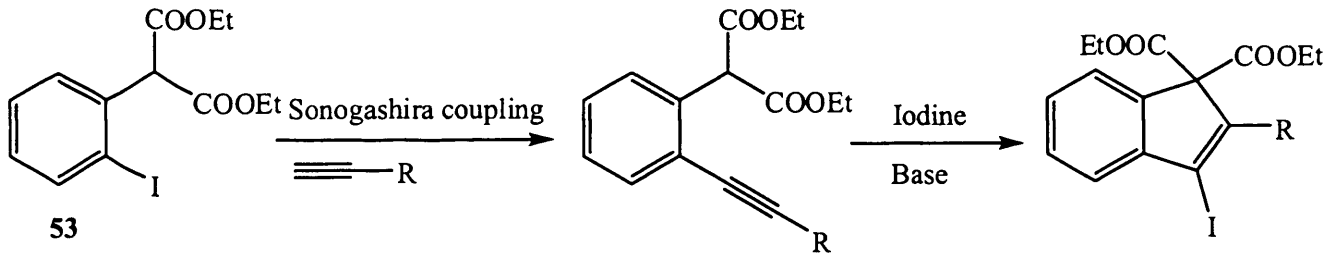
126 **127**

Scheme 23. The synthesis 4-iodo-3,5-dihydroisoxazole**128**.

2.4 Project outlines

We are unaware of reports on the synthesis of 3-iodo-1*H*-indenes by electrophilic cyclisations of 2-substituted ethynylmalonate as a key starting material. Recently, there has been a growing interest in developing a general and versatile synthesis of 3-iodo-1*H*-indene derivatives. An intriguing article from the work of Larock *et al.* served as starting point for our studies [9]. Scheme 3 summarizes the results of their attempts to cyclise 2-substituted alkynyl malonate by transition metals.

Therefore, a two step approach, which involves the Sonogashira coupling of terminal alkynes with an appropriately functionalized aryl iodide to form 2-substituted alkynyl malonates, followed by the reaction of resulting substrates with iodine under basic conditions (Scheme 24). The iodine mediated synthesis of 3-iodo-*1H*-indenes would have major advantages over traditional methods. For example, the reaction conditions might be mild and most important functional groups can be readily accommodated. We believe that this approach to 3-iodo-*1H*-indenes should prove quite useful in the synthesis, particularly when one considers that there are many ways to transform the resulting iodide functionality to other substituents. For example, the carbocyclic iodides should be particularly useful as intermediates in many palladium catalysed processes like Sonogashira [22], Suzuki [23], and Heck cross-coupling reactions [24]. Additionally, they were used for the *in situ* generation of hypervalent iodine reagents for C-H functionalisation of carbonyl compounds [25].

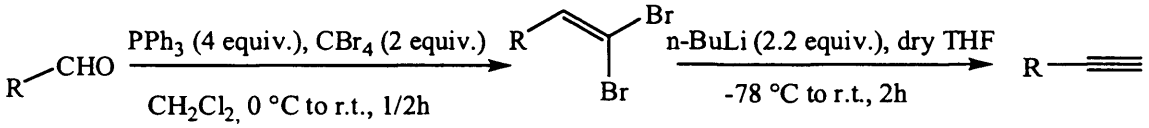


Scheme 24. Proposed synthetic route to 3-iodo-1*H*-indenes.

2.5 Results and discussion

2.5.1 Synthesis of terminal alkynes

Phenylacetylene (**132a**) and 1-heptyne (**132f**) were commercially purchased from *Alfa Aesar* and used without further purification. The terminal acetylenes bearing 3-methoxyphenyl (**132b**) and 2-naphthyl (**132c**) moieties were synthesised by using the Corey-Fuchs reaction [26]. The synthetic sequences for the Corey- Fuchs reaction were described in Scheme 25. The aldehydes **128** and **129** were treated with a mixture of carbon tetrabromide triphenylphosphine to form dibromolefins **130** and **131** via the Wittig type reaction in good yields (Scheme 25).



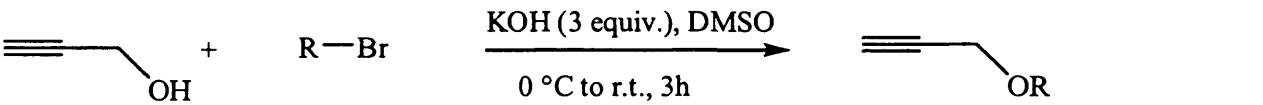
128 R = 3-methoxyphenyl
129 R = 2-naphthyl

130 R = 3-methoxyphenyl (78%)
131 R = 2-naphthyl (88%)

132b R = 3-methoxyphenyl (90%)
132c R = 2-naphthyl(69%)

Scheme 25. Synthesis of terminal acetylenes by the Corey-Fuchs reaction.

The reaction of dibromoolefins compounds with more than 2 equiv. of *n*-BuLi in THF resulted in rapid formation of organolithium derivative and simple hydrolysis afforded terminal acetylenes in good yields (Scheme 25).



133

134 R = benzyl
135 R = 2-phenylbenzyl

132d R = benzyl (59%)
132e R = 2-phenylbenzyl (68%)

Scheme 26. The protection of propargyl alcohol **133**.

Propargyl alcohol **133** was protected by a benzyl and 2-phenybenzyl moiety as per literature protocol [27]. The corresponding ethers **132d** and **132e** were synthesized in 59% and 68% yields respectively (Scheme 26).

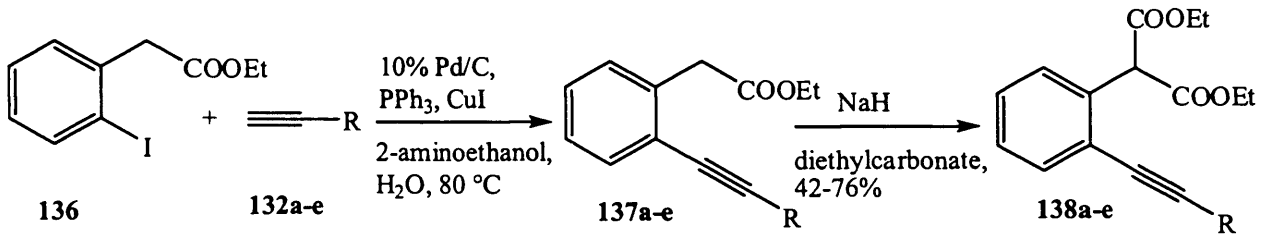
2.5.2 Sonogashira Cross Coupling of terminal Acetylenes with aryl iodides

The Sonogashira reaction of terminal acetylenes with aryl or vinyl halides is a powerful tool for $C(sp^2)$-C(sp) bond formation, which has been widely applied to diverse areas such as natural product synthesis and material sciences [28]. The organic solvents/water mixture provides a useful, robust and efficient medium for Pd/C-catalyzed Sonogashira coupling.

The Sonogashira coupling of terminal acetylenes was carried out in water without organic solvent by using Pd/C-PPh_3-CuI catalysis facilitated by 2-aminoethanol as a cheaper amine base [29] (Table 1). The reaction was carried out at 80 °C. The decreases in temperature afforded low yields of coupled product even for long reaction time. These observation indicated the *in situ* generation of a new Pd(0) species from Pd/C-PPh_3 at higher temperature, which essentially catalyzed the cross coupling reactions [29].

The synthesis of alkynyl malonates proceeded smoothly starting from ethyl (2-iodophenyl) acetate **136**. Sonogashira coupling led to alkynes coupled products **137a-e** in reasonable to good yields (42-76%), which were then treated (**137a-e**) with sodium hydride [9] and diethyl carbonate (59-76%) to obtain the starting materials **138** for the carbocyclisation reactions (Table 1).

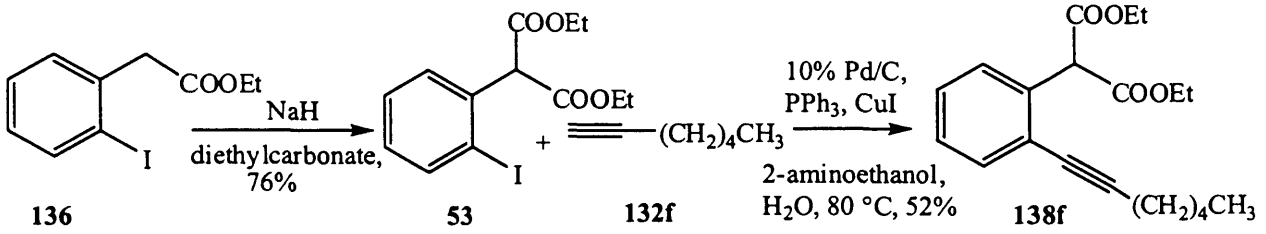
Table 1 Synthesis of 2-substituted acetylene malonates **138a-e**.



Entry	R	Reaction time (h)	Coupled products	Yields (%)
1	Phenyl (**132a**)	16	**137a**	76
2	3-Methoxyphenyl (**132b**)	14	**137b**	60
3	2-Naphthyl(**132c**)	13	**137c**	64
4	Benzyloxymethyl (**132d**)	16	**137d**	42
5	2-Phenylbenzyloxymethyl(**132e**)	24	**137e**	48

The above mentioned Sonogashira cross coupling reaction conditions gave good yields with terminal acetylene bearing aromatic substituents (entries 1, 2 & 3, Table 1). The reaction gave poor yields with slow reacting terminal acetylenes having propargylic ethers and aliphatic moieties (entry 4 & 5 Table 1 & Scheme 27). Alternatively, the condensation of ethyl (2-iodophenyl) acetate **136** with diethylcarbonate in the presence of base led to the formation of compound **53** in excellent yield. Compound **53** was subjected to a Sonogashira cross coupling reaction with slow reacting 1-heptyne (**132f**) to give acceptable yield of substrate **138f** bearing an aliphatic moiety (Scheme 27). This was due to the dimerization of

slow reaction terminal acetylenes as a significant side reaction. The overall process for synthesis of precursor molecules displays generality as well as good functional group tolerance (Table 1 and Scheme 27).

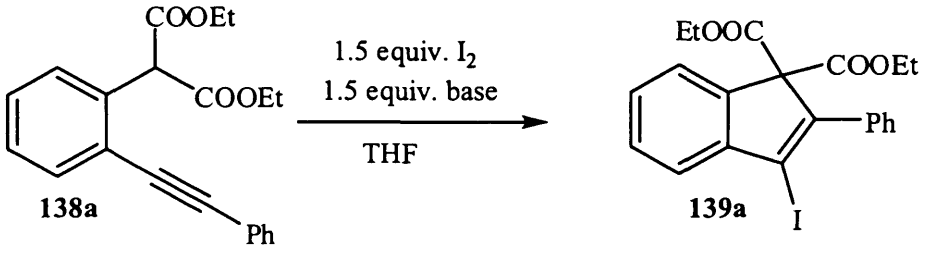


Scheme 27. Synthesis of substrate **138f** with aliphatic moiety.

2.5.3 Optimisation of iodocarbocyclisation conditions

To test the feasibility of this possible iodine mediated carbocyclisation of alkynyl malonate several reagent combinations and reaction conditions were screened. The precursor molecule **138a** was treated with NaH before iodine was added, and the reaction mixture was refluxed for 2 h (entry 1, Table 2). Pleasingly, the desired cyclised product **139a** was obtained as a crystalline solid in 77% yield after the purification by column chromatography (entry 1, Table 2). The structure of desired iodocyclised product **139a** was confirmed by ^{1}H and ^{13}C NMR spectra and additionally through single crystal X-ray analysis (Figure 1).

Table 2 Screening of reaction conditions for substrate **138a**.



Entry	Base	Time (h)	Temperature (°C)	Yields (%)
1	NaH	2	65	77[a]
2	Pyridine	2	65	0
3	*t*-BuONa	2	65	74
4	*t*-BuONa	80	20	69

(a) 1.2 equiv. of base and iodine was used.

The reaction of compound **138a** with iodine in the presence of organic base like pyridine led to complete recovery of the starting material after a couple of hours reflux in THF (entry 2,

Table 2). This observation suggested that the metal counter ion was necessary to stabilise the enolate.

The combination of NaO*t*-Bu and iodine was known to generate *tert.*-butyl hypoiodite [30]. The treatment of substrate **138a** with NaO*t*-Bu/I_2 in THF and heated to reflux for couple of hours resulted in 74% yield of cyclised product **139a** after purification (Table 2, entry 3).

Under the similar reaction conditions involving the use of NaO*t*-Bu and iodine combination, cyclised product **139a** was obtained in slightly lower yield after several hours of stirring at room temperature (Table 2, entry 4). All the reaction conditions except those shown in entry 2 were almost equally effective for carbocyclisation, resulted in clean conversion toward the cyclised products.

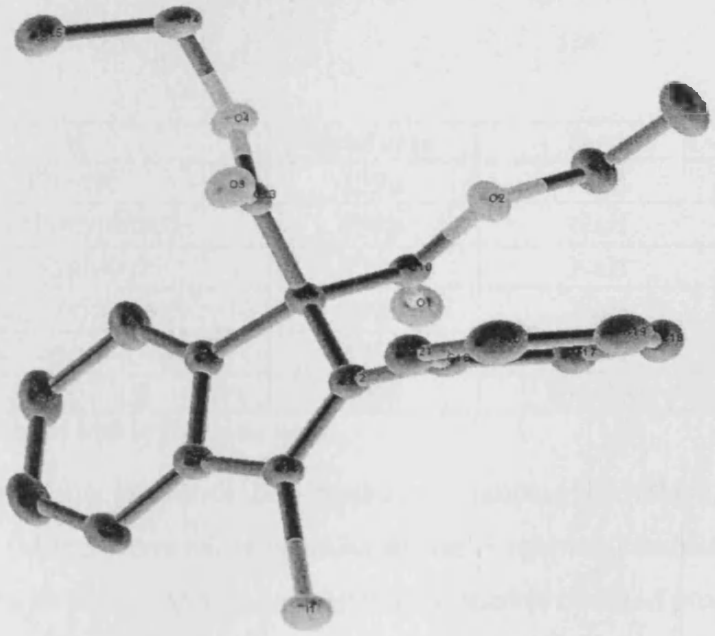


Figure 1. Single crystal X-ray structure of compound **139a**.

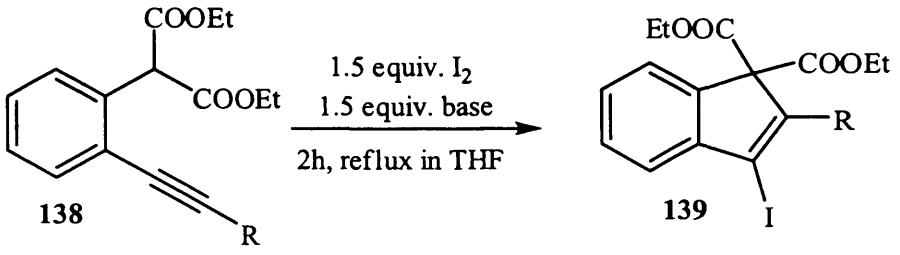
2.5.4 Scope of iodocarbocyclisations

The next objective was to investigate the scope of the carbocyclisation reactions. Therefore, various substituted terminal acetylenes were employed by using appropriate synthetic sequences to form the 2-substituted alkynyl malonate. A variety 2-substituted alkynyl malonate bearing aromatic, aliphatic and propargylic functionality **138a-f** were successfully

transformed to the cyclised products under optimized conditions in very good yields as shown in Table 3.

The aryl moieties bearing different electronic groups exhibit different reactivity. When R was an electron donating group like 3-methoxyphenyl, the yield of cyclised product **139b** was slightly improved (entry 2, Table 3). Furthermore, simple phenyl and 2-naphthyl moieties exhibited lower yields of carbocycles **139a** & **139c** respectively (entry 1 and 3, Table 3).

Table 3. Formation of 3-iodo-1*H*-indene derivatives **139**.



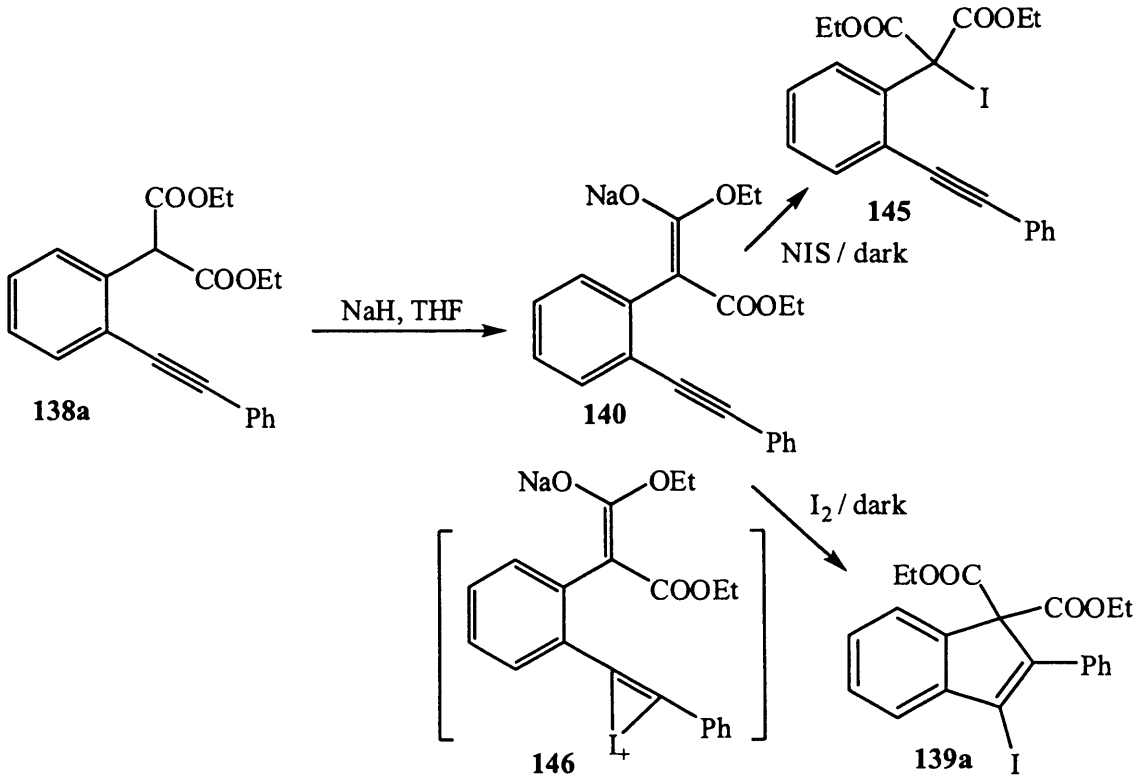
Entry	R	Products	Base	Yields (%)
1[a]	Phenyl-	**139a**	NaH	77
2	3-Methoxyphenyl-	**139b**	NaH	78
3	2-Naphthyl	**139c**	NaH	71
4	Benzyloxymethyl-	**139d**	NaH	67
5	2-Phenylbenzyloxymethyl-	**139e**	NaH	62
6	$-(CH_2)_4CH_3$	**139f**	*t*BuONa	71

(a) 1.2 equiv. of base and iodine was used.

The sensitive organic functionalities like methoxy, propargylic ethers, and ester group (entries 2, 4, and 5, Table 3) were tolerated under the mild reaction conditions. Substrate **138f** bearing an aliphatic side chain was successfully transformed to cyclised product **139f** by using NaO*t*Bu and iodine at room temperature stirring in THF (entry 6, Table 4). Surprisingly, the aliphatic substituent was equally effective to give good yield of cyclised product **139f** as aromatic 2-naphthyl moiety (entry 6, entry 3 & Table 3). Among the various substituents, 3-methoxyphenyl moiety gave the desired cyclised product **139b** in the best yield (entry 2, Table 3).

2.5.5 Reaction Mechanism

The mechanism of these cyclisations was not clear in every detail, however literature evidence [31] and the course of the reaction revealed that first step was an addition of iodine to the deprotonated malonate **140** and might resulted in the formation of α-iodomalonate **145** [32].

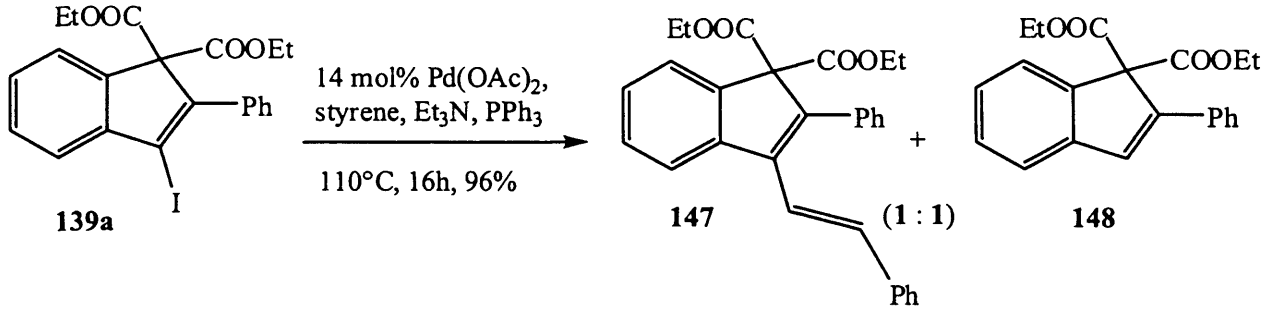


Scheme 28. Mechanistic consideration.

This quite unstable compound has also been identified, but only as a mixture together with starting material **138a**. In the presence of iodide (NaI) or by reaction with elemental iodine the formation of the cyclised product **139a** via intermediate **146** was the most likely route of the reaction (Scheme 28). This mechanism may however not be the only one operating; a free radical mechanism was also possible [32b]. Therefore, ionic as well as free radical mechanisms can be envisioned for such iodocarbocyclisation reactions.

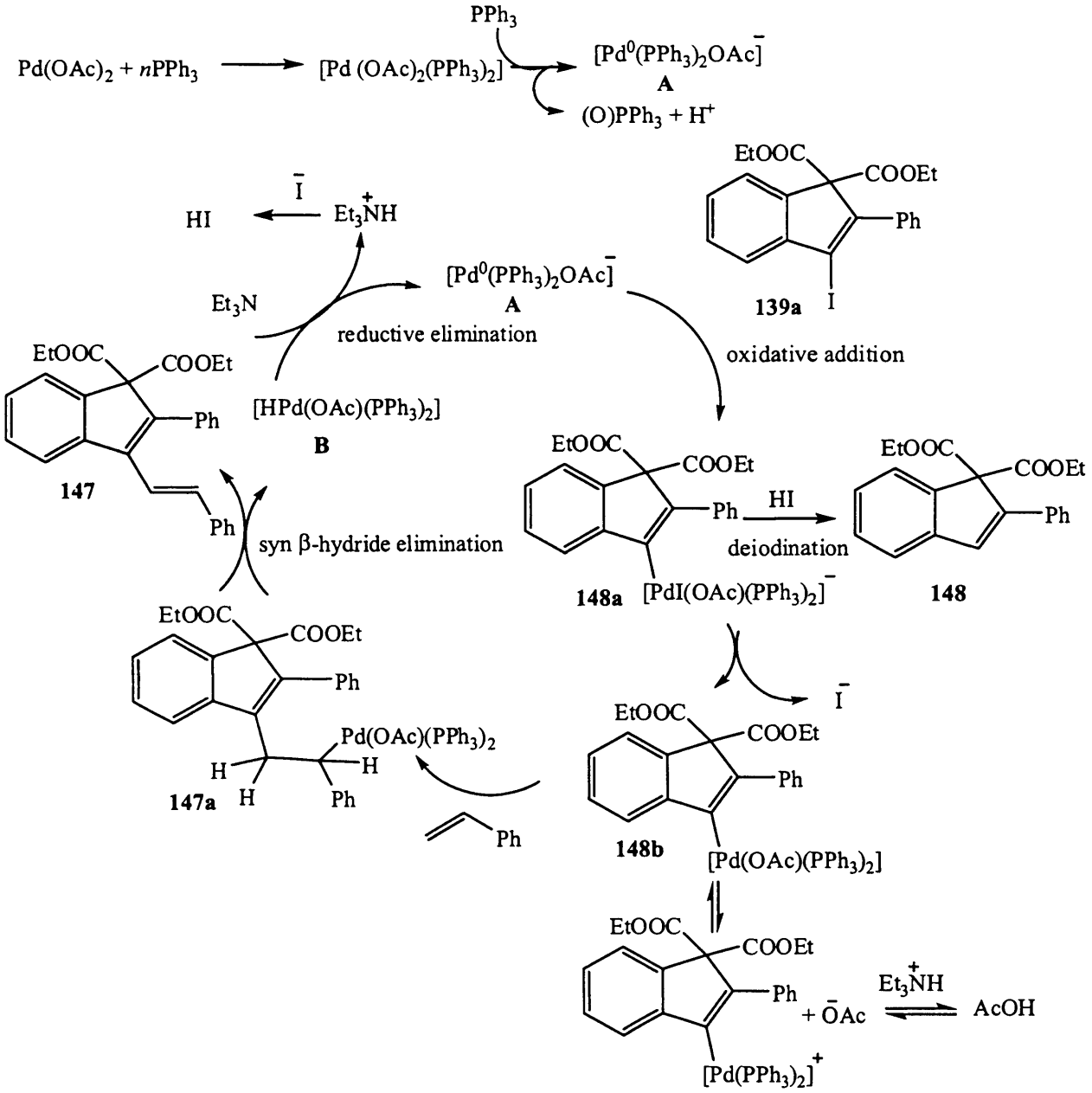
2.5.6 The Mizoroki-Heck reaction of 3-iodo-1*H*-indene 139a

In order to exploit the potential of C-I bond and rapid generation of molecular complexity and diversity, compound **139a** was subjected to the Mizoroki-Heck reaction [33] conditions. This has resulted in the formation of a mixture of two compounds **147** and **148**, which could not be separated through column chromatography (Scheme 29). The compound **147** was identified as the Heck reaction cross coupled product from ^{1}H NMR spectroscopic observation of the mixture. The compound **148** was the deiodinated product and its spectroscopic data matched with the similar compound reported by Larock *et al* [9]. The mixture was analysed by GC-MS and ^{1}H NMR spectrum, and a ratio of 1:1 (**147**:**148**) was established. After the oxidative insertion of the palladium species in the carbon-halogen bond, the carbon was made more nucleophilic and may have accepted a proton from HI generated *in situ* during the formation of the Heck cross coupled product.



Scheme 29. The Mizoroki-Heck reaction of 3-iodo-1*H*-indene derivative **139a**.

A plausible mechanism for this conversion is given in Scheme 30. The mechanism of the Mizoroki-Heck reaction is not fully understood and the exact mechanistic pathway appeared to vary with changing reaction condition [34]. Scheme 30 showed a sequence of events beginning with generation of the active Pd (0) catalyst. The rate determining step is oxidative addition of Pd(0) into C-I bond. The earlier studies by the Amatore and Jutand have shown that the ligands on the palladium precatalyst can influence the mechanism of the Heck reaction whereas acetate anion derived from $Pd(OAc)_2$ and phosphine ligands initiates a catalytic cycle involving anionic Pd(0) and Pd(II) intermediates as shown in Scheme 30. The Pd(0) catalyst generated *in situ* from $Pd(OAc)_2$ and PPh_3 was an anionic species **A**. The oxidative addition of Pd(0) catalyst **A** to compound **139a** gave penta co-ordinated complex **148a**, in which both acetate and iodide anion remain co-ordinated to the Pd(II) centre (Scheme 30).

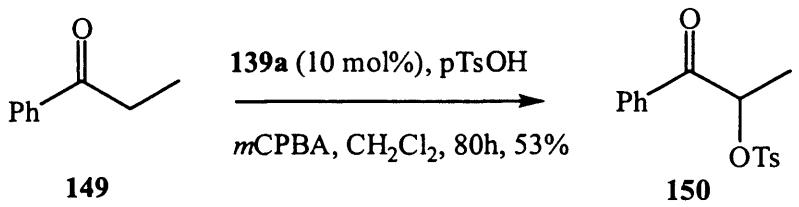


Scheme 30. The catalytic cycle for the Mizoroki-Heck reaction of compound **139a**.

This short lived intermediate loses the iodide ion to yield a new Pd(II) complex, *trans*-**148b**. The increased reactivity of complex **148b** compared to that of **148a** has been attributed to bidentate nature of acetate ligand, which may assist to open co-ordination site for alkene. Migratory insertion provides the σ-alkylpalladium complex **147a** which undergo β-hydride elimination to yield alkene product **147** and hydridopalladium complex **B** (Scheme 30). The deprotonation of hydridopalladium complex **B** by a base such as Et_3N yielded Pd(0) species **A** [34].

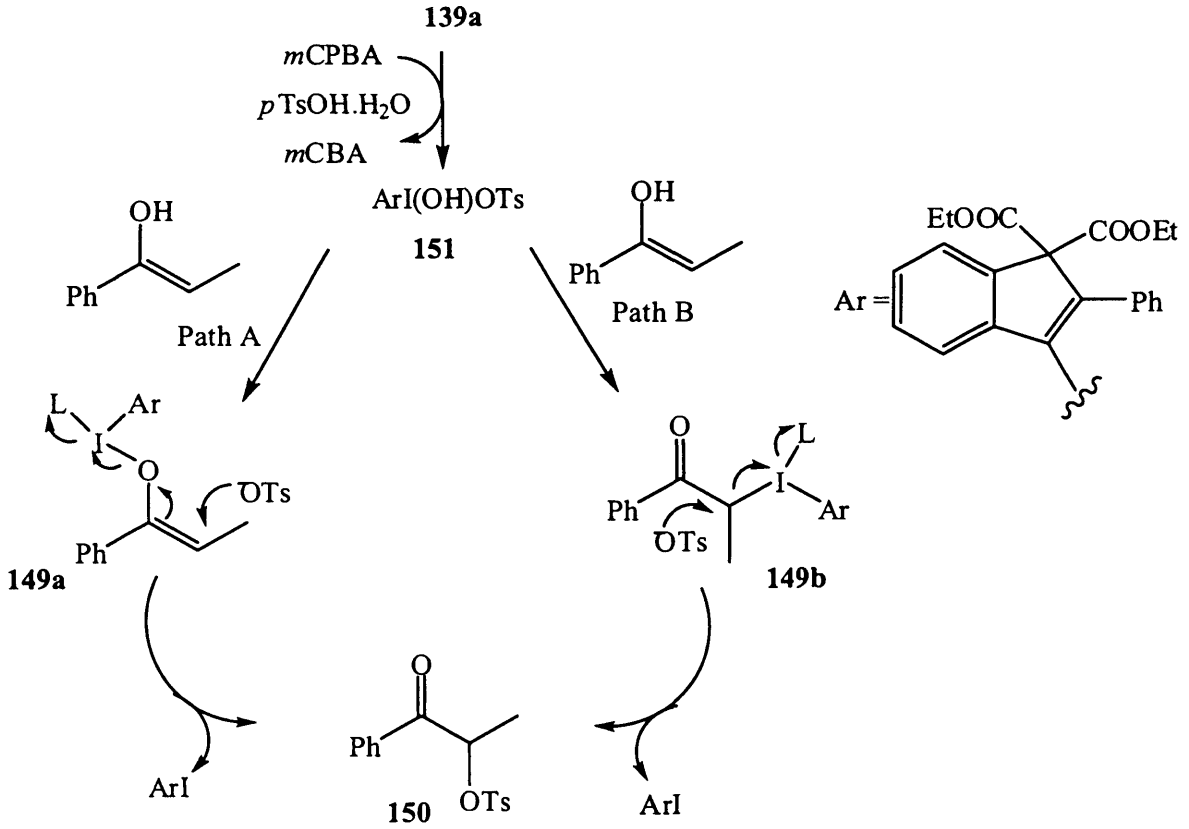
2.5.7 α-Oxytosylation of propiophenone

The iodine compounds can be used as catalysts for the *in situ* generation of hypervalent iodine compounds [35]. The α-oxytosylation of propiophenone **149** can be performed by using catalytic amount of **139a** leading to the product **150** in 53% yield (Scheme 31).



Scheme 31. α-Oxytosylation of propiophenone **149** catalyzed by 3-iodo-1*H*-indene **139a**.

The precise mechanism for the α-oxytosylation of carbonyl compounds is not fully clear. Generally, two possible routes of mechanisms were taken into account as most likely mechanistic pathways and discussed here in detail (Scheme 32).



Scheme 32. The possible mechanisms for the α-oxytosylation of propiophenone by **139a** as catalyst.

The enol tautomer of propiophenone reacts with the Koser-type iodane **151** generated *in situ* from the iodoarene (path **A**) and a subsequent S_N2 type attack of the tosylate to **149a** replaces the iodine moiety. The facile reduction of λ^3-iodane to an iodine(I) compound in the reductive elimination step could be the driving force for this reaction [36, 37].

Another mechanistic possibility was that the hypervalent iodine atom to be attacked by the double bond electrons of the enol tautomer to form **149b** with subsequent S_N2-type replacement by the tosylate (path **B**) [38]. The terminal alkynes bearing enantiomerically pure substituents could be synthesised and incorporated to previously mentioned synthetic sequences to form enantioenriched 2-substitiuted 3-iodo-1*H*-indenes [35] catalyst to perform enantioselective α-oxytosylation of ketones.

2.6 Summary

In this study, a facile synthesis of 3-iodo-1*H*-indene derivatives from easily accessible starting materials was established. The reaction proceeds under mild conditions and can tolerate significant organic functionalities, and generally gave acceptable to good yields. A range of terminal acetylenes bearing aromatic, aliphatic and propargylic moieties can be employed to boost the scope of reaction. The mechanism of these cyclisations involved the initial formation of α-iodomalonate by attack of the malonate anion on the electophile, in the presence of an iodide anion and activation of the the triple bond by iodine electrophile leading to the desired cyclised products. There was an ambiguity lies in the literature about mechanism of these cyclisations and obviously was a subject of debate.

Within this study, we were able to show that the 3-iodo-1*H*-indene can be used as a synthetic platform not only for the palladium chemistry but also as a catalyst for the *in situ* generation of λ^3-hypervalent iodine reagents. In spite of the merits of previously reported methodologies for indene system, due to operational simplicity as well as easy isolation and purification procedure for the products, this methodology becomes even more attractive. This approach to the 3-iodo-1*H*-indene system was a versatile and prototypical methodology possessing usable functionalities for the diversification. These carbocycles were of interest in organic synthesis, medicinal chemistry, and material sciences. The present results demonstrated the potential for making enantiopure 3-iodo-1*H*-indenes to perform enantioselective α-oxytosylation of ketones [39].

2.7 References

[1] Clegg, N. J.; Paruthiyil, S.; Leitman, D. C.; Scanlan, T. S. *J. Med. Chem.* **2005**, *48*, 5989.

[2] Palm, J.; Boegesoe, K. P.; Liljefors, T. *J. Med. Chem.* **1993**, *36*, 2878.

[3] Huang, H.-C.; Chamberlain, T. S.; Seibert, K.; Koboldt, C. M.; Isakson, P. C.; Reitz, D. B. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2377.

[4] Dillard, R. D.; Hagishita, Sanji; Ohtani, Mitsuaki. PCT Int. Appl. 9603120, *Chem. Abstr.* **1996**, *125*, 341826.

[5] Kikuchi, T.; Tottori, K.; Uwahodo, Y.; Tanaka, H.; Ichikawa, H.; Ono, Y.; Nakai, S. PCT Int. Appl. 9621449, *Chem. Abstr.* **1996**, *125*, 554895.

[6] Alcalde, E.; Mesquida, N.; Lopez-Perez, S.; Frigola, J.; Merce, R. *J. Med. Chem.* **2009**, *52*, 675.

[7] Alt, H. G.; Koeppl, A. *Chem. Rev.* **2000**, *100*, 1205.

[8] Zhang, D.; Yum, E. K.; Liu, Z.; Larock, R. C. *Org. Lett.* **2005**, *7*, 4963.

[9] Zhang D.; Liu Z.; Yum E. K.; Larock R. C. *J. Org. Chem.* **2007**, *72*, 251.

[10] Bi, H.-P.; Guo, L.-N.; Duan, X.-H.; Gou, F.-R.; Huang, S.-H.; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2007**, *9*, 397.

[11] Zhou, X.; Zhang, H.; Xie, X.; Li, Y. *J. Org. Chem.* **2008**, *73*, 3958.

[12] Zhu, X.; Mitsui, C.; Tsuji, H.; Nakamura, E. *J. Am. Chem. Soc.* **2009**, *131*, 13596.

[13] Nakamura, I.; Kamada, M.; Yamamoto, Y. *Tetrahedron Lett.* **2004**, *45*, 2903.

[14] Yang, M.; Zhang, X.; Lu, X. *Org. Lett.* **2007**, *9*, 5131.

[15] Guan, Z.-H.; Ren, Z.-H.; Zhao, L.-B.; Liang, Y.-M. *Org. Biomol. Chem.* **2008**, *6*, 1040.

[16] Xi, Z.; Guo, R.; Mito, S.; Yan, H.; Kanno, K.-I.; Nakajima, K.; Takahashi, T. *J. Org. Chem.* **2003**, *68*, 1252.

[17] Deng, R.; Sun, L.; Li, Z. *Org. Lett.* **2007**, *9*, 5207.

[18] Barluenga, J.; Palomas, D.; Rubio, E.; Gonzalez, J. M. *Org. Lett.* **2007**, *9*, 2823.

[19] Barluenga, J.; Trincado, M.; Rubio, Eduardo; Gonzalez, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2406.

[20] Yue D.; Yao T.; Larock R. C. *J. Org. Chem.* **2005**, *70*, 10292.

[21] (a) Bew, S. P.; El-Taeb, G. M. M.; Jones, S.; Knight, D. W.; Tan, W.-F. *Eur. J. Org. Chem.* **2007**, 5759. (b) Foot, O. F.; Knight, D. W.; Low, A. C. L.; Li, Y.-F. *Tetrahedron Lett.* **2007**, *48*, 647.

[22] Yin, L.; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133.

[23] Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

[24] Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427.

[25] Richardson, R. D.; Page, T. K.; Altermann, S.; Paradine, S. M.; French, A. N.; Wirth, T. *Synlett* **2007**, 538.

[26] Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769.

[27] Trost, B. M.; Xie, J. *J. Am. Chem. Soc.* **2006**, *128*, 6044.

[28] (a) Sonogashira, K. In Metal-Catalyzed Cross-Coupling Reactions; Diederich, F.; Stang, P. J.; Eds.; Wiley-VCH: New York, **1998**; Chapter 5. (b) Sonogashira, K. In Comprehensive Organic Synthesis; Trost B. M.; Ed.; Pergamon: New York, **1991**; Vol. 3, Chapter 2.4.

[29] Batchu, V. R.; Subramanian, V.; Parasuraman, K.; Swamy, N. K.; Kumar, S.; Pal, M. *Tetrahedron* **2005**, *61*, 9869.

[30] (a) Montoro, R.; Wirth, T. *Org. Lett.* **2003**, *5*, 4729. (b) Montoro, R.; Wirth, T. *Synthesis* **2005**, 1473. (c) Minakata, S.; Morino, Y.; Ide, T.; Oderaotoshi, Y.; Komatsu, M. *Chem. Commun.* **2007**, 3279.

[31] Beckwith, A. L. J.; Tozer, M. J. *Tetrahedron Lett.* **1992**, *33*, 4975.

[32] (a) Curran, D. P.; Chen, M. H.; Spletzer, E.; Seong, C. M.; Chang, C. T. *J. Am. Chem. Soc.* **1989**, *111*, 8872. (b) Curran, D. P.; Chang, C. T. *J. Org. Chem.* **1989**, *54*, 3140.

[33] Dieck, H. A.; Heck, R. F. *J. Am. Chem. Soc.***1974**, *96*, 1133.

[34] Amatore, C.; Jutand, A. *Acc. Chem. Res.***2000**, *33*, 314.

[35] (a) Richardson, R. D.; Wirth, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4402. (b) Farooq, U.; Schäfer, S.; Shah, A. A.; Freudendahl, D. M.; Wirth, T. *Synthesis* **2010**, 1023.
(c) Altermann, S. M.; Richardson, R. D.; Page, T. K.; Schmidt, R. K.; Holland, E.; Mohammed, U.; Paradine, S. M.; French, A. N.; Richter, C.; Bahar, A. M.; Witulski, B.; Wirth, T. *Eur. J. Org. Chem.* **2008**, 5315.

[36] Ochiai, M.; Takeuchi, Y.; Katayama, T.; Sueda, T.; Miyamoto, K. *J. Am. Chem. Soc.* **2005**, *127*, 12244.

[37] Ochiai; M. In *Chemistry of Hypervalent Compounds* (Ed.: K.-y. Akiba), Wiley-VCH: New York, **1999**.

[38] Moriarty, R.; Prakash, O.; Duncan, M. P. *J. Chem. Soc., Perkin Trans. 1* **1987**, 559.

[39] Khan, Z. A.; Wirth, T. *Org. Lett.* **2009**, *11*, 229.

Chapter 3

Syntheses of Indanes and Tetrahydronaphthalenes

The biological importance of indane and tetrahydronaphthalene compounds is highlighted in the third chapter. A literature overview for the syntheses of indane and tetrahydronaphthalene derivatives along with key mechanistic aspects of some classical approaches is discussed. Herein the cyclisation cascades involving C–C bond formations followed by lactonization reactions to provide fast access to structurally complex tricyclic indane and tetrahydronaphthalene derivatives in one-pot by utilizing stilbene malonate derivatives as precursor molecules is described.

3.1 Applications of indanes and tetrahydronaphthalenes

Fused carbocyclic compounds containing an aromatic moiety such as tetrahydronaphthalenes and indanes are important building blocks of biologically active natural products and compounds exhibiting pharmacological properties [1].

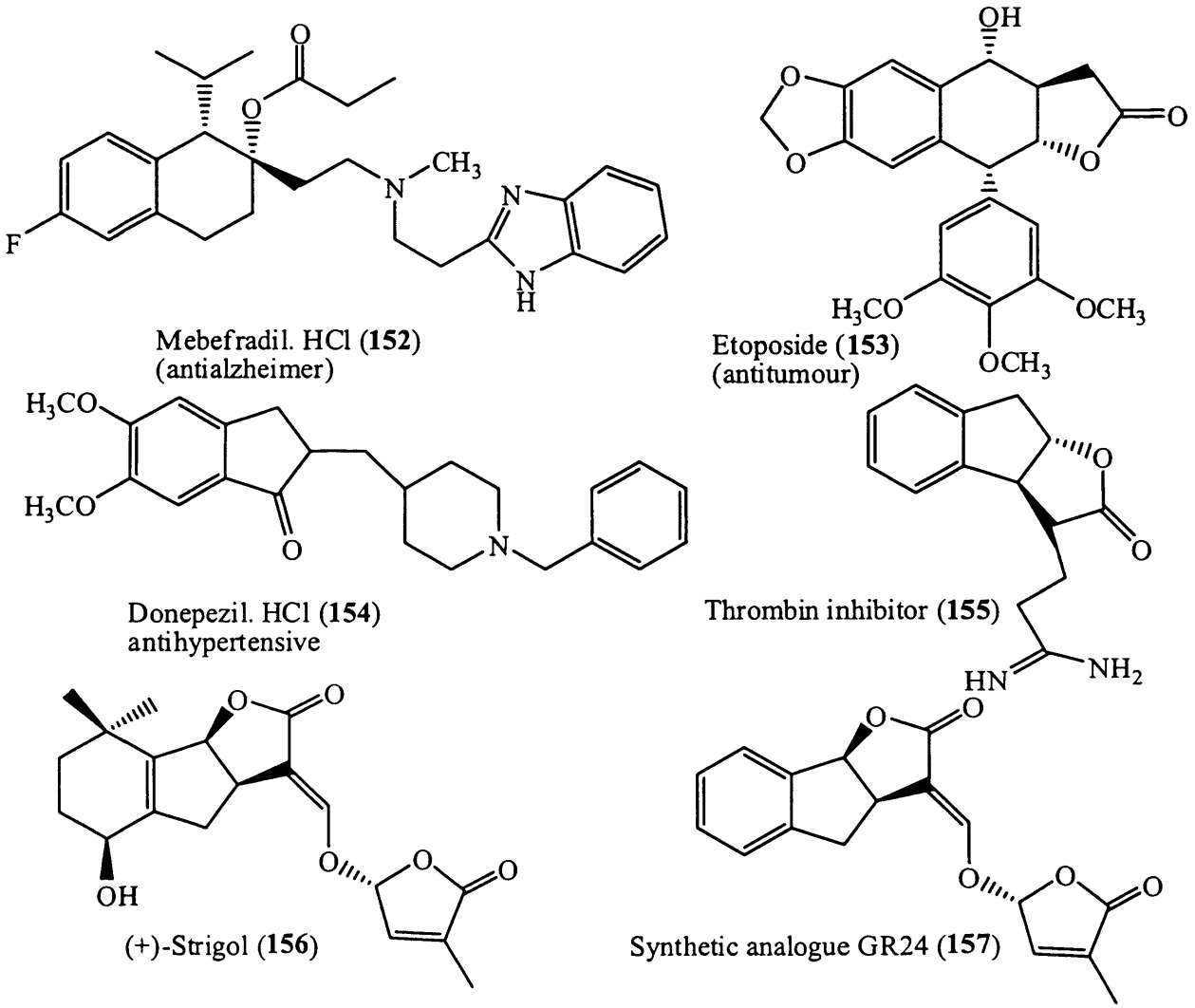


Figure 1. Biologically important indanes and tetrahydronaphthalenes.

Often they contain one or more carbon or heteroatom substituents on the aromatic segment, thereby introducing elements of stereochemistry and functional diversity. Figure 1 showed the structures of a select group of biologically and medically relevant molecules that harbour indane and tetrahydronaphthalene motifs [1]. Etoposide derivatives such as compound **153** of the aryltetralin lignan lactone podophyllotoxin are clinically important anti-cancer agents. The structure of podophyllotoxin included four contiguous chiral centres contained within a stereochemically unstable *trans*-fused tetrahydronaphthalene lactone skeleton. Reflecting this challenging structure and important biological role there has been long-standing interest in developing efficient stereocontrolled synthesis of this class of natural products [2]. Strigolactones were a group of sesquiterpene lactones and their synthetic analogues could act as hormone stimulants for seed-germination / symbiotic fungi and even as shoot branching inhibitors [3]. The representative chemical structures of strigolactones **156** and **157** were given in Figure 1.

Furthermore, the elevated aldosterone levels were key effectors for the development and progression of congestive heart failure and mycocardial fibrosis. Indane and tetrahydronaphthalene derivatives were found to be potent and selective inhibitiors of aldosterone synthase an enzyme responsible for elevated aldosterone levels [4]. Additionally, enantiopure tetrahydronaphthalenes could be used as chiral auxiliaries in Reformatsky-type reactions [5]. Similarly, indane derivatives have also been used as versatile ligands in asymmetric ruthenium catalysed transfer hydrogenation reaction of ketones [6].

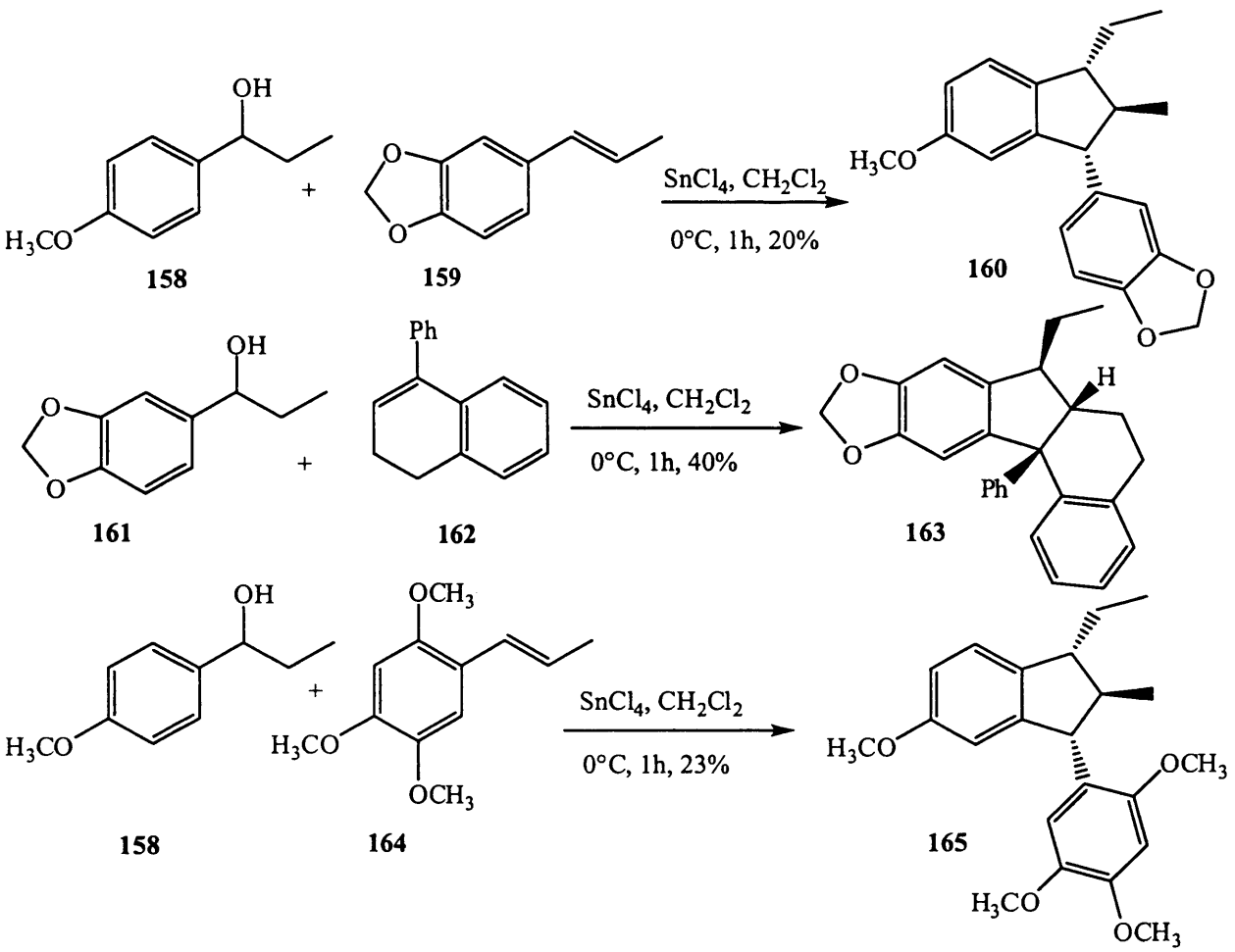
3.2 Literature overview for the synthesis of indanes and tetrahydronaphthalenes

Due to the diverse applications of these classes of compounds in chemical biology and synthetic organic chemistry a number of synthetic methodologies have been developed. Some of these classical approaches will be discussed in detail.

3.2.1. [3+2] Cycloadditions for the synthesis of 3-arylindanes

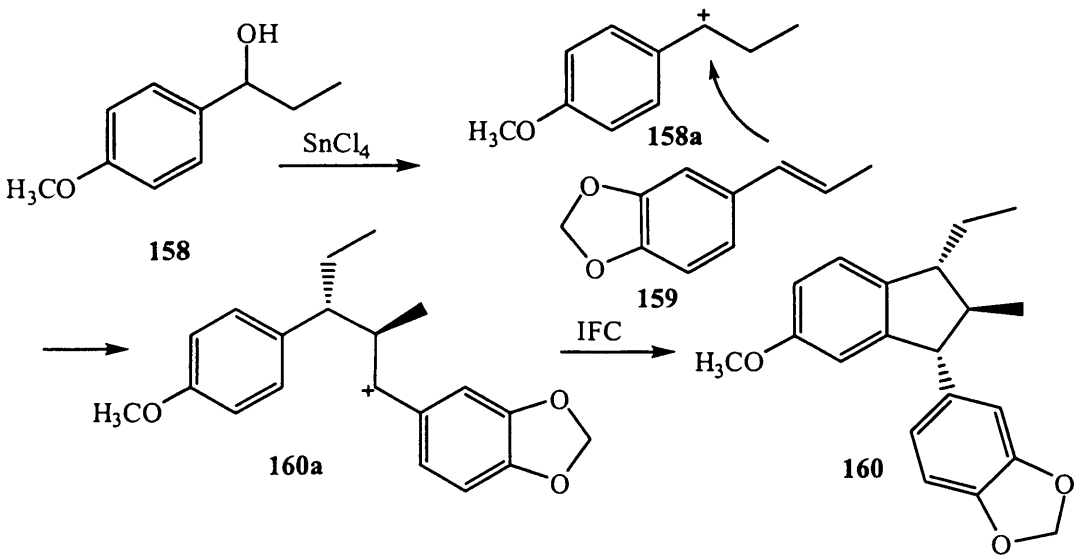
Moltrasio *et al.* reported the synthesis of several indane derivatives via a Lewis acid mediated [3+2] cycloaddition of benzylic alcohols with styrene and cyclic alkenes [7]. The reaction between alcohol **158** with styrene **159** gave a low yield (about 20%) of the adduct **160** which corresponded to a single diastereomer. The reaction of benzylic alcohol **161** with cyclic alkene such as phenyl-1,2-dihydronaphthalene **162** with $SnCl_4$ afforded pentacyclic compound **163** as a single diastereomer in 40% yield. Further, the reaction of benzylic alcohol

158 with electron rich styrene **164** resulted in formation of indane derivative **165** in 23% yield (Scheme 1) [7].



Scheme 1. Synthesis of 3-arylindanes as a single diastereomer via [3+2] cycloadditions.

A possible mechanism for the formal [3+2] cycloaddition reaction was given in Scheme 2.

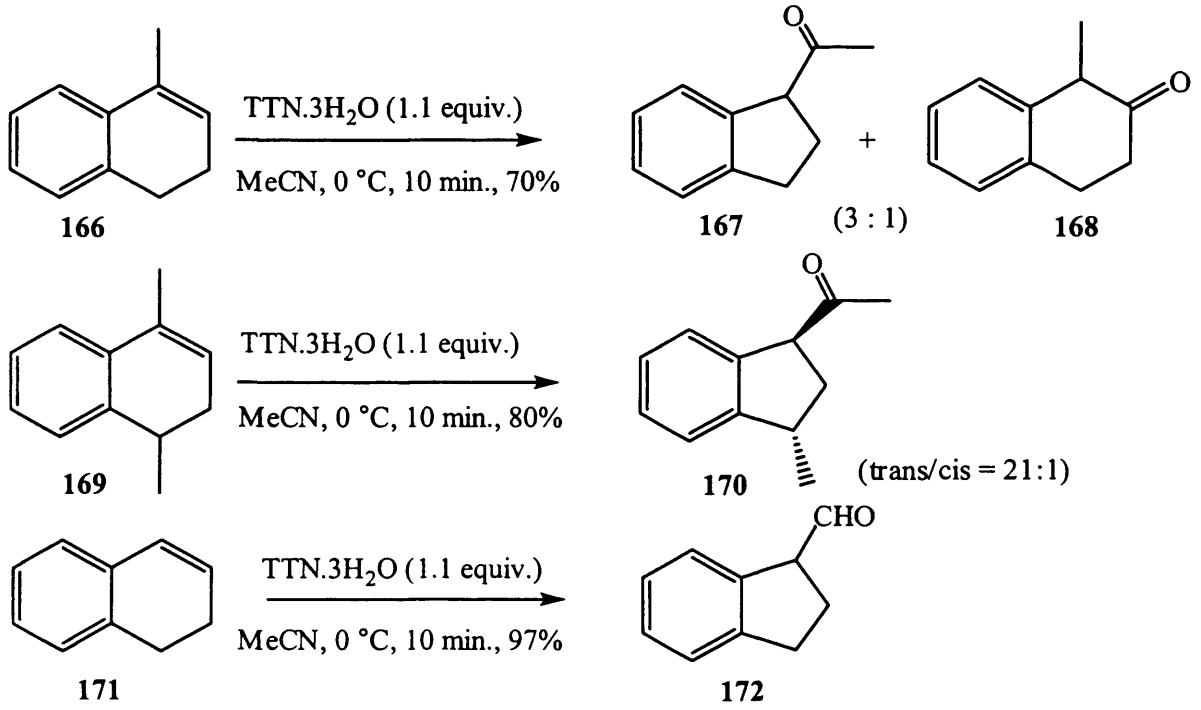


Scheme 2. Plausible mechanism for [3+2] cycloaddition reaction.

The Lewis acid activates the hydroxyl moiety of benzylic alcohol **158** which resulted in the cleavage of the carbon oxygen bond to give benzylic cation **158a** which undergoes intermolecular nucleophilic attack of styrene **159**. This would furnish another stable (due to mesomeric affect) benzylic cation **160a** which undergoes intramolecular Friedel-Crafts (IFC) reaction to give cyclic indane derivative **160** with loss of proton.

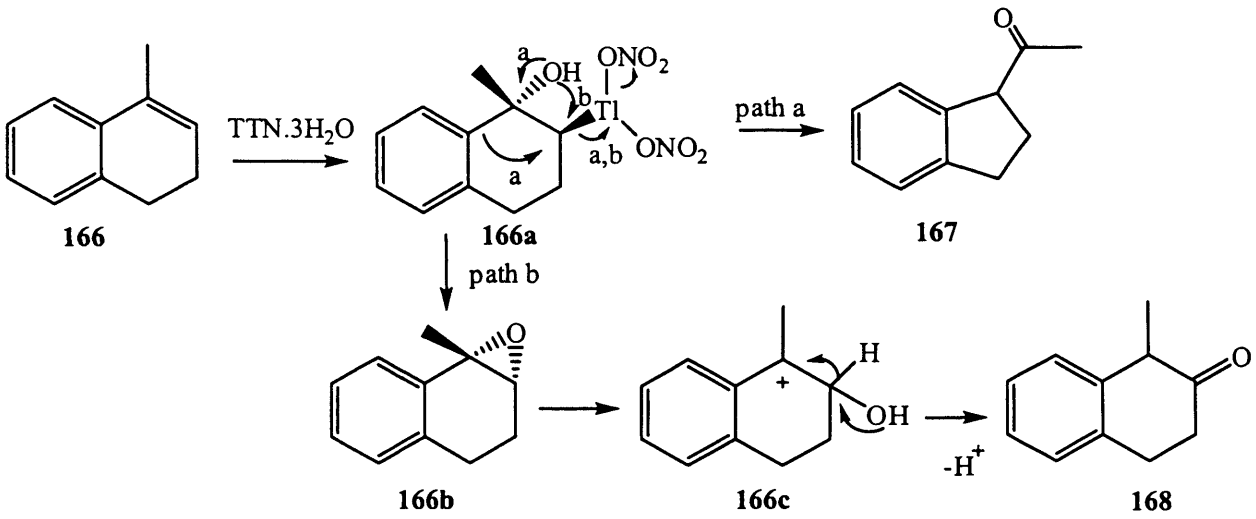
3.2.2 Synthesis of indanes via ring contraction of dihydronaphthalenes

Silva *et al.* reported the synthesis of *trans*-1,3-disubstituted indanes are conveniently accessed by a stereoselective ring contraction of 1,2-dihydronaphthalenes upon treatment with thallium(III)nitrate trihydrate ($TTN.3H_2O$) in acetonitrile [8].



Scheme 3. Ring contraction of 1, 2-dihydronaphthalene promoted by thallium(III)nitrate.

Under optimized conditions, the reaction of dihydronaphthalene **166** with thallium(III)nitrate in acetonitrile resulted in the formation of a mixture of indane **167** and tetralone **168** in 3:1 ratio respectively (Scheme 3). In the case of compound **169** under similar conditions, the only observed result was the formation of indane ring contraction product **170** in 80% yield as 21:1 (*trans*:*cis*) mixture of diastereomers. When 1,2-dihydronaphthalene **171** was treated with thallium(III) nitrate in acetonitrile indane **172** was obtained in high yield [8] (Scheme 3).

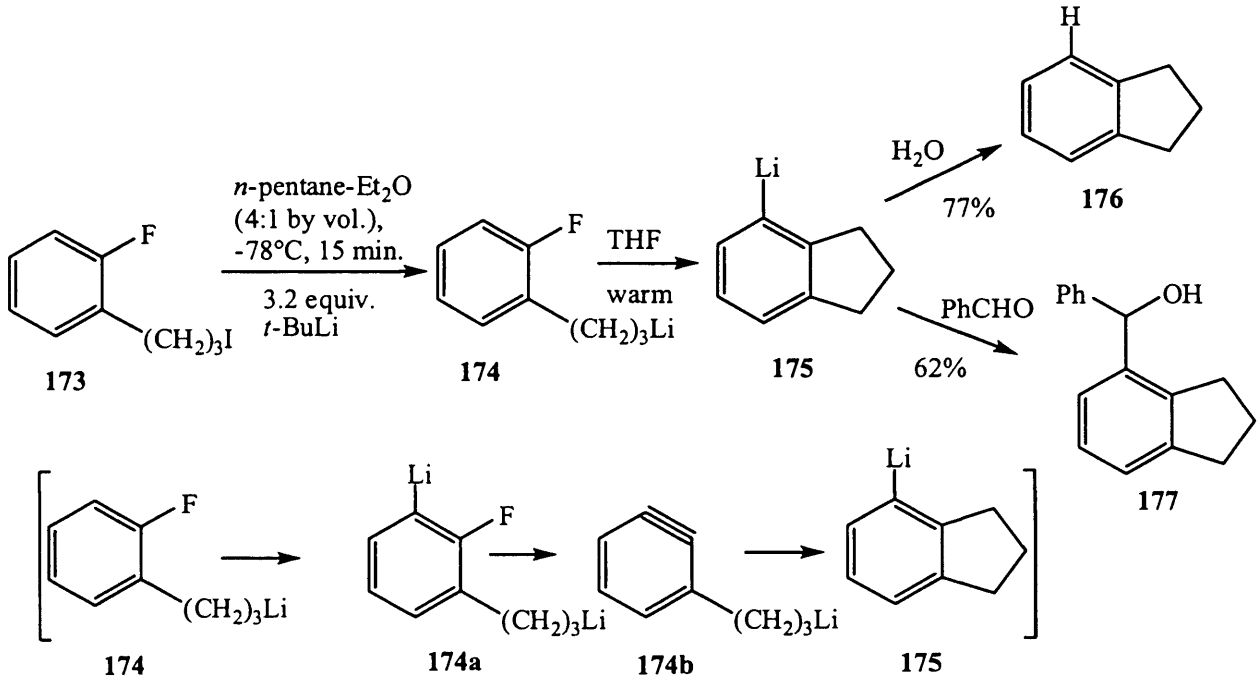


Scheme 4. Proposed mechanism for the formation of compounds **167** and **168**.

The proposed mechanistic route for the formation of compounds **167** and **168** is given in Scheme 4. Presumably, ketone **167** formed through direct rearrangement of the oxythallated adduct **166a** via path a (Scheme 4) whereas the tetralone **168** might arise from the competitive formation of the epoxide **166b** followed by ring opening to the tertiary benzylic cation **166c** and finally 1,2-hydride migration [8].

3.2.3 Synthesis of 4-substituted indanes

Bailey *et al.* demonstrated the synthesis of 4-substituted indanes as involving three discrete steps each of which finds sufficient literature guide.

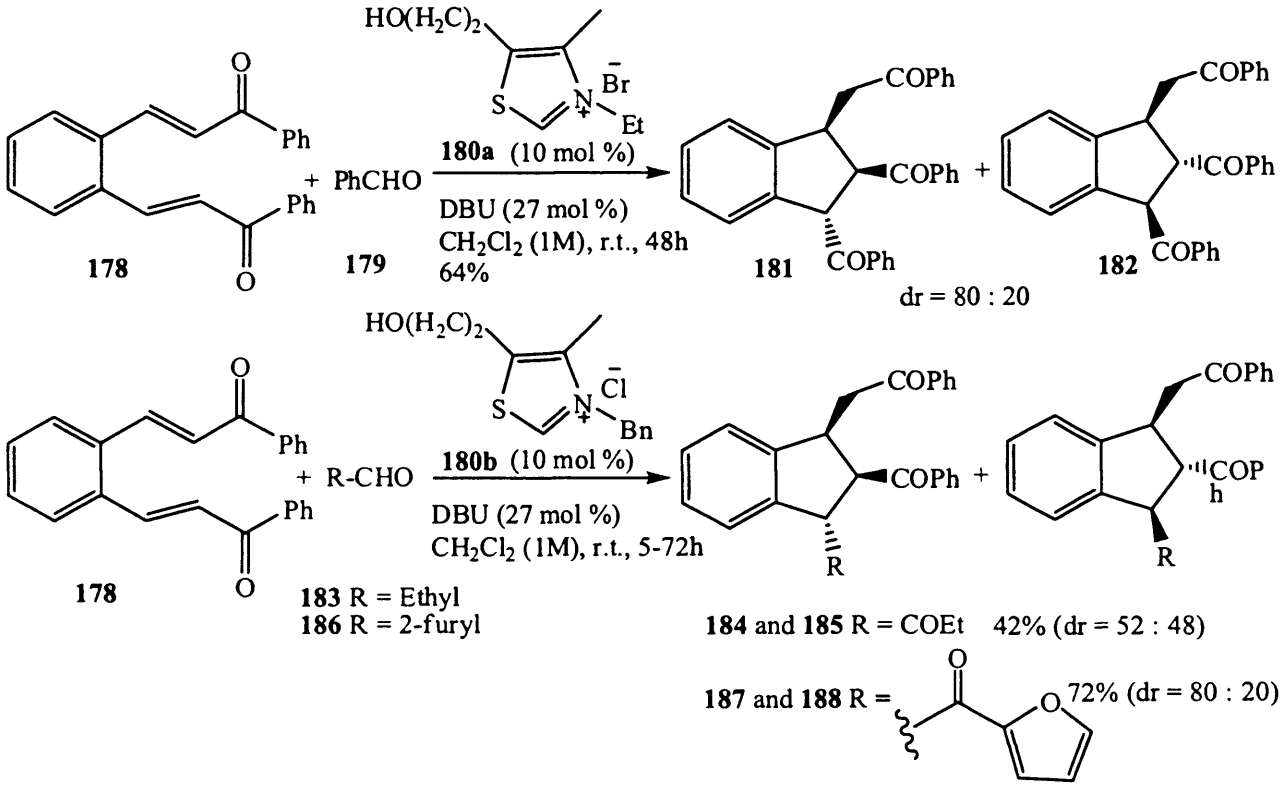


Scheme 5. Cyclisation of benzyne-tethered alkyllithium to 4-substituted indanes.

The treatment of compound **173** with *t*-BuLi resulted in lithium-iodine exchange to give the 3-(2-fluorophenyl)propyllithium **174**. The next step was the regioselective abstraction of the proton *ortho* to the fluorine substituent to generate dilithio species **174a** followed by the rapid loss of LiF to deliver the 1,2-dehydrobenzene or benzyne intermediate **174b**. The benzyne intermediate **174b** undergoes 5-*exo* cyclisation to deliver 4-indanyllithium **175**. The synthetic module **175** was quenched with various electrophiles such as water and benzaldehyde to give 4-substituted indanes **176** and **177** in good yields (Scheme 5) [9].

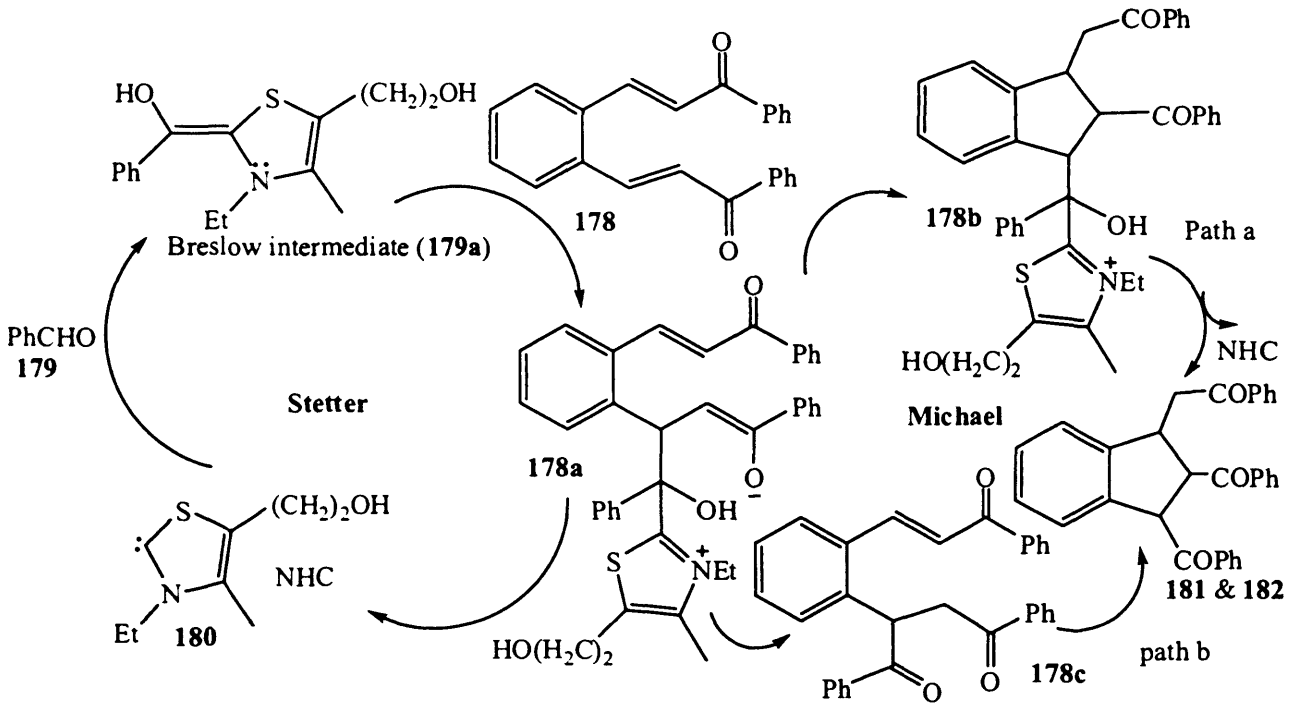
3.2.4. Diastereoselective synthesis of indanes via a domino Stetter-Michael reaction

Gravel *et al.* reported that *N*-heterocyclic carbenes (NHC) could be used to catalyse the Stetter-Michael reaction for the synthesis of highly fuctionalised indanes in good yields and diastereomeric ratios [10]. The aromatic **179**, aliphatic **183**, and heteroaromatic **186** aldehydes were successfully employed to give an acceptable to good yields of corresponding highly substituted indane products (Scheme 6).



Scheme 6. Domino Stetter-Michael reaction for the synthesis of indanes.

The proposed mechanistic route for the formation of diastereomers **181** and **182** was shown in Scheme 7.



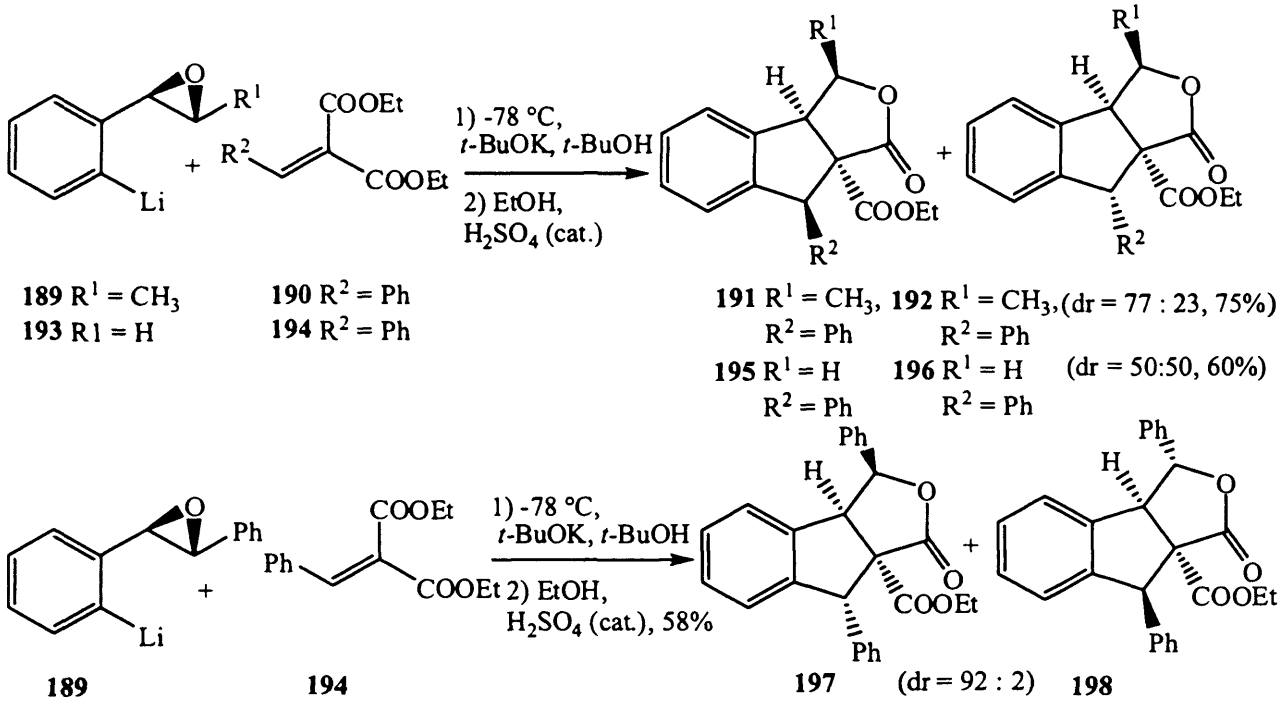
Scheme 7. Domino Stetter Michael Reaction.

The reaction of an aldehyde **179** with an NHC **180** to form a Breslow intermediate **179a**, which then attacks the Michael acceptor **178** to yield enolate intermediate **178a**. Subsequently, this intermediate can undergo two possible cyclisation pathways. In path a, the enolate **178a** would directly cyclise to desired compounds **181** & **182**. In path b, proton transfer and ejection of the catalyst would form a simple Stetter product **178c**. Under the basic reaction condition, resulting diketone **178c** could then regenerate the required enolate to afford the indanes **181** and **182** (Scheme 7).

3.2.5 Synthesis of tetrahydroindenofuranones

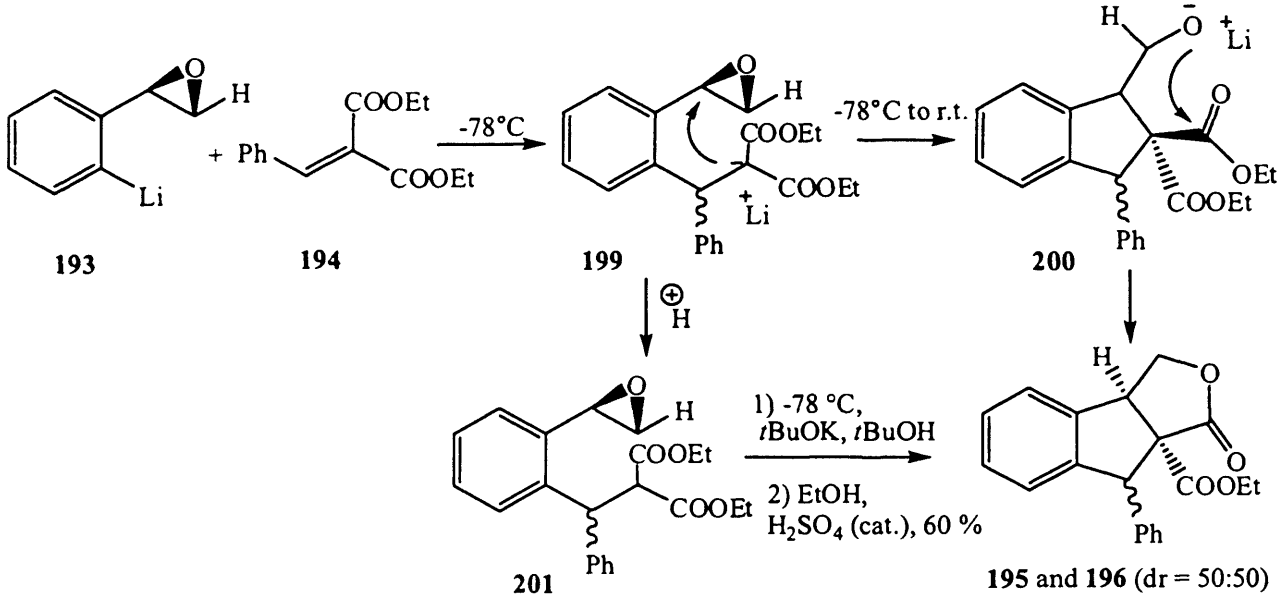
Florio *et al.* reported an efficient synthesis of tetrahydroindenofuranones based on the Michael addition of *ortho*-lithiated aryloxiranes to alkylidene malonates followed by the nucleophilic oxirane ring opening and subsequent lactonization [11]. The reaction of substrates **189** and **190** with *t*BuOK in an aprotic solvent such as THF resulted in the complete recovery of starting material. The use of EtOLi, EtONa, or *t*-BuOK in EtOH or *t*-BuOH at room temperature gave tetrahydroindenofurans as a mixture of ester and corresponding carboxylic acids because of partial hydrolysis. Therefore, it was necessary to treat the crude product mixture with EtOH/ H_2SO_4 (cat.) in order to obtain tetrahydroindenofurans **191** and **192** exclusively. They have also employed a one-pot

methodology for the synthesis of tetrahydroindenofurans after stirring for longer time (Scheme 8) [11].



Scheme 8. An efficient domino reaction for the synthesis of tetrahydroindenofuranones.

The organolithium compound **193** reacted with benzylidene malonate **194** to give an equimolar mixture of diastereomers of tetrahydroindenofuranones **195** and **196**. Similarly, the reaction of benzylidene malonate **194** under the identical reaction conditions resulted in the formation of a diastereomeric mixture of compounds **197** and **198** in 92:2 ratios. A plausible mechanistic sequence was described in Scheme 9.



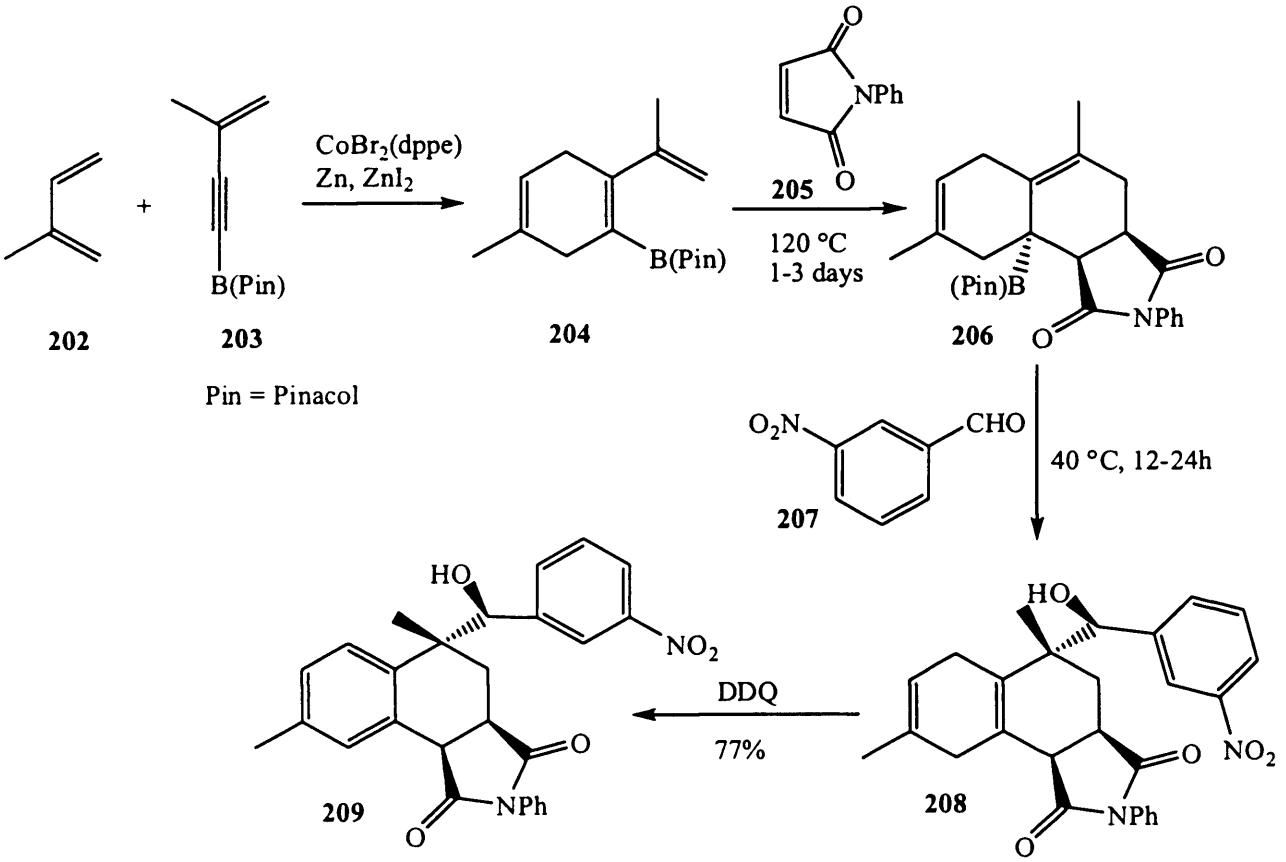
Scheme 9. The proposed route for synthesis of tetrahydroindenofuranones.

A domino reaction was started with the 1,4-addition of organolithium compound **193** to benzylidene malonate **194** to give the intermediate **198** which then cyclises on the oxirane ring via a stereospecific intramolecular S_N2 (5-*exo-tet* mode) leading to successive lactonization and furnishing tetrahydroindenofuranones **195** & **196**. Alternatively, the treatment of compound **201** with KO*t*Bu followed by esterification led to the formation of equimolar mixture of diastereomers **195** and **196**.

Common routes for the synthesis of tetrahydronaphthalenes were by reduction of 3,4-dihydronaphthalen-1(2*H*)ones [12] or by Friedel-Crafts alkylations [13] or by dehydration of alcohols [14]. Some of methodologies for the synthesis of structurally complex tetrahydronaphthalenes will be discussed in detail.

3.2.6 A multicomponent reaction cascade for the synthesis of tetrahydronaphthalenes

Hilt *et al.* reported a cobalt(I) catalysed Diels-Alder reaction of a boron enyne with diene as a key step in a two step reaction cascade interconverting four simple starting materials to obtain polycyclic multifunctionalised products in good yields and with a very high degree of diastereoselectivity [15].

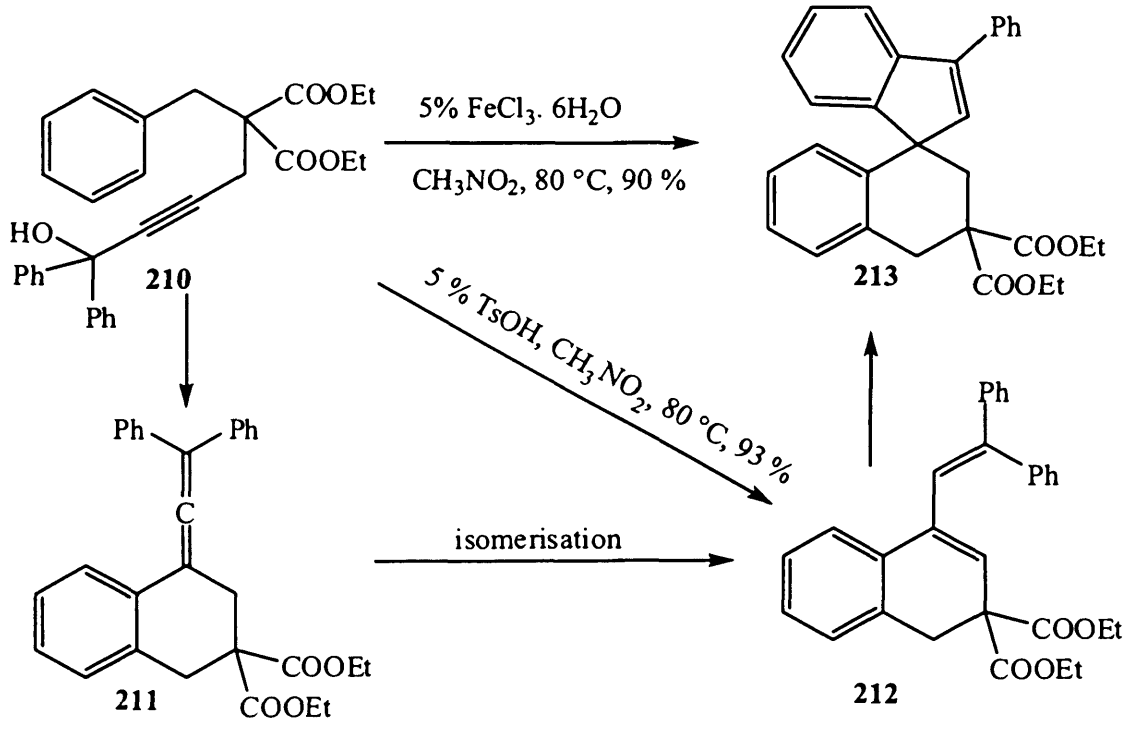


Scheme 10. A multicomponent reaction for the diversity oriented synthesis of tetrahydronaphthalenes.

The acyclic 1,3-diene **202** could be reacted with boron functionalized enyne derivative **203** under mild reaction conditions using cobalt(I) catalysed system to generate boron functionalised 1,3-diene **204**. This key intermediate was converted in a thermal Diels-Alder reaction with an activated dienophile **205** to a highly substituted boron functionalised 1,4-diene **206** containing an allyl boron subunit. Consequently, the allylboration of an aldehyde **207** led to the cyclohexadiene derivative **208** that could be oxidized with DDQ to the corresponding tetrahydronaphthalene derivative **209** [15] (Scheme 10). Various types of aromatic and aliphatic aldehydes along with activated dienophiles having electron withdrawing groups could be used to enhance the scope of the reaction [15].

3.2.7 Synthesis of tetrahydronphthalenes from aryl-substituted propargylic alcohols

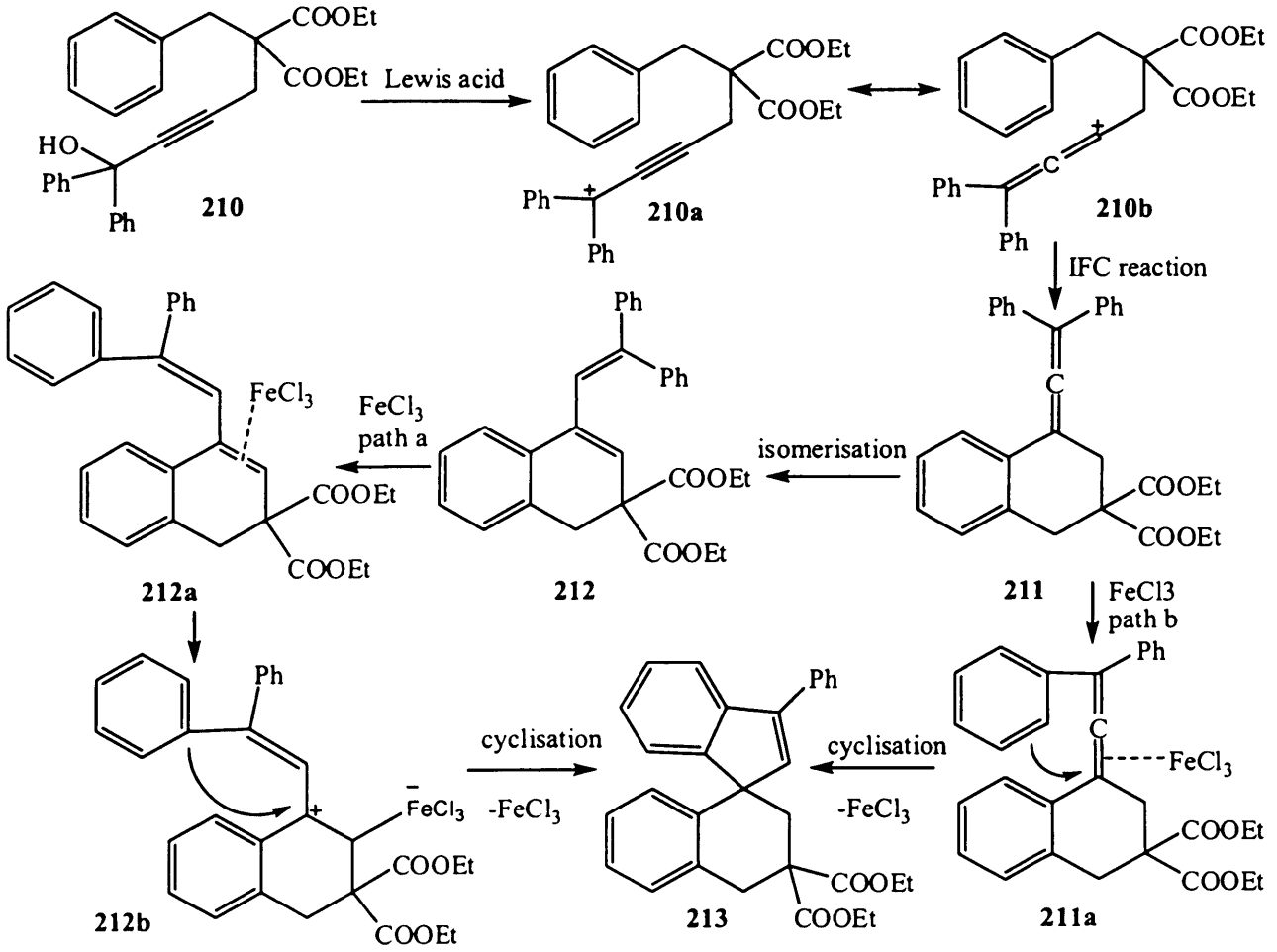
Zhou *et al.* have developed [16] a new and convenient method for the synthesis of spirocyclic tetrahydronaphthalene systems **213** from aryl-substituted propargylic alcohols **210** by $FeCl_3$ or TsOH-catalysed multiple activation of unsaturated C-C and C-H bonds. The C-OH activation by acid leads to propargylic cation which isomerizes to allenylic cation and undergoes a subsequent intramolecular Friedel-Crafts reaction (IFC) giving naphthalene derivative **211** while isomerisation of **211** gave dihydronaphthalene **212** (Scheme 11).



Scheme 11. Tandem reaction of aryl substituted propargylic alcohol catalyzed by Lewis acid/ Brønsted acid.

The endocyclic double bond of dihydronaphthalene was again activated by a Lewis acid resulting in the formation of an allyl cation followed by the attack of an arene generating spirocyclic tetrahydronaphthalene derivative **213**. Treatment of substrate **210** with TsOH in CH_3NO_2 at 80 °C afforded the corresponding 1,2-dihydronaphthalene **212** through an intramolecular Friedel-Crafts reaction (IFC) reaction followed by successive isomerisation in excellent yield (Scheme 11).

The detailed mechanistic route for the synthesis of spirocyclic tetrahydronaphthalenes was given in Scheme 12. The carbon oxygen bond of propargyl alcohol **210** was activated by the acid resulting in the formation of propargylic cation **210a**. Isomerization of propargylic cation **210a** to allenylic cation **210b** and subsequent intramolecular Friedel-Crafts reaction (IFC) gives naphthalene derivative **211**, while isomerisation of **211** gives dihydronaphthalene **212**. The formation of the allyl cation intermediate **212b** occurred by the reaction of dihydronaphthalene **212** with $FeCl_3$ via intermediate **212a**, followed by the attack of the arene to generate tetrahydronaphthalene derivative **213.**



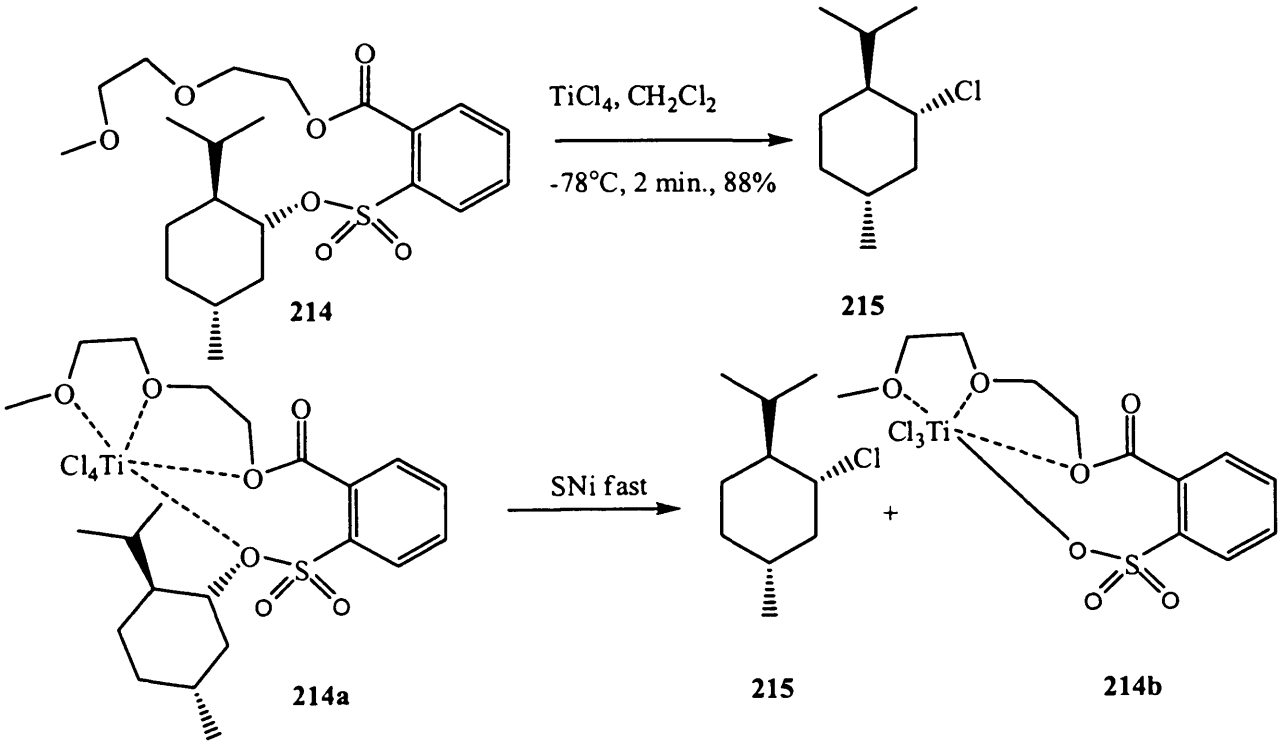
Scheme 12. Plausible mechanism for the synthesis of spirocyclic tetrahydronaphthalenes catalysed by iron(III) chloride.

Alternatively, tetrahydronaphthalene derivative **213** could be the result of direct hydroarylation reaction of the allene derivative **211** promoted by Lewis acid via intermediate **211a** (Scheme 12) [16].

3.3 Substitution reactions with retention of configuration

3.3.1 Substitution nucleophilic internal (S_Ni)

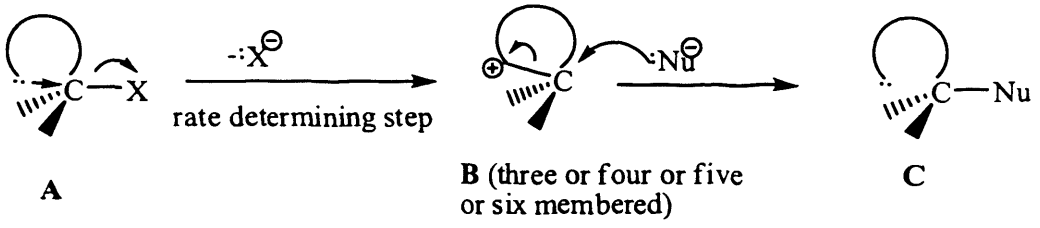
The difference between the S_N1 and S_Ni mechanisms is that the ion pair (carbocation and leaving group) is not completely dissociated and therefore, no real carbocation is formed, which would otherwise lead to racemisation. The S_Ni reaction is linked to many forms neighbouring group participation. These reactions proceed with complete retention of configuration. In 2006, Lepore and co-workers have shown that arylsulfonates of hindered alcohols could be converted to the corresponding alkyl chlorides very rapidly and in good yields in the presence of titanium tetrachloride at low temperature with exclusively retention of configuration. As shown in Scheme 13, the highly efficient leaving groups containing chelating units capable of attracting nucleophiles. The chlorination reaction likely proceeds via a front side S_Ni type mechanism. The alkyl chloride **215** formation via S_Ni type transition state **214a** stabilized by the intramolecular chelation which may account for the rapid conversion rates. The leaving group is isolated as highly stabilised salt **214b** [17].



Scheme 13. Reaction of sulfonate esters with $TiCl_4$ leading to alkyl chlorides with retention of configuration.

3.3.2 Unimolecular S_N reaction with neighbouring group participation

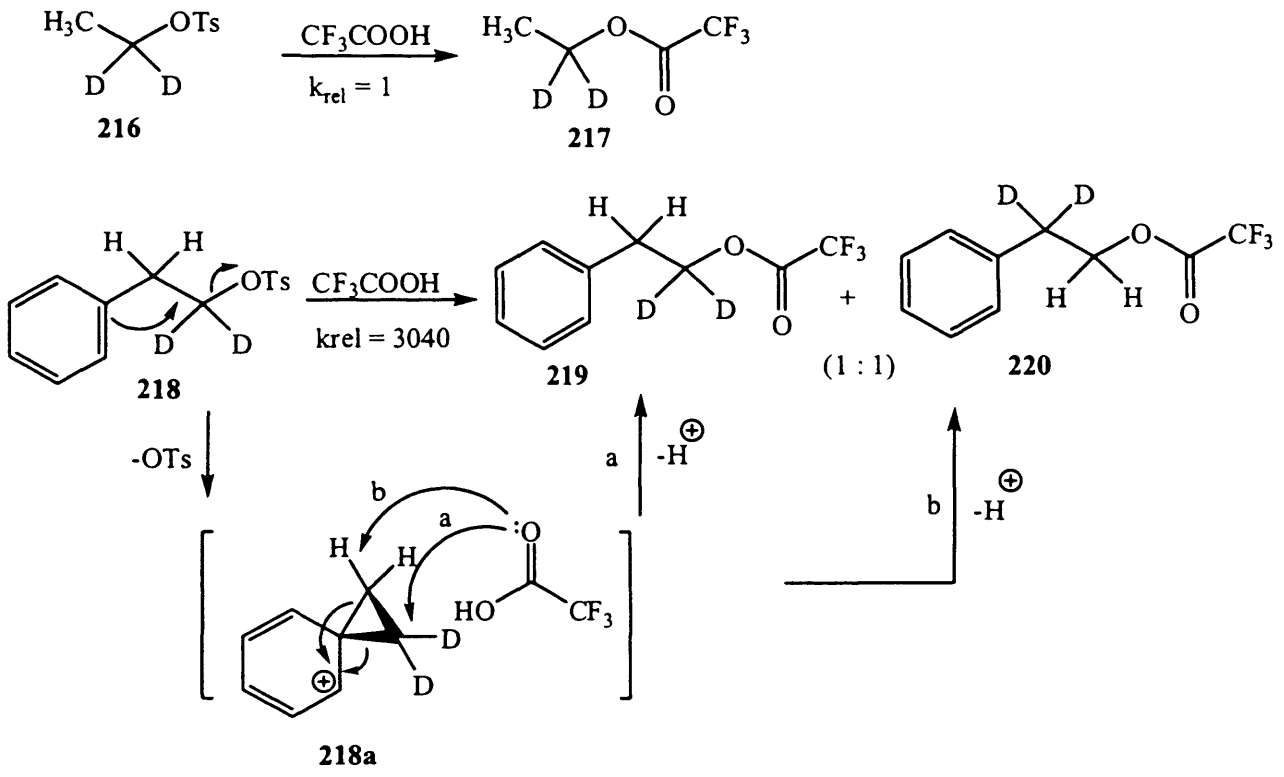
The neighbouring group participation is the direct interaction of the reaction centre with a lone pair of electrons of an atom or with the electrons of a sigma or π-bond contained within the parent molecule. The structure element on which this electron pair is localized is called a neighbouring group. It displaces the leaving group stereoselectively through a backside attack. This attack corresponds to that of an S_N2 reaction. Because substitution through the neighbouring group takes place intramolecularly, it represents an unimolecular process. In spite of this, the organic chemist, who wants to emphasize the mechanistic relationship and not rate law, should classify substitution reactions with neighbouring participation as S_N2 reactions [18].



Scheme 14. General representation of neighbouring group participation.

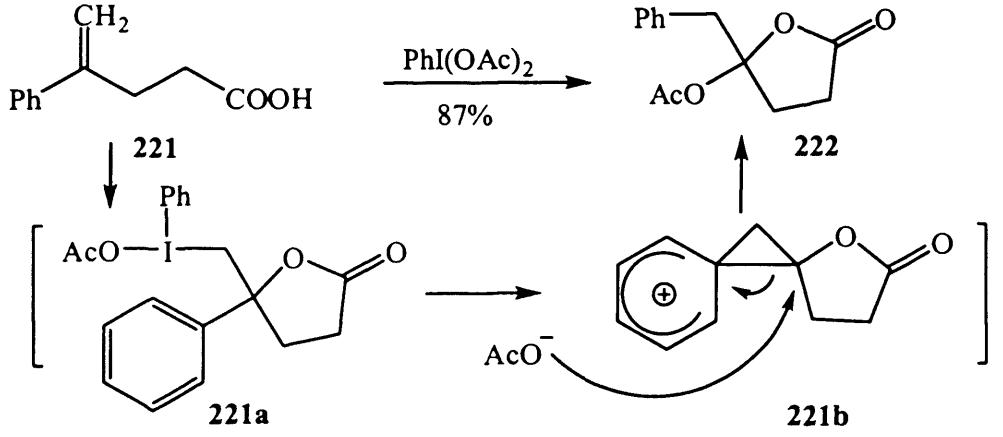
Because of neighbouring group participation a cyclic and possibly strained (depending on the ring size) intermediate **B** is formed from the alkylating agent. This intermediate **B** contains a positively charged centre which represents a leaving group X. This is displaced in a second step by the nucleophile through another backside attack (S_N2 reaction). In the reaction product **C**, the nucleophile occupies the same position the leaving group X originally had. Reactions of this type thus take place with complete retention of configuration at carbon centre under attack. This distinguishes S_N reaction with neighbouring participation both from substitutions according to S_N2 mechanism and from substitution according to S_N1 mechanism. The nucleophilic electron pair of neighbouring group can be non-bonding or a π bond or in a special case in an σ-bond [18]. Generally they can displace the leaving group when this produces a three or four or five and even six membered cyclic intermediate. Herein the neighbouring group participation of phenyl moiety is described in Scheme 15 and 16.

Phenethyl tosylate **218** solvolysis in CF_3COOH orders of magnitude fasters than ethyl tosylate **216** (Scheme 15). Because of neighbouring phenyl ring can make a π electron pair available, a phenonium ion intermediate **218a** is formed [18]. Phenonium ion intermediate **218a** are derivatives of the spirooctadienyl cation is shown in Scheme 15.



Scheme 15. The neighbouring group participation via phenonium ion intermediate.

Wirth *et al.* reported the cyclisation of unsaturated carboxylic acid **221** to synthesise lactone **222** with diacetoxy iodobenzene leading to the formation of phenonium ion intermediate **221b** via initial addition product **221a**.



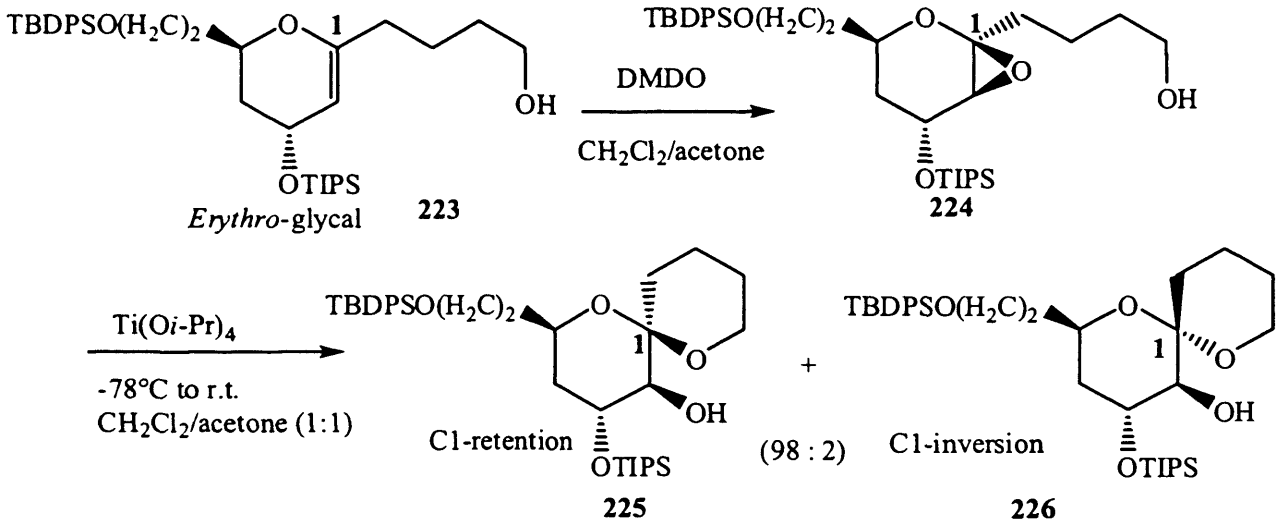
Scheme 16. The phenonium ion intermediate participation to form lactone derivative **222**.

This can be rationalized by a neighbouring group participation of phenonium ion intermediate **221b**. The high leaving group ability of the hypervalent iodine moiety in the intermediate could be the driving force of neighbouring phenyl group participation [19]. A 1,2-phenyl

migration accompanies the opening of the phenonium ion intermediate by the acetoxy nucleophile (Scheme 16).

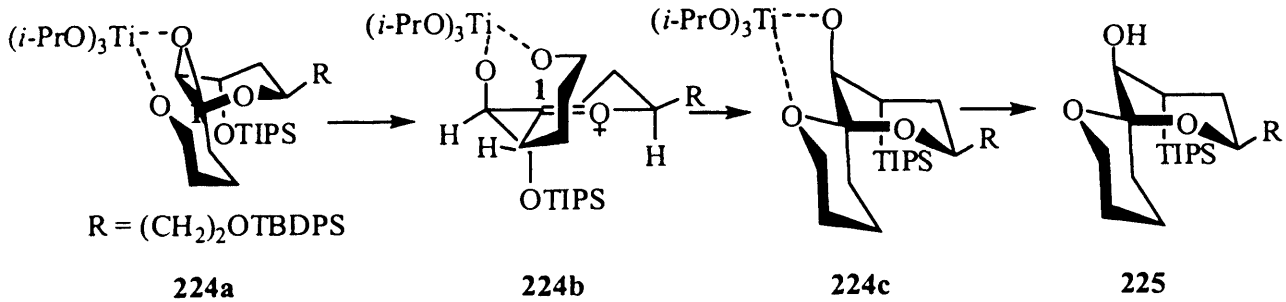
3.3.3 Ti(O*i*-Pr)$_4$-Mediated kinetic spirocyclization of glycal epoxides

Tan *et al.* reported the stereocontrolled synthesis of spiroketals via Ti(O*i*-Pr)$_4$ mediated kinetic spirocyclization of glycal epoxides with retention of configuration [20].



Scheme 17. Strategy for stereocontrolled synthesis of spiroketals via epoxide opening spirocyclisations with retention (**225**) or inversion (**226**) of configuration at the anomeric carbon.

The epoxidation of compound **223** with DMDO provided the reactive glycal epoxide **224**, which began to cyclise spontaneously even at reduced temperatures (-65 °C). The various multidentate Lewis acids were added directly to nascent epoxide at -78 °C and analyses the resulting product ratios after warming to room temperatures. In particular, Ti(O*i*-Pr)$_4$ provided the spiroketal **225** with retention of configuration almost exclusively as demonstrated in Scheme 17.



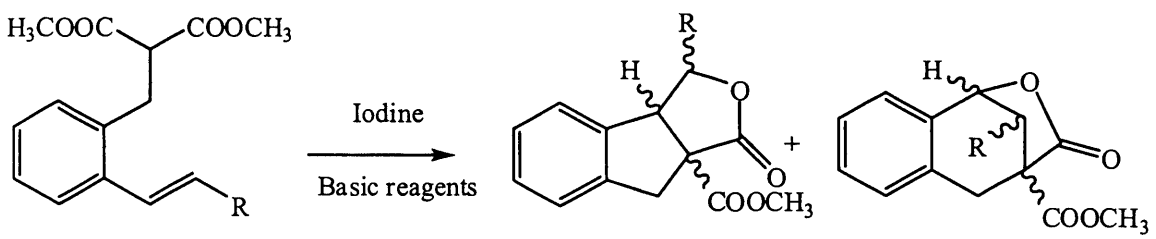
Scheme 18. Proposed tethered mechanism for kinetic spirocyclisation with retention of configuration at anomeric carbon (C-1).

A proposed mechanistic route for the kinetic spirocyclisation with retention of configuration at the anomeric carbon (C-1) is given in Scheme 18. The multidentate Lewis acid might serve as a noncovalent tether between the epoxide oxygen and the oxygen of the side chain hydroxyl moiety (Scheme 18). The Lewis acid could then activate the epoxide electrophile **224a** to form an oxonium intermediate **224b** then deliver the side chain oxygen nucleophile to the desired β-face of the anomeric carbon. In this manner the required epoxide opening with retention of configuration might be achieved in a kinetically controlled manner [20].

3.4 Project outline

The presence of hydrogenated naphthalene and indane ring skeleton in number of naturally occurring compounds and synthetic materials, fixed with their role in the fine-tuning of the physico-organic properties of the compounds for ultimate application, illustrates the need for development of new functionalised tetrahydronaphthalene and indane-based structures and new methods for their construction. Inspite of intrinsic worth, current methods for the synthesis of functionalized tetrahydronaphthalenes and indanes do not address the combined advantages of introducing diversity in the aromatic portion, while also considering functional and stereochemical issues relative to the carbocyclic core.

Recently, we reported an efficient synthesis of 3-iodo-1*H*-indene derivatives [21] and also described in chapter 2. In continuation of our interests on the applications of iodine mediated carbocyclisations, it would be a natural extention for us to further extend previously reported iodine mediated carbocyclisation conditions to stilbene malonate derivatives with a hope to develop a new synthetic methodology for functionalised indane and tetahydronaphthalene carbocyclic systems. We are pleased to observe that a tandem reaction of stilbene malonate with iodine under basic reagents furnished indanes and tetrahydronaphthalenes with three new stereogenic centres. This is the first report for the synthesis of indanes and tetrahydronaphthalenes via iodine promoted reaction of stilbene malonate derivatives as key starting materials (Scheme 19). The Wirth group has recently reported selenium mediated carbocyclisations of similar substrates [22].

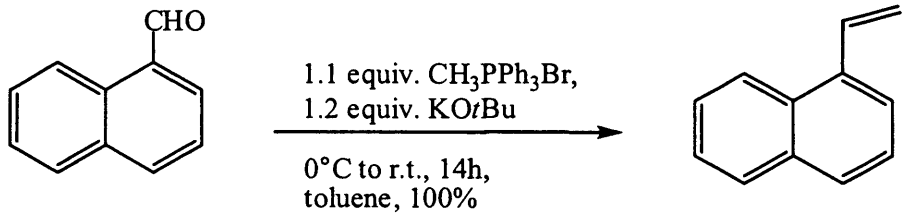


Scheme 19. Proposed route for the synthesis of indanes and tetrahydronaphthalenes.

3.5 Results and discussion

3.5.1 Synthesis of starting materials

The styrenes (**228a**), 4-methylstyrene (**228b**), 4-chlorostyrene (**228c**), 2-vinylnaphthalene (**228d**), 2,6-dichlorostyrene (**228e**), and 2-chlorostyrene (**228f**) used in this study were commercially available with an exception of 1-vinylnaphthalene (**228g**).



227 **228g**

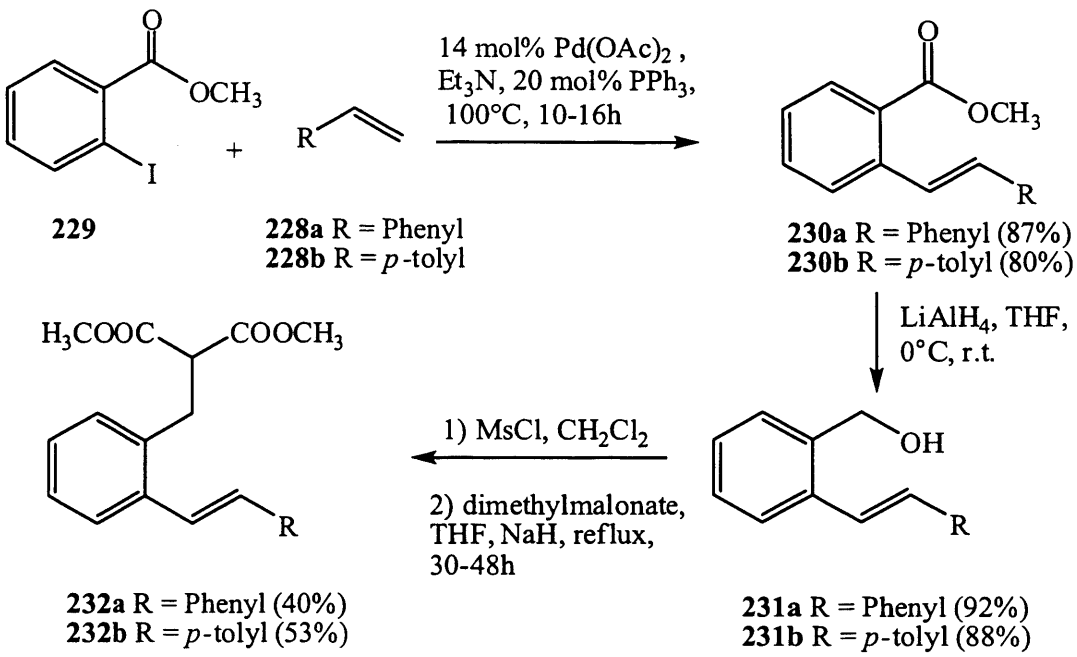
Scheme 20. Synthesis of compound **228g** via Wittig reaction.

1-Vinyl naphthalene **228g** was synthesised by the Wittig reaction from its corresponding aldehyde **227** in quantitative yields as shown in Scheme 20 [23].

3.5.1.1 Mizoroki-Heck reaction

The Pd(0)-catalysed vinylation of aryl halides was first reported over 35 years ago in an independent study by Mizoroki and Heck [24]. The transformation that has come to be known as the Mizoroki-Heck reaction is now broadly defined as the Pd(0)-mediated coupling of an aryl or vinyl halide or triflate with an alkene. The palladium catalysed Mizoroki-Heck reaction has been intensively developed for its important synthetic applications in the field of organic chemistry. During the past four decades, the applications of this reaction as a powerful tool for the creation of carbon carbon bonds in natural product synthesis have flourished [25]. The Mizoroki-Heck reaction [26] has been used as a key step in the synthesis of stilbene malonate derivatives as shown in Scheme 21 and Table 1.

Commercially available methyl 2-iodophenyl carboxylate (**229**) was subjected to Heck reaction conditions with styrene **228a** & **228b** to furnish Mizoroki-Heck cross coupled products **230a** and **230b** in 87% and 80% yield respectively. The ester moiety was reduced to alcohols **231a** and **231b** using $LiAlH_4$ in excellent yields [27] (Scheme 21). Finally, the mesylation followed by condensation with dimethylmalonate to furnish stilbene malonate **232a** and **232b** in 40% and 53% yield respectively [27].



229

228a R = Phenyl
228b R = *p*-tolyl

230a R = Phenyl (87%)
230b R = *p*-tolyl (80%)

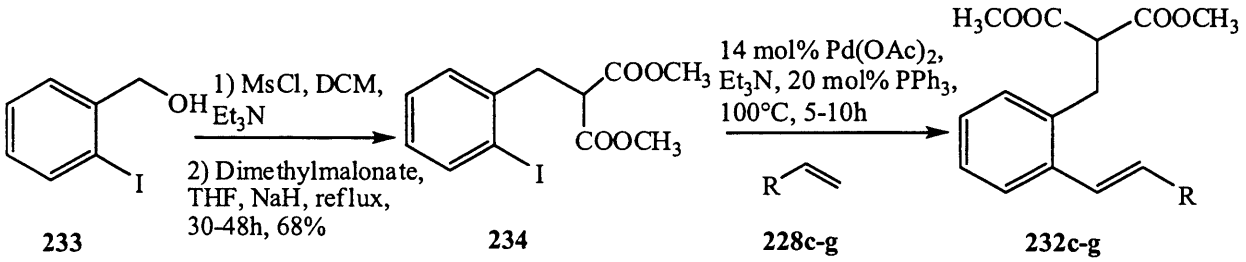
231a R = Phenyl (92%)
231b R = *p*-tolyl (88%)

232a R = Phenyl (40%)
232b R = *p*-tolyl (53%)

Scheme 21. Syntheses of stilbene malonate derivatives **232a** and **232b**.

Alternatively, stilbene derivatives **232c-g** could be synthesised from commercially available 2-iodobenzyl alcohol **233** by mesylation and condensation with dimethyl malonate to deliver compound **234** followed by a Mizoroki-Heck reaction to yield the desired stilbene malonate derivatives **232c-g** (Table 1).

Table 1. Syntheses of precursor molecules **232c-g**.

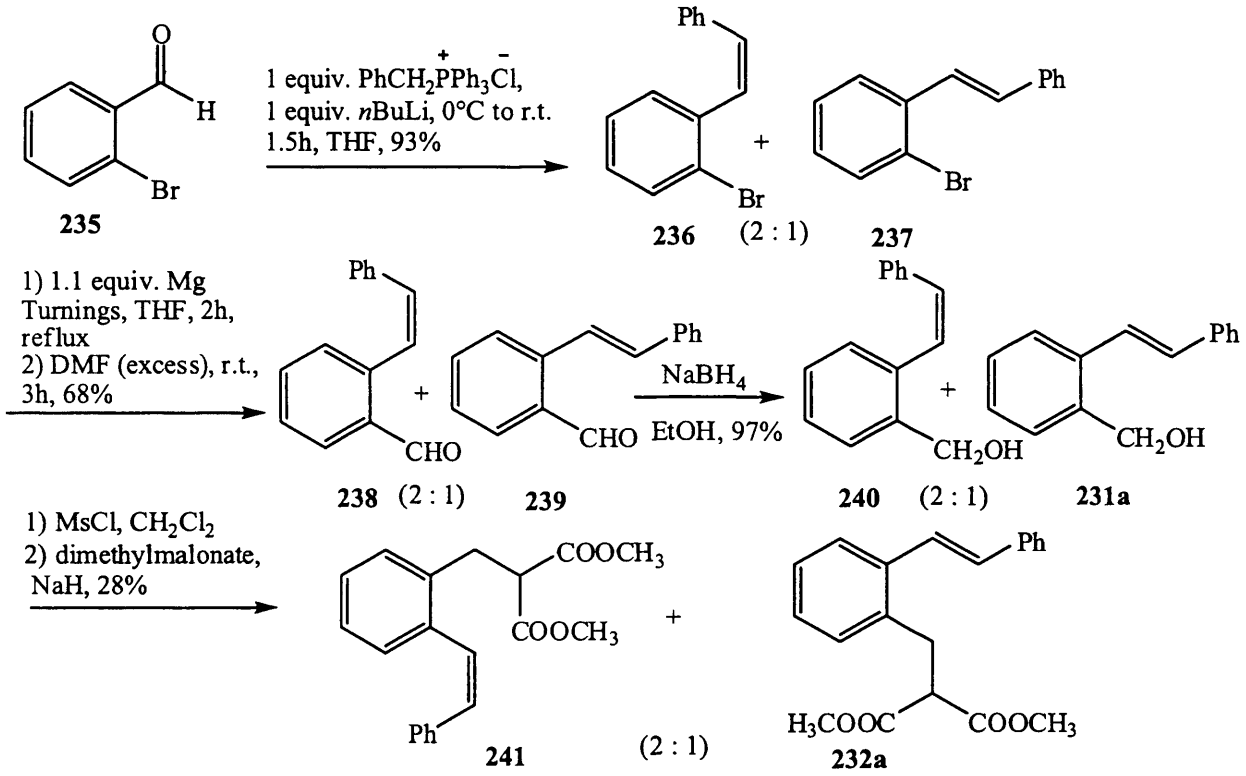


233 **234** **228c-g** **232c-g**

Entry	R (228c-g)	Reaction time (h)	Heck products (232c-g)	% yield
1	2-naphthyl (**228c**)	6	**232c**	76
2	4-chlorophenyl (**228d**)	5	**232d**	72
3	2,6- dicholorphenyl (**228e**)	8	**232e**	66
4	2-chlorophenyl(**228f**)	10	**232f**	73
5	1-naphthyl (**228g**)	8	**232g**	89

3.5.1.2 Synthesis of *Z*-stilbene malonate derivative 241

The Wittig olefination of *o*-bromobenzaldehyde **235** with benzyl triphenylphosphonium chloride gave a mixture of mainly *o*-bromo-*cis*-stilbene **236** and a small amount of *trans*-**237** in 93% combined yield [28]. The Grignard reagent formation is accomplished by the reaction of *E*-and *Z*-isomer of 1-bromo-2-(2-phenylethenyl)benzene (**237** and **236**) with magnesium turnings in THF under reflux for 2h (Scheme 22).



Scheme 22. The synthetic route for the synthesis of *Z*-stilbene malonate **241**.

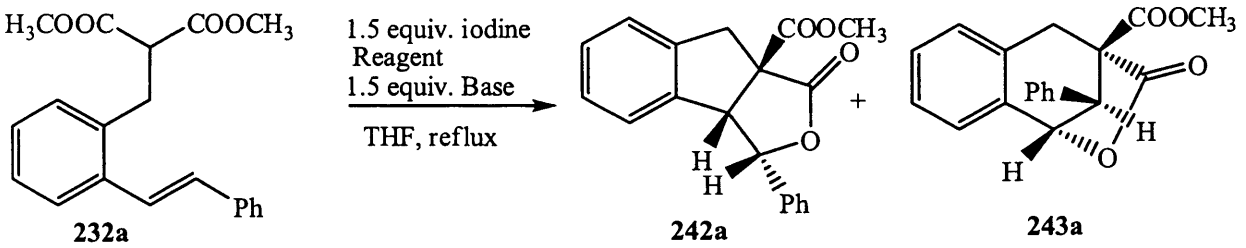
The reaction mixture was cooled slowly and followed by addition of excess of DMF to furnished *E*- and *Z*-isomers of 1-formyl-2-(2-phenylethenyl)-benzene **239** and **238** in 68% overall yield [29]. The aldehyde moiety is reduced using $NaBH_4$ to primary alcohols **240** and **231a** in excellent yield [30].

Finally, mesylation and condensation of mesylate with dimethylmalonate to furnish the desired *Z*-stilbene malonate derivative **241** along with *E*-isomer **232a** (2:1 ratio respectively) in 28% combined yield. The reaction sequences for the formation of *Z*-stilbene **230** along with *E*-stilbene derivative **221a** in 2:1 ratio respectively are described in Scheme 22.

3.5.2 Optimisation of reaction conditions

Our study commenced with the cyclisation of stilbene malonate **232a** by using basic reagents in the presence of iodine electrophile. In the very first attempt, compound **232a** was treated with iodine and NaH in anhydrous THF under reflux (entry 1, Table 2). We were delighted to observe the complete consumption of stilbene malonate **232a** in 1.5 h and compounds **242a** and **243a** are isolated as a mixture in 70% combined yield. In an attempt to further improve the reaction conditions, we have carried out a series of experiments with different bases. The reaction of compound **232a** with iodine and pyridine led to the complete recovery of starting material (entry 2, Table 2). Therefore, metallic counterion seems to be necessary in order to stabilize the malonate anion. When stilbene malonate **232a** was also treated with bis{(trifluoroacetoxy)iodo}benzene in dichloromethane as a solvent in the absence of base, an unidentified mixture of products was formed (entry 3, Table 2). Further, compound **232a** (Ar = Ph) was treated with NaH followed by addition of ICl and refluxed in THF for one hour in the formation of some addition of iodine monochloride to the double bond and mostly recovery of starting material resulted (entry 4, Table 2). This observation suggested that the nucleophilic character of the iodide counter ion was essential in order to accomplish this transformation.

Table 2. Screening of reaction conditions for the cyclisation of substrate **232a**.



232a **242a** **243a**

Entry	Electrophilic Reagent	Base	Time (h)	%Yield (242a)	% Yield (243a)
1[a]	I_2	NaH	1.5	52	18
2[a]	I_2	Pyridine	3	0	0
3[b,c]	$PhI(OCOCF_3)_2$	-	16	0	0
4[a]	ICl	NaH	1	0	0
5[b]	I_2	KO*t*Bu	30	48	15
6[a,d]	I_2	K_2CO_3	4.5	28	34

[a] Reaction performed at 65°C [b] Reaction performed at 20°C.[c] The reaction was carried out in CH_2Cl_2.[d] 3 equiv. of base and iodine was used.

When potassium *t*-butoxide was used as a base at room temperature with stirring for several hours, similar carbocyclic products **242a** and **243a** were observed (entry 5, Table 2). *t*-Butyl hypoiodite was formed upon the reaction of iodine with potassium *t*-butoxide [31]. Using a weaker base such as potassium carbonate (entry 6, Table 2) resulted in an increased amount of 6-*endo-trig* cyclised product **243a**. The best reaction conditions observed for these cyclisations were the iodine with NaH and KO*t*Bu as bases with combined yields of 70% and 63% respectively (entries 1 and 5, Table 2).

3.5.3 Stereochemistry Assignment

The mixture of cyclised products was subjected to flash chromatography and the compounds **242a** and **243a** were successfully isolated and characterized by ^{1}H and ^{13}C NMR spectroscopy. The product **242a** was formed by an initial *5-exo-trig* mode of iodocarbocyclisation of the malonate anion onto the activated double by iodine elctrophile followed by the apparent nucleophilic attack of oxygen of ester group to replace iodide to form a second γ-lactone ring. Similarly, the product **243a** was formed by initial 6-*endo-trig* mode of iodocarbocyclisation and then lactonization to form δ-lactone ring. Both the compounds formed as single diastereomers as judged from their ^{1}H and ^{13}C NMR spectra (Figure 3). The cyclised product **242a** was a colourless crystalline compound and stereochemistry was established by single crystal X-ray analysis as shown in Figure 2.

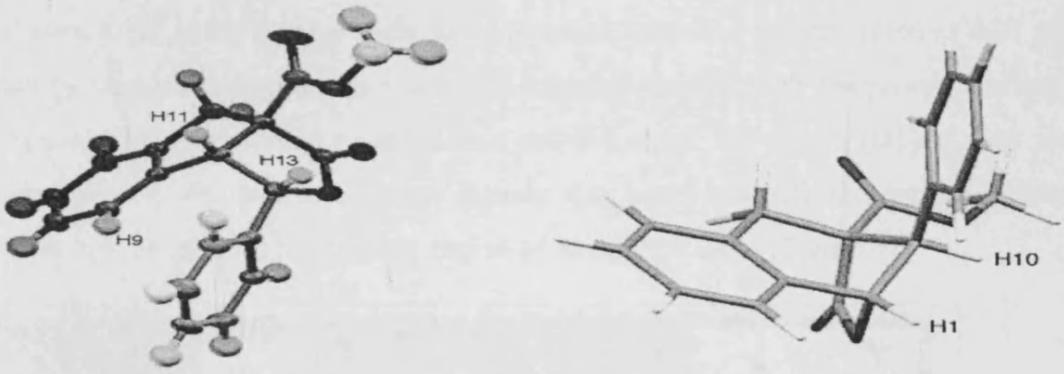


Figure 2. X-ray structure of **242a** and optimized structure of **243a** by calculations.

The *cis*-relationship between hydrogens H11 and H13 was noteworthy in the case of compound **242a**. The close proximity to the phenyl substituent as evidenced by the X-ray structure of compound **242a** (Figure 2) leads to a high-field shift of proton H9 due to anisotropic effect of π-electrons of phenyl moiety. As a result, the H9 proton was observed at δ = 5.57 ppm in ^{1}H NMR spectrum of compound **242a** (Figure 3).

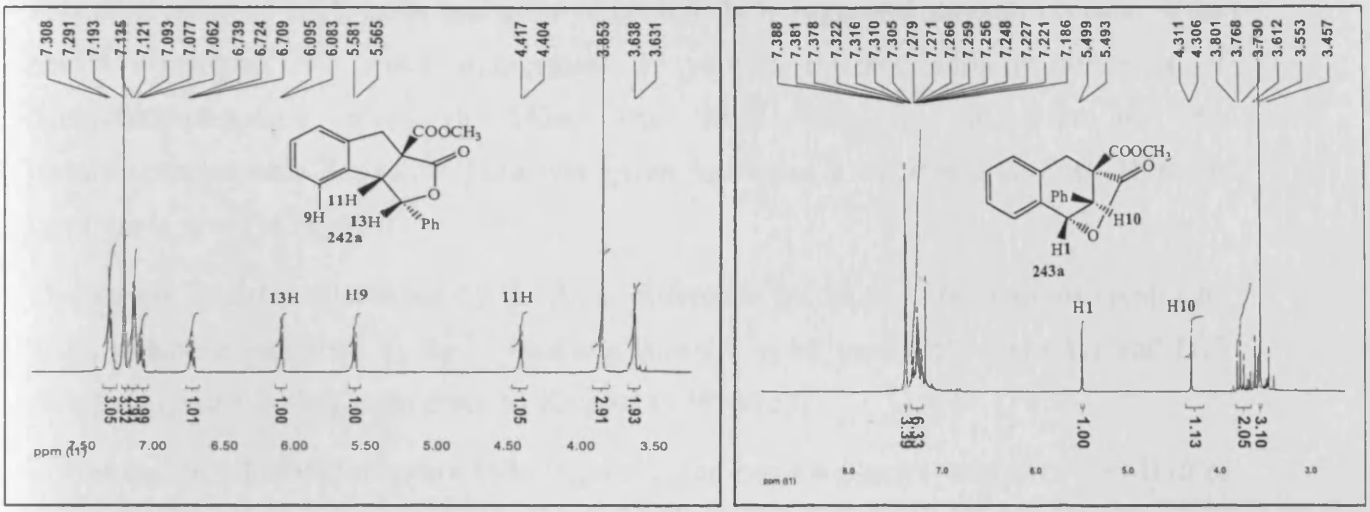


Figure 3. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compounds **242a** and **243a**.

In many cases of interpretation of NMR spectra it would be helpful to distinguish protons by spatial location within the molecule. A practical method for solving these problems is nuclear overhauser enhancement (NOE) difference spectroscopy. This technique is particularly well suited to the problems involving the location of substituents around an aromatic ring and stereochemical differences in alkenes or in bicyclic compounds [32]. This technique was based on the same phenomenon that gives rise to the NOE effect. The NOE difference spectrum thus obtained was expected to show a negative signal for protons that has been irradiated. All the other nuclei that were not affected by the irradiation will appear as very weak or absent. In an NOE experiment for compound **243a**, the proton (H10) at 4.31 ppm is irradiated by the decoupler frequency is tuned to match exactly with the proton H-10. There has been a 4.93% enhancement regarded as a positive signal for proton (H1) at 5.49 ppm is observed. Rest of the aromatic proton signals that were less affected by the irradiation appeared as very weak such as aromatic region of compound **243a** (Figure 4).

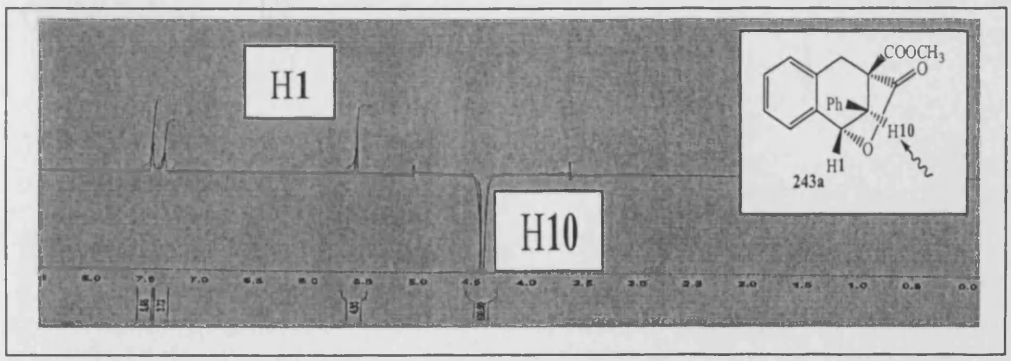


Figure 4. NOE difference spectrum of compound **243a** (400 MHz, $CDCl_3$).

This observation of NOE experiments for compound **243a** suggested an axial position of the phenyl substituent and *trans* arrangement of protons H1 and H10 in the case of tetrahydronaphthalene derivative **243a**. The NOE difference spectrum for the tetrahydronaphthalene derivative **243a** was given in Figure 4 whereas a normal ^{1}H NMR spectrum is given in Figure 3.

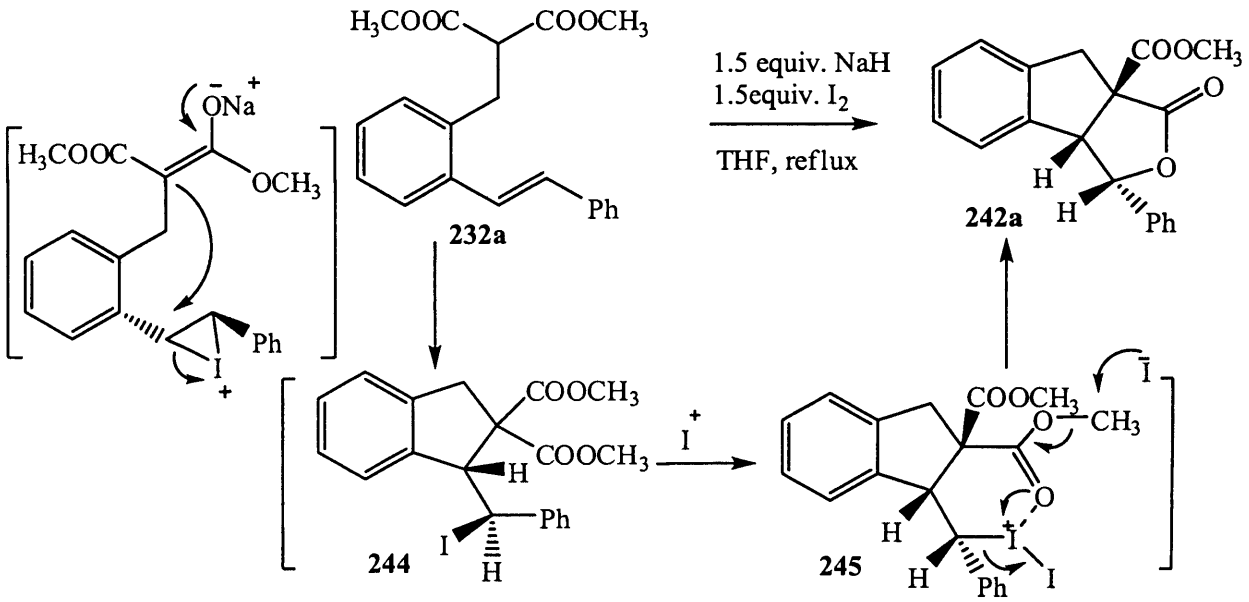
This stereochemistry established by the NOE difference spectrum in the case of compound **243a**, is further supported by the J^3-coupling constant value between protons H1 and H10 correlation with dihedral angle given by Karplus in 1963 [33].

Therefore, the calculated structure **243a** (Figure 2) indicated a dihedral angle H1-C-C-H10 of 50° with an axial phenyl substituent, whereas calculations of the other possible stereoisomer **246** with an equatorial phenyl substituent showed a dihedral angle of 88°. The value of coupling constant between H1 and H10 was determined to be J = 3.0 Hz from ^{1}H NMR spectrum of compound **243a**, which, according to the Karplus equation [33], correlates to a torsion angle of about 50°.

3.5.4 Mechanistic studies

In the case of compound **242a**, the *cis*-relationship between hydrogens H11 and H13 is noteworthy (Figure 2). Therefore, the mechanistic sequence cannot consist of an iodocarbocyclisation followed by an S_N2 substitution of the iodine with one of the ester moieties, as this would lead to a *trans*-arrangement of these two hydrogen atoms. A subsequent S_N1 type substitution was very unlikely under the basic reaction conditions and would lead to the thermodynamically favoured *trans*-isomer. The computational studies have shown that the *cis*-isomer **242a** was 0.22 kcal/mol higher in energy than that of *trans*-isomer **246** [34]. This result suggested that *cis*-isomer **242a** was kinetically stable whereas *trans*-isomer **246** was thermodynamically stable.

We proposed an activation of the iodine by the reaction with an iodonium cation followed by a reductive elimination towards the tricyclic lactone derivative as shown in Scheme 23. Alternatively, the formation of *cis*-isomer **242a** can be explained by an initial diiodination of alkene followed by two subsequent S_N2 reactions. In the case of compound **242a**, the observed stereochemistry is an example of the retention of configuration rather than inversion. After an initial *exo-dig* cyclisation to form an indane ring via S_N2 mechanism, S_Ni type transition state stabilized by a capable leaving iodine molecule containing oxygen of ester moiety as chelating units capable of attracting oxygen nucleophile which may account for rapid conversion to form second lactone ring.



Scheme 23. The proposed mechanistic route for the synthesis of compound **242a**.

The reaction occurs via a front side attack of the oxygen nucleophile of the ester moiety with retention of configuration (Scheme 23). As a tentative experiment the reaction of the mixture of *E* and *Z*-stilbene derivative **232a** and **241** (1:2) under identical reaction condition (NaH/I_2 on reflux in THF) gave tricyclic lactone **246, 243a** and **242a** in 0.5:1:0.4 ratios as single diastereomers respectively as shown in Scheme 24 and their ratios were calculated from ^{1}H-NMR spectrum (Figure 5(a)). In a comparative study of these results with our previous observation of ratio of products in the case of pure *E*-stilbene malonate derivative **232a** (NaH/I_2 on reflux in THF) helped to deduce a ratio of 1:1.6 between compound **246** and **243a** (obtained from *Z*-stilbene malonate **241**, Scheme 24).

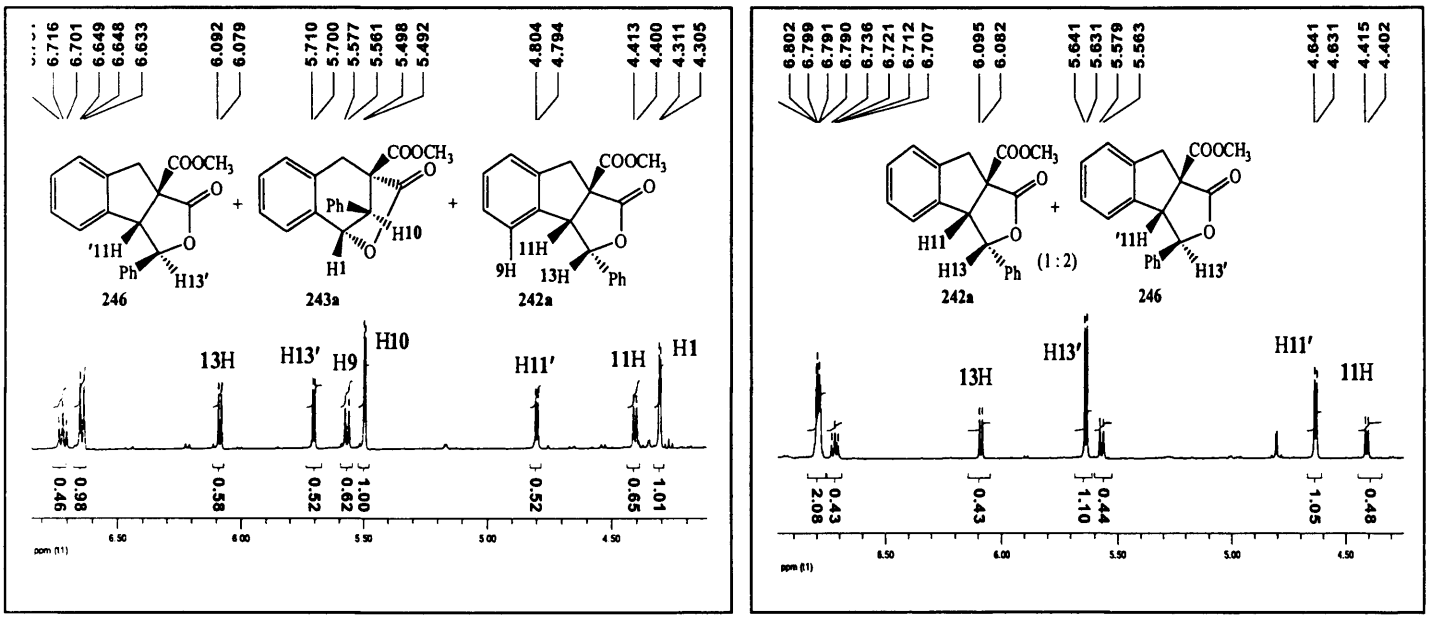
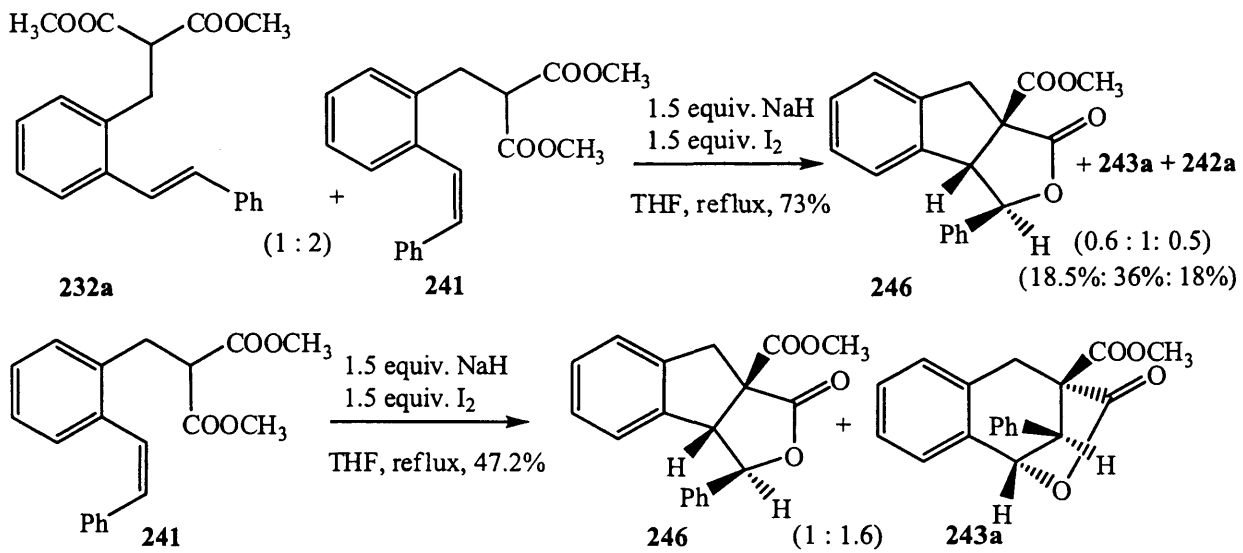
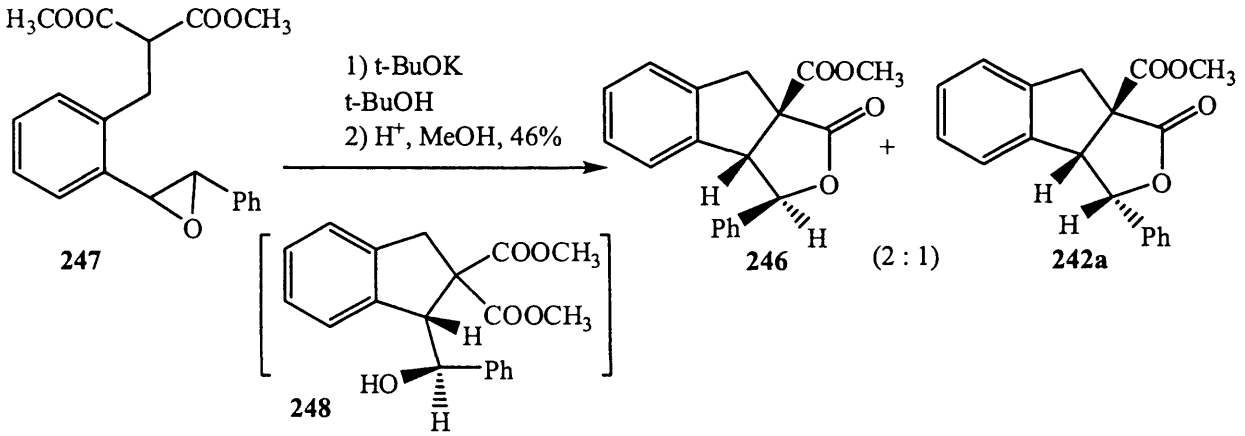


Figure 5. (a) ^{1}H NMR (500 MHz, $CDCl_3$) spectrum showing prominent proton signals in order to determine the ratios of compounds **246, 243a** and **242a** obtained from mixture of *E*/*Z* -stilbene **232a** & **241** mixture (1:2) (b) ^{1}H NMR (500 MHz, $CDCl_3$) spectrum showing prominent proton signals in order to determine the ratios of compounds **246 and 242a** obtained from epoxide malonate **247**.



Scheme 24. The products obtained by the reaction of *Z*-stilbene malonate with NaH/I_2.

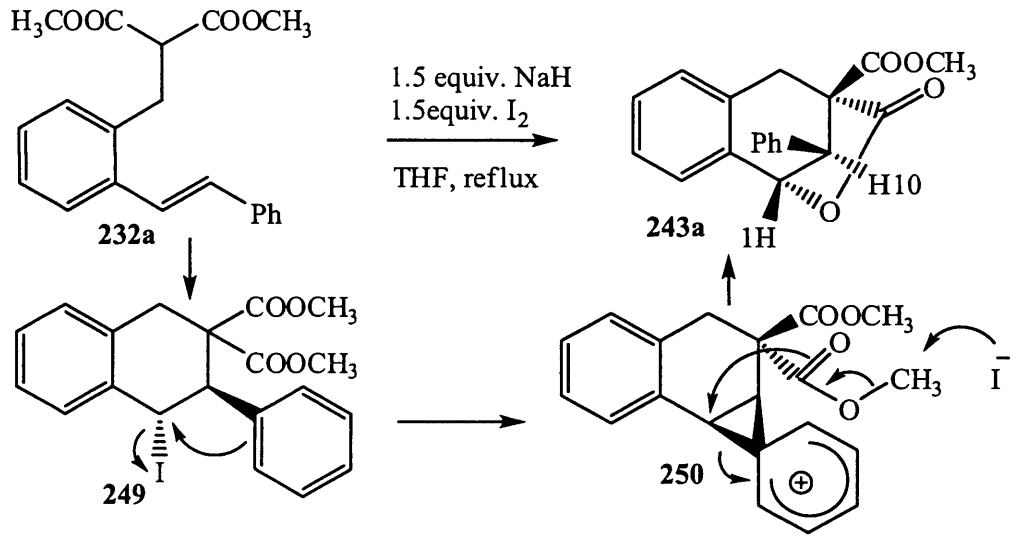
The reaction of *E*-stilbene **232** to tetrahydroindenofuranones **242** was a stereospecific reaction and in additional experiments it was confirmed that no epimerization is taking place under the reaction conditions. Product mixture of compounds **242a** and **243a** was subjected to NaH/I_2 under reflux for two hours. The crude ^1H NMR spectrum after work up showed no change in the ratios as well as no epimerization was observed. Recently, the related compounds **242** have been synthesised as a mixture of diastereomers using lithiated aryloxiranes and alkylidene malonates [11]. Compound **232a** was epoxidized with *m*CPBA in 95% yield and the resulting epoxide **247** treated with potassium *t*-butoxide in *t*-butanol. After re-esterification using methanol and sulfuric acid the compounds **246** and **242a** were obtained in 46% overall yield as shown in Scheme 25.



Scheme 25. The reaction of *trans*-epoxide under basic condition to form tetrahydroindenofuranones **246** and **242a** in 2:1 ratio respectively.

Under the reaction conditions, however, epimerisation occurred towards the thermodynamically more stable diastereomer **246.** A ratio of 1:2 is established between compounds **242a** and **246** on the basis of ^{1}H NMR spectrum of mixture (Figure 5 (b)).

The *trans*-arrangement of the hydrogens H1 and H10 in the case of compound **243a** was noteworthy; such an isomer cannot be formed by a simple S_N2 dispacement of the iodine in **249** after the initial iodocyclisation reaction. In order to account for the observed stereochemistry, we suggested the activation of the iodine in **232a** by iodine electrophile and a neighbouring participation of the phenyl substituent. This will lead to the intermediate phenonium ion **250**, which is then opened to **243a** by the oxygen nucleophile of one ester moiety as shown in Scheme 26.



Scheme 26. Proposed mechanistic route for the synthesis of compound **243a**.

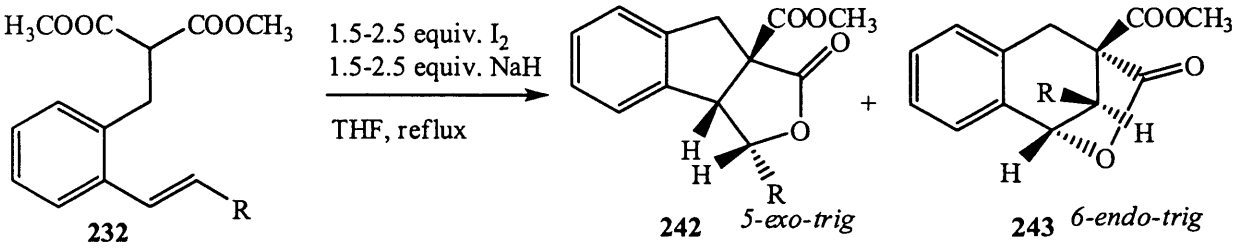
The involvement of phenonium ions in hypervalent iodine mediated cyclisations of unsaturated carboxylic acids has already been published in the literature (Scheme 16) [19] and Scheme 15 [18].

3.5.5 Scope of cyclisation reactions

Our next objective was to study the scope of this protocol for differentially substituted stilbene malonates. Consequently, we have prepared various aryl substituted stilbene derivatives by employing appropriate synthetic sequences. The reaction tolerated a variety of different aryl substituents. As shown in Table 3, the nature (electronic factors such as inductive and mesomeric affect) as well as position of the substituents on the aromatic ring affects the yields of the reaction. Similarly, the ratio of *exo*-cyclisation (leading to **242**) and

endo-cyclisation (leading to **243**) was also influenced by the nature of the substituents R. The preference of an *exo*-cyclisation over an *endo*-cyclisation was found for most substrates (entries 1, 2, 3 and 5, Table 3).

Table 3. The scope of iodine mediated carbocyclisation of stilbene malonate derivatives.



232 **242** *5-exo-trig* **243** *6-endo-trig*

Entry	R	Time [h]	% Yield (242)	Yield (243)	Ratio (242 : 243)
1	Ph (**232a**)	1.5	52	18	3:1
2	4-Me-C_6H_4 (**232b**)	3	53	24	2:1
3	2-Naphthyl (**232c**)	3.5	55	19	3:1
4[a]	4-Chlorophenyl (**232d**)	3	37	37	1:1
5	2,6- Dichlorophenyl (**232e**)	3	47	0	1:0
6[a]	2-Chlorophenyl (**232f**)	3	20	59	1:3
7[a]	1-Naphthyl (**232g**)	2.5	18	55	1:3

[a] The product mixture of **242** and **243** could not be separated, ratios were determined by ^{1}H NMR spectroscopy.

In contrast to the formation of tetrahydronaphthalene, we found in the case of substrate **232e** that only five membered compound tetrahydroindenofuranone derivative **242e** is formed. Hence, *ortho*-disubstituted derivative **232e** leading exclusively to the *5-exo-trig* cyclised product **242e** (entry 5, Table 3) could be seen as another proof for the mechanism depicted in Scheme 25. The formation of a phenonium ion intermediate **250** is not possible with precursor molecule **232e** whereas both *ortho*-positions in the aryl moiety are blocked by chlorine atoms. Compounds **232** with one substituent in the *ortho*-position were found to react preferentially via an *endo-trig* cyclisation route as evidenced by **232g** (R = 1-naphthyl, entry 7, Table 3) and **232f** (R = 2-Cl-C_6H_4, entry 6, Table 3) with a ratio of about 1:3 for the *exo*:*endo* cyclisation.

3.6 Summary

In summary, a tandem iodine mediated cyclisation of stilbene malonate derivatives under basic conditions to structurally complex indanes and tetrahydronaphthalenes was established. Unluckily, the products were obtained as a mixture of tetrahydroindenofuranones and tetrahydronaphthalenes which decreases practical significance of this methodology. In the present study, a unique stereochemistry was observed in the case of tetrahydroindenofuranones and confirmed by single crystal X-ray analysis. The stereochemistry observed in the case of tetrahydroindenofuranones is different from the literature examples reported by Kitagawa and coworkers [35]. Whereas the stereochemistry of tetrahydronaphthalene derivatives was established by spectroscopic techniques (NOE experiment and Karplus equation).

Our initial efforts were focussed on the assessment of the mechanism of these cyclisations. In keeping with our observations, we projected an ionic mechanism for these cyclisations. A rationale for the *cis*-stereochemistry in the case of indanes derivatives from *E*-stilbene malonates might involve the formation of second lactone ring via a S_Ni type front side attack of oxygen of ester moiety or might be kinetically favourable. These cyclisations proceeded exclusively with the retention of configuration to form tetrahydroindenofuranones. The established stereochemistry in the case of tetrahydronaphthalenes derivatives could be explained on the basis of neighbouring group participation of aryl moiety. Although it is still impossible at present to decide conclusively whether the iodocarbocyclisation reactions reported with stilbene malonate derivatives are ionic or radical in nature. Due to the initial work of Curran *et al.* it was suggested that an ionic as well as free radical mechanism for the NaH/I_2 mediated carbocyclisation of malonate derivatives [36]. A more detailed investigation of the mechanistic and synthetic implications is in hand.

A range of aromaric substituents can readily be accomplished to boost scope and generality of indanes and tetrahydronaphthalene derivatives. We believe that the methodology described in this chapter offers a significant alternative to existing techniques for the synthesis of structurally complex tetrahydroindenofuranone (with retention of configuration) and tetrahydronaphthalene derivatives as a single diastereomer. The indane and tetrahydronaphthalene derivatives could serve as potential lead compounds to further explore biological activities [37].

3.7 References

[1] Galatsis, P. *Ann. Rep. Med. Chem.* **1998**, *33*, 327.

[2] Sellars, J. D.; Steel, P. G. *Eur. J. Org. Chem.* **2007**, 3815.

[3] (a) Akiyama, K.; Matsuzaki, K.-I.; Hayashi, H. *Nature* **2005**, *435*, 824. (b) Umehara M.; Hanada A.; Yoshida S.; Akiyama K.; Arite T.; Takeda-Kamiya N.; Magome H.; Kamiya Y.; Shirasu K.; Yoneyama K.; Kyozuka J.; Yamaguchi S. *Nature* **2008**, *455*, 195.
(c) Gomez-Roldan, V.; Fermas, S.; Brewer, P. B.; Puech-Pages, V.; Dun, E. A.; Pillot, J.-P.; Letisse, F.; Matusova, R.; Danoun, S.; Portais, J.-C.; Bouwmeester, H.; Becard, G.; Beveridge, C. A.; Rameau, C.; Rochange, S. F. *Nature* **2008**, *455*, 189.
(d) Schachtschabel, D.; Boland, W. *ChemBioChem* 2009, *10*, 221.

[4] Ulmschneider, S.; Mueller-Vieira, U.; Klein, C. D.; Antes, I.; Lengauer, T.; Hartmann, R. W. *J. Med. Chem.* **2005**, *48*, 1563.

[5] Orsini, F.; Sello, G.; Manzo, A. M.; Lucci, E. M. *Tetrahedron*: *Asymmetry* **2005**, *16*, 1913.

[6] a) Palmer, M. J.; Kenny, J. A.; Walsgrove, T.; Kawamoto, A. M.; Wills, M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 416.
(b) Rodriguez-Escrich, S.; Sola, L.; Jimeno, C.; Rodriguez-Escrich, C.; Pericas, M. A. *Adv. Synth. & Catal.* 2008, *350*, 2250.

[7] Lantano, B.; Aguirre, J. M.; Ugliarolo, E. A.; Benegas, M. L.; Moltrasio, G. Y. *Tetrahedron* **2008**, *64*, 4090.

[8] Ferraz, H. M. C.; Carneiro, V. M. T.; Silva, L. F., Jr. Synthesis **2009**, *3*, 385.

[9] Bailey, W. F.; Longstaff, S. C. *J. Org. Chem.* **1998**, 63, 432.

[10] Sanchez-Larios, E.; Gravel, M. *J. Org. Chem.* **2009**, *74*, 7536.

[11] Salomone, A.; Capriati, V.; Florio, S.; Luisi, R. *Org. Lett.* **2008**, *10*, 1947.

[12] Nishiyama, Y.; Hamanaka, S.; Ogawa, A.; Kambe, N.; Sonoda, N. *J. Org. Chem.* **1988**, *53*, 1326.

[13] Kurteva, V. B.; Santos, A. G.; Afonso, C. A. M. *Org. & Biomol. Chem.* **2004**, *2*, 514.

[14] Kropp, P. J.; Breton, G. W.; Craig, S. L.; Crawford, S. D.; Durland, W. F., Jr.; Jones, J. E.; Raleigh, J. S. *J. Org. Chem.* **1995**, *60*, 4146.

[15] Hilt, G.; Lueers, S.; Smolko, K. I. *Org. Lett.* **2005**, *7*, 251.

[16] Huang, W.; Zheng, P.; Zhang, Z.; Liu, R.; Chen, Z.; Zhou, X. *J. Org. Chem.* **2008**, *73*, 6845.

[17] Lepore, S. D.; Bhunia, A. K.; Mondal, D.; Cohn, P. C.; Lefkowitz, C. *J. Org. Chem.* **2006**, *71*, 3285.

[18] (a) March, J. "Advanced Organic Chemistry" fourth Ed., John Wiley and Sons Inc. © **1992**. (b)Bruckner, Reinhard, "Advanced organic Chemistry reaction mechanisms, Harcourt academic press, **©2002.**

[19] Boye, A. C.; Meyer, D.; Ingison, C. K.; French, A. N.; Wirth, T. *Org. Lett.* **2003**, *5*, 2157.

[20] Moilanen, S. B.; Potuzak, J. S.; Tan, D. S. *J. Am. Chem. Soc.* **2006**, *128*, 1792.

[21] Khan, Z. A.; Wirth, T. *Org. Lett.* **2009**, *11*, 229.

[22] Shahzad, S. A.; Wirth, T. *Angew. Chem.* **2009**, *121*, 2626; *Angew. Chem. Int. Ed.* **2009**, *48*, 2588.

[23] Vinczer, P.; Novak, L.; Szantay, C. *Org. Prep. Proced. Intl.***1991**, *23*, 443.

[24] (a) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581.
(b) Heck, R. F.; Nolley, J. P., Jr. *J. Org. Chem.* **1972**, *37*, 2320.

[25] (a) De Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379.
(b) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945.

[26] Dieck, H. A.; Heck, R. F. *J. Am. Chem. Soc.* **1974**, *96*, 1133.

[27] (a) Inoue, T.; Kitagawa, O.; Oda, Y.; Taguchi, T. *J. Org. Chem.* **1996**, *61*, 8256.
(b) Xu, X.-X.; Dong, H.-Q. *J. Org. Chem.* **1995**, *60*, 3039.
(c) Ciufolini, M. A.; Browne, M. E. *Tetrahedron Lett.* **1987**, *28*, 171.

[28] De Meijere, A.; Song, Z. Z.; Lansky, A.; Hyuda, S.; Rauch, K.; Noltemeyer, M.; Koenig, B.; Knieriem, B. *Eur. J. Org. Chem.* **1998**, 2289.

[29] Munro, D. P.; Sharp, J. T. *J. Chem. Soc., Perkin Trans. 1* **1984**, 849.

[30] Chaikin, S. W.; Brown, W. G. *J. Am. Chem. Soc.* **1949**, *71*, 122.

[31] (a) Montoro, R.; Wirth, T. *Org. Lett.* **2003**, *5*, 4729. (b) Montoro, R.; Wirth, T. *Synthesis* **2005**, 1473. (c) Minakata, S.; Morino, Y.; Ide, T.; Oderaotoshi, Y.; Komatsu, M. *Chem. Commun.* **2007**, 3279.

[32] Pavia, D. L.; Lampman, G. M.; Kriz, G. S. "Introduction to spectroscopy" third edition, © **2001**, Thomson Learning.

[33] Karplus, M. *J. Am. Chem. Soc.* **1963**, *85*, 2870.

[34] Ab initio calculations were performed by using Gaussian 03 program (revision B.04). Geometries were fully optimized at B3LYP/6-31G (d) level, and the obtained energy minimum structures were characterized by frequency calculation at the same calculation level. The energies were corrected with zero-point energies. Calculations performed by Professor Michio Iwaoka.

[35] (a) Kitagawa, O.; Inoue, T.; Taguchi, T. *Tetrahedron Lett.***1992**, *33*, 2167.
(b) Kitagawa, O.; Inoue, T.; Hirano, K.; Taguchi, T. *J. Org. Chem.* **1993**, *58*, 3106.
(c) Inoue, T.; Kitagawa, O.; Oda, Y.; Taguchi, T. *J. Org. Chem.* **1996**, *61*, 8256.

[36] (a) Curran, D. P.; Chen, M.-H.; Spletzer, E.; Seong, C. M.; Chang, C.-T. *J. Am. Chem. Soc.* **1989**, *111*, 8872. (b) Curran, D.P.; Chang, C. *J. Org. Chem.* **1989**, *54*, 3140.

[37] Khan, Z. A; Iwaoka, M.; Wirth, T. *Tetrahedron*, **2010**, *66*, 6639-6646.

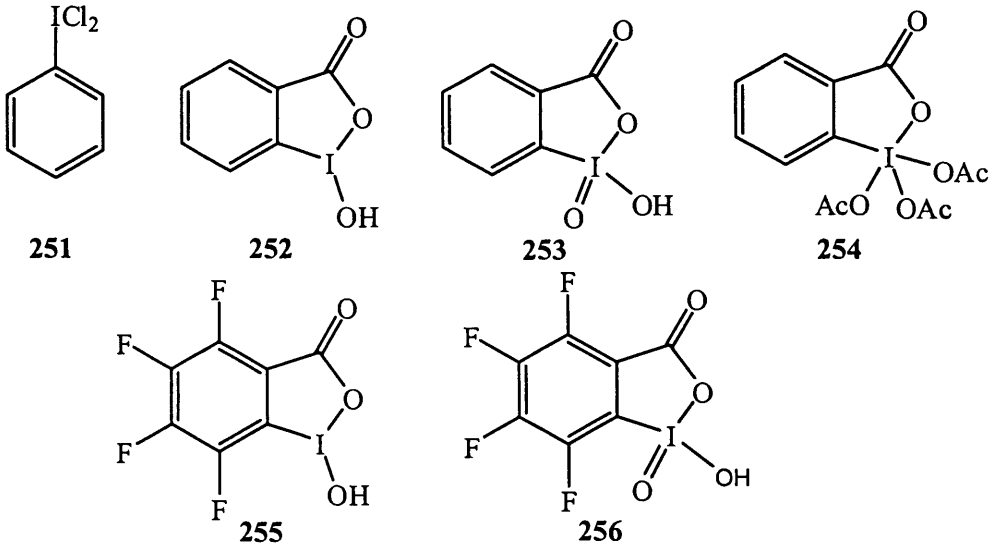
Chapter 4

Syntheses of Hypervalent Iodine(III) Reagents

In the past few decades, the organic chemistry of hypervalent iodine compounds has experienced an immense development. Applications of these reagents allow mild and highly chemoselective oxidative transformations in a facile and environmentally friendly manner.
In this chapter a brief introduction of hypervalent iodine chemistry and literature overview of simplified analogues of *ortho*-iodosobenzoic acid (IBA) is given. The oxidative transformation of α,β-diiodoacrylic acid to λ^3-iodane is described. Further, these novel hypervalent iodine(III) reagents are utilised in well-known reactions as mild oxidants.

4.1 Introduction

Dichloroiodobenzene (**251**) (Figure 1) was the first example of hypervalent iodine reagents synthesised by Willgerodt in 1886 [1]. After this discovery, the synthetic potential of this new class of compounds has not been much explored for six decades. After this period, there has been growing interest among synthetic organic community and reviews about this class of compounds appeared in literature in early 1960. After the discovery of more reactive hypervalent iodine reagents several reviews, books and research articles were published during and after 1990. Due to the low toxicity, environmentally benign behaviour, mild oxidant quality, good leaving group ability, commercial availability and easy handling of hypervalent iodine compounds make this class of compounds even more attractive for an organic chemist. These reagents have been used in the total syntheses of a variety of natural products including quinones, alkaloids, flavonoids, carbohydrate derivatives, and antibiotics [2].



251 **252** **253** **254** **255** **256**

Figure 1. Acyclic and cyclic λ^3- and λ^5- iodanes.

The cyclic iodanes such as *ortho*-iodosobenzoic acid, IBA (**252**) formed by the oxidation of *ortho*-iodobenzoic acid in general of special interest in comparison to non-cyclic iodanes [3]. The direct oxidation of o-iodobenzoic acid leads first to "*ortho*-iodosobenzoic acid" abbreviated as IBA (**252**) a λ^3-iodane and then to "*ortho*-iodoxybenzoic acid" abbreviated as IBX (**253**) is also cyclic λ^5-iodane (Figure 1). A widely used oxidant was the Dess-Martin reagent (**254**), a λ^5-iodane, was derived from IBX (**253**) upon treatment with acetic anhydride [4].

In 2007, Wirth *et al.* discovered more reactive fluorine substituted analogues of *o*-iodosobenzoic acid and *o*-iodoxybenzoic acid abbreviated as F-IBA (**255**) and F-IBX (**256**) respectively. They further utilized these new fluorine substituted polyvalent iodine reagents in well established reported reactions [5].

4.1.1 General terms used in hypervalent iodine chemistry

All known organic polyvalent iodine derivatives belong to three general structural types: first category of iodine(III) compounds, second category belongs to iodine(V) compounds and third category belongs to iodine(VII) compounds. The term iodane refers to hydrogen iodide (HI), a colourless non-flammable gas. According to IUPAC recommendations, compounds with non-standard bonding number are shown by the lambda notation; thus, H_3I is called λ^3-iodane. Similarly H_5I and H_7I is called λ^5- and λ^7-iodane respectively. The common hypervalent iodine compounds are aryl-λ^3-iodanes ($ArIL_2$) with a decet structure (10 electrons) and pseudotrigonal bipyramidal geometry and aryl-λ^5-iodanes ($ArIL_4$) with dodecet structure (12 electrons) and square pyramidal geometry. The ligands (L) could be a heteroatom or electronegative atom or group. The nomenclature of these compounds is not satisfactory and several names of these compounds are often in use [2].

The compounds containing elements of groups 5-8 bearing more electrons than the octet in the valence shell are described as hypervalent molecules [3].

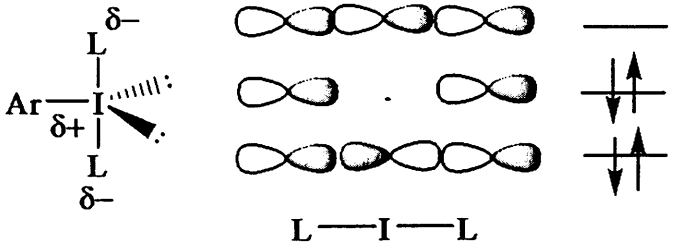
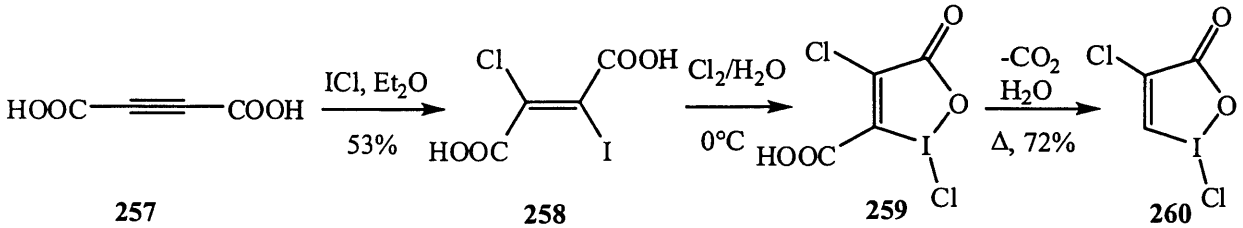


Figure 2. Pseudotrigonal bipyramid structure and molecular orbital of the 3c-4e bond.

Descriptions of such system using molecular orbital theory led to the proposal of 3-centre-4-electron (3c-4e) bonds as hypervalent bond. The two lower energy molecular orbitals, bonding and non-bonding orbitals of the three-centre-four-electron bond for hypervalent iodine are filled (Figure 2). The partial positive charge developed on the central iodine atom whereas partial negative charge developed on apical heteroatom ligands. The filled non-bonding molecular orbital has a node at central iodine (Figure 2). The partial positive on the iodine of the highly polarized 3c-4e bond would make aryl-λ^3-iodane an electrophilic agent [2].

4.2 Literature overview of simplified analogues of IBA

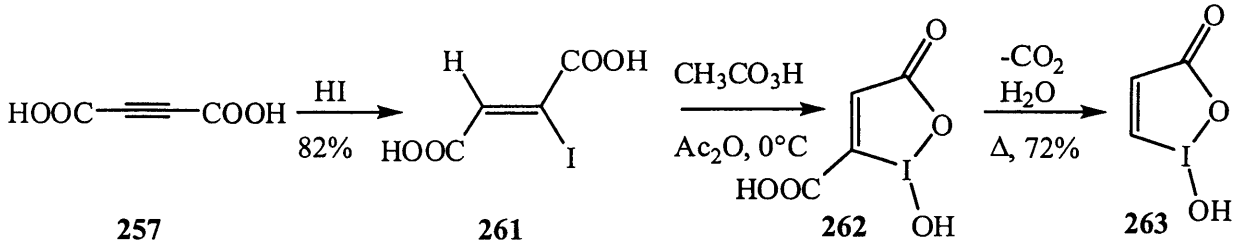
In 1989, Moss *et al* reported simplified analogues of *o*-iodosobenzoic acid **252** (IBA), the phenyl moiety of **IBA** is replaced with olefinic bond [6]. The synthetic sequences for preparation of the iodinane reagents were outlined in scheme 1. The treatment of a solution of acetylenedicarboxylate (**257**) in diethyl ether with ICl gave the addition product *E*-α-chloro-β-iodofumaric acid (**258**) in 53% yield. The chlorination afforded the carboxychloro iodinane **259** which decarboxylated and hydrolysed to λ^3-iodane **260** in 72% yield (Scheme 1).



257 **258** **259** **260**

Scheme 1. Synthesis of λ^3-iodane **260** described by Moss *et al.*

Furthermore, the addition of HI to acetylenedicarboxylic acid (**257**) afforded α-iodofumaric acid (**261**) in 82% yields. The oxidation of compound **261** with 30% peracetic acid in acetic anhydride brought about both the oxidation at iodine and cyclisation, yielding an unstable carboxyiodoxolone **262**. The carboxyiodoxolone **262** undergoes decarboxylation under the reaction conditions to give λ^3-iodane **263** in 72% yield (Scheme 2).

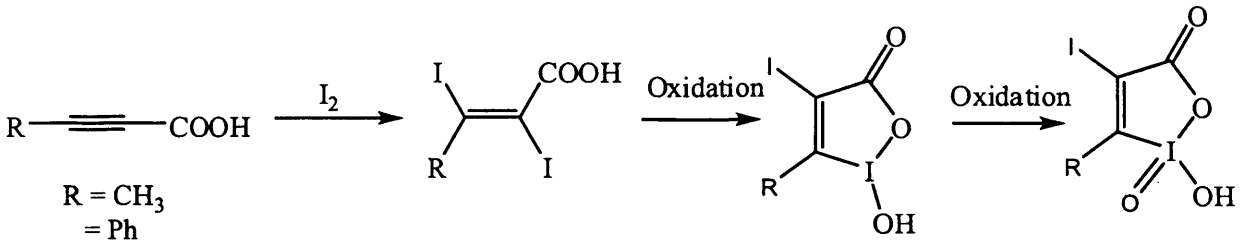


257 **261** **262** **263**

Scheme 2. Synthesis of λ^3-iodane **263** described by Moss *et al.*

4.3 Plan of work

An extensive development has been made by the chemistry of hypervalent iodine reagents since early 1990. Due to our continuous interest in the development of new reagents of hypervalent iodine compounds the work of Moss *et al.* described in scheme 1 served as a driving force for us to further extend this approach to other simplified analogues of IBA. Our proposed synthetic route for the synthesis of simplified analogues of IBA (λ^3-iodane) and IBX (λ^5-iodane) is given in Scheme 3.

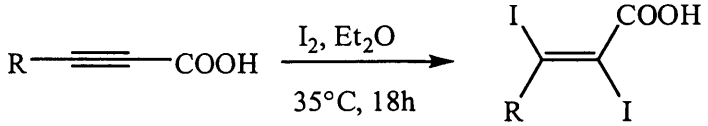


Scheme 3. Plan of work.

4.4 Results and discussion

4.4.1 Synthesis of precursor molecules

α,β-Diiodoacrylic acids were synthesised according to a literature protocol [7] starting from commercially available but-2-ynoic acid (**264**) and phenylpropiolic acid (**265**). In this procedure, the ether solution of alk-2-ynoic acid **264** and **265** was treated with iodine. The resulting reaction mixture was heated at 35 °C for 18h. After the workup the crude product was crystallized from CH_2Cl_2. The addition products **266** and **267** were obtained as colourless crystalline solids in 43% and 60% yields respectively (Scheme 4). In both the cases, under the reaction conditions addition of iodine to the alk-2-ynoic acids were regio- and stereoselective, resulting in the *trans*-addition across the triple bond and *E*/*Z* ratio was always in the favour of the *E*-isomer. According to the literature protocol [7] a traces of *Z*-isomer products formation under the similar reaction conditions also reported.



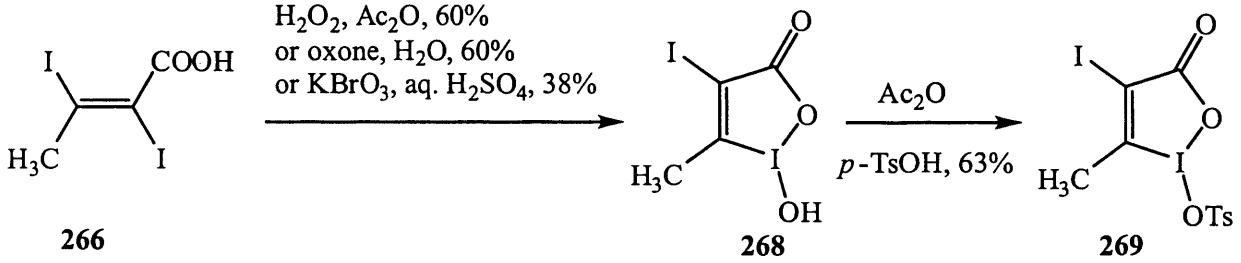
264 R = CH_3
265 R = Ph

266 R = CH_3(60%)
267 R = Ph (43%)

Scheme 4. The synthesis of precursor molecules α,β-diiodoacrylic acids **266** and **267**.

4.4.2 Oxidation of 2,3-diiodoalk-2-enoic acids to λ^3-iodane

The oxidation of 2,3-diiodoalk-2-enoic acids to λ^3-iodane was performed according to the literature procedures. The oxidation of (*E*)-2,3-diiodobut-2-enoic acid (**266**) with hydrogen peroxide in acetic anhydride resulted in the formation of λ^3-iodane **268** in 60% yield [8]. The use of oxone® ($2KHSO_5$, $KHSO_4$, K_2SO_4) in deionized water provides also a practical entry to λ^3-iodane **268** in similar yields [9]. Additionally, the oxidation of (*E*)-2,3-diiodobut-2-enoic acid (**266**) to λ^3-iodane **268** was performed by using potassium bromate in lower yields (Scheme 5) [5]. The comparative study of ^{13}C NMR spectrum revealed that the *ipso* carbon atom attached to the iodine (C-2) undergoes a downfield of $\Delta\delta$ = 48.4 ppm for λ^3-iodane **268** compared to their iodine(I) counterparts **266** (Figure 3). The sulfonate derivative **269** of λ^3-iodane could be formed as microcrystalline precipitate by reaction with *p*-TsOH in 63% in the presence of Ac_2O as solvent [10]. The hypervalent iodine compounds **268** and **269** were stable at room temperature and without exclusion of oxygen as were IBA (**252**), IBX (**253**), and DMP (**254**).



Scheme 5. Synthesis of λ^3-iodanes **268** and its tosylate derivative **269**.

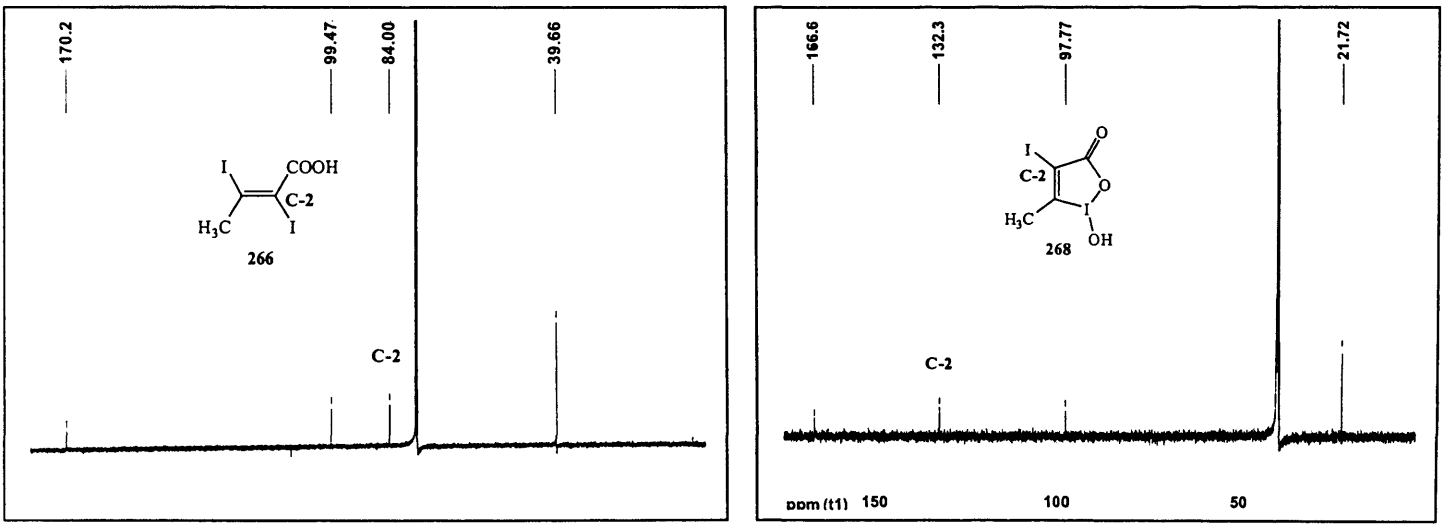


Figure 3. ^{13}C NMR (125 MHz, $CDCl_3$) spectrum to show comparison of $\Delta\delta$ of C-2 for α,β-diiodoacrylic acid **266** and λ^3-iodane **268.**

The compound **268** was recystallized by using acetone:water mixture (1:1) and its structure was confirmed by the single crystal X-ray crystallography technique (Figure 4).

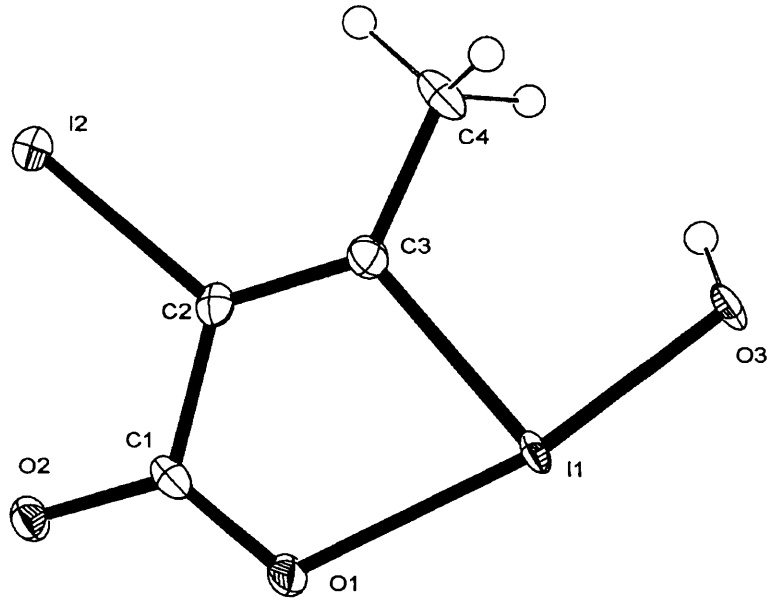
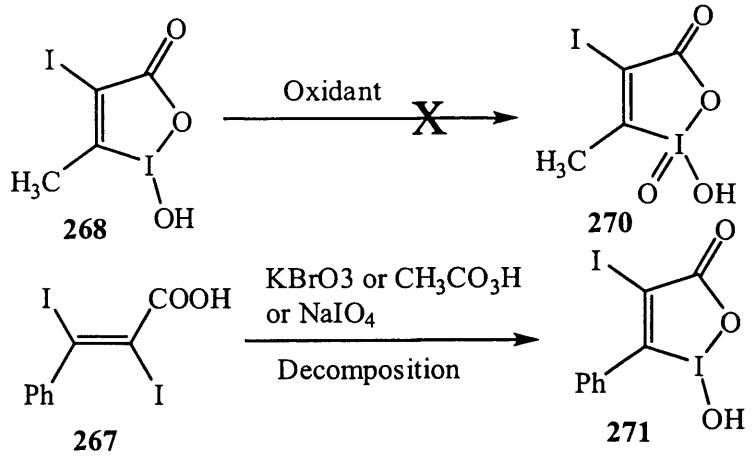


Figure 4. ORTEP diagram for compound **268**.

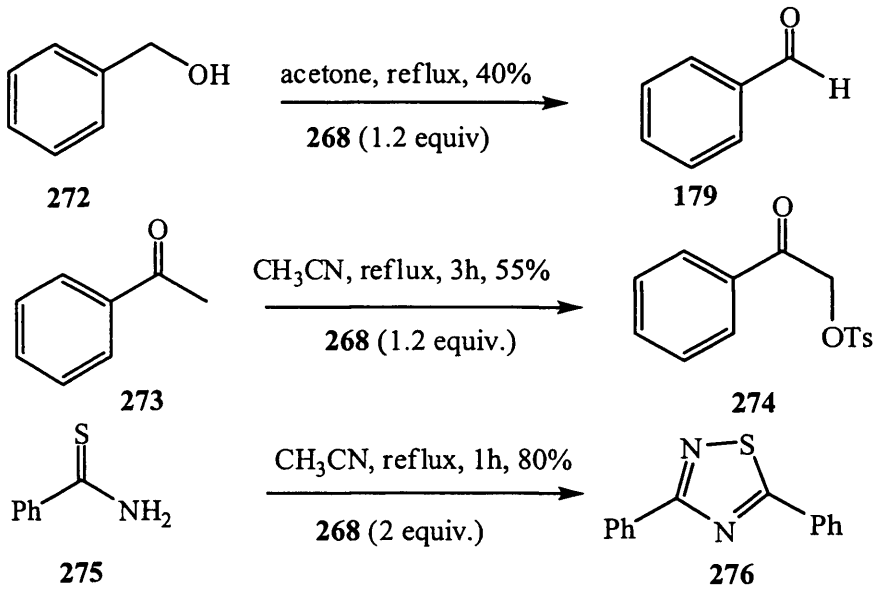
We were unable to oxidize the λ^3-iodane **268** to λ^5-iodane **270** (Scheme 6). Different oxidants were employed for the synthesis of the λ^3-iodane derivative **271** having phenyl moiety from precursor molecule **267**. Unfortunately, oxidation of **267** always led to decomposition of the starting material under various reaction conditions ($KBrO_3$, $NaIO_4$ and AcO_3H).



Scheme 6. Failed attempts towards the λ^5-iodane **270** and the λ^3-iodane **271**.

4.4.3 Oxidative transformations

Different oxidative transformations have been performed with the new hypervalent iodine reagent **268**. Simple oxidation reactions such as benzyl alcohol **272** to benzaldehyde **179**, α-oxytosylations of acetophenone **273** to compounds **274**, as well as the synthesis of heterocyclic compounds such as thiadiazole **276** from thioamide **275** have been investigated and are summarised in Scheme 7.



Scheme 7. Various oxidative transformations by using λ^3-iodane **268**.

4.5 Summary

Oxidation reactions consist of a number of important transformations in organic synthesis. They were widely used not only in abundant academic research studies but also in the productions of a variety of fine chemicals including pharmaceuticals, agrochemicals, and their intermediates. However utilization of hypervalent iodine reagents, largely in consideration of economical and environmental viewpoints, was an attractive strategy due to their unique features as extremely useful oxidants, with mild, safe, and environmentally friendly characteristics. The present invention relates generally to user and eco-friendly simplified analogues of IBA. The oxidation of (*E*)-2,3-diiodobut-2-enoic acid (**266**) by various oxidants resulted in the formation of new λ^3-iodane reagent (**268**) (can be regarded as simplified analogue of IBA) in acceptable yields. Additionally, the reaction of this new reagent with *p*-TsOH gave its tosylate derivative (**269**). Various well established oxidative transformations such as oxidation of benzylalcohol to benzaldehyde, α-oxytosylations of acetophenone and thiadiazole from thioamide can be performed with new λ^3-iodane reagent [11].

4.6 References

[1] Willgerodt, C. J. *J. Prakt. Chem.* **1886**, *33*, 154.
[2] Wirth, T. Hypervalent Iodine Chemistry; Springer: Berlin, **2003**, Vol. *224*.
[3] Shefter, E.; Wolf, W. *Nature* **1964**, *203*, 512.
[4] Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
[5] Richardson, R.D.; Page, Zayed, J. M.; Altermann, S.; Smith, D.; Wirth, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 6529.
[6] Moss, R. A.; Wilk, B.; Krogh-Jespersen, K.; Blair, J. T.; Westbrook, J. D. *J. Am. Chem. Soc.* **1989**, *111*, 250.
[7] Langle, S.; Ngi, S. I.; Anselmi, E.; Abarbri, M.; Thibonnet, J.; Duchene, A. *Synthesis* **2007**, 1724.
[8] Panetta, C. A.; Garlick, S. M.; Durst, H. D.; Longo, F. R.; Ward, J. R. *J. Org. Chem.* **1990**, *55*, 5202.
[9] Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537.
[10] Zhdankin, V. V.; Kuehl, C. J.; Bolz, J. T.; Formaneck, M. S.; Simonsen, A. J. *Tetrahedron Lett.* **1994**, *35*, 7323.
[11] Shah, A. A.; Khan, Z. A.; Choudhary, N.; Loholter, C.; Schäfer, S.; Marie, G. P. L.; Farooq, U.; Witulski, B.; Wirth, T. *Org. Lett.* **2009**, *11*, 3578.

Chapter 5

Experimental

5.1 General remarks

All the reactions were carried out by using standard procedure and laboratory equipment. Air sensitive reactions were performed in vacuum dried glass ware. The vacuum was replaced by inert atmosphere of argon. All the reaction were agitated by magnetic stirrer and when needed, warmed to defined constant temperature by hotplates with temperature probe control in silicon oil or heating blocks.

Büchi B-461, B-481 or B-490 rotary evaporators (reduced pressure down to 15 mbar) were used for solvent evaporations. A Büchi GKR-50 Kügelrohr distillation apparatus was employed for Kugelrohr distillation.

All high purity solvents and chemicals were purchased from Aldrich, Alfa Aesar and Fluka. For inert reactions freshly distilled organic solvents by using standard procedure of drying. The CH_2Cl_2 was dried over calcium hydride and THF was distilled before use over Na/benzophenone. The reactions performed at low temperatures were stirred in vessels cooled in a dry ice/acetone bath (-78 °C), ice/water/NaCl bath (-15 °C) or ice/ water bath (0 °C).

5.2 Physical data

^{1}H NMR spectroscopy

^{1}H NMR spectrums were recorded on Bruker DPX 250 (250MHz), Bruker DPX 400 (400 MHz) and Bruker DPX 500 (500 MHz) instruments. The multiplicity was designated: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, td = triplet of doublet, q = quartet, m = multiplet. The chemical shifts δ were given in ppm downfield shift of tetramethylsilane(δ = 0 ppm). The samples were dissolved in deuterated solvents such as $CDCl_3$, acetone-d_6 and DMSO-d_6.

^{13}C NMR spectroscopy

The ^{13}C NMR specta were recorded on Bruker DPX 250 (62.5 MHz), Bruker DPX 400 (100 MHz) and Bruker DPX 500 (125 MHz) instruments. The pure compound and crude reaction mixtures are dissolved in deuterated solvents such as $CDCl_3$, acetone-d_6 and DMSO-d_6. The coupling constant are given in hertz (Hz) and chemical shifts δ are given in ppm downfield shift of tetramethylsilane (δ = 0 ppm).

Mass spectrometry

Waters LCR Premier XE-tof

Mass spectrometric measurements have been performed by R. Jenkins/R. Hicks/D.Walker at Cardiff University and also EPSRC Mass Spectrometry Service Centre, Swansea University. Ions were generated by the atmospheric pressure ionization techniques voltage applied corana discharge pin (APCI), Electospray (ES) or Electron Ionization (EI). Mass fragments usually are in atomic mass units per elementary charges (m/z) with relative abundance of ion in percentage (%). The high resolution mass spectrometry for most of the compounds was carried out at EPSRC Mass Spectrometry Service Centre, Swansea University. The molecular ion peaks values quoted for either molecular ion (M^+), Molecular ion plus hydrogen ($M+H^+$) or molecular ion peaks plus ammonium ion ($M+NH_4^+$) or Molecular ion peak minus hydrogen ($M-H^-$).

Gas chromatography mass spectrometry (GC-MS)

The GC-MS spectrum were measured on Perkin Elmer 8700, beta-column.

Infrared spectroscopy

The IR spectra were recorded on a Perkin Elmer 1600 series FT-IR and major peaks were reported in cm^{-1}. The samples were measured either neat or KBr disc.

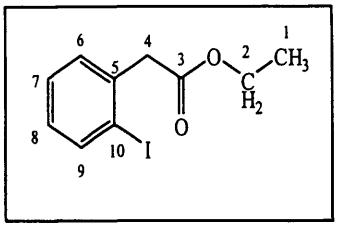
Chromatography

Column chromatrography was performed on Merk Kieselgel 60 silica (230-400 Mesh). Thin layer chromatography was performed on aluminium plates pre-coated with Merck Kieselgel 60 F254 and visulaized by UV radiation/by staining with ceric aluminium molybdate or 1% aqueous potassium per magnate dried with heat gun.

Melting point

The melting points of solid compounds were measured on Gallenkamp variable heater in open capillary tube. All melting points were taken uncorrected.

5.3 Experimental procedures and characterisation of compounds



GP-1 Ethyl ester of 2-Iodophenylacetic acid (136)

Esterification of 2-iodophenyl acetic acid was performed according to the literature protocol [1]. 2-Iodophenyl actic acid (7.63 mmol, 2 g) was dissolved in ethanol (40 mL). After the addition of a few drops of conc. H_2SO_4 the reaction mixture was refluxed for 4 h. The reaction mixture was cooled to r.t. and quenched with water. Further reaction mixture was extracted with diethyl ether (3 x 20 mL). The organic layer was washed with aqueous saturated aqueous $NaHCO_3$. The crude product was further purified by column chromatography on silica (ethyl acetate:hexane (1:10) to yield **136** in 91% (6.99 mmol, 2 g) as white crystalline solid. This is a known compound. Spectroscopic data are in agreement with literature [1].

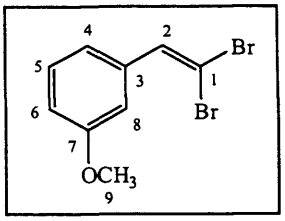
m.p. = 34°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 1.29 (3H, t, J = 7.1 Hz, 1-C*H*$_3$), 3.81 (2H, s, 4-C*H*$_2$), (2H, q, J = 7.1 Hz, 2-C*H*$_2$), 6.97 (1H, td, J = 7.7 Hz, 2.1 Hz, 8-C*H*, aromatic), 7.29-7.36 (2H, m, 6-C*H* and 7-C*H*, aromatic), 7.87 (1H, d, J = 8.89 Hz, 9-C*H*, aromatic).

Synthesis of terminal acetylenes

GP-2 Corey-Fuchs reaction [2]

The aldehyde (11.0 mmol) was added to a solution of PPh_3 (44.0 mmol, 11.52 g), CBr_4 (22.0 mmol, 7.30 g) in CH_2Cl_2 (40 mL) at 0 °C. The reaction mixture was stirred at r.t. for 30 min. Ice cold water (40 mL) was added and the reaction mixture extracted with hexane (5 x 25 mL). The combined organic phases were evaporated and the crude 1,1-dibromoalkene was purified by column chromatography on silica using hexane as eluent.

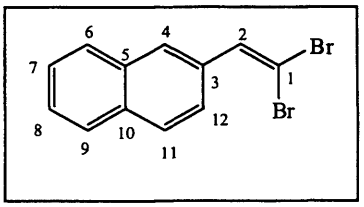
To a solution of the 1,1-dibromoolefin (8.45 mmol) in THF at –78 °C *n*-BuLi (2.2 equiv., 18.6 mmol, 2.5 M solution in hexane) was added. After stirring for 1 h at –78 °C, the reaction mixture was warm up to r.t. and stirred for 1 h. After aqueous work-up and extraction with diethyl ether (3 x 20 mL) the combined organic phases were evaporated and the crude product purified by column chromatography on silica (hexane) as eluent to afford the terminal acetylenes.



1-(2,2-Dibromovinyl)-3-methoxybenzene (130)

The title compound **130** was synthsized according to the **GP-2** from commercially available 3-methoxybenzaldehyde (**128**) (11.0 mmol, 1.50 g) in 78% yield (8.56 mmol, 2.50 g) as yellow oil. This is a known compound. Spectroscopic data are in agreement with literature [3].

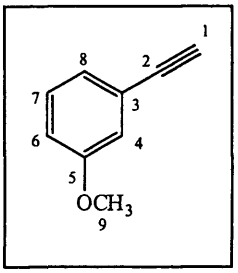
^{1}H-NMR ($CDCl_3$, 500 MHz): δ (ppm) = 3.75 (3H, s, 9-C*H*$_3$), 6.80-6.83 (2H, m, aromatic), 7.34 (1H, s, 2-C*H*), 7.44 (2H, m, 5-C*H* and 6-C*H*, aromatic).



2-(2,2-Dibromovinyl)naphthalene (131)

The title compound **131** was synthesised according to **GP-2** starting from commercially available 2-naphthaldehyde (**129**) (11.0 mmol, 1.72g) in 88% yield (9.68 mmol, 3 g) as colourless solid. This is a known compound. Spectroscopic data are in agreement with literature [4].

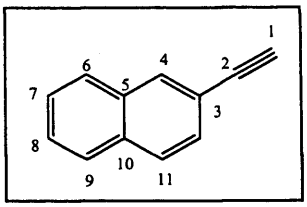
m.p. = 96 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.04 (1H, s, 4-C*H*, aromatic), 7.51-7.54 (2H, m, aromatic), 7.66-7.68 (2H, m), 7.84-7.88 (3H, m, aromatic).



1-Ethynyl-3-methoxybenzene (132b)

The title compound **132b** was obtained according to **GP-2** starting from 1-(2, 2-dibromovinyl)-3-methoxybenzene (**130**) (8.45 mmol, 2.47 g) as a colourless oil in 90 % yield (7.80 mmol, 1.03 g). This is a known compound. Spectroscopic data are in agreement with literature [5].

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 2.97 (1H, s, 1-C*H*), 3.68 (3H, s, 9-C*H*$_3$), 6.80 (1H, dd, *J* = 8.3 Hz, 2.5 Hz, 6-C*H*, aromatic), 6.92 (1H, d, *J* = 1.5 Hz, 4-C*H*, aromatic), 6.99 (1H, d, *J* = 7.6 Hz, 8-C*H*, aromatic), 7.12 (1H, t, *J* = 7.8 Hz , 7-C*H*, aromatic).



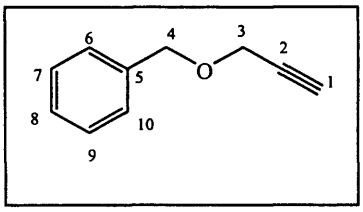
2-Ethynylnaphthalene (132c)

The title compound **132c** was synthesized according to **GP-2** starting from 2-(2,2-dibromovinyl)naphthalene (**131**) (8.45 mmol, 2.63 g) as colourless oil in 69% yield (5.78 mmol, 0.88 g). This is a known compound. Spectroscopic data are in agreement with literature [6].

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 3.17 (1H, s, 1-C*H*), 7.52-7.56 (3H, m, aromatic), 7.80-7.85 (3H, m, aromatic), 8.06 (1H, s, 4-C*H*, aromatic).

GP-3 Synthesis of propargyl ethers [7]

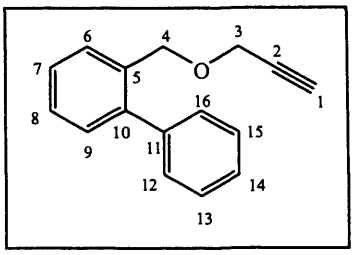
KOH (55.7 mmol, 3.12 g) and propargyl alcohol (18.5 mmol, 1.04 g) were dissolved in DMSO (15 mL) at 0 °C. After stirring for 10 min, the aryl bromide (19.0 mmol) was added at 0 °C. The reaction mixture was further stirred for 3 h at r.t. The resulting yellow/brown suspension was diluted with water (30 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic layer was again washed with water (40 mL), brine and dried over anhydrous $MgSO_4$. Filteration and evaporation of the solvents under reduced pressure afforded yellow oil. The crude product was purified by flash chromatography using ethyl acetate:hexane (1:10) as eluent affording the product as colourless oils.



{(Prop-2-ynyloxy) methyl} benzene (132d)

The title compound **132d** is synthesised according to **GP-3** by the reaction of propargyl alcohol (18.5 mmol, 1.04 g) with benzyl bromide (19.0 mmol, 3.5 g) as colourless oil in 59% yield (10.9 mmol, 1.59 g). This is a known compound. Spectroscopic data are in agreement with literature [5].

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.40 (1H, t, J = 2.4 Hz, 1-CH), 4.11 (2H, d, J = 2.4 Hz, 3-CH_2), 4.54 (2H, s, 4-CH_2), 7.23-7.31 (5H, m, aromatic).



{(Prop-2-ynyloxy) methyl} biphenyl (132e)

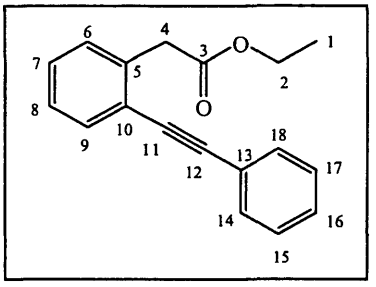
The title compound **132e** is synthesized according to **GP-3** by the reaction of propargyl alcohol (18.5 mmol, 1.04 g) with 2-phenylbenzyl bromide (19.0 mmol, 4.69 g) as colourless oil in 68% yield (12.6 mmol, 2.79 g). This is a known compound. Spectroscopic data are in agreement with literature [8].

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 2.45 (1H, t, J = 2.0 Hz, 1-C*H*), 4.20 (2H, dd, J = 1.0 Hz, 1.3 Hz, 3-CH_2), 4.57 (2H, d, J = 1.6 Hz, 4-CH_2), 7.38 (1H, d, J = 7.5 Hz, aromatic), 7.39-7.50 (7H, m, aromatic), 7.63 (1H, d, J = 7.8 Hz, aromatic).

Phenylacetylene (**132a**) and 1-heptyne (**132f**) were commercially purchased from *Alfa Aesar* and used without further purification.

GP-4 Sonogashira coupling products [9]

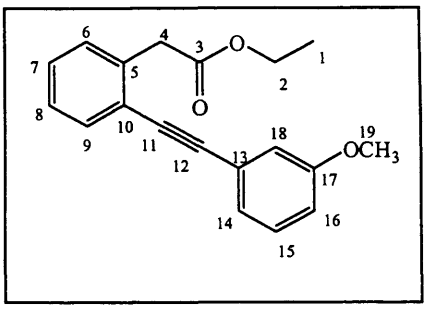
A mixture of aryl iodide (3.5 mmol), 10% Pd/C (0.12 mmol, 0.13 g), PPh_3 (0.65 mmol, 0.17 g), CuI (0.16 mmol, 0.03 g) and 2-aminoethanol (0.6 mL) in H_2O (11 mL) was stirred at 35 °C for 30 min under argon. To this reaction mixture terminal alkyne (5.1 mmol) was added. The reaction mixture was stirred at 85 °C for 10-24 h. The mixture was cooled to r.t. and ethyl acetate (60 mL) was added. After fitration of the reaction mixture through celite, the residue was purified by column chromatography using ethyl acetate:hexane (1:20) as eluent. The products were obtained as oils.



Ethyl 2-{2-(phenylethynyl)phenyl}acetate (137a)

The title compound **137a** was obtained according to **GP-4** by the reaction of ethyl ester of 2-iodophenylacetic acid (**136**) (3.5 mmol, 1.02 g) with phenyl acetylene (**132a**) as yellow oil in 76% yield (2.68 mmol, 0.71 g). This is a known compound. Spectroscopic data are in agreement with literature [1].

^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 1.27 (3H, t, J = 7.1 Hz, 1-CH_3), 3.96 (2H, s, 4-CH_2), 4.22 (2H, q, J = 7.1 Hz, 2-CH_2), 7.32-7.43 (6H, m, aromatic), 7.60-7.63 (3H, m, aromatic).



Ethyl 2-[2-{(3-methoxyphenyl)ethynyl}phenyl]acetate (137b)

The title compound **137b** was synthesised according to **GP-4** by the reaction of ethyl ester of 2-iodophenylacetic acid (**136**) (3.5 mmol, 1.02 g) with 3-methoxyphenylacetylene (**132b**) as yellow oil in 64% yield (2.24 mmol, 0.66 g).

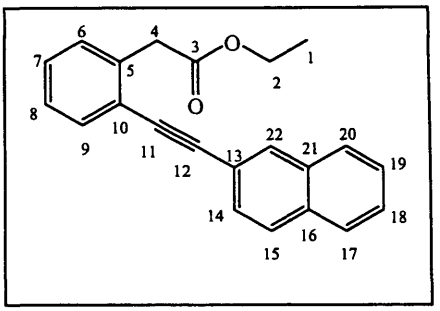
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.24 (3H, t, J = 7.1 Hz, 1-CH_3), 3.85 (3H, s, 19-CH_3), 3.92 (2H, s, 4-CH_2), 4.18 (2H, q, J = 7.1, 2-CH_2), 6.92 (1H, dd, J = 8.8, 2.5 Hz, aromatic), 7.09 (1H, d, J = 2.2 Hz, aromatic, 18-C*H*), 7.16 (1H, d, J = 7.6 Hz, aromatic), 7.27-7.34 (4H, m, aromatic), 7.56 (1H, d, J = 7.4 Hz, aromatic).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 14.2 (1-C), 40.3 (4-C), 55.3 (19-C), 60.9 (2-C), 87.3, 93.8, 115.0, 116.4, 123.5, 124.1, 124.2, 127.1, 128.6, 129.4, 129.9, 132.1, 136.5, 159.4, 171.2 (3-C).

LR-MS: m/z (% abundance of ions) = 312.2 ($M+NH_4$, 100%), 295.1 (82 %), 294.1 (13 %), 270.2 (5%), 178.2 (8 %), 52.2 (4 %).

IR neat: ν (cm^{-1}) = 2982 (w), 2936 (w), 1733 (s), 1596 (w), 1573 (w), 1457 (w), 1321 (w), 1231 (m), 1157 (m), 1034 (m), 757 (m), 682 (w).

HR-MS: $[M+H]^+$ Calcd for $[C_{19}H_{18}O_3.H]^+$: 295.1329; found: 295. 1333.



Ethyl2-{2-{(naphthalene-2-yl)ethynyl}phenyl]acetate (137c)

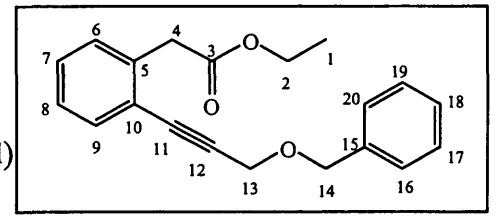
The title compound **137c** was synthesised according to **GP-4** by the reaction of ethyl ester of 2-iodophenylacetic acid (**136**) (3.5 mmol, 1.02 g) with 2-ethynylnaphthalene **(132c)** as yellow oil in 60% yield (2.10 mmol, 0.66 g).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.28 (3H, t, J = 7.1 Hz, 1-CH_3), 4.02 (2H, s, 4-CH_2), 4.24 (2H, q, J = 7.1 Hz, 2-CH_2), 7.33-7.39 (3H, m, aromatic), 7.53-7.56 (2H, m, aromatic), 7.65 (2H, d, J = 8.0 Hz, aromatic), 7.85-7.88 (3H, m, aromatic), 8.12 (1H, s, aromatic).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 14.3 (1-C), 40.4 (4-C), 61.0 (2-C), 88.0, 94.4, 120.6, 123.6, 126.7, 126.8, 127.0, 127.2, 127.6, 127.9, 128.1, 128.4, 128.6, 130.0, 131.4, 132.2, 133.1, 136.6, 171.3 (3-C).

IR neat: ν (cm^{-1}) = 3052 (w), 2988 (w), 2360 (w), 1724 (s), 1461 (w), 1364 (w), 1244 (s), 1184 (m), 1027 (m), 819 (m), 755 (m).

HR-MS: $[M+NH_4]^+$ Calcd for $[C_{22}H_{18}O_2.NH_4]^+$ 332.1645; found: 332.1647.



Ethyl 2-[2-{3-(benzyloxy)prop-1-ynyl}phenyl]acetate (137d)

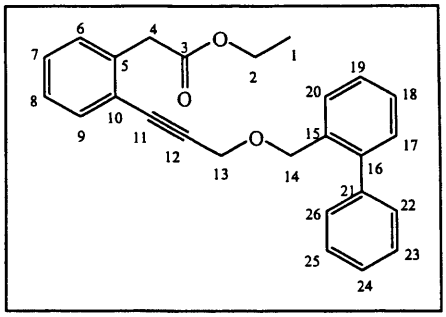
The title compound **137d** was synthesized according to the **GP-4** by the reaction of ethyl ester of 2-iodophenylacetic acid (**136**) (3.5 mmol, 1.02 g) with {(Prop-2-ynyloxy) methyl}benzene (**132d**) as yellow oil in 42% (1.47 mmol, 0.45 g) yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.25 (3H, t, J = 7.1 Hz, 1-CH_3), 3.87 (2H, s, 4-CH_2), 4.17(2H, q, J = 7.1Hz), 4.46 (2H, s, 13-CH_2), 4.71(2H, s, 14-CH_2), 7.26- 7.35 (4H, m, aromatic), 7.38-7.44 (4H, m, aromatic), 7.51 (1H, d, J = 7.4 Hz, aromatic).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 14.2 (1-C), 40.0 (4-C), 57.9 (13-C), 60.9 (2-C), 71.6 (14-C), 84.6, 89.5, 123.0, 127.1, 127.9, 128.2 (2xC), 128.5 (2xC), 128.7, 129.8, 132.5, 136.5, 137.5, 171.1 (3-C).

IR neat: ν (cm^{-1}) = 2978 (w), 2951 (w), 2849 (w), 1733 (s), 1248 (m), 1207 (m), 1156 (m), 1068 (m), 1027 (m), 755 (m), 695 (w).

HR-MS: $[M+NH_4]^+$ Calcd for $[C_{20}H_{20}O_3.NH_4]^+$ 326.1751; found: 326.1753.



Ethyl 2-[2-{(3-biphenyl-2-ylmethoxy) prop-1-ynyl} phenyl] acetate (137e)

The title compound **137e** was synthesised according to **GP-4** by the reaction of ethyl ester of 2-iodophenylacetic acid (**136**) (3.5 mmol, 1.02 g) with ((Prop-2-ynyloxy) methyl) biphenyl (**132e**) in 48% yield (1.69 mmol, 0.65 g) as colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.26 (3H, t, J = 7.1 Hz, 1-CH_3), 3.81 (2H, s, 4-CH_2), 4.17 (2H, q, J = 7.1 Hz, 2-CH_2), 4.45 (2H, s, 13-CH_2), 4.64 (2H, s, 14-CH_2), 7.28(1H, t, J = 7.1 Hz), 7.34-7.48 (11H, m), 7.66 (1H, d, J = 8.7 Hz).

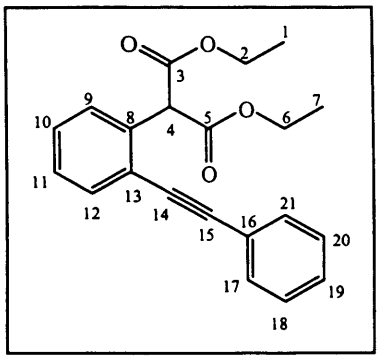
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 14.3 (1-C), 40.0 (4-C), 58.2 (13-C), 60.9 (2-C), 69.7 (14-C), 84.6, 89.7, 123.0, 127.0, 127.2, 127.5, 128.0, 128.2, 128.7, 129.4, 129.72, 129.74, 130.1, 132.5, 134.9, 136.5, 140.8, 142.3, 171.1 (3-C).

IR neat: ν (cm^{-1}) = 3052 (w), 2978 (w), 2932 (w), 2849 (w), 2360 (w), 1733 (s), 1479 (w), 1437 (w), 1244 (w), 1207 (w), 1156 (m), 1068 (m), 1027 (w), 755 (m), 699 (w).

HR-MS: $[M+NH_4]^+$ Calcd for $[C_{26}H_{24}O_3.NH_4]^+$ 402.2064; found: 402.2066.

GP-5 Synthesis of Diethyl malonate derivatives [1]

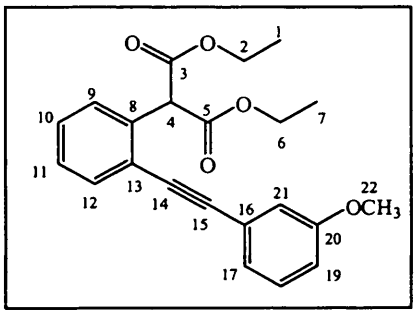
To a solution of compounds **136** or **137** (1.6 mmol) in diethylcarbonate (10 mL) NaH (60% in mineral oil, 7.2 mmol, 0.29 g) was added. The resulting mixture was stirred at room temperature for 15 h. The reaction was poured into a saturated aqueous solution of ammonium chloride (10 mL) and extracted with diethyl ether (3 x 15mL). The ether extract was adsorbed on silica gel. The crude product mixture was subjected to flash chromatography by using ethyl acetate:hexane (1:10) as eluent.



Diethyl 2-(2-phenylethynyl)phenyl}malonate (138a)

The title compound **138a** was synthesised according to **GP-5** by the reaction of compound **137a** (1.6 mmol, 0.42 g) with diethylcarbonate and NaH as yellow oil in 76% (1.21 mmol, 405.0 mg) yield. This is a known compound. Spectroscopic data are in agreement with literature [1].

^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 1.27-1.37 (6H, m, 1, 7-C*H*$_3$), 4.21-4.33 (4H, m, 2, 6-C*H*$_2$), 5.43 (1H, s, 4-C*H*), 7.35-7.41 (5H, m, aromatic), 7.53-62 (4H, m, aromatic).



Diethyl 2-[2-{(3-methoxyphenyl)ethynyl}phenyl]malonate (138b)

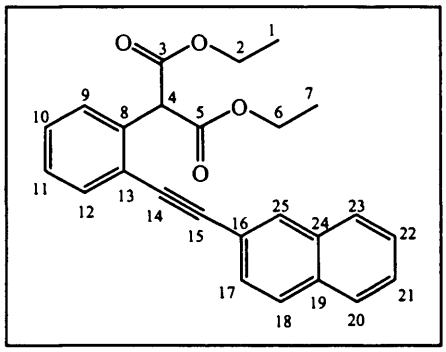
The title compound **138b** was synthesised according to **GP-5** by the reaction of compound **137b** (1.6 mmol, 0.47 g) with diethylcarbonate and NaH as a yellow oil in 79% yield (1.26 mmol, 0.46 g).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.19 (6H, t, *J* = 7.1 Hz, 1, 7-CH_3), 3.76 (3H, s, 22-CH_3), 4.12-4.20 (4H, m, 2, 6-CH_2), 5.29 (1H, s, 4-CH), 6.84 (1H, dd, *J* = 8.3 Hz, 2.5 Hz, aromatic), 7.06 (1H, sd, J = 2.5 Hz, aromatic), 7.08 (1H, d, *J* = 7.6 Hz), 7.19 (1H, t, *J* = 7.9 Hz, aromatic), 7.25 (1H, t, *J* = 7.5 Hz, aromatic), 7.29 (1H, t, *J* = 7.7 Hz, aromatic), 7.40 (1H, dd, *J* = 7.8 Hz, 1.5 Hz), 7.49 (1H, dd, *J* = 7.5 Hz, 1.4 Hz, aromatic).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 14.1 (1, 7-C), 55.4 (22-C), 56.1 (4-C), 61.9 (2, 6-C), 86.7, 94.5, 115.1, 116.5, 123.7, 123.9, 124.2, 127.9, 128.6, 128.7, 129.5, 132.1, 135.0, 159.4, 168.2 (3, 5-C).

IR neat: ν (cm^{-1}) = 2972 (w), 2927 (w), 1751 (s), 1732 (s), 1596 (w), 1572 (w), 1491 (w), 1457 (w), 1226 (m), 1148 (m), 1034 (m), 783 (w), 755 (m).

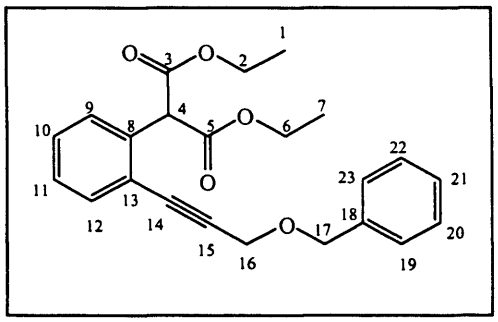
LR-MS: m/z (% abundance of ion) = 384.2 ($M+NH_4$, 58%), 367.1 (100%), 221.4 (7%), 178.2 (26%).
HR-MS: $[M+H]^+$ Calcd for $[C_{22}H_{22}O_5.H]^+$ 367.1540; found: 367.1537.



Diethyl 2-{2(naphthalene-2-ylethynyl)phenyl}malonate (138c)

The title compound **138c** was synthesised according to **GP-5** by the reaction of compound **137c** (1.6 mmol, 502 mg) with diethylcarbonate and NaH as yellow oil in 74% yield (1.18 mmol, 456 mg).

^1H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.20 (6H, t, J = 7.1 Hz, 1,7-CH_3), 4.15-4.22 (4H, m, 2,6-CH_2), 5.37 (1H, s, 4-CH), 7.25-7.33 (2H, m, aromatic), 7.41-7.45 (3H, m, aromatic), 7.51 (2H, td, J = 7.6 Hz, 1.1Hz, aromatic), 7.74-7.77 (3H, m, aromatic), 7.99 (1H, s, aromatic).
^{13}C NMR (125 MHz, $CDCl_3$): 14.1 (1, 7-C), 56.2 (4-C), 61.9 (2, 6-C), 87.3, 95.0, 120.2, 123.8, 126.7, 126.9, 127.83, 127.84, 128.0, 128.1, 128.3, 128.68, 128.71, 131.5, 132.1, 132.97, 133.0, 135.0, 168.2 (3, 5-C).
LR-MS: m/z (% abundance of ion) = 404.4 ($M+NH_4$, 34%), 387.3 (100%), 386.3 (32%), 241.4 (5%), 178.2 (25%), 161.4 (11%).
IR neat: ν (cm^{-1}) = 3062 (w), 2978 (w), 1751 (s), 1733 (s), 1502 (w), 1451 (w), 1364 (w), 1304 (m), 1216 (w), 1142 (m), 1027(m), 815 (w), 750 (m).
HR-MS: $[M+H]^+$ Calcd for $[C_{25}H_{22}O_4.H]^+$ 387.1591; found: 387.1590.



Diethyl 2-[2-{3-(benzyloxy)prop-1-ynyl}phenyl]malonate (138d)

The title compound **138d** was synthesised according to **GP-5** by the reaction of compound **137d** (1.6 mmol, 0.49 g) with diethylcarbonate and NaH as yellow oil in 59% (0.94 mmol, 356.0 mg) yield.

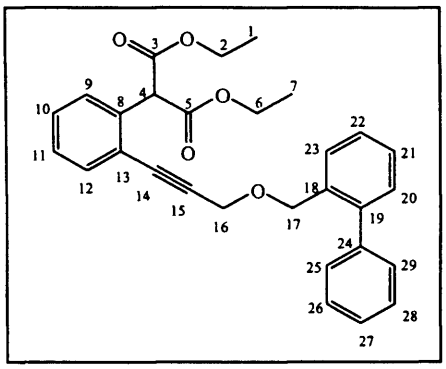
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.27 (6H, t, J = 7.1 Hz, 1, 7-CH_3), 4.20-4.29 (4H, m, 2, 6-CH_2), 4.46 (2H, s, 16-CH_2) 4.71 (2H, s, 17-CH_2), 5.34 (1H, s, 4-CH), 7.31-7.35 (2H, m, aromatic), 7.37-7.43 (5H, m, aromatic), 7.52-7.54 (2H, m, aromatic).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 14.1 (1, 7-C), 55.7 (4-C), 57.8 (16-C), 61.9 (2, 6-C), 71.6 (17-C), 84.1, 90.2, 123.2, 127.9 (2xC), 128.2 (2xC), 128.5 (2xC), 128.8, 128.9, 132.5, 134.9, 137.4, 168.0 (3, 5-C).

LR-MS: m/z (% abundance) = 398.3 (100 %, M+NH_4), 381.3 (24 %), 275.3 (42 %), 274.3 (11 %), 178.2 (32 %), 107.3 (36 %), 91.1 (18 %), 52.2 (43 %).

IR neat: ν (cm^{-1}) = 2978 (w), 2923 (w), 2859 (w), 1751 (s), 1728 (s), 1451 (w), 1304 (w), 1211 (w), 1147 (w), 755 (m), 695 (w).

HR-MS: $[M+NH_4]^+$ Calcd for $[C_{23}H_{24}O_5.NH_4]^+$ 398.1962; found: 398.1962.



Diethyl 2-[2-{3-(biphenyl-2-ylmethoxy)prop-1-ynyl}phenyl]malonate (138e)

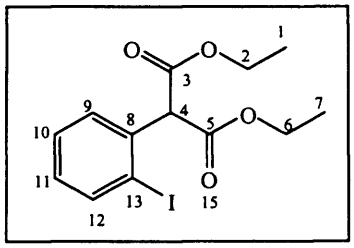
The title compound **138e** was synthesised according to **GP-5** by the reaction of compound **137e** (1.6 mmol, 0.61 g) with diethylcarbonate and NaH as pale yellow oil in 72% yield (1.15 mmol, 0.52 g).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.25 (6H, J = 7.1 Hz, 1,7-CH_3), 4.18-4.25 (4H, m, 2, 6-CH_2), 4.41 (2H, s, 16-CH_2), 4.58 (2H, s, 17-CH_2), 5.27 (1H, s, 4-CH), 7.31 (1H, dd, J = 7.6, 1.3 Hz, aromartic), 7.32-7.36 (2H, m, aromatic), 7.37-7.44 (8H, m, aromatic), 7.51 (1H, d, J = 7.1 Hz, aromatic), 7.60-7.62 (1H, m, aromatic).

^{13}C NMR ($CDCl_3$, 125MHz): δ (ppm) = 14.0 (1, 7-C), 55.7 (4-C), 58.1 (16-C), 61.8 (2, 6-C), 69.7 (17-C), 83.9, 90.3, 123.2, 127.2, 127.5, 127.9, 128.0, 128.1, 128.7, 128.8, 129.3, 129.8, 130.1, 132.5, 134.7, 134.9, 140.7, 142.3, 168.0 (3, 5-C).

IR neat: ν (cm^{-1}) = 3052 (w), 2978 (w), 2895 (w), 2369 (w), 1747 (s), 1733 (s), 1474 (w), 1438 (w), 1364 (w), 1304 (w), 1216 (w), 1147(m), 1073 (m), 1027 (w), 755 (m), 699 (w).

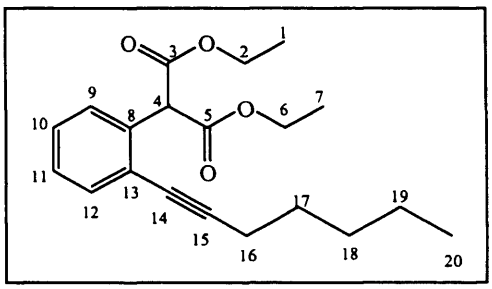
HR-MS: $[M+NH_4]^+$ Calcd for $[C_{29}H_{28}O_5.NH_4]^+$ 474.2275; found: 474.2271.



Diethyl 2-(2-iodophenyl) malonate (53)

The title compound was synthesised according to **GP-5** by the reaction of ethyl ester of 2-iodophenylacetic acid (**136**) (1.6 mmol, 0.46 g) with diethylcarbonate and NaH as a yellow oil in 76% yield (1.22 mmol, 0.44 g). This is a known compound. Spectroscopic data are in agreement with literature [1].

^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 1.31 (6H, t, J = 7.1 Hz, 1,7-2xCH_3), 4.28 (4H, m, J = 7.1 Hz, 2,6- 2xCH_2), 5.15 (1H, s, 4-CH), 7.03 (1H, td, J = 7.8 Hz, 1.7 Hz, 11-C*H*, aromatic), 7.40 (1H, t, J = 7.8 Hz, 10-C*H*, aromatic), 7.50 (1H, dd, J = 7.8 Hz, 1.7 Hz, 9-C*H*, aromatic), 7.88 (1H, dd, J = 1.7 Hz, 7.9 Hz, 12-C*H*, aromatic).



Diethyl 2-{2-(hept-1-ynyl)phenyl}malonate (138f)

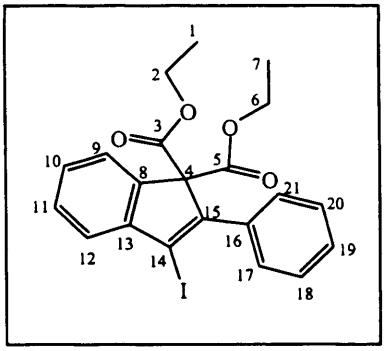
The title compound was synthesised according to **GP-4** by the reaction of diethyl 2-(2-iodophenyl) malonate (**53**) (3.5 mmol, 1.27 g) with 1-heptyne (**132f**) as yellow oil in 52% yield (1.82 mmol, 0.55 g). This is a known compound. Spectroscopic data are in agreement with literature [1].

^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 0.95 (3H, t, J = 7.0 Hz , 20-CH_3), 1.30 (6H, *t*, J = 7.1 Hz, 1,7-2xCH_3), 1.38-1.71 (6H, m, 17, 18, 19-CH_2), 2.46 (2H, t, J = 7.0 Hz , 16-CH_2), 5.35 (1H, s, 4-C*H*), 7.27-7.36 (2H, m, aromatic), 7.44-7.49 (2H, m, aromatic).

GP-6 Iodocarbocyclisation reactions

(a) 2-Substituted alkynyl malonate **138** (0.13 mmol) was dissolved in THF (6 mL) followed by the addition of 60% NaH in oil (1.5 equiv., 0.195 mmol). The reaction mixture was stirred for 15 min at r.t. Elemental iodine (1.5 equiv., 0.195 mmol) was added and the reaction mixture was refluxed for 2 h. The reaction mixture was cooled to r.t. After addition of aqueous sat. sodium thiosulfate (5 mL), the reaction mixture was extracted with diethyl ether (3 x 10 mL). The combined organic phases were washed with brine (5 mL) and water (5 mL). The organic layer was dried over anhydrous Na_2SO_4. After filteration and evaporation of the solvent at reduced pressure, the reaction mixture was purified by column chromatography using ethyl acetate : hexane (1:10) eluent (entries 1, 2, 3, 4, and 5, Table 3, Chapter 2).

(b) 2-Substituted alkynyl malonate **138** (0.13 mmol) was dissolved in THF (6 mL) and NaO*t*Bu (1.5 equiv., 0.195 mmol, 19.0 mg) was added. The reaction mixture was stirred for 5 min at r.t. Elemental iodine (1.5 equiv., 0.195 mmol, 49.53 mg) was added and the reaction mixture refluxed for 2 h. After addition of sat. sodium thiosulfate (5 mL), the reaction mixture was extracted with diethyl ether (3 x 10 mL). The combined organic phases were washed with brine (5 mL) and water (5 mL). The organic layer was dried over anhydrous Na_2SO_4. After filteration and evaporation of the solvent at reduced pressure, the reaction mixture was purified by column chromatography using ethyl acetate:hexane (1:10) eluent (entry 3, Table 2, and entry 6, Table 3, Chapter 2). This reaction can be performed at r.t. stirring without reflux for several hours (entry 4, Table 2, Chapter 2).



Diethyl 3-iodo-2-phenyl-*1H*-indene-1,1-dicaboxylate (139a) [12]

The title compound **139a** was synthesised according to **GP-6** from precursor molecule **138a** (0.13 mmol, 44 mg) as yellow crystalline solid in 77% Yield (0.10 mmol, 47 mg).

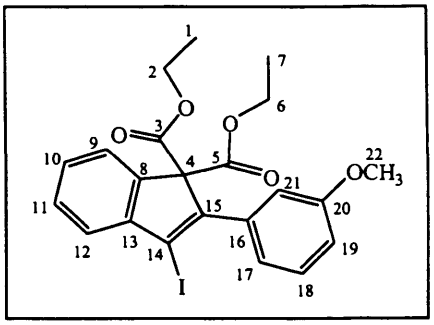
mp = 83°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.02 (6H, t, *J* = 7.1 Hz, 1, 7-CH_3), 4.02-4.09 (4H, m, 2, 6-CH_2), 7.27 (1H, td, *J* = 7.5 Hz, 1.0 Hz, aromatic), 7.30-7.34 (6H, m, aromatic), 7.39 (1H, td, *J* = 7.5, 0.6 Hz, aromatic), 7.51 (1H, d, *J* = 7.5 Hz, aromatic).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 13.8 (1, 7-C), 62.2 (2, 6-C), 73.6 (4-C), 102.9 (14-C), 123.7, 124.2, 127.7, 127.9 (2xC), 128.4, 129.2, 129.8 (2xC), 136.3, 139.4, 145.2, 147.9, 166.9 (3, 5-C).

IR neat: ν (cm^{-1}): 2978 (w), 2914 (w), 1719 (s), 1456 (w), 1262 (w), 1202 (w), 1032 (w), 750 (w), 700 (w).

LR-MS: m/z (% abundance of ion) = 480.2 ($M+NH_4$, 38 %), 463.1 (22%), 357.4 (6%), 356.4 (34%), 354.3 (68%), 337.2 (100 %), 284.4 (18 %), 282.3 (56 %), 108.3 (5 %), 52.3 (83 %).

HR-MS: $[M+H]^+$ Calcd for $[C_{21}H_{19}O_4I.H]^+$ 463.0401; found: 463.0403.



Diethyl 3-iodo-2-(3-methoxyphenyl)-*1H*-indene-1,1-dicarboxylate (139b) [12]

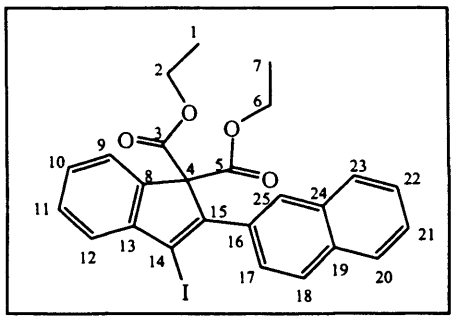
The title compound **139b** was synthesised according to **GP-6** by the reaction of precursor molecule **138b** (0.13 mmol, 48 mg) with NaH and iodine as yellow oil in 78% yield (0. 101 mmol, 50 mg).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.03 (t, 6H, *J* = 7.1 Hz, 1, 7-C*H*$_3$), 3.75 (s, 3H, 22-C*H*$_3$), 4.02-4.1 (4H, m, 2, 6-CH_2), 6.84 (1H, dd, *J* = 8.3 Hz, 2.5 Hz, aromatic), 6.90 (1H, d, *J* = 7.6 Hz, aromatic), 6.93 (1H, d, *J* = 2.0 Hz, aromatic, 21-C*H*), 7.23 (1H, t, *J* = 8.0, aromatic), 7.26 (1H, t, *J* = 7.5 Hz, aromatic), 7.35 (1H, d, *J* = 7.5 Hz, aromatic), 7.39 (1H, t, *J* = 7.5 Hz, aromatic), 7.50 (1H, d, *J* = 7.5 Hz, aromatic).

^{13}C NMR (125 MHz, $CDCl_3$):13.8 (1, 7-C), 55.3 (22-C), 62.2 (2, 6-C), 73.6 (4-C), 102.9 (14-C), 114.0, 115.5, 122.2, 123.6, 124.2, 127.7, 128.9, 129.2, 137.5, 139.4, 145.2, 147.7, 159.1, 166.9 (3, 5-C).

IR neat: ν (cm^{-1}) = 2972(w), 2930(w), 1728(s), 1605(w), 1528(w), 1445(m), 1230(s), 1043(m), 760 (m).

HR-MS: $[M+H]^+$ Calcd for $[C_{22}H_{21}O_5I.H]^+$ 493.0506; found: 493.0505.



Diethyl 3-iodo-2-(naphthalen-2-yl)-*1H*-indene-1,1-dicarboxylate (139c) [12]

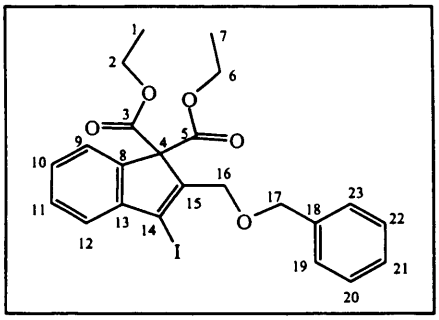
The title compound **139c** was synthesised according to **GP-6** by the reaction of precursor molecule **138c** (0.13 mmol, 50.2 mg) with NaH and iodine as yellow oil in 71% yield (0.092 mmol, 47.1 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.00 (6H, t, *J* = 7.1 Hz, 1, 7-C), 4.01-4.11(4H, m, 2, 6-C), 7.28 (1H, td, *J* = 7.5 Hz, 1.3 Hz), 7.34 (1H, d, *J* = 7.2 Hz), 7.40-7.46 (4H, m, aromatic), 7.54 (1H, d, *J* = 7.6 Hz, aromatic), 7.77-7.83 (4H, m, aromatic).

^{13}C NMR (125 MHz, $CDCl_3$): 13.8 (1, 7-C), 62.2 (2, 6-C), 73.7 (4-C), 103.3 (14-C), 123.6, 124.3, 126.1, 126.5, 127.3, 127.6, 127.71, 127.74, 128.3, 129.27, 129.29, 132.9, 133.1, 133.8, 139.5, 145.3, 147.8, 166.9 (3, 5-C).

IR neat: ν (cm^{-1}) = 3052 (w), 2978 (w), 1714 (s), 1442 (w), 1262 (m), 1216 (m), 1064 (w), 745(m), 723 (w).

HR-MS: $[M+H]^+$ Calcd for $[C_{25}H_{21}O_4I.H]^+$ 513.0557; found: 513.0548.



Diethyl 2-(benzyloxymethyl)-3-iodo-*1H*-indene-1,1-dicarboxylate (139d) [12]

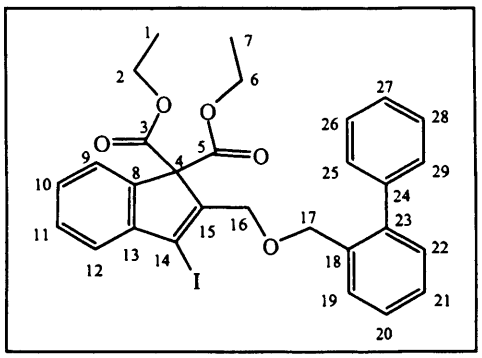
The title compound **139d** was synthesised according to **GP-6** by the reaction of precursor molecule **138d** (0.13 mmol, 49.4 mg) with NaH and iodine as yellow oil in 67% yield (0.087 mmol, 44.0 mg).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.11 (6H, t, *J* = 7.1 Hz, 1, 7-CH_3), 4.00-4.10 (4H, m, 2, 6-CH_2), 4.46 (2H, s, 16-CH_2), 4.58 (2H, s, 17-CH_2), 7.20 (1H, d, *J* = 7.1 Hz, aromatic), 7.23-7.30 (6H, m, aromatic), 7.35 (1H, t, *J* = 8.4 Hz, aromatic), 7.52 (1H, d, *J* = 8.1 Hz, aromatic).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 13.9 (1, 7-C), 62.3 (2, 6-C), 68.3 (16-C), 71.1 (17-C), 72.9 (C-4), 103.7, 123.2, 124.6, 127.6, 127.85, 127.87 (2xC), 128.2 (2xC), 129.0, 138.3, 139.7, 144.6, 144.9, 166.9 (3, 5-C).

IR neat: ν (cm^{-1}) = 2969 (w), 2859 (w), 1733 (s), 1456 (w), 1359 (w), 1230 (s), 1087 (w), 1050 (w), 755 (w), 695 (w).

HR-MS: $[M+H]^+$ Calcd for $C_{23}H_{24}O_5I$ 507.0663; found: 507.0654.



Diethyl 2-{(biphenyl-2-ylmethoxy) methyl}-3-iodo-1*H*-indene-1,1-dicarboxylate (139e) [12]

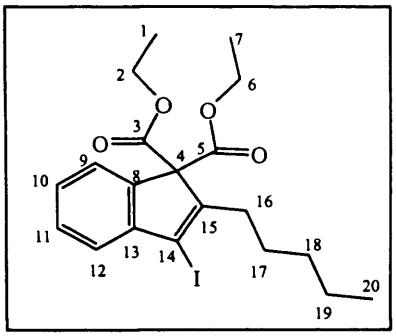
The title compound **139e** was synthesised according to **GP-6** by the reaction of precursor molecule **138e** (0.13 mmol, 59.3 mg) with NaH and iodine as yellow oil in 62% yield (0.080 mmol, 47.0 mg).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.05 (6H, t, J = 7.1 Hz, 1, 7-CH_3), 3.97-4.05 (4H, m, 2, 6-CH_2), 4.37 (2H, s, 16-CH_2), 4.51 (2H, s, 17-CH_2), 7.19-7.35 (11H, m, aromatic), 7.50 (2H, t, J = 8.1 Hz, aromatic).

^{13}C NMR (125 MHz, $CDCl_3$): 12.8 (1, 7-C), 61.2 (2, 6-CH_2), 67.3 (16-C), 69.9 (17-C), 70.1 (4-C), 102.4 (14-C), 122.1, 123.6, 126.1, 126.3, 126.5, 126.8, 127.1 (2xC), 128.0, 128.3 (3xC), 128.8, 134.4, 138.5, 139.8, 140.6, 143.6, 143.9, 165.9 (3, 5-C).

IR neat: ν (cm^{-1}) = 3052 (w), 2978 (w), 2859 (w), 1733 (s), 1469 (w), 1235 (s), 1198 (w), 1050 (m), 750 (m), 699 (w).

HR-MS: $[M+NH_4]^+$ Calcd for $[C_{29}H_{27}O_5I.NH_4]^+C_{29}H_{31}NIO_5$ 600.1241; found 600.1232.



Diethyl 3-iodo-2-pentyl-1*H*-indene-1, 1-dicarboxylate (139f) [12]

The title compound **139f** was synthesised according to **GP-6** by the reaction of precursor molecule **138f** (0.13mmol, 39.3 mg) with NaO*t*-Bu and iodine as yellow oil in 71% yield (0.092 mmol, 42 mg).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 0.84 (3H, t, J = 6.9 Hz, 20-CH_3), 1.17 (6H, t, J = 7.1 Hz, 1, 7-CH_3), 1.30-1.48 (6H, m, 17, 18, 19-CH_2), 2.56 (2H, t, J = 5.9 Hz, 16-CH_2), 4.08-4.17 (4H, m, 2, 6-CH_2), 7.15 (1H, d, J = 7.5, aromatic), 7.17 (1H, td, J = 7.5, 1Hz, aromatic), 7.31 (1H, td, J = 7.5Hz, 1.0 Hz, aromatic), 7.44 (1H, d, J = 7.5, aromatic).

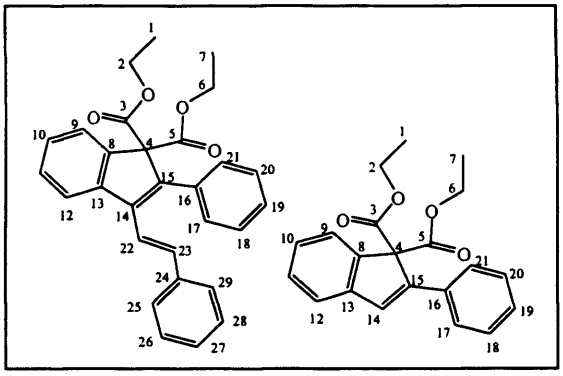
^{13}C NMR (125MHz, $CDCl_3$): 14.0 (1, 7-C), 14.1 (20-C), 22.4 (19-C), 27.8 (18-C), 31.3 (17-C), 32.3 (16-C), 62.2 (2, 6-CH_2), 71.9 (4-C), 100.2 (14-C), 122.1, 124.4, 126.8, 129.0, 138.9, 145.25, 149.2, 167.3 (3, 5-C).

IR (neat): ν (cm^{-1}) = 2970 (m), 2925 (m), 2858 (v), 1735 (s), 1457 (w), 1235 (s), 1096 (w), 1046 (m), 752 (m).

HR-MS: $[M+H]^+$ Calcd. for $[C_{20}H_{26}O_4I.H]$ 457.0870; found: 457.0871.

GP-7 Heck reaction of 3-iodo-1*H*-indene [10, 12]

3-Iodo-*1H*-indene **139a** (0.3g, 0.649 mmol), Pd $(OAc)_2$ (0.14 equiv., 0.0909 mmol, 20.3 mg), PPh_3 (0.2 equiv., 0.1298 mmol, 34 mg), styrene (1.2 equiv., 0.78 mmol, 81 mg) and Et_3N in excess were heated at 110°C for 16h. The reaction mixture was cooled to r.t. The solid products were isolated by diluting the reaction mixtures with 200 ml of 10% aq. hydrochloric acid with stirring to dissolve the salts and excess of amine. The crude product was extracted with ethyl acetate (3 x 20 mL). The combined organic phases were dried with $MgSO_4$ and evaporated under reduced pressure. Finally, the crude product was purified by column chromatography. The mixture was absorbed into silica and subjected to column chromatography by using ethyl acetate and hexane (1:20) as eluent to furnish mixture of compounds **147** and **148** as yellow oil in 96% overall yield. A 1:1 ratio for mixture of compounds **147** and **148** is established on the basis of ^{1}H NMR and GC-MS analysis.



(*E*)-Diethyl-2-phenyl-3-styryl-*1H*-indene-1,1-dicarboxylate (147) and Diethyl-2-phenyl-*1H*-indene-1,1-dicarboxylate (148)

The title compounds **147** and **148** were synthesised according to **GP-7**. The compound **147** is a mixture along with compound **148** as yellow oil in 48% (0.311 mmol, 136.5 mg) yield.

^{1}H-NMR (500MHz, $CDCl_3$): δ 6.92 (1H, d, J = 16.8 Hz). Rest of the proton signals are merged alongwith compound **148**.

^{1}H NMR (500 MHz, $CDCl_3$): 6.94 (1H, d, J = 17.5 Hz), Most of signals are merged with each other.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8, 62.0, 72.6, 121.6, 122.1, 124.8, 126.6, 126.7, 127.8, 127.9, 128.0, 128.68, 128.72, 130.4, 133.4, 135.4, 137.4, 140.5, 141.3, 142.0, 143.3, 168.2.

IR neat: ν (cm^{-1}) = 2971(w), 2921 (w), 1457 (w), 1717 (s), 1234 (m).

LR-MS: *m/z* (% abundance of ion) = 439.3(4%), 438.2 (M^+, 11%), 337.2 (10%), 336.2 (45%), 318.2 (15%), 289.2 (26%), 291.2 (100%), 91.1 (12%), 77.2 (11%). The compound **148** is obtained in 48% (0.311 mol, 104.5 mg) yield. This is a known compound. Spectroscopic data are in agreement with literature [1].

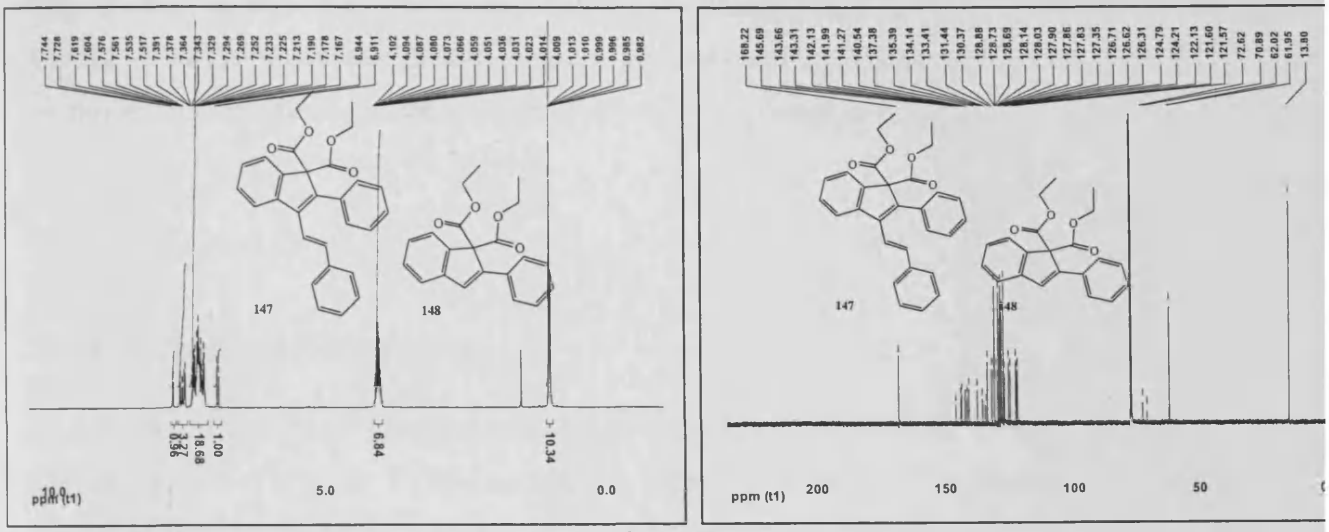
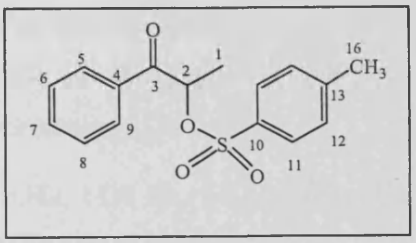


Figure 1. (a) ^{1}H NMR (500 MHZ, $CDCl_3$) (b)^{13}C NMR (125 MHz, $CDCl_3$) of mixture **147** & **148**.

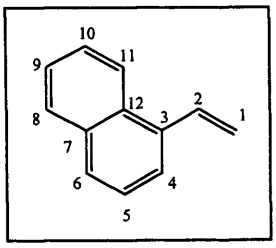


GP-8 1-Oxo-1-phenylpropan-2-yl-4-methylbenzenesulfonate (150)

The title compound **150** was synthesised by the reaction of propiophenone (1.05 mmol, 0.14 g) in CH_3CN (1 mL) was added to a solution of 3-iodo-1*H*-indene **139a** (0.0105 mmol, 48.51 mg), *p*TsOH. H_2O (3 equiv., 3.15 mmol, 0.54 g) and *m*CPBA (3 equiv., 3.15 mmol, 77% wet with H_2O, 0.705 g) in acetonitrile (2mL) at r.t. The resulting solution was stirred at r.t. for 80h then quenched by the addition of sat. aqueous $Na_2S_2O_3$ (5mL) and sat. aqueous Na_2CO_3 (5mL). The mixture was extracted with EtOAc (3 x 5 mL), the combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 80:20 hexane: ethyl acetate) to yield tosylate **150** (5.59 mmol, 0.17 g, 53%) as a white powder. This is a known compound [11].

^{1}H NMR (250 MHz, $CDCl_3$): 1.52 (3H, d, J = 6.9 Hz, 1-CH_3), 2.33 (1H, s, 16-CH_3), 5.71 (1H, q, J = 6.9 Hz, 2-C*H*), 7.21 (2H, d, J = 8.3 Hz , aromatic), 7.38 (2H, m, aromatic), 7.52 (1H, t, J = 7.3 Hz , aromatic), 7.68 (2H, d, J = 8.3 Hz , aromatic), 7.80 (2H, d, J = 7.9 Hz, aromatic).

The styrene (**228a**), 4-methylstyrene (**228b**), 4-chlorostyrene (**228c**), 2-vinylnaphthalene (**228d**), 2,6-dichlorostyrene (**228e**), and 2-chlorostyrene (**228f**) used in this study were commercially available with the exception of 1-vinyl naphthalene (**228g**).



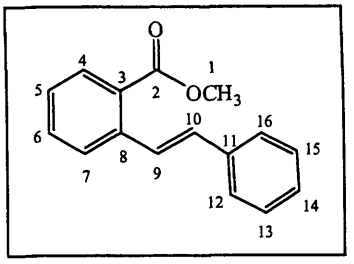
GP-9 1-Vinylnaphthalene (228g)

A mixture of CH_3PPh_3Br (12.9 mmol, 4.61 g) and KO*t*Bu (14.0 mmol, 1.57g) in dry toluene (30 mL) stirred at 0 °C for 30 min and further stirred at r.t for 4 h. The reaction mixture was cooled to 0 °C followed by addition of 1-naphthaldehyde (**227**) (11.8 mmol, 1.84 g). The reaction mixture was stirred overnight at r.t. The solvent was evaporated under reduced pressure. The crude product was purified by column chromatography using hexane as eluent to yield the title compound **228g** (11.8 mmol, 1.816 g, 100%) as colourless oil. This is a known compound. Spectroscopic data are in agreement with literature [13].

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 5.69 (1H, dd, J = 1.45 Hz, 11.0 Hz, 1-C*H*), 6.06 (1H, dd, J = 17.3 Hz, 1.45 Hz, 1-C*H*), 7.64-7.72 (4H, m), 7.85 (1H, d, J = 7.1 Hz, aromatic), 7.99 (1H, d, J = 8.2 Hz, aromatic), 8.06 (1H, d, J = 8.1 Hz), 8.34 (1H, d, J = 8.1 Hz, aromatic).

GP-10 Mizoroki-Heck Reaction

A mixture of methyl 2-iodo-benzoate **229** (15.26 mmol, 4.0 g), styrene (1.2 equiv., 18.24 mmol, 1.87 g), triethylamine (32.0 mmol, 3.26 g, 4.4 mL), palladium acetate (0.14 equiv., 2.1 mmol, 470.4 mg) and triphenylphosphine (0.2 equiv., 3.0 mmol, 786 mg) were heated under reflux at 100-110 °C for 5-16 h. Solid products were isolated by diluting the reaction mixtures with 200 ml of 10% aq. hydrochloric acid with stirring to dissolve the salts and excess of amine. The crude product was extracted with ethyl acetate (3 x 20 mL). The combined organic phases were dried over $MgSO_4$ and evaporated under reduced pressure. Finally, the crude product was purified by column chromatography (EtOAc:hexane, 1:12) [10, 14].

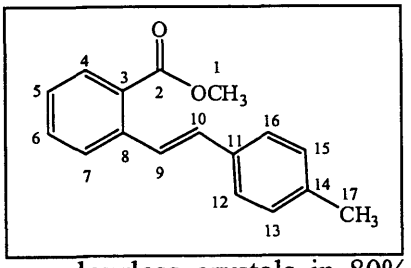


(*E*)-Methyl 2-styrylbenzoate (230a)

The title compound **230a** was obtained according to **GP-10** and isolated as yellow oil in 87 % yield (13.23 mmol, 3.15 g) after purification. This is a known compound. Spectroscopic data are in agreement with literature [15].

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 3.96 (3H, s, 1-*CH*$_3$) 7.04 (1H, d, *J* = 16.0 Hz, 10-C*H*), 7.31-42 (4H, m, aromatic), 7.54 (1H, td, *J* = 8.0 Hz, 1.1 Hz, aromatic), 7.60 (2H, d, *J* = 7.5 Hz, aromatic), 7.76 (1H, d, *J* = 8.0 Hz, aromatic), 7.97 (1H, dd, *J* = 8.0 Hz, 1.3 Hz, aromatic), 8.03 (1H, d, *J* = 16.0 Hz, 9-C*H*).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 52.2 (1-C), 126.9 (2xC), 127.0, 127.2, 127.5, 127.9, 128.6, 128.7 (2xC), 130.7, 131.5, 132.2, 137.5, 139.3, 167.9 (2-C).



(*E*)-Methyl 2-(4-methylstyryl)benzoate (230b)

The title compound **230b** was obtained according to **GP-10** as colourless crystals in 80% yield (12.19 mmol, 3.07 g) after purification. This is a known compound. Spectroscopic data are in agreement with literature [16].

m.p.: 74 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 2.29 (3H, s, 17-C*H*$_3$), 3.85 (3H, s, 1-C*H*$_3$), 6.92 (1H, d, *J* = 16.2 Hz, 10-*CH*), 7.10 (2H, d, *J* = 7.5 Hz, aromatic), 7.23 (1H, td, *J* = 7.5 Hz, 1.1 Hz, aromatic), 7.38 (2H, d, *J* = 8.0 Hz, aromatic), 7.44 (1H, td, *J* = 7.5 Hz, 1.3 Hz, aromatic), 7.64 (1H, d, *J* = 8.0 Hz, aromatic), 7.84 (1H, d, *J* = 8.0 Hz, aromatic), 7.88 (1H, d, *J* = 16.2 Hz, 9-C*H*).

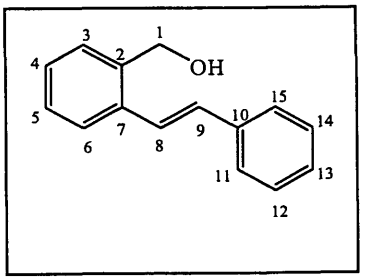
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 21.3 (17-C), 52.1 (1-C), 126.4, 126.8 (2xC), 126.9, 127.0, 128.5, 129.4 (2xC), 130.7, 131.4, 132.1, 134.7, 137.8, 139.4, 168.0 (2-C).

IR (ν): (cm^{-1}) = 3041 (w), 2936 (w), 1715 (s), 1591(w), 1510 (w), 1289 (w), 1255 (w), 1242 (w), 1126 (w), 1073 (w), 962 (w), 804 (w), 740 (w).

HR-MS (ESI): $[M + H]^+$ Calcd. for $[C_{17}H_{16}O_2.H]^+$ 253.1223; found: 253.1222.

GP-11 Reduction of 2-substituted stilbenes esters

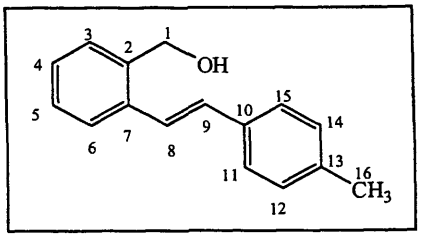
A solution of corresponding ester (9.0 mmol) dissolved in dry diethyl ether (20 mL) was added to suspension of $LiAlH_4$ (10.8 mmol, 410.4 mg) in dry diethyl ether (100 mL) at 0 °C. After stirring for 2-15 h at r.t., the reaction was quenched with few drops of water at 0 °C followed by the addition of few drops of 1M aqueous NaOH solution. The reaction was further diluted with with 2 mL of water. The resulting mixture was stirred for half an hour until organic phase was separated from white precipitate. The white precipitates were filtered, washed with ethyl acetate (3x10mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography with petroleum ether/ethyl acetate (4:1) as eluent to give corresponding alcohols in good yields [17, 18].



(*E*)-(2-Styrylphenyl)methanol (231a)

The title compound **231a** was obtained according to **GP-11** by the reaction of corresponding ester **230a** (9.0 mmol, 2.14 g) with $LiAlH_4$ (10.8 mmol, 410.4 mg) to give 92 % yield (8.28 mmol, 1.74 g) of the alcohol **231a** as colourless crystals after purification. This is a known compound. Spectroscopic data are in agreement with literature [19].

m.p.: 103 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 4.86 (2H, s, 1-C*H*$_2$), 7.08 (1H, d, *J* = 16.2 Hz, 8-C*H*), 7.30-7.42 (6H, m, aromatic), 7.48 (1H, d, *J* = 16.2 Hz, 9-C*H*), 7.57 (2H, d, *J* = 7.5 Hz, aromatic), 7.70 (1H, d, *J* = 7.5 Hz, aromatic).
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 63.7 (1-C), 125.4, 126.0, 126.7 (2xC), 127.8, 127.9, 128.3, 128.6, 128.7 (2xC), 131.3, 136.4, 137.4, 137.9.



(*E*)-(2-(4-methylstyryl)phenyl)methanol (231b)

The title compound **231b** was obtained according to **GP-11** by the reaction of corresponding ester **230b** (9.0 mmol, 2.26 g) with $LiAlH_4$ (10.8 mmol, 410 mg) to gave 88 % yield (7.9 mmol, 1.76 g) as colourless crystals after purification. This is a known compound. Spectroscopic data are in agreement with literature [16].

m.p.: 127 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 2.29 (3H, s, 16-C*H*$_3$), 4.75 (2H, s, 1-C*H*$_2$), 6.95 (1H, d, *J* = 16.0 Hz, 9-C*H*), 7.11-7.08 (2H, m, aromatic), 7.19-7.30 (4H, m), 7.35 (2H, d, *J* = 8.0 Hz, aromatic), 7.58 (1H, d, *J* = 7.2 Hz, aromatic).

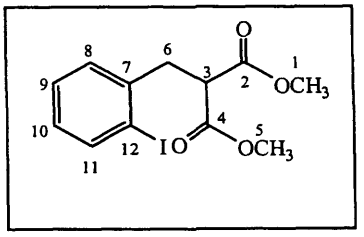
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 21.3 (16-C), 63.7 (1-C), 124.3, 125.9, 126.6 (2xC), 127.6, 128.3, 128.6, 129.4 (2xC), 131.2, 134.6, 136.6, 137.75, 137.80.

IR neat: υ (cm^{-1}) = 3356 (broad peak OH), 3025 (w), 2917 (w), 2863 (w), 1512 (w), 1478 (w), 1044 (m), 966 (m), 809 (m), 750 (w), 717 (w).

HR-MS: $[M+NH_4]^+$ Calcd for $[C_{16}H_{16}O.NH_4]^+$: 242.1539; found: 242.1540.

GP-12 Synthesis of malonate derivatives [20]

To a solution of corresponding alcohol (7.0 mmol) in CH_2Cl_2 (25 mL) Et_3N (9.0 mmol, 918.0 mg) and methanesulfonyl chloride (8.0 mmol, 916.0 mg) were added at 0 °C. After being stirred for 1 h at r.t. the mixture was poured into 10% aqueous HCl (15 mL) and extracted with ether (3 x 15mL). The combined organic phases were dried on $MgSO_4$ and evaporated under reduced pressure. The mesylate was dissolved in dry THF (5 mL) and added to a solution of NaH (60 % in mineral oil, 9.0 mmol, 0.36 g) and dimethylmalonate (9 mmol, 1.18 g) in THF (30 mL), then the reaction mixture was refluxed for 6-36 h. The mixture was poured into 10% aqueous HCl (15 mL) and extracted with diethyl ether (3 x 20 mL). The combined diethyl ether extracts were dried over $MgSO_4$ and evaporated under reduced pressure. The residue was subjected to flash chromatography (12:1 hexane/EtOAc) to give the malonate derivatives.

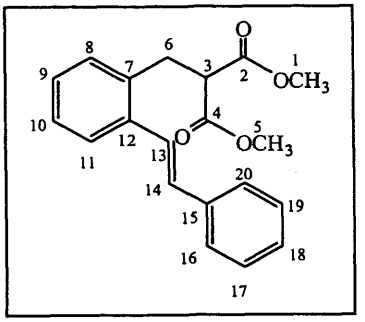


Dimethyl 2-(2-iodobenzyl)malonate (234)

The title compound **234** was prepared according to **GP-12** by the reaction of 2-iodobenzyl alcohol (**233**) (11 mmol, 2.57 g) in 68 % yield (8.28 mmol, 2.60 g) as colourless oil. This is a known compound. Spectroscopic data are in agreement with literature [20].

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 3.35 (2H, d, *J* = 7.8 Hz, 6-C*H*$_2$), 3.72 (6H, s, 1, 5-C*H*$_3$), 3.88 (1H, t, *J* = 7.8 Hz, 3-C*H*), 6.94(1H, td, *J* = 8.0 Hz, 2.1Hz aromatic), 7.28-7.23 (2H, m, aromatic), 7.84 (1H, dd, *J* = 8.0 Hz, 1.1 Hz, aromatic).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 39.4 (6-C), 51.6 (3-C), 52.6 (1, 5-C), 100.4 (12-C), 128.4, 128.8, 130.5, 139.8, 140.2, 168.9 (2, 4-C).



(*E*)-Dimethyl 2-(2-styrylbenzyl)malonate (232a) [16]

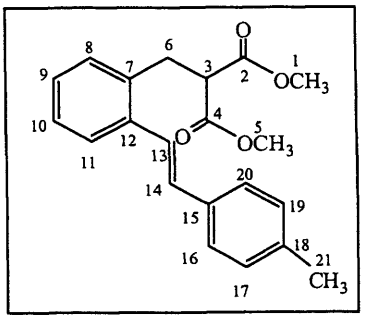
The title compound **232** was prepared by **GP-12** starting from corresponding alcohol **231a** (9.52 mmol, 2 g) as yellow oil in 40% yield (3.79 mmol, 1.23 g).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 3.43 (2H, d, *J* = 7.5 Hz, 6-C*H*$_2$), 3.70-3.73 (7H, m, 1, 5-CH_3 and 3-C*H*), 7.05 (1H, d, *J* = 16.0 Hz, 14-C*H*), 7.22 (2H, d, *J* = 7.5 Hz), 7.32-7.29 (2H, m), 7.39-743 (3H, m), 7.57 (2H, d, *J* = 8.0 Hz, aromatic), 7.64 (1H, d, *J* = 8.0 Hz, aromatic).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 32.4 (6-C), 52.7 (1, 5-C), 52.9 (3-C), 125.4, 126.1, 126.7 (2xC), 127.5, 127.8, 127.9, 128.8 (2xC), 130.2, 131.2, 135.5, 136.3, 137.4, 169.3 (2, 4-C).

IR: υ (cm^{-1}) = 3022 (w), 2944 (w), 2840 (w), 1752 (s), 1739 (s), 1595 (w), 1491 (w), 1436 (w), 1341 (w), 1280 (w), 1228 (w), 1155 (w), 1025 (w), 965 (w), 762 (w), 693 (w).

HR-MS (ES): $[M+NH_4]^+$ Calcd. for $[C_{20}H_{20}O_4.NH_4]^+$: 342.1700; found: 342.1702.



(*E*)-Dimethyl 2-{2-(4-methylstyryl)benzyl}malonate (232b) [21]

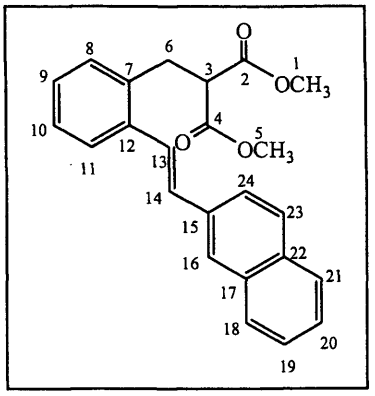
The title compound **232b** was prepared by **GP-12** starting from corresponding alcohol **231b** (7.5 mmol, 1.68 g) as yellow oil in 53% yield (3.97 mmol, 1.34 g).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 2.29 (3H, s, 21-C*H*$_3$), 3.32 (2H, d, *J* = 7.5 Hz, 6-C*H*$_2$), 3.62-3.60 (m, 7H, 1, 5-C*H*$_3$ and 3-C*H*), 6.92 (1H, d, *J* = 16 Hz, 14-C*H*), 7.09-7.17 (5H, m, aromatic), 7.26 (1H, d, *J* = 16.0 Hz, 13-C*H*), 7.36 (2H, d, *J* = 8.0 Hz, aromatic), 7.52 (1H, d, *J* = 7.5 Hz, aromatic).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 21.3 (21-C), 32.4 (6-C), 52.6 (1, 5-C), 52.9 (3-C), 124.4, 126.0, 126.6, 127.4, 127.6 (2xC), 129.5 (2xC), 130.2, 131.1, 134.7, 135.4, 136.5, 137.8, 169.3 (2, 4-C).

IR neat: υ (cm^{-1}): 2952 (w), 2917 (w), 2847 (w), 1750 (s), 1736 (s), 1600 (w), 1511 (w), 1432 (w), 1273 (w), 1225 (w), 1155 (w), 750 (w).

HR-MS: $[M+NH_4]^+$ Calcd for $[C_{21}H_{22}O_4.NH_4]^+$: 356.1856; found: 356.1855.



(*E*)-Dimethyl 2-[2-{2-(naphthalen-2-yl)vinyl}benzyl]malonate (232c) [21]

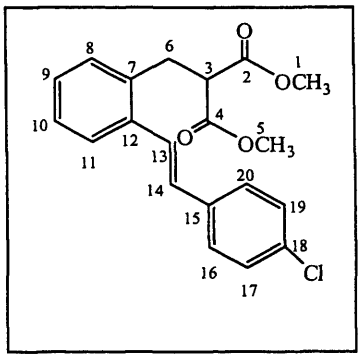
The title compound **232c** was prepared by the Mizoroki-Heck reaction of compound **234** (1.43 mmol, 0.5 g) with 2-vinylnaphthalene (**228c**) (1.71 mmol, 0.26 g) according to **GP-10** as colourless crystalline solid in 76 % yield (1.09 mmol, 0.41 g).

mp: 133-134 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 3.49 (2H, d, *J* = 7.5 Hz, 6-C*H*$_2$), 3.73 (6H, s, 1, 5-*CH*$_3$), 3.77 (1H, t, *J* = 8.0 Hz, 3-*CH*), 7.24 (1H, d, *J* = 16 Hz, 14-C*H*), 7.26-7.34 (3H, m, aromatic), 7.50 (2H, t, *J* =7.5 Hz, aromatic), 7.57 (1H, d, *J* = 16 Hz, 13-C*H*), 7.71 (1H, d, *J* = 8.0 Hz, aromatic), 7.81-7.91 (5H, m, aromatic).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 32.4 (6-C), 52.6 (1, 5-C), 53.0 (3-C), 123.6, 125.8, 126.05, 126.09, 126.4, 126.9, 127.5, 127.75, 127.82, 128.1, 128.4, 130.3, 131.3, 133.2, 133.7, 134.9, 135.6, 136.4, 169.3 (2, 4-C).

IR neat: ν (cm^{-1}) = 3446 (H_2O), 3031 (w), 2924 (w), 2851 (w), 1751 (s), 1733 (s), 1436 (w), 1339 (w), 1282 (w), 1220 (w), 1151 (w), 740 (w).

HR-MS: $[M+NH_4]^+$ calc. for $C_{24}H_{26}NO_4$: 392.1856; found: 392.1858.



(*E*)-Dimethyl 2-{2-(4-chlorostyryl)benzyl}malonate (232d) [21]

The title compound **232d** was prepared by the Mizoroki-Heck reaction of compound **234** (1.436 mmol, 0.5 g) with 4-chlorostyrene (**228d**) (1.71 mmol, 237 mg) according to **GP-10** as yellow oil in 72 % yield (1.034 mmol, 370.8 mg).

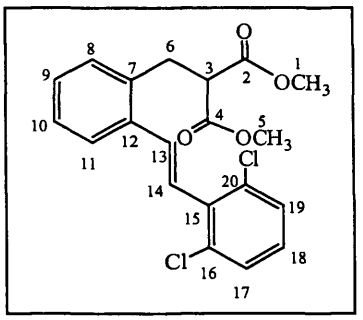
^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 3.32 (2H, d, J = 7.5 Hz, 6-CH_2), 3.59-3.62 (7H, m, 3-C*H* and 1, 5-CH_3), 6.89 (1H, d, J = 16 Hz, 14-C*H*), 7.14-7.11 (3H, m), 7.31-7.26 (3H, m), 7.39 (2H, d, J = 8.5 Hz, aromatic), 7.52 (1H, d, J = 7.5 Hz, aromatic).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 32.3 (6-C), 52.7 (1, 5-C), 52.9 (3-C), 126.1 (2xC), 127.5, 127.9 (2xC), 128.0, 128.9 (2xC), 129.8, 130.2, 133.4, 135.6, 135.9, 136.0, 169.2 (2, 4-C).

IR neat: ν (cm^{-1}) = 3470 (H_2O), 3065 (w), 3028 (w), 2952 (w), 2844 (w), 1749 (s), 1736 (s), 1599 (w), 1493 (m), 1435 (w), 1347 (w), 1275 (w), 1229 (w), 1153 (w), 1091, 1049 (w), 813 (w), 756 (w).

HR-MS: $[M+NH_4]^+$ Calcd. for $[C_{20}H_{19}O_4Cl.NH_4]^+$: 376. 1310 (100 % rel. abundanc); found: 376.1314 (100% rel. abundance) [^{35}Cl isotope].

$[M+NH_4]^+$ Calcd. for $[C_{20}H_{19}O_4Cl.NH_4]^+$: 378. 1281 (32% rel. abundance); found: 378.1284 (32% rel. abundance) [^{37}Cl isotope].



(*E*)-Dimethyl 2-{2-(2,6-dichlorostyryl)benzyl}malonate (232e) [21]

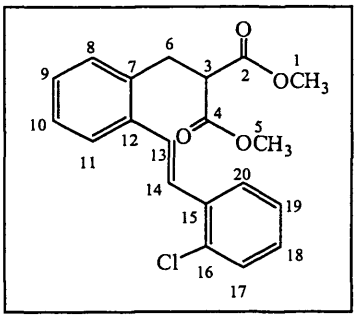
The title compound **232e** was prepared by the Mizoroki- Heck reaction of compound **234** (1.436 mmol, 0.5 g) with 2,6-dichlorostyrene (**228e**) (1.71 mmol, 296 mg) according to **GP-10** as yellow oil in 66% (0.947 mmol, 372 mg) as a yellow crystalline solid.

mp: 82-83 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 3.29 (2H, d, *J* = 6.5 Hz, 6-C*H*$_2$), 3.61 (6H, s, 1, 5-C*H*$_3$), 3.69 (1H, t, *J* = 6.5 Hz, 3-C*H*), 6.95 (1H, d, *J* = 16.5 Hz, 14-C*H*), 7.05 (1H, t, *J* = 8.0 Hz, aromatic), 7.12-7.24 (3H, m, aromatic), 7.29 (2H, d, *J* = 8.0 Hz, aromatic), 7.35 (1H, d, *J* = 16.5 Hz, 13-C*H*), 7.69 (1H, d, *J* = 8.0 Hz, aromatic).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 32.3 (6-C), 52.6 (1, 5-C), 52.8 (3-C), 125.3, 126.6, 127.5, 128.25, 128.33, 128.6 (2xC), 130.3, 134.1, 134.57, 134.61, 135.7, 136.2, 169.2 (2, 4-C).

IR neat: υ (cm^{-1}) = 3063 (w), 3015 (w), 2954 (w), 2928 (w), 2870 (w), 1740 (s), 1723 (s), 1578 (w), 1483 (w), 1454(w), 1432 (w), 1321(w), 1251 (m), 1161 (m), 1022 (w), 763 (m), 708 (w).

HR-MS: $[M+NH_4]^+$ Calcd for $[C_{20}H_{18}O_4Cl_2.NH_4]$: 410.0920; found: 410.0926 [^{35}Cl isotope].



(*E*)-Dimethyl 2-{2-(2-chlorostyryl)benzyl}malonate (232f) [21]

The title compound **232f** was prepared by the Mizoroki-Heck reaction of compound **234** (1.436 mmol, 0.5 g) with 2-chlorostyrene **228f** (1.71 mmol, 237 mg) according to **GP-10** as yellow oil in 73 % yield (1.05 mmol, 376 mg).

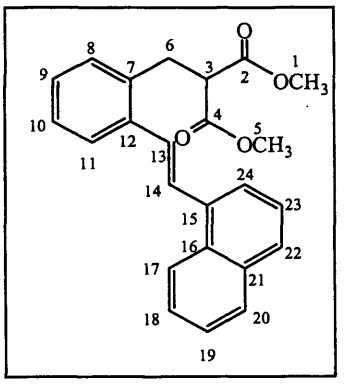
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 3.44 (2H, d, *J* = 7.5 Hz, 6-C*H*$_2$), 3.70-3.73 (7H, m, 3-C*H* and 1, 5-C*H*$_3$), 7.23-7.32 (5H, m), 7.41-7.44 (3H, m), 7.69 (1H, d, *J* = 7.5 Hz, aromatic), 7.77 (1H, d, *J* = 8.0 Hz, aromatic).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 32.2 (6-C), 52.6 (1, 5-C), 53.0 (3-C), 126.5, 126.8, 127.0, 127.2, 127.5, 128.1, 128.2, 128.7, 129.9, 130.2, 133.5, 135.5, 135.7, 136.2, 169.2 (2, 4-C).

IR neat: υ (cm^{-1}) = 3454 (H_2O), 3063, 3024 (w), 3015, 2952 (w), 1737 (s), 1723 (s), 1626 (w), 1487 (w), 1436 (m), 1348 (w), 1276 (m), 1260 (m), 1153 (w), 1049 (w), 751 (s).

HR-MS: $[M+NH_4]^+$ Calc. for $[C_{20}H_{19}O_4Cl.NH_4]^+$: 376.1310 (100% rel. abundance); found: 376.1315 (100% rel. abundance) [^{35}Cl isotope].

$[M+NH_4]^+$ Calc. for $[C_{20}H_{19}O_4Cl.NH_4]^+$: 378.1281 (32% rel. abundance); found: 378.1284 (32% rel. abundance) [^{37}Cl isotope].



(*E*)-Dimethyl 2-[2-{2-(naphth-1-yl)vinyl}benzyl]malonate (232g) [21]

The title compound **232g** was prepared by Mizoroki-Heck reaction of compound **234** (1.436 mmol, 0.5 g) with 1-vinylnaphthalene **228g** (1.71 mmol, 0.26 g) according to **GP-10** as yellow oil in 89 % yield (1.25 mmol, 0.47 g).

^1H NMR (500 MHz, $CDCl_3$): δ (ppm) = 3.35 (2H, d, *J* = 7.5 Hz, 6-C*H*$_2$), 3.58 (6H, s, 1, 5-C*H*$_3$), 3.65 (1H, t, *J* = 7.5 Hz, 3-C*H*), 7.13- 7.25 (3H, m), 7.33 (1H, d, *J* = 16.0 Hz), 7.42-7.48 (3H, m), 7.65 (1H, d, *J* = 7.5 Hz, aromatic), 7.75-7.70 (3H, m), 7.80 (1H, d, *J* = 7.5 Hz), 8.14 (1H, d, *J* = 8.0 Hz, aromatic).

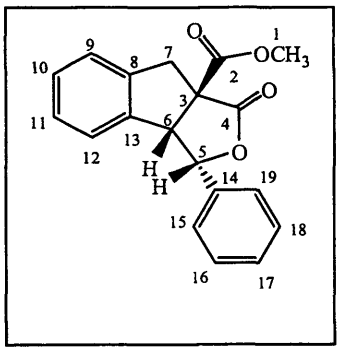
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 32.3 (6-C), 52.6 (1, 5-C), 52.9 (3-C), 123.8, 123.9, 125.8, 125.9, 126.2, 126.5, 127.5, 127.9, 128.3, 128.4, 128.6, 128.7, 130.2, 131.4, 133.8, 135.0, 135.6, 136.8, 169.2 (2, 4-C).

IR neat: υ (cm^{-1}) = 3032 (w), 2925 (w), 2851 (w), 1750 (s), 1736 (s), 1437 (w), 1221 (m), 1153 (w), 752 (w).

HR-MS: $[M+NH_4]^+$ Calcd for $[C_{24}H_{22}O_4.NH_4]^+$: 392.1856; found: 392.1858.

GP-13 Double cyclisation to indanes and tetrahydronaphthalenes

Sodium hydride (60% in oil, 1.5-2.5 equiv., 0.285 mmol-0.475 mmol) was added to a solution of stilbene malonate (0.19 mmol) in THF (15 mL) and the reaction mixture was stirred for five minutes at r.t. Iodine (1.5-2.5 equiv., 0.285 mmol-0.475 mmol) was added to the reaction mixture and heated to reflux for 1.5-3.5h. The reaction mixture was cooled to r.t. and a saturated solution of $Na_2S_2O_3$ (10 mL) was added. The aqueous layer was extracted with diethyl ether (2 x 15 mL). The combined organic phases were washed with water (2 x 5 mL) and brine (4 mL). After evaporation of the solvent in vacuum the crude mixture was purified by flash chromarography (EtOAc:hexane, 1:20). For some experiments KO*t*Bu (0.285 mmol, 1.5 equiv.) and K_2CO_3 (0.57 mmol, 3 equiv.) were used as bases instead of NaH (Table 1, entry 5, 6, Chapter 3).



(3*S,3a*R**,8a*S**)-Methyl 1-oxo-3-phenyl-3,3a,8,8a-tetrahydro-1*H*-indeno[2,1-c]furan-8a-carboxylate (242a)** [21]

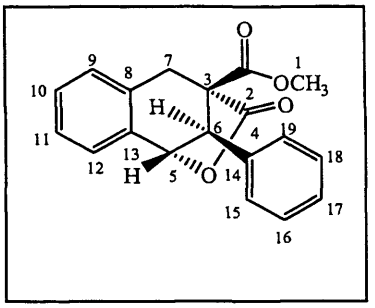
The title compound **242a** was prepared by the reaction of compound **232a** (0.19 mmol, 62 mg) as starting material according to **GP-13** as colourless crystalline solid in 52% yield (0.103 mmol, 32 mg).

m.p.: 131 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 3.63-3.67 (2H, m, 7-C*H*$_2$), 3.85 (3H, s, 1-C*H*$_3$), 4.41 (1H, d, *J* = 6.3 Hz, 6-C*H*), 5.58 (1H, d, *J* = 8.0 Hz, 12-C*H*), 6.08 (1H, d, *J* = 6.3 Hz, 5-C*H*), 6.72 (1H, t, *J* = 7.5 Hz, 11-C*H*), 7.07 (1H, t, *J* = 7.5 Hz, aromatic), 7.12 (3H, d, *J* = 7.5 Hz, aromatic), 7.28-7.31 (3H, m, aromatic).

^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) = 39.2 (7-C), 53.5 (1-C), 56.9 (6-C), 62.5 (3-C), 83.0 (5-C), 124.6, 126.2 (2xC), 126.4, 126.8, 128.40 (2xC), 128.43, 128.7, 134.9, 135.7, 141.0, 169.3 (1-C), 175.4 (4-C).

IR neat: υ (cm^{-1}) = 3066 (w), 2917 (w), 2947 (w), 1775 (s), 1734 (s), 1481 (w), 1436 (w), 1455 (w), 1247 (m), 1150 (m), 1027 (w), 762 (w).

HR-MS: $[M+NH_4]^+$ Calc. for $[C_{19}H_{16}O_4.NH_4]^+$: 326.1387; found: 326.1390.



(1*S,4*S**,10*S**)-Methyl 3-oxo-10-phenyl-1,3,4,5-tetrahydro-1,4-methanobenzo[*c*]-oxepine-4-carboxylate (243a)** [21]

The title compound **243a** was prepared by using compound **232a** (0.19 mmol, 62 mg) as starting material according to **GP-13** as yellow oil in 18% yield (0.034 mmol, 11 mg).

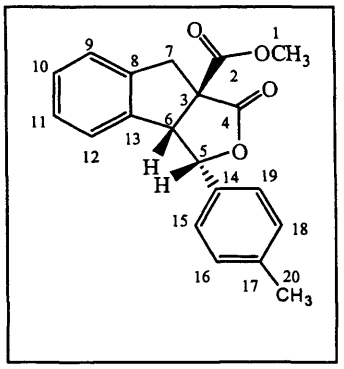
^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 3.56 (3H, s, 1-C*H*$_3$), 3.61-3.80 (2H, m, 7-C*H*$_2$), 4.31 (1H, d, *J* = 3.0 Hz, 6-C*H*), 5.49 (1H, d, *J* = 3 Hz, 5-C*H*), 7.20-7.32 (6H, m, aromatic), 7.37-7.39 (3H, m, aromatic).

^{13}C-NMR ($CDCl_3$, 125 MHz): δ (ppm) = 40.5 (7-C), 53.2 (1-C), 60.0 (6-C), 60.5 (3-C), 86.0 (5-C), 123.9, 125.1, 125.2 (2xC), 128.1, 128.5, 128.8 (2xC), 128.9, 139.0, 139.9, 140.7, 170.0 (1-C), 175.3 (2-C).

IR neat: υ (cm^{-1}) = 3435 (H_2O), 2954 (w), 2923 (w), 2852 (w), 1784 (s), 1736 (s), 1625 (w), 1560 (w), 1540 (w), 1458 (w), 1436 (w), 1247 (w), 1144 (w), 1035 (w), 799 (w), 762 (w), 698 (w).

HRMS: $[M+NH_4]^+$ calc. for $[C_{19}H_{16}O_4.NH_4]^+$: 326.1387; found: 326.1390.

NOE Experiment on compound **243a:** The proton at 4.31 ppm was irradiated and only a 4.93% enhancement in the signal for proton at 5.49 ppm was observed.



(3*S,3a*R**,8a*S**)-Methyl 1-oxo-3-(*p*-tolyl)-3,3a,8,8a-tetrahydro-1*H*-indeno[1,2-*c*]furan-8a-carboxylate (242b)** [21]

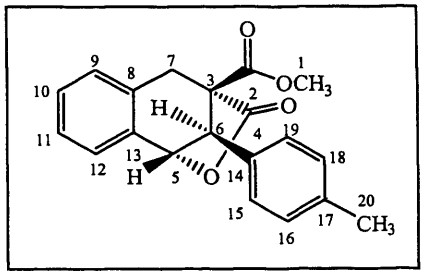
The title compound **242b** was prepared by using compound **232b** (0.19 mmol, 64.22 mg) as starting material according to **GP-13** as colourless crystalline solid in 53% yield (0.1 mmol, 32.42 mg).

m.p.: 136 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) = 2.32 (3H, s, 20-CH_3), 3.58-3.63 (2H, m, 7-CH_2), 3.84 (3H, s, 1-CH_3), 4.38 (1H, d, J = 6.5 Hz, 6-C*H*), 5.64 (1H, d, J = 7.5 Hz, 12-C*H*), 6.05 (1H, d, J = 6.5 Hz, 5-C*H*), 6.74 (1H, t, J = 7.5 Hz, 11-C*H*), 6.99 (2H, d, J = 7.5 Hz, aromatic), 7.08-7.13 (4H, m, aromatic).

^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) = 21.3 (20-C), 39.2 (7-C), 53.5 (1-C), 56.9 (6-C), 62.5 (3-C), 83.1 (5-C), 124.5, 126.2 (2xC), 126.4, 126.9, 128.3, 129.1 (2xC), 131.8, 135.8, 138.5, 141.0, 169.4 (1-C), 175.4 (4-C).

IR neat: υ (cm^{-1}) = 3446 (H_2O), 3025 (w), 2956 (w), 2925 (w), 2853 (w), 1770 (s), 1735 (s), 1608 (w), 1516 (w), 1431 (w), 1252 (w), 1182 (m), 1156 (m), 1021 (w), 751 (w).

HR-MS: $[M+NH_4]^+$ Calcd for $[C_{20}H_{18}O_4.NH_4]^+$: 340.1543; found: 340.1539.



(1*S,4*S**,10*S**)-Methyl 3-oxo-10-(*p*-tolyl)-1,3,4,5-tetrahydro-1,4-methanobenzo[*c*]- oxepine-4-carboxylate (243b)** [21]

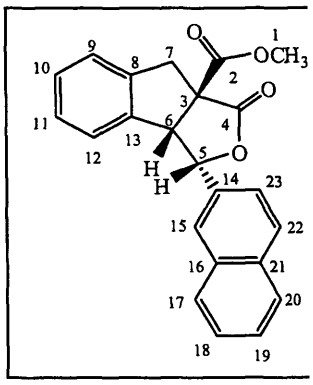
The title compound **243b** was prepared by using compound **232b** (0.19 mmol, 64.22 mg) as starting material according to **GP-13** as yellow oil in 24% yield (0.045 mmol, 15 mg).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 2.31 (s, 3H, 20-CH_3), 3.60-3.83 (2H, m, 7-CH_2), 3. 58 (3H, s, 1-CH_3), 4.29 (1H, d, J = 3.0 Hz, 6-C*H*), 5.45 (1H, d, J = 3.0 Hz, 5-C*H*), 7.08-7.17 (3H, m, aromatic), 7.21-7.27 (5H, m, aromatic).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 21.2 (20-C), 40.5 (7-C), 53.2 (1-C), 60.0 (6-C), 60.7 (3-C), 86.2 (5-C), 123.9, 125.1, 125.2 (2xC), 128.1, 128.8, 129.5 (2xC), 136.0, 140.8, 139.9, 138.3, 170.1 (1-C), 175.3 (4-C).

IR neat: υ (cm^{-1}) = 2953 (w), 2924 (w), 1780 (s), 1739 (s), 1608 (w), 1516 (w), 1459 (w), 1435 (w), 1285 (w), 1246 (m), 1041 (w), 752 (w).

HRMS: $[M+NH_4]^+$ Calcd for $[C_{20}H_{18}O_4.NH_4]^+$: 340.1543; found: 340.1539.



(3*R,3a*S**,8a*R**)-Methyl 3-(naphthalen-2-yl)-1-oxo-3,3a,8,8a-tetrahydro-1*H*-indeno-[1,2-*c*]furan-8a-carboxylate (242c)**

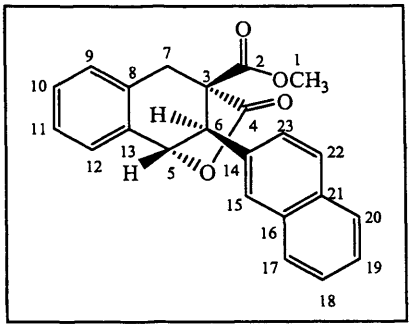
The title compound **242c** was prepared by the reaction of compound **232c** (0.19 mmol, 71 mg) as starting material according to **GP-13** as colourless crystalline solid in 55% yield (0.104 mmol, 37.4 mg).

m.p.: 183 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 3.65-3.70 (2H, m, 7-C*H*$_2$), 3.87 (3H, s, 1-C*H*$_3$), 4.51 (1H, d, *J* = 6.2 Hz, 6-C*H*), 5.54 (1H, d, *J* = 7.9 Hz, 12-C*H*), 6.25 (1H, d, *J* = 6.2 Hz, 5-C*H*), 6.58 (1H, t, *J* = 7.5 Hz), 7.04 (1H, t, *J* = 7.5 Hz, aromatic), 7.13 (1H, d, *J* = 7.5 Hz, aromatic), 7.18 (1H, d, *J* = 8.0 Hz, aromatic), 7.48-7.42 (2H, m, aromatic), 7.82-7.70 (3H, m, aromatic), 7.66 (1H, s, aromatic).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 39.2 (7-C), 53.6 (1-C), 56.8 (6-C), 62.6 (3-C), 83.2 (5-C), 123.9, 124.6, 125.5, 126.50, 126.53, 126.6, 126.8, 127.9, 128.16, 128.18, 128.4, 132.3, 133.0, 133.3, 135.6, 141.0, 169.3 (2-C), 175.4 (4-C).

IR neat: ν (cm^{-1}) = 3438 (H_2O), 2952 (w), 2922 (w), 2849 (w), 1782 (s), 1741 (s), 1605 (w), 1437 (w), 1289 (w), 1250 (m), 738 (w).

HR-MS: $[M+NH_4]^+$ Calcd for $[C_{23}H_{18}O_4.NH_4]^+$: 376.1543; found: 376.1546.



(1*S,4*S**,10*S**)-Methyl 10-(naphthalen-2-yl)-3-oxo-1,3,4,5-tetrahydro-1,4-methanobenzo[*c*]oxepine-4-carboxylate (243c)** [21]

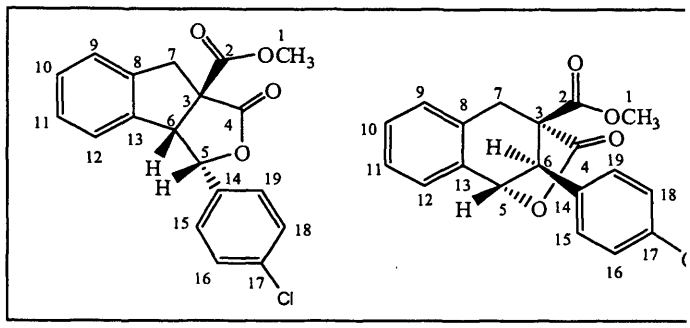
The title compound **243c** was prepared by using compound **232c** (0.19 mmol, 71.06 mg) as starting material according to **GP-13** as yellow oil in 19 % yield (0.036 mmol, 13.0 mg).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.49 (3H, s, 1-C*H*$_3$), 3.52-3.78 (2H, m, 7-C*H*$_2$), 4.39 (1H, d, *J* = 3.0 Hz, 6-C*H*), 5.66 (1H, d, *J* = 3.0 Hz, 5-C*H*), 7.23-7.34 (4H, m, aromatic), 7.45-7.50 (3H, m, aromatic), 7.80-7.83 (3H, m, aromatic), 7.88 (1H, d, *J* = 8.0 Hz, aromatic).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 40.5 (7-C), 53.2 (1-C), 60.0 (6-C), 60.6 (3-C), 86.1 (5-C), 122.8, 123.9, 124.3, 126.6, 125.1, 126.8, 127.8, 128.10, 128.14, 128.9, 129.0, 133.10, 133.14, 136.2, 140.0, 140.7, 170.0 (2-C), 175.4 (4-C).

IR neat: ν (cm^{-1}) = 3438 (H_2O), 3056 (w), 2952 (w), 2932 (w), 9232 (w), 2856 (w), 1780 (s), 1736 (s), 1603 (w), 1434 (w), 1245 (m), 1146 (w), 1044 (w), 748 (m).

HR-MS: $[M+NH_4]^+$ calc. for $[C_{23}H_{18}O_4.NH_4]^+$: 376.1543; found: 376.1546.



(3*S,3a*R**,8a*S**)-Methyl 3-(4-chlorophenyl)-1-oxo-3,3a,8,8a-tetrahydro-1*H*-indeno[1,2-*c*]furan-8a-carboxylate (242d) and**

(1*S,4*S**,10*S**)-Methyl 10-(4-chlorophenyl)-3-oxo-1,3,4,5-tetrahydro-1,4-methanobenzo[*c*]oxepine-4-carboxylate (243d)** [21]

The title compounds **242d** and **243d** were prepared by using compound **232d** (0.19 mmol, 68 mg) as starting material according to **GP-13** as oil in 74 % yield (0.134 mmol, 48 mg) as an inseparable mixture. Ratio of **242d** : **243d** is 1:1 revealed from ^{1}H-NMR spectrum analysis.

IR neat: υ (cm^{-1}) = 3454 (H_2O), 3063 (w), 3028 (w), 2951 (w), 2853 (w), 1778 (s), 1736 (s), 1598 (w), 1493 (w), 1458 (w), 1434 (w), 1411 (w), 1247 (m), 1148 (w), 1089 (w), 1042 (w), 1026 (w), 738 (w), 681 (w).

HR-MS: $[M+Na]^+$ Calc. for $C_{19}H_{15}ClO_4Na$: 365.0551 (100% rel. abundance); found: 365.0553 (100% rel. abundance) [^{35}Cl]

$[M+Na]^+$ Calc. for $C_{19}H_{15}ClO_4Na$: 367.0522 (32% rel. abundance); found: 367.0523 (32% rel. abundance) [^{37}Cl].

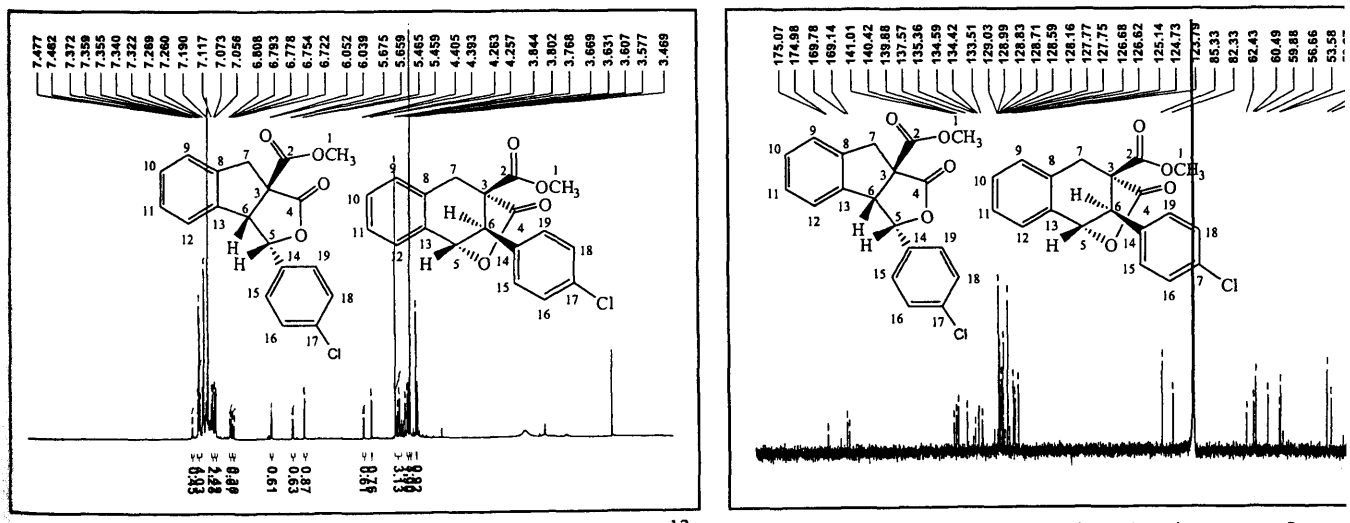
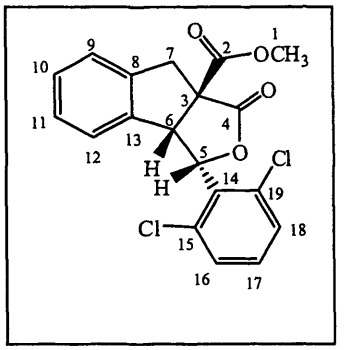


Figure 1. ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) of mixture of compounds **242d** and **243d**.



(3*S,3a*R**,8a*S**)-Methyl 3-(2,6-dichlorophenyl)-1-oxo-3,3a,8,8a-tetrahydro-1*H*-indeno[1,2-*c*]furan-8a-carboxylate (242e)** [21]

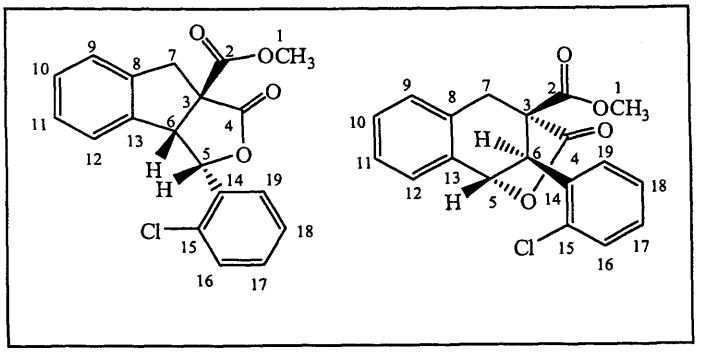
The title compound **242e** was prepared by using compound **232e** (0.19 mmol, 74.5 mg) as starting material according to **GP-13** as colourless crystalline solid in 47% yield (0.089 mmol, 33.6 mg).

m.p.: 151 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 3.67-3.83 (2H, m, 7-C*H*$_2$), 3.85 (3H, s, 1-C*H*$_3$), 4.66 (1H, d, *J* = 8.2 Hz, 6-C*H*), 5.95 (1H, d, *J* = 7.8 Hz, aromatic), 6.65 (1H, d, *J* = 8.2 Hz, 5-C*H*), 6.78 (1H, t, *J* = 7.7 Hz, aromatic), 7.00 (1H, d, *J* = 8.1 Hz, aromatic), 7.11-7.15 (3H, m, aromatic), 7.35 (1H, d, *J* = 8.1 Hz, aromatic).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 39.4 (7-C), 53.7 (1-C), 54.6 (6-C), 61.2 (3-C), 80.9 (5-C*H*), 124.5, 124.9, 126.7, 128.1, 128.4, 130.1, 130.5, 133.8, 134.5, 136.3, 136.9, 141.4, 169.6 (2-C), 175.1 (4-C).

IR neat: υ (cm^{-1}) = 3446 (H_2O), 3029 (w), 2952 (w), 2928 (w), 1775 (s), 1747 (s), 1560 (w), 1436 (w), 1284 (w), 1240 (m), 1158 (w), 1033 (w), 779 (w), 737 (w).

HR-MS: $[M]^+$ Calcd for $C_{19}H_{14}Cl_2O_4$: 376.0264; found: 376.0265 [^{35}Cl isotope].



(3*S,3a*R**,8a*S**)-Methyl 3-(2-chlorophenyl)-1-oxo-3,3a,8,8a-tetrahydro-1*H*-indeno[1,2-*c*]furan-8a-carboxylate (242f) and**

(1*S,4*S**,10*R**)-Methyl 10-(2-chlorophenyl)-3-oxo-1,3,4,5-tetrahydro-1,4-methanobenzo[*c*]oxepine-4-carboxylate (243f)**

The title compounds **242f** and **243f** were prepared by using compound **232f** (0.19 mmol, 68.11 mg) as starting material according to **GP-13** as oil in 79 % yield (0.15 mmol, 51.4 mg) as an inseparable mixture. Ratio of **242f**:**243f** is 20:59 revealed from ^{1}H-NMR spectrum analysis.

IR neat: υ (cm^{-1}) = 3453 (H_2O signal), 3062 (w), 2952 (w), 2847 (w), 1785 (s), 1733 (s), 1435 (w), 1244 (w), 1207 (w), 1099 (w), 1053 (w), 757 (m).

HRMS: $[M+NH_4]^+$ calc. for $[C_{19}H_{15}O_4ClNH_4]^+$: 360.0997 (100% rel. abundance); found: 360.1002 (100% rel. abundance) [^{35}Cl isotope].

$[M+NH_4]^+$ calc. for $[C_{19}H_{15}O_4ClNH_4]^+$: 362.0968 (32% rel. abundance); found: 362.0971 (32% rel. abundance) [^{37}Cl isotope].

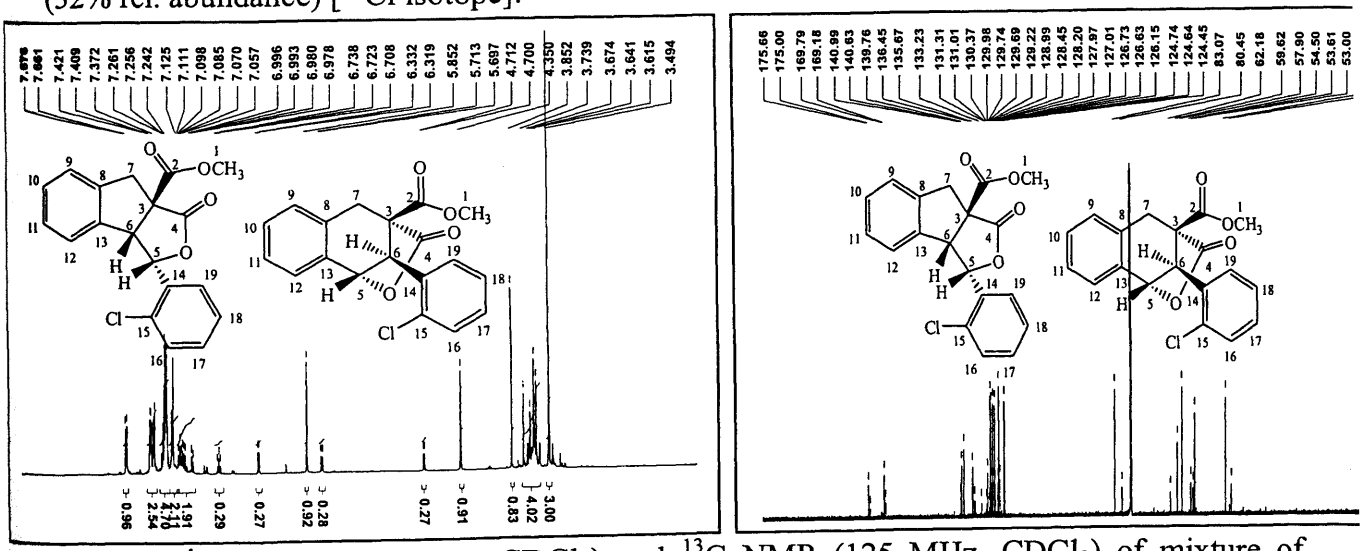
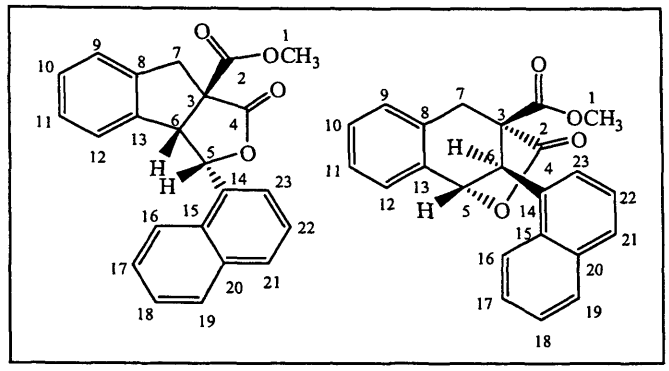


Figure 2. ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) of mixture of compounds **242f** and **243f**.



(3*R,3a*S**,8a*R**)-Methyl 3-(naphthalen-1-yl)-1-oxo-3,3a,8,8a-tetrahydro-1*H*-indeno[1,2-*c*]furan-8a-carboxylate (242g) and**

(1*S,4S*,10*S**)-Methyl 10-(naphthalen-1-yl)-3-oxo-1,3,4,5-tetrahydro-1,4-methanobenzo[*c*]oxepine-4-carboxylate (243g)**

The title compounds **242g** and **243g** were prepared by using compound **232g** (0.19 mmol, 71 mg) as starting material according to **GP-13** as an oil in 72% yield (0.136 mmol, 49 mg) as an inseparable mixture. Ratio of **242g** : **243g** is 18:55 revealed from ^{1}H-NMR spectrum analysis.

IR neat: υ (cm^{-1}) = 3055 (w), 2953 (w), 2927 (w), 2853 (w), 1790 (s), 1729 (s), 1602 (w), 1512 (w), 1435 (m), 1246 (m), 1058 (w), 776 (m), 734 (m).

^{1}H NMR (500 MHz, $CDCl_3$): 5.05 (1H, d, J = 6.5 Hz) and most of signals merged with 243g.

HRMS: $[M+NH_4]^+$ Calc. for $C_{23}H_{22}NO_4$: 376.1543; found: 376.1545.

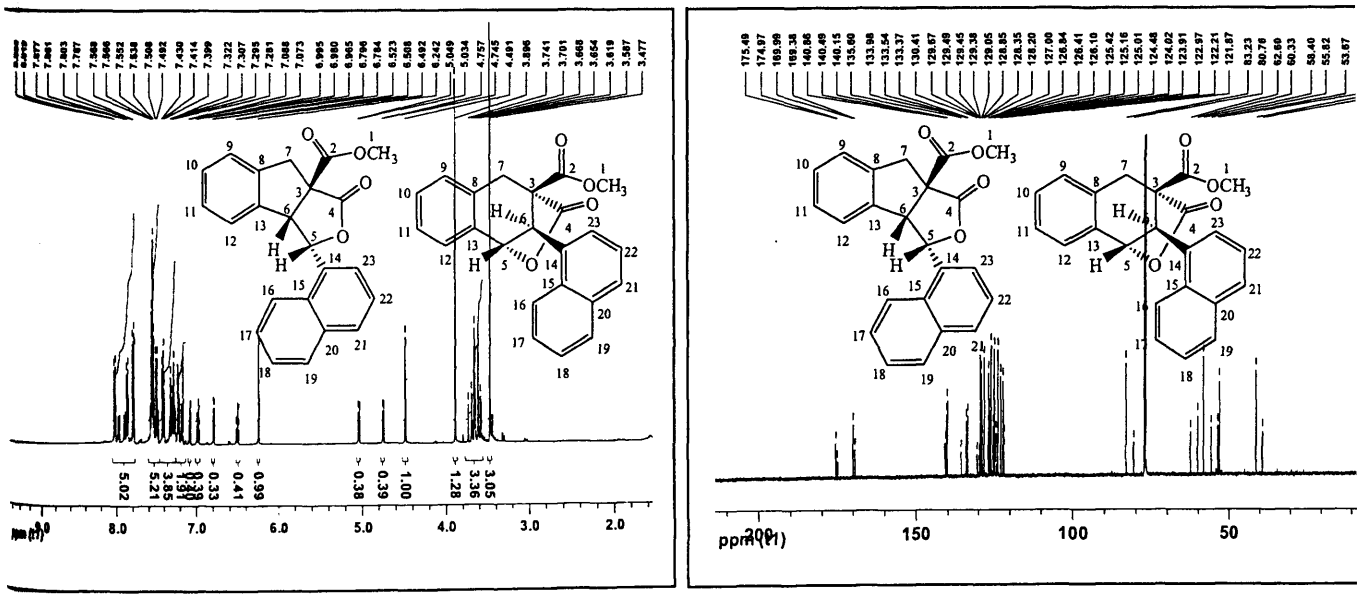
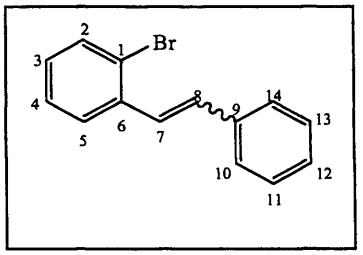


Figure 3. ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) of mixture of compounds **242g** and **243g**.

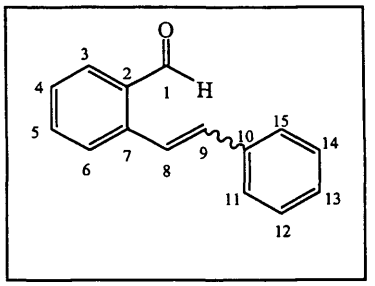


GP-14 (*E*)- and (*Z*)-1-bromo-2-(2-phenylethenyl)benzene (237 and 236) [22]

To a stirred solution of benzyltriphenylphosphonium chloride (10 mmol, 3.9 g) in dry THF (40 mL) at 0 °C was added dropwise *n*-BuLi (2.5 M solution in hexane, 10 mmol, 4 mL). The red solution was stirred for 0.5 h. A solution of 2-bromobenzaldehyde (10.0 mmol, 1.9 g) in dry THF (5 mL) was added dropwise. The reaction solution was warmed to room temperature and stirred for 1 h. After addition of water (100 mL), the reaction mixture was extracted with ethyl acetate (3 x 30 mL). The organic phases were dried over $MgSO_4$, filterd and evaporated at reduced pressure. The crude product was purified by flash chromatography using petroleum ether as eluent to give the product in 93% yield (9.57 mmol, 2.48 g) as colourless oil containing a mixture of (*E*)- and (*Z*)-isomer (1 : 2).

(*Z*)-isomer (**236**): The (*Z*)-1-bromo-2-(2-phenylethenyl) benzene (**236**) was prepared according to the **GP-14** as a mixture with *E*-substrate **237** in 2:1 ratio. This is a known compound. Spectroscopic data are in agreement with literature [22].

^{1}H NMR (500 MHz, $CDCl_3$): 6.73 (1H, d, J = 12.1 Hz, Ph-*CH*=*CH*-Ph), 6.66 (1H, d, J = 12.1 Hz, Ph-*CH*=*CH*-Ph), Rest of signals merged in aromatic region with *E*- substrate.
IR neat: ν (cm^{-1}) = 3152 (w), 3057 (w), 2969 (w), 2920 (w), 2854 (w), 1597 (w), 1558 (w), 1322 (w), 1217 (w), 1155 (w), 1112 (w), 1026 (w), 788 (w), 693 (w).

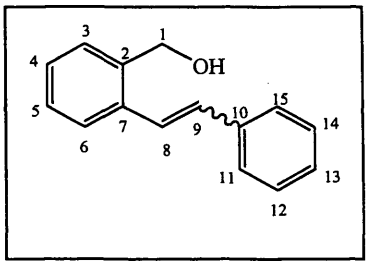


GP-15 (*E*)- and (*Z*)-1-formyl-2-(2-phenylethenyl)benzene (239 and 238)

The Grignard reagent [23] was prepared by refluxing *E*- and *Z*-1-bromo-2-(2-phenylethenyl) benzene (3.86 mmol, 1.0 g) and magnesium turnings (4.24 mmol, 101.7 mg) in dry THF (20 mL) for 2h. A solution of DMF (0.5 mL) in THF (5 mL) was added slowly. The reaction mixture was allowed to cool to room temperature. The reaction mixture was further stirred for 3h. The reaction mixture was quenched with aq. NH_4Cl (15 mL) and extracted with diethyl ether (2x20mL).The solvent was dreid over anhydrous Na_2SO_4, evaporated at reduced pressure. The crude product was purified by flash chromatography (ethyl acetate: hexane (1:10)) and obtained in 68% yield (2.59 mmol, 0.54 g) as yellow oil containing (*E*) and (*Z*)-isomers in a ratio of 1 : 2.

Z-isomer **238**: ^{1}H NMR (500 MHz, $CDCl_3$): 10.14 (1H, s, CHO); ^{13}C NMR (125 MHz, $CDCl_3$): 192.1 (aldehyde carbon); *E*-isomer: ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 10.20 (1H, s, -C*H*O) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.7 (aldehyde carbon) ppm; Rest of *E*- and *Z*-isomers signals are merged with each other. This is a know compound. Spectroscopic data are in agreement with literature [22].

IR neat: ν (cm $^{-1}$) = 3081 (w), 3060 (w), 3024 (w), 2957 (w), 2930 (m), 2869 (m), 2857 (m), 2745 (w), 1695 (s), 1596 (m), 1566, 1494 (w), 1466 (w), 1446 (w), 1392 (w), 1234 (w), 1193 (w), 1159 (w), 782 (m), 761 (m), 697 (m).



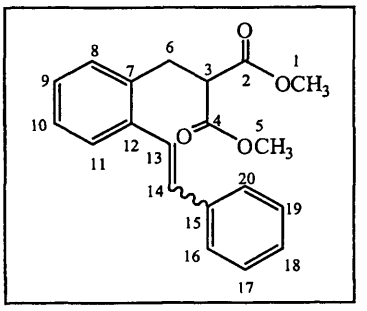
GP-16 (*E*) and (*Z*)-2-(styrylphenyl)methanol (231a and 240)

Sodium borohydride (4.71 mmol, 0.17 g) was added to a solution of (*E*)- and (*Z*)-1-formyl-2-(2-phenylethenyl)-benzene **239** and **238** (3.12 mmol, 0.65 g) in absolute ethanol (30 mL) at 0 °C. The reaction mixture was further stirred for 16 h at r.t. The reaction was cooled to 0 °C and aqueous HCl (1M, 15 ml) was added carefully. The reaction mixture was extracted with diethyl ether (3 x 20 mL). The organic layer was washed with brine, dried with Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash chromatography (ethyl acetate: hexane (1:10)) and the product (*E*:*Z* 1:2) was obtained in 97% yield (2.95 mmol, 0.62g) as an oil.

(*Z*)-isomer **240**: ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 6.65 (1H, d, *J* = 12.2 Hz, Ar-*CH*=*CH*-Ph); 6.58 (1H, d, *J* = 12.2 Hz, Ar-*CH*=*CH*-Ph), 4.55 (2H, s, -C*H*$_2$OH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 63.5 (-*C*H$_2$OH) ppm; Rest of signals for the (*Z*)-isomer are merged with the (*E*)-isomer.

IR neat: ν (cm $^{-1}$): 3381 (broad peak of OH), 3064 (w), 3021 (w), 2920 (w), 2851 (w), 1559 (w), 1443 (w), 1240 (w), 1207 (w), 1040, 984 (w), 788 (w), 762 (w), 697 (w).

HR-MS: $[M-H]^+$ calc. for $C_{15}H_{13}O$ 209.0972, found: 209.0970.



(*E*)-and (*Z*)-dimethyl 2-(2-styrylbenzyl)malonate (232a and 241)

The title compound was prepared according to **GP-12** starting from (*E*)- and (*Z*)-isomer of the corresponding alcohol (2.76 mmol, 0.58 g) in 28% yield (0.77 mmol, 0.25 g) as colourless oil [20].

Z-isomer **241**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.73 (1H, d, *J* = 12.2 Hz, Ar-*CH*=*CH*-Ph); 6.69 (1H, d, *J* = 12.2 Hz, Ar-*CH*=*CH*-Ph), 3.70 (6H, s, COOC*H*$_3$); 3.28 (2H, d, *J* = 8.0 Hz, C*H*$_2$) ppm; ^{13}C NMR (125MHz, $CDCl_3$): δ = 32.82 (-CH_2OH), 52.5 (COO*Me*), 52.6 (*C*HCOOMe), 169.3 (C=O) ppm. Rest of signals *Z*-isomers are merged with *E*-isomer.

IR neat: ν (cm^{-1}): 3461 (H_2O broad peak), 3060 (w), 3024 (w), 2952 (w), 2847 (w), 1754 (s), 1735 (s), 1559 (w), 1540 (w), 1495 (w), 1436 (w), 1346 (w), 1276 (w), 1229 (w), 1151 (w), 1024 (w), 783 (w), 762 (w), 694 (w).

HR-MS: $[M+H]^+$ Calc. for $[C_{20}H_{20}O_4.H]^+$ 325.1434; found 325.1441.

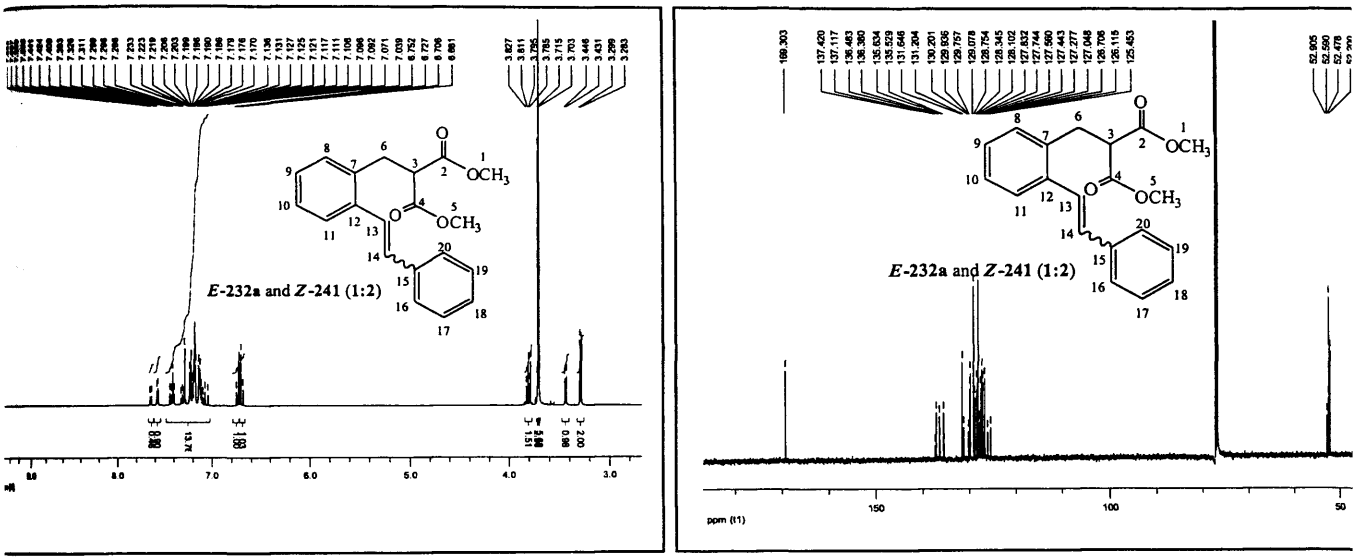
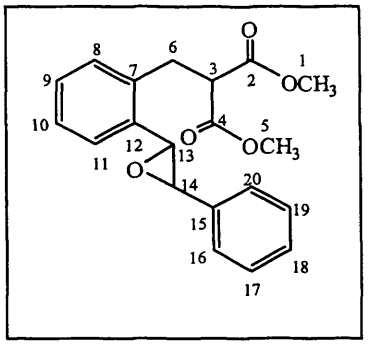


Figure 3. ^1H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of *E/Z* mixture of compounds **232a** and **241**.



GP-17 Synthesis of dimethyl 2-2{2-(3-phenyloxiran-2-yl)benzyl}malonate (247)

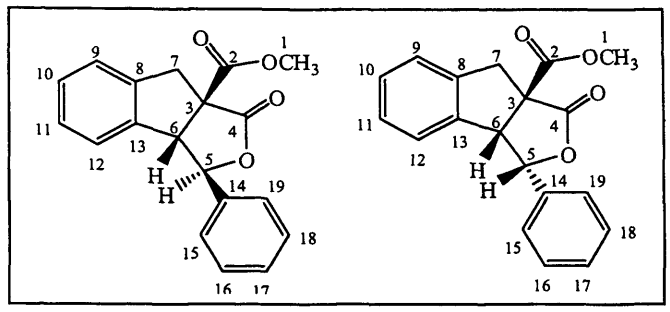
To a solution of compound **232a** (1.26 mmol, 428 mg) in chloroform (20 mL) was added 77% *m*CPBA (1.89 mmol, 423 mg). The reaction mixture was stirred at r. t. for 16 h. To the reaction mixture was added aqueous saturated solution of $NaHCO_3$ (2 x 15mL) and extracted with ether (3x20mL). The organic layer was dried over Na_2SO_4, evaporated at reduced pressure and subjected to column chromatography ethyl acetate: hexane (1:20). The title compound was obtained in 95% yield (1.20 mmol, 0.41 g) as colourless oil [24].

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42-7.36 (5H, m, Ar-*H*), 7.32-7.26 (3H, m, Ar-H), 7.21 (1H, d, *J* = 7.4 Hz), 4.10 (1H, d, *J* = 1.9 Hz), 3.80 (1H, d, *J* = 2.0 Hz), 3.69 (1H, t, *J* = 7.3 Hz), 3.64 (3H, s, COO*Me*), 3.60 (3H, s, COO*Me*), 3.32 (2H, d, *J* = 7.2 Hz) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.1, 169.0, 136.8, 135.8, 135.5, 129.5, 128.6, 128.4, 128.0, 127.5, 125.6, 124.7, 62.2, 60.4, 52.59, 52.55, 31.4 ppm;

IR neat: υ (cm^{-1}) = 3460 (H_2O peak), 3070 (w), 3034 (w), 2953 (w), 2847 (w), 1754 (s), 1734 (s), 1575 (w), 1559 (w), 1491 (w), 1456 (w), 1435 (w), 1346 (w), 1282 (w), 1153 (m), 1230 (w), 1153 (w), 1025 (w), 760 (m), 698 (w).

HR-MS: $[M+NH_4]^+$ calc. for $[C_{20}H_{20}O_5.NH_4]^+$ 358.1649, found: 358.1652.



GP-18 (3S*, 3aS*, 8aR*)-Methyl 1-oxo-phenyl-3,3a,8,8a-tetrahydro-1*H*-indeno[2,1-c]furan-8a-carboxylate (246)

t-BuOK (0.36 mmol, 40 mg) was added to a solution of epoxide **247** (0.18 mmol, 61 mg) in *t*-BuOH (3 mL). The reaction mixture was stirred for 6 h. The reaction mixture was quenched with aqueous 1M HCl (2 x 5 mL) and extracted with ethyl acetate (3x5 mL). The combined organic phases were washed with brine (3x5 mL), dried with Na_2SO_4 and evaporated under reduced pressure. The crude product was dissolved in MeOH (6 mL) and treated with a catalytic amount of conc. H_2SO_4 in the presence of molecular sieves (4Å). The reaction mixture was stirred at r.t. for 24 h. The reaction mixture was filtered. The filtrate was quenched with water (10 mL) and extracted with ethyl acetate (3x10 mL). The combined organic phases were washed with brine (3x5 mL), dried with Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography (ethyl acetate: hexane 1:10). The title compound **246** was obtained as a mixture with compound **242a** (1: 0.4) in 46 % overall yield (0.0825 mmol, 25 mg) [25].

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.80 (2H, m, Ar-*H*), 5.64 (1H, d, *J* = 5.0 Hz), 4.64 (1H, d, *J* = 5.0 Hz), 3.88 (3H, s, -$COOCH_3$) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 80.6, 56.0, 53.3, 49.8, 29.0 ppm. Other signals are merged with compound **242a**.

IR neat: υ (cm^{-1}) = 3461 (H_2O broad peak), 3034 (w), 2953 (w), 2925 (w), 2851 (w), 1780 (s), 1735 (s), 1559 (w), 1436 (w), 1282 (m), 1229 (w), 1154 (w), 1110 (w), 1055 (w), 789 (w), 700 (w).

HR-MS: $[M+H]^+$ Calcd for $[C_{19}H_{16}O_4.H]^+$: 309.1121, found: 309.1126.

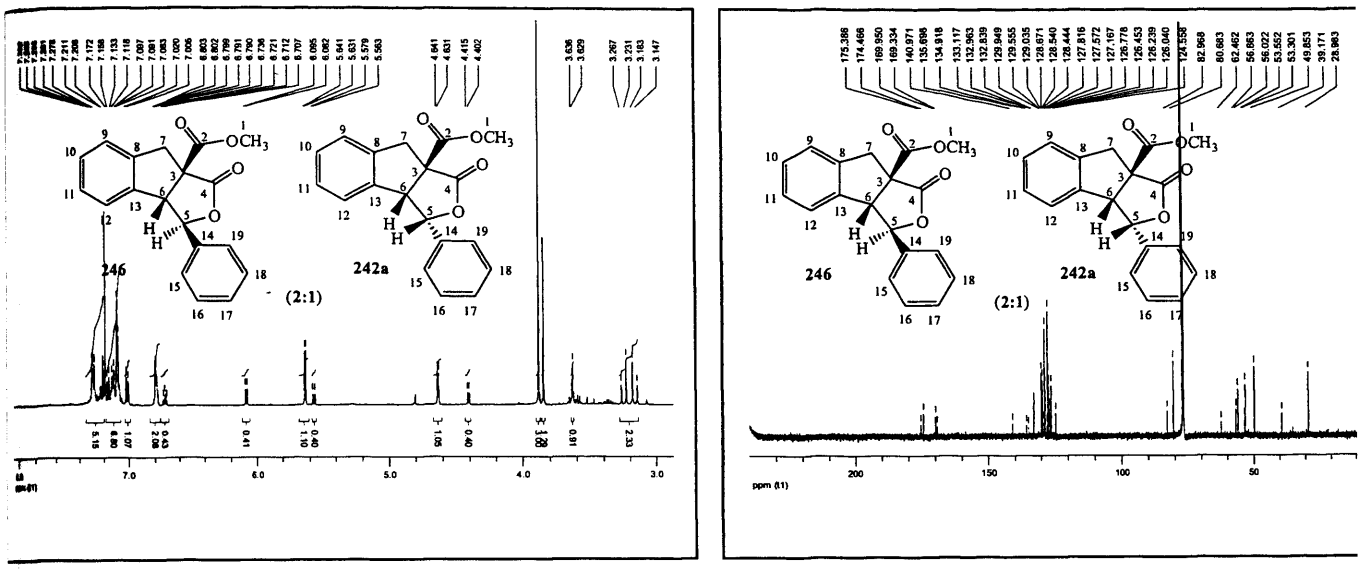
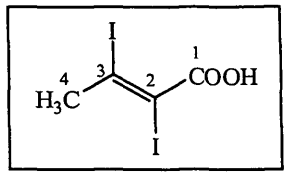


Figure 3. ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of *E/Z* mixture of compounds **242a** and **246**.

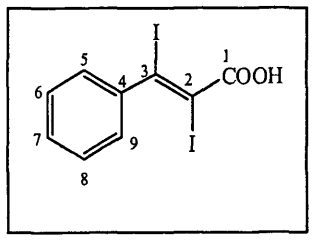


GP-19 (*E*)-2,3-Diiodobut-2-enoic acid (266) [26]

A solution of 2-butynoic acid (**264**) (0.06 mol, 5 g) in Et_2O (25 mL) was cooled with an ice-salt bath to -5°C under argon atmosphere. A solution of iodine (0.075mol) in Et_2O (25 mL) was added dropwise over 10 min while the reaction mixture was vigorously stirred. After the addition the resulting solution was stirred for an additional 18h at r.t. The reaction mixture was quenched with dropwise addition of aqueous saturated $NaHSO_3$ solution (30 mL). The aqueous layer was further extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were washed with aqueous saturated NaCl solution (25 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give title compound as crystalline solid.

The crude product was recrystallized from minimum amount of CH_2Cl_2 to give compound 266 in 60% yield (0.036 mol, 12 g) as a colourless crystalline solid. This is a known compound. Spectroscopic data are in agreement with literature [26].

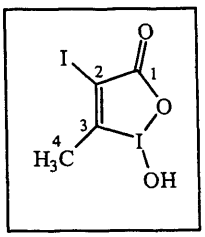
m.p. = 113-115°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 2.67 (3H, s, 4-CH_3).
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 39.7 (4-C), 84.0 (2-C), 99.5 (3-C), 170.3 (1-C).



(*E*)-2,3-Diiodo-3-phenylacrylic acid (267)

Similarly, the title compound **267** was prepared according to **GP-19** starting from propiolic acid (0.06 mol, 8.76 g) in 43 % yield (25.75 mmol, 10.3g) as colourless crystalline solid. This is a known compound. Spectroscopic data are in agreement with literature [26].

m.p. = 173-175 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.32-7.44 (5H, m, aromatic).
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 84.8 (2-C), 99.8 (3-C), 127.7 (2xC), 128.6 (2xC), 133.3, 145.4, 169.7 (1-C).



GP-20 1-Hydroxy-4-iodo-5-methyliodoxol-3(1*H*)-one (268) [27]

In a foremost method acetic anhydride (9.60 mL), and 30% aqueous H_2O_2 (2.40 mL) were stirred at 40 °C for 4 h. (*E*)-2,3-Diiodobut-2-enoic acid (**264**) (4.80 mmol, 1.62 g) was added in one portion and the mixture was stirred at 40 °C. After stirring for 20 h reaction mixture was diluted with water (50 mL). Further, the reaction mixture was stirred at r. t for 1 h. After filtration the colourless crystalline solid was washed with water and dried under reduced pressure to afford compound **268** (2.88 mmol, 1.02 g, 60%) [28].

By a second method [29] *(E)*-2,3-diiodobut-2-enoic acid (**264**) (2.1 mmol, 710 mg) was added to a solution of oxone® (2.60 mmol, 1.60 g) in deionised water (6.50 mL). The reaction mixture was heated to 70 °C for 20 minutes and stirred for 3.5 h at this temperature. The reaction mixture was then cooled to 5 °C and left at this temperature for 1.5 h with slow stirring. The mixture was filtered and the solid was repeatedly rinsed with water (50 mL) and acetone (50 mL) to afford **268** in 60% yields (1.26 mmol, 446 mg) colourless solid.

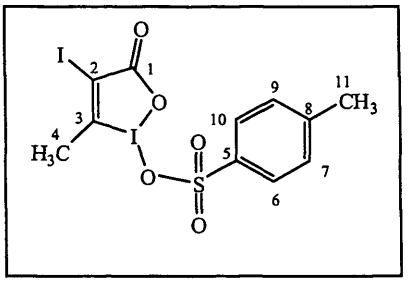
By a third procedure the *(E)*-2, 3-diiodobut-2-enoic acid (**264**) (2.1 mmol, 709 .8 mg) was added portion wise to a solution of potassium bromate (4.41 mmol, 736.5 mg) in aqueous sulphuric acid (3.5 mL, 2M) at 65 °C over 15 min. The resulting suspension was then stirred at 75 °C for 3h (bromine vapour liberated) during which reaction mixture turned orange, then returned to a white suspension in a colourless solution. The reaction mixture was cooled in ice/salt mixture until the internal temperature was below the -5°C. The solution was filtered and then filtrate washed with ice-cold water (2 x 10 mL) and ethanol (5 mL) and dried under reduced pressure to yield compound **268** in 38% yield (0.798 mmol, 282.5 mg) as colourless powder [30].

m.p. = 136-137 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) = 2.48 (s, 3H, 4-C*H*$_3$), 8.08 (s, 1H, O*H*).

^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) = 21.7 (4-C), 97.8 (3-C), 132.4 (2-C), 166.6 (1-C).

IR neat: υ (cm^{-1}) = 3458 (br), 2972 (w), 2907 (w), 1613 (s), 1304 (m), 969 (m), 490 (w).

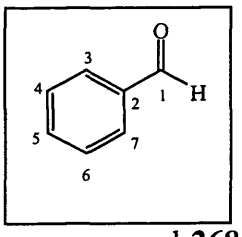
HR-MS: $[M+H]^+$ Calc. for $[C_4H_4I_2O_3.H]^+$: 354. 8323; found: 354.8331.



GP-21 1-Tosyloxy-4-iodo-5-methyliodoxol-3(1*H*)-one (269) [27]

To a stirred mixture of compound **268** (1.20 mmol, 425 mg) in acetic anhydride (6mL), *p*-TsOH. H_2O (2.40 mmol, 456 mg) was added at r.t. After 5 min of stirring a slightly exothermic reaction was observed while the suspension turned into a clear solution. The solution was stirred for additional 30 minutes until a colourless microcrystalline precipitate was formed. Then the reaction mixture was diluted with dry diethyl ether (20 mL). The precipitate was filtered off, washed with diethyl ether (3 x 20 mL) and dried under reduced pressure to afford **269** in 63% yield (0.756 mmol, 384 mg,) as colourless solid [31].

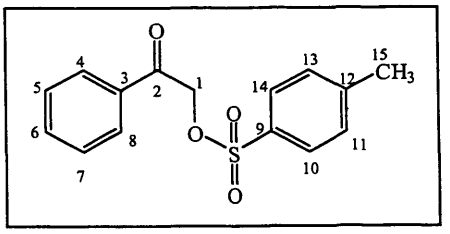
m.p. = 154-155 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) = 2.29 (s, 3H, 11-C*H*$_3$), 2.47 (s, 3H, 4-C*H*$_3$), 7.13 (d, *J* = 8.0 Hz, 2H, aromatic), 7.49 (d, *J* = 8.0 Hz, 2H, aromatic).
^{13}C NMR (126 MHz, DMSO-d_6): δ (ppm) = 20.7 (11-C), 21.7 (4-C), 97.8 (3-C), 125.5 (2xC), 128.1 (2xC), 132.4 (2-C), 137.9, 145.3, 166.6 (1-C).
IR neat: υ (cm $^{-1}$) = 3307 (broad), 2995 (w), 1606 (s), 1317 (m), 1179 (w), 958 (w), 756 (m), 733 (m), 571 (m).



GP-22 Benzaldehyde (179)

A mixture of benzyl alcohol (1.0 mmol, 108 mg) and hypervalent(III) iodine compound **268** (1.20 mmol, 425 mg) was refluxed in acetone (10 mL) for 3 h. The mixture was then subjected directly to column chromatography (silica gel; hexane/ethyl acetate; 9:1 v/v) to afford benzaldehyde (**179**) in 40% yield (0.401 mmol, 42.5 mg). This is a known compound. Spectroscopic data are in agreement with literature [32].

^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 7.50-7.60 (3H, m, aromatic), 7.84 (2H, d, *J* = 7.5 Hz, aromatic), 9.99 (1H, s, C*H*O).

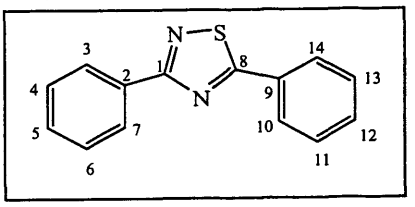


GP-23 α-Tosyloxyacetophenone (274) [33]

A mixture of acetophenone (1.0 mmol, 120 mg), *p*-TsOH. H_2O (1.0 mmol, 190 mg) and hypervalent iodine compound **268** (1.20 mmol, 425 mg) was refluxed in CH_3CN (10 mL) for 3 h. After completion of the reaction as indicated by TLC, the mixture was treated with sat. aqueous sodium bicarbonate solution (10 mL), extracted with CH_2Cl_2 (2x10 mL), dried over anhydrous sodium sulfate, concentrated under reduced pressure and purificated by column chromatography (silica gel; petroleum ether/ethyl acetate; 4:1 v/v) to afford compound **274** 55% yield (0.55 mmol, 160 mg). This is a known compound. Spectroscopic data are in agreement with literature [14].

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 2.40 (3H, s, 15-C), 5.20 (2H, s, 1-C), 7.36 (2H, d, *J* = 8.0 Hz, aromatic), 7.48 (2H, d, *J* = 8.0 Hz, aromatic), 7.62 (1H, td, J = 7.5 Hz, 1.2Hz, aromatic), 7.84-7.87 (4H, m, aromatic).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) = 21.7 (15-C), 69.9 (1-C), 128.0 (2xC), 128.1 (2xC), 128.9 (2xC), 129.9 (2xC), 132.7, 133.8, 134.2, 145.3, 190.3 (2-C).



GP-24 3,5-Diphenyl-1,2,4-thiadiazole (276) [34]

A mixture of thiobenzamide (2.0 mmol, 274 mg) and hypervalent iodine(III) compound **268** (2.0 mmol, 708 mg) in dry CH_3CN (10 mL) was heated to reflux for 1h. The reaction progress was monitored by TLC. After completion of the reaction, the mixture was quenched with water (10 mL) and extracted with acetonitrile (2 x 10mL). The organic phase was dried over $MgSO_4$. The solvent was distilled off and the residue obtained was subjected directly to column chromatography (silica gel; hexane/ethyl acetate; 6:1 v/v) to afford 3,5-diphenyl-1,2,4-thiadiazole (**276**) in 80% yield (0.80 mmol, 190 mg). This is a known compound. Spectroscopic data are in agreement with literature [15].

^{1}H NMR (500 MHz, acetone-d_6): δ (ppm) = 7.39-7.50 (6H, m, aromatic), 8.02 (2H, dd, *J* = 7.5 Hz, 1.5 Hz, aromatic), 8.27 (2H, dd, *J* = 8.0 Hz, 1.5 Hz, aromatic).

^{13}C NMR (125 MHz, acetone-d6): δ (ppm) = 128.3 (2xC). 129.1 (2xC), 129.7 (2xC), 130.4 (2xC), 131.4, 131.5, 133.1, 133.8, 174.5 (8-C), 189.3 (1-C).

5.4 References

[1] Zhang, D.; Liu, Z.; Yum, E. K.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 251.

[2] Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769.

[3] Ding, Y.; Green, J. R. *Synlett* **2005**, 271.

[4] Hwang, G. T.; Son, H. S.; Ku, J. K.; Kim, B. H. *J. Am. Chem. Soc.* **2003**, *125*, 11241.

[5] Ding, C.; Babu, G.; Orita, A.; Hirate, T.; Otera, J. *Synlett* **2007**, 2559.

[6] Hyacinth, M.; Chruszcz, M.; Lee, K. S.; Sabat, M.; Gao, G.; Pu, L. *Angew. Chem. Int. Ed.* **2006**, *45*, 5358.

[7] Trost, B. M.; Xie, J. *J. Am. Chem. Soc.* **2006**, *128*, 6044.

[8] Bowman, B.; Lightsey, D.; McKendall, M.; Smith, T.; Zhu, N.; Stevens, C. L. K.; Foroozesh, M. *J. Undergrad. Chem. Res.* **2005**, *4*, 57.

[9] Batchu, V. R.; Subramanian, V.; Parasuraman, K.; Swamy, N. K.; Kumar, S.; Pal, M. *Tetrahedron* **2005**, *61*, 9869.

[10] Dieck, H. A.; Heck, R. F. *J. Am. Chem. Soc.* **1974**, *96*, 1133.

[11] Richardson, R. D.; Page, T. K.; Altermann, S.; Paradine, S. M.; French, A. N.; Wirth, T. *Synlett* **2007**, 538.

[12] Khan, Z. A.; Wirth, T. *Org. Lett.* **2009**, *11*, 229.

[13] Denmark, S. E.; Butler, C. R. *Org. Lett.* **2006**, *8*, 63.

[14] Schoenberg, A.; Heck, R. F. *J. Am. Chem. Soc.* **1974**, 96, 7761.

[15] Pampin, M. C.; Estevez, J. C.; Estevez, R. J.; Suau, R.; Castedo, L. *Tetrahedron* **2003**, *59*, 8057.

[16] Shahzad, S. A.; Wirth, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 2588.

[17] (a) Inoue, T.; Kitagawa, O.; Oda, Y.; Taguchi, T. *J. Org. Chem.* **1996**, *61*, 8256. (b) Xu, X.-X., Dong, H.-Q. *J. Org. Chem.* **1995**, *60*, 3039.

[18] (a) Ciufolini, M. A.; Browne, M. E. *Tetrahedron Lett.* **1987**, *28*, 171. (b) Ihara, M.; Toyota, M.; Abe, M.; Ishida, Y.; Fukumoto, K.; Kametani, T. *J. Chem. Soc. Perkin Trans. 1* **1996**, 1543.

[19] Thiot, C.; Schumtz, M.; Wagner, A.; Mioskowski, C. *Chem. Eur. J.* **2007**, *13*, 8971.

[20] Bi, H.-P.; Guo, L.-N.; Duan, X.-H.; Gou, F.-R.; Huang, S.-H.; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2007**, *9*, 397.

[21] Khan, Z. A.; Iwaoka, M.; Wirth, T. *Tetrahedron* **2010**, *66*, 6639-6646.

[22] De Meijere, A.; Song, Z. Z.; Lansky, A.; Hyuda, S.; Rauch, K.; Noltemeyer, M.; Koenig, B.; Knieriem, B. *Eur. J. Org. Chem.* **1998**, 2289.

[23] Munro, D. P.; Sharp, J. T. *J. Chem. Soc., Perkin Trans. 1* **1984**, 849.

[24] Crotti, P.; Ferretti, M.; Macchia, F.; Stoppioni, A. *J. Org. Chem.* **1984**, *49*, 4706.

[25] Salomone, A.; Capriati, V.; Florio, S.; Luisi, R. *Org. Lett.* **2008**, *10*, 1947.

[26] Langle, S.; Ngi, S. I.; Anselmi, E.; Abarbri, M.; Thibonnet, J.; Duchene, A. *Synthesis* **2007**, 1724.

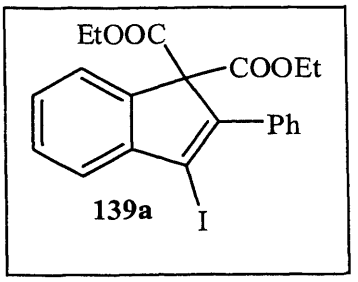
[27] Shah, A. A.; Khan, Z. A.; Choudhary, N.; Loholter, C.; Schafer, S.; Marie, G. P. L.; Farooq, U.; Witulski, B.; Wirth, T. *Org. Lett.* **2009**, *11*, 3578.

[28] Panetta, C. A.; Garlick, S. M.; Durst, H. D.; Longo, F. R.; Ward, J. R. *J. Org. Chem.* **1990**, *55*, 5202.

[29] Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537.
[30] Richardson, R.D.; Page, K.; Zayed, J. M.; Altermann, S.; Smith, D.; Wirth, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 6529.
[31] Zhdankin, V. V.; Kuehl, C. J.; Bolz, J. T.; Formaneck, M. S.; Simonsen, A. J. *Tetrahedron Lett.* **1994**, *35*, 7323.
[32] Binder, C. M.; Dixon, D. D.; Almaraz, E.; Tius, M. A.; Singaram, B. *Tetrahedron Lett.* **2008**, *49*, 2764.
[33] Karade, N. N.; Tiwari, G. B.; Shinde, S. V.; Gampawar, S. V.; Kondre, J. M. *Tetrahedron Lett.* **2008**, *49*, 3441.
[34] Cheng, D.; Chen, Z. *Synth. Commun.* **2002**, *32*, 2155.

Appendix 1

Single Crystal X-ray Structure of Compound 139a



139a

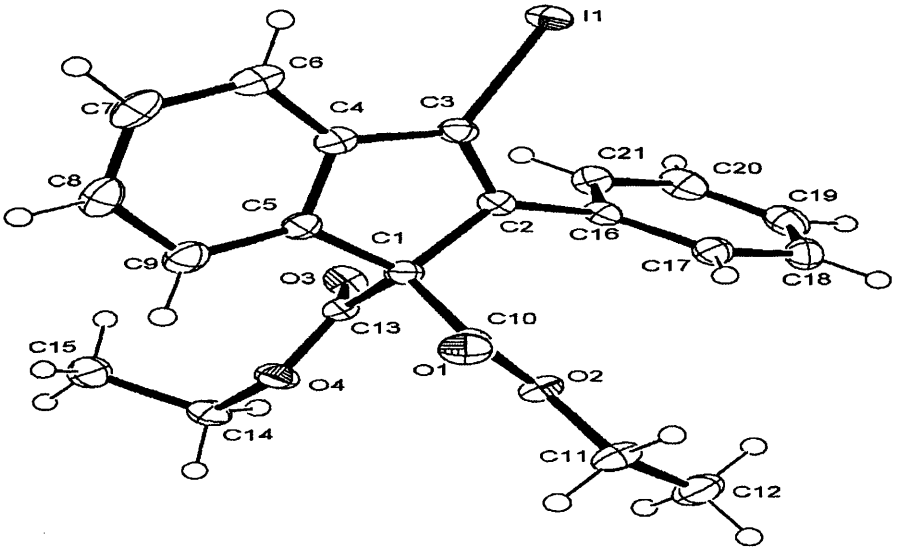


Table 1. Crystal data and structure refinement for compound **139a**.

Identification code	3-Iodo-1*H*-indene	
Empirical formula	C21 H19 I O4	
Formula weight	462.26	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.6950(4) Å	α = 115.752(2)°.
	b = 11.5360(5) Å	β = 94.831(2)°.
	c = 11.6870(6) Å	γ = 110.030(2)°.
Volume	953.62(8) $Å^3$	
Z	2	
Density (calculated)	1.610 Mg/m^3	
Absorption coefficient	1.702 mm^{-1}	
F(000)	460	
Crystal size	0.24 x 0.22 x 0.20 mm^3	

Theta range for data collection	3.05 to 27.49°.
Index ranges	-11<=h<=10, -14<=k<=13, -14<=l<=15
Reflections collected	6316
Independent reflections	4335 [R(int) = 0.0243]
Completeness to theta = 27.49°	99.0 %
Max. and min. transmission	0.7271 and 0.6855
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4335 / 0 / 237
Goodness-of-fit on F^2	1.082
Final R indices [I>2sigma(I)]	R1 = 0.0318, wR2 = 0.0645
R indices (all data)	R1 = 0.0402, wR2 = 0.0679
Largest diff. peak and hole	0.403 and -0.765 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for compound **139a**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	5047(3)	3478(2)	6529(2)	21(1)
C(2)	6950(3)	3974(2)	6559(2)	20(1)
C(3)	7144(3)	2939(3)	5547(2)	23(1)
C(4)	5509(3)	1690(2)	4762(2)	23(1)
C(5)	4255(3)	1978(2)	5341(2)	22(1)
C(6)	5124(4)	401(3)	3662(3)	30(1)
C(7)	3429(4)	-603(3)	3135(3)	35(1)
C(8)	2193(3)	-315(3)	3700(3)	34(1)
C(9)	2571(3)	992(3)	4819(3)	31(1)
C(10)	4297(3)	4413(2)	6304(2)	22(1)
C(11)	4134(4)	6626(3)	7306(3)	32(1)
C(12)	5013(4)	8006(3)	8580(3)	42(1)
C(13)	4746(3)	3400(2)	7771(2)	22(1)
C(14)	2610(4)	2973(3)	8865(3)	35(1)
C(15)	2132(4)	1458(3)	8553(3)	36(1)
C(16)	8349(3)	5351(3)	7601(2)	23(1)
C(17)	8581(3)	6638(3)	7674(3)	27(1)
C(18)	9956(3)	7880(3)	8624(3)	35(1)
C(19)	11104(3)	7852(3)	9489(3)	37(1)
C(20)	10898(3)	6575(3)	9412(3)	36(1)
C(21)	9521(3)	5330(3)	8473(3)	29(1)
O(1)	3438(2)	4086(2)	5265(2)	30(1)
O(2)	4743(2)	5633(2)	7417(2)	26(1)
O(3)	5788(2)	3482(2)	8583(2)	29(1)
O(4)	3141(2)	3176(2)	7790(2)	29(1)
I(1)	9411(1)	3049(1)	5066(1)	33(1)

Table 3. Bond lengths [Å] and angles [°] for compound **139a**.

C(1)-C(5)	1.527(3)
C(1)-C(13)	1.531(3)
C(1)-C(10)	1.535(3)
C(1)-C(2)	1.546(3)
C(2)-C(3)	1.340(3)
C(2)-C(16)	1.494(3)
C(3)-C(4)	1.472(3)
C(3)-I(1)	2.073(2)
C(4)-C(6)	1.379(3)
C(4)-C(5)	1.391(4)
C(5)-C(9)	1.384(3)
C(6)-C(7)	1.396(4)
C(7)-C(8)	1.370(4)
C(8)-C(9)	1.402(4)
C(10)-O(1)	1.196(3)
C(10)-O(2)	1.332(3)
C(11)-O(2)	1.464(3)
C(11)-C(12)	1.501(4)
C(13)-O(3)	1.204(3)
C(13)-O(4)	1.333(3)
C(14)-O(4)	1.458(3)
C(14)-C(15)	1.511(4)
C(16)-C(17)	1.390(3)
C(16)-C(21)	1.394(4)
C(17)-C(18)	1.391(4)
C(18)-C(19)	1.379(4)
C(19)-C(20)	1.383(4)
C(20)-C(21)	1.390(4)
C(5)-C(1)-C(13)	109.14(19)
C(5)-C(1)-C(10)	110.50(19)
C(13)-C(1)-C(10)	111.1(2)
C(5)-C(1)-C(2)	102.1(2)
C(13)-C(1)-C(2)	112.18(19)
C(10)-C(1)-C(2)	111.42(19)
C(3)-C(2)-C(16)	125.9(2)
C(3)-C(2)-C(1)	109.0(2)
C(16)-C(2)-C(1)	125.0(2)

C(2)-C(3)-C(4)	111.5(2)
C(2)-C(3)-I(1)	125.73(18)
C(4)-C(3)-I(1)	122.77(18)
C(6)-C(4)-C(5)	121.1(2)
C(6)-C(4)-C(3)	131.0(2)
C(5)-C(4)-C(3)	107.8(2)
C(9)-C(5)-C(4)	121.2(2)
C(9)-C(5)-C(1)	129.2(2)
C(4)-C(5)-C(1)	109.5(2)
C(4)-C(6)-C(7)	118.0(3)
C(8)-C(7)-C(6)	120.9(2)
C(7)-C(8)-C(9)	121.6(2)
C(5)-C(9)-C(8)	117.2(3)
O(1)-C(10)-O(2)	124.9(2)
O(1)-C(10)-C(1)	124.3(2)
O(2)-C(10)-C(1)	110.80(19)
O(2)-C(11)-C(12)	106.9(2)
O(3)-C(13)-O(4)	125.3(2)
O(3)-C(13)-C(1)	124.9(2)
O(4)-C(13)-C(1)	109.8(2)
O(4)-C(14)-C(15)	110.7(2)
C(17)-C(16)-C(21)	119.1(2)
C(17)-C(16)-C(2)	122.2(2)
C(21)-C(16)-C(2)	118.6(2)
C(16)-C(17)-C(18)	119.8(2)
C(19)-C(18)-C(17)	120.9(3)
C(18)-C(19)-C(20)	119.8(2)
C(19)-C(20)-C(21)	119.7(3)
C(20)-C(21)-C(16)	120.8(3)
C(10)-O(2)-C(11)	115.38(19)
C(13)-O(4)-C(14)	116.6(2)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for compound **139a**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

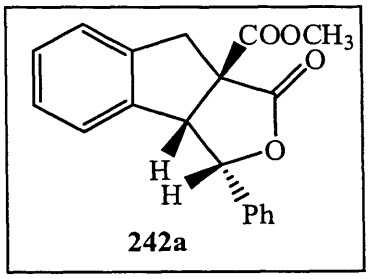
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	20(1)	21(1)	22(1)	10(1)	7(1)	10(1)
C(2)	19(1)	24(1)	20(1)	13(1)	5(1)	10(1)
C(3)	23(1)	26(1)	26(1)	16(1)	10(1)	14(1)
C(4)	28(1)	24(1)	20(1)	12(1)	7(1)	13(1)
C(5)	25(1)	21(1)	21(1)	10(1)	4(1)	11(1)
C(6)	42(2)	30(1)	24(1)	13(1)	10(1)	22(1)
C(7)	48(2)	23(1)	24(1)	5(1)	-3(1)	14(1)
C(8)	33(1)	24(1)	35(2)	12(1)	-8(1)	7(1)
C(9)	31(1)	25(1)	36(2)	15(1)	3(1)	14(1)
C(10)	18(1)	23(1)	25(1)	13(1)	9(1)	9(1)
C(11)	41(2)	30(1)	36(2)	18(1)	11(1)	23(1)
C(12)	42(2)	28(1)	51(2)	14(1)	8(2)	19(1)
C(13)	23(1)	18(1)	24(1)	8(1)	8(1)	10(1)
C(14)	38(2)	37(2)	41(2)	23(1)	27(1)	20(1)
C(15)	39(2)	37(2)	38(2)	23(1)	17(1)	16(1)
C(16)	20(1)	26(1)	22(1)	12(1)	8(1)	9(1)
C(17)	28(1)	29(1)	25(1)	14(1)	8(1)	11(1)
C(18)	35(1)	26(1)	35(2)	13(1)	13(1)	6(1)
C(19)	25(1)	36(2)	29(1)	8(1)	7(1)	2(1)
C(20)	26(1)	47(2)	28(1)	16(1)	3(1)	11(1)
C(21)	27(1)	30(1)	27(1)	14(1)	5(1)	10(1)
O(1)	29(1)	36(1)	28(1)	16(1)	5(1)	16(1)
O(2)	31(1)	24(1)	26(1)	11(1)	7(1)	16(1)
O(3)	27(1)	36(1)	25(1)	17(1)	6(1)	11(1)
O(4)	26(1)	36(1)	36(1)	22(1)	17(1)	17(1)
I(1)	32(1)	37(1)	42(1)	22(1)	23(1)	21(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for compound **139a**.

	x	y	z	U(eq)
H(6)	5984	202	3275	36
H(7)	3130	-1498	2375	42
H(8)	1050	-1019	3325	41
H(9)	1708	1191	5202	37
H(11A)	2884	6259	7159	39
H(11B)	4412	6759	6555	39
H(12A)	4749	7854	9317	63
H(12B)	4617	8697	8555	63
H(12C)	6246	8369	8702	63
H(14A)	1622	3205	9005	41
H(14B)	3551	3625	9691	41
H(15A)	1323	808	7674	53
H(15B)	1606	1303	9213	53
H(15C)	3157	1282	8570	53
H(17)	7804	6669	7078	33
H(18)	10106	8758	8676	41
H(19)	12034	8708	10137	44
H(20)	11695	6549	9998	43
H(21)	9377	4454	8426	35

Appendix 2

Single Crystal X-ray Structure of Compound 242a



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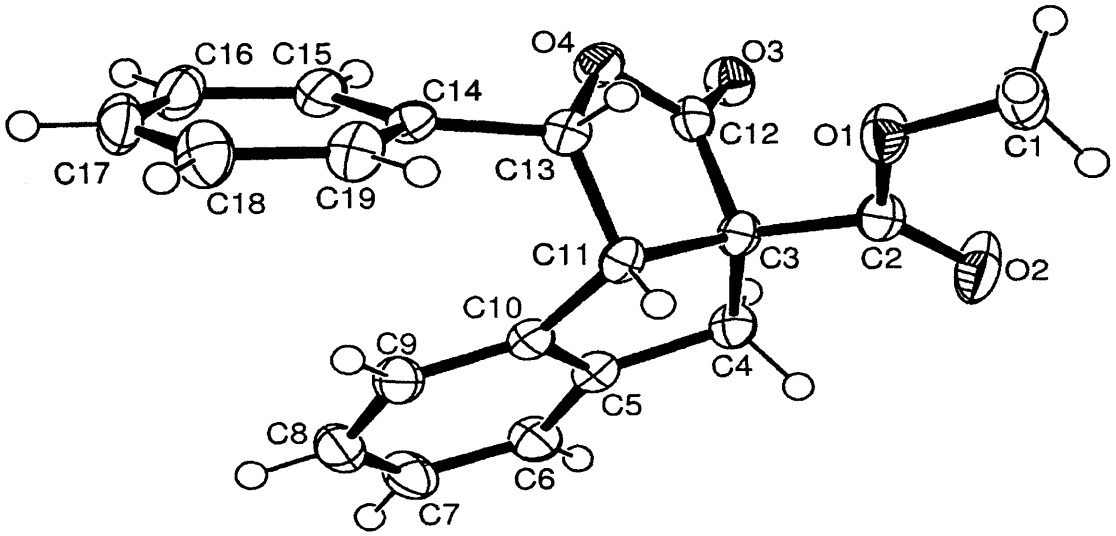


Table 1. Crystal data and structure refinement for Compound **242a.**

Identification code	Tetrahydroindenofuranone	
Empirical formula	C19 H16 O4	
Formula weight	308.32	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 5.9917(2) Å	α = 87.2410(10)°.
	b = 8.9194(3) Å	β = 79.9800(10)°.
	c = 14.3859(6) Å	γ = 84.356(2)°.
Volume	753.04(5) $Å^3$	
Z	2	
Density (calculated)	1.360 Mg/m^3	
Absorption coefficient	0.095 mm^{-1}	
F(000)	324	
Crystal size	0.36 x 0.36 x 0.30 mm^3	

Theta range for data collection	3.47 to 27.57°.
Index ranges	-7<=h<=7, -11<=k<=11, -18<=l<=18
Reflections collected	11975
Independent reflections	3445 [R(int) = 0.0946]
Completeness to theta = 27.57°	98.4 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9720 and 0.9665
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3445 / 0 / 209
Goodness-of-fit on F^2	1.061
Final R indices [I>2sigma(I)]	R1 = 0.0525, wR2 = 0.1267
R indices (all data)	R1 = 0.0682, wR2 = 0.1359
Largest diff. peak and hole	0.258 and -0.285 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for compound **242a**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	6138(3)	8371(2)	5788(1)	38(1)
C(2)	3640(3)	6432(2)	5899(1)	26(1)
C(3)	2472(2)	5275(2)	6572(1)	22(1)
C(4)	962(3)	4356(2)	6109(1)	25(1)
C(5)	1061(3)	2868(2)	6645(1)	24(1)
C(6)	-296(3)	1693(2)	6625(1)	30(1)
C(7)	99(3)	384(2)	7156(1)	34(1)
C(8)	1855(3)	237(2)	7679(1)	33(1)
C(9)	3235(3)	1396(2)	7692(1)	28(1)
C(10)	2810(2)	2733(2)	7180(1)	22(1)
C(11)	4055(2)	4154(2)	7084(1)	22(1)
C(12)	1044(2)	6117(2)	7413(1)	24(1)
C(13)	4176(2)	4966(2)	7998(1)	23(1)
C(14)	4461(3)	3966(2)	8849(1)	24(1)
C(15)	2621(3)	3609(2)	9526(1)	28(1)
C(16)	2945(3)	2595(2)	10262(1)	35(1)
C(17)	5083(3)	1921(2)	10324(1)	38(1)
C(18)	6932(3)	2275(2)	9658(1)	39(1)
C(19)	6621(3)	3308(2)	8928(1)	31(1)
O(1)	5001(2)	7157(1)	6316(1)	36(1)
O(2)	3349(3)	6681(2)	5100(1)	51(1)
O(3)	-737(2)	6857(1)	7408(1)	30(1)
O(4)	2016(2)	5908(1)	8188(1)	27(1)

Table 3. Bond lengths [Å] and angles [°] for compound **242a**.

C(1)-O(1)	1.450(2)
C(1)-H(1A)	0.9800
C(1)-H(1B)	0.9800
C(1)-H(1C)	0.9800
C(2)-O(2)	1.1997(19)
C(2)-O(1)	1.3241(19)
C(2)-C(3)	1.517(2)
C(3)-C(4)	1.531(2)
C(3)-C(12)	1.536(2)
C(3)-C(11)	1.558(2)
C(4)-C(5)	1.504(2)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
C(5)-C(6)	1.393(2)
C(5)-C(10)	1.397(2)
C(6)-C(7)	1.388(2)
C(6)-H(6)	0.9500
C(7)-C(8)	1.389(2)
C(7)-H(7)	0.9500
C(8)-C(9)	1.388(2)
C(8)-H(8)	0.9500
C(9)-C(10)	1.397(2)
C(9)-H(9)	0.9500
C(10)-C(11)	1.521(2)
C(11)-C(13)	1.548(2)
C(11)-H(11)	1.0000
C(12)-O(3)	1.1995(18)
C(12)-O(4)	1.3416(18)
C(13)-O(4)	1.4628(18)
C(13)-C(14)	1.503(2)
C(13)-H(13)	1.0000
C(14)-C(19)	1.389(2)
C(14)-C(15)	1.390(2)
C(15)-C(16)	1.386(2)
C(15)-H(15)	0.9500
C(16)-C(17)	1.376(3)
C(16)-H(16)	0.9500
C(17)-C(18)	1.384(3)

C(17)-H(17)	0.9500
C(18)-C(19)	1.388(2)
C(18)-H(18)	0.9500
C(19)-H(19)	0.9500

O(1)-C(1)-H(1A)	109.5
O(1)-C(1)-H(1B)	109.5
H(1A)-C(1)-H(1B)	109.5
O(1)-C(1)-H(1C)	109.5
H(1A)-C(1)-H(1C)	109.5
H(1B)-C(1)-H(1C)	109.5
O(2)-C(2)-O(1)	124.14(15)
O(2)-C(2)-C(3)	124.84(14)
O(1)-C(2)-C(3)	111.00(13)
C(2)-C(3)-C(4)	112.94(12)
C(2)-C(3)-C(12)	107.83(12)
C(4)-C(3)-C(12)	110.14(12)
C(2)-C(3)-C(11)	116.09(12)
C(4)-C(3)-C(11)	108.06(12)
C(12)-C(3)-C(11)	101.06(11)
C(5)-C(4)-C(3)	102.97(12)
C(5)-C(4)-H(4A)	111.2
C(3)-C(4)-H(4A)	111.2
C(5)-C(4)-H(4B)	111.2
C(3)-C(4)-H(4B)	111.2
H(4A)-C(4)-H(4B)	109.1
C(6)-C(5)-C(10)	120.92(15)
C(6)-C(5)-C(4)	127.44(14)
C(10)-C(5)-C(4)	111.60(13)
C(7)-C(6)-C(5)	118.81(15)
C(7)-C(6)-H(6)	120.6
C(5)-C(6)-H(6)	120.6
C(6)-C(7)-C(8)	120.45(15)
C(6)-C(7)-H(7)	119.8
C(8)-C(7)-H(7)	119.8
C(9)-C(8)-C(7)	121.04(15)
C(9)-C(8)-H(8)	119.5
C(7)-C(8)-H(8)	119.5
C(8)-C(9)-C(10)	118.90(14)
C(8)-C(9)-H(9)	120.5

C(10)-C(9)-H(9)	120.5
C(9)-C(10)-C(5)	119.85(14)
C(9)-C(10)-C(11)	128.97(13)
C(5)-C(10)-C(11)	111.15(13)
C(10)-C(11)-C(13)	117.74(12)
C(10)-C(11)-C(3)	101.97(11)
C(13)-C(11)-C(3)	103.45(11)
C(10)-C(11)-H(11)	111.0
C(13)-C(11)-H(11)	111.0
C(3)-C(11)-H(11)	111.0
O(3)-C(12)-O(4)	122.59(14)
O(3)-C(12)-C(3)	125.90(14)
O(4)-C(12)-C(3)	111.50(12)
O(4)-C(13)-C(14)	109.64(12)
O(4)-C(13)-C(11)	104.25(11)
C(14)-C(13)-C(11)	116.06(12)
O(4)-C(13)-H(13)	108.9
C(14)-C(13)-H(13)	108.9
C(11)-C(13)-H(13)	108.9
C(19)-C(14)-C(15)	119.08(14)
C(19)-C(14)-C(13)	118.64(14)
C(15)-C(14)-C(13)	122.17(13)
C(16)-C(15)-C(14)	120.17(15)
C(16)-C(15)-H(15)	119.9
C(14)-C(15)-H(15)	119.9
C(17)-C(16)-C(15)	120.41(17)
C(17)-C(16)-H(16)	119.8
C(15)-C(16)-H(16)	119.8
C(16)-C(17)-C(18)	119.95(16)
C(16)-C(17)-H(17)	120.0
C(18)-C(17)-H(17)	120.0
C(17)-C(18)-C(19)	119.85(16)
C(17)-C(18)-H(18)	120.1
C(19)-C(18)-H(18)	120.1
C(18)-C(19)-C(14)	120.51(16)
C(18)-C(19)-H(19)	119.7
C(14)-C(19)-H(19)	119.7
C(2)-O(1)-C(1)	118.01(13)
C(12)-O(4)-C(13)	111.37(11)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for compound **242a**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

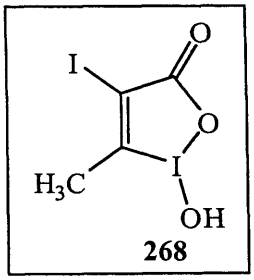
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	46(1)	37(1)	35(1)	10(1)	-8(1)	-19(1)
C(2)	24(1)	29(1)	24(1)	3(1)	-5(1)	-3(1)
C(3)	21(1)	26(1)	21(1)	3(1)	-5(1)	-2(1)
C(4)	24(1)	29(1)	25(1)	2(1)	-9(1)	-4(1)
C(5)	24(1)	27(1)	21(1)	-2(1)	-4(1)	-2(1)
C(6)	30(1)	30(1)	32(1)	-3(1)	-12(1)	-4(1)
C(7)	38(1)	26(1)	42(1)	-1(1)	-13(1)	-8(1)
C(8)	42(1)	24(1)	35(1)	2(1)	-12(1)	-2(1)
C(9)	29(1)	28(1)	28(1)	0(1)	-10(1)	1(1)
C(10)	22(1)	25(1)	20(1)	-2(1)	-3(1)	-1(1)
C(11)	19(1)	28(1)	19(1)	2(1)	-4(1)	-1(1)
C(12)	24(1)	23(1)	24(1)	4(1)	-4(1)	-6(1)
C(13)	21(1)	26(1)	22(1)	1(1)	-5(1)	-4(1)
C(14)	27(1)	26(1)	20(1)	-2(1)	-7(1)	-4(1)
C(15)	29(1)	31(1)	24(1)	0(1)	-3(1)	-2(1)
C(16)	42(1)	40(1)	23(1)	4(1)	-2(1)	-9(1)
C(17)	51(1)	37(1)	30(1)	10(1)	-19(1)	-9(1)
C(18)	34(1)	43(1)	43(1)	8(1)	-20(1)	-4(1)
C(19)	25(1)	39(1)	30(1)	5(1)	-8(1)	-6(1)
O(1)	44(1)	40(1)	29(1)	11(1)	-13(1)	-22(1)
O(2)	67(1)	65(1)	28(1)	19(1)	-20(1)	-37(1)
O(3)	25(1)	29(1)	33(1)	3(1)	-4(1)	2(1)
O(4)	28(1)	29(1)	22(1)	-1(1)	-5(1)	1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for compound **242a** .

	x	y	z	U(eq)
H(1A)	6105	8286	5114	58
H(1B)	7721	8308	5888	58
H(1C)	5357	9342	6004	58
H(4A)	-616	4838	6180	30
H(4B)	1570	4232	5429	30
H(6)	-1471	1786	6253	35
H(7)	-839	-417	7162	41
H(8)	2116	-670	8034	40
H(9)	4449	1281	8043	33
H(11)	5599	3978	6689	26
H(13)	5450	5633	7868	28
H(15)	1136	4061	9484	34
H(16)	1683	2365	10727	42
H(17)	5290	1212	10823	45
H(18)	8410	1813	9700	46
H(19)	7897	3567	8480	37

Appendix 3

Single Crystal X-ray Structure of Compound 268



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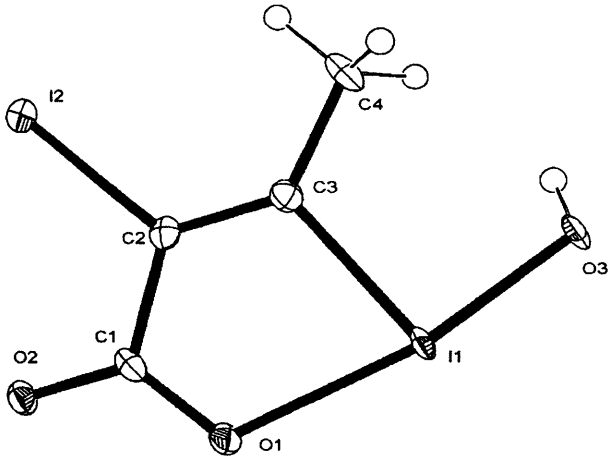

Table 1. Crystal data and structure refinement for compound **268**.

Identification code	Hypervalent iodine (III) reagent	
Empirical formula	C8 H8 I4 O6	
Formula weight	707.74	
Temperature	110(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P21/n	
Unit cell dimensions	a = 10.6510(6) Å	α= 90°.
	b = 5.2210(4) Å	β= 110.130(4)°.
	c = 13.9940(10) Å	γ = 90°.
Volume	730.65(9) $Å^3$	
Z	2	
Density (calculated)	3.217 Mg/m^3	
Absorption coefficient	8.544 mm^{-1}	
F(000)	632	
Crystal size	0.40 x 0.08 x 0.04 mm^3	
Theta range for data collection	2.95 to 27.46°.	
Index ranges	-13<=h<=13, -6<=k<=6, -14<=l<=18	
Reflections collected	3337	
Independent reflections	1624 [R(int) = 0.0749]	

Completeness to theta = 27.46°	96.7 %
Max. and min. transmission	0.7262 and 0.1313
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1624 / 0 / 84
Goodness-of-fit on F^2	1.128
Final R indices [I>2sigma(I)]	R1 = 0.0473, wR2 = 0.1166
R indices (all data)	R1 = 0.0501, wR2 = 0.1190
Largest diff. peak and hole	2.868 and -2.878 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for compound **268**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	3969(6)	5977(14)	6062(5)	16(1)
C(2)	2766(6)	4380(14)	5512(5)	14(1)
C(3)	2140(6)	4645(15)	4515(5)	17(1)
C(4)	912(8)	3398(16)	3814(5)	22(2)
O(1)	4338(5)	7543(10)	5512(4)	17(1)
O(2)	4541(4)	5708(10)	6994(3)	17(1)
O(3)	1795(5)	6707(10)	2485(3)	16(1)
I(1)	3032(1)	7503(1)	3863(1)	13(1)
I(2)	2142(1)	1759(1)	6386(1)	18(1)

Table 3. Bond lengths [Å] and angles [°] for compound **268**.

C(1)-O(2)	1.244(8)
C(1)-O(1)	1.273(9)
C(1)-C(2)	1.500(9)
C(2)-C(3)	1.331(9)
C(2)-I(2)	2.090(7)
C(3)-C(4)	1.488(9)
C(3)-I(1)	2.134(7)
C(4)-H(4A)	0.9800
C(4)-H(4B)	0.9800
C(4)-H(4C)	0.9800
O(1)-I(1)	2.247(5)
O(3)-I(1)	1.970(5)
O(3)-H(3)	0.8400
O(2)-C(1)-O(1)	124.4(7)
O(2)-C(1)-C(2)	119.9(6)
O(1)-C(1)-C(2)	115.7(6)
C(3)-C(2)-C(1)	120.7(6)
C(3)-C(2)-I(2)	122.4(6)
C(1)-C(2)-I(2)	116.8(4)
C(2)-C(3)-C(4)	130.9(7)
C(2)-C(3)-I(1)	112.6(5)
C(4)-C(3)-I(1)	116.4(5)
C(3)-C(4)-H(4A)	109.5
C(3)-C(4)-H(4B)	109.5
H(4A)-C(4)-H(4B)	109.5
C(3)-C(4)-H(4C)	109.5
H(4A)-C(4)-H(4C)	109.5
H(4B)-C(4)-H(4C)	109.5
C(1)-O(1)-I(1)	113.8(4)
I(1)-O(3)-H(3)	109.5
O(3)-I(1)-C(3)	91.4(2)
O(3)-I(1)-O(1)	167.6(2)
C(3)-I(1)-O(1)	77.1(2)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for compound **268**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	12(3)	22(4)	12(3)	-5(3)	2(2)	2(3)
C(2)	13(3)	18(3)	14(3)	1(3)	7(2)	4(3)
C(3)	13(3)	22(4)	15(3)	3(3)	3(2)	2(3)
C(4)	16(4)	28(4)	15(3)	-5(3)	-2(3)	3(3)
O(1)	10(2)	28(3)	13(2)	1(2)	2(2)	-1(2)
O(2)	15(2)	22(3)	12(2)	0(2)	2(2)	1(2)
O(3)	17(2)	18(3)	8(2)	-1(2)	-4(2)	0(2)
I(1)	10(1)	20(1)	7(1)	1(1)	-1(1)	3(1)
I(2)	20(1)	20(1)	16(1)	2(1)	7(1)	-1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for compound **268**.

	x	y	z	U(eq)
H(4A)	660	1970	4165	33
H(4B)	1085	2754	3213	33
H(4C)	182	4650	3602	33
H(3)	1634	5128	2438	25

Publications earned during the PhD endeavour

- Zulfiqar A. Khan; Thomas, Wirth. **Synthesis of Indene Derivatives via Electrophilic Cyclization.** *Org. Lett.* **2009**, 11(1), 229-231.

- Zulfiqar A. Khan; M. Iwaoka; Thomas, Wirth. **Novel Cyclization Cascades to Functionalized Indanes and Tetrahydronaphthalenes.** *Tetrahedron* **2010**, *66 (33)*, 6639-6646.

- Azhar-ul-Haq, A. Shah; Zulfiqar A. Khan; Naila, Choudhary; Christine, Loholter; Sascha, Schafer; Guillaume, P. L. Marie; Umar, Farooq; Bernhard, Witulski; Thomas, Wirth. **Iodoxolone-Based Hypervalent Iodine Reagents.** *Org. Lett.* **2009**, 11(16), 3578-3581.

- Thomas, Wirth; Zulfiqar, A. Khan. **Diisobutylaluminium Phenyl Selenide**. Electronic Encyclopedia of Reagents for Organic Synthesis, Ed. L. A. Paquette, John Wiley & Sons, **2008**.

- Thomas, Wirth; Zulfiqar, A. Khan. **Dimethyl Selenoxide**. Electronic Encyclopedia of Reagents for Organic Synthesis, Ed. L. A. Paquette, John Wiley & Sons, **2008**.