Biomimetic Light-Driven E/Z Switcher: Design and Synthesis

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Dottorando
Dott. Farina Grazia

Tutore
Prof. Zanirato Vinicio

Anni (2008-2010)
## INDEX

1. **INTRODUCTION**  
   1.1 Light  
   1.2 Photochromism  
   1.3 Reversible photoisomerizable switches  
      1.3.1 Diarylethene  
      1.3.2 Spiropyrrane  
      1.3.3 Azobenzene  
      1.3.4 Hemithioindigo  
   1.4 Photochromism in living system  
      1.4.1 Photoactive Yellow Protein (PYP)  
      1.4.2 Rhodopsin  

2. **DESIGN AND SYNTHESIS**  
   2.1 Design and development of a Light-Driven $E/Z$ Switcher  

3. **RESULTS AND CONCLUSIONS**  
   3.1 Synthetic development of second generation molecular switches (PSBII)
1. INTRODUCTION
1.1 Light

Life on Earth depends, both directly and indirectly, on the influence that light has on chemistry. The energy of the Sun’s visible and ultraviolet radiation promotes processes that not only permit the continued existence of life on the planet, but which quite probably led to the development and evolution of life itself. Photosynthesis in plants provides the most obvious example of chemistry driven by light that, at present stage of evolution, forms a vital link between the utilization of solar energy and the survival of life. The production of carbohydrates that can be used as energy sources by other life forms is just one of many examples like the production of oxygen, a major component of our atmosphere.\(^1\) As well as biological processes, light plays an important role in organic photochemistry. It is used to effect pericyclic (electrocyclic) reactions\(^2\) and cis-trans isomerisations in compounds that contain C=C, C=N and N=N moieties such as alkenes, imines, oximes and diazo compounds.\(^3\) By using these small organic molecules as simple models of more complex biological systems, scientists can examine the interaction of light with synthetic models and the interaction of these synthetic molecules with biomolecules in an attempt not only to improve our understanding of

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the truly complex and diverse nature of biological systems, but also to control and regulate many different biological activities.

1.2 Photochromism

Photochromism is defined as a reversible change of a single chemical species between two states having distinguishable different absorption spectra, such change being induced in at least one direction by the action of electromagnetic radiation (usually UV light). The thermodynamically stable form A is transformed by irradiation into form B (Figure 1).

![Figure 1](image)

The back reaction can occur thermally (Photochromism of type T) or photochemically (Photochromism of type P). In many systems, including spiropyrans, spirooxazines and chromenes, the back reaction is predominantly thermally driven, but in others the photochemically induced state is thermally stable and the back reaction must be driven photochemically, as in fulgides and
diarylethenes.\textsuperscript{4} Change in color (or absorption spectrum) is one of the accompanying properties with the photochromic structural change. Usually (but not always) one isomer is colorless and thermally more stable than the colored counterpart. The great difference in color of the isomers is required in order to achieve the highly biased ratio of the isomers at the photostationary states.\textsuperscript{5}

Photochromic molecules, which can be reversibly switched between two isomeric forms with different colors, structures, or functional properties by light at distinctive wavelengths, attract ubiquitous attention for applications as optical memory and logic devices, or as molecular motors, machines, or manipulators.\textsuperscript{6}

1.3 Reversible photoisomerizable switches

A photochromic molecule can exhibit properties analogous to a switch. Molecular switches consist of two stable states distinguishable by physical or chemical properties (response), which are interchangeable through the alteration of controllable parameters (stimuli) such as pH, temperature, light, redox potential and metal...


\textsuperscript{5} Masako Saito, Yasushi Yokoyama, Chiral photochemistry, CRC Press, 2004, p.235-259.

Chapter 1 Introduction

ions. These photoreversible compounds (Figure 1), where switching process is based on photochemically induced interconversion, are also called Photoswitches. The photochromic processes involved are typically cis-trans isomerization, photocyclization, photoinduced electron transfer and keto-enol tautomerism.

Molecular switches based on photochemical E/Z isomerization have been employed in different contexts to convert light-energy into “mechanical” motion at the molecular level. Currently, the design and preparation of molecular switches based on photochemical E/Z isomerization constitutes an attractive research target to obtain novel materials for nanotechnology. Despite the fact that the inevitable condition of photochemical bistability is fulfilled in these systems, a number of other requirements are essential. These features are well illustrated in Figure 2 where a model reaction path for an efficient (Figure 2a) and a less efficient (Figure 2b) switch are reported. Accordingly, an efficient photoisomerization would occur when the photoexcited reactant A* evolves along a barrierless excited-state path and finally relaxes to the energy minimum corresponding to

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photoproduct B. Furthermore, in an efficient switcher, the reaction coordinate connecting A* to B should be as simple as possible and linear (i.e. without intermediate energetic state along the process).

![Diagram](image.png)

**Figure 2**

In contrast, the reaction path of Figure 2b belongs to an inefficient switcher. In fact, the presence of excited state and/or ground-state intermediates (I* and I respectively) along the path allows for redistribution of the photon energy.

An additional desirable property of photochemical switchers is the stability of the isomers A and B with respect to thermal (i.e., ground state) Z/E isomerization. As shown in Figure 2a (see dashed energy profile), in an efficient switcher the barrier for thermal Z/E isomerization must be high enough to restrain the return of B to A and *vice versa.*
There are various classes of compounds that undergo reversible photoisomerisation. Many of these fit the criteria for efficient photoswitches and have been applied to biological systems. A few representative examples have been included below.

1.3.1 Diarylethene

The switching mechanism of photochromic diarylethenes is based on a photocyclization under UV light irradiation of the colorless open form resulting in colored closed form, which can undergo ring opening again with visible light\(^\text{10}\) (Figure 3).

Recently, the Diarylethene shown in fig. 3 has been extensively used by Takeshita \textit{et al.}\(^\text{11}\) for recognition of saccharides with important roles in biological system. The open-ring form has got two conformers: in the parallel conformation the heterocyclic rings are fixed to the mirror symmetry, while the anti-parallel one has got the rings in \(C_2\) symmetry (Figure 3).\(^\text{12}\) The parallel and anti-parallel conformations exchange rapidly at room temperature and only the anti-parallel conformer undergoes photoisomerization to give the closed-ring form by irradiation with UV light. In the parallel conformer two binding sites (boronic acid functional groups) face each other like tweezers. Saccharides have many hydroxyl groups which can form esters with boronic acids, therefore one can expect


the parallel conformer to form a 1:1 complex with saccharides because two faced boronic acids can form boronate linkages with four hydroxyl groups. On the other hand, in the closed-ring form the boronic acid groups are separated and cannot form the complex.

Figure 3

1.3.2 Spiropyran

Compounds of the spiropyran-type can be switched between two states, the closed spiropyran form and the open merocyanine dye. The ring opens upon irradiation with UV light and it closes again in the dark or upon irradiation with visible light (Figure 4).

These photoresponsive materials have found application as light filters (e.g. sun glasses) and as optical recording media; indeed,
numerous studies have been devoted to this class of photochromic compounds.\textsuperscript{13}

A very recent study nicely demonstrated the feasibility of the light-activation approach for the analysis of channel proteins.

A spiropyran-merocyanine photoswitchable mechanosensitive channel (MscL) from \textit{Escherichia coli} was constructed and embedded in liposomes. Upon irradiation with UV light (366 nm) the channel could be opened, and closure, if desired, was obtained by repeated irradiation with visible light at wavelengths above 460 nm.

This system might be useful for the light-gated delivery of bioactive molecules.\textsuperscript{14}

1.3.3 Azobenzene

Azobenzene can interconvert from the \textit{cis}-form to the \textit{trans}-one and \textit{vice versa} when a specific wavelength radiation is provided.

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{figure5.png}
\caption{Switches based on the \textit{E/Z} photoisomerization of the azobenzene (Ab) chromophore have been used to control ion complexation,\textsuperscript{15} electronic properties\textsuperscript{16} and catalysis\textsuperscript{17} or to trigger folding/unfolding of oligopeptide chains.\textsuperscript{18}}
\end{figure}

Recently, it has been described a photoswitch which directly controls ion channel activity in a light-dependent manner. Neurons have ion channels that are directly activated by voltage, ligands, temperature and mechanical forces, but none are known to be directly sensitive to light. Kramer et al.\textsuperscript{19} have devised a strategy that allows light to control ion channels and therefore neuronal function. This optical stimulation method is based on semi-synthetic light activated ion-channel called SPARK (Synthetic Photoisomerizable Azobenzene Regulated K\(^{+}\) channel) where a synthetic photoswitch is covalently attached to a genetically engineered Shaker K\(^{+}\) channel protein. SPARK opens up with short wavelength light (380-390nm), triggering a K\(^{+}\)-selective current that hyperpolarizes the membrane potential. Long wavelength light (500-505nm) accelerates the closure of the channel and turns off the current, restoring the original membrane potential. The photoswitch (MAL-AZO-QA) consists of a cysteine-reactive maleimide (MAL) group, an azobenzene (AZO) group, which is photoisomerizable, and a quaternary ammonium (QA) group, which is a blocker of the pore of K\(^{+}\) channels. The channel protein is engineered to allow attachment of the photoswitch to an extracellular cysteine positioned near the pore.

When the AZO is in \textit{trans} configuration, the QA can reach the pore, blocking ion flow. Photoisomerization to the \textit{cis} form shortens the AZO removing the QA, unblocking the pore, thus allowing K\(^+\) to flow out and hyperpolarize the cell. Hence MAL-AZO-QA acts as an artificial light-sensitive gate for the channel.

\textbf{1.3.4 Hemithioindigo}

Although less well studied than azobenzenes, Hemithioindigos are appealing candidates as components of photoswitchable
biomolecules.\textsuperscript{20} If compared to many azobenzene derivatives they isomerize at much longer wavelengths\textsuperscript{21} and are stable over thousands of cycles. Hemithioindigo amino acid derivative consists of two chemical parts: hemithioindigo combined with a hemistilbene moiety (Figure 7).

![Figure 7](image_url)

Importantly, its longer end-to-end distance entails that protein changes accompanying isomerization are substantial. Moreover, the chromophore dipole moment significantly changes its orientation following the photoisomerization. These combined effects make transduction of the isomerization event into a biochemical effect more probable.

A recent application of Hemithioindigo was described by Woolley \textit{et al.}\textsuperscript{22} They investigate the incorporation of Hemithioindigo chromophore into the peptide ion channel gramicidin. Photo-control

of ion channel offers the prospect of external control of cellular excitability. Models of gramicidin A were built with Hemithioindigo amino acid replacing valine at position 1 of the sequence. Analysis of the dipole moments showed that the photoisomerization from the Z form to the E form of the hemithioindigo-modified channel produces an increase in the single channel current. Representative structures of the Z and E forms of hemithioindigo gramicidin are shown in Figure 8.

Models of the dimeric gramicidin A channel with hemithioindigo amino acids incorporated at position 1. The top view shows the open ion-conduction pore through the structure. (Dipole moments are indicated with the arrowhead at the negative end of the dipole).

Figure 8
1.4 Photochromism in living system

1.4.1 Photoactive Yellow Protein (PYP)

Photoactive Yellow Protein (PYP) is a small water-soluble protein and a member of the xanthopsin photoreceptor family. PYP can be isolated from the purple phototropic eubacterium *Halorhodospira halophila*, and is presumed responsible for the initial steps of the homeostatic pathway that results in the negative phototaxis (the movement of an entire organism in response to light) of the bacterium to blue light. The availability of structural information for different functional states combined with the relatively simple photocycle, make PYP an ideal “laboratory” for the detailed study of biological light detection and the relation of structural change to protein function. It also holds considerable promise for optical data storage and computing applications. Indeed, in the past decade, PYP has become a model system for studying the photo-initiation and ensuing dynamics of photoreceptor proteins. The PYP protein domain consists of a single polypeptide chain of 125 residues, the Cys69 binds the p-coumaric acid chromophore via a thioester linkage (Figure 9). The coumaroyl chromophore has one isomerizable double bond and one ionizable oxygen atom (phenolic oxygen, O4’).
In the dark state (PYP\textsubscript{dark}), the double bond is in the \textit{trans} form\textsuperscript{23} and the \textit{p}-hydroxyphenyl moiety is deprotonated. Hydrogen-bonding interactions with the Tyr42 and Glu46 side chains as well as the presence of the Arg52 guanidinium group intervene to stabilize the chromophore.\textsuperscript{24} Schematic representation of the photochemistry relevant for the photocycle of PYP is shown in Figure 10.

In pG (PYP\textsubscript{dark}) the maximal absorbance of the chromophore is strongly red shifted. After blue light excitation, pG is converted into the short-lived intermediate pR (PYP\textsubscript{L}), where the chromophore is in the \textit{cis} configuration and still deprotonated.


Figure 10

In the dark, pR is subsequently converted to the long-lived intermediate pB (PYP$_{M}$), where the chromophore is in the *cis* configuration and protonated. Finally, pG is recovered in the last step of the photocycle.$^{25}$

1.4.2 Rhodopsin

The primary event in vision is one of the fastest and most efficient photochemical reactions in nature. The key step in this process is the *cis*-to-*trans* isomerization of 11-*cis* retinal chromophore in Rhodopsin. This 7-$\alpha$-helical transmembrane protein is the photoreceptor molecule present in vertebrate eyes, which senses light stimuli and initiates a signaling cascade mediated by the G protein. Rhodopsin consists of the protein moiety *opsin* and a reversibly

bound chromophore, 11-cis-retinal. The covalent bond is formed between the aldehyde group of retinal and ε-amino group of Lysine296 residue through a protonated Schiff base linkage.26

![Figure 11](image1)

**Figure 11**

The absorption of a photon causes the isomerization of the 11-cis isomer of the retinal protonated Schiff base (PSB11) to the all-trans state (PSBT), triggering a series of events that eventually produce electrical impulses to be sent to the brain along the optic nerve.

![Figure 12](image2)

**Figure 12**

In particular π-π* excitation of the 11-cis form of the chromophore yields in 200fs exclusively the all-trans form through a Z → E counterclockwise twist of the C11=C12 bound (Figure 12) and

Chapter 1 Introduction

occurs with a 67% quantum yield.\textsuperscript{27} The photoisomerization of PSB11 is extremely efficient because it is stereoselective, unidirectional, ultrafast and occurs with high quantum yield.

Although the attractive properties of the protein-embedded PSB11, when in solution\textsuperscript{28} the chromophore features an unselective isomerisation and a picoseCONDS excited-state lifetime.\textsuperscript{29} This problem prompts a search for artificial Rh-mimetic molecules replicating the excited-state properties of the protein embedded chromophore when in solution.

\textit{Work covered in this thesis will look at the design and synthesis of novel switches that replicate different aspects of the Z/E photoisomerization of rhodopsin with the aim of obtaining novel building blocks to be employed in different molecular environments.}

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2. DESIGN AND SYNTHESIS
2.1 Design and development of a Light-Driven E/Z Switcher

The purpose of this brief introduction is to describe the essential steps of a multidisciplinary work where photo-/computational chemistry and synthesis have contributed to formulate a new class of molecular switches miming different aspects of the Z/E photoisomerization process of Rhodopsin. As already noted, the photoisomerization of the 11-\textit{cis}-retinal-protonated Schiff base PSB11 (the chromophore of Rhodopsin) to its all-\textit{trans} isomer (PSBT) is the primary event of vision.\textsuperscript{30}

The high quantum yield associated with the ultrafast \textit{cis}/\textit{trans} isomerisation of C11-C12 double bond seems strictly connected to the complex chemical nature of the protein embedded chromophore. The spectacular properties of rhodopsin inspired several computational studies devoted to understand the intimate nature of the chromophore excited state which is at the basis of the efficient photoisomerization process. These theoretical studies pointed out that a penta-2,4-dieniminium moiety is the minimal structure replicating the photochemical properties of the more complex natural pigment. As a result, it was expected that molecules featuring such a conjugated system could act as PSB11 models and could in principle

behave as artificial molecular switches.\textsuperscript{31}

![Figure 13](image1)

On these basis, we embarked on the preparation of a small set of molecules featuring a pyrroline ring conjugated to an aromatic nucleus through a vinyl spacer (Figure 14).

![Figure 14](image2)

The 3-benzylidene-1-pyrroline \textbf{1neut}, was prepared by an aldol-like condensation between 3,4-dihydro-2H-pyrrole (as a trimer) and benzaldehyde.\textsuperscript{31}

The desired poly-conjugated iminium ion \textbf{1H} (as a mixture of \textit{E}- and \textit{Z} isomers) was in turn obtained after treatment of \textbf{1neut} with

trifluoroacetic acid. Successively, N-quaternization with methyl trifluoromethansulfonate was preferred in order to get stable iminium cations.

Reagents and conditions: (i) 1neut and p-MeO-1neut: MeOH, rt, 48h; p-NO₂-1neut: 0.6 M acetic acid/0.2 M sodium acetate, MeOH, 60°C, 24h.

Scheme 1

The inductive effect of the methyl group in direction of the positively charged nitrogen atom could be at the basis of the observed major
stability of these salts with respect to the previously prepared protonated forms.

In addition to compound 1Me, we synthesized \( p\text{-MeO-1Me} \) and \( p\text{-NO}_2\text{-1Me} \) (Scheme 1) thus acceding to a class of molecular switches called PSB\(^1\) (first generation of PSBs). The presence of electron-releasing or electron withdrawing groups on the aromatic ring allowed the modulation of the electronic density within the \( \pi \)-system. Even though these prototype compounds satisfied the general criteria required for a molecular switch, the quantum yields measured for their photoisomerization were too low. Responsible for the quite disappointing result we found the existence of competitive energy decay paths from the excited state, being the free rotation along the carbon-carbon single bond connecting the phenyl ring and the ethylene spacer the most important one.

Consequently, the next step was the design of molecules with the aim to overcome this critical aspect. We turned our attention to more rigid photoexcitable structures so as to prevent conformers generation. A suitable molecule would have the carbon-carbon double bond connecting the cyclic imine to the phenyl ring as the only site to spin in the excited state electronic structure.\(^{32}\)

After several investigations we were able to achieve an effective preparation of PSB\(^{\text{II}}\), once again a molecule featuring a pyrroline

moiety conjugated to an aromatic ring which, differently from the PSB\textsuperscript{1}, is part of the rigid indanyl nucleus.

![Image of PSB\textsuperscript{1} and PSB\textsuperscript{II}](image)

**Figure 15**

We addressed NAIP switch (N-alkylated indanylidene pyrroline) through different pathways which will be discussed about later. The photochemical and spectral characterization of NAIP showed it was a biomimetic molecular switch.\textsuperscript{33} As a matter of fact, NAIP switch in methanol solution displayed excited state very close to the one of Rh-embedded PSB\textsuperscript{11}.

![Image of NAIP](image)

**Figure 16**

These gratifying results prompted us to imagine potentially useful applications for this class of compounds.

We thought the \textit{Z/E} light induced isomerization of \textbf{NAIP} could provide the basis for the development of electrostatic photoswitches where a large dipole moment change was achievable via a ca. 180° rotation of a functionalized alkylidene unit.\textsuperscript{34}

Literature examples of electrostatic photoswitches are compounds of the spiropyran type that can change from a neutral and a zwitterionic state via photochemical ring opening reaction. This property has been employed in different experiments to reversibly modulate the activity of enzymes\textsuperscript{35} and channel protein\textsuperscript{36} or to achieve novel sensor.\textsuperscript{37} Furthermore, it has been shown that the strong permanent dipole moment in the zwitterionic form of nitrospiropyran units attached to specific peptide residues is responsible for light-induced $\alpha$-helix-random coil conformational transitions.\textsuperscript{38}

In this context, we designed achieving electrostatic photoswitches by placing a carboxyl functional group at C-2 of the \textbf{NAIP} pyrroline moiety.

Indeed, in the new molecule the external counterion would be replaced by the internal carboxylate to form a zwitterionic structure named \textbf{NAIPzw} whose synthesis is described in the following paragraph. Computational and spectroscopic studies performed on \textbf{NAIPzw} have shown it constitutes the prototype of a novel generation of electrostatic switches. \textbf{NAIPzw} undergoes a reversible light-induced dipole moment change on the order of 30 D: a behaviour which opens up a new perspective for the light-driven conformational control of macromolecular structures (as a protein) determined by polar interactions. In a situation where the indanylidene ring is held in a fixed orientation, light can be used to invert the dipole, yielding a dramatic change in the local electrostatic field. Such an event would destabilize the original equilibrium conformation thus leading to a conformational change. This charming result has stimulated the design of functionalized \textbf{NAIPzw} to be attached to a protein domain. In particular, we explored the possibility of synthesizing \textbf{NAIPzwaa}: an artificial \(\alpha\)-amino acid to be used in peptide synthesis.
Chapter 2  
Design and Synthesis

We commenced preparing the **NAIPaa** featuring a quaternary amino acid and the \(N\)-methyl iminium group at both ends of the photoisomerizable carbon-carbon double bound.

The successful preparation of the unnatural amino acid **NAIPaa** bearing a photoswitchable side chain, strongly supports the possibility to achieve semisynthetic peptides and proteins incorporating a dipole switch in a conformationally locked orientation.\(^{39}\)

The synthesis of **NAIPzwaa** is still under investigation. The following sections are dedicated to the synthesis of the different **NAIP** photoswitches. Our synthetic successes as well as the failures

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that so frequently accompany research-work are reported in a chronological order.
3. RESULTS AND CONCLUSIONS
3.1 Synthetic development of second generation molecular switches (PSBII)

A retrosynthetic analysis showed an intramolecular capture of nitrilium ion by a suitable located olefin group as a possible approach to the PSBII formulation.

\[ \text{Scheme 5} \]

Nitrilium ions acts as intermediates in several reactions and many different ways for their preparation are available.\textsuperscript{40} For example in the Beckmann’s rearrangement a nitrilium species is derived from oximes.\textsuperscript{41}

\[ \text{Scheme 6} \]

However, the synthetic applicability of this process is limited by the low stereospecificity: a single geometric isomer of the oxime is necessary to obtain a specific nitrilium ion.\textsuperscript{42} Gawley\textsuperscript{41} and


Angelastro\textsuperscript{43} developed an alternative strategy for the generation of the reactive nitrilium species through dehydration of secondary amides. In particular, it was found that nitrilium ions generated in situ by the action of trimethylsilyl polyphosphate (PPSE) on secondary amides, were promptly intercepted by an intramolecular olefin giving rise to six or to five membered nitrogen heterocycles (Scheme 7).

\begin{center}
\includegraphics[width=\textwidth]{scheme7.png}
\end{center}

Scheme 7

It was also demonstrated that the more nucleophilic character of the styryl terminator the easier was the cyclization reaction: the para-methoxyl group was beneficial to the nitrilium capture. Following this tip we designed a PSB\textsuperscript{II} structure where a methoxyl group is the substituent on the aromatic portion of the indane nucleus.

Starting from 5-methoxy-1-indanone two protocols have been optimized: their difference lying in the number of steps rather than in the kind of reagents or reactions. In the first synthetic approach (Scheme 8) the indanone derivative 1a treated with

cyclopropylmagnesium bromide afforded the cyclopropyl carbinol derivative 3a substrate of the key homoallylic rearrangement. Thus, its exposure to the action of HBr in AcOH led to the bromopropylidene derivative 4a as a 3:1 mixture of diastereomers. The subsequent bromide displacement with sodium azide gave 5a which furnished the acetamide 6a by the one-pot chemoselective hydrogenation in the presence of acetic anhydride.\textsuperscript{44} The latter, subjected to the action of PPSE led to the desired pyrroline derivative 7a as the main product (71%).

\textbf{Reagents and conditions:} (i) MeI, tBuOK, tBuOH, Et\textsubscript{2}O, reflux, 7h; (ii) Mg, ciclopropylbromide, THF, reflux, 3h; (iii) HBr, AcOH, 10min; (iv) NaN\textsubscript{3}, DMF, 60°C, 2.5h; (v) Lindlar catalyst, Ac\textsubscript{2}O, NaOAc, 60psi H\textsubscript{2}, 6h; (vi) P\textsubscript{2}O\textsubscript{5}, HMDSO, CCl\textsubscript{4}, reflux, 2h.

\textbf{Scheme 8}

The $^1$H NMR spectrum of compound 7a showed the presence of two diastereomers in 98:2 ratio; the respective geometries have been assigned on the basis of NOE difference spectroscopy. In details, a positive NOE between the proton at the aromatic C-7’ carbon (d, \( \delta = 7.2 \)) and the methyl at the C-5 of the pyrrolidine ring (m, \( \delta = 2.2 \)) was observed for the predominant isomer to which Z configuration could be assigned (Scheme 9).

![Z-7a](image)

**Scheme 9**

In the presence of HCl the imine function of 7a was converted to the corresponding protonated Schiff base. Later, we observed how the N-methylation with methyltriflate led to the more stable and tractable iminium product 7a-N$^+$Me.

![7a & 7a-N$^+$Me](image)

**Reagents and conditions:** (i) CF$_3$SO$_3$CH$_3$, benzene, rt, 10min.

**Scheme 10**

Concerning the above synthetic scheme we made the following considerations: a) the electron-releasing p-OMe group on the indanyl
moiety, in addition to greater the nucleophilicity of the styryl terminator, stabilized the carbocation intermediate in the key step; b) the geminal methyl groups at C-2 blocked the carbon-carbon double bond from the homoallylic rearrangement, in the exocyclic position.

![Diagram](image.png)

**Reagents and conditions:** (i) Mg, ciclopropylbromide, THF, reflux, 3h; HCl, AcOH, r.t., 30min.

**Scheme 11**

About item b) we found that, by using the commercial indanone 1 as the partner of the Grignard reagent, the homoallylic rearrangement furnished the undesired thermodynamically favoured indenyl derivative 2-endo (Scheme 11). The latter was also the resulting product in the alternative sequence entailing first a Wittig reaction with cyclopropylidene-triphenylphosphorane (generated in situ from 3-bromopropyld-phosphonium bromide and KHMDSA)\(^{45}\) then the HCl promoted rearrangement.

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Thus, the desired 3-exo product, formed in low yield, spontaneously isomerized to the 3e-endo from which compound 2-endo was eventually obtained through the usual rearrangement (Scheme 12).

Reagents and conditions: (i) tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1), THF, rt, 2h; (ii) HCl, AcOH, r.t., 1h.

Scheme 12

Thus we were forced to remove the α-hydrogen atoms of the starting 5-methoxy-1-indanone 1. This operation was easily achieved via exhaustive methylation of the indanone to give the bis-methyl derivative 1a (Scheme 13).46

Reagents and conditions: (i) MeI, tBuOK, tBuOH, Et2O, reflux, 7h;

Scheme 13

Chapter 3 Results and Conclusion

The appearance in the literature of a paper describing a Triflic acid promoted [3+2] cycloaddition between methylene cyclopropanes and acetonitrile (Scheme 14)\textsuperscript{47} gave us the stimulus to find out a more direct approach to Indanylidene Pyrrolines (IP).

\[
\text{Ph} + \text{MeCN} \xrightarrow{\text{TfOH, \text{r.t.}, 4h}} \begin{array}{c}
\begin{array}{c}
\text{Ph} \\
\text{Ph}
\end{array}
\end{array} + \begin{array}{c}
\begin{array}{c}
\text{Ph} \\
\text{Ph}
\end{array}
\end{array}
\]

Scheme 14

We realized that treatment of cyclopropylcarbinol 3a with Tf\textsubscript{2}O in the presence of acetonitrile could led “one-pot” to 7a (Scheme 15).

\[
\begin{array}{c}
\begin{array}{c}
\text{MeO} \\
\text{OH}
\end{array}
\end{array} \xrightarrow{i} \begin{array}{c}
\begin{array}{c}
\text{MeO} \\
\text{N}
\end{array}
\end{array}
\]

Reagents and conditions: (i) Tf\textsubscript{2}O, ACN, rt, 3h.

Scheme 15

We were confident that esterification of 3a (as triflate) would have triggered a tandem homoallylic rearrangement-nitrilium ion cyclization with the final production of the desired indanylidene pyrroline. A plausible mechanism could involve the cationic species I-III as shown in Scheme 16.

\textsuperscript{47} Huang, J.W.; Shi, M., *Synlett*, 2004, 2343.
We were delighted to find that following the “one-pot” protocol carbinol 3a gave compound 7a in satisfactory yield (62% over three steps) together with traces of the amide 6a.

**Reagents and conditions:** (i) MeI, tBuOK, tBuOH, Et₂O, reflux, 7h; (ii) Mg, ciclopropylbromide, THF, reflux, 3h; (iii) Tf₂O, ACN, r.t., 3h.

Scheme 16

3.2 Synthesis of zwitterionic switch (NAIPzw).

In a formal way, the desired switch 7bzw contemplates the substitution of an hydrogen atom at C-2 of 7aN⁺Me with a carboxyl group. For its preparation we reasoned on the possibility to fit the previous approach based on the fruitful chemistry of cyclopropyl...
reagents. It was apparent as a facile synthetic solution the use of a properly functionalized cyclopropyl magnesium reagent in the initial synthetic step.

As retrosynthetically depicted in Scheme 17, the compound 7b could be obtained via the one-pot rearrangement of carbinol 9 in turn achievable by nucleophilic addition of the cyclopropylmagnesium reagent derived from 8 to the carbonyl group of indanone 1a.

![Scheme 17](image)

Inspection of literature disclosed us that the preparation of the specific Grignard reagent we had to use had already been described by Knochel et al. They reported that a stabilized organometallic species was easily obtained by the metal-halogen exchange between i-PrMgCl and cis-2-iodocyclopropanecarboxylate. Thus, the in situ formed Grignard reagent was able to react with several kinds of electrophiles (Scheme 18).

![Scheme 18](image)

---

Despite the facile access to the new interesting organometallic reagent, the preparation of the pivotal \textit{cis}-2-iodocyclopropanecarboxylate $8$ was a rather tedious process (Scheme 21).

We found that the nucleophilic addition of the cyclopropylmagnesium reagent derived from $8$ to the carbonyl group of indanone $1\text{a}$ took place with concomitant lactonization to the spiro compound $10$. On the latter, we made an attempt to do ring-opening/nitrilium ring-closing reaction by using the system TfOH/CH$_3$CN. Unexpectedly, compound $10$ showed to be stable to the reaction conditions however, its exposure to the action of HBr/AcOH led to the $\alpha$-bromo indanylidene carboxylic acid $11$ as a 3:1 mixture of geometric isomers. The unpredictable result was in accord with the regioselective cyclopropyl ring-opening by the nucleophilic bromide.

After restoration of the ester group with (trimethylsilyl)diazomethane, we passed to install the acetamido group by usual elaboration of the tethered bromo propylidene carbon chain. Thus, bromide displacement with sodium azide, reduction to primary amine and $N$-acetylation led in high yield to $13$ (Scheme 19). The latter, subjected to the action of PPSE afforded the desired free imine $7\text{b}$, subsequently transformed into the corresponding iminium triflate $7\text{b-}N^+\text{Me}$ by $N$-alkylation with methyl triflate.
Reagents and conditions: (i) 1.2eq cis-2-ido-cyclopropane carboxylic acid ethyl ester, 1.3eq iPrMgCl, THF, -40°C to r.t, 2h; (ii) HBr in AcOH (1M), >15°C, 1h; (iii) a: Me₃SiCH₂N, THF/MeOH, r.t., 2h; b: NaN₃, CH₃CN/DMF, r.t, 48h; (iv) a: PPh₃, THF, o.n., then H₂O, 24h; b: MeCOCl, TEA, DCM, 0°C, 3h; (v) P₂O₅, HMDSO, CCl₄, reflux, 2h.

Scheme 19

To get the targeted zwitterion we proceeded effecting saponification of the methyl ester group with LiOH; after that, from the crude taken up in acetonitrile, lithium triflate spontaneously separated and the soluble fraction was purified by silica gel chromatography. The zwitterionic switch NAIPzw was isolated as a 9:1 mixture of Z/E isomers as inferred by NOE experiments.
Reagents and conditions: (i) trifluoromethanesulfonate, toluene, rt, 10min; (ii) LiOH, THF/H₂O, rt, 3h.

Scheme 20

Preparation of the cis-2-iodocyclopropanecarboxylate 8.

Hydroiodic conjugate addition to ethyl propiolate gave stereoselectively compound 14 from which the allylic alcohol 15 was recovered after DIBAL-H reduction. The subsequent cyclopropanation gave the cis-2-iodo-cyclopropylmethanol 16 in good yield. The particular reagent CF₃COOZnCH₂I was a powerful cyclopropanating medium with respect to the usual Simmon-Smith reagent.⁴⁹ Oxidation with PDC followed by esterification completed the preparation of compound 8 (for references and notes see Experimental Part).

---

Reagents and conditions: (i) NaI, AcOH, 70 °C, 12h; (ii) DIBAL-H (2 equiv) -78 °C, 1h; (iii) Et₂Zn, CF₃COOH, CH₂I₂,-78°C to 0°C, 30 min; (iv) PDC, DMF, 25 °C, 24 h ; (v) SOCl₂, EtOH.

Scheme 21

3.3 Exploring new synthetic routes to functionalized NAIPs.

Our work based on the nitrilium ion chemistry and devoted to find a practical access to photoswitches of the PSBⅡ generation gave the NAIP structure as a first result. Moreover, by making non-substantial modification of the original synthetic strategy, the NAIPaa as well as NAIPzw were successfully prepared. Spectroscopic and photochemical studies effected on the available compounds indeed confirmed they were prototypes of a new class of biomimetic molecular switches. The above acquisitions launched positively the project; however, at this stage we had to face the challenge of finding applicability for this class of compounds. We turned our attention to the possibility of grafting NAIP derivatives to biomolecules, an event practicable if synthesis could supply for suitable functionalized structures in a flexible way. This chapter
focuses on organic synthesis exercises we put into practice in order to test the flexibility of the synthetic strategy we originally selected to approach the NAIPs.

At first we looked for alternative ways of connecting suitably functionalized indanyl and cyclopropyl rings.

Scheme 22 shows a retrosynthetic analysis of an hydroxymethyl NAIP derivative where the salient step is a Suzuki coupling reaction between indenyl triflate and an O-protected 2-hydroxymethyl cyclopropylboronic acid.

![Scheme 22](image)

Recently Deng and coworkers\textsuperscript{50} describe a novel entry to stereodefined cyclopropyl-substituted alkenes, based on the Suzuki-type cross-coupling reaction between cyclopropylboronic acids and diverse kinds of alkenyl triflates, compound 19 included. However, the cyclopropyl boronic partners, ranged from 2-alkyl to 2-phenyl derivatives. Thus, having functionalized PSB\textsuperscript{II} analogues as the main goal, we were forced to prepare a suitable 2-substituted cyclopropyl boronic acid. Among the available methods, most notably is the hydroboration of alkynes with catecholborane or dihalaboranes,

followed by hydrolysis to boronic acids or alcoholysis to boronic esters (Scheme 23).

\[ R_1\equiv H + HBY_2 \to R_1\equiv HBY_2 \]

\( \gamma_2 : \)

\[ \gamma_2 : \]

\[ \text{Br}_2 \cdot \text{SMe}_2 \xrightarrow{2 \text{ROH}} (\text{OR})_2 \]

Scheme 23

Our attempts to hydroborate different \textit{O}-protected propargyl alcohols with 1,3,2-benzodioxaborole (“catechol-borane”) were invariably unfruitful (Scheme 24).

\[ \text{HO} \equiv \xrightarrow{i} \text{BnO} \equiv \xrightarrow{\text{BH}} \text{BnO} \equiv \xrightarrow{\text{BnO} \equiv \text{BH}} \text{BnO} \equiv \text{R} \]

\textbf{Reagent and conditions:} (i) \text{NaOH, DMSO, BzBr, 24h.}

Scheme 24

Indeed, in literature we found evidence for this unpredictable behaviour.\textsuperscript{51} Consequently, we turned our attention to a three-step one pot procedure based on the more reactive dicyclohexylborane (Scheme 25).

The in situ formed reagent, (from cyclohexene and BH₃·Me₂S) added *syn* stereoselectively to 3-benzyloxy propyne to give the corresponding alkenyl borane. The latter was oxidized to dicyclohexylboronate which transesterified with pinacol furnished the desired boronic ester. Despite the convenience of the one-pot protocol, we had some problems in the oxidative step. This operation entailed using the very expensive anhydrous trimethylamine oxide as the agent to selectively oxidize Csp³-Boron bonds. We tried to get it from the commercially available dihydrate following a reported protocol,⁵² but the result was rather unsatisfactory. In fact, we could accede to the alkenyl pinacol boronate only in low and not reproducible yields.

Suzuki and coworkers used (Ip)₂BH (diisopinocampheylborane from BH₃·Me₂S and twice the equivalents of α-pinene at 0°C) for the synthesis of functionalized 1-alkenylboronates (Scheme 26).

---

Reagents and conditions: (i) BH₃·SMₑ₂, THF, 0°C, on; (ii) THF, -35°C, 4h; (iii) acetaldehyde at 0°C, then rfx, on; (iv) 1,3 propanediol, THF, 12h, r.t.

Scheme 26

Although the main field of application of this borane reagent is the asymmetric hydroboration of alkenes, it has also been appreciated as hydroborating agent for alkynes. The inertness to many functional groups, as well as the high regioselectivity resulting from its bulkiness, and the final facile access to boronic esters under neutral conditions by the use of the inexpensive acetaldehyde in the oxidative step, were the attractive features (Ip)₂BH. Indeed, the hydroboration proceeded with high yield and excellent regioselectivity providing compound 22 which treated with acetaldehyde furnished the unstable diethyl boronate 23 eventually transesterified with 1,3 propanediol to 24.

It is known that alkylboronic esters are readily hydrolysed by water or moist air and are consequently difficult to be purified. Instead, esters from diols show marked differences in their behavior towards water and are less rapidly hydrolysed. In particular the reactivity
strongly depends on the size of heterocycle,\textsuperscript{53} being the 1,3,2-dioxaborinanes relatively stable. Unfortunately, we were incapable to produce pure compound 24 and consequently were discouraged to go on with the synthesis. However, once again we took comfort in literature.

Burke \textit{et al.}\textsuperscript{54} envisioned an innovative approach for the attenuation of the boronic esters reactivity. The purpose of the authors was the preparation of an highly robust ligand for haloboronic acid suitable to take part to iterative Suzuki-Miyaura couplings. As a protective group, the N-methyliminodiacetic (MIDA) boronate ligand survived to the coupling conditions and was removable by mild aqueous hydrolytic conditions (1M aq. NaOH/THF, 10 min.).

Transmetallation between boronic acids and Pd(II) requires formation of an electronically activated anionic boron “ate complex”. This mechanism needs a vacant and Lewis acidic boron p-orbital, as a consequence, rehybridization of the boron center from sp\textsuperscript{2} to sp\textsuperscript{3} via complexation with the trivalent ligand MIDA ultimately attenuates the transmetallation step in the catalytic cycle.

Indeed, we found that reacting (\textit{E})-3-(benzyloxypropenyl)boronic acid with MIDA gave a bench stable crystalline solid purifiable by silica gel chromatography. This very promising result allowed us to proceed with the synthesis by effecting the cyclopropanation of

\textsuperscript{53} Pietruszka, J.; Witt, A.; \textit{Synlett}, \textbf{2003}, 1, 91-94.
Chapter 3 Results and Conclusion

compound 26. To this end, following a reported protocol, the olefin was exposed to the carbene species resulting from the Pd(OAc)$_2$ catalyzed decomposition of diazomethane. Because of the impossibility to monitor the advances of the reaction by TLC we chose the analytical HPLC technique.

**Reagents and conditions:** (i) BH$_3$.SMe$_2$, THF, 0°C, on; (ii) THF, -35°C, 4h; (iii) acetaldehyde at 0°C, then rfx, on; (iv) NaOH 1M, THF, 1h; (v) benzene/DMSO, Dean-Stark, rfx, on; (vi) Pd(OAc)$_2$, CH$_2$N$_2$, THF/Et$_2$O, 0°C, 40min; (vii) NaOH 1M, THF, 23°C, 20min.

**Scheme 27**

Actually, in this way we were able to set up the cyclopropanation protocol so as to bring the reaction to completion. Removal of the

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MIDA ligand by mild hydrolysis gave the cyclopropylboronic acid 18 eventually used in the palladium catalyzed coupling reaction with indenyl triflate 19. Disappointingly, following Deng’s protocol we obtained the desired indenyl cyclopropane derivative 20 only in low yields.

\[
\text{Suzuki coupling: (i) Pd(PPh\textsubscript{3})\textsubscript{4}, NaBr, Cs\textsubscript{2}CO\textsubscript{3}, KF.2H\textsubscript{2}O, 80°C, 16h.}
\]

Scheme 28

Considering the acidic nature of the indene a plausible cause for the abortion of the Suzuki coupling we turned our attention to the 3,3-dimethyl indenyl triflates 28 and 29 as suitable partners of the cyclopropyl boronic acid 18.

\[
\begin{align*}
\text{Scheme 29}
\end{align*}
\]

The presence of the ethoxycarbonyl group at C-2 of compound 29 was precious to get bifunctionalized PSB\textsuperscript{H} (Scheme 30).

\[
\text{Scheme 30}
\]
Chapter 3  

Results and Conclusion

The enol triflates 28 and 29 were prepared from the corresponding indanones 36 and 37 (whose preparation is reported in the following) by the action of triflic anhydride and 2,6-di-\textit{t}-butyl-4-methylpyridine in dichloroethane.\textsuperscript{57} Gratifyingly, the higher yields in the Suzuki coupling gave credit to our previous assumption.

\[
\begin{align*}
\text{Suzuki coupling:} \quad & \text{(i) Pd(PPh}_3\text{)}_4, \text{ NaBr, Cs}_2\text{CO}_5, \text{ KF.2H}_2\text{O (ii) Pd(PPh}_3\text{)}_4, \text{ Toluene, K}_3\text{PO}_4.3\text{H}_2\text{O T} = 100^\circ\text{C.} \\
\text{Scheme 31}
\end{align*}
\]

Preparation of the indanones 36 and 37

Acetone was condensed with ethyl cyanoacetate in the presence of acetic acid and phenylalanine to afford unsaturated cyano-ester 33 with 93% yield.\textsuperscript{58} Addition of phenyl Grignard reagent in the presence of catalytic amount of CuI, gave the ester 34 that, subjected

to the one-pot decarbethoxylation-hydrolysis process\textsuperscript{59} by heating with KOH gave \textbf{35}. The latter, by Eaton’s reagent\textsuperscript{60} promoted intramolecular acylation gave the 5-methoxy-3,3-dimethylindanone \textbf{36} together with a small amount of the 7-methoxy isomer (9:1 ratio). Eventually, 2-ethoxycarbonylation with NaH and diethylcarbonate afforded the $\beta$-ketoester \textbf{37}.

\textbf{Reagents and conditions:} (i) Acetone, CH$_3$COOH, Phenylalanine, Benzene 130°C 12h, (ii) 3-Methoxyphenylmagnesiumbromide, CuI, Et$_3$O 60°C 12h; (iii) KOH, Ethylene glycol, 170°C 11h; (iv) Eaton’s reagent, 115°C, 3h; (v) NaH, (EtO)$_2$CO, 80°C, 0.5 h.

\textbf{Scheme 32}

Although we were able to optimize the yield of Suzuki coupling, the excessive length and the costs of the synthesis towards the required


\textsuperscript{60} Premasagar, V.; Palaniswamy, V.A.; Eisenbraun E.J.; \textit{J. Org. Chem.}, 1981, 46, 2974-2976.
cyclopropylboronic acid derivatives prompted us to explore a more convenient and straightforward access to functionalized NAIPs.

The intriguing properties that computational and photochemical chemists found for 7bzw made urgent to find a facile access to this molecule. By exploiting the body of knowledge on the palladium chemistry acquired on working at the Suzuki coupling strategy, we decided to test the correlative Heck reaction.

As depicted in Scheme 33 we planned to get indenyl cyclopropane derivative 40 starting once again from an indenyl triflate to which connect the acrylate group through a Pd (0) catalyzed reaction.

![Scheme 33](image)

It is well known how alkenyl triflates can act as electrophilic partners of ethyl acrylate in the Heck coupling. Thus, regioselective cyclopropanation of the adduct 39 would lead to the indenyl}

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cyclopropane 40, a substrate we expected reactive in the cyclopropyl ring-opening/nitrilium ring-closing tandem reaction giving 7e.

We found the planned Heck reaction between 38 and ethyl acrylate (3 eq.) by using PdCl$_2$(PPh$_3$)$_2$ (0.1eq), TEA (3eq.), in DMF at 80°C was unproductive and led in a few minutes (TLC analysis) to complete degradation of the starting material.

Experienced, we supposed the intrinsic instability of the 3-non substituted-indenyl triflate was the main problem. Indeed, we found the alkenyl triflate 38 was very unstable when treated with TEA in DMF at room temperature (probable polymerization!).

Thus, we preferred to shift our attention to the already reported compound 28 where two methyl groups replace the hydrogen atoms (Scheme 35).

After optimization of the protocol, we obtained compound 41 in excellent yield and, as expected, stereoselectively ($E$ geometry, $J=16\text{Hz}$ $^1\text{H}$ NMR spectrum.). Cyclopropanation of 41, accomplished using ethereal diazomethane solution in the presence of catalytic
Chapter 3

Results and Conclusion

Pd(OAc)$_2$

 gave the trans-substituted cyclopropane derivative 42. The desired regioselectivity of the cyclopropanation can be attributed to steric reasons. It was pleasant to find out that compound 42 in the presence of TfOH actually reacted with acetonitrile in the way we expected i.e. tandem homoallylic rearrangement-nitrilium cyclization process.

Reagents and conditions: (i) Tf$_2$O, 2,6-3-buty1-4-methylpyridine, 1,2-dichloroethane; (ii) Pd(OAc)$_2$, TEA, DMF; (iii) CH$_2$N$_2$, Pd(OAc)$_2$; (iv) TfOH, ACN, 3h, 60$^\circ$C.

Scheme 35

However, after a careful NMR investigation of the reaction product we concluded its structure was the one of 7e in Scheme 35. The

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univocal location of the ethoxycarbonyl group at C-3 of pyrrolidine is in accord with a regiospecific cyclopropyl ring opening. Interestingly, the carbon target of the acetonitrile attack must be the unsubstituted one, that is a course different from the one we observed for 10 (Scheme 19). In fact, as discussed, the bromide attacked the cyclopropyl carbon bearing the ethoxycarbonyl group.

3.4 Synthesis of NAIPzwaa

With the aim to prepare an unnatural $\alpha$-amino acid featuring a NAIP moiety as the conformationally locked side chain we have also carried out the synthesis of compound NAIPaa.

![Scheme 36](image)

Retrosynthetic analysis showed as a possible starting material the indanone derivative 43, which could be derived by suitable C-2 functionalization of commercial 5-methoxy indan-1-one 1.

![Scheme 37](image)
In detail, the synthesis begins with the ethoxycarbonylation of indanone 1 with NaH and diethyl carbonate followed by bromination with NBS to give compound 45 (Scheme 38).

**Reagents and conditions:** (i) a) NaH, (EtO)₂CO, 100°C, b) NBS AcOEt, 30 min.; (ii) a) NaN₃, DMF, r.t, 1h, b) PPh₃, THF, r.t., o.n.; c) (CF₃CO)₂O, r.t., 1h; (iii) Mg, cyclopropylbromide, THF, 0°C, 30 min.; (iv) Tf₂O, CH₃CN; (v) P₂O₅, HMDSO, CCl₄, reflux, 2h.; (vi) MeOTf, benzene.

Scheme 38

The subsequent nitrogen introduction with sodium azide, then Staudinger reaction and trifluoroacetylation of the resulting primary amine gave compound 43. The latter reacted with cyclopropylmagnesium bromide providing the cyclopropyl carbinol 44 which treated in the usual way (Tf₂O and CH₃CN) gave the
acetamide 46. Thus, in place of the expected tandem reaction, compound 44 gave only a Ritter type rearrangement. However, by promoting the dehydration of secondary amide 46 with PPSE we could prepare the desired free base 7f from which the photoswitchable amino acid 7f-N\(^{+}\)Me\(^{63}\) was obtained by the usual N-methylation. Arrived at the crucial stage of amino acid deprotection, a one more complication was waiting for us. We found that compound 7f-N\(^{+}\)Me was rather instable giving rise to the formation of the tetracyclic compound Pcy (Scheme 39).

Compound Pcy seems to be the result of an intramolecular acylation involving the intermediate enamine I in turn obtained by methyl deprotonation of 7f-N\(^{+}\)Me.

We had confirmation that this was the mechanism when we observed that \( \text{NAIPaa}_2 \) was a more stable compound (Scheme 40). For the preparation of \( \text{NAIPaa}_2 \) we used benzonitrile in place of the acetonitrile in the rearrangement step.

Ultimately, these findings indicated that the ester functional group at C-2 of the indane moiety and the methyl radical at C-5 of pyrrolidine were unsuitable to go on with the design of potential photoswitchable amino acid. *This part has mainly developed by the colleagues of Dipartimento di Chimica, Università di Siena.*

Importantly, as the accused methyl radical stems from acetonitrile, the pivotal reagent in the nitrilium cyclization step, we had to abandon the original synthetic strategy.

### 3.5 New developments

Looking for alternative synthesis pathways towards \( \text{NAIP} \) derivatives lacking the methyl radical at C-5 of pyrrolidine we envisioned a completely different strategy that is retrosynthetically depicted in Scheme 41. Two disconnections, corresponding to an intramolecular Heck reaction and an aldol-like condensation,
selected 3-(2-iodo-5-methoxyphenyl)-propanal 47 and the N-protected methyl 5-oxopirrolidine-2-carboxylate 48 as the starting materials.

![Scheme 41](image)

Remarkable in the new synthetic approach appears the construction of the indane moiety at a later stage and the adjustment of the oxidation state of the pre-existing heterocycle in the conclusive step. For the preparation of the aldehyde 47 we commenced with the Knovenagel condensation of 3-methoxybenzaldehyde giving in an easily and cheaply way the aryl propenoic acid 52 whose C3 carbon chain served to accede the targeted 3-(3-methoxyphenyl)-propanal. To this end we selected a two-step protocol entailing LiAlH₄ reduction of the corresponding ethyl ester then oxidation of the resulting primary alcohol with PCC (Scheme 43).
Reagents and conditions: (i) CH$_2$(COOH)$_2$, Py, Piperidine, 95 °C , 2h, then 115°C, 1h.

Scheme 42

Kim et al.$^{64}$ have found a practical and regioselective (para to a methoxy group) aromatic iodination making use of tetrabutylammonium peroxydisulfate (TBA)$_2$S$_2$O$_8$ and iodine in acetonitrile. The reaction mechanism is not clear, probably the sulfate free radical, produced by homolytic cleavage of (TBA)$_2$S$_2$O$_8$, oxidizes iodine to the electrophilic iodonium cation radical I$_2$$^{+*}$ via a one electron transfer process. In our hands however, the desired 3-(2-iodo-5-methoxyphenyl)-propanal 47 was formed in low yield.

Reagents and conditions: (i) a) ROH, SOCl$_2$, b) LiAlH$_4$, c) PCC; (ii): TBAPS, I$_2$.

Scheme 43

Better results in the iodination were obtained on substrates such as 3-(3-methoxyphenyl)-propanol or 3-(3-methoxyphenyl)-propanoic acid methyl ester (Scheme 44). However, both the routes were abandoned because of the problems arising in the successive redox steps.

Chapter 3  

Results and Conclusion

Reagents and conditions: (i) a) ROH, SOCl₂, b) LiAlH₄; (ii) TBAPS, I₂; (iii) PCC; (iv) a) ROH, SOCl₂, b) H₂, Pd/C; (v) TBAPS, I₂; (vi) a) DIBAH, b) PCC.

Scheme 44

What appeared a problem was promptly solved resorting to the Weinreb amide 54 easily prepared from the saturated acid 53 (Scheme 45). The iodination protocol applied on the amide 54 furnished in satisfactory yield compound 55 which gave the desired aldehyde 47 by DIBAH reduction.

Reagents and conditions: (i) H₂, Pd/C, EtOH, 2h; (ii) EDCI, Et₃N, MeONHMe.HCl, DMPA, CH₂Cl₂, r.t. 2h; (iii) TBAPS, I₂, CH₃CN, 48°C, 5h; (iv) DIBAH, THF, -78°C, 1h.

Scheme 45

65
Scheme 46 shows the way we followed for the preparation of the known L-pyroglutamate derivative 48.

![Scheme 46](image)

The lithium lactam enolate of 48, generated with LiHMDS, reacted at -78°C with the aldehyde 47 under Lewis acid catalysis (Et₂O•BF₃). Under these conditions, the aldolic product 58 was obtained in a good yield as diastereomeric mixture (Scheme 47). No attempts were made to separate them as in the following step both the chiral centers were cancelled.

![Scheme 47](image)

**Reagents and conditions:** (i) LiHMDS/THF- 78°C 1h, BF₃Et₂O -78°C 2h, (ii) Imidazole, PPh₃, I₂.

By applying classical systems such as MsCl-TEA or TFAA-DMAP dehydration of 58 was unfruitful so we decided for an unusual

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protocol recently proposed in literature. The authors reported the Garegg-Samuellsson reagent (triphenylphosphine-imidazole-iodine in CH$_2$Cl$_2$) was particular efficient for the one-step conversion of aldols into the corresponding olefins. Under these conditions Imidazole has probably a dual function acting both as a base and forming a partially solvated complex with triphenylphosphine and iodine.

In this way compound 49 was obtained as a 6:1 mixture of $E$/Z isomers which were chromatographically separable. The respective geometry being inferred from NOE experiments.

Because of the very low optical activity measurable both for $49E$ and $49Z$ we suspected they were a scalemic mixture resulting from a partial racemization in the reaction conditions.

---

However, samples of 49E prepared both from L- and D-pyroglutamate revealed to be homochiral when analyzed by HPLC on a chiral column (ChiralPak AD-H 250x4.6mm; Hexane/EtOH 65/35% v/v). Moreover, their CD (circular dichroism) spectra clearly showed they were enantiomers.

About the key Heck cyclization step, we surveyed various reaction conditions before optimizing the protocol. Thus, we examined different Pd(0) sources (Pd(PPh₃)₄, PdCl₂, Pd(OAc)₂), and ligands (PPh₃, (o-Tol)₃P). Instead, TEA and DMF were respectively the optimal base and solvent to use (Table 1).

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Ligand</th>
<th>Solvent</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd(PPh₃)₄</td>
<td></td>
<td>Toluene</td>
<td>36%</td>
</tr>
<tr>
<td>Pd(PPh₃)₄</td>
<td></td>
<td>DMF</td>
<td>34%</td>
</tr>
<tr>
<td>PdCl₂</td>
<td>PPh₃</td>
<td>Toluene</td>
<td>32%</td>
</tr>
<tr>
<td>Pd(OAc)₂</td>
<td>o-tolyl-phosphine</td>
<td>DMF</td>
<td>53%</td>
</tr>
<tr>
<td>Pd(OAc)₂</td>
<td>PPh₃</td>
<td>DMF</td>
<td>65%</td>
</tr>
</tbody>
</table>

Table 1

To resume, the Heck reaction conditions were: 2 eq. electrophile, 10mol % Pd(OAc)₂, 40mol % PPh₃, 3 eq. TEA in DMF at 110°C for 5 hours.
Chapter 3   Results and Conclusion

The stereospecificity is a well known feature of the Heck coupling reaction when using diastereomeric olefins. Thus, as expected, the prevalent compound 49E gave the indanylidene 50E, a result deriving from a syn migratory insertion followed by a syn β-hydride elimination (Scheme 50).

Of course, we were surprised to find out that 49Z also yielded the indanylidene 50E together with only minor quantity of the corresponding Z diastereomer (E/Z 10:1).

![Scheme 50](image)

We reasoned on the origin of this “wrong” stereoselectivity of the Heck cyclization concluding it was a result of the two competitive palladium hydride elimination processes (Scheme 51).

Thus, while the first one led directly to 50Z, the second led to form an intermediate (not detected) with an endocyclic unsaturation. At this stage a rapid isomerization, maybe palladium-mediated,
occurred to form the thermodynamically favored compound $50E$ (a more extensive conjugation is present).

Scheme 51

Again, to establish the enantiomeric purity of the Heck cyclization product we resorted to analytical HPLC on ChiralCel OD-H (250x4.6mm) column and Hexane/EtOH 70/30\% (v/v) as the eluent mixture.

We consider of a paramount importance the presence of a configurationally stable stereocenter in the photoswitch as it could control the direction of rotation. Thus, the enantiomerically pure compound $50E$ could be a precursor of a new class of single-
molecule light powered motors miming rhodopsin both in term of photoisomerization mechanism and unidirectionality of the rotation.

At this point a chemoselective controlled reduction of the lactam carbonyl of 50 was required in order to enter the desired NAIP 7g (Scheme 52). We conjectured to reach such a goal by using DIBAH or Lithium triethylborohydride (Superhydride) as hydride donors then subjecting the reaction mixture to an acidic medium to remove the N-protecting group and form the cyclic imine.

![Scheme 52](image)

Unfortunately, both tests haven’t yielded either positive or convincing result. In fact, by using DIBAH we recovered starting material, while Superhydride, against all predictions, reduced the ester group. We thought the extensive conjugation attenuating the electrophilic character of the lactam carbonyl group was the cause for the unexpected behavior. For this reason we attempted the reduction of compound 49 finding a similar inertness of the carbonyl group. Instead, an excess of the hydride donor led to the 1,4-addition product, a result that is in accordance with a better accessibility of the β-carbon of 49 with respect to the one of compound 50 to the nucleophilic species (Scheme 53).
3.6 Last development and Future work.

The next logical idea was performing the reduction of the lactam carbonyl group of the aldolic compound 58. To this end, we firstly preferred to protect the hydroxyl group as trimethylsilyl ether in order to avoid a retroaldolic reaction (Scheme 54).

Reagents and conditions: (i) Imidazole, TMSCl, 0°C, 2h; (ii) LiEt₃BH, -78°C, 20min; (iii) TFA, 3h, r.t.

At present, we haven’t got any clear results. The obtainment of a complex mixture of diastereomers makes the real chemical behavior of 59 to the hydride attack very difficult to be appreciated. We are currently working at the synthesis plan in order to get an Heck
cyclization product featuring the \textit{gem}-dimethyl groups at C-2 of the indanylidene moiety. In fact, we suspect the observed sluggish undesired reactivity of \textbf{50} towards hydride donors is also related to the lacking of this structural element.
4. EXPERIMENTAL
4.1 General methods.
Solvents were distilled prior to use, following standard procedures, and reactions were performed under nitrogen or argon atmosphere. Silica gel 60 F254 plates were used to monitor synthetic transformations, visualization being done under UV light or using 2% KMnO$_4$ solution. Organic solutions were dried over anhydrous magnesium sulfate and evaporated with a rotary evaporator. Chromatographic purifications were carried out using 70–230 mesh silica gel. Melting points were determined on a Büchi–Tottoli apparatus and are uncorrected. Infrared (IR) spectra were recorded on a FTIR Paragon 500 spectrometer. Light petroleum refers to the fractions boiling in the range 40–60 °C and ether to diethyl ether. Nuclear magnetic resonance spectra ($^1$H NMR and $^{13}$C NMR) were recorded on a Mercury Plus spectrometer at 400 MHz and 100 MHz, respectively. Chemical shifts (d values) are given in parts per million downfield from tetramethylsilane as the internal standard. Reverse-phase HPLC using a Beckman 116 liquid chromatography equipped with a Beckman 166 diode array detector. Nucleodur C$_{18}$ column (4.6mm x 100mm, 2µm particle size). Mobile phase containing solvent A (10% v/v, acetonitrile in 0.1% TFA) and solvent B (60% v/v, acetonitrile in 0.1% TFA). The column was perfused at a flow rate of 0.6ml/min using a linear gradient from 0% to 70% B over 25min. Molecular weights of compounds were determined with a mass spectrometer ESI Micromass ZMD-2000; values are expressed.
as MH⁺. Analytical conditions for chiral separations are reported in the following section.

I would like to express my deepest and special thanks to the “Department of Analytical Chemistry” GlaxoSmithKline S.p.A., Center of “Molecular Discovery Research”, Verona, Italy.
4.2 Experimental section.

Procedure for the Preparation of the Neutral Imine ((p-NO₂)-1neut).
A mixture of 1-pyrroline trimer (3.3 mmol) and \( p \)-nitro benzaldehyde (10 mmol) in methanol (25 ml) was stirred at room temperature for 48 hours. To the formed suspension a methanolic solution (75ml) of 0.6 M acetic acid/0.2 M sodium acetate was added and the mixture heated at 60°C for 24 h. After evaporation of the solvent, the residue was made basic by addition of \( \text{K}_2\text{CO}_3 \) and extracted with ethyl acetate. The organic phase was dried and the solvent removed \textit{in vacuo}. The final product was obtained after column chromatography (silica gel, ethyl acetate) of the crude.

\textit{E-4-(4-Nitro-benzylidene)- 3,4-dihydro-2H-pyrrole (E-(p-NO₂)-1neut).}

Yield: 43%; m.p. 105-108°C; IR (KBr): \( \nu \) 1593, 1511, 1341 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 2.84-2.91 (2H, m), 4.24-4.31 (2H, m), 6.89 (1H, t, \( J \ 2.8 \text{Hz} \)), 7.60 (2H, d, \( J \ 8.8 \text{Hz} \)), 7.94 (1H, t, \( J \ 2.4 \text{Hz} \)), 8.25 (2H, d, \( J \ 8.8 \text{Hz} \)); \(^{13}\)C NMR (CDCl\(_3\)) \( \delta \) 28.48, 62.46, 123.76, 124.43, 128.94, 143.09, 146.43, 147.40, 167.58.

Procedure for the Preparation of 1Me, \( p \)-MeO-1Me and \( p \)-NO₂-1Me.

0.3 mmol of CF\(_3\)SO\(_3\)CH\(_3\) were added to 0.3 mmol of 1neut, [(\( p \)-MeO)-1neut or (\( p \)-NO₂)-1neut] dissolved in 2 mL of anhydrous benzene; the reaction mixture was stirred at room temperature for 10
minutes. The precipitate was collected by filtration and dried under vacuum.

_E-4-Benzyldiene-1-methyl-3,4-dihydro-2H-pyrrolium trifluoromethanesulfonate (E-1Me)._  
Yield: 100% mp 112-113°C; $^1$H NMR (CD$_3$CN) $\delta$ 3.20 (2H, m), 3.59 (3H, s), 4.30 (2H, m), 7.42-7.68 (6H, m), 8.50 (1H, m); $^{13}$C NMR (CD$_3$CN) $\delta$ 28.36, 41.29, 61.13, 130.62, 132.24, 132.94, 135.38, 137.45, 145.32, 174.41; ESI MS m/z: 172.

_E-4-(4-Methoxybenzyldiene)-1-methyl-3,4-dihydro-2H-pyrrolium-trifluoromethanesulfonate. (p-MeO)- E-1Me)._  
Yield: 100%; mp 117-119°C; $^1$H NMR (CD$_3$CN) $\delta$ 3.26 (2H, m), 3.53 (3H, s), 3.86 (3H, s), 4.22 (2H, m), 6.99-7.10, 7.50-7.62 (5H, m), 8.40 (1H, m); $^{13}$C NMR (CD$_3$CN) $\delta$ 28.44, 41.03, 56.86, 60.99, 116.32, 128.29, 134.71, 135.34, 145.36, 164.05, 173.96; ESI MS m/z: 202.

_E-4-(4-Nitro-benzyldiene)-1-methyl-3,4-dihydro-2H-pyrrolium trifluoromethane-sulfonate (E- (p-NO$_2$)-1neut)._  
Yield: 100%; mp 96-98°C; $^1$H NMR (CD$_3$CN) $\delta$ 3.36 (2H, m), 3.62 (3H, s), 4.30 (2H, m), 7.68 (1H, m), 7.75-7.86, 8.20-8.33 (4H, m), 8.56 (1H, m); ESI MS m/z: 217.
5-Methoxy-2,2-dimethyl-indan-1-one (1a).

A solution of t-BuOK (3.4 g, 30.36 mmol) in t-BuOH (20 mL) was added dropwise to a cooled (0 °C) solution of 1-indanone 1 (1.5 g, 9.3 mmol) and methyl iodide (2.9 mL, 46.2 mmol) in ether (40 mL). The mixture was heated at reflux for 7 h, then water (10 mL) was added. The organic phase was separated and the aqueous phase was extracted with ether (3 x 50 mL). After the combined organic phases were dried, the solvent was removed in vacuo. The residue was purified by column chromatography (ether/petroleum ether 3:7) to give 1a (1.5 g, 85%) as a colourless oil.

IR (film): v 2960, 2926, 1704, 1599, 1264, 1089 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.16 (6H, s,), 2.89 (2H, s), 3.81 (3H, s), 6.80–6.85 (2H, m), 7.62 (1H, d, J 8.4 Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 25.3 (2C), 42.9, 45.6, 55.6, 109.7, 115.4, 125.9, 128.4, 155.1, 165.4, 209.6.

Cyclopropyl-5-methoxy-2,2-dimethyl-indan-1-ol (3a).

To magnesium turnings (0.2 g, 8.4 mmol) in dry THF (8 mL), a solution of cyclopropyl bromide (0.67 mL, 8.4 mmol) in dry THF (5 mL) was added dropwise with mild reflux. A solution of 1a (0.8 g, 4.2 mmol) in dry THF (8 mL) was then added dropwise and the mixture heated at 60°C for 3 h. Saturated NH\(_4\)Cl solution was added (20 mL) and the mixture was extracted with ether (3 x 20 mL). The combined organic phases were dried and concentrated in vacuo. The
residue was purified by column chromatography (ether/petroleum ether 3:7) to furnish 3a (0.86 g, 88%) as a colourless oil.

IR (film): $\nu$ 3514, 2959, 2870, 1607, 1490, 1268, 1142, 1032, 808 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.10–0.20 (1H, m), 0.35–0.47 (3H, m), 1.04 (3H, s), 1.20 (3H, s), 1.53 (1H, s), 2.63 (1H, d, J 15.6 Hz), 2.71 (1H, d, J 15.6 Hz), 3.76 (3H, s), 6.70–6.72 (2H, m), 7.18–7.23 (1H, m); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ -0.5, -0.2, 15.3, 23.6, 23.7, 45.5, 48.5, 55.2, 83.0, 110.2, 111.7, 124.6, 138.8, 143.6, 159.7.

1-(3-Bromo-propyliden)-5-methoxy-2,2-dimethylindan (4a).

A cooled (<10°C) solution of 33% HBr in acetic acid (2.5 mL) and acetic acid (10 mL) was poured into a flask containing 3a (0.45 g, 1.94 mmol) and stirring was continued for 10 min with ice bath cooling. After evaporation under reduced pressure, the residue was partitioned between H$_2$O (20 mL) and ether (20 mL). The aqueous phase was extracted with ether (3x20 mL), the combined organic extracts were dried and evaporated. The residue was purified by column chromatography (ether/petroleum ether 5:95) to afford 4a (Z/E mixture, 0.45 g, 79%) as a yellow oil.

IR (film): $\nu$ 2956, 2836, 1604, 1487, 1308, 1263, 1034 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (isomeric ratio 3:1) 1.24 (6H, s, major), 1.39 (6H, s, minor), 2.81 (2H, s, major), 2.84 (2H, s, minor), 2.95 (2H, q, J 7.2 Hz, minor), 3.03 (2H, q, J 7.2 Hz, major), 3.45 (2H, t, J 7.2 Hz, minor), 3.53 (2H, t, J 7.2 Hz, major), 3.82 (3H, s, minor), 3.84 (3H, s, major), 5.30 (1H, t, J 7.2 Hz, major), 5.72 (1H, t, J 7.2 Hz, minor), 6.70–6.72 (2H, m), 7.18–7.23 (1H, m); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ -0.5, -0.2, 15.3, 23.6, 23.7, 45.5, 48.5, 55.2, 83.0, 110.2, 111.7, 124.6, 138.8, 143.6, 159.7.
$Hz$, minor), 6.74–6.85 (4H, m, major and minor), 7.32 (1H, d, J 8.6 $Hz$, minor), 7.48 (1H, d, J 9.2 $Hz$, major); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ (major isomer) 29.4 (2C), 32.0, 32.6, 43.9, 46.9, 55.3, 110.3, 112.7, 115.1, 125.6, 132.4, 146.5, 151.80, 159.7.

**1-(3-Azido-propylidene)-5-methoxy-2,2-dimethylindan (5a).**

Sodium azide (1.66 g, 25.5 mmol) was added to a solution of 4a (1.5 g, 5.1 mmol) in DMF (25 mL) and the mixture was heated at 60°C for 2.5 h. After addition of water (100 mL), the solution was extracted with DCM (2x50 mL). The combined organic layers were washed with water (100 mL), dried and evaporated. Purification of the residue by column chromatography (ether/petroleum ether 5:95) afforded 5a (Z/E mixture, 1.25 g, 96%) as a yellow oil.

IR (film): $\nu$ 2957, 2096, 1604, 1487, 1464, 1262, 1034, 849 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (isomeric ratio 3:1) 1.21 (6H, s, major), 1.37 (6H, s, minor), 2.69 (2H, q, J 7.6 $Hz$, minor), 2.75 (2H, q, J 7.2 $Hz$, major), 2.78 (2H, s, major), 2.85 (2H, s, minor), 3.34–3.47 (4H, m, major and minor), 3.79 (3H, s, minor), 3.82 (3H, s, major), 5.25 (1H, t, J 7.2 $Hz$, major), 5.71 (1H, t, J 7.6 $Hz$, minor), 6.61– 6.82 (4H, major and minor), 7.31 (1H, d, J 8.8 $Hz$, minor), 7.48 (1H, d, J 8.0 $Hz$, major). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ (major isomer) 28.4, 29.4 (2C), 43.9, 47.0, 51.3, 55.3, 110.4, 112.6, 113.9, 125.7, 132.5, 146.5, 151.9, 159.7.
N-[3-(5-Methoxy-2,2-dimethyl-indan-1-ylidene)-propy l]-acetamide (6a).

A solution of 5a (0.26 g, 1 mmol), NaOAc (0.11 g, 1.2 mmol) and Ac<sub>2</sub>O (0.12 mL, 1.2 mmol) in EtOAc (20 mL) was stirred under 60 psi of hydrogen, in the presence of Lindlar catalyst (0.04 g), for 6 h at room temperature. The catalyst was removed by filtration and the filtrate was washed with water (15 mL) and brine (15 mL). The combined organic phases were dried and concentrated \textit{in vacuo}. The residue was purified by column chromatography (EtOAc) to give 6a (Z/E mixture, 0.23 g, 84%) as a yellow oil.

IR (film): ν 3290, 3084, 2956, 1651, 1487, 1262, 1033, 816 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ (isomeric ratio 3:1) 1.13 (6H, s, major), 1.30 (6H, s, minor), 1.91 (3H, s, major), 1.92 (3H, s, minor), 2.51 (2H, q, J 7.2 Hz, minor), 2.59 (2H, q, J 7.2 Hz, major), 2.73 (2H, s, major), 2.79 (2H, s, minor), 3.31–3.42 (4H, m, major and minor), 3.75 (3H, s, minor), 3.76 (3H, s, major), 5.17 (1H, t, J 7.2 Hz, major), 5.64 (1H, t, J 7.2 Hz, minor), 6.15 (2H, br, AcNH, major and minor), 6.63–6.76 (4H, m, major and minor), 7.25 (1H, d, J 8.8 Hz, minor), 7.48 (1H, d, J 8.4 Hz, major); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ (major isomer) 23.2, 29.3 (2C), 39.6, 43.8, 46.9, 49.3, 55.3, 110.1, 112.5, 114.9, 125.7, 132.6, 146.3, 151.5, 159.5, 170.4.

**PATHWAY A (SCHEME 8 in Results and Discussions).**

4-(5-Methoxy-2,2-dimethyl-indan-1-ylidene)-5-methyl-3,4-dihydro-2H-pyrrole (7a).
A trimethylsilyl polyphosphate (PPSE) solution, prepared by heating at reflux for 1.5 h a mixture of \( \text{P}_2\text{O}_5 \) (1.6 g, 11 mmol) and hexamethyldisiloxane (HMDSO, 3.3 mL, 15.4 mmol) in \( \text{CCl}_4 \) (15 mL), was added at room temperature to \( 6a \) (0.3 g, 1.1 mmol). The reaction mixture was heated at reflux for 2 h, cooled to room temperature and quenched with water (5 mL). The organic phase was separated and washed with 10% HCl (2x30 mL). The combined aqueous layers were cooled to 0 °C, brought to pH 9 by treatment with 6 N NaOH solution, and extracted with DCM (2x60 mL). The combined organic layers were washed with water (100 mL), dried and concentrated \textit{in vacuo}. The residue was purified by column chromatography (EtOAc/MeOH/Et\(_3\)N 9:1:0.2) to give \( 7a \) (92:8 Z/E mixture, 0.2 g, 71%) as a yellow oil.

IR (film): \( \nu \) 1702, 1600, 1576, 1291 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 1.25 (6H, s), 2.22 (3H, m), 2.77–2.80 (4H, m), 3.82–3.84 (5H, m), 6.70 (1H, dd, J 8.4, 2.0 Hz), 6.75 (1H, d, J 2.0 Hz), 7.20 (1H, d, J 8.4 Hz). A positive NOE between signal at \( \delta \) 2.22 (methyl at C-5 of 3,4-dihydro-2H-pyrrole) and signal at \( \delta \) 7.24 (H-7 on the aromatic ring) was detected; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 19.7, 25.1, 42.9, 49.0, 49.4, 55.5, 56.8, 109.9, 111.7, 126.1, 128.9, 131.4, 131.7, 148.0, 160.5, 174.6.

**General procedure for \( N \)-methylation.**

\( 4\)-(5-Methoxy-2,2-dimethyl-indan-1-ylidene)-1,5-dimethyl-3,4-dihydro-2H-pyrrolium chloride Z-(7a-\( N^+\)Me)Cl\(^{-}\).
0.3 mmol of CF$_3$SO$_3$CH$_3$ were added to a solution of Z/E-isomers (0.3 mmol) of 7a in anhydrous benzene (2ml); the reaction mixture was stirred at room temperature for 10 minutes. The precipitate was collected by filtration and dried under vacuum. Amberlite IRA-402 (1g) was previously activated by treatment with HCl 10% for 12h and then charged on a column chromatography. The resin was washed with water until pH= 7. The crude reaction was dissolved in 2ml mixture water/methanol (2/1) and the resulting solution was passed through Amberlite by elution with water. Water was removed and the residue was purified by column chromatography (MeOH/DCM 2:8) to give Z-(7a-N$^\text{+Me})$Cl (92:8 Z/E mixture, 0.2mmol g, 62%) as a yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$): δ 1.29 (6H, s), 2.67 (3H, m), 2.67 (2H, s), 3.21–3.25 (2H, m), 3.81 (3H, m), 3.84 (3H, m), 4.36 (2H, m) 6.36-6.40 (1H, m), 6.55-.6.60 (1H, m), 7.50 (1H, m). A positive NOE between signal at δ 2.67 (methyl at C-5 of 3,4-dihydro-2H-pyrrole) and signal at δ 6.55-6.60 (H-7 on the aromatic ring) was detected; $^{13}$C NMR (100 MHz, CDCl$_3$): δ 18.55, 25.75, 28.15, 29.35, 38.83, 49.40, 51.04, 55.36, 58.49, 125.57, 126.77, 128.13, 129.82, 132.32, 136.73, 148.48, 169.16, 180.50.

**3-(3-Chloro-propyl)-6-methoxy-1H-indene (2-endo).**

To magnesium turnings (0.24 g, 9.8 mmol) in dry THF (8 mL), a solution of cyclopropyl bromide (0.8 mL, 9.8 mmol) in dry THF (5 mL) was added dropwise with mild reflux. After the addition was
completed, a solution of 1 (0.8 g, 4.9 mmol) in dry THF (8 mL) was added dropwise and the mixture was heated at 60°C for 3 h. Saturated NH₄Cl solution (20 mL) was added and the mixture was extracted with ether (3x20 mL). The organic phases were combined, dried and concentrated in vacuo. The crude residue was stirred with 15% HCl solution in acetic acid (10 mL) for 1 h at room temperature, then 10% NaOH was added until pH 8. The mixture was extracted with DCM (3x20 mL) and the combined organic layers were dried and evaporated. The residue was purified by column chromatography (DCM/petroleum ether 3:7) to give 2-endo (0.33 g, 30%) as yellow oil.

IR (film): ν 2954, 1742, 1606, 1492, 1255, 732 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 2.04–2.23 (2H, m), 2.67–2.78 (2H, m), 3.34 (2H, d, J 1.8 Hz), 3.65 (2H, t, J 6.4 Hz), 3.87 (3H, s), 6.14 (1H, m), 6.90 (1H, dd, J 8.4, 2.4 Hz), 7.10 (1H, d, J 2.4 Hz), 7.29 (1H, d, J 8.4 Hz); ¹³C NMR (50 MHz, CDCl₃): δ 24.9, 30.87, 37.73, 44.8, 55.6, 110.4, 111.6, 119.1, 126.4, 138.2, 142.4, 146.3, 158.0.

1-Cyclopropylidene-5-methoxy-indan (3e-exo).

3-Cyclopropyl-6-methoxy-1H-indene (3e-endo).

A mixture of (3-bromopropyl)triphenylphosphonium bromide (2.3 g, 5 mmol, 1.3eq) and KHMSA (2 g, 10 mmol, 2.6eq) in 10 ml of dry THF under Argon was stirred for 3h at 20°C. A solution of 1 (0.5 g, 3.78 mmol) and tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1) in 7ml dry THF was added and the resulting reaction mixture stirred for
2h at 20°C. After dilution with 75ml n-pentane and adsorptive filtration through silica pad, the solvent was removed in vacuo. Flash chromatography of the residue (Ethyl Ether/Petroleum 1/20) afforded the 3e-exo (0.23g, 40%, colorless oil). After 1.5h room temperature in CDCl$_3$, $^1$H NMR showed that compound 3e-exo spontaneously is transformed in 3e-endo.

3e-exo: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.82–0.90 (4H, m), 2.13 (2H, m), 3.20 (2H, m), 3.86 (3H, s), 6.80 (1H, dd, J 8.4, 2.4 Hz), 6.95 (1H, d, J 2.4 Hz), 7.27 (1H, d, J 8.4 Hz).

3e-endo: white solid, mp 42–45 0°C; IR (KBr): $\nu$ 3447, 2960, 1604, 1258, 1073, 1015, 820 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.63–0.69 (2H, m), 0.85–0.92 (2H, m), 1.78 (1H, m), 3.28 (2H, s), 3.86 (3H, s), 5.91 (1H, m), 6.90 (1H, dd, J 8.4, 2.4 Hz), 7.07 (1H, d, J 2.4 Hz), 7.42 (1H, d, J 8.4 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 6.2 (2C), 8.5, 37.4, 55.6, 110.3, 111.6, 119.3, 123.0, 139.0, 146.2, 146.4, 157.9.

2e-endo was stirred with 15% HCl solution in acetic acid (7 mL) for 1 h at room temperature, then 10% NaOH was added until pH 8. The mixture was extracted with DCM (3x20 mL) and the combined organic layers were dried and evaporated. The residue was purified by column chromatography (DCM/petroleum ether 3:7) to give 2-endo (Yield: 80%, yellow oil).
PATHWAY B (Scheme 16 in Results and Discussions) 4-(5-Methoxy-2,2-dimethyl-indan-1-ylidene)-5-methyl-3,4-dihydro-2H-pyrrole (7a).

To a stirred solution of triflic anhydride (0.15 mL, 0.9 mmol) in CH$_3$CN (2 mL), a solution of 3a (0.21 g, 0.9 mmol) in CH$_3$CN (1 mL) was added dropwise at 0°C. The reaction mixture was slowly warmed to room temperature and stirred for 3 h. The solution was washed with 10% NaOH (5 mL) and the phases were separated. The aqueous phase was extracted with DCM (3x10 mL). The combined organic phases were dried and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/MeOH/Et$_3$N 9:1:0.2) to afford 7a (0.19 g, 83%) as a yellow oil.

5’-Methoxy-2’,2’-dimethyl-3-oxaspiro[bicyclo[3.1.0]hexane-2- Indan]-4-one (10).

The reaction was carried out following Knochel and co-workers’ procedure$^{48}$ using 1.2 equivalents of cis-2-iodo-cyclopropane carboxylic acid ethyl ester (1.97 g, 8.2 mmol), 1.3 equivalents of $i$PrMgCl (4.4 mL, 2.0 M in THF, 8.8 mmol) and 1.0 equivalents of 5-methoxy-2,2-dimethyl-indan-1-one (1a) to give a crude residue, which was purified by flash column chromatography on silica gel (diethyl ether/petroleum ether 1:1) affording 10 (945 mg, 54% yield) as a white solid, mixture of two diastereoisomers in the ratio of 65:35 as determined by integration of the benzylic hydrogens at $\delta$ 2.97.
(major) and 2.81 ppm (minor) as well as δ 2.69 (minor) and 2.56 ppm (major) in the $^1$H NMR spectrum. (white solid, mp: 92-94 °C, 54%).

IR (KBr): ν 2960, 1756, 1607, 1495, 1468, 1305, 1266, 934 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.25-7.23 (m, 1H, major), 7.20-7.19 (m, 1H, minor), 6.75-6.70 (m, 4H, major and minor), 3.76 (s, 6H, major and minor), 2.97 (d, 1H, J 15.7 Hz, major), 2.81 (d, 1H, J 15.3 Hz, minor), 2.69 (d, 1H, J 15.3 Hz, minor), 2.56 (d, 1H, J 15.7 Hz, major), 2.32-2.25 (m, 2H, major and minor), 2.20-2.13 (m, 2H, major and minor), 1.27-1.24 (m, 2H, major and minor), 1.19 (s, 3H, major), 1.15 (s, 3H, major), 1.17-1.12 (m, 2H, major and minor), 1.10 (s, 3H, minor), 0.98 (s, 3H, minor); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ (major) 175.2, 161.1, 144.7, 135.9, 124.0, 113.1, 110.2, 94.9, 55.4, 46.6, 44.3, 25.4, 23.2, 21.6, 19.2, 18.2. MS (EI): 258 (100), 229 (65), 215 (27), 199 (18), 187 (20), 115 (22).

2-Bromo-4-(5-methoxy-2,2-dimethyl-indan-1-ylidene)butyric acid (11).

A cooled (>15°C) 1.0 M solution of HBr in acetic acid (5.6 mL, 5.6 mmol) was poured into a cooled (>15°C) flask containing 10 (722 mg, 2.8 mmol) and stirring was continued for 1h. After evaporation of the solvent under vacuum, the residue was partitioned between H$_2$O (10 mL) and diethyl ether (30 mL). The aqueous phase was extracted with diethyl ether (3x30 mL) and the combined organic extracts were dried over Na$_2$SO$_4$. After evaporation of the solvent
under vacuum, the residual brown oil was purified by flash column chromatography on silica gel (diethyl ether/petroleum ether 8:2) to give 11 (Z/E mixture, 881 mg, 93% yield) as a light brown oil.

IR (neat): ν 3099, 2927, 2851, 1716, 1605, 1488, 1262, 1032, 817 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz): δ (isomeric ratio 3:1) 8.47 (br s, 2H, major and minor), 7.48 (d, 1H, J 9.2 Hz, major), 7.33 (d, 1H, J 8.6 Hz, minor), 6.83-6.72 (m, 4H, major and minor), 5.69 (t, 1H, J 7.4 Hz, minor), 5.23 (t, 1H, J 7.1 Hz, major), 4.41-4.31 (m, 2H, major and minor), 3.82 (s, 3H, major), 3.80 (s, 6H, major and minor), 3.25-3.10 (m, 4H, major and minor), 2.85 (s, 2H, minor), 2.78 (s, 2H, major), 1.39 (s, 3H, minor), 1.36 (s, 3H, minor), 1.19 (s, 6H, major); ¹³C NMR (CDCl₃, 50 MHz): δ (major) 175.1, 159.9, 153.3, 146.7, 132.0, 125.6, 112.7, 112.5, 110.4, 55.3, 46.9, 44.5, 44.1, 29.3, 26.9 (2C).

2-Bromo-4-(5-methoxy-2,2-dimethyl-indan-1-ylidene)butyric acid methyl ester.

A dry 100 mL round bottomed flask equipped with an addition funnel and a nitrogen inlet was charged with 11 (880 mg, 2.6 mmol) and 9 mL of a 3:1 mixture of dry THF/dry methanol. To the stirred solution was added dropwise a 2.0 M solution of (trimethylsilyl)diazomethane (3.9 mL, 7.8 mmol). After 2h the bright yellow solution was cooled to 0°C by means of an ice bath and quenched with sat. aq. NH₄Cl solution. The aqueous layer was extracted with diethyl ether (3x30 mL). The organic extracts were
combined and dried over Na$_2$SO$_4$. After evaporation of the solvent under vacuum, the residual oil was purified by flash column chromatography on silica gel (diethyl ether/petroleum ether 2:8) to give methyl ester derivative (Z/E mixture, 837 mg, 91% yield) as a yellow oil.

IR (neat): $\nu$ 2959, 2922, 1743, 1605, 1488, 1262, 1032, 803 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 200 MHz): $\delta$ (isomeric ratio 3:1) 7.50 (d, 1H, J 9.4 Hz, major), 7.32 (d, 1H, J 8.3 Hz, minor), 6.82-6.71 (m, 4H, major and minor), 5.67 (t, 1H, J 7.4 Hz, minor), 5.21 (t, 1H, J 7.1 Hz, major), 4.40-4.27 (m, 2H, major and minor), 3.82 (s, 6H, major and minor), 3.78 (s, 6H, major and minor), 3.37-3.06 (m, 4H, major and minor), 2.85 (s, 2H, minor), 2.78 (s, 2H, major), 1.39 (s, 3H, minor), 1.36 (s, 3H, minor), 1.19 (s, 6H, major); $^{13}$C NMR (CDCl$_3$, 50 MHz): $\delta$ (major) 169.9, 159.9, 152.9, 146.6, 131.9, 125.6, 113.5, 112.7, 110.3, 55.2, 52.8, 46.9, 44.7, 44.0, 33.7, 29.3, 29.1.

**2-Azido-4-(5-methoxy-2,2-dimethyl-indan-1-ylidene)butyric acid methyl ester (12).**

Sodium azide (292 mg, 4.5 mmol) was added to a solution of methyl ester derivative (794 mg, 2.25 mmol) in dry acetonitrile (20 mL) and dry DMF (2 mL) in a dry 100 mL round bottomed flask under nitrogen atmosphere, and the resulting mixture was stirred at room temperature. After 24 h, sodium azide (292 mg, 4.5 mmol) was newly added and the mixture was stirred at room temperature for additional 24 h. After addition of water, the aqueous layer was extracted with
diethyl ether (3x30 mL). The combined organic layers were washed with brine, then dried over Na₂SO₄, concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (diethyl ether/petroleum ether 1:9) to give 12 (Z/E mixture, 616 mg, 87% yield) as a yellow oil.

IR (neat): ν 2957, 2105, 1747, 1605, 1488, 1263, 1033 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz): δ (isomeric ratio 3:1) 7.52 (d, 1H, J 9.2 Hz, major), 7.33 (d, 1H, J 8.2 Hz, minor), 6.81-6.71 (m, 4H, major and minor), 5.73 (t, 1H, J 7.4 Hz, minor), 5.26 (t, 1H, J 7.2 Hz, major), 4.08-3.99 (m, 2H, major and minor), 3.81 (s, 6H, major and minor), 3.78 (s, 6H, major and minor), 3.04-2.96 (m, 4H, major and minor), 2.85 (s, 2H, minor), 2.78 (s, 2H, major), 1.37 (s, 6H, minor), 1.20 (s, 6H, major).

¹³C NMR (CDCl₃, 50 MHz): δ (major) 170.4, 159.8, 152.8, 146.5, 131.9, 125.6, 112.6, 111.4, 110.2, 61.9, 55.1, 52.3, 46.8, 44.0, 30.7, 29.0 (2C); MS (EI): 301 (95), 286 (51), 272 (19), 227 (22), 213 (100), 197 (21), 171 (20).

2-Acetamido-4-(5-methoxy-2,2-dimethyl-indan-1-ylidene)butyric acid methyl ester (13).

A solution of 12 (488 mg, 1.55 mmol) in dry THF (8 mL) under nitrogen atmosphere was cooled to 0°C by means of an ice bath. To the stirred solution triphenyl phosphine (608 mg, 2.32 mmol) was added portionwise. The cooling bath was then removed and the clear solution was allowed to warm to room temperature. After stirring overnight, the complete consumption of 12 was confirmed by TLC.
and then 2 mL of distilled water were added. The resulting mixture was stirred for 24h at room temperature. The reaction was quenched with sat. aq. NaHCO₃ solution, extracted with ethyl acetate (3x30 mL) and washed with brine. The organic layer was dried over Na₂SO₄ and evaporated to give 1.05 g of a residual mixture of a yellow oil and a white solid which contains the 2-amino-4-(5-methoxy-2,2-dimethyl-indan-1-ylidene)butyric acid methyl ester. The crude amine was then dissolved in freshly distilled CH₂Cl₂ (10 mL) under nitrogen. The solution was cooled to 0°C by means of an ice bath and triethylamine (TEA) (430 µL, 3.1 mmol) was added. After 5min a solution of acetyl chloride (220 µL, 3.1 mmol) in 2 mL of CH₂Cl₂ was added dropwise and the reaction mixture was stirred at 0°C. After 3h the reaction mixture was quenched with sat. aq. NaHCO₃ solution and extracted with CH₂Cl₂. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated under vacuum. The crude residue was purified by flash column chromatography on silica gel (diethyl ether/petroleum ether 6:4) affording 13 (Z/E mixture, 383 mg, 75% yield from 5) as a yellow oil.

IR (neat): ν 3314, 2960, 2251, 1745, 1660, 1606, 1215, 1031, 913, 733 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz): δ (isomeric ratio 3:1) 7.50 (d, 1H, J 9.3 Hz, major), 7.29 (d, 1H, J 8.1 Hz, minor), 6.78-6.70 (m, 4H, major and minor), 6.18-6.04 (m, 2H, major and minor), 5.58 (t, 1H, J 7.5 Hz, minor), 5.14 (t, 1H, J 7.3 Hz, major), 4.82-4.75 (m, 2H, major
Experimental

and minor), 3.81 (s, 3H, major), 3.80 (s, 3H, minor), 3.77 (s, 3H, minor), 3.72 (s, 3H, major), 3.10-2.87 (m, 4H, major and minor), 2.83 (s, 2H, minor), 2.76 (s, 2H, major), 2.02 (s, 3H, minor), 1.97 (s, 3H, major), 1.32 (s, 3H, minor), 1.27 (s, 3H, minor), 1.17 (s, 6H, major);

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ (major) 172.6, 169.8, 159.8, 153.0, 146.6, 131.9, 125.7, 112.6, 111.8, 110.3, 55.3, 52.3 (2C), 49.4, 46.9, 31.2, 29.4, 29.2, 23.1.

4-(5-Methoxy-2,2-dimethyl-indan-1-ylidene)-5-methyl-3,4-dihydro-2H-pyrrole-2-carboxylic acid methyl ester (7b).

A trimethylsilyl polyphosphate (PPSE) solution, prepared by heating at reflux for 1.5h a mixture of P$_2$O$_5$ (1.07 g, 7.5 mmol) and hexamethyldisiloxane (2.2 mL, 10.5 mmol) in CCl$_4$ (7 mL), was added at room temperature to 13 (248 mg, 0.75 mmol). The reaction mixture was heated at reflux for 3h, cooled to room temperature, diluted with CH$_2$Cl$_2$ and quenched with H$_2$O. The aqueous layer was brought to pH=9 by treatment with 6N NaOH solution and extracted with CH$_2$Cl$_2$ (3x30 mL). The combined organic layers were washed with H$_2$O, dried over Na$_2$SO$_4$ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether/TEA 1:1:0.5) to give 7b (Z/E mixture, 108 mg, 46% yield) as a viscous dark yellow oil.

IR (neat): $\nu$ 2929, 1732, 1603, 1588, 1254, 1157, 1026 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ (isomeric ratio 3:1) 7.38 (d, 1H, J 9.6 Hz, minor), 7.19 (d, 1H, J 8.8 Hz, major), 6.75-6.66 (m, 4H, major
and minor), 4.57 (dt, 1H, J 2.0, 6.8 Hz, major), 4.52-4.48 (m, 1H, minor), 3.78 (s, 3H, major and minor), 3.76 (s, 3H, major and minor), 3.25 (dd, 1H, J 6.4, 14.8 Hz, minor), 3.16 (dd, 1H, J 7.2, 14.8 Hz, minor), 3.06-2.96 (m, 2H, major), 2.93 (d, 1H, J 16.0 Hz, minor), 2.89 (d, 1H, J 15.2 Hz, major), 2.79 (d, 1H, J 16.0 Hz, minor), 2.66 (d, 1H, J 15.2 Hz, major), 2.47 (d, 3H, J 2.0 Hz, minor), 2.23 (d, 3H, J 2.0 Hz, major), 1.44 (s, 3H, minor), 1.38 (s, 3H, minor), 1.32 (s, 3H, major), 1.13 (s, 3H, major); $^{13}$C NMR (CDCl$_3$, 50 MHz): δ (major) 175.4, 173.0, 160.5, 150.4, 147.9, 130.4, 128.8, 127.2, 111.7, 109.8, 70.5, 55.2, 52.1, 49.3, 48.8, 35.7, 28.7, 26.1, 20.1; MS (ESI, + p ms): 314.5.

4-(5-Methoxy-2,2-dimethyl-indan-1-ylidene)-2-(methoxycarbonyl)-1,5-dimethyl-3,4-dihydro-2H-pyrrolium trifluoromethanesulfonate (7b-N$^+$Me).

A solution of methyl trifluoromethanesulfonate (34 µL, 0.3 mmol) in anhydrous benzene (3 mL) was added under nitrogen atmosphere to a solution of 7b (94 mg, 0.3 mmol) in anhydrous benzene (3 mL). The solution was stirred for 2h at room temperature and then concentrated under vacuum to give the crude pyrrolium salt. (143 mg, >98% conversion) as a viscous orange oil.

$^1$H NMR (CDCl$_3$, 400 MHz): δ (major, isomeric ratio >95:5) 7.36 (d, 1H, J 8.6 Hz), 6.81-6.76 (m, 2H), 5.51-5.18 (m, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.79-3.75 (m, 1H), 3.58 (s, 3H), 3.06 (dd, 1H, J 3.4, 15.2 Hz), 3.01 (d, 1H, J 15.7 Hz), 2.81 (d, 1H, J 15.7 Hz), 2.55 (s,
Chapter 4  

Experimental

3H), 1.38 (s, 3H), 1.21 (s, 3H). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ (major) 181.9, 173.0, 168.7, 164.3, 152.7, 131.2, 129.1, 122.8, 122.1, 118.9, 113.9, 110.3, 69.3, 55.7, 53.5, 51.5, 49.4, 37.3, 33.5, 26.4, 25.0. MS (ESI, + p ms): 328.6.

4-(5-Methoxy-2,2-dimethyl-indan-1-ylidene)-2-(methoxycarbonyl)-1,5-dimethyl-3,4-dihydro-2H-pyrrolium-2-carboxylic acid anion (7b zwitt).

The crude pyrrolium trifluoromethanesulfonate (143 mg, 0.3 mmol) was added in a 25 mL round-bottomed flask containing a 2:1 mixture of THF/H$_2$O (9 mL) and the bright yellow solution was cooled to 0°C by means of an ice bath. Then LiOH·H$_2$O (38 mg, 0.9 mmol) was added portionwise to the solution that rapidly turned into dark yellow-brown. The reaction was monitored by TLC (ethyl acetate/methanol 9:1 as the eluent). After 3h the solvent was evaporated under vacuum to give a residual solid that was dissolved in acetonitrile. The precipitation of a white solid occurred. The decanted clear yellow solution was transferred into a one-necked round-bottomed flask and concentrated under vacuum to give a gummy solid which was purified by flash column chromatography on silica gel (acetonitrile/H$_2$O 7:3) to afford 7b zwitt (Z/E mixture 90:10, 50 mg, 53% yield from 7b) as a viscous dark yellow oil. To the overriding geometric isomer the Z configuration was assigned, on the basis of NOE difference spectroscopy. In details: a positive NOE between the signal of the proton attached to the aromatic C-7 carbon
of the indanyliden moiety (d, \( \delta = 7.51 \) ppm, J 8.7 Hz) and the signal of the methyl group at the C-5 of the pyrrolium ring (s, \( \delta = 2.52 \) ppm) was detected.

IR (KBr): \( \nu \) 2962, 2925, 1635, 1584, 1262, 1094, 1028, 802 cm\(^{-1}\); \(^1\text{H}\) NMR (CD\(_3\)OD, 400 MHz): \( \delta \) 7.56 (d, 1H, J 8.8 Hz, E isomer), 7.51 (d, 1H, J 8.7 Hz, Z isomer), 6.93-6.82 (m, 4H, Z+E isomers), 4.69-4.66 (m, 1H, Z isomer), 4.64-4.61 (m, 1H, E isomer), 3.85 (s, 6H, Z+E isomers), 3.84-3.74 (m, 1H, E isomer), 3.51 (s, 6H, Z+E isomers), 3.24-3.15 (m, 3H, Z+E isomers), 3.09-3.02 (m, 2H, Z+E isomers), 2.93 (d, 1H, J 16.1 Hz, E isomer), 2.82 (d, 1H, J 15.6 Hz, Z isomer), 2.72 (s, 3H, E isomer), 2.52 (s, 3H, Z isomer), 1.53 (s, 3H, E isomer), 1.43 (s, 3H, E isomer), 1.41 (s, 3H, Z isomer), 1.19 (s, 3H, Z isomer); \(^{13}\text{C}\) NMR (CD\(_3\)OD, 100 MHz): \( \delta \) (Z isomer) 180.1, 172.1, 169.6, 163.9, 152.1, 130.6, 129.1, 124.2, 113.9, 109.7, 72.4, 54.8, 50.8, 49.0, 35.8, 34.7, 25.3, 24.1, 16.4. MS (ESI, + p ms): 314.7.

Synthesis of Z-3-iodo-acrylic acid ethyl ester (14) [J. Org. Chem. 1993, 58, 3148]

A 250 mL round-bottomed flask equipped with a magnetic stirring bar and an argon gas inlet was charged with 22.5 g (0.15 mol) of dry sodium iodide and 100 mL of glacial acetic acid. The stirred solution was added 10.1 mL (0.1 mol) of ethyl propiolate and the resulting mixture was heated at 70 °C during 12 h. The brown solution was cooled to rt and water (100 mL) and ether (100 mL) were added. The
A 100 mL dry four-necked round bottom flask equipped with a mechanical stirrer, an internal thermometer, a rubber septum and an argon gas inlet was charged with 11.3 g (50 mmol) of 14 and 100 mL of anhydrous CH₂Cl₂. The stirred solution was cooled to -78 °C by mean of a liquid nitrogen bath and 100 mL (100 mmol) of a 1 M solution of diisobutyl aluminium hydride in hexane was added dropwise via a syringe at such a rate that the temperature did not exceed -75 °C. The cooling bath was removed and the reaction mixture was allowed to warm to rt. Hydrolysis was carried out at -20 °C by dropwise addition of 50 mL of 1 M aq. HCl, followed by addition of ether (100 mL). The organic layer was separated, the aqueous layer extracted with ether (2x20 mL) and the combined organic layers dried over MgSO₄. After rotary evaporation of the
solvents, the residual oil was purified by flash column chromatography on silica gel (pentane/Et₂O 1:1) affording 15 (8.05 g, 88 %) as a yellow oil.

^1^H NMR (300 MHz, CDCl₃): δ 6.43 (dt, J 7.6, 5.5 Hz, 1H), 6.30 (d, J 7.6 Hz, 1H), 4.17 (d, J 5.5 Hz, 2H), 1.85 (s, 1H). ^1^C NMR (75 MHz, CDCl₃): δ 140.3, 83.0, 66.1.


To freshly distilled CH₂Cl₂ (50 mL) was added Et₂Zn (1.0 M in hexane, 53 mL, 53 mmol) under argon. The solution was cooled in an ice bath and a solution of trifluoroacetic acid (4.11 mL, 53 mmol) in CH₂Cl₂ (10 mL) was then dropped very slowly into the reaction mixture via syringe. Upon stirring for 20 min, a solution of CH₂I₂ (4.33 mL, 53 mmol) in CH₂Cl₂ (10 mL) was added. After an additional 20 min stirring, a solution of 15 (4.43 g, 24.1 mmol) in CH₂Cl₂ (10 mL) was added and the ice bath was removed. After an additional 30 min stirring, the reaction mixture was quenched with sat. aq. NH₄Cl and hexanes (50 mL) and the layers were separated. The aq. layer was extracted with hexanes. The combined organic layers were washed with sat. NaHCO₃, H₂O and brine, then dried over Na₂SO₄, filtered, concentrated and purified by flash column chromatography on silica gel (pentane/Et₂O 1:4) affording 16 (2.96 g, 62 %) as a yellow oil.
Chapter 4

Experimental

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 3.95 (dd, J 11.8, 5.0 Hz, 1H), 3.51 (dd, J 11.8, 8.8 Hz, 1H), 2.63 (dt, J 7.3, 5.0 Hz, 2H), 1.81 (s, 1H), 1.39-1.30 (m, 1H), 1.04-0.90 (m, 1H), 0.69 (dt, J 6.4, 5.0 Hz, 1H).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 68.4, 18.0, 14.1, 10.0.


A 50 mL dry round bottomed flask equipped with a mechanical stirrer, a rubber septum and an argon gas inlet was charged with 16 (3.3 g, 16.7 mmol) and 25.8 g (68.8 mmol) pyridinium dichromate dissolved in 50 mL of dry DMF. The reaction mixture was stirred for 24 h at rt. After this time, the reaction mixture was poured into 80 mL of water and the solution was acidified with 3 N HCl to pH 2.5. The water solution was extracted with Et$_2$O (3x30 mL). The combined organic layers were washed with water (2x20 mL), brine, dried over Na$_2$SO$_4$, filtered, concentrated and purified by flash column chromatography on silica gel (pentane/Et$_2$O 1:1) affording 17 (3.34 g, 95 %) as a white crystals.(mp: 65 °C).

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.07 (s, 1H), 2.90 (dt, J 8.0, 6.7 Hz, 1H), 1.93 (dt, J 8.1, 6.3 Hz, 1H), 1.61 (dt, J 8.1, 6.2 Hz, 2H), 1.44 (q, J 6.4 Hz, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 175.5, 19.3, 17.5, 14.3.

Synthesis of cis-2-iodo-cyclopropanecarboxylic acid ethyl ester (8) [J. Am. Chem. Soc. 1989, 111, 6729]
A mixture of 17 (1.91 g, 9.0 mmol), thionylchloride (1.3 mL, 18 mmol) and 3 drops of DMF was refluxed at 50 °C for 1h. Afterwards, excess of thionylchloride was removed by vacuum pump and the mixture was cooled to 0 °C. EtOH (0.8 mL, 13.5 mmol) was added and the reaction mixture was stirred for 2 h at 0 °C. After this time, the reaction mixture was poured into 20 mL of water and Et₂O (20 mL) and the layers were separated. The aq. layer was extracted with Et₂O. The combined organic layers were washed with sat. NaHCO₃, water, brine and dried (Na₂SO₄), filtered, concentrated and purified by flash column chromatography on silica gel (pentane/Et₂O 3:1) affording 8 (1.51 g, 70 %) as a yellow oil.

¹H NMR (300 MHz, CDCl₃): δ 4.21-4.11 (m, 2H), 2.74 (dt, J 8.1, 6.5 Hz, 1H), 1.80 (dt, J 8.2, 6.5 Hz, 1H), 1.48-1.30 (m, 2H), 1.24 (t, J 7.1 Hz, 3H).¹³C NMR (75 MHz, CDCl₃): δ 168.9, 60.2, 18.3, 15.3, 13.4, -15,6. MS (EI): 240 (100), 195 (63), 167 (30).

**Prop-2-ynyloxymethyl-benzene.**

To a solution of prop-2-yn-1-ol (0.10 moli) in DMSO (6 ml) was added NaOH 3N (50 ml). The reaction was cooled to -10°C and benzylbromide (0.15 mmol) was added dropwise. The resulting solution was allowed to rise to room temperature and stirred for 24h. After this time, the reaction mixture was poured into 20 mL of water and Et₂O (20 mL) and the layers were separated. The aq. layer was extracted with Et₂O (3x30 ml). The combined organic layers were
washed with sat. NaCl, dried (Na$_2$SO$_4$), and concentrated. The residue was purified by flash column chromatography on silica gel (Ethyl Ether/Petroleum 1:19) to give prop-2-ynyloxy methyl-benzene as a colorless oil (93%).

$^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 2.46-2.43 (1H, t); 4.16 (2H, s); 4.61 (2H, s) 7.35-7.29 (5H, m).

**Vynil-1,3,2-dioxaborinane (24)**

To a stirred solution of BH$_3$·SMe$_2$ (0.19 g) in THF (10 ml) at 0°C was added $\alpha$-pinene (0.68 g) dropwise. The reaction was stirred at 0°C over night and then cooled at -35°C. A solution of prop-2-ynyloxy methyl-benzene (0.35 g; 2.38 mmol) in THF (10 ml) was added dropwise and the resulting solution was stirred for 4h. The solution was allowed to rise to 0°C, then a solution of acetaldehyde (1.9 ml) freshly distilled in THF (5 ml) was added. The reaction was refluxed over night and then solvent was removed *in vacuo* to afford the crude 23. Then a solution of diol (0.181 g; 2.38 mmol) in THF (2.5 ml) was added to the residue. After 12h of stirring at room temperature, the compound was distilled. Distillation in vacuo gave the desired 24.

$^1$H NMR (200 MHz, CDCl$_3$) $\delta$: 1.89-1.92 (2H, m); 3.44-3.48 (4H, m); 3.98 (2H, m); 4.51 (2H, s); 5.56 (1H, d; J 1.7 Hz); 6.49-6.58 (1H, dt; J 18, J 1.7 Hz); 7-2-7.35 (5H, m).

**Vynil-(N-methyliminiodiacetoxy-O,O')borane (26).**
To a stirred solution of BH$_3$.SMe$_2$ (0.19 g) in THF (10 ml) at 0°C was added $\alpha$-pinene (6.8 g) dropwise. The reaction was stirred at 0°C over night and then cooled at -35°C. A solution of prop-2-ynyloxy methyl-benzene (0.35 g; 2.38 mmol) in THF (10 ml) was added dropwise and the resulting solution was stirred for 4h. The solution was allowed to rise to 0°C, then a solution of acetaldehyde (1.9 ml) freshly distilled in THF (5 ml) was added. The reaction was refluxed over night and then solvent was removed in vacuo to afford the crude 23.

The crude 23 was dissolved in THF (10 ml) and NaOH 1M (0.5 ml) was added. Stirring was maintained for 1h rt; Et$_2$O was added and organic phase was separated and dried over Na$_2$SO$_4$ to afford 25 as crude. In a roundbottom flask equipped with a stir bar was charged with crude 25, N-methyliminodiacetic acid (3 mmol), and benzene:DMSO (10:1, 10 ml). The flask was fitted with a Dean-Stark trap and a reflux condenser, and the mixture was refluxed with stirring for 16 hours. The reaction solution was allowed to cool to 23°C and the solvent was removed in vacuo. the residue was purified by column chromatography (AcOEt/MeOH 9.5:0.5) to afford 56 (20% over 3 steps).

$^1$H NMR (200 MHz, CDCl$_3$): δ 2.74 (3H, s); 3.83 (2H, d; J 16.6 Hz); 3.99 (2H, d; J 16.6 Hz); 4.01 (2H, m); 4.5 (2H, s); 5.64-5.73 (1H, dt; J 18 e J 1.7 Hz); 6.20-6.29 (1H, dt; J 18, J 7.1 Hz); 7.2-7.35 (5H, m).

Ciclopropyl-(N-methyliminodiacetoxy-O,O’N)borane (27).
To a stirred solution of 26 (0.121 g, 0.36 mmol) and Pd(OAc)$_2$ (0.0239 g, 0.011 mmol) in THF (12 mL) at 0°C in a 50 mL Schlenk flask was added a freshly prepared ethereal solution of diazomethane (3.5 mL of a 0.25 M solution, 8.8 mmol) dropwise over 20 minutes. Additional Pd(OAc)$_2$ was then added (0.0239 g, 0.011 mmol) as a solution in THF (1 mL) followed by the dropwise addition over 20 min of an additional 3.5 mL of 0.25 M ethereal diazomethane (0.88 mmol). The reaction was then allowed to warm to 23°C and the excess diazomethane was removed under a stream of N$_2$. The crude reaction mixture was then poured into 12 mL of 0.5 M pH 7 sodium phosphate buffer and extracted with THF:Et$_2$O 1:1 (3x12 mL). The combined organic fractions were then washed with brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. Purification by flash chromatography (SiO$_2$, Et$_2$O/CH$_3$CN 1:1) yielded 27 (0.34 mmol, 96%).

$^1$H NMR (200 MHz, CDCl$_3$): $\delta$ -0.40 -0.38 (1H, m); 0.42-0.44 (1H, m); 0.66-0.67 (1H, m); 1.23-1.25 (1H, m); 2.80 (3H, s); 3.84 (2H, app dd J 17, 9.5 Hz); 3.96 (2H, app dd J 17, 3 Hz); 4.01 (2H, m); 4.5 (2H, s); 7.2-7.35 (5H, m).

3-benzyloxypropenylboronic-acid (18). 

To a stirred solution of 27 (0.34 mmol) in THF (20 mL) was added 1M aq. NaOH (0.34 mmol) and the resulting mixture was stirred at 23°C for 20 minutes. The reaction was then quenched with the addition of 0.5 M pH 7 phosphate buffer (20 mL) and diluted with
Et₂O (20 mL). The layers were separated and the aq. layer was extracted with THF:Et₂O 1:1 (40 mL). The combined organic fractions were dried over MgSO₄ and concentrated in vacuo to yield the desired cyclopropylboronic acid 18 as a colorless oil. (0.33 mmol, 97%). Compound 18 was immediately used in next reaction without purifications and characterizations (very unstable).

**1H-inden-3yl trifluoromethanesulfonate (19)**

Triflic anhydride (0.649 g, 2.30 mmol) was added to a solution of 1-indanone 1 (0.290 g, 2.19 mmol) in dry 1,2-dichloroethane (12 ml) which was stirred under Argon at room temperature. 2,6-Di-tert-butyl-4-methylpyridine (0.48 g, 2.35 mmol) was added to the reaction mixture in one portion. The solution warmed up to about 40°C. After stirring for 0.5h at room temperature the reaction mixture was diluted with 1,2-dichloroethane, washed with 1N HCl and water, dried and concentrated under reduced pressure at room temperature. The residue was purified by flash chromatography (SiO₂ Ethyl ether/petroleum 0.3:9.7) to give 19 (0.545 g, 94% yield) as a colourless oil.

\[^1\text{H} \text{NMR (200MHz, CDCl}_3\)] \(\delta\): 3.47 (2H, br s,); 6.37 (1H, br, s); 7.25-7.60 (4H, m).

**3-(2-Benzzyloxymethyl-cyclopropyl)-1H-indene (20).**

To a stirred solution of 18 and 19 in toluene (4ml) was added a mixture of 3% Pd(PPh₃)₄, Cs₂CO₃ (0.242 g; 0.74 mmoli) and
KF.2H₂O (0.209 g; 2.22 mmoli) and NaBr (0.0954 g; 0.927 mmoli). The reaction was heated to 80°C for 16h. The mixture was filtered with Et₂O (3x10 ml) and washed with water. Organic phase was dried over Na₂SO₄ and evaporated. The final product was obtained after column chromatography (silica gel, petroleum/ethyl ether 25:1) of the crude 20 (30%).

¹H NMR (200 MHz, CDCl₃): δ 0.8-1.5 (4H, m) 3.31 (2H, m); 3.53-3.56 (2H, m) 4.61 (2H, s); 6.06-6.09 (1H, m); 7.22-7.55 (5H, 4H, m).

5-methoxy-3,3-dimethyl-2,3-dihydro-1H-inden-1-yl trifluoromethanesulfonate (28).

To a stirred solution of 36 (1 mmol) in 1,2-dichloroethane (5 ml) was added an equimolar amount of triflic anhydride and 2,6-t-butyl-4-methylpyridine under Argon atmosphere. The brown suspension was stirred 30 min at 40°C and 1h at rt. 1,2-dichloroethane (10 ml) was added and the organic phase was washed with HCl 5% (3x10 ml). Organic layers were washed with water (2x20 mL), brine, dried over Na₂SO₄, filtered, concentrated and purified by flash column chromatography on silica gel (petroleum/Et₂O 99:1) affording 28 (241 mg, 75 %).

¹H NMR (200MHz, CDCl₃) δ 1.36 (6H, s), 3.84 (3H, s), 6.84 (1H, s), 6.81-6.91 (2H, m), 7.20-7.25 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 24.5(2C), 46.51, 55.57, 108.51, 112.07, 119.18, 120.30, 127.25, 127.78, 145.38, 153.14, 159.83.
3-cyclopropyl-6-methoxy-1,1-dimethyl-1H-indene (30)

To a stirred solution of cyclopropylboronic acid (0.06 g, 0.698 mmol) and 28 (0.150 g, 0.466 mmol) in toluene (4 ml) was added a mixture of 6% Pd(PPh₃)₄, Cs₂CO₃ (0.120 g; 0.37 mmol) and KF·2H₂O (0.105 g; 1.12 mmol) and NaBr (0.048 g; 0.466 mmol). The reaction was heated to 80°C for 16 h. The mixture was filtered with Et₂O (3x10 ml) and washed with water. Organic phase was dried over Na₂SO₄ and evaporated. The crude 30 was purified by flash column chromatography on silica gel (petroleum/ethyl ether 9.5/0.5) affording 30 (70 mg 70%).

¹H NMR (200 MHz, CDCl₃) δ: 0.58-0.87 (4H, m); 1.25 (6H, s); 1.8-1.9 (1H, m); 3.84 (3H, s), 5.72 (1H, s), 6.79-6.89 (2H, m), 7.27-7.32 (1H, m).

Ethyl 6-methoxy-1,1-dimethyl-3-(((trifluoromethyl)sulfonyl)oxy)-2,3-dihydro-1H-indene-2-carboxylate (29)

TEA (0.302 g, 2.99 mmol) and DMAP (0.036 g, 0.03 mmol) were added to a solution of 37 (0.262 g, 1 mmol) in dry CH₂Cl₂ (50 ml). The reaction was stirred for 1 h at room temperature and then cooled to -78°C. Tf₂O (0.564 g, 2 mmol) was added over 2 min, and after 15 min at -78°C the mixture was warmed to room temperature and washed successively with HCl 1N, H₂O and brine. The aqueous layer was extracted with CH₂Cl₂ (3x15 mL). Organic phase was dried over Na₂SO₄ and evaporated. The final product was obtained after column
chromatography (silica gel, petroleum/ethyl ether 8:2) of the crude 29 (0.286 g, 78%).

$^1$H NMR (200MHz, CDCl$_3$) δ: 1.36-1.43 (3H, t, J 14 Hz), 1.51 (6H, s), 3.88 (3H, s), 4.31-4.42 (2H, q, J 22 Hz), 6.89 (1H, s), 6.94-6.96 (2H, m), 7.35-7.4 (1H, m).

**Ethyl-3-cyclopropyl-6-methoxy-1,1-dimethyl-1H-indene-2-carboxylate (31)**

To a stirred solution of 29 (0.760 g, 1.93 mmol) in toluene (10 ml) was added a mixture of cyclopropylboronic acid and K$_3$PO$_4$ (1.35 g, 6.36 mmol) and 3% Pd(PPh$_3$)$_4$. The reaction was heated to 100°C for 16h. The mixture was filtered with Et$_2$O (3x10 ml) and washed with water. Organic phase was dried over Na$_2$SO$_4$ and the solvent was evaporated. The crude product was purified by flash column chromatography on silica gel (petroleum/DCM 7:3) affording 31 (0.399 g, 80%).

$^1$H NMR (200MHz, CDCl$_3$) δ: 0.87-1.28 (4H, m), 1.37-1.409 (3H, t, J 7.8 Hz), 1.51 (6H, s), 3.88 (3H, s), 4.25 -4.36 (2H, q, J 22 Hz), 6.75-6.87 (2H, m), 7.30-7.34 (1H, m).

**Ethyl 2-cyano-3-methylbut-2-enoate (33)**

To a stirred solution of 32 (11.3 g, 100 mmol), Acetone (6.96 g, 120 mmol) and Acetic acid (2 g, 30 mmol) in Benzene (25 ml) was added L-phenylalanine (1 g, 6 mmol). The flask was fitted with a Dean-
Stark trap and a reflux condenser, and the mixture was refluxed with stirring for 14 hours. The reaction solution was allowed to cool to 23°C and the benzene was distilled. The mixture was filtrated and the solvent was evaporated. The crude 33 was distilled under reduced pressure at 120°C-135°C/0.1 mb affording 33 (14.2 g, 93%).

1H NMR (400MHz, CDCl₃) δ: 1.31-1.35 (3H, t, J 14 Hz), 2.3 (3H, s), 2.39 (3H, s) 4.23-4.29 (2H, q, J 22 Hz).

Ethyl 2-cyano-3-(3-methoxyphenyl)-3-methylbutanoate (34)

3-methoxyphenylmagnesiumbromide (1M in THF) (5.8 mmol, 5.8 ml ) and a catalytic amount of CuI was added to a solution of 33 (0.888 g, 5.8 mmol) in anhydrous Et₂O (10 ml). The mixture was heated under reflux over night. It was then cooled in an ice-bath, and decomposed with HCl(2N) and worked up with Et₂O (3x10 ml). Organic phase was dried over Na₂SO₄. After removal the solvent, the residue was distilled under reduced pressure at 160°C-180°C/0.1mb to afford an yellow oil 34 (1.06g, 70%).

1H NMR (200MHz,CDCl₃) δ: 1.05-1.12 (3H, t, J 14 Hz), 1.60 (6H, s), 3.57 (1H, s), 3.8 (3H, s), 4.0-4.072 (2H, q, J 14 Hz), 6.79-7.2(4H, m).

2-(3-methoxyphenyl)-2-methylpropanoic acid (35)

34 (1.306 g, 5 mmol) was added to a solution of KOH (2.24 g, 40 mmol) and 7.5 ml of ethylene glycol. The solution was heated under reflux for 11h at 170°C. When cool, it was diluted with H₂O, and a
small amount of a black oil was extracted with three portions of Et₂O. On acidification, the aqueous solution precipitated a dark oil which was extracted with two portions of ether. The extracts were washed with water and dried and the solvent was evaporated. The dark oil remaining was distilled under reduced pressure (to eliminate Ethylene glycol) affording 35 (0.776 g, 80%)

\[ 1^H \text{NMR (200 MHz, CDCl}_3\] \delta: 1.49 (6H, s), 2.62 (2H, s), 3.81 (3H, s), 6.78-6.98 (4H, m).

5-methoxy-3,3-Dimethyl-1-indanone (36)

A mixture of Eaton’s reagent (9.62 ml) and 35 (1.2 g, 5.77 mmol) was heated at 110°C for 3h. After the mixture was allowed to room temperature, it was cooled in an ice-salt bath and washed with water. The mixture was extracted with ether (3x20 ml); the combined ether extracts were washed with saturated NaHCO₃ and Brine and dried (Na₂SO₄). Removal of the solvent gave crude 36 as a yellow oil. The crude product was purified by flash column chromatography on silica gel (petroleum/ether 7:3) affording 36 (0.877 g, 80%).

IR (KBr): \( \nu \) 2977, 2947, 1654, 1577, 1081 cm\(^{-1}\); \( 1^H \text{NMR (200 MHz, CDCl}_3\] \delta: 1.39 (6H, s), 2.56 (2H, s), 3.89 (3H, s), 6.85-6.90 (2H, m), 7.63 (1H, d, J 9 Hz); \( 13^C \text{NMR (50 MHz, CDCl}_3\] \delta: 29.98, 38.47, 107.141, 114.98, 125.29, 128.77, 165.59, 166.89, 204.19. ESI MS m/z : 191.
Ethyl-5-Methoxy-3,3 dimethyl-1-oxo-indan-2-carboxylate (37).

To a stirred solution of NaH (60% mineral oil, 33.4 mmol) in (5 ml) diethyl carbonate was added a solution of 36 (2.95 g, 15.5 mmol) in (18 ml) diethyl carbonate. The mixture was refluxed at 80°C for 0.5h. After cooling to r.t., water (40 ml) was added. The aqueous phase was separated and extracted with DCM (4x10 ml). The combined organic extracts were dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The oil residue was subjected to chromatography (Ethyl Ether/ Petroleum 1:1) to yield 37 (2.44 g, 60%).

1 H NMR (200MHz, CDCl$_3$) δ: 1.36-1.41 (3H, t, J 10 Hz), 1.54 (6H, s), 3.45 (1H, s), 3.87 (3H, s), 4.18-4.23 (2H, q), 6.86-6.93 (2H, m,), 7.72 (1H, d, J 8.1 Hz)

3-(5-Methoxy-3,3-dimethyl-3H-inden-1-yl)-acrylic acid ethyl ester (41).

To a slurry of Pd(OAc)$_2$ (0.17 mmol, 10%) in dry DMF (15 mL) was added a solution 28 (1.7 mmol), ethyl acrylate (5.1 mmol), and triethylamine (6.8 mmol) in dry DMF (5 mL). The resulting mixture was heated at 75-80 °C in an argon atmosphere for 3 h, cooled to room temperature, and poured into ice-water. The resulting mixture was extracted with dichloromethane (3x30 mL), and the combined extracts were washed with water (2x30 mL), dried over sodium
sulfate, and concentrated under reduced pressure. Purification of the residue by chromatography with ether/petroleum ether 2:8 as the eluent gave 41 as a pale yellow oil (77%).

\[ ^{1}H \text{NMR (200 MHz, CDCl}_3 \] \( \delta \) 1.36 (3H, t, J 7.2 Hz), 3.84 (3H, s), 4.27 (2H, q, J 7.2 Hz), 6.47 (1H, d, J 16.4 Hz), 6.58 (1H, s), 6.81-6.83 (1H, m), 6.91-6.94 (1H, m), 7.48-7.50 (1H, m), 7.66 (1H, d, J 16.4 Hz); \[ ^{13}C \text{NMR (100 MHz, CDCl}_3 \] \( \delta \) 14.33, 24.66, 48.43, 55.51, 60.46, 108.47, 111.39, 119.24, 121.37, 132.76, 135.44, 138.55, 150.33, 156.09, 158.68, 167.32.

2-(5-Methoxy-3,3-dimethyl-3H-inden-1-yl)-cyclopropanecarboxylic acid ethyl ester (42).

The following procedure was carried out behind a safety shield using plastic-coated glassware free of scratches and ground glass Joints. 1-Methyl-3-nitro-1-nitrosoguanidine (5 mmol) was carefully added portionwise over 30 min to an Erlenmeyer flask containing a swirled mixture of aqueous NaOH (20 mL, 5 N) and diethyl ether (15 mL) at 0°C. After vigorous bubbling had ceased, the organic layer (containing diazomethane) was decanted into a chilled (0 °C) Erlenmeyer flask containing KOH chips (1 g). The mixture was swirled for 10 min, and the yellow solution was decanted into a dropping funnel. The solution of diazomethane was added over 30 min to an open flask containing a stirred mixture of 41 (1 mmol) and palladium acetate (0.03 mmol) in \( \text{CH}_2\text{Cl}_2 \) (10 mL) maintained at 0 °C. After the mixture was stirred for 1 h, a second batch of freshly
prepared diazomethane (5 mmol) in 15 mL of diethyl ether was added over 30 min. After the mixture was stirred for 1 h, the reaction was quenched with water (4 mL) and the mixture was poured into an aqueous saturated solution of NaHCO$_3$ (15 mL). The aqueous layer was extracted with EtOAc (3x10 mL). The organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (petroleum/Et$_2$O 9:1) affording 42 (55 %).

$^1$H NMR (200MHz, CDCl$_3$) $\delta$ 1.23-1.32 (2H, 3H, 3H, m), 1.42 (3H, s), 1.82-1.89 (1H, m), 2.32-2.36 (1H, m), 3.83 (2H, q, J 7.2 Hz), 3.86 (3H, s), 5.81 (1H, s), 6.77-6.82 (2H, m), 7.22 (1H, J 8.2 Hz).

4-(5-Methoxy-3,3-dimethyl-indan-1-ylidene)-5-methyl-3,4-dihydro-2H-pyrrole-3-carboxylic acid ethyl ester (7e).

Pathway B was used: 1eq TfOH, ACN, 60°C for 30min (65%). Yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.15 (3H, t, J 7 Hz), 1.32 (6H, d, J 3.4 Hz), 2.38 (2H, s), 3.6 (2H, dd, J 16.8 Hz), 4.04 (3H, s), 4.08–4.14 (5H, m), 6.79 (1H, m), 7.44 (1H, m).

Ethyl 5-methoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate

To a stirred suspension of NaH (11.00 mmol, 60% in mineral oil, 440 mg) in diethyl carbonate (2 ml) was added dropwise a solution
of 5-MeO-1-indanone (1) (5.00 mmol, 810 mg) in diethyl carbonate (20 ml). The mixture was warmed at 100°C in oil bath, until a solid spongy has been obtained. After cooling to rt, the spongy was diluted in CH₂Cl₂ and aqueous HCl 1N was added. The aqueous phase was separated and extracted in CH₂Cl₂. The combined organic extracts were dried (Na₂SO₄) and concentrated under reduced pressure. The residue was subjected to chromatography (Et₂O/petroleum ether 1:1), followed by crystallisation (from i-Pr₂O) to yield 1140 mg (97%) as a white crystalline solid (m.p.: 58-60°C)

¹H NMR (CDCl₃, 400 MHz) δ: 1.29 (3H, t, J 7.2 Hz), 3.28 (1H, dd, J₁ 8.0 Hz, J₂ 17.2 Hz), 3.48 (1H, dd, J₁ 4.0 Hz, J₂ 17.2 Hz), 3.68 (1H, dd, J₁ 4.0 Hz, J₂ 8.4 Hz), 3.88 (3H, s), 4.23 (2H, q, J 7.2 Hz), 6.90-6.91 (2H, m), 7.68 (1H, d, J 9.6 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ: 14.08, 30.19, 53.40, 55.58, 61.40, 109.44, 115.82, 126.00, 128.28, 156.68, 165.75, 169.30, 197.42; ESI-MS, m/z: [M-H⁺] = 233.2, [M+Na⁺] = 257.1, [2M+Na⁺] = 491.1.

**Ethyl-2-bromo-5-methoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (45)**

A mixture of β-ketoester (3.00 mmol, 702 mg), N-bromosuccinimide (3.15 mmol, 561 mg) and Amberlyst-15® (2.25 g) in ethyl acetate (30 ml) was stirred at room temperature for 30 min. After completion of the reaction, as indicated by TLC, the reaction mixture was filtered and washed with ethyl acetate. The combined organic extracts were dried over anhydrous Na₂SO₄, concentrated in
vacuo and the resulting product was directly purified by chromatography eluted with a mixture of ethyl acetate/petroleum ether (3:7) to afford 900 mg (96%) of the corresponding pure product 45 as yellow oil.

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$: 1.17 (3H, t, J 7.2 Hz), 3.52 (1H, d, J 18.4 Hz), 3.81 (3H, s), 4.06 (1H, d, J 18.0 Hz), 4.16 (2H, q, J 7.2 Hz), 6.81-6.88 (2H, m), 7.64 (1H, d, J 8.4 Hz); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$: 13.89, 43.80, 55.89, 59.35, 63.34, 109.45, 116.68, 125.04, 127.43, 153.38, 166.62, 167.05, 193.17; ESI-MS, m/z: [M+H$^+$] = 313.1-315.1, [M+Na$^+$] = 335.0-337.0, [2M+Na$^+$] = 648.5.

**Ethyl-2-azido-5-methoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate**

Sodium azide was added (4.36 mmol, 283 mg) to a solution of 45 (2.18 mmol, 680 mg) in dry DMF (3 ml) under nitrogen atmosphere and the resulting mixture was stirred at room temperature for 1h. After addition of H$_2$O, the aqueous layer was extracted in Et$_2$O. The combined organic layers were washed with brine, then dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The resulting product was directly purified by chromatography eluted with a mixture of ethyl acetate/petroleum ether (3:7) to yield 570 mg (95%).

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$: 1.18 (3H, t, J 7.2 Hz), 2.89 (1H, d, J 17.2 Hz), 3.55 (1H, d, J 17.6 Hz), 3.83 (3H, s), 4.15-4.22 (2H, m), 6.83-6.90 (2H, m), 7.64 (1H, d, J 8.4 Hz); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$: 13.89, 43.80, 55.89, 59.35, 63.34, 109.45, 116.68, 125.04, 127.43, 153.38, 166.62, 167.05, 193.17; ESI-MS, m/z: [M+H$^+$] = 313.1-315.1, [M+Na$^+$] = 335.0-337.0, [2M+Na$^+$] = 648.5.
MH\(_2\) \(\delta\): 13.88, 38.26, 55.80, 62.72, 70.39, 109.52, 116.58, 125.77, 127.04, 155.33, 166.70, 168.55, 195.22; ESI-MS, m/z: [M+Na\(^+\)] = 298.1, [2M+Na\(^+\)] = 572.9.

**Ethyl-5-methoxy-1-oxo-2-(2,2,2-trifluoroacetamido)-2,3-dihydro-1H-indene-2-carboxylate (43)**

Under nitrogen atmosphere, at a solution of azide (2.07 mmol, 570 mg) in THF dry (20 ml) was added Ph\(_3\)P (3.11 mmol, 814 mg). After 10 min at 0°C, the cooling bath was removed and the clear solution was allowed to warm to rt. After stirring overnight, the complete consumption of starting material was confirmed by TLC. Trifluoroacetic anhydride (4.14 mmol, 576 \(\mu\)l) was added and the mixture stirred for 1h. H\(_2\)O was added and the aqueous layer was extracted in Et\(_2\)O. The combined organic layers were dried over Na\(_2\)SO\(_4\) and concentrated under reduced pressure. The residue was purified by flash chromatography (ethyl acetate/petroleum ether 4:6) to afford 680 mg (95%) of the corresponding pure product 43 as white solid (m.p.: 106-108°C).

\(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\): 1.09 (3H, t, J 6.0 Hz), 3.37 (1H, d, J 17.2 Hz), 3.73 (1H, d, J 17.2 Hz), 3.84 (3H, s), 4.13 (2H, q, J 7.2 Hz), 6.88-6.92 (2H, m), 7.66-7.70 (2H, m); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\): 13.70, 37.99, 55.78, 63.39, 68.16, 109.40, 115.37 (q, J\(^1\) 286 Hz), 116.35, 126.75, 127.01, 155.00, 156.54 (q, J\(^2\) = 37 Hz), 166.62, 167.60, 193.66; ESI-MS, m/z: [M+H\(^+\)] = 346.1, [M-H\(^+\)] = 344.1, [M+Na\(^+\)] = 368.1, [2M+Na\(^+\)] = 712.5, [2M+K\(^+\)] = 728.9.
Ethyl-1-hydroxy-5-methoxy-2-(2,2,2-trifluoroacetamido)-1-cyclopropyl-2,3-dihydro-1H-indene-2-carboxylate (44)

To a solution of 43 (4.00 mmol, 1380 mg) in THF dry (40 ml) was added cyclopropylmagnesium bromide solution (0.5 M in THF dry, 24.00 ml) at 0°C. The resulting mixture was stirred at 0°C for 30 min, NH₄Cl (s.s.) was added and the crude was extracted in Et₂O. The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography (ethyl acetate/petroleum ether 1:9) to afford 1200 mg (78%) of the corresponding pure product 44 as white solid (m.p.: 92-95°C).

¹H NMR (CDCl₃, 400 MHz) δ: 0.08 (1H, m), 0.40-0.48 (3H, m), 0.91-0.98 (1H, m), 1.29 (3H, t, J 7.2 Hz), 2.32 (1H, bs), 3.35 (1H, d, J 16.8 Hz), 3.78 (3H, s), 3.86 (1H, d, J 16.8 Hz), 4.18-4.36 (2H, m), 6.71-6.79 (2H, m), 7.13 (1H, d, J 8.4 Hz), 7.72 (1H, bs); ¹³C NMR (CDCl₃, 50 MHz) δ: 0.30, 1.11, 13.79, 16.63, 37.99, 55.17, 61.89, 73.25, 84.51, 109.72, 113.21, 115.38 (q, J^1 286 Hz), 125.14, 132.33, 140.59, 156.89 (q, J^2 36 Hz), 160.64, 169.73; ESI-MS, m/z: [M-H]^+ = 386.2, [M+Na]^+ = 410.1.

Ethyl-1-(3-acetamidopropylidene)-5-methoxy-2-(2,2,2-trifluoroacetamido)-2,3-dihydro-1H-indene-2-carboxylate (46)

Under nitrogen atmosphere, trifluoromethanesulfonic anhydride was stirred (0.26 mmol, 43 µl) in CH₃CN dry (3 ml) for 15 min at room temperature. After cooling at 0°C, the compound 44 (0.26 mmol, 100
mg) was added, the resulting mixture was warming at room temperature and was stirred for 30 min. The reaction mixture was diluted with CH$_2$Cl$_2$ and quenched with NaOH 2N. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (ethyl acetate) to give 90 mg (81%) of the pure product 46 as yellow solid (m.p.: 46-48°C).

$^1$H NMR (CDCl$_3$, 400 MHz) δ: 1.14 (3H, t, J 7.2 Hz), 1.70 (3H, s), 2.38-2.44 (1H, m), 2.83-2.88 (1H, m), 3.11-3.16 (1H, m), 3.34 (1H, d, J 17.2 Hz), 3.50-3.55 (1H, m), 3.71 (1H, d, J 17.2 Hz), 3.78 (3H, s), 4.13-4.17 (2H, m), 5.47 (1H, dd, J$_1$ 6.4 Hz, J$_2$ 9.6 Hz), 6.04 (1H, m), 6.75-6.78 (2H, m), 7.54 (1H, d, J 8.4 Hz), 7.96 (1H, bs); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ: 13.77, 22.81, 28.65, 38.65, 41.40, 55.32, 62.52, 67.54, 109.48, 113.83, 115.53 (q, J$^1$ 286 Hz), 120.56, 125.52, 130.01, 141.13, 145.34, 156.60 (q, J$^2$ 38 Hz), 160.42, 170.83, 171.14; ESI-MS, m/z: [M+H$^+$] = 429.2, [M-H$^-$] = 427.2, [M+Na$^+$] = 451.1.

(E/Z) ethyl 5-methoxy-1-(5-methyl-2H-pyrrol-4(3H)-ylidene)-2-(2,2,2-trifluoroacetamido)-2,3-dihydro-1H-indene-2-carboxylate (7f)

A trimethylsilyl polyphosphate (PPSE) solution, prepared by heating at reflux for 1.5h a mixture of P$_2$O$_5$ (3.50 mmol, 497 mg) and hexamethyldisiloxane (4.91 mmol, 1.04 ml) in CCl$_4$ (5 ml), was added at room temperature to 46 (0.35 mmol, 150 mg). The reaction mixture was heated at reflux for 5h, cooled to room temperature,
diluted with CH₂Cl₂ and quenched with NaOH 2N. The aqueous层 was extracted with CH₂Cl₂, dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel conditioned with TEA and ethyl acetate as eluent to give 90 mg (63%) of product 7f as yellow oil.

¹H NMR (CDCl₃, 400 MHz) δ: 1.06 (3H, t, J 7.2 Hz, E isomer), 1.14 (3H, t, J 7.2 Hz, Z isomer), 2.13 (3H, s, Z isomer), 2.27 (3H, s, E isomer), 2.51-2.64 (2H, m, mix E/Z), 3.00-3.06 (2H, m, mix E/Z), 3.36-3.66 (4H, m, mix E/Z), 3.72-4.08 (4H, m, mix E/Z), 3.78 (6H, s, mix Z/E), 4.13 (2H, q, J 7.2 Hz, E isomer), 4.21 (2H, q, J 7.2 Hz, Z isomer), 6.73-6.84 (4H, m, E/Z mix), 7.31 (1H, d, J 8.4 Hz, E isomer), 7.50 (1H, d, J 8.8 Hz, Z isomer), 7.75 (1H, s, E isomer), 7.92 (1H, s, Z isomer); ESI MS, m/z: [M+H⁺] = 411.2, [M+Na⁺] = 433.1, [M-H⁺] = 409.2.

(E/Z)-4-(2-(ethoxycarbonyl)-5-methoxy-2-(2,2,2-trifluoroacetamido)-2,3-dihydro-1H-inden-1-ylidene)-1,5-dimethyl-3,4-dihydro-2H-pyrrolium trifluoromethanesulfonate (7f-N⁺Me)

Methyl trifluoromethanesulfonate (0.22 mmol, 25 µl) was added to a solution of 7f (0.22 mmol, 90 mg) in anhydrous benzene (5 ml). The product of reaction was recovered quantitatively as yellow-orange oil.
\(^1\)H NMR (CDCl\(_3\), 400 MHz) (Mix 1:1 Z/E) \(\delta\): 1.11 (3H, t, J 7.2 Hz, Z), 1.11 (3H, t, J 7.5 Hz, E), 2.56 (3H, s, E), 2.72 (3H, s, Z), 3.13 (1H, d, J 16.6 Hz, E), 3.18-3.30 (4H, m, mix E/Z), 3.40 (1H, d, J 16.6 Hz, Z), 3.52 (3H, s, E), 3.54 (3H, s, Z), 3.77 (1H, d, J 16.6 Hz, E), 3.90 (1H, d, J 16.6 Hz, Z), 4.10-4.30 (8H, m, mix E/Z), 6.83-7.00 (4H, m, mix E/Z), 7.51 (1H, d, J 9.7 Hz, Z), 7.54 (1H, d, J 9.2 Hz, E), 8.52 (1H, s, E), 8.90 (1H, s, Z). \(^1^3\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\): 13.50, 17.30, 17.43, 28.32, 32.02, 37.62, 37.90, 43.18, 45.38, 55.70, 57.67, 58.12, 63.46, 63.57, 69.35, 71.66, 109.18, 109.44, 114.43, 114.83, 115.41 (q, J\(^1\) 287 Hz), 118.82, 122.00, 127.93, 128.12, 129.28, 129.63, 130.92, 131.31, 149.73, 150.36, 151.19, 154.65, 156.60 (q, J\(^2\) 38 Hz), 156.70 (q, J\(^2\) 38 Hz), 163.56, 164.34, 167.64, 168.66; ESI MS, m/z: [M\(^+\)] = 425.

3,3-methoxyphenyl prop-2-enoic acid (52)

A stirred solution of Malonic acid (4.60 g, 40 mmol), 3-methoxy benzaldehyde (5.38 ml, 40 mmol), pyridine (3.20 ml, 40 mmol) and a catalytic amount of piperidine was refluxed at 90-95°C. After 2h the mixture was allowed to 115°C. After 1h the mixture was allowed to room temperature. The solution was poured in an ice-bath (water 40 ml) and it was acidify with HCl (6M). The mixture was filtered and it was dried under vacuum at 50°C over night affording 52 (6.60g, 37 mmol, 84%) as white solid m.p. (116°C-119°C).
\(^1\)H NMR (200 MHz; CDCl\(_3\)) \(\delta\): 3.84 (3H, s,); 6.44 (1H, d, \(J 15.8 \text{ Hz}\)); 6.96 (1H, m, \(J_{\text{PARA}} 0.80 \text{ Hz}; J_{\text{META}} 2.6 \text{ Hz}; J_{\text{ORTO}} 6.8 \text{ Hz}\)), 7.06 (1H, t, \(J 2.2 \text{ Hz}; J 3.8 \text{ Hz}\)); 7.14 (1H, d, \(J 7.6 \text{ Hz}\)); 7.32 (1H, t, \(J 7.8 \text{ Hz}; J 15.8 \text{ Hz}\)); 7.76 (1H, d, \(J 15.8 \text{ Hz}\)).

3-(3-methoxyphenyl)propanoic acid (53)

To a solution of 52 in EtOH (30 ml) was added 10% Pd/C and the flask was posed in a Shaker Type Hydrogenation Apparatus for 2h at 30 psi. The mixture was filtrated through celite pad with AcOEt. The mixture was concentrated \textit{in vacuo} affording 53 as a yellow oil. This oil at room temperature spontaneously affording 53 as a white cristal solid (6.65 g, 36.9 mmol, 98%) m.p. 40°C-45°C.

\(^1\)H NMR (200 MHz, CDCl\(_3\)) \(\delta\): 2.67 (2H, m); 2.94 (2H, m); 3.79 (3H, s,); 6.77 (3H, m); 7.21 (1H, m); 9.00 (1H, s,-COOH).

N-methoxy-3-(3-methoxyphenyl)-N-methylpropanamide (54)

A solution of 53 (3.32 g, 18 mmol) in CH\(_2\)Cl\(_2\) (50ml) was treated with N,O-dimethylhydroxylamine hydrochloride (3.00 g, 30 mmol), EDCI (5.74 gr, 30 mmol), pyridine (2.44 ml, 30 mmol) and catalytic amount of DMPA and stirred at room temperature for 2h. The reaction was quenched with HCl 5% (25ml) and H\(_2\)O (25ml). The aq. phase was extracted with AcOEt. The organic layers were dried over anhydrous sodium sulfate, and concentrated \textit{in vacuo} affording a crude 54 as yellow viscous oil (4.45 gr). Oil was dissolved in AcOEt
and it was washed with a saturated solution NaHCO$_3$. The mixture was extracted with AcOEt, dried over anhydrous sodium sulfate, and concentrated in vacuo affording 54 (3.46 g, 15 mmol, 84%) as clear yellow oil.

$^1$H NMR (200 MHz, CDCl$_3$) δ: 2.76 (2H, t); 2.92 (2H, m); 3.17 (3H, s); 3.79 (3H, s); 6.78 (3H, m); 7.20 (1H, dd).

**Tetrabutylammonium peroxydisulfate**

Tetrabutylammonium hydrogensulfate (21.2 g, 64.0 mmol) and potassium persulfate (8.70 g, 32.0 mmol) were dissolved in 140 mL of distilled water and the solution was stirred for 30 min at room temperature. The solution was extracted with CH$_2$Cl$_2$ (3x30 mL), and the combined organic layers were washed with distilled water (3x30 mL), dried over anhydrous Na$_2$SO$_4$, and filtered. Evaporation of the solvent in vacuo and subsequent drying under high vacuum gave TBPA (21.0 g, 31 mmol,) as a white solid in 97% yield. m.p. 118–120 °C

$^1$H NMR (200 MHz; CDCl$_3$) δ: 0.94 (12H, t); 1.43 (8H, m); 1.60 (8H, m); 3.28 (8H, t).

**3-(2-iodo-5-methoxyphenyl)-N-methoxy-N-methylpropanamide (55)**

To a stirred solution of 54 (1.35 g, 6.05 mmol) and TBPA (4.42 g, 6.05 mmol) in CH$_3$CN (30ml) was added a solution of I$_2$ (1.54 g, 6.05 mmol) in CH$_3$CN (70ml). The mixture was stirred for 5h at
48°C. The dark solution was allowed to room temperature and a solution of Na₂SO₃ 1M was added until bleaching of the reaction mixture. The aq. layer was extracted with AcOEt (3x20 ml) and the organic layers were washed with H₂O. The solvent was dried and concentrated in vacuo to give 55 (1.73 g, 4.95 mmol, 82%).

\[^1\text{H} \text{NMR} (200 \text{ MHz}; \text{CDCl}_3) \delta: 2.71 (2\text{H}, \text{ t}); 3.02 (2\text{H}, \text{ m}); 3.18 (3\text{H}, \text{ s}); 3.64 (3\text{H}, \text{ s}); 3.77 (3\text{H}, \text{ s}); 6.48-6.54 (1\text{H}, \text{ dd}, J_{13}, J_{25} 5.7 \text{ Hz}); 6.86 (1\text{H}, \text{ d}, J 3.2 \text{ Hz}); 7.66 (1\text{H}, \text{ d}, J 8.8 \text{ Hz}).\]

3-(2-iodo-5-methoxyphenyl)propanal (47)

A 50 ml dry four-necked round bottom flask equipped with a mechanical stirrer, an internal thermometer, a rubber septum and an argon gas inlet was charged with 500 mg of 55 (1.43 mmol) and 12.8 ml of anhydrous THF. The stirred solution was cooled to -78°C by mean of a liquid nitrogen bath and 7.16 ml (7.16 mmol) of a 1M solution of DIBAL-H in THF was added dropwise. After 1h the solution was allowed to 0°C and it was quenched with Acetone (0.41 ml, 7.16 mmol) and a solution of Rochelle (20ml). The mixture was allowed to room temperature and it was stirred at r.t. for 1h. It was extracted with AcOEt; dried over anhydrous Na₂SO₄, and concentrated in vacuo. The product 47 (360 mg, 1.24 mmol, 86.7%) was obtained after purification by flash column chromatography on silica gel (petroleum/AcOEt 8:2).

\[^1\text{H} \text{NMR} (200 \text{ MHz}; \text{CDCl}_3) \delta: 2.71 (2\text{H}, \text{ t}); 3.02 (2\text{H}, \text{ m}); 3.18 (3\text{H}, \text{ s}) 3.64 (3\text{H}, \text{ s}); 3.77 (3\text{H}, \text{ s}); 6.48-6.54 (1\text{H}, \text{ dd}, J 3, 5.7 \text{ Hz}); 6.86 (1\text{H}, \text{ d}, J 3.2 \text{ Hz}); 7.66 (1\text{H}, \text{ d}, J 8.8 \text{ Hz}).\]
(1H, d, J 3.2 Hz); 7.66 (1H, d, J 8.8 Hz). IR (film) ν: 2935; 1721; 1588-1566; 1465; 1278; 801 cm⁻¹

**Methyl (2S)-5-oxo-2-pyrrolidinecarboxylate (57)**

To a stirred solution of L-pyroglutamic acid (12.5 g, 97 mmol) in MeOH (150 ml) at 0 ºC was added thionyl chloride (14 ml, 194 mmol) dropwise over 5 minutes. The reaction was allowed to warm to r.t. and stirred for 2 hours. The reaction mixture was concentrated in vacuo, and the resulting yellow oil was dissolved in DCM (100 ml), washed with a saturated solution of NaHCO₃ (30 ml) and brine (30 ml). The combined aqueous layers were further extracted with DCM (5x30 ml). The organic layers were then dried over Na₂SO₄, filtered and concentrated in vacuo to yield 57 (14 g, 83%) as a clear oil, which was used without further purification.

**1-H NMR (200 MHz; CDCl₃) δ:** 2.27 (4H, m); 3.71 (1H, s); 4.23 (1H, m); 7.07 (1H, s).

**1-tert-Butyl 2-methyl (2S)-5-oxo-1,2-pyrrolidine dicarboxylate (48)**

To a stirred solution of 57 (5 g, 30 mmol) in CH₂Cl₂ (10 ml), was added di-tert-butylidicarbonate (9 g, 40 mmol) and DMAP (360 mg, 3 mmol). After 3 hours the reaction mixture was concentrated in vacuo to yield a dark orange oil. Purification by column chromatography eluting with EtOAc/Petroleum 4:6 to yield 48 (12.6 g, 70%) as white crystalline solid; m.p. 67-69°C.
[α]$_{D}^{22}$ -31.8 (c 1, CH$_3$Cl).

$^1$H NMR (200 MHz, CDCl$_3$) δ: 1.48 (9H, s); 2.00 (1H, m); 2.23 (1H, m); 2.50 (1H, m); 2.59 (1H, m); 3.77 (3H, s); 4.62 (1H, dd, J 10, 3 Hz). IR (film): ν 2996, 1755, 1737, 1701, 1301, 1142 cm$^{-1}$.

(2S)-1-tert-butyl 2-methyl 4-(1-hydroxy-3-(2-iodo-5-methoxy phenyl) propyl)-5-oxopyrrolidine-1,2-dicarboxylate (58)

To a solution of methyl N-BOC-pyroglutamate (48) (240 mg, 0.98 mmol) in dry THF (5mL) stirred at -78 °C was added a 1 M solution of lithium hexamethyldisilazide in THF (1 mL, 1 mmol). The reaction mixture was stirred for 1 h at -78 °C prior to the addition of a solution of the aldehyde (47) (300mg, 1.04 mmol) and Et$_2$0.BF$_3$ (125µl, 1 mmol) in THF (5 mL). The reaction mixture was stirred for 2 h at -78 °C and it was quenched with saturated NH$_4$Cl solution (5 mL), and H$_2$O (5 ml), and it was stirred at r.t. for 15 minutes and extracted with ethyl ether (3x20 mL). The combined organic phases were dried over Na$_2$SO$_4$, filtered, and evaporated to dryness. Purification of the crude 58 by flash chromatography (AcOEt/Petroleum 2:8) gave a mixture of aldols 58 (410 mg, 0.77 mmol, 78%)  

[α]$_{D}^{22}$ -14(c 1, CH$_3$Cl)

$^1$H NMR (400 MHz,CDCl$_3$) δ: 1.49 (9H, s); 1.658-1.746 (3H, m); 2.149-2.207 (2H, m); 2.614-2.663 (1H, m); 2.684-2.909 (2H, m);
3.76 (3H, s); 3.77 (3H, s, -COOCH$_3$); 4.37 (1H, s, -OH); 4.564 (1H, dd); 6.512 (1H, m); 6.844 (1H, d, J 3.2 Hz); 7.648 (1H, d, J 8.4 Hz).

(S)-1-tert-butyl 2-methyl 4-(3-(2-iodo-5-methoxyphenyl) propylidene)-5-oxopyrrolidine-1,2-dicarboxylate (49)

To a stirred solution of 58 (820 mg, 1.54 mmol) in dry CH$_2$Cl$_2$ (10ml) at 0°C was added Imidazole (314 mg, 4.62 mmol), Triphenylphosphine (444 mg, 1.70 mmol) and I$_2$ (430 mg, 1.70 mmol). After this solution was stirred at r.t. for 3h it was quenched with Na$_2$S$_2$O$_3$ (6 ml) and H$_2$O (4 ml). The mixture was extracted with CH$_2$Cl$_2$ (3x20 ml) and washed with Brine, dried over Na$_2$SO$_4$, filtered and evaporated in vacuo affording to crude 49 as diastereomeric mixture. After purification by flash chromatography (AcOEt/Petroleum 3:7) affording E (140 mg, 0.27 mmol) and Z (40 mg, 0.07 mmol), E+Z (610 mg, 1.18 mmol) (yield 88%).

E $[\alpha]^{22}_D$ +64 (c 1,CH$_3$Cl)

Z $[\alpha]^{22}_D$ -2.53 (c 1,CH$_3$Cl)

$^1$H NMR (400 MHz, CDCl$_3$) E $\delta$: 1.05 (9H, s); 2.419-2.523 (3H, m); 2.79-2.85 (3H, m); 3.75 (3H, s); 3.76 (3H, s, -COOCH$_3$); 4.58 (1H, dd, J 10.2, 3.2 Hz); 6.51 (1H, dd, J 8.8, 2.8 Hz); 6.72 (1H, d, J 3.2 Hz); 6.79 (1H, m); 7.65 (1H, d, J 8.4 Hz).$^{13}$C-NMR (400 MHz, CDCl$_3$) E $\delta$: 25.66; 28.01; 30.01; 39.46; 52.66; 55.46; 55.83; 83.71; 88.58; 114.34; 115.68; 129.67; 137.34; 140.06; 144.11; 149.96;
160.11; 165.80; 171.73. IR (film) ν: 2980; 1772; 1733; 1701; 1236; 1146; 718 cm\(^{-1}\) MS (m/z) 516.0; 459.9; 415.8; 275.7 m/z.

(S)-1-tert-butyl 2-methyl 4-(5-methoxy-2,3-dihydro-1H-inden-1-ylidene)-5-oxopyrrolidine-1,2-dicarboxylate (50)

To a stirred solution of 49 (200 mg, 0.38 mmol) in anhydrous DMF (6ml) was added Pd(OAc)\(_2\) (8.53 mg, 0.038 mmol), Triphenilphosphine (40.75 mg, 0.15 mmol) and TEA (116.3 mg 1.14 mmol). The mixture was heated at 110°C for 5h and it was washed with Brine. The aq. layers were extracted with Et\(_2\)O (3x20ml), and the organic phase was dried, filtered and evaporated. Flash chromatography on silica gel (AcOEt/Petroleum 3:7) afforded 50 (100 mg, 0.26 mmol, 66%) as yellow solid.

\[ [\alpha]_{D}^{22} +2.43 \]
\[ [\alpha]_{Hg}^{22} +5.74 \]

\(^1\)H NMR (400 MHz, CDCl\(_3\)) δ: 1.51 (9H, s); 2.93-2.98 (1H, dd, J 16.8, 2.8 Hz); 3.04 (2H, t, J 6.4); 3.29-3.47 (3H, m); 3.75 (3H, s); 3.84 (3H, s); 4.72 (1H, dd, J 10.6, 3.6 Hz); 6.85 (1H, dd, J 8.6, 2.4 Hz); 6.90 (1H, s); 7.40 (1H, d, J 8.4 Hz). \(^13\)C-NMR (400 MHz, CDCl\(_3\)) δ: 28.05; 28.31; 30.97; 31.47; 52.55; 55.52; 56.01; 83.12; 109.94; 114.04; 114.46; 126.67; 133.14; 150.46; 153.86; 155.21; 161.86; 167.61; 172.27. IR(film) ν: 2976; 1748; 1708; 1596-1488; 1149 cm\(^{-1}\) MS(m/z): 387.9; 331.9; 287.9.
Analytical conditions for chiral separation:

49 S: Enantiomer L – 49 R: Enantiomer D

System: HP Agilent 1100 HPLC

Column: ChiralPak AD-H 250 x 0.46 cm

Mobile phase: n-Hexane/EtOH 65/35% v/v

Flow rate: 0.8ml/min

DAD: 210/340 nm

CD: 240 nm

Enantiomer D

UV and CD Chromatograms of 49 R
Chapter 4  

Experimental

Enantiomer L

UV and CD Chromatograms of 49 S

L-D Mixture

UV and CD Chromatograms of mixture
**50S**: Enantiomer L – **50 R**: Enantiomer D

**System**: HP Agilent 1100 HPLC

**Column**: ChiralCel OD-H 250 x 0.46 cm

**Mobile phase**: n-Hexane/EtOH 70/30% v/v

**Flow rate**: 0.8ml/min

**DAD**: 210/340 nm

**CD**: 240 nm

Enantiomer D

[UV and CD Chromatograms of 50 R]
Chapter 4                                                                     Experimental

Enantiomer \( \mathbf{L} \)

UV and CD Chromatograms of 50 S

L-D Mixture

UV and CD Chromatograms of mixture
4.3 Abbreviations

Ac     Acetyl
ACN    Acetonitrile
DCM    Dichloromethane
DIPEA  N,N-Diisopropylethylamine
DMAP   4-Dimethylaminopyridine
DMF    Dimethylformamide
DMSO   Dimethyl sulfoxide
EDCI   1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide
KHMDS  Potassium Hexamethyldisilazane
LDA    Lithium diisopropylamide
LHMDS  Lithium Hexamethyldisilazane
LiHMDS Lithium bis(trimethylsilyl)amide
Ms,MsO Mesyl
NBS    N-bromosuccinimide-succinimide
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<tr>
<th>Abbreviation</th>
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<tr>
<td>PCC</td>
<td>Pyridinium Chloro Chromate</td>
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<tr>
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<td>Palladium on Carbon</td>
</tr>
<tr>
<td>PPSE</td>
<td>Trimethylsilyl polyphosphate</td>
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<tr>
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<td>Pyridine</td>
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<tr>
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<td>Tetrabutylammonium peroxydisulfate</td>
</tr>
<tr>
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<td>\textit{tert}-Butanol</td>
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<tr>
<td>$t$-BuOK</td>
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<tr>
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<td>Triethylamine</td>
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<td>Trifluoroacetic acid</td>
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