



Università degli Studi di Ferrara

**DOTTORATO DI RICERCA IN
SCIENZE FARMACEUTICHE**

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**SYNTHESIS OF BIOMIMETIC LIGHT-DRIVEN E/Z
MOLECULAR SWITCHES**

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1. INTRODUCTION

1.1 Nanotechnology.

Nanotechnology is the engineering of functional systems at the molecular scale that generally deals with structures of 100 nanometers (or smaller) and involves the development of materials and devices within that size.

In its original sense, nanotechnology (or “Nanotech” as is often shortened) refers to the projected ability to construct items *from the bottom up*, using techniques and tools developed to create high performance products ¹. This ability was envisioned by the renowned physicist Richard Feynman in his lecture “*There's Plenty of Room at the Bottom*”² given at an American Physical Society Meeting on December 1959. Feynman considered the interesting possibility of direct manipulating matter on an atomic scale using one set of precise tools and the bottom-up approach, which starts from atoms or molecules and builds up to nanostructures.

I want to build a billion tiny factories, models of each other, which are manufacturing simultaneously. . . The principles of physics, as far as I can see, do not speak against the possibility of manoeuvring things atom by atom. It is not an attempt to violate any laws; it is something, in principle, that can be done; but in practice, it has not been done because we are too big. — Richard Feynman, Nobel Prize winner in physics

Feynman envisioned a number of interesting applications and, in particular, the miniaturization of computer circuitry and the possibility to create new and more efficient microscopes.

Nowadays, nanotechnology is a very challenging sector to work in and it is considered a collection of different fields, touching on biology, medicine, material, computers, manufacturing, physics, and several others; this interdisciplinary aspect requires that people step outside of the confines of their own disciplines.

In this context, synthetic chemistry has acquired a powerful role as the science able to design and realize functional systems at the molecular scale. Indeed, the use of organic materials offers the advantage of easy fabrication, the possibility to shape organic

compounds into the desired structures by molecular engineering, the fine-tuning of a large variety of physical properties by small changes in the structure and the characterization of single isolated structures to allow the study of fundamental problems. The *bottom-up* design and construction of devices and machines at the molecular scale is a topic of great interest in nanotechnology and a fascinating challenge for chemists.

1.2 Molecular devices and machines.

In the macroscopic world, *devices* and *machines* are assemblies of components designed to achieve a specific function. Each component performs a simple act, while the entire assembly performs a more complex and useful function.

This macroscopic concept can be extended in a straightforward manner to the molecular level. Thus, a *molecular device* is an assembly of a discrete number of molecular components that cooperate to achieve a specific and useful function.

A *molecular machine* is a particular type of molecular device in which the relative positions of the component parts can change as a result of some external stimulus.

Molecular devices and machines operate via electronic and/or nuclear rearrangements and, like macroscopic devices and machines, need energy to operate and signals to communicate with the operator.

A particular type of molecular machine is the *Molecular Switch*.

1.3 Molecular Switch.

A *molecular switch* is a molecule that can interconvert among two or more stable states. These molecules may be shifted between the states in response to an external stimulus such as *pH*, light, temperature, an electrical current, microenvironment or in response to a ligand. In some cases, a combination of stimuli are utilized. The oldest forms of synthetic molecular switches are *pH* indicators, which display distinct colours as a function of *pH*.

Most examples of molecular switches typically consist of two states distinguishable by different physical or chemical properties. The basic requirement for these molecules is *bistability*, i.e., the occurrence of two different stable forms of a molecule, which can be interconverted by means of an external stimulus. The bistability can be based on a variety of properties of molecules such as electron transfer, isomerizations, and differences in complexation behavior^{3,4,5,6a,b}, whereas light, heat, pressure, magnetic or electric fields, *pH* change or chemical reactions can be used to achieve the interconversion between the stable states.

Photoreversible compounds, also called *Photoswitches* (Figure 1), where switching process is based on photochemically induced interconversion, are particularly attractive. Photochromism, which is largely defined as reversible change induced by light irradiation between two stable states of a molecule having different absorption spectra, is commonly associated with several systems. In figure 1, A and B represent the two forms, whereby λ_1 and λ_2 refer to the wavelengths used to effect the reversible switching behavior.

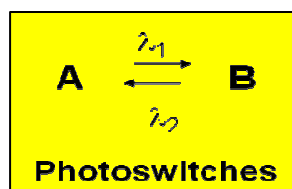
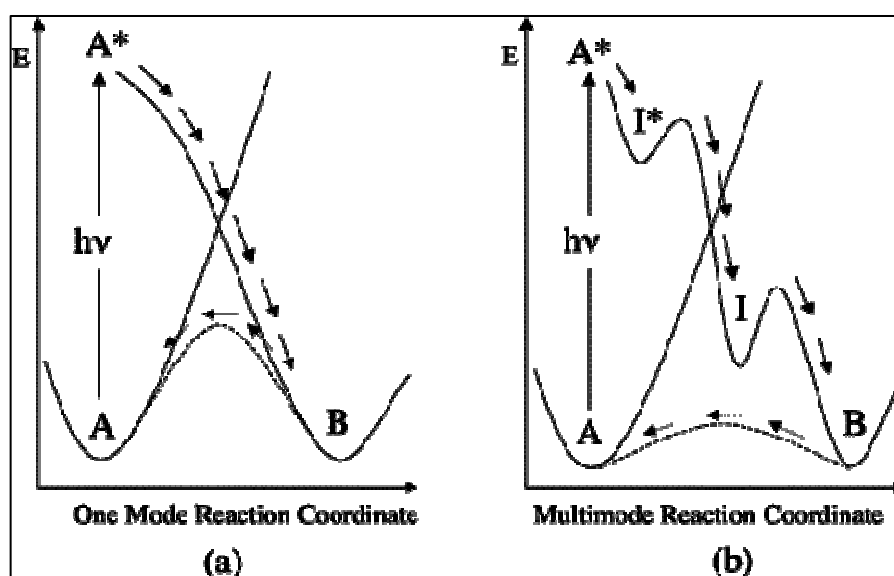


Figure 1

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^{6c, 1c}. In basically all applications, the induced interconversion between the two states results in a permanent or transient conformational change of a molecular scaffold bounded to the switch. 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 system, a number of other requirements are essential.

These features are well illustrated in Scheme 1 where a model reaction path for an efficient (Scheme 1a) and a less efficient (Scheme 1b) switch are reported⁷. 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 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). In contrast, the reaction path of Scheme 1b 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 Scheme 1a (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*.



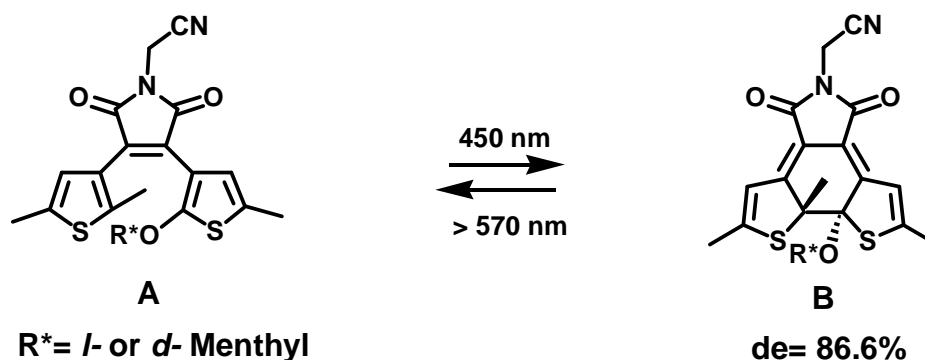
Scheme 1

Fast response time to stimulus, high rate of the interconversion process (nanoseconds reaction time scale) as well as high quantum yields of the reaction are additional and essential factors to define a “good molecular switch”.

The fascinating idea of casting single molecules capable to convert light-energy into useful applications prompted chemists to develop new systems. Indeed, literature shows different examples and a variety of photoreversible compounds including diarylethenes, spiropyrans, azobenzenes, sterically overcrowded stilbenes and retinal chromophore of rhodopsin proteins have been studied. The photochromic processes involved in these systems are typically photocyclization or (*cis-trans*) isomerization.

1.3.1 Diarylethenes.

For instance, Photochromic Diarylethenes, which undergo a reversible photocyclization, are among the most promising photoswitches known today. A reversible pericyclic reaction can take place in these compounds and irradiation with UV light of the open form leads to the closed form, which can undergo ring-opening again with visible light (Scheme 2)⁸. The presence of various substituents on the heteroarene moieties (in this case thiophene) eliminates the low thermal stability of open form, which is the main origin of the limited applicability of the reversible photocyclization of stilbene derivatives.

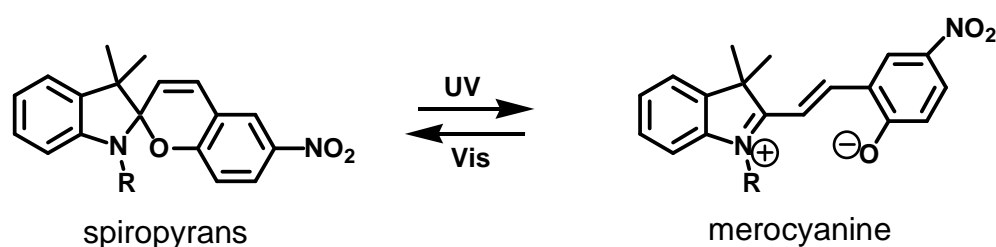


Scheme 2

By introduction of an *l*- or *d*-menthyl moiety at the 2-position of the benzo[*b*]thiophene ring in the diarylmaleimide-based switch **A**, a diastereoselective photocyclization could be accomplished. In fact, irradiation of **A** at 450 nm in toluene at 40 °C resulted in the formation of **B** with a diastereomeric excess (de) of 86.6%.

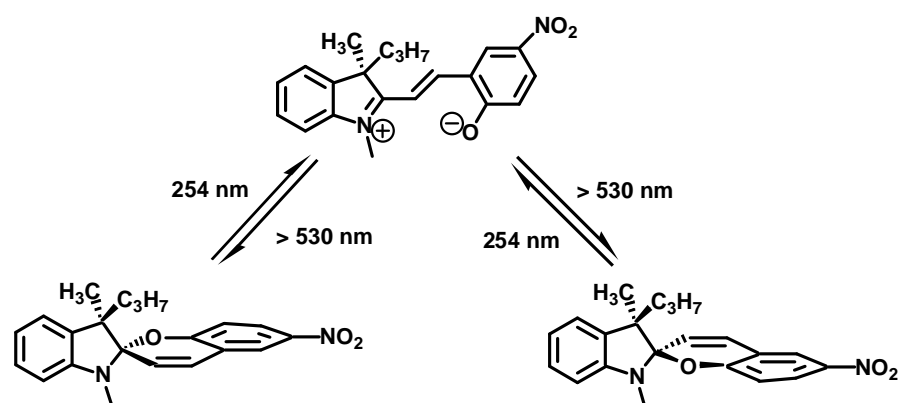
1.3.2 Spiropyrans.

Hirshberg proposed that the photochromism of spiropyrans could form the basis for a photochemical memory device⁹. These photoresponsive materials have found applications as light filters in, e.g. sun glasses, or as optical recording media and numerous studies have been devoted to this class of photochromic compounds. The photochromic (and thermochromic) behavior is due to the interconversion of the closed spiropyran form and the open merocyanine dye (Scheme 3).



Scheme 3

UV irradiation leads to the open form, which reverts to the closed form either thermally or by irradiation with visible light. The spirocarbon atom is a stereogenic center in the spiropyrans, but as a consequence of the achiral nature of the merocyanine form, the photochromic process will always lead to racemization.



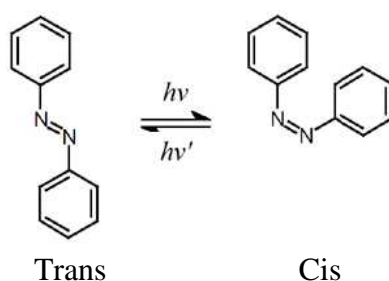
Scheme 4

By the introduction of a stereogenic center at position 3 vicinal to the spiro carbon, photochemical switching of optical activity could be accomplished (Scheme 4)¹⁰. In this case, a diastereomeric ratio of 1.6/1.0 was found.

1.3.3 Azobenzene.

Switches based on the *E/Z* photoisomerization of the azobenzene (Ab) chromophore have been used to control ion complexation¹¹, electronic properties¹² and catalysis¹³ or to trigger folding/unfolding of oligopeptide chains¹⁴. In particular, Isacoff *et al.*¹⁵ describe a general approach for manipulating allosteric control using this synthetic optical switch. Azobenzene can interconvert from the *cis*-form to the *trans*-one and *vice versa* when a specific wavelength radiation is provided (Scheme 5).

Azobenzene: Cis-trans isomerization.



Scheme 5

The interesting application of Isacoff is exemplified by the coupling of Ab with a specific ligand-gated ion channel of central importance in neuroscience, the ionotropic glutamate receptor (iGluR). In figure 2, when the left aromatic ring of the switch is functionalized with a maleimidic moiety, Ab can be linked in a covalent way on the receptor surface by the C-S single bond formation *via* a 1,4 Michael addition mechanism between the thiol group of Cysteine on the receptor and a sp^2 -C of maleimidic moiety. The right aromatic ring of Ab bears a Glutamate-residue, the ligand of the receptor. The photoisomerization of Ab into the *cis* stereoisomer allows the interaction of glutamate on the receptor and the resulting opening of the membrane channel. Using this intriguing stratagem, Isacoff *et al.* developed a light-activated channel, called LiGluR, in which the agonist is covalently tethered to the protein through the optical switch azobenzene moiety (Figure 2). The photostationary *cis/trans* ratio of azobenzenes depends on the wavelength, with maximum *cis* state occupancy typically observed at 380 nm and maximum *trans* state occupancy observed at 500 nm.

Photoswitching occurs on a millisecond time scale, with channel conductances that reflect the photostationary state of the azobenzene at a given wavelength. This device has potential uses not only in biology but also in bioelectronics and nanotechnology.

Ionotropic Glutamate Receptor control (iGluR)

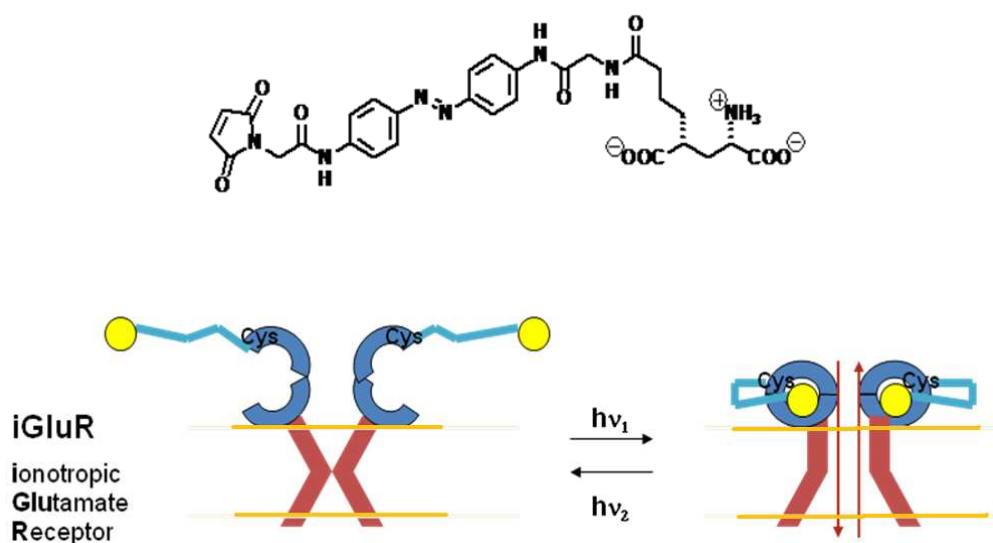


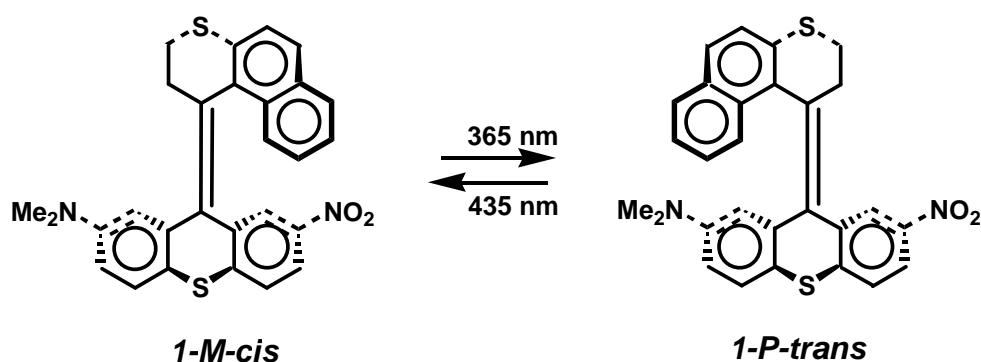
Figure 2

1.3.4 Overcrowded Alkenes.

Pseudoenantiomeric¹⁶ chiroptical switches are based on so-called sterically overcrowded alkenes (Feringa *et al.*)¹⁷. These molecules consist of an unsymmetrical upper part (tetrahydrophenanthrene or 2,3-dihydronaphtho(thio)pyran) connected via a double bond to a symmetric lower part (xanthene, thioxanthene, fluorene). To avoid unfavorable steric interactions around the central olefinic bond, the molecules are forced to adopt a helical shape. The chirality in these inherently dissymmetric alkenes, denoted with *M* and *P* for left- and right-handed helices respectively, therefore originates from distortion of the molecular framework.

The tetrahydrophenanthrene-type upper part is bulky enough to inhibit fast racemization by movement of the aromatic moieties of the upper and lower halves through the mean plane of the molecules, but there is sufficient conformational flexibility to undergo induced isomerization.

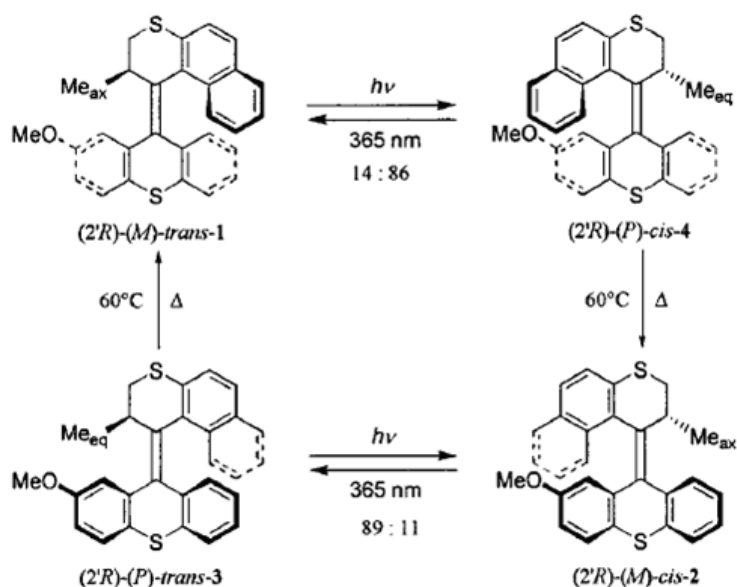
A remarkable enhanced stability and a highly stereoselective switching process was found with structure containing donor and acceptor substituents in the thioxanthene moiety. The substituent effects also result in a absorbance shift in the UV-Vis spectra of *1-M-cis* and *1-P-trans*, allowing the switching process to take place near the visible region of the spectrum. For example (Scheme 6)¹⁸, alternated irradiation of enantiomerically pure *1-M-cis* using 365 and 435 nm light resulted in diastereoselective interconversions from *1-M-cis* to *1-P-trans* and *vice versa* respectively.



Scheme 6

Most remarkably, a sophisticated evolution of the original molecule above led to the preparation of light-driven *molecular rotors* where chirality turned out to be an essential feature to impose unidirectional rotation (Scheme 7)¹⁹.

The new type of molecular rotor contains a chiral 2-methyl-2,3-dihydrothiopyran upper part and a (thio)xanthene lower part.



Scheme 7

As shown in scheme 7, the irradiation of $(2'R)\text{-}(M)\text{-trans-1}$ in *n*-hexane at 365 nm and 10 °C resulted in the formation of $(2'R)\text{-}(P)\text{-cis-4}$, with the methyl group at the 2'-position adopting an equatorial orientation as determined by ^1H NMR. A $(2'R)\text{-}(P)\text{-cis-4}$ to $(2'R)\text{-}(M)\text{-trans-1}$ ratio of 14:86 was observed. When the temperature of the solution of $(2'R)\text{-}(P)\text{-cis-4}$ was raised to 60 °C, a complete conversion to $(2'R)\text{-}(M)\text{-cis-2}$ was observed. Subsequent irradiation of $(2'R)\text{-}(M)\text{-cis-2}$ in *n*-hexane (10 °C) at 365 nm resulted in formation of $(2'R)\text{-}(P)\text{-trans-3}$ with the methyl group at the 2'-position again in an equatorial orientation as determined by ^1H NMR. A $(2'R)\text{-}(P)\text{-trans-3}$ to $(2'R)\text{-}(M)\text{-cis-2}$ ratio of 89:11 was observed. When the temperature of the solution of $(2'R)\text{-}(P)\text{-trans-3}$ was increased to 60 °C, a complete conversion to $(2'R)\text{-}(M)\text{-trans-1}$ was observed. Moreover, the experimental results show that the upper naphthothiopyran moiety undergoes a full 360° rotation in a counterclockwise sense relative to the lower thioxanthene part. Compared to the original molecular switch based on biphenanthrylidenes, it is remarkable that the presence of a single stereogenic center (C(2')) is a sufficient condition to accomplish unidirectional rotation.

1.3.5 The Green Fluorescent Protein (GFP).²⁰

The *green fluorescent protein* (GFP) is a protein composed of 238 amino acids (26.9 kDa) and was originally isolated from the jellyfish *Aequorea Victoria*.

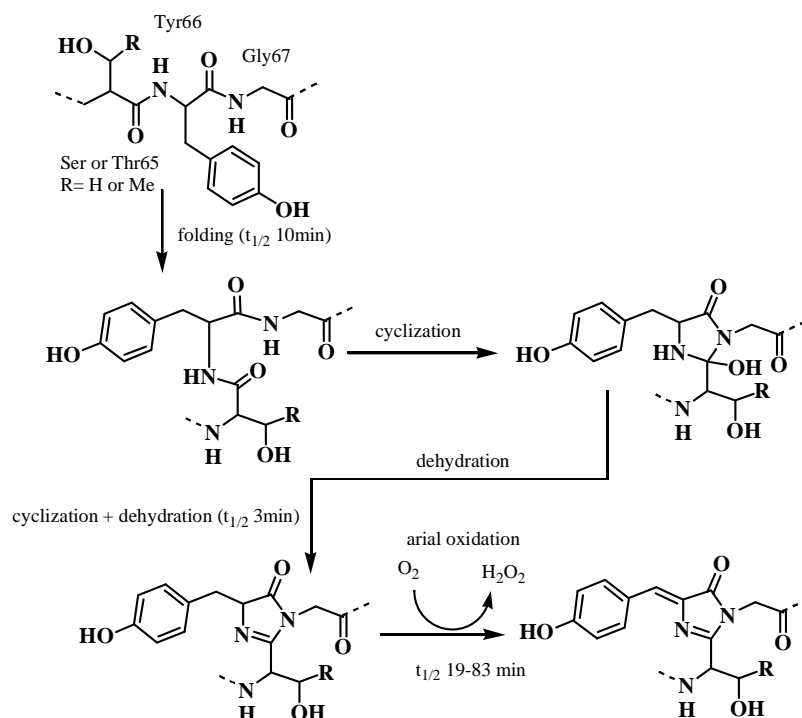
This class of molecules can be reversibly photoswitched between a fluorescent and a nonfluorescent state and acquires enormous potential in diverse fields, such as in vivo protein tracking and subdiffraction resolution light microscopy.

Osamu Shimomura, Martin Chalfie and Roger Y. Tsien shared the 2008 Nobel Prize in chemistry for the discovery and development of the green fluorescent protein, GFP, that has been key to improving our understanding of cell processes.

In fact, these GFP-like proteins allow the monitoring in time and space of an ever-increasing number of phenomena in living cells and organisms like gene expression, protein localization and dynamics, protein-protein interactions, cell division, chromosome replication and organization, intracellular transport pathways, organelle inheritance and biogenesis, to name but a few. In addition, the fluorescence from single GFP molecules has made it feasible to image at a spatial resolution higher than the diffraction limit. Furthermore, sensors that report *pH* values, Ca^{2+} concentrations and other essential features of the interior of living cells have been engineered from GFP-like proteins.

The technical revolution resulting from the discovery of GFP relates to a miraculous property of the chromophore that is responsible for its fluorescence. This chromophore is formed spontaneously from a tri-peptide motif in the primary structure of GFP (Figure 3), so that its fluorescence is “automatically” turned on in every organism where it is expressed. In other words, the maturation of the tri-peptide based chromophore in GFP only requires oxygen and does not depend on the presence of enzymes or other auxiliary factors. The tripeptide motif Ser65-Tyr66-Gly67- in the primary structure of unfolded or denatured GFP does not display any striking feature (Fig. 3, top). However, as the GFP protein folds into its native conformation, these three amino acids are forced into a sharp turn (Fig. 3, middle, left), greatly favouring a nucleophilic attack of the amide of Gly67 on the carbonyl of Ser65, leading to

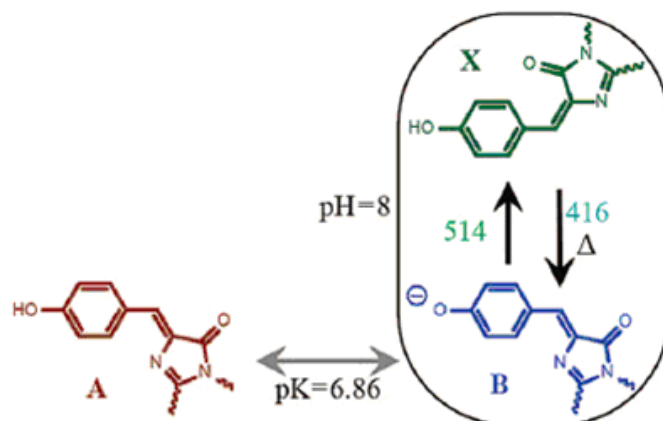
imidazolinone formation by cyclization (Fig. 3, middle, right) and dehydration (Fig. 3, bottom, left). At this point, GFP does not fluoresce (Heim *et al.*, 1994)²¹ but, conditional on the presence of molecular oxygen, the α - β bond of residue 66 is subsequently dehydrogenated into conjugation with the imidazolinone (Fig. 3, bottom, right), which results in maturation of the GFP chromophore to its fluorescent form (Heim *et al.*, 1994; Cubitt *et al.*, 1995)²¹.



Chemical reaction scheme accounting for the spontaneous formation of the GFP chromophore from the Ser65-Tyr66-Gly67 motif in the native conformation of the protein in the presence of molecular oxygen.

Figure 3.

Particularly, Luin *et al.*²² showed that the greenfluorescent protein (GFP) EYQ1 can be transferred from a nonfluorescent “off” to a fluorescent “on” state and back again, by green and blue light, respectively (Figure 4). Subsequent Raman spectra analysis and theoretical calculations on this protein demonstrated that upon the absorption of a green photon, the chromophore isomerizes from the **B** *cis* (off) to **X** *trans* (on) state. Moreover, for the case of EYQ1 (figure 4) Luin showed that at pH=8 the chromophore is anionic in the native form **B** and neutral *trans* in the photoconverted form **X**; it is neutral *cis* **A** in the native form at lower pH.



Proposed scheme for the considered states of the chromophore in (GFP) EYQ1.

Figure 4

1.3.6 The retinal protonated Schiff base (PSB) chromophores.

Chiral *E/Z* switches are also known in photobiology. For instance, the retinal chromophore of *Rhodopsin* (Rh) proteins²³, a large class of trans-membrane photoreceptors (also called PSBs, *Protonated Schiff Bases*) undergoes an efficient unidirectional photoisomerization that, ultimately, triggers a conformational change of the native protein scaffold. In fact, Rhodopsin consists of the protein moiety *opsin* and a reversibly covalently bound cofactor, *retinal*. Opsin, a bundle of seven transmembrane helices, binds retinal, a photoreactive chromophore, in a central pocket. Retinal is produced in the retina from Vitamin A.

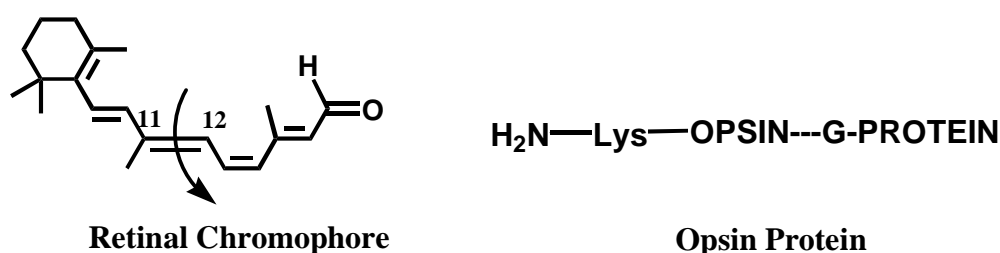
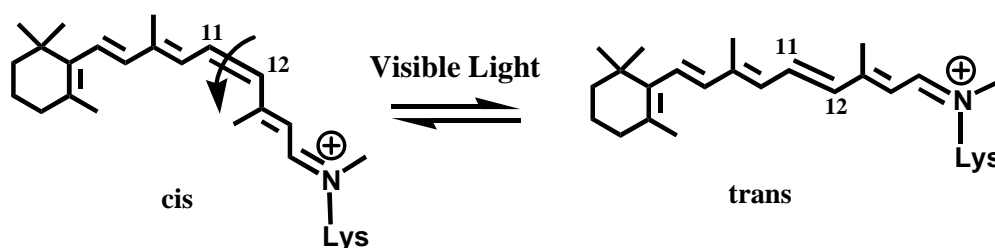


Figure 5

Isomerization of retinal operated by light, induces a conformational change in opsin that activates the associated G protein and triggers a second messenger cascade. The change in geometry initiates a series of events that eventually cause electrical impulses

to be sent to the brain along the optic nerve and are responsible of the vision mechanism.



Isomerization of 11-*cis*-rhodopsin into 11-*trans*-retinal induced by light.

Scheme 8

More precisely, in rhodopsin itself the p-p* excitation of the 11-*cis* form of the chromophore retinal yields exclusively the *all-trans* form through a *Z/E* counterclockwise twist of the C11=C12 bond and occurs with a quantum yield of 0.67.

This value is larger than the 0.25 value measured for the same chromophore in ethanol solution and also larger than the 0.28 and 0.51 values measured for the photoisomerization of *trans*- and *cis*-azobenzene, respectively. Due to its high photoisomerization efficiency, bacteriorhodopsin (a member of the same photoreceptor family) and its mutants, have been exploited to produce different light-driven molecular devices (see ref 24 and references therein).

The attractive properties of the protein-embedded PSB¹¹ (the isomerization selectivity, directionality, and efficiency of retinal chromophores are lost when they are irradiated in solution) make it an excellent reference for the design of alternative light-driven switches. *In other words, while it has been established that the efficiency of the PSB¹¹ reaction is enhanced by the complex protein environment, one may always try to design a nonnatural protonated Schiff base that replicates the excited-state properties of the protein-embedded chromophore with the final goal of obtaining photoactivable switches. This is the driving force of a current project that find computational, photochemical and synthetic chemists closely involved. The numerous and different synthetic aspects we had to face is the central core of the present thesis.*

2. RESULTS AND DISCUSSION

2.1 Molecular Switch of First Generation (PSB^I): Synthesis and Description.

As described in introduction, in Rhodopsin (Rh) the photoisomerization of the native 11-*cis*-retinal chromophore (PSB¹¹) to its *all-trans* form occurs with high efficiency. The high quantum yield associated with this process is closely connected to the feature chemical structure of this chromophore and, in particular, to the ultrafast *cis/trans* isomerisation of C11-C12 double bond²⁵.

This idea is supported by the fact that 13-demethyl-Rh (an isomer of Rh where the 13-methyl group of PSB¹¹ has been removed) and isorhodopsin (an isomer of Rh containing a 9-*cis*-retinal chromophore) isomerize more slowly and have lower quantum yields than Rh²⁶.

Combined computational and experimental studies showed that certain natural PSBs, such as retinal PSB¹¹, provide suitable “frameworks” for the design of biomimetic molecular switches.

An example is provided by the PSB model 4-*cis*- γ -methylnona-2,4,6,8-tetraeniminium (4-*cis*- γ -Me-C₉H₁₀-NH₂)⁺ (Figure 1) that represents one of the first framework identified²⁷. Furthermore, computational analysis on the isomerisation of the 2-*cis*- α -methyl-penta-2,4-dieniminium (2-*cis*- α -R-Me-C₅H₆NH₂)⁺, a minimal model of PSB¹¹ with a penta-2,4-dieniminium (-CH=CH-CH=CH-CH=NH⁺-) moiety, indicate that this system provides a more suitable backbone²⁸.

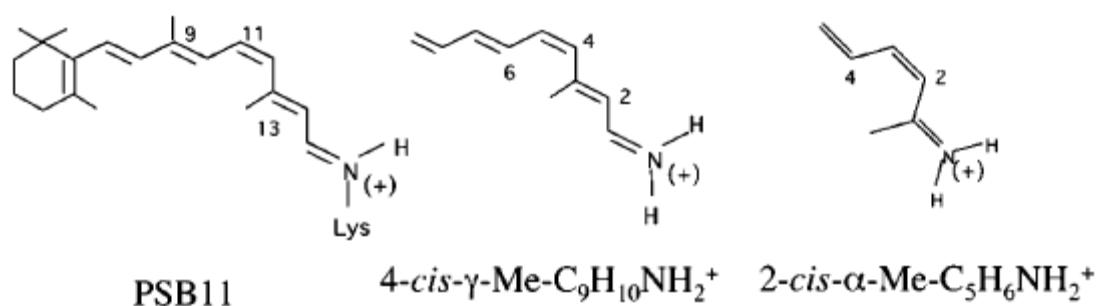


Figure 1

Up to now, attempts to synthesize compounds containing the penta-2,4-dieniminium biomimetic backbone to find support for the predicted behaviour have never been reported. On embarking on this project we were attracted by the known 4-benzylidene-3,4-dihydro-2H-pyrroline **1neut** (Scheme 1 and Figure 2), from which a suitable chromophoric unit could be easily derived. by *N*-methylation or protonation. Effectively, the targeted penta-2,4-dieniminium moiety is part of the molecular structure of **1Me** where a phenyl ring replace the terminal carbon/carbon double bond. We envisaged to prepare a class of molecular switches allowing preliminary photochemical analysis by simply varying substituents on the phenyl ring. Thus, in addition to compound **1Me**, we synthesized *p*-MeO-**1Me** and *p*-NO₂-**1Me**; this class of molecular switches is called **PSB^I** (Protonated Schiff Bases of first generation). In particular, *p*-OMe and *p*-NO₂ substituents (i.e. electron-releasing and electron-withdrawing group) on phenyl ring of 3-benzylidene-1-pyrrolines were chosen to allow modulation of electron density within the π -system: indeed it was shown that this simple modification can be used to “tune” the photochemical behaviour of these molecules.

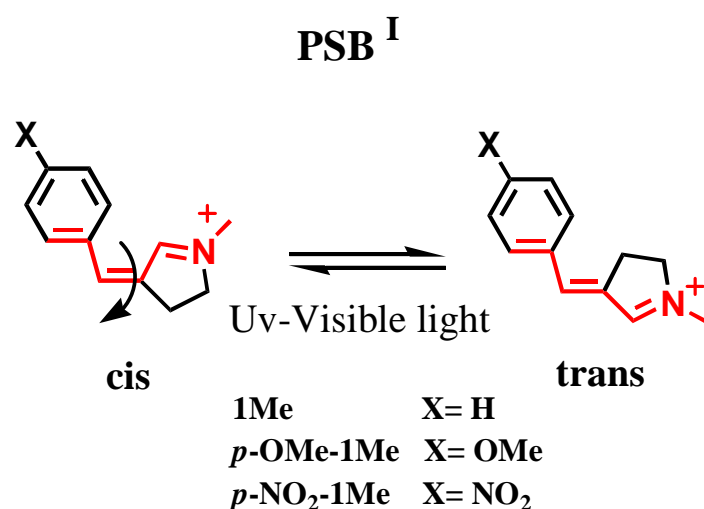
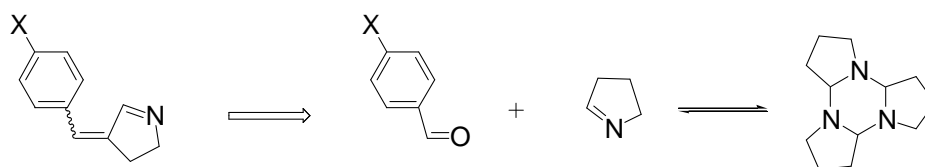


Figure 2

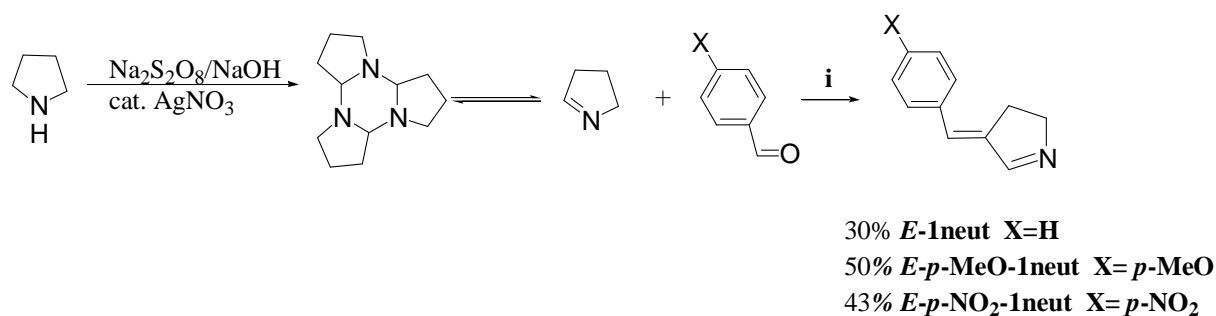
The most convenient route towards **PSB^I** seemed to be an aldol-like condensation between aromatic aldehydes and 1-pyrroline (Scheme 1). However, the material

referred to 1-pyrroline presents special difficulties due to its tendency to trimerize in 1,6,11-triazatetracyclo-[10.3.0.0.^{2,6}0^{7,11}]pentadecane.



Scheme 1

In 1982, Tomada *et al*²⁹ studied the synthesis of 1-pyrroline trimer by silver (I) catalyzed oxidation of pyrrolidine with peroxodisulfate (scheme 2) and found that this material reacted with benzaldehyde to furnish 3-benzylidene-1-pyrroline **1neut** in acceptable yield. Thus, as a synthetic equivalent, the predominant trimer is in equilibrium with 3,4-dihydro-2-H-pyrrole, that is in turn able to react with benzaldehyde in an aldol-like condensation²⁹.



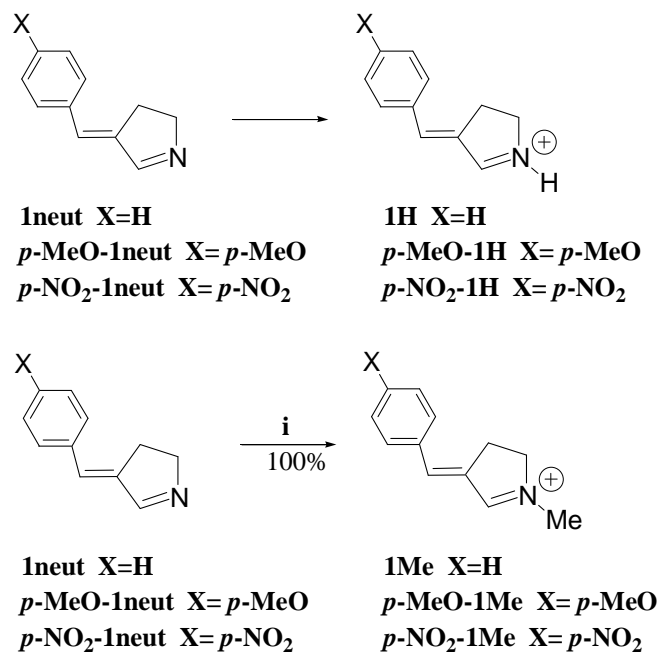
Reagents and conditions: (i) **1neut** and *p*-MeO-**1neut**: MeOH, rt, 48h; *p*-NO₂-**1neut**: 0.6 M acetic acid/0.2 M sodium acetate, MeOH, 60°C, 24h.

Scheme 2

The application of this protocol led us to obtain the derivatives **1neut**, *p*-MeO-**1neut** and *p*-NO₂-**1neut** simply by combining the trimer with benzaldehyde, *p*-methoxy- or *p*-nitro-benzaldehyde respectively. However, in the latter case, by adopting usual reaction conditions, only traces of the desired *p*-nitro-benzylidene derivative are formed; consequently, we decided to force the removal of water by heating a methanolic solution of this intermediate in the presence of AcOH/AcONa mixture, furnishing the desired compound in more than 43% yield.

Initially, **1neut**, *p*-MeO-**1neut** and *p*-NO₂-**1neut** were treated with trifluoroacetic acid to afford the corresponding PSBs **1H**, *p*-MeO-**1H** and *p*-NO₂-**1H** as a mixture of *E*-

and *Z*-isomers; afterwards, the neutral compounds were reacted with methyl trifluoromethanesulfonate leading quantitatively to the formation of the *E*- and *Z*-forms of **1Me**, *p*-**OMe-1Me** and *p*-**NO₂-1Me** (scheme 3).



Reagents and conditions: (i) CF₃SO₃CH₃ benzene, rt, 10min.

Scheme 3

The *N*-methyl derivatives were found to be more stable and tractable than the protonated forms. In particular, it was observed that the protonated *Z*-stereoisomers of **1H**, *p*-**MeO-1H**, and *p*-**NO₂-1H** tended to transform thermally to the corresponding *E*-stereoisomers. The higher stability of *N*-methyl compounds is qualitatively rationalized by the additional stabilization of the positive charge at *N* and by the decreased mobility of the alkyl group with respect to the proton.

The photochemical characterization of compounds **1Me**, *p*-**MeO-1Me** and *p*-**NO₂-1Me** (for complete description see ref. 7) showed that the absorption maximum (λ_{\max}) of **1Me** is 327 nm and that it is sensitive to the aromatic modulation with an electron-withdrawing (EW) or electron-releasing (ER) substituent in *para*-position. Indeed, for compound *p*-**MeO-1Me**, the λ_{\max} is red-shifted relative to **1Me**; on the other hand, for compound *p*-**NO₂-1Me**, the λ_{\max} is blue-shifted. Moreover, it was shown that *p*-MeO substituent has beneficial effects on the photochemical isomerisation pathway; on the

contrary, when the *p*-NO₂ substituent is placed, the photoisomerization has an inefficient profile.

Although some problems were identified, the photoisomerization path of these prototype compounds satisfied the general criteria required for a molecular switch.

Unfortunately, photochemical studies on **PSB^I** switches showed low quantum yield for these molecules and defined that the strong decrease of the *E/Z* isomerization quantum efficiency is mainly due to the free rotation allowed by the single double bond between the phenyl ring and ethylene spacer.

These considerations prompted us to look at related structures with the aim of increasing the photoisomerization efficiency. We envisaged the development of a second generation PSB switches by decreasing the number of freedom torsional degrees of the **PSB^I** backbone and especially the free rotation around the benzylic single bond. We translated these concepts into a simple working hypothesis for the synthesis of a novel unnatural protonated Schiff base (**PSB^{II}**, Protonated Schiff Bases of second generation) system where the carbon-carbon exocyclic double bond appears to be the only conformationally free site in the excited state electronic structure³⁰.

We disclose herein the results of our investigation to achieve an effective preparation of **PSB^{II}**, a molecule featuring a pyrrolinium moiety conjugated to an aromatic ring, the latter being embedded in a conformationally locked indanylidene nucleus (figure 3).

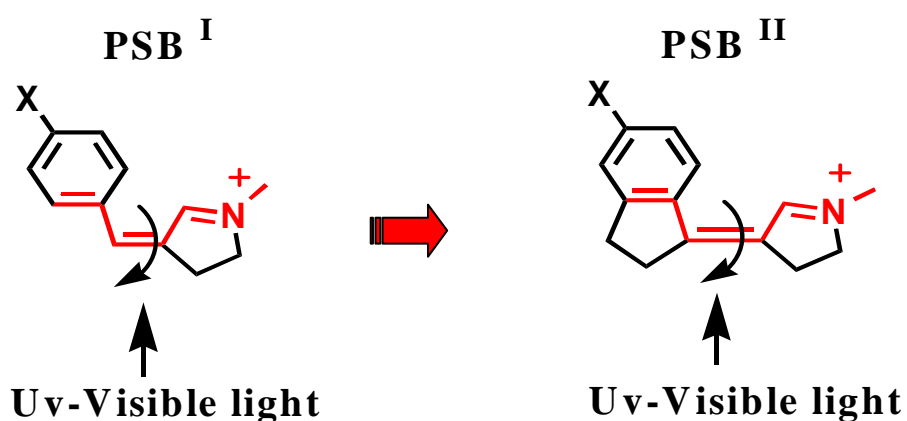
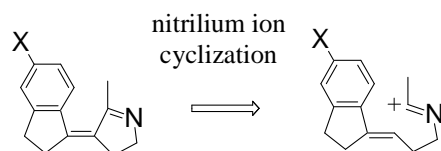


Figure 3

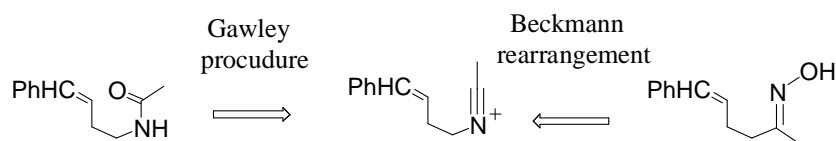
2.2 Molecular Switches of Second Generation (PSB^{II}): Synthesis.³¹

The first retrosynthetic approach we decided to undergo toward **PSB^{II}** is a intramolecular capture of a nitrilium ion by a suitable located olefin group. (Scheme 4).



Scheme 4

The cyclization of a nitrilium ion to form a heterocycle was first observed in the 19th century, but synthetically useful procedures have only emerged recently^{32, 33}. In some communications, it was shown that nitrilium ions may be prepared as efficiently from secondary amides as from oximes (Scheme 5).



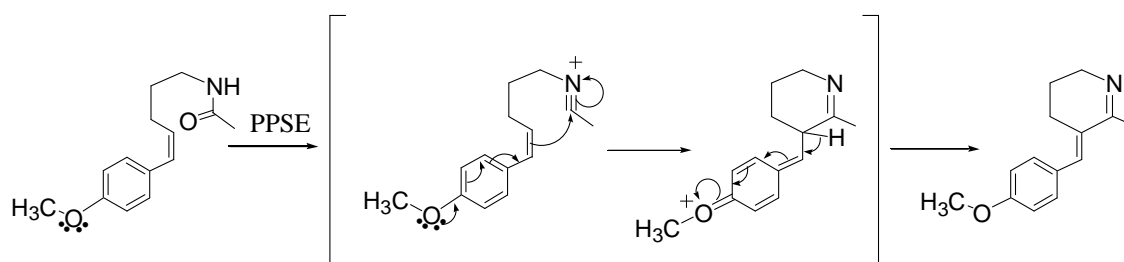
Scheme 5

Although the notation of generating a nitrilium ion from an oximes has some appeal because of the synthetic usefulness and general availability of oximes, the stereospecificity of the Beckmann rearrangement introduces a serious limitation. Specifically, obtaining any given nitrilium ion from an oximes is predicated on the availability of the oxime as a *single geometric isomer*. Oximation of almost all dialkyl ketones gives rise to a mixture of both oximes geometric isomers, which are usually difficult to be separated.

On the basis of these considerations, Gawley *et al.*³⁴ introduced their protocol by which nitrilium ions are generated by the action of trimethylsilyl polyphosphate (PPSE) on secondary amides in refluxing carbon tetrachloride.

Later, Angelastro *et al.*³⁵ (scheme 6) reported the formation of quinolizidines via a vinylogous Bischler-Napieralski nitrilium ion cyclization employing the PPSE

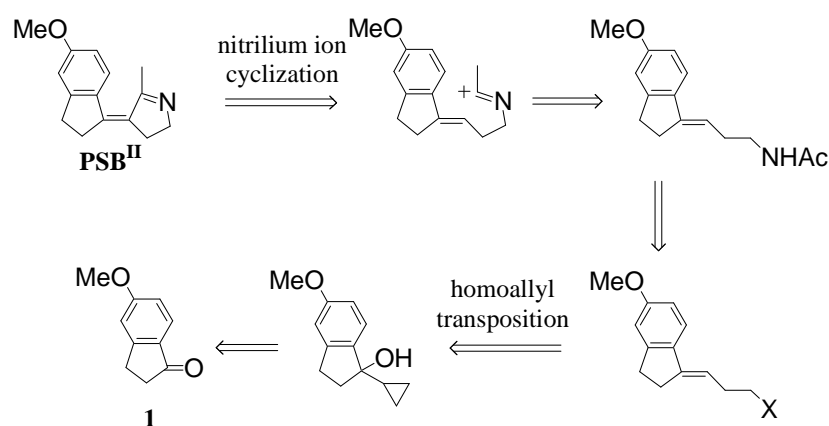
protocol and demonstrated that the desired cyclizations are achieved provided the olefinic terminator is sufficiently nucleophilic to react with the cationic center. In their effort to improve the rate of reaction via an increase of nucleophilic character of the styryl terminator, they noticed the advantage of having the *p*-methoxy substituent (Scheme 6).



Scheme 6

Additionally, taking into account the beneficial role played by this group in the photoreaction pathway of **PSB^I** we designed a **PSB^{II}** structure where X assumed the *p*-OMe value.

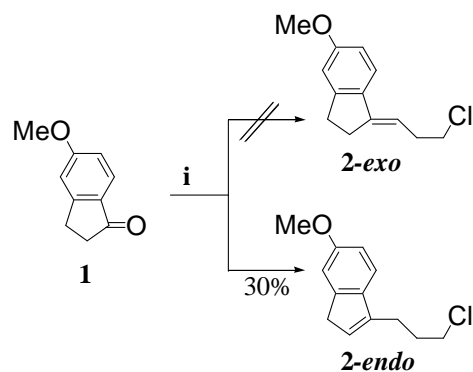
The **PSB^{II}** retrosynthetic analysis led us to identify the commercially available 5-methoxy-1-indanone **1** as the starting reagent (scheme 7) Thus, the synthesis called for the installation of a homoallylic halides as a versatile starting substrate to obtain the desired homoallyl acetamido group at the C-1 carbon of 5-methoxy-1-indanone.



Scheme 7

To this end, the well established acid promoted opening of cyclopropylcarbinols (Julia homoallyl transposition)³⁶ seemed to us a convenient procedure to obtain 3-halo-*n*-propylidene derivatives. Thus, we turned our attention to the protocol successfully employed by Perrone *et al.*³⁷ to prepare 1-(3-chloro-propylidene)-1,2,3,4-tetrahydronaphthalene from 1-cyclopropyl-1-tetralol. In their paper the authors stressed the importance of the short duration of the reaction with HCl 15% in order to obtain the kinetically favored 3-chloro-*n*-propylidene intermediate rather than the thermodynamically favored isomer having an endocyclic double bond.

Consequently, we reacted the indanone **1** with cyclopropylmagnesium bromide; the resulting adduct, without purification, was treated with HCl in acetic acid for 30 min at room temperature (Scheme 8).

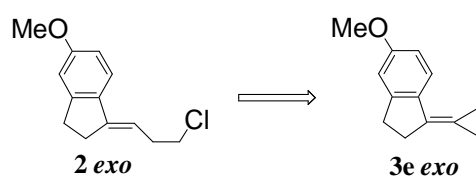


Reagents and conditions: (i) 1) Mg, cyclopropylbromide, THF, reflux, 3h; 2) HCl, AcOH, r.t., 30min.

Scheme 8

However, in our hands, only the undesired thermodynamically favored indenyl derivative **2-endo** was isolated in low yield from the reaction mixture. This unfavourable result was mainly attributed to the presence of mobile protons in position C-2 leading to dominant [1,3] shift.

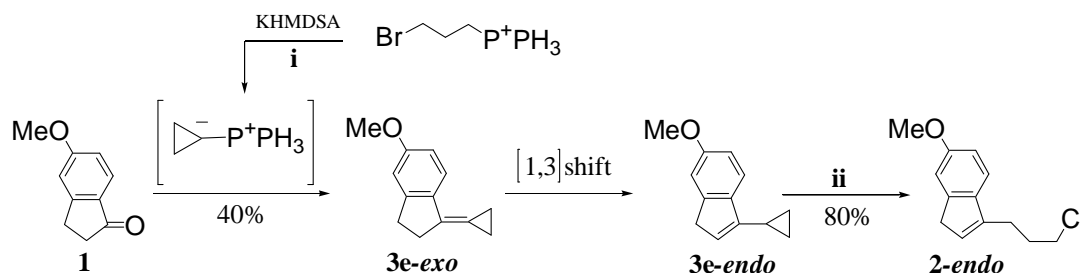
Furthermore, we also assumed possible to obtain the desired compound **2-exo** by treating the substituted methylenecyclopropane **3e-exo** with HCl (Scheme 9).



Scheme 9

With this aim, we reacted indanone **1** with cyclopropylidene-triphenylphosphorane generated in situ from 3-bromopropyl-phosphonium bromide and KHMDSA (potassium hexamethyldisilazide, see scheme 10).³⁸

Since olefination with cyclopropylidene doesn't usually work very well with readily enolizable carbonyls, the reaction afforded the desired unstable **3e-exo** product in low yield.

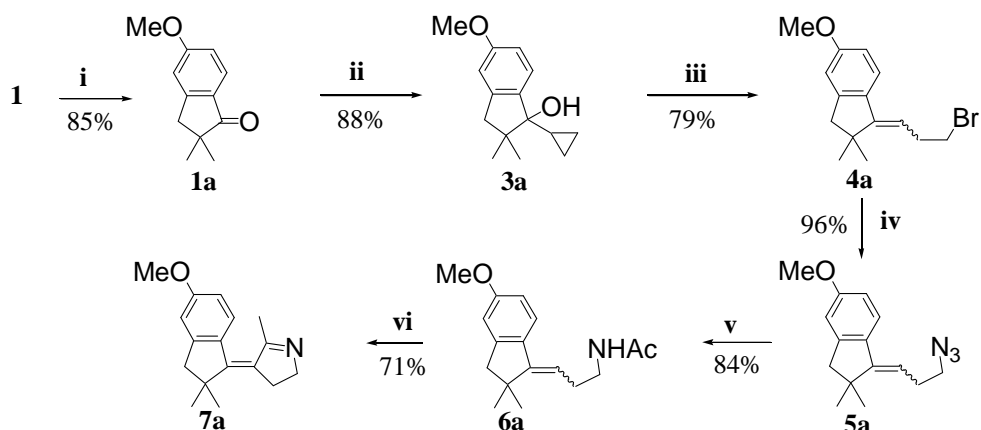


Reagents and conditions: (i) tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1), THF, rt, 2h; (ii) HCl, AcOH, r.t., 1h.

Scheme 10

Moreover, we found this *exo* isomer underwent a spontaneous rearrangement to the thermodynamically stable *endo* isomer thus confirming previous evidence displayed for **2-exo** (see Scheme 8). Eventually, compound **3e-endo** submitted to the action of HCl afforded **2-endo**.

Given the vital role played by the *exo*-olefin function in the nitrilium ion cyclization, we were forced to modify our original plan by removing the α -hydrogen atoms of the starting 5-methoxy-1-indanone **1** (Scheme 11). This was achieved via exhaustive methylation³⁹ and led to compound **1a**. The following treatment with the Grignard reagent afforded the cyclopropylcarbinol derivative **3a** that was submitted to the action of HBr in AcOH to undergo the expected rearrangement with the formation of the bromopropylidene derivative **4a** in good yield and as a 3:1 mixture of diastereomers (Scheme 11).



Reagents and conditions: (i) MeI, *t*BuOK, *t*BuOH, Et₂O, reflux, 7h; (ii) Mg, cyclopropylbromide, THF, reflux, 3h; (iii) HBr, AcOH, 10min; (iv) NaN₃, DMF, 60°C, 2.5h; (v) Lindlar catalyst, Ac₂O, AcONa, 60psi H₂, 6h; (vi) P₂O₅, HMDS, CCl₄, reflux, 2h.

Scheme 11

Conversion of **4a** to **6a** was obtained in high yield through bromide displacement with sodium azide followed by the one-pot transformation of the corresponding azido group to acetamide by chemoselective hydrogenation in presence of acetic anhydride using Lindlar catalyst.⁴⁰ The indanylidene compound **6a** was eventually submitted to Gawley's protocol conditions leading to the desired pyrroline derivative **7a** as the main product (71% yield).

The ¹H NMR spectrum of compound **7a** showed the presence of two diastereomers in 92:8 ratio; the respective geometry being inferred on the basis of NOE difference spectroscopy. In details, a positive NOE between the proton at the aromatic C-7' carbon (d, δ= 7.2) and the methyl at the C-5 of the pyrroline ring (m, δ = 2.2) was observed for the predominant isomer to which *Z* configuration could be assigned (Figure 4).

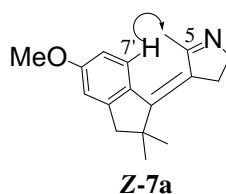
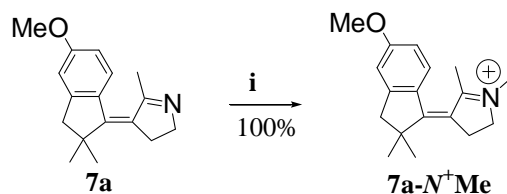


Figure 4

Conversion of the imine function of **7a** to an iminium ion was initially accomplished by protonation with HCl. At a later time, in agreement with PSB^I behaviour, we found

that the iminium salt **7a-N⁺Me** prepared by *N*-methylation with methyl triflate was a more stable and tractable than the protonated forms. (scheme 12).



Reagents and conditions: (i) CF₃SO₃CH₃ benzene, rt, 10min.

Scheme 12

Its photochemical characterization, described elsewhere⁷, has shown it shares certain electronic and geometrical features with PSB^{II} in rhod along the photoisomerization path. Thus, the designed nonnatural PSB^{II} represents a good prototype for the development of a novel class of light-driven biomimetic switches featuring a rigid molecular framework and a fully selective *Z/E* photoisomerization.

2.2.1 Synthesis of PSB^{II} Switches Analogues.

In order to enrich the class of PSB^{II} with new compounds, we envisaged a series of modifications of the ordinary scaffold of **7a-N⁺Me** (figure 5). In particular, we synthesized compound **7b** (lacking of the *p*-methoxy substituent on the aromatic ring), and compounds **7c** and **7d**, where indane part is replaced by a benzofurane moiety.

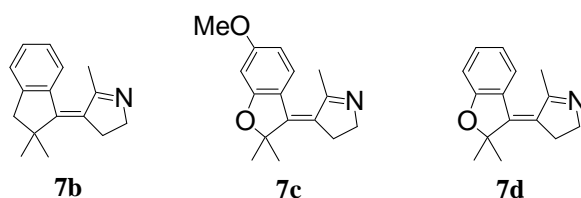
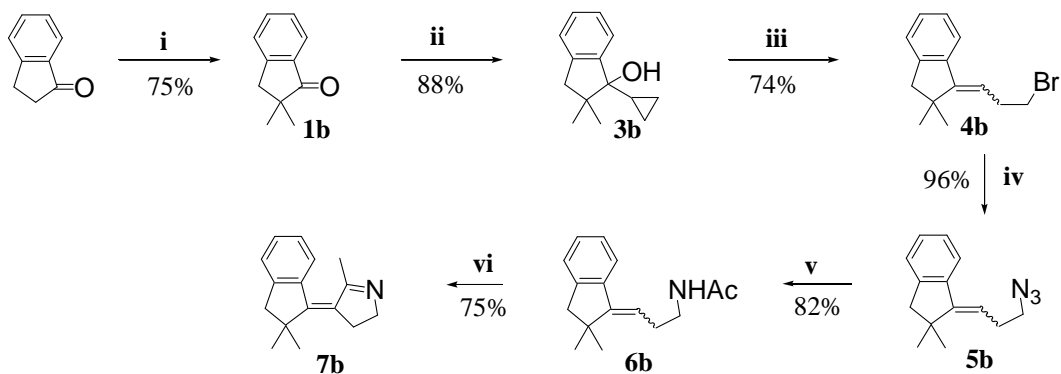


Figure 5

Compound **7b** was simply obtained using the synthetic pathway described for **7a**, starting in this case from the commercially available 1-indanone (Scheme 13).

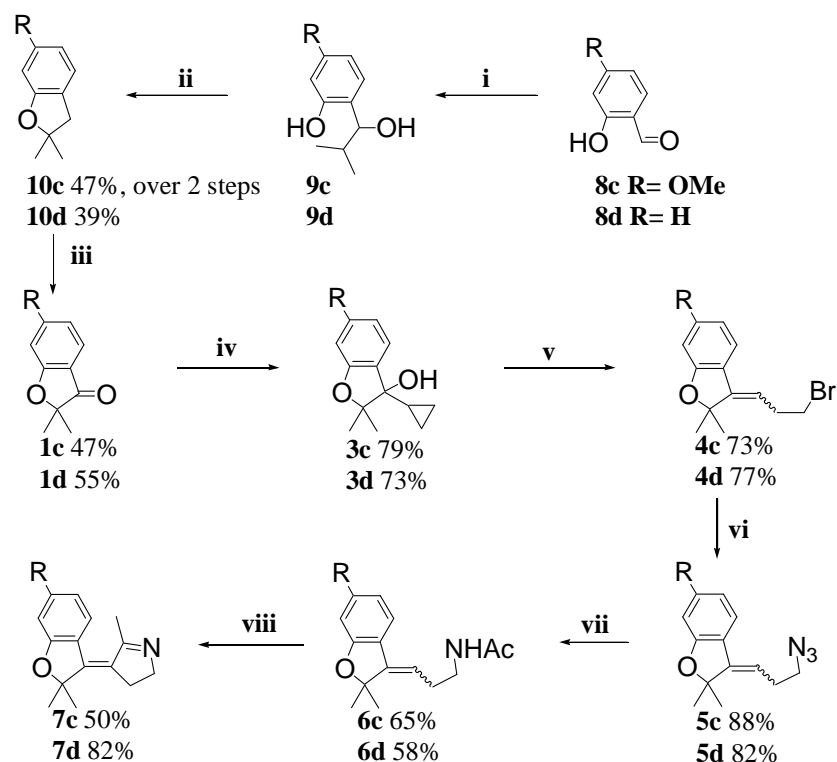


Reagents and conditions: (i) MeI, *t*BuOK, *t*BuOH, Et₂O, reflux, 7h; (ii) Mg, cyclopropylbromide, THF, reflux, 3h; (iii) HBr, AcOH, 10min; (iv) NaN₃, DMF, 60°C, 2.5h; (v) Lindlar catalyst, Ac₂O, AcONa, 60psi H₂, 6h; (vi) P₂O₅, HMDS, CCl₄, reflux, 2h.

Scheme 13

A similar approach was also used for the preparation of **7c** and **7d** but, in these cases, the syntheses needed the two not commercially available compounds **1c** and **1d** as starting materials (Scheme 14).

In 1984, Arduini *et al*⁴¹ described a convenient and efficient synthesis for 2,2-dimethyl-2,3-dihydrobenzofuran derivatives, starting from 2-hydroxybenzyl alcohols **9** in turn easily obtained by addition of *i*-propylmagnesiumbromide to the suitable salicylaldehydes (scheme 14). The ring closure, performed in toluene at 80°C in the presence of catalytic amount of polymer-supported sulfonic acid (Amberlyst 15), afforded **10c** and **10d** in moderate yields. The oxidation of benzylic position of these two compounds was achieved with a peroxydisulphate-copper(II) sulphate system in aqueous acetonitrile medium. Eventually, compounds **1c** and **1d** entered the well sound synthetic pathway to afford the desired products **7c** and **7d** respectively.



Reagents and conditions: (i) Mg, 2-bromopropane, Et₂O, rt, 2h; (ii) Amberlyst 15, toluene, 80°C, 24h; (iii) potassium peroxydisulfate, copper sulphate, water/ACN (iv) Mg, cyclopropylbromide, THF, reflux, 3h; (v) HBr, AcOH, 10min; (vi) NaN₃, DMF, 60°C, 2.5h; (vii) Lindlar catalyst, Ac₂O, AcONa, 60psi H₂, 6h; (viii) P₂O₅, HMDS, CCl₄, reflux, 2h.

Scheme 14

These derivatives were *N*-methylated using methyl triflate prior to effect photochemical characterizations (still under investigation) (figure 6).

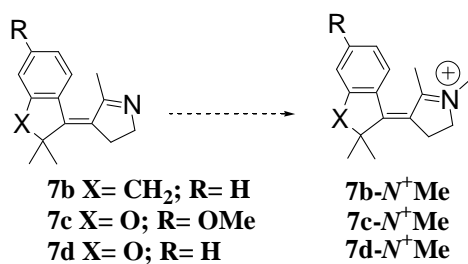
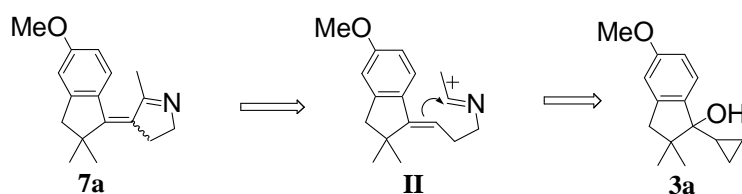


Figure 6

2.2.2 Short-Cut Toward PSB^{II}.

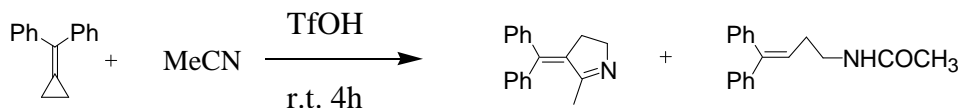
“Cyclopropyl ring-opening/nitrilium ion ring-closing tandem reaction”.

The six-step 33% overall yield synthetic route for **7a** described above (scheme 11) prompted the evaluation of a different approach characterized by a reduced synthetic effort. In devising a new and more convenient synthesis we took advantage of the Ritter reaction to accede to nitrilium ions i.e. through *N*-alkylation of acetonitrile.



Scheme 15

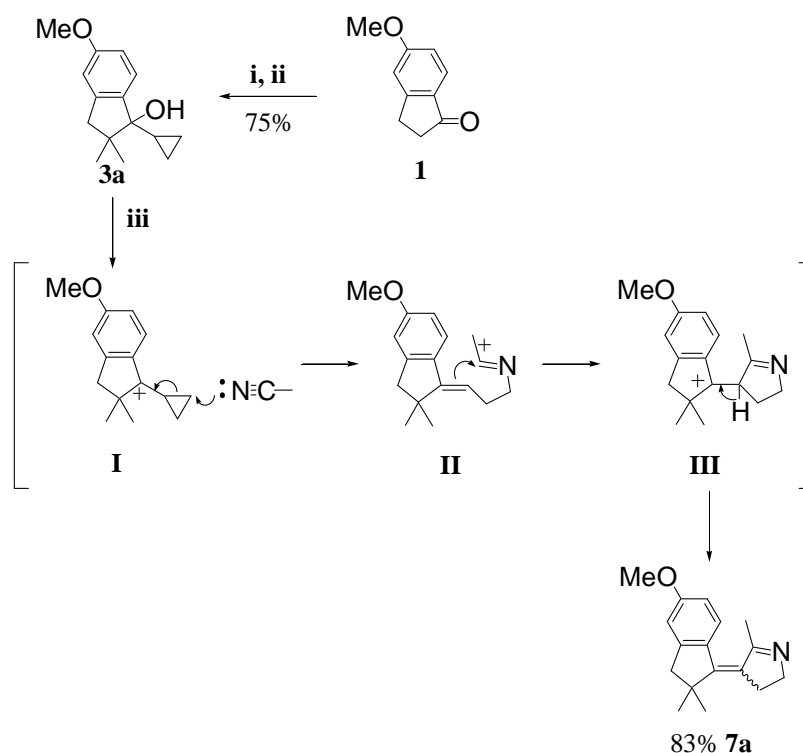
The use of alkyl triflates as electrophilic species able to react with nitriles was reported in the direct transformation of alcohols into secondary amides.⁴² Moreover, Shi *et al.*⁴³ have recently found that the ring-opening reaction of methylenecyclopropane (MCPs) with alcohols and other nucleophiles by Lewis acids [Ln(OTf)_n] (Ln= Sn, Yb, Sc) or Brønsted acid such as TfOH (CF₃SO₃H) takes place *via* homoallylic rearrangement to give the corresponding ring-opened products under mild conditions (scheme 16). In particular, they demonstrated that Brønsted acid TfOH is the best promoter for the transformation of MCP with acetonitrile to give the corresponding [3+2] cycloaddition product as the major product and ring-opened Ritter reaction amide in traces under mild conditions.



scheme 16

The chemistry described above supports the conjecture that the triflate ester of compound **3a** could be the precursor of the cyclopropylcarbiny cation (**I**), which, according to the Shi's domino process, would lead to compound **7a** via the nitrilium ion (**II**) and the tertiary-benzylic carbocation (**III**) (Scheme 17). Accordingly, the

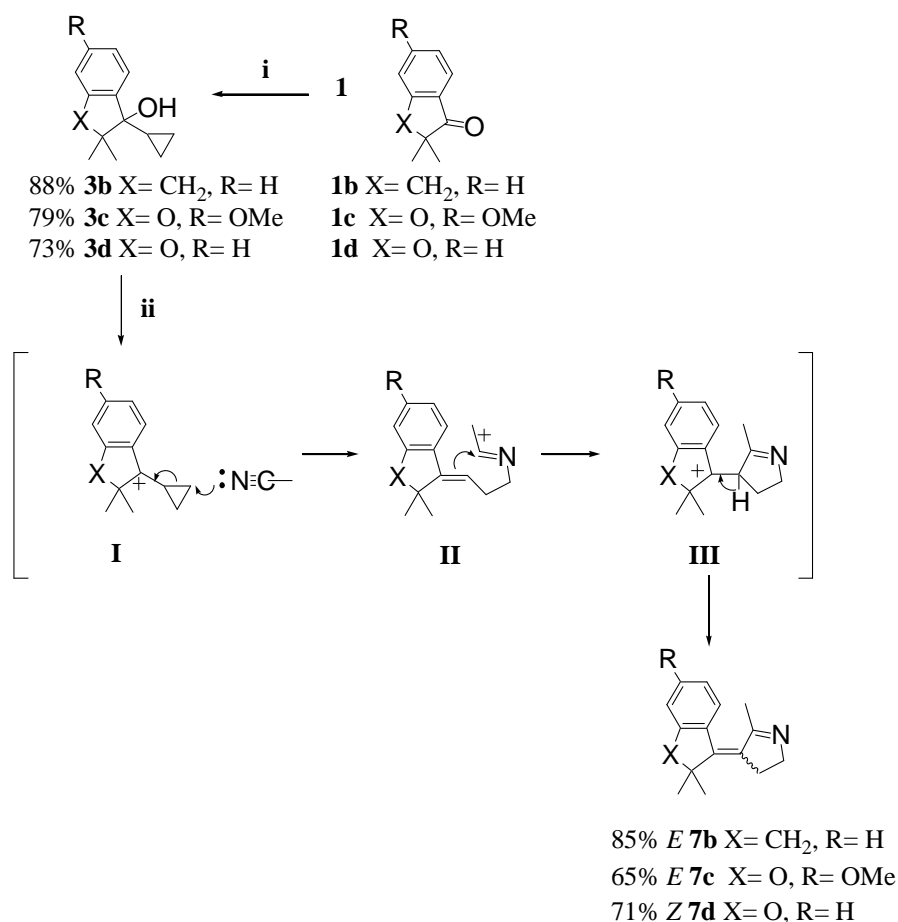
treatment of the cyclopropylcarbinol **3a** with acetonitrile in presence of Tf₂O furnished directly compound **7a** in satisfactory yield (62% over three steps) together with traces of the amide **6a**. The driving force for the transformation is provided by the relief of the cyclopropyl ring strain associated with the installation of an extended π -system on the backbone of the final compound.



Reagents and conditions: (i) MeI, *t*BuOK, *t*BuOH, Et₂O, reflux, 7h; (ii) Mg, cyclopropylbromide, THF, reflux, 3h; (iii) Tf₂O, ACN, rt, 3h.

Scheme 17

Once optimized for **7a**, the previous synthetic short-cut was successfully applied to obtain compounds **7b**, **7c** and **7d**. Thus intermediates **3b**, **3c** and **3d** were treated with Tf₂O in acetonitrile to give respectively **7b**, **7c** and **7d** via one-pot nitrilium ion cyclization (Scheme 18).



Reagents and conditions: (i) Mg, cyclopropylbromide, THF, reflux, 3h; (ii) Tf₂O, ACN, rt, 3h.

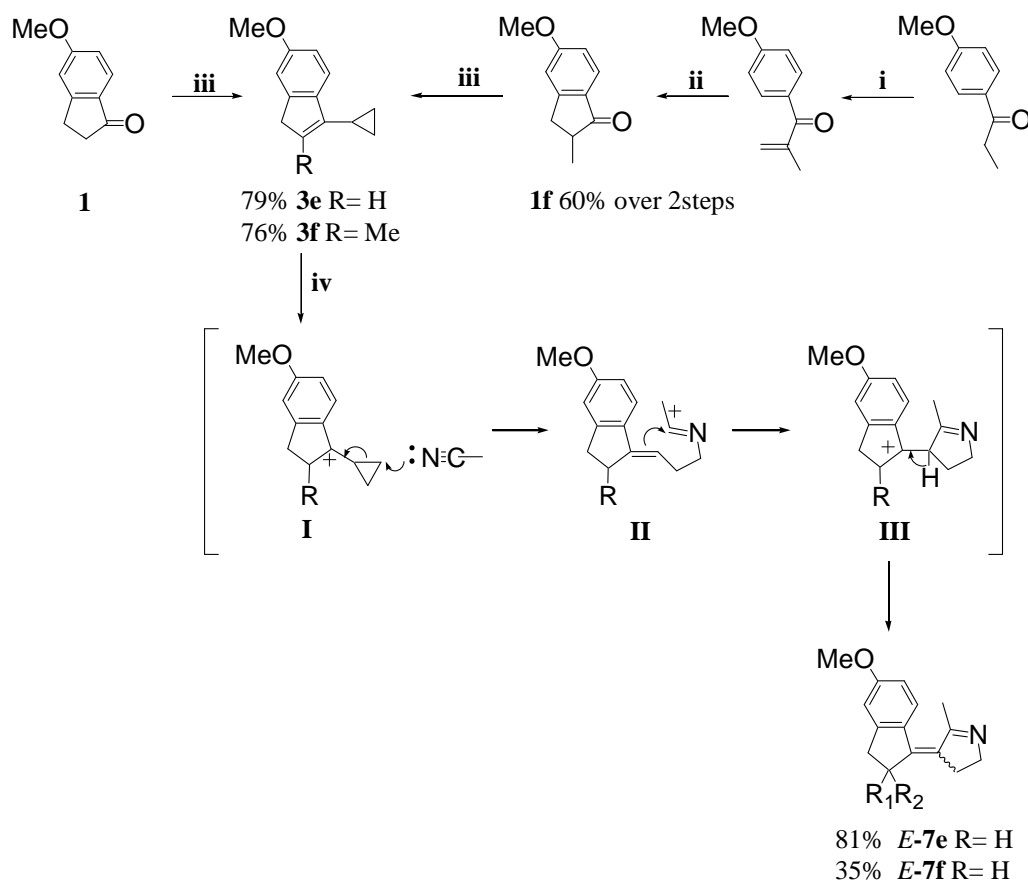
Scheme 18

As previously discussed, the presence of *gem*-dimethyl groups at C-2' of the 1-indanone assures the Gawley's nitrilium generation and reaction to occur, but, the possibility that the “**cyclopropyl ring-opening/nitrilium ion ring-closing tandem reaction**” (Scheme 17) would result to be insensitive to the presence of protons at that position opened the way to the preparation of switches **7e** and **7f** featuring a decreased steric encumbrance in the proximity of the exocyclic C-C double bond (Figure 7).



Figure 7

Accordingly, we reacted cyclopropylmagnesiumbromide with the indanone **1** and its monomethyl derivative **1f**, in turn obtained from 4-methoxypropiophenone via Mannich α -methylenation followed by acid catalyzed cyclization of the resulting acrylophenone.⁴⁴



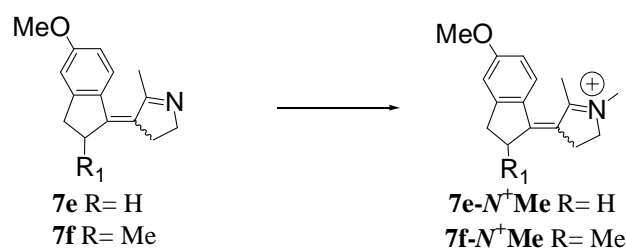
Reagents and conditions: (i) morpholine, aqueous formaldehyde, AcOH, reflux, 5h; (ii) H₂SO₄, 60°C, 1h; (iii) Mg, cyclopropylbromide, THF, reflux, 3h; (iv) TFOH, CH₃CN, r.t., 3h.

Scheme 19

As expected, both **1e** and **1f** gave the indenyl derivatives **3e** and **3f** in high yields following silica gel column chromatography of the crude Grignard adducts mixtures. Compounds **3e** and **3f** may be seen as the conjugated bases of cyclopropylcarbinyl **I** cations that could potentially trigger the domino process described above.

At this stage we hoped that the regioselective protonation of the these indenyl derivatives in the presence of acetonitrile would promote the cyclopropyl ring-

opening/nitrilium ion ring-closing sequence. Indeed, treatment of **3e** and **3f** with an equivalent of TfOH in CH₃CN solution at room temperature yielded the desired cyclic imines *E*-**7e** and *E*-**7f** as single geometric isomers. Photochemical studies are currently being undertaken for the iminium salt **7e-N⁺Me** and **7f-N⁺Me** obtained by *N*-methylation of the corresponding *N*-free bases.



Scheme 20

With the aim to define the spatial relationships throughout the new molecules, once again we resorted to NOE difference spectroscopy as outlined below (Figure 8). For the compound **7e**, irradiation of the signal at $\delta = 2.3$ (the methyl at C-5 of pyrroline) showed NOE to hydrogens at C-2' carbon of the indane as well as irradiation of the signal at $\delta = 7.4$ (the hydrogen at C-7' of indane) showed NOE to hydrogens at C-3 carbon of the pyrroline ring. For the compound **7f**, irradiation of the signal at $\delta = 1.1$ (the methyl at C-2' of indane) showed NOE to the methyl at C-5 of pyrroline and *vice versa*. Moreover, the hydrogen at C-2' of indane showed NOE enhancements to the methyl at C-5 of pyrroline nucleus. The data collected for compounds **7e** and **7f** agreed with the *E* geometry that is opposite to the one observed for compound **7a**.

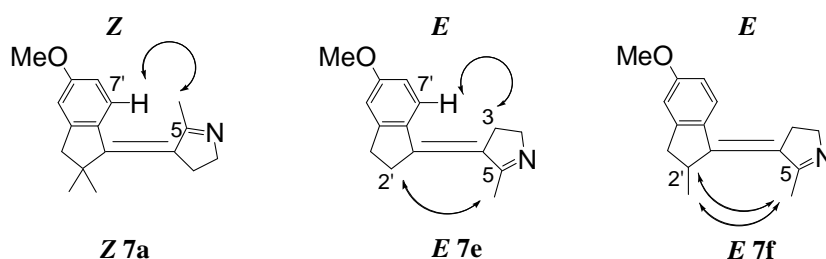


Figure 8

Consistently with previously reported computational results⁷, the C2' stereogenic center of compound **7f**, could induce helicity of molecular halves connected by the

photoisomerizable carbon-carbon double bond. It is reasonable that, similar to Feringa's second generation light-driven molecular rotors,^{6a} the photoinduced isomerization of the iminium salt of **7f** may occur with control over the direction of rotation. Ultimately, it is our expectation (see ref. 30) that compound **7f** provides 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.

2.2.3 A Fluorous PSB^{II}

The replacement of hydrogen with fluorine is an extensively used strategy in the design of analogues with different physical and chemical properties. In fact, fluorine influences the basicity, acidity and nonbonding interactions of neighboring group because of its extreme electronegativity. Replacement of hydrogen by fluorine is often regarded as an isosteric substitution despite the fact that their Van der Waals radii are different (1.20 vs 1.47 Å). For these reasons, plus the possibility to create a chiral center in position C-2', we decided to synthesize compound **7g** (Figure 9).

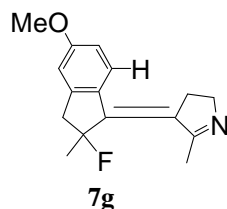


Figure 9

Electrofilic fluorination of enolates with N-F type reagents is a versatile method to directly replace hydrogen with fluorine at a specific site. Historically, electrophilic fluorination could be accomplished only by using toxic, corrosive and/or explosive gaseous materials such as molecular fluorine, FClO₃ or CF₃OF. Usually, specialized equipment and techniques were required. In an important advance that helped overcome these limitations, Barnette found that *N*-fluorosulfonamides (Figure 10) can effectively fluorinate carbanions⁴⁵. Thus, we decided to treat indanone **1f** with *N*-

fluorobenzenesulfonimide (NFSi)⁴⁶(scheme 21) as fluorinating agent and LHMDS (Lithium Hexamethyldisilazide) as base, in THF a -78°C (Scheme 21).

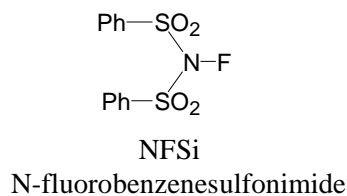
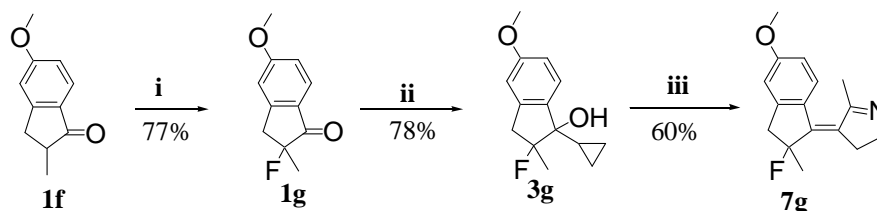


Figure 10



Reagents and conditions: (i) NFSi, LHMDS, THF, -50°C, 45min; (ii) *tert*-butyllithium, cyclopropylbromide, Et₂O, -78°C to rt, 16h; (iii) Tf₂O, CH₃CN, r.t., 30min.

Scheme 21

Reaction proceeded slowly and was monitored using HPLC. After 3h, almost complete conversion of starting material to the desired compound **1g** was detected. At this point, **1g** was usually reacted with cyclopropyl-Magnesium bromide, but all our attempts to effect a classical Grignard reaction resulted in complex mixtures. Since literature shows that most similar ketones react very well with organo-Lithium compound at very low temperature⁴⁷, we treated **1g** with cyclopropyllithium prepared from bromocyclopropane and *tert*-butyllithium at -78°C. The addition reaction proceeded smoothly and the resulting stable tertiary carbinol **3g**, when treated with 1.1 eq of triflic anhydride in acetonitrile at room temperature, afforded the fluoro-derivative **7g** in moderate yield.

2.3 Bifunctionalization of PSB^{II}: Future Applications and Synthetic Approches.

Experimental photochemical data collected for **7a** confirmed that it can be considered a biomimetic molecular switch, consequently we were urged to find potential applications for it. As an example, the controlled photochemical *E/Z* isomerisation of the switch could be employed to induce permanent or transient conformational changes of a molecular scaffold as an oligopeptide, linked to it. Demonstrating that the *cis-trans* isomerisation of PSB^{II}-oligopeptide chimer can still occur and that it can be used to influence the conformational state of an oligopeptide is our main goal.

Toward this aim, the creation of specific molecular linkages on PSB^{II} structure is required; preferable positions being C-2' of the indanyl-nucleus and C-2 or C-3 of the pyrrole moiety, we turned our attention to OH, CH₂OH, COOH or NH₂ as suitable functional groups to attach a peptide domain.

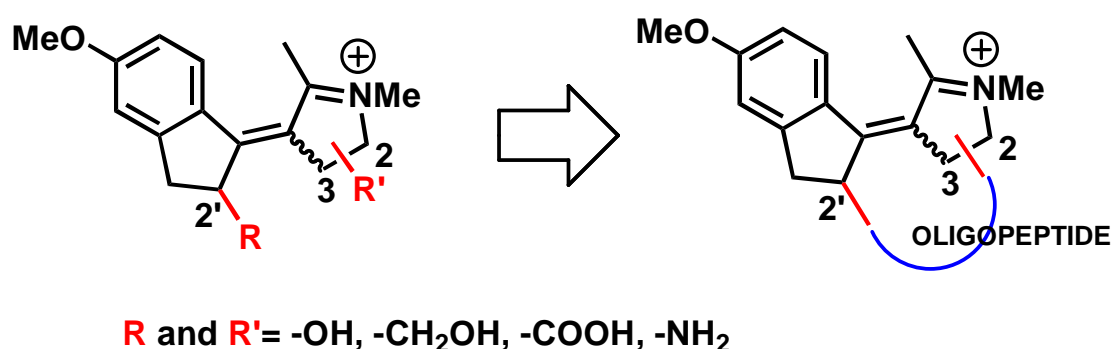


Figure 11

We initially selected the aminoacidic sequence -Arg-Gly-Asp- as the oligopeptide-part to couple with PSB^{II}. This sequence is able to bind a specific domain of the Integrin Adhesion Receptors and to modulate the adhesion signal assuming specific spatial conformations (Xiong J-P, *et al* Science 2001, 294, 339-345; Xiong J-P, Science 2002, 296, 151-155).

In view of this, we hope that the controlled photoinduced isomerisation of PSB^{II} scaffold can influence the conformational state of the peptidic ligand and consequently, can modulate the “on/off” activity of the receptor.

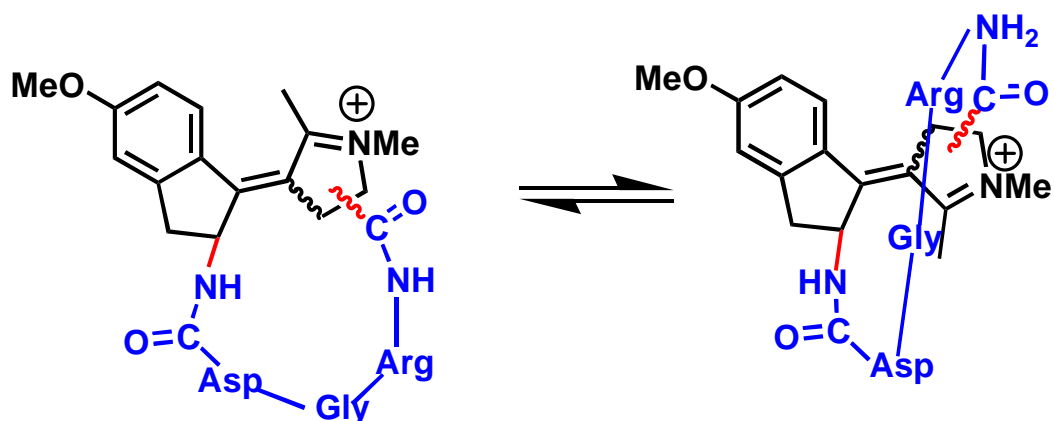
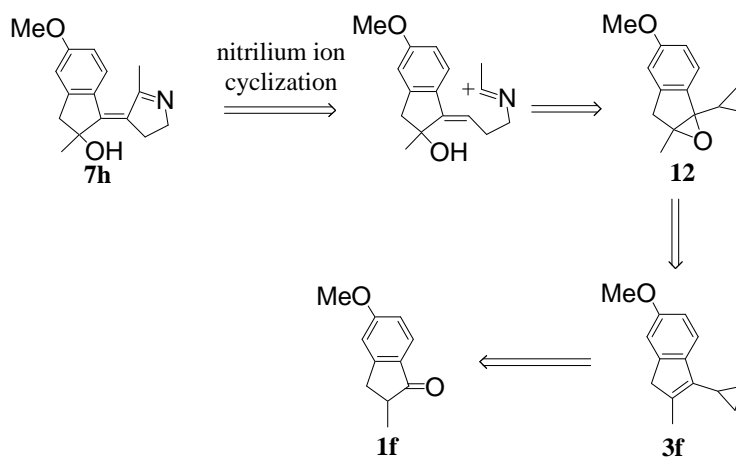


Figure 12

2.3.1 Functionalization of Indanyl-Moiety.

Operatively, we preferred to study the feasibility of effecting the required double functionalization of molecular switches step by step. We started studying the insertion of an hydroxyl group at position 2'. Thus, we defined a retrosynthetic approach to PSB^{II} **7h** in which the key intermediate is the epoxide **12**, that we expected to react with acetonitrile-TfOH giving the desired final product as described in Scheme 22. The required epoxide could be obtained via epoxidation of compound **3f** that comes from indan-1-one **1f** as seen before.



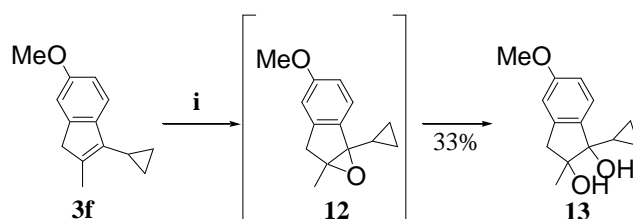
Scheme 22

Different epoxidation protocols available in literature were screened: we started with the classical oxidation using *m*-CPBA (2 eq) in DCM in the presence of phosphate

buffer (pH 8)⁴⁸ however, starting material was recovered together with some other undesired by-products. Since π -conjugation with the aromatic ring could result in inactivity of the carbon-carbon double bond, epoxidation procedures suitable for electron-deficient olefins were considered. In 1998, Jacobs *et al.*⁴⁹ reported that a catalytic amount of oxalate/oxalic buffer strongly enhances the efficiency in Mn-tmtacn complexes (Mn with the ligand 1,4,7-trimethyl-1,4,7-triazacyclononane) for epoxidation reactions of deactivated olefins with hydrogen peroxide. Furthermore, Yang *et al.*⁵⁰ in 1995 described that dioxiranes are powerful epoxidation reagents with high reactivity toward electron-deficient olefins, under neutral reaction conditions; this efficient method of epoxidation required the methyl(trifluoromethyl)dioxiranes, a powerful reagent that can be easily generated *in situ* from trifluoroacetone.

Unfortunately, both procedures applied on compound **3f** resulted in a complete degradation of starting material.

In 2002, Burgess *et al.*⁵¹ described a method for the epoxidation of both electron-rich and electron-deficient alkenes employing hydrogen peroxide as the terminal oxidant, while catalytic amounts of Mn(II) and bicarbonate act as promoters. Surprisingly, treating compound **3f** with 10 equiv. of H₂O₂, in *t*-BuOH /0.2 M NaHCO₃ containing catalytic amount of MnSO₄, only diol **13** could be recovered in moderate yields after 24h. The desired epoxide **12** is supposed to be highly unstable and the Lewis acid catalyst mediates its transformation to diol **13**.

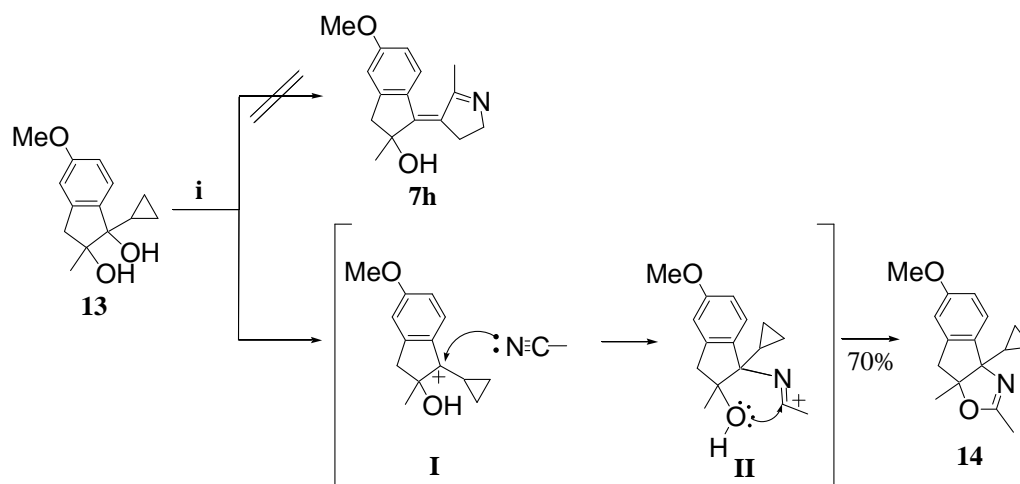


Reagents and conditions: (i) MnSO₄, 35% H₂O₂, 0.2 M NaHCO₃ (pH 8.0 buffer), DMF, rt, 16h.

Scheme 23

Different attempts to use diol **13** as a surrogate of epoxide **12** were envisioned: in detail, with the hope of obtaining compound **7h**, we treated compound **13** with triflic

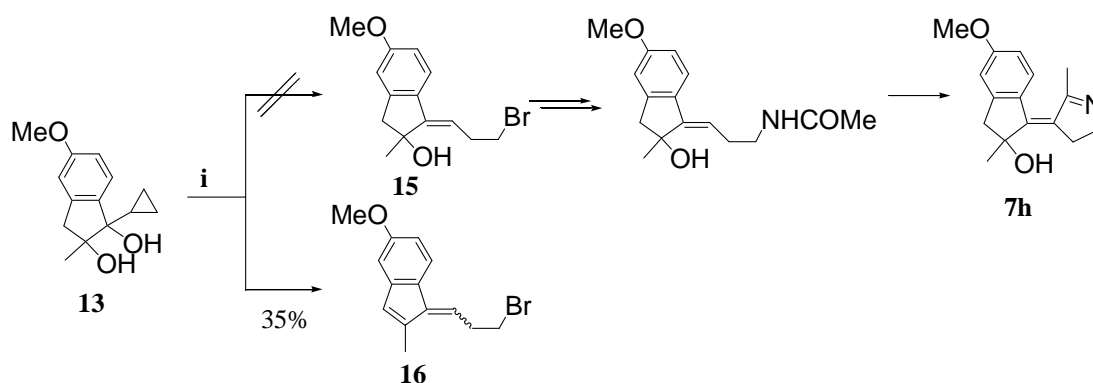
acid in acetonitrile. Instead, under these conditions, only the formation of the oxazoline **14** took place (scheme 24).



Reagents and conditions: (i) TfOH, CH_3CN , r.t., 3h.

Scheme 24

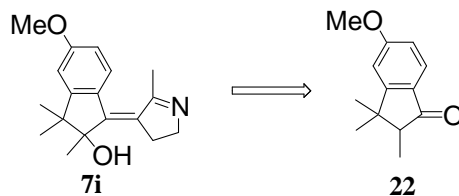
According to Senanayake *et al.*⁵², a plausible mechanism entails the acid-induced formation of C-1 carbenium **I** which, intercepting acetonitrile, generates the nitrilium intermediate **II** in turn able to quench the hydroxy group leading to oxazoline **14** (Scheme 24). Our second attempt was to react diol **13** with HBr, in order to obtain compound **15** that, following the six-steps route previously described (Schemes 7 and 11), could be used to obtain **7h** under Gawley cyclization procedure (scheme 25). Unfortunately, treatment of diol **13** with HBr gave compound **16** lacking the hydroxyl group; this result showed that strong acid conditions induce both cyclopropyl opening and dehydration.



Reagents and conditions: (i) HBr 15% in acetic acid, r.t, 1h.

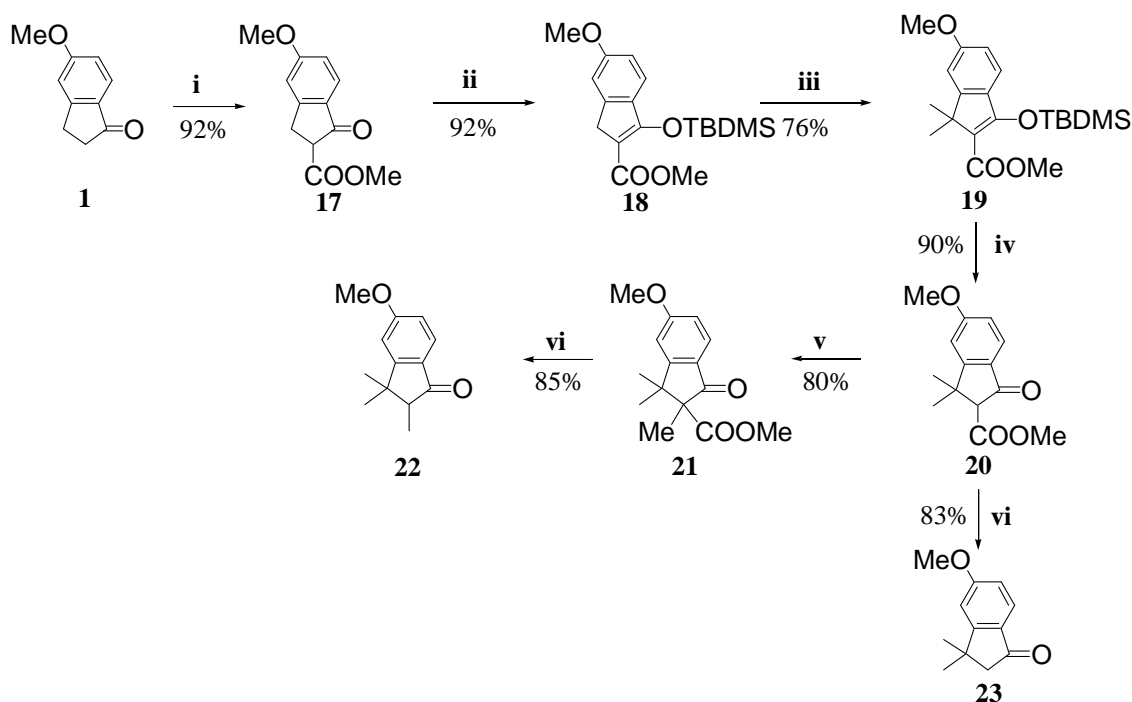
Scheme 25

This unfavourable behaviour, made possible because of the presence of mobile protons in position C-3', prompted us to design a synthetic strategy toward compound **7i**, where C-3' is a quaternary carbon (Scheme 26). We expected the presence of two methyl groups at C-3' carbon of **7i** would preserve it from acidic dehydration.



Scheme 26

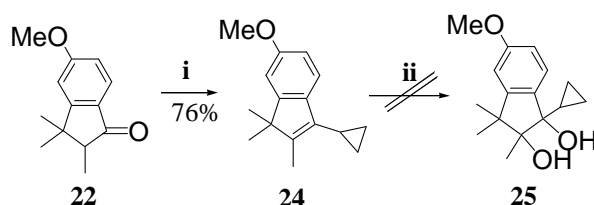
For the preparation of the starting substrate **22** we resorted to Matsumoto *et al*⁵³ protocol. In details (Scheme 27), treatment of 5-methoxy-1-indanone with sodium hydride and dimethyl carbonate gave the corresponding β -keto ester **17** which was silylated using TBDMSCl and BuLi. The resulting silylenolether **18** was subsequently reacted with LDA and Iodomethane at -78°C to introduce at the C-3' carbon of the indene nucleus the desired methyl groups.



Reagents and conditions: (i) NaH, dimethyl carbonate, 80°C , 2h (ii) NaH, TBDMSCl, DMF, 0°C , 1h; (iii) LDA, MeI, THF, -78°C , 1h; (iv) BF_3 etherate, CHCl_3 , rt, 4.5h; (v) K_2CO_3 , MeI, acetone, rfx, on; (vi) LiI, DMF, MW, 170°C , 15min.

Scheme 27

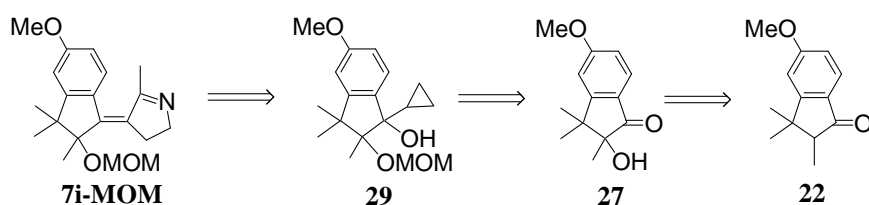
Thus, the dimethylindene **19** was desilylated with BF_3 etherate to β -keto ester **20**. Brief microwave irradiation of **20** at 200°C in wet DMF with a catalytic amount of LiI induced smooth Krapcho decarboalkoxylation⁵⁴ affording compound **23** (used in further investigations). Alternatively, the indanone **20** was α -methylated and then submitted to Krapcho procedure to afford the desired compound **22**. At this stage, its conversion to diol **25**, required reaction with cyclopropyl Magnesium chloride and the oxidation under Burgess conditions (MnSO_4 cat, H_2O_2 , pH 8) of the corresponding indenyl derivative **24**. Unfortunately, in our hands the latter substrate showed to be passive to the oxidizing agent (steric reasons) and starting material was recovered unaltered (scheme 28).



Reagents and conditions: (i) Mg, cyclopropylbromide, THF, reflux, 3h; (ii) MnSO_4 , 35% H_2O_2 , 0.2 M NaHCO_3 (pH 8.0 buffer), DMF, rt, 16h.

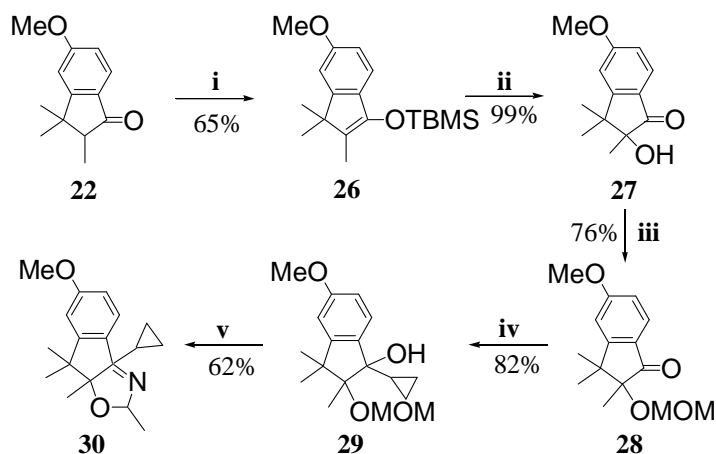
Scheme 28

The above result prompted the evaluation of a different route which is retrosynthetically analyzed for **7i-MOM** in Scheme 29. Compound **29** could be identified as the immediate precursor. For its preparation, the α -hydroxy ketone **27**, in turn derived from **22** was the key substrate (scheme 30).



Scheme 29

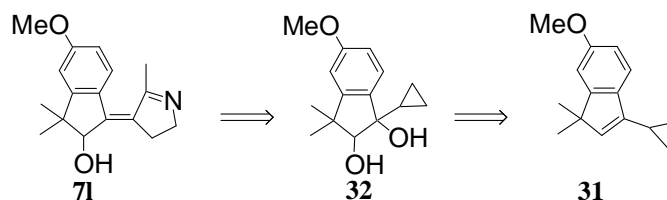
In 1995 Yang *et al.*⁵⁰ defined an efficient procedure to afford α -hydroxy ketone in high yield by oxidation with methyl(trifluoromethyl)dioxiran of the corresponding silyl enol ether. Since silyl enol ether of ketone **22** was easily prepared and purified, its in situ α -hydroxylation provided a safe entry to **27**. In details, the silylenoletherification of **22** gave **26** in good yield by using TBMS triflate-lutidine system, the later compound was treated with methyl-(trifluoromethyl)-dioxiran generated in situ by the action of a mixture of sodium bicarbonate (1.55 mmol) and Oxone on the trifluoroacetone. At this stage the MOM protection⁵⁵ of the alcohol **27** afforded compound **28** in quantitative yield. Its treatment with cyclopropyl magnesium chloride afforded cyclopropylcarbinol **29** readily submitted to one-pot nitrilium cyclization by treatment with Tf₂O in acetonitrile. Once again, the oxazoline **30** was the only product we could obtain from the reaction mixture. Clearly, the acidic MOM removal opened the way to the undesired heterocyclization as described in Scheme 24. Thus, we are working at the installation of a different protection on the hydroxyl group of compound **27**.



Reagents and conditions: (i) TEA, TBMSTf, rt, 2h; (ii) Na₂EDTA solution acetonitrile trifluoroacetone sodium bicarbonate Oxone, rt, 1h; (iii) NaI, MOM-chloride, DIPEA, 1,2-dimethoxyethane, rfx, on; (iv) Mg, cyclopropylbromide, THF, reflux, 3h (v) TfOH, CH₃CN, r.t., 3h.

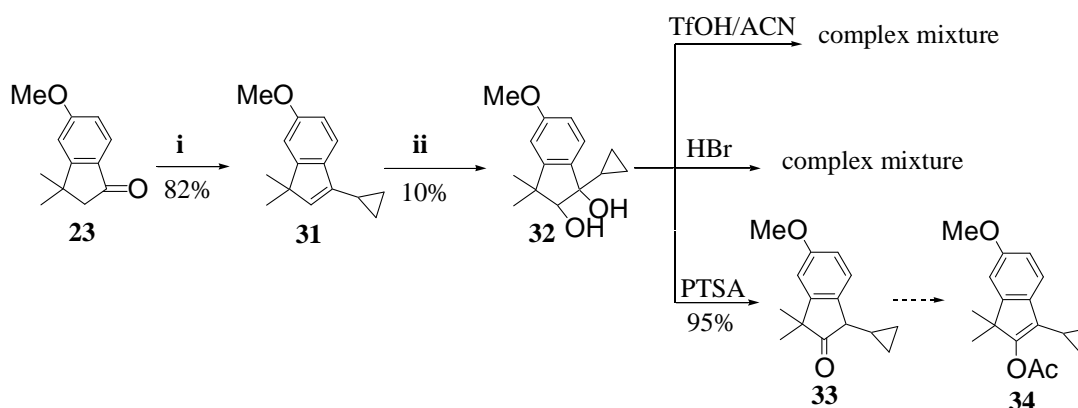
Scheme 30

We likewise worked at the synthesis of **71** following the retrosynthetic approach in scheme 31.



Scheme 31

Thus, compound **31**, easily prepared from **23**, was submitted to Burgess condition affording little amount of compound **32** (Scheme 32). Treatment of the latter with TfOH in acetonitrile and with HBr in acetic acid, equally afforded a complex mixture of products. However we found that compound **32** reacted with catalytic PTSA in DCM at room temperature to give ketone **33**. We thought that this unexpected compound could be useful to prepare the enolacetate **34** featuring both the double bond required for the one pot cyclization and the hydroxyl group protected as acetyl ester⁵⁶.



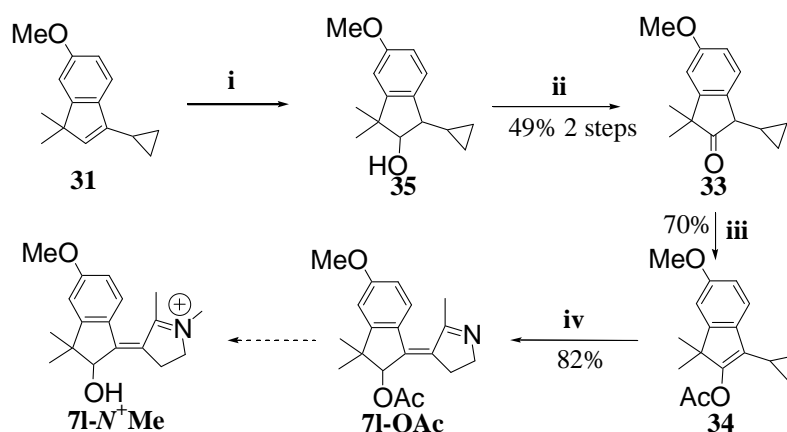
Reagents and conditions: (i) Mg, cyclopropylbromide, THF, reflux, 3h; (ii) MnSO₄, 35% H₂O₂, 0.2 M NaHCO₃ (pH 8.0 buffer), DMF, rt, 16h.

Scheme 32

In order to achieve the desired compound **34**, we envisioned a more direct and fruitful approach taking advantage of the alternative possibility to install the hydroxylic group

at C-2' via a regioselective hydroboration/oxidation sequence performed on compound **31** (scheme 33).

Hydroboration was carried out using $\text{BH}_3:\text{THF}$, the olefin **31** was added at $0\text{ }^\circ\text{C}$ and the reaction mixture further stirred at room temperature. After 3h, the basic hydrogen peroxide was added leading, after usual work up, to the alcohol **35**. The latter, as a crude, was used in the next oxidation step using Dess-Martin periodinane in DCM to give the targeted compound **33** in moderate yield (49% over two steps).



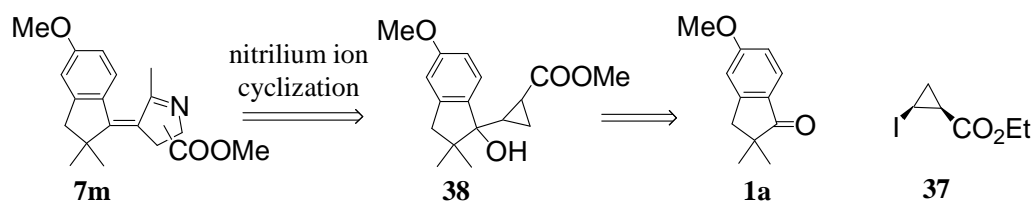
Reagents and conditions: (i) $\text{BH}_3:\text{THF}$, 30% H_2O_2 , 1 M NaOH , THF ; (ii) Dess-Martin periodinane, CH_2Cl_2 , rt, 20min; (iii) pyridine, acetyl chloride, $-50\text{ }^\circ\text{C}$ to rt, 48h; (iv) TfOH , CH_3CN , r.t., 3h.

Scheme 33

When submitted to standard enolesterification (Ac_2O -Py, 48h), the 2-indanone derivative **33** afforded compound **34** in 70% yield. The latter, by the nitrilium one-pot heterocyclization (TfOH in CH_3CN), smoothly furnished **71-OAc** a suitable precursor for the targeted functionalized molecular switch **71-N⁺Me**.⁵⁷

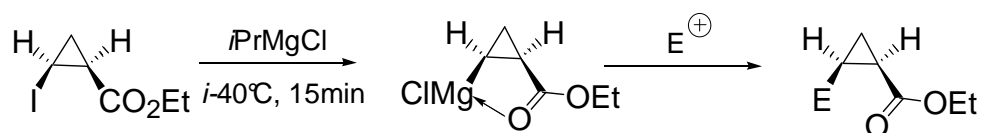
2.3.2 Functionalization of Pyrroline-Moiety.

Pursuing the modulation of the original **PSB^{II}** scaffold through functionalization of the pyrroline heterocycle with a carboxylic group we designed to exploit the fruitful cyclopropyl ring-opening/nitrilium ring-closing strategy. In particular, we reasoned on the possibility to obtain **7m** directly from the key intermediate **38** in turn preparable by the addition of a functionalized Grignard reagent to indanone **1a** (scheme 34).



Scheme 34

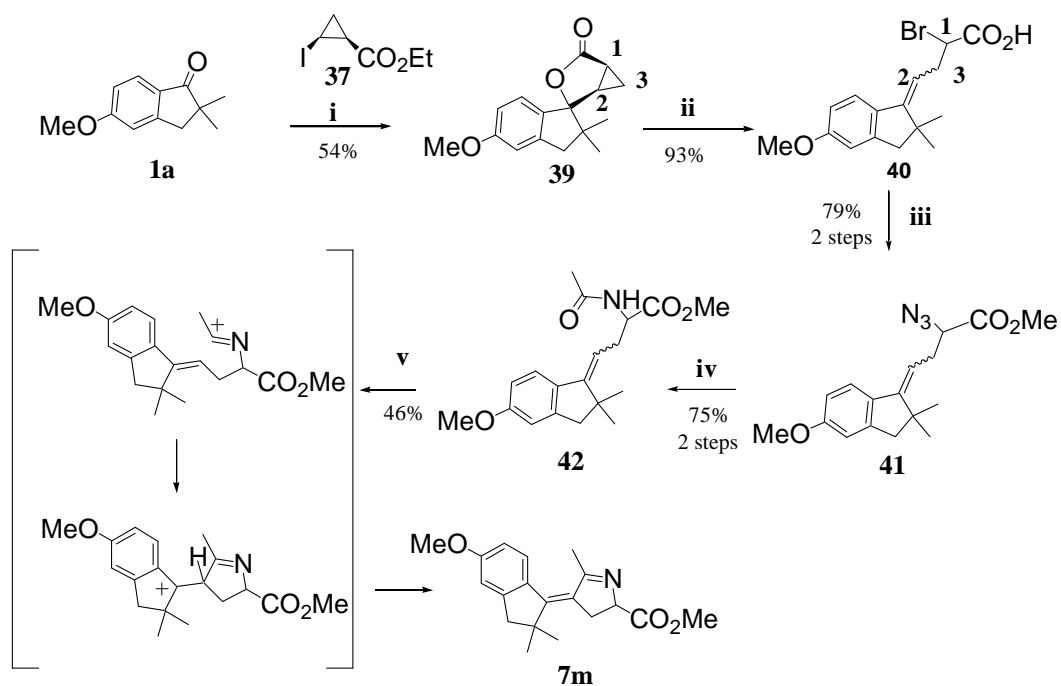
In 2002, Knochel *et al.*⁵⁸ reported the preparation of the first stereoselective functionalized cyclopropylmagnesium reagents bearing an ester group by an iodine-magnesium exchange (scheme 35). Indeed, the readily available 2 iodocyclopropanecarboxylate (section A) was treated with *i*PrMgCl (1.1 eq) in THF at -40°C for 15 min and afforded the corresponding *cis*-cyclopropylmagnesium chloride **37**.



Scheme 35

Because of the presence of the ester group which has stabilizing chelating and inductive effects, this reagent shows excellent stability. Knochel also described that this cyclopropylmagnesium chloride can react with a range of electrophiles either directly (i.e Grignard reaction on carbonyl species) or after catalytic transmetalation to copper or palladium.

As expected, the reaction between the Knochel reagent and 5-methoxy-2,2-dimethylindan-1-one **1a** afforded the key-intermediate spiro lactone **39** (scheme 36).



Reagents and conditions: (i) 1.2eq cis-2-iodo-cyclopropane carboxylic acid ethyl ester, 1.3eq $i\text{PrMgCl}$, THF, -40°C to r.t., 2h; (ii) HBr in AcOH (1M), $<15^\circ\text{C}$, 1h; (iii) a: $\text{Me}_3\text{SiCHN}_2$, THF/MeOH, r.t., 2h; b: NaN_3 , $\text{CH}_3\text{CN}/\text{DMF}$, r.t., 48h; (iv) a: PPh_3 , THF, o.n., then H_2O , 24h; b: MeCOCl , TEA, DCM, 0°C , 3h; (v) P_2O_5 , HMDSO, CCl_4 , reflux, 2h.

Scheme 36

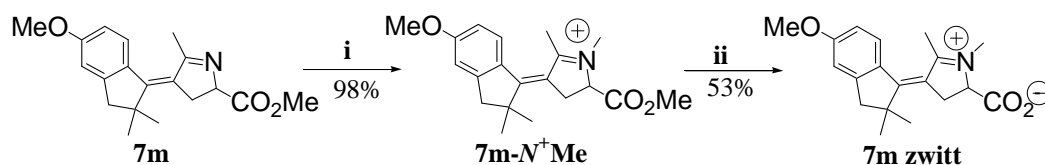
In order to achieve the tandem cyclopropyl ring-opening/nitrilium ring-forming process, we tried to react **39** with TfOH and CH_3CN ; disappointingly under usual reaction conditions, the spiro-lactone showed to be stable and only starting material was recovered. Thus, we were forced to use harsh conditions treating compound **39** with 1.0M HBr in acetic acid. We were delighted to find out that the crucial homoallylic rearrangement took place in a completely regioselective manner; the α -bromo indanylidene carboxylic acid **40** (as a 3:1 mixture of geometric isomers) being the only isolable compound. As a consequence, this beneficial result oriented our synthetic approach to Gawley's strategy in order to get the pyrroline ring construction. Restoration of the ester group by treatment of the carboxyl derivative with (trimethylsilyl)diazomethane, allowed the facile installation of the tethered acetamido group.

Thus, the well sound synthetic sequence of bromide displacement with sodium azide, reduction of the azido group and final *N*-acetylation, gave compound **42** in satisfactory yield. The following cyclization to obtain neutral free imine **7m** was carried out by treating the α -acetoamido derivate **42** with trimethylsilyl polyphosphate (PPSE) in CCl_4 at reflux. As usual, pyrroline alkylation, made with methyl triflate, served to establish the pivotal chromophore allowing us to fulfil the synthetic goal. In fact, the photoswitch **7m-N⁺Me** featuring a carboxylic group on the pyrroline half could be covalently connected to peptide domains.

The peculiar combination of carboxylic and iminium functional groups in **7m-N⁺Me** prompted us to attempt its transformation into a stable zwitterion: we envisioned the C-2 carboxylate as the counterion of the intramolecular iminium cation. In order to get the zwitterionic compound **7m zwitterion**, the methyl ester group was saponified with LiOH. From the crude taken up in acetonitrile we could precipitate the lithium triflate, after that, the soluble fraction containing the zwitterion was purified by silica gel column chromatography. The targeted zwitterionic switch **7m zwitterion** was isolated as a 9:1 mixture of *Z/E* isomers as inferred by NOE experiments.

This part has mainly been developed by the colleagues of Dipartimento di Chimica, Università di Siena.

Theoretical studies demonstrated that due to its large dipole moment, **7m zwitterion** may constitute the prototype of a generation of electrostatic switches achieving a reversible light-induced dipole moment inversion of the order of 30 Debye. A behaviour which opens up new perspective for light-driven conformational control of macromolecular structures determined by polar interactions.

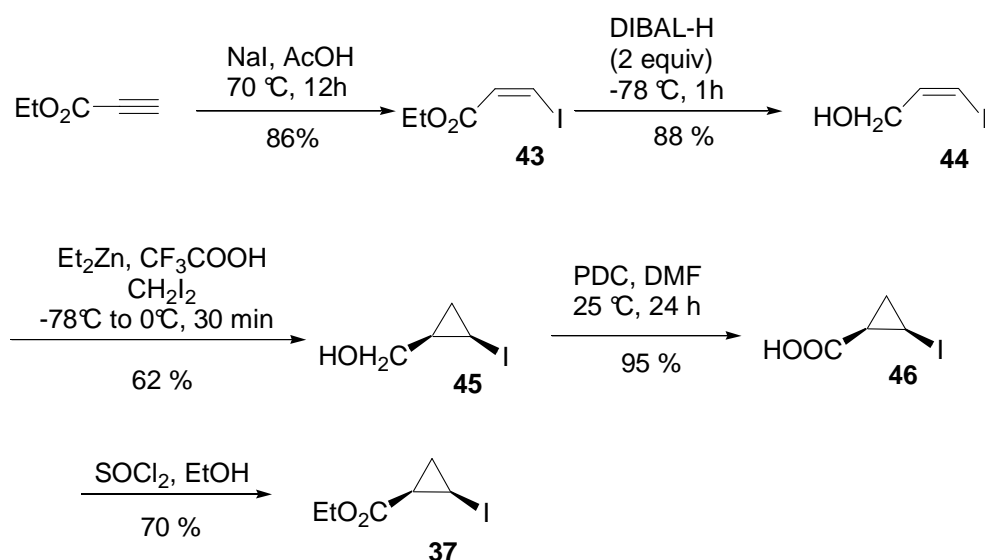


Reagents and conditions: (i) trifluoromethanesulfonate, toluene, rt, 10min; (ii) LiOH, THF/H₂O, rt, 3h.

Scheme 37

SECTION A

Herein, the preparation of **33** is reported (for references and notes see Experimental Part).



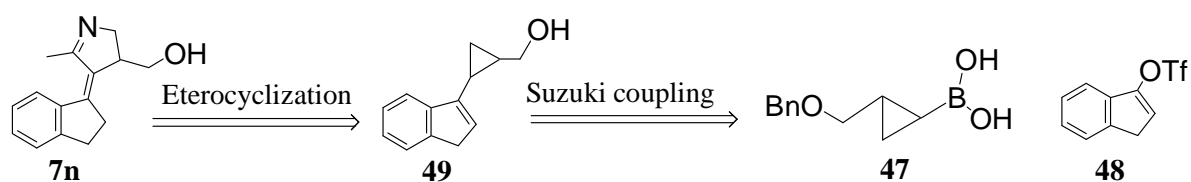
Scheme 38

Hydroiodic addition to ethyl propiolate by reaction with NaI in acetic acid afforded stereoselectively the *Z*-isomer **43**. Subsequent DIBAL-H reduction of ethyl ester furnished the allylic alcohol **44** that was submitted to cyclopropanation using a modified Simmon-Smith protocol described by Shi et al in 1998⁵⁹. They found that the cyclopropanation reagent CF₃COOZnCH₂I can accelerate the cyclopropanation reaction dramatically if compared with the usual IZnCH₂I reagent. The reagent can be easily prepared by addition of CH₂I₂ to a cooled solution of Et₂Zn and trifluoroacetic acid. Our reaction was completed within 30 min affording *cis*-2-iodo-cyclopropyl methanol **45** in good yield. Then, oxidation to carboxyl derivative **46** with PDC and esterification led to compound **37**.

2.3.3 Last Developments.

Unfortunately, we encountered unexpected difficulties when indanone compounds **1** and **1f** were the substrate for Knochel reagent, a result stressing the importance not to have enolizable hydrogens on the indanone reagents.

The need to dispose of efficient and flexible routes to functionalized photoswitches prompt the search for new reaction strategies in order to connect the indanyl and cyclopropyl rings. Thus a promising retrosynthetic analysis to **7n**, depicted in Scheme 38, is based on a Suzuki reaction between the enoltriflate **48** and the cyclopropyl boronic acid **47**. One can expect the resulting compound **49** successfully undergoing the already discussed heterocyclization *via* the “cyclopropyl ring-opening/nitrilium ion ring-closing tandem reaction”.



Scheme 38

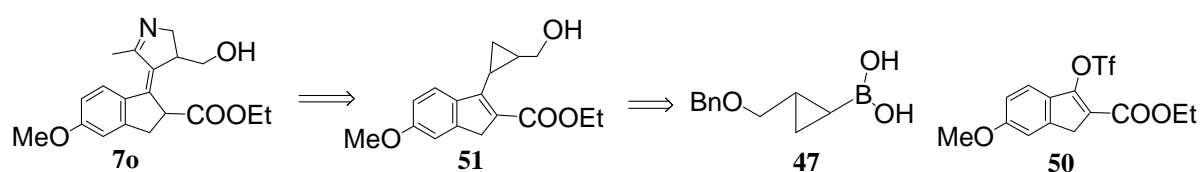
Embarking this new approach we found support from recent data of literature. In particular, Deng *et al.*⁶⁰ described an efficient Suzuki procedure to couple stereoselectively cyclopropylboronic acids with alkenyl triflates. In some entries (see table A), the enoltriflate of 1-indanone reacted with *trans*-alkyl-cyclopropylboronic acids in satisfying yield provided that the correct basic system were used. In particular, while electron poor enoltriflate reacted well both with K_3PO_4 and Cs_2CO_3 -KF, simple enoltriflate absolutely required the latter basic system.

Entry	Cyclopropylboronic acids (1)	Alkenyl triflate(2)	Product ^b (3)	Yield ^c (%)
1				3a 73(85)
2				3b 74(0)
3				3c 67(0)
4				3d 73(0)
5				3e 79(0)
6				3f 71(0)
7				3g 67(0)
8				3h 63(0)
9				3i 75(86)
10				3j 67(73)
11				3k 69(78)

a. cyclopropylboronic acid (1.1 mmol), alkenyl triflate(1.0 mmol), 3% mmol of Pd(PPh₃)₄, in toluene (4 ml). **Conditions A**: 3.3 equiv. K₃PO₄·3H₂O was used as the base at 100°C; **Conditions B**: 0.8 equiv. Cs₂CO₃ and 2.4 equiv. KF·2H₂O were used as the base and 1 equiv. NaBr was added at 80°C. b. All the products gave satisfactory elemental analysis; ¹H NMR; MS and IR spectra. c. Isolated yields based on alkenyl triflates under **conditions B** (the data in parenthesis are the yields under **conditions A**).

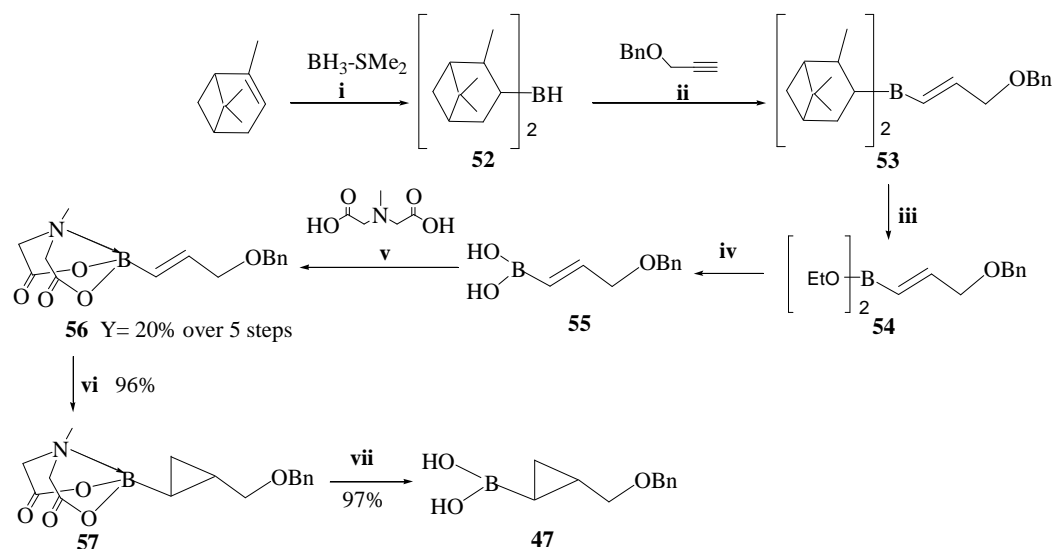
Table A⁶⁰

However, a severe limit of the protocol seemed to be the cyclopropyl boronic partners, the range being restricted to *trans* alkyl and phenyl cyclopropyl boronic acid derivatives. Anyway, the ease to accede to the key indenyl cyclopropane derivatives made the Suzuki protocol particularly attractive to us in order to arrive to mono- and bifunctionalized **PSB^{II}** analogues (scheme 39).



Scheme 39

We decided to investigate the reaction between enoltriflate **48** and cyclopropyl-boronic acid **47** (scheme 38). Thus, the preparation of the functionalized cyclopropyl boronic acid starting from the easily accessible benzyl-protected propargyl alcohol was our first goal. In 1993, Suzuki e Miyaura *et al*⁶¹ reported that the hydroboration of alkynyl compounds substituted at the C3 with heteroatoms could not be achieved using the classical procedure. Thus, they reported a three-step one pot procedure in which the diisopinocaneborano [HB(Ipc)₂] **52** is used as an efficient hydroborating agent (Scheme 40).



Reagents and conditions: (i) $\text{BH}_3 \cdot \text{SMe}_2$, 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) $\text{Pd}(\text{OAc})_2$, CH_2N_2 , THF/ Et_2O , 0°C , 40min; (vii) NaOH 1M, THF, 23°C , 20min.

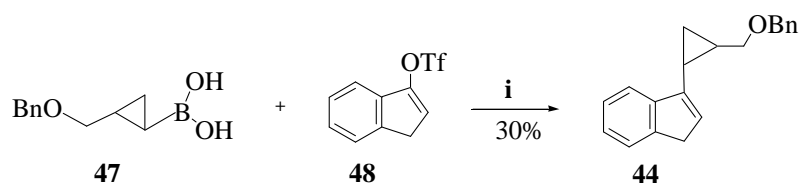
Scheme 40

Indeed, compound **53** was prepared following the action of [HB(Ipc)₂] **52**, formed in situ between BH₃:Me₂S and α-pinene, onto the protected alkyne. The regioselective hydroboration was followed by the propanal B-C bond oxidation to afford the ethylboronate **54**. The high instability of this compound prompted us to transform it into a more stable form by a formal transesterification using commercially available *N*-methyliminodiacetic acid (MIDA). In fact, Burke *et al.*⁶² reported that the general instability of most of the organo-boronate compounds (such as **54**) could be attenuated by rehybridization of the boron center from sp² to sp³ *via* complexation with the trivalent ligand MIDA. They further described that this ligand is cleavable using relatively mild reagents because heteroatom-boron bonds in tetrahedral adducts are predicted to be weaker than those in their tricoordinate counterparts. Remarkably, these pyramidalized boronate esters are stable and readily purified by silica gel chromatography.

Thus, compound **54** was hydrolyzed to boronic acid **55** that reacting with 1 equiv. of *N*-methyliminodiacetic acid in a mixture of benzene and DMSO at reflux for 16 h using a Dean-Stark trap afforded compound **56**. The latter compound, purified through a silica column, was storable at room temperature for several weeks without signals of decomposition.

Cyclopropanation of **56** was achieved using an excess of diazomethane under catalysis of Pd(OAc)₂; the progress of the reaction was monitored by HPLC⁶³.

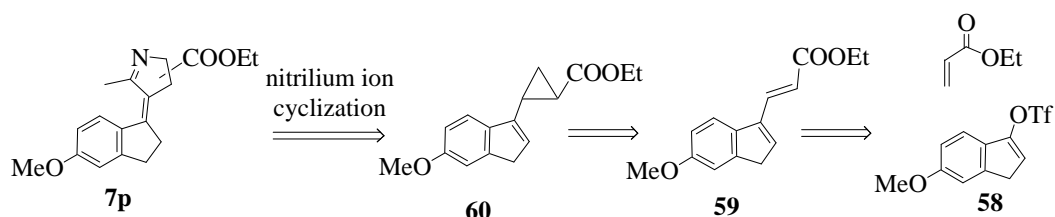
Subsequent deprotection of MIDA group under mild basic conditions afforded the boronic acid **47** to be used in the Suzuki coupling with the enoltriflate **48**⁶⁴. Following Deng protocol, the reaction occurred in disappointingly low yield prompting us to further investigation to ameliorate this key step.



Suzuki coupling (i) Pd(PPh₃)₄, NaBr, Cs₂CO₃, KF·2H₂O

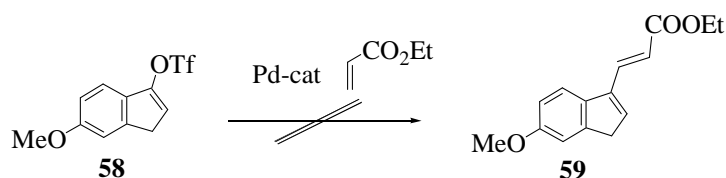
Scheme 41

A second approach was also explored toward the synthesis of PSB^{II} derivatives bearing a carboxylic group onto the pyrroline heterocycle. We considered compound **60** as the key intermediate undergoing the one-pot cyclization on the route to **7p**. For its preparation, we investigated the Heck reaction between the alkenyl triflate **58** and ethyl acrylate and then cyclopropanation as shown in Scheme 42⁶⁵.



Scheme 42

We tried the Heck reaction in the usual way by reacting alkenyl triflate **58** using PdCl₂(PPh₃) 0.1eq, TEA 3eq, ethyl acrylate 3eq in DMF 80°C. However, after a few minutes, TLC analysis showed complete decomposition of starting material without traces of desired product.

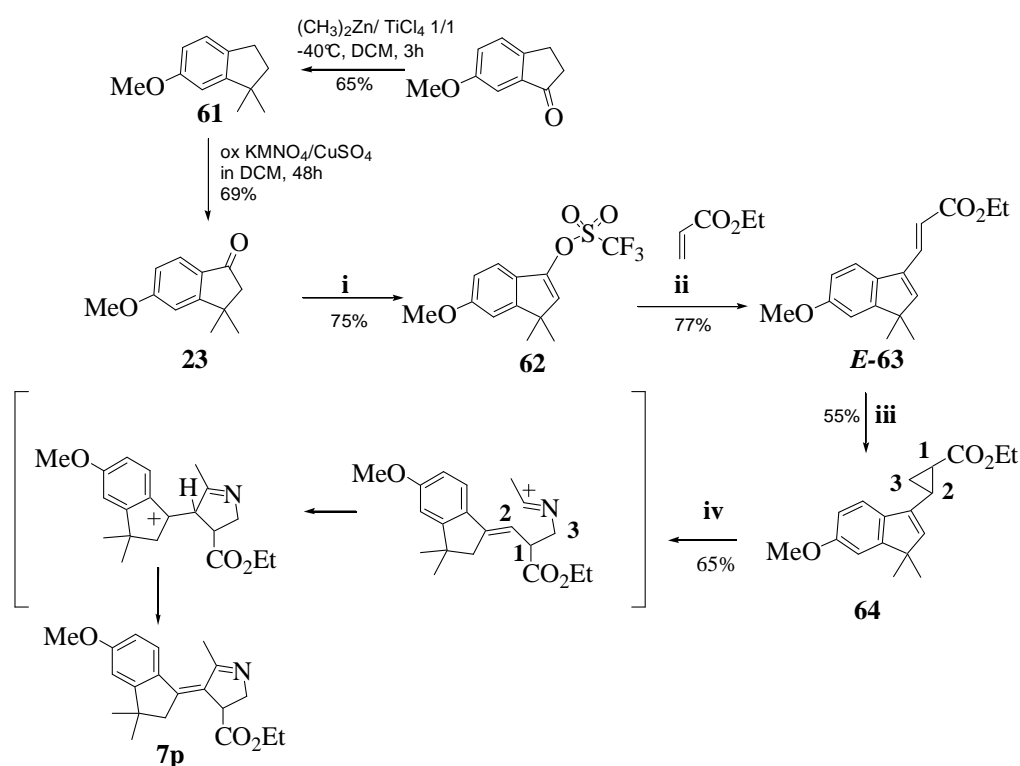


Scheme 43

This result prompted us to better investigate both the chemical behaviour of **58** and the coupling reaction conditions; thus, we found the alkenyl triflate **58** was very unstable when treated with TEA in DMF at room temperature (we were unable to identify none of the by-products). Moreover, compound **58** showed an intrinsic instability in organic solvents such as DCM and DMF at room temperature also in the absence of bases (probable polymerization!). As the chemical instability was attributable to the presence of acidic indenyl-triflate protons, we preferred to shift our attention to the already reported compound **23** (see Schemes 27 and 32), where two methyl groups replace the hydrogen atoms.

Compound **23** was prepared following a different route in order to reduce synthetic effort and time. Thus, following a reported protocol⁶⁶, 6-methoxy-1-indanone reacted with an excess of $(\text{CH}_3)_2\text{TiCl}_2$ generated in situ from Me_2Zn and TiCl_4 to give compound **61** in good yield.

Lee *et al.*⁶⁷, using permanganate adsorbed onto solid supports such as copper(II) sulfate pentahydrate, effected the oxidation of alcohols, as well as of benzylic carbons. We used the above heterogeneous oxidant in a DCM solution of substrate **61** obtaining indanone **23** in good yield.



Reagents and conditions: (i) Tf_2O , 2,6-*t*-butyl-4-methylpyridine, 1,2-dichloroethane; (ii) $\text{Pd}(\text{OAc})_2$, TEA, DMF; (iii) CH_2N_2 , $\text{Pd}(\text{OAc})_2$; (iv) TfOH , ACN, 3h, 60°C .

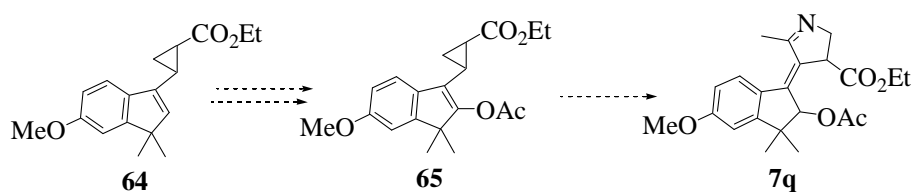
Scheme 44

Compound **62** was prepared by the action of equimolar amounts of triflic anhydride and 2,6-di-*t*-butyl-4-methylpyridine on a dichloroethane solution of indanone **23**⁶⁴. When applied to this substrate, the already tested reaction conditions for the Heck coupling led to intermediate **63** in 50% yield.

In order to maximize the conversion, we screened different Pd-catalysts; when the reaction was carried out using Pd(OAc)₂, ethylacrylate and TEA at 80°C in DMF for 3h, compound **63** was obtained in 80% yield. As expected, the Heck reaction gave only *trans*-**63** (¹H-NMR spectrum *J* coupling of 16Hz).

Among the plethora of methods employed for the preparation of three-membered ring, the Pd(OAc)₂/CH₂N₂-catalyzed cyclopropanation of alkenes seemed the more reliable for our substrate⁶⁵. In our expectation, the reaction of **63** would afford a mixture of three different compounds: the desired proximal cyclopropane derivative **64**, the distal and the *bis*-cyclopropane derivatives. We were delighted to find that cyclopropanation of **63** produced regio- and stereoselectively the *trans*-cyclopropane derivative **64** in good yields. Reasonably, the regioselectivity should derive from the minor encumbrance around the tethered double bond with respect to the indenyl nucleus. Accordingly to our expectations, compound **64** underwent the nitrilium ion heterocyclization when treated with TfOH in acetonitrile. With great pleasure, the tandem cyclopropyl ring-opening/pyrroline ring-forming transformation only led to compound **7p** where the carboxyl ester group is located at C-3 carbon of the heterocycle. As the observed regioselectivity depends on the ancillary homoallyl rearrangement, we can conclude that acetonitrile, acting as a nucleophile, opens the cyclopropyl ring of intermediate **64** attacking selectively its C-3 carbon (see Scheme 44). It is worthwhile to note that bromide ring-opening of intermediate **39** follows a different course, the C-1 cyclopropyl carbon being the target of the nucleophile for this substrate (see Scheme 36).

The “Heck approach” is still under investigation with the final goal of obtaining the bifunctionalized PSB^{II} molecular switch **7q** via the enolacetate **65**.



Scheme 45

3. CONCLUSIONS

- i) The design and synthesis of photoswitchable compounds have been realized by the elaboration of the minimal structure of the penta-2,4-dieniminium ion: the key framework related to the retinal protonated Schiff base chromophore of Rhodopsin proteins.
- ii) The photo- and computational characterization of the firstly prepared compounds, denominated **PSB^I**, stimulated the search for a second generation compounds, **PSB^{II}**, that were more effective light-driven molecular devices.
- iii) The new class of biomimetic switchers promises to be an attractive alternative (e.g., with high polarity and reduced molecular size) to the widely used azobenzene switch.
- iv) An elegant cyclopropyl ring-opening/nitrilium ion ring-closing tandem reaction was discovered and used to set up the polyene Schiff base skeleton, a common feature of the conformationally locked molecular switches.
- v) The above one-pot domino process was successful both for the preparation of indanylidene-pyrrolines and of benzofurane-pyrrolines.
- vi) The synthetic approach showed to be flexible and adjustable to the introduction of different functional groups on both halves of the switches, thus allowing their grafting to a peptide domain. As already reported for different molecular switches, the controlled photochemical *E/Z* isomerisation of **PSB^{II}** could be employed to induce permanent or transient conformational change of a molecular scaffold bounded to it.

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% KMnO₄ 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 (¹H NMR and ¹³C NMR) were recorded on a Mercury Plus spectrometer at 400 MHz and 100 MHz, respectively. Chemical shifts (δ values) are given in parts per million downfield from tetramethylsilane as the internal standard. Reverse-phase HPLC using a Beckman 116 liquid chromatograph equipped with a Beckman 166 diode array detector. Nucleodur C₁₈ 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⁺.

4.2 Experimental section.

Procedure for the Preparation of the Neutral Imines **1neut** and (*p*-MeO)-**1neut**.

A mixture of 1-pyrroline trimer (3.3mmol) and aromatic aldehyde (10 mmol) in methanol (25ml) was stirred at room temperature for 48 hours; then the solvent was removed *in vacuo* and the residue purified by silica gel column chromatography eluting with ethyl acetate.

***E*-4-Benzylidene-3,4-dihydro-2*H*-pyrrole (*E*-**1neut**).**

Yield: 30%; m.p. 70-72 °C; IR (KBr): ν 1568 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3) δ : 2.78-2.86 (2H, m), 4.16-4.24 (2H, m), 6.82 (1H, t, J 2.8 Hz), 7.26-7.49 (5H, m), 7.87 (1H, t, J 2.3 Hz); $^{13}\text{C-NMR}$ (CDCl_3) δ 28.29, 62.35, 127.01, 128.02, 128.71, 128.81, 136.79, 143.67, 168.48.

***E*-4-(4-Methoxy-benzylidene)- 3,4-dihydro-2*H*-pyrrole (*E*-(*p*-MeO)-**1neut**).**

Yield: 50%; m.p. 63-65 °C; IR (KBr): ν 1604, 1570, 1511 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3) δ 2.75-2.82 (2H, m), 3.83 (3H, s), 4.15-4.22 (2H, m), 6.78 (1H, t, J 2.7Hz), 6.92 (2H, d, J 6.8Hz), 7.41 (d, 2H, J 6.8Hz), 7.83 (1H, t, J 2.3Hz); $^{13}\text{C-NMR}$ (CDCl_3) δ 28.16, 55.38, 62.24, 114.19, 126.62, 129.58, 130.26, 141.55, 159.41, 166.61.

Procedure for the Preparation of the Neutral Imine (*p*-NO₂)-**1neut**.

A mixture of 1-pyrroline trimer (3.3mmol) and *p*-nitro benzaldehyde (10 mmol) in methanol (25ml) 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 K₂CO₃ and extracted with ethyl acetate. The organic phase was dried and the solvent removed *in vacuo*. The final product was obtained after column chromatography (silica gel, ethyl acetate) of the crude.

***E*-4-(4-Nitro-benzylidene)- 3,4-dihydro-2*H*-pyrrole (*E*-(*p*-NO₂)-**1neut**).**

Yield: 43%; m.p. 105-108°C; IR (KBr): ν 1593, 1511, 1341 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3) δ 2.84-2.91 (2H, m), 4.24-4.31 (2H, m), 6.89 (1H, t, J 2.8Hz), 7.60 (2H, d, J 8.8Hz), 7.94

(1H, t, J 2.4Hz), 8.25 (2H, d, J = 8.8Hz); ¹³C-NMR (CDCl₃) δ 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 CF₃SO₃CH₃ 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-Benzylidene-1-methyl-3,4-dihydro-2*H*-pyrrolium trifluoromethanesulfonate (*E*-1Me).**

Yield: 100% mp 112-113°C; ¹H-NMR (CD₃CN) δ 3.20 (2H, m), 3.59 (3H, s), 4.30 (2H, m), 7.42-7.68 (6H, m), 8.50 (1H, m); ¹³C-NMR (CD₃CN) δ 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-Methoxybenzylidene)-1-methyl-3,4-dihydro-2*H*-pyrrolium-trifluoromethanesulfonate. (*p*-MeO)- *E*-1Me).**

Yield: 100%; mp 117-119°C; ¹H-NMR (CD₃CN) δ 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); ¹³C-NMR (CD₃CN) δ 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-benzylidene)-1-methyl-3,4-dihydro-2*H*-pyrrolium trifluoromethanesulfonate (*E*- (*p*-NO₂)-1neut).**

Yield: 100%; mp 96-98°C; ¹H-NMR (CD₃CN) δ 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

3-(3-Chloro-propyl)-6-methoxy-1*H*-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 a yellow oil.

IR (film): ν 2954, 1742, 1606, 1492, 1255, 732 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3): 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); ^{13}C NMR (50 MHz, CDCl_3): 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 (2.3g, 5mmol, 1.3eq) and KHMSA (2g, 10mmol, 2.6eq) in 10 ml of dry THF under Argon was stirred for 3h at 20°C. A solution of **1** (0.5g, 3.78mmol) 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 that **3e-exo** (0.23g, 40%, colorless oil). After 1.5h room temperature in CDCl_3 , ^1H -NMR showed that compound **3e-exo** spontaneously transformed in **3e-endo** in 1.5h.

3e-exo: ^1H NMR (400 MHz, CDCl_3): δ 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; IR (KBr): ν 3447, 2960, 1604, 1258, 1073, 1015, 820 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 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): δ 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).

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 (3x50 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): ν 2960, 2926, 1704, 1599, 1264, 1089 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 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): δ 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_4Cl solution was added (20 mL) and the mixture was extracted with ether (3x20 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): ν 3514, 2959, 2870, 1607, 1490, 1268, 1142, 1032, 808 cm^{-1} ; ^1H NMR(400 MHz, CDCl_3): δ 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): δ -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 ($<10^\circ\text{C}$) 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_2O (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): ν 2956, 2836, 1604, 1487, 1308, 1263, 1034 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ (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), 6.74–6.85 (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): δ (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): ν 2957, 2096, 1604, 1487, 1464, 1262, 1034, 849 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ (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): δ (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)-propyl]-acetamide (6a).

A solution of **5a** (0.26 g, 1 mmol), NaOAc (0.11 g, 1.2 mmol) and Ac_2O (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 *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^{-1} ; ^1H NMR (400 MHz, CDCl_3): 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); ^{13}C NMR (100 MHz, CDCl_3): 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 11 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 P₂O₅ (1.6 g, 11 mmol) and hexamethyldisiloxane (HMDSO, 3.3 mL, 15.4 mmol) in CCl₄ (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 *in vacuo*. The residue was purified by column chromatography (EtOAc/MeOH/Et₃N 9:1:0.2) to give **7a** (92:8 *Z/E* mixture, 0.2 g, 71%) as a yellow oil.

IR (film): ν 1702, 1600, 1576, 1291 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 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 δ 2.22 (methyl at C-5 of 3,4-dihydro-2H-pyrrole) and signal at δ 7.24 (H-7 on the aromatic ring) was detected; ¹³C NMR (100 MHz, CDCl₃): δ 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 CF₃SO₃CH₃ were added to 0.3 mmol of *Z/E*-isomers of **7a**, (*p*-MeO)-**2** 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. 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⁺Me)Cl⁻** (92:8 Z/E mixture, 0.2mmol g, 62%) as a yellow oil.

¹H NMR (400 MHz, CDCl₃): 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; ¹³C NMR (100 MHz, CDCl₃): 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.

2,2-dimethyl-indan-1-one (1b).

Procedure for **1a**.

Yield 75%, colorless oil, diethyl ether/petroleum (2:8) as eluent.

IR (film) ν 2960, 1717, 1609, 1466, 1325; ¹H NMR (200MHz, CDCl₃) δ 1.16 (6H, s), 2.9 (2H, s), 7.28-7.36 (2H, m), 7.47 (1H, m), 7.66-7.69 (1H, m); ¹³C NMR (100 MHz, CDCl₃) δ 25.1 (2C), 42.7, 45.3, 124.2, 126.5, 127.3, 134.7, 135.2, 152.1, 211.4.

1-Cyclopropyl-2,2-dimethyl-indane-1-ol (3b).

Grignard reaction performed using the same procedure for **3a**.

Yield 88%, colorless oil, diethyl ether/petroleum (2:8) as eluent.

IR(film) ν 3476, 2964, 1474, 1018, 761 cm⁻¹; ¹H NMR (200MHz, CDCl₃) δ 0.10-0.19 (1H, m), 0.39-0.46 (3H, m), 1.02-1.06 (3H, m), 1.28-1.069 (4H, m), 2.74 (2H, m), 7.18-7.32 (4H, m); ¹³C NMR (50MHz, CDCl₃) δ -0.27, -0.034, 15.4, 23.6, 23.6, 45.4, 48.3, 83.6, 123.8, 124.8, 126.2, 127.9, 141.8, 146.6.

1-(3-Bromo-propylidene)-2,2-dimethyl-indan (4b)

Procedure for **4a**.

Yield 74%, colorless oil, diethyl ether/petroleum (2:8) as eluent.

IR (film) ν 2957, 2863, 1461, 1263, 770 cm⁻¹; ¹H NMR (200MHz, CDCl₃) δ (isomeric ratio 3/1) 1.27 (6H, s, major), 1.43 (6H, s, minor), 2.87 (2H, s, major), 2.94 (2H, s,

minor), 3.03 (2H, q, $J=7.2\text{Hz}$, minor) 3.10(2H, q, $J=7.2\text{Hz}$, major), 3.51 (2H, t, $J=7.2\text{Hz}$, minor), 3.57 (2H, t, $J=7.2\text{Hz}$, major), 5.45(1H, t, $J=7.2\text{ Hz}$, major), 5.96 (1H, t, $J=7.2\text{Hz}$, minor), 7.24-7.31 (6H, m, major and minor), 7.48-7.52(1H, m, minor), 7.56-7.62 (1H, m, major); ^{13}C NMR (50 MHz, CDCl_3) δ (major isomer) 29.3 (2C), 32.1, 32.6, 46.8, 49.3, 116.3, 126.5, 126.9, 127.8, 127.9, 139.5, 144.5, 152.3.

1-(3-Azido-propylidene)-2,2-dimethyl-indan (5b).

Procedure for **5a**

Yield 96%, colorless oil, diethyl ether/petroleum (2:8) as eluent.

IR (film) ν 2957, 2927, 2097, 1461, 1262, 770 cm^{-1} ; ^1H NMR (400MHz, CDCl_3) δ (isomeric ratio 3/1) 1.25 (s, 6H, major), 1.42 (s, 6H, minor), 2.72 (q, 2H, $J=7.6\text{Hz}$, minor), 2.82 (q, 2H, $J=7.2\text{Hz}$, major), 2.85 (s, 2H, major), 2.92 (s, 2H, minor), 3.41-3.50 (m, 4H, major and minor), 5.42 (t, 1H, $J=7.2\text{ Hz}$, major), 5.93 (t, 1H, $J=7.2\text{Hz}$, minor), 7.21-7.33 (m, 4H, major and minor), 7.42-7.48 (m, 1H, minor), 7.58-7.63 (m, 1H, major); ^{13}C NMR (100 MHz, CDCl_3) δ (major isomer) 28.6 (2C), 42.5, 46.8, 49.3, 51.3, 115.1, 124.9, 125.2, 126.4, 127.8, 139.7, 142.6, 151.7.

***N*-[3-(2,2-dimethyl-indan-1-ylidene)-propyl]-acetamide (6b)**

Procedure for **6a**.

Yield 82%, colorless oil, ethyl acetate as eluent.

IR (film) ν 3290, 3084, 2956, 1651, 1487, 1262, 1033, 816 cm^{-1} ; ^1H NMR (400MHz, CDCl_3) δ (isomeric ratio 3/1) 1.16 (s, 6H, major), 1.32 (s, 6H, minor), 1.93 (s, 3H, major), 1.95 (s, 3H, minor), 2.57 (q, 2H, $J=7.2\text{Hz}$ minor), 2.66 (q, 2H, $J=7.2\text{Hz}$ major), 2.77 (s, 2H, major), 2.84 (s, 2H, minor), 3.33-3.42 (m, 4H, major and minor), 5.32 (t, 1H, $J=7.2\text{Hz}$ major), 5.84 (t, 1H, $J=7.2\text{Hz}$ minor), 6.30 (broad, 2H, major and minor), 7.14-7.23 (m, 6H, major and minor), 7.35-7.37 (m, 1H, minor), 7.55-7.61 (m, 1H, major); ^{13}C NMR (100 MHz, CDCl_3) δ (major isomer) 23.1, 28.6 (2C), 39.5, 42.2, 46.7, 49.2, 117.4, 124.8, 125.3, 126.4, 127.7, 139.7, 142.3, 151.2, 170.3.

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

Used the same procedure for **7a** (PATHWAY A).

Yield 75%, brown oil, 7:1 *Z/E* mixture, (EtOAc/MeOH/Et₃N 9:1:0.2) as eluent.

IR(film) ν 1702, 1600, 1576, 1291 cm⁻¹; ¹H NMR (400MHz, CDCl₃) δ 1.26 (s, 6H), 2.23 (m, 3H), 2.79-2.83 (m, 4H), 3.82-3.84 (m, 2H), 7.15-7.29 (m, 4H). A positive NOE between signals at δ 1.26 (two methyl at C-2' of inadanylidene) and at δ 2.79-2.83 (hydrogens at C-3 of 3,4-dihydro-2H-pyrrole) was detected; ¹³C NMR (100 MHz, CDCl₃) δ 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 10c and 10d.

6-Methoxy-2,2-dimethyl-2,3-dihydro-benzofuran (10c).

To magnesium turnings (40mmol, 4eq) in dry Et₂O (20ml), a solution of 2-bromopropane (40mmol, 4eq) in dry Et₂O (20ml) was added dropwise with mild reflux. After the addition was completed, a solution of appropriate 2-hydroxybenzaldehyde (10mmol, 1eq) dissolved in dry diethyl ether (20ml) was added dropwise at 0°C. The reaction was stirred r.t. for 2h.

The reaction was quenched at 0°C adding 5ml of Methanol and 20ml of saturated aqueous ammonium chloride solution. The mixture was extracted with diethyl ether (3x50ml). The combined organic solutions were dried over anhydrous magnesium sulfate, filtered and the filtrate was evaporated *in vacuo*. The crude was used in next reaction without further purification.

The crude was dissolved in toluene (100ml) and Amberlyst 15 (10mmol, 1eq) was added and the mixture was warmed to 80°C for 24h. After filtration the solvent was removed *in vacuo* and the residue was purified by chromatography on silica gel with diethyl ether/petroleum (5:95) as eluent to give the desired product **4** as a colorless oil (4.7mmol, 47%).

6-Methoxy-2,2-dimethyl-2,3-dihydro-benzofuran (10c).

IR (film) ν 2971, 2931, 1622, 1595, 1498, 1197; ^1H NMR (400MHz, CDCl_3) δ 1.48 (s, 6H), 2.95 (s, 2H), 3.76 (s, 3H), 6.36-6.41 (m, 2H), 7.02 (d, 1H, $J=7.2\text{Hz}$); ^{13}C NMR (100 MHz, CDCl_3) δ 28.21 (2C), 42.22, 55.39, 87.63, 96.19, 105.44, 119.01, 125.10, 160.04, 160.33.

2,2-dimethyl-2,3-dihydro-benzofuran (10d).

Procedure for **10c**.

Yield 39%, colorless oil, diethyl ether/petroleum (5:95) as eluent.

IR (film) ν 2965, 2925, 1623, 1585, 1498; ^1H NMR (400MHz, CDCl_3) δ 1.49 (s, 6H), 3.0. (s, 2H), 6.74-6.85 (m, 2H), 7.12-7.18 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 28.31 (2C), 42.95, 86.56, 106.61, 120.23, 125.25, 127.17, 128.05, 158.91.

General oxidation procedure for 1c and 1d.

6-Methoxy-2,2-dimethyl-benzofuran-3-one (1c).

A solution of benzofuran **10c** (1.85g, 10.4mmol, 1eq) in 75ml of acetonitrile was added to a solution of potassium peroxydisulfate and copper sulphate in water 75ml. The resulting mixture was stirred at 65-70°C for 3h. The reaction mixture was then extracted with Et_2O (3x50ml) and the organic layer was washed with water (50ml), dried over Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel with diethyl ether/petroleum (2:8) as eluent to give the desired product **1c** as a yellow solid (4.7mmol, 47%, Yield over 2 steps).

6-Methoxy-2,2-dimethyl-benzofuran-3-one (1c).

IR (film) ν 2360, 1704, 1616, 1444, 1208; ^1H NMR (400MHz, CDCl_3) δ 1.41 (s, 6H), 3.83 (s, 3H), 6.45 (d, 2H, $J=2\text{Hz}$), 6.58 (dd, 1H, $J=8.8\text{Hz}$, $J=2\text{Hz}$), 7.51 (d, 1H, $J=8.8\text{Hz}$); ^{13}C NMR (100 MHz, CDCl_3) δ 23.1 (2C), 55.81, 88.85, 96.10, 111.53, 112.50, 125.85, 168.44, 173.30, 201.98.

2,2-dimethyl-benzofuran-3-one (1d).

Procedure for **1d**.

Yield 55%, colorless oil, diethyl ether/petroleum (2:8) as eluent.

IR (film) ν 2978, 1721, 1614, 1464, 1268; ^1H NMR (400MHz, CDCl_3) δ 1.41 (s, 6H), 7.01-7.07 (m, 2H), 7.58-7.66 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 23.01 (2C), 87.85, 113.61, 119.53, 121.68, 124.89, 138.12, 170.91, 204.37.

3-Cyclopropyl-6-methoxy-2,2-dimethyl-2,3-dihydro-benzofuran-3-ol (3c).

3-Cyclopropyl-2,2-dimethyl-2,3-dihydro-benzofuran-3-ol (3d).

Grignard reaction performed using the same procedure for **3a**.

3-Cyclopropyl-6-methoxy-2,2-dimethyl-2,3-dihydro-benzofuran-3-ol (3c).

Yield 79%, colorless oil diethyl ether/petroleum (2:8) as eluent.

IR(film) ν 3500, 2977, 2937, 1697, 1614, 1495, 1162, 828 cm^{-1} ; ^1H NMR (400MHz, CDCl_3) δ 0.36-0.42 (m, 1H), 0.49-0.58 (m, 2H), 0.61-0.69 (m, 1H), 1.02-1.09 (m, 1H) 1.41 (s, 3H), 1.45 (s, 3H), 3.76 (s, 3H), 6.36 (d, 1H, $J=2\text{Hz}$), 6.43 (dd, 1H, $J=8\text{Hz}$, $J=2\text{Hz}$), 7.22 (d, 1H, $J=8\text{Hz}$); ^{13}C NMR (100 MHz, CDCl_3) δ -1.41, 0.02, 14.03, 21.80, 23.89, 55.42, 79.44, 93.97, 96.68, 106.48, 124.55, 125.13, 159.75, 161.85.

3-Cyclopropyl-2,2-dimethyl-2,3-dihydro-benzofuran-3-ol (3d).

Yield 73%, colorless oil diethyl ether/petroleum (2:8) as eluent.

IR(film) ν 3480 1461, 102, 746 cm^{-1} ; ^1H NMR (400MHz, CDCl_3) δ 0.38-0.42 (m, 1H), 0.54-0.62 (m, 3H), 1.05-1.12 (m, 1H), 1.42 (s, 3H), 1.47 (s, 3H), 6.78-6.95 (m, 2H), 7.18-7.38 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ -1.33, 0.69, 13.98, 21.72, 23.79, 31.39, 79.86, 93.02, 110.90, 120.58, 124.22, 130.26, 132.88.

3-(3-Bromo-propylidene)-6-methoxy-2,2-dimethyl-2,3-dihydro-benzofuran (4c).

3-(3-Bromo-propylidene)-2,2-dimethyl-2,3-dihydro-benzofuran (4d).

Used the same procedure for **4a**.

3-(3-Bromo-propylidene)-6-methoxy-2,2-dimethyl-2,3-dihydro-benzofuran (4c).

Yield 73% colorless oil diethyl ether/petroleum (2:8) as eluent.

IR (film) ν 2974, 1616, 1495, 1294, 1201, 1098 cm^{-1} ; ^1H NMR (400MHz, CDCl_3) δ (isomeric ratio 5/1) 1.45 (s, 6H, major), 1.59 (s, 6H, minor), 2.81 (q, 2H, $J=7.2\text{Hz}$, minor) 2.97 (q, 2H, $J=7.2\text{Hz}$, major), 3.42 (t, 2H, $J=7.2\text{Hz}$, minor), 3.49 (t, 2H, $J=7.2\text{Hz}$, major), 3.77 (s, 3H, minor), 3.79 (s, 3H, major), 5.11(t, 1H, $J=7.2\text{Hz}$,

major), 5.60 (t, 1H, J=7.2Hz, minor), 6.33-6.49 (m, 4H, major and minor), 7.20 (d, 1H, J=8.4Hz, minor), 7.35 (d, 1H, J=8.8Hz, maor); ¹³C NMR (100 MHz, CDCl₃) δ (major isomer) 28.7 (2C), 31.7, 32.0, 55.5, 89.8, 96.1, 107.3, 113.1, 117.4, 124.9, 145.7, 162.1, 162.7.

3-(3-Bromo-propylidene)-2,2-dimethyl-2,3-dihydro-benzofuran (4d).

Yield 77% colorless oil, diethyl ether/petroleum (2:8) as eluent.

IR (film) ν 2974, 1616, 1495, 1294, 1201, 1098 cm⁻¹; ¹H NMR (400MHz, CDCl₃) δ (isomeric ratio 5/1) 1.47 (s, 6H, major), 1.58 (s, 6H, minor), 2.84 (q, 2H, J=7.2Hz, minor) 2.96 (q, 2H, J=7.2Hz, major), 3.47 (t, 2H, J=7.2Hz, minor), 3.53 (t, 2H, J=7.2Hz, major), 5.11(t, 1H , J=7.2 Hz, major), 5.74 (t, 1H, J=7.2Hz, minor), 6.69-7.05 (m, 4H, major and minor), 7.20-7.29 (m, 4H, major and minor).¹³C NMR (100 MHz, CDCl₃) δ (major isomer) 29.7 (2C), 31.9, 31.0, 89.8, 98.1, 108.3, 113.15, 117.47, 125.9, 145.7, 162.1, 162.7.

3-(3-Azido-propylidene)-6-methoxy-2,2-dimethyl-2,3-dihydro-benzofuran (5c).

3-(3-Azido-propylidene)-2,2-dimethyl-2,3-dihydro-benzofuran (5d).

Used the same procedure for preparation of **5a**.

3-(3-Azido-propylidene)-6-methoxy-2,2-dimethyl-2,3-dihydro-benzofuran (5c).

Yield 88% colorless oil diethyl ether/petroleum (3:7) as eluent.

IR (film) ν 2900, 2109, 1617, 1495, 1207, 1108 cm⁻¹; ¹H NMR (400MHz, CDCl₃) δ (isomeric ratio 5/1) 1.45 (s, 6H, major), 1.59 (s, 6H, minor), 2.55 (q, 2H, J=7.2Hz, minor) 2.71 (q, 2H, J=7.2Hz, major), 3.38 (t, 2H, J=7.2Hz, minor), 3.43 (t, 2H, J=7.2Hz, major), 3.77 (s, 3H, minor), 3.79 (s, 3H, major), 5.09 (t, 1H , J=7.2 Hz, major), 5.57 (t, 1H, J=7.2Hz, minor), 6.37-6.49 (m, 4H, major and minor), 7.18 (d, 1H, J=8.4Hz, minor), 7.38 (d, 1H, J=8.8Hz, major); ¹³C NMR (100 MHz, CDCl₃) δ (major isomer) 28.2 (2C), 28.7, 50.9, 55.5, 89.8, 96.1, 107.3, 111.8, 120.8, 125.1, 145.7, 162.1, 162.7.

3-(3-Azido-propylidene)-2,2-dimethyl-2,3-dihydro-benzofuran (5d).

Yield 88% colorless oil diethyl ether/petroleum (3:7) as eluent.

IR (film) ν 2975, 2098, 1615, 1495, 1296, 1201, 1108 cm⁻¹;

^1H NMR (400MHz, CDCl_3) δ (isomeric ratio 5/1) 1.45 (s, 6H, major), 1.59 (s, 6H, minor), 2.55 (q, 2H, $J=7.2\text{Hz}$, minor) 2.87 (q, 2H, $J=7.2\text{Hz}$, major), 3.48 (t, 2H, $J=7.2\text{Hz}$, minor), 3.51 (t, 2H, $J=7.2\text{Hz}$, major), 5.15 (t, 1H, $J=7.2\text{Hz}$, major), 5.77 (t, 1H, $J=7.2\text{Hz}$, minor), 6.97-7.04 (m, 4H, major and minor), 7.23-7.30 (m, 4H, major and minor); ^{13}C NMR (100 MHz, CDCl_3) δ (major isomer) 29.2 (2C), 31.7, 52.2, 90.8, 101.1, 107.3, 111.8, 120.8, 121.1, 147.7, 162.1, 163.7.

N-[3-(6-Methoxy-2,2-dimethyl-benzofuran-3-ylidene)-propyl]-acetamide (6c).

N-[3-(6-Methoxy-2,2-dimethyl-benzofuran-3-ylidene)-propyl]-acetamide (6d).

Used the same procedure for preparation of **6a**.

N-[3-(6-Methoxy-2,2-dimethyl-benzofuran-3-ylidene)-propyl]-acetamide (6c).

Yield 65% colorless oil, ethyl acetate as eluent.

IR (film) ν 3290, 2976, 1737, 1615, 1372, 1099, 831 cm^{-1} ; ^1H NMR (400MHz, CDCl_3) δ (isomeric ratio 4/1) 1.42 (s, 6H, major), 1.56 (s, 6H, minor), 1.94 (s, 3H, major), 1.96 (s, 3H, minor), 2.51 (q, 2H, $J=7.2\text{Hz}$ minor), 2.61 (q, 2H, $J=7.2\text{Hz}$ major), 3.31-3.43 (m, 4H, major and minor), 3.76 (s, 3H, minor), 3.76 (s, 3H, major), 5.04 (t, 1H, $J=7.2\text{Hz}$ major), 5.51 (t, 1H, $J=7.2\text{Hz}$ minor), 5.74 (broad, 2H, major and minor), 6.32-6.45 (m, 4H, major and minor), 7.18 (d, 1H, $J=8.8\text{Hz}$, minor), 7.48 (d, 1H, $J=8.8\text{Hz}$, major); ^{13}C NMR (100 MHz, CDCl_3) δ (major isomer) 23.3, 28.2, 28.8 (2C), 39.4, 55.5, 89.7, 96.1, 107.1, 110.2, 112.9, 125.1, 145.5, 160.9, 162.5, 170.4.

N-[3-(6-Methoxy-2,2-dimethyl-benzofuran-3-ylidene)-propyl]-acetamide (6d).

Yield 58% colorless oil ethyl acetate as eluent.

IR (film) ν 2876, 1650, 1372, 831 cm^{-1} ; ^1H NMR (400MHz, CDCl_3) δ (isomeric ratio 4/1) 1.49 (s, 6H, major), 1.59 (s, 6H, minor), 1.94 (s, 3H, major), 2.06 (s, 3H, minor), 2.61 (q, 2H, $J=7.2\text{Hz}$ minor), 2.81 (q, 2H, $J=7.2\text{Hz}$ major), 3.31-3.43 (m, 4H, major and minor), 5.24 (t, 1H, $J=7.2\text{Hz}$ major), 5.61 (t, 1H, $J=7.2\text{Hz}$ minor), 5.74 (broad, 2H, major and minor), 6.42-6.55 (m, 4H, major and minor), 7.28-7.32 m, 4H, major and minor). ^{13}C NMR (100 MHz, CDCl_3) δ (major isomer) 24.2, 29.2, 29.8 (2C), 39.4, 90.7, 98.2, 107.1, 111.2, 114.9, 125.8, 145.6, 161.9, 162.5, 170.4.

4-(6-Methoxy-2,2-dimethyl-benzofuran-3-ylidene)-5-methyl-3,4-dihydro-2H-pyrrole (7c)

4-(2,2-dimethyl-benzofuran-3-ylidene)-5-methyl-3,4-dihydro-2H-pyrrole (7d)

Used the same procedure for **7a** (PATHWAY A).

4-(6-Methoxy-2,2-dimethyl-benzofuran-3-ylidene)-5-methyl-3,4-dihydro-2H-pyrrole (7c)

Yield 50% brown oil, (DCM/MeOH/Et₃N 9:1:0.2) as eluent.

IR (film): ν 1702, 1600, 1576, 1291 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.73 (6H, s), 2.48 (3H, m), 2.96–2.99 (2H, m), 3.81 (3H, s), 3.92–3.95 (2H, m), 6.38 (1H, d, J 2.4 Hz), 6.52 (1H, d, J 8.8 Hz), 7.36 (1H, dd, J 8.8 2.4 Hz). ¹³C NMR (100 MHz, CDCl₃): δ 22.40, 28.51, 35.6, 55.57, 57.31, 90.04, 95.23, 107.47, 120.19, 126.67, 130.18, 162.71, 163.06, 169.66.

4-(2,2-dimethyl-benzofuran-3-ylidene)-5-methyl-3,4-dihydro-2H-pyrrole (7d)

Yield 72% brown oil, (DCM/MeOH/Et₃N 9:1:0.2) as eluent.

IR (film): ν 2935, 1606, 1583, 1492, 1278, 748 cm⁻¹; Isomeric ratio (2/1): ¹H NMR (400 MHz, CDCl₃): δ 1.61 (6H, s, minor), 1.73 (6H, s, major), 2.39 (3H, m, minor), 2.49 (3H, m, major), 2.84–2.87. (2H, m, minor), 3.12–3.03. (2H, m, major), 3.85–3.87 (2H, m, minor), 3.92–3.95 (2H, m, major), 6.81–6.93 (4H, m, major and minor), 7.10–7.21 (2H, m, major and minor), 7.44–7.48 (2H, m, major and minor). ¹³C NMR (100 MHz, CDCl₃): δ 21.08, 24.74, 28.52, 33.27, 35.75, 57.66, 90.94, 109.99, 120.25, 125.99, 127.45, 130.81, 140.74, 161.99, 169.51.

PATHWAY B (Scheme 17 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 CH₃CN (2 mL), a solution of **3a** (0.21 g, 0.9 mmol) in CH₃CN (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/Et₃N 9:1:0.2) to afford **7a** (0.19 g, 83%) as a yellow oil.

Pathway B was also used to obtain 7b, 7c, 7d from 3b, 3c, 3d respectively.

7b: Yield 85%

7c: Yield 65%

7d: Yield 71%

5-Methoxy-2-methyl-indan-1-one (1f).

Aqueous formaldehyde solution 36% (5.5 mL, 68.6 mmol) was added dropwise over 5 h to a refluxing mixture of 4-methoxypropiophenone (2 g, 12.2 mmol) and morpholine (0.53 mL, 6.1 mmol) in glacial acetic acid (20 mL). The mixture was refluxed overnight, then acetic acid was stripped off under reduced pressure and the residue was diluted with EtOAc (30 mL). The organic layer was washed successively with 10% HCl (15 mL), saturated NaHCO₃ (20 mL) and brine (20 mL), and then dried. The solvent was evaporated *in vacuo* and the residue was used in the next step without further purification.

The crude product was poured slowly into concentrated H₂SO₄ (10 mL) and the solution heated at 60 °C for 1 h. After being cooled at room temperature, the mixture was poured into water (50 mL) and extracted with ether (3x50 mL). The organic layer was washed with 10% NaHCO₃, dried and evaporated. The residue was purified by column chromatography (ether/petroleum ether 2:8) to afford **1f** (1.3 g, 60%) as a white solid, mp 66–68 °C.

IR (KBr): ν 1701, 1595, 1253, 1086, 851 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 1.28 (3H, d, J 7.0 Hz), 2.62–2.72 (2H, m), 3.27–3.40 (1H, m), 3.87 (3H, s), 6.85–6.90 (2H, m), 7.67 (1H, d, J 8.8 Hz); ¹³CNMR (50 MHz, CDCl₃): δ 16.6, 35.1, 42.2, 55.7, 109.7, 115.4, 125.7, 129.6, 156.5, 165.4, 207.8.

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

3-Cyclopropyl-6-methoxy-2-methyl-1H-indene (3f).

To magnesium turnings (0.23 g, 9.8 mmol) in dry THF (8 mL), a solution of cyclopropyl bromide (0.78 mL, 9.8 mmol) in dry THF (5 mL) was added dropwise

with mild reflux. After the addition was completed, a solution of ketone **1** or **1f** (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 was added (20 mL) at 0°C and the mixture was extracted with ether (3x20 mL). The combined organic solutions were dried and evaporated. The residue was purified by column chromatography (CH₂Cl₂/petroleum ether 3:7) to yield **3e** or **3f**.

Compound **3e** :

white solid (0.72 g, 79%), mp 42–45°C.

IR (KBr): ν 3447, 2960, 1604, 1258, 1073, 1015, 820 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 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); ¹³C NMR (100 MHz, CDCl₃): δ 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.

Compound **3f**:

colourless oil (0.74 g, 76%).

IR (film): ν 3000, 2906, 1478, 1266, 1037, 809 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 0.62–0.67 (2H, m), 0.83–0.89 (2H, m), 1.57–1.63 (1H, m), 2.12 (3H, s), 3.22 (2H, s), 3.82 (3H, s), 6.81 (1H dd, J 8.4, 2.6 Hz), 6.97 (1H, d, J 2.6 Hz), 7.28 (1H, d, J 8.4 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 4.4 (2C), 7.3, 14.5, 42.7, 55.7, 10.1, 111.3, 119.0, 136.4, 138.3, 140.3, 144.1, 157.1.

PATHWAY C (Scheme 19 in Results and Discussions).

4-(5-Methoxy-indan-1-ylidene)-5-methyl-3,4-dihydro-2H-pyrrole (7e).

4-(5-methoxy-2-methylindan-1-ylidene)-5-methyl-3,4-dihydro-2H-pyrrole (7f).

To a stirred and cooled (0 °C) solution of triflic acid (115 mL, 1.3 mmol) in CH₃CN (2 mL), a solution of indene **3e** or **3f** (1.3 mmol) in CH₃CN (1 mL) was added dropwise. The reaction mixture was slowly warmed to room temperature and stirring was continued for 3 h, before quenching with 10% NaOH (5 mL). The aqueous phase was extracted with DCM (3x10 mL) and the combined organic phases were dried and

concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc containing 2% Et₃N) to give **7e** or **7f**.

Compound **7e**:

brown solid (0.24 g, 81%), mp 58–60°C.

IR (KBr): ν 3434, 2921, 1583, 1293, 1248, 1024 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.37 (3H, m), 2.88–2.92 (2H, m), 3.01–3.07 (2H, m), 3.10–3.16 (2H, m), 3.83 (3H, s), 3.91–3.99 (2H, m), 6.79 (1H, dd, J 8.4, 2.6 Hz), 6.84 (1H, d, J 2.6 Hz), 7.47 (1H, d, J 8.4 Hz); a positive NOE between signal at δ 2.37 (methyl at C-5 of pyrroline ring) and signal at δ 3.15 (hydrogens at C-20 carbon of indane nucleus) was detected as well as between signal at δ 7.47 (hydrogen at C-70 of indane nucleus) and signal at δ 2.91 (hydrogen at C-3 carbon of pyrroline ring).

¹³C NMR (100 MHz, CDCl₃): δ 21.2, 31.0, 31.1, 31.8, 55.5, 57.8, 109.9, 113.2, 126.0, 135.1, 139.7, 147.3, 150.8, 160.4, 173.2.

Compound **7f**:

brown solid (0.10 g, 35%), mp 61–63 °C.

IR (KBr): ν 3390, 2930, 1600, 1583, 1486, 1249, 1031 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.15 (3H, d, J 6.8 Hz), 2.42 (3H, m), 2.56 (1H, d, J 16.0 Hz), 2.79 (1H, ddd, J 3.2, 8.0, 16.8 Hz), 2.99 (1H, ddd, J 3.2, 8.0, 16.8 Hz), 3.19 (1H, dd, J 7.2, 16.0 Hz), 3.61–3.70 (1H, m), 3.82 (3H, s), 3.84–3.89 (1H, m), 3.95–4.47 (1H, m), 6.80 (1H, dd, J 8.4, 2.6 Hz), 6.85 (1H, d, J 2.6 Hz), 7.45 (1H, d, J 8.4 Hz); a positive NOE between signal at δ 1.10 (methyl at C-20 of indane nucleus) and signal at δ 2.56 (methyl at C-5 of pyrroline ring) was detected; ¹³C NMR (100 MHz, CDCl₃): δ 20.73, 23.96, 32.17, 36.88, 39.8, 55.4, 57.9, 110.6, 112.8, 126.5, 132.4, 133.9, 144.4, 148.5, 160.2, 171.9.

2-Fluoro-5-methoxy-2-methyl-indan-1-one (1g).

In a 25-mL oven-dried two-necked round-bottomed flask fitted with an argon bubbler, a rubber septum, and a magnetic stirring bar was placed 5 mL of freshly distilled THF containing **1f** (0.2g, 1.14mmol). The reaction flask was cooled to -78 °C and a solution of LHMDS (0.48g, 2.85mmol, 1.1eq) in 4ml THF was added. The mixture was then stirred for 10 min at -78 °C, warmed to -50 °C and stirred for an additional 45 min. A

solution of the NFSi (0.4g, 1.25mmol, 1.1eq) in 5 mL of THF was quickly added to the reaction mixture. The reaction was stirred at -50°C and monitored by HPLC. After 1h the reaction mixture was quenched by addition of aqueous NH₄Cl (3 mL), ether (10 mL) at -50 °C was added, and the solution was warmed to room temperature. The aqueous layer was extracted with ether (2x5 mL), the combined organic phases were washed with water (10 mL), brine (10 mL) and dried (MgSO₄), and concentrated. The residue was purified by column chromatography (DCM/petroleum ether 1:7) to give **1g** (0.17 g, 77%) as a yellow oil.

IR (film): ν 1710, 1596, 1264, 1086, 1076 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.6 (3H, d, J_{H-F} 22.8 Hz), 3.19-3.41 (2H, m), 3.89 (3H, s), 6.84 (1H, m), 6.93 (1H, dd, J 8.4, 2.4 Hz), 7.74 (1H, d, J 8.4 Hz), 7.29 (1H, d, J 8.4 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 21.9, 40.87, 55.84, 97.1, 109.88, 116.34, 126.67, 127.09, 153.06, 166.55, 199.08.

1-Cyclopropyl-2-fluoro-5-methoxy-2-methyl-indan-1-ol (3g)

To a solution of bromocyclopropane (0.12g, 1mmol, 0.93eq) in 2ml diethylether at -78°C under Argon was added, dropwise, tert-butyllithium (0.55ml of a 1.7M solution in pentane, 0.91eq). Diethylether (1ml) was then added and the mixture stirred for 1h at -78°C. A solution of **1g** (0.2g, 1.031mmol) in diethyl ether (2ml) was then added dropwise. The reaction was stirred for 4 hours at -78°C then water (2ml) was added; the mixture was allowed to warm to room temperature for 16h. The mixture was extracted with diethyl ether (5mlx2). The combined organic layers were dried over sodium sulphate, filtered and evaporated. The crude was chromatographed using silica gel eluting with (DCM/petroleum ether 7:3) to give **3g** (0.19 g, 78%) as a yellow oil.

IR (film): ν 1607, 1489, 1376, 1271, 1137, 1028, 832 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 0.25–0.45 (1H, m), 0.48–0.57 (3H, m), 1.22-1.33 (2H, m), 1.56 (3H, d, J_{H-F} 22.8 Hz), 3.12-3.20 (2H, m), 3.79 (3H, s), 6.75–6.79 (2H, m), 7.34–7.40 (1H, m); ¹³C NMR (100 MHz, CDCl₃): δ -0.78, 12.30, 19.34, 43.25, 55.47, 81.25, 105.56, 107.36, 110.50, 112.96, 124.82, 137.61, 142.13, 160.58.

4-(2-Fluoro-5-methoxy-2-methyl-indan-1-ylidene)-5-methyl-3,4-dihydro-2H-pyrrole (7g).

Pathway B was used: 1eq Tf₂O, ACN, room temperature for 30min.

Compound **7g**:

brown solid (0.10 g, 60%), mp 59–62 °C. ¹H NMR (400 MHz, CDCl₃): δ 1.75 (3H, d, J_H 19.2 Hz), 2.47 (3H, m), 2.81–3.10 (3H, m), 2.39–2.42 (1H, m), 3.75–3.79 (1H, m), 3.82 (3H, s), 3.61–3.92–4.10(1H, m), 6.75–6.83 (1H, m), 7.42 (1H, d, J 8.4 Hz; ¹³C NMR (100 MHz, CDCl₃): δ 21.51, 27.33, 35.07, 46.85, 55.48, 57.54, 109.99, 112.73, 113.45, 126.84, 128.44, 132.60, 135.21, 143.54, 160.49, 171.35.

General procedure for Epoxidation/dihydroxylation Procedure (13)

DMF (23 mL) and MnSO₄ (1.69 mg, 0.01 mmol) were placed in a 100 ml 3-neck flask, equipped with a magnetic stirrer. To this solution, the alkene **3f** (0.10 mol) was added all at once. The flask was then placed in a water bath at 20 °C. A 50 mL 2-neck flask equipped with a magnetic stirrer was placed into a water bath maintained at 1 °C, and charged with 17 mL of 0.2 M NaHCO₃ pH 8.0 buffer and 0.87 mL of 35% H₂O₂. The aqueous solution of buffer/peroxide was then added dropwise to the DMF solution over a period of 16 h via a cannula. After the reaction was complete, the product was extracted into diethyl ether (10mL x 4), washed with brine (20 mL), and dried (Na₂SO₄). The organic fraction was concentrated and the residue was purified by chromatography on silica gel with diethyl ether/petroleum (3:7) as eluent to give the desired product **13**.

1-Cyclopropyl-5-methoxy-2-methyl-indan-1,2-diol (13).

Yield: 33%, colorless oil.

¹H NMR(400 MHz, CDCl₃): δ -0.057–0.044 (1H, m), 0.25–0.51 (3H, m), 0.81–1.01 (2H, m), 1.49 (3H, s), 2.41 (1H, s, OH), 2.73 (1H, s, OH), 2.92 (2H, s), 3.77 (3H, s), 6.7–6.73 (2H, m), 7.21–7.26 (1H, m); ¹³C NMR (100 MHz, CDCl₃): δ -0.5, -0.2, 14.23, 15.47, 21.70, 44.96, 55.42, 82.93, 83.62, 110.42, 112.72, 125.68, 136.68, 141.44, 160.13.

3a-Cyclopropyl-6-methoxy-2,8a-dimethyl-8,8a-dihydro-3aH-indeno[1,2-d]oxazole (14)

See **Pathway C**: 1eq TfOH, ACN, r.t. 3h.

Yield: 70%, colorless oil.

^1H NMR(400 MHz, CDCl_3): δ 0.47–0.49 (3H, m), 0.64–0.69 (1H, m), 0.89-0.93 (1H, m), 1.55 (3H, s), 1.85 (3H, s), 3.11 (1H, d, J 17.6 Hz), 3.34 (1H, d, J 17.6 Hz), 3.77 (3H, s), 6.71(1H, d, J 2.8 Hz), 6.79(1H, dd, J 8.4 Hz), 7.33(1H, d, J 8.4 Hz); ^{13}C NMR (100 MHz, CDCl_3): δ 0.19, 1.05, 14.5, 15.34, 21.50, 45.51, 55.9, 83.16, 95.93, 109.39, 113.71, 125.77, 138.57, 140.39, 159.91, 163.69.

1-(3-Bromo-propylidene)-5-methoxy-2-methyl-1H-indene (16).

See preparation **4a**: HBr 15% in acetic acid, 1h r.t.

Yield: 35%, colorless oil.

^1H NMR (200 MHz, CDCl_3): δ 2.12 (3H, m), 3.28 (2H, q, J 7.0 Hz), 3.59 (2H, t, J 7.0 Hz), 3.82 (3H, s), 6.08 (1H, t, J 7.0 Hz), 6.41 (1H, s), 6.60 (1H, dd, J 8.4, 2.4 Hz), 6.73 (1H, d, J 2.4 Hz), 7.46 (1H, d, J 8.4 Hz). ESI MS m/z: 279.

5-Methoxy-1-oxo-indan-2-carboxylic acid methyl ester (17).

To a stirred solution of NaH (80% mineral oil, 33.4mmol) in 5ml dimethyl carbonate was added a solution of **1** (15.5mmol) in 14ml dimethyl carbonate. The mixture was refluxed at 80°C for 2h. After cooling to r.t., water (40ml) was added. The aqueous phase was separated and extracted with DCM (4x10ml). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The oily residue was subjected to chromatography (Ethyl Ether/ Petroleum 2/8) to yield **17** (14.26mmol, 92%) as a white solid. (m.p. 59-61°C).

IR (KBr): ν 3462, 2954, 1735, 1708 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3): keto-enol (42-58%) δ 3.37 (1H, dd, J 17, 8 Hz), 3.55 (0.42H, dd, J 17, 4 Hz), 3.73 (1H, dd, J 8.4 Hz), 3.76 (3H, s), 3.80 (3H, s), 3.85 (0.58, s, OH-enol), 6.70–6.72 (2H, m), 7.18–7.23 (1H, m); ^{13}C NMR (50 MHz, CDCl_3): δ 30.2, 32.4, 52.7, 53.1, 55.8, 120.7, 124.6, 124.7, 126.5, 126.8, 127.8, 129.3, 135.2, 135.4, 153.5, 169.5, 199.3.

3-(tert-Butyl-dimethyl-silanyloxy)-6-methoxy-1H-indene-2-carboxylic acid methyl ester (18).

17 (1g, 4.5mmol) in DMF (7ml) was added to a suspension of NaH (0.20g, 5.1mmol, 60% mineral oil) in DMF (6ml) at 0°C under Argon atmosphere. After stirring for 1h, TBDMSCl (0.76g, 5mmol) was added to the suspension, and the reaction mixture was stirred for 40min. The reaction mixture was poured into ice water and extracted with ethyl acetate (3x10ml). The organic layer was washed with sat. aq. NaCl, dried over Na₂SO₄ and concentrated *in vacuo*. The residue was chromatographed on silica gel (Ethyl Ether/ Petroleum 1/9) to give **18** as a colorless solid (92%, m.p. 44.5-45.0°C).

IR (KBr): ν 29.33, 2857, 1713, 1597, 1578, 1096, 869 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): 0.28 (6H, s), 1.08 (9H, s), δ 3.57 (2H, s), 3.77 (3H, s), 3.84 (3H, s), 6.93 (1H, dd, J 8.1, 2.4 Hz), 7.04 (1H, d, J 2.4 Hz), 7.32 (1H, d, J 8.1 Hz); ¹³C NMR (50 MHz, CDCl₃): δ -4.1, 18.7, 25.8, 34.3, 50.7, 55.4, 105.4, 112.5, 115.2, 125.0, 134.7, 142.1, 158.9, 160.5, 165.1.

3-(tert-Butyl-dimethyl-silanyloxy)-6-methoxy-1,1-dimethyl-1H-indene-2-carboxylic acid methyl ester (19).

BuLi (1.63mol/L, 2ml, 3.3mmol) was added to a solution of diisopropylamine (0.5ml, 3.56mmol) in dry THF (6ml), at room temperature under Argon atmosphere. To the solution, **18** (1g, 3mmol) in dry THF (7ml) was added dropwise over 30 min at -78°C. After stirring for 30min, iodomethane (0.2ml, 3.28mmol) was added to the solution and stirred for 30min. To the solution LDA (3.3mmol, prepared from BuLi and diisopropylamine) was added and stirred for 30min, and then iodomethane (0.2ml, 3.28mmol) was added and stirred for 30min. The reaction mixture was poured into sat. aq. NaCl and extracted with ethyl acetate. The organic layer was washed with sat. aq. NaCl, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was chromatographed on silica gel (Ethyl Ether/ Petroleum 2/8) to give **19** as a yellow solid (76%, m.p 108-110°C).

IR (KBr): ν 2950, 2861, 1692, 1565, 1064, 922 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): 0.23 (6H, s), 1.07 (9H, s), 1.44 (6H, s), δ 3.80 (3H, s), 3.83 (3H, s), 6.95 (1H, dd, J 8.1,

2.4 Hz), 7.00 (1H, d, J 2.4 Hz), 7.27 (1H, d, J 8.1 Hz); ^{13}C NMR (50 MHz, CDCl_3): δ - 4.1, 18.7, 24.8, 25.8, 46.0, 50.3, 55.4, 105.8, 115.5, 121.9, 122.2, 138.9, 147.1, 158.9, 159.4, 164.8.

6-Methoxy-1,1-dimethyl-3-oxo-indan-2-carboxylic acid methyl ester (20).

BF_3 etherate (4.1mmol) was added to a solution of **19** (1g, 2.75mmol) in CHCl_3 (10ml) at 0°C under Argon atmosphere and stirred for 4.5h. Then, the reaction mixture was poured into sat.aq. NaHCO_3 and extracted with ethyl acetate (3x20ml). the organic layer was washed with sat. aq. NaCl , dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica gel (Ethyl Ether/ Petroleum 2/8) to give **20** as a mixture of keto and enol forms (7/3) (90%, m.p $56\text{-}60^\circ\text{C}$). IR (KBr): ν 2977, 2947, 1654, 1577, 1081 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3): 1.33 (3H, s), 1.54 (3H, s), 3.50 (1H, s), 3.75 (3H, s), 3.84 (3H, s), 6.86 (1H, dd, J 8.1, 2.4 Hz), 6.94 (1H, d, J 2.4 Hz), 7.72 (1H, d, J 8.1 Hz); ^{13}C NMR (50 MHz, CDCl_3): δ 24.7, 26.1, 42.1, 52.0, 55.6, 65.8, 105.0, 124.2, 125.0, 135.5, 155.2, 159.8, 169.5, 199.5.

6-Methoxy-1,1,2-trimethyl-3-oxo-indan-2-carboxylic acid methyl ester (21).

A mixture of **20** (1.3g, 5.2mmol) and K_2CO_3 in dry acetone (90ml) was heated to reflux for 30 min. Mixture was cooled at 0°C and iodomethane (0.65ml, 10.48mmol) was added dropwise. The heterogeneous reaction was refluxed overnight. Acetone was removed *in vacuo* and water (20ml) was added. Aqueous phase was extracted with ethyl ether (2x20ml) and the organic layer dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was subjected to chromatography (Ethyl Ether/ Petroleum 3/7) to give **21** (80%).

^1H NMR (200 MHz, CDCl_3): 1.22 (6H, d, J 4.6 Hz), 1.33 (3H, s), 3.53 (3H, s), 3.83 (3H, s), 6.86-6.88 (2H, m), 7.60 (1H, d, J 8.2 Hz); ESI MS m/z : 263.

5-Methoxy-2,3,3-trimethyl-indan-1-one (22).

21 (0.9g, 3.44mmol) and LiI (0.5g, 3.8mmol) were dissolved in 5ml wet DMF and the solution was heated to 170°C for 15 min under microwave irradiation (CEM apparatus, 200watt). Brown solution was cooled at room temperature and water (50ml)

was added. The mixture was extracted with ethyl ether (4x20ml). Organic layer dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The crude product was subjected to chromatography (Ethyl Ether/ Petroleum 3/7) to give **22** (85%).

¹H NMR (200 MHz, CDCl₃): 1.16 (6H, m), 1.42 (3H, s), 3.89 (3H, s), 6.85-6.90 (2H, m), 7.64 (1H, dd, J 8.2, 1 Hz); ESI MS m/z : 205.

5-Methoxy-3,3-dimethyl-indan-1-one (23).

(85%, yellow solid, m.p 45-50°C)

IR (KBr): ν 2977, 2947, 1654, 1577, 1081 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): 1.39 (6H, s), 2.56 (2H, s), 3.89 (3H, s), 6.85-6.90 (2H, m), 7.63 (1H, d, J 9); ¹³C NMR (50 MHz, CDCl₃): δ 29.98, 38.47, 107.141, 114.98, 125.29, 128.77, 165.59, 166.89, 204.19. ESI MS m/z : 191.

3-Cyclopropyl-6-methoxy-1,1,2-trimethyl-1H-indene (24).

See preparation **4a**. the Reaction was performed using 4eq cyclopropylmagnesium chloride.

colourless oil (0.74 g, 76%).

IR (film): ν 3000, 2906, 1478, 1266, 1037, 809 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 0.62–0.67 (2H, m), 0.83–0.89 (2H, m), 1.57–1.63 (1H, m), 1.49 (6H, s), 2.12 (3H, s), 3.82 (3H, s), 6.81 (1H dd, J 8.4, 2.6 Hz), 6.97 (1H, d, J 2.6 Hz), 7.28 (1H, d, J 8.4 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 4.4 (2C), 7.3, 14.5, 26.8 (2C), 42.7, 55.7, 10.1, 111.3, 119.0, 136.4, 138.3, 140.3, 144.1, 157.1.

tert-Butyl-(5-methoxy-2,3,3-trimethyl-3H-inden-1-yloxy)-dimethyl-silane (26).

To a stirred solution of **22** (1.5g, 7.35mmol) and lutidine (6.1ml, 44.1mmol) in dry DCM (20ml) at 0°C, TBMS-triflate was added dropwise. The resulting solution was stirred r.t. 2h then water (50ml) was added. The mixture was extracted with petroleum ether (4x20ml). Organic layer dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The crude product was subjected to chromatography (Ethyl Ether/ Petroleum 1/20) to give **26** (65%).

^1H NMR (200 MHz, CDCl_3): 0.16 (6H, s), 1.05 (9H, s), 1.19 (6H, s), 1.76 (3H, s), 3.82 (3H, s), 6.74 (1H, dd, J 8.2, 1 Hz), 6.76 (1H, d, J 1 Hz), , 6.9 (1H, d, J 8.2 Hz); ESI MS m/z : 319.

2-Hydroxy-5-methoxy-2,3,3-trimethyl-indan-1-one (27).

To an acetonitrile solution (1.5 mL) of **26** (0.2 mmol) was added an aqueous Na_2EDTA solution (1 mL, $4 \cdot 10^{-4}$ M). The resulting homogeneous solution was cooled to 0°C , followed by addition of trifluoroacetone (0.2 mL) *via* a precooled syringe. To this homogeneous solution was added in portions a mixture of sodium bicarbonate (1.55 mmol) and Oxone (1 mmol) over a period of 1 h (pH 7). The reaction was complete in 2 h as shown by TLC. The reaction mixture was then poured into water (20 mL), extracted with methylene chloride (3 x 20 mL), and dried with anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the residue was shown to be pure **27** by ^1H NMR (99% yield, yellow oil).

^1H NMR (200 MHz, CDCl_3): 1.16 (3H, m), 1.24 (3H, m), 1.39 (3H, m), 2.8. (1H, broad, OH), 3.82 (3H, s), 6.87-6.92 (1H, m), 7.65-7.70 (1H, m). ESI MS m/z : 193.

5-Methoxy-2-methoxymethoxy-2,3,3-trimethyl-indan-1-one (28).

To a stirred solution of NaI (1.1g, 7.8mmol) and MOM-chloride (0.69ml, 9.1mmol) in 5ml dimethoxyethane was added a solution of **27** (0.4g, 1.82mmol) and DIPEA. The resulting solution was refluxed over night. The reaction mixture was poured into sat. aq. NaHCO_3 and extracted with ethyl acetate. The organic layer was washed with sat.aq. NaCl, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica gel (Ethyl Ether/ Petroleum 1/1) to give **28** as a yellow oil (76%).

^1H NMR (200 MHz, CDCl_3): 1.17 (3H, s), 1.35 (6H, m), 3.18 (3H, s), 3.88 (3H, s), 4.88 (2H, m) 6.87-6.92 (2H, m), 7.65-7.70 (1H, m).

1-Cyclopropyl-5-methoxy-2-methoxymethoxy-2,3,3-trimethyl-indan-1-ol (29).

See preparation **4a**,

82% yield, colorless oil. ^1H NMR (200 MHz, CDCl_3): 0.4-0.65 (4H, m), 0.97 (1H, m), 1.3 (3H, s), 1.35 (3H, s), 1.42 (3H, s), 3.45 (3H, s), 3.85 (3H, s), 4.67 (1H, m), 5.2 (1H, m), 6.87-6.92 (2H, m), 7.15-7.20 (1H, m).

3a-Cyclopropyl-6-methoxy-2,8,8,8a-tetramethyl-8,8a-dihydro-3aH-indeno[1,2-d]oxazole (30).

See **Pathway C**: 1eq TfOH, ACN, r.t. 3h.

62% yield, colorless oil. ^1H NMR(400 MHz, CDCl_3): δ 0.47–0.49 (3H, m), 0.64–0.69 (1H, m), 0.89-0.93 (1H, m), 1.18-1.20 (3H, m), 1.36-1.40 (6H, m), 1.81 (3H, m), 3.79 (3H, s), 6.71(1H, d, J 2.8 Hz), 6.79(1H, dd, J 8.4 Hz), 7.33(1H, d, J 8.4 Hz). ESI MS m/z : 387.

3-Cyclopropyl-6-methoxy-1,1-dimethyl-1H-indene (31).

See preparation **4a**. Grignard reaction was performed using 4eq cyclopropylmagnesium chloride.

colourless oil (82%, white solid, mp 45-50°C).

IR (film): ν 3000, 2906, 1478, 1266, 1037, 809 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 0.62–0.67 (2H, m), 0.83–0.89 (2H, m), 1.57–1.63 (1H, m), 1.49 (6H, s), 3.82 (3H, s), 5.82 (1H, s), 6.81 (1H dd, J 8.4, 2.6 Hz), 6.97 (1H, d, J 2.6 Hz), 7.28 (1H, d, J 8.4 Hz); ^{13}C NMR (100 MHz, CDCl_3): δ 4.4 (2C), 7.3, 26.8 (2C), 42.7, 48.5, 55.7, 10.1, 111.3, 119.0, 136.4, 138.3, 140.3, 144.1, 157.1.

1-Cyclopropyl-5-methoxy-3,3-dimethyl-indan-1,2-diol (32)

See General procedure for Epoxidation/dihydroxylation (see procedure for compound **13**).

Yield: 10%, colorless oil.

^1H NMR(400 MHz, CDCl_3): δ -0.057–0.044 (1H, m), 0.25–0.51 (3H, m), 0.81-1.01 (2H, m), 1.29 (3H, s), 1.32 (3H, s), 1.49 (3H, s), 2.41 (1H, s, OH), 2.73 (1H, s, OH), 3.77 (3H, s), 6.7–6.73 (2H, m), 7.21–7.26 (1H, m); ^{13}C NMR (100 MHz, CDCl_3): δ -

0.5, -0.2, 14.23, 15.47, 21.70, 24.96, 25.63, 55.42, 82.93, 83.62, 110.42, 112.72, 125.68, 136.68, 141.44, 160.13.

3-Cyclopropyl-6-methoxy-1,1-dimethyl-indan-2-one (33).

Compound **32** (1mmol) was dissolved in MeOH and a catalytic amount of *p*-toluenesulfonic acid was added (0.01mmol). Reaction was stirred 30 min r.t. and the solvent removed *in vacuo*. The residue was chromatographed on silica gel (Ethyl Ether/ Petroleum 1/9) to give **33** as a yellow oil (95%).

¹H NMR(400 MHz, CDCl₃): δ 0.27–0.30 (1H, m), 0.25–0.51 (3H, m), 0.81–1.01 (1H, m), 1.29 (3H, s), 1.32 (3H, s), 2.94 (1H, d, J 8.2Hz), 6.73–6.80 (2H, m), 7.31–7.34 (1H, m); ¹³C NMR (100 MHz, CDCl₃): 2.34, 2.57, 14.06, 25.42, 25.95, 49.64, 53.44, 55.41, 108.27, 113.31, 125.59, 130.92, 148.91, 159.69, 222.101.

3-Cyclopropyl-6-methoxy-1,1-dimethyl-indan-2-ol (35).

3-Cyclopropyl-6-methoxy-1,1-dimethyl-indan-2-one (33).

To a stirred solution of **31**(1mmol) in dry THF (5ml) was added BH₃:THF (1M in THF, 1.5ml) dropwise at 0°C. reaction was stirred over night r.t. and then placed in an ice bath and quenched with EtOH (1 ml). 30% H₂O₂ (aq.) (2 ml) and 1 M NaOH (aq.) (2 ml) were added and the mixture was allowed to warm and stirred for 12 h at room temperature. The mixture was transferred to a separating funnel and Et₂O was added (20 ml). The organic extracts were washed with 1 M NaOH (aq.), brine and then dried over MgSO₄. The solvent was removed *in vacuo* to afford alcohol **35** that was used in next reaction without further purifications.

35 was dissolved in methylene chloride (8 mL) and the solution was added to a solution of Dess-Martin periodinane (0.5 g, 1.2 mmol) in methylene chloride (10 mL) with stirring. After 20 min the homogenous reaction mixture was diluted with 50 mL of ether, and the resulting suspension was added to 20 mL of 1 M NaOH. After the mixture was stirred for 10 min, the ether layer was separated and dried over Na₂SO₄. Solvent was removed and the residue was chromatographed on silica gel (Ethyl Ether/ Petroleum 1/1) to give **33** as a yellow oil (49% over 2 steps). For NMR see above.

Acetic acid 3-cyclopropyl-6-methoxy-1,1-dimethyl-1H-inden-2-yl ester (34)

To a stirred solution of **33** (2mmol) in DCM was added pyridine (2.8mmol) and acetyl chloride (2.5mmol); the resulting solution was stirred for 48h. Reaction was washed with HCl 5% (2x10ml) and water (3x10ml) and then dried over sodium sulphate. Evaporation of the solvent and subsequent chromatography on silica gel (Ethyl Ether/Petroleum 3/7) to give **34** as a yellow oil (70%).

¹H NMR(400 MHz, CDCl₃): δ 0.61–0.64 (1H, m), 0.75–0.77 (3H, m), 1.22 (6H, s), 1.24–1.28 (1H, m), 2.29 (3H, s), 3.81 (3H, s), 6.80–6.83 (2H, m), 7.24–7.28 (1H, m); ¹³C NMR (100 MHz, CDCl₃): 1.8, 9.6, 23.3(2C), 39.9, 56.4, 111.2, 111.8, 115.8, 125.0, 126.9, 137.4, 147.4, 160.9, 167.2.

***E*-Acetic acid 6-methoxy-1,1-dimethyl-3-(2-methyl-4,5-dihydro-pyrrol-3-ylidene)-indan-2-yl ester (7I-OAc).**

Pathway C: 1eq TfOH, ACN, r.t. 30min.

82% brown oil. IR (film): ν 1702, 1600, 1576, 1291 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.21 (3H, s), 1.30 (3H, s), 2.02 (3H, s), 2.77–2.81 (1H, m), 2.98–3.05 (1H, m), 3.82 (3H, s), 3.98–4.05 (1H, m), 4.10–4.15 (1H, m), 6.15 (1H, s), 6.70 (1H, m), 6.82–6.85 (1H, m), 7.46 (1H, d, J 8.4 Hz). A positive NOE between signal at δ 2.28 (methyl at C-5 of 3,4-dihydro-2H-pyrrole) and signal at δ 6.15 (H on the C2' of indanylidene) was detected; ¹³C NMR (100 MHz, CDCl₃): δ 20.40, 20.57, 29.60, 32.70, 46.84, 55.48, 58.20, 81.97, 108.09, 113.01, 126.0, 131.81, 133.48, 138.64, 155.92, 160.79, 170.84, 170.97.

5'-Methoxy-2',2'-dimethyl-3-oxaspiro[bicyclo[3.1.0]hexane-2-indan]-4-one (39).

The reaction was carried out following Knochel and co-workers' procedure^[58] 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 **39** (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 δ 2.97 (major) and 2.81 ppm (minor) as well as δ 2.69 (minor) and 2.56 ppm (major) in the $^1\text{H-NMR}$ spectrum. (white solid, mp: 92-94 °C, 54%).

IR (KBr): ν 2960, 1756, 1607, 1495, 1468, 1305, 1266, 934 cm^{-1} ; $^1\text{H-NMR}$ (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); $^{13}\text{C-NMR}$ (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 (40).

A cooled ($>15^\circ\text{C}$) 1.0 M solution of HBr in acetic acid (5.6 mL, 5.6 mmol) was poured into a cooled ($>15^\circ\text{C}$) flask containing **39** (722 mg, 2.8 mmol) and stirring was continued for 1h. After evaporation of the solvent under vacuum, the residue was partitioned between H_2O (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_2SO_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 **40** (*Z/E* mixture, 881 mg, 93% yield) as a light brown oil.

IR (neat): ν 3099, 2927, 2851, 2651, 1716, 1605, 1488, 1262, 1032, 817 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3 , 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); $^{13}\text{C-NMR}$ (CDCl_3 , 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 **40** (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 Na₂SO₄. 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): ν 2959, 2922, 1743, 1605, 1488, 1262, 1032, 803 cm⁻¹; ¹H-NMR (CDCl₃, 200 MHz): δ (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); ¹³C-NMR (CDCl₃, 50 MHz): δ (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 (41).

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 24h, sodium azide (292 mg, 4.5 mmol) was newly added and the mixture was stirred at room temperature for additional 24h. 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 **41** (*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 (42).

A solution of **41** (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 **41** 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 μ L, 3.1 mmol) was added. After 5min a solution of acetyl chloride (220

μL , 3.1 mmol) in 2 mL of CH_2Cl_2 was added dropwise and the reaction mixture was stirred at 0°C . After 3h the reaction mixture was quenched with sat. aq. NaHCO_3 solution and extracted with CH_2Cl_2 . The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude residue was purified by flash column chromatography on silica gel (diethyl ether/ petroleum ether 6:4) affording **42** (*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} ; $^1\text{H-NMR}$ (CDCl_3 , 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 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); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ (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 (7m).

A trimethylsilyl polyphosphate (PPSE) solution, prepared by heating at reflux for 1.5h a mixture of P_2O_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 **42** (248 mg, 0.75 mmol). The reaction mixture was heated at reflux for 3h, cooled to room temperature, diluted with CH_2Cl_2 and quenched with H_2O . The aqueous layer was brought to $\text{pH}=9$ by treatment with 6N NaOH solution and extracted with CH_2Cl_2 (3x30 mL). The combined organic layers were washed with H_2O , dried over Na_2SO_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 **7m** (*Z/E* mixture, 108 mg, 46% yield) as a viscous dark yellow oil.

IR (neat): ν 2929, 1732, 1603, 1588, 1254, 1157, 1026 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (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); $^{13}\text{C-NMR}$ (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 (7m- $N^+\text{Me}$).

A solution of methyl trifluoromethanesulfonate (34 μL , 0.3 mmol) in anhydrous benzene (3 mL) was added under nitrogen atmosphere to a solution of **7** (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.

$^1\text{H-NMR}$ (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, 3H), 1.38 (s, 3H), 1.21 (s, 3H). $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ (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 (7m zwitter).

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_2O (9 mL) and the bright

yellow solution was cooled to 0°C by means of an ice bath. Then LiOH·H₂O (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 eluant). 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/ H₂O 7:3) to afford **7m zwitter** (*Z/E* mixture 90:10, 50 mg, 53% yield from **7m**) 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 indanylidene 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): ν 2962, 2925, 1635, 1584, 1262, 1094, 1028, 802 cm⁻¹; ¹H-NMR (CD₃OD, 400 MHz): δ 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); ¹³C-NMR (CD₃OD, 100 MHz): δ (*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.

SECTION A

Synthesis of *Z*-3-iodo-acrylic acid ethyl ester (**43**) [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 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 organic layer was separated and the aqueous layer extracted twice with ether (20 mL). The combined organic layers were treated with 3 M aqueous KOH (3 x 50 mL) until the aq. phase becomes neutral (pH 7), washed with brine (50 mL) and dried over MgSO₄. After rotary evaporation of the solvent, the residual brown oil was distilled (bp 62 °C) to give **43** (19.4 g, 86 % yield) as a yellow oil.

¹H-NMR (300 MHz, CDCl₃): δ= 7.36 (d, J= 8.9 Hz, 1H), 6.82 (d, J= 8.9 Hz, 1H), 4.18 (q, J= 7.1 Hz, 2H), 1.25 (t, J= 7.1 Hz, 3H). ¹³C-NMR (75 MHz, CDCl₃): δ= 164.9, 130.3, 95.0, 61.1, 14.6.

Synthesis of *Z*-3-iodo-prop-2-en-1-ol (**44**) [*J. Org. Chem.* **1993**, 58, 3148]

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 **43** 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 (2 x 20 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 **44** (8.05 g, 88 %) as a yellow oil.

¹H-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). ¹³C-NMR (75 MHz, CDCl₃): δ= 140.3, 83.0, 66.1.

Synthesis of *cis*-(2-iodo-cyclopropyl)-methanol (**45**) [*Tetrahedron Lett.* **1998**, 39, 8621]

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, 53mmol) 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 **44** (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 **45** (2.96 g, 62 %) as a yellow oil.

¹H-NMR (300 MHz, CDCl₃): δ= 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). ¹³C-NMR (75 MHz, CDCl₃): δ= 68.4, 18.0, 14.1, 10.0.

Synthesis of *cis*-2-iodo-cyclopropanecarboxylic acid (**46**) [J. Am. Chem. Soc. **1989**, *111*, 6729]

A 50 mL dry round bottomed flask equipped with a mechanical stirrer, a rubber septum and an argon gas inlet was charged with **45** (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 Et₂O (3 x 30 mL). The combined organic layers were washed with water (2 x 20 mL), brine, dried over Na₂SO₄, filtered, concentrated and purified by flash column chromatography on silica gel (pentane: Et₂O 1:1) affording **46** (3.34 g, 95 %) as a white crystals.(mp: 65 °C).

¹H-NMR (300 MHz, CDCl₃): δ= 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). ¹³C-NMR (75 MHz, CDCl₃): δ= 175.5, 19.3, 17.5, 14.3.

Synthesis of *cis*-2-iodo-cyclopropanecarboxylic acid ethyl ester (**37**) [J. Am. Chem. Soc. **1989**, *111*, 6729]

A mixture of **46** (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 **37** (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-ynylloxymethyl-benzene.

To a solution of prop-2-yn-1-ol (0.10 mol) in DMSO (6 ml) was added NaOH 3N (50 ml). The reaction was cooled to -10°C and benzylbromide (0.15mmol) was added dropwise. The resulting solution was allowed to rise 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 (3x30ml). The combined organic layers were washed with sat. NaCl, dried (Na₂SO₄), and concentrated. The residue was purified by flash column chromatography on silica gel (Ethyl Ether/ Petroleum 1/19) to give prop-2-ynylloxymethyl-benzene as a colorless oil (93%). (pentane: Et₂O 3:1) affording desired product (1.51 g, 70 %) as a yellow oil. ¹H NMR (200 MHz, CDCl₃): δ 2.46-2.43(1H, t); 4.16(2H,s); 4.61(2H, s)7.35-7.29(5H, m).

Vinyl-(*N*-methyliminodiacetoxy-*O,O'*)borane (56**).**

To a stirred solution of BH₃:SMe₂ (0.19g) in THF (10ml) at 0°C was added α-pinene(6.8g; δ 0.858) dropwise. The reaction was stirred at 0°C over night and then

cooled at -35°C . A solution of prop-2-ynylloxymethyl-benzene (0.35g; 2.38 mmol) in THF (10ml) 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 (1.9ml; δ 0.78) freshly distilled in THF (5ml) was added. The reaction was refluxed over night and then solvent was removed *in vacuo* to afford the crude **54**.

The crude **54** was dissolved in THF (10ml) and NaOH 1M (0.5ml) was added. Stirring was maintained for 1h rt; Et₂O was added and organic phase was separated and dried over Na₂SO₄ to afford **55** as crude. In a roundbottom flask equipped with a stir bar was charged with crude **55**, *N*-methyliminodiacetic acid (3 mmol), and benzene:DMSO (10:1, 10ml). 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).

¹H NMR (CDCl₃): δ 2.74(3H, s); 3.83(2H, d; J 16.6Hz); 3.99(2H, d; J 16.6Hz); 4.5(2H, s); 4.01(2H, m); 5.73-5.64(1H, dt; J 18 e J 1.7Hz); 6.29-6.20(1H, dt; J 18Hz, J 7.1Hz); 7.35-7.2(5H, m).

Ciclopropyl-(*N*-methyliminodiacetoxy-*O,O'*N)borane (57**).**

To a stirred solution of **56** (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 N₂. The crude reaction mixture was then poured into 12 mL of 0.5 M pH 7 sodium phosphate buffer and extracted with THF:Et₂O 1:1 (3 x 12 mL). The combined organic fractions were then washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. Purification by flash chromatography (SiO₂, Et₂O:CH₃CN 1:1) yielded **57** (0.34mmol, 96%).

^1H NMR (200 MHz, CDCl_3): δ -0.38 -0.40(1H,m); 0.445-0.42(1H, m); 0.67-0.66(1H, m); 1.25-1.23(1H,m); 2.8(3H, s); 3.84(2H, app dd $J = 17\text{Hz}$, 9.5Hz)3.96(2H, app dd $J = 17\text{Hz}$ e 3Hz); 4.01(2H,m); 4.5(2H,s); 7.35-7.2(5H, m)

3-benzyloxypropenylboronic-acid (47).

To a stirred solution of **57** (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 Et_2O (20 mL). The layers were separated and the aq. layer was extracted with THF: Et_2O 1:1 (40 mL). The combined organic fractions were dried over MgSO_4 and concentrated *in vacuo* to yield the desired cyclopropylboronic acid **47** as a colorless oil. (0.33mmol, 97%).

To a stirred solution of **57** (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 Et_2O (20 mL). The layers were separated and the aq. layer was extracted with THF: Et_2O 1:1 (40 mL). The combined organic fractions were dried over MgSO_4 and concentrated *in vacuo* to yield the desired cyclopropylboronic acid **47** as a colorless oil. (0.33mmol, 97%). Compound **47** was immediately used in next reaction without purifications and characterizations (very unstable).

3-(2-Benzyloxymethyl-cyclopropyl)-1H-indene (44).

To a stirred solution of **47** and **48** in toluene (4ml) was added a mixture of 3% di $\text{Pd}(\text{PPh}_3)_4$, Cs_2CO_3 (0.242g; 0.74mmoli) e $\text{KF}\cdot 2\text{H}_2\text{O}$ (0.209g; 2.22mmoli) e NaBr (0.0954g; 0.927mmoli). The reaction was heated to 80°C for 16h. The mixture was filtered with Et_2O (3x10ml) and washed with water. Organic phase was dried over Na_2SO_4 and evaporated. The final product was obtained after column chromatography (silica gel, petroleum/ethyl ether 25/1) of the crude. (30%).

^1H NMR (200 MHz, CDCl_3): δ 1.5-0.8(4H, m) 3.31(2H, m); 3.56-3.53(2H, m) 4.61(2H, s); 6.09-6.06(1H, m); 7.55-7.22(5H, 4H, m).

6-Methoxy-1,1-dimethyl-indan (61).

In a dry 50ml flask equipped with Ar-inlet, clean TiCl_4 (1.2ml, 11mmol) was mixed with 20 ml of dry CH_2Cl_2 . Upon cooling to -30°C , $\text{Zn}(\text{CH}_3)_2$ (11mmol, 4M CH_2Cl_2 solution) is slowly added via a syringe. The mixture being agitated with a magnetic stirrer. Stirring is continued for 10min. To the above stirred solution 6-methoxy-1-indanone (0.81g, 5mmol) in CH_2Cl_2 (3ml) was added at -30°C . The mixture was slowly allowed to come to rt during a period of 2h and then was poured onto ice water. The aqueous phase is extracted with ether and combined organic phase washed with H_2O and NaHCO_3 . after drying over MgSO_4 , the solvent was removed and the product was purified by flash column chromatography on silica gel (petroleum: Et_2O 20:1) affording **61** (65 %, colorless oil).

^1H NMR (200MHz, CDCl_3) δ 1.25 (6H, s), 1.93 (2H, t, J 7.4Hz), 2.83 (2H, t, J 7.4Hz), 3.81 (3H, s), 6.69-6.72 (2H, m), 7.08-7.12 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ , 29.2(2C), 39.1, 40.4, 46.2, 56.3, 110.8, 111.2 128.5, 129.6, 145.9, 158.8.

5-Methoxy-3,3-dimethyl-indan-1-one (23).

61 (1.40 mmol) was dissolved in 20 mL of dichloromethane, and oxidant (3.2 g, mixture 1/1 $\text{KMnO}_4/\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$) were placed in a 50 mL round-bottomed flask and stirred vigorously under gentle reflux. After 72 h, the product was filtered through a Celite pad and the residue washed successively with dichloromethane (3x20 mL) and ether (3x20 mL). The combined organic layers were washed with water (2 x 20 mL), brine, dried over Na_2SO_4 , filtered, concentrated and purified by flash column chromatography on silica gel (petroleum: Et_2O 8:2) affording **23** (69 %).(Characterization reported before).

Trifluoro-methanesulfonic acid 5-methoxy-3,3-dimethyl-3H-inden-1-yl ester (62).

To a stirred solution of **23** (1mmol) in 1,2-dichloroethane (5ml) 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 rt. 1,2-dichloroethane (10ml) was added and the organic phase was washed with HCl 5%

(3x10ml). Organic layers was washed with water (2 x 20 mL), brine, dried over Na₂SO₄, filtered, concentrated and purified by flash column chromatography on silica gel (petroleum: Et₂O 99:1) affording **62** (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-(5-Methoxy-3,3-dimethyl-3H-inden-1-yl)-acrylic acid ethyl ester (63).

To a slurry of Pd(OAc)₂ (0.17 mmol, 10%) in dry DMF (15 mL) was added a solution **62** (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 **63** as a pale yellow oil (77%).

¹H NMR (200MHz, CDCl₃) δ 1.36 (3H, t, J 7.2Hz), 3.84 (3H, s), 4.27 (2H, q, J 7.2Hz), 6.47 (1H, d, J 16.4Hz), 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 16.4Hz); ¹³C NMR (100 MHz, CDCl₃) δ 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 (64).

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 **63** (1 mmol) and palladium acetate (0.03 mmol) in CH₂Cl₂ (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 NaHCO₃ (15 mL). The aqueous layer was extracted with EtOAc (3x10 mL). The organic layers were washed with brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (petroleum: Et₂O 9:1) affording **64** (55 %).

¹H NMR (200MHz, CDCl₃) δ 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 7.2Hz), 3.86 (3H, s), 5.81 (1H, s), 6.77-6.82 (2H, m), 7.22 (1H, J 8.2Hz).

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

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

¹H NMR (400 MHz, CDCl₃): δ 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).

4.3 Abbreviations

Ac	Acetyl
ACN	Acetonitrile
DCM	Dichloromethane
DIPEA	N,N-Diisopropylethylamine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
KHMDS	Potassium Hexamethyldisilazane
LDA	Lithium diisopropylamide
LHMDS	Lithium Hexamethyldisilazane
<i>m</i> -CPBA	<i>meta</i> -Chloroperoxybenzoic acid
MOM	Methoxymethyl
Ms, MsO	Mesyl
NBS	<i>N</i> -bromosuccinimide- <i>succinimide</i>
NFSi	<i>N</i> -fluorobenzenesulfonimide
PCC	Pyridinium Chloro Chromate
PPSE	Trimethylsilyl polyphosphate
PTSA	<i>para</i> -Toluene sulfonic acid
Py	Pyridine
TBAF	tetra- <i>n</i> -Butylammonium fluoride
TBDMSCl	<i>tert</i> -Butyldimethylchlorosilane
<i>t</i> -BuOH	<i>tert</i> -Butanol
<i>t</i> -BuOK	Potassium <i>tert</i> -butoxide
TDA-1	Tris(2-(2-methoxyethoxy)ethyl)amine
TEA	Triethylamine
TFA	Trifluoroacetic acid
Tf, TfO	Triflate
THF	Tetrahydrofuran
TBMS	<i>tert</i> -Butyldimethylsilyl
Ts, TsO	Tosyl

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