Università degli Studi di Ferrara

DOTTORATO DI RICERCA IN

"SCIENZE FARMACEUTICHE"

CICLO XXIII

COORDINATORE Prof. Manfredini Stefano

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

Settore Scientifico Disciplinare CHIM/08

Dottorando

Dott. Farina Grazia

GraziaFarina

Tutore

Prof. Zanirato Vinicio

Anni (2008-2010)

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1. INTRODUCTION

1.1 Light

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

[1] Wayne, C.E.; Wayne, R.P., *Photochemistry*, **1996** ,Oxford University Press.
[2] Coxon, J.M.; Halton, B., *Organic Photochemistry*, **1987**, 2nd ed.; Cambridge University Press.
[3] Suginome, H., *CRC Handbook of Organic Photochemistry and Photobiology*; CRC Press, Inc: **1995**, p 825-840.

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

1.2 Photochromism

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

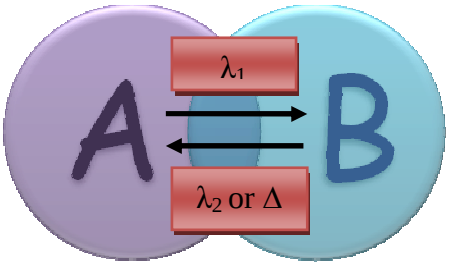

Figure **1**

The back reaction can occur thermally (*Photochromism of type T*) or photochemically (*Photochromism of type P*). In many systems, including spiropyrans, spirooxazines and chromenes, the back reaction is predominantly thermally driven, but in others the photochemically induced state is thermally stable and the back reaction must be driven photochemically, as in fulgides and

diarylethenes.[4] Change in color (or absorption spectrum) is one of the accompanying properties with the photochromic structural change. Usually (but not always) one isomer is colorless and thermally more stable than the colored counterpart. The greate difference in color of the isomers is required in order to achieve the highly biased ratio of the isomers at the photostationary states.[5]

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

1.3 Reversible photoisomerizable switches

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

[4] Bamfield, P.; Hutchings, M.G.; *Chromich Phenomena: Technological Applications of Colour Chemistry*, RSC Publishing, **2010**.
[5] Masako Saito, Yasushi Yokoyama, *Chiral photochemistry*, CRC Press, **2004**, p.235-259.
[6] a) Feringa, B., Ed. *Molecular switches*; Wiley-VCH: Weinheim, **2001**. b) Balzani, V.; Credi, A.; Venturi, M. *Molecular devices and machines*; Wiley-VCH:Weinheim, **2008**.

ions.[7] These photoreversible compounds (Figure **1**), where switching process is based on photochemically induced interconversion, are also called *Photoswitches*. The photochromic processes involved are typically *cis-trans* isomerization, photocyclization, photoinduced electron transfer and keto-enol tautomerism.

Molecular switches based on photochemical *E/Z* isomerization have been employed in different contexts to convert light-energy into "mechanical" motion at the molecular level.[8] Currently, the design and preparation of molecular switches based on photochemical *E/Z* isomerization constitutes an attractive research target to obtain novel materials for nanotechnology. Despite the fact that the inevitable condition of photochemical bistability is fulfilled in these systems, a number of other requirements are essential. These features are well illustrated in Figure **2** where a model reaction path for an efficient (Figure **2a**) and a less efficient (Figure **2b**) switch are reported.[9] 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

[7] Richmond, C.J.; Parenty, Alexis D.C; Song, Yu-Fei; Cooke, G.; Cronin, L., *J. Am. Chem. Soc*., **2008**, 130, 13059-13065.
[8] a) Sauvage, J.P., Ed. *Molecular Machines and Motors*; **2001**; Springer-Verlag, Berlin, London; Vol. 99. b) Drexler, K.E., *Nanosystems: Molecular Machinery, Manufacturing and Computation*; John Wiley & Sons: New York, NY, **1992**.
[9] Sampedro, D.; Migani, A.; Pepi, A.; Busi, E.; Basosi, R.; Latterini, L.; Elisei, F.; Fusi, S.; Ponticelli, F.; Zanirato, V.; Olivucci, M., *J. Am. Chem. Soc.*, **2004**, *126*, 9349-9359.

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).

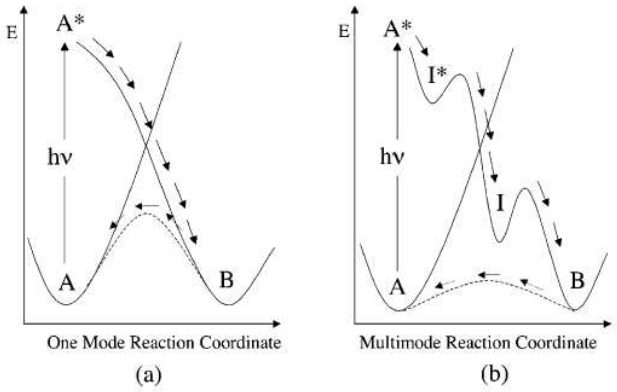

Figure **2**

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

An additional desirable property of photochemical switchers is the stability of the isomers A and B with respect to thermal (i.e., ground state) *Z/E* isomerization. As shown in Figure **2a** (see dashed energy profile), in an efficient switcher the barrier for thermal *Z/E* isomerization must be high enough to restrain the return of B to A and *vice versa*.

There are various classes of compounds that undergo reversible photoisomerisation. Many of these fit the criteria for efficient photoswitches and have been applied to biological systems. A few representative examples have been included below.

1.3.1 Diarylethene

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

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

[10] Irie, M., *Chiroptical Molecular Switches*, Wiley-VCH, Weinheim, **2001**.
[11] Takeshita, M.; Uchida, K.; Irie, M.; *Chem. Comm*., **1996**, 1807-1808.
[12] Uchida, K.; Nakayama, Y.; Irie, M., *Bull. Chem. Soc. Jpn.*, **1990**, 63, 1311.

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

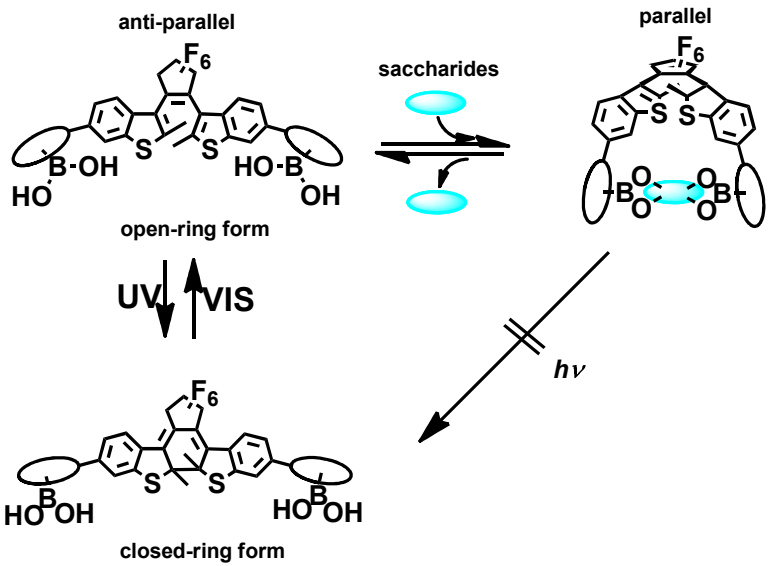

Figure **3**

1.3.2 Spiropyrane

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

These photoresponsive materials have found application as light filters (e.g. sun glasses) and as optical recording media; indeed,

numerous studies have been devoted to this class of photochromic compounds.[13]

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

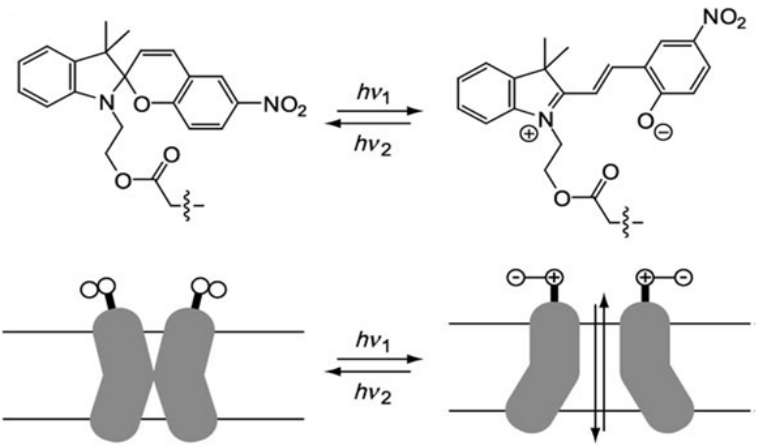

Figure **4**

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

[13] Feringa, B.L.; van Delden, R.A.; Koumura, N.; Geertsema, E.M.; *Chem. Rev.*, **2000**, 100, 1789-1816.

This system might be useful for the light-gated delivery of bioactive molecules.[14]

1.3.3 Azobenzene

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

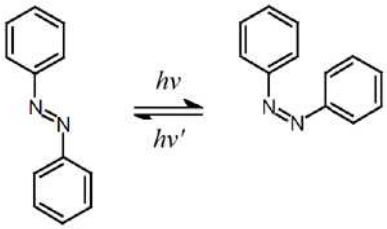

Figure **5**

Switches based on the *E/Z* photoisomerization of the azobenzene (Ab) chromophore have been used to control ion complexation,[15]electronic properties[16] and catalysis[17] or to trigger folding/unfolding of oligopeptide chains.[18]

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[14] Mayer, G.; Heckel, A.; *Ang. Chem., Int. Ed.*, **2006**, 45, 4900-4921.
[15] a) Shinkai, S.; Kusano, Y.; Manabe, O.; Nakaji, T.; Nishida, Y.; Ogawa, T.; *J. Am. Chem. Soc*., **1980**, 102, 5860-5865. b) Shinkai, S.; Minami, T.; Kusano, Y.; Manabe, O.; *J. Am. Chem. Soc.*, **1983**, 105, 1851-1856.
[16] Jousselme, B.; Blanchard, P.; Gallego-Planas, N.; Delaunay, J.; Allain, M.; Richomme, P.; Levillain, E.; Roncali, J.; *J. Am. Chem. Soc*., **2003**, 125, 2888-2889.
[17] Cacciapaglia, R.; Stefano, S.D.; Mandolini, L.; *J. Am. Chem. Soc*., **2003**, 125, 2224-2227.
[18] a) Bredenbeck, J.; Helbing, J.; Sieg, A.; Schrader, T.; Zinth, W.; Renner, C.; Behrendt, R.; Moroder, L.; Wachtveitl, J.; Hamm, P., *Proc. Natl. Acad. Sci. U.S.A.*, **2003**, 100, 6452-6457. b) Ulysse, L.; Cubillos, J.; Chmielewski, J.; *J. Am. Chem. Soc;*. **1995**, 117, 8466-8467. c) Sporlein, S.; Carstens, H.; Satzger, H.; Renner, C.;

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

Behrendt, R.; Moroder, L.; Tavan, P.; Zinth, W.; Wachtveitl, J.; *Proc. Natl. Acad. Sci. U.S.A.*, **2002**, 99, 7998-8002.

[19] Chambers, J.; Banghart, M.R.; Trauner, D.; Kramer, R.H., *J. Neurophysiol*, **2006**, 96, 2792-2796.

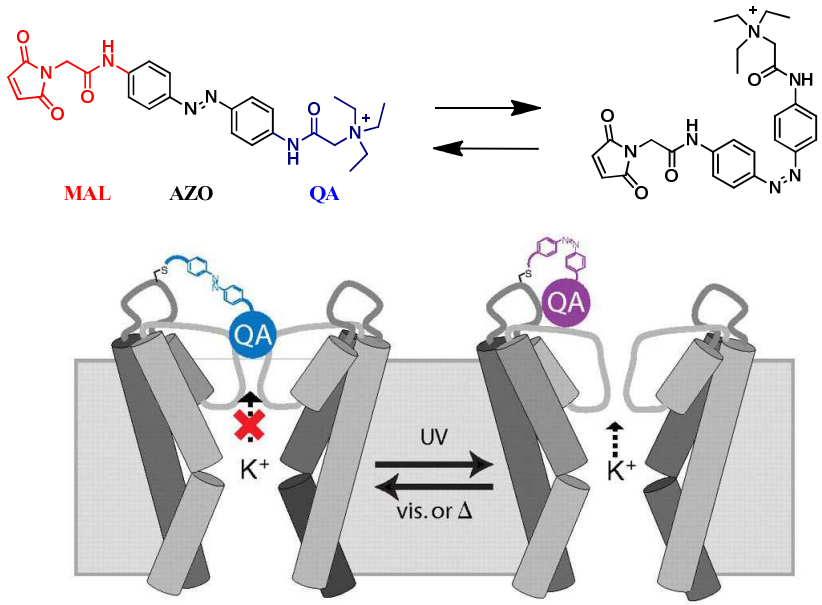


Figure **6**

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

1.3.4 Hemithioindigo

Although less well studied than azobenzenes, Hemithioindigos are appealing candidates as components of photoswitchable

biomolecules.[20] If compared to many azobenzene derivatives they isomerize at much longer wavelengths[21] and are stable over thousands of cycles. Hemithioindigo amino acid derivative consists of two chemical parts: hemithioindigo combined with a hemistilbene moiety (Figure **7**).

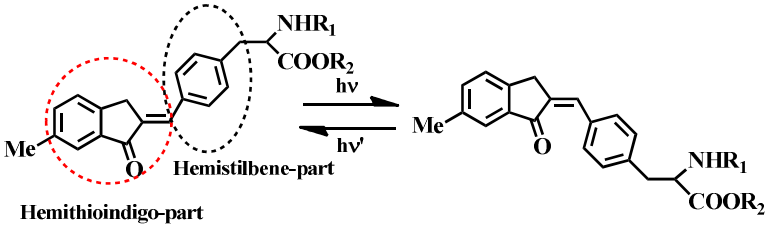


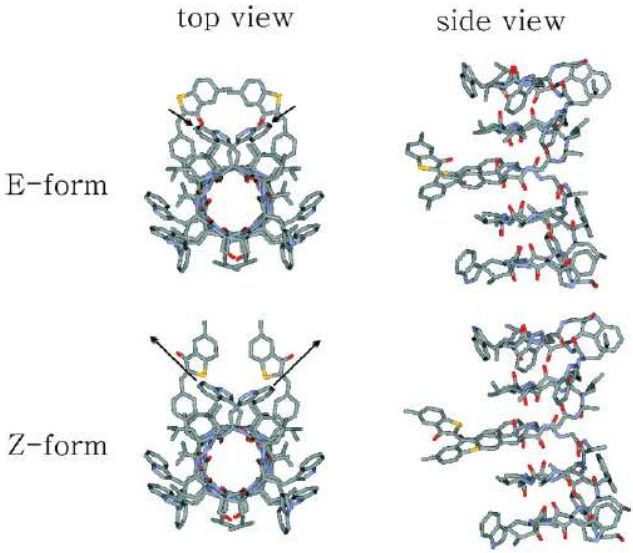
Figure **7**

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

A recent application of Hemithioindigo was described by Woolley *et al.*[22] They investigate the incorporation of Hemithioindigo chromophore into the peptide ion channel gramicidin. Photo-control

[20] Lougheed, T.; Borisenko, V.; Hennig, T.; Rück Braun, K.; Woolley, G.A.; *Org. Biomol. Chem.*, **2004**, 2, 2798-2801.
[21] Yamaguchi, T.; Seki, T.; Tamaki, T.; Ichimura, K.; *Bull. Chem. Soc. Jpn.*, **1992**, 65, 649–656.
[22] Lougheed, T.; Borisenko, V.; Hennig, T.; Rück Braun, K.; Woolley, G.A.; *Org. Biomol. Chem.*, **2004**, 2, 2798-2801.

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



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

Figure **8**

1.4 Photochromism in living system

1.4.1 Photoactive Yellow Protein (PYP)

Photoactive Yellow Protein (PYP) is a small water-soluble protein and a member of the xanthopsin photoreceptor family. PYP can be isolated from the purple phototropic eubacterium *Halorhodospira halophila*, and is presumed responsible for the initial steps of the homeostatic pathway that results in the negative phototaxis (the movement of an entire organism in response to light) of the bacterium to blue light. The availability of structural information for different functional states combined with the relatively simple photocycle, make PYP an ideal "laboratory" for the detailed study of biological light detection and the relation of structural change to protein function. It also holds considerable promise for optical data storage and computing applications. Indeed, in the past decade, PYP has become a model system for studying the photo-initiation and ensuing dynamics of photoreceptor proteins. The PYP protein domain consists of a single polypeptide chain of 125 residues, the Cys69 binds the p-coumaric acid chromophore via a thioester linkage (Figure **9**). The coumaroyl chromophore has one isomerizable double bond and one ionizable oxygen atom (phenolic oxygen, O4').

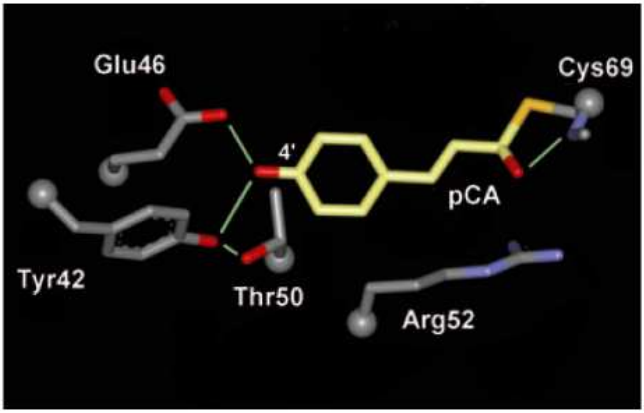


Figure **9**

In the dark state (PYP_{dark}), the double bond is in the *trans* form[23] and the *p*-hydroxyphenyl moiety is deprotonated. Hydrogen-bonding interactions with the Tyr42 and Glu46 side chains as well as the presence of the Arg52 guanidinium group intervene to stabilize the chromophore.[24] Schematic representation of the photochemistry relevant for the photocycle of PYP is shown in Figure **10**.

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

[23] a) Baca, M.; Borgstahl, G.E.; Boissinot, M.; Burke, P.M.; Williams D.R.; Slater, K.A.; Getzoff, E.D.; *Biochemistry*, **1994**, 33, 14369-14377. b) Kim, M.; Mathies, R.A; Hoff, W.D.; Hellingwerf, K.J.; *Biochemistry*, **1995**, 34, 12669-12672.
[24] Borgstahl, G.E.; Williams, D.R.; Getzoff, E.D.; *Biochemistry*, **1995**, 34, 6278-6287.

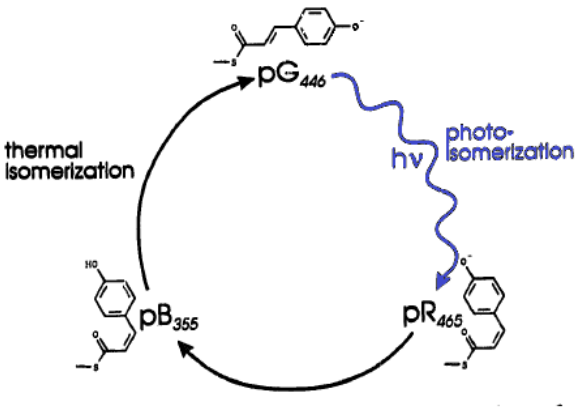


Figure **10**

In the dark, pR is subsequently converted to the long-lived intermediate pB (PYP_M), where the chromophore is in the *cis* configuration and protonated. Finally, pG is recovered in the last step of the photocycle.[25]

1.4.2 Rhodopsin

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

[25] Kort, R.H.; Vonk, X.Xu; Hoff, W.D; Crielaard, W.; Hellingwerf, K.J.; *FEBS Letters*, **1996**, 382, 73-78.

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

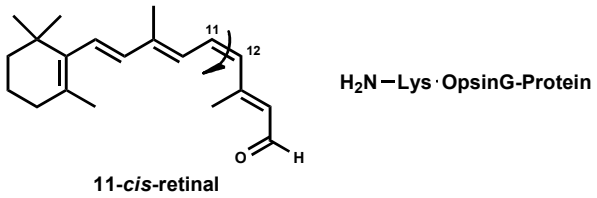


Figure **11**

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

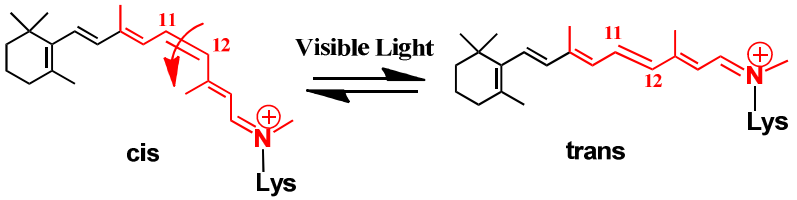


Figure **12**

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

[26] a) Bownds, D; *Nature*, **1967**, 216, 1178-1181; b) Wang, J.K.; McDowell, J.H.; Hargrave, P.A.; *Biochemistry*, **1980**, 19, 5111-5117.

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

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

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

[27] Lumento, F.; Zanirato, V.; Fusi, S.; Busi, E.; Latterini, L.; Elisei, F.; Sinicropi, A.; Andruniów, T.; Ferré, N.; Basosi, R.; Olivucci, M.; *Angew. Chem, Int. Ed*., **2007**, 46, 414-420.

[28] a) Klok, M.; *J. Am. Chem. Soc.*, **2008** ,130, 10484–10485. b) Roos, B.O.; *Adv. Chem. Phys.*, **1987,** Ed Lawley KP Wiley, New York, pp 399–446.

[29] Kandori, H.; Shichida, Y.; Yoshizawa, T.; *Biochemistry (Moscow),* **2001**, 66, 1483–1498.

2. DESIGN AND SYNTHESIS

2.1 Design and development of a Light-Driven *E*/Z Switcher

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

The high quantum yield associated with the ultrafast *cis/trans* isomerisation of C11-C12 double bond seems strictly connected to the complex chemical nature of the protein embedded chromophore.

The spectacular properties of rhodopsin inspired several computational studies devoted to understand the intimate nature of the chromophore excited state which is at the basis of the efficient photoisomerization process. These theoretical studies pointed out that a penta-2,4-dieniminium moiety is the minimal structure replicating the photochemical properties of the more complex natural pigment. As a result, it was expected that molecules featuring such a conjugated system could act as PSB11 models and could in principle

[30] Vreven, T.; Bernardi, F.; Garavelli, M.; Olivucci, M.; Robb, A. M.; Schlegel, H.B., *J. Am. Chem. Soc.*, **1997**, 119, 12687-12688.

behave as artificial molecular switches.[31]

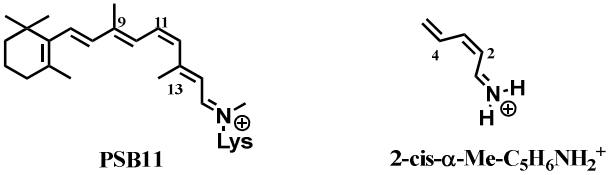


Figure **13**

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

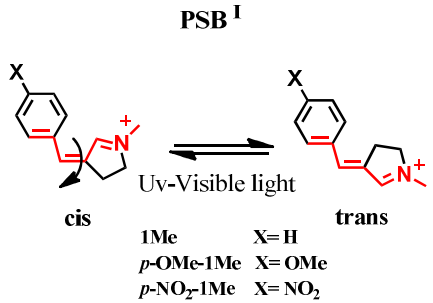


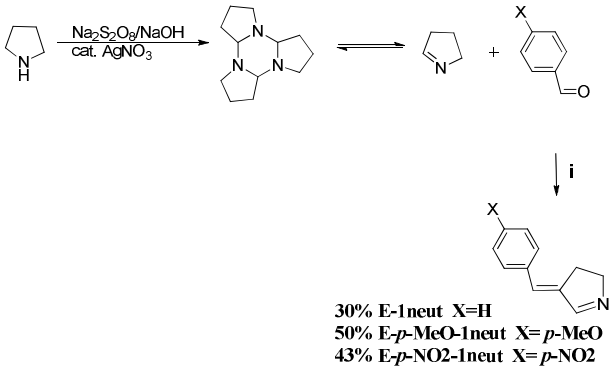
Figure **14**

The 3-benzylidene-1-pyrroline **1neut**, was prepared by an aldol-like condensation between 3,4-dihydro-2H-pyrrole (as a trimer) and benzaldehyde.[31]

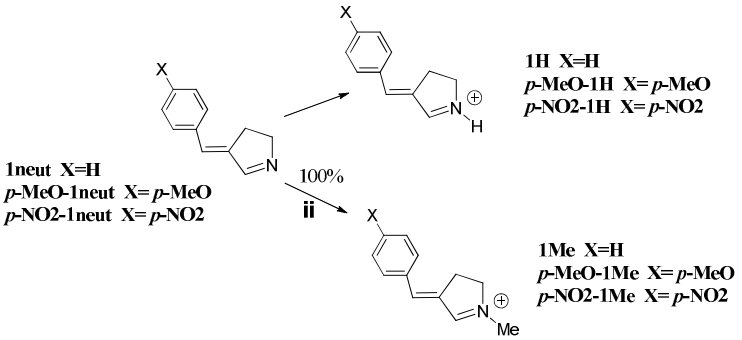
The desired poly-conjugated iminium ion **1H** (as a mixture of *E*- and *Z* isomers) was in turn obtained after treatment of **1neut** with

[31] Sampedro, D.; Migani, A.; Pepi, A.; Busi, E.; Basosi, R.; Latterini, L.; Elisei, F.; Fusi, S.; Ponticelli, F.; Zanirato, V.; Olivucci, M., *J. Am. Chem. Soc*, **2004**, 126, 9349-9359.

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



Reagents and conditions: (i) 1neut and *p*-MeO-1neut: MeOH, rt, 48h; *p*-NO_2-1neut: 0.6 M acetic acid/0.2 M sodium acetate, MeOH, 60°C, 24h.



Reagents and conditions: (ii) $CF_3SO_3CH_3$ benzene, rt, 10min.

Scheme **1**

The inductive effect of the methyl group in direction of the positively charged nitrogen atom could be at the basis of the observed major

stability of these salts with respect to the previously prepared protonated forms.

In addition to compound **1Me**, we synthesized ***p*-MeO-1Me** and ***p*-NO_2-1Me** (Scheme **1**) thus acceding to a class of molecular switches called PSB^I (first generation of PSBs). The presence of electron-releasing or electron withdrawing groups on the aromatic ring allowed the modulation of the electronic density within the π-system.

Even though these prototype compounds satisfied the general criteria required for a molecular switch, the quantum yields measured for their photoisomerization were too low. Responsible for the quite disappointing result we found the existence of competitive energy decay paths from the excited state, being the free rotation along the carbon-carbon single bond connecting the phenyl ring and the ethylene spacer the most important one.

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

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

[32] Zanirato, V.; Pollini, G.P.; De Risi, C.; Valente, F.; Melloni, A.; Fusi, S.; Barbetti, J.; Olivucci, M.; *Tetrahedron*, **2007**, 63, 4975–4982.

moiety conjugated to an aromatic ring which, differently from the PSB[I], is part of the rigid indanyl nucleus.

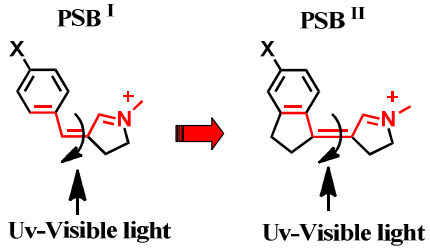


Figure **15**

We addressed **NAIP** switch (N-alkylated indanylidene pyrroline) through different pathways which will be discussed about later. The photochemical and spectral characterization of **NAIP** showed it was a biomimetic molecular switch.[33] As a matter of fact, **NAIP** switch in methanol solution displayed excited state very close to the one of Rh-embedded PSB11.

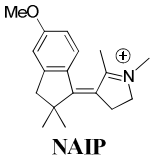


Figure **16**

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

[33] Lumento, F.; Zanirato, V.; Fusi, S.; Busi, E.; Latterini, L.; Elisei, F.; Sinicropi A.; Andruniow, T.; Ferré, N.; Basosi, R.; Olivucci, M., *Angew. Chem., Int. Ed.*, **2007**, 46, 414.

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

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

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

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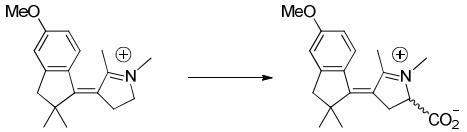
[34] Melloni, A.; Rossi Paccani, R.; Donati, D.; Zanirato, V.; Sinicropi, A.; Parisi, M.L.; Martin, E.; Ryazantsev, M.; Ding, W.J.; Frutos, L.M.; Basosi R.; Fusi, S.; Latterini, L.; Ferré, N.; Olivucci, M., *J. Am. Chem. Soc.*, **2010**, 132, 9310-9319.
[35] a) Hug, D.H.; O'Donnel, P.S.; Hunter J.K., *Photochem. Photobiol.*, **1980**, 32, 841-848; b) Aizawa, M.; Namba, K.; Suzuki, S., *Arch. Biochem. Biophys.*, **1977**, 180, 41-48; c) Mayer, G.; Heckel, A., *Angew. Chem., Int. Ed.*, **2006**, 45, 4900-4921.
[36] Kocer, A.; Walko, M.; Meijberg, W.; Feringa, B.L., *Science*, **2005**, 309, 755-758.
[37] Fölling, J.; Belov, V.; Kunetsky, R.; Medda, R.; Schönle, A.; Egner, A.; Eggeling, C.; Bossi, M.; Hell, S.W., *Angew. Chem., Int. Ed.*, **2007**, 46, 6266-6270.
[38] Angelini, N.; Corrias, B.; Fissi, A.; Pieroni, O.; Lenci, F., *Biophys. J.*, **1998**, 74, 2601-2610.



NAIP **NAIPzw**

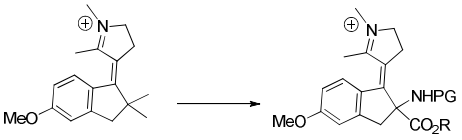
Scheme **2**

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

NAIPzw **NAIPzwaa**

Scheme **3**

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



NAIP **NAIPaa**

Scheme **4**

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

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

[39] Melloni, A; Rossi P., R.; Donati, D.; Zanirato, V.; Sinicropi, A.; Parisi, M.L.; Martin, E.; Ryazantsev, M.; Ding, W.J.; Frutos, L.M.; Basosi, R.; Fusi, S.; Latterini, L.; Ferré, N.; Olivucci, M., *J. Am. Chem. Soc*., **2010**, 132, 9310-9319.

that so frequently accompany research-work are reported in a chronological order.

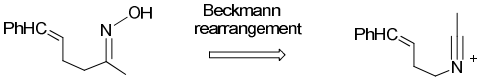
3. RESULTS AND CONCLUSIONS

3.1 Synthetic development of second generation molecular switches (PSB^{II})

A retrosynthetic analysis showed an intramolecular capture of nitrilium ion by a suitable located olefin group as a possible approach to the PSB^{II} formulation.

Scheme **5**

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



Scheme **6**

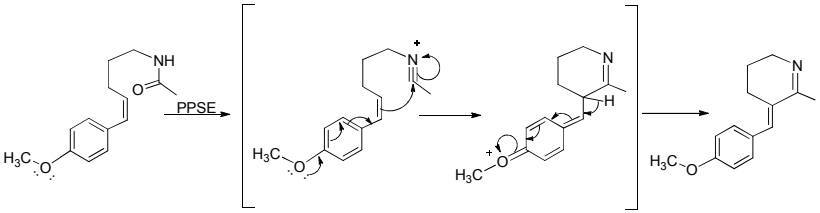
However, the synthetic applicability of this process is limited by the low stereospecificity: a single geometric isomer of the oxime is necessary to obtain a specific nitrilium ion.[42] Gawley[41] and

[40] a) Henninger, J.; Polborn, K.; Mayr, H., *J. Org. Chem.*, **2000**, 65, 3569; b) Al-Talib, M.; Zaki, M.; Hehl, S.; Stumpf, R.; Fischer, H.; Jochims, J.C., *Synthesis* **1996**, 1115; c) Jochims, J.C.; Glocker, M.O., *Chem. Ber.*, **1990,** *123*, 1537; d) Moustafa, A.H., *Synthesis*, **2003**, 837.

[41] Gawley, R.E.; Termine, E.J. , *J. Org. Chem* , **1984**, 49, 1946.

[42] Zanirato, V.; Pollini, G.P.; De Risi, C.; Valente, F.; Melloni, A.; Fusi, S.; Barbetti, J.; Olivucci, M., *Tetrahedron*, **2007**, 63, 4975-4982.

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



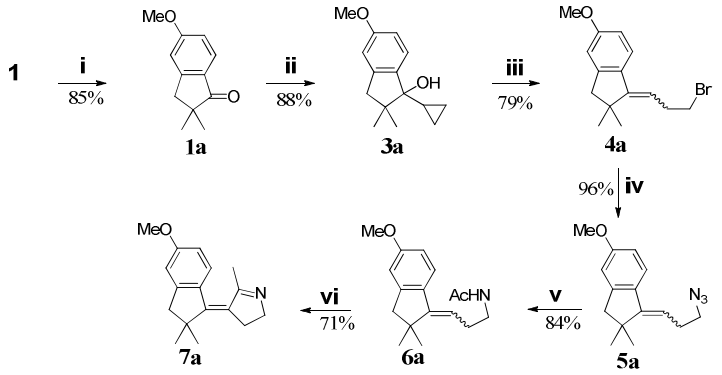
Scheme **7**

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

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

[43] a) Gawley, R.E.; Chemburkar, S.R., *Heterocycles*, **1989**, *29*, 1283. b) Marquart, A.L.; Podlogar, B.L.; Huber, E.W.; Demeter, D.A.; Peet, N.P.; Weintraub, H.J.R.; Angelastro, M.R., *J. Org. Chem.*, **1994**, 59, 2092.

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

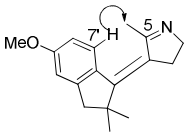


Reagents and conditions: (i) MeI, *t*BuOK, *t*BuOH, Et_2O, reflux, 7h; (ii) Mg, ciclopropylbromide, THF, reflux, 3h; (iii) HBr, AcOH, 10min; (iv) NaN_3, DMF, 60°C, 2.5h; (v) Lindlar catalyst, Ac_2O, NaOAc, 60psi H2, 6h; (vi) P_2O_5, HMDSO, CCl4, reflux, 2h.

Scheme **8**

[44] Chen, L.; Zhang, X.; Schultz, A., *Tetrahedron Lett.* **2002**, *43*, 4711.

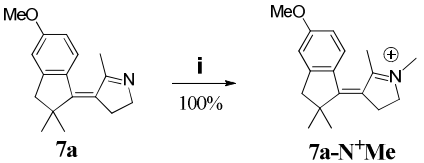
The ^{1}H NMR spectrum of compound **7a** showed the presence of two diastereomers in 98:2 ratio; the respective geometries have been assigned on the basis of NOE difference spectroscopy. In details, a positive NOE between the proton at the aromatic C-7' carbon (d, δ= 7.2) and the methyl at the C-5 of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



Z-7a

Scheme **9**

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



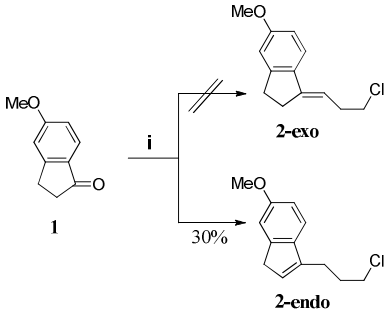
7a **7a-N$^+$Me**

Reagents and conditions: (i) $CF_3SO_3CH_3$, benzene, rt, 10min.

Scheme **10**

Concerning the above synthetic scheme we made the following considerations: a) the electron-releasing *p*-OMe group on the indanyl

moiety, in addition to greater the nucleophilicity of the styryl terminator, stabilized the carbocation intermediate in the key step; b) the geminal methyl groups at C-2 blocked the carbon-carbon double bond from the homoallylic rearrangement, in the exocyclic position.



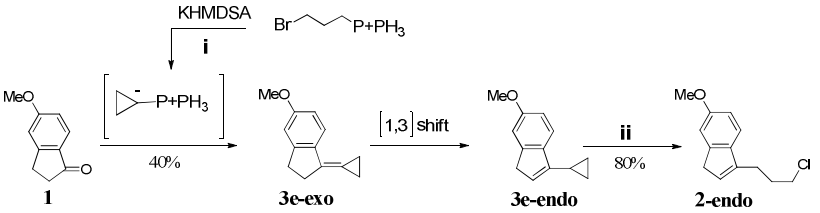
Reagents and conditions: (i) Mg, ciclopropylbromide, THF, reflux, 3h; HCl, AcOH, r.t., 30min.

Scheme **11**

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

[45] a) Dyker, G.; Hillebrand, G.; Ernst, L.; Dix, I.; Jones, P.G., *Liebigis Ann.*, **1996**, 1769-1771. b) Stafford, J.A.; McMurry, J.E., *Tetrahedron Lett.*, **1998**, *29*, 2531-2534.

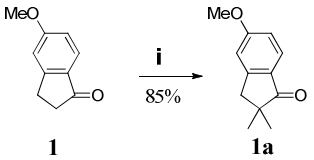
Thus, the desired **3-exo** product, formed in low yield, spontaneously isomerized to the **3e-endo** from which compound **2-endo** was eventually obtained through the usual rearrangement (Scheme **12**).



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

Scheme **12**

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

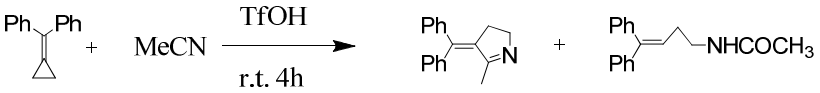


Reagents and conditions: (i) MeI, *t*BuOK, *t*BuOH, Et_2O, reflux, 7h;

Scheme **13**

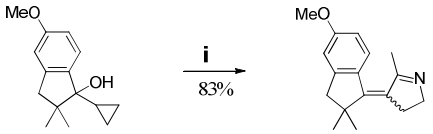
[46] Zanirato, V.; Pollini, G.P.; De Risi, C.; Valente, F.; Melloni, A.; Fusi, S.; Barbetti, J.; Olivucci, M., *Tetrahedron*, **2007**, 63, 4975-4982.

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



Scheme **14**

We realized that treatment of cyclopropylcarbinol **3a** with Tf_2O in the presence of acetonitrile could led "one-pot" to **7a** (Scheme **15**).



3a **7a**

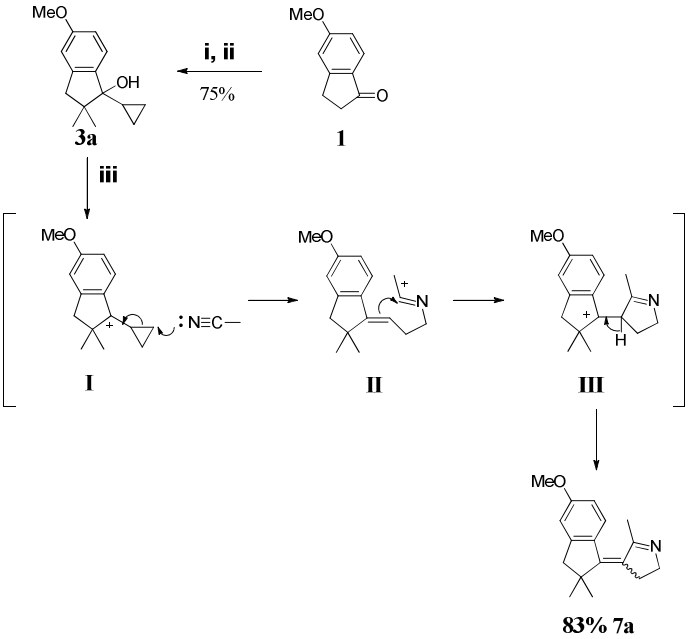
Reagents and conditions:(i) Tf_2O, ACN, rt, 3h.

Scheme **15**

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

[47] Huang, J.W.; Shi, M., *Synlett*, **2004**, 2343.

We were delighted to find that following the "one-pot" protocol carbinol **3a** gave compound **7a** in satisfactory yield (62% over three steps) together with traces of the amide **6a**.



Reagents and conditions: (i) MeI, *t*BuOK, *t*BuOH, Et_2O, reflux, 7h; (ii) Mg, ciclopropylbromide, THF, reflux, 3h; (iii) Tf_2O, ACN, r.t., 3h.

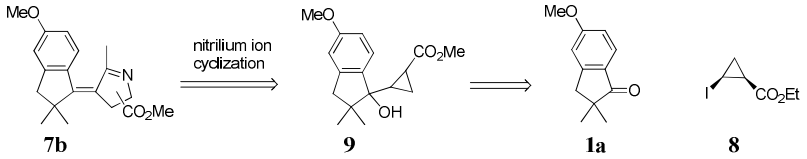
Scheme **16**

3.2 Synthesis of zwitterionic switch (NAIPzw).

In a formal way, the desired switch **7bzw** contemplates the substitution of an hydrogen atom at C-2 of **7aN$^+$Me** with a carboxyl group. For its preparation we reasoned on the possibility to fit the previous approach based on the fruitful chemistry of cyclopropyl

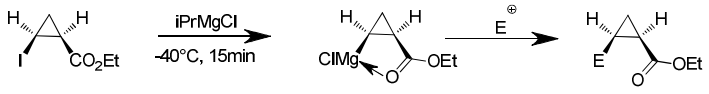
reagents. It was apparent as a facile synthetic solution the use of a properly functionalized cyclopropyl magnesium reagent in the initial synthetic step.

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



Scheme **17**

Inspection of literature disclosed us that the preparation of the specific Grignard reagent we had to use had already been described by Knochel *et al*.[48] They reported that a stabilized organometallic species was easily obtained by the metal-halogen exchange between *i*-PrMgCl and *cis*-2-iodocyclopropanecarboxylate. Thus, the in situ formed Grignard reagent was able to react with several kinds of electrophiles (Scheme **18**).



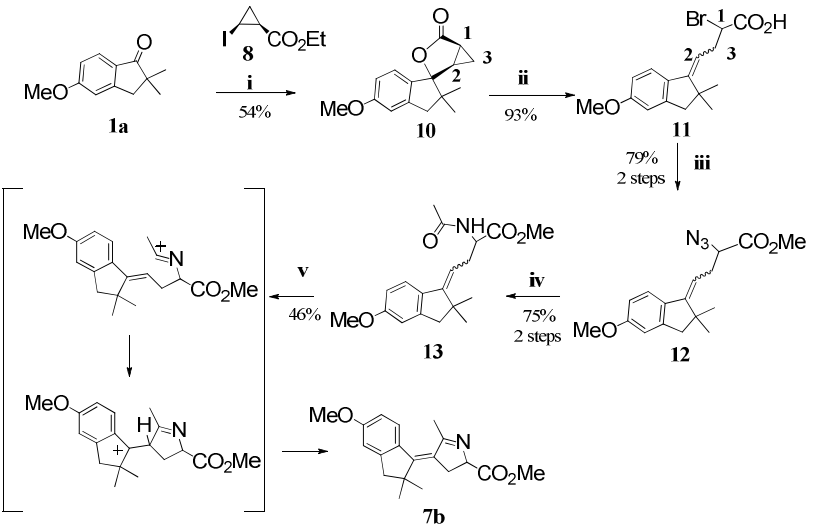
Scheme **18**

[48] Anh Vu, V.; Marek, I.; Polborn, K.; Knochel, P., *Angew. Chem, Int. Ed.*, **2002**, 41, 351-352.

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

We found that the nucleophilic addition of the cyclopropylmagnesium reagent derived from **8** to the carbonyl group of indanone **1a** took place with concomitant lactonization to the spiro compound **10**. On the latter, we made an attempt to do ring-opening/nitrilium ring-closing reaction by using the system TfOH/CH_3CN. Unexpectedly, compound **10** showed to be stable to the reaction conditions however, its exposure to the action of HBr/AcOH led to the α-bromo indanylidene carboxylic acid **11** as a 3:1 mixture of geometric isomers. The unpredictable result was in accord with the regioselective cyclopropyl ring-opening by the nucleophilic bromide.

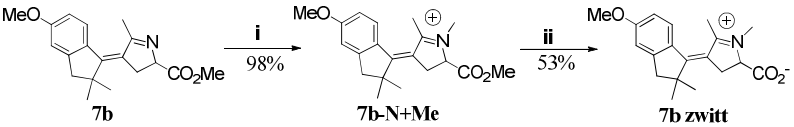
After restoration of the ester group with (trimethylsilyl)diazomethane, we passed to install the acetamido group by usual elaboration of the tethered bromo propylidene carbon chain. Thus, bromide displacement with sodium azide, reduction to primary amine and *N*-acetylation led in high yield to **13** (Scheme **19**). The latter, subjected to the action of PPSE afforded the desired free imine **7b**, subsequently transformed into the corresponding iminium triflate **7b-N$^+$Me** by *N*-alkylation with methyl triflate.



Reagents and conditions: (i) 1.2eq *cis*-2-iodo-cyclopropane carboxylic acid ethyl ester, 1.3eq *i*PrMgCl, THF, -40°C to r.t, 2h; (ii) HBr in AcOH (1M), >15°C, 1h; (iii) a: Me_3SiCHN_2, THF/MeOH, r.t., 2h; b: NaN_3, CH_3CN/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 **19**

To get the targeted zwitterion we proceeded effecting saponification of the methyl ester group with LiOH; after that, from the crude taken up in acetonitrile, lithium triflate spontaneously separed and the soluble fraction was purified by silica gel chromatography. The zwitterionic switch **NAIPzw** was isolated as a 9:1 mixture of Z/E isomers as inferred by NOE experiments.



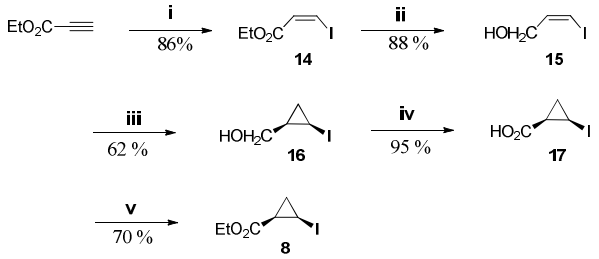
Reagents and conditions: (i) trifluoromethanesulfonate, toluene, rt, 10min; (ii) LiOH, THF/H_2O, rt, 3h.

Scheme **20**

Preparation of the *cis*-2-iodocyclopropanecarboxylate **8**.

Hydroiodic conjugate addition to ethyl propiolate gave stereoselectively compound **14** from which the allylic alcohol **15** was recovered after DIBAL-H reduction. The subsequent cyclopropanation gave the *cis*-2-iodo-cyclopropylmethanol **16** in good yield. The particular reagent $CF_3COOZnCH_2I$ was a powerful cyclopropanating medium with respect to the usual Simmon-Smith reagent.[49] Oxidation with PDC followed by esterification completed the preparation of compound **8** (for references and notes see Experimental Part).

[49] Yang, Z.; Lorenz, J.C.; Shi, Y., *Tetrahedron Lett.*, **1998**, 39, 8621-8624.



Reagents and conditions: (i) NaI, AcOH, 70 °C, 12h; (ii) DIBAL-H (2 equiv) -78 °C, 1h; (iii) Et_2Zn, CF_3COOH, CH_2I_2,-78°C to 0°C, 30 min; (iv) PDC, DMF, 25 °C, 24 h ; (v) $SOCl_2$, EtOH.

Scheme **21**

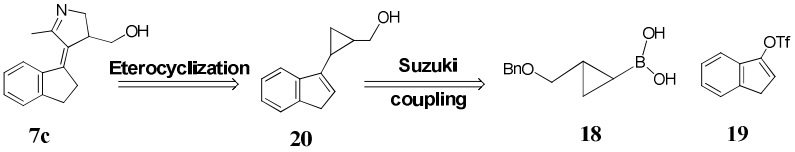
3.3 Exploring new synthetic routes to functionalized NAIPs.

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

focuses on organic synthesis exercises we put into practice in order to test the flexibility of the synthetic strategy we originally selected to approach the **NAIPs**.

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

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

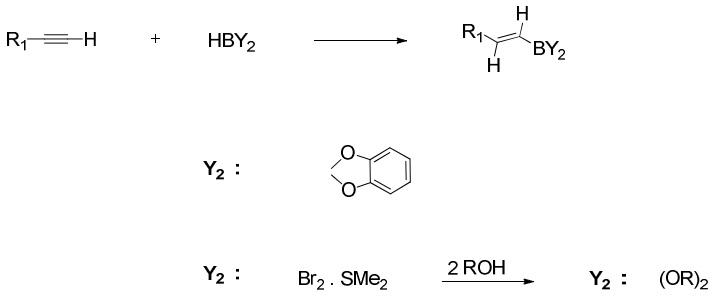


Schema **22**

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

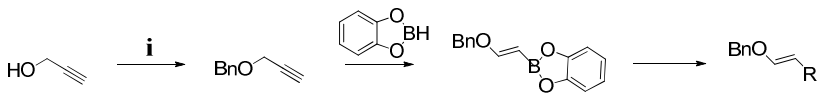
[50] Yao, M.L.; Deng, M.Z., *Tetrahedron Lett.*, **2000**, 41,9083-9087.

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



Scheme **23**

Our attempts to hydroborate different *O*-protected propargyl alcohols with 1,3,2-benzodioxaborole ("catechol-borane") were invariably unfruitful (Scheme **24**).

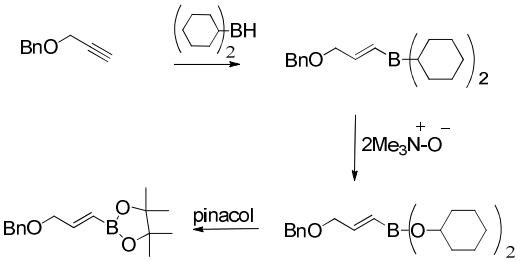


Reagent and conditions: (i) NaOH, DMSO, BzBr, 24h.

Scheme **24**

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

[51] a) Kamabuchi, A.; Moriya, T.; Miyaura, N.; Suzuki, A.; *Synth. Commun.*, **1993**, 23(20), 2851-2859. b) Hoffmann, R.W.; Dresely, S., *Synthesis*, **1988**, 103-106.

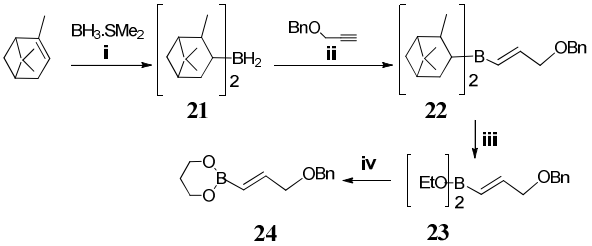


Scheme **25**

The in situ formed reagent, (from cyclohexene and BH_3.Me_2S) added *syn* stereoselectively to 3-benzyloxy propyne to give the corresponding alkenyl borane. The latter was oxidized to dicyclohexylboronate which transesterified with pinacol furnished the desired boronic ester. Despite the convenience of the one-pot protocol, we had some problems in the oxidative step. This operation entailed using the very expensive anhydrous trimethylamine oxide as the agent to selectively oxidize Csp^3-Boron bonds. We tried to get it from the commercially available dihydrate following a reported protocol,[52] but the result was rather unsatisfactory. In fact, we could accede to the alkenyl pinacol boronate only in low and not reproducible yields.

Suzuki and coworkers used $(Ip)_2BH$ (diisopinocampheylborane from BH_3.Me_2S and twice the equivalents of α-pinene at 0°C) for the synthesis of functionalized 1-alkenylboronates (Scheme **26**).

[52] Soderquist, J.A.; Anderson, C.L., *Tetrahedron Lett.*, **1986**, 27, 3961-3962.



Reagents and conditions: (i) BH_3**.**SMe_2, THF, 0°C, on; (ii) THF, -35°C, 4h; (iii) acetaldehyde at 0°C, then rfx, on; (iv) 1,3 propanediol, THF, 12h, r.t.

Scheme **26**

Although the main field of application of this borane reagent is the asymmetric hydroboration of alkenes, it has also been appreciated as hydroborating agent for alkynes. The inertness to many functional groups, as well as the high regioselectivity resulting from its bulkiness, and the final facile access to boronic esters under neutral conditions by the use of the inexpensive acetaldehyde in the oxidative step, were the attractive features $(Ip)_2BH$. Indeed, the hydroboration proceeded with high yield and excellent regioselectivity providing compound **22** which treated with acetaldehyde furnished the unstable diethyl boronate **23** eventually transesterified with 1,3 propanediol to **24**.

It is known that alkylboronic esters are readily hydrolysed by water or moist air and are consequently difficult to be purified. Instead, esters from diols show marked differences in their behavior towards water and are less rapidly hydrolysed. In particular the reactivity

strongly depends on the size of heterocycle,[53] being the 1,3,2-dioxaborinanes relatively stable. Unfortunately, we were incapable to produce pure compound **24** and consequently were discouraged to go on with the synthesis. However, once again we took comfort in literature.

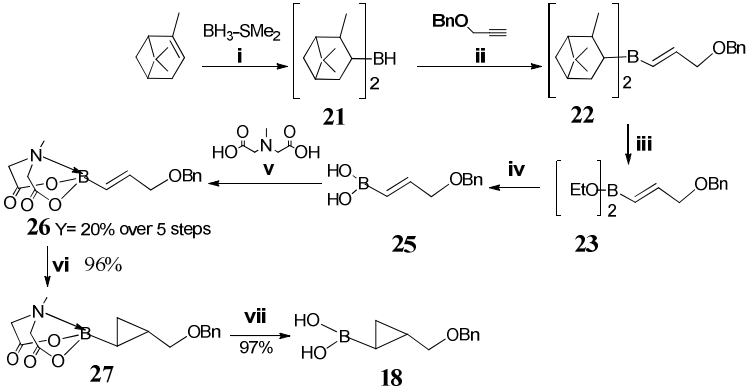
Burke *et al.*[54] envisioned an innovative approach for the attenuation of the boronic esters reactivity. The purpose of the authors was the preparation of an highly robust ligand for haloboronic acid suitable to take part to iterative Suzuki-Miyaura couplings. As a protective group, the N-methyliminodiacetic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

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

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

[53] Pietruszka, J.; Witt, A.; *Synlett*, **2003**, 1, 91-94.
[54] Gillis, E.P.; Burke, M.D., *J. Am. Chem. Soc.*, **2007**, 129, 6716-6717.

compound **26**. To this end, following a reported protocol,[55] the olefin was exposed to the carbene species resulting from the $Pd(OAc)_2$ catalyzed decomposition of diazomethane. Because of the impossibility to monitor the advances of the reaction by TLC we chose the analytical HPLC[56] technique.



Reagents and conditions: (i) $BH_3.SMe_2$, THF, 0°C, on; (ii) THF, -35°C, 4h; (iii) acetaldehyde at 0°C, then rfx, on; (iv) NaOH 1M, THF, 1h; (v) benzene/DMSO, Dean-Stark, rfx, on; (vi) $Pd(OAc)_2$, CH_2N_2, THF/Et_2O, 0°C, 40min; (vii) NaOH 1M, THF, 23°C, 20min.

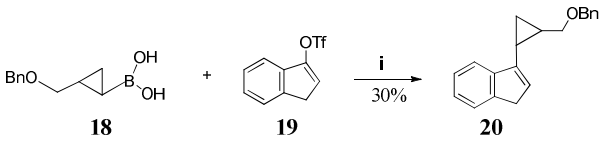
Scheme **27**

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

[55] a) Luithle, J.E.A.; Pietruszka, J., *J. Org. Chem.*, **1999**, 64, 8287-8297. b)Vangveravong, S.; Kanthasamy, A.; Lucaites, V.L.; Nelson, D.L.; Nichols, D.E., *J. Med. Chem*., **1998**, 41(25), 4995-5001.

[56] Viet Anh, V.; Marek, I.; Polborn, K.; Knochel, P.; *Angew. Chem., Int. Ed*., **2002**, 41, 351-352.

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

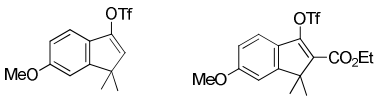


18 **19** **20**

Suzuki coupling: (i) $Pd(PPh_3)_4$, NaBr, Cs_2CO_5, $KF.2H_2O$, 80°C, 16h.

Scheme **28**

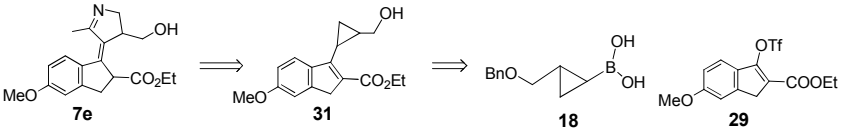
Considering the acidic nature of the indene a plausible cause for the abortion of the Suzuki coupling we turned our attention to the 3,3-dimethyl indenyl triflates **28** and **29** as suitable partners of the cyclopropyl boronic acid **18**.



28 **29**

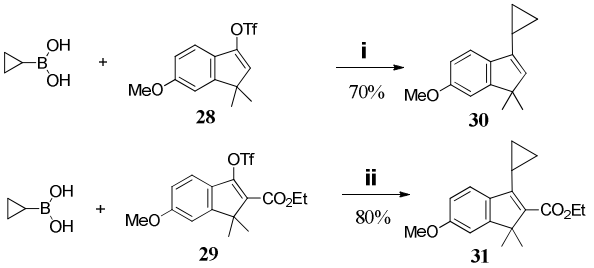
Scheme **29**

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



Scheme **30**

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



Suzuki coupling: (i) $Pd(PPh_3)_4$, NaBr, Cs_2CO_5, $KF.2H_2O$ (ii) $Pd(PPh_3)_4$, Toluene, $K_3PO_4.3H_2O$ T = 100 °C.

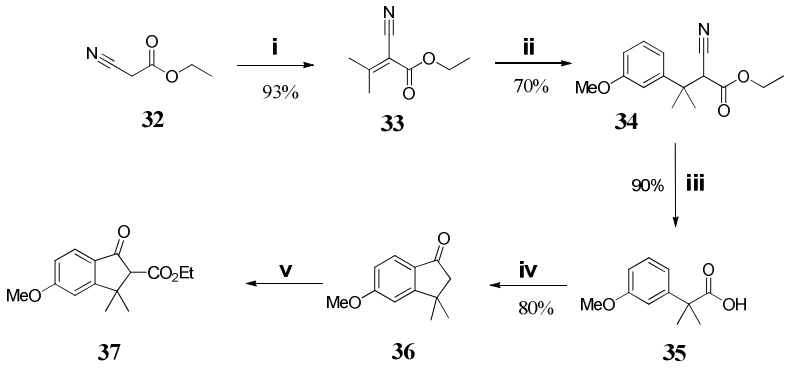
Scheme **31**

Preparation of the indanones **36** and **37**

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

[57] Rossi, R.; Bellina, F.; Ciucci, D.; Carpita, A.; Fanelli, C.; *Tetrahedron*, **1998,** 54, 7595-7614.
[58] Mosher, W.A.; Berger, P.W.; Foldi, A.P.; Gardner, J.E.; Kelly, T.J.; Nebel, C.; *J. Chem. Soc*., **1969**, 121-124.

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



Reagents and conditions: (i) Acetone, CH_3COOH, Phenylalanine, Benzene 130°C 12h, (ii) 3-Methoxyphenylmagnesiumbromide, CuI, Et_2O 60°C 12h; (iii) KOH, Ethylene glycol, 170°C 11h; (iv) Eaton's reagent, 115°C, 3h; (v) NaH, $(EtO)_2CO$, 80°C, 0.5 h.

Scheme **32**

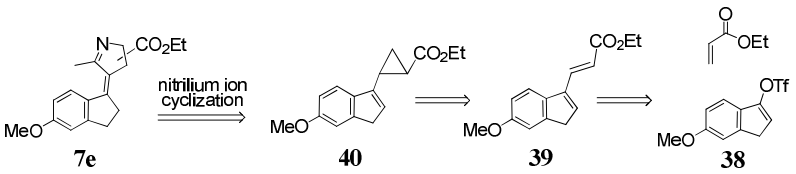
Although we were able to optimize the yield of Suzuki coupling, the excessive length and the costs of the synthesis towards the required

[59] Winstein, S.; Heck, R.F.; *J. Org. Chem*, **1972**, 37, 825-836.
[60] Premasagar, V.; Palaniswamy, V.A.; Eisenbraun E.J.; *J. Org. Chem*., **1981**, 46, 2974-2976.

cyclopropylboronic acid derivatives prompted us to explore a more convenient and straightforward access to functionalized **NAIPs**.

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

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



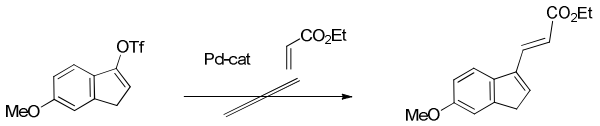
Scheme **33**

It is well known how alkenyl triflates can act as electrophilic partners of ethyl acrylate in the Heck coupling.[61] Thus, regioselective cyclopropanation of the adduct **39** would lead to the indenyl

[61] a) Yokoyama, Y.; Takahashi, M.; Takashima, M.; Kohno, Y.; Kobayashi, H.; Katoaka, K.; Shidori, K.; Murakami, Y.; *Chem. Pharm. Bull* , **1994**, 42, 832-838. b) Cappelli, A.; Anzini, M.; Vomero, S.; Canullo, L.; Mennuni, L.; Makovec, F.; Doucet, E.; Hamon, M.; Menziani, M.C.; De Benedetti, P.G.; Bruni, G.; Romeo, M.R.; Giorgi, G.; Donati, A.; *J. Med. Chem.*, **1999**, 42 (9), 1556-1575. c) Malapel-Andrieu, B.; Mérour, J.Y.; *Tetrahedron*, **1998**, 54, 1079-11094. d) Stadler, A.; Henrik von Schenck; Vallin, Karl S.A; Larhed, M.; Hallberg, A.; *Adv. Synth. Catal.* **2004**, 346, 1773–1781.

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

We found the planned Heck reaction between **38** and ethyl acrylate (3 eq.) by using $PdCl_2(PPh_3)$ (0.1eq), TEA (3eq.), in DMF at 80°C was unproductive and led in a few minutes (TLC analysis) to complete degradation of the starting material.



38 **41**

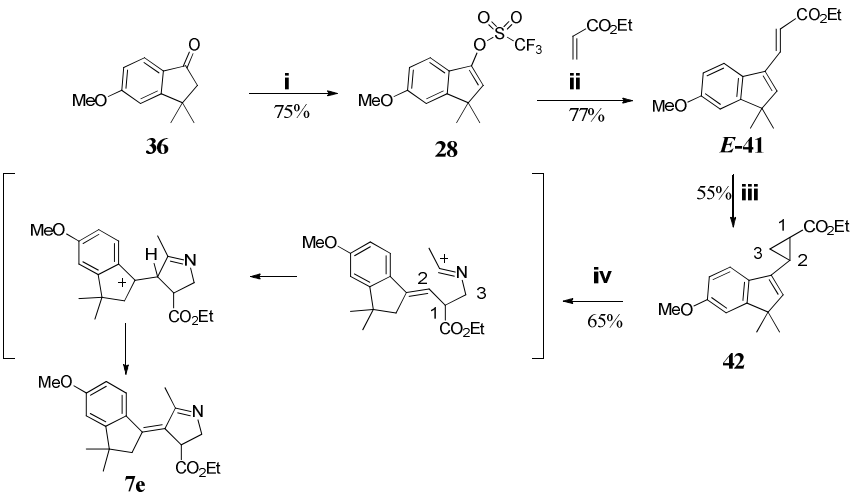
Scheme **34**

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

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

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

$Pd(OAc)_2$[62] gave the *trans*-substituted cyclopropane derivative **42**. The desired regioselectivity of the cyclopropanation can be attributed to steric reasons. It was pleasant to find out that compound **42** in the presence of TfOH actually reacted with acetonitrile in the way we expected i.e. tandem homoallylic rearrangement-nitrilium cyclization process.



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

Scheme **35**

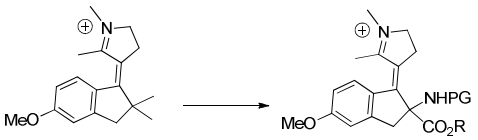
However, after a careful NMR investigation of the reaction product we concluded its structure was the one of **7e** in Scheme **35**. The

[62] a) Luithle, J.E.A.; Pietruszka, J., *J. Org. Chem.*, **1999**, 64, 8287-8297. b)Vangveravong, S.; Kanthasamy, A.; Lucaites, V.L.; Nelson, D.L.; Nichols, D.E., *J. Med. Chem.*, **1998**, 41(25), 4995-5001.

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

3.4 Synthesis of NAIPzwaa

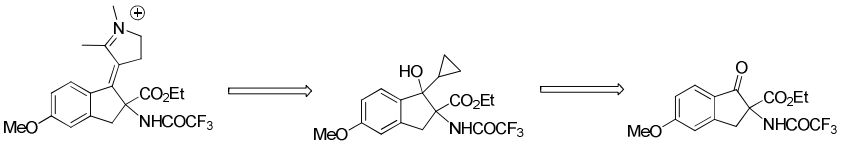
With the aim to prepare an unnatural α-amino acid featuring a **NAIP** moiety as the conformationally locked side chain we have also carried out the synthesis of compound **NAIPaa**.



NAIPzw **NAIPaa**

Scheme **36**

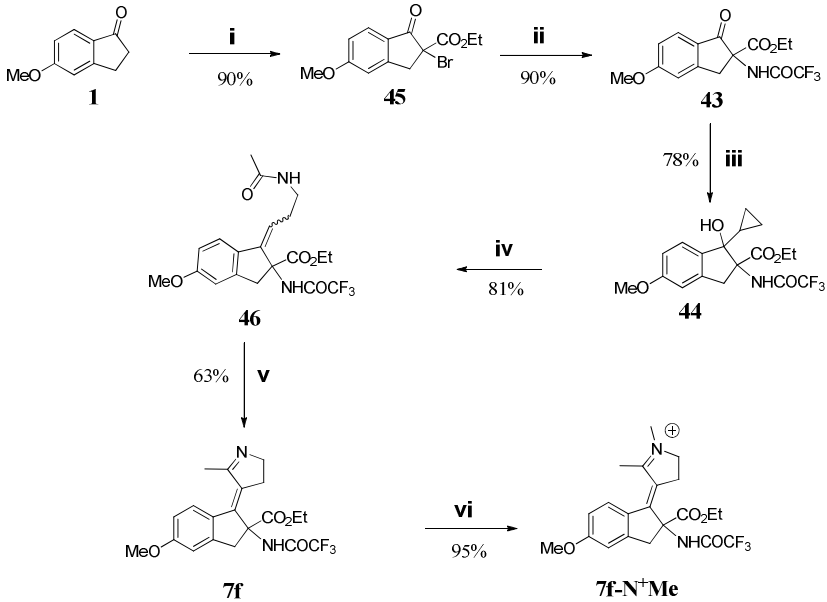
Retrosynthetic analysis showed as a possible starting material the indanone derivative **43**, which could be derived by suitable C-2 functionalization of commercial 5-methoxy indan-1-one **1**.



7f **44** **43**

Scheme **37**

In detail, the synthesis begins with the etoxycarbonilation of indanone **1** with NaH and diethylcarbonate followed by bromination with NBS to give compound **45** (Scheme **38**).



Reagents and conditions: (i) a) NaH, $(EtO)_2CO$, 100°C, b) NBS AcOEt, 30 min.; (ii) a) NaN_3, DMF, r.t, 1h, b) PPh_3, THF, r.t., o.n.; c) $(CF_3CO)_2O$, r.t., 1h; (iii) Mg, ciclopropylbromide, THF, 0°C, 30 min.; (iv) Tf_2O, CH_3CN; (v) P_2O_5, HMDSO, CCl_4, reflux, 2h.; (vi) MeOTf, benzene.

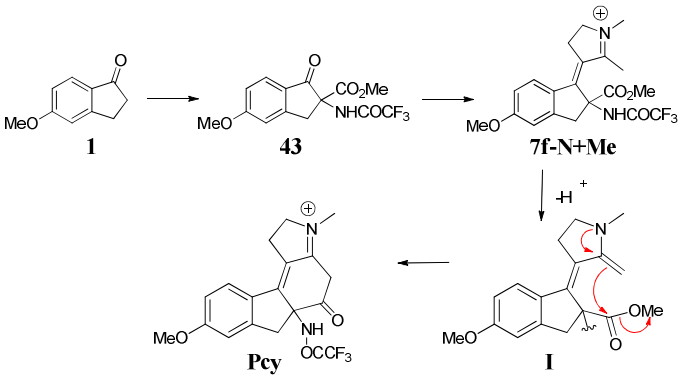
Scheme **38**

The subsequent nitrogen introduction with sodium azide, then Staudinger reaction and trifluoroacetylation of the resulting primary amine gave compound **43**. The latter reacted with cyclopropylmagnesium bromide providing the cyclopropyl carbinol **44** which treated in the usual way (Tf_2O and CH_3CN) gave the

acetamide **46**. Thus, in place of the expected tandem reaction, compound **44** gave only a Ritter type rearrangement.

However, by promoting the dehydration of secondary amide **46** with PPSE we could prepare the desired free base **7f** from which the photoswitchable amino acid **7f-N$^+$Me** [63] was obtained by the usual *N*-methylation. Arrived at the crucial stage of amino acid deprotection, a one more complication was waiting for us. We found that compound **7f-N$^+$Me** was rather instable giving rise to the formation of the tetracyclic compound **Pcy** (Scheme **39**).

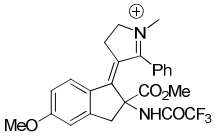
Compound **Pcy** seems to be the result of an intramolecular acylation involving the intermediate enamine **I** in turn obtained by methyl deprotonation of **7f-N$^+$Me**.



Scheme **39**

[63] Melloni, A; Rossi, P.R.; Donati, D.; Zanirato, V.; Sinicropi, A.; Parisi, M.L.; Martin, E.; Ryazantsev, M.; Ding, W.J.; Frutos, L.M.; Basosi, R.; Fusi, S.; Latterini, L.; Ferré, N.; Olivucci, M.; *J. Am. Chem. Soc*., **2010**, 132, 9310-9319.

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



NAIPaa$_2$

Scheme **40**

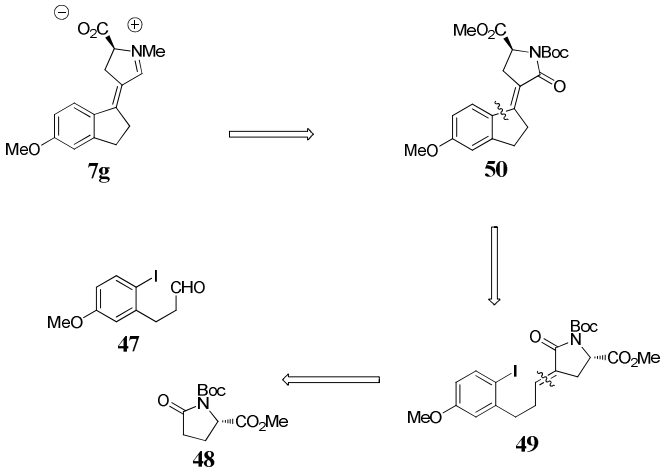
Ultimately, these findings indicated that the ester functional group at C-2 of the indane moiety and the methyl radical at C-5 of pyrroline were unsuitable to go on with the design of potential photoswitchable amino acid. *This part has mainly developed by the colleagues of Dipartimento di Chimica, Università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

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

3.5 New developments

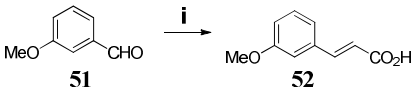
Looking for alternative synthesis pathways towards **NAIP** derivatives lacking the methyl radical at C-5 of pyrroline we envisioned a completely different strategy that is retrosynthetically depicted in Scheme **41**. Two disconnections, corresponding to an intramolecualr Heck reaction and an aldol-like condensation,

selected 3-(2-iodo-5-methoxyphenyl)-propanal **47** and the *N*-protected methyl 5-oxopirrolidine-2-carboxylate **48** as the starting materials.



Scheme **41**

Remarkable in the new synthetic approach appears the construction of the indane moiety at a later stage and the adjustment of the oxidation state of the pre-existing heterocycle in the conclusive step. For the preparation of the aldehyde **47** we commenced with the Knovenagel condensation of 3-methoxybenzaldehyde giving in an easily and cheaply way the aryl propenoic acid **52** whose C3 carbon chain served to accede the targeted 3-(3-methoxyphenyl)-propanal. To this end we selected a two-step protocol entailing $LiAlH_4$ reduction of the corresponding ethyl ester then oxidation of the resulting primary alcohol with PCC (Scheme **43**).

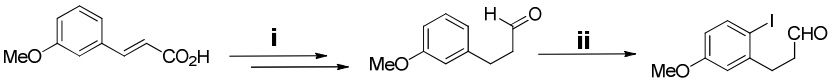


51 **52**

Reagents and conditions: (i) $CH_2(COOH)_2$, Py, Piperidine, 95 °C , 2h, then 115°C, 1h.

Scheme **42**

Kim *et al*.[64] have found a practical and regioselective (*para* to a methoxy group) aromatic iodination making use of tetrabutylammonium peroxydisulfate $(TBA)_2S_2O_8$ and iodine in acetonitrile. The reaction mechanism is not clear, probably the sulfate free radical, produced by homolytic cleavage of $(TBA)_2S_2O_8$, oxidizes iodine to the electrophilic iodonium cation radical $I_2^{\bullet+}$ via a one electron transfer process. In our hands however, the desired 3-(2-iodo-5-methoxyphenyl)-propanal **47** was formed in low yield.

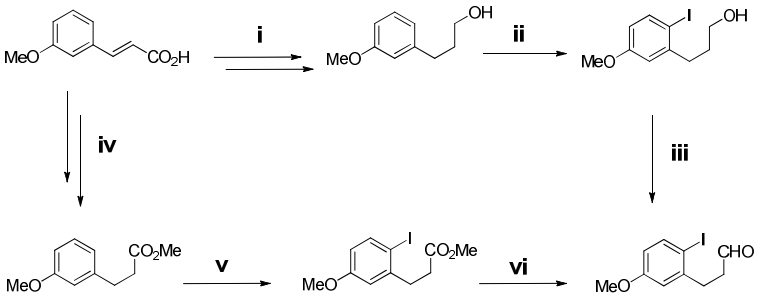


Reagents and conditions: (i) a) ROH, $SOCl_2$, b) $LiAlH_4$, c) PCC; (ii): TBAPS, I_2.

Scheme **43**

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

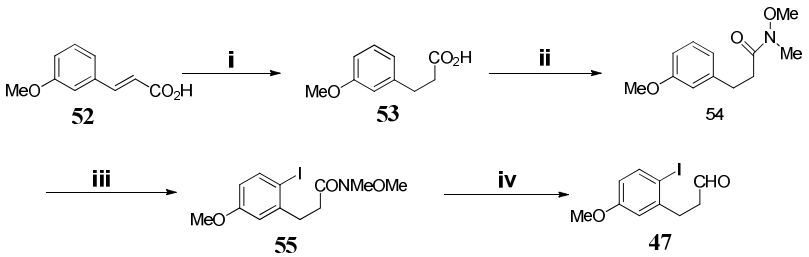
[64] a) Yang, S.G.; Kim, Y.H.; *Tetrahedron Lett.*, **1999**, 40, 6051-6054. b) Choi, H.C.; Cho, K.; Kim, Y.H.; *Synlett*, **1995**, 207-208. c) Seung Gak, Y.; Je Pil, H.; Min Young, P.; Kieseung, L.; Yong Hae, K.; *Tetrahedron*, **2007**, 63, 5184-5188.



Reagents and conditions: (i) a) ROH, $SOCl_2$, b) $LiAlH_4$; (ii) TBAPS, I_2; (iii) PCC; (iv) a) ROH, $SOCl_2$, b) H_2, Pd/C; (v) TBAPS, I_2; (vi) a) DIBAH, b) PCC.

Scheme **44**

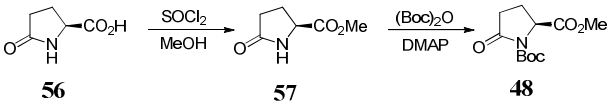
What appeared a problem was promptly solved resorting to the Weinreb amide **54** easily prepared from the saturated acid **53** (Scheme **45**). The iodination protocol applied on the amide **54** furnished in satisfactory yield compound **55** which gave the desired aldehyde **47** by DIBAH reduction.



Reagents and conditions: (i) H_2, Pd/C, EtOH, 2h; (ii) EDCI, Et_3N, MeONHMe.HCl, DMPA, CH_2Cl_2, r.t. 2h; (iii) TBAPS, I_2, CH_3CN, 48°C, 5h; (iv) DIBAH, THF, -78°C, 1h.

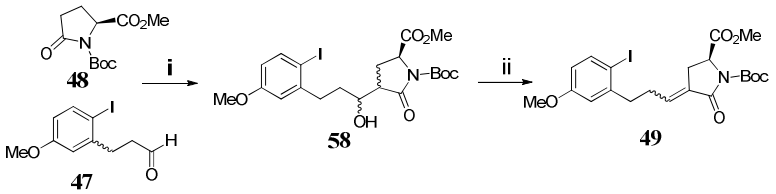
Scheme **45**

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



Scheme **46**

The lithium lactam enolate of **48**, generated with LiHMDS, reacted at -78°C with the aldehyde **47** under Lewis acid catalysis ($Et_2O•BF_3$).[65] Under these conditions, the aldolic product **58** was obtained in a good yield as diastereomeric mixture (Scheme **47**). No attempts were made to separate them as in the following step both the chiral centers were cancelled.



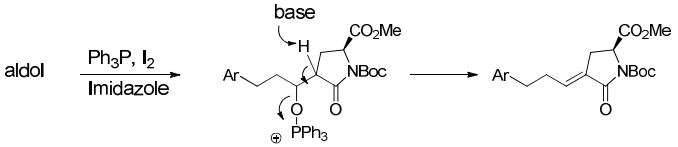
Reagents and conditions: (i) LiHMDS/THF- 78°C 1h, $BF_3{\cdot}Et_2O$ -78°C 2h, (ii) Imidazole, PPh_3, I_2.

Scheme **47**

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

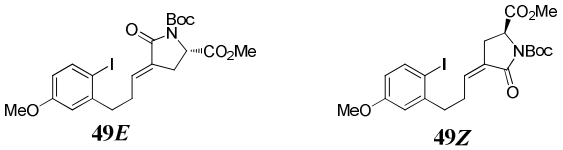
[65] Ezquerra, J.; Pedregal, C.; Yruretagoyena, B.; Rubio, A.; Carreño, M.C.; Escribano, A.; García Ruano, J.L.; *J. Org. Chem.*, **1995**, 60, 2925-2930.

protocol recently proposed in literature.[66] The authors reported the Garegg-Samuellsson reagent (triphenylphosphine-imidazole-iodine in CH_2Cl_2) was particular efficient for the one-step conversion of aldols into the corresponding olefins. Under these conditions Imidazole has probably a dual function acting both as a base and forming a partially solvated complex with triphenylphosphine and iodine.[67]



Scheme **48**

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



Scheme **49**

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

[66] Cohen, J.L.; Chamberlin A.R.; *J. Org. Chem.*, **2007**, 72, 9240-9247.
[67] Garegg, P.J.; Samuelsson, B.; *Synthesis*, **1979**, 469-470.

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

About the key Heck cyclization step, we surveyed various reaction conditions before optimizing the protocol. Thus, we examined different Pd(0) sources ($Pd(PPh_3)_4$, $PdCl_2$, $Pd(OAc)_2$), and ligands (PPh_3, (o-Tol)$_3$P). Instead, TEA and DMF were respectively the optimal base and solvent to use (Table **1**).

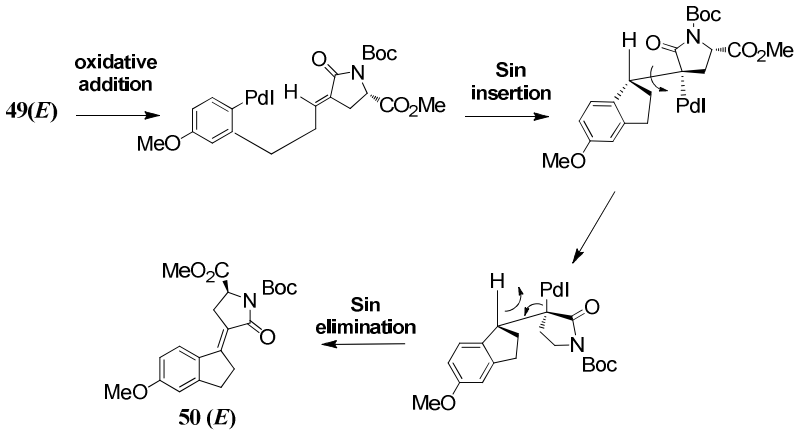
Catalyst	**Ligand**	**Solvent**	**Yield**
$Pd(PPh_3)_4$		Toluene	*36%*
$Pd(PPh_3)_4$		DMF	*34%*
$PdCl_2$	PPh_3	Toluene	*32%*
$Pd(OAc)_2$	o-tolyl-phosphine	DMF	*53%*
$Pd(OAc)_2$	PPh_3	DMF	*65%*

Table **1**

To resume, the Heck reaction conditions were: 2 eq. electrophile, 10mol % $Pd(OAc)_2$, 40mol % PPh_3, 3 eq. TEA in DMF at 110°C for 5 hours.

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

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

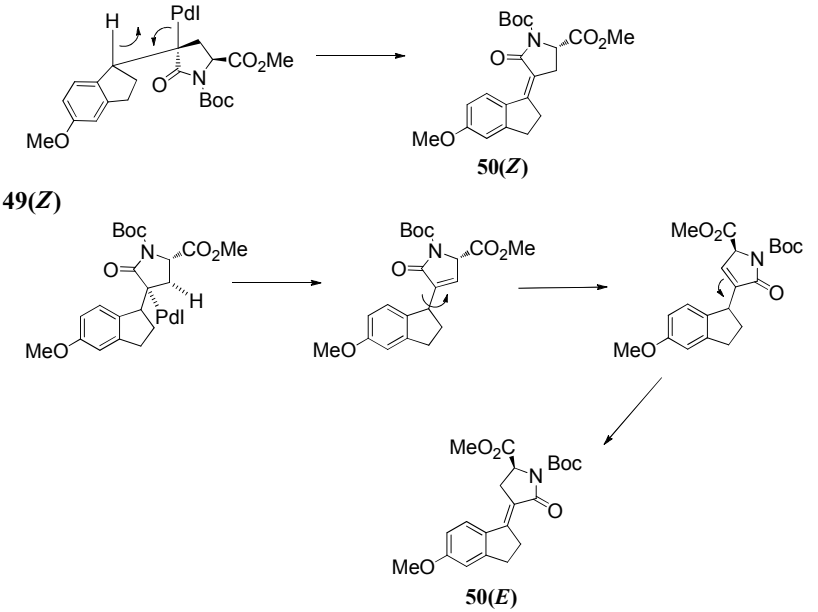


Scheme **50**

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

Thus, while the first one led directly to **50*Z***, the second led to form an intermediate (not detected) with an endocyclic unsaturation. At this stage a rapid isomerization, maybe palladium-mediated,

occurred to form the thermodynamically favored compound **50*E*** (a more extensive conjugation is present).



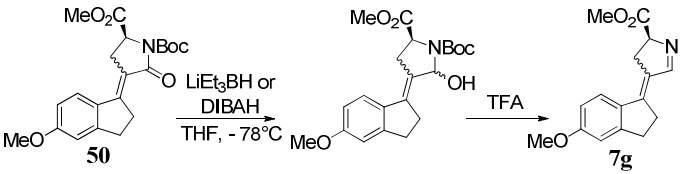
Scheme **51**

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

We consider of a paramount importance the presence of a configurationally stable stereocenter in the photoswitch as it could control the direction of rotation. Thus, the enantiomerically pure compound **50*E*** could be a precursor of a new class of single-

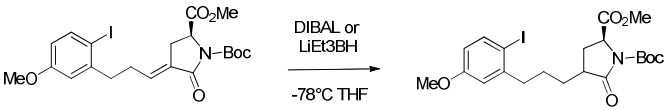
molecule light powered motors miming rhodopsin both in term of photoisomerization mechanism and unidirectionality of the rotation.

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



Scheme **52**

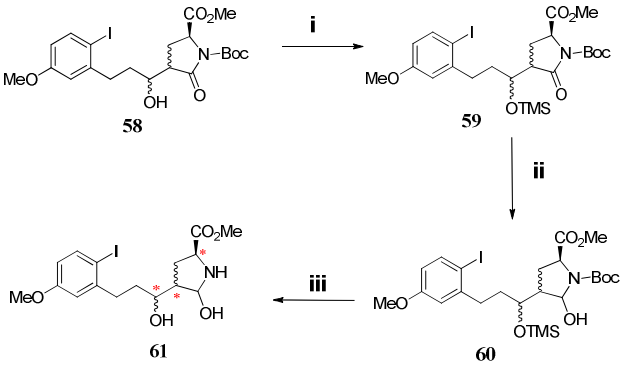
Unfortunately, both tests haven't yielded either positive or convincing result. In fact, by using DIBAH we recovered starting material, while Superhydride, against all predictions, reduced the ester group. We thought the extensive conjugation attenuating the electrophilic character of the lactam carbonyl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



Scheme **53**

3.6 Last development and Future work.

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



Reagents and conditions: (i) Imidazole, TMSCl, 0°C, 2h; (ii) $LiEt_3BH$,-78°C, 20min; (iii) TFA , 3h, r.t.

Scheme **54**

At present, we haven't got any clear results. The obtainment of a complex mixture of diastereomers makes the real chemical behavior of **59** to the hydride attack very difficult to be appreciated. We are currently working at the synthesis plan in order to get an Heck

cyclization product featuring the *gem*-dimethyl groups at C-2 of the indanylidene moiety. In fact, we suspect the observed sluggish undesired reactivity of **50** towards hydride donors is also related to the lacking of this structural element.

4. EXPERIMENTAL

4.1 General methods.

Solvents were distilled prior to use, following standard procedures, and reactions were performed under nitrogen or argon atmosphere. Silica gel 60 F254 plates were used to monitor synthetic transformations, visualization being done under UV light or using 2% $KMnO_4$ solution. Organic solutions were dried over anhydrous magnesium sulfate and evaporated with a rotary evaporator. Chromatographic purifications were carried out using 70–230 mesh silica gel. Melting points were determined on a Büchi–Tottoli apparatus and are uncorrected. Infrared (IR) spectra were recorded on a FTIR Paragon 500 spectrometer. Light petroleum refers to the fractions boiling in the range 40–60 °C and ether to diethyl ether. Nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Mercury Plus spectrometer at 400 M*Hz* and 100 M*Hz*, respectively. Chemical shifts (d values) are given in parts per million downfield from tetramethylsilane as the internal standard. Reverse-phase HPLC using a Beckman 116 liquid chromatography equipped with a Beckman 166 diode array detector. Nucleodur C_{18} column (4.6mm x 100mm, 2µm particle size). Mobile phase containing solvent A (10% v/v, acetonitrile in 0.1% TFA) and solvent B (60% v/v, acetonitrile in 0.1% TFA).The column was perfused at a flow rate of 0.6ml/min using a linear gradient from 0% to 70% B over 25min. Molecular weights of compounds were determined with a mass spectrometer ESI Micromass ZMD-2000; values are expressed

as MH^+. Analytical conditions for chiral separations are reported in the following section.

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

4.2 Experimental section.

Procedure for the Preparation of the Neutral Imine ((*p*-NO_2)-1neut).

A mixture of 1-pyrroline trimer (3.3mmol) and *p*-nitro benzaldehyde (10 mmol) in methanol (25 ml) was stirred at room temperature for 48 hours. To the formed suspension a methanolic solution (75ml) of 0.6 M acetic acid/0.2 M sodium acetate was added and the mixture heated at 60°C for 24 h. After evaporation of the solvent, the residue was made basic by addition of K_2CO_3 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*-NO_2)-1neut).**

Yield: 43%; m.p. 105-108°C; IR (KBr): *v* 1593, 1511, 1341 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.84-2.91 (2H, m), 4.24-4.31 (2H, m), 6.89 (1H, t, J 2.8*Hz*), 7.60 (2H, d, J 8.8*Hz*), 7.94 (1H, t, J 2.4*Hz*), 8.25 (2H, d, J 8.8*Hz*); ^{13}C NMR ($CDCl_3$) 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*-NO_2-1Me.

0.3 mmmol of $CF_3SO_3CH_3$ were added to 0.3 mmol of **1neut**, [**(*p*-MeO)-1neut** or **(*p*-NO_2)-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; ^{1}H NMR (CD_3CN) δ 3.20 (2H, m), 3.59 (3H, s), 4.30 (2H, m), 7.42-7.68 (6H, m), 8.50 (1H, m); ^{13}C NMR (CD_3CN) 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; ^{1}H NMR (CD_3CN) 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); ^{13}C NMR (CD_3CN) 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 trifluoromethane-sulfonate (*E*- (*p*-NO_2)-1neut).**

Yield: 100%; mp 96-98°C; ^{1}H NMR (CD_3CN) 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

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}; ^{1}H NMR (400 M*Hz*, $CDCl_3$): 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 M*Hz*, $CDCl_3$): 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): *v* 3514, 2959, 2870, 1607, 1490, 1268, 1142, 1032, 808 cm^{-1}; ^{1}H NMR(400 M*Hz*, $CDCl_3$): 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 M*Hz*, $CDCl_3$): 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°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): *v* 2956, 2836, 1604, 1487, 1308, 1263, 1034 cm^{-1}; ^{1}H NMR (400 M*Hz*, $CDCl_3$): 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 M*Hz*, $CDCl_3$): 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): *v* 2957, 2096, 1604, 1487, 1464, 1262, 1034, 849 cm^{-1}; ^{1}H NMR (400 M*Hz*, $CDCl_3$) 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 M*Hz*, $CDCl_3$): 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): *v* 3290, 3084, 2956, 1651, 1487, 1262, 1033, 816 cm^{-1}; ^1H NMR (400 M*Hz*, $CDCl_3$): 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 M*Hz*, $CDCl_3$): 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 8 in Results and Discussions).

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

A trimethylsilyl polyphosphate (PPSE) solution, prepared by heating at reflux for 1.5 h a mixture of P_2O_5 (1.6 g, 11 mmol) and hexamethyldisiloxane (HMDSO, 3.3 mL, 15.4 mmol) in CCl_4 (15 mL), was added at room temperature to **6a** (0.3 g, 1.1 mmol). The reaction mixture was heated at reflux for 2 h, cooled to room temperature and quenched with water (5 mL). The organic phase was separated and washed with 10% HCl (2x30 mL). The combined aqueous layers were cooled to 0 °C, brought to pH 9 by treatment with 6 N NaOH solution, and extracted with DCM (2x60 mL). The combined organic layers were washed with water (100 mL), dried and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc/MeOH/Et_3N 9:1:0.2) to give **7a** (92:8 *Z/E* mixture, 0.2 g, 71%) as a yellow oil.

IR (film): *v* 1702, 1600, 1576, 1291 cm^{-1}; ^1H NMR (400 M*Hz*, $CDCl_3$): 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; ^{13}C NMR (100 M*Hz*, $CDCl_3$): 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 mmmol of $CF_3SO_3CH_3$ were added to a solution of ***Z/E***-isomers (0.3 mmol) of **7a** in anhydrous benzene (2ml); the reaction mixture was stirred at room temperature for 10 minutes. The precipitate was collected by filtration and dried under vacuum. Amberlite IRA-402 (1g) was previously activated by treatment with HCl 10% for 12h and then charged on a column chromatography. The resin was washed with water until pH= 7. The crude reaction was dissolved in 2ml mixture water/methanol (2/1) and the resulting solution was passed through Amberlite by elution with water. Water was removed and the residue was purified by column chromatography (MeOH/DCM 2:8) to give ***Z*-(7a-*N*$^+$Me)Cl$^-$** (92:8 *Z/E* mixture, 0.2mmol g, 62%) as a yellow oil.

^{1}H NMR (400 M*Hz*, $CDCl_3$): δ 1.29 (6H, s), 2.67 (3H, m), 2.67 (2H, s), 3.21–3.25 (2H, m), 3.81 (3H, m), 3.84 (3H, m), 4.36 (2H, m) 6.36-6.40 (1H, m), 6.55-.6.60 (1H, m), 7.50 (1H, m). A positive NOE between signal at δ 2.67 (methyl at C-5 of 3,4-dihydro-2H-pyrrole) and signal at δ 6.55-6.60 (H-7 on the aromatic ring) was detected; ^{13}C NMR (100 M*Hz*, $CDCl_3$): δ 18.55, 25.75, 28.15, 29.35, 38.83, 49.40, 51.04, 55.36, 58.49, 125.57, 126.77, 128.13, 129.82, 132.32, 136.73, 148.48, 169.16, 180.50.

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

To magnesium turnings (0.24 g, 9.8 mmol) in dry THF (8 mL), a solution of cyclopropyl bromide (0.8 mL, 9.8 mmol) in dry THF (5 mL) was added dropwise with mild reflux. After the addition was

completed, a solution of **1** (0.8 g, 4.9 mmol) in dry THF (8 mL) was added dropwise and the mixture was heated at 60°C for 3 h. Saturated NH_4Cl solution (20 mL) was added and the mixture was extracted with ether (3x20 mL). The organic phases were combined, dried and concentrated *in vacuo*. The crude residue was stirred with 15% HCl solution in acetic acid (10 mL) for 1 h at room temperature, then 10% NaOH was added until pH 8. The mixture was extracted with DCM (3x20 mL) and the combined organic layers were dried and evaporated. The residue was purified by column chromatography (DCM/petroleum ether 3:7) to give **2-*endo*** (0.33 g, 30%) as yellow oil.

IR (film): ν 2954, 1742, 1606, 1492, 1255, 732 cm^{-1}; ^1H NMR (200 M*Hz*, $CDCl_3$): 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 M*Hz*, $CDCl_3$): 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 (2.3 g, 5 mmol, 1.3eq) and KHMSA (2 g, 10 mmol, 2.6eq) in 10 ml of dry THF under Argon was stirred for 3h at 20°C. A solution of **1** (0.5 g, 3.78 mmol) and tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1) in 7ml dry THF was added and the resulting reaction mixture stirred for

2h at 20°C. After dilution with 75ml n-pentane and adsorptive filtration through silica pad, the solvent was removed *in vacuo*. Flash chromatography of the residue (Ethyl Ether/Petroleum 1/20) afforded the **3e-*exo*** (0.23g, 40%, colorless oil). After 1.5h room temperature in $CDCl_3$, ^1H NMR showed that compound **3e-exo** spontaneously is transformed in **3e-*endo***.

3e-*exo*: ^1H NMR (400 M*Hz*, $CDCl_3$): 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 0°C; IR (KBr): *v* 3447, 2960, 1604, 1258, 1073, 1015, 820 cm^{-1}; ^1H NMR (400 M*Hz*, $CDCl_3$): 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 M*Hz*, $CDCl_3$): 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).

PATHWAY B (Scheme 16 in Results and Discussions)4-(5-Methoxy-2,2-dimethyl-indan-1-ylidene)-5-methyl-3,4-dihydro-2H-pyrrole (7a).

To a stirred solution of triflic anhydride (0.15 mL, 0.9 mmol) in CH_3CN (2 mL), a solution of **3a** (0.21 g, 0.9 mmol) in CH_3CN (1 mL) was added dropwise at 0°C. The reaction mixture was slowly warmed to room temperature and stirred for 3 h. The solution was washed with 10% NaOH (5 mL) and the phases were separated. The aqueous phase was extracted with DCM (3x10 mL). The combined organic phases were dried and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc/MeOH/Et_3N 9:1:0.2) to afford **7a** (0.19 g, 83%) as a yellow oil.

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

The reaction was carried out following Knochel and co-workers' procedure[48] using 1.2 equivalents of *cis*-2-iodo-cyclopropane carboxylic acid ethyl ester (1.97 g, 8.2 mmol), 1.3 equivalents of *i*PrMgCl (4.4 mL, 2.0 M in THF, 8.8 mmol) and 1.0 equivalents of 5-methoxy-2,2-dimethyl-indan-1-one (**1a**) to give a crude residue, which was purified by flash column chromatography on silica gel (diethyl ether/ petroleum ether 1:1) affording **10** (945 mg, 54% yield) as a white solid, mixture of two diastereoisomers in the ratio of 65:35 as determined by integration of the benzylic hydrogens at δ 2.97

(major) and 2.81 ppm (minor) as well as δ 2.69 (minor) and 2.56 ppm (major) in the ^{1}H NMR spectrum. (white solid, mp: 92-94 °C, 54%).

IR (KBr): *v* 2960, 1756, 1607, 1495, 1468, 1305, 1266, 934 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 M*Hz*): δ 7.25-7.23 (m, 1H, major), 7.20-7.19 (m, 1H, minor), 6.75-6.70 (m, 4H, major and minor), 3.76 (s, 6H, major and minor), 2.97 (d, 1H, J 15.7 *Hz*, major), 2.81 (d, 1H, J 15.3 *Hz*, minor), 2.69 (d, 1H, J 15.3 *Hz*, minor), 2.56 (d, 1H, J 15.7 *Hz*, major), 2.32-2.25 (m, 2H, major and minor), 2.20-2.13 (m, 2H, major and minor), 1.27-1.24 (m, 2H, major and minor), 1.19 (s, 3H, major), 1.15 (s, 3H, major), 1.17-1.12 (m, 2H, major and minor), 1.10 (s, 3H, minor), 0.98 (s, 3H, minor); ^{13}C NMR ($CDCl_3$, 100 M*Hz*): δ (major) 175.2, 161.1, 144.7, 135.9, 124.0, 113.1, 110.2, 94.9, 55.4, 46.6, 44.3, 25.4, 23.2, 21.6, 19.2, 18.2. MS (EI): 258 (100), 229 (65), 215 (27), 199 (18), 187 (20), 115 (22).

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

A cooled (>15°C) 1.0 M solution of HBr in acetic acid (5.6 mL, 5.6 mmol) was poured into a cooled (>15°C) flask containing **10** (722 mg, 2.8 mmol) and stirring was continued for 1h. After evaporation of the solvent under vacuum, the residue was partitioned between H_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 **11** (*Z/E* mixture, 881 mg, 93% yield) as a light brown oil.

IR (neat): *v* 3099, 2927, 2851, 2651, 1716, 1605, 1488, 1262, 1032, 817 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 M*Hz*): 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}C NMR ($CDCl_3$, 50 M*Hz*): δ (major) 175.1, 159.9, 153.3, 146.7, 132.0, 125.6, 112.7, 112.5, 110.4, 55.3, 46.9, 44.5, 44.1, 29.3, 26.9 (2C).

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

A dry 100 mL round bottomed flask equipped with an addition funnel and a nitrogen inlet was charged with **11** (880 mg, 2.6 mmol) and 9 mL of a 3:1 mixture of dry THF/dry methanol. To the stirred solution was added dropwise a 2.0 M solution of (trimethylsilyl)diazomethane (3.9 mL, 7.8 mmol). After 2h the bright yellow solution was cooled to 0°C by means of an ice bath and quenched with sat. aq. NH_4Cl solution. The aqueous layer was extracted with diethyl ether (3x30 mL). The organic extracts were

combined and dried over Na_2SO_4. After evaporation of the solvent under vacuum, the residual oil was purified by flash column chromatography on silica gel (diethyl ether/petroleum ether 2:8) to give methyl ester derivative (*Z/E* mixture, 837 mg, 91% yield) as a yellow oil.

IR (neat): *v* 2959, 2922, 1743, 1605, 1488, 1262, 1032, 803 cm^{-1}; ^1H NMR ($CDCl_3$, 200 M*Hz*): 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); ^{13}C NMR ($CDCl_3$, 50 M*Hz*): 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 (12).

Sodium azide (292 mg, 4.5 mmol) was added to a solution of methyl ester derivative (794 mg, 2.25 mmol) in dry acetonitrile (20 mL) and dry DMF (2 mL) in a dry 100 mL round bottomed flask under nitrogen atmosphere, and the resulting mixture was stirred at room temperature. After 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 Na_2SO_4, concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (diethyl ether/petroleum ether 1:9) to give **12** (*Z/E* mixture, 616 mg, 87% yield) as a yellow oil.

IR (neat): *v* 2957, 2105, 1747, 1605, 1488, 1263, 1033 cm^{-1}; ^1H NMR ($CDCl_3$, 200 M*Hz*): 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).^{13}C NMR ($CDCl_3$, 50 M*Hz*): δ (major) 170.4, 159.8, 152.8, 146.5, 131.9, 125.6, 112.6, 111.4, 110.2, 61.9, 55.1, 52.3, 46.8, 44.0, 30.7, 29.0 (2C); MS (EI): 301 (95), 286 (51), 272 (19), 227 (22), 213 (100), 197 (21), 171 (20).

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

A solution of **12** (488 mg, 1.55 mmol) in dry THF (8 mL) under nitrogen atmosphere was cooled to 0°C by means of an ice bath. To the stirred solution triphenyl phosphine (608 mg, 2.32 mmol) was added portionwise. The cooling bath was then removed and the clear solution was allowed to warm to room temperature. After stirring overnight, the complete consumption of **12** was confirmed by TLC

and then 2 mL of distilled water were added. The resulting mixture was stirred for 24h at room temperature. The reaction was quenched with sat. aq. $NaHCO_3$ solution, extracted with ethyl acetate (3x30 mL) and washed with brine. The organic layer was dried over Na_2SO_4 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 CH_2Cl_2 (10 mL) under nitrogen. The solution was cooled to 0°C by means of an ice bath and triethylamine (TEA) (430 μL, 3.1 mmol) was added. After 5min a solution of acetyl chloride (220 μL, 3.1 mmol) in 2 mL of 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 **13** (*Z/E* mixture, 383 mg, 75% yield from **5**) as a yellow oil.

IR (neat): *v* 3314, 2960, 2251, 1745, 1660, 1606, 1215, 1031, 913, 733 cm^{-1}; ^1H NMR ($CDCl_3$, 200 M*Hz*): 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}C NMR ($CDCl_3$, 100 M*Hz*): 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 (7b).

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 **13** (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 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 **7b** (*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}H NMR ($CDCl_3$, 400 M*Hz*): 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}C NMR ($CDCl_3$, 50 M*Hz*): δ (major) 175.4, 173.0, 160.5, 150.4, 147.9, 130.4, 128.8, 127.2, 111.7, 109.8, 70.5, 55.2, 52.1, 49.3, 48.8, 35.7, 28.7, 26.1, 20.1; MS (ESI, + p ms): 314.5.

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

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

^{1}H NMR ($CDCl_3$, 400 M*Hz*): 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}C NMR ($CDCl_3$, 100 M*Hz*): 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 (7b zwitt).

The crude pyrrolium trifluoromethanesulfonate (143 mg, 0.3 mmol) was added in a 25 mL round-bottomed flask containing a 2:1 mixture of THF/H_2O (9 mL) and the bright yellow solution was cooled to 0°C by means of an ice bath. Then LiOH·$H_2$0 (38 mg, 0.9 mmol) was added portionwise to the solution that rapidly turned into dark yellow-brown. The reaction was monitored by TLC (ethyl acetate/methanol 9:1 as the eluent). After 3h the solvent was evaporated under vacuum to give a residual solid that was dissolved in acetonitrile. The precipitation of a white solid occurred. The decanted clear yellow solution was transferred into a one-necked round-bottomed flask and concentrated under vacuum to give a gummy solid which was purified by flash column chromatography on silica gel (acetonitrile/H_2O 7:3) to afford **7b zwitt** (*Z/E* mixture 90:10, 50 mg, 53% yield from **7b**) as a viscous dark yellow oil. To the overriding geometric isomer the *Z* configuration was assigned, on the basis of NOE difference spectroscopy. In details: a positive NOE between the signal of the proton attached to the aromatic C-7 carbon

of the indanylidene moiety (d, δ=7.51 ppm, J 8.7 *Hz*) and the signal of the methyl group at the C-5 of the pyrrolium ring (s, δ=2.52 ppm) was detected.

IR (KBr): *v* 2962, 2925, 1635, 1584, 1262, 1094, 1028, 802 cm^{-1}; ^{1}H NMR (CD_3OD, 400 M*Hz*): 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); ^{13}C NMR (CD_3OD, 100 M*Hz*): 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.

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

A 250 mL round-bottomed flask equipped with a magnetic stirring bar and an argon gas inlet was charged with 22.5 g (0.15 mol) of dry sodium iodide and 100 mL of glacial acetic acid. The stirred solution was added 10.1 mL (0.1 mol) of ethyl propiolate and the resulting mixture was heated at 70 °C during 12 h. The brown solution was cooled to rt and water (100 mL) and ether (100 mL) were added. The

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 (3x50 mL) until the aq. phase becomes neutral (pH 7), washed with brine (50 mL) and dried over $MgSO_4$. After rotary evaporation of the solvent, the residual brown oil was distilled (bp 62 °C) to give **14** (19.4 g, 86 % yield) as a yellow oil.

^{1}H NMR (300 M*Hz*, $CDCl_3$): 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).^{13}C NMR (75 M*Hz*, $CDCl_3$): δ 164.9, 130.3, 95.0, 61.1, 14.6.

Synthesis of *Z*-3-iodo-prop-2-en-1-ol (**15**) [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 **14** and 100 mL of anhydrous CH_2Cl_2. The stirred solution was cooled to -78 °C by mean of a liquid nitrogen bath and 100 mL (100 mmol) of a 1 M solution of diisobutyl aluminium hydride in hexane was added dropwise via a syringe at such a rate that the temperature did not exceed -75 °C. The cooling bath was removed and the reaction mixture was allowed to warm to rt. Hydrolysis was carried out at -20 °C by dropwise addition of 50 mL of 1 M aq. HCl, followed by addition of ether (100 mL). The organic layer was separated, the aqueous layer extracted with ether (2x20 mL) and the combined organic layers dried over $MgSO_4$. After rotary evaporation of the

solvents, the residual oil was purified by flash column chromatography on silica gel (pentane/Et_2O 1:1) affording **15** (8.05 g, 88 %) as a yellow oil.

^{1}H NMR (300 M*Hz*, $CDCl_3$): 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). ^{13}C NMR (75 M*Hz*, $CDCl_3$): δ 140.3, 83.0, 66.1.

Synthesis of *cis*-(2-iodo-cyclopropyl)-methanol (**16**) [*Tetrahedron Lett.* **1998**, *39*, 8621]

To freshly distilled CH_2Cl_2 (50 mL) was added Et_2Zn (1.0 M in hexane, 53 mL, 53 mmol) under argon. The solution was cooled in an ice bath and a solution of trifluoroacetic acid (4.11 mL, 53 mmol) in CH_2Cl_2 (10 mL) was then dropped very slowly into the reaction mixture via syringe. Upon stirring for 20 min, a solution of CH_2I_2 (4.33 mL, 53 mmol) in CH_2Cl_2 (10 mL) was added. After an additional 20 min stirring, a solution of **15** (4.43 g, 24.1 mmol) in CH_2Cl_2 (10 mL) was added and the ice bath was removed. After an additional 30 min stirring, the reaction mixture was quenched with sat. aq. NH_4Cl and hexanes (50 mL) and the layers were separated. The aq. layer was extracted with hexanes. The combined organic layers were washed with sat. $NaHCO_3$, H_2O and brine, then dried over Na_2SO_4, filtered, concentrated and purified by flash column chromatography on silica gel (pentane/Et_2O 1:4) affording **16** (2.96 g, 62 %) as a yellow oil.

^{1}H NMR (300 M*Hz*, $CDCl_3$): 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). ^{13}C NMR (75 M*Hz*, $CDCl_3$): δ 68.4, 18.0, 14.1, 10.0.

Synthesis of *cis*-2-iodo-cyclopropanecarboxylic acid (**17**) [*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 **16** (3.3 g, 16.7 mmol) and 25.8 g (68.8 mmol) pyridinium dichromate dissolved in 50 mL of dry DMF. The reaction mixture was stirred for 24 h at rt. After this time, the reaction mixture was poured into 80 mL of water and the solution was acidified with 3 N HCl to pH 2.5. The water solution was extracted with Et_2O (3x30 mL). The combined organic layers were washed with water (2x20 mL), brine, dried over Na_2SO_4, filtered, concentrated and purified by flash column chromatography on silica gel (pentane/Et_2O 1:1) affording **17** (3.34 g, 95 %) as a white crystals.(mp: 65 °C).

^{1}H NMR (300 M*Hz*, $CDCl_3$): 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). ^{13}C NMR (75 M*Hz*, $CDCl_3$): δ 175.5, 19.3, 17.5, 14.3.

Synthesis of *cis*-2-iodo-cyclopropanecarboxylic acid ethyl ester (**8**) [*J. Am. Chem. Soc.* **1989**, *111*, 6729]

A mixture of **17** (1.91 g, 9.0 mmol), thionylchloride (1.3 mL, 18 mmol) and 3 drops of DMF was refluxed at 50 °C for 1h. Afterwards, excess of thionylchloride was removed by vacuum pump and the mixture was cooled to 0 °C. EtOH (0.8 mL, 13.5 mmol) was added and the reaction mixture was stirred for 2 h at 0 °C. After this time, the reaction mixture was poured into 20 mL of water and Et_2O (20 mL) and the layers were separated. The aq. layer was extracted with Et_2O. The combined organic layers were washed with sat. $NaHCO_3$, water, brine and dried (Na_2SO_4), filtered, concentrated and purified by flash column chromatography on silica gel (pentane/Et_2O 3:1) affording **8** (1.51 g, 70 %) as a yellow oil.

^{1}H NMR (300 M*Hz*, $CDCl_3$): 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).^{13}C NMR (75 M*Hz*, $CDCl_3$): δ 168.9, 60.2, 18.3, 15.3, 13.4, -15,6. MS (EI): 240 (100), 195 (63), 167 (30).

Prop-2-ynyloxymethyl-benzene.

To a solution of prop-2-yn-1-ol (0.10 moli) in DMSO (6 ml) was added NaOH 3N (50 ml). The reaction was cooled to -10°C and benzylbromide (0.15 mmol) was added dropwise. The resulting solution was allowed to rise to room temperature and stirred for 24h. After this time, the reaction mixture was poured into 20 mL of water and Et_2O (20 mL) and the layers were separated. The aq. layer was extracted with Et_2O (3x30 ml). The combined organic layers were

washed with sat. NaCl, dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography on silica gel (Ethyl Ether/Petroleum 1:19) to give prop-2-ynyloxymethyl-benzene as a colorless oil (93%).

^{1}H NMR (200 M*Hz*, $CDCl_3$): δ 2.46-2.43(1H, t); 4.16(2H,s); 4.61(2H, s)7.35-7.29(5H, m).

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

To a stirred solution of $BH_3.SMe_2$ (0.19 g) in THF (10 ml) at 0°C was added α-pinene (0.68 g) dropwise. The reaction was stirred at 0°C over night and then cooled at -35°C. A solution of prop-2-ynyloxymethyl-benzene (0.35 g; 2.38 mmoli) in THF (10 ml) was added dropwise and the resulting solution was stirred for 4h. The solution was allowed to rise to 0°C, then a solution of acetaldehyde (1.9 ml) freshly distilled in THF (5 ml) was added. The reaction was refluxed over night and then solvent was removed *in vacuo* to afford the crude **23**. Then a solution of diol (0.181 g; 2.38 mmol) in THF (2.5 ml) was added to the residue. After 12h of stirring at room temperature, the compound was distilled. Distillation in vacuo gave the desired **24**.

^{1}H NMR (200 M*Hz*, $CDCl_3$) δ: 1.89-1.92 (2H, m); 3.44-3.48 (4H, m); 3.98 (2H, m); 4.51 (2H, s); 5.56 (1H, d; J 1.7 *Hz*); 6.49-6.58 (1H, dt; J 18, J 1.7*Hz*); 7-2-7.35 (5H, m).

Vynil-(*N*-methyliminiodiacetoxy-*O,O'*)borane (26).

To a stirred solution of $BH_3.SMe_2$ (0.19 g) in THF (10 ml) at 0°C was added α-pinene (6.8 g) dropwise. The reaction was stirred at 0°C over night and then cooled at -35°C. A solution of prop-2-ynyloxymethyl-benzene (0.35 g; 2.38 mmoli) in THF (10 ml) was added dropwise and the resulting solution was stirred for 4h. The solution was allowed to rise to 0°C, then a solution of acetaldehyde (1.9 ml) freshly distilled in THF (5 ml) was added. The reaction was refluxed over night and then solvent was removed *in vacuo* to afford the crude **23**.

The crude **23** was dissolved in THF (10 ml) and NaOH 1M (0.5 ml) was added. Stirring was maintained for 1h rt; Et_2O was added and organic phase was separated and dried over Na_2SO_4 to afford **25** as crude. In a roundbottom flask equipped with a stir bar was charged with crude **25**, *N*-methyliminodiacetic acid (3 mmol), and benzene:DMSO (10:1, 10 ml). The flask was fitted with a Dean-Stark trap and a reflux condenser, and the mixture was refluxed with stirring for 16 hours. The reaction solution was allowed to cool to 23°C and the solvent was removed *in vacuo*. the residue was purified by column chromatography (AcOEt/MeOH 9.5:0.5) to afford **56** (20% over 3 steps).

^{1}H NMR (200 M*Hz*, $CDCl_3$): δ 2.74 (3H, s); 3.83 (2H, d; J 16.6 *Hz*); 3.99 (2H, d; J 16.6 *Hz*); 4.01 (2H, m); 4.5 (2H, s); 5.64-5.73 (1H, dt; J 18 e J 1.7 *Hz*); 6.20-6.29 (1H, dt; J 18, J 7.1 *Hz*); 7.2-7.35 (5H, m).

Ciclopropyl-(N-methyliminodiacetoxy-O,O'N)borane (27).

To a stirred solution of **26** (0.121 g, 0.36 mmol) and $Pd(OAc)_2$ (0.0239 g, 0.011 mmol) in THF (12 mL) at 0°C in a 50 mL Schlenk flask was added a freshly prepared ethereal solution of diazomethane (3.5 mL of a 0.25 M solution, 8.8 mmol) dropwise over 20 minutes. Additional $Pd(OAc)_2$ was then added (0.0239 g, 0.011 mmol) as a solution in THF (1 mL) followed by the dropwise addition over 20 min of an additional 3.5 mL of 0.25 M ethereal diazomethane (0.88 mmol). The reaction was then allowed to warm to 23°C and the excess diazomethane was removed under a stream of N_2. The crude reaction mixture was then poured into 12 mL of 0.5 M pH 7 sodium phosphate buffer and extracted with THF:Et_2O 1:1 (3x12 mL). The combined organic fractions were then washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, Et_2O/CH_3CN 1:1) yielded **27** (0.34 mmol, 96%).

^{1}H NMR (200 M*Hz*, $CDCl_3$): δ -0.40 -0.38 (1H, m); 0.42-0.44 (1H, m); 0.66-0.67 (1H, m); 1.23-1.25 (1H, m); 2.80 (3H, s); 3.84 (2H, app dd J 17, 9.5 *Hz*); 3.96 (2H, app dd J 17, 3 *Hz*); 4.01 (2H, m); 4.5 (2H, s); 7.2-7.35 (5H, m).

3-benzyloxypropenylboronic-acid (18).

To a stirred solution of **27** (0.34 mmol) in THF (20 mL) was added 1M aq. NaOH (0.34 mmol) and the resulting mixture was stirred at 23°C for 20 minutes. The reaction was then quenched with the addition of 0.5 M pH 7 phosphate buffer (20 mL) and diluted with

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 **18** as a colorless oil. (0.33 mmol, 97%).Compound **18** was immediately used in next reaction without purifications and characterizations (very unstable).

1H-inden-3yl trifluoromethanesulfonate (19)

Triflic anhydride (0.649 g, 2.30 mmol) was added to a solution of 1-indanone **1** (0.290 g, 2.19 mmol) in dry 1,2-dichloroethane (12 ml) which was stirred under Argon at room temperature. 2,6-Di-*t*-butyl-4-methylpyridine (0.48 g, 2.35 mmol) was added to the reaction mixture in one portion. The solution warmed up to about 40°C. After stirring for 0.5h at room temperature the reaction mixture was diluted with 1,2-dichloroethane, washed with 1N HCl and water, dried and concentrated under reduced pressure at room temperature. The residue was purified by flash chromatography (SiO_2 Ethyl ether/petroleum 0.3:9.7) to give **19** (0.545 g, 94% yield) as a colourless oil.

^{1}H NMR (200M*Hz*, $CDCl_3$) δ: 3.47 (2H, br s,); 6.37 (1H, br, s); 7.25-7.60 (4H, m).

3-(2-Benzyloxymethyl-cyclopropyl)-1H-indene (20).

To a stirred solution of **18** and **19** in toluene (4ml) was added a mixture of 3% $Pd(PPh_3)_4$, Cs_2CO_3 (0.242 g; 0.74 mmoli) and

$KF.2H_2O$ (0.209 g; 2.22 mmoli) and NaBr (0.0954 g; 0.927 mmoli). The reaction was heated to 80°C for 16h. The mixture was filtered with Et_2O (3x10 ml) 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 **20** (30%).

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

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

To a stirred solution of **36** (1 mmol) in 1,2-dichloroethane (5 ml) was added an equimolar amount of triflic anhydride and 2,6-*t*-butyl-4-methylpyridine under Argon atmosphere. The brown suspension was stirred 30 min at 40°C and 1h at rt. 1,2-dichloroethane (10 ml) was added and the organic phase was washed with HCl 5% (3x10 ml). Organic layers were washed with water (2x20 mL), brine, dried over Na_2SO_4, filtered, concentrated and purified by flash column chromatography on silica gel (petroleum/Et_2O 99:1) affording **28** (241 mg, 75 %).

^{1}H NMR (200M*Hz*, $CDCl_3$) 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); ^{13}C NMR (100 M*Hz*, $CDCl_3$) δ 24.5(2C), 46.51, 55.57, 108.51, 112.07, 119.18, 120.30, 127.25, 127.78, 145.38, 153.14, 159.83.

3-cyclopropyl-6-methoxy-1,1-dimethyl-1H-indene (30)

To a stirred solution of cyclopropilboronic acid (0.06 g, 0.698 mmol) and **28** (0.150 g,0.466 mmol) in toluene (4 ml) was added a mixture of 6% $Pd(PPh_3)_4$, Cs_2CO_3 (0.120 g; 0.37 mmol) and $KF.2H_2O$ (0.105 g; 1.12mmol) and NaBr (0.048 g; 0.466 mmol). The reaction was heated to 80°C for 16h. The mixture was filtered with Et_2O (3x10 ml) and washed with water. Organic phase was dried over Na_2SO_4 and evaporated. The crude **30** was purified by flash column chromatography on silica gel (petroleum/ethyl ether 9.5/0.5) affording **30** (70 mg 70%).

^{1}H NMR (200M*Hz*, $CDCl_3$) δ: 0.58-0.87 (4H, m); 1.25 (6H, s); 1.8-1.9 (1H, m); 3.84 (3H, s), 5.72 (1H, s), 6.79-6.89 (2H, m), 7.27-7.32 (1H, m).

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

TEA (0.302 g, 2.99 mmol) and DMAP (0.036 g,0.03 mmol) were added to a solution of **37** (0.262 g, 1 mmol) in dry CH_2Cl_2 (50 ml). The reaction was stirred for 1h at room temperature and then cooled to -78°C. Tf_2O (0.564 g, 2 mmol) was added over 2 min, and after 15 min at -78°C the mixture was warmed to room temperature and washed successively with HCl 1N, H_2O and brine. The aqueous layer was extracted with CH_2Cl_2 (3x15 mL). Organic phase was dried over Na_2SO_4 and evaporated. The final product was obtained after column

chromatography (silica gel, petroleum/ethyl ether 8:2) of the crude **29** (0.286 g, 78%).

^{1}H NMR (200M*Hz*, $CDCl_3$) δ: 1.36-1.43 (3H, t, J 14 *Hz*),1.51 (6H, s), 3.88 (3H, s), 4.31-4.42 (2H, q, J 22 *Hz*), 6.89 (1H, s), 6.94-6.96 (2H, m), 7.35-7.4 (1H, m).

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

To a stirred solution of **29** (0.760 g,1.93 mmol) in toluene (10 ml) was added a mixture of cyclopropilboronic acid and K_3PO_4 (1,35 g, 6.36 mmol) and 3% $Pd(PPh_3)_4$. The reaction was heated to 100°C for 16h. The mixture was filtered with Et_2O (3x10 ml) and washed with water. Organic phase was dried over Na_2SO_4 and the solvent was evaporated. The crude product was purified by flash column chromatography on silica gel (petroleum/DCM 7:3) affording **31** (0.399 g , 80 %).

^{1}H NMR (200M*Hz*, $CDCl_3$) δ:0.87-1.28 (4H, m), 1.37-1.409 (3H, t, J 7.8 *Hz*) 1.51 (6H, s), 3.88 (3H, s), 4.25 -4.36 (2H, q, J 22 *Hz*), 6.75-6.87 (2H, m), 7.30-7.34 (1H, m).

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

To a stirred solution of **32** (11.3 g, 100 mmol) , Acetone (6.96 g, 120 mmol) and Acetic acid (2 g, 30 mmol) in Benzene (25 ml) was added L-phenylalanine (1 g, 6 mmol). The flask was fitted with a Dean-

Stark trap and a reflux condenser, and the mixture was refluxed with stirring for 14 hours. The reaction solution was allowed to cool to 23°C and the benzene was distilled. The mixture was filtrated and the solvent was evaporated. The crude **33** was distilled under reduced pressure at 120°C-135°C/0.1 mb affording **33** (14.2 g, 93%) .

^{1}H NMR (400M*Hz* $CDCl_3$) δ: 1.31-1.35 (3H, t, J 14 *Hz*), 2.3 (3H, s), 2.39 (3H, s) 4.23-4.29 (2H, q, J 22 *Hz*).

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

3-methoxyphenylmagnesiumbromide (1M in THF) (5.8 mmol, 5.8 ml) and a catalytic amount of CuI was added to a solution of **33** (0.888 g, 5.8 mmol) in anhydrous Et_2O (10 ml). The mixture was heated under reflux over night. It was then cooled in an ice-bath, and decomposed with HCl(2N) and worked up with Et_2O (3x10 ml). Organic phase was dried over Na_2SO_4.After removal the solvent, the residue was distilled under reduced pressure at 160°C-180°C/0.1mb to afford an yellow oil **34** (1.06g, 70%).

^{1} H NMR (200MHz,$CDCl_3$) δ: 1.05-1.12 (3H, t, J 14 *Hz*), 1.60 (6H, s), 3.57 (1H, s), 3.8 (3H, s), 4.0-4.072 (2H, q, J 14 *Hz*), 6.79-7.2(4H, m).

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

34 (1.306 g, 5 mmol) was added to a solution of KOH (2.24 g, 40 mmol) and 7.5 ml of ethylene glycol. The solution was heated under reflux for 11h at 170°C. When cool, it was diluted with H_2O, and a

small amount of a black oil was extracted with three portions of Et_2O. On acidification, the aqueous solution precipitated a dark oil which was extracted with two portions of ether. The extracts were washed with water and dried and the solvent was evaporated . The dark oil remaining was distilled under reduced pressure (to eliminate Ethylene glycol) affording **35** (0.776 g, 80%)

^{1}H NMR (200M*Hz*, $CDCl_3$) δ: 1.49 (6H, s),2.62 (2H, s), 3.81 (3H, s), 6.78-6.98 (4H, m).

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

A mixture of Eaton's reagent (9.62 ml) and **35** (1.2 g, 5.77 mmol) was heated at 110°C for 3h. After the mixture was allowed to room temperature, it was cooled in an ice- salt bath and washed with water. The mixture was extracted with ether (3x20 ml); the combined ether extracts were washed with saturated $NaHCO_3$ and Brine and dried (Na_2SO_4). Removal of the solvent gave crude **36** as a yellow oil. The crude product was purified by flash column chromatography on silica gel (petroleum/ether 7:3) affording **36** (0.877 g, 80 %).

IR (KBr): *v* 2977, 2947, 1654, 1577, 1081 $cm^{-1;}$ ^{1}H NMR (200 M*Hz*, $CDCl_3$): 1.39 (6H, s), 2.56 (2H, s), 3.89 (3H, s), 6.85-6.90 (2H, m), 7.63 (1H, d, J 9 *Hz*); ^{13}C NMR (50 M*Hz*, $CDCl_3$): δ 29.98, 38.47, 107.141, 114.98, 125.29, 128.77, 165.59, 166.89, 204.19. ESI MS m/z : 191.

Ethyl-5-Methoxy-3,3 dimethyl-1-oxo-indan-2-carboxylate (37).

To a stirred solution of NaH (60% mineral oil, 33.4 mmol) in (5 ml) diethyl carbonate was added a solution of **36** (2.95 g, 15.5 mmol) in (18 ml) diethyl carbonate. The mixture was refluxed at 80°C for 0.5h. After cooling to r.t., water (40 ml) was added. The aqueous phase was separated and extracted with DCM (4x10 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The oil residue was subjected to chromatography (Ethyl Ether/ Petroleum 1:1) to yield **37** (2.44 g, 60%).

^{1} H NMR (200M*Hz*, CDCl3) δ: 1.36-1.41 (3H, t, J 10 *Hz*), 1.54 (6H, s), 3.45 (1H, s), 3.87 (3H, s), 4.18-4.23 (2H, q), 6.86-6.93 (2H, m,), 7.72 (1H, d, J 8.1 *Hz*)

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

To a slurry of $Pd(OAc)_2$ (0.17 mmol, 10%) in dry DMF (15 mL) was added a solution **28** (1.7 mmol), ethyl acrylate (5.1 mmol), and triethylamine (6.8 mmol) in dry DMF (5 mL). The resulting mixture was heated at 75-80 °C in an argon atmosphere for 3 h, cooled to room temperature, and poured into ice-water. The resulting mixture was extracted with dichloromethane (3x30 mL), and the combined extracts were washed with water (2x30 mL), dried over sodium

sulfate, and concentrated under reduced pressure. Purification of the residue by chromatography with ether/petroleum ether 2:8 as the eluent gave **41** as a pale yellow oil (77%).

^{1}H NMR (200M*Hz*, $CDCl_3$) δ 1.36 (3H, t, J 7.2 *Hz*), 3.84 (3H, s), 4.27 (2H, q, J 7.2 *Hz*), 6.47 (1H, d, J 16.4 *Hz*), 6.58 (1H, s), 6.81-6.83 (1H, m), 6.91-6.94 (1H, m), 7.48-7.50 (1H, m), 7.66 (1H, d, J 16.4 *Hz*); ^{13}C NMR (100 M*Hz*, $CDCl_3$) 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 (42).

The following procedure was carried out behind a safety shield using plastic-coated glassware free of scratches and ground glass Joints. 1-Methyl-3-nitro-1-nitrosoguanidine (5 mmol) was carefully added portionwise over 30 min to an Erlenmeyer flask containing a swirled mixture of aqueous NaOH (20 mL, 5 N) and diethyl ether (15 mL) at 0°C. After vigorous bubbling had ceased, the organic layer (containing diazomethane) was decanted into a chilled (0 °C) Erlenmeyer flask containing KOH chips (1 g). The mixture was swirled for 10 min, and the yellow solution was decanted into a dropping funnel. The solution of diazomethane was added over 30 min to an open flask containing a stirred mixture of **41** (1 mmol) and palladium acetate (0.03 mmol) in CH_2Cl_2 (10 mL) maintained at 0 °C. After the mixture was stirred for 1 h, a second batch of freshly

prepared diazomethane (5 mmol) in 15 mL of diethyl ether was added over 30 min. After the mixture was stirred for 1 h, the reaction was quenched with water (4 mL) and the mixture was poured into an aqueous saturated solution of $NaHCO_3$ (15 mL). The aqueous layer was extracted with EtOAc (3x10 mL). The organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (petroleum/Et_2O 9:1) affording **42** (55 %).

^{1}H NMR (200M*Hz*, $CDCl_3$) 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 7.2 *Hz*), 3.86 (3H, s), 5.81 (1H, s), 6.77-6.82 (2H, m), 7.22 (1H, J 8.2 *Hz*).

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

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

^{1}H NMR (400 M*Hz*, $CDCl_3$): 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).

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

To a stirred suspension of NaH (11.00 mmol, 60% in mineral oil, 440 mg) in diethyl carbonate (2 ml) was added dropwise a solution

of 5-MeO-1-indanone **(1)** (5.00 mmol, 810 mg) in diethyl carbonate (20 ml). The mixture was warmed at 100°C in oil bath, until a solid spongy has been obtained. After cooling to rt, the spongy was diluted in CH_2Cl_2 and aqueous HCl 1N was added. The aqueous phase was separated and extracted in CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was subjected to chromatography (Et_2O/petroleum ether 1:1), followed by crystallisation (from i-Pr_2O) to yield 1140 mg (97%) as a white cristalline solid (m.p.: 58-60°C)

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.29 (3H, t, J 7.2 *Hz*), 3.28 (1H, dd, J_1 8.0 *Hz*, J_2 17.2 *Hz*), 3.48 (1H, dd, J_1 4.0 *Hz*, J_2 17.2 *Hz*), 3.68 (1H, dd, J_1 4.0 *Hz*, J_2 8.4 *Hz*), 3.88 (3H, s), 4.23 (2H, q, J 7.2 *Hz*), 6.90-6.91 (2H, m), 7.68 (1H, d, J 9.6 *Hz*); ^{13}C NMR ($CDCl_3$, 100 M*Hz*) δ: 14.08, 30.19, 53.40, 55.58, 61.40, 109.44, 115.82, 126.00, 128.28, 156.68, 165.75, 169.30, 197.42; ESI-MS, m/z: [M-H^+] = 233.2, [M+Na^+] = 257.1, [2M+Na^+] = 491.1.

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

A mixture of **β-ketoester** (3.00 mmol, 702 mg), N-bromosuccinimide (3.15 mmol, 561 mg) and Amberlyst-15®(2.25 g) in ethyl acetate (30 ml) was stirred at room temperature for 30 min. After completion of the reaction, as indicated by TLC, the reaction mixture was filtered and washed with ethyl acetate. The combined organic extracts were dried over anhydrous Na_2SO_4, concentrated *in*

vacuo and the resulting product was directly purified by chromatography eluted with a mixture of ethyl acetate/petroleum ether (3:7) to afford 900 mg (96%) of the corresponding pure product **45** as yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.17 (3H, t, J 7.2 *Hz*), 3.52 (1H, d, J 18.4 *Hz*), 3.81 (3H, s), 4.06 (1H, d, J 18.0 *Hz*), 4.16 (2H, q, J 7.2 *Hz*), 6.81-6.88 (2H, m), 7.64 (1H, d, J 8.4 *Hz*); ^{13}C NMR ($CDCl_3$, 100 M*Hz*) δ: 13.89, 43.80, 55.89, 59.35, 63.34, 109.45, 116.68, 125.04, 127.43, 153.38, 166.62, 167.05, 193.17; ESI-MS, m/z: [M+H$^+$] = 313.1-315.1, [M+Na$^+$] = 335.0-337.0, [2M+Na$^+$] = 648.5.

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

Sodium azide was added (4.36 mmol, 283 mg) to a solution of **45** (2.18 mmol, 680 mg) in dry DMF (3 ml) under nitrogen atmosphere and the resulting mixture was stirred at room temperature for 1h. After addition of H_2O, the aqueous layer was extracted in Et_2O. The combined organic layers were washed with brine, then dried over Na_2SO_4 and concentrated under reduced pressure. The resulting product was directly purified by chromatography eluted with a mixture of ethyl acetate/petroleum ether (3:7) to yield 570 mg (95 %).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.18 (3H, t, J 7.2 *Hz*), 2.89 (1H, d, J 17.2 *Hz*), 3.55 (1H, d, J 17.6 *Hz*), 3.83 (3H, s), 4.15-4.22 (2H, m), 6.83-6.90 (2H, m), 7.64 (1H, d, J 8.4 *Hz*); ^{13}C NMR ($CDCl_3$, 100

M*Hz*) δ: 13.88, 38.26, 55.80, 62.72, 70.39, 109.52, 116.58, 125.77, 127.04, 155.33, 166.70, 168.55, 195.22; **ESI-MS**, m/z: [M+Na^+] = 298.1, [2M+Na^+] = 572.9.

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

Under nitrogen atmosphere, at a solution of azide (2.07 mmol, 570 mg) in THF dry (20 ml) was added Ph_3P (3.11 mmol, 814 mg). After 10 min at 0° C, the cooling bath was removed and the clear solution was allowed to warm to rt. After stirring overnight, the complete consumption of starting material was confirmed by TLC. Trifluoroacetic anhydride (4.14 mmol, 576 μl) was added and the mixture stirred for 1h. H_2O was added and the aqueous layer was extracted in Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (ethyl acetate/petroleum ether 4:6) to afford 680 mg (95%) of the corresponding pure product **43** as white solid (m.p.: 106-108°C).

^{1}H NMR ($CDCl_3$, 400 M*Hz*) δ: 1.09 (3H, t, J 6.0 *Hz*), 3.37 (1H, d, J 17.2 *Hz*), 3.73 (1H, d, J 17.2 *Hz*), 3.84 (3H, s), 4.13 (2H, q, J 7.2 *Hz*,), 6.88-6.92 (2H, m), 7.66-7.70 (2H, m); ^{13}C NMR ($CDCl_3$, 100 M*Hz*) δ: 13.70, 37.99, 55.78, 63.39, 68.16, 109.40, 115.37 (q, J^1 286 *Hz*), 116.35, 126.75, 127.01, 155.00, 156.54 (q, J^2 = 37 Hz), 166.62, 167.60, 193.66; ESI-MS, m/z: [M+H^+] = 346.1, [M-H^+] = 344.1, [M+Na^+] = 368.1, [2M+Na^+] = 712.5, [2M+K^+] = 728.9.

Ethyl-1-hydroxy-5-methoxy-2-(2,2,2-trifluoroacetamido)-1-cyclopropyl-2,3-dihydro-1*H*-indene-2-carboxylate (44)

To a solution of **43** (4.00 mmol, 1380 mg) in THF dry (40 ml) was added cyclopropylmagnesium bromide solution (0.5 M in THF dry, 24.00 ml) at 0°C. The resulting mixture was stirred at 0° C for 30 min, NH_4Cl (s.s.) was added and the crude was extracted in Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (ethyl acetate/petroleum ether 1:9) to afford 1200 mg (78%) of the corresponding pure product **44** as white solid (m.p.: 92-95°C).

^{1}H NMR ($CDCl_3$, 400 M*Hz*) δ: 0.08 (1H, m), 0.40-0.48 (3H, m), 0.91-0.98 (1H, m), 1.29 (3H, t, J 7.2 *Hz*), 2.32 (1H, bs), 3.35 (1H, d, J 16.8 *Hz*), 3.78 (3H, s), 3.86 (1H, d, J 16.8 *Hz*), 4.18-4.36 (2H, m), 6.71-6.79 (2H, m), 7.13 (1H, d, J 8.4 *Hz*), 7.72 (1H, bs); ^{13}C NMR ($CDCl_3$, 50 M*Hz*) δ: 0.30, 1.11, 13.79, 16.63, 37.99, 55.17, 61.89, 73.25, 84.51, 109.72, 113.21, 115.38 (q, J^1 286 *Hz*), 125.14, 132.33, 140.59, 156.89 (q, J^2 36 *Hz*), 160.64, 169.73; ESI-MS, m/z: [M-H^+] = 386.2, [M+Na^+] = 410.1.

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

Under nitrogen atmosphere, trifluoromethanesulfonic anhydride was stirred (0.26 mmol, 43 μl) in CH_3CN dry (3 ml) for 15 min at room temperature. After cooling at 0°C, the compound **44** (0.26 mmol, 100

mg) was added, the resulting mixture was warming at room temperature and was stirred for 30 min. The reaction mixture was diluted with CH_2Cl_2 and quenched with NaOH 2N. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (ethyl acetate) to give 90 mg (81%) of the pure product **46** as yellow solid (m.p.: 46-48°C).

^{1}H NMR ($CDCl_3$, 400 M*Hz*) δ: 1.14 (3H, t, J 7.2 *Hz*), 1.70 (3H, s), 2.38-2.44 (1H, m), 2.83-2.88 (1H, m), 3.11-3.16 (1H, m), 3.34 (1H, d, J 17.2 *Hz*), 3.50-3.55 (1H, m), 3.71 (1H, d, J 17.2 *Hz*), 3.78 (3H, s), 4.13-4.17 (2H, m), 5.47 (1H, dd, J_1 6.4 *Hz*, J_2 9.6 *Hz*), 6.04 (1H, m), 6.75-6.78 (2H, m), 7.54 (1H, d, J 8.4 *Hz*), 7.96 (1H, bs); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.77, 22.81, 28.65, 38.65, 41.40, 55.32, 62.52, 67.54, 109.48, 113.83, 115.53 (q, J^1 286 Hz), 120.56, 125.52, 130.01, 141.13, 145.34, 156.60 (q, J^2 38 Hz), 160.42, 170.83, 171.14; ESI-MS, m/z: $[M+H^+]$ = 429.2, $[M-H^+]$ = 427.2, $[M+Na^+]$ = 451.1.

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

A trimethylsilyl polyphosphate (PPSE) solution, prepared by heating at reflux for 1.5h a mixture of P_2O_5 (3.50 mmol, 497 mg) and hexamethyldisiloxane (4.91 mmol, 1.04 ml) in CCl_4 (5 ml), was added at room temperature to **46** (0.35 mmol, 150 mg). The reaction mixture was heated at reflux for 5h, cooled to room temperature,

diluted with CH_2Cl_2 and quenched with NaOH 2N. The aqueous layer was extracted with CH_2Cl_2, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel conditioned with TEA and ethyl acetate as eluent to give 90 mg (63%) of product **7f** as yellow oil.

^{1}H NMR ($CDCl_3$, 400 M*Hz*) δ: 1.06 (3H, t, J 7.2 *Hz*, E isomer), 1.14 (3H, t, J 7.2 *Hz*, Z isomer), 2.13 (3H, s, Z isomer), 2.27 (3H, s, E isomer), 2.51-2.64 (2H, m, mix E/Z), 3.00-3.06 (2H, m, mix E/Z), 3.36-3.66 (4H, m, mix E/Z), 3.72-4.08 (4H, m, mix E/Z), 3.78 (6H, s, mix Z/E), 4.13 (2H, q, J 7.2 *Hz*, E isomer), 4.21 (2H, q, J 7.2 *Hz*, Z isomer), 6.73-6.84 (4H, m, E/Z mix), 7.31 (1H, d, J 8.4 Hz, E isomer), 7.50 (1H, d, J 8.8 Hz, Z isomer), 7.75 (1H, s, E isomer), 7.92 (1H, s, Z isomer); ESI MS, m/z: $[M+H^+]$ = 411.2, $[M+Na^+]$ = 433.1, $[M-H^+]$ = 409.2.

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

Methyl trifluoromethanesulfonate (0.22 mmol, 25 μl) was added to a solution of **7f** (0.22 mmol, 90 mg) in anhydrous benzene (5 ml). The product of reaction was recovered quantitatively as yellow-orange oil.

^{1}H NMR ($CDCl_3$, 400 M*Hz*) (Mix1:1 Z/E) δ: 1.11 (3H, t, J 7.2 *Hz*, Z), 1.11 (3H, t, J 7.5 *Hz*, E), 2.56 (3H, s, E), 2.72 (3H, s, Z), 3.13 (1H, d, J 16.6 *Hz*, E), 3.18-3.30 (4H, m, mix E/Z), 3.40 (1H, d, J 16.6 *Hz*, Z), 3.52 (3H, s, E), 3.54 (3H, s, Z), 3.77 (1H, d, J 16.6 *Hz*, E), 3.90 (1H, d, J 16.6 *Hz*, Z), 4.10-4.30 (8H, m, mix E/Z), 6.83-7.00 (4H, m, mix E/Z), 7.51 (1H, d, J 9.7 *Hz*, Z), 7.54 (1H, d, J 9.2 *Hz*, E), 8.52 (1H, s, E), 8.90 (1H, s, Z). ^{13}C NMR ($CDCl_3$, 100 M*Hz*) δ: 13.50, 17.30, 17.43, 28.32, 32.02, 37.62, 37.90, 43.18, 45.38, 55.70, 57.67, 58.12, 63.46, 63.57, 69.35, 71.66, 109.18, 109.44, 114.43, 114.83, 115.41 (q, J^1 287 *Hz*), 118.82, 122.00, 127.93, 128.12, 129.28, 129.63, 130.92, 131.31, 149.73, 150.36, 151.19, 154.65, 156.60 (q, J^2 38 *Hz*), 156.70 (q, J^2 38 *Hz*), 163.56, 164.34, 167.64, 168.66; ESI MS, m/z: [M^+] = 425.

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

A stirred solution of Malonic acid (4.60 g,40 mmol), 3-methoxy benzaldehyde (5.38 ml,40 mmol), pyridine (3.20 ml,40 mmol) and a catalytic amount of piperidine was refluxed at 90-95°C. After 2h the mixture was allowed to 115°C. After 1h the mixture was allowed to room temperature. The solution was poured in an ice-bath (water 40 ml). and it was acidify with HCl (6M). The mixture was filtered and it was dried under vacuum at 50°C over night affording **52** (6.60g, 37 mmol**,** 84%) as white solid m.p. (116°C-119°C).

^{1}H NMR (200M*Hz*; $CDCl_3$) δ: 3.84 (3H, s,); 6.44 (1H, d, J 15.8 *Hz*); 6.96(1H, m, J_{PARA} 0.80 *Hz*; J_{META} 2.6 *Hz*; J_{ORTO} 6.8 *Hz*), 7.06 (1H, t, J 2.2 *Hz*; J 3.8 *Hz*); 7.14 (1H, d, J 7.6 *Hz*); 7.32 (1H, t, J 7.8 *Hz*; J 15.8 *Hz*); 7.76 (1H, d, J 15.8 *Hz*).

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

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

^{1}H NMR (200 M*Hz*,$CDCl_3$) δ: 2.67 (2H, m); 2.94 (2H, m); 3.79 (3H, s,); 6.77 (3H, m) ; 7.21 (1H, m); 9.00 (1H, s,-COOH).

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

A solution of **53** (3.32 g, 18 mmol) in CH_2Cl_2 (50ml) was treated with N,O-dimethylhydroylamine hydrochloride (3.00 g, 30 mmol), EDCI (5.74 gr, 30 mmol), pyridine (2,44 ml, 30 mmol) and catalytic amount of DMPA and stirred at room temperature for 2h. The reaction was quenched with HCl 5% (25ml) and H_2O (25ml). The aq. phase was extracted with AcOEt. The organic layers were dried over anhydrous sodium sulfate, and concentrated *in vacuo* affording a crude **54** as yellow viscous oil (4.45 gr). Oil was dissolved in AcOEt

and it was washed with a saturated solution $NaHCO_3$. The mixture was extracted with AcOEt, dried over anhydrous sodium sulfate, and concentrated *in vacuo* affording **54** (3.46 g, 15 mmol, 84%) as clear yellow oil.

^{1}H NMR (200 M*Hz*, CDCl3) δ: 2.76 (2H, t); 2.92 (2H, m); 3.17 (3H, s); 3.79 (3H, s); 6.78 (3H, m); 7.20 (1H, dd).

Tetrabutylammonium peroxydisulfate

Tetrabutylammonium hydrogensulfate (21.2 g, 64.0 mmol) and potassium persulfate (8.70 g, 32.0 mmol) were dissolved in 140 mL of distilled water and the solution was stirred for 30 min at room temperature. The solution was extracted with CH_2Cl_2 (3x30 mL), and the combined organic layers were washed with distilled water (3x30 mL), dried over anhydrous Na_2SO_4, and filtered. Evaporation of the solvent *in vacuo* and subsequent drying under high vacuum gave TBPA (21.0 g, 31 mmol,) as a white solid in 97% yield. m.p. 118–120 °C

^{1}H NMR (200 M*Hz*; $CDCl_3$) δ: 0.94 (12H, t); 1.43 (8H, m); 1.60 (8H, m); 3.28 (8H, t).

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

To a stirred solution of **54** (1.35 g, 6.05 mmol) and TBPA (4.42 g, 6.05 mmol) in CH_3CN (30ml) was added a solution of I_2 (1.54 g, 6.05 mmol) in CH_3CN (70ml). The mixture was stirred for 5h at

48°C. The dark solution was allowed to room temperature and a solution of Na_2SO_3 1M was added until bleaching of the reaction mixture. The aq. layer was extracted with AcOEt (3x20 ml) and the organic layers were washed with H_2O. The solvent was dried and concentrated *in vacuo* to give **55** (1.73 g, 4.95 mmol, 82%).

^{1}H NMR (200 M*Hz*; $CDCl_3$)δ: 2.71 (2H, t); 3.02 (2H, m); 3.18 (3H, s); 3.64 (3H, s); 3.77 (3H, s); 6.48-6.54 (1H, dd, j_1 3, j_2 5.7 *Hz*); 6.86 (1H, d, j 3.2 *Hz*); 7.66 (1H, d, j 8.8*Hz*).

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

A 50 ml dry four-necked round bottom flask equipped with a mechanical stirrer, an internal thermometer, a rubber septum and an argon gas inlet was charged with 500 mg of **55** (1.43 mmol) and 12.8 ml of anhydrous THF. The stirred solution was cooled to -78°C by mean of a liquid nitrogen bath and 7.16 ml (7.16 mmol) of a 1M solution of DIBAL-H in THF was added dropwise. After 1h the solution was allowed to 0°C and it was quenched with Acetone (0.41 ml, 7.16 mmol) and a solution of Rochelle (20ml). The mixture was allowed to room temperature and it was stirred at r.t. for 1h. It was extracted with AcOEt; dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The product **47** (360 mg, 1.24 mmol, 86.7%) was obtained after purification by flash column chromatography on silica gel (petroleum/AcOEt 8:2).

^{1}H NMR (200 M*Hz*; CDCl3)δ: 2.71 (2H, t); 3.02 (2H, m); 3.18 (3H, s) 3.64 (3H, s); 3.77 (3H, s); 6.48-6.54 (1H, dd, J 3, 5.7*Hz*); 6.86

(1H, d, J 3.2 *Hz*); 7.66 (1H, d, J 8.8 *Hz*). IR (film) ν: 2935; 1721; 1588-1566; 1465; 1278; 801 cm^{-1}

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

To a stirred solution of L-pyroglutamic acid (12.5 g, 97 mmol) in MeOH (150 ml) at 0 ºC was added thionyl chloride (14 ml, 194 mmol) dropwise over 5 minutes. The reaction was allowed to warm to r.t. and stirred for 2 hours. The reaction mixture was concentrated *in vacuo*, and the resulting yellow oil was dissolved in DCM (100 ml), washed with a saturated solution of $NaHCO_3$ (30 ml) and brine (30 ml). The combined aqueous layers were further extracted with DCM (5x30 ml). The organic layers were then dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield **57** (14 g, 83%) as a clear oil, which was used without further purification.

^{1}H NMR (200 MHz; $CDCl_3$) δ: 2.27 (4H, m); 3.71 (1H, s); 4.23 (1H, m,); 7.07 (1H, s).

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

To a stirred solution of **57** (5 g, 30 mmol) in CH_2Cl_2 (10 ml), was added di-*tert*-butyldicarbonate (9 g, 40 mmol) and DMAP (360 mg, 3 mmol). After 3 hours the reaction mixture was concentrated *in vacuo* to yield a dark orange oil. Purification by column chromatography eluting with EtOAc/Petroleum 4:6 to yield **48** (12.6 g, 70%) as white crystalline solid; m.p. 67-69°C.

$[\alpha]^{22}_{D}$ -31.8 (*c* 1,CH_3Cl).

^{1}H NMR (200 M*Hz*, $CDCl_3$)δ: 1.48 (9H, s); 2.00 (1H, m); 2.23 (1H, m); 2.50 (1H, m); 2.59 (1H, m); 3.77 (3H, s); 4.62 (1H, dd, J 10, 3 *Hz*). IR (film): ν 2996, 1755, 1737, 1701, 1301, 1142 cm^{-1}.

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

To a solution of methyl N-BOC-pyroglutamate **(48)** (240 mg, 0.98 mmol) in dry THF (5mL) stirred at -78 °C was added a 1 M solution of lithium hexamethyldisilazide in THF (1 mL, 1 mmol). The reaction mixture was stirred for 1 h at -78 °C prior to the addition of a solution of the aldehyde **(47)** (300mg, 1.04 mmol) and $Et_20.BF_3$ (125µl, 1 mmol) in THF (5 mL). The reaction mixture was stirred for 2 h at -78 °C and it was quenched with saturated NH_4Cl solution (5 mL), and H_2O (5 ml), and it was stirred at r.t. for 15 minutes and extracted with ethyl ether (3x20 mL). The combined organic phases were dried over Na_2SO_4, filtered, and evaporated to dryness. Purification of the crude **58** by flash chromatography (AcOEt/Petroleum 2:8) gave a mixture of aldols **58** (410 mg, 0.77 mmol, 78%)

$[\alpha]^{22}_{D}$ -14(*c*1,CH_3Cl)

^{1}H NMR (400 M*Hz*,$CDCl_3$)δ: 1.49 (9H, s); 1.658-1.746 (3H, m); 2.149-2.207 (2H, m); 2.614-2.663 (1H, m); 2.684-2.909 (2H, m);

3.76 (3H, s); 3.77 (3H, s, -$COOCH_3$); 4.37 (1H, s, -OH); 4.564 (1H, dd); 6.512 (1H, m);6.844 (1H, d, J 3.2 *Hz*); 7.648 (1H, d, J 8.4*Hz*).

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

To a stirred solution of **58** (820 mg, 1.54 mmol) in dry CH_2Cl_2 (10ml) at 0°C was added Imidazole (314 mg, 4.62 mmol), Triphenylphosphine (444 mg, 1.70 mmol) and I_2 (430 mg, 1.70 mmol). After this solution was stirred at r.t. for 3h it was quenched with $Na_2S_2O_3$ (6 ml) and H_2O (4 ml). The mixture was extracted with CH_2Cl_2 (3x20 ml) and washed with Brine, dried over Na_2SO_4, filtered and evaporated *in vacuo* affording to crude **49** as diastereomeric mixture. After purification by flash chromatography (AcOEt/Petroleum 3:7) affording *E* (140 mg, 0.27 mmol) and *Z* (40 mg, 0.07 mmol), *E*+*Z* (610 mg, 1.18 mmol) (yield 88%).

E $[\alpha]^{22}_D$ +64 (*c* 1,CH_3Cl)

Z $[\alpha]^{22}_D$ -2.53 (*c* 1,CH_3Cl)

^{1}H NMR (400 M*Hz*, $CDCl_3$) *E* δ: 1.05 (9H, s); 2.419-2.523 (3H, m); 2.79-2.85 (3H, m); 3.75 (3H, s); 3.76 (3H, s, -$COOCH_3$); 4.58 (1H, dd, J 10.2, 3.2 *Hz*); 6.51 (1H, dd, J 8.8, 2.8 *Hz*); 6.72 (1H, d, J 3.2 *Hz*); 6.79 (1H, m); 7.65 (1H, d, J 8.4 *Hz*).^{13}C-NMR (400 M*Hz*, $CDCl_3$) *E* δ: 25.66; 28.01; 30.01; 39.46; 52.66; 55.46; 55.83; 83.71; 88.58; 114.34; 115.68; 129.67; 137.34; 140.06; 144.11; 149.96;

160.11; 165.80; 171.73. IR (film)ν : 2980; 1772; 1733; 1701; 1236; 1146; 718 cm^{-1} MS (m/z) 516.0; 459.9; 415.8; 275.7 m/z.

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

To a stirred solution of **49** (200 mg, 0.38 mmol) in anhydrous DMF (6ml) was added $Pd(OAc)_2$ (8.53 mg, 0.038 mmol), Triphenilphosphine (40.75 mg, 0.15 mmol) and TEA (116.3 mg 1.14 mmol). The mixture was heated at 110°C for 5h and it was washed with Brine. The aq. layers were extracted with Et_2O (3x20ml), and the organic phase was dried, filtered and evaporated. Flash chromatography on silica gel (AcOEt/Petroleum 3:7) afforded **50** (100 mg, 0.26 mmol, 66%) as yellow solid.

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

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

^{1}H NMR (400 M*Hz*,$CDCl_3$)δ :1.51 (9H, s); 2.93-2.98 (1H, dd, J 16.8, 2.8*Hz*); 3.04 (2H, t, J 6.4); 3.29-3.47(3H, m); 3.75 (3H, s); 3.84 (3H, s); 4.72 (1H, dd, J 10.6,3.6 *Hz*); 6.85 (1H, dd, J 8.6, 2.4 *Hz*); 6.90 (1H, s); 7.40 (1H, d, J 8.4*Hz*).^{13}C-NMR (400 M*Hz*,$CDCl_3$)δ: 28.05 ; 28.31; 30.97; 31.47; 52.55; 55.52; 56.01; 83.12; 109.94; 114.04; 114.46; 126.67 ;133.14 ;150.46; 153.86; 155.21; 161.86 ;167.61 ;172.27. IR(film)ν: 2976; 1748; 1708; 1596-1488; 1149 cm^{-1} MS(m/z): 387.9; 331.9; 287.9.

Analytical conditions for chiral separation:

49 S: Enantiomer **L – 49 R:** Enantiomer **D**

System: HP Agilent 1100 HPLC

Column: ChiralPak AD-H 250 x 0.46 cm

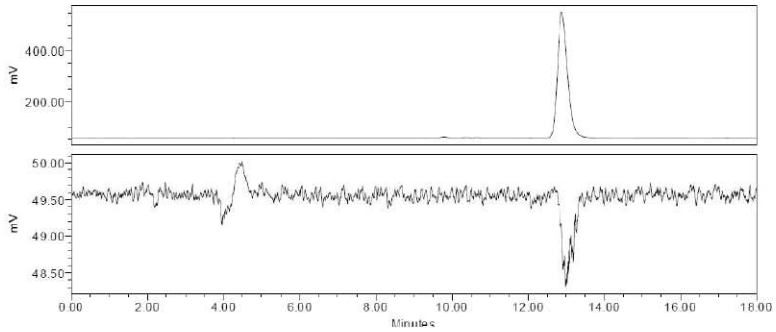
Mobile phase: n-Hexane/EtOH 65/35% v/v

Flow rate: 0.8ml/min

DAD: 210/340 nm

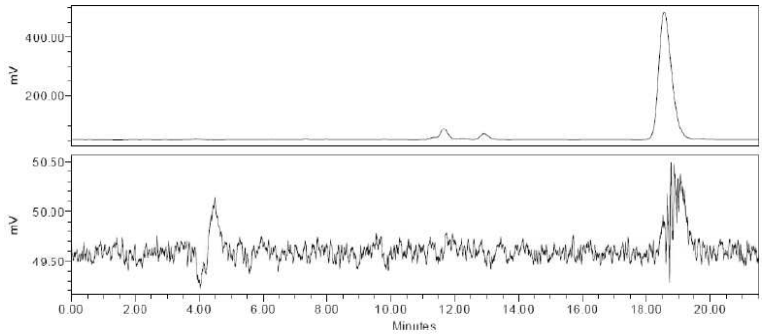
CD: 240 nm

Enantiomer **D**



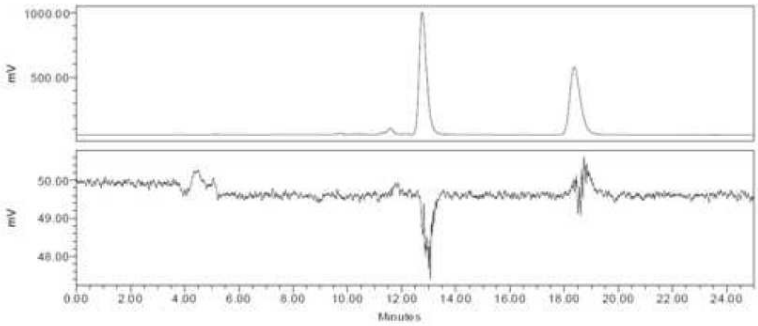
UV and CD Chromatograms of 49 R

Enantiomer **L**



UV and CD Chromatograms of 49 S

L-D Mixture



UV and CD Chromatograms of mixture

50S: Enantiomer **L – 50 R:** Enantiomer **D**

System: HP Agilent 1100 HPLC

Column: ChiralCel OD-H 250 x 0.46 cm

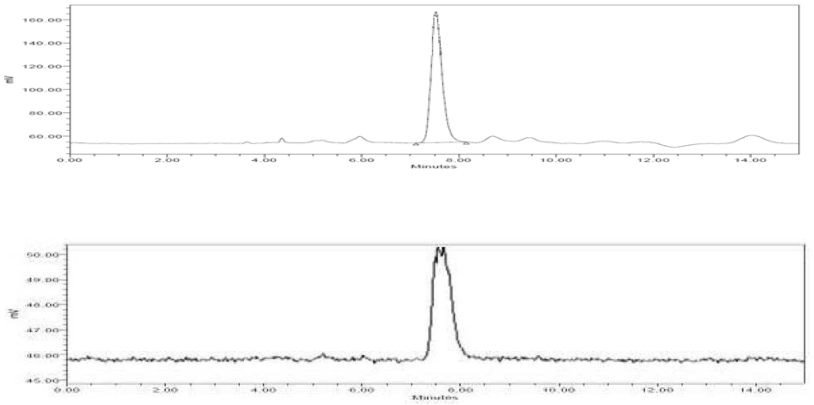
Mobile phase: n-Hexane/EtOH 70/30% v/v

Flow rate: 0.8ml/min

DAD: 210/340 nm

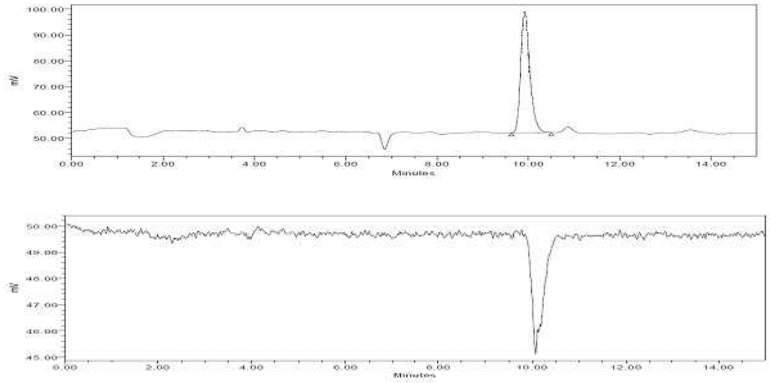
CD: 240 nm

Enantiomer **D**



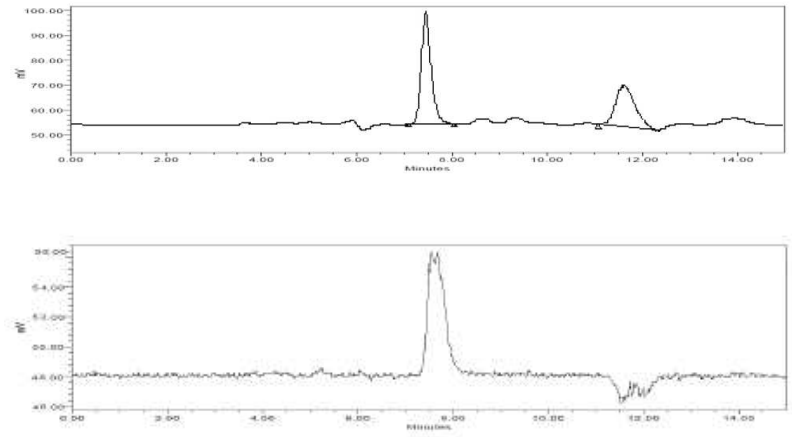
UV and CD Chromatograms of 50 R

Enantiomer **L**



UV and CD Chromatograms of 50 S

L-D Mixture



UV and CD Chromatograms of mixture

4.3 Abbreviations

Ac	Acetyl
ACN	Acetonitrile
DCM	Dichloromethane
DIPEA	N,N-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
EDCI	1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide
KHMDS	Potassium Hexamethyldisilazane
LDA	Lithium diisopropylamide
LHMDS	Lithium Hexamethyldisilazane
LiHMDS	Lithium bis(trimethylsilyl)amide
Ms,MsO	Mesyl
NBS	*N*-bromosuccinimide-*succinimide*

PCC	Pyridinium Chloro Chromate
Pd/C	Palladium on Carbon
PPSE	Trimethylsilyl polyphosphate
PTSA	*para*-Toluene solfonic acid
Py	Pyridine
TBAF	tetra-*n*-Butylammonium fluoride
TBPA	Tetrabutylammonium peroxydisulfate
t-BuOH	*tert*-Butanol
t-BuOK	Potassium *tert*-butoxide
TDA-1	Tris(2-(2-methoxyethoxy)ethyl)amine
TEA	Triethylamine
TFA	Trifluoroacetic acid
Tf, TfO	Triflate
THF	Tetrahydrofuran
TBMS	*tert*-Butyldimethylsilyl
Ts, TsO	Tosyl