UNIVERSITY OF CAMBRIDGE

Development of a Catalytic Enantioselective Assembly of Complex Molecules Containing Embedded Quaternary Stereogenic Centers From Simple Phenol Derivatives and its application to the synthesis of natural products

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SEVENTH FRAMEWORK PROGRAMME

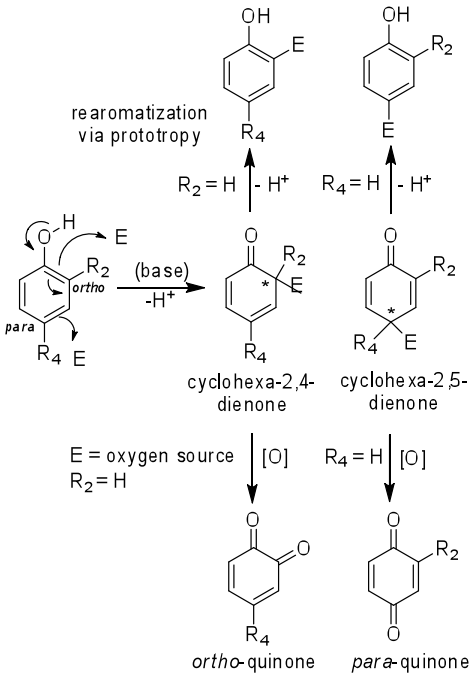
1.- INTRODUCTION

Despite the changing face of organic chemistry one aspect remains persistent: the ability to make molecules is something that, even now, is still unique to the synthetic chemist. What is changing in synthesis is the way that we go about achieving our goal. The use of catalysts to control the synthesis of architecturally complex and enantiopure molecules is a key aspect for the future of organic chemistry.[1-3] Not only does this concept impact strongly on all aspects of chemical synthesis but also the continued development of chemical biology, medicinal chemistry and materials science. The challenge for the synthetic chemist is to develop novel strategies for complex molecule synthesis that combine the factors of atom economy, catalysis and stereocontrol.

The continually increasing challenges associated with the treatment of new and existing diseases often demands that potential therapeutics contain higher levels of molecular complexity in order to achieve potency, selectivity and desirable physical properties. Of particular relevance is the emergence of drug candidates with one or more non-racemic asymmetric centres.[4] Single enantiomer compounds, whether they be natural products or therapeutic agents, are however significantly more difficult to synthesize. Although conventional asymmetric synthesis has coped for many years, new enantioselective methods are now required to meet these challenges that are robust, efficient and generally applicable in a range of environments. The rapid generation of molecular complexity through asymmetric catalytic methods has become a key factor in the chemical synthesis of natural products and molecules of biological and medicinal relevance. While enantioselective catalytic methods have unlocked access to a plethora of non-racemic small molecules the formation of more complex architectures is not always straightforward.[5] Chemists have often strived to mimic Nature's elegant synthesis machinery in achieving this goal but it is an ideal that is rarely achieved.[6] Of particular note are the recent developments of catalyst controlled cascade reactions that have led to a significant advance in this field, however, the molecules that are accessible from such strategies are often small, 'building block' type molecules that still require much synthetic endeavour to reach the desired target.[7-9]

In complex natural product synthesis, phenol ring has been widely used over the years. The richness of the chemistry of phenols is quite remarkable when one

realized that it is simply the presence of a hydroxy group on a benzene ring that renders this otherwise quasi-inert aromatic system amenable to many chemical transformations.[10] The relatively weak bond dissociation energy of their O-H bond opens the door to radical reactions via one-electron dehydrogenative oxidation. Then, it is converted into delocalized phenoxy radicals, which notably underlie the (bio)synthetic implications of various phenolic precursors in the structural elaboration of numerous complex natural products,[11] including biopolymers such as lignins. An important asset of a dearomatization of phenols for organic synthesis resides in the fact that one of the sp^2-hybridized carbon centers of a planar achiral starting material is thus transformed into a sp^3-hybridized carbon center and, hence possibly chiral (*Scheme 1*). If this new created chirality can be enantio- or diastereoselectively controlled, it then offers tremendous opportunities for inducing asymmetry in subsequent reactions.



Scheme 1

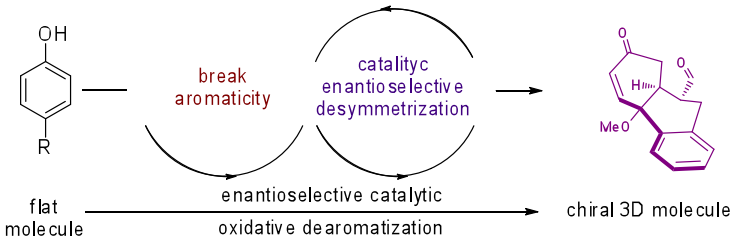
Phenol dearomatization processes have been extensively used in organic synthesis.[12] However, it remains to evoke the different tactics by which such a transformation can be achieved. These tactics have been extensively discussed in several recent reviewarticles.[13-16] Briefly, this is possible due the phenolic hydroxyl group ability to shuttle electrons out of the phenyl ring. In this context, the nucleophilic reactivity of the phenol remains center stage. As depicted in *scheme 1*,

this reactivity can, for example, be exploited to directly install a desired substituent at an already substituted *ortho*/*para* position. Usually, the nucleophilic substitution process suffers from a lack of regioselectivity, which is difficult to control with most electrophilic partners and is further impeded by the steric demand of the process.[17] Alternatively, the desired substituent can first be included in the phenolic oxygen atom and then transferred to a substituted *ortho*-carbon center This is, for example, the case in the classical O-allylation/Claisen rearrangement sequence.[18, 19] Another option is to take advantage of the susceptibility of the phenol toward oxidation by electron-transfer processes. For example, under neutral or slightly acidic anodic oxidation conditions, it is possible to convert a phenol into a phenoxenium cation intermediate (see *Scheme 1*) that can then be trapped by nucleophilic species. In spite of this appealing potential for synthesis, anodic oxidation processes are, unfortunately, not always credited with a high preparative value and often require some special electrochemical apparatus for ensuring selective transformations.[16] However, this tactical option is of fundamental importance, for it conceptually unearths the possibility of oxidatively switching the reactivity of phenols from being nucleophiles into becoming electrophiles.

Annulated arene heterocycles and carbocycles can be conveniently prepared by the electrophilic cyclization of arenes bearing heteroatom- or carbon-tethered olefins, respectively. However, only a few examples of the analogous chemistry of alkynes have been reported,[20, 21] although this would appear to be a very efficient route to a wide range of useful, functionally substituted heterocycles and carbocycles.[22] All previously reported reactions of this type have employed *ortho*-substituted arenes. In that regard, spiro[4,5]trienones can be accessed via intramolecular *ipso*-halocyclization of simple methoxy-substituted 4-aryl-1alkynes.[22]

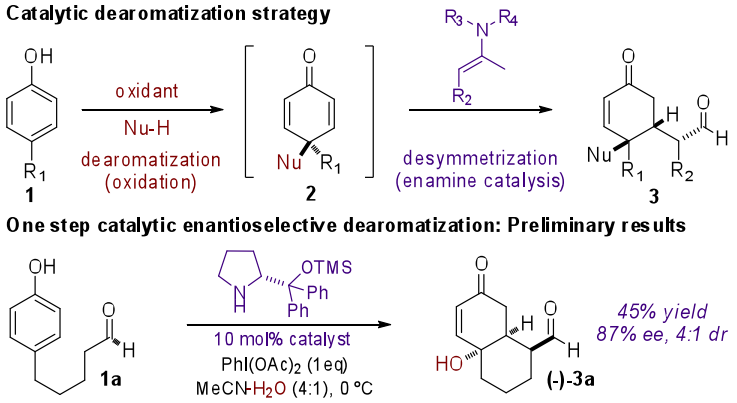
The inherent reactivity and functionality stored within aromatic systems provide numerous possibilities for the synthesis of 3D organic structures via dearomatization processes.[23, 24] Under oxidation conditions, the dearomatization of *ortho*- and *para*-substituted phenols forms cyclohexadienones, and these products have found widespread use in the chemical synthesis of natural products. Additionally, the groups of Feringa,[25] Hayashi,[26] and Rovis[27] have developed catalytic desymmetrization methods to convert the cyclohexadienone motif into useful enantioenriched molecules. The elegance of these stepwise tactics leads us to speculate that a catalytic asymmetric process that can directly transform an aromatic

motif into the nonracemic structure would provide a powerful strategy for the rapid chemical synthesis of complex molecules (*Scheme 2*).



Scheme 2

This process directly converts a *para*-substituted phenol to a highly functionalized chiral molecule via oxidative dearomatization and amine-catalyzed enantioselective desymmetrizing Michel reaction (*Scheme 3*). This one-step transformation reveals a complex structure formed with exquisite control of three new stereogenic centers and an array of exploitable orthogonal functionality directly from a flat molecule that is devoid of architectural complexity.[28]



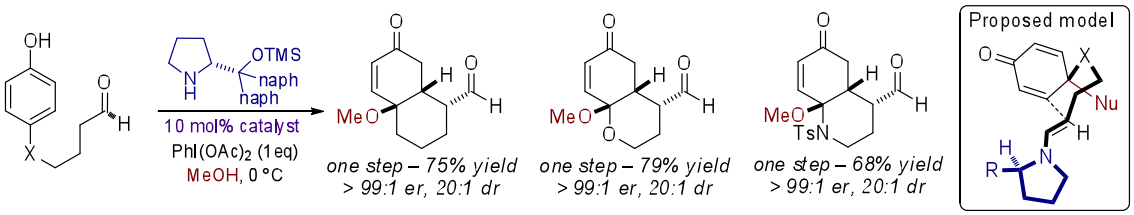
Scheme 3

The key-point of this project is the development of synthetic strategies that address the necessity to formulate complex molecular architectures by empowering controlled chemo-catalytic cascade reactions. This proposal outlines our blueprint for chemo-catalytic cascade processes for single step complex molecules synthesis that provides an unprecedented approach to rapid generation of molecular complexity.

2.- <u>SUBPROJECT I</u>: Development of an electrophile-triggered catalytic enantioselective dearomatization process

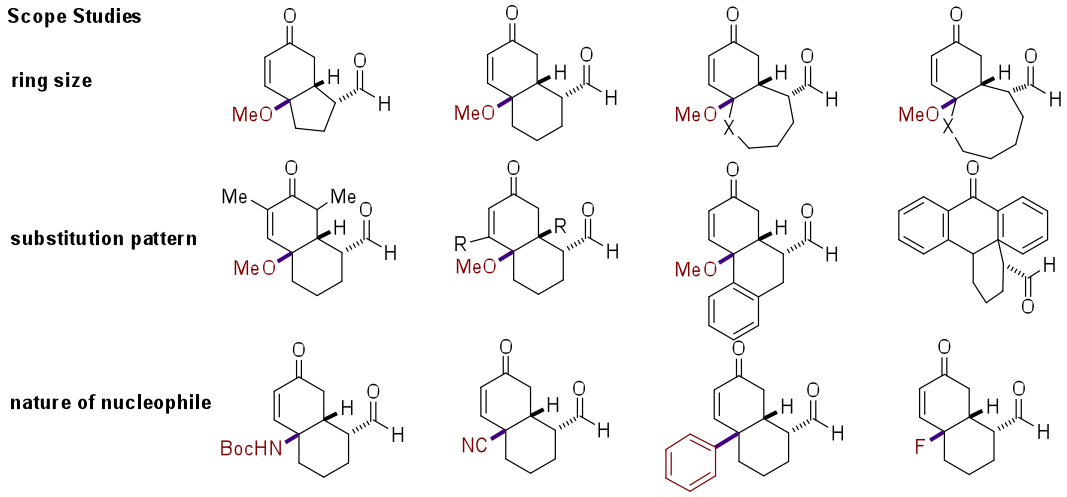
Many biologically active natural products and molecules of therapeutic value exhibit quaternary stereogenic centers at the heart of their structures.[29] Accessing these molecules in an asymmetric form is not trivial; furthermore, the synthesis of compounds with fully substituted stereocenters that display valuable orthogonal functionality for further manipulation often requires multiple chemical transformations. Accordingly, the asymmetric synthesis of these demanding motifs has inspired many research programs,[30-40] and the development of new catalytic enantioselective strategies that rapidly install quaternary stereogenic centers embedded within complex molecular architectures remains a significant and important challenge to the continued advancement of chemical synthesis.[41-44]

Initial experiments conducted in our lab, towards an oxidative enantioselective organocatalytic dearomatization (CED) process wherein a phenol derivative can be directly converted to a highly substituted decalin framework.[28] Early studies have identified that the optimal catalyst is the prolinol derived[45] and that reaction in polar and/or protic solvents (MeCN/MeOH) affords the product excellent er (>99:1), high dr (20:1) and very good yield.[28] This simple transformation forms three new chiral centres, two ring systems and latent orthogonal functionality directly from a simple flat molecule. A general mechanism (*Scheme 6*) shows the $PhI(OAc)_2$ (PIDA) oxidizes the phenol[11, 46-49] with the concomitant addition of a nucleophile to the *para*-position of the aromatic ring. The resulting intermediate is a *meso*-cyclohexadieneone that undergoes desymmetrizing intramolecular Michael addition[26] with the pendant aldehyde via the catalytically generated chiral enamine. Hydrolysis of iminium returns the catalyst and releases the product.



Scheme 4

It also has been established that this reaction works on more than one substrate (*Scheme 4*). In all cases the reaction works extremely well, delivering high er products in very good yield as single isomers and promises many exciting opportunities for the broad applicability of this new process. The scope of this new concept can be defined by the a number of factors and ideally, it can be implemented to (i) a range of aldehyde tether units can be accommodated including changing the ring size, in addition to (ii) functionality and substitution patterns and also (iii) different nucleophiles (O, N, C, F etc) can be used in the dearomatization step (*Scheme 5*).

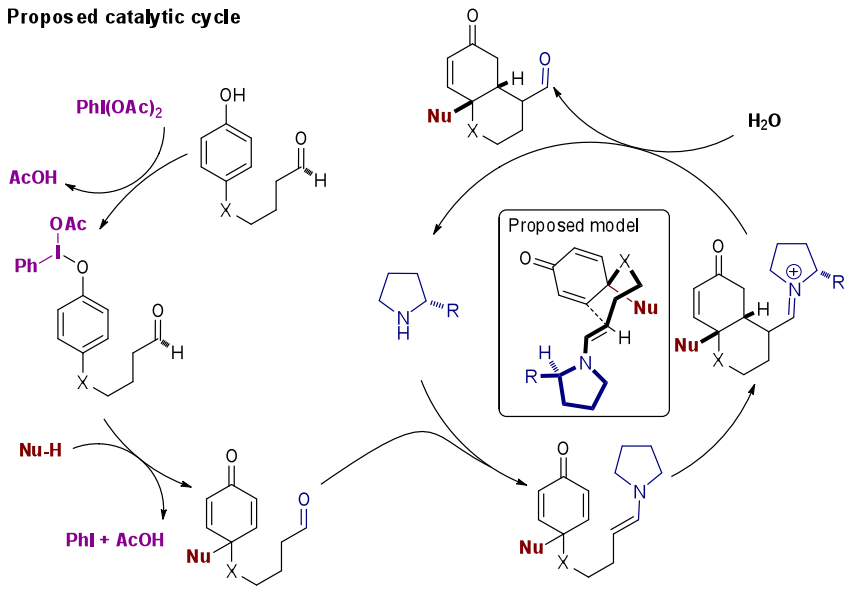


Scheme 5

The overall transformation generates highly functionalised ring systems, creates numerous new stereocenters and bonds from a flat achiral molecule. This process can also be extended to cascade processes and in this way we aim to be able to synthesise complex molecule targets where the majority of the architecture can be formed in one chemical operation.

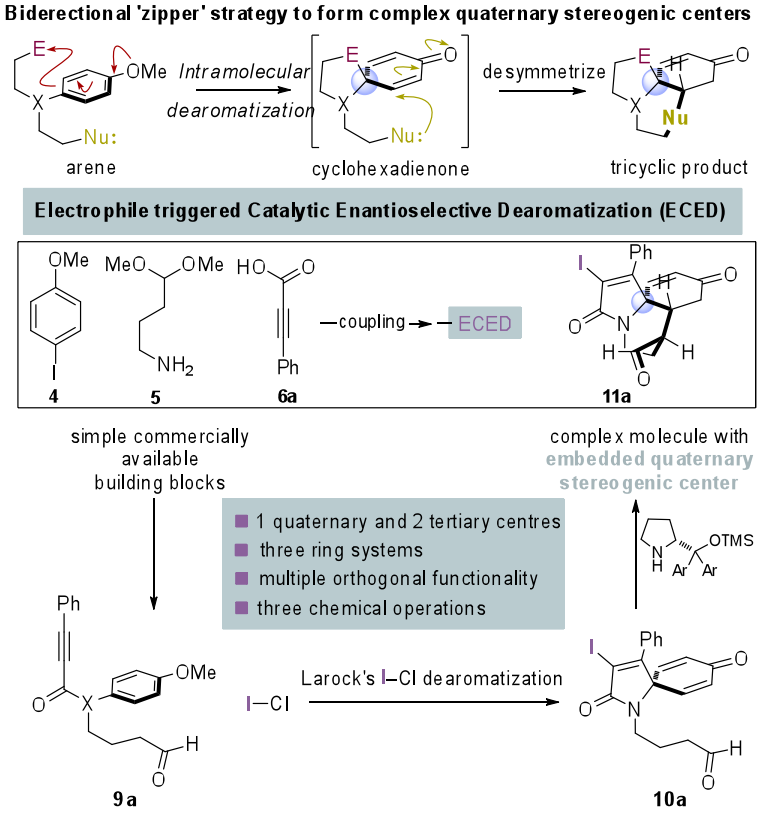
Oxidative dearomatization reactions provide a powerful method of building complex molecules from simple starting materials.[11, 23, 50-52] Moreover, *para*-substituted phenols undergo oxidative dearomatization in the presence of nucleophiles to form symmetrical cyclohexadienone intermediates, and Feringa,[25] Rovis,[27] You,[53] and our own group[28] have identified that the dearomatization event can be coupled with a catalytic enantioselective desymmetrization step (Heck, organocatalytic[54] Stetter, oxy-Michael and Hayashi's[26] Michael additions), to form functionalized

decalin-type molecules in high ee which display a quaternary stereogenic center at the ring junction.



Scheme 6

As part of an overarching aim towards catalytic enantioselective processes that rapidly generate products of high molecular complexity, we questioned whether we could engineer a process that would begin with an intramolecular dearomatization event, forming a spiro-substituted cyclohexadienone, and then intercept this reactive intermediate with a desymmetrization reaction as part of a two directional process that would 'zip-up' a simple arene to a complex non-racemic product (*Scheme 7*). Here, we describe that an electrophile-triggered catalytic enantioselective dearomatization (ECED) transformation converts simple planar anisidine derivatives into complex tricyclic structures containing a quaternary stereogenic center embedded within a densely functionalized molecule (*Scheme 7*). The products are isolated in good yield and excellent enantiomeric excess, display intricate architecture and remarkably versatile orthogonal functionality, and can be accessed in just three chemical operations from commercial materials.

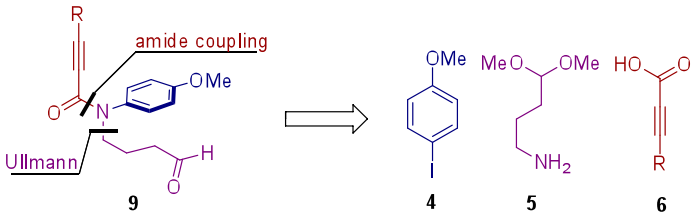


Scheme 7

At the outset of our studies, a pivotal aspect of our design plan focused on identifying an intramolecular dearomatization event triggered by an external reagent that would install a further usable functional group in the spirocyclic cyclohexadienone product. With this in mind, we noted that Larock's *ipso*-iodocyclization[20-22] of alkynyl arenes to iodine-substituted spirocyclic cyclohexadienones would provide a suitable first step for our ECED strategy. The electrophilic ICl activates the alkyne towards a 5-endo-dig *ipso*-iodocyclization, inducing the dearomatization that is accompanied by loss of the methyl group. Accordingly, we were able to synthesize a suitable test substrate **9a** in just two steps from commercially *para*-iodoanisole **4**, 4-aminobutanal dimethyl acetal **5**, phenyl propiolic acid **6a** using a copper-catalyzed amination and an amide bond formation.

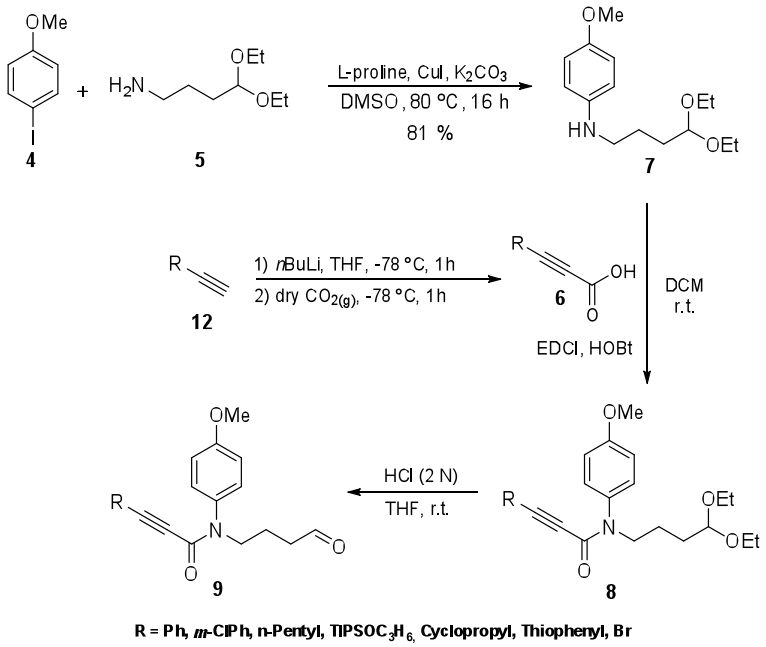
2.1.- Retrosynthetic analysis and synthesis of the starting material for the ECED process.

The retrosynthetic analysis of **9** showed easy accessibility via an amide coupling between an activated carboxylic acid and a secondary amine, which could be obtained in an Ullmann coupling from 4-iodoaniline (**4**) and 4-diethoxybutylamine (**5**) (*Scheme 8*). The carboxylic acids could be derived from their corresponding alkynes by deprotonation and interception with carbon dioxide.



Scheme 8

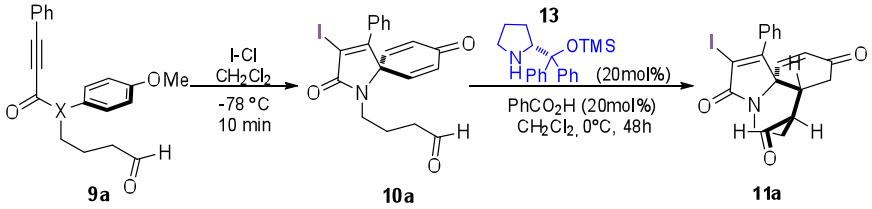
The syntheses of the aldehydes **9a-h** started with the L-proline catalysed Ullmann-coupling of 4-iodoaniline (**4**) and 4-diethoxybutylamine (**5**) to give the common intermediate **7** in 81% isolated yield (*Scheme 9*).[55] The used carboxylic acids **6a**, **6c** and **6g** were commercial and **6b**, **6e** and **6f** were prepared from the corresponding alkynes **12** by deprotonation with *n*-butyl lithium to form the lithium alkynylates, which were intercepted with gaseous carbon dioxide to form the carboxylic acids.[56] Formation of the amide bond between the secondary amine **7** and the correspondent carboxylic acids required the activation with *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDCI) under base free conditions with the use of a catalytic amount of 1-hydroxybenzotriazole hydrate (HOBt). For good turnover of this reaction the rigorous exclusion of water and aceotroping amine and carboxylic acid with toluene prior to the reaction was essential. Deprotection of the aldehyde using 2 N HCl in THF gave the desired starting materials **9g-h** for the alkylative CED-process good yields.



R = Ph, *m*-ClPh, n-Pentyl, $TIPSOC_3H_6$, Cyclopropyl, Thiophenyl, Br

Scheme 9

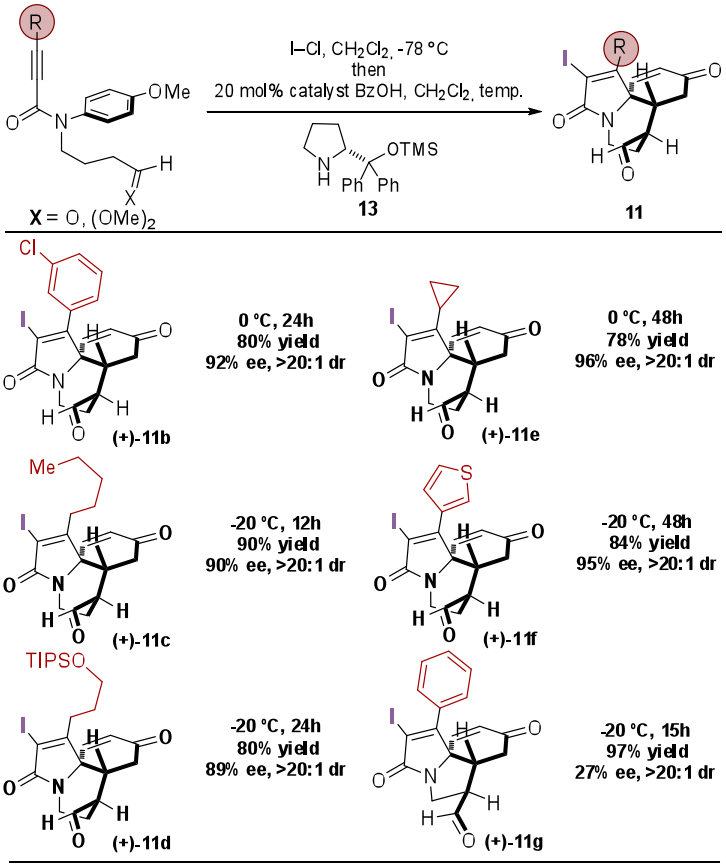
In order to initially assess the reaction we chose to remove the acetal protecting group prior to dearomatization. Treatment of **9a** with ICl in anhydrous dichloromethane at -78˚C cleanly generated the iodospiro-cyclohexadienone, in line with Larock's observations,[22] and we immediately advanced this dearomatization tactic to the enantioselective desymmetrizing part of the ECED reaction using secondary amine catalyzed intramolecular Michael addition. We assessed a range of catalysts and solvents at 0˚C and found that derivatives of the Hayashi-Jørgensen pyrrolidine catalyst[57] led to superior enantioselectivities when the reaction was run in dichloromethane. Further improvement to the selectivity was observed upon the addition of benzoic acid resulting in the isolation of **(+)-11a** 89% yield, 92% ee, and a >20:1 dr over the two steps from aldehyde **9a**. Lactam **(+)-11a** is contained within a tricyclic structure that supports three contiguous chiral centres, comprising an embedded quaternary stereogenic center and two tertiary chiral carbon atoms; it also displays aldehyde, enone and vinyl iodide functionality, all versatile reactive groups that can be orthogonally transformed to increase the structurally complexity of the ECED products.



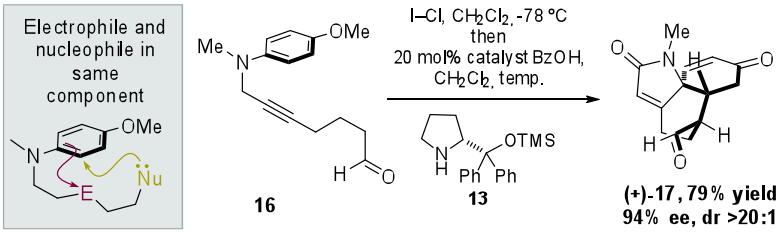
Scheme 10: Optimized conditions for ECED process

The capacity of the new transformation was next investigated by examining the scope of the alkyne substituent (*Table 1*); our preliminary investigations showed that aryl, heteroaryl, alkyl, cyclopropyl, and protected oxygen substituents were all accommodated by the ECED process and gave excellent yields of the tricyclic products in >90% ee and >20:1 dr using the optimized conditions **11b-f**. Although the ECED process also works on substrates that contain a shorter linking unit between the aldehyde and amide function to form the five-memebred ring, the ee of the reaction was low in comparison to the longer chain homolog (27% ee, **11g**). An electron rich thiophene group is not affected by the iodocyclization conditions,[22] and gives the desired product **(–)-11f** in excellent yield and ee. We were also pleased to find that the ECED process can also be performed directly on the acetal precursors, precluding the extra step to reveal the aldehyde motif, and without compromising the yield and enantiomeric excess of the reaction (see **11f**).

Table 1. Scope of ECED transformation.



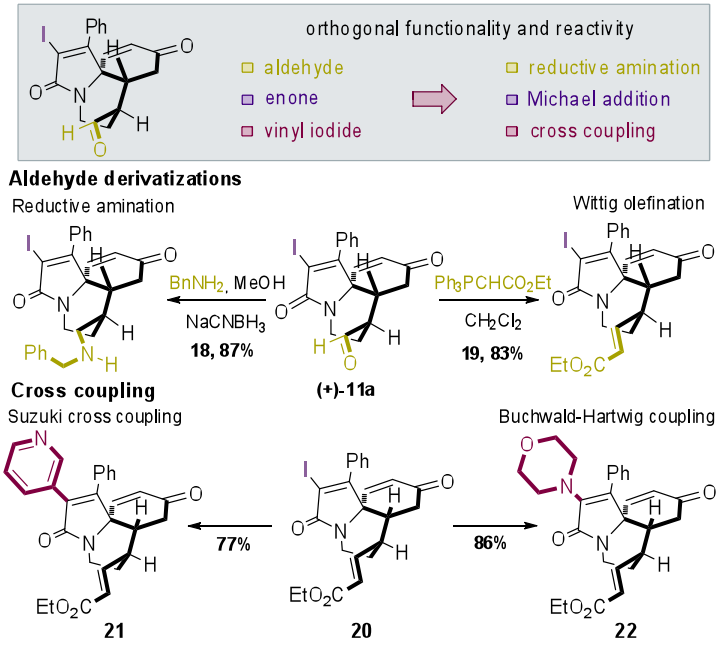
The ECED transformations shown in Table 1 display the electrophile and nucleophile in separate anisidine side chains, leading to a two directional closure to the tricyclic structure. Accordingly, the scope of the reaction was further extended through the successful demonstration that the aldehyde motif and electrophilic alkyne can be incorporated into the same chain **16**, leading to a 'linear' ECED process (*Scheme 11*). In this system the ECED transformation forms a similar, but constitutionally different tricyclic ring system **(+)-17** in excellent yield and enantiomeric excess.



Scheme 11: Linear 'zipper-type ECED reaction

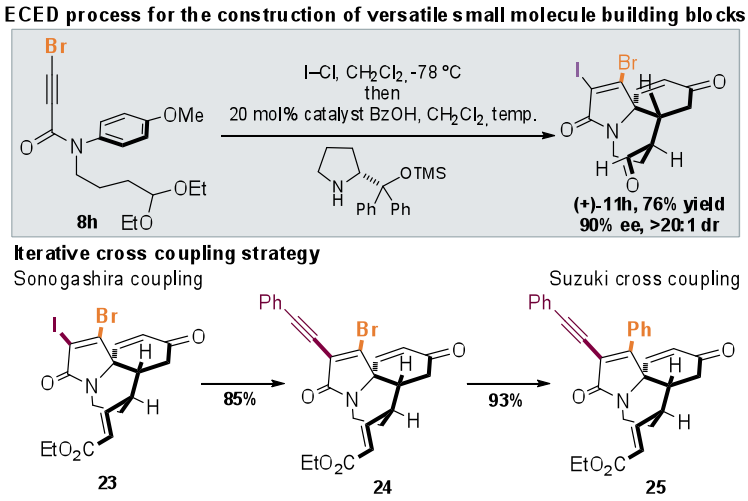
Taking advantage of the orthogonal functionality displayed by these complex quaternary center containing molecules, we showed that the aldehyde motif in **(+)-11a**

undergoes selective reductive amination to **(+)-18** or Wittig olefination to **(+)-19**, and the vinyl iodide is ideal for Pd(0)-catalyzed cross coupling (*Scheme 12*). We were pleased to find that selective Suzuki cross coupling with 3-pyridine boronic acid (77%, **(+)-21**) and Buchwald-Hartwig amination with morpholine (86%, **(+)-22**) provided representative examples to demonstrate this functionalization idea (*see experimental part 1*). Taken together, these simple transformations provide branching points along numerous vectors that will enable the chemist to probe the chemical space around this rigid complex small molecule scaffold. Furthermore, each of these processes occur in excellent yields, do not affect the structural framework of the molecule and would be compatible with library synthesis.



Scheme 12: Structure and functional group diversigication of 11a

While our complexity generating transformation provides numerous opportunities to exploit the potential of post-ECED orthogonal functionalization, we are restricted by the nature of the alkyne substituent that we need to install as part of our starting materials. To address this limitation, we speculated that a bromo-substituted alkyne motif may also be compatible with the ECED process and would accordingly result in a versatile handle for further functionalization that would be facilitate a wide range of groups.



Scheme 13

Moreover, using selective cross coupling techniques it should be possible to discriminate the C–I motif and the C–Br bond, introducing different groups at each position, thereby dramatically increasing the efficacy of the ECED process. Accordingly, bromo-acetal **8h** was assembled in two steps from 4-iodoanisole and was successfully subjected to the ECED transformation to form the desired tricyclic structure **(+)-11h** in a pleasing 89% yield, >20:1 dr and 92% ee but importantly displaying the vicinal C–I and C-Br bonds. We elected to test the selective functionalization strategy using Pd-cross coupling methods and using representative examples we were pleased to find that selective Suzuki cross coupling with 3-pyridine boronic acid, Buchwald-Hartwig amination with morpholine, and Sonogashira coupling with phenylacetylene proceeded selectively at the C–I group in 77%, 86% and 85% yield respectively. We further showed that the C-Br bond could also be utilized through a Suzuki coupling with phenyl boronic in 93% yield to give **25** thereby demonstrating proof of concept for the highly versatile ECED strategy.

2.2.- Conclusions Subproject I

In summary, we have developed an electrophile-triggered catalytic enantioselective dearomatization (ECED) transformation that converts simple anisidine derivatives into complex tricyclic structures containing a quaternary stereogenic center embedded in a densely functionalized molecule. The architecturally complex molecules display multiple stereochemical features and orthogonal functional groups that can be utilized in downstream diversification. The

ECED transformation should be broadly applicable in natural product synthesis and in the synthesis of novel molecules of therapeutic interest; current investigations are focused on these applications and will be reported in due course.

3.- <u>SUBPROJECT II</u>: Aplication of the catalytic enantioselective dearomatization process to the total synthesis of morphine

Morphine is a potent opiate analgesic medication considered to be the prototypical opioid.[58] The powerful analgesic nature of the opium poppy has been known for centuries and used by many cultures for both medicinal and recreational purposes.[59] (−)-Morphine is the main constituent of Indian Opium, the black resin isolated from the poppy Papaver somniferum (*Figure 1*). Morphine is regarded as the gold standard of analgesics used to relieve severe or agonizing pain and suffering. Morphine acts directly on the central nervous system on the opioid receptors.

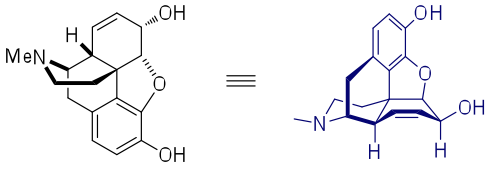
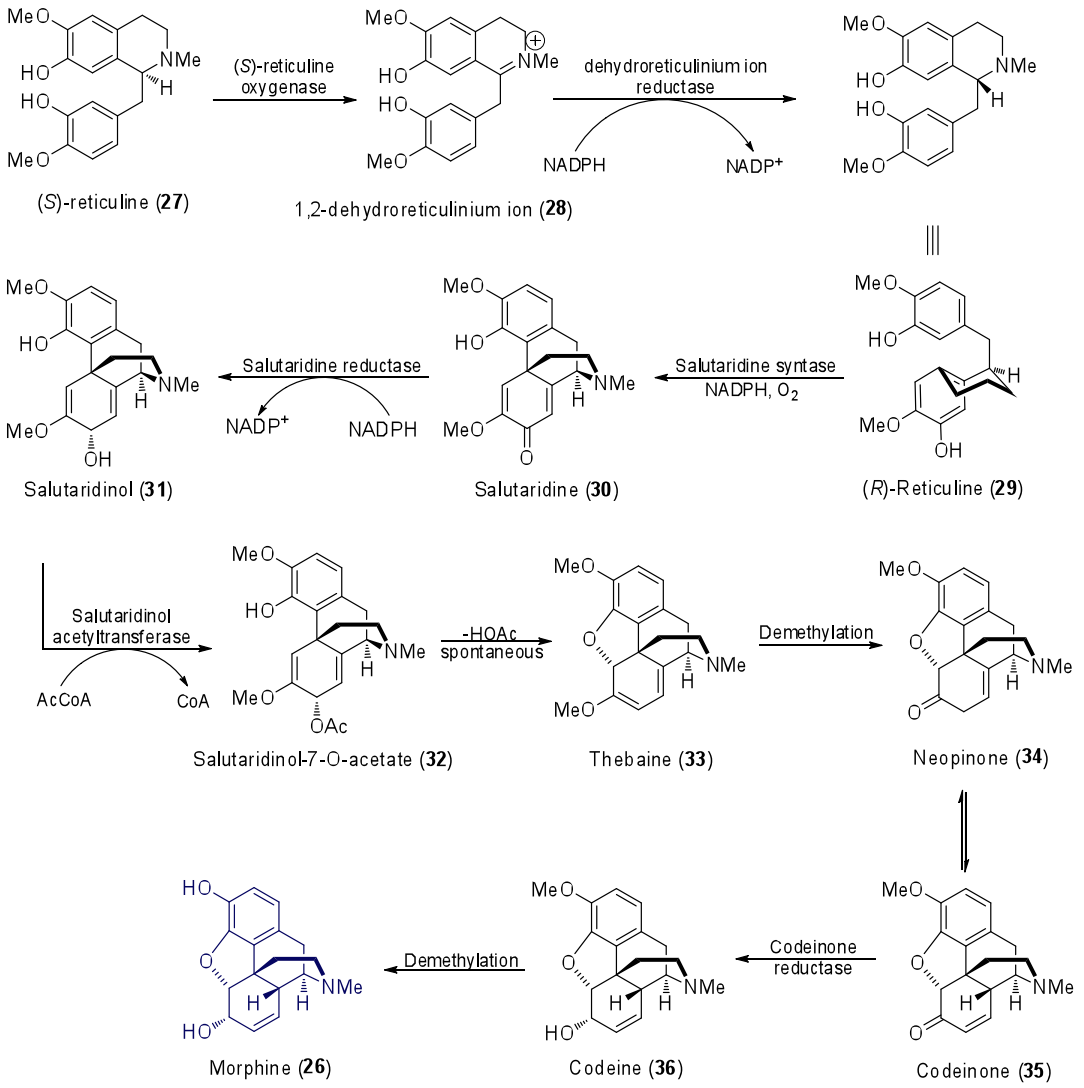


Figure 1: 3D structure of (–)-morphine

(–)-Morphine is a benzylisoquinoline alkaloid with two additional ring closures containing five contiguous stereocentres and one carbon quaternary centre. The biosynthesis of morphine is almost completely elucidated.[60] Recent investigations have shown that morphine and its congeners are produced not only in plants (papaver somniferum) but also in mammalian organisms along essentially analogous pathways. The first crucial key intermediate is (*S*)-reticuline (**27**, *Scheme 14*), whose biosynthesis proceeds from L-tyrosine via intermediates (*S*)-norcuclaurine, (*S*)-coclaurine, (*S*)-N-methylcoclaurine, and (*S*)-3'-hydroxy-N-methylcoclaurine.[61] Then it is converted into its (*R*)-enantiomer via an (*S*)-reticuline-oxydase-mediated oxidation to the 1,2-dehydroreticulinium ion (**28**, *Scheme 14*), wich is stereospecifically reduced to (R)-reticuline (**29**) by 1,2-dehydroreticuline reductase.[62] This NADPH-dependent enzyme does not catalyze the physiologically reverse reaction in vitro. (*R*)-reticuline is then converted into salutaridine (**30**) by an oxidative phenol couplin that stablishes the characteristic stereochemistry of the morphinan skeleton.



Scheme 14: Biosynthetic route of (–)-morphine

This coupling is catalyzed by salutaridine syntase, a microsomal NADPH-dependent cytochrome P-450 enzyme[63, 64] wich defines a new role for cytochrome P-450 in alkaloid biosynthesis. Salutaridine syntase functions as an oxidase rather than as a mono-oxigenase. The mechanism of oxidation of phenol ring involves single-electron transfer to afford phenolic radicals that for new C-C and C-O bonds by radical coupling. The substrate and stereospecificity of the reacton refutes the possibility that this reaction could be catalyzed in vivo by nonspecific phenol oxidases, lactases, and peroxidases.

Salutaridine (**30**) is then reduced by the NADPH-dependent salutaridine reductases to form salutaridinol (**31**),[65, 66] followed by the closure of the oxygen bridge between C4 and C5 to form the characteristic pentacyclic morphinan skeleton. In effect this operation proceeds via an S_N^2-type reaction involving the allylic alcohol

moiety in the C ring. First the hydroxyl group is activated by an acetylation catalyzed by salutaridinol 7-O-acetyltransferase. Salutaridinol-7-O-acetate (**32,** *Scheme 14*) undergoes a spontaneous S_N2' cyclization to produce thebaine (**33**, *Scheme 14*). Thebaine is demethylated to neopinone (**34**), wich exists in an equilibrium with its carbonyl-conjugated regioisomer, codeinone (**35**). Codeinone is reduced to codeine (**36**) by codeinone reductase and finally codeine is demethylated to morphine.

The average consumption of morphine was just 4.90 mg per person worldwide in 2005. However, the majority of the global morphine supply was consumed in North America (55.5 mg per capita) and in Western European countries (24 mg per capita). Consumption per capita only amounted to 1.0 mg in Latin America. It remained below 0.3 mg in Africa and the Middle East, and was even lower (0.2 mg per capita) in continental Asia. Morphine consumption rates significantly lower than those of Western Europe betray an extensive gap between the supplies, and actual need for essential poppy-based medicines. Most countries in the world have little to no access to morphine.

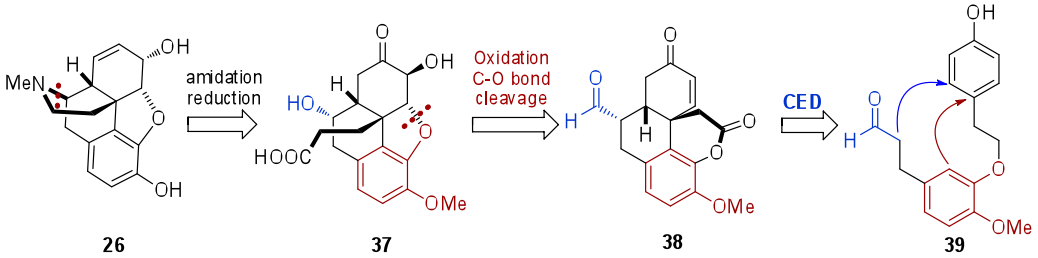
In 2005, to meet the pain needs of the end-stage HIV/AIDS and cancer patients in Latin America, a further 6.6 metric tons of morphine was needed, but just 600 kg of morphine was actually used, leaving 91% of these patient's pain needs unmet. In 2005, 98% of the pain needs of dying HIV/AIDS and cancer patients in Asia went unmet. The 2 million people who died of HIV/AIDS and cancer in sub-Saharan Africa in 2005 consumed less than 1% of the quantity of morphine they needed. An enormous quantity of morphine would be required worldwide to meet the needs for the treatment of pain associated with end stage cancer and AIDS alone.[67, 68]

An efficient synthetic route to morphine would ensure a constant supply of the pharmaceutical to satisfy the demand for medicinal painkillers. Additionally, (−)-morphine (**26**) represents an interesting synthetic target. Approaches to morphine have fascinated chemist for decades[69] but despite more than 25 total and formal syntheses, no route comes close to the efficiency of the biosynthesis and there remains no commercial synthesis of this important compound. Therefore, new approaches to its synthesis are of considerable importance. In this context, we would like to highlight the potential of cascade CED reactions towards a rapid and concise synthesis of (–)-morphine (**26**). Using the biogenetic oxidative biaryl coupling as a linchpin component of our catalytic dearomatization strategy, we envision a direct

conversion of a biaryl starting material to a tetracyclic intermediate that will form the key architecture of the natural product.

3.1.- Retrosynthesis

The enantioselective oxidative dearomatization methodology previously developed in our lab and further exploited in **subproject I** allows simultaneous functionalization in the *para*- and *meta*- positions of a phenol ring, together with a highly enantioselective method of generating a quaternary stereocentre. Inspired by the biosynthetic route to (-)-morphine (**26**), it was speculated that an oxidative coupling between phenol and aryl ring could furnish the challenging quaternary centre, which could be rendered asymmetric through enamine catalyzed desymmetrization (*Scheme 15*).



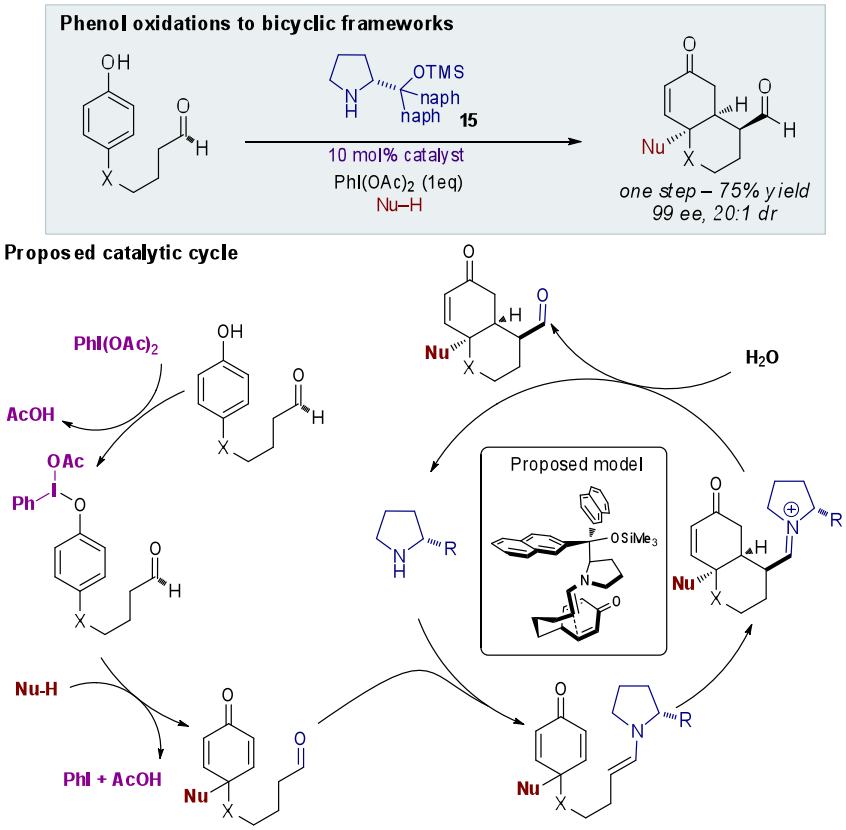
Scheme 15: Proposed retrosynthesis of (–)-morphine

The piperidine ring of (-)-morphine **26** could be formed by a sequential amidation and then reduction of the amide carbonyl. The formation of dihydrofuran **37** would be accessed from a tandem epoxide opening process under oxidative conditions, comprising nucleophilic epoxidation of the enone, together with Baeyer-Villiger oxidation of the aldehyde, and upon basic work-up, saponification of the lactone and formate motifs. To synthesize the tetralin framework **38**, we envisaged that catalytic enantioselective dearomatization could provide the key step. The design of a suitable linear precursor, such as **39** that could incorporate two aryl motifs held within relative proximity, such that the oxidative dearomatization would lead to a suitable substrate for the amine catalyzed desymmetrization. This approach would directly fold linear precursor **39** into a complex molecular architecture through two successive cyclization reactions. This annulation process would form two rings and two new carbon-carbon bonds at adjacent positions around the cyclohexadienone ring.

3.2.- Previous results

3.2.1.- CED methodology

As previously described, previous work within the group showed that a phenol derivative can be directly converted into a highly substituted decalin framework (*Scheme 16*).[28]



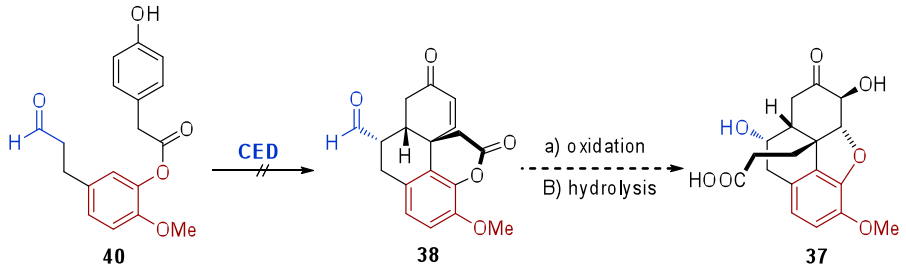
Scheme 16: Catalytic enantioselective dearomatization methodology

These studies showed that the optimal catalyst is the prolinol derived structure,[45] affording the desired product with excellent stereoselectivity and good yield.[28] This transformation forms three new chiral centres, two ring systems and orthogonal functionality directly from a simple, planar molecule. The general mechanism shows that PIDA oxidizes the phenol with the concomitant addition of a nucleophile to the *para*-position of the aromatic ring. The dienone product undergoes desymmetrizing intramolecular Michael addition with the pendant aldehyde *via* the

catalytically generated chiral enamine. Hydrolysis of the iminium returns the catalyst and releases the product.

3.2.2.- Ester strategy

Previously, Rob Pace conducted studies on the CED process and towards the total synthesis of (−)-morphine.[70] The initial target substrate to test the intramolecular oxidative dearomatization was ester **40** (*Scheme 17*). The strategy was to convert this linear molecule **40** into the complex molecular architecture of **30** *via* a CED process, followed by the cleavage of the C-O bond in order to form the dihydrofuran ring **37** of (-)-morphine **26**.



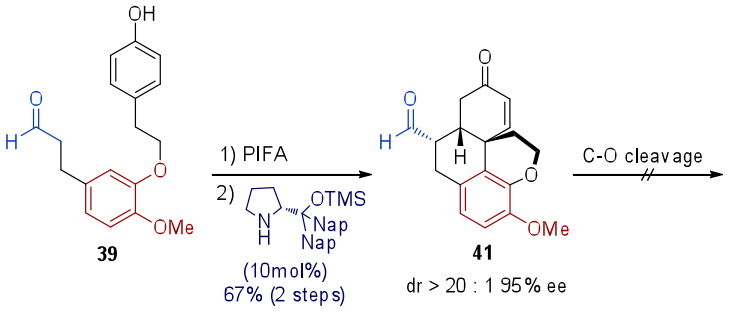
40 **38** **37**

Scheme 17: Proposed retrosynthesis of (–)-morphine

Substrate **40** was synthesized with the ester functionality preinstalled. Unfortunately, despite extensive experimentation, no conditions could be found that led to the required dearomatized compound. Disappointed by the lack of reactivity, it was postulated that the aromatic ring required to act as nucleophile in the process was simply not nucleophilic enough to intercept the phenoxonium ion.

3.2.3.- Ether strategy

Since experimental observations suggested that the desired oxidative dearomatization was extremely unlikely to be successful on the ester system, the synthetic plan was modified in order to alleviate the requirement for the problematic ester group. To test this theory the ester linkage was replaced with the ether **39** (*Scheme 18*). Whilst this would be difficult to cleave in order to complete the synthesis of the natural product it would provide useful evidence as to whether, if a suitable tether could be incorporated, the key enantioselective oxidative dearomatization could be achieved.

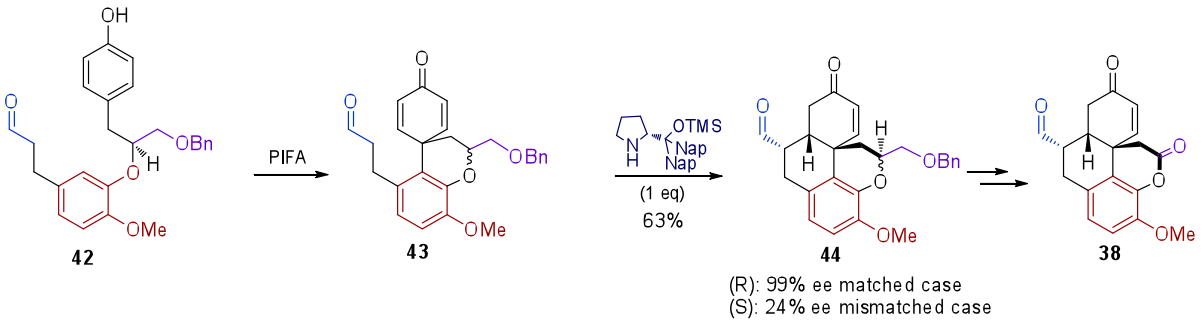


Scheme 18: (–)-Morphine strategy with ether precursor 39

Pleasingly, they managed to obtain an excellent yield of aldehyde **41**, which was achieved as a single stereoisomer and both the *enantio*- and *diastereo*-selectivity were very efficiently controlled by the amine catalyst. Unfortunately, all the attempts to cleave the C-O bond failed and it was decided that an alternative substrate should be synthesized with a more readily cleavable linkage.

3.2.4.- Benzyl monoprotected diol strategy

Further investigations in order to avoid the difficulties associated with the C-O bond cleavage, the reaction was tested with a benzyl monoprotected diol substrate **42** with the view to generating carbonyl **38** *via* subsequent steps (*Scheme 19*). The substrate contains an undefined stereocentre, which is required to be sufficiently remote so as to not affect the (now diastereoselective) Michael reaction. This should lead to a 1:1 mixture of epimers, which can be converged during the oxidative cleavage, destroying the pre-existing stereocentre.



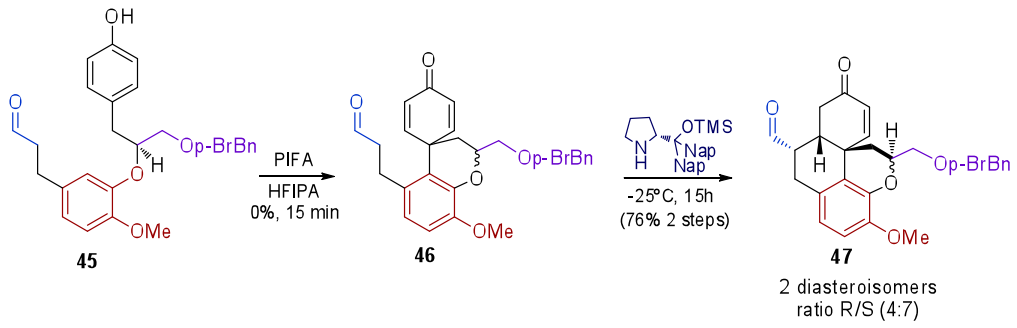
Scheme 19: (–)-Morphine strategy with benzyl monoprotected diol 42

The dearomatization step furnished a (5:1) mixture of this desired cyclohexadienone **43**. The analytical data suggested this *spiro*-fused structure due to

the nucleophilicity of the protected alcohol. During the reaction a side product arises from the protected primary alcohol present in phenol **42** having sufficient nucleophilicity to compete with the aryl group for interception of the phenoxonium ion generated during the dearomatization. If the nucleophilicity of the oxygen could be tempered by altering the electronic nature of the protecting group then this deleterious side reaction could be prevented. The Michael cyclization on the desired cyclohexadienone **43** afforded the tetralin **44** as a mixture of two diastereoisomers, favouring one epimer over the other with 99% ee. The different enantiomeric excess in the two epimers clearly showed a matched and mismatched case. Although after a few manipulations, this stereocentre could be removed by conversion to a carbonyl converging both epimers would therefore lead to an averaged and greatly reduced enantiomeric excess.

3.2.5.- p-Bromobenzyl monoprotected diol strategy

The key oxidative dearomatization yielded tetralin **44** in high levels of enantiomeric excess, however the reaction showed a matched and mismatched case, with one epimer showing significantly higher enantiomeric excesses (*Scheme 20*). The original plan to converge both epimers to lactone **38** would have resulted in compromised enantiomeric excess. Therefore, it seemed that exploitation of the matched case could result in extremely high enantioselectivity for the key lactone fragment **38** and ultimately (–)-morphine. In addition, the *p*-bromobenzyl protecting group was chosen in order to temper the nucleophilicity of the protected alcohol and to prevent the background cyclization.

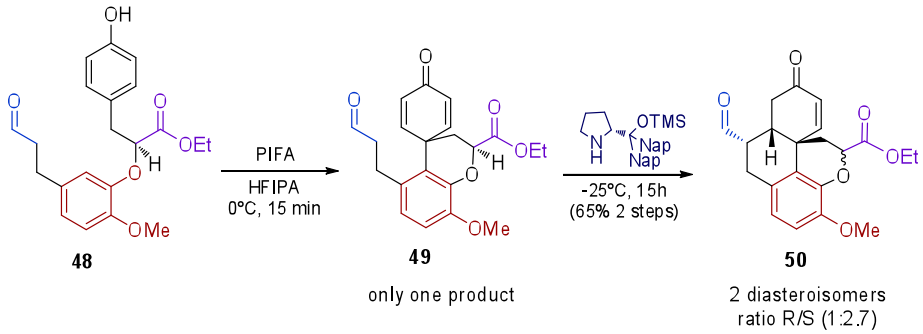


Scheme 20: (–)-Morphine strategy with enantiopure p-Brbenzyl monoprotected diol 45

Pleasingly, dearomatization gave cyclohexadienone **46** as the only product in the NMR of the crude material and no background cyclization was observed. These results validated our hypothesis for use of the *p*-bromobenzyl protecting group in order to temper the nucleophilicity of the alcohol and prevent the competitive cyclization. Michael addition was performed on the crude dearomatized intermediate **46** using a stoechiometric amount of (*R*)-naphthyl catalyst **40** to yield tetralin **47** in 76% yield as a mixture of two diastereoisomers with a (4:7) ratio. At this stage phenol **45** represents the wrong enantiomer for the synthesis of (−)-morphine **26** and would lead to a mismatched case after the CED steps. It would be possible to generate the required enantiomer and explore the synthetic route with solely the matched case of the enamine desymmetrization. Precursor **46** proved to be very difficult to obtain, and CED reaction worked with low diastereoselectivity of the enamine desymmetrization. Therefore, it was decided to revise the strategy and improve the coupling partners.

3.2.6.- α-hydroxy ester strategy

In order to improve the coupling of the two partners, it was proposed that an α-hydroxyester group rather than the diol would increase the electrophilicity of the α-carbon and facilitate the addition of the phenol during the Mitsunobu[71] reaction. Therefore, a new synthetic route towards (−)-morphine **26** starting from L-tyrosine, a cheap chiral source (*Scheme 21*). It was hoped that the CED steps would afford the tetralin **49** with good *diastereo*- and *enantio*-selectivities. Eventually, lactone **38**, common intermediate with the previous proposed synthetic route, would be synthesized following a selective reduction of the ester group using DIBAL-H followed by a copper-mediated oxidative C-C bond cleavage of a-oxygenated aldehyde leading to the end-game towards (−)-morphine **26**.

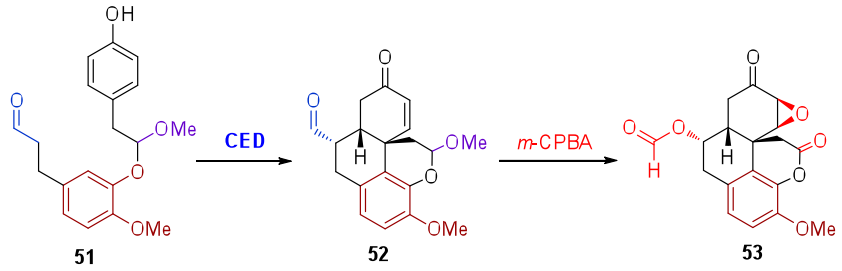


Scheme 21: (–)-Morphine strategy with enantiopure α–hydroxy ester 47

The synthetic approach using the α-hydroxyester linear substrate **48** proved to be more efficient and the CED steps afforded the desired tetralin **49** with a satisfactory yield. Unfortunately, a complex mixture of diastereoisomers **50** was obtained, with epimerization of the defined stereocentre in carbon C6 and the aldehyde with very poor selectivities.

3.2.7.- Acetal strategy

Another alternative involves masking the carbonyl functionality as an acyclic acetal linear precursor **51** (*Scheme 22*). The cyclic acetal CED product **52** would be converted to lactone **53** by oxidation using *m*-CPBA.



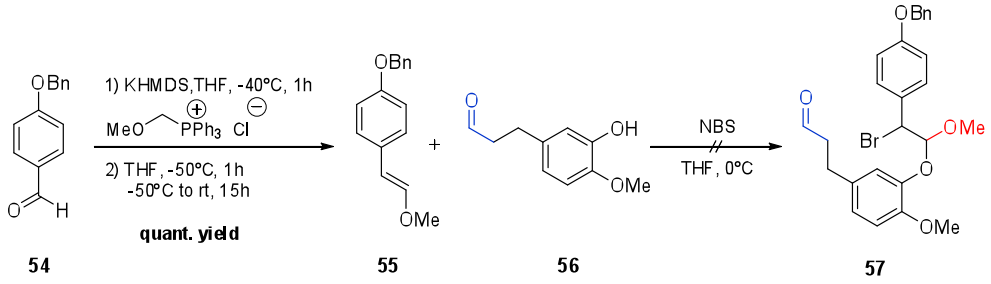
Scheme 22: (–)-Morphine strategy with mixed acetal 51

The reductive acetylation following Rychnovsky's procedure was next investigated. Unfortunately, these conditions weren't mild enough to provide the acetal **51** and we observed reduction of ester to the corresponding alcohol and phenol together with acetylation of the resulting alcohol.

3.3.- Results and discussion

3.3.1.- Mixed acetal strategy; electrophilic activation of alkene 94

Following previous results our first strategy to try was to form the mixed acetal **51** by halogen electrophile activation of alkene **55** using NBS to form the corresponding vinyl bromide.



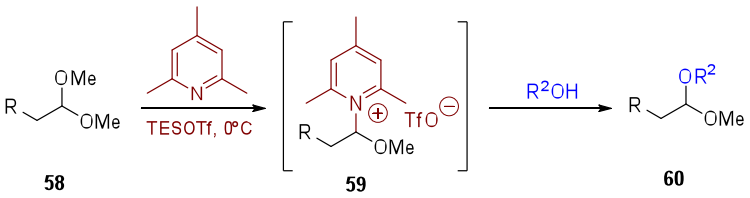
Scheme 23: Attempts to form the mixed acetal 57 from alkene 55

Table 2**: Conditions used to form acetal **57

Entry	Temp. (°C)	Time	Solvent	additive	Yield %	Observations
1	0	20 min	THF	-	-	decomposition
2	0	20 min	DCM	-	-	Starting material
3	0	1 h	DCM	K_2CO_3	-	Starting material
4	rt	1h	DCM	-	-	Starting material
5	rt	2 h	DCM	$CsCO_3$	-	Starting material
6	rt	12 h	DCM	$CsCO_3$	-	Starting material

Enolate **55**, prepared by Wittig reaction from the *p*-benzyloxybenzaldehyde **54**, was submitted to reaction with phenol **56** adding NBS portionwise at 0ºC. Unfortunately only degradation of the starting material was observed after 30 min.

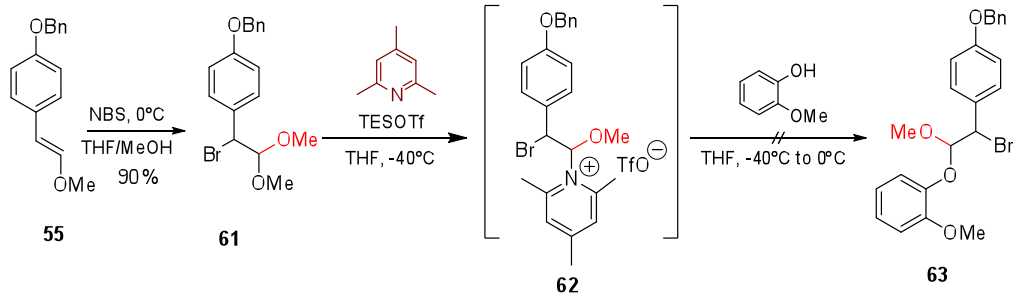
Enolate **55** was quite sensitive under the used conditions and phenolic derivate **56** wasn't nucleophilic enough to perform the nucleophilic attack to the electrophile-activated alkene **55**. In order to increase the reactivity of the alkene we used the method developed by Kita *et al.*[72] for the formation of *O,O*-mixed acetals. The reaction of acetal-protected aldehydes with TESOTf in presence of 2,4,6-collidine forms a polar intermediate determined to be pyridinium-type salts **59**. These collidinium salts have a improved electrophilicity, and nucleophiles can react with these salts.



58 59 60

Scheme 24: Kita's protocol for the synthesis of mixed acetals

In our system, we were able to form the collidinium salt as the appearance of a white suspension after the addition of TESOTf.



55 61 62 63

Scheme 25: Attempts to obtain acetal 63 as model system for CED precursor 56

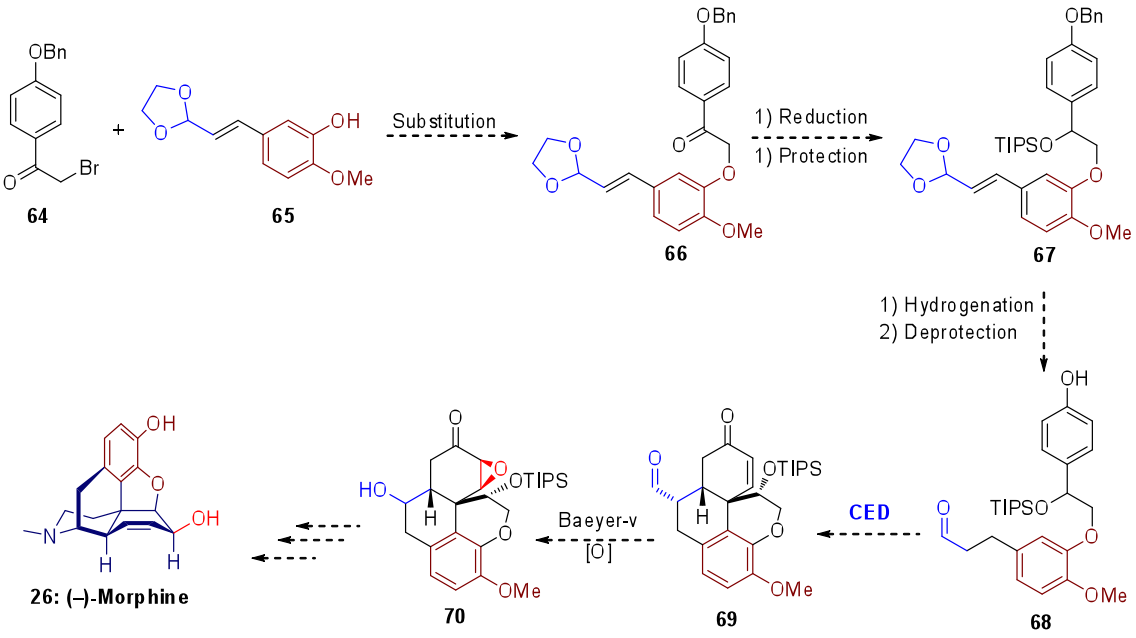
Unfortunately, addition of methoxyphenol, as a model of our desire final compound, did not yield the corresponding mixed acetal **63** (*Scheme 25*) and only decomposition was observed after 30 min reaction.

3.3.2.- 1,2-Diol strategy

Previously, we have demonstrated the possibility to use 1,2-diols to yield the desired core structure **38** (*Scheme 15*) as the precursor of (−)-morphine **26**. In previous attempts this strategy leads to a matched/mismatched case. After different attempts to achieve the right enantiomer for the key CED step, results showed that the enantiomer obtained was the mismatched case. Synthesis of the precursor **45** (*Scheme 20*) was very difficult and therefore, a new strategy was designed. In this case our aim was to form a 1,2-diol .

Starting from α-bromo ketone **64** (*Scheme 26*), compound **66** can be easily obtained by nucleophilic substitution in basic conditions. Subsequent reduction of ketone and TIPS protection of the formed alcohol will afford the fully protected derivate **67** (*Scheme 26*). Hydrogenation of **67** will form desired acetal which treatment in acidic conditions will form the CED aldehyde precursor **68**.

Dearomatization with concomitant intramolecular nucleophilic attack of the electron-rich aromatic ring should afford the symmetrical dienone that undergoes enantioselective amine catalyzed Michael addition to form the tretracyclic core precursor of morphine architecture **69**.

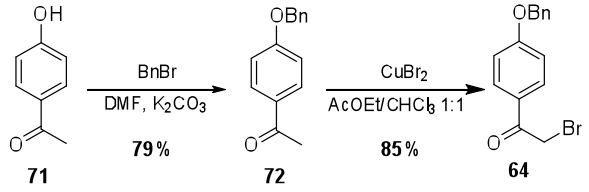


Scheme 26: Proposed synthesis of (–)-Morphine from diol 67

Treatment of enone **69** with basic peroxide solution should result in a facially selective epoxidation reaction form the open lower α-face of the tetracycle, together with Baeyer-Villiger oxidation of the aldehyde. Basic workup would lead to saponification of the formate and lactone, presumably with epoxide opening to yield diol **70**. After some synthetic steps and treatment with the $MeNH_2$.HCl and i-PrMgCl could form the amide and reveal the majority of the morphine structure. Mesylation of the two hydroxyl functions would spontaneously undergo intramolecular displacement will again follow the stereocontrol factors that controlled the previous epoxidation. Eventually, formation of the allylic alcohol by deprotonative epoxide fragmentation and reduction of the amide will form codeine that can be converted through a known demethylation to complete the total synthesis of (−)-morpnine **26**.

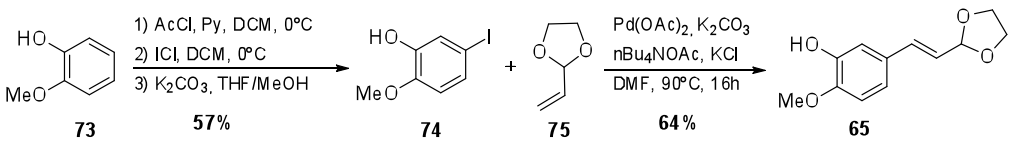
3.3.2.1.- Synthesis of the of α-phenoxy-ethanone 66

Synthesis of α-phenoxy-ethanone **66** (*Scheme 26*) was achieved by coupling fragments **64** and **65**. Both fragments can be obtained by simple procedures readily available. Compound 64 was synthesized starting form *p*-hydroxyphenyl ethanone by benzyl protection of the alcohol. Further treatment with cooper bromide in 1:1 mixture ethyl acetate, chloroform under reflux yielded the α-bromo-ketone **64** (*Scheme 27*) in 84% yield.



Scheme 27: Synthetic approach to bromo benzyl derivative 64

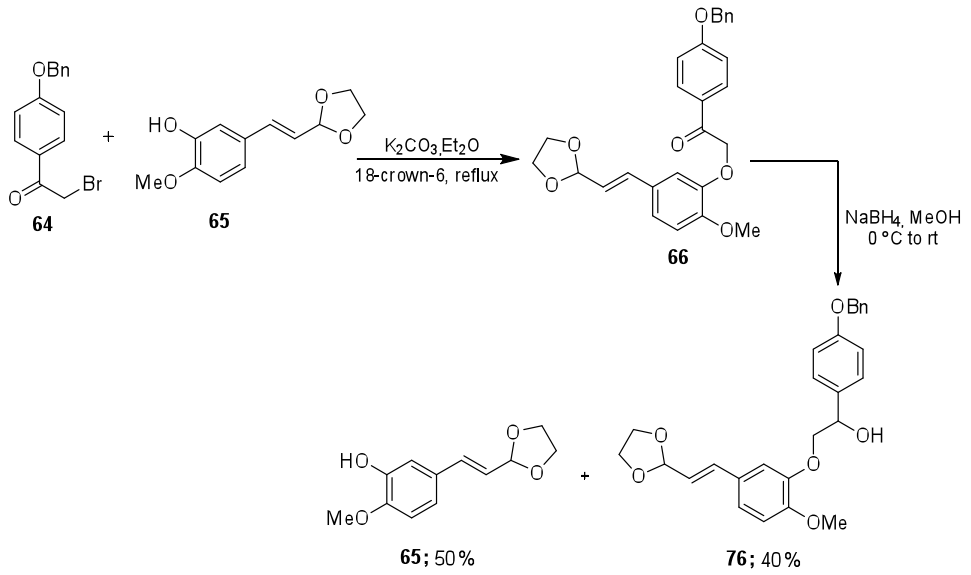
Following previous results in the lab, aryl iodide **74** (*Scheme 28*) was obtained using Feldman's procedure[73] in a three-step sequence from guaicol **73** (*Scheme 28*). The side chain was introduced *via* Heck reaction of the aryl iodide **74** with vinyl dioxolane **75**. The Heck reaction proceeded smoothly under the conditions developed by Norrby[74] to afford phenol **65** in 64% yield in 4 steps.



Scheme 28: Synthesis of phenol 65

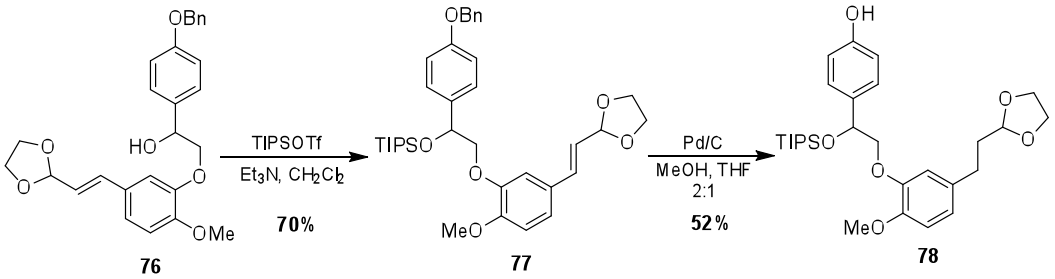
Following the proposed synthetic route, both partners were coupled using 18-crown-6 in presence of potassium carbonate in diethyl ether under reflux. Compound **66** was obtained in an encouraging 85% yield and we were able to scale-up the reaction up to 1 g reaction with the same yield. Next proposed step was ketone reduction and alcohol protection as TIPS derivate. By using this protecting group we ensure the stability under subsequent deprotection steps (hydrogenation and treatment in acidic conditions). Ketone **66** reduction with sodium borohydride in methanol at 0ºC furnished alcohol **76** (*Scheme 29*) as desired but unpleasantly in low yield, 40%. The explanation for this low yield was found when phenol **65** was isolated. In

presence of sodium borohydride, hydride is transferred to the carbon releasing the sodium alkoxide form. The negative charge present is able to perform a nucleophilic substitution to eliminate phenol **65** and generate the corresponding epoxide although we were not able to isolate it.



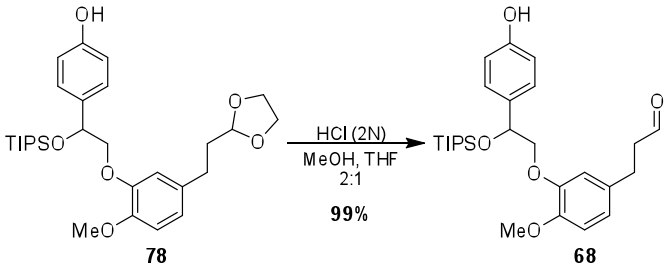
Scheme 29: Reduction of ketone 66 to alcohol 76

Alcohol **76** was then protected as TIPS derivate by reaction with TIPSOTf in presence of Et_3N in 70% yield. Subsequent hydrogenation with Pd on charcoal as catalyst released the phenol and reduced the alkene to generate compound **78** (*Scheme 30*) in 52% yield. In this case, low yield can be explained by the fact that the TIPS protected alcohol is in a bencylic position, therefore, hydrogenation can affect this alcohol and reduce it.



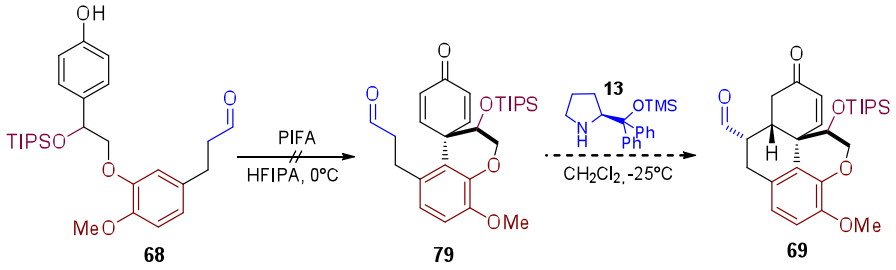
Scheme 30: Alcohol TIPS protection and single-step reduction-deprotection of 77

Finally, acid-mediated removal of the acetal-protecting group furnished linear precursor **68** in 99% yield (*Scheme 31*).



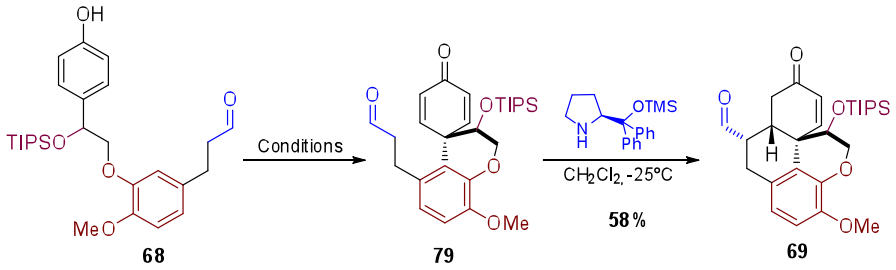
Scheme 31: Acid-mediated removal of the acetal group

With the key precursor **68** in hand, we were able to study the CED key step of our synthetic route towards (−)-morphine (*Scheme 32*).



Scheme 32: CED steps to the synthesis of tetralin 81

Unfortunately, initial attempts of oxidative dearomatization did not form the desire cyclohexadienone **79** (*Scheme 32*) in the conditions previously used with similar systems. Therefore, we tried several conditions for the dearomatization step including the use of different temperatures, solvents, oxidants and times of reaction (Table 3).



Scheme 33: CED optimization

Table 3: *Initial attempts to the dearomatization process from precursor* ***68***

Entry	T[a] (°C)	Time (min)	Solvent	Conditions	Yield %
1	0	15	HFIPA	PIFA	decomposition
2	-10	15	HFIPA	PIFA	decomposition
3	-30	15	TFE	PIFA	decomposition
4	-40	15	TFE	PIFA	decomposition
5	**-40**	**60**	**TFE**	**PIDA**	**≈ 60%**

Previously described conditions were based in the use of PIFA as oxidant in HFIPA at 0 ºC over 15 min to yield the desired dearomatized compound. In this case, these conditions lead to decomposition of starting material **68**. As our system seems to be more sensitive to oxidants we tried in the first instance to decrease the temperature to slow down the reaction. Attempts at -10, -30 and -40 ºC resulted just in decomposition of starting material but very pleasantly, the selection of a less powerful oxidant, PIDA, resulted in the formation of the desired cyclohexadienone **79** (*Scheme 33*), in 60% yield.

Michael addition was performed on the crude dearomatized intermediate **79** using catalytic amount of phenyl catalyst **13** at -25ºC to yield tetralin **69** in 50% yield. Very surprisingly, NMR analysis of tetralin **69**, showed the formation of only one diastereoisomer of intermediate **69**, which can indicate that only one enantiomer of the linear TIPS protected alcohol, might be reacting in the desymmetrizing Michael reaction step.

With all this information in hand we decided to review our synthetic route to the linear CED precursor in order to optimize the overall yield. Several problems were identified and different improvements were proposed.

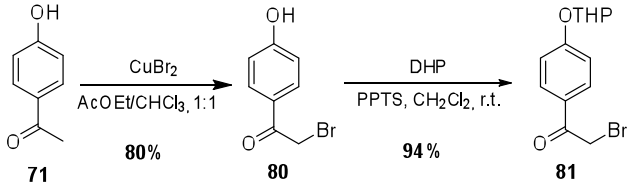
3.3.3.- 1,2-Diol strategy optimization

It was our aim to improve the yield for the CED precursor, as several problems were identified. We tried to improve the yield of the reduction from ketone **66** to alcohol **68**. Sodium borohydride reduction was low yielding due to the formation of the alkoxide intermediate that lead to the decomposition of the CED precursor **68**. A second problem was the hydrogenation step to reduce the alkene moiety at the same time that we achieve the deprotection of the phenolic ring. This hydrogenation was low yielding presumably by the fact that the TIPS protected alcohol is in a benzylic position that might be affected by the catalytic hydrogenation. A third problem was the enantioselective catalytic step where initial investigations showed only one enantiomer of the aldehyde **68** was reacting to furnish the desired tetralin intermediate **69** in the total synthesis of (–)-morphine **26**. Initial NMR studies showed one set of signals corresponding to one of the diastereoisomers but not the other, therefore if only one enantiomer of **68** is reacting we will expect only 50% yield. We decided to include several modifications in the synthesis of **66** starting form

the initial fragments.

3.3.3.1.- Synthesis of fragment 81

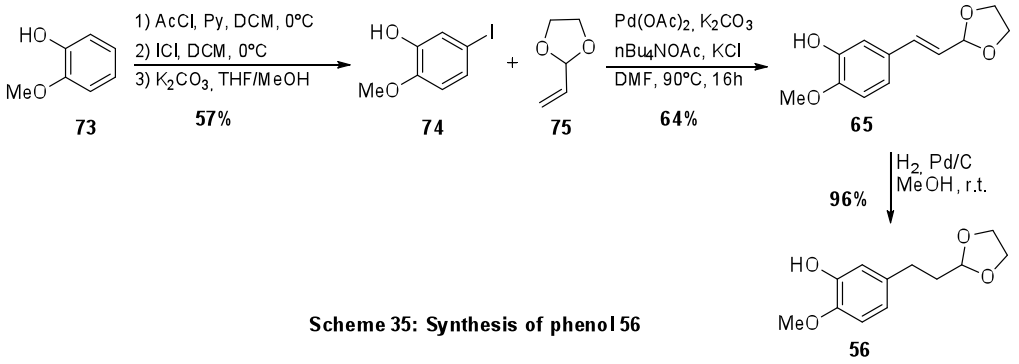
In this case, we changed the protecting group of the aromatic alcohol. We decided to use a THP protecting group that will allow us to perform a global deprotection together with the dioxolane protecting group present in compound **78** (*Scheme 34*). In this case, synthesis of fragment **81** started with the insertion of bromide in 1-(4-hydroxyphenyl)ethanone using the same conditions previously described. Then, treatment with DHP and PPTS in dichloromethane furnished fragment **81** in 87% overall yield.



Scheme 34: Synthesis of fragment 81

3.3.3.2.- Synthesis of fragment 56

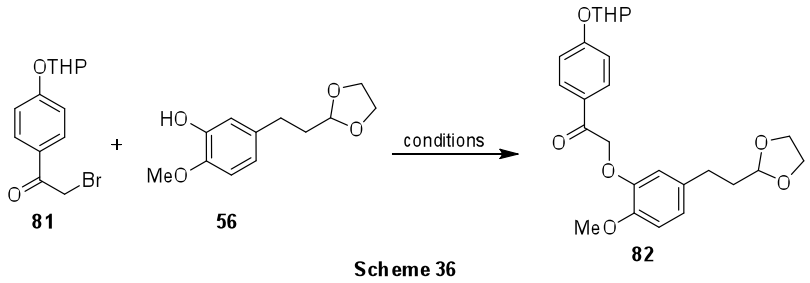
Synthesis of fragment **56** (*Scheme 35*) was achieved using the same synthetic protocol previously described. But in this case the alkene moiety inserted in the lateral chain in the Heck reaction was reduced by hydrogenation. Reducing the insaturation in this step we were able to avoid further problems described above.



Scheme 35: Synthesis of phenol 56

Treatment of **65** with molecular hydrogen in methanol and using palladium on charcoal as catalyst furnished the saturated chain with the latent aldehyde functionality in a satisfactory 96% yield. With this synthetic modification we obtained derivate **56** in grams scale.

We next investigated the coupling of both fragments to generate the ketone intermediate. We used similar conditions as previously but we studied this bromide displacement in order to improve the yield. As this reaction undergoes presumably in a S_N^2 mechanism, the influence of the solvent can be prominent. Therefore, we investigated different solvents and additives (Table 4).



Scheme 36

Table 4: *Optimization studies towards the synthesis of* ***82****.*

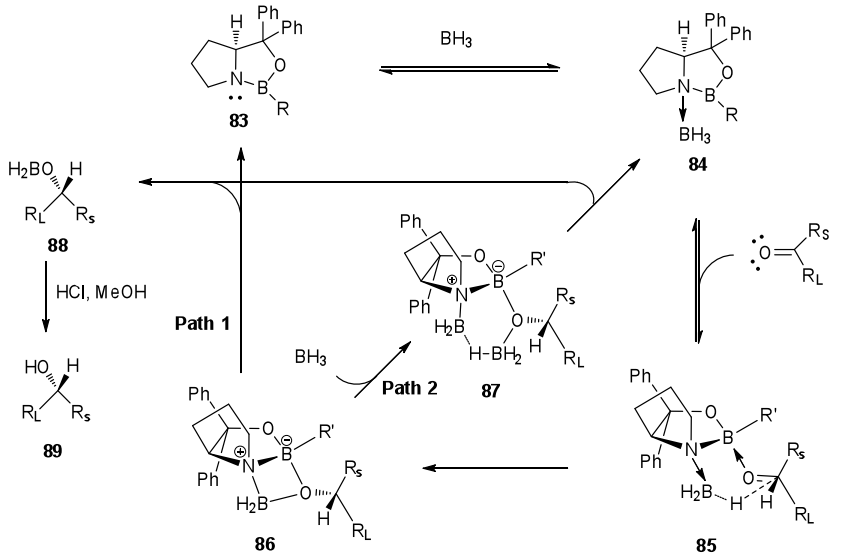
Entry	T[a] (ºC)	Time (h)	Solvent	Conditions	Yield A %
1	60	6 h	THF	-	72
2	60	6 h	ACN	-	78
3	60	15 min	DMF	-	56
4	60	6 h	Dioxane	-	Starting material
5	60	30 min	THF	NaH	Decomposition
6	60	overnight	ACN	-	83
7	**60**	**8 h**	**ACN**	**Di-cyhex-18-crown-6**	**92**

Very pleasingly we identified the best conditions as the reaction performed in acetonitrile with catalytic amount (20 mol%) of dicyclohexyl-18-crown-6 over 8 h at 60 ºC to furnish compound **82** in 92 % yield.

We envisaged that reduction of the ketone moiety using the Corey-Bakshi-Shibata reduction would hopefully install the corresponding alcohol in high yields together with high enantio and diastereoselectivities. This enantioselective reduction will allow us to selectively design the reaction in order to obtain the correct enantiomer with the right stereocenters for the synthesis of the natural (–)-morphine **26**. Careful retrosynthetic analysis of (–)-morphine showed the need of *S*-stereochemistry in the new chiral center. The proximity of this chiral center to the reactive centers in the enantioselective Michael addition and the high steric effect induced by the voluminous TIPS protecting group will induce an effect over the final chirality of the tetralin intermediate. By controlling the stereochemistry of the generated alcohol we will ensure the right stereochemistry in the total synthesis of (–)-morphine at the same time that we improve the overall yield in our designed total

synthesis. The CBS reduction will help us to solve two of the problems previously described, the low yielding reduction with sodium borohydride and the selection of one diastereoisomers in the tetralin intermediate **69** that decreased the yield to a maximum of 50%.

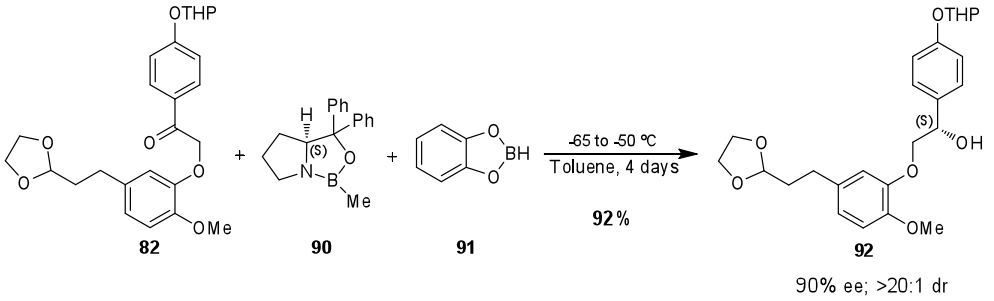
The first step of the mechanism involves the coordination of BH_3 to the nitrogen atom of the oxazaborolidine CBS catalyst **83**. This coordination serves to activate the BH_3 as a hydride donor and to enhance the Lewis acidity of the catalyst's endocyclic boron. Subsequently, the endocyclic boron of the catalyst coordinates to the ketone at the sterically more accessible electron lone pair (i.e. the lone pair closer to the smaller substituent, Rs). This preferential binding in **85** acts to minimize the steric interactions between the ketone (the large RL substituent directed away) and the R' group of the catalyst, and aligns the carbonyl and the coordinated borane for a favourable, face-selective hydride transfer through a six-membered transition state **86**. Hydride transfer yields the corresponding, chiral boron enolate **88**, which upon acidic workup yields the chiral alcohol **89**. The last step to regenerate the catalyst may take place by two different pathways (Path 1 or 2).



Scheme 37: Corey-Bakshi-Shibata reduction mechanism

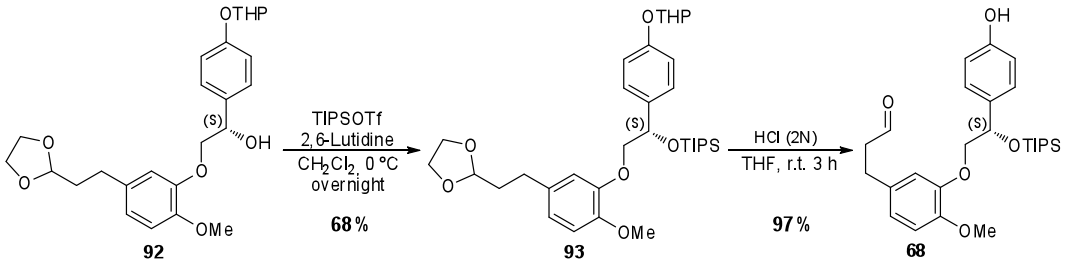
The predominant driving force for this face-selective, intramolecular hydride transfer is the simultaneous activation of the borane reagent by coordination to the Lewis basic nitrogen and the enhancement of the Lewis acidity of the endocyclic catalyst boron for coordination to the ketone.

After some optimization we obtained the best conditions using the (*S*)-Me-CBS catalyst [(*S*)-2-Methyl-CBS-oxazaborolidine] in catalytic amount (15 mol%) and catecholborane as hydride source to yield the desired alcohol in 92% yield and excellent 90% ee and high 20:1 diastereoselectivity.



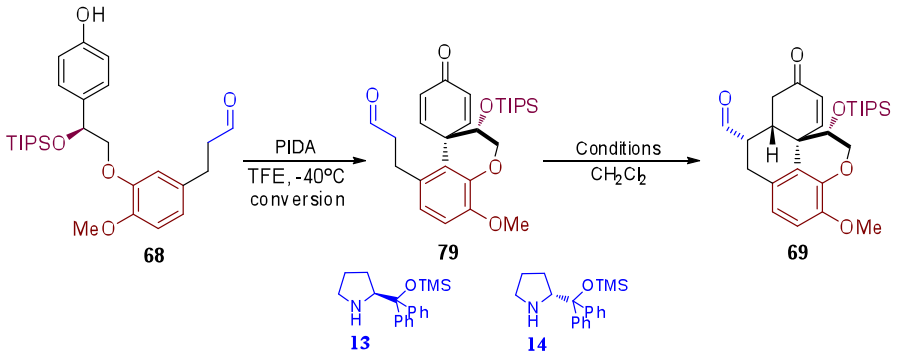
Scheme 38: CBS reduction of ketone 82 to form chiral alcohol 97

Finally, alcohol **92** was protected as silyl derivate using the acidic stable TIPS derivate. Reaction of compound **92** with TIPSOTf in presence of 2,6-lutidine (freshly distilled) in dry dichloromethane yielded the protected alcohol **(*S*)-93** in 68% yield. Further treatment with hydrogen chloride (1 mL/mmol) in THF over one hour furnished the final CED deprotected precursor **(*S*)-68** in excellent yield.



Scheme 39: TIPS protection and acid-mediated global deprotection of acetals

Dearomatization on linear precursor **(*S*)-68** in the presence of PIDA in TFE furnished the desired cyclohexadienone **79** in 60 to 70 % conversion, the cyclic compound was sent directly to the enantioselective Michael addition reaction with prolinol derived catalyst. Catalyst and conditions were screened in this reaction with different temperatures and additives such as benzoic acid. Tetralin **69** was obtained with satisfactory yields over the two-step CED process and interesting results on diastereoselectivities and enantiomeric excesses (Table 5).



Scheme 40: CED optimization

Table 5: *Catalytic enantioselective key step optimization.*

Entry	Conversion	T[a] (ºC)	Catalyst	Additive	Yield %	dr 1	ee1(%)	ee 2 (%)
1	80%	0	13 + 14	-	41	racemic mixture		
2	60 %	0	13	-	30	-	-	-
3	50 %	0	13	-	35	-	-	-
4	80%	0	13	-	48	1:3	6	45
5	-	0	13	$PhCO_2H$	34	1:5	8	59
6	-	-25	13	-	41	1:1.4	37	21
7	**-**	**-25**	**13**	**$PhCO_2H$**	**34**	**1:18**	**99**	**73**
8	-	-25	13	-	63	1:4	15	39
9	-	-25	14	-	16	-	-	-

As shown in Table 5, optimization of the catalytic enantioselective key step for the enantioselective construction of tetralin **69** gave interesting results. Reaction with catalyst **(S)-13** at 0ºC in CH_2Cl_2 yielded tetralin **69** in a 1:3 dr ration with 6% ee for the minor diastereoisomer and encouraging 45% ee for mayor diastereoisomer (entry 4). Similar results were obtained when the reaction was performed in the same conditions but at -25ºC, in this case it was obtained in a 1:1.4 dr ratio with a slightly better ee (entry 6). Very interesting were the reactions performed in the presence of benzoic acid as additive. In those cases, reactions performed at 0ºC and -25ºC showed a highly encouraging improvement in dr ratio and ee. Entry 5 shows the reaction performed at 0ºC with a 1:5 dr excess and improvement to 59% ee in the mayor diastereoisomer. Our best result to the date is marked as entry 7 which shows a very good dr (1:18) and high enantioselectivities of 99% ee for the minor enantiomer and 73% ee for the mayor enantiomer.

These results clearly showed a change in the type of catalysis for the obtention tetralin **69.** In those cases where only prolinol based catalyst is used, there is two different types of catalysis acting at the same time, the enamine catalysis pathway that works with high enantioselectivities and the normal basic catalysis pathway that

yields the racemic mixture. When benzoic acid is used as additive in catalytic amount, the basicity of the catalyst is blocked and only the enantioselective enamine cycle catalysis yields the desired compound with high enantioselectivities.

3.4.- Conclusion Subproject II

To summarize we have design a simple dearomatization process of phenolic derivatives coupled to a single desymmetrization step mimicking nature. Until now, only nature was able to obtain these complex alkaloids through dearomatization processes in highly controlled environments that chemists have unsuccessfully tried to reproduce until now. This strategy has been validated as a viable synthetic tool to allow rapid access to the tricyclic morphine skeleton.

The key diastereoselective oxidative dearomatization has been achieved with good levels of enantioselectivity. Further developments and optimization will ensure the perfect scenario to the total synthesis of (−)-morphine with the shortest synthetic route designed.

4.- EXPERIMENTAL

4.1.- Experimental Subproject I

General Information

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded using a Bruker AM 400 (400 MHz) or an Avance 500 (500 MHz) spectrometer. Carbon nuclear magnetic resonance (^{13}C NMR) were recorded using a Bruker AM 400 (100 MHz) or an Avance 500 (125 MHz) spectrometer. All spectra were recorded at ambient temperature (298 K). Chemical shifts (δ) are quoted in ppm relative to residual solvent and coupling constants (*J*) are quoted in hertz (Hz). Multiplicity is reported with the following abbreviations: s=singlet, d=doublet, t=triplet, q=quartet, septet=sp, m=multiplet, b=broad, app=apparent.

Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum One-FT-IR spectrometer as thin films deposited in dichloromethane. HRMS were measured either at the University of Cambridge on a Micromass Q-TOF spectrometer using electrospray ionisation (ESI) or at the EPSRC Mass Spectrometry Service at the University of Swansea. Optical rotations were measured in $CHCl_3$ on a Perkin Elmer 343 Polarimeter; $[\alpha]_D$ values are reported in 10^{-1} degrees cm^2 g^{-1} at 589 nm. Chiral HPLC analysis was performed n HP Agilent 1100 apparatus. Melting points (m.p.) were recorded using a Reichert hot stage apparatus and are reported uncorrected.

Analytical thin layer chromatography (TLC) was performed using pre-coated Merck glass backed silica gel plates (Silicagel 60 F254). Flash column chromatography was undertaken on Merck Kieselgel 60 (230-400 mesh) under a positive pressure of nitrogen unless otherwise stated.

All solvents used were dried and distilled using standard methods. Dichloromethane was distilled from calcium hydride and 1,2-dichloroethane was purchased in anhydrous form. All reagents were purchased at the highest commercial quality. All reactions were monitored by TLC or from ^{1}H NMR spectra taken from reaction samples, with conversions confirmed by use of an NMR standard. Reactions were carried out under an atmosphere of nitrogen unless otherwise stated.

1: General procedure for amine coupling with 3-substituted-prop-2-ynoic acid

3-substituted-prop-2-ynoic acid (1eq), EDCI (1.2eq) and HOBT (0.1eq) were added to a solution of (*N*-4,4-diethoxyalkyl)-4-methoxyaniline (1eq) in CH_2Cl_2 (0.26 M) at room temperature. The resulting solution was stirred at room temperature until completion, quenched with $NaHCO_{3(aq.)}$ and extracted twice with CH_2Cl_2. The combined organic layers were washed with water and brine, dried over $MgSO_4$, concentrated in vacuo and purified by flash chromatography on silica gel to afford the desired compounds.

2: General procedure for acetal removal

2N HCl (1.2 mL/mmol) was added dropwise to a solution of acetal (1 eq) in THF (6 mL/mmol) at room temperature, and the resulting solution was stirred until completion. The reaction was quenched with aqueous $NaHCO_3$ solution and extracted

with diethyl ether. The organic layer was dried over $MgSO_4$, concentrated in vacuo and purified by flash chromatography on silica gel.

3: General procedure for ECED transformation

ICl (2 eq) in CH_2Cl_2 (1 M) was added to a solution of the aldehyde **1** (1 eq) (**method A**) or the corresponding diethoxyacetal (1 eq) (**method B)** in CH_2Cl_2 (0.1 mM) at -78 ºC over a period of 15 minutes. The resulting solution was stirred for 10-30 minutes and quenched with saturated aqueous $Na_2S_2O_3$ solution. It was allowed to warm up to room temperature and extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, concentrated in vacuo to afford the corresponding iodo-cyclohexadienone that was subjected directly to enantioselective desymmetrizing cyclization without further purification.

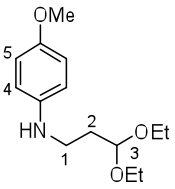
Catalyst (**15**) (0.2 eq) and benzoic acid (0.2 eq) were added to the solution of aldehyde **9** (1 eq) in CH_2Cl_2 (0.3 M) at 0 or -20 ºC. The resulting mixture was stirred for 1.5 h to 48 h, quenched by water and extracted with CH_2Cl_2 (2 x 7 mL). The combined organic layers were dried over $MgSO_4$, concentrated in vacuo and purified by flash chromatography on silica gel.

The ee of the reaction was determined by HPLC analysis of the corresponding Wittig olefination product (**19**), formed using the procedure outlined below (4).

4: General procedure for Wittig reaction

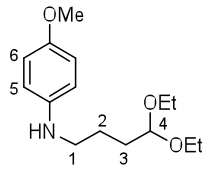
(tert-Butoxycarbonylmethylene)triphenylphosphorane (1.5 eq) or (Carbethoxy-methylene)triphenylphosphorane (1.5 eq) was added to a solution of the corresponding aldehyde at -78 ºC. The solution was stirred for 12 h, slowly warming to room temperature. The reaction mixture was quenched with water and extracted with CH_2Cl_2 (2x), the combined organic layers were dried over $MgSO_4$, concentrated in vacuo and purified by flash chromatography on silica gel.

***N*-(3,3-diethoxypropyl)-4-methoxyaniline (94)**



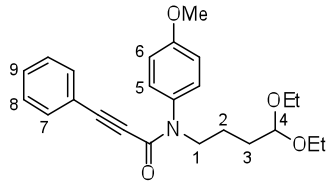
DMSO (5 mL) was added to a mixture of 4-iodoanisole (0.5 g, 2.14 mmol), CuI (0.0406 g, 0.21 mmol), L-proline (0.0493 g, 0.43 mmol) and K_2CO_3 (powdered) (0.59 g, 4.27 mmol) in a round bottom flask, and it was flushed with N_2 (3 times), followed by addition of 3,3-diethoxypropan-1-amine (0.52 mL, 3.21 mmol). The reaction mixture was degassed and stirred under N_2 atmosphere at 80ºC for 26h, diluted with water and extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$, concentrated in vacuo and purified by flash chromatography on silica gel (Pet-ether:Et_2O; 0 – 15%) to afford the product as a yellow oil (**94**) (0.45 g, 83% yield); Rf 0.52 (Pet.-Ether:Diethyl ether, 1:1); λ_{max} (film) / cm^{-1} 3389, 1511, 1233, 1121, 1039, 977, 817; ^1H NMR (400 MHz, CD_3Cl_3) δ_H 6.78 (2H, d, J = 9.1 Hz, H^4), 6.60 (2H, d, J = 8.8 Hz, H^5), 4.63 (1H, t, J = 5.3 Hz, H^3), 3.73 (3H, s, $OC\underline{H_3}$), 3.69-3.53 (2H, m, $OC\underline{H_2}CH_3$), 3.50-3.42 (2H, m, $OC\underline{H_2}CH_3$), 3.18 (2H, t, J = 6.4 Hz, H^1), 1.95-1.82 (2H, m, H^2), 1.23 (6H, t, J = 6.8 Hz, $OCH_2C\underline{H_3}$); ^{13}C NMR (100 MHz, CD_3Cl_3) δ_C 152.6, 142.9, 115.3, 114.7, 102.6, 61.9, 56.2, 41.6, 33.6, 15.8; HRMS (ES^+) mass calc'd. For $C_{14}H_{23}NO_3$ 253.1678; found [$(M+H)^+$] 254.1759.

(*N*-4,4-diethoxyalkyl)-4-methoxyaniline (7)



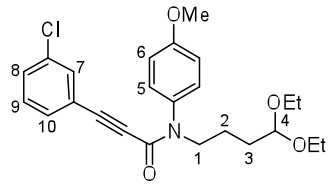
DMSO (40 mL) was added to a mixture of 4-iodoanisole (5 g, 21.36 mmol), CuI (0.405 g, 2.1 mmol), L-proline (0.493 g, 4.3 mmol) and K_2CO_3 (powdered) (5.9 g, 42.7 mmol) in a round bottom flask, and it was flushed with N_2 (3 times), followed by addition of 4,4-diethoxybutan-1-amine (5.16 g, 32.04 mmol). The reaction mixture was degassed and stirred under N_2 atmosphere at 80ºC for 26h, diluted with water and extracted with diethyl ether (3 x 25mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$, concentrated in vacuo and purified by flash chromatography on silica gel (CH_2Cl_2:Et_2O; 0 – 15%) to afford the product as a yellow oil (**15**) (4.83 g, 85% yield); Rf 0.52 (Pet.-Ether:Diethyl ether, 1:1); λ_{max} (film) / cm^{-1} 3389, 2874, 1511, 1233, 1121, 1037, 816; ^1H NMR (400 MHz, C_6D_6) δ_H 6.90 (2H, d, J = 8.9 Hz, H^5), 6.50 (2H, d, J = 8.9 Hz, H^6), 4.47 (1H, t, J = 5.6 Hz, H^4), 3.58 (2H, dq, J = 9.3 Hz, J = 7.0 Hz, OC$\underline{H_2}$CH$_3$), 3.45 (3H, s, OC$\underline{H_3}$), 3.40 (2H, dq, J = 9.3 Hz, J = 7.0 Hz, OC$\underline{H_2}$CH$_3$), 2.92 (2H, t, J = 7.0 Hz, H^1), 1.75-1.68 (2H, m, H^2), 1.63-1.54 (2H, m, H^3), 1.19 (6H, t, J = 7.0 Hz, OCH$_2$C$\underline{H_3}$); ^{13}C NMR (100 MHz, C_6D_6) δ_C 152.8, 143.3, 115.4, 114.3, 103.0, 61.0, 55.5, 44.9, 31.7, 25.5, 15.8; HRMS (ES^+) mass calc'd. For $C_{15}H_{25}NO_3$ 267.1834; found [$(M+H)^+$] 268.1916.

***N*-(4,4-diethoxybutyl)-*N*-(4-methoxyphenyl)-3-phenylpropiolamide (8a)**



General procedure **1**, *N*-(4,4-diethoxybutyl)-4-methoxyaniline (**7**) (2.0 g, 7.48 mmol) and 3-phenylprop-2-ynoic acid (1.09 g, 7.51 mmol), EDCI (1.72 g, 8.92 mmol), HOBT (101 mg, 0.75 mmol) and CH_2Cl_2 (30 mL), 16 h, chromatography on silica gel (CH_2Cl_2:Et_2O, 0-5 %) to afford compound **8a** as a yellow oil (2.95 g, 95% yield); Rf 0.40 (Pet-Ether:Diethyl ether, 1:1); λ_{max} (film) / cm^{-1} 2973, 2214, 1631, 1510, 1392, 1293, 1247, 1058, 835, 757, 689; ^1H NMR (400 MHz, C_6D_6) δ_H 7.12-7.07 (2H, m, Ph), 7.03 (2H, d, J = 8.9 Hz, H^5), 6.92-6.88 (1H, m, H^9), 6.86-6.80 (2H, m, Ph), 6.71 (2H, d, J = 8.9 Hz, H^6), 4.49-4.43 (1H, m, H^4), 3.86-3.83 (2H, m, H^1), 3.54 (2H, dq, J = 9.3 Hz, J = 7.0 Hz, OC$\underline{H_2}$CH$_3$), 3.37 (2H, dq, J = 9.3 Hz, J = 7.0 Hz, OC$\underline{H_2}$CH$_3$), 3.32 (3H, s, OC$\underline{H_3}$), 1.79-1.67 (4H, m, H^2, H^3), 1.12 (6H, t, J = 7.0 Hz, OCH$_2$C$\underline{H_3}$); ^{13}C NMR (100 MHz, C_6D_6) δ_C 159.4, 154.1, 135.1, 132.5, 130.1, 129.7, 121.3, 114,4, 102.7, 90.4, 84.3, 61.0, 55.0, 48.4, 31.2, 23.4, 15.6; HRMS (ES^+) mass calc'd. For $C_{24}H_{29}NO_4$ 395.2097; found [$(M+Na)^+$] 418.2002.

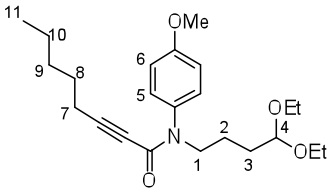
3-(3-chlorophenyl)-*N*-(4,4-diethoxybutyl)-*N*-(4-methoxyphenyl)propiolamide (8b)



General procedure **1**, *N*-(4,4-diethoxybutyl)-4-methoxyaniline (**7**) (500 mg, 1.87 mmol) and 3-chlorophenyl-propiolic acid (370.2 mg, 2.05 mmol), EDCI (553.5 mg, 2.80 mmol), HOBT (25.2 mg, 0.18 mmol) and CH_2Cl_2 (5 mL), 16 h, chromatography on silica gel (pet-ether:EtOAc, 7:3) to afford compound **11b** as a yellow oil (781 mg, 97% yield); Rf 0.45 (pet.-ether/EtOAc, 6:4); λ_{max} (film) / cm^{-1} 1679, 1586, 1562, 1472, 1399, 1298, 1269, 1214, 1080, 1032, 971, 934, 901, 783, 735, 719, 679;

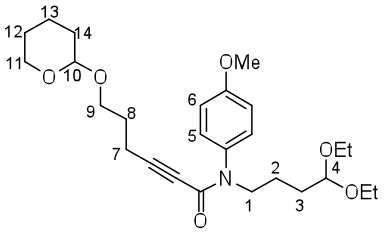
^{1}H NMR (500 MHz, C_6D_6) δ_H 7.00-6.86 (3H, m, H^5, H^7), 6.81-6.71 (2H, m, H^8, H^9), 6.63 (2H, d, J = 8.9, H^6), 6.44 (1H, t, J = 7.9 Hz, H^{10}), 4.44 (1H, t, J = 4.9, H^4), 3.79 (2H, t, J = 6.8, H^1), 3.5 (2H, dq, J = 9.3 Hz, J = 7.0 Hz, OC$\underline{H_2}$CH$_3$), 3.33 (2H, qd, J = 9.3 Hz, J = 7.0 Hz, OC$\underline{H_2}$CH$_3$), 3.25 (3H, s, OC$\underline{H_3}$), 1.87-1.56 (4H, m, H^2, H^3), 1.09 (6H, t, J = 7.0 Hz, OCH$_2$C$\underline{H_3}$); ^{13}C NMR (125 MHz, C_6D_6) δ_C 159.5, 153.8, 134.9, 134.3, 133.4, 130.3, 130.1, 129.8, 129.7, 123.0, 114.4, 102.7, 88.7, 85.1, 61.1, 55.0, 48.4, 31.2, 23.4, 15.6; HRMS (ES$^+$) mass calc'd. For $C_{24}H_{28}ClNO_4$ 429.1707; found [(2M+NH$_4$)$^+$] 876.3756.

_N_-(4,4-diethoxybutyl)-_N_-(4-methoxyphenyl)oct-2-ynamide (8c)



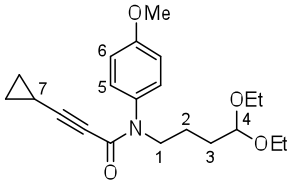
General procedure **1**, *N*-(4,4-diethoxybutyl)-4-methoxyaniline (**7**) (300 mg, 1.12 mmol) and 2-octynoic acid (188 mg, 1.34 mmol), EDCI (257 mg, 1.34 mmol), HOBT (15 mg, 0.11 mmol) and CH_2Cl_2 (10 mL), 14 h, chromatography on silica gel (CH_2Cl_2:acetone, 0-5%) to afford compound **8c** as a colourless oil (432 mg, 99% yield); Rf 0.52 (CH_2Cl_2:acetone, 95:5); λ_{max} (film) / cm^{-1} 2971, 2229, 1633, 1510, 1393, 1291, 1246, 1058, 834, 733; ^{1}H NMR (500 MHz, C_6D_6) δ_H 6.95 (2H, d, J = 7.2 Hz, H^5), 6,65 (2H, d, J = 7.2 Hz, H^6), 4.43 (1H, t, J = 6.4 Hz, H^4), 3.83-3.75 (2H, m, H^1), 3.50-3.38 (2H, m, OC$\underline{H_2}$CH$_3$), 3.37-3.21 (2H, m, OC$\underline{H_2}$CH$_3$), 3.25 (3H, s, OC$\underline{H_3}$), 1.81-1.62 (6H, m, H^2, H^3, H^7), 1.10 (6H, t, J = 5.6 Hz, OCH$_2$C$\underline{H_3}$), 1.09-0.82 (4H, m, H^8, H^9), 0.86-0.67 (2H, m, H^{10}), 0.74 (3H, t, J = 5.6 Hz, H^{11}); ^{13}C NMR (125 MHz, C_6D_6) δ_C 159.2, 154.3, 135.6, 130.1, 114.4, 102.7, 92.8, 76.6, 61.0, 54.8, 48.4, 31.2, 30.8, 27.6, 23.4, 22.3, 18.7, 15.6, 13.9; HRMS (ES$^+$) mass calc'd. For $C_{23}H_{35}NO_4$ 389.2566; found [(M+Na)$^+$] 412.2476.

_N_-(4,4-diethoxybutyl)-_N_-(4-methoxyphenyl)-6-(tetrahydro-2_H_-pyran-2-yloxy)hex-2-ynamide (95)



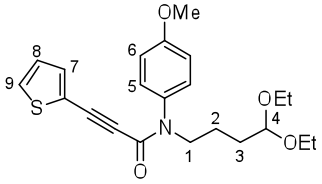
General procedure **1**, *N*-(4,4-diethoxybutyl)-4-methoxyaniline (**7**) (400 mg, 1.5 mmol) and 6-(tetrahydro-2*H*-pyran-2-yloxy)hex-2-ynoic acid (382 mg, 1.8 mmol), EDCI (345 mg, 1.8 mmol), HOBT (20 mg, 0.15 mmol) and CH_2Cl_2 (12 mL), 15 h, chromatography on silica gel (CH_2Cl_2:acetone, 9:1) to afford compound **95** as a yellow oil (450 mg, 87% yield). Rf 0.40 (CH_2Cl_2:acetone, 9:1); λ_{max} (film) / cm^{-1} 2938, 1634, 151, 1247, 1032, 835, 733; ^{1}H NMR (500 MHz, C_6D_6) δ_H 6.94 (2H, d, J = 8.9 Hz, H^5), 6.71 (2H, d, J = 8.9 Hz, H^6), 4.48 (1H, t, J = 8.9 Hz, H^{10}), 4.45 (1H, t, J = 3.3 Hz, H^4), 3.82-3.69 (2H, m, H^1), 3.75-3.66 (1H, m, H^{11a}), 3.60-3.49 (3H, m, OC$\underline{H_2}$CH$_3$, H^{14a}), 3.44-3.33 (3H, m, OC$\underline{H_2}$CH$_3$, H^{14b}), 3.32 (3H, s, OC$\underline{H_3}$), 3.08-3.01 (1H, m, H^{11b}), 2.05-1.93 (2H, m, H^9), 1.78-1.65 (4H, m, H^2, H^3), 1.59-1.53 (2H, m, H^7), 1.44-1.22 (6H, m, H^8, H^{12}, H^{13}), 1.14 (6H, t, J = 7.05 Hz, OCH$_2$C$\underline{H_3}$);^{13}C NMR (125 MHz, C_6D_6) δ_C 159.3, 154.2, 135.5, 130.0, 114.4, 102.7, 98.4, 92.3, 76.7, 65.3, 61.4, 60.9, 54.9, 48.3, 31.2, 30.8, 28.3, 25.7, 23.4, 19.4, 15.7, 15.6; HRMS (ES$^+$) mass calc'd. For $C_{26}H_{39}NO_6$ 461.2777; found [(M+H)$^+$] 462.2834.

3-cyclopropyl-*N*-(4,4-diethylbutyl)-*N*-(4-methoxyphenyl)propiolamide (8e)



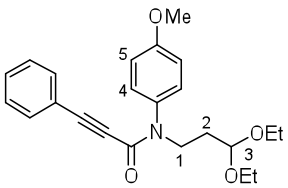
General procedure **1**, *N*-(4,4-diethoxybutyl)-4-methoxyaniline (**7**) (1.0 g, 4.50 mmol) and cyclopropylpropiolic acid (545 mg, 4.95 mmol), EDCI (2.44 g, 12.3 mmol), HOBT (91.2 mg, 0.68 mmol) and CH_2Cl_2 (20 mL), 20 h, chromatography on silica gel (pet-ether:EtOAc, 7:3) to afford compound **8e** as a yellow oil (1.39 g, 86% yield); Rf 0.48 (Pet-Ether:EtOAc, 6:4); λ_{max} (film) / cm^{-1} 2973, 2343, 2226, 1630, 1511, 1443, 1395, 1292, 1248, 1170, 1125, 1059, 1032, 888, 836, 732**;** ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.90 (2H, d, J = 8.8 Hz, H^5), 6.67 (2H, d, J = 8.8 Hz, H^6), 4.26-4.21 (1H, m, H^4), 3.58 (3H, s, OC$\underline{H_3}$), 3.48-3.39 (2H, m, H^1), 3.37 (2H, dq, J = 9.2 Hz, J = 7.0 Hz, C$\underline{H_2}$CH$_3$), 3.21 (2H, dq, J = 9.2 Hz, J = 7.0 Hz, OC$\underline{H_2}$CH$_3$), 1.45-1.32 (4H, m, H^2, H^3), 0.92 (6H, t, J = 7.0 Hz, CH$_2$C$\underline{H_3}$), 0.88-0.82 (1H, m, H^7), 0.48-0.32 (2H, m, C$\underline{H_2}$, cycloprop.), 0.25-0.16 (2H, m, C$\underline{H_2}$, cycloprop.); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 159.7, 155.2, 135.3, 130.3, 114.9, 103.2, 98.3, 70.9, 61.9, 56.1, 48.5, 31.4, 23.4, 15.9, 9.6, 9.5, 0.0; HRMS (ES^+) mass calc'd. For $C_{21}H_{29}NO_4$ 359.2097; found [$(M+H)^+$] 360.2170.

***N*-(4,4-diethoxybutyl)-*N*-(4-methoxyphenyl)-3-(thiophen-2-yl)propiolamide (8f)**



General procedure **1**, *N*-(4,4-diethoxybutyl)-4-methoxyaniline (**7**) (500 mg, 1.87 mmol) and 3-(thiophen-2-yl)propiolic acid (345.6 mg, 2.27 mmol), EDCI (435.84 mg, 2.27 mmol), HOBT (24.3 mg, 0.18 mmol) and CH_2Cl_2 (5 mL), 17 h, chromatography on silica gel (CH_2Cl_2:Et_2O, 0-5 %) to afford compound **8f** as a yellow oil (714 mg, 97% yield); Rf 0.45 (Pet.-Ether:AcOEt, 6:4); λ_{max} (film) / cm^{-1} 2972, 2875, 2357, 1633, 1511, 1389, 1294, 1249, 1127, 915, 789; ^{1}H NMR (500 MHz, C_6D_6) δ_H 7.00 (2H, d, J = 8.9 Hz, H^5), 6.92 (1H, dd, J = 2.9 Hz, J = 1.0 Hz, H^9), 6.68 (2H, d, J = 8.9 Hz, H^6), 6.62 (1H, dd, J = 5.0 Hz, J = 1.0 Hz, H^7), 6.49 (1H, dd, J = 5.0 Hz, J = 2.9 Hz H^8), 4.46 (1H, t, J = 4.7 Hz, H^4), 3.85 (2H, t, J = 6.5 Hz, H^1), 3.55 (2H, dq, J = 9.3 Hz, J = 7.0 Hz, OC$\underline{H_2}$CH$_3$), 3.38 (2H, dq, J = 9.3 Hz, J = 7.0 Hz, OC$\underline{H_2}$CH$_3$), 3.28 (3H, s, OC$\underline{H_3}$), 1.81-1.69 (4H, m, H^2, H^3), 1.14 (6H, t, J = 7.0 Hz, , OCH$_2$C$\underline{H_3}$); ^{13}C NMR (125 MHz, C_6D_6) δ_C 159.4, 154.2, 135.1, 131.8, 130.1, 125.6, 120.5, 114,4, 102.7, 85.9, 84.4, 61.0, 54.9, 48.4, 31.2, 23.4, 15.6; HRMS (ES^+) mass cal'd. For $C_{22}H_{27}NO_4S$ 401.1661; found [$(M+H)^+$] 402.1732.

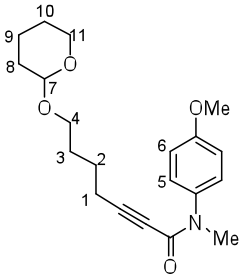
***N*-(3,3-diethoxypropyl)-*N*-(4-methoxyphenyl)-3-phenylpropiolamide (96)**



General procedure **1**, *N*-(3,3-diethoxypropyl)-4-methoxyaniline **94** (0.1 g, 0.39 mmol) and 3-phenylprop-2-ynoic acid (0.058 g, 0.39 mmol), EDCI (90.4 mg, 0.47 mmol), HOBT (5.26 mg, 0.039 mmol) and CH_2Cl_2 (5 mL), 15 h, chromatography on silica gel (CH_2Cl_2:acetone, 0-5 %) to afford compound **96** as a yellow oil (0.15 g, 99% yield); Rf 0.45 (CH_2Cl_2:acetone, 95:5); λ_{max} (film) / cm^{-1} 2974, 2215, 1632, 1510, 1247, 1054, 835, 757; ^{1}H NMR (400 MHz, C_6D_6) δ_H 7.06 (2H, d, J = 8.9.Hz, H^4), 7.00 (2H, d, J = 8.9 Hz, H^5), 6.81-6.75 (5H, m, Ph), 4.58 (1H, t, J = 4.6 Hz, H^3), 3.99-3.83 (2H, m, H^1), 3.57-3.46 (2H, m, OC$\underline{H_2}$CH$_3$), 3.38-3.29 (2H, m, OC$\underline{H_2}$CH$_3$), 3.22 (3H, s, OC$\underline{H_3}$), 2.02-1.97 (2H, m, H^2), 1.12 (6H, t, J = 6.9 Hz, OCH$_2$C$\underline{H_3}$); ^{13}C NMR (100

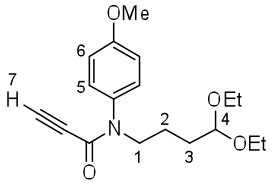
MHz, C_6D_6) δ_C 159.4, 154.1, 135.3, 132.6, 130.2, 129.6, 121.4, 114.4, 101.5, 90.3, 84.3, 61.3, 54.9, 45.3, 32.4, 15.6; HRMS (ES^+) mass calc'd. For $C_{23}H_{27}NO_4$ 381.1940; found [$(M+H)^+$] 382.1994.

_N_-(4-methoxyphenyl)-_N_-methyl-7-(tetrahydro-2_H_-pyran-2-yloxy)hept-2-ynamide (97)



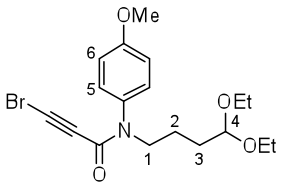
General procedure **1**, 4-Methoxy-*N*-methylaniline (330 mg, 2.40 mmol) and 7-(tetrahydro-2*H*-pyran-2-yloxy)hept-2-ynoic acid (700 mg, 3.09 mmol), EDCI (552 mg, 2.98 mmol), HOBT (33 mg, 0.24 mmol) and CH_2Cl_2 (15 mL), 17 h, chromatography on silica gel (CH_2Cl_2:acetone, 95:5) to afford compound **97** as a yellow oil (500 mg, 60% yield). Rf 0.42 (CH_2Cl_2:acetone, 95:5); λ_{max} (film) / cm^{-1} 2940, 2224, 1634, 1510, 1368, 1246, 1031, 836, 733; ^1H NMR (400 MHz, C_6D_6) δ_H 7.16 (2H, d, J = 8.9 Hz, H^5), 6.88 (2H, d, J = 8.9 Hz, H^6), 4.51 (1H, t, J = 3.6 Hz, H^7), 3.83-3.77 (4H, m, OC$\underline{H_3}$, H^{11a}), 3.62-3.54 (1H, m, H^{11b}), 3.50-3.44 (1H, m, H^{4a}), 3.27-3.20 (4H, m, NC$\underline{H_3}$, H^{4b}), 2.13 (2H, t, J = 6.7 Hz, H^1), 1.87-1.63 (2H, m, H^8), 1.61-1.46 (4H, m, H^{10}, H^9), 1.61-1.36 (4H, m, H^3, H^2); ^{13}C NMR (100 MHz, C_6D_6) δ_C 159.3, 154.3, 137.2, 129.1, 114.5, 98.7, 92.6, 76.8, 66.8, 61.8, 55.1, 36.3, 31.2, 28.9, 26.1, 25.0, 19.8, 18.7; HRMS (ES+) mass calc'd. For $C_{20}H_{27}NO_4$ 345.1940; found [$(M+Na)^+$] 368.1822.

_N_-(4,4-diethoxybutyl)-_N_-(4-methoxyphenyl)propiolamide (98)



General procedure **1**, *N*-(4,4-diethoxybutyl)-4-methoxyaniline (**7**) (1.00 g, 3.74 mmol) and propiolic acid (288.18 mg, 4.11 mmol), EDCI (860.23 mg, 4.48 mmol), HOBT (50.50 mg, 0.374 mmol) and CH_2Cl_2 (50 mL), 15 h, chromatography on silica gel (CH_2Cl_2:Et_2O, 0-5 %) to afford compound **98** as a yellow oil (1.19 g, 79% yield); Rf 0.52 (Pet-Ether:Diethyl ether, 1:1); λ_{max} (film) / cm^{-1} 2974, 2104, 1634, 1510, 1395, 1247, 1031, 835, 736; ^1H NMR (400 MHz, C_6D_6) δ_H 6.90 (2H, d, J = 8.9 Hz, H^5), 6.65 (2H, d, J = 8.9 Hz, H^6), 4.43 (1H, t, J = 4.9 Hz, H^4), 3.73 (2H, t, J = 6.9 Hz, H^1), 3.52 (2H, dq, J = 9.3 Hz, J = 7.0 Hz, OC$\underline{H_2}$CH$_3$), 3.35 (2H, dq, J = 9.3 Hz, J = 7.0 Hz, OC$\underline{H_2}$CH$_3$), 3.25 (3H, s, OC$\underline{H_3}$), 2.21 (1H, s, H^7), 1.70-1.65 (4H, m, H^2, H^3), 1.12 (6H, t, J = 7.0 Hz, OCH$_2$C$\underline{H_3}$); ^{13}C NMR (100 MHz, C_6D_6) δ_C 159.3, 152.8, 134.3, 129.7, 114,2, 102.7, 78.7, 77.3, 60.8, 54.6, 48.3, 30.8, 22.9, 15.3; HRMS (ES^+) mass calc'd. For $C_{18}H_{25}NO_4$ 319.1784; found [$(M+Na)^+$] 342.1676.

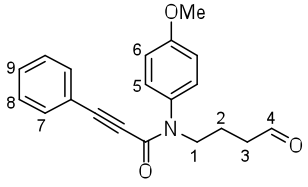
3-bromo-_N_-(4,4-diethoxybutyl)-_N_-(4-methoxyphenyl)propiolamide (8h)



N-(4,4-diethoxybutyl)-*N*-(4-methoxyphenyl)propiolamide (**98**) (400 mg, 1.25 mmol) was placed in a flask and dissolved in dry acetone (30 mL). Silver nitrate was added (106.16 mg, 0.62 mmol) to the solution at room temperature. After 5 min the solution was cooled to 0 ºC and NBS (232.51 mg, 1.31 mmol) was added portion-wise over 30 min. The mixture was stirred until completion. The solids were filtered off on a pad of celite that was washed several times with acetone. After removal of the acetone under reduced pressure the residue was purified by column chromatography on silica gel (CH_2Cl_2:Et_2O, 0-10 %) to afford compound **8h** as a colourless oil (420.7 mg, 86%

yield); Rf 0.42 (Pet.-Ether:AcOEt, 6:4); λ_{max} (film) / cm^{-1} 2974, 2104, 1717, 1636, 1511, 1396, 1292, 1127, 1033, 836, 728; ^1H NMR (500 MHz, C_6D_6) δ_H 6.80 (2H, d, *J* = 8.9 Hz, H^5), 6.57 (2H, d, *J* = 8.9 Hz, H^6), 4.39 (1H, t, *J* = 5.2 Hz, H^4), 3.67 (2H, t, *J* = 6.9 Hz, H^1), 3.48 (2H, dq, *J* = 9.3 Hz, *J* = 7.0 Hz, $OC\underline{H_2}CH_3$), 3.31 (2H, dq, *J* = 9.3 Hz, *J* = 7.0 Hz, $OC\underline{H_2}CH_3$), 3.16 (3H, s, $OC\underline{H_3}$), 1.68-1.58 (4H, m, H^2, H^3), 1.12 (6H, t, *J* = 7.0 Hz, $OCH_2C\underline{H_3}$); ^{13}C NMR (125 MHz, C_6D_6) δ_C 159.4, 152.6, 134.3, 129.8, 114,2, 102.4, 75.7, 61.8, 55.1, 54.8, 48.5, 31.1, 23.1, 15.6; HRMS (ES^+) mass calc'd. For $C_{18}H_{24}BrNO_4$ 397.0889; found $[(M+NH_4)^+]$ 415.1230.

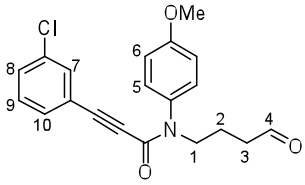
_N_-(4-methoxyphenyl)-_N_-(4-oxobutyl)-3-phenylpropiolamide (9a)



General procedure **2**, *N*-(4,4-diethoxybutyl)-*N*-(4-methoxyphenyl)-3-phenylpropiolamide (**8a**) (1 g, 2.53 mmol), 4 h, chromatography on silica gel (CH_2Cl_2:Et_2O, 0-10%) to afford compound **9a** as a colourless oil (817 mg, 99% yield); Rf 0.40 (CH_2Cl_2:acetone, 96:4) λ_{max} (film) / cm^{-1} 2936, 2214, 1721, 1629, 1509, 1391, 1247, 1028, 835, 757, 689; ^1H NMR (400 MHz, C_6D_6) δ_H 9.33 (1H, s, H^4), 7.16-7.12 (2H, m, Ph), 6.97 (2H, d, *J* = 8.9 Hz, H^5), 6.92-6.77 (3H, m, Ph), 6.72 (2H, d, *J* = 8.9 Hz, H^6), 3.67 (2H, t, *J* = 7.3 Hz, H^1), 3.29 (3H, s, $OC\underline{H_3}$), 1.94 (2H, t, *J* = 7.3 Hz, H^3), 1.64 (2H, dt, *J* = 7.3 Hz, *J* = 7.3 Hz, H^2); ^{13}C NMR (100 MHz, C_6D_6) δ_C 199.9, 159.7, 154.5, 135.2, 132,7, 130,2, 129.9, 128.6, 121.4, 114.6, 90.8, 84.3, 55.2, 48.0, 41.1, 20.7; HRMS (ES^+) mass calc'd. For $C_{20}H_{19}NO_3$ 321.1365; found $[(M+H)^+]$ 322.1449.

3-(3-chlorophenyl)-_N_-(4-methoxyphenyl)-_N_-(4-oxobutyl)propiolamide (9b)

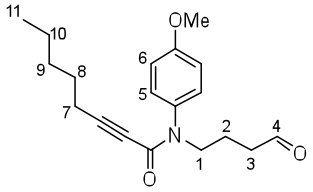
General procedure **2**, 3-(3-chlorophenyl)-*N*-(4,4-diethoxybutyl)-*N*-(4-methoxyphenyl)propiolamide (**8b**) (790 mg, 1.84 mmol), 15 h, chromatography on silica gel (pet.-ether/EtOAc, 7:3) to afford compound **9b** as yellow oil (568 mg, 87%).



Rf 0.29 (pet.-ether/EtOAc, 6:4); λ_{max} (film) / cm^{-1} 2974, 2930, 2219, 1634, 1591, 1562, 1474, 1442, 1392, 1295, 1248, 1169, 1124, 1058, 1032, 996, 956, 882, 835, 786, 729, 694, 680; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.70 (1H, s, H^4), 7.21-7.25 (1H, m, H^8), 7.19 (1H, s, H^7), 7.16 (2H, d, *J* = 9.0 Hz, H^5), 7.11 (1H, dd, *J* = 8.3 Hz, *J* = 8.0 Hz, H^9), 7.09-6.92 (1H, m, H^{10}), 6.90 (2H, d, *J* = 9.0 Hz, H^6), 3.79 (3H, s, $OC\underline{H_3}$), 3.72-3.76 (2H, m, H^1), 2.47 (2H, dt, *J* = 7.3 Hz, *J* = 1.0 Hz, H^3), 1.86-1.80 (2H, m, H^2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 201.5, 159.9, 154.8, 134.6, 134.5, 132.6, 130.8, 130.6, 130.0, 128.5, 122.6, 114.9, 90.0, 83.8, 56.0, 48.2, 41.4, 20.5; HRMS (ES^+) mass calc'd. For $C_{20}H_{18}ClNO_3$ 355.0975; found $[(M+H)^+]$ 356.1047.

_N_-(4-methoxyphenyl)-_N_-(4-oxobutyl)oct-2-ynamide (9c)

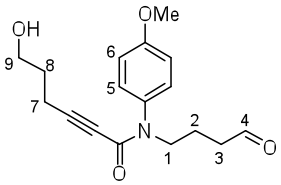
General procedure **2**, *N*-(4,4-diethoxybutyl)-*N*-(4-methoxyphenyl)oct-2-ynamide (**8c**) (300 mg, 0.77 mmol), 16 h, chromatography by (CH_2Cl_2:acetone, 95:5) to afford compound **9c** as a colourless oil (0.240 g, 99% yield).



Rf 0.55 (CH_2Cl_2:acetone, 95:5); λ_{max} (film) / cm^{-1} 2932, 2230, 1721, 1629, 1510, 1393, 1292, 1245, 1031, 834, 733; ^1H NMR (500 MHz, C_6D_6) δ_H 9.24 (1H, s, CHO), 6.89 (2H, d, *J* = 6.8 Hz, H^5), 6.65 (2H, d, *J* = 6.8 Hz, H^6), 3.57 (2H, t, *J* = 5.6 Hz, H^1), 3.25 (3H, s, $OC\underline{H_3}$), 1.85 (2H, t, *J* = 5.6 Hz, H^3), 1.77-1.62 (2H, m, H^2), 1.60-1.56 (2H, m, H^7), 1.10-0.87 (4H, m, H^9, H^8), 0.88-

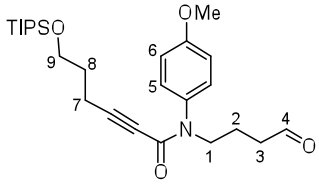
0.72 (2H, m, H^{10}), 0.75 (2H, t, J = 5.6 Hz, H^{11}); ^{13}C NMR (125 MHz, C_6D_6) δ_C 199.6, 159.1, 154.1, 135.1, 129.7, 114.2, 92.9, 76.2, 54.6, 47.6, 40.7, 30.5, 27.3, 22.1, 20.2, 18.5, 13.7; HRMS (ES^+) mass calc'd. For $C_{19}H_{25}NO_3$ 315.1834; found 316.1904.

6-hydroxy-*N*-(4-methoxyphenyl)-*N*-(4-oxobutyl)hex-2-ynamide (99)



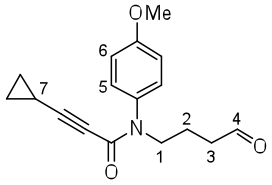
General procedure **2**, *N*-(4,4-diethoxybutyl)-*N*-(4-methoxyphenyl)-6-(tetrahydro-2*H*-pyran-2yloxy)-hex-2-ynamide (**95**) (400 g, 0.87 mmol), 36 h, chromatography by (CH_2Cl_2:acetone, 6:4) to afford compound **99** as a colourless oil (0.210 g, 80% yield). Rf 0.33 (CH_2Cl_2:acetone, 6:4); λ_{max} (film) / cm^{-1} 3413, 2938, 2231, 1720, 1619, 1511, 1403, 1248, 1034, 837, 736; ^{1}H NMR (500 MHz, C_6D_6) δ_H 9.32 (1H, s, CHO), 6.93 (2H, d, J = 8.9 Hz, H^5), 6.72 (2H, d, J = 8.9 Hz, H^6), 3.59 (2H, t, J = 7.1 Hz, H^1), 3.33 (3H, s, OC$\underline{H_3}$), 3.17 (2H, t, J = 6.1 Hz, H^9), 3.09 (1H, s, O$\underline{H}$), 1.98-1.76 (4H, m, H^3, H^7), 1.65 (2H, dt, J = 7.1 Hz, J = 7.1 Hz, H^2), 1.22 (2H, tt, J = 6.8 Hz, H^8); ^{13}C NMR (125 MHz, C_6D_6) δ_C 200.0, 159.5, 154.6, 135.1, 129.9, 114.5, 93.4, 76.3, 60.6, 55.0, 47.8, 40.9, 30.7, 20.4, 15.2; HRMS (ES^+) mass calc'd. For $C_{17}H_{21}NO_4$ 303.1471; found [$(M+H)^+$] 304.1541.

***N*-(4-methoxyphenyl)-*N*-(4-oxobutyl)-6-(triisopropylsilyloxy)hex-2-ynamide (8d)**



Triethylamine (171 µL, 1.23 mmol) and DMAP (6 mg, 0.049 mmol) were added to a solution of 6-hydroxy-*N*-(4-methoxyphenyl)-*N*-(4-oxobutyl)hex-2-ynamide (**99)** (150 mg, 0.49 mmol) in CH_2Cl_2 (6 mL), followed by TIPSCl solution (126 µL, 0.59 mmol). The resulting mixture was stirred at room temperature for 48 h and quenched by aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, concentrated in vacuo and purified by flash chromatography on silica gel (CH_2Cl_2:acetone, 95:5) to afford compound **9d** as a colourless oil (170 mg, 75% yield). Rf 0.6 (CH_2Cl_2:acetone, 95:5); λ_{max} (film) / cm^{-1} 3390, 2962, 2256, 1633, 1394, 1249, 994, 733; ^{1}H NMR (500 MHz, C_6D_6) δ_H 9.29 (1H, s, CHO), 6.95 (2H, d, J = 8.9 Hz, H^5), 6.70 (2H, d, J = 8.9 Hz, H^6), 3.59 (2H, t, J = 7.1 Hz, H^1), 3.38 (2H, t, J = 5.8 Hz, H^9), 3.30 (3H, S, OC$\underline{H_3}$), 2.03 (2H, t, J = 7.1 Hz, H^3), 1.89 (2H, t, J = 5.8 Hz, H^7), 1.59 (2H, dt, J = 7.1 Hz, J = 7.1 Hz, H^2), 1.32 (2H, dt, J = 5.8 Hz, J = 5.8 Hz, H^8), 1.09-0.95 (21H, m, TIPS); ^{13}C NMR (125 MHz, C_6D_6) δ_C 199.8, 159.3, 154.3, 135.3, 129.9, 114.4, 92.9, 76.4, 61.6, 54.9, 47.8, 40.9, 31.4, 20.5, 18.2, 15.3, 12.2; HRMS (ES^+) mass calc'd. For $C_{26}H_{41}NO_4Si$ 459.2805; found [$(M+H)^+$] 460.2864.

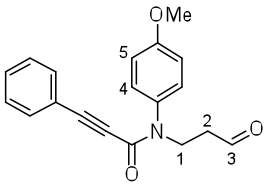
3-cyclopropyl-*N*-(4-methoxyphenyl)-*N*-(4-oxobutyl)propiolamide (9e)



General procedure **2**, 3-cyclopropyl-*N*-(4,4-diethylbutyl)-*N*-(4-methoxyphenyl)propiolamide (**8e**) (1 g, 2.78 mmol), 5 h, chromatography on silica gel (petrol ether/EtOAc, 7:3) to afford compound **9e** as yellow oil (732 mg, 92%). Rf 0.18 (pet.-ether/EtOAc, 7:3); λ_{max} (film) / cm^{-1} 2938, 2838, 2222, 1720, 1626, 1510, 1442, 1395, 1292, 1247, 1180, 1107, 1059, 1030, 938, 890, 836, 814, 732; ^{1}H NMR (500 MHz, C_6D_6) δ_H 9.26 (1H, s, H^4), 6.85 (2H, d, J = 8.9 Hz, H^5), 6.63 (2H, d, J = 8.9 Hz, H^6), 3.55 (2H, t, J = 7.2 Hz, H^1), 3.24 (3H, s, OC$\underline{H_3}$), 1.86 (2H, t, J = 7.2 Hz, H^3), 1.67 (2 H, tt, J = 7.2 Hz, J = 7.2 Hz, H^2),

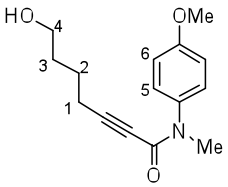
0.68-0.64 (1H, m, H^7), 0.29-0.23 (2H, m, C$\underline{H_2}$, cycloprop.), 0.16-0.10 (2H, m, C$\underline{H_2}$, cycloprop.); ^{13}C NMR (125 MHz, C_6D_6) δ_C 199.8, 159.3, 154.3, 135.3, 129.9, 114.3, 96.8, 71.5, 54.9, 47.7, 40.9, 20.5, 8.8, 0.00; HRMS (ES^+) mass calc'd. For $C_{17}H_{19}NO_3$ 285.1365; found [$(M+H)^+$] 286.1432.

_N_-(4-methoxyphenyl)-N-(3-oxopropyl)-3-phenylpropiolamide (100)



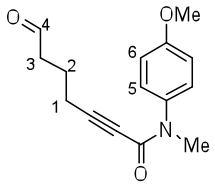
General procedure **2**, *N*-(3,3-diethoxypropyl)-*N*-(4-methoxyphenyl)-3-phenylpropiolamide (**96**) (0.35 g, 092 mmol), 4 h, chromatography on silica gel (CH_2Cl_2:acetone, 0-5%) to afford compound **100** as a colourless oil (0.28 g, 91% yield); Rf 0.40 (CH_2Cl_2:acetone, 96:4) λ_{max} (film) / cm^{-1} 2962, 2214, 1720, 1627, 1509, 1392, 1293, 1246, 1027, 835, 757; ^{1}H NMR (400 MHz, C_6D_6) δ_H 9.33 (1H, s, H^3), 7.03 (2H, d, J = 8.8 Hz, H^4), 6.88 (2H, d, J = 8.8 Hz, H^5), 6.81-6.62 (5H, m, Ph), 3.88 (2H, t, J = 7.0 Hz, H^1), 3.22 (3H, s, OC$\underline{H_3}$), 2.17 (2H, m, H^2); ^{13}C NMR (100 MHz, C_6D_6) δ_C 198.9, 159.6, 154.2, 134.7, 132.6, 130.1, 129.8, 121.1, 114.5, 90.8, 83.8, 54.9, 42.9, 42.3; HRMS (ES^+) mass calc'd. For $C_{19}H_{17}NO_3$ 307.1208; found [$(M+H)^+$] 308.1287.

7-hydroxy-_N_-(4-methoxyphenyl)-_N_-methylhept-2-ynamide (101)



*p*TsOH (12 mg, 0.063 mmol) was added to a solution of *N*-(4-methoxyphenyl)-*N*-methyl-7-(tetrahydro-2*H*-pyran-2-yloxy)hept-2-ynamide (**97**) (400 mg, 1.16 mmol) in MeOH (8 mL) at room temperature. The resulting mixture was stirred for 6 h, quenched with aqueous $NaHCO_3$solution and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, concentrated in vacuo and purified by flash chromatography on silica gel (CH_2Cl_2:acetone, 75:25) to afford compound **101** as a colourless oil (290 mg, 96% yield). Rf 0.45 (CH_2Cl_2:acetone, 75:25); λ_{max} (film) / cm^{-1} 3413, 2937, 2226, 1619, 1510, 1375, 1246, 1169, 1030, 836, 733; ^{1}H NMR (400 MHz, C_6D_6) δ_H 6.90 (2H, d, J = 8.9 Hz, H^5), 6.75 (2H, d, J = 8.9 Hz, H^6), 3.34 (3H, s, OC$\underline{H_3}$), 3.31 (2H, t, J = 5.2 Hz, H^4), 3.13 (3H, s, NC$\underline{H_3}$), 1.81 (2H, t, J = 6.4 Hz, H^1), 1.25-1.12 (4H, m, H^2, H^3); ^{13}C NMR (100 MHz, C_6D_6) δ_C 159.3, 154.5, 137.1, 129.1, 114.5, 93.2, 76.7, 62.0, 55.1, 36.3, 31.9, 24.4, 18.7; HRMS (ES^+) mass calc'd. For $C_{15}H_{19}NO_3$ 261.1365; found [$(M+H)^+$] 262.1436.

_N_-(4-methoxyphenyl)-_N_-methyl-7-oxohept-2-ynamide (16)

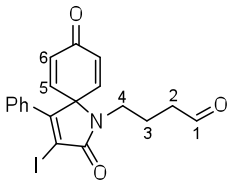


Dess Martin Peridinone (DMP) (424 mg, 1.15 mmol) was added to a solution of 7-hydroxy-*N*-(4-methoxyphenyl)-*N*-methylhept-2 ynamide (**101**) (255 mg, 0.98 mmol) in CH_2Cl_2 (12 ml) at 0 ºC. The reaction mixture was allowed warm up to room temperature over a period of 1 h and quenched with aqueous $NaHCO_3$ solution. It was extracted with CH_2Cl_2 (3 x 15 ml), dried over $MgSO_4$, concentrated in vacuo and purified by flash chromatography on silica gel (CH_2Cl_2:acetone, 9:1) to afford compound **16** as a colourless oil (250 mg, 99% yield). Rf 0.63 (CH_2Cl_2:acetone, 9:1); λ_{max} (film) / cm^{-1} 2940, 2225, 1720, 1629, 1509, 1368, 1245, 1155, 1029, 836, 733; ^{1}H NMR (400 MHz, C_6D_6) δ_H 9.17 (1H, s, CHO), 6.85 (2H, d, J = 8.8 Hz, H^5), 6.66 (2H, d, J = 8.8 Hz, H^6), 3.34 (3H, s, OC$\underline{H_3}$), 3.12 (3H, s, NC$\underline{H_3}$), 1.67 (2H, t, J = 6.7 Hz, H^3), 1.58 (2H, t, J = 7.6 Hz, H^1), 1.10 (2H, tt, J = 7.6 Hz, J = 6.7 Hz, H^2); ^{13}C NMR (100 MHz, C_6D_6) δ_C 199.9, 159.3, 154.0, 137.0, 129.1,

114.5, 91.4, 77.3, 55.1, 42.2, 36.3, 20.3, 18.0; HRMS (ES^+) mass calc'd. For $C_{15}H_{17}NO_3$ 259.1208; found [$(M+H)^+$] 260.1280.

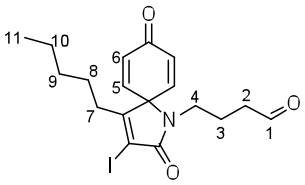
Even though the ECED process does not require the isolation of the iodo-cyclohexadienone, we have included the full data for their characterization. This data was obtained from a separate experiment.

4-(3-iodo-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-3,6,9-trien-1-yl)butanal (10a)



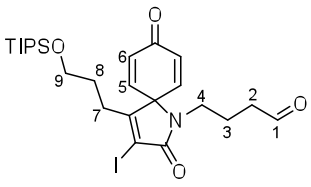
Method A: *N*-(4-methoxyphenyl)-*N*-(4-oxobutyl)-3-phenylprop-2-ynamide (**9a**) (100 mg, 0.311 mmol), CH_2Cl_2 (7 mL), ICl (622 μL), 30 min, chromatography on silica gel (CH_2Cl_2:acetone, 95:5) to afford compound **10a** as a colourless oil (100 mg, 75% yield); Rf 0.42 (CH_2Cl_2:acetone, 95:5); λ_{max} (film) / cm^{-1} 3050, 1666, 1694, 1389, 1060, 873, 723; ^1H NMR (400 MHz, C_6D_6) δ_H 9.33 (1H, s, CHO), 7.15-7.00 (5H, m, Ph), 6.02 (2H, d, J = 10.1 Hz, H^5), 5.53 (2H, d, J = 10.1 Hz, H^6), 3.00 (2H, t, J = 7.10 Hz, H^4), 1.87 (2H, t, J = 7.1 Hz, H^2), 1.59 (2H, dt, J = 7.10 Hz, J = 7.10 Hz, H^3); ^{13}C NMR (100 MHz, C_6D_6) δ_C 199.9, 183.3, 167.7, 158.6, 144.1, 133.1, 132.9, 130.2, 128.9, 128.3, 128.2, 127.9, 99.5, 70.9, 41.6, 41.4, 22.8; HRMS (ES^+) mass calc'd. For $C_{19}H_{16}INO_3$ 433.0175; found [$(M+H)^+$] 434.0265.

4-(3-iodo-2,8-dioxo-4-pentyl-1-azaspiro[4.5]deca-3,6,9-trien-1-yl)butanal (10c)



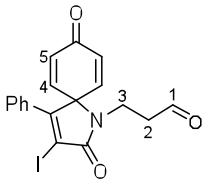
Method A: *N*-(4-methoxyphenyl)-*N*-(4-oxobutyl)oct-2-ynamide (**9c**) (100 mg, 0.32 mmol), CH_2Cl_2 (10 mL), ICl (640 μL), 30 min, chromatography on silica gel (CH_2Cl_2:acetone, 95:5) to afford compound **10c** as a colourless oil (110 mg, 80% yield). Rf 0.40 (CH_2Cl_2:acetone, 95:5); λ_{max} (film) / cm^{-1} 2929, 1664, 1388, 1059, 858, 732; ^1H NMR (500 MHz, C_6D_6) δ_H 9.25 (1H, s, CHO), 6.07 (2H, d, J = 8.0 Hz, H^5), 5.35 (2H, d, J = 8.4 Hz, H^6), 2.89 (2H, t, J = 5.6 Hz, H^4), 1.89-1.77 (4H, m, H^2, H^3), 1.52-1.47 (2H, m, H^{10}), 1.28-1.21 (2H, m, H^7), 1.17-1.11 (2H, m, H^8), 1.07-1.01 (2H, m, H^9), 0.82 (3H, t, J = 5.6 Hz, H^{11}) ;^{13}C NMR (125 MHz, C_6D_6) δ_C 199.7, 183.3, 167.5, 159.7, 144.5, 132.6, 97.2, 70.6, 41.2, 40.9, 31.8, 29.2, 27.9, 22.5, 22.3, 13.9; HRMS (ES^+) mass calc'd. For $C_{18}H_{22}IN0_3$ 427.0644; found [$(M+H)^+$] 428.0722.

4-(3-iodo-2,8-dioxo-4-(3-((triisopropylsilyl)oxy)propyl)-1-azaspiro[4.5]deca-3,6,9-trien-1-yl)butanal (10d)



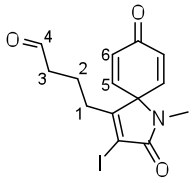
Method A: *N*-(4-methoxyphenyl)-*N*-(4-oxobutyl)-6 (triisopropylsilyloxy)-hex-2-ynamide (**9d**) (40 mg, 0.087 mmol), CH_2Cl_2 (2 mL), ICl (170 μL), chromatography on silica gel (CH_2Cl_2:acetone, 95:5) to afford compound **10d** as a colourless oil (39 mg, 78% yield). Rf 0.45 (CH_2Cl_2:acetone, 95:5); λ_{max} (film) / cm^{-1}, ^1H NMR (400 MHz, C_6D_6) δ_H (NA),^{13}C NMR (100 MHz, C_6D_6) δ_C (NA) ; HRMS (ES^+) mass calc'd. For $C_{25}H_{38}INO_4Si$ 571.1615; found [$(M+H)^+$] 572.1686.

4-(3-iodo-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-3,6,9-trien-1-yl)butanal (102)



Method A: *N*-(4-methoxyphenyl)-*N*-(4-oxobutyl)-3-phenylprop-2-ynamide (**100**) (20 mg, 0.065 mmol), CH_2Cl_2 (3 mL), ICl (65 µL), 30 min, chromatography on silica gel (CH_2Cl_2:acetone, 95:5) to afford compound **102** as a colourless oil (0.025 g, 95% yield); Rf 0.40 (CH_2Cl_2:acetone, 95:5); λ_{max} (film) / cm^{-1} 2971, 1693, 1389, 1059, 876, 724; ^1H NMR (400 MHz, CD_3Cl_3) δ_H 9.70 (1H, s, H^1), 7.15-7.39-7.24 (5H, m, Ph), 6.50 (2H, d, J = 10.1 Hz, H^4), 6.39 (2H, d, J = 10.1 Hz, H^5), 3.62 (2H, t, J = 7.0 Hz, H^3), 2.79 (2H, t, J = 7.1 Hz, H^2), ^{13}C NMR (100 MHz, C_6D_6) δ_C 199.3, 182.1, 165.3, 155.2, 140.1, 132.3, 130.1, 128.2, 128.1, 127.3, 127.0, 125.9, 98.1, 70.3, 43.6, 40.4; HRMS (ES^+) mass calc'd. For $C_{18}H_{14}INO_3$ 419.0018; found $[(M+H)^+]$ 420.0097.

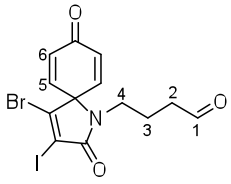
4-(3-iodo-1-methyl-2,8-dioxo-1-azaspiro[4.5]deca-3,6,9-trien-4-yl)butanal (103)



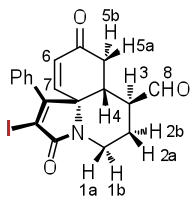
Method A: *N*-(4-methoxyphenyl)-*N*-methyl-7-oxohept-2-ynamide (**101**) (50 mg, 0.193 mmol), CH_2Cl_2 (3 mL), ICl (390 µL), chromatography on silica gel (CH_2Cl_2:acetone, 9:1) to afford compound **103** as a colourless oil (0.065 g, 91% yield). Rf 0.42 (CH_2Cl_2:acetone, 9:1); λ_{max} (film) / cm^{-1} 2956, 2300, 1690, 1367, 1265, 1063, 1005, 856, 733; ^1H NMR (500 MHz, C_6D_6) δ_H 9.19 (1H, s, CHO), 6.06 (2H, d, J = 10.1 Hz, H^5), 5.06 (2H, d, J = 10.1 Hz, H^6), 2.40 (3H, s, NCH_3), 1.70-1.62 (2H, m, H^3), 1.59 (2H, t, J = 7.2 Hz, H^1), 1.39-1.34 (2H, m, H^2); ^{13}C NMR (125 MHz, C_6D_6) δ_C 199.1, 183.0, 166.6, 158.6, 144.0, 133.0, 98.2, 69.9, 42.9, 28.3, 26.3, 20.6; HRMS (ES^+) mass calc'd. For $C_{14}H_{14}INO_3$ 371.0018; found $[(M+H)^+]$ 372.0087.

4-(4-bromo-3-iodo-2,8-dioxo-1-azaspiro[4.5]deca-3,6,9-trien-1-yl)butanal (10h)

Method B: 3-bromo-*N*-(4,4-diethoxybutyl)-*N*-(4-methoxyphenyl) propiolamide (**9h**) (150 mg, 0.376 mmol), CH_2Cl_2 (20 mL), ICl (753 µL), 30 min, chromatography on silica gel (CH_2Cl_2:acetone, 0-5%) to afford compound **10h** colourless oil (160 mg, 97% yield); Rf 0.30 (CH_2Cl_2:MeOH, 95:5); λ_{max} (film) / cm^{-1} 2944, 2726, 1707, 1510, 1669, 1632, 1388, 1141, 1061, 870, 745; ^1H NMR (500 MHz, C_6D_6) δ_H 9.19 (1H, CHO), 6.08 (2H, d, J = 10.1 Hz, H^5), 5.08 (2H, d, J = 10.1 Hz, H^6), 2.89 (2H, t, J = 7.0 Hz, H^4), 1.98 (2H, t, J = 7.0 Hz, H^2) 1.53 (2H, dt, J = 7.0 Hz, J = 7.0 Hz, H^3); ^{13}C NMR (125 MHz, C_6D_6) δ_C 199.5, 182.9, 177.3, 164.2, 142.6, 133.6, 124.3, 69.0, 41.60, 30.7, 24.7; HRMS (ES^+) mass calc'd. For $C_{13}H_{11}BrINO_3$ 434.8967; found $[(M+H)^+]$ 435.9037.

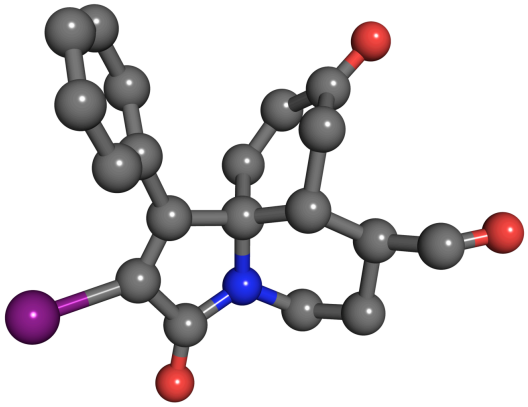


2-iodo-3,9-dioxo-1-phenyl-5,6,7,7a,8,9-hexahydro-3*H*-pyrrolo[2,1-j]quinoline-7-carbaldehyde (4a)

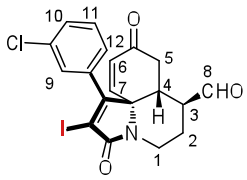


Method B: *N*-(4-methoxyphenyl)-*N*-(4-oxobutyl)-3-phenylpropiolamide (**9a**) (500 mg, 1.55 mmol), CH_2Cl_2 (30 mL), ICl (3.1 mL) form 4-(3-Iodo-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-3,6,9-trien-1-yl)butanal **10a**; then catalyst (75.13 mg, 0.23 mmol), benzoic acid (28.08 mg, 0.20 mmol), 48 h at 0 °C, chromatography on silica gel (CH_2Cl_2:acetone, 0-5%) gives compound **11a** as a white solid (452 mg, 90% yield); Rf 0.55 (CH_2Cl_2:MeOH, 95:5); MP: 232-234 ºC; λ_{max}

(film) / cm^{-1} 3056, 2920, 2729, 1624, 1679, 1399, 1298, 1031, 733; ^1H NMR (500 MHz, C_6D_6) δ_H 8.80 (1H, d, J = 1.6 Hz, CHO), 6.99-6.94 (3H, m, Ph), 6.86-6.83 (2H, m, Ph), 5.85 (1H, d, J = 10.1 Hz, H^7), 5.12 (1H, dd, J = 10.1 Hz, J = 1.8 Hz, H^6), 4.19 (1H, ddd, J = 13.2 Hz, J = 4.8 Hz, J = 1.9 Hz, H^{1b}), 2.13 (1H, app. dt, J = 13.2 Hz, J = 2.9 Hz, H^{1a}), 2.08-2.00 (2H, m, H^{5a},H^4), 1.75 (1H, ddt, J = 12.9 Hz, J = 3.7 Hz, J = 1.5 Hz, H^3), 1.65 (1H, dd, J = 17.3 Hz, J = 13.2 Hz, H^{5b}), 0.95 (1H, app. dq, J = 13.1 Hz, J = 3.1 Hz, H^{2b}), 0.60 (1H, app. dq, J = 12.3 Hz, J = 4.7 Hz, H^{2a}); ^{13}C NMR (125 MHz, C_6D_6) δ_C 199.7, 194.6, 165.1, 163.0, 144.6, 135.3, 134.4, 130.2, 129.6, 128.9, 100.6, 69.1, 49.7, 39.5, 38.9, 37.5, 25.9; HRMS (ES^+) mass calc'd. For $C_{19}H_{16}INO_3$ 433.0175; found $[(M+H)^+]$ 434.0273. $[\alpha]_D^{25}$ = + 168.00° (C = 0.67 mg/ml), $CHCl_3$ for 92% ee. HPLC:DAICEL AD Chiralpak, 8:2 Hexane/isopropanol, flow 1 mL/min, retention time: major 22.78 min, minor enantiomer 25.67 min. CCDC number: pending. CIF file included.



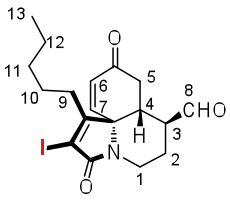
1-(3-chlorophenyl)-2-iodo-3,9-dioxo-5,6,7,7a,8,9-hexahydro-3*H*-pyrrolo[2,1-j]quinoline-7-carbaldehyde (11b)



Method B: 3-(3-chlorophenyl)-*N*-(4,4-diethoxybutyl)-*N*-(4-methoxyphenyl)propiolamide (**8b**) (100 mg, 0.23 mmol), CH_2Cl_2 (15 mL), ICl (465 µL) form 4-(3-Iodo-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-3,6,9-trien-1-yl)butanal; then catalyst (15 mg, 0.046 mmol), benzoic acid (5.61 mg, 0.046 mmol), CH_2Cl_2 (40 mL), 48 h at 0°C, chromatography on silica gel (CH_2Cl_2:acetone, 0-5%) gives aldehyde **11b** as a white solid (85 mg, 80%). MP: 188-190 ºC. Rf 0.12 (pet.-ether/EtOAc 6:4); λ_{max} (film) / cm^{-1} 2921, 1682, 1586, 1562, 1472, 1451, 1400, 1299, 1270, 1214, 1080, 1032, 934, 901, 782, 735, 719, 678; ^1H NMR (400 MHz, C_6D_6) δ_H 8.90 (1H, d, J = 1.6 Hz, CHO), 7.17 (1H, t, J = 1.6 Hz, H^9), 7.10 (1H, ddd, J = 8.0 Hz, J = 2.3 Hz, J = 1.2 Hz , H^{10}), 6.82 (1H, dd, J = 7.9 Hz, J = 7.8 Hz, H^{11}), 6.76 (1H, dt, J = 7.8 Hz, J = 1.2 Hz, H^{12}), 5.95 (1H, d, J = 10.0 Hz, H^7), 5.16 (1H, dd, J = 10.0 Hz, J = 2.0 Hz, H^6), 4.32 (1H, ddd, J = 13.4 Hz, J = 4.7 Hz, J = 1.9 Hz, H^{1b}), 2.24 (1H, app. dt, 13.1 Hz, J = 3.1 Hz, H^{1a}), 2.20 (1H, app. d, J = 17.5 Hz, H^{5a}), 2.14-2.08 (1H, m, H^4), 1.87 (1H, ddt, J = 12.2 Hz, J = 3.8 Hz, J = 1.9 Hz, H^3), 1.78 (1H, dd, J = 17.5 Hz, J = 5.3 Hz, H^{5b}), 1.09 (1H, app. dq, J = 13.1 Hz, J = 3.1 Hz, H^{2b}), 0.76 (1H, app. dq, J = 12.9 Hz, J = 4.7 Hz, H^{2a}); ^{13}C NMR (100 MHz, C_6D_6) δ_C 199.6, 194.0, 164.3, 160.7, 144.2, 136.7, 135.2, 134.1, 130.0,

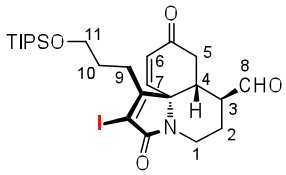
130.7, 128.3, 126.3, 77.9, 68.8, 49.2, 39.0, 38.5, 37.1, 25.6; HRMS (ES^+) mass calc'd. For $C_{19}H_{15}ClINO_3$ 466.9785; found $[(M+H)^+]$ 467.9776. $[\alpha]_D^{25}$ = - 113.20º (C = 1.27 mg/ml), $CHCl_3$ for 92% ee.

2-iodo-3,9-dioxo-1-pentyl-5,6,7,7a,8,9-hexahydro-3*H*-pyrrolo[2,1-j]quinoline-7-carbaldehyde (11c)



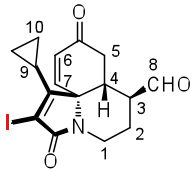
Method A: 4-(3-Iodo-2,8-dioxo-4-pentyl-1-azaspiro[4.5]deca-3,6,9-trien-1-yl)butanal (**10c**) (10 mg, 0.023 mmol), catalyst (1.49 mg, 0.0046 mmol), benzoic acid (0.561 mg, 0.046 mmol), 12 h at -20 ºC, chromatography on silica gel (CH_2Cl_2:acetone, 9:1) gives ketone **11c** as a colourless oil (9 mg, 90% yield). Rf 0.48 (CH_2Cl_2:acetone, 9:1); λ_{max} (film) / cm^{-1} 2928, 1676, 1399, 1031, 746; ^1H NMR (500 MHz, C_6D_6) δ_H 8.7 (1H, d, *J* = 1.7 Hz, CHO), 5.82 (1H, d, *J* = 10.2 Hz, H^7), 4.92 (1H, dd, *J* = 10.2 Hz, *J* = 2.0 Hz, H^6), 4.11 (1H, ddd, *J* = 13.3 Hz, *J* = 4.7 Hz, *J* = 1.9 Hz, H^{1b}), 2.46-2.41 (2H, m, H^{1a}, H^{5a}), 2.08-2.00 (2H, m, H^9), 1.88-1.80 (1H, m, H^4), 1.70 (1H, ddt, *J* = 11.6 Hz, *J* = 3.8 Hz, *J* = 1.7 Hz, H^3), 1.48-1.41 (1H, m, H^{5b}), 1.25-1.12 (6H, m, H^{10}, H^{12}, H^{11}), 0.92-0.79 (4H, m, H^{2b}, H^{13}), 0.45 (1H, app. dq, *J* = 12.9 Hz, *J* = 4.4 Hz, H^{2a}); ^{13}C NMR (125 MHz, C_6D_6) δ_C 199.0, 193.9, 164.4, 163.0, 146.2, 132.7, 98.7, 67.7, 49.7, 39.2, 38.3, 36.6, 32.0, 30.9, 27.8, 25.3, 22.2, 14.0; HRMS (ES^+) mass calc'd. For $C_{18}H_{22}INO_3$ 427.0644; found $[(M+H)^+]$ 428.0708; $[\alpha]_D^{25}$ = + 130.00º (C = 1 mg/mL), $CHCl_3$ for 90% ee; HPLC:DAICEL AD Chiralpak, 8:2 Hexane/isopropanol, flow 1 mL/min, retention time: major enantiomer 11.28 min, minor enantiomer 12.93 min.

2-iodo-3,9-dioxo-1-(3-((triisopropylsilyl)oxy)propyl)-5,6,7,7a,8,9-hexahydro-3*H*-pyrrolo[2,1-j]quinoline-7-carbaldehyde (11d)



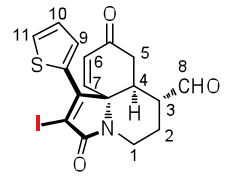
Method A: 4-(3-iodo-2,8-dioxo-4-(3-(triisopropylsilyloxy)propyl-1-azaspiro[4.5]deca-3,6,9-trien-1-yl)butanal (**10d**) (10 mg, 0.017 mmol), catalyst (1.5 mg, 0.034 mmol) and benzoic acid (0.6 mg, 0.034 mmol), 24 h at -20 ºC, chromatography on silica gel (CH_2Cl_2:acetone, 9:1) gives aldehyde **11d** as a colourless oil (8 mg, 80% yield). Rf 0.40 (CH_2Cl_2:acetone, 9:1); λ_{max} (film) / cm^{-1} 2941, 1688, 1399, 1103, 882, 747; ^1H NMR (500 MHz, C_6D_6) δ_H 8.76 (1H, d, *J* = 1.7 Hz, CHO), 5.89 (1H, d, *J* = 10.2 Hz, H^7), 4.97 (1H, dd, *J* = 10.2 Hz, *J* = 2.0 Hz, H^6), 4.14 (1H, ddd, *J* = 13.3 Hz, *J* = 4.7 Hz, *J* = 1.9 Hz, H^{1b}), 3.55 (1H, dt, *J* = 9.9 Hz, *J* = 4.8 Hz, H^{11a}), 3.45 (1H, ddd, *J* = 9.9 Hz, *J* = 8.5.1 Hz, *J* = 4.9 Hz, H^{11b}), 2.91 (1H, dd, *J* = 17.8 Hz, *J* = 5.4 Hz, H^{5b}), 2.53 (1H, dt, *J* = 13.2 Hz, *J* = 2.9 Hz, H^{5a}), 2.61-2.49 (1H, m, H^{9a}), 2.47-2.38 (1H, m, H^{9b}), 2.04 (1H, app. dt, *J* = 13.6 Hz, *J* = 3.0 Hz, H^{1a}), 2.0-1.92 (1H, m, H^4), 1.86-1.75 (1H, m, H^{10a}), 1.78-1.70 (1H, m, H^3), 1.49 (1H, ddt, *J* = 12.8 Hz, *J* = 8.5 Hz, *J* = 4.2 Hz, H^{10b}), 1.10-0.87 (21H, m, TIPS), 1.20 (1H, app. dq, *J* = 13.0 Hz, *J* = 2.9 Hz, H^{2b}), 1.20 (1H, app. dq, *J* = 13.0 Hz, *J* = 4.7 Hz, H^{2a}); ^{13}C NMR (125 MHz, C_6D_6) δ_C 199.0, 194.0, 164.4, 162.8, 145.8, 132.9, 99.0, 67.9, 62.8, 49.7, 39.4, 38.3, 36.6, 31.1, 27.8, 25.4, 18.2, 12.2; HRMS (ES^+) mass calc'd. For $C_{25}H_{38}INO_4Si$ 571.1615; found $[(M+H)^+]$ 572.1697; $[\alpha]_D^{25}$ = - 45.45º (C = 0.66 mg/mL), $CHCl_3$ for 89% ee; HPLC:DAICEL AD-H Chiralpak, 9:1 Hexane/isopropanol, flow 1 mL/min, retention time: major enantiomer 22.66 min, minor enantiomer 27.29 min.

1-cyclopropyl-2-iodo-3,9-dioxo-5,6,7,7a,8,9-hexahydro-3*H*-pyrrolo[2,1-j]quinoline-7-carbaldehyde (11e)



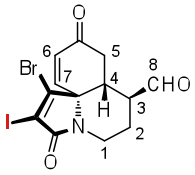
Method A: 3-cyclopropyl-*N*-(4-methoxyphenyl)-*N*-(4-oxobutyl)propiolamide (**9e**) (100 mg, 0.35 mmol), CH_2Cl_2 (15 mL), ICl (700 µL) form 4-(3-Iodo-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-3,6,9-trien-1-yl)butanal; then catalyst (22.7 mg, 0.07 mmol), benzoic acid (8.54 mg, 0.07 mmol), 48 h at 0°C, chromatography on silica gel (CH_2Cl_2:acetone, 0-5%) gives aldehyde **11e** as a white solid (108.8 mg, 78% yield); MP: 168-170 ºC; Rf 0.46 (CH_2Cl_2:MeOH, 95:5); λ_{max} (film) / cm^{-1} 2924, 2726, 1720, 1674, 1599, 1404, 1299, 1211, 1028, 955, 867, 732, 698; ^1H NMR (400 MHz, C_6D_6) δ_H 8.75 (1H, d, J = 1.6 Hz, CHO), 5.81 (1H, d, J = 10.2 Hz, H^7), 4.96 (1H, dd, J = 10.2 Hz, J = 1.9 Hz, H^6), 4.08 (1H, ddd, J = 13.4 Hz, J = 4.7 Hz, J = 1.9 Hz, H^{1b}), 2.82 (1H, dd, J = 17.8 Hz, J = 5.2 Hz, H^{5b}), 2.41 (1H, dt, J = 17.8 Hz, J = 0.9 Hz, H^{5a}), 2.00 (1H, app. dt, J = 13.4 Hz, J = 1.9 Hz, H^{1a}), 1.90-1.80 (1H, m, H^4), 1.78-1.72 (1H, ddt, J = 13.7 Hz, J = 3.6 Hz, J = 1.6 Hz, H^3) 1.32-1.26 (1H, m, H^9), 0.91 (1H, app. dq, J = 12.9 Hz, J = 3.0 Hz, H^{2b}), 0.79-0.57 (2H, m, Cycloprop, H^{10}), 0.53 (1H, app. dq, J = 12.9 Hz, J = 4.8 Hz, H^{2a}), 0.40-0.27 (2H, m, Cycloprop, H^{10}); ^{13}C NMR (100 MHz, C_6D_6) δ_C 199.4, 194.7, 164.9, 160.9, 146.6, 132.9, 92.9, 68.7, 49.9, 39.2, 38.9, 36.8, 25.3, 12.2, 8.6, 7.4; HRMS (ES^+) mass cal'd. For $C_{16}H_{16}INO_3$ 397.0175; found $[(M+H)^+]$ 398.0247. $[\alpha]_D^{25}$ = - 69.70° (C = 1.15 mg/ml), $CHCl_3$ for 96% ee.

2-iodo-3,9-dioxo-1-(thiophen-2-yl)-5,6,7,7a,8,9-hexahydro-3*H*-pyrrolo[2,1-j]quinoline-7-carbaldehyde (11f)



Method B: *N*-(4,4-diethoxybutyl)-*N*-(4-methoxyphenyl)-3-(thiophen-2-yl)propiolamide (**8f**) (100 mg, 0.25 mmol), CH_2Cl_2 (10 mL), ICl (500 µL) form 4-(3-iodo-2,8-dioxo-4-(thiophen-2-yl)-1-azaspiro[4.5]deca-3,6,9-trien-1-yl)butanal; then catalyst (16.27 mg, 0.05 mmol), benzoic acid (6.10 mg, 0.05 mmol), 48 h at -20°C, chromatography on silica gel (CH_2Cl_2:acetone, 0-10%) gives aldehyde **11f** as a white solid (92.7 mg, 84% yield); MP: 215-217 ºC; Rf 0.46 (CH_2Cl_2:MeOH, 95:5); λ_{max} (film) / cm^{-1} 2971, 2908, 1720, 1683, 1400, 1298, 1067, 748; ^1H NMR (500 MHz, C_6D_6) δ_H 8.73 (1H, d, J = 1.6 Hz, CHO), 6.79 (1H, dd, J = 2.9 Hz, J = 1.2 Hz, H^{11}), 6.72 (1H, dd, J = 4.9 Hz, J = 2.9 Hz, H^{10}), 6.67 (1H, dd, J = 4.9 Hz, J = 1.2 Hz, H^9), 5.86 (1H, d, J = 10.1 Hz, H^7), 5.09 (1H, dd, J = 10.1 Hz, J = 2.0 Hz, H^6), 4.18 (1H, ddd, J = 13.1 Hz, J = 4.8 Hz, J = 1.9 Hz, H^{1b}), 2.12-2.06 (2H, m, H^{1a}, H^{5a}), 1.95-1.85 (1H, m, H^4), 1.75-1.68 (2H, m, H^3, H^{5b}), 0.90 (1H, app. dq, J = 13.4 Hz, J = 3.1 Hz, H^{2b}), 0.56 (1H, app. dq, J = 13.1 Hz, J = 4.8 Hz, H^{2a}); ^{13}C NMR (125 MHz, C_6D_6) δ_C 198.9, 193.9, 164.3, 157.0, 144.0, 134.1, 133.9, 127.1, 126.6, 125.1, 99.1, 68.1, 49.2, 39.3, 38.1, 36.8, 25.3; HRMS (ES^+) mass cal'd. For $C_{17}H_{14}INO_3S$ 438.9739; found $[(M+H)^+]$ 439.9811. $[\alpha]_D^{25}$ = + 72.40° (C = 1.32 mg/ml), $CHCl_3$ for 95% ee.

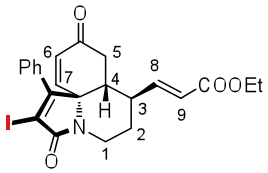
1-bromo-2-iodo-3,9-dioxo-5,6,7,7a,8,9-hexahydro-3*H*-pyrrolo[2,1-j]quinoline-7-carbaldehyde (11h)



Method B: 3-bromo-*N*-(4,4-diethoxybutyl)-*N*-(4-methoxyphenyl)-propiolamide (**8h**) (150 mg, 0.376 mmol), CH_2Cl_2 (20 mL), ICl (753 µL) form 4-(4-bromo-3-iodo-2,8-dioxo-1-azaspiro[4.5]deca-3,6,9-

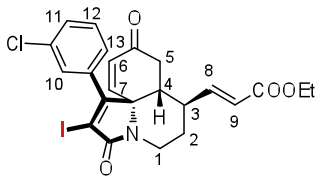
trien-1-yl)butanal; then catalyst (24.48 mg, 0.075 mmol), benzoic acid (9.18 mg, 0.075 mmol), 48 h at 0 °C, chromatography on silica gel (CH_2Cl_2:acetone, 0-5%) gives compound **11h** as a white solid (124.3 mg, 76% yield); Rf 0.44 (CH_2Cl_2:MeOH, 95:5); MP: 226-228 ºC; λ_{max} (film) / cm^{-1} 2925, 2124, 1724, 1679, 1572, 1398, 1299, 1040, 741; ^{1}H NMR (500 MHz, C_6D_6) δ_H 8.69 (1H, s, CHO), 5.85 (1H, d, *J* = 10.5 Hz, H^7), 4.80 (1H, dd, *J* = 10.5 Hz, *J* = 2.0 Hz, H^6), 4.04 (1H, ddd, *J* = 13.3 Hz, *J* = 4.7 Hz, *J* = 1.9 Hz, H^{1b}), 3.03 (1H, dd, *J* = 18.1 Hz, *J* = 5.4 Hz, H^{5b}), 2.31 (1H, dt, *J* = 18.1 Hz, *J* = 1.5 Hz, H^{5a}), 1.90 (1H, app. dt, *J* = 13.3 Hz, *J* = 3.2 Hz, H^{1a}), 1.64 (1H, ddt, *J* = 12.4 Hz, *J* = 5.6 Hz, *J* = 1.9 Hz, H^3), 1.60-1.53 (1H, m, H^4), 0.79 (1H, app. dq, *J* = 13.3 Hz, *J* = 3.1 Hz, H^{2b}), 0.43 (1H, app. dq, *J* = 13.3 Hz, *J* = 4.7 Hz, H^{2a}); ^{13}C NMR (125 MHz, C_6D_6) δ_C 198.7, 193.6, 163.3, 146.9, 143.6, 133.8, 103.6, 68.5, 49.3, 38.9, 38.5, 37.0, 25.0; HRMS (ES^+) mass calc'd. For $C_{13}H_{11}BrINO_3$ 434.8967; found $[(M+H)^+]$ 435.9041. $[\alpha]_D^{25}$ = - 128.40° (C = 1.65 mg/ml), $CHCl_3$ for 90% ee.

Ethyl 2-iodo-3,9-dioxo-1-phenyl-5,6,7,7a,8,9-hexahydro-3*H*-pyrrolo[2,1-j]quinolin-7-yl)acrylate (19)



General procedure **5**, (carbethoxymethylene)triphenylphosphine (358.8 mg, 1.03 mmol) was added to the solution of 2-iodo-3,9-dioxo-1-phenyl-5,6,7,7a,8,9-hexahydro-3*H*-pyrrolo[2,1-j]quinoline-7-carbaldehyde (**4a**) (300 mg, 0.69 mmol) in CH_2Cl_2 (30 mL) at -78 ºC. The reaction mixture was stirred for 12h, slowly warming to room temperature. The reaction was quenched with water and extracted with CH_2Cl_2 (2 x 15 mL), the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Chromatography on silica gel (CH_2Cl_2:acetone, 0-2%) to afford compound **7b** as a white solid (289 mg, 83% yield). Rf 0.54 (CH_2Cl_2:MeOH, 95:5); MP: 234-236 ºC. λ_{max} (film) / cm^{-1} 2979, 2874, 1685, 1654, 1395, 1297, 1187, 1139, 1046, 986, 940, 884, 749, 749, 703; ^{1}H NMR δ_H (500 MHz, C_6D_6) δ_H 7.05-6.93 (3H, m, Ph), 6.92-6.87 (2H, m, Ph), 6.31 (1H, dd, *J* = 15.6, *J* = 10.1 Hz, H^8), 5.81 (1H, d, *J* = 10.1 Hz, H^7), 5.64 (1H, d, *J* = 15.6 Hz, H^9), 5.10 (1H, dd, *J* = 10.1 Hz, *J* = 1.9 Hz, H^6), 4.17 (1H, ddd, *J* = 13.2 Hz, *J* = 5.1 Hz, *J* = 2.0 Hz, H^{1b}), 4.08-3.88 (2H, m, CH_2CH_3), 2.16 (1H, app. dt, *J* = 13.2 Hz, *J* = 3.1 Hz, H^{1a}), 1.93 (1H, dt, *J* = 17.1 Hz, *J* = 1.8 Hz, H^{5a}), 1.75 (1H, ddt, *J* = 17.1 Hz, *J* = 11.5 Hz, *J* = 3.1 Hz, H^3), 1.47 (1H, dd, *J* = 17.1 Hz, *J* = 5.1 Hz, H^{5b}), 1.36-1.23 (1H, m, H^4), 0.94 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 0.87 (2H, app. dq, *J* = 12.9 Hz, *J* = 2.1 Hz, H^{2b}), 0.72 (1H, app. dq, *J* = 12.9 Hz, *J* = 5.1 Hz, H^{2a}); ^{13}C NMR (125 MHz, C_6D_6) δ_C 193.7, 165.2, 164.1, 161.8, 147.9, 143.8, 134.8, 133.5, 129.3, 128.7, 127.9, 124.2, 100.4, 68.8, 60.1, 43.0, 40.5, 37.7, 36.9, 30.5, 13.9; HRMS (ES^+) mass calc'd. For $C_{23}H_{22}INO_4$ 503.0594; found $[M+1]^+$ 504.0675. $[\alpha]_D^{25}$ = + 38.40° (C = 1.65 mg/ml), $CHCl_3$ for 92% ee.

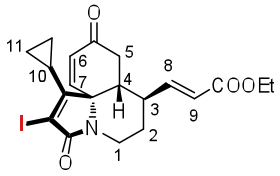
Ethyl 3-(1-(3-chlorophenyl)-2-iodo-3,9-dioxo-5,6,7,7a,8,9-hexahydro-3*H*-pyrrolo[1,2-*j*]quinolin-7-yl)acrylate (104)



General procedure **5**, 1-(3-chlorophenyl)-2-iodo-3,9-dioxo-5,6,7,7a,8,9-hexahydro-3*H*-pyrrolo[1,2-*j*]quinoline-7-carbaldehyde (**11b**) (40 mg, 0.085 mmol) in dry CH_2Cl_2 (12 mL), (carbethoxymethylene)triphenylphosphorane (44.50 mg, 0.127 mmol) was added at –78 °C, chromatography on silica gel (pet.-ether/EtOAc, 6:4) afforded **104** as a white solid. (28 mg, 61% yield). Rf 0.33 (pet.-ether/EtOAc, 6:4);

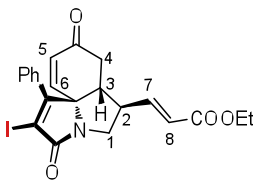
MP: 182-184 ºC; λ_{max} (film) / cm^{-1} 2922, 1683, 1586, 1563, 1471, 1396, 1323, 1297, 1270, 1233, 1182, 1141, 1097, 1032, 988, 947, 864, 782, 751, 719; ^1H NMR (500 MHz, C_6D_6) δ_H 7.11 (1H, s, H^{10}), 6.98 (1H, ddd, J = 7.8 Hz, J = 2.1 Hz, J = 1.4 Hz, H^{11}), 6.78-6.61 (2H, m, H^{12}, H^{13}), 6.38 (1H, dd, J = 15.6 Hz, J = 9.4 Hz, H^8), 5.80 (1H, d, J = 10.1 Hz, H^7), 5.68 (1H, d, J = 15.6 Hz, H^9), 5.05 (1H, dd, J = 10.1 Hz, J = 2.1 Hz, H^6), 4.18 (1H, ddd, J = 13.4 Hz, J = 4.6 Hz, J = 1.8 Hz, H^{1b}), 4.07-3.94 (2H, m, C$\underline{H_2}$CH$_3$), 2.16 (1H, dt, J = 13.1 Hz, J = 3.1 Hz, H^{1a}), 1.94 (1H, app. d, J = 17.2 Hz, H^{5a}), 1.75 (1H, ddt, J = 15.4 Hz, J = 11.7 Hz, J = 3.9 Hz, H^3), 1.46 (1H, dd, J = 17.3 Hz, J = 5.1 Hz, H^{5b}), 1.27-1.21 (1H, m, H^4), 0.99 (3H, t, J = 7.1 Hz, CH$_2$C$\underline{H_3}$) 0.89 (1H, app. dq, J = 13.4 Hz, J = 1.9 Hz, H^{2b}), 0.78 (1H, app. dq, J = 11.7 Hz, J = 5.7 Hz, H^{2a}); ^{13}C NMR (125 MHz, C_6D_6) δ_C 193.6, 165.4, 164.0, 160.2, 147.8, 143.7, 136.7, 135.0, 133.9, 130.3, 129.7, 125.9, 124.5, 101.6, 69.0, 60.4, 53.3, 43.1, 40.7, 37.9, 37.2, 30.7, 14.2; HRMS (ES^+) mass calc'd. For $C_{23}H_{21}ClINO_4$ 537.0204; found [$(M+H)^+$] 538.0276; $[\alpha]_D^{25}$ = + 102.65º (C = 0.82 mg/ml), $CHCl_3$ for 92% ee; HPLC:DAICEL AD Chiralpak, 8:2 Hexane/isopropanol, flow 1 ml/min, retention time: major enantiomer 11.75 min, minor enantiomer 15.84 min.

(*E*)-ethyl 3-(1-cyclopropyl-2-iodo-3,9-dioxo-5,6,7,7a,8,9,-hexahydro-3*H*-pyrrolo[1,2-*j*]quinolin-7-yl)acrylate (105)



General procedure **5**, 1-cyclopropyl-2-iodo-3,9-dioxo-5,6,7,7a,8,9-hexahydro-3*H*-pyrrolo[1,2-*j*]quinoline-7-carbaldehyde (**11e**) (1.00 eq.) in dry CH_2Cl_2 (15 mL), (Carbethoxy-methylene)triphenylphosphorane (176 mg, 0.504 mmol) was added at –78 °C, 14 h, chromatography on silica (pet.-ether/EtOAc, 6:4) to afford **105** as a white solid (92.6 mg, 59% over 3 steps). Rf 0.32 (pet.-ether/EtOAc, 6:4); Mp: 222-226 ºC; λ_{max} (film) / cm^{-1} 2981, 1676, 1600, 1450, 1403, 1369, 1323, 1299, 1269, 1254, 1233, 1183, 1146, 1054, 1029, 1005, 974, 929, 877, 825, 773, 750, 733; ^1H NMR (500 MHz, $CDCl_3$) δ_H 6.54 (1H, dd, J =16.5 Hz, J = 9.5 Hz, H^8), 6.35 (1H, d, J = 10.0 Hz, H^7), 6.24 (1H, dd, J = 10.0 Hz, J = 2.0 Hz, H^6), 5.85 (1H, d, J = 16.5 Hz, H^9), 4.38 (1H, dd, J = 13.5 Hz, J = 4.6 Hz, H^{1b}), 4.17-4.08 (2H, m, C$\underline{H_2}$CH$_3$), 3.24 (1H, dd, J =17.8 Hz, J = 5.5 Hz, H^{5b}), 2.89 (1H, app. dt, J = 13.3 Hz, J = 2.9 Hz, H^{1a}), 2.64 (1H, app. d, J = 17.7 Hz, H^{5a}), 2.44 (1H, ddt, J = 15.3 Hz, J = 11.8 Hz, J = 3.8 Hz, H^3), 2.09-2.01 (1H, m, H^4), 1.70-1.62 (2H, m, H^{2b}, cycloprop.), 1.47-1.32 (2H, m, H^{2a}, cycloprop.), 1.26 (3H, t, J = 7.0 Hz, CH$_2$C$\underline{H_3}$), 1.14-1.05 (2H, m, cycloprop.), 0.96-0.89 (1H, m, cycloprop.); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 196.3, 166.1, 166.0, 161.7, 147.9, 147.4, 133.7, 125.1, 91.9, 70.3, 60.9, 44.1, 42.4, 38.9, 38.0, 31.5, 14.5, 12.6, 9.3, 8.1; HRMS (ES^+) mass calc'd. For $C_{20}H_{22}INO_4$ 467.0594; found [$(M+H)^+$] 468.0669. $[\alpha]_D^{25}$ = + 27.77º (C = 1.77 mg/ml), $CHCl_3$ for 96% ee; HPLC:DAICEL AD Chiralpak, 8:2 Hexane/isopropanol, flow 1 ml/min, retention time: major enantiomer 14.46 min, minor enantiomer 18.57 min.

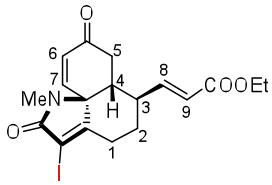
Ethyl 3-(2-iodo-3,8-dioxo-1-phenyl-3,5,6,6a,7,8-hexahydropyrrolo[2,1-i]indol-6-yl)acrylate (106)



Method A: Catalyst (**14**) (0.0024 g, 0.007 mmol) and benzoic acid (0.007 mmol) was added to the solution of 3-(3-iodo-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-3,6,9-trien-1-yl)propanal (**10g**) (0.015 g, 0.036 mmol) in CH_2Cl_2 at -20 ºC. The resulting mixture was stirred for 1.5 h at -20 ºC, quenched

by water and extracted with CH_2Cl_2 (2 x 7 ml). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and dissolved in CH_2Cl_2 (1.5 ml). After cooling to -78 ºC, (carbethoxymethylene)-triphenylphosphine (0.018 g, 0.052 mmol) was added. The reaction mixture was stirred for 12 h, slowly warming to room temperature. The reaction was quenched with water and extracted with CH_2Cl_2 (2 x 7 ml), the combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure. Chromatography on silica gel (CH_2Cl_2:acetone, 95:5) afforded compound **106** as a colourless oil (0. 0.017g, 97% yield). Rf 0.40 (CH2Cl2:acetone, 95:5); λ_{max} (film) / cm^{-1} 3675, 2972, 1709, 1262, 1066, 762; ^{1}H NMR δ_H (500 MHz, C_6D_6) δ_H 6.99-6.93 (3H, m, Ph), 6.91-6.85 (2H, m, Ph), 6.41 (1H, dd, *J* = 15.5, *J* = 9.1 Hz, H^7), 5.69 (1H, d, *J* = 10.1 Hz, H^6), 5.52 (1H, dd, *J* = 10.1 Hz, *J* = 2.0 Hz, H^5), 5.46 (1H, d, *J* = 15.5 Hz, H^8), 4.05-3.96 (2H, m, CH_2CH_3), 4.17 (1H, dd, *J* = 11.6 Hz, *J* = 8.8 Hz, *J* = 2.0 Hz, H^{1b}), 2.16 (1H, dd, *J* = 11.6 Hz, *J* = 8.8 Hz, H^{1a}), 2.43 (1H, ddt, *J* = 17.8 Hz, *J* = 8.8 Hz, *J* = 2.0 Hz, H^2), 1.87 (1H, dt, *J* = 17.6 Hz, *J* = 1.7 Hz, H^{4a}), 1.47 (1H, dd, *J* = 17.6 Hz, *J* = 5.5 Hz, H^{4b}), 1.46-1.31 (1H, m, H^3), 0.99 (3H, t, *J* = 7.1 Hz, CH_2CH_3); ^{13}C NMR (125 MHz, C_6D_6) δ_C193.1, 170.3, 165.1, 164.4, 144.8, 144.5, 133.7, 131.7, 129.6, 124.3, 98.5, 75.9, 60.4, 50.3, 47.4, 45.5, 35.3, 14.2; HRMS (ES^+) mass calc'd. For $C_{22}H_{20}INO_4$ 489.0437; found $[M+1]^+$ 490.0485. $[\alpha]_D^{25}$ = - 9.0º (C = 1.33mg/ml), $CHCl_3$ for 25% ee; HPLC:DAICEL AD Chiralpak, 9:1 Hexane/isopropanol, flow 1 ml/min, retention time: major enantiomer 32.55 min, minor enantiomer 47.68 min.

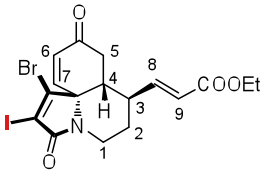
Ethyl 3-(3-iodo-1-methyl-2,8-dioxo-1,2,4,5,6,6a,7,8-octahydrobenzo[*h*]indol-6-yl)acrylate (107)



Method A: 4-(3-iodo-1-methyl-2,8-dioxo-1-azaspiro[4.5]deca-3,6,9-trien-1 yl)butanal (**101**) (20 mg, 0.058 mmol), catalyst **14** (4 mg, 0.012 mmol) and benzoic acid (1.4g, 0.012 mmol) in CH_2Cl_2 at 0 ºC. The resulting mixture was stirred for 12 h at 0 ºC, quenched with water and extracted with CH_2Cl_2 (2 x 7 ml). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and taken up in CH_2Cl_2 (2ml). After cooling to -78 ºC, (carbethoxymethylene)triphenylphosphine (30 mg, 0.086 mmol) was added. The solution was stirred for 4 h, slowly warming to room temperature. The reaction was quenched with water and extracted with CH_2Cl_2 (2 x 10 ml), the combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure. Chromatography on silica gel (CH_2Cl_2:acetone, 9:1) afforded compound **107** as a white solid (20 mg, 79% yield). MP: 216-218 ºC; Rf 0.60 (CH_2Cl_2:acetone, 9:1); λ_{max} (film) / cm^{-1} 3674, 2923, 2300, 1681, 1367, 1231, 1021, 875, 757; ^{1}H NMR (500 MHz, C_6D_6) δH 6.38 (1H, dd, *J* = 15.6 Hz, *J* = 10.0 Hz, H^8), 5.83 (1H, d, *J* = 10.2 Hz, H^7), 5.71 (1H, d, *J* = 15.6 Hz, H^9), 4.69 (1H, dd, *J* = 10.2 Hz, *J* = 2.0 Hz, H^6), 4.20-3.92 (2H, m, CH_2CH_3), 2.50 (3H, s, NCH_3), 2.37 (1H, ddd, *J* = 13.4 Hz, *J* = 3.9 Hz, *J* = 2.7 Hz, H^{1b}), 2.21 (1H, dt, *J* = 17.7 Hz, *J* = 1.1 Hz, H^{5a}), 2.04 (1H, dd, *J* = 17.7 Hz, *J* = 5.2 Hz, H^{5b}), 1.59 (1H, ddt, *J* = 15.6 Hz, *J* = 11.8 Hz, *J* = 4.0 Hz, H^3), 1.40 (1H, app. dt, *J* = 13.6 Hz, *J* = 4.7 Hz, H^{1a}), 1.14-1.09 (1H, m, H^4), 1.02 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 0.77-0.69 (1H, app. dq, *J* = 13.2 Hz, *J* = 1.8 Hz, H^{2b}), 0.64 (1H, app. dq, *J* = 13.3 Hz, *J* = 3.9 Hz, H^{2a}); ^{13}C NMR (125 MHz, C_6D_6) δ_C 194.4, 166.5, 165.5, 164.0, 148.3, 141.3, 133.0, 124.4, 91.8, 66.8, 60.4, 45.4, 42.9, 38.4, 31.9, 28.3, 27.7, 14.2. HRMS (ES^+) mass calc'd. For $C_{18}H_{20}INO_4$ 441.0437 found $[(M+H)^+]$ 442.0501;

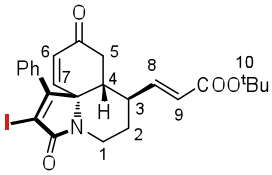
$[\alpha]_D^{25}$ = - 15.00º (C = 4 mg/ml), $CHCl_3$ for 94% ee; HPLC:DAICEL AD Chiralpak, 8:2 Hexane/isopropanol, flow 1 ml/min, retention time: major enantiomer 21.43 min, minor enantiomer 25.55 min.

Ethyl 3-(1-bromo-2-iodo-3,9-dioxo-5,6,7,7a,8,9-hexahydro-3*H*-pyrrolo[2,1-j]quinolin-7-yl)acrylate (23)



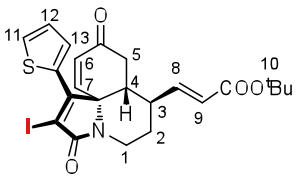
General procedure **5**, (carbethoxymethylene)triphenylphosphine (240.38 mg, 0.69 mmol) was added to a solution of 1-bromo-2-iodo-3,9-dioxo-5,6,7,7a,8,9-hexahydro-3*H*-pyrrolo[2,1-j]quinoline-7-carbaldehyde (**11h**) (200 mg, 0.46 mmol) in CH_2Cl_2 (15 mL), at -78 ºC, 16 h, chromatography on silica gel (CH_2Cl_2:acetone, 9:1) to afford compound **23** as a white solid (205 mg, 90% yield). Rf 0.54 (CH_2Cl_2:MeOH, 95:5); MP: 218-220 ºC; λ_{max} (film) / cm^{-1} 2979, 2292, 1704, 1684, 1394, 1272, 1186, 1146, 1051, 851, 742; ^1H NMR (500 MHz, C_6D_6) δ_H 6.30 (1H, ddd, *J* = 15.6, *J* = 10.0 Hz, *J* = 3.9 Hz, H^8), 5.87 (1H, d, *J* = 10.0 Hz, H^7), 5.68 (1H, dd, *J* = 15.6 Hz, *J* = 2.5 Hz, H^9), 4.88 (1H, dd, *J* = 10.0 Hz, *J* = 2.5 Hz, H^6), 4.11-4.00 (3H, m, H^{1a}, C<u>H_2</u>CH_3), 2.86 (1H, dd, *J* = 17.7 Hz, *J* = 7.1 Hz, H^{5b}), 2.25 (1H, app. d, *J* = 17.7 Hz, H^{5a}), 1.99 (1H, app. dt, *J* = 13.2 Hz, *J* = 3.0 Hz, H^{1a}), 1.66 (1H, ddt, *J* = 15.6 Hz, *J* = 11.8 Hz, *J* = 4.7 Hz, H^3), 1.01 (3H, t, *J* = 7.1 Hz, CH_2C<u>H_3</u>), 0.82-0.73 (2H, m, H^{2b}, H^4), 0.62 (1H, app. dq, *J* = 13.2 Hz, *J* = 4.7 Hz, H^{2a}); ^{13}C NMR (125 MHz, C_6D_6) δ_C 193.9, 165.4, 163.4, 147.9, 147.1, 143.6, 133.8, 124.5, 103.8, 69.2, 60.4, 42.8, 41.0, 38.2, 37.4, 30.6, 14.2; HRMS (ES^+) mass calc'd. For $C_{17}H_{17}BrINO_4$ 504.9386; found [$(M+NH_4)^+$] 522.9712. $[\alpha]_D^{25}$ = + 83.4º (C = 1.95 mg/ml), $CHCl_3$ for 90% ee.

***tert*-butyl 3-(2-iodo-3,9-dioxo-1-phenyl-5,6,7,7a,8,9-hexahydro-3*H*-pyrrolo[2,1-*j*]quinolin-7-yl)acrylate (108)**



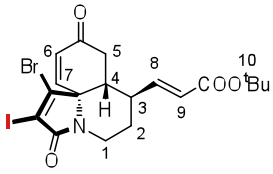
General procedure **5**, (tert-Butoxycarbonylmethylene)triphenylphosphorane (130 mg, 0.34 mmol) was added to a solution of 2-iodo-3,9-dioxo-1-phenyl-5,6,7,7a,8,9-hexahydro-3*H*-pyrrolo[2,1-j]quinoline-7-carbaldehyde (**11a**) (100 mg, 0.23 mmol) in CH_2Cl_2 (10 mL), at -78 ºC, 12 h, slowly warming to room temperature. Chromatography on silica gel (CH_2Cl_2:acetone, 1-2%) to afford compound **108** as a white solid (98 mg, 80% yield). Rf 0.59 (CH_2Cl_2:MeOH, 95:5); MP: 224-226 ºC; λ_{max} (film) / cm^{-1} 3053, 2927, 2923, 1679, 1393, 1326, 1153, 1136, 984, 847, 733, 701; ^1H NMR (500 MHz, C_6D_6) δ_H 7.13-6.98 (3H, m, <u>Ph</u>), 6.95-6.91 (2H, m, <u>Ph</u>), 6.41 (1H, dd, *J* = 15.5, *J* = 10.0, H^8), 5.87 (1H, d, *J* = 10.0 Hz, H^7), 5.71 (1H, d, *J* = 15.5 Hz, H^9), 5.14 (1H, dd, *J* = 10.0 Hz, *J* = 1.9 Hz, H^6), 4.23 (1H, ddd, *J* = 14.2 Hz, *J* = 4.6 Hz, *J* = 1.7 Hz, H^{1b}), 2.21 (1H, app. dt, *J* = 13.1 Hz, *J* = 2.9 Hz, H^{1a}), 2.02 (1H, app. d, *J* = 16.8 Hz, H^{5a}), 1.83 (1H, ddt, *J* = 15.2 Hz, *J* = 11.9 Hz, *J* = 3.9 Hz, H^3), 1.51 (1H, dd, *J* = 16.8 Hz, *J* = 5.0 Hz, H^{5b}), 1.44 (9H, s, H^{10}), 1.42-36 (1H, m, H^4), 0.95 (1H, app. dq, *J* = 12.6 Hz, *J* = 1.9 Hz, H^{2b}), 0.80 (1H, app. dq, *J* = 12.6 Hz, *J* = 5.0 Hz, H^{2a}); ^{13}C NMR (125 MHz, C_6D_6) δ_C 193.7, 164.6, 164.0, 161.7, 146.9, 143.8, 134.8, 133.5, 129.3, 128.7, 128.0, 125.7, 100.4, 79.9, 68.8, 42.9, 40.3, 37.7, 36.9, 30.6, 27.8; HRMS (ES^+) mass calc'd. For $C_{25}H_{26}INO_4$ 531.0907; found [$(M+NH_4)^+$] 549.1238. $[\alpha]_D^{25}$ = + 46.1º (C = 4.1 x10^{-3} g/mL), $CHCl_3$ for 92% ee;

***tert*-butyl (2*E*)-3-(2-iodo-3,9-dioxo-1-phenyl-5,6,7,7a,8,9-hexahydro-3*H*-pyrrolo[2,1-*j*]quinolin-7-yl)acrylate (109)**



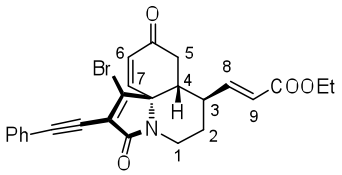
General procedure **5**, (tert-Butoxycarbonylmethylene) triphenylphosphorane (59.52 mg, 0.170 mmol) was added to a solution of 2-iodo-3,9-dioxo-1-(thiophen-2-yl)-5,6,7,7a,8,9-hexahydro-3*H*-pyrrolo[2,1-j]quinoline-7-carbaldehyde (**11f**) (50 mg, 0.114 mmol) in CH_2Cl_2 (5 mL), at -78 ºC, 13 h, chromatography on silica gel (CH_2Cl_2:acetone, 0-2%) to afford compound **109** as a white solid (42 mg, 69% yield). Rf 0.61 (CH_2Cl_2:MeOH, 95:5); MP: 220-222 ºC; λ_{max} (film) / cm^{-1} 2978, 1701, 1393, 1298, 1153, 989, 846, 749; ^{1}H NMR (500 MHz, C_6D_6) δ_H 6.90-6.86 (1H, m, H^{11}), 6.74-6.71 (2H, m, H^{12}, H^{13}),6.34 (1H, dd, *J* = 2.5 Hz, *J* = 1.7 Hz, H^8),5.85 (1H, d, *J* = 10.1, H^7), 5.68 (1H, d, *J* = 15.5, H^9), 5.1 (1H, dd, *J* = 13.1 Hz, *J* = 2.0 Hz, H^6), 4.20 (1H, ddd, *J* = 13.1 Hz, *J* = 4.5 Hz, *J* = 2.0 Hz, H^{1b}), 2.15 (1H, app. dt, *J* = 13.1 Hz, *J* = 2.0 Hz, H^{1a}), 2.00 (1H, dt, *J* = 17.2 Hz, *J* = 0.9 Hz, H^{5a}), 1.78 (1H, ddt, *J* = 15.5 Hz, *J* = 12.6 Hz, *J* = 4.5 Hz, H^3), 1.48 (1H, dd, *J* = 17.2 Hz, *J* = 4.5 Hz, H^{5b}), 1.42 (9H, s, H^{10}), 1.22-1.13 (1H, m, H^4), 0.90 (1H, app. dq, *J* = 13.2 Hz, *J* = 2.0 Hz, H^{2b}), 0.75 (1H, app. dq, *J* = 12.6 Hz, *J* = 5.0 Hz, H^{2a}); ^{13}C NMR (125 MHz, C_6D_6) δ_C 194.1, 164.4, 164.3, 157.4, 147.2, 144,0, 134.4, 133.4, 126.9, 126.9, 125.7, 125.0, 100.3, 80.2, 68.7, 43.5, 40.6, 37.6, 37.2, 30.7, 28.0; HRMS (ES^+) mass calc'd. For $C_{23}H_{24}INO_4S$ 537.0471; found [$(M+H)^+$] 538.0543. $[\alpha]_D^{25}$ = - 59.5º (C = 2.2 x 10^{-3} g/mL), $CHCl_3$ for 95% ee; HPLC:DAICEL AD Chiralpak, 8:2 Hexane/isopropanol, flow 1 mL/min, retention time: major 15.39 min, minor enantiomer 12.15 min.

***tert*-butyl 3-(1-bromo-2-iodo-3,9-dioxo-5,6,7,7a,8,9-hexahydro-3*H*-pyrrolo[2,1-*j*]quinolin-7-yl)acrylate (110)**



General procedure **5**, (tert-Butoxycarbonylmethylene) triphenylphosphorane (64.7 mg, 0.17 mmol) was added to a solution of 1-bromo-2-iodo-3,9-dioxo-5,6,7,7a,8,9-hexahydro-3*H*-pyrrolo[2,1-j]quinoline-7-carbaldehyde **11h** (50 mg in CH_2Cl_2 (7 mL), at -78 ºC, 15 h, chromatography on silica gel (CH_2Cl_2:acetone, 0-2%) to afford compound **110** as a white solid (47.5 mg, 77% yield). Rf 0.57 (CH_2Cl_2:MeOH, 95:5); MP: 222-224; λ_{max} (film) / cm^{-1} 3330, 2973, 2883, 1698, 1409, 1380, 1327, 1161, 1087, 1046, 880,739; ^{1}H NMR (500 MHz, C_6D_6) δ_H 6.26 (1H, dd, *J* = 15.5, *J* = 10.1 Hz, H^8), 5.81 (1H, d, *J* = 10.1 Hz, H^7), 5.64 (1H, d, *J* = 15.5 Hz, H^9), 4.83 (1H, dd, *J* = 10.1 Hz, *J* = 2.0 Hz, H^6), 4.02 (1H, ddd, *J* = 13.2 Hz, *J* = 4.6 Hz, *J* = 1.8 Hz, H^{1b}), 2.80 (1H, dd, *J* = 17.7 Hz, *J* = 5.6 Hz, H^{5b}), 2.23 (1H, app. d, *J* = 17.7 Hz, H^{5a}), 1.94 (1H, app. dt, *J* = 13.2 Hz, *J* = 3.4 Hz, H^{1a}), 1.64 (1H, ddt, *J* = 15.5 Hz, *J* = 11.4 Hz, *J* = 3.4 Hz, H^3), 1.39 (9H, s, H^{10}), 0.79-0.69 (2H, m, H^{2b}, H^4), 0.60 (1H, app. dq, *J* = 11.4 Hz, *J* = 3.4 Hz, H^{2a}); ^{13}C NMR (125 MHz, C_6D_6) δ_C 193.9, 164.9, 163.4, 161.4, 147.1, 143.7, 133.7, 126.8, 103.9, 80.3, 69.2, 42.8, 40.9, 38.3, 37.4, 30.7, 28.1; For $C_{19}H_{21}BrINO_4$ 532.9699; found [$(M+NH_4)^+$] 551.0033. $[\alpha]_D^{25}$ = + 75.7º (C = 2.8 x10^{-3} g/mL), $CHCl_3$ for 90% ee; HPLC:DAICEL AD Chiralpak, 8:2 Hexane/isopropanol, flow 1 mL/min, retention time: major 12.74 min, minor enantiomer 15.95 min.

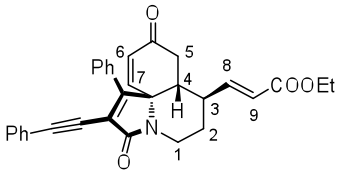
Ethyl 3-(1-bromo-3,9-dioxo-2-(phenylethynyl)-5,6,7,7a,8,9-hexahydro-3*H*-pyrrolo[2,1-j]quinolin-7-yl)acrylate (24)



Et3N/Benzene (5:1) (9.2 ml) was added to a mixture of compound **11h** (130 mg, 0.25 mmol), CuI (5 mg, 0.026 mmol) and $PdCl_2(PPh_3)_2$ (18.2 mg, 0.026 mmol), followed by the addition of ethynylbenzene (31.6 mg, 0.31 mmol). The reaction was stirred at room temperature for 24h. After the reaction was completed, it was filtrated over a pad of celite, extracted with CH_2Cl_2 and organic layer dried over $MgSO_4$. The solvent was evaporated under reduced pressure and chromatography on silica gel (CH_2Cl_2:acetone, 0-4%) gave compound **24** as a white solid (105 mg, 85% yield). Rf 0.70 (CH_2Cl_2:MeOH, 95:5) MP:198-200 ºC. λ_{max} (film) / cm^{-1} 2348, 1695, 1490, 1400, 1296, 1188, 1071, 996, 759; ^1H NMR (500 MHz, C_6D_6) δ_H 7.57-7.54 (2H, m, Ph), 7.03-6.90 (3H, m, Ph), 6.37 (1H, dd, J = 15.6, J = 10.1 Hz, H^8), 5.94 (1H, d, J = 10.1 Hz, H^7), 5.72 (1H, d, J = 15.6 Hz, H^9), 5.04 (1H, dd, J = 10.1 Hz, J = 2.0 Hz, H^6), 4.17 (1H, ddd, J = 13.2 Hz, J = 4.5 Hz, J = 1.6 Hz, H^{1b}), 4.13-4.00 (2H, m, CH_2CH_3), 3.00 (1H, dd, J = 17.1 Hz, J = 5.6 Hz, H^{5b}), 2.33 (1H, app. d, J = 17.8 Hz, H^{5a}), 2.08 (1H, app. dt, J = 13.2 Hz, J = 3.0 Hz, H^{1b}), 1.74 (1H, ddt, J = 15.2 Hz, J = 12.6 Hz, J = 4.0 Hz, H^3), 1.03 (3H, t, J = 7.1 Hz, CH_2CH_3), 0.98-0.93 (1H, m, H^4), 0.85 (2H, app. dq, J = 13.5 Hz, J = 2.1 Hz, H^{2a}), 0.71 (1H, app. dq, J = 12.6 Hz, J = 5.1 Hz, H^{2a}); ^{13}C NMR (125 MHz, C_6D_6) δ_C 194.0, 165.4, 162.6, 148.1, 144.0, 142.1, 134.0, 132.4, 129.6, 128.7, 126,0, 124.5, 122.2, 101.7, 80.6, 65.9, 60.4, 43.2, 41.3, 38.2, 36.8, 30.6, 14.2; HRMS (ES^+) mass calc'd. For $C_{25}H_{22}BrINO_4$ 479.0732; found $[(M+NH_4)^+]$ 497.1068. $[\alpha]_D^{25}$ = + 131.1º (C = 0.85 mg/ml), $CHCl_3$ for 90% ee.

See, Camerel, F.; Ulrich, G.; Retailleau, P.; Ziessel, R., Ethynyl-boron subphthalocyanines displaying efficient cascade energy transfer and large Stokes shifts. *Angew Chem Int Ed Engl*, **2008,** 47, (46), 8876-80.

***tert*-butyl 3-(1-bromo-2-iodo-3,9-dioxo-5,6,7,7a,8,9-hexahydro-3*H*-pyrrolo[2,1-*j*]quinolin-7-yl)acrylate (25)**

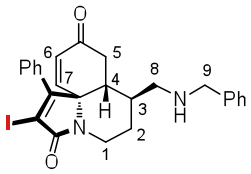


In air, $Pd(OAc)_2$ (0.77 mg, 0.004 mmol, 10%), PPh_3 (2.09 mg, 0.008 mmol, 20%), phenyl boronic acid (7.67mg, 0.063 mmol), compound **24** (20 mg, 0.042 mmol) and K_2CO_3 (11.6 mg, 0.084 mmol) were placed in a vial equipped with a stir bar. The vial was sealed with a septum screw-cap, and then it was evacuated and filled with argon (three cycles). Benzene/H_2O (5/1, 2.4 mL) was added, and the resulting heterogeneous reaction mixture was stirred vigorously for 15 hours at 60 ºC. The reaction mixture was then poured into Et_2O (30 mL), filtered through a short pad of celite, concentrated under reduced pressure, and purified by flash chromatography on silica gel (CH_2Cl_2:acetone, 0-5%) to afford compound **25** as a white solid (18.6 mg, 93%). Rf 0.66 (CH_2Cl_2:MeOH, 95:5); Mp: 174-176 ºC; λ_{max} (film) / cm^{-1} 2979, 2903, 1705, 1685, 1572, 1406, 1299, 1239, 759; ^1H NMR (500 MHz, C_6D_6) δ_H 7.37 (2H, dd, J = 8.0 Hz, J = 1.5 Hz, Ph), 7.31 (2H, dd, J = 7.4 Hz, J = 2.0 Hz, Ph), 7.15-6.99 (6H, m, Ph), 6.42 (1H, dd, J = 15.6 Hz, J = 9.5 Hz, H^8), 5.99 (1H, d, J = 10.1 Hz, H^7), 5.71 (1H, d, J = 15.6 Hz, H^9), 5.40 (1H, dd, J = 10.1 Hz, J = 2.0 Hz, H^6), 4.32 (1H, ddd, J = 13.2 Hz, J = 4.5 Hz, J = 1.6 Hz, H^{1b}), 4.13-4.00 (2H, m, CH_2CH_3), 2.22 (1H, app. dt, J = 13.1 Hz, J = 3.1 Hz, H^{1a}), 2.02 (1H, dt, J = 17.8 Hz, J = 0.9 Hz, H^{5a}), 1.87 (1H,

ddt, J = 17.2 Hz, J = 11.7 Hz, J = 3.9 Hz, H^3), 1.69 (1H, dd, J = 17.2 Hz, J = 5.0 Hz, H^{5b}), 1.47-1.23 (2H, m, H^{2b}, H^4), 1.00 (3H, t, J = 7.1 Hz, $CH_2C\underline{H_3}$), 0.87 (1H, app. dq, J = 12.7 Hz, J = 4.7 Hz, H^{2a}); ^{13}C NMR (125 MHz, C_6D_6) δ_C 194.2, 165.4, 164.6, 159.4, 148.1, 144.7, 134.1, 134,0, 132.4, 129.7, 129.0, 128.7, 128.5, 124.4, 122.7, 122.0, 98.7, 81.8, 65.9, 60.3, 43.9, 40.9, 38.0, 36.6, 30.7, 14.1; HRMS (ES^+) mass calc'd. For $C_{31}H_{27}NO_4$ 477.1940; found [$(M+H)^+$] 478.2012. $[\alpha]_D^{25}$ = + 46.6° (C = 0.6 mg/ml), $CHCl_3$ for 90% ee.

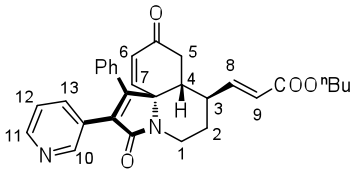
See, Lunazzi, L.; Mancinelli, M.; Mazzanti, A., Arylbiphenylene Atropisomers: Structure, Conformation, Stereodynamics, and Absolute Configuration. *The Journal of Organic Chemistry* **2008,** 73, (6), 2198-2205.

7-((benzylamino)methyl)-2-iodo-1-phenyl-6,7,7a,8-tetrahydro-3*H*-pyrrolo[2,1-j]quinoline-3,9(5H)-dione (18)



Benzylamine (12.4 mg, 0.116 mmol) was added to the solution of 2-iodo-3,9-dioxo-1-phenyl-5,6,7,7a,8,9-hexahydro-3*H*-pyrrolo[2,1-j]quinoline-7-carbaldehyde (**11a**) (50 mg, 0.116 mmol) in 1,2-dichloroethane (5 mL) and it was stirred for 1h. The reaction mixture was then treated with sodium triacetoxyborohydride (31.9 mg, 0.150 mmol) at 0ºC. The mixture was stirred at rt under N_2 atmosphere for 16 h. The reaction mixture was quenched by adding aqueous saturated $NaHCO_3$ solution, and the product was extracted with CH_2Cl_2 (3 x 10 mL). The organic layer was dried over $MgSO_4$, and the solvent was concentrated under reduced pressure. Flash chromatography on silica gel (CH_2Cl_2:acetone, 0-10%) afforded compound **18** as a white solid (53 mg, 87% yield). Rf 0.24 (CH_2Cl_2:MeOH, 95:5); MP: 154-156 ºC. λ_{max} (film) / cm^{-1} 3060, 2921, 2342, 1682, 1452, 1400, 1210, 1028, 932, 805, 744, 702; ^{1}H NMR (500 MHz, CH_2Cl_2) δ_H 7.59-7.35 (3H, m, Ph), 7.33-7.19 (7H, m, Ph), 6.38 (1H, dd, J = 10.1, J = 2.0 Hz, H^6), 6.27 (1H, d, J = 10.1 Hz, H^7), 4.39 (1H, ddd, J = 13.4 Hz, J = 4.5 Hz, J = 2.0 Hz, H^{1b}), 3.75 (2H, d, J = 13.3 Hz, H^{9a}), 3.65 (2H, d, J = 13.3 Hz, H^{9b}), 2.92 (1H, app. dt, J = 13.2 Hz, J = 2.9 Hz, H^{1a}), 2.70 (1H, dd, J = 12.5 Hz, J = 3.1 Hz, H^{8b}), 2.47 (1H, dd, J = 12.4 Hz, J = 6.5 Hz, H^{8a}), 2.30-2.21 (2H, m, H^4, H^{5a}), 1.88 (1H, app. dq, J = 13.3 Hz, J = 2.2 Hz, H^{2b}), 1.78-1.71 (2H, m, H^3, H^{5b}), 1.35 (1H, app. dq, J = 12.8 Hz, J = 4.2 Hz, H^{2a}); ^{13}C NMR (125 MHz, CH_2Cl_2) δ_C 196.1, 164.8, 162.7, 145.0, 135.0, 133.9, 129.7, 129.1, 128.5, 128.4, 127.9, 127.2, 99.6, 70.20, 63.5, 50.9, 43.1, 41.7, 38.5, 37.5, 36.7, 30.0; HRMS (ES^+) mass calc'd. For $C_{26}H_{25}IN_2O_2$ 524.0961; found [$(M+H)^+$] 525.1027. $[\alpha]_D^{25}$ = + 86.32° (C = 1.42 mg/ml), $CHCl_3$ for 92% ee.

Butyl 3,9-dioxo-1-phenyl-2-(pyridin-3-yl)-5,6,7,7a,8,9-hexahydro-3*H*-pyrrolo[2,1-j]quinolin-7-yl)acrylate (21)

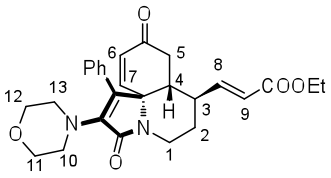


An-oven dried tube was charged with $Pd_2(dba)_3$ (3.6 mg, 0.004 mmol), X-Fos (0.016 mmol), 3-pyridine boronic acid (7.3 mg, 0.06 mmol), ethyl 2-iodo-3,9-dioxo-1-phenyl-5,6,7,7a,8,9-hexahydro-3*H*-pyrrolo[2,1-j]quinolin-7-yl)acrylate (**19**) (20 mg, 0.04 mmol) and powdered anhydrous K_3PO_4 (16.9 mg, 0.08 mmol). The tube was capped with a rubber septum and then evacuated and backfilled with argon (this sequence was carried out three times). *n*-butanol (1 mL) was added via syringe, through the septum. The septum was then replaced with a Teflon screwcap and the

vial tube was sealed. The reaction mixture was heated to 100 ºC overnight. After completion the reaction mixture was allowed to cool to room temperature. The reaction solution was then filtered through a short pad of celite (eluting with DCM) and the eluent was concentrated under reduced pressure. The crude material obtained was purified *via* flash chromatography on silica gel (CH_2Cl_2:acetone, 5-30%) to afford compound **21** as a white solid (14 mg, 77% yield) (^{t}-Butyl esther isolated). Rf 0.15 (CH_2Cl_2:MeOH, 95:5); MP: 170-172 ºC. λ_{max} (film) / cm^{-1} 2958, 2871, 2343, 2144, 1682, 1407, 1300, 1233, 1185, 1066, 943, 818, 760, 699; ^{1}H NMR δ_H (500 MHz, CD_2Cl_2) δ_H 8.49 (1H, d, J = 1.5 Hz, H^{10}), 8.42 (1H, dd, J = 4.8 Hz, J = 1.5 Hz, H^{13}), 7.81 (1H, dd, J = 8.1 Hz, J = 1.5 Hz, H^{11}), 7.44-7.33 (3H, m, Ph), 7.23 (1H, dd, J =8.1 Hz, J = 4.8 Hz, H^{12}), 7.21-7.15 (2H, m, Ph), 6.54-6.49 (2H, m, H^7, H^8), 6.36 (1H, d, J = 10.1 Hz, H^9), 5.81 (1H, dd, J = 15.6 Hz, J = 0.5 Hz, H^6), 4.49 (1H, ddd, J = 13.5 Hz, J = 4.7 Hz, J = 1.9 Hz, H^{1b}), 4.07 (2H, t, J = 7.1 Hz, J = 0.99 Hz, $OCH_2CH_2CH_2CH_3$), 2.97 (1H, app. dt, J = 13.1 Hz, J = 2.9 Hz, H^{1a}), 2.48 (1H, ddd, J = 21.2 Hz, J = 11.8 Hz, J = 3.8 Hz, H^3), 2.24-2.06 (2H, m, H^{5b}, H^4), 1.76 (1H, app. dq, J = 13.5 Hz, J = 2.6 Hz, H^{2b}), 1.72 (1H, dd, J = 17.7 Hz, J = 5.6 Hz, H^{5a}), 1.60 (2H, dt, J = 14.4 Hz, J = 7.4 Hz, $OCH_2CH_2CH_2CH_3$), 1.52 (1H, app. dq, J = 13.5 Hz, J = 5.7 Hz, H^{2a}), 1.40-1.32 (2H, m, $OCH_2CH_2CH_2CH_3$), 0.91 (3H, t, J = 7.4 Hz, $OCH_2CH_2CH_2CH_3$); ^{13}C NMR (125 MHz, CD_2Cl_2) δ_C 195.9, 166.9, 166.2, 155.9, 149.9, 148.8, 148.2, 145.9, 137.9, 134.8, 133.7, 131.9, 130.0, 129.8, 129.0, 127.7, 124.9, 123.6, 66.6, 64.9, 44.0, 42.0, 38.5, 37.4, 31.8, 31.2, 19.7, 14.0; HRMS (ES^+) mass calc'd. For $C_{30}H_{30}N_2O_4$ 482.2206; found [$(M+H)^+$] 483.2267. $[\alpha]_D^{25}$ = + 29.3^o (C = 0.45 mg/ml), $CHCl_3$ for 92% ee.

See, Billingsley, K.; Buchwald, S. L., Highly efficient monophosphine-based catalyst for the palladium-catalyzed suzuki-miyaura reaction of heteroaryl halides and heteroaryl boronic acids and esters. *J Am Chem Soc* **2007,** 129, (11), 3358-66.

Ethyl 2-morpholino-3,9-dioxo-1-phenyl-5,6,7,7a,8,9-hexahydro-3*H*-pyrrolo[2,1-j]quinolin-7-yl)acrylate (22)



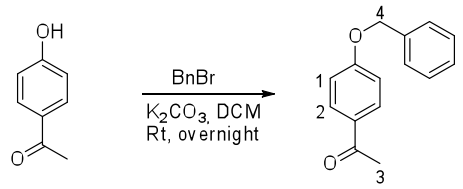
An-oven dried tube was charged with $Pd_2(dba)_3$ (3.6 mg, 0.004 mmol), BINAP (7.4 mg, 0.012 mmol), ethyl 2-iodo-3,9-dioxo-1-phenyl-5,6,7,7a,8,9-hexahydro-3*H*-pyrrolo[2,1-j]quinolin-7-yl)acrylate (**19**) (20 mg, 0.04 mmol) and powdered anhydrous $CsCO_3$ (65.2 mg, 0.2 mmol). The tube was capped with a rubber septum and then evacuated and backfilled with argon (this sequence was carried out three times). Toluene (1 mL) was added via syringe through the septum and morpholine (5.2 mg, 0.06 mmol) in the same manner. The septum was then replaced with a Teflon screwcap and the vial tube was sealed. The reaction mixture was heated to 120 ºC overnight. When the reaction was completed, the reaction mixture was allowed to cool to room temperature. The reaction solution was then filtered through a short pad of celite (eluting with DCM) and the eluent was concentrated under reduced pressure. The crude material obtained was purified via flash chromatography on silica gel (CH_2Cl_2:acetone, 5-15%) to afford compound **22** as a white solid (16 mg, 86% yield). Rf 0.57 (CH_2Cl_2:MeOH, 95:5); MP: 178-180 ºC. λ_{max} (film) / cm^{-1} 2926, 2343, 2144, 1681, 1629, 1382, 1269, 1163, 1114, 762, 701; ^{1}H NMR δ_H (500 MHz, C_6D_6) δ_H 7.03-6.91 (5H, m, Ph), 6.48 (1H, dd, J = 15.6, J = 9.4 Hz, H^8), 5.93 (1H, d, J = 10.1 Hz, H^7), 5.72 (1H, d, J = 15.6 Hz, H^9), 5.36 (1H, dd, J = 10.1 Hz, J = 1.9 Hz, H^6), 4.29 (1H, ddd, J = 13.4 Hz, J = 4.6 Hz, J = 1.6 Hz, H^{1b}), 4.08-3.88 (2H, m, CH_2CH_3),

3.62-3.53 (2H, m, H^{10a}, H^{13a}), 3.52-3.44 (4H, m, H^{11}, H^{12}), 2.85-2.78 (2H, m, H^{10b}, H^{13b}), 2.23 (1H, ddd, J = 13.1 Hz, J = 5.3 Hz, J = 2.9 Hz, H^{1b}), 2.06 (1H, app. d, J = 17.1 Hz, H^{5a}), 1.94-1.85 (1H, m, H^{3}), 1.60-1.47 (2H, m, H^{5b}), 1.36-1.29 (1H, m, H^{4}), 0.97 (3H, t, J = 7.1 Hz, $CH_2C\underline{H_3}$), 0.94-0.89 (1H, m, H^{2b}), 0.83 (1H, app. dq, J = 12.9 Hz, J = 4.7 Hz, H^{2a}); ^{13}C NMR (125 MHz, C_6D_6) δ_C 194.6, 165.5, 164.4, 148.8, 147.0, 139.6, 135.2, 132.6, 130.6, 130.5, 128.5, 127.3, 124.3, 67.0, 63.0, 60.3, 49.7, 44.0, 41.7, 38.0, 36.3, 31.0, 14.2; HRMS (ES^+) mass calc'd. For $C_{27}H_{30}N_2O_5$ 462.2155; found [$(M+H)^+$] 463.2219. $[\alpha]_D^{25}$ = + 76.1^o (C = 0.9 mg/ml), $CHCl_3$ for 92% ee.

See, Meyers, C.; Maes, B. U.; Loones, K. T.; Bal, G.; Lemiere, G. L.; Dommisse, R. A., Study of a new rate increasing "base effect" in the palladium-catalyzed amination of aryl iodides. *J Org Chem* **2004,** 69, (18), 6010-7.

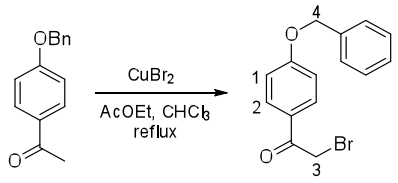
4.2.- Experimental Subproject II

1-(4-(benzyloxy)phenyl)ethanone (72)



Benzyl bromide (20.7 g, 121.0 mmol) was added to a mixture of 4-hydroxyacetophenone **71** (15.0 g, 110.2 mmol) K_2CO_3 (30.0 g, 220 mmol) in DMF (80 mL) at r.t. The mixture was stirred for 20 h. The reaction was quenched with water and extracted twice with AcOEt (100 mL). The combined organic layer was washed with brine (100 mL), dried over $MgSO_4$, filtered, and the filtrate was concentrated to give a white solid **72** (19.0 g, 79%), which was used for the next reaction without further purification. An analytical sample was obtained by preparative TLC (silica gel, hexane/AcOEt = 1/1). TLC R*f* = 0.33 (AcOEt/hexane = 4/1); λ_{max} (film) / cm^{-1} 1675, 1600, 1360, 1305, 1260, 1180, 1020, 835, 765, 720; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.93 (2H, d, J = 9.0 Hz, H^2), 7.45-7.31 (5H, m, Ph,), 7.01 (2H, d, J = 9.0 Hz, H^1), 5.13 (2H, s, H^4), 2.55 (3H, s, H^3);

Synthesis of 2-bromo-1-(4-benzyloxy)phenylethanone (64)



Under argon atmosphere, 4.44 g of copper(II) bromide were suspended in 40 ml of ethyl acetate and then was added a solution of 3 g of 1-(4-benzyloxy)-phenylethanone **72** in 40 ml of chloroform with agitation. The mixture was refluxed for 9 h. When the reaction was finish the mixture was cooled down to rt., diluted with 50 ml of chloroform, followed by filtration of the suspension and evaporation under a reduced pressure. The filtrate is concentrated and the product **64** (3.45 g, 85 %) was purified

by flash chromatography (dichloromethane/pet.-ether 1:1). M.p.: 58-59 ºC; λ_{max} (film) / cm^{-1} 3335, 2472, 2109, 1662, 1596, 1513, 1282, 1171, 973, 836; ^1H NMR (400 MHz, $CDCl_3$) δ_H 8.00 (d, J = 8.9 Hz, 2H, H^2), 7.56 (5H, m, Ph), 7.06 (2H, d, J = 8.9 Hz, H^1), 5.17 (2H, s, H^4), 4.42 (2H, s, H^3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 190.3, 163.6, 136.3, 131.8, 131.0, 129.1, 128.7, 127.9, 115.3, 70.7, 31.7.

(**Careful, HBr is generated during the reaction, use two traps with concentrated $NaHCO_3$**).

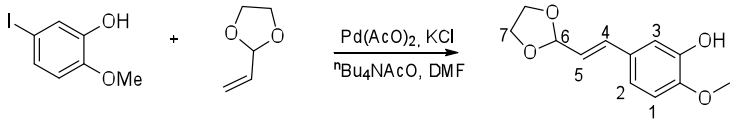
5-iodo-2-methoxyphenol (74)

Guaiacol (**73**) (2.00 g, 16.1 mmol, 1.0 eq) was dissolved in dichloromethane (40 ml, 0.4 M) and cooled to 0°C. Pyridine (3.0 ml, 37.4 mmol, 2.2 eq) was added followed by dropwise addition of acetyl chloride (1.3 ml, 18.0 mmol, 1.1 eq) and the solution stirred at 0°C for 20 min. The reaction was poured into ice cold (1M) phosphoric acid and the aqueous layer extracted into dichloromethane three times. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated *in vacuo*.

Iodine monochloride (3.09 g, 19.0 mmol, 1.2 eq) was dissolved in dichloromethane (20 ml, 1.0 M) and protected from light (covered with foil). This solution was added dropwise over 2h *via* syringe-pump to a solution of the crude acetate in dichloromethane (40 ml, 0.4 M) at 0°C. The solution was stirred for a further 4h then poured into ice cold saturated sodium thiosulfate solution and the aqueous layer extracted into dichloromethane three times. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. (CAREFUL – really difficult extraction, use a large separation funnel and do the extraction as fast as possible)

The crude acetate was dissolved in 2:2:1 tetrahydrofuran : methanol : water (35 ml, 0.4 M) and cooled to 0°C. Lithium hydroxide monohydrate (2.30 g, 56.0 mmol, 4.0 eq) was added and the solution stirred at rt for 14h. The reaction was poured into ice cold (1M) hydrochloric acid and the aqueous layer extracted into ethyl acetate three times. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The product was purified by crystallisation from ethyl acetate/60-80 petroleum ether to yield iodo guaiacol **74** (2.29 g, 9.18 mmol, **57 %** on 3 steps) as a pale yellow solid. The data were in agreement with the reported data. ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.23 (d, J = 2.3 Hz, 1H, H^3), 7.15 (1H, dd, J = 8.5, 2.3 Hz, H^2), 6.59 (1H, d, J = 8.5 Hz, H^1), 5.58 (1H, s, OH), 3.87 (3H, s, OMe); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 147.1, 147.0, 129.4, 123.8, 112.9, 83.4, 56.4.

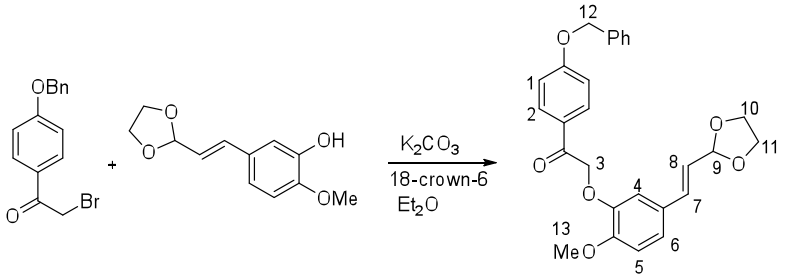
(*E*)-5-(2-(1,3-dioxolan-2-yl)vinyl)-2-methoxyphenol (65)



A dry flask was charged with iodo-guaiacol **74** (2.5 g, 10.0 mmol), palladium acetate (44.8 mg, 0.20 mmol, 2mol%), ground potassium carbonate (2.07 g, 15 mmol), potassium chloride (746 mg, 10.00 mmol) and tetrabutyl ammonium acetate (6.03 g, 20.00 mmol). *N,N*-dimethylformamide (40.0 ml) was added followed by acrolein ethylene acetal (**75**) (3 g, 30.00 mmol) and heated to 90°C for 16h. The reaction was

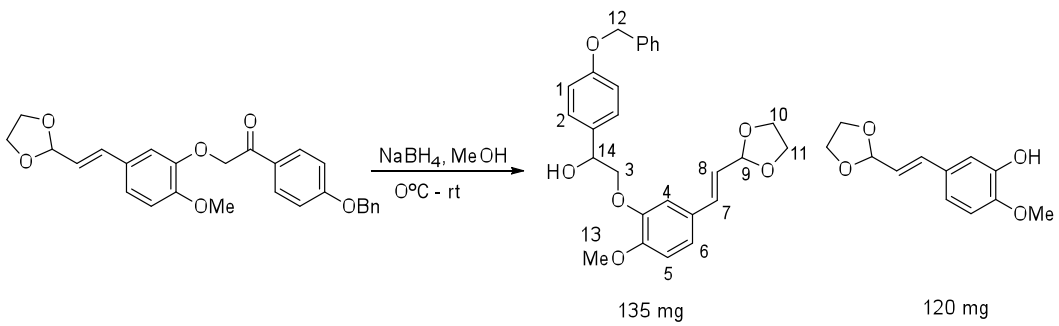
cooled, diluted with diethyl ether and poured into dilute sodium bicarbonate. The aqueous layer was extracted into diethyl ether three times, the combined organic layers washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The product was purified by crystallization from ethyl acetate/60-80 petroleum ether to yield phenol **65** (1.31 g, 6.04 mmol, **60 %**) as a yellow solid. Mp: 98-100 °C; λ_{max} (film) / cm^{-1} 3337, 2963, 2883, 1656, 1614, 1583, 1514, 1442; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.03 (1H, d, J = 2.3 Hz, H^3), 6.89 (1H, dd, J = 8.5, 2.3 Hz, H^2), 6.79 (1H, d, J = 8.5 Hz, H^1), 6.67 (1H, d, J = 15.8 Hz, H^4), 6.02 (1H, dd, J = 15.8, 6.0 Hz, H^5), 5.56 (1H, s, O*H*), 5.40 (1H, d, J = 6.0 Hz, H6), 4.07-4.04 (2H, m, H^7), 3.96-3.93 (2H, m, H^7), 3.89 (3H, s, O*C*H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 147.3, 146.0, 135.1, 129.9, 123.7, 120.1, 112.9, 110.8, 104.5, 65.6, 56.3; HRMS (ES^+) mass calc'd. For $C_{12}H_{14}O_4Na$ 245.0784; found[M + Na]+ 245.0776.

2-(5-(2-(1,3-dioxolan-2-yl)vinyl)-2-methoxyphenoxy)-1-(4-(benzyloxy)phenyl) ethanone (66)



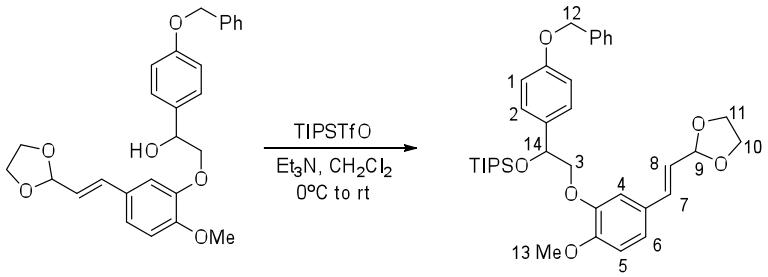
Bromoacetophenone **64** (100 mg, 0.32 mmol), in 2 mL of anhydrous diethyl ether, was added dropwise to a solution of phenol **65** (64.4 g, 0.3 mmol), ground K_2CO_3 (72.0 mg), and 18-crown-6 (8.5 mg) in 3 mL of anhydrous diethyl ether. The reaction was refluxed for 3 h under nitrogen. After cooling to rt the solid was filtered off and the solution was extracted with aqueous K_2CO_3 (3×5 mL) and dried over $NaSO_4$. The solvent was evaporated and the residue was purified by chromatography on silica gel column using DCM (100%) as the eluant to give 129.6 mg, 85% of compound **66** as a colourless oil; λ_{max} (film) / cm^{-1} 3367, 2942, 2871, 2343, 1691, 1600, 1510, 1441, 1224, 1139, 1022, 953, 838; ^1H NMR (400 MHz, CD_2Cl_2) δ_H 7.89 (2H, d, J = 8.9 Hz, H^2), 7.40-7.22 (5H, m, Ph), 6.97 (2H, d, J = 8.9 Hz, H^1), 6.93 (1H, dd, J = 8.3 Hz, J = 1.9 Hz, H^5), 6.85 (1H, d, J = 1.9 Hz, H^4), 6.78 (1H, d, J = 8.3 Hz, H^6), 6.54 (1H, d, J = 15.9 Hz, H^7), 5.87 (1H, dd, J = 15.9 Hz, J = 6.4 Hz, H^8), 5.24 (1H, d, J = 6.4 Hz, H^9), 5.18 (2H, s, H^3), 5.06 (2H, s, H12), 3.90 (2H, dd, J = 8.6 Hz, J = 5.08 Hz, H^{10}), 3.84-3.78 (2H, m, H^{11}), 3.77 (3H, s, H^{13}); ^{13}C NMR (100 MHz, CD_2Cl_2) δ_C (NA)

2-(5-(2-(1,3-dioxolan-2-yl)vinyl)-2-methoxyphenoxy)-1-(4-benzyloxyphenyl)ethanol (76)



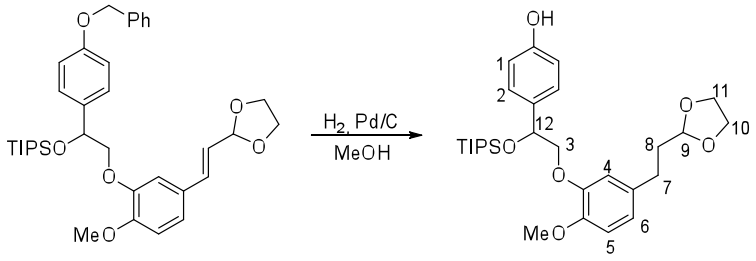
To a solution of **66** (330 mg, 0.74 mmol) in MeOH (10 mL), $NaBH_4$ (30.7 mg, 1.1 equivalent) was added portionwise at 0 ºC. The mixture was stirred at 0 ºC for 30 min. Water was added and extracted with ethyl ether (3 × 10 mL). The organic extracts were combined, washed with distilled water, 5% $NaHCO_3$ solution and then dried over Na_2SO_4. Filtration and evaporation *in vacuo* afforded a mixture of racemic alcohols and the residue was purified by chromatography on silica gel column using DCM (100%) as the eluant to give 135 mg (0.30 mmol, 40 %) of compound **76** and compound **65** as a byproduct (100 mg, 0.44 mmol); Rf = 0.15 (Pet. Ether/EtOAc, 7:3); λ_{max} (film) / cm^{-1} 3465, 2343, 1668, 1596, 1510, 1266, 1127, 1018, 803; ^1H NMR (400 MHz, CD_2Cl_2) δ_H 7.46-7.16 (8H, m, Ph, H^2, H^4), 7.02-6.84 (3H, m, H^1, H^5), 6.78 (1H, d, J = 8.9 Hz, H^6), 6.55 (1H, d, J = 15.9 Hz, H^7), 5.89 (1H, dd, J = 15.9Hz, J = 6.2 Hz, H^8), 5.30-5.18 (1H, m, H^9), 4.98 (2H, s, H^{12}), 4.92 (1H, dd, J = 8.9 Hz, J = 2.9 Hz, H^{14}), 4.03 (1H, dd, J = 9.8 Hz, J = 3.1 Hz, H^{3a}), 3.94-3.83 (3H, m, H^{3b}, H^{11}), 3.95 (2H, m, H^{10}), 3.76 (3H, s, H^{13}). ^{13}C NMR (100 MHz, CD_2Cl_2) δ_C 159.4, 151.2, 148.9, 137.9, 134.7, 133.1, 129.9, 129.3, 128.7, 128.4, 128.3, 124.5, 122.4, 115.5, 114.0, 112.6, 104.7, 76.6, 72.7, 70.7, 65.8, 56.6.

(2-(5-(2-1,3-dioxolan-2-yl)vinyl)-2-methoxyphenoxy)-1-(4-benzyloxyphenylethoxy) triisopropylsilane (77)



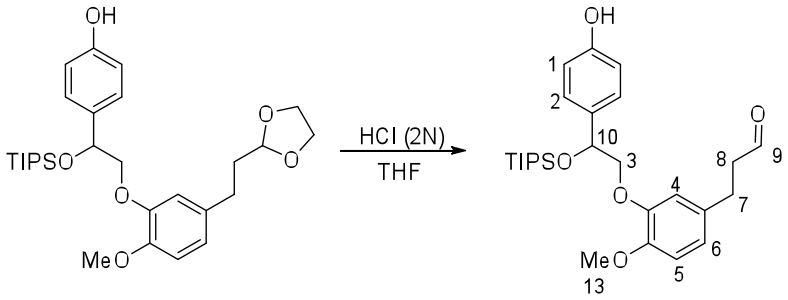
TIPSOTf (101.1 mg, 0.33 mmol) was added to a solution of alcohol **76** (135 mg, 0.3 mmol) and Et_3N (45.5 mg, 0.45 mmol) in dry CH_2Cl_2 (5 mL) at 0 ºC. The bath was removed and the reaction was allowed to warm to rt. After 4.5 h, the reaction was quenched with aqueous saturated solution of $NaHCO_3$. The mixture was extracted with diethyl ether (3 x 5 mL) and the organic layer dried over Na_2SO_4. The solvent was removed *in vacuo* and the mixture was purified by flash chromatography on silica gel using (100% DCM) to afford **77** (125 mg, 0.21 mmol, 70%) as colourless oil. Rf = 0.35 (Pet. Ether/EtOAc, 7:3); λ_{max} (film) / cm^{-1} (NA); ^1H NMR (400 MHz, CD_2Cl_2) δ_H 7.41-7.19 (1H, m, Ph, H^2), 6.87 (2H, d, J = 8.7 Hz, H^1), 6.78 (2H, m, H^4, H^6), 6.70 (1H, d, J = 8.7 Hz, H^5), 6.52 (1H, d, J = 15.9 Hz, H^7), 5.86 (1H, dd, J = 15.9 Hz, J = 6.3 Hz, H^8), 5.23 (1H, d, J = 6.3 Hz, H^9), 5.05 (1H, dd, J = 6.9 Hz, J = 4.9 Hz, H^{14}), 4.95 (2H, s, H^{12}), 4.02 (1H, dd, J = 9.6 Hz, J = 7.1 Hz, H^{3a}), 3.94-3.85 (2H, m, H^{11}), 3.86-3.71 (3H, m, H^{3b}, H^{10}), 3.68 (3H, s, H^{13}), 0.97 (21H, m, TIPSO). ^{13}C NMR (100 MHz, CD_2Cl_2) δ_C 159.2, 150.8, 149.4, 138.0, 135.7, 135.1, 129.5, 129.3, 128.7, 128.6, 128.4, 124.1, 121.4, 115.1, 112.4, 111.8, 104.9, 76.0, 74.1, 70.7, 65.8, 56.5, 18.6, 13.18.

4-(2-(5-(2-(1,3-dioxolan-2-yl)ethyl)-2-methoxyphenoxy)-1-((triisopropylsilyl)oxy) ethyl)phenol (78)



Alkene **77** (125 mg, 0.21 mmol) was dissolved in methanol (6 mL) and added to a flask with catalytic amount of Pd/C (10%) under nitrogen. The atmosphere was replaced by hydrogen (balloons) and the reaction stirred for 12h. The suspension was filtered through celite, washed with methanol and the solvent volume was reduced *in vacuo*. The solution was diluted with DCM and water, the aqueous layer was extracted into DCM three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to yield phenol **78** (68 mg, 0.13 mmol, 62%) as a yellow oil. λ_{max} (film) / cm^{-1} (NA); ^1H NMR (400 MHz, CD_2Cl_2) δ_H 7.33 (2H, d, J = 8.4 Hz, H^2), 6.84 (2H, d, J = 8.4, H^1), 6.77 (1H, s, H^4), 6.72 (1H, d, J = 8.1 Hz, H^5), 6.65 (1H, m, H^6), 5.65 (1H, s, O*H*), 5.12 (1H, t, J = 5.8 Hz, H^9), 4.86 (1H, t, J = 4.7 Hz, H^{12}), 4.14 (1H, dd, J = 9.7 Hz, J = 6.7 Hz, H^{3a}), 4.03-3.95 (1H, m, H^{3b}), 3.94-3.82 (4H, m, H^{10}, H^{11}), 3.76 (3H, s, OC*H*$_3$), 2.74-3.84 (2H, m, H^7), 1.96-1.78 (2H, m, H^8), 1.03 (21H, m, TIPSO); ^{13}C NMR (100 MHz, CD_2Cl_2) δ_C 156.2, 149.3, 148.6, 135.5, 135.1, 128.8, 121.4, 115.7, 115.0, 113.2, 104.6, 76.2, 74.2, 65.7, 56.7, 36.5, 35.2, 31.1, 30.4, 18.5, 13.2;

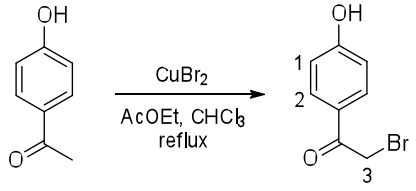
3-(3-(2-(4-hydroxyphenyl)-2-((triisopropylsilyl)oxy)ethoxy)-4-methoxyphenyl) propanal (68)



2N HCl (1 mL) was added dropwise to a solution of acetal **78** (68 mg, 0.13 mmol) in THF (3 mL) at room temperature, and the resulting solution was stirred until completion. The reaction was quenched with aqueous $NaHCO_3$ solution and extracted with diethyl ether (3 x 5 mL). The organic layer was dried over Na_2SO_4, concentrated *in vacuo* and purified by flash chromatography on silica gel (DCM/acetone 99:1) to afford compound **68** as a colourless oil (60 mg, 99% yield); Rf (Pet. Ether/EtOAc, 7:3) = 0.35; λ_{max} (film) / cm^{-1} 3411, 2942, 2865, 2359, 1987,1720, 1613, 1513, 1257, 1233, 1100, 977, 882; ^1H NMR (500 MHz, CD_2Cl_2) δ_H 9.7 (s, 1H, H9), 7.32 (2H, d, J = 8.5 Hz, H^2), 6.81 (2H, d, J = 8.5 Hz, H^1), 6.77 (2H, d, J = 8.1, H^5), 6.70 (1H, dd, J = 8.1 Hz, J = 2.1 Hz, H^6), 6.64 (1H, d, J = 2.0 Hz, H^4), 5.11 (1H, dd, J = 6.8 Hz, J = 5.1 Hz, H^{10}), 4.10 (1H, dd, J = 9.7 Hz, J = 6.7 Hz, H^{3a}), 3.88 (1H, dd, J = 9.7 Hz, J = 5.1 Hz, H^{3b}), 3.74 (3H, s, OC*H*$_3$), 2.82 (2H, t, J = 7.6 Hz, H^8), 2.68 (2H, dt, J = 7.6 Hz, H^7), 1.07 (21H, m, TIPSO); ^{13}C NMR (125 MHz, CD_2Cl_2) δ_C 201.9, 155.4, 148.8, 148.4, 135.2, 133.3, 128.3, 120.7, 115.1, 114.3, 112.5, 75.6, 73.6, 56.2, 45.67, 27.9,

18.0, 17.9, 12.1; HRMS (ES^+) mass calc'd. For $C_{27}H_{40}O_5Si$: 472.2645, found $[M+NH_4]^+$ 490.2983.

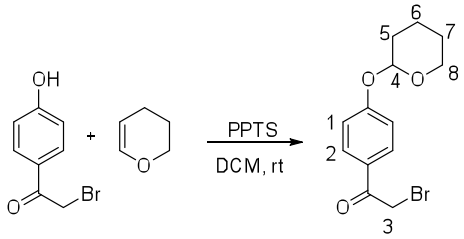
Synthesis of 2-bromo-1-(4-hidroxy)phenylethanone (80)



Under argon atmosphere, 7.4 g of copper(II) bromide were suspended in 100 ml of ethyl acetate and then was added a solution of 5 g of 1-(4-hydroxyphenyl)ethanone (**71**) in 100 ml of chloroform with agitation while heating under reflux. After agitation for 5.5 hours, the mixture was cooled down to rt. and it was diluted with 100 ml of chloroform, followed by filtration of the suspension and evaporation under a reduced pressure. The filtrate is concentrated by evaporation and the product is purified by flash chromatography (dichloromethane/petroleum ether 1:1) to afford compound **80** (6.32 g, 80%) as a white solid. m.p. 125-126 °C; λ_{max} (film) / cm^{-1} 3335, 3271, 2336, 2109, 1676, 1661, 1574, 1515, 1282, 1198, 1174, 992, 838; ^1H NMR (400 MHz, MeOD) δ_H 7.94 (2H, d, J = 8.8 Hz, H^2), 6.88 (2H, d, J = 8.8, H^1), 4.90 (2H, s, H^3); ^{13}C NMR (100 MHz, MeOD) δ_C 191.3, 163.6, 133.3, 125.8, 129.1, 115.3, 31.7

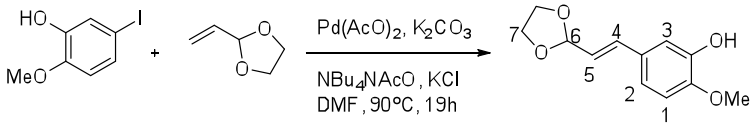
D. N. Ridge, J. W. Hanifin, L. A. Harten, B. D. Johnson, J. Menschik, G. Nicolau, A. E. Sloboda, D. E. Watts, *J. Phar. Sci.* **1979**, *22*, 1385-1389.

2-bromo-1-(4-(tetrahydro-2*H*-pyran-2-yl-oxy)phenyl)ethanone (81)



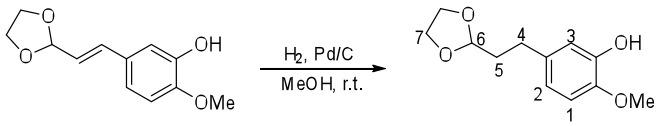
2-bromo-1-(4-hydroxyphenyl)ethanone **80** (7.5 g, 34.9 mmol) and PPTS (0.88 g 3.5 mmol) were dissolved in 80 mL of CH_2Cl_2 and 3,4-dihydropyran (4.4 g, 52.3 mmol) was added, stirred for 17 hours at room temperature. The reaction mixture was washed with saturated aq. $NaHCO_3$, the organic layer was dried over $MgSO_4$, and concentrated *in vacuo* to afford 9.8 g of **81** as a white solid (32.7 mmol, 94%). λ_{max} (film) / cm^{-1} 3310, 2943, 2871, 2324, 1689, 1597, 1579, 1509, 1281, 1198, 1168, 916, 842; ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.94 (2H, d, J = 8.9 Hz, H2), 7.12 (2H, d, J = 8.9, H^1), 5.53 (1H, t, J = 3.1, H^4), 4.45 (2H, s, H^3), 3.82 (1H, ddd, J = 11.6 Hz, J = 10.0 Hz, J = 2.9 Hz, H^{8a}), 3.06 (1H, m, H^{8a}), 2.09-1.92 (1H, m, H^{5a}), 1.94-1.79 (2H, m, H^{5b}, H^{7a}), 1.77-1.63 (2H, m, H^{7b}, H^{6a}), 1.59 (1H, m, H^{6b}); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 190.1, 162.0, 131.2, 127.7, 116.5, 96.5, 62.4, 31.6, 30.30, 25.3, 18.8; HRMS (ES^+) mass calc'd. For $C_{13}H_{15}BrO_3$ 298.0205; found $[M + H]^+$ 299.0285.

(*E*)-5-(2-(1,3-dioxolan-2-yl)vinyl)-2-methoxyphenol (65)



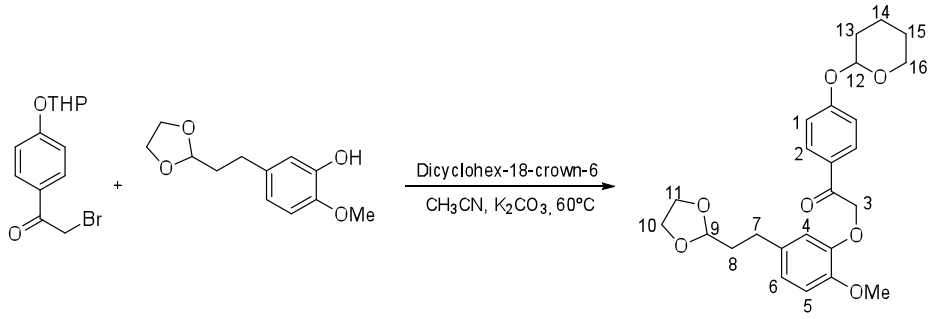
A dry flask was charged with iodo-guaiacol **74** (2.5 g, 10.0 mmol, 1.0 eq), palladium acetate (44.8 mg, 0.20 mmol, 2mol%), ground potassium carbonate (2.1 g, 15.0 mmol, 44.8 eq), potassium chloride (746 mg, 10.0 mmol, 1.0 eq) and tetrabutyl ammonium acetate (6.03 g, 20.0 mmol, 2.0 eq). *N,N*-dimethylformamide (40.0 ml) was added followed by acrolein ethylene acetal (3 g, 30.0 mmol, 3.0 eq) and heated to 90°C for 16h. The reaction was cooled, diluted with diethyl ether and poured into dilute sodium bicarbonate. The aqueous layer was extracted into diethyl ether three times, the combined organic layers washed with brine, dried over sodium sulfate and concentrated under reduced presure. The product was purified by crystallization from ethyl acetate/60-80 petroleum ether (50%) to yield **65** (1.42 g, 1.04 mmol, **64 %**) as a yellow solid. Mp: 98-100°C; λ_{max} (film) / cm^{-1} 3337, 2963, 2883, 1656, 1614, 1583, 1514, 1442; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.03 (d, *J* = 2.3 Hz, 1H, H3), 6.89 (dd, *J* = 8.5, 2.3 Hz, 1H, H2), 6.79 (d, *J* = 8.5 Hz, 1H, H1), 6.67 (d, *J* = 15.8 Hz, 1H, H4), 6.02 (dd, *J* = 15.8, 6.0 Hz, 1H, H5), 5.56 (s, 1H, OH), 5.40 (d, *J* = 6.0 Hz, 1H, H6), 4.07-4.04 (m, 2H, H7), 3.96-3.93 (m, 2H, H7), 3.89 (s, 3H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 147.3, 146.0, 135.1, 129.9, 123.7, 120.1, 112.9, 110.8, 104.5, 65.6, 56.3; HRMS (ES^+) mass calc'd. For $C_{12}H_{14}O_4Na$ 245.0784; found $[M + Na]^+$ 245.0776.

5-(2-(1,3-dioxolan-2-yl)ethyl)-2-methoxyphenol (56)



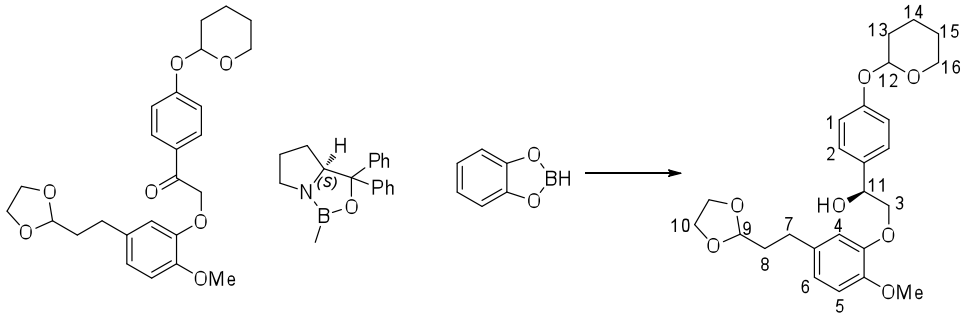
5-(2-(1,3-dioxolan-2-yl)vinyl)-2-methoxyphenol **65** (4.5 g, 7.4 mmol, 20.2 eq) was dissolved in methanol (120 ml) and added to a flask with catalytic amount of Pd/C under nitrogen. The atmosphere was replaced by hydrogen (balloons) and the reaction stirred for 16h. The suspension was filtered through Celite, washing with methanol and the solvent volume was reduced *in vacuo*. The solution was diluted with DCM and water, the aqueous layer was extracted into CH_2Cl_2 three times. The combined organic layers were washed with brine, dried over sodium sulphate and concentrated *in vacuo*. Purification by flash chromatography (dichloromethane/acetone, 4%) afforded phenol **56** (4.5 g, 7.16 mmol, **99%**) as a colourless oil (white amorphous solid in the fridge). Rf (EtOAc/Pet. Ether, 3:7) =0.48; λ_{max} (film) / cm^{-1} 3415, 2953, 2886, 1590, 1509, 1442, 1272; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.79 (1H, d, *J* = 2.0 Hz, H^3), 6.77 (1H, d, *J* = 8.3 Hz, H^1), 6.68 (1H, dd, *J* = 8.3, 2.0 Hz, H^2), 5.54 (1H, s, O*H*), 4.88 (1H, t, *J* = 4.8 Hz, H^6), 4.01-3.97 (2H, m, H^7), 3.88-3.84 (2H, m, H^7), 3.86 (3H, s, O*CH*$_3$), 2.68-2.64 (2H, m, H^4), 1.97-1.92 (2H, m, H^5); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 145.9, 145.2, 135.3, 120.0, 115.0, 111.1, 104.3, 65.3, 56.4, 36.0, 29.9; HRMS (ES^+) mass calc'd. For $C_{12}H_{16}O_4Na$ 247.0941; found $[M + Na]^+$ 247.0943.

2-(5-(2-(1,3-dioxolan-2-yl)ethyl)-2-methoxyphenoxy)-1-(4-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)ethanone (82)



2-bromo-1-(4-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)ethanone **81** (800 mg, 2.7 mmol) was added portionwise to a solution of phenol (500.0 mg, 2.23 mmol), ground K_2CO_3 (919.0 mg, 3 mmol), and dicyclohexyl-18-crown-6 (83.8 mg, 0.22 mmol) in 15 mL of anhydrous acetonitrile at 60 ºC over 1 h. The reaction mixture was heated at 60 ºC for 9 h. After cooling to rt the solid was filtered off and the solution was extracted with aqueous K_2CO_3 (3×10 mL) and dried over $NaSO_4$. The solvent was evaporated and the residue was purified by chromatography on silica gel using DCM/acetone (0% to 4%) as the eluant to give 900.0 mg (92%) of compound **82** as a yellow oil; Rf (Pet.-Ether/EtOAc, 7:3) = 0.3; λ_{max} (film) / cm^{-1} 2943, 1694, 1600, 1510, 1442, 1358, 1228, 1121, 1035, 953, 917, 838; ^{1}H NMR (500 MHz, CD_2Cl_2) δ_H 8.02 (d, *J* = 8.9 Hz, 2H, H^2), 7.04 (d, *J* = 8.9, 2H, H^1), 6.93 (d, *J* = 1.9 Hz, 1H, H^4), 6.76 (dd, *J* = 8.1 Hz, *J* = 1.9 Hz, 1H, H^6), 6.63 (d, *J* = 8.1 Hz,1H, H^5), 5.2 (t, *J* = 2.7, 1H, H^{12}), 4.96 (s, 2H, H^3), 4.35 (t, *J* = 5.7 Hz, 1H, H^9), 3.63 (dt, *J* = 11.9 Hz, *J* = 2.8 Hz, 1H^{16a}), 3.45(s, 3H, OC*H*$_3$), 3.41-3.28 (m, 1H, H^{16b}), 3.19 (s, 4H, $H^{10,11}$), 2.70-2.58 (m, 1H, H^7), 1.97 (ddd, *J* = 9.4 Hz, *J* = 7.8 Hz, *J* = 5.9 Hz, 2H, H^8), 1.91-1.69 (m, 1H, THP), 1.67-1.55 (m, 1H, THP), 1.56-1.44 (m, 1H, THP), 1.42-1.19 (m, 2H, THP), 1.17 (m, 1H, THP); ^{13}C NMR (125 MHz, CD_2Cl_2) δ_C 193.2, 161.5, 148.9, 148.7, 134.8, 130.9, 129.3, 122.1, 116.5, 116.2, 113.3, 103.7, 95.9, 72.9, 61.4, 55.8, 52.3, 34.6, 30.7, 30.1, 25.2, 18.5. HRMS (ES^+) mass calc'd. For $C_{25}H_{30}O_7$: 442.5015, found $[M + H]^+$ 443.2065.

(1S)-2-(5-(2-(1,3-dioxolan-2-yl)ethyl)-2-methoxyphenoxy)-1-(4-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)etanol (92)

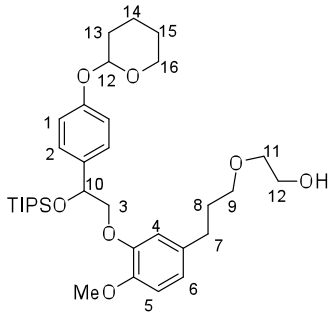


Enantioselective synthesis. Ketone **82** (500 mg, 1.13 mmol), azeotropically dried with toluene) was treated with (S)-2-methyl-CBS-oxaborolidine **90** (230 µL of a 1.0 M solution in toluene, 0.23 mmol) and toluene (70 mL). Upon being cooled to -65ºC, catecholborane **91** (1.35 mL, 1.35 mmol of a 1 M solution in THF) was added dropwise into the reaction mixture and stirring was continued at -65ºC for 12 hours. The reaction was allowed to warm up to -55ºC for 20 h and then to -50 ºC 12h. When the reaction finished, methanol (5 mL) was added down the side of the flask and the

reaction was allowed to warm to room temperature. After dilution with Et_2O (20 mL) the solution was washed with buffer (pH= 13, 1N NaOH / saturated aqueous $NaHCO_3$, 2:1) until the aqueous washings were colorless. The dark aqueous washes were extracted with Et_2O (2 x 50 mL). The combined organic extracts were washed with brine (2 x 50 mL, saturated aqueous solution), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (DCM/acetone, 0 – 5%) to provide alcohol **92** as a colorless oil (460 mg, 92%): Rf (EtOAc/Pet. Ether, 3:7) = 0.30; λ_{max} (film) / cm^{-1} 3365, 2933, 2871, 2301, 1612, 1592, 1579, 1513, 1230, 1136, 1023, 984, 811. ^1H NMR (500 MHz, CD_2Cl_2) δ_H 8.00 (2H, d, J = 8.9 Hz, H^2), 7.16 (2H, d, J = 8.9 Hz, H^1), 6.87 (1H, d, J = 8.2 Hz, H^5), 6.82 (1H, dd, J = 8.2 Hz, J = 1.9 Hz, H^6), 6.71 (1H, d, J = 1.9 Hz, H^4), 5.57 (1H, t, J = 3.1 Hz, H^{12}), 5.36-5.35 (1H, m, H^{11}), 5.30-5.28 (1H, m, H^9), 4.32 (1H, app t, J = 5.7 Hz, H^{3a}), 3.86 (4H, s, H^{10}), 3.86 (4H, m, $OC\underline{H_3}$, H^{16a}), 3.76-3.57 (1H, m, H^{3b}), 3.31 (5H, m, H^{10}, H^{16b}), 2.58 (1H, dd, J = 8.9 Hz, J = 7.0 Hz, H^7), 2.37-1.96 (1H, m, THP), 1.95-1.81 (4H, m, THP, H^8), 1.78-1.50 (3H, m, THP); ^{13}C NMR (125 MHz, CD_2Cl_2) δ_C 147.9, 147.44, 134.4, 130.6, 130.0, 128.3, 121.6, 116.1, 115.4, 114.9, 112.2, 103.8, 96.2, 71.6, 62.1, 55.9, 52.6, 34.3, 30.2, 30.1, 25.1, 18.5; HRMS (ES^+) mass calc'd. For $C_{25}H_{32}O_7$: 444.2148, found $[M + NH_4]^+$ 462.2475; HPLC:DAICEL IC Chiralpak, 8:2 Hexane/isopropanol, flow 1 ml/min, mixture of diasteroisomers, retention time: Diasteroisomer 1: minor enantiomer 23.44 min, major enantiomer 29.76.46 min; Diasteroisomer 2: minor enantiomer 24.95 min, major enantiomer 32.03 min,

Racemic synthesis (gives over-reduction as well): DIBAL (11.2 mg, 0.079 mmol) was added dropwise over 30 min to a solution of ketone **82** (35 mg, 0.079 mmol) in THF previously cooled to -78 ºC. After stirring for another 10 min, the reaction was quenched by adding MeOH (1 mL) dropwise to the reaction mixture at -78ºC and warmet to 0ºC. The reaction mixture was extracted with a saturated solution of Rochelle's salt and DCM. The combined organic layer was dried over Na_2SO_4, concentrated *in vacuo* and the product purified by flash column chromatography on silica gel (DCM/acetone, 0 – 5%) to provide racemic alcohol **92** as a colorless oil (25 mg, 71%).

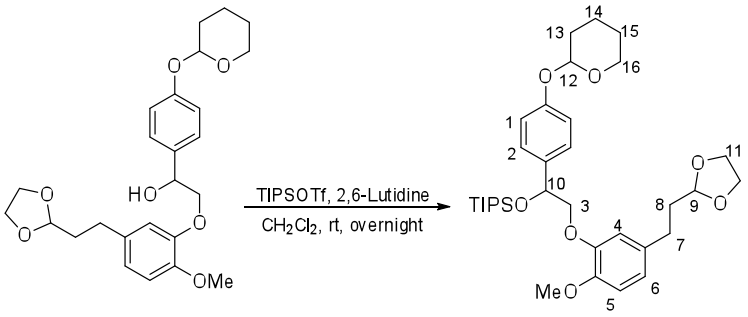
2-(3-(4-methoxy-3-(2-(4-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)-2-((triisopropylsilyl)oxy)ethoxy)phenyl)propoxy)ethanol



This compound appears during the synthesis of **92** racemic mixtureas a secondary product. Rf (EtOAc/Pet. Ether, 4:6) = 0.44; λ_{max} (film) / cm^{-1} 3355, 2941, 2865, 2194, 1610, 1588, 1509, 1463, 1424, 1258, 1231, 1109, 967, 882; ^1H NMR (400 MHz, CD_2Cl_2) δ_H 7.28 (2H, d, J = 8.6 Hz), 6.92 (2H, d, J = 8.6 Hz), 6.83-6.55 (3H, m), 5.30

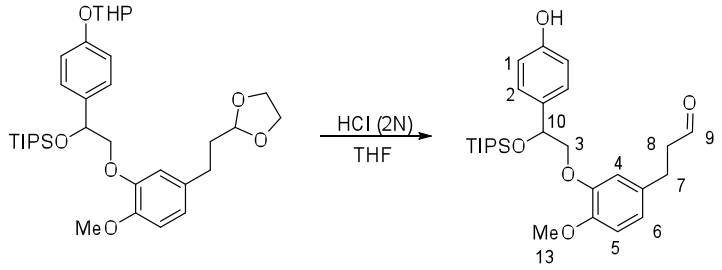
(1H, app t, J = 3.2 Hz), 5.04 (1H, dd, J = 6.5 Hz, J = 5.3 Hz), 4.74 (1H, t, J = 4.7 Hz), 4.04-3.9 (1H, m), 3.91-3.68 (6H, m), 3.65 (3H, s), 3.60-3.38 (1H, m), 2.59-2.45 (2H, m), 2.10-1.83 (1H, m), 1.83-1.68 (4H, m), 1.66-1.38 (3H, m), 0.99-0.84 (21H, m). ^{13}C NMR (100 MHz, CD_2Cl_2) δ_C 157.5, 149.2, 148.6, 136.5, 135.1, 128.4, 121.2, 116.8, 114.7, 112.9, 104.6, 97.4, 76.0, 74.1, 65.7, 62.9, 56.7, 36.6, 31.3, 30.5, 26.1, 19.8, 18.6, 13.2. HRMS (ES^+) mass calc'd. For $C_{34}H_{52}O_7Si$: 602.3482, found $[M+NH_4]^+$ 620.3977.

(2-(5-(2-(1,3-dioxolan-2-yl)ethyl)-2-methoxyphenoxy)-1-(4-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)ethoxy)triisopropylsilane (93)



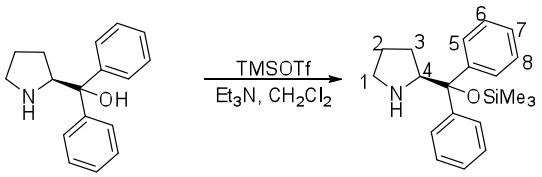
TIPSOTf (414.2 mg, 1.35 mmol) was added to a solution of alcohol **92** (460 mg, 1.05 mmol) and 2,6-lutidine (135.0 mg, 1.26 mmol) in dry CH_2Cl_2 (15 mL) at 0 ºC. The bath was removed and the reaction was allowed to warm to rt. After 14 h, the reaction was quenched with aqueous saturated solution of $NaHCO_3$. The mixture was extracted with diethyl ether (3 x 15 mL) and the organic layer dried over Na_2SO_4. The solvent was removed *in vacuo* and the mixture was purified by flash chromatography on silica gel (DCM/acetone, 0 – 0.5%) to afford **93** (430 mg, 68%) as colourless oil. Rf (Pet.-Ether/EtOAc, 8:2) = 0.52; λ_{max} (film) / cm^{-1} 2942, 2865, 2100, 1742, 1610, 1509, 1232, 1122, 1035, 966, 920, 835, 680; ^{1}H NMR (400 MHz, CD_2Cl_2) δ_H 7.28 (2H, d, J = 8.6 Hz, H^2), 6.92 (2H, d, J = 8.6 Hz, H^1), 6.78-6.54 (m, 3H, H^4, H^5, H^6), 5.30 (1H, app t, J = 3.2 Hz, H^{12}), 5.09 (1H, t, J = 5.6 Hz, H^9), 4.21 (1H, t, J = 5.7 Hz, H^{10}), 4.01 (1H, dd, J = 9.6 Hz, J = 7.0 Hz, H^{3a}), 3.80 (2H, m, H^{3b}, H^{16a}), 3.66 (s, 3H, OC$\underline{H_3}$), 3.54-3.43 (1H, m, H^{16b}), 3.2 (4H, m, H^{11}), 2.48-2.39 (2H, m, H^7), 2.00-1.81 (1H, m, H^{13a}), 1.82-1.65 (4H, m, H^8, H^{14}), 1.68-1.38 (3H, m, H^{13b}, H^{15}), 0.99-0.84 (m, 21H, TIPSO); ^{13}C NMR (100 MHz, CD_2Cl_2) δ_C 157.4, 149.2, 148.6, 136.5, 135.2, 128.4, 121.3, 116.8, 114.7, 112.9, 104.6, 97.3, 76.1, 76.0, 74.2, 74.1, 62.9, 56.7, 35.2, 31.2, 31.1, 26.1, 19.8, 18.6, 18.5, 13.1; HRMS (ES^+) mass calc'd. For $C_{34}H_{52}O_7Si$: 600.3482, found $[M+NH_4]^+$ 620.3977.

3-(3-(2-(4-hydroxyphenyl)-2-((triisopropylsilyl)oxy)ethoxy)-4-methoxyphenyl) propanal (68)



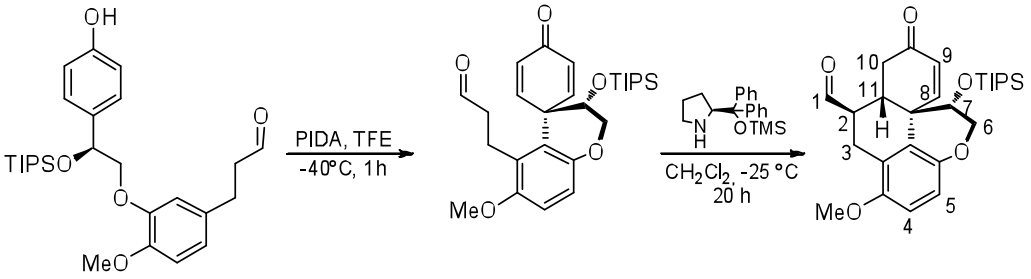
2N HCl (2 mL) was added dropwise to a solution of acetal **93** (430 mg, 0.71 mmol) in THF (10 mL) at room temperature, and the resulting solution was stirred until completion. The reaction was quenched with aqueous $NaHCO_3$ solution and extracted with diethyl ether. The organic layer was dried over Na_2SO_4, concentrated *in vacuo* and purified by flash chromatography on silica gel (DCM/acetone, 0 – 1%) to afford **68** as colourless oil (330 mg, 97%). Rf (EtOAc/Pet. Ether, 3:7) = 0.35; λ_{max} (film) / cm^{-1} 3411, 2942, 2865, 2359, 1987,1720, 1613, 1513, 1257, 1233, 1100, 977, 882; ^1H NMR (500 MHz, CD_2Cl_2) δ_H 9.7 (s, 1H, H9), 7.32 (2H, d, J = 8.5 Hz, H^2), 6.81 (2H, d, J = 8.5 Hz, H^1), 6.77 (2H, d, J = 8.1, H^5), 6.70 (1H, dd, J = 8.1 Hz, J = 2.1 Hz, H^6), 6.64 (1H, d, J = 2.0 Hz, H^4), 5.11 (1H, dd, J = 6.8 Hz, J = 5.1 Hz, H^{10}), 4.10 (1H, dd, J = 9.7 Hz, J = 6.7 Hz, H^{3a}), 3.88 (1H, dd, J = 9.7 Hz, J = 5.1 Hz, H^{3b}), 3.74 (3H, s, OC$\underline{H_3}$), 2.82 (2H, t, J = 7.6 Hz, H^8), 2.68 (2H, dt, J = 7.6 Hz, H^7), 1.07 (21H, m, TIPSO); ^{13}C NMR (125 MHz, CD_2Cl_2) δ_C 201.9, 155.4, 148.8, 148.4, 135.2, 133.3, 128.3, 120.7, 115.1, 114.3, 112.5, 75.6, 73.6, 56.2, 45.67, 27.9, 18.0, 17.9, 12.1; HRMS (ES^+) mass calc'd. For $C_{27}H_{40}O_5Si$: 472.2645, found $[M+NH_4]^+$ 490.2983.

(S)-2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (14)



(S)-(–)-α,α-Diphenyl-2-pyrrolidinemethanol (500 mg, 1.96 mmol) was suspended in DCM (20 mL) and cooled to 0 ºC. Triethylamine (405 µL, 2.96 mmol) was added followed by trimethylsilyl trifluoromethanesulfonate (444 µL, 2.46 mmol). The homogeneous solution was stirred for 2 hours at room temperature then poured intor water and the aqueous layer was extracted into DCM three times. Te combined organic layers were wahed with brine, dried over sodium sulphate and concentrated *in vacuo*. The product was purified by flash column chromatography with 7:3 hexane/pet.-ether as the eluant to yield amine **14** (620 mg, 97 %) The data were in agreement with the published data. λ_{max} (film) / cm^{-1}3058, 2954, 1599, 1491, 1446, 1248; ^1H NMR (400 MHz, CD_2Cl_2) δ_H 7.45 (2H, m ArH), 7.34 (2H, m ArH), 7.24 (6H, m, ArH, 4.03 (1H, t J = 7.2 Hz, H^4), 2.82 (2H, m, H^1), 1.57 (3H, m $H^{2,3,3'}$), 1.36 (1H, m $H^{2'}$), 0.09 (9H, s, Si$\underline{Me_3}$). ^{13}C NMR (125 MHz, CD_2Cl_2) δ_C 147.2, 146.2, 128.8, 128.0, 127.9, 127.3, 127.1, 83.6, 65.8, 47.5, 27.9, 25.4, 2.6; $[\alpha]_D^{25}$ = -43º (c = 10 mg/mL, $CHCl_3$).

8-methoxy-2-oxo-5-((triisopropylsilyl)oxy)-2,5,6,11,12,12a-hexahydro-1*H*-naphtho[1,2-de]chromene-12-carbaldehyde (69)



Phenol **68** (70 mg, 0.15 mmol, 1.0 eq) was dissolved in freshly distilled 2,2,2-trifluoro ethanol (15 ml) and cooled to -40 °C. Biscetoxyiodo-benzene (52.5 mg, 0.16 mmol, 1.1 eq) was added in 3 portions and the reaction stirred for 1h. The blue solution was poured into dilute sodium bicarbonate and the aqueous layer extracted into dichloromethane three times. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The crude dienone **79** was dissolved in dichloromethane (40 mL) and cooled to -25°C. Amine **14** (9.7 mg, 0.03 mmol, 20mol%) was added and the solution stirred at -25°C for 30h. The reaction was quenched with water. The aqueous layer was extracted into dichloromethane three times and the combined organic layers were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The product was purified by flash column chromatography on silica gel with DCM/acetone: (0 – 0.25%) to yield **69** (45.0 mg, **63 %** on 2 steps) as colourless oil. Rf (EtOAc/Pet. Ether, 3:7) = 0.38; λ_{max} (film) / cm^{-1} 2942, 2866, 2085, 1723, 1662, 1581, 1484, 1243, 1222, 1098, 806; ^{1}H NMR (500 MHz, CD_2Cl_2) δ_H 9.66 (1H, d, *J* = 2.3 Hz, H^{1}), 6.79 (1H, d, *J* = 8.2 Hz, H^{5}), 6.68 (1H, d, *J* = 8.2 Hz, H^{4}), 6.66 (1H, dd, *J* = 10.1 Hz, *J* = 2.0 Hz, H^{8}), 6.00 (1H, dd, *J* = 10.1 Hz, *J* = 2.0 Hz, H^{9}), 4.51 (1H, app t, *J* = 1.7 Hz, H^{7}), 4.40 (1H,dd, *J* = 12.5 Hz, *J* = 1.7 Hz, H^{6a}), 4.32 (1H,dd, *J* = 12.5 Hz, *J* = 1.9 Hz, H^{6b}), 3.80 (3H, s, $OC\underline{H_3}$), 3.21-3.07 (1H, m, H^{11}), 2.94 (1H, dd, *J* = 17.7 Hz, *J* = 4.8 Hz, H^{3a}), 2.90-2.78 (3H, m, H^{2}, H^{10a}, H^{10b}), 2.52 (1H, ddd, *J* = 17.6 Hz, *J* = 2.2 Hz, *J* = 1.2 Hz, H^{3b}), 0.99-0.92 (21H, m, TIPSO),; ^{13}C NMR (125 MHz, CD_2Cl_2) δ_C 202.5, 196.0, 151.8, 146.9, 142.3, 129.1, 126.7, 122.2, 119.8, 111.6, 69.2, 68.9, 56.4, 47.9, 43.6, 38.3, 34.4, 27.9, 18.1, 17.9, 13.2; HRMS (ES^{+}) mass calc'd. For $C_{27}H_{38}O_5Si$: 470.2489, found $[M + NH_4]^{+}$ 488.2814. HPLC:DAICEL ADH Chiralpak, 9:1 Hexane/isopropanol, flow 1 ml/min, mixture of diasteroisomers, retention time: Diasteroisomer 1: enantiomer 1: 5.65 min; enantiomer 2: 7.65 min; Diasteroisomer 2: enantiomer 1: 9.42 min, enantiomer 2: 12.27 min.

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