PALLADIUM- AND GOLD-CATALYZED SYNTHESIS OF POLYHYDROXYLATED HETERO CYCLES WITH RESTRICTED CONFORMATIONAL MOBILITY

Dottorando
Dott. Martina Petrović-Hunjadi

Tutore
Prof. Ernesto G. Occhiato
DOTTORATO DI RICERCA IN SCIENZE CHIMICHE

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COORDINATORE Prof. PIERO BAGLIONI

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Settore Scientifico Disciplinare CHIM/06

Dottorando
Dott. Martina Petrović-Hunjadi

Tutore
Prof. Ernesto G. Occhiato

(firma)  (firma)

Coordinatore
Prof. Piero Baglioni

(firma)

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Abstract

The introduction of conformational restrictions into biologically active molecules is a commonly used strategy in drug design because locking the compound into its favourable binding conformation might enhance the potency and the selectivity, improve the pharmacokinetic profile and reduce the side effects. Polyhydroxylated piperidines, also known as iminosugars, are potent inhibitors of many carbohydrate-processing enzymes what makes them potential antiviral, anticancer and antidiabetic agents in different therapeutic areas as well as in agrochemical science. Among many naturally occurring iminosugars, deoxynojirimycin, swainsonine and castanospermine have been used as the starting point in the drug development for many years but due to the lack of selectivity or potency only few compounds have been progressed beyond the discovery phase.

The main challenge in the development of the iminosugars as therapeutic agents is to overcome promiscuous inhibition by modulating the selectivity and the potency toward given biological target. It has already been demonstrated that the use of cyclopropane and cyclopentane as conformational restrictions can help and therefore, the development of new synthetic methods for the construction of conformationally restricted N-heterocycles is essential for achieving additional diversity. In this thesis, the methodologies for merging a piperidine core and other N-heterocycles with cyclopropane and cyclopentane rings were explored.

In general, the synthesis of cyclopropane-fused piperidine core 4 presented within this thesis is based on the OH-directed Simmons-Smith cyclopropanation of corresponding enecarbamate ester 2 (Scheme 1). The different hydroxylated enecarbamate esters could be prepared through a Pd-catalyzed methoxycarbonylation of valerolactam-derived enol phosphates. To this end, enantiopure 5-hydroxy-piperidin-2-one and 4,5-dihydroxy-piperidin-2-one were prepared according to a previously developed methodology from commercially available (S)-(+) γ-hydroxymethyl-γ-butyrolactone and 2-deoxy-o-ribose, while racemic 5-hydroxy-6-hydroxymethyl-piperidin-2-one was prepared from δ-valerolactam.

Scheme 1. Synthesis of polyhydroxylated cyclopropane-fused piperidine core.

The fact that gold(I) catalysis has become a very powerful methodology for the construction of 5-membered rings, prompted us to explore the tandem gold(I)-catalyzed rearrangement/cyclization reactions of piperidine-derived enynyl acetates 6, 9 and 14. Among the explored methods, the tandem gold(I)-catalyzed [3,3]-rearrangement/Nazarov reaction of piperidine-derived enynyl acetates bearing a C-2 propargylic ester side-chain (6) was the most robust and reliable (Scheme 2). To understand the influence of the reaction conditions and substrate structural features the whole process was studied in details both experimentally and computationally. The scope and the limitations of the reaction were assessed by varying the substituents on the propargylic side-chain and on the piperidine ring as well as the N-heterocycle. Since the protected hydroxyl groups at C-5 and C-6 in substrate 6 were well tolerated in the gold(I)-catalyzed step, this method is then suitable for the synthesis of conformationally restricted iminosugars.
Scheme 2. Cyclopenta-fused piperidines 8 via gold(I)-catalyzed [3,3]-rearrangement/Nazarov cyclization.

The shift of the propargylic ester side-chain from position C-2 to C-3 of the piperidine ring (Scheme 3) influenced the reactivity of intermediate 10 thus giving the corresponding cyclopenta-fused product with alternate position of C=O group on the five-membered ring, although in moderate yield.


Instead, indole-derived enynyl acetates bearing a C-3 propargylic ester side-chain (12) provided 3,4-dihydro-cyclopenta[b]indol-1-ones (13) in excellent yields (15 examples, up to 84% yield). These cyclopenta[b]indoles possess a substitution pattern on the five-membered ring which allows an easy entry to the bruceollines and other natural products possessing the cyclopenta[b]indol-1-one nucleus.


Finally, modification of the propargylic moiety (14) allowed us the preparation of cyclopenta-fused compound with C=O group at the central position of the five-membered ring (Scheme 5).
Scheme 5. Gold(I)-catalyzed Rautenstrauch rearrangement of enynyl acetate 14.

All these pentannulated piperidines will be in future converted into novel polyhydroxylated conformationally restricted iminosugars and tested toward the suitable targets.
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Chapter 1: Conformational Restriction

The conformational restriction could be defined as any structural feature of the molecule that causes decreased freedom of molecular motion, particularly the rotation around the chemical bonds. The introduction of conformational restrictions is a well known and commonly used strategy in modern drug design to improve the selectivity and the potency of biologically active molecules, or to improve their pharmacokinetic and pharmacodynamic profile. In general, flexible molecules could be rigidified by introducing extended network of intramolecular hydrogen bonds or other weak interactions, bulky substituents, small rings such as cyclopropane, or by incorporating the flexible part of the molecule into a new ring.

However, this approach should not be oversimplified. When it comes to the thermodynamics of the binding, a flexible molecule has to adopt the active conformation in order to bind to the active site of the target enzyme or receptor. Adopting the binding conformation results in a decrease in entropy which consequently affects the free energy of the binding and thus lower the binding affinity. Assuming that the binding interactions are exactly the same, a molecule locked in its active conformation will bind to the active site without loss of the entropy.\(^1\)

\[
\Delta G = \Delta H - T\Delta S \\
\Delta G = -RT\ln K_i
\]

(\(\Delta G\) – the free energy of the binding; \(\Delta H\) – the energy of the binding interactions; \(\Delta S\) – the entropy; \(K_i\) – the binding affinity)

The conformation-constrained strategy has been used in drug discovery for many years and there are many examples in different research areas.\(^2\) Since the main focus of my research was to develop methodologies for merging cyclopropane and cyclopentane with piperidine rings with the potential of being converted into new conformationally restricted polyhydroxylated \(N\)-heterocycles, next chapter will focus on iminosugars and their conformationally restricted analogues.

References
Chapter 2: Polyhydroxylated N-Heterocycles (Iminosugars)

Iminosugars, whether of natural or synthetic origin, are small organic molecules that resemble monosaccharides; the oxygen atom within the pyranose ring has been replaced by the more basic nitrogen atom. Structurally, iminosugars are derivatives of pyrrolidine, piperidine, azepane, pyrrolizidine, indolizidine and nortropane (Figure 1). These mono- and bicyclic templates are typically substituted by hydroxyls, which makes them polyhydroxylated N-heterocycles, but many other functional groups such as carboxylic acids and amides could be present in both natural and synthetic analogues.

![Figure 1. General structures of iminosugars.](image)

Historically, iminosugars are known as very potent inhibitors of glycosidases, enzymes involved in many biologically important processes, such as intestinal digestion, post-translational processing of the sugar chain of glycoproteins and lysosomal catabolism of glycoconjugates.\(^1\) Hence, they have been used as lead compounds for the development of new therapeutic agents in a wide range of diseases such as diabetes, viral infections or lysosomal storage disorders.\(^2\) Among over two hundred of naturally-occurring iminosugars, deoxyxojirimycin, swainsonine and castanospermine have commonly been used as the lead compounds in the drug development process. Although the synthesis of iminosugar derivatives is very challenging because of the polar nature, the lack of UV chromophores and stereochemical complexity,\(^3\) many compounds have been synthesized and tested against many different biological targets but only few of them have been progressed to the clinical trials. The main limitation associated with the use of iminosugars is the lack of adequate selectivity which results to detrimental side effects for the therapeutic application.

Taking into account the amazing diversity of enzymes that could be inhibited by iminosugars and scientific tendency and effort to develop the perfect inhibitor for a specific enzyme, huge number of compounds have been synthesized and tested during the last 50 years.\(^4\) The purpose of the next section is just to emphasize the importance of conformational restrictions in the design of novel iminosugar analogues.

**NOTE:** According to the standard rules of carbohydrate nomenclature,\(^5\) the term “iminosugar” refers to the imino-analogue of glycoside. The anomeric hydroxyl could be replaced either by hydrogen to give “iminoalditol” or any other substituent to give “imino-C-glycoside”. Azasugars are the synthetic analogues of monosaccharides where the anomeric carbon has been replaced by a nitrogen atom and the oxygen by a methylene group.

![Image showing the structures of iminosugar, iminoalditol, imino-C-glycoside, and 1-Azasugar.](image)
2.1. Iminosugars as Glycosidase Inhibitors

Glycosidases, sometimes also called glycoside hydrolases, are enzymes responsible for the hydrolysis of the glycosidic bonds in complex carbohydrates and glycoconjugates. They can be classified into families on the basis of substrate specificity (glucosidase, mannosidase, maltase, etc.) and the mechanism of bond cleavage (inversion or retention of anomeric configuration).

In general, the putative mechanism of enzymatic hydrolysis of disaccharide involves the formation of an oxycarbocation, cleavage of the glycosidic bond and the charge neutralization.

Inosugars, as carbohydrate mimics, simulate the shape and the functionalities of the natural substrates in the ground or transition state. Factors that contribute to the transition state character of an iminosugar are half-chair conformation, proper relative configuration of hydroxyl groups, geometry at anomeric carbon, charge distribution, and the ability to be directionally protonated.

In general, the spatial arrangement of the hydroxyl groups is important for the recognition by specific glycosidase, whereas the nitrogen atom has an impact on the conformation and electrostatic properties of the molecule and hence the strength of the binding.

2.2. Conformational Restrictions in Iminosugars

The very first iminosugar isolated from natural source was nojirimycin. It was a good inhibitor of both α- and β-glucosidases, which was not very surprising given its structural resemblance to the D-glucose. However, due to the instability of hemiaminal function at neutral pH the use of nojirimycin and similar iminosugars is quite limited.

The removal of the hydroxyl group from the anomeric position via catalytic hydrogenation over PtO₂ or reduction of nojirimycin with NaBH₄ led to the formation of much more stable 1-
The finding of 1-deoxynojirimycin's biological activity as inhibitor of α-glucosidases by Bayer chemists in 1976 triggered an enormous interest in imino-analogues of glycosides. Since then, many of the analogues have been synthesized but also, due to the improvement of purification techniques and procedures more than 200 analogues have been isolated from different plants, bacteria, fungi and marine organisms.

1-Deoxynojirimycin (DNJ)   Glyset (Miglitol)   Zavesca (Miglustat)

**Figure 4.** 1-Deoxynojirimycin and its N-substituted analogues used in the treatment of type II diabetes (Glyset) and type I Gaucher disease (Zavesca).

Bicyclic iminosugars have attracted huge attention because of their high and specific glycosidase inhibitory activity which has been attributed to their rigid structure. Natural products of this class always possess a fused bicyclic system with nitrogen atom in the ring junction (Figure 5). It is worth to mention that many synthetic analogues have the bridgehead nitrogen whereas the examples where the nitrogen is not in the ring junction are very rare. A development of the methods for the pentannulation of piperidines and pyrrolidines would therefore enlarge the diversity of analogues.

Swainsonine   Castanospermine   Australine   Casuarine

**Figure 5.** Naturally occurring bicyclic iminosugars.

One of the most studied bicyclic iminosugars is castanospermine. It appears almost as a result of rational drug design; it is a more potent inhibitor of almond β-glucosidase than 1-deoxynojirimycin and it is inactive against yeast α-glucosidase. Structurally, castanospermine is a polyhydroxylated indolizidine analogue but also it could be seen as an analogue of 1-deoxynojirimycin where a conformationally restricted ethylene bridge is inserted between the hydroxymethyl group and the nitrogen. Structure – activity studies have shown that the incorporation of second ring forced the 6-hydroxyl group of deoxynojirimycin to be locked in axial position, this conformation being responsible for the observed higher enzyme specificity in comparison with monocyclic 1-deoxynojirimycin (Figure 6).

**Figure 6.** Castanospermine as conformationally restricted 1-deoxynojirimycin.

To further improve the potency and the selectivity of castanospermine, all four stereogenic centers have been systematically modified by inversion of the configuration, removed or transformed into other functional groups but all modifications were found to abolish the biological activity. The fact that the rigidification of flexible 1-deoxynojirimycin influenced the potency and the selectivity toward β-glucosidase stimulated the synthesis of conformationally restricted analogues with novel
bicyclic cores (Figure 7) such as 5-azacastanospermine (1), 2-oxacastanospermine (2), perhydrazaazulene (3), 1-aza-bicyclo[5.3.0]octane (4) and tetrahydropyridino-imidazole (5).

![Figure 7](image)

Figure 7. Polyhydroxylated N-heterocycles as iminosugar analogues.

### 2.2.1. Cyclopropane as Conformational Restriction

Jérôme Désiré and Michael Shipman incorporated a cyclopropane as a conformational restriction into deoxymannojirimycin. The cyclopropane moiety was introduced in highly selective Simmons-Smith cyclopropanation of imino glucal 7, prepared from tetra-O-benzyl-D-glucopyranose 6 in 7 steps (Scheme 6).

![Scheme 6](image)


To rationalize the stereoselectivity, the authors suggested that imino glucal 7 adopts a half-chair conformation in which the substituents at C-4 and C-5 adopt pseudo equatorial orientations. Carbenoid addition anti to the OBN substituent at C-3 accounts for the formation of the observed diastereomer. The deprotection of nitrogen and hydroxyls afforded conformationally constrained deoxymannojirimycin analogue 9 in quantitative yield as its hydrochloride salt. Based on the coupling constants of cyclopropane-fused piperidine 8, authors excluded the chair conformation. The biological tests revealed that, in comparison with 1-deoxynojirimycin, the introduction of cyclopropane did not improve the target inhibitory activity against α-mannosidase.

Laroche et al. used cyclopropane ring to conformationally restrain pyrrolidine-derived iminosugars 10 and 11, potent α-fucosidase inhibitors (Figure 8). They prepared a small library of spirocyclopropyl azasugars 12 and evaluated their inhibitory activities. Among tested compounds, compound 13 showed the best profile. Although weaker, compound 13 was more selective α-L-fucosidase inhibitor than analogues 10 or 11.
2.2.2. Cyclopentane as Conformational Restriction

In 2013, Marta Magdycz and Sławomir Jarosz merged the cyclopentane ring with a piperidine which resulted in new unnatural iminosugar derivatives 24 and 25 (Scheme 8). These compounds could be considered as castanospermine analogues with the nitrogen atom shifted from the ring junction to the 6-membered ring. The key intermediate, highly functionalyzed polyhydroxylated unsaturated aldehyde 19, was obtained in a Lewis acid-induced fragmentation of d-glucose-configured allyltin 18. A typical procedure for the preparation of sugar derived allyltin compounds starts with the conversion of partially protected hexose (d-glucose, d-galactose, d-mannose) or pentose (d-ribose, d-xylene) into homologated allylic alcohol (Scheme 7). The allylic alcohol is then converted into xanthates which undergo the thermal rearrangement into thiocarbonates. The thiocarbonate in the last step reacts with tributyltin hydride affording the allyltin sugar as a mixture of geometrical isomers, with the (E)-form strongly predominating.

Imine formed in acid-catalysed condensation between unsaturated aldehyde 19 and tosylamine underwent spontaneously hetero Diels-Alder cyclization giving the cyclopenta-fused piperidine derivative 21 in yield of 66% as a single stereoisomer.

Scheme 7. Synthesis of cyclopenta-fused piperidine derivative 21. Reagents and conditions: i) 1. Swern oxidation, 2. Ph₃P=CHCO₂Me, 3. DIBAL-H; ii) NaH, CS₂, MeI; iii) toluene, 110°C, 2 h; iv) Bu₃SnH, toluene, 110°C, 2 h; v) ZnCl₂; vi) TsNH₂, TsOH.
The cis-dihydroxylation of olefin 21 afforded diol 22 as a single stereoisomer in 85 % yield while the trans-dihydroxylation of 21 (formic acid/H₂O₂ then NaOH) afforded the mixture of two stereoisomeric diols in a 6 : 1 ratio in favour of 23 (Scheme 8). The deprotection afforded unnatural iminosugars 24 and 25 respectively.


In the same paper, the synthesis of azepane analogue 31 was described (Scheme 9). The reaction of unsaturated aldehyde 19 with hydroxylamine gave derivative 27 whose formation was rationalized through the 1,3-dipolar cycloaddition also known as olefin/oxime cyclization. The latter was then converted into tricyclic derivative 29 via allylation followed by ring closing metathesis. Osmylation of 29 under standard catalytic conditions gave diol 30. The cleavage of the O–N bond carried out with an excess of metallic zinc and the removal of the benzyl groups with sodium in liquid ammonia provided free polyhydroxylated aza-bicyclo[5.3.0]decane 31. Conformationally restricted iminosugars 24, 25 and 31 were tested against α-glucosidase, β-glucosidase, α-mannosidase and α-fucosidase but they did not show significant inhibitory activity.

Scheme 9. Synthesis of polyhydroxylated cyclopenta-fused azepane analogue 31. Reagents and conditions: i) NH₂OH; ii) allylation; iii) RCM; iv) OsO₄, NMO, THF/t-BuOH/H₂O; v) 1. Zn; 2. Na/NH₃, -78°C, THF.
There are some points related to this first synthesis of cyclopenta-fused piperidine and azepane cores which should be emphasized. Although not very long, the reaction sequence comprised the use and the synthesis of nasty sulphur and tin derivatives. The hydroxyl groups on the 5-membered ring are coming from the starting material and therefore their number and the stereochemistry are defined in starting sugar. The type of the ring fusion depends on the cyclization reaction; Diels-Alder reaction of 20 afforded trans cyclopenta-fused piperidine, while 1,3-dipolar cycloaddition of 26 led to the formation of cis cyclopenta-fused azepane. Furthermore, the synthesis of derivatives bearing alkyl chain at C-2 position is not straightforward, whereas reductive amination and alkylation of nitrogen are an easy entry to the new derivatives.

2.3. Conformational Restrictions in Azasugars

Azasugars are the synthetic analogues of monosaccharides where the anomeric carbon has been replaced by a nitrogen atom and the oxygen by a methylene group. In 1994 Bols et al. designed and prepared isofagomine (32), an isomer of natural product fagomine, as a potential transition state-like analogue inhibitor of glycosidase enzymes. Isofagomine turned out to be very potent inhibitor of β-glucosidase and glycogen phosphorylase (Table 1).

Table 1. Kᵢ values in μM of deoxynojirimycin (DNJ) and isofagomine (32) toward various glycosidases.

<table>
<thead>
<tr>
<th>Enzyme inhibition IC₅₀ (μM)</th>
<th>α-glucosidase (yeast)</th>
<th>β-glucosidase (almond)</th>
<th>Isomaltase (yeast)</th>
<th>Glucoamylase (a. Awamori)</th>
<th>α-mannosidase (jack bean)</th>
<th>Glycogen phosphorylase (pig liver)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNJ</td>
<td>25</td>
<td>47</td>
<td>11</td>
<td>9.8</td>
<td>270</td>
<td>55000</td>
</tr>
<tr>
<td>32</td>
<td>86</td>
<td>0.11</td>
<td>7.2</td>
<td>3.7</td>
<td>770</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Since then, Bols’s group prepared deoxyisofagomine analogues, analogues with other substituents at positions 3, 4, 5 and 6, analogues bearing nitrogen and oxygen at position 2, but the inhibitory activity was not significantly improved.

Figure 9. Isofagomine in proposed binding conformation and its synthetic analogues.

With the aim of investigating the binding conformation of isofagomine to α-and β-glucosidase, Bols’s group opted to conformationally restrict isofagomine into its boat conformations (33 and 34) using 6-azabicyclo[3.1.0]hexane ring system (Figure 9). The compounds 33 and 34 were tested against α- and β-glucosidase and since they did not show significant inhibitory activity the conclusion is that isofagomine does not bind the investigated glycosidases in the boat conformation.
In addition, Schoenfeld et al.\textsuperscript{30} prepared conformationally restricted 1-azasugars 35 and 36 as mimetics of d-galactose and d-mannose (Figure 10). Both 35 and 36 were tested against yeast α-glucosidase, almond β-glucosidase, green coffee bean α-galactosidase, bovine liver β-galactosidase, and jack bean α-mannosidase. Despite its resemblance to the galactose, racemic 35 had no effect on any of the enzymes while racemic 36 inhibited α-mannosidase only.

![Figure 10. Galactose and its conformationally restricted analogues.](image)

References


Chapter 3: Homogeneous Gold Catalysis: Gold(I)-Catalyzed Pentannulation

“While the ancient alchemists investigated the question of how to make gold, now the question is what to make with gold”

Stephen K. Hashmi

Gold is a precious metal unaffected by air, moisture and most corrosive reagents. Through the centuries the primary use of the gold was making the jewellery and ornamental objects to unveil the wealth and power. Due to its chemical resistance and conductivity, from 20th century it has been widely used in electronic industry as a thin layer coating for electrical connectors, switches and relay contacts, connecting wires and connection strips.

In the field of the catalysis, gold was traditionally considered to be catalytically inactive because of its inertness in elemental state. Since the beginning of the 1970’s the area of heterogeneous gold catalysis has been developing, but until 20 years ago only a few chemists dared to use gold for the catalysis of organic reactions under homogeneous conditions. All changed in 1998 when Teles et al. of BASF described cationic gold(I) complexes as highly efficient catalysts for the addition of alcohols to alkynes. Since then the chemists around the world changed their view of gold and the number of methodological and mechanistic studies on gold-catalyzed organic reactions has been rapidly increasing.

For example, gold(I) complexes have been proven to efficiently catalyse the cycloisomerization reactions of 1,n-enynes, enynes bearing propargylic carboxylates or ethers, addition of N, O, S and C nucleophiles to the C-C multiple bonds, hydroarylation reactions, hydrogenation of C-C multiple bonds and activation of sp, sp² and sp³ C-H bonds. Owing to the mild reaction conditions, high atom economy, high functional group tolerance and often increase in molecular complexity, some of these recently developed methods have found application in the synthesis of natural products.

Although there are examples of the transformations catalyzed by gold(III) complexes under homogenous conditions, this chapter is intended to give only the general aspects of gold(I) catalysis without focusing on a particular transformation and a personal selection of gold(I)-catalyzed pentannulations.

3.1. Gold(I) Catalyst Systems

Commonly used gold precatalysts are commercially available as a bench stable LAu(I) halides where L is spectator ligand such as phosphine, phosphite, phosphoramidite or NHC-carbene. These linear covalent complexes are catalytically inactive and have to be activated (Figure 1).

![Figure 1. Gold(I) precatalysts (R = alkyl or aryl; R' = alkyl).](image-url)
The dominant method for the generation of catalytically active cationic gold species $[\text{LAu}]^+$ is in situ anion metathesis between LAuCl complexes and silver salts whose anion does not coordinate strongly to the gold center such as AgSbF$_6$, AgBF$_4$, AgNTf$_2$, AgPF$_6$ or AgOTf. Formed gold species enters catalytic cycle by ligand exchange with unsaturated substrate (Scheme 1).

$$\text{LAuCl} + \text{AgX} \rightarrow [\text{LAu}]^+\text{X}^- + \text{AgCl}$$

Scheme 1. Formation of catalytically active gold(I) species by an anion exchange between gold(I) chloride and silver salt ($X = \text{SbF}_6, \text{BF}_4, \text{NTf}_2, \text{PF}_6$ or OTf).

Although this two component catalytic system is quite easy to handle and many gold and silver salts are readily available, it suffers from several limitations. For example, silver salts are poorly soluble in organic solvents, light sensitive and highly hydroscopic causing the difficulties during the weighing. Due to the high affinity of the silver toward the gold and the chloride, less reactive gold intermediates could be formed during the anion metathesis.$^5$ In addition, there is the evidence that silver chloride formed as the by-product in anion exchange has an impact on the rate and the selectivity of some gold(I)-catalyzed reactions$^8$ and therefore the alternative, silver-free methods for catalyst activation are developed.

For example, the use of AgNTf$_2$ as a source of very weakly coordinating anion enabled the isolation of cationic LAuNTf complexes free of silver.$^9$ Copper salts,$^{10}$ TfOH$^{11}$ as well as alkali metal salts of borates$^{12}$ have all successfully been used as activating reagents for LAuCl precatalyst.

A very attractive alternative to anion metathesis is the protonolysis of alkyl gold (LAu-CH$_3$),$^{14}$ phthalimide gold (LAu-Pht)$^{15}$ and gold hydroxide (NHC-Au-OH)$^{16}$ precatalysts with Brønsted acids such as TfOH, MsOH, TfaNH, HBF$_4$ or H$_3$PW$_{12}$O$_{40}$.

**Figure 2.** Commonly used achiral and chiral gold(I) species (for example $X = \text{SbF}_6, \text{OTf, NTf}_2$).
The reactivity and the selectivity of gold could be easily tuned by the choice of the ligand. For example, while gold(I) complexes containing phosphine ligands are more electrophilic than those with electron-donating \(N\)-heterocyclic carbene ligands, complexes bearing phosphite ligands are the most electrophilic species. The use of dinuclear gold(I) complexes \(\text{LAu}_2\text{Cl}_2\) bearing the chiral diphosphine ligands led to the development of efficient asymmetric gold-catalyzed transformations. The effect of an aurophilic interaction between gold centres in \(\text{LAu}_2\text{X}_2\) on the enantioselectivity remains to be elucidated.

Although there is no guideline to the optimum choice of the counterion and a certain degree of screening is still necessary, the influence of the counterion on the chemoselectivity, regioselectivity and stereoselectivity is well documented in literature and has been recently reviewed.\(^{17}\)

![Figure 3. Chiral counterion used in asymmetric gold-catalysis.](image)

Gold-catalyzed reactions could be carried out in a wide range of organic solvents among which halogenated solvents (DCM, DCE, CHCl\(_3\)) and arenes (toluene, benzene) are the most abundant.

### 3.2. Gold as a “Soft” Lewis Acid (\(\pi\)-acidity)

According to the general definition of Lewis acid, every metal cation and metal cationic complex belongs to this category. The species capable to accept the electron density from C-C multiple bonds and therefore making them electrophilic are “soft” Lewis acids or \(\pi\)-acids. Among the late transition metals, gold(I) is the most effective in electrophilic activation of unsaturated systems. This strong \(\pi\)-acidity\(^{18}\) and consequently the observed reactivity are related to strong relativistic effect; the contraction of the 6s and 6p orbitals and the expansion of the 5d orbitals.\(^{19}\) While the contraction of 6s orbitals results in strong L-AuX bond, expanded d orbitals have diffused character that ensures high affinity for the \(\pi\)-systems. Calculations on Au(I) – ethylene and Au(I) – ethyne complexes\(^{20}\) indicate that the largest bonding contribution has the overlap between the \(\pi\)-system with a gold d orbital of suitable symmetry. Some back-donation occurs due to the overlap between filled Au 5d orbitals and lower-energy non-bonding p-orbitals of \(\pi\)-system. Thus, the strong electron donation of \(\pi\)-system to the Au(I) and weak back-bonding from Au(I) into \(\pi\)-system render these complexes electron deficient and prone to the nucleophilic addition.

### 3.3. Gold(I) Catalytic Cycle

In general, all homogeneous gold(I)-catalyzed reactions are initiated by the coordination of C-C multiple bonds to the cationic gold centre. As a soft \(\pi\)-acid, gold(I) is not very selective in the coordination of the multiple bonds and therefore coordinates to alkynes, allenes, alkenes and arenes but the formed \(\pi\)-complexes show significant difference in the reactivity.\(^{21,22}\) In other words, the
pronounced alkynophilicity of the gold is not related to the coordination preference for the triple bond but to the high reactivity of the formed alkyne-gold complex. Since the alkyne-gold complex is the most reactive it is used to describe the general gold(I) catalytic cycle (Figure 4).

![Figure 4. General mechanism of gold(I)-catalyzed transformations.](image)

As a very electrophilic species, formed alkyne-gold complex immediately undergoes nucleophilic attack in either intra- or intermolecular fashion. In most cases an anti attack takes place resulting in the formation of the trans alkenyl-gold intermediate. The experimental evidences and computational studies suggest that depending on the type of the gold ligand and the substrate, formed organogold intermediate can exist as gold coordinated carbocation or gold stabilized carbene. Depending on the exact nature of that gold intermediate, various rearrangements, fragmentations, eliminations or additions are possible.

The final step of the gold(I) catalytic cycle is the protodeauration where gold is replaced by hydrogen and thus regenerated. There are many examples in literature where instead of the replacement with hydrogen gold is replaced by other electrophiles such as iodine or electrophilic C-atoms.

In gold catalyzed reactions either the electrophilic activation or the protodeauration could be the rate determining step, and both could be controlled by the choice of the ligand. While electron-poor ligands will accelerate the electrophilic activation, protodeauration will be accelerated by electron-rich ligands. Furthermore, the additives which are hydrogen bond acceptors such as DMPU, pyridine N-oxide and benzotriazole can efficiently promote the protodeauration.

3.4. **Gold(I) Deactivation**

The drawback of many gold-catalyzed reactions is the relatively high catalyst loading or low turnover number due to the disproportionation of active gold(I) species. Although cationic complex [LAu]\(^+\)X is relatively stable in itself, when unsaturated systems are present it decays at fast rates into non-reactive Au(0) and [L\(_2\)Au]\(^+\) species.

The detailed experimental study on the deactivation of cationic gold\(^25\) has shown that the choice of the ligand and the counterion has an enormous effect on the stability of cationic gold in reaction media. In general, the use of electron-rich ligands could enhance the stability of cationic gold. While electron-donating ligands could have a detrimental effect on reactivity, ligands containing a \(\sigma\)-biphenyl steric handle can reduce the decay without influencing the reactivity.
The turnover number of gold catalyzed reactions could be significantly reduced due to the poisoning of the active catalyst by the halides, bases and other high gold affinity impurities present in solvents, drying agents and substrates. Kumar et al. demonstrated that the portion of catalyst deactivated in this way could be regenerated by suitable acid activator such as TfOH and In(OTf)3.26

3.5. Pentannulations Using Alkynes

3.5.1. Rearrangements of Propargylic Carboxylates and Acetates

In general, propargylic esters and acetals are versatile substrates for gold(I) catalysis (Figure 6). After the electrophilic activation of the alkyne, the carbonyl unit acts as the nucleophile and based on the substitution pattern undergoes 1,2- or 1,3-migration through 5-exo-dig or 6-endo-dig cyclization.

When terminal alkynes are used 1,2- migration of the acetate affords vinyl metal species which can result in the formation of the “carbenoid” species. In contrast, internal alkynes undergo 1,3-acyloxy migration to form allenyl acetate, which can be additionally activated in the presence of the metal catalyst. Once formed, the gold vinyl carbenoid species or allene-gold complex can react in inter- or intramolecular fashion giving complex skeletons in a step economic way.

**Pentannulations triggered by Au(I)-catalyzed 1,2-migration**

Toste’s group explored the gold(I)-catalyzed isomerisation of indole-derived propargyl acetate 1 and acetal 4. Propargyl acetate 1 underwent gold(I)-catalyzed Rautenstrauch rearrangement giving the cyclopenta[b]indole 3 in good yield but in poor enantioselectivity even when chiral phosphine ligands were used because the reaction was under the control of chiral transition state 3 (Scheme 2).
Scheme 2. Rautenstrauch rearrangement of indole-derived propargylic acetate 1. Used catalysts and ee values: Ph₃PAuC!/AgSbF₆ (72% yield), [(S)-DTMB-Segphos](AuCl)₂/AgSbF₆ (9% ee), [(S)-DTMB-MeO-biphep(AuCl)₂/AgSbF₆ 38% ee).

Replacing the acetate by acetal functionality (Scheme 3), the cleavage of the C-O bond in oxonium species 5 became rapid and gave planar gold-intermediate 7 whose cyclization was under control of the chiral phosphine ligand and allowed the synthesis of cyclopenta[b]indoles in excellent enantioselectivities.²⁷

Pentannulations triggered by Au(I)-catalyzed 1,3-migration

In 2004, Zhang and Wang demonstrated that electrophilic activation of 1,3-enynes bearing propargylic carboxylate (9) triggers 1,3-acyloxy migration and gives pentadienylic cation 10 that undergoes Nazarov cyclization (Scheme 4).^28^ Selective protodeauration of Au-containing cyclopentenylic cation led to the formation of acetate 13 which can hydrolyse spontaneously under the reaction conditions giving the cyclopentenone 14. Mild reaction conditions, good functional group tolerance and excellent control of the double bond position in the cyclopentenone ring render this method an attractive approach for the synthesis of pentannulated carbocycles such as 15 and 16.

Malacria’s group showed that in case when the side-chain (\(R^3\)) bears alkene functionality, the cyclopentadienyl gold species 11 (in resonance with gold carbene 12) could undergo an electrophilic cyclopropanation giving rise to valuable polycyclic compounds.^29^ Thus, starting from enynyl acetates 17, tetracyclic 19 was prepared in one single step, in excellent yield and as a single diastereomer (Scheme 5). Furthermore, cycloisomerization of enantioenriched substrates led to the formation of enantioenriched products.

In addition, gold(I) was efficient in the synthesis of indenes (Scheme 6).^30^ Electrophilic activation of aryl derived propargylic acetates 20 triggers 1,3-acyloxy migration followed by hydroarylation. While the reaction of \(\text{para}\)-substituted arenes was chemoselective, \(\text{ortho}\)-substituted arenes and terralary acetates led to the formation of indenes 23 as minor products.

3.5.2. Oxidative Reactions of Alkynes

In general, alkynes could be oxidized via gold(I)-catalyzed addition of nucleophilic oxygen from oxidants such as sulfoxides, pyridine N-oxides, nitrones, as well as nitroso- and nitrobenzenes (Scheme 7, $Z = \text{S and N}$). The cleavage of $Z-O$ bond gives very electrophilic $\alpha$-oxo-gold carbene that could be trapped in intra- or intermolecular fashion by different nucleophiles. From a general point of view the formation of $\alpha$-oxo-gold carbene is favoured by strongly $\sigma$-donating and weakly $\pi$-acidic ligand in combination with a highly electron-deficient leaving group.

Scheme 7. General mechanism of Au(I)-catalyzed alkyne oxidation. DMSO, pyridine $N$-oxide, piperidine-derived nitrone and nitrobenzene as examples of oxidant species $Z^*\text{-O}^-$. 

In 2011, Liu’s group demonstrated that the alkyne substitution influences the oxidation step (Scheme 8). In case of terminal alkynes the oxidation was favoured at the C-2 alkynyl carbon atom (25) while aminoalkynes preferred the oxidation of C-1 carbon atom (26).
Two years later, the same group showed that α-oxo-carbene intermediate 30 reacts reversibly with 8-methylquinoline (Z, by-product of alkyne oxidation) to generate adduct 31 (Scheme 9). The ylide intermediate 32, formed from 31 after dissociation of the gold, undergoes intramolecular [3+2] cycloaddition with electron-deficient alkene affording polycyclic derivative 33. To suppress the formation of cyclopropyl indanone as the side-product external 8-methylquinoline was added.

Scheme 9. Gold-catalyzed oxidative cycloaddition of 1,5-enynes to quinolone.

3.5.3. Pentannulations via Dual-Gold Catalysis

A new reactivity pattern of Au(I) in which two gold centres synchronously activate a diyne system (Scheme 10) was independently described by Zhang and Hashmi. Initially, one gold(I) species coordinates the terminal alkyne forming a gold–acetylide 34 whereas the other acts as π-Lewis acid activating the disubstituted triple bond. Nucleophilic addition of gold-acetylide to the previously activated triple bond in a 5-endo-dig fashion will generate highly reactive gold–vinylidene 36 which undergoes C(sp^3)–H insertion and protodeauration to form tricyclic product 38.
Dual-gold catalyzed cyclization of 3,4-substituted thiophenes 39 resulted therefore in new pentaleno[cc]thiophene scaffold 40. Different alkanes were tolerated in C(sp$^3$)-H insertion leading to the tricyclic, tetracyclic or spirocyclic products in moderate to high yields (Scheme 11).

When sulfonamide or OH groups were present in one alkyne chain of starting dialkyne, gold vinylidene 36 inserts readily into N-H and O-H leading to the formation of tricyclic pyrrole 42 or furan 44 (Scheme 12). The choice of the catalyst and the base were crucial for this transformation; BrettPhos ligand in a combination with weak base like pyridine N-oxide was superior catalytic system.
3.5.4. Pentannulations Triggered by Addition of Heteronucleophiles to Alkynes

Once the alkyne is activated it can undergo addition of O- or N-nucleophile in inter- or intramolecular fashion. Trapping the vinyl gold intermediate with an electrophile other than proton allows the formation of new bonds and thus increasing the molecular complexity of the product. This strategy has often been used for the synthesis of cyclopenta-fused heterocycles.

For example, indenoindoles 49 were prepared by tandem gold(I)-catalyzed cycloisomerization/Friedel-Crafts alkylation from 2-aminophenylpropargylic alcohols 45 (Scheme 13). The reaction started with the intramolecular addition of the N-nucleophile to the Au(I)-activated triple bond in a 5-exo-dig manner. The protodeauration of 47 followed by intramolecular Friedel-Crafts alkylation afforded indenyl-fused indoles.

Scheme 13. Tandem cycloisomerization/Friedel–Crafts alkylation.

Cyclopenta[b]indoles 53 were prepared from 2-aminophenyl propargylic secondary alcohols 49 via Au(I)/Brønsted acid catalyzed sequential one-pot two-step process (Scheme 14). Once indoline 50 was formed, the addition of a Brønsted acid promoted the formation of an indolylmethyl cation which was trapped by the 1,3-dicarbonyl compound. The reaction displayed significant tolerance towards various alkynols bearing electron-donating and electron-withdrawing aryl groups, heteroaryls and the alkyl groups (R1 and R2). Furthermore, alkyl and aryl-bearing 1,3-diketones, 1,3,5-triketones, β-ketoesters and β-ketoamides were also well tolerated under the reaction conditions.
Scheme 14. Au(I)/Brønsted acid catalyzed tandem process.

In case $R^2$ is alkene, under the acidic conditions indolinole 55 is transformed to pentadienyl cation which undergoes Nazarov cyclization (Scheme 15).\(^{39}\)

Scheme 15. Au(I)/Brønsted acid catalyzed hydroamination/Nazarov cyclization.

In 2013, Zi and Toste demonstrated that cyclopentannulated compounds could be obtained in carboalkoxylation of alkynes with high enantioselectivity and excellent yields (Scheme 16).\(^{40}\) Mechanistic studies suggested that coordination of the chiral cationic gold(I) complex $L(AuCl)_2$ to the alkyne moiety followed by alkoxylation led to the chiral intermediate 58. Rearrangement to the achiral oxocarbenium intermediate 59 enabled the cyclization under the control of the chiral catalyst.
3.6. Pentannulations Using Allenes

Differently substituted cyclopenta[b]indoles 62 were prepared in good yields via selective electrophilic activation of 3-allenyldiones 61 (Scheme 17). As for the mechanism, the authors suggested intramolecular addition of the indole to the gold-activated allene intermediate followed by deprotonative rearomatization and protodeauration.

In addition, 3-allenyldione bearing terminal allene underwent regioselective Au(I)-catalyzed imino-Nazarov cyclization giving indole-fused cyclopentenamides 64 (Scheme 18).
Scheme 18. Au(I)-catalyzed imino-Nazarov reaction.

Under the gold(I) catalysis, indole bearing allene side-chain (65) underwent [3+2] cycloaddition reaction affording indole-fused tricyclic system 69 with several contiguous stereocenters in an atom-economical way. A plausible mechanism involves the allene activation, nucleophilic attack of indole onto the Au-allene complex and formation of the product through tandem cyclization, hydride migration and an elimination process through cationic intermediate 67 and Au-carbene intermediate 68 (Scheme 19).


While gold(I)-catalyzed pentannulation of indoles bearing structurally different unsaturated side-chains at C-2 or C-3 position is a widely explored research area, the examples of gold(I)-catalyzed pentannulation of other N-heterocycles are very rare. For instance, the cyclic enamides bearing a propargylic or allene moiety at position C-2 or C-3 have never been exposed to the gold(I) catalysis and therefore their behaviour is unknown. The fact that these substrates would allow an easy entry to cyclopenta-fused N-heterocycles, prompted us to explore if and how the presence of the nitrogen atom influence the rate and the regiochemical outcome of tandem gold(I)-catalyzed rearrangement/cyclization reactions.

References


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Scope of the Work

Taking into account the benefits of conformational restrictions in drug development, especially when incorporated into promiscuous molecules to improve selectivity, the methodologies for merging piperidines and other N-heterocycles with cyclopropane and cyclopentane rings have been explored. The synthesis of the cyclopropane-fused piperidine core is based on OH-directed Simmons-Smith cyclopropanation of corresponding enecarbamate esters, an approach which has already been used in our group to prepare conformationally restricted piceolic acids. Within this thesis, relying on this approach, dihydroxylated piperidine was successfully merged with a cyclopropane ring.

![Figure 1. Polyhydroxylated cyclopropane-fused piperidine derivatives synthesized within this thesis.](image)

Another approach toward conformationally restricted piperidines and other N-heterocycles is based on merging the heterocyclic core with a cyclopentane and for this purpose we exploited tandem gold(I)-catalyzed rearrangement/electrocyclization processes. Suitably assembled piperidine-derived enynyl acetates 4-6 undergo gold(I)-catalyzed tandem processes giving rise to pentannulated piperidines 7-9.

![Scheme 1. Synthesis of cyclopenta-fused piperidines via gold(I)-catalyzed tandem rearrangement/cyclization processes explored within this thesis.](image)

In a view of possible application to the synthesis of conformationally restricted polyhydroxylated N-heterocycles, the gold(I)-catalyzed tandem [3,3]-rearrangement/Nazarov cyclization of 4 is the most general and robust method. In addition, simple and preliminary chemical modifications of 7 (Figure 2), such as hydrogenation of double bond, reduction of carbonyl group and α-hydroxylation, were carried out in high diastereoselectivity.
Furthermore, gold(I)-catalyzed pentannulation of $N$-heterocycles would represent a new synthetic approach to cyclopenta-fused piperidines, azepanes and indoles, core structures of many natural products. The synthetic potential of this methodology was demonstrated in this thesis by the first total synthesis of bruceolline H.

Finally, with the aim to transfer the solution phase synthesis of piperine derivatives to the solid support, diazenyl protected $\delta$-valerolactam 14 was synthesized in solution via RuO$_4$ catalyzed oxidation of triazene 13. This oxidation, successfully extended to other diazenyl-protected $N$-heterocycles (pyrrolidine, azepane), presents a new entry to functionalized lactams.
Results and Discussion

Chapter 4: Synthesis of Polyhydroxylated Cyclopropane-Fused Piperidines

The general approach for the synthesis of polyhydroxylated cyclopropane-fused piperidine analogs is shown in Scheme 1 and entails the conversion of suitably functionalized enantiopure or racemic lactams 4 into the corresponding enecarbamate esters 3 by means of Pd-catalyzed methoxycarbonylation of the lactam-derived enol phosphates, followed by the stereoselective, OH-directed cyclopropanation. To demonstrate the suitability of this approach in the synthesis of polyhydroxylated derivatives, enantiopure lactam 7 was transformed into a series of cis-4,5-dihydroxy cyclopropane-fused piperidines.

![Scheme 1](image1)

Scheme 1. Retrosynthetic analysis for the synthesis of polyhydroxylated cyclopropane-fused piperidines.

Just as a mention, on the basis of this approach 4-hydroxy-substituted cyclopropane piperic acid methyl ester 5 and all four stereoisomers of 5-hydroxy piperic acid derivative 6 have already been prepared and used as conformationally restricted templates for linear and cyclic peptidomimetics.

![Scheme 2](image2)

Scheme 2. 4-OH and 5-OH-cyclopropane-fused piperidines as templates for peptidomimetics.

As we have seen in previous chapters, to affect the selectivity and activity, the conformational restriction has to lock an active molecule into its favourable binding conformation. In case of iminosugars and their analogs that means the right position and the right orientation of hydroxyls on the N-heterocyclic core. Therefore, for the success of the aforementioned approach, the availability of polyhydroxylated enantiopure or racemic lactams is of the crucial importance.

![Scheme 3](image3)

Scheme 3. Examples of different di- and trihydroxylated δ-valerolactams.

Taking into account the importance of 6-substituted trans-5-hydroxypiperidin-2-ones 8 as the key intermediate in the synthesis of piperidine alkaloids, we decided to investigate if the methodology applied to the synthesis of both enantiomers of trans-3-hydroxy-piperic acid combined with the
oxidation of $N$-tosyl protected piperidines 10 and 11 into corresponding lactams 12$^9$ and 13$^{10}$ could furnish protected lactam 14.

![Scheme 4](image)

Scheme 4. The oxidation of sulfonamines into sulfonamides as the final step in the synthesis of lactam 14.

4.1. Syntheses of Hydroxylated Lactams

Enantiopure cis-4,5-dihydroxy δ-valerolactam 7 was prepared from commercially available 2-deoxy-L-ribose in 4 steps in overall yield of 36 % according to previously established procedure (Scheme 5)$^4$. Oxidation of 2-deoxy-L-ribose with Br$_2$ in water for 5 days led to the formation of 2-deoxy-$d$-ribonolactone 18 in good yield (75 %) after chromatography. In the next step, the treatment of lactone 18 with 4-toluenesulfonyl chloride in pyridine at $-15$ °C and then leaving the reaction mixture at 0 °C for 7 h, led to the isolation of corresponding primary O-tosyl derivative 19 in 57 % yield after chromatography. Nucleophilic substitution of tosylate with azide was accomplished using NaN$_3$ in acetonitrile at reflux for 18 h in 90 % yield. Hydrogenation of obtained azido-L-ribonolactone 20 at atmospheric pressure over 10 % Pd/C gave pure dihydroxylated lactam (4R,5S)-7 in 95 % yield.

![Scheme 5](image)

Scheme 5. Synthesis of enantiopure cis-4,5-dihydroxylated lactam 7. Reagents and conditions: (a) Br$_2$, H$_2$O, 5 days (75 %); (b) TsCl, pyridine, $-15$ - 0 °C, $\sim$ 7h (57 %); (c) NaN$_3$, 15-crown-5, ACN, reflux, $\sim$ 18h (90 %); (d) H$_2$, Pd/C, MeOH, rt, 16h (95 %).

Starting from commercially available $d$-pipelic acid, protected 6-(hydroxymethyl)piperidin-2-one 13 was prepared in 5 steps in 40 % overall yield (Scheme 6). Thus, conditions for the synthesis of more complex analogue 14 were tested and optimized. The final and the key step of the sequence, the RuO$_4$-catalyzed oxidation of sulfonamine 11, was achieved in moderate but acceptable yield of 55 %. In the past, both enantiomers of 6-(hydroxymethyl)piperidin-2-one bearing different protecting groups
have been prepared many times using starting material from the chiral pool,\textsuperscript{11} but also relying on asymmetric transformations of achiral synthons.\textsuperscript{12} 

![Diagram of Scheme 6](image)

**Scheme 6.** Synthesis of enantiopure protected lactam 13. Reagents and conditions: (a) SOCl\textsubscript{2}, MeOH, 0 °C, 3 h (98 %); (b) TsCl, Et\textsubscript{3}N, DMAP, DCM, r.t., on (84 %); (c) LiBH\textsubscript{4}, THF, r.t., on (95 %); (d) TBSCl, imidazole, THF, r.t., on, (97 %); (e) RuO\textsubscript{2}-nH\textsubscript{2}O, NaIO\textsubscript{4}, EtOAc/H\textsubscript{2}O, r.t., on (55 %).

The protection of δ-valerolactam followed by the transformation into corresponding phosphate and the Suzuki coupling with 2-furanyl boronic acid afforded the enesulfonamide 24 (Scheme 7). Surprisingly, the product was unstable and it was isolated in only 60 % yield over two consecutive purifications. The next step, hydroboration/oxidation carried out with BH\textsubscript{3}/DMS/NaOH at room temperature, provided racemic alcohol 25 in moderate yield (44 %) which was protected as silyl ether. The expected trans stereochemistry in 25 was assigned on the basis of coupling constant values for protons at C-2 and C-3, which appear as broad singlets at δ = 5.17 and 4.24 ppm, respectively, in the \textsuperscript{1}H NMR spectrum because of their equatorial orientation. Consequently, both the furyl and OH groups are axially oriented.

![Diagram of Scheme 7](image)

**Scheme 7.** Synthesis of lactam 30. Reagents and conditions: (a) 1. n-BuLi, THF, -78 °C, TsCl (86 %), 2. KHMDS, -78 °C, 1.5 h; then (PhO)\textsubscript{2}POCl, -78 °C, 1 h (80 %), 3. (Ph\textsubscript{3}P)\textsubscript{2}PdCl\textsubscript{2}, 2-furanyl boronic acid, Na\textsubscript{2}CO\textsubscript{3}/THF, 40 °C, 2 h (70 %); (b) 1. (CH\textsubscript{3})\textsubscript{3}S-BH\textsubscript{3}, THF, 25 °C, on, 2. EtOH, H\textsubscript{2}O\textsubscript{2}, NaOH, 1 h, reflux (43 %); (c) TBSOTf, DIPEA, DCM, r.t., on (93 %); (d) 1. RuO\textsubscript{2}-nH\textsubscript{2}O, NaIO\textsubscript{4}, EtOAc/H\textsubscript{2}O/ACN, r.t., 25 min, 2. Cs\textsubscript{2}CO\textsubscript{3}, Mel, DMF, 25 °C, 16 h (68 %); (e) DIBAL-H, THF, 0 °C, 1 h (57 %); (f) TBSCl, imidazole, DCM, 25 °C, 16 h (83 %); (g) RuO\textsubscript{2}-nH\textsubscript{2}O, NaIO\textsubscript{4}, EtOAc/H\textsubscript{2}O, 25 °C, 24 h (74 %).
In next step, the furyl ring in 26 was oxidized under standard oxidative conditions. The reaction was carried out with catalytic amount of RuO$_2$·nH$_2$O using 5 eq of NaI0$_4$ as co-oxidant in EtOAc/H$_2$O mixture. The $^1$H NMR analysis of crude reaction mixture showed desired carboxylic acid in a mixture with unidentified impurities. Since all attempts to purify resulting carboxylic acid on silica gel and direct reduction to the alcohol 28 failed, the crude carboxylic acid was immediately subjected to esterification in DMF using Cs$_2$CO$_3$ and Mel. Methyl ester 27 was reduced to corresponding alcohol 28 which was protected as silyl ether (29) in next step. Oxidation of sulfonamine 29, the final step of the synthesis, was carried out under previously optimised conditions giving valerolactam 30 in yield of 74%.

4.2. Cyclopropanation


Enantiopure (4R,5S)-7 was chosen as the model substrate to set up the methodology for the synthesis of polyhydroxylated cyclopropane-fused piperidine derivatives.

First, hydroxy groups were protected as acetonide in 75 % yield (Scheme 8) and then the nitrogen atom was protected as benzyl carbamate (83 %). Protected valerolactam 32 was transformed into enol phosphate 33 by treatment with potassium bis(trimethylsilyl)amide (KHMDS) at -78 °C in THF followed by the addition of diphenylchlorophosphate. Palladium-catalyzed methoxycarbonylation reaction of phosphate 33, carried out in anhydrous DMF at 1 atm of CO at 75 °C in the presence of an excess of MeOH, led to the formation of enecarbamate ester 34 in 72 % yield over two steps. The deprotection of 34 to obtain intermediate 35 had to be performed very carefully, with a strict control of both reaction times and acidity to avoid epimerization at C-4 giving epi-35 through the formation of the allylic carbocation. The reaction was thus carried out with trifluoroacetic acid (TFA) in a mixture with a chloroform and water in 1 : 5 : 0.1 ratio, respectively, and stopped after 10 min, to provide a 1 : 1 mixture of 34 and 35. These were separated by chromatography and the 34 subjected again to the same reaction conditions. Repeating this sequence three times, compound 35 was isolated in the overall yield of 60 %.

![Scheme 8](image-url)

**Scheme 8.** Synthesis of 4,5-dihydroxy enecarbamate ester 35. Reagents and conditions: (a) pTsOH, MeOH, 55 °C, 3 h (75 %); (b) CbzCl, n-BuLi, -78 °C, THF (83 %); (c) (PhO)$_2$POCl, KHMDS, THF, -78 °C; (d) Pd(OAc)$_2$, PPh$_3$, CO, DMF, Et$_3$N, MeOH, 75°C (60 %); (e) CHCl$_3$ : TFA : H$_2$O = 5 : 1 : 0.1, r.t., 10 min (60%).
The deprotection of 34 set the stage for the OH-directed cyclopropanation (Scheme 9). Since the Simmons–Smith cyclopropanation of similar carbocyclic diols has rarely been reported in literature,\(^\text{13}\) the reaction was carried out under the optimized reaction conditions for the cyclopropanation of corresponding 4-hydroxy derivative by using Charette's zinc carbenoid.\(^\text{2}\) It was anticipated that in this process, immediately after the formation of Zn-carbenoid from Et\(_2\)Zn and CH\(_2\)I\(_2\), 4-OH and/or 5-OH groups will coordinate Zn and direct the delivery of the carbenoid onto the double bond in stereoselective manner. Reaction was initially carried out at room temperature with an excess amount (6 equiv) of Charette's zinc carbenoid, but it was very slow and reached only 50 % conversion after 16 h. However, repeating the reaction under reflux conditions conversion was complete in 1 h providing the target compound 36 in yield of 59 % after chromatography. Removal of Cbz group by hydrogenation over 10 % Pd/C at 1 atm gave conformational restricted cis-4,5-dihydroxyated pipecolic acid derivative (37) which could be used, for example as a template for the synthesis of peptidomimetics.

![Scheme 9](image)

**Scheme 9.** Simmons-Smith cyclopropanation of 35. Reagents and conditions: (a) TCP, Et\(_2\)Zn, CH\(_2\)I\(_2\), -40 °C, 15 min, then reflux, 1 h (59%); (b) H\(_2\), Pd/C, EtOAc (80%).

The cyclopropane-fused diol 36 was benzylated with BnBr/NaH in DMF affording 38 in yield of 74 % (Scheme 10). The reduction of the ester group was carried out with Super-H in THF at 0 °C and led to the formation of 39 in 92% yield after acidic work-up. After the hydrogenation over 10 % Pd/C at 1 atm under slightly acidic conditions, compound 40 was isolated as hydrochloride salt. Since hydroxylated derivatives of pipecolic acid are incorporated in biologically active substances,\(^\text{14}\) the reliable synthesis of compounds 36 and 39 could also be of interest for the agro- and pharmaceutical industry.

![Scheme 10](image)

**Scheme 10.** Reagents and conditions: (a) NaH, BnBr, TBAI, DMF, r.t., 3 h (74%); (b) Super-H, THF, 0 °C, 1.5 h (92%); (c) H\(_2\), Pd/C, HCl, MeOH, r.t., 16 h (92%).

Some of very potent glycosidase inhibitors are in form of glycoside\(^\text{15}\) and therefore 39 was coupled to the glucose (Scheme 11). Benzyl protected glucopyranosyl trichloroacetamidate 41 had been chosen as a glucosyl donor and the reaction was carried out in diethyl ether at -20 °C in the presence of TMSOTf.\(^\text{16,17}\) Product 42 was obtained in high yield but as a mixture of \(\alpha/\beta\)-anomers in 1:1 ratio. In the final step of the synthesis, the protecting groups were removed by hydrogenation over Pd/C under slightly acidic conditions and product 43 was purified by DOWEX 50WX8 resin.
The herein presented synthesis of polyhydroxylated cyclopropane-fused piperidine derivatives 37, 40 and 43 demonstrated that OH-directed cyclopropanation is feasible approach toward conformationally restricted iminosugars. In addition, the syntheses of protected 6-hydroxymethyl-piperidin-2-one 13 and 5-hydroxy-6-hydroxymethyl-piperidin-2-one 30 together with previously developed methodology for the synthesis of both cis- and trans-4,5-dihydroxy-piperidin-2-one (7) offer versatility in the view of the number, position and the orientation of hydroxyls for the future syntheses of cyclopropane-fused piperidines as conformationally restricted iminosugar analogues.

4.3. Experimental Part

General Information

Solvents and reagents were used either as received from commercial suppliers or, when necessary, purified using standard laboratory techniques according to methods published in “Purification of Laboratory Chemicals” by Perrin, Armarago, and Perrin (Pergamon Press, 1966). All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of dry nitrogen. Chromatographic separations were performed under pressure on silica gel by flash-column techniques; Rf values refer to TLC carried out on 0.25-mm silica gel plates (Merck F254), with the same eluent as indicated for the column chromatography. Melting points were recorded on a Buchi-540 melting point apparatus and are uncorrected. Optical rotation values were recorded on a Jasco DIP-370 polarimeter at indicated temperature in the specified solvents and concentrations. 1H NMR and 13C NMR spectra were recorded at 400 and 100.4 MHz, respectively, in the specified deuterated solvent at room temperature. Solvent reference lines were set at 7.26 and 77.00 (CDCl3), 2.05 and 29.84 (acetone-d6), 3.31 and 49.00 (CD3OD) in 1H and 13C NMR spectra, respectively. Mass spectra were carried out by direct inlet of a 20 ppm solution either in CH3OH or CH3OH + 0.1% HCO2H on a LCQ Fleet™ Ion Trap LC/MS system (Thermo Fisher Scientific) with an electrospray ionization (ESI) interface in the positive mode. Microanalyses were carried out with a CHN Thermo FlashEA 1112 Series elemental analyzer.

Piperidine-2-carboxylic acid methyl ester hydrochloric salt (21).

SOCl2 (0.74 mL, 10.16 mmol) was added dropwise to the cooled suspension of D-pipelic acid (1 g, 7.74 mmol) in MeOH (7.75 mL) over 10 min. Formed solution was stirred for 20 h. Methanol and the excess of SOCl2 were evaporated and obtained yellow solid was suspended in methyl tert-butyl ether (10 mL). The solid was collected by filtration and washed with chilled methyl tert-butyl ether (3 x 5 mL). The drying under reduced pressure afforded 21 as a white solid (1.35 g, 98 %) with the spectroscopic
data identical to those of the racemic compound.\textsuperscript{18} M.p. = 157.8 – 159.0 °C. \([\alpha]_D^{20} = +7.9 \ (c = 1.2, \ H_2O).

\[\text{N} \quad \text{O} \quad \text{Ts} \quad \text{O} \]

1-(Toluene-4-sulfonyl)-piperidine-2-carboxylic acid methyl ester (22).
A solution of tosyl chloride (1.7 g, 8.91 mmol) in DCM (10 mL) was added dropwise to the cooled solution of 21 (1.33 g, 7.42 mmol), Et₃N (4.2 mL, 29.7 mmol) and DMAP (181 mg, 1.48 mmol) in DCM (50 mL). The ice bath was removed and reaction mixture was stirred at room temperature for 20 h. Saturated NaHCO₃ (60 mL) was added and layers were separated. The product was extracted with DCM (2 x 30 mL) and organic layer was dried over anhydrous Na₂SO₄ for 30 min, filtered and concentrated. The oily residue was purified by flash chromatography (heptane/EtOAc, 2 : 1, Rₜ = 0.3) to give the product 22 (1.95 g, 84 %) as a colourless oil with the spectroscopic data identical to those of the enantiomeric compound.\textsuperscript{19} \([\alpha]_D^{23} = +39.5 \ (c = 0.98, \ DCM).

\[\text{N} \quad \text{OH} \quad \text{Ts} \]

[1-(Toluene-4-sulfonyl)-piperidin-2-yl]-methanol (23).
To the cooled solution of 22 (1.6 g, 5.38 mmol) in THF (35 mL) LiBH₄ (705 mg, 32.3 mmol) was added portionwise. The reaction mixture was stirred at room temperature for 48 h. The excess of LiBH₄ was quenched with MeOH (3 mL). Reaction mixture was neutralized with 2M HCl and the product was extracted with EtOAc (3 x 40 mL). Combined organic layer was dried over anhydrous Na₂SO₄ for 30 min, filtered and concentrated. The oily residue was purified by flash chromatography (heptane/EtOAc, 3 : 2, Rₜ = 0.28) to give the product 23 (1.38 g, 95 %) as a colourless oil with the spectroscopic data identical to those of the enantiomeric compound.\textsuperscript{20} \([\alpha]_D^{4} = +34.3 \ (c = 1.16, \ DCM).

\[\text{N} \quad \text{Ts} \quad \text{TBS} \]

2-(tert-Butyl-dimethyl-silanyloxymethyl)-1-(toluene-4-sulfonyl)-piperidine (11).
To the solution of 23 (1.38, 5.12 mmol) in THF (52 mL) imidazole (522 mg, 7.68 mmol) and TBSCl (1.16 g, 7.68 mmol) were added at 0 °C. Reaction mixture was stirred at room temperature. After 20 h water (50 mL) was added and the product was extracted with EtOAc (3 x 40 mL). Combined organic layer was dried over anhydrous Na₂SO₄ for 30 min, filtered and concentrated. The oily residue was purified by flash chromatography (heptane/EtOAc, 5 : 1, Rₜ = 0.38) to give the product 11 (1.90 g, 97 %) as a colourless oil. \([\alpha]_D^{23} = +32.2 \ (c = 0.48, \ DCM). \ \ ^1H\ NMR \ (400 MHz, CDCl₃) \ \delta = 7.72 \ (d, J = 8.2 Hz, 2H, Ts), 7.49 \ (d, J = 8.2 Hz, 2H, Ts), 4.05 – 3.97 \ (m, 1H, 2-H), 3.80 – 3.69 \ (m, 2H, 6-H and 2-H₂OTBS), 3.60 \ (dd, J = 9.9, 5.4 Hz, 1-H, 2-CH₂OTBS), 3.01 \ (td, J = 13.7, 2.6 Hz, 1H, 6-H), 2.42 \ (s, 3H, CH₃-Ts), 1.84 \ (d, J = 13.7 Hz, 1H, 5-H), 1.53 – 1.48 \ (m, 2H, 4-H), 1.40 – 1.20 \ (m, 3H, 5-H and 3-H), 0.86 \ (s, 9H, CH₃-TBS), 0.02 \ (s, 3H, CH₃-TBS) ppm. \ ^13C\ NMR \ (100.4 MHz, CDCl₃) \ \delta = 142.6 \ (s, Ts), 138.6 \ (s, Ts), 129.3 \ (d, 2C, Ts), 126.8 \ (d, 2C, Ts), 61.3 \ (t, CH₂OTBS), 53.0 \ (d, C-2), 41.6 \ (t, C-6), 24.4 \ (t, C-3), 27.3 \ (t, C-5), 21.3 \ (t, C-4), 18.4 \ (q, 3C, CH₃-TBS) ppm. MS (ESI) \ m/z \ (%) : 384 \ ([M+1]^+), 25.\textsuperscript{21} \text{Elemental analysis calcd (%) for C_{19}H_{33}NO_{3}Si: C 59.49; H 8.67; N 3.65; found C 59.61, H 8.62, N 3.70.}
6-(tert-Butyl-dimethyl-silyl oxy)dimethyl-1-(toluene-4-sulfonyl)-piperidin-2-one (13).

NaO4 (5.3 g, 24.8 mmol) was dissolved in water (20 mL) and RuO2-nH2O (200 mg, 1.48 mmol) was added under nitrogen atmosphere, to the solution which rapidly turned yellow while being stirred. Then a solution of 11 (1.90 g, 4.95 mmol) in EtOAc (30 mL) was added and the reaction mixture was stirred at room temperature. After 24 h the catalyst was quenched by the addition of i-ProH (1 mL). Reaction mixture was filtered and the two phases were separated. The aqueous layer was extracted with EtOAc (2 x 50 mL), and the combined organic layer was dried over sodium sulfate. After filtration and evaporation of the solvent the crude was purified by flash chromatography (heptane/EtOAc, 5 : 1, Rf = 0.36) to give pure 13 (1.06 g, 55 %) as a white wax. [α]D2 = + 41.8 (c = 0.44, DCM). 1H NMR (400 MHz, CDCl3) δ = 7.90 (d, J = 8.3 Hz, 2H, Ts), 7.28 (d, J = 8.3 Hz, 2H, Ts), 4.66 – 4.55 (m, 1H, 6-H), 3.88 (dd, J = 10.1, 3.4 Hz, 1H, 6-CH2OTBS), 3.76 (dd, J = 10.1, 7.8 Hz, 1H, 6-CH2OTBS), 2.45 (m, 1H, 3-H), 2.41 (s, 3H, CH3-Ts), 2.39 – 2.27 (m, 1H, 4-H), 2.25 – 2.18 (m, 1H, 5-H), 2.03 – 1.92 (m, 1H, 3-H), 1.87 – 1.77 (m, 1H, 5-H), 1.72 – 1.64 (m, 1H, 4-H), 0.84 (s, 9H, CH3-TBS), 0.10 (s, 3H, CH3-TBS), 0.05 (s, 3H, CH3-TBS) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 170.1 (s, C2), 144.3 (s, Ts), 136.5 (s, Ts), 129.1 (d, 2C, Ts), 128.8 (d, 2C, Ts), 63.9 (t, CH2OTBS), 56.8 (d, C6), 33.6 (t, C3), 25.6 (q, CH3Ts), 24.9 (t, C4), 21.6 (t, C5), 18.1 (q, TBS), 16.6 (q, C3, TBS), -5.5 (q, TBS), -5.7 (q, TBS) ppm. MS (ESI) m/z (%): 398 ([M+1]+), 100.21 Elemental analysis calc’d (%) for C19H31NO4S: C 57.39; H 7.86; N 3.52; found C 57.36, H 7.84, N 3.56.

6-Furan-2-yl-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridine (24).

An aqueous Na2CO3 (2 M, 100 mL), (Ph3P)2PdCl2 (550 mg, 0.78 mmol) and 2-furanylboronic acid (2.63 g, 23.5 mmol) were added to a solution of phosphate (7.57 g, 15.6 mmol) in THF (200 mL). The mixture was heated at 40 °C for 2 h, then diluted with H2O (100 mL) and the product extracted with EtOAc (3 x 100 mL). The combined organic layer was dried with K2CO3. After filtration and evaporation of the solvent, the crude was purified twice by flash chromatography (heptane/EtOAc, 4 : 1, Rf = 0.26) to afford 24 (3.26 g, 70 %) which was not stable and decomposed when neat. 1H NMR (400 MHz, CDCl3) δ = 7.66 (d, J = 8.2 Hz, Ts), 7.33 (bs, 1H, 5'-H), 7.27 (d, J = 8.2 Hz, Ts), 6.42 – 6.36 (m, 2H, 3' and 4'-H), 5.73 (t, J = 4.0 Hz, 1H, 3-H), 3.64 – 3.61 (m, 2H, 6-H), 2.42 (s, 3H, CH3-Ts), 2.07 – 2.02 (m, 2H, 4-H), 1.51 – 1.45 (m, 2H, 5-H) ppm.

2-Furan-2-yl-1-(toluene-4-sulfonyl)-piperidin-3-ol (25).

A solution of 2 M (CH3)2S-BH3 in THF (11 mL, 21 mmol) was added to a solution of 24 (3.2 g, 10.5 mmol) in anhydrous THF (30 mL) at 0 °C under N2 atmosphere. The cooling bath was removed and the mixture was stirred at room temperature for 24 h. The reaction was cooled to 0 °C and EtOH (10 mL), 3M solution of NaOH (9 mL) and H2O2 (35 %, 4 mL) were added. The resulting mixture was heated to reflux for 1 h. The solution was transferred into a flask that contained ice and the product was extracted with EtOAc (3 x 75 mL). The combined organic extracts were dried with Na2SO4. After filtration and evaporation of the solvent, the residue was purified by chromatography (heptane/EtOAc, 3 : 2, Rf = 0.3) to give 25 (1.45 g, 43 %) as a colourless yellow oil. 1H NMR (400 MHz, CDCl3) δ = 7.62 (d, J = 8.3 Hz, 2H, Ts), 7.21 – 7.19 (m, 3H, 5'-H and Ts), 6.23 (dd, J = 3.2, 1.8 Hz, 1H, 4'-H), 6.07 (d, J
= 3.2 Hz, 1H, 3'-H), 5.17 (bs, 1H, 2-H), 4.24 (bs, 1H, 3-H), 3.75 – 3.66 (m, 1H, 6-H), 3.07 (td, J = 12.7, 2.8 Hz, 1H, 6-H), 2.39 (s, 3H, CH₂-Ts), 2.29 (d, J = 7.5 Hz, 1H, OH), 1.98 – 1.85 (m, 1H, 4-H), 1.83 – 1.72 (m, 2H, 5-H), 1.53 – 1.44 (m, 1H, 4-H) ppm. ¹³C NMR (100.4 MHz, CDCl₃) δ = 150.6 (s, C1'), 143.1 (s, Ts), 142.0 (s, Ts), 136.7 (d, C4'), 129.3 (d, 2C, Ts), 127.3 (d, 2C, Ts), 110.2 (d, C3'), 108.6 (d, C2'), 66.6 (d, C3), 57.3 (d, C2), 41.8 (t, C6), 26.3 (t, C5), 21.5 (q, CH₃-Ts), 18.7 (C4) ppm. Elemental analysis calc (%) for C₁₆H₁₉NO₄S; C 59.79; H 5.96; N 4.36; found C 59.92, H 6.00, N 4.41.

3-(tert-Butyl-dimethyl-silyloxy)-2-furan-2-yl-1-(toluene-4-sulfonyl)-piperidine (26).
To the solution of 25 (1 g, 3.11 mmol) in DCM (31 mL) DIPEA (1.1 mL, 6.23 mmol) and TBSOTf (1.07 mL, 4.6 mmol) were added at 0 °C. Reaction mixture was stirred at room temperature. After 20 h water (50 mL) was added and the product was extracted with EtOAc (3 x 40 mL). Combined organic layer was dried over anhydrous Na₂SO₄ for 30 min, filtered and concentrated. The oily residue was purified by flash chromatography (heptane/EtOAc, 5 : 1, Rr = 0.32) to give the product 26 (1.26 g, 93 %) as a colourless oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.76 (d, J = 8.2 Hz, 2H, Ts), 7.28 (bs, 1H, 5'-H), 7.26 (d, J = 8.2 Hz, Ts), 6.29 (dd, J = 3.2, 1.8 Hz, 1H, 4'-H), 6.22 (d, J = 3.2 Hz, 1H, 3'-H), 5.16 (bs, 1H, 2-H), 4.32 (d, J = 2.6 Hz, 1H, 3-H), 3.48 – 3.40 (m, 1H, 6-H), 3.17 (td, J = 12.9, 2.8 Hz, 1H, 6-H), 2.40 (s, 3H, CH₃-Ts), 2.01 – 1.85 (m, 1H, 4-H), 1.67 – 1.57 (m, 2H, 5-H), 1.36 – 1.28 (m, 1H, 4-H), 0.94 (s, 9H, TBS), 0.15 (s, 3H, TBS), 0.11 (s, 3H, TBS) ppm. ¹³C NMR (100.4 MHz, CDCl₃) δ = 151.8 (s, C1'), 142.6 (s, Ts), 141.8 (d, C4'), 137.6 (s, Ts), 129.1 (d, 2C, Ts), 127.4 (d, 2C, Ts), 110.1 (d, C3'), 108.0 (d, C2'), 66.9 (d, C3), 57.4 (d, C2), 41.7 (t, C6), 27.4 (t, C5), 25.9 (q, 3C, TBS), 21.5 (q, Ts), 18.5 (t, C-4), 17.9 (s, TBS), -4.9 (q, 2C, TBS). MS (ESI) m/z (%): 436 ([M+1]+, 100).²¹ Elemental analysis calc (%) for C₂₂H₃₃NO₄SSi; C 60.65; H 7.63; N 3.22; found C 60.70, H 7.65, N 3.30.

3-(tert-Butyl-dimethyl-silyloxy)-1-(toluene-4-sulfonyl)-piperidine-2-carboxylic acid methyl ester (27).
To a solution of NaIO₄ (1.55 g, 7.25 mmol) in EtOAc (5 mL)/ACN (13 mL)/H₂O (7 mL) cooled to 0 °C, RuO₂·nH₂O (4 mg, 0.03 mmol) was added. The reaction was stirred at 0 °C for 10 min and then a solution of 26 (640 mg, 1.45 mmol) in EtOAc (8 mL) was slowly added. After 25 min at room temperature, i-PrOH (2 mL) was added and the reaction mixture was filtered through the celite. Water was added to the mother liquid and the product was extract with EtOAc (3 x 15 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and evaporated. The crude carboxylic acid was dissolved in DMF (5 mL) and Cs₂CO₃ (260 mg, 0.8 mmol) and Mel (98 µL, 1.58 mmol) were added. Reaction mixture was left to stir at room temperature and after 72 h water (50 mL) was added. The product was extract with Et₂O (4 x 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated. The oily residue was purified by flash chromatography (n-hexane/EtOAc, 10 : 1, Rr = 0.26) to give the product 27 (420 g, 68 %) as a yellow wax. ¹H NMR (400 MHz, CDCl₃) δ = 7.79 (d, J = 7.8 Hz, 2H, Ts), 7.25 (d, J = 7.8 Hz, 2H, Ts), 4.60 (d, J = 2.9 Hz, 1H, 2-H), 4.36 (dd, J = 6.3, 2.8 Hz, 1H, 3-H), 3.68 (s, 3H, OCH₃), 3.48 – 3.41 (m, 1H, 6-H), 3.21 (td, J = 12.7, 3.1 Hz, 1H, 6-H), 2.41 (s, 3H, CH₃-Ts), 1.99 – 1.84 (m, 1H, 5-H), 1.65 (dq, J = 13.6, 2.8 Hz, 1H, 4-H), 1.51 – 1.43 (m, 1H, 1-H), 1.39 – 1.31 (m, 1H, 5-H), 0.91 (s, 9H, CH₃-TBS), 0.13 (s, 3H, CH₃-TBS), 0.10 (s, 3H, CH₃-TBS) ppm. ¹³C NMR (100.4 MHz, CDCl₃) δ = 170.0 (s, CO), 143.1 (s, Ts), 137.6 (s, Ts), 129.1 (d, 2C, Ts), 127.5 (d, 2C, Ts), 66.2 (d, C2), 61.8 (d, C3), 52.2 (q, OCH₃), 42.6 (t, C6), 28.3 (t, C5), 25.7 (q, 3C, CH₃-TBS), 21.5 (q, CH₃-Ts), 18.2 (t, C3), 18.1 (s, TBS), -5.1 (q, 2C, CH₃-TBS). MS (ESI) m/z (%): 428 ([M+1]+, 43), 450 ([M+Na]+, 16), 876 ([2M+Na]+, 100). Elemental
[3-(tert-Butyl-dimethyl-silyloxy)-1-(toluene-4-sulfonyl)-piperdin-2-yl]-methanol (28).

The solution of 27 (403 mg, 0.94 mmol) in dry DCM (13 mL) was cooled by ice bath and 1 M solution of Dibal-H (1.1 mL, 1.1 mmol) was added. Reaction mixture was left to stir on ice bath and after 1 h saturated aqueous solution of Rochelle salt (15 mL) was added. The formed two-phase system was left to stir for 45 min. The layers were separated and the product was extracted with DCM (3 x 10 mL). The combined organic layer was dried over Na₂SO₄. After filtration and evaporation of the solvent, the crude was purified by flash chromatography (n-hexane/EtOAc, 2 : 1; Rf = 0.19) affording compound 28 (215 mg, 57 %) as a colourless oil. ¹H NMR (400 MHz, CDCl₃): δ = 7.82 (d, J = 8.4 Hz, 2H, Ts), 7.22 (d, J = 8.4 Hz, 2H, Ts), 3.97 – 3.87 (m, 2H, 2-H and 3-H), 3.85 – 3.75 (m, 1H, CH₂OH), 3.70 – 3.60 (m, 1H, CH₂OH), 3.38 (dt, J = 13.0, 3.2 Hz, 1H, 6-H), 3.07 (td, J = 12.8, 3.2 Hz, 1H, 6-H), 2.37 (s, 3H, CH₃-Ts), 2.19 (m, 1H, OH), 1.83 – 1.66 (m, 1H, 4-H), 1.67 – 1.52 (m, 2H, 4-H and 5-H), 1.30 (dt, J = 13.0, 3.3 Hz, 1H, 5-H), 0.83 (s, 9H, CH₃-TBS), 0.01 (s, 3H, CH₃-TBS), -0.00 (s, 3H, CH₃-TBS) ppm. ¹³C NMR (100.4 MHz, CDCl₃) δ = 143.0 (s, Ts), 137.8 (s, Ts), 129.4 (d, 2C, Ts), 127.4 (d, 2C, Ts), 65.4 (d, C3), 61.8 (d, C2), 60.7 (t, CH₂OH), 41.5 (t, C2), 27.8 (t, C4), 25.8 (q, 3C, CH₃-TBS), 21.4 (q, CH₃-Ts), 18.6 (t, C5), 18.2 (s, TBS), -4.92 (q, 2C, CH₃-TBS) ppm. MS (ESI) m/z (%): 400 ([M+1]⁺, 31), 422 ([M+Na]⁺, 30), 821 ([2M+Na]⁺, 100). Elemental analysis calcd (%) for C₁₉H₃₃NO₄S; C 57.11; H 8.32; N 3.51; found C 56.99, H 8.27, N 3.49.

3-(tert-Butyl-dimethyl-silyloxy)-2-(tert-butyl-dimethyl-silyloxymethyl)-1-(toluene-4-sulfonyl)-piperidine (29).

Compound 29 was prepared from compound 28 (200 mg, 0.5 mmol) following the procedure for the synthesis of compound 11. After the flash chromatography (n-hexane/EtOAc, 25 : 1; Rf = 0.20) compound 29 (214 mg, 83 %) was obtained as a white solid. M.p. = 88.5 – 90.2 °C. ¹H NMR (400 MHz, CDCl₃) δ = 7.84 (d, J = 8.0 Hz, 2H, Ts), 7.23 (d, J = 8.0 Hz, 2H, Ts), 4.22 (dd, J = 5.1, 2.4 Hz, 1H, 3-H), 4.04 – 3.95 (m, 1H, 2-H), 3.79 – 3.68 (m, 2H, CH₂OTBS), 3.46 – 3.35 (m, 1H, 6-H), 3.00 (td, J = 12.9, 2.8 Hz, 1H, 6-H), 2.39 (s, 3H, CH₃-Ts), 1.85 – 1.66 (m, 2H, 4-H and 5-H), 1.66 – 1.57 (m, 1H, 4-H), 1.27 (m, 1H, 5-H), 0.89 (s, 9H, CH₃-TBS), 0.88 (s, 9H, CH₃-TBS), 0.07 (s, 3H, CH₃-TBS), 0.06 (s, 6H, CH₃-TBS), 0.04 (s, 3H, CH₃-TBS) ppm. ¹³C NMR (100.4 MHz, CDCl₃) δ = 142.8 (s, Ts), 138.3 (s, Ts), 129.2 (d, 2C, Ts), 127.2 (d, 2C, Ts), 64.5 (d, C3), 62.1 (t, CH₂OTBS), 60.2 (d, C2), 41.6 (t, C6), 26.5 (t, C4), 25.8 (q, 6C, CH₃-TBS), 21.4 (q, CH₃-Ts), 18.2 (t, C5), 18.1 (s, 2C, TBS), -4.9 (q, CH₃-TBS), -5.0 (q, CH₃-TBS), -5.4 (q, CH₃-TBS), -5.6 (q, CH₃-TBS) ppm. MS (ESI) m/z (%): 514 ([M+1]⁺, 58), 536 ([M+Na]⁺, 29), 1048 ([2M+Na]⁺, 100). Elemental analysis calcd (%) for C₂₁H₄₀NO₄S; C 58.43; H 9.22; N 2.73; found C 58.45, H 9.20, N 2.75.

5-(tert-Butyl-dimethyl-silyloxy)-6-(tert-butyl-dimethyl-silyloxymethyl)-1-(toluene-4-sulfonyl)-piperidine-2-one (30).

Compound 30 was prepared from compound 29 (100 mg, 0.19 mmol) following the procedure for the synthesis of compound 13. After the flash chromatography (n-hexane/EtOAc, 10 : 1; Rf = 0.18) compound 30 (74 mg, 74 %) was obtained as a white solid. M.p. = 158.4 – 155.2 °C. ¹H NMR (400 MHz, CDCl₃) δ = 7.84 (d, J = 8.4 Hz, 2H, Ts), 7.23 (d, J = 8.4 Hz, 2H, Ts), 4.22 (dd, J = 5.1, 2.4 Hz, 1H, 3-H), 4.04 – 3.95 (m, 1H, 2-H), 3.79 – 3.68 (m, 2H, CH₂OTBS), 3.46 – 3.35 (m, 1H, 6-H), 3.00 (td, J = 12.9, 2.8 Hz, 1H, 6-H), 2.39 (s, 3H, CH₃-Ts), 1.85 – 1.66 (m, 2H, 4-H and 5-H), 1.66 – 1.57 (m, 1H, 4-H), 1.27 (m, 1H, 5-H), 0.89 (s, 9H, CH₃-TBS), 0.88 (s, 9H, CH₃-TBS), 0.07 (s, 3H, CH₃-TBS), 0.06 (s, 6H, CH₃-TBS), 0.04 (s, 3H, CH₃-TBS) ppm. ¹³C NMR (100.4 MHz, CDCl₃) δ = 142.8 (s, Ts), 138.3 (s, Ts), 129.2 (d, 2C, Ts), 127.2 (d, 2C, Ts), 64.5 (d, C3), 62.1 (t, CH₂OTBS), 60.2 (d, C2), 41.6 (t, C6), 26.5 (t, C4), 25.8 (q, 6C, CH₃-TBS), 21.4 (q, CH₃-Ts), 18.2 (t, C5), 18.1 (s, 2C, TBS), -4.9 (q, CH₃-TBS), -5.0 (q, CH₃-TBS), -5.4 (q, CH₃-TBS), -5.6 (q, CH₃-TBS) ppm. MS (ESI) m/z (%): 514 ([M+1]⁺, 58), 536 ([M+Na]⁺, 29), 1048 ([2M+Na]⁺, 100). Elemental analysis calcd (%) for C₂₁H₄₀NO₄S; C 58.43; H 9.22; N 2.73; found C 58.45, H 9.20, N 2.75.
MHZ, CDCl₃) δ = 7.81 (d, J = 8.2 Hz, 2H, Ts), 7.19 (d, J = 8.2 Hz, 2H, Ts), 4.45 – 4.30 (m, 2H, 5-H and 6-H), 3.94 (ddd, J = 10.5, 3.7 Hz, 1H, CH₂OTBS), 3.60 (dd, J = 10.5, 8.7 Hz, 1H, CH₂OTBS), 2.47 (ddd, J = 18.0, 12.0, 7.6 Hz, 1H, 3-H), 2.35 (s, 3H, CH₃-Ts), 2.28 (ddd, J = 18.0, 7.3, 1.4 Hz, 1H, 3-H), 2.07 (ddd, J = 14.1, 12.0, 7.0, 2.2 Hz, 1H, 4-H), 1.74 – 1.62 (m, 1H, 4-H), 0.84 (s, 9H, CH₃-TBS), 0.82 (s, 9H, CH₃-TBS), 0.08 (s, 3H, CH₃-TBS), 0.06 (s, 3H, CH₃-TBS), 0.03 (s, 6H, CH₂-TBS) ppm. ¹³C NMR (100.4 MHZ, CDCl₃) δ = 167.0 (s, CO), 144.3 (s, Ts), 136.5 (s, Ts), 129.0 (d, 2C, Ts), 128.6 (d, 2C, Ts), 65.0 (d, C6), 64.6 (t, CH₂OTBS), 64.0 (d, C5), 28.6 (t, C3), 25.7 (q, 6C, CH₃), 24.3 (t, C4), 21.5 (q, CH₃-Ts), 18.0 (q, 2C, CH₃-TBS), -4.5 (q, 2C, CH₃-TBS), -5.6 (q, CH₃-TBS) ppm. MS (ESI) m/z (%): 528 ([M+H]+, 33), 1077 ([2M+Na]+, 100). Elemental analysis calcd (%) for C₂₅H₄₅NO₅SSi₂; C 56.88; H 8.59; N 2.65; found C 56.95, H 8.52, N 2.70.

### (3aR,7aS)-Benzylic 2,2-Dimethyl-6-oxotetrahydro[1,3]dioxolo[4,5-c]-pyridine-5(4H)-carboxylate (32).

A solution of protected lactam 31 (980 mg, 5.75 mmol) in dry THF (58 mL) was cooled to -78 °C and a 1.6 M solution of n-BuLi (3.6 mL, 5.75 mmol) was slowly added, keeping the temperature below -70 °C during the addition. The mixture was stirred for 15 min and then benzylic chloroformate (785 µL, 5.75 mmol) was added dropwise. After 10 min, the cooling bath was removed and the mixture allowed to warm to 0 °C. Saturated NaHCO₃ (25 mL) and water (25 mL) were added and the product extracted with DCM (4 x 30 mL). The combined organic extracts were dried with Na₂SO₄, filtered and evaporated. After purification by flash chromatography (n-hexane/EtOAc, 1 : 2; Rₚ = 0.30) pure 32 was obtained as a white solid (1.45 g, 83 %). Spectroscopic and analytical data identical to those reported for racemic compound. M. p. = 115.9 - 117.6 °C, [α]D¹² +57.0 (c = 0.23, CHCl₃). Elemental analysis calcd (%) for C₁₉H₁₉NO₅; C 62.94, H 6.27, N 4.59; found C 63.10, H 6.41, N 4.49.

### 5-Benzyl 6-Methyl (3aR,7aS)-2,2-dimethyl-3a,7a-dihydro[1,3]dioxolo[4,5-c]pyridine-5,6(4H)-dicarboxylate (34).

A 0.5 M solution of KHMS in toluene (12.9 mL, 6.43 mmol) was diluted in anhydrous THF (48 mL) and cooled to -78 ºC. A solution of 32 (1.57 g, 5.15 mmol) in anhydrous THF (16 mL) was added dropwise, keeping the temperature below -70 °C. The resulting mixture was stirred for 1.5 h below -70 °C and diphenylchlorophosphatate (1.34 mL, 6.43 mmol) was slowly added. After 1 h, the mixture was allowed to warm to 0 ºC. Aqueous 10 % NaOH (130 mL) was slowly added and the product extracted with Et₂O (4 x 65 mL). The combined organic extracts were washed with 10 % NaOH (120 mL) and dried over K₂CO₃ for 30 min. After filtration and evaporation of the solvent, the crude was purified over a short pad of silica gel (n-hexane/EtOAc, 2 : 1 + 1 % Et₃N; Rₚ = 0.24) affording pure 33 (2.75 g, 99 %) as a pale yellow oil. The product was used immediately for the next step. Spectroscopic and analytical data identical to those reported for racemic compound.

A solution of phosphate 33 (2.75 g, 5.11 mmol), Pd(OAc)₂ (114.7 mg, 0.511 mmol) and Ph₃P (268 mg, 1.02 mmol) in anhydrous DMF (13 mL) was prepared under nitrogen atmosphere. The reaction mixture was flushed and saturated with carbon monoxide. After 10 min Et₃N (1.3 mL, 10.22 mmol) and anhydrous MeOH (8.3 mL, 204 mmol) were added. The mixture was stirred under CO atmosphere (balloon) at 55 °C (external bath) for 3 h. After cooling, water (130 mL) was added and the product...
extracted with Et₂O (5 x 60 mL). The combined organic extracts were dried over Na₂SO₄. After filtration and evaporation of the solvent, crude was purified by flash chromatography (n-hexane/EtOAc, 2 : 1 + 1 % Et₃N; R cref=0.2) affording pure 34 (1.28 g, 72 % after two steps) as a colourless oil. Spectroscopic and analytical data identical to those reported for racemic compound. [α]D²¹ = +37.2 (c = 0.95, CHCl₃). Elemental analysis calcd (%) for C₁₈H₂₂NO₆; C 62.24, H 6.09, N 4.03; found: C 62.27, H 5.79, N 4.26.

(4S,5R)-1-Benzyl 2-Methyl 4,5-Dihydroxy-5,6-dihydropyridine-1,2(4H)-dicarboxylate (35). A mixture of trifluoroacetic acid and water (7.15 mL, TFA/H₂O, 0.1 : 1) was added to a solution of compound 34 (1.23 g, 3.54 mmol) in CHCl₃ (32.5 mL). The reaction mixture was left to stir 10 min at room temperature and, after cooling to 0 °C, the reaction was quenched adding K₂CO₃ (7.5 g). After 3 min a satd. solution of NaHCO₃ (65 mL) was slowly added and the layers were separated. The product was extracted with CHCl₃ (3 x 40 mL) and the combined organic extracts were dried over anhydrous K₂CO₃. After filtration and evaporation of the solvent, the crude was purified by flash chromatography (CHCl₃/acetone, 3 : 1; R cref=0.33) affording pure product 35 (430 mg, 40 %) as a colourless gummy oil and starting material 34 (462 mg) which was treated again as reported above providing pure product 35 (148 mg, 36 %) and starting material 34 (143 mg). A further treatment of residual 34 led to total yield of 60 %. [α]D²¹ +68.2 (c = 0.98, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ = 7.38 - 7.30 (m, 5 H, Ph), 5.87 (d, J = 3.6 Hz, 1H, 3-H), 5.15 (s, 2 H, CH₂Ph), 4.31 (bm, 1 H, 4-H), 3.95 (bm, 1H, 5-H), 3.81 (dd, J = 13.1, 2.8 Hz, 1 H, 6-Heq), 3.70 (dd, J = 13.1, 7.8 Hz, 1 H, 6-Hax), 3.57 (s, 3 H, OCH₃), 2.57 (d, J = 5.8 Hz, 1H, OH), 2.42 (d, J = 7.0 Hz, 1H, OH) ppm. ¹³C NMR (100.4 MHz, CDCl₃) δ = 164.7 (s, CO), 154.4 (NCO₂Bn), 135.3 (C_arom), 133.3 (C2), 128.5 (2C_arom), 128.4 (2C_arom), 120.3 (C3), 68.5 (CH₂Ph), 66.2 (C4), 64.6 (C5), 52.3 (OCH₃), 47.3 (C6) ppm. MS (ESI) m/z (%): 638 (100) [2M+Na]+, 330 (34) [M+Na]+, 308 (15) [M+Na]+. Elemental analysis calcd (%) for C₁₅H₁₂NO₆; C 53.63, H 5.58, N 4.56; found: C 53.23, H 5.32, N 4.02.

2-Benzyl 1-Methyl (1R,4R,5S,6S)-4,5-Dihydroxy-2-azabicyclo[4.1.0]heptane-1,2-dicarboxylate (36). To a solution of 2,4,6-trichlorophenol (395 mg, 2 mmol) in anhydrous CH₂Cl₂ (10 mL), cooled to –40 °C and under nitrogen atmosphere, 1 M solution of Et₂Zn in hexane (2 mL, 2 mmol) was slowly added. The mixture was stirred for 15 min, then CH₂Cl₂ (160 μL, 6 eq) was added dropwise. After 15 min at –40 °C, a solution of 35 (103 mg, 0.33 mmol) in anhydrous DCM (1 mL) was added and the cooling bath was removed. The reaction mixture was stirred under reflux for 1 h. The suspension was cooled on an ice bath and a 10 % solution of citric acid (8 mL) was added dropwise under vigorous stirring. When the solution became clear, the layers were separated. The product was extracted with DCM (4 x 8 mL). The combined organic layers were washed with a saturated solution of Na₂CO₃ (2 x 20 mL) and dried over Na₂SO₄. After filtration and evaporation of the solvent, the crude was purified by flash chromatography (CHCl₃/acetone, 3 : 1; R cref=0.33) affording compound 36 (55 mg, 53 %) as white gummy solid. [α]D²¹ +27.4 (c = 0.98, CHCl₃). ¹H NMR (400 MHz, CDCl₃) (3:1 mixture of rotamers) δ = 7.36 – 7.25 (m, 5H, Ph, both rotamers), 5.23 (part A of an AB system, J = 12.8 Hz, 1H, major rotamer), 5.17 (AB system, J = 16.8 Hz, 2 H, minor rotamer), 5.08 (part B of an AB system, J = 12.8 Hz, 1H, major rotamer), 4.25 (dd, J = 14.2, 4.0 Hz, 1 H, 3-Heq, major rotamer), 4.16 (t, J = 4.2 Hz, 1H, 5-H, major rotamer), 2.20 (s, 3 H, OCH₃), 1.52 (d, J = 7.0 Hz, 3 H, OCH₃). MS (ESI) m/z (%) 550 (100) [2M+Na]+, 422 (34) [M+Na]+, 400 (15) [M+Na]+. Elemental analysis calcd (%) for C₁₅H₁₄NO₆; C 53.23, H 5.32, N 4.02; found: C 53.63, H 5.58, N 4.56.
minor rotamer), 4.17 – 4.10 (m, 2 H, 3-H$_{eq}$, minor rotamer and 5-H, major rotamer) 4.01 (t, $J$ = 4.2 Hz, 1H, 4-H, major rotamer), 3.94 (t, $J$ = 3.7 Hz, 1H, 4-H, minor rotamer), 3.71 (s, 3H, OCH$_3$, minor rotamer), 3.55 (s, 3 H, OCH$_3$, major rotamer), 2.96 (dd, $J$ = 14.0, 1.2 Hz, 1H, 3-H$_{ax}$, minor rotamer), 2.89 (dd, $J$ = 14.2, 0.8 Hz, 1H, 3-H$_{ax}$, major rotamer), 1.96–1.86 (m, 2H, 6-H, both rotamers and 7-H, minor rotamer), 1.81 (dd, $J$ = 10.2, 4.6 Hz, 1H, 7-H, major rotamer), 1.50 – 1.43 (m, 1H, 7-H', both rotamers) ppm. $^{13}$C NMR (100.4 MHz, CDCl$_3$) (major rotamer) $\delta$ = 172.1 (CO), 157.6 (NO$_2$Bn), 136.4 (Carom), 128.4 (2Carom), 127.9 (2Carom), 127.4 (Carom), 67.5 (CH$_2$Ph), 67.3 (C4), 64.7 (C5), 52.3 (OCH$_3$), 46.6 (C1), 41.2 (C3) 27.9 (C6), 21.7 (C7) ppm. MS (ESI) m/z (%): 662 (100) [2M+Na]$^+$, 344 (31) [M+Na]$^+$, 321 (26) [M+Na]$^+$. Elemental analysis calcld (%) for C$_{16}$H$_{19}$NO$_6$; C 59.81, H 5.96, N 4.36; found C 59.48, H 6.11, N 4.67.


To a solution of 36 (28 mg, 0.087 mmol) in ethyl acetate (2 mL), under nitrogen atmosphere, was added 10 % Pd/C (7 mg). The resulting suspension was stirred under an H$_2$ atmosphere (balloon) at room temperature for 3 h. After filtration through a Celite pad and evaporation of the solvent, pure amino ester 37 (14 mg, 86 %) was obtained as a yellow oil. $[\alpha]_D^{18}$ = +72.3 (c = 0.72, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 4.10 (dd, $J$ = 7.3, 5.1 Hz, 1H, 5-H), 3.81 (dd, $J$ = 7.3, 3.8 Hz, 1H, 4-H), 3.72 (s, 3H, OCH$_3$), 2.97 (dd, $J$ = 13.3, 3.8 Hz, 1H, 3-H$_{eq}$), 2.61 (dd, $J$ = 13.3, 1.2 Hz, 1H, 3-H$_{ax}$), 2.48 (bs, 3H, NH and OH), 1.92 (dt, $J$ = 10.2, 7.4 Hz, 1H, 6-H), 1.55 (dd, $J$ = 10.2, 4.4 Hz, 1H, 7-H), 1.33 (dd, $J$ = 7.4, 4.4 Hz, 1H, 7-H') ppm. $^{13}$C NMR (100.4 MHz, CDCl$_3$) $\delta$ = 174.7 (CO), 66.4 (C4), 65.1 (C5), 52.6 (OCH$_3$), 47.4 (C3), 42.3 (C1), 26.1 (C6), 24.2 (C7) ppm. MS (ESI) m/z (%): 397 (100) [2M+Na]$^+$, 210 (79) [M+Na]$^+$, 188 (93) [M]$^+$. Elemental analysis calcld (%) for C$_9$H$_{13}$NO$_4$; C 51.33, N 7.48, H 7.00; found C 51.52, N 7.16, H 6.77.

4,5-Bis-benzylxylo-2-aza-bicyclo[4.1.0]heptane-1,2-dicarboxylic acid 2-benzyl ester 1-methyl ester (38).

The solution of 36 (170 mg, 0.53 mmol) and TBAI (39 mg, 0.1 mmol) in DMF (4 mL) was cooled to 0 °C and NaH (63.6 mg, 1.6 mmol) was added. After 30 min, a solution of benzyl bromide (0.19 mL, 36 mg, 0.53 mmol) and TBAI (39 mg, 0.1 mmol) in DMF (4 mL) was cooled to 0 °C and NaH (63.6 mg, 1.6 mmol) was added. After 4 h, water (50 mL) was added and the product was extracted with Et$_2$O (3 x 10 mL). The combined organic layer was dried over Na$_2$SO$_4$. After filtration and evaporation of the solvent, the crude was purified by flash chromatography (n-hexane/EtOAc, 4 : 1; $R_f$ = 0.24) affording compound 38 (195 mg, 80 %) as a colourless oil. $[\alpha]_D^{18}$ = +3.62 (c = 0.69, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$) (mixture of rotamers 2 : 1) $\delta$ = 7.44 – 7.18 (m, 15H, Ar, both rotamers), 5.25 (d, $J$ = 12.6 Hz, 1H, CH$_2$-Cbz, both rotamers), 5.19 – 5.08 (m, 1H, CH$_2$-Cbz, both rotamers), 4.73 – 4.40 (m, 4H, CH$_2$-Bn, both rotamers), 4.36 (dd, $J$ = 13.8, 4.8 Hz, 1H, 3-H, major rotamer), 4.16 – 4.02 (m, 1H, 3-H, minor rotamer), 3.96 (dd, $J$ = 5.9, 4.1 Hz, 1H, 5-H, minor rotamer), 3.92 (t, $J$ = 4.6 Hz, 1H, 5-H, major rotamer), 3.78 (t, $J$ = 3.7 Hz, 1H, 4-H, major rotamer), 3.71 (s, 4H, OCH$_3$ and 4-H, minor rotamer), 3.55 (s, 3H, OCH$_3$, major rotamer), 2.96 (dd, $J$ = 13.5, 2.1 Hz, 1H, 3-H, minor rotamer), 2.79 (d, $J$ = 12.6 Hz, 1H, 3-H, major rotamer), 2.04 – 1.83 (m, 2H, 6-H and 7-H, both rotamers), 1.78 – 1.66 (m, 1H, 7-H, both rotamers) ppm. $^{13}$C NMR (100.4 MHz, CDCl$_3$) (major rotamer) $\delta$ = 172.5 (s, CO), 156.9 (s, CO), 137.9 (s, 2C, Ar), 136.8 (s, Ar), 128.8 - 127.3 (d, Ar), 72.2 (d, C4), 71.4 (d, C5), 71.0 (t, Bn), 70.1 (t, Bn), 67.2 (t, Cbz), 52.3 (q, OCH$_3$), 43.4 (t, C3), 40.4 (s, C1), 26.4 (d, C3), 22.3 (t, C7) ppm. MS (ESI) m/z (%): 1024 (100) [2M+Na]$^+$, 524 (15) [M+Na]$^+$, 501 (10) [M+1]$^+$. 

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Elemental analysis calcd (%) for C$_{30}$H$_{31}$NO$_6$; C 71.84, N 2.79, H 6.23; found C 72.01, N 2.82, H 6.18.

4,5-Bis-benzyloxy-1-hydroxymethyl-2-aza-bicyclo[4.1.0]heptane-2-carboxylic acid benzyl ester (39).

The solution of 38 (180 mg, 0.36 mmol) in dry THF (4 mL) was cooled by ice bath and 1 M solution of Super-H (0.9 mL, 0.9 mmol) was added. Reaction mixture was left to stir on ice bath and after 1.5 h diluted AcOH (5 mL) was added. The product was extracted with DCM (3 x 5 mL). The combined organic layers were dried over Na$_2$SO$_4$. After filtration and evaporation of the solvent, the crude was purified by flash chromatography (n-hexane/EtOAc, 1 : 1; Rf = 0.16) affording compound 39 (157 mg, 92 %) as a colourless oil. [$\alpha$]$_D^{20}$ = + 15.2 (c = 0.75, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$) (mixture of rotamers 3 : 2) $\delta$ = 7.39 – 7.20 (m, 15 H, Ar and Bn), 5.27 (d, $J$ = 12.4 Hz, 1H, CH$_2$-Cbz, minor rotamer), 5.17 (d, $J$ = 12.4 Hz, 1H, CH$_2$-Cbz, minor rotamer), 5.13 (d, $J$ = 12.1 Hz, 1H, CH$_2$-Cbz, major rotamer), 5.06 (d, $J$ = 12.1 Hz, 1H, CH$_2$-Cbz, major rotamer), 4.70 – 4.45 (m, 3H, CH$_2$-Bn, both rotamers), 4.47 – 4.36 (m, 1H, 3-H, both rotamers), 4.19 – 4.06 (m, 2H, 5-H, major rotamer, CH$_2$-Bn, both rotamers), 4.01 – 3.88 (m, 2H), 3.84 (d, $J$ = 11.5 Hz, 1H, 1-CH$_2$OH, both rotamers), 3.77 (t, $J$ = 4.2 Hz, 1H, 5-minor rotamer), 3.69 (t, $J$ = 4.1 Hz, 1H, 4-H, major rotamer), 3.52 (d, $J$ = 11.5 Hz, 1H, 1-CH$_2$OH, both rotamers), 3.12 (d, $J$ = 11.0 Hz, 1H, 4-H, minor), 2.76 (d, $J$ = 13.8 Hz, 1H, 3-H, major rotamer), 2.69 (d, $J$ = 13.8 Hz, 1H, 3-H, minor rotamer), 1.58 – 1.47 (m, 1H, 7-H, both rotamers), 1.43 – 1.28 (m, 2H, 7-H and 6-H, both rotamers) ppm. $^{13}$C NMR (100.4 MHz, CDCl$_3$) (major rotamer) $\delta$ = 158.9 (s, CO), 138.1 (s, Ar), 135.9 (s, Ar), 128.5 - 126.9 (d, Ar), 72.2 (d, C5), 71.9 (d, C4), 71.4 (t, Bn), 69.7 (t, Bn), 67.8 (t, CBz), 67.3 (s, C1), 44.6 (t, C3), 21.9 (d, C6), 17.1 (t, C7) ppm. MS (ESI) m/z (%): 968 (100) [2M+Na]$^+$, 469 (20) [M+Na]$^+$, 474 (8) [M+1]$^+$. Elemental analysis calcd (%) for C$_{29}$H$_{31}$NO$_6$; C 73.55, N 2.96, H 6.60; found C 73.70, N 2.99, H 6.52.

1-Hydroxymethyl-2-aza-bicyclo[4.1.0]heptane-4,5-diol (40).

Prepared as reported for 37 starting from 39 (48 mg, 0.1 mmol). Reaction carried out under slightly acidic conditions. After drying under reduced pressure pure 40 (18 mg, 92 %) was obtained as a gummy white solid. [$\alpha$]$_D^{20}$ = -19.4 (c = 0.59, CH$_3$OH). $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ = 4.19 – 4.09 (m, 1H, 5-H), 4.07 – 3.94 (m, 1H, 4-H), 3.68 (d, $J$ = 12.3 Hz, 1H, 1-CH$_2$OH), 3.55 (d, $J$ = 12.3 Hz, 1H, 1-CH$_2$OH), 3.16 (dd, $J$ = 12.3, 4.8 Hz, 1H, 3-H), 2.97 (d, $J$ = 12.3 Hz, 1H, 3-H), 1.67 (t, $J$ = 6.5 Hz, 1H, 7-H), 1.49 (m, 1H, 6-H), 0.96 (dd, $J$ = 9.8, 6.5 Hz, 1H, 7-H) ppm. $^{13}$C NMR (100.4 MHz, CDCl$_3$) $\delta$ = 64.9 (s, C1), 64.2 (d, C4), 62.8 (d, C5), 45.9 (t, C3), 43.5 (t, CH$_2$OH), 19.9 (d, C6), 12.3 (t, C7) ppm. MS (ESI) m/z (%): 160 (100) [M+1]$^+$. Elemental analysis calcd for C$_{14}$H$_{14}$NO$_3$Cl; C 42.97, N 7.16, H 7.21; found C 43.02, N 7.05, H 7.23.
4,5-Bis-benzylxylo-1-(3,4,5-tris-benzylxymethyl-6-benzylxymethyl-tetrahydro-pyran-2-yloxymethyl)-2-aza-bicyclo[4.1.0]heptane-2-carboxylic acid benzyl ester (42).

A solution of 39 (51 mg, 0.109 mmol) and benzyl protected glucopyranosyl trichloroacetamidate (126 mg, 0.185 mmol) in dry Et2O (2.5 mL) was cooled to -20 °C and catalytic amount of TMSOTf was added. After 1 h reaction was warmed to room temperature, diluted with Et2O (10 mL) and washed with sat. Na2CO3. The organic layer was dried over Na2SO4. After filtration and evaporation of the solvent, the crude was purified by flash chromatography (n-hexane/Et2O, 1 : 1; RF = 0.18) affording compound 42 (104 mg, 95%) as a colourless oil. Compound 42 was obtained as a mixture of α/β anomers in 1 : 1 ratio. MS (ESI) m/z (%): 1018 (100) [M+Na]+, 996 (9) [M+1]+. Elemental analysis calcld (%) for C63H85NO10Cl; C 75.96, N 1.41, H 6.58; found C 76.29, N 1.32, H 6.29.

2-(4,5-Dihydroxy-2-aza-bicyclo[4.1.0]hept-1-ylmethoxy)-6-hydroxymethyl-tetrahydro-pyran-3,4,5-triol (43).

Prepared as reported for 37 starting from 42 (117 mg, 0.12 mmol). After the purification on DOWEX 50WX8 resin, pure 43 (34 mg, 88 %) was obtained as a colourless oil. Compound 43 was obtained as a mixture of α and β anomers in 1 : 1 ratio. 1H NMR (400 MHz, CDCl3) δ = 4.79 (d, J = 6.6 Hz, 1H, 1'-H), 4.34 (d, J = 7.9 Hz, 1H, 1'-H), 4.15 – 4.03 (m, 1H, 5-H), 3.83 – 3.50 (m, 7H, 4-H, 3-H, 1-CH2-O-sugar and 5'-CH2OH), 3.45 – 3.13 (m, 4H, 2'-H, 3'-H, 4'-H and 5'-H), 1.15 (tt, J = 10.2, 6.5 Hz, 1H, 6-H), 1.07 – 0.98 (m, 1H, 7-H), 0.73 (dt, J = 10.2, 5.2 Hz, 1H, 7-H) ppm.

References


[21] Mass spectra were carried out by injection of a 20 ppm solution in CH$_3$CN/H$_2$O on LC/MS system using XBridge analytical column C18 5μm 4.6 x 50 mm with an electrospray ionization (ESI) interface in the positive mode; solvent system 0 – 100% ACN/ammonium formate (10 mM) in water.

[22] See synthesis of 12a in chapter 5.

Chapter 5: Synthesis of Cyclopentane-Fused Piperidines

5.1. General Approach

A complementary approach toward conformationally restricted piperidines and other N-heterocycles is based on merging the heterocyclic core with a cyclopentane ring. The fact that many traditionally used strategies for the assemblage of cyclopenta-fused heterocyclic motifs like the Lewis acid catalyzed Nazarov reaction, the Pauson-Khand reaction, the ring-closing metathesis or the [3+2] cycloadditions often suffer from the lack of availability of the starting materials, harsh reaction conditions, multi-step synthetic sequence, low selectivity and/or troublesome purification, prompted us to explore gold(I) catalysis. Relying on the fact that electrophilic activation of suitably assembled enynyl esters triggers ester migration to form pentadienyl cations, which after electrocyclization, protodeauration and eventual hydrolysis provide cyclopentenones (see Chapter 3), we assumed that the same approach would furnish pentannulated piperidines and other N-heterocycles.

However, a few issues have to be addressed. First of all, the presence of the nitrogen atom could influence the stability of positively charged intermediates and therefore their reactivity. Since the gold(I) activates the triple bond toward nucleophilic addition, nitrogen atom has to be protected. Taking into account that closely related N-Boc enynes undergo gold(I)-catalyzed rearrangement to form cyclic urethane, the choice of the nitrogen protecting group could be of crucial importance. Further question arises about the influence of gold(I) on the torquoselectivity in ring closing step. Finally, to declare a tandem gold(I)-catalyzed rearrangement/electrocyclization process a useful strategy for the pentannulation of N-heterocycles, both the reaction sequence for the synthesis of corresponding enynyl acetate and the tandem process have to be general, robust and scalable.

To this end, the piperidine-derived enynyl acetates 7aa-9 (Figure 1) were prepared as a model substrates and subjected to the gold(I) catalysis. The detailed experimental studies supported by DFT calculations demonstrated that these processes are more complex than that previously reported for non-heterocyclic systems, with a whole series of elements influencing the reaction outcome.
5.2. Gold(I)-Catalyzed Tandem [3,3]-Rearrangement/Nazarov Reaction of N-Heterocycles Bearing Propargyl Moiety at C-2


5.2.1. Preliminary Results and Optimisation of Reaction Conditions

In order to avoid any possible interference by a N-alkoxycarbonyl group, the optimisation of the reaction conditions for the sequential [3,3]-rearrangement/Nazarov cyclization was carried out with model compound 7aa, bearing a N-Ts protecting group. The synthesis of this model compound was carried out by converting the N-Ts δ-valerolactam (11aa) into the corresponding enol phosphate 12aa which was immediately subjected to the Sonogashira coupling\(^\text{2a}\) with 1-heptyn-3-ol to give alcohol 13aa in 62 % after chromatography. In next step alcohol 13aa was treated with acetic anhydride to provide acetate 7aa in 79 % yield (Scheme 2).

![Scheme 2](image)

Scheme 2. Synthesis of model substrate 7aa. Reagents and conditions: (a) n-BuLi, THF, -78 °C, 30 min; then TsCl (86 %), (b) KHMDS, -78 °C, 1.5 h; then (PhO)\(_2\)POCl, -78 °C, 1 h (80 %); (c) heptyn-3-ol, 15 mol % CuI, 6 mol % (Ph\(_3\))\(_2\)PdCl\(_2\), CHCl\(_3\)-Et\(_3\)N, 1 : 2, 55 °C, 7 h (62 %); (d) Ac\(_2\)O, Et\(_3\)N, DMAP, DCM, 0 °C to r.t., on (79 %).

The treatment of enynyl acetate 7aa with 3 mol % of Ph\(_3\)PAuCl/AgSbF\(_6\) in anhydrous DCM at room temperature led to the formation of cyclopentenone 17aa along with the mixture of acetates 14aa and 16aa in approximate 1 : 1 : 1 ratio (Table 1, entry 1). Since the water is necessary for the hydrolysis of the acetates under the reaction conditions, the reaction was carried out in DCM that was not dried prior use. In this case, the yield of cyclopentenone 17aa was increased to 70 %, while acetate 14aa was obtained in 14 % yield (entry 2). When wet DCM was used as the reaction solvent, the concurrent hydrolysis of acetate 16aa was faster to provide 17aa again as the major product but in a lower ratio with residual acetate 14aa (entry 3). Similarly, a lower ratio between 17aa and 14aa was obtained when the reaction was carried out with AgSbF\(_6\) in chloroform (entry 4).

Given the role that silver can have in gold-catalyzed reaction\(^3\) in order to exclude AgCl from the reaction medium the solution of Ph\(_3\)PAuCl and AgSbF\(_6\) was filtered through a Celite layer (entry 5). Since the decomposition of the catalyst during this operation has been reported\(^4\) a larger amount of precatalyst (6 mol %) was used. The reaction occurred as usual, thus demonstrating that the silver halide does not affect neither the reaction rate nor the selectivity. On the other hand, AgSbF\(_6\) alone (entry 6) did catalyze the reaction, albeit to a very low extent.

| Table 1. | Gold(I)-catalyzed [3,3]-rearrangement/Nazarov reaction of acetate 7aa using | |
Ph₃PAuCl/AgSbF₆ catalyst system. a  

![Chemical structure](image)

Table 2. Optimization of reaction conditions. a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst b</th>
<th>Conditions c</th>
<th>Time (h) d,e</th>
<th>Yield f (a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>14aa</td>
<td>15aa</td>
</tr>
<tr>
<td>1</td>
<td>Ph₃PAuCl/AgSbF₆</td>
<td>dry DCM</td>
<td>5 (0)</td>
<td>18 g</td>
</tr>
<tr>
<td>2</td>
<td>Ph₃PAuCl/AgSbF₆</td>
<td>DCM</td>
<td>2.5</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>Ph₃PAuCl/AgSbF₆</td>
<td>wet DCM</td>
<td>5 (0)</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>Ph₃PAuCl/AgSbF₆</td>
<td>CHCl₃</td>
<td>2 (0.5)</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>Ph₃PAuCl/AgSbF₆</td>
<td>DCM</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>6</td>
<td>AgSbF₆</td>
<td>DCM</td>
<td>3</td>
<td>-</td>
</tr>
</tbody>
</table>

Reactions carried out on 0.1-0.15 mmol, at 25 °C and left under stirring 16 h after consumption of the starting material. An aqueous work-up was carried out to recover the products from the reaction mixture. b Catalysts were prepared by adding the silver salt to a 0.004 M solution of the gold(I) chloride in the reaction solvent. c Solvents were not dried before use unless otherwise indicated. d Time to reach complete conversion of the starting material. e In brackets, time left for hydrolysis. f Yield after chromatography unless otherwise indicated. g By ¹H NMR analysis of the crude reaction mixture. h Reaction carried out with 6 mol % of precatalyst and after filtration of AgCl. i Conversion was not complete and degradation of the starting material occurred.

In order to investigate the influence of the counterion on the outcome of the reaction, different silver
salts were screened (Table 2). All reactions were carried out in DCM at room temperature with 3 % of precatalyst loading, monitored by TLC and after complete consumption of enynyl acetate 7aa reactions were left to stir at room temperature overnight. Lower ratio between cyclopentenone 17aa and acetate 14aa and lower overall yield were obtained using AgBF₄ and AgNTf₂. Interestingly, using AgOTf the yield of acetate 14aa was increased to 51%, while cyclopentenone 17aa was obtained in 35% yield after chromatography. When Cu(OTf)₂ was used to generate the active gold(I) catalyst, cyclopentenones 17aa and 15aa were obtained in a 1.5 : 1 ratio and 48 % yield. Repeating the reaction in refluxing DCM (entry 5), consumption of the starting material was complete in 40 min and hydrolysis in 3 h, providing again a mixture of the two regioisomers in a 1 : 1.4 ratio. It is interesting to note here that only with Cu(OTf)₂ the hydrolysis of acetate 14aa was observed because copper triflate remains in solution and due to its Lewis acid character it accelerates the hydrolysis of both acetates.

To increase the ratio between products 14aa and 17aa the reaction was carried out with 3 mol % of Ph₃PAuCl/AgOTf in different solvents. In toluene at room temperature (entry 6) the ratio was increased to 3 : 1 in favour of acetate 14aa. Decreasing the temperature to 0 °C (entry 7) this ratio was additionally improved to 4 : 1 but the reaction was slower and accompanied by the degradation of the starting material which results in a lower overall yield. The degradation of starting enynyl acetate 7aa was even more significant in THF. Acetonitrile and 1,4-dioxane were not suitable solvents for this transformation while silver triflate and copper triflate alone did not catalyze the reaction efficiently (entries 11-12).

**Table 3. Hydrolysis of acetate 14aa.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Time (h)</th>
<th>15aa</th>
<th>17aa</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TfOH, DCM: MeOH = 1 : 1</td>
<td>20</td>
<td>66</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>pTsOH x H₂O, DCM/MeOH = 1 : 1</td>
<td>20</td>
<td>93</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>K₂CO₃, MeOH</td>
<td>4</td>
<td>degradation</td>
<td></td>
</tr>
</tbody>
</table>

Furthermore, isolated acetate 14aa was subjected to the hydrolysis (Table 3). When dissolved in dichloromethane/MeOH and treated with a catalytic amount of monohydrate pTsOH, it slowly provided the corresponding cis fused cyclopentenone 15aa as the main product and cyclopentenone 17aa, whose formation could be accounted for an acid catalyzed [1,5]H shift. In the hydrolysis of 14aa with 1 % TfOH in DCM/MeOH the shift was more pronounced as 15aa and 17aa were obtained in 2 : 1 ratio. On the contrary, attempts at basic hydrolysis (K₂CO₃ in MeOH) of 14aa and isomerisation of 15aa under basic conditions (NaOMe in MeOH and DBU in THF) led to the formation of very complex crude reaction mixtures.

5.2.2. **Nitrogen Protecting Group**

The best reaction conditions (3 mol % Ph₃PAuCl/AgSbF₆ in DCM at room temperature) found for enyne 7aa were extended to the corresponding substrates protected as N-Boc (7b), N-Cbz (7c) and N-CO₂Me (7d), all prepared in good overall yields as described for 7aa starting from the corresponding protected lactams (Scheme 3).
The reaction of N-Boc derivative 7b (Table 4, entries 1-3) only provided degradation products plus about 20% of the oxayauration product 18b when the reaction was carried out in toluene. The cyclic urethane intermediate 18b was not isolated. The crude reaction mixture was analyzed by ^1H NMR. Diagnostic signals, the triplet at 4.71 ppm and the singlet at 5.56 ppm were assigned to protons H_a and H_c, respectively. Proton H_b resonates at 5.15 ppm as a triplet. The formation of this byproduct could be rationalized as a competing 6-endo-dig attack of the carbamate carbonyl group to the activated triple bond (Scheme 4).

![Scheme 4. Formation of cyclic urethane 18b.](image)

**Table 4. Sequential gold(I)-catalyzed rearrangement/Nazarov reaction of acetates 7b-d.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conditions</th>
<th>Time (h)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7b</td>
<td>DCM, 25 °C</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>7b</td>
<td>Toluene, 25 °C to reflux</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>7b</td>
<td>Acetone, 25 °C to reflux</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>4^a</td>
<td>7b</td>
<td>DCM, 25 °C</td>
<td>20</td>
<td>48</td>
</tr>
<tr>
<td>5^a</td>
<td>7b</td>
<td>DCM, reflux</td>
<td>3</td>
<td>61</td>
</tr>
<tr>
<td>6</td>
<td>7b</td>
<td>DCM, 25 °C</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>7b</td>
<td>DCM, reflux</td>
<td>2^a</td>
<td>64</td>
</tr>
<tr>
<td>8</td>
<td>7b</td>
<td>Toluene, reflux</td>
<td>1.5^x</td>
<td>50</td>
</tr>
<tr>
<td>9</td>
<td>7b</td>
<td>THF, reflux</td>
<td>1.5^x</td>
<td>45</td>
</tr>
</tbody>
</table>

**a** Reactions carried out on 0.15-0.2 mmol, with 5 mol % of catalyst unless otherwise indicated. ^b^ Catalysts were prepared by adding the silver salt to the 0.004 M solution of the gold(I) chloride in the reaction solvent. ^c^ Solvents were not dried before use unless otherwise indicated. ^d^ Time to reach complete conversion of the starting material. ^e^ Yield after chromatography unless otherwise indicated. ^f^ Complete degradation of the starting material occurred. ^g^ Not detected by ^1H NMR analysis of the crude reaction mixture. ^h^ Reaction carried out with 8 mol % of catalyst. ^i^ Reaction carried out on a 0.075 mmol scale. ^j^ Degradation occurred at a certain extent. ^k^ Then left 16 h at room temperature.
Better results, but only when the catalyst loading was increased to 8 mol % and temperature risen to reflux, were obtained with N-Cbz derivative 7c (Table 4, entries 4 and 5) which underwent reaction providing cyclopentenone 17c in 61 % yield after chromatography as the sole product. In this case, both consumption of the starting material and hydrolysis were complete after 3 h. In addition, some degradation of the starting material occurred, albeit in a much lower extent than with N-Boc compound 7b.

Also with N-CO₂Me protected compound the reaction did not take place if not by heating in refluxing dichloromethane (Table 4, entries 6 and 7) with 5 mol % of catalyst. Interestingly, monitoring the reaction by TLC revealed the formation of two spots corresponding to the two acetate isomers and during the course of the reaction, only one disappeared to form a more polar spot corresponding to Nazarov product 17d. After the chromatography, Nazarov compound 17d was isolated as the major product in 64 %, while acetate 14d in 14 %. Carrying the reaction in THF and toluene the yield and the ratio between 14d and 17d were not improved.

5.2.3. **Mechanistic Study**

According to the literature and experimental results, the mechanism shown in Scheme 5 was proposed. Pentadienylic cation 20aa generated via gold-catalyzed [3,3]-rearrangement of enynyl acetate 7aa subsequently undergoes 4π electrocyclization giving Au-containing cyclopentadienylic cation 21aa with two available protons for protodeauration step. Acetate 16aa is formed via extraction of proton from the ring junction and hydrolyzes in situ giving thermodynamically more stable α,β-unsaturated ketone 17aa while extraction of proton from β position with respect to the gold leads to acetate 14aa that is resistant to hydrolysis under the reaction conditions.

![Scheme 5. Proposed reaction mechanism and 1H NMR spectra of reaction carried out in CDCl₃ after 0.5 h (red), 1 h (green) and 2.5 h (purple).](image-url)

To demonstrate that the formation of ketone 17aa occurs via in situ hydrolysis of acetate intermediate 16aa, we set up one experiment in CDCl₃ and monitored the progress of the reaction by 1H NMR spectroscopy (Scheme 5). Aliquots of the reaction mixture were filtered on a Celite layer and diluted after 0.5 h, 1 h and 2.5 h from the addition of the catalyst. After 30 min, 1H NMR analysis actually showed three new sets of signals, of which one for cyclopentenone 17aa and two for acetates 14aa and 16aa. The ratio between intermediates 14aa and 16aa decreased during the reaction concurrently.
to a relative increase of 17aa. At the end of the reaction, only the signals of 17aa and acetate 14aa were present in the spectrum. In addition, based on the experimental results [1,5]-H-shift from 14aa to 16aa could be excluded while there is no solid evidence to exclude [1,5]-H-shift from 16aa to 14aa.

5.2.4. DFT Calculations

In order to understand this process in more detail, and help identifying the structures and energies of the critical steps, the DFT calculations were carried out. For the sake of the simplicity, the model substrates which contain the methyl in the propargylic position, and the N-tosyl or the N-CO$_2$Me moiety were used in calculations. The overall discussion presented here is based on model Ia because the results with the N-tosyl derivative are very similar and reinforce the conclusions.

The structures were located using the B3LYP density functional theory method as implemented in the Gaussian suite of programs. The alkynyl-gold(I) cationic complex Ia was considered as the starting point of the mechanism (G = 0 kcal/mol), and all reported energies in the following discussion are relative to it. The energy values correspond to Gibbs free energies ($\Delta G$), computed at B3LYP/6-31G** level (LANL2DZ for gold atom).

Scheme 6. Computed reaction profile. Energies are in kcal/mol.

Initially, the coordination of the gold atom to the triple bond induces a rapid two step acetate rearrangement to form the pre-Nazarov cyclization complex IIa (Scheme 6). The attack of the acetate carbonyl oxygen of Ia to the gold-activated alkyne leads to the formation of a cyclic intermediate IIa and the subsequent C-O bond breaking event renders an allylic cation (IIIa) stabilized by the presence of the gold atom. Noteworthy, the computed energies indicate that Ia and IIIa are isoenergetic (0.1 kcal/mol difference), and that the activation energies of both steps are fairly low, ca. 10 kcal/mol, meaning that in the absence of further evolution, Ia and IIIa would be in an almost 1:1 equilibrium. However, complex IIIa evolves through an easy cyclization to IVa, a process that presents a very low barrier of 5.1 kcal/mol (TS3a). In accordance to the conrotatory nature of the Nazarov reaction under
thermal conditions, the reaction is predicted to be diastereoselective, with formation of the C-C bond that presents the two H atoms in a trans relationship.

The results with the N-tosyl derivative (Ib) are comparable, showing activation energies of 11.4 and 10.9 kcal/mol for the two step acetate rearrangement process, a reaction energy of +0.7 kcal/mol in the formation of IIIb, and an activation barrier of 4.0 kcal/mol for the Nazarov cyclization.

At this point, we attempted to explain the diene formation through a single-step intramolecular hydride shift with concomitant C-Au bond breaking. In fact, the corresponding transition structure TS4a was located, but its accompanying activation energy (30 kcal/mol from IVa to TS4a) is too high to be feasible under the experimental reaction conditions. Therefore, an external base is needed for the deprotonation, and it is important to highlight that several possible candidates exist in the reaction media, like the gold cation in the gold(I) salt, the anion forming the silver or copper salt or water molecules.

We were particularly interested in the proton abstraction step since, based on our experimental findings, the regioselectivity of the reaction seems to be determined at this stage. Once the final diene-acetates VI and VI' are formed, there are not evident signs of significant equilibration between them during the reaction. So, as a plausible approximation, and without knowing the exact nature of the molecule responsible for the abstraction, to demonstrate that this is actually the regiodetermining stage, the deprotonation step was computed by using the triflate anion as the base (Figure 2). The computational results indicate that the triflate mediated hydrogen abstraction is, in fact, not highly regioselective, the difference between TS5a and TS5a' being of only 0.8 kcal/mol in favour of the formation of VI' isomer. In the case of the N-tosyl group, the difference is 0.4 kcal/mol (favouring TS5b'). The experimental data show a regioselectivity that ranges from 4 : 1 when using AgOTf as the source of the non-coordinating anion, to 1 : 5 when AgSbF6 was used which computationally accounts for a difference of less than 1 kcal/mol in each sense. Thus, the computed activation energies are in agreement with the experimental data, noting that this conclusion has to be taken with care without knowing the exact nature of the actual base in the system and that with different types of substrates the regioselectivity using AgSbF6 was complete in favour of type VII ketones derived from hydrolysis of VI. It is also clear that the computed thermodynamic preference for V over V', and for VI' over VI are not affecting the final selectivity due to the lack of equilibration.

Figure 2. Transition states TS5 and TS5' in the presence of triflate anion and compounds formed thereafter.
After the formation of VI-type dienes, the most logical process would follow via hydrolysis to the final products (Scheme 7). There is a final interesting question at this point, regarding the very different experimental hydrolysis rates of both diene types, 14 and 16. Once again, as the exact nature of the protonating species is unknown, we chose triflic acid and H$_3$O$^+$ as simple models to study computationally this issue, and the transition states for the hydrogen transfer were located. Noteworthy, the protonation of VI (model of diene 16) is predicted to be three or four orders of magnitude faster than the corresponding protonation of VI' (model of 14), as derived from 3.5 kcal/mol (H$_3$O$^+$) or 5.7 kcal/mol (TfOH) energy difference in favour of the former. This data easily explains why non-hydrolyzed 14 and hydrolyzed 16 are the final adducts of the reaction. The result can be understood in light of the dienamine structure of compound 14 (VI'), and the donor character of the nitrogen atom, which can induce a stabilization of that structure making it less prone to hydrolysis.

Concerning the lower reaction rates of N-alkoxycarbonyl protected substrates 7b-d, as we have hypothesized, DFT calculations predict the formation of a non-productive cyclized intermediate VIIIa, which is more stable than the starting material, thus sequestering the gold catalyst for a while and reducing the reaction rate (Scheme 8). The starting compound 1a can proceed through acetate rearrangement to form IIIa or through cyclization with the methyl ester to form VIIIa. The three complexes VIIIa, 1a, and IIIa are in equilibrium, which is shifted towards the non-productive, but low in energy (-6.1 kcal/mol) side complex VIIIa. Only the irreversible Nazarov cyclization from IIIa to IVa is finally able to displace this equilibrium towards the formation of the bicyclic adducts.

Scheme 7. Hydrolysis of diene-acetates VI and VI' in the presence of a model acids (TfOH and H$_3$O$^+$).

<table>
<thead>
<tr>
<th>ΔG$^\ddagger$TS6' - ΔG$^\ddagger$TS6</th>
</tr>
</thead>
<tbody>
<tr>
<td>TFOH 5.7 kcal/mol</td>
</tr>
<tr>
<td>H$_3$O$^+$ 3.5 kcal/mol</td>
</tr>
</tbody>
</table>

Scheme 8. DFT predicted formation of the non-productive VIIIa intermediate.
5.2.5. Torquoselectivity

A synthetically important aspect of the Nazarov reaction is the torquoselectivity of the ring closure. In order to evaluate the torquoselectivity, model compounds 7e and 7f were prepared from corresponding tosyl protected δ-valerolactams (Scheme 12).

The reaction of enyne 7e was first carried out in DCM at room temperature (Scheme 9) in the presence of 5 mol % of Ph₃PAuSbF₆ as the catalyst and provided only cyclopentenone 17e in 78 % yield after chromatography. ¹H NMR analysis of the crude reaction mixture revealed a mixture of diastereomers in 6 : 1 ratio, with the cis compound being predominant. As the pre-Nazarov complex is a vinylgold species, a few ligands with different properties were screened to evaluate their possible role in the ring closure selectivity.

![Scheme 9](image)

Scheme 9. Influence of different gold ligands on the torquoselectivity: (a) L = Ph₃P, 78 % yield, cis-17e : trans - 17e = 6 : 1; (b) L = (Cy)₃P, 91% yield, cis-17e : trans - 17e = 10 : 1.

When the electron-rich (Cy)₃P ligand was used, both the torquoselectivity (10 : 1) and the yield (91 %) were improved whereas the use of electron-poor [(pCF₃C₆H₄)₃P] ligand and NHC-carbene ligand led to the formation of very complex mixtures of cyclopentenones, acetates and the degradation products.

The formation of the cis compound as predominant isomer is consistent with previous observations on the torquoselectivity in the Nazarov reaction. For stereoelectronic reasons, the ring closure occurs in a way to form the new bond on the opposite side of the axially oriented 6-Me group. The bases for the lower torquoselectivity in the gold-catalyzed process are not easy to understand, and could be kinetic (i.e. both clockwise and counterclockwise ring closures could take place at different rate in the putative intermediate IXa, Scheme 10) or steric (i.e. the geometry of the oxyallyl cation before ring closure).

![Figure 3](image)

Figure 3. X-Ray structure of cis-17e.
DFT Calculations carried out on model compound IX (Scheme 10) revealed that the preference for IXa is clear, with a difference over IXa' of 2.3 kcal/mol because of the steric reasons. Thus the major cis dimethyl diastereomer (Xa) is formed by a counterclockwise conrotatory ring closure of IXa, with a low activation energy of 6.4 kcal/mol (TS7), whereas its trans diastereomer Xla is formed by conrotatory clockwise ring closure from IXa (TS7', 9.4 kcal/mol). Because of the predominance of intermediate IXa it is likely that the alternative pathway from IXa' is never operative.

Scheme 10. DFT study on the torquoselectivity of the ring closure.

The torquoselectivity with 4-methyl substitute enyne 7f was in line with that observed for 7e using Ph3PAuSbF6 as the catalyst. A separable 6 : 1 mixture of cis and trans isomers 17f was obtained in 66 % yield after chromatography, while acetate 14f was isolated in 14% after chromatography (Scheme 11). In this case, the use of other ligands did not improve the torquoselectivity and led to the formation of very complex mixtures of all acetates and cyclopentenone isomers.

Scheme 11. 14% yield for 14f, 78 % yield for 17f, cis-17f : trans-17f = 6 : 1.

5.2.6. Scope of the Reaction

To assess the scope of the reaction, a series of enynyl acetates (Scheme 12) was prepared by varying the substituents on the alkyne moiety and on the piperidine ring as well as the heterocycle. All piperidine and azepane derived acetates 7a-l were prepared in good yield over two or three steps from lactam-derived enol phosphates 12a-l. In addition, pyrrolidine-2-one derivatives 7m and 7n, indole-derived enynyl acetate 7o and C-3 substituted piperidine enynyl acetate 7p were obtained from enol triflates 12m15 and 12n16 12o17 and 12p respectively. Pyrrolidine derived triflates 12m and 12n as well as 6-methyl substituted phosphate 12e, proved to be much less stable and were used directly as crude reaction mixtures in the next Sonogashira step.
Once isolated, enynyl acetates 7 were subjected to the gold(I)-catalyzed rearrangement/Nazarov reaction in DCM using Ph3PAuCl/AgSbF6 as the catalytic system. The results are summarized in Schemes 13 - 15. The number of alkyl groups at alkyl side chain affected the reactivity and the reaction outcome. Reaction of unsubstituted acetate 7ab was very slow and accompanied with the decomposition at room temperature. However, complete and clean conversion into 17ab was achieved in refluxing DCM. This could be due to a slower rearrangement of the propargyl acetate moiety as a positive charge develops on a primary C atom (C-3') in the transition state. Interestingly, no traces of acetate 14ab or the corresponding ketone were found in the crude reaction mixture, meaning that proton abstraction is much more favoured if occurs at the more substituted position to generate the most substituted double bond.
Incompatibility in case of not compatible with Furthermore, piperidine derivative acts a nucleophile by trapping the acyl cation which is released in the final step of the process. Chromatography, substrate Piperidine derivatives bearing hydroxyl both protected and unprotected at positions C-6 (7a) and C-5 (7b) were compatible with reaction conditions. However, while 7g furnished Nazarov compound 17ad in 86 % yield. With the 3'-phenyl-substituted enyne 7ae the reaction provided expected cyclopentenone 17ae in 55 % after chromatography. Acetate 14ae formed during the reaction in mixture with 17ae in cca. 1 : 1 ratio, during the purification underwent [1,5]H shift giving a complex mixture of few acetate isomeric products. A small amount of pure 14ae was treated with pTsOH (Scheme 14), and it was converted into a mixture of 15ae (95 %) and 17ae. With compound 15ae it was possible to demonstrate by 1H NMR studies the cis fusion of the rings (in analogy to the corresponding carbocyclic systems) and the structure of most populated conformer. 7a-H is a doublet with a low coupling constant (6.8 Hz) with 4a-H indicating its equatorial orientation, further confirmed by the lack of any NOE of 7a-H with 2-Hax and 4-Hax. Consequently, 4a-H is axially oriented. Similarly, in compound 15aa (Table 3) 7a-H is a doublet with a low coupling constant (6.9 Hz) with 4a-H confirming the cis fusion also for this compound. Piperidine derivatives bearing hydroxyl both protected and unprotected at positions C-6 (7h) or C-5 (7ga, 7gb) were compatible with reaction conditions. However, while 7ga and 7h provided corresponding cyclopentenones 17ga and 17h as the sole products in 75 % and 73 % yield after chromatography, substrate 7gb furnished the acetylated derivatives 22 as the major compound (75 %), accompanied by a minor amount of the corresponding alcohol 17gb (16 %). Clearly, the free OH group acts a nucleophile by trapping the acyl cation which is released in the final step of the process. Furthermore, piperidine derivatives bearing protected hydroxyl or ketone at position C-4 (7i–7k) were not compatible with the reaction condition. In all cases very complex reaction mixtures were obtained. Incompatibility in case of 7i and 7j was attributed to the instability of protected allylic alcohol that under
reaction conditions could easily be protonated and expelled form the molecule resulting in the formation of very reactive allylic cation. To prevent the formation of allylic cation carbony group protected as ketal was installed at C-4 but to no avail.

![Chemical structure and reaction scheme]

**Scheme 14.** Hydrolysis of acetates 16ad and 14ae.

Also 7-membered rings as in 7la and 7lb were compatible as these substrates provided, after complete hydrolysis of the corresponding acetate intermediates, Nazarov compounds 17la (81 %) and 17lb (83 %) only and in excellent yield after chromatography (Scheme 15). As in the case of 7aa, the reaction of 7lb required refluxing conditions, too. In both cases, disappearance of the starting material was faster than with the corresponding six-membered heterocycles and no traces of acetate isomers 14la and 14lb were detected by \(^1\)H NMR analysis of the crude reaction mixture.

![Chemical structure and reaction scheme]

**Scheme 15.** Gold(I)-catalyzed tandem [3,3]-rearrangement/Nazarov reaction of azepane- and indole-derived enynyl acetates. Notes: [a] Reaction carried out under reflux.

The ring closure of five-membered derivatives 7m and 7n did not occur at room temperature or in refluxing DCM. In both cases residual starting material was recovered with a certain amount of unidentified degradation compounds. The reaction of 7n was also carried out in refluxing toluene, but to no avail. As already reported,\(^{18}\) derivatives 7m and 7n did not undergo reaction presumably due to the ring strain in the intermediate azabicyclo[3.3.0]octenyl cation and the greater difficulty in the ring closure to give a 5/5 fused system.

On the other hand, indole-derived propargyl acetate 7o containing a N-CO\(_2\)Me protected indole nucleus reacted smoothly in refluxing DCM, to provide the corresponding cyclopenta-fused system 17o in 84 % yield after 1.5 h, thus paving a new way for the synthesis of natural compounds containing the cyclopenta[\(\beta\) ]indole nucleus (Scheme 15).
The construction of quaternary stereocenters is one of the most demanding challenges in the organic synthesis.\textsuperscript{19} Gold(I)-catalyzed [3,3]-rearrangement/Nazarov cyclization of piperidine-derived enynyl acetates bearing a substituent on the position C-3 on a piperidine core would present a new entry to cyclopenta-fused systems with quaternary stereogenic center at a ring junction. Enynyl acetate bearing a methyl at C-3 (7p) was prepared as a model substrate and subjected to gold catalysis. In this case, the presence of the methyl at C-3 restrict the protodeauration step and therefore only the formation of acetate 14p and corresponding ketone 15p were possible (Table 5).

**Table 5.** Gold(I)-catalyzed rearrangement/Nazarov reaction of acetate 7p.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst\textsuperscript{b}</th>
<th>Conditions</th>
<th>Time (h)</th>
<th>Yield\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10% Ph\textsubscript{3}PAuCl/AgOTf</td>
<td>DCM, 50°C</td>
<td>4</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>10% Ph\textsubscript{3}PAuCl/AgOTf</td>
<td>DCE, 80°C</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>5% Ph\textsubscript{3}PAuCl/AgOTf</td>
<td>Toluene, 100°C</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>5% Ph\textsubscript{3}PAuCl, 25% Cu(OTf)\textsubscript{2}</td>
<td>Toluene, 100°C</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>5% CyJohnPhosAuCl/AgOTf</td>
<td>DCM, 50°C</td>
<td>2</td>
<td>-</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reactions carried out on 0.1-0.15 mmol. An aqueous work-up was carried out to recover the products from the reaction mixture. \textsuperscript{b}Catalysts were prepared by adding the silver salt to a 0.004 M solution of the gold(I) chloride in the reaction solvent. \textsuperscript{c}Yield after chromatography.

The acetate 7p was less reactive than 7aa and therefore the reactions were carried out at higher temperature and with higher catalyst loading. The treatment of enynyl acetate 7p with 10 mol % of Ph\textsubscript{3}PAuCl/AgSbF\textsubscript{6} in refluxing DCM led to the formation of cyclopentenone 15p along with the acetate 14p (Table 5, entry 1) in overall yield of 42\%. Since enynyl acetate 7p was recovered from crude reaction mixture in 28\%, in order to improve the yield the reaction was carried out in different solvents and using the different catalyst systems but without significant improvement. Observed lower reactivity could be attributed to the methyl group at C-3 which presents sterical hinderence during the cyclization step.
5.3. Gold(I)-Catalyzed Tandem [3,3]-Rearrangement/Nazarov Reaction of N-Heterocycles Bearing Propargyl Moiety at C-3

5.3.1. Preliminary Results and Optimisation of Reaction Conditions

In an effort to broaden the scope of the reaction and the diversity of products, we assumed that N-heterocycles bearing propargyl side-chain at C-3 when treated with gold(I) would deliver a cyclopenta-fused heterocyclic system with alternate position of C=O group on the five-membered ring (Scheme 16) and therefore piperidine derived enynyl acetate 29a was prepared as a model compound (Scheme 18).


Owing to the stability and perceived compatibility with gold(I) catalysis, p-toluensulfonyl group was selected again to be the protecting group on the nitrogen atom. The synthesis of the model compound 29a started with the reduction of the N-Ts δ-valerolactam (11a) into the corresponding lactamol (Scheme 17). Lactamol 23a was transformed into enesulfonamide 25a by conversion into α-sulfonyl derivative 24a followed by base induced elimination of methanesulfonic acid. In the next step, electrophilic addition of iodine monochloride to the double bond of enesulfonamide 25a followed by a nucleophilic attack of methanol onto formed iodonium ion afforded α-methoxy-β-iodo piperidine derivative 26a as a single stereoisomer. The treatment of 26a with catalytic amount of trifluoroacetic acid in toluene at 140 °C in 7 min led to the elimination of the methanol and provided 3-iodo enesulfonamide 27a in 77 % yield. To avoid the use of this harsh reaction conditions, we employed other methods but the iodination or bromination of 25a proved to be more difficult than anticipated. For example, attempts to obtain 3-iodo derivative 27a using I2/Cs2CO3 in dioxane, NIS in DMF, NIS/AgNO3 in acetonitrile and NIS/TFA in DCM failed completely or provided desired product in complex mixture with unknown products.

Scheme 17. Synthesis of 3-iodoenesulfonamide 27a. Reagents and conditions: (a) DIBAL-H, THF, -78 °C, 1 h; (b) MsCl, Et3N, DMAP, DCM, 0 - 25 °C, 16 h (80 %); (c) ICl or NIS, MeOH, 25 °C, 1 h (91 %); (d) TFA (cat), toluene 140 °C, 7 min (77 %).
Then, iodoenesulfonamide 27a was coupled with (±)-butyn-3-ol under Sonogashira conditions\textsuperscript{27} to afford enynyl alcohol 28a which was treated with acetic anhydride to provide enynyl acetate 29a in yield of 72\% over two steps (Scheme 18).

Scheme 18. Synthesis of enynyl acetate 29a. Reagents and conditions: (a) (±)-butyn-3-ol, 10 mol \% CuI, 5 mol \% (Ph\textsubscript{3}P)\textsubscript{2}PdCl\textsubscript{2}, Et\textsubscript{2}NH - DMF, 1 : 2, 40 °C, 10 min (85 \%), (b) Ac\textsubscript{2}O, Et\textsubscript{3}N, DMAP, DCM, 0 - 25 °C, on (84 \%).

The treatment of enynyl acetate 29a with 5 mol \% of Ph\textsubscript{3}PAuCl/AgSbF\textsubscript{6} in DCM at room temperature led to the formation of cyclopentenone 30a in 66 \% yield. In comparison with tandem gold(I)-catalyzed [3,3]-rearrangement/Nazarov reaction of enynyl acetate 7aa, the cyclization of 29a to 30a was slower and accompanied by many unknown compounds whose formation could be rationalized either via side reactions of gold intermediates or degradation of the starting enynyl acetate. Since the reaction profile was very dirty, all attempts to isolate and identify any of these side products failed. In order to increase the reaction rate and decrease the amount of side-products, different precatalysts were used, reactions carried out at higher temperature, but with no success (Table 6).

Table 6. Gold(I)-catalyzed [3,3]-rearrangement/Nazarov reaction of 29a.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst\textsuperscript{b}</th>
<th>Solvent\textsuperscript{c}</th>
<th>Time (h)</th>
<th>Yield\textsuperscript{d}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph\textsubscript{3}PAuCl/AgSbF\textsubscript{6}</td>
<td>DCM</td>
<td>6</td>
<td>66 %</td>
</tr>
<tr>
<td>2</td>
<td>(cHex)\textsubscript{3}PAuCl/AgSbF\textsubscript{6}</td>
<td>DCM</td>
<td>6</td>
<td>10%</td>
</tr>
<tr>
<td>3</td>
<td>(4-CF\textsubscript{3}Ph)\textsubscript{3}PAuCl/AgSbF\textsubscript{6}</td>
<td>DCM</td>
<td>6</td>
<td>49 %</td>
</tr>
<tr>
<td>4</td>
<td>Ph\textsubscript{3}PAuCl/AgSbF\textsubscript{6}</td>
<td>Dry DCM</td>
<td>1</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>5</td>
<td>Ph\textsubscript{3}PAuCl/AgSbF\textsubscript{6}</td>
<td>DCM\textsuperscript{e}</td>
<td>48</td>
<td>- %</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reactions carried out on 0.15-0.2 mmol, with 5 mol \% of catalyst r.t. \textsuperscript{b} Catalysts were prepared by adding the silver salt to the 0.004 M solution of the gold(I) chloride in the reaction solvent. \textsuperscript{c} Solvents were not dried before use. \textsuperscript{d} Yield after chromatography unless otherwise indicated. \textsuperscript{e} Detected by \textsuperscript{1}H NMR analysis of the crude reaction mixture. \textsuperscript{f} Reaction carried out in refluxing solvent. \textsuperscript{g} Conversion detected by \textsuperscript{1}H NMR.

In analogy with the gold(I)-catalyzed [3,3]-rearrangement/Nazarov reaction of azepane-derived enynyl acetates 7la and 7lb which were faster than the reactions of corresponding piperidine analogues 7ab and 7ac, enynyl acetate 29l was prepared (Scheme 19). Since the reduction of caprolactam followed by the base catalyzed elimination of MsOH failed, the enesulfonamide 25l was prepared via palladium catalyzed reduction of corresponding phosphate 12l.\textsuperscript{28} Iodination and Sonogashira coupling followed by acetylation led to the formation of desired enynyl acetate 29l whose treatment with 5 \% of Ph\textsubscript{3}PAuCl/AgSbF\textsubscript{6} in DCM in 6 h afforded cyclopenta-fused product 30l in 54 \% yield.
Scheme 19. Synthesis of 30l. Reagents and conditions: (a) 5 mol % Pd(OAc)$_2$, 10% Ph$_3$P, HCO$_2$H, Et$_3$N, DME, 40 °C, 40 min (62%); (b) 1. ICl, MeOH, 25 °C, 1 h; 2. TFA (cat), toluene 140 °C, 7 min (86% two steps); (c) 1. (±)-butyn-3-ol, 10 mol % Cul, 5 mol % (Ph$_3$P)$_2$PdCl$_2$, Et$_2$NH - DMF, 1:2, 40 °C, 10 min (71%); 2. Ac$_2$O, Et$_3$N, DMAP, DCM, 0-25 °C, on (84%); (d) 5 mol % Ph$_3$PAuCl/AgSbF$_6$, DCM, 25 °C, 6 h (54%).

It is known that the π-donating ability of the nitrogen atom in enamines gives them both nucleophilic (C-3) and electrophilic (C-2) properties which could be controlled by adjusting the nitrogen protecting group.$^{29}$ Therefore, in an attempt to tune the enamine reactivity, a carbamate protected analogue 29c was prepared from N-Cbz δ-valerolactam 11c and subjected to the gold catalysis (Scheme 20). The use of 5 mol % of Ph$_3$PAuCl/AgSbF$_6$ in DCM led to the formation of very complex crude and careful analysis of $^1$H NMR spectra revealed the signals of desired cyclopetafused product, α,β-unsaturated ketone and starting material in a mixture with unknown products. The change of the precatalyst and counterion did not improve the reaction rate or the reaction profile. The cleanest reaction profile was observed when the reaction was carried out with 5 % of p(CF$_3$Ph)$_3$PAuCl/AgSbF$_6$ in a mixture of DCM and t-BuOH. After 20 h, Nazarov product 30c and α,β-unsaturated ketone 31c were formed in 1:1 ratio. Chromatography afforded Nazarov compound 30c in 26% yield, while α,β-unsaturated ketone 31c in 28% yield.

Scheme 20. Reagents and conditions: (a) 1. DIBAL-H, THF, -78 °C, 1 h; 2. MsCl, Et$_3$N, DMAP, DCM, 0-25 °C, 16 h (61% two steps); (b) 1. ICl, MeOH, 25 °C, 1 h; 2. TFA (cat), toluene 140 °C, 7 min (75% two steps); (c) 1. (±)-butyn-3-ol, 10 mol % Cul, 5 mol % (Ph$_3$P)$_2$PdCl$_2$, Et$_2$NH - DMF, 1:2, 40 °C, 10 min (75%); 2. Ac$_2$O, Et$_3$N, DMAP, DCM, 0-25 °C, on (85%); (d) 5 mol % p(CF$_3$Ph)$_3$PAuCl/AgSbF$_6$, DCM : t-BuOH = 1:1, 25 °C, 20 h.
5.3.2. DFT Calculations

In order to identify the structures and the energies of the critical steps of the mechanism, the potential reaction coordinates of the whole tandem [3,3]-rearrangement/Nazarov cyclization were studied computationally. As the model substrate, compound 29a was used. The structures were located using the B3LYP density functional theory method as implemented in the Gaussian suite of programs. The alkynyl-gold(I) cationic complexes I was considered as the starting point of the mechanism (G = 0 kcal/mol), and all reported energies in the following discussion are relative to it. The energy values correspond to Gibbs free energies (ΔG), computed at B3LYP/6-31G** level (LANL2DZ for gold atom).

Scheme 21. Computed reaction profile. Energies are in kcal/mol.

In comparison with gold(I)-catalyzed [3,3]-rearrangement/Nazarov reaction of 7aa where the acetate rearrangement was the rate-determining step (ΔG = 10 kcal/mol) while the cyclization was a fast process (ΔG = 4.9 kcal/mol, Scheme 6 on page 51), the computational study carried out on substrate 29a resulted in the cyclization of pentadienyl cation III being the rate-limiting step (ΔG = 16.9 kcal/mol). It is worth to notice that the acetate rearrangement proceeds with a quite high activation barrier (ΔG = 13.6 kcal/mol) but the formation of intermediate III is exergonic process (ΔG = -20.7 kcal/mol). The stability of this intermediate could be attributed to the π-donating ability of the nitrogen atom to stabilize the positive charge. The facts that intermediate III is very stable and the activation energy for the cyclization process is very high, allow intermediate III to evolve through side processes.
5.4. Gold(I)-Catalyzed Rautenstrauch Rearrangement of Piperidine-Derived Propargyl Acetate

In 1984, the first metal-catalyzed rearrangement of propargyl acetates to give 2-cyclopentenones was reported by Rautenstrauch.\textsuperscript{30} It was proposed that the coordination of the Pd(II) species to the terminal alkyne effects 1,2-acetoxy migration to give metal carbene species 33 that is in equilibrium with pentadienyl cation 34 (Scheme 22). Although both intermediates can undergo cyclization and ester hydrolysis to form cyclopentenone 36, 4π-electrocyclization is today widely accepted. The fact that the catalyst is so close to the site where new a bond is formed stimulates the development of enantioselective variant of this reaction.\textsuperscript{31}

![Scheme 22. Pd(II)-catalyzed 1,2-acetoxy migration/cyclization (Rautenstrauch rearrangement).](image)

In 2005, Toste and co-workers reported a gold(I)-catalyzed transformation of propargylic pivolates 37 to 2-cyclopentenones 41 (Scheme 23). To rationalize the high degree of observed chirality transfer for the reactions of chiral substrates, it was proposed that the cyclization occurs through helical, pentadienyl cationic intermediate 38.\textsuperscript{32}

![Scheme 23. Gold(I)-catalyzed Rautenstrauch rearrangement.](image)

Interested in the generation of pentadienyl cation which will undergo ring closure to afford cyclopentenone, we decided to investigate if the same approach could furnish pentannulated N-heterocycles with the C=O group at the central position of the 5-membered ring. The substrates 45 and 48 were synthesized as shown in Scheme 24. N-Tosyl protected δ-valerolactam 11a was transformed into corresponding phosphate 12a which was subjected to Pd-catalyzed
methoxycarbonylation. Obtained enecarbamate ester 42 was reduced to alcohol and then oxidized to aldehyde 43 because the selective reduction of 42 to 43 at low temperature (T < -50 °C) did not work well. Reaction of aldehyde with lithiated hexine gave desired propargylic alcohol 44 in 92 % yield, whereas the reaction with lithiated triethylsilylacetylene led to the formation of desired terminal alkyne 47 in poor yield. Compound 47 was obtained as minor product in a mixture with secondary alcohol 46 which is formed via nucleophilic addition of n-BuLi to the carbonyl group of 43. However, both propargylic alcohol 44 and 47 were acetylated under standard conditions to give propargyl acetates 45 and 48 in excellent yields.

The treatment of 45 with 5 mol % of Ph₃PAu/AgSbF₆ in DCM at room temperature (Scheme 25) afforded complex crude for which ¹H NMR analysis indicated the formation of cyclised product. The purification afforded only few milligrams of relatively pure compound whose structure was assigned as 49 based on ¹H NMR, gCOSY and HSQC spectra. If the structure is correctly assigned, then 49 was formed via expected 1,2-acetoxy migration followed by 4π-cyclization in less than 10 % yield. The formation of complex crude could be rationalized through electrophilic activation of the alkyne followed by non-selective 1,2- and 1,3-acetoxy migration.
On the contrary, terminal propargyl acetate 48 when treated with 5 mol % of Ph$_3$PAuCl/AgSbF$_6$ in DCM at room temperature in 30 min was transformed into pure acetate 52 which was hydrolyzed to ketone 53 (Scheme 26).33

Formation of the planar acetate 52 led to the conclusion that the proton necessary for the protodeautration step is abstracted from the ring junction of the oxyallyl cation 50, thus removing the chiral information that could be, in case of enantioenriched propargyl acetate transferred through cyclization step. In addition, the observed difference in the protodeauration step in comparison with the gold(I)-catalyzed tandem process described by Toste32 could be attributed to the influence of the nitrogen atom.

Although the preliminary results showed that gold(I)-catalyzed Rautenstrauch rearrangement of 48 followed by the hydrolysis led to the formation of cyclopenta-fused piperidine 53, we decided not to explore this process in detail due to the formation of planar acetate 52 which indicate the possible loss of chiral information in reactions of chiral or enantioenriched propargyl acetates. In addition, we predicted narrow scope of the reaction due to the observed incompatibility of alkyl substituted propargyl acetate 45.

5.5. Experimental Part

General information
Solvents and reagents were used either as received from commercial suppliers or, when necessary, purified using standard laboratory techniques according to methods published in “Purification of Laboratory Chemicals” by Perrin, Armarego, and Perrin (Pergamon Press, 1966). All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of dry nitrogen. Chromatographic separations were performed under pressure on silica gel by flash-column techniques; R$_f$ values refer to TLC carried out on 0.25-mm silica gel plates (Merck F$_254$), with the same eluent as indicated for the column chromatography. Melting points were recorded on a Buchi-540 melting point apparatus and are uncorrected. Optical rotation values were recorded on a Jasco DIP-370 polarimeter at indicated temperature in the specified solvents and concentrations. $^1$H NMR and $^{13}$C NMR spectra were recorded at 400 and 100.4 MHz, respectively, in the specified deuterated solvent at room temperature. Solvent reference lines were set at 7.26 and 77.00 (CDCl$_3$) in $^1$H and $^{13}$C NMR spectra, respectively. Mass spectra were carried out by direct inlet of a 20 ppm solution either in CH$_3$OH or CH$_3$OH + 0.1% HCO$_2$H on a LCQ Fleet$^TM$ Ion Trap LC/MS system (Thermo Fisher Scientific) with an electrospray ionization (ESI) interface in the positive mode. Microanalyses were carried out with a CHN Thermo FlashEA 1112 Series elemental analyzer.
Compounds 10g, 10i, 10j, 11f, 11j, 11m, 11n, 11o, 11p were prepared as reported, whereas starting \( \delta \)-valerolactames as well as compounds 11e, 11f, 11h, 17e, 17f, 17d, 17ae, 25a and 25c are known.

8-(Toluene-4-sulfonyl)-1,4-dioxo-8-aza-spiro[4.5]decane-7-one (11k).

NaIO\(_4\) (18.2 g, 84.3 mmol) was dissolved in water (50 mL) and RuO\(_2\) x \( \text{H}_2\text{O} \) (600 mg, 4.44 mmol) was added. The solution rapidly turned yellow while being stirred. Then a solution of 8-(toluene-4-sulfonyl)-1,4-dioxo-8-aza-spiro[4.5]decane (5 g, 16.8 mmol) in EtOAc (100 mL) was added, the reaction mixture was stirred at room temperature, and the course of reaction was monitored by TLC. After 24 h the catalyst was quenched by the addition of i-ProOH (5 mL). Reaction mixture was filtered and the two phases were separated. The aqueous layer was extracted with EtOAc (2 x 60 mL), and the combined organic layer was dried over \( \text{Na}_2\text{SO}_4\). After filtration and evaporation of the solvent, the crude was purified by flash chromatography (pepate/EtOAc, 1 : 1, \( R_f = 0.16 \)) to give 11k (1.3 g, 20%) as a yellow oil. \(^{1}\text{H NMR}\) (400 MHz, CDCl\(_3\)) \( \delta = 7.89 \) (d, \( J = 8.4 \) Hz, 2H, Ts), 7.30 (d, \( J = 8.4 \) Hz, 2H, Ts), 3.98 (t, \( J = 6.2 \) Hz, 2H, 6-H), 3.94 (s, 4H, OCH\(_2\)), 2.63 (s, 2H, 3-H), 2.43 (s, 3H, CH\(_3\)-Ts), 2.06 (t, \( J = 6.9 \) Hz, 2H, 5-H) ppm.

**General procedure for N-tosylation (11).**

A 1.6 M solution of \( n \)-BuLi in hexane (0.7 mL, 1.1 mmol) was added dropwise to the solution of \( \delta \)-valerolactam (1 mmol) in THF (8 mL) at -78 °C. After 30 min, a solution of 4-toluenesulfonyl chloride (195 mg, 1.1 mmol) in THF (2.5 mL) was added dropwise and the resulting mixture was stirred for an additional 30 min below -70 °C. The temperature was risen slowly to 0 °C and the reaction was quenched with saturated NaHCO\(_3\) solution (5 mL) and water (5 mL). The product was extracted with Et\(_2\)O (3 x 5 mL), dried over anhydrous Na\(_2\)SO\(_4\), filtered and concentrated. Flash chromatography afforded pure product 11.

(5S)-5-(tert-Butyl-dimethyl-silanyloxy)-1-(toluene-4-sulfonyl)-piperidin-2-one (11g).

Compound 11g was prepared according to the general procedure starting from 10g (467 mg, 2.04 mmol). After chromatography (\( n \)-hexane/EtOAc, 2 : 1; \( R_f = 0.29 \)) product 11g was obtained (547 mg,
A 0.5 M solution of KHMDS (2.5 mL, 1.25 mmol) in toluene was diluted in anhydrous THF (8 mL) and 5.87
100), 39.0 (t, C Ts), 129.2 (d, 2C, Ts), 129.1 (d, 2C, Ts)
CH Hz, 1H
58
%]

\[
\text{\(C \quad 25.6 \ (q, 3C, SiC(CH_3)_3), 21.6 \ (q, CH_3-Ts), 17.9 \ (s, SiC(CH_3)_2), -4.9 \ (q, 2C, Si(CH_3)_2) \ ppm. MS (ESI) m/z (%): 789 ([M+Na]^+, 100), 406 ([M+Na]^+, 18), 384 ([M+1]^+, 29). Elemental analysis calcd (%) for C}_{18}H_{29}NO_2SiS: C 56.36, H 7.62, N 3.65; found: C 56.46, H 7.85, N 3.56.}
\]

4-tert-Butoxy-1-(toluene-4-sulfonyl)-piperidin-2-one (11i).

Compound 11i was prepared according to the general procedure starting from 10i (707 mg, 4.13 mmol). After chromatography (n-hexane/EtOAc, 3 : 1; \(R_f = 0.28\) product 11i was obtained (670 mg, 50 %) as a yellow solid. \([\alpha]_D^{20} = -0.3 \ (c = 1.25, \text{CHCl}_3). \text{M.p. : 99.3 - 100.7 °C.} \text{H NMR (400 MHz, CDCl}_3 \delta = 7.87 \ (d, J = 8.0 Hz, 2H, Ts), 7.28 \ (d, J = 8.0 Hz, 2H, Ts), 4.07 - 4.00 \ (m, 1H, 4-H), 3.95 - 3.87 \ (m, 2H, 6-H), 2.56 - 2.51 \ (m, 1H, 3-H), 2.40 \ (s, 3H, CH_3-Ts), 2.40 - 2.34 \ (m, 1H, 3-H), 1.98 - 1.86 \ (m, 2H, 5-H) 1.13 \ (s, 9H, t-Bu) ppm. 13C NMR (100.4 MHz, CDCl}_3 \delta = 169.3 \ (s, C2), 144.6 \ (s, Ts), 136.2 \ (s, Ts), 129.2 \ (d, 2C, Ts), 128.4 \ (d, 2C, Ts), 74.3 \ (d, C4), 63.2 \ (s, C-t-Bu), 42.9 \ (t, C3), 42.8 \ (t, C6), 31.1 \ (t, C5), 28.1 \ (q, 3C, C-t-Bu), 21.6 \ (q, CH_3-Ts) ppm. MS (ESI) m/z (%): 672 ([M+Na]^+, 100), 348 ([M+Na]^+, 14), 325.60 ([M]^+, 35).

2,2-Dimethyl-5-(toluene-4-sulfonyl)-tetrahydro-[1,3]dioxolo[4,5-c]pyridin-6-one (11j).

Compound 11j was prepared according to the general procedure starting from 10j (147 mg, 0.86 mmol). After chromatography (n-hexane/EtOAc, 1 : 1; \(R_f = 0.31\) product 11j was obtained (162 mg, 58 %) as a white solid. \([\alpha]_D^{20} = -10.6 \ (c = 0.8, \text{CHCl}_3). \text{M.p. : 191.6 - 193.0 °C.} \text{H NMR (400 MHz, CDCl}_3 \delta = 7.96 \ (d, J = 8.4 Hz, 2H, Ts), 7.29 \ (d, J = 8.4 Hz, 2H, Ts), 4.67 \ (dd, J = 15.0, 2.1 Hz, 1H, 3-H), 4.60 \ (ddd, J = 7.6, 3.8, 2.1 Hz, 1H, 2-H), 4.53 \ (dt, J = 7.6, 2.1 Hz, 1H, 2-H), 3.48 \ (dd, J = 15.0, 1.8 Hz, 1H, 4-H), 2.68 \ (dd, J = 15.0, 2.2 Hz, 1H, 5-H), 2.46 - 2.36 \ (m, 4H, 5-H and CH_3-Ts), 1.27 \ (s, 3H, CH_3), 1.01 \ (s, 3H, CH_3) ppm. 13C NMR (100.4 MHz, CDCl}_3 \delta = 167.6 \ (s, CO), 144.6 \ (s, Ts), 135.5 \ (s, Ts), 129.2 \ (d, 2C, Ts), 129.1 \ (d, 2C, Ts), 109.0 \ (s, C(CH_3)_2), 72.0 \ (d, C3), 71.6 \ (d, C4), 47.0 \ (t, C2), 39.0 \ (t, C5), 25.2 \ (q, CH_3), 23.8 \ (q, CH_3), 21.6 \ (q, CH_3-Ts) ppm. MS (ESI) m/z (%): 672 ([M+Na]^+, 100), 347 ([M+Na]^+, 22), 325 ([M+1]^+, 21). Elemental analysis calcd (%) for C_{18}H_{29}NO_3S: C 55.37, H 5.87, N 4.30; found: C 55.41, H 5.60, N 4.69.

General procedure for phosphate preparation (12).

A 0.5 M solution of KHMDS (2.5 mL, 1.25 mmol) in toluene was diluted in anhydrous THF (8 mL) and cooled to -78 °C. A solution of protected δ-valerolactam 11 (1 mmol) in anhydrous THF (4 mL) was added dropwise. The resulting mixture was stirred for 1.5 h at -78 °C and then diphenylchloro-
phosphate (260 mL, 1.25 mmol) was slowly added and the stirring continued below -70 °C for 1 h. The mixture was first allowed to warm to 0 °C and then quenched with aqueous 10% NaOH (25 mL). The product was extracted with Et₂O (4 x 12 mL); the combined organic extracts were washed with 10% NaOH (12 mL) and dried over anhydrous K₂CO₃ for 30 min. After filtration and evaporation of the solvent, the crude was purified by flash chromatography (eluent containing 1% Et₃N) and obtained phosphate was stored at 4 °C as 0.1 M solution in the eluent containing 1% Et₃N until use.

**Phosphoric Acid Diphenyl Ester 1-(Toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-2-yl ester (12a).**

Compound 12a was prepared according to the general procedure starting from 1-(toluene-4-sulfonyl)-piperidin-2-one (900 mg, 3.55 mmol). After chromatography (n-hexane/EtOAC, 2 : 1 + 1% Et₃N; Rᵣ = 0.29) product 12a was obtained (1.38 g, 80%) as a colourless oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.75 (d, J = 8.2 Hz, 2H, Ts), 7.35 – 7.17 (m, 12H, Ts and Ph), 5.25 (dd, J = 6.6, 3.8 Hz, 1H, 3-H), 3.66 – 3.64 (m, 2H, 4-H), 2.37 (s, 3H, C₆), 2.08 – 2.03 (m, 2H, 4-H), 1.56 – 1.51 (m, 2H, 5-H) ppm. ¹³C NMR (100.4 MHz, CDCl₃) δ = 150.4 (s, C₂), 143.7 (s, Ts), 137.7 (s, 2C, Ts), 129.7 (d, 2C, Ts), 129.6 (d, 2C, Ts), 127.6 (d, 2C, Ts), 125.5 (d, 2C, Ph), 120.4 (d, 4C, Ph), 100.5 (d, C₃), 47.5 (t, C₆), 21.5 (q, CH₃-Ts), 21.3 (t, C₄), 20.9 (t, C₅) ppm. MS (ESI) m/z (%): 993 ([M+Na]+, 100), 508 ([M+Na]+, 13.1), 486 ([M+1]+, 8).

**Phosphoric Acid (±)-6-Methyl-1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-2-yl Ester Diphenyl Ester (12e).**

Compound 12e was prepared according to the general procedure starting from 11e (566 mg, 2.12 mmol). After chromatography (n-hexane/EtOAC, 3 : 1 +1% Et₃N; Rᵣ = 0.19) phosphate 12e was obtained (807 mg, 76%) as a colourless oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.72 (d, J = 8.3 Hz, 2H, Ts), 7.34 – 7.16 (m, 12H, Ts and Ph), 5.27 (dd, J = 6.6, 3.8 Hz, 1H, 3-H), 4.58 – 4.41 (m, 1H, 4-H), 2.37 (s, 3H, CH₃-Ts), 2.11 – 1.96 (m, 2H, 4-H and 5-H), 1.46 – 1.34 (m, 2H, 4-H’ and 5-H’), 1.12 (d, J = 6.8 Hz, 3H, 6-CH₃) ppm. ¹³C NMR (100.4 MHz, CDCl₃) δ = 150.4 (s, C₂), 143.7 (s, Ts), 137.7 (s, 2C, Ph), 136.7 (s, Ts), 129.7 (d, 4C, Ph), 129.6 (d, 2C, Ts), 127.6 (d, 2C, Ts), 125.5 (d, 2C, Ph), 120.4 (d, 4C, Ph), 100.2 (d, C₃), 51.9 (d, C₆), 25.1 (t, C₄), 21.5 (q, CH₃-Ts), 18.0 (t, C₅), 16.7 (q, C₆-CH₃) ppm. MS (ESI) m/z (%): 1021 ([M+Na]+, 100), 522 ([M+Na]+, 10), 500 ([M+1]+, 6).

**Phosphoric Acid (±)-4-Methyl-1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-2-yl Ester Diphenyl Ester (12f).**

Compound 12f was prepared according to the general procedure starting from 11f (550 mg, 2.05 mmol). After chromatography (n-hexane/EtOAc, 3 : 1 +1% Et₃N; Rᵣ = 0.20) phosphate 12f was obtained (855 mg, 84%) as a colourless oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.75 (d, J = 8.4 Hz, 2H, Ts), 7.36 – 7.31 (m, 4H, Ph), 7.24 – 7.17 (m, 8H, Ph and Ts), 5.14 (m, 1H, 3-H), 3.73 (dd, J = 13.8, 6.9, 3.1 Hz, 1H, 4-H), 3.54 (dd, J = 13.8, 9.0, 2.8 Hz, 1H, 6-H’), 2.37 (s, 3H, CH₃-Ts), 2.34 – 2.27 (m, 1H, 4-H), 1.66 – 1.61 (m, 1H, 5-H), 1.16 – 1.08 (m, 1H, 5-H’), 0.86 (t, J = 7.0 Hz, 3H, 4-CH₃) ppm. ¹³C NMR (100.4 MHz, CDCl₃) δ = 150.4 (s, C₂), 143.8 (s, Ts), 139.1 (s, 2C, Ph), 136.7 (s, Ts), 129.7 (d, 4C, Ph), 129.5 (d, 2C, Ts), 127.7 (d, 2C, Ts), 125.5 (d, 2C, Ph), 120.1 (d, 4C, Ph), 106.0 (d, C₃), 46.3
Phosphoric Acid (5S)-5-(tert-Butyl-dimethyl-silylamoxy)-1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-2-yl Ester Diphenyl Ester (12g).

Compound 12g was prepared according to the general procedure starting from 11g (530 mg, 1.4 mmol). After chromatography (n-hexane/EtOAc, 3 : 1 +1% Et3N; Rf = 0.24) phosphate 12g was obtained (640 mg, 74 %) as a colourless oil. 1H NMR (400 MHz, CDCl₃) δ = 7.75 (d, J = 8.4 Hz, 2H, Ts), 7.35 – 7.13 (m, 12H, Ts and Ph), 5.15 (dd, J = 6.4, 3.8 Hz, 1H, 3-H), 3.91 (dd, J = 13.0, 3.9 Hz, 1H, 6-H), 3.81 – 3.73 (m, 1H, 5-H), 3.16 (dd, J = 13.0, 9.7 Hz, 1H, 6-H), 2.36 – 2.27 (m, 4H, CH₂-Ts and 4-H), 1.98 (ddt, J = 17.6, 7.5, 3.8 Hz, 1H, 4-H), 0.87 (s, 9H, SiC(CH₃)₃), 0.07 (s, 3H, SiCH₃), 0.04 (s, 3H, SiCH₃) ppm. 13C NMR (100.4 MHz, CDCl₃) δ = 150.3 (s, C2), 143.8 (s, T5g), 139.0 (s, 2C, Ph), 137.3 (s, T5g), 129.7 (d, 4C, Ph), 129.6 (d, 2C, Ts), 127.5 (d, 2C, Ts), 125.6 (d, 2C, Ph), 120.1 (d, 4C, Ph), 97.6 (d, C3), 63.7 (d, C5), 52.3 (t, C6), 31.6 (t, C4), 25.7 (q, 3C, SiC(CH₃)₃), 21.5 (q, CH₂-Ts), 18.0 (s, SiC(CH₃)₃), -4.8 (q, SiCH₃), -4.9 (q, SiCH₃) ppm. MS (ESI) m/z (%): 1253 ([M+Na]+, 100), 638 ([M+Na]+, 93), 616 ([M+1]+, 5).

Phosphoric acid 6-(tert-butyl-dimethyl-silylamoxy)methyl)-1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-2-yl ester diphenyl ester (12h).

Compound 12h was prepared according to the general procedure starting from 11h (1.050 g, 2.65 mmol). After chromatography (heptane/EtOAc, 4 : 1 +1 % Et3N; Rf = 0.24) phosphate 12h was obtained (1.63 g, 98 %) as a yellowish oil. 1H NMR (400 MHz, CDCl₃) δ = 7.80 (d, J = 8.3 Hz, 2H, Ts), 7.37 – 7.16 (m, 12H, Ts and Ph), 5.28 – 5.25 (m, 1H, 3-H), 4.47 – 4.38 (m, 1H, 6-H), 3.62 (dd, J = 10.0, 6.4 Hz, 1H, 6-CH₂TBS), 3.46 (dd, J = 10.0, 8.5 Hz, 1H, 6-CH₂TBS), 2.37 (s, 3H, CH₂-Ts), 2.05 – 1.96 (m, 2H, 4-H), 1.90 – 1.78 (m, 1H, 5-H), 1.41 – 1.30 (m, 1H, 5-H), 0.85 (s, 9H, CH₃-TBS), 0.10 (s, 3H, CH₃-TBS), 0.00 (s, 3H, CH₃-TBS) ppm. 13C NMR (100.4 MHz, CDCl₃) δ = 155.9 (s, C2), 149.4 (s, 2C, Ph), 144.1 (s, T5g), 142.2 (s, T5g), 135.3 (d, Ar), 133.3 (d, Ar), 131.0 (d, Ar), 125.8 (d, Ar), 105.5 (d, C3), 66.9 (t, CH₂TBS), 62.6 (d, C6), 35.3 (t, C5), 31.1 (q, 3C, CH₃), 27.1 (t, C4), 26.0 (s, TBS), 23.8 (q, CH₃-Ts), 0.3 (q, CH₃-TBS), -0.3 (q, CH₃-TBS). MS (ESI) m/z (%): 630 ([M+1]+, 35).

Phosphoric acid 4-tert-butoxy-1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-2-yl ester diphenyl ester (12i).

Compound 12i was prepared according to the general procedure starting from 11i (690 mg, 2.12 mmol). After chromatography (n-hexane/EtOAc, 3 : 1 +1 % Et3N; Rf = 0.28) phosphate 12i was obtained (860 mg, 73 %) as a colourless oil. The compound was highly unstable and decomposed in NMR tube during the characterization. The product was immediately used in next step.
Phosphoric acid 2,2-dimethyl-5-(toluene-4-sulfonyl)-3a,4,5,7a-tetrahydro-[1,3]dioxolo[4,5-c]pyridin-6-yl ester diphenyl ester (12j).

Compound 12j was prepared according to the general procedure starting from 11j (158 mg, 0.49 mmol). After chromatography (n-hexane/EtOAc, 3 : 1 + 1% Et3N; Rf = 0.3) phosphate 12j was obtained (253 mg, 93 %) as a colourless oil. 1H NMR (400 MHz, CDCl3) δ = 7.75 (d, J = 8.0 Hz, 2H, Ts), 7.52 – 6.88 (m, 12H, Ph and Ts), 5.48 – 5.42 (m, 1H, 3-H), 4.55 – 4.47 (m, 1H, 4-H), 4.17 – 4.08 (m, 1H, 6-H), 3.99 (dd, J = 13.3, 4.4 Hz, 1H, 6-H), 3.26 (dd, J = 13.3, 9.1 Hz, 1H, 5-H), 2.37 (s, 3H, CH3-Ts), 1.41 (s, 3H, CH3), 1.33 (s, 3H, CH3) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 150.1 (s, C2), 144.3 (s, C2, Ph), 142.2 (s, Ts), 136.9 (s, Ts), 129.8 (d, Ar) 129.7 (d, Ar), 127.5 (d, Ar), 125.7 (d, Ar), 121.0 (d, Ar), 109.7 (d, C3), 96.5 (s, C(CH3)2), 71.3 (d, C4), 69.9 (d, C5), 48.3 (t, C6), 27.8 (q, CH3), 25.6 (q, CH3), 21.3 (q, CH3-Ts) ppm. MS (ESI) m/z (%): 1136 ([2M+Na]+), 100, 579 ([M+Na]+, 31), 557 ([M+1]+, 9).

Phosphoric acid diphenyl ester 8-(toluene-4-sulfonyl)-1,4-dioxoaza-spiro[4.5]dec-6-en-7-yl ester (12k).

Compound 12k was prepared according to the general procedure starting from 11k (1.3 g, 4.18 mmol). After chromatography (heptane/EtOAc, 3 : 2 + 1% Et3N; Rf = 0.22) phosphate 12k was obtained (860 mg, 73 %) as a colourless oil and used immediately in next step. 1H NMR (400 MHz, CDCl3) δ = 7.72 (d, J = 8.3 Hz, 2H, Ts), 7.34 – 7.14 (m, 12H, Ts and Ph), 5.13 (s, 1H, 3-H), 3.94 – 3.82 (m, 6H, 6-H and OCH2-TBS), 2.34 (s, 3H, CH3-Ts), 1.87 – 1.79 (m, 2H, 5-H) ppm.

Phosphoric Acid Diphenyl Ester 1-(Toluene-4-sulfonyl)-4,5,6,7-tetrahydro-1H-azepin-2-yl ester (12l).

Compound 12l was prepared according to the general procedure starting from 1-(toluene-4-sulfonyl)-azepan-2-one (600 mg, 2.24 mmol). After chromatography (n-hexane/EtOAc, 2 : 1 + 1% Et3N; Rf = 0.23) phosphate 12l was obtained (958 mg, 86 %) as a colourless oil. 1H NMR (400 MHz, CDCl3) δ = 7.79 (d, J = 8.3 Hz, 2H, Ts), 7.31 – 7.11 (m, 12H, Ts and Ph), 5.69 (td, J = 6.9, 3.2 Hz, 1H, 3-H), 3.50 – 3.39 (m, 2H, 7-H), 2.35 (s, 3H, CH3-Ts), 2.09 – 2.02 (m, 2H, 4-H), 1.87 – 1.75 (m, 2H, 6-H), 1.56 – 1.45 (m, 2H, 5-H) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 150.3 (s, C2), 143.8 (s, Ts), 143.5 (s, C2, Ph), 137.5 (s, Ts), 129.7 (d, 4C, Ph), 129.5 (d, 2C, Ts), 127.5 (d, 2C, Ts), 125.5 (d, 2C, Ph), 120.0 (d, 4C, Ph), 113.9 (d, C3), 46.3 (t, C7), 29.8 (t, C6), 23.8 (t, C4), 23.6 (t, C5), 21.5 (q, CH3-Ts) ppm. MS (ESI) m/z (%): 1021 ([2M+Na]+), 100, 522 ([M+Na]+, 24), 499 ([M]+, 7).
Trifluoro-methanesulfonic acid 3-methyl-1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-2-yl ester (12p).

A 0.5 M solution of KHMDMS (6.5 mL, 3.25 mmol) in toluene was diluted in anhydrous THF (16 mL) and cooled to -78 °C. A solution of 11p (700 mg, 2.6 mmol) in anhydrous THF (4 mL) was added dropwise. The resulting mixture was stirred for 1.5 h at -78 °C and then N-phenyl-bis(trifluoromethane-sulfonimide) (1.2 g, 3.25 mmol) was slowly added and the stirring continued below -70 °C for 1 h. The mixture was first allowed to warm to 0 °C and then quenched with aqueous 10 % NaOH (50 mL). The product was extracted with Et2O (4 x 25 mL); the combined organic extracts were washed with 10 % NaOH (25 mL) and dried over anhydrous K2CO3 for 30 min. After filtration and evaporation of the solvent, the crude was purified by flash chromatography (n-hexane/EtOAc, 3 : 1 +1 % Et3N; Rf = 0.44) and phosphate 12p (890, 86 %) was obtained as a colourless oil. 1H NMR (400 MHz, CDCl3) δ = 7.75 (d, J = 8.0 Hz, 2H, Ts), 7.33 (d, J = 8.0 Hz, 2H, Ts), 3.57 - 3.54 (m, 2H, 6-H), 2.45 (s, 3H, CH3-Ts), 2.00 – 1.96 (m, 2H, 4-H), 1.83 (s, 3H, CH3), 1.55 – 1.39 (m, 2H, 5-H) ppm. 13C NMR (101 MHz, CDCl3) δ = 144.7 (s, C2), 135.3 (s, Ts), 134.2 (s, Ts), 129.9 (d, 2C, Ts), 128.0 (d, 2C, Ts), 122.4 (d, C3), 119.9 (s, CF3), 48.1 (t, C-6), 27.7 (t, C-5), 21.7 (t, C-4), 20.1 (q, CH3-Ts), 17.2 (q, CH3). MS (ESI) m/z (%): 821 ([2M+Na]+, 98.8), 422 ([M+Na]+, 72), 399 ([M]+, 63.98).

General procedure for the synthesis of enynyl acetates (7).

Step A: Sonogashira coupling (13)2a
Phosphate/triflate 12 (1 mmol) was dissolved in an anhydrous 2 : 1 Et3N/CHCl3 mixture (6 mL), and alkyne (1 mmol), Cul (19 mg, 0.1 mmol) and (Ph3P)2PdCl2 (35 mg, 0.05 mmol) were added under nitrogen atmosphere. The reaction mixture was heated at 55 °C (external) for 3 h and then a second portion of alkyne (0.5 mmol), Cul (9.5 mg, 0.05 mmol) and (Ph3P)2PdCl2 (7 mg, 0.01 mmol) was added. Heating was continued at 55 °C for 3 h. The mixture was cooled to room temperature and water (15 mL) was added. The product was extracted with Et2O (3 x 15 mL) and the combined organic extracts were dried over anhydrous K2CO3 for 30 min. After filtration and evaporation of the solvent, the crude was purified by flash chromatography and used immediately in the next step.

Step B: Acetylation (7)
A solution of enynyl alcohol 13 (1 mmol), DMAP (24 mg, 0.2 mmol) and Et3N (0.38 mL, 3 mmol) in DCM (4 mL) was cooled (ice bath) and Ac2O (0.19 mL, 2 mmol) was added. The reaction mixture was stirred at room temperature and followed by TLC. When the conversion was complete, satd solution of NaHCO3 (10 mL) was added and the product extracted with DCM (3 x 10 mL). The combined organic extracts were dried over anhydrous K2CO3 for 30 min. After filtration and evaporation of the solvent, the crude was purified by flash chromatography and stored at 4 °C as 0.1 M solution in the eluent containing 1 % Et3N until use.
Acetic Acid 1-[1-(Toluene-4-sulfonfonyl)-1,4,5,6-tetrahydro-pyridin-2-yylethynyl]-pentyl Ester (7aa).
Sonogashira coupling of phosphate 12a (1.16 g, 2.4 mmol) and (-)-heptyl-3-ol after chromatography (n-hexane/EtOAc, 2 : 1 + 1 % Et3N; Rr = 0.30) afforded enynyl alcohol 13aa as a pale yellow oil (515 mg, 62 %). 1H NMR (400 MHz, CDCl3) δ = 7.72 (d, J = 8.2 Hz, 2H, Ts), 7.30 (d, J = 8.2 Hz, 2H, Ts), 5.63 (t, J = 4.3 Hz, 1H, 3-H), 4.43 (t, J = 6.6 Hz, 1H, 1'H), 3.68 – 3.65 (m, 2H, 6-H), 2.42 (s, 3H, CH3-Ts), 2.06 (td, J = 6.6, 4.3 Hz, 3H, 4-H and OH), 1.76 – 1.59 (m, 4H, 5-H and 2'-H), 1.47 – 1.23 (m, 4H, 3'-H and 4'-H), 0.91 (t, J = 7.2 Hz, 3H, 5'-H) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 143.5 (s, Ts), 137.3 (s, Ts), 129.5 (d, 2C, Ts), 127.4 (d, 2C, Ts), 123.6 (d, C3), 120.4 (s, C2), 90.9 (s, C2a), 80.9 (s, C2b), 62.8 (d, C1'), 46.0 (t, C6), 37.2 (t, C2'), 27.2 (t, C5), 23.2 (t, C4), 22.4 (t, C3'), 22.3 (q, CH3 Ts), 21.5 (t, C4'), 13.9 (q, C5') ppm. MS (ESI) m/z (%): 717 ([M+Na]+, 100), 348 ([M+1]⁺, 14).

According to the above described procedure, compound 13aa (515 mg, 1.48 mmol) was subjected to acetylation. After chromatography (n-hexane/EtOAc, 8 : 1 + 1 % Et3N; Rr = 0.21) pure 7aa was obtained as a pale yellow oil (455 mg, 79 %). 1H NMR (400 MHz, CDCl3) δ = 7.77 (d, J = 8.2 Hz, 2H, Ts), 7.29 (d, J = 8.2 Hz, 2H, Ts), 5.65 (t, J = 4.2 Hz, 1H, 3-H), 5.45 (t, J = 6.6 Hz, 1H, 1'H), 3.64 – 3.62 (m, 2H, 6-H), 2.42 (s, 3H, CH3-Ts), 2.08 (s, 3H, CH3-Ac), 2.06 – 2.03 (m, 2H, 4-H), 1.72 – 1.74 (m, 2H, 5-H), 1.65 – 1.59 (m, 2H, 2'-H), 1.44 – 1.31 (m, 4H, 3'-H and 4'-H), 0.90 (t, J = 7.2 Hz, 3H, 5'-H) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 170.0 (s, CO), 143.4 (s, Ts), 137.2 (s, Ts), 129.5 (d, 2C, Ts), 127.5 (d, 2C, Ts), 124.4 (d, C3), 120.2 (s, C2), 97.2 (s, C2b), 81.1 (s, C2a), 64.4 (d, C1'), 46.0 (t, C6), 34.2 (t, C2'), 27.0 (t, C3'), 23.2 (t, C4), 22.2 (t, C4'), 21.5 (q, CH3-Ts), 21.0 (q, CH3-Ac), 21.0 (t, C5), 13.9 (q, C5') ppm. MS (ESI) m/z (%): 801 ([2M+Na]+, 100), 412 ([M+Na]+, 13).

Acetic Acid 3-[1-(Toluene-4-sulfonfonyl)-1,4,5,6-tetrahydro-pyridin-2-yl]-prop-2-ynyl Ester (7ab).
Sonogashira coupling of phosphate 12a (220 mg, 0.45 mmol) and propargyl alcohol after chromatography (n-hexane/EtOAc, 2 : 1 + 1 % Et3N; Rr = 0.22) afforded enynyl alcohol 13ab as a colourless oil (80 mg, 60 %). 1H NMR (400 MHz, CDCl3) δ = 7.77 (d, J = 8.4 Hz, 2H, Ts), 7.30 (d, J = 8.4 Hz, 2H, Ts), 5.65 (t, J = 4.1 Hz, 1H, 3-H), 4.33 (s, 2H, 1'H), 3.67 – 3.64 (m, 2H, 6-H), 2.42 (s, 3H, CH3-Ts), 2.06 (td, J = 6.6, 4.1 Hz, 2H, 4-H), 1.63 – 1.57 (m, 2H, 5-H) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 143.6 (s, Ts), 137.2 (s, Ts), 129.5 (d, 2C, Ts), 127.5 (d, 2C, Ts), 124.1 (d, C3), 120.4 (s, C2), 87.9 (s, C2'), 81.8 (s, C3'), 51.5 (t, C1'), 45.9 (t, C6), 23.2 (t, C4), 21.5 (q, CH3-Ts), 20.9 (t, C5) ppm. MS (ESI) m/z (%): 314 ([M+Na]+, 100), 291 ([M]⁺, 24).

According to the above described procedure, compound 13ab was subjected to acetylation. After chromatography (n-hexane/EtOAc, 3 : 1 + 1 % Et3N; Rr = 0.17) pure 7ab was obtained as a colourless oil (73 mg, 88 %). 1H NMR (400 MHz, CDCl3) δ = 7.77 (d, J = 8.2 Hz, 2H, Ts), 7.29 (d, J = 8.2 Hz, 2H, Ts), 5.69 (t, J = 4.2 Hz, 1H, 3-H), 4.79 (s, 2H, 1'H), 3.65 – 3.62 (m, 2H, 6-H), 2.42 (s, 3H, CH3-Ts), 2.09 (s, 3H, CH3-Ac), 2.06 (td, J = 6.6, 4.2 Hz, 2H, 4-H), 1.65 – 1.59 (m, 2H, 5-H) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 170.2 (s, CO), 143.5 (s, CO), 137.2 (s, Ts), 129.5 (d, 2C, Ts), 127.5 (d, 2C, Ts), 124.9 (d, C3), 120.1 (s, C2), 83.6 (s, C2'), 82.4 (s, C3'), 52.6 (d, C1'), 45.9 (t, C6), 23.2 (t, C4), 21.5 (q, CH3-Ts), 20.9 (q, CH3-Ac), 20.7 (t, C5) ppm. MS (ESI) m/z (%): 689 ([2M+Na]+, 100), 356 ([M+Na]+, 53), 334 ([M+1]⁺, 8).
Acetic Acid 1-Methyl-3-[1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-2-yl]-prop-2-ynyl Ester (7ac).

Sonogashira coupling of phosphate 12a (775 mg, 1.6 mmol) and (±)-butyn-3-ol after chromatography (n-hexane/EtOAc, 4 : 1 + 1 % Et3N; Rf = 0.23) afforded 13ac which was used immediately in the next step. 

According to the above described procedure, compound 13ac was subjected to acetylation. After chromatography (n-hexane/EtOAc, 8 : 1 + 1 % Et3N; Rf = 0.16) pure 7ac was obtained as a colourless oil (372 mg, 67 % after two steps). 

Acetic Acid 1,1-Dimethyl-3-[1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-2-yl]-prop-2-ynyl Ester (7ad).

Sonogashira coupling of phosphate 12a (193 mg, 0.4 mmol) and 2-methyl-3-butyn-2-ol after chromatography (n-hexane/EtOAc, 2 : 1 + 1 % Et3N; Rf = 0.23) afforded 13ad which was used immediately in the next step. 

According to the above described procedure, compound 13ad was subjected to acetylation. After chromatography (n-hexane/EtOAc, 15 : 1 + 1 % Et3N; Rf = 0.14) pure 7ad was obtained as a pale yellow oil (90 mg, 62 % after two steps). 

Acetic Acid 1-Phenyl-3-[1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-2-yl]-prop-2-ynyl Ester (7ae).

Sonogashira coupling of phosphate 12a (210 mg, 0.43 mmol) and (±)-1-phenyl-2-propyn-1-ol after chromatography (n-hexane/EtOAc, 2 : 1 + 1 % Et3N; Rf = 0.20) afforded 13ae which was used.
immediately in the next step. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.77\) (d, \(J = 8.4\) Hz, 2H, Ts), 7.55 – 7.53 (m, 2H, Ph), 7.38 – 7.30 (m, 3H, Ph), 7.19 (d, \(J = 8.4\) Hz, 2H, Ts), 5.66 (t, \(J = 4.1\) Hz, 1H, 3-H), 5.54 (s, 1H, 1'-H), 3.66 – 3.63 (m, 2H, 6'-H), 2.37 (s, 3H, CH\(_3\)-Ts), 2.04 (td, \(J = 6.4, 4.1\) Hz, 2H, 4'-H), 1.63 – 1.57 (m, 2H, 5'-H) ppm.

According to above describe procedure, compound 13ae was subjected to acetylation. After chromatography (n-hexane/EtOAc, 5 : 1 + 1 % Et\(_3\)N; \(R_f = 0.17\)) pure 7ae was obtained as a pale yellow oil (109 mg, 62 % after two steps). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.70\) (d, \(J = 8.4\) Hz, 2H, Ts), 7.56 – 7.53 (m, 2H, Ph), 7.41 – 7.34 (m, 3H, Ph), 7.20 (d, \(J = 8.4\) Hz, 2H, Ts), 6.57 (s, 1H, 1'-H), 5.70 (t, \(J = 4.0\) Hz, 1H, 3-H), 3.69 – 3.59 (m, 2H, 6'-H), 2.38 (s, 3H, CH\(_3\)-Ts), 2.11 (s, 3H, CH\(_3\)-Ac), 2.09 – 2.04 (m, 2H, 4'-H), 1.67 – 1.61 (m, 2H, 5-H) ppm. \(^{13}\)C NMR (100.4 MHz, CDCl\(_3\)) \(\delta = 169.7\) (s, CO), 143.3 (s, Ts), 137.0 (s, Ts), 136.6 (s, Ph), 129.4 (d, 2C, Ts), 128.8 (d, 2C, Ph), 128.6 (d, 2C, Ph), 127.9 (d, Ph), 127.4 (d, 2C, Ts), 124.7 (d, C3), 120.0 (s, C2), 85.9 (s, C3'), 82.8 (s, C2'), 65.9 (d, C1'), 45.9 (t, C6), 23.1 (t, C4), 21.5 (q, CH\(_3\) Ts), 21.0 (q, CH\(_3\) Ac), 20.9 (t, C5) ppm. MS (ESI) \(m/z\) (%): 841 ([2M+Na]\(^+\), 100), 432 ([M+Na]\(^+\), 7).

6-(3-Acetoxyhept-1-ynyl)-3,4-dihydro-2H-pyridine-1-carboxylic Acid tert-Butyl Ester (7b).

Sonogashira coupling of phosphate 12b (536 mg, 1.24 mmol) and (±)-heptyn-3-ol after chromatography (n-hexane/Et\(_2\)O, 7 : 1 + 1 % Et\(_3\)N; \(R_f = 0.28\)) afforded enynyl alcohol 13b which was used immediately in the next step. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 5.54\) (t, \(J = 4.0\) Hz, 1H, 5-H), 4.47 (t, \(J = 6.6, 1H, 3'-H\)), 3.57 – 3.48 (m, 2H, 2-H), 2.48 – 2.27 (bs, 1H, OH), 2.17 – 2.12 (m, 2H, 4'-H), 1.82 – 1.66 (m, 4H, 3-H and 4'-H), 1.49 (s, 9H, C(CH\(_3\)_3)), 1.48 – 2.29 (m, 4H, 5'-H and 6'-H), 0.90 (t, \(J = 6.6\) Hz, 3H, 7'-H) ppm.

According to the above described procedure, compound 13b was subjected to acetylation. After chromatography (n-hexane/EtOAc, 18 : 1 + 1 % Et\(_3\)N; \(R_f = 0.14\)) pure 7b was obtained as a pale yellow oil (250 mg, 60 % after two steps). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 5.56\) (t, \(J = 3.8\) Hz, 1H, 5-H), 5.52 (t, \(J = 6.6\) Hz, 1H, 3'-H), 3.61 – 3.46 (m, 2H, 2-H), 2.17 – 2.13 (m, 2H, 4'-H), 2.05 (s, 3H, CH\(_3\)-Ac), 1.80 – 1.73 (m, 4H, 3-H and 4'-H), 1.49 (s, 9H, C(CH\(_3\)_3)), 1.45 – 1.30 (m, 4H, 5'-H and 6'-H), 0.90 (t, \(J = 7.2\) Hz, 3H, 7'-H) ppm. \(^{13}\)C NMR (100.4 MHz, CDCl\(_3\)) \(\delta = 169.9\) (s, CO-Ac), 153.0 (s, CO-Boc), 123.5 (d, C5), 121.7 (s, C6), 84.6 (s, C1'), 82.4 (s, C2'), 81.2 (s, C(CH\(_3\)_3)), 64.5 (d, C3'), 43.3 (t, C2), 34.6 (t, C4'), 28.2 (q, 3C, C(CH\(_3\)_3)), 27.1 (t, C5'), 23.7 (t, C4'), 22.6 (t, C6'), 22.2 (q, CH\(_3\)-Ac), 21.0 (t, C3), 13.9 (q, C7') ppm. MS (ESI) \(m/z\) (%): 358 ([M+Na]\(^+\), 100).

6-(3-Acetoxyhept-1-ynyl)-3,4-dihydro-2H-pyridine-1-carboxylic Acid Benzyl Ester (7c).

Sonogashira coupling of phosphate 12c (242 mg, 0.52 mmol) and (±)-heptyn-3-ol after chromatography (n-hexane/Et\(_2\)O, 2 : 1 + 1 % Et\(_3\)N; \(R_f = 0.31\)) afforded enynyl alcohol 13c which was used immediately in the next step. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.42 – 7.29\) (m, 5H, Cbz), 5.59 (t, \(J = 4.1\) Hz, 1H, 5-H), 5.18 (s, 2H, CH\(_2\)-Ph), 4.29 (t, \(J = 6.6\) Hz, 1H, 3'-H), 3.66 – 3.61 (m, 2H, 2-H), 2.18 – 2.14 (m, 2H, 4'-H), 1.84 – 1.76 (m, 3H, 3-H and OH), 1.63 – 1.54 (m, 2H, 4'-H), 1.45 – 1.24 (m, 4H, 5'-H and 6'-H), 0.88 (t, \(J = 6.6\) Hz, 3H, 7'-H) ppm.

According to the above described procedure, compound 13c was subjected to acetylation. After chromatography (n-hexane/EtOAc, 20 : 1 + 1 % Et\(_3\)N; \(R_f = 0.14\)) pure 7c was obtained as an orange oil (118 mg, 61 % after two steps). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.38 – 7.29\) (m, 5H, Cbz), 5.61 (t, \(J = 6.6\) Hz, 1H, 5-H), 5.18 (s, 2H, CH\(_2\)-Ph), 4.29 (t, \(J = 6.6\) Hz, 1H, 3'-H), 3.66 – 3.61 (m, 2H, 2-H), 2.18 – 2.14 (m, 2H, 4'-H), 1.84 – 1.76 (m, 3H, 3-H and OH), 1.63 – 1.54 (m, 2H, 4'-H), 1.45 – 1.24 (m, 4H, 5'-H and 6'-H), 0.88 (t, \(J = 6.6\) Hz, 3H, 7'-H) ppm.
6-(3-Acetoxy-hept-1-ynyl)-3,4-dihydro-2H-pyridine-1-carboxylic Acid Methyl Ester (7d).
Sonogashira coupling of phosphate 12d (385 mg, 0.99 mmol) and (±)-heptyn-3-ol after chromatography (n-hexane/ETIOAc, 4 : 1 + 1 % Et3N; Rf = 0.28) afforded enynyl alcohol 13d which was used immediately in the next step. 1H NMR (400 MHz, CDCl3) δ = 5.59 (t, J = 4.1 Hz, 1H, 5-H), 4.56 – 4.38 (m, 1H, 3'-H), 3.74 (s, 3H, OCH3), 3.63 – 3.58 (m, 2H, 2-H), 2.53 – 2.38 (bs, 1H, OH), 2.21 – 2.12 (m, 2H, 4-H), 1.85 – 1.63 (m, 4H, 3-H and 4'-H), 1.52 – 1.22 (m, 4H, 5'-H and 6'-H), 0.91 (t, J = 7.0 Hz, 3H, 7''H) ppm.
According to the above described procedure, compound 13d was subjected to acetylation. After chromatography (n-hexane/ETIOAc, 15 : 1 + 1 % Et3N; Rf = 0.16) pure 7d was obtained as an orange oil (200 mg, 69 % after two steps). 1H NMR (400 MHz, CDCl3) δ = 5.61 (t, J = 4 Hz, 1H, 5-H), 5.45 (t, J = 6.6 Hz, 1H, 3'-H), 3.73 (s, 3H, OCH3), 3.65 – 3.54 (m, 2H, 2-H), 2.16 (dt, J = 6.7, 4.0 Hz, 2H, 4'-H), 2.06 (s, 3H, CH3-Ac), 1.80 – 1.72 (m, 4H, 3-H and 4'-H), 1.46 – 1.29 (m, 4H, 5'-H and 6'-H), 0.9 (t, J = 7.2 Hz, 3H, 7''H) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 170.0 (s, CO-Ac), 154.4 (s, CO2CH3), 123.8 (d, C5), 121.1 (s, C6), 85.3 (s, C1'), 81.6 (s, C2'), 64.5 (d, C3'), 52.6 (q, CO2CH3), 43.7 (t, C2), 34.4 (t, C4'), 27.0 (t, C5'), 23.5 (t, C4), 22.4 (q, CH2-Ac), 22.2 (t, C6'), 21.0 (t, C3), 13.9 (q, C7') ppm. MS (ESI) m/z (%): 316 ([M+Na]+, 100), 294 ([M+Na]+, 5).

Acetic Acid 1-Methyl-3-[6-methyl-1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-2-yl]-prop-2-ynyl Ester (7e).
Sonogashira coupling of phosphate 12e (807 mg, 1.62 mmol) and (±)-3-butyln-2-ol after chromatography (n-hexane/ETIOAc, 2 : 1 + 1 % Et3N; Rf = 0.29) afforded enynyl alcohol 13e which was used immediately in the next step. 1H NMR (400 MHz, CDCl3) δ = 7.76 (d, J = 8.3 Hz, 2H, Ts), 7.29 (d, J = 8.3 Hz, 2H, Ts), 5.67 – 5.62 (m, 1H, 3-H), 4.61 – 4.57 (m, 1H, 6-H), 4.57 – 4.49 (m, 1H, 1'H), 2.41 (s, 3H, CH3-Ts), 2.32 – 2.18 (m, 1H, OH), 2.14 – 2.02 (m, 1H, 5-H), 2.00 – 1.91 (m, 1H, 4-H), 1.53 – 1.31 (m, 5H, 1'-CH3, 4'-H and 5'-H'), 1.14 (d, J = 6.8 Hz, 3H, 6-CH3) ppm.
According to the above described procedure, compound 13e was subjected to acetylation. After chromatography (n-hexane/ETIOAc, 8 : 1 + 1 % Et3N; Rf = 0.17) pure 7e was obtained as a pale yellow oil (350 mg, 60 % after two steps). 1H NMR (400 MHz, CDCl3) δ = 7.74 (d, J = 8.3 Hz, 2H, Ts), 7.27 (d, J = 8.3 Hz, 2H, Ts), 5.66 (d, J = 4.0 Hz, 1H, 3-H), 5.56 – 5.49 (m, 1H, 1'H), 4.53 – 4.47 (m, 1H, 6-H), 2.40 (s, 3H, CH3-Ts), 2.07 – 1.93 (m, 5H, CH3-Ac and 4-H), 1.46 (m, 4H, 1'-CH3 and 5-H), 1.38 – 1.29 (m, 1H, 5'-H'), 1.09 (d, J = 6.8 Hz, 6-CH3) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 169.9 (s, CO), 143.3 (s, Ts), 137.1 (s, Ts), 129.5 (d, 2C, Ts), 127.4 (d, 2C, Ts), 124.0 (d, C3), 117.6 (s, C2), 87.8 (s, C3'), 81.4 (s, C2'), 60.6 (d, C1'), 49.7 (d, C6), 25.0 (t, C4'), 21.5 (q, CH2-Ts), 21.1 (q, CH2-Ac), 20.9 (q, C1'-CH3), 19.2 (t, C5), 17.3 (q, C6-CH3) ppm. MS (ESI) m/z (%): 745 ([2M+Na]+, 100), 384 ([M+Na]+, 9), 76
Acetic Acid 1-Methyl-3-[4-methyl-1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-2-yl]-prop-2-ynyl Ester (7f).

Sonogashira coupling of phosphate 12f (855 mg, 2.05 mmol) and (±)-3-butyne-2-ol after chromatography (n-hexane/EtOAc, 2:1 + 1 % Et3N; Rf = 0.24) afforded enynyl alcohol 13f which was used immediately in the next step. 1H NMR (400 MHz, CDCl3) δ = 7.76 (d, J = 8.2 Hz, 2H, Ts), 7.29 (d, J = 8.2 Hz, 2H, Ts), 5.50 (d, J = 3.4 Hz, 1H, 3-H), 4.60 (q, J = 6.5 Hz, 1H, 1'-H), 3.79 – 3.73 (m, 1H, 6-H), 3.54 – 3.47 (m, 1H, 6-H), 2.55 – 2.33 (m, 4H, CH2-Ts and OH), 2.27 – 2.21 (m, 1H, 4-H), 1.72 – 1.65 (m, 1H, 5-H), 1.43 (d, J = 6.5 Hz, 3H, 1'-CH3), 1.22 – 1.14 (m, 1H, 5-H'), 0.87 (d, J = 7.0 Hz, 3H, 4-CH3) ppm.

According to the above described procedure, compound 13f was subjected to acetylation. After chromatography (n-hexane/EtOAc, 8 : 1 + 1 % Et3N; Rf = 0.17) pure 7f was obtained as a pale yellow oil (350 mg, 57% after two steps). 1H NMR (400 MHz, CDCl3) δ = 7.75 (d, J = 8.1 Hz, 2H, Ts), 7.28 (d, J = 8.1 Hz, 2H, Ts), 5.56 – 5.51 (m, 2H, 3-H and 1'-H), 3.77 – 3.70 (m, 1H, 6-H), 3.51 – 3.45 (m, 1H, 6-H'), 2.40 (s, 3H, CH3-Ts), 2.26 – 2.20 (m, 1H, 4-H), 2.06 (s, 3H, CH3-Ac), 1.72 – 1.65 (m, 1H, 5-H), 1.48 (d, J = 6.7 Hz, 3H, 1'-CH3), 1.23 – 1.15 (m, 1H, 5-H'), 0.86 (d, J = 7.1 Hz, 4-CH3) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 169.9 (s, CO), 143.5 (s, Ts), 136.9 (s, Ts), 130.1 (d, C3), 129.5 (d, 2C, Ts), 127.5 (d, 2C, Ts), 119.1 (s, C2), 87.5 (s, C3'), 80.5 (s, C2'), 60.6 (d, C'), 44.7 (t, C6), 29.0 (t, C5), 28.6 (d, C4), 21.6 (q, CH3-Ts), 21.1 (q, CH3-Ac), 20.9 (q, C1'-CH3), 20.6 (q, C6-CH3) ppm. MS (ESI) m/z (%): 745 ([M+Na]+, 100), 384 ([M+Na]+, 38).

Acetic Acid 3-[5-(tert-Butyl-dimethyl-silyloxy)-1-(toluene-4-sulfonyl)-1,4,5,6-tetra-hydro-pyridin-2-yl]-prop-2-ynyl Ester (13ga).

Sonogashira coupling of phosphate 12g (640 mg, 1.04 mmol) and propargyl alcohol after chromatography (n-hexane/EtOAc, 2 : 1 + 1 % Et3N; Rf = 0.16) afforded enynyl alcohol 13ga which was used immediately in the next step. 1H NMR (200 MHz, CDCl3) δ = 7.79 (d, J = 8.2 Hz, 2H, Ts), 7.31 (d, J = 8.2 Hz, 2H, Ts), 5.56 (t, J = 4.0 Hz, 1H, 3-H), 4.31 (s, 2H, 1'-H), 4.01 (dd, J = 12.7, 3.1 Hz, 1H, 6-H), 3.82 – 3.63 (m, 1H, 5-H), 3.03 (dd, J = 12.7, 9.8 Hz, 1H, 6-H'), 2.43 – 2.27 (m, 4H, CH2-Ts and 4-H), 2.00 (ddd, J = 19.1, 7.8, 4.0 Hz, 1H, 4-H'), 1.77 (bs, 1H, OH), 0.86 (s, 9H, Si(CH3)3), 0.06 (s, 6H, Si(CH3)2) ppm.

According to the above described procedure, compound 13ga was subjected to acetylation. After chromatography (n-hexane/EtOAc, 3 : 1 + 1 % Et3N; Rf = 0.22) pure 7ga was obtained as a pale yellow oil (202 mg, 42 % after two steps). [α]D31 = + 61.6 (c = 0.98, CHCl3). 1H NMR (400 MHz, CDCl3) δ = 7.76 (d, J = 8.0 Hz, 2H, Ts), 7.29 (d, J = 8.0 Hz, 2H, Ts), 5.58 (t, J = 4.0 Hz, 1H, 3-H), 4.72 (s, 2H, 1'-H), 3.98 (ddd, J = 12.8, 3.9, 1.1 Hz, 1H, 6-H), 3.75 (ddddd, J = 9.9, 8.0, 5.7, 3.9 Hz, 1H, 5-H), 2.99 (dd, J = 12.8, 9.9 Hz, 1H, 6-H'), 2.41 (s, 3H, CH3-Ts), 2.34 (dt, J = 19.2, 5.7 Hz, 1H, 4-H), 2.08 (3H, 3H-CH3-Ac), 1.99 (ddd, J = 19.2, 8.0, 4.0 Hz, 1H, 4-H'), 0.87 (s, 9H, Si(CH3)3), 0.07 (s, 3H, Si(CH3)2), 0.04 (s, 3H, Si(CH3)2) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 170.1 (s, CO), 143.6 (s, Ts), 137.3 (s, Ts), 129.5 (d, 2C, Ts), 127.4 (d, 2C, Ts), 122.6 (d, C3), 119.6 (s, C2), 84.2 (s, C3'), 81.6 (s, C2'), 63.6 (t, C1'), 52.4 (t, C6), 51.2 (d, C5), 33.4 (t, C4), 25.7 (q, 3C, Si(CH3)3), 21.5 (q, CH3-Ts), 20.7 (q, CH3-Ac), 18.0 (s, Si(CH3)3), -4.8 (q, SiCH3), -4.9 (q, SiCH3) ppm. MS (ESI) m/z (%): 949 ([M+Na]+, 100), 486
Acetic acid 3-[6-(tert-butyl-dimethyl-silanyloxymethyl)-1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-2-yl]-prop-2-ynyl ester (7h)

Sonogashira coupling of phosphate 12h (1.63 g, 2.6 mmol) and propargyl alcohol after chromatography (heptane/EtOAc, 2 : 1 + 1 % Et3N; Rf = 0.34) afforded enynyl alcohol 13h which was used immediately in the next step. 1H NMR (400 MHz, CDCl3) δ = 7.78 (d, J = 8.2 Hz, 2H, Ts), 7.29 (d, J = 8.2 Hz, 2H, Ts), 5.66 (t, J = 3.8 Hz, 1H, 3-H), 4.46 – 4.37 (m, 1H, 6-H), 4.31 (s, 2H, 3'-H), 3.64 (dd, J = 10.0, 6.3 Hz, 1H, 6-CH2OTBS), 3.76 (dd, J = 10.0, 8.9 Hz, 1H, 6-CH2OTBS), 2.42 (s, 3H, CH3-Ts), 2.06 – 1.86 (m, 4H, 4 and 5-H), 0.86 (s, 9H, CH3-TBS), 0.04 (s, 3H, CH3-TBS), 0.03 (s, 3H, CH3-TBS) ppm.

According to the above described procedure, compound 13h was subjected to acetylation. After chromatography (heptane/EtOAc, 3 : 1 + 1 % Et3N; Rf = 0.31) pure 7h was obtained as a pale yellow oil (550 mg, 44 % after two steps). 1H NMR (400 MHz, CDCl3) δ = 7.78 (d, J = 8.2 Hz, 2H, Ts), 7.28 (d, J = 8.2 Hz, 2H, Ts), 5.70 (t, J = 3.8 Hz, 1H, 3-H), 4.75 (s, 2H, 3'-H), 4.46 – 4.39 (m, 1H, 6-H), 3.63 (dd, J = 9.6, 6.3 Hz, 1H, 6-CH2OTBS), 3.45 (t, J = 6.3 Hz, 1H, 6-CH2OTBS), 2.42 (s, 3H, CH3-Ts), 2.10 (s, 3H, CH3-Ac), 2.04 – 1.87 (m, 3H, 4 and 5-H), 1.32 – 1.21 (m, 1H, 5-H), 0.86 (s, 9H, CH3-TBS), 0.04 (s, 3H, CH3-TBS), 0.03 (s, 3H, CH3-TBS) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 175.6 (s, CO), 149.1 (s, Ts), 142.3 (s, Ts), 134.9 (d, 2C, Ts), 132.8 (d, 2C, Ts), 130.5 (d, C3), 123.8 (s, C2), 88.7 (s, C1'), 88.5 (s, C2'), 66.8 (t, C3'), 60.3 (t, 6-CH2), 58.2 (d, C6), 31.4 (q, 3C, CH3-TBS), 27.2 (t, C4), 26.4 (t, C5), 25.0 (q, CH3-Ts), 23.8 (q, CH3-Ac), 0.2 (q, CH3-TBS), 0.0 (q, CH3-TBS) ppm. MS (ESI) m/z (%): 478 ([M+Na]+, 65).

Acetic acid 3-[4-tert-butoxy-1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-2-yl]-prop-2-ynyl ester (7i)

Sonogashira coupling of phosphate 12i (530 mg, 0.7 mmol) and propargyl alcohol after chromatography (n-hexane/EtOAc, 2 : 1 + 1 % Et3N; Rf = 0.30) afforded enynyl alcohol 13i which was used immediately in the next step. 1H NMR (400 MHz, CDCl3) δ = 7.76 (d, J = 8.3 Hz, 2H, Ts), 7.29 (d, J = 8.0 Hz, 2H, Ts), 5.48 (d, J = 4.3 Hz, 1H, 3-H), 4.32 (s, 2H, 1'-H), 4.04 (dt, J = 12.8, 3.7, 1H, 4-H), 3.87 (q, J = 4.4 Hz, 1H, 6-H), 3.39 - 3.34 (m, 1H, 6-H), 2.42 (s, 3H, CH3-Ts), 1.75 - 1.76 (m, 3H, 5-H, OH), 1.16 (s, 9H, CH3-t-Bu) ppm.

According to the above described procedure, compound 13i was subjected to acetylation. After chromatography (n-hexane/EtOAc, 3 : 1 + 1 % Et3N; Rf = 0.43) pure 7i was obtained as a colourless oil (82 mg, 30 % after two steps). 1H NMR (400 MHz, CDCl3) δ = 7.75 (d, J = 8.3 Hz, 2H, Ts), 7.28 (d, J = 8.3 Hz, 2H, Ts), 5.50 (d, J = 4.3 Hz, 1H, 3-H), 4.75 (s, 2H, 1'-H), 3.02 (dt, J = 9.0, 3.9, 1H, 4-H), 3.91 (q, J = 4.3, 1H, 6-H), 3.38 - 3.31 (m, 1H, 6-H), 2.41 (s, 3H, CH3-Ts), 2.09 (s, 3H, CH3-Ac), 1.72 (q, J = 4.15 Hz, 2H, 5-H), 1.15 (s, 9H, t-Bu) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 170.1 (s, CO), 143.6 (s, Ts), 137.1 (s, Ts), 129.5 (s, 2C, Ts), 127.4 (s, 2C, Ts), 124.0 (d, C3), 120.9 (s, C2), 85.1 (s, C1'), 81.5 (s, C2'), 74.3 (d, C4), 60.5 (t, C3), 52.4 (s, t-Bu), 42.6 (s, C6), 31.3 (s, C5) 28.2 (s, 3C, CH3-t-Bu), 21.5 (q, CH3-Ts), 20.7 (s, CH3-Ac) ppm. MS (ESI) m/z (%): 832 ([2M+Na]+, 100), 428 ([M+Na]+, 25).
Acetic acid 3-[2,2-dimethyl-5-(toluene-4-sulfonyl)-3a,4,5,7a-tetrahydro-[1,3]dioxolo[4,5-c]pyridin-6-yl]-1-methyl-prop-2-ynyl ester (7j)
Sonogashira coupling of phosphate 12j (250 mg, 0.45 mmol) and (±)-3-butenyl-2-ol after chromatography (heptane/EtOAc, 2 : 1 + 1 % Et3N; Rf = 0.28) afforded enynyl alcohol 13j which was used immediately in the next step. 1H NMR (400 MHz, CDCl₃) δ = 7.80 (d, J = 8.2 Hz, 2H, Ts), 7.31 (d, J = 8.1 Hz, 2H, Ts), 5.73 (d, J = 4.7 Hz, 1H, 3-H), 4.58 (q, J = 6.6 Hz, 1H, 3'-H), 4.38 (dd, J = 5.9, 3.8 Hz, 1H, 4-H), 4.25 – 4.00 (m, 2H, 6-H), 3.09 (dt, J = 12.1, 3.8 Hz, 1H, 5-H), 2.43 (s, 3H, CH₃-Ts), 1.42 (d, J = 6.6 Hz, 3H, 3'-CH₃), 1.37 (s, 3H, CH₃), 1.33 (s, 3H, CH₃) ppm.
According to the above described procedure, compound 13j was subjected to acetylation. After chromatography (n-hexane/EtOAc, 8 : 1 + 1 % Et3N; Rf = 0.19) pure 7j was obtained as a yellowish oil (75 mg, 41 % after two steps). 1H NMR (400 MHz, CDCl₃) δ = 7.80 (d, J = 8.2 Hz, 2H, Ts), 7.30 (d, J = 8.2 Hz, 2H, Ts), 5.86 – 5.62 (m, 1H, 3-H), 5.52 (q, J = 6.7 Hz, 1H, 3'-H), 4.37 (dd, J = 6.0, 4.4 Hz, 1H, 4-H), 4.20 – 4.10 (m, 1H, 6-H), 4.04 (dd, J = 12.9, 4.4 Hz, 1H, 5-H), 3.01 (ddd, J = 12.9, 9.5, 8.0 Hz, 1H, 6-H), 2.42 (s, 3H, CH₃-Ts), 2.08 (s, 3H, CH₃-Ac), 1.46 (d, J = 6.7 Hz, 3H, 3'-CH₃), 1.35 (s, 3H, CH₃), 1.32 (s, 3H, CH₃) ppm. 13C NMR (100.4 MHz, CDCl₃) δ = 169.6 (s, CO), 143.5 (s, Ts), 136.7 (s, Ts), 129.4 (d, 2C, Ts), 127.5 (d, 2C, Ts), 122.9 (s, C2), 119.5 (d, C3), 108.9 (s, C(CH₃)₂), 90.4 (s, C1'), 78.9 (s, C2'), 70.6 (d, C5), 68.9 (d, C4), 60.3 (d, C3'), 47.1 (t, C6), 27.8 (q, CH₃), 24.9 (q, CH₃), 21.5 (q, CH₃), 20.9 (q, CH₃) 20.7 (q, CH₃) ppm. MS (ESI) m/z (%): 860 ([M+Na]+, 100), 441 ([M+Na]+, 74), 419 ([M+1]+, 25).

Acetic acid 1-methyl-3-[8-(toluene-4-sulfonyl)-1,4-dioxa-8-aza-spiro[4.5]dec-6-en-7-yl]-prop-2-ynyl ester (7k)
Sonogashira coupling of phosphate 12k (2.1 g, 2.86 mmol) and (±)-3-butenyl-2-ol after chromatography (heptane/EtOAc, 3 : 2 + 1 % Et₃N; Rf = 0.30) afforded enynyl alcohol 13k which was used immediately in the next step. 1H NMR (400 MHz, CDCl₃) δ = 7.76 (d, J = 8.3 Hz, 2H, Ts), 7.27 (d, J = 8.3 Hz, 2H, Ts), 5.30 (s, 1H, 3-H), 4.57 (q, J = 6.6 Hz, 1H, 3'-H), 3.91 – 3.87 (m, 4H, OCH₂), 3.84 – 3.81 (m, 2H, 6-H), 2.42 (s, 3H, CH₃-Ts), 1.86 – 1.81 (m, 2H, 5-H), 1.40 (d, J = 6.6 Hz, 3H, 3'-CH₃) ppm. 13C NMR (100.4 MHz, CDCl₃) δ = 170.0 (s, CO), 143.8 (s, Ts), 136.6 (s, Ts), 129.5 (d, 2C, Ts), 127.4 (d, 2C, Ts), 123.1 (s, C2), 119.5 (d, C3), 102.8 (s, C4), 90.9 (s, C1'), 78.9 (s, C2'), 64.7 (t, 2C, OCH₂), 60.4 (d, C3'), 45.8 (t, C6), 32.6 (t, C5), 21.6 (q, CH₃), 21.0 (q, CH₃-Ts), 20.6 (q, CH₃-Ac) ppm. MS (ESI) m/z (%): 406 ([M+1]+, 100).
Acetic Acid 1-Methyl-3-[1-(toluene-4-sulfonyl)-4,5,6,7-tetrahydro-1H-azepin-2-yl]-prop-2-ynyl ester (7la).
Sonogashira coupling of phosphate 12l (838 mg, 1.68 mmol) and (±)-3-butyn-2-ol after chromatography (n-hexane/EtOAc, 3 : 2 + 1 % Et3N; Rf = 0.20) afforded enynyl alcohol 13la which was used immediately in the next step. 1H NMR (200 MHz, CDCl3) δ = 7.86 (d, J = 8.0 Hz, 2H, Ts), 7.33 (d, J = 8.0 Hz, 2H, Ts), 6.15 (t, J = 6.9 Hz, 1H, 3-H), 4.50 (q, J = 6.6 Hz, 1H, 1'-H), 3.50 – 3.34 (m, 2H, 7-H), 2.43 (s, 3H, CH3-Ts), 2.32 – 2.16 (m, 2H, 4-H), 1.94 – 1.81 (m, 2H, 5-H), 1.77 – 1.61 (bs, 1H, OH), 1.58 – 1.43 (m, 2H, 6-H), 1.37 (d, J = 6.6 Hz, 3H, CH3) ppm.

According to the above described procedure, compound 13la was subjected to acetylation. After chromatography (n-hexane/EtOAc, 4 : 1 + 1 % Et3N; Rf = 0.26) pure 7la was obtained as a colourless oil (362 mg, 60 % after two steps). 1H NMR (400 MHz, CDCl3) δ = 7.88 (d, J = 8.4 Hz, 2H, Ts), 7.28 (d, J = 8.4 Hz, 2H, Ts), 6.18 (t, J = 6.9 Hz, 1H, 3-H), 5.46 (q, J = 6.7 Hz, 1H, 1'-H), 3.40 – 3.31 (m, 2H, 7-H), 2.41 (s, 3H, CH3-Ts), 2.24 – 2.22 (m, 2H, 4-H), 2.05 (s, 3H, CH3-Ac), 1.90 – 1.82 (m, 2H, 5-H), 1.54 – 1.45 (m, 2H, 6-H), 1.39 (d, J = 6.4 Hz, 3H, 1'-CH3). 13C NMR (100.4 MHz, CDCl3) δ = 169.7 (s, CO), 143.2 (s, Ts), 138.4 (s, C2), 137.8 (s, Ts), 129.3 (d, 2C, Ts), 127.5 (d, 2C, Ts), 124.6 (d, C3), 87.0 (s, C3'), 81.3 (s, C2'), 60.4 (d, C1'), 49.8 (t, C7), 30.7 (t, C6), 27.4 (t, C5), 23.3 (t, C4), 21.5 (q, CH3-Ts), 21.0 (q, CH3-Ac), 20.9 (q, C1'-CH3) ppm. MS (ESI) m/z (%): 745 ([2M+Na]+, 100), 362 ([M+1]+, 11).

Acetic Acid 3-[1-(Toluene-4-sulfonyl)-4,5,6,7-tetrahydro-1H-azepin-2-yl]-prop-2-ynyl Ester (7lb).
Sonogashira coupling of phosphate 12l (382 mg, 0.764 mmol) and propargyl alcohol after chromatography (n-hexane/EtOAc, 2 : 1 + 1 % Et3N; Rf = 0.24) afforded enynyl alcohol 13lb which was used immediately in the next step. 1H NMR (200 MHz, CDCl3) δ = 7.84 (d, J = 8.2 Hz, 2H, Ts), 7.29 (d, J = 8.2 Hz, 2H, Ts), 6.16 (t, J = 6.9 Hz, 1H, 3-H), 4.24 (s, 2H, 1'-H), 3.41 – 3.36 (m, 2H, 7-H), 2.42 (s, 3H, CH3-Ts), 2.28 – 2.15 (m, 2H, 6-H), 2.02 – 1.77 (m, 3H, 4-H and OH), 1.57 – 1.42 (m, 2H, 5-H) ppm.

According to the above described procedure, compound 13lb was subjected to acetylation. After chromatography (n-hexane/EtOAc, 3 : 2 + 1 % Et3N; Rf = 0.22) pure 7lb was obtained as a colourless oil (156 mg, 59 % after two steps). 1H NMR (400 MHz, CDCl3) δ = 7.83 (d, J = 8.2 Hz, 2H, Ts), 7.28 (d, J = 8.2 Hz, 2H, Ts), 6.19 (t, J = 6.9 Hz, 1H, 3-H), 4.65 (s, 2H, 1'-H), 3.41 – 3.33 (m, 2H, 7-H), 2.41 (s, 3H, CH3-Ts), 2.25 – 2.21 (m, 2H, 4-H), 2.07 (s, 3H, CH3-Ac), 1.88 – 1.82 (m, 2H, 5-H), 1.51 – 1.47 (m, 2H, 6-H) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 170.1 (s, CO), 143.3 (s, Ts), 138.5 (s, C2), 137.8 (s, Ts), 129.3 (d, 2C, Ts), 127.6 (d, 2C, Ts), 124.6 (d, C3), 83.1 (s, C3'), 82.8 (s, C2'), 52.4 (t, C1'), 49.9 (t, C7), 30.7 (t, C6), 27.4 (t, C5), 23.4 (t, C4), 21.5 (q, CH3-Ts), 20.7 (q, CH3-Ac) ppm. MS (ESI) m/z (%): 717 ([2M+Na]+, 100).

Acetic Acid 3-[5-Methyl-1-(toluene-4-sulfonyl)-4,5-dihydro-1H-pyrrol-2-yl]-prop-2-ynyl Ester (7m).
Sonogashira coupling of triflate 12m (454 mg, 1.18 mmol) and propargyl alcohol after chromatography (n-hexane/EtOAc, 1 : 1 + 1 % Et3N; Rf = 0.17) afforded enynyl alcohol 13m which was used immediately in the next step. 1H NMR (200 MHz, CDCl3) δ = 7.76 (d, J = 8.2 Hz, 2H, Ts), 7.30 (d, J =
According to the above described procedure, compound 13m was subjected to acetylation. After chromatography (n-hexane/EtOAc, 4:1 + 1 % Et3N; Rf = 0.24) pure 7m was obtained as a colourless oil (168 mg, 43 % after three steps). 1H NMR (400 MHz, CDCl3) δ = 7.76 (d, J = 8.5 Hz, 2H, Ts), 7.29 (d, J = 8.5 Hz, 2H, Ts), 5.52 (t, J = 3.3 Hz, 1H, 3-H), 4.85 (s, 2H, 1'-H), 4.24 – 4.12 (m, 1H, 5-H), 2.43 – 2.36 (m, 4H, CH3-Ts and 4-H), 2.11 (s, 3H, CH3-Ac), 1.94 (dt, J = 18.0, 3.3 Hz, 1H, 4'-H), 1.35 (d, J = 6.5 Hz, 3H, 5-CH3) ppm.

According to the above described procedure, compound 13n was subjected to acetylation. After chromatography (n-hexane/EtOAc, 3:1 + 1 % Et3N; Rf = 0.15) afforded enynyl alcohol 13n which was used immediately in the next step. 1H NMR (200 MHz, CDCl3) δ = 7.81 (d, J = 8.2 Hz, 2H, Ts), 7.33 (d, J = 8.2 Hz, 2H, Ts), 5.51 (t, J = 3.0 Hz, 1H, 3-H), 4.73 (q, J = 6.6 Hz, 1H, 1'-H), 3.75 (t, J = 9.9 Hz, 2H, 5-H), 2.48 – 2.33 (m, 5H, 4-H and CH3-Ts), 1.54 (d, J = 6.6 Hz, 1'-CH3) ppm.

According to the above described procedure, compound 13o was subjected to acetylation. After chromatography (n-hexane/EtOAc, 3:1 + 1 % Et3N; Rf = 0.27) pure 7n was obtained as a colourless oil (143 mg, 36 % after three steps). 1H NMR (400 MHz, CDCl3) δ = 7.80 (d, J = 8.2 Hz, 2H, Ts), 7.32 (d, J = 8.2 Hz, 2H, Ts), 5.62 (q, J = 6.7 Hz, 1H, 1'-H), 5.52 (t, J = 3.0 Hz, 1H, 3-H), 3.74 (t, J = 9.0 Hz, 2H, 5-H), 2.43 (s, 3H, CH3-Ts), 2.38 (td, J = 9.0, 3.0 Hz, 2H, 4-H), 2.10 (s, 3H, CH3-Ac), 1.58 (d, J = 6.7 Hz, 3H, 1'-CH3) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 170.2 (s, CO), 143.7 (s, Ts), 134.6 (s, Ts), 129.5 (d, 2C, Ts), 127.7 (d, 2C, Ts), 123.24 (d, C3), 123.21 (s, C2), 87.3 (s, C3'), 80.0 (s, C2'), 57.6 (t, C1'), 52.5 (d, C5), 36.5 (t, C4), 23.4 (q, C5-CH3), 21.5 (q, CH3-Ts), 20.7 (q, CH3-Ac) ppm. MS (ESI) m/z (%): 689 ([2M+Na]+, 100), 334 ([M+1]+, 9).

2-(3-Acetoxybut-1-ynyl)-indo1-carboxylic Acid Methyl Ester (7o).

Sonogashira coupling of triflate 12o (359 mg, 1.11 mmol) and (±)-3-buten-2-ol after chromatography (n-hexane/EtOAc, 2:1 + 1 % Et3N; Rf = 0.15) afforded enynyl alcohol 13o which was used immediately in the next step. 1H NMR (200 MHz, CDCl3) δ = 8.11 (d, J = 8.1 Hz, 1H, 1'-H), 7.50 – 7.21 (m, 2H, 5-H and 6-H), 6.90 (s, 1H, 3-H), 4.82 – 4.75 (m, 1H, 3'-H), 4.06 (s, 3H, OCH3), 2.18 – 2.05 (bs, 1H, OH), 1.59 (d, J = 6.6 Hz, 3H, 4'-H) ppm.

According to the above described procedure, compound 13o was subjected to acetylation. After chromatography (n-hexane/EtOAc, 6:1 + 1 % Et3N; Rf = 0.28) pure 7o was obtained as a yellowish oil (158 mg, 50 % after three steps). 1H NMR (400 MHz, CDCl3) δ = 8.16 (d, J = 8.2 Hz, 1H, 4-H), 7.52 (d, J = 7.8 Hz, 1H, 7-H), 7.56 – 7.29 (m, 1H, 6-H), 6.94 (s, 1H, 3-H), 5.73 (q, J = 6.5 Hz, 1H, 3'-H), 4.06 (s, 3H, OCH3), 2.13 (s, 3H, CH3-Ac), 1.63 (d, J = 6.6 Hz, 3H, 4'-H) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 169.8 (s, CO-Ac), 151.4 (s, CO2CH3), 136.0 (s, C7a), 128.4 (s, C3a), 125.9 (d, C5), 123.5 (d, C4), 120.8 (d, C6), 119.3 (s, C2), 117.3 (d, C3), 115.5 (d, C7), 93.1 (s, C1'), 76.7 (s, C2'), 60.8 (d, C3'), 53.5 (q, CO2CH3), 21.1 (q, C4'), 21.0 (q, CH3-Ac) ppm. MS (ESI) m/z (%):
derivatives. Residue was purified by flash chromatography to give the corresponding cyclopentane

According to the above described procedure, compound 13p was subjected to acetylation. After chromatography (n-hexane/EtOAc, 2 : 1 + 1 % Et3N; Rf = 0.23) pure 7p was obtained as a yellowish oil (177 mg, 57 % after two steps). 1H NMR (400 MHz, CDCl3) δ = 7.25 (d, J = 8.0 Hz, 2H, Ts), 7.26 (d, J = 8.0 Hz, 2H, Ts), 5.53 (q, J = 8.0 Hz, 1H, 1'-H), 3.56 - 3.54 (m, 2H, 2-H), 2.40 (s, 3H, CH3-Ts), 2.06 - 2.01 (m, 2H, 4-H), 2.05 (s, 3H, CH3-Ac), 1.85 (s, 3H, 3-CH3), 1.68 - 1.62 (m, 2H, 5-H), 1.45 (d, J = 8.0 Hz, 3H, 1'-CH3) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 169.8 (s, CO), 143.1 (s, Ts), 137.8 (s, Ts), 134.3 (s, C2), 129.4 (d, 2C, Ts), 127.4 (d, 2C, Ts), 115.2 (s, C3), 91.9 (s, C1'), 79.5 (s, C2'), 60.7 (d, C3'), 45.7 (t, C6), 28.9 (q, CH3-3), 21.8 (q, CH3-Ts), 21.5 (t, C4), 21.0 (q, CH3-Ac), 20.9 (t, C5), 20.8 (q, CH3-3') ppm. MS (ESI) m/z (%): 745.01 ([2M+Na]+, 65), 384 ([M+23]+, 100), 378 ([M+18]+, 14).

Acetic acid (5S)-3-[5-Hydroxy-1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-2-yl]-prop-2-ynyl Ester (7gb).
To the solution of enynyl acetate 7ga (133 mg, 0.29 mmol) in THF (14 mL), a freshly prepared solution of TBAF·3H2O (0.33 mmol, 104 mg) in THF (0.33 mL) was added at room temperature. After 1 h THF was removed under reduced pressure. After chromatography (n-hexane/EtOAc, 1 : 1 + 1 % Et3N; Rf = 0.40) pure 7gb was obtained as a pale yellow oil (82 mg, 82 %). [α]D21 = + 8.7 (c = 0.86, CHCl3). 1H NMR (400 MHz, CDCl3) δ = 7.81 (d, J = 8.2 Hz, 2H, Ts), 7.30 (d, J = 8.2 Hz, 2H, Ts), 5.59 (t, J = 4.1 Hz, 1H, 3-H), 4.72 (s, 2H, 1'-H), 4.07 – 4.01 (m, 1H, 5-H), 3.74 – 3.67 (m, 1H, 6-H), 3.59 (dd, J = 13.1, 7.2 Hz, 1H, 6-H'), 2.51 – 2.38 (m, 5H, OH, 4-H and CH3-Ts), 2.20 – 2.05 (m, 4H, 4'-H' and CH3-Ac) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 170.1 (s, CO), 143.7 (s, Ts), 137.3 (s, Ts), 129.5 (d, 2C, Ts), 127.6 (d, 2C, Ts), 121.4 (d, C3), 119.7 (s, C2), 84.6 (s, C3'), 81.2 (s, C2'), 62.8 (t, C1'), 52.4 (t, C6), 50.8 (d, C5), 32.5 (t, C4), 21.5 (q, CH3-Ts), 20.7 (q, CH3-Ac) ppm. MS (ESI) m/z (%): 721 ([2M+Na]+, 100).

General procedure for gold(I)-catalyzed Nazarov reaction.
Precatalyst LAuCl (3 mol %, 0.006 mmol) was dissolved in DCM (1.5 mL) and silver salt (3 mol %, 0.006 mmol) was added. The formed suspension was left to stir at room temperature under nitrogen atmosphere. After 20 min a solution of enynyl acetate 7 (0.2 mmol) in DCM (2.5 mL) was added and reaction mixture was stirred at room temperature. The progress of the reaction was followed by TLC. After complete consumption of enynyl acetate (1 – 5 h) the reaction mixture was left to stir at room temperature overnight. Water (5 mL) was added and the product extracted with DCM (3 x 5 mL). The combined organic extracts were dried over anhydrous Na2SO4, filtered and concentrated. The oily residue was purified by flash chromatography to give the corresponding cyclopentane-fused piperidine derivatives.
5-Butyl-1-(toluene-4-sulfonyl)-1,2,3,4,5,6-hexahydropyridin-7-one (17aa).

Compound 17aa was prepared according to the above described procedure starting from 7aa (59 mg, 0.15 mmol). Reaction was carried out with 3 mol % of Ph₃PdCl/AgSbF₅. Chromatography (n-hexane/EtOAc, 6:1) afforded pure ketone 17aa (R_f = 0.17; 37 mg, 70%) as a yellow oil and acetate 14aa (R_f = 0.24; 8 mg, 14%) as an orange oil.

17aa: ^1^H NMR (400 MHz, CDCl₃) δ = 7.99 (d, J = 8.2 Hz, 2H, Ts), 7.29 (d, J = 8.2 Hz, 2H, Ts), 3.50 – 3.36 (m, 2H, 2-H), 2.72 – 2.68 (m, 1H, 5-H), 2.60 (dd, J = 18.2, 6.4 Hz, 1H, 6-H), 2.47 (dt, J = 19.9, 6.8 Hz, 1H, 4-H), 2.41 (s, 3H, CH₃-Ts), 2.28 (dt, J = 19.9, 6.4 Hz, 1H, 4'H), 2.13 (dd, J = 18.2, 2.2 Hz, 1H, 6'H), 2.01 – 1.99 (m, 2H, 3-H), 1.76 – 1.71 (m, 1H, 1'H), 1.43 – 1.21 (m, 5H, 1'-H, 2'-H and 3'-H), 0.90 (t, J = 7.0 Hz, 3H, 4'-H) ppm. ^13^C NMR (100.4 MHz, CDCl₃) δ = 200.1 (s, C7), 162.6 (s, C7a), 143.6 (s, Ts), 138.2 (s, C4a), 137.5 (s, Ts), 129.5 (d, 2C, Ts), 127.9 (d, 2C, Ts), 46.2 (t, C2), 40.1 (t, C6), 39.3 (s, C5), 32.9 (t, C1'), 29.0 (t, C2'), 24.1 (t, C4), 22.9 (t, C3'), 21.9 (t, C3), 21.7 (q, CH₃-Ts), 14.1 (q, C4') ppm. MS (ESI) m/z (%): 717 ([2M+Na]^+), 100, 370 ([M+Na]^+), 12. Elemental analysis calcd (%) for C₁₉H₂₆NO₃S: C 65.68, H 7.25, N 4.03; found: C 65.36, H 7.43, N 4.07.

14aa: ^1^H NMR (400 MHz, CDCl₃) δ = 7.67 (d, J = 8.0 Hz, 2H, Ts), 7.25 (d, J = 8.0 Hz, 2H, Ts), 6.03 (s, 3H, 1H, 6-H), 4.16 – 4.09 (m, 1H, 2-H), 3.05 (td, J = 13.6, 2.8 Hz, 1H, 2-H'), 2.41 (s, 3H, CH₃-Ts), 2.21 – 2.03 (m, 7H, CH₃-Ac, 4-H, 4a-H and 1'H), 1.64 – 1.56 (m, 1H, 3'-H), 1.48 – 1.23 (m, 5H, 3'-H, 2'-H and 3'-H), 1.04 (qd, J = 12.8, 3.6 Hz, 1H, 4-H'), 0.88 (t, J = 7.2 Hz, 2.2'H) ppm. ^13^C NMR (100.4 MHz, CDCl₃) δ = 168.5 (s, CO), 150.3 (s, C7), 143.6 (s, Ts), 137.4 (s, Ts), 129.5 (d, 2C, Ts), 127.4 (d, 2C, Ts), 123.7 (s, C7a), 122.9 (d, C6), 49.5 (t, C2), 45.5 (d, C4a), 30.7 (t, C2'), 29.7 (s, C5), 28.4 (t, C4), 28.1 (t, C1'), 25.0 (t, C3), 22.4 (t, C3'), 21.5 (q, CH₃-Ts), 20.7 (q, CH₃-Ac), 13.9 (q, C4') ppm. MS (ESI) m/z (%): 801 ([2M+Na]^+), 100, 390 ([M+Na]^+), 12. Elemental analysis calcd (%) for C₁₉H₂₅NO₃S: C 64.75, H 6.99, N 3.06; found: C, 64.82, H 7.08, N 3.04.

5-Butyl-7-oxo-2,3,4,5,6,7-hexahydropyridine-1-carboxylic Acid Benzyl Ester (17c).

Compound 17c was prepared according to the above described procedure starting from 7c (28 mg, 0.075 mmol). Reaction was carried out with 8 mol % of Ph₃PdCl/AgSbF₅ in refluxing DCM. Chromatography (n-hexane/EtOAc, 6:1; R_f = 0.17) afforded pure ketone 17c (15 mg, 62%) as a yellow oil. ^1^H NMR (400 MHz, CDCl₃) δ = 7.40 – 7.27 (m, 5H, Cbz), 5.17 (s, 2H, CH₂Ph), 3.61 – 3.58 (m, 2H, 2-H), 2.72 – 2.64 (m, 1H, 5-H), 2.58 (dd, J = 18.0, 6.4 Hz, 1H, 6-H), 2.49 (dt, J = 19.6, 6.8 Hz, 1H, 4-H), 2.25 (dt, J = 19.6, 6.6 Hz, 1H, 4'H), 2.12 (dd, J = 18.0, 1.8 Hz, 1H, 6'H), 1.92 – 1.86 (m, 2H, 3-H), 1.77 – 1.66 (m, 1H, 1'H), 1.37 – 1.20 (m, 5H, 1'-H, 2'-H and 3'-H), 0.90 (t, J = 6.8 Hz, 3H, 4'-H) ppm. ^13^C NMR (100.4 MHz, CDCl₃) δ = 199.0 (s, C7), 160.7 (s, CO-Cbz), 153.9 (s, C7a), 138.3 (s, C4a), 136.2 (s, Cbz), 128.4 (d, 2C, Cbz), 128.1 (d, 2C, Cbz), 68.0 (t, CH₂Ph), 44.3 (t, C2), 40.5 (t, C6), 38.8 (d, C5), 32.8 (t, C1'), 29.0 (t, C2'), 24.3 (t, C4), 22.7 (t, C3'), 22.3 (t, C3), 13.2 (q, C4') ppm. MS (ESI) m/z (%): 677 ([2M+Na]^+), 100, 328 ([M+Na]^+), 4. Elemental analysis calcd (%) for C₂₉H₂₅NO₃S: C 73.37, H 7.70, N 4.28; found: C 73.67, H 7.77, N 4.52.
5-Butyl-7-oxo-2,3,4,5,6,7-hexahydro-[1]pyrindine-1-carboxylic Acid Methyl Ester (17d).

Compound 17d was prepared according to the above described procedure starting from 7d (37 mg, 0.13 mmol). Reaction was carried out with 5 mol % of Ph3PAuCl/AgSbF6 in refluxing DCM. Chromatography (n-hexane/EtOAc, 5 : 1) afforded pure ketone 17d (Rf = 0.16; 20 mg, 64 %) as a yellow oil and acetate 14d (Rf = 0.29; 5 mg, 14 %) as a yellow oil.

17d: 1H NMR (400 MHz, CDCl3) δ = 3.73 (s, 3H, OCH3), 3.63 – 3.49 (m, 2H, 2-H), 2.72 – 2.62 (m, 1H, 5-H), 2.58 (dd, J = 18.0, 6.5 Hz, 1H, 6-H), 2.47 (dt, J = 19.8, 6.6 Hz, 1H, 4-H), 2.25 (dt, J = 19.8, 6.5 Hz, 1H, 4-H'), 2.13 (dd, J = 18.0, 2.0 Hz, 1H, 6-H'), 1.92 – 1.86 (m, 2H, 3-H), 1.77 – 1.71 (m, 1H, 1'-H), 1.41 – 1.17 (m, 5H, 1'-H, 2'-H and 3'-H), 0.89 (t, J = 7.0 Hz, 3H, 4'-H) ppm. Spectroscopical data identical to those reported in the literature.39

14d: 1H NMR (400 MHz, CDCl3) δ = 5.92 (s, 1H, 6-H), 4.33 – 4.09 (m, 1H, 2-H), 3.69 (s, 3H, OCH3), 2.92 – 2.81 (m, 1H, 2'-H), 2.62 (dd, J = 12.6, 5.5 Hz, 1H, 4a-H), 2.33 – 2.18 (m, 3H, 4-H and 1'-H), 2.15 (s, 3H, CH3-Ac), 1.93 – 1.84 (m, 1H, 3-H), 1.84 – 1.71 (m, 1H, 3'-H), 1.54 – 1.40 (m, 2H, 2'-H), 1.40 – 1.27 (m, 2H, 3'-H), 1.14 (qd, J = 12.6, 3.7 Hz, 1H, 4-H'), 0.89 (t, J = 7.2 Hz, 3H, 4'-H) ppm.

Acetic Acid 5,5-Dimethyl-1-(toluene-4-sulfonyl)-2,3,4,5-tetrahydro-1H-[1]pyrindin-7-yl Ester (16ad).

Compound 16ad was prepared according to the above described procedure starting from 7ad (90 mg, 0.25 mmol). Reaction was carried out with 3 mol % of Ph3PAuCl/AgSbF6. Chromatography (n-hexane/EtOAc, 1 : 1 + 1 % Et3N; Rf = 0.14) afforded pure acetate 16ad (72 mg, 86 %) as a yellow solid. M.p. = 108.0 – 109.4 °C. 1H NMR (400 MHz, CDCl3) δ = 7.65 (d, J = 8.2 Hz, 2H, Ts), 7.24 (d, J = 8.2 Hz, 2H, Ts), 5.93 (s, 1H, 6-H), 3.54 – 3.51 (m, 2H, 2-H), 2.41 (s, 3H, CH3-Ts), 2.19 (s, 3H, CH3-Ac), 1.91 (t, J = 6.6 Hz, 2H, 4-H), 1.36 – 1.33 (m, 2H, 3-H), 1.09 (s, 6H, 5-CH3) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 168.8 (s, CO), 144.3 (s, C7), 143.4 (s, Ts), 142.1 (s, C7a), 136.1 (s, Ts), 129.7 (s, C4a), 129.4 (d, 2C, Ts), 127.7 (d, 2C, Ts), 127.5 (d, C6), 47.4 (t, C2), 45.7 (s, C5), 22.6 (q, 2C, C5-Ch3), 21.5 (q, CH3-Ts), 21.1 (q, CH3-Ac), 18.9 (t, C4), 18.6 (t, C3) ppm. MS (ESI) m/z (%): 745 ([2M+Na]+, 100), 384 ([M+Na]+, 20), 362 ([M+1]+, 14). Elemental analysis calcd (%) for C19H23NO3S: C 63.13, H 6.14, N 3.88; found: C 62.93, H 6.22, N 3.79.

1-(Toluene-4-sulfonyl)-1,2,3,4,5,6-hexahydro-[1]pyrindin-7-one (17ab).

Compound 17ab was prepared according to the above described procedure starting from 7ab (36 mg, 0.11 mmol). Reaction was carried out with 5 mol % of Ph3PAuCl/AgSbF6 in refluxing DCM. Chromatography (n-hexane/EtOAc, 2 : 1; Rf = 0.26) afforded pure ketone 17ab (26 mg, 83 %) as a white solid. M.p. = 138.1 – 141.1 °C. 1H NMR (400 MHz, CDCl3) δ = 8.00 (d, J = 8.1 Hz, 2H, Ts), 7.30 (d, J = 8.1 Hz, 2H, Ts), 3.44 – 3.41 (m, 2H, 2-H), 2.53 – 2.50 (m, 2H, 6-H), 2.45 - 2.48 (m, 2H, 5-H), 2.41 – 2.38 (m, 5H, CH3-Ts and 4-H), 2.02 – 1.96 (m, 2H, 3'-H) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 200.6 (s, C7), 159.8 (s, C7a), 143.4 (s, Ts), 138.0 (s, C4a), 137.6 (s, Ts), 129.3 (d, 2C, Ts), 127.7 (d, 2C, Ts), 46.2 (t, C2), 33.4 (t, C6), 27.5 (t, C5), 26.1 (t, C4), 21.8 (t, C3), 21.5 (q, CH3 Ts) ppm. MS (ESI)
m/z (%): 605 ([2M+Na]⁺, 100), 292 ([M+1]⁺, 18). Elemental analysis calcd (%) for C₁₉H₁₇NO₃S: C 61.83, H 5.88, N 4.81; found: C 61.48, H 5.84, N 4.76.

5-Methyl-1-(toluene-4-sulfonyl)-1,2,3,4,5,6-hexahydro-[1]pyrindin-7-one (17ac).
Compound 17ac was prepared according to the above described procedure starting from 7ac (68 mg, 0.2 mmol). Reaction was carried out with 5 mol % of Ph₃PAuCl/AgSbF₆. Chromatography (n-hexane/EtOAc, 5 : 1) afforded pure ketone 17ac (Rₛ = 0.16; 44 mg, 72 %) as a yellow oil and acetate 14ac (Rₜ = 0.24; 8 mg, 14 %) as a grey solid.

17ac: ¹H NMR (400 MHz, CDCl₃) δ = 8.00 (d, J = 8.1 Hz, 2H, Ts), 7.30 (d, J = 8.1 Hz, 2H, Ts), 3.49 – 3.36 (m, 2H, 2H), 2.82 – 2.75 (m, 1H, 5-H), 2.69 (dd, J = 17.8, 6.5 Hz, 1H, 6-H), 2.49 (dt, J = 19.9, 6.8 Hz, 1H, 4-H), 2.41 (s, 3H, CH₃-Ts), 2.24 (dt, J = 19.9, 6.6 Hz, 1H, 4-H'), 2.04 (dd, J = 17.8, 2.0 Hz, 1H, 6-H'), 2.01 – 1.97 (m, 2H, 3-H), 1.19 (d, J = 7.1, 3H, 5-CH₃) ppm. ¹³C NMR (100.4 MHz, CDCl₃) δ = 199.8 (s, C₇), 163.3 (s, C₇a), 143.4 (s, Ts), 138.1 (s, C₄a), 136.9 (s, Ts), 129.3 (d, 2C, Ts), 127.8 (d, 2C, Ts), 46.0 (t, C₂), 42.4 (t, C₆), 33.8 (d, C₅), 23.6 (t, C₄), 21.8 (t, C₃), 21.5 (q, CH₃-Ts), 19.1 (q, C₅-CH₃) ppm. MS (ESI) m/z (%): 633 ([2M+Na]⁺, 100), 306 ([M+Na]⁺, 10). Elemental analysis calcd (%) for C₁₆H₁₉NO₃S: C 62.93, H 6.27, N 4.59; found: C 62.79, H 6.05, N 4.41.

5-Phenyl-1-(toluene-4-sulfonyl)-1,2,3,4,5,6-hexahydro-[1]pyrindin-7-one (17ae).
Compound 17ae was prepared according to the above described procedure starting from 7ae (86 mg, 0.2 mmol). Reaction was carried out with 3 mol % of Ph₃PAuCl/AgSbF₆ in toluene. Chromatography (n-hexane/EtOAc, 8 : 1; Rₛ = 0.16) afforded pure ketone 17ae (37 mg, 55 %) as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ = 8.04 (d, J = 8.4 Hz, 2H, Ts), 7.35 – 7.25 (m, 5H, Ph), 7.11 (d, J = 8.4 Hz, 2H, Ts), 3.87 (br d, J = 7.0 Hz, 1H, 5-H), 3.40 – 3.40 (m, 2H, 2H), 2.98 (dd, J = 18.3, 7.0 Hz, 1H, 6-H), 2.44 (dd, J = 18.3, 2.2 Hz, 1H, 6-H'), 2.43 (s, 3H, CH₃-Ts), 2.16 – 2.08 (m, 2H, 4-H), 1.96 – 1.90 (m, 2H, 3-H) ppm. Spectroscopic data identical to those reported in the literature.⁴⁰

Acetic Acid 5-Phenyl-1-(toluene-4-sulfonyl)-2,3,4,4a-tetrahydro-1H-[1]pyrindin-7-yl Ester (14ae).
The reaction was carried out with 3 mol % of Ph₃PAuCl/AgOTf in toluene according to the above described procedure. Starting from 7ae (58 mg, 0.14 mmol) acetate 14ae was obtained in a mixture...
with ketone 17ae in 3.4 : 1 ratio. During the purification on silica gel (n-hexane/EtOAc, 6 : 1; Rf = 0.27) 14ae was isolated in 34 % (19 mg) due to [1,5]H-shift. Attempts of the purification under basic (Et3N) and neutral (alumina) conditions led to hydrolysis and [1,5]H-shift. M.p. = 65.0 – 67.0 °C. 1H NMR (400 MHz, CDCl3) δ = 7.72 (d, J = 8.0 Hz, 2H, Ts), 7.33 – 7.20 (m, 7H, Ph and Ts), 6.70 (s, 1H, 6-H), 4.20 – 4.12 (m, 1H, 2-H), 3.17 (td, J = 13.6, 2.8 Hz, 1H, 2-H'), 2.78 (dd, J = 12.8, 5.2 Hz, 1H, 4a-H), 2.41 (s, 3H, CH3 Ts), 2.27 – 2.19 (m, 4H, CH2-Ac and 4-H), 1.66 – 1.59 (m, 1H, 3-H), 1.50 (qt, J = 13.6, 3.6 Hz, 1H, 3-H'), 1.17 (qd, J = 12.8, 3.6 Hz, 1H, 4-H') ppm. 13C NMR (100.4 MHz, CDCl3) δ = 168.4 (s, CO), 146.9 (s, C5), 143.5 (s, Ts), 143.1 (s, C7), 137.3 (s, Ts), 134.0 (s, Ph), 129.7 (d, 2C, Ts), 128.4 (s, 2C, Ph), 127.5 (d, Ph), 127.4 (d, 2C, Ts), 126.4 (s, C7a), 125.7 (d, 2C, Ph), 124.1 (d, C6), 49.9 (t, C2), 43.9 (d, C4a), 30.0 (t, C4), 25.8 (t, C3), 21.6 (q, CH3-Ts), 20.7 (q, CH3-Ac) ppm. MS (ESI) m/z (%): 841 ([2M+Na]+, 100), 432 ([M+Na]+, 18), 410 ([M+1]+, 16). Elemental analysis calcd (%) for C23H23NO2S: C 67.46, H 5.66, N 3.42; found: C 67.92, H 5.81, N 3.76.

2,5-Dimethyl-1-(toluene-4-sulfonyl)-1,2,3,4,5,6-hexahydro-[1]pyridin-7-one (17e).

Compound 17e was prepared according to the above described procedure starting from 7e (52 mg, 0.15 mmol). Reaction was carried out with 5 mol % of (Cy3)PAuCl/AgSbF6. Chromatography (n-hexane/EtOAc, 6 : 1; Rf = 0.16) afforded pure cis ketone 17e (37 mg, 83 %) as a white solid. 1H NMR (400 MHz, CDCl3) δ = 8.00 (d, J = 8.4 Hz, 2H, Ts), 7.27 (d, J = 8.4 Hz, 2H, Ts), 4.37 – 4.30 (m, 1H, 2-H) 2.89 – 2.82 (m, 1H, 5-H), 2.78 (dd, J = 18.0, 7.0 Hz, 1H, 6-H), 2.46 – 2.36 (m, 4H, CH2-Ts and 4-H), 2.26 (dd, J = 20.0, 6.5 Hz, 1H, 6-H'), 2.11 – 2.03 (m, 1H, 4-H'), 1.99 (d, J = 19.0 Hz, 1H, 3-H), 1.79 – 1.73 (m, 1H, 3-H'), 1.17 (d, J = 7.0 Hz, 3H, 5-CH3), 0.85 (d, J = 8.9 Hz, 3H, 2-CH3) ppm. Spectroscopical data identical to those reported in the literature.15

4,5-Dimethyl-1-(toluene-4-sulfonyl)-1,2,3,4,5,6-hexahydro-[1]pyridin-7-one (17f).

Compound 17f was prepared according to the above described procedure starting from 7f (76 mg, 0.2 mmol). Reaction was carried out with 5 mol % of Ph3PAuCl/AgSbF6. Chromatography (n-hexane/EtOAc, 6 : 1) afforded cis ketone 17f (Rf = 0.16; 37 mg, 56 %) as a white solid and acetate 14f (Rf = 0.22; 14 mg, 18 %) as a colourless oil. 17f: 1H NMR (400 MHz, CDCl3) δ = 7.97 (d, J = 8.4 Hz, 2H, Ts), 7.28 (d, J = 8.4 Hz, 2H, Ts), 3.54 (ddd, J = 13.6, 7.0, 2.9 Hz, 1H, 2-H), 3.31 (ddd, J = 13.6, 8.7, 2.7 Hz, 1H, 2-H'), 2.96 – 2.89 (m, 1H, 5-H), 2.70 (dd, J = 18.3, 6.6 Hz, 1H, 6-H), 2.64 – 2.57 (m, 1H, 3-H), 2.41 (s, 3H, CH3-Ts), 2.10 – 2.03 (m, 1H, 3-H'), 2.04 (dd, J = 18.3, 1.2 Hz, 1H, 6-H'), 1.72 – 1.64 (m, 1H, 4-H), 1.16 (d, J = 7.1 Hz, 3H, 5-CH3), 1.13 (d, J = 7.2 Hz, 3H, 4-CH3) ppm. Spectroscopical data identical to those reported in the literature.15

14f: 1H NMR (200 MHz, CDCl3) δ = 7.67 (d, J = 8.4 Hz, 2H, Ts), 7.27 (d, J = 8.4 Hz, 2H, Ts), 6.08 – 6.04 (m, 1H, 6-H), 4.07 (ddd, J = 14.0, 4.2, 2.4 Hz, 1H, 2-H), 3.05 (td, J = 14.0, 2.4 Hz, 1H, 2-H'), 2.42 (s, 3H, CH3-Ts), 2.17 (s, 3H, CH3-Ac), 2.00 (d, J = 1.6 Hz, 3H, 5-CH3), 1.81 (d, J = 11.1 Hz, 1H, 4a-H), 1.54 – 1.28 (m, 3H, 4-H and 3-H), 1.05 (d, J = 6.2 Hz, 3H, 4-CH3) ppm.
(3S)-3-(tert-Butyl-dimethyl-silyloxy)-1-(toluene-4-sulfonyl)-1,2,3,4,5,6-hexahydro-[1]pyrindin-7-one (17ga).

Compound 17ga was prepared according to the above described procedure starting from 7ga (69 mg, 0.15 mmol). Reaction was carried out with 5 mol % of Ph3PAuCl/AgSbF6 in refluxing DCM. Chromatography (n-hexane/EtOAc, 4:1; Rf = 0.21) afforded ketone 17ga (47 mg, 75 %) as a yellow foam. [α]D20 = -74.4 (c = 0.91, CHCl3). M.p. = 61.7 – 63.4 °C. 1H NMR (400 MHz, CDCl3) δ = 8.00 (d, J = 8.3 Hz, 2H, Ts), 7.31 (d, J = 8.3 Hz, 2H, Ts), 4.32 – 4.23 (m, 1H, 3-H), 3.80 (dd, J = 13.0, 4.0 Hz, 1H, 2-H), 2.83 (dd, J = 13.0, 10.0 Hz, 1H, 2-H), 2.70 (dd, J = 20.0, 6.3 Hz, 1H, 4-H), 2.61 – 2.49 (m, 7H, 5-H, 6-H and CH3-Ts), 2.27 (dd, J = 20.0, 8.2 Hz, 1H, 4-H'), 0.91 (s, 9H, SiC(CH3)3), 0.15 (s, 3H, SiC(CH3)2), 0.14 (s, 3H, SiC(CH3)3) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 199.6 (s, C7), 158.7 (s, C7a), 143.6 (s, Ts), 138.3 (s, C4a), 137.3 (s, Ts), 129.3 (d, 2C, Ts), 127.8 (d, 2C, Ts), 126.7 (d, C3), 51.7 (t, C2), 36.9 (t, C6), 34.1 (t, C5), 27.1 (t, C4), 25.8 (t, 3C, SiC(CH3)3), 21.5 (q, CH3 Ts) 18.0 (s, SiC(CH3)3), -4.68 (q, SiCH3), -4.95 (q, SiCH3) ppm. MS (ESI) m/z (%): 865 ([M+Na]+), 444 ([M+Na]+), 8. Elemental analysis calcd (%) for C22H33NO2SSi: C 58.82, H 7.41, N 3.32; found: C 60.04, H 7.13, N 3.49.

2-(tert-Butyl-dimethyl-silyloxymethyl)-1-(toluene-4-sulfonyl)-1,2,3,4,5,6-hexahydro-[1]pyrindin-7-one (17h).

Compound 17h was prepared according to the above described procedure starting from 7h (550 mg, 1.15 mmol). Reaction was carried out with 5 mol % of Ph3PAuCl/AgSbF6 in refluxing DCM. Chromatography (heptane/EtOAc, 3:1; Rf = 0.21) afforded ketone 17h (375 mg, 75%) as a yellow solid. [α]D20 = -68.2 (c = 1, DCM). M.p. = 105.7 – 106.5 °C. 1H NMR (400 MHz, CDCl3) δ = 8.02 (d, J = 8.3 Hz, 2H, Ts), 7.29 (d, J = 8.3 Hz, 2H, Ts), 4.27 – 4.19 (m, 1H, 2-H), 3.29 (dd, J = 10.2, 6.3 Hz, 1H, 2-CH2OTBS), 3.20 (dd, J = 10.2, 8.4 Hz, 1H, 2-CH2OTBS), 2.62 – 2.46 (m, 3H), 2.41 (s, 3H, CH3-Ts), 2.40 – 2.21 (m, 3H), 2.17 – 2.07 (m, 1H), 2.04 – 1.93 (m, 1H), 0.76 (s, 9H, CH3-TBS), -0.12 (s, 6H, CH3-TBS) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 206.6 (s, C7), 164.7 (s, C7a), 149.2 (s, Ts), 143.5 (s, Ts), 141.8 (s, C4a), 134.9 (d, 2C, Ts), 133.7 (d, 2C, Ts), 67.3 (t, 2-CH2OTBS), 61.4 (d, C2), 39.2 (t, C6), 33.2 (t, C5), 31.4 (q, 3C, TBS), 28.6 (t, C4), 27.7 (t, C3), 25.1 (q, CH3-Ts), 23.9 (s, TBS), 0.2 (q, TBS), 0.1 (q, TBS) ppm. MS (ESI) m/z (%): 436 ([M+Na]+), 100. Elemental analysis calcd (%) for C22H33NO2SSi: C 60.65; H 7.63; N 3.22; found: C 60.55, H 7.65, N 3.24.

Acetic acid (3S)-7-Oxo-1-(toluene-4-sulfonyl)-2,3,4,5,6,7-hexahydro-1H-[1]pyrindin-3-yl ester (22) and (3S)-3-Hydroxy-1-(toluene-4-sulfonyl)-1,2,3,4,5,6-hexahydro-[1]pyrindin-7-one (17gb).

Compound 22 was prepared according to the above described procedure starting from 7gb (50 mg, 0.14 mmol). Reaction was carried out with 5 mol % of Ph3PAuCl/AgSbF6 in refluxing DCM. Chromatography (n-hexane/EtOAc, 1:1) afforded pure ketone 22 (Rf = 0.29; 37 mg, 75 %) as a white foam and product 17gb as white solid (Rf = 0.14; 12 mg, 16 %).
C6), 32.2 (t, C4), 27.1 (t, C5), 21.5 (q, CH3 Ts), 21.2 (q, CH3 Ac) ppm. MS (ESI) m/z (%): 720 ([2M+Na]+, 100), 372 ([M+Na]+, 3). Elemental analysis calcd (%) for C17H19NO3S: C 58.44, H 5.48, N 4.01; found: C 58.72, H 5.17, N 3.89.

\[ \alpha = 28.5 \] (c = 0.33, CHCl3). M.p. = 172.6 - 177.8 °C. \(^1\)H NMR (400 MHz, CDCl3) \( \delta = 8.04 \) (d, \( J = 8.3 \) Hz, 2H, Ts), 7.31 (d, \( J = 8.3 \) Hz, 2H, Ts), 4.36 - 4.34 (m, 1H, 3-H), 3.68 (dd, \( J = 13.8, 5.6 \) Hz, 1H, 1-H), 2.68 (dd, \( J = 13.8, 2.0 \) Hz, 1H, 2-H), 2.68 - 2.44 (m, 7H, 4-H, 5-H, 6-H and OH), 2.43 (s, 3H, CH3-Ts) ppm. \(^{13}\)C NMR (100.4 MHz, CDCl3) \( \delta = 199.7 \) (s, C7), 157.4 (s, C7a), 143.8 (s, Ts), 138.0 (s, C4a), 137.2 (s, Ts), 129.4 (d, 2C, Ts), 127.8 (d, 2C, Ts), 62.8 (d, C3), 51.1 (t, C2), 35.1 (t, C4), 33.7 (t, C6), 27.4 (t, C5), 21.6 (q, CH3-Ts) ppm. MS (ESI) m/z (%): 637 ([2M+Na]+, 100), 330 ([M+Na]+, 8), 308 ([M+[1]+, 4).

Elemental analysis calcd (%) for C15H17NO3S: C 58.61, H 5.57, N 4.56; found: C 58.93, H 5.22, N 4.23.

![Image](image-url)

6-Methyl-1-(toluene-4-sulfonyl)-2,3,4,5,6,7-hexahydro-1H-cyclopenta[b]azepin-8-one (17la).

Compound 17la was prepared according to the above described procedure starting from 7la (135 mg, 0.37 mmol). Reaction was carried out with 5 mol % of Ph3PdCu/AgSbF5 in DCM at room temperature. Chromatography (n-hexane/THOAc, 4 : 1; Rf = 0.22) afforded pure ketone 17la (98 mg, 82 %) as a pale orange solid. M.p. = 98.7 - 100.5 °C. \(^1\)H NMR (400 MHz, CDCl3) \( \delta = 8.08 \) (d, \( J = 8.2 \) Hz, 2H, Ts), 7.30 (d, \( J = 8.2 \) Hz, 2H, Ts), 3.37 - 3.02 (m, 2H, 2-H), 2.82 (m, 1H, 6-H), 2.71 (dd, \( J = 18.4, 6.5 \) Hz, 1H, 7-H), 2.57 - 2.44 (m, 2H, 5-H), 2.41 (s, 3H, CH3-Ts), 2.08 (dd, \( J = 18.4, 1.5 \) Hz, 1H, 7-H), 1.77 - 1.68 (m, 1H, 4-H), 1.59 - 1.49 (m, 1H, 4-H'), 1.21 (d, \( J = 7.1 \) Hz, 3H, 6-H) ppm. \(^{13}\)C NMR (100.4 MHz, CDCl3) \( \delta = 202.1 \) (s, C8), 177.1 (s, C8a), 143.4 (s, Ts), 140.0 (s, C5a), 137.3 (s, Ts), 129.2 (d, 2C, Ts), 128.4 (d, 2C, Ts), 48.9 (t, C2), 42.3 (t, C5), 32.5 (t, C7), 30.37 (d, C6), 29.45 (t, C4), 23.9 (t, C3), 21.5 (q, CH3-Ts), 19.0 (q, C6-CH3) ppm. MS (ESI) m/z (%): 661 ([2M+Na]+, 100), 319 ([M]+, 5).

Elemental analysis calcd (%) for C17H17NO3S: C 63.92, H 6.63, N 4.39; found: C 63.67, H 6.91, N 4.02.

![Image](image-url)

1-(Toluene-4-sulfonyl)-2,3,4,5,6,7-hexahydro-1H-cyclopenta[b]azepin-8-one (17lb).

Compound 17lb was prepared according to the above described procedure starting from 7lb (103 mg, 0.30 mmol). Reaction was carried out with 5 mol % of Ph3PdCu/AgSbF5 in refluxing DCM. Chromatography (n-hexane/THOAc, 3 : 2; Rf = 0.22) afforded pure ketone 17lb (75 mg, 83 %) as a white solid. M.p. = 115.0 - 118.5 °C. \(^1\)H NMR (400 MHz, CDCl3) \( \delta = 8.06 \) (d, \( J = 8.2 \) Hz, 2H, Ts), 7.29 (d, \( J = 8.2 \) Hz, 2H, Ts), 3.24 - 3.11 (m, 2H, 2-H), 2.62 - 2.54 (m, 2H, 6-H), 2.53 - 2.47 (m, 2H, 5-H), 2.47 - 2.40 (m, 2H, 7-H), 2.40 (s, 3H, CH3-Ts), 1.91 - 1.85 (m, 2H, 3-H), 1.69 - 1.59 (m, 2H, 4-H) ppm. \(^{13}\)C NMR (100.4 MHz, CDCl3) \( \delta = 202.9 \) (s, C8), 173.5 (s, C8a), 143.5 (s, Ts), 140.6 (s, C5a), 137.3 (s, Ts), 129.3 (d, 2C, Ts), 128.4 (d, 2C, Ts), 49.0 (t, C2), 33.8 (t, C7), 31.7 (t, C5), 30.3 (t, C6), 29.5 (t, C3), 23.6 (t, C4), 21.6 (q, CH3-Ts) ppm. MS (ESI) m/z (%): 633 ([2M+Na]+, 100), 328 ([M+Na]+, 5).

Elemental analysis calcd (%) for C18H19NO3S: C 62.93, H 6.27, N 4.59; found: C 63.11, H 5.96, N 4.34.

![Image](image-url)

1-Methyl-3-oxo-2,3-dihydro-1H-cyclopenta[b]indole-4-carboxylic Acid Methyl Ester (17o).
Compound 17o was prepared according to above described procedure starting from 7o (66 mg, 0.23 mmol). Reaction was carried out with 5 mol % of Ph3PdAuCl/AgSbF6 in refluxing DCM. Chromatography (n-hexane/EtOAc, 6 : 1; Rf = 0.26) afforded pure ketone 17o (47 mg, 84 %) as a yellow solid. M.p. = 113.4 – 115.2 °C. 1H NMR (400 MHz, CDCl3) δ = 8.33 (d, J = 8.6 Hz, 1H, 8-H), 7.70 (d, J = 8.2 Hz, 1H, 5-H), 7.55 – 7.51 (m, 1H, 6-H), 7.37 – 7.33 (m, 1H, 7-H), 4.07 (s, 3H, OCH3), 3.51 – 3.44 (m, 1H, 1-H), 3.25 (dd, J = 18.3, 6.6 Hz, 1H, 2-H), 2.60 (dd, J = 18.3, 2.3 Hz, 1H, 2-H), 1.48 (d, J = 7.4 Hz, 3H, 1-CH3) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 189.9 (s, C3), 158.0 (s, CO2CH3), 151.3 (s, C4a), 143.1 (s, C3a), 137.4 (s, C8a), 129.1 (d, C7), 124.4 (s, C8b), 123.7 (d, C6), 121.5 (d, C8), 116.9 (d, C5), 54.0 (t, C2), 50.4 (q, OCH3), 27.4 (d, C1), 20.4 (q, C1-CH3) ppm. MS (ESI) m/z (%): 509 ([2M+Na]+, 100), 266 ([M+Na]+, 9), 244 ([M+1]+, 8). Elemental analysis calcd (%) for C14H13NO3: C 69.12, H 5.39, N 3.13; found: C 69.37, H 5.14, N 5.47.

Acetic acid 4a,5-dimethyl-1-(toluene-4-sulfonyl)-2,3,4,4a-tetrahydro-1H-[1]pyrindin-7-yl ester (14p) and 4a,5-Dimethyl-1-(toluene-4-sulfonyl)-1,2,3,4,4a,7a-hexahydro-[1]pyrindin-7-one (15p).

Compound 14p was prepared according to the above described procedure starting from 7p (115 mg, 0.32 mmol). Reaction was carried out with 10 mol % of Ph3PdAuCl/AgOTf in refluxing DCM. Chromatography (n-hexane/EtOAc, 5 : 1) afforded acetate 14p (Rf = 0.39; 20 mg, 17 %) as a yellow oil and ketone 15p as colourless oil (Rf = 0.17; 25 mg, 25 %).

**14p:** 1H NMR (400 MHz, CDCl3) δ = 7.75 (d, J = 8.0 Hz, 2H, Ts), 7.24 (d, J = 8.0 Hz, 2H, Ts), 5.90 (s, 1H, 6-H), 3.99 (dd, J = 8.0, 4.0 Hz, 1H, 2-H), 2.99 (td, J = 12.0, 4.0 Hz, 1H, 2-H), 2.39 (s, 3H, CH3-Ts), 2.10 (s, 3H, CH3-Ac), 1.87 - 1.74 (m, 2H, 5-H), 1.79 (d, J = 4.0 Hz, 3H, 5-CH3), 1.60 – 1.54 (m, 1H, 4-H), 1.15 (td, J = 16.0, 4.0 Hz, 1H, 4-H), 0.77 (s, 3H, 4a-CH3) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 168.3 (s, CO), 151.5 (s, C7a), 143.1 (s, Ts), 140.0 (s, C7), 138.7 (s, Ts), 129.4 (d, 2C, Ts), 128.7 (s, C5), 127.2 (d, 2C, Ts), 121.3 (d, C=6), 49.3 (t, C2), 47.6 (s, C4a), 33.6 (t, C4), 22.8 (q, CH3-Ac), 21.4 (CH3-Ts), 20.7 (t, C3), 17.9 (CH3-5), 12.4 (CH3-4a) ppm. MS (ESI) m/z (%): 745 ([2M+Na]+, 100), 379 ([M+1]+, 17), 362 ([M+1]+, 32).

**15p:** 1H NMR (400 MHz, CDCl3) δ = 7.86 (d, J = 8.0 Hz, 2H, Ts), 7.30 (d, J = 8.0 Hz, 2H, Ts), 5.91 (s, 1H, 6-H), 4.32 (s, 1H, 7a-H), 3.61 (dt, J = 12.0, 8.0 Hz, 1H, 2-H), 2.82 - 2.76 (m, 1H, 2-H), 2.42 (s, 3H, CH3-Ts), 2.02 (s, 3H, 5-CH3), 1.74 - 1.58 (m, 2H, 3-H), 1.46 – 1.40 (m, 1H, 4-H), 1.33 (s, 3H, 4a-CH3), 1.29 – 1.25 (m, 1H, 4-H) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 202.2 (s, CO), 180.6 (d, C-6), 143.1 (s, Ts), 137.4 (s, Ts), 129.3 (d, 2C, Ts), 127.7 (d, 2C, Ts), 127.7 (s, C5), 66.8 (s, C4a), 45.1 (d, C7a), 42.1 (t, C2), 32.7 (5-CH3), 21.7 (t, C-5), 21.5 (q, CH3-Ts), 18.4 (t, C-4), 15.0 (q, CH3-4a) ppm. MS (ESI) m/z (%): 661.24 ([2M+Na]+, 100), 337 ([M+1]+, 28), ([M+1]+, 24). Elemental analysis calcd (%) for C14H21NO3S: C 63.92, H 6.63, N 4.39; found: C 64.02, H 6.50, N 4.21.

**General procedure for acetate hydrolysis**

Catalytic amount of pTsOH was added to the solution of the acetate (0.06 mmol) in 1 : 1 mixture of DCM and MeOH (3 mL) and the reaction mixture was left to stir at room temperature. After 20 h the solvent was concentrated and the oily residue was dissolved in DCM (3 mL); the organic solution was washed with water (3 mL) and dried over anhydrous Na2SO4. After filtration and evaporation of the solvent, the desired product was obtained and, when it was necessary, purified by flash chromatography. In some cases, the desired product was obtained in a mixture with ketone 23 due to [1,5]H-shift (up to 10%).
5-Butyl-1-(toluene-4-sulfonyl)-1,2,3,4,4a,7a-hexahydro-[1]pyrindin-7-one (15aa).

According to the above described procedure, hydrolysis of acetate 14aa (23 mg, 0.06 mmol) afforded ketone 15aa (20 mg, 96 %) as a pale yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.87 (d, J = 8.3 Hz, 2H, Ts), 7.30 (d, J = 8.3 Hz, 2H, Ts), 5.91 (s, 1H, 6-H), 4.72 (d, J = 6.8 Hz, 1H, 7a-H), 3.66 (dt, J = 12.5, 6.1 Hz, 1H, 2-H), 2.98 (q, J = 6.8 Hz, 1H, 4a-H), 2.78 (ddd, J = 12.5, 7.3, 4.9 Hz, 1H, 2'-H), 2.44 – 2.36 (m, 4H, CH$_3$-Ts and 1'-H), 2.32 – 2.24 (m, 1H, 1'-H$^+$), 2.09 – 2.01 (m, 1H, 4-H), 1.63 – 1.44 (m, 3H, 3-H and 2'-H), 1.42 – 1.30 (m, 3H, 3-H$^+$ and 3''-H), 1.28 – 1.18 (m, 1H, 4'-H$^+$), 2.01 (t, J = 9.3 Hz, 4'-H$^+$) ppm. $^{13}$C NMR (100.4 MHz, CDCl$_3$) $\delta$ = 203.4 (s, C7), 182.3 (s, C5), 143.2 (s, Ts), 137.5 (s, Ts), 129.4 (d, 2C, Ts), 127.7 (d, 2C, Ts), 126.3 (d, C6), 60.4 (d, C7a) 42.3 (t, C2), 41.0 (d, C4a), 31.5 (t, C1'), 28.5 (t, C2'), 26.6 (t, C3'), 22.4 (t, C4), 21.5 (q, CH$_3$ Ts), 19.4 (t, C3) 13.8 (q, C4') ppm. MS (ESI) m/z (%): 717 [(M+Na$^+$), 100], 370 [(M+Na$^+$), 5], 348 [(M+1)$^+$, 6]. Elemental analysis calcd (%) for C$_{15}$H$_{25}$NO$_2$: C 65.68, H 7.25, N 4.03; found: C 65.36, H 7.43, N 4.07.

![Diagram of 5-Butyl-1-(toluene-4-sulfonyl)-1,2,3,4,4a,7a-hexahydro-[1]pyrindin-7-one (15aa)](image)

5-Methyl-1-(toluene-4-sulfonyl)-1,2,3,4,4a,7a-hexahydro-[1]pyrindin-7-one (15ac).

According to the above described procedure, hydrolysis of acetate 14aa (142 mg, 0.41 mmol) afforded ketone 15aa (98 mg, 80 %) in a mixture with ketone 17ac (8 %). M.p. = 114.5 – 115.8 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.86 (d, J = 8.2 Hz, 2H, Ts), 7.30 (d, J = 8.2 Hz, 2H, Ts), 5.94 (s, 1H, 6-H), 4.71 (d, J = 6.8 Hz, 1H, 7a-H), 3.65 (dt, J = 12.6, 6.3 Hz, 1H, 2-H), 2.93 (q, J = 6.8 Hz, 1H, 4a-H), 2.80 (ddd, J = 12.6, 7.3, 5.1 Hz, 1H, 2-H), 2.07 (s, 3H, CH$_3$-Ts), 2.05 (s, 3H, CH$_3$-5), 1.56 – 1.42 (m, 1H, 4-H), 1.39 – 1.26 (m, 1H, 5-H), 1.29 – 1.19 (m, 2H, 4-H and 5-H) ppm. $^{13}$C NMR (100.4 MHz, CDCl$_3$) $\delta$ = 203.4 (s, C7), 177.65, 143.3 (s, Ts), 137.3 (s, Ts), 129.3 (d, 2C, Ts), 127.4 (s, 2C, Ts), 60.6 (d, C-7a), 42.4 (t, C-2), 41.7 (d, C-4a), 25.3 (q, CH$_3$), 21.4 (q, CH$_3$-Ts), 18.8 (t, C-3), 18.1 (t, C-4). MS (ESI) m/z (%): 632 [(M+Na$^+$), 100], 327 [(M+Na$^+$), 48], 305 [(M+1)$^+$, 37]. Elemental analysis calcd (%) for C$_{16}$H$_{25}$NO$_2$: C 62.93, H 6.27, N 4.57; found: C 62.80, H 6.36, N 4.55.

![Diagram of 5-Methyl-1-(toluene-4-sulfonyl)-1,2,3,4,4a,7a-hexahydro-[1]pyrindin-7-one (15ac)](image)

5,5-Dimethyl-1-(toluene-4-sulfonyl)-1,2,3,4,5,6-hexahydro-[1]pyrindin-7-one (17ad).

According to the above described procedure, hydrolysis of acetate 16ad (72 mg, 0.19 mmol) afforded ketone 17ad (55 mg, 86 %) after flash chromatography (n-hexane/EtOAc, 4 : 1; R$_f$ = 0.21) as a yellow solid. M.p. = 102.3 – 104.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.99 (d, J = 8.4 Hz, 2H, Ts), 7.30 (d, J = 8.4 Hz, 2H, Ts), 3.41 – 3.39 (m, 2H, 2-H), 2.41 (s, 3H, CH$_3$-Ts), 2.34 (s, 2H, 6-H), 2.33 (t, J = 6.5 Hz, 2H, 4-H), 2.01 – 1.95 (m, 2H, 3-H), 1.21 (s, 6H, 5-CH$_3$) ppm. $^{13}$C NMR (100.4 MHz, CDCl$_3$) $\delta$ = 199.3 (s, C7), 166.2 (s, C7a), 143.4 (s, Ts), 137.9 (s, Ts), 135.6 (s, C4a), 129.3 (d, 2C, Ts), 127.7 (d, 2C, Ts), 50.0 (t, C6), 45.8 (t, C2), 38.5 (s, C5), 27.2 (q, 2C, C5-C6H$_3$), 21.6 (t, C4), 21.5 (q, CH$_3$-Ts), 20.5 (t, C3 ppm. MS (ESI) m/z (%): 661 [(2M+Na$^+$), 100], 342 [(M+Na$^+$), 12], 320 [(M+1)$^+$, 11]. Elemental analysis calcd (%) for C$_{17}$H$_{21}$NO$_3$: C 63.92, H 6.63, N 4.39; found C 63.54, H 6.42, N 4.59.
5-Phenyl-1-(toluene-4-sulfonyl)-1,2,3,4,4a,7a-hexahydro-[1]pyrindin-7-one (15ae).

According to the above described procedure, hydrolysis of acetate 14ae (13 mg, 0.032 mmol) afforded ketone 15ae (6 mg, 51 %) after flash chromatography (n-hexane/EtOAc, 4 : 1; Rf = 0.25) as a yellow oil. 1H NMR (400 MHz, CDCl3) δ = 7.91 (d, J = 8.2 Hz, 2H, Ts), 7.65 – 7.61 (m, 2H, Ph), 7.50 – 7.44 (m, 3H, Ph), 7.29 (d, J = 8.2 Hz, 2H, Ts), 6.55 (s, 1H, 6-H), 4.92 (d, J = 6.9 Hz, 1H, 7a-H), 3.73 (dt, J = 12.6, 6.1 Hz, 1H, 2-H), 3.67 (q, J = 6.9 Hz, 1H, 4a-H), 2.87 (ddd, J = 12.6, 7.8, 4.7 Hz, 1H, 2-H'), 2.21 (ddd, J = 10.3, 6.9, 3.0 Hz, 1H, 4-H'), 1.61 – 1.51 (m, 1H, 3-H), 1.46 – 1.38 (m, 1H, 3-H'), 1.37 – 1.28 (m, 1H, 4-H') ppm. 13C NMR (100.4 MHz, CDCl3) δ = 202.9 (s, C7), 173.53 (s, C5), 143.3 (s, Ts), 137.5 (s, Ts), 132.3 (s, Ph), 131.6 (d, Ph), 129.5 (d, 2C, Ts), 129.2 (d, 2C, Ph), 127.7 (d, 2C, Ts), 127.0 (d, 2C, Ph), 124.0 (d, C6), 61.0 (d, C7a) 42.6 (t, C2), 38.3 (d, C4a), 27.9 (t, C4), 21.5 (q, CH3-Ts), 19.8 (t, C3) ppm. MS (ESI) m/z (%): 757 ([2M+Na]+, 100), 390 ([M+Na]+, 12), 368 ([M+1]+, 11). Elemental analysis calcd (%) for C23H22NO3S: C 68.64, H 5.76, N 3.81; found C 68.49, H 5.41, N 3.64.

1-(Toluen-4-sulfonyl)-1,2,3,4-tetrahydro-pyridine (25a).

A solution of 11a (500 mg, 2 mmol) in DCM (10 mL) was cooled to -78 °C and 1 M solution of DIBAL-H (2.2 mL, 2.2 mmol) was slowly added keeping the temperature below -70 °C. Reaction mixture was stirred below -70 °C and after 1 h MeOH (1 mL) was added following by satd solution of Rochelle salt. Formed two-phase system was stirred at room temperature for 1 h. Layers were separated, 1-(toluen-4-sulfonyl)-piperidin-2-ol was extracted with DCM (2 x 15 mL) and the organic layer was dried over anhydrous Na2CO3 for 30 min. After filtration and evaporation of the solvent, obtained 1-(toluen-4-sulfonyl)-piperidin-2-ol was dissolved in DCM (10 mL) and DMAP (9.6 mg, 0.08 mmol) and Et3N (0.83 mL, 6 mmol) were added. This solution was cooled to 0 °C and MsCl (0.3 mL, 3 mmol) was added. Reaction was stirred at room temperature. After 3 h satd solution of NH2Cl (10 mL) was added and the product extracted with DCM (3 x 10 mL). The organic extracts were dried over anhydrous Na2CO3 for 30 min. After filtration and evaporation of the solvent, flash chromatography (n-hexane/EtOAc, 5 : 1; Rf = 0.40) afforded pure 1-(toluen-4-sulfonyl)-1,2,3,4-tetrahydro-pyridine (333 mg, 70 %) as a white wax. 1H NMR (400 MHz, CDCl3): δ = 7.69 (d, J = 7.6 Hz, 2H, Ts), 7.33 (d, J = 7.6 Hz, 2H, Ts), 6.66 (d, J = 8.4 Hz, 1H, 2-H), 4.98 (bs, 1H, 3-H), 3.39 (t, J = 3.6 Hz, 2H, 6-H), 2.44 (s, 3H, CH3-Ts), 1.92 (bs, 2H, 4-H), 1.68 – 1.65 (m, 2H, 5-H) ppm. Spectroscopical data correspond to the literature values.13

3,4-Dihydro-2H-pyridine-1-carboxylic acid benzyl ester (25c).

A solution of 11c (1.16 g, 5 mmol) in THF (10 mL) was cooled to -78 °C and 1 M solution of Super-H (6 mL, 6 mmol) was slowly added keeping the temperature below -70 °C. Reaction mixture was stirred below -70 °C and after 1 h NaHCO3 (25 mL) was added followed by 35 % solution of H2O2 (5 mL). Reaction mixture was stirred on ice bath for 1 h. The product, 2-hydroxy-piperidine-1-carboxylic acid benzyl ester, was extracted with DCM (3 x 30 mL) and the organic layer was dried over anhydrous Na2CO3 for 30 min. After filtration and evaporation of the solvent, obtained material was dissolved in
DCM (25 mL) and DMAP (245 mg, 0.2 mmol) and Et3N (1.52 mL, 15 mmol) were added. This solution was cooled to 0 °C and MsCl (0.6 mL, 7.5 mmol) was added. Reaction was stirred at room temperature overnight. A satd solution of NH4Cl (30 mL) was added and the product extracted with DCM (3 x 30 mL). The organic extracts were dried over anhydrous Na2SO4 for 30 min. After filtration and evaporation of the solvent, flash chromatography (n-hexane/DMF, 8 : 1; Rf = 0.36) afforded pure 25c (660 mg, 62 %) as a colourless oil. 1H NMR (400 MHz, CDCl3) δ = 7.43 - 7.27 (m, 5 H, PhH), 6.89 (d, J = 8.6 Hz, 0.4 H, 2-H), 6.80 (d, J = 8.6 Hz, 0.6 H, 2-H), 5.18 (s, 2 H, CH2O), 4.97 (m, 0.4 H, 2-H), 4.86 (m, 0.6 H, 3-H), 3.63 (m, 2 H, 6-H), 2.04 (m, 2 H, 4-H), 1.83 (m, 2 H, 5-H) ppm. Spectroscopical data correspond to the literature values.44

General procedure for synthesis of enesulfonamides derived enynyl acetates.

STEP A: Iodination of enesulfonamides (27)
Enesulfonamide (1 mmol) and NaOCl (105 mg, 2 mmol) were suspended in MeOH (4 mL) and 1 M solution of ICl in DCM (1.1 mL, 1.1 mmol) was added dropwise. Resulting brown suspension was stirred at room temperature for 30 min and then a 10 % aqueous solution of Na2S2O3 was added and stirring continued for 30 min. The layers were separated; organic layer was dried over Na2SO4, filtered and concentrated to give brown oil. Obtained oil was dissolved in toluene (8 mL) and a solution of TFA (11 μL, 0.15 mmol) in toluene (20 μL) was added. Obtained purple solution was submersed into an oil bath preheated to 140 °C. After 5 min, reaction flask was put on ice and immediately, a solution of Et3N (62 μL, 0.5 mmol) in toluene (200 μL) was added. Reaction mixture was concentrated and crude was purified by flash chromatography to give the corresponding β-iodo-enesulfonamides.

STEP B: Sonogashira coupling (28)
β-Iodo-enesulfonamide 27 (1 mmol), Cul (19 mg, 0.1 mmol) and (Ph3)2PdCl2 (35 mg, 0.05 mmol) were dissolved in an anhydrous 4 : 1 Et2NH/DMF mixture (10 mL) and alkyne (1.2 mmol) was added under nitrogen atmosphere. The reaction mixture was heated at 40 °C for 10 min, and water (15 mL)
was added. The product was extracted with Et₂O (3 x 10 mL) and the combined organic extracts were dried over anhydrous K₂CO₃ for 30 min. After filtration and evaporation of the solvent, the crude was purified by flash chromatography and obtained enynyl alcohol was used in the next step.

**STEP C: Acetylation (29)**

A solution of enynyl alcohol 28 (1 mmol), DMAP (24 mg, 0.2 mmol) and Et₃N (0.38 mL, 3 mmol) in DCM (4 mL) was cooled by ice bath and Ac₂O (0.19 mL, 2 mmol) was added. The reaction mixture was stirred at room temperature and followed by TLC. When the conversion was complete, satd solution of NaHCO₃ (10 mL) was added and the product extracted with DCM (3 x 10 mL). The combined organic extracts were dried over anhydrous K₂CO₃ for 30 min. After filtration and evaporation of the solvent, the crude was purified by flash chromatography and stored at 4°C as 0.1 M solution in the eluent containing 1 % Et₃N until use.

Acetic acid 1-methyl-3-[1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-3-yl]-prop-2-ynyl ester (29a).

Compound 27a was prepared according to the above described procedure starting from 25a (230 mg, 1 mmol). Flash chromatography (n-hexane/EtOAc, 3 : 2; Rₜ = 0.22) afforded 13 (327 mg, 77 %) contaminated by unknown impurity. ¹H NMR (400 MHz, CDCl₃) δ = 7.65 (d, J = 8.3 Hz, 2H, Ts), 7.32 (d, J = 10.8 Hz, 2H, Ts), 7.12 (s, 1H, 2-H), 3.22 – 3.12 (m, 2H, 6-H), 2.43 (s, 3H, CH₃-Ts), 2.32 (td, J = 6.3, 2.7 Hz, 2H, 4-H). 1.76 – 1.66 (m, 2H, 5-H) ppm. ¹³C NMR (100.4 MHz, CDCl₃) δ = 143.9 (s, Ts), 134.6 (s, Ts), 130.4 (d, C-2), 129.9 (d, 2C, Ts), 128.9 (d, 2C, Ts), 87.7 (s, C3), 42.2 (t, C4), 34.0 (t, C4), 23.0 (t, C5), 21.4 (q, CH₃-Ts) ppm. MS (ESI) m/z (%): 364 ([M+H⁺]⁺, 100), 385 ([M+Na⁺]⁺, 8).

Sonogashira coupling of β-iodo-enesulfonylamides 27a (193 mg, 0.9 mmol) and (+)-3-butyln-2-ol after flash chromatography (n-hexane/EtOAc, 3 : 1 + 1 % Et₃N; Rₜ = 0.16) afforded enynyl alcohol 28a which was used immediately in the next step (220 mg, 80 %).

¹H NMR (400 MHz, CDCl₃) δ = 7.66 (d, J = 8.3 Hz, 2H, Ts), 7.31 (d, J = 8.3 Hz, 2H, Ts), 7.06 (s, 1H, 2-H), 4.63 (q, J = 6.6 Hz, 1H, 3'-H), 3.35 – 3.31 (m, 2H, 6-H), 2.43 (s, 3H, CH₃-Ts), 2.05 – 2.02 (m, 4-H), 1.77 (bs, 1H, OH), 1.71 – 1.65 (m, 2H, 5-H), 1.45 (d, J = 6.6 Hz, 3H, 3'-CH₃) ppm. ¹³C NMR (100.4 MHz, CDCl₃) δ = 144.0 (s, Ts), 134.8 (s, Ts), 130.7 (d, C2), 129.9 (d, 2C, Ts), 127.0 (d, 2C, Ts), 109.9 (s, C3), 89.4 (s, C1), 83.7 (C2'), 58.9 (C3'), 43.6 (t, C6), 25.5 (C4), 24.5 (q, CH₃-3'), 21.6 (q, CH₃-Ts), 20.6 (t, C-5) ppm. MS (ESI) m/z (%): 306 ([M+Na⁺]⁺, 100), 328 ([M+Na⁺]⁺, 31), 633 ([2M+Na⁺]⁺, 35).

According to the above described procedure, compound 28a was subjected to acetylation. After flash chromatography (n-hexane/EtOAc, 6 : 1 + 1 % Et₃N; Rₜ = 0.18) pure 15 was obtained as a colourless oil (210 mg, 84 %). ¹H NMR (400 MHz, CDCl₃) δ = 7.66 (d, J = 8.3 Hz, 2H, Ts), 7.32 (d, J = 8.0 Hz, 2H, Ts), 7.09 (s, 1H, 2-H), 5.69 – 5.44 (m, 1H, 3'-H), 3.43 – 3.21 (m, 2H, 6-H), 2.43 (s, 3H, CH₃-Ts), 2.08 (s, 3H, CH₃-Ac), 2.04 (td, J = 6.2, 1.3 Hz, 2H, 4-H), 1.73 – 1.63 (m, 2H, 5-H), 1.49 (d, J = 6.7 Hz, 3H, 3'-CH₃) ppm. ¹³C NMR (100.4 MHz, CDCl₃) δ = 169.9 (s, CO), 144.1 (s, Ts), 134.8 (s, Ts), 131.3 (d, C2), 129.9 (d, 2C, Ts), 127.0 (d, 2C, Ts), 100.5 (C3), 85.8 (s, C1'), 84.4 (s, C2'), 60.9 (s, C3'), 43.4 (t, C6), 25.3 (q, CH₃-Ac), 21.6 (q, CH₃-3'), 21.5 (q, CH₃-Ts), 21.1 (t, C-4), 20.6 (t, C-5) ppm. MS (ESI) m/z (%): 288 ([C₁₆H₁₇NO₂S]⁺, 100), 369 ([M+Na⁺]⁺, 17).
5-(3-Acetoxy-but-1-ynyl)-3,4-dihydro-2H-pyridine-1-carboxylic acid benzyl ester (29c).

Compound 27c was prepared according to the above described procedure starting from 25c (340 mg, 1.56 mmol). Flash chromatography (n-hexane/EtOAc, 10 : 1; Rf = 0.24) afforded 27c (353 mg, 66 %).

1H NMR (400 MHz, CDCl₃) δ = 7.44 – 7.28 (m, 5H, Ph), 7.27 – 7.25 (s, 1H, 2-H), 5.18 (s, 2H, CH₂O), 3.70 – 3.59 (m, 2H, 6-H), 2.46 (t, J = 7.0 Hz, 4-H), 1.95 – 1.84 (m, 2H, 5-H) ppm.

Sonogashira coupling of β-iodo-ene-carbamate 27c (177 mg, 0.52 mmol) and (±)-3-butyln-2-ol after flash chromatography (n-hexane/EtOAc, 5:2 + 1 % Et₃N; Rf = 0.19) afforded enynyl alcohol 28c which was used immediately in the next step (120 mg, 75 %). 1H NMR (400 MHz, CDCl₃) δ = 7.42 – 7.32 (m, 5H, Ph), 7.18 (s, 1H, 2-H), 4.66 – 4.60 (m, 1H, 3'-H), 3.62 – 3.56 (m, 2H, 6-H), 2.16 (t, J = 5.7 Hz, 2H, 4-H), 1.88 – 1.79 (bs, 2H, 5-H), 1.46 (d, J = 6.6 Hz, 4H) ppm.

According to the above described procedure, compound 28c was subjected to acetylation. After flash chromatography (n-hexane/EtOAc, 6 : 1 + 1 % Et₃N; Rf = 0.21) pure 29c was obtained as a colourless oil (108 mg, 85 %). 1H NMR (400 MHz, CDCl₃) δ = 7.40 – 7.29 (m, 5H, Ph), 7.20 (s, 1H, 2-H), 5.57 (q, J = 6.5 Hz, 1H, 3'-H), 5.19 (s, 2H, CH₂O), 3.63 – 3.54 (m, 2H, 6-H), 2.16 (t, J = 5.9 Hz, 2H, 4-H), 2.06 (s, 3H, CH₃Ac), 1.85 – 1.75 (m, 2H, 5-H), 1.49 (d, J = 6.6 Hz, 3H) ppm. 13C NMR (100.4 MHz, CDCl₃) δ = 169.9 (s, CO-Ac), 152.5 (s, CO-Cbz), 135.8 (s, Cbz), 131.4 (d, Cbz), 128.7 (d, 2C, Cbz) 128.5 (d, 2C, Cbz), 128.1 (d, C2), 99.1 (s, C3), 84.9 (s, C1'), 68.0 (C2'), 67.9 (t, CH₂-Cbz), 61.0 (d, C3'), 41.9 (t, C6), 25.8 (d, C4), 21.7 (d, C5), 21.2 (q, CH₃-5'), 21.0 (q, CH₃-Ac) ppm. MS (ESI) m/z (%): 268 ([M-OAc]+, 100), 349 ([M+Na]+, 34), 676 ([2M+Na]+, 7).

Acetic acid 1-methyl-3-[1-(toluene-4-sulfonyl)-4,5,6,7-tetrahydro-1H-azepin-3-yl]-prop-2-ynyl ester (29l).

Compound 27l was prepared according to the above described procedure starting from 25l (156 mg, 0.62 mmol). Flash chromatography (n-hexane/EtOAc, 3 : 2; Rf = 0.22) afforded 27l (201 mg, 85 %) contaminated by unknown impurity. 1H NMR (400 MHz, CDCl₃) δ = 7.70 (d, J = 8.2 Hz, 2H, Ts), 7.32 (d, J = 8.2 Hz, 2H, Ts), 6.92 (s, 1H, 7-H), 3.60 – 3.52 (m, 2H, 6-H), 2.72 – 2.59 (m, 2H, 5-H), 2.44 (s, 3H, CH₃-Ts), 1.78 – 1.66 (m, 2H, 5-H), 1.47 (dt, J = 12.2, 6.1 Hz, 2H, 4-H) ppm.

Sonogashira coupling of 27l (193 mg, 0.51 mmol) and (±)-3-butyln-2-ol after flash chromatography (n-hexane/EtOAc, 3 : 1 + 1 % Et₃N; Rf = 0.16) afforded enynyl alcohol 28l which was used immediately in the next step (115 mg, 71 %). 1H NMR (400 MHz, CDCl₃) δ = 7.71 (d, J = 8.2 Hz, 2H, Ts), 7.32 (d, J = 8.2 Hz, 2H, Ts), 6.84 (s, 1H, 2-H), 4.62 (q, J = 6.6 Hz, 1H, 1'-H), 3.55 (t, J = 6.3 Hz, 2H, 7-H), 2.43 (s, 3H, CH₃-Ts), 2.35 – 2.21 (t, J = 6.2 Hz, 2H, 4-H), 1.72 (dt, J = 12.2, 6.3 Hz, 3H, 6-H and OH), 1.55 (dt, J = 12.2, 6.2 Hz, 2H, 5-H), 1.46 (d, J = 6.6 Hz, 3H, 1'-CH₃) ppm.

According to the above described procedure, compound 28l was subjected to acetylation. After flash chromatography (n-hexane/EtOAc, 6 : 1 + 1 % Et₃N; Rf = 0.18) pure 29l was obtained as a colourless oil (100 mg, 84 %). 1H NMR (400 MHz, CDCl₃) δ = 7.69 (d, J = 8.2 Hz, 2H, Ts), 7.31 (d, J = 8.2 Hz, 2H, Ts), 6.86 (s, 1H, 2-H), 5.54 (q, J = 6.7 Hz, 1H, 3'-H), 3.46 (t, J = 6.1 Hz, 2H, 7-H), 2.42 (s, 3H, CH₃-Ts), 2.27 (t, J = 6.0 Hz, 2H, 4-H), 2.06 (s, 3H, CH₃-Ac), 1.70 (dt, J = 12.2, 6.1 Hz, 2H, 6-H), 1.54 (dt, J = 12.2, 6.0 Hz, 2H, 5-H), 1.47 (d, J = 6.7 Hz, 3H, 3'-CH₃) ppm. 13C NMR (100.4 MHz, CDCl₃) δ = 169.9 (s, CO), 143.8 (s, Ts), 136.1 (s, Ts), 135.7 (d, C2), 129.8 (d, 2C, Ts), 126.7 (d, 2C, Ts), 109.5 (s, C3'), 85.8 (s, C2'), 85.4 (d, C1'), 60.9 (d, C3'), 48.8 (t, C7), 31.2 (t, C6), 28.0 (t, C4), 24.03 (t, C5), 21.4 (q,
CH$_3$-Ac), 21.5 (q, CH$_3$-Ts), 21.1 (q, CH$_3$-3') ppm. MS (ESI) m/z (%): 302 ([M-OAc]$^+$, 100), 384 ([M+Na]$^+$, 49), 744 ([2M+Na]$^+$, 6).

7-Methyl-1-{(toluene-4-sulfonyl)-1,2,3,4,6,7-hexahydro-[1]pyrindin-5-one (30a). Compounds 30a was prepared according to the general procedure for the Au(1)-catalyzed Nazarov reaction starting from 29a (52 mg, 0.16 mmol). Reaction was carried out with 5 mol % of Ph$_3$PAuCl/AgSbF$_6$ in DCM at room temperature. Flash chromatography (n-hexane/ElOAc, 3 : 1; R$_f$ = 0.15) afforded pure product 30a (32 mg, 66%) as a white solid. $^1$H NMR (400 MHz, CDCl$_3$) δ = 7.63 (d, J = 14.8 Hz, 2H, Ts), 7.33 (d, J = 8.4 Hz, 2H, Ts), 3.83 (ddd, J = 13.6, 5.0, 3.5 Hz, 1H, 2-H), 3.67 (p, J = 6.7 Hz, 1H, 7-H), 3.41 – 3.27 (m, 1H, 2-H), 2.71 (dd, J = 18.4, 6.8 Hz, 1H, 6-H), 2.48 – 2.37 (m, 4H, CH$_3$-Ts and 4-H), 2.13 – 1.95 (m, 2H, 6-H and 5-H), 1.72 – 1.54 (m, 1H, 5-H), 1.41 (d, J = 6.8 Hz, 2H, 7-CH$_3$) ppm. $^{13}$C NMR (100.4 MHz, CDCl$_3$) δ = 204.1 (s, CO), 170.1 (s, C7a), 144.8 (s, C5), 135.3 (s, C5), 130.2 (d, 2H, Ts), 127.1 (d, 2C, Ts), 123.8 (s, C4a), 74.7 (s, C6), 43.0 (t, C2), 35.4 (t, C7), 22.1 (t, C5), 21.6 (q, CH$_3$-Ts), 19.3 (t, C4), 18.3 (q, CH$_3$-7) ppm. MS (ESI) m/z (%): 306 ([M+1]+, 100), 328 ([M+Na]$^+$, 15), 633 ([2M+Na]$^+$, 35). Elemental analysis calcd (%) for C$_{18}$H$_{19}$NO$_3$S: C 62.93, H 6.27, N 4.59; found: C 62.70, H 6.33, N 4.54.

8-Methyl-1-{(toluene-4-sulfonyl)-2,3,4,5,7,8-hexahydro-1H-cyclopenta[b]aze pin-6-one (30l). Compounds 30l was prepared according to the general procedure for the Au(1)-catalyzed Nazarov reaction starting from 29l (50 mg, 0.14 mmol). Reaction was carried out with 5 mol % of Ph$_3$PAuCl/AgSbF$_6$ in DCM at room temperature. Flash chromatography (n-hexane/ElOAc, 3 : 1; R$_f$ = 0.15) afforded pure product 30a (24 mg, 54%) as a white solid. M.p. = 118.4 – 119.0 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ = 7.72 (d, J = 8.3 Hz, 2H, Ts), 7.32 (d, J = 8.3 Hz, 2H, Ts), 4.31 (dt, J = 15.0, 3.7 Hz, 1H, 2-H), 3.62 – 3.49 (m, 1H, 8-H), 3.12 (ddd, J = 15.3, 12.3, 3.3 Hz, 1H, 2-H), 2.78 (dd, J = 19.5, 8.8 Hz, 1H, 7-H), 2.47 – 2.33 (m, 4H, CH$_3$-Ts and 5-H), 2.09 (dd, J = 19.5, 1.7 Hz, 1H, 7-H), 1.88 – 1.73 (m, 1H, 3-H), 1.67 – 1.45 (m, 3H, 3-H and 4-H), 1.41 – 1.32 (m, 1H, 5-H), 1.21 (d, J = 7.0 Hz, 3H, 8-CH$_3$) ppm. $^{13}$C NMR (100.4 MHz, CDCl$_3$) δ = 205.7 (s, C6), 174.3 (s, C8a), 144.3 (s, Ts), 137.2 (s, Ts), 133.7 (s, C6a), 129.9 (d, 2C, Ts), 126.9 (d, 2C, Ts), 52.4 (t, C7), 135.3 (t, C7), 28.1 (t, C5), 22.9 (t, C3), 21.6 (t, C4), 21.6 (q, CH$_3$-Ts), 20.3 (q, CH$_3$-8) ppm. MS (ESI) m/z (%): 320 ([M+1]$^+$, 100). Elemental analysis calcd (%) for C$_{17}$H$_{21}$NO$_3$S: C 63.92, H 6.63, N 4.39; found: C 62.93, H 6.53, N 4.06.

7-Methyl-5-oxo-2,3,4,5,6,7-hexahydro-[1]pyrindine-1-carboxylic acid benzyl ester (30c) and 5-But-2-enoyl-3,4-dihydro-2H-pyridine-1-carboxylic acid benzyl ester (31c). Compound 30c was prepared according to the above described procedure for gold(I)-catalyzed reaction starting from 29c (50 mg, 0.15 mmol). Reaction was carried out with 5 mol % of Ph$_3$PAuCl/AgOTf in DCM : t-BuOH = 1 : 1. Chromatography (n-hexane/ElOAc, 3 : 1) afforded α,β-unsaturated ketone 31c (R$_f$ = 0.57; 12 mg, 28%) as a yellow oil and Nazarov product 30c as an orange oil (R$_f$ = 0.28; 12 mg, 26%).

30c. $^1$H NMR (400 MHz, CDCl$_3$) δ = 7.43 – 7.29 (m, 5H, Ph), 5.23 (s, 2H, CH$_2$O), 4.08 (dt, J = 9.6, 4.7 Hz, 1H, 6-H), 3.75 – 3.65 (m, 1H, 7-H), 3.45 (ddd, J = 12.6, 9.6, 3.0 Hz, 1H, 6-H), 2.65 (dd, J = 18.2, 6.8 Hz, 1H, 6-H), 2.20 (t, J = 6.6 Hz, 2H, 4-H), 1.99 (d, J = 18.2 Hz, 1H, 6-H), 1.91 – 1.71 (m, 2H, 3-H), 1.14 (d, J = 6.8 Hz, 3H, CH$_3$) ppm.
31c. mixture of E/Z isomers: $^1$H NMR (400 MHz, CDCl$_3$) $\delta = 7.79 - 7.68$ (bs, 1H, 2-H), $7.45 - 7.29$ (m, 5H, Ph), $6.87$ (q, $J = 6.9$ Hz, 0.35H, 7-H), $6.84$ (q, $J = 6.9$ Hz, 0.65H, 7-H), $6.75 - 6.62$ (bs, 0.65H, 6-H), $6.62 - 6.49$ (bs, 0.35H, 6-H), $5.26$ (s, 2H, CH$_2$O) $3.66 - 3.63$ (m, 2H, 2-H), $2.36$ (t, $J = 6.0$ Hz, 2H, 4-H), $1.89$ (d, $J = 6.9$ Hz, 3H, CH$_3$), $1.87 - 1.82$ (m, 2H, 5-H) ppm.

1-(Toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridine-2-carboxylic acid methyl ester (42).

Phosphate 12a (949 mg, 1.96 mmol) was dissolved in DMF (5 mL) and Pd(OAc)$_2$ (44 mg, 0.2 mmol) and Ph$_3$P (103 mg, 0.4 mmol) were added. Reaction mixture was flushed with CO and Et$_3$N (0.5 mL, 3.9 mmol) and MeOH (3.2 mL, 80 mmol) were added. The reaction mixture was stirred at 60 °C under CO atmosphere. After 2.5 h, water (50 mL) was added and the product extracted with EtO (3 x 40 mL). The combined organic extracts were dried over anhydrous K$_2$CO$_3$ for 30 min. After filtration and evaporation of the solvent, the crude was purified by flash chromatography (hexane/ EtOAc, 2 : 1 $R_f = 0.31$) pure 42 (405 mg, 70 %) was obtained as a colourless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta = 7.85$ (d, $J = 8.2$ Hz, 2H, Ts), $7.31$ (d, $J = 8.2$ Hz, 2H, Ts), $6.31$ (t, $J = 3.9$ Hz, 1H, 3-H), $3.83$ (s, 3H, OCH$_3$), $3.51 - 3.05$ (m, 2H, 6-H), $2.43$ (s, 3H, CH$_3$-Ts), $2.15$ (td, $J = 6.7$, 3.9 Hz, 2H, 4-H), $1.80 - 1.47$ (m, 2H, 5-H) ppm. $^{13}$C NMR (100.4 MHz, CDCl$_3$) $\delta = 165.7$ (s, CO), $144.0$ (s, Ts), $135.9$ (s, C2), $131.2$ (s, Ts), $129.5$ (d, 2C, Ts), $127.9$ (d, 2C, Ts), $126.5$ (d, C3), $52.0$ (q, OCH$_3$), $44.9$ (t, C6), $22.3$ (t, C4), $21.6$ (t, C5), $20.1$ (q, CH$_3$-Ts) ppm. Elemental analysis calcd (%): for C$_{13}$H$_{17}$NO$_3$: C 56.93, H 5.80, N 4.74; found N 4.91, C 56.98, H 5.68.

1-(Toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridine-2-carbaldehyde (43).

A solution of 42 (295 mg, 1 mmol) in DCM (16 mL) was cooled to 0 °C and 1 M solution of DIBAL-H (1.25 mL, 1.25 mmol) was slowly added. Reaction mixture was stirred on ice bath for 2 h. The reaction was quenched by the addition of MeOH (5 mL) and satd solution of Rochelle salt (20 mL). Formed two-phase system was stirred for 1 h and then the layers were separated. The organic layer was dried over anhydrous Na$_2$CO$_3$ for 30 min. After filtration and evaporation of the solvent, obtained material was dissolved in DCM (10 mL), cooled to 0 °C and Dess-Martin periodinane (509 mg, 1.2 mmol) was added. The reaction mixture was stirred at room temperature for 2 h, poured into satd solution of Na$_2$S$_2$O$_3$ and stirred for 30 min. The layers were separated and the product extracted with DCM (3 x 6 mL). The organic extracts were dried over anhydrous Na$_2$CO$_3$ for 30 min. After filtration and evaporation of the solvent, flash chromatography (n-hexane/EtOAc, 3 : 1; $R_f = 0.27$) afforded pure 43 (223 mg, 84 %) as a colourless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta = 9.56$ (s, 1H), $7.71$ (d, $J = 8.5$ Hz, 2H, Ts), $7.31$ (d, $J = 8.5$ Hz, 2H, Ts), $6.38$ (t, $J = 4.0$ Hz, 1H, 3-H), $3.49 - 3.46$ (m, 2H, 4-H), $2.43$ (s, 3H, CH$_3$-Ts), $2.13$ (td, $J = 6.6$, 4.0, 2H, 4-H), $1.36 - 1.31$ (m, 2H, 5-H) ppm. $^{13}$C NMR (100.4 MHz, CDCl$_3$) $\delta = 187.7$ (s, CO), $144.33$ (s, Ts), $138.4$ (s, Ts), $135.6$ (s, C2), $129.8$ (d, 2C, Ts), $128.9$ (d, 2C, Ts), $127.8$ (d, C3), $45.1$ (t, C6), $22.6$ (t, C4), $21.6$ (t, C5), $19.6$ (q, CH$_3$-Ts) ppm. MS (ESI) $m/z$ (%): 265 ([M]$^+$, 12), 288 ([M+Na]$^+$, 35), 553 ([2M+Na]$^+$, 100). Elemental analysis for C$_{13}$H$_{15}$NO$_3$: calcd N 5.28, C 58.85, H 5.70, O 18.90, S 12.09; found N 5.33, C 58.73, H 5.71.
Acetic acid 1-[1-(toluene-4-sulfonfonyl)-1,4,5,6-tetrahydro-pyridin-2-yl]-prop-2-ynyl ester (48).

A solution of triethylsilylacetylene (0.135 mL, 0.75 mmol) in THF (2 mL) was cooled to -78 °C and 1.6 M solution of n-BuLi (0.45 mL, 0.75 mmol) was slowly added keeping the temperature below -70 °C. Reaction mixture was stirred below -70 °C and after 30 min a solution of 43 (150 mg, 0.57 mmol) in THF (5 mL) was added. After 30 min the temperature was slowly risen to 0 °C and NaHCO₃ (8 mL) was added. The product was extracted with Et₂O (3 x 5 mL) and the organic layer was dried over anhydrous Na₂CO₃ for 30 min. After filtration and evaporation of the solvent, obtained material was dissolved in CDCl₃ and crude was dissolved in CDCl₃ (8 mL) was added. The reaction was monitored by TLC and it was complete in 1 h. The product was extracted with Et₂O (3 x 10 mL). The organic extracts were dried over anhydrous Na₂CO₃ for 30 min. After filtration and evaporation of the solvent, column chromatography (n-hexane/Et₂O, 3:1 + 1% Et₃N; Rₑ = 0.36) afforded pure 47 (14 mg, 6 %) as a colourless oil and 46 (111 mg, 46 %) as a yellow oil.

A solution of enynyl alcohol 47 (14 mg, 0.048 mmol), DMAP (1.2 mg, 0.01 mmol) and Et₃N (0.02 mL, 0.144 mmol) in DCM (0.5 mL) was cooled by ice bath and Ac₂O (9 μL, 0.1 mmol) was added. The reaction mixture was stirred at room temperature and after 1 h reaction mixture was concentrated. Flash chromatography (n-hexane/EtOAc, 3:1 + 1% Et₃N; Rₑ = 0.4) afforded enynyl acetate 48 (13.1 mg, 82 %). ¹H NMR (400 MHz, CDCl₃) δ = 7.73 (d, J = 8.2 Hz, 2H, Ts), 7.29 (d, J = 8.2 Hz, 2H, Ts), 6.64 (brs, 1H, 1',-H), 6.04 (t, J = 3.8 Hz, 1H, 3'-H), 3.72 – 3.54 (m, 1H, 6'-H), 3.39 (ddd, J = 14.0, 7.3, 4.9 Hz, 1H, 6'-H), 2.57 (t, J = 2.2 Hz, 1H, 3'-H), 2.42 (s, 3H, CH₃-Ts), 2.10 (s, 3H, CH₃-Ac), 1.98 (ddd, J = 8.1, 6.7, 2.6 Hz, 2H, 4'-H), 1.41 – 1.23 (m, 2H, 5'-H) ppm.

Acetic acid 1-(toluene-4-sulfonfonyl)-2,3,4,5-tetrahydro-1H-[1]pyrindin-6-yl ester (52).

Compound 52 was prepared according to the above described procedure for gold(I)-catalyzed reactions starting from 48 (13.1 mg, 0.04 mmol). Reaction was carried out in DCM with 5 % of Ph₃PAuCl/AgSbF₆. Since the reaction was carried out on a very small scale, catalyst was added as 0.05 M stock solution. The reaction was monitored by TLC and it was complete in 1 h. Solvent was evaporated and crude was dissolved in CDCl₃. Based on the analysis of ¹H NMR and gCOSY spectra compound 52 was obtained. ⁶¹H NMR (400 MHz, CDCl₃) δ = 7.55 (d, J = 8.6 Hz, 2H, Ts), 7.20 (d, J = 8.6 Hz, 2H, Ts), 6.55 (s, 1H, 7'-H), 3.54 – 3.51 (m, 2H, 2'-H), 3.02 (s, 2H, 5'-H), 2.34 (s, 3H, CH₃-Ts), 2.13 (s, 3H, CH₃-Ac), 2.02 (t, J = 6.4 Hz, 2H, 4'-H), 1.39 – 1.35 (m, 2H, 3'-H) ppm.

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1-(Toluene-4-sulfonyl)-1,2,3,4,4a,5-hexahydro-[1]pyrindin-6-one (53).

To the solution of 52 in DCM/MeOH = 1 : 1 (1 mL) catalytic amount of pTsOH was added and reaction mixture was stirred at room temperature for 20 min. Solvent was evaporated and the crude was dissolved in CDCl₃. Analysis of ¹H NMR revealed the product in the mixture with pTsOH.⁴⁵ ¹H NMR (400 MHz, CDCl₃) δ = 7.71 (d, J = 8.4 Hz, 2H, Ts), 7.30 (d, J = 8.5 Hz, 2H, Ts), 6.18 (s, 1H, 7-H), 3.84 – 3.78 (m, 1H, 2-H), 3.73 – 3.65 (m, 1H, 2-H), 2.91 – 2.79 (m, 1H, 4a-H), 2.69 (dd, J = 18.6, 6.4 Hz, 1H, 5-H), 2.39 – 2.34 (m, 4H, CH₃-Ts and 3-H), 2.12 – 2.05 (m, 1H, 4-H), 1.94 – 1.75 (m, 2H, 3-H), 1.25 – 1.18 (m, 1H, 4-H) ppm.

1-(Toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-2-yl]-hept-2-yn-1-ol (44).

A solution of hexyne (28 µL, 0.24 mmol) in THF (2.5 mL) was cooled to -78 °C and 1.6 M solution of n-BuLi (150 µL, 0.24 mmol) was slowly added keeping the temperature below -70 °C. Reaction mixture was stirred below -70 °C and after 30 min a solution of 43 (49 mg, 0.19 mmol) in THF (5 mL) was added. After 30 min the temperature was slowly risen to 0 °C and NaHCO₃ (8 mL) was added. The product was extracted with Et₂O (3 x 5 mL) and the organic layer was dried over anhydrous Na₂CO₃ for 30 min. After filtration and evaporation of the solvent, obtained material was immediately used in next step. ¹H NMR (200 MHz, CDCl₃) δ = 7.74 (d, J = 8.4 Hz, 2H, Ts), 7.30 (d, J = 8.4 Hz, 2H, Ts), 6.00 (t, J = 4.0 Hz, 1H, 3-H), 5.45 (bs, 1H, 1'-H), 3.80 (m, 2H, 6-H and OH), 3.38 (ddd, J = 14.0, 9.0, 3.4 Hz, 6-H), 2.43 (s, 3H, CH₃-Ts), 2.32 – 2.0 (m, 2H, 4-H), 2.02 – 1.94 (m, 2H, 4'-H), 1.62 – 1.14 (m, 6H, 5-H, 5'-H and 6'-H), 0.90 (t, J = 6.9 Hz, 3H, 7'-H) ppm.

Acetic acid 1-(Toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-2-yl]-hept-2-ynyl ester (45).

A solution of enynyl alcohol 44 (60 mg, 0.17 mmol), DMAP (4.2 mg, 0.04 mmol) and Et₃N (67 µL, 0.52 mmol) in DCM (1.5 mL) was cooled by ice bath and Ac₂O (33 µL, 0.35 mmol) was added. The reaction mixture was stirred at room temperature and after 1 h reaction mixture was concentrated. Flash chromatography (n-hexane/EtOAc; 5 : 1 + 1 % Et₃N; Rf = 0.27) afforded enynyl acetate 45 (48 mg, 72 %). ¹H NMR (200 MHz, CDCl₃) δ = 7.75 (d, J = 8.4 Hz, 2H, Ts), 7.28 (d, J = 8.4 Hz, 2H, Ts), 6.60 (bs, 1H, 1'-H), 6.05 (t, J = 4.0 Hz, 1H, 3-H), 3.78 – 3.61 (m, 1H, 6-H), 3.41 – 3.25 (m, 1H, 6-H), 2.43 (s, 3H, CH₃-Ts), 2.27 – 2.20 (m, 2H, 4-H), 2.10 (s, 3H, CH₃-Ac), 2.09 – 1.92 (m, 2H, 4'-H), 1.63 – 1.25 (m, 6H, 5-H, 5'-H and 6'-H), 0.90 (t, J = 6.9 Hz, 3H, 7'-H) ppm.

Acetic acid 6-butyl-1-(toulene-4-sulfonyl)-2,3,4,4a-tetrahydro-1H-[1]pyrindin-5-yl ester (49).

Propargylic acetate 45 (45 mg, 0.116 mmol) was treated with 5 mol % of Ph₃P/AuCl/AgSbF₆ in DCM at room temperature according to the general procedure for gold(I)-catalyzed reactions. The reaction was monitored by TLC and it was complete in 1 h. The reaction mixture was concentrated and the crude was purified by column chromatography. Among 4 sets of fractions, only one was pure enough to carry on with the analysis. Based on the analysis of ¹H NMR, gCOSY and HSQC spectra structure 49 (Rf = 0.29, 4.5 mg) was assigned. ¹H NMR (200 MHz, CDCl₃) δ = 7.57 (d, J = 8.3 Hz, 2H, Ts), 7.25 (d, J = 8.3 Hz, 2H, Ts), 5.81 (s, 1H, 7-H), 4.52 (dd, J = 7.0, 3.0 Hz, 1H, 4a), 3.73 – 3.65 (m, 1H, 2-H), 3.50 (ddd, J = 11.9, 10.1, 4.8 Hz, 1H, 2-H), 2.60 (ddt, J = 9.4, 6.1, 3.0 Hz, 1H, 4-H), 2.54 – 2.34 (m, 5H, 1'-H and CH₃-Ts), 2.34 – 2.18 (m, 1H, 3-H), 2.06 – 1.96 (m, 1H, 4-H), 1.97 (s, 3H, CH₃-Ac), 1.76 (ddt, J =
14.1, 9.4, 4.8 Hz, 1H, 3-H), 1.53 (m, 2H, 2'-H), 1.45 – 1.29 (m, 2H, 3'-H), 0.92 (t, J = 7.3 Hz, 3H, 4'-H) ppm.

References


[7] DFT calculations carried out in colaboration with prof. Enrique Gómez - Bengoa (Universidad del País Vasco-Euskal Herriko Unibertsitatea, University of the Basque country)


[11] This species could also be considered as a gold-carbene, although it should be more adequately described as a gold-stabilized carbocation. A. Fürstner, L. Morency, Angew. Chem. Int. Ed. 2008, 47, 5030 – 5033.

[12] This [1,2]H shift process has been postulated to be the rate-limiting step in the tandem [3,3]-rearrangement/Nazarov reaction of simpler enynyl acetates in the gas phase.


[45] Reaction was carried out only once and on a small scale. The product was not purified and therefore the yield was not given. 1H NMR and gCOSY were recorded and confirmed the structure.
Chapter 6: Transformations of Pentannulated Piperidines

In a view of possible applications of pentannulated piperidines as conformationally restricted iminosugar analogues, we decided to explore a few preliminary transformations such as hydrogenation of the double bond, reduction of the carbonyl group and α-hydroxylation of compounds prepared in previous chapter.

![Scheme 1](image)

**Scheme 1.** Transformations of cyclopentenone 1.

### 6.1. Hydrogenation

The hydrogenation of cyclopentenones 1, obtained via gold(I)-catalyzed tandem [3,3]-rearrangement/Nazarov cyclization of piperidine-derived propargyl acetates (see section 5.2), gave corresponding ketones 3 in moderate to high diastereoselectivity (Scheme 2). It was assumed that the delivery of the hydrogen was preferred from the less hindered face of α,β-unsaturated ketone 1 thus providing isomer 3 as the major product. The cis ring fusion was assigned on the basis of coupling constant of 6–8 Hz between bridgehead protons on the ring junction (7a-H and 4-aH). Assigned cis-configuration was further confirmed by crystal structure of alcohol 4a, obtained after the reduction of the ketone 3a.

![Scheme 2](image)

**Scheme 2.** Hydrogenation of cyclopentenones 1a-d. Note: a Diastereomeric ratio determined by 1H NMR of crude reaction mixture. b Reaction carried out under pressure of 4 bar.

The hydrogenation of C-5 alkyl substituted compounds 1a and 1b led to the formation of corresponding diastereomers 3a and 3b in a mixture with epi-3a and epi-3b in diastereomeric ratio 9 : 1 and 10 : 1 respectively. The hydrogenation of substrate bearing a C-5-phenyl ring (1c) or a C-2-side chain (1d) was completely selective. In both cases we could not detect any trace of the corresponding diastereomer in the 1H NMR spectra of crude reaction mixture.
6.2. Carbonyl Reduction

The reduction of the ketones 3a, 3b and 3d using DIBAL-H in THF at -78 °C provided alcohols 4a, 4b and 4d, respectively, with notably high selectivity (Scheme 3).

Scheme 3. Reduction of the carbonyl group in 3.

The diastereoselectivity in the reduction of the mixtures 3a/epi-3a and 3b/epi-3b was very high since we could detect only trace (< 5%) of the isomer in 1H NMR spectrum of crude reaction mixture. The reduction of 3d provided 4d in enantiopure form. A recrystallization of 4a from DCM/hexane = 1 : 1 solution provided material suitable for X-ray crystallography thereby confirming the tentatively assigned structures on Schemes 2 and 3.

6.3. α-Hydroxylation

The initial strategy for installing α-hydroxyl into unsymmetrical ketones 3 was based on the generation of enolate 5 under the kinetic control, which would be oxidized in the next step (Scheme 4). Unfortunately, all attempts to selectively generate and trap enolate 5a at -78 °C in THF using LiHDMS or KHDMs as a base and TMSCl or TIPSCI as a trapping electrophile failed. In addition, the direct oxidation of metal enolate 5b using oxaziridine failed too, and therefore we sought for an alternative procedure.
Hypervalent iodine oxidation, also known as Moriarity two-step approach for the preparation α-hydroxyl derivatives from enolisable carbonyl compounds\(^3\) led to the formation of desired product along with unknown side-products. In the first step, the treatment of \(3a\) with iodosobenzene diacetate (DIB) in methanolic potassium hydroxide led to the formation of hydroxyl dimethylketal \(7a\) in a mixture with unknown side-products. However, the crude α-hydroxydimethylacetal \(7a\) was treated with 10 % H\(_2\)SO\(_4\) in DCM and after chromatography gave α-hydroxyl ketone \(6a\) in 30 % yield (Scheme 5). The assignment of the stereochemistry was based on the evaluation of the vicinal coupling constant of 8.7 Hz between methine protons on the five membered ring.

\[3a \xrightarrow{a} 7a\]  
\[7a \xrightarrow{b} 6a + epi-6a\]

**Scheme 5.** α-Hydroxylation of \(3a\). Reagents and conditions: (a) DIB, KOH, MeOH, 2 h; (b) 10 % H\(_2\)SO\(_4\) in DCM, 1h.

The experimentally observed difficulties to prepare α-hydroxylated products \(6\) were attributed to the acidity of the proton on the ring junction (\(7a\)-H, Scheme 1) that prevents the generation of desired, kinetic enolate in selective manner and therefore we resorted to explore α-hydroxylation of α,β-unsaturated ketone \(1b\). Attempts of oxidation with Pb(OAc)\(_4\) in cyclohexane,\(^4\) Phl(OAc)\(_2\) in KOH/MeOH\(^3\) and enolization with KHMDS were all unsuccessful. Enolization of \(1b\) with LiHMDS in THF at -78 °C followed by trapping of the formed enol with TMSCI led to the formation of triethylsilyl enol ether which was isolated, and the crude material was subsequently treated with \(m\)CPBA at -78 °C in DCM to accomplish α-hydroxylation.\(^5\) The \(^1\)H NMR of crude reaction mixture revealed 70 % conversion and formation of diastereomers. The flash chromatography afforded the mixture of diastereomers in 2:1 ratio and the yield of 61 %. The HPLC purification allowed the isolation of major diastereomer and its complete characterization. The vicinal coupling constant of 3.2 Hz between methine protons on the five membered ring (C-5 and C-6) indicated the \(trans\) relationship between these protons and therefore the structure \(9b\) could tentatively be assigned to the major product. On the other hand, the coupling constant of 6.5 Hz in minor diastereomer \(epi-9b\) is consistent with \(cis\) relationship between methine protons as in \(6b\).

\[1b \xrightarrow{a} 8b\]  
\[8b \xrightarrow{b} 9b + epi-9b\]

**Scheme 6.** α-Hydroxylation of \(1b\). Reagents and conditions: (a) LiHMDS, THF, -78 °C, 30 min followed by the addition of TMSCI, -78 – 0 °C, 1.5 h; (b) \(m\)CPBA, NaHCO\(_3\), DCM, -78 °C, 1h (\(9b : epi-9b = 2 : 1, 61\) %).
6.4. Experimental Part

General information
Solvents and reagents were used either as received from commercial suppliers or, when necessary, purified using standard laboratory techniques according to methods published in “Purification of Laboratory Chemicals” by Perrin, Armarego, and Perrin (Pergamon Press, 1966). All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of dry nitrogen. Chromatographic separations were performed under pressure on silica gel by flash-column techniques; Rf values refer to TLC carried out on 0.25-mm silica gel plates (Merck F254), with the same eluent as indicated for the column chromatography. Melting points were recorded on a Buchi-540 melting point apparatus and are uncorrected. Optical rotation values were recorded on a Jasco DIP-370 polarimeter at indicated temperature in the specified solvents and concentrations. 1H NMR and 13C NMR spectra were recorded at 400 and 100.4 MHz, respectively, in the specified deuterated solvent at room temperature. Solvent reference lines were set at 7.26 and 77.00 (CDCl3) in 1H and 13C NMR spectra, respectively. Mass spectra were carried out by direct inlet of a 20 ppm solution either in CH3OH or CH3OH + 0.1% HCOOH on a LCQ FleetTM Ion Trap LC/MS system (Thermo Fisher Scientific) with an electrospay ionization (ESI) interface in the positive mode. Microanalyses were carried out with a CHN Thermo FlashEA 1112 Series elemental analyzer.

General procedure for hydrogenation.
Cyclopenta-fused piperidine 1 (1 mmol) was dissolved in anhydrous ethanol (10 mL) under a nitrogen atmosphere. Then, 10 % Pd/C catalyst (15 mol %) was added and the reaction flask flushed first with N2 and then with hydrogen and left under a hydrogen atmosphere (balloon) at room temperature for 48 h. The suspension was filtered through a Celite pad and the filtrate concentrated under vacuum. The purification of the crude by flash chromatography afforded desired product.

5-Butyl-1-(toluene-4-sulfonyl)-octahydro-[1]pyrindin-7-one (3a).
Compound 3a was prepared according to the above described procedure for hydrogenation starting from 5-butyl-1-(toluene-4-sulfonyl)-1,2,3,4,5,6-hexahydro-[1]pyrindin-7-one (125 mg, 0.36 mmol). Flash chromatography (n-hexane/EtO, 3:1; Rf = 0.25) afforded product 3a (111 mg, 89 %) in a mixture with diastereomer in 9:1 ratio. 1H NMR (400 MHz, CDCl3) δ = 7.76 (d, J = 10.4 Hz, 2H, Ts), 7.28 (d, J = 10.4 Hz, 2H, Ts), 4.64 (d, J = 6.2 Hz, 1H, 7a-H), 3.73 – 3.57 (m, 1H, 2-H), 2.58 (td, J = 13.1, 2.5 Hz, 1H, 2-H), 2.42 (s, 3H, CH3-Ts), 2.41 – 2.38 (m, 2H, 6-H), 2.39 – 2.21 (m, 2H, 4a-H and 5-H), 1.78 – 1.65 (m, 1H, 4-H), 1.60 – 1.52 (m, 1H, 3-H), 1.44 – 1.21 (m, 7H, 3-H, 1’-H, 2’-H and 3’H), 0.89 (t, J = 6.9 Hz, 3H), 0.93 – 0.89 (m, 1H, 4-H) ppm. 13C NMR (100 MHz, CDCl3) δ = 212.5 (s, C7), 142.9 (s, Ts), 137.7 (s, Ts), 129.3 (d, 2C, Ts), 127.4 (d, 2C, Ts), 65.2 (d, C7a), 42.4 (d, C2), 38.5 (t, C6), 36.5 (d, C5), 34.9 (d, C4a), 30.2 (t, C1’), 29.5 (t, C2’), 23.2 (t, C3), 22.7 (t, C3’), 21.6 (q, CH3-Ts), 20.6 (t, C4), 13.7 (q, C4’) ppm. MS (ESI) m/z (%): 349 ([M+1]+, 100), 372 ([M+1]+, 42). Elemental analysis calcd (%) for C19H27NO2S: C 65.3, H 7.79, N 4.01; found: C 65.13, H 7.53, N 3.86.
5-Methyl-1-(toluene-4-sulfonyl)-octahydro-[1]pyrindin-7-one (3b).

Compound 3b prepared according to the procedure for hydrogenation starting from 5-methyl-1-(toluene-4-sulfonyl)-2,3,4,5,6-hexahydro-[1]pyrindin-7-one (372 mg, 1.22 mmol). The crude was purified by flash chromatography (n-hexane/EtOAc, 4:1; Rf = 0.28) affording product 3b (290 mg, 77%) in a mixture with diasteromer in 10:1 ratio. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.76 (d, $J$ = 8.4 Hz, 2H, Ts), 7.27 (d, $J$ = 8.4 Hz, 2H, Ts), 4.65 (d, $J$ = 6.8 Hz, 1H, 7a-H), 3.66 (d, $J$ = 12.6 Hz, 1H, 2-H), 2.57 (td, $J$ = 12.6, 2.3 Hz, 1H, 2-H), 2.40 (s, 3H, Ts), 2.47 - 2.32 (m, 2H, 6-H), 2.24 - 2.11 (m, 1H, 4a-H), 1.82 - 1.63 (m, 2H, 4-H and 5-H), 1.63 - 1.48 (m, 1H, 3-H), 1.43 - 1.25 (m, 1H, 3-H), 1.03 (d, $J$ = 6.3 Hz, 3H, CH$_3$-5), 0.83 (m, 1H, 4-H) ppm. $^{13}$C NMR (100.4 MHz, CDCl$_3$) $\delta$ = 212.5 (s, C7), 142.6 (s, Ts), 137.7 (s, Ts), 129.3 (d, 2C, Ts), 127.3 (d, 2C, Ts), 65.2 (d, C7a), 42.4 (t, C2), 39.5 (t, C6), 37.7 (d, C5), 29.1 (d, C4a), 22.9 (t, C3), 21.3 (q, CH$_3$-Ts), 20.6 (t, C4), 15.2 (q, CH$_3$) ppm. MS (ESI) m/z (%): 307 ([M+1]$^+$, 32), 330 ([M+Na]$^+$, 33), 636 ([2M+Na]$^+$, 100). Elemental analysis calc (%) for C$_{18}$H$_2$N$_2$O$_3$S: C 62.11, H 7.49, N 4.53; found: C 62.71, H 6.70, N 4.47.

5-Phenyl-1-(toluene-4-sulfonyl)-octahydro-[1]pyrindin-7-one (3c).

Prepared according to the procedure for hydrogenation starting from 5-phenyl-1-(toluene-4-sulfonyl)-2,3,4,5,6-hexahydro-[1]pyrindin-7-one (90 mg, 0.25 mmol). The crude was purified by flash chromatography (n-hexane/EtOAc, 4:1; Rf = 0.28) affording pure product 3c (68 mg, 75%) as a white solid. M.p. = 74.2 - 75.1 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.81 (d, $J$ = 8.2 Hz, 2H, Ts), 7.38 - 7.22 (m, 5H, Ph), 7.18 (d, $J$ = 8.2 Hz, 2H, Ph), 4.90 (d, $J$ = 6.8 Hz, 1H, 7a-H), 3.60 - 3.62 (m, 2H, 2-H), 0.99 (m, $J$ = 8.4 Hz, 2H, 6-H), 1.23 (s, 3H, CH$_3$-5), 0.79 (m, $J$ = 8.4 Hz, 2H, 4-H) ppm. $^{13}$C NMR (100.4 MHz, CDCl$_3$) $\delta$ = 211.6 (s, C7), 143.3 (s, Ts), 137.9 (s, Ts), 137.4 (s, Ph), 129.4 (d, 2C, Ar), 128.5 (d, 2C, Ar), 127.4 (d, 2C, Ar), 127.3 (d, 2C, Ar), 126.9 (d, Ar), 65.3 (d, C7a), 42.4 (t, C2), 39.9 (t, C6), 39.2 (d, C5), 36.1 (d, C4a), 23.1 (t, C3), 21.6 (q, CH$_3$-Ts), 21.4 (t, C4) ppm. MS (ESI) m/z (%): 370 ([M+1]$^+$, 57), 392 ([M+Na]$^+$, 52), 760 ([2M+Na]$^+$, 100). Elemental analysis calc (%) for C$_{22}$H$_{23}$N$_2$O$_3$: C 68.27, H 6.27, N 3.79; found: C 68.15, H 6.33, N 3.77.

2-(tert-Butyl-dimethyl-silanyloxy)methyl)-1-(toluene-4-sulfonyl)-octahydro-[1]pyrindin-7-one (3d).

Prepared according to the procedure for hydrogenation starting from 2-(tert-butyl-dimethyl-silanyloxy)methyl)-1-(toluene-4-sulfonyl)-1,2,3,4,5,6-hexahydro-[1]pyrindin-7-one (370 mg, 0.85 mmol). Reaction was carried out under pressure of 4 bar. After 72 h at conversion of 80% reaction was stopped. The crude was purified by flash chromatography (n-hexane/EtOAc, 3:1; Rf = 0.25) affording pure product 3d (220 mg, 60%) as a white solid. M.p. = 117.7 - 118.5 °C. $[\alpha]_{D}^{22}$ = + 84 (c = 0.86, DCM). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.86 (d, $J$ = 7.2 Hz, 2H, Ts), 7.36 (d, $J$ = 7.2 Hz, 2H, Ts), 4.58 (d, $J$ = 7.9 Hz, 1H, 7a-H), 3.80 (bs, 1H, 2-H), 3.57 - 3.43 (m, 1H, 2-CH$_2$OTS), 3.26 (t, $J$ = 12.0 Hz, 1H, 2-CH$_2$OTS), 2.49 (s, 3H, CH$_3$-Ts), 2.46 - 2.06 (m, 5H, 3-H, 4a-H and 6-H), 1.96 - 1.90 (m, 1H, C-4), 1.84 - 1.79 (m, 1H, 5-H), 1.25 - 1.16 (m, 2H, 4-H and 6-H), 0.87 (s, 9H, TBS), -0.00 (s, 6H, TBS) ppm. $^{13}$C NMR (100.4 MHz, CDCl$_3$) $\delta$ = 214.1 (s, C7), 43.4 (s, Ts), 137.8 (s, Ts), 129.7 (d, 2C, Ts), 127.2 (d,
2C, Ts), 62.1 (d, C7a), 60.5 (t, CH₂OTBS), 52.7 (d, C2), 33.1 (t, C6), 31.2 (t, C5), 25.6 (q, 3C, TBS), 23.8 (d, C4a), 21.7 (t, C3), 21.5 (q, CH₃-Ts), 20.3 (t, C4), 18.1 (s, TBS), -5.22 (q, 2C, TBS) ppm.

MS (ESI) m/z (%): 438 ([M+1]⁺, 100). Elemental analysis calcd (%) for C₂₂H₃₅NO₃SSi; C 60.37; H 8.06; N 3.20; found: C 60.40, H 8.10, N 3.21.

**General procedure for carbonyl reduction.**
A solution of 3 (1 mmol) in DCM (10 mL) was cooled to -78 °C and a 1 M DIBAL-H solution in hexane (1 mL, 1 mmol) was slowly added at -78 °C under nitrogen atmosphere. After 1 h, the excess of the reagent was quenched by addition of MeOH (1 mL) and saturated aqueous solution of Rochelle salt (10 mL). The reaction mixture was warmed to room temperature and poured into DCM (10 mL). The formed 2-phase system was stirred for 30 min and then the layers were separated and the product was extracted with EtOAc (2 x 10 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ for 30 min, filtered and concentrated. The crude was purified by flash chromatography to give the product.

![5-Butyl-1-(toluene-4-sulfonyl)-octahydro-[1]pyrindin-7-ol (4a).](image)

Prepared according to the procedure for hydrogenation starting from 3a (65 mg, 0.19 mmol). The crude was purified by flash chromatography (n-hexane/EtOAc, 4 : 1; Rf = 0.35) affording pure product 4a (52 mg, 78 %) as a white solid. The product was recrystallized from DCM : hexane; 1 : 1. M.p. = 90.0 – 91.2 °C. ¹H NMR (400 MHz, CDCl₃) δ = 7.73 (d, J = 8.2 Hz, 2H, Ts), 7.30 (d, J = 8.2 Hz, 2H, Ts), 4.32 (dt, J = 6.8, 3.5 Hz, 1H, 7-H), 3.80 (t, J = 6.8 Hz, 1H, 7a-H), 3.75 – 3.67 (m, 1H, 2-H), 3.30 (td, J = 12.4, 3.0 Hz, 1H, 2-H), 2.42 (s, 3H, CH₃-Ts), 2.24 (dt, J = 14.2, 8.0 Hz, 1H, 6-H), 1.96 (s, 1H, OH), 1.82 – 1.58 (m, 3H, 4a-H, 5-H and 3-H), 1.58 – 1.41 (m, 1H, 4-H), 1.39 – 1.06 (m, 9H, 1'-H, 2'-H, 3'-H, 6-H and 4-H), 0.86 (t, J = 7.0 Hz, 3H, 4'-'H) ppm. ¹³C NMR (100.4 MHz, CDCl₃) δ = 143.3 (s, Ts), 137.1 (s, Ts), 129.7 (d, 2C, Ts), 127.1 (s, 2C, Ts), 73.3 (d, C7), 59.1 (d, C7a), 44.4 (t, C2), 39.3 (d, C4a), 38.4 (d, C5), 38.1 (t, C6), 30.4 (t, C1'), 30.0 (t, C2'), 23.5 (t, C3), 23.0 (t, C3'), 21.5 (q, CH₃-Ts), 20.1 (t, C4), 13.9 (q, C4') ppm. MS (ESI) m/z (%): 310 ([M+1]⁺, 42), 333 ([M+Na]⁺, 8), 641 ([2M+Na]⁺, 100). Elemental analysis calcd (%) for C₁₅H₂₀NO₃S: C 64.92, H 8.32, N 3.98; found: C 64.83, H 8.52, N 3.68.

![5-Methyl-1-(toluene-4-sulfonyl)-octahydro-[1]pyrindin-7-one (4b).](image)

Prepared according to the procedure for the ketone reduction starting from 5-methyl-1-(toluene-4-sulfonyl)-octahydro-[1]pyrindin-7-one (75 mg, 0.24 mmol). The crude was purified by flash chromatography (n-hexane/EtOAc, 5 : 1; Rf = 0.23) affording product 4b (73 mg, 97 %). ¹H NMR (400 MHz, CDCl₃) δ = 7.74 (d, J = 8.2 Hz, 2H, Ts), 7.31 (d, J = 8.2 Hz, 2H, Ts), 4.39 – 4.31 (m, 1H, 7-H), 3.83 (t, J = 6.8 Hz, 1H, 7a-H), 3.73 (dt, J = 14.4, 3.2 Hz, 1H, 2-H), 3.30 (td, J = 12.5, 3.2 Hz, 1H, 2-H), 2.43 (s, 3H, CH₃-Ts), 2.30 – 2.18 (m, 1H, 6-H), 1.91 (d, J = 3.1 Hz, OH), 1.85 (m, 1H, 5-H), 1.75 – 1.62 (m, 2H, 4a-H and 3-H), 1.55 – 1.47 (m, 1H, 4-H), 1.39 – 1.26 (m, 1H, 6-H), 1.26 – 1.11 (m, 2H, 3-H and 4-H), 0.95 (d, J = 6.8 Hz, 3H, CH₃-5) ppm. ¹³C NMR (100.4 MHz, CDCl₃) δ = 143.2 (s, Ts), 137.1 (s, Ts), 129.7 (d, 2C, Ts), 126.9 (d, 2C, Ts), 73.8 (d, C7), 59.4 (d, C7a), 44.6 (t, C2), 40.8 (d, C-4a), 39.7 (t, C6), 32.8 (d, C5), 23.5 (t, C3), 21.5 (q, CH₃-Ts), 20.1 (t, C4), 14.7 (q, CH₃-5) ppm. MS (ESI) m/z (%): 310 ([M+1]⁺, 42), 331 ([M+Na]⁺, 7), 641 ([2M+Na]⁺, 100). Elemental analysis calcd (%) for
2-((tert-Butyl-dimethyl-silanyloxy)methyl)-1-((toluene-4-sulfonyl)-octahydro-1H-pyrindin-7-ol (4d).

A solution of 3d (150 mg, 0.34 mmol) in DCM (4.25 mL) was cooled to -78 °C and a 1.2 M DIBAL-H solution in toluene (0.6 mL, 0.68 mmol) was slowly added at -78 °C under nitrogen atmosphere. After 2 h, the excess of the reagent was quenched by addition of MeOH (2 mL) and saturated aqueous solution of Rochelle salt (10 mL) at -78 °C. Reaction mixture was warmed to room temperature and poured into DCM (10 mL). The formed 2-phase system was stirred for 30 min and then the layers were separated and the product was extracted with DCM (2 x 5 mL). The combined organic extracts were dried over anhydrous Na2SO4 for 30 min, filtered and concentrated. The oily residue was purified by flash chromatography (heptanes/EtOAc, 4:1; Rf = 0.30) to give the product 4d (110 mg, 77 %) as a colourless oil. [α]D252 = -3.3 (c = 0.9, DCM). 1H NMR (400 MHz, CDCl3) δ 7.71 (d, J = 8.0 Hz, 2H, Ts), 7.29 (d, J = 8.0 Hz, 2H, Ts), 4.17 – 4.11 (m, 1H, 7a-H), 3.02 (dd, J = 9.9, 7.1 Hz, 1H, 2-CH2OTBS), 3.84 – 3.78 (m, 2H, 7αa-H and 2-H), 3.70 (dd, J = 9.9, 4.4 Hz, 1H, 2-CH2OTBS), 3.45 (bs, 1H, OH), 2.42 (s, 3H, Ts), 2.01 – 1.89 (m, 1H, 3-H), 1.89 – 1.80 (m, 1H, 5-H), 1.75 – 1.64 (m, 3H, 5-H, 6-H and 4a-H), 1.64 – 1.51 (m, 1H, 6-H), 1.42 – 1.30 (m, 1H, 4-H), 1.30 – 1.08 (m, 2H, 3-H and 4-H), 0.93 (s, 9H, TBS), 0.12 (s, 6H, TBS ppm. 13C NMR (100.4 MHz, CDCl3) δ = 143.3 (s, Ts), 136.8 (s, Ts), 129.7 (d, 2C, Ts), 127.1 (d, 2C, Ts), 73.5 (d, C7), 65.2 (t, CH2OTBS-2), 59.5 (d, C7a), 54.3 (d, C2), 33.8 (d, C4a), 30.9 (t, C6), 29.1 (s, C-TBS), 25.8 (q, 3C, CH3-TBS), 23.2 (t, C4), 22.2 (t, C2), 21.4 (q, CH3-Ts), 18.17 (t, C5), -5.40 (q, 2C, CH3-TBS) ppm. Elemental analysis calc (%) for C22H37NO4SSi: C 60.10; H 8.48; N 3.19; found: C 60.03, H 8.50, N 3.16.

6-Hydroxy-5-methyl-1-((toluene-4-sulfonyl)-1,2,3,4,5,6-hexahydro-1H-pyrindin-7-one (9b).

A solution of 5-methyl-1-((toluene-4-sulfonyl)-1,2,3,4,5,6-hexahydro-1H-pyrindin-7-one (130 mg, 0.42 mmol) in dry THF (4.2 mL) was cooled to -78 °C and a 1 M solution of LiHMDS in THF (0.462 mL, 0.462 mmol) was added dropwise. The resulting mixture was stirred for 30 min at -78 °C and then TMSCI (57 µL, 0.462 mmol) was slowly added and the stirring continued below -70 °C for another 30 min. The mixture was allowed to warm to 0 °C and then quenched with water (5 mL). The product was extracted with EtOAc (4 x 5 mL); the combined organic extracts were dried over anhydrous Na2SO4 for 30 min. After filtration and evaporation of the solvent, obtained yellow oil was dissolved in DCM (8 mL) and NaHCO3 (84 mg, 1.05 mmol) was added. The resulting suspension was cooled to -78 °C and then mCPBA (72.5 mg, 0.42 mmol) was added. After 1 h at -78 °C, saturated Na2S2O3 (4 mL) and NaHCO3 (4 mL) were added, cooling bath was removed and the formed 2-phase system was vigorously stirred for 1 h. Layers were separated and the product was extracted with DCM (2 x 10 mL). The combined organic extracts were dried over anhydrous Na2SO4 for 30 min, filtered and concentrated. The oily residue was purified by flash chromatography (n-hexane/EtOAc, 3 : 2; Rf = 0.14) to give α-hydroxylated product as a 2 : 1 mixture of diastereomers (82 mg, 61 %). Analytically pure major diastereomer 9b was obtained by HPLC purification (35 % ACN, 65 % H2O, Rf = 16.5 min). 1H NMR (400 MHz, CDCl3) δ = 7.97 (d, J = 8.2 Hz, 2H, Ts), 7.32 (d, J = 8.2 Hz, 2H, Ts), 3.97 (d, J = 3.2 Hz, 1H, 6-H), 3.92 (dt, J = 13.5, 3.5 Hz, 1H, 2-H), 2.98 – 2.88 (m, 1H, 2-H), 2.83 (bs, 1H, OH), 2.65 – 2.56 (m, 1H, 5-H), 2.54 – 2.45 (m, 1H, 4-H), 2.43 (s, 3H, CH3-Ts), 2.28 – 2.14 (m, 1H, 4-H), 1.97 (m, 2H, 3-H), 1.34 (d, J = 7.2 Hz, 1H, CH3) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 200.1 (s, C7), 158.3 (s, C7a), 143.9 (s, Ts), 137.2 (s, C4a), 134.0 (s, Ts), 129.4 (d, 2C, Ts), 127.8 (d, 2C, Ts), 78.8 (d, C6), 45.5 (t,
C2), 42.6 (d, C5), 23.1 (t, CH3-Ts), 21.5 (t, C3), 16.26 (q, CH3-5). MS (ESI) m/z (%): 322 ([M+1]+, 34), 344 ([M+Na]+, 92), 665 ([2M+Na]+, 100). Elemental analysis calcd (%) for C16H19NO4S: C 59.79, H 5.96, N 4.36; found: C 59.82, H 5.99, N 4.32.

References
Chapter 7: Synthesis of Cyclopenta[b]indoles

The work described in this chapter was published as “Construction of Cyclopenta[b]indol-1-ones by a Tandem Gold(I)-Catalyzed Rearrangement/Nazarov Reaction and Application to the Synthesis of Bruceolline H” in Org. Lett. 2016, 18, 3922 – 3925.

Cyclopenta[b]indoles are commonly found in many natural and biologically active compounds and therefore there has been much interest in the development of new methods for the pentannulation of indoles. During the last decade, gold(I) catalysis has emerged as a powerful tool for the pentannulation of indoles. As shown in introduction, cyclization reactions triggered by electrophilic activation of an unsaturated side chain of the heterocycle, sequential gold(I)-catalyzed hydroamination/cyclization reactions, and cascade gold(I)-catalyzed rearrangement/cyclization processes, have all successfully been employed for the pentannulation of indoles (Chapter 3).

Scheme 1. Au(I)-catalyzed [3,3]-rearrangement/Nazarov cyclization of indole-derived enynyl acetates 1 and 4.

The fact that indole bearing a propargylic ester moiety at position 2 (1, Chapter 5) in the presence of a gold(I) catalyst undergoes [3,3]-sigmatropic rearrangement thus generating pentadienyl cation 2 which after the cyclization gives cyclopentannulated indoles 3, prompted us to investigate if indole bearing the propargylic moiety at position 3 under the gold(I) catalysis could provide cyclopenta-fused indoles 6 (Scheme 1) with a substitution pattern on the five-membered ring which would allow an easy entry to the bruceollines and other natural products possessing the cyclopenta[b]indol-1-one nucleus.

7.1. Optimization of Reaction Conditions

The synthesis of the model compound 4a (Scheme 2) was carried out by iodination of the indole at position C3 followed by N-protection. This time CO₂Me was chosen as nitrogen protecting group because it did not cause trouble in gold(I)-catalyzed [3,3]-rearrangement/Nazarov cyclization of 1 and it is easier to remove than the tosyl group. Sonogashira coupling of N-CO₂Me 3-iodoindole (13a) with (-)-3-butyln-2-ol gave alcohol 14a whose O-acetylation provided compound 4a in 86 % after chromatography.
Interestingly, while monitoring the reaction, we could not observe any NMR signal associated to hours when ligand \(\text{[(4-}
\text{room temperature.}

In an attempt to optimize the reaction conditions, chromatography indicated that cyclization of \(C\) side chain at position \(C2\). The reaction mixture was left to stir and the progress of the reaction was monitored by TLC. After 6 h, the starting material was consumed and the analysis of \(^1\text{H NMR spectra}\) of the crude reaction mixture revealed cyclopenta-fused indole \(6a\) in the mixture with \(\alpha,\beta\)-unsaturated ketone \(7a\) (3 : 1 \(E/Z\) mixture). The clean reaction profile and isolation of \(6a\) in 79 % yield after chromatography indicated that \(4a\) shows different reactivity in comparison with already described cyclization of C-3 substituted piperidine analogue (Chapter 5.2.).

Initially, model substrate \(4a\) was treated with 3 mol % of \(\text{Ph}_3\text{PAuCl/AgSbF}_6\) in DCM at room temperature, the optimized reaction conditions for the cyclization of \(N\)-heterocycles bearing propargyl side chain at position \(C2\). The reaction mixture was left to stir and the progress of the reaction was monitored by TLC. After 6 h, the starting material was consumed and the analysis of \(^1\text{H NMR spectra}\) of the crude reaction mixture revealed cyclopenta-fused indole \(6a\) in the mixture with \(\alpha,\beta\)-unsaturated ketone \(7a\) (3 : 1 \(E/Z\) mixture). The clean reaction profile and isolation of \(6a\) in 79 % yield after chromatography indicated that \(4a\) shows different reactivity in comparison with already described cyclization of C-3 substituted piperidine analogue (Chapter 5.2.).

In an attempt to optimize the reaction conditions, the reaction was carried out by varying gold ligand, counterion and the solvent (Table 1). The experiments were carried out with 3 mol % of \(\text{LauCl/AgX}\) at room temperature. Monitoring the reaction by \(^1\text{H NMR}\) revealed that the reaction was complete in two hours when ligand \([4-(\text{CF}_3\text{C}_3\text{H}_4)\text{P}]\) was used, providing cyclopenta[b]indole \(6a\) in 83 % yield (entry 2). Interestingly, while monitoring the reaction, we could not observe any NMR signal associated to acetate intermediate, which according to the mechanism, is formed after the cyclization process, due to its immediate transformation into final compound \(6a\).

### Table 1. 

**Au(I)-catalyzed [3,3]-rearrangement/Nazarov cyclization of \(4a\).**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand, (L)</th>
<th>Anion, (X)</th>
<th>Time (h)</th>
<th>Yield(^*)</th>
<th>(6a)</th>
<th>(7a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{Ph}_3\text{P})</td>
<td>(\text{SbF}_6)</td>
<td>6</td>
<td>94 (79)(^c)</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>((4-\text{CF}_3\text{C}_3\text{H}_4)\text{P})</td>
<td>(\text{SbF}_6)</td>
<td>2</td>
<td>98 (83)(^c)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>(\text{cHexP})</td>
<td>(\text{SbF}_6)</td>
<td>22</td>
<td>77</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>(\text{t-BuP})</td>
<td>(\text{TF}_5\text{N}^+)</td>
<td>24</td>
<td>37</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>(\text{cHexJohnPhos})</td>
<td>(\text{SbF}_6)</td>
<td>24</td>
<td>31 traces</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>((2,4-\text{di-t-BuC}_3\text{H}_4\text{O})\text{P})</td>
<td>(\text{SbF}_6)</td>
<td>1.5</td>
<td>79 (73)(^c)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>((4-\text{CF}_3\text{C}_3\text{H}_4)\text{P})</td>
<td>(\text{TF}_5\text{N}^+)</td>
<td>4</td>
<td>99</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>((4-\text{CF}_3\text{C}_3\text{H}_4)\text{P})</td>
<td>(\text{TI}^+)</td>
<td>2</td>
<td>96</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>((4-\text{CF}_3\text{C}_3\text{H}_4)\text{P})</td>
<td>&quot;\text{BARF}&quot;</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>-</td>
<td>(\text{SbF}_6)</td>
<td>2</td>
<td>6</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

\(^*\)Reactions carried out on 0.2 mmol. \(^\dagger\) Conversion measured by \(^1\text{H NMR}\). \(^\circ\) Yield after chromatography. 

\(\text{NaBARF}\) was used.
When more electron-rich ligands were used (Cy₃P, t-Bu₃P, and CyJohnPhos), the reaction was very slow, with only partial conversions even after 24 h and the formation of higher (up to 23 %) relative amounts of α,β-unsaturated compound 7a (entries 3-5). Given the marked effect of electron-poor phosphine, a phosphite ligand was used (entry 6) but, although the reaction was slightly faster, a lower yield than with [(4-CF₃C₆H₄)₃P] was obtained because of the formation of unidentified side products. Less important was the role of the counterion: using ligand [(4-CF₃C₆H₄)₃P], the reaction rates were approximately the same with SbF₆⁻ (entry 2) and TfO⁻ (entry 8) and slightly lower with Tf₂N⁻ (entry 7). With 3 mol % of AgSbF₆ alone, the reaction did occur but the conversion was only 6 % after 2 h, thus showing that the Au(I) complex is the real catalyst for this process (entry 10).

Figure 1. Effect of phosphine ligands on the reaction rate.

7.2. Scope of the Reaction

The scope of the reaction was investigated with a series of differently substituted enynyl acetates 4 and (4-CF₃C₆H₄)₃PAuCl precatalyst. To this end, N-protected 3-iodoindoles 13a-j, bearing various electron-withdrawing and electron-donating groups, were coupled to alkyn-3-ols under Sonogashira conditions to provide, after O-acetylation of alcohols 14a-o, requisite substrates 4a-o (Scheme 3) in good to excellent overall yields (51 – 91 %, unstable when neat).

Figure 2. X-Ray structure of 6h.
Scheme 3.  Synthesis of substrates 4 from commercially available indoles. Reagents and conditions: (a) 1. I₂, KOH, DMF, 0 – 25 °C, 1 h, 2. CH₃COCl, Et₃N, THF, 0 – 25 °C, 3 h; (b) (±)-3-butyne-2-ol, 3 mol % CuI, 5 mol % (Ph₃P)₂PdCl₂, DMF-Et₃N, 1 : 5, 40 °C, 3 h; (c) Ac₂O, Et₃N, DMAP, DCM, 0 – 25 °C, 3 h. Yield given over 2 steps, from 2 to 4.

The prepared substrates (4b-4o) were subjected to the 3 mol % of (4-CF₃C₆H₄)₃PAu/AgSbF₆ in DCM at 25 °C and monitored by TLC. Analysis of the results revealed that the outcome of the tandem reaction varied with the electronic properties of the substituent on the indole ring (Scheme 4), with EWGs (in 4l-o) lowering both the reaction rate and conversion into the Nazarov product. In the cases of 4m and 4o, bearing an EWG at position 5, a particularly high amount of the corresponding α,β-unsaturated compound 7 was also obtained (37 % and 50 %, respectively). With ED groups, the isolated yields of cyclopenta[b]indolones 6 were good to excellent and reaction rates very high, especially with methoxy-substituted substrates 4f-k where conversion was complete in less than 1 h.
To further confirm the effect of the indole substituent on the outcome of the reaction and to exclude influence of factors we are not able to control, a competition experiment was carried out on a 1:1 mixture of 6-MeO- and 6-CO₂Me-substituted substrates 4i and 4n, respectively, in the presence of 3 mol % of the catalyst. Monitoring the reaction by ¹H NMR revealed the almost immediate conversion (less than 15 min) of the substrate with the ED group on the ring into 6i, whereas substrate 4n was completely converted into 6n in 4 h.


7.3. Reaction Mechanism and DFT Calculations

The formation of α,β-unsaturated ketone 7a and its relative increase when the reaction becomes very slow on changing the phosphine ligand or by effect of an EWG on the indole ring, suggest that the Nazarov cyclization is the rate determining step of the whole process. When the cyclization of intermediate 5a to form oxyallyl cation 8a is very slow (Scheme 5), dissociation of LAu⁺ from 5a could become a competing pathway providing 7a via hydrolysis and protodeauration or through putative acetoxy allene intermediate 9a. However, the formation of 6a through classical Lewis-acid assisted Nazarov cyclization of 7a could be ruled out because 7a when treated with 3 mol % of the gold(I) in DCM did not undergo cyclization.
In order to identify the structures and the energies of the critical steps of the mechanism, especially the formation of 7a, and to understand the very strong ligand influence on the reaction rate, the potential reaction coordinates of the whole tandem [3,3]-rearrangement/Nazarov cyclization were studied computationally. The structures were located using the B3LYP density functional theory method as implemented in the Gaussian suite of programs. The alkynyl-gold(I) cationic complex 1a was considered as the starting point of the mechanism (G = 0 kcal/mol), and all reported energies in the following discussion are relative to it. The energy values correspond to Gibbs free energies (ΔG), computed at B3LYP/6-31G** level (LANL2DZ for gold atom) and include single-point refinements at M06/6-311+G(d,p) (SDD for Au) level of theory.

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Scheme 5. Postulated reaction pathways.

Scheme 6. Computed reaction profile for the reaction of 4a. Energies are in kcal/mol.
From the computed reaction profile (Scheme 6) it could be seen that the acetate rearrangement proceeds with a low activation barrier ($\Delta G_{\text{act}} = 8.6 \text{ kcal/mol}$) and in a slightly exergonic fashion ($\Delta G_{\text{react}} = -2.6 \text{ kcal/mol}$) to form intermediate III (i.e. 5a). The next cyclization step, from III to IV (i.e. 8a) has the highest activation barrier ($\Delta G_{\text{act}} = 14.8 \text{ kcal/mol}$) and therefore it is a rate-determining step which is in accordance with experimental observations. Final step, deprotonation and protodeauration of IV is highly exergonic (-19.6 kcal/mol) ensuring the irreversibility of the overall process.

On these grounds, the effect of the indole substituents and gold ligands on the reaction rate can be easily explained. The electrophilic attack by the cationic side chain is favoured by electron-donating substituents which make the indole ring in intermediate III more electron-rich, and disfavoured by EWGs. On the other hand, the accelerating effect by electron-poor gold ligands could be justified by a more electrophilic, and thus more reactive, allylic side chain.12

According to the calculations, $\alpha,\beta$-unsaturated ketone 7a should directly derive from 5a ($\Delta G_{\text{react}} = +8.1 \text{ kcal/mol}$) because alternative pathway which includes the formation of allene 9a from 5a is energetically very demanding ($\Delta G_{\text{react}} = +31.7 \text{ kcal/mol}$) and thus never operative (Scheme 7).

![Scheme 7. Computed possible pathways for the formation of $\alpha,\beta$-unsaturated ketone 7a.](image)

**Scheme 7.** Computed possible pathways for the formation of $\alpha,\beta$-unsaturated ketone 7a.

### 7.4. Synthesis of Bruceolline H

To demonstrate the synthetic usefulness of the methodology, we exploited the high reactivity of methoxy-substituted indole derivatives to synthesize bruceolline H. While the synthesis of unsubstituted bruceollines has been described,4a bruceolline H has been isolated quite recently and its synthesis never reported.2a

![Scheme 8. The structures of bruceolline family of natural products.](image)

**Scheme 8.** The structures of bruceolline family of natural products.
Scheme 9. Synthesis of Bruceolline H (12). Reagents and conditions: (a) SeO₂, dioxane, reflux (82 %); (b) 1. t-BuNH₂, MeOH reflux, 2. BBr₃, DCM (93 %).

To this end, cyclopenta[b]indolone 6j was first oxidized into the corresponding diketo derivative 11 (82 %) by using SeO₂ in refluxing dioxane. Sequential N-deprotection¹³ and O-demethylation¹⁴ completed the synthesis of this natural product, which was obtained in 69 % overall yield from the corresponding 3-iodindole (Scheme 9). ¹H and ¹³C NMR spectra of 12 were identical to those reported for the natural product.²a

Figure 3. X-Ray structure of Bruceolline H (12).

7.5. Experimental Part

General Information
Solvents and reagents were used either as received from commercial suppliers or, when necessary, purified using standard laboratory techniques according to methods published in “Purification of Laboratory Chemicals” by Perrin, Armarego, and Perrin (Pergamon Press, 1966). All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of dry nitrogen. Chromatographic separations were performed under pressure on silica gel by flash-column techniques; Rᵢ values refer to TLC carried out on 0.25-mm silica gel plates (Merck F₂₅₄), with the same eluent as indicated for the column chromatography. Melting points were recorded on a Buchi-540 melting point apparatus and are uncorrected. ¹H NMR and ¹³C NMR spectra were recorded at 400 and 100.4 MHz, respectively, in the specified deuterated solvent at room temperature. Solvent reference lines were set at 7.26 and 77.00 (CDCl₃), 2.05 and 29.84 (acetone-d₆), 3.31 and 49.00 (CD₃OD), 2.50 and 39.52 ppm (DMSO-d₆) in ¹H and ¹³C NMR spectra, respectively. Mass spectra were carried out by direct inlet of a 20 ppm solution either in CH₃OH or CH₃OH + 0.1% HCO₂H on a LCQ Fleet™ Ion Trap LC/MS system (Thermo Fisher Scientific) with an electrospray ionization (ESI) interface in the positive mode. Microanalyses were carried out with a CHN Thermo FlashEA 1112 Series elemental analyzer.
General procedure for the preparation of methyl 3-iodoindole-1-carboxylates (13).\(^5\)

Crushed KOH (1.4 g, 25 mmol) was added to a solution of the indole (10 mmol) in anhydrous DMF (18 mL) and the resulting suspension was stirred at room temperature for 20 min. A solution of \(I_2\) (2.54 g, 10 mmol) in anhydrous DMF (3 mL) was then dropwise added and, after 1 h, the reaction mixture was poured into ice water (230 mL) containing NH\(\text{H}_2\)OH (0.5 %) and K\(\text{S}_2\)O\(\text{S}\) (0.1 %). A precipitate immediately formed was collected by filtration, washed with chilled water (30 mL) and dried under reduced pressure. The obtained 3-iodo-1\(H\)-indole was immediately used in next step.

In few cases, as no filterable precipitate formed, the product was extracted with a 1 : 1 mixture of \(n\)-hexane and EtOAc (3 x 100 mL) and the combined organic extracts were washed once with chilled water (150 mL) and dried over anhydrous Na\(\text{SO}_4\). After filtration and evaporation of the solvent, the obtained 3-iodoindole was used in the next step without any further purification.

3-Iodo-1\(H\)-indole (10 mmol) was dissolved in anhydrous DCM or THF (60 mL) and, after cooling at 0°C (ice bath), Et\(\text{S}N\) (4.2 mL, 30 mmol) and methyl chloroformate (1.5 mL, 20 mmol) were added. After 10 minutes, the ice bath was removed and the reaction mixture was stirred at room temperature until complete consumption of the starting material (TLC; usually 2-3 h). Water was then added (60 mL) and the product extracted with DCM (3 x 60 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL) and dried over anhydrous Na\(\text{SO}_4\). After filtration and evaporation of the solvent, the product was isolated either by flash chromatography or by crystallization from acetone.

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\text{Methyl 3-iodo-5-methylindole-1-carboxylate (13d).}
\]

3-Iodo-5-methyl-1\(H\)-indole was prepared starting from 5-methyl-1\(H\)-indole (262 mg, 2 mmol) and isolated by filtration.\(^2\) \(^1\)H NMR (400 MHz, CDCl\(\text{3}\)) \(\delta = 8.24\) (bs, 1 H), 7.27-7.24 (m, 3 H), 7.07 (d, \(J = 8.0\) Hz, 1 H), 2.49 (s, 3 H) ppm. The protection step was carried out in THF. Crystallization from acetone afforded pure 13d (428 mg, 68 %) as a white solid. M.p. = 117.4 – 118.9 °C. \(^1\)H NMR (400 MHz, DMSO-d6) \(\delta = 7.98\) (d, \(J = 8.5\) Hz, 1 H), 7.89 (s, 1 H), 7.26 (d, \(J = 8.5\) Hz, 1 H), 7.18 (s, 1 H), 3.99 (s, 3 H), 2.45 (s, 3 H) ppm. \(^{13}\)C NMR (100.4 MHz, DMSO-d6) \(\delta = 150.5\) (s), 133.4 (s), 133.0 (s), 132.2 (s), 130.3 (d), 127.3 (d), 121.5 (d), 114.8 (d), 67.3 (s), 54.6 (q), 21.6 (q) ppm. MS (ESI) \(m/z\) (%): 338 ([M+Na]\(^+\), 100). Elemental analysis calcd (%) for C\(_{11}\)H\(_{10}\)INO\(_2\): C 41.93, H 3.20, N 4.45; found: C 42.04, H 3.14, N 4.45.

\[
\text{Methyl 3-iodo-6-methylindole-1-carboxylate (13e).}
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3-Iodo-6-methyl-1\(H\)-indole was prepared starting from 6-methyl-1\(H\)-indole (250 mg, 1.9 mmol) and isolated by filtration. \(^1\)H-NMR (400 MHz, CDCl\(\text{3}\)) \(\delta = 8.18\) (bs, 1 H), 7.33 (d, \(J = 8.0\) Hz, 1 H), 7.20 (d, \(J = 2.0\) Hz, 1 H), 7.16 (s, 1 H), 7.04 (d, \(J = 8.4\) Hz, 1 H), 2.48 (s, 3 H) ppm. The protection step was carried out in THF. Purification by flash chromatography (\(n\)-hexane/EtOAc, 10 : 1; \(R_t = 0.38\)) afforded pure 13e (421 mg, 70 %) as a pink solid. M.p. = 92.5 – 94.1 °C. \(^1\)H NMR (400 MHz, CDCl\(\text{3}\)) \(\delta = 7.97\) (s, 1 H), 7.67 (s, 1 H), 7.27 (d, \(J = 7.7\) Hz, 1 H), 7.15 (d, \(J = 7.7\) Hz, 1 H), 4.03 (s, 3 H), 2.51 (s, 3 H) ppm. \(^{13}\)C NMR (100.4 MHz, CDCl\(\text{3}\)) \(\delta = 150.3\) (s), 136.2 (s), 135.0 (s), 130.0 (s), 128.4 (d), 125.3 (d), 121.5 (d), 114.7 (d), 66.5 (s), 54.0 (q), 21.9 (q) ppm. MS (ESI) \(m/z\) (%): 338
Methyl 3-ido-4-methoxyindole-1-carboxylate (13f).

3-ido-4-methoxy-1H-indole was prepared starting from 4-methoxy-1H-indole (174 mg, 1.2 mmol) and isolated by extraction. \(^3\) \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta = 8.34\) (bs, 1 H, N-H), 7.18 (s, 1 H, 2-H), 7.13 (t, J = 8.0 Hz, 1 H), 7.01 (d, J = 8.4 Hz, 1 H), 6.53 (d, J = 7.6 Hz, 1 H), 3.95 (s, 3 H) ppm.

The protection step was carried out in DCM. Purification by flash chromatography (n-hexane/EtOAc, 8 : 1; \(R_f = 0.39\)) afforded pure 13f (288 mg, 74 %) as a pale pink solid. M.p. = 103.9 – 104.8 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.83\) (d, J = 8.6 Hz, 1 H), 7.65 (s, 1H, 2-H), 7.29 (d, J = 8.0 Hz, 1 H), 6.71 (d, J = 8.0 Hz, 1 H), 4.03 (s, 3 H), 3.94 (s, 3 H) ppm. \(^13\)C NMR (100.4 MHz, CDCl\(_3\)) \(\delta = 153.3\) (s), 150.4 (s), 136.4 (s), 129.6 (d), 126.3 (d), 119.5 (s), 107.9 (d), 104.4 (d), 58.7 (s), 55.4 (q), 54.0 (q) ppm. MS (ESI) \(m/z\) (%): 332 ([M+1]\(^+\), 100), 205 ([M+1-1]\(^+\), 100). Elemental analysis calcd (%) for \(C_{11}H_{12}NO_2\): C 39.90, H 3.04, N 4.22.

Methyl 3-ido-5-methoxyindole-1-carboxylate (13h).

3-ido-5-methoxy-1H-indole was prepared starting from 5-methoxy-1H-indole (200 mg, 1.36 mmol) and isolated by filtration. \(^17\) \(^1\)H NMR (200 MHz, CDCl\(_3\)) \(\delta = 8.26\) (bs, 1 H), 7.29-7.24 (m, 3 H), 6.88 (s, 1 H), 3.90 (s, 3 H) ppm.

The protection step was carried out in DCM. Purification by flash chromatography (n-hexane/EtOAc, 15 : 1; \(R_f = 0.35\)) afforded pure 13h (278 mg, 62 %) as a purple solid. M.p. = 98.8 – 101.0 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 8.02\) (d, J = 8.6 Hz, 1 H), 7.72 (s, 1 H), 6.98 (dd, J = 8.6, 2.5 Hz, 1 H), 6.84 (d, J = 2.5 Hz, 1 H), 4.03 (s, 3 H), 3.89 (s, 3 H) ppm. \(^13\)C NMR (100.4 MHz, CDCl\(_3\)) \(\delta = 156.8\) (s), 150.4 (s), 132.9 (s), 130.1 (d), 129.2 (s), 115.9 (d), 114.7 (d), 103.8 (d), 66.2 (s), 55.7 (q), 54.0 (q) ppm. MS (ESI) \(m/z\) (%): 569 ([2M+Na]\(^+\), 100), 274 ([M+1]\(^+\), 74). Elemental analysis calcd (%) for \(C_{11}H_{12}NO_2\): C 39.90, H 3.04, N 4.22.

Methyl 3-ido-6-methoxyindole-1-carboxylate (13i).

3-ido-6-methoxy-1H-indole was prepared starting from 6-methoxy-1H-indole (263 mg, 1.79 mmol) and isolated by filtration. \(^18\) \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 8.19\) (bs, 1 H), 7.32 (d, J = 9.2 Hz, 1 H), 7.17 (d, J = 2.4 Hz, 1 H), 6.87 (d, J = 7.2 Hz, 1 H), 3.85 (s, 3 H) ppm.

The protection step was carried out in DCM. Purification by flash chromatography (n-hexane/EtOAc, 6 : 1; \(R_f = 0.45\)) afforded pure 13i (399 mg, 67 %) as a pale pink solid. M.p. = 66.2 – 67.5 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.71\) (bs, 1 H), 7.59 (s, 1 H), 7.25 (d, J = 8.8 Hz, 1 H), 6.94 (dd, J = 8.8, 2.4 Hz, 1 H), 4.01 (s, 3 H), 3.88 (s, 3 H) ppm. \(^13\)C NMR (100.4 MHz, CDCl\(_3\)) \(\delta = 158.7\) (s), 150.4 (s), 135.6 (s), 128.1 (d), 125.7 (s), 122.0 (d), 112.8 (d), 98.8 (d), 66.2 (s), 55.7 (q), 53.9 (q) ppm. MS (ESI) \(m/z\) (%): 332 ([M+1]\(^+\), 15), 205 ([M+1-1]\(^+\), 100). Elemental analysis calcd (%) for \(C_{11}H_{10}NO_3\): C 39.90, H 3.04, N 4.23; found: C 40.25, H 3.24, N 3.93.
3-Iodoindole-1,4-dicarboxylic acid dimethyl ester (13i).

3-Iodo-4-carbomethoxy-1H-indole was prepared starting from 4-carbomethoxy-1H-indole (230 mg, 1.31 mmol) and isolated by extraction. 1H-NMR (400 MHz, CDCl3) δ = 8.65 (bs, 1 H, N-H), 7.54-7.51 (m, 2 H), 7.43 (d, J = 2.8 Hz, 1 H), 7.25 (m, 1 H), 4.03 (s, 3 H) ppm. The protection step was carried out in THF. Purification by flash chromatography (n-hexane/EtOAc, 6 : 1; Rf = 0.25) afforded pure 13i (317 mg, 61 %) as a pale yellow solid. M.p. = 108.9 – 110.2 °C. 1H NMR (400 MHz, CDCl3) δ = 8.40 (d, J = 8.4 Hz, 1 H), 7.89 (s, 1 H), 7.57 (d, J = 7.6 Hz, 1 H), 7.40 (t, J = 8.4 Hz, 1 H), 4.05 (s, 3 H), 4.01 (s, 3 H) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 167.6 (s), 150.1 (s), 135.6 (s), 133.3 (d), 127.6 (s), 126.3 (s), 124.8 (d), 124.6 (d), 117.7 (d), 61.6 (s), 54.3 (q), 52.1 (q) ppm. MS (ESI) m/z (%): 382 ([M+Na]+, 26), 360 ([M+1]+, 41), 232 ([M+1-I]+, 100). Elemental analysis calcd (%) for C12H10INO4: C 40.13, H 2.81, N 3.90; found: C 40.39, H 2.75, N 3.84.

3-Iodoindole-1,5-dicarboxylic acid dimethyl ester (13m).

3-Iodo-5-carbomethoxy-1H-indole was prepared starting from 5-carbomethoxy-1H-indole (350 mg, 2.0 mmol) and isolated by filtration. 1H NMR (400 MHz, acetone-d6) δ = 11.0 (bs, 1 H, N-H), 8.12 (s, 1 H), 7.88 (dd, J = 8.4, 1.2 Hz, 1 H), 7.65 (s, 1 H), 7.55 (d, J = 8.4 Hz, 1 H), 3.91 (s, 3 H) ppm. The protection step was carried out in THF. Crystallization from acetone afforded pure 13m (543 mg, 76 %) as a white solid. M.p. = 157.2 – 158.3 °C. 1H NMR (400 MHz, DMSO-d6) δ = 8.18 (d, J = 8.8 Hz, 1 H), 8.04 (s, 1 H), 8.01 (dd, J = 8.8, 1.6 Hz, 1 H), 7.94 (d, J = 1.2 Hz, 1 H), 4.01 (s, 3 H), 3.90 (s, 3 H) ppm. 13C NMR (100.4 MHz, DMSO-d6) δ = 166.0 (s), 149.8 (s), 137.0 (s), 131.8 (s), 131.6 (d), 126.2 (d), 125.0 (s), 122.7 (d), 115.0 (d), 67.5 (s), 54.6 (q), 52.2 (q) ppm. MS (ESI) m/z (%): 360 ([M+1]+, 22), 232 ([M+1-I]+, 100). Elemental analysis calcd (%) for C12H10INO4: C 40.13, H 2.81, N 3.90; found: C 40.11, H 2.74, N 3.79.

3-Iodoindole-1,6-dicarboxylic acid dimethyl ester (13n).

3-Iodo-6-carbomethoxy-1H-indole was prepared starting from 6-carbomethoxy-1H-indole (350 mg, 2.0 mmol) and isolated by filtration. 1H NMR (200 MHz, CDCl3) δ = 8.59 (bs, 1 H), 8.14 (s, 1 H), 7.89 (d, J = 8.4 Hz, 1 H), 7.51-7.45 (m, 2 H), 3.95 (s, 3 H) ppm. The protection step was carried out in THF. Purification by flash chromatography (n-hexane/EtOAc, 10 : 1; Rf = 0.43) afforded pure 13n (500 mg, 70 %) as a white solid. M.p. = 126.2 – 127.1 °C. 1H NMR (400 MHz, DMSO-d6) δ = 8.62 (d, J = 1.2 Hz, 1 H), 8.06 (s, 1 H), 7.90 (dd, J = 8.3, 1.2 Hz, 1 H), 7.43 (d, J = 8.3 Hz, 1 H), 4.01 (s, 3 H), 3.89 (s, 3 H) ppm. 13C NMR (100.4 MHz, DMSO-d6) δ = 166.3 (s), 149.6 (s), 135.4 (s), 133.9 (s), 132.9 (d), 126.2 (s), 123.9 (d), 121.3 (d), 115.9 (d), 66.7 (s), 54.6 (q), 52.3 (q) ppm. MS (ESI) m/z (%): 360 ([M+1]+, 57), 232 ([M+1-I]+, 100). Elemental analysis calcd (%) for C12H10INO4: C 40.13, H 2.81, N 3.90; found: C 40.36, H 2.94, N 3.85.
Methyl 3-iodo-5-nitroindole-1-carboxylate (13o).

3-iodo-5-nitro-1H-indole was prepared starting from 5-nitro-1H-indole (330 mg, 2.0 mmol) and isolated by filtration.\textsuperscript{21} \textsuperscript{1}H NMR (200 MHz, CDCl\textsubscript{3}) \(\delta = 8.72\) (bs, 1 H), 8.46 (d, \(J = 2.4\) Hz, 1 H), 8.17 (dd, \(J = 9.2, 2.2\) Hz, 1 H), 7.48 (s, 1 H), 7.45 (d, \(J = 7.4\) Hz, 1 H) ppm. The protection step was carried out in THF. Purification by flash chromatography (\(n\)-hexane/EtOAc, 5:1; \(R_f = 0.50\)) afforded pure 11j (540 mg, 78 \%) as a yellow solid. M.p. = 150.4 – 151.0 °C. \textsuperscript{13}C NMR (100.4 MHz, DMSO) \(\delta = 149.6\) (s), 143.7 (s), 137.6 (s), 133.4 (d), 132.0 (s), 120.5 (d), 117.0 (d), 115.6 (d), 67.4 (s), 54.9 (q) ppm. MS (ESI) \(m/z\) (%): 369 ([M+Na]\textsuperscript{+}, 100). Elemental analysis calcd (%) for C\textsubscript{10}H\textsubscript{7}N\textsubscript{2}IO\textsubscript{4}: C 34.71, H 2.04, N 8.09; found: C 34.79, H 2.42, N 7.98.

**General procedure for the synthesis of indole derived enynyl acetates (4).**

**STEP A Sonogashira coupling (14):**

A 5:1 (v/v) solution of Et\textsubscript{3}N/DMF (4.5 mL) was added in a round bottom flask containing 3-iodoindole-1-carboxylic acid methyl ester 13 (1 mmol), (Ph\textsubscript{3}P)\textsubscript{2}PdCl\textsubscript{2} (35.1 mg, 0.05 mmol) and CuI (5.7 mg, 0.03 mmol), followed by 0.5 mL increments of DMF as necessary to complete dissolve 11.\textsuperscript{1} The alkynol (1.2 mmol) was then added and the reaction mixture heated at 40 or 55 °C (external) under vigorous stirring until complete consumption of the starting material (TLC; usually 1-3 h). The mixture was cooled at rt and quenched by water (12.5 mL). The product was extracted by EtOAc (3 x 10 mL) and the combined organic extracts dried over anhydrous K\textsubscript{2}CO\textsubscript{3}. After filtration and evaporation of the solvent, the crude was purified by flash chromatography affording the intermediate 14 that was used in the next step.

**STEP B Acetylation (4):**

A solution of enynyl alcohol 13 (1 mmol) in anhydrous DCM (10 mL) was cooled at 0 °C (ice bath) and DMAP (6 mg, 0.05 mmol), Et\textsubscript{3}N (0.42 mL, 3 mmol) and Ac\textsubscript{2}O (0.25 mL, 2 mmol) were added. After 10 min, the ice bath was removed and the reaction mixture was stirred at room temperature for 3 h, then quenched by addition of a satd solution of NaHCO\textsubscript{3} (10 mL). After separation of the phases, the aqueous layer was extracted with DCM (2 x 10 mL) and the combined organic extracts were dried over anhydrous K\textsubscript{2}CO\textsubscript{3}. After filtration and evaporation of the solvent, crude 4 was obtain. This was purified by flash chromatography and pure acetate 4 was stored at 4 °C as 0.1 M solution in the eluent + 1% Et\textsubscript{3}N until use.
3-(3-Acetoxybut-1-ynyl)-indole-1-carboxylic acid methyl ester (4a).

Compound 14a was obtained by Sonogashira coupling of 13a (301 mg, 1 mmol) and (±)-3-butyne-2-ol (94 µL, 1.2 mmol), heating at 40 °C for 3 h. Purification of the crude by flash chromatography (n-hexane/EtOAc, 3 : 1 + 1 % Et₃N; Rₓ = 0.22) afforded pure enynyl alcohol 14a which was used immediately in the next step. ¹H NMR (400 MHz, CDCl₃) δ = 8.16 (d, J = 8.4 Hz, 1 H), 7.76 (s, 1 H), 7.66 (d, J = 8.0 Hz, 1 H), 7.38 (t, J = 7.2 Hz, 1 H), 7.32 (t, J = 7.2 Hz, 1 H), 4.83 (q, J = 6.8 Hz, 1 H), 4.06 (s, 3 H), 1.61 (d, J = 6.8 Hz, 3 H) ppm.

Acetylation of compound 14a afforded 4a, which was purified by flash chromatography (n-hexane/EtOAc, 6 : 1 + 1 % Et₃N; Rₓ =0.28). Pure 4a was obtained as a colourless oil (240 mg, 86% over 2 steps). ¹H NMR (400 MHz, CDCl₃) δ = 8.15 (d, J = 8.0 Hz, 1 H), 7.79 (s, 1 H), 7.66 (d, J = 7.6 Hz, 1 H), 7.38 (td, J = 7.6, 1.2 Hz, 1 H), 7.32 (td, J = 7.6, 1.2 Hz, 1 H), 5.74 (q, J = 6.8 Hz, 1 H), 4.05 (s, 3 H), 2.12 (s, 3 H), 1.63 (d, J = 6.8 Hz, 3 H), ppm. ¹³C NMR (100.4 MHz, CDCl₃) δ = 170.0 (s), 150.9 (s), 134.5 (s), 130.3 (s), 128.9 (d), 125.5 (d), 123.6 (d), 120.1 (d), 115.1 (d), 103.4 (s), 91.3 (s), 76.3 (s), 60.9 (d), 54.1 (q), 21.6 (q), 21.1 (q) ppm. MS (ESI) m/z (%): 226 ([M-CO₂Me]⁺, 100).

3-(3-Acetoxyhept-1-ynyl)-indole-1-carboxylic acid methyl ester (4b).

Compound 14b was obtained by Sonogashira coupling of 13a (301 mg, 1 mmol) and (±)-2-heptyne-3-ol (155 µL, 1.2 mmol), heating at 40 °C for 4 h. Purification of the crude by flash chromatography (n-hexane/EtOAc, 3 : 1 + 1 % Et₃N; Rₓ = 0.33) afforded pure enynyl alcohol 14b which was used immediately in the next step. ¹H NMR (400 MHz, CDCl₃) δ = 8.15 (d, J = 8.0 Hz, 1 H), 7.76 (s, 1 H), 7.65 (d, J = 8.0 Hz, 1 H), 7.38 (t, J = 7.2 Hz, 1 H), 7.32 (t, J = 7.2 Hz, 1 H), 4.66 (t, J = 6.8 Hz, 1 H), 4.05 (s, 3 H), 1.88-1.82 (m, 2 H), 1.59-1.51 (m, 2 H), 1.47-1.37 (m, 2 H), 0.96 (t, J = 7.2 Hz, 3 H) ppm. Acetylation of compound 14b afforded 4b, which was purified by flash chromatography (n-hexane/EtOAc, 6 : 1 + 1 % Et₃N; Rₓ = 0.39). Pure 4b was obtained as a colourless oil (274 mg, 84% over 2 steps). ¹H NMR (400 MHz, CDCl₃) δ = 8.15 (d, J = 8.0 Hz, 1 H), 7.78 (s, 1 H), 7.65 (d, J = 7.2 Hz, 1 H), 7.37 (td, J = 7.6, 1.2 Hz, 1 H), 7.31 (td, J = 7.6, 1.2 Hz, 1 H), 5.65 (t, J = 6.8 Hz, 1 H), 4.04 (s, 3 H), 2.13 (s, 3 H), 1.93-1.87 (m, 2 H), 1.57-1.49 (m, 2 H), 1.46-1.37 (m, 2 H), 0.96 (t, J = 7.2 Hz, 3 H) ppm. ¹³C NMR (100.4 MHz, CDCl₃) δ = 170.0 (s), 150.8 (s), 134.5 (s), 130.3 (s), 128.8 (d), 125.4 (d), 123.5 (d), 120.0 (d), 115.1 (d), 103.4 (s), 90.5 (s), 76.9 (s), 64.7 (d), 54.0 (q), 34.6 (t), 27.2 (t), 22.2 (t), 21.1 (q), 13.9 (q) ppm. MS (ESI) m/z (%): 677 ([2M+Na]⁺, 67), 350 ([M+Na]⁺, 100), 268 ([M-CO₂Me]⁺, 67).
3-(3-Acetoxyprop-1-ynyl)-indole-1-carboxylic acid methyl ester (4c).
Compound 14c was obtained by Sonogashira coupling of 13a (139 mg, 0.46 mmol) and propargylic alcohol (32 µL, 0.55 mmol), heating at 40 °C for 3.5 h. Purification of the crude by flash chromatography (n-hexane/EtOAc, 2 : 1 + 1 % Et3N; Rf = 0.10) afforded pure enynyl alcohol 14c which was used immediately in the next step. 1H NMR (400 MHz, CDCl3) δ = 8.16 (d, J = 7.8 Hz, 1 H), 7.78 (s, 1 H), 7.68 (d, J = 8.0 Hz, 1 H), 7.39 (td, J = 8.4, 1.2 Hz, 1 H), 7.32 (td, J = 7.6, 1.2 Hz), 4.57 (s, 2 H), 4.06 (s, 3 H) ppm.

Acetylation of compound 14c afforded 4c, which was purified by flash chromatography (n-hexane/EtOAc, 6 : 1 + 1 % Et3N; Rf = 0.27). Pure 4c was obtained as a colourless oil (64 mg, 51 % over 2 steps). 1H NMR (400 MHz, CDCl3) δ = 8.16 (d, J = 8.0 Hz, 1 H), 7.81 (s, 1 H), 7.68 (d, J = 7.6 Hz, 1 H), 7.39 (td, J = 8.4, 1.2 Hz, 1 H), 7.32 (td, J = 7.6, 1.2 Hz), 4.97 (s, 2 H), 4.06 (s, 3 H), 2.15 (s, 3 H) ppm.

13C NMR (100.4 MHz, CDCl3) δ = 170.3 (s), 150.8 (s), 134.5 (s), 130.3 (s), 129.2 (d), 125.5 (d), 123.6 (d), 120.1 (d), 115.2 (d), 130.3 (s), 86.7 (s), 78.3 (s), 54.1 (q), 52.9 (l), 20.8 (q) ppm. MS (ESI) m/z (%): 294 ([M+Na]+, 41), 212 ([M - CO2Me]+, 100).

3-(3-Acetoxybut-1-ynyl)-5-methylindole-1-carboxylic acid methyl ester (4d).
Compound 14d was obtained by Sonogashira coupling of 13d (315 mg, 1 mmol) and (±)-3-butyne-2-ol (94 µL, 1.2 mmol), heating at 40 °C for 1 h. Purification of the crude by flash chromatography (n-hexane/EtOAc, 3 : 2 + 1 % Et3N; Rf = 0.20) afforded pure enynyl alcohol 14d which was used immediately in the next step. 1H NMR (400 MHz, CDCl3) δ = 8.01 (d, J = 8.5 Hz, 1 H), 7.71 (s, 1 H), 7.43 (s, 1 H), 7.19 (d, J = 8.5 Hz, 1 H), 4.83 (q, J = 6.6 Hz, 1 H), 4.04 (s, 3 H), 2.47 (s, 3 H), 2.19 - 2.23 (br s, 1 H), 1.61 (d, J = 6.6 Hz, 3 H) ppm.

Acetylation of compound 14d afforded 4d, which was purified by flash chromatography (n-hexane/EtOAc, 6 : 1 + 1 % Et3N; Rf = 0.19). Pure 4d was obtained as a yellow oil (210 mg, 70 % over 2 steps). 1H NMR (400 MHz, CDCl3) δ = 8.01 (d, J = 9.0 Hz, 1 H), 7.75 (s, 1 H), 7.43 (s, 1 H), 7.19 (d, J = 9.0 Hz, 1 H), 5.75 (q, J = 6.7 Hz, 1 H), 4.04 (s, 3 H), 2.47 (s, 3 H), 2.13 (s, 3 H), 1.63 (d, J = 6.7 Hz, 3 H) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 169.9 (s), 150.8 (s), 133.2 (s), 132.8 (s), 130.6 (s), 129.2 (d), 126.6 (d), 120.1 (d), 114.7 (d), 102.8 (s), 90.8 (s), 76.5 (s), 60.9 (d), 54.2 (q), 21.6 (q), 21.3 (q), 21.1 (q) ppm. MS (ESI) m/z (%): 620 ([2M+Na]+, 12), 321 ([M+Na]+, 43), 240 ([M-CO2Me]+, 100).

3-(3-Acetoxybut-1-ynyl)-6-methylindole-1-carboxylic acid methyl ester (4e).
Compound 14e was obtained by Sonogashira coupling of 13c (315 mg, 1 mmol) and (±)-3-butyne-2-ol
(94 μL, 1.2 mmol), heating at 40 °C for 1 h. Purification of the crude by flash chromatography (n-hexane/EtOAc, 3 : 1 + 1 % Et₃N; Rᵣ = 0.20) afforded pure enynyl alcohol 14e which was used immediately in the next step. ¹H NMR (400 MHz, CDCl₃) δ = 7.97 (s, 1 H), 7.68 (s, 1 H), 7.52 (d, J = 8.0 Hz, 1 H), 7.13 (d, J = 8.0 Hz, 1 H), 4.81 (q, J = 6.6 Hz, 1 H), 4.04 (s, 3 H), 2.49 (s, 3 H), 1.59 (d, J = 6.6 Hz, 3 H) ppm.

Acetylation of compound 14e afforded 4e, which was purified by flash chromatography (n-hexane/EtOAc, 6 : 1 + 1 % Et₃N; Rᵣ = 0.19). Pure 4e was obtained as a colourless oil (188 mg, 63 % over 2 steps). ¹H NMR (400 MHz, CDCl₃) δ = 7.76 (d, J = 8.4 Hz, 1 H), 7.62 (s, 1 H), 7.25 (t, J = 8.4 Hz, 1 H), 6.69 (d, J = 8.0 Hz, 1 H), 4.79 (q, J = 6.4 Hz, 1 H), 4.02 (s, 3 H), 3.92 (s, 3 H), 1.58 (d, J = 6.4 Hz, 3 H) ppm. ¹³C NMR (100.4 MHz, CDCl₃) δ = 169.9 (s), 150.9 (s), 135.5 (s), 134.7 (s), 128.3 (d), 128.0 (s), 125.0 (d), 119.5 (d), 115.3 (d), 103.2 (s), 90.9 (s), 76.5 (s), 60.9 (d), 54.0 (q), 21.9 (q), 21.6 (q), 21.1 (q) ppm. MS (ESI) m/z (%): 620 ([2M+Na]+, 10), 321 ([M+Na]+, 38), 240 ([M-CO₂Me]+, 100).

3-(3-Acetoxybut-1-ynyl)-4-methoxyindole-1-carboxylic acid methyl ester (4f).

Compound 14f was obtained by Sonogashira coupling of 13f (266 mg, 0.80 mmol) and (±)-3-butyne-2-ol (76 μL, 0.96 mmol), heating at 55 °C for 3 h. Purification of the crude by flash chromatography (n-hexane/EtOAc, 2 : 1 + 1 % Et₃N; Rᵣ = 0.15) afforded pure enynyl alcohol 14f which was used immediately in the next step. ¹H NMR (400 MHz, CDCl₃) δ = 7.76 (d, J = 8.4 Hz, 1 H), 7.62 (s, 1 H), 7.25 (t, J = 8.4 Hz, 1 H), 6.69 (d, J = 8.0 Hz, 1 H), 4.79 (q, J = 6.4 Hz, 1 H), 4.02 (s, 3 H), 3.92 (s, 3 H), 1.58 (d, J = 6.4 Hz, 3 H) ppm.

Acetylation of compound 14f afforded 4f, which was purified by flash chromatography (n-hexane/EtOAc, 6 : 1 + 1 % Et₃N; Rᵣ =0.18). Pure 4f was obtained as a white solid (154 mg, 61 % over 2 steps). ¹H NMR (400 MHz, CDCl₃) δ = 7.77 (d, J = 8.4 Hz, 1 H), 7.69 (s, 1 H), 7.27 (t, J = 8.4 Hz, 1 H), 6.70 (d, J = 7.6 Hz, 1 H), 5.73 (q, J = 6.8 Hz, 1 H), 4.03 (s, 3 H), 3.93 (s, 3 H), 2.11 (s, 3 H), 1.62 (d, J = 6.8 Hz, 3 H) ppm. ¹³C NMR (100.4 MHz, CDCl₃) δ = 169.9 (s), 153.9 (s), 150.7 (s), 136.0 (s), 128.4 (d), 126.4 (d), 119.2 (s), 108.0 (d), 104.4 (d), 101.5 (s), 89.3 (s), 78.1 (s), 61.1 (d), 55.5 (q), 54.0 (q), 21.4 (q), 21.1 (q) ppm. MS (ESI) m/z (%): 653 ([2M+Na]+, 47), 338 ([M+Na]+, 82), 256 ([M-CO₂Me]+, 100).

3-(3-Acetoxy-3-methylbut-1-ynyl)-4-methoxyindole-1-carboxylic acid methyl ester (4g).

Compound 14g was obtained by Sonogashira coupling of 13f (127 mg, 0.38 mmol) and 3-methyl-3-butyne-2-ol (45 μL, 0.46 mmol), heating at 55 °C for 2 h. Purification of the crude by flash chromatography (n-hexane/EtOAc, 2 : 1 + 1 % Et₃N; Rᵣ = 0.36) afforded pure enynyl alcohol 14g which was used immediately in the next step. ¹H NMR (400 MHz, CDCl₃) δ = 7.77 (d, J = 8.4 Hz, 1 H), 7.64 (s, 1 H), 7.27 (t, J = 8.4 Hz, 1 H), 6.70 (d, J = 8.0 Hz, 1 H), 4.03 (s, 3 H), 3.93 (s, 3 H), 1.65 (s, 6 H) ppm.

Acetylation of compound 14g was carried out by increasing the amounts of both Ac₂O (3 eq) and Et₃N.
(5 eq) and by prolonging the reaction time up to 16 h. The purification of the crude by flash chromatography (n-hexane/EtOAc, 6 : 1 + 1 % Et3N; Rf = 0.16) afforded pure 4g as a colourless oil (82 mg, 66 % over 2 steps). 1H NMR (400 MHz, CDCl3) δ = 7.76 (d, J = 8.4 Hz, 1 H), 7.69 (s, 1 H), 7.26 (t, J = 8.4 Hz, 1 H), 6.69 (d, J = 8.0 Hz, 1 H), 4.02 (s, 3 H), 3.94 (s, 3 H), 2.06 (s, 3 H), 1.80 (s, 6 H) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 169.3 (s), 154.0 (s), 150.8 (s), 136.1 (s), 128.2 (d), 126.3 (d), 119.5 (s), 108.0 (d), 104.4 (d), 92.1 (s), 77.5 (s), 72.8 (s), 55.5 (q), 54.0 (q), 29.0 (q, 2 C), 22.0 (q) ppm. MS (ESI) m/z (%): 681 ([2M+Na]+, 84), 352 ([M+Na]+, 55), 270 ([M-CO2Me]+), 100.

3-(3-Acetoxybut-1-ynyl)-5-methoxyindole-1-carboxylic acid methyl ester (4h).

Compound 14h was obtained by Sonogashira coupling of 13h (270 mg, 0.82 mmol) and (±)-3-butyn-2-ol (77 µL, 0.98 mmol), heating at 40 °C for 1 h. Purification of the crude by flash chromatography (n-hexane/EtOAc, 3 : 2 + 1 % Et3N; Rf = 0.30) afforded pure enynyl alcohol 14h which was used immediately in the next step. 1H NMR (400 MHz, CDCl3) δ = 8.02 (d, J = 8.9 Hz, 1 H), 7.73 (s, 1 H), 7.08 (d, J = 2.5 Hz, 1 H), 6.98 (dd, J = 8.9, 2.5 Hz, 1 H), 4.90 – 4.74 (m, 1 H), 4.03 (s, 3 H), 3.89 (s, 3 H), 1.93 – 1.88 (br s, 1 H), 1.61 (d, J = 6.6 Hz, 3 H) ppm. Acetylation of compound 14h afforded 4h, which was purified by flash chromatography (n-hexane/EtOAc, 6 : 1 + 1 % Et3N; Rf = 0.24). Pure 4h was obtained as a yellow oil (190 mg, 77 % over 2 steps). 1H NMR (400 MHz, CDCl3) δ = 8.00 (d, J = 8.7 Hz, 1 H), 7.74 (s, 1 H), 7.07 (t, J = 2.2 Hz, 1 H), 6.96 (dt, J = 8.7, 2.2 Hz, 1 H), 5.74 (q, J = 6.7 Hz, 1 H), 4.02 (s, 3 H), 3.88 (s, 3 H), 1.63 (d, J = 6.7 Hz, 3 H) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 169.3 (s), 156.7 (s), 150.8 (s), 131.2 (s), 129.4 (d), 129.0 (s), 115.9 (d), 114.4 (d), 103.2 (s), 102.2 (d), 91.3 (s), 76.1 (s), 60.8 (d), 55.5 (q), 54.0 (q), 21.2 (q), 20.9 (q) ppm. MS (ESI) m/z (%): 652 ([2M+Na]+, 3), 337 ([M+Na]+, 10), 256 ([M-CO2Me]+), 100.

3-(3-Acetoxybut-1-ynyl)-6-methoxyindole-1-carboxylic acid methyl ester (4i).

Compound 14i was obtained by Sonogashira coupling of 13i (295 mg, 0.9 mmol) and (±)-3-butyn-2-ol (85 µL, 1.1 mmol), heating at 40 °C for 1 h. Purification of the crude by flash chromatography (n-hexane/EtOAc, 3 : 2 + 1 % Et3N; Rf = 0.23) afforded pure enynyl alcohol 14i which was used immediately in the next step. 1H NMR (400 MHz, CDCl3) δ = 7.72 (bs, 1 H), 7.61 (s, 1 H), 7.49 (d, J = 8.6 Hz, 1 H), 6.93 (dd, J = 8.6, 2.3 Hz, 1 H), 4.80 (q, J = 6.6 Hz, 1 H), 4.03 (s, 3 H), 3.88 (s, 3 H), 1.59 (d, J = 6.6 Hz, 3 H) ppm. Acetylation of compound 14i afforded 4i, which was purified by flash chromatography (n-hexane/EtOAc, 6 : 1 + 1 % Et3N; Rf = 0.28). Pure 4i was obtained as a yellow oil (170 mg, 73 % over 2 steps). 1H NMR (400 MHz, CDCl3) δ = 7.74 (br s, 1 H), 7.67 (s, 1 H), 7.51 (d, J = 8.6 Hz, 1 H), 6.94 (dd, J = 8.6, 2.3 Hz, 1 H), 5.72 (q, J = 6.6 Hz, 1 H), 4.03 (s, 3 H), 3.88 (s, 3 H), 2.11 (s, 3 H), 1.62 (d, J = 6.6 Hz, 3 H) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 170.0 (s), 158.5 (s), 150.9 (s), 135.5 (s), 127.6 (s), 124.0 (d), 120.6 (d), 112.8 (d), 102.9 (s), 99.3 (d), 90.9 (s), 76.5 (s), 61.0 (d), 55.7 (q), 54.1 (q), 21.5 (q), 21.0 (q) ppm. MS (ESI) m/z (%): 652 ([2M+Na]+, 15), 337 ([M+Na]+, 41), 256 ([M-CO2Me]+), 100.
3-(3-Acetoxy-3-methylbut-1-ynyl)-6-methoxyindole-1-carboxylic acid methyl ester (4j).

Compound 14j was obtained by Sonogashira coupling of 13i (87 mg, 0.26 mmol) and 3-methyl-3-butyn-2-ol (31 µL, 0.32 mmol), heating at 40 °C for 1 h. Purification of the crude by flash chromatography (n-hexane/EtOAc, 2 : 1 + 1 % Et3N; Rf = 0.26) afforded pure enynyl alcohol 14j which was used immediately in the next step. 1H NMR (400 MHz, CDCl3) δ = 7.73 (br s, 1 H), 7.62 (s, 1 H), 7.49 (d, J = 8.4 Hz, 1 H), 6.93 (dd, J = 8.4, 2.0 Hz, 1 H), 4.03 (s, 3 H), 3.88 (s, 3 H), 1.66 (s, 6 H) ppm.

Acetylation of compound 14j was carried out by increasing the amounts of both Ac2O (3 eq) and Et3N (5 eq) and by prolonging the reaction time up to 16 h. The purification of the crude by flash chromatography (n-hexane/EtOAc, 6 : 1 + 1 % Et3N; Rf = 0.19) afforded pure 4j as a colourless oil (78 mg, 91 % over 2 steps). 1H NMR (400 MHz, CDCl3) δ = 7.72 (bs, 1 H), 7.65 (s, 1 H), 7.54 (d, J = 8.8 Hz, 1 H), 6.94 (dd, J = 8.4, 2.4 Hz, 1 H), 4.02 (s, 3 H), 3.88 (s, 3 H), 2.06 (s, 3 H), 1.78 (s, 6 H) ppm.

13C NMR (100.4 MHz, CDCl3) δ = 169.4 (s), 158.5 (s), 151.0 (s), 135.6 (s), 127.1 (d), 124.2 (s), 120.7 (d), 112.8 (d), 103.6 (s), 99.1 (d), 93.9 (s), 75.8 (s), 72.5 (s), 55.7 (q), 54.0 (q), 29.2 (q, 2 C), 22.0 (q) ppm. MS (ESI) m/z (%): 368 ([M+K]+, 100), 352 ([M+Na]+, 16), 270 ([M-CO2Me]+, 48).

3-(3-Acetoxy-3-phenylprop-1-ynyl)-6-methoxyindole-1-carboxylic acid methyl ester (4k).

Compound 14k was obtained by Sonogashira coupling of 13i (210 mg, 0.63 mmol) and (±)-1-phenyl-2-propyn-1-ol (93 µL, 0.76 mmol), heating at 40 °C for 1 h. Purification of the crude by flash chromatography (n-hexane/EtOAc, 3 : 1 + 1 % Et3N; Rf = 0.16) afforded pure enynyl alcohol 14k which was used immediately in the next step. 1H NMR (400 MHz, CDCl3) δ = 7.72 (bs, 1 H), 7.65 (s, 1 H), 7.66-7.63 (m, 2 H), 7.52 (d, J = 8.8 Hz, 1 H), 7.46-7.40 (m, 3 H), 6.94 (dd, J = 8.4, 2.4 Hz, 1 H), 5.75 (s, 1 H), 4.03 (s, 3 H), 3.88 (s, 3 H) ppm.

Acetylation of compound 14k afforded 4k, which was purified by flash chromatography (n-hexane/EtOAc, 6 : 1 + 1 % Et3N; Rf = 0.13). Pure 4k was obtained as a yellow oil (204 mg, 86 % over 2 steps). 1H NMR (400 MHz, CDCl3) δ = 7.74 (br s, 1 H), 7.71 (s, 1 H), 7.64-7.61 (m, 2 H), 7.52 (d, J = 8.8 Hz, 1 H), 7.46-7.38 (m, 3 H), 6.94 (dd, J = 8.4, 2.4 Hz, 1 H), 6.74 (s, 1 H), 4.04 (s, 3 H), 3.88 (s, 3 H) ppm. 13C NMR (100.4 MHz, CDCl3): δ = 169.8 (s), 158.6 (s), 150.8 (s), 137.1 (s), 135.6 (s), 128.9 (d), 128.7 (d, 2 C), 127.8 (d, 2 C), 127.3 (s, 2 C), 123.9 (s), 120.5 (d), 112.8 (d), 103.0 (s), 99.3 (d), 89.1 (s), 79.1 (s), 66.2 (d), 55.6 (q), 54.0 (q), 21.1 (q), 21.0 (q) ppm. MS (ESI) m/z (%): 777 ([2M+Na]+, 100), 695 ([2M-CO2Me]+, 75), 400 ([M+Na]+, 36), 318 ([M-CO2Me]+, 82).
3-(3-Acetoxybut-1-ynyl)-indole-1,4-dicarboxylic acid dimethyl ester (4l).

Compound 14l was obtained by Sonogashira coupling of 13l (260 mg, 0.72 mmol) and (±)-3-butyne-2-ol (68 µL, 0.86 mmol), heating at 40 °C for 1 h. Purification of the crude by flash chromatography (n-hexane/EtOAc, 3 : 2 + 1 % Et3N; Rf = 0.23) afforded pure enynyl alcohol 14l which was used immediately in the next step. 1H NMR (400 MHz, CDCl3) δ = 8.41 (d, J = 8.5 Hz, 1 H), 7.88 (s, 1 H), 7.70 (d, J = 8.5 Hz, 1 H), 7.40 (t, J = 8.5 Hz, 1 H), 4.77 (q, J = 6.6 Hz, 3 H), 4.06 (s, 3 H), 3.98 (s, 3 H), 2.30 – 2.21 (br s, 1 H), 1.56 (d, J = 6.6 Hz, 3 H) ppm.

Acetylation of compound 14l afforded 4l, which was purified by flash chromatography (n-hexane/EtOAc, 3 : 2 + 1 % Et3N; Rf = 0.21). Pure 4l was obtained as a yellow oil (84 mg, 51 % over 2 steps). 1H NMR (400 MHz, CDCl3) δ = 8.39 (d, J = 8.0 Hz, 1 H), 7.94 (s, 1 H), 7.71 (d, J = 8.0 Hz, 1 H), 7.40 (t, J = 8.0 Hz, 1 H), 5.74 (q, J = 6.7 Hz, 1 H), 4.05 (s, 3 H), 3.98 (s, 3 H), 2.10 (s, 3 H), 1.61 (d, J = 6.7 Hz, 3 H) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 169.9 (s), 167.4 (s), 150.6 (s), 135.3 (s), 132.5 (d), 126.6 (s), 125.4 (d), 125.3 (s), 124.8 (d), 118.7 (d), 103.2 (s), 90.1 (s), 77.5 (s), 60.8 (d), 54.6 (q), 51.2 (q), 21.9 (q), 21.0 (q) ppm. MS (ESI) m/z (%): 708 ([2M+Na]+, 35), 365 ([M+Na]+, 43), 283 ([M-CO2Me]+, 100).

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3-(3-Acetoxybut-1-ynyl)-indole-1,5-dicarboxylic acid dimethyl ester (4m).

Compound 14m was obtained by Sonogashira coupling of 13m (360 mg, 1 mmol) and (±)-3-butyne-2-ol (94 µL, 1.2 mmol), heating at 40 °C for 1 h. Purification of the crude by flash chromatography (n-hexane/EtOAc, 3 : 2 + 1 % Et3N; Rf = 0.25) afforded pure enynyl alcohol 14m which was used immediately in the next step. 1H NMR (400 MHz, CDCl3) δ = 8.26 (d, J = 8.0 Hz, 1 H), 7.94 (s, 1 H), 7.71 (d, J = 8.0 Hz, 1 H), 7.40 (t, J = 8.0 Hz, 1 H), 5.74 (q, J = 6.7 Hz, 1 H), 4.05 (s, 3 H), 3.98 (s, 3 H), 2.10 (s, 3 H), 1.61 (d, J = 6.7 Hz, 3 H) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 169.9 (s), 167.4 (s), 150.9 (s), 136.9 (s), 130.1 (d), 126.6 (d), 125.6 (s), 122.3 (d), 115.0 (d), 103.8 (s), 91.6 (s), 77.2 (s), 60.8 (d), 54.6 (q), 52.1 (q), 21.5 (q), 21.1 (q) ppm. MS (ESI) m/z (%): 708 ([2M+Na]+, 18), 365 ([M+Na]+, 40), 284 ([M-CO2Me]+, 100).
3-(3-Acetoxybut-1-ynyl)-indole-1,6-dicarboxylic acid dimethyl ester (4n).

Compound 14n was obtained by Sonogashira coupling of 13n (360 mg, 1 mmol) and (±)-3-butyln-2-ol (94 µL, 1.2 mmol), heating at 40 °C for 1 h. Purification of the crude by flash chromatography (n-hexane/EtOAc, 3 : 2 + 1 % Et3N; Rf = 0.33) afforded pure enynyl alcohol 14n which was used immediately in the next step. 1H NMR (400 MHz, CDCl3) δ = 8.83 (s, 1 H), 8.01 (d, J = 8.2 Hz, 1 H), 7.89 (s, 1 H), 7.69 (d, J = 8.2 Hz, 1 H), 4.85 – 4.78 (m, 1 H), 4.10 (s, 3 H), 3.96 (s, 3 H), 1.99 – 1.93 (bs, 1 H), 1.61 (d, J = 6.6 Hz, 3 H) ppm.

Acetylation of compound 14n afforded 4n, which was purified by flash chromatography (n-hexane/EtOAc, 6 : 1 + 1 % Et3N; Rf = 0.27). Pure 4n was obtained as a white solid (240 mg, 70 % over 2 steps). 1H NMR (400 MHz, CDCl3) δ = 8.80 (s, 1 H), 8.00 (dd, J = 8.2, 1.1 Hz, 1 H), 7.90 (s, 1 H), 7.67 (d, J = 8.2 Hz, 1 H), 5.72 (q, J = 6.7 Hz, 1 H), 4.08 (s, 3 H), 3.94 (s, 3 H), 2.12 (s, 3 H), 1.62 (d, J = 6.7 Hz, 3 H) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 170.1 (s), 166.7 (s), 150.5 (s), 133.7 (s), 131.3 (d), 127.1 (s), 125.0 (d), 120.0 (d), 116.9 (d), 103.3 (s), 92.0 (s), 75.5 (s), 60.8 (d), 54.6 (q), 52.1 (q), 21.5 (q), 21.0 (q) ppm. MS (ESI) m/z (%): 708 ([2M+Na]+, 6), 365 ([M+Na]+, 7), 284 ([M-CO2Me]+, 100).

3-(3-Acetoxybut-1-ynyl)-5-nitroindole-1-carboxylic acid methyl ester (4o).

Compound 14o was obtained by Sonogashira coupling of 13o (345 mg, 1 mmol) and (±)-3-butyln-2-ol (94 µL, 1.2 mmol), heating at 40 °C for 1 h. Purification of the crude by flash chromatography (n-hexane/EtOAc, 3 : 2 + 1 % Et3N; Rf = 0.20) afforded pure enynyl alcohol 14o which was used immediately in the next step. 1H NMR (400 MHz, CDCl3) δ = 8.80 (s, 1 H), 8.00 (dd, J = 8.2, 1.1 Hz, 1 H), 7.90 (s, 1 H), 7.67 (d, J = 8.2 Hz, 1 H), 5.72 (q, J = 6.7 Hz, 1 H), 4.08 (s, 3 H), 3.94 (s, 3 H), 2.12 (s, 3 H), 1.62 (d, J = 6.7 Hz, 3 H) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 169.8 (s), 150.1 (s), 144.2 (s), 137.4 (s), 131.3 (d), 130.3 (s), 120.7 (d), 116.5 (d), 115.5 (d), 104.3 (s), 92.8 (s), 74.5 (s), 60.7 (d), 54.7 (q), 21.2 (q), 21.1 (q) ppm. MS (ESI) m/z (%): 682 ([2M+Na]+, 17), 352 ([M+Na]+, 44), 270 ([M-CO2Me]+, 100).
General procedure for gold(I)-catalyzed Nazarov reaction (6).

The solution of 4 in the eluent was concentrated and dried under vacuum (no heating) for 30 minutes. Gold(I) complex \((4\text{-CF}_3\text{C}_6\text{H}_4)_3\text{PAuCl}\) (3 mol %, 0.006 mmol) was dissolved in DCM (1.2 mL, 0.005 M) and AgSbF\(_6\) (3 mol %, 0.006 mmol) was added. The formed suspension was left to stir at room temperature under nitrogen atmosphere. After 20 min a solution of enynyl acetate 4 (0.2 mmol) in DCM (2.8 mL; final concentration 0.05 M) was added and reaction mixture was stirred at room temperature. After complete consumption of 4 (TLC monitoring), water (5 mL) was added; the phases were separated and the aqueous layer was extracted with DCM (2 x 5 mL). The organic layer was dried over anhydrous Na\(_2\text{SO}_4\), filtered and concentrated. The oily residue was purified by flash chromatography followed by trituration with Et\(_2\)O to give the corresponding cyclopentane-fused indole derivative.

3-Methyl-1-oxo-2,3-dihydro-1\(H\)-cyclopenta[b]indole-4-carboxylic acid methyl ester (6a).

Compound 6a was prepared starting from 4a (67 mg, 0.24 mmol). Purification by flash chromatography \((n\text{-hexane/EtOAc, 3 : 1; R}_r = 0.16)\) followed by trituration with Et\(_2\)O afforded pure 6a (48 mg, 83 %) as a yellow solid. M.p. = 126.8 – 127.8 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 8.13\) (d, \(J =8.0\) Hz, 1 H), 7.88 (d, \(J = 8.0\) Hz, 1 H), 7.39 - 7.31 (m, 2 H), 4.12 (s, 3 H), 3.73 (m, 1 H), 3.24 (dd, \(J = 18.0, 6.8\) Hz, 1 H), 2.55 (dd, \(J = 18.0, 1.2\) Hz, 1 H), 1.45 (d, \(J = 6.8\) Hz, 3 H) ppm. \(^{13}\)C NMR (100.4 MHz, CDCl\(_3\)) \(\delta = 196.4\) (s), 171.0 (s), 150.8 (s), 140.8 (s), 125.6 (d), 124.9 (s), 124.6 (d), 122.1 (s), 120.8 (d), 115.9 (d), 54.3 (q), 49.8 (t), 32.2 (d), 20.7 (q) ppm. MS (ESI) \(m/z\) (%): 244 ([M+1]\(^+\), 100).

Elemental analysis calcd (%) for C\(_{14}\)H\(_{13}\)NO\(_3\): C 69.12, H 5.39, N 5.76; found: C 69.08, H 5.44, N 5.82.

3-Butyl-1-oxo-2,3-dihydro-1\(H\)-cyclopenta[b]indole-4-carboxylic acid methyl ester (6b).

Compound 6b was prepared starting from 4b (177 mg, 0.54 mmol). Purification by flash chromatography \((n\text{-hexane/EtOAc, 4 : 1; R}_r = 0.26)\) followed by trituration with Et\(_2\)O afforded pure 6b (105 mg, 68 %) as a yellow solid. M.p. = 106.6 – 108.1 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 8.13\) (d, \(J = 7.6\) Hz, 1 H), 7.88 (d, \(J = 7.6\) Hz, 1 H), 7.39 – 7.31 (m, 2 H), 4.11 (s, 3 H), 3.64 (t, \(J = 6.8\) Hz, 1 H), 3.13 (dd, \(J = 18.0, 6.4\) Hz, 1 H), 2.65 (d, \(J = 18.0\) Hz, 1 H), 2.07 - 2.01 (m, 1 H), 1.53 – 1.44 (m, 1 H), 1.41 – 1.25 (m, 4 H), 0.90 (t, \(J = 6.4\) Hz, 3 H) ppm. \(^{13}\)C NMR (100.4 MHz, CDCl\(_3\)) \(\delta = 196.5\) (s), 170.0 (s), 150.8 (s), 140.8 (s), 125.5 (d), 125.3 (s), 124.6 (d), 122.1 (s), 120.8 (d), 115.8 (d), 54.2 (q), 47.4 (t), 37.2 (d), 34.1 (t), 29.4 (t), 22.5 (t), 13.9 (q) ppm. MS (ESI) \(m/z\) (%): 593 ([2M+Na]\(^+\), 64), 368 ([M+Na]\(^+\), 27), 286 ([M+1]\(^+\), 100). Elemental analysis calcd (%) for C\(_{17}\)H\(_{19}\)NO\(_3\): C 71.56, H 6.71, N 4.91; found: C 71.23, H 6.51, N 5.19.

1-Oxo-2,3-dihydro-1\(H\)-cyclopenta[b]indole-4-carboxylic acid methyl ester (6c).

Compound 6c was prepared starting from 4c (57 mg, 0.21 mmol). Purification by flash chromatography \((n\text{-hexane/EtOAc, 2 : 1; R}_r = 0.16)\) followed by trituration with Et\(_2\)O afforded pure 6c (28 mg, 48 %) as a yellow solid. M.p. = 126.8 – 127.8 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 8.13\) (d, \(J = 8.0\) Hz, 1 H), 7.88 (d, \(J = 8.0\) Hz, 1 H), 7.39 – 7.31 (m, 2 H), 4.12 (s, 3 H), 3.73 (m, 1 H), 3.24 (dd, \(J = 18.0, 6.8\) Hz, 1 H), 2.55 (dd, \(J = 18.0, 1.2\) Hz, 1 H), 1.45 (d, \(J = 6.8\) Hz, 3 H) ppm. \(^{13}\)C NMR (100.4 MHz, CDCl\(_3\)) \(\delta = 196.4\) (s), 171.0 (s), 150.8 (s), 140.8 (s), 125.6 (d), 124.9 (s), 124.6 (d), 122.1 (s), 120.8 (d), 115.9 (d).
(37 mg, 76 %) as a white solid. M.p. = 153.8 – 155.2 °C. ¹H NMR (400 MHz, CDCl₃) δ = 8.14 (d, J = 7.2 Hz, 1 H), 7.87 (dd, J = 6.4, 1.6 Hz, 1 H), 7.39 – 7.31 (m, 2 H), 4.09 (s, 3 H), 3.30 – 3.28 (m, 2 H), 2.96 – 2.93 (m, 2 H) ppm. ¹³C NMR (100.4 MHz, CDCl₃) δ = 196.8 (s), 167.1 (s), 151.0 (s), 140.7 (s), 125.5 (s and d, 2 C), 124.6 (d), 122.3 (s), 120.7 (d), 115.7 (d), 54.3 (q), 40.4 (t), 24.9 (t) ppm. MS (ESI) m/z (%): 230 ([M+Na]⁺, 100). Elemental analysis calcd (%) for C₁₅H₁₅NO₃: C 69.91, H 5.82, N 5.13.

3,7-Dimethyl-1-oxo-2,3-dihydro-1H-cyclopenta[b]indole-4-carboxylic acid methyl ester (6d).

Compound 6d was prepared starting from 4d (59 mg, 0.20 mmol). Purification by flash chromatography (n-hexane/EtOAc, 2 : 1; Rf = 0.22) followed by trituration with Et₂O afforded pure 6d (41 mg, 80 %) as a white solid. M.p. = 125.5 – 126.8 °C. ¹H NMR (400 MHz, CDCl₃) δ = 7.98 (d, J = 8.6 Hz, 1 H), 7.69 (s, 1 H), 7.18 (d, J = 8.6 Hz, 1 H), 4.12 (s, 3 H), 3.71 (m, 1 H), 3.24 (dd, J = 18.0, 6.5 Hz, 1 H), 2.55 (dd, J = 18.0, 1.2 Hz, 1 H), 2.44 (s, 3 H), 1.45 (d, J = 6.9 Hz, 3 H) ppm. ¹³C NMR (100.4 MHz, CDCl₃) δ = 196.6 (s), 171.0 (s), 150.6 (s), 138.7 (s), 134.6 (s), 126.7 (d), 124.3 (d), 121.9 (s), 120.7 (d), 115.5 (d), 54.1 (q), 49.6 (t), 31.8 (d), 21.5 (q), 20.8 (q) ppm. MS (ESI) m/z (%): 236 ([M+Na]⁺, 100), 280 ([M+Na]⁺, 9), 258 ([M+1]+, 53). Elemental analysis calcd (%) for C₁₅H₁₅NO₃: C 70.02, H 5.88, N 5.44; found: C 69.93, H 5.79, N 5.31.

3,6-Dimethyl-1-oxo-2,3-dihydro-1H-cyclopenta[b]indole-4-carboxylic acid methyl ester (6e).

Compound 6e was prepared starting from 4e (139 mg, 0.47 mmol). Purification by flash chromatography (n-hexane/EtOAc, 2 : 1; Rf = 0.21) followed by trituration with Et₂O afforded pure 6e (99 mg, 82 %) as a white solid. M.p. = 140.1 – 140.8 °C. ¹H NMR (400 MHz, CDCl₃) δ = 7.95 (s, 1 H), 7.74 (d, J = 8.2 Hz, 1 H), 7.16 (d, J = 8.2 Hz, 1 H), 4.11 (s, 3 H), 3.76 – 3.63 (m, 1 H), 3.22 (dd, J = 18.0, 6.5 Hz, 1 H), 2.53 (dd, J = 18.0, 1.3 Hz, 1 H), 2.48 (s, 3 H), 1.43 (d, J = 6.9 Hz, 3 H) ppm. ¹³C NMR (100.4 MHz, CDCl₃) δ = 196.3 (s), 170.5 (s), 151.0 (s), 140.7 (s), 136.0 (s), 125.7 (d), 124.7 (s), 120.4 (d), 119.7 (s), 116.0 (d), 54.1 (q), 49.8 (t), 32.2 (d), 22.0 (q), 20.8 (q) ppm. MS (ESI) m/z (%): 236 ([2M+Na]⁺, 14), 258 ([M+1]+, 100). Elemental analysis calcd (%) for C₁₅H₁₅NO₃: C 70.02, H 5.88, N 5.44; found: C 69.91, H 5.82, N 5.13.

8-Methoxy-3-methyl-1-oxo-2,3-dihydro-1H-cyclopenta[b]indole-4-carboxylic acid methyl ester (6f).

Compound 6f was prepared starting from 4f (60 mg, 0.19 mmol). Purification by flash chromatography (n-hexane/EtOAc, 3 : 2; Rf = 0.16) followed by trituration with Et₂O afforded pure 6f (39 mg, 75 %) as a pale yellow solid. M.p. = 191.5 – 193.2 °C. ¹H NMR (400 MHz, CDCl₃) δ = 7.77 (d, J = 8.4 Hz, 1 H), 7.31 (t, J = 8.4 Hz, 1 H), 6.80 (d, J = 8.0 Hz, 1 H), 4.11 (s, 3 H), 4.00 (s, 3 H), 3.75-3.68 (m, 1 H), 3.25 (dd, J = 18.0, 6.8 Hz, 1 H), 2.57 (dd, J = 18.0, 1.2 Hz, 1 H), 1.43 (d, J = 6.8 Hz, 3 H) ppm. ¹³C NMR (100.4 MHz, CDCl₃) δ = 195.1 (s), 170.0 (s), 154.0 (s), 150.8 (s), 142.1 (s), 126.9 (d), 124.2 (s), 112.6...
(s), 108.6 (d), 105.8 (d), 56.1 (q), 54.3 (q), 49.7 (t), 31.9 (d), 20.9 (q) ppm. MS (ESI) m/z (%): 569 ([M+Na]⁺, 100), 274 ([M+1]⁺, 69). Elemental analysis calcd (%) for C₁₃H₁₃NO₄·½H₂O: C 64.86, H 5.62, N 5.04; found: C 64.94, H 5.50, N 4.87.

8-Methoxy-3,3-dimethyl-1-oxo-2,3-dihydro-1Η-cyclopenta[b]indole-4-carboxylic acid methyl ester (6g).

Compound 6g was prepared starting from 4g (76 mg, 0.23 mmol). Purification by flash chromatography (n-hexane/EtOAc, 2 : 1; Rf = 0.19) followed by trituration with Et₂O afforded pure 6g (41 mg, 62 %) as a pale yellow solid. The product decomposed at 175 °C. ¹H NMR (400 MHz, CDCl₃) δ = 7.72 (d, J = 8.4 Hz, 1 H), 7.31 (t, J = 8.4 Hz, 1 H), 6.80 (d, J = 8.0 Hz, 1 H), 4.13 (s, 3 H), 4.01 (s, 3 H), 2.93 (s, 2 H), 1.60 (s, 6 H) ppm. ¹³C NMR (100.4 MHz, CDCl₃) δ = 194.5 (s), 151.2 (s), 129.2 (d), 125.1 (s), 115.7 (d), 105.7 (d), 59.4 (t), 56.0 (q), 54.2 (q), 39.2 (s), 26.8 (q, 2 C) ppm. MS (ESI) m/z (%): 597 ([M+Na]⁺, 100), 288 ([M+1]⁺, 36). Elemental analysis calcd (%) for C₁₆H₁₄NO₄: C 66.89, H 5.96, N 4.88; found: C 66.67, H 5.71, N 4.66.

7-Methoxy-3-methyl-1-oxo-2,3-dihydro-1Η-cyclopenta[b]indole-4-carboxylic acid methyl ester (6h).

Compound 6h was prepared starting from 4h (155 mg, 0.50 mmol). Purification by flash chromatography (n-hexane/EtOAc, 2 : 1; Rf = 0.27) followed by trituration with Et₂O afforded pure 6h (112 mg, 84 %) as a yellow solid. M.p. = 158.3 – 159.9 °C. ¹H NMR (400 MHz, CDCl₃) δ = 7.99 (d, J = 9.2 Hz, 1 H), 7.34 (d, J = 2.6 Hz, 1 H), 6.94 (dd, J = 9.2, 2.6 Hz, 1 H), 4.10 (s, 3 H), 3.85 (s, 3 H), 3.77 – 3.64 (m, 1 H), 3.23 (dd, J = 18.0, 6.5 Hz, 1 H), 2.54 (dd, J = 18.0, 1.2 Hz, 1 H), 1.45 (d, J = 6.9 Hz, 3 H) ppm. ¹³C NMR (100.4 MHz, CDCl₃) δ = 196.7 (s), 159.9 (s), 135.3 (s), 124.6 (s), 122.8 (s), 116.6 (d), 114.7 (d), 103.2 (d), 55.7 (q), 54.2 (q), 49.6 (t), 32.2 (d) , 20.6 (q) ppm. MS (ESI) m/z (%): 296 ([M+Na]⁺, 6), 274 ([M+1]⁺, 100). Elemental analysis calcd (%) for C₁₆H₁₅NO₄·½H₂O: C 65.92, H 5.53, N 5.13; found: C 65.64, H 5.68, N 4.99.

6-Methoxy-3-methyl-1-oxo-2,3-dihydro-1Η-cyclopenta[b]indole-4-carboxylic acid methyl ester (6i).

Compound 6i was prepared starting from 4i (75 mg, 0.24 mmol). Purification by flash chromatography (n-hexane/EtOAc, 2 : 1; Rf = 0.24) followed by trituration with Et₂O afforded pure 6i (55 mg, 84 %) as a white solid. M.p. = 98.1 – 99.0 °C. ¹H NMR (400 MHz, CDCl₃) δ = 7.72 (d, J = 8.6 Hz, 1 H), 7.72 (d, J = 2.2 Hz, 1 H), 6.94 (dd, J = 8.6, 2.2 Hz, 1 H), 4.10 (s, 3 H), 3.87 (s, 3 H), 3.71 – 3.65 (m, 1 H), 3.21 (dd, J = 18.0, 6.4 Hz, 1 H), 2.52 (dd, J = 18.0, 1.2 Hz, 1 H), 1.43 (d, J = 6.9 Hz, 3 H) ppm. ¹³C NMR (100.4 MHz, CDCl₃) δ = 196.4 (s), 170.0 (s), 158.4 (s), 150.9 (s), 142.2 (s), 124.8 (s), 121.2 (d), 115.7 (s), 112.5 (d), 100.9 (d), 55.8 (q), 54.3 (q), 49.8 (t), 32.3 (d), 20.8 (q) ppm. MS (ESI) m/z (%): 568 ([2M+Na]⁺, 18), 295 ([M+Na]⁺, 5), 274 ([M+1]⁺, 100). Elemental analysis calcd (%) for C₁₅H₁₄NO₄·½H₂O: C
6-Methoxy-3,3-dimethyl-1-oxo-2,3-dihydro-1H-cyclopenta[b]indole-4-carboxylic acid methyl ester (6j).
Compound 6j was prepared starting from 4j (66 mg, 0.20 mmol). Purification by flash chromatography (n-hexane/EtOAc, 2 : 1; Rf = 0.24) followed by trituration with Et2O afforded pure 6j (47 mg, 82 %) as a white solid. M.p. = 152.2 ‒ 154.1 °C. 1H NMR (400 MHz, CDCl3) δ = 7.78 (d, J = 8.8 Hz, 1 H), 7.70 (d, J = 2.0 Hz, 1 H), 6.96 (dd, J = 8.8, 2.0 Hz, 1 H), 4.13 (s, 3 H), 3.88 (s, 3 H), 2.90 (s, 2 H), 1.60 (s, 6 H) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 196.1 (s), 171.4 (s), 158.5 (s), 150.8 (s), 142.0 (s), 124.9 (s), 121.2 (d), 115.5 (s), 112.3 (d), 101.8 (d), 59.3 (t), 55.8 (q), 54.2 (q), 39.9 (s), 26.9 (q, 2 C) ppm. MS (ESI) m/z (%): 597 ([2M+Na]+, 100), 288 ([M+1]+, 38). Elemental analysis calcd (%) for C16H17NO4: C 66.89, H 5.96, N 4.88; found: C 67.00, H 5.82, N 5.03.

6-Methoxy-3-phenyl-1-oxo-2,3-dihydro-1H-cyclopenta[b]indole-4-carboxylic acid methyl ester (6k).
Compound 6k was prepared starting from 4k (95 mg, 0.25 mmol). Purification by trituration with Et2O and n-hexane afforded pure 6k (51 mg, 61 %) as a yellow solid. M.p. = 141.7 ‒ 143.1 °C. Rf = 0.18 (n-hexane-EtOAc, 3 : 1). 1H NMR (400 MHz, CDCl3) δ = 7.84 (d, J = 8.8 Hz, 1 H), 7.77 (d, J = 2.0 Hz, 1 H), 7.31 ‒ 7.19 (m, 3 H), 7.07 ‒ 7.05 (m, 2 H), 7.00 (dd, J = 8.4, 2.0 Hz, 1 H), 4.78 (dd, J = 7.2, 1.6 Hz, 1 H), 3.88 (s, 3 H), 3.70 (s, 3 H), 3.48 (dd, J = 18.0, 7.2 Hz, 1 H), 2.78 (dd, J = 18.0, 1.6 Hz, 1 H) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 196.0 (s), 165.9 (s), 158.8 (s), 150.3 (s), 142.4 (s), 142.0 (s), 128.9 (d, 2 C), 127.0 (d), 126.6 (s), 126.5 (d, 2 C), 121.4 (d), 115.4 (s), 113.1 (d), 100.7 (d), 55.7 (q), 53.7 (q), 51.6 (t), 43.3 (d) ppm. MS (ESI) m/z (%): 693 ([2M+Na]+, 100), 336 ([M+1]+, 79). Elemental analysis calcd (%) for C20H17NO4: C 71.63, H 5.11, N 4.18; found: C 71.42, H 4.91, N 4.53.

3-Methyl-1-oxo-2,3-dihydro-1H-cyclopenta[b]indole-4,8-dicarboxylic acid dimethyl ester (6l).
Compound 6l was prepared starting from 4l (55 mg, 0.16 mmol). Purification by flash chromatography (n-hexane/EtOAc, 2 : 1; Rf = 0.22) afforded pure 6l (40 mg, 83 %) as a white solid. M.p. = 104.2 ‒ 105.8 °C. 1H NMR (400 MHz, CDCl3) δ = 8.31 (d, J = 9.3 Hz, 1 H), 7.68 (d, J = 8.5 Hz, 1 H), 7.44 ‒ 7.34 (m, 1 H), 4.12 (s, 3 H), 4.00 (s, 3 H), 3.78 ‒ 3.66 (m, 1 H), 3.21 (dd, J = 17.8, 6.8 Hz, 1 H), 2.54 (dd, J = 17.8, 1.3 Hz, 1 H), 1.44 (d, J = 6.9 Hz, 3 H) ppm. 13C NMR (100.4 MHz, CDCl3) δ = 194.1 (s), 171.7 (s), 168.6 (s), 150.8 (s), 140.7 (s), 126.2 (s), 125.2 (d, 2 C), 123.8 (s), 120.6 (s), 118.7 (d), 54.2 (q), 52.3 (q), 49.9 (t), 31.2 (d), 20.9 (q) ppm. MS (ESI) m/z (%): 625 ([2M+Na]+, 100), 302 ([M+1]+, 54). Elemental analysis calcd (%) for C16H15NO5: C 63.78, H 5.05, N 4.65; found: C 63.52, H 4.96, N 4.43.
3-Methyl-1-oxo-2,3-dihydro-1H-cyclopenta[b]indole-4,7-dicarboxylic acid dimethyl ester (6m).

Compound 6m was prepared starting from 4m (135 mg, 0.40 mmol). Purification by flash chromatography (n-hexane/EtOAc, 2 : 1; Rf = 0.24) followed by trituration with Et₂O afforded pure 6m (52 mg, 43 %) as a yellow solid. M.p. = 153.0 – 154.9 °C. ¹H NMR (400 MHz, CDCl₃) δ = 8.45 (s, 1 H), 8.05 (d, J = 8.8 Hz, 1 H), 7.97 (d, J = 8.8 Hz, 1 H), 4.10 (s, 3 H), 3.90 (s, 3 H), 3.79 – 3.56 (m, 1 H), 3.20 (dd, J = 18.0, 6.5 Hz, 1 H), 2.52 (dd, J = 18.0 Hz, 1 H), 1.43 (d, J = 6.6 Hz, 3 H) ppm. ¹³C NMR (100.4 MHz, CDCl₃) δ = 195.7 (s), 172.0 (s), 166.5 (s), 150.5 (s), 143.3 (s), 126.9 (d), 126.5 (s), 124.8 (s), 122.4 (d), 121.7 (s), 115.6 (d), 54.6 (q), 52.0 (q), 49.9 (t), 32.3 (d), 20.7 (q) ppm. MS (ESI) m/z (%): 625 ([2M+Na]⁺, 100), 302 ([M+1]⁺, 54). Elemental analysis calcd (%) for C₁₆H₁₅NO₅: C 63.78, H 5.05, N 4.65; found: C 64.00, H 4.93, N 4.44.

3-Methyl-1-oxo-2,3-dihydro-1H-cyclopenta[b]indole-4,6-dicarboxylic acid dimethyl ester (6n).

Compound 6n was prepared starting from 4n (175 mg, 0.51 mmol). Purification by flash chromatography (n-hexane/EtOAc, 2 : 1; Rf = 0.24) followed by trituration with Et₂O afforded pure 6n (98 mg, 64 %) as a pale yellow solid. M.p. = 128.6 – 130.0 °C. ¹H NMR (400 MHz, CDCl₃) δ = 8.78 (s, 1 H), 8.03 (d, J = 8.2 Hz, 1 H), 7.90 (d, J = 8.2 Hz, 1 H), 4.16 (s, 3 H), 3.95 (s, 3 H), 3.77 (m, 1 H), 3.26 (dd, J = 18.1, 6.6 Hz, 1 H), 2.57 (dd, J = 18.1, 1.0 Hz, 1 H), 1.48 (d, J = 6.9 Hz, 3 H) ppm. ¹³C NMR (100.4 MHz, CDCl₃) δ = 195.7 (s), 172.9 (s), 166.8 (s), 150.6 (s), 140.6 (s), 127.3 (s), 126.0 (d), 125.7 (s), 124.4 (s), 120.4 (d), 117.8 (d), 54.6 (q), 52.4 (q), 49.6 (t), 32.2 (d), 20.6 (q) ppm. MS (ESI) m/z (%): 625 ([2M+Na]⁺, 100), 302 ([M+1]⁺, 54). Elemental analysis calcd (%) for C₁₆H₁₅NO₅: C 63.78, H 5.05, N 4.65; found: C 63.51, H 4.92, N 4.31.

3-Methyl-7-nitro-1-oxo-2,3-dihydro-1H-cyclopenta[b]indole-4-carboxylic acid methyl ester (6o).

Compound 6o was prepared starting from 4o (66 mg, 0.20 mmol). Purification by flash chromatography (n-hexane/EtOAc, 2 : 1; Rf = 0.24) followed by trituration with Et₂O afforded pure 6o (17 mg, 30 %) as a yellow solid. M.p. = 128 °C. ¹H NMR (400 MHz, CDCl₃) δ = 8.76 (d, J = 1.9 Hz, 1 H), 8.33 – 8.23 (m, 2 H), 4.18 (s, 3 H), 3.80 (m, 1 H), 3.30 (dd, J = 18.5, 6.6 Hz, 1 H), 2.62 (d, J = 18.5 Hz, 1 H), 1.50 (d, J = 6.9 Hz, 3 H) ppm. ¹³C NMR (100.4 MHz, CDCl₃) δ = 195.5 (s), 172.9 (s), 144.7 (s), 143.4 (s), 124.7 (s), 122.2 (s), 120.9 (d), 116.8 (d), 116.3 (d), 54.9 (q), 49.6 (t), 32.5 (d), 20.6 (q) ppm. MS (ESI) m/z (%): 598 ([2M+Na]⁺, 40), 289 ([M+1]⁺, 100). Elemental analysis calcd (%) for C₁₄H₁₂N₂O₅: C 58.33, H 4.20, N 9.72; found: C 58.13, H 4.43, N 9.62.
6-Methoxy-3,3-dimethyl-1,2-dioxo-2,3-dihydro-1H-cyclopenta[b]indole-4-carboxylic acid methyl ester (11).

Compound 6j (42 mg, 0.15 mmol) was dissolved in 1,4-dioxane (1.6 mL) and SeO₂ (65 mg, 0.58 mmol) was then added in one portion. The mixture was heated at 100 °C (external) for 23 h; after cooling to room temperature, water (27 mL) was added and the product extracted with EtOAc (3 x 7 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated. Purification of the crude by flash chromatography (n-hexane/EtOAc, 2 : 1; Rᵣ = 0.37) afforded pure 11 (37 mg, 82 %) as a yellow solid. M.p. = 193.4 – 195.1 °C. ¹H NMR (400 MHz, CDCl₃) δ = 7.89 (d, J = 8.4 Hz, 1 H), 7.72 (d, J = 2.0 Hz, 1 H), 7.02 (dd, J = 8.4, 2.0 Hz, 1 H), 4.19 (s, 3 H), 3.90 (s, 3 H), 1.58 (s, 6 H) ppm. ¹³C NMR (100.4 MHz, CDCl₃) δ = 204.7 (s), 177.7 (s), 169.6 (s), 159.9 (s), 150.2 (s), 139.9 (s), 127.4 (s), 122.4 (d), 115.4 (s), 113.2 (d), 101.8 (d), 55.8 (q), 54.9 (q), 45.9 (s), 22.5 (q, 2 C) ppm. MS (ESI) m/z (%) for C₁₆H₁₅NO₅: 681, 683 (2M+Na)⁺, 100, 252 (M+Na)⁺, 180, 320 (M+1)⁺, 10. Elemental analysis calcd (%) for C₁₆H₁₅NO₅: C 63.78, H 5.02, N 4.65; found: C 63.95, H 4.82, N 4.49.

**Bruceolline H (12).**

Compound 11 (25 mg, 0.08 mmol) was suspended in MeOH (1.6 mL) and tert-butylamine (514 µL, 4.9 mmol) was added. The clear solution was heated at 90 °C (external) for 30 min and, after cooling, volatiles were removed under vacuum. The obtained crude intermediate was used in the next step.⁷ ¹H NMR (400 MHz, CD₃OD) δ = 7.82 (d, J = 8.8 Hz, 1 H), 7.05 (d, J = 2.4 Hz, 1 H), 6.95 (dd, J = 8.8, 2.4 Hz, 1 H), 3.88 (s, 3 H), 1.48 (s, 6 H) ppm.

A suspension of the crude intermediate (20 mg, 0.08 mmol) in anhydrous DCM (0.82 mL) was cooled at 0 °C (ice bath) and BBr₃ (31 µL, 0.32 mmol) was dropwise added.¹⁴ The temperature was allowed to warm to room temperature over 15 h. The mixture was cooled again at 0 °C, quenched by anhydrous MeOH (100 µL) and left under stirring for 10 minutes. The ice bath was removed and after 20 min the solvent was removed under vacuum. Purification of the residue by flash chromatography (n-hexane/EtOAc, 1 : 4; Rᵣ = 0.26) afforded 12 that was further triturated with n-hexane. Pure Bruceolline H (12) was so obtain as a yellow solid (18 mg, 93 %). M.p. = 291-292 °C. ¹H NMR (400 MHz, acetone-d₆) δ = 7.70 (d, J = 8.4 Hz, 1 H), 7.05 (d, J = 2.0 Hz, 1 H), 6.90 (dd, J = 8.4, 2.0 Hz, 1 H), 1.48 (s, 6 H) ppm.¹⁰ ¹³C NMR (100.4 MHz, acetone-d₆) δ = 207.0 (s), 175.9 (s), 171.3 (s), 157.2 (s), 142.7 (s), 123.6 (s), 122.8 (d), 115.5 (s), 113.4 (d), 100.1 (d), 42.7 (s), 23.4 (q, 2 C) ppm.¹⁰ ¹H NMR (400 MHz, CD₃OD) δ = 7.73 (J = 8.4 Hz, 1 H), 6.91 (d, J = 2.4 Hz, 1 H), 6.82 (dd, J = 8.4, 2.0 Hz, 1 H), 1.46 (s, 3 H) ppm. ¹³C NMR (100.4 MHz, CD₃OD) δ = 207.4 (s), 176.7 (s), 174.1 (s), 158.2 (s), 143.8 (s), 124.0 (s), 123.6 (d), 115.5 (s), 114.0 (d), 100.3 (d), 43.1 (s), 23.4 (q, 2 C) ppm. MS (ESI) m/z (%): 481 ([2M+Na]⁺, 100), 252 ([M+Na]⁺, 61), 230 ([M+1]⁺, 10). Elemental analysis calcd (%) for C₁₃H₁₁NO₃: C 68.11, H 4.84, N 6.11; found: C 67.87, H 5.24, N 5.74.

**References**


DFT calculations carried out in collaboration with prof. Enrique Gómez - Bengoa (Universidad del País Vasco-Euskal Herriko Unibertsitatea, University of the Basque country).


Chapter 8: Diazetyl-Protected Lactams

The work described in this chapter was accepted for publication as “Oxidation of Diazetyl-protected N-Heterocycles – a New Entry to Functionalized Lactams” in RSC Advances.

8.1. General Approach

The immobilization of δ-valerolactam on the solid-support and the transfer of chemistry developed in the solution (Scheme 1) would allow combinatorial chemistry and thus a rapid synthesis of many piperidine derivatives without tedious and time consuming purifications.


The transformations of chemical functionalities on the solid-support are similar to those in conventional solution-phase chemistry. Usually the choice of the linker plays a pivotal role in the success of the solid-phase organic chemistry and possibility of its application to combinatorial chemistry. Traditionally linkers are designed to release one particular functional group, acting more or less like bulky protecting
groups. These types of linkers could be defined as monofunctional linkers. On the other hand, so-called multifunctional linkers are susceptible to cleavage upon treatment with different building blocks thus offering the opportunity to incorporate additional diversities.

One of the well-known multifunctional linkers is the triazene 4. It has already been used in the transformation of primary amines into different amides, ureas, thioureas and guanidines (Scheme 2). In general, triazenes 4 and 5 are stable toward daylight, oxygen, moisture, transition metal complexes, reducing and oxidizing agents and under neutral and basic conditions. However, in the presence of Brønsted or Lewis acid they will cleave to give the diazonium salt and the corresponding product 6.

\[
N=N^+X^+ + H^+ \rightarrow N=N + R^1 \quad (3) \\
N=N + R^2 \rightarrow R^2NCO, R^2X \\
N=N + R^2NCS \rightarrow R^2NCS, AgNO_3, R^2NH_2 \\
N=N \rightarrow R^2COCl \\
N=N \rightarrow R^2NCO, R^2X \\
N=N \rightarrow R^2NCS \\
N=N \rightarrow H^+ \rightarrow R^2NCO, R^2X \\
N=N \rightarrow R^2NCS \
\]

Scheme 2. Transformations of primary amines into amides, ureas, thioureas and guanidines on diazonium T2 resin.

With the aim to develop the synthesis of piperidine analogues on the diazonium resin in future, within this thesis in the context of my four-month secondment at KIT, the chemistry of diazenyl protected lactams 2 was explored in solution. Thus, a series of lactams 2 were prepared via RuO₄ oxidation of diazenyl protected N-heterocycles.

\[
R^2 \text{Et}, N=O, OMe, Br \\
R^1 = CO_2Et, NO_2 \\
n = 0-4 \\
9 \text{ examples} \quad 10-65\% \
\]

8.2. Oxidation of Diazeneyl-Protected N-Heterocycles

In the past, it has been shown that lactams can be synthesized by the oxidation of corresponding heterocyclic amines protected as amides, carbamates or sulfonamides. In most of the oxidation procedures, ruthenium(VIII) and electrochemical oxidation have been used. In addition, a few N-diazenyl-protected piperidines have been oxidized by KMnO₄ producing the corresponding lactams in very low yield (up to 25%). The lack of the tools for the latter conversion and the fact that the diazenyl protected lactams are unexplored class of compounds, prompted us to search for novel oxidation protocols.

![Scheme 4](image)

Scheme 4. Synthesis of N-diazenyl protected piperidine 1a. Reagents and conditions: (a) BF₃·Et₂O, isopentyl nitrite, THF, 0 °C, 2 h; (b) piperidine, Et₃N, THF, 0 °C, 2 h (85 %).

Aiming for the identification of an efficient oxidation strategy, N-diazenyl protected piperidine 1a was chosen as a model system. The synthesis of this model compound was carried out by converting the 4-amino-benzoic acid ethyl ester (3a) into the corresponding diazonium salt 4a which reacted with piperidine to give triazene 1a in 85 % after chromatography (Scheme 4).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pre-catalyst</th>
<th>Oxidant</th>
<th>Solvent</th>
<th>2a Time</th>
<th>Temp</th>
<th>Yield (%)[^c]</th>
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<tr>
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<td>RuCl₂·H₂O</td>
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<td>NaI₂</td>
<td>2.5 eq</td>
<td>2/2/3</td>
<td>39 %</td>
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<td>4 eq</td>
<td>TBHP</td>
<td>3 eq</td>
<td>ACN</td>
<td>19 %</td>
</tr>
<tr>
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<td>DIB</td>
<td>4 eq</td>
<td>H₂O₂</td>
<td>3 eq</td>
<td>ACN</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Rh₃(OAc)₃</td>
<td>5 eq</td>
<td>T-HYDRO</td>
<td>20 eq</td>
<td>ACN</td>
<td>22 %</td>
</tr>
<tr>
<td>5</td>
<td>Rh₃(OAc)₃</td>
<td>5 eq</td>
<td>T-HYDRO</td>
<td>20 eq</td>
<td>ACN</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Co(OAc)₂</td>
<td>5 eq</td>
<td>-</td>
<td>-</td>
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<td>-</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>-</td>
<td>CrO₃·DMP</td>
<td>20 eq</td>
<td>DCM</td>
<td>n.d.</td>
</tr>
<tr>
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<td>30 %</td>
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<td>5 eq</td>
<td>DCM</td>
<td>44 %</td>
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<tr>
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<td>30 %</td>
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<tr>
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<td>30 %</td>
<td>NaI₂</td>
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<tr>
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<td>NaI₂</td>
<td>5 eq</td>
<td>CCl₄/ACN/H₂O 2/2/3</td>
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<tr>
<td>14</td>
<td>RuCl₂·H₂O</td>
<td>30 %</td>
<td>NaI₂</td>
<td>5 eq</td>
<td>CCl₄/ACN/buffer (pH = 8) 2/2/3</td>
<td>2 h</td>
</tr>
</tbody>
</table>

[^a] Reaction carried out on 0.2 mmol scale.[^b] Yield after chromatography.[^c] Reaction carried out on 2 mmol scale.
Triazene 1a was subjected to the oxidation based on formerly published oxidation strategies (Table 1). In metal-free DIB/TBHP oxidation protocol, active species bis(tert-butylperoxy)iodobenzene generated in situ by the reaction between diacetoxyiodobenzene and tert-butyl hydroperoxide was also able to activate the C–H methylene bond next to the nitrogen atom giving the desired product (2a) in 19% yield (entry 2). Oxidation catalyzed by Rh₂(cap)₄/T-HYDRO system led to the formation of desired N-diazenyl protected lactam in 22% yield while Rh₂(OAc)₂ under the same reaction conditions was not able to catalyze the reaction. N-Hydroxyphthalimide combined with cobalt salt was ineffective catalyst, too (entry 6). On the other hand, with the CrO₃·3,5-dimethylpyrazole complex we were able to carry out the oxidation of triazene 1a but it was not possible to get rid of 3,5-dimethylpyrazole after two consecutive chromatographies (entry 7). Among tested methods, RuO₄ generated in situ from RuCl₃·nH₂O and NaIO₄ in CCl₄/ACN/H₂O was the most efficient catalyst for the oxidation of triazene 1a (entry 1) and therefore it was chosen for further optimization. The increase of the catalyst loading to 30% and oxidant to 5 eq resulted in yield of 44% (entry 8). When the reaction was carried out in less toxic solvent such as DCM, CHCl₃ and EtOAc product 2a was obtained in low yields (entries 9-12). The use of RuO₂ did not affect the outcome of the reaction (entry 13). The yield of 2a was further improved to 52% by the use of phosphate buffer (entry 14).

![Scheme 5. Synthesis of N-diazenyl protected heterocycles. Reagents and conditions: (a) BF₃·Et₂O, isopentyl nitrite, THF, 0 °C, 2 h; (b) piperidine, Et₃N, THF, 0 °C – 25 °C, 2 h (85%).](image-url)
Triazenes 1a-i were oxidized under optimized reaction conditions to lactams 2a-i in yields ranging from 28 to 65%, i.e. much higher than those reported with KMnO₄. All reactions were carried out on 1 mmol scale, except the oxidation of 1a which was repeated on a 2 mmol scale (Scheme 6).

The electronic properties of the aryl ring influenced the outcome of the reaction. The yields were diminished when the aryl ring was bearing electron-donating substituents making the triazene linker more electron-rich and therefore more susceptible to the oxidation.

In addition, N-diazenyl protected tetrahydroisoquinoline (1f), pyrrolidine (1h) and azepane (1i) were all successfully oxidized into corresponding lactams in good yields. Only oxidation of azetidine derivative 1g proceeded in low yield.

Figure 4. X-Ray structure of triazene 1h.

Scheme 6. Oxidation of 1a-i to N-diazenyl-protected lactams 2a-i. Notes: [a] Reaction carried out on 2 mmol scale; [b] Reaction carried out on 1 mmol scale.
Under the herein described conditions, the obtained arenes are not degraded, and also the triazene linker was not oxidized. The structures of products 2a-2i were confirmed by standard techniques while the X-ray structure of compound 2a revealed that those lactams crystallize in s-trans conformation. In addition all products were stable at room temperature. At the time of writing this thesis, they have been kept at 4 °C for more than 14 months without decomposition.

Although the N-diazenyl protected lactams are obtained in moderate yields it is worth to mention that the herein described RuO₄ mediated oxidation of triazenes is the first strategy for the synthesis of lactams with diazenyl unit from commercially available and very cheap starting materials. The fact that the functionalized lactams are highly important class of heterocycles in both material science and medicinal chemistry makes N-diazenyl protected lactams promising building blocks in the synthesis of novel materials as well as biologically active compounds. In addition, hydrolysis of ester group under basic conditions allows the anchoring on the solid support.

8.3. Transformations of N-Diazenyl Protected Lactams

As a preliminary investigation the alkylation of lactam 2d was carried out under strong basic conditions, using LiHMDS as the base and Mel as the electrophile (Scheme 7). Gratifyingly, the reaction provided the 3-methyl substituted lactam 7 in good yield (59 %) without decomposition or degradation of the protecting group.

![Scheme 7. Alkylation of N-diazenyl-protected lactam 2d. Reagents and conditions: (a) LiHMDS, THF, -78 °C; (b) Mel, -78 – 25 °C (59 %).](image_url)

With the aim to extend the utility of these compounds for the preparation of N-heterocyclic libraries on the solid support in combinatorial mode, we explored the possibility of forming new C-C bonds by Pd(0)-catalyzed cross coupling reactions. Therefore N-diazenyl protected valerolactam 2a was transformed into enol phosphate 8 in quantitative yield and subjected to Pd-catalyzed methoxycarbonylation and Suzuki coupling under the conditions previously optimized for N-Ts and N-CO₂R (R = Me, CH₂Ph, C(CH₃)₃)² but to no avail. In all cases, phosphate was consumed in less than 2 h but the ¹H NMR analysis revealed complex crude without signals related to the desired products. All attempts to isolate and identify formed side-products failed. At this stage, due to the completion of my KIT secondement, no further experiments were performed.
Scheme 8. Attempts of Pd-catalyzed methoxycarbonylation and Suzuki coupling. Reagents and conditions: (a) KHMDS, THF, -78 °C, 1.5 h, then (PhO)2POCl, -78 - 0 °C; (b) phenylboronic acid, 5% Pd(Ph3P)4, Na2CO3, DMF/H2O, 40 °C, 2 h; (c) phenylboronic acid, 5% (Ph3P)PdCl2, 2 M Na2CO3/THF, 40 °C, 2 h; (d) 10 % Pd(OAc)2, 20 % Ph3P, Et3N, MeOH/DMF, 40 °C, 1.5 h.

8.4. Experimental Part

General information

1H and 13C NMR spectra were recorded on Bruker-AC-250 instrument using CDCl3 as solvent. The coupling constant J was assigned in Hertz (Hz). MS (EI) (electron impact mass spectrometry) and EI-HRMS: Finnigan MAT 90 (70 eV). The molecular fragments are quoted as the relation between mass and charge (m/z), the intensities as a percentage value relative to the intensity of the base signal (100%). IR spectra of solids were recorded in KBr, and of oils as thin films on KBr. The deposit of the absorption band is given in wave numbers in cm⁻¹. Melting points were recorded on a Buchi-540 melting point apparatus and are uncorrected. Chromatographic separations were performed under pressure on silica gel by flash-column techniques; Rf values refer to TLC carried out on 0.25-mm silica gel plates (Merck F254), with the same eluent as indicated for the column chromatography. Solvents and chemicals used for reactions were purchased from commercial suppliers. Solvents and chemicals were used without further purification.

General procedure for the synthesis of triazenes (1).

Triazenes were prepared under basic conditions in reaction between diazonium salt and cyclic amine according to the known procedure.17 A solution of aniline (1 mmol) in DCM (4 mL) was rapidly added to the solution of BF3·Et2O (2 mmol) in THF (8 mL) at 0 °C. Few minutes later, isopentyl nitrite (2 mmol) was slowly added to the reaction mixture and the ice bath was removed. The reaction mixture was stirred at room temperature for 2 h. Formed precipitate was collected by filtration, washed with Et2O and the obtained diazonium salt was used in the next step.
A solution of cyclic amine (2 mmol) and Et₃N (4 mmol) in THF (4 mL) was cooled by ice bath and the diazonium salt (1 mmol) was added portion-wise. The ice bath was removed and the reaction was stirred at room temperature for 30 min. Water (5 mL) was added and the product was extracted with Et₂O (3 x 5 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude was purified by column chromatography.

![Chemical structure](image)

4-(Piperidin-1-ylazo)-benzoic acid ethyl ester (1a).

Compound 1a was synthesized according above described procedure from 4-aminobenzoic acid ethyl ester (3 mmol) and piperidine (6 mmol). After chromatography (cyclohexane/EtOAc = 10 : 1 + 1 % Et₃N) pure 1a (675 mg, 85 %) was obtained as a yellow solid. - Rf (cyclohexane/EtOAc = 10 : 1) = 0.21. - m.p. = 128.4 - 129.5 °C. - ¹H NMR (250 MHz, CDCl₃) δ = 8.01 (d, J = 8.7 Hz, 2 H), 7.45 (d, J = 8.7 Hz, 2 H), 4.36 (q, J = 7.7 Hz, 2 H), 3.90 - 3.78 (m, 4 H), 1.81 - 1.67 (m, 6 H), 1.39 (t, J = 7.7 Hz, 3 H) ppm. - ¹³C NMR (63 MHz, CDCl₃) δ = 167.7, 155.4, 131.6, 128.3, 121.2, 61.7, 27.9, 26.4, 25.3, 15.4 ppm. MS (ESI) m/z (%): 543 (100) [2M+Na]⁺, 284 (11) [M+Na]⁺, 262 (30) [M+1]⁺. - EA (C₁₄H₁₉N₃O₂): calc. C 64.35, H 7.33, N 16.08; found C 64.27, H 7.12, N 15.96.

(4-Bromo-phenyl)-piperidin-1-yl-diazene (1b).

Compound 1b (291 mg, 72 %) was obtained as a brown solid. - Rf (cyclohexane/EtOAc = 10 : 1) = 0.27. - m.p. = 55.9 - 56.6 °C. - ¹H NMR (250 MHz, CDCl₃) δ = 7.46 - 7.41 (m, 2 H), 7.33 - 7.28 (m, 2 H), 3.82 - 3.74 (m, 4 H), 1.76 - 1.65 (m, 6 H) ppm. - ¹³C NMR (63 MHz, CDCl₃) δ = 150.1, 132.1, 122.3, 118.7, 27.3, 25.5, 24.6 ppm. - MS (EI), m/z (%): 267 (18) [C₁₁H₇BrN₃]⁺, 183 (46) [C₆H₄BrN₃]⁺, 155 (100) [C₆H₄Br]⁺. - HRMS (C₁₁H₇BrN₃): calc. 267.0366, found 267.0364. - IR (ATR, ν): 2931, 2849, 1747, 1426, 1394, 1349, 1295, 1258, 1216, 1184, 1106, 1000, 926, 888, 828, 704, 628, 578, 544, 517, 478 cm⁻¹. - EA (C₁₁H₁₄BrN₃): calc. C 42.97, H 5.26, N 15.67; found C 42.95, H 5.26, N 15.46.

(4-Nitro-phenyl)-piperidin-1-yl-diazene (1c).³

Compound 1c was synthesized according above described procedure from 4-nitroaniline (1.5 mmol) and piperidine (3 mmol). After chromatography (cyclohexane/EtOAc = 10 : 1 + 1 % Et₃N), pure product 1c (234 mg, 67 %) was obtained as an orange solid. - Rf (cyclohexane/EtOAc = 10 : 1) = 0.27. - m.p. = 89.3 - 91.6 °C. - ¹H NMR (300 MHz, CDCl₃) δ = 8.20 (d, J = 9.1 Hz, 2 H), 7.51 (d, J = 9.1 Hz, 2 H), 4.00 - 3.80 (m, 4 H), 1.87 - 1.65 (m, 6 H) ppm. - ¹³C NMR (75 MHz, CDCl₃) δ = 156.1, 144.6, 124.8, 120.4, 53.5, 43.8, 26.4, 24.5, 24.1 ppm. - HRMS (C₁₁H₁₄N₄O₂): calc. 234.1111, found. 234.1112. - IR (ATR, ν): 2947, 2858, 1585, 1508, 1401, 1317, 1287, 1220, 1186, 1101, 1015, 992, 850, 753, 692, 564, 515, 492 cm⁻¹. - EA (C₁₁H₁₄N₄O₂): calc. C 56.40, H 6.02, N 23.92; found C 56.33, H 6.03, N 23.85.
(4-Methoxy-phenyl)-piperidin-1-yl-diazene (1d). Compound 1d was synthesized according described procedure from 4-methoxyaniline (1.5 mmol) and piperidine (3 mmol). After chromatography (cyclohexane/EtOAc = 10 : 1 + 1 % Et3N), pure 1d (271 mg, 83 %) was obtained as an orange solid. - IR (ATR, ν): 2960, 1700, 1601, 1433, 1407, 1365, 1336, 1268, 1176, 1154, 1081, 1028, 954, 939, 885 cm⁻¹. - MS (EI), m/z (%): 309 (26) [M⁺].

4-(1,4-Dioxo-8-aza-spiro[4.5]dec-8-ylazo)-benzoic acid ethyl ester (1e). Compound 1e was synthesized according described procedure from 4-aminobenzoic acid ethyl ester (2 mmol) and 1,4-dioxo-8-aza-spiro[4.5]decane (4 mmol). After chromatography (cyclohexane/EtOAc = 10 : 1 + 1 % Et3N), pure product 1e (350 mg, 55 %) was obtained as an orange solid. - IR (ATR, ν): 2960, 1700, 1601, 1433, 1407, 1365, 1336, 1268, 1176, 1154, 1081, 1028, 942, 911, 856, 772, 700, 659, 604, 559, 528, 493, 460 cm⁻¹. - EA (C₁₃H₁₂N₃O₄): calc. C 60.14, H 6.49, N 13.20.

4-(3,4-Dihydro-1H-isoquinolin-2-ylazo)-benzoic acid ethyl ester (1f). Compound 1f was synthesized according described procedure from 4-aminobenzoic acid ethyl ester (2 mmol) and 1,2,3,4-tetrahydroisoquinoline (4 mmol). After chromatography (cyclohexane/EtOAc = 20 : 1 + 1 % Et3N), pure product 1f (490 mg, 80 %) was obtained as an orange solid. - IR (ATR, ν): 2983, 1703, 1598, 1498, 1454, 1422, 1400, 1364, 1345, 1306, 1267, 1205.3, 1157, 1099, 1042, 1012, 942, 914, 852, 773, 750, 702, 587, 560, 524, 484, 436 cm⁻¹. - EA (C₁₈H₁₉N₃O₂): calc. C 69.88, H 6.19, N 13.58; found C 69.80, H 6.20, N 13.37.
4-(Azetidin-1-ylazo)-benzoic acid ethyl ester (1g).
Di azonium salt, synthesized according above described procedure from 4-aminobenzoic acid ethyl ester (1 mmol), was slowly added to the cold solution of azetidin hydrochloride (2 mmol) in NaOH (1 M, 5 mL). The product was extracted with Et2O (3 x 5 mL) and combined organic layers were dried over Na2SO4, filtered and concentrated. After chromatography (cyclohexane/EtOAc = 10 : 1 + 1 % Et3N) pure 3a (145 mg, 62 %) was obtained as a yellow solid. - Rf (cyclohexane/EtOAc = 10 : 1) = 0.36. - m.p. = 54.1 °C. - 1H NMR (250 MHz, CDCl3) δ = 7.95 (d, J = 8.6 Hz, 2 H), 7.38 (d, J = 8.6 Hz, 2 H), 4.50 – 4.11 (m, 6 H), 2.47 – 2.16 (m, 2 H), 1.32 (t, J = 7.1 Hz, 3 H) ppm. - 13C NMR (63 MHz, CDCl3) δ = 166.6, 154.2, 130.7, 120.3, 60.5, 55.7, 15.7, 14.5 ppm. MS (EI), m/z (%): 233 (30) [M]+, 188 (9) [C9H15NO]+, 177 (40) [C9H8NO]+. - HRMS (C12H15N3O2): calc. 233.1159, found 233.1160. - IR (ATR, ν): 2976, 1705, 1596, 1455, 1370, 1242, 1212, 1137, 1096, 1023, 860, 773, 699, 548, 522, 503, 424 cm⁻¹. - EA (C12H15N3O2): calc. C 61.79, H 6.48, N 18.01; found C 61.76, H 6.38, N 17.76.

4-(Pyrrolidin-1-ylazo)-benzoic acid ethyl ester (1h). 19
Compound 1h was synthesized according above described procedure from 4-aminobenzoic acid ethyl ester (2 mmol) and pyrrolidine (4 mmol). After chromatography (cyclohexane/EtOAc = 20 : 1 + 1 % Et3N), pure 1h (384 mg, 78 %) was obtained in form of yellow crystals. - Rf (cyclohexane/EtOAc = 20 : 1) = 0.34. - m.p. = 65.2 – 65.4°C. - 1H NMR (300 MHz, CDCl3) δ = 8.00 (d, J = 8.6 Hz, 2 H), 7.44 (d, J = 8.6 Hz, 2 H), 4.35 (q, J = 7.1 Hz, 2 H), 4.09 – 3.84 (m, 2 H), 3.84 – 3.58 (m, 2 H), 2.16 – 1.93 (m, 4 H), 1.39 (t, J = 7.1 Hz, 3 H) ppm. - 13C NMR (75 MHz, CDCl3) δ = 166.7, 154.8, 130.7, 126.8, 120.3, 60.5, 23.7, 14.4 ppm. - HRMS (C13H17N3O2): calc. 247.1315, found 247.1317. - IR (ATR, ν): 2973, 2875, 1707, 1597, 1504, 1476, 1451, 1421, 1388, 1341, 1312, 1260, 1222, 1148, 1099, 1021, 857, 772, 698, 611, 550, 524, 500, 416 cm⁻¹. - EA (C13H17N3O2): calc. C 63.14, H 6.93, N 16.99; found C 63.21, H 6.92, N 16.91.

4-(Azepan-1-ylazo)-benzoic acid ethyl ester (1i).
Compound 1i was synthesized according described procedure from 4-aminobenzoic acid ethyl ester (2 mmol) and hexamethyleneimine (4 mmol). After chromatography (cyclohexane/EtOAc = 20 : 1 + 1 % Et3N), pure product 1i (402 mg, 73 %) was obtained as a red solid. - Rf (cyclohexane/EtOAc = 20 : 1) = 0.24. - m.p. = 60.2 – 62.1 °C. - 1H NMR (300 MHz, CDCl3) δ = 8.00 (d, J = 8.6 Hz, 2 H), 7.44 (d, J = 8.6 Hz, 2 H), 4.35 (q, J = 7.1 Hz, 2 H), 4.01 – 3.98 (m, 2 H), 3.83 – 3.79 (m, 2 H), 1.94 – 1.80 (m, 4 H), 1.62 – 1.53 (m, 4 H), 1.38 (t, J = 7.1 Hz, 3 H) ppm. - 13C NMR (75 MHz, CDCl3) δ = 167.2, 155.0, 130.3, 126.2, 119.6, 60.5, 54.6, 48.9, 29.9, 28.7, 28.4, 25.1, 14.2 ppm. - MS (m/z, %): 275 (18) [M]+, 149 (100) [C9H8O2]+. - HRMS (C15H21N3O2): calc. 275.1628, found 275.1628. - IR (ATR, ν): 2989, 2930, 2854, 1709, 1599, 1444, 1389, 1341, 1305, 1268, 1211, 1189, 1147, 1097, 1020, 990, 894, 861, 847, 798, 772, 734, 701, 557, 526, 501, 437, 394 cm⁻¹. - EA (C15H21N3O2): calc. C 65.43, H 7.69, N
General procedure for the oxidation of triazenes into N-diazenyl protected lactams (2).

To a stirred mixture of phosphate buffer (pH = 8, c = 0.3 M)/CCl₄/ACN = 3 : 2 : 2 (10 mL) were added NaIO₄ (5 mmol) and RuCl₃·H₂O (0.3 mmol). After 5 minutes the substrate (1 mmol) was slowly added and reaction mixture was left to stir at room temperature and the progress of the reaction was monitored by TLC. Isopropanol was added and formed precipitate was removed by filtration through the Celite pad (washed with 10 mL of DCM). Mother liquid was washed with water (10 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated. The crude was purified by flash chromatography.

15.26; found C 65.37, H 7.59, N 14.62.

4-(2-Oxo-piperidin-1-ylazo)-benzoic acid ethyl ester (2a).

Compound 2a was synthesized following above described procedure from corresponding triazene 1a (1.91 mmol). After chromatography (cyclohexane/EtOAc = 4 : 1 + 1 % Et₃N), pure product 2a (320 mg, 61 %) was obtained as a yellow solid. - Rₗ(cyclohexane/ EtOAc = 4 : 1) = 0.19. - m.p. = 128.4 – 129.5 °C. - ¹H NMR (300 MHz, CDCl₃) δ = 8.09 (d, J = 8.6 Hz, 2 H), 7.70 (d, J = 8.6 Hz, 2 H), 4.38 (q, J = 7.1 Hz, 2 H), 3.92 (t, J = 6.2 Hz, 2 H), 2.77 (t, J = 6.5 Hz, 2 H), 2.11 – 1.97 (m, 2 H), 1.92 – 1.82 (m, 2 H), 1.40 (t, J = 7.1 Hz, 3 H) ppm. - ¹³C NMR (75 MHz, CDCl₃) δ = 169.2, 166.3, 151.7, 130.6, 122.5, 122.3, 61.1, 34.1, 22.5, 20.4, 14.2 ppm. MS m/z, (%): 275 (26) [M]+, 177 (79) [(C₉H₉N₂O₃)]+, 164 (100) [(C₉H₈O₃)]+. - HRMS (C₁₄H₁₉N₃O₂): calc. 275.1266; found 275.1264.

- IR (ATR, ν): 2944, 1688, 1602, 1463, 1378, 1345, 1273, 1190, 1151, 1125, 1107, 1083, 1066, 1022, 987, 907, 864, 821, 770, 743, 698, 647, 548, 477, 383 cm⁻¹. EA (C₁₄H₁₇N₃O₃): calc. C 61.08, H 6.22, N 15.26; found C 60.05, H 6.17, N 15.13.

1-(4-Bromo-phenyl-diazenyl)-piperidin-2-one (2b).

Compound 2b was synthesized following above described procedure from corresponding triazene 1b (1 mmol). After chromatography (cyclohexane/ EtOAc = 4 : 1 + 1 % Et₃N), pure product 2b (70 mg, 25 %) was obtained. Recrystallization from DCM/cyclohexane gave brownish crystals. - Rₗ(cyclohexane/EtOAc = 4 : 1) = 0.19. - m.p. = 59.7 – 60.2 °C. - ¹H NMR (300 MHz, CDCl₃) δ = 7.66 – 7.45 (m, 4 H), 3.89 (t, J = 6.3 Hz, 2 H), 2.75 (t, J = 6.6 Hz, 2 H), 2.05 – 1.93 (m, 2 H), 1.95 – 1.79 (m, 2 H) ppm. - ¹³C NMR (75 MHz, CDCl₃) δ = 168.6, 147.5, 132.3, 124.3, 123.17, 45.3, 34.2, 22.4, 20.3 ppm. MS m/z, (%): 281 (14) [C₁₁H₁₂Br₇N₃O⁺], 183 (47) [C₆H₆Br₇N₂⁺], 155 (100) [C₆H₆Br⁺]. - HRMS (C₁₁H₁₂N₃O⁷⁺Br): calc. 281.0158, found 281.0160. - IR (ATR, ν): 2952, 2881, 1683, 1571, 1480, 1457, 1398, 1377, 1295, 1191, 1172, 1146, 1064, 1006, 988, 910, 827, 705, 659, 639, 546, 522, 473, 385 cm⁻¹. EA (C₁₁H₁₂BrN₃O): calc. C 46.83, H 4.29, Br 28.32, N 14.89; found C 46.50, H 4.28, N 14.17.
1-(4-Nitro-phenyl-diazenyl)-piperidin-2-one (2c).
Compound 2c was synthesized following above described procedure from corresponding triazene 1c (1 mmol). After chromatography (cyclohexane/EtOAc = 4 : 1 + 1 % Et$_3$N), pure product 2c (114 mg, 49 %) was obtained as a yellow solid. - R$_f$ (cyclohexane/EtOAc = 4 : 1) = 0.19. - m.p. = 153.3 – 154.1 °C. - $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ = 8.29 (d, $J$ = 8.8 Hz, 2 H), 7.79 (d, $J$ = 8.8 Hz, 2 H), 3.95 (t, $J$ = 6.3 Hz, 2 H), 2.80 (t, $J$ = 6.5 Hz, 2 H), 2.14 – 2.00 (m, 2 H), 2.00 – 1.85 (m, 2 H) ppm. - $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ = 169.2, 152.9, 147.5, 124.6, 123.1, 45.9, 33.9, 21.7, 19.6 ppm. - MS (ESI) m/z, (%): 271 (44) [M+Na]$^+$, 519 (100) [2M+Na]$^++$. - HRMS (C$_{11}$H$_{12}$N$_4$O$_3$): calc. 248.0904 found 248.0902. - IR (ATR, $\nu$): 3103, 2952, 2879, 1684, 1611, 1526, 1454, 1376, 1340, 1190, 1170, 1149, 1110, 1082, 1008, 986, 912, 865, 847, 755, 685, 662, 555, 520, 494, 385 cm$^{-1}$. - EA (C$_{11}$H$_{12}$N$_4$O$_3$): calc. C 53.22, H 4.87, N 22.57; found C 52.87, H 4.91, N 22.33.

1-(4-Methoxy-phenyl-diazenyl)-piperidin-2-one (2d).
Compound 2d was synthesized following above described procedure from corresponding triazene 1d (1 mmol). After chromatography (cyclohexane/EtOAc = 4 : 1 + 1 % Et$_3$N), pure product 2d (88 mg, 38 %) was obtained as a brown solid. - R$_f$ (cyclohexane/EtOAc = 4 : 1) = 0.20. - m.p. = 103.8 – 104.5 °C. - $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ = 7.68 (m, 2 H), 6.92 (m, 2 H), 6.94 – 3.84 (m, 2 H), 3.83 (s, 3 H), 2.79 – 2.71 (m, 2 H), 2.04 – 1.95 (m, 2 H), 1.92 – 1.83 (m, 2 H) ppm. - $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ = 168.5, 160.5, 141.8, 123.0, 113.8, 54.4, 44.3, 33.3, 21.8, 19.9 ppm. MS m/z, (%): 233 (18) [M]$^+$, 135 (52) [C$_{12}$H$_{10}$N$_2$O]$.^+$, 107 (100) [C$_7$H$_7$O]$^+$$. - HRMS (C$_{12}$H$_{15}$N$_3$O$_2$): calc. 233.1033, found. 233.1032. - IR (ATR, $\nu$): 2953, 1690, 1597, 1503, 1476, 1452, 1382, 1296, 1259, 1188, 1143, 1068, 1024, 986, 906, 834, 792, 713, 635, 600, 571, 518, 472, 411 cm$^{-1}$. - EA (C$_{12}$H$_{15}$N$_3$O$_2$): calc. C 61.79, H 6.48, N 18.01; found C 61.21, H 6.48, N 18.24.

4-(7-Oxo-1,4-dioxo-8-aza-spiro[4.5]dec-8-ylazo)-benzoic acid ethyl ester (2e).
Compound 2e was synthesized following above described procedure from corresponding triazene 1e (1 mmol). After chromatography (cyclohexane/EtOAc = 4 : 1 + 1 % Et$_3$N), pure product 2e (196 mg, 59 %) was obtained as a yellow solid. - R$_f$ (cyclohexane/EtOAc) = 0.19. - m.p. = 121.2 – 122.3 °C. - $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ = 8.04 (d, $J$ = 8.6 Hz, 2 H), 7.65 (d, $J$ = 8.6 Hz, 2 H), 4.33 (q, $J$ = 7.1 Hz, 2 H), 4.11 – 3.71 (m, 6 H), 2.92 (s, 2 H), 2.12 (t, $J$ = 6.5 Hz, 2 H), 1.34 (t, $J$ = 7.1 Hz, 3 H) ppm. - $^{13}$C NMR (63 MHz, CDCl$_3$) $\delta$ = 167.0, 166.0, 152.1, 131.2, 130.5, 122.5, 105.3, 65.06, 61.2, 44.0, 41.7, 31.4, 14.4 ppm. - MS (EI), m/z (%): 333 (11) [M]$^+$, 177 (58) [C$_9$H$_8$N$_2$O]$^+$, 149 (100) [C$_9$H$_8$O$_2$]$^+$$. - HRMS (C$_{16}$H$_{14}$N$_2$O$_3$): calc. 333.1319, found 333.1320. - IR (ATR, $\nu$): 2900, 1694, 1604, 1465, 1368, 1269, 1173, 1131, 1094, 1057, 1000, 963, 927, 866, 774, 718, 696, 670, 568, 523, 503, 423 cm$^{-1}$. - EA (C$_{16}$H$_{14}$N$_2$O$_3$) calc. C 57.65, H 5.75, N 12.61; found C 57.76, H 5.77, N 12.37.
4-(1-Oxo-3,4-dihydro-1H-isooquinolin-2-ylazo)-benzoic acid ethyl ester (2f).

Compound 2f was synthesized following above described procedure from corresponding triazene 1f (1 mmol). After chromatography (cyclohexane/EtOAc = 4 : 1 + 1 % Et3N), pure product 1f (149 mg, 47 %) was obtained as a yellow solid. - Rf (cyclohexane/EtOAc = 4 : 1) = 0.20. - m.p. = 137.2 – 138.0 °C. - 1H NMR (300 MHz, CDCl3) δ = 8.22 (d, J = 7.5 Hz, 1 H), 8.07 (d, J = 8.5 Hz, 2 H), 7.73 (d, J = 8.5 Hz, 2 H), 7.49 (t, J = 7.5 Hz, 1 H), 7.36 (t, J = 7.5 Hz, 1 H), 7.25 (d, J = 7.5 Hz, 1 H), 4.38 – 4.26 (m, 4 H), 3.14 (t, J = 6.5 Hz, 2 H), 1.35 (t, J = 7.1 Hz, 3 H) ppm. - 13C NMR (75 MHz, CDCl3) δ = 165.8, 162.7, 151.8, 138.7, 133.4, 130.8, 130.6, 129.5, 127.5, 127.3, 123.4, 122.4, 61.1, 41.5, 27.5, 16.2, 13.9 ppm. - MS (EI), m/z (%): 323 (17) [M]+, 177 (73) [C9H8N2O]+, 149 (100) [C9H9O2]+. - HRMS (C18H17N3O3): calc. 323.1264, found 323.1263.

4-(2-Oxo-azetidin-1-ylazo)-benzoic acid ethyl ester (2g).

Compound 2g was synthesized according above described procedure from corresponding triazene 1g (1 mmol). After chromatography (cyclohexane/EtOAc = 4 : 1 + 1 % Et3N), pure product 2g (12.8 mg, 10 %) was obtained as a brown solid. - Rf (cyclohexane/EtOAc = 4 : 1) = 0.22. - m.p. = 97.6 – 98.2 °C. - 1H NMR (250 MHz, CDCl3) δ = 8.07 (d, J = 9.8 Hz, 2 H), 7.66 (d, J = 9.8 Hz, 2 H), 4.35 (q, J = 7.1 Hz, 2 H), 3.86 (t, J = 5.2 Hz, 2 H), 3.17 – 2.91 (t, J = 5.2 Hz, 2 H), 1.36 (t, J = 7.1 Hz, 3 H) ppm. - MS (EI), m/z (%): 247 (27) [M]+, 177 (33) [C9H8N2O]+, 149 (100) [C9H9O2]+. - HRMS (C12H13N3O3): calc. 247.0951, found 247.0950. - IR (ATR, ν): 2977, 1773, 1706, 1601, 1453, 1408, 1368, 1322, 1273, 1242, 1184, 1098, 1044, 870, 774, 698, 541, 525, 463, 393 cm⁻¹. - EA (C12H13N3O3) calc. C 58.29, H 5.30, N 16.99; found. C 58.39, H 5.54, N 17.12.

4-(2-Oxo-pyrrolidin-1-ylazo)-benzoic acid ethyl ester (2h).

Compound 2h was synthesized according above described procedure from corresponding triazene 1h (1 mmol). After chromatography (cyclohexane/EtOAc = 4 : 1 + 1 % Et3N), pure product 1h (169 mg, 65 %) was obtained as a pale orange solid. - Rf (cyclohexane/EtOAc = 4 : 1) = 0.32. - m.p. = 127.9 – 128.8 °C. - 1H NMR (300 MHz, CDCl3) δ = 8.03 (d, J = 8.5 Hz, 2 H), 7.66 (d, J = 8.5 Hz, 2 H), 4.32 (q, J = 7.1 Hz, 2 H), 3.98 – 3.81 (m, 2 H), 2.67 (t, J = 8.1 Hz, 2 H), 2.25 – 2.06 (m, 2 H), 1.34 (t, J = 7.1 Hz, 3 H) ppm. - 13C NMR (75 MHz, CDCl3) δ = 172.9, 166.0, 152.0, 131.3, 130.3, 122.1, 61.1, 44.4, 31.1, 16.2, 13.9 ppm. - MS (EI), m/z (%): 261 (28) [M]+, 177 (50) [C9H9N2O]+, 149 (100) [C9H9O2]+. - HRMS (C12H13N3O3): calc. 261.1108, found 261.1109. - IR (ATR, ν): 2986, 1734, 1706, 1601, 1456, 1404, 1352, 1317, 1273, 1229, 1151, 1125, 1097, 1019, 867, 775, 695, 645, 559, 503, 476, 396 cm⁻¹. - EA (C12H13N3O3) calc. C 59.76, H 5.79, N 16.08; found C 59.76, H 5.78, N 15.84.
4-(2-Oxo-azepan-1-ylazo)-benzoic acid ethyl ester (2i).

Compound 2i was synthesized following above described procedure from corresponding triazene 1i (1 mmol). After chromatography (cyclohexane/EtOAc = 4 : 1 + 1 % Et$_2$N), pure product 2i (134 mg, 47 %) was obtained as an orange oil. - R$_r$ (cyclohexane/EtOAc = 4:1) = 0.32. - $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ = 8.03 (d, $J$ = 8.5 Hz, 2 H), 7.65 (d, $J$ = 8.5 Hz, 2 H), 4.35 - 4.25 (m, 4 H), 2.80 - 2.77 (m, 2 H), 1.88 - 1.65 (m, 4 H), 1.87 - 1.57 (s, 2 H), 1.34 (t, $J$ = 7.1 Hz, 3 H) ppm. - $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ = 174.2, 165.9, 151.3, 130.8, 130.4, 122.2, 60.9, 41.5, 37.8, 29.5, 27.3, 23.7, 14.4 ppm. - MS (EI), m/z (%): 289 (23) [M$^+$]*, 177 (57) [C$_6$H$_5$N$_2$O]$, ^+$, 149 (100) [C$_6$H$_3$O$_2$]$^+$. - HRMS (C$_{15}$H$_{18}$N$_2$O$_2$): calc. 289.1421, found 289.1421. - IR (ATR, $\nu$): 2930, 1706, 1603, 1477, 1377, 1269, 1137, 1096, 1077, 1014, 951, 919, 845, 773, 699, 584 cm$^{-1}$. - EA (C$_{15}$H$_{18}$N$_2$O$_2$): calc. C 62.27; H 6.62; N 14.52; found C 62.01, H 6.74, N 14.34.

1-(4-Methoxy-phenyl-diazenyl)-3-methyl-piperidin-2-one (7).

Compound 2d (61 mg, 0.26 mmol) was dissolved in anhydrous THF (3.2 mL) and, after cooling to -78 °C, a 1.0 M solution of LiHMDS in THF (290 mL, 0.29 mmol) was added dropwise, keeping the temperature below -70 °C. The resulting mixture was stirred for 1.5 h at -45 °C and then quenched with aqueous 10 % NaOH (25 mL). The product was extracted with Et$_2$O (5 mL), water was added (10 mL) and, after separation of the phases, the aqueous layer was extracted with Et$_2$O (2 x 10 mL). The combined organic extracts were dried over anhydrous K$_2$CO$_3$. After filtration and evaporation of the solvent, the crude was purified by flash chromatography (n-hexane/EtOAc, 3 : 1 + 1 % Et$_2$N), affording pure 7 as an orange solid (38 mg, 59 %). - R$_r$ (n-hexane/EtOAc, 3 : 1) = 0.24. - m.p. = 87.7 - 89.2 °C. - $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.67 (d, $J$ = 9.1 Hz, 2 H), 6.92 (d, $J$ = 9.1 Hz, 2 H), 4.05 (dddd, $J$ = 13.5, 5.8, 4.6, 1.4 Hz, 1H), 3.83 (s, 3H), 3.71 (ddd, $J$ = 13.5, 9.2, 5.3 Hz, 1H), 2.78 - 2.67 (m, 1H), 2.17 - 1.99 (m, 2H), 1.97 - 1.84 (m, 1H), 1.65 - 1.54 (m, 1H), 1.39 (d, $J$ = 9.2 Hz, 3H) ppm. - $^{13}$C NMR (100.3 MHz, CDCl$_3$) $\delta$ = 172.5, 160.6, 142.5, 124.0, 114.1, 55.6, 45.4, 38.6, 28.5, 21.08, 17.6 ppm. - MS (ESI) m/z (%): 517 (100) [2M+Na]$^+$, 270 (23) [M+Na]$^+$. - EA (C$_{13}$H$_{17}$N$_3$O$_2$) calc C 63.14, H 6.93, N 16.99; found: C 62.99, H 7.38, N 17.21.

4-[6-(Diphenoxy-phosphoryloxy)-3,4-dihydro-2H-pyrindin-1-ylazo]-benzoic acid ethyl ester (8).

A 0.5 M solution of KHMS (0.45 mL, 0.22 mmol) in toluene was diluted in anhydrous THF (1 mL) and cooled to -78 °C. A solution of 2a (50 mg, 0.2 mmol) in anhydrous THF (1.5 mL) was added dropwise. The resulting mixture was stirred for 1.5 h at -78 °C and then diphenylchlorophosphate (45 µL, 0.22 mmol) was slowly added and the stirring continued below -70 °C for 1 h. The mixture was first allowed to warm to 0 °C and then quenched with aqueous 10 % NaOH (25 mL). The product was extracted with Et$_2$O (4 x 3 mL); the combined organic extracts were washed with 10 % NaOH (3 mL) and dried over anhydrous K$_2$CO$_3$ for 30 min. After filtration and evaporation of the solvent, the crude was purified by flash chromatography (n-hexane/EtOAc, 10 : 1 + 1 % Et$_3$N; R$_r$ = 0.24) to give product 8 (112 mg,


100 %) as a colourless oil. \( R_1 (n\text{-hexane/EtOAc, } 2:1) = 0.48. \) - \(^1\text{H NMR (400 MHz, CDCl}_3\) \( \delta = 7.88 \) (d, \( J = 8.5 \text{ Hz, } 2H\)), 7.35 (d, \( J = 8.5 \text{ Hz, } 2H\)), 7.30 – 7.05 (m, 10H), 4.93 (dd, \( J = 7.2, 4.4 \text{ Hz, } 1H\)), 4.30 (q, \( J = 7.1 \text{ Hz, } 2H\)), 4.06 – 3.93 (m, 2H), 2.26 – 2.15 (m, 2H), 1.92 – 1.82 (m, 2H), 1.33 (t, \( J = 7.1 \text{ Hz, } 3H\)) ppm. - \(^13\text{C NMR (100.3 MHz, CDCl}_3\) \( \delta = 166.3, 153.0, 150.3, 141.4, 130.4, 129.8, 129.0, 128.3, 128.2, 125.6, 125.3, 121.2, 120.1, 120.1, 110.5, 92.9, 60.7, 43.3, 21.1, 21.0, 14.3.

References

[1] Research carried out in collaboration with prof. Stefan Bräse at Karlsruhe Institute of Technology (DE)


[7] As far as we know, only a few examples of diazenyl-protected valerolactams, one pyrrolidinone and several phthalimides have been reported and their chemistry is not well explored.


Conclusions

The synthesized series of polyhydroxylated cyclopropane-fused piperidine derivatives demonstrated that OH-directed cyclopropanation is feasible approach toward conformationally restricted iminosugars. The syntheses of protected 6-hydroxymethyl-piperidin-2-one and 5-hydroxy-6-hydroxymethyl-piperidin-2-one together with previously developed methodology for the synthesis of 4,5-dihydroxy-piperidin-2-one offer versatility in the view of the number, position and the orientation of hydroxyls for the future syntheses of cyclopropane-fused piperidines as conformationally restricted iminosugar analogues (Chapter 4).

The developed tandem gold(I)-catalyzed [3,3]-rearrangement/Nazarov cyclization of N-heterocycles bearing propargylic ester either at C2 or C3 position are general, reliable and scalable methods for the synthesis of cyclopenta-fused piperidine, azepane and indole derivatives. The two classes of compounds have been studied in detail: piperidine-derived enynyl acetates bearing propargylic moiety at position C2 (Chapter 5) and indole-derived enynyl acetates bearing propargylic moiety at position C3 (Chapter 7).

Preliminary transformations, hydrogenation of the double bond, reduction of the carbonyl group and α-hydroxylation of cyclopenta-fused piperidines prepared via tandem gold(I)-catalyzed [3,3]-rearrangement/Nazarov cyclization demonstrated that herein developed pentannulations of piperidines is feasible approach toward conformationally restricted iminosugars (Chapter 6). Also, the developed methodologies present easy entry to cyclopenta-fused N-heterocycles, motif found in many natural products.

Indole derivatives bearing propargylic moiety on C3 underwent tandem gold(I)-catalyzed [3,3]-rearrangement/Nazarov cyclization providing cyclopenta[b]indol-1-ones as useful precursors for the synthesis of natural and bioactive compounds. It has been shown that both, gold(I) ligand and the substitution pattern on the indole core influence the reaction rate. Finally, this new strategy for cyclopenta-fused indole formation was applied to the first total synthesis of bruceolline H which was accomplished in yield of 46 % over 7 steps from commercially available 6-methoxy-1H-indole (Chapter 7).

With the aim to develop solid-phase synthesis of piperidine derivatives using multifunctional triazene linker, the diazenyl protected lactams were prepared in solution via RuO₄ oxidation of corresponding triazenes (Chapter 8). This oxidation presents the first strategy for the synthesis of functionalized lactams with diazenyl unit. Obtained δ-valerolactam was successfully transformed into corresponding phosphate but the Pd-catalyzed methoxycarbonylation and Suzuki cross coupling reaction failed. Therefore, to use triazene linker in the solid-phase synthesis of piperidine derivatives, the further work to explore the reactivity of diazenyl protected lactams is necessary.
Abbreviations

Ac  acetyl
Ac₂O  acetic anhydride
ACN  acetonitrile
aq  aqueous
Ar  aryl
BARF  tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
Bn  benzyl
Boc  tert-butoxycarbonyl
br  broad
BrettPhos  2-(dicyclohexylphosphino)3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl
n-Bu  butyl
°C  degrees Celsius
calcd  calculated
cap  caprolactam
cat  catalytic
Cbz  Carboxybenzyl
Cy  cyclohexyl
δ  chemical shift
DBU  1,8-diazabicyclo(5.4.0)undec-7-ene
DCE  1,2-dichloroethane
DCM  dichloromethane
DNJ  deoxynojirimycin
DFT  density functional theory
DIB  (diacetoxyiodo)benzene
DIBAL-H  diisobutylaluminium hydride
DIPEA  N,N-diisopropylethylamine
DMAP,  4-dimethylaminopyridine
DME  1,2-dimethoxyethane
DMF  dimethylformamide
DMP  Dess-Martin periodinane
DMPU  1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO  dimethylsulfoxide
DOWEX 50WX8  type of ion exchange resin
E⁺  electrophile
ED/EDG  electron-donating group
E.I.  electron ionisation
eq  equivalent
Et  ethyl
EWG  electron-withdrawing group
gCOSY  the gradient selected coorrelation spectroscopy
h  hour
HMPA  hexamethyldiphosphoramide
HPLC  High Performance Liquid Chromatography
HRMS  High Resolution Mass Spectroscopy
HSQC  Heteronuclear Single Quantum Coherence Spectroscopy
Hz  Hertz
IPr  [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]
\( J \) coupling constant

JohnPhos (2-biphenyl)di-tert-butylphosphine

KHMDS potassium bis(trimethylsilyl)amide

LHMDS lithium bis(trimethylsilyl)amide

mCPBA meta-chloroperoxybenzoic acid

Me methyl

Ms mesyl

min minutes

mol mole

M.p. melting point

MS mass spectroscopy

NHC N-heterocyclic carbene

NHPI N-hydroxyphthalimide

NIS N-lodosuccinimide

NJ Nojirimycin

NMO N-methylmorpholine N-oxide

NMR Nuclear Magnetic Resonance

NOE Nuclear Overhauser Effect

on overnight

Ph phenyl

Pht phthalimide

PTSA para-toluenesulfonic acid

ppm parts per million

\( i \)-Pr iso-propyl

RCM ring closing metathesis

Rf retention factor

rt/r.t. room temperature

sat. saturated

Super-H lithium triethylborohydride

\( t \)-Bu tert-butyl

T-HYDRO 70\% tert-butyl hydroperoxide in water

TBAF tetra-\( n \)-butylammonium fluoride

TBAI tetra-\( n \)-butylammonium iodide

TBHP tert-butyl hydroperoxide

TBS tert-butyl(dimethyl)silyl

TCP 2,4,6-trichlorophenol

Tf trifluoromethanesulfonate

TFA trifluoroacetic acid

THF tetrahydrofuran

TIPS triisopropylsilyl

TLC thin layer chromatography

TMS trimethylsilyl

Ts para-toluenesulfonyl (tosyl)

UV Ultraviolet

\([(S)-DTMB-Segphos]\) (S)-(\(+\))-5,5\'-Bis[di(3,5-di-tert-butyl-4-methoxyphenyl)phosphino]-4,4\'-bi-1,3-benzodioxole

\([(S)-DTMB-MeO-biphep]\) (\(-\))-5,5\'-Dichloro-6,6\'-dimethoxy-1,1\'-biphenyl)-2,2\'-diyl-bis(diphenylphosphine)
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