PALLADIUM- AND GOLD-CATALYZED SYNTHESIS OF

POLYHYDROXYLATED HETEROCYCLES WITH

RESTRICTED CONFORMATIONAL MOBILITY

Dottorando
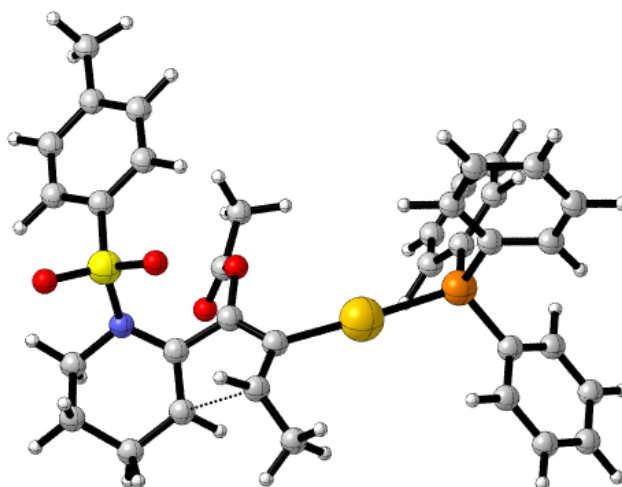Dott. Martina Petrović-Hunjadi

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Settore Scientifico Disciplinare CHIM/06

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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-D-ribose, while racemic 5-hydroxy-6-hydroxymethyl-piperidin-2-one was prepared from *δ*-valerolactam.
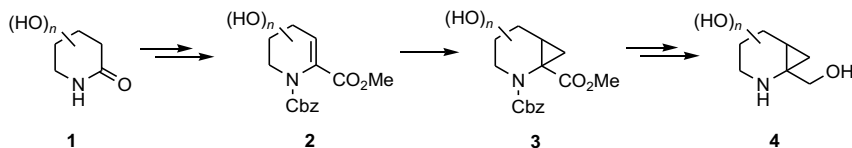
Scheme 1.   Synthesis of polyhydroxylated cyclopropane-fused piperidine core.

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.
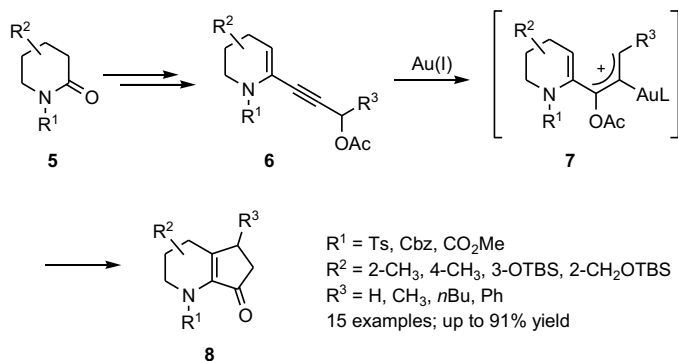
Scheme 2. Cyclopenta-fused piperidines **8** via gold(I)-catalyzed [3,3]-rearrangement/Nazarov cyclization.

R^1 = Ts, Cbz, CO$_2$Me
R^2 = 2-CH$_3$, 4-CH$_3$, 3-OTBS, 2-CH$_2$OTBS
R^3 = H, CH$_3$, *n*Bu, Ph
15 examples; up to 91% yield

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.
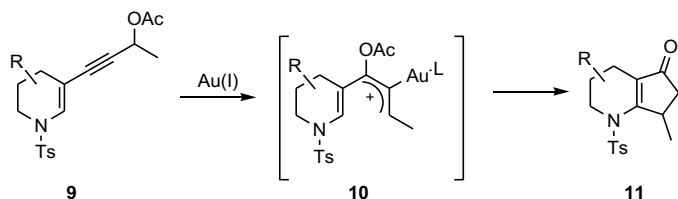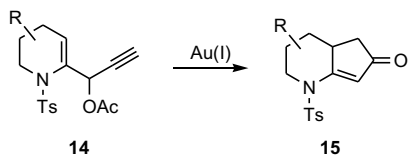

Scheme 3. Gold(I)-catalyzed [3,3]-rearrangement/Nazarov cyclization of enynyl acetate **9**.

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 naural products possessing the cyclopenta[*b*]indol-1-one nucleus.
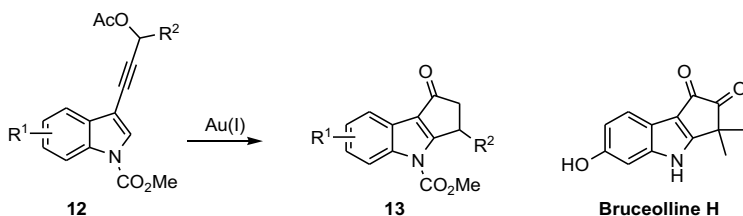
Scheme 4. Gold(I)-catalyzed [3,3]-rearrangement/Nazarov cyclization of indole-derived enynyl acetate **12**.

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.

Contents

Introduction

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]

$$\Delta G = \Delta H - T\Delta S$$
$$\Delta G = - RT \ln K_i$$

(ΔG – the free energy of the binding; ΔH – the energy of the binding interactions;
ΔS – 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
[1] Gram L. Patrick in *An Introduction to Medicinal Chemistry*, 4th edition, OXFORD University Press **2009**, Chapter 13, 234 – 237.
[2] Z. Fang, Y. Song, P. Zhan, Q. Zhang, X. Liu, *Future Med. Chem.* **2014**, *8*, 885 – 901.

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.

Pyrrolidine   Piperidine   Azepane   Pyrolizidine   Indolizidine   Nortropane
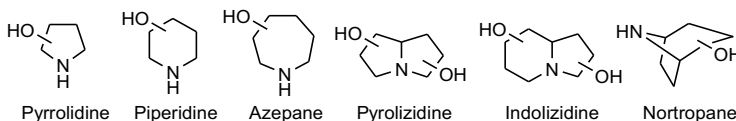
Figure 1.   General structures of iminosugars.

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, deoxynojirimycin, 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.

Iminosugar   Iminoalditol   Imino-C-glycoside   1-Azasugar
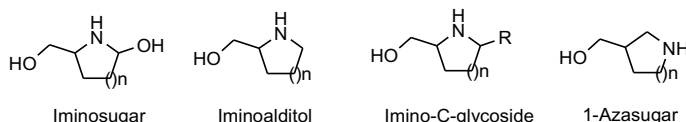
2.1. Iminosugars as Glycosidase Inhibitors

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.

Proposed transition state
of glycosidase hydrolysis

1-Deoxynojirimycin   Isofagomine   Tetrahydropyridino-imidazole
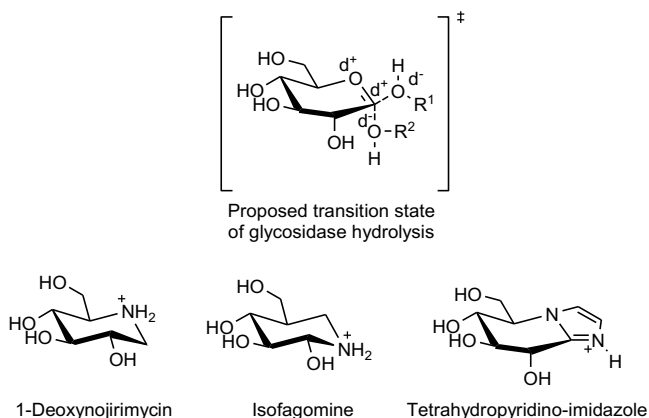
Figure 2. Transition state of enzymatic glycoside hydrolysis and proposed transition state mimicry of different iminosugars.

Iminosugars, as a 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.[6]

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.[7] It was a good inhibitor of both *α*- and *β*-glucosidases, which was not very suprising giving 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.

D-Glucose   Nojirimycin (NJ)   Mannojirimycin   Galactonojirimycin
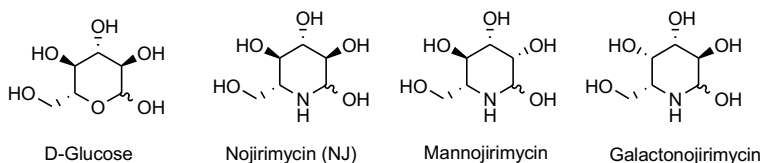
Figure 3. D-Glucose in pyranose form and naturally occurring analogues.

The removal of the hydroxyl group from the anomeric position via catalytic hydrogenation over PtO_2 or reduction of nojirimycin with $NaBH_4$ led to the formation of much more stable 1-

deoxyderivative (iminoalditol) known as 1-deoxynojirimycin.[7b] The finding of 1-deoxynojirimycin's biological activity as inhibitor of α-glucosidases by Bayer chemists in 1976[8] 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)
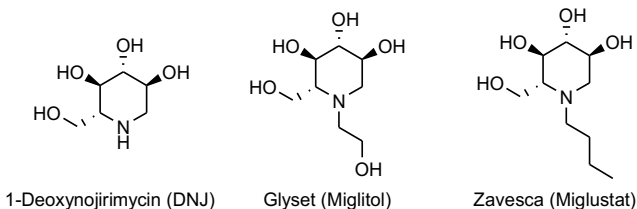
Figure 4. 1-Deoxynojirimycin and its *N*-substituted analogues used in the treatment of type II diabetes (Glyset) and type I Gaucher disease (Zavesca).

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.
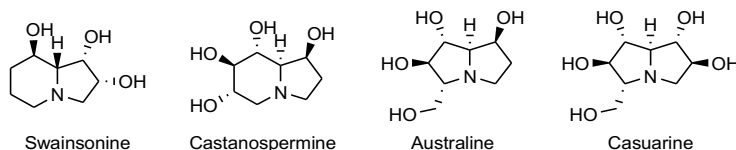

Swainsonine   Castanospermine   Australine   Casuarine

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.[9] 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).[6a,10]

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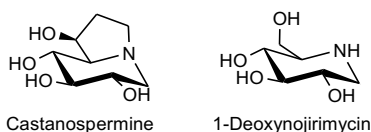
Figure 6. Castanospermine as conformationally restricted 1-deoxynojirimycin.

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.[11]
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**),[12] 2-oxacastanospermine (**2**),[13] perhydrazaazulene (**3**),[14] 1-aza-bicyclo[5.3.0]octane (**4**)[15] and tetrahydropyridino-imidazole (**5**).[16]
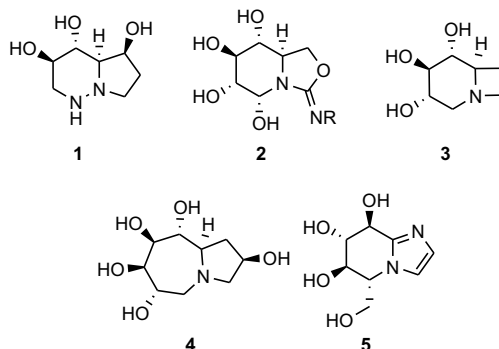
Figure 7.   Polyhydroxylated *N*-heterocycles as iminosugar analogues.

2.2.1.   Cyclopropane as Conformational Restriction

Jérôme Désiré and Michael Shipman incorporated a cyclopropane as a conformational restriction into deoxymannojirimycin.[17] The cyclopropane 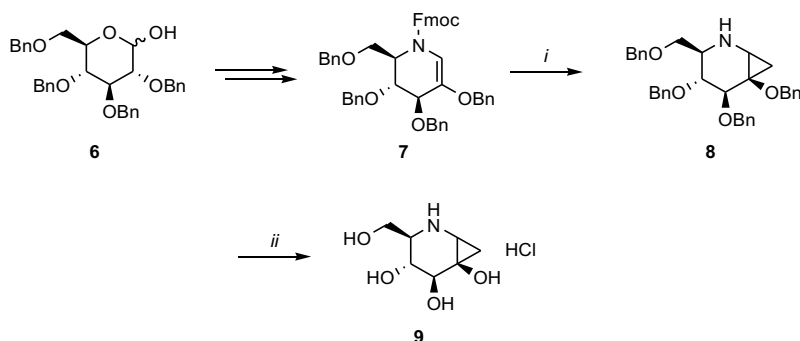moiety was introduced in highly selective Simmons-Smith cyclopropanation of imino glucal **7**, prepared from tetra-*O*-benzyl-D-glucopyranose **6** in 7 steps (Scheme 6).[18]

Scheme 6.   Synthesis of cyclopropane-fused deoxymannojirimycin **9**. Reagents and conditions: *i*) 1. Et$_2$Zn, CH$_2$I$_2$, toluene, 2. morpholine; *ii*) H$_2$, Pd/C, HCl in EtOH.

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).[19] They prepared a small library of spirocyclopropyl azasugars **12** and evaluated their inhibitory activities.[20] 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**.
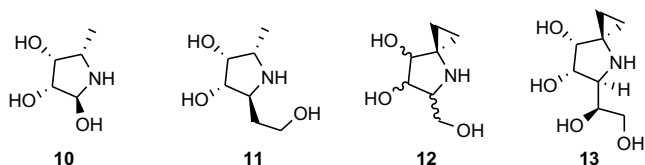
Figure 8. Pyrrolidine-derived iminosugars and their spiro-analogues.

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.[21]

The key intermediate, highly functionalyzed polyhydroxylated unsaturated aldehyde **19**, was obtained in a Lewis acid-induced fragmentation of D-*gluco*-configured allyltin **18**.[22] A typical procedure for the preparation of sugar derived allyltin compounds starts with the conversion of partially protected hexose (D-*gluco*, D-*galacto*, D-*manno*) or pentose (D-*ribo*, D-*xylo*) 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.[23]

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.
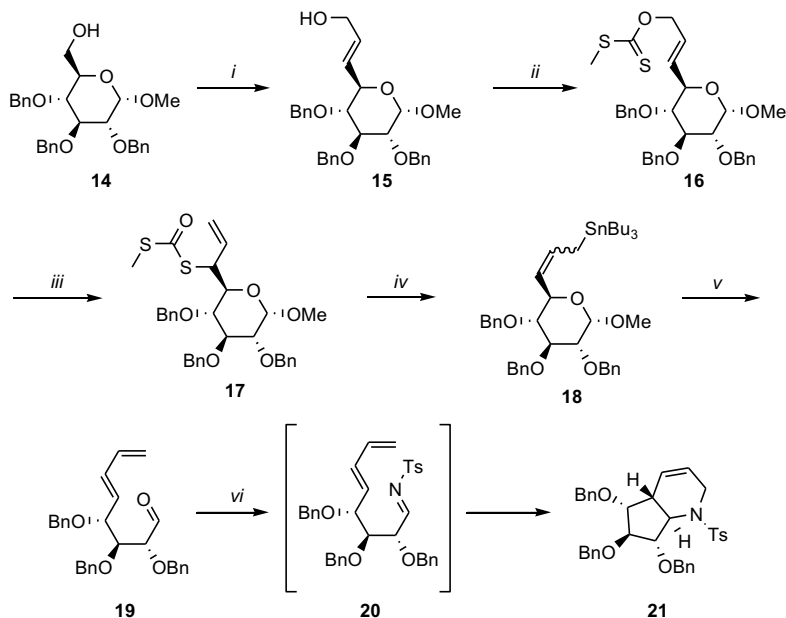
Scheme 7. Synthesis of cyclopenta-fused piperidine derivative **21**. Reagents and conditions: *i*) 1. Swern oxidation, 2. Ph₃P=CHCO₂Me, 3. DIBAL-H; *ii*) NaH, CS₂, MeI; *iii*) toluene, 110°C, 2 h; *iv*) Bu₃SnH, toluene, 110°C, 2 h; *v*) ZnCl₂; *vi*) TsNH₂, TsOH.

The *cis*-dihydroxylation of olefin **21** afforded diol **22** as a single stereoisomer in 85 % yield while the *trans*-dihydroxylation of **21** (formic acid/H_2O_2 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.
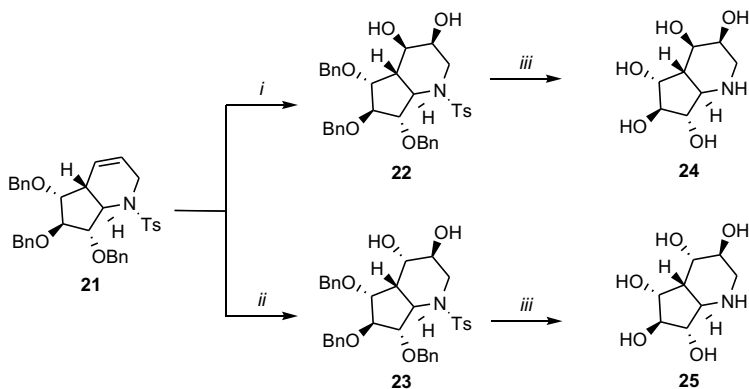
Scheme 8.   Dihydroxylation of **21**. Reagents and conditions: *i*) OsO_4, NMO, THF/*t*-BuOH/H_2O (85 %); *ii*) 1. HCO_2H, H_2O_2, 2. NaOH in MeOH (55 %); *iii*) Na/NH_3, -78°C, THF.

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[24] 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.
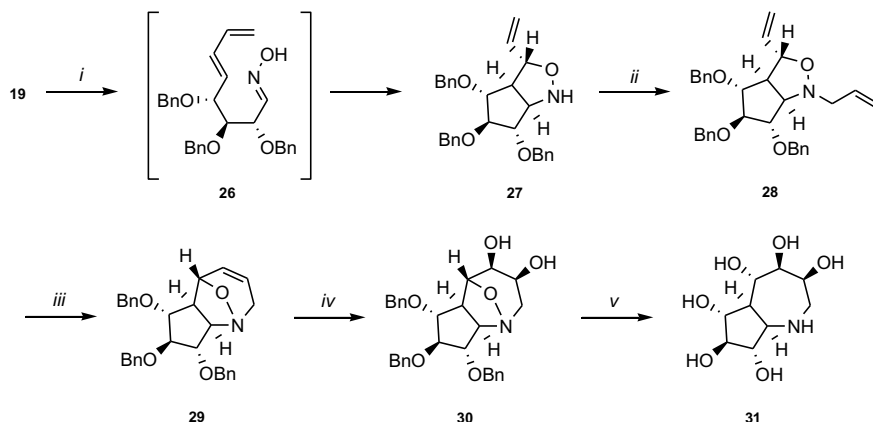
Scheme 9.   Synthesis of polyhydroxylated cyclopenta-fused azepane analogue **31**. Reagents and conditions: *i*) NH_2OH; *ii*) allylation; *iii*) RCM; *iv*) OsO_4, NMO, THF/*t*-BuOH/H_2O; *v*) 1. Zn; 2. Na/NH_3, -78°C, THF.

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 com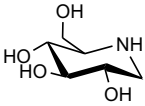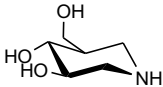ing from the starting material and therefore their number and the stereochemistry are defined in starting sugar. The type of the ring fusion depends on the cyclization reaction; Diels-Alder reaction of **20** afforded *trans* cyclopenta-fused piperidine, while 1,3-dipolar cycloaddition of **26** led 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.[25] Isofagomine turned out to be very potent inhibitor of β-glycosidase and glycogen phosphorylase (Table 1).

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

	Enzyme inhibition IC$_{50}$ (µM)					
	α-glucosidase (yeast)	β-glucosidase (almond)	Isomaltase (yeast)	Glucoamylase (a. Awamori)	α-mannosidase (jack bean)	Glycogen phosphorylase (pig liver)
DNJ	25	47	11	9.8	270	55000
32	86	0.11	7.2	3.7	770	0.7

Since then, Bols's group prepared deoxyisofagomine analogues, analogues with other substituents at positions 3, 4, 5 and 6,[26] analogues bearing nitrogen[27] and oxygen[28] at position 2, but the inhibitory activity was not significantly improved.

Isofagomine (**32**) (boat)   **33**   **34**
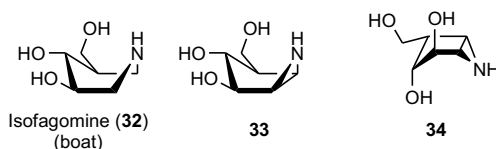
Figure 9.   Isofagomine in proposed binding conformation and its synthetic analogues.

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).[29] 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.[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.
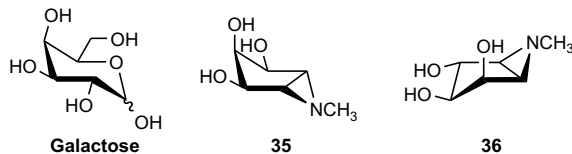
Figure 10. Galactose and its conformationally restricted analogues.

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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"[1]

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,[2] but until 20 years ago only a few chemists dared to use gold for the catalysis of organic reactions under homogeneous conditions.[3] 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.[4] 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, sp^2 and sp^3 C-H bonds.[1,5] 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.[6]

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.
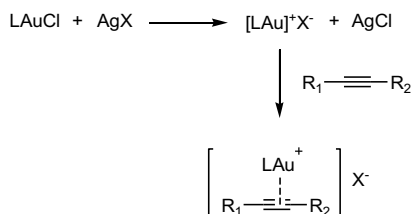
3.1. Gold(I) Catalyst Systems

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).
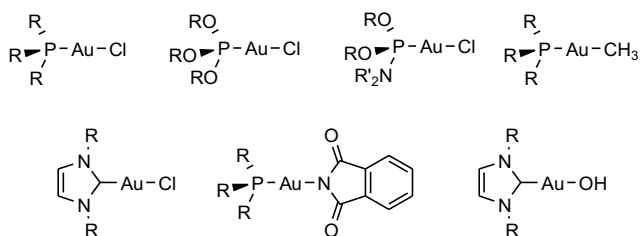
Figure 1. Gold(I) precatalysts (R = alkyl or aryl; R' = alkyl).

The dominant method for the generation of catalytically active cationic gold species [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).

$$LAuCl + AgX \longrightarrow [LAu]^+X^- + AgCl$$

$$\downarrow R_1 \!\!\equiv\!\! R_2$$

$$\left[\begin{array}{c} LAu^+ \\ R_1 \!\!=\!\!\!\vdots\!\!\!=\!\! R_2 \end{array} \right] X^-$$

Scheme 1.   Formation of catalytically active gold(I) species by an anion exchange between gold(I) chloride and silver salt (X = SbF$_6$, BF$_4$, NTf$_2$, 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.[1] 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, Tf$_2$NH, HBF$_4$ or H$_3$PW$_{12}$O$_{40}$.
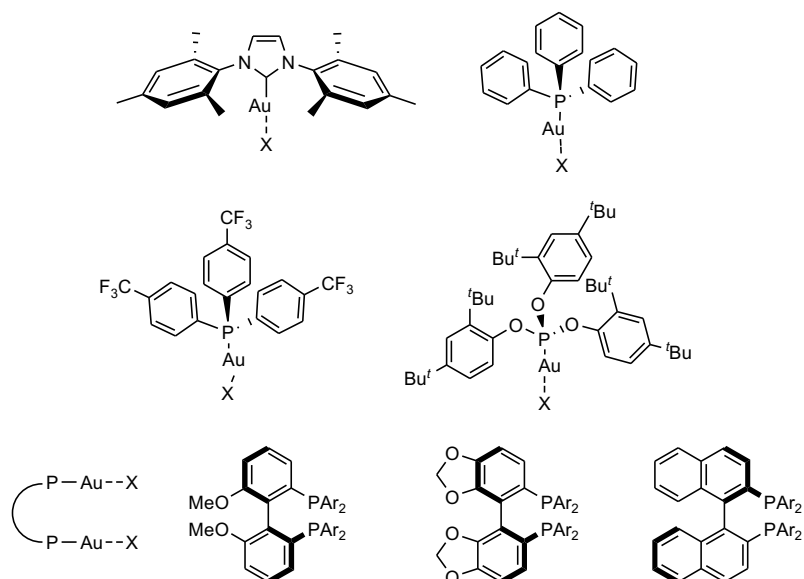
Figure 2.   Commonly used achiral and chiral gold(I) species (for example X = SbF$_6$, OTf, NTf$_2$).

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 LAu_2Cl_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 LAu_2X_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]
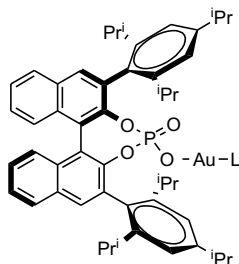
Figure 3.   Chiral counterion used in asymmetric gold-catalysis.

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 (π-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 π-acids.

Among the late transition metals, gold(I) is the most effective in electrophilic activation of unsaturated systems. This strong π-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 π-systems.

Calculations on Au(I) – ethylene and Au(I) – ethyne complexes[20] indicate that the largest bonding contribution has the overlap between the π-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 π-system. Thus, the strong electron donation of π-system to the Au(I) and weak back-bonding from Au(I) into π-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 π-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 π-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).
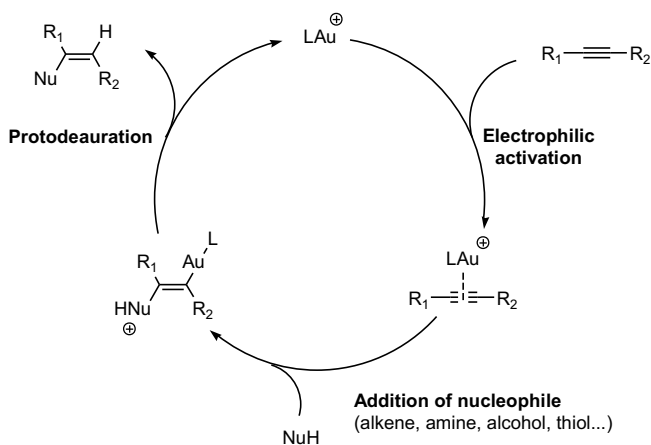
Figure 4. General mechanism of gold(I)-catalyzed transformations.

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.[23] 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.[24]

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 *o*-biphenyl steric handle can reduce the decay without influencing the reactivity.
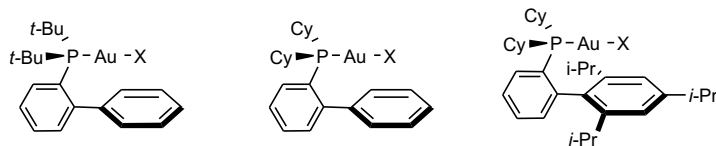
Figure 5. Gold(I) catalysts with enhanced stability.

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.
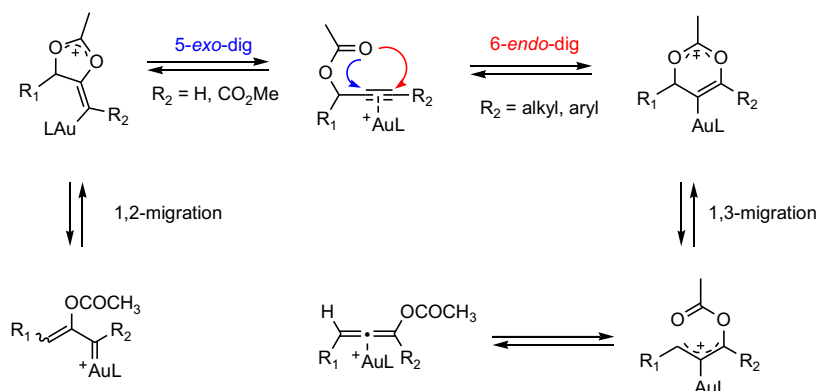

Figure 6. General pathways in the isomerisation of propargylic acetates.

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).
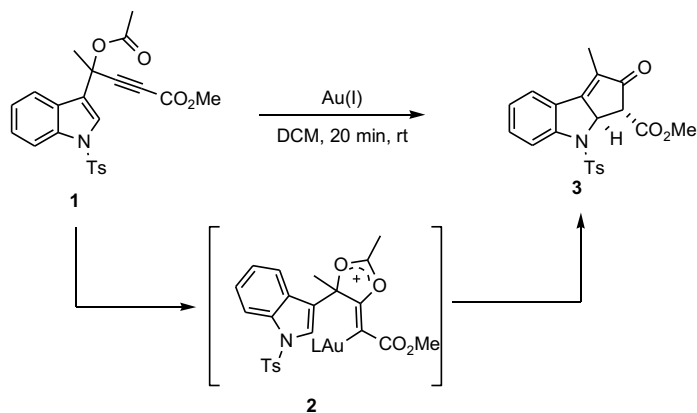
Scheme 2. Rautenstrauch rearrangement of indole-derived propargylic acetate **1**. Used catalysts and ee values: Ph$_3$PAuCl/AgSbF$_6$ (72% yield), [(S)-DTMB-Segphos](AuCl)$_2$/AgSbF$_6$ (9% ee), [(S)-DTMB-MeO-biphep(AuCl)$_2$/AgSbF$_6$ 38% ee).

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]
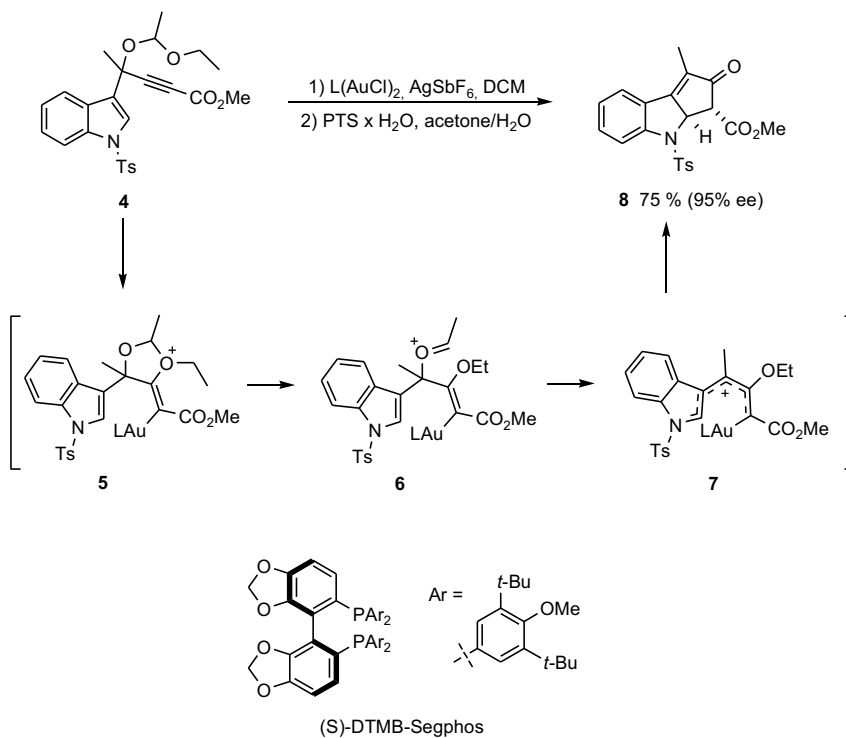
Scheme 3. Mechanistic rationale for enantioselective Rautenstrauch rearrangement of indole-derived propargylic acetal **4**.

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**.
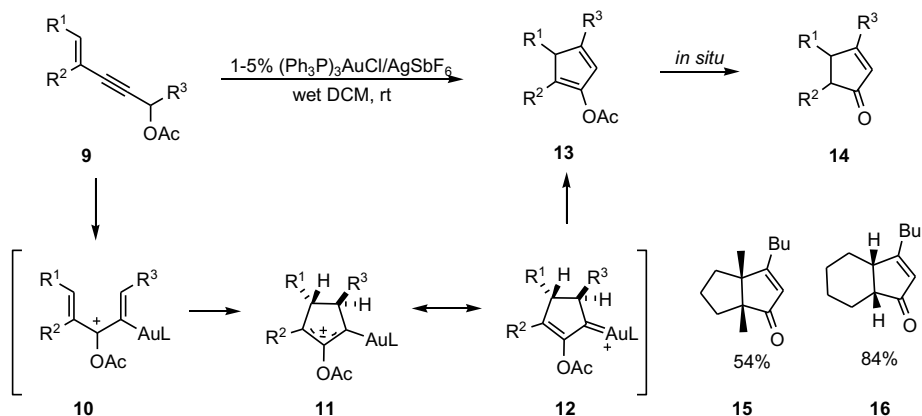
Scheme 4. Tandem Au(I)-catalyzed [3,3]-rearrangement/Nazarov reaction.
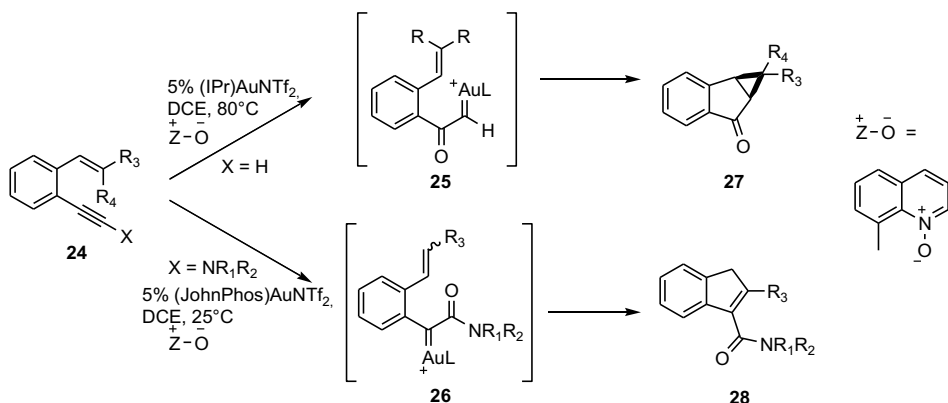
Malacria's group showed that in case when the side-chain (R^3) bears alkene functionality, the cyclopentadienyl gold species **11** (in resonance with gold carbene **12**) could undergo an electrophilic cyclopropanation giving rise to valuable polycyclic compounds.[29] Thus, starting from enynyl acetates **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.
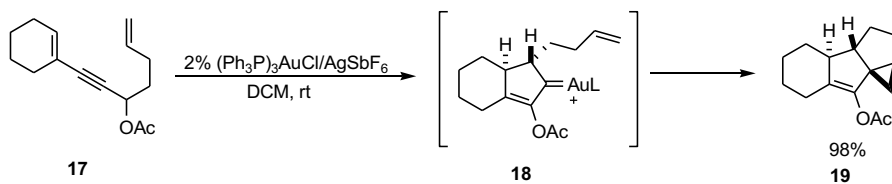
Scheme 5. Tandem gold(I)-catalyzed [3,3]-rearrangement, Nazarov reaction and electrophilic cyclopropanation.

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 *para*-substituted arenes was chemoselective, *ortho*-substituted arenes and tertinary acetates led to the formation of indenes **23** as minor products.

Scheme 6. Indene synthesis via tandem [3,3]-rearrangement/hydroarylation.

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 = S and N).[31] The cleavage of Z-O bond gives very electrophilic *α*-oxo-gold carbene that could be trapped in intra- or intermolecular fashion by different nucleophiles. From a general point of view the formation of *α*-oxo-gold carbene is favoured by strongly σ-donating and weakly π-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 nitrozobenzene as examples of oxidant species Z⁺-O⁻.

In 2011, Liu's group demonstrated that the alkyne substitution influences the oxidation step (Scheme 8).[32] In case of terminal alkynes the oxidation was favoured at the C-2 alkynyl carbon atom (**25**) while aminoalkynes prefered the oxidation of C-1 carbon atom (**26**).

Scheme 8. Oxidative cyclizations of 1,5-enynes.

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).[33] 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.
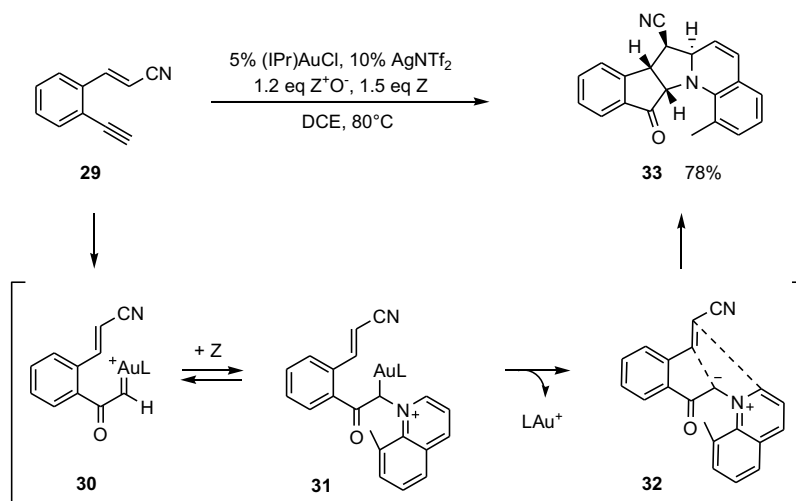
**Scheme 9.** Gold-catalyzed oxidative cycloaddition of 1,5-enynes to quinolone.

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[34] and Hashmi.[35] 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**.
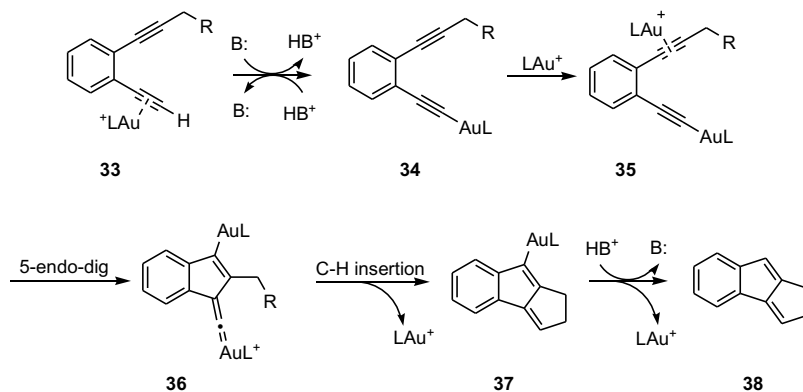
Scheme 10. General mechanism for dual-gold-catalyzed cyclization of diyne systems.

Dual-gold catalyzed cyclization of 3,4-substituted thiophenes **39** resulted therefore in new pentaleno[*c*]thiophene scaffold **40**.[36] 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).
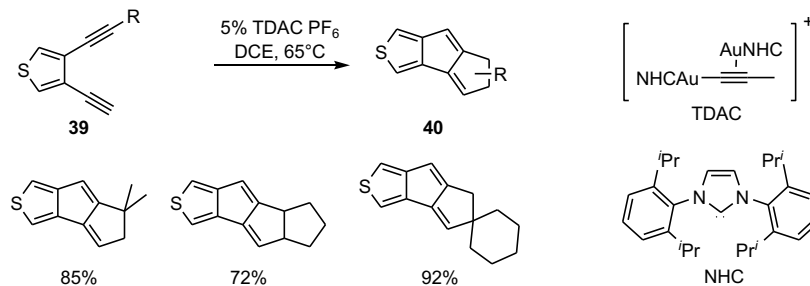
**Scheme 11.** Pentaleno[*c*]thiophenes prepared via dual-gold-catalysis.

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.
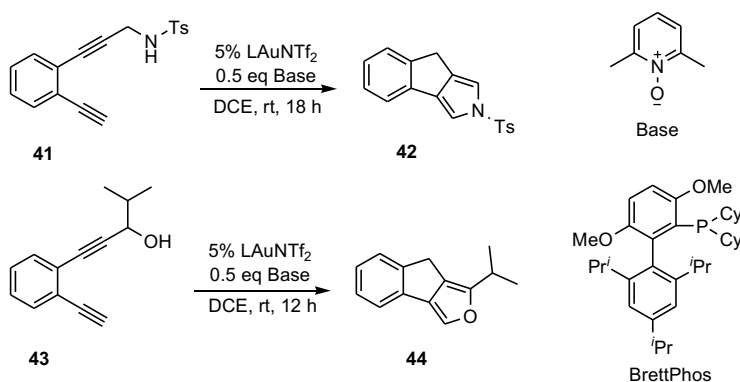
Scheme 12. Pyrrole and furan derivatives prepared via dual-gold-catalysis.

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).[37] 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.
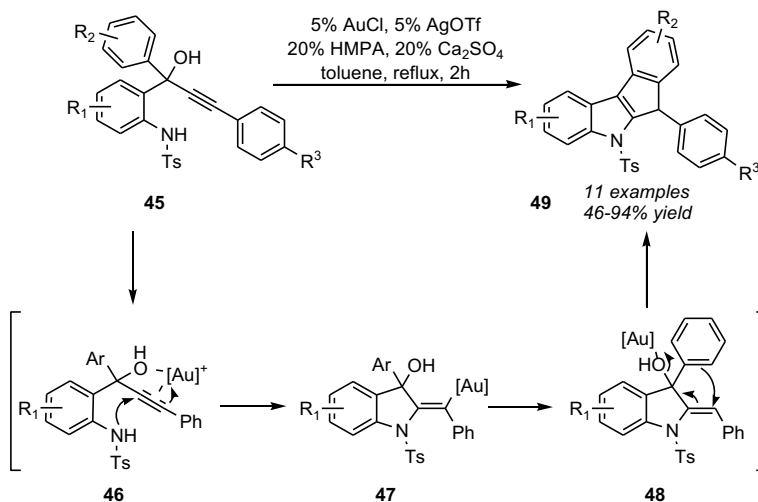

Scheme 13.   Tandem cycloisomerization/Friedel–Crafts alkylation.

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).[38] 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 (R^1 and R^2). 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.
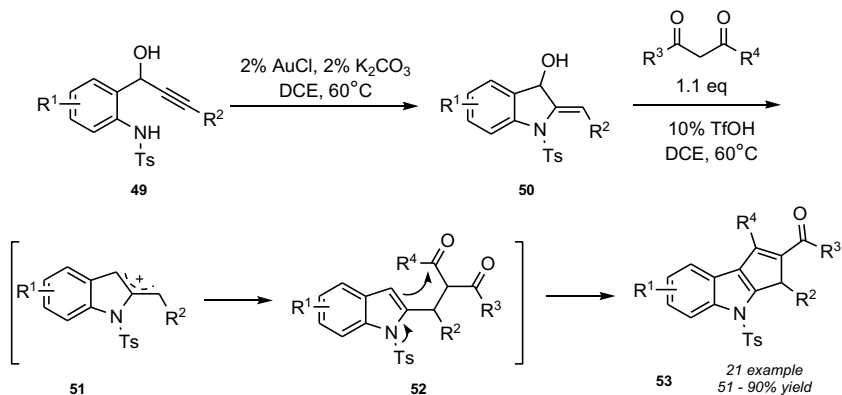
Scheme 14. Au(I)/Brønsted acid catalyzed tandem process.

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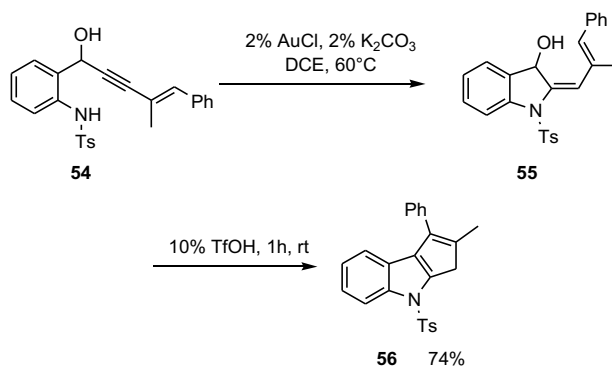

Scheme 15. Au(I)/Brønsted acid catalyzed hydroamination/Nazarov cyclization.

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.

Scheme 16.   Enantioselective carboalkoxylation of alkynes.
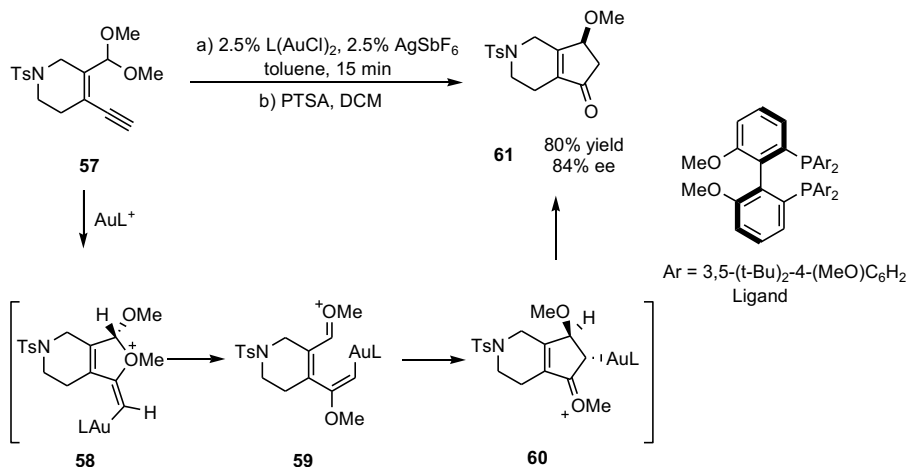
3.6.   Pentannulations Using Allenes

Differently substituted cyclopenta[*b*]indoles **62** were prepared in good yields via selective electrophilic activation of 3-allenylindoles **61** (Scheme 17).[41] As for the mechanism, the authors suggested intramolecular addition of the indole to the gold-activated allene intermediate followed by deprotonative rearomatization and protodeauration.

Scheme 17.   Au(I)-catalyzed cyclization of 3-allenylindoles.
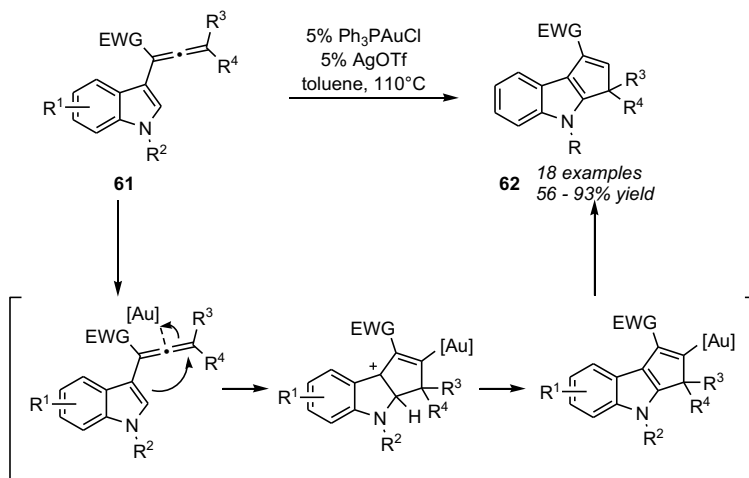
In addition, 3-allenylindole bearing terminal allene underwent regioselective Au(I)-catalyzed imino-Nazarov cyclization giving indole-fused cyclopentenamides **64** (Scheme 18).
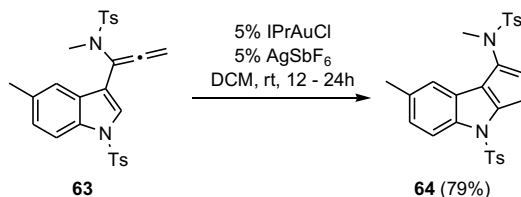
Scheme 18. Au(I)-catalyzed imino-Nazarov reaction.

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.[43] A plausible mechanism involves the allene activation, nucleophilic atack of indole (C3) 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).
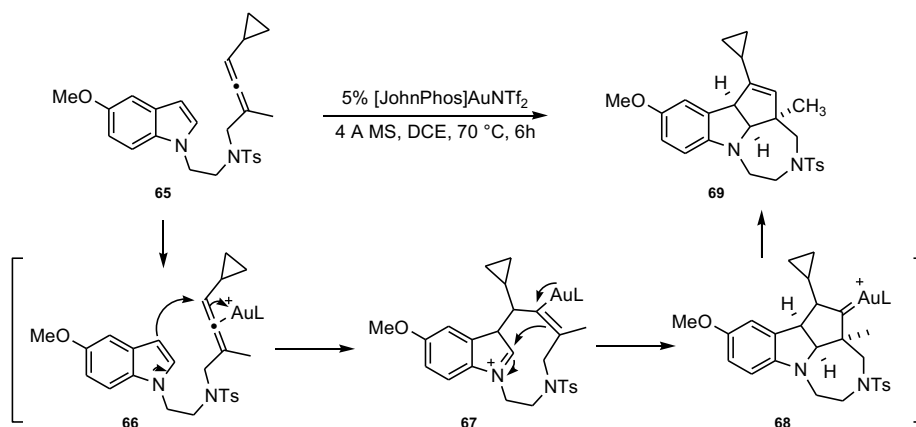
Scheme 19. Intramolecular Au(I)-catalyzed [3+2] cycloaddition of allene and indole.

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.

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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 pipecolic acids. Within this thesis, relying on this approach, dihydroxylated piperidine was successfully merged with a cyclopropane ring.
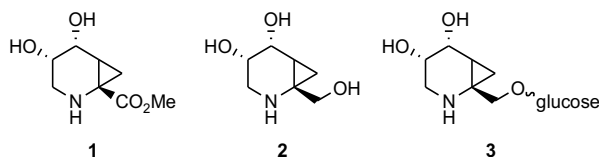
Figure 1. Polyhydroxylated cyclopropane-fused piperidine derivatives synthesized within this thesis.

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**.
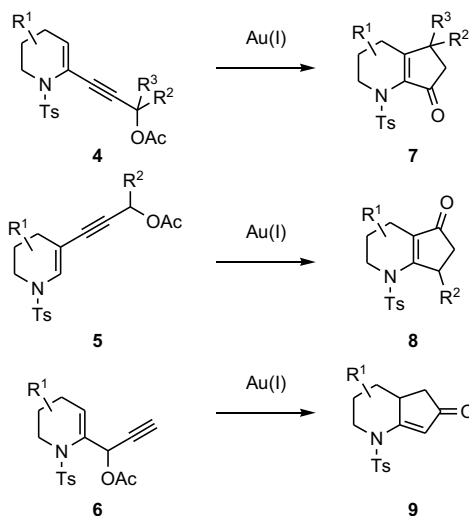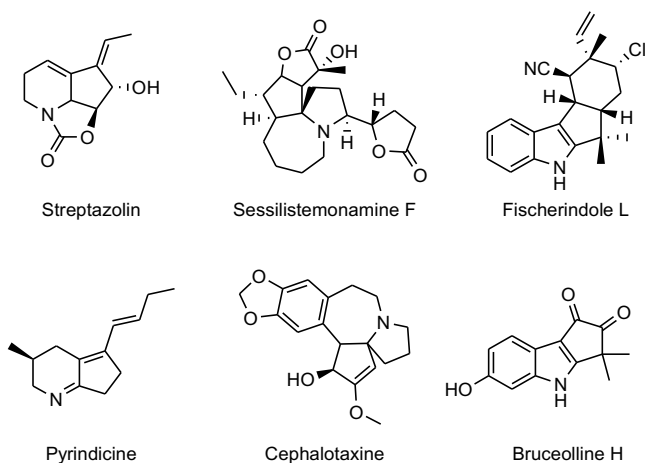

Scheme 1. Synthesis of cyclopenta-fused piperidines via gold(I)-catalyzed tandem rearrangement/cyclization processes explored within this thesis.

In a view of possible application to the synthesis of conformationally restricted polyhydroxylated *N*-heterocycles, the gold(I)-catalyzed tandem [3,3]-rearrangemet/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.
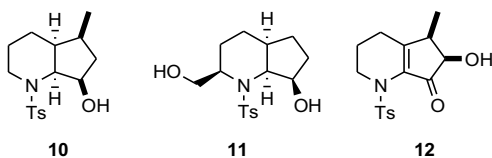
Figure 2. Functionalization of cyclopenta-fused piperidines **7**.

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.

Streptazolin   Sessilistemonamine F   Fischerindole L

Pyrindicine   Cephalotaxine   Bruceolline H

Figure 3. Natural compounds containing a cyclopenta-fused *N*-heterocyclic core.

Finally, with the aim to transfer the solution phase synthesis of piperine derivatives to the solid support, diazenyl protected *δ*-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.
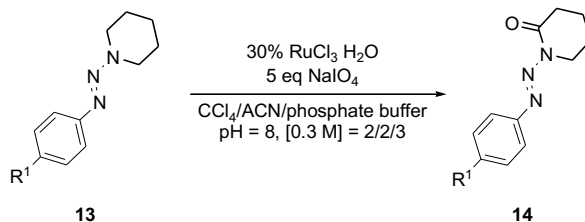
Scheme 2. Synthesis of *δ*-valerolactam via oxidation of diazenyl protected piperidine.

Results and Discussion

Chapter 4: Synthesis of Polyhydroxylated Cyclopropane-Fused Piperidines

The general approach for the synthesis of polyhydroxylated cyclopropane-fused piperidine analogus 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.
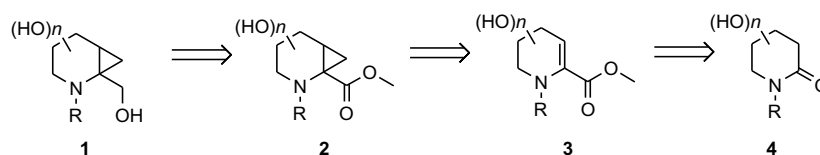
Scheme 1. Retrosynthetic analysis for the synthesis of polyhydroxylated cyclopropane-fused piperidines.

Just as a mention, on the basis of this approach 4-hydroxy-substituted cyclopropane pipecolic acid methyl ester **5**[1] and all four stereoisomers of 5-hydroxy pipecolic acid derivative **6**[2] have already been prepared and used as conformationally restricted templates for linear and cyclic peptidomimetics.[3]

5 **6**

R = Boc, CO$_2$Me
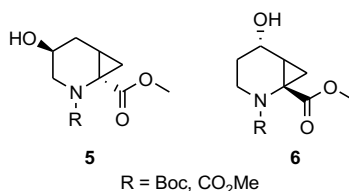
**Scheme 2.** 4-OH and 5-OH-cyclopropane-fused piperidines as templates for peptidomimetics.

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 analogus 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.

7 **8** **9**
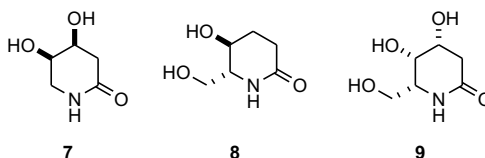
Scheme 3. Examples of different di- and trihydroxylated *δ*-valerolactams.[4-6]

Taking into account the importance of 6-substituted *trans*-5-hydroxypiperidin-2-ones **8** as the key intermediate in the synthesis of piperidine alkaloids,[7] we decided to investigate if the methodology applied to the synthesis of both enantiomers of *trans*-3-hydroxy-pipecolic acid[8] 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**.

10 R = CH$_3$
11 R = CH$_2$OTBS

12 R = CH$_3$
13 R = CH$_2$OTBS

14   **15**   **16**   **17**
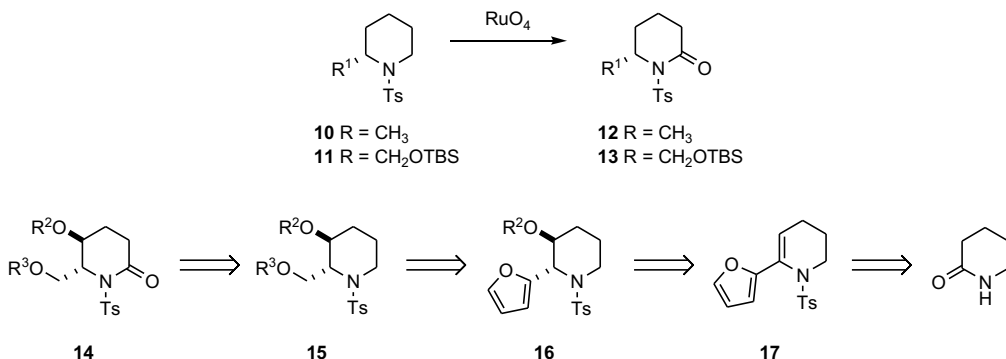
Scheme 4.   The oxidation of sulfonamines into sulfonamides as the final step in the synthesis of lactam **14**.

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 acomplished 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 (4*R*,5*S*)-**7** in 95 % yield.

2-deoxy-L-ribose   **18**   **19**

20   (4*R*,5*S*)-**7**
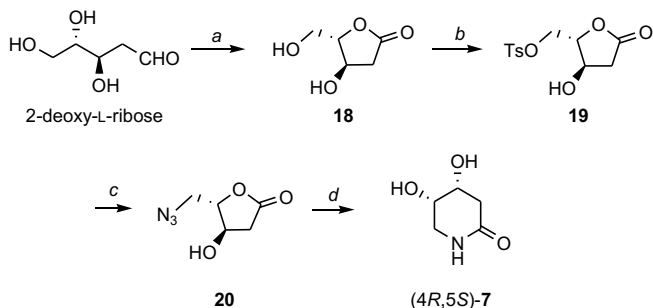
Scheme 5.   Synthesis of enantiopure *cis*-4,5-dihydroxylated lactam **7**. Reagents and conditions: (*a*) Br$_2$, H$_2$O, 5 days (75 %); (*b*) TsCl, pyridine, -15 - 0°C, ~ 7h (57 %); (*c*) NaN$_3$, 15-crown-5, ACN, reflux, ~ 18h (90 %); (*d*) H$_2$, Pd/C, MeOH, rt, 16h (95 %).

Starting from commercially available D-pipecolic 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,[11] but also relying on asymmetric transformations of achiral synthons.[12]
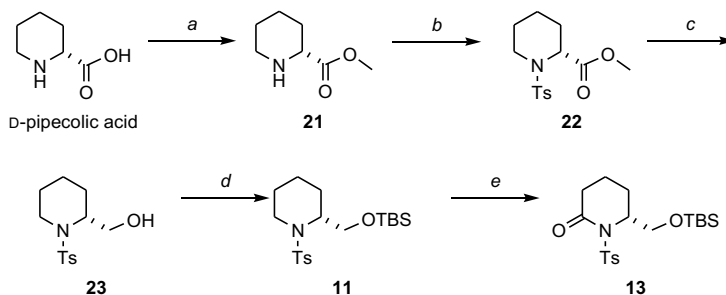
Scheme 6. Synthesis of enantiopure protected lactam **13**. Reagents and conditions: (*a*) SOCl$_2$, MeOH, 0 °C, 3 h (98 %); (*b*) TsCl, Et$_3$N, DMAP, DCM, r.t., on (84 %); (*c*) LiBH$_4$, THF, r.t., on (95 %); (*d*) TBSCl, imidazole, THF, r.t., on, (97 %); (*e*) RuO$_2$·nH$_2$O, NaIO$_4$, EtOAc/H$_2$O, 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$_3$·DMS/NaOH-H$_2$O$_2$ 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 ^{1}H NMR spectrum because of their equatorial orientation. Consequently, both the furyl and OH groups are axially oriented.
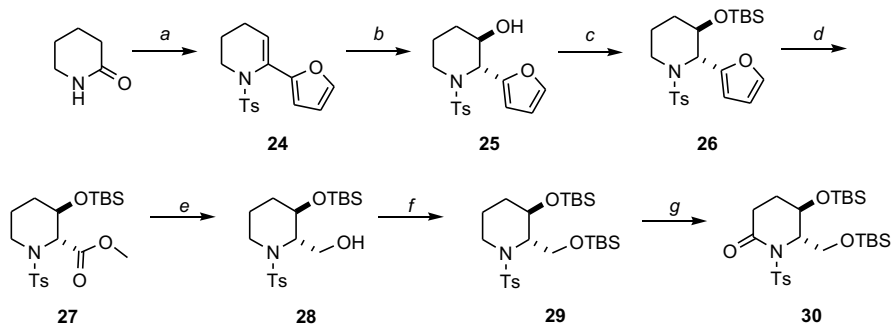
Scheme 7. Synthesis of lactam **30**. Reagents and conditions: (*a*) 1. *n*-BuLi, THF, -78 °C, TsCl (86 %), 2. KHMDS, -78 °C, 1.5 h; then (PhO)$_2$POCl, -78 °C, 1 h (80 %), 3. (Ph$_3$P)$_2$PdCl$_2$, 2-furanyl boronic acid, Na$_2$CO$_{3(aq)}$/THF, 40 °C, 2 h (70 %); (*b*) 1. (CH$_3$)$_2$S·BH$_3$, THF, 25 °C, on, 2. EtOH, H$_2$O$_2$, NaOH, 1 h, reflux (43 %); (*c*) TBSOTf, DIPEA, DCM, r.t., on (93 %); (*d*) 1. RuO$_2$·nH$_2$O, NaIO$_4$, EtOAc/H$_2$O/ACN, r.t., 25 min, 2. Cs$_2$CO$_3$, MeI, 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$_2$·nH$_2$O, NaIO$_4$, EtOAc/H$_2$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 $RuO_2 \cdot nH_2O$ using 5 eq of $NaIO_4$ as co-oxidant in $EtOAc/H_2O$ 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_2CO_3 and MeI. 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

The synthesis of cyclopropane-fused piperidine derivatives described in this section was published as a part in "*Cyclopropane Pipecolic Acids as Templates for Linear and Cyclic Peptidomimetics. Application to the Synthesis of RGD-Containing Peptide as a new Integrin Ligand*" in *Chem. Eur. J.* **2014**, *20*, 11187 – 11203.

Enantiopure (4*R*,5*S*)-**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 %.
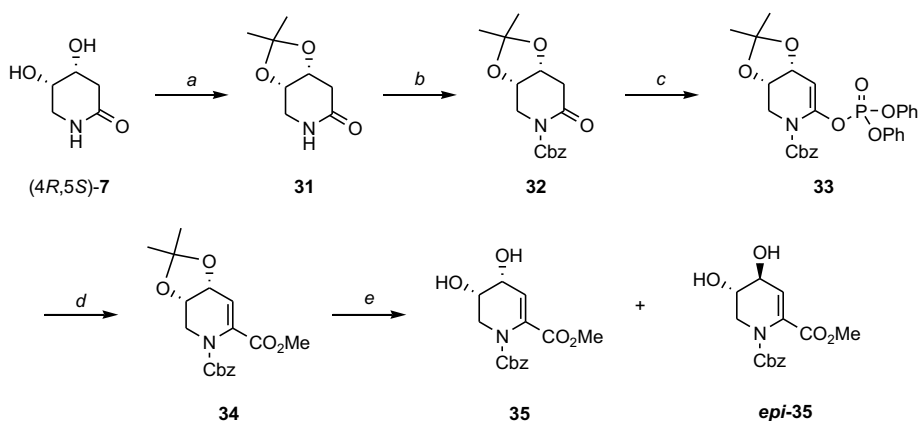

Scheme 8. Synthesis of 4,5-dihydroxy enecarbamate ester **35**. Reagents and conditions: (*a*) *p*TsOH, MeOH, 55 °C, 3 h (75 %); (*b*) CbzCl, *n*-BuLi, -78 °C, THF (83 %); (*c*) (PhO)₂POCl, KHMDS, THF, -78 °C; (*d*) Pd(OAc)₂, PPh₃, CO, DMF, Et₃N, MeOH, 75°C (60 %); (*e*) CHCl₃ : TFA : H₂O = 5 : 1 : 0.1, 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,[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.[2] It was anticipated that in this process, immediately after the formation of Zn-carbenoid from Et_2Zn and CH_2I_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-dihydroxylated pipecolic acid derivative (**37**) which could be used, for example as a template for the synthesis of peptidomimetics.
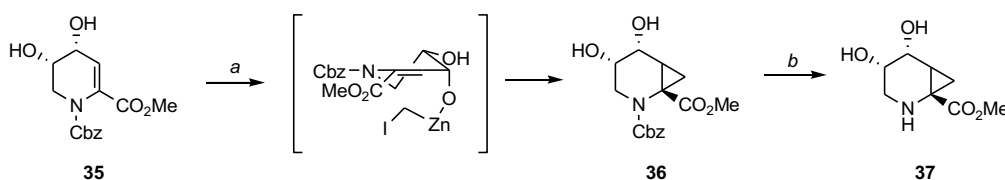

Scheme 9. Simmons-Smith cyclopropanation of **35**. Reagents and conditions: (*a*) TCP, Et_2Zn, CH_2I_2, -40 °C, 15 min, then reflux, 1 h (59%); (b) H_2, Pd/C, EtOAc (80%).

The cylopropane-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,[14] the reliable synthesis of compounds **36** and **39** could also be of interest for the agro- and pharmaceutical industry.
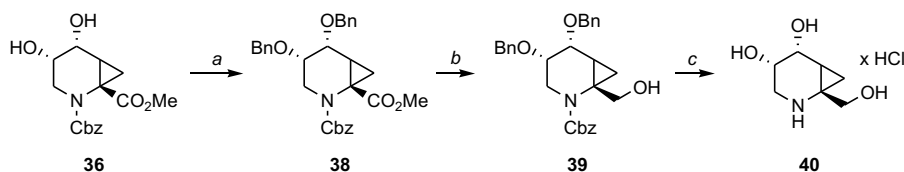
Scheme 10. Reagents and conditions: (*a*) NaH, BnBr, TBAI, DMF, r.t., 3 h (74 %); (*b*) Super-H, THF, 0 °C, 1.5 h (92 %); (*c*) H_2, Pd/C, HCl, MeOH, r.t., 16 h (92 %).

Some of very potent glycosidase inhibitors are in form of glycoside[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.[16,17] Product **42** was obtained in high yield but as a mixture of *α/β*-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.
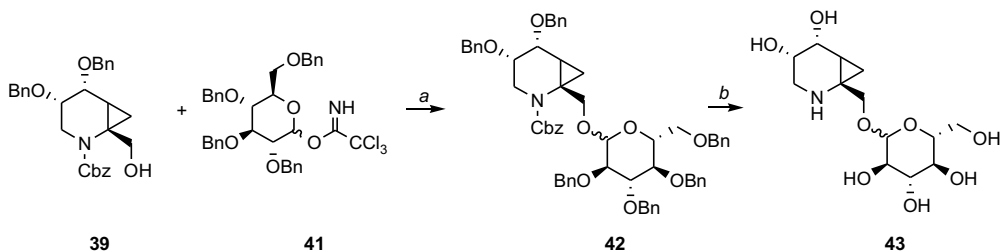
Scheme 11. Synthesis of glycoside **43**. Reagents and conditions: (*a*) TMSOTf, Et$_2$O, -20 °C, 1 h (96 %); (*b*) H$_2$, HCl, Pd/C, HCl, MeOH, r.t., 16 h (90 %).

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, 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$_3$), 2.05 and 29.84 (acetone-d6), 3.31 and 49.00 (CD$_3$OD) 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.
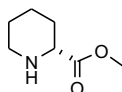
**Piperidine-2-carboxylic acid methyl ester hydrochloric salt (21).**

SOCl$_2$ (0.74 mL, 10.16 mmol) was added dropwise to the cooled suspension of D-pipecolic 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 SOCl$_2$ 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.[18] M.p. = 157.8 – 159.0 °C. $[\alpha]_D^{20}$ = + 7.9 (c = 1.2, H$_2$O).
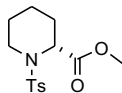
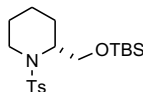
1-(Toluene-4-sulfonyl)-piperidine-2-carboxylic acid methyl ester (22).

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), Et$_3$N (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 NaHCO$_3$ (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 Na$_2$SO$_4$ for 30 min, filtered and concentrated. The oily residue was purified by flash chromatography (heptane/EtOAc, 2 : 1, R$_f$ = 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.[19] $[\alpha]_D^{23}$= + 39.5 (c = 0.98, DCM).
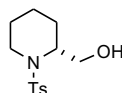
[1-(Toluene-4-sulfonyl)-piperidin-2-yl]-methanol (23).

To the cooled solution of **22** (1.6 g, 5.38 mmol) in THF (35 mL) LiBH$_4$ (705 mg, 32.3 mmol) was added portionwise. The reaction mixture was stirred at room temperature for 48 h. The excess of LiBH$_4$ 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 Na$_2$SO$_4$ for 30 min, filtered and concentrated. The oily residue was purified by flash chromatography (heptane/EtOAc, 3 : 2, R$_f$ = 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.[20] $[\alpha]_D^{24}$ = + 34.3 (c = 1.16, DCM).


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 Na$_2$SO$_4$ for 30 min, filtered and concentrated. The oily residue was purified by flash chromatography (heptane/EtOAc, 5 : 1, R$_f$ = 0.38) to give the product **11** (1.90 g, 97 %) as a colourless oil. $[\alpha]_D^{23}$ = + 32.2 (c = 0.48, DCM). ^{1}H NMR (400 MHz, CDCl$_3$) δ = 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-CH$_2$OTBS), 3.60 (dd, J = 9.9, 5.4 Hz, 1-H, 2-CH$_2$OTBS), 3.01 (td, J = 13.7, 2.6 Hz, 1H, 6-H), 2.42 (s, 3H, CH$_3$-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, CH$_3$-TBS), 0.03 (s, 3H, CH$_3$-TBS), 0.02 (s, 3H, CH$_3$-TBS) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) δ = 142.6 (s, Ts), 138.6 (s, Ts), 129.3 (d, 2C, Ts), 126.8 (d, 2C, Ts), 61.3 (t, CH$_2$OTBS), 53.0 (d, C-2), 41.6 (t, C-6), 25.8 (q, CH$_3$-Ts), 24.4 (t, C-3), 23.9 (t, C-5), 21.3 (t, C-4), 18.4 (q, 3C, CH$_3$-TBS) 18.7 (s, TBS), 5.5 (q, CH$_3$-TBS), 5.7 (q, CH$_3$-TBS) ppm. MS (ESI) m/z (%): 384 ([M+1]+, 25).[21] Elemental analysis calcd (%) for C$_{19}$H$_{33}$NO$_3$SSi: C 59.49; H 8.67; N 3.65; found C 59.61, H 8.62, N 3.70.
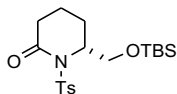
6-(tert-Butyl-dimethyl-silanyloxymethyl)-1-(toluene-4-sulfonyl)-piperidin-2-one (13).
$NaIO_4$ (5.3 g, 24.8 mmol) was dissolved in water (20 mL) and $RuO_2 \cdot nH_2O$ (200 mg, 1.48 mmol) was added under nitrogen atmosphere, to the solution which rapidly turned yellow while being stirred. Then a solution 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, R_f = 0.36) to give pure **13** (1.06 g, 55 %) as a white wax. $[\alpha]_D^{22}$ = + 41.8 (c = 0.44, DCM). ^{1}H NMR (400 MHz, CDCl$_3$) 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-CH$_2$OTBS), 3.76 (dd, *J* = 10.1, 7.8 Hz, 1H, 6-CH$_2$OTBS), 2.45 (m, 1H, 3-H), 2.41 (s, 3H, CH$_3$-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, CH$_3$-TBS), 0.10 (s, 3H, CH$_3$-TBS), 0.05 (s, 3H, CH$_3$-TBS) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) 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, CH$_2$OTBS), 56.8 (d, C6), 33.6 (t, C3), 25.6 (q, CH$_3$Ts), 24.9 (t, C4), 21.6 (t, C5), 18.1 (q, TBS), 16.6 (q, 3C, TBS), -5.5 (q, TBS), -5.7 (q, TBS) ppm. MS (ESI) *m/z* (%): 398 ([M+1]+, 100).[21] Elemental analysis calcd (%) for C$_{19}$H$_{31}$NO$_4$SSi: C 57.39; H 7.86; N 3.52; found C 57.36, H 7.84, N 3.56.
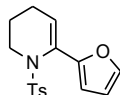
**6-Furan-2-yl-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridine (24).**
An aqueous Na$_2$CO$_3$ (2 M, 100 mL), (Ph$_3$P)$_2$PdCl$_2$ (550 mg, 0.78 mmol) and 2-furanylboronic acid (2.63 g, 23.5 mmol) were added to a solution of phosphate[22] (7.57 g, 15.6 mmol) in THF (200 mL). The mixture was heated at 40 °C for 2 h, then diluted with H$_2$O (100 mL) and the product extracted with EtOAc (3 x 100 mL). The combined organic layer was dried with K$_2$CO$_3$. After filtration and evaporation of the solvent, crude was purified twice by flash chromatography (heptane/EtOAc, 4 : 1, R_f = 0.26) to afford **24** (3.26 g, 70 %) which was not stable and decomposed when neat. ^{1}H NMR (400 MHz, CDCl$_3$) 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, CH$_3$-Ts), 2.07 – 2.02 (m, 2H, 4-H), 1.51 – 1.45 (m, 2H, 5-H) ppm.
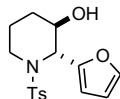
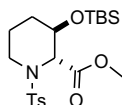
2-Furan-2-yl-1-(toluene-4-sulfonyl)-piperidin-3-ol (25).
A solution of 2 M (CH$_3$)$_2$S·BH$_3$ in THF (11 mL, 21 mmol) was added to a solution of **24** (3.2 g, 10.5 mmol) in anhydrous THF (30 mL) at 0 °C under N$_2$ atmosphere. The cooling bath was removed and the mixture was stirred at room temperature for 24 h. The reaction was cooled to 0 °C and EtOH (10 mL), 3M solution of NaOH (9 mL) and H$_2$O$_2$ (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 Na$_2$SO$_4$. After filtration and evaporation of the solvent, the residue was purified by chromatography (heptane/EtOAc, 3 : 2, R_f = 0.3) to give **25** (1.45 g, 43 %) as a colourless yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$) 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, CH$_3$-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. ^{13}C NMR (100.4 MHz, CDCl$_3$) 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, CH$_3$-Ts), 18.7 (C4) ppm. Elemental analysis calcd (%) for C$_{16}$H$_{19}$NO$_4$S; C 59.79; H 5.96; N 4.36; found C 59.92, H 6.00, N 4.41.
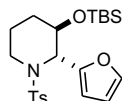
3-(tert-Butyl-dimethyl-silanyloxy)-2-furan-2-yl-1-(toluene-4-sulfonyl)-piperidine (26).
To the solution of **25** (1 g, 3.11 mmol) in DCM (31 mL) DIPEA (1.1 mL, 6.23 mmol) and TBSOTf (1.07 mL, 4.6 mmol) were added at 0 °C. Reaction mixture was stirred at room temperature. After 20 h water (50 mL) was added and the product was extracted with EtOAc (3 x 40 mL). Combined organic layer was dried over anhydrous Na$_2$SO$_4$ for 30 min, filtered and concentrated. The oily residue was purified by flash chromatography (heptane/EtOAc, 5 : 1, R$_f$ = 0.32) to give the product **26** (1.26 g, 93 %) as a colourless oil. ^{1}H NMR (400 MHz, CDCl$_3$) 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, CH$_3$-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. ^{13}C NMR (100.4 MHz, CDCl$_3$) 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, C-5), 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 calcd (%) for C$_{22}$H$_{33}$NO$_4$SSi; C 60.65; H 7.63; N 3.22; found C 60.70, H 7.65, N 3.30.
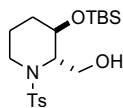

3-(tert-Butyl-dimethyl-silanyloxy)-1-(toluene-4-sulfonyl)-piperidine-2-carboxylic acid methyl ester (27).
To a solution of NaIO$_4$ (1.55 g, 7.25 mmol) in EtOAc (5 mL)/ACN (13 mL)/H$_2$O (7 mL) cooled to 0 °C, RuO$_2 \cdot n$H$_2$O (4 mg, 0.03 mmol) was added. The reaction was stirred at 0 °C for 10 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 Na$_2$SO$_4$, filtered and evaporated.

The crude carboxylic acid was dissolved in DMF (5 mL) and Cs$_2$CO$_3$ (260 mg, 0.8 mmol) and MeI (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 Et$_2$O (4 x 10 mL). The combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered and and concentrated. The oily residue was purified by flash chromatography (n-hexane/EtOAc, 10 : 1, R$_f$ = 0.26) to give the product **27** (420 g, 68 %) as a yellow wax. ^{1}H NMR (400 MHz, CDCl$_3$) 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, OCH$_3$), 3.48 – 3.41 (m, 1H, 6-H), 3.21 (td, J = 12.7, 3.1 Hz, 1H, 6-H), 2.41 (s, 3H, CH$_3$-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, 4-H), 1.39 – 1.31 (m, 1H, 5-H), 0.91 (s, 9H, CH$_3$-TBS), 0.13 (s, 3H, CH$_3$-TBS), 0.10 (s, 3H, CH$_3$-TBS) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) 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, OCH$_3$), 42.6 (t, C6), 28.3 (t, C5), 25.7 (q, 3C, CH$_3$-TBS), 21.5 (q, CH$_3$-Ts), 18.2 (t, C3), 18.1 (s, TBS), -5.1 (q, 2C, CH$_3$-TBS). MS (ESI) m/z (%): 428 ([M+1]$^+$, 43), 450 ([M+Na]$^+$, 16), 876 ([2M+Na]$^+$, 100). Elemental

analysis calcd (%) for $C_{20}H_{33}NO_5SSi$; C 56.17; H 7.78; N 3.28; found C 56.21, H 7.80, N 3.28.
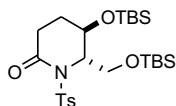

[3-(tert-Butyl-dimethyl-silanyloxy)-1-(toluene-4-sulfonyl)-piperidin-2-yl]-methanol (28).

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 Na_2SO_4. After filtration and evaporation of the solvent, the crude was purified by flash chromatography (n-hexane/EtOAc, 2 : 1; R_f = 0.19) affording compound **28** (215 mg, 57 %) as a colourless oil. ^{1}H NMR (400 MHz, CDCl$_3$): 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, CH$_2$OH), 3.70 – 3.60 (m, 1H, CH$_2$OH), 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, CH$_3$-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, CH$_3$-TBS), 0.01 (s, 3H, CH$_3$-TBS), -0.00 (s, 3H, CH$_3$-TBS) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) 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, CH$_2$OH), 41.5 (t, C2), 27.8 (t, C4), 25.8 (q, 3C, CH$_3$-TBS), 21.4 (q, CH$_3$-Ts), 18.6 (t, C5), 18.2 (s, TBS), -4.92 (q, 2C, CH$_3$-TBS) ppm. MS (ESI) m/z (%): 400 ([M+1][+], 31), 422 ([M+Na][+], 30), 821 ([2M+Na][+], 100). Elemental analysis calcd (%) for $C_{19}H_{33}NO_4SSi$; C 57.11; H 8.32; N 3.51; found C 56.99, H 8.27, N 3.49.
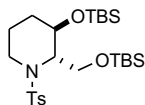
3-(tert-Butyl-dimethyl-silanyloxy)-2-(tert-butyl-dimethyl-silanyloxymethyl)-1-(toluene-4-sulfonyl)-piperidine (29).

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; R_f = 0.20) compound **29** (214 mg, 83 %) was obtained as a white solid. M.p. = 88.5 – 90.2 °C. ^{1}H NMR (400 MHz, CDCl$_3$) 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, CH$_2$OTBS), 3.46 – 3.35 (m, 1H, 6-H), 3.00 (td, J = 12.9, 2.8 Hz, 1H, 6-H), 2.39 (s, 3H, CH$_3$-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, CH$_3$-TBS), 0.88 (s, 9H, CH$_3$-TBS), 0.07 (s, 3H, CH$_3$-TBS), 0.06 (s, 6H, CH$_3$-TBS), 0.04 (s, 3H, CH$_3$-TBS) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) 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, CH$_2$OTBS), 60.2 (d, C2), 41.6 (t, C6), 26.5 (t, C4), 25.8 (q, 6C, CH$_3$-TBS), 21.4 (q, CH$_3$-Ts), 18.2 (t, C5), 18.1 (s, 2C, TBS), -4.9 (q, CH$_3$-TBS), -5.0 (q, CH$_3$-TBS), -5.4 (q, CH$_3$-TBS), -5.6 (q, CH$_3$-TBS) ppm. MS (ESI) m/z (%): 514 ([M+1][+], 58), 536 ([M+Na][+], 29), 1048 ([2M+Na][+], 100). Elemental analysis calcd (%) for $C_{25}H_{47}NO_4SSi_2$; C 58.43; H 9.22; N 2.73; found C 58.45, H 9.20, N 2.75.

5-(tert-Butyl-dimethyl-silanyloxy)-6-(tert-butyl-dimethyl-silanyloxymethyl)-1-(toluene-4-sulfonyl)-piperidin-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; R_f = 0.18) compound **30** (74 mg, 74 %) was obtained as a white solid. M.p. = 158.4 – 155.2 °C. ^{1}H NMR (400

MHz, CDCl$_3$) 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 (dd, J = 10.5, 3.7 Hz, 1H, CH$_2$OTBS), 3.60 (dd, J = 10.5, 8.7 Hz, 1H, CH$_2$OTBS), 2.47 (ddd, J = 18.0, 12.0, 7.6 Hz, 1H, 3-H), 2.35 (s, 3H, CH$_3$-Ts), 2.28 (ddd, J = 18.0, 7.3, 1.4 Hz, 1H, 3-H), 2.07 (dddd, 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, CH$_3$-TBS), 0.82 (s, 9H, CH$_3$-TBS), 0.08 (s, 3H, CH$_3$-TBS), 0.06 (s, 3H, CH$_3$-TBS), 0.03 (s, 6H, CH$_3$-TBS) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) 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, CH$_2$OTBS), 64.0 (d, C5), 28.6 (t, C3), 25.7 (q, 6C, CH$_3$-TBS), 24.3 (t, C4), 21.5 (q, CH$_3$-Ts), 18.0 (q, 2C, CH$_3$-TBS), -4.5 (q, 2C, CH$_3$-TBS), -5.6 (q, CH$_3$-TBS) ppm. MS (ESI) m/z (%): 528 ([M+1]$^+$, 33), 1077 ([2M+Na]$^+$, 100). Elemental analysis calcd (%) for C$_{25}$H$_{45}$NO$_5$SSi$_2$; C 56.88; H 8.59; N 2.65; found C 56.95, H 8.52, N 2.70.
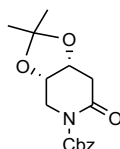
(3a*R*,7a*S*)-Benzyl 2,2-Dimethyl-6-oxotetrahydro[1,3]dioxolo[4,5-c]pyridine-5(4*H*)-carboxylate (32).

A solution of protected lactam **31**[4] (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 benzyl 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 NaHCO$_3$ (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 Na$_2$SO$_4$, filtered and evaporated. After purification by flash chromatography (*n*-hexane/EtOAc, 1 : 2; R$_f$ = 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.[23] M.p. = 115.9 - 117.6 °C. $[\alpha]_D^{21}$ = −57.0 (c = 0.23, CHCl$_3$). Elemental analysis calcd (%) for C$_{16}$H$_{19}$NO$_5$; C 62.94, H 6.27, N 4.59; found C 63.10, H 6.41, N 4.49.
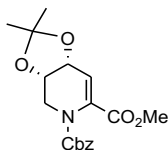

5-Benzyl 6-Methyl (3a*R*,7a*S*)-2,2-dimethyl-3a,7a-dihydro[1,3]dioxolo[4,5-c]pyridine-5,6(4H)-dicarboxylate (34).

A 0.5 M solution of KHMDS in toluene (12.9 mL, 6.43 mmol) was diluted in anhydrous THF (48 mL) and cooled to -78 °C. 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 diphenylchlorophosphate (1.34 mL, 6.43 mmol) was slowly added. After 1 h, the mixture was allowed to warm to 0 °C. Aqueous 10 % NaOH (130 mL) was slowly added and the product extracted with Et$_2$O (4 x 65 mL). The combined organic extracts were washed with 10 % NaOH (120 mL) and dried over K$_2$CO$_3$ 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 % Et$_3$N; R$_f$ = 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.[23]

A solution of phosphate **33** (2.75 g, 5.11 mmol), Pd(OAc)$_2$ (114.7 mg, 0.511 mmol) and Ph$_3$P (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 Et$_3$N (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 Et_2O (5 x 60 mL). The combined organic extracts were dried over Na_2SO_4. After filtration and evaporation of the solvent, crude was purified by flash chromatography (n-hexane/EtOAc, 2 : 1 + 1 % Et_3N; R_f = 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.[23] $[\alpha]_D^{21}$ = +37.2 (c = 0.95, $CHCl_3$). Elemental analysis calcd (%) for $C_{18}H_{21}NO_6$; C 62.24, H 6.09, N 4.03; found: C 62.27, H 5.79, N 4.26.
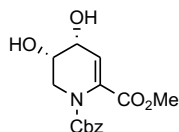
(4S,5R)-1-Benzyl 2-Methyl 4,5-Dihydroxy-5,6-dihydropyridine-1,2(4H)-dicarboxylate (35).
A mixture of trifluoroacetic acid and water (7.15 mL, TFA/H_2O, 0.1 : 1) was added to a solution of compound **34** (1.23 g, 3.54 mmol) in $CHCl_3$ (32.5 mL). The reaction mixture was left to stir 10 min at room temperature and, after cooling to 0 °C, the reaction was quenched adding K_2CO_3 (7.5 g). After 3 min a satd. solution of $NaHCO_3$ (65 mL) was slowly added and the layers were separated. The product was extracted with $CHCl_3$ (3 x 40 mL) and the combined organic extracts were dried over anhydrous K_2CO_3. After filtration and evaporation of the solvent, the crude was purified by flash chromatography ($CHCl_3$/acetone, 3 : 1; R_f = 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 %. $[\alpha]_D^{21}$ +68.2 (c = 0.98, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38 - 7.30 (m, 5 H, Ph), 5.87 (d, *J* = 3.6 Hz, 1H, 3-H), 5.15 (s, 2 H, CH_2Ph), 4.31 (bm, 1H, 4-H), 3.95 (bm, 1H, 5-H), 3.81 (dd, *J* = 13.1, 2.8 Hz, 1 H, 6-H_{eq}), 3.70 (dd, *J* = 13.1, 7.8 Hz, 1H, 6-H_{ax}), 3.57 (s, 3 H, OCH_3), 2.57 (d, *J* = 5.8 Hz, 1H, OH), 2.42 (d, J = 7.0 Hz, 1H, OH) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$) δ = 164.7 (s, CO), 154.4 (NCO_2Bn), 135.3 (C_{arom}), 133.3 (C2), 128.5 ($2C_{arom}$), 128.4 ($2C_{arom}$), 128.2 (C_{arom}), 120.3 (C3), 68.5 (CH_2Ph), 66.2 (C4), 64.6 (C5), 52.3 (OCH_3), 47.3 (C6) ppm. MS (ESI) m/z (%): 638 (100) $[2M+Na]^+$, 330 (34) $[M+Na]^+$, 308 (15) $[M+Na]^+$. Elemental analysis calcd (%) for $C_{15}H_{17}NO_6$; C 53.63, H 5.58, N 4.56; found: C 53.23, H 5.32, N 4.02.
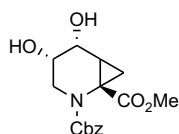
**2-Benzyl 1-Methyl (1R,4R,5S,6S)-4,5-Dihydroxy-2-azabicyclo[4.1.0]heptane-1,2-dicarboxylate (36).**
To a solution of 2,4,6-trichlorophenol (395 mg, 2 mmol) in anhydrous CH_2Cl_2 (10 mL), cooled to –40 °C and under nitrogen atmosphere, 1 M solution of Et_2Zn in hexane (2 mL, 2 mmol) was slowly added. The mixture was stirred for 15 min, then CH_2I_2 (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 Na_2CO_3 (2 x 20 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent, the crude was purified by flash chromatography ($CHCl_3$/acetone, 3 : 1; R_f = 0.33) affording compound **36** (55 mg, 53 %) as white gummy solid. $[\alpha]_D^{21}$ = +27.4 (c = 0.98, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) (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, 1 H, 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-H_{eq}, major rotamer), 4.16 (t, *J* = 4.2 Hz, 1H, 5-H,

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) δ = 172.1 (CO), 157.6 (NCO$_2$Bn), 136.4 (C$_{arom}$), 128.4 (2C$_{arom}$), 127.9 (2C$_{arom}$), 127.4 (C$_{arom}$), 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 calcd (%) 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.
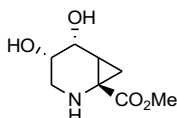
1-Methyl (1R,4R,5S,6S)-4,5-Dihydroxy-2-azabicyclo[4.1.0]heptane-1-carboxylate (37).

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$_3$) δ = 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$_3$) δ = 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 calcd (%) for C$_8$H$_{13}$NO$_4$; C 51.33, N 7.48, H 7.00; found C 51.52, N 7.16, H 6.77.
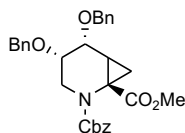
4,5-Bis-benzyloxy-2-aza-bicyclo[4.1.0]heptane-1,2-dicarboxylic acid 2-benzyl ester 1-methyl ester (38).

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, 1.6 mmol) in DMF (1 mL) 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. $[\alpha]_D^{21}$ = + 3.62 (c = 0.69, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) (mixture of rotamers 2 : 1) δ = 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) δ = 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]$^+$.

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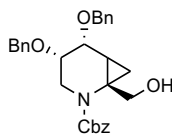
4,5-Bis-benzyloxy-1-hydroxymethyl-2-aza-bicyclo[4.1.0]heptane-2-carboxylic acid benzyl ester (39).

The 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; R$_f$ = 0.16) affording compound **39** (157 mg, 92 %) as a colourless oil. $[\alpha]_D^{24}$ = + 15.2 (c = 0.75, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) (mixture of rotamers 3 : 2) δ = 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) δ = 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$_5$; C 73.55, N 2.96, H 6.60; found C 73.70, N 2.99, H 6.52.
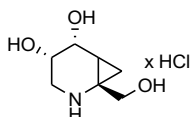
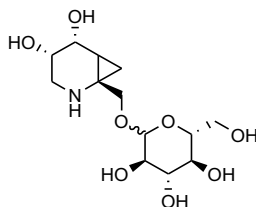## 1-Hydroxymethyl-2-aza-bicyclo[4.1.0]heptane-4,5-diol (40).

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) δ = 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$_3$) δ = 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$_7$H$_{14}$NO$_3$Cl; C 42.97, N 7.16, H 7.21; found C 43.02, N 7.05, H 7.23.
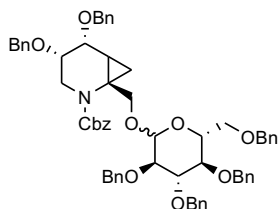
4,5-Bis-benzyloxy-1-(3,4,5-tris-benzyloxy-6-benzyloxymethyl-tetrahydro-pyran-2-yloxymethyl)-2-aza-bicyclo[4.1.0]heptane-2-carboxylic acid benzyl ester (42).

A solution of **39** (51 mg, 0.109 mmol) and benzyl protected glucopyranosyl trichloroacetamidate (126 mg, 0.185 mmol) in dry Et_2O (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 Et_2O (10 mL) and washed with sat. Na_2CO_3. The organic layer was dried over Na_2SO_4. After filtration and evaporation of the solvent, the crude was purified by flash chromatography (n-hexane/Et_2O, 1 : 1; R_f = 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 calcd (%) for $C_{63}H_{65}NO_{10}Cl$; 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. ^{1}H NMR (400 MHz, CDCl$_3$) 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-CH$_2$-O-sugar and 5'-CH$_2$OH), 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.

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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,[1] 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.

Scheme 1.   Gold(I)-catalyzed synthesis of cyclopentenones.
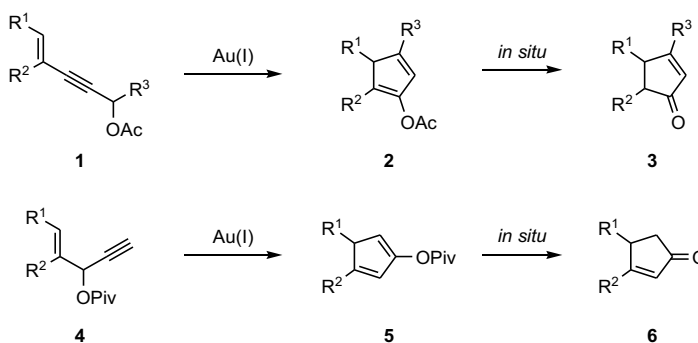
However, a few issues have to be addressed. First of all, the presence of the nitrogen atom could influence the stability of positively charged intermediates and therefore their reactivity. Since the gold(I) activates the triple bond toward nucleophilic addition, nitrogen atom has to be protected. Taking into account that closely related *N*-Boc enynes undergo gold(I)-catalyzed rearrangement to form cyclic urethane,[2] 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/electrocylization 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.


Figure 1.   Piperidine-derived enynyl acetates.
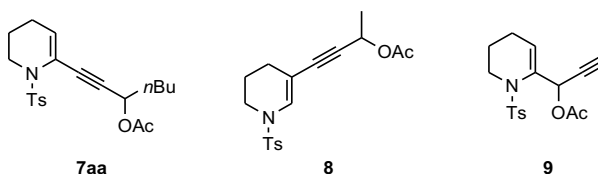
To this end, the piperidine-derived enynyl acetates **7aa**-**9** (Figure 1) were prepared as a model substrates and subjected to the gold(I) catalysis. The detailed experimental studies supported by DFT calculations demonstrated that these processes are more complex than that previously reported for 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

The work described in this section was published as *"Annulated N-Heterocycles by Tandem Gold(I)-catalyzed [3,3]-Rearrangement/Nazarov Reaction of Propargylic Ester Derivatives: an Experimental and Computational Study"* in *Eur. J. Org. Chem.* **2015**, *18,* 3943 – 3956.

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[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).
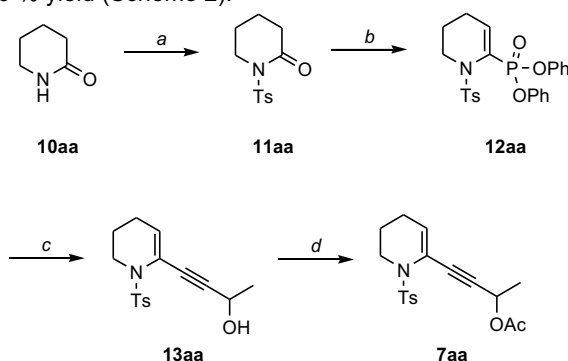
Scheme 2. Synthesis of model substrate **7aa**. Reagents and conditions: (*a*) *n*-BuLi, THF, -78 °C, 30 min; then TsCl (86 %), (*b*) KHMDS, -78 °C, 1.5 h; then (PhO)$_2$POCl, -78 °C, 1 h (80 %); (*c*) heptyn-3-ol, 15 mol % CuI, 6 mol % (Ph$_3$P)$_2$PdCl$_2$, CHCl$_3$-Et$_3$N, 1 : 2, 55 °C, 7 h (62 %); (*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

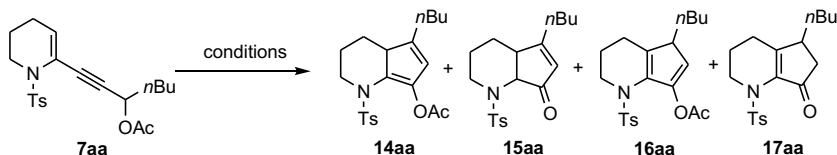Ph$_3$PAuCl/AgSbF$_6$ catalyst system.[a]
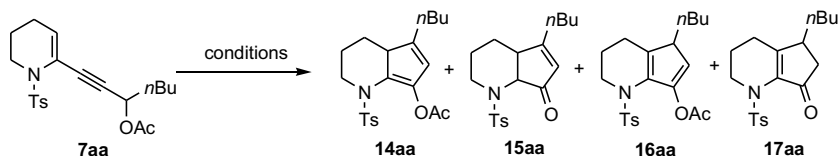
Entry	Catalyst[b]	Conditions[c]	Time (h)[d,e]	Yield[f]			
				14aa	15aa	16aa	17aa
1	Ph$_3$PAuCl/AgSbF$_6$	dry DCM	5 (0)	18[g]	-	22[g]	19[g]
2	Ph$_3$PAuCl/AgSbF$_6$	DCM	2.5	14	3	-	70
3	Ph$_3$PAuCl/AgSbF$_6$	wet DCM	5 (0)	30	-	-	55
4	Ph$_3$PAuCl/AgSbF$_6$	CHCl$_3$	2 (0.5)	30	-	-	60
5	Ph$_3$PAuSbF$_6$[h]	DCM	3	18	-	-	64
6	AgSbF$_6$	DCM	3	-	-	-	<5[g,i]

[a] 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 the hydrolysis. [f] Yield after chromatography unless otherwise indicated. [g] By ^{1}H 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.

Table 2. Optimization of reaction conditions.[a]

Entry	Catalyst[b]	Conditions[c]	Time (h)[d,e]	Yield[f]			
				14aa	15aa	16aa	17aa
1	Ph$_3$PAuCl/AgBF$_4$	DCM	3	18	5	-	62
2	Ph$_3$PAuCl/AgNTf$_2$·ACN	DCM	6	18	5	-	50
3	Ph$_3$PAuCl/AgOTf	DCM	1.5	51	-[g]	-	35
4	Ph$_3$PAuCl/Cu(OTf)$_2$	DCM	6[h]	-	19	-	29
5	Ph$_3$PAuCl/Cu(OTf)$_2$	DCM reflux	0.7 (3)	-	58[g]	-	42[g]
6	Ph$_3$PAuCl/AgOTf	Toluene	1	61	-	-	18
7	Ph$_3$PAuCl/AgOTf	Toluene, 0 °C	5	60	-	-	15
8	Ph$_3$PAuCl/AgOTf	THF	3	32	-	-	31
9	Ph$_3$PAuCl/AgOTf	1,4-dioxane	24[i]	-	-	-	-
10	Ph$_3$PAuCl/AgOTf	ACN	24[i]	-	-	-	-
11	AgOTf	DCM	3	-	-	-	<5[h]
12	Cu(OTf)$_2$	DCM	16 (0)	-	-	-	-

[a] 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 ^{1}H NMR analysis of the crude reaction mixture. [h] Conversion was not complete and degradation of the starting material occurred. [i] No reaction, degradation of starting material.

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 AgBF$_4$ and AgNTf$_2$. 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,[5] 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 regiomers 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 Ph$_3$PAuCl/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**.

Entry	Conditions	Time (h)	Yield	
			15aa	**17aa**
1	TfOH, DCM: MeOH = 1 : 1	20	66	34
2	*p*TsOH x H$_2$O, DCM/MeOH = 1 : 1	20	93	7
3	K$_2$CO$_3$, MeOH	4	degradation	

Furthermore, isolated acetate **14aa** was subjected to the hydrolysis (Table 3). When dissolved in dichloromethane/MeOH and treated with a catalytic amount of monohydrate *p*TsOH, 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 (K$_2$CO$_3$ in MeOH) of **14aa** and isomerisation of **15aa**[6] 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 % Ph$_3$PAuCl/AgSbF$_6$ 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*-CO$_2$Me (**7d**), all prepared in good overall yields as described for **7aa** starting from the corresponding protected lactams (Scheme 3).

11b R = Boc
11c R = Cbz
11d R = CO$_2$Me

12b R = Boc (95%)
12c R = Cbz (80%)
12d R = CO$_2$Me (78%)

13b R = Boc
13c R = Cbz
13d R = CO$_2$Me

7b R = Boc (60%, two steps)
7c R = Cbz (61%, two steps)
7d R = CO$_2$Me (69%, two steps)
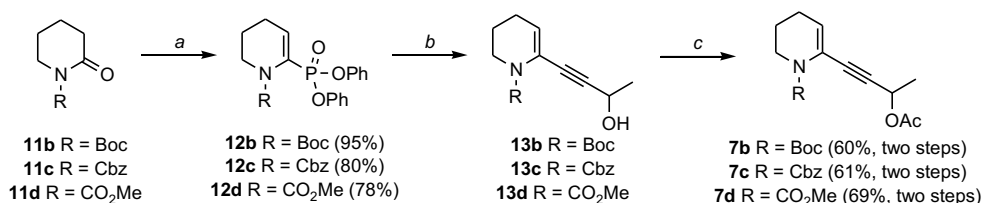
Scheme 3. Reagents and conditions: (*a*) KHMDS, -78 °C, 1.5 h; then (PhO)$_2$POCl, -78 °C, 1 h; (*b*) heptyn-3-ol, 15 mol % CuI, 6 mol % (Ph$_3$P)$_2$PdCl$_2$, CHCl$_3$-Et$_3$N, 1 : 2, 55 °C, 7 h; (*c*) Ac$_2$O, Et$_3$N, DMAP, DCM, 0 °C to r.t., on.

The reaction of *N*-Boc derivative **7b** (Table 4, entries 1-3) only provided degradation products plus about 20% of the oxyauration 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 ^{1}H NMR. Diagnostic signals, the triplet at 4.71 ppm and the singlet at 5.56 ppm were assigned to protons H$_a$ and H$_b$, respectively. Proton H$_c$ 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).
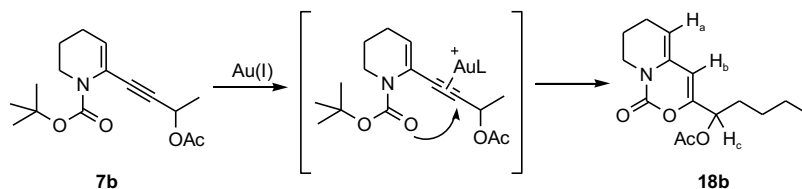
Scheme 4. Formation of cyclic urethane **18b**.

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

Entry	Substrate	Conditions[c]	Time (h)[d]	Yield[e]			
				14	15	16	17
1	**7b**	DCM, 25 °C	16[f]	-[g]	-	-	-
2		Toluene, 25 °C to reflux	3[f]	-	-	-	-
3		Acetone, 25 °C to reflux	3[f]	-	-	-	-
4[h]	**7c**	DCM, 25 °C	20[j]	-	-	-	48
5[h,i]		DCM, reflux	3	-	-	-	61
6	**7d**	DCM, 25 °C	2	-	-	-	-
7		DCM, reflux	2[k]	14	-	-	64
8		Toluene, reflux	1.5[k]	11	-	-	50
9		THF, reflux	1.5[k]	15	-	-	45

[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 ^{1}H 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*-CO$_2$Me 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 raction 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.
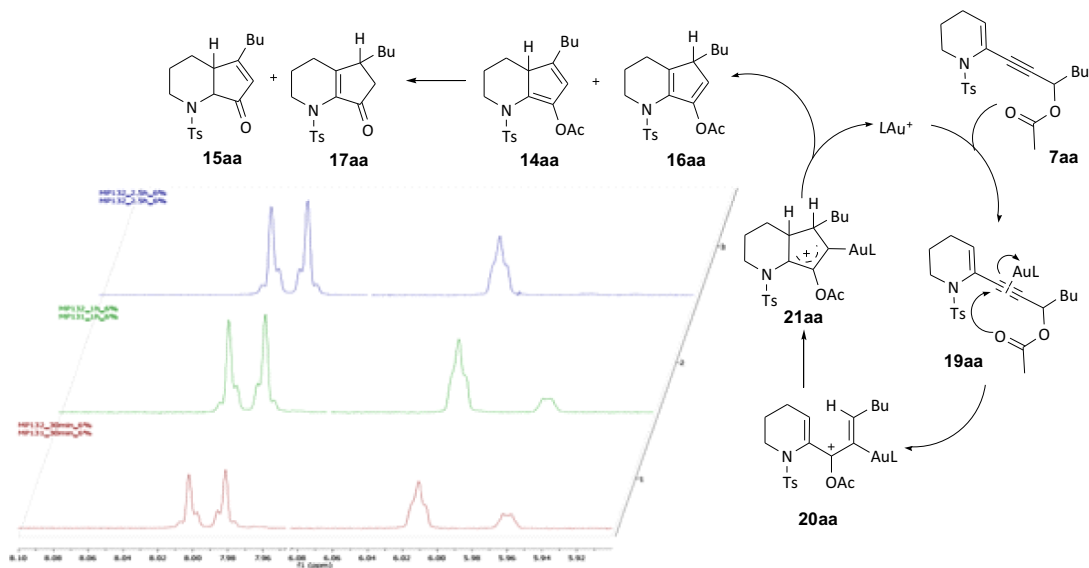
Scheme 5. Proposed reaction mechanism and ^{1}H NMR spectra of reaction carried out in CDCl$_3$ after 0.5 h (red), 1 h (green) and 2.5 h (purple).

To demonstrate that the formation of ketone **17aa** occurs via *in situ* hydrolysis of acetate intermediate **16aa**, we set up one experiment in CDCl$_3$ and monitored the progress of the reaction by ^{1}H 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, ^{1}H 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

50

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.[7] 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[8] density functional theory method as implemented in the Gaussian suite of programs.[9] 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 (ΔG), computed at B3LYP/6-31G** level (LANL2DZ[10] for gold atom).
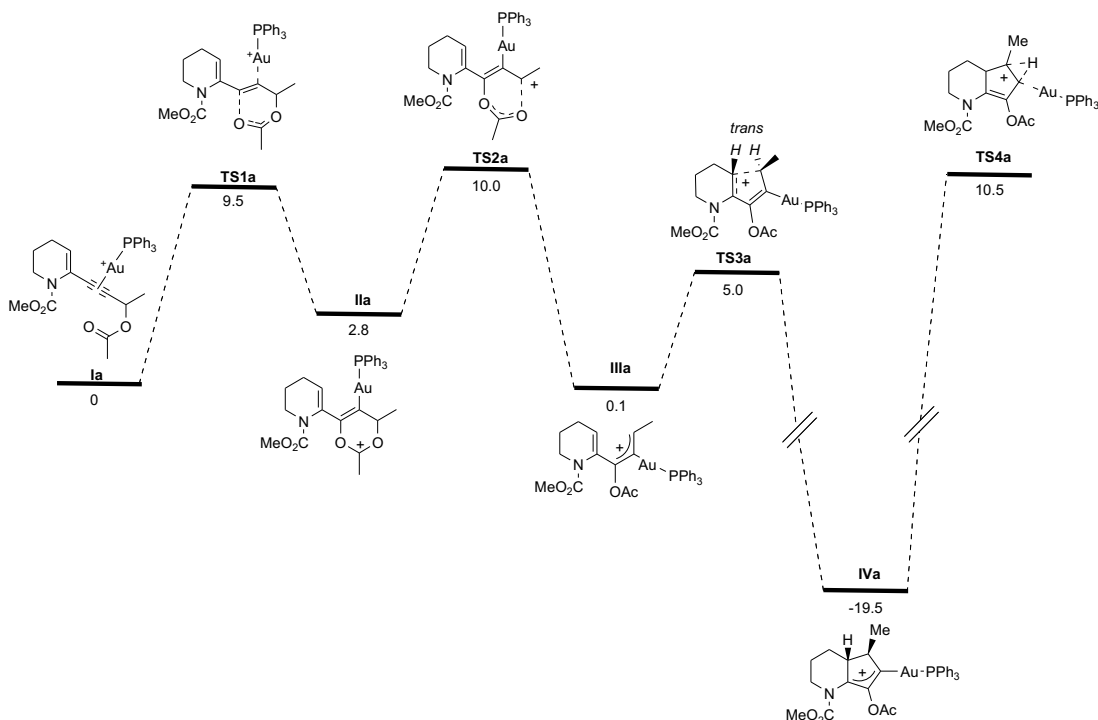
Scheme 6. Computed reaction profile. Energies are in kcal/mol.

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 **IIIa** (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.[11] 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, cca. 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.[12] 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 counterion 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 **V'** 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 AgSbF$_6$ 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 AgSbF$_6$ 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.
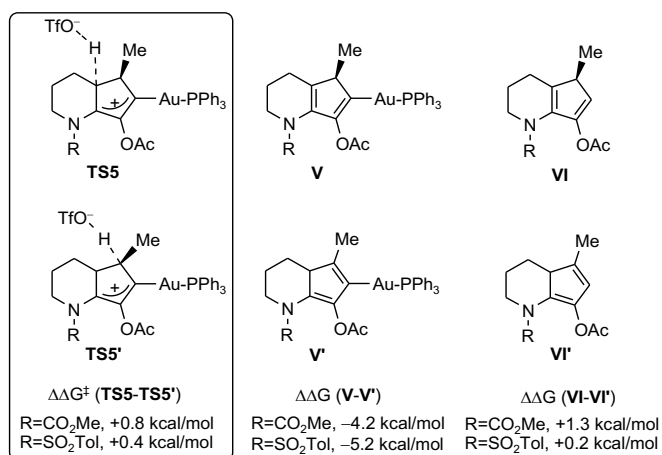
Figure 2. Transition states **TS5** and **TS5'** in the presence of triflate anion and compounds formed thereafter.

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_3O^+ 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_3O^+) 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.

Protonation step

	$\Delta G^{\ddagger}TS6' - \Delta G^{\ddagger}TS6$
TfOH	**5.7** kcal/mol
H_3O^+	**3.5** kcal/mol
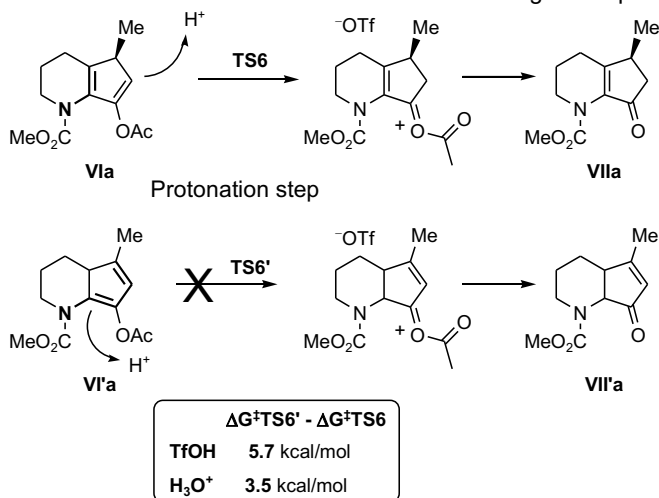
Scheme 7.   Hydrolysis of diene-acetates **VI** and **VI'** in the presence of a model acids (TfOH and H_3O^+).

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 **Ia** can proceed through acetate rearrangement to form **IIIa** or through cyclization with the methyl ester to form **VIIIa**. The three complexes **VIIIa**, **Ia**, 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.
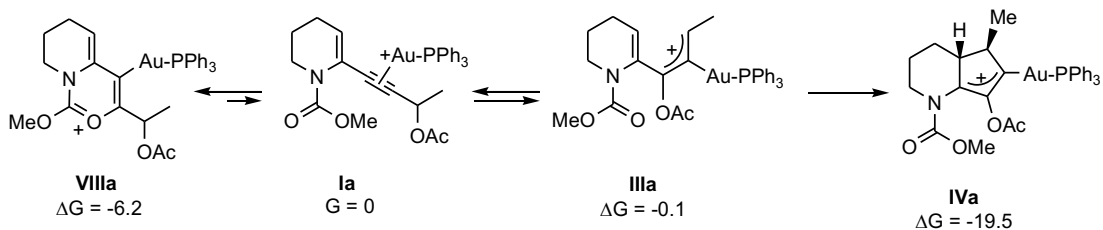
Scheme 8.   DFT predicted formation of the non-productive **VIIIa** intermediate.

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 Ph$_3$PAuSbF$_6$ as the catalyst and provided only cyclopentenone **17e** in 78 % yield after chromatography. ^{1}H NMR analysis of the crude reaction mixture revealed a mixture of diastereomers in 6 : 1 ration, 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.
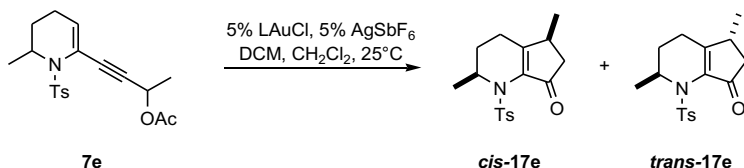
Scheme 9. Influence of different gold ligands on the torquoselectivity: (*a*) L = Ph$_3$P, 78 % yield, **cis-17e** : **trans - 17e** = 6 : 1; (*b*) L = (Cy)$_3$P, 91% yield, **cis-17e** : **trans - 17e** = 10 : 1.

When the electron-rich (Cy)$_3$P ligand was used, both the torquoselectivity (10 : 1) and the yield (91 %) were improved whereas the use of electron-poor [(*p*CF$_3$C$_6$H$_4$)$_3$P] 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.[13] 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).
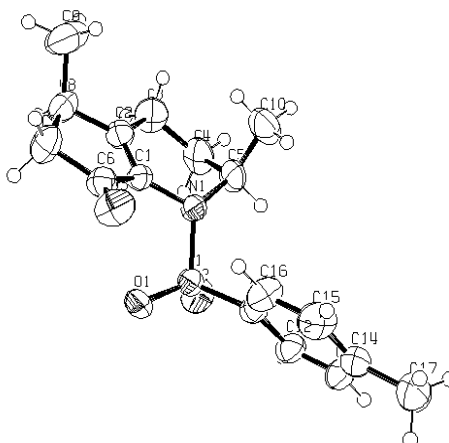
Figure 3. X-Ray structure of **cis-17e**.

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.[14] 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 **XIa** 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.

IXa, G = 0   **IXa'**, ΔG = +2.3

TS7
ΔG‡ = +6.4

TS7'
ΔG‡ = +9.4

TS7"
ΔG‡ = +9.6

Xa   **XIa**
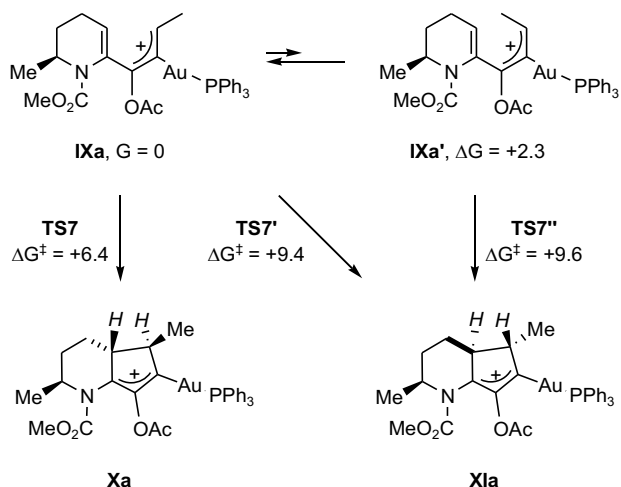
Scheme 10. DFT study on the torquoselectivity of the ring closure.

The torquoselectivity with 4-methyl substitute enyne **7f** was in line with that observed for **7e** using Ph$_3$PAuSbF$_6$ 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.

5% Ph$_3$AuCl, 5% AgSbF$_6$
DCM, CH$_2$Cl$_2$, 25°C

7f   **14f**   *cis*-**17f**   *trans*-**17f**
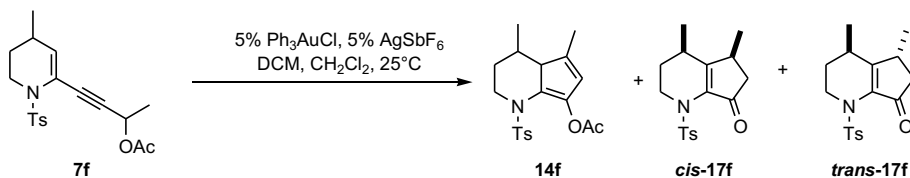
Scheme 11. 14% yield for **14f**, 78 % yield for **17f**, *cis*-**17f** : *trans*-**17f** = 6 : 1.

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 **7e**-**l** were prepared in good yield over two or three steps from lactam-derived enol phosphates **12e**-**l**. In addition, pyrrolidin-2-one derivatives **7m** and **7n**, indole-derived enynyl acetate **7o** and C-3 substituted piperidine enynyl acetate **7p** were obtained from enol triflates **12m**[15] and **12n**,[16] **12o**[17] 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.
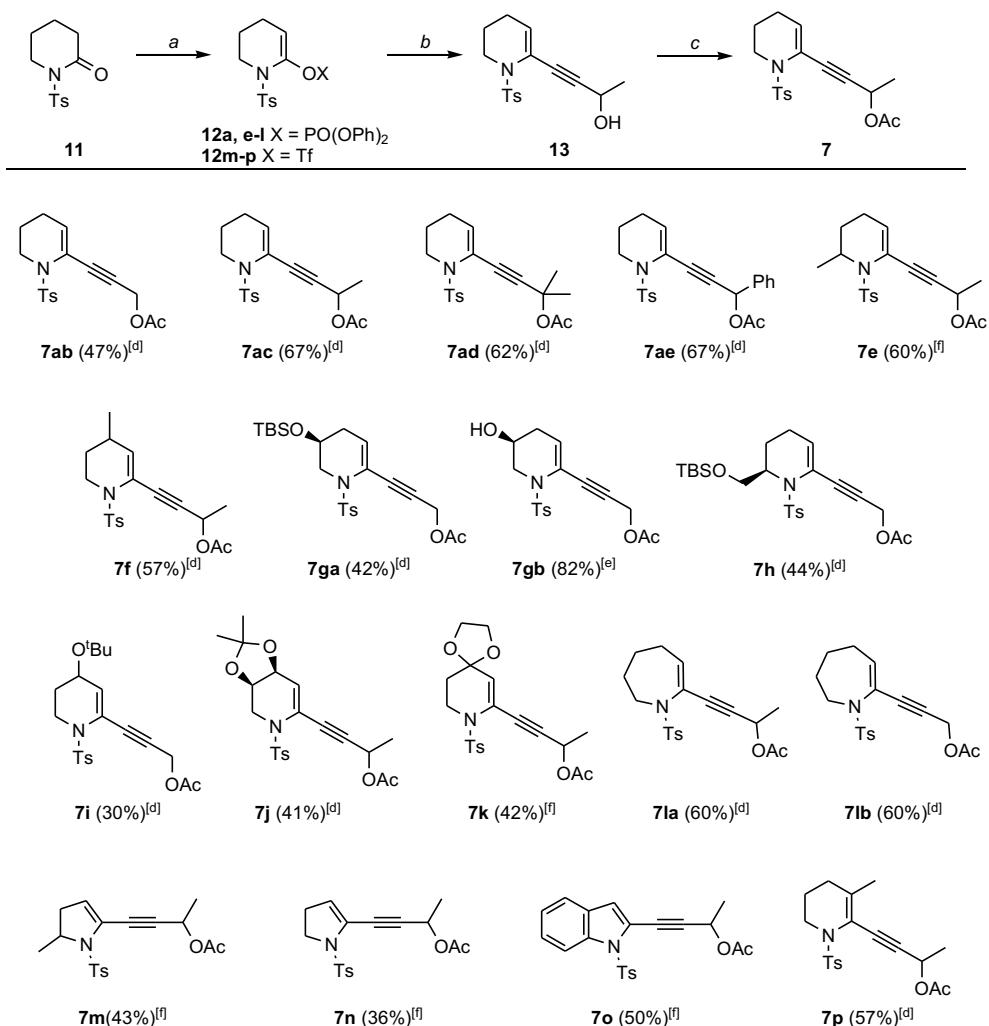
Scheme 12. Synthesis of enynyl acetates **7ab-p**. Reagents and conditions: (*a*) KHMDS, -78 °C, 1.5 h; then (PhO)$_2$POCl or PhNTf$_2$, -78 °C, 1 h, -78 °C, 1 h; (*b*) alkynol, 15 mol % CuI, 6 mol % (Ph$_3$P)$_2$PdCl$_2$, CHCl$_3$-Et$_3$N, 1 : 2, 55 °C, 7 h; (*c*) Ac$_2$O, Et$_3$N, DMAP, DCM, 0 °C to r.t., on. *Notes*: [d] Yield over two steps; [e] Prepared from **7ga**; [f] Yield over three steps.

Once isolated, enynyl acetates **7** were subjected to the gold(I)-catalyzed rearrangement/Nazarov reaction in DCM using Ph$_3$PAuCl/AgSbF$_6$ 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.
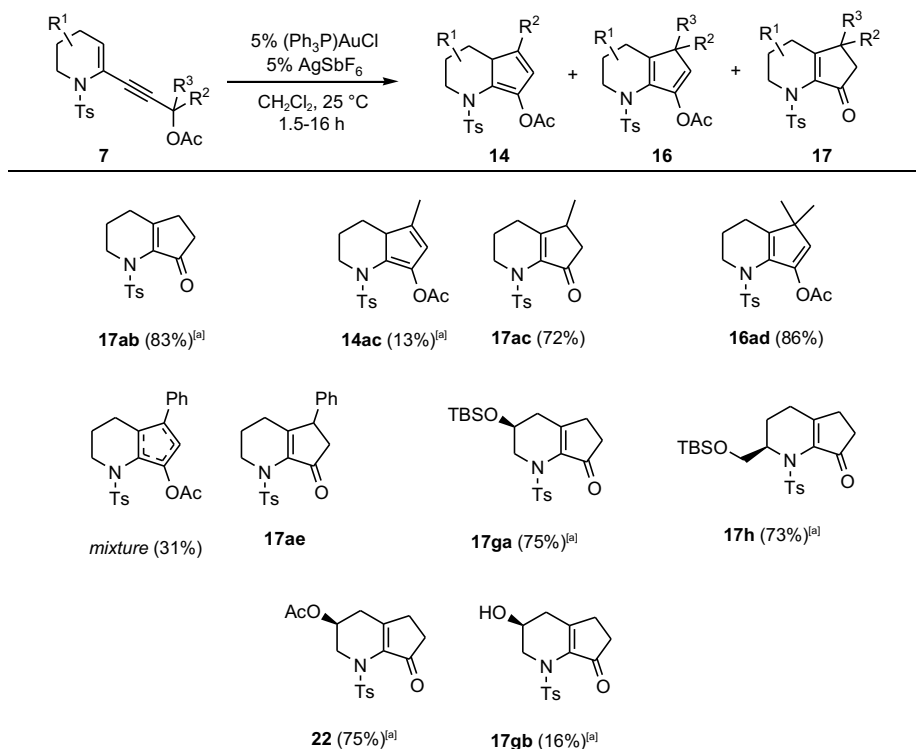
Scheme 13. Gold(I)-catalyzed tandem [3,3]-rearrangement/Nazarov reaction of **7**.
Note: [a] reaction carried out under reflux.

The results obtained with 3'-methyl-substituted **7ac** were in line with those for our model compound **7aa** whereas, curiously, dimethyl-substituted acetate **7ad** provided acetate **16ad** (86 %) only, which did not hydrolyze spontaneously. This was later done by the treatment with pTsOH (Scheme 14) which 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 ^{1}H NMR studies the *cis* fusion of the rings (in analogy to the corresponding carbocyclic systems)[6a] 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-H_{ax} and 4-H_{ax}. 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 compatibile 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 compatibile 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

57

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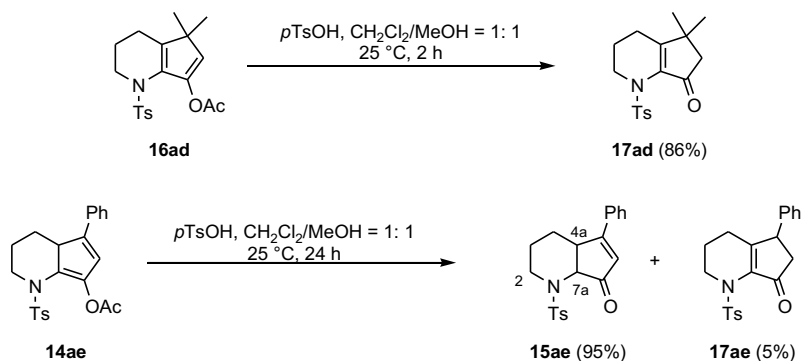
Scheme 14. Hydrolysis of acetates **16ad** and **14ae**.

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 17**la** (81 %) and 17**lb** (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.
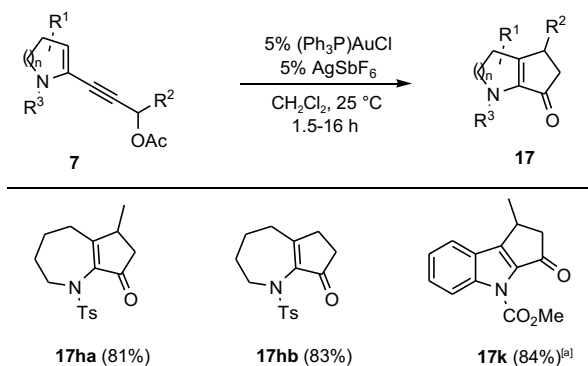
Scheme 15. Gold(I)-catalyzed tandem [3,3]-rearrangement/Nazarov reaction of azepane- and indole-derived enynyl acetates. *Notes*: [a] Reaction carried out under reflux.
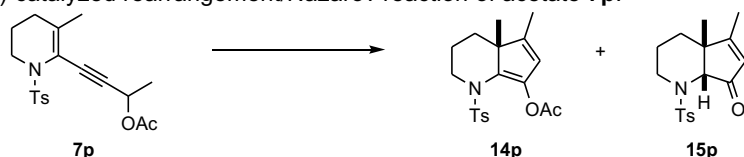
The ring closure of five-membered derivatives **7m** and **7n** did not occur at room temperature or in refluxing DCM. In both cases residual starting material was recovered with a certain amount of unidentified degradation compounds. The reaction of **7n** was also carried out in refluxing toluene, 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[*b*]indole nucleus (Scheme 15).

The construction of quaternary stereocenters is one of the most demanding challenges in the organic synthesis.[19] Gold(I)-catalyzed [3,3]-rearrangemet/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**.[a]

Entry	Catalyst[b]	Conditions	Time (h)	Yield[c]	
				14p	**15p**
1	10% Ph₃PAuCl/AgOTf	DCM, 50°C	4	25	17
2	10% Ph₃PAuCl/AgOTf	DCE, 80°C	4	-	40
3	5% Ph₃PAuCl/AgOTf	Toluene, 100°C	2	-	36
4	5% Ph₃PAuCl, 25% Cu(OTf)₂	Toluene, 100°C	2	-	23
5	5% CyJohnPhosAuCl/AgOTf	DCM, 50°C	2	-	30

[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. [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] 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 Ph₃PAuCl/AgSbF₆ 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 recoverd 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).
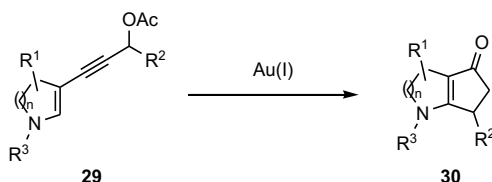
Scheme 16. Gold(I)-catalyzed [3,3]-rearrangement/Nazarov cyclization of *N*-heterocyclic enynyl acetates **29**.

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 transforrmed into enesulfonamide **25a** by conversion into α-sulfonyl derivative **24a** followed by base induced elimination of methanesulfonic acid.[20] In the next step, electrophilic addition of iodine monochloride to the double bond of enesulfonamide **25a** followed by an nucleophilic attack of methanol onto formed iodonium ion afforded α-methoxy-β-iodo piperidine derivative **26a** as a single stereoisomer.[21] 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.[22] 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 I_2/Cs_2CO_3 in dioxane,[23] NIS in DMF,[24] NIS/AgNO$_3$ in acetonitrile[25] and NIS/TFA in DCM[26] failed completely or provided desired product in complex mixture with unknown products.
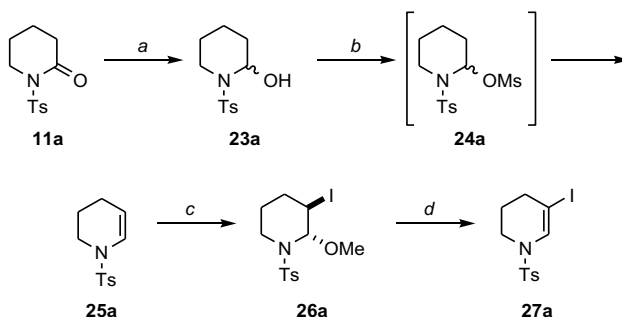
Scheme 17. Synthesis of 3-iodoenesulfonamide **27a**. Reagents and conditions: (*a*) DIBAL-H, THF, -78 °C, 1 h; (*b*) MsCl, Et$_3$N, DMAP, DCM, 0 - 25 °C, 16 h (80 %); (*c*) ICl or NIS, MeOH, 25 °C, 1 h (91 %); (*d*) TFA (cat), toluene 140 °C, 7 min (77 %).

Then, iodoenesulfonamide **27a** was coupled with (±)-butyn-3-ol under Sonogashira conditions[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).
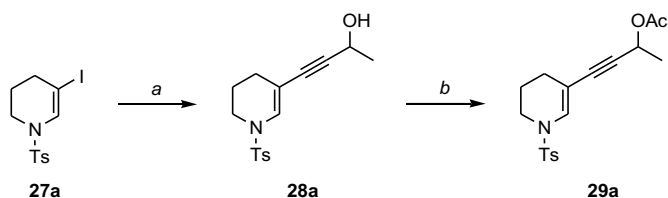
Scheme 18. Synthesis of enynyl acetate **29a**. Reagents and conditions: (*a*) (±)-butyn-3-ol, 10 mol % CuI, 5 mol % (Ph$_3$P)$_2$PdCl$_2$, Et$_2$NH - DMF, 1 : 2, 40 °C, 10 min (85 %), (*b*) Ac$_2$O, Et$_3$N, DMAP, DCM, 0 - 25 °C, on (84 %).

The treatment of enynyl acetate **29a** with 5 mol % of Ph$_3$PAuCl/AgSbF$_6$ 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 decrese 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**.[a]
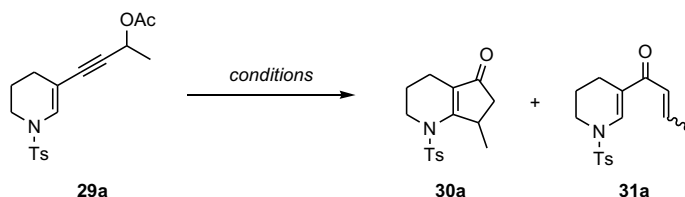
Entry	Catalyst[b]	Solvent[c]	Time (h)	Yield[d]	
				30a	31a
1	Ph$_3$PAuCl/AgSbF$_6$	DCM	6	66	-[e]
2	(cHex)$_3$PAuCl/AgSbF$_6$	DCM	6	10[g]	-
3	(4-CF$_3$Ph)$_3$PAuCl/AgSbF$_6$	DCM	6	49	-[e]
4	Ph$_3$PAuCl/AgSbF$_6$	Dry DCM	1	< 5[g]	-
5	Ph$_3$PAuCl/AgSbF$_6$	DCM[f]		48	-[e]

[a] Reactions carried out on 0.15-0.2 mmol, with 5 mol % of catalyst ar r.t. [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. [d] Yield after chromatography unless otherwise indicated. [e] Detected by ^{1}H NMR analysis of the crude reaction mixture. [f] Reaction carried out in refluxing solvent. [g] Conversion detected by ^{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**.[28] Iodination and Sonogashira coupling followed by acetylation led to the formation of desired enynyl acetate **29l** whose treatment with 5 % of Ph$_3$PAuCl/AgSbF$_6$ in DCM in 6 h afforded cyclopenta-fused product **30l** in 54 % yield.
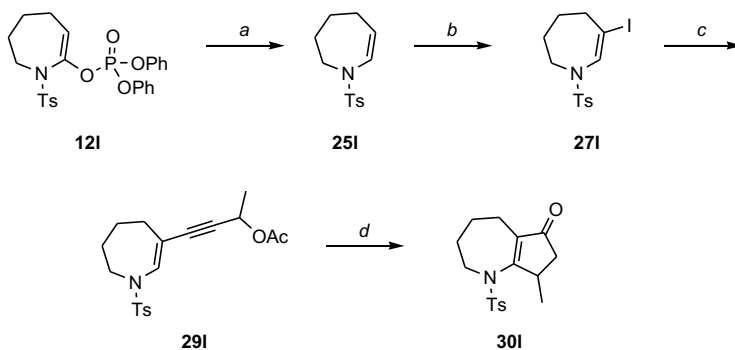
Scheme 19. Synthesis of **30l**. Reagents and conditions: (*a*) 5 mol % Pd(OAc)$_2$, 10 % Ph$_3$P, HCO$_2$H, Et$_3$N, DME, 40 °C, 40 min (62 %); (*b*) 1. ICl, MeOH, 25 °C, 1 h; 2. TFA (cat), toluene 140 °C, 7 min (86 % two steps); (*c*) 1. (±)-butyn-3-ol, 10 mol % CuI, 5 mol % (Ph$_3$P)$_2$PdCl$_2$, 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$_3$PAu/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 cyclopenta-fused 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.
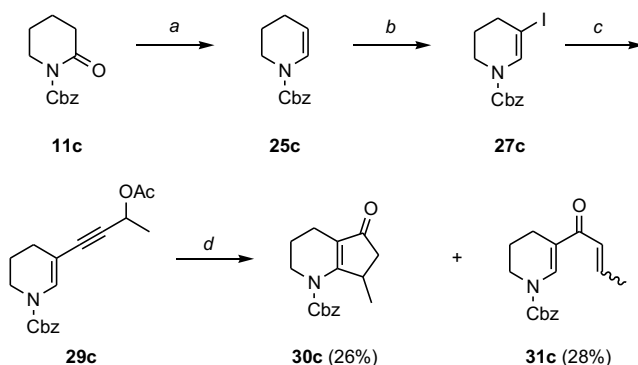
Scheme 20. Reagents and conditions: (*a*) 1. DIBAL-H, THF, -78 °C, 1 h; 2. MsCl, Et$_3$N, DMAP, DCM, 0 - 25 °C, 16 h (61 % two steps); (*b*) 1. ICl, MeOH, 25 °C, 1 h; 2. TFA (cat), toluene 140 °C, 7 min (75 % two steps); (*c*) 1. (±)-butyn-3-ol, 10 mol % CuI, 5 mol % (Ph$_3$P)$_2$PdCl$_2$, Et$_2$NH - 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.[7] As the model substrate, compound **29a** was used. The structures were located using the B3LYP[8] density functional theory method as implemented in the Gaussian suite of programs.[9] 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[10] for gold atom).
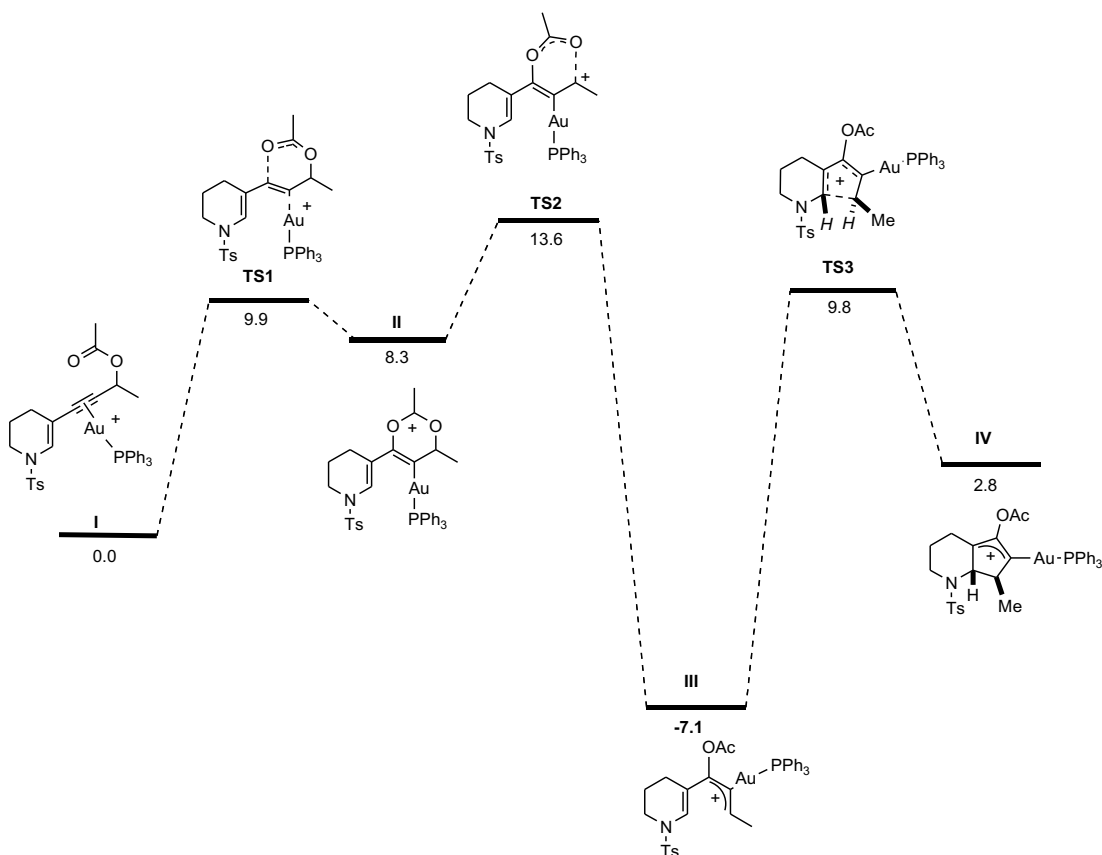
Scheme 21.   Computed reaction profile. Energies are in kcal/mol.

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 positve 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.[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.[31]
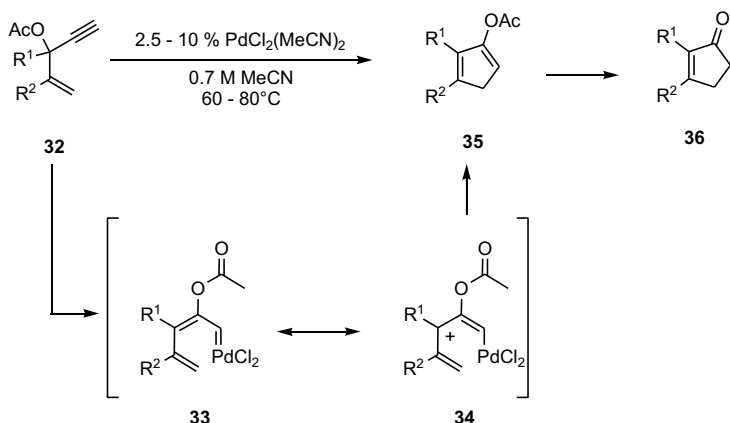
Scheme 22. Pd(II)-catalyzed 1,2-acetoxy migration/cyclization (Rautenstrauch rearrangement).

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**.[32]
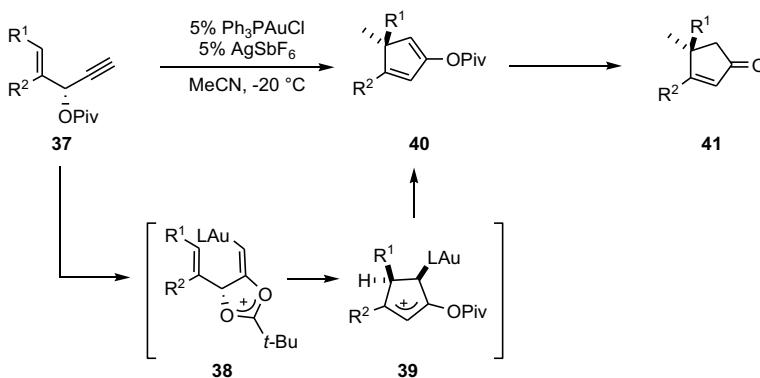
Scheme 23. Gold(I)-catalyzed Rautenstrauch rearrangement.

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.
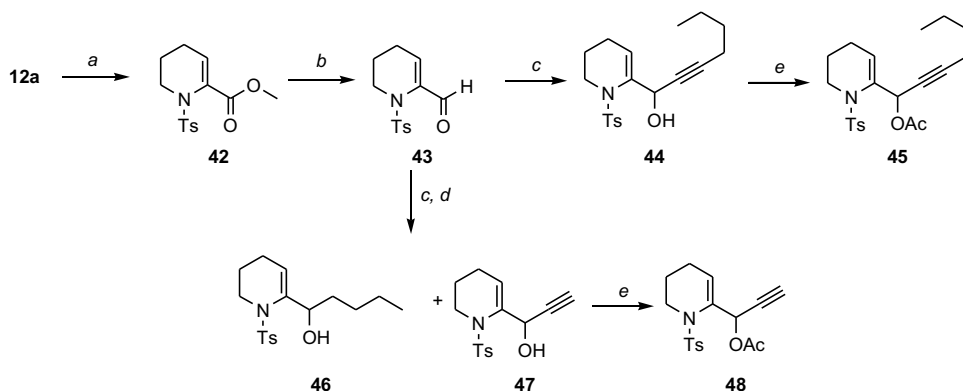
Scheme 24. Synthesis of propargyl acetates **45** and **48**. Reagents and conditions: (*a*) 20 % Pd(OAc)$_2$, 40 % Ph$_3$P, CO, Et$_3$N, MeOH, DMF, 60 °C, 2.5 h (70 %); (*b*) 1. DIBAL-H, DCM, 0 °C, 2. DMP, 0 °C (62 %); (*c*), *n*-BuLi, alkyne, THF, -78 °C (93 % for **44**); (*d*), TBAF, THF, 0 °C, 1 h (11 % for **47** over 2 steps); (*e*) Ac$_2$O, Et$_3$N, DMAP, DCM, r.t., on.

The treatment of **45** with 5 mol % of Ph$_3$PAu/AgSbF$_6$ in DCM at room temperature (Scheme 25) afforded complex crude for which ^{1}H 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 ^{1}H 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.
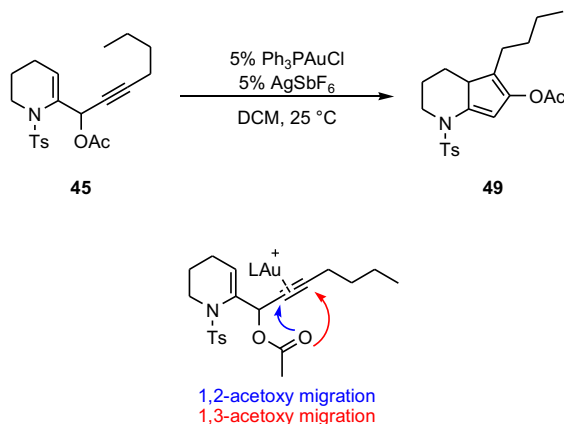
Scheme 25. Au(I)-catalyzed Rautenstrauch rearrangement of **45**.

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]
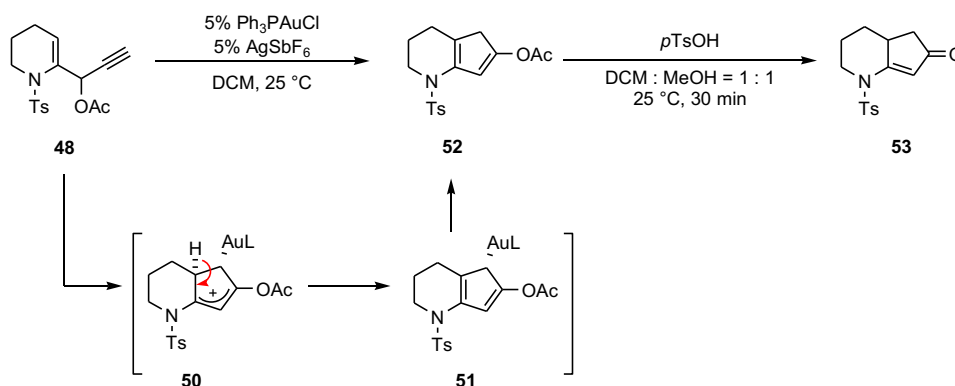
Scheme 26. Au(I)-catalyzed Rautenstrauch rearrangement of **48**.

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 Toste[32] 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.

10g   **10i**   **10j**   **11e**   **11f**   **11e**

11l   **11m**   **11n**   **11o**   **11p**

Compounds **10g**,[41] **10i**,[33] **10j**,[42] **11l**,[37] **11m**,[16] **11n**,[16] **11o**,[17] **11p**,[18] **12b**,[34] **12c**,[35] **12d**,[36] **12m**,[38] **12n**,[15] and **12o**[17] were prepared as reported, whereas starting δ-valerolactames as well as compounds **11e**,[15] **11f**,[15] **17e**,[15] **17f**,[15] **17d**,[39] **17ae**,[40] **25a**[43] and **25c**[44] are known.
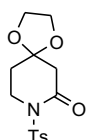
8-(Toluene-4-sulfonyl)-1,4-dioxa-8-aza-spiro[4.5]decan-7-one (11k).

$NaIO_4$ (18.2 g, 84.3 mmol) was dissolved in water (50 mL) and RuO_2 x nH_2O (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-dioxa-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-PrOH (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 Na_2SO_4. After filtration and evaporation of the solvent, the crude was purified by flash chromatography (hepatane/EtOAc, 1 : 1, R_f = 0.16) to give **11k** (1.3 g, 20 %) as a yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ = 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.
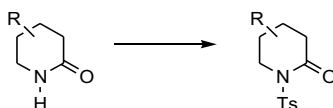
General procedure for N-tosylation (11).

A 1.6 M solution of n-BuLi in hexane (0.7 mL, 1.1 mmol) was added dropwise to the solution of δ-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**.
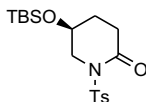
(5S)-5-(*tert*-Butyl-dimethyl-silanyloxy)-1-(toluene-4-sulfonyl)-piperidin-2-one (11g).
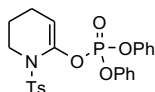
Compound **11g** was prepared according to the general procedure starting from **10g** (467 mg, 2.04 mmol). After chromatography (*n*-hexane/EtOAc, 2 : 1; R_f = 0.29) product **11g** was obtained (547 mg,

70 %) as a white solid. M.p. = 188.9 – 189.5 °C. $[\alpha]_D^{24}$ = - 8.57 (*c* = 0.88, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) *δ* = 7.89 (d, *J* = 8.3 Hz, 2H, Ts), 7.28 (d, *J* = 8.3 Hz, 2H, Ts), 4.26 (m, 1H, 5-H), 3.97 (dd, *J* = 12.6, 4.0 Hz, 1H, 6-H), 3.82 (dd, *J* = 12.6, 3.1 Hz, 1H, 6-H'), 2.60 (ddd, *J* = 17.6, 10.3, 7.0 Hz, 1H, 3-H), 2.46 – 2.32 (m, 4H, 3-H' and CH$_3$-Ts), 1.95 – 1.78 (m, 2H, 4-H), 0.85 (s, 9H, SiC(CH$_3$)$_3$), 0.11 (s, 3H, SiCH$_3$), 0.08 (s, 3H, SiCH$_3$) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) *δ* = 169.7 (s, C2), 144.6 (s, Ts), 136.1 (s, Ts), 129.2 (d, 2C, Ts), 128.5 (d, 2C, Ts), 64.0 (d, C5), 53.3 (t, C6), 29.5 (t, C3), 28.2 (t, C4), 25.6 (q, 3C, SiC(CH$_3$)$_3$), 21.6 (q, CH$_3$-Ts), 17.9 (s, SiC(CH$_3$)$_3$), -4.9 (q, 2C, Si(CH$_3$)$_2$) ppm. MS (ESI) *m/z* (%): 789 ([2M+Na]$^+$, 100), 406 ([M+Na]$^+$, 18), 384 ([M+1]$^+$, 29). Elemental analysis calcd (%) for C$_{18}$H$_{29}$NO$_4$SiS: C 56.36, H 7.62, N 3.65; found: C 56.46, H 7.85, N 3.56.
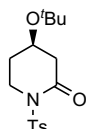
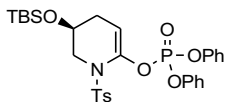### 4-tert-Butoxy-1-(toluene-4-sulfonyl)-piperidin-2-one (11i).

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. $[\alpha]_D^{22}$ = - 0.3 (*c* = 1.25, CHCl$_3$). M.p. = 99.3 - 100.7 °C. ^{1}H NMR (400 MHz, CDCl$_3$) *δ* = 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. ^{13}C NMR (100.4 MHz, CDCl$_3$) *δ* = 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 ([2M+Na]$^+$, 100), 348 ([M+Na]$^+$, 14), 325.60 ([M]$^+$, 35).
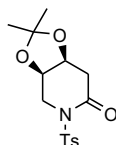
2,2-Dimethyl-5-(toluene-4-sulfonyl)-tetrahydro-[1,3]dioxolo[4,5-c]pyridin-6-one (11j).
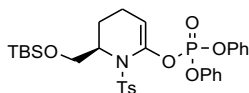
Compound **11j** was prepared according to the general procedure starting from **10j** (147 mg, 0.86 mmol). After chromatography (*n*-hexane/EtOAc, 1 : 1; R$_f$ = 0.31) product **11j** was obtained (162 mg, 58 %) as a white solid. $[\alpha]_D^{20}$ = - 10.6 (*c* = 0.8, CHCl$_3$). M.p. = 191.6 – 193.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$) *δ* = 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. ^{13}C NMR (100.4 MHz, CDCl$_3$) *δ* = 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 ([2M+Na]$^+$, 100), 347([M+Na]$^+$, 22), 325 ([M+1]$^+$, 21). Elemental analysis calcd (%) for C$_{15}$H$_{19}$NO$_5$S: C 55.37, H 5.87, N 4.30; found: C 55.41, H 5.60, N 4.69.
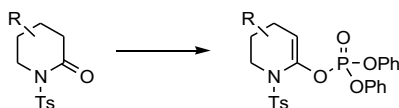
General procedure for phosphate preparation (12).

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 Et$_2$O (4 x 12 mL); the combined organic extracts were washed with 10 % NaOH (12 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 (eluent containing 1 % Et$_3$N) and obtained phosphate was stored at 4 °C as 0.1 M solution in the eluent containing 1 % Et$_3$N 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 % Et$_3$N; R$_f$ = 0.29) product **12a** was obtained (1.38 g, 80 %) as a colourless oil. ^{1}H NMR (400 MHz, CDCl$_3$) *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, 6-H), 2.37 (s, 3H, CH$_3$-Ts), 2.08 – 2.03 (m, 2H, 4-H), 1.56 – 1.51 (m, 2H, 5-H) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) *δ* = 150.4 (s, C2), 143.8 (s, Ts), 139.6 (s, 2C, Ph), 137.0 (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), 100.5 (d, C3), 47.5 (t, C6), 21.5 (q, CH$_3$-Ts), 21.3 (t, C4), 20.9 (t, C5) ppm. MS (ESI) *m/z* (%): 993 ([2M+Na]$^+$, 100), 508 ([M+Na]$^+$, 13.1), 486 ([M+1]$^+$, 8).
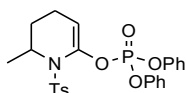
Phosphoric Acid (±)-6-Methyl-1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-2-yl Ester Diphenyl Ester (12e).

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 % Et$_3$N; R$_f$ = 0.19) phosphate **12e** was obtained (807 mg, 76 %) as a colourless oil. ^{1}H NMR (400 MHz, CDCl$_3$) *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, 6-H), 2.37 (s, 3H, CH$_3$-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-CH$_3$) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) *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, CH$_3$ Ts), 18.0 (t, C5), 16.7 (q, C6-CH$_3$) ppm. MS (ESI) *m/z* (%): 1021 ([2M+Na]$^+$, 100), 522 ([M+Na]$^+$, 10), 500 ([M+1]$^+$, 6).
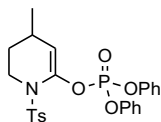
Phosphoric Acid (±)-4-Methyl-1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-2-yl Ester Diphenyl Ester (12f).

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 % Et$_3$N; R$_f$ = 0.20) phosphate **12f** was obtained (855 mg, 84 %) as a colourless oil. ^{1}H NMR (400 MHz, CDCl$_3$) *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 (ddd, *J* = 13.8, 6.9, 3.1 Hz, 1H, 6-H), 3.54 (ddd, *J* = 13.8, 9.0, 2.8 Hz, 1H, 6-H'), 2.37 (s, 3H, CH$_3$-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-CH$_3$) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) *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

(t, C6), 29.1 (d, C4), 27.3 (t, C5), 21.5 (q, CH_3 Ts), 21.0 (q, C4-CH_3) ppm. MS (ESI) m/z (%): 1021 ([2M+Na]$^+$, 100), 522 ([M+Na]$^+$, 5), 500 ([M+1]$^+$, 2).


Phosphoric Acid (5S)-5-(tert-Butyl-dimethyl-silanyloxy)-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% Et$_3$N; R$_f$ = 0.24) phosphate **12g** was obtained (640 mg, 74 %) as a colourless oil. ^{1}H NMR (400 MHz, CDCl$_3$) 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, CH$_3$-Ts and 4-H), 1.98 (ddt, J = 17.6, 7.5, 3.8 Hz, 1H, 4-H'), 0.87 (s, 9H, SiC(CH$_3$)$_3$), 0.07 (s, 3H, SiCH$_3$), 0.04 (s, 3H, SiCH$_3$) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) δ = 150.3 (s, C2), 143.8 (s, Ts), 139.0 (s, 2C, Ph), 137.3 (s, Ts), 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(CH$_3$)$_3$), 21.5 (q, CH_3 Ts), 18.0 (s, SiC(CH$_3$)$_3$), -4.8 (q, SiCH$_3$), -4.9 (q, SiCH$_3$) ppm. MS (ESI) m/z (%): 1253 ([2M+Na]$^+$, 100), 638 ([M+Na]$^+$, 93), 616 ([M+1]$^+$, 5).

Phosphoric acid 6-(tert-butyl-dimethyl-silanyloxymethyl)-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 % Et$_3$N; R$_f$ = 0.24) phosphate **12h** was obtained (1.63 g, 98 %) as a yellowish oil. ^{1}H NMR (400 MHz, CDCl$_3$) 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-CH$_2$OTBS), 3.46 (dd, J = 10.0, 8.5 Hz, 1H, 6-CH$_2$OTBS), 2.37 (s, 3H, CH$_3$-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, CH$_3$-TBS), 0.10 (s, 3H, CH$_3$-TBS), 0.00 (s, 3H, CH$_3$-TBS) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) δ = 155.9 (s, C2), 149.4 (s, 2C, Ph), 144.1 (s, Ts), 142.2 (s, Ts), 135.3 (d, Ar), 133.3 (d, Ar), 131.0 (d, Ar), 125.8 (d, Ar), 105.5 (d, C3), 66.9 (t, CH$_2$OTBS), 62.6 (d, C6), 35.3 (t, C5), 31.4 (q, 3C, CH_3), 27.1 (t, C4), 26.0 (s, TBS), 23.8 (q, CH$_3$-Ts), 0.3 (q, CH$_3$-TBS), -0.3 (q, CH$_3$-TBS). MS (ESI) m/z (%): 630 ([M+1]+, 35).
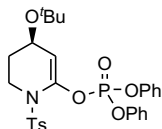
Phosphoric acid 4-tert-butoxy-1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-2-yl ester diphenyl ester (12i).

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 % Et$_3$N; R$_f$ = 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.
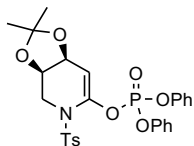
Phosphoric acid 2,2-dimethyl-5-(toluene-4-sulfonyl)-3a,4,5,7a-tetrahydro-[1,3]dioxolo[4,5-c]pyridin-6-yl ester diphenyl ester (12j).

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% Et$_3$N; R$_f$ = 0.3) phosphate **12j** was obtained (253 mg, 93 %) as a colourless oil. ^{1}H NMR (400 MHz, CDCl$_3$) *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, CH$_3$-Ts), 1.41 (s, 3H, CH$_3$), 1.33 (s, 3H, CH$_3$) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) *δ* = 150.1 (s, C2), 144.3 (s, 2C, 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), 120.1 (d, Ar), 109.7 (d, C3), 96.5 (s, C(CH$_3$)$_2$), 71.3 (d, C4), 69.9 (d, C5), 48.3 (t, C6), 27.8 (q, CH$_3$), 25.6 (q, CH$_3$), 21.3 (q, CH$_3$-Ts) ppm. MS (ESI) *m/z* (%): 1136 ([2M+Na]$^+$, 100), 579 ([M+Na]$^+$, 31), 557 ([M+1]$^+$, 9).
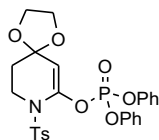
Phosphoric acid diphenyl ester 8-(toluene-4-sulfonyl)-1,4-dioxa-8-aza-spiro[4.5]dec-6-en-7-yl ester (12k).

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 % Et$_3$N; R$_f$ = 0.22) phosphate **12k** was obtained (860 mg, 73 %) as a colourless oil and used immediately in next step. ^{1}H NMR (400 MHz, CDCl$_3$) *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 OCH$_2$-TBS), 2.34 (s, 3H, CH$_3$-Ts), 1.87 – 1.79 (m, 2H, 5-H) ppm.
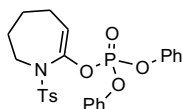
Phosphoric Acid Diphenyl Ester 1-(Toluene-4-sulfonyl)-4,5,6,7-tetrahydro-1*H*-azepin-2-yl ester (12l).

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 % Et$_3$N; R$_f$ = 0.23) phosphate **12l** was obtained (958 mg, 86 %) as a colourless oil. ^{1}H NMR (400 MHz, CDCl$_3$) *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, CH$_3$-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. ^{13}C NMR (100.4 MHz, CDCl$_3$) *δ* = 150.3 (s, C2), 143.8 (s, Ts), 143.5 (s, 2C, 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, CH$_3$-Ts) ppm. MS (ESI) *m/z* (%): 1021 ([2M+Na]$^+$, 100), 522 ([M+Na]$^+$, 24), 499 ([M]$^+$, 7).
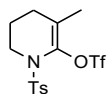
Trifluoro-methanesulfonic acid 3-methyl-1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-2-yl ester (12p).

A 0.5 M solution of KHMDS (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 Et_2O (4 x 25 mL); the combined organic extracts were washed with 10 % NaOH (25 mL) and dried over anhydrous K_2CO_3 for 30 min. After filtration and evaporation of the solvent, the crude was purified by flash chromatography (*n*-hexane/EtOAc, 3 : 1 +1 % Et_3N; R_f = 0.44) and phosphate **12p** (890, 86 %) was obtained as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) 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, CH_3-Ts), 2.00 – 1.96 (m, 2H, 4-H), 1.83 (s, 3H, CH_3), 1.55 – 1.39 (m, 2H, 5-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) 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, CF_3), 48.1 (t, C-6), 27.7 (t, C-5), 21.7 (t, C-4), 20.1 (q, CH_3-Ts), 17.2 (q, CH_3). 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).
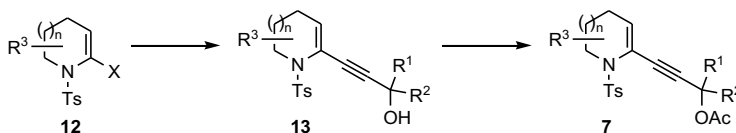
Step A: Sonogashira coupling (13)2a

Phosphate/triflate **12** (1 mmol) was dissolved in an anhydrous 2 : 1 Et_3N/$CHCl_3$ mixture (6 mL), and alkyne (1 mmol), CuI (19 mg, 0.1 mmol) and $(Ph_3P)_2PdCl_2$ (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), CuI (9.5 mg, 0.05 mmol) and $(Ph_3P)_2PdCl_2$ (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 Et_2O (3 x 15 mL) and the combined organic extracts were dried over anhydrous K_2CO_3 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 Et_3N (0.38 mL, 3 mmol) in DCM (4 mL) was cooled (ice bath) and Ac_2O (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 $NaHCO_3$ (10 mL) was added and the product extracted with DCM (3 x 10 mL). The combined organic extracts were dried over anhydrous K_2CO_3 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 % Et_3N until use.
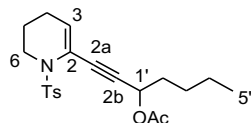
Acetic Acid 1-[1-(Toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-2-ylethynyl]-pentyl Ester (7aa).
Sonogashira coupling of phosphate **12a** (1.16 g, 2.4 mmol) and (±)-heptyn-3-ol after chromatography (*n*-hexane/Et$_2$O, 2 : 1 + 1 % Et$_3$N; R$_f$ = 0.30) afforded enynyl alcohol **13aa** as a pale yellow oil (515 mg, 62 %). ^{1}H NMR (400 MHz, CDCl$_3$) *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, CH$_3$-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. ^{13}C NMR (100.4 MHz, CDCl$_3$) *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, CH$_3$ Ts), 21.5 (t, C4'), 13.9 (q, C5') ppm. MS (ESI) *m/z* (%): 717 ([2M+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% Et$_3$N; R$_f$ = 0.21) pure **7aa** was obtained as a pale yellow oil (455 mg, 79 %). ^{1}H NMR (400 MHz, CDCl$_3$) *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, CH$_3$-Ts), 2.08 (s, 3H, CH$_3$-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. ^{13}C NMR (100.4 MHz, CDCl$_3$) *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, CH$_3$-Ts), 21.0 (q, CH$_3$-Ac), 21.0 (t, C5), 13.9 (q, C5') ppm. MS (ESI) *m/z* (%): 801 ([2M+Na]$^+$, 100), 412 ([M+Na]$^+$, 13).
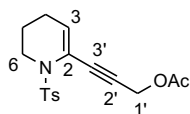
Acetic Acid 3-[1-(Toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-2-yl]-prop-2-ynyl Ester (7ab).
Sonogashira coupling of phosphate **12a** (220 mg, 0.45 mmol) and propargyl alcohol after chromatography (*n*-hexane/EtOAc, 2 : 1 + 1 % Et$_3$N; R$_f$ = 0.22) afforded enynyl alcohol **13ab** as a colourless oil (80 mg, 60 %). ^{1}H NMR (400 MHz, CDCl$_3$) *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, CH$_3$ Ts), 2.06 (td, *J* = 6.6, 4.1 Hz, 2H, 4-H), 1.63 – 1.57 (m, 2H, 5-H) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) *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, *C*H$_3$ 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 % Et$_3$N; R$_f$ = 0.17) pure **7ab** was obtained as a colourless oil (73 mg, 88 %). ^{1}H NMR (400 MHz, CDCl$_3$) *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, CH$_3$-Ts), 2.09 (s, 3H, CH$_3$-Ac), 2.06 (td, *J* = 6.6, 4.2 Hz, 2H, 4-H), 1.65 – 1.59 (m, 2H, 5-H) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) *δ* = 170.2 (s, CO), 143.5 (s, Ts), 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, CH$_3$-Ts), 20.9 (q, CH$_3$-Ac), 20.7 (t, C5) ppm. MS (ESI) *m/z* (%): 689 ([2M+Na]$^+$, 100), 356 ([M+Na]$^+$, 53), 334 ([M+1]$^+$, 8).
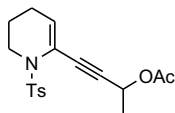
Acetic Acid 1-Methyl-3-[1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-2-yl]-prop-2-ynyl Ester (7ac).

Sonogashira coupling of phosphate **12a** (775 mg, 1.6 mmol) and (±)-butyn-3-ol after chromatography (*n*-hexane/EtOAc, 4 : 1 + 1 % Et$_3$N; R$_f$ = 0.23) afforded **13ac** which was used immediately in the next step. ^{1}H NMR (400 MHz, CDCl$_3$) *δ* = 7.78 (d, *J* = 8.2 Hz, 2H, Ts), 7.30 (d, *J* = 8.2 Hz, 2H, Ts), 5.63 (t, *J* = 4.2 Hz, 1H, 3-H), 4.60 (q, *J* = 6.8 Hz, 1H, 1'-H), 3.68 – 3.65 (m, 2H, 6-H), 2.43 (s, 3H, CH$_3$ Ts), 2.06 (td, *J* = 6.7, 4.2 Hz, 2H, 4-H), 1.64 – 1.58 (m, 2H, 5-H), 1.44 (d, *J* = 6.8 Hz, 3H, 1'-CH$_3$) ppm.

According to the above described procedure, compound **13ac** was subjected to acetylation. After chromatography (*n*-hexane/EtOAc, 8 : 1 + 1 % Et$_3$N; R$_f$ = 0.16) pure **7ac** was obtained as a colourless oil (372 mg, 67 % after two steps). ^{1}H NMR (400 MHz, CDCl$_3$) *δ* = 7.76 (d, *J* = 8.2 Hz, 2H, Ts), 7.28 (d, *J* = 8.2 Hz, 2H, Ts), 5.64 (t, *J* = 4.0 Hz, 1H, 3-H), 5.53 (q, *J* = 6.6 Hz, 1H, 1'-H), 3.63 – 3.61 (m, 2H, 6-H), 2.41 (s, 3H, CH$_3$-Ts), 2.06 (s, 3H, CH$_3$-Ac), 2.05 – 2.01 (m, 2H, 4-H), 1.63 – 1.57 (m, 2H, 5-H), 1.47 (d, *J* = 6.6 Hz, 3H, 1'-CH$_3$) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) *δ* = 169.8 (s, CO), 143.4 (s, Ts), 137.1 (s, Ts), 129.4 (d, 2C, Ts), 127.4 (d, 2C, Ts), 124.4 (d, C3), 120.0 (s, C2), 87.8 (s, C3'), 80.6 (s, C2'), 60.5 (d, C1'), 45.9 (t, C6), 23.2 (t, C4), 21.5 (q, CH$_3$-Ts), 21.0 (q, CH$_3$-Ac), 20.9 (t, C5), 20.8 (q, C1'-*CH*$_3$) ppm. MS (ESI) *m/z* (%): 717 ([2M+Na][+], 100).
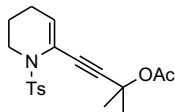
Acetic Acid 1,1-Dimethyl-3-[1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-2-yl]-prop-2-ynyl Ester (7ad).

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 % Et$_3$N; R$_f$ = 0.23) afforded **13ad** which was used immediately in the next step. ^{1}H NMR (400 MHz, CDCl$_3$) *δ* = 7.77 (d, *J* = 8.4 Hz, 2H, Ts), 7.29 (d, *J* = 8.4 Hz, 2H, Ts), 5.59 (t, *J* = 4.1 Hz, 1H, 3-H), 3.66 – 3.63 (m, 2H, 6-H), 2.42 (s, 3H, CH$_3$-Ts), 2.06 (td, *J* = 6.6, 4.1, Hz, 2H, 4-H), 1.63 – 1.57 (m, 2H, 5-H), 1.49 (s, 6H, 1'-CH$_3$) ppm.

According to the above described procedure, compound **13ad** was subjected to acetylation. After chromatography (*n*-hexane/EtOAc, 15 : 1 + 1 % Et$_3$N; R$_f$ = 0.14) pure **7ad** was obtained as a pale yellow oil (90 mg, 62 % after two steps). ^{1}H NMR (400 MHz, CDCl$_3$) *δ* = 7.81 (d, *J* = 8.6 Hz, 2H, Ts), 7.30 (d, *J* = 8.6 Hz, 2H, Ts), 5.64 (t, *J* = 4.1 Hz, 1H, 3-H), 3.63 – 3.60 (m, 2H, 6-H), 2.41 (s, 3H, CH$_3$ Ts), 2.04 – 2.00 (m, 5H, CH$_3$-Ac and 4-H), 1.68 (s, 6H, 1'-CH$_3$), 1.59 – 1.56 (m, 2H, 5-H) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) *δ* = 169.3 (s, *C*O), 143.3 (s, Ts), 137.0 (s, Ts), 129.5 (d, 2C, Ts), 127.4 (d, 2C, Ts), 123.9 (d, C3), 120.2 (s, C2), 90.4 (s, C3'), 80.3 (s, C2'), 72.3 (s, C1'), 46.0 (t, C6), 28.5 (q, 2C, C1'-*CH*$_3$), 23.1 (t, C4), 21.9 (q, CH$_3$ Ac), 21.5 (q, CH$_3$ Ts), 20.7 (t, C5) ppm. MS (ESI) *m/z* (%): 745 ([2M+Na][+], 100), 384 ([M+Na][+], 3).
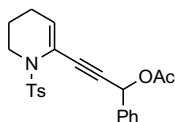
Acetic Acid 1-Phenyl-3-[1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-2-yl]-prop-2-ynyl Ester (7ae).

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 % Et$_3$N; R$_f$ = 0.20) afforded **13ae** which was used

immediately in the next step. ^{1}H NMR (400 MHz, CDCl$_3$) δ = 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$_3$) δ = 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$_3$) δ = 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).
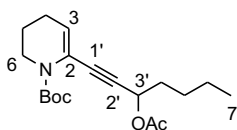
6-(3-Acetoxyhept-1-ynyl)-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid *tert*-Butyl Ester (7b).

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$_3$) δ = 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$_3$) δ = 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$_3$) δ = 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).
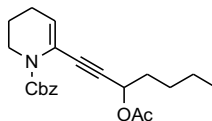
6-(3-Acetoxyhept-1-ynyl)-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid Benzyl Ester (7c).

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$_3$) δ = 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$_3$) δ = 7.38 – 7.29 (m, 5H, Cbz), 5.61 (t, J

= 3.8 Hz, 1H, 5-H), 5.37 (t, J = 6.6 Hz, 1H, 3'-H), 5.19 (part A of an AB system, J = 12.6 Hz, 1H, CH$_2$Ph), 5.14 (part B of an AB system, J = 12.6 Hz, 1H, CH$_2$Ph), 3.61 – 3.55 (m, 2H, 2-H), 2.16 – 2.03 (m, 2H, 4-H), 1.99 (s, 3H, CH$_3$-Ac), 1.78 – 1.72 (m, 2H, 3-H), 1.68 – 1.59 (m, 2H, 4'-H) 1.33 – 1.22 (m, 4H, 5'-H and 6'-H), 0.84 (t, J = 7.2 Hz, 3H, 7'-H) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) δ = 169.9 (s, CO-Ac), 153.6 (s, CO-Cbz), 136.3 (s, Cbz), 128.4 (d, 2C, Cbz), 128.0 (d, Cbz), 127.9 (d, 2C, Cbz), 124.2 (d, C5), 121.2 (s, C6), 85.5 (s, C1'), 81.7 (s, C2'), 67.5 (t, Cbz), 64.5 (d, C3'), 43.9 (t, C2), 34.4 (t, C4'), 27.0 (t, C5'), 23.6 (t, C4), 22.4 (q, CH$_3$-Ac), 22.2 (t, C6'), 21.0 (t, C3), 13.9 (q, C7') ppm. MS (ESI) m/z (%): 761 ([2M+Na]$^+$, 100), 392 ([M+Na]$^+$, 9).
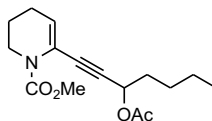
6-(3-Acetoxy-hept-1-ynyl)-3,4-dihydro-2H-pyridine-1-carboxylic Acid Methyl Ester (7d).
Sonogashira coupling of phosphate **12d** (385 mg, 0.99 mmol) and (±)-heptyn-3-ol after chromatography (*n*-hexane/EtOAc, 4 : 1 + 1 % Et$_3$N; R$_f$ = 0.28) afforded enynyl alcohol **13d** which was used immediately in the next step. ^{1}H NMR (400 MHz, CDCl$_3$) δ = 5.59 (t, J = 4.1 Hz, 1H, 5-H), 4.56 – 4.38 (m, 1H, 3'-H), 3.74 (s, 3H, OCH$_3$), 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/EtOAc, 15 : 1 + 1 % Et$_3$N; R$_f$ = 0.16) pure **7d** was obtained as an orange oil (200 mg, 69 % after two steps). ^{1}H NMR (400 MHz, CDCl$_3$) δ = 5.61 (t, J = 4 Hz, 1H, 5-H), 5.45 (t, J = 6.6 Hz, 1H, 3'-H), 3.73 (s, 3H, OCH$_3$), 3.65 – 3.54 (m, 2H, 2-H), 2.16 (dt, J = 6.7, 4.0 Hz, 2H, 4-H), 2.06 (s, 3H, CH$_3$-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. ^{13}C NMR (100.4 MHz, CDCl$_3$) δ = 170.0 (s, CO-Ac), 154.4 (s, CO$_2$CH$_3$), 123.8 (d, C5), 121.1 (s, C6), 85.3 (s, C1'), 81.6 (s, C2'), 64.5 (d, C3'), 52.6 (q, CO$_2$CH$_3$), 43.7 (t, C2), 34.4 (t, C4'), 27.0 (t, C5'), 23.5 (t, C4), 22.4 (q, CH$_3$-Ac), 22.2 (t, C6'), 21.0 (t, C3), 13.9 (q, C7') ppm. MS (ESI) m/z (%): 316 ([M+Na]$^+$, 100), 294 ([M+1]$^+$, 5).
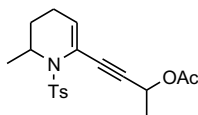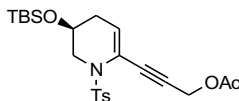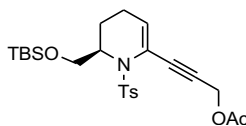

Acetic Acid 1-Methyl-3-[6-methyl-1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-2-yl]-prop-2-ynyl Ester (7e).
Sonogashira coupling of phosphate **12e** (807 mg, 1.62 mmol) and (±)-3-butyn-2-ol after chromatography (*n*-hexane/EtOAc, 2 : 1 + 1 % Et$_3$N; R$_f$ = 0.29) afforded enynyl alcohol **13e** which was used immediately in the next step. ^{1}H NMR (400 MHz, CDCl$_3$) 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, CH$_3$-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'-CH$_3$, 4-H' and 5'-H), 1.14 (d, J = 6.8 Hz, 3H, 6-CH$_3$) ppm.

According to the above described procedure, compound **13e** was subjected to acetylation. After chromatography (*n*-hexane/EtOAc, 8 : 1 + 1 % Et$_3$N; R$_f$ = 0.17) pure **7e** was obtained as a pale yellow oil (350 mg, 60 % after two steps). ^{1}H NMR (400 MHz, CDCl$_3$) 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, CH$_3$-Ts), 2.07 – 1.93 (m, 5H, CH$_3$-Ac and 4-H), 1.46 (m, 4H, 1'-CH$_3$ and 5-H), 1.38 – 1.29 (m, 1H, 5-H'), 1.09 (d, J = 6.8 Hz, 6-CH$_3$) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) 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, CH$_3$-Ts), 21.1 (q, CH$_3$-Ac), 20.9 (q, C1'-CH$_3$), 19.2 (t, C5), 17.3 (q, C6-CH$_3$) ppm. MS (ESI) m/z (%): 745 ([2M+Na]$^+$, 100), 384 ([M+Na]$^+$, 9),

362 ([M+1]$^+$, 13).
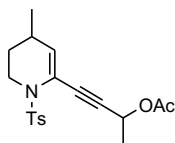
Acetic Acid 1-Methyl-3-[4-methyl-1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-2-yl]-prop-2-ynyl Ester (7f).

Sonogashira coupling of phosphate **12f** (855 mg, 2.05 mmol) and (±)-3-butyn-2-ol after chromatography (*n*-hexane/EtOAc, 2:1 + 1 % Et$_3$N; R$_f$ = 0.24) afforded enynyl alcohol **13f** which was used immediately in the next step. ^{1}H NMR (400 MHz, CDCl$_3$) *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, CH$_3$-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'-CH$_3$), 1.22 – 1.14 (m, 1H, 5-H'), 0.87 (d, *J* = 7.0 Hz, 3H, 4-CH$_3$) ppm.

According to the above described procedure, compound **13f** was subjected to acetylation. After chromatography (*n*-hexane/EtOAc, 8 : 1 + 1 % Et$_3$N; R$_f$ = 0.17) pure **7f** was obtained as a pale yellow oil (350 mg, 57% after two steps). ^{1}H NMR (400 MHz, CDCl$_3$) *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, CH$_3$-Ts), 2.26 – 2.20 (m, 1H, 4-H), 2.06 (s, 3H, CH$_3$-Ac), 1.72 – 1.65 (m, 1H, 5-H), 1.48 (d, *J* = 6.7 Hz, 3H, 1'-CH$_3$), 1.23 – 1.15 (m, 1H, 5-H'), 0.86 (d, *J* = 7.1 Hz, 4-CH$_3$) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) *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, C1'), 44.7 (t, C6), 29.0 (t, C5), 28.6 (d, C4), 21.6 (q, CH$_3$-Ts), 21.1 (q, CH$_3$-Ac), 20.9 (q, C1'-CH$_3$), 20.6 (q, C6-CH$_3$) ppm. MS (ESI) *m/z* (%): 745 ([2M+Na]$^+$, 100), 384 ([M+Na]$^+$, 38).

Acetic Acid 3-[5-(*tert*-Butyl-dimethyl-silanyloxy)-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 % Et$_3$N; R$_f$ = 0.16) afforded enynyl alcohol **13ga** which was used immediately in the next step. ^{1}H NMR (200 MHz, CDCl$_3$) *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, CH$_3$-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, SiC(CH$_3$)$_3$), 0.06 (s, 6H, Si(CH$_3$)$_2$) ppm.

According to the above described procedure, compound **13ga** was subjected to acetylation. After chromatography (*n*-hexane/EtOAc, 3 : 1 + 1 % Et$_3$N; R$_f$ = 0.22) pure **7ga** was obtained as a pale yellow oil (202 mg, 42 % after two steps). $[\alpha]_D^{21} = + 61.6$ (*c* = 0.98, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) *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 (dddd, *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, CH$_3$-Ts), 2.34 (dt, *J* = 19.2, 5.7 Hz, 1H, 4-H), 2.08 (s, 3H, CH$_3$-Ac), 1.99 (ddd, *J* = 19.2, 8.0, 4.0 Hz, 1H, 4-H'), 0.87 (s, 9H, SiC(CH$_3$)$_3$), 0.07 (s, 3H, SiCH$_3$), 0.04 (s, 3H, SiCH$_3$) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) *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, SiC(CH$_3$)$_3$), 21.5 (q, CH$_3$-Ts), 20.7 (q, CH$_3$-Ac), 18.0 (s, SiC(CH$_3$)$_3$), -4.8 (q, SiCH$_3$), -4.9 (q, SiCH$_3$) ppm. MS (ESI) *m/z* (%): 949 ([2M+Na]$^+$, 100), 486

([M+Na]$^+$, 6).

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 % Et$_3$N; R$_f$ = 0.34) afforded enynyl alcohol **13h** which was used immediately in the next step. ^{1}H NMR (400 MHz, CDCl$_3$) 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-CH$_2$OTBS), 3.76 (dd, J = 10.0, 8.9 Hz, 1H, 6-CH$_2$OTBS), 2.42 (s, 3H, CH$_3$-Ts), 2.06 – 1.86 (m, 4H, 4 and 5-H), 0.86 (s, 9H, CH$_3$-TBS), 0.04 (s, 3H, CH$_3$-TBS), 0.03 (s, 3H, CH$_3$-TBS) ppm.

According to the above described procedure, compound **13h** was subjected to acetylation. After chromatography (heptane/EtOAc, 3 : 1 + 1 % Et$_3$N; R$_f$ = 0.31) pure **7h** was obtained as a pale yellow oil (550 mg, 44 % after two steps). ^{1}H NMR (400 MHz, CDCl$_3$) 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-CH$_2$OTBS), 3.45 (t, J = 6.3 Hz, 1H, 6-CH$_2$OTBS), 2.42 (s, 3H, CH$_3$-Ts), 2.10 (s, 3H, CH$_3$-Ac), 2.04 – 1.87 (m, 3H, 4 and 5-H), 1.32 – 1.21 (m, 1H, 5-H), 0.86 (s, 9H, CH$_3$-TBS), 0.04 (s, 3H, CH$_3$-TBS), 0.03 (s, 3H, CH$_3$-TBS) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) 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-*CH$_2$*), 58.2 ((d, C6), 31.4 (q, 3C, CH$_3$-TBS), 27.2 (t, C4), 26.4 (t, C5), 25.0 (q, CH$_3$-Ts), 23.8 (q, CH$_3$-Ac), 0.2 (q, CH$_3$-TBS), 0.0 (q, CH$_3$-TBS) ppm. MS (ESI) *m/z* (%): 478 ([M+1]+, 65).
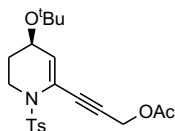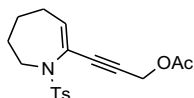

Acetic acid 3-[4-tert-butoxy-1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-2-yl]-prop-2-ynyl ester (7i)

Sonogashira coupling of phosphate **12i** (530 mg, 0.7 mmol) and propargyl alcohol after chromatography (*n*-hexane/EtOAc, 2 : 1 + 1 % Et$_3$N; R$_f$ = 0.30) afforded enynyl alcohol **13i** which was used immediately in the next step. ^{1}H NMR (400 MHz, CDCl$_3$) 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, CH$_3$-Ts), 1.75 - 1.76 (m, 3H, 5-H, OH), 1.16 (s, 9H, CH$_3$-*t*-Bu) ppm.

According to the above described procedure, compound **13i** was subjected to acetylation. After chromatography (*n*-hexane/EtOAc, 3 : 1 + 1 % Et$_3$N; R$_f$ = 0.43) pure **7i** was obtained as a colourless oil (82 mg, 30 % after two steps). ^{1}H NMR (400 MHz, CDCl$_3$) 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, CH$_3$-Ts), 2.09 (s, 3H, CH$_3$-Ac), 1.72 (q, J = 4.15 Hz, 2H, 5-H), 1.15 (s, 9H, *t*-Bu) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) 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, CH$_3$-*t*-Bu), 21.5 (q, CH$_3$-Ts), 20.7 (s, CH$_3$-Ac) ppm. MS (ESI) m/z (%): 832 ([2M+Na]$^+$, 100), 428 ([M+Na]$^+$, 25).
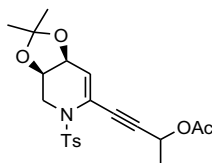
Acetic acid 3-[2,2-dimethyl-5-(toluene-4-sulfonyl)-3a,4,5,7a-tetrahydro-[1,3]dioxolo[4,5-c]pyridin-6-yl]-1-methyl-prop-2-ynyl ester (7j)

Sonogashira coupling of phosphate **12j** (250 mg, 0.45 mmol) and (±)-3-butyn-2-ol after chromatography (heptane/EtOAc, 2 : 1 + 1 % Et$_3$N; R$_f$ = 0.28) afforded enynyl alcohol **13j** which was used immediately in the next step. ^{1}H NMR (400 MHz, CDCl$_3$) 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, CH$_3$-Ts), 1.42 (d, J = 6.6 Hz, 3H, 3'-CH$_3$), 1.37 (s, 3H, CH$_3$), 1.33 (s, 3H, CH$_3$) ppm.

According to the above described procedure, compound **13j** was subjected to acetylation. After chromatography (n-hexane/EtOAc, 8 : 1 + 1 % Et$_3$N; R$_f$ = 0.19) pure **7j** was obtained as a yellowish oil (75 mg, 41 % after two steps). ^{1}H NMR (400 MHz, CDCl$_3$) 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, CH$_3$-Ts), 2.08 (s, 3H, CH$_3$-Ac), 1.46 (d, J = 6.7 Hz, 3H, 3'-CH$_3$), 1.35 (s, 3H, CH$_3$), 1.32 (s, 3H, CH$_3$) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) 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*(CH$_3$)$_2$), 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, CH$_3$), 24.9 (q, CH$_3$), 21.5 (q, CH$_3$), 20.9 (q, CH$_3$) 20.7 (q, CH$_3$) ppm. MS (ESI) *m/z* (%): 860 ([2M+Na]$^+$, 100), 441 ([M+Na]$^+$, 74), 419 ([M+1]$^+$, 25).
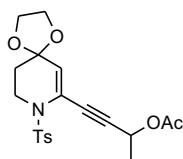
Acetic acid 1-methyl-3-[8-(toluene-4-sulfonyl)-1,4-dioxa-8-aza-spiro[4.5]dec-6-en-7-yl]-prop-2-ynyl ester (7k)

Sonogashira coupling of phosphate **12k** (2.1 g, 2.86 mmol) and (±)-3-butyn-2-ol after chromatography (heptane/EtOAc, 3 : 2 + 1 % Et$_3$N; R$_f$ = 0.30) afforded enynyl alcohol **13k** which was used immediately in the next step. ^{1}H NMR (400 MHz, CDCl$_3$) 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, OCH$_2$), 3.84 – 3.81 (m, 2H, 6-H), 2.42 (s, 3H, CH$_3$-Ts), 1.86 – 1.81 (m, 2H, 5-H), 1.40 (d, J = 6.6 Hz, 3H, 3'-CH$_3$) ppm.

According to the above described procedure, compound **13k** was subjected to acetylation. After chromatography (heptane/EtOAc, 2 : 1 + 1 % Et$_3$N; R$_f$ = 0.19) pure **7k** was obtained as a yellowish oil (120 mg, 11 % after two steps). ^{1}H NMR (400 MHz, CDCl$_3$) δ = 7.77 (d, J = 8.3 Hz, 2H, Ts), 7.30 (d, J = 8.3 Hz, 2H, Ts), 5.54 (q, J = 6.7 Hz, 1H, 3'-H), 5.35 (s, 1H, 3-H), 3.96 – 3.88 (m, 4H, OCH$_2$), 3.85 – 3.82 (m, 2H, 6-H), 2.42 (s, 3H, CH$_3$-Ts), 2.08 (s, 3H, CH$_3$-Ac), 1.87 – 1.85 (m, 2H, 5-H), 1.50 (d, J = 6.4 Hz, 3H, 3'-CH$_3$) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) 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, OCH$_2$), 60.4 (d, C3'), 45.8 (t, C6), 32.6 (t, C5), 21.6 (q, CH$_3$), 21.0 (q, CH$_3$-Ts), 20.6 (q, CH$_3$-Ac) ppm. MS (ESI) m/z (%): 406 ([M+1]$^+$, 100).
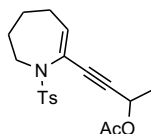
Acetic Acid 1-Methyl-3-[1-(toluene-4-sulfonyl)-4,5,6,7-tetrahydro-1*H*-azepin-2-yl]-prop-2-ynyl ester (7la).

Sonogashira coupling of phosphate **12l** (838 mg, 1.68 mmol) and (±)-3-butyn-2-ol after chromatography (*n*-hexane/EtOAc, 3 : 2 + 1 % Et$_3$N; R$_f$ = 0.20) afforded enynyl alcohol **13la** which was used immediately in the next step. ^{1}H NMR (200 MHz, CDCl$_3$) *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, CH$_3$-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, CH$_3$) ppm.

According to the above described procedure, compound **13la** was subjected to acetylation. After chromatography (*n*-hexane/EtOAc, 4 : 1 + 1 % Et$_3$N; R$_f$ = 0.26) pure **7la** was obtained as a colourless oil (362 mg, 60 % after two steps). ^{1}H NMR (400 MHz, CDCl$_3$) *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, CH$_3$-Ts), 2.24 – 2.22 (m, 2H, 4-H), 2.05 (s, 3H, CH$_3$-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'-CH$_3$) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) *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, CH$_3$-Ts), 21.0 (q, CH$_3$-Ac), 20.9 (q, C1'-CH$_3$) 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 % Et$_3$N; R$_f$ = 0.24) afforded enynyl alcohol **13lb** which was used immediately in the next step. ^{1}H NMR (200 MHz, CDCl$_3$) *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, CH$_3$-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 % Et$_3$N; R$_f$ = 0.22) pure **7lb** was obtained as a colourless oil (156 mg, 59 % after two steps). ^{1}H NMR (400 MHz, CDCl$_3$) *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, CH$_3$-Ts), 2.25 – 2.21 (m, 2H, 4-H), 2.07 (s, 3H, CH$_3$-Ac), 1.88 – 1.82 (m, 2H, 5-H), 1.51 – 1.47 (m, 2H, 6-H) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) *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, CH$_3$-Ts), 20.7 (q, CH$_3$-Ac) ppm. MS (ESI) *m/z* (%): 717 ([2M+Na]$^+$, 100).
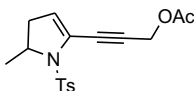
Acetic Acid 3-[5-Methyl-1-(toluene-4-sulfonyl)-4,5-dihydro-1H-pyrrol-2-yl]-prop-2-ynyl Ester (7m).

Sonogashira coupling of triflate **12m** (454 mg, 1.18 mmol) and propargyl alcohol after chromatography (*n*-hexane/EtOAc, 1 : 1 + 1 % Et$_3$N; R$_f$ = 0.17) afforded enynyl alcohol **13m** which was used immediately in the next step. ^{1}H NMR (200 MHz, CDCl$_3$) *δ* = 7.76 (d, *J* = 8.2 Hz, 2H, Ts), 7.30 (d, *J* =

8.2 Hz, 2H, Ts), 5.49 (t, *J* = 3.3 Hz, 1H, 3-H), 4.45 (s, 2H, 1'-H), 4.29 – 4.04 (m, 1H, 5-H), 2.70 – 2.24 (m, 5H, OH, 4-H and CH$_3$-Ts), 1.92 (dt, *J* = 17.9, 3.3 Hz, 1H, 4-H), 1.35 (d, *J* = 6.5 Hz, 3H, 5-CH$_3$) ppm.

According to the above described procedure, compound **13m** was subjected to acetylation. After chromatography (*n*-hexane/EtOAc, 4 : 1 + 1 % Et$_3$N; R$_f$ = 0.24) pure **7m** was obtained as a colourless oil (168 mg, 43 % after three steps). ^{1}H NMR (400 MHz, CDCl$_3$) *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, CH$_3$-Ts and 4-H), 2.11 (s, 3H, CH$_3$-Ac), 1.94 (dt, *J* = 18.0, 3.3 Hz, 1H, 4-H'), 1.35 (d, *J* = 6.5 Hz, 3H, 5-CH$_3$) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) *δ* = 170.2 (s, *C*O), 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-CH$_3$), 21.5 (q, CH$_3$-Ts), 20.7 (q, CH$_3$-Ac) ppm. MS (ESI) *m/z* (%): 689 ([2M+Na]$^+$, 100), 334 ([M+1]$^+$, 9).
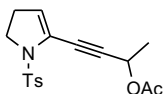
Acetic Acid 1-Methyl-3-[1-(toluene-4-sulfonyl)-4,5-dihydro-1H-pyrrol-2-yl]-prop-2-ynyl Ester (7n).
Sonogashira coupling of triflate **12n** (450 mg, 1.2 mmol) and (±)-3-butyn-2-ol after chromatography (*n*-hexane/EtOAc, 3 : 1 + 1 % Et$_3$N; R$_f$ = 0.15) afforded enynyl alcohol **13n** which was used immediately in the next step. ^{1}H NMR (200 MHz, CDCl$_3$) *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 CH$_3$-Ts), 1.54 (d, *J* = 6.6 Hz, 1'-CH$_3$) ppm.

According to the above described procedure, compound **13n** was subjected to acetylation. After chromatography (*n*-hexane/EtOAc, 3 : 1 + 1 % Et$_3$N; R$_f$ = 0.27) pure **7n** was obtained as a colourless oil (143 mg, 36 % after three steps). ^{1}H NMR (400 MHz, CDCl$_3$) *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, CH$_3$-Ts), 2.38 (td, *J* = 9.0, 3.0 Hz, 2H, 4-H), 2.10 (s, 3H, CH$_3$-Ac), 1.58 (d, *J* = 6.7 Hz, 3H, 1'-CH$_3$) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) *δ* = 169.9 (s, CO), 143.8 (s, Ts), 133.8 (s, Ts), 129.5 (d, 2C, Ts), 128.1 (d, 2C, Ts), 124.5 (s, C2), 122.5 (d, C3), 92.5 (s, C3'), 75.6 (s, C2'), 60.5 (d, C1'), 49.3 (t, C5), 28.2 (t, C4), 21.5 (q, CH$_3$-Ts), 21.0 (q, C1'-CH$_3$), 20.7 (q, CH$_3$-Ac) ppm. MS (ESI) *m/z* (%): 689 ([2M+Na]$^+$, 100).
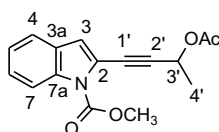
2-(3-Acetoxybut-1-ynyl)-indole-1-carboxylic Acid Methyl Ester (7o).
Sonogashira coupling of triflate **12o** (359 mg, 1.11 mmol) and (±)-3-butyn-2-ol after chromatography (*n*-hexane/EtOAc, 2 : 1 + 1 % Et$_3$N; R$_f$ = 0.15) afforded enynyl alcohol **13o** which was used immediately in the next step. ^{1}H NMR (200 MHz, CDCl$_3$) *δ* = 8.11 (d, *J* = 8.1 Hz, 1H, 4-H), 7.52 (d, *J* = 7.0 Hz, 1H, 7-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, OCH$_3$), 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 % Et$_3$N; R$_f$ = 0.28) pure **7o** was obtained as a yellowish oil (158 mg, 50 % after three steps). ^{1}H NMR (400 MHz, CDCl$_3$) *δ* = 8.16 (d, *J* = 8.2 Hz, 1H, 4-H), 7.52 (d, *J* = 7.8 Hz, 1H, 7-H), 7.39 – 7. 35 (m, 1H, 6-H), 7.27 – 7.24 (m, 1H, 5-H), 6.94 (s, 1H, 3-H), 5.73 (q, *J* = 6.6 Hz, 1H, 3'-H), 4.06 (s, 3H, OCH$_3$), 2.13 (s, 3H, CH$_3$-Ac), 1.63 (d, *J* = 6.6 Hz, 3H, 4'-H) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) *δ* = 169.8 (s, CO-Ac), 151.4 (s, CO$_2$CH$_3$), 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, CO$_2$CH$_3$), 21.1 (q, C4'), 21.0 (q, CH$_3$-Ac) ppm. MS (ESI) *m/z* (%):

593 ([2M+Na]+, 100), 308 ([M+Na]+, 25).
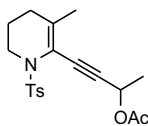
Acetic acid 1-methyl-3-[3-methyl-1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-2-yl]-prop-2-ynyl ester (7p).

Sonogashira coupling of triflate **12p** (345 mg, 0.86 mmol) and (±)-3-butyn-2-ol after chromatography (*n*-hexane/EtOAc, 3 : 2 + 1 % Et$_3$N; R$_f$ = 0.40) afforded enynyl alcohol **13p** which was used immediately in the next step. ^{1}H NMR (400 MHz, CDCl$_3$) *δ* = 7.78 (d, *J* = 8.0 Hz, 2H, Ts), 7.30 (d, *J* = 8.0 Hz, 2H, Ts), 4.61 (q, *J* = 8.0 Hz, 1H, 1'-H), 3.63 - 3.60 (m, 2H, 6-H), 2.43 (s, 3H, CH$_3$-Ts), 2.27 – 2.03 (m, 2H, 4-H), 1.88 (s, 3H, 3-CH$_3$), 1.69 – 1.63 (m, 2H, 5-H), 1.43 (d, *J* = 4.0 Hz, 3H, 1'-CH$_3$) ppm. According to the above described procedure, compound **13p** was subjected to acetylation. After chromatography (*n*-hexane/EtOAc, 2 : 1 + 1 % Et$_3$N; R$_f$ = 0.23) pure **7p** was obtained as a yellowish oil (177 mg, 57 % after two steps). ^{1}H NMR (400 MHz, CDCl$_3$) *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, 6-H), 2.40 (s, 3H, CH$_3$-Ts), 2.06 – 2.01 (m, 2H, 4-H), 2.05 (s, 3H, CH$_3$-Ac), 1.85 (s, 3H, 3-CH$_3$), 1.68 – 1.62 (m, 2H, 5-H), 1.45 (d, *J* = 8.0 Hz, 3H, 1'-CH$_3$) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) *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, *CH$_3$*-3), 21.8 (q, CH$_3$-Ts), 21.5 (t, C4), 21.0 (q, CH$_3$-Ac), 20.9 (t, C5), 20.8 (q, CH$_3$-3') ppm. MS (ESI) m/z (%): 745.01 ([2M+Na]+, 65), 384 ([M+23]+, 100), 378 ([M+18]+, 14).
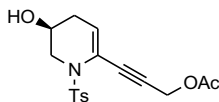
Acetic Acid (5*S*)-3-[5-Hydroxy-1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-2-yl]-prop-2-ynyl Ester (7gb).

To the solution of enynyl acetate **7ga** (133 mg, 0.29 mmol) in THF (14 mL), a freshly prepared solution of TBAF·3H$_2$O (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 % Et$_3$N; R$_f$ = 0.40) pure **7gb** was obtained as a pale yellow oil (82 mg, 82 %). $[\alpha]_D^{21} = + 8.7$ (*c* = 0.86, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) *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 CH$_3$-Ts), 2.20 – 2.05 (m, 4H, 4-H' and CH$_3$-Ac) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) *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, CH$_3$-Ts), 20.7 (q, CH$_3$-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 Na$_2$SO$_4$, filtered and concentrated. The oily residue was purified by flash chromatography to give the corresponding cyclopentane-fused piperidine derivatives.
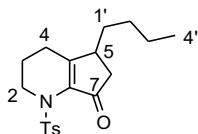
5-Butyl-1-(toluene-4-sulfonyl)-1,2,3,4,5,6-hexahydro-[1]pyrindin-7-one (17aa).

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 Ph$_3$PAuCl/AgSbF$_6$. 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, CDCl$_3$) 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, CH$_3$-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, CDCl$_3$) 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 (d, C5), 32.9 (t, C1'), 29.0 (t, C2'), 24.1 (t, C4), 22.9 (t, C3'), 21.9 (t, C3), 21.7 (q, CH$_3$-Ts), 14.1 (q, C4') ppm. MS (ESI) *m/z* (%): 717 ([2M+Na]$^+$, 100), 370 ([M+Na]$^+$, 12). Elemental analysis calcd (%) for C$_{19}$H$_{25}$NO$_3$S: C 65.68, H 7.25, N 4.03; found: C 65.36, H 7.43, N 4.07.
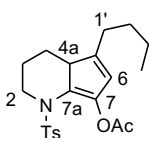
14aa: ^{1}H NMR (400 MHz, CDCl$_3$) δ = 7.67 (d, *J* = 8.0 Hz, 2H, Ts), 7.25 (d, *J* = 8.0 Hz, 2H, Ts), 6.03 (bs, 1H, 6-H), 4.16 – 4.09 (m, 1H, 2-H), 3.05 (td, *J* = 13.6, 2.8 Hz, 1H, 2-H'), 2.41 (s, 3H, CH$_3$-Ts), 2.21 – 2.03 (m, 7H, CH$_3$-Ac, 4-H, 4a-H and 1'-H), 1.64 – 1.56 (m, 1H, 3-H), 1.48 – 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, 4'-H) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) 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, CH$_3$-Ts), 20.7 (q, CH$_3$-Ac), 13.9 (q, C4') ppm. MS (ESI) *m/z* (%): 801 ([2M+Na]$^+$, 100), 390 ([M+Na]$^+$, 12). Elemental analysis calcd (%) for C$_{21}$H$_{27}$NO$_4$S: C 64.75, H 6.99, N 3.06; found: C, 64.82, H 7.08, N 3.04.
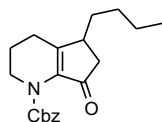

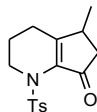**5-Butyl-7-oxo-2,3,4,5,6,7-hexahydro-[1]pyrindine-1-carboxylic Acid Benzyl Ester (17c).**

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 Ph$_3$PAuCl/AgSbF$_6$ 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, CDCl$_3$) δ = 7.40 – 7.27 (m, 5H, Cbz), 5.17 (s, 2H, CH$_2$Ph), 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, CDCl$_3$) 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), 128.0 (d, Cbz), 68.0 (t, CH$_2$Ph), 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 C$_{20}$H$_{25}$NO$_3$: C 73.37, H 7.70, N 4.28; found: C 73.67, H 7.77, N 4.52.
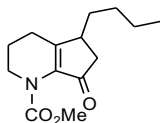
5-Butyl-7-oxo-2,3,4,5,6,7-hexahydro-[1]pyrindine-1-carboxylic Acid Methyl Ester (17d).

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 Ph$_3$PAuCl/AgSbF$_6$ in refluxing DCM. Chromatography (*n*-hexane/EtOAc, 5 : 1) afforded pure ketone **17d** (R$_f$ = 0.16; 20 mg, 64 %) as a yellow oil and acetate **14d** (R$_f$ = 0.29; 5 mg, 14 %) as a yellow oil.

17d: ^{1}H NMR (400 MHz, CDCl$_3$) *δ* = 3.73 (s, 3H, OCH$_3$), 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]
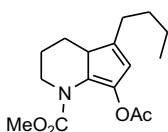
14d: ^{1}H NMR (400 MHz, CDCl$_3$) *δ* = 5.92 (s, 1H, 6-H), 4.33 – 4.09 (m, 1H, 2-H), 3.69 (s, 3H, OCH$_3$), 2.92 – 2.81 (m, 1H, 2-H'), 2.62 (dd, *J* = 12.6, 5.5 Hz, 1H, 4a-H), 2.33 – 2.18 (m, 3H, 4-H and 1'-H), 2.15 (s, 3H, CH$_3$-Ac), 1.93 – 1.84 (m, 1H, 3-H), 1.84 – 1.71 (m, 1H, 3-H'), 1.54 – 1.40 (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.
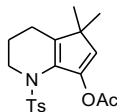
Acetic Acid 5,5-Dimethyl-1-(toluene-4-sulfonyl)-2,3,4,5-tetrahydro-1H-[1]pyrindin-7-yl Ester (16ad).

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 Ph$_3$PAuCl/AgSbF$_6$. Chromatography (*n*-hexane/EtOAc, 10 : 1 + 1 % Et$_3$N; R$_f$ = 0.14) afforded pure acetate **16ad** (72 mg, 86 %) as a yellow solid. M.p. = 108.0 – 109.4 °C. ^{1}H NMR (400 MHz, CDCl$_3$) *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, CH$_3$-Ts), 2.19 (s, 3H, CH$_3$-Ac), 1.91 (t, *J* = 6.6 Hz, 2H, 4-H), 1.36 – 1.33 (m, 2H, 3-H), 1.09 (s, 6H, 5-CH$_3$) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) *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-CH$_3$), 21.5 (q, CH$_3$-Ts), 21.1 (q, CH$_3$-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 C$_{19}$H$_{23}$NO$_4$S: 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 Ph$_3$PAuCl/AgSbF$_6$ in refluxing DCM. Chromatography (*n*-hexane/EtOAc, 2 : 1; R$_f$ = 0.26) afforded pure ketone **17ab** (26 mg, 83 %) as a white solid. M.p. = 138.1 – 141.1 °C. ^{1}H NMR (400 MHz, CDCl$_3$) *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, CH$_3$-Ts and 4-H), 2.02 – 1.96 (m, 2H, 3-H) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) *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, CH$_3$ Ts) ppm. MS (ESI)
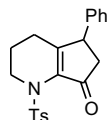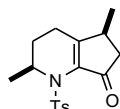
5-Methyl-1-(toluene-4-sulfonyl)-1,2,3,4,5,6-hexahydro-[1]pyrindin-7-one (17ac).

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 Ph$_3$PAuCl/AgSbF$_6$. Chromatography (*n*-hexane/EtOAc, 5 : 1) afforded pure ketone **17ac** (R$_f$ = 0.16; 44 mg, 72 %) as a yellow oil and acetate **14ac** (R$_f$ = 0.24; 8 mg, 14 %) as a grey solid.

17ac: ^{1}H NMR (400 MHz, CDCl$_3$) 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, 2-H), 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, CH$_3$-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-CH$_3$) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) 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, CH$_3$-Ts), 19.1 (q, C5-CH$_3$) ppm. MS (ESI) m/z (%): 633 ([2M+Na]$^+$, 100), 306 ([M+Na]$^+$, 10). Elemental analysis calcd (%) for C$_{16}$H$_{19}$NO$_3$S: C 62.93, H 6.27, N 4.59; found: C 62.79, H 6.05, N 4.41.
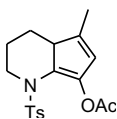
14ac: M.p. = 100.8 – 102.2 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ = 7.67 (d, J = 8.0 Hz, 2H, Ts), 7.26 (d, J = 8.0 Hz, 2H, Ts), 6.04 – 6.01 (m, 1H, 6-H), 4.17 – 4.09 (m, 1H, 2-H), 3.06 (td, J = 13.6, 2.8 Hz, 1H, 2-H'), 2.41 (s, 3H, CH$_3$-Ts), 2.19 (s, 3H, CH$_3$-Ac), 2.12 – 2.06 (m, 2H, 4-H, 4a-H), 1.87 (d, J = 1.6 Hz, 3H, 5-CH$_3$), 1.62 – 1.56 (m, 1H, 3-H), 1.33 (qt, J = 14, 3.2 Hz, 1H, 3-H'), 1.03 (qd, J = 13.2, 3.2 Hz, 1H, 4-H') ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) δ = 168.8 (s, CO), 145.4 (s, C7), 143.4 (s, Ts), 142.6 (s, C7a), 137.4 (s, Ts), 134.1 (d, C6), 129.6 (d, 2C, Ts), 127.4 (d, 2C, Ts), 124.1 (s, C5), 49.4 (t, C2), 46.5 (d, C4a), 27.9 (t, C3), 24.9 (t, C4), 21.5 (q, CH$_3$ Ts), 20.8 (q, CH$_3$ Ac), 14.4 (q, C5-CH$_3$) ppm. MS (ESI) m/z (%): 717 ([2M+Na]$^+$, 100), 370 ([M+Na]$^+$, 3), 348 ([M+1]$^+$, 19). Elemental analysis calcd (%) for C$_{18}$H$_{21}$NO$_4$S: C 62.23, H 6.09, N 4.03; found: C 61.92, H 5.81, N 3.96.

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 Ph$_3$PAuCl/AgSbF$_6$ in toluene. Chromatography (*n*-hexane/EtOAc, 8 : 1; R$_f$ = 0.16) afforded pure ketone **17ae** (37 mg, 55 %) as a pale yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$) 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, 2-H), 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, CH$_3$-Ts), 2.16 – 2.08 (m, 2H, 4-H), 1.96 – 1.90 (m, 2H, 3-H) ppm. Spectroscopical data identical to those reported in the literature.[40]
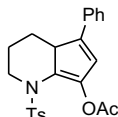
Acetic Acid 5-Phenyl-1-(toluene-4-sulfonyl)-2,3,4,4a-tetrahydro-1H-[1]pyrindin-7-yl Ester (14ae).

The reaction was carried out with 3 mol % of Ph$_3$PAuCl/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; R_f = 0.27) **14ae** was isolated in 34 % (19 mg) due to [1,5]H-shift. Attempts of the purification under basic (Et$_3$N) and neutral (alumina) conditions led to hydrolysis and [1,5]H-shift. M.p. = 65.0 – 67.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$) 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, CH_3 Ts), 2.27 - 2.19 (m, 4H, CH$_3$-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. ^{13}C NMR (100.4 MHz, CDCl$_3$) 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), 128.6 (d, 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, CH$_3$-Ts), 20.7 (q, CH$_3$-Ac) ppm. MS (ESI) m/z (%): 841 ([2M+Na]$^+$, 100), 432 ([M+Na]$^+$, 18), 410 ([M+1]$^+$, 16). Elemental analysis calcd (%) for C$_{23}$H$_{23}$NO$_4$S: 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]pyrindin-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 (Cy)$_3$PAuCl/AgSbF$_6$. Chromatography (*n*-hexane/EtOAc, 6 : 1; R_f = 0.16) afforded pure *cis* ketone **17e** (37 mg, 83 %) as a white solid.
^{1}H NMR (400 MHz, CDCl$_3$) 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, CH$_3$-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-CH$_3$), 0.85 (d, J = 8.9 Hz, 3H, 2-CH$_3$) ppm. Spectroscopical data identical to those reported in the literature.[15]
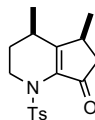
4,5-Dimethyl-1-(toluene-4-sulfonyl)-1,2,3,4,5,6-hexahydro-[1]pyrindin-7-one (17f).
Compound **17f** was prepared according to the above described procedure starting from **7f** (76 mg, 0.2 mmol). Reaction was carried out with 5 mol % of Ph$_3$PAuCl/AgSbF$_6$. Chromatography (*n*-hexane/EtOAc, 6 : 1) afforded *cis* ketone **17f** (R_f = 0.16; 37 mg, 56 %) as a white solid and acetate **14f** (R_f = 0.22; 14 mg, 18 %) as a colourless oil.
17f: ^{1}H NMR (400 MHz, CDCl$_3$) 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, CH$_3$-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-CH$_3$), 1.13 (d, J = 7.2 Hz, 3H, 4-CH$_3$) ppm. Spectroscopical data identical to those reported in the literature.[15]
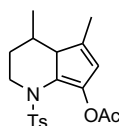

14f: ^{1}H NMR (200 MHz, CDCl$_3$) δ = 7.67 (d, J = 8.4 Hz, 2H, Ts), 7.27 (d, J = 8.4 Hz, 2H, Ts), 6.08 – 6.04 (m, 1H, 6-H), 4.07 (ddd, J = 14.0, 4.2, 2.4 Hz, 1H, 2-H), 3.05 (td, J = 14.0, 2.4 Hz, 1H, 2-H'), 2.42 (s, 3H, CH$_3$-Ts), 2.17 (s, 3H, CH$_3$-Ac), 2.00 (d, J = 1.6 Hz, 3H, 5-CH$_3$), 1.81 (d, 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-CH$_3$) ppm.
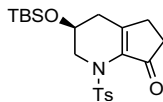
(3S)-3-(*tert*-Butyl-dimethyl-silanyloxy)-1-(toluene-4-sulfonyl)-1,2,3,4,5,6-hexahydro-[1]pyridin-7-one (17ga).

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 Ph$_3$PAuCl/AgSbF$_6$ in refluxing DCM. Chromatography (*n*-hexane/EtOAc, 4 : 1; R$_f$ = 0.21) afforded ketone **17ga** (47 mg, 75 %) as a yellow foam. $[\alpha]_D^{22}$ = - 74.4 (*c* = 0.91, CHCl$_3$). M.p. = 61.7 – 63.4 °C. ^{1}H NMR (400 MHz, CDCl$_3$) *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 CH$_3$-Ts), 2.27 (dd, *J* = 20.0, 8.2 Hz, 1H, 4-H'), 0.91 (s, 9H, SiC(CH$_3$)$_3$), 0.15 (s, 3H, SiCH$_3$), 0.14 (s, 3H, SiCH$_3$) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) *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), 64.7 (d, C3), 51.7 (t, C2), 36.9 (t, C6), 34.1 (t, C5), 27.1 (t, C4), 25.8 (q, 3C, SiC(CH$_3$)$_3$), 21.5 (q, CH$_3$ Ts) 18.0 (s, SiC(CH$_3$)$_3$), -4.68 (q, SiCH$_3$), -4.95 (q, SiCH$_3$) ppm. MS (ESI) *m/z* (%): 865 ([2M+Na]$^+$, 100), 444 ([M+Na]$^+$, 8). Elemental analysis calcd (%) for C$_{21}$H$_{31}$NO$_4$SSi: C 59.82, H 7.41, N 3.32; found: C 60.04, H 7.13, N 3.49.
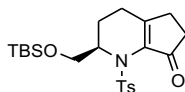
2-(tert-Butyl-dimethyl-silanyloxymethyl)-1-(toluene-4-sulfonyl)-1,2,3,4,5,6-hexahydro-[1]pyridin-7-one (17h).

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 Ph$_3$PAuCl/AgSbF$_6$ in refluxing DCM. Chromatography (heptane/EtOAc, 3:1; R$_f$ = 0.21) afforded ketone **17h** (375 mg, 75%) as a yellow solid. $[\alpha]_D^{22}$ = - 68.2 (*c* = 1, DCM). M.p. = 105.7 – 106.5 °C. ^{1}H NMR (400 MHz, CDCl$_3$) *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-CH$_2$OTBS), 3.20 (dd, *J* = 10.2, 8.4 Hz, 1H, 2-CH$_2$OTBS), 2.62 – 2.46 (m, 3H), 2.41 (s, 3H, CH$_3$-Ts), 2.40 – 2.21 (m, 3H), 2.17 – 2.07 (m, 1H), 2.04 – 1.93 (m, 1H), 0.76 (s, 9H, CH$_3$-TBS), -0.12 (s, 6H, CH$_3$-TBS) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) *δ* = 206.6 (s,C-7), 164.7 (s, C-7a), 149.2 (s, Ts), 143.5 (s, Ts), 141.8 (s, C-4a), 134.9 (d, 2C, Ts), 133.7 (d, 2C, Ts), 67.3 (t, 2-CH$_2$OTBS), 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, CH$_3$-Ts), 23.9 (s, TBS), 0.2 (q, TBS), 0.1 (q, TBS) ppm. MS (ESI) *m/z* (%):436 ([M+1]$^+$, 100). Elemental analysis calcd (%) for C$_{22}$H$_{33}$NO$_4$SSi; 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-1*H*-[1]pyridin-3-yl ester (22) and (3S)-3-Hydroxy-1-(toluene-4-sulfonyl)-1,2,3,4,5,6-hexahydro-[1]pyridin-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 Ph$_3$PAuCl/AgSbF$_6$ in refluxing DCM. Chromatography (*n*-hexane/EtOAc, 1 : 1) afforded pure ketone **22** (R$_f$ = 0.29; 37 mg, 75 %) as a white foam and product **17gb** as white solid (R$_f$ = 0.14; 12 mg, 16 %).


22: $[\alpha]_D^{21}$ = + 69.7 (*c* = 0.24, CHCl$_3$). M.p. = 65.2 – 67.8 °C. ^{1}H NMR (400 MHz, CDCl$_3$) *δ* = 7.94 (d, *J* = 8.3 Hz, 2H, Ts), 7.28 (d, *J* = 8.3 Hz, 2H, Ts), 5.27 – 5.21 (m, 1H, 3-H), 4.10 (dd, *J* = 13.4, 5.1 Hz, 1H, 2-H), 3.29 (d, *J* = 13.4, 1H, 2-H), 2.76 (dd, *J* = 20.3, 5.6 Hz, 1H, 4-H), 2.56 – 2.35 (m, 8H, 4-H, 5-H, 6-H and CH$_3$-Ts), 2.13 (s, 3H, CH$_3$-Ac) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) *δ* = 199.6 (s, C7), 170.6 (s, CO-Ac), 155.2 (s, C7a), 143.4 (s, Ts), 138.7 (s, C4a), 137.7 (s, Ts), 129.1 (d, 2C, Ts), 127.6 (d, 2C, Ts), 64.4 (d, C3), 47.9 (t, C2), 33.6 (t,

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 C₁₇H₁₉NO₅S: C 58.44, H 5.48, N 4.01; found: C 58.72, H 5.17, N 3.89.
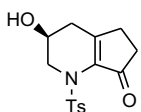
17gb: $[\alpha]_D^{21}$ = + 28.5 (*c* = 0.33, CHCl₃). M.p. = 172.6 - 177.8 °C. ¹H NMR (400 MHz, CDCl₃) *δ* = 8.04 (d, *J* = 8.3 Hz, 2H, Ts), 7.31 (d, *J* = 8.3 Hz, 2H, Ts), 4.36 – 4.34 (m, 1H, 3-H), 3.68 (dd, *J* = 13.8, 5.6 Hz, 1H, 2-H), 2.68 (dd, *J* = 13.8, 2.0 Hz, 1H, 2-H), 2.68 – 2.44 (m, 7H, 4-H, 5-H, 6-H and OH), 2.43 (s, 3H, CH₃-Ts) ppm. ¹³C NMR (100.4 MHz, CDCl₃) *δ* = 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 C₁₅H₁₇NO₄S: C 58.61, H 5.57, N 4.56; found: C 58.93, H 5.22, N 4.23.
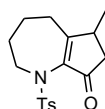
6-Methyl-1-(toluene-4-sulfonyl)-2,3,4,5,6,7-hexahydro-1H-cyclopenta[b]azepin-8-one (17la).
Compound **17la** was prepared according to the above described procedure starting from **7la** (135 mg, 0.37 mmol). Reaction was carried out with 5 mol % of Ph₃PAuCl/AgSbF₆ in DCM at room temperature. Chromatography (*n*-hexane/EtOAc, 4 : 1; R*f* = 0.22) afforded pure ketone **17la** (98 mg, 82 %) as a pale orange solid. M.p. = 98.7 – 100.5 °C. ¹H NMR (400 MHz, CDCl₃) *δ* = 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'), 2.02 – 1.82 (m, 2H, 3-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-CH₃) ppm. ¹³C NMR (100.4 MHz, CDCl₃) *δ* = 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), 35.2 (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 C₁₇H₂₁NO₃S: C 63.92, H 6.63, N 4.39; found: C 63.67, H 6.91, N 4.02.
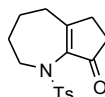
1-(Toluene-4-sulfonyl)-2,3,4,5,6,7-hexahydro-1H-cyclopenta[b]azepin-8-one (17lb).
Compound **17lb** was prepared according to the above described procedure starting from **7lb** (103 mg, 0.30 mmol). Reaction was carried out with 5 mol % of Ph₃PAuCl/AgSbF₆ in refluxing DCM. Chromatography (*n*-hexane/EtOAc, 3 : 2; R*f* = 0.22) afforded pure ketone **17lb** (75 mg, 83 %) as a white solid. M.p. = 115.0 – 118.5 °C. ¹H NMR (400 MHz, CDCl₃) *δ* = 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. ¹³C NMR (100.4 MHz, CDCl₃) *δ* = 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 C₁₆H₁₉NO₃S: C 62.93, H 6.27, N 4.59; found: C 63.11, H 5.96, N 4.34.
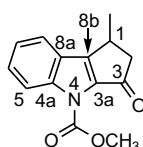
1-Methyl-3-oxo-2,3-dihydro-1H-cyclopenta[b]indole-4-carboxylic Acid Methyl Ester (17o).

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 Ph₃PAuCl/AgSbF₆ in refluxing DCM. Chromatography (*n*-hexane/EtOAc, 6 : 1; R$_f$ = 0.26) afforded pure ketone **17o** (47 mg, 84 %) as a yellow solid. M.p. = 113.4 – 115.2 °C. ^{1}H 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. ^{13}C 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 5.76; 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 Ph₃PAuCl/AgOTf in refluxing DCM. Chromatography (*n*-hexane/EtOAc, 5 : 1) afforded acetate **14p** (R$_f$ = 0.39; 20 mg, 17 %) as a yellow oil and ketone **15p** as colourless oil (R$_f$ = 0.17; 25 mg, 25 %).
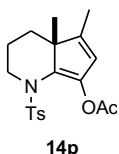
14p: ^{1}H NMR (400 MHz, CDCl₃) δ = 7.75 (d, *J* = 8.0 Hz, 2H, Ts), 7.24 (d, *J* = 8.0 Hz, 2H, Ts), 5.90 (s, 1H, 6-H), 3.99 (dd, *J* = 8.0, 4.0 Hz, 1H, 2-H), 2.99 (td, *J* =12.0, 4.0 Hz, 1H, 2-H), 2.39 (s, 3H, CH₃-Ts), 2.10 (s, 3H, CH₃-Ac), 1.87 - 1.74 (m, 2H, 5-H), 1.79 (d, *J* = 4.0 Hz, 3H, 5-CH₃), 1.60 – 1.54 (m, 1H, 4-H), 1.15 (td, *J* = 16.0, 4.0 Hz, 1H, 4H), 0.77 (s, 3H, 4a-CH₃) ppm. ^{13}C 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+18]⁺, 17), 362 ([M+1]⁺,32).
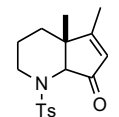
15p: ^{1}H NMR (400 MHz, CDCl₃) *δ* = 7.86 (d, *J* = 8.0 Hz, 2H, Ts), 7.30 (d, *J* = 8.0 Hz, 2H, Ts), 5.91 (s, 1H, 6-H), 4.32 (s, 1H, 7a-H), 3.61 (dt, *J* =12.0, 8.0 Hz, 1H, 2-H), 2.82 - 2.76 (m, 1H, 2-H), 2.42 (s, 3H, CH₃-Ts), 2.02 (s, 3H, 5-CH₃), 1.74 - 1.58 (m, 2H, 3-H), 1.46 – 1.40 (m, 1H, 4-H), 1.33 (s, 3H, 4a-CH₃), 1.29 – 1.25 (m, 1H, 4-H) ppm. ^{13}C 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+18]⁺, 28), ([M+1]⁺,24). Elemental analysis calcd (%) for C₁₇H₂₁NO₃S: 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 *p*TsOH 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%).
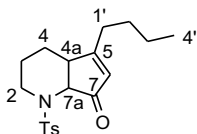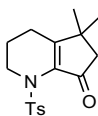
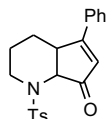**5-Butyl-1-(toluene-4-sulfonyl)-1,2,3,4,4a,7a-hexahydro-[1]pyrindin-7-one (15aa).**

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$_3$) δ = 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$_3$) δ = 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 ([2M+Na]$^+$, 100), 370 ([M+Na]$^+$, 5), 348 ([M+1]$^+$, 6). Elemental analysis calcd (%) for C$_{19}$H$_{25}$NO$_3$S: C 65.68, H 7.25, N 4.03; found: C 65.36, H 7.43, N 4.07.
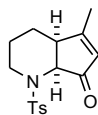
5-Methyl-1-(toluene-4-sulfonyl)-1,2,3,4,4a,7a-hexahydro-[1]pyrindin-7-one (15ac).

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$_3$) δ = 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$_3$) δ = 203.4 (s, C-7), 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 ([2M+Na]$^+$, 100), 327 ([M+Na]$^+$, 48), 305 ([M+1]$^+$, 37). Elemental analysis calcd (%) for C$_{16}$H$_{19}$NO$_3$S: C 62.93, H 6.27, N 4.57; found: C 62.80, H 6.36, N 4.55.


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$_3$) δ = 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$_3$) δ = 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-CH$_3$), 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$_3$S: 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; R_f = 0.25) as a yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$) *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 (dtd, *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. ^{13}C NMR (100.4 MHz, CDCl$_3$) *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, CH$_3$-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 C$_{21}$H$_{21}$NO$_3$S: C 68.64, H 5.76, N 3.81; found C 68.49, H 5.41, N 3.64.
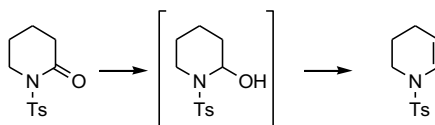
1-(Toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridine (25a).

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 followed by satd solution of Rochelle salt. Formed two-phase system was stirred at room temperature for 1 h. Layers were separated, 1-(toluene-4-sulfonyl)-piperidin-2-ol was extracted with DCM (2 x 15 mL) and the organic layer was dried over anhydrous Na$_2$CO$_3$ for 30 min. After filtration and evaporation of the solvent, obtained 1-(toluene-4-sulfonyl)-piperidin-2-ol was dissolved in DCM (10 mL) and DMAP (9.6 mg, 0.78 mmol) and Et$_3$N (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 NH$_4$Cl (10 mL) was added and the product extracted with DCM (3 x 10 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, 5 : 1; R_f = 0.40) afforded pure 1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridine (333 mg, 70 %) as a white wax. ^{1}H NMR (400 MHz, CDCl$_3$): *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, CH$_3$-Ts), 1.92 (bs, 2H, 4-H), 1.68 – 1.65 (m, 2H, 5-H) ppm. Spectroscopical data correspond to the literature values.[43]
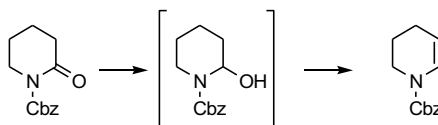
**3,4-Dihydro-2H-pyridine-1-carboxylic acid benzyl ester (25c).**

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 NaHCO$_3$ (25 mL) was added followed by 35 % solution of H$_2$O$_2$ (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 Na$_2$CO$_3$ 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 Et$_3$N (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 NH$_4$Cl (30 mL) was added and the product extracted with DCM (3 x 30 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, 8 : 1; R$_f$ = 0.36) afforded pure **25c** (660 mg, 62 %) as a colourless oil. ^{1}H NMR (400 MHz, CDCl$_3$) mixture of rotamers: *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, CH$_2$O), 4.97 (m, 0.4 H, 3-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]
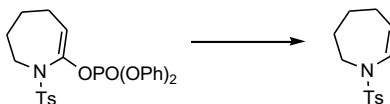
1-(Toluene-4-sulfonyl)-2,3,4,5-tetrahydro-1H-azepine (25l).

A solution of **12l** (975 mg, 1.94 mmol) in DME (5 mL), Pd(OAc)$_2$ (21.8 mg, 0.097 mmol) and PPh$_3$ (49.8 mg, 0.19 mmol) was prepared under nitrogen atmosphere. This solution was added dropwise, under nitrogen atmosphere, into a solution of formic acid (0.147 mL, 3.9 mmol) and Et$_3$N (0.75 mL, 5.82 mmol) in DME (5 mL). Reaction mixture was refluxed (85 °C) for 30 min and then cooled to room temperature. Water (10 mL) was added, and the product was extracted with EtOAc (3 x 10 mL). The organic phase was dried over Na$_2$SO$_4$ and concentrated. Flash chromatography (*n*-hexane/EtOAc, 10 : 1; R$_f$ = 0.22) afforded desired product (290 mg, 62 %) as a white solid. M.p. = 59.2 – 60.8 °C. ^{1}H NMR (400 MHz, CDCl$_3$) *δ* = 7.70 (d, *J* = 8.2 Hz, 2H, Ts), 7.29 (d, *J* = 8.2 Hz, 2H, Ts), 6.41 (d, *J* = 8.8 Hz, 1H, 7-H), 5.09 (dt, *J* = 8.8, 5.7 Hz, 1H, 6-H), 3.50 (t, 2H, *J* = 6.1 Hz, 2-H), 2.42 (s, 3H, CH$_3$-Ts), 2.11 – 2.06 (m, 2H, 5-H), 1.71 – 1.68 (m, 2H, 3-H), 1.50 – 1.44 (m, 2H, 4-H) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) *δ* = 143.4 (s, Ts), 136.7 (s, Ts), 129.8 (d, 2C, Ts), 129.2 (d, C-7), 126.9 (d, 2C, Ts), 116.8 (d, C6), 49.7 (t, C2), 28.9 (t, C5), 26.1 (t, C3), 24.9 (t, C4), 21.5 (q, CH$_3$-Ts). MS (ESI) *m/z* (%): 252 ([M+1]$^+$, 100), 274 ([M+Na]$^+$, 32), 524 ([2M+Na]$^+$, 11). Elemental analysis calcd (%) for C$_{13}$H$_{17}$NO$_2$S: C 62.12, H 6.82, N 5.57; found C 61.63, H 6.58, N 5.63.
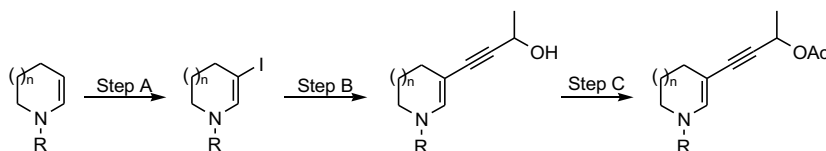
General procedure for synthesis of enesulfonamides derived enynyl acetates.

STEP A: Iodination of enesulfonamides (27)

Enesulfonamide (1 mmol) and NaOCH$_3$ (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 Na$_2$S$_2$O$_3$ was added and stirring continued for 30 min. The layers were separated; organic layer was dried over Na$_2$SO$_4$, 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 Et$_3$N (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), CuI (19 mg, 0.1 mmol) and (Ph$_3$P)$_2$PdCl$_2$ (35 mg, 0.05 mmol) were dissolved in an anhydrous 4 : 1 Et$_2$NH/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 Et_2O (3 x 10 mL) and the combined organic extracts were dried over anhydrous K_2CO_3 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 Et_3N (0.38 mL, 3 mmol) in DCM (4 mL) was cooled by ice bath and Ac_2O (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 $NaHCO_3$ (10 mL) was added and the product extracted with DCM (3 x 10 mL). The combined organic extracts were dried over anhydrous K_2CO_3 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 % Et_3N until use.
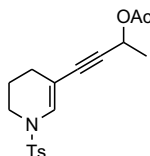
Acetic acid 1-methyl-3-[1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-3-yl]-prop-2-ynyl ester (29a).

Compound **27a** was prepared according to the above described procedure starting from **25a** (230 mg, 1 mmol). Flash chromatography (n-hexane/EtOAc, 3 : 2; R_f = 0.22) afforded **13** (327 mg, 77 %) contaminated by unknown impurity. ^{1}H NMR (400 MHz, $CDCl_3$) $δ$ = 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, CH_3-Ts), 2.32 (td, J = 6.3, 2.7 Hz, 2H, 4-H), 1.76 – 1.66 (m, 2H, 5-H) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$) $δ$ = 143.9 (s, Ts), 134.6 (s, Ts), 130.4 (d, C-2), 129.9 (d, 2C, Ts), 126.9 (d, 2C, Ts), 87.7 (s, C3), 42.2 (t, C6), 34.0 (t, C4), 23.0 (t, C5), 21.4 (q, CH_3-Ts) ppm. MS (ESI) *m/z* (%): 364 ([M+1][+], 100), 385 ([M+Na][+], 8).

Sonogashira coupling of $β$-iodo-enesulfonamides **27a** (193 mg, 0.9 mmol) and (±)-3-butyn-2-ol after flash chromatography (n-hexane/EtOAc, 3 : 1 + 1 % Et_3N; R_f = 0.16) afforded enynyl alcohol **28a** which was used immediately in the next step (220 mg, 80 %).

^{1}H NMR (400 MHz, $CDCl_3$) $δ$ = 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, CH_3-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'-CH_3) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$) $δ$ = 144.0 (s, Ts), 134.8 (s, Ts), 130.7 (d, C2), 129.9 (d, 2C, Ts), 127.0 (d, 2C, Ts), 100.9 (s, C3), 89.4 (s, C1'), 83.7 (C2'), 58.9 (C3'), 43.6 (t, C6), 25.5 (C4), 24.5 (q, CH_3-3'), 21.6 (q, CH_3-Ts), 20.6 (t, C-5) ppm. MS (ESI) *m/z* (%): 306 ([M+1][+], 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 % Et_3N; R_f = 0.18) pure **15** was obtained as a colourless oil (210 mg, 84 %). ^{1}H NMR (400 MHz, $CDCl_3$) $δ$ = 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, CH_3-Ts), 2.08 (s, 3H, CH_3-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'-CH_3) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$) $δ$ = 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, CH_3-Ac), 21.6 (q, CH_3-3'), 21.5 (q, CH_3-Ts), 21.1 (t, C-4), 20.6 (t, C-5) ppm. MS (ESI) *m/z* (%): 288 ([$C_{16}H_{18}NO_2S$][+], 100), 369 ([M+Na][+], 17).
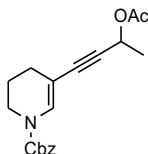
5-(3-Acetoxy-but-1-ynyl)-3,4-dihydro-2H-pyridine-1-carboxylic acid benzyl ester (29c).

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; R_f = 0.24) afforded **27c** (353 mg, 66 %). ^{1}H NMR (400 MHz, CDCl$_3$) δ = 7.44 – 7.28 (m, 5H, Ph), 7.27 – 7.25 (s, 1H, 2-H), 5.18 (s, 2H, CH$_2$O), 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-enecarbamate **27c** (177 mg, 0.52 mmol) and (±)-3-butyn-2-ol after flash chromatography (n-hexane/EtOAc, 5:2 + 1 % Et$_3$N; R_f = 0.19) afforded enynyl alcohol **28c** which was used immediately in the next step (120 mg, 75 %). ^{1}H NMR (400 MHz, CDCl$_3$) 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 % Et$_3$N; R_f = 0.21) pure **29c** was obtained as a colourless oil (108 mg, 85 %). ^{1}H NMR (400 MHz, CDCl$_3$) 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, CH$_2$O), 3.63 – 3.54 (m, 2H, 6-H), 2.16 (t, J = 5.9 Hz, 2H, 4-H), 2.06 (s, 3H, CH$_3$-Ac), 1.85 – 1.75 (m, 2H, 5-H), 1.49 (d, J = 6.6 Hz, 3H) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) 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, CH$_2$-Cbz), 61.0 (d, C3'), 41.9 (t, C6), 25.8 (d, C4), 21.7 (d, C5), 21.2 (q, CH$_3$-3'), 21.0 (q, CH$_3$-Ac) ppm. MS (ESI) *m/z* (%): 268 ([M-OAc]$^+$, 100), 349 ([M+Na]$^+$, 34), 676 ([2M+Na]$^+$, 7).
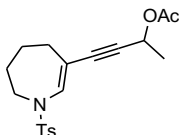
Acetic acid 1-methyl-3-[1-(toluene-4-sulfonyl)-4,5,6,7-tetrahydro-1H-azepin-3-yl]-prop-2-ynyl ester (29l).

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; R_f = 0.22) afforded **27l** (201 mg, 85 %) contaminated by unknown impurity. ^{1}H NMR (400 MHz, CDCl$_3$) 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, 2-H), 2.72 – 2.59 (m, 2H, 5-H), 2.44 (s, 3H, CH$_3$-Ts), 1.78 – 1.66 (m, 2H, 3-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-butyn-2-ol after flash chromatography (*n*-hexane/EtOAc, 3 : 1 + 1 % Et$_3$N; R_f = 0.16) afforded enynyl alcohol **28l** which was used immediately in the next step (115 mg, 71 %). ^{1}H NMR (400 MHz, CDCl$_3$) 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, CH$_3$-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'-CH$_3$) ppm.

According to the above described procedure, compound **28l** was subjected to acetylation. After flash chromatography (*n*-hexane/EtOAc, 6 : 1 + 1 % Et$_3$N; R_f = 0.18) pure **29l** was obtained as a colourless oil (100 mg, 84 %). ^{1}H NMR (400 MHz, CDCl$_3$) 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, CH$_3$-Ts), 2.27 (t, J = 6.0 Hz, 2H, 4-H), 2.06 (s, 3H, CH$_3$-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'-CH$_3$). ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) 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,

CH₃-Ac), 21.5 (q, CH₃-Ts), 21.1 (q, CH₃-3') ppm. MS (ESI) *m/z* (%): 302 ([M-OAc]⁺, 100), 384 ([M+Na]⁺, 49), 744 ([2M+Na]⁺, 6).
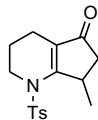
7-Methyl-1-(toluene-4-sulfonyl)-1,2,3,4,6,7-hexahydro-[1]pyrindin-5-one (30a).

Compound **30a** was prepared according to the general procedure for the Au(I)-catalyzed Nazarov reaction starting from **29a** (52 mg, 0.16 mmol). Reaction was carried out with 5 mol % of Ph₃PAuCl/AgSbF₆ in DCM at room temperature. Flash chromatography (n-hexane/EtOAc, 3 : 1; R*f* = 0.15) afforded pure product **30a** (32 mg, 66 %) as a white solid. ¹H NMR (400 MHz, CDCl₃) *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, CH₃-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-CH₃) ppm. ¹³C NMR (100.4 MHz, CDCl₃) *δ* = 204.1 (s, CO), 170.1 (s, C7a), 144.8 (s, Ts), 135.3 (s, Ts), 130.2 (d, 2C, Ts), 127.1 (d, 2C, Ts), 123.8 (s, C4a), 47.9 (d, C6), 43.0 (t, C2), 35.4 (d, C7), 22.1 (t, C5), 21.6 (q, CH₃-Ts), 19.3 (t, C4), 18.3 (q, CH₃-7) ppm. MS (ESI) *m/z* (%): 306 ([M+1]+, 100), 328 ([M+Na]⁺, 15), 633 ([2M+Na]⁺, 35). Elemental analysis calcd (%) for C₁₆H₁₉NO₃S: C 62.93, H 6.27, N 4.59; found: C 62.70, H 6.33, N 4.54.
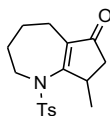
8-Methyl-1-(toluene-4-sulfonyl)-2,3,4,5,7,8-hexahydro-1H-cyclopenta[b]azepin-6-one (30l).

Compound **30l** was prepared according to the general procedure for the Au(I)-catalyzed Nazarov reaction starting from **29l** (50 mg, 0.14 mmol). Reaction was carried out with 5 mol % of Ph₃PAuCl/AgSbF₆ in DCM at room temperature. Flash chromatography (*n*-hexane/EtOAc, 3 : 1; R*f* = 0.15) afforded pure product **30a** (24 mg, 54 %) as a white solid. M.p. = 118.4 – 119.0 °C. ¹H NMR (400 MHz, CDCl₃) *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, CH₃-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-CH₃) ppm. ¹³C NMR (100.4 MHz, CDCl₃) *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), 43.0 (t, C2), 35.6 (t, C8), 28.1 (d, C5), 22.9 (t, C3), 21.6 (t, C4), 21.6 (q, CH₃-Ts), 20.3 (q, CH₃-8) ppm. MS (ESI) *m/z* (%): 320 ([M+1]⁺, 100). Elemental analysis calcd (%) for C₁₇H₂₁NO₃S: 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 Ph₃PAuCl/AgOTf in DCM : *t*-BuOH = 1 : 1. Chromatography (*n*-hexane/EtOAc, 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%).
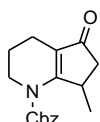

30c. ¹H NMR (400 MHz, CDCl₃) *δ* = 7.43 – 7.29 (m, 5H, Ph), 5.23 (s, 2H, CH₂O), 4.08 (dt, *J* = 9.6, 4.7 Hz, 1H, 6-H), 3.75 – 3.65 (m, 1H, 7-H), 3.45 (ddd, *J* = 12.6, 9.6, 3.0 Hz, 1H, 6-H), 2.65 (dd, *J* = 18.2, 6.8 Hz, 1H, 6-H), 2.20 (t, *J* = 6.6 Hz, 2H, 4-H), 1.99 (d, *J* = 18.2 Hz, 1H, 6-H), 1.91 – 1.71 (m, 2H, 3-H), 1.14 (d, J = 6.8 Hz, 3H, CH₃) ppm.
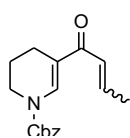
31c. mixture of E/Z isomers: ^{1}H NMR (400 MHz, CDCl$_3$) δ = 7.79 – 7.68 (bs, 1H, 2-H), 7.45 – 7.29 (m, 5H, Ph), 6.87 (q, J = 6.9 Hz, 0.35H, 7-H), 6.84 (q, J = 6.9 Hz, 0.65H, 7-H), 6.75 – 6.62 (bs, 0.65H, 6-H), 6.62 – 6.49 (bs, 0.35H, 6-H), 5.26 (s, 2H, CH$_2$O) 3.66 – 3.63 (m, 2H, 2-H), 2.36 (t, J = 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.
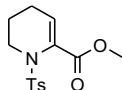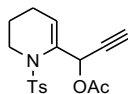
1-(Toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridine-2-carboxylic acid methyl ester (42).

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 Et$_2$O (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. After chromatography (n-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$_3$) δ = 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$_3$) δ = 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$_{14}$H$_{17}$NO$_4$S: C 56.93, H 5.80, N 4.74; found N 4.91, C 56.98, H 5.68.
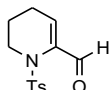
1-(Toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridine-2-carbaldehyde (43).

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$_3$) δ = 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, H-6), 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$_3$) δ = 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$_3$S: 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-sulfonyl)-1,4,5,6-tetrahydro-pyridin-2-yl]-prop-2-ynyl ester (48).

A solution of triethysilylacetylene (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 NaHCO$_3$ (8 mL) was added. The product was extracted with Et$_2$O (3 x 5 mL) and 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 THF (10 mL) and TBAF (237 mg, 0.75 mmol) was added. Reaction was stirred at room temperature and after 1 h water was added. The product was extracted with Et$_2$O (3 x 10 mL). The organic extracts were dried over anhydrous Na$_2$CO$_3$ for 30 min. After filtration and evaporation of the solvent, column chromatography (*n*-hexane/Et$_2$O, 3 : 1 + 1 % Et$_3$N; R$_f$ = 0.36) afforded pure **47** (14 mg, 6 %) as a colourless oil and **46** (111 mg, 46 %) as a yellow oil.
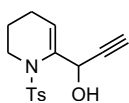
47: ^{1}H NMR (200 MHz, CDCl$_3$) *δ* = 7.75 (d, *J* = 8.3 Hz, 2H, Ts), 7.32 (d, *J* = 8.3 Hz, 2H, Ts), 6.02 (t, *J* = 3.8 Hz, 1H, 3-H), 5.49 (s, 1H, 1'-H), 3.69 (ddd, *J* = 14.1, 6.3, 3.6 Hz, 1H, 6-H), 3.35 (ddd, *J* = 14.1, 9.2, 3.6 Hz, 1H, 6-H), 2.61 (d, *J* = 2.3 Hz, 1H, 3'-H), 2.42 (s, 3H, CH$_3$-Ts), 1.99 – 1.93 (m, 2H, 4-H), 1.23 – 1.16 (m, 2H, 5-H) ppm.
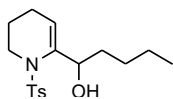
46: ^{1}H NMR (200 MHz, CDCl$_3$) *δ* =7.73 (d, *J* = 8.3 Hz, 2H, Ts), 7.30 (d, *J* = 8.3 Hz, 2H, Ts), 5.63 (t, *J* = 3.8 Hz, 1H, 3-H), 4.49 (t, *J* = 6.7 Hz, 1'-H), 3.56 – 3.44 (m, 2H, 6-H), 2.43 (s, 3H, CH$_3$-Ts), 1.94 – 1.83 (m, 2H, 4-H), 1.81 – 1.59 (m, 2H, 2'-H), 1.18 – 1.39 (m, 6H, 5-H, 3'-H and 4'-H), 0.90 (t, *J* = 7.0 Hz, 3H, 5'-H) ppm.

A solution of enynyl alcohol **47** (14 mg, 0.048 mmol), DMAP (1.2 mg, 0.1 mmol) and Et$_3$N (0.02 mL, 0.144 mmol) in DCM (0.5 mL) was cooled by ice bath and Ac$_2$O (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 % Et$_3$N; R$_f$ = 0.4) afforded enynyl acetate **48** (13.1 mg, 82 %). ^{1}H NMR (400 MHz, CDCl$_3$) *δ* = 7.73 (d, *J* = 8.2 Hz, 2H, Ts), 7.29 (d, *J* = 8.2 Hz, 2H, Ts), 6.64 (bs, 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 (d, J = 2.2 Hz, 1H, 3'-H), 2.42 (s, 3H, CH$_3$-Ts), 2.10 (s, 3H, CH$_3$-Ac), 1.98 (ddd, *J* = 8.1, 6.7, 2.6 Hz, 2H, 4-H), 1.41 – 1.23 (m, 2H, 5-H) ppm.
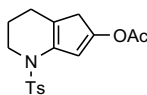

Acetic acid 1-(toluene-4-sulfonyl)-2,3,4,5-tetrahydro-1H-[1]pyrindin-6-yl ester (52).

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 Ph$_3$PAuCl/AgSbF$_6$. 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 CDCl$_3$. Based on the analysis of ^{1}H NMR and gCOSY spectra compound **52** was obtained.[45] ^{1}H NMR (400 MHz, CDCl$_3$) *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, CH$_3$-Ts), 2.13 (s, 3H, CH$_3$-Ac), 2.02 (t, *J* = 6.4 Hz, 2H, 4-H), 1.39 – 1.35 (m, 2H, 3-H) ppm.
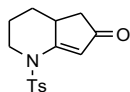
1-(Toluene-4-sulfonyl)-1,2,3,4,4a,5-hexahydro-[1]pyrindin-6-one (53).

To the solution of **52** in DCM/MeOH = 1 : 1 (1 mL) catalytic amount of *p*TsOH was added and reaction mixture was stirred at room temperature for 20 min. Solvent was evaporated and the crude was dissolved in CDCl$_3$. Analysis of ^{1}H NMR revealed the product in the mixture with *p*TsOH.[45] ^{1}H NMR (400 MHz, CDCl$_3$) 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, CH$_3$-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.
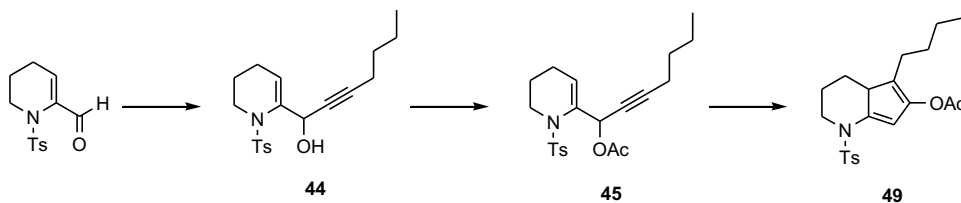
1-[1-(Toluene-4-sulfonyl)-1,4,5,6-tetrahydro-pyridin-2-yl]-hept-2-yn-1-ol (44).

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 NaHCO$_3$ (8 mL) was added. The product was extracted with Et$_2$O (3 x 5 mL) and the organic layer was dried over anhydrous Na$_2$CO$_3$ for 30 min. After filtration and evaporation of the solvent, obtained material was immediately used in next step. ^{1}H NMR (200 MHz, CDCl$_3$) 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, CH$_3$-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-[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 Et$_3$N (67 μL, 0.52 mmol) in DCM (1.5 mL) was cooled by ice bath and Ac$_2$O (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 % Et$_3$N; R$_f$ = 0.27) afforded enynyl acetate **45** (48 mg,   72 %). ^{1}H NMR (200 MHz, CDCl$_3$) 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, CH$_3$-Ts), 2.27 – 2.20 (m, 2H, 4-H), 2.10 (s, 3H, CH$_3$-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-(toluene-4-sulfonyl)-2,3,4,4a-tetrahydro-1H-[1]pyrindin-5-yl ester (49)

Propargy acetate **45** (45 mg, 0.116 mmol) was treated with 5 mol % of Ph$_3$PAuCl/AgSbF$_6$ 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 ^{1}H NMR, gCOSY and HSQC spectra structure **49** (R$_f$ = 0.29, 4.5 mg) was assigned. ^{1}H NMR (200 MHz, CDCl$_3$) 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 (dtd, *J* = 9.4, 6.1, 3.0 Hz, 1H, 4-H), 2.54 – 2.34 (m, 5H, 1'-H and CH$_3$-Ts), 2.34 – 2.18 (m, 1H, 3-H), 2.06 – 1.96 (m, 1H, 4-H), 1.97 (s, 3H, CH$_3$-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.

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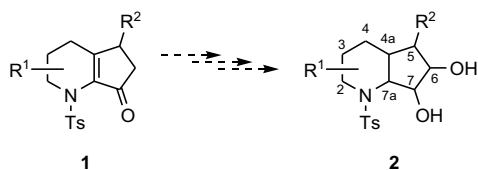
Scheme 1.   Transformations of cyclopentenone **1**.

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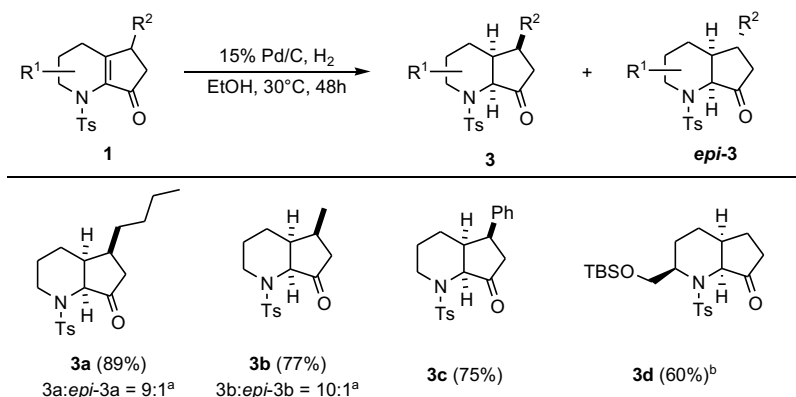
Scheme 2.   Hydrogenation of cyclopentenones **1a-d**. *Note*: [a] Diastereomeric ratio determined by
^{1}H NMR of crude reaction mixture. [b] Reaction carried out under pressure of 4 bar.

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 ^{1}H 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).
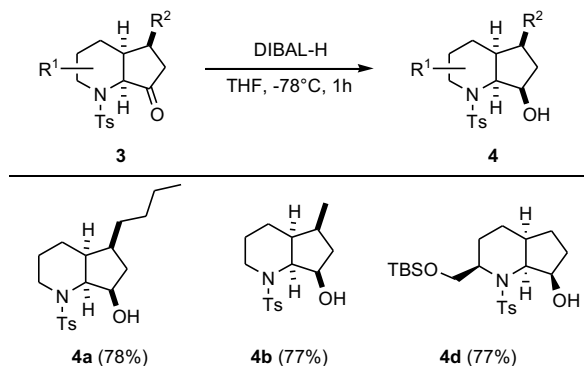
Scheme 3.   Reduction of the carbonyl group in **3**.

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 ^{1}H NMR sprectrum 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.
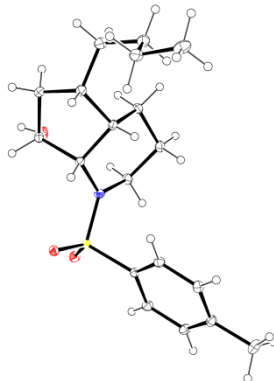
Figure 1.   X-Ray structure of **4a**.

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 TIPSCl as a trapping electrophile failed.[1] In addition, the direct oxidation of metal enolate **5b** using oxaziridine failed too,[2] and therefore we sought for an alternative procedure.
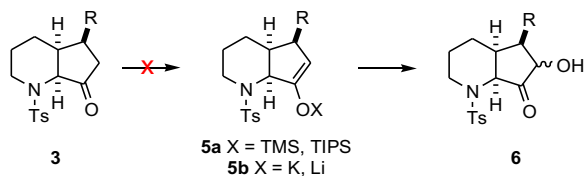
Scheme 4. Initial startegy for the α-hydroxylation of **3**.

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 iodobenzene 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_2SO_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.
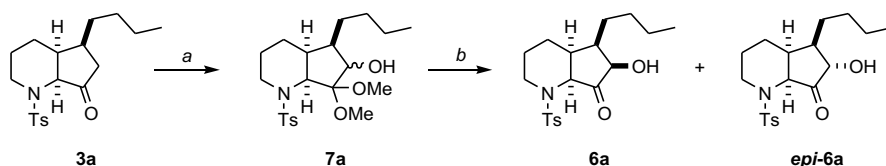
Scheme 5. α-Hydroxylation of **3a**. Reagents and conditions: (*a*) DIB, KOH, MeOH, 2 h; (*b*) 10 % H_2SO_4 in DCM, 1h.

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] $PhI(OAc)_2$ 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 TMSCl 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 ¹H 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**.
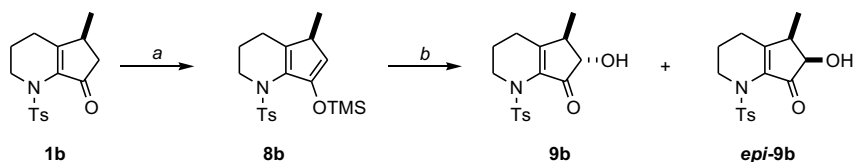
Scheme 6. α-Hydroxylation of **1b**. Reagents and conditions: (*a*) LiHMDS, THF, -78 °C, 30 min followed by the addition of TMSCl, -78 – 0 °C, 1.5 h; (*b*) *m*CPBA, NaHCO₃, DCM, -78 °C, 1h (**9b** : *epi*-**9b** = 2 : 1, 61 %).

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; 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_3OH or CH_3OH + 0.1% HCO_2H 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.

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 N_2 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.
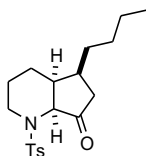
5-Butyl-1-(toluene-4-sulfonyl)-octahydro-[1]pyrindin-7-one (3a).
Compound **3a** was prepared according to the above described procedure for hydrogenation starting from 5-butyl-1-(toluene-4-sulfonyl)-1,2,3,4,5,6-hexahydro-[1]pyrindin-7-one (125 mg, 0.36 mmol). Flash chromatography (*n*-hexane/Et_2O, 3 : 1; R_f = 0.25) afforded product **3a** (111 mg, 89 %) in a mixture with diastereomer in
9 : 1 ratio. ^{1}H NMR (400 MHz, $CDCl_3$) 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, CH_3-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. ^{13}C NMR (100.4 MHz, $CDCl_3$) 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 (t, 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, CH_3-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 $C_{19}H_{27}NO_3S$: C 65.3, H 7.79, N 4.01; found: C 65.13, H 7.53, N 3.86.
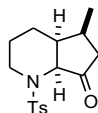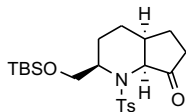
5-Methyl-1-(toluene-4-sulfonyl)-octahydro-[1]pyrindin-7-one (3b).

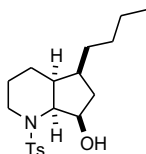Compound **3b** prepared according to the procedure for hydrogenation starting from 5-methyl-1-(toluene-4-sulfonyl)-1,2,3,4,5,6-hexahydro-[1]pyrindin-7-one (372 mg, 1.22 mmol). The crude was purified by flash chromatography (*n*-hexane/EtOAc, 4 : 1; R_f = 0.28) affording product **3b** (290 mg, 77 %) in a mixture with diastereomer in 10 : 1 ratio. ^{1}H NMR (400 MHz, CDCl$_3$) *δ* = 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$_3$) *δ* = 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 calcd (%) for C$_{16}$H$_{21}$NO$_3$S: C 62.11, H 7.49, N 4.53; found: C 62.71, H 6.70, N 4.47.
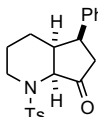
5-Phenyl-1-(toluene-4-sulfonyl)-octahydro-[1]pyrindin-7-one (3c).

Prepared according to the procedure for hydrogenation starting from 5-phenyl-1-(toluene-4-sulfonyl)-1,2,3,4,5,6-hexahydro-[1]pyrindin-7-one (90 mg, 0.25 mmol). The crude was purified by flash chromatography (*n*-hexane/EtOAc, 4 : 1; R_f = 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$_3$) *δ* = 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), 3.80 – 3.62 (m, 2H, 2-H), 2.71 – 2.47 (m, 3H, 3-H and 6-H), 2.43 (s, 3H, CH$_3$-Ts), 1.52 - 1.49 (m, 1H, 4a-H), 1.37 - 1.23 (m, 2H, 3-H and 4-H), 0.79 (qd, J = 13.4, 3.0 Hz, 1H, 4-H) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) *δ* = 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 calcd (%) for C$_{21}$H$_{23}$NO$_3$S: C 68,27, H 6,27, N 3,79; found: C 68.15, H 6.33, N 3.77.

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

Prepared according to the procedure for hydrogenation starting from 2-(tert-butyl-dimethyl-silanyloxymethyl)-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*-heptane/EtOAc, 3 : 1; R_f = 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$_3$) *δ* = 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$_2$OTBS), 3.26 (t, *J* = 12.0 Hz, 1H, 2-CH$_2$OTBS), 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$_3$) *δ* = 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, CH$_2$OTBS), 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, CH$_3$-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 C$_{22}$H$_{35}$NO$_4$SSi; 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 Na$_2$SO$_4$ 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).

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; R$_f$ = 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. ^{1}H NMR (400 MHz, CDCl$_3$) 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, CH$_3$-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, H-3, 6-H and 4-H), 0.86 (t, J = 7.0 Hz, 3H, 4'-H) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) 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, CH$_3$-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 C$_{19}$H$_{29}$NO$_3$S: C 64.92, H 8.32, N 3.98; found: C 64.83, H 8.52, N 3.68.
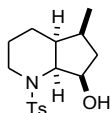
5-Methyl-1-(toluene-4-sulfonyl)-octahydro-[1]pyrindin-7-ol (4b).

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; R$_f$ = 0.23) affording product **4b** (73 mg, 97 %). ^{1}H NMR (400 MHz, CDCl$_3$) 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, CH$_3$-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, CH$_3$-5) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) 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, CH$_3$-Ts), 20.1 (t, C4), 14.7 (q, CH$_3$-5) ppm. MS (ESI) m/z (%): 310 ([M+1]$^+$, 42), 331 ([M+Na]$^+$, 7), 641 ([2M+Na]$^+$, 100). Elemental analysis calcd (%) for

C$_{16}$H$_{23}$NO$_3$S: C 62,11, H 7,49, N 4,53; found: 62.12, H 7.29, N 4.61.
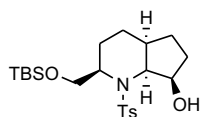
2-(tert-Butyl-dimethyl-silanyloxymethyl)-1-(toluene-4-sulfonyl)-octahydro-[1]pyrindin-7-ol (4d).
A solution of **3d** (150 mg, 0.34 mmol) in DCM (4.25 mL) was cooled to -78 °C and a 1.2 M DIBAL-H solution in toluene (0.6 mL, 0.68 mmol) was slowly added at -78 °C under nitrogen atmosphere. After 2 h, 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 Na$_2$SO$_4$ for 30 min, filtered and concentrated. The oily residue was purified by flash chromatography (heptanes/EtOAc, 4:1; R$_f$ = 0.30) to give the product **4d** (110 mg, 77 %) as a colourless oil. $[\alpha]_D^{22}$ = - 3.3 (c = 0.9, DCM). ^{1}H NMR (400 MHz, CDCl$_3$) 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), 4.02 (dd, J = 9.9, 7.1 Hz, 1H, 2-CH$_2$OTBS), 3.84 – 3.78 (m, 2H, 7a-H and 2-H), 3.70 (dd, J = 9.9, 4.4 Hz, 1H, 2-CH$_2$OTBS), 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. ^{13}C NMR (100.4 MHz, CDCl$_3$) 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, CH$_2$OTBS-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, CH$_3$-TBS), 23.2 (t, C4), 22.2 (t, C2), 21.4 (q, CH$_3$-Ts), 18.17 (t, C5), -5.40 (q, 2C, CH$_3$-TBS) ppm. Elemental analysis calcd (%) for C$_{22}$H$_{37}$NO$_4$SSi; C 60.10; H 8.48; N 3.19; found: C 60.03, H 8.50, N 3.16.
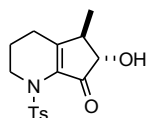
6-Hydroxy-5-methyl-1-(toluene-4-sulfonyl)-1,2,3,4,5,6-hexahydro-[1]pyrindin-7-one (9b).
A solution of 5-methyl-1-(toluene-4-sulfonyl)-1,2,3,4,5,6-hexahydro-[1]pyrindin-7-one (130 mg, 0.42 mmol) in dry THF (4.2 mL) was cooled to -78 °C and a 1 M solution of LiHMDS in THF (0.462 mL, 0.462 mmol) was added dropwise. The resulting mixture was stirred for 30 min at -78 °C and then TMSCl (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 Na$_2$SO$_4$ for 30 min. After filtration and evaporation of the solvent, obtained yellow oil was dissolved in DCM (8 mL) and NaHCO$_3$ (84 mg, 1.05 mmol) was added. The resulting suspension was cooled to -78 °C and then *m*CPBA (72.5 mg, 0.42 mmol) was added. After 1 h at -78 °C, saturated Na$_2$S$_2$O$_3$ (4 mL) and NaHCO$_3$ (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 Na$_2$SO$_4$ for 30 min, filtered and concentrated. The oily residue was purified by flash chromatography (*n*-hexane/EtOAc, 3 : 2; R$_f$ = 0.14) to give α-hydroxylated product as a 2 : 1 mixture of diastereomers (82 mg, 61 %). Analyticaly pure major diastereomer **9b** was obtained by HPLC purification (35 % ACN, 65 % H$_2$O, R$_t$ = 16.5 min). ^{1}H NMR (400 MHz, CDCl$_3$) 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, CH$_3$-Ts), 2.28 – 2.14 (m, 1H, 4-H), 1.97 (m, 2H, 3-H), 1.34 (d, J = 7.2 Hz, 1H, CH$_3$) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) 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, C4), 21.8 (q, 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 $C_{16}H_{19}NO_4S$: C 59.79, H 5.96, N 4.36; found: C 59.82, H 5.99, N 4.32.

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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[1,2] and therefore there has been much interest in the development of new methods for the pentannulation of indoles.[3,4] 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).
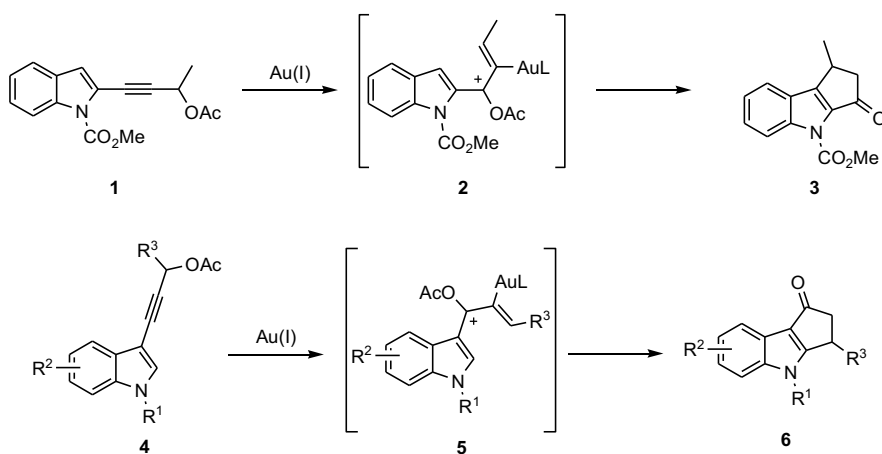
Scheme 1.   Au(I)-catalyzed [3,3]-rearrangement/Nazarov cyclization of indole-derived enynyl acetates **1** and **4**.

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[2] 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 CO_2Me 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 then the tosyl group. Sonogashira coupling[5] of *N*-CO_2Me 3-iodoindole (**13a**) with (±)-3-butyn-2-ol gave alcohol **14a** whose *O*-acetylation provided compound **4a** in 86 % after chromatography.
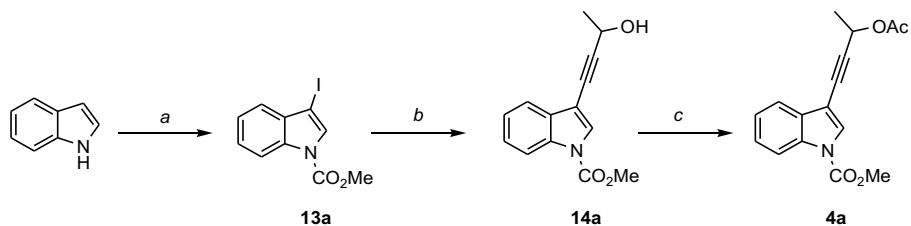
Scheme 2. Synthesis of **4a**. Reagents and conditions: (*a*) 1. I$_2$, KOH, DMF, 0 – 25 °C, 1 h, 2. CH$_3$COCl, Et$_3$N, THF, 0 – 25 °C, 3 h (86 % two steps); (*b*) (±)-3-butyn-2-ol, 3 mol % CuI, 5 mol % (Ph$_3$P)$_2$PdCl$_2$, DMF-Et$_3$N, 1 : 5, 40 °C, 3 h; (*c*) Ac$_2$O, Et$_3$N, DMAP, DCM, 0 – 25 °C, 3 h (86 % two steps).

Initially, model substrate **4a** was treated with 3 mol % of Ph$_3$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}H NMR spectra of the crude reaction mixture revealed cyclopenta-fused indole **6a** in the mixture with *α,β*-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 LAuCl/AgX at room temperature. Monitoring the reaction by ^{1}H NMR revealed that the reaction was complete in two hours when ligand [(4-CF$_3$C$_6$H$_4$)$_3$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**.[a]
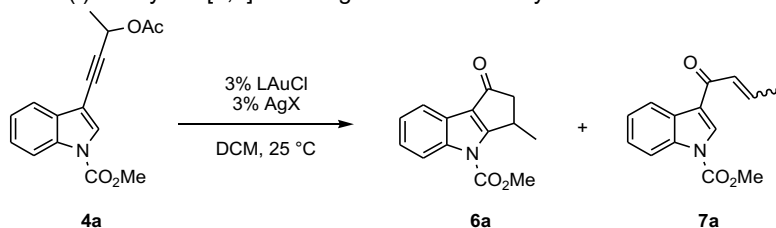
Entry	Ligand, L	Anion, X	Time (h)	Yield[b] 6a	7a
1	Ph$_3$P	SbF$_6^-$	6	94 (79)[c]	6
2	(4-CF$_3$C$_6$H$_4$)$_3$P	SbF$_6^-$	2	98 (83)[c]	2
3	*c*Hex$_3$P	SbF$_6^-$	22	77	23
4	*t*-Bu$_3$P	Tf$_2$N$^-$	24	37	3
5	*c*HexJohnPhos	SbF$_6^-$	24	31	traces
6	(2,4-di-*t*-BuC$_6$H$_3$O)$_3$P	SbF$_6^-$	1.5	79 (73)[c]	-
7	(4-CF$_3$C$_6$H$_4$)$_3$P	Tf$_2$N$^-$	4	99	1
8	(4-CF$_3$C$_6$H$_4$)$_3$P	TfO$^-$	2	96	4
9	(4-CF$_3$C$_6$H$_4$)$_3$P	[d]BARF$^-$	4	-	-
10	-	SbF$_6^-$	2	6	

[a] Reactions carried out on 0.2 mmol. [b] Conversion measured by ^{1}H NMR. [c] Yield after chromatography. [d] NaBARF was used.

When more electron-rich ligands were used (Cy$_3$P, t-Bu$_3$P, 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 phospine, a phospite ligand was used (entry 6) but, although the reaction was slightly faster, a lower yield than with [(4-CF$_3$C$_6$H$_4$)$_3$P] was obtained because of the formation of unidentified side products. Less important was the role of the counterion: using ligand [(4-CF$_3$C$_6$H$_4$)$_3$P], the reaction rates were approximately the same with SbF$_6^-$ (entry 2) and TfO$^-$ (entry 8) and slightly lower with Tf$_2$N$^-$ (entry 7). With 3 mol % of AgSbF$_6$ 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).
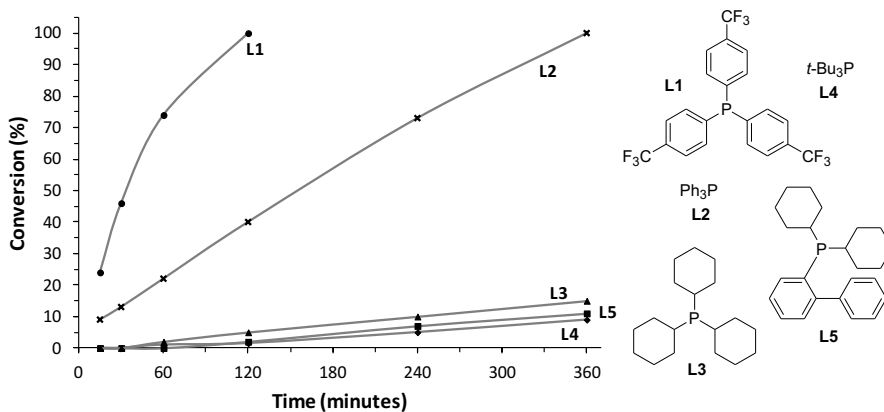
Figure 1. Effect of phosphine ligands on the reaction rate.

7.2. Scope of the Reaction

The scope of the reaction was investigated with a series of differently substituted enynyl acetates **4** and (4-CF$_3$C$_6$H$_4$)$_3$PAuCl 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).
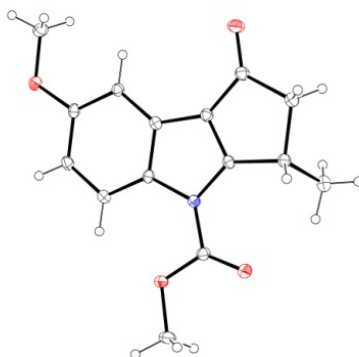
Figure 2. X-Ray structure of **6**h.

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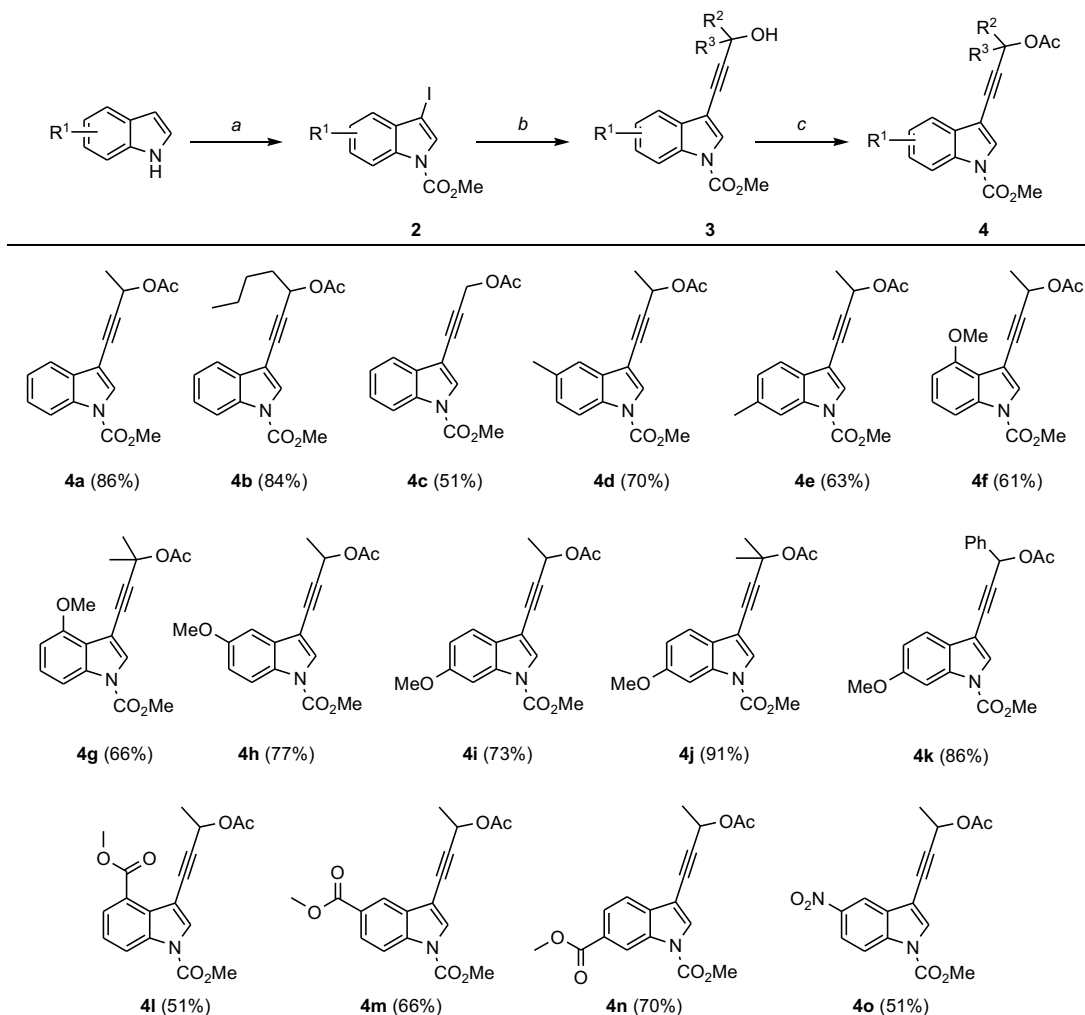
Scheme 3. Synthesis of substrates **4** from commercially available indoles. Reagents and conditions: (*a*) 1. I_2, KOH, DMF, 0 – 25 °C, 1 h, 2. CH_3COCl, Et_3N, THF, 0 – 25 °C, 3 h; (*b*) (±)-3-butyn-2-ol, 3 mol % CuI, 5 mol % $(Ph_3P)_2PdCl_2$, DMF-Et_3N, 1 : 5, 40 °C, 3 h; (*c*) Ac_2O, Et_3N, DMAP, 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 $(4\text{-}CF_3C_6H_4)_3PAu/AgSbF_6$ 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,[6] a competition experiment was carried out on a 1 : 1 mixture of 6-MeO- and 6-CO$_2$Me-substituted substrates **4i** and **4n**, respectively, in the presence of 3 mol % of the catalyst. Monitoring the reaction by ^{1}H 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.
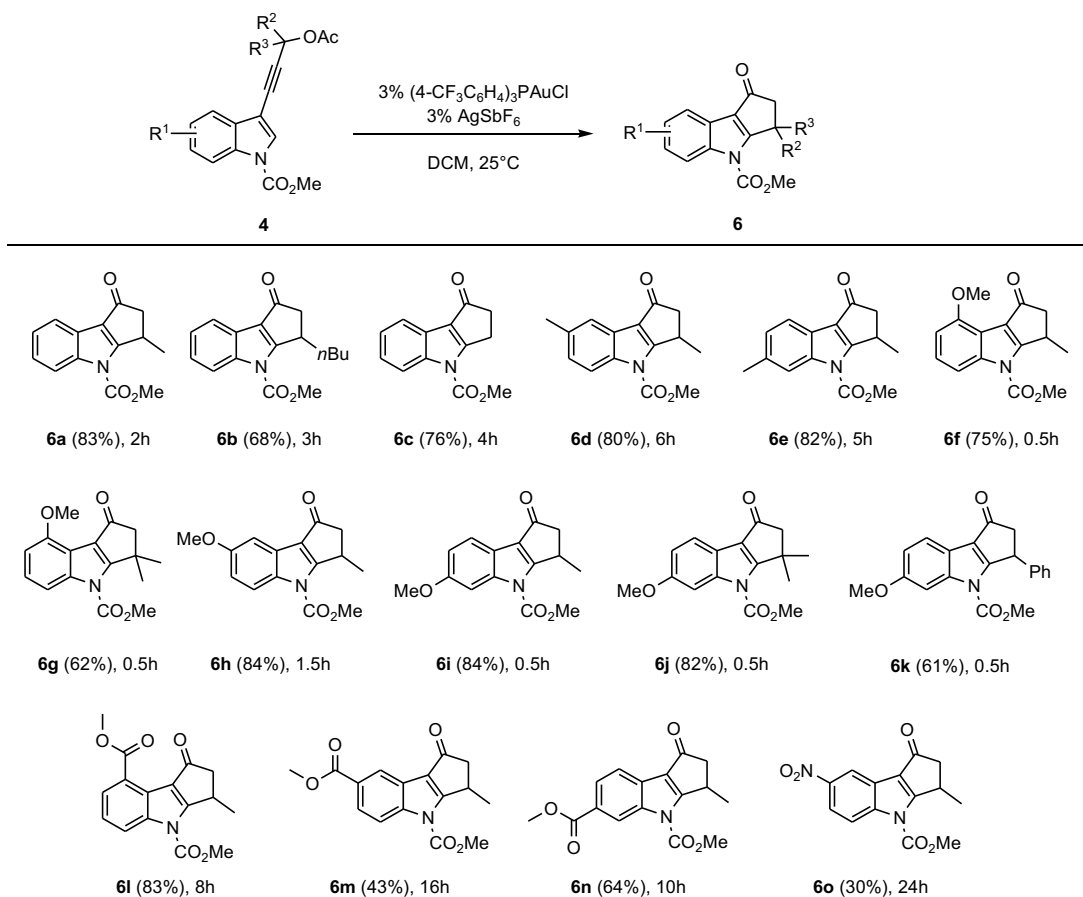
Scheme 4. Scope of the Au(I)-catalyzed [3,3]-rearrangement/Nazarov cyclization of **4**.

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 acetyloxy 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.
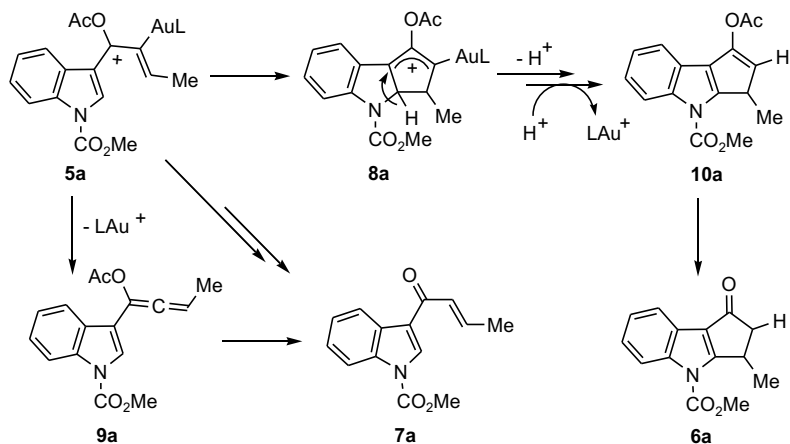
Scheme 5. Postulated reaction pathways.

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.[7]

The structures were located using the B3LYP[8] density functional theory method as implemented in the Gaussian suite of programs.[9] The alkynyl-gold(I) cationic complexe **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 (ΔG), computed at B3LYP/6-31G** level (LANL2DZ[10] for gold atom) and include single-point refinements at M06/6-311+G(d,p) (SDD for Au) level of theory.[11]
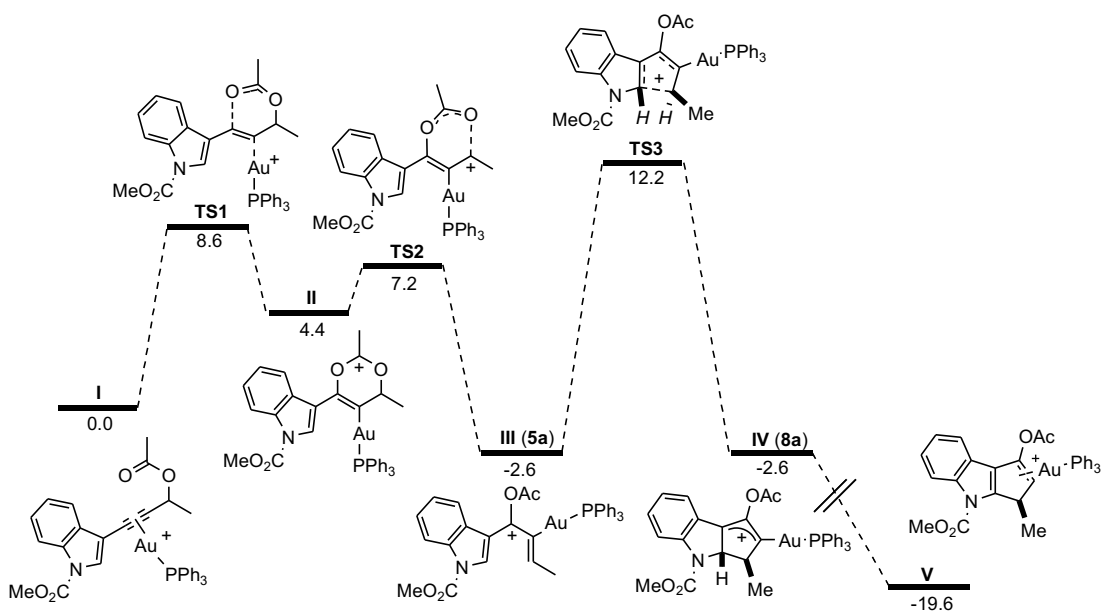
Scheme 6. Computed reaction profile for the reaction of **4a**. Energies are in kcal/mol.

From the computed reaction profile (Scheme 6) it could be seen that the acetate rearrangement proceeds with a low activation barrier (ΔG_{act} = 8.6 kcal/mol) and in a slightly exergonic fashion (ΔG_{react} = - 2.6 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 (ΔG_{act} = 14.8 kcal/mol) and therefore it is a rate-determining step what 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 makes 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, α,β-unsaturated ketone **7a** should directly derive from **5a** (ΔG_{react} = +8.1 kcal/mol) because alternative pathway which includes the formation of allene **9a** from **5a** is energetically very demanding (ΔG_{react} = + 31.7 kcal/mol) and thus never operative (Scheme 7).
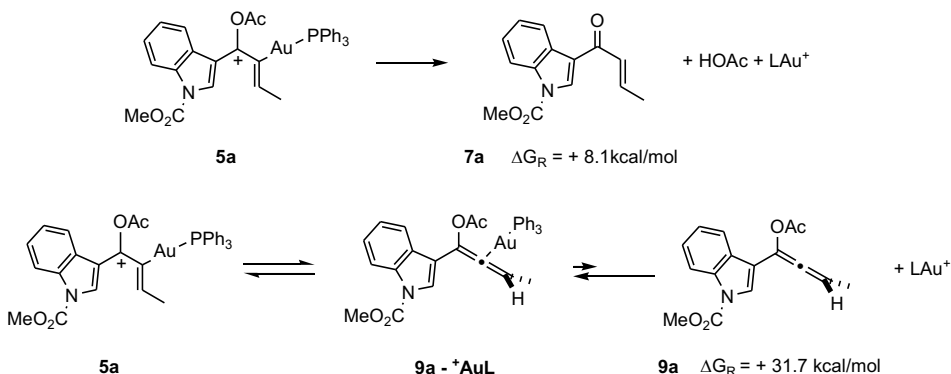
Scheme 7.   Computed possible pathways for the formation of α,β-unsaturated ketone **7a**.

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]
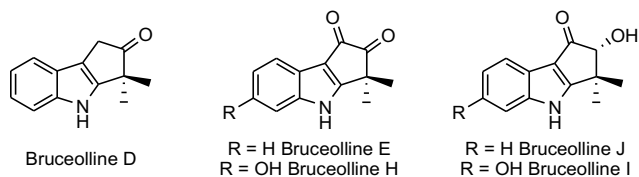
Scheme 8.   The structures of bruceolline family of natural products.
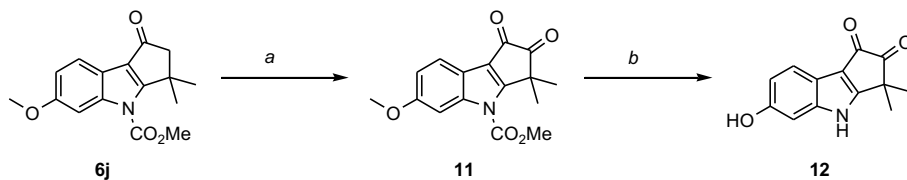
Scheme 9. Synthesis of Bruceolline H (**12**). Reagents and conditions: (*a*) SeO$_2$, dioxane, reflux (82 %); (*b*) 1. *t*-BuNH$_2$, MeOH reflux, 2. BBr$_3$, DCM (93 %).

To this end, cyclopenta[*b*]indolone **6j** was first oxidized into the corresponding diketo derivative **11** (82 %) by using SeO$_2$ in refluxing dioxane.[4b] Sequential *N*-deprotection[13] and *O*-demethylation[14] completed the synthesis of this natural product, which was obtained in 69 % overall yield from the corresponding 3-iodoindole (Scheme 9). ^{1}H and ^{13}C NMR spectra of **12** were identical to those reported for the natural product.[2a]
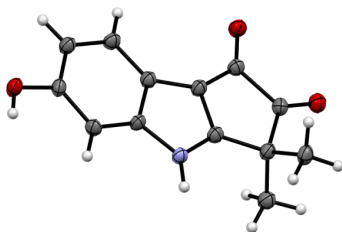
Figure 3. X-Ray structure of Bruceolline H (**12**).

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; 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. ^{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$_3$), 2.05 and 29.84 (acetone-d6), 3.31 and 49.00 (CD$_3$OD), 2.50 and 39.52 ppm (DMSO-d6) 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.
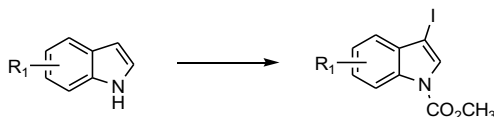
General procedure for the preparation of methyl 3-iodoindole-1-carboxylates (13).[5]

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_4OH (0.5 %) and $K_2S_2O_5$ (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-1H-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_2SO_4. After filtration and evaporation of the solvent, the obtained 3-iodoindole was used in the next step without any further purification.

3-Iodo-1H-indole (10 mmol) was dissolved in anhydrous DCM or THF (60 mL) and, after cooling at 0°C (ice bath), Et_3N (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_2SO_4. After filtration and evaporation of the solvent, the product was isolated either by flash chromatography or by crystallization from acetone.
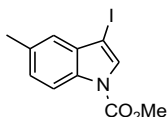
Methyl 3-Iodo-5-methylindole-1-carboxylate (13d).

3-Iodo-5-methyl-1H-indole was prepared starting from 5-methyl-1H-indole (262 mg, 2 mmol) and isolated by filtration.[2] ^{1}H NMR (400 MHz, CDCl₃) δ = 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) δ = 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) δ = 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.
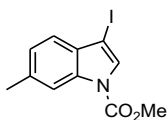
Methyl 3-Iodo-6-methylindole-1-carboxylate (13e).

3-Iodo-6-methyl-1H-indole was prepared starting from 6-methyl-1H-indole (250 mg, 1.9 mmol) and isolated by filtration. ^{1}H-NMR (400 MHz, CDCl₃) δ = 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_f = 0.38) afforded pure **13e** (421 mg, 70 %) as a pink solid. M.p. = 92.5 – 94.1°C. ^{1}H NMR (400 MHz, CDCl₃) δ = 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, CDCl₃) δ = 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

([M+Na]$^+$, 33), 189 ([M+1-I]$^+$, 100). Elemental analysis calcd (%) for $C_{11}H_{10}INO_2$: C 41.93, H 3.20, N 4.45; found: C 42.08, H 3.17, N 4.25.
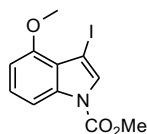
Methyl 3-Iodo-4-methoxyindole-1-carboxylate (13f).

3-Iodo-4-methoxy-1*H*-indole was prepared starting from 4-methoxy-1*H*-indole (174 mg, 1.2 mmol) and isolated by extraction.[3] ^{1}H-NMR (400 MHz, CDCl$_3$) *δ* = 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$_3$) *δ* = 7.83 (d, *J* = 8.4 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$_3$) *δ* = 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]$^+$, 40), 205 ([M+1-I]$^+$, 100). Elemental analysis calcd (%) for $C_{11}H_{10}INO_3$: C 39.90, H 3.04, N 4.23; found: C 40.09, H 3.21, N 4.22.
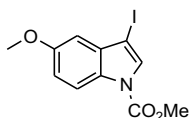
Methyl 3-Iodo-5-methoxyindole-1-carboxylate (13h).

3-Iodo-5-methoxy-1*H*-indole was prepared starting from 5-methoxy-1*H*-indole (200 mg, 1.36 mmol) and isolated by filtration.[17] ^{1}H NMR (200 MHz, CDCl$_3$) *δ* = 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$_3$) *δ* = 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$_3$) *δ* = 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 $C_{11}H_{10}INO_3$: C 39.90, H 3.04, N 4.23; found: C 40.06, H 2.82, N 4.04.
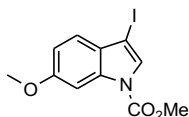
Methyl 3-Iodo-6-methoxyindole-1-carboxylate (13i).

3-Iodo-6-methoxy-1*H*-indole was prepared starting from 6-methoxy-1*H*-indole (263 mg, 1.79 mmol) and isolated by filtration.[18] ^{1}H NMR (400 MHz, CDCl$_3$) *δ* = 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$_3$) *δ* = 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$_3$) *δ* = 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-I]$^+$, 100). Elemental analysis calcd (%) for $C_{11}H_{10}INO_3$: C 39.90, H 3.04, N 4.23; found: C 40.25, H 3.24, N 3.93.
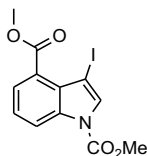
3-Iodoindole-1,4-dicarboxylic acid dimethyl ester (13l).

3-Iodo-4-carbomethoxy-1*H*-indole was prepared starting from 4-carbomethoxy-1*H*-indole (230 mg, 1.31 mmol) and isolated by extraction.[19] ^{1}H-NMR (400 MHz, CDCl$_3$) 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.
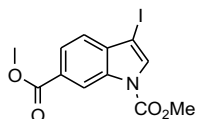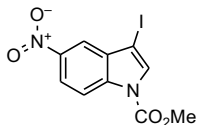
The protection step was carried out in THF. Purification by flash chromatography (*n*-hexane/EtOAc, 6 : 1; R$_f$ = 0.25) afforded pure **13l** (317 mg, 61 %) as a pale yellow solid. M.p. = 108.9 – 110.2 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ = 8.40 (d, *J* = 8.4 Hz, 1 H), 7.89 (s, 1 H), 7.57 (d, *J* = 7.6 Hz, 1 H), 7.40 (t, *J* = 8.4 Hz, 1 H), 4.05 (s, 3 H), 4.01 (s, 3 H) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) 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 C$_{12}$H$_{10}$INO$_4$: C 40.13, H 2.81, N 3.90; found: C 40.39, H 2.75, N 3.84.
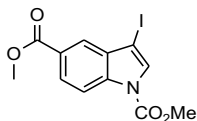
3-Iodoindole-1,5-dicarboxylic acid dimethyl ester (13m).

3-Iodo-5-carbomethoxy-1*H*-indole was prepared starting from 5-carbomethoxy-1*H*-indole (350 mg, 2.0 mmol) and isolated by filtration.[20] ^{1}H 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. ^{1}H 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. ^{13}C 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 C$_{12}$H$_{10}$INO$_4$: 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-1*H*-indole was prepared starting from 6-carbomethoxy-1*H*-indole (350 mg, 2.0 mmol) and isolated by filtration.[21] ^{1}H NMR (200 MHz, CDCl$_3$) 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; R$_f$ = 0.43) afforded pure **13n** (500 mg, 70 %) as a white solid. M.p. = 126.2 – 127.1 °C. ^{1}H 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. ^{13}C 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 C$_{12}$H$_{10}$NIO$_4$: 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-1*H*-indole was prepared starting from 5-nitro-1*H*-indole (330 mg, 2.0 mmol) and isolated by filtration.[21] ^{1}H NMR (200 MHz, CDCl$_3$) δ = 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. ^{1}H NMR (400 MHz, DMSO) δ = 8.29 (m, 2 H), 8.24 (s, 1 H), 8.15 (bs, 1 H), 4.03 (s, 3 H) ppm. ^{13}C NMR (100.4 MHz, DMSO) δ = 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]$^+$, 100). Elemental analysis calcd (%) for C$_{10}$H$_7$N$_2$IO$_4$: C 34.71, H 2.04, N 8.09; found: C 34.79, H 2.42, N 7.98.

13 **14** **4**
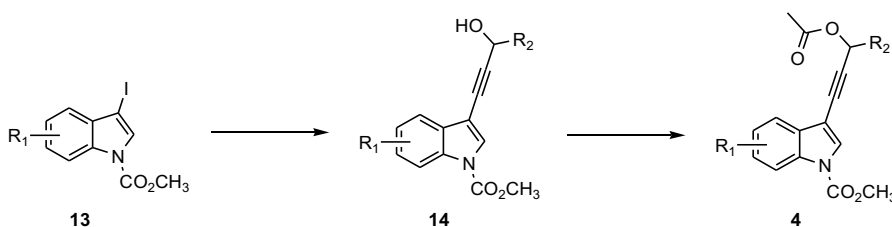
General procedure for the synthesis of indole derived enynyl acetates (4).

STEP A Sonogashira coupling (14)[5]

A 5 : 1 (v/v) solution of Et$_3$N/DMF (4.5 mL) was added in a round bottom flask containing 3-iodoindole-1-carboxylic acid methyl ester **13** (1 mmol), (Ph$_3$P)$_2$PdCl$_2$ (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**.[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 the 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$_2$CO$_3$. 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$_3$N (0.42 mL, 3 mmol) and Ac$_2$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$_3$ (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$_2$CO$_3$. 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$_3$N until use.
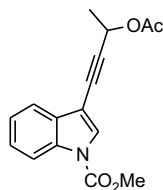
3-(3-Acetoxybut-1-ynyl)-indole-1-carboxylic acid methyl ester (4a).

Compound **14a** was obtained by Sonogashira coupling of **13a** (301 mg, 1 mmol) and (±)-3-butyn-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 % Et$_3$N; R$_f$ = 0.22) afforded pure enynyl alcohol **14a** which was used immediately in the next step. ^{1}H NMR (400 MHz, CDCl$_3$) *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 % Et$_3$N; R$_f$ =0.28). Pure **4a** was obtained as a colourless oil (240 mg, 86 % over 2 steps). ^{1}H NMR (400 MHz, CDCl$_3$) *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. ^{13}C NMR (100.4 MHz, CDCl$_3$) *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-CO$_2$Me]$^+$, 100).
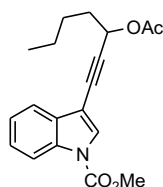
3-(3-Acetoxyhept-1-ynyl)-indole-1-carboxylic acid methyl ester (4b).

Compound **14b** was obtained by Sonogashira coupling of **13a** (301 mg, 1 mmol) and (±)-2-heptyn-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 % Et$_3$N; R$_f$ = 0.33) afforded pure enynyl alcohol **14b** which was used immediately in the next step. ^{1}H NMR (400 MHz, CDCl$_3$) *δ* = 8.16 (d, *J* = 8.4 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 % Et$_3$N; R$_f$ = 0.39). Pure **4b** was obtained as a colourless oil (274 mg, 84 % over 2 steps). ^{1}H NMR (400 MHz, CDCl$_3$) *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. ^{13}C NMR (100.4 MHz, CDCl$_3$) *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-CO$_2$Me]$^+$, 67).
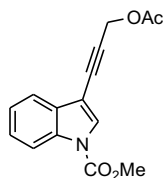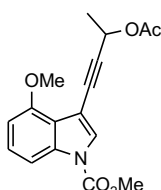
3-(3-Acetoxyprop-1-ynyl)-indole-1-carboxylic acid methyl ester (4c).

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 % Et$_3$N; R$_f$ = 0.10) afforded pure enynyl alcohol **14c** which was used immediately in the next step. ^{1}H NMR (400 MHz, CDCl$_3$) 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 % Et$_3$N; R$_f$ = 0.27). Pure **4c** was obtained as a colourless oil (64 mg, 51 % over 2 steps). ^{1}H NMR (400 MHz, CDCl$_3$) 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. ^{13}C NMR (100.4 MHz, CDCl$_3$) 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 (t), 20.8 (q) ppm. MS (ESI) *m/z* (%): 294 ([M+Na]$^+$, 41), 212 ([M-CO$_2$Me]$^+$, 100).
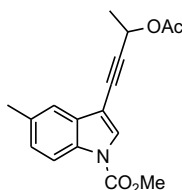
3-(3-Acetoxybut-1-ynyl)-5-methylindole-1-carboxylic acid methyl ester (4d).

Compound **14d** was obtained by Sonogashira coupling of **13d** (315 mg, 1 mmol) and (±)-3-butyn-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 % Et$_3$N; R$_f$ = 0.20) afforded pure enynyl alcohol **14d** which was used immediately in the next step. ^{1}H NMR (400 MHz, CDCl$_3$) 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 % Et$_3$N; R$_f$ =0.19). Pure **4d** was obtained as a yellow oil (210 mg, 70 % over 2 steps). ^{1}H NMR (400 MHz, CDCl$_3$) 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. ^{13}C NMR (100.4 MHz, CDCl$_3$) 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-CO$_2$Me]$^+$, 100).
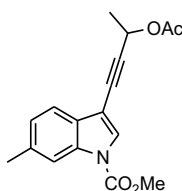
3-(3-Acetoxybut-1-ynyl)-6-methylindole-1-carboxylic acid methyl ester (4e).

Compound **14e** was obtained by Sonogashira coupling of **13c** (315 mg, 1 mmol) and (±)-3-butyn-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 % Et$_3$N; R$_f$ = 0.20) afforded pure enynyl alcohol **14e** which was used immediately in the next step. ^{1}H NMR (400 MHz, CDCl$_3$) *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 % Et$_3$N; R$_f$ = 0.19). Pure **4e** was obtained as a colourless oil (188 mg, 63 % over 2 steps). ^{1}H NMR (400 MHz, CDCl$_3$) *δ* = 7.97 (s, 1 H), 7.71 (s, 1 H), 7.52 (d, *J* = 8.4 Hz, 1 H), 7.14 (d, *J* = 8.4 Hz, 1 H), 5.73 (q, *J* = 6.7 Hz, 1 H), 4.04 (s, 3 H), 2.49 (s, 3 H), 2.12 (s, 3 H), 1.62 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) *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-CO$_2$Me]$^+$, 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-butyn-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 % Et$_3$N; R$_f$ = 0.15) afforded pure enynyl alcohol **14f** which was used immediately in the next step. ^{1}H NMR (400 MHz, CDCl$_3$) *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 % Et$_3$N; R$_f$ =0.18). Pure **4f** was obtained as a white solid (154 mg, 61 % over 2 steps). ^{1}H NMR (400 MHz, CDCl$_3$) *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. ^{13}C NMR (100.4 MHz, CDCl$_3$) *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-CO$_2$Me]$^+$, 100).
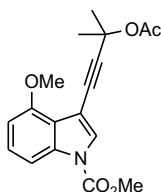
3-(3-Acetoxy-3-methylbut-1-ynyl)-4-methoxyindole-1-carboxylic acid methyl ester (4g).

Compound **14g** was obtained by Sonogashira coupling of **13f** (127 mg, 0.38 mmol) and 3-methyl-3-butyn-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 % Et$_3$N; R$_f$ = 0.36) afforded pure enynyl alcohol **14g** which was used immediately in the next step. ^{1}H NMR (400 MHz, CDCl$_3$) *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 Ac$_2$O (3 eq) and Et$_3$N

(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 % Et$_3$N; R$_f$ =0.16) afforded pure **4g** as a colourless oil (82 mg, 66 % over 2 steps). ^{1}H NMR (400 MHz, CDCl$_3$) *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. ^{13}C NMR (100.4 MHz, CDCl$_3$) *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), 102.0 (s), 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-CO$_2$Me]$^+$, 100).
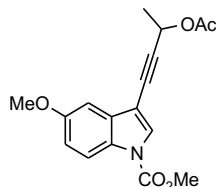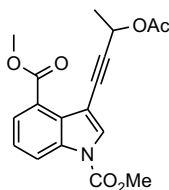

3-(3-Acetoxybut-1-ynyl)-5-methoxyindole-1-carboxylic acid methyl ester (4h).

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 % Et$_3$N; R$_f$ = 0.30) afforded pure enynyl alcohol **14h** which was used immediately in the next step. ^{1}H NMR (400 MHz, CDCl$_3$) *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 % Et$_3$N; R$_f$ = 0.24). Pure **4h** was obtained as a yellow oil (190 mg, 77 % over 2 steps). ^{1}H NMR (400 MHz, CDCl$_3$) *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. ^{13}C NMR (100.4 MHz, CDCl$_3$) *δ* = 169.8 (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-CO$_2$Me]$^+$, 100).
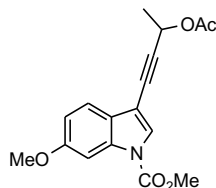
3-(3-Acetoxybut-1-ynyl)-6-methoxyindole-1-carboxylic acid methyl ester (4i).

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 % Et$_3$N; R$_f$ = 0.23) afforded pure enynyl alcohol **14i** which was used immediately in the next step. ^{1}H NMR (400 MHz, CDCl$_3$) *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 % Et$_3$N; R$_f$ = 0.28). Pure **4i** was obtained as a yellow oil (170 mg, 73 % over 2 steps). ^{1}H NMR (400 MHz, CDCl$_3$) *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. ^{13}C NMR (100.4 MHz, CDCl$_3$) *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-CO$_2$Me]$^+$, 100).
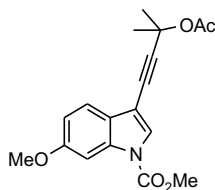
3-(3-Acetoxy-3-mehylbut-1-ynyl)-6-methoxyindole-1-carboxylic acid methyl ester (4j).

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; R$_f$ = 0.26) afforded pure enynyl alcohol **14j** which was used immediately in the next step. ^{1}H 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; R$_f$ = 0.19) afforded pure **4j** as a colourless oil (78 mg, 91 % over 2 steps). ^{1}H 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. ^{13}C 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).
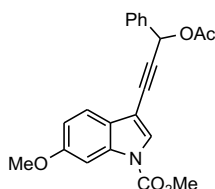
3-(3-Acetoxy-3-phenylprop-1-ynyl)-6-methoxyindole-1-carboxylic acid methyl ester (4k).

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; R$_f$ = 0.16) afforded pure enynyl alcohol **14k** which was used immediately in the next step. ^{1}H NMR (400 MHz, CDCl₃) *δ* = 7.74 (br s, 1 H), 7.67 (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.
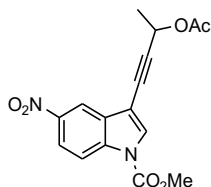
Acetylation of compound **14k** afforded **4k**, which was purified by flash chromatography (*n*-hexane/EtOAc, 6 : 1 + 1 % Et₃N; R$_f$ = 0.13). Pure **4k** was obtained as a yellow oil (204 mg, 86 % over 2 steps). ^{1}H NMR (400 MHz, CDCl₃) *δ* = 7.74 (br s, 1 H), 7.71 (s, 1 H), 7.64-7.61 (m, 2 H), 7.52 (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), 2.15 (s, 3 H) ppm. ^{13}C 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), 127.7 (d, 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-butyn-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 % Et$_3$N; R$_f$ = 0.23) afforded pure enynyl alcohol **14l** which was used immediately in the next step. ^{1}H NMR (400 MHz, CDCl$_3$) $δ$ = 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, 4 : 1 + 1 % Et$_3$N; R$_f$ = 0.21). Pure **4l** was obtained as a yellow oil (84 mg, 51 % over 2 steps). ^{1}H NMR (400 MHz, CDCl$_3$) $δ$ = 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 = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) $δ$ = 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-CO$_2$Me]$^+$, 100).
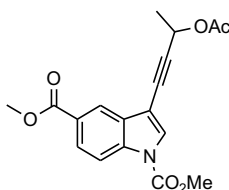
3-(3-Acetoxybut-1-ynyl)-indole-1,5-dicarboxylic acid dimethyl ester (4m).

Compound **14m** was obtained by Sonogashira coupling of **13m** (360 mg, 1 mmol) and (±)-3-butyn-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 % Et$_3$N; R$_f$ = 0.25) afforded pure enynyl alcohol **14m** which was used immediately in the next step. ^{1}H NMR (400 MHz, CDCl$_3$) $δ$ = 8.26 (s, 1 H), 8.10 (d, J = 8.7 Hz, 1 H), 8.00 (d, J = 8.7 Hz, 1 H), 7.69 (s, 1 H), 4.83 (q, J = 6.6 Hz, 1 H), 4.04 (s, 3 H), 3.94 (s, 3 H), 1.60 (d, J = 6.6 Hz, 3 H) ppm.

Acetylation of compound **14m** afforded **4m**, which was purified by flash chromatography (n-hexane/EtOAc, 4 : 1 + 1 % Et$_3$N; R$_f$ =0.18). Pure **4m** was obtained as a colourless oil (220 mg, 66 % over 2 steps). ^{1}H NMR (400 MHz, CDCl$_3$) $δ$ = 8.31 (s, 1 H), 8.14 (d, J = 8.7 Hz, 1 H), 8.02 (d, J = 8.7 Hz, 1 H), 7.79 (s, 1 H), 5.74 (q, J = 6.7 Hz, 1 H), 4.04 (s, 3 H), 3.94 (s, 3 H), 2.11 (s, 3 H), 1.63 (d, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) $δ$ = 170.2 (s), 167.4 (s, 5-CO), 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), 54.3 (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-CO$_2$Me]$^+$, 100).
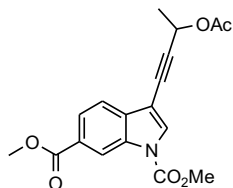
3-(3-Acetoxybut-1-ynyl)-indole-1,6-dicarboxylic acid dimethyl ester (4n).

Compound **14n** was obtained by Sonogashira coupling of **13n** (360 mg, 1 mmol) and (±)-3-butyn-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; R$_f$ = 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; R$_f$ = 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-butyn-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; R$_f$ = 0.20) afforded pure enynyl alcohol **14o** which was used immediately in the next step. ¹H NMR (400 MHz, CDCl₃) *δ* = 8.57 (s, 1 H), 8.36 − 8.21 (m, 2 H), 7.89 (s, 1 H), 4.85 (q, *J* = 6.6 Hz, 1 H), 1.63 (d, *J* = 6.6 Hz, 3 H) ppm.

Acetylation of compound **14o** afforded **4o**, which was purified by flash chromatography (*n*-hexane/EtOAc, 4 : 1 + 1 % Et₃N; R$_f$ = 0.19). Pure **4o** was obtained as a colourless oil (168 mg, 51 % over 2 steps). ¹H NMR (400 MHz, CDCl₃) *δ* = 8.52 (s, 1 H), 8.28 − 8.20 (m, 2 H), 7.89 (s, 1 H), 5.73 (q, *J* = 6.7 Hz, 1 H), 4.09 (s, 3 H), 2.13 (s, 3 H), 1.64 (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).
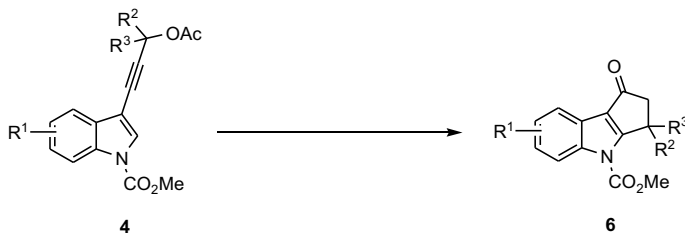
General procedure for gold(I)-catalyzed Nazarov reaction (6).

The solution of **4** in the eluent was concentrated and dried under *vacuum* (no heating) for 30 minutes. Gold(I) complex (4-CF$_3$C$_6$H$_4$)$_3$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$_2$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.
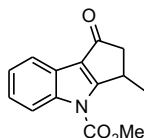
3-Methyl-1-oxo-2,3-dihydro-1*H*-cyclopenta[*b*]indole-4-carboxylic acid methyl ester (6a).
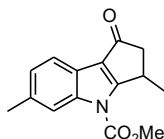
Compound **6a** was prepared starting from **4a** (67 mg, 0.24 mmol). Purification by flash chromatography (*n*-hexane/EtOAc, 3 : 1; R$_f$ = 0.16) followed by trituration with Et$_2$O afforded pure **6a** (48 mg, 83 %) as a yellow solid. M.p. = 126.8 – 127.8 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ = 8.13 (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$_3$) δ = 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.
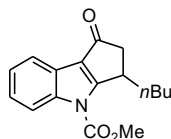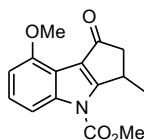

3-Butyl-1-oxo-2,3-dihydro-1*H*-cyclopenta[*b*]indole-4-carboxylic acid methyl ester (6b).

Compound **6b** was prepared starting from **4b** (177 mg, 0.54 mmol). Purification by flash chromatography (*n*-hexane/EtOAc, 4 : 1; R$_f$ = 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$_3$) δ = 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, 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$_3$) δ = 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), 308 ([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.
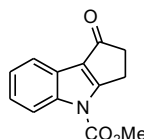
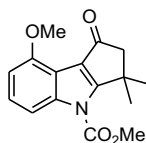**1-Oxo-2,3-dihydro-1*H*-cyclopenta[*b*]indole-4-carboxylic acid methyl ester (6c).**

Compound **6c** was prepared starting from **4c** (57 mg, 0.21 mmol). Purification by flash chromatography (*n*-hexane/EtOAc, 2 : 1; R$_f$ = 0.16) followed by trituration with Et$_2$O afforded pure **6c**

(37 mg, 76 %) as a white solid. M.p. = 153.8 – 155.2 °C. ^{1}H NMR (400 MHz, CDCl$_3$) 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. ^{13}C NMR (100.4 MHz, CDCl$_3$) 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+1]$^+$, 100). Elemental analysis calcd (%) for C$_{13}$H$_{11}$NO$_3$: C 68.11, H 4.84, N 6.11; found: C 67.96, H 4.52, N 6.25.
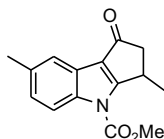
3,7-Dimethyl-1-oxo-2,3-dihydro-1H-cyclopenta[b]indole-4-carboxylic acid methyl ester (6d).
Compound **6d** was prepared starting from **4d** (59 mg, 0.20 mmol). Purification by flash chromatography (n-hexane/EtOAc, 2 : 1; R$_f$ = 0.22) followed by trituration with Et$_2$O afforded pure **6d** (41 mg, 80 %) as a white solid. M.p. = 125.5 – 126.8 °C. ^{1}H NMR (400 MHz, CDCl$_3$) 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. ^{13}C NMR (100.4 MHz, CDCl$_3$) δ = 196.6 (s), 171.0 (s), 150.6 (s), 138.7 (s), 134.6 (s), 126.7 (d), 124.3 (s), 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 (%):536 ([2M+Na]$^+$, 100), 280 ([M+Na]$^+$, 9), 258 ([M+1], 53). Elemental analysis calcd (%) for C$_{15}$H$_{15}$NO$_3$: 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; R$_f$ = 0.21) followed by trituration with Et$_2$O afforded pure **6e** (99 mg, 82 %) as a white solid. M.p. = 140.1 – 140.8 °C. ^{1}H NMR (400 MHz, CDCl$_3$) 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. ^{13}C NMR (100.4 MHz, CDCl$_3$) δ = 196.3 (s), 170.5 (s), 151.0 (s), 141.4 (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 (%): 536 ([2M+Na]$^+$, 14), 258 ([M+1]$^+$, 100). Elemental analysis calcd (%) for C$_{15}$H$_{15}$NO$_3$: C 70.02, H 5.88, N 5.44; found: C 69.91, H 5.82, N 5.13.

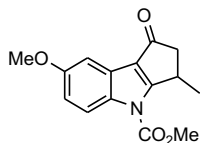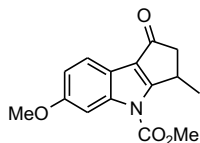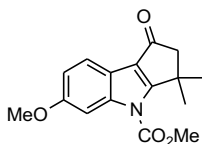**8-Methoxy-3-methyl-1-oxo-2,3-dihydro-1H-cyclopenta[b]indole-4-carboxylic acid methyl ester (6f).**
Compound **6f** was prepared starting from **4f** (60 mg, 0.19 mmol). Purification by flash chromatography (n-hexane/EtOAc, 3 : 2; R$_f$ = 0.16) followed by trituration with Et$_2$O afforded pure **6f** (39 mg, 75 %) as a pale yellow solid. M.p. = 191.5 – 193.2 °C. ^{1}H NMR (400 MHz, CDCl$_3$) 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. ^{13}C NMR (100.4 MHz, CDCl$_3$) 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 C$_{15}$H$_{15}$NO$_4$·¼H$_2$O: 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-1*H*-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; R$_f$ = 0.19) followed by trituration with Et$_2$O afforded pure **6g** (41 mg, 62 %) as a pale yellow solid. The product decomposed at 175 °C. ^{1}H NMR (400 MHz, CDCl$_3$) *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. ^{13}C NMR (100.4 MHz, CDCl$_3$) *δ* = 194.5 (s), 171.2 (s), 154.0 (s), 150.8 (s), 142.2 (s), 126.9 (d), 124.3 (s), 112.3 (s), 109.0 (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-I]$^+$, 36). Elemental analysis calcd (%) for C$_{16}$H$_{17}$NO$_4$: 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-1*H*-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; R$_f$ = 0.27) followed by trituration with Et$_2$O afforded pure **6h** (112 mg, 84 %) as a yellow solid. M.p. = 158.3 – 159.9 °C. ^{1}H NMR (400 MHz, CDCl$_3$) *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. ^{13}C NMR (100.4 MHz, CDCl$_3$) *δ* = 196.7 (s), 171.1 (s), 157.1 (s), 150.5 (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 C$_{15}$H$_{15}$NO$_4$: 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-1*H*-cyclopenta[*b*]indole-4-carboxylic acid methyl ester (6i).
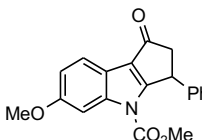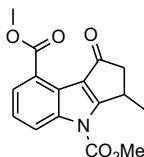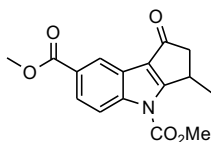
Compound **6i** was prepared starting from **4i** (75 mg, 0.24 mmol). Purification by flash chromatography (*n*-hexane/EtOAc, 2 : 1; R$_f$ = 0.24) followed by trituration with Et$_2$O afforded pure **6i** (55 mg, 84 %) as a white solid. M.p. = 98.1 – 99.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$) *δ* = 7.74 (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. ^{13}C NMR (100.4 MHz, CDCl$_3$) *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 C$_{15}$H$_{15}$NO$_4$: C

65.92, H 5.53, N 5.13; found: C 66.02, H 5.68, N 4.80.

6-Methoxy-3,3-dimethyl-1-oxo-2,3-dihydro-1*H*-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; R$_f$ = 0.24) followed by trituration with Et$_2$O afforded pure **6j** (47 mg, 82 %) as a white solid. M.p. = 152.2 – 154.1 °C. ^{1}H NMR (400 MHz, CDCl$_3$) *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. ^{13}C NMR (100.4 MHz, CDCl$_3$) *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 C$_{16}$H$_{17}$NO$_4$: 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-1*H*-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 Et$_2$O and *n*-hexane afforded pure **6k** (51 mg, 61 %) as a yellow solid. M.p. = 141.7 – 143.1 °C. R$_f$ = 0.18 (*n*-hexane-EtOAc, 3 : 1). ^{1}H NMR (400 MHz, CDCl$_3$) *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. ^{13}C NMR (100.4 MHz, CDCl$_3$) *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 C$_{20}$H$_{17}$NO$_4$: C 71.63, H 5.11, N 4.18; found: C 71.42, H 4.91, N 4.53.
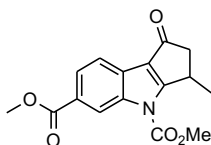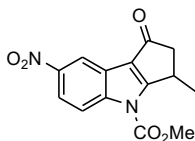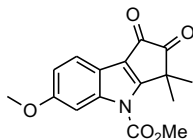

3-Methyl-1-oxo-2,3-dihydro-1*H*-cyclopenta[*b*]indole-4,8-dicarboxylic acid dimethyl ester (6l).

Compound **6l** was prepared starting from **4l** (55 mg, 0.16 mmol). Purification by flash chromatography (*n*-hexane/EtOAc, 2 : 1; R$_f$ = 0.22) afforded pure **6l** (40 mg, 83 %) as a white solid. M.p. = 104.2 – 105.8 °C. ^{1}H NMR (400 MHz, CDCl$_3$) *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. ^{13}C NMR (100.4 MHz, CDCl$_3$) *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 C$_{16}$H$_{15}$NO$_5$: 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-1*H*-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; R_f = 0.24) followed by trituration with Et$_2$O afforded pure **6m** (52 mg, 43 %) as a yellow solid. M.p. = 153.0 – 154.9 °C. ^{1}H NMR (400 MHz, CDCl$_3$) 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 (d, *J* = 18.0 Hz, 1 H), 1.43 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100.4 MHz, CDCl$_3$) 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 C$_{16}$H$_{15}$NO$_5$: 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-1*H*-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; R_f = 0.24) followed by trituration with Et$_2$O afforded pure **6n** (98 mg, 64 %) as a pale yellow solid. M.p. = 128.6 – 130.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$) 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. ^{13}C NMR (100.4 MHz, CDCl$_3$) 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]$^+$, 26), 302 ([M+1], 100). Elemental analysis calcd (%) for C$_{16}$H$_{15}$NO$_5$: C 63.78, H 5.02, N 4.65; found: C 63.51, H 5.02, N 4.31.


3-Methyl-7-nitro-1-oxo-2,3-dihydro-1*H*-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; R_f = 0.24) followed by trituration with Et$_2$O afforded pure **6o** (17 mg, 30 %) as a yellow solid. M.p. = 128 °C. ^{1}H NMR (400 MHz, CDCl$_3$) 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. ^{13}C NMR (100.4 MHz, CDCl$_3$) δ = 195.5 (s), 172.9 (s), 149.9 (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 C$_{14}$H$_{12}$N$_2$O$_5$: 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-1*H*-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 SeO_2 (65 mg, 0.58 mmol) was then added in one portion.[4] 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 Na_2SO_4, filtered and concentrated. Purification of the crude by flash chromatography (*n*-hexane/EtOAc, 2 : 1; R_f = 0.37) afforded pure **11** (37 mg, 82 %) as a yellow solid. M.p. = 193.4 – 195.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) 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. ^{13}C NMR (100.4 MHz, $CDCl_3$) 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* (%): 625 ([2M+Na]$^+$, 100), 324 ([M+Na]$^+$, 18), 302 ([M+1]$^+$, 4). Elemental analysis calcd (%) for C16H15NO5: C 63.78, H 5.02, N 4.65; found: C 63.95, H 4.82, N 4.49.
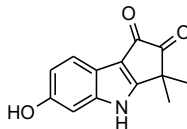
Bruceolline H (12).[2a]

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.[13] ^{1}H NMR (400 MHz, CD_3OD) 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 BBr_3 (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; R_f = 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. ^{1}H 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] ^{13}C 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]

^{1}H NMR (400 MHz, CD_3OD) 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. ^{13}C NMR (100.4 MHz, CD_3OD) 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.

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Chapter 8: Diazenyl-Protected Lactams

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

8.1. General Approach[1]

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.
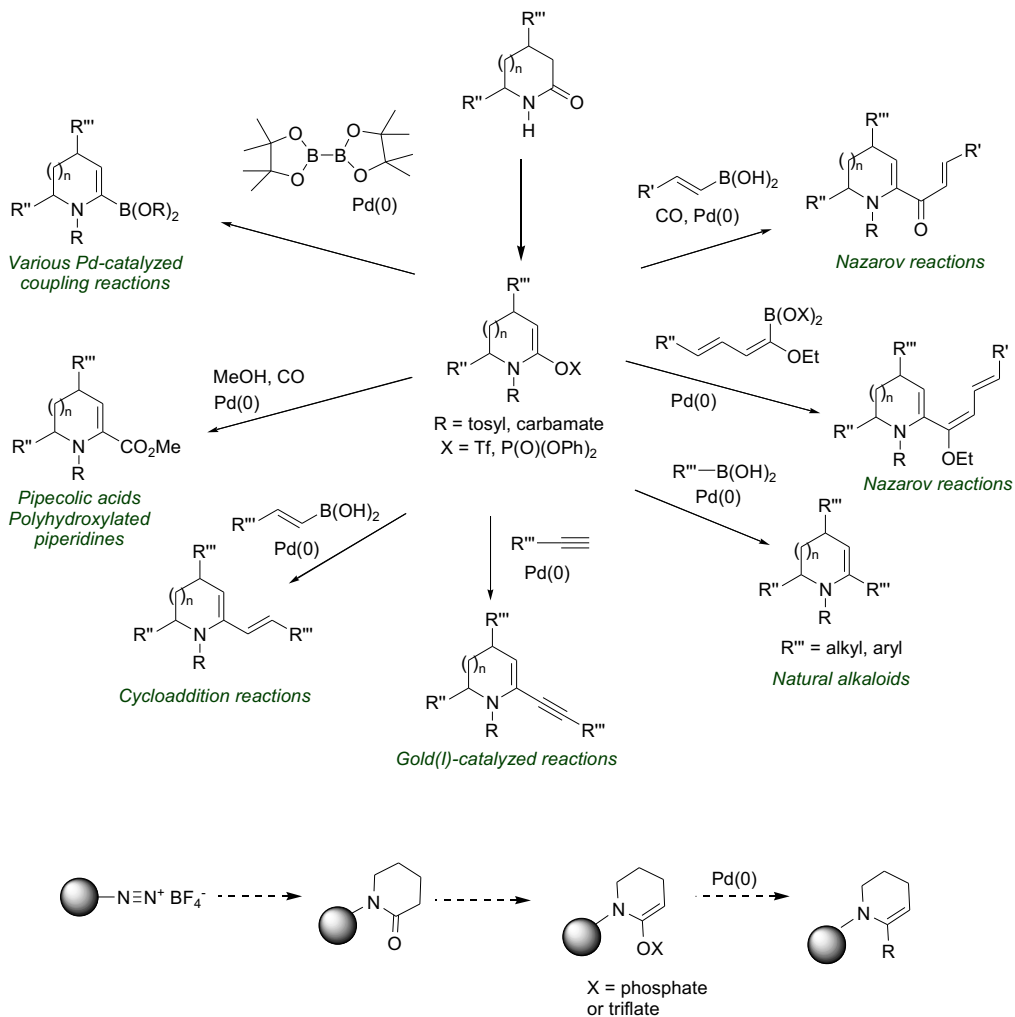
Scheme 1.   Solution-phase[2] and alternative solid-phase synthesis of piperidine derivatives via Pd-catalyzed cross-coupling reactions of lactam derived enol triflates and phosphates.

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.[3] 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**.[4] It has already been used in the transformation of primary amines into different amides, ureas,[5] thioureas and guanidines (Scheme 2).[6] 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**.
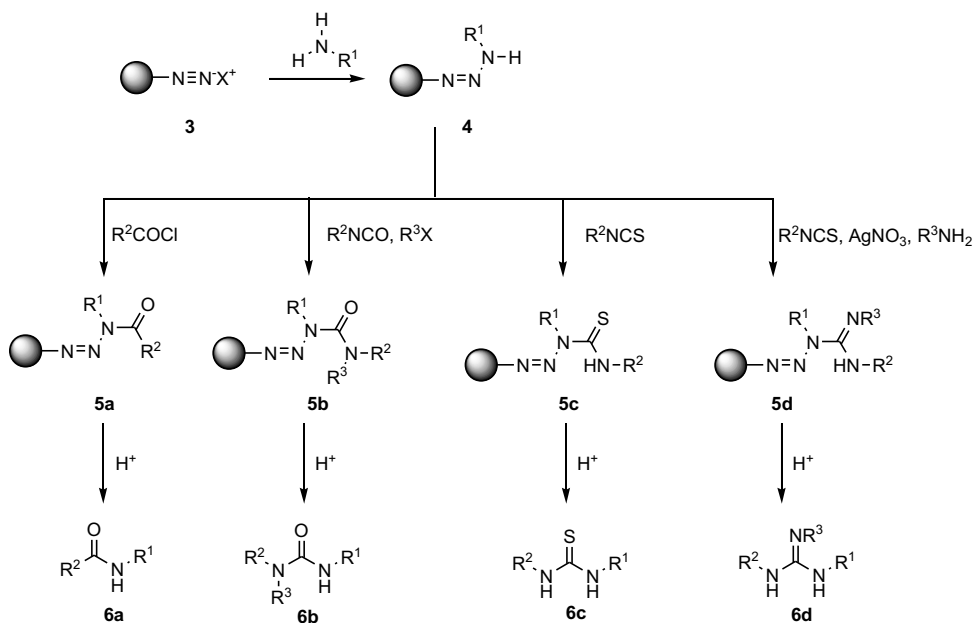
Scheme 2.   Transformations of primary amines into amides, ureas, thioureas and guanidines on diazonium T2 resin.

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.[7,8] Thus, a series of lactams **2** were prepared via RuO$_4$ oxidation of diazenyl protected *N*-heterocycles.
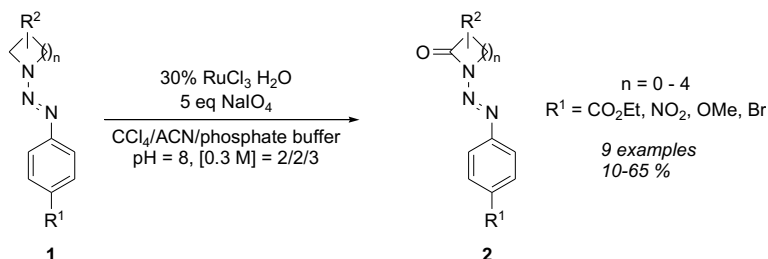
Scheme 3.   Synthesis of diazenyl-protected lactams via RuO$_4$ catalyzed oxidation of triazenes.

8.2. Oxidation of Diazenyl-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 sulfonamines. In most of the oxidation procedures, ruthenium(VIII)[9] and electrochemical oxidation[10] 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%).[8a] 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.

3a   **4a**   **1a**
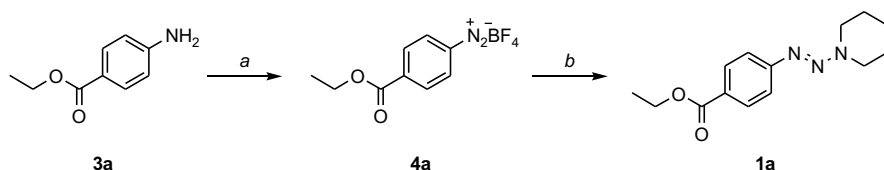
Scheme 4. Synthesis of *N*-diazenyl protected piperidine **1a**. Reagents and conditions: (*a*) BF$_3$·Et$_2$O, isopentyl nitrite, THF, 0 °C, 2 h; (*b*) piperidine, Et$_3$N, THF, 0 °C, 2 h (85 %).

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 1. Oxidation of N-diazenyl protected piperidine **1a**.[a]

1a   **2a**
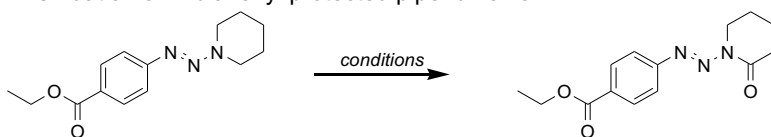
Entry	Pre-catalyst		Oxidant		Solvent	Time	Temp	Yield (%)[b]
1	RuCl$_3$ H$_2$O	15 %	NaIO$_4$	2.5 eq	CCl$_4$/ACN/H$_2$O 2/2/3	2.5 h	RT	39 %
2	DIB	4 eq	TBHP	3 eq	ACN	14 h	RT	19 %
3	DIB	4 eq	H$_2$O$_2$	3 eq	ACN	14 h	RT	-
4	Rh$_2$(cap)$_4$	5 %	T-HYDRO	20 eq	ACN	14 h	RT	22 %
5	Rh$_2$(OAc)$_4$	5 %	T-HYDRO	20 eq	ACN	14 h	RT	-
6	NHPI (3eq) Co(OAc)$_2$	5 %	-	-	ACN	3 h	RT - 80°C	-
7	-	-	CrO$_3$-DMP	20	DCM	14 h	RT	n.d.
8	RuCl$_3$·H$_2$O	30 %	NaIO$_4$	5 eq	CCl$_4$/ACN/H$_2$O 2/2/3	2 h	RT	44 %
9	RuCl$_3$·H$_2$O	30 %	NaIO$_4$	5 eq	DCM/H$_2$O 1/1	14 h	RT	10 %
10	RuCl$_3$·H$_2$O	30 %	NaIO$_4$	3 eq	DCM/ACN/H$_2$O 2/1/2	14 h	RT	16 %
11	RuCl$_3$·H$_2$O	30 %	NaIO$_4$	3 eq	CHCl$_3$/ACN/H$_2$O 2/1/2	14 h	RT	10 %
12	RuCl$_3$·H$_2$O	45 %	NaIO$_4$	5 eq	EtOAc/ACN/H$_2$O 2/0.4/2	2.5 h	RT	16 %
13	RuO$_2$·H$_2$O	30 %	NaIO$_4$	5 eq	CCl$_4$/ACN/H$_2$O 2/2/3	14 h	RT	47 %
14	RuCl$_3$·H$_2$O	30 %	NaIO$_4$	5 eq	CCl$_4$/ACN/buffer (pH = 8) 2/2/3	2 h	RT	52 % (61 %)[c]

[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).[11-14] In metal-free DIB/TBHP oxidation protocol,[11] 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 $Rh_2(cap)_4$/T-HYDRO[12] system led to the formation of desired *N*-diazenyl protected lactam in 22 % yield while $Rh_2(OAc)_2$ under the same reaction conditions was not able to catalyze the reaction. *N*-Hydroxyphthalimide combined with cobalt salt[13] was ineffective catalyst, too (entry 6). On the other hand, with the $CrO_3 \cdot$ 3,5-dimethylpyrazole complex[14] 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, RuO_4 generated *in situ* from $RuCl_3 \cdot nH_2O$ and $NaIO_4$ in CCl_4/ACN/H_2O was the most efficient catalys 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, $CHCl_3$ and EtOAc product **2a** was obtained in low yields (entries 9-12). The use of RuO_2 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).

1a (85%)   **1b** (72%)   **1c** (67%)

1d (83%)   **1e** (55%)   **1f** (80%)

1g (62%)   **1h** (78%)   **1i** (73%)
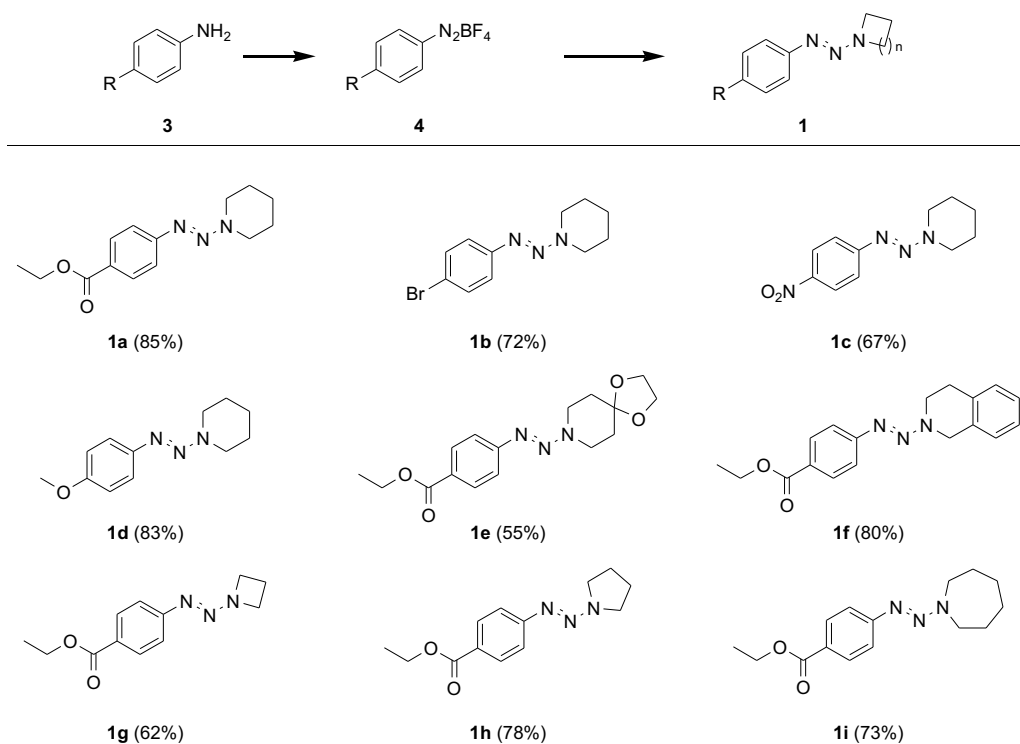
Scheme 5.   Synthesis of *N*-diazenyl protected heterocycles. Reagents and conditions: (*a*) $BF_3 \cdot Et_2O$, isopentyl nitrite, THF, 0 °C, 2 h; (*b*) piperidine, Et_3N, THF, 0 °C – 25 °C, 2 h (85 %).

To explore the scope of the reaction a set of *N*-diazenyl protected heterocycles was prepared by varying the ring size, substituent pattern on the ring and electronic properties of the aryl moiety (Scheme 5). All *N*-diazenyl heterocycles **1b-1i** were prepared in good yields from corresponding diazonium salts and cyclic amines. It is important to notice that among the prepared compounds are quite rare azetinyldiazenes.[15] In addition, all compounds are stable at room temperature and in the contact with air.
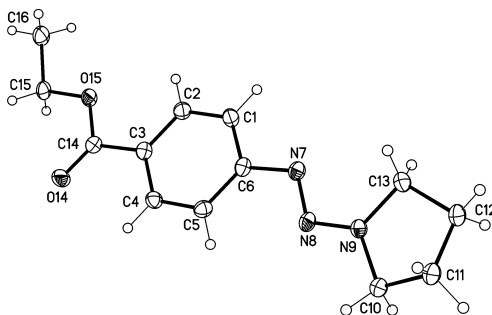
Figure 4. X-Ray structure of triazene **1h**.

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 $KMnO_4$.[8a] 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.
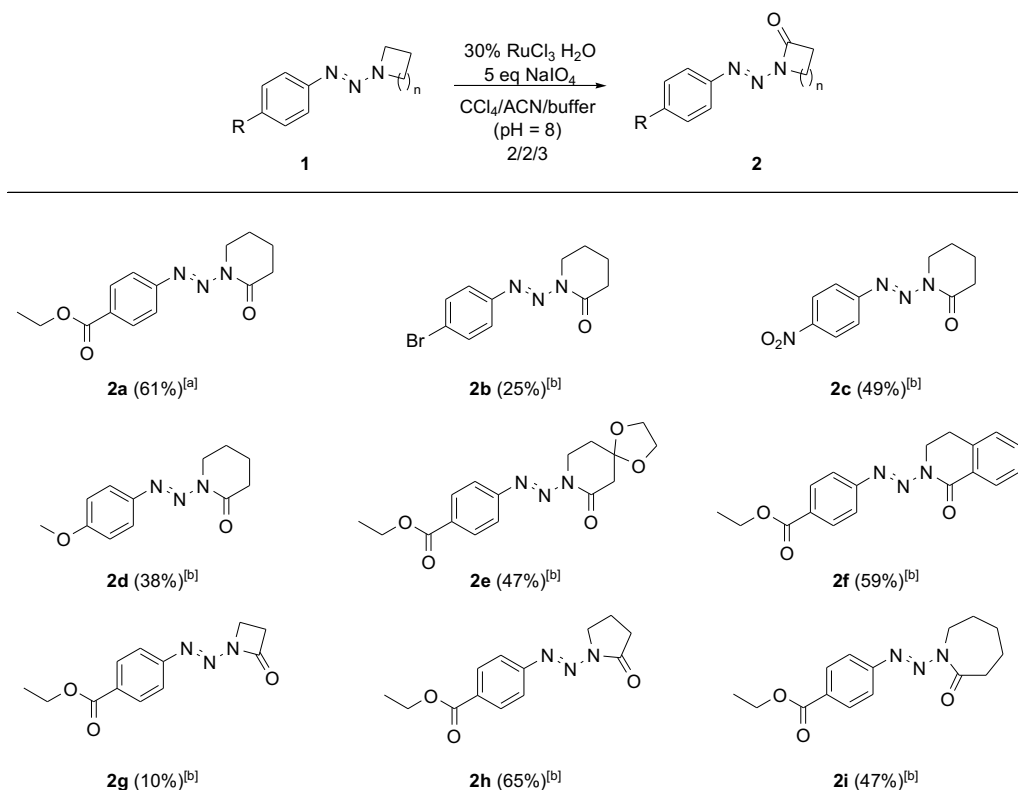
Scheme 6. Oxidation of **1a-i** to *N*-diazenyl-protected lactams **2a-i**. *Notes*: [a] Reaction carried out on 2 mmol scale; [b] Reaction carried out on 1 mmol scale.

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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.
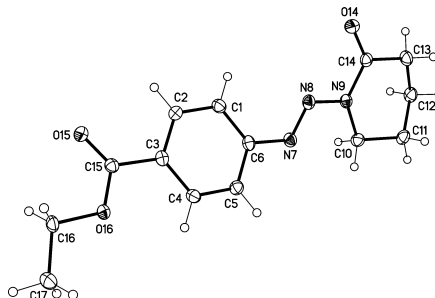
Figure 5. X-Ray structure of **2a**.

Althought the *N*-diazenyl protected lactams are obtained in moderate yields it is worth to mention that the herein described RuO_4 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[16] 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 MeI 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.
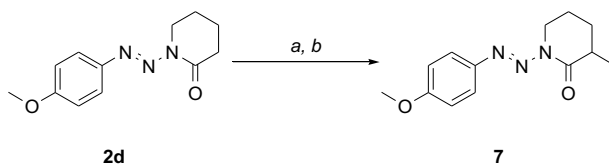
Scheme 7. Alkylation of *N*-diazenyl-protected lactam **2d**. Reagents and conditions: (*a*) LiHMDS, THF, -78 °C; (*b*) MeI, -78 – 25 °C (59 %).

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*-CO_2R (R = Me, CH_2Ph, $C(CH_3)_3$)[2a] but to no avail. In all cases, phosphate was consumed in less than 2 h but the ^{1}H 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.
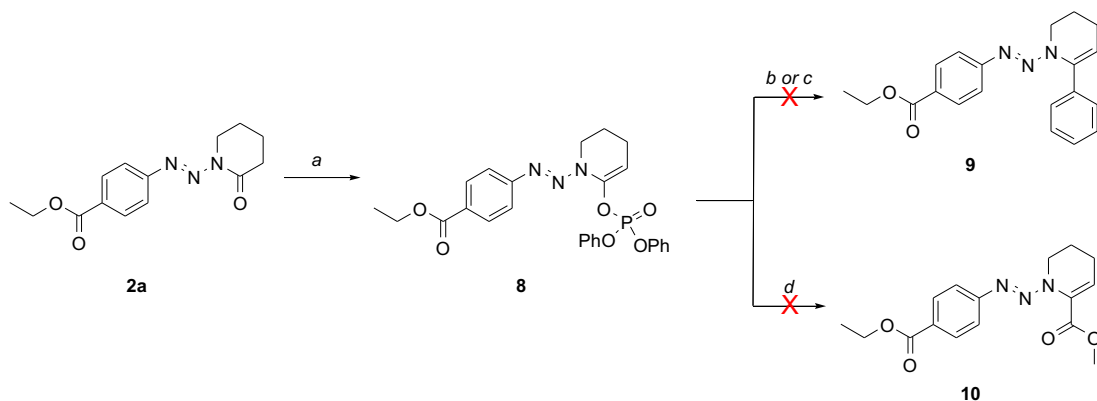
Scheme 8. Attempts of Pd-catalyzed methoxycarbonylation and Suzuki coupling. Reagents and conditions: (*a*) KHMDS, THF, -78 °C, 1.5 h, then (PhO)$_2$POCl, - 78 - 0 °C; (*b*) phenylboronic acid, 5% Pd(Ph$_3$P)$_4$, Na$_2$CO$_3$, DMF/H$_2$0, 40 °C, 2 h; (*c*) phenylboronic acid, 5% (Ph$_3$P)PdCl$_2$, 2 M Na$_2$CO$_3$/THF, 40 ° C, 2 h; (*d*) 10 % Pd(OAc)$_2$, 20 % Ph$_3$P, Et$_3$N, MeOH/DMF, 40 °C, 1.5 h.

8.4. Experimental Part

General information

^{1}H and ^{13}C NMR spectra were recorded on Bruker-AC-250 instrument using CDCl$_3$ 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; 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. Solvents and chemicals used for reactions were purchased from commercial suppliers. Solvents and chemicals were used without further purification.
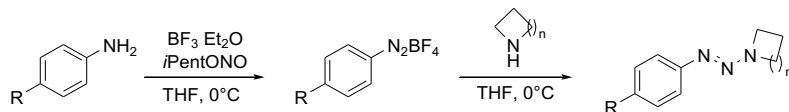
General procedure for the synthesis of triazenes (1).

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 BF$_3$·Et$_2$O (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 Et$_2$O 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.
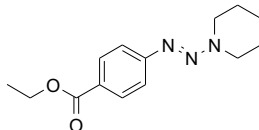
4-(Piperidin-1-ylazo)-benzoic acid ethyl ester (1a).

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. - R_f (cyclohexane/EtOAc = 10 : 1) = 0.21. - m.p. = 128.4 - 129.5 °C. - ^{1}H 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.
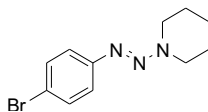
(4-Bromo-phenyl)-piperidin-1-yl-diazene (1b).

Compound **1b** was synthesized according above described procedure from 4-bromoaniline (1.5 mmol) and piperidine (3 mmol). After chromatography (cyclohexane/EtOAc = 10 : 1 + 1 % Et₃N), pure product **1b** (291 mg, 72 %) was obtained as a brown solid. - R_f (cyclohexane/EtOAc = 10 : 1) = 0.27. - m.p. = 55.9 – 56.6 °C. - ^{1}H 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. - ^{13}C 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) [C₁₁H₁₄^{79}BrN₃]⁺, 183 (46) [C₆H₄^{79}BrN₂]⁺, 155 (100) [C₆H₄^{79}Br]⁺. - HRMS (C₁₁H₁₄N₃^{79}Br): calc. 267.0366, found 267.0364. - IR (ATR, ν): 2931, 2849, 1477, 1426, 1394, 1349, 1295, 1258, 1216, 1184, 1106, 1000, 926, 888, 828, 704, 628, 578, 544, 517, 478 cm⁻¹. - EA (C₁₁H₁₄BrN₃): calc. C 49.27, H 5.26, N 15.67; found C 49.05, H 5.26, N 15.46.
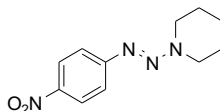
(4-Nitro-phenyl)-piperidin-1-yl-diazene (1c).[18]

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. - R_f (cyclohexane/EtOAc = 10 : 1) = 0.27. - m.p. = 89.3 – 91.6 °C. - ^{1}H 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. - ^{13}C 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.
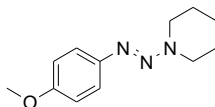
(4-Methoxy-phenyl)-piperidin-1-yl-diazene (1d).[18]

Compound **1d** was synthesized according above described procedure from 4-methoxyaniline (1.5 mmol) and piperidine (3 mmol). After chromatography (cyclohexane/EtOAc = 10 : 1 + 1 % Et$_3$N), pure **1d** (271 mg, 83 %) was obtained as an orange solid. - R$_f$ (cyclohexane/EtOAc = 10 : 1) = 0.31. - m.p. = 50.7 – 51.3 °C. - ^{1}H NMR (250 MHz, CDCl$_3$) δ = 7.39 (d, J = 9.0 Hz, 2 H), 6.88 (d, J = 9.0 Hz, 2 H), 3.79 (s, 3 H), 3.73 - 68 (m, 4 H), 1.74 – 1.68 (m, 6 H) ppm. - ^{13}C NMR (63 MHz, CDCl$_3$) δ = 157.9, 144.5, 121.5, 114.4, 55.6, 48.2, 25.2, 24.5 ppm.
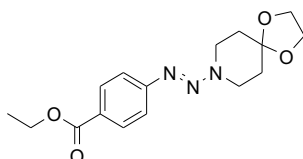
4-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-ylazo)-benzoic acid ethyl ester (1e).

Compound **1e** was synthesized according above described procedure from 4-aminobenzoic acid ethyl ester (2 mmol) and 1,4-dioxa-8-aza-spiro[4.5]decane (4 mmol). After chromatography (cyclohexane/EtOAc = 10 : 1 + 1 % Et$_3$N), pure product **1e** (350 mg, 55 %) was obtained as an orange solid. - R$_f$ (cyclohexane/EtOAc = 10 : 1) = 0.34. - m.p. = 64.8 – 65.4 °C. ^{1}H NMR (250 MHz, CDCl$_3$) δ = 8.02 (d, J = 8.6 Hz, 2 H), 7.46 (d, J = 8.6 Hz, 2 H), 4.36 (q, J = 7.1 Hz, 2 H), 4.02 (s, 4 H), 3.98 (m, 4 H), 1.91 – 1.79 (m, 4 H), 1.39 (t, J = 7.1 Hz, 3 H) ppm. - ^{13}C NMR (63 MHz, CDCl$_3$) δ = 166.6, 154.0, 130.2, 127.6, 120.2, 107.2, 64.8, 60.8, 14.5 ppm. - MS (EI), m/z (%): 319 (62) [M]$^+$, 274 (13) [C$_{14}$H$_{16}$N$_3$O$_3$]$^+$, 177 (58) [C$_9$H$_9$N$_2$O]$^+$, 149 (100) [C$_9$H$_9$O$_2$]$^+$. - HRMS (C$_{16}$H$_{21}$N$_3$O$_4$): calc. 319.1527, found 319.1527. - 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 (C$_{16}$H$_{21}$N$_3$O$_4$): calc. C 60.17, H 6.63, N 13.16,; found C 60.14, H 6.49, N 13.20.
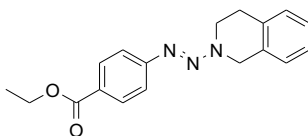
4-(3,4-Dihydro-1H-isoquinolin-2-ylazo)-benzoic acid ethyl ester (1f).

Compound **1f** was synthesized according above described procedure from 4-aminobenzoic acid ethyl ester (2 mmol) and 1,2,3,4-tetrahydroisoquinoline (4 mmol). After chromatography (cyclo-hexane/EtOAc = 20 : 1 + 1 % Et$_3$N), pure product **1f** (490 mg, 80 %) was obtained as an orange solid. - R$_f$ (cyclohexane/EtOAc = 20 : 1) = 0.26. - m.p. = 76.6 – 77.2 °C. - ^{1}H NMR (300 MHz, CDCl$_3$) δ = 7.96 (d, J = 8.4 Hz, 2 H), 7.43 (d, J = 8.4 Hz, 2 H), 7.26 - 7.09 (m, 4 H), 4.92 (s, 2 H), 4.29 (q, J = 7.1 Hz, 2 H), 4.25 - 3.98 (m, 2 H), 3.01 (t, J = 5.8 Hz, 2 H), 1.32 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$) δ = 166.6, 154.4, 130.6, 128.4, 127.2, 127.0, 126.8, 120.3, 60.7, 14.4 ppm. - MS (EI), m/z (%): 309 (26) [M]$^+$, 149 (100) [C$_9$H$_9$O$_2$]$^+$, 132 (76) [C$_9$H$_9$N]$^+$. - HRMS (C$_{18}$H$_{19}$N$_3$O$_2$): calc. 309.1472, found 309.1473. - 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 (C$_{18}$H$_{19}$N$_3$O$_2$) calc. C 69.88, H 6.19, N 13.58; found C 69.80, H 6.20, N 13.37.
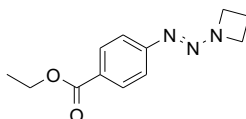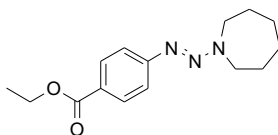
4-(Azetidin-1-ylazo)-benzoic acid ethyl ester (1g).

Diazonium 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 (1M, 5 mL). The product was extracted with Et_2O (3 x 5 mL) and combined organic layers were dried over Na_2SO_4, filtered and concentrated. After chromatography (cyclohexane/EtOAc = 10 : 1 + 1 % Et_3N) pure **3a** (145 mg, 62 %) was obtained as a yellow solid. - R_f (cyclohexane/EtOAc = 10 : 1) = 0.36. - m.p. = 54.1 – 54.8 °C. - ^{1}H NMR (250 MHz, $CDCl_3$) 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. - ^{13}C NMR (63 MHz, $CDCl_3$) δ = 166.6, 154.2, 130.7, 128.0, 120.3, 60.5, 55.7, 15.7, 14.5 ppm. MS (EI), m/z (%): 233 (30) $[M]_+$, 188 (9) $[C_9H_{10}N_3O]^+$, 177 (40) $[C_9H_9N_2O]^+$, 149 (100) $[C_9H_9O_2]^+$. - HRMS ($C_{12}H_{15}N_3O_2$): 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 ($C_{12}H_{15}N_3O_2$): calc. C 61.79, H 6.48, N 18.01; found. C 61.76, H 6.38, N 17.76.
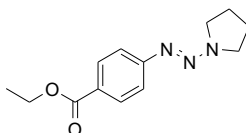
4-(Pyrrolidin-1-ylazo)-benzoic acid ethyl ester (1h).[19]

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 % Et_3N), pure **1h** (384 mg, 78 %) was obtained in form of yellow crystals. - R_f (cyclohexane/EtOAc = 20 : 1) = 0.34. - m.p. = 65.2 – 65.4°C. - ^{1}H NMR (300 MHz, $CDCl_3$) 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. - ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.7, 154.8, 130.7, 130.5, 126.8, 120.3, 60.5, 23.7, 14.4 ppm. - HRMS ($C_{13}H_{17}N_3O_2$): 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 ($C_{13}H_{17}N_3O_2$): calc. C 63.14, H 6.93, N 16.99; found C 63.21, H 6.92, N 16.91.

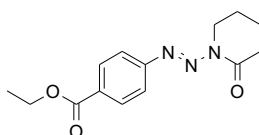### 4-(Azepan-1-ylazo)-benzoic acid ethyl ester (1i).

Compound **1i** was synthesized according above described procedure from 4-aminobenzoic acid ethyl ester (2 mmol) and hexamethyleneimine (4 mmol). After chromatography (cyclohexane/EtOAc = 20 : 1 + 1 % Et_3N), pure product **1i** (402 mg, 73 %) was obtained as a red solid. - R_f (cyclohexane/EtOAc = 20 : 1) = 0.24. - m.p. = 60.2 – 62.1 °C. - ^{1}H NMR (300 MHz, $CDCl_3$) 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. - ^{13}C NMR (75 MHz, $CDCl_3$) 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) $[C_9H_9O_2]^+$. - HRMS ($C_{15}H_{21}N_3O_2$): 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 ($C_{15}H_{21}N_3O_2$): calc. C 65.43, H 7.69, N

15.26; found C 65.37, H 7.59, N 14.62.
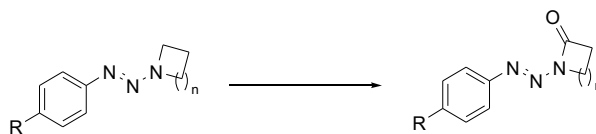
General procedure for the oxidation of triazenes into *N*-diazenyl protected lactams (2).

To a stirred mixture of phosphate buffer (pH = 8, c = 0.3 M)/CCl$_4$/ACN = 3 : 2 : 2 (10 mL) were added NaIO$_4$ (5 mmol) and RuCl$_3$ · H$_2$O (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 Na$_2$SO$_4$, filtered and concentrated. The crude was purified by flash chromatography.

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 % Et$_3$N), pure product **2a** (320 mg, 61 %) was obtained as a yellow solid. - R$_f$ (cyclohexane/EtOAc = 4 : 1) = 0.19. - m.p. = 128.4 – 129.5 °C. - ^{1}H NMR (300 MHz, CDCl$_3$) 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. - ^{13}C NMR (75 MHz, CDCl$_3$) δ = 169.2, 166.3, 151.7, 130.6, 122.5, 122.3, 61.1, 45.9, 34.1, 22.5, 20.4, 14.2 ppm. MS m/z, (%): 275 (26) [M]$^+$, 177 (79) [(C$_9$H$_9$N$_2$O$_3$]$^+$, 164 (100) [(C$_9$H$_8$NO$_2$]$^+$. - HRMS (C$_{14}$H$_{19}$N$_3$O$_2$): 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 (C$_{14}$H$_{17}$N$_3$O$_3$): calc. C 61.08, H 6.22, N 15.26; found C 60.05, H 6.17, N 15.13.
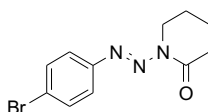
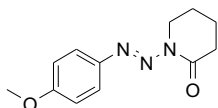**1-(4-Bromo-phenyl-diazenyl)-piperidin-2-one (2b).**

Compound **2b** was synthesized following above described procedure from corresponding triazene **1b** (1 mmol). After chromatography (cyclohexane/EtOAc = 4 : 1 + 1 % Et$_3$N), pure product **2b** (70 mg, 25 %) was obtained. Recrystallization from DCM/cyclohexane gave brownish crystals. - R$_f$ (cyclohexane/EtOAc = 4 : 1) = 0.19. - m.p. = 59.7 – 60.2 °C. - ^{1}H NMR (300 MHz, CDCl$_3$) 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. - ^{13}C NMR (75 MHz, CDCl$_3$) 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) [C$_{11}$H$_{12}$^{79}BrN$_3$O]$^+$, 183 (47) [C$_6$H$_4$^{79}BrN$_2$]$^+$, 155 (100) [C$_6$H$_4$^{79}Br]$^+$. - HRMS (C$_{11}$H$_{12}$N$_3$O^{79}Br): calc. 281.0158, found 281.0160. - IR (ATR, ν): 2952, 2881, 1683, 1571, 1480, 1457, 1398, 1377, 1327, 1295, 1191, 1172, 1146, 1064, 1006, 988, 910, 827, 705, 659, 639, 546, 522, 473, 385 cm^{-1}. EA (C$_{11}$H$_{12}$BrN$_3$O): calc. C 46.83, H 4.29, Br 28.32, N 14.89; found C 46.50, H 4.28, N 14.17.
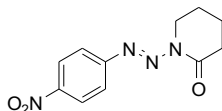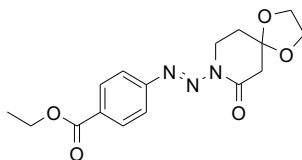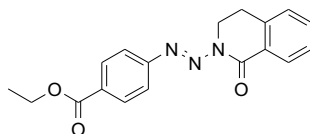
1-(4-Nitro-phenyl-diazenyl)-piperidin-2-one (2c).

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$_3$) δ = 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$_3$) δ = 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, v): 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$_3$) δ = 7.68 (m, 2 H), 6.92 (m, 2 H), 3.94 – 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$_3$) δ = 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$_7$H$_7$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, v): 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.

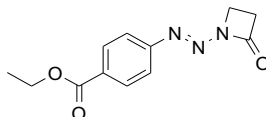### 4-(7-Oxo-1,4-dioxa-8-aza-spiro[4.5]dec-8-ylazo)-benzoic acid ethyl ester (2e).

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$_3$) δ = 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$_3$) δ = 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$_9$N$_2$O]$^+$, 149 (100) [C$_9$H$_9$O$_2$]$^+$. - HRMS (C$_{16}$H$_{19}$N$_3$O$_5$): calc. 333.1319, found 333.1320. – IR (ATR, v): 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$_{19}$N$_3$O$_5$) calc. C 57.65, H 5.75, N 12.61; found C 57.76, H 5.77, N 12.37.
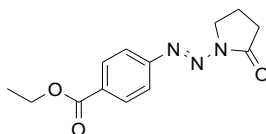
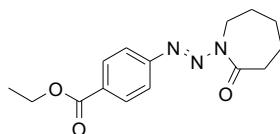**4-(1-Oxo-3,4-dihydro-1H-isoquinolin-2-ylazo)-benzoic acid ethyl ester (2f).**

Compound **2f** was synthesized following above described procedure from corresponding triazene **1f** (1 mmol). After chromatography (cyclohexane/EtOAc = 4 : 1 + 1 % Et$_3$N), pure product **1f** (149 mg, 47 %) was obtained as a yellow solid. - R$_f$ (cyclohexane/EtOAc = 4 : 1) = 0.20. - m.p. = 137.2 – 138.0 °C. - ^{1}H NMR (300 MHz, CDCl$_3$) 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), 7.38 (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. ^{13}C NMR (75 MHz, CDCl$_3$) δ = 165.8, 162.7, 151.8, 138.7, 133.4, 130.8, 130.6, 130.6, 129.5, 128.7, 127.5, 127.3, 123.4, 122.4, 61.1, 41.5, 27.5, 14.1 ppm. - MS (EI), m/z (%): 323 (17) [M]$^+$, 177 (73) [C$_9$H$_9$N$_2$O]$^+$, 149 (100) [C$_9$H$_9$O$_2$]$^+$. - HRMS (C$_{18}$H$_{17}$N$_3$O$_3$): calc. 323.1264, found 323.1263. – IR (ATR, ν): 2978, 1713, 1682, 1603, 1460, 1410, 1367, 1310, 1270, 1227, 1185, 1125, 1091, 1009, 959, 890, 859, 789, 770, 739, 696, 643, 597, 528, 483, 414 cm^{-1}. - EA (C$_{18}$H$_{17}$N$_3$O$_3$) calc. C 66.86, H 5.30, N 13.00, O 14.84; found. C 66.30, H 5.27, N 13.56.

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 % Et$_3$N), pure product **2g** (12.8 mg, 10 %) was obtained as a brown solid. - R$_f$ (cyclohexane/EtOAc = 4 : 1) = 0.22. - m.p. = 97.6 – 98.2 °C. - ^{1}H NMR (250 MHz, CDCl$_3$) 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) [C$_9$H$_9$N$_2$O]$^+$, 149 (100) [C$_9$H$_9$O$_2$]$^+$. - HRMS (C$_{12}$H$_{13}$N$_3$O$_3$): calc. 247.0951, found 247.0950. - IR (ATR, ν): 2977, 1773, 1702, 1602, 1453, 1408, 1368, 1322, 1273, 1242, 1184, 1098, 1044, 870, 774, 698, 541, 525, 463, 393 cm^{-1}. - EA (C$_{12}$H$_{13}$N$_3$O$_3$) 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 % Et$_3$N), pure product **1h** (169 mg, 65 %) was obtained as a pale orange solid. - R$_f$ (cyclohexane/EtOAc = 4 : 1) = 0.32. - m.p. = 127.9 – 128.8 °C. - ^{1}H NMR (300 MHz, CDCl$_3$) δ = 8.03 (d, J = 8.5 Hz, 2 H), 7.65 (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. - ^{13}C NMR (75 MHz, CDCl$_3$) 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) [C$_9$H$_9$N$_2$O]$^+$, 149 (100) [C$_9$H$_9$O$_2$]$^+$. - HRMS (C$_{13}$H$_{15}$N$_3$O$_3$): 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 (C$_{13}$H$_{15}$N$_3$O$_3$) calc. C 59.76, H 5.79, N 16.08; found C 59.76, H 5.78, N 15.84.
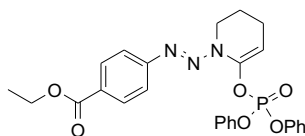
4-(2-Oxo-azepan-1-ylazo)-benzoic acid ethyl ester (2i).

Compound **2i** was synthesized following above described procedure from corresponding triazene **1i** (1 mmol). After chromatography (cyclohexane/EtOAc = 4 : 1 + 1 % Et₃N), pure product **2i** (134 mg, 47 %) was obtained as an orange oil. - R$_f$ (cyclohexane/EtOAc = 4:1) = 0.32. - ^{1}H NMR (300 MHz, CDCl₃) δ = 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, CDCl₃) δ = 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) [C₉H₉N₂O]$^{+}$, 149 (100) [C₉H₉O₂]$^{+}$. - HRMS (C₁₅H₁₉N₃O₃): calc. 289.1421, found 289.1421. - IR (ATR, ν): 2930, 1706, 1603, 1477, 1377, 1269, 1137, 1096, 1077, 1014, 951, 922, 862, 845, 773, 699, 584 cm^{-1}. - EA (C₁₅H₁₉N₃O₃): calc. C 62.27; H 6.62; N 14.52; found C 62.01, H 6.74, N 14.34.
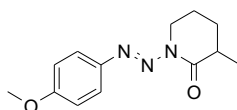
1-(4-Methoxy-phenyl-diazenyl)-3-methyl-piperidin-2-one (7).

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 under nitrogen at -78 °C; after 1 h, MeI (18 mL, 0.29 mmol) was slowly added and, after 10 min, the cooling bath was removed and the mixture stirred at room temperature for 2 h. After the dilution with Et₂O (5 mL), water was added (10 mL) and, after separation of the phases, the aqueous layer was extracted with Et₂O (2 x 10 mL). The combined organic extracts were dried over anhydrous K₂CO₃. After filtration and evaporation of the solvent, the crude was purified by flash chromatography (n-hexane/EtOAc, 3 : 1 + 1 % Et₃N), affording pure **7** as an orange solid (38 mg, 59 %). - R$_f$ (n-hexane/EtOAc, 3 : 1) = 0.24. – m.p. = 87.7 - 89.2 °C. - ^{1}H NMR (400 MHz, CDCl₃) δ = 7.67 (d, J = 9.1 Hz, 2H), 6.92 (d, J = 9.1 Hz, 2H), 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, CDCl₃) δ = 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 (C₁₃H₁₇N₃O₂) 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-pyridin-1-ylazo]-benzoic acid ethyl ester (8)

A 0.5 M solution of KHMDS (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 Et₂O (4 x 3 mL); the combined organic extracts were washed with 10 % NaOH (3 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, 10 : 1 + 1 % Et₃N; R$_f$ = 0.24) to give product **8** (112 mg,

100 %) as a colourless oil. R$_f$ (*n*-hexane/EtOAc, 2 : 1) = 0.48. - ^{1}H NMR (400 MHz, CDCl$_3$) *δ* = 7.88 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.30 – 7.05 (m, 10H), 4.93 (dd, *J* = 7.2, 4.4 Hz, 1H), 4.30 (q, *J* = 7.1 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 Hz, 3H) ppm. - ^{13}C NMR (100.3 MHz, CDCl$_3$) *δ* = 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.

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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-1*H*-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 RuO_4 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
Ac$_2$O	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	hexamethylphosphoramide
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*-Iodosuccinimide
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
R$_f$	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*-butyldimethylsilyl
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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