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Palladium catalyzed cyclization reactions of acetylenic lactams

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Dedicated to Professor Jean F. Normant on the occasion of his 65th birthday

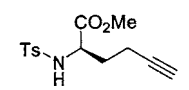
Abstract

Lactams and oxazolidinones containing a 3-butynyl side chain at the four- and the three-position, respectively, have been prepared by reductive alkylation of cyclic imides or by S_N2'-substitution of bromopropadiene with highly functionalized enantiopure organozinc reagents. Treatment of these compounds with aryl halides and one vinyl bromide using $Pd(PPh_3)_4$ as a catalyst gives rise to a coupling-cyclization reaction, yielding bicyclic enamides in which the aryl or vinyl moiety is incorporated. Remarkably, these groups are transferred stereoselectively *cis* with respect to the nitrogen nucleophile onto the triple bond. Structural proof for this unusual stereochemical outcome has been obtained by crystal structure analysis and NOE-difference spectroscopy of the cyclized products.

Keywords: Palladium; Cyclization reactions; Acetylenic lactams

1. Introduction

The construction of *N*-heterocycles is an important goal in organic synthesis due to the abundance of these compounds in natural and pharmaceutical products [1]. Well-established methods for the preparation of such compounds are heteroannulation processes involving unsaturated functionality and Pd-catalysis [2,3]. In our group, we recently focused on processes involving cross-coupling reactions and cyclizations in a single synthetic operation by treating alkynes that are tethered to a heteroatom nucleophile with vinyl or aryl halides and a palladium catalyst [4,5]. For example, (*R*)-propargylglycine derivative **1** was converted in our laboratory to enamide **2**, when treated with iodobenzene, $Pd(PPh_3)_4$, K_2CO_3 and tetrabutylammonium chloride in acetonitrile [6]. The organic part of the halide (e.g. the phenyl group of iodobenzene) was transferred stereospecifically *trans* with respect to the nucleophile. This stereochemical outcome is generally encountered in these types of reactions and probably stems from a reductive elimination of an intermediate vinylpalladium complex (e.g. **3**), which is formed after *anti* attack of the nucleophile onto the palladium-activated triple bond [4,5].



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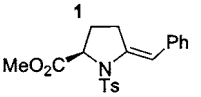

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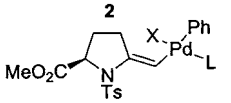

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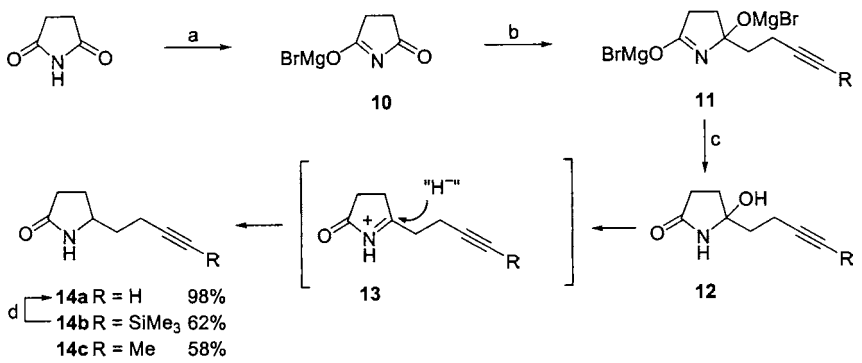
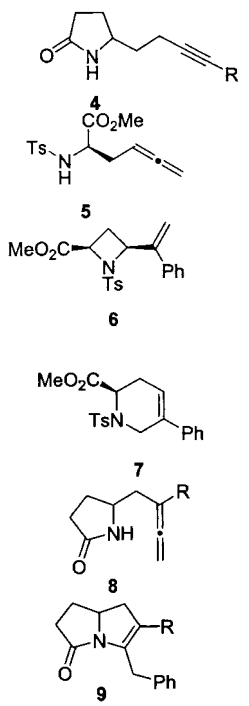


Scheme 1. Reagents and conditions: (a) MeMgBr (1 equiv), THF, 0°C to rt, 1 h; (b) RC + CCH_2CH_2MgBr (2 equiv), THF, 0°C to rt, 1 h; (c) $NaBH_3CN$, THF/HOAc, pH 3, rt, 1 h; (d) TBAF, THF, 0°C, 30 min.

In conjunction with this work, we now present palladium-catalyzed cyclizations of acetylenic lactams **4** in which the alkyne is also separated from the nucleophile by a three carbon tether (cf. **1**). We were particularly interested in compounds containing a cyclic lactam nucleophile, because we observed recently that the nature of the nucleophile determines strongly the regiochemical outcome in related allene cyclizations. For example, we showed that linear allenic amino acid derivatives (**5**) can be converted selectively to azetidines (**6**) and tetrahydropyridines (**7**) when treated with iodobenzene in the presence of a palladium catalyst [7], whereas cyclic allenic lactams (**8**) underwent a highly unusual and unprecedented reaction in which the nitrogen atom attacked the central carbon atom of the allene to give bicyclic enamides (**9**) [8,9][4].



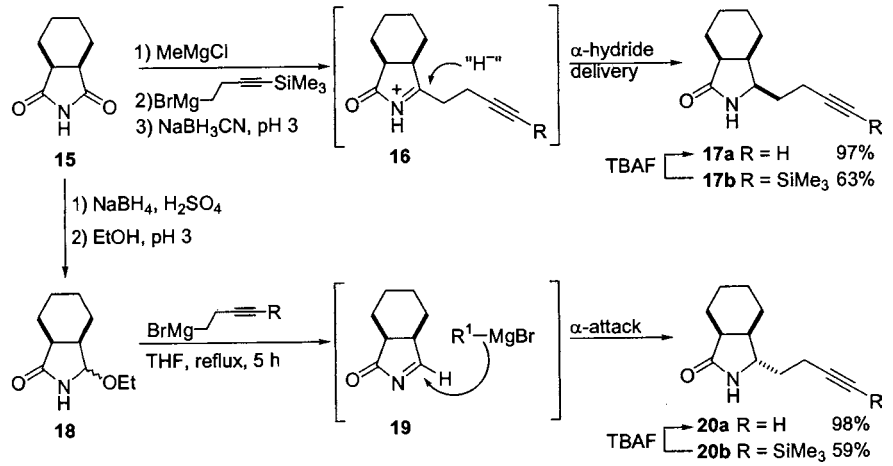
[4] This difference between cyclic and acyclic nucleophiles was also found in the case of palladium catalyzed 1,2-oxidations of allenes.

2. Preparation of the starting materials

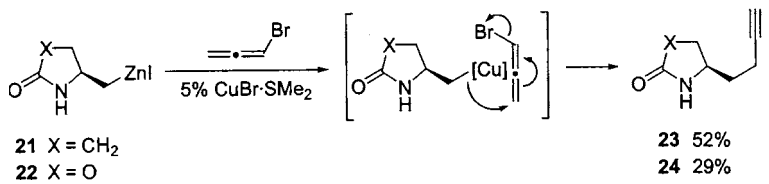
In order to obtain the desired cyclization precursors, we decided to use a one pot reductive alkylation of cyclic imides [10]. The method involves addition of the Grignard reagent of the desired side chain to one of the imide carbonyls, followed by reduction of the resulting hydroxylactam to the lactam. The advantages of this pathway are that readily available starting materials can be used and that the use of protective groups is avoided.

Thus, deprotonation of succinimide with methylmagnesium bromide (one equivalent) led to the magnesium salt **10**. This intermediate was allowed to react with the Grignard reagent derived from 4-bromo-1-trimethylsilylbut-1-yne (two equivalents), leading to addition product **11** (Scheme 1). At this point sodium cyanoborohydride was added and the mixture was acidified to pH 3 with acetic acid, resulting in the solvolysis of the bis-magnesium salt to the corresponding hydroxylactam **12**. In the acidic medium, this *N*,*O*-acetal was converted easily into the *N*-acyliminium ion **13**, which was reduced by the hydride donor to give pyrrolidinone **14b** in a yield of 62%. Deprotection of the Me_3Si–acetylene with TBAF in THF, afforded the terminal acetylene **14a** (98%), whereas methyl substituted acetylene **14c** was obtained in 58% yield using the same procedure with the Grignard reagent derived from 1-bromo-3-pentyne.

Subjection of bicyclic imide **15** to this process led to the introduction of the side chain in a *cis* fashion with respect to the cyclohexyl moiety, thus affording acetylenic lactam **17b** in a yield of 63%. The stereochemical outcome of this process can be explained by the steric crowding at the top face of *N*-acyliminium ion **16**. The hydride donor approaches **16** from the convex side of the sterically demanding cyclohexyl moiety, resulting in the observed *cis* stereochemistry. As before, desilylation using TBAF afforded the terminal acetylene **17a** in almost quantitative yield (Scheme 2).



Scheme 2.

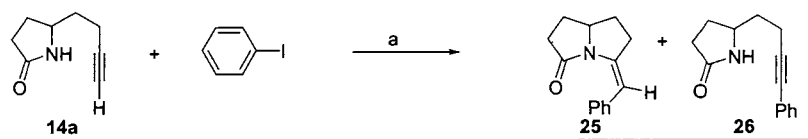


Scheme 3.

The *trans* substituted bicyclic lactams could be prepared following an elimination-addition protocol, starting from the same imide as for the preparation of the *cis* isomers. Reduction of the imide with $NaBH_4$ and immediate ethanolysis afforded the ethoxylactam **18** [11], which on treatment with 4-trimethylsilylbut-3-ynylmagnesium bromide (2.5 equivalents) generated the imine **19** by elimination of ethanol. This reactive intermediate was attacked from the least hindered side by a second equivalent of the Grignard reagent, introducing the acetylenic side chain opposite to the cyclohexyl moiety to give the *trans* acetylenic lactam **20b**. Thus, by simply changing the order of steps, the stereochemical outcome of the reaction can be changed (Scheme 3).

Acetylenes can also be prepared by an S_N2' reaction of organocopper reagents with allenyl halides [12]. By analogy, it was envizaged that reaction of bromoallene [13] with the previously used organozinc reagents **21** [8b,14] and **22** [8,15], after transmetallation to copper, would provide enantiopure acetylenic lactams and oxazolidinones. Indeed, preparation of the organozinc reagents from the corresponding iodides followed by treatment with a catalytic amount of $CuBr{\cdot}SMe_2$ (0.05 equivalents) and bromoallene (1.1 equivalents) in DMF

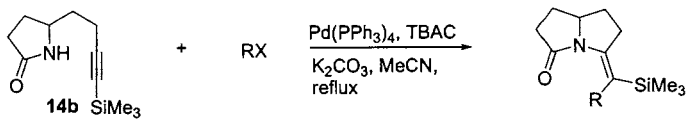
Table 1

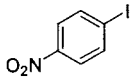
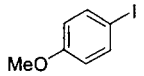
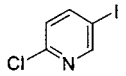


entry	catalytic system	TBAC	solvent	t (h)	yield	yield
1	$Pd(PPh_3)_4$	+	MeCN	3	40%	16%
2	" "	-	MeCN	3	10%	11%
3	" "	+	DMF	5	31%	44%
4	" "	-	DMF	6	33%	n.d.
5	" "	+	THF	20	19%	n.d.
6	$Pd(OAc)_2$/ 2 PPh_3	+	MeCN	3	8%	n.d.
7	$Pd_2(dba)_3$/ 4 PPh_3	+	MeCN	3	12%	n.d.

Reagents and conditions: (a) **14a** (1 mmol), catalyst (0.1 equiv Pd), n-Bu_4NCl (0 or 1.5 equiv), K_2CO_3 (4 equiv), PhI (4 equiv), indicated solvent (0.05 M), 80 °C (THF, 67 °C).

Table 2



entry	RX	time	product	yield
1		3 h	**27**	64%
2		1.5 h	**28**	74%
3		6 h	**29**	<10%
4		2 h	**30**	78%
5		18 h	**31**[a]	34%[b]
6		3 h	**32**	69%

Notes: (a) reaction occurred at the iodide position; (b) 50% starting material recovered

afforded the acetylenic lactam **23** in a good yield of 52% (X = CH_2). On the other hand, using the oxazolidinone derived organozinc reagent **24** (X = O) in THF afforded the desired acetylene **36** in only 29% yield.

3. Cyclization reactions

With the precursors in hand, several reaction conditions to effect cyclization were compared in terms of yield and reaction time. First, identical conditions were applied as for the cyclizations of the isomeric allenic lactams [8]. Treatment of **14a** with $Pd(PPh_3)_4$, iodobenzene, tetrabutylammonium chloride (TBAC) and K_2CO_3 in acetonitrile, afforded bicyclic enamide **25** in 40% yield, along with 16% of the non-cyclized 'Sonogashira type' coupling product **26** (entry 1, Table 1). Remarkably, the phenyl group was incorporated in a *cis* fashion with respect to the nitrogen nucleophile, which contrasts with the usually observed stereochemical outcome of these types of cyclization reactions.

Unfortunately, we were not able to improve the yield of the cyclic product, by varying solvent, palladium source or omitting the tetrabutylammonium chloride. Without this chloride source being present in acetonitrile, the yield dropped dramatically[5] [16] and the ratio of cyclized product to coupling product decreased to 1:1 (entry 2).

The use of DMF as a solvent was not advantageous either (entries 3 and 4); the yield was lower, and the formation of **26** appeared the major reaction pathway (entry 3). In THF, the reaction was sluggish, the starting material being completely consumed after 20 h, while the yield of 20% was quite disappointing (entry 5). A detrimental effect on the yield was also observed if the source of palladium was changed, along with the palladium to phosphine ratio (entries 6 and 7).

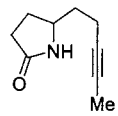
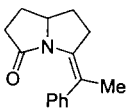
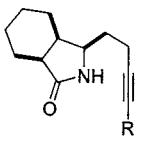
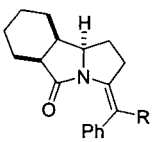
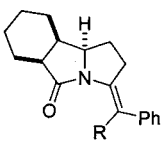
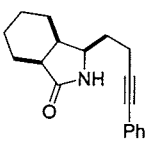
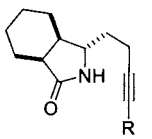
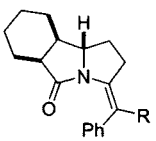
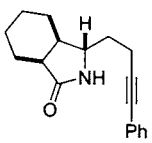
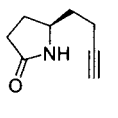
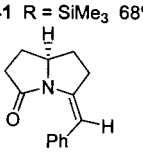
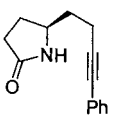
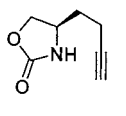
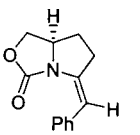
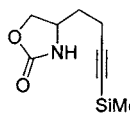
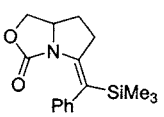
Being unable to suppress the formation of coupling product **26**, it was decided to use the Me_3Si-protected acetylenes in the cyclization reaction. Indeed, using the conditions of entry 1 in Table 1, the Me_3Si-substituted acetylene **14b** afforded bicyclic enamide **27** cleanly with a yield of 64%, while the Sonogashira pathway was blocked efficiently[6] (Table 2, entry 1).

Having established a satisfactory cyclization protocol, the Me_3Si-protected acetylenic lactam **14b** was allowed to react under the same conditions with several aromatic and vinylic halides, as depicted in Table 2. When the phenyl ring was substituted with an electron-withdrawing nitro group, a smooth cyclization occurred to give 74% of **28**, whereas the use of the electron rich *para*-iodoanisole had a detrimental effect. A complex mixture of products was obtained and although the

[5] This beneficial effect of the use of quaternary ammonium chlorides was observed previously for the coupling/cyclization of acetylenic carboxylic acids (see Ref. [4c]) and acetylenic tosyl carbamates (Refs. [5a,b])

[6] The TBAC should be dried before use in order to prevent desilylation under the reaction conditions.

Table 3
Cyclizations of several acetylenic lactams with iodobenzene

entry	acetylenic lactam	products, yield		
1	 **14c**	 **33** 66%		
2	 **17a** R = H	 **34** R = H 37%	 **35** R = H 5%	 **36** 29%
3	**17b** R = $SiMe_3$	**37** R = $SiMe_3$ 41%[a]	**38** R = $SiMe_3$ 12%[b]	
4	 **20a** R = H	 **39** R = H 60%	 **40** 25%	
5	**20b** R = $SiMe_3$	**41** R = $SiMe_3$ 68%[c]		
6	 **23**	 **42** 40%	 **43** 20%	
7	 **24**	 **44** 60%		
8	 **45**	 **46** 71%		

Notes: (a) 9% of desilylated product **34** was also formed; (b) 5% of **35** was also formed; (c) 11% of **39** was also formed

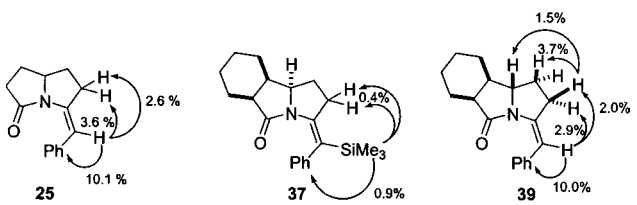


Fig. 1. NOE-enhancements of compounds **25**, **37** and **39**.

cyclization product **29** was detectable on NMR (< 10%) it was not isolated. Heteroaromatic halides could be successfully applied in the cyclization reaction as illustrated by the use of 2-bromothiophene (entry 4) and 2-chloro-5-iodopyridine[17] (entry 5). Although the yield was relatively low (34%) in the latter case, 50% of **14b** could be recovered, correcting the yield to 68%.

2-Bromopropene, an example of a vinyl halide, afforded the cyclic product **32** in a good yield of 69%. Remarkably, the use of vinyl triflates did not lead to the formation of the desired bicyclic compounds.

The results of the cyclization reactions of several acetylenic lactams with iodobenzene are summarized in Table 3. The methyl-substituted acetylene **14c** effectively cyclized to the (*Z*)-substituted enamide **33** (entry 1), although the reaction was sluggish and needed to be stirred at reflux temperature for 18 h. Mixtures of double bond isomers were obtained when bicyclic lactams **17a** and **17b** were subjected to the cyclization conditions (entries 2 and 3).

Unprotected acetylene **17a** afforded the tricyclic (*Z*)-enamide **34** as a major product (37%), accompanied by 5% of the (*E*)-isomer **35**. The non-cyclized coupling

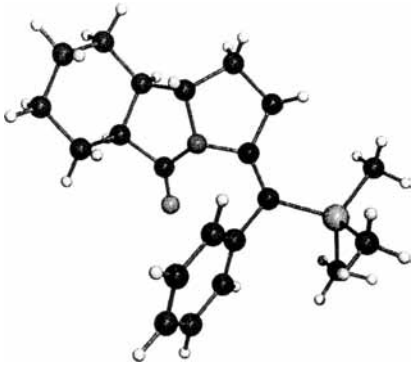


Fig. 2. Crystal structure of compound **41**.

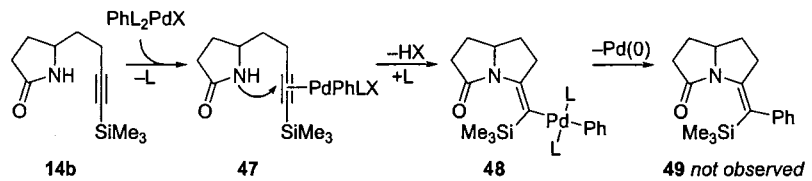
product **36** was obtained in a considerable yield of 29%. Me_3Si-protection of the acetylene (**17b**) blocked the Sonogashira reaction and a similar mixture of double bond isomers **37** and **38** was obtained, but due to the required long reaction time desilylation occurred to some extent, leading to products **34** and **35**.

If the cyclohexyl group and the acetylenic tether are *trans* with respect to each other, the stereoselectivity is restored: the phenyl group was introduced exclusively *cis* with respect to the nitrogen at the double bond when the *trans* substituted bicyclic lactams **20a** and **20b** were subjected to the cyclization conditions to give **39** and **41**, respectively. However, the unprotected alkyne **20a** gave rise to the formation of a considerable amount of the uncyclized byproduct **40**, whereas in the case of the Me_3Si-protected analogue **20b** a small amount of desilylated product **39** was also formed.

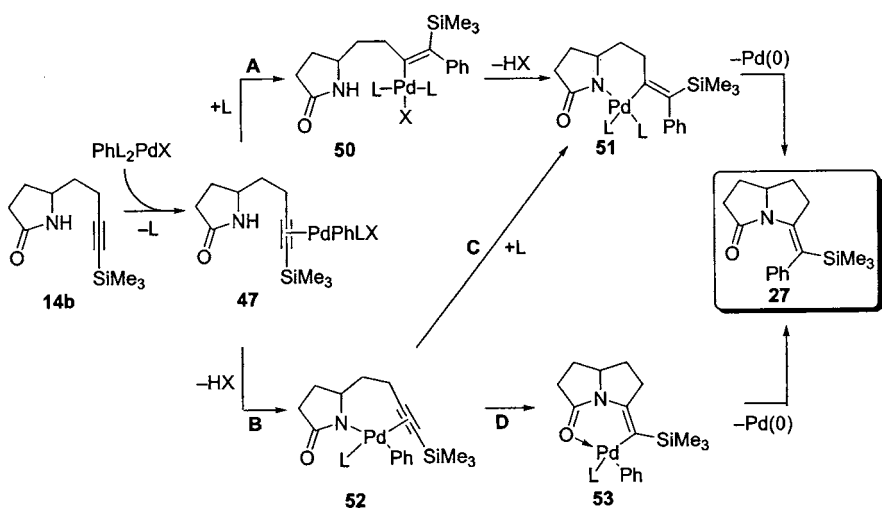
The enantiopure alkyne **23** reacted in the same way as the racemate (cf. entry 1, Table 1), giving the bicyclic enamide **42** in 40% yield, with concomitant formation of non cyclized coupling product **43** (entry 6). The enantiopure oxazolidinone **24** gave rise to the formation of **44** in 60% yield, but the Sonogashira type product was not formed in this reaction (entry 7). Moreover, oxazolidinone **45** — prepared from 5-methoxy-2-oxazolidone and 4-trimethylsilylbut-3-ynylmagnesium bromide — afforded bicyclic product **46**, illustrating that acetylenic oxazolidinones behave similarly under these cyclization conditions (entry 8).

4. Structural proof

Proof for the highly unusual stereochemistry of the enamide double bond for this type of reactions was obtained by NOE-difference spectroscopy. A NOE-enhancement of the signals of the allylic protons (2.6 and 3.6%) was observed upon irradiation of the vinylic proton of enamide **25** which clearly established the (*Z*)-configuration of the double bond. The signal of the aromatic protons in the *ortho*-position showed a NOE-enhancement of 10.1%. Similar proof was obtained in the case of the tricyclic enamides **37** and **39**. Irradiation of the signal of the Me_3Si-protons of **37** caused a small



Scheme 4.



Scheme 5.

but reproducible NOE-enhancement (0.4%) of the signal of the allylic protons. A stronger effect was observed in the case of **39** as illustrated in Fig. 1. The double bond geometry of all other compounds was not explicitly proven, but assigned via comparison of ^{1}H- and ^{13}C-NMR data.

The most convincing evidence for the double bond geometry, however, was obtained by an X-ray crystal structure determination of the tricyclic product **41**[7]. It unambiguously proved the *cis* orientation of the phenyl group with respect to the lactam nitrogen (Fig. 2).

5. Mechanistic considerations

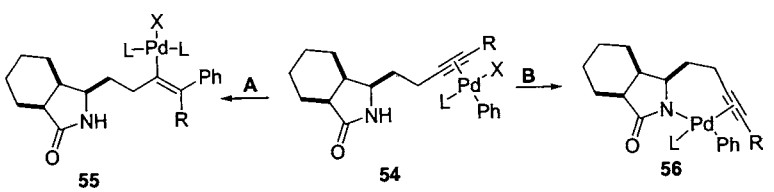
Because the isolated products have the opposite double bond geometry of what is normally observed, the mechanistic details have to be different than in the case of acyclic nucleophiles. The mechanism for the 'normal' mode of cyclization as is most frequently found in literature [4,5], predicts the wrong stereochemistry (Scheme 4). Oxidative addition of palladium(0) in the phenyl iodide bond affords a phenylpalladium(II) intermediate which can coordinate to the triple bond to give π-complex **47**. The acetylene is now sufficiently activated by the metal to undergo nucleophilic attack by the tethered nitrogen. The attack of the nucleophile should occur *trans* leading to bisorganopalladium intermediate **48**. Reductive elimination of palladium(0) regenerates the catalyst and affords product **49**.

In the present case however, the nucleophile was attached to the same side of the triple bond as the phenyl group, implying that the nitrogen–carbon bond formation takes place within the coordination sphere of the palladium. In other words, there has to be an intermediate in the reaction mechanism in which the palladium is coordinated to the amide before the nitrogen–carbon bond is formed [18].

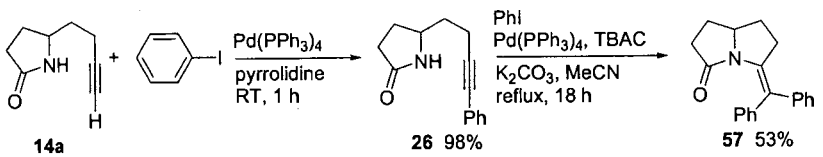
This leaves several possibilities for the order of steps. However, it is most likely that π-complex **47** is formed at the start of the catalytic cycle (Scheme 5). This π-complex has two possible modes of reaction. One might consider a carbopalladation reaction (A), which results in the formation the *cis* adduct **50**. With the stereochemistry fixed at the double bond, the nitrogen nucleophile can coordinate to the palladium giving the six-membered ring chelate **51**, which after reductive elimination affords the observed product **27**. Although a reductive elimination of vinylpalladium amide complexes is not precedented in literature, the corresponding process of arylpalladium amide complexes has recently been described [19].

Secondly, **47** might undergo an intramolecular ligand exchange reaction to give chelate **52** (B). This intermediate has also two plausible modes of reaction; a carbopalladation (C) would afford the already discussed six-membered palladacycle **51**, but is also possible that the nitrogen ligand migrates instead of the phenyl group (D) [20][8]. This would lead to the bisorganopalladium intermediate **53**. This process seems feasible as the lactam carbonyl might assist this migration by stabilizing the proposed intermediate **53**. Reductive elimination yields the observed product and the palladium(0) catalyst.

Although it is difficult to differentiate between path A or B, path B seems the most likely route. This is based on the results obtained with cyclization precursors **17a** and **17b**, which are the only examples in which a mixture of double bond isomers was obtained. After the initial formation of π-complex **54** (Scheme 6), path A should not be affected by steric crowding at the lactam because the acetylenic side chain can rotate away from the steric bulk to give **55**. Therefore, if path A would be the reaction pathway, **17a** and **17b** should lead to the exclusive *cis* introduction of the phenyl



Scheme 6.



Scheme 7.

[7] See Section 8.

[8] Similar insertions of acetylenes into palladium-halide bonds instead of palladium–nitrogen bonds have been reported.

group and the nitrogen nucleophile, which was not the case. On the other hand, path B would lead to **56**, with the palladium in close proximity of the cyclohexyl group. Due to the shape of this chelate the palladium and the coordinated ligands are expected to experience a considerable steric repulsion by the proximal bulk, destabilizing this intermediate. This opens the way for a competitive reaction pathway such as direct nucleophilic attack of the amide onto the triple bond of **54** (*cf* **47**→**48**, Scheme 4), leading to the formation of *trans*-enamides.

In case of the terminal acetylenes there is an additional possibility. In principle, the isolated byproduct **26** in the cyclization of **14a** to **25** can be an intermediate in the reaction mechanism, since it is known that acetylenic amides can be cyclized under the influence of base to give (*Z*)-enamides [21]. In order to investigate this possibility, **26** was prepared separately according to a modified Sonogashira procedure [22] from **14a** and subjected to our standard cyclization conditions (Scheme 7). In this case **25** was not formed, but the only isolated product was the tetrasubstituted enamide **57**, indicating that **26** is not an intermediate in the formation of **25**.

Despite the fact that the exact details of the mechanism remain unclear, the products can be explained by the mechanism presented in Scheme 5, most likely via path B.

6. Conclusions

The preparation of ω-homopropargyl substituted lactams was described by means of an efficient one-pot reductive alkylation procedure of unprotected imides. In the case of bicyclic imides, this process occurred stereoselectively to give exclusively the *cis*-addition products. If the order of steps was reversed (i.e. reduction before alkylation) the *trans* isomers were obtained selectively. Enantiopure acetylenic lactams and oxazolidinones could be prepared using highly functionalized organozinc reagents that were also used for the preparation of the isomeric allenes [8b]. The palladium catalyzed cyclizations of these acetylenic lactams with a variety of organic halides proceeded in generally good yield. Due to coordination of the lactam nitrogen to the palladium, the organic part of the halide and the nitrogen nucleophile were introduced *cis* with respect to each other.

7. Experimental

All reactions were carried out under an inert atmosphere of dry nitrogen. Infrared (IR) spectra were obtained from $CHCl_3$ solutions or neat, using a Perkin–Elmer 298 spectrophotometer or a Bruker IFS 28 FT-spectrophotometer and wavelengths (ν) are reported in cm^{-1}. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were determined in $CDCl_3$ using a Bruker AC 200 (200 MHz), a Bruker ARX 400 (400 MHz) or a Varian Inova (500 MHz) spectrometer. The latter machines were also used for ^{13}C-NMR (APT) spectra (100 MHz and 125 MHz, respectively) in $CDCl_3$. Chemical shifts (δ) are given in ppm downfield from tetramethylsilane. Mass spectra and accurate mass measurements were carried out using a JEOL JMS-SX/SX 102 A Tandem Mass Spectrometer, a Varian NIAT 711 or a VG Micromass ZAB-HFQQ instrument. Elemental analyses were performed by Dornis u. Kolbe Mikroanalytisches Laboratorium, Mülheim an der Ruhr, Germany. Optical rotations were measured with a Perkin–Elmer 241 polarimeter in a 1-dm cell in the indicated solvent. R_f values were obtained by using thin layer chromatography (TLC) on silica gel-coated plastic sheets (Merck silica gel 60 F_{254}) with the indicated solvent (mixture). Flash column chromatography was performed with Merck silica gel 60 (230–400 mesh). Melting and boiling points are uncorrected. Dry THF and Et_2O were distilled from sodium benzophenone ketyl prior to use. Dry DMF, CH_2Cl_2, and MeCN were distilled from CaH_2 and stored over MS 4 Å under a dry nitrogen atmosphere. All commercially available reagents were used as received, unless indicated otherwise.

7.1. 5-(But-3-ynyl)pyrrolidin-2-one (14a)

A solution of **14b** (208 mg, 1.0 mmol) in THF (2 ml) was cooled to 0°C and a 1.0 M solution (THF) of TBAF was added (1.2 ml, 1.2 mmol). The reaction mixture was stirred at 0°C for 30 min followed by concentration in vacuo. The residue was dissolved in EtOAc (25 ml) and washed with water (3 × 15 ml) and brine (15 ml). Drying (Na_2SO_4), concentration and flash chromatography (5% MeOH in EtOAc) gave **14a** (134 mg, 0.98 mmol, 98%) as a white solid; R_f 0.2 (EtOAc); m.p. 94–95°C (EtOAc/PE); IR ($CHCl_3$) 3431, 3016, 1687, 1421; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.50 (br s, 1H), 3.83–3.76 (m, 1H), 2.38–2.34 (m, 5H), 2.00 (t, $J = 2.7$ Hz, 1H), 1.80–1.67 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 178.5, 83.0, 69.2, 53.6, 34.9, 30.0, 26.9, 15.2; Anal. Calc. for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.45; H, 8.00; N, 10.08%.

7.2. 5-(4-(Trimethylsilyl)but-3-ynyl)pyrrolidin-2-one (14b)

A solution of succinimide (2.97 g, 30 mmol) in THF (100 ml) was cooled to 0°C, and MeMgBr (10.0 ml, 3.0 M in THF, 30 mmol) was added dropwise. After the mixture was stirred at room temperature (r.t.) for 1 h,

it was recooled to 0°C and a solution of the Grignard reagent prepared from 1-bromo-4-trimethylsilyl-3-butyne (60 ml, 1 M in THF, 60 mmol) was slowly added. The suspension was stirred at r.t. and after TLC (EtOAc) indicated full conversion of starting material, $NaBH_3CN$ (1.89 g, 30 mmol) and a few drops of methylorange were added. The mixture was acidified with acetic acid until the indicator turned from yellow to pink and stirred for another 45 min. Neutralization (5% aq. NaOH) and removal of the solvents in vacuo, gave a solid residue that was dissolved into a saturated aqueous solution of $NaHCO_3$ (200 ml) and extracted with EtOAc (3×150 ml). Washing of the combined extracts with water (150 ml) and brine (150 ml), followed by drying (Na_2SO_4) and concentration in vacuo gave the crude product, which after silicagel column chromatography gave **14b** (3.89 g, 18.9 mmol, 62%) as a white solid; R_f 0.4 (EtOAc/Acetone 1:1); m.p. 96–97°C (EtOAc/PE); IR ($CHCl_3$) 3428, 2962, 2173, 1690; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.89 (br s, 1H), 3.82–3.72 (m, 1H), 2.75–2.25 (m, 5H), 1.80–1.68 (m, 3H), 0.16 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 178.2, 105.6, 85.9, 53.9, 35.1, 30.0, 27.1, 16.8, 0.0; Anal. Calc. for $C_{11}H_{19}NOSi$: C, 63.11; H, 9.15; N, 6.69. Found: C, 62.73; H, 8.99; N, 6.62%.

7.3. 5-(Pent-3-ynyl)pyrrolidin-2-one (**14c**)

Using the same procedure as for the preparation of **14b**, succinimide (991 mg, 10 mmol) was deprotonated with EtMgBr (10 ml, 1.0 M in THF, 10 mmol) and subsequently reacted with the Grignard reagent derived from 1-bromopent-3-yne (20 ml, 1 M in THF, 20 mmol). Reduction with $NaBH_3CN$ (628 mg, 10 mmol) at pH 3 (AcOH) and workup gave after chromatography **14c** (874 mg, 5.78 mmol, 58%) as a colorless solid; R_f 0.4 (EtOAc/acetone = 1/1); m.p. 84–85°C; IR (neat) 3230, 2920, 1684; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.46 (br s, 1H), 3.68–3.63 (m, 1H), 2.22–2.06 (m, 5H), 1.63 (t, $J = 2.5$ Hz, 3H), 1.61–1.48 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 178.7, 77.5, 76.2, 53.7, 35.4, 30.0, 26.8, 15.4, 3.17; HRMS (EI) Calc. for $C_9H_{13}NO_2$ 151.0997. Found 151.0989.

7.4. (3R*,3aR*,7aS*)-3-(But-3-ynyl)octahydroisoindol-1-one (**17a**)

Using the same procedure as for the preparation of **14a**, **17b** (659 mg, 2.5 mmol) was deprotected with TBAF, to give after chromatography (EtOAc/PE 4:1) the terminal acetylene **17a** (467 mg, 2.44 mmol, 97%) as a white solid; R_f 0.2 (EtOAc/PE 2:1); m.p. 163–165°C (EtOAc/PE); IR ($CHCl_3$) 3307, 2937, 2861, 1695; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.36 (br s, 1H), 3.66 (td, $J = 6.8$, 4.9 Hz, 1H), 2.48 (br t, $J = 5.9$ Hz, 1H), 2.37–2.20 (m, 3H), 2.16 (br d, $J = 13.3$ Hz, 1H), 2.00 (t, $J = 2.7$ Hz, 1H), 1.72–1.67 (m, 3H), 1.60–1.52 (br m, 2H), 1.46–1.37 (m, 1H), 1.26–1.03 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 178.7, 83.2, 69.3, 55.7, 42.7, 38.6, 28.0, 23.8, 22.8, 22.5, 22.4, 15.9; Anal. Calc. for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.20; H, 8.94; N, 7.21%.

7.5. (3R*,3aR*,7aS*)-3-(4-(Trimethylsilyl)but-3-ynyl)octahydroisoindol-1-one (**17b**)

Using the same procedure as for the preparation of **13b**, hexahydro-isoindole-1,3-dione (**21**) (2.08 g, 13.7 mmol) was deprotonated with MeMgBr and subsequently reacted with the Grignard reagent derived from 1-bromopent-3-yne (20 ml, 1 M in THF, 20 mmol). Reduction with $NaBH_3CN$ (860 mg, 13.7 mmol) at pH 3 (AcOH) and work up gave after chromatography **17b** (2.26 g, 8.6 mmol, 63%) as a white solid; R_f 0.3 (EtOAc/PE 1:1); m.p. 128–129°C (PE); IR ($CHCl_3$) 3431, 3004, 2937, 2860, 2172, 1692; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.57 (br s, 1H), 3.61 (br q, $J = 6.2$ Hz, 1H), 2.48 (br t, $J = 5.8$ Hz, 1H), 2.34–2.23 (m, 3H), 2.15 (br d, $J = 13.8$ Hz, 1H), 1.70–1.65 (m, 3H), 1.60–1.52 (br m, 2H), 1.44–1.35 (m, 1H), 1.20–1.01 (m, 3H), 0.12 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 178.4, 105.8, 85.7, 56.0, 42.7, 38.7, 28.0, 23.8, 22.8, 22.5, 22.4, 17.4, –0.1; Anal. Calc. for $C_{15}H_{25}NOSi$: C, 68.38; H, 9.56; N, 5.32. Found: C, 68.27; H, 9.43; N, 5.21%.

7.6. (3S*,3aR*,7aS*)-3-(But-3-ynyl)octahydroisoindol-1-one (**20a**)

The Me_4Si-protected acetylene **20b** (920 mg, 3.5 mmol) was treated with TBAF, following the same procedure as described for the preparation of **14a**, to give after work up and chromatography **20a** (659 mg, 3.4 mmol, 98%) as a white solid; R_f 0.2 (EtOAc/PE 3:1); m.p. 120–121°C (EtOAc/PE); IR ($CHCl_3$) 3433, 3006, 2936, 2858, 1691; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.26 (br s, 1H), 3.30–3.26 (m, 1H), 2.51 (q, $J = 6.2$ Hz, 1H), 2.37–2.26 (m, 2H), 2.10–2.04 (m, 1H), 1.97 (t, $J = 2.6$ Hz, 1H) 1.89–1.82 (m, 1H), 1.76–1.16 (m, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 179.1, 83.0, 69.3, 57.0, 39.7, 39.4, 32.2, 27.4, 23.3, 23.3, 23.0, 15.8; Anal. Calc. for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 74.91; H, 8.94; N, 7.09%.

7.7. (3S*,3aR*,7aS*)-3-(4-(Trimethylsilyl)but-3-ynyl)-octahydroisoindol-1-one (**20b**)

To a solution of 3-ethoxy-octahydro-isoindol-1-one (**18**) (1.83 g, 10 mmol) in THF (100 ml) was added a 1 M solution of the Grignard reagent derived from 1-bromo-4-trimethylsilylbut-3-yne in THF (25 ml, 25 mmol) and the reaction mixture was refluxed for 5 h, after which time all starting material was consumed

(TLC). A saturated aqueous solution of NH_4Cl (100 ml) was added, and the aqueous layer was extracted with EtOAc (2 × 50 ml). The combined organic layers were washed with brine (2 × 75 ml), dried (Na_2SO_4) and concentrated in vacuo. Purification by chromatography afforded **20b** (1.55 g, 5.9 mmol, 59%) as a white solid; R_f 0.3 (EtOAc/PE 3:1); m.p. 81–83°C (PE); IR ($CHCl_3$) 3433, 3006, 2936, 2172, 1691; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.78 (br s, 1H), 3.33–3.29 (m, 1H), 2.49 (q, $J = 6.2$ Hz, 1H), 2.32 (t, $J = 6.9$ Hz, 2H), 2.17–2.11 (m, 1H), 1.94–1.87 (m, 1H), 1.78–1.26 (m, 9H), 0.16 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 178.8, 105.6, 85.9, 57.1, 39.7, 39.3, 32.2, 27.4, 23.4, 23.3, 23.1, 17.2, –0.1; Anal. Calc. for $C_{15}H_{25}NOSi$: C, 68.38; H, 9.56; N, 5.32. Found: C, 68.17; H, 9.60; N, 5.29%.

7.8. (5R)-5-(But-3-ynyl)pyrrolidin-2-one (23)

A solution of the organozinc reagent derived from (*S*)-5-iodomethylpyrrolidin-2-one (1.13 g, 5 mmol) in DMF (5 ml) [8,14], was added to CuBrDMS (5 mol%) in THF (15 ml) at −78°C. The mixture was briefly stirred at 0°C (10 min), cooled to −78°C after which bromoallene [13] (1.1 equivalents) was added by syringe. The mixture was stirred at −30°C for 4 h and then allowed to reach ambient temperature overnight. After the addition of saturated aqueous NH_4Cl (100 ml), the aqueous layer was extracted with EtOAc (3 × 50 ml). The combined organic layers were dried (Na_2SO_4), concentrated and purified by flash column chromatography (2.5% MeOH in EtOAc) to give **23** (357 mg, 2.6 mmol, 52%) as a white solid; m.p. 50–51°C; $[\alpha]_D = +33.6$ (*c* 1.1, $CHCl_3$); All other data identical to those of **14a**.

7.9. (4R)-4-(3-Butynyl)-1,3-oxazolidin-2-one (24)

A solution of the organozinc reagent derived from (4*S*)-4-(iodomethyl)-1,3-oxazolidin-2-one (750 mg, 3.3 mmol) in THF (5 ml) [15] was added to a mixture of CuBrDMS (5 mol%) and bromoallene [13] (1.1 equivalents) in THF (15 ml) at −30°C. The reaction mixture was stirred at −30°C for 4 h and then allowed to reach ambient temperature overnight. After the addition of saturated aqueous NH_4Cl (100 ml), the aqueous layer was extracted with EtOAc (3 × 50 ml). The combined organic layers were dried (Na_2SO_4), concentrated and purified by flash column chromatography (EtOAc/PE 3:1) to give **36** (135 mg, 0.97 mmol, 29%) as a light yellow oil, contaminated with a small amount (< 5%) of the isomeric terminal allene. **24**: R_f 0.25 (EtOAc/PE 3:1); $[\alpha]_D$ +34.1 (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) 1753, 1690; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.72 (br s, 1H), 4.51 (t, $J = 7.8$ Hz, 1H), 4.14–4.00 (m, 2H), 2.30 (td, $J = 6.9$, 2.6 Hz, 2H), 2.00 (t, $J = 2.6$ Hz, 1H), 1.85–1.73 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.9, 82.2, 69.9, 69.8, 51.8, 33.5, 14.9; HRMS (EI) Calc. for $C_7H_9NO_2$: 139.0633. Found 139.0635.

7.10. (5Z)-5-Benzylidenehexahydropyrrolidin-2-one (25)

To a mixture of K_2CO_3 (553 mg, 4.0 mmol), Bu_4NCl (416 mg, 1.5 mmol) was added benzene (5 ml) and the solvent was removed in vacuo. After this evaporation was repeated twice, $Pd(PPh_3)_4$ (115 mg, 0.1 mmol) was added and the flask was purged with argon. MeCN was added (20 ml) followed by PhI (816 mg, 4.0 mmol) and **14a** (140 mg, 1.02 mmol) in MeCN (1 ml), the resulting yellow mixture was refluxed for 2–3 h (TLC showed complete conversion). The mixture was cooled, diluted with water (50 ml) and extracted with ether (3 × 50 ml). The combined ether extracts were washed with water (50 ml) and brine (50 ml), dried (Na_2SO_4) and concentrated. Flash chromatography (EtOAc/PE 1:2) afforded **25** (88 mg, 0.41 mmol, 40%) as a white solid, along with **26** (35 mg, 0.16 mmol, 16%) as a light yellow solid. **25**: R_f 0.7 (EtOAc); m.p. 130–131°C; IR ($CHCl_3$) 3006, 1704, 1655; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.27–7.21 (m, 4H), 7.14–7.03 (m, 1H), 5.94 (br s, 1H), 4.29 (dq, $J = 9.5$, 6.8 Hz, 1H), 2.91 (ddt, $J = 16.5$, 9.7, 2.1 Hz, 1H), 2.82–2.73 (m, 2H), 2.49 (ddd, $J = 16.9$, 9.6, 3.1 Hz, 1H), 2.45–2.36 (m, 1H), 2.17–2.09 (m, 1H), 1.90–1.80 (m, 1H), 1.48 (dq, $J = 12.2$, 9.8 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.8, 137.0, 133.7, 128.1, 127.4, 125.9, 111.8, 63.7, 34.2, 33.4, 30.1, 25.9; Anal. Calc. for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.45; H, 7.10; N, 6.44%.

7.11. 5-(4-Phenylbut-3-ynyl)pyrrolidin-2-one (26)

Obtained as a by-product in the cyclization of **14a**, but also prepared separately: A solution of 5-but-3-ynylpyrrolidin-2-one (**14a**) (446 mg, 3.37 mmol) in pyrrolidine (3 ml) was degassed by bubbling trough with N_2 for 15 min. Iodobenzene (453 ml, 4.04 mmol) was added, followed by $Pd(PPh_3)_4$ (97 mg, 0.08 mmol) and the resulting solution was stirred at r.t. for 1.5 h. The solvent was removed in vacuo and the residue taken up in EtOAc (75 ml). Washing with dilute HCl (30 ml, 0.5 M) and brine (2 × 30 ml) followed by drying (Na_2SO_4) and chromatography gave **26** (702 mg, 3.29 mmol, 98%) as a white solid. R_f 0.4 (EtOAc/Acetone 1:1); IR (neat) 3431, 3015, 1691; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.52–7.08 (m, 5H), 6.8 (br s, 1H), 3.83–3.77 (m, 1H), 2.50 (t, $J = 6.8$ Hz, 2H), 2.41–2.24 (m, 3H), 1.83–1.71 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 178.1, 131.4, 128.2, 127.2, 123.3, 88.3, 81.5, 53.7, 35.3, 29.9, 27.1, 16.3; Anal. Calc. for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.49; H, 7.12; N, 6.59%.

7.12. (5E)-5-(Phenyl(trimethylsilyl)methylene)-hexahydropyrrolizin-3-one (27)

Following the same procedure as for the preparation of **25**, **14b** (312 mg, 1.50 mmol) in MeCN (0.05 M) was treated with PhI (4 equiv) in the presence of TBAC (1.5 equivalents), K_2CO_3 and $Pd(PPh_3)_4$ (0.1 equivalents). After reflux for 3 h, work up and chromatography gave **27** (283 mg, 1.0 mmol, 64%) as an off white solid; R_f 0.3 (EtOAc/PE 1:1), m.p. 92–93°C (PE); IR ($CHCl_3$) 3005, 1670, 1609; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.21 (t, $J = 7.6$ Hz, 2H), 7.08 (br t, 7.4 Hz, 1H), 6.98 (br d, $J = 7.5$ Hz, 2H), 4.06 (dq, $J = 9.6$, 6.8 Hz, 1H), 2.88 (ddd, $J = 16.5$, 10.0, 2.4 Hz, 1H), 2.72 (ddd, $J = 16.5$, 9.7, 8.2 Hz, 1H), 2.46 (dt, $J = 17.0$, 10.3 Hz, 1H), 2.27–2.19 (m, 2H), 2.18–2.11 (m, 1H), 1.73–1.63 (m, 1H), 1.47 (dq, $J = 12.2$, 9.9 Hz, 1H), 0.09 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.3, 144.0, 141.2, 128.4, 127.1, 125.0, 124.6, 62.1, 34.4, 32.4, 30.6, 25.8, 0.2; Anal. Calc. for $C_{17}H_{23}NOSi$: C, 71.53; H, 8.12; N, 4.91. Found: C, 71.45; H, 8.20; N, 4.84%.

7.13. (5E)-5-((4-Nitrophenyl)(trimethylsilyl)-methylene)hexahydropyrrolizin-3-one (28)

Following the same procedure as for the preparation of **25**, **14b** (209 mg, 1.0 mmol) in MeCN (0.05 M) was treated with 1-iodo-4-nitro-benzene (4 equiv) in the presence of TBAC (1.5 equivalents), K_2CO_3 and $Pd(PPh_3)_4$ (0.1 equivalents). After reflux for 3 h, work up and chromatography gave **28** (244 mg, 0.74 mmol, 74%) as a light yellow solid; R_f 0.4 (EtOAc/PE 1:2); m.p. 139–141°C (EtOAc/PE); IR (neat) 2953, 2242, 1712, 1589, 1506; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.07 (d, $J = 8.8$ Hz, 2H), 7.12 (d, $J = 8.8$ Hz, 2H), 4.13 (dq, $J = 9.9$, 6.8 Hz, 1H), 2.91 (ddd, $J = 16.8$, 9.8, 2.0 Hz, 1H), 2.76 (ddd, $J = 16.8$, 10.3, 8.1 Hz, 1H), 2.49 (dt, $J = 17.1$, 10.3 Hz, 1H), 2.32–2.16 (m, 3H), 1.77–1.66 (m, 1H), 1.55–1.41 (dq, $J = 12.2$, 10.1 Hz, 1H), 0.11 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.7, 152.4, 145.2, 142.6, 129.0, 122.7, 122.5, 62.5, 34.6, 32.9, 30.7, 25.7, 0.2; HRMS (EI) Calc. for $C_{17}H_{22}N_2O_3Si$ 330.1400. Found 330.1410.

7.14. (5E)-5-(2-Thienyl(trimethylsilyl)methylene)-hexahydropyrrolizin-3-one (30)

Following the same procedure as for the preparation of **25**, **14b** (209 mg, 1.0 mmol) in MeCN (0.05 M) was treated with 2-bromothiophene (four equivalents) in the presence of TBAC (1.5 equivalents), K_2CO_3 and $Pd(PPh_3)_4$ (0.1 equivalents). After reflux for 2 h, work up and chromatography gave **30** (226 mg, 0.78 mmol, 78%) as a white solid R_f 0.3 (EtOAc/PE 1: 2); m.p. 101–102°C (EtOAc/PE); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.05 (dd, $J = 5.1$, 1.0 Hz, 1H), 6.91 (dd, $J = 5.1$, 3.5 Hz, 1H), 6.68 (dd, $J = 3.5$, 1.0 Hz, 1H), 4.11 (dq, $J = 9.7$, 6.9 Hz, 1H), 2.88 (ddd, $J = 16.8$, 10.0, 2.2 Hz, 1H), 2.72 (ddd, $J = 16.8$, 9.9, 8.2 Hz, 1H), 2.57 (dt, $J = 16.6$, 10.3 Hz, 1H), 2.34–2.24 (m, 2H), 2.14 (m, $J = 12.2$, 8.2, 6.3, 2.2 Hz, 1H), 1.70 (m, $J = 12.9$, 11.1, 9.6, 7.2 Hz, 1H), 1.46 (dq, $J = 12.2$, 9.9 Hz, 1H), 0.16 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.5, 144.8, 144.1, 126.3, 124.6, 122.2, 116.2, 62.3, 34.8, 33.0, 30.5, 26.1, 0.2.

7.15. (5E)-5-[(6-Chloro-3-pyridiny)trimethylsilyl-methylene)hexahydropyrrolizin-3-one (31)

Following the same procedure as for the preparation of **25**, **14b** (65 mg, 0.31 mmol) in MeCN (0.05 M) was treated with 2-chloro-5-iodo-pyridine (four equivalents) in the presence of TBAC (1.5 equivalents), K_2CO_3 and $Pd(PPh_3)_4$ (0.1 equivalents). After work up and chromatography **31** (34 mg, 0.11 mmol, 34%) was obtained as a light yellow solid. Unreacted **14b** (32 mg, 50%) could be recovered by continued elution (EtOAc). **31**; R_f 0.3 (EtOAc/PE 1: 1); m.p. 101–106°C (Et_2O/PE); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.89 (d, $J = 2.3$ Hz, 1H), 7.36 (dd, $J = 2.3$, 8.4 Hz, 1H), 7.18 (d, $J = 8.4$, 1H), 4.13–4.03 (m, 1H), 2.88 (ddd, $J = 2.3$, 10.0, 16.8 Hz, 1H), 2.71 (ddd, $J = 8.2$, 9.8, 16.8 Hz, 1H), 2.50 (dt, $J = 17.2$, 10.3 Hz, 1H), 2.30–2.23 (m, 2H), 2.16 (m, $J = 2.3$, 6.1, 8.4, 12.2 Hz, 1H), 1.78–1.69 (m, 1H), 1.54–1.41 (dq, $J = 12.2$, 9.9 Hz, 1H), 0.10 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.7, 148.1, 147.4, 143.7, 139.5, 139.0, 122.7, 119.6, 62.2, 34.3, 32.4, 30.5, 25.7, −0.1; HRMS (EI) Calc. for $C_{16}H_{21}ClN_2OSi$ 320.1111. Found 320.1112.

7.16. (5E)-5-(3-Methyl-1-(trimethylsilyl)but-2-enylidene)hexahydropyrrolizin-3-one (32)

Following the same procedure as for the preparation of **25**, **14b** (105 mg, 0.5 mmol) in MeCN (0.05 M) was treated with 1-bromo-2-methyl-propene (four equivalents) in the presence of TBAC (1.5 equivalents), K_2CO_3 and $Pd(PPh_3)_4$ (0.1 equivalents). After work-up and chromatography **32** (78 mg, 0.34 mmol, 69%) was obtained as a colorless oil; R_f 0.3 (EtOAc/PE 1:2); IR (neat) 2965, 1713, 1608; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.74 (br s, 1H), 4.00 (dq, $J = 9.5$, 7.0 Hz, 1H), 2.77 (ddt, $J = 16.4$, 10.3, 2.4 Hz, 1H), 2.66 (ddd, $J = 16.4$, 10.9, 9.7 Hz, 1H), 2.59–2.50 (m, 1H), 2.37 (ddd, $J = 16.4$, 9.4, 2.2 Hz, 1H), 2.29–2.21 (m, 1H), 2.05 (m, $J = 12.2$, 8.6, 6.1, 2.4 Hz, 1H), 1.73–1.63 (m, 1H), 1.65 (d, $J = 1.1$ Hz, 3H), 1.47–1.36 (dq, $J = 12.2$, 9.8 Hz, 1H), 1.31 (d, $J = 0.9$ Hz, 3H), 0.06 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.7, 139.2, 127.1, 126.4, 120.6, 61.5, 35.1, 31.5, 30.3, 26.4, 24.8, 18.5, −0.6; HRMS (EI) Calc. for $C_{15}H_{25}NOSi$ 263.1705. Found 263.1699.

7.17. (5Z)-5-(1-Phenylethylidene)hexahydropyrrolizin-3-one (33)

Following the same procedure as for the preparation of **25**, **14c** (151 mg, 1.0 mmol) in MeCN (0.05 M) was treated with PhI (four equiv) in the presence of TBAC (1.5 equivalents), K_2CO_3 and $Pd(PPh_3)_4$ (0.1 equivalents). After work-up and chromatography **33** (151 mg, 0.66 mmol, 66%) was obtained as a light yellow oil; R_f 0.3 (EtOAc/PE 1:1); IR ($CHCl_3$) 3002, 1706; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.31–7.25 (m, 4H), 7.16–7.12 (m, 1H), 4.17 (dq, $J = 9.7$, 6.8 Hz, 1H), 2.82 (br dd, $J = 16.6$, 10.3 Hz, 1H), 2.72–2.64 (m, 1H), 2.61–2.51 (m, 1H), 2.36–2.28 (m, 2H), 2.21–2.14 (m, 1H), 2.05 (s, 3H), 1.79–1.69 (m, 1H), 1.47 (dq, $J = 12.2$, 10.0 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.7, 143.4, 130.2, 127.6, 126.9, 125.8, 119.6, 62.7, 34.0, 30.9, 30.6, 25.7, 20.1; HRMS (EI) Calc. for $C_{15}H_{17}NO$ 227.1310. Found 227.1321.

7.18. (3Z,5aS*,9aR*,9bR*)-3-Benzylidenedecahydropyrrolo[2,1-a]isoindol-5-one (34)

Following the same procedure as for the preparation of **25**, **17a** (96 mg, 0.5 mmol) in MeCN (0.05 M) was treated with PhI (four equivalents) in the presence of TBAC (1.5 equivalents), K_2CO_3 and $Pd(PPh_3)_4$ (0.1 equivalents). After work-up and chromatography (EtOAc/PE 1:2) a mixture of **34** and **35** (**34**/**35** = 1:0.13, 56 mg, 0.21 mmol, 42%) as a yellow solid. Continued elution with EtOAc afforded the non-cyclized coupling product **36** (39 mg, 29%, 0.15 mmol). Fractional crystallization from dichloromethane/hexane afforded an analytically pure sample of **34** as off white crystals; R_f 0.3 (EtOAc/PE 1:2); m.p. 130–131°C (CH_2Cl_2/hexane); IR ($CHCl_3$) 1704; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.23 (br t, $J = 7.3$ Hz, 2H), 7.16 (br d, $J = 7.1$ Hz, 2H), 7.11 (br t, $J = 7.2$ Hz, 1H), 5.88 (br s, 1H), 4.41–4.36 (ddd, $J = 8.2$, 6.4, 5.4Hz, 1H), 2.92 (br t, $J = 5.7$ Hz, 1H), 2.85–2.67 (m, 2H), 2.44–2.37 (m, 1H), 2.14 (br d, $J = 12$ Hz, 1H), 1.93–1.83 (m, 2H), 1.68 (br d, $J = 10$ Hz, 2H), 1.52–0.93 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.6, 137.1, 133.6, 128.1, 127.3, 125.7, 110.3, 64.7, 46.1, 39.1, 33.5, 23.9, 23.2, 22.7, 22.2, 19.8; Anal. Calc. for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.32; H, 7.87; N, 5.14%.

7.19. (3E,5aS*,9aR*,9bR*)-3-Benzylidenedecahydropyrrolo[2,1-a]isoindol-5-one (35)

Formed as a by-product in the cyclization of **17a** to **48**. Crystallization from EtOAc/hexane afforded an analytically pure sample of **35** as off white crystals; R_f 0.3 (EtOAc/PE 1:2); m.p. 168–171°C (EtOAc/hexane); IR ($CHCl_3$) 1706; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.31–7.26 (m, 5H), 7.13 (br t, $J = 6.7$ Hz, 1H), 4.20 (dt, $J = 10.9$, 5.4 Hz, 1H), 3.11 (dd, $J = 16.0$, 7.8 Hz, 1H), 3.03–2.93 (m, 2H), 2.37–2.30 (m, 1H), 2.25 (br d, $J = 15.9$ Hz, 1H), 1.84–1.71 (m, 3H), 1.63–1.54 (br m, 2H), 1.48–1.40 (m, 1H), 1.26–1.07 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.7, 137.8, 136.8, 128.1, 127.7, 125.3, 108.4, 64.1, 48.3, 37.0, 33.1, 23.8, 23.5, 22.9, 22.6, 20.1.

7.20. (3R*,3aR*,7aS*)-3-(4-(Phenyl)but-3-ynyl)-octahydro-isoindol-1-one (36)

Formed as a by-product in the cyclization of **17a** to **34**. Chromatography (EtOAc) afforded **36** as a light yellow solid; R_f 0.3 (EtOAc/PE 3:1); IR ($CHCl_3$) 3415, 1696; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.40–7.38 (m, 2H), 7.30–7.27 (m, 3H), 6.45 (br s, 1H), 3.76–3.72 (m, 1H), 2.59–2.44 (m, 3H), 2.38 (m, 1H), 2.19 (br d, $J = 13.1$ Hz, 1H), 1.78 (q, $J = 7.0$ Hz, 2H), 1.68 (br d, $J = 11$ Hz, 1H), 1.59 (br t, $J = 12$ Hz, 2H), 1.50–1.39 (m, 1H), 1.27–1.08 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 178.5, 131.4, 128.2, 127.8, 123.2, 88.5, 81.5, 55.9, 42.8, 38.7, 28.2, 23.8, 22.9, 22.6, 22.5, 17.0; HRMS (EI) Calc. for $C_{18}H_{21}NO$ 267.1623. Found 267.1606.

7.21. (3E,5aS*,9aR*,9bR*)-3-(Phenyl(trimethylsilyl)-methylene)decahydropyrrolo[2,1-a]isoindol-5-one (37)

Following the same procedure as for the preparation of **25**, **17b** (395 mg, 1.5 mmol) in MeCN (0.05 M) was treated with PhI (four equivalents) in the presence of TBAC (1.5 equivalents), K_2CO_3 and $Pd(PPh_3)_4$ (0.1 equivalents). Work-up and chromatography (EtOAc/PE 1:5) gave **37** (209 mg, 0.61 mmol, 41%) as a light yellow oil and a fraction containing a mixture of **34**, **35** and **38** (0.75:0.42:1, 117 mg, 0.39 mmol, 26%). **37**; IR ($CHCl_3$) 2930, 1716, 1607; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.21 (br t, $J = 7.3$ Hz, 2H), 7.07 (br t, $J = 7.4$ Hz, 1H), 6.99 (br d, $J = 7.8$ Hz, 2H), 4.11 (ddd, $J = 5.3$, 6.8, 8.4 Hz, 1H), 2.78–2.64 (m, 2H), 2.59 (app t, 1H), 2.29–2.22 (m, 1H), 1.96–1.79 (m, 2H), 1.67–1.59 (br m, 2H), 1.44–1.41 (br m, 1H), 1.26–0.87 (m, 5H), 0.10 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.2, 143.8, 141.1, 128.5, 127.2, 124.6, 123.8, 62.8, 45.9, 38.4, 32.1, 23.9, 23.2, 22.6, 22.3, 20.1, 0.3.

7.22. (3Z,5aS*,9aR*,9bS*)-3-Benzylidenedecahydropyrrolo[2,1-a]isoindol-5-one (39)

Following the same procedure as for the preparation of **25**, **20a** (191 mg, 1.0 mmol) in MeCN (0.05 M) was treated with PhI (four equivalents) in the presence of TBAC (1.5 equivalents), K_2CO_3 and $Pd(PPh_3)_4$ (0.1 equivalents). The mixture was refluxed for 3 h, after which time work up and chromatography (EtOAc/PE 1:2) afforded **39** (161 mg, 0.60 mmol, 60%) as a light

yellow oil. Continued elution afforded impure **40** (ca. 25%); **39**: R_f 0.3 (EtOAc/PE 1:2; IR ($CHCl_3$) 2937, 1704, 1657; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.25–7.17 (m, 4H), 7.11 (br t, $J = 7.1$ Hz, 1H), 5.90 (br s, 1H), 4.18 (dt, $J = 6.6$, 8.3 Hz, 1H), 2.92 (dddd, $J = 16.4$, 3.6, 10.0, 1.8 Hz, 1H), 2.78 (m, 1H), 2.49 (dt, $J = 11.1$, 6.6 Hz, 1H), 2.28–2.22 (m, 1H), 2.13 (m, $J = 12.1$, 6.7, 8.2, 3.6 Hz, 1H), 2.06–1.99 (m, 1H), 1.76–143 (m, 7H), 1.28–1.19 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 174.4, 137.1, 134.1, 128.1, 127.3, 125.7, 111.0, 64.8, 46.7, 40.8, 33.8, 27.8, 25.2, 24.8, 23.4, 21.6; HRMS (EI) Calc. for $C_{18}H_{21}NO$ 267.1623. Found: 267.1627.

7.23. (3E,5aS,9aR*,9bS*)-3-(Phenyl(trimethylsilyl)-methylene)decahydropyrrolo[2,1-a]isoindol-5-one (**41**)*

Following the same procedure as for the preparation of **25**, **20b** (138 mg, 0.5 mmol) in MeCN (0.05 M) was treated with PhI (four equivalents) in the presence of TBAC (1.5 equivalents), K_2CO_3 and $Pd(PPh_3)_4$ (0.1 equivalents). The mixture was refluxed for 5 h, after which time work up and chromatography (EtOAc/PE 1:2) afforded **41** (114 mg, 0.34 mmol, 68%) as a white solid. Continued elution afforded the desilylated product **39** (15 mg, 0.06 mmol, 11%); **41**: R_f 0.3 (EtOAc/PE 1:2); m.p. 114–115°C (Hexane); IR ($CHCl_3$) 2939, 1697; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.20 (br t, $J = 7.6$ Hz, 2H), 7.06 (br t, $J = 7.4$ Hz, 1H), 6.97 (br d, $J = 7.5$ Hz, 2H), 3.98 (td, $J = 8.7$, 6.6 Hz, 1H), 2.89 (ddd, $J = 16.4$, 10.3, 2.8 Hz, 1H), 2.75 (dt, $J = 16.6$, 8.8 Hz, 1H), 2.26–2.08 (m, 3H), 1.65–1.56 (m, 4H), 1.54–1.35 (m, 3H), 1.26–1.04 (m, 2H), 0.11 (2, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.4, 144.0, 141.6, 128.9, 127.1, 124.6, 123.8, 62.8, 47.4, 40.8), 32.8, 28.7, 24.9, 24.3, 23.3, 21.5, 0.3; Anal. Calc. for $C_{21}H_{29}NOSi$: C, 74.28; H, 8.61; N, 4.13. Found: C, 74.33; H, 8.64; N, 4.08%.

7.24. Crystal structure determination (see Section 8)

Recrystallization of **41** from hot hexane gave crystals suitable for X-ray analysis: $C_{21}H_{29}NOSi$, $M_r = 339.55$. A colorless, block-shaped crystal ($0.1 \times 0.2 \times 0.3$ mm^3) was glued on a Lindemann-glass capillary and transferred into the cold nitrogen stream on a Nonius Kappa CCD area detector system on rotating anode. The measured crystal was monoclinic, space group $P2_1/c$ (no. 14) with $a = 13.4482(12)$, $b = 8.9962(12)$, $c = 19.647(2)$ Å, $\beta = 126.60(6)°$, $V = 1908.3(15)$ Å^3, $Z = 4$, $D_x = 1.182$ g cm^{-3}, $F(000) = 736$, $\mu(\text{Mo–K}_\alpha) = 0.13$ mm^{-1}. A total of 33485 reflections were measured, 4499 of which were independent, $R_{int} = 0.0417$ ($1.5 < \theta < 28.5°$, $T = 150$ K, Mo–K_α radiation, graphite monochromator, λ 0.71073 Å, ϕ scan with distance crystal to detector 29 mm, ω scan with distance crystal to detector 50 mm, data reduction by DENZO [23], refined mosaicity 0.370(1)°, no absorption correction). The structure was solved by direct methods (SHELXS-97) [24] and refined on F^2 using SHELXL-97-2 [25]. Hydrogen atoms were located on a difference Fourier map and their coordinates were included as parameters in the refinement. All non-hydrogen atoms were refined with anisotropic displacement parameters; hydrogen atoms were refined with a fixed isotropic displacement parameter related to the value of the equivalent isotropic displacement parameter of their carrier atoms by a factor of 1.5 for the methyl hydrogen atoms and 1.2 for the other hydrogen atoms. Refinement of 304 parameters converged at $wR_2 = 0.1044$, $w = 1/[\sigma^2(F^2) + (0.0495P)^2 + 0.69P]$, where $P = (\max(F_o^2, 0) + 2F_c^2)/3$, $R_1 = 0.0372$ (for 3817 $I > 2\sigma(I)$), $S = 1.086$ and $-0.28 < \Delta\rho < 0.24$ e Å^{-3}.

*7.25. (5Z,R)-5-Benzylidenehexahydropyrrolidin-2-one (**42**)*

Following the same procedure as for the preparation of **25**, **23** (95 mg, 0.69 mmol) in MeCN (0.05 M) was treated with PhI (four equivalents) in the presence of TBAC (1.5 equivalents), K_2CO_3 and $Pd(PPh_3)_4$ (0.1 equivalents). After work-up and chromatography **42** (59 mg, 0.28 mmol, 40%) was obtained as a white solid; m.p. 96–97°C (EtOAc/PE); $[\alpha]_D$ + 256 (*c* 0.84, $CHCl_3$); All other data identical to those for **25** (= *rac*-**57**).

*7.26. (5Z,R)-5-(Benzylidene)tetrahydropyrrolo[1,2-c]-oxazol-3-one (**44**)*

Following the same procedure as for the preparation of **25**, **24** (100 mg, 0.72 mmol, contaminated with 5% of the analogous allene) in MeCN (0.05 M) was treated with PhI (four equivalents) in the presence of TBAC (1.5 equivalents), K_2CO_3 and $Pd(PPh_3)_4$ (0.1 equivalents). After work-up and chromatography **44** (90 mg, 0.42 mmol, 60%) was obtained as a white solid; m.p. 153–155°C (EtOAc/PE); $[\alpha]_D$ + 143 (*c* 1.0, $CHCl_3$); R_f 0.4 (EtOAc/PE 1:1); IR ($CHCl_3$) 3014, 1765, 1384; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.47 (d, $J = 7.4$ Hz, 2H), 7.30–7.28 (m, 2H), 7.18–7.14 (m, 1H), 6.05 (s, 1H), 4.60 (td, $J = 8.4$, 1.1 Hz), 4.26–4.19 (m, 2H), 2.90 (dd, $J = 16.9$, 9.5 Hz, 1H), 2.78–2.68 (m, 1H), 2.18–2.11 (m, 1H), 1.74–1.63 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 135.8, 128.1, 127.9, 126.5, 114.9, 60.8, 31.0, 28.9; Anal. Calc. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.21; H, 6.10; N, 6.23%.

*7.27. 4-(4-Trimethylsilylbut-3-ynyl)-1,3-oxazolidin-2-one (**45**)*

Using the same procedure as for the preparation of **14b**, 4-methoxy-oxazolidin-2-one [26] (1.17 g, 10 mmol) in THF (10 ml) was treated with the Grignard reagent

derived from 1-bromo-4-trimethylsilyl-3-butyne (30 ml, 1 M in THF, 30 mmol). After work-up and column chromatography **45** (858 mg, 4.1 mmol, 41%) was obtained as a white solid; R_f 0.3 (EtOAc/PE 1:2); m.p. 92–93°C; IR ($CHCl_3$) 1760; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.54 (br s, 1H), 4.51 (t, $J = 8.4$ Hz, 1H), 4.08 (dd, $J = 8.6$, 6.1Hz, 1H), 4.02–3.96 (m, 1H), 2.32 (td, $J = 6.9$, 1.7 Hz, 2H), 1.85–1.70 (m, 2H), 0.13 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.7, 105.3, 83.4, 70.1, 52.0, 33.2, 16.1; HRMS (EI) Calc. for $C_{10}H_{17}NO_2Si$ 211.1029. Found 211.1020.

*7.28. (5Z)-5-(Phenyl(trimethylsilyl)methylene)-tetrahydropyrrolo[1,2-c]oxazol-3-one (**46**)*

Following the same procedure as for the preparation of **25**, **45** (211 mg, 1.0 mmol) in MeCN (0.05 M) was treated with PhI (four equivalents) in the presence of TBAC (1.5 equivalents), K_2CO_3 and $Pd(PPh_3)_4$ (0.1 equivalents). After work up and chromatography **46** (205 mg, 0.71 mmol, 71%) was obtained as a white solid; m.p. 97–98°C (CH_2Cl_2/PE); R_f 0.4 (EtOAc/PE 1:2); IR ($CHCl_3$) 2954, 1769, 1623, 1247; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.26-7.22 (m, 2H), 7.14–7.07 (m, 3H), 4.36 (dd, $J = 8.8$, 7.7 Hz, 1H), 4.06 (dd, $J = 8.8$, 2.8Hz, 1H), 4.01–3.94 (m, 1H), 2.88 (ddd, $J = 16.8$, 9.9, 1.5 Hz, 1H), 2.64 (ddd, $J = 16.9$, 10.6, 8.0 Hz, 1H), 2.20–2.13 (m, 1H), 1.72–1.61 (m, 1H), 0.09 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 155.5, 143.0, 142.6, 128.7, 128.6, 127.1, 124.9, 66.4, 59.1, 30.7, 29.6, −0.2; HRMS (EI) Calc. for $C_{16}H_{41}NO_2Si$ 287.1342. Found 287.1344.

*7.29. 5-(Diphenylmethylene)hexahydropyrrolizin-3-one (**57**)*

Following the same procedure as for the preparation of **25**, **26** (107 mg, 0.50 mmol) in MeCN (0.05 M) was treated with PhI (four equivalents) in the presence of TBAC (1.5 equivalents), K_2CO_3 and $Pd(PPh_3)_4$ (0.1 equivalents). After reflux for 18 h, work-up and chromatography (EtOAc) gave **57** (77 mg, 0.26 mmol, 53%) as a light yellow solid; R_f 0.3 (EtOAc/PE 1:2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.37–7.13 (m, 10H), 4.23 (quint, $J = 7.6$ Hz, 1H), 3.00 (ddd, $J = 16.9$, 10.7, 3.7 Hz, 1H), 2.62 (ddd, $J = 16.7$, 11.1, 9.5 Hz, 1H), 2.48 (dt, $J = 16.9$, 8.5 Hz, 1H), 2.41–2.32 (m, 2H), 2.16–2.07 (m, 1H), 1.83–1.73 (m, 1H), 1.60–1.51 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.3, 142.5, 142.0, 132.1, 130.0, 128.7, 127.9, 127.6, 127.4, 126.7, 126.0, 62.1, 34.9, 31.4, 29.7, 27.4; HRMS (EI) Calc. for $C_{20}H_{19}NO$ 289.1467. Found 289.1473.

8. Supplementary material

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC no. 150989 for compound **41**. Copies of this information may be obtained from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1233-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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