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Synthesis of Vinylogous Amides by Gold(I)-catalyzed Cyclization of *N*-Boc-protected 6-Alkynyl-3,4-dihydro-2*H*-pyridines

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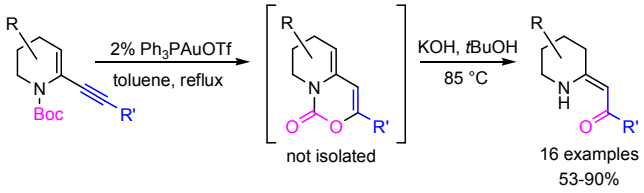
TOC



Abstract. The gold(I)-catalyzed cyclization of N-Boc-protected 6-alkynyl-3,4-dihydro-2*H*-pyridines, prepared by the Sonogashira coupling of lactam-derived enol triflates or phosphates, provides vinylogous amides which are useful intermediates in the synthesis of natural compounds. The Au(I)-catalyzed reaction is carried out with $Ph_3PAuOTf$ as a catalyst and proceeds via a 6-*endo* dig cyclization to form a vinylgold species which, after protodeauration, generates a cyclic carbamate intermediate. This is in most cases not isolated, but the addition to the reaction mixture of a base rapidly and quantitatively delivers the target vinylogous amide. The first synthesis of a natural compound from *Sonneratia hainanensis* has been accomplished by this approach.

Introduction

Exocyclic vinylogous amides built on pyrrolidine and piperidine rings (Figure 1), form a valuable class of intermediates for the synthesis of a variety of N-heterocyclic compounds. Anisomycin,[1] apomitomycin,[2] mesembrenone,[3] desoxoprosophylline,[4] cassine,[5] pinidinone and related 2,6-piperidine derivatives,[6] deoxyfebrifugine,[7] and sedacryptine,[8] are just some examples of natural alkaloids obtained by exploiting the reactivity of these compounds. A number of methods have been established for the preparation of exocyclic vinylogous amides, especially from enolizable lactams. Traditionally, the formation of vinylogous amides relies on the sulfide contraction procedure developed by the Eschenmoser's group.[9] The Knoevenagel-based modification using preformed (alkylthio)alkylideniminium salts[10] or lactam-derived iminium chlorides, lactim ethers and lactim

thioethers[11] provides an alternative to the Eschenmoser procedure. Another general method is the direct condensation of chiral lactim ethers with β-ketoesters in the presence of catalytic nickel acetylacetonate followed by decarboxylation.[6,12,13] Some useful and generally relevant approaches in which the heterocyclic system is built at the last stage of the synthesis include the intramolecular aza-Wittig reaction of ω-azido β-dicarbonyl derivatives,[14] and the Horner–Wadsworth–Emmons [3+2]-1,3-dipolar cycloaddition reaction cascade of 5-azidoaldehyde derivatives.[4,5,15] Also, exocyclic vinylogous amides were obtained by quite a long sequence from pyridine-2-carboxaldehyde and Grignard reagents.[16]

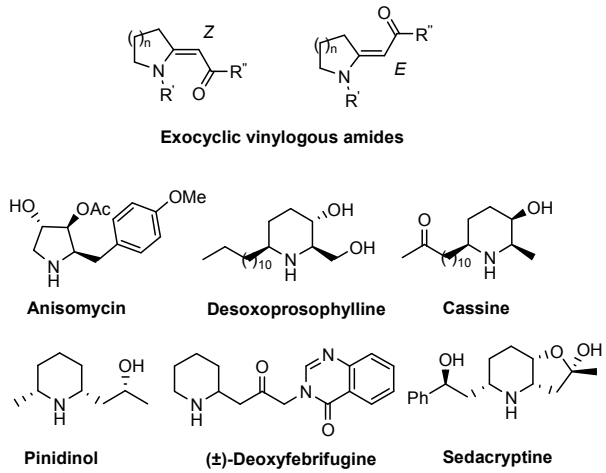
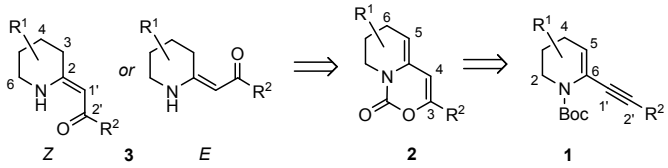


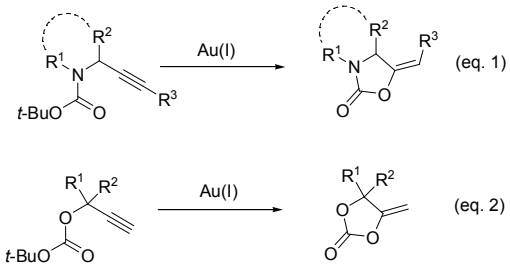
Figure 1. Vinylogous amides and some natural compounds prepared from them

In continuation of our studies on the chemistry and synthetic applications of lactam-derived enol phosphates[17] and triflates,[18] we envisaged that the gold(I)-catalyzed cyclization of N-Boc-protected 6-alkynyl-3,4-dihydro-2*H*-pyridines **1** (Scheme 1), obtained by Sonogashira coupling of the above electrophiles with various alkynes, should provide cyclic urethane intermediates **2** which are then easily converted into the target *E* or *Z* vinylogous amides **3**.



Scheme 1

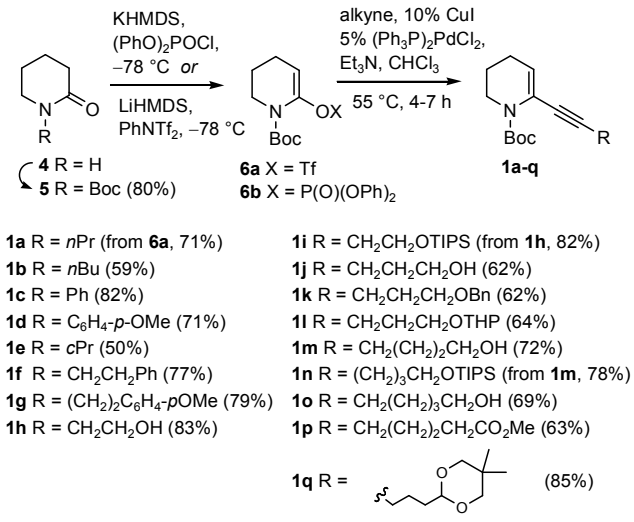
As in similar Au(I)-catalyzed cycloisomerization of *N*-Boc protected propargylamines to 1,3-oxazolidinones[19,20] (eq. 1) as well as in the cyclization of propargyl carbonates,[21] (eq. 2) the *t*-butyl group should be eliminated after carbonyl addition to the alkyne to produce an intermediate vinyl-gold species.[22] However, whereas in those cases the vinyl-gold moiety is exocyclic following a 5-*exo*-dig cyclization (with an exception in which a 2-ethynyl-N-Boc pyrrolidine reacted to give a small amount of 6-*endo*-dig product),[19c] we envisaged that the larger bond angle at C6 (120° instead of 109.5°) in enyne **1** should instead force a 6-*endo* pathway, thus providing the six-membered cyclic urethane **2** after proto-deauration. Related 6-*endo*-dig gold-catalyzed cyclizations have been previously observed in the case of 2-alkynylphenyl carbonyl derivatives, as in the formation of isocoumarines.[23]



Results and discussion

In order to test our assumption and find the optimal reaction conditions, we first synthesized simple carbamate **1a** (R^1 = H, R^2 = *n*Pr) as the model substrate. This was realized by converting *N*-Boc δ-valerolactam **5** into the corresponding enol triflate **6a** by treatment with LiHMDS at -78 °C, and then trapping the enolate with *N*-phenyl triflimide (Scheme 2). The enol triflate was not purified but

used directly in the next Sonogashira coupling with 1-pentyne to give enyne **1a** in 71% yield.[24] This compound, as well as most of the other enynes **1** we prepared, proved quite labile when neat, as they started to decompose soon after the chromatographic purification on silica gel. So, they were better stored in solution or immediately used after their preparation.[25]

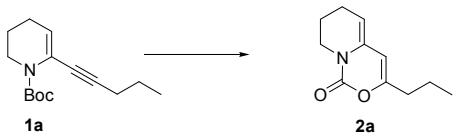


Scheme 2

The gold-catalyzed cyclization of **1a** was initially carried out in the presence of 2 mol % of $Ph_3PAuOTf$ as the catalyst (Table 1) to examine the effect of the solvent and reaction temperature (entries 1-7). The catalyst was prepared by suspending the gold salt (Ph_3PAuCl) in a solvent and then adding AgOTf either as a solid or in a solution of the same solvent at a known concentration, causing the immediate precipitation of AgCl. The latter approach was the most reproducible and used for the evaluation of the scope of the reaction (see infra). We were pleased to find that the reaction occurred in both dichloromethane (entry 1) and dichloroethane (entry 2), though slowly, with conversion into **2a** of 20 and 30% (by GLC), respectively after 1 h at room temperature (after which time the reaction was stopped). Acetonitrile, THF, and DME were much poorer solvents as the reaction did not proceed at all or the conversion was less than 9% (DME) after 1 h at room temperature. Even when the reactions were carried out in refluxing acetonitrile (81-82 °C, entry 3)

and THF (65-67 °C, entry 4) the conversion into compound **2a** was very low, in DME (85 °C, entry 5) was barely acceptable (58%), whereas in boiling DCE (83 °C, entry 6) the reaction was almost complete (84%) in 1 h.

Table 1. Gold(I)-catalyzed Cyclization of 6-Alkynyl-3,4-dihydro-2*H*-pyridine 1a[a]



Entry	Solvent	Catalyst/Additive	T (°C)	T (min)	Conv.[b] (%)
1	DCM	2% $Ph_3PAuOTf$	25	60	20
2	DCE	2% $Ph_3PAuOTf$	25	60	30
3	CH_3CN	2% $Ph_3PAuOTf$	82	60	6
4	THF	2% $Ph_3PAuOTf$	67	60	15
5	DME	2% $Ph_3PAuOTf$	85	60	58
6	DCE	2% $Ph_3PAuOTf$	83	60	84
7	toluene	2% $Ph_3PAuOTf$	111	20	>99
8	toluene	2% Ph_3PAuBF_4	111	60	9
9	toluene	2% $Ph_3PAuSbF_6$	111	60	69
10	toluene	2% Ph_3PAuPF_6	111	60	59
11	toluene	-	111	60	0
12	toluene	5% Ph_3PAuCl	111	60	0
13	toluene	5% AgOTf	111	60	15
14	toluene	1% $Ph_3PAuOTf$	111	60	57
15	toluene	1% $Ph_3PAuOTf$/AcOH[c]	111	15	>99
16	toluene	0.5% $Ph_3PAuOTf$/AcOH[c]	111	60	90

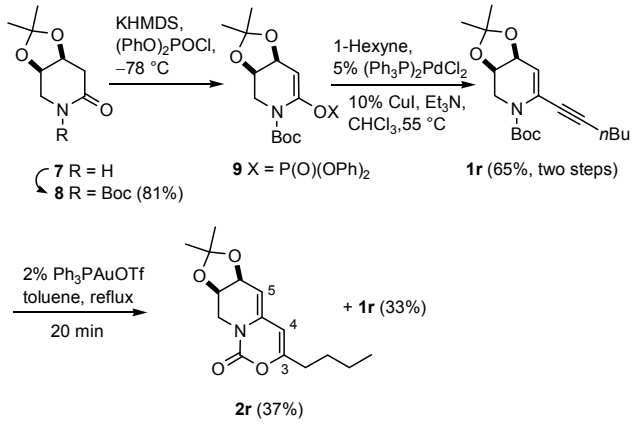
17	toluene	AcOH[c]	111	60	0

[a]Typical reaction conditions: a solution of **1a** (1 mmol) in the solvent (5 mL) is added to a solution of the catalyst in the solvent (5 mL), then heating as reported. [b]Conversion measured by GLC. [c]2 equiv.

Eventually, when performing the reaction in boiling toluene (110-111 °C, entry 7) we observed the complete conversion of **1a** into **2a** after just 20 min. In this case we tried to isolate **2a** by chromatography but this cyclic carbamate was in our hand very prone to decomposition. In fact, we were never able to keep neat **2a** for a long time as a quick degradation occurred within minutes. Besides the $Ph_3PAuOTf$ catalyst, we tried also the corresponding tetrafluoroborate (entry 8), hexafluoroantimonate (entry 9), and hexafluorophosphate (entry 10) gold complexes (2 mol %) in refluxing toluene, but they were all less competent than $Ph_3PAuOTf$, with $Ph_3PAuSbF_6$ being the best one (69% conversion into **2a** after 1 h). Control experiments were carried out without catalyst (entry 11), triflate source (entry 12) and gold source (entry 13) and in no case we observed formation of **2a** after 1 h in refluxing toluene with the exception of the latter case in which a minimal amount (15%) of product was formed in the presence of only a high loading (5%) of AgOTf, arguably because of the catalysis exerted by Ag(I).[26]

When we reduced the catalyst loading to 1 mol % of $Ph_3PAuOTf$ (Table 1, entry 14) the conversion was 57% after 1 h. However, the addition of 2 equiv. of acetic acid as a proton source increased the reaction rate and the conversion into **2a** was complete in just 15 min with 1 mol % of catalyst (entry 15) and almost complete (90%) in 60 min with 0.5 mol % of $Ph_3PAuOTf$ (entry 16).[27] No reaction at all occurred without catalyst in the presence of acetic acid (entry 17). Despite the lower catalyst amount required in the presence of AcOH, we envisaged that the presence of the latter could not be tolerated by a range of substrates under the reaction conditions and so we opted for a general procedure which uses 2 mol % of catalyst without acetic acid in boiling toluene.

Despite its quick decomposition when neat, we were able to assign the structure of **2a** - and thus confirm our initial hypothesis about the reaction outcome - as in the ^{1}H NMR spectrum of **2a** the signal assigned to vinylic proton H4 resonates at 5.37 ppm as a singlet (in the 5-*exo* dig product it should be a triplet because of the ^{3}J coupling with the methylene hydrogens of the side chain). In one case, intermediate **2r**, prepared by Sonogashira coupling of enol phosphate **9** with 1-hexyne, as reported in Scheme 3**,** proved instead more stable and could be purified by flash chromatography on silica gel.[28]

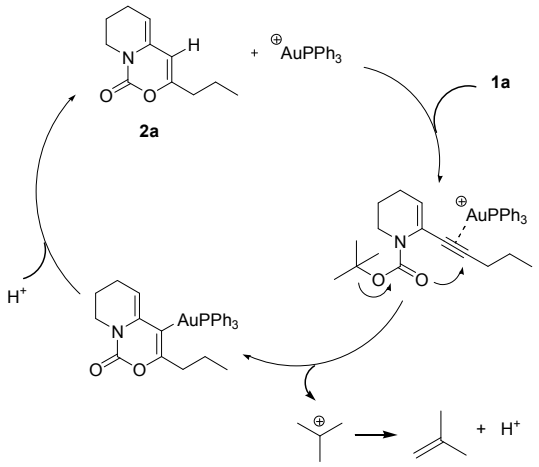


Scheme 3

Again, in its ^{1}H NMR spectrum, the vinylic H4 proton diagnostically resonates as a singlet at 5.43 ppm, whereas the other olefinic proton (H5) resonates as a doublet at about 4.65 ppm. In both **2a** and **2r**, the ^{13}C resonances for C4 as doublets at 99.2 and 99.3 ppm, respectively, are in accordance with the proposed structure of the intermediate.

A mechanism for the formation of cyclic urethane **2a** is depicted in Scheme 4. This is similar to that previously reported for the formation of 5-methylene-1,3-oxazolidinones from *N*-Boc protected propargylamines,[19] with the main difference being the oxy-auration step of the triple bond which occurs in an 6-*endo* fashion to furnish a neutral *endo* vinyl-gold species with concurrent or subsequent *t*-butyl fragmentation to isobutene. Protodeauration would then provide cyclic urethane

2a with the concomitant regeneration of the gold(I)-catalyst. Compared with the 5-*exo*-dig processes leading to oxazolidinones,[19] the conversion of enyne **1a** into cyclic urethane **2a** requires higher temperatures and longer reaction times if acetic acid is not added. With 1 mol % of catalyst ($Ph_3PAuNTf_2$ or $Ph_3PAuSbF_6$), the cyclization of a *N*-Boc 2-alkynylpiperidine in which the side chain is on a sp^3 C atom quantitatively generates the corresponding 1,3-oxazolidinones after 1 h at room temperature,[19a] whereas in our case enyne **1a** requires boiling toluene to be completely converted in 20 min in the presence of 2 mol % of catalyst. This could be due to a greater difficulty in the nucleophilic attack by the carbonyl group to the activated alkyne due to the larger bond angle at C6.



Scheme 4

Because of the intrinsic instability of compound **2a**, we decided to hydrolyze this carbamate to the corresponding vinylogous amide **3a** (Scheme 5) in the same reaction vessel after the gold-catalyzed reaction was complete (monitoring by TLC). Amongst the tested methods, those in which a base (KOH) and a co-solvent (*t*BuOH or MeOH) were added proved optimal. With *t*BuOH as a co-solvent and KOH as a base (6 equiv), the reaction was complete after 30 min at 85 °C, whereas with MeOH as a co-solvent and heating at 65 °C the reaction was, as expected, much slower and it was complete in 2 h. Of the two possible isomers, only one was produced during the hydrolysis step. A

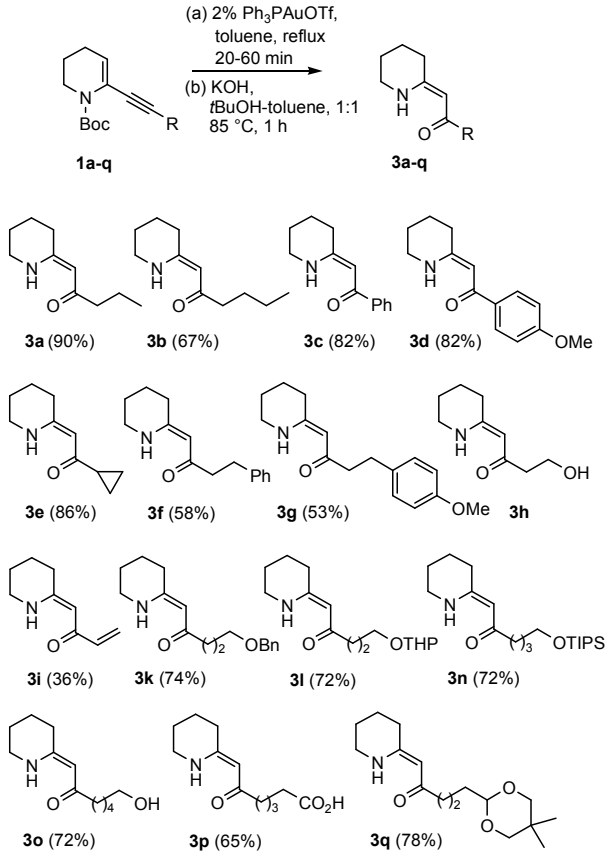
NOESY experiment on compound **3a** (and then on all of the other vinylogous amides **3**) showed a correlation between olefinic 1-H' and the proton(s) on C3 of the ring, consistent with a Z geometry of the double bond. This could arise from thermodynamic factors, as the formation of the intramolecular H-bonding N-H···O should be favored, as already reported in other cases.[5,6]

Having assessed the general methodology for the conversion of lactams into vinylogous amides, to explore the scope of the reaction we coupled lactam-derived enol phosphate **6b** (Scheme 2) to alkynes bearing differently substituted alkyl and aryl groups. Functional groups such as hydroxyl, carbonyl and carboxyl were chosen as these are generally present in the side chains of natural piperidines synthesized from vinylogous amides.

For the synthesis of compound **1g**, **1k-l**, and **1p-q**, the corresponding alkynes were prepared as reported or according to standard procedures. Lactam-derived enol phosphates are generally more stable than the corresponding triflates and are prepared by trapping the corresponding enolates with diphenylchlorophosphate. Whereas the Sonogashira coupling of lactam-derived enol triflates has been reported,[24] the same reaction with the corresponding enol phosphates like **6b** has never been carried out. We found that the conditions we had reported for imide-derived enol phosphates [5% $(Ph_3P)_2PdCl_2$, 10% CuI, in Et_3N-$CHCl_3$, at 55 °C)][17c] were suitable to successfully convert **6b** into enynes **1**. In all cases, these enynes were unstable when neat and were either used immediately after a chromatographic purification or stored in the eluent. In some cases (**1e**, **1l**, and **1q**) it was not possible to obtain the enynes in pure form by chromatography, however this did not affect the reaction outcome and rate when they were subjected to the next Au(I)-catalyzed reaction.

The gold(I)-catalyzed cyclization of enynes **1b-q** (Scheme 5) was carried out in the presence of 2 mol % of catalyst in boiling toluene according to the general procedure, and the subsequent hydrolysis carried out *in situ* by addition of KOH (6 equiv) and *t*-BuOH (1:1 ratio with toluene) and then heating at 85 °C. With enynes **1b-f**, bearing no particular functionality on the side chain, the

reaction occurred smoothly providing vinylogous amides **3b-f** with *Z* geometry (as demonstrated by nOe studies) in generally good yield (58-86% over two steps) after chromatography.[29] Of these, vinylogous amide **3c** is of particular interest because it has recently been used to prepare a series of Sedamine alkaloids.[9b] Instead with enyne **1h**, bearing a β-hydroxy group, whereas the gold-catalyzed cyclization occurred without any problem (as seen by TLC monitoring), the next hydrolysis step caused either the partial or complete elimination of water providing the α,β-unsaturated vinylogous amide **3i**.[30] This occurred also with substrate **1i**, prepared by protecting the OH group of **1h** as TIPS ether.



Scheme 5

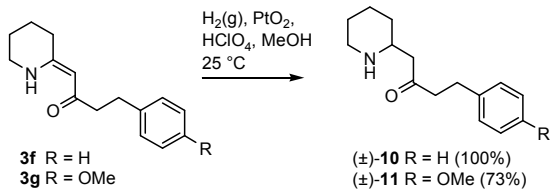
When instead the reaction was carried out with substrate **1j** (from 4-pentyn-1-ol) the gold-catalyzed cyclization did not occur at all. Even with 5% mol of catalyst, or in the presence of AcOH, we

recovered, after 1 h in boiling toluene, the unaltered substrate. The same occurred with enyne **1m** deriving from 5-hexyn-1-ol. The reason for the unsuitability of a γ- or δ-hydroxy group as in substrate **1j** and **1m** is unclear, but it is possible that an Au(I)-promoted cyclization onto C2' involving the side chain OH group takes place to form a vinyl-gold species in which proto-deauration is prevented by coordination of gold to the Boc carbonyl group.[31] In fact, when the OH group was protected both as benzyl ether (**1k**) and THP ether (**1l**) the whole process took place smoothly and vinylogous amides **3k** and **3l** were obtained in 74% and 72% yield, respectively after chromatography. Similarly, when carrying out the reaction on *O*-TIPS protected enyne **1n** (in this case obtained directly from **1m**), vinylogous amide **3n** was obtained in 72% yield after chromatography. Interestingly, and reasonably because of the less favored formation of a seven-membered ring in the competing pathway, the Au(I)-catalyzed reaction of enyne **1o**, obtained from 6-heptyn-1-ol, did occur although it was much slower than usual, requiring 2.5 hours to reach a complete conversion into **3o** with 6 mol % of catalyst. In any case, the above results suggest that a protection of the OH group in the side chain is either necessary or preferable.

The ester group of enyne **1p** was compatible with the conditions for the Au(I)-catalyzed reaction, but as expected it was converted into carboxylate under the next basic step. However, carboxylic acid **3p** was obtained in good yield (65%) after an acidic work-up and subsequent chromatography. Because aldehydes do not generally tolerate strong basic conditions, the carbonyl group has to be protected, for example as in enyne **1q** prepared from 5,5-dimethyl-2-pent-4-ynyl-[1,3]dioxane. The cyclic acetal moiety of **1q**, like the tetrahydropyranyl ether in **1l**, proved compatible with the reaction conditions and the sequence provided the corresponding vinylogous amide **3q** in 78% yield.

Having assessed the scope of the reaction, a specific substrate (**1g**) was prepared and subjected to the usual sequence providing the corresponding vinylogous amide **3g** (Scheme 5) in 53% yield. We

used this as an intermediate for the first synthesis of a natural product (compound **11**, Scheme 6) isolated as a racemate from the leaves of the Chinese coast mangrove *Sonneratia hainanensis*.[32] Thus, reduction of the double bond was carried out by catalytic hydrogenation[9b] providing compound **11** in 73% yield and with ^{1}H and ^{13}C NMR spectra identical to those reports for the natural compound.[32] Its unsubstituted analogue **10** was also prepared according to the same route.



Scheme 6

Conclusion

In conclusion we have demonstrated that the gold(I)-catalyzed cyclization of N-Boc-protected 6-alkynyl-3,4-dihydro-2*H*-pyridines allows for a facile synthesis of vinylogous amides which are useful intermediates in the synthesis of natural compounds. The substrates are prepared by the Sonogashira coupling of lactam-derived enol triflates and phosphates, which provides the corresponding enynes in good yields. The next Au(I)-catalyzed reaction is carried out with $Ph_3PAuOTf$ as a catalyst and proceeds via a 6-*endo* dig cyclization to form a vinylgold species which after protodeauration generates a cyclic carbamate intermediate. This is in most cases not isolated, but the addition to the reaction mixture of KOH and *t*-BuOH at 85 °C rapidly and quantitatively delivers the target vinylogous amide. Albeit in one particular case the strong basic conditions caused elimination of water from the side chain, the preparation of a series of products with different substituents and protecting groups on the side chain shows that this methodology has a wide scope and is well suited for the preparation of natural products embedding a 2-substituted

piperidine moiety. Accordingly, the first synthesis of a natural compound from *Sonneratia hainanensis* has been accomplished by this approach.

Experimental Section

General. 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, with the same eluent as indicated for the column chromatography. ^{1}H NMR spectra were recorded at 200 or 400 MHz and ^{13}C NMR spectra were recorded at 50.33 or 100.4 MHz, both in $CDCl_3$ solution. Solvent reference line was set at 7.26 ppm. Mass spectra were either recorded at an ionizing voltage of 70 eV or carried out by direct inlet of a 10 ppm solution in CH_3OH on an Ion Trap LC/MS system with an electrospray ionization (ESI) interface in the positive mode. Pent-4-ynyloxymethylbenzene,[33] 1-but-3-ynyl-4-methoxybenzene[34] and 6-heptyn-1-ol[35] were prepared as reported. Compounds **6a**[18g] and **6b**[36] are known.

6-(Pent-1-ynyl)-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid *tert*-Butyl Ester (1a).

Triflate **6a** (1 mmol) was dissolved in anhydrous THF (0.1 M), under nitrogen atmosphere; LiCl (1 mmol), diisopropylamine (4 mmol), $Pd(OAc)_2$ (0.05 mmol), Ph_3P (0.1 mmol), CuI (0.1 mmol) and the alkyne (1.5 mmol) were then added and the resulting mixture left under stirring at room temperature overnight. Satd aqueous NH_4Cl (10 mL) was added and the product extracted with Et_2O (3 x 10 mL); the combined organic extracts were washed once with brine (15 mL) and dried over anhydrous K_2CO_3. After filtration and evaporation of the solvent, crude enyne **1a** was purified by flash chromatography (eluent: petroleum ether-EtOAc, 9:1 containing 1% Et_3N; R_f = 0.25) and stored at 4 °C as 0.1 M solution in the eluent until use.

Colourless oil (177 mg, 71%). ^{1}H NMR (200 MHz) δ (ppm): 5.41 (t, *J* = 4.1 Hz, 1 H), 3.53-3.39 (m, 2 H), 2.23 (t, *J* = 7.0 Hz, 2 H), 2.12-2.04 (m, 2 H), 1.76-1.74 (m, 2 H), 1.56-1.44 (m, 2 H), 1.43 (s, 9 H), 0.93 (t, *J*

= 7.5 Hz, 3 H). ^{13}C NMR (50.33 MHz) δ (ppm): 153.0 (s), 122.5 (s), 120.9 (d), 87.8 (s), 80.5 (s), 77.7 (s), 43.4 (t), 28.2 (q, 3 C), 23.5 (t), 22.6 (t), 21.9 (t), 21.2 (t), 13.5 (q). MS (EI) *m/z* %: 249 ([M]$^+$, 55), 193 (45), 148 (90), 121 (85), 57 (100).

Sonogashira coupling (general procedure from phosphate **6b***)*. Phosphate **6b** (1 mmol) was dissolved in anhydrous 3:1 Et_3N-$CHCl_3$ mixture (0.13 M) and the alkyne (1 mmol), CuI (0.1 mmol) and $(Ph_3P)_2PdCl_2$ (0.05 mmol) were added. The resulting solution was heated at 55 °C (external) for 2 h, after which time a second portion of alkyne (0.5 mmol) and $(Ph_3P)_2PdCl_2$ (0.025 mmol) were added, if necessary. The mixture was heated at 55 °C until completion (TLC, usually in 4-7 h). After cooling at r.t., water (12 mL) was added and the product extracted with Et_2O (3 x 12 mL); the combined organic extracts were dried over anhydrous K_2CO_3. After filtration and evaporation of the solvent, crude enyne **1** was purified by flash chromatography (eluent containing 1% Et_3N) and stored at 4 °C as 0.1 M solution in the eluent until use.

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

Colourless oil (155 mg, 59%). R_f = 0.68 (*n*-hexane-EtOAc, 3:1). FCC eluent: *n*-hexane-EtOAc, 20:1 + 1% Et_3N. ^{1}H NMR (400 MHz) δ (ppm): 5.45 (t, *J* = 4.1 Hz, 1 H), 3.55-3.52 (m, 2 H), 2.30 (t, *J* = 6.8 Hz, 2 H), 2.15-2.10 (m, 2 H), 1.78-1.72 (m, 2 H), 1.54-1.38 (m, 4 H), 1.48 (s, 9 H), 0.90 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (100.4 MHz) δ (ppm): 153.2 (s), 122.6 (s), 121.1 (d), 88.1 (s), 80.7 (s), 77.6 (s), 43.5 (t), 30.7 (t), 28.3 (q, 3 C), 23.6 (t), 22.7 (t), 22.0 (t), 19.1 (t), 13.6 (q). MS (ESI) *m/z* %: 549 ([2M+Na]$^+$, 25), 286 ([M+Na]$^+$, 19).

6-Phenylethynyl-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid *tert*-Butyl Ester (1c).

Pale yellow solid (232 mg, 82%). R_f = 0.35 (petroleum ether-EtOAc, 95:5). ^{1}H NMR (200 MHz) δ (ppm): 7.38-7.35 (m, 2 H), 7.25-7.20 (m, 3 H), 5.60 (t, *J* = 4.0 Hz, 1 H), 3.59-3.54 (m, 2 H), 2.13-2.04 (m, 2 H), 1.75-1.63 (m, 2 H), 1.43 (s, 9 H). ^{13}C NMR (50.33 MHz) δ (ppm): 153.0 (s), 131.1 (d, 2 C), 128.1 (d, 2 C),

127.8 (d), 123.2 (s), 122.5 (s), 122.2 (d), 87.2 (s), 86.8 (s), 80.9 (s), 43.2 (t), 28.1 (q, 3 C), 23.6 (t), 22.5 (t). MS (EI) *m/z* %: 283, ([M]$^+$, 5), 227 (75), 182 (85), 127 (25), 57 (100).

6-(4-Methoxyphenylethynyl)-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid *tert*-Butyl Ester (1d).

White solid (223 mg, 71%). R_f = 0.32 (petroleum ether-EtOAc, 95:5). ^{1}H NMR (200 MHz) δ (ppm): 7.30 (d, *J* = 9.0 Hz, 2 H), 6.77 (d, *J* = 9.0 Hz, 2 H), 5.56 (t, *J* = 4.0 Hz, 1 H), 3.71 (s, 3 H), 3.57-3.52 (m, 2 H), 2.19-2.10 (m, 2 H), 1.81-1.68 (m, 2 H), 1.42 (s, 9 H). ^{13}C NMR (50.33 MHz) δ (ppm): 159.2 (s), 153.1 (s), 132.5 (d, 2 C), 122.3 (s), 121.9 (d), 115.3 (s), 113.8 (d, 2 C), 87.1 (s), 85.2 (s), 80.1 (s), 55.0 (q), 43.2 (t), 28.1 (q, 3 C), 23.6 (t), 22.5 (t). MS (EI) *m/z* %: 313 ([M]$^+$, 15), 257 (100), 212 (80), 198 (55), 57 (35).

6-Cyclopropylethynyl-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid *tert*-Butyl Ester (1e).

Pale yellow oil (124 mg, 50%, 81% purity by ^{1}H NMR). R_f = 0.45 (petroleum ether-EtOAc, 9:1). ^{1}H NMR (200 MHz) δ (ppm): 5.39 (t, *J* = 4.0 Hz, 1 H), 3.49-3.44 (m, 2 H), 2.11-2.02 (m, 2 H), 1.75-1.63 (m, 2 H), 1.44 (s, 9 H), 1.43-1.42 (m, 1 H), 0.76-0.63 (m, 4 H). ^{13}C NMR (50.33 MHz) δ (ppm): 153.0 (s), 122.3 (s), 121.3 (d), 90.8 (s), 80.7 (s), 72.8 (s), 43.2 (t), 28.1 (q, 3 C), 23.4 (t), 22.5 (t), 8.0 (t, 2 C), 0.8 (d). MS (EI) *m/z* %: 247 ([M]$^+$, 5), 191 (100), 146 (75), 132 (20), 57(45).

6-(4-Phenylbut-1-ynyl)-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid *tert*-Butyl Ester (1f).

Pale yellow oil (240 mg, 77%). R_f = 0.28 (*n*-hexane-EtOAc, 25:1 + 1% Et_3N). ^{1}H NMR (400 MHz) δ (ppm): 7.31-7.18 (m, 5 H), 5.46 (t, *J* = 4.1 Hz, 1 H), 3.57-3.54 (m, 2 H), 2.87 (t, *J* = 7.8 Hz, 2 H), 2.60 (t, *J* = 7.8 Hz, 2 H), 2.17-2.12 (m, 2 H), 1.80-1.74 (m, 2 H), 1.49 (s, 9 H). ^{13}C NMR (100.4 MHz) δ (ppm): 153.1 (s), 140.7 (s), 128.4 (d, 2 C), 128.3 (d, 2 C), 126.2 (d), 122.5 (s), 121.4 (d), 87.3 (s), 80.7 (s), 78.3 (s), 43.5 (t), 35.1 (t),

28.3 (q, 3 C), 23.6 (t), 22.7 (t), 21.6 (t). MS (ESI) *m/z* %: 645 ($[2M+Na]^+$, 22), 324 ($[M+Na]^+$, 100), 312 ($[M+1]^+$, 9).

6-[4-(4-Methoxyphenyl)but-1-ynyl]-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid *tert*-Butyl Ester (1g).

Pale yellow oil (270 mg, 79%, 96% purity by ^{1}H NMR). R_f = 0.27 (*n*-hexane-EtOAc, 14:1 + 1% Et_3N). ^{1}H NMR (400 MHz) δ (ppm): 7.14 (d, *J* = 8.6 Hz, 2 H), 6.83 (d, *J* = 8.6 Hz, 2 H), 5.46 (t, *J* = 3.9 Hz, 1 H), 3.79 (s, 3 H), 3.57-3.53 (m, 2 H), 2.81 (t, *J* = 7.4 Hz, 2 H), 2.56 (t, *J* = 7.4 Hz, 2 H), 2.16-2.12 (m, 2 H), 1.79-1.73 (m, 2 H), 1.49 (s, 9 H). ^{13}C NMR (100.4 MHz) δ (ppm): 158.1 (s), 153.1 (s), 132.9 (s), 129.4 (d, 2 C), 122.5 (s), 121.4 (d), 113.8 (d, 2 C), 87.4 (s), 80.7 (s), 78.3 (s), 55.2 (q), 43.5 (t), 34.2 (t), 28.3 (q, 3 C), 23.6 (t), 22.7 (t), 21.9 (t). MS (ESI) *m/z* %: 705 ($[2M+Na]^+$, 37), 364 ($[M+Na]^+$, 100), 342 ($[M+1]^+$, 7).

6-(4-Hydroxybut-1-ynyl)-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid *tert*-Butyl Ester (1h).

Pale yellow oil (208 mg, 83%). R_f = 0.24 (*n*-hexane-EtOAc, 3:1 + 1% Et_3N). ^{1}H NMR (400 MHz) δ (ppm): 5.48 (t, *J* = 4.1 Hz, 1 H), 3.73 (t, *J* = 5.7 Hz, 2 H), 3.56-3.53 (m, 2 H), 2.53 (t, *J* = 5.7 Hz, 2 H), 2.15-2.10 (m, 2 H), 1.79-1.75 (m, 2 H), 1.47 (s, 9 H). ^{13}C NMR (100.4 MHz) δ (ppm): 152.7 (s), 121.8 (s), 120.7 (d), 86.1 (s), 81.0 (s), 79.8 (s), 60.9 (t), 44.0 (t), 28.3 (q, 3 C), 23.9 (t), 23.3 (t), 22.6 (t). MS (EI) *m/z* %: 251 ($[M]^+$, 7), 194 (23), 150 (32), 125 (15), 57 (45).

6-(4-Triisopropylsilanoxybut-1-ynyl)-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid *tert*-Butyl Ester (1i).

Imidazole (35 mg, 0.52 mmol) and triisopropylsilyl chloride (40 μL, 0.19 mmol) were added under nitrogen atmosphere to a solution of alcohol **1h** (44 mg, 0.17 mmol) in anhydrous DMF (525 μL). The resulting mixture was heated at 40 °C for 1 h. After cooling at room temperature, water was added (6 mL) and the product extracted with Et_2O (5 x 6 mL). The combined organic extracts were dried over anhydrous K_2CO_3.

After filtration and evaporation of the solvent crude **1i** was obtained and purified by flash chromatography (eluent: *n*-hexane-EtOAc, 25:1 + 1% Et_3N; R_f = 0.25), affording pure **1i** (58 mg, 82%) as a colourless oil.

^{1}H NMR (400 MHz) δ (ppm): 5.47 (t, *J* = 4.1 Hz, 1 H), 3.82 (t, *J* = 7.4 Hz, 2 H), 3.55-3.52 (m, 2 H), 2.56 (t, *J* = 7.4 Hz, 2 H), 2.15-2.10 (m, 2 H), 1.79-1.73 (m, 2 H), 1.49 (s, 9 H), 1.05 (m, 21 H). ^{13}C NMR (100.4 MHz) δ (ppm): 153.2 (s), 122.4 (s), 121.6 (d), 84.6 (s), 80.8 (s), 78.8 (s), 62.1 (t), 43.4 (t), 28.3 (q, 3 C), 23.8 (t), 23.6 (t), 22.7 (t), 17.9 (q, 6 C), 11.9 (d, 3 C). MS (ESI) *m/z* %: 430 ($[M+Na]^+$, 100).

6-(5-Hydroxypent-1-ynyl)-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid *tert*-Butyl Ester (1j).

Pale yellow oil (165 mg, 62%). R_f = 0.24 (*n*-hexane-EtOAc, 2:1 + 1% Et_3N). ^{1}H NMR (400 MHz) δ (ppm): 5.47 (t, *J* = 4.1 Hz, 1 H), 3.76 (t, *J* = 6.1 Hz, 2 H), 3.55-3.52 (m, 2 H), 2.45 (t, *J* = 6.8 Hz, 2 H), 2.15-2.10 (m, 2 H), 1.81-1.72 (m, 4 H), 1.48 (s, 9 H). ^{13}C NMR (100.4 MHz) δ (ppm): 152.9 (s), 122.3 (s), 121.4 (d), 87.5 (s), 80.8 (s), 78.2 (s), 61.7 (t), 43.7 (t), 31.0 (t), 28.3 (q, 3 C), 23.5 (t), 22.7 (t), 16.2 (t). MS (ESI) *m/z* %: 553 ($[2M+Na]^+$, 62), 288 ($[M+Na]^+$, 100).

6-(5-Benzyloxypent-1-ynyl)-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid *tert*-Butyl Ester (1k).

Colourless oil (220 mg, 62%, 75% purity by ^{1}H NMR). R_f = 0.82 (petroleum ether-EtOAc, 9:1). ^{1}H NMR (200 MHz) δ (ppm): 7.41-7.26 (m, 5 H), 5.44 (t, *J* = 4.1 Hz, 1 H), 4.52 (s, 2 H), 3.59 (t, *J* = 6.1 Hz, 2 H), 3.58-3.52 (m, 2 H), 2.45 (t, *J* = 7.2 Hz, 2 H), 2.20-2.08 (m, 2 H), 1.93-1.72 (m, 4 H), 1.50 (s, 9 H). ^{13}C NMR (50.33 MHz) δ (ppm): 152.9 (s), 138.3 (s), 128.2 (d, 2 C), 127.4 (d, 2 C), 127. 1 (d), 122.3 (s), 121.4 (d), 87.4 (s), 80.7 (s), 77.9 (s), 72.8 (t), 68.8 (t), 43.6 (t), 28.8 (t), 28.3 (q, 3 C), 23.6 (t), 22.7 (t), 16.2 (t). MS (EI) *m/z* %: 355 ($[M]^+$, 5), 298 (30), 254 (40), 121 (100), 91 (50), 57 (45).

6-[5-(Tetrahydropyran-2-yloxy)pent-1-ynyl]-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid *tert*-Butyl Ester (1l).

Colourless oil (223 mg, 64%, 71% purity by ^{1}H NMR). R_f = 0.75 (petroleum ether-EtOAc, 4:1). ^{1}H NMR (200 MHz) δ (ppm): 5.47 (t, *J* = 4.1 Hz, 1 H), 4.55-4.30 (m, 1 H), 3.72-3.65 (m, 2 H), 3.55-3.52 (m, 4 H, 2-H), 2.42 (t, *J* = 6.8 Hz, 2 H), 2.35-2.30 (m, 2 H), 1.80-1.40 (m, 10 H), 1.48 (s, 9 H). ^{13}C NMR (50.33 MHz) δ (ppm): 154.0 (s), 123.3 (s), 121.2 (d), 99.6 (d), 87.5 (s), 81.4 (s), 80.5 (s), 65.8 (t), 62.0 (d), 43.5 (t), 30.5 (t), 28.6 (t), 28.1 (q, 3 C), 25.3 (t), 23.4 (t), 22.5 (t), 19.6 (t), 19.3 (t). MS (EI) *m/z* %: 349 ([M]$^+$, 1), 165 (100), 121 (73), 57 (85).

6-(6-Hydroxyhex-1-ynyl)-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid *tert*-Butyl Ester (1m).

Colourless oil (201 mg, 72%). R_f = 0.38 (*n*-hexane-EtOAc, 1:1 + 1% Et_3N). ^{1}H NMR (400 MHz) δ (ppm): 5.46 (t, *J* = 4.1 Hz, 1 H), 3.67 (t, *J* = 6.1 Hz, 2 H), 3.55-3.51 (m, 2 H), 2.36 (t, *J* = 6.8 Hz, 2 H), 2.15-2.10 (m, 2 H), 1.78-1.73 (m, 2 H), 1.72-1.60 (m, 4 H), 1.48 (s, 9 H). ^{13}C NMR (100.4 MHz) δ (ppm): 153.0 (s), 122.4 (s), 121.3 (d), 87.9 (s), 80.7 (s), 78.0 (s), 62.2 (t), 43.6 (t), 31.8 (t), 28.3 (q, 3 C), 24.7 (t), 23.5 (t), 22.7 (t), 19.1 (t). MS (ESI) *m/z* %: 581 ([2M+Na]$^+$, 47), 302 ([M+Na]$^+$, 100).

6-(6-Triisopropylsilanoxyhex-1-ynyl)-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid *tert*-Butyl Ester (1n).

Prepared as reported for **1i**, starting from **1m** (75 mg, 0.27 mmol).

Colourless oil (90 mg, 78%). R_f = 0.27 (*n*-hexane-EtOAc, 20:1 + 1% Et_3N). ^{1}H NMR (400 MHz) δ (ppm): 5.46 (t, *J* = 4.1 Hz, 1 H), 3.70 (t, *J* = 5.9 Hz, 2 H), 3.56-3.53 (m, 2 H), 2.34 (t, *J* = 6.6 Hz, 2 H), 2.16-2.11 (m, 2 H), 1.79-1.73 (m, 2 H), 1.66-1.61 (m, 4 H), 1.49 (s, 9 H), 1.06-1.03 (m, 21 H). ^{13}C NMR (100.4 MHz) δ (ppm): 153.2 (s), 122.6 (s), 121.2 (d), 88.0 (s), 80.7 (s), 77.8 (s), 62.8 (t), 43.5 (t), 32.3 (t), 28.3 (q, 3 C), 25.2 (t), 23.6 (t), 22.8 (t), 19.3 (t), 18.0 (q, 6 C), 12.0 (d, 3 C). MS (ESI) *m/z* %: 893 ([2M+Na]$^+$, 10), 458 ([M+Na]$^+$, 100).

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

Pale yellow oil (202 mg, 69%). R_f = 0.29 (*n*-hexane-EtOAc, 2:1 + 1% Et_3N). ^{1}H NMR (400 MHz) δ (ppm): 5.44 (t, *J* = 3.9 Hz, 1 H), 3.61 (t, *J* = 6.4 Hz, 2 H), 3.53-3.49 (m, 2 H), 2.30 (t, *J* = 6.6 Hz, 2 H), 2.14-2.08 (m, 2 H), 1.90 (br s, 1 H), 1.76-1.70 (m, 2 H), 1.59-1.50 (m, 4 H), 1.49-1.42 (m, 2 H), 1.46 (s, 9 H). ^{13}C NMR (100.4 MHz) δ (ppm): 153.1 (s), 122.4 (s), 121.3 (d), 87.9 (s), 80.7 (s), 77.7 (s), 62.5 (t), 43.5 (t), 32.1 (t), 28.2 (q, 3 C), 24.9 (t, 2 C), 23.4 (t), 22.7 (t), 19.3 (t). MS (ESI) *m/z* %: 609 ($[2M+Na]^+$, 52), 316 ($[M+Na]^+$, 100).

6-(6-Methoxycarbonylhex-1-ynyl)-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid *tert*-Butyl Ester (1p).

Pale yellow oil (202 mg, 63%). R_f = 0.30 (*n*-hexane-EtOAc, 10:1 + 1% Et_3N). ^{1}H NMR (400 MHz) δ (ppm): 5.46 (t, *J* = 3.9 Hz, 1 H), 3.66 (s, 3 H), 3.55-3.52 (m, 2 H), 2.35-2.25 (m, 4 H), 2.15-2.10 (m, 2 H), 1.79-1.70 (m, 4 H), 1.61-1.53 (m, 2 H), 1.48 (s, 9 H). ^{13}C NMR (100.4 MHz) δ (ppm): 173.8 (s), 153.1 (s), 122.5 (s), 121.4 (d), 87.4 (s), 80.7 (s), 78.1 (s), 51.5 (q), 43.5 (t), 33.6 (t), 28.3 (q, 3 C), 28.0 (t), 24.2 (t), 23.6 (t), 22.7 (t), 19.1 (t). MS (ESI) *m/z* %: 344 ($[M+Na]^+$, 100).

6-[6-(5,5-Dimethyl-[1,3]dioxan-2-yl)hex-1-ynyl]-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid *tert*-Butyl Ester (1q).

Pale yellow oil (309 mg, 85%, 93% purity by ^{1}H NMR). R_f = 0.64 (petroleum ether-EtOAc, 4:1 + 1% Et_3N). ^{1}H NMR (200 MHz) δ (ppm): 5.44 (t, *J* = 4.0 Hz, 1 H), 4.45-4.39 (m, 1 H), 3.60-3.48 (m, 4 H), 3.44-3.35 (m, 2 H), 2.33 (t, *J* = 6.8 Hz, 2 H), 2.18-2.07 (m, 2 H), 1.83-1.63 (m, 6 H), 1.48 (s, 9 H), 1.16 (s, 3 H), 0.69 (s, 3 H). ^{13}C NMR (50.33 MHz) δ (ppm): 153.1 (s), 122.5 (s), 121.3 (d), 101.7 (d), 87.6 (s), 80.7 (s), 78.0 (s), 77.2 (t, 2 C), 43.4 (t), 33.9 (s), 30.1 (t), 28.3 (q, 3 C), 23.6 (t), 23.0 (t), 22.7 (t), 21.8 (q, 2 C), 19.2 (t). MS (EI) *m/z* %: 363 ($[M]^+$, 2), 307 (5), 178 (100), 141 (60), 121 (55), 57 (41).

(±)-4,5-*O*-Isopropylidene-4,5-dihydroxy-5,6-dihydro-2-(hex-1-ynyl)-4*H*-pyridine-1-carboxylic Acid *tert*-Butyl Ester (1r).

Pale yellow oil (218 mg, 65%). R_f = 0.06 (*n*-hexane-EtOAc, 20:1 + 1% Et_3N). ^1H NMR (400 MHz) δ (ppm): 5.61 (d, *J* = 3.9 Hz, 1 H), 4.46 (dd, *J* = 6.2, 2.3 Hz, 1 H), 4.21-4.16 (m, 1 H), 3.89 (dd, *J* = 12.9, 4.1 Hz, 1 H), 3.15 (dd, *J* = 12.9, 8.4 Hz, 1 H), 2.31 (t, *J* = 7.0 Hz, 2 H), 1.54-1.46 (m, 2 H), 1.47 (s, 9 H), 1.45-1.38 (m, 2 H), 1.42 (s, 3 H), 1.34 (s, 3 H), 0.89 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (100.4 MHz) δ (ppm): 152.7 (s), 126.2 (s), 118.1 (d), 108.9 (s), 91.1 (s), 81.3 (s), 76.3 (s), 72.5 (d), 69.9 (d), 46.0 (t), 30.4 (t), 28.1 (q, 3 C), 27.8 (q), 25.6 (q), 21.9 (t), 19.0 (t), 13.5 (t). MS (ESI) *m/z* %: 693 ($[2M+Na]^+$, 19), 358 ($[M+Na]^+$, 100).

Gold-catalyzed rearrangement and hydrolysis procedure. A volume of the enyne solution containing 1 mmol of substrate was concentrated and dried under *vacuum* (no heating) for 30 minutes before dissolving in anhydrous toluene. A 0.2 M AgOTf and a 4 mM Ph_3PAuCl solutions, both in anhydrous toluene, were prepared. The AgOTf solution (100 μL, 0.02 mmol) was added at r.t. to the 4 mM Ph_3PAuCl solution (5 mL, 0.02 mmol), under stirring and nitrogen atmosphere, and a white precipitate immediately formed. A solution of the enyne **1** (1.0 mmol) in anhydrous toluene (5 mL) was then added and the resulting mixture heated under reflux until disappearance of the starting material (TLC, usually 30 minutes). After cooling at 85 °C (external), the mixture was diluted with *tert*-butanol (10 mL) and powdered KOH (6 mmol) was added. The mixture was the heated at 85 °C until completion (TLC, usually 1 h). After cooling at r.t., water (15 mL) was added and the product extracted with EtOAc (3 x 10 mL); the combined organic extracts were washed once with brine (15 mL) and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, crude vinylogous amide **3** was purified by flash chromatography to obtain the pure compound.

Intermediate **2a** was isolated by filtration over a Celite pad of the mixture resulting from the gold-catalyzed rearrangement. The solvent was removed under *vacuum* and the residue analyzed without any purification.

Intermediate **2r**, isolated as reported for **2a**, was enough stable to be purified by flash chromatography (eluent: *n*-hexane-EtOAc, 10:1 + 1% Et_3N; R_f = 0.09) and pure **2r** could be characterized.

3-Propyl-7,8-dihydro-6*H*-pyrido[1,2-*c*][1,3]oxazin-1-one (2a).

Yellow oil (191 mg, 99%). ^{1}H NMR (200 MHz) δ (ppm): 5.37 (s, 1 H), 4.63 (t, *J* = 4.2 Hz, 1 H), 3.80-3.74 (m, 2 H), 2.27-2.08 (m, 2 H), 1.93-1.84 (m, 2 H), 1.71-1.52 (m, 4 H), 0.99 (t, *J* = 7.4 Hz, 3 H). ^{13}C NMR (50.33 MHz) δ (ppm): 151.1 (s), 148.6 (s), 132.0 (s), 100.4 (d), 99.2 (d), 42.4 (t), 33.8 (t), 21.2 (t), 20.5 (t), 19.1 (t), 13.2 (q).

(±)-6,7-*O*-Isopropylidene-6,7-dihydroxy-3-butyl-7,8-dihydro-6*H*-pyrido[1,2-*c*][1,3]oxazin-1-one (2r).

Colourless oil (103 mg, 37%). ^{1}H NMR (400 MHz) δ (ppm): 5.43 (s, 1 H), 4.66 (d, *J* = 4.1 Hz, 1 H), 4.55 (t, *J* = 4.9 Hz, 1 H), 4.27-4.23 (m, 1 H), 3.98 (dd, *J* = 13.5, 9.2 Hz, 1 H), 3.59 (dd, *J* = 13.5, 7.4 Hz, 1 H), 2.21 (t, *J* = 7.2 Hz, 2 H), 1.57-1.52 (m, 2 H), 1.45 (s, 3 H), 1.38 (s, 3 H), 1.38-1.30 (m, 2 H), 0.91 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (100.4 MHz) δ (ppm): 154.6 (s), 148.4 (s), 134.1 (s), 109.2 (s), 99.3 (d), 96.3 (d), 70.1 (d), 69.0 (d), 42.6 (t), 31.8 (t), 28.6 (t), 27.9 (q), 26.3 (q), 22.0 (t), 13.7 (q). MS (ESI) *m/z* %: 581 ($[2M+Na]^+$, 32), 302 ($[M+Na]^+$, 100).

(*Z*)-1-Piperidin-2-ylidene-pentan-2-one (3a).[12c]

Pale yellow oil (151 mg, 90%). R_f = 0.15 (Petroleum ether-EtOAc, 4:1). ^{1}H NMR (400 MHz) δ (ppm): 11.1 (br s, 1 H), 4.86 (s, 1 H), 3.31 (td, *J* = 5.9, 1.8 Hz, 2 H), 2.35 (t, *J* = 6.4 Hz, 2 H), 2.19 (t, *J* = 7.4 Hz, 2 H), 1.81-1.75 (m, 2 H), 1.73-1.65 (m, 2 H), 1.64-1.55 (m, 2 H), 0.92 (t, *J* = 7.4 Hz, 3 H). ^{13}C NMR (50.33 MHz) δ (ppm): 197.1 (s), 163.9 (s), 92.8 (d), 43.7 (t), 40.7 (t), 28.3 (t), 22.1 (t), 19.6 (t), 19.2 (t), 13.9 (q). MS (ESI)

m/z %: 357 ([2M+Na]$^+$, 100), 190 ([M+Na]$^+$, 18), 168 ([M+1]$^+$, 17). $C_{10}H_{17}NO$ (167.25): calcd C, 71.81; H, 10.25; N, 8.37. Found: C, 71.45, H, 10.32, N 8.17.

(*Z*)-1-Piperidin-2-ylidene-hexan-2-one (3b).

Pale yellow oil (121 mg, 67%). R_f = 0.16 (*n*-Hexane-EtOAc, 3:1). ^{1}H NMR (400 MHz) δ (ppm): 11.1 (br s, 1 H), 4.86 (s, 1 H), 3.31 (td, *J* = 6.1, 2.3 Hz, 2 H), 2.35 (t, *J* = 6.4 Hz, 2 H), 2.21-2.17 (m, 2 H), 1.81-1.75 (m, 2 H), 1.73-1.66 (m, 2 H), 1.59-1.51 (m, 2 H), 1.37-1.27 (m, 2 H), 0.89 (t, *J* = 7.4 Hz, 3 H). ^{13}C NMR (100.4 MHz) δ (ppm): 197.5 (s), 164.0 (s), 92.9 (d), 41.7 (t), 40.9 (t), 28.6 (t), 28.4 (t), 22.7 (t), 22.3 (t), 19.3 (t), 13.9 (q). MS (ESI) *m/z* %: 182 ([M+1]$^+$, 100). $C_{11}H_{19}NO \cdot 1/10\ H_2O$ (183.07): calcd C, 72.17; H, 10.57; N, 7.65. Found: C, 72.09; H, 10.90; N, 7.58.

(*Z*)-2-Phenyl-1-piperidin-2-ylidene-ethanone (3c).[9b,12c,13]

Yellow solid (165 mg, 82%). R_f = 0.18 (*n*-Hexane-EtOAc, 3:1). M. p. 57.6-58.2 °C. ^{1}H NMR (400 MHz) δ (ppm): 11.7 (br s, 1 H), 7.86-7.82 (m, 2 H), 7.41-7.35 (m, 3 H), 5.57 (s, 1 H), 3.41 (td, *J* = 5.9, 2.3 Hz, 2 H), 2.51 (t, *J* = 6.4 Hz, 2 H), 1.87-1.81 (m, 2 H), 1.80-1.73 (m, 2 H). ^{13}C NMR (100.4 MHz) δ (ppm): 187.0 (s), 165.8 (s), 140.7 (s), 130.1 (d), 128.1 (d, 2 C), 126.7 (d, 2 C), 90.4 (d), 41.1 (t), 28.9 (t), 22.2 (t), 19.3 (t). MS (ESI) *m/z* %: 425 ([2M+Na]$^+$, 100), 224 ([M+Na]$^+$, 10), 202 ([M+1]$^+$, 12). $C_{13}H_{15}NO$ (201.26): calcd C, 77.58; H, 7.51; N, 6.96. Found: C, 77.40, H, 7.54, N 6.58.

(*Z*)-2-(4-Methoxyphenyl)-1-piperidin-2-ylidene-ethanone (3d).

Yellow solid (190 mg, 82%). R_f = 0.20 (*n*-Hexane-EtOAc, 2:1). M. p. 230 °C (dec.). ^{1}H NMR (400 MHz) δ (ppm): 11.6 (br s, 1 H), 7.82 (d, *J* = 8.8 Hz, 2 H), 6.88 (d, *J* = 8.8 Hz, 2 H), 5.53 (s, 1 H), 3.84 (s, 3 H), 3.40 (t, *J* = 5.7 Hz, 2 H), 2.50 (t, *J* = 6.4 Hz, 2 H), 1.86-1.80 (m, 2 H), 1.79-1.73 (m, 2 H). ^{13}C NMR (100.4 MHz)

δ (ppm): 189.3 (s), 165.2 (s), 161.3 (s), 133.3 (s), 128.5 (d, 2 C), 113.3 (d, 2 C), 89.7 (d), 55.3 (q), 41.1 (t), 28.9 (t), 22.3 (t), 19.4 (t). MS (ESI) *m/z* %: 485 ($[2M+Na]^+$, 100), 254 ($[M+Na]^+$, 14), 232 ($[M+1]^+$, 41). $C_{14}H_{17}NO_2$ (231.29): calcd C, 72.70; H, 7.41; N, 6.06. Found: C, 72.44; H, 7.71; N, 6.33.

(*Z*)-2-Cyclopropyl-1-piperidin-2-ylidene-ethanone (3e).

Yellow oil (142 mg, 86%). R_f = 0.21 (*n*-Hexane-EtOAc, 3:1). ^{1}H NMR (400 MHz) δ (ppm): 11.0 (br s, 1 H), 5.03 (s, 1 H), 3.30 (td, *J* = 5.9, 2.3 Hz, 2 H), 2.37 (t, *J* = 6.2 Hz, 2 H), 1.80-1.74 (m, 2 H), 1.73-1.66 (m, 2 H), 1.63-1.56 (m, 1 H), 0.93-0.89 (m, 2 H), 0.69-0.65 (m, 2 H). ^{13}C NMR (100.4 MHz) δ (ppm): 195.9 (s), 163.2 (s), 92.9 (d), 40.9 (t), 28.4 (t), 22.3 (t), 19.5 (d), 19.4 (t), 8.3 (t, 2 C). MS (ESI) *m/z* %: 353 ($[2M+Na]^+$, 100), 188 ($[M+Na]^+$, 26), 166 ($[M+1]^+$, 32). $C_{10}H_{15}NO$ (165.23): calcd C, 72.69; H, 9.15; N, 8.48. Found: C, 72.33, H, 9.07, N 8.78.

(*Z*)-4-Phenyl-1-piperidin-2-ylidene-butan-2-one (3f).

Pale yellow foam (133 mg, 58%). R_f = 0.31 (*n*-Hexane-EtOAc, 3:1). ^{1}H NMR (400 MHz) δ (ppm): 11.2 (br s, 1 H), 7.29-7.14 (m, 5 H), 4.88 (s, 1 H), 3.33 (td, *J* = 5.6, 2.3 Hz, 2 H), 2.94-2.89 (m, 2 H), 2.55-2.51 (m, 2 H), 2.35 (t, *J* = 6.4 Hz, 2 H), 1.82-1.76 (m, 2 H), 1.75-1.67 (m, 2 H). ^{13}C NMR (100.4 MHz) δ (ppm): 195.6 (s), 164.3 (s), 142.2 (s), 128.3 (d, 2 C), 128.2 (d, 2 C), 125.6 (d), 92.9 (d), 43.4 (t), 41.0 (t), 32.3 (t), 28.5 (t), 22.3 (t), 19.4 (t). MS (ESI) *m/z* %: 230 ($[M+1]^+$, 100). $C_{15}H_{19}NO$ (229.32): calcd C, 78.56; H, 8.35; N, 6.11. Found: C, 78.91; H, 8.29; N, 5.89.

(*Z*)-4-(4-Methoxyphenyl)-1-piperidin-2-ylidene-butan-2-one (3g).

Pale yellow solid (137 mg, 53%). R_f = 0.28 (*n*-Hexane-EtOAc, 1:1). M.p. 59.1-60.2 °C. ^{1}H NMR (400 MHz) δ (ppm): 11.2 (br s, 1 H), 7.13 (d, *J* = 8.8 Hz, 2 H), 6.81 (d, *J* = 8.8 Hz, 2 H), 4.87 (s, 1 H), 3.77 (s, 3 H), 3.32

(td, *J* = 5.9, 2.3 Hz, 2 H), 2.87-2.83 (m, 2 H), 2.51-2.46 (m, 2 H), 2.34 (t, *J* = 6.4 Hz, 2 H), 1.81-1.75 (m, 2 H), 1.73-1.66 (m, 2 H). ^{13}C NMR (100.4 MHz) δ (ppm): 195.8 (s), 164.3 (s), 157.6 (s), 134.3 (s), 129.1 (d, 2 C), 113.6 (d, 2 C), 92.9 (d), 55.2 (q), 43.7 (t), 40.9 (t), 31.4 (t), 28.4 (t), 22.2 (t), 19.3 (t). MS (ESI) *m/z* %: 541 ($[2M+Na]^+$, 100), 282 ($[M+Na]^+$, 42), 260 ($[M+1]^+$, 23). $C_{16}H_{21}NO_2$ (259.34): calcd C, 74.10; H, 8.16; N, 5.40. C, 73.84; H, 7.97; N, 5.45.

(*Z*)-1-Piperidin-2-ylidene-3-buten-2-one (3i).

Starting from **1i**. Pale yellow oil (54 mg, 36%). R_f = 0.22 (*n*-Hexane-EtOAc, 1:1). ^{1}H NMR (400 MHz) δ (ppm): 11.7 (br s, 1 H), 6.27 (dd, *J* = 17.2, 10.2 Hz, 1 H), 6.09 (dd, *J* = 17.2, 2.1 Hz, 1 H), 5.41 (dd, *J* = 10.2, 2.1 Hz, 1 H), 4.97 (s, 1 H), 3.37 (td, *J* = 6.1, 2.1 Hz, 2 H), 2.42 (t, *J* = 6.4 Hz, 2 H), 1.84-1.78 (m, 2 H), 1.75-1.69 (m, 2 H). ^{13}C NMR (100.4 MHz) δ (ppm): 184.8 (s), 166.2 (s), 138.0 (d), 121.8 (t), 93.9 (d), 41.1 (t), 28.5 (t), 22.1 (t), 19.2 (t). MS (ESI) *m/z* %: 325 ($[2M+Na]^+$, 100), 152 ($[M+1]^+$, 93). $C_9H_{13}NO$ (151.21): calcd C, 71.49; H, 8.67; N, 9.26. Found: C, 71.72; H, 8.59; N, 8.87.

(*Z*)-5-Benzyloxy-1-piperidin-2-ylidene-pentan-2-one (3k).

Pale yellow oil (202 mg, 74%). R_f = 0.23 (Petroleum ether-EtOAc, 8:1). ^{1}H NMR (400 MHz) δ (ppm): 11.1 (br s, 1 H), 7.34-7.29 (m, 5 H), 4.87 (s, 1 H), 4.50 (s, 2 H), 3.51 (t, *J* = 6.6 Hz, 2 H), 3.32 (td, *J* = 6.0, 2.0 Hz, 2 H), 2.36-2.28 (m, 4 H), 1.97-1.88 (m, 2 H), 1.82-1.76 (m, 2 H), 1.73-1.67 (m, 2 H). ^{13}C NMR (100.4 MHz) δ (ppm): 196.4 (s), 164.2 (s), 138.7 (s), 128.3 (d, 2 C), 127.6 (d, 2 C), 127.4 (d), 93.0 (d), 72.7 (t), 70.1 (t), 40.9 (t), 38.2 (t), 28.4 (t), 26.3 (t), 22.3 (t), 19.3 (t). MS (ESI) *m/z* %: 569 ($[2M+Na]^+$, 100), 296 ($[M+Na]^+$, 66), 274 ($[M+1]^+$, 86). $C_{17}H_{23}NO_2$ (273.37): calcd C, 74.69; H, 8.48; N, 5.12. Found: C, 74.81; H, 8.83; N, 4.83.

(*Z*)-1-Piperidin-2-ylidene-5-(tetrahydropyran-2-yloxy)pentan-2-one (3l).

Pale yellow oil (192 mg, 72%). R_f = 0.23 (*n*-Hexane-EtOAc, 3:1). ^{1}H NMR (400 MHz) δ (ppm): 11.1 (br s, 1 H), 4.82 (s, 1-H), 4.52 (m, 1 H), 3.82-3.78 (m, 1 H), 3.71-3.65 (m, 1 H), 3.44-3.40 (m, 1 H), 3.39-3.33 (m, 1 H), 3.27-3.24 (m, 2 H), 2.31-2.21 (m, 4 H), 1.86-1.79 (m, 2 H), 1.78-1.70 (m, 2 H), 1.69-1.60 (m, 2 H), 1.57-1.38 (m, 4 H). ^{13}C NMR (100.4 MHz) δ (ppm): 196.3 (s), 163.9 (s), 98.5 (d), 92.8 (d), 67.1 (t), 62.0 (t), 40.8 (t), 38.2 (t), 30.6 (t), 28.3 (t), 26.2 (t), 25.4 (t), 22.2 (t), 19.4 (t), 19.2 (t). MS (ESI) *m/z* %: 557 ($[2M+Na]^+$, 14), 535 ($[2M+1]^+$, 16). $C_{15}H_{25}NO_3$ (267.36): calcd C, 67.38; H, 9.42; N, 5.24. Found: C, 67.12; H, 9.34; N, 5.18.

(*Z*)-1-Piperidin-2-ylidene-6-triisopropylsilanyloxy-hexan-2-one (3n).

Pale yellow oil (54 mg, 72%). R_f = 0.23 (*n*-Hexane-EtOAc, 6:1). ^{1}H NMR (400 MHz) δ (ppm): 11.1 (br s, 1 H), 4.87 (s, 1 H), 3.68 (t, *J* = 6.6 Hz, 1 H), 3.34-3.30 (m, 2 H), 2.35 (t, *J* = 6.4 Hz, 2 H), 2.22 (t, *J* = 7.2 Hz, 2 H), 1.81-1.76 (m, 2 H), 1.73-1.52 (m, 6 H, 4-H), 1.07-1.04 (m, 21 H). ^{13}C NMR (100.4 MHz) δ (ppm): 197.1 (s), 163.9 (s), 92.9 (d), 63.2 (t), 41.6 (t), 40.8 (t), 32.8 (t), 28.4 (t), 22.7 (t), 22.2 (t), 19.3 (t), 17.9 (q, 6 C), 11.9 (d, 3 C). MS (ESI) *m/z* %: 729 ($[2M+Na]^+$, 40), 376 ($[M+Na]^+$, 10), 354 ($[M+1]^+$, 100). $C_{20}H_{39}NO_2Si$ (353.61): calcd C, 67.93; H, 11.12; N, 3.96. Found: C, 67.79; H, 11.34; N, 4.18.

(*Z*)-7-Hydroxy-1-piperidin-2-ylidene-heptan-2-one (3o).

Pale yellow oil (152 mg, 72%). R_f = 0.22 (EtOAc). ^{1}H NMR (400 MHz) δ (ppm): 11.1 (br s, 1 H), 4.84 (s, 1 H), 3.62 (t, *J* = 6.4 Hz, 2 H), 3.30 (td, *J* = 5.9, 2.1 Hz, 2 H), 2.34 (t, *J* = 6.4 Hz, 2 H), 2.20 (t, *J* = 7.2 Hz, 2 H), 2.00 (br s, 1 H), 1.80-1.74 (m, 2 H), 1.71-1.65 (m, 2 H), 1.63-1.52 (m, 4 H), 1.40-1.32 (m, 2 H). ^{13}C NMR (100.4 MHz) δ (ppm): 197.0 (s), 164.2 (s), 93.0 (d), 62.6 (t), 41.6 (t), 40.9 (t), 32.5 (t), 28.4 (t), 25.9 (t), 25.5 (t), 22.2 (t), 19.3 (t). MS (ESI) *m/z* %: 445 ($[2M+Na]^+$, 100), 234 ($[M+Na]^+$, 9), 212 ($[M+1]^+$, 30). $C_{12}H_{21}NO_2$ (211.30): calcd C, 68.21; H, 10.02; N, 6.63. Found: C, 68.35; H, 10.17; N, 6.88.

(*Z*)-6-Oxo-1-piperidin-2-ylidene-heptanoic Acid (3p).

Prepared as reported according to the general procedure. Work-up: after cooling to r.t., water (15 mL) was added followed by 1 N HCl to reach pH 3; the product was then extracted with EtOAc (3 x 10 mL) and the combined organic extracts were washed once with brine (15 mL) and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, crude vinylogous amide **3p** was purified by flash chromatography to obtain the pure compound as a pale yellow oil (146 mg, 65%). R_f = 0.21 (*n*-Hexane-EtOAc, 1:3 + 1% AcOH). ^{1}H NMR (400 MHz) δ (ppm): 11.1 (br s, 1 H), 9.7 (br s, 1 H), 4.85 (s, 1 H), 3.33 (t, *J* = 5.9 Hz, 2 H), 2.37-2.31 (m, 4 H), 2.25-2.21 (m, 2 H), 1.81-1.75 (m, 2 H), 1.73-1.68 (m, 2 H), 1.68-1.63 (m, 4 H). ^{13}C NMR (100.4 MHz) δ (ppm): 196.3 (s), 178.2 (s), 165.0 (s), 93.1 (d), 41.0 (t), 40.9 (t), 34.1 (t), 28.4 (t), 25.8 (t), 24.8 (t), 22.1 (t), 19.2 (t). MS (ESI) *m/z* %: 473 ($[2M+Na]^+$, 100), 248 ($[M+Na]^+$, 6), 226 ($[M+1]^+$, 9). $C_{12}H_{19}NO_3$ (225.28): calcd C, 63.98; H, 8.50; N, 6.22. Found: C, 64.21; H, 8.21; N, 6.17.

(*Z*)-6-(5,5-Dimethyl-[1,3]dioxan-2-yl)-1-piperidin-2-ylidene-hexan-2-one (3q).

Pale yellow solid (219 mg, 78%). R_f = 0.24 (*n*-Hexane-EtOAc, 1:1). M.p. 68.6-70.4 °C. ^{1}H NMR (400 MHz) δ (ppm): 11.1 (br s, 1 H), 4.84 (s, 1 H), 4.41 (t, *J* = 4.9 Hz, 1 H), 3.57 (d, *J* = 11.1 Hz, 2 H), 3.39 (d, *J* = 10.9 Hz, 2 H), 3.30 (t, *J* = 5.7 Hz, 2 H), 2.33 (t, *J* = 6.4 Hz, 2 H), 2.21 (t, *J* = 7.0 Hz, 2 H), 1.81-1.74 (m, 2 H), 1.72-1.60 (m, 6 H, 4-H), 1.17 (s, 3 H), 0.69 (s, 3 H). ^{13}C NMR (100.4 MHz) δ (ppm): 196.6 (s), 164.1 (s), 102.2 (d), 93.0 (d), 77.2 (t, 2 C), 41.5 (t), 40.9 (t), 34.6 (t), 30.1 (s), 28.5 (t), 23.0 (q), 22.3 (t), 21.9 (q), 20.9 (t), 19.4 (t). MS (ESI) *m/z* %: 585 ($[2M+Na]^+$, 100), 304 ($[M+Na]^+$, 7), 282 ($[M+1]^+$, 5). $C_{16}H_{27}NO_3$ (281.39): calcd C, 68.29; H, 9.67; N, 4.98. Found: C, 68.35; H, 9.78; N, 5.03.

(±)-4,5-*O*-Isopropylidene-4,5-dihydroxy-2-oxopiperidine-1-carboxylic acid *tert*-butyl ester (8).

Et_3N (320 μL, 2.29 mmol), di-*tert*-butyl dicarbonate (460 mg, 1 eq) and DMAP (25 mg, 0.21 mmol) were added to a solution of **7** (356 mg, 2.08 mmol) in anhydrous DCM (12.5 mL), under stirring and nitrogen atmosphere. The resulting solution was heated under reflux for 6 h and every 1.5 h a further amount of di-

tert-butyl dicarbonate (230 mg, 0.5 eq) was added (in all 2.5 eq of di-*tert*-butyl dicarbonate were used). After cooling at room temperature, water (15 mL) was added and the product extracted with DCM (6 mL). The combined organics extracts were washed with aqueous 5% $KHSO_4$ (15 mL), satd $NaHCO_3$ (15 mL), H_2O (15 mL), brine (15 mL) and finally dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, crude **8** was purified by FCC (eluent: *n*-hexane-EtOAc, 1:1; R_f = 0.20) and pure **8** (455 mg, 81%) was obtained as a white solid.

M.p. 79.4-80.4 °C. ^{1}H NMR (400 MHz) δ (ppm): 4.59 (dt, *J* = 7.8, 2.9 Hz, 1 H), 4.45 (dt, *J* = 7.8, 2.3 Hz, 1 H), 4.36 (dd, *J* = 14.6, 2.3 Hz, 1 H), 3.20 (dd, *J* = 14.6, 2.1 Hz, 1 H), 2.75 (dd, *J* = 16.0, 2.9 Hz, 1 H), 2.43 (dd, *J* = 16.0, 3.3 Hz, 1 H), 1.47 (s, 9 H), 1.34 (s, 3 H), 1.28 (s, 3 H). ^{13}C NMR (100.4 MHz) δ (ppm): 168.5 (s), 151.6 (s), 108.9 (s), 82.9 (s), 72.4 (d), 71.5 (d), 46.3 (t), 39.2 (t), 27.8 (q, 3 C), 26.0 (q), 24.1 (q). MS (ESI) *m/z* %: 565 ($[2M+Na]^+$, 100), 294 ($[M+Na]^+$, 15), 272 ($[M+1]^+$, 4). $C_{13}H_{21}NO_5$ (271.31): calcd C, 57.57; H, 7.80; N, 5.16. Found: C, 57.57; H, 7.98; N, 5.21.

(±)-3,4-*O*-Isopropylidene-6-(diphenoxyphosphoryloxy)-3,4-dihydroxy-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid *tert*-Butyl Ester (9).

A solution of 0.5 M KHMDS in toluene (2.4 mL, 1.20 mmol) was diluted in anhydrous THF (6.3 mL) and cooled at -78°C. A solution of **8** (218 mg, 0.80 mmol) in anhydrous THF (3.7 mL) was then added dropwise, keeping the temperature below -70 °C, and the resulting mixture was stirred for 1.5 h. Diphenylchlorophosphate (250 μL, 1.20 mmol) was slowly added and, after 1 h, the mixture was allowed to warm at 0°C. Aqueous 10% NaOH (19 mL) was slowly added and the product extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with 10% NaOH (10 mL) and dried over K_2CO_3 for 30 min. After filtration and evaporation of the solvent, the crude was purified over a short pad of silica gel, eluting with *n*-hexane-EtOAc, 2:1 containing 1% Et_3N (R_f 0.21), affording pure **9** as a colourless oil (399 mg, 99%). This was stored as ~1.0 M solution in the same eluent and concentrated under *vacuum* immediately before use for the next step.

^{1}H NMR (400 MHz) δ (ppm): 7.36-7.32 (m, 4 H), 7.28-7.17 (m, 6 H), 5.31-5.29 (m, 1 H), 4.71-4.68 (m, 1 H), 4.31-4.27 (m, 1 H), 3.91 (dd, *J* = 13.7, 4.9 Hz, 1 H), 3.55 (dd, *J* = 13.7, 1.9 Hz, 1 H), 1.45 (s, 3 H), 1.43 (s, 9 H), 1.35 (s, 3 H). ^{13}C NMR (100.4 MHz) δ (ppm): 153.1 (s), 150.3 (s), 144.2 (s), 144.1 (s), 129.8 (d, 4 C), 125.6 (d, 2 C), 120.1 (d, 2 C), 120.0 (d, 2 C), 110.0 (s), 99.6 (d), 73.6 (d), 71.0 (d), 48.7 (t), 28.0 (q, 3 C), 27.7 (q), 25.7 (q).

(±)-4-Phenyl-1-piperidin-2-ylbutan-2-one (10).

Vinylogous amide **3f** (20.9 mg, 0.09 mmol) was dissolved in CH_3OH (4 mL); PtO_2 (1% mol) and 70% $HClO_4$ (7 μL) were added and the mixture was flushed with H_2 and vigorously stirred under H_2 atmosphere for 19 h. The mixture was neutralized by K_2CO_3 (s) and left under stirring for 30 min. After filtration over a short Celite pad, the solvent was removed under *vacuum* and the residue taken up into DCM (5 mL). The organic phase was washed once with water (5 mL) and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent pure amine **10** (21 mg, quantitative) was obtained as a pale yellow oil.

R_f = 0.30 (EtOAc-MeOH, 2:1). ^{1}H NMR (400 MHz) δ (ppm): 7.28-7.24 (m, 2 H), 7.19-7.14 (m, 3 H), 2.99-2.95 (m, 1 H), 2.95-2.70 (m, 1 H), 2.88 (t, *J* = 7.4 Hz, 2 H), 2.74-2.70 (m, 2 H), 2.69-2.62 (m, 1 H), 2.44 (d, *J* = 6.2 Hz, 2 H), 2.05-1.95 (s br, 1 H), 1.75-1.72 (m, 1 H), 1.60-1.50 (m, 2 H), 1.42-1.27 (m, 2 H), 1.16-1.06 (m, 1 H). ^{13}C NMR (100.4 MHz) δ (ppm): 209.5 (s), 140.9 (s), 128.4 (d, 2 C), 128.2 (d, 2 C), 126.1 (d), 52.4 (d), 50.0 (t), 46.8 (t), 44.8 (t), 32.6 (t), 29.6 (t), 26.0 (t), 24.6 (t). MS (ESI) *m/z* %: 232 ([M+1]$^+$, 100). $C_{15}H_{21}NO$ (231.33): calcd C, 77.88; H, 9.15; N, 6.05. Found: C, 77.99; H, 9.08; N, 6.13.

(±)-4-(4-Methoxyphenyl)-1-piperidin-2-ylbutan-2-one (11).[32]

Prepared as reported for **10**, starting from **3g** (51 mg, 0.19 mmol) and obtaining, after chromatographic purification, pure **11** (36 mg, 73%) as a pale yellow oil.

R_f = 0.30 (EtOAc-MeOH, 2:1). ^{1}H NMR (400 MHz) δ (ppm): 7.06 (d, *J* = 8.6 Hz, 2 H), 6.80 (d, *J* = 8.6 Hz, 2 H), 3.76 (s, 3 H), 2.99-2.96 (m, 1 H), 2.96-2.88 (m, 1 H), 2.81 (t, *J* = 7.6 Hz, 2 H), 2.69-2.66 (m, 2 H), 2.66-2.58 (m, 1 H), 2.43 (d, *J* = 6.4 Hz, 2 H), 1.77-1.68 (m, 1 H), 1.60-1.48 (m, 2 H), 1.43-1.27 (m, 2 H), 1.15-1.06 (m, 1 H). ^{13}C NMR (100.4 MHz) δ (ppm): 209.7 (s), 157.9 (s), 132.9 (s), 129.2 (d, 2 C), 113.9 (d, 2 C), 55.2 (q), 52.4 (d), 50.1 (t), 46.8 (t), 45.1 (t), 32.6 (t), 28.7 (t), 26.0 (t), 24.6 (t). MS (ESI) *m/z* %: 262 ($[M+1]^+$, 100). $C_{16}H_{23}NO_2$ (261.36): calcd C, 73.53; H, 8.87; N, 5.36. Found: C, 73.48; H, 8.92; N, 5.52.

6-Heptynoic Acid Methyl Ester.

Prepared as reported for 5-hexynoic acid methyl ester,[37] starting from 6-heptynoic acid (378 mg, 3.0 mmol). The so obtained methyl ester was used without further purification in the Sonogashira coupling reaction.

Colourless oil (290 mg, 69%). R_f = 0.41 (*n*-Hexane-EtOAc, 10:1). ^{1}H NMR (200 MHz) δ (ppm): 3.67 (s, 3 H), 2.34 (t, *J* = 7.3 Hz, 2 H), 2.21 (td, *J* = 7.0, 2.6 Hz, 2 H), 1.95 (t, *J* = 2.6 Hz, 2 H), 1.82-1.63 (m, 2 H), 1.62-1.47 (m, 2 H).

5,5-Dimethyl-2-pent-4-ynyl-[1,3]dioxane.

5-Hexynal[38] (136 mg, 1.4 mmol) was dissolved in dry toluene (30 ml) and 2,2-dimethyl-1,3-propanediol (190 mg, 1.3 eq,) and *p*-TSA monohydrate (100 mg, 0.5 mmol) were added. The reaction mixture was heated under reflux and water was removed by Dean-Stark azeotropic distillation. After 15 h, reaction was quenched by addition of water (10 ml) and the product was extracted with Et_2O (3 x 10 mL); the combined organic extracts were washed with aqueous 10% NaOH solution (15 ml), brine and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, crude alkyne was purified by flash column chromatography (eluent: petroleum ether-EtOAc, 4:1; R_f = 0.62) to yield 5,5-dimethyl-2-pent-4-ynyl[1,3]dioxane (133 mg, 70%) as a colourless oil.

^{1}H NMR (200 MHz) δ (ppm): 4.38-4.33 (m, 1 H), 3.56-3.46 (m, 2 H), 3.41-3.27 (m, 2 H), 2.20-2.08 (m, 2 H), 1.92-1.85 (m, 1 H), 1.72-1.50 (m, 4 H), 1.10 (s, 3 H), 0.63 (s, 3 H).

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Supporting Information

Copies of the ^{1}H and ^{13}C NMR spectra of compounds **1a-r**, **2a** and **2r**, **3a-q**, **8-11,** 6-heptynoic acid methyl ester and 5,5-dimethyl-2-pent-4-ynyl[1,3]dioxane. This material is available free of charge via the Internet at http://pubs.acs.org.

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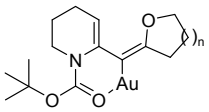
(29) Two of these vinylogous amides were known: compound **3a**[12c] and **3c**.[9b,12c,13]

(30) Vinylogous amide **3h** was identified in the crude reaction mixture by its diagnostic ^{1}H NMR singlet at 4.90 ppm and the side chain signals at 3.62 (t, J = 7.0 Hz) and 2.38 (t, J = 7.0 Hz) ppm.

(31) This could result in the sequestration of Au(I) and the interruption of any catalytic cycle.



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