Diastereoselective Preparation of Silylated Pyrrolidones through Palladium-Catalysed Cyclisations

Serge Thorimbert,[a] Giuliano Giambastiani,[a,b][‡] Claude Commandeur,[a] Maxime Vitale,[b] Giovanni Poli,*[b] and Max Malacria*[a]

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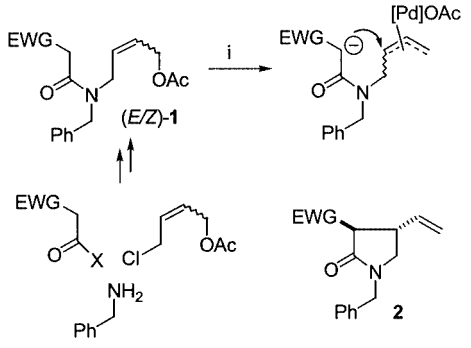
A new palladium-catalysed allylic alkylation affording silylated 3-vinylpyrrolidones has been developed. The method relies upon the interaction between a stabilized acetamide enolate anion and a silicon-containing, nitrogen-tethered η^3-allylpalladium moiety. Two variants have been studied, involving the location of the silicon atom on either olefinic carbon atom of the cyclisation precursor. In both cases 5-*exo* ring closure was the only cyclisation process observed. The stereoselectivity of these processes is discussed. These results contrast with related β-oxo ester cyclisations, in which competitive 7-*endo* mode is observed.

Introduction

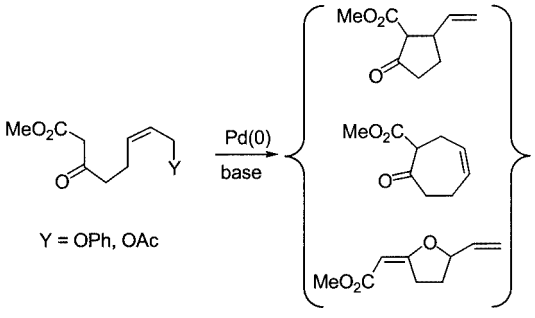
Some of us recently reported a novel Pd-catalysed route to 3,4-disubstituted pyrrolidones.[1] Such a cyclisation process was based on the interaction between a resonance-stabilized carbanion and an allylic acetate function, tethered through a nitrogen atom (Scheme 1). Careful analysis of the reaction products in all the cases studied revealed that the reaction is completely regio- and stereoselective. In fact, the *trans*-3,4-disubstituted pyrrolidone was always obtained as the only isomer (Scheme 1).

Although the pyrrolidone ring was the expected cyclisation product, the total absence of azepinone, arising from a potential competitive 7-*endo* process, could not have been anticipated from the outset. The above regiochemical result is of special interest in view of the fact that the Pd-catalysed cyclisation of methyl 3-oxo-8-phenoxy-6-octenoate and methyl 8-acetoxy-3-oxo-6-octenoate, which may be regarded as carbon-tethered analogues of the above cyclisation precursors, was reported to give a mixture of tetrahydrofuran, vinylcyclopentanone and cycloheptenone in



Scheme 1. Reagents and conditions: $Pd_2(dba)_3$ (0.05 equiv.), PPh_3 (0.5 equiv.), BSA (1.2 equiv.), AcOK (0.1 equiv.), THF reflux, 12 h; EWG: CO_2Me, COMe, CN, SO_2Ph, $PO(OEt)_2$

proportions highly dependent on the reaction conditions (Scheme 2).[2,3]



Scheme 2. Pd^0-catalysed cyclisation of 8-alkoxy-3-oxo-6-octenoates

On the other hand, it is known that the presence of a trialkylsilyl group can profoundly modify the reactivity of

[a] Laboratoire de Chimie Organique, UMR 7611, Université P. et M. Curie,
4, Place Jussieu BP 229, 75252 Paris Cedex 05, France
Fax: (internat.) + 33-1/44277360
E-mail: malacria@ccr.jussieu.fr
[b] Laboratoire de Chimie Organique, UMR 7611, Université P. et M. Curie,
4, Place Jussieu BP 183, 75252 Paris Cedex 05, France
Fax: (internat.) + 33-1/44277567
E-mail: poli@ccr.jussieu.fr
[‡] Present address: CNR, Institute of Chemistry of Organometallic Compounds (ICCOM), Florence Research Area,
Via Madonna del Piano, 50019 Sesto Fiorentino, Firenze, Italy

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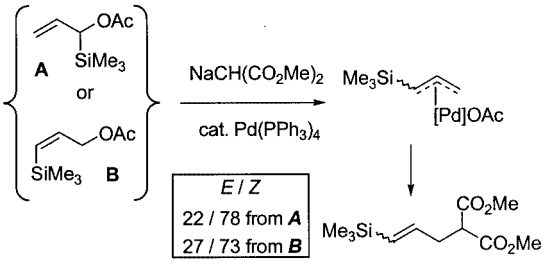
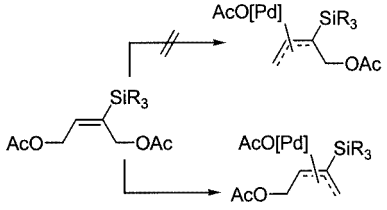
η^3-allylpalladium complexes.[4] Hirao and co-workers,[5,6] for example, were the first to report that Me_3Si-substituted η^3-allylpalladium complexes direct the addition of nucleophiles exclusively to the distal position relative to the silicon atom, thereby affording the corresponding vinylsilanes (Scheme 3). Such a regioselectivity may be accounted for in terms of steric factors, charge distribution of the allyl complex,[7] as well as the stability of the newly formed (olefin)Pd^0 complex.[8]



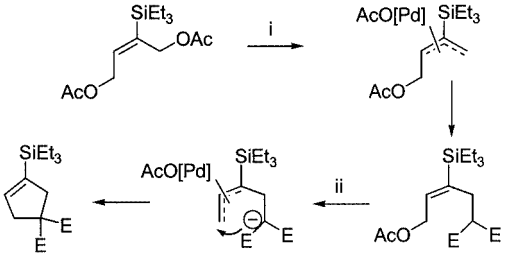
Scheme 3. The directing effect of the silicon atom in the addition of nucleophiles to η^3-allylpalladium complexes

Some of us have reported that the ionisation of 1,4-diallyl systems carrying an R_3Si group on the vinylic carbon atom takes place with complete chemoselectivity so as to expel the acetoxy group vicinal to the silicon atom (Scheme 4).[9,10] Although it is tempting to invoke acetoxy−silicon coordination to explain the above selectivity, stereoelectronic factors are in fact responsible for such behaviour.[11]



Scheme 4. The directing effect of the silicon atom in the Pd^0-catalysed ionisation of 1,4-diallyl systems

These studies allowed the development of a new palladium-catalysed cyclisation reaction, through which 1,4-diacetoxy-2-(triethylsilyl)but-2-ene is converted into a silyl-substituted cyclopentene.[12] The role of the silicon atom in this overall annulation process is crucial and twofold. In fact, as anticipated above, in the former C−C bond formation the bulky trialkylsilyl donor group regiodirects the ionisation of the starting diallyl system. In addition, the same group is expected to prefer *syn* disposition in the transiently generated η^3-allylpalladium complex,[13] so as to allow a remarkable 5-*endo* process to take place (Scheme 5).

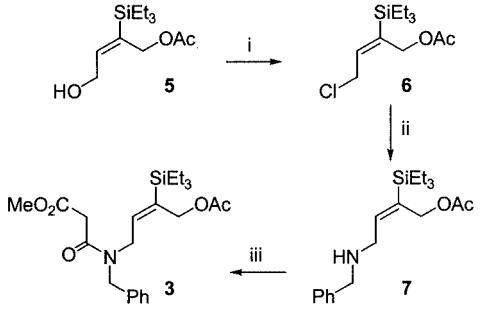


Scheme 5. Reagents and conditions: i: $NaCH(CO_2Me)_2$, 5% $Pd(PPh_3)_4$, THF, room temp. (85%); ii: NaH, 5% $Pd(PPh_3)_4$, THF, 60 °C (74%)

We thus decided to start a joint project to study the effect of silicon substitution on an amide-based cyclisation such as those presented above. In particular, we were intrigued to verify whether such modifications could still permit cyclisations, and, in positive cases, to effect a possible 5-*exo* versus 7-*endo* preference. In this paper we present our results in full detail.[14]

Results and Discussion

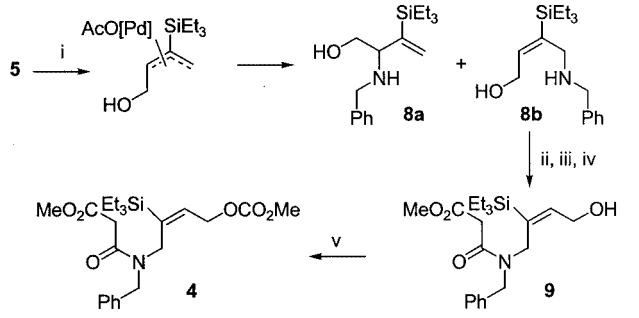
As discussed above, we set out to prepare two cyclisation precursors (**3** and **4**) carrying the trialkylsilyl moiety on either alkenyl carbon atom, so as to study their Pd-catalysed cyclisation. The first cyclisation precursor **3** was obtained in three steps from the silylated allylic alcohol **5**.[9] Chlorination of the alcohol function gave the corresponding chloride **6**, which was immediately treated with benzylamine to give the secondary allylic amine **7**. Malonylation under standard conditions gave the desired precursor **3** (Scheme 6).



Scheme 6. Preparation of the cyclisation precursor **3**; reagents, conditions: i: PPh_3, CCl_4; ii: $PhCH_2NH_2$, MeCN (63% from **5**); iii: MeO_2CCH_2COCl, NEt_3, CH_2Cl_2 (81%)

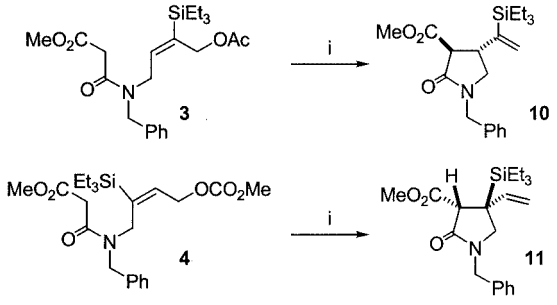
The second cyclisation precursor was obtained from the same key vinylsilane **5** as used in the previous synthetic sequence. Palladium-catalysed allylic amination of **5** in the presence of benzylamine afforded the regioisomeric secondary amines **8a** and **8b** in a 24:76 ratio, the major isomer being a stereohomogeneous amino alcohol[15] deriving from amine addition to the less substituted η^3-allyl terminus. At this stage, *N*-malonylation of the major isomer **8b**, followed

by *O*-derivatisation, was necessary. Surprisingly, *N*-malonylation of this amino alcohol took place with competitive *O*-malonylation. Ironically enough, treatment of the same amino alcohol with acetic anhydride gave exclusively nitrogen acetylation. The problem was solved by temporary protection of the hydroxy function as the TMS derivative before the *N*-malonylation step. The desired precursor **4** was eventually obtained in nearly quantitative yield by treatment of allylic alcohol **9** with methyl chloroformate (Scheme 7).



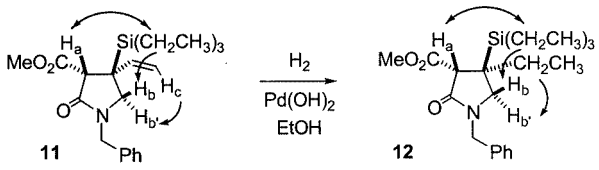
Scheme 7. Preparation of the cyclisation precursor **4**; reagents, conditions: i: $PhCH_2NH_2$, NEt_3, 5% $Pd(OAc)_2$, 10% dppe, THF, room temp. (68%); ii: Me_3SiCl, NEt_3, THF, room temp.; iii: MeO_2CCH_2COCl, NEt_3, CH_2Cl_2; iv: 10% HCl until pH = 2−3, THF, room temp. (82% from **8b**); v: MeO_2CCl, pyridine, CH_2Cl_2, room temp. (≥ 98%)

After some misleading preliminary cyclisation experiments, we found that treatment of the sodium enolate of **3** with 5% $Pd(OAc)_2$ and 10% 1,2-bis(diphenylphosphanyl)-ethane (dppe) in DMF at 100 °C for 30 min cleanly gave the pyrrolidone **10** in a completely regio- and stereoselective way (Scheme 8). More interestingly, subjection of the silylated derivative **4** to the same reaction conditions gave pyrrolidone **11** as a single isomer.



Scheme 8. Pd-catalysed cyclisation of precursors **3** and **4**; reagents and conditions: i: $Pd(OAc)_2$ (5%), dppe (10%), NaH, DMF, 100 °C (**3** → **10**: 90%; **4** → **11**: 52%)

A 3,4-*trans* stereochemistry was assigned to compound **10** on the basis of our previous results[1] and of the expected base-promoted equilibration after C−C bond formation. On the other hand, the same argument could not be applied to the cyclisation of amide **4**. Accordingly, the alkenylpyrrolidone **11** was hydrogenated to provide the saturated pyrrolidone **12** for analytical purposes, and both compounds were subjected to careful NMR analysis (Scheme 9).



Scheme 9. Hydrogenation of alkenylpyrrolidone **11** to **12** and their relevant NOE interactions

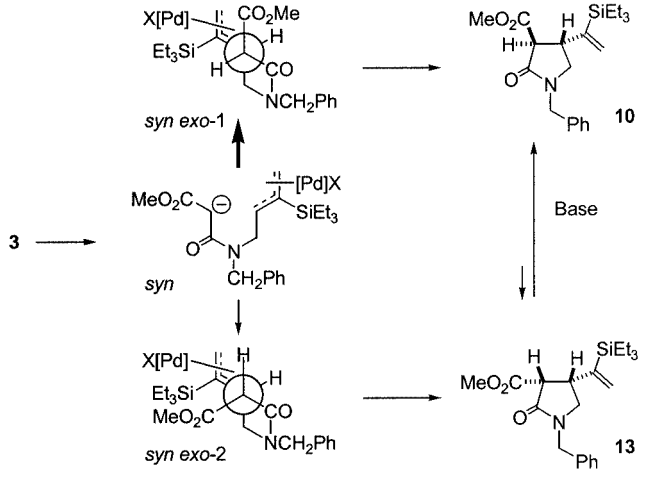
Inspection of the NOE difference spectra for the two pyrrolidones in either $CDCl_3$ or C_6D_6 allowed assignment of the relative stereochemistry as indicated in Scheme 9. Indeed, in both the compounds examined, irradiation of the methylene groups directly bound to the silicon atom brought about a significant signal enhancement of H_a and H_b. Furthermore, irradiation either of H_c in **11** or of the methylene group linked at C-4 in **12** gave rise to a considerable signal enhancement of $H_{b'}$ without affecting H_a (Scheme 9). The above results are thus in agreement with a *trans*-CO_2Me/$SiEt_3$ disposition in **11** and **12**.

Coming back to the regiochemical issue, the above results reveal the intrinsic and total preference of substrates **3** and **4** for a 5-*exo* process, even when the C−C bond formation involves reaction at the η^3-allyl terminus bearing the bulky trialkylsilyl group. It should be pointed out, however, that the significant decrease in yield (90 vs. 52%) observed on passing from the former to the latter cyclisation, well reflects the difference in the efficiencies of the two processes.

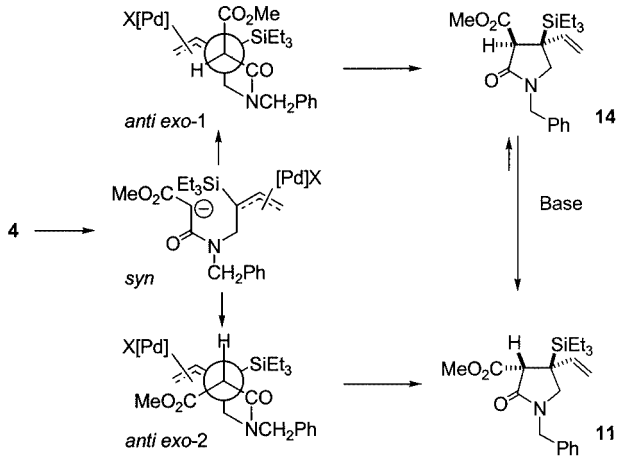
Generation of a *syn*-configured η^3-allylpalladium complex as the main transient species is expected in the first step of the former cyclisation process.[16−19] More precisely, evolution to the observed pyrrolidone **10** should involve the more favoured *syn-exo*-1 transition state, in which CO_2Me/$SiEt_3$ interactions are minimised (Scheme 10). Furthermore, any minor *cis* diastereoisomer **13** possibly formed via the alternative *syn-exo*-2 transition state would be in any case converted into the *trans* isomer **10** by base-promoted equilibration. Therefore, the *trans* diastereoisomer **10** turns out to be both kinetically (with reference to the C−C bond formation) and thermodynamically favoured.

Conversely, the structures *anti-exo*-1 and/or *anti-exo*-2, in which the bulky silicon atom occupies the *syn* position and the rest of the chain is forced to occupy the *anti* one, would be expected to be the main species involved in the cyclisation of the silylated precursor **4** (Scheme 11). Here, again, reversible base-promoted deprotonation of the initially formed kinetic cyclised product(s) **14** is expected to drive the equilibrium toward the most stable diastereoisomer **11**, in which the bulky trialkylsilyl group and the vicinal methoxycarbonyl group are *trans*-disposed to one another.

The constant and exclusive formation of pyrrolidone structures from the above amide precursors indicates that a 7-*endo*-type approach is forbidden in this case. Such a phenomenon, which contrasts with what was observed with the related β-oxo esters, is certainly associated with the am-



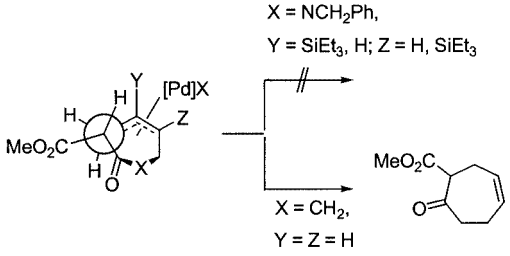
Scheme 10. Stereochemical outcome in the cyclisation of amide **3** to pyrrolidone **10**



Scheme 11. Stereochemical outcome in the cyclisation of amide **4** to pyrrolidone **11**

ide bond.[20] Indeed, the nature of such a function would be expected to force the C−C(O)−*N*−C dihedral angle value of the reacting cyclisation precursors toward a planar arrangement (0 or 180°), thereby disfavouring the 7-*endo* cyclisation. Obviously, such a strong torsional constraint is absent in β-oxo esters (Scheme 12).

Finally, an alkylation experiment was carried out on the 4-(triethylsilyl)-4-vinylpyrrolidone **11**, in order to verify the synthetic potential of this C−C bond formation for future applications. In the event, deprotonation of **11** with NaH in DMF, followed by treatment of the thus formed enolate



Scheme 12. 7-*endo* approach in the intramolecular allylic alkylation: comparison between β-amido- and β-oxo esters

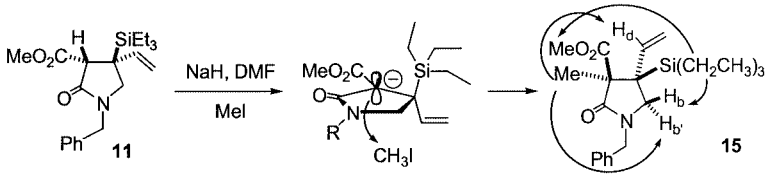
with methyl iodide, gave rise to the methylated pyrrolidone **15** as the only diastereoisomer (Scheme 13). Inspection of its NOE difference spectrum revealed an unambiguous spatial proximity between the methyl group of the ester function and the methylene groups directly bound to the silicon atom, thereby allowing assignment of the relative stereochemistry as shown in Scheme 13. The above alkylation is clearly an irreversible process, devoid of particular coordination or chelation effects, and final equilibration is no longer possible (see above). Consequently, the observed selectivity can be explained on purely steric grounds, in which the overwhelming hindrance of the triethylsilyl group stereodirects alkylation *anti* to itself. This result may be of interest for future synthetic applications.

Conclusion

This new investigation has shown that the formal introduction of a trialkylsilyl group into either position of the double bond in the precursor still permits the cyclisation to take place. As in the previous studies, only 5-*exo* cyclisations are observed, thereby producing 3-vinylpyrrolidones silylated at strategic positions. These results contrast with related β-oxo ester cyclisations, in which a competitive 7-*endo* mode is observed. In both cases the cyclisations were completely diastereoselective, and should involve a final base-promoted equilibration of the acidic position. Furthermore, the presence of a 4-(trialkylsilyl) substituent in the resulting pyrrolidone allows alkylation to take place exclusively from the face opposite to it. Further modifications of the obtained products, exploiting the rich chemistry of allyl- and vinylsilanes,[21] are planned in future studies.

Experimental Section

General Remarks: All reactions requiring anhydrous conditions were performed under a positive pressure of nitrogen or argon in



Scheme 13. Diastereoselective methylation of pyrrolidone **11** and relevant NOE interactions in **15**

oven-dried glassware. All solvents were purified and distilled by standard methods. Final product solutions were dried with $MgSO_4$ or Na_2SO_4 and filtered, and the solvents were evaporated under reduced pressure in a rotary evaporator. Thin layer chromatography (TLC) was performed on Merck Silica gel 60 F254. Chromatographic purifications were conducted on 40−63 μm or 15−40 μm silica gel. All compounds were isolated as oils unless otherwise specified, and their purities were determined to be > 95% by NMR analysis. ^1H and ^{13}C NMR spectra were recorded with Bruker spectrometers (200 MHz AC 200 and 400 MHz ARX 400). Chemical shifts are given in ppm, referenced to the residual proton resonances of the solvents (δ = 7.26 ppm for $CDCl_3$; δ = 7.16 ppm for C_6D_6). Coupling constants (*J*) are given in Hertz (Hz). The letters m, s, d, t, q, quint mean multiplet, singlet, doublet, triplet, quadruplet, quintuplet, respectively. The letters br. mean broad. IR spectra were recorded with a Perkin−Elmer 1420 spectrometer. Elemental analyses were performed by the Service Régional de Microanalyse de l'Université Pierre et Marie Curie (Paris VI).

4-Hydroxybut-2-ynyl Acetate: Distilled NEt_3 (20.9 mL, 150.4 mmol) was added to a solution of 2-butyne-1,4-diol (12.95 g, 150.4 mmol) in dry CH_2Cl_2/THF (60 mL/20 mL), and the resulting suspension was stirred at room temperature until dissolution was complete. Acetic anhydride (13 mL, 138.4 mmol) was then added to the reaction mixture at 0 °C dropwise over 30 min. The reaction mixture was then warmed to room temperature and stirred for further 4 h. Water was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 40 mL). The collected organic layers were dried and the solvents were evaporated in vacuo. Flash chromatography of the crude products (EtOAc/hexanes, 40:60) gave the pure monoacetate as a colourless oil (46%). ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.04 (s, 3 H), 3.42 (s, 1 H), 4.25 (s, 2 H), 4.65 (s, 2 H) ppm.

(*E*)-4-Acetoxy-3-(triethylsilyl)but-2-en-1-ol (5) and (*E*)-4-Acetoxy-2-(triethylsilyl)but-2-en-1-ol (5′): Et_3SiH (1.72 mL, 10.7 mmol) and $H_2PtCl_6{\cdot}6H_2O$ (0.1 M solution in THF, 0.060 mL, 0.006 mmol) were added in that order, under nitrogen, to a solution of 4-hydroxybut-2-ynylacetate (1.31 g, 10.2 mmol) in dry THF (25 mL), and the resulting reaction mixture was stirred at room temperature overnight. The solvent was then removed in vacuo and the crude product was purified by flash chromatography (EtOAc/hexanes, 20:80) to afford the two hydrosilylated regioisomers (**5**: 56%; **5′**: 13%).

5: ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.65 (q, *J* = 8 Hz, 6 H), 0.94 (t, *J* = 8 Hz, 9 H), 2.05 (s, 3 H), 4.31 (d, *J* = 6.1 Hz, 2 H), 4.72 (s, 2 H), 6.09 (t, *J* = 6.1 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 2.9, 7.2, 20.9, 59.2, 62.9, 134.2, 144.3, 171.0 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3400, 2940, 2900, 1740, 1610, 1230, 1010, 720 cm^{-1}. $C_{12}H_{24}O_3Si$: calcd. C 58.97, H 9.90; found C 59.03, H 9.82.

5′: ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.61 (q, *J* = 8 Hz, 6 H), 0.92 (t, *J* = 8 Hz, 9 H), 2.06 (s, 3 H), 2.15 (br. s, 1 H), 4.25 (s, 2 H), 4.73 (d, *J* = 11 Hz, 2 H), 5.82 (t, *J* = 10.2 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 2.9, 7.3, 21.0, 60.6, 61.5, 136.3, 142.6, 171.0.

(2*E*)-4-(Benzylamino)-2-(triethylsilyl)but-2-en-1-yl Acetate (7) via the Chloride 6: PPh_3 (0.304 g, 1.16 mmol) was added under N_2 to a solution of the acetate **5** (0.189 g, 0.77 mmol) in dry CH_3CN (8 mL), and the resulting suspension was gently warmed until dissolution was complete. CCl_4 (0.224 mL, 2.32 mmol) was then added, and the resulting solution was heated at reflux for 20 min. The thus formed allylic chloride **6** was then cooled to room temperature, and benzylamine (0.253 mL, 2.32 mmol) was added dropwise. After 2 h of heating at reflux with stirring, the reaction mixture was treated with water (10 mL) and subjected to standard extractive workup with CH_2Cl_2 (3 × 15 mL). Flash chromatography (hexanes/ethyl acetate/triethylamine, 80:17:3) gave the pure amine **7** (63%). ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.60−0.68 (6 H), 0.88−0.96 (9 H), 1.77 (br. s, 1 H), 2.03 (s, 3 H), 3.41 (d, *J* = 6.2 Hz, 2 H), 3.78 (s, 2 H), 4.68 (s, 2 H), 6.00 (t, *J* = 6.2 Hz, 1 H), 7.24−7.32 (5 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 3.1, 7.3, 20.9, 47.0, 53.5, 63.1, 127.1, 128.3, 128.5, 134.8, 139.9, 143.9, 170.8 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3685, 3029, 2956, 2912, 2878, 1728 cm^{-1}. MS (EI): *m*/*z* (%) = 304 (3.66) [M^+ − Et], 154 (60), 91(100). $C_{19}H_{31}NO_2Si$ (333.54): calcd. C 68.42, H 9.37, N 4.20; found C 68.40, H 9.19, N 4.31.

Methyl 3-{[(2*E*)-4-Acetoxy-3-(triethylsilyl)but-2-enyl](benzyl)-amino}-3-oxopropanoate (3): NEt_3 (64 μL, 0.46 mmol) and methyl 3-chloro-3-oxopropanoate (49 μL, 0.46 mmol) were added dropwise at 0 °C, in that order, to a solution of the allyl(benzyl)amine **7** (0.102 g, 0.31 mmol) in CH_2Cl_2 (5 mL). After stirring at room temperature for 6 h, the reaction mixture was treated with water (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The collected organic layers were dried and the solvents were evaporated in vacuo. Flash chromatography of the crude product (EtOAc/hexanes, 40:60) gave the pure amide **3** (81%). ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.54 (q, *J* = 8 Hz, 6 H), 0.85 (t, *J* = 8 Hz, 9 H), 1.92 (s, 3 H, 40%), 1.97 (s, 3 H, 60%), 3.47 (s, 2 H, 40%), 3.49 (s, 2 H, 60%), 3.69 (s, 3 H, 40%), 3.73 (s, 3 H, 60%), 4.01 (d, *J* = 5.6 Hz, 2 H, 60%), 4.19 (d, *J* = 5.6 Hz, 2 H, 40%), 4.48−4.61 (4 H), 5.63 (t, *J* = 5.4 Hz, 1 H, 60%), 5.77 (t, *J* = 5.4 Hz, 1 H, 40%), 7.13−7.32 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 2.8, 2.9, 7.2, 20.8, 41.0, 41.1, 44.1, 46.5, 49.2, 51.4, 52.4, 62.2, 62.3, 126.4, 127.6, 127.9, 128.2, 128.7, 129.0, 135.9, 136.7, 136.9, 137.4, 139.9, 166.3, 166.4, 167.9, 168.0, 170.5, 170.6 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3030, 2954, 2914, 2875, 1740, 1642, 1425 cm^{-1}. MS (EI): *m*/*z* (%) = 374 (11) [M^+ − OAc], 345 (38), 91 (100). $C_{23}H_{35}NO_5Si$ (433.61): calcd. C 63.71, H 8.14, N 3.23; found C 63.68, H 8.26, N 3.21.

2-(Benzylamino)-3-(triethylsilyl)but-3-en-1-ol (8a) and (*E*)-4-(Benzylamino)-3-(triethylsilyl)but-2-en-1-ol (8b): A solution of **5** (3.15 g, 12.89 mmol) in dry THF (60 mL), NEt_3 (8.96 mL, 64.44 mmol) and benzylamine (7.04 mL, 64.44 mmol) were added in that order, under argon, to a well-stirred solution of $Pd(OAc)_2$ (0.144 g, 0.64 mmol) and dppe (0.513 g, 1.29 mmol) in dry THF (30 mL), warmed in a water bath (ca. 35 °C). The reaction mixture was stirred at 50 °C for 3 h. A saturated aqueous solution of NH_4Cl (30 mL) and brine (30 mL) were added and a standard extractive workup with Et_2O (3 × 30 mL) was performed. The collected organic layers were dried and the solvents were evaporated in vacuo. Flash chromatography of the crude product (EtOAc/hexanes/triethylamine, 25:75:3.5) gave the pure compounds (**8a**: 17%: **8b**: 52%).

8a: ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.61 (t, *J* = 8 Hz, 6 H), 0.96 (t, *J* = 8 Hz, 9 H), 2.56 (br. s, 2 H), 3.19 (dd, *J* = 10.5, 9.2 Hz, 1 H), 3.45 (m, 1 H), 3.61 (m, 2 H), 3.85 (m, 1 H), 5.61 (s, 1 H), 5.93 (s, 1 H), 7.22−7.42 (5 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 1.5, 5.8, 49.7, 61.8, 63.8, 125.2, 125.6, 126.7, 127.0, 138.8, 145.8.

8b: ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.57 (q, *J* = 8 Hz, 6 H), 0.90 (t, *J* = 7.8 Hz, 9 H), 3.34 (s, 2 H), 3.81 (s, 2 H), 3.92 (br. s, 2 H), 4.20 (d, *J* = 5.2 Hz, 2 H), 6.26 (t, *J* = 5.4 Hz, 1 H), 7.32 (s, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 2.7, 7.4, 47.5, 53.9, 60.4, 127.3, 128.3, 128.5, 138.3, 138.6, 145.1 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3048, 2982, 2953, 2908, 2875, 1422, 1253 cm^{-1}. MS (EI): *m*/*z* (%) = 292 (58) [M^+ +1], 274 (19). $C_{17}H_{29}NOSi$ (291.50): calcd. C 70.04, H 10.02, N 4.81; found C 69.60, H 10.24, N 4.48.

Methyl 3-{(Benzyl)[(2*E*)-4-hydroxy-2-triethylsilyl-but-2-enyl]-amino}-3-oxopropanoate (9): NEt_3 (0.633 mL, 4.55 mmol) and Me_3SiCl (0.578 mL, 4.55 mmol) were added in that order, under nitrogen, to a solution of the allyl(benzyl)amine **8b** (1.204 g, 4.14 mmol), in dry THF (50 mL), cooled in a water/ice bath. After stirring at room temperature for 10 min, a white suspension formed. Brine (40 mL) was added, and the resulting biphasic system was subjected to a standard extractive workup with Et_2O (3 × 20 mL). The resulting crude *O*-silylated amine was then dissolved in dry CH_2Cl_2 (50 mL) and cooled in a water/ice bath. NEt_3 (0.633 mL, 4.55 mmol) and methyl 3-chloro-3-oxopropanoate (0.488 mL, 4.55 mmol) were then added in that order. The reaction mixture was warmed to room temperature while stirring for further 20 min. After addition of brine (40 mL) and a standard extractive workup with CH_2Cl_2 (3 × 20 mL), the crude *O*-silylated amide was dissolved in THF (50 mL) and treated with 10% HCl solution to pH ≈ 2. The resulting mixture was stirred at room temperature for 10 min, and then treated at 0 °C with a few drops of a saturated aqueous $NaHCO_3$ to neutralize the acid. The aqueous phase was extracted with Et_2O (3 × 20 mL), the collected organic layers were dried, and the solvents were evaporated in vacuo. Flash chromatography of the crude product (EtOAc/hexanes, 40:60) gave the pure amide **9** (82%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.51−0.62 (m, 6 H), 0.84−0.91 (m, 9 H), 2.52 (br. s, 1 H), 3.72−3.39 (m, 5 H), 3.89−4.19 (m, 4 H), 4.45−4.55 (m, 2 H), 6.05−6.15 (m, 1 H), 7.08−7.37 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 2.6, 2.9, 7.2, 41.3, 43.1, 47.4, 47.7, 49.6, 52.3, 58.8, 59.0, 125.5, 127.2, 127.4, 127.6, 128.5, 129.0, 134.2, 135.5, 145.0, 145.9, 166.4, 167.5 ppm. IR (CH_2Cl_2): ṽ = 3056, 2987, 2876, 1739, 1644, 1420, 1255 cm^{-1}. MS (EI): *m*/*z* (%) = 362 (10) [M^+ − Et], 158 (22), 91 (100).

Methyl 3-((Benzyl){(2*E*)-2-triethylsilyl-4-[(methoxycarbonyl)oxy]-but-2-enyl}amino)-3-oxopropanoate (4): Pyridine (0.100 mL, 1.25 mmol), methyl chloroformate (0.096 mL, 1.25 mmol) and 4-DMAP (6 mg, 0.05 mmol), were added in that order, under nitrogen at 0 °C, to a solution of the amide **9** (0.406 g, 1.04 mmol) in dry CH_2Cl_2 (10 mL). After stirring at room temperature for 6 h, brine (10 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 6 mL). The collected organic layers were dried and the solvents were evaporated in vacuo. Flash chromatography of the crude product (EtOAc/hexanes, 40:60) afforded the expected carbonate **4** (> 98%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.48−0.59 (6 H), 0.80−0.87 (9 H), 3.37−3.90 (9 H), 4.19−4.52 (5 H), 5.97 (m, 1 H), 7.03−7.28 (5 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 2.3, 2.7, 7.0, 41.1, 42.3, 47.1, 47.4, 48.9, 52.1, 54.5, 63.7, 63.9, 125.4, 127.1, 127.3, 127.4, 128.3, 128.8, 135.1, 135.9, 137.7, 138.3, 139.4, 155.0, 166.1, 167.2 ppm. IR ($CHCl_3$): ṽ = 2955, 2912, 2876, 1745, 1645, 1422 cm^{-1}. MS (EI): *m*/*z* (%) = 420 (14) [M^+ − Et], 374 (4), 91 (100).

General Procedure for the Synthesis of Methyl *trans*-1-Benzyl-2-oxo-4-[1-(triethylsilyl)vinyl]pyrrolidine-3-carboxylate (10) and Methyl *trans*-1-Benzyl-2-oxo-4-(triethylsilyl)-4-vinylpyrrolidine-3-carboxylate (11): NaH (60% dispersion in mineral oil, 0.22 mmol) was added under argon to a solution of the appropriate acyclic precursor (**3** or **4**, 0.20 mmol) in dry DMF (2 mL), cooled in a water/ice bath, and the solution was stirred at room temperature for 10 min. The enolate generated was cannulated under positive argon pressure into a Pd^0 complex solution, previously prepared in a separate flask by dissolution of $Pd(OAc)_2$ (2.5 mg, 0.01 mmol) and dppe (8 mg, 0.02 mmol) in dry DMF (2 mL). After stirring at 100 °C for 30 min, the reaction mixture was treated with a 25 wt.% aqueous NH_4Cl solution (20 mL) and the aqueous phase was extracted with Et_2O (3 × 10 mL). The collected organic phases were dried and the solvent was evaporated under vacuum. Flash chromatography (hexanes/EtOAc, 75:25) gave the pure compounds (**11**: 52%; **10**: 90%).

10: ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.49−0.63 (6 H), 0.85 (t, *J* = 8 Hz, 9 H), 2.95−2.99 (m, 1 H), 3.38−3.54 (3 H), 3.78 (s, 3 H), 4.47 (AB system, 2 H), 5.43 (s, 1 H), 5.72 (s, 1 H), 7.21−7.34 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 2.7, 7.1, 40.5, 46.9, 51.9, 52.7, 54.5, 126.8, 127.8, 128.2, 128.8, 135.8, 147.8, 169.3, 170.3 ppm. IR ($CDCl_3$): ṽ = 2957, 2938, 2912, 2877, 1736, 1686, 1431 cm^{-1}. MS (EI): *m*/*z* (%) = 344 (37) [M^+ − Et], 285 (63), 91(100). $C_{21}H_{31}NO_3Si$ (373.56): calcd. C 67.52, H 8.36, N 3.75; found C 67.58, H 8.43, N 3.90.

11: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.59 (m, 6 H), 0.94 (t, *J* = 8.0 Hz, 9 H), 3.29 (d, part of AB system, *J* = 9.6 Hz, 1 H), 3.60 (s, 1 H), 3.63 (d, part of AB system, *J* = 17.6 Hz, 1 H), 3.68 (s, 3 H), 4.20 (d, part of AB system, *J* = 14.6 Hz, 1 H), 4.68 (d, *J* = 17.6 Hz, 1 H), 4.85 (d, part of AB system, *J* = 14.6 Hz, 1 H), 5.03 (d, *J* = 11.0 Hz, 1 H), 5.85 (dd, *J* = 17.6, 11.0 Hz, 1 H), 7.26−7.39 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 1.6, 7.9, 47.1, 51.8, 52.0, 52.7, 55.7, 113.3, 127.8, 128.5, 128.7, 135.6, 137.4, 169.6, 170.5 ppm. ^{1}H NMR (C_6D_6, 400 MHz): δ = 0.53 (q, *J* = 8 Hz, 6 H), 0.94 (t, *J* = 8 Hz, 9 H), 3.16 (d, *J* = 9.4 Hz, 1 H), 3.39 (s, 3 H), 3.71 (d, *J* = 9.4 Hz, 1 H), 3.89 (s, 1 H), 4.16 (d, *J* = 14.6 Hz, 1 H), 4.56 (d, *J* = 17.5 Hz, 1 H), 4.89 (d, *J* = 14 Hz, 1 H), 4.92 (d, *J* = 10.9 Hz, 1 H), 5.91 (dd, *J* = 17.5, 10.9 Hz, 1 H), 7.17−7.42 (m, 5 H) ppm. ^{13}C NMR (C_6D_6, 50 MHz): δ = 1.7, 7.8, 36.6, 46.9, 51.3, 51.6, 56.7, 112.8, 127.8, 128.7, 128.8, 136.4, 138.0, 169.5, 169.7 ppm. IR ($CHCl_3$): ṽ = 3064, 3041, 2956, 2931, 2880, 1737, 1688, 1649 cm^{-1}. MS (EI): *m*/*z* (%) = 373 (1.5) [M^+], 315 (19), 314 (99), 91 (100), 59 (71).

Methyl *trans*-1-Benzyl-4-ethyl-2-oxo-4-(triethylsilyl)pyrrolidine-3-carboxylate (12): $Pd(OH)_2$ (10 mol %) was added to a solution of pyrrolidone **11** (17 mg, 0.046 mmol) in EtOH (1 mL), and the system was purged three times with hydrogen and evacuated. The heterogeneous solution was stirred overnight under hydrogen and was then filtered through Celite. The solvent was removed under reduced pressure and the residue was purified on silica (EtOH) to give 14 mg (82% yield) of the expected product **12** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.63 (q, *J* = 8 Hz, 6 H), 0.84 (t, *J* = 7 Hz, 3 H), 0.96 (t, *J* = 7.6 Hz, 9 H), 1.44−1.62 (m, AB system, 2 H), 3.14 (d, *J* = 10.2 Hz, 1 H), 3.26 (d, *J* = 10.2 Hz, 1 H), 3.54 (s, 1 H), 3.75 (s, 3 H), 4.23 (d, *J* = 14.2 Hz, 1 H), 4.72 (d, *J* = 14.8 Hz, 1 H), 7.28−7.36 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 2.6, 7.9, 10.8, 26.7, 51.9, 53.2, 55.5, 127.7, 128.4, 128.6, 135.6, 169.6, 170.7. IR (neat): ṽ = 2953, 1737, 1694, 1500, 1450, 1433, 1164, 729, 702 cm^{-1}. MS (EI): *m*/*z* (%) = 375 (5), 347 (25), 317 (100), 91 (25), 59 (13). $C_{21}H_{33}NO_3Si$ (375.58): calcd. C 67.16, H 8.85, N 3.73; found C 67.52, H 9.19, N 3.28.

Methyl *cis*-1-Benzyl-3-methyl-2-oxo-4-(triethylsilyl)-4-vinylpyrrolidine-3-carboxylate (15): Solid NaH (60% dispersion in mineral oil) (4 mg, 1.1 equiv.) was slowly added at 0 °C to a solution of pyrrolidone **11** (34 mg, 0.09 mmol) in DMF (1 mL). After the reaction mixture had been stirred for 20 min, CH_3I (0.05 mL, 9 equiv.) was added and the reaction mixture was allowed to reach room temperature and stirred for 1 h. Water (5 mL) and saturated aqueous NH_4Cl solution (1 mL) were then added, and the aqueous phase was subjected to standard extractive workup with Et_2O (3 × 10 mL). Flash chromatography (hexanes/EtOAc, 80:20) gave the pure methylated compound **15** in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.61 (q, *J* = 8 Hz, 6 H,), 0.92 (t, *J* = 7.6 Hz, 9 H), 1.39 (s, 3 H), 3.29 (d, AB system, *J* = 11 Hz, 1 H),

3.44 (d, AB system, J = 11 Hz, 1 H), 3.71 (s, 3 H), 4.45 (d, AB system, J = 14 Hz, 1 H), 4.55 (d, AB system, J = 14 Hz, 1 H), 4.62 (d, J = 18 Hz, 1 H), 5.02 (d, J = 11 Hz, 1 H), 5.85 (dd, J = 17, 11 Hz, 1 H), 7.36−7.28 (m, 5 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 2.3, 8.2, 17.2, 41.7, 47.4, 48.4, 52.3, 58.0, 112.6, 127.8, 128.6, 128.8, 136.1, 137.1, 172.8, 173.3 ppm. IR (neat): ṽ = 2950, 2921, 2876, 1737, 1674 (br), 1449, 731 cm^{-1}. MS (EI): *m*/*z* (%) = 387 (5), 359 (20), 329 (100), 91 (30), 59 (15). $C_{22}H_{33}NO_3Si$ (387.59): calcd. C 68.17, H 8.58, N 3.61; found C 68.49, H 8.85, N 3.30.

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