Stereoselective cyclization of silylated epoxy aldehydes into piperidines. Effect of the silicon group

Cécile Boglio, Marie-Céline Lamas, Serge Thorimbert,*and Max Malacria*

Université Pierre et Marie Curie-Paris 6, Laboratoire de chimie organique (UMR CNRS 7611), Institut de chimie moléculaire (FR 2769), BP 229, 4 place Jussieu, 75005 Paris, France
E-mail: max.malacria@upmc.fr, serge.thorimbert@upmc.fr

Submitted to honor the 70th anniversary of Prof. Guy Queguiner

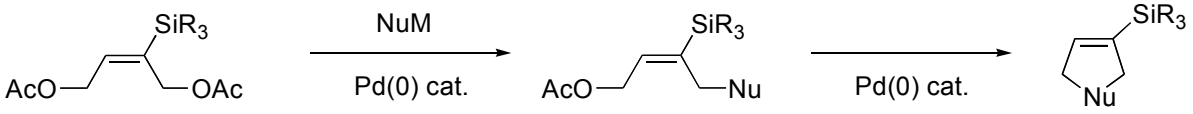
Abstract
A series of 2- or 3-silyl-epoxy aldehydes derivatives bearing a glycinyl sidechain have been prepared and tested in intramolecular aldolization. Highly stereoselective cyclization occurs and provides the N-heterocycle framework which is useful for the synthesis of polyhydroxylated piperidines. The presence of the silicon group on the epoxy moiety strongly influenced the stereochemical outcome of the reaction.

Keywords: Silicon atom, aldolization, palladium catalysis, amination, piperidines

Introduction

Palladium plays an important role in organic chemistry due to the broad scope and versatility of its utilization in homogeneous[1] or heterogeneous reactions.[2] Among others, palladium-catalyzed allylation of various nucleophiles (the Tsuji–Trost reaction) is one of the major achievements in this field. However, the possibility of controlling the chemo-, regio- and enantio-selectivity of the attack of the nucleophiles onto the η^3-allyl ligand is still a challenging research area.[3] Much work has dealt with the variation of the ligands around the metal,[4] the role of the solvent,[5] or the steric and electronic influence of the substituents of the allyl moiety.[6] Silicon groups have been recognized as strong directing substituents.[7] Organosilicon compounds are also versatile and powerful reagents leading to many applications in organic synthesis.[8] They have attracted considerable attention not only as biologically acceptable analogues of natural products[9] but also because silicon acts as a directing atom that increases[10] or reverses selectivities usually observed for its carbon analogues.[11] Since the first reports of Hiyama, organosilanes have also been extensively studied in cross-coupling reactions catalyzed by palladium.[12] Some years ago, we demonstrated for the first time the highly chemo- and stereoselective alkylation of 2-silylbut-2-ene-1,4-diol derivatives.[13] Depending on its position, the silicon group strongly influences the

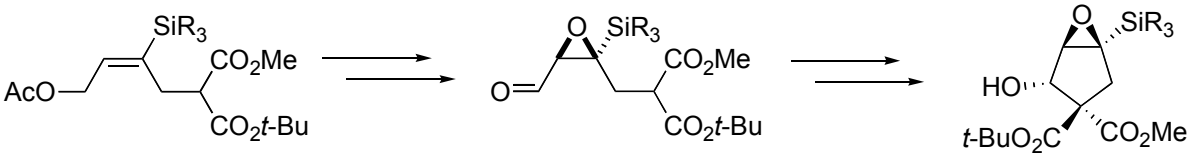
formation and the reactivity of the cationic π-allyl palladium complex.[14] The ionization takes place with complete chemoselectivity so as to expel the acetoxy group vicinal to silicon. These studies allowed the development of a new palladium-catalyzed cyclization reaction, wherein 2-trialkylsilyl-1,4-diacetoxy-but-2-ene are converted, *via* two palladium-catalyzed reactions, into silyl-substituted cyclopentenes (Scheme 1).



Scheme 1. Palladium-catalyzed reactions controlled by a silicon group.

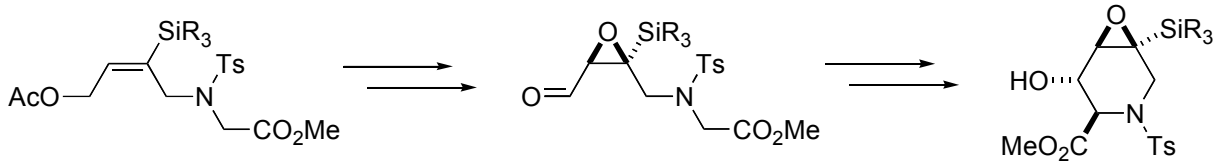
In this overall annulation process the role of silicon is crucial and twofold. In fact, in the first C-C bond formation the bulky trialkylsilyl group regiodirects the ionization of the starting bis-allylic system. In addition, the same group is expected to prefer a *syn* disposition in the transiently generated η^3-allylpalladium complex,[15] so as to allow the 5-*endo* process to take place in the second reaction.[16]

We also took advantage of these efficient alkylations giving stereoselectively *(E)* compounds, to prepare in few steps some silylated epoxy cyclopentanols.[17] The high level of stereoselectivity observed during the aldolization was attributed, in part, to the presence of the three membered ring in the tether (Scheme 2).



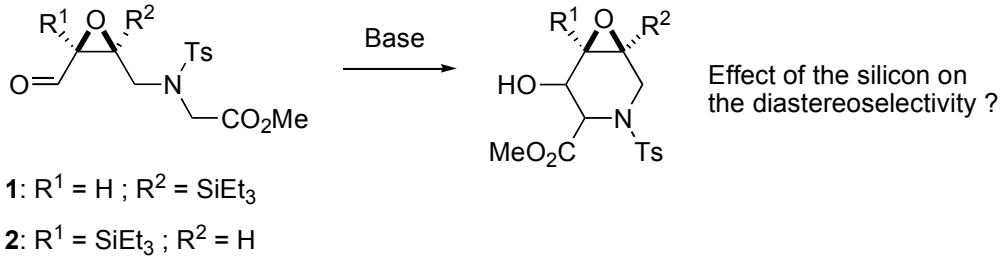
Scheme 2. Stereoselective intramolecular aldolization.

We recently extended this process towards the construction of a 6-membered nitrogen heterocycle.[18] Substituted piperidines, in general,[19] and polyhydroxylated derivatives[20] more precisely, have been the targets of a large number of synthetic approaches[21] due to their potential as therapeutic agents, and the need to find efficient access to biologically active analogues. Our synthetic approach to the piperidine skeleton is based on the stereoselective palladium-catalyzed amination as well as an intramolecular aldol condensation (Scheme 3).[22]



Scheme 3. Preparation of piperidines.

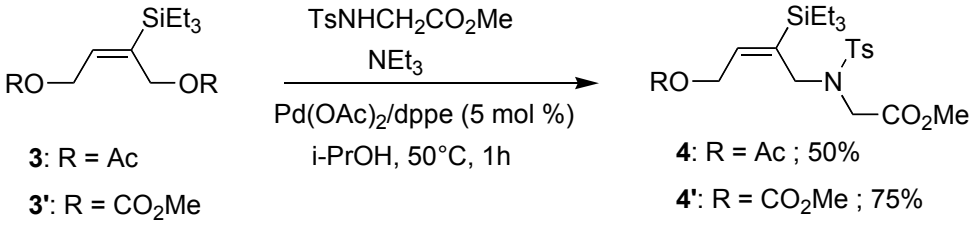
We decided to study the effect of the silicon substitution on the above cyclization. In particular, we were intrigued to verify the effect of the presence of the silyl group vicinal to the carbonyl function. We report herein the preparation and the result of the cyclization of two epoxy aldehydes **1** and **2** substituted by a triethylsilyl group at the 2 or 3 position, respectively (Scheme 4).



Scheme 4. Diastereoselective aldolization.

Results and Discussion

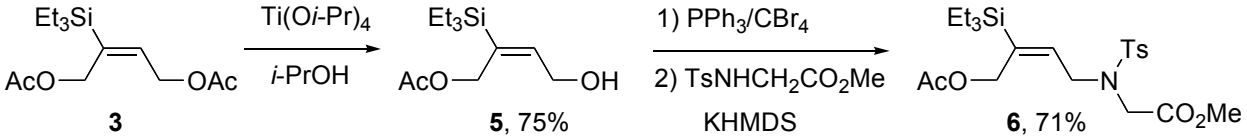
Our synthesis started from either the silyl derivative **3** bearing two allylic acetates or the corresponding dicarbonate **3'**. As previously reported,[18] the direct palladium-catalyzed chemo- and stereo-selective amination gave the expected compound **4** in 50% yield with no detectable trace of the product derived from the substitution of the other acetate (Scheme 5). The same reaction using the more reactive dicarbonate **3'** delivered the expected product **4'** in 75% yield in a 90/10 *E/Z* ratio. Again, no product coming from the ionization of the second leaving group was detected.



Scheme 5. Chemo- and stereo-selective palladium-catalyzed amination.

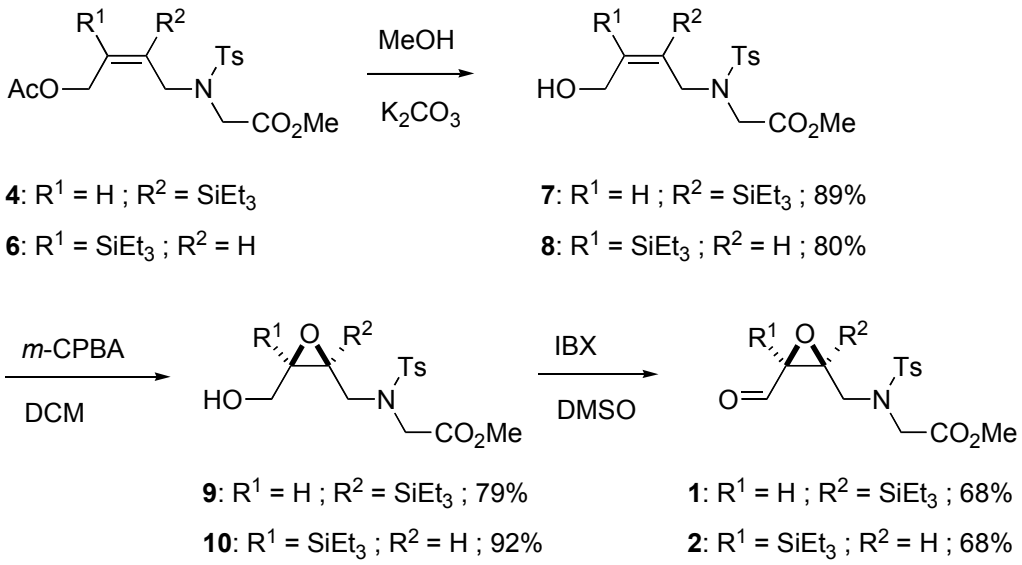
To prepare the other regioisomer, some more steps were required. Indeed, **3** has two primary allylic acetates and the less hindered one needed to be deprotected. This was efficiently realized using the transesterification protocol developed by Seebach.[23] One should notice that it is crucial to use a relatively hindered alcoholic solvent to perform the mild deprotection with a good chemoselectivity. Moreover, it is important to control the evolution of the reaction and to stop it when traces of the corresponding diol appear, which usually requires three hours at room

temperature. Purification by flash chromatography allowed the isolation of the desired allylic alcohol **5** in 75% yield (Scheme 6). After transformation of the alcohol into bromide, the reaction with the potassium salt of the N-tosyl glycine methyl ester delivered the desired allylic amino derivative **6** in 71% overall yield.



Scheme 6. Preparation of compound **6**.

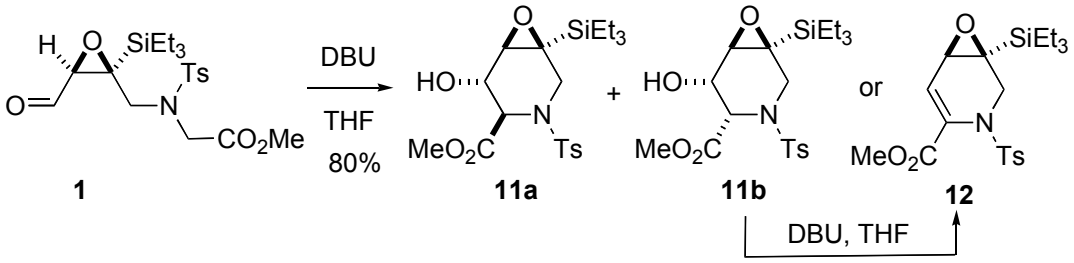
Having in hand the two regioisomers of the amino- allylic acetates **4** and **6**, we pursued the synthesis of the targeted precursors. Methanolysis of the acetate function of **4** and **6** delivered, in good yields, the corresponding allylic alcohols **7** and **8**, which were then transformed into the silylated epoxides **9** and **10** in 79 and 92% yields, respectively (Scheme 7). The mild oxidations of the primary alcohols into the desired aldehydes bearing all the functions needed for the construction of the piperidine ring were performed with IBX in DMSO. The stable precursors **1** and **2** were both isolated in 68 % yield.



Scheme 7. Preparation of the silylated epoxy aldehydes **1** and **2**.

We first studied the acyclic precursor **1** bearing the triethylsilyl group at the position remote from the aldehyde function. After some misleading preliminary experiments, using KHMDS, LDA or NEt_3, we found that DBU in THF at room temperature was a correct base to convert **1** into the corresponding piperidine ring **11**. Careful examination of the ^1H NMR of the crude material indicated two diastereomers (**11a** and **11b**) in a 80/20 mixture (Scheme 8). These two

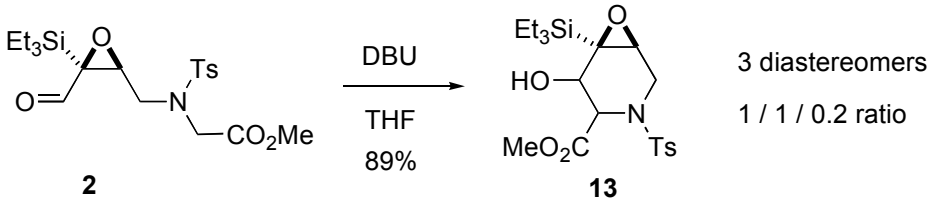
compounds were difficult to separate by flash chromatography. However, as expected, the *trans*-relationship between the oxirane and the created hydroxyl was totally controlled. The two diastereomers **11a** and **11b** correspond to the two epimers at the ester position. In the major product **11a**, the ester function is *trans*- relative to the hydroxyl group. Attempts to improve the diastereoselectivity, by lowering the temperature considerably decrease the kinetics of the cyclization and degradation started to be competitive.



Scheme 8. Stereoselective preparation of piperidines.

To facilitate the purification and the isolation of the major diastereomer, we reasoned that in our basic conditions, only the minor diastereomer **11b** could dehydrate into the corresponding enamino ester **12**. To our pleasure, after a reaction time of 3 days, **1** gives a 75/25 mixture of **11a** and the expected dehydroamino ester **12**. This allowed for an easier isolation of pure **11a** in 65% yield.

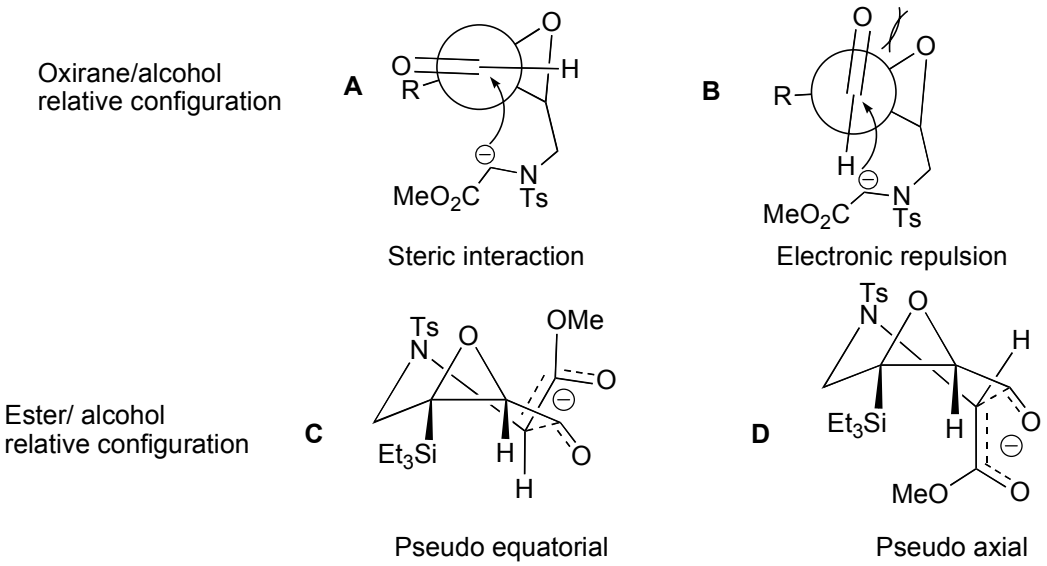
The second acyclic precursor **2** bearing the vicinal aldehyde and silyl functions was mixed with an equivalent amount of DBU in THF. We observed a fast consumption of the starting material and isolated after 4 hours a 1/1/0.2 mixture of three diastereomers **13** in 89% yield (Scheme 9). Attempts to separate these piperidine derivatives by flash chromatography were unsuccessful. We thus decided to apply a longer reaction time in order to favor the diastereoselective dehydration. Unfortunately, after 4 days we still isolated, in a moderate 57% yield, a mixture of the same three diastereomers.



Scheme 9. Stereoselective preparation of piperidines.

Thus we can conclude that the presence or the absence of the triethylsilyl group adjacent to the aldehyde strongly influence the overall selectivity of the cyclization. Indeed, cyclization of **1** furnished only two diastereomers whereas from **2** we isolated **13** as a mixture of three diastereomers. We propose a model to explain the control of the relative configuration between

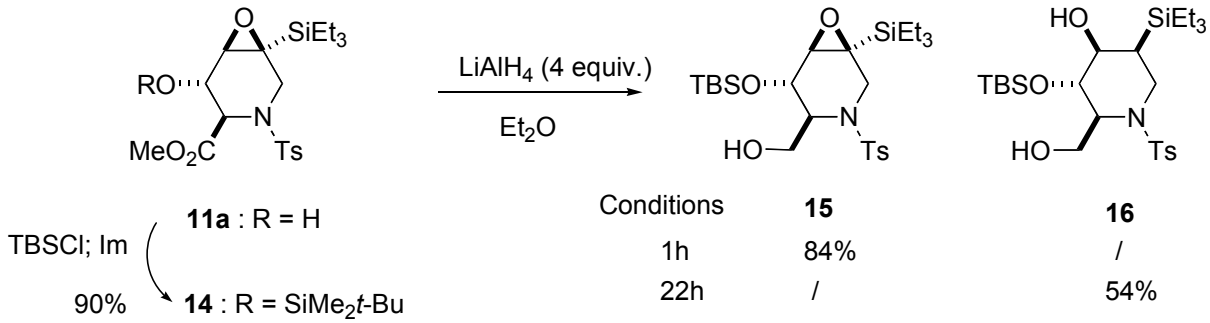
the oxiranyl and the hydroxyl functions (Scheme 10). Starting from **1**, where R is a hydrogen atom, we consider a Felkin–Ahn type model where the attack of the nucleophile occurs *anti*- to the electronegative group (the oxiranyl function).[24] This approach should be much more favored than the approach **B** which develops electronic repulsions between the two oxygen atoms. On the other hand, starting from the molecule **2** (R = $SiEt_3$), the presence of the triethylsilyl group adjacent to the carbonyl group should develop strong steric interactions in the conformation **A**. Since the carbonyl group will no longer be securely *syn*- to a hydrogen, it could rotate to the conformation **B**. That might explain the loss of stereocontrol in this series and contribute to the production of the minor diastereomer of **13**.



Scheme 10. Models.

To explain the major *trans*- relative configuration between the ester group and the hydroxyl function in the piperidine **11**, we consider a chair-like transition state. Due to the pseudo-equatorial position of the ester function, the approach **C** seems to be more favorable than **D**. This model could explain why **11a**, the *anti*-*anti* isomer, is the major isomer (**11a**/**11b**: 80/20).

Finally, we further demonstrate that the obtained piperidines could be selectively functionalized. For example, after protection of the secondary alcohol of **11a** as a silyl ether, the ester group of **14** could be smoothly reduced using $LiAlH_4$. After 1h at 0°C in Et_2O, the primary alcohol **15** could be isolated in 84% yield (Scheme 11).



Scheme 11. Functionalization of the piperidine ring.

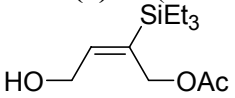
On the other hand, longer reaction times allowed the clean reduction of both the ester and epoxide groups of **14**. After 22h at room temperature, we isolated the mono-protected triol **16** in 54% yield as well as traces of the corresponding detosylated analogue of **16**. As expected, the reduction of the epoxysilane function is totally chemoselective and controlled by the silicon group.[25]

In conclusion, we report an original access to hydroxylated piperidines. The preparation of the first acyclic precursor has been performed by a chemo- and stereo-selective palladium-catalyzed amination of a silylated diacetate. The piperidine cycle could be obtained in a highly stereoselective aldolization. The presence or the absence of a triethylsilyl group in a neighboring position relative to the aldehyde strongly influences the overall selectivity of the cyclization. Work is underway to extend this approach to more functionalized piperidines in an enantiomeric version.

Experimental Section

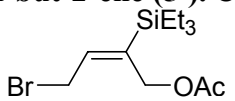
General Proedures. Reagents and chemicals were purchased from commercial sources and used as received. All reactions requiring anhydrous conditions were performed under a positive pressure of argon in oven-dried glassware. All solvents were purified and distilled by standard methods. Thin layer chromatography (TLC) was performed on 0.25 mm E. Merck silica gel (60F-254) plates using UV light, *p*-anisaldehyde or ninhydrin. Column chromatography was carried out on Merck silica gel 60 (40-63 μm). NMR spectra were recorded on a Bruker ARX 400. ^{1}H NMR were recorded at 400 MHz, and ^{13}C NMR at 100 MHz with the sample solvent being $CDCl_3$ unless otherwise noted. Chemical shifts are given in ppm, referenced to the residual proton resonances of the solvents. Coupling constants (*J*) are given in Hertz (Hz). The letters m, s, d, t, q mean respectively multiplet, singlet, doublet, triplet, quartet: *br* means that the signal is broad. IR spectra were recorded on a Bruker Tensor 27 using ATR method. Elemental analyses were carried out by the "Service de microanalyse", ICSN - CNRS, 91198 Gif sur Yvette, France or by the "Service de microanalyse", SIARE, 4 place Jussieu 75252 Paris cedex 05, France. Compounds **3**, **4** and **4'** have already been described in refs 13b,14 and 18, respectively.

(*E*)-4-Acetoxy-3-triethylsilyl-but-2-en-1-ol (5). Ti(O-*i*-Pr)$_4$ (23.5 mL, 78.5 mmol, 1 equiv.) was



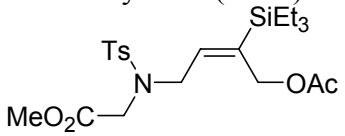
added to a solution of diacetate **3** (22.5 g, 78.5 mmol) in dry *i*-PrOH under argon atmosphere. After stirring 2-3 h at room temperature, Et_2O (100 mL) and HCl 10% (100 mL) were added to the mixture. The aqueous phase was extracted with Et_2O. The organic layer was neutralized with aqueous $NaHCO_3$, washed with brine until neutral pH, dried over $MgSO_4$ and concentrated under vacuum. The yellow oil was purified on a silica gel column (PE/EA 8/2-6/4) in order to afford **5** (11.5 g, 47.1 mmol, 60% yield) as a colorless oil. R_f= 0.3 (PE/EA 75/25); IR: 3400 (large), 2940, 2860, 1740, 1610, 1230, 1010, 720 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ= 0.64 (q, *J*= 7.4 Hz, 6H); 0.90 (t, *J*= 7.4 Hz, 9H); 2.03 (s, 3H); 4.3 (d, *J*= 6.0 Hz, 2H); 4.70 (s, 2H); 6.08 (t, *J*= 6.0 Hz, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ= 3.1 (CH_2); 7.6 (CH_3); 21.3 (CH_3); 60.8 (CH_2); 61.7 (CH_2); 136.5 (Cq); 143.0 (CH); 171.5 (Cq). Anal. Calcd. for $C_{12}H_{24}O_3Si$ (244.28): C 58.97, H 9.90. Found: C 59.03, H 9.82.

(*E*)-4-Acetoxy-1-bromo-3-triethylsilyl-but-2-ene (5'). CBr_4 (984 mg, 2.97 mmol, 1.15 equiv.)



was added at 0°C to a solution of the allylic alcohol **5** (630 mg, 2.58 mmol) in CH_2Cl_2 (5 mL). Then a solution of triphenylphosphine (880 mg, 3.35 mmol, 1.3 equiv.) in CH_2Cl_2 (5 mL) was transferred into the reaction mixture. After 30 min, the mixture was concentrated under vacuum to afford **5'** as a colorless oil. The crude product was sufficiently clean to be used directly in the next step. R_f: 0.7 (PE/EA 8/2); IR: 2954, 2874, 1739, 1459, 1378, 1222, 1095, 1021, 961, 716, 673 cm^{-1}; ^{1}H-NMR: δ=0.65 (q, *J*= 8 Hz, 6H); 0.94 (t, *J*= 8 Hz, 9H); 2.07 (s, 3H); 4.08 (d, *J*= 8 Hz, 2H), 4.78 (s, 2H); 6.15 (t, *J*= 8 Hz, 1H). Anal. Calcd. for $C_{12}H_{23}O_2BrSi$ (307.30): C 46.90, H 7.54; Found: C 48.28, H 7.86.

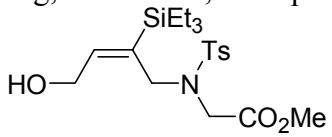
(*E*)-[(4-Acetoxy-3-triethylsilyl-but-2-enyl)-(toluene-4-sulfonyl)-amino]-acetic acid methyl ester (6). To a cold (0°C) solution of **5'** in dry THF (8 mL) was added a preformed solution of



the potassium salt of N-tosyl methyl glycinate (690 mg, 2.84 mmol, 1.1 equiv.) in THF (5 mL). The solution was stirred 2 h at 0°C, then quenched with a saturated solution of NH_4Cl. The aqueous phase was extracted twice with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified on a silica gel column (PE/EA 8/2) to afford **6** (856 mg, 1.82 mmol, 71% yield over 2 steps) as a colorless oil. R_f= 0.2 (PE/EA 8/2); IR: 2952, 2875, 1740, 1437, 1340, 1226, 1160, 1100, 1000, 930, 720, 655 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 0.57 (q, *J*= 7.8 Hz, 6H); 0.87 (t, *J*= 7.8 Hz, 9H); 2.00 (s, 3H); 2.44 (s, 3H); 3.64 (s, 3H); 4.01 (s, 2H); 4.08 (d, *J*= 6.8 Hz, 2H); 4.58 (s, 2H); 5.72 (t, *J*= 6.8 Hz, 1H); 7.31 (d, *J*= 8.0 Hz, 2H); 7.74 (d, *J*= 8.0 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 2.8 (CH_2); 7.2 (CH_3); 20.9 (CH_3); 21.5 (CH_3); 45.9 (CH_2); 47.4 (CH_2);

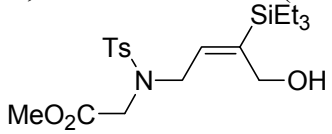
52.1 (CH_3); 61.9 (CH_2); 127.4 (CH); 129.7 (CH); 136.8 (Cq); 138.8 (CH); 142.5 (Cq); 143.6 (Cq); 169.6 (Cq); 171.1 (Cq); Anal. Calcd. for $C_{22}H_{35}NO_6SSi$ (469.67): C 56.26, H 7.51, N 2.98; Found: C 56.09, H 7.60, N 3.11.

(*E*)-[(4-Hydroxy-2-triethylsilyl-but-2-enyl)-(toluene-4-sulfonyl)-amino]-acetic acid methyl ester (7). Potassium carbonate (531 mg, 3.85 mmol, 0.2 equiv.) was added to a solution of the



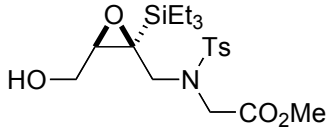
allylic acetate **4** (9.05 g, 19.25 mmol) in MeOH (50 mL). The resulting suspension was stirred 16 h at room temperature. The methanol was removed under reduced pressure and a mixture of water/Et_2O (1/1) was added. After extraction with Et_2O, the organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The oil was purified on a silica gel column in order to afford **7** (7.42 g, 17.36 mmol, 89% yield) as a colorless oil. R_f= 0.25 (EP/AE 6/4); IR: 3600, 2950, 2875, 1740, 1460, 1330, 1210, 1160, 1100, 1000, 914, 720, 650 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 0.66 (q, *J*= 7.8 Hz, 6H); 0.92 (t, *J*= 7.8 Hz, 9H); 2.45 (s, 3H); 3.52 (s, 3H); 3.93 (s, 2H); 4.07 (s, 2H); 4.22 (d, *J*= 6.3 Hz, 2H); 6.21 (t, *J*= 6.3 Hz, 1H); 7.33 (d, *J*= 8.1 Hz, 2H); 7.70 (d, *J*= 8.1 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 2.6 (CH_2); 7.4 (CH_3); 21.6 (CH_3); 45.7 (CH_2); 46.0 (CH_2); 52.0 (CH_3); 59.0 (CH_2); 127.5 (CH); 129.5 (CH); 133.6 (Cq); 135.9 (Cq); 143.6 (Cq); 147.5 (CH); 169.6 (Cq). Anal. Calcd. for $C_{20}H_{33}NO_5SSi$ (427.63): C 56.17, H 7.78, N 3.28; Found: C 57.66, H 8.08, N 2.71.

(*E*)-[(4-Hydroxy-3-triethylsilyl-but-2-enyl)-(toluene-4-sulfonyl)-amino]- acetic acid methyl ester (8). Following the same method, from the acetate **6** (856 mg, 1.82 mmol), the alcohol **8**



was obtained as a colorless oil (620 mg, 1.45 mmol, 80% yield). R_f= 0.25 (PE/EA 7/3); IR: 3600, 2950, 2875, 1740,1430, 1340, 1210, 1155,1100, 1000, 925, 715, 655 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 0.58 (q, *J*= 8.0 Hz, 6H); 0.89 (t, *J*= 8.0 9H); 1.27 (s, 1H); 2.44 (s, 3H); 3.65 (s, 3H); 4.04 (s, 2H); 4.08 (d, *J*= 6.8 Hz, 2H); 4.17 (s, 2H); 5.66 (t, *J*= 6.8 Hz, 1H); 7.32 (d, *J*= 8.3 Hz, 2H); 7.74 (d, *J*= 8.3 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 2.8 (CH_2); 7.3 (CH_3); 21.4 (CH_3); 45.6 (CH_2); 47.5 (CH_2); 52.2 (CH_3); 59.8 (CH_2); 127.3 (CH); 129.5 (CH); 136.7 (CH); 136.5 (Cq); 143.5 (Cq); 144.2 (Cq); 169.5 (Cq). Anal. Calcd. for $C_{20}H_{33}NO_5SSi$ (427.63): C 56.17, H 7.78, N 3.28; Found: C 55.99, H 7.90, N 3.35.

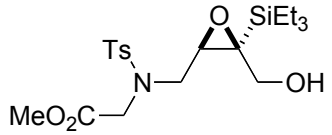
***trans*-[[(4-Hydroxymethyl)-(2-triethylsily)-oxiranylmethyl]-(toluene-4-sulfonyl)-amino]-acetic acid methyl ester (9).** To a solution of the allylic alcohol **7** (5 g, 11.71 mmol) in CH_2Cl_2



(40 mL) was added at 0°C the *m*-CPBA (5.77 g, 23.42 mmol, 70% *m*-CPBA in H_2O, 2 equiv.). The resulting suspension was stirred at room temperature for 14 h. The reaction mixture was

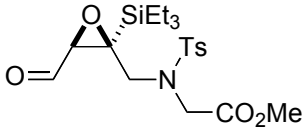
treated with aqueous NaOH (1*M*). The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (3 times). The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified on a silica gel column in order to afford **9** (4.10 g, 9.25 mmol, 79% yield) as a colorless oil. R_f= 0.2 (PE/EA 7/3); IR: 3600, 2950, 2875, 1740, 1437, 1340, 1157, 1100, 1000, 720 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 0.78 (q, *J*= 8.0 Hz, 6H); 1.01 (t, *J*= 8.0 Hz, 9H); 2.45 (s, 3H); 3.07 (t, *J*= 5.4 Hz, 1H); 3.46 (d, *J*= 14.3 Hz, 1H); 3.47 (s, 3H); 3.79 (d, *J*= 5.4 Hz, 2H); 3.90 (d, *J*= 14.3 Hz, 1H); 4.17 (d, *J*= 18.4 Hz, 1H); 4.35 (d, *J*= 18.4 Hz, 1H); 7.31 (d, *J*= 8.1 Hz, 2H); 7.66 (d, *J*= 8.1 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 1.6 (CH_2); 7.3 (CH_3); 21.6 (CH_3); 47.46 and 47.54 (2xCH_2); 51.8 (CH_3); 55.8 (Cq); 58.4 (CH); 62.4 (CH_2); 127.4 (CH); 129.5 (CH); 136.0 (Cq); 143.6 (Cq); 168.9 (Cq). Anal. Calcd. for $C_{20}H_{33}NO_6SSi$ (443.63): C 54.15, H 7.50, N 3.16; Found: C 53.75, H 7.59, N 2.78.

***trans*-[[(3-Hydroxymethyl)-(3-triethylsilyl)-oxiranylmethyl]-(toluene-4-sulfonyl)-amino]-acetic acid methyl ester (10).** From the allylic alcohol **8** (600 mg, 1.40 mmol), the epoxy-



alcohol **10** (575 mg, 1.30 mmol, 92% yield) was obtained as a white solid. m.p. 85°C. R_f= 0.5 (PE/EA 7/3); IR: 3600, 2950, 2875, 1740, 1330 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 0.65 (q, *J*= 8.0 Hz, 6H); 0.98 (t, *J*= 8.0 Hz, 9H); 1.90 (s, 1H); 2.45 (s, 3H); 3.07 (dd, *J*= 6.5 and 4.5 Hz, 1H); 3.33 (dd, *J*= 15.4 and 6.5 Hz, 1H); 3.66 (s, 3H); 3.72 (s, 2H); 3.80 (dd, *J*= 15.4 and 4.5 Hz, 1H); 4.21 (s, 2H); 7.33 (d, *J*= 8.5 Hz, 2H); 7.74 (d, *J*= 8.5 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 1.8 (CH_2); 7.4 (CH_3); 21.7 (CH_3); 47.3 (CH_2); 49.1 (CH_2); 52.4 (CH_3); 56.4 (Cq); 58.1 (CH); 62.5 (CH_2); 127.5 (CH); 129.9 (CH); 136.5 (CH); 144.0 (Cq); 169.4 (Cq). Anal. Calcd. for $C_{20}H_{33}NO_6SSi$ (443.63): C 54.15, H 7.50, N 3.16. Found: C 53.98, H 7.61, N 3.22.

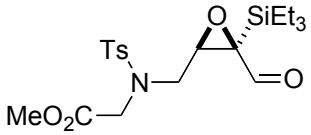
***trans*-[[3-Formyl-(2-triethylsilyl)-oxiranylmethyl]-(toluene-4-sulfonyl)-amino]-acetic acid methyl ester (1).** A solution of IBX (2.19 g, 7.82 mmol, 1.1 equiv.) in DMSO (20 mL) was



added to a solution of the epoxy-alcohol **9** (3.15 g, 7.11 mmol) in DMSO (25 mL). The resulting mixture was stirred for 3h at room temperature, then cooled to 0°C, and aqueous $NaHCO_3$ (40 mL) was added. The solution was filtered to remove the white precipitate, and extracted with AcOEt. The organic layer was then washed with brine and dried over $MgSO_4$. The crude material was purified by flash chromatography on silica gel (PE/EA 75/25) to afford **1** (2.1 g, 4.76 mmol, 68% yield) as a colorless oil. R_f = 0.3 (PE/EA 75/25); IR: 3400, 2915, 2875, 1747, 1435, 1337, 1160, 1010, 950, 700 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 0.75 (q, *J*= 7.6 Hz, 6H); 1.01 (t, *J*= 7.6 Hz, 9H); 2.42 (s, 3H); 3.22 (d, *J*= 4.6 Hz, 1H); 3.46 (s, 3H); 3.61 (d, *J*= 14.4 Hz, 1H); 3.90 (d, *J*= 14.4 Hz, 1H); 4.17 (d, *J*= 18.6 Hz, 1H); 4.35 (d, *J*= 18.6 Hz, 1H); 7.29 (d, *J*= 8.0 Hz, 2H); 7.61 (d, *J*= 8.0 Hz, 2H); 9.49 (d, *J*= 4.6 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$):

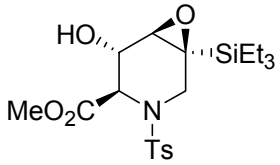
δ= 1.5 (CH_2); 7.4 (CH_3); 21.6 (CH_3); 46.9 and 47.6 ($2CH_2$); 52.0 (CH_3); 59.5 (CH); 61.3 (Cq); 127.4 (CH); 129.6 (CH); 135.7 (Cq); 144.0 (Cq); 168.2 (Cq); 199.2 (Cq). Anal. Calcd. for $C_{20}H_{31}NO_6SSi$ (441.62): C 54.40, H 7.08, N 3.17. Found: C 54.71, H 7.32, N 2.95.

***trans*-[[3-Formyl-(3-triethylsilyl)-oxiranylmethyl]-(toluene-4-sulfonyl)-amino]-acetic acid methyl ester (2).** From the epoxy-alcohol **10** (540 mg, 1.22 mmol), the aldehyde **2** (368 mg, 0.83



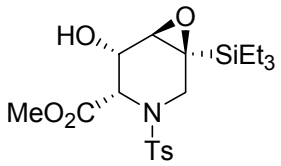
mmol) was isolated in 68 % yield. mp 82°C. R_f= 0.5 (PE/EA 7/3); IR: 3600, 2950, 2875, 1740, 1330 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 0.67 (q, *J*= 7.6 Hz, 6H); 0.97 (t, *J*= 7.6 Hz, 9H); 2.44 (s, 3H); 3.08 (dd, *J*= 15.4 and 8 Hz, 1H); 3.66 (s, 3H); 3.77 (dd, *J*= 15.4 and 3 Hz, 1H); 4.18 (d, *J*= 18.3 Hz, 1H); 4.24 (d, *J*= 18.3 Hz, 1H); 7.32 (d, *J*= 8.3 Hz, 2H); 7.70 (d, *J*= 8.3 Hz, 2H); 9.51 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 1.7 (CH_2); 7.3 (CH_3); 21.7 (CH_3); 48.3 and 48.9 ($2CH_2$); 52.4 (CH_3); 60.4 (CH); 60.8 (Cq); 127.5 (CH); 129.5 (CH); 136.2 (Cq); 144.1 (Cq); 169.1 (Cq); 202.1 (Cq). Anal. Calcd. for $C_{20}H_{31}NO_6SSi$ (441.62): C 54.40, H 7.08, N 3.17. Found: C 54.25, H 7.25, N 3.18.

(*1R*, 4R*, 5S*, 6R)-5-Hydroxy-3-(toluene-4-sulfonyl)-1-triethylsilyl-7-oxa-3-aza-bicyclo [4.1.0]heptane-4-methylcarboxylate (11a).** Diazabicycloundecene (0.2 mL, 1.4 mmol,



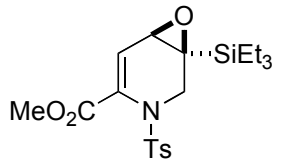
1.25 equiv.) was added to a solution of the epoxy- aldehyde **1** (496 mg, 1.12 mmol) in dry THF (25 mL). The solution was stirred 3 days at room temperature. Then aqueous NH_4Cl was added and the aqueous layer was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. After purification by flash chromatography, the cyclic product **11a** was recrystallized from a mixture of pentane/EA (321 mg, 0.73 mmol, 65% yield). mp 75°C. R_f= 0.3 (Et_2O/PE 6/4); IR: 3495, 2955, 2875, 1735, 1445, 1335, 1160, 1100, 1030, 905, 720, 655 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 0.59 (q, *J*= 7.8 Hz, 6H); 0.93 (t, *J*= 7.8 Hz, 9H); 2.44 (s, 3H); 3.12 (d, *J*= 2.8 Hz, 1H); 3.57 (s, 3H); 3.62 (d, *J*= 14.5 Hz, 1H); 3.89 (d, *J*= 14.5 Hz, 1H); 4.62 (d, *J*= 2.8 Hz, 1H); 4.83 (*pseudo* dt, *J*= 10 and 2.8 Hz, 1H); 7.32 (d, *J*= 8.0 Hz, 2H); 7.71 (d, *J*= 8.0 Hz, 2 H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 1.1 (CH_2); 7.2 (CH_3); 21.6 (CH_3); 41.3 (CH_2); 52.1 (CH_3); 52.4 (Cq); 55.0 (CH); 58.2 (CH); 66.9 (CH); 127.4 (CH); 129.5 (CH); 135.7 (Cq); 143.8 (Cq); 167.7 (Cq); Anal. Calcd. for $C_{20}H_{31}NO_6SSi$ (441.62): C 54.39, H 7.08, N 3.17. Found: C 54.30, H 7.09, N 3.22.

(*1R*, 4S*, 5S*, 6R)-5-Hydroxy-3-(toluene-4-sulfonyl)-1-triethylsilyl-7-oxa-3-aza-bicyclo[4.1.0]heptane-4-methylcarboxylate (11b).** The other isomer, **11b**, was isolated as a



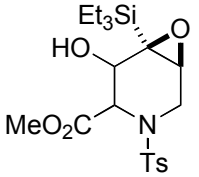
colorless oil (87 mg, 0.20 mmol, 17% yield). ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 0.58 (q, *J*= 7.3 Hz, 6H); 0.93 (t, *J*= 7.3 Hz, 9H); 2.42 (s, 3H); 3.08 (s, 1H); 3.41 (d, *J*= 14.6 Hz, 1H); 3.57 (s, 3H); 3.96 (d, *J*= 14.6 Hz, 1H); 4.69 (d, *J*= 6.8 Hz, 1H); 4.03 (dd, *J*= 8.6 and 6.8 Hz, 1H); 7.31 (d, *J*= 8.3 Hz, 2H); 7.68 (d, *J*= 8.3 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 2.4 (CH_2); 6.9 (CH_3); 21.3 (CH_3); 42.9 (CH_2); 51.8 (CH); 52.1 (CH_3); 54.5 (CH); 57.1 (CH); 64.5 (CH); 127.2 (CH); 129.2 (CH); 135.8 (Cq); 142.5 (Cq); 169.9 (Cq).

(*1R*,7R)-3-(Toluene-4-sulfonyl)-1-triethylsilyl-7-oxa-3-aza-bicyclo[4.1.0]hept-4-ene 4-methylcarboxylate (12).** From a mixture of the cyclic compounds **11a** and **11b**, a quantitative



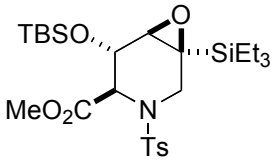
dehydration took place for **11b** in the presence of DBU in THF. Pure product **12** has been isolated in 10% yield (21 mg, 0.05 mmol) after 3 days at room temperature. R_f= 0.35 (Et_2O/PE 6/4); IR: 2950, 2875, 1733, 1435, 1360, 1250, 1190, 1090, 1055, 1015, 945, 815, 735, 705, 685 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 0.55 (q, *J*= 7.8 Hz, 6H); 0.91 (t, *J*= 7.8 Hz, 9H); 2.43 (s, 3H); 3.04 (d, *J*= 4.5 Hz, 1H); 3.09 (d, *J*= 15.1 Hz, 1H); 3.83 (s, 3H); 4.00 (d, *J*= 15.1 Hz, 1H); 6.60 (d, *J*= 4.5 Hz, 1H); 7.30 (d, *J*= 7.8 Hz, 2H); 7.69 (d, *J*= 7.8 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 1.3 (CH_2); 7.1 (CH_3); 21.6 (CH_3); 47.0 (CH_2); 51.9 (Cq); 52.7 (CH_3); 65.9 (CH); 125.2 (CH); 128.2 (CH); 129.2 (CH); 132.4 (Cq); 135.1 (Cq); 143.7 (Cq); 164.5 (Cq).

2-Hydroxy-4-(toluene-4-sulfonyl)-1-triethylsilyl-7-oxa-4-aza-bicyclo[4.1.0]heptane 3-methyl carboxylate (13). From the aldehyde **2** (150 mg, 0.29 mmol), in the presence of DBU, a



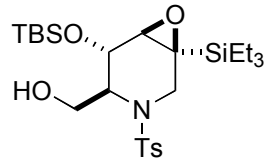
mixture of cyclic products **13** could be isolated. Careful purification allowed the isolation of fractions containing a mixture of two diastereomers (57 mg, 0.13 mmol, 45 % yield). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.55-0.70 (2xq, 2x6H); 0.95 (2xt, 2x9H); 2.43 (s, 3H, dia1); 2.44 (s, 3H dia2); 3.14 (d, *J*= 4Hz, 1H, dia1); 3.20 (d, *J*= 4 Hz, 1H, dia2); 3.46 (s, 3H, dia2); 3.48 (s, 3H, dia1); 3.71 (d, *J*= 13 Hz, 1H, dia1); 3.82 (dd, *J*= 13.5 and 4 Hz, 1H, dia2); 4.02 (dd, *J*= 13 and 4 Hz, 1H, dia1); 4.13 (d, *J*= 13.5 Hz, 1H, dia2); 4.54 (d, *J*= 2.8 Hz, 1H, dia1); 4.60 (s, 1H, dia2); 4.63 (d, *J*= 5.8 Hz, 1H, dia2); 4.71 (dd, *J*= 11 and 2.8 Hz, 1H, dia1); 7.31 (m, 2x2H); 7.68 (m, 2x2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 1.5 (CH_2); 7.3 (CH_3); 21.6 (CH_3); 39.7 (CH_2); 51.7 (Cq); 52.4 (CH_3); 58.8 (CH); 69.5 (CH); 127.5 (CH); 129.5 (CH); 135.2 (Cq); 143.7 (Cq); 168.1 (Cq).

(*1R*, 4R*, 5S*, 6R)-5-(*tert*-Butyldimethyl-silyloxy)-3-(toluene-4-sulfonyl)-1-triethylsilyl-7-oxa-3-aza-bicyclo[4.1.0)heptane 4-methylcarboxylate (14).** Dimethyl *tert*-butylsilyl chloride



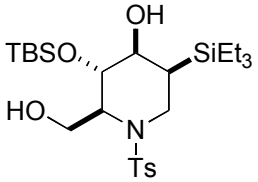
(143.3 mg, 0.95 mmol, 1.5 equiv.) and imidazole (86 mg, 1.27 mmol, 2.0 equiv.) were added to a solution of alcohol **11a** (280 mg, 0.63 mmol) in dry DMF (1 mL) at 0°C. The mixture was stirred for 4h and reaction stopped by adding a solution of aqueous NH_4Cl, and extracted with Et_2O. The organic combined layer were washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The crude was purified by flash chromatography (PE/EA 9/1) to afford **14** (318 mg, 0.57 mmol, 90% yield) as a colorless oil. R_f= 0.6 (PE/EA 7/3); IR: 2955, 2875, 1735, 1460, 1335, 1255, 1160, 1100, 1035, 1000, 835, 775, 730, 655 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 0.20 (s, 3H); 0.23 (s, 3H); 0.49 (q, *J*= 8 Hz, 6H); 0.90 (m, 18H); 2.41 (s, 3H); 2.95 (s, 1H); 3.50 (m, 2H); 3.64 (s, 3H); 4.62 (d, *J*= 2 Hz, 1H); 4.90 (d, *J*= 2 Hz, 1H); 7.27 (d, *J*= 8 Hz, 2H); 7.78 (d, *J*= 8 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ= -3.6 et -4.9 ($2CH_3$); 1.0 (CH_2); 7.0 (CH_3); 14.2 (Cq); 21.5 (CH_3); 25.7 (CH_3); 41.1 (CH_2); 51.9 (Cq); 52.2 (CH_3); 55.3 (C_b), 58.1 (CH); 67.7 (CH); 127.7 (CH); 129.3 (CH); 136.6 (Cq); 143.4 (Cq); 168.8 (C_q). HRMS Calc for $C_{26}H_{45}NO_6NaSi_2S$: 578.2407. Found: 578.2404. Anal. Calcd: C 56.18, H 8.16, N 2.52. Found: C 56.69, H 8.42, N 2.61.

(*1R*, 4S*, 5S*, 6R)-5-[(*tert*-Butyldimethyl-silyloxy)-3-(toluene-4-sulfonyl)-1-triethylsilyl-7-oxa-3-aza-bicyclo[4.1.0]hept-4-yl]-methanol (15).** To the ester **14** (50 mg, 0.09 mmol) diluted



in Et_2O (0.5 mL) was added at 0°C, a solution of $LiAlH_4$ (10.5 mg, 0.27 mmol, 3 equiv.) in Et_2O (1 mL). After 1h at 0°C, the mixture was quenched with a saturated solution of Na_2SO_4. The white-grey precipitate was filtered over Celite and washed with Et_2O. The organic layer was dried with Na_2SO_4, filtered and concentrated under vacuum. The alcohol **15** was isolated by flash chromatography as a colorless oil (40 mg, 0.076 mmol, 84% yield). R_f= 0.6 (PE/EA 7/3); IR: 3600, 2955, 2875, 1335, 1255, 1160, 1035, 1000, 835, 775, 730, 655 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 0.10 and 0.12 (2 s, 6H); 0.46 (q, *J*= 7.7 Hz, 6 H); 0.86 (t, *J*= 7.7 Hz, 9H); 0.89 (s, 9H); 2.41 (s, 3H); 2.96 (d, *J*= 2 Hz, 1H); 3.53 (d, *J*= 14.9 Hz, 1H); 3.67 (d, *J*= 14.9 Hz, 1H); 3.88 (dd, *J*= 11.5 and 7 Hz, 1H); 3.98 (td, *J*= 6.5 and 1.2 Hz, 1H); 4.32 (t, *J*= 2 Hz, 1H); 7.26 (d, *J*= 8.3 Hz, 2H); 7.82 (d, *J*= 8.3 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ= -3.6 et -4.9 (CH_3); 1.0 (CH_2); 7.1 (CH_3); 18.2 (Cq); 21.5 (CH_3); 25.8 (CH_3); 41.9 (CH_2); 52.2 (Cq); 55.7 (CH), 60.7 (CH); 61.6 (CH_2); 66.4 (CH); 127.9 (CH); 129.9 (CH); 136.7 (Cq); 143.4 (Cq).

(2*S*, 3S*, 4R*, 5S)-3-(*tert*-Butyldimethyl-silyloxy)-2-hydroxymethyl-1-(toluene-4-sulfonyl) -5-triethylsilyl-piperidin-4-ol (16).** $LiAlH_4$ (90 mg, 2.30 mmol, 4 equiv.) was added to



a solution of **14** (318 mg, 0.58 mmol) in Et_2O at 0°C. The mixture was stirred at room temperature during 22h then quenched with a saturated solution of Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by flash chromatography (PE/EA 7/3) to afford **16** (0.172 g, 0.31 mmol, 54% yield) which slowly crystallized. m.p. 114°C. ^{1}H-NMR (400 MHz, $CDCl_3$) : δ= 0.08 (s, 3H), 0.12 (s, 3H), 0.51 (m, 6H), 0.84 (t, *J*= 7.8 Hz, 9H), 0.91 (s, 9H), 1.43 (ddd, *J*= 13.4, 4.0 and 1.8 Hz, 1H), 2.42 (s, 3H), 3.30 (dd, *J*= 14 and 4 Hz, 1H), 3.53 (d, *J*= 14 Hz, 1H), 3.69 (s, 1H), 3.83 (dd, *J*= 3.3 and 1.5 Hz, 1H), 3.95 (dd, *J*= 11.1 and 3.6 Hz, 1H), 4.02 (dd, *J*= 11.1 and 6.3 Hz, 1H), 4.08 (m, 1H), 7.24 (d, *J*= 8.4 Hz, 2H), 7.83 (d, *J*= 8.1 Hz, 2H) ; ^{13}C-NMR : -4.98 (CH_3), -4.92 (CH_3), 2.5 (3 CH_2), 7.3 (3 CH_3), 18.1 (Cq), 21.1 (CH_3), 21.5 (CH), 25.8 (3xCH_3), 39.1 (CH_2), 60.2 (CH), 64.9 (CH_2), 69.0 (CH), 70.8 (CH), 127.6 (CH), 129.4 (CH), 137.8 (Cq), 143.0 (Cq). Anal. Calcd. For $C_{25}H_{47}NO_5SSi_2$ (529.987): C 56.67, H 8.94, N 2.64. Found: C 56.78, H 9.15, N 2.68. HRMS Calcd for $C_{25}H_{47}NO_5SSi_2Na$: 552.2595. Found 552.2611.

Acknowledgements

We gratefully acknowledge financial support from UPMC, CNRS, and Institut Universitaire de France of which M.M. is a senior member.

References and Notes

1. (a) Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: New York, 1995. (b) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: New York, 2002. (c) See a recent Tetrahedron Symposia-in-print. Guest Ed. Fairlamb, I. J. S., Development and application of highly active and selective palladium catalysts. *Tetrahedron* **2005,** *61*, 9657.
2. For two recent reviews on the utilization of Pd/C in coupling reactions, see (a) Seki, M. *Synthesis* **2006**, *18*, 2975. (b) Yin, L.; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133. (c) See also Astruc, D. *Inorg. Chem.* **2007**, *46*, 1884.
3. For a review, see: Ansell, J.; Wills, M. *Chem. Soc. Rev.* **2002**, *31*, 259.

4. More than 1000 ligands have been described to date. (a) Woska, D.; Prock, A.; Giering, W. P. *Organometallics* **2000**, *19*, 4929. (b) Trost, B. M.; Machacek, M. R.; Aponick, A. *Acc. Chem. Res.* **2006**, *39*, 747.
5. For a review on water as solvent, see: (a) Shaughnessy, K. H. *Eur. J. Org. Chem.* **2006**, *8*, 1827. For a review on catalytic reactions in ionic liquids, see: Sheldon, R. *Chem. Commun.* **2001**, 2399.
6. (a) For a DFT study dealing with the influence of the electronic factors on the regioselectivity of palladium-catalyzed alkylations, see: Branchadell, V.; Moreno-Mañas, M.; Pajuelo, F.; Pleixats, R. *Organometallics* **1999**, *18*, 4934. (b) See also: Steinhuebel, D.; Palucki, M.; Davies, I.W. *J. Org. Chem.* **2006**, *71*, 3282.
7. (a) Hirao, T.; Enda, J.; Ohshiro, Y.; Agawa, T. *Tetrahedron Lett.* **1981**, *22*, 3079. (b) Branchadell, V.; Moreno-Mañas, M.; Pleixats, R. *Organometallics* **2002**, *21*, 2407.
8. (a) Langkopf, E.; Schinzer, D. *Chem. Rev.* **1995**, *95*, 1375. (b) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063. (c) Liu, D.; Kozmin, S. A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4757. (d) Chabaud, L.; James, P.; Landais, Y. *Eur. J. Org. Chem.* **2004**, 3173. (e) Fauvel, A.; Deleuze, H.; Landais, Y. *Eur. J. Org. Chem.* **2005**, 3900.
9. (a) Büttner, M. W.; Penka, M.; Doszczak, L.; Krapft, P.; Tacke, R. *Organometallics* **2007**, *26*, 1295. (b) Tacke, R.; Schmid, T.; Merget, M. *Organometallics* **2005**, *24*, 1780. (c) Cavelier, F.; Vivet, B.; Martinez, J.; Aubry, A.; Didierjean, C.; Vicherat, A.; Marraud, M. *J. Am. Chem. Soc.* **2002**, *124*, 2917. (d) Bolm, C.; Kasyan, A.; Drauz, K.; Günther, K.; Raabe, G. *Angew. Chem. Int. Ed.* **2000**, *39*, 2288.
10. (a) Itami, K.; Nokami, T.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 5600. (b) Inami, H.; Ito, T.; Urabe, H.; Sato, F. *Tetrahedron Lett.* **1993**, *34*, 5919. (c) Olofsson, K.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **1998**, *63*, 5076.
11. Ollivier, J.; Girard, N.; Salaün, J. *Synlett* **1999**, 1539.
12. For monographs dealing with the behavior of organosilicon compounds in palladium-catalyzed cross-coupling reactions, see (a) Hiyama, T. *J. Organomet. Chem.* **2002**, *653*, 58. (b) Nakao, Y.; Imanaka, H.; Chen, J.; Yada, A.; Hiyama, T. *J. Organomet. Chem.* **2007**, *692*, 585. (c) Denmark, S.E.; Yang, S.M. *Tetrahedron* **2004**, *60*, 9695.
13. (a)Thorimbert, S.; Malacria, M. *Tetrahedron Lett.* **1996**, *37*, 8483. (b) Commandeur, C.; Thorimbert, S.; Malacria, M. *J. Org. Chem.* **2003**, *68*, 5588. (c) For a recent application of the silicon effect in palladium-catalyzed alkylation, see: Vitale, M.; Prestat, G.; Lopes, D.; Madec, D.; Poli, G. *Synlett* **2006**, 2231.
14. Branchadell, V.; Moreno-Mañas, M.; Pleixats, R.; Thorimbert, S.; Commandeur, C.; Boglio, C.; Malacria, M. *J. Organomet. Chem.* **2003**, *687*, 337.
15. Otha, T.; Hosokawa, T.; Murahashi, S.-I.; Miki, K.; Kasai, N. *Organometallics*, **1985**, *4*, 2080.
16. Thorimbert, S.; Malacria, M. *Tetrahedron Lett.* **1998**, *39*, 9659.
17. (a) Humilière, D.; Thorimbert, S.; Malacria, M. *Synlett* **1998**, 1255. (b) Thorimbert, S.; Taillier, C.; Bareyt, S.; Humilière, D.; Malacria, M. *Tetrahedron Lett.* **2004**, *45*, 9123.

18. Boglio, C.; Stahlke, S.; Thorimbert, S.; Malacria, M. *Org. Lett.* **2005**, *7*, 4851.
19. For some reviews see: (a) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781. (b) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953. (c) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693. (d) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701.
20. For recent reviews see (a) Pearson, M. S. M.; Mathé-Allainmat, M.; Fargeas, V.; Lebreton, J. *Eur. J. Org. Chem.* **2005**, 2159. (b) Huang, P.-Q. *Synlett* **2006**, 1133.
21. For selected approaches see (a) Sletten, E. M.; Liotta, L. J. *J. Org. Chem.* **2006**, *71*, 1335. (b) Calderón, F.; Doyagüez, E. G.; Fernández-Mayorales, A. *J. Org. Chem.* **2006**, *71*, 6258. (c) Guo, H.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 1609. (d) Wang, R.-W.; Quing, F.-L. *Org. Lett.* **2005**, *7*, 2189. (e) Segraves, N. L.; Crews, P. *J. Nat. Prod.* **2005**, *68*, 118. (f) Goodenough, K. M.; Raubo, P.; Harrity, J. P. A. *Org. Lett.* **2005**, *7*, 2993. (g) Martìn, R.; Murruzzu, C.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **2005**, *70*, 2325. (h) Legault, C. Y.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 8966. (i) Takahata, H.; Banba, Y.; Sasatani, M.; Nemoto, H.; Kato, A.; Adachi, I. *Tetrahedron* **2004**, *60*, 8199. (j) Adelbrecht, J. C.; Craig, D.; Dymock, B. W.; Thorimbert, S. *Synlett* **2002**, 467.
22. For related intramolecular aldolizations see: (a) Danieli, B.; Lesma, G.; Palmisano, G. *Tetrahedron Lett.* **1981**, *22*, 1827. (b) Chandrakala, P. S.; Katz, A. M.; Carell, H. L.; Sailaje, P. R.; Podile, A. R.; Nangia, A.; Desiraju, G. R. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2597. (c) Bravin, F. M.; Busnelli, G.; Colombo, M.; Gatti, F.; Manzoni, L.; Scolastico, C. *Synthesis* **2004**, 353.
23. Seebach, D.; Hungerbuhler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B. *Synthesis*, **1982**, 138.
24. (a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1978**, *18*, 2199. (b) Anh, N. T.; Eisenstein, O.; Lefour, J. M.; Trân Huu Dâu, M. E. *J. Am. Chem. Soc.* **1973**, *95*, 6146. (c) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191.
25. (a) Eisch, J. J.; Trainor, J. T. *J. Org. Chem.* **1963**, *28*, 2870. (b) Fristad, W. E.; Bailey, T. R.; Paquette, L. A.; Gleiter, R.; Boehm, M. C. *J. Am. Chem. Soc.* **1979**, *101*, 4420.