Notes

Free-Radical Cyclization in the Synthesis of a 1-Aza-5-silabicyclo[5.2.0]nonan-9-one, a Silicon-Containing β-Lactam

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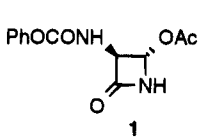
More than 50 years after the discovery of the antibacterial effect of penicillin in man, β-lactam antibiotics are still under active investigation by organic chemists.[1] New, more selective antibiotics, or antibiotics with a broad spectrum of action, are needed since the frequency of antimicrobial-resistant infections has increased in both the hospital and the community.[2] Intense investigations have resulted in the discovery of several natural and synthetic biologically-active substances containing the β-lactam ring, including cephalosporins,[3] carbapenems,[4] penems,[5] oxa- and carbacephems[6] as well as monobactams,[7] nocardicin derivatives,[8] clavams,[9] or other spiranic[10] or multicyclic ring systems.[11] Most of the variations have been introduced by keeping the β-lactam moiety intact but changing the atoms, functional groups and the size of the B ring.[12] It is surprising that given the enormous amount of work in β-lactam chemistry and in the field of organosilicon chemistry,[13] no example of a β-lactam antibiotic having a silicon atom in the B ring has been reported.[14] There is also little information on simple β-lactams containing group 14 elements.[15]

We describe in this paper the synthesis of a silylated β-lactam (formally a 2-silahomocepham or 1-aza-5-silabicyclo[5.2.0]nonan-9-one) which shows antimicrobial activity against Gram positive bacteria.

From a basic knowledge of the structure activity studies on β-lactams,[16] it is well known that an active structure should contain an acidic residue close to the heterocyclic nitrogen and an amido, ethyl, or hydroxyethyl group on the carbon α to the lactam carbonyl.

To prepare a silicon-containing β-lactam having these structural requirements, we designed a synthesis starting from a β-lactam available as a single enantiomer. Even though compound **1** appears to be a suitable starting material, it can only be prepared[17] in a low yielding, multistep procedure starting from a derivative of methyl penicillanate 1-oxide. We therefore chose the commercially available compound **2** as the starting material, leaving the transformation of the hydroxyethyl group into an NH_2 to the last steps of the synthesis.



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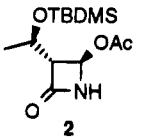

2

The silicon moiety was introduced into compound **2** using the Grignard reagent of (chloromethyl)vinyldimethylsilane (**3**). Silane **3** was prepared from vinylmagnesium bromide and (choromethyl)dimethylchlorosilane. The corresponding Grignard reagent was prepared using activated magnesium and required a further activation "in situ" with 1,2-dibromoethane. Slow addition (automatic pump syringe) of the Grignard solution in ether to a cooled solution of **2** in THF followed by acidic hydrolysis and column chromatography gave product **4** in 85% yield (Scheme 1).

In order to produce the B ring we needed a cyclization reaction that would employ the double bond of the vinylsilane without fragmentation of the carbon–silicon bonds. Following the pioneering work of Bachi,[18] we decided to pursue the intramolecular free-radical annulation of a carbon-centered radical to the carbon–carbon double bond of the vinylsilane. Silyl lactam **4** was

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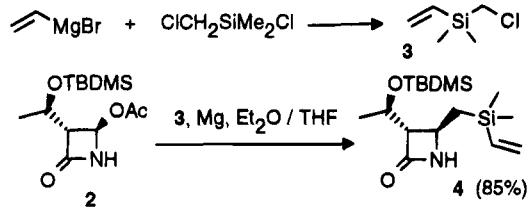
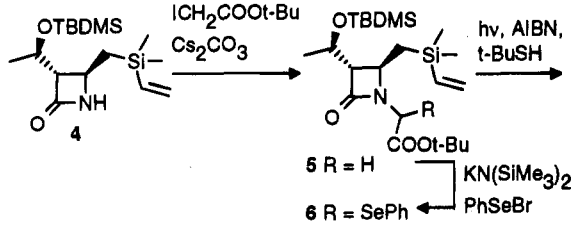
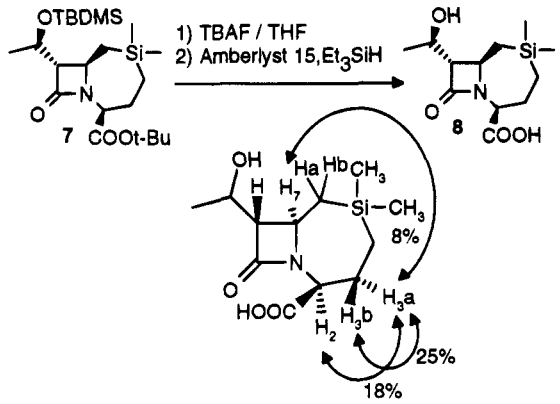
Scheme 1



Scheme 2



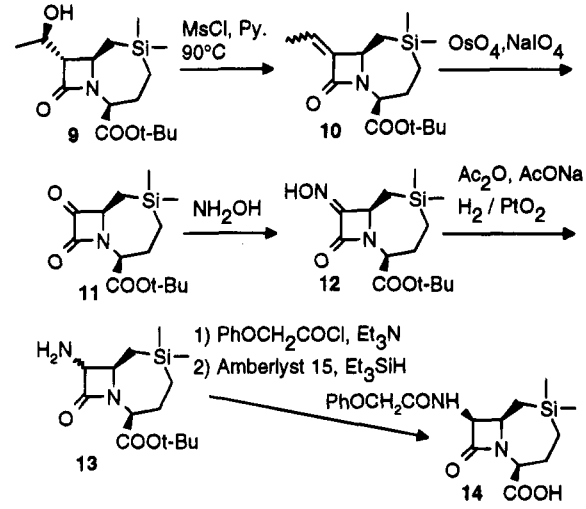


therefore alkylated at nitrogen using *tert*-butyl iodoacetate in the presence of Cs_2CO_3 (79%) (Scheme 2). Treatment of the product **5** with $KN(SiMe_3)_2$ in THF, followed by phenylselenyl bromide, formed lactam **6** in 64% yield. Strict control of the amount of phenylselenyl bromide (1 equiv) and the temperature of the reaction (−78 °C) is necessary in order to minimize the formation of the corresponding *gem* bis(phenylseleno) derivative.

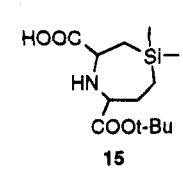
The ring closure was successfully performed by irradiation with a high vacuum mercury lamp of a solution of **6** in dry benzene in the presence of 10% AIBN and 2 equiv of *t*-BuSH employed as the hydrogen donor (*caution, the reaction solution contains the stinking t-BuSH*). Bicyclic β-lactam **7** was isolated after flash chromatography, in 84% yield, as the sole isomer.[19] Despite the presence of the silicon, the alkenyl β-lactam preferred to undergo a 7-*endo*-radical cyclization. The formation of the seven-membered ring was confirmed by ^1H NMR analysis. The proton adjacent to the carbonyl showed the typical pattern for an ABX system The multiplicity was not consistent with a six-membered ring wherein the proton adjacent to the carboxyl should couple with only one other proton. The TBDMSO group of lactam **7** was removed using TBAF in THF, and the *tert*-butyl ester was hydrolyzed using a proton exchange resin to afford acid **8** in 67% yield.

The stereochemistry of acid **8** was confirmed by NOE experiments. Upon irradiation at H_{3a}, significative enhancements were observed at H_7 and H_2, indicating that these protons are on the same side of the molecule. Irradiation at H_{3b} did not induce any enhancement at H_7 and H_2, confirming the stereochemistry to be that of **7**. Unfortunately, this product did not show any antimicrobial activity.

Scheme 3



Disappointed by this result, we decided to transform the hydroxyethyl group into an NH_2, hoping that the bicyclic β-lactam would survive the reaction conditions.[20] Lactam **9** was treated with methanesulfonyl chloride in pyridine at 90 °C to give, after hydrolytic workup, alkene **10** in 82% yield (Scheme 3). Although we did not observe any racemization of this compound, alkene **10** was obtained as a mixture of *E* and *Z* isomers in a 75:25 ratio. Catalytic osmylation of the double bond in the presence of 4-methylmorpholine 4-oxide, followed by treatment with sodium periodate, gave the ketolactam **11** in 74% yield after isolation. Treatement of **11** with NH_2OH·HCl and triethylamine in methanol afforded oxime **12** in 75% yield. Reduction of the corresponding acetate, prepared from acetic anhydride and sodium acetate with H_2/Pd at 2 atm gave amine **13** in 85% yield as a mixture of diastereoisomers. The amine was acylated with phenoxyacetyl chloride in the presence of triethylamine and DMAP. Finally, deprotection of the carboxylic group with Amberlyst 15 in MeOH gave lactam **14** in 74% yield as a 5:1 mixture of the *cis*:*trans* isomers. Pure **14** was obtained by fractional crystallization from diisopropyl ether. The most difficult aspect of these straightforward transformations was the isolation of ketolactam **11**. It had to be extracted during the reaction since it undergoes further oxidation to give a mixture of products from which we were able to isolate and identify compounds **15** and **16**.



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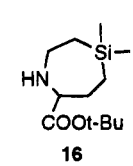

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The sililated bicyclic lactam **14** was tested against a selection of Gram positive and Gram negative bacteria

(19) Product **7** was isolated in lower yields from a thermic radical reaction performed by refluxing the reagents mixed in the same ratio in benzene. Moreover, it is noteworthy that in absence of AIBN the photochemical annulation did not work well.

(20) To our knowledge, there are no examples of such a transformation performed on the "sensitive" bicyclic β-lactams. For the procedure described in this paper, we were inspired by: Chiba, K.; Mori, M.; Ban, Y. *Tetrahedron* **1985**, *41*, 387.

and showed a MIC of 64 μg/mL against *Staphylococcus aureus* ATCC 25923 and 16 μg/mL against *Micrococcus luteus* ATCC 9341.

With the preparation of **14** we have demonstrated that it is possible to synthesize a skeleton very similar to that of the cephalosporins containing a silicon atom as the heteroatom. Furthemore, this kind of compound shows weak antimicrobial activity against Gram positive bacteria. We cannot determine at present if the silicon atom plays a role in this activity (we can only speculate that the seven-membered ring containing silicon should have a strain comparable to that of a six-membered carbo- or heterocyclic ring), but we have shown that silicon is compatible with antibiotic activity. We hope that our results will stimulate further synthetic research in contest with the search for new antibiotic structures.

Experimental Section

(Chloromethyl)dimethylvinylsilane (3). (Chloromethyl)-dimethylchlorosilane (4 g, 28 mmol) was dissolved in dry ether (10 mL) and cooled to 0 °C under nitrogen and magnetic stirring. Vinylmagnesium bromide (28 mL of a 1 M THF solution, 28 mmol) was added slowly and the mixture stirred at rt for 1 h. After the mixture was cooled to 0 °C, ether (100 mL) was added followed by a saturated solution of NH_4Cl. After separation of the organic layer, drying over anhydrous Na_2SO_4, and evaporation of the solvent, the product was isolated by fractional distillation. A total of 2.8 g of product **3** (74% yield) was obtained: bp 122−126°; MS (70 eV) *m/z* 136 (M^+ + 2, 22), 134 (M^+, 66), 99 (45), 72 (100).

[3*S*,4*S*,(1′*R*)]-3-[1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-[(vinyldimethylsilyl)methyl]-2-azetidinone (4). To magnesium turnings (previously washed with 10% NH_4Cl solution followed by washing with water, ethanol, and diethyl ether and dried at 100 °C overnight) (271 mg, 11.3 mmol) covered with dry ether and under nitrogen atmosphere was added 1,2-dibromomethane (10 mg), immediately followed by dropwise addition of **3** (1.47 g, 11 mmol) in ether (5 mL). In order to activate the reaction, the flask was warmed at 35 °C. After 30 min of stirring at this temperature, the flask containing this black-gray mixture was cooled to −15 °C and β-lactam **2** (1.05 g, 3.65 mmol) in dry THF (15 mL) was added during 1 h using an automatic pump syringe. After 30 min of stirring at −15 °C, ether was added (50 mL) followed by a saturated solution of NH_4Cl. The organic layer was separated, washed with brine, and dried over anhydrous Na_2SO_4. After evaporation of the solvent, column chromatography on silica gel (eluent 2:5 hexane: ethyl acetate) gave product **4** (1.02 g, 85% yield): ^1H NMR (200 MHz, $CDCl_3$) δ 0.06 (s, 3H,), 0.07 (s, 3H), 0.12 (s, 3H), 0.14 (s, 3H), 0.87 (s, 9H), 1.05 (m, 2H), 1.22 (d, 3H, J = 6 Hz), 2.73 (m, 1H), 3.74 (m, 1H), 4.12 (dq, 1H, J_a= 7 Hz, J_b = 5 Hz), 5.66−6.20 (m, 4H); ^{13}C NMR (50 MHz, CDCl3) δ −6.2, −6.0, −2.2, −0.3, 15.0, 20.7, 25.1, 28.9, 38.4, 51.5, 65.0, 134.2, 140.2, 178.2; MS (70 eV) *m/z* 327 (M^+, 10), 300 (6), 284 (16), 196 (18), 127 (90), 74 (100). Anal. Calcd for $C_{16}H_{33}NO_2Si_2$: C, 58.68; H, 10.16; N, 4.28. Found: C, 58.48; H, 10.10; N, 4.23.

[3*S*,4*S*,(1′*R*)]-3-[1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-1-[(phenylselenyl)(*tert*-butyloxycarbonyl)methyl]-4-[(vinyldimethylsilyl)methyl]-2-azetidinone (6). To a stirred solution of β-lactam **4** (1.55 g, 4.73 mmol) in acetonitrile (50 mL), was added *tert*-butyl iodoacetate (2.3 g, 9.46 mmol) and Cs_2CO_3 (1.96 g, 6 mmol). The reaction mixture was warmed at 55 °C for 1 h and then cooled to rt and stirred at this temperature for 5 days. Ether (100 mL) was added, and the organic layer was separated and dried over anhydrous sodium sulfate. After evaporation of the solvent, the crude product was dissolved in dry THF (10 mL) and added dropwise to a mixture of hexamethyldisilazane (0.6 g, 3.6 mmol) and BuLi (2.25 mL of a 1.6 M solution, 3.6 mmol) cooled to −78 °C. After 3 h of stirring at this temperature, phenylselenyl bromide (0.77 g, 3.27 mmol) in dry THF (10 mL) was added. After 30 min of stirring at −78 °C, ether (100 mL) was added, followed by a saturated solution of NH_4Cl. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, column chromatography on silica gel (eluent 6:1 hexane:ethyl acetate) gave product **6** as an oil (1.0 g, 51% yield): ^1H NMR (200 MHz, $CDCl_3$) δ 0.01 (m, 3H), 0.04 (s, 3H), 0.17 (s, 3H); 0.19 (s, 3H); 0.82 (s, 9H), 0.90−1.22 (m, 2H), 1.20 (d, 3H, J = 8Hz), 1.40 (s, 9H), 2.68 (m, 1H), 4.15 (m, 1H), 4.31 (m, 1H), 5.64 (s, 1H), 5.7−6.3 (m, 3H), 7.2−7.8 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ −6.1, −3.2, −2.2, −1.7, 15.0, 17.6, 20.8, 22.8, 29.0, 42.0, 49.0, 51.4, 65.3, 72.9, 121.0, 126.4, 127.7, 129.0, 130.0, 140.2, 171.0, 176.4; MS (70 eV) *m/z* 596 (M^+, 1), 539 (6), 495 (5), 440 (10), 196 (60), 74 (100), 57 (100). Anal. Calcd for $C_{28}H_{47}NO_4SeSi_2$: C, 59.03; H, 8.32; N, 2.46. Found: C, 58.97; H, 8.30; N, 2.44.

[2*S*,7*S*,8*S*,(1′*R*)]-8-[1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-5,5-dimethyl-9-oxo-1-aza-5-silabicyclo[5.2.0]nonane-2-carboxylic Acid *tert*-Butyl Ester (7). A solution of β-lactam **6** (1.0 g, 1.68 mmol) in dry benzene (168 mL) and AIBN (55 mg, 0.33 mmol) was degassed by being bubbled through argon for 10 min, and then *tert*-butanethiol (0.16 g, 1.85 mmol) was added. The mixture was exposed to a high vacuum mercury lamp for 2 h, maintaining the temperature at 20 °C. The solvent was evaporated, and the residue was purified by column chromatography on silica gel (eluent 6:1 hexane:ethyl acetate) to give **7** as an oil (0.62 g, 84% yield): ^1H NMR (200 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.08 (s, 6H), 0.65−0.73 (m, 2H), 0.87 (s, 9H), 0.98−1.10 (m, 2H), 1.27 (d, 3H, J = 6 Hz), 1.46 (s, 9H), 1.80−2.20 (m, 2H), 2.66 (dd, 1H, J_a = 8 Hz, J_b = 2 Hz), 4.18 (X part of a ABX system, 2H), 4.50 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ −4.4, −3.5, −1.5, −1.32, 12.4, 18.4, 22.6, 23.3, 26.1, 26.3, 28.6, 55.7, 55.8, 66.9, 67.9, 82.2, 168.6, 170.1; MS (70 eV) *m/z* 441 (M^+, 5), 384 (16), 340 (20), 76 (80), 57 (100). Anal. Calcd for $C_{22}H_{43}NO_4Si_2$: C, 59.83; H, 9.82; N, 3.17. Found: C, 59.88; H, 9, 86; N, 3.19.

[2*S*,7*S*,8*S*,(1′*R*)]-8-(1-Hydroxyethyl)-5,5-dimethyl-9-oxo-1-aza-5-silabicyclo[5.2.0]nonane-2-carboxylic Acid (8). To a stirred solution of β-lactam **7** (0.36 g, 0.814 mmol) in THF (6 mL) cooled to 0 °C was added tetrabutylammonium fluoride trihydrate (0.308 g, 0.97 mmol) in THF (5 mL). After the solution was stirred for 5 h at rt, ether (40 mL) was added followed by a saturated solution of NH_4Cl. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the product was dissolved in dichloromethane (5 mL), and Amberlyst 15 (0.25 g) was added followed by triethylsilane (0.59 g, 5.12 mmol). The mixture was stirred at room temperature for 6 days, and then the Amberlyst was filtered away, the solvent was evaporated, and product **8** was purified by column chromatography on silica gel (eluent 4:1 ethyl acetate:methanol), obtaining 0.18 g of the compound (84% yield): ^1H NMR (200 MHz, $CDCl_3$) δ 0.1 (s, 6H), 0.6−0.8 (m, 2H), 0.9−1.1 (m, 2H), 1.27 (d, 3H, J = 6 Hz), 2.04 (m, 2H), 2.77 (m, 1H), 4.2−4.4 (m, 2H), 4.47 (m, 1H), 6.2 bs 1H), 9.2 (bs, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ −2.0, −1.2, 12.7, 21.6, 23.1, 24.48, 59.9, 56.8, 65.0, 66.2, 171.1, 173.9; MS (70 eV) *m/z* 270 (M^+, 1), 270 (5), 226 (10), 186 (18), 158 (45), 114 (100), 75. Anal. Calcd for $C_{12}H_{21}NO_4$: C, 53.11; H, 7.81; N, 5.16. Found: C, 53.19; H, 7.88; N, 5.18.

(2*S*,7*S*)-5,5-Dimethyl-8-ethylidene-9-oxo-1-aza-5-silabicyclo[5.2.0]nonane-2-carboxylic Acid *tert*-Butyl ester (10). To a solution of **9** (0.55 g, 1.68 mmol) in dry pyridine (5 mL) was added methansulfonyl chloride (0.21, 1.8 mmol), and the mixture was warmed at 90 °C for 8 h. After cooling, the mixture was added to a refrigerated (0 °C) 10% HCl solution (15 mL) and the product extracted with ether (20 mL). The combined extracts were washed with 5% HCl and brine. After the extracts were dried over anhydrous Na_2SO_4, the solvent was evaporated and product **10** purified by column chromatography on silica gel (eluent 3:1 hexane:ethyl acetate) (0.43 g, 84% yield): ^1H NMR (200 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.07 (s, 3H), 0.69−0.75 (m, 2H), 0.96−1.2 (m, 2H), 1.45 (s, 9H), 1.86 (d, 3H, J = 7 Hz), 2.00 (m, 2H), 4.20 (dd, 1H, J_a = 8 Hz, J_b = 2 Hz), 4.42 (X part of an ABX system, 1H), 6.30 (m, 1H, major isomer), 6.41 (m, minor isomer); ^{13}C NMR (50 MHz, $CDCl_3$) δ −2.1, −1.8, 8.4, 12.8, 17.3, 23.7, 29.9, 46.3, 60.6, 78.2, 130.2, 134.4, 163.4, 172.0; MS (70eV) *m/z* 309 (M^+, 3), 252 (11), 208 (20), 75 (80), 57 (100). Anal. Calcd for $C_{16}H_{27}NO_3Si$: C, 62.10; H, 8.97; N, 4.53. Found: C, 62,03; H, 8.95; N, 4.49.

(2*S*,7*S*)-5,5-Dimethyl-8-(hydroxyimino)-9-oxo-1-aza-5-silabicyclo[5.2.0]nonane-2-carboxylic Acid *tert*-Butyl Ester (12). To a solution of 4-methylmorpholine 4-oxide (0.17 g,

1.5 mmol) and OsO_4 (1 mL of a 1% solution in *t*-BuOH, 0.039 mmol) in acetone–water (3:1, 5 mL) was added **10** (0.4 g, 1.3 mmol) in acetone (1 mL). The mixture was stirred for 48 h, and then sodium metaperiodate (0.197 g, 0.9 mmol) was added followed by diethyl ether–pentane (1:1, 10 mL). The mixture was vigorously stirred for 4 days. The organic layer was separated and washed with a 10% sodium metabisulfite solution and brine. After the organic layer was dried over anhydrous Na_2SO_4 (in the dark), the solvent was evaporated under vacuum, being careful that the temperature of the flask did not reach 20 °C. The crude was dissolved in methanol, and to this solution was added triethylamine (0.5 g, 5 mmol) and $NH_2OH{\cdot}HCl$ (0.35 g, 5 mmol) and the mixture stirred at rt for 48 h. After dilution with 25 mL of water containing 2.5 mL of concentrated NH_4OH, the product was extracted with $CHCl_3$ and the combined extracts were washed with brine. The $CHCl_3$ was dried over anhydrous Na_2SO_4 and the solvent evaporated to give crude **12** (0.35 g, 75%). An analytical sample was obtained after crystallization from ethyl acetate/hexane (mp 123–125 °C): ^1H NMR (200 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.60–0.70 (m, 2H), 0.96–1.2 (m, 2H), 1.50 (s, 9H), 2.10 (m, 2H), 4.02 (dd, 1H, J_a = 8 Hz, J_b = 2 Hz), 4.35 (X part of an ABX system, 1H), 5.30 (bs, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) −2.1, −1.8, 8.4, 12.8, 17.3, 23.7, 29.9, 46.3, 60.6, 78.2, 152.9, 168.8, 172.0; MS (70 eV), *m/z* 312 (M^+, 0.8), 294 (1), 255 (5), 241 (10), 237 (15), 221 (20), 123 (60), 75 (80), 57 (100). Anal. Calcd for $C_{14}H_{24}N_2O_4Si$: C, 53.82; H, 7.74; N, 8.97. Found: C, 53.78; H, 7.70; N, 8.90.

(2*S*,7*S*,8*S*)-5,5-Dimethyl-9-oxo-8-[(2-phenoxyacetyl)amino]-1-aza-5-silabicyclo[5.2.0]nonane-2-carboxylic Acid (14). Oxime **12** (0.3 g, 0.96 mmol) was dissolved in Ac_2O (2 mL) containing sodium acetate (0.5 g) and the mixture stirred at rt for 6 h. Diethyl ether was added followed by a cooled solution of 10% NH_4OH. After separation of the organic layer and drying over anhydrous Na_2SO_4, the solvent was evaporated and replaced with MeOH (5 mL) and the solution transferred to a vial. PtO_2 (10 mg) was added and the vial inserted in the bottle of a Parr hydrogenation apparatus and submitted to 2 atm of H_2 for 3 days. After this period, the catalyst was replaced with a new portion (10 mg) and the sample hydrogenated for an additional 2 days. After filtration of the catalyst and evaporation of the solvent, the crude was dissolved in dichloromethane (5 mL) and triethylamine (0.5 g, 5 mmol) and DMAP (50 mg) and phenoxyacetyl chloride (0.17 g, 1 mmol) were added. The mixture was stirred for 8 h, and then water was added and the product extracted with additional dichloromethane. The combined extracts were washed with 5% HCl solution, saturated $NaHCO_3$ solution, and brine. After the extracts were dried over anhydrous Na_2SO_4, Amberlyst 15 (350 mg) was added together with Et_3SiH (0.116 g, 1 mmol) to the dichloromethane solution and the mixture stirred for 5 days at rt. After filtration, the solvent was evaporated and column chromatography on silica gel (eluent 10:1 ethyl acetate:MeOH) gave product **14** (0.198 g, 55% yield) as a 5:1 mixture of isomers. The 7,8 *syn* isomer selectively crystallized (slowly) from diisopropyl ether (mp 127–128 °C): ^1H NMR (200 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.08 (s, 3H), 0.60–0.70 (m, 2H), 0.96–1.2 (m, 2H), 2.10 (m, 2H), 4.02 (ddd, 1H, J_a = 8 Hz, J_b = 4 Hz, J_c = 2 Hz), 4.35 (X part of an ABX system, 1H), 4.5 (s, 2H), 4.86 (dd, J_a= 8 Hz, J_b = 4 Hz), 6.80 (bs, 1H,), 6.9–7.4 (m, 5H), 9.3 (bs, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ −0.6, −0.1, 10.7, 16.4, 25.5, 46.7, 55.6, 59.3, 77.9, 114.6, 120.1, 129.5, 156.7, 170.3, 172.3, 177.9; MS (70 eV), *m/z* 376 (M^+, 2), 331 (5), 283 (5), 239 (41), 93 (100), 75 (40), 65 (80). Anal. Calcd for $C_{18}H_{24}N_2O_5Si$: C, 57.43; H, 6.43; N, 7.44. Found: C, 57.40; H, 6.39; N, 7.40.

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