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Formation of Medium-Sized Nitrogen Heterocycles from γ-Silyloxy-γ-Lactams

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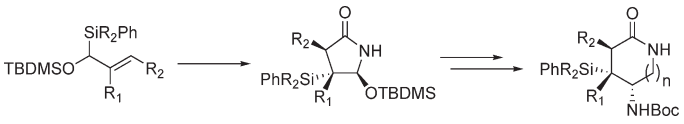

Nitrogen heterocycles can be prepared by performing ring-expansion reactions of γ-silyloxy-γ-lactams, which are available by the annulation reactions of allylic silanes. Nucleophilic substitution of the annulation products and subsequent translactamization of nitrogen-tethered γ-lactams provide six-, seven-, and eight-membered ring lactams. An enantiomerically enriched δ-lactam formed from this method was elaborated to form the hydroxypiperidine core structure of the pseudodistomin alkaloids.

Introduction

The importance of nitrogen-containing heterocycles in natural products chemistry and the pharmaceutical industry has motivated considerable research toward developing methods for the synthesis of these compounds. Five- and six-membered rings are the most common ring sizes, so a number of methods have been developed for the synthesis of these ring systems.[1] Medium-ring nitrogen heterocycles are also found in biologically active natural products.[1] The syntheses of these structures generally involve the manipulation of an acyclic chain followed by closure of the ring.[1,2]

The annulation reactions of allylic silanes provide powerful methods for the formation of five-membered ring nitrogen heterocycles. Cycloaddition reactions with nitrogen-containing electrophiles have been developed, and in most cases, these reactions are stereoselective and stereospecific.[3] Because the silyl moiety in the annulation adducts can be oxidized to form a hydroxyl group, these reactions have been applied to the synthesis of alkaloids.[4] The annulation reactions of allylic silanes are currently limited to the formation of four- and five-membered rings.[3,5]

In this paper, we report that the annulation reactions of α-silyloxy allylic silanes[6] with chlorosulfonyl isocyanate form adducts that can be converted to nitrogen heterocycles of various ring sizes. The annulation reactions provide *N*,*O*-acetals that undergo highly diastereoselective substitution reactions with nucleophiles. When the nucleophile contains a nitrogen atom, translactamization can be achieved to form highly substituted six-, seven-, and eight-membered ring nitrogen heterocycles. The utility of this method is illustrated by the stereoselective synthesis of the hydroxypiperidine core structure of the pseudodistomin alkaloids.[7,8]

(1) (a) Pinder, A. R. *Nat. Prod. Rep.* **1992**, *9*, 17–23. (b) Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2862–2892. (c) Weintraub, P. M.; Sabol, J. S.; Kane, J. A.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953–2989.

(2) (a) Bieräugel, H.; Jansen, T. P.; Schoemaker, H. E.; Hiemstra, H.; Maarseveen, J. H. v. *Org. Lett.* **2002**, *4*, 2673–2674. (b) Krishnan, S.; Bagdanoff, J. T.; Ebner, D. C.; Ramtohul, Y. K.; Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 13745–13754.

(3) (a) Akiyama, T.; Ishikawa, K.; Ozaki, S. *Chem. Lett.* **1994**, 627–630. (b) Panek, J. S.; Jain, N. F. *J. Org. Chem.* **1994**, *59*, 2674–2675. (c) Schneider, M.-R.; Mann, A.; Taddei, M. *Tetrahedron Lett.* **1996**, *37*, 8493–8496. (d) Roberson, C. W.; Woerpel, K. A. *J. Org. Chem.* **1999**, *64*, 1434–1435. (e) Isaka, M.; Williard, P. G.; Nakamura, E. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2115–2116.

(4) (a) Roberson, C. W.; Woerpel, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 11342–11348. (b) For a review describing the oxidation of silanes, see: Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599–7662.

(5) Piperidine formation from an allylic silane has been accomplished via palladium−trimethylenemethane intermediates: Goodenough, K. M.; Moran, W. J.; Raubo, P.; Harrity, J. P. A. *J. Org. Chem.* **2005**, *70*, 207–213.

(6) (a) Hosomi, A.; Hashimoto, H.; Sakurai, H. *J. Org. Chem.* **1978**, *43*, 2551–2552. (b) Romero, A.; Woerpel, K. A. *Org. Lett.* **2006**, *8*, 2127–2130.

(7) (a) Ishibashi, M.; Ohizumi, Y.; Sasaki, T.; Nakamura, H.; Hirata, Y.; Kobayashi, J. *J. Org. Chem.* **1987**, *52*, 450–453. (b) Freyer, A. J.; Patil, A. D.; Killmer, L.; Troupe, N.; Mentzer, M.; Carte, B.; Faucette, L.; Johnson, R. K. *J. Nat. Prod.* **1997**, *60*, 986–990.

(8) For an example of an asymmetric synthesis of a pseudodistomin alkaloid, see: Trost, B. M.; Fandrick, D. R. *Org. Lett.* **2005**, *7*, 823–826. This article also includes references to earlier efforts towards their synthesis.

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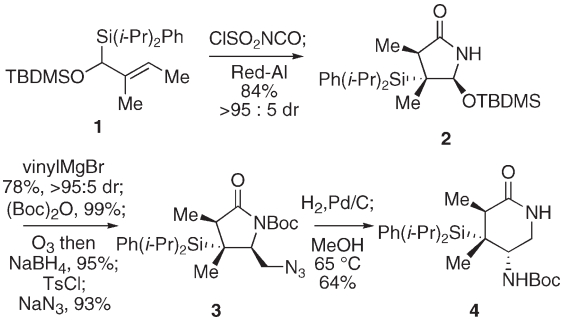
Results and Discussion

The feasibility of ring expansion of γ-silyloxy-γ-lactams was demonstrated by developing a synthesis of a δ-lactam (Scheme 1).[9] Annulation of allylic silane **1** with chlorosulfonyl isocyanate ($ClSO_2NCO$) followed by reduction of the resulting *N*-chlorosulfonyl lactam provided *N*,*O*-acetal **2**.[6b] Nucleophilic substitution with vinylmagnesium bromide followed by standard functional group transformations provided azide **3** as a single diastereomer.[10] Reduction of the azido group revealed a primary amine that underwent translactamization upon heating to afford δ-lactam **4** (Scheme 1).[9,11,12] The Boc group on the amide nitrogen atom of azide **3** was necessary to activate the endocyclic carbonyl group for translactamization; details are provided as Supporting Information.

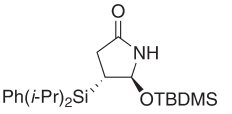
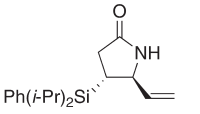
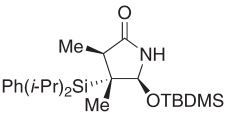
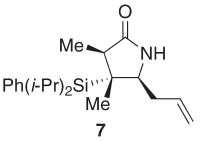
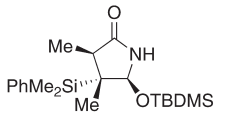
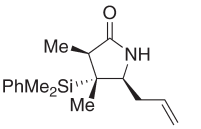
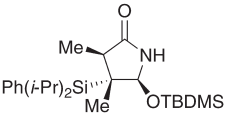
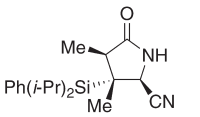
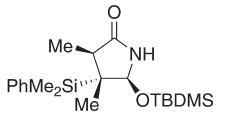
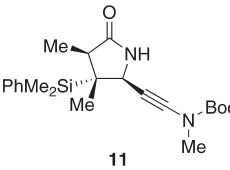
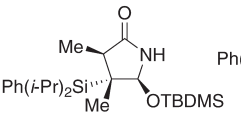
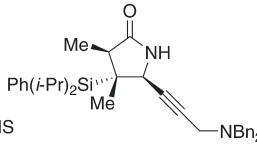
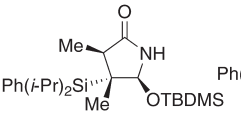
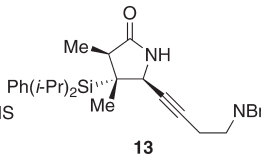
SCHEME 1. δ-Lactam Synthesis by Annulation/Ring Expansion



The nucleophilic substitution reaction of a γ-silyloxy-γ-lactam, which is the key step of the ring-expansion method, was high-yielding and stereoselective for a number of nucleophiles (Table 1). Substitutions with Grignard reagents, such as vinylmagnesium bromide and allylmagnesium chloride, provided γ-lactams **6**, **7**, and **9** with good control of stereochemistry (entries 1−3). Substitutions of γ-silyloxy-γ-lactams with Et_2AlCN provided nitriles cleanly (entry 4). Because substitution was successful with Et_2AlCN, the use of functionalized aluminum reagents was investigated. Substituted alkynylaluminum reagents containing tethered nitrogen atoms were prepared by deprotonation of the corresponding alkyne with *n*-BuLi followed by transmetalation with Me_2AlCl.[13] Heating the alkynylalanes with γ-lactams **2** and **8** in toluene afforded substitution products **11**−**13** as single diastereomers in good yield (Table 1, entries 5−7).

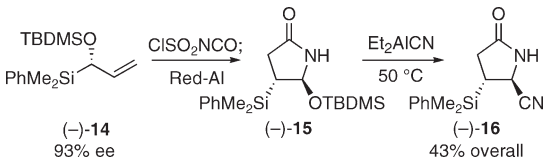
Because chiral, nonracemic α-silyloxy allylic silanes are available,[6b,14] enantiomerically enriched lactams can be obtained using this method (Scheme 2). The allylic silane (−)-**14** was prepared in 93% ee by reduction of the corresponding acylsilane with (+)-diisopinocampheylchloroborane[14a] and protection as its silyl ether. Annulation with $ClSO_2NCO$ provided the unstable lactam (−)-**15**, which was not purified but was subjected to substitution with Et_2AlCN to form the nitrile (−)-**16**. The trans configuration of (−)-**16** was confirmed by X-ray crystallography; details are

TABLE 1. Substitution Reactions of γ-Silyloxy-γ-lactams

Entry	γ-Silyloxy-γ-lactam	Product	Yield (dr)[a]
1	 **5**	 **6**	71% (>95:5)
2	 **2**	 **7**	82% (>95:5)
3	 **8**	 **9**	83% (85:15)
4	 **2**	 **10**	84% (>95:5)
5	 **8**	 **11**	62% (>95:5)
6	 **2**	 **12**	77% (>95:5)
7	 **2**	 **13**	90% (>95:5)

[a]Isolated yields. Diastereoselectivities determined by ^1H NMR spectroscopy.

SCHEME 2. Synthesis of Enantiomerically Enriched Lactams



(9) Ring-expansion reactions of five-membered ring lactams to form six-membered ring lactams have been employed in the synthesis of the pseudodistomin alkaloids: (a) Langlois, N. *Org. Lett.* **2002**, *4*, 185–187. (b) Tanaka, K.; Maesoba, T.; Sawanishi, H. *Heterocycles* **2006**, *68*, 183–192.

(10) The stereochemistry was assigned by analogy to the X-ray crystal structure of the tosylate. Details are provided as Supporting Information.

(11) (a) Tanaka, K.; Nemoto, H.; Sawanishi, H. *Tetrahedron: Asymmetry* **2005**, *16*, 809–815. (b) Tanaka, K.; Nemoto, H.; Sawanishi, H. *Tetrahedron: Asymmetry* **2005**, *16*, 1989–1995.

(12) For an alternative strategy to achieve ring-expansion reactions of five-membered ring nitrogen heterocycles to six-membered ring compounds, see: Déchamps, I.; Gomez Pardo, D.; Cossy, J. *Tetrahedron* **2007**, *63*, 9082−9091 and references cited therein.

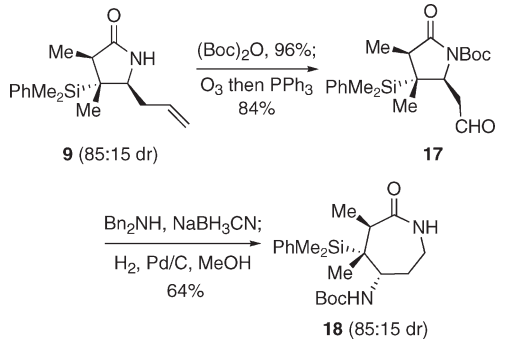
(13) Schwartz, J.; Carr, D. B.; Hansen, R. T.; Dayrit, F. M. *J. Org. Chem.* **1980**, *45*, 3053–3061.

(14) (a) Buynak, J. D.; Strickland, J. B.; Lamb, G. W.; Khasnis, D.; Modi, S.; Williams, D.; Zhang, H. *J. Org. Chem.* **1991**, *56*, 7076–7083. (b) Sakaguchi, K.; Higashino, M.; Ohfune, Y. *Tetrahedron* **2003**, *59*, 6647–6658.

provided as Supporting Information. An alternative substitution reaction, involving treatment of (−)-**15** with Me_3SiCN and a Lewis acid, resulted in elimination of the silyl group.

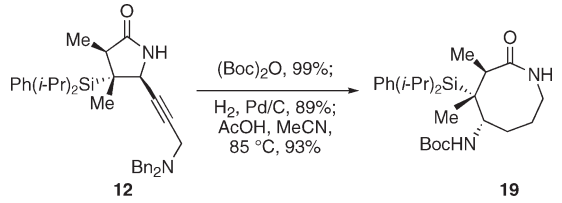
In addition to the ring expansion to provide six-membered ring lactams (Scheme 1), ring-expansion reactions of nucleophilic substitution products led to the synthesis of medium-ring lactams. A seven-membered ring lactam was prepared by functionalization of lactam **9** (Scheme 3). Acylation of lactam **9** and cleavage of the alkene moiety with ozone

SCHEME 3. Ring Expansion To Form a Seven-Membered-Ring Lactam



provided aldehyde **17**. Reductive amination with dibenzylamine and sodium cyanoborohydride provided a dibenzylamino-substituted γ-lactam, which was deprotected to provide a primary amine that underwent intramolecular transamidation in situ.[11] An eight-membered ring lactam was prepared by acylation of lactam **12** followed by hydrogenation, deprotection of the side chain, and translactamization (Scheme 4).

SCHEME 4. Ring Expansion To Form an Eight-Membered-Ring Lactam



The lactams resulting from the ring expansion proved to be synthetically useful. It was envisioned that the lactam could be reduced to an *N*,*O*-acetal, and subsequent nucleophilic substitutions would provide substituted piperidines. This idea was demonstrated with lactam (−)-**20**, which was derived from nitrile (−)-**16** (Scheme 2). Acylation followed by hydrogenation in acetic acid resulted in both reduction and in situ translactamization at room temperature to provide δ-lactam (−)-**20** (Scheme 5). Protection of the lactam nitrogen and subsequent reduction provided *N*,*O*-acetal (+)-**21** in 91% yield over two steps. Nucleophilic substitution with allyltrimethylsilane and functionalized allylic silane **23** in the presence of $BF_3 \cdot OEt_2$ provided piperidines **22** and (−)-**24** as single diastereomers (entries 1 and 2, Table 2).[15] Substitution with a vinyl cuprate afforded piperidine (−)-**25** as a single diastereomer in 60% yield (entry 3, Table 2). The

(15) The stereochemistry of the product was established by NOE experiments.

SCHEME 5. Synthesis of *N*,*O*-Acetal (+)-21

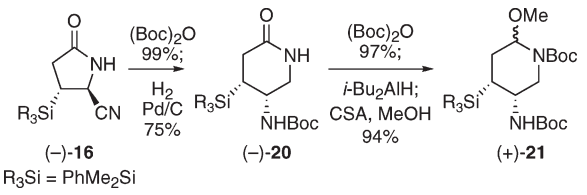
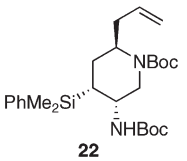
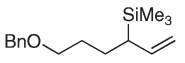
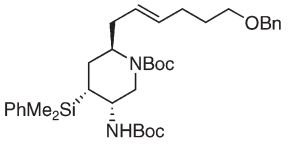
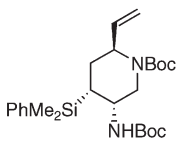


TABLE 2. Substitution Reactions of *N*,*O*-Acetal (+)-21

Entry	Nucleophile	Product	Yield[a] (d.r.)
1[b]	Me_3Si		73% (>95:5)
2			94% (>95:5)
3	$(\text{allyl})_2CuMgBr$		60% (>95:5)

[a]Yields are reported for purified materials. Diastereoselectivities were determined by analysis of the unpurified product mixtures by ^{1}H NMR spectroscopy. [b]Reaction performed with racemic **21**.

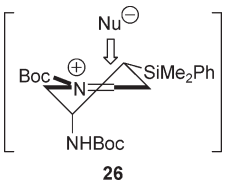


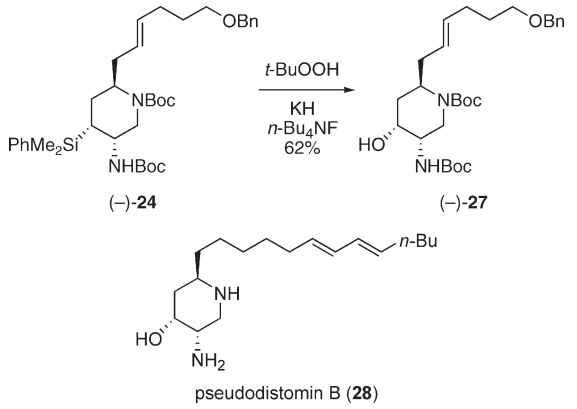
FIGURE 1. Nucleophilic attack on *N*-acyliminium ion.

stereochemical courses of these reactions are consistent with stereoelectronically controlled nucleophilic attack on an *N*-acyliminium ion that adopts the half-chair conformation **26**, placing the large silyl group in the equatorial position (Figure 1).[16]

The potential utility of the annulation/ring-expansion method to natural product synthesis was revealed after oxidation of the silyl group. Although the oxidation of $PhMe_2Si$ groups to hydroxyl groups generally require acidic

(16) This conformer also places the electronegative nitrogen atom in the electrostatically favored axial orientation, as would be expected based upon studies of the related oxocarbenium ions: (a) Miljković, M.; Yeagley, D.; Deslongchamps, P.; Dory, Y. L. *J. Org. Chem.* **1997**, *62*, 7597–7604. (b) Ayala, L.; Lucero, C. G.; Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 15521–15528.

SCHEME 6. Synthesis of the Hydroxypiperidine Core Structure of Pseudodistomin Alkaloids



conditions,[4b] it was anticipated that the *tert*-butoxycarbonyl groups of carbamate (−)-**24** might be removed by acids. Oxidation under basic conditions,[17] however, provided alcohol (−)-**27**, which contains the 2,4,5-trisubstituted piperidine core structure found in three of the six pseudodistomin alkaloids,[7] represented by pseudodistomin B (Scheme 6).[18]

In summary, the manipulation of γ-silyloxy-γ-lactams provides a route to medium-sized nitrogen heterocycles. Substitution with nucleophiles and subsequent translactamization of nitrogen-tethered γ-lactams provided six-, seven-, and eight-membered ring lactams. The synthetic utility of this method was demonstrated by the conversion of an enantiomerically enriched δ-lactam to the hydroxypiperidine core structure of the pseudodistomin alkaloids.

Experimental Section

General experimental details are provided as Supporting Information.

α-Siloxy Allylic Silane 1. To a solution of Ph-*i*-Pr_2SiCl[19] (8.43 g, 37.0 mmol) in THF (75 mL) was added lithium wire (1.30 g, 185 mmol). The suspension was stirred at 24 °C for 18 h. The resultant red solution was transferred to a dry flask and cooled to −78 °C as a solution of *trans*-2-methyl-2-butenal (3.00 mL, 31.0 mmol) in THF (50 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 2 h. The reaction mixture was diluted with saturated aqueous NH_4Cl (100 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with saturated aqueous NaCl (100 mL). The resultant organic phase was dried with $MgSO_4$ and filtered. The filtrate was concentrated in vacuo to afford a yellow oil. The oil was dissolved in DMF (10 mL), and TBDMSCl (9.35 g, 62.0 mmol) and imidazole (3.17 g, 46.5 mmol) were added. The reaction mixture was stirred at 24 °C for 18 h. The reaction mixture was diluted with saturated aqueous NH_4Cl (100 mL) and hexanes (50 mL). The layers were separated, and the aqueous layer was extracted with hexanes (3 × 75 mL). The combined organic layers were washed with saturated aqueous NaCl (75 mL). The resultant organic phase was dried with $MgSO_4$ and filtered. The filtrate was concentrated in vacuo to afford unpurified **1** as a colorless oil. Purification by flash chromatography (hexanes) provided **1** as a colorless oil (8.82 g, 73%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63 (m, 2H), 7.30 (m, 3H), 5.35 (q, J = 6.7, 1H), 4.36 (s, 1H), 1.52 (d, J = 6.8, 3H), 1.44−1.33 (m, 2H), 1.39 (s, 3H), 1.12 (m, 9H), 1.01 (d, J = 7.5, 3H), 0.88 (s, 9H), 0.02 (s, 3H), −0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.1, 135.9, 135.5, 128.8, 127.3, 119.4, 72.7, 26.2, 18.9, 18.7, 18.6, 18.5, 18.4, 14.6, 13.4, 11.7, 11.0, −3.8, −5.2; IR (thin film) 2929, 2865, 1465, 1254 cm^{-1}; HRMS (ESI) m/z calcd for $C_{23}H_{43}OSi_2$ $(M + H)^+$ 391.2852, found 391.2845. Anal. Calcd for $C_{23}H_{42}OSi_2$: C, 70.70; H, 10.83. Found: C, 70.98; H, 10.99.

γ-Lactam 2. To a cooled (0 °C) solution of α-siloxy allylic silane **1** (5.00 g, 12.8 mmol) in CH_2Cl_2 (65 mL) was added *N*-chlorosulfonyl isocyanate (2.22 mL, 25.6 mmol). The reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (10 mL), and the CH_2Cl_2 was removed in vacuo. The resultant aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated aqueous NaCl (15 mL). The resultant organic phase was dried over $MgSO_4$ and filtered. The filtrate was concentrated in vacuo to afford the *N*-chlorosulfonyl γ-lactam as a white solid. The *N*-chlorosulfonyl γ-lactam was dissolved in toluene (130 mL) and cooled to −78 °C as Red-Al (4.30 mL, 65% w/w solution in toluene, 14.1 mmol) was added dropwise. After 2 h, the reaction mixture was diluted with water (2.8 mL) and stirred at 24 °C for 1 h. The resultant slurry was filtered, and the solids were washed with toluene (40 mL). The filtrate was concentrated in vacuo to afford unpurified **2** as a white slurry. Purification by flash chromatography (20:80 EtOAc/hexanes) provided **2** as a white solid (4.65 g, 84%, >95:5 diastereomer ratio as determined by ^{1}H NMR spectroscopy): mp 135−137 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50 (m, 2H), 7.36 (m, 3H), 6.45 (br s, 1H), 5.26 (s, 1H), 2.65 (q, J = 7.5, 1H), 1.65−1.54 (m, 2H), 1.28 (d, J = 7.4, 6H), 1.18 (d, J = 7.5, 3H), 1.16 (d, J = 7.6, 3H), 1.13 (d, J = 7.6, 3H), 1.08 (s, 3H), 0.81 (s, 9H), −0.05 (s, 3H), −0.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.6, 135.9, 134.5, 129.2, 128.0, 82.9, 41.5, 34.8, 25.8, 20.7, 20.3, 19.8, 19.6, 18.0, 14.8, 13.7, 11.9, 11.7, −4.3, −4.9; IR (thin film) 1702 cm^{-1}; HRMS (ESI) m/z calcd for $C_{24}H_{43}NNaO_2Si_2$ $(M + Na)^+$ 456.2730, found 456.2717. Anal. Calcd for $C_{24}H_{43}NO_2Si_2$: C, 66.45; H, 9.99. Found: C, 66.18; H, 9.97.

Azide 3. To a cooled (−78 °C) solution of lactam **2** (2.00 g, 4.61 mmol) in THF (20 mL) was added vinylmagnesium bromide (23.0 mL, 1.0 M solution in THF, 23 mmol). The reaction mixture was warmed to 24 °C over 1.5 h. The reaction mixture was stirred at 24 °C for 1.5 h. The reaction mixture was cooled to 0 °C, and saturated aqueous NH_4Cl (20 mL) was added dropwise. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated aqueous NaCl (30 mL). The resultant organic phase was dried with Na_2SO_4 and filtered. The filtrate was concentrated in vacuo to afford the alkene as a yellow oil. Purification by flash chromatography (20:80 to 50:50 EtOAc/hexanes) provided the product as a white solid (1.19 g, 78%, >95:5 diastereomer ratio as determined by ^{1}H NMR spectroscopy): mp 114−116 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 (m, 2H), 7.36 (m, 3H), 5.64 (m, 1H), 5.41(br s, 1H), 5.14 (s, 1H), 5.10 (d, J = 7.4, 1H), 4.26 (d, J = 7.0, 1H), 2.71 (q, J = 7.4, 1H), 1.67−1.57 (m, 2H), 1.32 (d, J = 5.7, 3H), 1.30 (d, J = 5.7, 3H) 1.18 (d, J = 7.6, 3H), 1.16 (d, J = 7.6, 3H), 1.05 (s, 3H), 1.04 (d, J = 7.5, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.3, 136.4, 135.8, 134.4, 129.2, 127.9, 117.36, 60.7, 43.1, 33.3, 20.6, 19.8, 19.7, 14.9, 12.3, 11.8, 11.7; IR (thin film) 1696 cm^{-1}; HRMS (ESI) m/z calcd for $C_{20}H_{32}NOSi$ $(M + H)^+$ 330.2253, found 330.2249. Anal. Calcd for $C_{20}H_{31}NOSi$: C, 72.89; H, 9.48. Found: C, 73.08; H, 9.56.

To a solution of the alkene (1.08 g, 3.28 mmol) and DMAP (0.441 g, 3.61 mmol) in MeCN (50 mL) at 24 °C was added

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di-*tert*-butyl dicarbonate (1.13 mL, 4.92 mmol). The reaction mixture was stirred at 24 °C for 2 h. The reaction mixture was diluted with saturated aqueous NH_4Cl (50 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with saturated aqueous NaCl (50 mL). The resultant organic phase was dried with Na_2SO_4 and filtered. The filtrate was concentrated in vacuo to an orange oil. Purification by flash chromatography (10:90 EtOAc/hexanes) provided the Boc-protected lactam as a white solid (1.39 g, 99%, >95:5 diastereomer ratio as determined by ^{1}H NMR spectroscopy): mp 82−84 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 (m, 2H), 7.35 (m, 3H), 5.68 (ddd, J = 17.1, 10.3, 7.8, 1H), 5.17 (d, J = 10.3, 1H), 5.07 (d, J = 17.0, 1H), 4.76 (d, J = 7.8, 1H), 2.89 (q, J = 7.6, 1H), 1.65−1.45 (m, 2H), 1.44 (s, 9H), 1.30 (d, J = 7.5, 3H), 1.28 (d, J = 7.5, 3H), 1.19 (d, J = 7.6, 3H), 1.16 (d, J = 7.7, 3H), 1.14 (d, J = 7.7, 3H), 1.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.8, 149.4, 136.5, 135.5, 133.7, 129.4, 128.0, 117.5, 82.6, 65.2, 44.5, 28.0, 27.8, 20.4, 20.3, 19.6, 15.6, 15.0, 11.5, 11.4; IR (thin film) 1783, 1742, 1719 cm^{-1}; HRMS (ESI) m/z calcd for $C_{25}H_{39}NNaO_3Si$ $(M + Na)^+$ 452.2597, found 452.2594. Anal. Calcd for $C_{25}H_{39}NO_3Si$: C, 69.88; H, 9.15. Found: C, 69.85; H, 9.20.

To a cooled (−78 °C) solution of the Boc-protected lactam (0.050 g, 0.116 mmol) in MeOH (10 mL) was bubbled ozone. When the solution became bright blue, oxygen was bubbled through the solution until it became clear. Sodium borohydride (0.013 g, 0.349 mmol) was added, and the reaction mixture was warmed to 0 °C. The reaction mixture was stirred at 0 °C for 30 min. The reaction mixture was diluted with H_2O (15 mL) and EtOAc (15 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated aqueous NaCl (15 mL). The resultant organic phase was dried with $MgSO_4$ and filtered. The filtrate was concentrated in vacuo to a viscous oil. Purification by flash chromatography (10:90 to 30:70 EtOAc/hexanes) provided the alcohol as a white foam (0.048 g, 96%, >95:5 diastereomer ratio as determined by ^{1}H NMR spectroscopy): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.52 (m, 2H), 7.35 (m, 3H), 4.30 (dd, J = 4.4, 2.7, 1H), 3.92 (ddd, J = 12.3, 7.6, 2.7, 1H), 3.61 (dt, J = 12.3, 4.4, 1H), 2.86 (dd, J = 7.6, 4.5, 1H), 2.82 (q, J = 7.4, 1H), 1.69−1.58 (m, 2H), 1.48 (s, 9H), 1.32 (d, J = 7.5, 3H), 1.30 (d, J = 7.5, 3H), 1.20 (d, J = 7.5, 3H), 1.16 (d, J = 7.4, 3H), 1.15 (s, 3H), 1.14 (d, J = 7.5, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.5, 151.3, 135.4, 133.7, 129.3, 127.9, 83.4, 64.3, 62.3, 44.4, 28.0, 27.4, 20.5, 20.3, 19.6, 19.5, 14.1, 13.2, 11.7, 11.4; IR (thin film) 3367, 1775, 1717 cm^{-1}; HRMS (ESI) m/z calcd for $C_{24}H_{39}NNaO_4Si$ $(M + Na)^+$ 456.2546, found 456.2556. Anal. Calcd for $C_{24}H_{39}NO_4Si$: C, 66.47; H, 9.06. Found: C, 66.17; H, 9.24.

To a solution of the alcohol (1.91 g, 4.40 mmol), toluenesulfonyl chloride (1.00 g, 5.29 mmol), and DMAP (0.591 g, 4.84 mmol) in CH_2Cl_2 (25 mL) at 24 °C was added Et_3N (1.23 mL, 8.80 mmol). The reaction mixture was stirred at 24 °C for 12 h. The reaction mixture was concentrated in vacuo and diluted with saturated aqueous NH_4Cl (20 mL) and EtOAc (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with saturated aqueous NaCl (30 mL). The resultant organic phase was dried with $MgSO_4$ and filtered. The filtrate was concentrated in vacuo to a yellow oil. Purification by flash chromatography (15:85 to 40:60 EtOAc/hexanes) provided the tosylate as a white solid (2.43 g, 94%, >95:5 diastereomer ratio as determined by ^{1}H NMR spectroscopy): mp 108−110 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (m, 2H), 7.47 (m, 2H), 7.33 (m, 5H), 4.42 (dd, J = 4.2, 1.7, 1H), 4.27 (dd, J = 10.4, 4.2, 1H), 4.00 (dd, J = 10.4, 1.7, 1H), 2.92 (q, J = 7.6, 1H), 2.42 (s, 3H), 1.62−1.47 (m, 2H), 1.35 (s, 9H), 1.25 (d, J = 7.6, 3H), 1.23 (d, J = 7.6, 3H), 1.20 (s, 3H), 1.18 (d, J = 7.5, 3H), 1.16 (d, J = 7.6, 3H), 1.10 (d, J = 7.5, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.7, 149.1, 145.2, 135.3, 133.2, 132.4, 130.1, 129.6, 128.1, 83.2, 66.7, 60.6, 43.8, 27.9, 26.0, 21.8, 20.4, 20.2, 19.6, 19.5, 14.4, 13.8, 11.4, 11.2; IR (thin film) 1785, 1748 cm^{-1}; HRMS (ESI) m/z calcd for $C_{31}H_{45}NNaO_6SSi$ $(M + Na)^+$ 610.2635, found 610.2628. Anal. Calcd for $C_{31}H_{45}NO_6SSi$: C, 63.34; H, 7.72. Found: C, 63.24; H, 7.58.

A suspension of the tosylate (1.80 g, 3.06 mmol) and sodium azide (1.00 g, 15.3 mmol) in DMF (30 mL) was heated to 50 °C for 20 h. The reaction mixture was diluted with saturated aqueous NH_4Cl (30 mL) and EtOAc (30 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with saturated aqueous NaCl (30 mL). The resultant organic phase was dried with $MgSO_4$ and filtered. The filtrate was concentrated in vacuo to afford unpurified **3** as a yellow oil. Purification by flash chromatography (20:80 to 30:70 EtOAc/hexanes) provided **3** as a viscous oil (1.38 g, 99%, >95:5 diastereomer ratio as determined by ^{1}H NMR spectroscopy): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50 (m, 2H), 7.35 (m, 3H), 4.42 (dd, J = 5.6, 2.0, 1H), 3.73 (dd, J = 12.9, 5.6, 1H), 3.37 (dd, J = 12.9, 2.0, 1H), 2.93 (q, J = 7.6, 1H), 1.64−1.51 (m, 2H), 1.48 (s, 9H), 1.28 (d, J = 7.6, 3H), 1.26 (d, J = 7.5, 3H), 1.25 (d, J = 7.6, 3H), 1.19 (d, J = 7.5, 3H), 1.18 (s, 3H), 1.13 (d, J = 7.6, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.0, 149.8, 135.4, 133.4, 129.7, 128.2, 83.5, 61.2, 50.9, 44.0, 28.2, 26.1, 20.5, 20.3, 19.7, 19.6, 14.6, 14.4, 11.5, 11.3; IR (thin film) 2107, 1785, 1748, 1706 cm^{-1}; HRMS (ESI) m/z calcd for $C_{24}H_{38}N_4NaO_3Si$ $(M + Na)^+$ 481.2611, found 481.2597. Anal. Calcd for $C_{24}H_{38}N_4O_3Si$: C, 62.85; H, 8.35. Found: C, 63.01; H, 8.36.

***δ*-Lactam 4.** A suspension of azide **3** (0.100 g, 0.218 mmol) and Pd/C (0.100 g) in MeOH (20 mL) at 24 °C was stirred under an atmosphere of hydrogen for 20 h. The reaction mixture was filtered through Celite and washed with MeOH (10 mL). The filtrate was heated to 65 °C for 18 h. The reaction mixture was cooled to 24 °C and concentrated in vacuo to afford unpurified **4** as a clear oil. Purification by flash chromatography (20:80 to 40:60 EtOAc/hexanes) provided **4** as a white solid (0.060 g, 64%, >95:5 diastereomer ratio as determined by ^{1}H NMR spectroscopy): mp 66−70 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54 (m, 2H), 7.37 (m, 3H), 6.40 (br s, 1H), 4.50 (br s, 1H), 3.76 (dd, J = 9.1, 2.1, 1H), 2.94 (m, 1H), 2.82−2.72 (m, 1H), 2.75 (q, J = 7.3, 1H), 1.64 (m, 2H), 1.42 (s, 9H), 1.33 (d, J = 7.4, 3H), 1.32 (d, J = 7.4, 3H), 1.20 (d, J = 7.5, 3H), 1.17 (d, J = 7.5, 3H), 1.06 (d, J = 7.3, 3H), 1.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 179.6, 156.4, 135.9, 134.6, 129.3, 128.0, 79.8, 59.7, 43.3, 43.1, 32.8, 28.5, 20.6, 19.8, 19.7, 13.2, 11.8, 11.6, 11.5; IR (thin film) 3305, 1771, 1696 cm^{-1}; HRMS (ESI) m/z calcd for $C_{24}H_{41}N_2O_3Si$ $(M + H)^+$ 433.2866, found 433.2875. Anal. Calcd for $C_{24}H_{40}N_2O_3Si$: C, 66.62; H, 9.32. Found: C, 66.83; H, 9.45.

Allylic Silane (−)-14. To a cooled (−78 °C) solution of (+)-diisopinocampheylchloroborane (11.33 g, 35.31 mmol) in THF (30 mL) was added a solution of dimethylphenylpropenoylsilane (5.60 g, 29.4 mmol) in THF (30 mL).[14a] The reaction mixture was warmed to 24 °C and stirred for 60 h. Acetaldehyde (3.30 mL, 58.8 mmol) was added, and the reaction was stirred at 24 °C for 2.5 h. The reaction mixture was concentrated in vacuo, and the residual pinene was removed under reduced pressure (~0.1 Torr). The resulting slurry was dissolved in Et_2O (200 mL), and diethanolamine (11.3 mL, 118 mmol) was added. The reaction mixture was stirred at 24 °C for 20 h. The resulting suspension was filtered through Celite, and the solids were washed with Et_2O. The filtrate was concentrated in vacuo to form a clear oil. The enantiomerically enriched α-hydroxy allylic silane was isolated in 93% ee by chiral HPLC (Chiralcel OD-H column, 99.5:0.5 hexanes/IPA, 1 mL/min, 220/254 nm), $[\alpha]^{23}_D$ −10.5 (c 0.50, $CHCl_3$). Spectral data for this allylic silane were identical to those reported in literature.[14a] The α-hydroxy

allylic silane was dissolved in DMF (60 mL) and stirred at 24 °C as TBDMSCl (8.87 g, 58.8 mmol) and imidazole (3.00 g, 44.1 mmol) were added. The reaction mixture was stirred at 24 °C for 18 h. The reaction mixture was diluted with saturated aqueous NH_4Cl (100 mL) and hexanes (50 mL). The layers were separated, and aqueous layer was extracted with hexanes (3 × 30 mL). The combined organic layers were washed with saturated aqueous NaCl (50 mL). The resultant organic phase was dried with $MgSO_4$ and filtered. The filtrate was concentrated in vacuo to afford unpurified (−)-**14** as a colorless oil. Purification by flash chromatography (hexanes) provided (−)-**14** as a colorless oil (8.34 g, 93%). Spectral data were identical to those reported in the literature:[6b] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.53 (m, 2H), 7.34 (m, 3H), 5.83 (ddd, J = 17.1, 10.6, 5.3, 1H), 5.02 (d, J = 17.0, 1H), 4.89 (J = 10.6, 1H), 4.12 (d, J = 5.2, 1H), 0.87 (s, 9H), 0.31 (s, 3H), 0.27 (s, 3H), −0.06 (s, 3H), −0.15 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.4, 137.2, 134.5, 129.3, 127.7, 110.4, 68.9, 26.0, 18.4, −4.4, −5.2, −5.7, −5.8; IR (thin film) 2958, 2858, 1252 cm^{-1}; $[\alpha]^{23}_D$ −7.0 (*c* 0.35, $CHCl_3$). Anal. Calcd for $C_{17}H_{30}OSi_2$: C, 66.60; H, 9.86. Found: C, 66.70; H, 10.01.

Nitrile (−)-16. This compound was most conveniently prepared without purification of the intermediate silyloxylactam (−)-**15**. To a cooled (0 °C) solution of (−)-**14** (1.36 g, 4.44 mmol) in CH_2Cl_2 (25 mL) was added chlorosulfonyl isocyanate (0.77 mL, 8.8 mmol). The reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (15 mL), and the CH_2Cl_2 was removed in vacuo. Saturated aqueous NH_4Cl (10 mL) was added, and the resultant aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with saturated aqueous NaCl (20 mL). The resultant organic phase was dried over $MgSO_4$ and filtered. The filtrate was concentrated in vacuo to afford the *N*-chlorosulfonyl γ-lactam as a clear oil. The *N*-chlorosulfonyl γ-lactam was dissolved in toluene (50 mL) and cooled to −78 °C as Red-Al (1.50 mL, 65% w/w solution in toluene, 4.88 mmol) was added dropwise. After 2 h, the reaction mixture was diluted with water (0.98 mL) and stirred at 24 °C for 2 h. The resultant suspension was filtered, and the solids were washed with toluene (20 mL). The filtrate was cooled to 0 °C as diethylaluminum cyanide (13.3 mL, 1.0 M solution in toluene, 13 mmol) was added. The reaction mixture was heated to 50 °C for 24 h. The reaction mixture was cooled to 0 °C and diluted with 1 N aqueous HCl (40 mL) and EtOAc (20 mL). The resulting heterogeneous mixture was warmed to 24 °C, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with saturated aqueous NaCl (60 mL). The resultant organic phase was dried with $MgSO_4$ and filtered. The filtrate was concentrated in vacuo to afford (−)-**16** as an orange oil. Purification by flash chromatography (50:50 to 75:25 EtOAc/hexanes) provided (−)-**16** as a white solid (0.460 g, 43%, > 95:5 diastereomer ratio as determined by ^{1}H NMR spectroscopy): mp 121−123 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50 (m, 2H), 7.43 (m, 3H), 6.62 (br s, 1H), 4.20 (d, J = 6.9, 1H), 2.58 (m, 1H), 2.27−2.13 (m, 2H), 0.44 (s, 3H), 0.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.4, 133.9, 130.5, 128.6, 118.9, 45.0, 31.0, 27.3, −4.9, −5.0; IR (thin film) 3213, 1702 cm^{-1}; HRMS (ESI) m/z calcd for $C_{13}H_{16}N_2NaOSi$ $(M + Na)^+$ 267.0930, found 267.0933; $[\alpha]^{23}_D$ −2.79 (*c* 0.55, $CHCl_3$). Anal. Calcd for $C_{13}H_{16}N_2OSi$: C, 63.90; H, 6.60. Found: C, 63.70; H, 6.57.

The intermediate silyloxylactam (−)-**15** could be purified by flash chromatography (20:80 to 45:55 EtOAc/hexanes) to give (−)-**15** as a clear oil (0.855 g, 60%, > 95:5 diastereomer ratio as determined by ^{1}H NMR spectroscopy). Spectral data were identical to those reported for the racemate:[6b] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49 (m, 2H), 7.38 (m, 3H), 6.03 (br s, 1H), 5.15 (s, 1H), 2.74 (dd, J = 17.5, 10.5, 1H), 2.12 (dd, J = 17.5, 3.9, 1H), 1.74 (dd, J = 10.4, 3.9, 1H), 0.81 (s, 9H), 0.33 (s, 3H), 0.32 (s, 3H), −0.05 (s, 3H), −0.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.5, 136.2, 133.9, 129.8, 128.2, 81.7, 31.6, 30.4, 25.7, 17.8, −4.4, −4.6, −4.8, −5.2; IR (thin film) 1698 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{31}NNaO_2Si_2$ $(M + Na)^+$ 372.1791, found 372.1788. $[\alpha]^{23}_D$ −1.33 (*c* 0.60, $CHCl_3$).

Aldehyde 17. To a solution of lactam **9** (0.700 g, 2.44 mmol) and DMAP (0.447 g, 3.66 mmol) in MeCN (24 mL) at 24 °C was added di-*tert*-butyl dicarbonate (0.62 mL, 2.9 mmol). The reaction mixture was stirred at 24 °C for 12 h. The reaction mixture was diluted with saturated aqueous NH_4Cl (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with saturated aqueous NaCl (30 mL). The resultant organic phase was dried with Na_2SO_4 and filtered. The filtrate was concentrated in vacuo to an orange oil. Purification by flash chromatography (20:80 to 40:60 EtOAc/hexanes) provided the Boc-protected lactam as a clear oil (0.907 g, 96%, 85:15 diastereomer ratio as determined by ^{1}H NMR spectroscopy): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.50 (m, 2H), 7.37 (m, 3H), 5.70 (m, 1H), 5.00 (m, 2H), 4.23 (dd, J = 6.7, 5.5, 1H), 2.60 (q, J = 7.6, 1H), 2.50 (m, 1H), 2.28 (m, 1H), 1.50 (s, 9H), 1.20 (d, J = 7.7, 3H), 1.04 (s, 3H), 0.32 (s, 3H), 0.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.4, 150.0, 135.2, 135.1, 134.5, 129.8, 128.1, 117.4, 82.8, 60.9, 43.9, 37.4, 28.1, 26.4, 14.6, 13.2, −5.9, −6.1; IR (thin film) 1783, 1744, 1713, 1301, 1254 cm^{-1}; HRMS (ESI) m/z calcd for $C_{22}H_{33}NNaO_3Si$ $(M + Na)^+$ 410.2127, found 410.2127.

To a cooled (−78 °C) solution of the Boc-protected lactam (0.426 g, 1.10 mmol) in 1:1 MeOH/CH_2Cl_2 (30 mL) was bubbled ozone. When the solution became bright blue, oxygen was bubbled until the solution became clear. Triphenylphosphine (1.15 g, 4.38 mmol) was added, and the reaction mixture was warmed to 24 °C. The reaction mixture was stirred at 24 °C for 3 h. The reaction mixture was diluted with H_2O (30 mL) and EtOAc (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with saturated aqueous NaCl (25 mL). The resultant organic phase was dried with $MgSO_4$ and filtered. The filtrate was concentrated in vacuo to afford unpurified **17** as a viscous oil. Purification by flash chromatography (30:70 EtOAc/hexanes) provided **17** as a white foam (0.358 g, 84%, 85:15 diastereomer ratio as determined by ^{1}H NMR spectroscopy): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.63 (d, J = 2.3, 1H), 7.53 (m, 2H), 7.39 (m, 3H), 4.59 (dd, J = 6.6, 3.8 1H), 2.53 (d, J = 7.3, 1H), 2.48 (ddd, J = 17.2, 6.5, 2.5, 1H), 2.33 (dd, J = 17.2, 3.8, 1H), 1.47 (s, 9H), 1.12 (d, J = 7.3, 3H), 0.95 (s, 3H), 0.45 (s, 3H), 0.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.9, 176.2, 151.1, 135.1, 134.4, 130.1, 128.4, 83.8, 56.8, 45.8, 44.5, 28.1, 28.0, 14.3, 12.2, −4.9, −5.3; HRMS (ESI) m/z calcd for $C_{21}H_{31}NNaO_4Si$ $(M + Na)^+$ 412.1920, found 412.1925.

ε-Lactam 18. To a solution of **17** (0.220 g, 0.565 mmol) in MeOH (4 mL) was added dibenzylamine (0.22 mL, 1.13 mmol). The solution was stirred at 24 °C for 15 min. A solution of sodium cyanoborohydride (0.071 g, 1.13 mmol) in MeOH (2 mL) was added. The reaction mixture was stirred at 24 °C for 18 h. The reaction mixture was diluted with saturated aqueous NH_4Cl (15 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated NaCl (20 mL). The resultant organic phase was dried with Na_2SO_4 and filtered. The filtrate was concentrated in vacuo to afford a yellow oil. The oil was dissolved in MeOH (10 mL), and 10% Pd/C (0.200 g) was added. The reaction mixture was stirred under an atmosphere of hydrogen for 24 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated in vacuo to afford unpurified **18** as a colorless oil. Purification

by flash chromatography (EtOAc) provided **18** as a viscous oil (0.146 g, 64%, 85:15 diastereomer ratio as determined by ^{1}H NMR spectroscopy): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50 (m, 2H), 7.38 (m, 3H), 6.18 (br s, 1H), 4.49 (br s, 1H), 3.58 (m, 1H), 3.17−2.94 (m, 2H), 2.50 (q, J = 7.2, 1H), 1.46 (s, 9H), 1.30 (m, 2H), 1.00 (d, J = 7.2, 3H), 0.91 (s, 3H), 0.38 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 179.9, 156.4, 136.4, 134.5, 129.8, 128.2, 79.8, 60.3, 55.2, 42.9, 32.4, 28.5, 18.6, 11.4, 11.1, −4.6, −4.8; HRMS (ESI) m/z calcd for $C_{21}H_{34}N_2NaO_3Si$ $(M + Na)^+$ 413.2236, found 413.2228.

Eight-membered Ring Lactam 19. To a solution of **12** (0.800 g, 1.49 mmol) and DMAP (0.200 g, 1.64 mmol) in MeCN (15 mL) at 24 °C was added di-*tert*-butyl dicarbonate (0.510 mL, 2.24 mmol). The reaction mixture was stirred at 24 °C for 1 h. The reaction mixture was diluted with saturated aqueous NH_4Cl (15 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated NaCl (20 mL). The resultant organic phase was dried with Na_2SO_4 and filtered. The filtrate was concentrated in vacuo to a yellow oil. Purification by flash chromatography (hexanes to 20:80 EtOAc/hexanes) provided the Boc-protected lactam as a white foam (0.935 g, 99%, >95:5 diastereomer ratio as determined by ^{1}H NMR spectroscopy): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 (m, 2H), 7.38−7.21 (m, 13H), 5.08 (s, 1H), 3.63 (s, 4H), 3.24 (d, J = 1.6, 2H), 2.78 (q, J = 7.5, 1H), 1.68−1.58 (m, 2H), 1.36 (s, 9H), 1.33 (d, J = 6.2, 6H), 1.32 (d, J = 7.3, 3H), 1.24 (d, J = 6.7, 3H), 1.21 (d, J = 7.4, 3H), 1.15 (d, J = 7.5, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.7, 149.5, 139.0, 135.6, 133.5, 129.6, 129.2, 128.5, 128.2, 127.3 83.2, 82.2, 82.0, 57.9, 55.3, 45.0, 41.5, 28.3, 28.2, 20.6, 20.4, 19.7, 19.6, 16.7, 13.4, 11.8, 11.6; IR (thin film) 1783, 1746, 1719 cm^{-1}; HRMS (ESI) m/z calcd for $C_{40}H_{53}N_2O_3Si$ $(M + H)^+$ 637.3826, found 637.3833. Anal. Calcd for $C_{40}H_{52}N_2O_3Si$: C, 75.43; H, 8.23. Found: C, 75.17; H, 8.39.

A suspension of the Boc-protected lactam (0.840 g, 1.32 mmol) and 10% Pd/C (0.842 g) in MeOH (20 mL) at 24 °C was stirred under an atmosphere of hydrogen for 18 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated in vacuo to a colorless oil. Purification by flash chromatography (9:1:0.1 CH_2Cl_2/MeOH/NH_4OH) provided the primary amine as a viscous oil (0.543 g, 89%, >95:5 diastereomer ratio as determined by ^{1}H NMR spectroscopy): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.45 (m, 2H), 7.28 (m, 3H), 4.28 (dd, J = 7.1, 4.9, 1H), 2.87 (q, J = 7.7, 1H), 2.52 (t, J = 7.0, 2H), 1.72−1.61 (m, 1H), 1.61−1.52 (m, 1H), 1.44 (s, 9H), 1.45−1.35 (m, 2H), 1.32−1.23 (m, 2H), 1.23 (d, J = 7.5, 3H), 1.19 (d, J = 7.5, 3H), 1.18 (d, J = 7.8, 3H), 1.11 (d, J = 7.6, 3H), 1.08 (s, 3H), 1.07 (d, J = 7.6, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.7, 150.0, 135.6, 133.9, 129.3, 127.9, 82.7, 61.7, 44.6, 42.4, 31.9, 30.9, 28.2, 27.6, 20.6, 20.4, 19.6, 19.5, 15.1, 14.6, 11.5, 11.4; IR (thin film) 1781, 1740, 1713 cm^{-1}; HRMS (ESI) m/z calcd for $C_{26}H_{45}N_2O_3Si$ $(M + H)^+$ 461.3199, found 461.3208. Anal. Calcd for $C_{26}H_{44}N_2O_3Si$: C, 67.78; H, 9.63. Found: C, 67.38; H, 9,85.

A solution of the primary amine (0.100 g, 0.217 mmol) and acetic acid (0.060 mL, 1.1 mmol) in MeCN (20 mL) was heated at reflux for 12 h. The reaction mixture was concentrated in vacuo to afford unpurified **19** as a yellow oil. Purification by flash chromatography (EtOAc) provided **19** as a white solid (0.930 g, 93%, >95:5 diastereomer ratio as determined by ^{1}H NMR spectroscopy): mp 115−117 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.51 (m, 2H), 7.37 (m, 3H), 6.26 (br s, 1H), 4.54 (br s, 1H), 3.68 (dd, J = 6.7, 5.8, 1H), 3.06−2.90 (m, 2H), 2.75 (q, J = 7.3, 1H), 1.66−1.54 (m, 2H), 1.49−1.40 (m, 1H), 1.44 (s, 9H), 1.36−1.27 (m, 1H), 1.31 (d, J = 7.3, 6H), 1.22−1.11 (m, 2H), 1.18 (d, J = 8.0, 3H), 1.16 (d, J = 8.0, 3H), 1.04 (d, J = 7.3, 3H), 1.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 180.3, 156.2, 135.8, 134.8, 129.2, 127.9, 79.2, 58.5, 43.2, 40.3, 33.4, 29.2, 28.6, 28.2, 20.6, 20.5, 19.8, 19.7, 13.5, 11.8, 11.7, 11.6; IR (thin film) 3228, 1686 cm^{-1}; HRMS (ESI) m/z calcd for $C_{26}H_{45}N_2O_3Si$ $(M + H)^+$ 461.3199, found 461.3196. Anal. Calcd for $C_{26}H_{44}N_2O_3Si$: C, 67.78; H, 9.63. Found: C, 67.73; H, 9.72.

***δ*-Lactam (−)-20.** To a solution of (−)-**16** (0.110 g, 0.450 mmol) and DMAP (0.083 g, 0.68 mmol) in MeCN (10 mL) was added di-*tert*-butyl dicarbonate (0.21 mL, 0.90 mmol). The reaction mixture was stirred at 24 °C for 3 h. The reaction mixture was diluted with saturated aqueous NH_4Cl (10 mL) and EtOAc (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with saturated aqueous NaCl (20 mL). The resultant organic phase was dried with Na_2SO_4 and filtered. The filtrate was concentrated in vacuo to a yellow oil. Purification by flash chromatography (20:80 to 40:60 EtOAc/hexanes) provided the Boc-protected lactam as a white solid (0.153 g, 99%, >95:5 diastereomer ratio as determined by ^{1}H NMR spectroscopy): mp 107−110 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.50−7.40 (m, 5H), 4.49 (d, J = 6.2, 1H), 2.80 (dd, J = 17.8, 10.0, 1H), 2.40 (dd, J = 17.8, 7.5, 1H), 1.99 (ddd, J = 10.0, 7.5, 6.2, 1H), 1.53 (s, 9H), 0.46 (s, 3H), 0.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.5, 148.5, 133.9, 133.5, 130.7, 128.7, 118.2, 85.3, 48.9, 33.4, 28.1, 23.4, −4.9, −5.0; IR (thin film) 1794, 1762, 1721 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{24}N_2NaO_3Si$ $(M + Na)^+$ 367.1451, found 367.1448; $[\alpha]^{23}_D$ −1.75 (c 0.55, $CHCl_3$). Anal. Calcd for $C_{18}H_{24}N_2O_3Si$: C, 62.76; H, 7.02. Found: C, 62.81; H, 7.07.

A suspension of the Boc-protected lactam (0.020 g, 0.058 mmol) and 10% Pd/C (0.080 g) in acetic acid (100 mL) at 24 °C was stirred under an atmosphere of H_2 for 18 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated in vacuo to afford unpurified (−)-**20** as a colorless oil. Purification by flash chromatography (EtOAc) provided (−)-**20** as a white foam (0.015 g, 75%, >95:5 diastereomer ratio as determined by ^{1}H NMR spectroscopy): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49 (m, 2H), 7.37 (m, 3H), 5.87 (br s, 1H), 4.65 (br s, 1H), 3.65 (m, 1H), 3.08 (m, 1H), 2.97 (m, 1H), 2.43 (dd, J = 17.2, 10.5, 1H), 2.21 (dd, J = 17.2, 8.9, 1H), 1.52 (m, 1H), 1.43 (s, 9H), 0.36 (s, 3H), 0.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.3, 156.3, 136.2, 134.0, 129.8, 128.3, 79.7, 57.0, 46.2, 32.5, 28.5, 24.0, −4.7; IR (thin film) 3299, 1686 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{28}N_2NaO_3Si$ $(M + Na)^+$ 371.1767, found 371.1766; $[\alpha]^{23}_D$ −21.7 (c 0.75, $CHCl_3$).

***N,O*-Acetal (+)-21.** To a solution of (−)-**20** (0.255 g, 0.732 mmol) and DMAP (0.098 g, 0.81 mmol) in CH_2Cl_2 (7 mL) at 24 °C was added di-*tert*-butyl dicarbonate (0.19 mL, 0.81 mmol). The reaction mixture was stirred at 24 °C for 2 h. The reaction mixture was diluted with saturated aqueous NH_4Cl (3 mL) and the CH_2Cl_2 removed in vacuo. The resulting slurry was diluted with NH_4Cl (10 mL) and EtOAc (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with saturated aqueous NaCl (20 mL). The resultant organic phase was dried with Na_2SO_4 and filtered. The filtrate was concentrated in vacuo to a yellow oil. Purification by flash chromatography (30:70 to 50:50 EtOAc/hexanes) provided the Boc-protected lactam as a white foam (0.318 g, 97%, >95:5 diastereomer ratio as determined by ^{1}H NMR spectroscopy): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.47 (m, 2H), 7.37 (m, 3H), 4.70 (br s, 1H), 4.09 (br s, 1H), 3.35 (m, 2H), 2.80 (dd, J = 18.3, 11.1, 1H), 2.35 (dd, J = 18.3, 3.7, 1H), 1.61 (m, 1H), 1.49 (s, 9H), 1.43 (s, 9H), 0.32 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.2, 156.3, 150.1, 135.4, 133.8, 129.9, 128.3, 83.4, 79.8, 59.5, 44.2, 33.6, 28.5, 28.1, 19.6, −5.2; IR (thin film) 3367, 1779, 1755, 1715 cm^{-1}; HRMS (ESI) m/z calcd for $C_{23}H_{36}N_2NaO_5Si$ $(M + Na)^+$ 471.2291, found 471.2291; $[\alpha]^{23}_D$ +9.05 (c 1.00, $CHCl_3$). Anal. Calcd for $C_{23}H_{36}N_2O_5Si$: C, 61.58; H, 8.09. Found: C, 61.44; H, 7.88.

To a cooled (−42 °C) solution of the Boc-protected lactam (1.00 g, 2.23 mmol) in THF (22 mL) was added DIBAL-H (14.9 mL, 1.5 M in toluene, 22 mmol). The reaction mixture was stirred at −42 °C for 3 h. The reaction mixture was diluted with EtOAc (20 mL) and H_2O (35 mL) and warmed to 24 °C. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with saturated aqueous NaCl (50 mL). The resultant organic phase was dried with $MgSO_4$ and filtered. The filtrate was concentrated in vacuo to afford a colorless oil. The oil was dissolved in MeOH (9 mL), and camphorsulfonic acid (0.104 g, 0.446 mmol) was added. The reaction was stirred at 24 °C for 2 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (15 mL) and EtOAc (15 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with saturated aqueous NaCl (30 mL). The resultant organic phase was dried with Na_2SO_4 and filtered. The filtrate was concentrated in vacuo to afford (+)-**21** as a yellow oil. Purification by flash chromatography (10:90 to 30:70 EtOAc/hexanes) provided (+)-**21** as a colorless oil (0.974 g, 94%, >95:5 diastereomer ratio as determined by ^{1}H NMR spectroscopy): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46 (m, 2H), 7.34 (m, 3H), 5.20 (br s, 1H), 5.13 (m, 1H), 3.92 (m, 1H), 3.40 (m, 1H), 3.31 (s, 3H), 3.03 (m, 1H), 1.86 (dd, J = 11.8, 6.4, 1H), 1.65 (m, 1H), 1.60 (m, 1H), 1.46 (s, 9H), 1.43 (s, 9H), 0.34 (s, 3H), 0.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.4, 154.6, 136.8, 134.0, 129.6, 128.1, 89.6, 80.8, 78.7, 59.5, 55.2, 44.7, 34.5, 28.6, 28.5, 25.3, −4.1, −4.5; IR (thin film) 3375, 1698 cm^{-1}; HRMS (ESI) m/z calcd for $C_{24}H_{40}N_2NaO_5Si$ (M + Na)$^+$ 487.2604, found 487.2599; $[\alpha]^{23}_D$ +1.7 (*c* 0.28, $CHCl_3$).

Piperidine 22. To a cooled (−78 °C) solution of allyltrimethylsilane (0.06 mL, 0.3 mmol) and **21** (0.040 g, 0.086 mmol, as the racemate) in CH_2Cl_2 (3 mL) was added $BF_3\cdot OEt_2$ (0.02 mL, 0.2 mmol). The reaction was warmed to −42 °C and stirred for 3 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (5 mL), and the CH_2Cl_2 was removed in vacuo. The resultant aqueous layer was diluted with saturated aqueous NH_4Cl (10 mL) and EtOAc (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with saturated aqueous NaCl (35 mL). The resultant organic phase was dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuo to afford unpurified **22** as a yellow oil. Purification by flash chromatography (10:90 to 20:80 EtOAc/hexanes) provided **22** as a colorless oil (0.030 g, 73%, >95:5 diastereomer ratio as determined by ^{1}H NMR spectroscopy): ^{1}H NMR (DMSO, 500 MHz) δ 7.48 (m, 2H), 7.33 (m, 3H), 5.88 (br s, 1H), 5.72 (ddt, J = 17.2, 10.3, 7.0, 1H), 4.99 (ddd, 17.1, 3.7, 1.5, 1H), 4.97 (ddd, J = 9.1, 2.2, 1.1, 1H), 3.83 (ddd, J = 6.1, 5.6, 5.5, 1H), 3.67 (m, 1H), 3.12 (dd, J = 13.4, 6.1, 1H), 3.02 (dd, J = 13.4, 5.6, 1H), 2.41 (m, 1H), 2.12 (m, 1H), 1.84−1.73 (m, 2H), 1.58 (m, 1H), 1.40 (s, 9H), 1.38 (m, 9H), 0.26 (s, 3H), 0.25 (s, 3H); ^{13}C NMR (DMSO, 125 MHz) δ 155.5, 153.4, 137.0, 135.4, 133.5, 128.9, 127.6, 116.4, 78.2, 77.3, 59.6, 57.4, 43.2, 40.0, 30.5, 28.1, 28.0, 24.3, −4.2, −5.0; IR (thin film) 3354, 1686 cm^{-1}; HRMS (ESI) m/z calcd for $C_{26}H_{42}N_2NaO_4Si$ (M + Na)$^+$ 497.2812, found 497.2814.

Piperidine (−)-24. To a cooled (−78 °C) solution of allylic silane[20] **23** (1.10 g, 4.18 mmol) and (+)-**21** (0.324 g, 0.697 mmol) in CH_2Cl_2 (15 mL) was added $BF_3\cdot OEt_2$ (0.53 mL, 4.2 mmol). The reaction was warmed to −42 °C and stirred for 6 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (15 mL), and the CH_2Cl_2 was removed in vacuo. The resultant aqueous layer was diluted with saturated aqueous NH_4Cl (10 mL) and EtOAc (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with saturated aqueous NaCl (35 mL). The resultant organic phase was dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuo to afford unpurified (−)-**24** as a colorless oil. Purification by flash chromatography (10:90 to 20:80 EtOAc/hexanes) provided (−)-**24** as a colorless oil (0.407 g, 94%, >95:5 diastereomer ratio as determined by ^{1}H NMR spectroscopy): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.47 (m, 2H), 7.32 (m, 7H), 7.24 (m, 1H), 5.45 (m, 1H), 5.35 (m, 1H), 5.30−4.90 (br s, 1H), 4.46 (s, 2H), 3.38 (m, 1H), 3.73 (m, 1H), 3.44 (t, J = 6.4, 2H), 3.29 (m, 1H), 3.12 (m, 1H), 2.33 (m, 1H), 2.15−1.98 (m, 3H), 1.74 (m, 2H), 1.65 (m, 2H), 1.45 (s, 9H), 1.43 (s, 9H), 1.47−1.38 (m 1H), 0.32 (s, 3H), 0.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.3, 155.3, 139.0, 137.3, 134.0, 132.6, 129.5, 128.5, 128.1, 127.7, 127.6, 127.2, 79.9, 78.9, 73.1, 70.0, 60.5, 58.9, 46.0, 38.8, 31.4, 29.8, 29.4, 28.7, 28.6, 26.9, −3.8, −4.5; IR (thin film) 3363, 1696 cm^{-1}; HRMS (ESI) m/z calcd for $C_{36}H_{54}N_2NaO_5Si$ (M + Na)$^+$ 645.3700 found 645.3714; $[\alpha]^{23}_D$ −3.39 (*c* 0.30, $CHCl_3$). Anal. Calcd for $C_{36}H_{54}N_2O_5Si$: C, 69.41; H, 8.74. Found: C, 69.44; H, 8.91.

Piperidine (−)-25. To a cooled (−42 °C) suspension of $CuBr\cdot SMe_2$ (0.442 g, 2.15 mmol) in Et_2O (7 mL) was added vinylmagnesium bromide (2.20 mL, 1.0 M in THF, 2.2 mmol). The reaction mixture was stirred for 15 min at −42 °C and cooled to −78 °C as $BF_3\cdot OEt_2$ (0.27 mL, 2.2 mmol) was added. The reaction mixture was stirred at −78 °C for 15 min, and a solution of (+)-**21** (0.200 g, 0.430 mmol) in Et_2O (4 mL) was added. The reaction mixture was warmed to 24 °C over 12 h. The reaction mixture was diluted with a 6:1 mixture of NH_4Cl/NH_4OH (14 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with saturated aqueous NaCl (30 mL). The resultant organic phase was dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuo to afford unpurified (−)-**25** as a white foam. Purification by flash chromatography (10:90 to 30:70 EtOAc/hexanes) provided (−)-**25** as a white foam (0.118 g, 60%, >95:5 diastereomer ratio as determined by ^{1}H NMR spectroscopy): ^{1}H NMR (DMSO, 400 MHz) δ 7.46 (m, 2H), 7.32 (m, 3H), 6.25 (dd, J = 4.2, 2.1, 1H), 6.15 (br s, 1H), 4.89 (m, 2H), 4.10 (m, 1H), 3.11 (m, 1H), 3.00 (m, 1H), 2.47 (m, 2H, and m, 1H), 2.29 (dd, J = 5.2, 3.0, 1H), 1.40 (s, 9H), 1.37 (s, 9H), 0.22 (s, 3H), 0.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.5, 152.5, 136.3, 133.9, 129.6, 128.0, 109.5, 80.6, 79.1, 59.2, 45.6, 45.1, 36.9, 35.7, 28.5, 28..4, −5.5, −5.6; HRMS (ESI) m/z calcd for $C_{25}H_{40}N_2NaO_4Si$ (M + Na)$^+$ 483.6714, found 683.6709; $[\alpha]^{23}_D$ −19.4 (*c* 0.35, $CHCl_3$).

Hydroxypiperidine (−)-27. To a cooled (0 °C) suspension of potassium hydride (0.114 g, 2.84 mmol) in THF (5 mL) was added *tert*-butyl hydrogen peroxide (0.4 mL, 70% w/w solution in H_2O, 3 mmol). The reaction mixture was warmed to 24 °C, and a solution of (−)-**24** (0.290 g, 0.466 mmol) in THF (5 mL) was added. The reaction mixture was stirred for 15 min, and *t*-Bu_4NF (0.98 mL, 1.0 M in THF, 0.98 mmol) was added. The reaction mixture was heated at 50 °C for 12 h. The reaction mixture was diluted with Na_2SO_3 (20 mL), and the layers were separated. The aqueous layer was extracted with *t*-BuOMe (3 × 20 mL). The combined organic layers were washed with saturated aqueous NaCl (30 mL). The resultant organic phase was dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuo to afford unpurified (−)-**27** as a yellow oil. Purification by flash chromatography (10:90 to 60:40 EtOAc/hexanes) provided (−)-**27** as a colorless oil (0.146 g, 62%, >95:5 diastereomer ratio as determined by ^{1}H NMR spectroscopy): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.32 (m, 4H), 7.25 (m, 1H), 5.48 (m, 1H), 5.34 (m, 1H), 5.10 (br s, 1H), 4.48 (s, 2H), 4.16 (m, 1H), 3.95 (m, 1H), 3.70 (m, 1H), 3.45 (t, J = 6.5, 2H), 3.27 (m, 1H), 3.16 (m, 1H), 2.50 (m, 1H), 2.18−2.05 (m, 3H), 1.90 (m, 2H), 1.68 (m, 2H), 1.48 (s, 9H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ

(20) The preparation and characterization data of this compound are provided as Supporting Information.

156.6, 155.2, 138.9, 133.2, 128.5, 127.7, 127.6, 126.2, 80.2, 79.5, 73.0, 72.8, 69.9, 67.5, 57.0, 43.5, 38.5, 37.7, 29.7, 29.4, 28.61, 28.57; IR (thin film) 3396, 1694, 1675 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{44}N_2NaO_6$ $(M + Na)^+$ 527.3097, found 527.3101; $[\alpha]^{23}_D$ −2.17 (*c* 0.85, $CHCl_3$).

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Supporting Information Available: Complete experimental procedures and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.