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# Synthesis of the Tripeptide Domain of Sanglifehrins Using Asymmetric Phase-Transfer Catalysis

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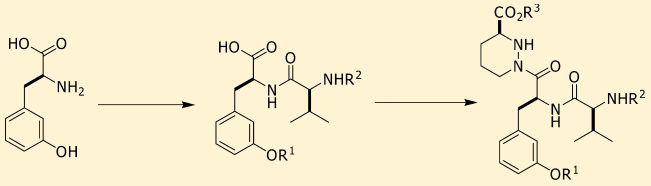
Supporting Information

**ABSTRACT:** The tripeptide (*S*)-valinyl-(*S*)-*m*-hydroxyphenylalanyl-(3*S*)-piperazate common to immunosuppressant sanglifehrins was synthesized from the constituent amino acid residues in nine steps and 42% overall yield. A key construction was the installation of (*S*) absolute configuration in *m*-hydroxyphenylalanine using asymmetric phase-transfer catalysis in the presence of *N*-(1-naphthyl)cinchonidinium bromide. Cbz-protected (*S*)-valine was first coupled to the amino group of (*S*)-*m*-triisopropylsilyloxyphenylalanine *tert*-butyl ester, and the resulting dipeptide after ester cleavage was linked to (3*S*)-methyl piperazate.




Sanglifehrins (e.g., **1** and **2**, Figure 1) comprise a family of macrolides produced by *Streptomyces* sp. A92-308110 with notewothy immunosuppressive activity.[1,2] This property is displayed in the case of **1** by inhibition of mitogen-induced B-cell proliferation without influencing T-cell receptor-mediated cytokine production.[3] The immunosuppressive activity of sanglifehrins was assessed in two-way mixed lymphocyte reaction experiments which found that sanglifehrins A (**1**) and B (**2**) possessed $IC_{50}$ values of 170 and 120 nM, respectively. Both compounds showed affinity for cyclophylin A at a level 20-fold higher than cyclosporine A.[1]

The chemical structures including absolute configuration of sanglifehrins were determined by NMR techniques in combination with X-ray crystallographic analysis of the complex formed by **1** with cyclophilin A.[4] These studies revealed that sanglifehrins are characterized structurally by two principal domains, a [5.5]-spirolactam portion and a 22-membered macrolide, connected by a nine-carbon chain. Spanning C13−C23 of the macrolide of each sanglifehrin is a tripeptide segment **3** ($R^1$ = H) containing linked (*S*)-valine, (*S*)-*m*-hydroxyphenylalanine and (3*S*)-piperazic acid residues. The impressive biological properties of sanglifehrins have invited synthetic interest from many sources with the result that total syntheses of sanglifehrin A have been completed by Nicolaou[5] and by Paquette.[6] Contributions to this effort have also been made by the Novartis group[7] and others.[8] Our initial focus on the synthesis of sanglifehrins was directed at the C1−N12 tripeptide segment **3** within the macrolide portion, and our strategy (Scheme 1) envisioned an approach via dipeptide **4** anchored at the central amino acid *m*-hydroxyphenylalanine (**5**). Elaboration outward from amine and carboxylic acid termini of core unit **5** would add sequentially valine and piperazic acid residues. We now report a route to the sanglifehrin tripeptide in which a catalytic phase transfer reaction provides the key to installing asymmetry in the central *m*-hydroxyphenylalanine residue.

Our initial blueprint for assembling the C1−N12 tripeptide of the sanglifehrins envisioned coupling of a hydroxyl-protected version of *m*-hydroxyphenylalanine (**5**) with a Boc-protected valine and subsequent linkage of the resultant dipeptide **4** with an ester of piperazic acid. Construction of a (*S*)-*m*-hydroxyphenylalanine residue in enantioenriched form was a primary goal of this plan, and for this operation we chose the catalytic asymmetric phase-transfer methodology developed by O'Donnell.[9] The key step in this method is alkylation of the enolate of a *N*-dibenzylideneglycine ester with a benzylic halide in the presence of a *Cinchona* alkaloid derivative.

The starting point for this approach was *m*-hydroxybenzaldehyde (**6**), which was converted to its triisopropylsilyl (TIPS) ether **7** before reduction to primary alcohol **8** (Scheme 2). The derived benzylic iodide **9** was then used to alkylate imino ester **10** in the presence of *N*-(1-naphthyl)cinchonidinium bromide **11**.[10] This carefully optimized reaction was carried out in a mixed solvent system consisting of toluene and dichloromethane[11] at −10 °C and afforded (*S*)-imino ester **12** in good yield.[12] A projection depicting attack by **9** at the less sterically hindered *si* face of the (*Z*)-enolate of **10** in the presence of **11** is shown in Figure 2. Enantiomers of racemic **12** could not be separated by chiral high-performance liquid chromatography and therefore it was not possible to determine the enantiomeric excess of **12** directly. However, selective removal of the silyl ether from **12** gave phenol derivative **13** which was amenable to measurement of its enantiomeric excess by chiral HPLC. The measured value of 88% ee for **13** is likely to be a low estimate since partial racemization is believed to have occurred during cleavage of the TIPS ether from **12** with TBAF.

Continuation from **12** toward **3** required selective hydrolysis of the imine, a transformation achieved in good yield with aqueous acetic acid in THF (Scheme 3). The resulting amino

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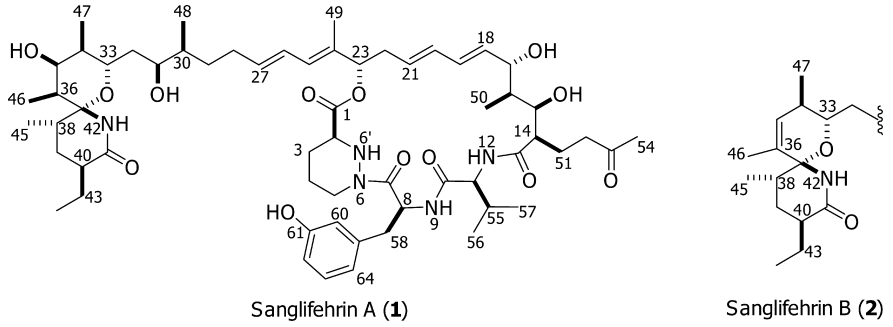
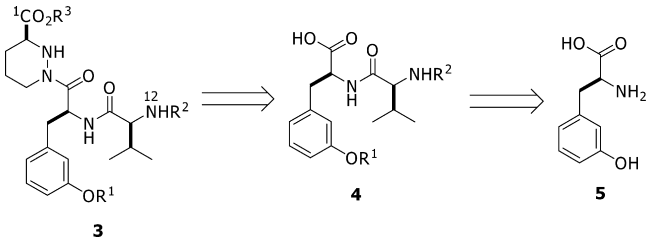
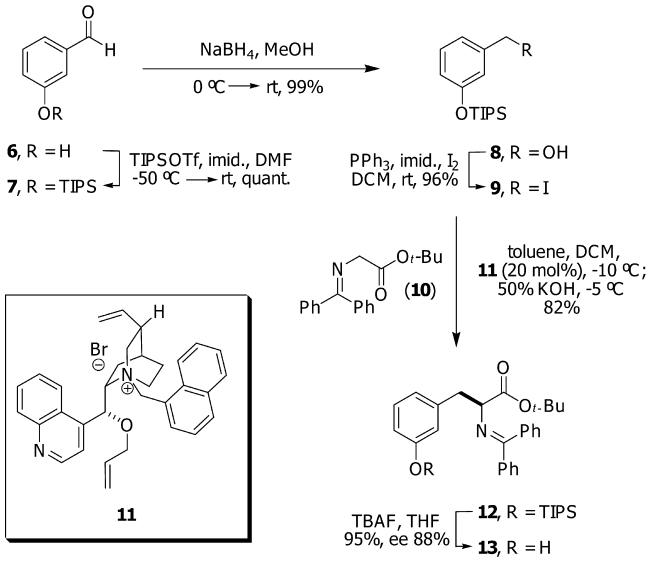



**Figure 1.** Structures of sanglifehrins A and B.

**Scheme 1. Sequence Strategy for Assembly of Sanglifehrin Tripeptide 3 from *m*-Hydroxyphenylalanine (5)**




**Scheme 2. Asymmetric Phase-Transfer Synthesis of *m*-Hydroxyphenylalanine Derivative 13**



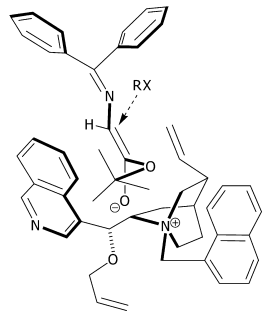



**Figure 2.** Stereoview of the attack trajectory by iodide **9** on the ion pair formed between the (*Z*)-enolate of imino ester **10** and catalyst **11**.

ester **14** was coupled to *N*-Boc (*S*)-valine (**15**) in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and 1-hydroxybenzotriazole (HOBt) to produce a high yield of dipeptide **16** as the sole detectable stereoisomer by $^{13}$C NMR after chromatography. We had expected that selective cleavage of the *tert*-butyl ester from **16** could be accomplished following a protocol reported by Yadav,[13] but exposure of **16** to the published conditions using iodine in acetonitrile with a trace of water gave no indication that carboxylic acid **17** was formed. Not surprisingly, more vigorous conditions resulted in removal of both Boc protection and the *tert*-butyl ester from **16**, a consequence that rendered access to tripeptide **3** via controlled coupling with valine and piperazic acid moieties untenable.

A solution to the deprotection problem with **16** was sought by linking **14** with *N*-carbobenzyloxy-(*S*)-valine (**18**). This reaction, carried out with *N*,*N*,*N*′,*N*′-tetramethyl-*O*-7-azabenzotriazol-1-yluronium hexafluorophosphate (HATU) and Hunig's base in DMF, furnished dipeptide **19** as a single stereoisomer after chromatographic purification according to $^{13}$C NMR. The *tert*-butyl ester of **19** was cleaved with complete chemoselectivity using thioanisole and trifluoroacetic acid,[14] affording carboxylic acid **20** ready for coupling with a (3*S*)-piperazic acid residue.

Hale and co-workers have devised a synthesis of (3*R*)-piperazic acid using (4*R*)-benzyloxazolidin-2-one[15] as a chiral adjuvant to generate absolute configuration; our route to the (3*S*) piperazate enantiomer was patterned after Hale's but in the opposite enantiomeric series (Scheme 4). Thus, (4*S*)-benzyloxazolidin-2-one was acylated with 5-bromopentanoyl chloride, prepared from *δ*-valerolactone,[16] to yield acyloxazolidinone **21**. This compound underwent stereoselective addition to the *re* face of its (*Z*)-lithium enolate by di-*tert*-butyl azodicarboxylate to produce piperazate derivative **22** as a 9:1 mixture of diastereomers as determined by $^{13}$C NMR spectroscopy. After chromatographic purification, **22** was hydrolyzed with aqueous lithium hydroxide to remove the chiral auxiliary and obtain carboxylic acid **23**. The acid was converted to methyl ester **24** with trimethylsilyldiazomethane in MeOH, and subsequent cleavage of the pair of Boc protecting groups with TFA furnished (3*S*)-methyl piperazate (**25**) as its trifluoroacetate salt. The latter was identical spectroscopically with the same substance prepared by Hale.[15]

Condensation of dipeptide **20** selectively at *N*(1) of methyl piperazate **25** using HATU as coupling agent[17] gave **26** as a single diastereomer after chromatographic purification according to $^{13}$C NMR; final hydrogenolysis of the Cbz-protected tripeptide then yielded amino ester **27** (Scheme 5).

In summary, tripeptide **27** representing C1−N12 of the macrocyclic domain of the sanglifehrins was synthesized in nine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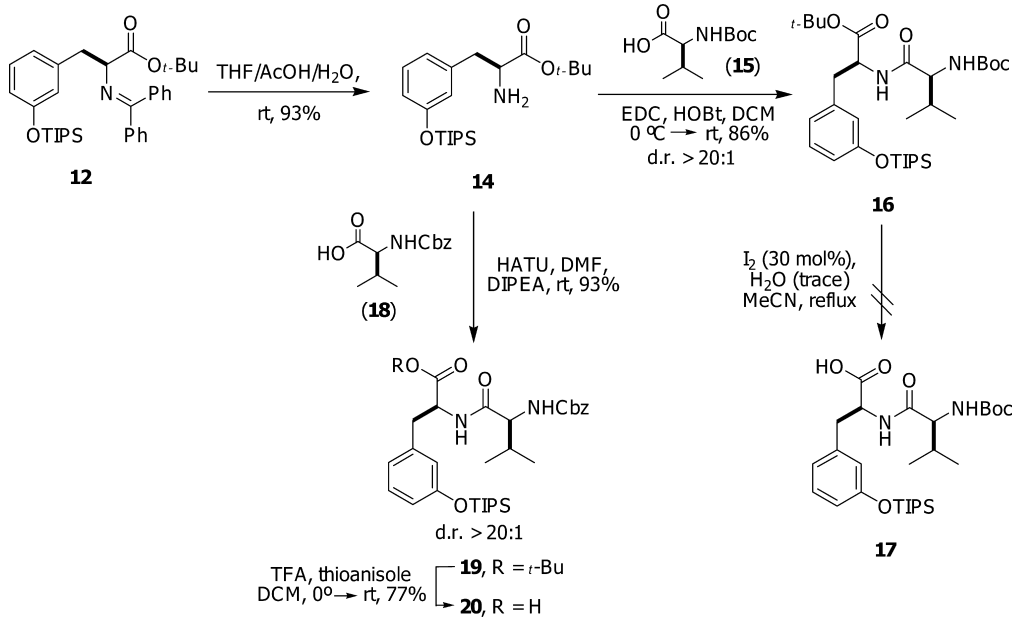
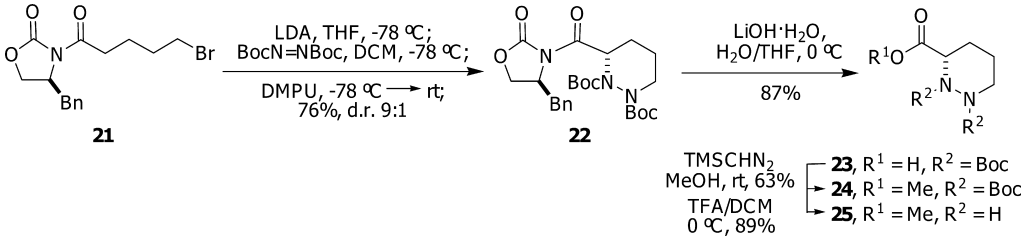
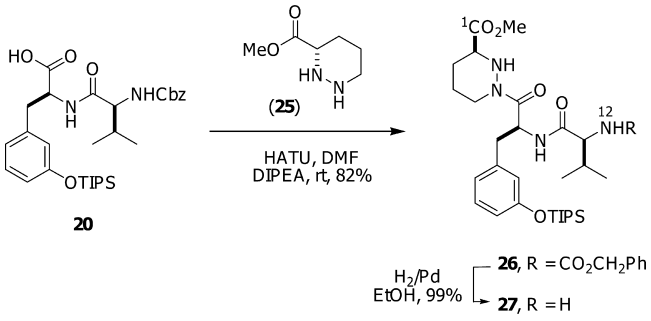
**Scheme 3. Synthesis of Boc-Protected Dipeptide 16 and Cbz-Protected Dipeptide 20**




**Scheme 4. Synthesis of (3*S*)-Methyl Piperazate (25)**




**Scheme 5. Synthesis of Sanglifehrin Tripeptide 27**




steps from *m*-hydroxybenzaldehyde (**6**) in an overall yield of 42%. This tripeptide stands ready for connection at its N12 terminus to a carboxylic acid housing C13−C19 of the sanglifehrin macrolactone, while the carboxylate at C1 will provide the locus for eventual macrolactonization and completion of this substructure of the sanglifehrins.

## EXPERIMENTAL SECTION

**General Techniques.** All reactions requiring anhydrous conditions were conducted in flame-dried glass apparatus under an atmosphere of argon. THF, $Et_2O$, $CH_2Cl_2$, DMF, benzene, and acetonitrile were dried by passage through an activated alumina column under argon. DMSO was distilled from $CaH_2$ at 15 mmHg and stored over activated 4 Å molecular sieves. Anhydrous MeOH was freshly distilled from $CaH_2$. Preparative chromatographic separations were performed on silica gel (35−75 $\mu$m); reactions were followed by TLC analysis using silica plates with fluorescent indicator (254 nm) and visualized with a UV lamp or phosphomolybdic acid. All commercially available reagents were purchased and used as received unless stated otherwise. Melting points were measured on a capillary melting point apparatus. Optical rotations were measured with a polarimeter at ambient temperature using a 1 mL capacity cell with 1 dm path length. Infrared (IR) spectra were recorded using a thin film supported on KBr disks or dispersed in a KBr pellet. $^1$H and $^{13}$C NMR spectra were recorded in Fourier transform mode at the field strength specified on a 300, 400, or 700 MHz spectrometer. Spectra were obtained on $CDCl_3$ solutions in 5 mm diameter tubes; chemical shifts in ppm (parts per million) are quoted relative to the residual signals of chloroform ($\delta$H 7.26 ppm, or $\delta$C 77.0 ppm). Multiplicities in the $^1$H NMR spectra are described as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad; coupling constants ($J$) are reported in hertz. Low (MS) and high (HRMS) resolution mass spectra were measured using a quadrupole analyzer and are reported with ion mass/charge ($m/z$) ratios as values in atomic mass units. High performance liquid chromatography (HPLC) was carried out using a Daicel Chiralcel OD column with 9:1 hexane/2-propanol as eluting solvent at a flow rate of 1 mL/min.

**3-(Triisopropylsilyloxy)benzaldehyde (7).** To a solution of 3-hydroxybenzaldehyde (**6**) (1.12 g, 9.89 mmol) and imidazole (2.02 g, 29.66 mmol) in DMF (33 mL) at −50 °C was added dropwise TIPSOTf (4.54 g, 14.83 mmol). The stirred mixture was allowed to warm to room temperature, and after 10 h, it was partitioned between EtOAc (60 mL) and water (24 mL). The aqueous layer was extracted with a mixture of EtOAc and hexanes (1:1, 3 × 48 mL), and the combined extract was washed with brine, dried over anhydrous $Na_2SO_4$, and concentrated under vacuum. The residue was purified by flash chromatography (10% $Et_2O$ in hexanes) to give 7 (3.05 g, 99%) as a colorless oil: IR (neat) 2945, 2889, 2868, 2723, 1705, 1598, 1583,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1483, 1446, 1387, 1279, 1167, 1146, 1073, 1003, 968, 920, 882, 829, 789, 733, 683, 644 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 1.13 (d, $J$ = 7.2 Hz, 18H), 1.34−1.27 (m, 3H), 7.17 (d, $J$ = 8.0 Hz, 1H), 7.39−7.42 (m, 2H), 7.46−7.48 (d, $J$ = 7.6 Hz, 1H), 9.97 (s, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 12.6, 17.9, 119.6, 123.2, 126.3, 130.0, 138.0, 156.8, 192.0.

**(3-(Triisopropylsilyloxy)phenyl)methanol (8).** To a stirred solution of **7** (2.87 g, 10.31 mmol) in MeOH (50 mL) at room temperature was added $NaBH_4$ (585 mg, 15.46 mmol), and the resulting suspension was stirred for 40 min. The reaction mixture was concentrated under vacuum, the residue was triturated with $H_2O$ (30 mL), and the mixture was extracted with EtOAc (3 × 50 mL). The extract was washed with brine, dried over anhydrous $Na_2SO_4$, and filtered, and the filtrate was concentrated under vacuum to give virtually pure **8** (2.87 g, 99%) as a colorless oil: IR (neat) 3331 (br), 2945, 2892, 2867, 1604, 1587, 1486, 1464, 1444, 1385, 1367, 1281, 1166, 1004, 958, 920, 883, 821, 782, 689 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 1.13 (d, $J$ = 7.6 Hz, 18H), 1.26−1.33 (m, 3H), 2.00 (br s, 1H), 4.66 (s, 2H), 6.83 (d, $J$ = 8.0 Hz, 1H), 6.92−6.95 (m, 2H), 7.22 (t, $J$ = 8.0 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 12.7, 17.9, 65.2, 118.4, 119.0, 119.4, 129.5, 142.5, 156.3; HRMS (CI) calcd for $C_{16}H_{28}O_2Si$ $[M]^+$ $m/z$ 280.1859, found $m/z$ 280.1851. This material was used in the next step without further purification.

**(3-(Iodomethyl)phenoxy)triisopropylsilane (9).** To a stirred solution of $PPh_3$ (561 mg, 2.14 mmol) and imidazole (146 mg, 2.14 mmol) in $CH_2Cl_2$ (10 mL) at room temperature was added $I_2$ (543 mg, 2.14 mmol). After 15 min, a solution of **8** (500 mg, 1.78 mmol) in $CH_2Cl_2$ (5 mL) was added dropwise to the reaction mixture, and stirring was continued for 30 min. The resulting suspension was passed through a short column of silica and eluted with $CH_2Cl_2$. The eluate was shaken with saturated aqueous $Na_2S_2O_3$ (15 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to give virtually pure **9** (669 mg, 96%) as a pale yellow oil: IR (neat) 2944, 2891, 2866, 1602, 1584, 1484, 1464, 1440, 1385, 1282, 1173, 1156, 1072, 1003, 978, 920, 882, 817, 782, 690 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 1.13 (d, $J$ = 7.2 Hz, 18H), 1.23−1.32 (m, 3H), 4.42 (s, 2H), 6.77 (d, $J$ = 8.0 Hz, 1H), 6.92 (s, 1H), 6.96 (d, $J$ = 7.6 Hz, 1H), 7.15 (t, $J$ = 7.6 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 5.5, 12.7, 17.9, 119.5, 120.4, 121.3, 129.6, 140.6, 156.2; HRMS (EI) calcd for $C_{16}H_{27}IOSi$ $[M]^+$ $m/z$ 390.0876, found $m/z$ 390.0873. This material was used in the next step without further purification.

**(*S*)-*tert*-Butyl 2-(Diphenylmethyleneamino)-3-(3-(triisopropylsilyloxy)phenyl)propanoate (12).** To a stirred solution of **9** (2.50 g, 6.40 mmol) in a mixture of $CH_2Cl_2$ (25 mL) and toluene (50 mL) at −10 °C were added **10** (1.89 g, 6.40 mmol) and **11** (556 mg, 1.02 mmol). To this solution was added a 50% aqueous KOH solution (50 mL), and the resulting mixture was stirred vigorously at −5 °C for 33 h. Heptane (65 mL) and water (65 mL) were added to the mixture, and the separated aqueous layer was extracted with heptane (2 × 100 mL). The combined organic extract was washed with water (200 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (10% EtOAc in hexanes with 1% $Et_3N$) to give **12** (2.92 g, 82%) as a viscous orange oil: $[\alpha]^{22}_D$ −110.6 ($c$ 1.00, $CHCl_3$); IR (neat) 3059, 3020, 2944, 2892, 2867, 1735, 1624, 1601, 1585, 1485, 1463, 1445, 1391, 1368, 1272, 1152, 1073, 1030, 1004, 980, 910, 883, 850, 805, 780, 694 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 1.05 (d, $J$ = 7.2 Hz, 18H), 1.13−1.19 (m, 3H), 1.47 (s, 9H), 3.12 (dd, $J$ = 9.2, 13.2 Hz, 1H), 3.23 (dd, $J$ = 4.4, 13.2 Hz, 1H), 4.14 (dd, $J$ = 4.4, 9.2 Hz, 1H), 6.64−6.75 (m, 5H), 7.07 (t, $J$ = 8.0 Hz, 1H), 7.29−7.41 (m, 6H), 7.63 (d, $J$ = 8.0 Hz, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 12.6, 17.9, 28.1, 39.6, 67.9, 81.0, 117.6, 121.4, 122.5, 127.8, 127.9, 128.1, 128.2, 128.8, 128.9, 130.0, 136.5, 139.6, 139.9, 155.8, 170.2, 170.8; HRMS (ES) calcd for $C_{35}H_{48}NO_3Si$ $[M + H]^+$ $m/z$ 558.3403, found $m/z$ 558.3384.

**(*S*)-*tert*-Butyl 2-(Diphenylmethyleneamino)-3-(3-hydroxyphenyl)propanoate (13).** To a stirred solution of **12** (50.0 mg, 0.0896 mmol) in THF (0.45 mL) at room temperature was added TBAF (1 M solution in THF, 0.11 mL, 0.110 mmol), and the resulting solution was stirred at room temperature for 4 h. The reaction was quenched with water (0.50 mL), and the aqueous phase was extracted with $Et_2O$ (3 × 0.50 mL). The combined extract was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (10% to 30% EtOAc in hexanes) gave **13** (34.2 mg, 95%) as a colorless oil: $[\alpha]^{25}_D$ −137.6 ($c$ 1.00, $CHCl_3$); IR (neat) 3414, 3059, 2977, 2928, 1729, 1602, 1589, 1488, 1454, 1393, 1369, 1275, 1152, 1076, 1029, 1000, 978, 934, 911, 876, 845, 780, 698 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 1.46 (s, 9H), 3.12 (dd, $J$ = 9.2, 13.2 Hz, 1H), 3.20 (dd, $J$ = 4.4, 13.2 Hz, 1H), 4.15 (dd, $J$ = 4.4, 9.2 Hz, 1H), 5.48 (br s, 1H), 6.55 (s, 1H), 6.62−6.71 (m, 4H), 7.06 (t, $J$ = 8.0 Hz, 1H), 7.28−7.37 (m, 6H), 7.59 (d, $J$ = 7.6 Hz, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 28.1, 39.4, 67.8, 81.4, 113.3, 116.8, 122.1, 127.7, 128.0, 128.1, 128.4, 128.8, 129.3, 130.2, 136.3, 139.5, 140.0, 155.6, 170.8, 170.9; HRMS (ES) calcd for $C_{26}H_{28}NO_3$ $[M + H]^+$ $m/z$ 402.2069, found $m/z$ 402.2055.

**(*S*)-*tert*-Butyl 2-Amino-3-(3-(triisopropylsilyloxy)phenyl)-propanoate (14).** To a stirred mixture of **12** (302 mg, 0.542 mmol) in THF (1.1 mL) and water (1.1 mL) at room temperature was added acetic acid (1.1 mL), and the mixture was stirred at room temperature for 6 h. The mixture was cooled to 0 °C, diluted with water (3.0 mL), and brought to neutral pH by addition of solid $Na_2CO_3$ (ca. 2 g). The aqueous phase was extracted with EtOAc (3 × 5.0 mL), and the combined extract was washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (30% EtOAc in hexanes) to afford **14** (197 mg, 93%) as a pale yellow oil: $[\alpha]^{20}_D$ +4.5 ($c$ 1.00, $CHCl_3$); IR (neat) 2944, 2867, 1732, 1603, 1584, 1486, 1464, 1445, 1391, 1367, 1277, 1156, 1005, 883, 837, 782, 688 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 1.12 (d, $J$ = 7.6 Hz, 18H), 1.24−1.32 (m, 3H), 1.47 (s, 9H), 1.55 (br s, 2H), 2.80 (dd, $J$ = 7.6, 13.6 Hz, 1H), 3.02 (dd, $J$ = 5.2, 13.6 Hz, 1H), 3.62 (br s, 1H), 6.77−6.82 (m, 3H), 7.14−7.18 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 12.7, 17.9, 28.0, 41.2, 56.3, 81.2, 118.0, 121.1, 122.1, 129.3, 139.1, 156.1, 174.2; HRMS (ES) calcd for $C_{22}H_{40}NO_3Si$ $[M + H]^+$ $m/z$ 394.2777, found $m/z$ 394.2748.

**(*S*)-*tert*-Butyl 2-((*S*)-2-(*tert*-Butoxycarbonyl)-3-methylbutanamido)-3-(3-(triisopropylsilyloxy)phenyl)propanoate (16).** To a stirred solution of **14** (170.9 mg, 0.434 mmol), **15** (141.5 mg, 0.651 mmol), and HOBt (167.2 mg, 1.237 mmol) in $CH_2Cl_2$ (3.0 mL) at 0 °C was added EDCI (249.7 mg, 1.303 mmol). The mixture was allowed to warm to room temperature and was stirred at that temperature for 3 h. The mixture was diluted with water (3.0 mL), and the layers were separated. The aqueous phase was extracted with EtOAc (3 × 5 mL), and the combined extract was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (20% EtOAc in hexanes) afforded **16** (221.9 mg, 86%) as a colorless foam: $[\alpha]^{21}_D$ +19.5 ($c$ 1.00, $CHCl_3$); IR (neat) 3316 (br), 2965, 2929, 2868, 1737, 1656, 1604, 1585, 1530, 1487, 1447, 1392, 1367, 1278, 1160, 1005, 920, 883, 844, 784, 737, 688 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 0.90 (d, $J$ = 6.8 Hz, 3H), 0.97 (d, $J$ = 6.8 Hz, 3H), 1.12 (d, $J$ = 7.2 Hz, 18H), 1.24−1.31 (m, 3H), 1.41 (s, 9H), 1.47 (s, 9H), 2.11−2.19 (m, 1H), 2.98−3.10 (m, 2H), 3.95 (br s, 1H), 4.70−4.75 (m, 1H), 5.04 (br s, 1H), 6.29 (br s, 1H), 6.74−6.77 (m, 3H), 7.12−7.15 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 12.7, 17.9, 19.2, 27.9, 28.3, 31.0, 38.1, 53.5, 59.8, 82.3, 118.2, 121.1, 122.2, 129.2, 137.5, 156.1, 170.3, 170.9; HRMS (ES) calcd for $C_{32}H_{56}N_2O_6NaSi$ $[M + Na]^+$ $m/z$ 615.3805, found $m/z$ 615.3809.

**(*S*)-*tert*-Butyl 2-((*S*)-2-(Benzyloxycarbonyl)-3-methylbutanamido)-3-(3-(triisopropylsilyloxy)phenyl)propanoate (19).** To a stirred solution of **18** (597 mg, 2.375 mmol) and HATU (903 mg, 2.375 mmol) in DMF (14 mL) at room temperature was added DIPEA (1.24 mL, 7.126 mmol). The mixture was stirred for 5 min, at which point a solution of **14** (850 mg, 2.159 mmol) in DMF (14 mL) was added. The mixture was stirred for 45 min and then was diluted with EtOAc (30 mL). The resulting solution was washed with water (30 mL) and brine (30 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash chromatography (10% EtOAc in hexanes) to give **19** (1.258 g, 93%) as a colorless foam: $[\alpha]^{20}_D$ +20.1 ($c$ 1.00, $CHCl_3$); IR (neat) 3309 (br),


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2965, 2944, 2868, 1732, 1657, 1604, 1585, 1537, 1486, 1455, 1392, 1368, 1279, 1246, 1159, 1105, 1028, 1005, 919, 883, 833, 784, 735, 695, 661 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 0.91 (d, $J$ = 6.8 Hz, 3H), 0.97 (d, $J$ = 6.8 Hz, 3H), 1.11 (d, $J$ = 7.2 Hz, 18H), 1.22−1.28 (m, 3H), 1.41 (s, 9H), 2.11−2.16 (m, 1H), 3.00−3.05 (m, 2H), 4.02−4.04 (m, 1H), 4.70−4.75 (m, 1H), 5.12 (s, 2H), 5.39 (d, $J$ = 8.4 Hz, 1H), 6.29 (d, $J$ = 8.0 Hz, 1H), 6.72−6.76 (m, 3H), 7.11 (t, $J$ = 8.4 Hz, 1H), 7.32−7.38 (m, 5H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 12.7, 17.6, 17.9, 19.1, 27.9, 29.7, 31.2, 38.0, 53.6, 60.2, 67.0, 82.4, 118.2, 121.1, 122.2, 128.0, 128.1, 128.5, 129.3, 136.4, 137.4, 156.1, 156.2, 170.3, 170.5; HRMS (CI) calcd for $C_{35}H_{55}O_6N_2Si$ $[M + H]^+$ $m/z$ 627.3829, found $m/z$ 627.3852.

**(*S*)-2-((*S*)-2-(Benzyloxycarbonyl)-3-methylbutanamido)-3-(3-(triisopropylsilyloxy)phenyl)propanoic Acid (20).** To a solution of **19** (10.0 mg, 0.0160 mmol) and thioanisole (0.04 mL, 0.340 mmol) in $CH_2Cl_2$ (0.40 mL) at 0 °C was added TFA (0.04 mL, 0.522 mmol). The stirred mixture was allowed to warm to room temperature, and after 5 h a second portion of TFA (0.30 mL) was added. The mixture was stirred for a further 4 h and then was concentrated under reduced pressure. The residue was purified by flash chromatography (30% EtOAc in hexanes) to furnish **20** (7.0 mg, 77%) as a colorless solid: mp 120−122 °C; $[\alpha]^{20}_D$ +73.6 ($c$ 3.71, $CHCl_3$); IR (film) 3310, 3066, 3035, 2961, 2945, 2867, 1717, 1653, 1603, 1585, 1540, 1487, 1446, 1279, 1248, 1162, 1004, 883, 831, 694 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 0.86 (d, $J$ = 6.1 Hz, 3H), 0.91 (d, $J$ = 6.5 Hz, 3H), 1.10 (d, $J$ = 7.2 Hz, 18H), 1.21−1.30 (m, 3H), 2.04−2.10 (m, 1H) 3.05−3.06 (m, 1H), 3.12−3.15 (m, 1H), 4.02−4.09 (m, 1H), 4.80−4.83 (m, 1H), 5.07−5.15 (AB quartet, 2H), 5.56 (br s, 1H), 6.54 (br s, 1H), 6.74−6.76 (m, 3H), 7.10 (t, $J$ = 7.9 Hz, 1H), 7.30−7.38 (m, 5H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 12.7, 17.7, 17.9, 19.0, 30.3, 31.0, 37.3, 53.2, 60.4, 60.5, 67.2, 118.7, 120.8, 122.0, 128.0, 128.2, 128.5, 129.5, 137.2, 156.3, 156.5, 171.5, 174.5; HRMS (CI) calcd for $C_{31}H_{47}N_2O_6Si$ $[M + H]^+$ $m/z$ 571.3203, found $m/z$ 571.3220.

**(*S*)-Di-*tert*-butyl 3-((*S*)-4-Benzyl-2-oxooxazolidine-3-carbonyl)piperazine-1,2-dicarboxylate (22).** To a stirred solution of **21** (2.57 g, 7.56 mmol) in THF (9.3 mL) at −78 °C was added dropwise a freshly prepared LDA solution (1 M solution in THF, 8.32 mL, 8.32 mmol). The mixture was stirred at −78 °C for 55 min, at which point a precooled (−78 °C) solution of di-*tert*-butyl azodicarboxylate (2.09 g, 9.07 mmol) in $CH_2Cl_2$ (13.6 mL) was added in one portion via cannula. The solution was stirred at −78 °C for 1 h during which DMPU (23.7 mL, 197 mmol) was added dropwise (by the end of the addition, the reaction mixture had frozen). The mixture was slowly warmed to room temperature, stirred for 6 h, and then added to $Et_2O$ (190 mL) layered above a saturated aqueous solution of $KH_2PO_4$ (70 mL). The two layers were shaken briefly but vigorously and the aqueous phase was extracted with $Et_2O$ (3 × 70 mL). The combined extract was washed with saturated aqueous $NaHCO_3$ (70 mL) and $H_2O$ (120 mL) and was dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated in vacuo to afford a yellow oily residue which was purified by flash chromatography (1:1 $Et_2O$/hexanes) to afford **22** (2.80 g, 76%) as a colorless foam: $[\alpha]^{30}_D$ +29.0 ($c$ 1.00, MeOH); IR (neat) 3055, 3022, 2978, 2932, 2853, 1783, 1698, 1478, 1455, 1393, 1367, 1296, 1253, 1220, 1166, 1111, 1071, 1049, 1031, 988, 911, 881, 854, 823, 753, 737, 704 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 1.50 (m), 1.70−2.20 (m), 2.60−2.71 (m), 2.90 (br s), 3.95 (br s), 4.10−4.25 (m), 4.70 (br s), 5.80 (br s), 6.05 (br s), 7.20−7.49 (m); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 28.1, 28.2, 37.6, 55.6, 66.5, 80.3, 81.3, 127.4, 129.0, 129.4, 135.2, 152.6, 170.4; HRMS (CI) calcd for $C_{25}H_{35}N_3O_7$ $[M]^+$ $m/z$ 489.2475, found $m/z$ 489.2481.

**(*S*)-1,2-Bis(*tert*-butoxycarbonyl)piperazine-3-carboxylic Acid (23).** To a stirred solution of **22** (2.22 g, 4.53 mmol) in THF (17.8 mL) at −5 °C was added a solution of $LiOH·H_2O$ (438 mg, 10.43 mmol) in $H_2O$ (8.9 mL). The mixture was stirred vigorously for 2 h at 0 °C and then was diluted with water (22 mL) and extracted with $Et_2O$ (3 × 55 mL). The combined extract was washed with saturated aqueous $NaHCO_3$ (55 mL), and the aqueous layers were combined, acidified to pH 2 with solid $NaHSO_4$, and extracted with EtOAc (3 × 110 mL). The combined extract was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford pure carboxylic acid **23** (1.31 g, 87%) as colorless prisms: mp 103−106 °C; $[\alpha]^{26}_D$ −18.2 ($c$ 1.00, MeOH); IR (neat) 3200−2500 (br), 2979, 2934, 1732, 1479, 1457, 1417, 1367, 1317, 1254, 1156, 1086, 1064, 1050, 1033, 967, 919, 881, 852, 735, 704, 647, 614 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 1.45 (s), 1.48 (s), 1.36−2.30 (br m), 2.85 (br m), 3.10 (br m), 3.90 (m), 4.03 (m), 4.60−5.08 (br m); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 20.2, 20.5, 23.4, 23.7, 28.0, 28.1, 42.2, 44.2, 56.9, 82.7, 83.3, 83.6, 152.7, 170.9, 171.5; HRMS (EI) calcd for $C_{15}H_{27}O_6N_2$ $[M + H]^+$ $m/z$ 331.1869, found $m/z$ 331.1861.

**(*S*)-1,2-Di-*tert*-butyl 3-Methyl Piperazine-1,2,3-tricarboxylate (24).** To a cooled (0 °C) solution of **23** (1.22 g, 3.70 mmol) in MeOH (20 mL) was added dropwise a solution of $TMSCHN_2$ (2*M* solution in $Et_2O$, 2.8 mL, 5.56 mmol) at 0 °C. The mixture was allowed to warm to room temperature with stirring, and after 12.5 h the reaction was quenched with 10% aqueous AcOH (10 mL). The mixture was extracted with $Et_2O$ (3 × 30 mL), and the combined extract was washed with saturated $NaHCO_3$ (30 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (1:7 $Et_2O$/hexanes 10−40% then EtOAc/hexanes) to afford **24** (0.80 g, 63%) as a colorless oil: $[\alpha]^{30}_D$ −36.4 ($c$ 1.00, $CHCl_3$); IR (neat) 2977, 2931, 2856, 1740, 1703, 1478, 1456, 1393, 1367, 1326, 1297, 1252, 1168, 1127, 1086, 1051, 1033, 1007, 952, 910, 880, 857, 755 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 1.48 (s), 1.49 (s), 1.75 (br m), 1.90 (br m), 2.20 (m), 2.85 (br m), 3.74 (s), 3.95 (br), 4.12 (m), 4.81 (br), 5.01 (br); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 20.0, 24.3, 28.2, 42.7, 51.9, 54.5, 80.2, 81.7, 154.0, 154.6, 170.4; HRMS (CI) calcd for $C_{16}H_{29}N_2O_6$ $[M + H]^+$ $m/z$ 345.2026, found $m/z$ 345.2014.

**(*S*)-Methyl Piperazine-3-carboxylate (25).** To a stirred solution of **24** (776 mg, 2.25 mmol) in $CH_2Cl_2$ (7.5 mL) at 0 °C was added TFA (7.5 mL) over 1 min. The mixture was allowed to warm to room temperature and was stirred for 1 h, then was concentrated in vacuo. The oily residue was azeotroped with toluene to remove residual traces of acid. This furnished crude **25** (743 mg, 89%) as a pale yellow oil: $[\alpha]^{23}_D$ +2.5 ($c$ 1.00, $CHCl_3$); IR (neat) 3420, 3259, 2960, 2922, 2851, 2747, 1734, 1682, 1444, 1204, 1139, 840, 801, 723 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 1.94−2.01 (m, 3H), 2.18−2.21 (m, 1H), 3.30−3.40 (m, 2H), 3.82 (s, 3H), 3.99−4.02 (m, 1H), 6.20 (br s, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 19.7, 24.7, 45.1, 52.8, 55.8, 171.4; HRMS (CI) calcd for $C_6H_{11}N_2O_2$ $[M-H]^+$ $m/z$ 143.0821, found $m/z$ 143.0813. This material was used in the next step without further purification.

**(*S*)-Methyl 1-((*S*)-2-((*S*)-2-(Benzyloxycarbonyl)-3-methylbutanamido)-3-(3-(triisopropylsilyloxy)phenyl)propanoyl)-piperazine-3-carboxylate (26).** To a solution of **20** (4.5 mg, 7.9 $\mu$mol) in DMF (0.10 mL) at room temperature were added HATU (3.6 mg, 9.5 $\mu$mol) and DIPEA (4.9 $\mu$L, 28.4 $\mu$mol). The mixture was stirred for 5 min, at which point a solution of **25** (2.9 mg, 7.9 $\mu$mol) in DMF (0.10 mL) was added. The mixture was stirred for 2 h and diluted with EtOAc (2 mL), and the resulting solution was washed with brine (2 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (20−40% EtOAc in hexanes) to give **26** (4.5 mg, 82%) as a colorless oil: $[\alpha]^{20}_D$ −25.4 ($c$ 1.00, $CHCl_3$); IR (neat) 3302, 3066, 3032, 2945, 2867, 1745, 1642, 1537, 1486, 1442, 1271, 1236, 1164, 1004, 983, 883, 834, 757, 695 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 0.81 and 0.96 (d, $J$ = 6.8 Hz, 3H), 0.90 (d, $J$ = 6.8 Hz, 3H), 1.11 (d, $J$ = 7.2 Hz, 18H), 1.22−1.28 (m, 3H), 1.42−1.51 (m, 2H), 1.61−1.86 (m, 3H), 2.02−2.18 (m, 1H), 2.50−2.61 (m, 1H), 2.83−2.96 (m, 2H), 3.23 and 3.47 (d, $J$ = 11.0 Hz, 1H), 3.72 and 3.76 (s, 3H), 4.03−4.08 (m, 1H), 4.03−4.08 and 4.48−4.52 (m, 1H), 5.10−5.17 (m, 2H), 5.38 (br s, 1H), 5.61−5.66 and 5.73−5.78 (m, 1H), 6.51 (m, 1H), 6.67−6.79 (m, 3H), 7.09−7.14 (m, 1H), 7.32−7.39 (m, 5H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 12.7, 17.3 and 17.5, 17.9, 19.2, 22.4 and 22.9, 28.2 and 28.7, 31.4 and 31.7, 39.1 and 39.5, 41.9 and 42.0, 49.7 and 50.0, 52.1, 57.7 and 58.4, 60.0 and 60.2, 67.0, 118.1, 121.0 and 121.4, 122.2 and 122.4, 128.1, 128.5, 129.1 and 129.2, 136.4, 138.0, 156.0, 156.1, 156.3, 170.2 and 170.4, 171.5 and


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171.7, 172.3; HRMS (ES) calcd for $C_{37}H_{57}N_4O_7Si$ $[M + H]^+$ $m/z$ 697.3997, found $m/z$ 697.3976.

**(*S*)-Methyl 1-((*S*)-2-((*S*)-2-Amino-3-methylbutanamido)-3-(3-(triisopropylsilyloxy)phenyl)propanoyl)piperazine-3-carboxylate (27).** A suspension of **26** (164 mg, 0.236 mmol) and 10% Pd/C in EtOH (12.0 mL) was stirred under $H_2$ (1 atm) for 19 h. The catalyst was removed by filtration, and the filtrate was concentrated under vacuum. The residue was purified by flash chromatography (10% MeOH in $CH_2Cl_2$ + 1% $Et_3N$) to afford **27** (131 mg, 99%) as a pale yellow oil: $[\alpha]^{20}_D$ −21.5 (*c* 1.00, $CHCl_3$); IR (neat) 3336, 3245, 2925, 2867, 1746, 1652, 1603, 1585, 1486, 1443, 1273, 1164, 1004, 982, 883, 834, 688, 662 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 0.84−1.00 (m, 6H), 1.10 (d, $J$ = 7.2 Hz, 18H), 1.21−1.29 (m, 3H), 1.40−1.80 (m, 4H), 2.01−2.30 (m, 3H), 2.70−2.95 (m, 3H), 3.50 (br s, 1H), 3.60−3.70 (m, 6H), 4.20−4.30 (m, 1H), 5.65−5.72 (m, 1H), 6.69−6.90 (m, 3H), 7.05−7.12 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ (ppm) 12.7, 14.1, 17.1, 17.5, 17.9, 19.2, 22.7, 28.2, 29.7, 29.7, 30.6, 30.8, 38.0, 39.0, 41.7, 49.7, 52.1, 57.9, 59.9, 70.6, 118.0, 120.9, 121.4, 122.4, 129.1, 129.2, 138.3, 138.6, 156.0, 156.1, 171.8, 172.1, 172.5; HRMS (ES) calcd for $C_{29}H_{51}N_4O_5Si$ $[M + H]^+$ $m/z$ 563.3629, found $m/z$ 563.3615.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

$^1H$ and $^{13}C$ NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interests.

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