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Silanediol Inhibitors of Angiotensin-Converting Enzyme. Synthesis and Evaluation of Four Diastereomers of Phe[Si]Ala Dipeptide Analogues[1]

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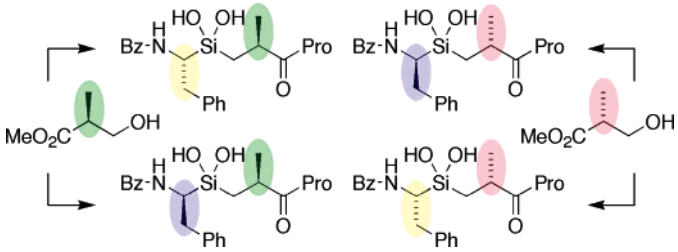

Four stereoisomers of a Phe-Ala silanediol dipeptide mimic have been evaluated as inhibitors of angiotensin-converting enzyme (ACE) and compared to ketone-based inhibitors reported by Almquist et al. One stereogenic center of the isomers was derived from the individual enantiomers of methyl 3-hydroxy-2-methylpropionate, with separation of diastereomers after introduction of the second stereogenic center. The diastereomeric identities were established by X-ray crystallography of an intermediate. Inhibition of ACE by three of the silanediol diastereomers (IC_{50} = 3.8−207 nM) closely paralleled that of the corresponding diastereomeric ketones (IC_{50} = 1.0−46 nM). The fourth diastereomer, corresponding to the least inhibitory ketone (IC_{50} = 3200 nM), exhibited an unexpected level of inhibition in the silanediol (IC_{50} = 72 nM), suggesting an alternative mode of binding to the enzyme.

Inhibition of angiotensin-converting enzyme (ACE) is a classic medicinal chemistry approach to the treatment of hypertension, with 10 inhibitors currently sold in the U.S.[2] Captopril, **1ad** Figure 1, was the first protease inhibitor to achieve commercial success. Despite the long-standing importance of this enzyme, its crystal structure has only recently been reported.[3]

ACE is a metalloprotease[4] and inhibitors incorporate a functional group (**X**, Figure 1) that interacts with the active site zinc ion: thiol **a**, carboxylates **b** and **c** (R = H), and the phosphinic acid of **4** (R = H). Among the commercially successful inhibitors, most are based on the alanine-derived fragment **1**, with one of three substituents **a**−**c**, and proline or a proline surrogate (**d**−**j**).[2]

Our interest in exploring the use of a silanediol group as a central, zinc chelating component of a protease inhibitor[6−10] was motivated by both the similarity and the dissimilarity of carbon and silicon chemistry. Silicon

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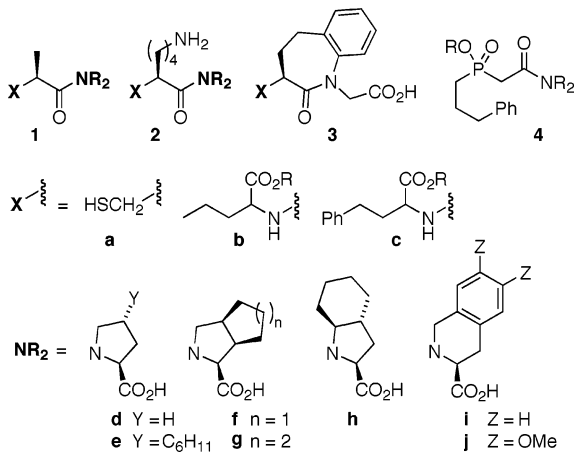

FIGURE 1. Components of commercial ACE inhibitors.[5]

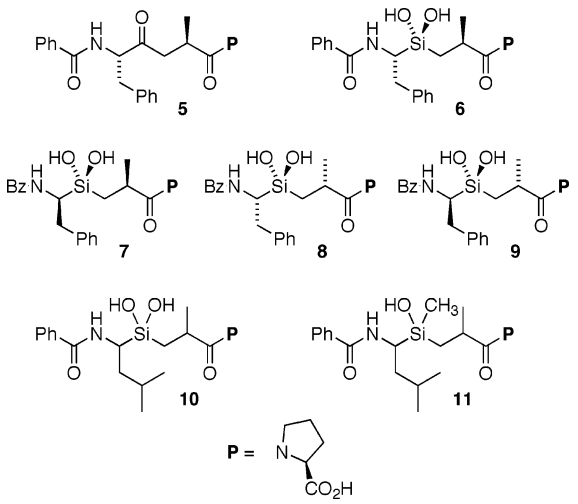

FIGURE 2. Almquist's ketone inhibitor **5**, silanediol analogues **6**−**9**, and the first silanediol inhibitor structures **10** and **11**.

is the element most closely related to carbon, but it forms double bonds only under duress. This property allows silanediols to act as tetrahedrally stable mimics of a hydrated carbonyl, although as a second row element the silane would be marginally larger. Silanediols may have advantages over other hydrated carbonyl isosteres because they are neutral at physiological pH. Phosphinic acids **4** and carboxylates **b** and **c** have pK_a values below 5 and can require delivery as ester prodrugs.

We targeted ACE as our initial foray into metalloprotease inhibition with silanediols because of the maturity of this enzyme's structure−activity mapping, its ready availability, and its importance as a pharmaceutical target. A critical issue, however, was the choice of an inhibitor structure with which one could formulate a first-generation silanediol-based inhibitor, a structure with a degree of steric hindrance surrounding the zinc-binding element.

Silanediols are best known as unstable precursors of siloxane polymers.[11] The stability of silanediols is intrinsically linked to the steric shielding provided by the two organic groups that flank the silanediol.[12] Introduction of a silanediol group into one of the commercial ACE inhibitors, Figure 1, at a position that would interact with the active site zinc ion, would replace the thiol or the carboxylate groups in partial structures **a**−**c**, or the phosphorus in **4**. Unfortunately, none of the resulting structures would have provided a silanediol environment commensurate with unequivocally suppressing oligomer formation. In contrast, Almquist's ketone **5**,[13−15] Figure 2, has a more substantial peptide-like structure, with what appeared to be an ideal level of substitution on either side of the ketone. The ketone is presumably bound to the enzyme as the ketone hydrate.[16,17] At the outset of this project, the literature contained approximately 100 characterized silanediols.[18] None, however, contained stereogenic centers or functional groups. The effect of the latter on the silanediols was, therefore, unknown.

In our first exercise in silanediol-based protease inhibitor synthesis, the initial structures to be prepared included silanediol **10** and methylsilanol **11**.[7] Silanediol **10** was the structure most analogous to ketone **5**, but carried an isobutyl group where **5** has a benzyl group. In addition, the two stereogenic carbons flanking the silanediol were not controlled, yielding a mixture of four diastereomers. Nevertheless, this diastereomeric mixture was found to inhibit ACE with an IC_{50} value of 14 nM. Considering that only one of the four diastereomers would be expected to provide most of the inhibition, this was considered a highly successful outcome. In comparison, replacement of the central silanediol, anticipated to be important for interaction with the enzyme active site, with a methylsilanol group, **11**, gave little enzyme inhibition (IC_{50} > 3000 nM). These results were consistent with the silanediol group interacting with the enzyme as a transition state analogue inhibitor of ACE, and provided impetus for additional investigation.

The publications of Almquist et al. included ACE inhibition data for **5**, and for the three individual diastereomers derived by systematically changing the stereochemistry of the methyl and benzyl substituents.[15] We therefore set out to prepare the exact silanediol analogue **6** and each of the analogous diastereomers **7**−**9** for comparison with their respective ketones.

(5) Captopril (**1ad**), perindopril (**1bg**), enalapril (**1cd**), ramipril (**1cf**), trandolapril (**1ch**), quinapril (**1ci**), moexipril (**1cj**), lisinopril (**2cd**), benzapril (**3c**), fosinopril (**4e**).

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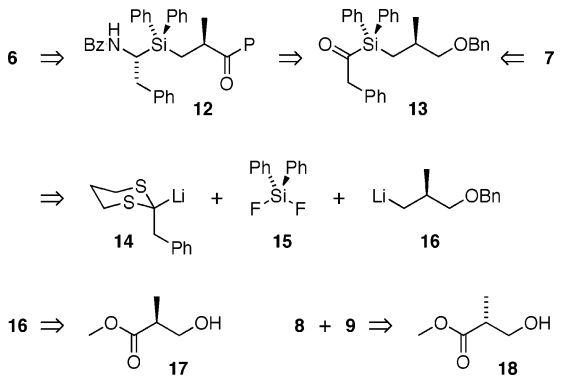
SCHEME 1. Retrosynthesis of 6–9



Results and Discussion

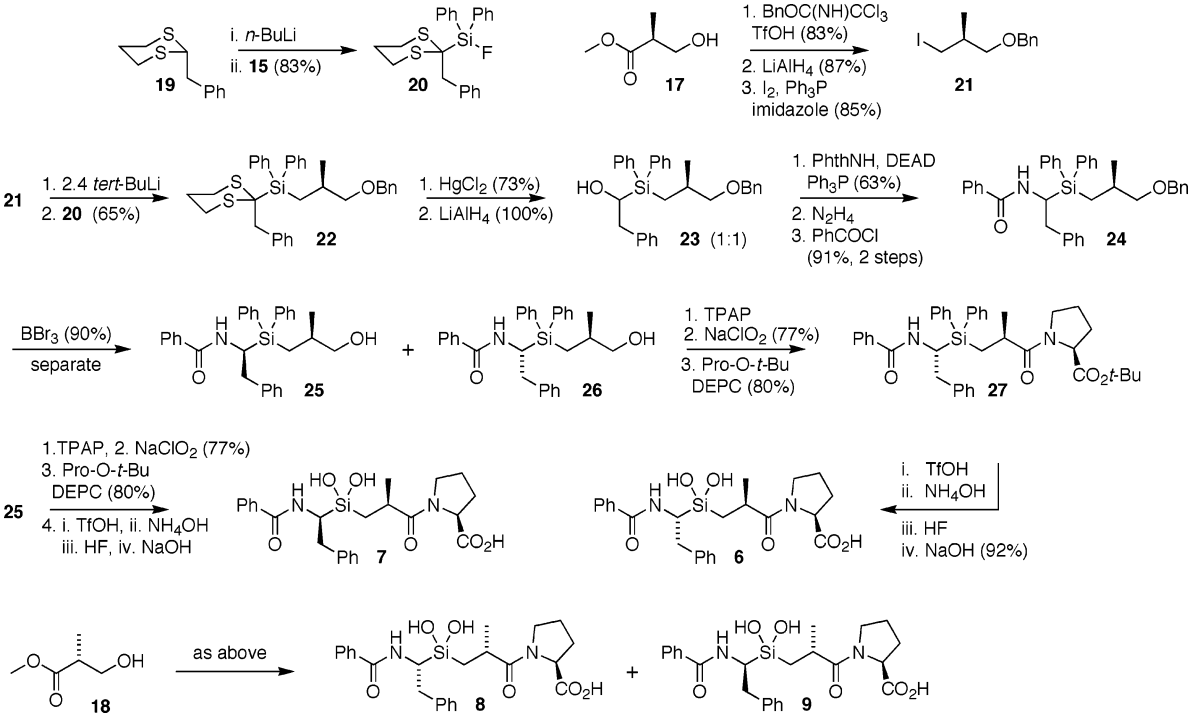
To prepare the individual stereoisomers **6**–**9**, we adopted the retrosynthetic plan shown in Scheme 1. Using our previously successful approach, acidic hydrolysis of a diphenylsilane to reveal the silanediol in the last stage of the synthesis,[6–8,19] the direct precursor of **6** became diphenylsilane **12**. α-Aminosilane **12** would be prepared from the ketone **13**. Indiscriminant reduction the carbonyl of **13** would yield two diastereomers, and ultimately both **6** and **7**. The ketone **13** would be prepared via three-component coupling of nucleophiles **14** and **16** with diphenyldifluorosilane **15**. The enantiomerically pure lithium reagent **16** would be derived from the commercially available (*S*)-**17**. In a similar fashion, silanediols **8** and **9** would be prepared from the commercially available (*R*) isomer **18**.

Assembly of the silanediols is shown in Scheme 2, which begins with dithiane **19**. Metalation of **19** followed by transfer of the anion to a slight excess of difluorodiphenylsilane at −78 °C gave the fluorosilane **20** in 83% yield, ready for introduction of the nucleophile **16**. Nucleophile **16** was prepared in four steps, beginning with (*S*)-**17**, following the method of White et al.[20] *O*-Benzylation of the alcohol using benzyl trichloromethylimidate (83%), followed by reduction of the ester by lithium aluminum hydride (87%) and conversion of the resulting alcohol to the iodide using iodine and triphenylphosphine (85%), gave **21**. This iodide was converted to the corresponding lithium reagent **16** using 2 equiv of *tert*-butyllithium.[21,22] Addition of this anion to fluorosilane **20** gave the silane **22** in 65% yield. Hydrolysis of the dithiane using mercuric chloride in aqueous acetonitrile gave the yellow, sensitive silyl ketone **13** (73%),[23–25] which was immediately reduced to a 1:1 mixture of diastereomeric alcohols **23** in quantitative yield.

Alcohols **23** proved to be difficult to separate and the next four stages of the syntheses were conveniently carried out on the diastereomeric mixture. Displacement of the alcohol with phthalimide using Mitsunobu conditions (63%), followed by removal of the phthalimide group using hydrazine, gave a primary amine that was condensed with benzoyl chloride to furnish amide **24** (91% for two steps). Removal of the benzyl protecting group with boron tribromide then gave a mixture of **25** and **26** (90%). With an alcohol and a secondary amide adjacent to the two stereogenic centers, these diastereomers could be readily separated over silica gel. For the two diastereomers, one of the stereogenic centers was established by its source in **17**, but the relatively remote α-aminosilane stereocenter of the (*S*,*S*) and (*S*,*R*) isomers was more difficult to define and was eventually resolved by X-ray crystallography (see below).

Completion of the silanediol synthesis was conducted using the individual stereoisomers **25** and **26**. Alcohol **26** was oxidized to the acid in two stages, using Ley's perruthinate method to give the aldehyde,[26] immediately followed by Pinnick oxidation[27] to the acid using buffered

SCHEME 2. Synthesis of Silanediols 6–9



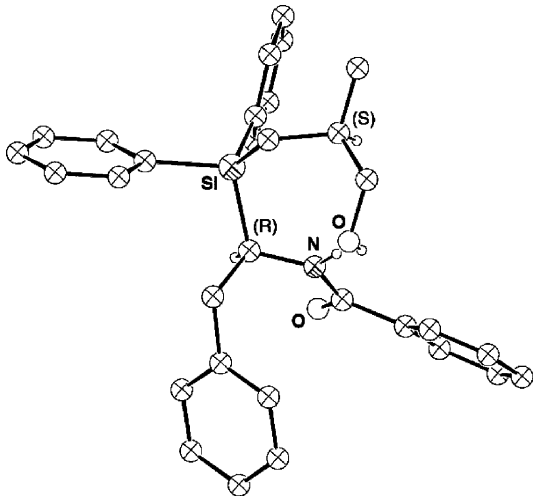


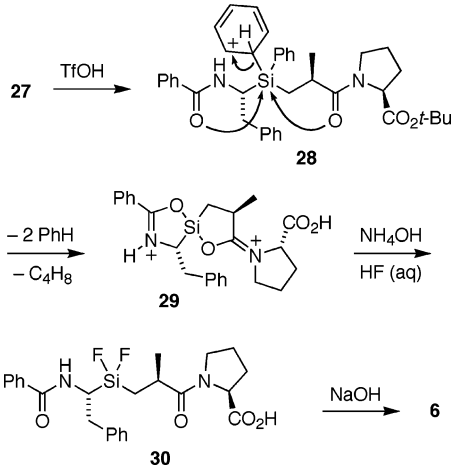
FIGURE 3. Crystal structure of alcohol **26**.

sodium chlorite (77% for the two steps). The acid was then coupled with the *tert*-butyl ester of L-proline using diethyl cyanophosphonate to give diamide **27** (80%).[28] The ultimate step in the preparation of the silanediol was acidic hydrolysis of the diphenylsilane **27** with simultaneous removal of the *tert*-butyl ester, to give the silanediol **6**, performed using triflic acid. The two remaining diastereomeric silanediols **8** and **9** were prepared from the (*R*) hydroxy ester **18**, with a set of reactions identical with those used with **17**.

It is notable that the L-proline adducts of the stereoisomers derived from (*S*)-alcohol **17** exhibited well-resolved signals in the NMR spectra. In contrast, the (*R*)-alcohol **18**-derived adducts with L-proline gave the appearance of a mixture in their NMR spectra. These were conformation/rotamer-based subspecies of the pure substances, shown by heating the samples to 105 °C in DMSO-d_6, which collapsed the multiplicity of NMR absorbances into a single set of peaks.

The hydroxyamide stereoisomer **26** provided crystals and a crystal structure, Figure 3, revealing the relative stereochemistry of the two stereogenic centers.[29] The crystal structure of **26** shows the alcohol forming an eight-membered ring hydrogen bond to the secondary amide. The derivation of **26** from (*S*)-**17** coupled with the relative stereochemistry shown in the crystal structure defined the absolute configurations of **25** and **26**, and therefore **6** and **7**. With the origin of **8** and **9** from (*R*)-**18**, the chromatographic properties of *ent*-**25** and *ent*-**26** fully clarified the identity of the stereoisomers of their progeny **8** and **9**, setting the stage for evaluation of their ability to inhibit ACE.

SCHEME 3. Hydrolysis of the Diphenylsilanes to Silanediols



Hydrolysis of the diphenylsilanes merits discussion. The protolytic cleavage of aryl groups from silicon is a long-established transformation, involving *ipso* protonation of the aromatic ring followed by cleavage of the silicon−carbon bond, a bond cleavage that requires simultaneous attack of a nucleophile on silicon, Scheme 3.[30] In the case of the diphenylsilane **27** and its stereoisomers, two amides are poised for intramolecular attack to yield a postulated spirocyclic intermediate **29**. Addition of ammonium hydroxide allows the silyl ethers, which are strained,[31] to hydrolyze to the silanediol. In some cases, the silanediol **6** can be isolated directly following the ammonium hydroxide treatment; however, acidic and basic conditions promote polymerization of dialkylsilanediols.[32] To counteract any oligomer formation, we have incorporated the addition of 48% HF to the hydrolysis procedure, which converts any silicon−heteroatom bond to a silicon−fluorine bond, yielding the monomeric difluorosilane **30**.[33,34] This procedure has proven to be particularly valuable for silanediols less sterically protected than **6**−**9**,[9] and when used with the compounds described here lead to very clean, monomeric difluorides and silanediols. As in prior examples, treatment of the difluorosilane **30** with sodium hydroxide led to a rapid hydrolysis to the silanediol.

Evaluation of the silanediols **6**−**9** was conducted using Holmquist's modification[35] of the enzyme assay described

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(29) Compound **26** crystallizes from acetonitrile in the monoclinic space group $P21$ with $a = 13.8822(8)$ Å, $b = 8.4270(6)$ Å, $c = 24.2031(14)$ Å, $b = 92.353(5)°$, $V = 2829.0(3)$ Å^3, $Z = 4$, and $d_{calc} = 1.126$ g/cm^3. Final least-squares refinement using 9016 unique reflections with $I > 3\sigma(I)$ gave R (R_w) = 0.1060 (0.1933).
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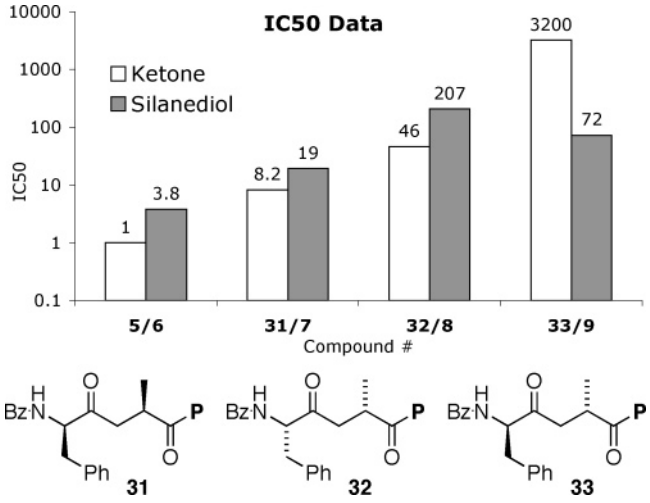

FIGURE 4. Comparative IC_{50} data for silanediols **6**−**9** and ketones **5** and **31**−**33**.[15] **P** indicates proline.

by Cushman and Cheung,[35,36] employing commercially available enzyme and fluorescent substrate,[37] and the results are shown in Figure 4. Gratifyingly, the potency of the most effective silanediol inhibitor **6** was nearly as effective as the corresponding ketone **5**, less inhibitory by a factor of 4. Similarly, silanediols **7** and **8** were slightly less potent inhibitors than the ketone diastereomers **31** and **32**, by a factor of 2.3 and 4.5, respectively, confirming the greater sensitivity of the methyl stereochemistry relative to the benzyl group. Surprisingly, inverting both stereogenic centers relative to the most potent inhibitors led to a silanediol (**9**) that was more potent of an inhibitor of ACE than simply changing the methyl stereochemistry (**8**). This is in stark contrast to the effect of these stereogenic centers with the ketone **33** where the effect is synergistic; inverting both stereogenic centers relative to **5** results in a structure with very low inhibitory activity. This result may indicate that the silanediol **9**, with its slightly altered bond lengths and bond angles relative to the carbonyl hydrate, can interact with the enzyme in a different manner. Additional studies are in progress.

Experimental Section

[[(2*R*)-3-Iodo-2-methylpropoxy]methyl]benzene (*ent*-21).[38] To a 0 °C solution of (2*S*)-2-methyl-3-(phenylmethoxy)-1-propanol[20] (3.99 g, 22.17 mmol), triphenylphosphine (6.30 g, 24.0 mmol), and imidazole (1.63 g, 23.9 mmol) in ether (40 mL) and CH_3CN (25 mL) under nitrogen was added a solution of iodine (6.05 g, 23.8 mmol) in ether (35 mL). The reaction was kept at 0 °C for 3.5 h. The solution was transferred to a separatory funnel with ether (50 mL). The solution was washed successively with saturated $Na_2S_2O_3$ (60 mL), saturated Cu_2SO_4 (30 mL), water (40 mL), and brine (40 mL). The organic portions were dried over $MgSO_4$, filtered, and concentrated. Cold hexanes was added to precipitate triphenylphosphine oxide, which was removed by vacuum filtration. The filtrate was concentrated and purified by flash chromatography (0:1−2:98 ethyl acetate/hexanes) to produce *ent*-**21** (5.47 g, 85%) as a clear oil.

(*S*)-21: $[\alpha]^{20}_D$ 14.5 (*c* 1.41, $CHCl_3$); IR (neat) 3029, 2868, 1453, 1361, 1199, 1100, 736, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39−7.26 (m, 5H), 4.53 (s, 2H), 3.43−3.28 (m, 4H), 1.85−1.75 (m, 1H), l.00 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 128.3, 127.6, 74.1, 73.1, 35.1, 17.6, 13.9.

(*R*)-*ent*-21: $[\alpha]^{20}_D$ −10.0 (*c* 5.4 CH_2Cl_2); R_f 0.42 (1:19 ethyl acetate/hexanes); IR (neat) 3029.0, 2960.6, 1453.3, 1361.7, 1101.3, 697.2 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.33 (m, 5H), 4.53 (s, 2H), 3.42−3.29 (m, 4H), 1.85−1.75 (m, 1H), l.00 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 128.3, 127.6, 74.0, 73.1, 35.1, 17.6, 13.9; exact mass (FAB) MH^+ calcd for $C_{11}H_{16}IO$ 291.0246, found 291.0240.

[2-(Phenylmethyl)-1,3-dithian-2-yl]fluorodiphenylsilane (20). To a 0 °C solution of 2-benzyl-1,3-dithiane (**19**) (9.86 g, 46.9 mmol) in THF (200 mL) was added *n*-butyllithium (2.5 M in hexane, 20.0 mL, 50 mmol). The resulting solution was stirred for 1.25 h at 0 °C, cooled to −78 °C, and then transferred by cannula to a −78 °C solution of diphenyldifluorosilane (12.46 g, 56.56 mmol) in THF (100 mL) over 10 min. After 1 h at −78 °C, the solution was allowed to gradually warm to room temperature over 5 h and then stirred overnight. After addition of water (200 mL), the aqueous phase was extracted with CH_2Cl_2 (3 × 200 mL). The combined organics were then washed with brine and dried over Na_2SO_4. The solution was concentrated and purified by flash chromatography (5:95 ethyl acetate/hexanes) to give **20** as a colorless solid (16.06 g, 83%). Mp 83−84 °C; R_f 0.42 (5:95 ethyl acetate/hexanes); IR (neat) 3112, 2924, 1442, 1289, 1121, 862, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94−7.27 (m, 15H), 3.34 (s, 2H), 2.73−2.67 (m, 2H), 2.52−2.45 (m, 2H), 1.80−1.76 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 135.4, 131.48, 131.39, 130.7, 127.8, 127.5, 126.9, 44.2, 38.0 (d due to F, J = 56.0 Hz), 25.6, 23.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −168.5; exact mass (FAB) $(M - H)^+$ calcd 409.0916, found 409.0911.

[(2*R*)-2-Methyl-3-(phenylmethoxy)-1-propyl][2-(phenylmethyl)-1,3-dithian-2-yl]diphenylsilane (*ent*-22). To a solution of [[(2*R*)-3-iodo-2-methylpropoxy]methyl]benzene (*ent*-**21**) (7.47 g, 25.8 mmol) in pentane (150 mL) and ether (105 mL) at −78 °C was added *tert*-butyllithium (1.38 M, 44.0 mL, 60.7 mmol) slowly over 2 min. After being stirred for 30 min at −78 °C, the solution was warmed to room temperature over 20 min, then recooled to −78 °C. this solution was transferred by cannula over 5 min to a −78 °C solution of (2-benzyl[l,3]-dithian-2-yl)fluorodiphenylsilane (**20**) (10.9 g, 26.6 mmol) in ether (105 mL). After 3 h at −78 °C the solution was allowed to slowly warm to room temperature over 6 h and kept at room temperature overnight. After addition of water (200 mL) and extraction of the aqueous phase with CH_2Cl_2 (3 × 250 mL), the combined organics were washed with brine, dried over Na_2SO_4, concentrated, and purified by flash chromatography (1:1 methylene chloride/hexanes) to give *ent*-**22** as a clear viscous oil (9.31 g, 65%): R_f 0.28 (5:95 ethyl acetate/hexanes); $[\alpha]^{20}_D$ 18.7 (*c* 0.87 $CHCl_3$); IR (neat) 3054, 2966, 1422, 1265, 911, 745, 650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06−7.41 (m, 20 H), 4.53 (s, 2H), 3.60 (s, 2H), 3.34−3.29 (m, 2H), 2.65−2.58 (m, 2H), 2.52−2.47 (m, 2H), 2.29−2.16 (m, 1H), 2.02−1.94 (m, 2H), 1.77 (dd, J = 4.2, 15.2 Hz, 1H), 1.34 (dd, J = 8.0, 15.2 Hz, 1H), 0.92 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz $CDCl_3$) δ 138.9, 138.4, 136.9, 133.2, 132.7, 131.5, 129.6, 128.2, 127.7, 127.4, 127.3, 126.7, 77.7, 72.6, 47.0, 37.6, 29.5, 25.2, 23.4, 20.3, 14.8; exact mass (FAB) MNa calcd for $C_{34}H_{38}ONaS_2Si$ 577.2031, found 577.2052.

(*S*)-22: $[\alpha]^{20}_D$ −16.6 (*c* 0.82, $CHCl_3$); IR (neat) 3003, 2900, 1467, 1427, 1101, 752, 704 cm^{-1}; ^1H NMR (300 MHz, $CDCI_3$) δ 7.84−7.17 (m, 20 H), 4.31 (s, 2H), 3.38 (s, 2H), 3.15−3.01 (m, 2H), 2.45−2.35 (m, 2H), 2.31−2.24 (m, 2H), 2.00−1.90 (m, 1H), 1.83−1.71 (m, 2H), 1.56 (dd, J = 4.9, 5.8 Hz, 1H), 1.12 (dd, J = 8.0, 7.4 Hz, 1H), 0.70 (d, J = 6.6 Hz, 3H); ^{13}C NMR (63 MHz $CDCl_3$) δ 138.9, 138.4, 136.9, 133.2, 132.7, 131.5, 129.6, 128.2, 127.7, 127.4, 127.3, 126.7, 77.7, 72.6, 47.0, 37.6,

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29.5, 25.2, 23.4, 20.3, 14.8; exact mass (FAB) $[M - H]^+$ calcd for $C_{34}H_{37}OS_2Si$ 553.2055, found 553.2051.

[(2*R*)-2-Methyl-3-(phenylmethoxy)-1-propyl][2-phenyl-1-oxoethyl]diphenylsilane. To a solution of [(2*R*)-2-methyl-3-(phenylmethoxy)-1-propyl][2-(phenylmethyl)-1,3-dithian-2-yl]diphenylsilane (*ent*-**22**) (1.71 g, 3.08 mmol) in CH_3CN (66 mL) was added $HgCl_2$ (4.27 g, 15.7 mmol) and water (8.5 mL). The resulting milky white suspension was stirred at room temperature for 1.25 h. The suspension was concentrated under reduced pressure, diluted with water (200 mL), and extracted thrice with 200-mL portions of hexanes. The combined organic extracts were washed with brine, dried over $MgSO_4$, and filtered through a 1 in. pad of Celite. The filtrate was concentrated under reduced pressure and purified by flash chromatography (1:9 ethyl acetate/hexanes) to give [(2*R*)-2-methyl-3-(phenylmethoxy)-1-propyl][2-phenyl-1-oxoethyl]diphenylsilane as a clear yellow oil (1.05 g, 73%): R_f 0.47 (1:9 ethyl acetate/hexanes); $[\alpha]^{20}_D$ 11.0 (*c* 1.65 $CHCl_3$); IR (neat) 3028.1, 2869.7, 1649.0, 1453.3, 1428.2, 1110.0, 734.8, 698.2 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60−6.84 (m, 20H), 4.29 (s. 2H), 3.84 (s, 2H), 3.17 (d, J = 6.3 Hz, 2H), 2.03−1.92 (m, 1H), 1.49 (dd, J = 6.0, 15.3 Hz, lH), 1.13 (dd, J = 8.1, 15.3 Hz, 1H), 0.83 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 240.2, 138.4, 135.5, 135.4, 132.8, 132.2, 132.1, 130.0, 129.8, 128.2, 128.0, 127.4, 127.3, 126.4, 77.2, 72.5, 55.6, 29.6, 20.3, 16.5; MS *m/e* (rel intensity) 487 (MNa, 3), 137 (26), 155 (11), 177 (100), 199 (38), 259 (26), 375 (30), 439 (24)

(*S*): $[\alpha]^{20}_D$ −11.5 (*c* 0.82 $CHCl_3$); IR (neat) 33069, 2822, 1648, 1421, 1111, 735, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60−6.84 (m, 20H), 4.31 (m. 2H), 3.84 (s, 2H), 3.17 (dd, J = 1.5, 6.5 Hz, 2H), 2.03−1.92 (m, 1H), 1.49 (dd, J = 5.9, 14.9 Hz, lH), 1.13 (dd, J = 7.9, 15.1 Hz, 1H), 0.83 (d, J = 6.6 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 240.5, 138.6, 135.6, 132.9, 132.3, 132.2, 130.0, 129.9, 128.3, 128.1, 127.5, 127.4, 126.5, 77.3, 72.6, 55.7, 29.6, 20.3, 16.5; exact mass (FAB) (MNa^+) calcd for $C_{31}H_{32}O_2SiNa$ 487.2069, found 487.2048.

[(2*R*)-2-Methyl-3-(phenylmethoxy)-1-propyl][2-phenyl-1-hydroxyethyl]diphenylsilane (*ent*-23). To a 0 °C solution of $LiAlH_4$ (0.206 g, 5.4 mmol) in ether (40 mL) was added dropwise a solution of 1-[(3-benzyloxy-2(*R*)-methylpropyl)-diphenylsilanyl]-2-phenylethanone (0.51 g, 1.1 mmol) in ether (10 mL) over 10 min. The reaction mixture was maintained at 0 °C for 1 h and then warmed to room temperature over 2 h. The reaction was quenched with water (1 mL), 1 M NaOH (1 mL), and water (2 mL). $MgSO_4$ was added and the solution was filtered and concentrated to afford a clear oil that was purified by flash chromatography (2:98−1:4 ethyl acetate/hexanes) to give a mixture of the two diastereomers 1-[(3-benzyloxy-2(*R*)-methylpropyl)diphenylsilanyl]-2-phenylethanol (*ent*-**23**) as a clear colorless oil (0.51 g, quantitative): R_f 0.36 (1:9 ethyl acetate/hexanes); IR (neat) 3549.8, 3027.1, 2855.4, 1453.3, 1427.2, 1109.0, 1076.2, 733.9, 699.2 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81−7.27 (m, 20H), 4.49 (s, 1H), 4.43 (d, J = 6.4 Hz, 1H), 4.26−4.24 (m, 1H), 3.36−3.31 (m, 2H), 3.04−2.99 (m, lH), 2.85−2.78 (m, 1H), 2.22−2.16 (m, 1H), 1.99 (br s, 1H), 1.66 (dd, J = 5.6, 14.8 Hz, 1H), 1.25 (dd, J = 8.0, 14.8 Hz, 1H), 1.01 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 138.4, 135.5, 134.3, 134.1, 129.4, 129.0, 128.4, 128.2, 127.8, 127.5, 127.4, 126.2, 77.6, 72.7, 65.2, 39.8, 29.6, 20.6, 15.6; exact mass (FAB) (MNa^+) calcd for $C_{31}H_{34}O_2SiNa$, 489.2226, found 489.2235.

(*S*)-23: IR (neat) 3412, 3022, 2901, 1420, 1113, 721, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67−7.14 (m, 20H), 4.38 (s, 1H), 4.33 (d, J = 2.7 Hz, 1H), 4.18−4.10 (m, 1H), 3.22 (t, J = 6.3 Hz, 2H), 2.94−2.85 (m, lH), 2.74−2.63 (m, 1H), 2.09−2.01 (m, 1H), 1.78 (dd, J = 4.2, 23.5 Hz, 1H), 1.49−1.39 (m, IH), 1.17−0.99 (m, 1H), 0.87 (dd, J = 2.6, 6.6 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 139.8, 138.47, 135.57, 134.45, 134.21, 129.5, 129.1, 128.52, 128.50, 127.90, 127.58, 127.42, 126.30, 77.7, 72.8, 65.3, 39.9, 29.7, 20.6, 15.8.

2-[[1-[(2*R*)-2-Methyl-3-(phenylmethoxy)-1-propyl]diphenylsilyl]-2-phenylmethyl]-1*H*-isoindole-1,3(2*H*)-dione. To a solution of the mixture of two diastereomers of 1-[(3-benzyloxy-2(*R*)-methylpropyl)diphenylsilanyl]-2-phenylethanol (*ent*-**23**) (0.568 g, 1.22 mmol), phthalimide (0.248 g, 1.68 mmol), and triphenylphosphine (0.48 g, 1.83 mmol) in THF (12.0 mL) at 0 °C was added diethyl azodicarboxylate (DEAD, 0.36 mL, 2.28 mmol) over 2 min. The flask was removed from the cooling bath, and the resulting yellow solution was stirred at room temperature for 24 h. The resulting mixture was concentrated and purified by flash chromatography (2:98−1:9 ethyl acetate/hexanes) to provide an inseparable mixture of the two diastereomers of 2-[1-[(3-benzyloxy-2(*R*)-methylpropyl)diphenylsilanyl]-2-phenylethyl]isoindole-1,3-dione as a viscous oil (0.458 g, 63%): R_f 0.32 (15:85 ethyl acetate/hexanes); IR (neat) 3027.1, 2855.4, 1773.4, 1705.9, 1454.2, 1385.8, 1102.3, 735.8, 699.2 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80−7.15 (m, 24H), 4.83 (t, J = 13.2 Hz, 1H), 4.42 (s, 2H), 3.50−3.40 (m, 1H), 3.31−3.17 (m, 3H), 2.08−2.00 (m, 1H), 1.77 (dd, J = 4.8, 9.6 Hz, 1H), 1.34 (dd, J = 4.8, 15.2 Hz, 1H), 0.90 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1 (br), 139.2, 138.6, 135.7, 135.4, 134.1, 133.9, 133.3, 133.2, 131.6, 129.6, 128.5, 128.2, 127.8, 127.6, 127.4, 127.2, 126.2, 77.4, 72.4, 41.6, 35.0, 29.5, 20.2, 16.0; exact mass (FAB) MNa, calcd for $C_{39}H_{37}NO_3NaSi$ 618.2440, found 618.2432.

(*S*): IR (neat) 3021, 1724, 1408, 1112, 721, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62−6.96 (m, 24H), 4.61 (t, J = 13.2 Hz, 1H), 4.24 (s, 2H), 3.31−3.20 (m, 1H), 3.11−2.98 (m, 3H), 1.87−1.82 (m, 1H), 1.56 (dd, J = 4.8, 8.0 Hz, 1H), 1.14 (dd, J = 8.8, 15.2 Hz, 1H), 0.70 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8 (br), 139.2, 138.6, 135.6, 135.5, 135.4, 134.0, 133.3, 133.2, 131.5, 129.6, 128.4, 128.1, 127.7, 127.3, 127.2, 126.2, 77.4, 72.5, 41.9, 35.1, 29.5, 20.3, 16.1; exact mass (FAB) MNa^+, calcd for $C_{39}H_{37}NO_3SiNa$ 618.2440, found 618.2427.

[(2*R*)-2-Methyl-3-(phenylmethoxy)-1-propyl][1-(benzoylamino)-2-phenylethyl]diphenylsilane (*ent*-24). To a solution of 1-{[(3-benzyloxy-2(*R*)-methylpropyl)diphenylsilanyl]-2-phenylethyl}isoindole-1,3-dione (135 mg, 0.227 mmol) in absolute ethanol (3.5 mL) was added hydrazine (0.10 mL, 3.1 mmol), and the mixture was heated to reflux for 6 h, during which a white precipitate was observed. The mixture was cooled and filtered through a plug of glass wool, concentrated, resuspended in ether, and filtered through a short pad of silica gel. The filtrate was concentrated, diluted with ether (3.0 mL) and saturated $NaHCO_3$ (1.0 mL), and cooled to 0 °C. Benzoyl chloride (0.03 mL, 36.3 mg, 0.258 mmol) was added and after 1.5 h the solution was washed with saturated NH_4Cl solution. The aqueous portion was extracted with ether (3 × 10 mL), and the combined organic extracts were washed with saturated NaCl (15 mL), dried over Na_2SO_4, concentrated, and purified by flash column chromatography (2:98−1:4 ethyl acetate/hexanes) to yield a mixture of diastereomers of *ent*-**24** (117 mg, 91%): R_f 0.27 (15:85 ethyl acetate/hexanes); IR (neat) 3027.1, 2906.6, 1658.7, 1650.0, 1643.3, 1601.8, 1515.0, 1486.1, 1313.5, 1105.2, 1076.2, 733.9, 698.2 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51−7.02 (m, 25H), 5.89 (d, J = 10.4 Hz, 1H), 4.77−4.71 (m, 1H), 4.24 (d, J = 4.4 Hz, 2H), 3.06−2.92 (m, 3H), 2.50 (t, J = 14.0 Hz, 1H), 1.84−1.76 (m, 1H), 1.38 (dd, J = 4.8, 8.0 Hz, 1H), 0.97−0.90 (m, 1H), 0.70 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 139.1, 138.4, 135.5, 135.4, 135.3, 133.7, 133.3, 132.9, 130.8, 129.8, 128.8, 128.32, 128.22, 128.09, 127.6, 127.4, 127.3, 126.4, 126.1, 77.6, 72.8, 38.9, 37.7, 29.6, 20.4, 16.2; exact mass (FAB) (MH^+) calcd for $C_{38}H_{40}NO_2Si$ 570.2828, found 570.2809.

(S)-24: IR (neat) 3428, 3312, 3104, 2881, 1688, 1541, 1485, 1112, 721, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52−7.04 (m, 25H), 5.93 (d, J = 10.0 Hz, 1H), 4.80−4.73 (m, 1H), 4.25 (d, J = 4.4 Hz, 2H), 3.11−2.95 (m, 3H), 2.52 (t, J = 11.2 Hz, 1H), 1.87−1.79 (m, 1H), 1.42 (dd, J = 4.8, 9.6 Hz, 1H), 1.00−0.92 (m, 1H), 0.72 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 139.1, 138.4, 135.5, 135.4, 135.3, 133.6, 133.3, 132.8, 130.8, 129.8, 128.8, 128.3, 128.2, 128.1, 127.6, 127.4,

127.3, 126.4, 126.1, 77.6, 72.8, 38.9, 37.6, 29.6, 20.4, 16.2; exact mass (FAB) (MH^+) calcd for $C_{38}H_{40}NO_2Si$ 570.2828, found 570.2854.

[(2*R*)-2-Methyl-3-(phenylmethoxy)-1-propyl][1-amino-2-phenylethyl]diphenylsilane. A sample of the intermediate amine was also characterized: IR (neat) 3359, 3083, 2908, 1494, 1427, 1109, 732, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56−7.02 (m, 20H), 4.26 (s, 2H), 3.13−3.05 (m, 2H), 2.99−2.93 (m, 2H), 2.21 (t, J = 12.8 Hz, 1H), 1.91−1.86 (m, 1H), 1.40 (t, J = 5.2 Hz, 1H), 0.96 (dd, J = 5.2, 8.8 Hz, 1H), 0.87 (br s, 2H), 0.77 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 138.6, 135.6, 134.1, 134.0, 129.4, 128.9, 128.3, 127.8, 127.3, 126.0, 77.7, 72.6, 41.3, 40.3, 29.6, 20.4, 15.7; exact mass (FAB) MNa^+ calcd for $C_{31}H_{36}NOSiNa$ 466.2566, found 466.2561.

[(2*R*)-2-Methyl-3-hydroxy-1-propyl][(1*S*)-1-(benzoylamino)-2-phenylethyl]diphenylsilane and [(2*R*)-2-Methyl-3-hydroxy-1-propyl][(1*R*)-1-(benzoylamino)-2-phenylethyl]-diphenylsilane (*ent*-25 + *ent*-26). To a −78 °C solution of *N*-[1-[(3-benzyloxy-2(*R*)-methylpropyl)diphenylsilanyl]-2-phenylethyl]benzamide (*ent*-**24**) (460 mg, 0.807 mmol) in CH_2Cl_2 (8.2 mL) was slowly added BBr_3 (2.42 mL, 1.0 M in CH_2C1_2) and the resulting solution was stirred and allowed to warm to room temperature over 5 h. The solution was recooled to −78 °C and methanol (4 mL) was carefully added. The mixture was warmed to room temperature over 20 min and concentrated, and the resulting oil was then taken up in CH_2Cl_2 (20 mL) and transferred to a separatory funnel, and water was added until the yellow color had faded (10 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organics were washed with brine (20 mL), dried over Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (2:98−1:4 ethyl acetate/hexanes) to yield (*S*,*R*)-*ent*-**26** (higher R_f, 191.5 mg, 49.5%) and (*R*,*R*)-*ent*-**25** (lower R_f, 153.3 mg, 40%).

(*S*,*R*)-*ent*-26: $[\alpha]^{20}_D$ 80 (*c* 0.1, CH_2Cl_2); R_f 0.29 (4:6 ether/hexanes); IR (neat) 3310.6, 3036.6, 2922.0, 1633.6, 1539.1, 1427.2, 1326.0, 1109.0, 698.2 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67−7.13 (m, 20H), 5.91 (d, J = 10.0 Hz, 1H), 4.94 (dt, J = 4.4, 12.0 Hz, 1H), 3.49 (dd, J = 4.8, 10.4 Hz, lH), 3.23−3.17 (m, 2H), 2.57 (dd, J = 12.0, 14.8 Hz, 1H), 2.47 (br s, 1H), 1.86−1.82 (m, 1H), 1.51 (dd, J = 5.2, 14.8 Hz, 1H), 0.91 (dd, J = 8.0, 15.2 Hz, 1H), 0.67 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDC1_3$) δ 167.4, 139.0, 135.5, 135.4, 134.7, 133.3, 133.1, 131.1, 130.0, 129.9, 128.6, 128.4, 128.3, 128.2, 128.1, 126.5, 126.3, 69.8, 38.9, 37.2, 31.7, 19.9, 15.5; exact mass (FAB) (MH^+) calcd for $C_{31}H_{34}NO_2Si$ 480.2359, found 480.2353.

(*R*,*R*)-*ent*-25: $[\alpha]^{20}_D$ −90 (*c* 0.2, CH_2Cl_2); R_f 0.24 (4:6 ether/hexanes); IR (neat) 3317.4, 3067.6, 2923.9, 1644.2, 1517.9, 1316.3, 1109.0, 698.2 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67−7.09 (m, 20H), 5.89 (d, J = 10.0 Hz, 1H), 4.83 (dt, J = 4.4, 10.8 Hz, 1H), 3.31 (dd, J = 6.0, 10.8 Hz, 1H), 3.25 (dd, J = 6.4, 10.4 Hz, 1H), 3.15 (dd, J = 4.4, 14.8 Hz, 1H), 2.64 (dd, J = 10.8, 14.4 Hz, 1H), 1.78 (br s, 1H), 1.76−1.70 (m, 1H), 1.37 (dd, J = 5.6, 14.8 Hz, 1H), 1.06 (dd, J = 8.0, 15.2 Hz, 1H), 0.75 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDC1_3$) δ 167.0, 139.1, 135.5, 135.3, 135.1, 133.8, 133.0, 131.0, 129.9, 128.8, 128.4, 128.2, 126.5, 126.2, 70.0, 39.0, 37.6, 32.0, 19.8, 16.1; exact mass (FAB) (MH^+) calcd for $C_{31}H_{34}NO_2Si$ 480.2359, found 480.2371.

(*R*,*S*)-26: $[\alpha]^{20}_D$ −45 (*c* 0.24, $CHCl_3$); IR (neat) 3300, 3086, 2902, 1634, 1520, 1421, 1105, 699 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.67−7.11 (m, 20H), 5.85 (d, J = 10.0 Hz, 1H), 4.94 (m, 1H), 3.49 (dd, J = 4.9, 10.6 Hz, lH), 3.23−3.17 (m, 2H), 2.57 (dd, J = 11.8, 14.8 Hz, 1H), 2.07 (s, 1H), 1.91−1.78 (m, IH), 1.51 (dd, J = 5.4, 15.0 Hz, 1H), 0.91 (dd, J = 7.7, 15.0 Hz, 1H), 0.67 (d, J = 6.7 Hz, 3H); ^{13}C NMR (63 MHz, $CDC1_3$) δ 128.5, 167.5, 139.1, 135.6, 135.5, 134.7, 133.3, 133.2, 131.2, 130.04, 129.98, 128.6, 128.3, 128.2, 126.6, 126.3, 69.9, 38.9, 37.3, 31.8, 19.9, 15.6.

(*S*,*S*)-25: $[\alpha]^{20}_D$ 72.5 (*c* 0.4, $CHCl_3$); IR (neat) 3389, 3301, 3084, 2901, 1640, 1512, 1419, 1097, 688 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.67−7.09 (m, 20H), 5.86 (d, J = 9.9 Hz, 1H), 4.83 (m, 1H), 3.36−3.22 (m, 2H), 3.15 (dd, J = 4.4, 14.5 Hz, 1H), 2.64 (dd, J = 10.9, 14.5 Hz, 1H), 1.79−1.66 (m, 1H), 1.60 (s, 1H), 1.37 (dd, J = 5.6, 15.1 Hz, 1H), 1.06 (dd, J = 8.0, 15.0 Hz, 1H), 0.75 (d, J = 6.7 Hz, 3H); ^{13}C NMR (63 MHz, $CDC1_3$) δ 167.0, 128.5, 128.3, 139.2, 135.5, 135.3, 135.2, 133.8, 133.1, 130.99, 129.95, 128.2, 126.5, 126.3, 70.1, 39.0, 37.7, 32.1, 19.9, 16.2. 129.92, 128.9; exact mass (FAB) (MH^+) calcd for $C_{31}H_{34}NO_2Si$ 480.2359, found 480.2376.

(2*R*)-3-[[(1*R*)-1-(Benzoylamino)-2-phenylethyl]diphenylsilyl]-2-methylpropanoic Acid. To a solution of *N*-[1-(*R*)-[(3-hydroxy-2(*R*)-methylpropyl)diphenylsilanyl]-2-phenylethyl]-benzamide ((*R*,*R*)-*ent*-**25**) (88 mg, 0.183 mmol) in CH_2Cl_2 (1.0 mL) at room temperature were added consecutively *N*-methylmorpholine *N*-oxide (27 mg, 0.23 mmol), powdered 4 Å molecular sieves (300 mg), and TPAP (3.8 mg, 0.011 mmol). The solution was stirred for 2.5 h, then filtered through a pad of silica with 1:9 ethyl acetate/CH_2Cl_2. Concentration of the filtrate produced the crude aldehyde as a clear colorless oil.

To the aldehyde in *t*-BuOH (4.0 mL) and water (1.0 mL) was added NaH_2PO_4 (42.0 mg, 0.35 mmol) and 2-methyl-2-butene (1.0 mL), followed by addition of $NaClO_2$ (25.9 mg, 0.28 mmol). The resulting solution was stirred at room temperature for 4 h and then diluted with saturated NH_4Cl (12 mL) and CH_2Cl_2 (10 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with saturated NaCl (15 mL), dried over Na_2SO_4, concentrated, and purified by flash column chromatography (2:98 methanol/methylene chloride) to afford 3-[(1(*R*)-benzoylamino-2-phenylethyl)diphenylsilanyl]-2(*R*)-methylpropionic acid as a white foam (69 mg, 77%).

(*R*,*R*): $[\alpha]^{20}_D$ −7.8 (*c* 1.0, CH_2Cl_2); R_f 0.44 (1:15 methanol/methylene chloride); IR ($CHCl_3$) 3684.8, 3619.2, 3021.3, 1705.9, 1652.9, 1516.9, 1428.2, 1217.9, 1110.9, 928.7, 771.5 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63−7.13 (m, 20 H), 5.92 (d, J = 10 Hz, 1H), 4.85 (dt, J = 4.0, 10.8 Hz, 1H), 3.15 (dd, J = 4.0, 14.4 Hz, 1H), 2.60 (dd, J = 10.8, 14.4 Hz, 1H), 2.53−2.48 (m, 1H), 1.71 (dd, J = 7.2, 14.8 Hz, 1H), 1.31 (dd, J = 6.8, 15.2 Hz, 1H), 1.07 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDC1_3$) δ 182.2, 167.1, 138.9, 135.5, 135.3, 134.9, 132.7, 132.0, 131.0, 130.0, 128.8, 128.4, 128.2, 126.5, 126.3, 38.8, 37.3, 35.0, 20.5, 16.3; exact mass (FAB) MNa^+ calcd for $C_{31}H_{31}NO_3NaSi$ 516.1971, found 516.1965.

(*S*,*R*): $[\alpha]^{20}_D$ 8.3 (*c* 0.7, CH_2Cl_2); R_f 0.44 (1:15 methanol/methylene chloride); IR ($CHCl_3$) 3684.8, 3625.9, 3024.2, 1705.0, 1652.7, 1519.8, 1428.2, 1219.0, 1045.4, 928.7, 772.4 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63−7.07 (m, 20 H), 6.08 (d, J = 10.4 Hz, 1H), 4.93 (dt, J = 3.6, 11.2 Hz, 1H), 3.10 (dd, J = 4.0, 14.8 Hz, 1H), 2.58 (dd, J = 12.0, 14.4 Hz, 1H), 2.52−2.47 (m, 1H), 1.73 (dd, J = 8.0, 15.2 Hz, 1H), 1.18 (dd, J = 6.0, 14.4 Hz, 1H), 1.00 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDC1_3$) δ 178.8, 167.0, 139.0, 135.0, 134.5, 132.8, 132.4, 130.6, 129.6, 129.5, 128.5, 127.9, 127.80, 127.77, 127.69, 126.4, 125.8, 39.1, 36.5, 34.6, 19.8, 15.7; exact mass (FAB) MH^+ calcd for $C_{31}H_{32}NO_3Si$ 494.2151, found 494.2174.

(*R*,*S*): mp 70−72 °C; $[\alpha]^{20}_D$ −48.6 (*c* 0.7, $CHCl_3$); R_f 0.44 (1:15 methanol/methylene chloride); IR (neat) 3345, 3080, 2912, 1721, 1647, 1535, 1431, 1120, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63−7.13 (m, 20 H), 5.90 (d, J = 10.0 Hz, 1H), 4.87 (dt, J = 4.0, 11.6 Hz, 1H), 3.15 (dd, J = 4.0, 14.8 Hz, 1H), 2.66−2.56 (m, 2H), 1.71 (dd, J = 5.6, 15.2 Hz, 1H), 1.25 (dd, J = 7.2, 16.0 Hz, 1H), 0.94 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.6, 167.6, 138.8, 135.5, 135.4, 134.5, 132.2, 132.0, 131.3, 130.2, 128.7, 128.5, 128.3, 126.6, 126.4, 39.0, 37.2, 34.9, 19.6, 16.5; exact mass (FAB) (MH^+) calcd for $C_{31}H_{32}NO_3Si$ 494.215, found 494.214.

(*S*,*S*): mp 78−80 °C; $[\alpha]^{20}_D$ 50.3 (*c* 0.4, $CHCl_3$); R_f 0.44 (1:15 methanol/methylene chloride); IR (neat) 3310, 3062, 2912, 1710, 1528, 1421, 1115, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63−7.13 (m, 20 H), 5.84 (d, J = 10.0 Hz, 1H), 4.83 (dt, J = 4.4, 11.2 Hz, 1H), 3.17 (dd, J = 4.0, 14.4 Hz, 1H), 2.60 (dd, J = 11.2, 14.4 Hz, 1H), 2.56−2.46 (m, 1H), 1.73 (dd, J = 7.6,

15.2 Hz, 1H), 1.32 (dd, J = 6.8, 15.2 Hz, 1H), 1.06 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.0, 167.1, 138.9, 135.5, 135.4, 135.0, 132.7, 132.0, 131.0, 130.1, 128.9, 128.4, 128.2, 126.5, 126.3, 38.8, 37.4, 35.0, 20.5, 16.3; exact mass (FAB) (MNa^+) calcd for $C_{31}H_{31}NO_3SiNa$ 516.1971, found 516.1976.

(2*S*)-1-[3-[[(1*R*)-1-(Benzoylamino)-2-phenylethyl]diphenylsilyl]-2-methyl-1-oxopropyl]-l-proline 1,1-Dimethylethyl Ester (27). To a 0 °C solution of 3-[(1-(*R*)-benzoylamino-2-phenylethyl)diphenylsilanyl]-2(*S*)-methylpropionic acid (50.4 mg, 0.102 mmol) and l-proline *tert*-butyl ester (25.3 mg, 0.148 mmol) in DMF (2 mL) was added diethyl cyanophosphonate (19 μL, 0.12 mmol) followed by triethylamine (32 L, 0.23 mmol). The reaction was maintained at 0 °C for 3 h, and warmed to room temperature overnight. The mixture was diluted with ethyl acetate (10 mL) and water (5 mL), the organic phase was washed with 5-mL portions of 5% HCl, saturated $NaHCO_3$, water, and saturated NaCl, dried over Na_2SO_4, concentrated, and purified by flash column chromatography (30:70, ethyl acetate/hexanes) to give **27** (*RS*) as a colorless foam (53.1 mg, 80%): mp 65−66 °C; R_f 0.47 (1:2 ethyl acetate/hexanes); $[\alpha]^{20}_D$ −61.8 (*c* 0.22, $CHCl_3$); IR (KBr) 3321, 2929, 1724, 1637, 1617, 1511, 1278, 1165, 707 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82−7.00 (m, 21H, including NH), 4.69−4.63 (m, 1H), 3.55 (dd, J = 3.6, 8.4 Hz, 1H), 3.05−3.02 (m, 1H), 2.99 (dd, J = 4.4, 14.0 Hz, 1H), 2.77 (dd, J = 9.2, 14.0 Hz, 1H), 2.42−2.37 (m, 1H), 2.30−2.25 (m, 1H), 1.63−1.51 (m, 5H), 1.35 (s, 9H), 1.23−1.19 (m, 1H), 1.12 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 170.9, 167.3, 139.5, 135.5, 135.3, 135.2, 134.2, 130.8, 129.6, 129.3, 128.3, 127.9, 127.7, 127.3, 126.0, 80.9, 58.9, 45.8, 39.5, 37.5, 34.8, 28.6, 27.9, 24.1, 21.5, 13.8; exact mass (FAB) MH^+ calcd for $C_{40}H_{47}N_2O_4Si$ 647.336, found 647.331.

(*S*,*S*): 36 mg, 73%; mp 150−151 °C; $[\alpha]^{20}_D$ 19.3 (*c* 0.27, $CHCl_3$); R_f 0.45 (1:2 ethyl acetate/hexanes); IR (KBr) 3304, 2921, 1732, 1644, 1631, 1545, 1420, 1153, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59−7.12 (m, 20H), 6.56 (d, J = 10.0 Hz, 1H), 4.75 (dt, J = 4.0, 11.2 Hz, 1H), 4.20 (dd, J = 4.0, 8.4 Hz, 1H), 3.37−3.32 (m, 1H), 3.19 (dd, J = 4.0, 14.0 Hz, 1H), 2.97−2.91 (m, 1H), 2.70−2.64 (m, 1H), 2.52 (dd, J = 11.2, 14.0 Hz, 1H), 2.02−1.72 (m, 5H), 1.43 (s, 9H), 1.29−1.24 (m, 1H), 1.20 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 171.4, 166.8, 139.4, 135.6, 135.3, 135.2, 133.9, 133.1, 130.8, 129.7, 128.9, 128.3, 128.0, 127.97, 127.92, 126.7, 126.0, 80.9, 59.5, 46.4, 38.9, 37.6, 34.0, 28.9, 28.0, 24.5, 21.7, 16.2; exact mass (El) MH^+ calcd for $C_{40}H_{47}N_2O_4Si$ 647.3305, found 647.3319.

(*R*,*R*): R_f 0.42 (1:2 ethyl acetate/hexanes); IR (KBr) 3423, 2975, 1736, 1638, 1527, 1426, 1151, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74−7.13 (m, 20H), 5.96 (d, J = 9.6 Hz, 1H), 4.78−4.72 (m, 1H), 3.00 (dd, J = 4.0, 14.4 Hz, 1H), 3.61 (dd, J = 3.8, 8.0 Hz, 1H), 3.13−3.06 (m, 8H), 2.85−2.71 (m, 3H), 2.60−2.32 (m, 5H), 2.08−2.01 (m, 1H), 1.81−1.38 (m, 12H), 1.35 (s, 9H), 1.34 (s, 9H), 1.09 (d, J = 6.8 Hz, 3H), 1.04 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCI_3$) δ 176.8, 171.5, 166.9, 139.6, 135.6, 135.3, 133.9, 133.3, 132.7, 130.8, 129.9, 129.6, 129.0, 128.4, 128.2, 128.1, 127.9, 126.7, 126.1, 81.7, 59.7, 46.6, 39.4, 37.4, 33.9, 31.2, 27.9, 24.6, 22.2, 17.7; exact mass (FAB) MNa, calcd for $C_{40}H_{46}N_2O_4NaSi$ 669.3125, found 669.3143.

(*S*,*R*): R_f 0.42 (1:2 ethyl acetate/hexanes); IR (KBr) 3450, 2976, 1737, 1641, 1626, 1425, 1151, 1108, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74−7.13 (m, 40H), 6.00 (d, J = 10.0 Hz, 1H), 4.78−4.72 (m, 2H), 4.23 (dd, J = 3.6, 8.4 Hz, 1H), 3.61 (dd, J = 3.8, 8.0 Hz, 1H), 3.13−3.06 (m, 8H), 2.85−2.71 (m, 3H), 2.60−2.32 (m, 5H), 2.08−2.01 (m, 1H), 1.81−1.38 (m, 12H), 1.35 (s, 9H), 1.34 (s, 9H), 1.09 (d, J = 6.8 Hz, 3H), 1.04 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 171.3, 167.3, 139.4, 135.7, 135.5, 135.3, 134.9, 133.5, 130.8, 129.9, 129.7, 129.2, 128.9, 128.3, 128.2, 128.1, 127.2, 126.6, 126.1, 81.7, 59.5, 46.5, 39.2, 37.5, 34.6, 29.7, 27.9, 24.6, 22.2, 16.0; exact mass (FAB) MNa, calcd for $C_{40}H_{46}N_2O_4NaSi$ 669.3125, found 669.3142.

(2*S*)-1-[3-[[(1*S*)-1-(Benzoylamino)-2-phenylethyl]difluorosilyl]-2-methyl-1-oxopropyl]-l-proline (30). To a 0 °C solution of (*S*,*S*)-**27** (70 mg, 0.108 mmol) in CH_2Cl_2 (5.0 mL) was added trifluoromethane sulfonic acid (0.60 mL, 2.8 mmol). After 1 h the solution was diluted with CH_2Cl_2 (10.0 mL), followed by 14.8 N NH_4OH (0.30 mL). The solution was stirred for 35 min at 0 °C and 48% HF solution (0.20 mL) was added, to give a pH of 2−3. Stirring was continued for 10 min. After addition of CH_2Cl_2 (20 mL), the solution was washed with water (10 mL) and saturated NaCl (10 mL), dried over Na_2SO_4, filtered, and concentrated to give (*S*,*S*)-**30** (47 mg, 92%) as a light yellow solid: R_f 0.75 on RP-TLC (C_{18}, 1:1 ethanol/water); mp 90−91 °C dec; IR (KBr) 3419, 2961, 1734, 1605, 1559, 1456, 1333, 1190, 707 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 9.10 (br s, 1H), 7.99−7.20 (m, 10H), 4.15 (dd, J = 2.8, 8.0 Hz, 1H), 3.56−3.47 (m, 2H), 3.24−3.15 (m, 2H), 2.93−2.73 (m, 2H), 1.86−1.81 (m, 2H), 1.60−1.56 (m, 2H), 1.22−1.18 (m, 1H), 1.13 (d, J = 6.8 Hz, 3H), 1.04−1.01 (m, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 178.1, 173.0, 170.3, 141.3, 134.2, 130.0, 129.7, 129.2, 128.8, 127.0, 59.7, 47.5, 44.6 (dd, J = 20.9, 30.3 Hz, due to F), 37.0, 34.6, 28.7, 25.2, 23.0 (dd, J = 19.2, 24.9 Hz, due to F), 20.7; ^{19}F NMR (376 MHz, acetone-d_6) δ 0.00 ($CFCl_3$), −122.7, −123.8; exact mass (FAB) M − F^+ calcd for $C_{24}H_{28}N_2O_4FSi$ 455.1802, found 455.1812.

(*R*,*S*): R_f 0.72 on RP-TLC (C_{18}, 1:1 ethanol/water); mp 150−151 °C dec; IR (KBr) 3451, 2968, 1726, 1628, 1606, 1442, 1096, 702 cm^{-1}; ^{1}H NMR (400 MHz, 1% D_2O in acetone-d_6) δ 7.91−7.17 (m, 10H), 4.21 (dd, J = 4.0, 8.4 Hz, 1H), 3.60−3.56 (m, 2H), 3.20−3.06 (m, 2H), 2.96−2.88 (m, 2H), 1.90−1.77 (m, 4H), 1.10 (d, J = 6.8 Hz, 3H), 0.86−0.82 (m, 2H); ^{13}C NMR (100 MHz, acetone-d_6) δ 178.5, 173.0, 170.7, 141.3, 134.2, 130.0, 129.8, 129.7, 129.3, 128.9, 127.1, 59.9, 47.6, 44.3 (t, J = 25.2 Hz, due to F), 36.9, 34.6, 28.7, 25.3, 22.7 (t, J = 20.0 Hz, due to F), 20.9; ^{19}F NMR (376 MHz, acetone-d_6) δ 0.00 ($CFCl_3$), −127.7, −131.5; exact mass (FAB) M − F^+ calcd for $C_{24}H_{28}N_2O_4$-FSi 455.1802, found 455.1794.

(*S*,*R*): R_f 0.72 on RP-TLC (C_{18}, 1:1 ethanol/water); mp 161−162 °C dec; IR (KBr) 3312, 2973, 1733, 1718, 1617, 1456, 1326, 1092, 709 cm^{-1}; ^{1}H NMR (400 MHz, acetonitrile-d_3) δ 8.13 (br s, 1H), 7.92−7.23 (m, 10H), 4.42 (d, J = 8. Hz, 1H), 3.63 (dt, J = 3.2, 10.4 Hz, 1H), 3.47 (dd, J = 9.6, 16.4 Hz, 1H), 3.18 (dd, J = 3.2, 17.0 Hz, 1H), 3.09−3.06 (m, 1H), 2.94−2.89 (m, 1H), 2.80 (dd, J = 10.4, 13.6 Hz, 1H), 2.17−2.14 (m, 2H), 1.90−1.70 (m, 2H), 1.32−1.17 (m, 1H), 1.12 (d, J = 6.4 Hz, 3H), 0.93−0.90 (m, 1H); ^{13}C NMR (100 MHz, acetonitrile-d_3) δ 180.7, 172.8, 170.9, 141.1, 134.4, 130.3, 129.8, 129.5, 129.4, 128.9, 127.3, 61.0, 48.3, 44.1 (t, J = 25.3 Hz, due to F) 36.7, 34.9, 28.2, 25.3, 22.7 (t, J = 20.7 Hz, due to F), 20.3; ^{19}F NMR (376 MHz, acetonitrile-d_3) δ 0.00 ($CFCl_3$), −127.7, −131.5.

(*R*,*R*): R_f 0.75 on RP-TLC (C_{18}, 1:1 ethanol/water); mp 92−94 °C dec; IR (KBr) 3421, 2968, 1735, 1604, 1562, 1449, 1158, 707 cm^{-1}; ^{1}H NMR (400 MHz, acetonitrile-d_3) δ 8.10 (brs, 1H), 7.80−7.21 (m, 10H), 4.42 (dd, J = 2.8, 8.0 Hz, 1H), 3.47 (m, 2H), 3.18 (dd, J = 3.6, 14.0 Hz, 1H), 3.12−3.08 (m, 1H), 2.85−2.82 (m, 1H), 2.77 (dd, J = 10.0, 13.6 Hz, 1H), 2.17−2.11 (m, 1H), 2.01−1.96 (m, 1H), 1.88−1.68 (m, 2H), 1.30−1.15 (m, 1H), 1.12 (d, J = 6.4 Hz, 3H), 0.99−0.93 (m, 1H); ^{13}C NMR (100 MHz, acetonitrile-d_3) δ 180.6, 172.8, 170.8, 141.1, 134.4, 130.2, 129.9, 129.5, 128.9, 127.4, 61.0, 48.4, 44.2 (t, J = 25.6 Hz, due to F), 36.8, 34.8, 28.3, 25.3, 22.6 (t, J = 21.1 Hz, due to F), 20.1; ^{19}F NMR (376 MHz, acetonitrile-d_3) δ −128.2, −129.4.

(2*R*)-1-[3-[[(1*S*)-1-(Benzoylamino)-2-phenylethyl]dihydroxysilyl]-2-methyl-1-oxopropyl]-l-proline Sodium Salt (6). To a 0 °C solution of 1-[3-[(1-(*R*)-benzoylamino-2-phenylethyl)difluorosilanyl]-2-(*S*)-methylpropionyl]pyrrolidine-3-(*S*)-carboxylic acid (3 mg, 6.3 μmol) in 1:99 CD_3CN/D_2O (0.4 mL) was added a 0.2 M NaOH solution in D_2O (0.1 mL) at room temperature. The reaction was monitored by ^{19}F NMR and after 20 min, the reaction was judged to be complete and quantitative by ^{1}H, ^{13}C, and ^{19}F.

6: ^{1}H NMR (400 MHz, 1% CD_3CN in D_2O) δ 7.47−7.10 (m, 10H), 4.02 (dd, J = 4.4, 8.8 Hz, 1H), 3.66 (dd, J = 3.2, 12.8

Hz, 1H), 3.43−3.29 (m, 2H), 3.07 (dd, J = 3.2, 14.0 Hz, 1H), 2.72−2.66 (m, 2H), 1.97−1.92 (m, 1H), 1.76−1.65 (m, 2H), 1.60−1.54 (m, 1H), 1.08 (d, J = 6.8 Hz, 3H), 0.78 (dd, J = 3.2, 14.8 Hz, 1H), 0.58 (dd, J = 10.8, 14.8 Hz, 1H); ^{13}C NMR (100 MHz, 1% CD_3CN in D_2O) δ 179.8, 179.0, 169.4, 140.8, 134.0, 131.4, 129.0, 128.4, 128.0, 126.5, 125.7, 62.4, 48.3, 44.8, 36.6, 33.5, 30.4, 25.0, 20.2, 18.9.

7: ^{1}H NMR (400 MHz, 1% CD_3CN in D_2O) δ 7.49−7.11 (m, 10H), 4.08 (dd, J = 4.4, 8.8 Hz, 1H), 3.62 (dd, J = 3.2, 12.8 Hz, 1H), 3.53−3.32 (m, 2H), 3.05 (dd, J = 3.2, 14.0 Hz, 1H), 2.86−2.79 (m, 1H), 2.68 (t, J = 12.8 Hz, 1H), 2.04−2.00 (m, 1H), 1.82−1.62 (m, 3H), 1.06 (d, J = 6.8 Hz, 3H), 0.76 (dd, J = 4.4, 15.2 Hz, 1H), 0.60 (dd, J = 10.0, 14.8 Hz, 1H); ^{13}C NMR (100 MHz, 1% CD_3CN in D_2O) δ 182.1, 181.1, 171.8, 142.9, 136.1, 133.6, 131.0, 130.6, 130.2, 128.7, 127.9, 63.8, 49.6, 46.6, 37.5, 34.7, 31.5, 26.1, 21.3, 20.5.

8: ^{1}H NMR (400 MHz, 1% CD_3CN in D_2O) δ 7.50−7.10 (m, 10H), 4.12 (dd, J = 4.4, 8.8 Hz, 1H), 3.58 (dd, J = 3.2, 12.8 Hz, 1H), 3.51−3.31 (m, 2H), 3.01 (dd, J = 3.2, 14.0 Hz, 1H), 2.87−2.86 (m, 1H), 2.70 (t, J = 12.8 Hz, 1H), 2.14−2.08 (m, 1H), 1.89−1.69 (m, 3H), 1.03 (d, J = 6.0 Hz, 3H), 0.76 (dd, J = 4.4, 15.2 Hz, 1H), 0.60 (dd, J = 10.0, 14.8 Hz, 1H); ^{13}C NMR (100 MHz, 1% CD_3CN in D_2O) δ 180.9, 180.0, 170.6, 141.9, 135.3, 132.4, 129.9, 129.5, 129.1, 127.6, 126.9, 63.4, 47.9, 46.0, 36.5, 34.1, 32.1, 25.1, 20.7, 19.9.

9: ^{1}H NMR (400 MHz, D_2O) δ 7.50−7.10 (m, 10H), 4.28 (dd, J = 2.4, 8.4 Hz, 1H), 3.61 (dd, J = 2.8, 12.8 Hz, 1H), 3.34−3.28 (m, 2H), 2.97 (dd, J = 2.8, 14.0 Hz, 1H), 2.70−2.67 (m, 1H), 2.63 (t, J = 7.6 Hz, 1H), 2.05−1.84 (m, 2H), 1.63−1.56 (m, 2H), 0.94 (d, J = 6.8 Hz, 3H), 0.83 (dd, J = 4.0, 15.2 Hz, 1H), 0.68 (dd, J = 5.2, 15.2 Hz, 1H); ^{13}C NMR (100 MHz, 1% CD_3CN in D_2O) δ 180.9, 179.9, 170.9, 141.7, 135.2, 132.5, 130.0, 129.5, 129.2, 127.7, 126.9, 63.4, 48.4, 45.4, 36.5, 33.9, 32.2, 25.0, 20.7, 19.8.

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Supporting Information Available: NMR spectra of all new structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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