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Serine-*cis*-proline and Serine-*trans*-proline Isosteres: Stereoselective Synthesis of (*Z*)- and (*E*)-Alkene Mimics by Still−Wittig and Ireland−Claisen Rearrangements

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Two new amide isosteres of Ser-*cis*-Pro and Ser-*trans*-Pro dipeptides were designed and stereoselectively synthesized to be incorporated into potential inhibitors of the phosphorylation-dependent peptidylprolyl isomerase Pin1, an essential regulator of the cell cycle. The cis mimic, the (*Z*)-alkene isomer, was formed through the use of a Still−Wittig [2,3]-sigmatropic rearrangement, while the trans mimic, the (*E*)-alkene, was synthesized through the use of an Ireland−Claisen [3,3]-sigmatropic rearrangement. Starting from *N*-Boc-Ser(OBn)-N(OMe)Me, both mimics were synthesized in Boc-protected form suitable for peptide synthesis with an overall yield of 20% in 10 steps for the cis mimic and 13% in eight steps for the trans mimic.

Because proline is the only proteinogenic amino acid in which the α-amino group is dialkylated, there are lower energy differences for the resulting tertiary Xaa-Pro *cis*- and *trans*-amide bonds ($\Delta G° = 0.5$ kcal/mol) than for typical secondary amide bonds in proteins ($\Delta G° = 2.6$ kcal/mol).[1] The resulting propensity of proline for cis−trans isomerization[2] imparts unique structural and functional features to proteins.[3] Cis−trans isomerization of proline-containing peptides has been implicated in a number of biologically important processes. The phosphorylation-dependent peptidylprolyl isomerase (PPIase) Pin1[4] is suggested to regulate mitosis via cis−trans isomerization of phospho-Ser-Pro amide bonds in a variety of cell cycle proteins,[5] particularly Cdc25 phosphatase,[6,7] a key regulator of the Cdc2/cyclinB complex in mitosis.[8] The central role Pin1 plays in the cell cycle makes it an interesting target for inhibition, both for potential anticancer activity and for elucidation of the mechanism of mitosis.

One of the ideal peptide bond surrogates is the alkene because of the similar geometrical disposition of substituents attached to either of these functional groups.[9] We have reviewed peptidomimetics of *cis*- and *trans*-prolines.[9] We have stereoselectively synthesized an Ala-*cis*-Pro (*Z*)-alkene isostere that inhibited the PPIase activity of cyclophilin ($IC_{50} = 6.5\ \mu M$).[10,11] The alkene isostere was indeed an amide bond surrogate, and the alkene was not a substrate for the peptidylprolyl isomerase. Fluoroalkene isosteres of Ala-*trans*-Pro[12] have been incorporated into potent inhibitors of dipeptidyl protease IV.[12,13] An (*E*)-alkene *trans*-Pro mimic was shown to inhibit the PPIase activity of FKBP.[14] Organocuprate routes to (*E*)-alkene Xaa-*trans*-Pro dipeptide mimics were published recently.[15] Relatively fewer (*Z*)-alkenes[16] have been made due to the difficulty of (*Z*)-alkene formation and the possibility of isomerization of the β,γ-unsaturated carbonyl to the more stable α,β-unsaturated carbonyl compounds.[17]

Our previous success in Ala-*cis*-Pro (*Z*)-alkene isostere synthesis[10] and the various synthetic methods available for (*E*)-alkene formation led us to design analogous inhibitors based on the best substrate for Pin1, WFYpSPR-

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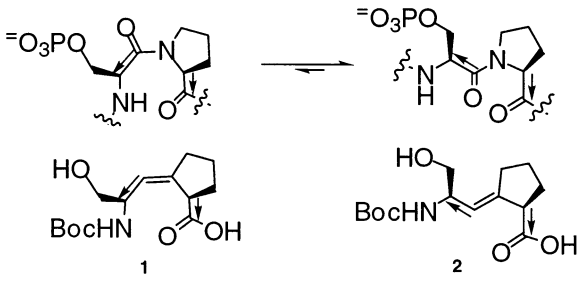


FIGURE 1. Phospho-Ser-*cis*/*trans*-Pro equilibrium and (*Z*)- and (*E*)-alkene conformationally locked Ser-Pro mimics. Arrows indicate alkene isostere bond vectors that superimpose on amide vectors.

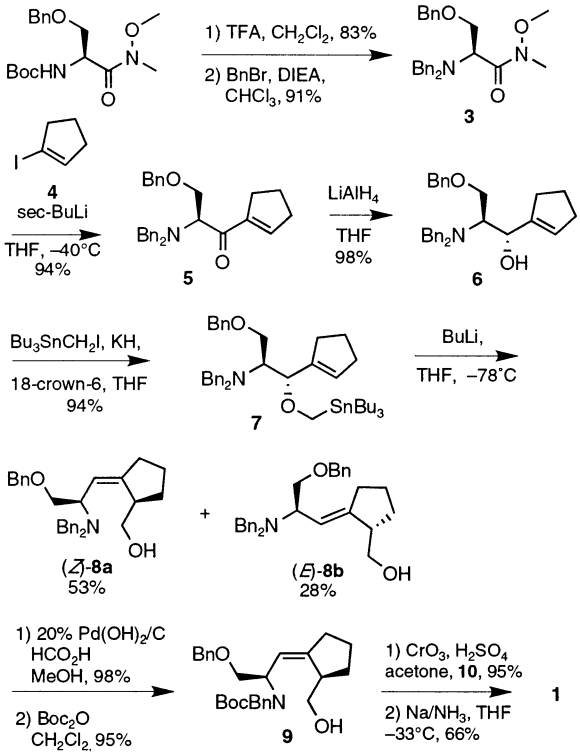
*p*NA ($k_{cat}/K_m = 2 \times 10^7$ $M^{-1}s^{-1}$).[5] We now report the stereoselective synthesis of a Ser-*cis*-Pro alkene mimic, **1**, and the corresponding Ser-*trans*-Pro alkene mimic, **2** (Figure 1). These mimics will be used for Pin1 inhibition and elucidation of the role of this essential regulator in the cell cycle. Preliminary reports of the (*Z*)-alkene mimic have been published.[18,19] The (*Z*)- and (*E*)-alkenes serve as conformationally locked surrogates for *cis*- and *trans*-proline amide bonds without incorporating additional functional groups or steric bulk.

Results and Discussion

Optically active amino acids are versatile synthons for stereoselective synthesis. Starting with the optically pure amino acid N-terminal to Pro not only provides the source for stereoselective synthesis, but also imparts generality to the synthesis of any Xaa-Pro alkene mimic. In this case, *N*-Boc-*O*-benzyl-L-serine, used in Merrifield peptide synthesis,[20] was chosen as the starting material for the syntheses of both Ser-*cis*-Pro and Ser-*trans*-Pro mimics. Because Ser is so highly functionalized, significant challenges and side reactions were encountered during the synthesis of these particular Pro mimics.[19] A Still−Wittig [2,3]-sigmatropic rearrangement[21] could be used to form both the (*Z*)- and (*E*)-alkene stereoisomers, but the (*E*)-alkene was synthesized more efficiently by an Ireland−Claisen [3,3]-sigmatropic rearrangement.

Still−Wittig Route to the Ser-*cis*-Pro Mimic. The key steps in the synthesis of Boc-Ser-Ψ[(*Z*)CH=C]-Pro-OH were stereoselective reduction of ketone **5** to the (*S*,*S*)-alcohol **6**, and Still−Wittig rearrangement to (*Z*)-alkene **8** (Scheme 1). Starting with the Weinreb amide[22] of Boc-Ser(OBn)-OH,[23] ketone **5** was formed by condensation with cyclopentenyllithium derived from iodide **4**. The reagent 1-iodo-cyclopentene[24] (**4**) was prepared most easily by the method of Barton[25] in two steps with 50% overall yield from cyclopentanone. Reduction of ketone

SCHEME 1. Synthesis of Boc-Ser-Ψ[(*Z*)CH=C]-Pro-OH by Still−Wittig Rearrangement



5 with $LiAlH_4$ proceeded with Felkin−Ahn stereoselectivity[26,27] to give (*S*,*S*)-alcohol **6**. A single diastereomer was observed in the crude ^1H NMR spectrum. The relative stereochemistry was established by derivatization of a mixture of diastereomers as the oxazolidinones (Supporting Information).[28] The iodomethyltributyltin reagent was prepared by the method of Steitz et al.[29] Fractional distillation is recommended. After the intermediate tributylstannylmethyl ether **7** was formed, Still−Wittig rearrangement[21] gave a 53% (*Z*)-**8a** to 28% (*E*)-**8b** ratio of alkenes.[19] The ratio varies and appears to be temperature and scale sensitive. The diastereomers were separated by column chromatography. The *E*/*Z* stereochemistry of these alkenes was determined by 1D NOE.[19]

With (*Z*)-alkene **8a** in hand, it was necessary to remove the benzyl protection and reprotect the amine for peptide synthesis. (Alternative amine protection, such as trityl or Boc, gave poor stereoselectivity and/or yields in some of the previous reactions.) Monodebenzylation of amine **8a** was accomplished by catalytic transfer hydrogenation with formic acid on Pearlman's catalyst[30] selectively in the presence of the benzyl ether and the alkene. A side product in this reaction was avoided by keeping the reaction time short. Interestingly, the (*E*)-alkene **8b** cannot be deprotected in this reduction.

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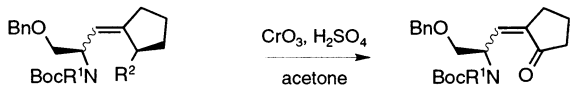
SCHEME 2. Ketone Side Product from Jones Oxidation of 9 and 17



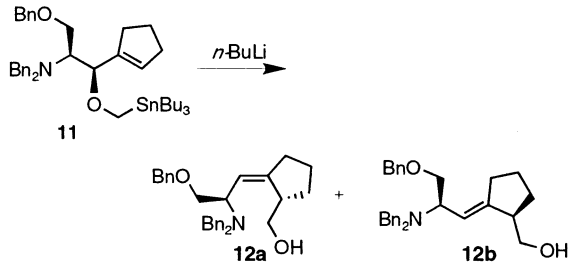
9: R^1 = Bn, R^2 = CH_2OH, (*Z*)
17: R^1 = H, R^2 = CH(OH)COOH, (*E*)

Carbamate protection (Boc) to give **9** was required to remove the second benzyl. At this stage, it was possible to remove the second benzyl from **9** by Na/NH_3 reduction; however, Jones oxidation[31] of the resulting alcohol, with the Boc-protected amine, did not afford the corresponding acid. In contrast, Jones oxidation of the doubly protected Boc-benzylamine **9** produced acid **10** in 95% yield. Initially, we observed a ketone as a major side product from the Jones oxidation of **9**, probably resulting from allylic oxidation and C−C bond cleavage (Scheme 2). This side product was minimized by adding an excess of the Jones reagent to the alcohol and keeping the reaction at 0 °C. Final benzyl deprotection by Na/NH_3 reduction yielded Boc-Ser-Ψ[(*Z*)CH=C]-Pro-OH (**1**). Again, a large excess of sodium was required to minimize the cyclization of the side chain oxyanion onto the Boc carbonyl to produce a cyclic carbamate. Presumably benzyl ether deprotection is slightly more rapid than benzylamine deprotection, and the large excess of sodium increases the rate for both to improve the yield of the desired product.

Still−Wittig Route to the (*E*)-Alkene Ser-*trans*-Pro Mimic. Recently we reported syntheses of (*E*)-**8b**, precursor to the L-Ser-*trans*-D-Pro mimic, and (*Z*)-**8a**, precursor to the L-Ser-*cis*-L-Pro mimic, and a computational analysis explaining solvent-dependent *E*- or *Z*-selectivity of the Still−Wittig rearrangement.[19] The preference for the formation of (*E*)-**8b** in toluene (3:1 *E*:*Z*) was particularly interesting since our work necessitates comparisons between *cis*- and *trans*-Pro analogues. However (*E*)-**8b** bears the wrong stereochemistry (*S*) in the cyclopentyl ring necessary to mimic L-Pro. To mimic the structure of naturally occurring amino acids, the (*R*,*E*,*R*)-**12b** mimic of L-Ser-*trans*-L-Pro was required (Scheme 3).

We synthesized stannane **11** (Scheme 3 and Supporting Information) expecting the Still−Wittig rearrangement to yield (*E*)-**12b** with solvent selectivity similar to that observed for the rearrangement of **7**.[19] Stereochemical control in the synthesis of stannane **11** could be accomplished via Luche 1,2-reduction[32] of the Boc-protected cyclopentenyl ketone **14** (Scheme 4). Unfortunately, favorable *E*-selectivity was not observed in the Still−Wittig rearrangement of **11** in toluene, and the highest yield of (*E*)-**12b** was 33% in refluxing THF, although the average was 26% (Scheme 3). In either THF or toluene at various temperatures, (*E*)-**12b** was not obtained selectively or in reasonable yield. Although the Still−Wittig rearrangement allows stereocontrolled access to eight isomeric compounds of interest in our work (the enantiomers of **7** and **11** provide access to the D-Ser analogues), a more efficient route to the (*E*)-alkene was desired.

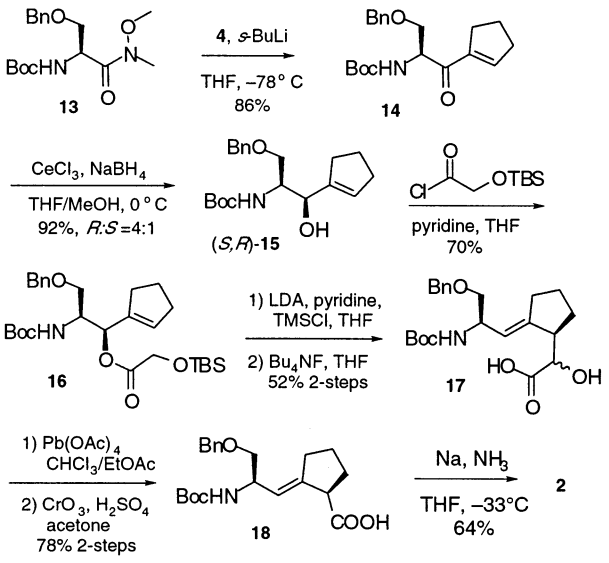
SCHEME 3. Still−Wittig Rearrangement of Stannane 11[a]



solvent	temp (°C)	% yields		ratio (*Z*:*E*)
		(*R*,*Z*,*S*)-12a	(*R*,*E*,*R*)- 12b	
THF	−78	71	not isolated	—
THF	+66	46	26	1.8:1
toluene	−78	45	< 8	> 5:1
toluene	+50	54	16	3.4:1

[a] Yields in THF at 66 °C and toluene at 50 °C are averages of multiple reactions.

SCHEME 4. Synthesis of Boc-Ser-Ψ[(*E*)CH=C]-Pro-OH by Ireland−Claisen Rearrangement



Ireland−Claisen Route to the (*E*)-Alkene Ser-*trans*-Pro Mimic. The Ireland−Claisen rearrangement was more successful at producing the desired (*E*)-alkene, both in stereoselectivity and in yield (Scheme 4). Weinreb amide **13** was prepared easily from *N*-Boc-*O*-benzyl-L-serine.[23] The reaction of **13** with cyclopentenyllithium gave the desired ketone **14** in 86% yield. The reaction was difficult to bring to completion, even with excess cyclopentenyllithium, probably due to deprotonation of the carbamate. The yield was increased to 86% by adding 3 equiv of cyclopentenyllithium in portions.

The chelation-controlled Luche reduction[32] of ketone **14** gave a 4:1 mixture of diastereomers in good yield (92%). The minor diastereomer was removed by precipitation. The major diastereomer of **15** proved to be the desired (*S*,*R*) by derivatization as the oxazolidinones (Supporting Information).[28] Alcohol **15** was readily transformed to the Ireland−Claisen precursor ester **16**[33] by reaction with *tert*-butyldimethylsilyloxyacetyl chloride, prepared according to the published procedure.[34] The

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Ireland−Claisen rearrangement of ester **16** was the key step in our synthesis of the Ser-*trans*-Pro mimic (Scheme 4). The standard Ireland−Claisen procedure[33,35] was not successful, and only starting material was recovered. Activation of TMSCl by pyridine was necessary.[36] The intermediate TBS-protected alcohol was unstable toward silica gel, but subsequent removal of the TBS protecting group by *tert*-butylammonium fluoride (TBAF) in THF gave the α-hydroxy acid **17** as a stable product. The crude ^{1}H NMR of **17** showed three minor diastereomers in addition to the major isomer, but the stereochemistry at the alcohol center is eliminated by oxidation in the next step. After oxidation, the major diastereomer of **18** was isolated readily by chromatography. The NOESY spectrum of **18** showed the (*E*)-alkene as the major product of the rearrangement (Supporting Information).

Initial attempts using the Jones reagent to oxidatively decarboxylate α-hydroxy acid **17** and oxidize the resulting aldehyde in one step afforded little of the desired acid **18** (10% yield). The major product identified was the α,*β*-unsaturated ketone directly analogous to the ketone side product from Jones oxidation of the (*Z*)-alkene (Scheme 2). For decarboxylation of α-hydroxy acid **17**, several types of oxidizing reagents failed, including sodium periodate[37] and tetrabutylammonium periodate.[38] Lead(IV) tetraacetate[39] was the only reagent that cleanly gave high yields of the *β*,*γ*-unsaturated aldehyde.

The *β*,*γ*-unsaturated aldehyde was oxidized further without purification. Isomerization of the *β*,*γ*-unsaturated aldehyde to the more stable α,*β*-unsaturated aldehyde occurred readily during basic workup (aqueous $NaHCO_3$) or silica gel purification, so the aldehyde was handled as little as possible. Jones oxidation of the aldehyde yielded the corresponding *β*,*γ*-unsaturated carboxylic acid **18**, without loss of the acid-sensitive Boc group. As an alternative to the Jones oxidation, sodium chlorite led only to decomposition of the aldehyde.[40] The ketone side product from allylic oxidation was not observed in this oxidation of the aldehyde. The *β*,*γ*-unsaturated acid **18** was stable toward isomerization under aqueous acidic or basic conditions. A single diastereomer of **18** was obtained after chromatography. The (*E*)-alkene stereochemistry of **18** was demonstrated by NOESY (Supporting Information). The benzyl protection on oxygen was successfully removed with Na/NH_3 to give the desired Boc-Ser-Ψ[(*E*)CH═C]-Pro-OH (**2**).

Conclusions

We have synthesized new (*Z*)- and (*E*)-alkene isosteres **1** and **2** of Ser-*cis*-Pro and Ser-*trans*-Pro with high stereoselectivity. The Ser-*cis*-Pro mimic **1** was synthesized in 10 steps and 20% overall yield from Weinreb amide *N*-Boc-Ser(OBn)-N(OMe)Me. The Ser-*trans*-Pro mimic **2** was synthesized in eight steps and 13% overall yield from the Weinreb amide. Both mimics **1** and **2** can be used in peptide synthesis without protection of the side chain alcohol, or they may be reprotected as the Fmoc-amine, TBS ether for Fmoc-based peptide synthesis (S. A. Hart, X. J. Wang, and F. A. Etzkorn, unpublished results). The Ser-Pro mimics will be incorporated into Pin1 substrate analogues for inhibition and mechanistic studies of Pin1 enzymology and cancer biology.

Experimental Section

General Information. Unless otherwise indicated, all reactions were carried out under N_2 in flame-dried glassware. THF, toluene, and CH_2Cl_2 were dried by passage through alumina. Anhydrous (99.8%) DMF was available commercially and used directly from SureSeal bottles. Dimethyl sulfoxide (DMSO) was anhydrous and dried with 4 Å molecular sieves. Triethylamine (TEA) was distilled from CaH_2, and $(COCl)_2$ was distilled before use each time. Diisopropylethylamine (DIEA) was distilled from CaH_2 under a N_2 atmosphere. Brine (NaCl), $NaHCO_3$, and NH_4Cl refer to saturated aqueous solutions unless otherwise noted. Flash chromatography was performed on 32−63 μm or 230−400 mesh, ASTM silica gel with reagent grade solvents. Melting points were uncorrected. NMR spectra were obtained at ambient temperature in $CDCl_3$ unless otherwise noted. Proton (300 MHz) NMR spectra were obtained for compounds **1**, **3**, **6**, and **8**−**12**, and carbon-13 (75 MHz) NMR spectra for compounds **1**−**6** and **8**−**12**. Proton (500 MHz) NMR spectra were obtained for compounds **2**, **4**, **5**, **7**−**9**, and **13**−**18**, and carbon-13 (125 MHz) NMR spectra for compounds **7** and **13**−**18**. Coupling constants *J* are given in hertz.

***N,N,O*-Tribenzyl Serine Weinreb Amide (3).** *N*-Boc-*O*-benzyl serine Weinreb amide[23] (24.1 g, 71.2 mmol) was dissolved in CH_2Cl_2 (400 mL), TFA (125 mL) was added, and the solution was stirred for 30 min. The mixture was concentrated and then quenched with $NaHCO_3$ until gas evolution ceased. The aqueous mixture was extracted with CH_2Cl_2 (8 × 300 mL), dried on $MgSO_4$, and concentrated. Chromatography on silica with 50% EtOAc in petroleum ether to remove impurities, followed by product elution with 10% MeOH in EtOAc yielded 13.1 g (83%) of the amine as a clear oil: ^{1}H NMR δ 7.40−7.20 (m, 5H), 4.57 (d, J = 12.1, 1H), 4.52 (d, J = 12.1, 1H), 4.06 (m, 1H), 3.67 (s, 3H), 3.66−3.45 (m, 2H), 3.20 (s, 3H), 1.88 (br s, 2H). The amine (13 g, 58 mmol) was dissolved in CH_2Cl_2 (50 mL), and then benzyl bromide (24.8 g, 145 mmol) and DIEA (37.4 g, 290 mmol) were added. After 4 d at rt, the reaction was diluted with EtOAc (600 mL), washed with NH_4Cl (4 × 200 mL) and brine (200 mL), dried on $MgSO_4$, and concentrated. Chromatography on silica with 10% EtOAc in petroleum ether to remove benzyl bromide and then 50% EtOAc in petroleum ether to elute the product yielded 21.4 g (91%) of dibenzylamine **3** as a clear oil: ^{1}H NMR δ 7.40−7.17 (m, 15H), 4.56 (d, J = 11.9, 1H), 4.48 (d, J = 11.9, 1H), 4.13 (m, 1H), 3.98−3.84 (m, 4H), 3.76 (d, J = 14.1, 2H), 3.28 (br s, 3H), 3.20 (br s, 3H); ^{13}C NMR δ 171.5, 140.0, 138.2, 128.7, 128.1, 127.9, 127.3, 126.6, 73.0, 68.6, 60.8, 56.4, 55.0, 30.9. Anal. Calcd for $C_{26}H_{30}N_2O_3$: C, 74.61; H, 7.22; N, 6.69. Found: C, 74.31; H, 7.32; N, 6.40.

1-Iodocyclopentene[24] (4). This compound was prepared by the method of Barton et al.[25] Cyclopentanone (44 mL, 0.50 mol) and hydrazine monohydrate (115 mL, 2.37 mol) were combined at rt and heated at reflux for 16 h. The reaction was poured into water (500 mL), extracted with CH_2Cl_2 (4 × 200 mL), washed with brine (200 mL), dried over Na_2SO_4, and concentrated to give 40 g (80%) of the hydrazone as a colorless liquid: ^{1}H NMR δ 4.80 (s, 2H), 2.33−2.30 (t, 2H), 2.16−2.12

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(m, 2H), 1.85−1.67 (m, 4H). To a solution of I_2 (97.5 g, 384 mmol) in Et_2O (600 mL) was added a solution of tetramethylguanidine (265 mL, 2.09 mol) in Et_2O (400 mL) slowly (*caution! exothermic*), and the resulting solution was stirred for 2.5 h. A solution of cyclopentanone hydrazone (17.3 g, 174 mmol) in Et_2O (200 mL) was added dropwise over 2.5 h (*caution! exothermic*), and the resulting solution was stirred for 16 h and then heated at reflux for 2 h. The reaction was cooled to rt, filtered to remove the solids, and concentrated to remove Et_2O. The solution was reheated at 80−90 °C for 3 h. The reaction was cooled to rt, diluted with Et_2O (500 mL), washed with 2 N HCl (3 × 150 mL), $Na_2S_2O_3$ (3 × 100 mL), $NaHCO_3$ (100 mL), and brine (100 mL), dried over $MgSO_4$, and concentrated to give 21.1 g (62%) of **4** as a pale yellow liquid that was stored under N_2 at −20 °C and used without further purification, usually within a week of synthesis (the product may be purified, if necessary, by chromatography with petroleum ether on silica): ^{1}H NMR δ 6.12−6.10 (m, 1H), 2.64−2.58 (m, 2H), 2.36−2.30 (m, 2H), 1.98−1.90 (m, 2H).

Ketone 5. Cyclopentenyllithium was generated by adding fresh *s*-BuLi (1.3 M in cyclohexane, 50 mL, 65 mmol) to a solution of freshly prepared **4** (10.0 g, 51.5 mmol) in THF (100 mL) at −40 °C. The solution was maintained at −40 °C for 70 min, and Weinreb amide **3** (7.40 g, 17.7 mmol) in THF (30 mL) was cooled to −40 °C and added slowly via cannula. The mixture was stirred for 1 h at −40 °C. The reaction was quenched with NH_4Cl (20 mL), diluted with EtOAc (600 mL), washed with NH_4Cl (3 × 100 mL) and brine (100 mL), dried over Na_2SO_4, and concentrated. Chromatography on silica with 5% EtOAc in hexanes yielded 7.1 g (94%) of the ketone **5**: ^{1}H NMR δ 7.39−7.20 (m, 15H), 6.11 (m, 1H), 4.55 (d, J = 12.3, 1H), 4.48 (d, J = 12.3, 1H), 4.24 (app t, J = 6.6, 1H), 3.90 (d, J = 6.6, 2H), 3.79 (d, J = 13.6, 2H), 3.71 (d, J = 14.1, 2H), 2.59−2.39 (m, 4H), 1.98−1.84 (m, 2H); ^{13}C NMR δ 197.8, 145.5, 144.7, 139.7, 138.2, 128.8, 128.2, 128.1, 127.5, 126.9, 73.3, 67.6, 60.6, 54.8, 33.9, 30.5, 22.6. Anal. Calcd for $C_{29}H_{31}NO_2$: C, 81.85; H, 7.34; N, 3.29. Found: C, 81.51; H, 7.42; N, 3.52.

(*S*,*S*)-Alcohol 6. Ketone **5** (6.8 g, 16 mmol) was dissolved in THF (250 mL), and $LiAlH_4$ (6.0 g, 160 mmol) was added. After 1 h, the reaction was quenched with MeOH (50 mL) and then NH_4Cl (50 mL), diluted with EtOAc (500 mL), and washed with NH_4Cl (150 mL) and 1 M sodium potassium tartrate (2 × 150 mL). The aqueous layers were extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to yield 6.68 g (98%) of alcohol **6** as a colorless oil: ^{1}H NMR δ 7.49−7.24 (m, 15H), 5.65 (m, 1H), 4.62 (d, J = 11.9, 1H), 4.53 (d, J = 11.9, 1H), 4.48 (s, 1H), 4.26 (d, J = 10.1, 1H), 4.02 (d, J = 13.2, 2H), 3.80−3.70 (m, 3H), 3.58 (dd, J = 10.6, 3.1, 1H), 3.07 (m, 1H), 2.43−2.17 (m, 3H), 2.00−1.75 (m, 3H); ^{13}C NMR δ 144.1, 139.0, 138.2, 129.2, 129.0, 128.3, 127.5, 127.4, 127.1, 73.2, 67.5, 66.4, 59.7, 54.3, 32.0, 29.5, 23.0. Anal. Calcd for $C_{29}H_{33}NO_2$: C, 81.46; H, 7.78; N, 3.28. Found: C, 81.25; H, 7.66; N, 3.11.

Stannane 7. To a solution of alcohol **6** (2.20 g, 5.15 mmol) in THF (40 mL) were added 18-crown-6 (4.09 g, 15.5 mmol) in THF (10 mL), KH (1.03 g, 7.73 mmol, 35% suspension in mineral oil) in THF (10 mL), and Bu_3SnCH_2I,[29] purified by fractional distillation at reduced pressure (3.33 g, 7.73 mmol), in THF (10 mL), and the resulting solution was stirred for 30 min at rt. The reaction was quenched with MeOH, diluted with EtOAc (400 mL), washed with NH_4Cl (2 × 100 mL) and brine (100 mL), dried on $MgSO_4$, and concentrated. Purification by chromatography on silica with 3% EtOAc in hexanes yielded 3.51 g (94%) of stannane **7** as a clear liquid: ^{1}H NMR δ 7.40−7.26 (m, 15H), 5.60 (br s, 1H), 4.45 (d, J = 12.0, 1H), 4.37 (d, J = 12.0, 1H), 4.05 (d, J = 7.8, 1H), 3.99 (d, J = 13.7, 2H), 3.83 (d, J = 13.7, 2H), 3.74 (dm, J = 9.9, 1H), 3.60 (dd, J = 9.6, 5.7, 1H), 3.53 (dd, J = 9.6, 4.6, 1H), 3.41 (dm, J = 9.6, 1H), 2.99 (m, 1H), 2.40−2.28 (m, 2H), 1.99 (br s, 2H), 1.82 (m, 2H), 1.54 (m, 6H), 1.33 (m, 6H), 0.91 (m, 15H); ^{13}C NMR (125 MHz) δ 143.0, 141.6, 138.9, 129.1, 128.6, 128.4, 128.0, 127.6, 126.5, 85.4 (s), 85.4 (d, J_{C-Sn} = 51), 73.2, 70.6, 59.2, 58.6, 55.8, 32.3, 31.1, 29.4 (s), 29.4 (d, J_{C-Sn} = 20), 27.6 (s), 27.6 (d, J_{C-Sn} = 54), 23.5, 13.9, 9.0 (s), 9.0 (dd, J_{C-Sn} = 316, 7.6).

(*Z*)-Alkene 8a and (*E*)-Alkene 8b. Stannane **7** (9.60 g, 13.1 mmol) was dissolved in THF (150 mL) and cooled to −78 °C. *n*-BuLi (2.5 M in hexane, 15 mL, 39 mmol) was cooled to −78 °C, added slowly via cannula, and stirred for 1.5 h at −78 °C. The reaction was quenched with MeOH and concentrated. The residue was diluted with EtOAc (700 mL), washed with NH_4Cl (2 × 150 mL) and brine (150 mL), dried on Na_2SO_4, and concentrated. Chromatography on silica with 15% EtOAc in hexanes yielded 3.0 g (53%) of (*Z*)-**8a** and 1.57 g (28%) of (*E*)-**8b** as clear oils. (NOE spectra are included in the Supporting Information of the preliminary communication.[19]) Data for (*E*)-**8b**: ^{1}H NMR δ 7.38−7.27 (m, 15H), 5.43 (br d, J = 9.4, 1H), 4.51 (d, J = 12.1, 1H), 4.47 (d, J = 12.1, 1H), 3.84 (d, J = 13.9, 2H), 3.73 (m, 1H), 3.64−3.47 (m, 6H), 2.65 (m, 1H), 2.05 (m, 2H), 1.85 (m, 1H), 1.69 (m, 1H), 1.56 (m, 2H); ^{13}C NMR δ 148.6, 140.3, 138.5, 129.4, 128.5, 128.2, 128.0, 127.5, 127.3, 126.6, 117.6, 72.6, 71.7, 65.4, 57.3, 54.7, 47.0, 29.6, 29.2, 24.1. Data for (*Z*)-**8a**: ^{1}H NMR δ 7.38−7.26 (m, 15H), 5.55 (br d, J = 8.7, 1H), 4.57 (d, J = 12.2, 1H), 4.53 (d, J = 12.2, 1H), 4.12 (br s, 1H), 3.89 (d, J = 13.3, 2H), 3.79 (m, 1H), 3.67 (m, 4H), 3.33 (m, 1H), 3.27 (m, 1H), 2.53 (m, 1H), 2.31−2.18 (m, 2H), 1.71−1.47 (m, 4H); ^{13}C NMR δ 149.0, 139.2, 138.4, 129.4, 128.3, 128.0, 127.5, 126.8, 120.9, 73.2, 69.7, 64.8, 57.3, 55.0, 43.5, 33.1, 29.4, 23.1. Anal. Calcd for $C_{30}H_{35}NO_2$: C, 81.59; H, 7.99; N, 3.17. Found: C, 81.42; H, 8.27; N, 3.25.

Boc-benzylamine 9. (*Z*)-Alkene **8** (1.44 g, 3.26 mmol) and 20% $Pd(OH)_2/C$ (150 mg) were blanketed with Ar, and MeOH (100 mL) was added, followed by 96% HCOOH (20 mL). After being stirred for exactly 20 min, the reaction was filtered immediately through Celite, concentrated, neutralized with solid $NaHCO_3$ until gas evolution ceased, extracted with CH_2Cl_2 (5 × 100 mL), dried over Na_2SO_4, and concentrated to yield 1.1 g (98%) of the monobenzylamine without further purification: ^{1}H NMR (500 MHz) δ 7.36−7.30 (m, 10H), 5.50 (br d, J = 8.3, 1H), 4.56 (br d, J = 1.6, 2H), 3.72 (d, J = 11.2, 1H), 3.66−3.60 (m, 3H), 3.55−3.50 (m, 1H), 3.48−3.45 (dd, J = 10.8, 4.3, 1H), 3.41−3.37 (m, 1H), 2.83 (m, 1H), 2.37−2.22 (m, 2H), 1.89−1.85 (m, 1H), 1.64 (m, 1H), 1.54−1.38 (m, 2H); HRMS (FAB$^+$) m/z calcd for $C_{23}H_{30}NO_2$ $(M + 1)^+$ 352.2276, found 352.2278. The monobenzylamine (1.10 g, 3.12 mmol) was dissolved in CH_2Cl_2 (60 mL), di-*tert*-butyl dicarbonate (1.70 g, 7.79 mmol) was added, and the resulting solution was stirred for 17 h. The mixture was concentrated, and purification by chromatography on silica with 20% EtOAc in hexanes yielded 1.3 g (95%) of the Boc-benzylamine **9** as a pale yellow oil: ^{1}H NMR (500 MHz) δ 7.36−7.16 (m, 10H), 5.36 (br d, J = 8.9, 1H), 5.18 (br s, 1H), 4.47−4.37 (m, 4H), 3.48−3.46 (m, 5H), 2.87 (br s, 1H), 2.20 (m, 2H), 1.75 (m, 1H), 1.65 (m, 2H), 1.54 (m, 1H), 1.34 (br s, 9H); ^{13}C NMR δ 155.7, 149.2, 139.9, 138.1, 127.9, 127.8, 127.2, 126.7, 126.3, 117.8, 79.8, 72.3, 71.1, 64.3, 54.1, 47.3, 43.9, 33.2, 29.1, 28.0, 23.0; HRMS m/z calcd for $C_{28}H_{37}NO_4$ (MH^+) 452.2801, found 452.2813.

Boc-benzylamino Acid 10. Boc-benzylamine **9** (2.2 g, 4.9 mmol) was dissolved in acetone (220 mL) and cooled to 0 °C. Jones reagent (2.7 M H_2SO_4, 2.7 M CrO_3; 4.5 mL, 12 mmol) was added, and the resulting solution was stirred for 30 min at 0 °C. The reaction was quenched with 2-propanol (50 mL) and stirred for 5 min. The mixture was diluted with water (400 mL), extracted with CH_2Cl_2 (10 × 50 mL), dried on $MgSO_4$, and concentrated. Chromatography on silica with 20% EtOAc in petroleum ether yielded 2.1 g (95%) of the acid **10** as a pale yellow oil: ^{1}H NMR δ 7.34−7.16 (m, 10H), 5.53 (br d, J = 9.2, 1H), 4.92 (br s, 1H), 4.47−4.27 (m, 4H), 3.69−3.24 (m, 3H), 2.46 (m, 1H), 2.28 (m, 1H), 2.11 (m, 1H), 1.89 (m, 2H), 1.62 (m, 1H), 1.38 (br s, 9H); ^{13}C NMR ($CDCl_3$) δ 179.1, 155.6, 145.7, 139.8, 138.3, 128.2, 128.1, 127.4, 127.1, 126.6, 120.9, 80.0, 72.6, 72.0, 55.6, 49.0, 45.9, 33.5, 31.0, 28.3, 23.8; HRMS m/z calcd for $C_{28}H_{36}NO_5$ (MH^+) 466.2593, found 466.2601.

Boc-Ser-Ψ[(*Z*)CH=C]-Pro-OH (1). NH_3 (ca. 160 mL) was distilled into 40 mL of THF at −78 °C and allowed to warm to reflux (−33 °C). Na (ca. 2.0 g, 87 mmol) was added until a deep blue solution was sustained. A solution of acid **10** (2.0 g, 4.3 mmol) in THF (10 mL) was added directly to the Na/NH_3 solution slowly via cannula over ca. 5 min. After being stirred for 45 min at reflux, the reaction was quenched with NH_4Cl (10 mL) and then allowed to warm to rt with concentration to ca. 30 mL (*caution! NH_3 evolved*). The mixture was diluted with NH_4Cl (50 mL), acidified with 1 N HCl to pH 7, and extracted with $CHCl_3$ (10 × 50 mL), dried on $MgSO_4$, and concentrated to give 810 mg (66%) of the alcohol **1** as a pale yellow oil (further purification can be achieved by chromatography on silica with 3% MeOH in $CHCl_3$ if desired): ^{1}H NMR (DMSO-d_6) δ 6.48 (br d, J = 6.2, 1H), 5.20 (d, J = 8.4, 1H), 4.08 (m, 1H), 3.36 (m, 1H), 3.28 (dd, J = 10.6, 5.7, 1H), 3.13 (dd, J = 10.6, 6.6, 1H), 2.20 (m, 2H), 1.81 (m, 2H), 1.67 (m, 1H), 1.47 (m, 1H), 1.31 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 175.4, 154.8, 142.7, 122.5, 77.4, 64.0, 51.9, 45.5, 33.5, 31.2, 28.3, 24.1; HRMS m/z calcd for $C_{14}H_{23}NO_5$ (MH^+) 286.1654, found 286.1653.

Boc-Ser(OBn) Weinreb Amide (13).[23] *N*-Boc-Ser(OBn)-OH (2.95 g, 10.0 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (1.85 g, 20.0 mmol), and DIEA (5.2 g, 40 mmol) were dissolved in 1:1 CH_2Cl_2/DMF (100 mL) and cooled to 0 °C. 1-Hydroxy-1*H*-benzotriazole (HOBt, 1.84 g, 12.0 mmol), DCC (2.48 g, 12.0 mmol), and DMAP (ca. 30 mg) were added, and the reaction was stirred for 24 h. The reaction was filtered to remove dicyclohexylurea and concentrated. The resulting slurry was diluted with 150 mL of ethyl acetate and washed with NH_4Cl (2 × 50 mL), $NaHCO_3$ (2 × 50 mL), and brine (50 mL). The organic layer was dried on $MgSO_4$ and concentrated. Chromatography on silica with 30% EtOAc in hexane gave 3.04 g (90%) of **13** as a colorless syrup: ^{1}H NMR δ 7.35−7.23 (m, 5H), 5.42 (d, J = 8.5, 1H), 4.87 (br s, 1H), 4.56 (d, J = 12.5, 1H), 4.49 (d, J = 12.5, 1H), 3.71 (s, 3H), 3.66 (m, 2H), 3.17 (s, 3H), 1.43 (s, 9H).

Ketone 14. To a solution of **4** (7.59 g, 39.1 mmol) in 100 mL of THF at −40 °C was added *s*-BuLi (1.3 M in cyclohexane, 60 mL, 78 mmol). The reaction was stirred at −40 °C for 3 h to generate cyclopentenyllithium. Then the mixture was added via syringe in three portions to a solution of Weinreb amide **13** (4.41 g, 13.0 mmol) in THF (50 mL), dried over 3 Å molecular sieves for 3 h, at −78 °C. The mixture was stirred for 3 h at −78 °C, quenched with NH_4Cl (20 mL), diluted with EtOAc (200 mL), washed with NH_4Cl (2 × 50 mL), $NaHCO_3$ (50 mL), and brine (50 mL), dried over $MgSO_4$, and concentrated. Chromatography on silica with 8% EtOAc in hexane and then 12% EtOAc in hexane gave 3.88 g (86%) of ketone **14** as a yellow oil: ^{1}H NMR δ 7.34−7.22 (m, 5H), 6.79 (m, 1H), 5.57 (d, J = 10.5, 1H), 5.00 (m, 1H), 4.54 (d, J = 12.4, 1H), 4.43 (d, J = 12.0, 1H), 3.71 (d, J = 4.4, 2H), 2.62 (m, 1H), 2.54 (m, 3H), 2.00−1.82 (m, 2H), 1.44 (s, 9H); ^{13}C NMR δ 195.0, 155.5, 145.5, 143.3, 137.7, 128.4, 127.8, 127.6, 79.8, 73.2, 71.1, 56.4, 34.3, 31.0, 28.4, 22.5. Anal. Calcd for $C_{20}H_{27}O_4N$: C, 69.54; H, 7.88; N, 4.05. Found: C, 69.54; H, 7.74; N, 4.01.

Alcohol 15. Ketone **14** (3.78 g, 11.0 mmol) was dissolved in 2.5:1 THF/MeOH (125 mL) and cooled to 0 °C. $CeCl_3$ (4.91 g, 13.2 mmol) was added, followed by $NaBH_4$ (0.84 g, 22 mmol). After being stirred for 2 h at 0 °C, the reaction was quenched with NH_4Cl (50 mL), diluted with EtOAc (200 mL), washed with NH_4Cl (2 × 100 mL) and brine (100 mL), dried on $MgSO_4$, and concentrated. Chromatography on silica with 15% EtOAc in hexane yielded 3.49 g (92%) of a white solid as a 4:1 mixture of diastereomers, mp 67−68 °C. The major diastereomer was isolated by precipitation from EtOAc/*n*-hexane: ^{1}H NMR δ 7.36−7.28 (m, 5H), 5.65 (m, 1H), 5.35 (d, J = 8.4, 1H), 4.51 (d, J = 11.6, 1H), 4.42 (d, J = 12.0, 1H), 4.33 (br s, 1H), 3.84 (br s, 1H), 3.71−3.68 (dd, J = 3.4, 13.4, 1H), 3.60−3.55 (dd, J = 2.6, 9.4, 1H), 3.18 (d, J = 8.4, 1H), 2.35−2.20 (m, 4H), 1.87 (m, 2H), 1.44 (s, 9H); ^{13}C NMR δ 155.9, 144.7, 137.6, 128.7, 128.2, 128.1, 126.7, 79.7, 74.1, 74.0, 70.6, 52.1, 32.4, 28.6, 23.9. Anal. Calcd for $C_{20}H_{29}O_4N$: C, 69.14; H, 8.41; N, 4.03. Found: C, 69.42; H, 8.54; N, 4.12.

Ester 16. To a solution of alcohol **15** (3.26 g, 9.38 mmol) and pyridine (2.28 mL, 28.2 mmol) in THF (4 mL) was added a solution of *tert*-butyldimethylsilyloxyacetyl chloride[34] (2.05 g, 9.40 mmol) in THF (4 mL) dropwise at 0 °C. The reaction was stirred for 3 h at rt, then diluted with 30 mL of Et_2O, washed with 0.5 N HCl (2 × 20 mL), $NaHCO_3$ (10 mL), and brine (10 mL), dried on $MgSO_4$, and concentrated. Chromatography with 4% EtOAc in hexanes on silica gave 3.48 g (70%) of ester **16** as a yellow oil: ^{1}H NMR δ 7.35−7.28 (m, 5H), 5.67 (s, 1H), 5.58 (d, J = 8.0, 1H), 4.83 (d, J = 9.4, 1H), 4.51 (d, J = 11.9, 1H), 4.42 (d, J = 11.9, 1H), 4.16 (s, 2H), 4.04 (m, 1H), 3.55 (dd, J = 3.5, 9.4, 1H), 3.48 (dd, J = 3.3, 9.5, 1H), 2.41 (m, 1H), 2.33−2.21 (m, 3H), 1.83 (m, 2H), 1.40 (s, 9H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR δ 170.6, 155.3, 139.9, 138.0, 130.2, 128.5, 127.8, 127.7, 79.5, 73.3, 72.6, 68.5, 61.8, 51.0, 32.4, 31.6, 28.4, 25.8, 23.2, 18.4, −5.4. Anal. Calcd for $C_{28}H_{45}NO_4Si$: C, 64.70; H, 8.73; N, 2.69. Found: C, 64.58; H, 8.89; N, 2.69.

α-Hydroxy Acid 17. To a solution of diisopropylamine (3.3 mL, 24 mmol) in THF (40 mL) was added *n*-butyllithium (2.5 M in hexane, 8.6 mL, 22 mmol) at 0 °C. The mixture was stirred for 15 min to generate LDA. Then a mixture of chlorotrimethylsilane (7.52 mL, 59.2 mmol) and pyridine (5.22 mL, 64.6 mmol) in THF (15 mL) was added dropwise to the LDA solution at −100 °C. After 5 min, a solution of ester **16** (2.83 g, 5.38 mmol) in THF (18 mL) was added dropwise, and the reaction was stirred at −100 °C for 25 min, then warmed slowly to rt over 1.5 h, and stirred at rt for 1.5 h. The reaction was quenched with 1 N HCl (70 mL), and the aqueous layer was extracted with Et_2O (2 × 150 mL). The organic layer was dried on $MgSO_4$ and concentrated to give 1.98 g (crude yield 70%) of colorless glassy oil. Without further purification, the product was dissolved in 10 mL of THF. Tetrabutylammonium fluoride (2.8 g, 11 mmol) in THF (10 mL) was added at 0 °C, and the resulting solution was stirred at 0 °C for 5 min and then at rt for 1 h. The reaction was quenched with 0.5 N HCl (50 mL), extracted with EtOAc (100 mL), dried on $MgSO_4$, and concentrated. Chromatography with 50% EtOAc in hexane on silica gave 1.16 g (52%) of α-hydroxy acid **17** as a colorless foam: ^{1}H NMR (DMSO-d_6) δ 7.36−7.24 (m, 5H), 6.84 (d, J = 7.35, 1H), 5.28 (d, J = 7.80, 1H), 4.50 (d, J = 11.9, 1H), 4.44 (d, J = 12.2, 1H), 4.31 (br s, 1H), 3.84 (d, J = 6.0, 1H), 3.40−3.32 (m, 2H), 3.27 (dd, J = 5.1, 10.1, 1H), 2.70−2.61 (m, 1H), 2.41−2.37 (m, 1H), 2.17−2.10 (m, 1H), 1.74−1.67 (m, 2H), 1.55−1.42 (m, 2H), 1.37 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 175.3, 155.7, 145.4, 139.2, 128.7, 127.9, 127.8, 121.6, 78.0, 74.0, 72.5, 72.3, 50.5, 47.6, 30.0, 29.6, 28.8, 24.6. Anal. Calcd for $C_{22}H_{31}NO_6$: C, 65.17; H, 7.71; N, 3.45. Found: C, 65.03; H, 7.80; N, 3.47.

Acid 18. Lead tetraacetate (2.69 g, 6.06 mmol) in $CHCl_3$ (13.5 mL) was added dropwise to a solution of acid **17** (2.28 g, 5.51 mmol) in EtOAc (81 mL) at 0 °C. The reaction was stirred for 10 min, then quenched with ethylene glycol (8 mL), diluted with EtOAc (150 mL), washed with H_2O (4 × 15 mL) and brine (15 mL), dried on Na_2SO_4, and concentrated to give 2.02 g (100% crude yield) of aldehyde as yellow oil: ^{1}H NMR ($CHCl_3$) δ 9.38 (d, J = 2.8, 1H), 7.36−7.27 (m, 5H), 5.39 (dd, J = 2.2, 8.6, 1H), 4.95 (d, J = 7.1, 1H), 4.55 (d, J = 12.2, 1H), 4.47 (d, J = 12.2, 1H), 4.41 (br s, 1H), 3.50 (dd, J = 4.3, 9.3, 1H), 3.43 (dd, J = 5.0, 9.4, 1H), 3.25 (m, 1H), 2.55 (m, 1H), 2.24 (m, 1H), 1.99 (m, 1H), 1.86 (m, 1H), 1.72 (m, 2H), 1.43 (s, 9H). The product was dissolved in acetone (140 mL) and cooled to 0 °C. Jones reagent (2.7 M H_2SO_4, 2.7 M CrO_3; 4 mL, 11 mmol) was added dropwise. The reaction was stirred at 0 °C for 0.5 h, quenched with isopropyl alcohol (12 mL), and stirred for 10 min. The precipitate was filtered out, and the solvent was evaporated. The residue was extracted with EtOAc (3 × 200 mL), washed H_2O (50 mL) and brine (50 mL), dried on Na_2SO_4, and concentrated. Chromatography on silica with 30% EtOAc in hexane gave 1.65 g (78%) of acid **18** as a colorless oil: ^{1}H NMR ($CHCl_3$) δ 7.30 (m, 5H), 5.55 (d, J = 6.7, 1H),

4.93 (br s, 1H), 4.53 (d, J = 12.1, 1H), 4.51 (d, J = 12.1, 1H), 4.39 (br s, 1H), 3.47 (dd, J = 3.5, 9.2, 1H), 3.41 (dd, J = 5.3, 9.6, 1H), 3.36 (t, J = 7.0, 1H), 2.54 (m, 1H), 2.29 (m, 1H), 2.04−1.84 (m, 3H), 1.66 (m, 1H), 1.43 (s, 9H); ^{13}C NMR ($CHCl_3$) δ 179.9, 155.6, 143.8, 138.2, 128.5, 127.7, 127.6, 122.6, 79.4, 73.1, 72.1, 50.4, 49.5, 30.1, 29.4, 28.5, 25.1; IR (cm^{-1}) 3000−2800 (br), 1701 (s), 1162, 731, 697; HRMS m/z calcd for $C_{21}H_{29}NO_5$ (MH^+) 376.2124, found 376.2133.

Boc-Ser-Ψ[(*E*)CH=C]-Pro-OH (2). NH_3 (35 mL) was distilled and allowed to warm to reflux (−33 °C), and Na (ca. 330 mg, 14 mmol) was added until a deep blue solution was sustained. Acid **18** (575 mg, 1.50 mmol) in THF (13 mL) was added directly to the Na/NH_3 solution via syringe. After being stirred for 15 min at reflux, the reaction was quenched with NH_4Cl (20 mL) and then allowed to warm to rt. NH_4Cl (40 mL) was added, and the mixture was extracted with $CHCl_3$ (5 × 30 mL). The aqueous layer was acidified with 1 N HCl and extracted with $CHCl_3$ (6 × 50 mL). The $CHCl_3$ layer was dried on $MgSO_4$ and concentrated to give 280 mg (64%) of the acid as a yellow oil: ^{1}H NMR (DMSO-d_6) δ 6.66 (d, J = 7.4, 1H), 5.31 (dd, J = 2.1, 8.7, 1H), 4.61 (br s, 1H), 4.06 (s, 1H), 3.27 (dd, J = 7.1, 10.8, 1H), 3.20 (dd, J = 5.7, 10.5, 1H), 3.16 (m, 1H), 2.39 (m, 1H), 2.22 (m, 1H), 1.80 (m, 3H), 1.52 (m, 1H), 1.36 (s, 9H); ^{13}C NMR δ 175.4, 155.7, 143.6, 122.5, 78.0, 64.0, 52.9, 49.6, 30.1, 29.5, 28.8, 25.0; HRMS m/z calcd for $C_{14}H_{23}NO_5$ (MH^+) 286.1654, found 286.1661.

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Supporting Information Available: Experimental details for **11**, **12**, **19**, and **20** and NMR spectra for compounds **1**, **2**, **9**−**12**, and **18**−**20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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