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Building constrained peptidomimetics: a convenient approach to 3-phenyl-5-vinyl substituted proline derivatives

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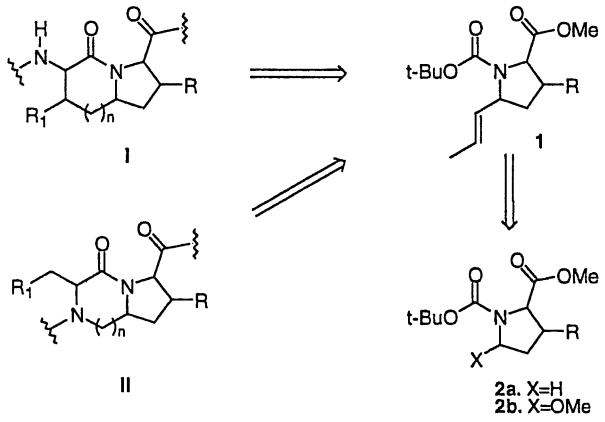
Abstract—An approach to the synthesis of 3-phenyl-5-vinyl substituted prolines starting from readily available 2,3-disubstituted pentenoic acid derivatives is reported. The route converts the pentenoic acid derived starting materials into cyclic *N*-acyliminium ion precursors with the use of a hydroboration–Swern oxidation sequence. This overall transformation worked best when the initial alkylborane product was treated sequentially with excess MCPBA and then acetone prior to the Swern oxidation. In this way, a 70% yield of the desired *N*-acyliminium ion precursor could be obtained. Once in hand, the cyclic *N*-acyliminium ion precursor was used to make the desired 3-phenyl-5-vinyl substituted prolines.

As part of an effort to provide general routes to constrained peptidomimetics, we have reported the synthesis of a variety of bicyclic peptide building blocks like **I** and **II** (Scheme 1).[1] In these examples, the N-terminal side of the molecule was constructed by annulating a ring onto a proline derivative (**2a**, X=H). This was accomplished by first functionalizing the proline derivative using an anodic methoxylation reaction and then converting the resulting methoxylated product (**2b**, X=OMe) into a 5-vinyl proline derivative **1**. The vinyl proline derivatives were used to build bicyclic structures like **I** via an olefin metathesis based strategy[2] and bicyclic structures like **II** via an intramolecular reductive amination route.[3]



Scheme 1.

While both routes have proven to be very effective, little has been done to apply the chemistry to the synthesis of building blocks containing non-proline (R≠H) *C*-terminal groups. Efforts in this area have been hindered by the lack of a convenient method for synthesizing the required 3-substituted-5-vinyl proline starting materials (**1**). We found this problem particularly perplexing in our efforts to build analogs for the Phe7–Phe8 region of substance P.[3] In this work, a series of bicyclic analogs of type **II** was required where both R and R_1 were phenyl rings. In addition, it was essential that the stereochemistry of both the proline α-carbon and the phenyl substituent at C_3 of the proline ring be varied relative to the bridgehead carbon of the bicyclic peptidomimetic. While several intriguing routes to 3,5-disubstituted prolines had been reported (Scheme 2),[4] these approaches were not directly applicable to the 3-phenyl-5-vinyl substituted substrates (**1**, R=Ph) that were needed. For example, the strategy outlined in Eq. (1) (Scheme 2) provided a nice route to 3-carbomethoxy-5-alkoxy prolines.[4a] However, the key reaction in this sequence led to a 3:1 ratio of stereoisomers and by necessity afforded a product having a methyl ester at C_3 of the proline ring. Hence, the conversion of a product obtained from this route into a building block like **1** having a phenyl ring at C_3 of the proline ring required a series of additional steps. The need for these additional steps combined with the formation of stereoisomers in the key step rendered such an approach cumbersome for making the quantities of material needed for using the final proline derivatives as starting materials for the subsequent synthetic efforts. Similar problems limited the utility of the approaches to 3,5-disubstituted prolines outlined in Eqs. (2)[4b] and (3) (Scheme 2).[4c] While in both cases the chemistry developed leads to a 3,5-disubstituted proline derivative, the length of the route required to make substrates like **1** and the lack of

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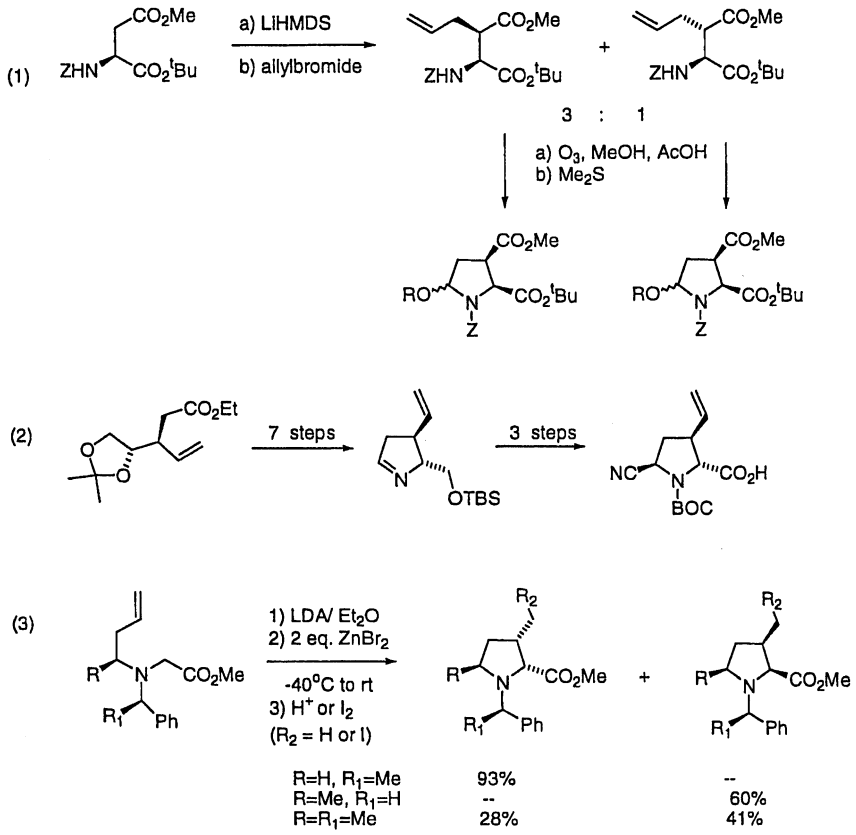
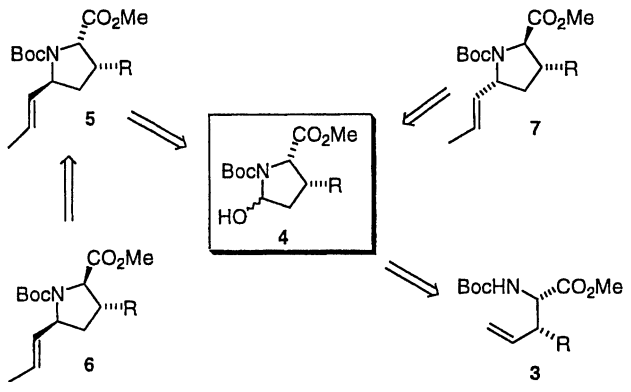


Scheme 2.

stereochemical versatility in the syntheses again limited the utility of both routes for building the starting materials needed for constructing the desired bicyclic peptidomimetics.

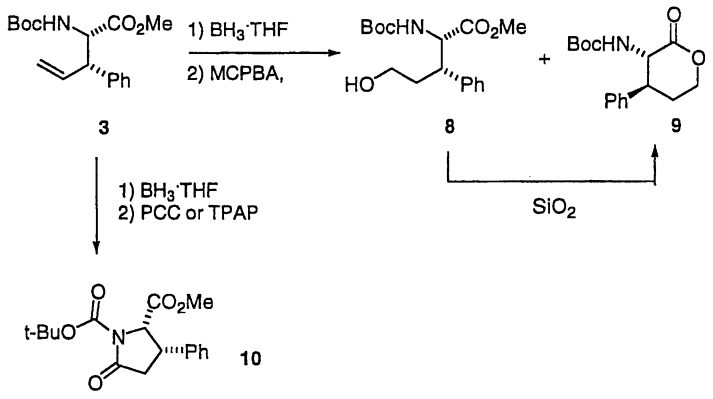
More general approaches to 3-substituted prolines like **2a** were available,[5] and as in earlier studies the C_5 position of these products could be functionalized using an anodic oxidation reaction.[2,3] However, since the products from these efforts were to be used as starting materials, we hoped to develop a more efficient strategy for constructing building blocks like **1** that would directly generate 3-substituted proline rings with functionality at C_5 already in place. For this reason, we began to investigate what appeared to be a very straightforward route to the required building blocks



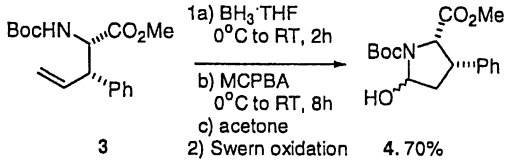
Scheme 3.

(Scheme 3).[6] This route was enticing because both disubstituted pentenoic acid derivatives like **3** and their enantiomers can be readily synthesized in high optical purity.[7] In principle, conversion of these starting materials into cyclic *N*-acyliminium ion precursors (**4**) would provide rapid access to a number of 3,5-disubstituted proline derivatives. For example, compound **5** would be made from **4** with the use of a cuprate addition reaction, compound **6** would be made from **5** by epimerization of the carbon bearing the methyl ester, and compound **7** would be made from **4** by accomplishing the epimerization reaction prior to the cuprate addition reaction. If the enantiomer of **3** were used as the starting material,[7] then the opposite enantiomer of each of the 3,5-disubstituted proline derivatives would be available.

With this in mind, the syntheses of the 3-phenyl-5-vinyl substituted proline derivatives required for the substance P efforts were undertaken.[2c] However, while the route designed appeared straightforward and the starting methyl ester (**3**) was readily assembled using the known asymmetric Claisen rearrangement,[7] the desired conversion of **3** into the cyclic *N*-acyliminium ion precursor proved problematic. Efforts to generate an alcohol intermediate (**8**) from the hydroboration step were complicated by a competitive lactonization reaction (**9**) involving the methyl ester (Scheme 4). While this competitive cyclization could be minimized during the reaction by oxidizing the intermediate alkylborane with MCPBA, only very low yields of the alcohol could be obtained following purification. Efforts to avoid purification of the alcohol also met with



Scheme 4.

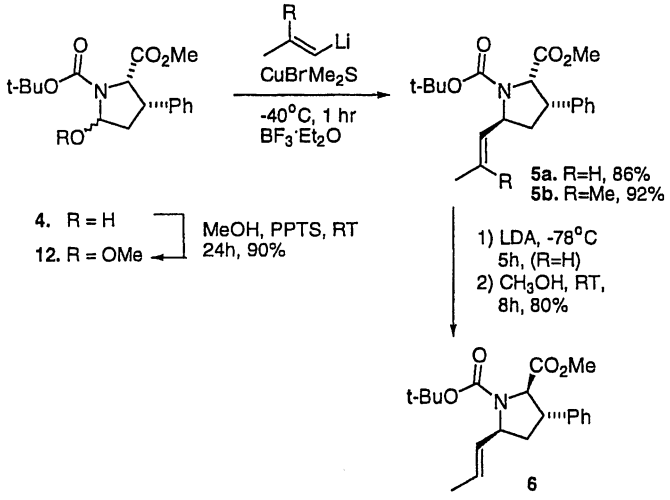


Scheme 5.

limited success. Oxidation methods using PCC and TPAP to directly convert alkylboranes into aldehydes led to the generation of **4** and the formation of the imide derivative (**10**) following overoxidation. The overoxidation could be avoided if the hydroboration using MCPBA in the workup was employed and then the crude alcohol oxidized using Swern conditions. Yet while successful to a certain degree, this route required removing any of excess MCPBA from the alcohol prior to the oxidation. The net result was a delicate balance between having enough MCPBA present to efficiently oxidize the alkylborane (a reaction that benefits from excess MCPBA) and limiting the excess MCPBA in order to optimize the Swern oxidation. This led to a difficult reaction that typically afforded only 30–40% yields of the desired **4**.

For these reasons, we sought a method for removing excess MCPBA from the crude reaction product while avoiding the need to purify the alcohol intermediate. To this end, we found that adding acetone to the hydroboration–oxidation sequence prior to workup was very helpful. The resulting Baeyer–Villiger reaction generated methylacetate and *m*-chlorobenzoic acid. The acid was separated from the alcohol with the use of a saturated sodium carbonate wash. Following concentration, the crude alcohol left behind could be used as the substrate for the Swern oxidation without further purification. In this fashion, starting material **3** was converted into **4** in a 70% isolated yield (Scheme 5).

Once compound **4** was in hand, attention was turned to making building blocks **5**–**7**. In an initial step, the alcohol was exchanged for a methyl ether (**12**, Scheme 6). The methyl ether was then treated with the cuprate reagent derived from *trans*-1-lithio-1-propene and copper bromide dimethylsulfide complex in the presence of $BF_3{\cdot}Et_2O$. Like all previous cuprate reactions of this type,[8] the vinyl group was added to the face of the proline ring opposite that of the methyl ester. None of the isomer having the vinyl group and the methyl ester groups *cis* to each other was observed. This was also true for the addition of 2-methylpropenyllithium (leading to **5b**) which could be used in place of the more difficult to obtain *trans*-1-lithio-propene for building blocks



Scheme 6.

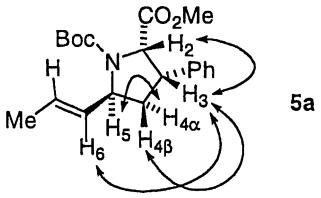
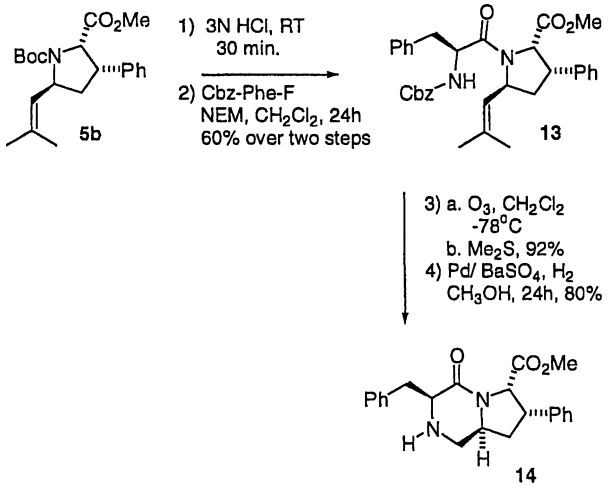


Figure 1.

where the steric bulk of the olefin did not matter (the less substituted olefins are normally used in building blocks made for olefin metathesis based strategies). The relative stereochemistry of building blocks was established with the use of a NOESY experiment. The key interactions used to make this assignment are illustrated for **5a** in Fig. 1.

Since the building blocks were to be used in conformational probes, it was important to confirm that the absolute stereochemistry of **5a** and **5b** were assigned correctly and to establish that the stereochemistry of the building block would remain intact when it was incorporated into the desired bicyclic peptidomimetic. To this end, **5b** was converted into the bicyclic lactam **14** (Scheme 7).

At no time during this synthesis was a second stereoisomer observed, a fact that was constistent with the literature observation[7] that the preparation of the carboxylic acid leading to **3** afforded an enantiomeric excess greater than 99%. As with **5a**, the relative stereochemistry of **14** was established with the use of a NOESY experiment. The key interactions used in this assignment are illustrated in Fig. 2.



Scheme 7.

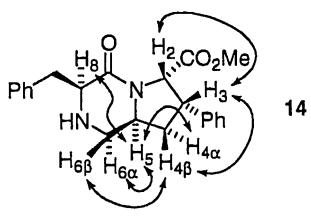


Figure 2.

This work established both that the *cis*-stereochemistry between the methyl ester and phenyl substituents was preserved and that the stereochemistry at C_5 was not altered during the ozonolysis and reductive amination steps. Assignment of the stereochemistry of the proline relative to the known center in phenylalanine confirmed that the absolute stereochemistry of **5a** and **5b** had been assigned correctly.

Building block **5a** was converted into stereoisomer **6** by treating it with LDA at −78°C for 5 h (Scheme 6). The reaction was quenched with methanol to afford an 80% yield of the epimerized product. The 5 h reaction time for the epimerization was important. Quenching the reaction after 2 h led to a 1:1 mixture of **5a** and **6**, while longer reaction times led to decreased yields of the product. The progress of the epimerization could be monitored by the proton chemical shift observed for the methyl ester. In **5a**, the methyl group was located in the shielding cone of the aromatic ring and gave rise of a signal with a chemical shift of ca. 3.2 ppm in the proton NMR spectrum. The signal for the methyl ester in **6** was found at a chemical shift of ca. 3.7 ppm. The relative stereochemistry of this isomer was also confirmed with the use of a NOESY experiment. The key interactions used to make the assignment are highlighted in Fig. 3.

A reversal of the cuprate addition–epimerization reaction sequence led to stereoisomer **7** (Scheme 8). In this case, the methoxylated compound **12** was treated with LDA and the resulting enolate quenched with methanol after a period of 5 h. A 75% isolated yield of the epimerized product was obtained. This material was then treated with the cuprate reagent derived from *trans*-1-lithio-1-propene and copper bromide dimethylsulfide complex in the presence of $BF_3{\cdot}Et_2O$. As in the earlier case, the vinyl group added to the face of the incipient *N*-acyliminium ion that was *trans* to the methyl ester. The relative stereochemistry of the product was again established using a NOESY experiment (Fig. 4).

The enantiomers of building blocks **5**–**7** (Fig. 5) were made by starting with the enantiomer of **3**.[6] The chemistry used in

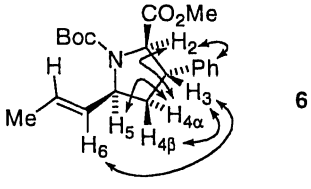
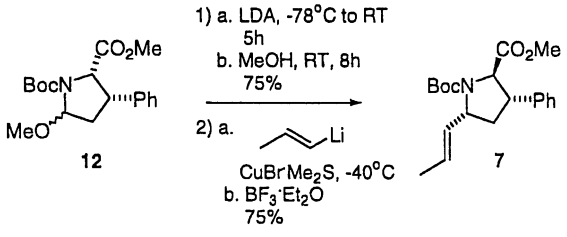


Figure 3.



Scheme 8.

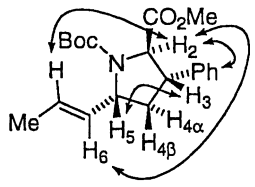


Figure 4.

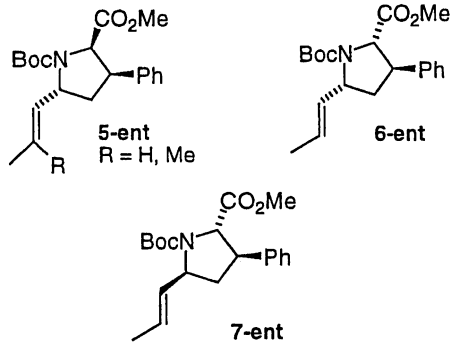
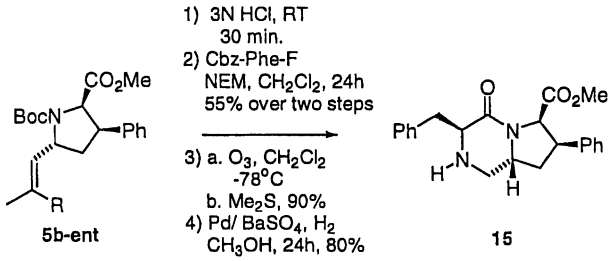


Figure 5.

this effort was identical to that described above, and the absolute stereochemistry for the series confirmed by converting the enantiomer of **5b** (**5b-ent**) into a bicyclic lactam derivative **15** (Scheme 9). As with the earlier diastereomer **14**, the stereochemistry of **15** was assigned using a 2D-NOESY experiment (Fig. 6).

In conclusion, we have found that a series of 5-vinyl substituted proline derivatives needed for generating bicyclic lactam peptidomimetics can be rapidly synthesized from known chiral pentenoic acid derivatives. The key to this transformation was a hydroboration–oxidation sequence that benefited from the use of MCPBA followed by acetone in the workup of the hydroboration step.



Scheme 9.

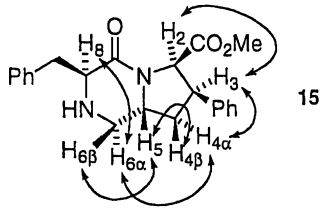


Figure 6.

1. Experimental[9]

1.1. Data for compounds

1.1.1. Methyl (2*S*,3*S*)-2-[*N*-(*tert*-butyloxycarbonyl) amino]-3-phenyl-4-pentenate (3). (2*S*,3*S*)-2-[*N*-(*tert*-butyloxycarbonyl) amino]-3-phenyl-4-pentenoic acid[7] (2.72 g, 9.3 mmol) was dissolved in 40 mL of CH_3OH and 4 mL of water was added. The solution was titrated to pH=7.0 (pH paper) with a 20% aqueous solution of Cs_2CO_3 (~8 mL). The mixture was evaporated to dryness and the residue was reevaporated twice from 15 mL of toluene. The yellowish solid cesium salt obtained was stirred with 1.16 mL (18.6 mmol) of iodomethane in 15 mL of DMF for 1 day. The mixture was partitioned between EtOAc (150 mL) and water (150 mL). The organic phase was separated and washed with saturated NaCl solution twice, dried over $MgSO_4$, and evaporated to dryness. The crude product was chromatographed through 200 g of silica gel that was slurry packed with a 4:1 hexane in ether solution. Elution with the same solvent afforded 2.7 g (92%) of the desired product **3** as a white crystal: TLC (Et_2O/hexane (1:4)) R_f=0.2; ^{1}H NMR ($CDCl_3$/300 MHz) δ 1.37 (s, 9H), 3.66 (s, 3H), 3.76 (t, 1H, J=7.8 Hz), 4.67 (t, 1H, J=7.8 Hz), 4.83 (d, 1H, J=8.7 Hz), 5.17 (d, 1H, J=11.4 Hz), 5.18 (d, 1H, J=15.6 Hz), 6.03–6.13 (m, 1H), 7.17–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 171.8, 155.0, 138.7, 136.4, 128.5, 127.9, 127.1, 117.3, 79.9, 57.3, 54.2, 53.4, 52.2, 51.8, 51.4, 27.9; IR (neat/NaCl) 3028, 2976, 1744, 1715, 1496, 1367, 1165, 700 cm^{-1}; LRMS (FAB) 306 (MH^+, 15), 250 (45), 206 (50), 185 (37), 137 (37), 117 (22), 93 (100); HRMS $C_{17}H_{24}NO_4$ (MH^+) calcd 306.1705, found 306.1707.

1.1.2. (3*S*)-*N*-*tert*-Butyloxycarbonyl-5-hydroxy-3-phenyl-L-proline methyl ester (4). To a solution of **3** (156 mg, 0.5 mmol) in 2 mL of THF at 0°C was added 1 mL of 1.0 M BH_3·THF solution (1.0 mmol). The mixture was stirred and allowed to slowly warm to room temperature. After 1 h, the reaction was then cooled to 0°C and 1.3 g (4.0 mmol) of MCPBA in 8 mL of THF added. The mixture was allowed to warm slowly to room temperature and stirred overnight. Then 1 mL of acetone was added and the reaction was stirred for 10 min. The reaction was then diluted with ether, transferred to a separatory funnel, washed three times with saturated Na_2CO_3 solution, and then washed with saturated NaCl solution. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. This residue was redissolved in 2 mL of CH_2Cl_2 and cooled to −78°C. To this solution was added 80 μL of DMSO (1.1 mmol), then followed with 60 μL of freshly distilled $(COCl)_2$ (0.55 mmol). After 15 min, 0.35 mL of triethylamine (2.50 mmol) was added and the reaction was allowed to warm to room temperature. Water (5 mL) was added and the reaction was then transferred to a separatory funnel. The organic phase was separated and the inorganic phase was extracted with additional CH_2Cl_2 (25 mL×3). The combined organic phase was washed successively with brine, 1% HCl, H_2O and 5% Na_2CO_3, dried over $MgSO_4$ and concentrated in vacuo. The crude product was chromatographed through 20 g of silica gel that was slurry packed with a 1:1 hexane in ether solution. Elution with the same solvent afforded 110 mg (70%) of a 7:4 mixture of isomers (**4**) as a yellowish oil: TLC (Et_2O/hexane (1:1)) R_f=0.21, 0.14; ^{1}H NMR

($CDCl_3$/300 MHz) δ 1.38 (s, 3.6H), 1.39 (s, 3.6H), 1.47 (s, 0.9H), 1.58 (s, 0.9H), 2.10–2.20 (m, 0.5H), 2.40–2.74 (m, 1.5H), 3.20 (s, 0.3H), 3.22 (s, 1.2H), 3.25 (s, 0.3H), 3.27 (s, 1.2H), 3.54–3.80 (m, 0.7H), 4.01–4.19 (m, 0.3H), 4.48–4.68 (m, 1H), 5.57–5.83 (m, 1H), 7.18–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 171.1, 154.0, 136.2, 136.1, 129.1, 129.0, 128.9, 128.4, 128.3, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 82.4, 82.2, 81.7, 81.5, 81.2, 81.1, 64.6, 64.4, 51.5, 51.3, 45.3, 44.9, 44.4, 44.0, 38.2, 36.3, 35.9, 35.2, 28.4, 28.3, 28.2, 28.1, 28.0; IR(neat/NaCl) 3300, 2950, 1720, 1659, 1320, 1300, 1050, 725 cm^{-1}.

The product was carried to the next step without further characterization.

1.1.3. (3*S*)-*N*-*tert*-Butyloxycarbonyl-5-methoxy-3-phenyl-L-proline methyl ester (12). To the solution of **4** (104 mg, 0.33 mmol) in 1 mL of methanol, 15 mg PPTS (0.06 mmol) was added and the reaction was stirred under room temperature overnight. Then the reaction mixture was diluted with 10 mL of ethyl acetate, successively washed with 1% HCl, saturated $NaHCO_3$ and brine, dried over $MgSO_4$, concentrated in vacuo. The crude product was chromatographed through 20 g of silica gel that was slurry packed with a 4:1 hexane in ether solution. Elution with the same solvent afforded 90 mg (90, 63% over the three steps from **3**) of the desired product **12** as a colorless oil: TLC (Et_2O/hexane (1:1)) R_f=0.5; ^1H NMR ($CDCl_3$/300 MHz) δ 1.38 (s, 6H), 1.50 (s, 3H), 2.05 (dd, 1H, J=5.4, 12.3 Hz), 2.58 (ddd, 1H, J=5.4, 13.8, 26.4 Hz), 3.19 (s, 1.1H), 3.22 (s, 1.9H), 3.42 (s, 1.07H), 3.46 (s, 1.93H), 4.01–4.10 (m, 1H), 4.48 (d, 0.66H, J=8.7 Hz), 4.52 (d, 0.34H, J=8.7 Hz), 5.25 (d, 0.34H, J=5.1 Hz), 5.45 (d, 0.66H, J=4.8 Hz), 7.18–7.39 (m, 5H); ^{13}C NMR($CDCl_3$/75 MHz) δ 171.2, 154.0, 136.2, 136.1, 129.1, 128.3, 128.3, 127.7, 127.8, 127.5, 127.5, 89.0, 88.8, 81.1, 80.8, 64.8, 64.2, 56.4, 56.2, 51.4, 51.2, 44.9, 44.0, 35.1, 34.1, 28.3, 28.1; IR (neat/NaCl) 3028, 2971, 2950, 1744, 1708, 1387, 1367, 1318, 1204, 1173, 1085, 700 cm^{-1}; LRMS (FAB) 304 (MH^+-CH_3OH, 45), 204 (100), 144 (85); HRMS $C_{17}H_{22}NO_4$ (MH^+CH_3OH) calcd 304.1549, found 304.1548.

1.1.4. (3*S*,5*S*)-*N*-*tert*-Butyloxycarbonyl-3-phenyl-5-(*trans*-1-propenyl)-L-proline methyl ester (5a). In a flame-dried 25 mL round bottom flask under argon, 23 mg of lithium wire (containing 0.5% Na, 3.27 mmol) was cut and washed three times with hexane. Anhydrous ether (3.5 mL) was added and the mixture was cooled to −20°C. To this solution was added 0.14 mL of *trans*-1-bromo-1-propene (1.64 mmol). After 2 h at −20°C, this solution was cannulated into a 50 mL flask containing 0.34 g $CuBr{\cdot}Me_2S$ (1.64 mmol) in 1 mL of anhydrous ether at −40°C. The resulting dark brown solution was stirred at −40°C for 1 h, cooled to −78°C, and then treated with 0.20 mL of $BF_3{\cdot}Et_2O$ (1.64 mmol). After 5 min, 137 mg of **12** (0.41 mmol) was added to the solution and the cooling bath was removed. After 15 min, the reaction mixture was quenched with a 1:1 NH_4OH/saturated NH_4Cl solution and diluted with CH_2Cl_2. The layers were separated and the inorganic phase was extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was chromatographed through 20 g of silica gel that was slurry packed with a 4:1 hexane in ether solution. Elution with the same solvent afforded 120 mg (85.7%) of the desired product as a colorless oil: TLC (Et_2O/hexane (1:1)) R_f=0.40; $[\alpha]_D^{20}$=−15.9° (*c* 0.252, ether); ^1H NMR ($CDCl_3$/600 MHz) δ 1.38 (s, 5.4H), 1.44 (s, 3.6H), 1.73 (d, 3H, J=6.6 Hz), 1.85–1.88 (m, 1H), 2.73–2.83 (m, 1H), 3.23 (s, 1.2H), 3.26 (s, 1.8H), 3.68–3.82 (m, 1H), 4.48 (d, 0.6H, J=9.0 Hz), 4.55 (d, 0.4H, J=9.0 Hz), 4.59 (t, 0.4H, J=6.6 Hz), 4.72 (t, 0.6H, J=6.6 Hz), 5.48–5.68 (m, 2H), 7.20–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$/150 MHz) δ 171.6, 153.4, 136.5, 136.4, 131.3, 131.2, 128.3, 128.3, 127.9, 127.8, 127.5, 127.4, 125.6, 125.5, 80.1, 80.0, 64.9, 64.3, 58.8, 58.4, 51.3, 51.2, 45.2, 44.3, 34.2, 33.4, 28.4, 28.2, 17.6, 17.5; IR (neat/NaCl) 3028, 2976, 2950, 1746, 1705, 1692, 1452, 1392, 1367, 1209, 1176, 1132, 964, 783, 698 cm^{-1}; LRMS (FAB) 346 (MH^+, 6), 344 (8), 290 (58), 246 (100), 230 (57), 204 (26), 186 (56), 93 (34); HRMS $C_{20}H_{28}NO_4$ (MH^+) calcd 346.2018, found 346.2022.

1.1.5. (3*S*,5*S*)-*N*-*tert*-Butyloxycarbonyl-3-phenyl-5-(2-methyl-1-propenyl)-L-proline methyl ester (5b). Vinyl substituted proline derivative **5b** was made in a fashion identical to that described for the synthesis of **5a**. TLC (Et_2O/hexane (1:2)) R_f=0.3; ^1H NMR ($CDCl_3$/300 MHz) δ 1.38 (s, 5.4H), 1.44 (s, 3.6H), 1.73 (s, 2.1H), 1.74 (s, 2.1H), 1.79 (s, 0.9H), 1.80 (s, 0.9H), 1.76–1.85 (m, 1H), 2.76–2.92 (m, 1H), 3.24 (s, 0.34H), 3.28 (s, 0.66H), 3.77–3.90 (m, 1H), 4.52 (d, 0.6H, J=9.0 Hz), 4.60 (d, 0.4H, J=9.0 Hz), 4.86 (t, 0.4H, J=9.0 Hz), 4.96 (t, 0.6H, J=9.0 Hz), 5.31 (t, 1H, J=9.0 Hz), 7.20–7.34 (m, 5H); ^{13}C NMR($CDCl_3$/75 MHz) δ 171.8, 154.4, 153.4, 136.7, 136.6, 133.5, 132.1, 128.3, 127.9, 127.8, 127.4, 126.5, 79.9, 79.8, 64.9, 64.3, 55.4, 55.3, 51.3, 51.2, 45.8, 44.8, 35.7, 35.0, 28.4, 28.3, 25.8, 25.6, 18.1, 18.0; IR (neat/NaCl) 3054, 3028, 2971, 2945, 1744, 1705, 1692, 1452, 1390, 1364, 1253, 1207, 1170, 1126, 899, 791, 698 cm^{-1}; LRMS (FAB) 366 (M+Li, 22), 358(50), 304(60), 258(78), 204(100), 144(34), 91(32); HRMS $C_{21}H_{29}NO_4$ (M+Li) calcd 366.2256, found 366.2252.

1.1.6. (3*S*,5*S*)-*N*-(Cbz–Phe)-3-Phenyl-5-(2-methyl-1-propenyl)-L-proline methyl ester (13). The vinyl substituted proline **5b** (490 mg, 1.3 mmol) was dissolved in 5 mL of 3N HCl in ethyl acetate (V_{HCl}/V_{EtOAc}=1:3) and the reaction was stirred at room temperature for 30 min. The solvent was removed and the residue was dried in vacuo. The residue was then dissolved in 5 mL of CH_2Cl_2. To this solution was added 0.33 mL of *N*-ethylmorpholine (2.6 mmol) and 0.9 g of Cbz–Phe–F (2.6 mmol) in 5 mL of CH_2Cl_2. The stirring was continued for one day. The reaction was then diluted with 15 mL of CH_2Cl_2 and washed successively with 5% citric acid (two times), 5% $NaHCO_3$ (two times), and brine. The resulting organic layer was dried over $MgSO_4$ concentrated in vacuo. The crude product was chromatographed through 50 g of silica gel that was slurry packed with 1:1 ether in hexane. Elution with the same solvent afforded 450 mg (60%) of the coupling product **13** as a pale yellow solid: TLC (Et_2O/hexane (1:1)) R_f=0.14; ^1H NMR ($CDCl_3$/300 MHz) δ 1.67–1.70 (m, 6H), 2.01–2.15 (m, 2H), 2.38–2.48 (m, 1H), 2.82–3.24 (m, 2H), 3.25–3.26 (m, 3H), 3.65–3.79 (m, 2H), 4.09–4.14 (m, 1H), 4.21–4.25 (m, 1H), 4.62–4.88 (m, 1H), 5.03–5.21 (m, 1H), 5.24–5.42 (m, 1H), 7.14–7.31 (m, 15H); ^{13}C NMR ($CDCl_3$/75 MHz) δ

173.4, 171.3, 170.3, 155.6, 140.3, 136.6, 136.3, 135.9, 134.3, 129.4, 128.4, 128.3, 128.2, 127.9, 127.7, 127.5, 126.8, 126.5, 126.2, 70.1, 66.7, 65.4, 64.3, 55.4, 53.0, 51.3, 47.6, 44.0, 39.5, 39.1, 36.3, 33.4, 32.9, 25.8, 18.1; IR (neat/NaCl) 3374, 3286, 3023, 2945, 1741, 1715, 1640, 1491, 1439, 1232, 1044, 732, 695 cm^{-1}; LRMS (FAB) 547 (M+Li, 100), 487 (6), 296 (10), 266 (18), 210 (16), 160 (20), 91(62); HRMS $C_{33}H_{36}N_2O_5Li$ (M+Li) calcd 547.2784, found 547.2783.

1.1.7. (3*S*,6*S*,8*S*,9*S*)-1,4-Diaza-3-benzyl-9-carbomethoxy-8-phenyl-2-oxo bicyclo-[4, 3, 0]nonane (14). In a 50 mL of round bottom flask fitted with stir bar, 440 mg of the coupling product **13** (0.83 mmol) was dissolved in 5 mL of CH_2Cl_2. The solution was cooled to −78°C and then ozone bubbled through until a blue color persisted. After the solution turned blue, the ozone was bubbled for additional 10 min. The flow of ozone was then terminated and oxygen bubbled through the solution till the blue color disappeared. The reaction was then treated with 0.3 mL of Me_2S (4.1 mmol) at −78°C, allowed to warm to room temperature, and stirred overnight. The solvent was removed in vacuo and the crude product was chromatographed through 20 g of silica gel using 4:1 ether in hexane as elutant to afford 370 mg (90%) of product (two isomers, ~5:3) as a white solid: TLC (Et_2O/hexane (1:1)) R_f=0.30, 0.14; ^1H NMR ($CDCl_3$/300 MHz) δ 2.15–2.28 (m, 1H), 2.48–2.52 (m, 1H), 3.11–3.30 (m, 2H), 3.31 (s, 3H), 3.44 (s, 1H), 3.74–3.87 (m, 1H), 4.60–4.62 (m, 1H), 4.96 (d, 1H, J=8.7 Hz), 5.17 (s, 2H), 5.46 (s, 1H), 7.04–7.46 (m, 15H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 169.9, 167.5, 155.8, 155.6, 138.2, 135.5, 135.0, 129.8, 129.3, 128.9, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.8, 127.7, 127.5, 126.9, 126.7, 81.0, 68.9, 67.8, 66.8, 63.2, 60.3, 57.3, 51.7, 44.8, 38.2, 37.0, 33.1, 31.5, 22.6, 14.0; IR (neat/NaCl) 3400, 3028, 2950, 1739, 1705, 1679, 1449, 1405, 1307, 1209, 749, 698 cm^{-1}; LRMS (FAB) 521 (M+Li, 46), 312 (16), 210 (20), 160 (18), 121 (12), 91 (100); HRMS $C_{30}H_{30}N_2O_6Li$ (M+Li) calcd 521.2264, found 521.2259.

To finish the synthesis of **14**, a solution of 220 mg of the ozonolysis product (0.44 mmol) in 3 mL of anhydrous methanol was treated with 80 mg of 5% palladium on $BaSO_4$. The reaction was then placed under hydrogen balloon for one day. Following this period, the reaction mixture was filtered through celite and the filtrate concentrated in vacuo. The crude product was chromatographed through 20 g of silica gel using ether/methanol (9:1) as the elutant to afford 121 mg (80%) of pure product **14** as a yellowish oil: TLC (CH_3OH/Et_2O (1:50)) R_f=0.16; ^1H NMR ($CDCl_3$/300 MHz) δ 1.84 (br. s, 1H), 2.11–2.19 (m, 1H), 2.36 (dd, 1H, J=11.4, 24.3 Hz), 2.98 (dd, 1H, J=11.4, 13.8 Hz), 3.03 (dd, 1H, J=11.4, 21.9 Hz), 3.17 (dd, 1H, J=3.6, 12 Hz), 3.22 (s, 3H), 3.26 (dd, 1H, J=3.6, 14.1 Hz), 3.65–3.76 (m, 2H), 3.88–3.98 (m, 1H), 4.72 (d, 1H, J=9.0 Hz), 7.22–7.36 (m, 10H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 170.3, 169.6, 138.6, 135.8, 129.4, 128.6, 128.3, 127.9, 127.6, 126.5, 63.7, 59.9, 58.1, 51.5, 45.4, 43.8, 37.4, 32.6; IR(neat/NaCl) 3462, 3328, 3059, 3023, 2945, 1741, 1643, 1496, 1452, 1431, 1369, 1323, 1207, 1176, 783, 729, 695 cm^{-1};

1.1.8. (3*S*,5*S*)-*N*-*tert*-Butyloxycarbonyl-3-phenyl-5-(*trans*-1-propenyl)-D-proline methyl ester (6). In a flame-dried 10 mL of pear flask fitted with N_2 inlet and magnetic stir bar, 0.14 mL of diisopropylamine (1.0 mmol) was dissolved in 1 mL of freshly distilled THF, cooled to −78°C, then 0.44 mL *n*-BuLi (2.5 M in hexane, 1.1 mmol) was added. After 30 min, this solution was cannulated into a 25 mL of round bottom flask containing the starting material **5a** (60 mg, 0.2 mmol) in 1 mL of THF at −78°C. The reaction was allowed to slowly warm to room temperature. After 5 h, 5 mL of anhydrous methanol was added and the reaction was stirred for 8 h. The reaction mixture was then neutralized with dilute HCl to pH=7 and 5 mL of water was added. The organic layer was separated and the inorganic layer was extracted three times with CH_2Cl_2. The combined organic layer was washed with saturated NaCl solution, dried over Na_2SO_4, and concentrated in vacuo. The crude product was chromatographed through 10 g of silica gel that was slurry packed with a 4:1 hexane in ether solution. Elution with the same solvent afforded 48 mg (80%) of the desired product **6** as a colorless oil: TLC (Et_2O/hexane (1:1)) R_f=0.40; $[\alpha]_D^{20}$=+31.5° (*c* 0.127, ether); ^1H NMR ($CDCl_3$/300 MHz) δ 1.42 (s, 9H), 1.75 (d, 3H, J=6.3 Hz), 2.09 (m, 1H), 2.22–2.32 (m, 1H), 3.44–3.54 (m, 1H), 3.68 (s, 3H), 4.21–4.56 (m, 2H), 5.30–5.87 (m, 2H), 7.22–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 173.2, 153.3, 139.2, 131.2, 130.8, 128.7, 127.1, 126.5, 80.2, 66.6, 65.8, 59.7, 59.2, 51.8, 47.9, 47.0, 40.2, 29.6, 28.3, 17.8; IR (neat/NaCl) 3033, 2971, 2935, 1752, 1692, 1452, 1392, 1364, 1253, 1196, 1165, 1121, 964, 762, 698 cm^{-1}; LRMS (FAB) 346 (MH^+, 10), 246 (44), 230 (18), 204 (15), 185 (50), 154 (42), 137 (32), 93 (100); HRMS $C_{20}H_{28}NO_4$ (MH^+) calcd 346.2018, found 346.2021.

1.1.9. (3*S*)-*N*-*tert*-Butyloxycarbonyl-5-methoxy-3-phenyl-D-proline methyl ester. A procedure identical to that used to prepare **6** from **5a** was used. To this end, 130 mg of **12** afforded 97 mg (75%) of the epimerized product as a colorless oil. TLC (Et_2O/hexane (1:4)) R_f=0.12; ^1H NMR ($CDCl_3$/300 MHz) δ 1.43 (s, 6.3H), 1.52 (s, 2.7H), 2.11–2.16 (m, 1H), 2.24–2.30 (m, 1H), 3.48 (s, 0.9H), 3.51 (s, 2.1H), 3.69 (s, 3H), 3.71–3.77 (m, 1H), 4.27 (d, 0.7H, J=9.6 Hz), 4.42 (d, 0.3H, J=9.3 Hz), 5.30 (d, 0.3H, J=4.5 Hz), 5.40 (d, 0.7H, J=4.5 Hz), 7.27–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 172.6, 154.0, 139.2, 128.7, 127.3, 88.2, 87.9, 81.1, 80.8, 66.3, 65.5, 55.6, 55.2, 52.1, 52.00, 47.4, 46.6, 41.8, 40.6, 28.3, 28.1, 25.00; IR (neat/NaCl) 2971, 2945, 1754, 1708, 1452, 1385, 1364, 1315, 1199, 1170, 1085, 765, 698 cm^{-1}; LRMS (FAB) 304 (MH^+-CH_3OH, 16), 204 (100), 144 (28), 93 (26); HRMS $C_{17}H_{22}NO_4$ (MH^+-CH_3OH) calcd 304.1549, found 304.1544.

1.1.10. (3*S*,5*R*)-*N*-*tert*-Butyloxycarbonyl-3-phenyl-5-(*trans*-1-propenyl)-D-proline methyl ester (7). In a procedure similar to that used to prepare **5a** from **12**, 64 mg of the methoxy compound prepared in the proceeding experiment was converted into 48 mg (75%) of **7** as a colorless oil. TLC (Et_2O/hexane (1:1)) R_f=0.36; $[\alpha]_D^{20}$=−21.1° (*c* 0.10, ether); ^1H NMR ($CDCl_3$/300 MHz) δ 1.40 (s, 4.5H), 1.41 (s, 4.5H), 1.65 (d, 3H, J=5.1 Hz), 1.87–1.97 (m, 1H), 2.44–2.50 (m, 1H), 3.33–3.41 (m, 1H), 3.68 (s, 3H), 4.36–4.48 (m, 2H), 5.25–5.66 (m, 2H), 7.21–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 173.2, 172.3, 154.5, 153.2, 140.2, 139.9,

132.5, 131.8, 128.7, 128.6, 128.0, 127.1, 126.1, 80.1, 79.9, 66.8, 66.1, 60.8, 52.0, 51.9, 47.9, 47.2, 41.0, 40.5, 28.2, 17.6, 17.4; IR (neat/NaCl) 3033, 2971, 2935, 1749, 1710, 1690, 1452, 1392, 1364, 1253, 1199, 1173, 959, 757, 698 cm^{-1}; LRMS (FAB) 346 (MH^+, 6), 246 (20), 204 (17), 185 (54), 137 (500), 93 (100); HRMS $C_{20}H_{28}NO_4$ (MH^+) calcd 346.2018, found 346.2013.

1.1.11. (3*R*,5*R*)-*N*-*tert*-Butyloxycarbonyl-3-phenyl-5-(*trans*-1-propenyl)-D-proline methyl ester (5a-ent). Starting from (2*R*,3*R*)-2-*N*-(*tert*-butyloxycarbonyl) amino]-3-phenyl-4-pentenoic acid[aa] the enantiomer of **5a** (**5a-ent**) was synthesized in a fashion identical to that described above for **5**. TLC (Et_2O/hexane (1:1)) R_f=0.40; $[\alpha]_D^{20}$=+14.6° (*c* 0.205, ether); ^1H NMR ($CDCl_3$/300 MHz) δ 1.38 (s, 5.4H), 1.44 (s, 3.6H), 1.71–1.74 (m, 3H), 1.83–1.90 (m, 1H), 2.70–2.86 (m, 1H), 3.22 (s, 1.2H), 3.26 (s, 1.8H), 3.71–3.84 (m, 1H), 4.49–4.74 (m, 2H), 5.50–5.70 (m, 2H), 7.12–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 171.6, 171.5, 153.3, 136.5, 136.4, 131.1, 128.3, 127.9, 127.8, 127.4, 125.5, 80.0, 79.9, 64.9, 64.2, 58.3, 51.1, 45.2, 44.3, 34.2, 33.3, 28.3, 28.2, 17.7, 17.5; IR (neat/NaCl) 3033, 2981, 2950, 1749, 1708, 1695, 1390, 1367, 1176, 1132, 786, 698 cm^{-1}; LRMS (FAB) 346 (MH^+, 6), 344 (8), 290 (58), 246 (100), 230 (57), 204 (26), 186 (56), 93 (34); HRMS $C_{20}H_{28}NO_4$ (MH^+) calcd 346.2018, found 346.2023.

1.1.12. (3*R*,5*R*)-*N*-*tert*-Butyloxycarbonyl-3-phenyl-5-(*trans*-1-propenyl)-L-proline methyl ester (6-ent). The enantiomer of **6** (**6-ent**) was synthesized in a fashion identical to that used to prepare **6**. TLC (Et_2O/hexane (1:1)) R_f=0.45; $[\alpha]_D^{20}$=−25.0° (*c* 0.16, ether); ^1H NMR ($CDCl_3$/600 MHz) δ 1.42 (s, 5.4H), 1.44 (s, 3.6H), 1.75 (d, 3H, *J*=6.6 Hz), 2.08 (m, 1H), 2.28 (m, 1H), 3.48–3.52 (m, 1H), 3.67 (s, 1.8H), 3.69 (s, 1.2H), 4.22–4.57 (m, 2H), 5.62–5.90 (m, 2H), 7.23–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$/150 MHz) δ 173.2, 154.2, 153.3, 140.1, 139.3, 131.3, 130.8, 128.7, 128.7, 128.5, 128.3, 128.2, 127.8, 127.3, 127.1, 126.4, 80.2, 80.0, 66.6, 65.8, 59.7, 59.2, 52.1, 51.8, 47.9, 47.0, 40.2, 39.6, 29.6, 28.2, 17.8, 17.6; IR (neat/NaCl) 3033, 2971, 2935, 1752, 1702, 1695, 1454, 1392, 1364, 1250, 1196, 1168, 1121, 964, 760, 698 cm^{-1}; LRMS (FAB) 346 (MH^+, 10), 290 (35), 246 (100), 230 (44), 204 (32), 186 (40), 157 (20), 117 (20), 91 (30); HRMS $C_{20}H_{28}NO_4$ (MH^+) calcd 346.2018, found 346.2021.

1.1.13. (3*R*,5*S*)-*N*-*tert*-Butyloxycarbonyl-3-phenyl-5-(*trans*-1-propenyl)-L-proline methyl ester (7-ent). The enantiomer of **7** (**7-ent**) was prepared in a fashion identical to that described for the preparation of **7**. TLC (Et_2O/hexane (1:1)) R_f=0.36; $[\alpha]_D^{20}$=+15.9° (*c* 0.315, ether); ^1H NMR ($CDCl_3$/600 MHz) δ 1.40 (s, 4.5H), 1.42 (s, 4.5H), 1.65–1.67 (m, 3H), 1.90–1.95 (m, 1H), 2.44–2.51 (m, 1H), 3.35–3.39 (m, 1H), 3.69 (s, 3H), 4.35–4.50 (m, 2H), 5.27–5.65 (m, 2H), 7.25–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$/600 MHz) δ 173.3, 172.8, 154.5, 153.3, 140.3, 140.0, 132.6, 131.9, 128.6, 127.1, 126.2, 126.1, 80.1, 79.9, 66.9, 66.2, 60.8, 52.1, 51.9, 48.0, 47.2, 41.1, 40.5, 28.2, 17.7, 17.4; IR (neat/NaCl) 3033, 2971, 2935, 1749, 1710, 1692, 1452, 1395, 1367, 1253, 1199, 1168, 959, 757, 698 cm^{-1}; LRMS (FAB) 346 (MH^+, 6), 344 (8), 290 (48), 246 (100), 204 (20), 186 (47), 1579 (16), 117 (18), 93 (52); HRMS $C_{20}H_{28}NO_4$ (MH^+) calcd 346.2018, found 346.2017.

1.1.14. (3*S*,6*R*,8*R*,9*R*)-1,4-Diaza-3-benzyl-9-carbomethoxy-8-phenyl-2-oxo bicyclo-[4, 3, 0] nonane (15). Starting from **5b-ent**, the bicyclic analog **15** was prepared in a fashion identical to that described for the preparation of **14** from **5b**. TLC (Et_2O/CH_3OH (9:1)) R_f=0.30; ^1H NMR ($CDCl_3$/600 MHz) δ 1.78 (bs, 1H), 2.02 (dt, 1H, *J*=10.8, 15.6 Hz), 2.29–2.34 (m, 1H), 2.56 (dd, 1H, *J*=12.6, 14.4 Hz), 3.04 (dd, 1H, *J*=10.2, 16.8 Hz), 3.24 (s, 3H), 3.28 (dd, 1H, *J*=10.8, 15.6 Hz), 3.39 (dd, 1H, *J*=4.8, 16.8 Hz), 3.68 (dd, 1H, *J*=11.4, 3.6 Hz), 3.77 (dt, 1H, *J*=4.8, 10.8 Hz), 4.19–4.25 (m, 1H), 5.16 (d, 1H, *J*=10.8 Hz) 7.17–7.36 (m, 10H); ^{13}C NMR ($CDCl_3$/150 MHz) δ 169.6, 168.9, 139.2, 137.8, 129.3, 128.5, 128.2, 128.0, 127.2, 126.6, 63.8, 59.6, 59.2, 51.4, 48.8, 44.2, 38.5, 36.2; IR (neat/NaCl) 3486, 3222, 3027, 2945, 1743, 1647, 1496, 1452, 1431, 1370, 1202, 1178, 754, 699 cm^{-1}; LRMS (FAB) 371 (M+Li, 100), 337 (10), 280 (30), 218 (12), 134 (10), 91 (16); HRMS $C_{22}H_{24}N_2O_3Li$ (M+Li) calcd 371.1947, found 371.1937.

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Appendix A. Supplementary material available

The proton and carbon spectra are included for all new compounds along with 2D-NOESY data for compounds **5a**, **6**, **7**, **14**, and **15** (42 pages).

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