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Asymmetric Synthesis of *cis*-5-*tert*-Butylproline with Metal Carbenoid NH Insertion

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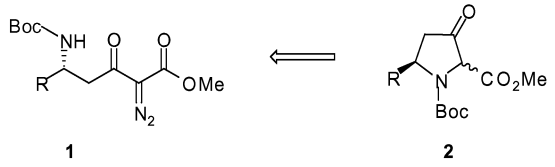
The highly stereoselective intramolecular metal carbenoid insertion reaction of sulfinimine-derived δ-amino α-diazoesters is used to prepare *cis*-5-*tert*-butylproline. A concerted or nearly concerted metal carbenoid N−H insertion reaction mechanism is proposed.

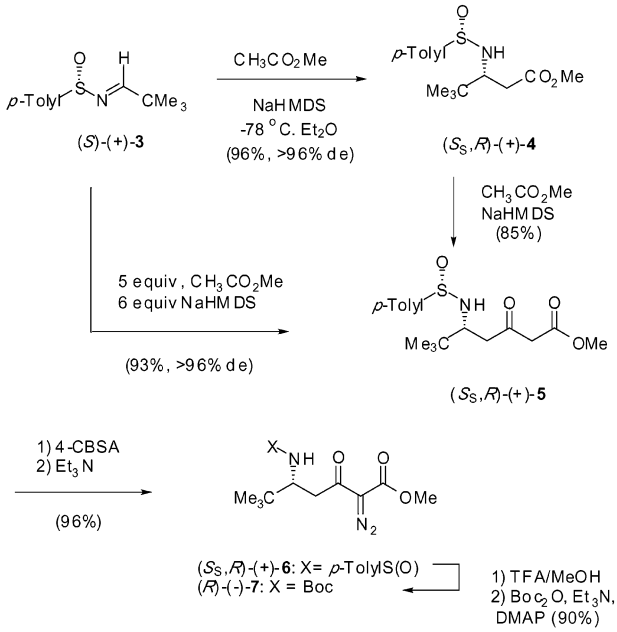
Recently we introduced new methodology for the asymmetric synthesis of substituted prolines from enantiopure *N*-sulfinyl δ-amino β-keto esters, a new polyfunctionalized chiral building block.[1,2] The key step in this transformation was the facile intramolecular NH-insertion of a metal carbenoid derived from an enantiopure *N*-Boc δ-amino α-diazo β-keto ester **1**. A single diastereomeric 3-oxo-5-substituted proline **2** was produced, but racemized at C-2 furnishing a mixture of inseparable cis/trans isomers (Scheme 1).[1] The oxo proline **2** was elaborated into *cis*-5-phenyl proline.[1] To examine the stereochemistry of the insertion reaction, and to expand and determine the limitations of the methodology, we disclose here the enantioselective syntheses of (2*S*,5*R*)-(−)-5-*tert*-butylproline methyl ester by two different routes. This target was chosen because of the bulky 5-*tert*-butyl group and the fact that this cyclic amino acid has found utility in probing peptide conformations.[3,4] Lubell and co-workers also described an efficient six-step asymmetric synthesis of this proline from glutamic acid 5-methyl ester.[3]

SCHEME 1



1 **2**

SCHEME 2



Results and Discussion

Synthesis from the δ-Amino β-Keto Ester. The requisite *N*-sulfinyl δ-amino β-keto ester (S_S,*R*)-(+)-(**5**) was prepared in one pot, in 93% yield and >96% de, by treatment of (*S*)-(+)-*N*-(2,2-dimethylpropylidene)-*p*-toluenesulfinamde (**3**)[5] with 5 equiv of the sodium enolate of methyl acetate as described earlier (Scheme 2).[2c] Alternatively (+)-**5** was prepared in 85% yield and >96% de by reaction of β-amino acid (S_S,*R*)-(+)-**4** with 4 equiv of the sodium enolate of methyl acetate. On reaction of (+)-**5** with commercially available 4-carboxybenzenesulfonyl azide (4-CBSA) the *N*-sulfinyl δ-amino α-diazo β-keto ester (+)-**6** was obtained in 96% yield. The diazo compound, without purification, was treated with TFA/MeOH to remove the sulfinyl group, concentrated, dissolved in THF, and on reaction with Boc_2O/Et_3N and a catalytic amount of DMAP afforded the *N*-Boc-protected product (*R*)-(−)-**7** in 90% yield.

With the diazo compound in hand, treatment with 3 mol % of $Rh_2(OAc)_4$ gave a 97% isolated yield of 5-*tert*-butyl-3-oxo-proline (−)-**8** as a single isomer. In contrast to **2** (R = Ph), where racemization at C-2 was facile on chromatographic workup,[1] similar purification of (−)-**8**

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(3) Beausoleil, E.; L'Archeveque, B.; Belec, L.; Atfani, M.; Lubell, W. D. *J. Org. Chem.* **1996**, *61*, 9447.
(4) Halab, L.; Belec, L.; Lubell, W. D. *Tetrahedron* **200**1, *57*, 6439.
(5) Davis, F. A.; Zhang, Y.; Andemichael, Y.; Fang, T.; Fanelli, D. L.; Zhang, H. *J. Org. Chem.* **1999**, *64*, 1403.

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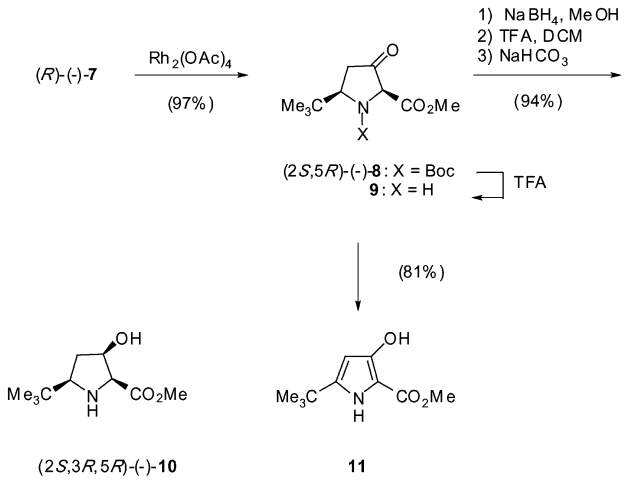
SCHEME 3

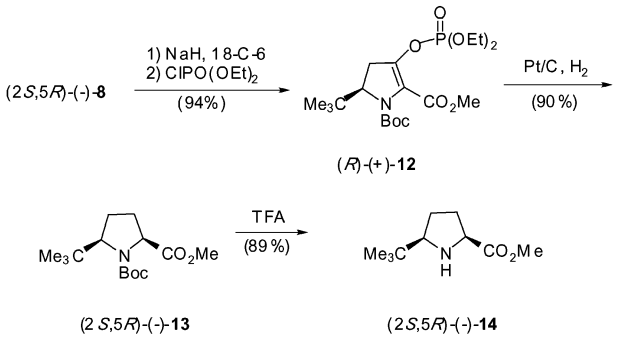


afforded a single isomer (Scheme 3). Attempts to determine the stereochemistry of this adduct by NMR (NOSEY) were unsuccessful. To resolve this problem the 3-oxo group was reduced, and removal of the Boc group afford a single alcohol (−)-**10**. A NOSEY spectrum of the alcohol indicated a strong NOE between the C-2 and C-5 protons suggesting a cis relationship for these protons.

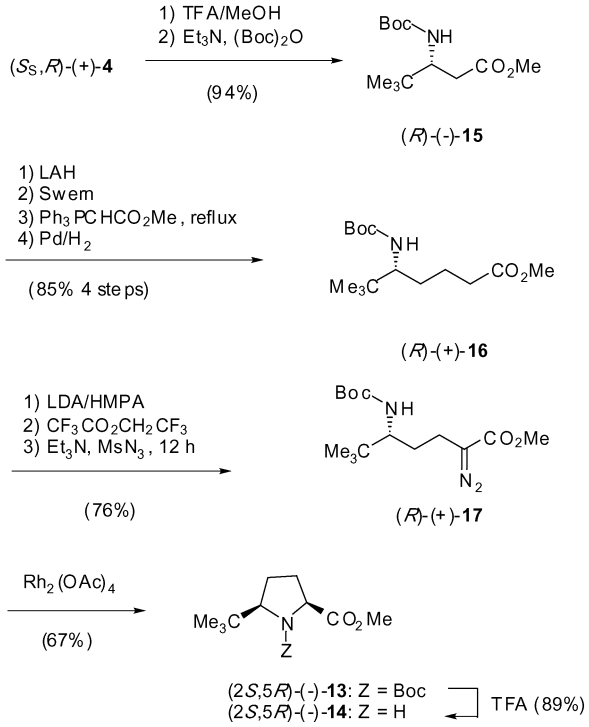
Interestingly, when (−)-**8** was treated with TFA to remove the Boc group the ^{1}H NMR indicated that **9** was formed in nearly quantitative yield, but with some epimerization at C-2 (Scheme 3). However, with preparative chromatographic purification, pyrrole **11** was obtained in 81% yield. Over a period of 6 days, on standing in an NMR tube **9** was slowly transformed into **11**. It seems likely that aromatization of **9** involves air oxidation, probably via the intermediate enol, although this species was not detected. The structure of **11** was based on the downfield shift of the C-4 proton, the lack of protons at C-2, C-4, and C-5, as well as HRMS.[6] The $Rh_2(OAc)_4$-mediated decomposition of α-(*N*-tosyl)amino-*β*-keto-α-diazo to give similar pyrroles has recently been reported.[7]

To transform the oxy proline (−)-**8** into *cis*-5-*tert*-butyl proline (−)-**14** it was necessary to remove the 3-oxo group. This was efficiently accomplished via the enol phosphonate (*R*)-(+)-**12**, which was prepared by treatment of (−)-**8**, first with NaH, 18-crown-6 and then with diethyl chlorophosphate. The enol phosphoate, **12**, obtained as a single regioisomer in 94%, was hydrogenated (Pt/C, H_2) to give (−)-**13**, and the Boc group was removed to afford proline (2*S*,5*R*)-(−)-**14** in 80% yield for the two steps (Scheme 4).

SCHEME 4



SCHEME 5

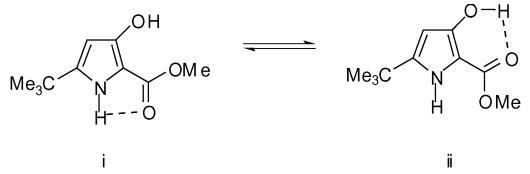


Synthesis from *δ*-Amino Pentanoate. To further probe the intramolecular carbenoid N−H insertion methodology it was of interest to prepare *cis*-proline (−)-**14** from a diazonium precursor where eventual removal of the 3-oxo group would not be an issue. Here possible epimerization at C-2 would be improbable and the stereochemistry of the metal carbenoid NH insertion reaction could be more easily evaluated. This method requires the asymmetric synthesis of methyl (*R*)-(−)-3-(*tert*-butoxycarbonylamino)-4,4-dimethylpentanoate (**15**), which was prepared as outlined in Scheme 5.

Our synthesis begins with replacing the *N*-sulfinyl group in *β*-amino acid (*S*$_S$,*R*)-(+)-**4** with an *N*-Boc group to give (*R*)-(−)-**15** in 94% yield. Reduction of the ester with LAH and Swern oxidation of the crude alcohol gives the aldehyde, which is not purified, but heated at 80 °C for 14 h with methyl (triphenylphosphoranylidene)-acetate to give the alkene. On hydrogenation (Pd/H_2) the alkene furnished (*R*)-(+)-**16** in 85% yield for the four steps (Scheme 5).

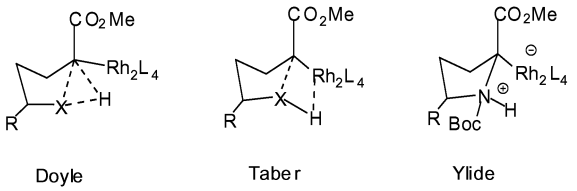
Next the α-diazo ester was prepared via diazo transfer with use of mesyl azide, as described by Danheiser,[8] to give (*R*)-(+)-**17** in 76% yield after purification by flash

(6) The C-2, C-3, and C-5 quaternary carbons were not easily detectable in the ^{13}C NMR spectra of **11** when the sample was taken in $CDCl_3$. However, in CD_3OD these carbons were easily observable. We speculate that hydrogen bonding, i and ii, may be responsible for broadening the signals of these carbons in the former solvent.



(7) Deng, G.; Jiang, N.; Ma, Z.; Wang, J. *Synlett* **2002**, 1913.

SCHEME 6



chromatography. Treatment of the diazo compound, as before, with 3 mol % of $Rh_2(OAc)_4$ gave (−)-**13** as a single isomer and removal of the *N*-Boc group gave (−)-**14** (Scheme 5).

Mechanism of NH Insertion. The mechanism of the diazo dirhodium tetracarboxylate-catalyzed carbenoid insertion into C−H bonds has been extensively explored.[9] The rate-limiting step is thought to be formation of the metal carbenoid with C−H activation and C−C bond formation being concerted.[10] Experimentally the concerted nature of the reaction is consistent with the fact that retention of configuration is observed at the C−H carbon.[11] The Doyle[12] and Taber[13] (X = CH_2) transition state models have been suggested for this transformation (Scheme 6),[9,10] and are supported by BSLyP density functional calculations.[9] The situation for metal carbenoid insertion into polar X−H (N−H) bonds is less clear, but stepwise mechanisms involving ylides followed by proton transfer have generally been considered (Scheme 6).[14] Here calculations suggest that the two-step ylide process, followed by rearrangement, will be much faster than the concerted equivalent.[15] However, the exclusive formation of *cis*-5-substituted prolines (−)-**8** and (−)-**13** from diazo esters (*R*)-(−)-**7** and (*R*)-(+)-**17** seems to be more consistent with a concerted or nearly concerted process for metal carbenoid insertion into the N−H bond. We speculate that in the Doyle and Taber models (X = *N*-Boc) the carbomethoxy group is first forced into the axial position by the metal and proton transfer would be envisioned as a concerted process resulting in cis stereochemistry. In the case of the ylide, dissociation of the metal forms an anion at C-2 and very fast proton transfer would be required for the observed cis stereochemistry. Alternatively the proton could be transferred to the metal and then to C-2 in a reductive elimination procedure. It is interesting to note that in the synthesis of (+)-thienamycin via metal, carbenoid insertion into an N−H bond affords the bicyclic β-lactam ring with exclusive trans stereochemistry.[16] Additional studies will be necessary to clarify the intriguing mechanistic question raised in these studies.

In summary, the rhodium-mediated N−H insertion of δ-amino α-diazo esters is highly stereoselective affording *cis*-5-substituted 3-oxo prolines exclusively. The stereospecificity is consistent with a concerted or nearly concerted metal carbenoid NH insertion reaction mechanism. The 5-substituted 3-oxo prolines are readily elaborated to *cis*-5-substituted prolines.

Experimental Section

General Procedures. Column chromatography was performed on silica gel, Merck grade 60 (230−400 mesh). TLC plates were visualized with UV, in an iodine chamber, or with phosphomolybdic acid, unless otherwise noted. ^{1}H NMR and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively.

Dichloromethane was distilled over calcium hydride under an inert atmosphere. THF and ether were freshly distilled under argon from a purple solution of sodium and benzophenone ketyl. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification. (*S*)-(+)-*N*-(1,1-Dimethylethylidene)-*p*-toluenesulfinamide (**3**) was prepared as previously described.[17]

Methyl (S_S,*R*)-(+)-4,4-dimethyl-*N*-(*p*-toluenesulfinyl)-3-aminopentanoate (4). In a 250-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed ether (80 mL) and NaHMDS (14.4 mL, 1.0 M solution in THF) and the solution was cooled to −78 °C. Anhydrous methyl acetate (1.07 g, 14.4 mmol) was added dropwise and the reaction mixture was stirred for 1 h. At this time a solution of (*S*)-(+)-**3** (2.14 g 9.6 mmol) in ether (100 mL) was added via cannula, and the reaction mixture was stirred at this temperature for 1 h and then quenched by addition of saturated aqueous NH_4Cl (10 mL). The solution was warmed to room temperature and extracted with EtOAc (2 × 30 mL), and the combined organic phases were washed with brine (25 mL), dried (Na_2SO_4), and concentrated. Chromatography (20−30% EtOAc/hexane) afforded 2.56 g (96%) of an oil (>99% de); $[\alpha]^{20}_D$ +130 (*c* 0.91, $CHCl_3$); IR (neat) 3196, 2955, 1738 cm^{-1}; ^{1}H NMR ($CHCl_3$) δ 7.61 (d, *J* = 6.8 Hz, 2 H), 7.28 (d, *J* = 6.8 Hz, 2H), 4.28 (d, *J* = 7.2 Hz, 1 H), 3.73 (s, 3 H), 3.60 (m, 1 H), 2.72 (dd, *J* = 3.2, 11.8 Hz, 1 H), 2.50 (dd, *J* = 6, 11.8 Hz, 1 H), 2.40 (s, 3 H), 0.96 (s, 9 H); ^{13}C NMR δ 172.9, 143.8, 141.7, 129.9, 125.7, 63.1, 52.4, 37.7, 36.1, 26.9, 21.7. HRMS calcd for $C_{15}H_{23}NO_3S$ (M + Na) 320.1296, found 320.1301.

Methyl (S_S,*R*)-(+)-6,6-Dimethyl-3-oxo-5-(*p*-toluenesulfinylamino)heptanoate (5) (Two-Step Method). In a 25-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon inlet was placed NaHMDS (0.92 mL, 1.0 M solution in THF) in THF (2 mL) and the solution was cooled to −78 °C. Methyl acetate (0.073 mL, 0.92 mmol) was added via syringe and the reaction mixture was stirred at −78 °C for 1 h. At this time a solution of (S_S,*R*)-(+)-**4** (0.068 g, 0.23 mmol) in THF (1 mL) was added and the reaction mixture was stirred for 4 h. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (2 mL) and H_2O (1 mL) at −78 °C. The reaction mixture was warmed to room temperature and extracted with ethyl acetate

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(14) See ref 9e, Chapter 8.

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(2 × 4 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated. Flash chromatography (1:1 EtOAc/hexane) gave 0.066 g (85%) of a white solid, mp 85−86 °C; $[\alpha]^{20}_D$ +143.3 (*c* 1.0, $CHCl_3$); IR (neat) 3198, 2956, 1745, 1718 cm^{-1}; ^1H NMR δ 7.57 (d, J = 6.8 Hz, 2 H), 7.28 (d, J = 6.8 Hz, 2 H), 4.04 (d, J = 7.6 Hz, 1 H), 3.74 (s, 3 H), 3.73 (m, 1 H), 3.59 (d, J = 12.4 Hz, 1 H), 3.57 (d, J = 12.4 Hz, 1 H), 2.91 (dd, J = 3.2, 13.6 Hz, 1 H), 2.82 (dd, J = 5.6, 13.6 Hz, 1 H), 2.41 (s, 3 H), 0.95 (s, 9 H); ^{13}C NMR δ 201.7, 168.3, 143.5, 141.8, 130.0, 125.7, 61.5, 52.8, 50.3, 46.0, 35.8, 26.9, 21.8. HRMS calcd for $C_{17}H_{25}NO_4S$ (M + Na) 362.1410, found 362.1402.

One-Step Method. In a 500-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon inlet was placed THF (120 mL) and NaHMDS (45.6 mL, 1.0 M solution in THF). The solution was cooled to −78 °C, methyl acetate (3.10 mL, 38.0 mmol) was added via syringe, and the reaction mixture was stirred at this temperature for 1 h. At this time anhydrous ether (100 mL) was added followed by (S_S,*R*)-(+)-**3** (1.70 g, 7.6 mmol) in THF (15 mL). The reaction mixture was stirred at −78 °C for 1 h, warmed to −20 °C for another 3 h, and quenched at −78 °C with saturated aqueous NH_4Cl (40 mL). The solution was extracted with ethyl acetate (3 × 100 mL), and the combined organic phases were dried (Na_2SO_4) and concentrated. Purification was by flash chromatography (1:1 EtOAc/hexane) to give 2.4 g (93%, >96% de) of an oil.

Methyl (S_S,*R*)-(+)-2-Diazo-6,6-dimethyl-3-oxo-*N*-(*p*-toluenesulfinyl)-5-aminoheptanoate (6). In an oven-dried 100-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed 2.04 g (6.0 mmol) of (S_S,*R*)-(+)-**5** and 4-carboxylbenzenesulfonyl azide (4-CBSA, 1.5 g, 6.6 mmol) in acetonitrile (40 mL). The reaction mixture was cooled to 0 °C, Et_3N (2.50 mL, 18.0 mmol) was added, and after 3 h the white precipitate was removed by filtration. The filtrate was concentrated, EtOAc (50 mL) was added, and the organic phase was washed with H_2O (30 mL), 1 N NaOH (30 mL), and brine (30 mL) and dried (Na_2SO_4). Concentration give 2.1 g (96%) of colorless gum; $[\alpha]^{20}_D$ +130.7 (*c* 0.84, $CHCl_3$); IR (neat): 3278, 2958, 2140, 1717, 1653 cm^{-1}; ^1H NMR δ 7.57 (d, J = 6.4 Hz, 2 H), 7.27 (d, J = 6.4 Hz, 2 H), 4.19 (d, J = 6.8 Hz, 1 H), 3.81 (s, 3 H), 3.66 (m, 1 H), 3.13 (dd, J = 3.2, 11.4 Hz, 1 H), 3.03 (dd, J = 7.6, 11.4 Hz, 1 H), 2.40 (s, 3 H), 0.99 (s, 9 H); ^{13}C NMR δ 191.8, 162.8, 143.8, 141.6, 129.9, 125.5, 62.6, 52.6, 42.3, 36.3, 26.8, 21.8 (C=N_2 was not observed). HRMS calcd for $C_{17}H_{23}N_3O_4S$ (M + H) 366.1488, found 366.1497.

Methyl (*R*)-(−)-2-Diazo-6,6-dimethyl-3-oxo-*N*-(*tert*-butoxycarbonyl)-5-aminoheptanoate (7). In a 100-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon-filled balloon was placed 1.5 g (4.1 mmol) of (S_S,*R*)-(+)-**6** in MeOH (25 mL). The solution was cooled to 0 °C, TFA (1.58 mL, 2.3 g, 20.5 mmol) was added, and the reaction mixture was stirred at room temperature for 2 h. At this time the solution was concentrated, the residue was dissolved in THF (20 mL), the solution was cooled to 0 °C, and Et_3N (3.4 mL, 2.5 g, 24.6 mmol) was added, followed by 4-(dimethylamino)pyridine (ca. 0.01 g). To the reaction mixture was added di-*tert*-butyl dicarbonate (0.95 g, 4.92 mmol) and the solution was stirred for 4 h at this temperature. At this time the reaction mixture was quenched with ice and water (30 mL) and extracted with EtOAc (2 × 30 mL). The combined organic phases were washed with H_2O (20 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated. Chromatography (5%−30% EtOAc/hexane) afforded 1.2 g (90%) of a white solid, mp 73−74 °C; $[\alpha]^{20}_D$ −15.9 (*c* 0.68, $CHCl_3$); IR (neat) 3369, 2134, 1719, 1693 cm^{-1}; ^1H NMR δ 4.59 (d, J = 8.4 Hz, 1 H), 3.90 (m, 1 H), 3.85 (s, 3 H), 3.24 (dd, J = 2.4, 10.6 Hz, 1 H), 2.64 (t, J = 9.2 Hz, 1 H), 1.40 (s, 9 H), 0.95 (s, 9 H); ^{13}C NMR δ 192.1, 162.4, 156.2, 79.5, 56.7, 52.7, 42.0, 35.3, 28.7, 26.7 (C=N_2 was not observed). HRMS calcd for $C_{15}H_{25}N_3O_5$ (M + Na) 350.1692, found 350.1693.

Methyl (2*S*,5*R*)-(−)-*N*-(*tert*-Butyloxycarbonyl)-3-oxo-5-(*tert*-butyl)pyrrolidine-2-carboxylate (8). In a 100-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and an argon-filled balloon was placed (*R*)-(−)-**7** (0.78 g, 2.38 mmol) in CH_2Cl_2 (30 mL). To the solution was added $Rh_2(OAc)_4$ (0.050 g, 0.1 mmol), and the reaction mixture was stirred for 2.5 h at room temperature and then concentrated. Chromatography (5%−20% EtOAc/hexane) afforded 0.69 g (97%) of a white solid, mp 119−120 °C; $[\alpha]^{20}_D$ −114.0 (*c* 1.3, $CHCl_3$); IR (neat) 2959, 1753, 1715 cm^{-1}; ^1H NMR δ 4.64−4.74 (br, 1 H), 4.12−4.20 (br, 1 H), 3.84 (s, 3 H), 2.54 (m, 1 H), 2.53 (d, J = 18 Hz, 1 H), 1.44−1.50 (br, 9 H), 0.94 (s, 9 H); ^{13}C NMR δ 204.4, 167.1, 155.9, 81.8, 66.9, 62.6, 53.0, 41.0, 37.1, 28.8, 26.7. HRMS calcd for $C_{15}H_{25}NO_5$ (M + Na) 322.1630, found 322.1626.

Methyl (2*S*,3*R*,5*R*)-(−)-5-*tert*-Butyl-3-hydroxypyrrolidine-1-dicarboxylate (10). In a 50-mL, single-necked, round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an argon-filled balloon was placed (−)-**8** (0.074 g, 0.247 mmol) in dry MeOH (10 mL). The solution was cooled to −78 °C, $NaBH_4$ (0.011 g (0.297 mmol) was added, and the mixture was stirred for 1 h. After warming to room temperature the reaction was quenched with cold H_2O (2 mL) and concentrated, and H_2O (5 mL) and EtOAc (15 mL) were added. The reaction mixture was extracted with EtOAc (2 × 10 mL), and the organic phases were dried (Na_2SO_4) and concentrated. The residue was dissolved in CH_2Cl_2 (10 mL), TFA (0.34 mL, 4.94 mmol) was added, and the solution was stirred at room temperature for 3 h. At this time the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL), the aqueous phase was extracted with EtOAc (2 × 10 mL), and the combined organic phases were dried (Na_2SO_4) and concentrated. Chromatography (40%−60% EtOAC/hexane) afforded 0.07 g (94%, >96% de) of a white solid, mp 69−70 °C; $[\alpha]^{20}_D$ −23.9 (*c* 0.83 $CHCl_3$); IR (neat) 3132, 2955, 1747 cm^{-1}; ^1H NMR δ 4.44 (m, 1 H), 3.76 (s, 3 H), 3.68 (d, J = 3.6 Hz, 1 H), 2.83 (t, J = 6.8 Hz, 1 H), 2.10 (m, 1 H), 2.05−2.25 (br, 2 H), 1.52 (m, 1 H), 0.936 (s, 9 H); ^{13}C NMR δ 172.1, 73.7, 67.1, 66.8, 52.3, 36.9, 33.2, 26.9. HRMS calcd for $C_{10}H_{19}NO_3$ (M + H) 202.1443, found 202.1445.

5-*tert*-Butyl-3-hydroxy-1*H*-pyrrole-2-carboxylic Acid Methyl Ester (11). In a 25-mL, round-bottomed flask equipped with magnetic stirring bar and argon balloon was placed (−)-**8** (0.055 g, 0.18 mmol) in CH_2Cl_2 (5 mL) and anhydrous TFA (1 mL) was added. The reaction mixture was stirred at room temperature for 3 h, at which time saturated aqueous $NaHCO_3$ (3 mL) and H_2O (1 mL) were added. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 3 mL). The combined organic phases were dried (Na_2SO_4) and concentrated.

^1H NMR of the crude product indicated epimerization at C(2) and a spectrum consistent with **9**. Crude **9**, in CH_2Cl_2 (2 mL), was place in a 25-mL, round-bottomed flask equipped with magnetic stirring bar, and 1 g of silica gel was added. After being stirred for 5 min, at room temperature, the solvent was concentrated, and the flask was equipped with a rubber septum and an oxygen balloon. The solid was stirred for 4 h at room temperature, EtOAc (6 mL) was added, and the reaction mixture was stirred for 10 min. The solution was filtered and concentrated. Preparative TLC (20% EtOAc/hexane) gave 0.029 g (81%) of a white solid, mp 110−111 °C; IR (neat) 3480, 3327, 2962, 1677 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.15 (br, 0.5H), 7.75 (br, 1H), 6.43 (br, 0.5H), 5.66 (s, 1H), 3.85 (s, 3H), 1.28 (s, 9 H); ^{13}C NMR (CD_3OD) δ 164.4, 154.7, 149.2, 105.8, 95.3, 51.5, 33.3, 30.6; ^{13}C NMR ($CDCl_3$) δ 94.7, 51.2, 32.3, 30.3. HRMS calcd for $C_{10}H_{15}NO_3$ 197.1052, found 197.1050.

(*R*)-(+)-5-*tert*-Butyl-3-(diethoxyphosphoryloxy)-4,5-dihydropyrrole-1,2-dicarboxy Acid 1-*tert*-Butyl Ester 2-Methyl Ester (12). In a 100-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and an argon-filled balloon were placed (−)-**8** (0.45 g, 1.5 mmol) and 18-crown-6 (1.05 g, 4.0 mmol) in THF (20 mL). The solution was cooled to

0 °C, NaH (0.054 g, 2.3 mmol) was added, and the solution was stirred at this temperature for 20 min. At this time the reaction mixture was warmed to room temperature for another 20 min and then cooled to 0 °C and $(EtO)_2POCl$ (0.38 g, 2.2 mmol) in THF (5 mL) was added dropwise. After 3 h the reaction mixture was carefully quenched with saturated aqueous $NaHCO_3$ (20 mL) and extracted with EtOAc (2 × 15 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. Chromatography (20%−40% EtOAc/hexane) gave 0.59 g (94%) of a colorless thick oil; $[\alpha]^{20}_D$ +62.9 (*c* 0.50, $CHCl_3$); IR (neat) 2975, 1733, 1712, 1291, 1031 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.15−4.25 (m, 4 H), 4.00 (dd, J = 2.0, 7.0 Hz, 1 H), 3.79 (s, 3 H), 3.11 (m, 1 H), 2.60 (m, 1 H), 1.42 (s, 9 H), 1.33−1.39 (m, 6 H), 0.92 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 161.8, 156.2, 145.0 (d, $^2J_{CP}$ = 6.2 Hz), 121.7 (d, $^3J_{CP}$ = 9.4 Hz), 81.7, 67.3, 65.5 (t, $^2J_{CP}$ = 9.6 Hz), 52.0, 36.5, 32.4, 28.7, 25.8, 16.5 (t, $^3J_{CP}$ = 3 Hz). HRMS calcd for $C_{19}H_{34}NO_8P$ (M + Na) 458.1920, found 458.1932.

Methyl (2*S*,5*R*)-(−)-*N*-(*tert*-Butyloxycarbonyl)-5-(*tert*-butylpyrrolidine)-2-carboxylate (13). In a 50-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and an H_2 balloon was placed (+)-**12** (0.30 g, 0.69 mmol) in EtOH (15 mL). Platinum on activated carbon (5%, 0.5 g) was added, and the suspension was stirred for 18 h under an H_2 atmosphere at balloon pressure. The reaction mixture was filtered through a short Celite column and the filtrate was concentrated. Chromatography (5%−10% EtOAc/hexane) gave 0.177 g (90%) of a colorless oil; $[\alpha]^{20}_D$ −31.3 (*c* 1.56, $CHCl_3$) [lit.[3] $[\alpha]^{20}_D$ −32 (*c* 1, CH_3OH)]. Spectral properties were identical with literature values.[3]

Methyl (2*S*,5*R*)-(−)-5-*tert*-Butylpyrrolidine-2-carboxylate (14). In a 5-mL, round-bottom flask equipped with a stirring bar and a rubber septa under an argon atmosphere was placed 0.033 g (0.12 mmol) of (−)-**13** in DCM (2 mL), the solution was cooled to 0 °C, and TFA (180 μL, 2.31 mmol) was added. The reaction mixture was stirred for 3 h at room temperature, quenched with saturated aqueous $NaHCO_3$ (2 mL), and stirred for 20 min. The organic phase was separated, and the aqueous phase was extracted with DCM (3 × 3 mL). The combined organic phases were washed with brine (5 mL), dried (Na_2SO_4), and concentrated. Chromatography (hexane/EtOAc 1:1) gave 0.019 g (89%) of **14** as a yellow low-melting solid, $[\alpha]^{20}_D$ −20.1 (*c* 1.0, $CHCl_3$) [lit.[3] $[\alpha]^{20}_D$ −18.7 (*c* 0.4, CH_3OH)]. Spectral properties were identical with literature values.[3]

Methyl (*R*)-(−)-*N*-(*tert*-Butoxycarbonyl)-3-amino-4,4-dimethylpentanoate (15). In a 100-mL, one-necked, round-bottom flask equipped with a stirring bar, a rubber septum, and an argon balloon was placed 1.30 g (4.37 mmol) of (+)-**4** in MeOH (30 mL). The solution was cooled to 0 °C, 2.02 mL (26.2 mmol) of TFA was added, and the reaction mixture was warmed to room temperature and stirred for 2 h. At this time the solution was concentrated, THF (30 mL) was added, and the reaction mixture was cooled to 0 °C. Successively added to the solution were 5.9 mL (43.7 mmol) of Et_3N, 0.053 g (0.44 mmol) of DMAP, and a solution of 1.16 g (5.25 mmol) of $(Boc)_2O$ in THF (5 mL). The reaction mixture was cooled to 0 °C, stirred for 2 h, and quenched with ice-cold H_2O (15 mL). The solution was warmed to room temperature and diluted with EtOAc (20 mL), the phases were separated, and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), and concentrated. Chromatography (hexane/EtOAc 20:1) gave 1.05 g (94%) of a white solid, mp 61.5−62.5 °C; $[\alpha]^{20}_D$ −23.7 (*c* 1.0, $CHCl_3$); IR (neat) 3361.7, 2967.3, 1700.2, 1521.7, 1367.4, 1171.7 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.62 (d, J = 10.0 Hz, 1 H), 3.88 (td, J = 10.0, 4.0 Hz, 1 H), 3.64 (s, 3 H), 2.60 (dd, J = 4.0, 14.0 Hz, 1 H), 2.24 (dd, J = 10.0, 14.0 Hz, 1 H), 1.41(s, 9 H), 0.90 (s, 9 H); the other rotamer δ 4.25 (br, 1 H), 3.82 (br, 1 H), 3.64 (s, 3 H), 2.55 (br, 1 H), 2.22 (br, 1 H), 1.45 (s, 9 H), 0.90 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 173.0, 155.9, 79.5, 56.4, 52.2, 36.7, 35.2, 28.7, 26.6; the other rotamer δ 173.0, 155.9, 79.5, 57.9, 52.2, 36.7, 35.2, 28.7, 26.6. HRMS calcd for $C_{13}H_{25}NO_4Na$ (M + Na) 282.1681, found 282.1691.

Methyl (*R*)-(+)-5-(*tert*-Butoxycarbonylamino)-6,6-dimethylheptanoate (16). In a one-necked, 25-mL, round-bottom flask equipped with a stirring bar and a rubber septum under an argon atmosphere was placed 0.322 g (1.24 mmol) of (−)-**15** in Et_2O (10 mL). The solution was cooled to −78 °C and was transferred via a double-ended needle to a second 100-mL, single-necked, round-bottom flask equipped with a stirring bar and a rubber septum containing 0.124 g (3.10 mmol) of LAH in Et_2O (15 mL) at −78 °C. After the solution was stirred at this temperature for 4 h, H_2O (0.12 mL), 20% NaOH (0.12 mL), and H_2O (0.36 mL) were added. The reaction mixture was warmed to room temperature, stirred for 1 h, and filtered through Celite. The organic phase was dried (Na_2SO_4) and concentrated in a 25-mL, single-necked, round-bottom flask to give the crude alcohol as white solid. The crude alcohol was dissolved in DCM (10 mL) and cooled to −78 °C. In a second 100-mL, one-necked, round-bottom flask equipped with a stirring bar, a rubber septa, and an argon-filled balloon was added 1.36 mL (2.73 mmol) of oxalyl chloride in DCM (30 mL), and the solution was cooled to −78 °C. At this time 0.42 mL (5.95 mmol) of DMSO was added and after 10 min the solution of crude alcohol in DCM was transferred via a double-ended needle to the DMSO solution. After the solution was stirred for 10 min at −78 °C, 1.0 mL (7.4 mmol) of Et_3N was added and the reaction mixture was warmed to room temperature and stirred for 4 h. The reaction mixture was concentrated, Et_2O (40 mL) was added, and the precipitated salts were removed by filtration. The organic phase was washed with H_2O (2 × 10 mL), the aqueous phase was extracted with Et_2O (2 × 10 mL), and the combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), and concentrated in a 100 mL, single-necked, round-bottom flask to give the crude aldehyde. The crude aldehyde was dissolved in THF (30 mL) and 635 mg (1.86 mmol) of methyl (triphenylphosphoranylidene)acetate was added. The reaction mixture was refluxed at 80 °C for 14 h, cooled, and concentrated. Purification by silica gel column chromatography (hexane/EtOAc 5:1) gave the alkene intermediate as a white solid. The alkene intermediate was dissolved in MeOH (20 mL) in a 50-mL two-necked, round-bottom flask equipped with a stirring bar, three-necked adapter, and hydrogen-filled balloon and a catalytic amount of Pd/C was added. The reaction mixture was stirred at room temperature for 2 h. Upon completion of the reaction, the Pd/C catalyst was filtered and the organic solvent was concentrated. Purification by chromatography (hexane/EtOAc 5:1) gave 0.30 g (85%) of a white solid, mp 42.0−43.5 °C; $[\alpha]^{20}_D$ +9.5 (*c* 1.1, $CHCl_3$); IR (neat) 3355.9, 2965.4, 1700.2, 1365.5, 1171.7 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.25 (d, J = 10.0 Hz, 1 H), 3.62 (s, 3 H), 3.32 (td, J = 12.0, 2.0 Hz, 1 H), 1.72 (m, 1 H), 2.30 (m, 2 H), 1.58 (m, 2 H), 1.40 (s, 9 H), 1.09 (m, 1 H), 0.84 (s, 9 H); the other rotamer δ 4.10 (d, J = 10.0 Hz, 1 H), 3.62 (s, 3 H), 3.20 (t, J = 12.0 Hz, 1 H), 2.30 (m, 2 H), 1.72 (m, 1 H), 1.58 (m, 2 H), 1.43 (s, 9 H), 1.09 (m, 1 H), 0.88 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 173.4, 156.6, 79.2, 58.8, 51.8, 35.1, 34.0, 30.1, 28.8, 26.7, 22.6; the other rotamer δ 173.4, 156.6, 80.0, 60.4, 51.8, 35.1, 34.0, 30.1, 28.8, 26.7, 22.6. HRMS calcd for $C_{15}H_{29}NO_4Na$ (M + Na) 310.399, found 310.1984.

Methyl (*R*)-(+)-2-Diazo-5-(*tert*-butoxycarbonylamino)-6,6-dimethylheptanoate (17). In a 25-mL, single-necked, round-bottom flask equipped with a stirring bar and a rubber septum under an argon atmosphere was placed (+)-**16** (0.144 g, 0.5 mmol) in THF (5 mL). The solution was cooled to −78 °C, 1.67 mL (2.5 mmol, 1.5 M solution in cyclohexane) of LDA was added, and the reaction mixture was stirred for 1 h. At this time 0.44 mL (2.5 mmol) of redistilled HMPA was added, the reaction mixture was stirred for 1 h, and 0.67 mL (5.0 mmol) of $CF_3CO_2CH_2CF_3$ was added all at once. After 5 min the solution was concentrated, MeCN (5 mL) and H_2O (0.5 mL) were added, followed by Et_3N (2.0 mL) and a solution of 0.185 g (1.5 mmol) of MsN_3[8] in MeCN (2 mL). The reaction mixture

was stirred at room temperature for 12 h and concentrated, and the residue was dissolved in Et_2O (15 mL). The organic phase was washed with 10% NaOH (3 × 5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. Chromatography (hexane/EtOAc 20:1) gave 0.12 g (76%) of a yellow solid, mp 92.0−94.0 °C; $[\alpha]^{20}_D$ +1.7 (*c* 1.5, $CHCl_3$); IR (neat) 3361.7, 2966.3, 2083.0, 1700.2, 1172.6 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.29 (d, J = 11.0 Hz, 1 H), 3.754 (s, 3 H), 3.40 (td, J = 11.0, 1.5 Hz, 1 H), 2.43 (m, 1 H), 2.24 (m, 1 H), 1.82 (m, 1 H), 1.43 (s, 9 H), 1.30 (m, 1 H), 0.89 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 168.3, 156.7, 79.6, 59.0, 52.2, 35.4, 29.3, 29.0, 26.9, 22.1 (C=N_2 was not observed). HRMS calcd for $C_{15}H_{27}N_3O_4Na$ (M + Na) 336.1899, found 336.1887.

Methyl (2*S*,5*R*)-(−)-*N*-(*tert*-Butyloxycarbonyl)-5-(*tert*-butylpyrolidine)-2-carboxylate (13). 13 was prepared from (+)-**17.** In a 10-mL, single-necked, round-bottom flask equipped with a stirring bar and a rubber septa under an argon atmosphere was placed 0.0023 g (0.005 mmol) of $Rh_2(OAc)_4$ in CH_2Cl_2 (2 mL). In a separate 10-mL sample vial equipped with a stirring bar and a rubber septum under an argon atmosphere was placed 0.055 g (0.174 mmol) of (+)-**17** in CH_2Cl_2 (2 mL). This solution was transferred via syringe to the rhodium catalyst solution at room temperature and the solution was stirred for 30 min. Concentration and chromatography (hexane/EtOAc 10:1) gave 0.033 g (67%, >94% de) of a yellow oil; $[\alpha]^{20}_D$ −31.7 (*c* 0.9, $CHCl_3$). Spectral properties were identical with those of (−)-**13** prepared above.

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Supporting Information Available: Spectral data for compounds where only HRMS is available. This material is available free of charge via the Internet at http://pubs.acs.org.

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