The First Enantioselective Synthesis of the *cis*-2-Carboxy-5-phenylpyrrolidine

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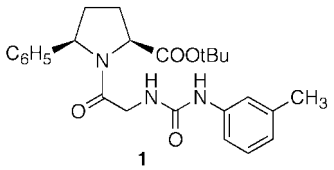
Cholecystokynin (CCK) is a polypeptide hormone which exists in several biologically active forms (CCK-4, CCK-8, CCK-33, etc.) depending on the number of amino acids contained in the structure.[1,2] It plays an important role in the digestive tract where it predominantly interacts with CCK-A receptors,[3−5] and also in the central nervous system where it essentially acts as a neurotransmitter through CCK-B type receptors.[6]

Over the past years, a variety of nonpeptide CCK antagonists have been synthesized, which demonstrates a great interest in this area.[1,2] In particular, the (+)-RP 66803 **1**, a pyrrolidine derivative, has been prepared recently by resolution and has had a high affinity for the CCK receptors.[7] The pyrrolidine moiety was obtained by a nonstereoselective arylation of an acyliminium derived from proline by an anodic oxidation.



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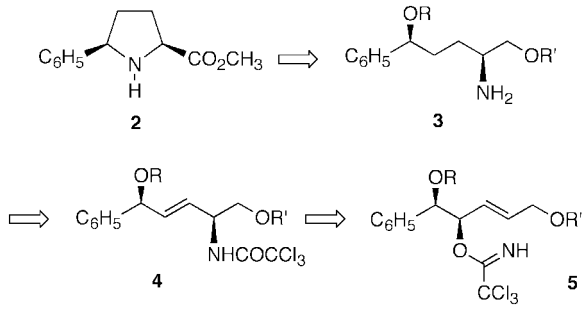
We thought that these substituted 2-carboxypyrrolidines would be furnished by the cyclization of stereoselectively substituted 1,4-amino alcohols such as **3** after activation of the hydroxy function. One possible method for accessing such compounds would be the use of the Overman rearrangement of appropriate trichloroacetimidates **5** derived from allylic alcohols (Scheme 1).[8] This rearrangement has been widely used for the synthesis of nitrogen-containing compounds, especially for amino acids,[9] amino sugars,[10] and other complex natural products.[11]

To access the required *cis*-pyrrolidine by an intramolecular substitution, it was necessary to start from a *syn*-1,4-amino alcohol. Since the Overman rearrangement takes place through a highly ordered chair transition state, such a *syn*-amino alcohol could be obtained from a *syn*-(*E*)-1,2-monoprotected diol with a 1*R*,2*R* configuration.

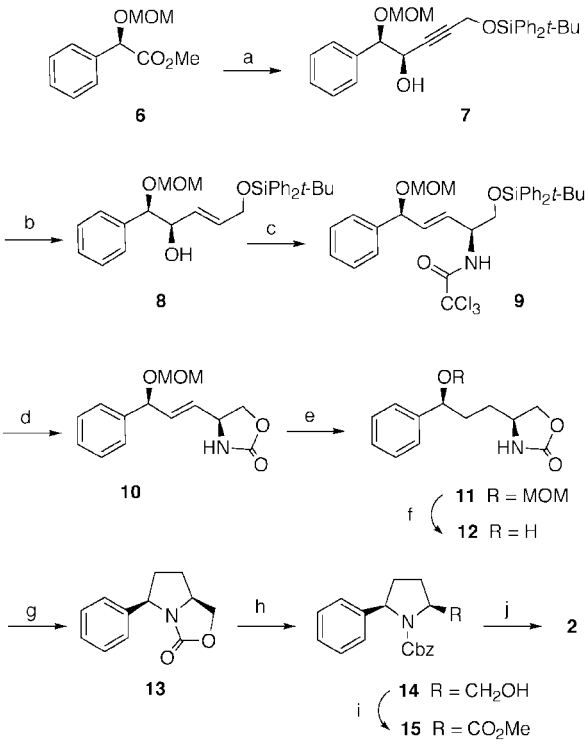
For this purpose, the methyl ester of (*R*)-mandelic acid was protected as a MOM ether **6** and reduced into

Scheme 1



2 **3** **4** **5**

Scheme 2[a]



6 **7** **8** **9** **10** **13**

[a] Reagents and conditions: (a) (i) DIBAL-H, 1/1 ether/pentane, −78 °C, (ii) *t*-BuPh$_2$SiOCH$_2$C≡CMgBr, Et$_2$O; (b) Red-Al, ether, −20 °C; (c) (i) CCl$_3$CN, cat. HNa, Et$_2$O, (ii) xylene, reflux, 6 h; (d) Bu$_4$NF, THF, 12 h; (e) H$_2$, cat. PtO$_2$, AcOEt; (f) 3 M HCl, MeOH, 40 °C, 30 h; (g) MsCl, Et$_3$N, THF; (h) BnOLi, THF, 65 °C; (i) (i) 1 M Jones reagent, acetone, (ii) CH$_2$N$_2$, Et$_2$O; (j) Me$_2$S, BF$_3$/Et$_2$O, CH$_2$Cl$_2$, 24 h.

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aldehyde by DIBAL-H at low temperatures. However, it was not necessary to isolate this, and the magnesium acetylide derived from a silylated ether of propargylic alcohol was directly reacted at low temperatures with the intermediate aluminoxi acetal without hydrolysis according to a procedure previously described by Burke.[12] Such a strategy allowed us to obtain the acetylenic alcohol **7** in a 98/2 syn/anti ratio.[13] Reduction of this alcohol with RedAl in ether[14] afforded the purely (*E*)-allylic alcohol **8** in 72% yield. It must be noted that it was necessary to carry out these reactions at −20 °C to avoid the cleavage of the silyl ether.

The alcohol **8** was then reacted with trichloroacetonitrile in the presence of a catalytic amount of sodium hydride, and the resulting trichloroacetimidate was submitted to thermal rearrangement by refluxing in anhydrous xylene. The trichloroacetamide **9** was thus obtained as a single diastereomer as judged by ^{1}H and ^{13}C NMR. The silyl group was then removed by reaction with tetrabutylammonium fluoride. A concomitant cleavage of the trichloroacetamide resulting from an intramolecular nucleophilic addition of the intermediate alcoholate followed by an elimination of the trichloromethyl anion afforded the oxazolidinone **10** in one step in accordance with previous results.[9b] To effect the cyclization, the double bond was reduced. Due to the presence of the OMOM group in both the allylic and benzylic positions, this reduction was difficult to achieve by catalytic hydrogenation, and products resulting from hydrogenolysis were obtained in the presence of palladium. However, the use of platinum oxide as a catalyst allowed us to isolate the oxazolidinone **11** in a nearly quantitative yield.

With **11** in hand, we could then investigate the cyclization to pyrrolidine. This cyclization was achieved in two ways. In the first experiment, the alcohol **12** resulting from the cleavage of the MOM ether was reacted with diethylazodicarboxylate in the presence of triphenylphosphine under the conditions of Mitsunobu.[15] The corresponding pyrrolidine was obtained, but it was extremely difficult to separate it from triphenylphosphine oxide. Alternatively, we decided to activate the alcohol as a mesylate, and we were pleased to isolate the cyclization product **13** directly by reaction with mesyl chloride in THF in the presence of triethylamine without isolating the intermediate mesylate.

The oxazolidinone was then cleaved with sodium hydroxide in refluxing methanol to give the free amino alcohol in 80% yield. However, after several attempts, we were unable to selectively protect the secondary amine as a *tert*-butyl carbamate. Therefore, we set out to modify our strategy. The oxazolidinone **13** was reacted with lithium benzylate in refluxing THF to afford the N-protected pyrrolidine **14** which was in turn oxidized with Jones reagent into acid and esterified with diazomethane to give the N-protected proline derivative **15**. The cleavage of the benzyloxycarbamate by catalytic hydrogenation in the presence of palladium on charcoal was unsuccessful and only afforded the opening of the pyrrolidine due to the hydrogenolysis of the benzylic C−N bond. This cleavage was then achieved by reaction with dimethyl sulfide in the presence of boron trifluoride according to the method described by Fujita[16] and gave the pyrrolidine **2** which proved to be identical in all respects to the previously described compound.[7]

In summary, this synthesis demonstrates that the [3,3] sigmatropic rearrangement of trichloroacetimidates derived from monoprotected allylic diols allows access to 2,5-disubstituted pyrrolidines by an approach which offers the potential to functionalize the 3,4-positions of the pyrrolidine ring.

Experimental Section

General Methods. Infrared spectra were taken on a FT-IR instrument using KBr film. ^{1}H NMR and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, in $CDCl_3$ unless specified otherwise. Chemical shifts are expressed in parts per million from internal TMS. Mass spectra were recorded with a 70 eV ionizing voltage; ammonia was used for chemical ionization. Melting points were determined on a Kofler apparatus and are uncorrected. Flash chromatography was performed using Merck Kieselgel 60 silica gel (230−400 mesh).

(1*R*,2*R*)-5-[(*tert*-Butyldiphenylsilyl)oxy]-1-(methoxymethoxy)-1-phenylpent-3-yn-2-ol (7). Compound **6** (3.15 g, 15 mmol) was dissolved in Et_2O/pentane (1/1, 60 mL) under an argon atmosphere, cooled to −78 °C, and treated dropwise with 18 mL of DIBAL-H (1 M in hexanes). The mixture was stirred for 1 h before addition, through cannula, of a Grignard solution of magnesium acetylide, prepared as follows. An ethereal solution (30 mL) of protected propargyl alcohol (6.62 g, 22.5 mmol) was treated with 15.46 mL of *n*-BuLi (1.6 M in hexanes) at −20 °C under an inert atmosphere. The mixture was stirred for 1 h at this temperature, warmed to 0 °C, and recooled to −30 °C. An ethereal magnesium bromide solution, obtained from magnesium (1.44 g, 60 mmol) and 1,2-dibromoethane (11.16 g, 60 mmol), was then cannulated, and the reaction mixture was allowed to warm to 23 °C while stirring was continued overnight. On the next day, the solution was cooled to −20 °C and the reaction quenched by addition of a 10% HCl solution (30 mL), and the mixture was diluted with water (50 mL). The organic extract was washed with brine, dried over $MgSO_4$, and concentrated. Flash chromatography (4/1 cyclohexane/EtOAc) gave **7** (6.2 g, 87%) as an oil: $[\alpha]^{20}_D = -66$ (*c* 0.7, $CHCl_3$); IR (film) ν 3430 (br), 2955, 2930, 2890, 2860, 1425 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.07 (s, 9H), 2.72 (d, $J = 5$ Hz, 1H), 3.41 (s, 3H), 4.25−4.38 (m, 2H), 4.48−4.58 (m, 1H), 4.62−4.80 (m, 3H), 7.26−7.50 (m, 10H), 7.65−7.80 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.07, 26.60, 52.48, 55.83, 66.49, 80.85, 82.54, 84.90, 94.67, 127.65, 127.90, 128.19, 128.34, 129.74, 132.95, 135.56, 137.14; MS (CI, NH_3) *m*/*z* (relative intensity) 492 ($M + NH_4^+$, 22%), 198 (100%). Anal. Calcd for $C_{29}H_{34}SiO_4$: C, 73.38; H, 7.21. Found: C, 73.10; H, 7.29.

(1*R*,2*R*,3*E*)-5-[(*tert*-Butyldiphenylsilyl)oxy]-1-(methoxymethoxy)-1-phenylpent-3-en-2-ol (8). In a four-necked, 500 mL, round-bottomed flask fitted with a mechanical stirrer, a thermometer, an addition funnel, and an argon inlet was placed the propargylic alcohol **7** (4.75 g, 10 mmol) in 100 mL of anhydrous Et_2O. The solution was cooled to −25 °C and treated via a syringe with a 3.2 M solution of bis(methoxyethoxy)-aluminum hydride in toluene (4.8 mL, 15 mmol). The reaction, monitored by HPLC (column, Merck LichroCART 250-4, 100RP-18.5 mm), was generaly complete within 5 h. The reaction was quenched by dropwise addition of 1 M H_2SO_4 (30 mL). The organic layer was separated and washed with H_2O (2 × 50 mL) and brine (50 mL). After drying ($MgSO_4$), the ethereal phase was concentrated in vacuo, and the residual oil was chromato-

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graphed (4/1 cyclohexane/AcOEt) to afford the ethylenic compound **8** (3.43 g, 72%): $[\alpha]^{20}_D = -40.8$ (*c* 1.24, $CHCl_3$); IR (film) ν 3445, 2955, 2930, 2890, 2855, 1700, 1425 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.12 (s, 9H), 3.16−3.24 (m, 1H), 3.48 (s, 3H), 4.18−4.52 (m, 3H), 4.58 (d, $J = 7.6$ Hz, 1H), 4.71 (s, 2H), 5.71−6.01 (m, 2H), 7.33−7.56 (m, 10H), 7.65−7.82 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.05, 26.64, 55.66, 63.34, 75.11, 82.33, 94.35, 126.81, 127.50, 127.82, 128.01, 128.21, 129.47, 131.18, 133.43, 135.31, 137.90; MS (CI, NH_3) *m/z* (relative intensity) 494 ($M + NH_4^+$, 18%), 342 (100%). Anal. Calcd for $C_{29}H_{36}SiO_4$: C, 73.07; H, 7.60. Found: C, 73.37; H, 7.75.

(1*S*,2*E*,4*S*)-*N*-[5-[(*tert*-Butyldiphenylsilyl)oxy]-1-(methoxymethoxy)-1-phenylpent-2-en-4-yl] 2,2,2-Trichloroacetamide (9). A suspension of sodium hydride (116 mg of a 60% dispersion in mineral oil, 2.89 mmol), which had been previously washed three times with pentane, was placed into 40 mL of anhydrous ether and treated dropwise with an ether solution of **8** (2.76 g, 5.79 mmol). The mixture was stirred for 15 min before being cooled to −5 °C, and trichloroacetonitrile (0.87 mL, 8.68 mL) was added dropwise. The solution was allowed to warm to 23 °C and then concentrated. Pentane [30 mL containing methanol (0.117 mL, 2.89 mmol)] was added and the mixture stirred vigorously for 2 min before being filtered through a pad of Celite. Evaporation of the solvent gave the crude imidate which was used without purification. Thus, the above imidate was dissolved in xylene (40 mL) and heated at reflux for 6 h. After cooling, the solvent was evaporated in vacuo and the dark residue purified by flash chromatography (9/1 cyclohexane/AcOEt) to afford the compound **9** as a pale yellow solid (2.5 g, 70%): mp 98 °C; $[\alpha]^{20}_D = +7.4$ (*c* 1.11, CH_2Cl_2); IR ($CHBr_3$) ν 3420, 3020, 1715, 1500, 1140, 1120, 1030 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.14 (s, 9H), 3.46 (s, 3H), 3.90 (AB part of ABX system, $J_{AB} = 10.4$ Hz, 2H), 4.57−4.87 (m, 1H + AB system, $J_{AB} = 6.7$ Hz, 2H), 5.26 (d, $J = 4.6$ Hz, 1H), 5.88−6.08 (m, 2H), 7.29−7.58 (m, 10H), 7.63−7.8 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.06, 26.61, 53.67, 55.33, 65.04, 76.83, 92.62, 93.49, 126.98, 127.77, 128.03, 128.37, 129.90, 132.22, 132.33, 132.96, 133.24, 134.67, 135.31, 135.36, 140.00, 160.90; MS (CI, NH_3) *m/z* (relative intensity) 637 ($M + NH_2^-$, 100%). Anal. Calcd for $C_{31}H_{36}Cl_3NO_4Si$: C, 59.95; H, 5.83; N, 2.25. Found: C, 59.94; H, 5.84; N, 2.21.

(1′*E*,3′*S*,4*S*)-4-[3-(Methoxymethoxy)-3-phenylpropenyl]-oxazolidin-2-one (10). To a stirred solution of compound **9** (2.51 g, 4.04 mmol) in THF (30 mL) at 23 °C was added *n*-Bu_4NF in THF (1 M, 6 mL, 6.0 mmol). The mixture was stirred overnight and diluted with water (50 mL). The product was extracted with Et_2O (2 × 40 mL) and dried over $MgSO_4$, and the solvent was evaporated in vacuo. Flash chromatography (3/7 cyclohexane/AcOEt) yielded the title compound (0.85 g, 80%) as an oil: $[\alpha]^{20}_D = -28.1$ (*c* 1.12, CH_2Cl_2); IR ($CHBr_3$) ν 3010, 1750, 1400, 1140 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.35 (s, 3H), 3.95−4.2 (m, 1H), 4.3−4.7 (m, 2H + AB system, $J_{AB} = 6.6$ Hz, 2H), 5.11 (d, $J = 5.8$ Hz, 1H), 5.71, (dd, $J = 6.6$, 15.4 Hz, 1H), 5.88 (dd, $J = 6$, 15.4 Hz, 1H), 6.22−6.45 (m, 1H), 7.25−7.45 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 54.14, 55.47, 69.94, 76.62, 93.63, 126.99, 127.99, 128.56, 129.18, 134.68, 139.67, 159.48; MS (CI, NH_3) *m/z* (relative intensity) 281 ($M + NH_4^+$, 14.7%), 202 (100%). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.50; N, 5.32. Found: C, 63.75; H, 6.58; N, 5.21.

(3′*S*,4*S*)-4-[3-(Methoxymethoxy)-3-phenylpropyl]oxazolidin-2-one (11). The ethylenic compound **10** (1.07 g, 4.06 mmol) was dissolved in EtOAc (30 mL), and PtO_2 (46 mg, 0.2 mmol) was added. Hydrogen (1 atm) was applied, and the reaction mixture was stirred at 23 °C for 5 h. After filtration through Celite, the solvent was evaporated to afford **11** (1.05 g, 97%) as a colorless oil: $[\alpha]^{20}_D = -11.4$ (*c* 1.25, CH_2Cl_2); IR ($CHBr_3$) ν 3020, 1710 (br), 1145 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.43−2.35 (m, 4H), 3.35 (s, 3H), 3.38−4.06 (m, 2H), 4.44 (t, $J = 8$ Hz, 1H), 4.51 (s, 2H), 4.55−4.65 (m, 1H), 6.38 (s, 1H), 7.22−7.42 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 31.49, 33.33, 52.39, 55.67, 70.06, 77.35, 94.12, 126.65, 127.85, 128.50, 141.13, 159.83; MS (CI, NH_3) *m/z* (relative intensity) 283 ($M + NH_4^+$, 40.6%), 266 (100%). Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.21; N, 5.28. Found: C, 63.29; H, 7.14; N, 5.24.

(3′*S*,4*S*)-4-(3-Hydroxy-3-phenylpropyl)oxazolidin-2-one (12). The protected alcohol **11** (1 g, 3.77 mmol) was placed in MeOH (30 mL), and concentrated HCl (3 drops) was added. The solution was heated at 40 °C for 30 h (reaction monitored by TLC). The mixture was cooled, diluted with water (40 mL), and extracted with EtOAc (3 × 30 mL). The combined organic phases were washed with brine. The usual workup gave a white solid (0.77 g, 92%): mp 137−138 °C (from CH_2Cl_2); $[\alpha]^{20}_D = -53.3$ (*c* 0.92, MeOH); IR ($CHBr_3$) ν 3278 (br), 3128 (br), 3019, 1746 (br) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 1.2−1.9 (m, 4H), 3.6−4.0 (m, 2H), 4.33 (t, $J = 8.2$ Hz, 1H), 4.45−4.65 (m, 1H), 5.23 (d, $J = 4.6$ Hz, 1H), 7.1−7.6 (m, 5H), 7.75 (s(br), 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 31.40, 34.70, 51.61, 69.18, 71.78, 125.75, 126.67, 127.98, 146.15, 158.83; MS (CI, NH_3) *m/z* (relative intensity) 239 ($M + NH_4^+$, 9.1%), 222 (100%). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.82; N, 6.33. Found: C, 65.01; H, 6.90; N, 6.40.

(5*R*,7a*S*)-5-Phenyltetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one (13). **A**lcohol **12** (1 g, 4.52 mmol) and triethylamine (1.26 mL, 9.04 mmol) were dissolved in THF (30 mL), and the mixture was cooled to 0 °C under argon. Mesyl chloride (525 mL, 6.72 mmol) was added dropwise via a syringe through a septum. The mixture was allowed to reach 23 °C and stirred for 48 h. The mixture was partitioned between Et_2O and water and extracted once more with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to give a solid residue which was flash chromatographed (2/3 cyclohexane/EtOAc) to give a white crystal (551 mg, 60%): mp 145 °C; $[\alpha]^{20}_D = +23.4$ (*c* 0.9, CH_2Cl_2); IR ($CHBr_3$) ν 3020, 1725, 1140 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.8−2.25 (m, 3H), 2.52−2.8 (m, 1H), 4.12−4.30 (m, 1H), 4.31−4.52 (m, 1H), 4.52−4.67 (m, 1H), 4.72 (dd, $J = 8.85$ Hz, 1H), 7.12−7.47 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.66, 39.0, 58.56, 61.03, 69.51, 126.33, 127.71, 128.67, 140.05, 155.06; MS (CI, NH_3) *m/z* (relative intensity) 204 ($M + H^+$, 100%). Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.44; N, 6.89. Found: C, 70.86; H, 6.45; N, 6.98.

(2*S*,5*R*)-*N*-(Benzyloxycarbonyl)-2-(hydroxymethyl)-5-phenylpyrrolidine (14). To a stirred solution of benzyl alcohol (383 mg, 3.54 mmol) in THF (20 mL) at 0 °C (ice bath) was added a 1.6 M hexanes solution of *n*-butyllithium (2.2 mL, 3.54 mmol). The bath was removed, and the solution was stirred for 30 min. Bicyclic compound **13** (480 mg, 2.36 mmol) diluted in THF (3 mL) was then added via a syringe, and the mixture was refluxed for 15 h. After cooling, the solution was diluted with water (40 mL) and extracted with $CHCl_3$ (2 × 30 mL). The usual workup gave a crude oil which was purified by flash chromatography (3/2 cyclohexane/EtOAc) giving a colorless oil (397 mg, 54%): $[\alpha]^{20}_D = +23.3$ (*c* 1.455, CH_2Cl_2); IR ($CHBr_3$) ν 3440 (br), 3140, 1690 (br), 1460, 1420, 1360, 1150 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.6−2.15 (m, 3H), 2.17−2.45 (m, 1H), 3.65−4.05 (m, 2H), 4.1−4.32 (m, 1H), 4.6−5.2 (m, 4H), 6.7−7.45 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.82, 33.91, 62.02, 62.87, 66.17, 66.98, 125.38, 126.62, 127.14, 127.51, 128.02, 128.23, 135.88, 143.22, 157.18; MS (CI, NH_3) *m/z* (relative intensity) 312 ($M + H^+$, 100%). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.79; N, 4.5. Found: C, 73.78; H, 6.88; N, 4.33.

Methyl (2*S*,5*R*)-*N*-(Benzyloxycarbonyl)-5-phenylpyrrolidine-2-carboxylate (15). Alcohol **14** (380 mg, 1.22 mmol) in acetone (20 mL) was treated with Jones reagent, prepared from CrO_3 (10 g), H_2SO_4 (14 g), and H_2O (100 mL), while the mixture was being stirred at 23 °C until a lasting orange color was obtained. Total disappearance of the starting material was checked by TLC (3/7 cyclohexane/EtOAc). The mixture was diluted with MeOH (30 mL), and the solvents were removed. Water (30 mL) was added, and the product was extracted with $CHCl_3$ (2 × 30 mL). The extract was dried ($MgSO_4$) and evaporated to give a residue, which was used directly in the next step. The crude acid was diluted with Et_2O (25 mL) and treated with a solution of diazomethane in Et_2O until the yellow color was maintained. After the mixture was stirred for 15 min and in vacuo concentration, the crude oil was purified by flash chromatography (7/3 cyclohexane/EtOAc) to give the corresponding ester **15** (320 mg, 77%): $[\alpha]^{20}_D = +15$ (*c* 1.3, CH_2Cl_2); IR ($CHBr_3$) ν 3010, 1745 (br), 1700 (br), 1410, 1340, 1140 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) (two conformers) δ 1.9−2.5 (m, 4H), 3.7 (s, 1H), 3.84 (s, 2H), 4.40−4.65 (m, 1H), 4.85−5.10 (m, 3H), 6.78−6.98 (m, 1H), 7.05−7.45 (m, 7H), 7.47−7.65 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) (two conformers) δ 28.45, 29.12, 34.39, 35.44, 52.19, 60.39, 60.77, 62.69, 66.94, 126.12, 126.80, 127.17, 127.48, 127.70, 128.08, 136.13, 142.39, 143.16, 154.36, 155.19, 173.04;

MS (CI, NH_3) *m*/*z* (relative intensity) 357 ($M + NH_4^+$, 17.2%), 340 ($M + H^+$, 100%). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.23; N, 4.12. Found: C, 71.23; H, 6.44; N, 4.51.

Methyl (2*S*,5*R*)-5-Phenylpyrrolidine-2-carboxylate (2). Compound **15** (316 mg, 0.93 mmol) was dissolved in dry CH_2Cl_2 (20 mL) and the mixture treated with dimethyl sulfide (1.9 mL, 26 mmol) and boron trifluoride etherate (1.8 mL, 9.3 mmol). The mixture was stirred for 2 h at 23 °C before a second addition of dimethyl sulfide (1 mL, 13.6 mmol). The reaction mixture was stirred for another 24 h and poured into water (20 mL) and 10% aqueous NH_4OH (40 mL). Extraction with $CHCl_3$ (2 × 30 mL), washing (H_2O, brine), and drying ($MgSO_4$) gave, after concentration in vacuo, a crude oil which was purified by flash chromatography (3/2 cyclohexane/EtOAc) to furnish the pyrrolidine **2** (110 mg, 58%): $[\alpha]^{20}_D = +15.3$ (*c* 1.22, CH_2Cl_2); IR (neat) ν 2951 (br), 1735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.55−1.74 (m, 1H), 1.97−2.24 (m, 4H), 3.70 (s, 3H), 3.87 (dd, $J = 8.36, 5.18$ Hz, 1H), 4.13 (dd, $J = 9.24, 5.64$ Hz, 1H), 7.15−7.45 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 29.67, 30.52, 52.15, 60.00, 63.53, 126.73, 127.17, 128.45, 143.29, 175.60; MS (CI, NH_3) *m*/*z* (relative intensity) 206 ($M + H^+$, 100%). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.36; N, 6.82. Found: C, 70.19; H, 7.31; N, 6.85.

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