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Asymmetric Synthesis of 4- and 5-Substituted Pipecolic Esters by Ring-Closing Metathesis and Palladium-Catalyzed Formate Reduction

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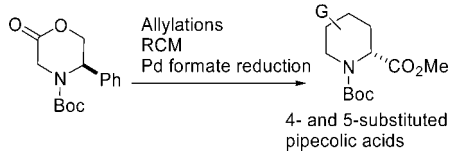
Received April 28, 2008



Asymmetric synthesis of 4- and 5-substituted pipecolic esters was achieved by the sequence of allylation, ring-closing metathesis, and palladium-catalyzed formate reduction.

Synthesis of 4- and 5-substituted pipecolic acids has received attention because these compounds are components of some biologically very potent molecules.[1] For example, the FDA-approved thrombin inhibitor Argatroban contains 4-methylpipecolic acid, and human immunodeficiency virus (HIV) protease inhibitor Palinavir incorporates 4-hydroxypipecolic acid.[2,3] 5-Hydroxypipecolamide was found in TNF-α, an effective tumor necrosis-converting enzyme inhibitor (Figure 1).[4] Kadouri–Puchot's group developed a clever method to synthesize 4-methyl- and 4-hydroxypipecolic acids asymmetrically, where

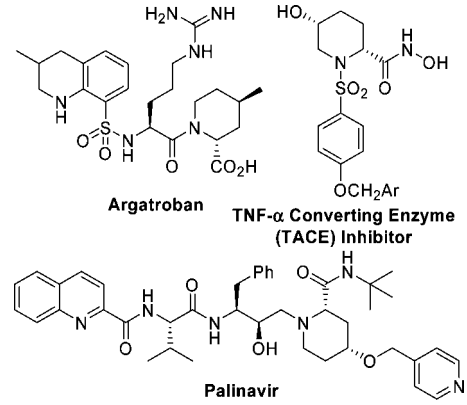
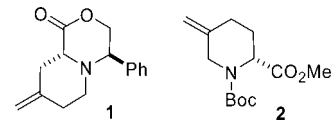


FIGURE 1. Compounds containing 4- and 5-substituted pipecolic acids.

the 4-methylenelactone **1** serves as the key synthetic intermediate.[5] Recently, we reported the sequence of ring-closing metathesis (RCM) and the following regioselective palladium-catalyzed formate reduction to form *N*-heterocycles bearing an exo-olefin.[6] Therefore, the problem of regioselectivity in modifying the cycloalkenes formed by RCM is circumvented. We report herein our progress in applying this methodology to prepare the lactone **1** and the corresponding 5-methylenepipecolic acid derivative **2**.



The chiral glycine enolate synthon, 5-phenylmorpholin-2-one (**3**),[7] was alkylated with 2-(iodomethyl)allyl benzoate (**4**)[8] to give diastereomerically pure **5** (Scheme 1). The Boc protecting group was removed with trifluoroacetic acid, and diene **6** for RCM was generated after *N*-allylation. Several common practices for the allylation on the secondary amine were tested (Table 1). We found that the typical reaction conditions for *N*-alkylation provided a low yield and product accompanied by the hydrolyzed lactone.[9] Instead, using the sterically hindered diisopropylethylamine and anhydrous acetonitrile as the reaction solvent provided the desired product cleanly. Later, we found that microwave irradiation at 150 °C improved the yield to 70%.[10] Ring-closing metathesis under acidic conditions gave the oxazin-1-one **7**. The stereochemistry of **7** was confirmed by ^{1}H−^{1}H COSY and NOE experiment. The key intermediate, *exo*-olefin **1**, was produced after the palladium-catalyzed formate reduction. Use of 2-di-*tert*-butylphosphino-2′-methylbiphenyl (**8**) as a

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10.1021/jo8008885 CCC: $40.75 © 2008 American Chemical Society
Published on Web 07/29/2008

SCHEME 1. Asymmetric Synthesis of 1

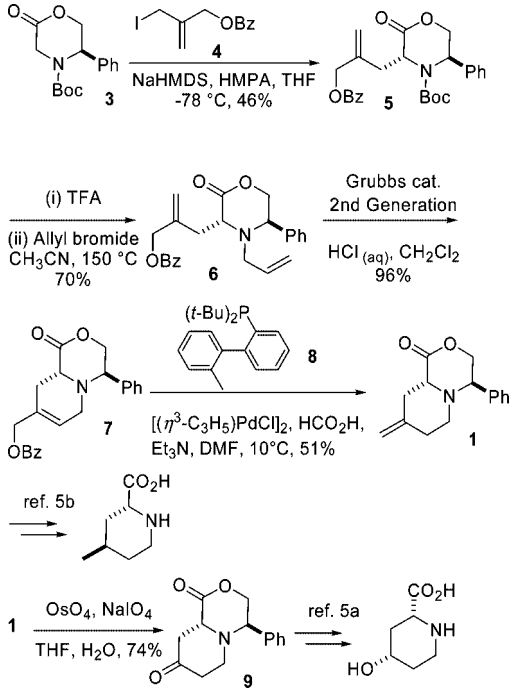
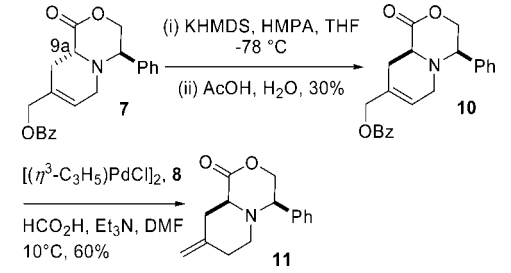


TABLE 1. Reaction Conditions for *N*-Allylation To Prepare 6

entry	base	solvent	temp (°C)	time (h)	yield (%)
1	Na_2CO_3, Bu_4NBr	CH_3CN	75	14	13[a]
2	Ag_2O, $CaSO_4$	C_6H_6	60	14	0[b]
3	$(i\text{-Pr})_2NEt$	CH_3CN	75	14	14
4	$(i\text{-Pr})_2NEt$	CH_3CN	120[c]	0.8	25
5	$(i\text{-Pr})_2NEt$	CH_3CN	150[c]	0.6	70

[a] Accompanied with hydrolyzed lactone (41%). [b] Starting material recovered. [c] Microwave irradiation (150 W, sealed tube).

SCHEME 2. Epimerization of 7



complexing agent gave **1** as the only product. Its oxidation was achieved with osmium tetroxide and sodium periodate to provide ketone **9**,[5a] the precursor to (2*R*,4*S*)-4-hydroxypipecolic acids. To form the other enantiomeric pipecolic acids, the **9a** stereocenter of **7** was inverted by a deprotonation/protonation protocol to give diastereomer **10**,[11] which was then converted to the *exo*-olefin **11** (Scheme 2).

Alternating the sequence of the two allylations also allows the preparation of 5-substituted pipecolic acids (Scheme 3). Thus, allylation of **3** with allyl bromide proceeded readily to give **12**.[11] However, *N*-allylation of the deprotected **12** with **4** was difficult. To facilitate the second allylation, the chiral auxiliary was removed to generate the methyl allylglycinate **13**,[12]

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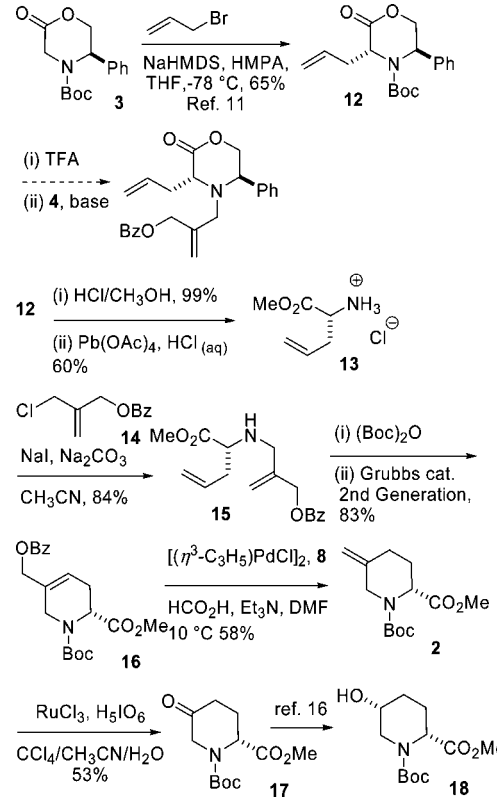
SCHEME 3. Asymmetric Synthesis of 2



a primary amine that smoothly underwent *N*-allylation with **14** to afford diene **15**. Subsequent protection followed by RCM gave the unsaturated pipecolic ester **16** in good yield.[13] Palladium-catalyzed, regioselective formate reduction then yielded 5-methylenepipecolic ester **2**,[14] which could be oxidized to the ketone **17**.[15] This could be selectively reduced in turn to the *cis*-5-hydroxypipecolic ester **18**.[16]

In conclusion, both 4- and 5-substituted pipecolic acids can be prepared by the sequence of asymmetric allylation, ring-closing metathesis and palladium-catalyzed, regioselective formate reduction. The ability to form both isomeric methylene-pipecolic acids by this methodology demonstrates the generality of the reaction. The introduction of the functionalized allyl halides **4** or **14**[8] makes conversion of the *endo* olefin to the *exo* position practical and clearly increases the synthetic application of metathesis.

Experimental Section

(3*R*,5*R*)-*tert*-Butyl 3-(2-Benzoyloxymethylallyl)-2-oxo-5-phenylmorpholine-4-carboxylate (5). To a solution of **3** (390 mg, 1.4 mmol), allyl iodide **4** (510 mg, 1.7 mmol), and hexamethylphosphoramide (HMPA, 367 μL, 2.1 mmol) in THF (5 mL) was added sodium bis(trimethylsilyl)amide (NaHMDS, 2 M in THF, 1.05 mL, 2.1 mmol) at −78 °C. The reaction mixture was stirred for another 2 h at −78 °C, quenched with sat. $NH_4Cl_{(aq)}$ (5 mL), warmed to rt, diluted with water (5 mL), and extracted with diethyl ether (3 ×

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(13) The alternative sequence: RCM of the protonated **15** then Boc-protection, gave 40% yield.

(14) The previously reported ligand, 2-di-*tert*-butylphosphinobiphenyl (ref 6), provided a lower exo:endo ratio (80:20) for this substrate.

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10 mL). The combined organic layer was washed with sat. $NaCl_{(aq)}$ (10 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:3; R_f 0.27) to give **5** (292 mg, 0.65 mmol, 46%) as a colorless solid. Mp 117.0−120.0 °C; $[\alpha]^{20}_D$ −130.0 (*c* 2.51, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, J = 7.5 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 7.7 Hz, 2H), 7.33−7.24 (m, 3H), 7.07 (d, J = 7.4 Hz, 2H), 5.32 (s, 1H), 5.18 (s, 1H), 5.17−5.04 (m, 2H), 4.94−4.88 (m, 2H), 4.83 (d, J = 11.8 Hz, 1H), 4.38 (d, J = 8.2 Hz, 1H), 2.91 (d, J = 10.4 Hz, 1H), 2.77 (s, 1H), 1.24−1.11 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 166.1, 153.5, 139.9, 138.9, 133.0, 129.9, 129.7, 128.8, 128.3, 127.7, 125.3, 117.2, 81.3, 69.7, 66.4, 55.9, 54.7, 37.7, 27.8; HRMS-FAB (*m*/*z*) $[M + H]^+$ calcd for $C_{26}H_{30}O_6N$ 452.2073, found 452.2082; IR (neat) 3031, 2976, 2930, 1757, 1716, 1698, 1270, 1119 cm^{-1}.

(3*R*,5*R*)-2-(4-Allyl-2-oxo-5-phenylmorpholin-3-ylmethyl)allyl Benzoate (6). A solution of **5** (447.3 mg, 0.93 mmol) and trifluoroacetic acid (2 mL) in dichloromethane (2 mL) was stirred at rt for 1 h. The solvent and TFA were removed under vacuum. The solution of deprotected **5**, allyl bromide (560 mg, 4.6 mmol), diisopropylethyl amine (360 mg, 2.78 mmol), and acetonitrile (3.5 mL) was placed in a pressure tube that was heated to 150 °C (150 W, monitored by IR temperature sensor) over 10 min, then this temperature was maintained for another 40 min. After cooling to rt, the reaction mixture was concentrated and purified by column chromatography (SiO_2, EtOAc/hexanes, 1:3; R_f 0.45) to give **6** (254.5 mg, 0.65 mmol, 70%) as a colorless oil. $[\alpha]^{20}_D$ −8.4 (*c* 1.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (dd, J = 8.3, 1.2 Hz, 2H), 7.55 (t, J = 7.5 Hz, 1H), 7.44−7.41 (m, 2H), 7.34−7.27 (m, 5H), 5.70−5.62 (m, 1H), 5.32 (d, J = 0.9 Hz, 1H), 5.23 (d, J = 0.65 Hz, 1H), 5.14−5.08 (m, 2H), 4.90 (q, J = 10.9 Hz, 2H), 4.66 (dd, J = 11.5, 5.1 Hz, 1H), 4.45−4.41 (m, 1H), 4.28−4.25 (m, 1H), 3.99 (t, J = 6.9 Hz, 1H), 3.21 (dd, J = 14.0, 6.0 Hz, 1H), 3.09 (dd, J = 14, 6.5 Hz, 1H), 2.77 (d, J = 6.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 166.1, 140.0, 137.7, 134.3, 133.1, 130.0, 129.6, 128.8, 128.4, 128.0, 127.3, 118.8, 116.3, 70.2, 67.1, 58.3, 56.8, 52.4, 32.6; HRMS-FAB (*m*/*z*) $[M + H]^+$ calcd for $C_{24}H_{26}NO_4$ 392.1862, found 392.1852; IR (neat) 3064, 3030, 2952, 1749, 1720, 1653, 1601, 1451, 1270, 1111 cm^{-1}.

(4*R*,9a*R*)-8-Benzoyloxymethyl-4-phenyl-3,4,9,9a-tetrahydro-6*H*-pyrido[2,1-*c*][1,4]oxazin-1-one (7). Five drops of 1 N hydrochloric acid was added to a solution of **6** (90 mg, 0.23 mmol) in CH_2Cl_2 (2 mL), and the solvent and excess HCl were then removed under vacuum to give the protonated **6**. Another 4 mL of CH_2Cl_2 and Grubbs catalyst[17] (9.5 mg, 0.115 mmol) were added to the flask, and the resulting solution was refluxed for 3 h. After being cooled to rt, the reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with sat. $NaHCO_{3(aq)}$ (5 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:3; R_f 0.22) to give **7** (80 mg, 0.22 mmol, 96%) as a colorless solid. Mp 147.0−148.0 °C(dec; $[\alpha]^{20}_D$ +42.5 (*c* 2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03−8.01 (m, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.41 (t, J = 7.7 Hz, 2H), 7.37−7.29 (m, 5H), 5.71 (s, 1H), 4.72 (s, 2H), 4.65 (dd, J = 11.1, 4.5 Hz, 1H), 4.59 (dd, J = 11.1, 6.2 Hz, 1H), 4.05−4.03 (m, 1H), 3.75 (t, J = 7.5 Hz, 1H), 3.18 (s, 2H), 2.59 (d, J = 6.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 166.2, 135.2, 133.1, 130.2, 129.9, 129.6, 128.9, 128.6, 128.5, 128.4, 122.8, 72.8, 67.4, 58.0, 55.1, 48.3, 26.9; HRMS-FAB (*m*/*z*) $[M + Na]^+$ calcd for $C_{22}H_{21}NO_4Na$ 386.1368, found 386.1374; IR (neat): 3061, 3030, 2953, 2925, 2801, 1743, 1718, 1600, 1452, 1270, 1110 cm^{-1}.

4*R*,9a*R*)-8-Methylene-4-phenylhexahydropyrido[2,1-*c*][1,4]oxazin-1-one (1) .[5a] Allyl palladium chloride dimer (6.05 mg, 0.017 mmol) and 2-di-*tert*-butylphosphino-2′-methylbiphenyl (20.6 mg, 0.066 mmol) were dissolved in DMF (0.5 mL) and the mixtue was stirred for 5 min. Formic acid (37.4 μL, 0.99 mmol), triethylamine (139 μL, 0.99 mmol), and **7** (60 mg, 0.17 mmol) in DMF (1.1 mL) were added in that order. After being stirred at 10 °C for 6 h and rt for 16 h under nitrogen, the reaction mixture was concentrated and purified by column chromatography (SiO_2, EtOAc/hexanes, 1:3; R_f 0.47) to give **1** (20.2 mg, 0.083 mmol, 51%). $[\alpha]^{20}_D$ −38 (*c* 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.29 (m, 5H), 4.75 (s, 1H), 4.69 (s, 1H), 4.64 (dd, J = 11.0, 4.4 Hz, 1H), 4.47 (dd, J = 11.0, 5.5 Hz, 1H), 4.10 (t, J = 4.9 Hz, 1H), 3.34 (dd, J = 10.9, 3.8 Hz, 1H), 2.91 (d, J = 11.6 Hz, 1H), 2.67 (dd, J = 13.5, 3.5 Hz, 1H), 2.52−2.48 (m, 1H), 2.29 (td, J = 11.5, 3 Hz, 1H), 2.24−2.18 (m, 1H), 2.04 (d, J = 16.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 143.4, 135.0, 128.8, 128.5, 109.8, 72.8, 59.2, 58.5, 51.5, 35.1, 32.1; HRMS-FAB (*m*/*z*) $[M + H]^+$ calcd for $C_{15}H_{18}NO_2$ 244.1338, found 244.1342; IR (neat) 3030, 2947, 2908, 1742, 1653, 1494, 1455, 1224 cm^{-1}.

(4*R*,9a*R*)-4-Phenylhexahydropyrido[2,1-*c*][1,4]oxazine-1,8-dione (9). To a solution of **1** (28 mg, 0.115 mmol) in THF (0.7 mL) and water (0.7 mL) were added osmium tetroxide (OsO_4 2.5 wt % in *t*-BuOH, 59 μL, 5.7 × 10^{-3} mmol) and sodium periodate ($NaIO_4$, 123.2 mg, 0.58 mmol). The reaction mixture was stirred at rt for 1.5 h, quenched with sat. $Na_2S_2O_3$ (3 mL), and extracted with ether (3 × 5 mL). The combined organic layer was dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:1; R_f 0.47) to give **9** (21 mg, 0.086 mmol, 74%) as a colorless oil. $[\alpha]^{20}_D$ −2.0 (*c* 0.53, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40−7.34 (m, 5H), 4.61 (dd, J = 11.3, 4.3 Hz, 1H), 4.48 (dd, J = 11.3, 7.1 Hz, 1H), 4.16 (dd, J = 7.1, 4.3 Hz, 1H), 3.84 (dd, J = 8.5, 6.9 Hz, 1H), 3.15 (dd, J = 7.7, 5.0 Hz, 1H), 2.81 (d, J = 8.5 Hz, 2H), 2.69−2.64 (m, 1H), 2.49−2.43 (m, 1H), 2.32−2.24 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.3, 168.8, 134.8, 129.7, 129.1, 128.1, 72.5, 58.9, 57.5, 48. 9, 41.0, 39.5; HRMS-FAB (*m*/*z*) $[M + Na]^+$ calcd for $C_{14}H_{15}NO_3Na$ 268.0950, found 268.0949; IR (neat) 2960, 2922, 1746, 1723, 1577, 1455, 1227 cm^{-1}.

(4*R*,9a*S*)-8-Benzoyloxymethyl-4-phenyl-3,4,9,9a-tetrahydro-6*H*-pyrido[2,1-*c*][1,4]oxazin-1-one (10). Potassium bis(trimethylsilyl)amide (KHMDS, 0.5 M in toluene, 368 μL, 0.18 mmol) was added to a solution of **7** (33.4 mg, 0.092 mmol) in THF (2 mL) at −78 °C, and this solution was stirred for 0.5 h. Hexamethylphosphoramide (HMPA, 33 μL, 0.18 mmol) and acetic acid (80%, 35 μL, 0.46 mmol) were added to the solution at −78 °C. After the addition, the mixture was stirred for 15 min, quenched with sat. $NH_4Cl_{(aq)}$ (3 mL), and warmed to rt. The reaction mixture was diluted with water (5 mL) and extracted with ether (3 × 5 mL). The combined organic layer was washed with water (10 mL) and sat. $NaCl_{(aq)}$ (10 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:3; R_f 0.41) to give **10** (10 mg, 0.028 mmol, 30%) as a colorless oil. $[\alpha]^{20}_D$ −118.2 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05−8.02 (m, 2H), 7.57−7.52 (m, 1H), 7.45−7.35 (m, 7H), 5.66 (dd, J = 3.2, 1.1 Hz, 1H), 4.75 (s, 2H), 4.36 (t, J = 11.2 Hz, 1H), 4.24 (dd, J = 11.2, 3.7 Hz, 1H), 3.63 (dd, J = 10.8, 3.7 Hz, 1H), 3.37−3.32 (m, 1H), 3.19−3.12 (m, 1H), 2.86−2.80 (m, 1H), 2.63−2.54 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 166.2, 135. 5, 133.1, 131.3, 129.9, 129.7, 129.0, 128.9, 128.4, 128.4, 122.4, 72.7, 67.2, 64.1, 60.3, 51.6, 30.1; HRMS-FAB (*m*/*z*) $[M + Na]^+$ calcd for $C_{22}H_{21}NO_4Na$ 386.1368, found 386.1372; IR (neat) 3030, 2932, 2852, 1742, 1717, 1652, 1456, 1269, 1100 cm^{-1}.

(4*R*,9a*S*)-8-Methylene-4-phenylhexahydropyrido[2,1-*c*][1,4]oxazin-1-one (11). The procedure used to prepare **1** was followed. Starting with **10** (10 mg, 0.028 mmol), the *exo*-olefin **11** (4.0 mg, 0.016 mmol, 60%) was produced after column chromatography (SiO_2, EtOAc/hexanes, 1:3; R_f 0.78) as a light yellow oil. $[\alpha]^{20}_D$ −126.3 (*c* 0.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.29 (m, 5H), 4.80 (d, J = 1.5 Hz, 1H), 4.72 (d, J = 1.8 Hz, 1H), 4.35−4.18 (m, 2H), 3.57 (dd, J = 10.5, 3.9 Hz, 1H), 2.99−2.90 (m, 2H), 2.85−2.79 (m, 1H), 2.44−2.35 (m, 1H), 2.20−2.08 (m, 2H), 1.71 (td, J = 11.4, 3.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 143.9, 136.3, 129.0, 128.7, 128.3, 109.9, 72.9, 64.7, 64.3, 53.0,

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36.6, 33.6; HRMS-FAB (*m*/*z*) $[M + H]^+$ calcd for $C_{15}H_{18}NO_2$ 244.1338, found 244.1335; IR (neat) 3069, 2945, 1746, 1455, 1179 cm^{-1}.

(*R*)-Methyl *N*-(*tert*-Butyloxycarbonyl)-4-methylenepiperidine-2-carboxylate (2). Allyl palladium chloride dimer (4.3 mg, 0.012 mmol) and 2-di-*tert*-butylphosphino-2′-methylbiphenyl (14.6 mg, 0.047 mmol) were dissolved in DMF (0.4 mL) and the mixture was stirred for 5 min. Formic acid (26.6 μL, 0.7 mmol), triethylamine (98.1 μL, 0.70 mmol), and **16** (44 mg, 0.12 mmol) in DMF (770 μL) were added in that order. After being stirred at 10 °C for 6 h and rt for 16 h under nitrogen, the reaction mixture was concentrated and purified by column chromatography (SiO_2, EtOAc/hexanes, 1:9; R_f 0.31) to give **2** (17.2 mg, 0.068 mmol, 58%) as a light yellow oil. $[\alpha]^{20}_D$ +61.8 (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.89 (s, 0.5H), 4.84 (d, J = 14.7 Hz, 1H), 4.75 (s, 1H), 4.68 (s, 0.5H), 4.37 (d, J = 13 Hz, 0.5H), 4.25 (d, J = 15.1 Hz, 0.5H), 3.72 (s, 3H), 3.69−3.57 (m, 1H), 2.26−2.23 (m, 2H), 2.08−2.02 (m, 1H), 1.76 (s, 1H), 1.45−1.41 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (rotamer) 172.4, 155.5, 141.6, 110.2, 110.0, 80.3, 54.8, 53.6, 52.1, 48.2, 46.9, 29.7, 28.3, 27.3; HRMS-FAB (*m*/*z*) $[M + H]^+$ calcd for $C_{13}H_{22}O_4N$ 256.1549, found 256.1551; IR (neat) 3075, 2973, 2929,, 1745, 1702, 1659, 1172 cm^{-1}.

(*R*)-Methyl *N*-(*tert*-Butyloxycarbonyl)-4-oxopiperidine-2-carboxylate (17).[16] To a solution of **2** (20 mg, 0.08 mmol) in CCl_4 (100 μL), acetonitrile (100 μL), and water (0.7 mL) were added ruthenium(III) chloride (0.8 mg, 3.9×10^{-3} mmol) and periodic acid (53.6 mg, 0.24 mmol). The reaction mixture was stirred at rt for 2.5 h, diluted with CH_2Cl_2 (5 mL) and washed with water (3 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, EtOAc/hexanes, 1:5; R_f 0.23) to give **17** (10.7 mg, 0.042 mmol, 53%) as a colorless oil. $[\alpha]^{20}_D$ +2.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ (rotamer) 4.80−4.75 (m, 0.5H), 4.58−4.55 (m, 0.5H), 4.38 (d, J = 18.9 Hz, 0.5H), 4.27 (d, J = 18.9 Hz, 0.5H), 3.88 (dd, J = 25.3 Hz, 19 Hz, 1H), 3.75 (s, 3H), 2.45−2.37 (m, 2H), 2.37−2.31 (m, 1H), 2.17−2.07 (m, 0.5H), 2.07−2.02 (m, 0.5H), 1.43−1.37 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (rotamer) 205.5, 172.5, 172.2, 162.7, 154.8, 154.3, 81.4, 54.5, 53.0, 52.4, 52.3, 50.9, 35.9, 35.7, 28.2, 23.8, 23.6; IR (neat) 2956, 2922, 2851, 1742, 1713, 1152 cm^{-1}.

Acknowledgment. This research was supported by the National Science Council (NSC 95-2113-M-008-007), Taiwan. The authors thank Prof. John C. Gilbert, Santa Clara University, for helpful comments. We are grateful to Ms. Ping-Yu Lin at the Institute of Chemistry, Academia Sinica, and Valuable Instrument Center in National Central University for obtaining mass analysis. Thanks are also due to the National Center for High-performance Computing for computer time and facilities.

Supporting Information Available: Experimental procedure for preparing compounds **13**, **15**, and **16**, and characterizing data including ^{1}H−^{1}H COSY and NOE spectra of **7** and ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8008885