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Diastereoselective Synthesis of Polysubstituted Pyrrolidinone as a Key Intermediate for the Anticancer Agents by Palladium(II)-Catalyzed Carboxylation

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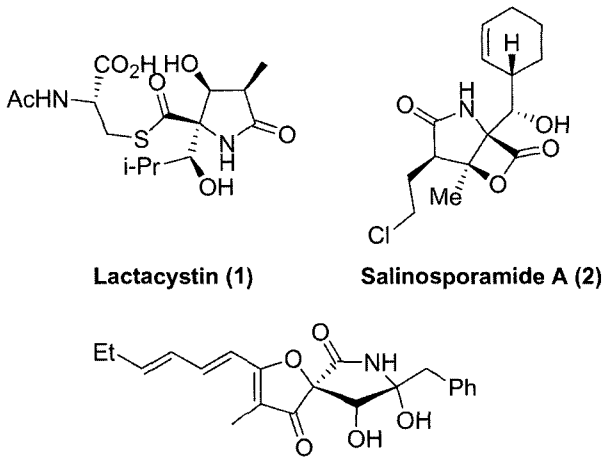
Palladium(II)-catalyzed carboxylation of chiral olefins **6a-d** has been examined under various conditions. In the weak basic condition (K_2CO_3), **7a-d** were obtained in good yields. Alternatively, in the strong basic condition, pyrrolidinones **8a-d** were obtained resulting in excellent yields and with high diastereoselectivity.

Key words: Palladium, Carboxylation, Pyrrolidinone, Stereocontrol

INTRODUCTION

The pyrrolidinone ring system is one of the most common structural subunits in natural products and of biological significance synthetic compounds (Harrison, 1995). In addition, the possibility for the functionalization of pyrrolidinone (γ-lactam) and modification of the pyrrolidinone moiety allows for the preparation of many types of natural products as well as the preparation of biologically active molecules (Castelhano *et al*, 1984; Petersen *et al*, 1984).

Many examples, (+)-Lactacystin (**1**) (Omura *et al*, 1991; Corey *et al*, 1998), salinosporamide A (**2**) (Feling *et al*, 2003; Reddy *et al*, 2004), and azaspirene (**3**) (Asami *et al*, 2002; Hayashi *et al*, 2002) are notable examples of natural products that not only include the densely functionalized pyrrolidinone unit in their structure but they also display extremely interesting biological activities. Consequently, the synthesis of optically active polyfunctionalized pyrrolidinones has attracted a great deal of interest. Although there have been many studies in the preparation of pyrrolidinone (Meyers *et al*, 1998; Overman and Remarchuk, 2002; Yoon *et al*, 2003; Sun *et al*, 2003; Huang *et al*, 2003; Alcaide *et al*, 2004), there is considerable interest in exploring new routes of synthesizing pyrrolidinone. This study reports of a novel synthesis of polysubstituted pyrrolidinone *via* palladium(II)-catalyzed olefin carboxylation.



Lactacystin (1) **Salinosporamide A (2)**

(-)-Azaspirene (3)

Fig. 1. Natural products of polyfunctionalized pyrrolidinone

MATERIALS AND METHOD

General procedure for hydroxy benzamide 5

1N HCl (50 mL, 50 mmol) was added to a stirred solution of oxazoline **4** (10 mmol) in methanol (25 mL) and THF (25 mL). After being stirred at room temperature for 12 h, 100 mL of saturated aqueous sodium bicarbonate

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solution was added carefully and stirred at room temperature for overnight. The solution was extracted with ethyl acetate. The organic layer was washed with brine, dried, and concentrated. The residue was purified by column chromatography.

(-)-*N*-((*2S,3S*)-3-Hydroxy-1-phenyl-4-pentenyl)benzamide (5a)

Purification by silica gel chromatography (ethyl acetate/hexane = 2/1) gave **5a**: 87% yield; colorless needles; mp 153-154°C (light petroleum/hexane); $[\alpha]_D^{20}$ -73.2° (*c* 1.0, $CHCl_3$); IR (neat) 3380, 1625 cm^{-1} ; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.06 (d, *J* =7.6 Hz, 2 H), 4.25 (m, 1 H), 4.34 (m, 1 H), 5.16 (dt, *J* = 1.4, 10.5 Hz, 1 H), 5.30 (dt, *J* = 1.4, 17.2 Hz, 1 H), 5.90 (ddd, *J* = 5.2, 10.5, 17.2 Hz, 1 H), 6.53 (d, *J* = 8.6 Hz, 1 H), 7.21-7.49 (m, 8 H), 7.66-7.68 (m, 2 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 37.7, 55.3, 72.3, 116.1, 126.6, 126.9, 128.5, 128.6, 129.3, 131.5, 134.5, 138.0, 138.3, 167.8; HRMS calcd for $C_{18}H_{19}NO_2$ (M + H) 282.1494, found 282.1495. Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.53; H, 6.77; N, 4.99.

(-)-*N*-((*1S,2S*)-2-Hydroxy-1-phenyl-3-butenyl)benzamide (5b)

Purification by silica gel chromatography (ethyl acetate/hexane = 2:1) gave **5b**: 83% yield; colorless needles; mp 143-145°C (ethyl acetate/hexane); $[\alpha]_D^{20}$ -48.9° (*c* 1.0, $CHCl_3$); IR (neat) 3438, 1657 cm^{-1} ; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.32 (d, *J* = 4.0 Hz, 1 H), 4.57 (ddd, *J* = 3.5, 3.5, 5.0 Hz, 1 H), 5.24-5.26 (m, 2 H), 5.43 (dt, *J* = 1.5, 17.0 Hz, 1 H), 5.96 (ddd, *J* = 5.0, 10.5, 17.0 Hz, 1 H), 6.97 (d, *J* = 7.5 Hz, 1 H), 7.29-7.53 (m, 8 H), 7.80-7.82 (m, 2 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 57.7, 75.4, 116.7, 126.8, 127.0, 127.7, 128.6, 128.8, 131.6, 134.3, 137.3, 139.5, 167.5; HRMS calcd for $C_{17}H_{17}NO_2$ (M +H) 268.1338, found 268.1337. Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.32; H, 6.34; N, 5.26.

(-)-*N*-((3S,*4S*)-3-hydroxy-6-methyl-1-heptenyl)benzamide (5c)

Purification by silica gel chromatography (ethyl acetate/hexane = 3:1) gave **5c**: 72% yield; colorless needles; mp 101-102°C (ethyl acetate/hexane); $[\alpha]_D^{20}$ -58.9° (*c* 1.0, $CHCl_3$); IR (neat) 3346, 1638 cm^{-1} ; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.97 (d, *J* = 6.5 Hz, 1 H), 1.48-1.74 (m, 3 H), 4.24-4.30 (m, 2 H), 5.19 (d, *J* = 10.5 Hz, 1 H), 5.31 (d, *J* = 16.5 Hz, 1 H), 5.94 (ddd, *J* = 6.0, 10.5, 16.5 Hz, 1 H), 6.29 (d, *J* = 8.5 Hz, 1 H), 7.41-7.51 (m, 3H), 7.75-7.77 (m, 2 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 22.9, 24.0, 25.7, 41.7, 52.6, 75.6, 116.9, 127.6, 129.3, 132.2, 135.3, 138.9, 168.5; HRMS calcd for $C_{15}H_{21}NO_2$ (M + H) 248.1651, found 248.1650.

(-)-*N*-((*2S,3S*)-3-Hydroxy-1-cyclohexyl-4-pentenyl) benzamide (5d)

Purification by silica gel chromatography (ethyl acetate/hexane = 3:1) gave **5d**: 70% yield; colorless needles; mp 136-137°C (ethyl acetate/hexane); $[\alpha]_D^{20}$ -58.3° (*c* 1.0, $CHCl_3$); IR (neat) 3345, 1638 cm^{-1} ; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.81-1.63 (m, 13H), 4.15 (m, 1 H), 4.21 (m, 1 H), 5.10 (dt, *J* = 1.2, 10.5 Hz, 1H), 5.24 (dt, *J* = 1.2, 17.1 Hz, 1 H), 5.86 (ddd, *J* = 5.6, 10,5, 17.1 Hz, 1 H), 6.23 (d, *J* = 9.0 Hz, 1 H), 7.19-7.42 (m, 3 H), 7.67-7.69 (m, 2 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 26.1, 26.3, 26.5, 32.8, 33.9, 34.5, 39.4, 51.3, 74.9, 116.2, 126.9, 128.5, 131.4, 134.7, 138.3, 167.8; HRMS calcd for $C_{18}H_{25}NO_2$ (M + H) 288.1964, found 288.1963.

General procedure for *tert*-butylsilanyloxy benzamide 6

Imidazole (13.0 mmol) and *tert*-butyldimethylsilyl chloride (12.0 mmol) were added to a stirred solution of hydroxy benzamide **5** (10.0 mmol) in DMF (50 mL), and stirring was allowed to continue at room temperature for 5 h. The reaction mixture was quenched with H_2O (50 mL), then extracted with ethyl acetate (50 mL × 2), and this was followed by washing with brine, dried, and evaporated *in vacuo*. The residue was purified by column chromatography.

(-)-*N*-(*1S, 2S*)-[1-Benzyl-2-(*tert*-butyldimethylsilanyloxy)-but-3-enyl]-benzamide (6a)

Purification by silica gel chromatography (ethyl acetate/hexane = 1/6) gave **6a**: 97% yield; white solid; mp 113-118°C; $[\alpha]_D^{20}$ 33.7 (c 0.2, CH_2Cl_2); IR (neat) 1638 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.00 (s. 3H), 0.08 (s, 3H), 0.93 (s, 9H), 2.88 (m, 2H), 4.21 (d, *J* = 6.31 Hz, 1H), 4.37 (m, 1H), 5.05 (m, 1H), 5.07 (m, 2H), 5.78 (m, 1H), 6.42 (d, *J* = 7.83 Hz, 1H), 7.14-7.22 (m, 5H), 7.61-7.62 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -4.8, -3.9, 18.2, 26.0, 37.8, 55.4, 73.3, 116.3, 126.4, 126.7, 128.5, 128.6, 129.2, 131.3, 138.4, 166.8.

(-)-*N*-(*1S, 2S*)-[2-(*tert*-Butyldimethylsilanyloxy)-1-phenyl-but-3-enyl]-benzamide (6b)

Purification by silica gel chromatography (ethyl acetate/hexane = 1/6) gave **6b**: 98% yield; white solid; mp 117-121°C; $[\alpha]_D^{20}$ 58.2 (c 0.2, CH_2Cl_2); IR (neat) 1631 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ -0.46 (s, 1H), -0.13 (s, 3H), 0.85 (s, 9H), 4.47 (m, 1H), 5.22 (m, 2H), 5.37 (dt, *J* = 16.5 Hz, 1H), 6.00 (ddd,, *J* = 5.0 Hz, 10.5 Hz, 16.5Hz, 1H), 7.09 (d, 1H), 7.23-7.55 (m, 8H), 7.81-7.83 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -4.6, -3.5, 18.9, 26.8, 55.8, 72.3, 116.1, 125.1, 126.7, 128.5, 128.6, 129.1, 130.8, 137.3, 166.2.

(-)-*N*-(*1S, 2S*)-[2-(*tert*-Butyldimethylsilanyloxy)-1-isobutyl-but-3-enyl]-benzamide (6c)

Purification by silica gel chromatography (ethyl acetate/hexane = 1/10) gave **6c**: 96% yield; white solid; mp 133-140°C; $[\alpha]_D^{20}$ 53.8 (c 0.2, CH_2Cl_2); IR (neat) 1634 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.04 (S, 1H), 0.09 (s, 1H), 0.92 (s, 9H), 1.18 (m, 3H), 1.30 (m, 1H), 1.42 (m, 2H), 1.65 (m, 2H), 5.09 (d, *J* = 10.7 Hz, 1H), 5.19 (d, *J* = 17.6 Hz, 1H), 5.82 (m, 1H), 6.20 (d, *J* = 10.8 Hz, 1H), 7.43 (m, 3H), 7.71 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -4.9, -4.2, 18.2, 25.9, 26.2, 26.3, 26.5, 33.0, 33.9, 34.3, 39.7, 51.3, 74.6, 115.8, 126.7, 128.6, 131.2, 134.9, 138.4, 166.8.

(-)-*N*-(*1S, 2S*)-[2-(*tert*-Butyldimethylsilanyloxy)-1-cyclohexylmethyl-but-3-enyl]-benzamide (6d)

Purification by silica gel chromatography (ethyl acetate/hexane = 1/10) gave **6d**: 98% yield; white solid; mp 102-106°C; $[\alpha]_D^{20}$ 43.6 (c 0.2, CH_2Cl_2); IR (neat) 1629 cm^{-1} ; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.05 (s, 3H), 0.88 (s, 9H), 0.91 (d, *J* = 6.59 Hz, 6H), 1.40 (m, 2H), 1.60 (m, 1H), 4.18 (br s, 2H), 5.04 (d, *J* = 10.2Hz, 1H), 5.16 (d, *J* = 17.1 Hz, 1H), 5.78 (m, 1H), 6.18 (d, *J*=7.8 Hz, 1H), 7.35-7.43 (m, 3H), 7.67-7.69 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -4.6, -3.9, 18.5, 22.7, 23.5, 25.2, 26.2, 41.7, 52.3, 75.0, 116.1, 127.1, 128.9, 131.6, 135.2, 138.8, 167.1.

General procedure for dicarboxylation

Olefins **6** (1 mmol) was added to a flask contaning $PdCl_2$ (0.1 mmol), $CuCl_2$ (3.0 mmol), and K_2CO_3 (1.0 mmol). This mixture was purged with a balloon of CO and then this mixture was dissolved in trimethyl orthoacetate (5 mL) via a syringe. The mixture was stirred at room temperature for 24 h, during which time the reaction was monitored by TLC. The mixture was diluted with ethyl acetate (50 mL) and washed with 5% NH_4Cl-5% NH_3 (15 mL × 2). The organic layer was dried, filtered, and concentrated *in vacuo*. The residue was chromatographed over silica gel (hexane-ethyl acetate gradient) to give a mixture of trans-**7** and cis-**7**.

Methyl (-)-(*3R, 4S, 5S*)-5-(*N*-Benzoyl)amino-4-(*tert*-butyldimethylsilanyl)oxy-3-methoxycarbonyl-5-benzyl pentanoate (7a)

Purification by silica gel chromatography (ethyl acetate/hexane = 1/6) gave **7a**: 82% yield; $[\alpha]_D^{20}$ 39.7 (c 0.2, CH_2Cl_2); IR (neat) 1631, 1765, 1780 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ -0.93 (s, 3H), 0.00 (s, 3H), 0.72 (s, 9H), 2.15 (dd, *J* = 17.3, 9.0 Hz, 1H), 3.14 (s, 3H), 3.32 (s, 3H), 3.85 (m, 1H), 4.14 (m, 1H), 6.32 (d, *J* = 7.83 Hz, 1H), 6.95-7.06 (m, 5H), 7.13-7.24 (m, 3H), 7.4 (m, 2H).

Methyl (-)-(*3R, 4S, 5S*)-5-(*N*-Benzoyl)amino-4-(*tert*-butyldimethylsilanyl)oxy-3-methoxycarbonyl-5-phenyl pentanoate (7b)

Purification by silica gel chromatography (ethyl acetate/hexane = 1/6) gave **7b**: 85% yield; $[\alpha]_D^{20}$ 20.3 (*c* 0.2, CH_2Cl_2); IR (neat) 1629, 1766, 1780 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ -0.59 (s, 3H), -0.02 (s, 3H), 0.89 (s, 9H), 2.68 (dd, *J* = 5.5, 6.0, 9.0 Hz, 1H), 3.63 (s, 3H), 3.66 (s, 3H), 4.40 (dd, *J* = 1.5, 6.0 Hz, 1H), 5.31 (d, *J* = 8.0 Hz, 1H), 7.23-7.57 (m, 8H), 7.88-7.90 (m, 2H).

Methyl (-)-(*3R, 4S, 5S*)-5-(*N*-Benzoyl)amino-4-(tert-butyldimethylsilanyl)oxy-3-methoxycarbonyl-5-isobutyl pentanoate (7c)

Purification by silica gel chromatography (ethyl acetate/hexane = 1/6) gave **7c**: 68% yield; $[\alpha]_D^{20}$ 8.2 (c 0.2, CH_2Cl_2); IR (neat) 1625, 1763, 1778 cm^{-1} ; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.09 (s, 3H), 0.80 (s, 9H), 0.82 (m, 4H), 1.38 (m, 2H), 1.49 (m, 2H), 1.57 (m, 2H), 2.93 (m, 1H), 3.35 (s, 3H), 3.50 (s, 3H), 3.52 (m, 1H), 3.99 (m, 1H), 4.12 (m, 1H), 7.28-7.36 (m, 3H), 7.62 (d, *J* = 7.8 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ -4.6, -4.3, 18.1, 22.2, 23.1, 25.0, 25.9, 33.0, 39.9, 45.4, 51.2, 51.3, 51.8, 52.0, 72.7, 126.8, 128.6, 131.5, 166.3, 172.6, 173.5.

Methyl (-)-(*3R, 4S, 5S*)-5-(*N*-Benzoyl)amino-4-(*tert*-butyldimethylsilanyl)oxy-3-methoxycarbonyl-5-cyclohexylmethyl pentanoate (7d)

Purification by silica gel chromatography (ethyl acetate/hexane = 1/6) gave **7d**: 76% yield; $[\alpha]_D^{20}$ 13.2 (c 0.2, CH_2Cl_2); IR (neat) 1633, 1760, 1783 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 1H), 0.09 (s, 1H), 0.89 (s, 9H), 0.82 (m, 2H), 1.08 (m, 5H), 1.41 (m, 6H), 1.68 (m, 1H), 2.56 (dd, *J* = 9.3, 7.3 Hz, 1H), 3.34 (s, 1H), 3.50 (s, 3H), 3.99 (m, 1H), 4.14 (br s, 1H), 6.15 (d, *J* = 8.6 Hz, 1H), 7.29-7.37 (m, 3H), 7.62 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -4.6, 4.3, 18.1, 25.9, 26.2, 26.3, 26.5, 32.9, 33.0, 33.9, 34.5, 38.2, 45.3, 50.6, 51.8, 52.0, 72.6, 126.8, 128.6, 131.5, 134.2, 166.3, 172.6, 173.5.

General procedure for pyrrolidinone 8

Into a flask containing $PdCl_2$ (0.1 mmol), $CuCl_2$ (3.0 mmol), and NaH (1.0 mmol) in trimethyl orthoacetate (5 mL), purged with carbon monoxide *via* a balloon, was added olefins **6** (1 mmol) dissolved in trimethyl orthoacetate (5 mL) *via* syringe. The mixture was stirred at room temperature for 24 h, during which time the reaction was monitored by TLC. The mixture was diluted with ethyl acetate (50 mL) and washed with 5% NH_4Cl-5% NH_3 (15 mL × 2). The organic layer was dried, filtered, and concentrated *in vacuo*. The residue was chromatographed over silica gel (hexane-ethyl acetate gradient) and gave a mixture of *trans*-**8** and *cis*-**8**.

(+)-(*3S, 4S, 5S*)-[1-Benzoyl-4-(*tert*-butyldimethylsilanyl-oxy)-2-oxo-5-phenyl-pyrrolidin-3-yl]-acetic acid methyl ester (8a)

Purification by silica gel chromatography (ethyl acetate/hexane = 1/4) gave **8a**: 91% yield; $[\alpha]_D^{20}$ +22.8 (c 0.2, CH_2Cl_2); IR (neat) 1640, 1712, 1769 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ -0.17 (s, 3H), 0.00 (s, 3H), 0.87 (s, 9H), 2.39 (dd, *J* = 17.6, 5.1 Hz, 1H), 2.48 (dd, *J* = 17.6, 4.4 Hz, 1H), 3.53 (s, 3H), 4.43 (dd, *J* = 10.2, 7.8 Hz, 1H), 4.75 (m, 1H), 7.06-7.41 (m, 10H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -5.1, -4.5, 18.0, 25.8, 29.2, 30.4, 33.4, 46.3, 51.9, 59.6, 70.9, 126.8, 127.6, 128.3, 128.7, 130.6, 131.7, 134.7, 137.1, 169.9, 171.5, 172.3.

(+)-(*3S, 4S, 5S*)-[1-Benzoyl-5-benzyl-4-(*tert*-butyldi-methylsilanyloxy)-2-oxo-pyrrolidin-3-yl]-acetic acid methyl ester (8b)

Purification by silica gel chromatography (ethyl acetate/hexane = 1/4) gave **8b**: 84% yield; $[\alpha]_D^{20}$ +18.2 (c 0.2, CH_2Cl_2); IR (neat) 1644, 1709, 1768 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ -0.25 (s, 3H), 0.01 (s, 3H), 0.72 (s, 9H), 2.66 (dd, *J* = 5.0, 17.5 Hz, 1H), 2.85 (dd, *J* = 10.5, 17.5 Hz, 1H), 3.11 (ddd, *J* = 5.0, 9.0, 10.5 Hz, 1H), 3.73 (s, 3H), 4.69 (dd, *J* = 7.0, 9.0 Hz, 1H), 5.53 (d, J = 10.5 Hz, 1H), 7.27-7.53 (m, 8H), 7.68-7.70 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -4.4, -3.9, 18.4, 26.2, 31.5, 48.0, 52.8, 64.4, 71.3, 128.5, 128.57, 128.64, 129.0, 129.7, 132.8, 135.2, 136.3, 170.3, 172.2, 174.2.

(+)-(*3S, 4S, 5S*)-[1-Benzoyl-4-(*tert*-butyldimethylsilanyl-oxy)-5-isobutyl-2-oxo-pyrrolidin-3-yl]-acetic acid methyl ester (8c)

Purification by silica gel chromatography (ethyl acetate/hexane = 1/4) gave **8c**: 84% yield; $[\alpha]_D^{20}$ +29.9 (c 0.2, CH_2Cl_2); IR (neat) 1636, 1717, 1771 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.07 (s, 1H), 0.11 (s, 1H), 0.87-0.99 (s, 9H), 1.14 (br s, 3H), 1.23 (br s, 1H), 1.45-1.56 (m, 1H), 1.66 (m, 3H), 1.79-1.92 (m, 3H), 2.56 (dd, *J* = 6.6, 17.2 Hz, 1H), 2.62 (dd, *J* = 5.4, 17.2 Hz, 1H), 3.09 (m, 1H), 3.66 (s, 3H), 4.38 (dd, *J* = 9.7Hz, 9.8 Hz, 1H), 4.66 (m, 1H), 7.36-7.39 (m, 2H), 7.46-7.48 (m, 1H), 7.50-7.59 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -5.0, -4.5, 17.9, 22.0, 23.6, 25.0, 25.7, 30.7, 38.0, 46.3, 51.9, 56.8, 71.1, 127.9, 128.8, 123.0, 134.8, 170.3, 171.6, 172.5.

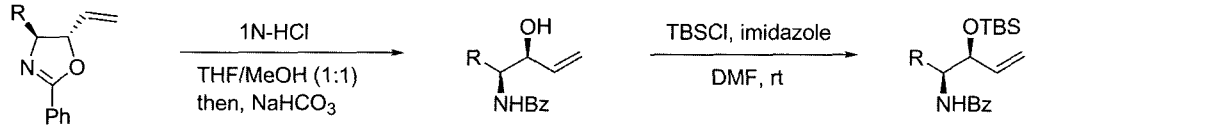
(+)-(*3S, 4S, 5S*)-[1-Benzoyl-4-(*tert*-butyldimethylsilanyl-oxy)-5-cyclohexylmethyl-2-oxo-pyrrolidin-3-yl]-acetic acid methyl ester (8d)

Purification by silica gel chromatography (ethyl acetate/hexane = 1/4) gave **8d**: 87% yield; $[\alpha]_D^{20}$ +35.6 (c 0.2, CH_2Cl_2); IR (neat) 1638, 1725, 1762 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.03 (s, 3H), 0.83 (s, 9H), 0.88 (m, 6H), 1.45 (m, 2H), 1.54-1.62 (m, 1H), 1.66-1.73 (m, 1H), 2.48 (dd, *J* = 17.1, 6.1 Hz, 1H), 2.56 (dd, *J* = 17.1, 5.6 Hz, 1H), 3.03 (m, 1H), 3.58 (s, 3H), 4.31 (dd, *J* = 10.0, 7.3 Hz, 1H), 4.59 (m, 1H), 7.32 (m, 2H), 7.42 (m, 1H), 7.52 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -5.0, -4.5, 17.9, 22.0, 23.6, 25.0, 25.7, 30.7, 38.0, 51.9, 56.8, 71.1, 127.9, 128.8, 132.0, 170,3, 171.6, 172.5.

RESULTS AND DISCUSSION

This laboratory is interested in developing effective and convenient methods for the synthesis of highly functionalized pyrrolidinones (γ-lactam). For this purpose, efforts have been focused on the palladium(II)-catalyzed olefin carboxylation reaction (Stille and Divakaurni, 1979; Tamaru, 1991; Nefkens *et al*, 1993). Chiral amino olefins for the palladium catalyzed carboxylation reaction were synthesized as follows (Scheme 1). The acid-catalyzed hydrolysis of trans-oxazolines **4** (Lee *et al*, 1999) gave the corresponding alcohols **5** which were reacted with TBSCl at 25°C to produce chiral amino olefins **6** in 96~98% yields in a two steps process.

Conditions for the palladium catalyzed carboxylation reaction of olefins **6** were extensively explored by examining the effects on bases, solvents, and additives as summarized in Table I. The initial attempt at palladium(II)-catalyzed carboxylation reaction of chiral olefins began with **6a**. When **6a** was subjected to $PdCl_2$ (0.1 equiv.) and $CuCl_2$ (3.0 equiv.) as a reoxidant in trimethyl orthoacetate (MOA) under 1 atmosphere of carbon monoxide, **7a** was produced with a 10% yield. No reaction proceeded in the presence of $PdCl_2$ (0.1 equiv.), $CuCl_2$ (3.0 equiv.) and NaOAc (3.0 equiv.) as a base in MeOH under 1 atmosphere of carbon monoxide (entry 2). The use of AcOH or MOA



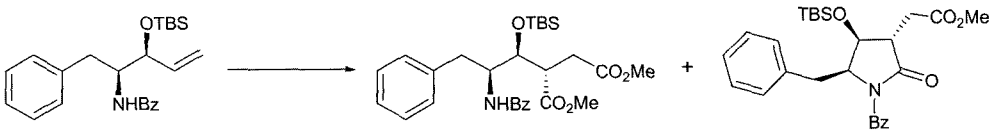
4a R = Benzyl
4b R = Phenyl
4c R = isobutyl
4d R = cyclohexylmethyl

5a R = Benzyl
5b R = Phenyl
5c R = isobutyl
5d R = cyclohexylmethyl

6a R = Benzyl (97%)
6b R = Phenyl (98%)
6c R = isobutyl (98%)
6d R = cyclohexylmethyl (96%)

Scheme 1. Synthesis of chiral amino olefins 6

Table I. Effects of additives, bases, and solvents on Pd(ii)-catalyzed carboxylation of olefin **6a**

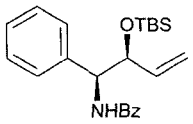
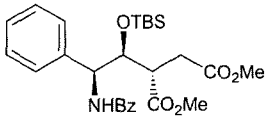
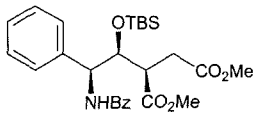
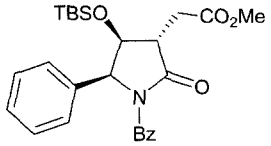
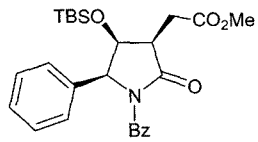
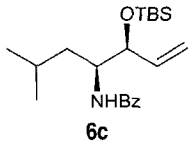
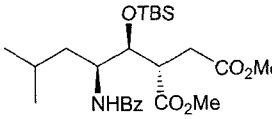
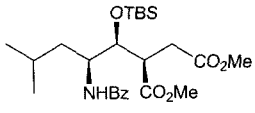
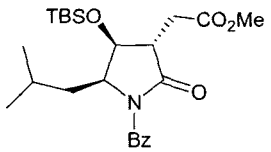
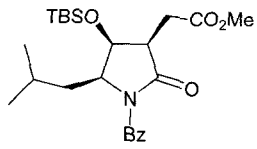
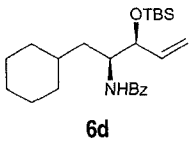
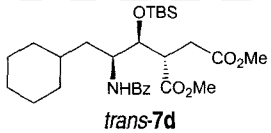
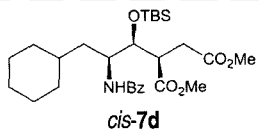
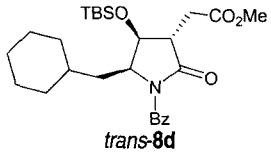
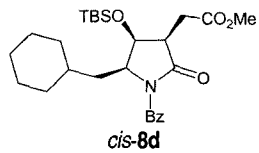


6a **7a** **8a**

run	$PdCl_2$ (equiv.)	$CuCl_2$ (equiv.)	base (equiv.)	additives (equiv.)	solvent	Temp(°C)/ Time(h)	% isolated yield[a] **7a** or **8a** (*trans*: *cis*)[b]
1	0.1	3.0	none	none	MOA	25/24	**7** : 10[c]
2	0.1	3.0	NaOAc (3.0)	none	MeOH	25/12	No rxn
3	0.1	3.0	NaOAc (3.0)	AcOH (18)	MeOH	25/12	No rxn
4	0.1	3.0	NaOAc (3.0)	MOA (18)	MeOH	25/12	Trace[c]
5	0.1	3.0	K_2CO_3 (1.0)	none	MOA	25/24	**7a** : 82 (8.6:1)
6	0,1	3.0	NaH (1.0)	none	MOA	25/24	**8a** : 91 (>20:1)

a) Yields refer to isolated and chromatographically pure products
b) Ratios were determined by ^{1}H-NMR
c) Yields and ratios were not determined

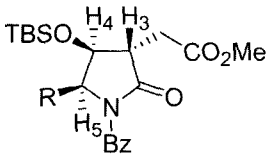
Table II. Pd(II)-Catalyzed Carboxylation of Olefins **6**

Entry	substrate	Condition[a]	Product	Yield(%)[b] [ratio][c]
1	 **6b**	A	 *trans*-**7b**  *cis*-**7b**	85 [9:1]
		B	 *trans*-**8b**  *cis*-**8b**	84 [>20:1]
2	 **6c**	A	 *trans*-**7c**  *cis*-**7c**	76 [7:1]
		B	 *trans*-**8c**  *cis*-**8c**	84 [>20:1]
3	 **6d**	A	 *trans*-**7d**  *cis*-**7d**	68 [7.2:1]
		B	 *trans*-**8d**  *cis*-**8d**	87 [>20:1]

a) *Reaction Condition* : A. $PdCl_2$ (0.1 equiv.), $CuCl_2$ (3.0 equiv.), K_2CO_3 (1.0 equiv.), CO (1 atm), MOA, 25 °C, 1 day; B. $PdCl_2$ (0.1 equiv.), $CuCl_2$ (3.0 equiv.), NaH (1.0 equiv.), CO (1 atm), MOA, 35 °C, 1 day.
b) *Yield refer to isolated and chromatographically pure products.*
c) Ratios were determined by ^{1}H-NMR.

as an additive under the same conditions gave the same results (entries 3 and 4). The reaction of **6a** with K_2CO_3 in the presence of $PdCl_2$ and $CuCl_2$ in MOA under carbon monoxide at room temperature for 24 hours proceeded smoothly to produce an 8.6:1 mixture of *trans*-**7a** and *cis*-**7a** with an 82% yield (entry 5). It was found that using NaH as a base under the same conditions generated pyrrolidinone **8a** with a 91% yield that was the desired product (entry 6).

Table III. Coupling constants of 2-pyrrolidinones **8**



R	Chemical shift (ppm)			Coupling Constant (Hz)	
	H-3	H-4	H-5	$J_{3,4}$	$J_{4,5}$
Bn	2.59	4.44	4.75	10.2	8.0
Ph	3.11	4.69	5.53	9.0	7.0
Cyclohexylmethyl	3.03	4.31	4.59	10.0	7.0
Isobutyl	3.01	4.57	4.57	10.0	7.0

Chiral amino olefins **6** having benzyl, isobutyl, and cyclohexylmethyl as substituent groups reacted with K_2CO_3 or NaH in the presence of $PdCl_2$ and $CuCl_2$ in MOA under 1atmosphere of carbon monoxide produced the *trans*-**7** or *trans*-**8**. *Trans*-**7** and *trans*-**8** were the major products with a 68~87% yield along with a minor amount of *cis*-**7** or *cis*-**8**. The results were summarized in Table II.

To determine the stereochemistry of **7**, these compounds were converted into their cyclic compounds using NaH in DMF. The spectroscopic data of the resulting compounds were completely identical to those of pyrrolidinones **8** formed from palladium catalyzed carboxylation reaction with NaH as a base. The stereochemistry of the pyrrolidinones **8** obtained above was elucidated by the ^{1}H-NMR data, as shown in Table III. The J values ($J_{4,5}$ = 7-8 Hz) observed in all major isomers indicate that the compound probably possesses the assigned trans structure. In addition, the stereochemistries of the obtained products were all determined by NOESY spectra (Fig. 2). The cis orientation between the proton at the C4 and the methylene proton of the methylacetate group at the C3 was confirmed by the existence of NOE. The key interactions are illustrated here (Fig. 3).

A proposed rationale for the stereochemical outcome of

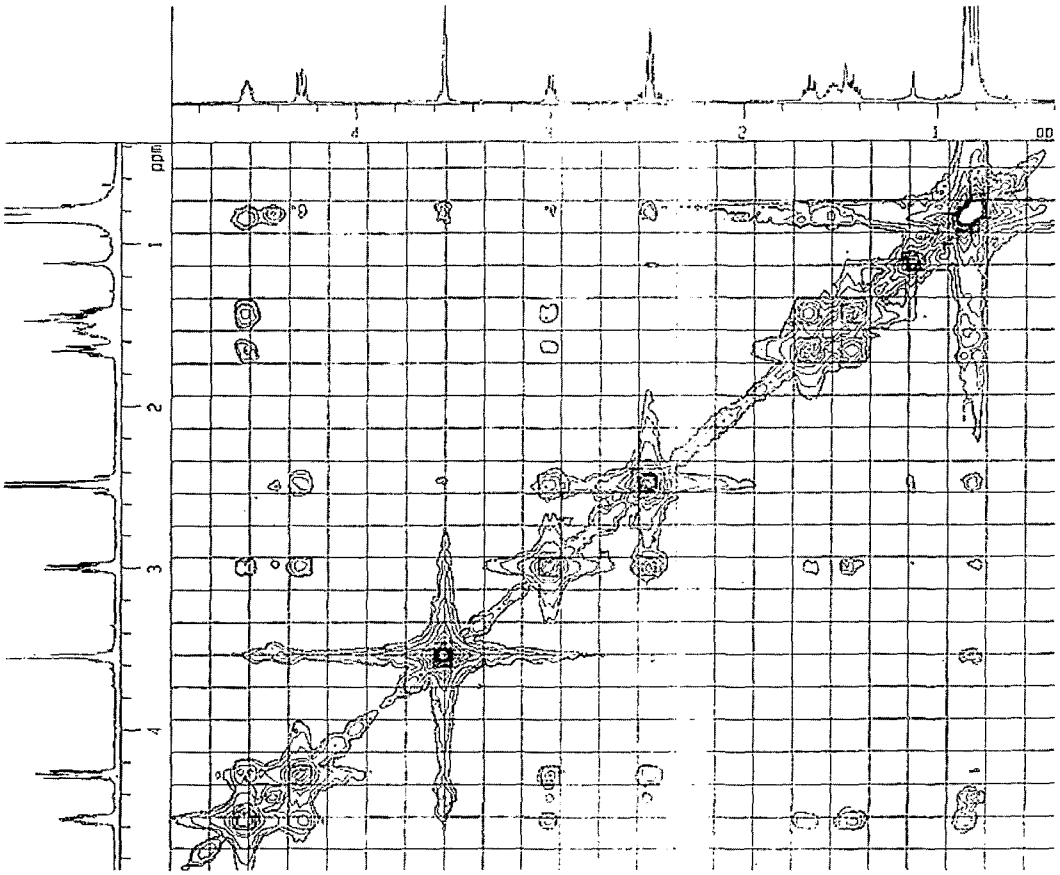


Fig. 2. NOESY Spectrum of **8c**

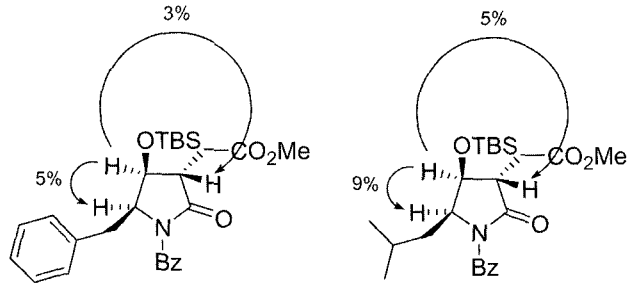


Fig. 3. Selected NOE experiment of 2-pyrrolidinone

the process is based on a consideration of the interconverting transition state of carbomethoxy palladium complex **A** and **B** for dicarboxylation (Fig. 4). Equilibration between **A** and **B** occurs by chelation. It is expected that the transition state **A**, forming the trans product, would be of a lower energy because of the absence of the steric repulsion that is present in the transition state **B**.

Under the weak base condition (K_2CO_3), it is reasonable to assume that the cis addition of palladium and the coordination of the carbomethoxy ligand yields a σ-bonded β-carbomethoxy palladium complex. Further CO

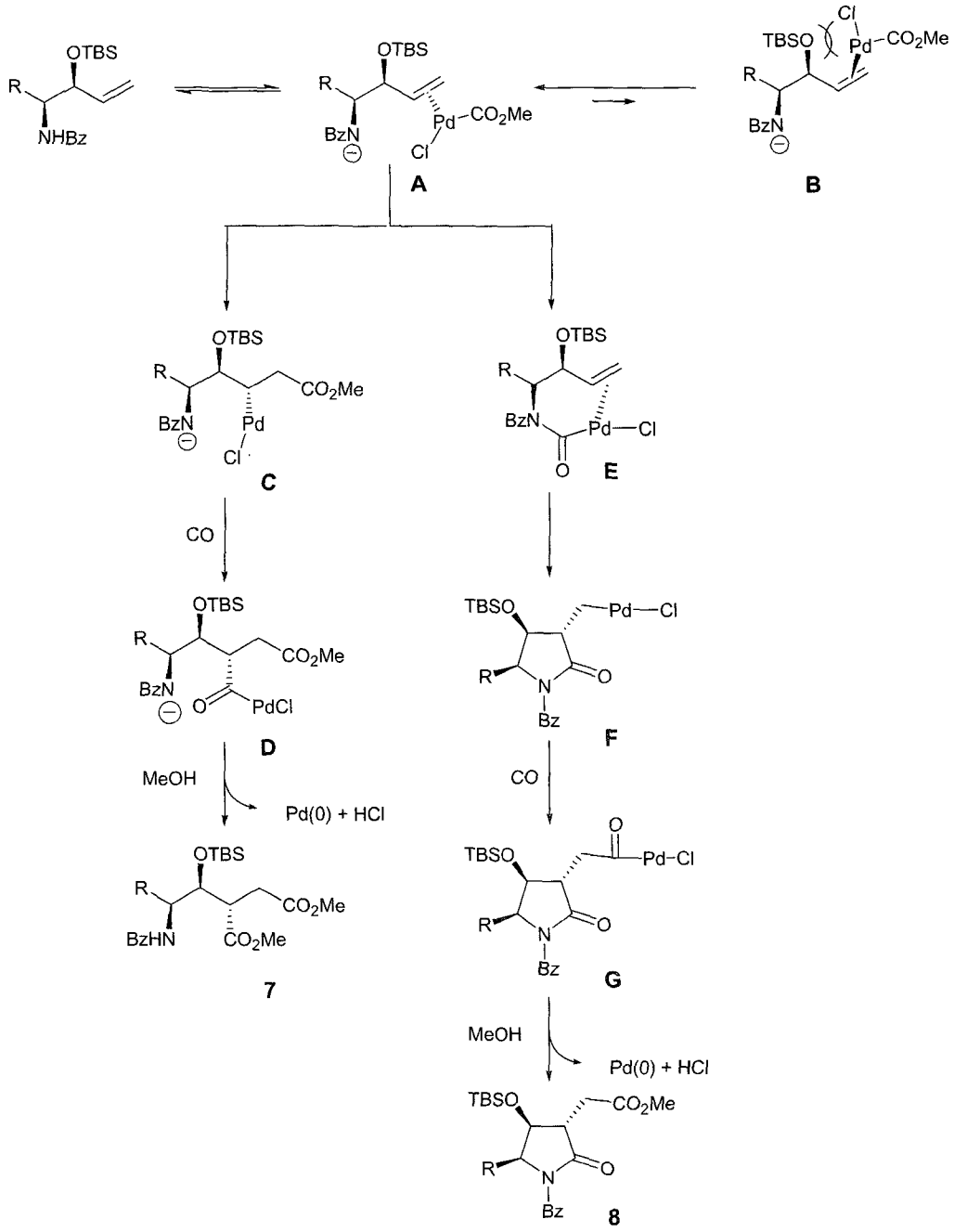


Fig. 4. Mechanism of dicarboxylation

insertion into **C** produces the acyl palladium intermediate **D.** Its alcoholysis yields the dicarboxy compounds **7**.

The influence of NaH on the dicarboxylation therefore is to increase the transition state **E** to that extent. Probably this reaction does occur in the weak base condition (K_2CO_3) as well.

At this time, it is difficult to fully realize the significance of all the results that have been observed. However, continuing to explore the chemistry of pyrrolidinone is to better understand the parameters controlling these reactions.

In conclusion, our study has described a simple and novel route to creating polyfunctionalized pyrrolidinone *via* palladium(II)-catalyzed carboxylation of olefins.

ACKNOWLEDGEMENT

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