CHEMOSELECTIVITY IN THE INTRAMOLECULAR AZA-WITTIG REACTION OF *N*-[2-(TRISUBSTITUTED PHOSPHORANYLIDENE)AMINOBENZOYL]-2-PYRROLIDONE-5-CARBOXYLIC ACID DERIVATIVES†

Tomohiro Okawa,[a] Toshiyuki Sugimori,[a] Shoji Eguchi,[a,*] and Akikazu Kakehi[b]

[a]*Department of Molecular Design and Engineering, Graduate School of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-01, Japan*
[b]*Department of Chemistry and Material Engineering, Faculty of Engineering, Shinshu University, Wakasato, Nagano 380, Japan*

Abstract - The intramolecular aza-Wittig reaction of (5*S*)-*N*-[2-(trisubstituted phosphoranylidene)aminobenzoyl]-2-pyrrolidone-5-carboxylic acid derivatives gave chemoselectively pyrrolo[2,1-*c*][1,4]benzodiazepin derivatives or pyrrolo[2,1-*b*]quinazoline derivatives depending on their substituents and phosphorus reagent

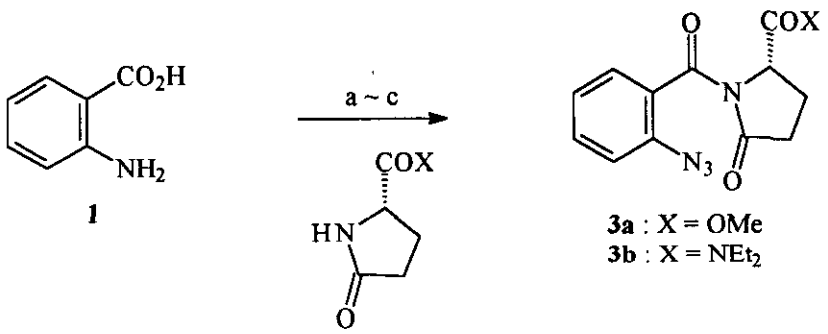
Over the past decade, not only intermolecular but also intramolecular aza-Wittig methodology has been demonstrated to be a powerful tool for the formation of carbon-nitrogen double bonds (*e.g.* imines, imidates, and amidines) and heterocumulene bonds (*e.g.* isocyanates and carbodiimides, *etc.*).[1] The key intermediate iminophosphoranes,[2] aza-ylides, are conveniently generated by the Staudinger reaction or the modified Kirsanov reaction *i.e.*, Appel's method *etc* [3] We and other workers have recently reported that the intramolecular aza-Wittig reaction is a useful methodology for synthesis of 5-8 membered nitrogen heterocyclic compounds[4] including natural products such as *O*-Bn-DC-81,[5] DC-81,[6] batracylin,[7] *l*-vasicinone[8] and (–)-benzomalvin A[9] *etc.* 5-Pyrrolo[2,1-*c*][1,4]benzodiazepinone derivatives[10] are known to recognize and bind to specific sequences of DNA. Such compounds have potential as regulators of gene expression with possible application as therapeutic agents in the treatment of certain genetic disorders including some cancers. Also, pyrrolo[2,1-*b*]quinazoline derivatives[11] are known to be one of alkaloids including natural products, *e.g.*, vasicinone[12] *etc* We have reported the chemoselective formation of 7-membered [1,4]benzodiazepine derivatives and 6-membered pyrrolo[2,1-*b*]quinazoline derivatives in the intramolecular aza-Wittig reaction of (5*S*)-*N*-[2-(trisubstituted phosphoranylidene)aminobenzoyl]-2-pyrrolidone-5-carboxylic acid derivatives in a preliminary communication.[13] We wish to describe here the above mentioned results in detail.

(5*S*)-*N*-(2-Azidobenzoyl)-2-pyrrolidone-5-carboxylic acid derivatives (**3**) were readily accessible from (5*S*)-

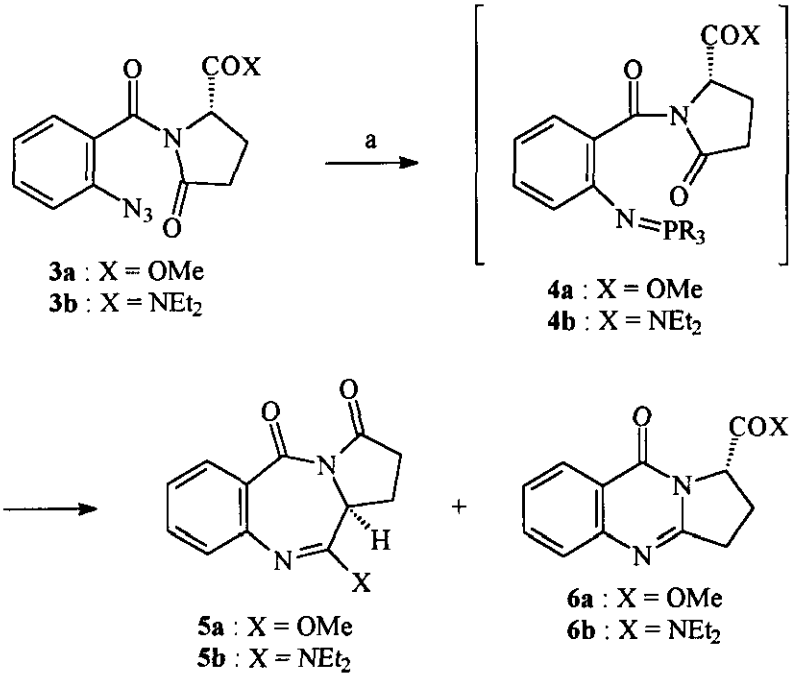
†Dedicated to Professor Koji Nakanishi on the occasion of his 75th birthday

2-pyrrolidone-5-carboxylic acid ester (**2a**) or amide (**2b**)[14] and 2-azidobenzoyl chloride, which was prepared from azidation of anthranilic acid (**1**) followed by treatment with thionyl chloride (Scheme 1).

The intramolecular aza-Wittig reaction of (5*S*)-*N*-[2-(trisubstituted phosphoranylidene)aminobenzoyl]-2-pyrrolidone-5-carboxylic acid derivatives was carried out as follows (Scheme 2). To a solution of azide derivatives (**3**) in dry benzene or xylene were added phosphorus reagents (Ph_3P, n-Bu_3P, $(EtO)_3P$). The mixture was stirred at ambient temperature for appropriate time to complete the Staudinger reaction. After



Scheme 1 *Reagents and conditions* : (a) $NaNO_2$, HCl (aq.) then NaN_3, AcONa, −10 °C, 30 min, 80 %. (b) $SOCl_2$ (neat), reflux, 2 h. (c) **2**, LDA, −78 °C, 1 h, 67 % (**3a**) and 33 % (**3b**) from *o*-azidobenzoic acid.



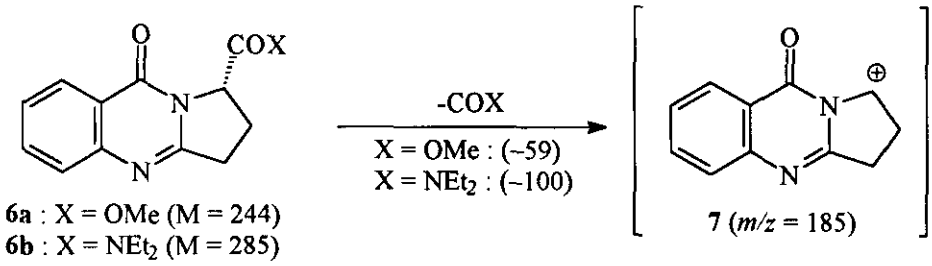
Scheme 2 *Reagents and conditions* : (a) PR_3 (Ph, n-Bu, OEt), reaction conditions (see, Table 1).

disappearance of **3**, the mixture was heated at 80 °C ~ 140 °C to complete the intramolecular aza-Wittig reaction Since iminophosphoranes are known to react with both ester carbonyl and imide carbonyl functions in the intramolecular aza-Wittig reaction, two kinds of cyclic compounds (**5**, **6**) could be competitively produced (Table 1). The structures of two cyclic compounds were distinguished by various spectral data, in particular, fragment ion peaks of mass spectrometric analysis. Maximal fragment ion peaks of both six-membered compounds (**6a**) and (**6b**) were 185. These peaks suggested evidently that methoxycarbonyl and diethylaminocarbonyl functions were eliminated from **6a** and **6b**, respectively (Scheme 3). In addition, main fragment ion peaks of seven-membered compound (**5a**) were 161 and 146. These characteristic peaks were assignable to fragmentations of 2-pyrrolidone ring and methyl function from **5a** (Scheme 4). Compound (**5a**) had a large optical rotation value $[\alpha]_D^{23\,9} = +919.2°$ in analogy with those of 2-pyrrolo[2,1-c][1,4]benzodiazepinone derivatives such as *O*-Bn-DC-81 [5,13] Thus, **5a** was suggested to have 5-pyrrolo[2,1-*c*][1,4]benzodiazepinone skeleton. Furthermore, the structure of **5a** was accurately established by X-Ray crystallographic analysis (Figure 1, Tables 2 and 3). Diethylamide derivative (**4b**) was specifically led to **6b** because the reactivity of amide carbonyl function was much lower than that of imide carbonyl function. Yields were determined after conversion[15] (HCl/THF, rt, 3 h) of **5a** to **6a** because **5a** was sensitive to moisture and accurate yields were difficult to determine. Ratios of **5** to **6** were based on ^{1}H NMR spectra of the reaction mixture. From the results summarized in Table 1, the formation ratio of heterocyclic compounds (7-membered ring *versus* 6-membered ring) was considerably depended upon carbonyl function (X = OMe, NEt_2) and phosphorus reagents. It is known that the oxazaphosphetane, an important

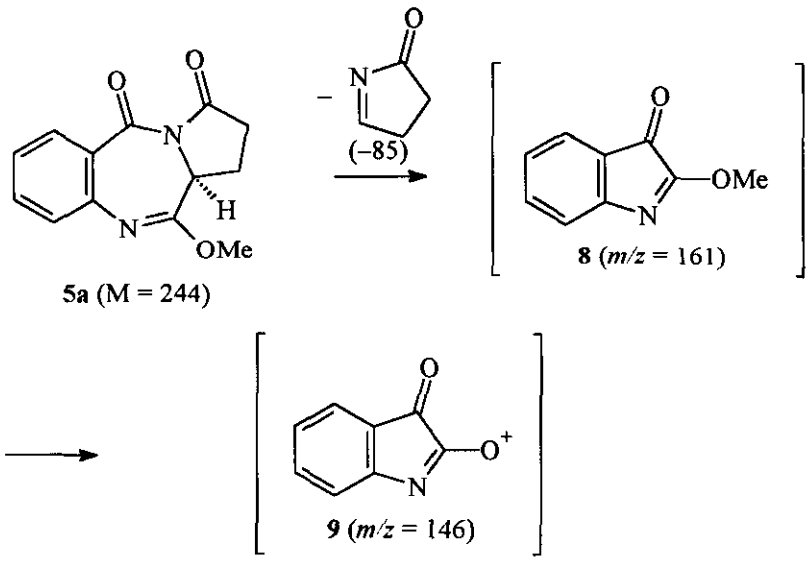
Table 1 Chemoselectivity in the Staudinger reaction/the intramolecular aza-Wittig reaction of *N*-(2-azidobenzoyl)-2-pyrrolidone-5-carboxylic acid derivatives (**3**)

Entry	X	R [a]	Reaction conditions	Yield (%)[b]	Ratio (**5** : **6**)[c]
1	OMe	*n*-Bu	rt, 3 h	79	88 : 12
2	OMe	Ph	rt, 4 h then 80 °C, 9 h	63	97 : 3
3	OMe	EtO	rt, 6 h then 80 °C, 9 h	45	36 : 64
4	OMe	EtO	rt, 6 h then 80 °C, 12 h	69	36 : 64
5	NEt_2	*n*-Bu	rt, 3 h then 80 °C, 4 h	91	trace : >99
6	NEt_2	Ph	rt, 4 h then 110 °C, 2 h then 140 °C, 6.5 h	98	trace : >99

[a] 1.1 Equivalent was used.
[b] After conversion of **5a** to **6a**, yields were determined.
[c] Determined by ^{1}H NMR spectra.



Scheme 3 Mass spectral fragmentation of **6a** and **6b**.



Scheme 4 Fragmentation of **5a** by Mass spectra.

intermediate of the aza-Wittig reaction, for six-membered ring formation is influenced by steric effect of the substituent of phosphorus reagent (Ph_3P > n-Bu_3P > $(EtO)_3P$).[16] Thus, seven-membered ring compound was predominantly formed with use of Ph_3P or n-Bu_3P. Also, with use of $(EtO)_3P$, which is smaller as well as more mild reagent, six membered ring compound was predominantly formed. Both of [1,4]benzodiazepine and pyrrolo[2,1-*b*]quinazoline derivatives are pharmacologically important including natural products such as antibiotics, alkaloids and so on. In view of this, present results may be useful for molecular design of related heterocyclic compounds by aza-Wittig methodology. Further studies of synthesis of heterocyclic compounds including natural products are under way in our laboratory.

EXPERIMENTAL

General Methods. Most of the general experimental methods have been reported previously.[5] Optical rotations were measured with a JASCO DIP-1000 polarimeter. Flash chromatography was performed with a silica gel column (Fuji Davison BW-300 silica gel) eluted with mixed solvents (AcOEt, n-Hexane). All reagents were of commercial quality. Solvents were dried prior to use when deemed necessary: THF was freshly distilled from Na and benzophenone. Benzene and xylene were dried over Na.

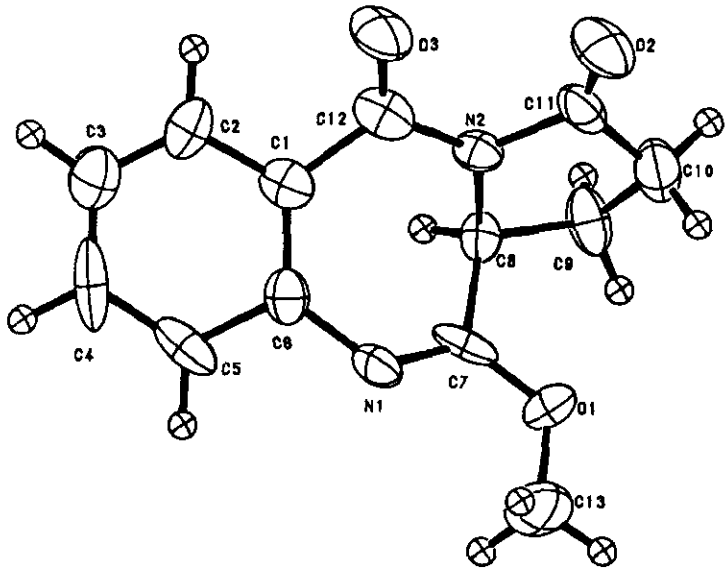


Figure 1 X-Ray structure of (11a*S*)-(+)-1,11a-dihydro-11-methoxy-2*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-3,5-dione (**5a**) showing the atom labeling

Table 2 Selected bond length (Å) of **5a**

C13-O1	1.46(2)	C1-C12	1.51(2)	C8-C7	1 54(2)
O1-C7	1 31(1)	C12-O3	1.19(1)	C8-C9	1.54(1)
C7-N1	1.28(1)	C12-N2	1.42(1)	C11-N2	1.44(1)
N1-C6	1.43(1)	N2-C8	1.47(1)	C11-O2	1.18(2)
C6-C1	1.41(2)				

Table 3 Selected bond angle (°) of **5a**

C13-O1-C7	116(1)	C8-N2-C12	125(1)	C12-C1-C6	126(1)
O1-C7-N1	125(1)	O2-C11-N2	126(1)	C2-C1-C6	119(1)
O1-C7-C8	114(1)	C11-N2-C12	122(1)	C5-C6-C1	117(1)
C7-C8-C9	116(1)	O3-C12-N2	123(1)	C5-C6-N1	116(1)
C7-C8-N2	108(1)	O3-C12-C1	122(1)	C1-C6-N1	127(1)
C9-C8-N2	104(1)	N2-C12-C1	115(1)	C6-N1-C7	123(1)
C8-N2-C11	113(1)	C12-C1-C2	115(1)	N1-C7-C8	114(1)

Mehtyl (5*S*)-(+)-2-pyrrolidone-5-carboxylate (2a): To a solution of (5*S*)-(+)-2-pyrrolidone-5-carboxylic acid (387 mg, 3.00 mmol) in MeOH (11.7 mL) was added a catalytic amount of thionyl chloride (0.03 mL, 0.41 mmol) and then stirred at rt for 24 h. After the solvent was evaporated, the residual oil was subjected to bulb-to-bulb distillation [130 °C (oven temp.)/ 6.0 mmHg] to give **2a** (342 mg, 80 %). *Rf* = 0.52 (AcOEt·MeOH = 3:1); colorless oil; $[\alpha]_D^{25.7}$ = +11.5° (c 1.10 EtOH), [ref. (*R*)-derivative. lit.,[17] $[\alpha]_D^{22}$ = –9.7° (c 1.10 EtOH)]; IR (neat) 3368, 2959, 1742, 1698, 1221 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.93 (1H, br s), 4.33-4.24 (1H, m), 3.78 (3H, s), 2.60-2.10 (4H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 178.86, 173.07, 55.55, 52.60, 29.30, 24.74; Anal. Calcd for $C_6H_9NO_3$: C, 50.35; H, 6.34; N, 9.79. Found: C, 49.59; H, 6.53; N, 9.72.

Diethyl (5*S*)-(+)-2-pyrrolidone-5-carboxamide (2b): To a solution of (5*S*)-(+)-2-pyrrolidone-5-carboxylic acid (258 mg, 2 0 mmol) and DMC[18,19] (2-chloro-1,3-dimethylimidazolinium chloride) (676 mg, 4 0 mmol) in dry THF (20 mL) under argon was added diethylamine (1.03 mL, 10 mmol) and triethylamine (0.84 mL, 6.0 mmol) at 0 °C. The mixture was stirred at 0 °C for 15 min and warmed to rt for 16 h. After the solvents were evaporated, flash chromatography of the residue gave **2b** (262 mg, 71 %). *Rf* = 0.34 (AcOEt·MeOH = 3:1); yellow oil, $[\alpha]_D^{31.0}$ = +5.37° (c 1.93 EtOH); IR (neat) 3272, 2976, 2938, 1694, 1640 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.35 (1H, br s), 4.46 (1H, dd, *J* = 8.4, 5.2 Hz), 3.47 (2H, q, *J* = 7.0 Hz), 3.33 (2H, q, *J* = 7.2 Hz), 2.55-1.97 (4H, m), 1.23 (3H, t, *J* = 7.2 Hz), 1.13 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 178.64, 171.03, 53.92, 41.20, 40.54, 29.54, 25.84, 14.49, 12.84; Anal. Calcd for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.20. Found: C, 58.67; H, 8.84; N, 15.00.

Methyl (*S*)-(+)-*N*-(*o*-azidobenzoyl)-2-pyrrolidone-5-carboxylate (3a): To a solution of LDA, prepared from *n*-BuLi (0.93 mL of 1 6 M hexane solution, 1.50 mmol) and diisopropylamine (0.21 mL, 1 50 mmol) in dry THF (1.5 mL) at –78 °C was added THF (3.0 mL) solution of **2a** (143 mg, 1.00 mmol) under a nitrogen atmosphere. The solution was stirred for 15 min and then added *o*-azidobenzoyl chloride, which was prepared form *o*-azidebenzoic acid (163 mg, 1.00 mmol) and thionyl chloride (0.73 mL, 10.0 mmol) at 80 °C for 2 h under a nitrogen atomsphere, in dry THF (5.0 mL). The mixture was stirred at –78 °C for 1 h. The reaction mixture was poured into water and extracted with CH_2Cl_2 (10 mL × 3). The combined organic layer was dried (Na_2SO_4) and evaporated to dryness. The residue was purified by flash chromatography (*n*-Hexane:AcOEt = 1:1) to afford **3a** (192 mg, 67 %). *Rf* = 0.58 (AcOEt:*n*-Hexane = 5:1); yellow solid; mp 83-86 °C; $[\alpha]_D^{26.5}$ = +51.2° (c 2.00 $CHCl_3$); IR (neat) 2130, 1750, 1680, 1319, 1211, 754 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.50 (1H, ddd, *J* = 8.2, 7 2, 1.6 Hz), 7.36 (1H, dd, *J* = 8.0 1.6 Hz), 7.24-7.16 (2H, m), 4.93 (1H, dd, *J* = 9.0, 3 2 Hz), 3.84 (3H, s), 2.82-2.34 (3H, m), 2.60-2.08 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.43, 171.78, 167.61, 137.96, 132.03, 129.12, 127.69, 125.06, 118.57, 58.10, 52.96, 31.53, 21.76; Anal. Calcd for $C_{13}H_{12}N_4O_4$: C, 54.17; H, 4.20; N, 19.44. Found: C, 54.17; H, 4.23; N, 19.09.

Diethyl (*S*)-(+)-*N*-(*o*-azidobenzoyl)-2-pyrrolidone-5-carboxamide (3b): 131 mg (33 %), *Rf* = 0.23 (AcOEt·*n*-Hexane = 1.1); yellow oil; $[\alpha]_D^{31.1}$ = +35.0° (c 2.13 $CHCl_3$); IR (neat) 2978, 2936, 2130, 1753, 1680, 1651, 756 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.48-7.38 (2H, m), 7.18 (1H, ddd, *J* = 7.2, 6.4, 1.2 Hz), 5.19 (1H, dd, *J* = 9.0, 2.6 Hz), 3.66-3.22 (4H, m), 2.95-2.70 (1H, m), 2.60-2.26 (2H, m), 2.02 (1H, ddd, *J* = 12.6, 7.2, 2.6 Hz), 1.35 (3H, t, *J* = 7 2 Hz), 1.16 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.23, 170.04, 167.80, 137.62, 131 71, 129 27, 127.97, 124.97, 118 45, 55.77, 42.01, 41.13, 31.66, 22.16,

14.55, 12.95; Anal. Calcd for $C_{16}H_{19}N_5O_3$: C, 58.35; H, 5.81; N, 21.26. Found: C, 58.69, H, 5.88; N, 20 83.

(11a*S*)-(+)-1,11a-Dihydro-11-methoxy-2*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-3,5-dione (5a): To a solution of **3a** (144 mg, 0.50 mmol) in dry benzene or xylene (25 mL) was added phosphine reagent (*n*-Bu_3P: 0 136 mL, 0 55 mmol, Ph_3P: 144 mg, 0.55 mmol, $(EtO)_3P$: 0.095 mL, 0.55 mmol) under a nitrogen atomsphere at rt and at reflux for appropriate time (see Table 1 for the reaction conditions). After the solvent was evaporated, flash chromatography (AcOEt:*n*-Hexane = 5:1) of the residue gave **5a** and **6a** (see Table 1 for yields of **5a** and **6a**). **5a**: *Rf* = 0.30 (AcOEt:*n*-Hexane = 5:1); white solid; mp 170-172 °C; $[\alpha]_D^{23.9}$ = +919.2° (c 0.63 $CHCl_3$); IR (neat) 1769, 1653, 1601, 1458, 1437, 1333, 1314, 1292, 1244, 1177, 1150, 1047, 988, 907, 851, 829, 758, 731, 704 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.96 (1H, ddd, *J* = 7.8, 1.6, 0.6 Hz), 7.54 (1H, ddd, *J* = 8.2, 7 4, 1.6 Hz), 7.24 (1H, ddd, *J* = 8.0, 7.4, 1.6 Hz), 7.18 (1H, ddd, *J* = 8.0, 1.4, 0.6 Hz), 4.51 (1H, dd, *J* = 8.6, 1.0 Hz), 3.97 (3H, s), 2.92-2.52 (3H, m), 2.27-2.10 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.69, 165.53, 162.60, 144.51, 133.57, 131.71, 127.01, 126.78, 125.14, 55.04, 54.24, 31.80, 18.45, MS (EI) *m/z* (%) $C_{13}H_{12}N_2O_3$ (244.25) 244 (M^+, 100), 216 (3), 161 (39), 146 (91).

Methyl [(1*S*)-(−)-2,3-Dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-on]-1-ylcarboxylate (6a): A solution of the above mentioned mixture of **5a** and **6a** in THF (5.0 mL) and a catalytic amount of HCl were stirred at rt for 3 h. After the solvents were evaporated, flash chromatography (AcOEt:*n*-Hexane = 5:1) of the residue gave **6a** *Rf* = 0.21 (AcOEt: *n*-Hexane = 5:1); white solid; mp 99-101 °C; $[\alpha]_D^{26.1}$ = −144.6° (c 0.63 $CHCl_3$); IR (neat) 1748, 1680, 1630, 1562, 1470, 1437, 1379, 1335, 1281, 1213, 1179, 1044, 990, 868, 774, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.27 (1H, ddd, *J* = 8.0, 1.4, 0.6 Hz), 7.76 (1H, ddd, *J* = 8.4, 6.8, 1 6 Hz), 7.67 (1H, ddd, *J* = 8.2, 1.6, 0.6 Hz), 7.46 (1H, ddd, *J* = 8.2, 6.8, 1.4 Hz), 5.18 (1H, dd, *J* = 9.4, 3.2 Hz), 3.82 (3H, s), 3.30 (1H, ddd, *J* = 17.4, 9.8, 8.8 Hz), 3.14 (1H, ddd, *J* = 17.6, 9.0, 3.8 Hz), 2.61 (1H, dddd, *J* = 13.6, 10.0, 9.4, 9.0 Hz), 2 37 (1H, dddd, *J* = 13.4, 9.0, 3.8, 3.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.77, 160.92, 159 22, 149.52, 134.91, 127 29, 126.93, 126.83, 120.76, 59.26, 53.09, 31.17, 24.32; MS (EI) *m/z* (%) $C_{13}H_{12}N_2O_3$ (244.25) 244 (M^+, 45), 213 (1), 185 (100); Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.96; H, 4.91; N, 11.47. Found: C, 64.04; H, 4.99; N, 11.16.

Diethyl [(1*S*)-(−)-2,3-Dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-on]-1-ylcarboxamide (6b): *Rf* = 0.28 (AcOEt: MeOH = 6:1); white solid; mp 101-102 °C; $[\alpha]_D^{31.4}$ = −52.6° (c 2.60 $CHCl_3$); IR (neat) 2976, 2934, 1680, 1651, 1628, 775 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.24 (1H, ddd, *J* = 8.0, 1.6, 0.8 Hz), 7.74 (1H, ddd, *J* = 8.2, 6.6, 1 6 Hz), 7 66 (1H, ddd, *J* = 8.4, 1.6, 0.8 Hz), 7 43 (1H, ddd, *J* = 8.2, 6.6, 1.6 Hz), 5.43 (1H, dd, *J* = 9.2, 2.2 Hz), 3.74-3.26 (5H, m), 3.12 (1H, ddd, *J* = 17.4, 9.4, 2.6 Hz), 2.51 (1H, ddt, *J* = 13.0, 10.2, 9.2 Hz), 2.22 (1H, ddt, *J* = 13.0, 9.4, 2.6 Hz), 1.40 (3H, t, *J* = 7.2 Hz), 1.16 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.17, 161.15, 160.28, 149.89, 134.68, 127.27, 126.78, 126.50, 120.82, 57.08, 42.27, 41.25, 31.62, 24.76, 14.79, 13.01; MS (EI) *m/z* (%) $C_{16}H_{19}N_3O_2$ (285.35) 285 (M^+, 32), 185 (93), 100 (100), 72 (93); Anal. Calcd for $C_{16}H_{19}N_3O_2$: C, 67.39; H, 6.66; N, 14.73. Found: C, 67.76; H, 6.82; N, 14.40.

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19 Use of general DCC-DMAP reagent system in stead of DMC did not give condensation products.

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