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Synthesis of Pyrazino[2,3-*e*][1,4]diazepin-5-one and Pyrazino[2,3-*e*]pyrrolo[1,2-*a*][1,4]diazepin-5-one Derivatives *via* the Intramolecular Aza-Wittig Reaction

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Abstract : 2-Alkoxy pyrazino[2,3-*e*][1,4]diazepin-5-one and 11-alkoxy pyrazino[2,3-*e*]pyrrolo[1,2-*a*][1,4]diazepin-5-one derivatives were synthesized *via* the corresponding iminophosphoranes derived from 3-aminopyrazine-2-carboxylic acid and α-amino acid derivatives, by the intramolecular aza-Wittig methodology (11*S*, 11a*S*)-1,2,3,10,11,11a-Hexahydro-11-alkoxy-pyrazino[2,3-*e*]pyrrolo[1,2-*a*][1,4]diazepin-5-one derivatives, *i.e.*, 6,9-diaza-analogs of porothramycin B *etc.*, were obtained.

Introduction

The aza-Wittig methodology has received considerable attention because of its utility in synthesis of nitrogen heterocycles.[1] We and other workers have demonstrated recently that the intramolecular aza-Wittig reaction is a powerful tool for synthesis of 5-8 membered heterocycles[1-3] including natural products such as DC-81,[4] *l*-vasicinone,[5] (−)-benzomalvin A,[6] (+)-fumiquinazoline G[7] *etc.* On the other hand, the intermolecular aza-Wittig reaction followed by electrocyclization, cycloaddition or heterocyclization, *i.e.*, the tandem aza-Wittig and cyclization sequence, has been applied for synthesis of nitrogen heterocycles by Molina,[8] Wamhoff,[9] Quintela,[10] Saito,[11] Noguchi[12], Weinreb[13] and Katritzky[14] *et al.* Also, *N*-vinyliminophosphoranes are utilized for synthesis of certain heterocycles by Nitta[15] and Palacios[16] *et al.* We have been interested in preparation of *N*-heteroaryliminophosphoranes because these species seem to be much less studied, and they are promising building blocks for synthesis of nitrogen heterocycles such as 4(3*H*)-pteridinone derivatives.[17] As an extension of our study on the intramolecular aza-Wittig reaction, we wish to report here a facile synthesis of novel pyrazino[2,3-*e*][1,4]diazepin-5-one and pyrazino[2,3-*e*]pyrrolo[1,2-*a*][1,4]diazepin-5-one derivatives by using the corresponding *N*-heteroaryliminophosphoranes.

1,4-Benzodiazepines are biologically active, *e.g.*, anti-tumor antibiotics and psychotropics. Especially, the pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) derivatives can 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 cancer. These compounds exert their biological activity by covalently binding of the N2 of guanine in the minor groove of DNA to imine, carbinolamine or carbinolamine methyl ether functionality at N10-C11 of PBD derivatives. Synthetic methods of PBD derivatives have been extensively studied.[18] In addition, the solid-phase synthesis of 1,4-benzodiazepine derivatives has been reported.[19] Thus, intensive studies of 1,4-benzodiazepines and related compounds have drawn considerable attention to discover a new synthetic route and modified ring systems with new activities. Thus, we examined synthesis of pyrazino[2,3-*e*][1,4]diazepin-5-ones, 6,9-diaza-analogues of 1,4-benzodiazepines, which are of interest from their potential new activities. The foregoing was based on the relation between methotrexate and its deaza-analogues, that the activity of the former was stronger than that of the latter.[20] This paper describes detailed data and the

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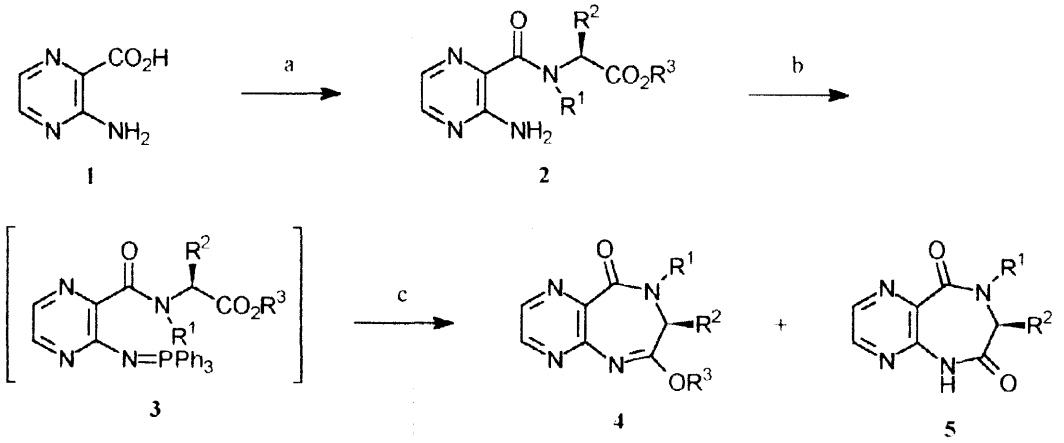
Scheme 1 Synthesis of pyrazino[2,3-*e*][1,4]diazepine derivatives **4** and/or **5** *via* the intramolecular aza-Wittig reaction. *a*



a Reagents and conditions: (a) α-amino acid derivatives, condensation reagent (see, Table 1), Et_3N, DME, 0 °C, 1 h → r.t., 1 h, 69 ~ 100 %; (b) PPh_3, C_2Cl_6, Et_3N, benzene, reflux, 2 h; (c) xylene (See, Table 2), 140 °C, 24 ~ 480 h, 26 ~ 85 % (**4**).

Table 1 Synthesis of amide derivatives **2**.

Entry	α-Amino acid derivatives	Method *a*	Amides *b*	Yield (%) *c*
1	Sarcosine methyl ester	A	**2a**	72
2	L-Proline methyl ester	A	**2b**	98
3	(2*RS*, 4*R*)-2-Phenylthiazolidine-4-carboxylic acid ethyl ester	A	**2c**	75
4	*N*-Benzyl glycine methyl ester	A	**2d**	95
5	*N*-Benzyl glycine ethyl ester	A	**2e**	100
6	*N*-(1,1-Diphenylmethyl) glycine methyl ester	B	**2f**	69
7	*N*-(4-Methoxyphenylmethyl) glycine methyl ester	A	**2g**	100
8	*N*-(2,4-Dimethoxyphenylmethyl) glycine methyl ester	A	**2h**	80
9	*N*-Benzyl L-alanine methyl ester	A	**2i**	99
10	*N*-(4-Methoxyphenylmethyl) L-alanine methyl ester	A	**2j**	95

a In method A, DEPC (diethyl phosphorocyanidate) was used and in method B, DMC (2-chloro-1,3-dimethylimidazolinium chloride) was used

b For R^1, R^2 and R^3, see Table 2.

c Isolated yield

Table 2. Synthesis of pyrazino[2,3-*e*][1,4]diazepine derivatives **4** and/or **5** *via* the intramolecular aza-Wittig reaction.

Entry	Amides	R^1	R^2	R^3	Reaction time (h)	Products	Yield (%) [c]
1	**2a**	Me	H	Me	135	**4a** + **5a**	50 + 34
2	**2b**	-$(CH_2)_3$-		Me	24	**4b** + **5b**	77 + 18
3 [a]	**2b**	-$(CH_2)_3$-		Me	24	**4b** + **5b**	0 + 77
4 [b]	**2b**	-$(CH_2)_3$-		Me	168	**4b** + **5b**	0 + 81
5	**2c**	-C(Ph)HSCH_2-		Et	15	**4c** + **5c**	47 + 45 [d]
6	**2d**	Bn	H	Me	72	**4d** + **5d**	76 + 22
7	**2e**	Bn	H	Et	72	**4e** + **5e**	54 + 23
8	**2f**	Ph_2CH	H	Me	480	**4f** + **5f**	26 + 0
9	**2g**	MPM [e]	H	Me	72	**4g** + **5g**	59 + 19
10	**2h**	DMPM [f]	H	Me	72	**4h** + **5h**	10 + 32
11	**2i**	Bn	Me	Me	24	**4i** + **5i**	61 + Trace
12	**2j**	MPM	Me	Me	24	**4j** + **5j**	85 + 11

[a] No filtration. [b] From amide **2e** directly. [c] Isolated yield.

[d] Diastereomer mixture. [e] MPM = 4-methoxyphenylmethyl. [f] DMPM = 2,4-dimethoxyphenylmethyl.

application of the preliminary communication.[21]

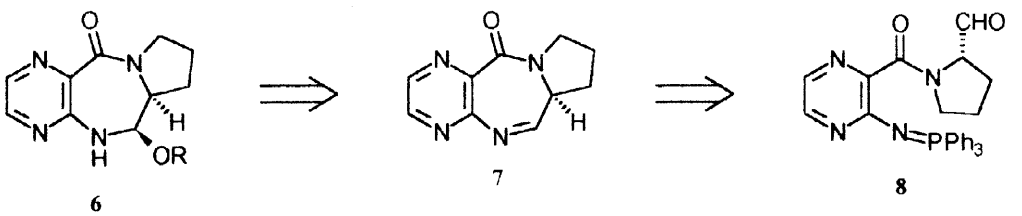
Results and Discussion

3-Aminopyrazine-2-carboxylic acid **1** and α-amino acid ester were condensed to form the corresponding amides **2**, and then the primary amine function was converted into the iminophosphorane by the Kirsanov type reaction. At first, DCC failed to form amide **2b** from **1** and L-proline methyl ester, but DEPC (diethyl phosphorocyanidate)[22] (0 °C, 1 h; r.t., 1 h in DME) gave **2b** (98 % yield). Thus, amide derivatives **2** were similarly prepared from **1** and α-amino acid esters in good yields (Scheme 1 and Table 1). Amide derivatives **2a** and **2b** were derived from α-amino acid hydrochloride (Entries 1 and 2 in Table 1) and the other amide derivatives **2c** - **2j** were prepared from α-amino acid derivatives. The amide **2c** having thiazole ring was obtained from ethyl (2*RS*, 4*R*)-2-phenylthiazolidine-4-carboxylate derived from L-cysteine ethyl ester hydrochloride and benzaldehyde (Entry 3 in Table 1).[23] The required *N*-protected amino acids were prepared by the condensation of α-amino acid, benzaldehyde and triethylamine, followed by the addition of sodium borohydride[24] in stead of the previous report.[21] *N*-(1,1-Diphenylmethyl) glycine methyl ester was prepared from glycine methyl ester hydrochloride, triethylamine and α-bromodiphenylmethane in DMPU (1,3-dimethyl-3,4,5,6-tertahydro-2(1*H*)-pyrimidinone)[25] in 81 % yield. The amide **2f** could be synthesized by DMC (2-chloro-1,3-dimethylimidazolinium chloride)[26] because *N*-(1,1-diphenylmethyl) glycine methyl ester was not obtained by DEPC due to steric hindrance (Entry 6 in Table 1).

The synthesis of seven membered compounds, pyrazino[2,3-*e*][1,4]diazepin-5-one derivatives **4** and/or **5** were investigated as follows. These amides **2** having the primary amine function were converted into the corresponding iminophosphoranes by triphenylphosphine-hexachloroethane-triethylamine reagent system (Scheme 1). The iminophosphorane having *sec*-amide derivative was not cyclized even at reflux in xylene, because very strong intramolecular hydrogen bonding between the iminophosphorane and the amide proton inhibits the intramolecular aza-Wittig reaction.[27] However, when *tert*-amide derivative **2b** was treated similarly (the reaction time was 24 h), the cyclization to pyrazino[2,3-*e*]pyrrolo[1,2-*a*][1,4]diazepin-5-one derivative proceeded smoothly. This compound was turned out to be **5b**, a hydrolyzed product of the imidate function of **4b** (77 % yield, Entry 3 in Table 2, Scheme 1). The cyclization to **5b** without the iminophosphorane proceeded also but very sluggishly only under more severe conditions (140 °C, 168 h, 81 %, Entry 4 in Table 2). In addition, the aza-Wittig reaction after removal of triethylamine hydrochloride generated in the Kirsanov reaction by filtration afforded the desired product, **4b** in 77 % yield accompanied with **5b** in 18 % yield as a by-product (Entry 2 in Table 2). A series of pyrazino[2,3-*e*][1,4]diazepin-5-one derivatives was prepared in the same way by using *N*-mono-alkylated α-amino acid esters (Table 2). Pyrazino[2,3-*e*][1,4]diazepin-5-one derivatives fused thiazole ring **4c** and **5c** were obtained as separable diastereomers, respectively (Entry 5 in Table 2). Nevertheless, the structures of these compounds could not be distinguished by the data of ^{1}H NMR and NOESY. The amide derivative **2f** having 1,1-diphenylmethyl function was strenuous to cyclize into pyrazino[2,3-*e*][1,4]diazepin-5-one **4f** at 140 °C for long time giving only 26 % yield (Entry 8 in Table 2).

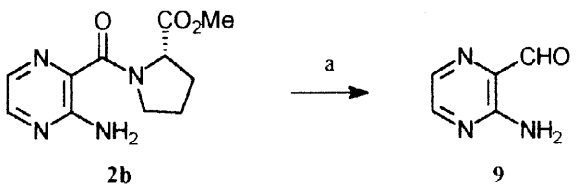
Next step, we scrutinized the synthesis of pyrazino[2,3-*e*]pyrrolo[1,2-*a*][1,4]diazepin-5-one derivatives **6**, which were 6,9-diaza-analogs of porothramycin B *etc*. According to our previous reports,[4a] we required the precursor **7** with N(10)-C(11) imine function and its precursor **8** with both of aldehyde and iminophosphorane functions (Scheme 2).

Scheme 2. Retrosynthesis of pyrazino[2,3-*e*]pyrrolo[1,2-*a*][1,4]diazepine derivatives **6**



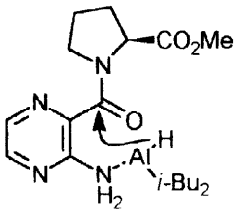
At first, we examined the formation of aldehyde derivatives. However, reduction of the amide ester derivative **2b** by DIBALH afforded 3-aminopyrazine-2-carbaldehyde **9**[28] (28 % yield) accompanied with recovered starting material (42 % yield) instead of the corresponding aldehyde or the cyclized seven membered compound (Scheme 3). In this reaction, coordination of DIBALH to amino function of **2b** accelerated the reduction of the amide carbonyl by the intramolecular version (Figure 1). Therefore, amine function of **2b** was protected by Boc group and was converted into the other appropriate functions (chloro, azido and phosphoranylideneamino). In using these compounds, however, the desired compounds **6** could not be synthesized because the corresponding aldehyde derivative **8** was not afforded. Next, we inspected an oxidative method (Scheme 4). Amide derivative **11** derived from **1** and TBDPS-protected L-prolinol **10** (100 % yield) was successfully deprotected by TBAF to produce

Scheme 3. Reduction of **2b** by DIBALH. [a]

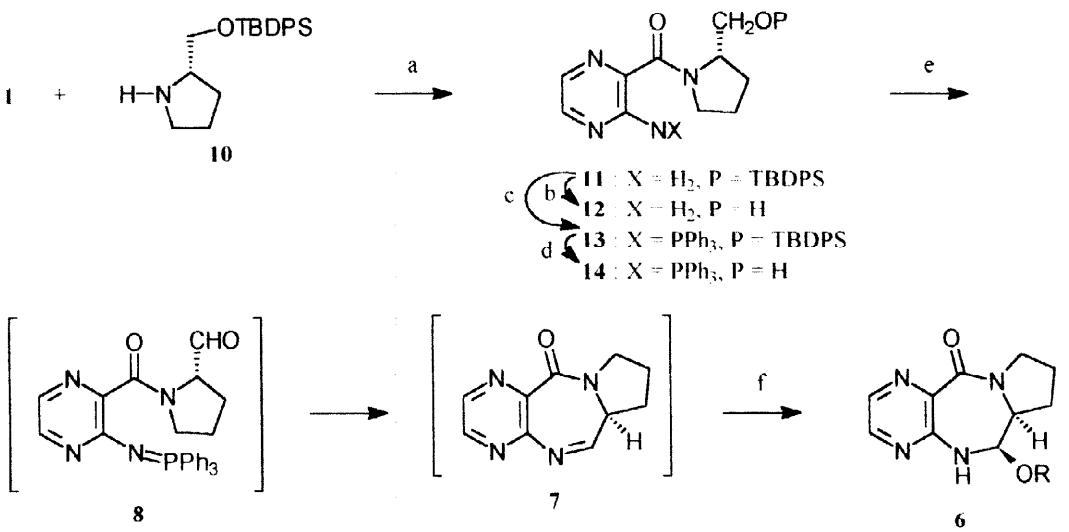


[a] Reagents and conditions: (a) DIBALH (1.0 eq.), CH_2Cl_2, −78 °C, 1 h, 28 %.

Figure 1. Proposed mechanism of reduction by DIBALH.



Scheme 4. Synthesize pyrazino[2,3-*e*]pyrrolo[1,2-*a*][1,4]diazepine derivatives **6**. [a]



[a] Reagents and conditions: (a) DEPC, Et_3N, DME, 0 °C, 1 h → r.t., 1 h, 100 %, (b) TBAF, THF, r.t., 1 h, 98 %; (c) PPh_3, C_2Cl_6, Et_3N, benzene, reflux, 2 h, (d) TBAF, THF, r.t., 2 h, overall yield 99 % from **11**; (e) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C, 5 min., → r.t.; (f) ROH (R = Me, Et), r.t., 60 and 59 %.

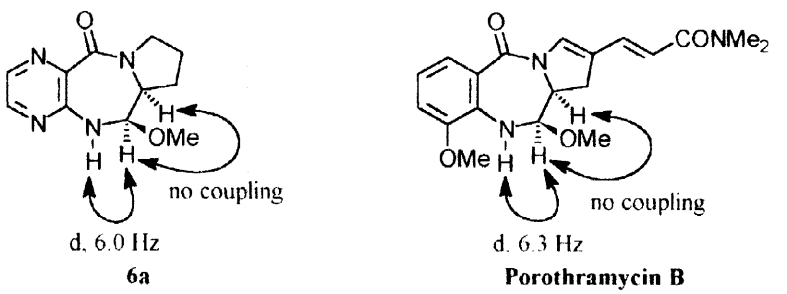
Table 3. Synthesis of **6**.

Entry	R	Products	Yield (%) [a]	Yield (%) of PPh_3=O
1	Me	**6a**	60	79
2	Et	**6b**	59	83

[a] Isolated yield.

alcohol derivative **12** (98 % yield). Direct oxidation of **12** by Swern's method[29] or PCC did not produce the desired compound. *O*-TBDPS-protected amide **11** was converted into iminophosphorane **13** and then, *in situ*, alcohol derivative **14** was prepared by desilylation with TBAF (overall 99 % yield from **11**). The Swern oxidation of **14** followed by the addition of alcohol furnished pyrazino[2,3-*e*]pyrrolo[1,2-*a*][1,4]diazepin-5-one derivatives having aminal function **6** (Scheme 4). This reaction was rationalized as follows. The Swern oxidation of **14** afforded the corresponding aldehyde **8**, which then immediately formed seven membered compound **7** by the intramolecular aza-Wittig reaction. Although **7** could not be isolable by silica gel chromatography, only triphenylphosphine oxide, inevitable by-product, was isolated. However, when an appropriate alcohol was added to the reaction mixture, **6** and triphenylphosphine oxide were obtained (Table 3). Based on ^{1}H and ^{13}C NMR data of the compounds **6**, they were concluded to be produced stereospecifically. According to Fukuyama's report,[30] the ^{1}H NMR data of NH and H-11 of (+)-porothramycin B were 6.18 (1H, d, J = 6.2 Hz) and 4.68 (1H, d, J = 6.4 Hz), respectively. Moreover, those of **6a** were 6.35 (1H, d, J = 5.8 Hz) and 4.66 (1H, d, J = 6.2 Hz), respectively. These results suggested that the obtained compounds **6** were single isomers and the configuration of C-11 was *R*, respectively (Figure 2).

Figure 2. The comparison of **6a** and porothramycin B by ^{1}H NMR



Conclusion

In conclusion, we have demonstrated a facile route to pyrazino[2,3-*e*][1,4]diazepin-5-one derivatives with N(1)-C(2) imidate function **4a**, **4c** - **4j** and pyrazino[2,3-*e*]pyrrolo[1,2-*a*][1,4]diazepin-5-one derivatives with N(10)-C(11) imidate function **4b** from 3-aminopyrazine-2-carboxylic acid **1** and α-amino acid derivatives, by the intramolecular aza-Wittig methodology. Moreover, pyrazino[2,3-*e*]pyrrolo[1,2-*a*][1,4]diazepin-5-one derivatives with aminal function **6**, 6,9-diaza-analogs of porothramycin B, were obtained.

Experimental Section

General Methods. Most of the general experimental methods have been reported previously.[4a] 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 (hexane (H), ethyl acetate (A)). All reagents were of commercial quality. Solvents were dried prior to use when deemed necessary.

General procedure for the synthesis of amide derivatives 2:

To a mixture of 3-aminopyrazine-2-carboxylic acid **1** (714 mg, 5.13 mmol) and L-proline methyl ester hydrochloride (1020 mg, 6.16 mmol, 1.2 equiv.) in dry DME (30.0 mL) was added dropwise DEPC (93 %, 1.00 mL, 6.16 mmol, 1.2 equiv.) and triethylamine (1.70 mL, 12.2 mmol, 2.4 equiv.), respectively at 0 °C. The resultant solution was

stirred at 0 °C for 1 h and at 40 °C for 1 h under nitrogen. The mixture was diluted with ethyl acetate (500 mL) and washed with water (50 mL × 2), saturated sodium hydrogen carbonate solution (50 mL × 2), water (50 mL × 2) and saturated sodium chloride solution (50 mL) successively. The combined organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to afford the crude product, which was purified on a silica gel column chromatography using A and H (1:2, v/v) as an eluent to give amide derivative **2b** (oil, 1259 mg, 5.03 mmol, 98 %). The other amide derivatives **2a** and **2c - 2j** were obtained by the similar method (see, Table 1).

_N_-Methoxycarbonylmethyl-_N_-methyl-3-aminopyrazine-2-carboxamide 2a:

A mixture of *syn* and *anti* rotamers (1:1); yield 72 %; *Rf* = 0.10 (A:H 1:1); oil; IR (neat) 3456, 3339, 1748, 1630, 1609, 1435, 1213, 1076, 1034 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.07 (0.5H, d, *J* = 2.4 Hz), 8.04 (0.5H, d, *J* = 2.6 Hz), 7.89 (0.5H, d, *J* = 2.4 Hz), 7.77 (0.5H, d, *J* = 2.4 Hz), 6.12 (1H, br), 5.81 (1H, br), 4.39 (1H, s), 4.26 (1H, s), 3.80 (1.5H, s), 3.76 (1.5H, s), 3.25 (1.5H, s), 3.20 (1.5H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.52, 169.96, 168.59, 168.15, 155.68, 154.77, 145.02, 144.65, 132.12, 131.68, 131.35, 130.24, 53.75, 52.49, 52.35, 50.21, 38.65, 36.79; MS (EI) *m z* (rel. intensity) 224 (77 %, M), 165 (57), 122 (64), 102 (61), 95 (54), 94 (100), 67 (31); MS (CI) 225 (MH); HRMS Calcd. for $C_9H_{12}N_4O_3$ 224.0909, Found 224.0911; Anal. Calcd. for $C_9H_{12}N_4O_3$: C, 48.21; H, 5.39; N, 24.99. Found C, 48.30; H, 5.42; N, 24.87.

Methyl (2*S*)-_N_-(2-aminopyrazinecarbonyl)pyrrolidine-2-carboxylate 2b:

A mixture of *syn* and *anti* rotamers (57:43); yield 98 %; *Rf* = 0.18 (A:H 1:1); oil; $[\alpha]_D^{25}$ = –52.3° (c 0.68, $CHCl_3$); IR (neat) 3441, 3329, 2984, 1744, 1613, 1441, 1209, 1038, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.06 (0.43H, d, *J* = 2.4 Hz), 8.03 (0.57H, d, *J* = 2.4 Hz), 7.87 (0.43H, d, *J* = 2.4 Hz), 7.72 (0.57H, d, *J* = 2.4 Hz), 6.54 (1.14H, br), 6.28 (0.86H, br), 5.06 (0.57H, dd, *J* = 8.3, 3.3 Hz), 4.65 (0.43H, dd, *J* = 7.8, 4.8 Hz), 4.08-4.00 (1H, m), 3.96-3.70 (1H, m), 3.78 (1.29H, s), 3.69 (1.71H, s), 2.34-1.88 (4H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 173.87, 173.25*, 166.50*, 166.28, 156.96, 155.72*, 145.35, 145.12*, 131.81*, 130.84, 130.70, 129.73*, 62.23, 60.63*, 52.50*, 52.29*, 50.44, 48.68, 32.00, 28.71*, 25.71*, 21.86, the peak of minor product was shown such as asterisk; MS (EI) *m z* (rel. intensity) 250 (35 %, M), 191 (31), 128 (100), 122 (39), 94 (42), 70 (15); MS (CI) 251 (MH); HRMS Calcd. for $C_{11}H_{14}N_4O_3$ 250.1066, Found 250.1068; Anal. Calcd. for $C_{11}H_{14}N_4O_3$: C, 52.79; H, 5.64; N, 22.39. Found C, 52.89; H, 5.66; N, 22.27.

Ethyl (2*RS*,4*R*)-_N_-(2-aminopyrazinecarbonyl)-2-phenylthiazolidine-4-carboxylate 2c:

A mixture of *syn* and *anti* rotamers (9:5); yield 75 %; *Rf* = 0.41 (A:H 1:1); oil; IR (neat) 3461, 3341, 2982, 1748, 1624, 1599, 1437, 1192 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.07 (0.64H, d, *J* = 2.2 Hz), 7.84 (0.36H, d, *J* = 2.4 Hz), 7.79-7.75 (2H, m), 7.59 (0.64H, d, *J* = 2.2 Hz), 7.54 (0.36H, s), 7.40-7.14 (3H, m), 6.94 (0.36H, s), 6.55 (0.64H, s), 6.49 (1.29H, br), 5.92 (0.71H, br), 5.55 (0.64H, dd, *J* = 6.7, 5.1 Hz), 5.17 (0.36H, t, *J* = 6.8 Hz), 4.34 (1.29H, q, *J* = 7.1 Hz), 4.29 (0.71H, q, *J* = 7.1 Hz), 3.46 (0.36H, d, *J* = 6.8 Hz), 3.41 (0.64H, d, *J* = 6.8 Hz), 3.36-3.19 (1H, m), 1.37 (1.07H, t, *J* = 7.2 Hz), 1.31 (1.93H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.42, 170.20*, 166.81, 166.65*, 156.26, 154.86*, 146.06, 145.16*, 141.06*, 139.92, 131.46*, 130.89, 130.76*, 130.19, 128.71, 128.38*, 128.23, 127.93*, 127.11, 126.92*, 69.53, 68.95*, 66.35, 65.92*, 62.98*, 61.69, 35.22, 31.78*, 14.29, 14.23*; MS (EI) *m z* (rel. intensity) 358 (2 %, M), 237 (11), 236 (100), 122 (8), 94 (14); MS (CI) 359 (MH); HRMS Calcd. for $C_{17}H_{18}N_4O_3S$ 358.1100, Found 358.1089; Anal. Calcd. for $C_{17}H_{18}N_4O_3S$: C, 56.97; H, 5.06; N, 15.63. Found C, 57.10; H, 5.08; N, 15.48.

_N_-Benzyl-_N_-methoxycarbonylmethyl-3-aminopyrazine-2-carboxamide 2d:

A mixture of *syn* and *anti* rotamers (1:1); yield 95 %; *Rf* = 0.36 (A:H 1:1); oil; IR (neat) 3468, 3353, 3017, 1748, 1632, 1603, 1437, 1215, 1146, 999, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.05 (1H, d, *J* = 2.0 Hz), 7.84

(0.5H, d, J = 2.6 Hz), 7.77 (0.5H, d, J = 2.4 Hz), 7.39-7.30 (5H, m), 6.23 (1H, br), 5.88 (1H, br), 4.88 (1H, s), 4.83 (1H, s), 4.26 (1H, s), 4.09 (1H, s), 3.76 (1.5H, s), 3.72 (1.5H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.68, 170.09, 168.70, 168.18, 155.86, 154.69, 145.20, 144.77, 136.66, 136.42, 132.32, 131.74, 131.35, 130.20, 129.11, 129.06, 128.69, 128.43, 128.31, 128.11, 53.80, 52.47, 52.29, 51.40, 50.57, 47.06; MS (EI) m z (rel. intensity) 300 (13 %, M), 179 (9), 178 (100), 118 (11), 94 (11), 91 (30); MS (CI) 301 (MH); HRMS Calcd. for $C_{15}H_{16}N_4O_3$ 300.1222, Found 300.1238; Anal. Calcd. for $C_{15}H_{16}N_4O_3$: C, 59.99; H, 5.37; N, 18.66. Found C, 60.15; H, 5.46; N, 18.41.

N-Benzyl-N-ethoxycarbonylmethyl-3-aminopyrazine-2-carboxamide 2e:

A mixture of *syn* and *anti* rotamers (1:1); yield 100 %; Rf = 0.23 (A:H 1:2); oil; IR (neat) 3464, 3349, 2984, 1744, 1632, 1607, 1439, 1202, 1146, 1001, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.04 (1H, d, J = 2.4 Hz), 7.84 (0.5H, d, J = 2.6 Hz), 7.76 (0.5H, d, J = 2.4 Hz), 7.38-7.30 (5H, m), 6.24 (1H, br), 5.88 (1H, br), 4.88 (1H, s), 4.81 (1H, s), 4.25 (1H, s), 4.22 (1H, q, J = 7.2 Hz), 4.16 (1H, q, J = 7.2 Hz), 4.08 (1H, s), 1.28 (1.5H, t, J = 7.2 Hz), 1.23 (1.5H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.12, 169.57, 168.64, 168.20, 155.82, 154.58, 145.10, 144.63, 136.69, 136.43, 132.97, 132.31, 131.26, 130.33, 129.07, 129.03, 128.69, 128.40, 128.27, 128.06, 61.60, 61.28, 53.73, 51.44, 50.75, 47.16, 14.18, 14.13; MS (EI) m z (rel. intensity) 314 (9 %, M), 193 (10), 192 (100), 122 (7), 118 (11), 94 (12), 91 (27); MS (CI) 315 (MH); HRMS Calcd. for $C_{16}H_{18}N_4O_3$ 314.1379, Found 314.1383; Anal. Calcd. for $C_{16}H_{18}N_4O_3$: C, 61.14; H, 5.77; N, 17.82. Found C, 61.41; H, 5.80; N, 17.52.

N-(1,1-Diphenylmethyl)-N-methoxycarbonylmethyl-3-aminopyrazine-2-carboxamide 2f:

A mixture of *syn* and *anti* rotamers (7:5); yield 69 %; Rf = 0.39 (A:H 1:1); oil; IR (neat) 3474, 3356, 3029, 1748, 1630, 1603, 1449, 1213, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.03 (1H, d, J = 2.4 Hz), 7.81 (0.42H, d, J = 2.2 Hz), 7.78 (0.58H, d, J = 2.4 Hz), 7.34-7.21 (10H + 0.58H, m), 6.96 (0.42H, s), 5.99 (1.17H, br s), 5.66 (0.83H, br s), 4.57 (1.17H, s), 4.19 (0.83H, s), 3.53 (1.25H, s), 3.29 (1.75H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.34, 169.47, 169.41, 168.83, 155.16, 153.90, 144.66, 144.31, 138.79, 138.70, 132.60, 132.25, 131.61, 131.10, 129.29, 129.00, 128.77, 128.75, 128.13, 127.97, 65.84, 62.29, 52.35, 52.13, 48.73, 46.13, major and minor compounds could not be distinguished; MS (EI) m z (rel. intensity) 376 (2 %, M), 255 (19), 254 (100), 167 (25), 165 (13), 91 (19); MS (CI) 377 (MH); HRMS Calcd. for $C_{21}H_{20}N_4O_3$ 376.1535, Found 376.1527; Anal. Calcd. for $C_{21}H_{20}N_4O_3$: C, 67.01; H, 5.36; N, 14.88. Found C, 67.21; H, 5.41; N, 14.63.

N-Methoxycarbonylmethyl-N-(4-methoxyphenylmethyl)-3-aminopyrazine-2-carboxamide 2g:

A mixture of *syn* and *anti* rotamers (1:1); yield 100 %; Rf = 0.26 (A:H 2:1); oil; IR (neat) 3459, 3347, 1748, 1628, 1613, 1512, 1437, 1248, 1209, 1177 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.05 (0.5H, d, J = 2.6 Hz), 8.03 (0.5H, d, J = 2.4 Hz), 7.86 (0.5H, d, J = 2.6 Hz), 7.75 (0.5H, d, J = 2.4 Hz), 7.32-7.24 (2H, m), 6.91-6.83 (2H, m), 6.16 (1H, br s), 5.80 (1H, br s), 4.79 (1H, s), 4.71 (1H, s), 4.22 (1H, s), 4.06 (1H, s), 3.795 (1.5H, s), 3.790 (1.5H, s), 3.75 (1.5H, s), 3.70 (1.5H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.74, 170.15, 168.56, 168.12, 159.87, 159.70, 155.82, 154.60, 145.14, 144.68, 132.37, 132.03, 131.37, 130.35, 130.23, 129.89, 128.63, 128.21, 114.44 (included isomer), 55.44 (included isomer), 53.13, 52.48, 52.29, 50.74, 50.26, 46.69; MS (EI) m z (rel. intensity) 330 (5 %, M), 209 (10), 208 (100), 148 (8), 121 (22); MS (CI) 331 (MH); HRMS Calcd. for $C_{16}H_{18}N_4O_4$ 330.1328, Found 330.1325; Anal. Calcd. for $C_{16}H_{18}N_4O_4$: C, 58.17; H, 5.49; N, 16.96. Found C, 58.45; H, 5.51; N, 16.66.

N-(2,4-Dimethoxyphenylmethyl)-N-methoxycarbonylmethyl-3-aminopyrazine-2-carboxamide 2h:

A mixture of *syn* and *anti* rotamers (7:5); yield 80 %; Rf = 0.35 (A:H 2:1); oil; IR (neat) 3461, 3337, 2988, 1750, 1613, 1508, 1439, 1292, 1209, 1034, 984 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.06 (0.58H, d, J = 2.4 Hz), 8.02 (0.42H, d, J = 2.4 Hz), 7.90 (0.58H, d, J = 2.6 Hz), 7.75 (0.42H, d, J = 2.4 Hz), 7.32 (0.42H, d, J = 8.8 Hz), 7.12

(0.58H, d, J = 8.2 Hz), 6.50-6.40 (2H, m), 6.07 (0.83H, br s), 5.72 (1.17H, br s), 4.79 (0.83H, s), 4.72 (1.17H, s), 4.35 (0.83H, s), 4.14 (1.17H, s), 3.804 (3H, s), 3.792 (1.25H, s), 3.73 (1.75H, s), 3.705 (1.75H, s), 3.695 (1.25H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.99*, 170.26, 168.57, 168.00*, 161.38, 161.05*, 159.26 (included isomer), 155.58*, 154.29, 144.77*, 144.16, 133.18, 132.38, 131.74*, 131.37*, 131.13, 131.05*, 117.13*, 116.49, 104.63*, 104.34, 98.68 (included isomer), 55.53 (included isomer), 55.48, 55.35*, 52.38, 52.21*, 50.88*, 48.67, 46.72, 45.98*; MS (EI) m/z (rel. intensity) 360 (7 %, M), 239 (14), 238 (100), 178 (8), 151 (15), 121 (6); MS (CI) 361 (MH); HRMS Calcd. for $C_{17}H_{20}N_4O_5$ 360.1434, Found 360.1436; Anal. Calcd. for $C_{17}H_{20}N_4O_5$: C, 56.66; H, 5.59; N, 15.55. Found C, 56.77; H, 5.62; N, 15.41.

_N_-Benzyl-_N_-((1_S_)-1-methoxycarbonyl)ethyl-3-aminopyrazine-2-carboxamide 2i:

A mixture of *syn* and *anti* rotamers (3:1); yield 99 %; Rf = 0.34 (A:H 1:1); pale yellow solid; mp 63-64 °C; $[\alpha]_D^{30}$ = −39.2° (c 0.68, $CHCl_3$); IR (KBr) 3463, 3351, 1742, 1626, 1613, 1439, 1155 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.06 (0.25H, d, J = 2.0 Hz), 8.00 (0.75H, d, J = 2.6 Hz), 7.80 (1H, d, J = 2.4 Hz), 7.44-7.24 (5H, m), 6.03 (0.5H, br s), 5.84 (1.5H, br s), 5.11 (0.25H, d, J = 16.0 Hz), 4.88 (0.75H, d, J = 15.6 Hz), 4.78 (0.75H, d, J = 16.0 Hz), 4.46 (0.25H, d, J = 15.6 Hz), 4.20 (1H, q, J = 7.0 Hz), 3.73 (2.25H, s), 3.63 (0.75H, s), 1.47 (3H, d, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 172.79*, 172.32, 168.96*, 168.23, 155.57*, 154.71, 144.86*, 144.52, 138.24*, 137.09, 132.13 (this peak may be included a peak of major product), 131.65*, 131.08*, 128.79 (included isomer), 128.32, 128.04*, 127.38 (included isomer), 57.45*, 55.93, 53.50, 52.44 (included isomer), 48.49*, 16.37*, 14.54; MS (EI) m/z (rel. intensity) 314 (10 %, M), 193 (14), 192 (100), 132 (19), 94 (15), 91 (35); MS (CI) 315 (MH); HRMS Calcd. for $C_{16}H_{18}N_4O_3$ 314.1379, Found 314.1377; Anal. Calcd. for $C_{16}H_{18}N_4O_3$: C, 61.14; H, 5.77; N, 17.82. Found C, 61.22; H, 5.80; N, 17.71.

_N_-((1_S_)-1-Methoxycarbonyl)ethyl-_N_-(4-methoxyphenylmethyl)-3-aminopyrazine-2-carboxamide 2j:

A mixture of *syn* and *anti* rotamers (3:1); yield 95 %; Rf = 0.14 (A:H 1:1); oil; $[\alpha]_D^{28}$ = −21.4° (c 0.52, $CHCl_3$); IR (neat) 3463, 3351, 1742, 1613, 1514, 1246, 1177, 1155 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.03 (1H, d, J = 2.6 Hz), 7.83 (1H, d, J = 2.6 Hz), 7.36 (2H, d, J = 8.6 Hz), 6.87 (2H, d, J = 8.8 Hz), 5.94 (0.5H, br s), 5.74 (1.5H, br s), 5.13 (0.25H, q, J = 7.1 Hz), 4.99 (0.25H, d, J = 15.4 Hz), 4.80 (0.75H, d, J = 15.4 Hz), 4.67 (0.75H, d, J = 15.4 Hz), 4.44 (0.25H, d, J = 15.6 Hz), 4.13 (0.75H, q, J = 7.1 Hz), 3.80 (3H, s), 3.73 (2.25H, s), 3.62 (0.75H, s), 1.46 (3H, d, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 172.81*, 172.38, 168.95*, 168.07, 159.69, 159.59*, 155.54*, 154.68, 144.83*, 144.48, 132.34 (included isomer), 132.25, 131.72*, 130.25*, 129.79, 128.96*, 128.87, 114.18, 114.04*, 57.37*, 55.81, 55.41 (included isomer), 53.08, 52.46 (included isomer), 48.00*, 16.40*, 14.54; MS (EI) m/z (rel. intensity) 344 (8 %, M), 233 (27), 222 (100), 162 (32), 121 (47), 94 (10); MS (CI) 345 (MH); HRMS Calcd. for $C_{17}H_{20}N_4O_4$ 344.1485, Found 344.1489; Anal. Calcd. for $C_{17}H_{20}N_4O_4$: C, 59.29; H, 5.85; N, 16.27. Found C, 59.44; H, 5.91; N, 16.06.

General procedure for the synthesis of 4 and/or 5:

To a mixture of **2b** (152 mg, 0.61 mmol), triphenylphosphine (239 mg, 0.91 mmol, 1.5 equiv.) and hexachloroethane (216 mg, 0.91 mmol, 1.5 equiv.) in dry benzene (5.0 mL) was added dropwise triethylamine (0.25 mL, 1.79 mmol, 3.0 equiv.). The mixture was heated at reflux in benzene for 2 h. After cooling, the mixture was filtered to remove the precipitates (Et_3N·HCl) and the filtrate was evaporated under reduced pressure. Then the residue was diluted by dry xylene (9.0 mL) and the mixture was heated at reflux in sealed glass tube for 24 h. The reactant was evaporated under reduced pressure to give a solid residue, which was purified on a silica gel column chromatography using A and H (1:1 → 2:1 → A only, v/v) as an eluent to afford pyrazino[2,3-*e*][1,4]diazepine derivative **4b** (109 mg, 0.47 mmol, 77 %) and the corresponding hydrolytic compound **5b** (24 mg, 0.11 mmol, 18 %). The other

pyrazino[2,3-*e*][1,4]diazepine derivatives **4a**, **4c** - **4j** and the corresponding hydrolytic compounds **5a**, **5c** - **5e** and **5g** - **5j** were also obtained by the similar method (see, Table 2).

3,4-Dihydro-2-methoxy-4-methyl-pyrazino[2,3-*e*][1,4]diazepin-5-one 4a:

Yield 50 %; *Rf* = 0.08 (A); oil; IR (neat) 1651, 1535, 1385, 1358, 1283, 1190, 1020, 752 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.64 (1H, d, *J* = 2.0 Hz), 8.58 (1H, d, *J* = 2.2 Hz), 4.06 (3H, s), 3.92 (2H, s), 3.31 (3H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 166.54, 165.28, 153.14, 146.28, 141.49, 140.46, 55.93, 48.64, 36.85; MS (EI) *m z* (rel. intensity) 206 (100 %, M), 191 (29), 177 (7), 149 (15), 148 (56), 120 (63), 93 (8); MS (CI) 207 (MH); HRMS Calcd. for $C_9H_{10}N_4O_2$ 206.0804, Found 206.0802.

3,4-Dihydro-4-methyl-pyrazino[2,3-*e*][1,4]diazepine-2,5(1*H*)-dione 5a:

Yield 34 %; *Rf* = 0.11 (A); pale yellow solid; mp 252-254 °C; IR (KBr) 1699, 1661, 1418, 1397, 1358, 1167, 984, 876 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ 11.14 (1H, br), 8.61 (1H, d, *J* = 2.4 Hz), 8.57 (1H, d, *J* = 2.2 Hz), 4.05 (2H, s), 3.14 (3H, s); ^{13}C NMR (DMSO-d_6 50 MHz) δ 170.00, 164.09, 146.67, 145.62, 141.02, 137.95, 51.93, 35.80; MS (EI) *m z* (rel. intensity) 192 (96 %, M), 164 (25), 163 (100), 135 (10), 121 (19), 93 (35), 66 (19); MS (CI) 193 (MH); HRMS Calcd. for $C_8H_8N_4O_2$ 192.0647, Found 192.0649.

(11a*S*)-1,2,3,11a-Tetrahydro-11-methoxy-pyrazino[2,3-*e*]pyrrolo[1,2-*a*][1,4]diazepin-5-one 4b:

Yield 77 %; *Rf* = 0.20 (A:M 10:1); oil; $[\alpha]_D^{25}$ = +294.7° (c 1.7, $CHCl_3$); IR (neat) 3474, 2990, 1651, 1535, 1462, 1387, 1329, 1279, 1167, 997, 839, 752 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.65 (1H, d, *J* = 2.2 Hz), 8.57 (1H, d, *J* = 2.2 Hz), 4.17-4.13 (1H, m), 4.05 (3H, s), 4.01-3.93 (1H, m), 3.67-3.53 (1H, m), 2.76-2.66 (1H, m), 2.24-1.99 (3H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 166.13, 163.24, 152.58, 146.32, 141.10, 140.09, 55.99, 54.94, 47.45, 26.67, 23.76; MS (EI) *m z* (rel. intensity) 233 (10 %, M+1), 232 (66, M), 218 (8), 217 (65), 148 (100), 120 (73), 93 (8); MS (CI) 233 (MH); HRMS Calcd. for $C_{11}H_{12}N_4O_2$ 232.0960, Found 232.0981.

(11a*S*)-1,2,3,11a-Tetrahydro-pyrazino[2,3-*e*]pyrrolo[1,2-*a*][1,4]diazepine-5,11(10*H*)-dione 5b:

Yield 18 %; *Rf* = 0.08 (A); pale yellow solid; mp 115-117 °C; $[\alpha]_D^{25}$ = +110.8° (c 1.2, DMSO); IR (KBr) 3449, 3223, 1701, 1647, 1414, 1236, 752 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 9.73 (1H, br), 8.65 (1H, d, *J* = 2.2 Hz), 8.62 (1H, d, *J* = 2.2 Hz), 4.23-4.18 (1H, m), 3.95-3.84 (1H, m), 3.79-3.65 (1H, m), 2.92-2.82 (1H, m), 2.17-1.97 (3H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.58, 162.48, 145.59, 145.51, 141.68, 138.00, 57.03, 47.92, 26.49, 23.23; MS (EI) *m z* (rel. intensity) 218 (57 %, M), 189 (34), 162 (36), 134 (16), 133 (24), 93 (14), 70 (100); MS (CI) 219 (MH); HRMS Calcd. for $C_{10}H_{10}N_4O_2$ 218.0804, Found 218.0805.

(3*R* or 3*S*,11a*R*)-11-Ethoxy-3-phenyl-1*H*,3*H*-pyrazino[2,3-*e*]thiazolo[3,4-*a*][1,4]diazepin-5(11a*H*)-one 4c:

(1) Yield 16 %; *Rf* = 0.24 (A); oil; $[\alpha]_D^{27}$ = –99.2° (c 0.50, $CHCl_3$); IR (neat) 2992, 1651, 1387, 1024, 752 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.77 (1H, d, *J* = 2.2 Hz), 8.57 (1H, d, *J* = 2.2 Hz), 7.38-7.22 (5H, m), 6.66 (1H, s), 4.70 (1H, d, *J* = 6.4 Hz), 4.61 (1H, dq, *J* = 10.8, 7.2 Hz), 4.52 (1H, dq, *J* = 10.8, 7.2 Hz), 3.70 (1H, d, *J* = 12.6 Hz), 3.39 (1H, dd, *J* = 12.6, 6.4 Hz), 1.46 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 164.09, 162.10, 151.96, 146.84, 141.40, 140.46, 140.17, 129.04, 128.26, 125.55, 66.32, 65.53, 58.25, 30.18, 13.90; MS (EI) *m z* (rel. intensity) 341 (16 %, M+1), 340 (100, M), 195 (21), 176 (22), 162 (20), 148 (15), 121 (16), 120 (29); MS (CI) 341 (MH); HRMS Calcd. for $C_{17}H_{16}N_4O_2S$ 340.0994, Found 340.0995.

(2) yield 21 %; *Rf* = 0.21 (A); oil; $[\alpha]_D^{27}$ = +321.4° (c 0.90, $CHCl_3$); IR (neat) 2990, 1651, 1385, 1316, 1269, 1022, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.69 (1H, d, *J* = 2.2 Hz), 8.62 (1H, d, *J* = 2.2 Hz), 7.36-7.28 (5H, m), 6.75 (1H, s), 4.57 (1H, dq, *J* = 10.8, 7.1 Hz), 4.51 (1H, dd, *J* = 8.7, 7.3 Hz), 4.47 (1H, dq, *J* = 10.8, 7.1 Hz), 3.83 (1H, ddd, *J* = 12.6, 8.6, 0.4 Hz), 3.27 (1H, ddd, *J* = 12.4, 7.2, 0.5 Hz), 1.31 (3H, t, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 164.08, 162.79, 152.89, 146.85, 141.70, 139.24, 138.62, 128.69, 128.42, 126.48, 67.12,

65.42, 58.39, 29.84, 13.76; MS (EI) *m z* (rel. intensity) 341 (20 %, M+1), 340 (100, M), 195 (17), 176 (21), 162 (19), 148 (14), 121 (17), 120 (22); MS (CI) 341 (MH); HRMS Calcd. for $C_{17}H_{16}N_4O_2S$ 340.0994, Found 340.0992.

(3*R* or *3S*,11a*R*)-3-Phenyl-1*H*,3*H*-pyrazino[2,3-*e*]thiazolo[3,4-*a*][1,4]diazepine-5,11(10*H*,11a*H*)-dione 5c:

(1) Yield 22 %; *Rf* = 0.35 (A); pale yellow solid; mp >280 °C; $[\alpha]_D^{27}$ = +14.4° (c 0.42, $CHCl_3$); IR (KBr) 1713, 1663, 1400, 1233 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ 11.40 (1H, br s), 8.69 (1H, d, *J* = 2.2 Hz), 8.61 (1H, d, *J* = 2.2 Hz), 7.39-7.27 (5H, m), 6.51 (1H, s), 5.31 (1H, d, *J* = 6.0 Hz), 3.66 (1H, d, *J* = 12.4 Hz), 3.18 (1H, dd, *J* = 12.3, 6.1 Hz); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 169.46, 160.78, 146.35, 145.45, 142.38, 141.20, 137.79, 128.66, 127.58, 125.19, 65.89, 60.16, 29.05; MS (EI) *m z* (rel. intensity) 313 (16 %, M+1), 312 (100, M), 176 (19), 164 (10), 163 (36), 162 (20), 137 (10), 121 (15); MS (CI) 313 (MH); HRMS Calcd. for $C_{15}H_{12}N_4O_2S$ 312.0681, Found 312.0680.

(2) Yield 23 %; *Rf* = 0.29 (A); pale yellow solid; mp >280 °C; $[\alpha]_D^{27}$ = +32.5° (c 0.22, $CHCl_3$); IR (KBr) 1698, 1665, 1399, 1240 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ 11.48 (1H, br s), 8.69 (1H, d, *J* = 2.4 Hz), 8.63 (1H, d, *J* = 2.2 Hz), 7.40-7.21 (5H, m), 6.52 (1H, s), 5.00 (1H, dd, *J* = 7.2, 5.0 Hz), 3.64 (1H, dd, *J* = 12.0, 5.0 Hz), 3.40 (1H, dd, *J* = 11.8, 7.2 Hz); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 170.16, 161.59, 146.49, 146.43, 141.29, 139.96, 136.62, 128.69, 128.17, 126.48, 66.65, 60.18, 29.63; MS (EI) *m z* (rel. intensity) 313 (13 %, M+1), 312 (100, M), 176 (18), 163 (34), 162 (21), 137 (10); MS (CI) 313 (MH); HRMS Calcd. for $C_{15}H_{12}N_4O_2S$ 312.0681, Found 312.0681.

4-Benzyl-3,4-dihydro-2-methoxy-pyrazino[2,3-*e*][1,4]diazepin-5-one 4d:

Yield 76 %; *Rf* = 0.19 (A); oil; IR (neat) 2998, 1651, 1356, 1279, 1190, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.64 (1H, d, *J* = 2.2 Hz), 8.61 (1H, d, *J* = 2.2 Hz), 7.38-7.34 (5H, m), 4.89 (2H, s), 3.88 (3H, s), 3.82 (2H, s); ^{13}C NMR ($CDCl_3$ 50 MHz) δ 166.96, 165.28, 153.27, 146.38, 141.50, 140.44, 136.11, 129.19, 128.82, 128.48, 55.64, 52.05, 45.91; MS (EI) *m z* (rel. intensity) 283 (16 %, M+1), 282 (89, M), 177 (15), 150 (22), 149 (100), 120 (11), 91 (46); MS (CI) 283 (MH); HRMS Calcd. for $C_{15}H_{14}N_4O_2$ 282.1117, Found 282.1130.

4-Benzyl-3,4-dihydro-pyrazino[2,3-*e*][1,4]diazepine-2,5(1*H*)-dione 5d:

Yield 22 % and 23 % from **2d** and **2e**, respectively; *Rf* = 0.36 (A); white solid; mp 189-190 °C; IR (KBr) 1701, 1659, 1414, 1364, 752 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ 11.13 (1H, br), 8.62 (1H, d, *J* = 2.2 Hz), 8.60 (1H, d, *J* = 2.2 Hz), 7.36-7.30 (5H, m), 4.79 (2H, s), 4.07 (2H, s); ^{13}C NMR (DMSO-d_6 50 MHz) δ 170.10, 164.20, 146.73, 145.78, 141.07, 137.55, 136.98, 128.93, 128.16, 127.89, 51.58, 50.66; MS (EI) *m z* (rel. intensity) 269 (15 %, M+1), 268 (100, M), 135 (23), 106 (73), 91 (64), 65 (11); MS (CI) 269 (MH); HRMS Calcd. for $C_{14}H_{12}N_4O_2$ 268.0960, Found 268.0963.

4-Benzyl-3,4-dihydro-2-ethoxy-pyrazino[2,3-*e*][1,4]diazepin-5-one 4e:

Yield 54 %; *Rf* = 0.21 (A); oil; IR (neat) 2988, 1651, 1373, 1275, 1030, 752 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.63 (1H, d, *J* = 2.2 Hz), 8.59 (1H, d, *J* = 2.2 Hz), 7.39-7.35 (5H, m), 4.89 (2H, s), 4.32 (2H, q, *J* = 7.1 Hz), 3.82 (2H, s), 1.24 (3H, t, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 166.39, 165.37, 153.49, 146.39, 141.39, 140.46, 136.29, 129.20, 128.92, 128.49, 64.80, 52.16, 46.33, 13.81; MS (EI) *m z* (rel. intensity) 297 (14 %, M+1), 296 (75, M), 191 (12), 164 (16), 163 (100), 135 (15), 120 (14), 91 (64); MS (CI) 297 (MH); HRMS Calcd. for $C_{16}H_{16}N_4O_2$ 296.1273, Found 296.1275.

3,4-Dihydro-4-(1,1-diphenylmethyl)-2-methoxy-pyrazino[2,3-*e*][1,4]diazepin-5-one 4f:

Yield 26 %; *Rf* = 0.12 (A:H 2:1); white solid; mp 86-87 °C; IR (KBr) 2998, 1651, 1454, 1387, 1279, 1113, 1022, 754, 704 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.65 (1H, d, *J* = 2.2 Hz), 8.62 (1H, d, *J* = 2.2 Hz), 7.42-7.34 (7H, m), 7.30-7.25 (4H, m), 3.90 (2H, s), 3.66 (3H, s); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 167.30, 165.37, 153.27,

146.42, 141.58, 140.44, 138.10, 129.17, 129.06, 128.38, 62.58, 55.25, 43.38; MS (EI) *m z* (rel. intensity) 359 (18 %, M+1), 358 (73, M), 182 (54), 177 (14), 167 (20), 165 (28), 152 (13), 150 (29), 149 (100); MS (CI) 359 (MH); HRMS Calcd. for $C_{21}H_{18}N_4O_2$ 358.1430, Found 358.1432.

3,4-Dihydro-2-methoxy-4-methoxyphenylmethyl-pyrazino[2,3-*e*][1,4]diazepin-5-one 4g:

Yield 59 %; *Rf* = 0.06 (A); oil; IR (neat) 2996, 1651, 1512, 1277, 1248, 1026, 752 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.64 (1H, d, *J* = 2.2 Hz), 8.60 (1H, d, *J* = 2.4 Hz), 7.33-7.26 (2H, m), 6.92-6.85 (2H, m), 4.82 (2H, s), 3.90 (3H, s), 3.81 (3H, s), 3.79 (2H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 167.05, 165.23, 159.99, 153.29, 146.38, 141.53, 140.57, 130.34, 128.21, 114.53, 55.72, 55.48, 51.46, 45.67; MS (EI) *m z* (rel. intensity) 313 (16 %, M+1), 312 (84, M), 177 (16), 150 (24), 149 (100), 136 (22), 121 (40); MS (CI) 313 (MH); HRMS Calcd. for $C_{16}H_{16}N_4O_3$ 312.1222, Found 312.1225.

3,4-Dihydro-4-methoxyphenylmethyl-pyrazino[2,3-*e*][1,4]diazepine-2,5(1*H*)-dione 5g:

Yield 19 %; *Rf* = 0.16 (A); pale yellow solid; mp 184-185 °C; IR (KBr) 1699, 1657, 1416, 1238, 1163 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ 11.09 (1H, br s), 8.61 (1H, d, *J* = 2.4 Hz), 8.59 (1H, d, *J* = 2.4 Hz), 7.32-7.25 (2H, m), 6.94-6.87 (2H, m), 4.70 (2H, s), 4.04 (2H, s), 3.74 (3H, s); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 170.23, 163.95, 159.08, 146.59, 145.62, 140.93, 137.52, 129.70, 128.83, 114.16, 55.10, 50.75, 50.24; MS (EI) *m z* (rel. intensity) 299 (13 %, M+1), 298 (74, M), 137 (9), 136 (100), 135 (13), 121 (26), 109 (26); MS (CI) 299 (MH); HRMS Calcd. for $C_{15}H_{14}N_4O_3$ 298.1066, Found 298.1057.

3,4-Dihydro-4-(2,4-dimethoxyphenylmethyl)-2-methoxy-pyrazino[2,3-*e*][1,4]diazepin-5-one 4h:

Yield 10 %; *Rf* = 0.06 (A); oil; IR (neat) 2936, 1653, 1615, 1508, 1464, 1209, 1159, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.61 (1H, d, *J* = 2.2 Hz), 8.58 (1H, d, *J* = 2.4 Hz), 7.37-7.24 (1H, m), 6.50-6.44 (2H, m), 4.84 (2H, s), 3.88 (2H + 3H, s), 3.84 (3H, s), 3.82 (3H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 167.40, 165.15, 161.43, 159.20, 153.27, 146.16, 141.40, 140.86, 132.38, 116.82, 104.70, 98.65, 55.61 (2C), 55.57, 46.42, 45.84; MS (EI) *m z* (rel. intensity) 343 (14 %, M+1), 342 (70, M), 166 (100), 164 (14), 163 (34), 151 (26), 150 (19), 149 (85), 121 (23); MS (CI) 343 (MH); HRMS Calcd. for $C_{17}H_{18}N_4O_4$ 342.1328, Found 342.1322.

3,4-Dihydro-4-(2,4-dimethoxyphenylmethyl)-pyrazino[2,3-*e*][1,4]diazepine-2,5(1*H*)-dione 5h:

Yield 32 %; *Rf* = 0.11 (A); pale yellow solid; mp 191-192 °C; IR (KBr) 2996, 1709, 1644, 1508, 1418, 1211, 1159, 1130 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ 10.59-10.52 (1H, br s), 8.60 (1H, d, *J* = 2.4 Hz), 8.57 (1H, d, *J* = 2.4 Hz), 7.14 (1H, d, *J* = 8.2 Hz), 6.57 (1H, d, *J* = 2.4 Hz), 6.50 (1H, dd, *J* = 8.4, 2.4 Hz), 4.65 (2H, s), 3.98 (2H, s), 3.78 (3H, s), 3.76 (3H, s); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 170.20, 163.96, 160.80, 158.78, 146.72, 145.60, 140.92, 137.67, 130.81, 116.33, 104.96, 98.63, 55.58, 55.35, 50.19, 46.42; MS (EI) *m z* (rel. intensity) 329 (12 %, M+1), 328 (64, M), 167 (14), 166 (100), 151 (19), 121 (14); MS (CI) 329 (MH); HRMS Calcd. for $C_{16}H_{16}N_4O_4$ 328.1172, Found 328.1160.

(3*S*)-4-Benzyl-3,4-dihydro-2-methoxy-3-methyl-pyrazino[2,3-*e*][1,4]diazepin-5-one 4i:

A mixture of *syn* and *anti* isomers (2:1); yield 61 %; *Rf* = 0.45 (A); white solid; mp 60-61 °C; $[\alpha]_D^{27}$ = −1.8° (c 1.5, $CHCl_3$); IR (KBr) 2998, 1696, 1659, 1391, 1177, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.62 (1H, d, *J* = 2.2 Hz), 8.59 (1H, d, *J* = 2.2 Hz), 7.40-7.26 (5H, m), 5.43 (0.33H, d, *J* = 14.4 Hz), 5.03 (0.67H, d, *J* = 15.6 Hz), 4.69 (0.67H, d, *J* = 15.6 Hz), 4.42 (0.33H, q, *J* = 7.6 Hz), 4.39 (0.33H, d, *J* = 14.6 Hz), 4.33 (0.67H, q, *J* = 7.0 Hz), 3.47 (3H, s), 1.47 (2H, d, *J* = 7.0 Hz), 0.88 (1H, d, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.76*, 169.88, 166.01, 163.78*, 149.13, 148.22*, 145.25, 145.02*, 141.61, 141.28*, 140.74, 140.55*, 137.75, 136.07*, 129.26*, 129.08, 129.01, 128.63*, 127.87*, 127.70, 59.70*, 53.49*, 51.94, 46.40, 33.15*, 32.24, 16.96*, 12.98; MS (EI) *m z* (rel. intensity) 297 (11 %, M+1), 296 (59, M), 205 (33), 191 (11), 165 (9), 164 (100), 163 (21), 91 (65); MS

(CI) 297 (MH); HRMS Calcd. for $C_{16}H_{16}N_4O_2$ 296.1273, Found 296.1279.

(3*S*)-4-Benzyl-3,4-dihydro-3-methyl-pyrazino[2,3-*e*][1,4]diazepine-2,5-dione 5i:

Trace; *Rf* = 0.24 (A); pale yellow solid; mp 45-46 °C; $[\alpha]_D^{23}$ = +11.2° (c 0.86, $CHCl_3$); IR (KBr) 3000, 1711, 1653, 1414, 1225, 752 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ 11.17 (1H, br s), 8.63 (1H, d, *J* = 2.2 Hz), 8.60 (1H, d, *J* = 2.2 Hz), 7.37-7.22 (5H, m), 4.83 (1H, d, *J* = 15.6 Hz), 4.65 (1H, d, *J* = 17.0 Hz), 4.54 (1H, q, *J* = 6.0 Hz), 1.29 (3H, d, *J* = 6.0 Hz); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 171.23, 165.40, 146.30, 145.78, 140.99, 138.18, 128.71, 127.28, 127.14, 50.97, 45.18, 11.97, one carbon could not be found; MS (EI) *m z* (rel. intensity) 283 (17 %, M+1), 282 (100, M), 177 (10), 150 (10), 149 (28), 148 (11), 106 (60), 91 (78); MS (CI) 283 (MH); HRMS Calcd. for $C_{15}H_{14}N_4O_2$ 282.1117, Found 282.1121.

(3*S*)-3,4-Dihydro-2-methoxy-4-methoxyphenylmethyl-3-methyl-pyrazino[2,3-*e*][1,4]diazepin-5-one 4j:

A mixture of *syn* and *anti* isomers (2:1); yield 85 %; *Rf* = 0.15 (A); oil; $[\alpha]_D^{28}$ = -102.5° (c 0.54, $CHCl_3$); IR (neat) 2996, 2949, 1651, 1514, 1246, 1177, 752 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.62 (1H, d, *J* = 2.2 Hz), 8.56 (1H, d, *J* = 2.2 Hz), 7.31 (1.33H, d, *J* = 8.6 Hz), 7.21 (0.67H, d, *J* = 7.8 Hz), 6.88 (1.33H, d, *J* = 8.6 Hz), 6.85 (0.67H, d, *J* = 7.8 Hz), 5.23 (0.33H, d, *J* = 15.2 Hz), 5.09 (0.67H, d, *J* = 14.4 Hz), 4.60 (0.67H, d, *J* = 14.6 Hz), 4.52 (0.33H, d, *J* = 15.2 Hz), 4.22 (1H, q, *J* = 7.6 Hz), 3.90 (2H, s), 3.81 (3H, s), 3.75 (1H, s), 1.54 (1H, d, *J* = 7.2 Hz), 0.91 (2H, d, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.69, 168.17*, 166.44*, 164.49, 159.93, 159.38*, 152.96*, 152.01, 146.44*, 146.18, 141.42*, 141.05, 130.36, 129.95 (included isomer), 129.11*, 128.49 (included isomer), 114.47, 114.26*, 55.64 (included isomer), 55.44 (included isomer), 55.25, 52.88, 49.85*, 45.36*, 16.28, 12.19*; MS (EI) *m z* (rel. intensity) 327 (12 %, M+1), 326 (61, M), 191 (12), 164 (18), 163 (100), 121 (20); MS (CI) 327 (MH); HRMS Calcd. for $C_{17}H_{18}N_4O_3$ 326.1379, Found 326.1379.

(3*S*)-3,4-Dihydro-4-methoxyphenylmethyl-3-methyl-pyrazino[2,3-*e*][1,4]diazepine-2,5(1*H*)-dione 5j:

Yield 11 %; *Rf* = 0.26 (A); pale yellow oil; $[\alpha]_D^{26}$ = +3.6° (c 1.1, $CHCl_3$); IR (neat) 3000, 1713, 1701, 1651, 1543, 1512, 1414, 1248, 1225, 1177, 1032, 812, 754 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ 11.11 (1H, br s), 8.62 (1H, d, *J* = 2.4 Hz), 8.59 (1H, d, *J* = 2.4 Hz), 7.21 (2H, d, *J* = 8.4 Hz), 6.87 (2H, d, *J* = 8.6 Hz), 4.81 (2H, d, *J* = 15.6 Hz), 4.53 (1H, d, *J* = 16.2 Hz), 4.52-4.42 (1H, m), 3.73 (3H, s), 1.31 (3H, d, *J* = 6.2 Hz); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 171.34, 165.40, 158.74, 146.36, 145.80, 141.03, 138.36, 130.15, 128.78, 114.11, 55.20, 44.53, 12.07; MS (EI) *m z* (rel. intensity) 313 (5 %, M+1), 312 (29, M), 150 (6), 149 (9), 137 (7), 136 (100), 121 (26); MS (CI) 313 (MH); HRMS Calcd. for $C_{16}H_{16}N_4O_3$ 312.1222, Found 312.1226.

Reduction of 2b by DIBALH:

To a solution of **2b** (140 mg, 0.56 mmol) in dry CH_2Cl_2 (5.0 mL) was added dropwise DIBALH (0.93 mol/l, 0.60 mL, 1.0 equiv.) at –78 °C. The mixture was stirred at same temperature for 1 h. The reactant was added saturated NH_4Cl solution (1.0 mL) and was stirred at room temperature for 30 min. The mixture was added $MgSO_4$ to dry over. The mixture was filtered in order to remove the precipitates and the filtrate was evaporated under reduced pressure to give a solid residue, which was purified on a silica gel column chromatography using A and H (1:2, v/v) as an eluent to afford 3-aminopyrazine-2-carbaldehyde **9** (19 mg, 0.15 mmol, 28 %) and starting material **2b** (59 mg, 0.24 mmol, 42 %). *Rf* = 0.66 (A:H 2:1); pale yellow solid; mp 98-100 °C; IR (KBr) 3407, 3274, 1686, 1620, 1532, 1435, 1181, 926 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 10.06 (1H, s), 8.24 (1H, d, *J* = 2.2 Hz), 8.09 (1H, d, *J* = 2.2 Hz), 7.0-6.0 (2H, br); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 195.60, 155.07, 148.59, 135.10, 130.96; MS (EI) *m z* (rel. intensity) 123 (100 %, M), 95 (55), 94 (8), 68 (25), 67 (21); MS (CI) 124 (MH); HRMS Calcd. for $C_5H_5N_3O$ 123.0433, Found 123.0431; Anal. Calcd. for $C_5H_5N_3O$: C, 48.78 ; H, 4.09 ; N, 34.13. Found C, 48.92; H, 4.11; N, 33.97.

Synthesis of *N*-{(2*S*)-2-(*O*-*tert*-butyldiphenylsiloxymethyl)pyrrolidine}-3-aminopyrazine-2-carboxamide 11:

This compound was synthesized by the similar method of formation of **2**. A mixture of *syn* and *anti* rotamers (4:3); yield 100 %; *Rf* = 0.46 (A:H 2:1); oil; $[\alpha]_D^{28}$ = –69.6° (c 0.46, $CHCl_3$); IR (neat) 3432, 3322, 2959, 2859, 1738, 1611, 1427, 1111, 704 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.03 (0.57H, d, *J* = 2.4 Hz), 7.96 (0.43H, d, *J* = 2.4 Hz), 7.87 (0.57H, d, *J* = 2.6 Hz), 7.71-7.54 (4H + 0.43H, m), 7.43-7.24 (6H, m), 6.17-6.14 (2H, br s), 5.04-4.94 (0.43H, m), 4.54-4.43 (0.57H, m), 4.02-3.66 (2H + 1H + 0.57H, m), 3.41 (0.43H, dd, *J* = 9.8, 7.4 Hz), 2.27-1.77 (4H, m), 1.06 (5.14H, s), 1.01 (3.86H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 166.42, 166.18*, 155.56, 155.40*, 144.62*, 144.48, 136.02, 135.86*, 133.93, 133.79*, 132.07, 131.87, 131.62*, 131.42*, 130.02, 129.96*, 128.05, 127.97*, 64.99*, 63.69, 59.74*, 59.69, 50.59, 47.91*, 28.97*, 26.98, 26.85*, 26.67*, 25.23, 21.30*, 19.35, 19.25*; MS (EI) *m z* (rel. intensity) 460 (1 %, M), 405 (16), 404 (58), 403 (100), 199 (13), 191 (67), 122 (26), 94 (28); MS (CI) 461 (MH); HRMS Calcd. for $C_{26}H_{32}N_4O_2Si$ 460.2295, Found 460.2296; Anal. Calcd. for $C_{26}H_{32}N_4O_2Si$: C, 67.79; H, 7.00; N, 12.16. Found C, 67.68; H, 7.05; N, 12.00.

Synthesis of *N*-{(2*S*)-2-hydroxymethylpyrrolidine}-3-aminopyrazine-2-carboxamide 12:

To a solution of **11** (390 mg, 0.85 mmol) in THF (10.0 mL) was added a solution of TBAF (524 mg, excess) in THF (2.0 mL) at room temperature. The mixture was stirred at ambient temperature for 1 h and then was evaporated under reduced pressure to afford the crude product, which was purified on a silica gel column chromatography using A and H (2:1, v/v) as an eluent to give alcohol derivative **12** (184 mg, 0.83 mmol, 98 %). A mixture of *syn* and *anti* rotamers (3:1); yield 98 %; *Rf* = 0.15 (A); oil; $[\alpha]_D^{27}$ = –91.7° (c 0.36, $CHCl_3$); IR (neat) 3436, 3326, 1682, 1603, 1454, 1426, 1204, 1152, 1046, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.12 (0.25H, s), 8.06 (0.75H, d, *J* = 2.4 Hz), 7.88 (0.75H, d, *J* = 2.2 Hz), 7.81 (0.25H, s), 6.27 (0.5H, br s), 6.15 (1.5H, br s), 4.67-4.53 (0.5H, m), 4.50-4.38 (1.5H, m), 3.91-3.77 (3H, m), 3.63 (0.25H, br s), 3.59 (0.75H, br s), 2.17-1.61 (4H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.31 (included isomer), 155.91*, 155.44, 145.42*, 144.95, 131.91, 131.49*, 130.45 (included isomer), 66.87, 64.61*, 62.54, 59.93*, 51.06, 46.07*, 29.02*, 27.99, 25.22, 21.22*; MS (EI) *m z* (rel. intensity) 222 (10 %, M), 192 (10), 191 (80), 122 (73), 100 (100), 94 (81), 70 (38), 67 (14); MS (CI) 223 (MH); HRMS Calcd. for $C_{10}H_{14}N_4O_2$ 222.1117, Found 222.1114; Anal. Calcd. for $C_{10}H_{14}N_4O_2$: C, 54.04; H, 6.35; N, 25.21. Found C, 54.24; H, 6.38; N, 24.98.

Synthesis of *N*-{(2*S*)-2-(hydroxymethyl)pyrrolidine}-3-(triphenylphosphoranylidene)aminopyrazine-2-carboxamide 14 from 11 (two steps):

To a mixture of **11** (162 mg, 0.35 mmol), triphenylphosphine (138 mg, 0.53 mmol, 1.5 equiv.) and hexachloroethane (125 mg, 0.53 mmol, 1.5 equiv.) in dry benzene (3.5 mL) was added dropwise triethylamine (0.15 mL, 1.08 mmol, 3.0 equiv.). The mixture was heated at reflux in benzene for 2 h to form *N*-{(2*S*)-2-(*O*-*tert*-butyldiphenylsiloxymethyl)pyrrolidine}-3-(triphenylphosphoranylidene)aminopyrazine-2-carboxamide **13** which was confirmed by TLC. After cooling, the mixture was filtered to remove the precipitates ($Et_3N{\cdot}HCl$) and the filtrate was evaporated under reduced pressure. Then the residue was diluted with THF (3.0 mL) and the mixture was added a solution of TBAF (524 mg, excess) in THF (2.0 mL) at room temperature. The mixture was stirred at ambient temperature for 2 h and then was evaporated under reduced pressure to afford the crude product, which was purified on a silica gel column chromatography using A and H (1:1 → 2:1 → A only → A:M (methanol) 20:1, v/v) as an eluent and by recrystallization from A and H to give alcohol derivative **14** (168 mg, 0.35 mmol, 99 %). *Rf* = 0.25 (A:M 10:1); white needle; mp 120-122 °C; $[\alpha]_D^{27}$ = –36.0° (c 0.48, $CHCl_3$); IR (KBr) 3360, 2976, 1618, 1510, 1433, 1113, 750, 721, 693 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.86-7.67 (8H, m), 7.60-7.39 (9H,

m), 5.34 (1H, br), 4.46 (1H, qd, J = 7.2, 2.6 Hz), 3.99-3.78 (2H, m), 3.51-3.31 (2H, m), 2.21-1.60 (4H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.42, 156.28 (J = 6.0 Hz), 145.99 (J = 25.3 Hz), 142.77, 142.32*, 133.41 (J = 9.9 Hz), 132.43 (J = 2.8 Hz), 131.63, 129.41 (J = 100.3 Hz), 128.98* (J = 100.4 Hz), 128.95* (J = 12.2 Hz), 128.87 (J = 12.3 Hz), 67.15, 64.43*, 61.82, 59.80*, 48.34, 46.22*, 29.82*, 28.84, 24.63, 22.86*; MS (EI) m/z (rel. intensity) 483 (10 %, M+1), 482 (32, M), 383 (13), 355 (32), 354 (100), 262 (9), 183 (15); MS (CI) 483 (MH); HRMS Calcd. for $C_{28}H_{27}N_4O_2P$ 482.1872, Found 482.1873; Anal. Calcd. for $C_{28}H_{27}N_4O_2P$: C, 69.70; H, 5.64; N, 11.61. Found C, 69.95; H, 5.68; N, 11.32.

General procedure for the synthesis of 6:

To a mixture of oxalyl chloride (0.021 mL, 0.24 mmol, 1.1 equiv.) and DMSO (0.039 mL, 0.56 mmol, 2.5 equiv.) in dry CH_2Cl_2 (1.0 mL) was added a solution of alcohol derivative **14** (107 mg, 0.22 mmol) in CH_2Cl_2 (2.0 mL) at –78 °C. The mixture was stirred at –78 °C for 15 min and then was added triethylamine (0.15 mL, 1.08 mmol, 4.9 equiv.). After the reaction mixture was stirred at –78 °C for 5 min and then at room temperature for 5 min. The mixture was not extracted[31] and was evaporated under reduced pressure to afford the crude product, which was purified on a silica gel column chromatography using A and H (2:1 → A only → A:M (methanol) 100:3, v/v) as an eluent to give **6a** (31 mg, 0.13 mmol, 60 %) and triphenylphosphine oxide (49 mg, 0.18 mmol, 79 %). The other pyrazino[2,3-*e*][1,4]diazepine derivative **6b** was also obtained by the similar method (see, Table 3).

(11*R*, 11a*S*)-1,2,3,10,11,11a-Hexahydro-11-methoxy-pyrazino[2,3-*e*]pyrrolo[1,2-*a*][1,4]diazepin-5-one 6a: Rf = 0.22 (A:M 5:1); oil; $[\alpha]_D^{27}$ = +407.1° (c 0.34, $CHCl_3$); IR (neat) 3204, 2984, 1630, 1553, 1441, 1364, 1186, 1167, 1080, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.27 (1H, d, J = 2.2 Hz), 8.19 (1H, d, J = 2.2 Hz), 6.35 (1H, d, J = 5.8 Hz), 4.66 (1H, d, J = 6.2 Hz), 3.96-3.73 (3H, m), 3.39 (3H, s), 2.41-1.76 (4H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 163.46, 150.97, 145.18, 136.35, 131.83, 87.73, 58.68, 54.88, 49.24, 30.83, 22.83; MS (EI) m/z (rel. intensity) 234 (38 %, M), 203 (19), 202 (63), 147 (19), 146 (13), 122 (13), 119 (14), 79 (9), 70 (100); MS (CI) 234 (MH); HRMS Calcd. for $C_{11}H_{14}N_4O_2$ 234.1117, Found 234.1122.

(11*R*, 11a*S*)-11-Ethoxy-1,2,3,10,11,11a-hexahydro-pyrazino[2,3-*e*]pyrrolo[1,2-*a*][1,4]diazepin-5-one 6b: Yield 59 % (Ph_3P=O: 83 %); Rf = 0.18 (A:M 5:1); oil; $[\alpha]_D^{26}$ = +186.0° (c 0.19, $CHCl_3$); IR (neat) 3212, 2976, 1632, 1551, 1439, 1364, 1186, 1167, 1078, 1059, 752 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.25 (1H, d, J = 2.2 Hz), 8.18 (1H, d, J = 2.2 Hz), 6.32 (1H, d, J = 5.6 Hz), 4.76 (1H, d, J = 6.0 Hz), 3.96-3.80 (3H, m), 3.762 + 3.753 (each, 1H, q, J = 7.1 Hz), 3.463 + 3.418 (each, 1H, q, J = 7.0 Hz), 2.41-1.73 (4H, m), 1.18 (3H, t, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 163.50, 151.04, 145.15, 136.23, 131.84, 86.29, 62.90, 58.74, 49.22, 30.84, 22.86, 15.00; MS (EI) m/z (rel. intensity) 248 (16 %, M), 203 (17), 202 (100), 174 (13), 147 (21), 146 (26), 95 (13), 70 (35); MS (CI) 249 (MH); HRMS Calcd. for $C_{12}H_{16}N_4O_2$ 248.1273, Found 248.1277.

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