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SYNTHESIS OF CHIRAL THIAZOLO[3,4-*a*]PYRAZINE-5,8-DIONES

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Abstract – A synthetic approach to chiral (3*R*,8a*R*)-3-phenyltetrahydro-thiazolo[3,4-*a*]pyrazine-5,8-diones starting from a (2*S*,4*R*)- and (2*R*,4*R*)-diastereoisomeric mixture of 2-phenylthiazolidine is described. The diastereoselective *N*-acylation of the thiazolidine followed by condensation with amines affords the chiral 1,3-thiazolidine-annulated system. The structure of (3*R*,8a*R*)-7-(methoxycarbonylmethyl)-3-phenyltetrahydrothiazolo[3,4-*a*]pyrazine-5,8-dione was determined by X-Ray crystallography.

INTRODUCTION

1,3-Thiazolidine-4-carboxylates are compounds of considerable importance, as some representatives show interesting biological activities.[1] They are well known as building blocks of natural penicillins and analogues, as well as precursors of other pharmaceuticals.[1] The most interesting aspect of thiazolidines reactivity is the possibility of carrying out diastereoselective reactions thus allowing the development of synthetic routes to chiral heterocycles.[2]

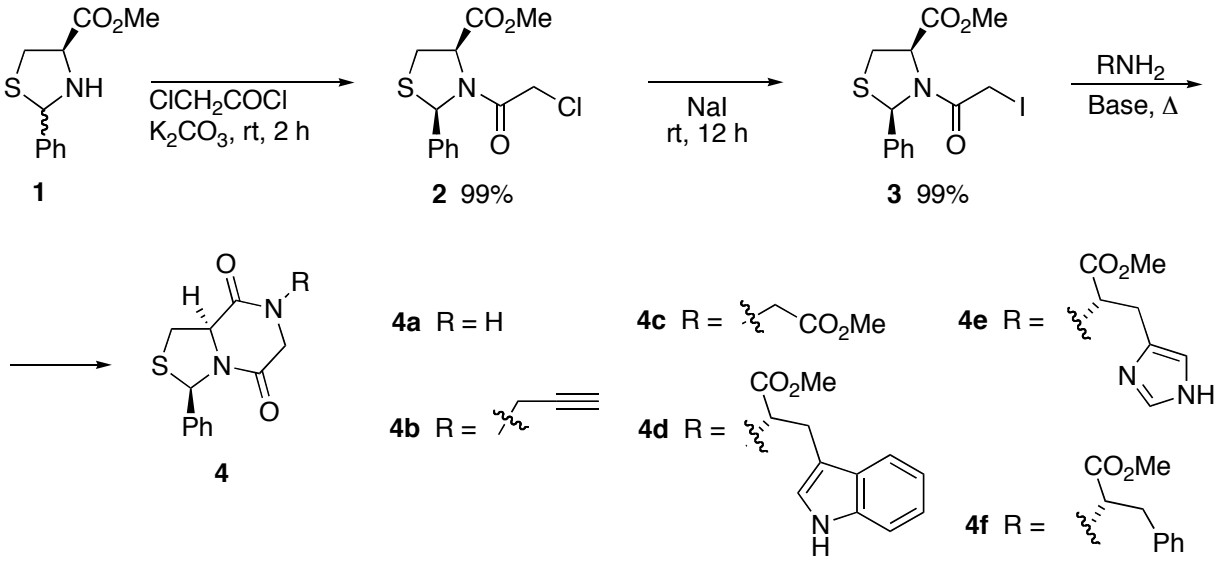
2-Substituted-1,3-thiazolidine-4-carboxylates are obtained from the reaction of aldehydes and *L*-cysteine esters in a process where a new chiral center at the C-2 position of the thiazolidine is created leading to a mixture of the (2*S*,4*R*)- and (2*R*,4*R*)-diastereoisomers. The acylation of the diastereomeric mixture can lead to the selective synthesis of *N*-acyl-2-substituted-1,3-thiazolidine-4-carboxylates as pure stereoisomers with (2*R*,4*R*) or (2*S*,4*R*) stereochemistry depending on the reaction conditions.[3] In fact, 2-substituted-1,3-thiazolidine-4-carboxylates can undergo selective inversion at C-2 through a mechanism involving the opening of the ring but the protection with the acyl group prevents this epimerization and allows the isolation of pure diastereoisomers.

In this context, we report a route to chiral thiazolo[3,4-*a*]pyrazine-5,8-diones starting from thiazolidines.

RESULTS AND DISCUSSION

The synthetic approach studied is outlined in Scheme 1. Thus, the diastereoselective acylation of 2-phenyl-1,3-thiazolidine-4-carboxylate (**1**) is required in order to obtain chiral thiazolo[3,4-*a*]pyrazine-5,8-diones. Although two reports of the use of a similar route to thiazolo[3,4-*a*]pyrazine-5,8-diones were known, the stereochemistry of the products was not determined.[4] We found that carrying out the *N*-acylation of thiazolidine (**1**) with chloroacetyl chloride at room temperature, in the presence of potassium carbonate, the methyl (2*R*,4*R*)-*N*-chloroacetyl-2-phenyl-1,3-thiazolidine-4-carboxylate (**2**) is obtained in diastereomeric pure form in 99% yield. Compound (**2**) can be converted quantitatively into (2*R*,4*R*)-*N*-iodoacetyl derivative (**3**).

The one-pot synthesis of the thiazolo[3,4-*a*]pyrazine-5,8-diones from thiazolidine (**3**) involves the reaction with amines which leads to nucleophilic halide displacement followed by cyclization. The synthesis of the *N*-unsubstituted (3*R*,8a*R*)-3-phenyl-tetrahydro-thiazolo[3,4-*a*]pyrazine-5,8-dione (**4a**) as single stereoisomer was achieved by reacting **3** with ammonium acetate in refluxing methanol. A more efficient synthesis of **4a** (60%) was obtained when a solution of **3** in methanol saturated with NH_3 was heated at reflux. The reaction of thiazolidine (**3**) and propargyl amine was carried out in refluxing acetonitrile giving *N*-prop-2-ynyl derivative (**4b**) in 72% yield (Table 1).



Scheme 1

The work was extended to the reaction of thiazolidine (**3**) with α-amino esters. The condensation reaction with methyl glycinate hydrochloride and triethylamine allowed the synthesis of the corresponding bicyclic system (**4c**) in 37% yield.

The structure of this compound was determined by X-Ray crystallography (Figure 1 and Table 2). The conformation of the five-membered ring is close to half-chair twisted on S2-C1, with Cremer&Pople[5] puckering parameters: q_2= 0.438(2) Å and φ_2=203.9(3)°. The six-membered ring has an average torsion angle of 27.95(9)° and boat conformation as shown by the puckering parameters q = 0.487(2) Å, θ = 94.9(2)°, φ = 126.3(2)°. The molecule has two chiral centers C3 and C8a corresponding to *R* configuration.

Table 1 - Synthesis of the thiazolo[3,4-*a*]pyrazine-5,8-diones 4 from (2*R*,4*R*)-*N*-iodoacetylthiazolidine (**3**).

Amine	Reaction conditions	Product	Yield
Ammonium acetate	Na_2CO_3, Refluxing MeOH, 48 h	**4a**	47%
NH_3	MeOH sat. with NH_3, Refluxing, 48 h	**4a**	60%
Propargyl amine	Na_2CO_3, Refluxing CH_3CN, 3 h	**4b**	72%
Methyl glycinate hydrochloride	NEt_3, Refluxing DMF, 3 h	**4c**	37%
L-Tryptophan methyl ester	$NaHCO_3$, Refluxing Toluene, 40 h	**4d**	51%
L-Histidine methyl ester	NEt_3, Refluxing MeOH, 24 h	**4e**	65%
L-Phenylalanine methyl ester	$NaHCO_3$, Refluxing toluene, 40 h	**4f**	64%

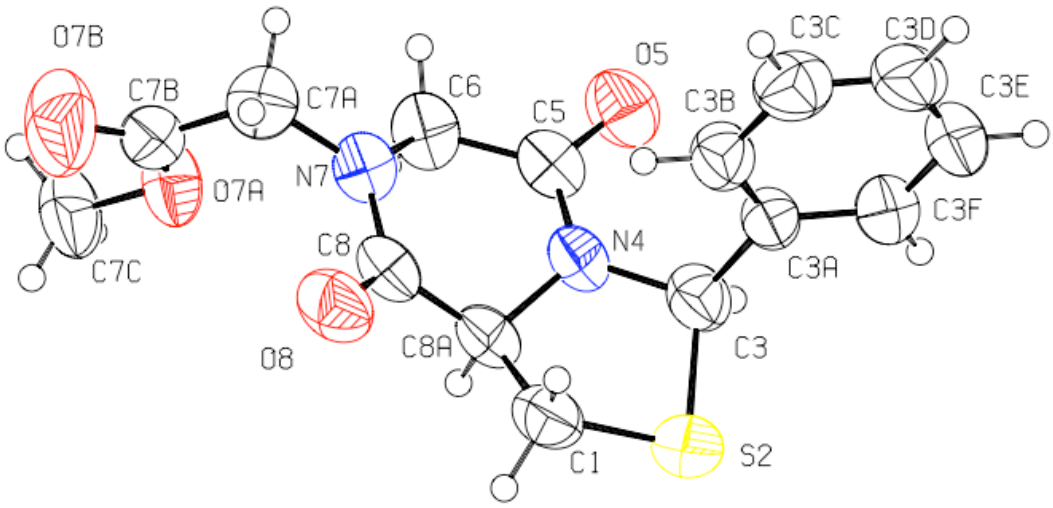


Figure 1 - X-Ray Structure of thiazolo[3,4-*a*]pyrazine-5,8-dione (**4c**).

Table 2 - Bond Lengths (Å) for compound (**4c**).

S2-C1	1.814(3)	C3A-C3	1.508(2)
S2-C3	1.825(2)	O5-C5	1.228(2)
N4-C5	1.342(3)	N7-C7A	1.454(3)
N4-C3	1.464(2)	N7-C6	1.457(2)
N4-C8A	1.474(2)	C5- C6	1.504(3)
O7A-C7B	1.326(3)	C3B-C3C	1.396(3)

This X-Ray analysis confirmed the stereochemistry assignment of the methyl (2*R*,4*R*)-*N*-iodoacetyl-2-phenyl-1,3-thiazolidine-4-carboxylate (**3**) and of the thiazolo[3,4-*a*]pyrazine-5,8-diones (**4**).

The same type of approach can be used to react (2*R*,4*R*)-*N*-iodoacetyl-2-phenyl-1,3-thiazolidine-4-carboxylate (**3**) with other α-amino esters namely *L*-tryptophan methyl ester, *L*-histidine methyl ester and *L*-phenylalanine methyl ester. This way (3*R*,8a*R*)-3-phenyltetrahydrothiazolo[3,4-*a*]pyrazine-5,8-diones (**4d**-**4f**) having an extra chiral center were obtained in good yield (51–65%).

CONCLUSION

A simple and efficient route to chiral thiazolo[3,4-*a*]pyrazine-5,8-diones is reported. A range of new (3*R*,8a*R*)-3-phenyltetrahydrothiazolo[3,4-*a*]pyrazine-5,8-diones, including derivatives bearing α-amino ester residues as side chain was obtained in good yield. The diastereoselective synthesis of methyl (2*R*,4*R*)-*N*-chloroacetyl-2-phenyl-1,3-thiazolidine-4-carboxylate and the subsequent condensation with amines leads to the chiral thiazolo[3,4-*a*]pyrazine-5,8-diones. The configuration assignment was confirmed by determining the structure of (3*R*,8a*R*)-7-(methoxycarbonylmethyl)-3-phenyltetrahydro-thiazolo[3,4-*a*]pyrazine-5,8-dione (**4c**) by X-Ray crystallography.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a nmr spectrometer operating at 300 MHz and 500 MHz. ^{13}C spectra were recorded on a nmr spectrometer operating at 75.5 MHz and 125 MHz. The solvent is deuteriochloroform. IR spectra were recorded on a Perkin Elmer 1720X FTIR spectrometer. Mass spectra were recorded on a HP GC 6890/MSD5973 instrument under electron impact (EI) except where indicated otherwise. Optical rotations were measured on an Optical Activity AA-5 electrical polarimeter. Microanalyses were performed using an EA 1108-CHNS-O Fisons instrument. Mp were recorded on a

Reichert hot stage and are uncorrected. Flash column chromatography was performed with Merck 9385 silica as the stationary phase. Methyl 2-phenylthiazolidine-4-carboxylate was prepared using the general procedure described in the literature and were isolated as mixture of the (*2R*,*4R*) and (*2S*,*4R*) diastereomers.[6]

Methyl (2*R*,4*R*)-*N*-chloroacetyl-2-phenylthiazolidine-4-carboxylate (2). Methyl 2-phenylthiazolidine-4-carboxylate (**1**) (2 g, 9 mmol) was dissolved in dry dichloromethane (40 mL). Anhydrous potassium carbonate (2 g, 14.5 mmol) was added followed by a solution of the chloroacetyl chloride (1.2 g, 10.8 mmol) in dichloromethane (10 mL). The reaction mixture was stirred under nitrogen at rt for 2 h. The organic solvent was evaporated giving a pale yellow solid (99%). mp 86.1-88.2 °C (from ethyl acetate-hexane). IR (KBr) 1666, 1745 and 2900 cm^{-1}; ^1H NMR *δ:* 3.35-3.43 (2H, m), 3.71 (1H, d, *J* = 13.0 Hz), 3.84 (1H, d, *J* = 13.0 Hz), 3.85 (3H, s), 5.08 (1H, approx. t, *J* = 6.5 Hz), 6.20 (1H, s), 7.35-7.43 (3H, m, Ar-H), 7.67-7.69 (2H, m, Ar-H); ^{13}C NMR *δ*: 31.9, 41.7, 52.9, 65.1, 65.8, 126.4, 128.9, 129.2, 139,9, 165.2, 169.9; MS (EI) m/z 299 (M^+, 2%), 264 (54), 222 (100), 164 (67) and 77 (61). Anal. Calcd for $C_{13}H_{14}NO_3ClS$: C, 52.09; H, 4.71; N, 4.67. Found: C, 52.14; H, 4.71; N, 4.24%. $[\alpha]_D^{25}$ = + 110 (c = 1, CH_2Cl_2).

Methyl (2*R*,4*R*)-*N*-iodoacetyl-2-phenylthiazolidine-4-carboxylate (3). A solution of sodium iodide (1 g, 7 mmol) in acetone (20 mL) was added to a solution of methyl (2*R*,4*R*)-*N*-chloroacetyl-2-phenylthiazolidine-4-carboxylate (**2**) (2 g, 7 mmol) in acetone (60 mL). The reaction mixture was stirred overnight. The organic solvent was evaporated giving quantitatively methyl (2*R*,4*R*)-*N*-iodoacetyl-2-phenylthiazolidine-4-carboxylate (**3**) as a yellow solid. mp 114.1-115.3 °C (from ethyl acetate-hexane). IR (KBr) 1665, 1734 and 3100 cm^{-1}; ^1H NMR *δ:* 3.26 (1H, dd, *J* = 6.9 and 12.1 Hz), 3.32 (1H, dd, J 0 6.5 and 12.1 Hz), 3.40 (1H, d, *J* = 10.1 Hz), 3.54 (1H, d, *J* = 10.1 Hz), 3.85 (3H, s), 5.01 (1H, approx. t, *J* = 6.7 Hz), 6.15 (1H, s), 7.25-7.43 (3H, m, Ar-H), 7.68-7.71 (2H, m, Ar-H); ^{13}C NMR *δ*: 31.9, 52.8, 65.3, 66.8, 126.2, 128.8, 129.1, 139,7, 166.8, 170.0; MS (EI) m/z 392 (MH^+, 0.1%), 332 (4), 264 (100), 222 (83) and 77 (20). Anal. Calcd for $C_{13}H_{14}NO_3IS$: C, 39.91; H, 3.61; N, 3.58. Found: C, 40.0; H, 3.35; N, 3.31%. $[\alpha]_D^{25}$ = + 130 (c = 1, CH_2Cl_2).

General procedure for the synthesis of the chiral thiazolo[3,4-*a*]pyrazine-5,8-diones (4). A solution of the amine (4.0 mmol in 10 mL of the appropriated solvent) was added to a solution of methyl (2*R*,4*R*)-*N*-iodoacetyl-2-phenylthiazolidine-4-carboxylate (1.5 g, 3.8 mmol) and a base (3.8 mmol) in 20 mL of the appropriated solvent. The reaction mixture was heated at reflux. The organic solvent was evaporated off and the crude product was purified by flash chromatography [hexane-ethyl acetate (1:3)] (see Table 1 for additional details).

(3*R*,8a*R*)-3-Phenyltetrahydrothiazolo[3,4-*a*]pyrazine-5,8-dione (4a) was obtained as a white solid (47%). mp 225-227 °C (from dichloromethane-ethyl ether).. IR (KBr) 1295, 1639, 1678 and 3257 cm^{-1}; ^1H NMR *δ:* 3.34-3.36 (2H, m), 3.55 (3H, s), 3.62-3.81 (1H, m), 4.13-4.21 (1H, m), 4.78 (1H, approx. t, *J* = 6.6 Hz), 6.43 (1H, s), 7.27-7.38 (5H, Ar-H); ^{13}C NMR *δ*: 34.7, 46.2, 60.3, 64.7, 126.8, 128.6, 128.7, 139.1, 161.1, 166.3; MS (EI) m/z 248 (M^+, 100%), 177 (25), 121 (36) and 77 (16). Anal. Calcd for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.87; N, 11.28. Found: C, 57.77; H, 5.23; N, 11.30%. $[\alpha]_D^{25}$ = + 310 (c = 0.5, CH_2Cl_2).

(3*R*,8a*R*)-3-Phenyl-7-prop-2-ynyltetrahydrothiazolo[3,4-*a*]pyrazine-5,8-dione (4b) was obtained as a white solid (72%). mp 122.2-123.8 °C (from ethyl acetate-hexane). IR (KBr) 1676, 2123, 3228 and 3288 cm^{-1}; ^1H NMR *δ:* 2.34 (1H, t, *J* = 2.5 Hz) 3.38 (1H, dd, *J* = 6.0 and *J* = 12.9 Hz) 3.46-3.53 (1H, m), 4.08 (1H, d, *J* = 17 Hz), 4.21 (1H, dd, *J* = 2.5 and *J* = 17.5 Hz), 4.26 (1H, d, *J* = 17 Hz), 4.47 (1H, dd, *J* = 2.5 and *J* = 17.5 Hz), 4.63 (1H, ddd, *J* = 0.9, J = 6.0 and *J* = 12.9 Hz) 6.25 (1H, s), 7.17-7.20 (2H, m, Ar-H), 7.26-7.35 (3H, m, Ar-H); ^{13}C NMR *δ*: 31.1, 34.9, 51.0, 63.6, 64.8, 73.3, 76.5, 125.1, 128.2, 128.8, 141.2, 163.5, 165.9; MS (EI) m/z 286 (M^+, 100%), 162 (23), 121 (34) and 77 (10). Anal.: Calcd. for $C_{15}H_{14}N_2O_2S$: C, 62.92; H, 4.93; N, 9.78. Found: C, 62.58; H, 5.07; N, 9.87%. $[\alpha]_D^{25}$ = + 115 (c = 1, CH_2Cl_2).

(3*R*,8a*R*)-7-Methoxycarbonylmethyl-3-phenyltetrahydrothiazolo[3,4-*a*]pyrazine-5,8-dione (4c) was obtained as a white solid (37%). mp 118.5-120.7 °C (from ethyl acetate-hexane). IR (KBr) 1677, 1745 and 2961 cm^{-1}; ^1H NMR *δ:* 3.37 (1H, dd, *J* = 5.8 and *J* = 12.3 Hz), 3.51 (1H, dd, *J* = 10.1 and *J* = 12.3 Hz), 3.79 (3H, s), 3.83 (1H, d, *J* = 17.6 Hz), 4.02 (1H, d, *J* = 17.6 Hz), 4.70 (1H, dd, *J* = 5.8 and *J* = 10.1 Hz), 6.23 (1H, s), 7.21-7.23 (2H, m, Ar-H), 7.25-7.28 (1H, m, Ar-H), 7.32-7.34 (2H, m, Ar-H); ^{13}C NMR *δ*: 30.8, 47.3, 52.7, 53.2, 63.4, 64.7, 125.0, 128.2, 128.8, 141.1, 163.4, 167.1, 168.33; MS (EI) m/z 320 (M^+, 100%), 302 (18), 177 (28), 121 (35), 102 (42) and 77 (89). Anal.: Calcd. for $C_{15}H_{16}N_2O_4S$: C, 56.24; H, 5.03; N, 8.74. Found: C, 56.11; H, 5.10; N, 8.50%. $[\alpha]_D^{25}$ = + 80 (c = 0.5, CH_2Cl_2).

(3*R*,8a*R*)-7-[(1*R*)-2-(1*H*-Indol-3-yl)-1-methoxycarbonylethyl]-3-phenyltetrahydrothiazolo[3,4-*a*]-pyrazine-5,8-dione (4d) was obtained as a solid (51%). mp 179.9-180.8 °C (from ethyl acetate-hexane). IR (KBr) 1680, 1735 and 3386 cm^{-1}; ^1H NMR *δ:* 3.08 (1H, dd, *J* = 12.0 and *J* = 14.8 Hz), 3.21-3.28 (2H, m), 3.48 (1H, dd, *J* = 4.8 and *J* = 14.8 Hz), 3.81 (3H, s), 3.88 (1H, d, *J* = 16.9 Hz), 4.10 (1H, d, *J* = 16.9 Hz), 4.57 (1H, ddd, *J* = 0.8, *J* = 6.7 and *J* = 10.0 Hz), 5.43 (1H, dd, *J* = 4.8 and *J* = 12.0 Hz), 6.11 (1H, s), 6.81-6.83 (2H, m, Ar-H), 7.18-7.29 (8H, m, Ar-H); ^{13}C NMR *δ*: 29.6, 30.3, 49.2, 52.7, 56.4, 63.6, 64.2, 109.3, 111.4, 118.3, 119.8, 122.3, 122.9, 124.8, 126.7, 127.8, 128.6, 136.2, 141.1, 163.8, 167.3, 170.5; MS (ES) m/z 450 (MH^+, 100%), 390 (29), 217 (17), 202 (12). Anal. Calcd for $C_{24}H_{23}N_3O_4S$: C, 64.13; H, 5.16; N, 9.35. Found: C, 64.27; H, 4.92; N, 9.13%. $[\alpha]_D^{25}$ = – 15 (c = 1, CH_2Cl_2).

(3*R*,8a*R*)-7-[(1*R*)-2-(1*H*-Imidazol-4-yl)-1-methoxycarbonylethyl]-3-phenyltetrahydrothiazolo[3,4-*a*]-pyrazine-5,8-dione (4e) was obtained as a solid (65%). mp 93.6-95.0 °C (from dichloromethane- diethyl ether). IR (KBr) 1669, 1738 and 3398 cm^{-1}; ^1H NMR *δ:* 3.79 (3H, s), 3.79 (3H, s), 3.90 (1H, d, *J* = 16.9 Hz), 4.14 (1H, d, *J* = 16.9 Hz), 4.59 (1H, dd, *J* = 6.1 and *J* = 10.3 Hz), 5.36 (1H, dd, *J* = 4.8 and *J* = 10.6 Hz), 6.17 (1H, s), 6.71 (1H, s), 7.03-7.06 (2H, m, Ar-H), 7.26-7.33 (3H, m, Ar-H), 7.46 (1H, s); ^{13}C NMR *δ*: 26.5, 30.6, 49.7, 52.7, 56.5, 63.6, 64.3, 65.8, 125.1, 126.3, 128.0, 128.7, 129.4, 135.2, 141.3, 164.0, 167.1, 170.3; MS (ES) m/z 401 (MH^+, 100%), 217 (6). $[\alpha]_D^{25}$ = + 40 (c = 0.25, CH_2Cl_2).

(3*R*,8a*R*)-7-[(1*R*)-2-Phenyl-1-methoxycarbonylethyl]-3-phenyltetrahydrothiazolo[3,4-*a*]pyrazine-5,8-dione (4f) was obtained as a solid (64%). mp 44.8-45.7 °C (from ethyl acetate-hexane). IR (KBr) 1678, 1742, 3025 and 3063 cm^{-1}; ^1H NMR *δ:* 3.07 (1H, dd, *J* = 12.0 and *J* = 14.8 Hz), 3.21-3.28 (2H, m), 3.44-3.51 (1H, m), 3.81 (3H, s), 3.88 (1H, d, *J* = 16.9 Hz), 4.10 (1H, d, *J* = 16.9 Hz), 4.56 (1H, ddd, *J* = 0.9, *J* = 6.2 and *J* = 9.6 Hz), 5.43 (1H, dd, *J* = 4.8 and *J* = 12.0 Hz), 6.11 (1H, s), 6.81-6.83 (2H, m, Ar-H), 6.91-7.30 (8H, m, Ar-H); ^{13}C NMR *δ*: 30.5, 33.9, 49.0, 52.8, 56.8, 63.7, 64.4, 124.7, 127.2, 127.8, 128.5, 128.8, 129.0, 135.5, 141.0, 163.5, 167.2, 170.0; MS (ES) m/z 411 (MH^+, 100%), 351 (16), 205 (7), 183 (15). $[\alpha]_D^{25}$ = + 60 (c = 0.25, CH_2Cl_2).

X-Ray structure determination of (3*R*,8a*R*)-7-methoxycarbonylmethyl-3-phenyl-tetrahydro-thiazolo[3,4-*a*]pyrazine-5,8-dione (4c)

Crystal data: $C_{15}H_{16}N_2O_4S$, *M* = 320.36, crystal dimensions 0.19x0.25x0.40 mm^3, monoclinic, $P2_1$, *a* = 11.1409(8) Å, *b* = 5.6755(5) Å, *c* = 12.7460(10) Å, *α* = 90º, β = 108.338(9)º, γ= 90º, *V* = 765.00(11) $Å^3$, *Z* = 2, ρ_{calc} = 1.391 gcm^{-3}, *μ* = 2.063 mm^{-1}, 5875 reflections measured, 3027 independent, *R* = 0.0369 (2862 reflections with $I > 2\sigma(I)$), R_w = 0.1101 for all reflections, GOF = 1.048, 200 parameters, non-H atoms refined anisotropically, H atoms refined as riding, residual density 0.196/-0.218 e $Å^{-3}$.

Data collection: The X-Ray data were collected on an Enraf-nonius Mach-3 single crystal diffractometer, at 298(3) K, using graphite-monochromated Cu Ka radiation (λ= 1.5418 Å). Intensities were recorded as full profiles of ω–θ scans.

Structure solution and refinement: The structures were solved by direct methods as implemented in SHELXS97 and refined by full-matrix least-squares using SHELXL97. Examination of the structure with PLATON confirmed the absence of voids in the crystal structures, which might be occupied by solvent molecules.

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