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SYNTHESIS OF (3*S*)-2,5-DIETHOXY-3,6-DIHYDRO-3-ISOPROPYL-6-METHYLSULFANYLPYRAZINES AND STEREOSELECTIVITY IN ALKYLATION OF THE ANIONS

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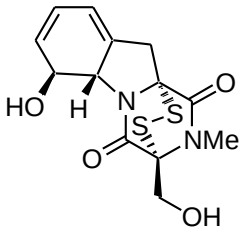
Abstract – The introduction of a sulfur function into Schöllkopf's bislactim ether was carried out to synthesize the diastereomers of (3*S*)-2,5-diethoxy-3,6-dihydro-3-isopropyl-6-methylsulfanylpyrazine. Stereoselectivity in the alkylation of the anions derived from those compounds was examined as a basic study of the synthesis of chiral α-sulfanylamino acids.

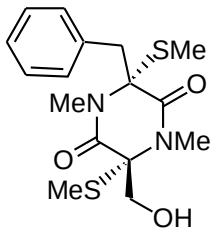
INTRODUCTION

Sulfur-containing diketopiperazines,[1] such as gliotoxins,[2] gliovictin,[3] sporidesmins,[4] aranotins,[5,6] verticillins,[7] chaetocins,[8] and leptosins[9,10] (Figure 1), make up a large category of natural products with significant importance because they exhibit various biological activities. We also had reported the isolation of cytotoxic natural products possessing the diketopiperazine structure with a sulfur function at the α-position, as the metabolites of fungi originally isolated from marine resources.[11,12] Several methods for the total synthesis of this type of natural products are available. However, most of them yielded racemic compounds.[13-19] in spite of the intensive effort to synthesize non-natural but chiral diketopiperazines bearing sulfur functions[20-27] Very recently, a great milestone was achieved by Movassaghi and co-workers who reported the total synthesis of (+)-11,11'-deoxyverticillin A.[28]

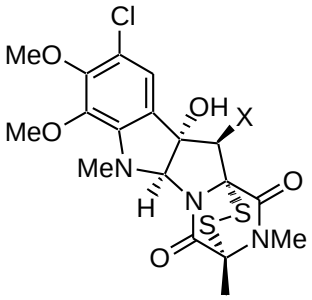
The asymmetric syntheses of sulfur-containing diketopiperazine natural products pose a great challenge for organic chemists and are a vital step in the development of new drugs. As we are interested in cyclic dipeptides consisting of two α-thioamino acids, the synthesis of the building block seems to be one possible way to achieve our goal. We had examined Schöllkopf's bislactim ether methodology[29-31] for the synthesis of chiral α-thioamino acids. Described herein is the synthesis of the diastereomers of (3*S*)-2,5-diethoxy-3,6-dihydro-3-isopropyl-6-methylsulfanylpyrazine and the stereoselective alkylation of the anions derived from them.[32]



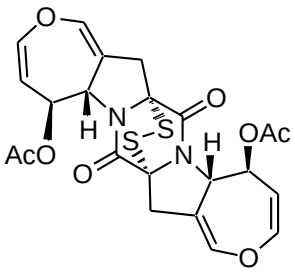
gliotoxin



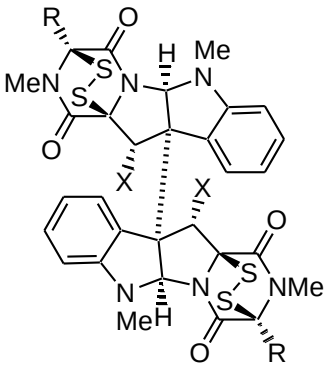
gliovictin



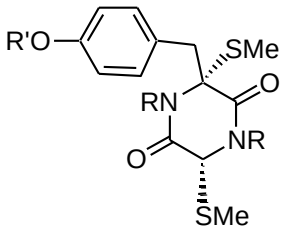
sporidesmin A: X = OH
sporidesmin B: X = H



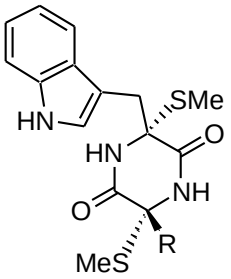
acetylaranotin



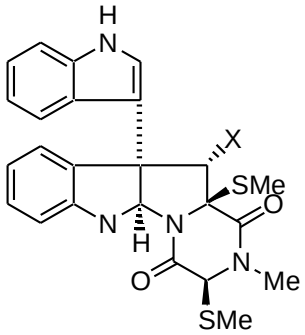
(+)-verticillin A: X = OH, R = CH_3
(+)-11,11'-dideoxyverticillin A: X = H, R = CH_3
(+)-chaetocin A: X = H, R = CH_2OH
(+)-leptosin K: X = H, R = $CH(CH_3)_2$



fusaperazine A: R = H, R' = H
natural product[33]: R = Me, R' = H
Sch 54794[34] (antipode): R = H, R' = isoprenyl
cis-bis(methylthio)silvatin[33,35](antipode): R = Me, R' = isoprenyl



glioperazine: R = $CH(OH)CH_3$ ($[\alpha]_D$ = +52.6)
polanzanine B[36]: R = $CH(CH_3)_2$ ($[\alpha]_D$ = –60)
(relative stereochemistry)

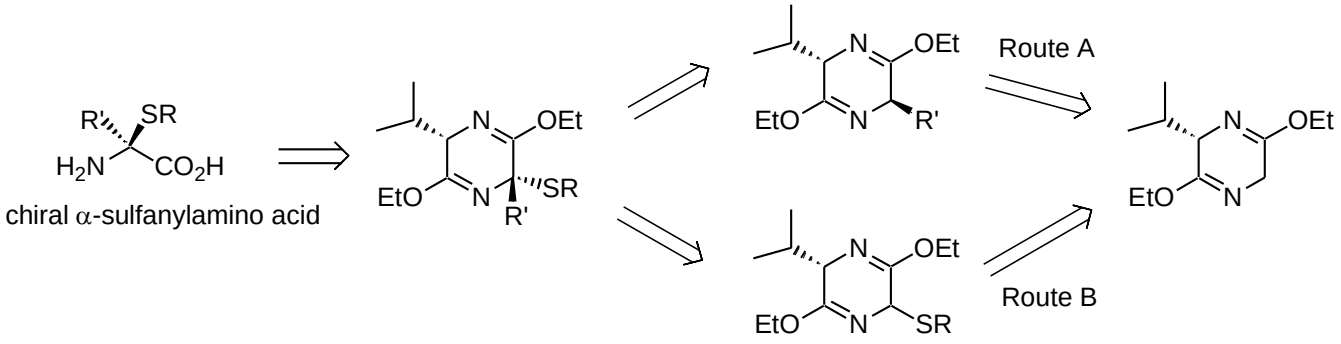


gliocladin A: X = OH
gliocladin B: X = H
(relative stereochemistry)

Figure 1. Structures of naturally occurring sulfur-containing diketopiperazines

RESULTS AND DISCUSSION

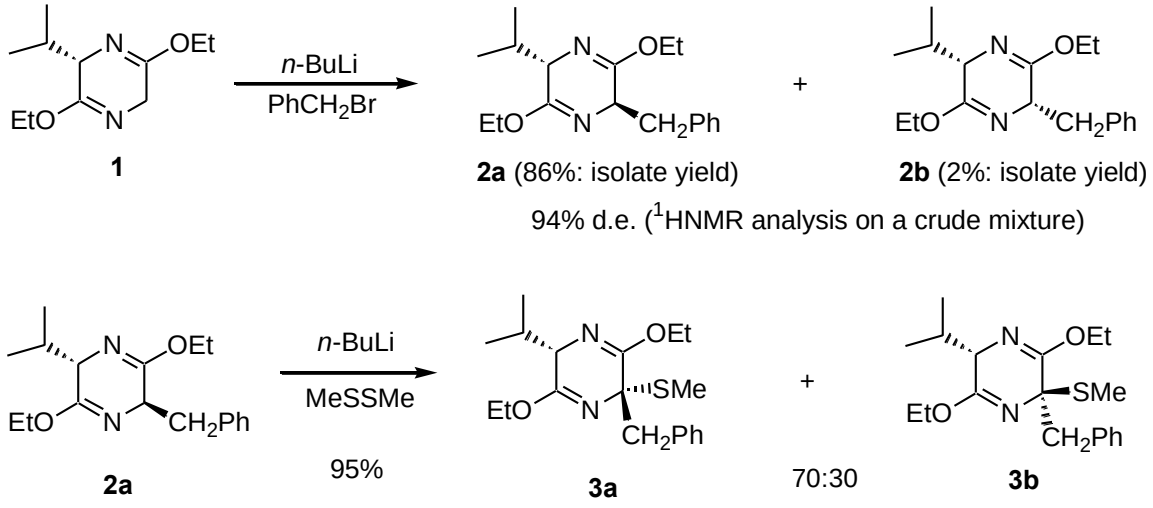
As summarized in Scheme 1, there are two ways to furnish α-sulfanylamino acid from Schöllkopf's bislactim ether **1**. Route A involves the initial alkylation, followed by α-sulfanylation. and route B involves the initial introduction of a sulfur function, followed by alkylation.



Scheme 1. Strategy for the preparation of chiral α-sulfanylamino acids

1. INTRODUCTION OF SULFUR FUNCTION INTO BENZYLATED BISLACTIM ETHER

Route A, our initial approach, is summarized in Scheme 2. Schöllkopf's bislactim ether **1** was lithiated with *n*-BuLi, and this was followed by the addition of benzyl bromide to give a mixture of benzylated diastereomers **2a** and **2b** in 94% d.e. Purely isolated major *trans*-isomer **2a** was treated with *n*-BuLi, and this was followed by the addition of dimethyl disulfide to afford products **3a** and **3b** in 95% yield with a ratio of approximately 70 : 30. The stereochemistry of **3a** and **3b** was deduced from the chemical shift of H-3, which was observed in the higher field at 2.98 ppm for **3a** due to the anisotropic effect of the benzyl group located on the same side, compared to 3.78 ppm for **3b**, as illustrated in Figure 2. This speculation was confirmed by NOESY analysis.



Scheme 2. Benzylation of Schöllkopf's bislactim ether **1** and methylsulfanylation of major product **2a**

A NOESY cross peak between H-3 and 6-SMe was observed for **3b** whereas 6-SMe/3-isopropyl methyls or 6-SMe/3-isopropyl methine cross peaks were observed for **3a**. It is generally accepted that the carbanion derived from **1** has an sp^2 hybrid and it mainly reacts with the electrophile at the side opposite

to the 3-isopropyl group to yield excellent stereoselectivity. Thus, the low stereoselectivity may be explained by the preference of the sp^3-like carbanion derived from **2a** for the π-π stabilizing interaction between the bislactim ether ring and the benzyl group.

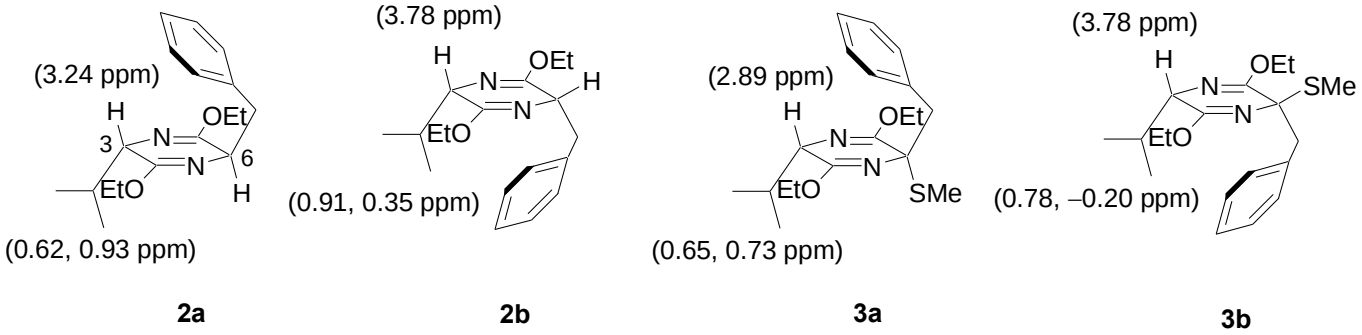
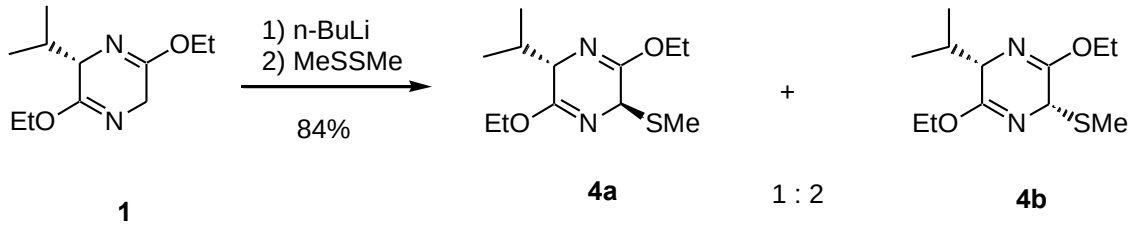


Figure 2. Conformations and ^{1}H-NMR chemical shifts of **2** and **3**

2. SYNTHESIS OF (3*S*)-6-METHYLSULFANYL-3-ISOPROPYLBISLACTIM ETHER

As the second approach via route B, bislactim ether **1** was treated with *n*-BuLi in THF at –78 °C, and this was followed by the addition of dimethyl disulfide to afford a mixture of diastereomers **4a** and **4b** in a ratio of ca. 1:2. To our surprise, major diastereomer **4b** had a *cis*-configuration between the 3-isopropyl group and the newly introduced 6-methylsulfanyl group. A cross peak between 3-isopropyl methyl/6-SMe in the NOESY spectrum of **4b** and cross peaks between H-3/6-SMe and 3-isopropyl methyl/6-H in the NOESY spectrum of **4a** confirmed their relative stereochemistry, as illustrated in Scheme 3. One possible explanation for this unusual stereoselectivity is the re-deprotonation of initially formed **4a** or **4b** by methylthiolate anion in the reaction system, followed by protonation from the less hindered side during the quenching process. However, quenching of the reaction with D_2O did not give any deuterated **4a** or **4b,** negating the above deduction. The reason why **4b** was formed predominantly under kinetically controlled conditions remains unknown.

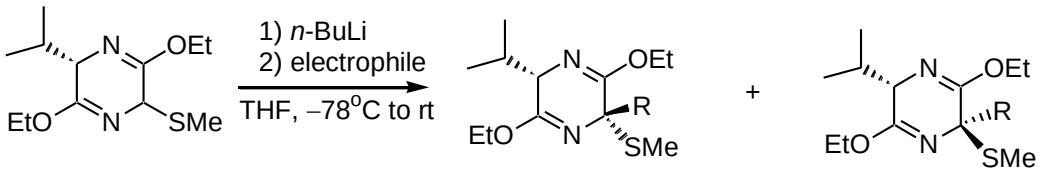


Scheme 3. Reaction of anion derived from Schöllkopf's bislactim ether **1** with dimethyldisulfide

3. ALKYLATION OF (3*S*)-6-METHYLSULFANYL-3-ISOPROPYLBISLACTIM ETHER

The stereoselectivity in the alkylation of the carbanion derived from **4a** or **4b** was investigated. The

electrophiles selected here will be useful for the synthesis of natural sulfur-containing diketopiperazines. The results are summarized in Table 1. Benzylation showed remarkable stereoselectivity, giving single product **3a** from either starting material **4a** or **4b** or mixture of both (entries 1-3). Methylation also showed the same stereoselectivity (**5a**:**5b** = ca. 3:1) from either starting material (entries 4 and 5). Similar low stereoselectivity in the methylation was seen in a previous study by Nagao and co-workers using (L)-serine-derived Schöllkopf's bislactim ether.[37] From the results described above, it became apparent that the stereochemistry of the starting material has no effect on the stereoselectivity of this reaction. Ethylation using iodoethane as an electrophile gave higher stereoselectivity than methylation whereas bromoethane did not yield the same result (entries 7 and 8). The reaction with iodopropane proceeded with excellent stereoselectivity (entry 9). The reaction with piperonyl bromide gave a single diastereomer **8d** in 30% yield along with aromatized product **11** (entry 10). The stereoselectivity of this reaction seemed to be related to the bulkiness of the electrophiles.



4a: β-SMe
4b: α-SMe

3a: R = Bn
5a: R = Me
6a: R = Et
7a: R = *iso*-Pr
8a: R = piperonyl

3b: R = Bn
5b: R = Me
6b: R = Et
7c: R = *iso*-Pr
8b: R = piperonyl

Scheme 4. Alkylation of anion derived from 6-methylsulfanyl-Schöllkopf's bislactim ether **4a** or **4b**

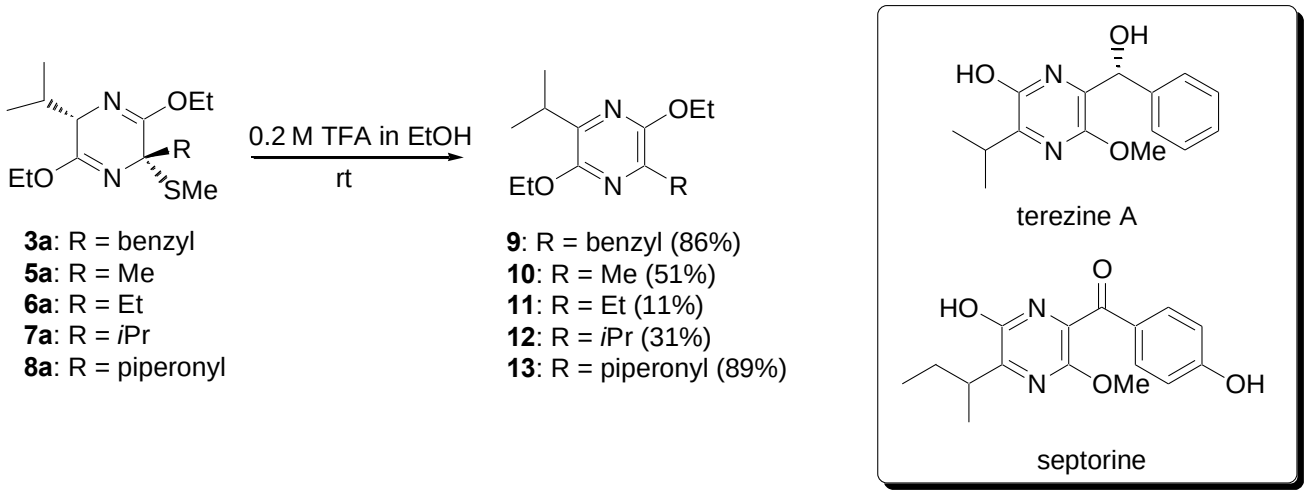
Table 1. Alkylation of **4a** or **4b**

run	substrate	electrophile	product (yield, %)	
1	**4b**	$PhCH_2Br$	**3a** (70)	**3b** (0)
2	**4a**	$PhCH_2Br$	**3a** (69)	**3b** (0)
3	mixture of **4a** and **4b**[a]	$PhCH_2Br$	**3a** (81)	**3b** (0)
4	**4b**	MeI	**5a** (47)	**5b** (15)
5	**4a**	MeI	**5a** (48)	**5b** (16)
6	mixture of **4a**and **4b**[a]	MeI	**5a** (58)	**5a** (19)
7	mixture of **4a** and **4b**[a]	EtBr	**6a** (0)	**6b** (0)
8[b]	mixture of **4a** and **4b**[a]	EtI	**6a** (48)	**6b** (8)[d]
9	mixture of **4a** and **4b**[a]	*iso*-PrI	**7a** (65)	**7b** (4)[d]
10[c]	mixture of **4a** and **4b**[a]	piperonyl bromide	**8a** (30)	**8b** (0)

a. Ratio **4a**: **4b** = ca 1:2. b. Starting material was recovered in 9% yield. c. Aromatized **13** was obtained in 20% yield.
d. Pure compounds could not be isolated. Yields were calculated from the ^{1}H-NMR spectra of the crude products.

4. ETHANOLYSIS OF 6-METHYLSULFANYL-BISLACTIM ETHER

The ethanolysis of bislactim ethers with trifluoroacetic acid was examined. Unfortunately, desulfanylated pyrazines were obtained as products **9**–**13** instead of the desired ethyl esters of α-methylsulfanylamino acids. Nevertheless, it is interesting that the resultant pyrazines, such as **9** or **13**, are closely related to fungal metabolites terezine A[38] and septorine.[39]



3a: R = benzyl
5a: R = Me
6a: R = Et
7a: R = *i*Pr
8a: R = piperonyl

9: R = benzyl (86%)
10: R = Me (51%)
11: R = Et (11%)
12: R = *i*Pr (31%)
13: R = piperonyl (89%)

Scheme 5. Ethanolysis of 6-methylsulfanyl-bislactim ether

CONCLUSION

We have synthesized the diastereomers of (3S)-2,5-diethoxy-3-isopropyl-6-methylsulfanylpiperazine and examined the stereoselectivity in the alkylation of the anions derived from them. Benzylation showed excellent stereoselectivity whereas methylsulfanylation of benzylated bislactim ether showed low selectivity. Acid-catalyzed hydrolysis gave not the desired α-sulfur substituted amino acids but desulfanylated and aromatized pyrazines.

EXPERIMENTAL

General Procedure. IR spectra were obtained with a JEOL FT/IR-680 Plus spectrometer. HRMS were determined with a JEOL JMS-700 (2) mass spectrometer. NMR spectra were recorded at 27 ^{o}C on Varian UNITY INOVA-500, Gemini-2000, and Mercury-3000 spectrometers in $CDCl_3$ with tetramethylsilane (TMS) as the internal standard. Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Specific rotations were determined by ORD measurements using a JASCO J-820 spectrometer. Liquid column chromatography was conducted over silica gel (SILICYCLE, SiliaFlash® F60, mesh 230–400). Analytical TLC was performed on precoated Merck aluminum sheets (DC-Alufolien Kieselgel 60 F_{254}), and compounds were viewed by spraying an ethanol solution of phosphomolybdic acid, followed by heating. Dry THF was distilled over sodium-benzophenone ketyl

under argon atmosphere.

Benzylation of 1

To a solution of **1** (862.5 mg, 4.1 mmol) in dry THF (50 mL) was added *n*-BuLi (1.6 M 2.8 mL, 4.5 mmol) at −78 °C under nitrogen atmosphere. After stirring for 30 min, benzyl bromide (0.53 mL, 4.5 mmol) was added and the reaction mixture was stirred overnight to allow the reaction temperature to reach rt. The reaction mixture was treated with aq NH_4Cl, evaporated to reduce the organic solvent, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and evaporated under reduced pressure to afford the crude product, which was purified by silica gel column chromatography (eluent: hexane:CH_2Cl_2 = 4:1) and preparative TLC (eluent: hexane:CH_2Cl_2 = 4:1) to give **2a** in 86% yield (1.08 g) and **2b** in 2% yield (23.2 mg). The product ratio appearing in the text was estimated from the ^{1}NMR spectrum of the crude product. **(3*S*,6*R*)-2,5-Diethoxy-3,6-dihydro-3-isopropyl-6-benzylpyrazine 2a**; oil; $[\alpha]_D^{25}$ −101.3 (c 0.43, EtOH); IR (liquid film) ν_{max} 1693 (C=C) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.62 (3H, d, *J* = 6.9 Hz, *i*Pr-C*H*$_3$), 0.93 (3H, d, *J* = 6.9 Hz, *i*Pr-C*H*$_3$), 1.25 (3H, t, *J* = 7.1 Hz, -OCH$_2$C*H*$_3$), 1.32 (3H, t, *J* = 7.1 Hz, -OCH$_2$C*H*$_3$), 2.16 (1H, sept d, *J* = 6.9, 3.3 Hz, -C*H*(CH_3)$_2$), 3.07 (1H, dd, *J* = 13.2, 4.7 Hz, PhC*H*H-), 3.11 (1H, dd, *J* = 13.2, 4.7 Hz, PhCH*H*-), 3.24 (1H, t, *J* = 3.3 Hz, H-3), 4.05–4.21 (4H, m, 2x -OC*H*$_2$CH$_3$), 4.30 (1H, td, *J* = 4.7, 3.3 Hz, H-6), 7.09–7.22 (5H, m, Ph); ^{13}C-NMR ($CDCl_3$) δ 14.3 (q), 14.4 (q), 16.4 (q), 19.0 (q), 31.1 (d), 40.0 (t), 56.6 (d), 60.1 (t), 60.4 (t), 60.5 (d), 126.1 (d), 127.7 (d), 130.0 (d), 137.4 (s), 161.9 (s), 163.5 (s); HRMS *m/z* calcd for $C_{18}H_{26}N_2O_2$ $(M)^+$ 302.1994, found 302.1993. **(3*S*,6*S*)-2,5-Diethoxy-3,6-dihydro-3-isopropyl-6-benzylpyrazine 2b**; oil; $[\alpha]_D^{25}$ +105.5 (c 0.32, EtOH); IR (liquid film) ν_{max} 1692 (C=C) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.35 (3H, d, *J* = 6.9 Hz, *i*Pr-C*H*$_3$), 0.91 (3H, d, *J* = 6.9 Hz, *i*Pr-C*H*$_3$), 1.25 (3H, t, *J* = 7.1 Hz, -OCH$_2$C*H*$_3$), 1.30 (3H, t, *J* = 7.1 Hz, -OCH$_2$C*H*$_3$), 1.86 (1H, sept d, *J* = 6.9, 4.6 Hz, -C*H*(CH_3)$_2$), 3.04 (1H, dd, *J* = 13.3, 6.9 Hz, PhCH*H*-), 3.13 (1H, dd, *J* = 13.3, 4.6 Hz, PhC*H*H-), 3.78 (1H, dd, *J* = 5.0, 4.3 Hz, H-3), 3.99–4.21 (4H, m, 2x -OC*H*$_2$CH$_3$), 4.27 (1H, dt, *J* = 6.9, 4.6 Hz, H-6), 7.09–7.25 (5H, m, Ph); ^{13}C-NMR ($CDCl_3$) δ 14.4 (q), 14.4 (q), 16.9 (q), 19.6 (q), 31.3 (d), 40.7 (t), 56.9 (d), 60.3 (t), 60.3 (t), 60.7 (d), 126.2 (d), 127.9 (d), 130.0 (d), 138.2 (s), 161.8 (s), 162.8 (s); HRMS *m/z* calcd for $C_{18}H_{26}N_2O_2$ $(M)^+$ 302.1994, found 302.1991.

Introduction of sulfur function into 2a

To a solution of **2a** (486.5 mg, 1.6 mmol) in THF (10 mL) was added *n*-BuLi (1.6 M 2.8 mL, 4.5 mmol) at −78 °C under nitrogen atmosphere. After stirring for 30 min, dimethyl disulfide (0.14 mL, 1.6 mmol) was added and the reaction mixture was stirred overnight to allow the reaction temperature to reach rt from −78 °C. The reaction mixture was evaporated to reduce the organic solvent, treated with aq Na_2CO_3,

and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and evaporated under reduced pressure to afford the crude product, which was purified by silica gel column chromatography (eluent: hexane:CH_2Cl_2 = 4:1) to give **3a** and **3b** in 95% yield (531.0 mg). The product ratio appearing in the text was estimated from the ^{1}H-NMR spectrum.

(3*S*,6*S*)-2,5-Diethoxy-3,6-dihydro-3-isopropyl-6-benzyl-6-methylsulfanylpyrazine 3a; pale yellow crystals (CH_2Cl_2); mp 65–73°C; $[\alpha]_D^{25}$ –11.4 (c 1.16, EtOH); IR (KBr) ν_{max} 1677 (C=C), 1495 (C=C), cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.65 (3H, d, *J* = 7.0 Hz, *i*Pr-C*H*$_3$), 0.93 (3H, d, *J* = 7.0 Hz, *i*Pr-C*H*$_3$), 1.28 (3H, t, *J* = 7.1 Hz, -OCH$_2$C*H*$_3$), 1.38 (3H, t, *J* = 7.1 Hz, -OCH$_2$C*H*$_3$), 2.11 (3H, s, SCH$_3$), 2.16 (1H, sept d, *J* = 7.0, 3.0 Hz, -C*H*(CH$_3$)$_2$), 2.98 (1H, d, *J* = 3.4 Hz, H-3), 3.10 (1H, d, *J* = 12.6 Hz, PhCH*H*-), 3.40 (1H, d, *J* = 12.6 Hz, PhC*H*H-), 4.07–4.29 (4H, m, -OC*H*$_2$CH$_3$), 7.03–7.07 (2H, m, Ar-H), 7.16–7.21 (3H, m, Ar -H); ^{13}C-NMR ($CDCl_3$) δ 12.8 (q), 14.3 (q), 14.5 (q), 17.1 (q), 19.4 (q), 30.4 (d), 45.9 (t), 60.2 (d), 60.91 (2 x t), 67.5 (s), 126.6 (d), 127.7 (d), 130.2 (d), 136.1 (s), 159.6 (s), 164.4 (s); HRMS *m/z* calcd for $C_{19}H_{29}N_2O_2S$ $(M+H)^+$ 349.1950, found 349.1949.

(3*S*,6*R*)-2,5-Diethoxy-3,6-dihydro-3-isopropyl-6-benzyl-6-methylsulfanylpyrazine 3b; oil; $[\alpha]_D^{25}$ –6.2 (c 0.33, $CHCl_3$); IR (liquid film) ν_{max} 1680 (C=C), 1495 (C=C) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ –0.20 (3H, d, *J* = 6.9 Hz, *i*Pr-C*H*$_3$), 0.83 (3H, d, *J* = 6.9 Hz, *i*Pr-C*H*$_3$), 1.30 (3H, t, *J* = 7.1 Hz, -OC*H*$_2$CH$_3$), 1.42 (3H, t, *J* = 7.1 Hz, -OC*H*$_2$CH$_3$), 1.93 (3H, s, SC*H*$_3$), 2.03 (1H, sept d, *J* = 6.9, 3.4 Hz, -C*H*(CH$_3$)$_2$), 3.12 (1H, d, *J* = 12.8 Hz, PhCH*H*-), 3.55 (1H, d, *J* = 12.8 Hz, PhC*H*H-), 3.80 (1H, d, *J* = 3.4 Hz, H-3), 4.14–4.28 (4H, m, -OC*H*$_2$CH$_3$), 7.11–7.21 (5H, m, Ar-H); ^{13}C-NMR ($CDCl_3$) δ 12.2 (q), 14.4 (q), 14.5 (q), 14.9 (q), 19.2 (q), 30.6 (d), 44.4 (t), 60.5 (d), 60.8 (t), 60.9 (t), 67.5 (s), 126.6 (d), 127.7 (d), 130.8 (d), 136.5 (s), 158.9 (s), 165.1 (s); HRMS *m/z* calcd for $C_{19}H_{29}N_2O_2S$ $(M+H)^+$ 349.1950, found 349.1944.

Introduction of sulfur function into 1

To a solution of **1** (202.2 mg, 0.9 mmol) in dry THF (4 mL) was added *n*-BuLi (1.6 M 0.62 mL, 0.99 mmol) at –78 °C under nitrogen atmosphere. After stirring for 30 min, dimethyl disulfide (0.1 mL, 1.08 mmol) was added and the reaction mixture was stirred overnight to allow the reaction temperature to reach rt. The reaction mixture was evaporated to reduce the organic solvent, treated with aq NH_4Cl, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and evaporated under reduced pressure to afford the crude product, which was purified by silica gel column chromatography (eluent: hexane:CH_2Cl_2 = 4:1) and preparative TLC (eluent: hexane:CH_2Cl_2 =10:1) to give a mixture of **4a** and **4b** in 84% yield (194.3 mg). The product ratio appearing in the text was estimated from the ^{1}NMR spectrum of the crude product.

(3*S*,6*R*)-2,5-Diethoxy-3,6-dihydro-3-isopropyl-6-methylsulfanylpyrazine 4a; pale yellow oil; $[\alpha]_D^{25}$ –94.2 (c 0.33, EtOH); IR (liquid film) ν_{max} 1685 (C=C) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.67 (3H, d, *J* = 6.8 Hz,

*i*Pr-C*H*$_3$), 1.07 (3H, d, *J* = 7.0 Hz, *i*Pr-C*H*$_3$), 1.30 (3H, t, *J* = 7.1 Hz, -OCH$_2$C*H*$_3$), 1.32 (3H, t, *J* = 7.1 Hz, -OCH$_2$C*H*$_3$), 2.02 (3H, s, 6-SC*H*$_3$), 2.35–2.42 (1H, qqd, *J* = 7.0, 6.8, 3.3 Hz, -C*H*(CH$_3$)$_2$), 3.95 (1H, dd, *J* =3.3, 3.1 Hz, H-3), 4.13–4.25 (4H, m, -OC*H*$_2$CH$_3$), 4.97 (1H, d, *J* = 3.1 Hz, H-6); ^{13}C-NMR (CDCl$_3$) δ 11.8 (q), 14.2 (q), 14.3 (q), 16.3 (q), 19.1 (q), 31.2 (d), 58.2 (d), 60.4 (d), 61.2 (t), 61.3 (t), 159.6 (s), 166.2 (s); HRMS *m/z* calcd for $C_{12}H_{21}N_2O_2S$ $(M-H)^+$ 257.1324, found 257.1328.

(3*S*,6*S*)-2,5-Diethoxy-3,6-dihydro-3-isopropyl-6-methylsulfanylpyrazine 4b; pale yellow oil; $[\alpha]_D^{25}$ −15.1 (c 0.11, EtOH); IR (liquid film) ν_{max} 1685 (C=C) cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 0.86 (3H, d, *J* = 6.8 Hz, *i*Pr-C*H*$_3$) 1.07 (3H, d, *J* = 6.8 Hz, *i*Pr-C*H*$_3$), 1.29 (3H, t, *J* = 7.1 Hz, -OCH$_2$C*H*$_3$), 1.32 (3H, t, *J* = 7.1 Hz, -OCH$_2$C*H*$_3$), 2.20 (1H, sept d, *J* = 6.8, 4.6 Hz, -C*H*(CH$_3$)$_2$), 2.36 (3H, s, 6-SC*H*$_3$), 3.90 (1H, dd, *J* = 4.6, 3.7 Hz, H-3), 4.07–4.29 (4H, m, 2x -OC*H*$_2$CH$_3$), 4.89 (1H, d, *J* = 3.7 Hz, H-6); ^{13}C-NMR (CDCl$_3$) δ 14.2 (q), 14.3 (q), 15.9 (q), 18.4 (q), 19.8 (q), 32.1 (d), 58.9 (d), 61.2 (t), 61.7 (d), 161.2 (s), 166.8 (s); HRMS *m/z* calcd for $C_{12}H_{22}N_2O_2S$ $(M)^+$ 258.1383, found 258.1397.

Alkylation of 4a or 4b

General procedure (Table 1): To a solution of **4a** or **4b** (ca. 50 mg) in dry THF (2.0 mL) was added *n*-BuLi (1.6 M 1.2 equiv.) at −78 °C under nitrogen atmosphere. After stirring for 30 min, an electrophile was added and the reaction mixture was stirred overnight to allow the reaction temperature to reach rt from −78 °C. The solvent was removed under reduced pressure to give a residue, which was treated with aq Na_2CO_3 and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure to afford a crude product that was purified by chromatography (eluent: hexane:EtOAc = 10:1) to afford the desired products. The product yield appearing in Table 1 was estimated from the isolated yield of the product mixture and the integration of the signals in the ^{1}H-NMR spectrum.

(3*S*,6*S*)-2,5-Diethoxy-3,6-dihydro-3-isopropyl-6-methyl-6-methylsulfanylpyrazine 5a; pale yellow oil; $[\alpha]_D^{25}$ +133.8 (c 0.33, EtOH); IR (liquid film) ν_{max} 1681 (C=C) cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 0.79 (3H, d, *J* = 6.6 Hz, *i*Pr-C*H*$_3$) 1.10 (3H, d, *J* = 6.8 Hz, *i*Pr-C*H*$_3$), 1.28 (3H, t, *J* = 8.1Hz, -OCH$_2$C*H*$_3$), 1.31 (3H, t, *J* = 7.1Hz, -OCH$_2$C*H*$_3$), 1.64 (3H, s, 6-Me), 2.10 (3H, s, 6-SC*H*$_3$), 2.33 (1H, m, -C*H*(CH$_3$)$_2$), 3.89 (1H, d, *J* = 3.9 Hz, H-3), 4.10–4.34 (4H, m, 2x -OC*H*$_2$CH$_3$); ^{13}C-NMR (CDCl$_3$) δ 13.1 (q), 14.2 (q), 14.3 (q), 17.6 (q), 19.7 (q), 28.2 (q), 31.1 (d), 60.9 (d), 61.00 (t), 61.02 (d), 62.7 (s), 162.3 (s), 163.7 (s); HRMS *m/z* calcd for $C_{13}H_{25}N_2O_2S$ $(M+H)^+$ 273.1637, found 273.1634.

(3*S*,6*R*)-2,5-Diethoxy-3,6-dihydro-6-ethyl-3-isopropyl-6-methylsulfanylpyrazine 5b; pale yellow oil; $[\alpha]_D^{25}$ −78.2 (c 0.11, EtOH); IR (liquid film) ν_{max} 1677 (C=C) cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 0.66 (3H, d, *J* = 7.0 Hz, *i*Pr-C*H*$_3$), 1.08 (3H, d, *J* = 7.0 Hz, *i*Pr-C*H*$_3$), 1.28 (3H, t, *J* = 7.1 Hz, -OCH$_2$C*H*$_3$), 1.30 (3H, t, *J* = 7.1 Hz, -OCH$_2$C*H*$_3$), 1.66 (3H, s, 6-Me), 1.88 (3H, s, 6-SC*H*$_3$), 2.32 (1H, sept d, *J* = 7.0, 3.2 Hz,

-C<u>H</u>(CH_3)$_2$), 3.99 (1H, d, *J* = 3.2 Hz, H-3), 4.10–4.30 (4H, m, 2x -OC*H*$_2$CH$_3$); ^{13}C-NMR ($CDCl_3$) δ 12.4 (q), 14.2 (q), 14.4 (q), 16.3 (q), 19.2 (q), 27.6 (q), 31.1 (d), 61.0 (t), 61.04 (d), 63.6 (t), 63.6 (s), 161.4 (s), 164.0 (s); HRMS *m/z* calcd for $C_{13}H_{25}N_2O_2S$ $(M+H)^+$ 273.1637, found 273.1639.

(3*S*,6*S*)-2,5-Diethoxy-6-ethyl-3,6-dihydro-3-isopropyl-6-methylsulfanylpyrazine 6a; oil; $[\alpha]_D^{25}$ +55.4 (c 0.73, EtOH); IR (liquid film) ν_{max} 1681 (C=C) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.74 (3H, t, *J* = 7.3 Hz, 6-CH$_2$C*H*$_3$), 0.78 (3H, d, *J* = 6.9 Hz, *i*Pr-C*H*$_3$), 1.10 (3H, d, *J* = 6.9 Hz, *i*Pr-C*H*$_3$), 1.29 (3H, t, *J* = 7.1 Hz, -OCH$_2$C*H*$_3$), 1.30 (3H, t, *J* = 7.1 Hz, -OCH$_2$C*H*$_3$), 1.85 (1H, dq, *J* = 13.1, 7.3 Hz, 6-C*H*$_A$H$_B$CH$_3$), 2.07 (3H, s, SCH$_3$), 2.12 (1H, dq, *J* = 13.1, 7.3 Hz, 6-CH$_A$*H*$_B$CH$_3$), 2.34 (1H, sept d, *J* = 6.9, 3.7 Hz, 3-C*H*(CH_3)$_2$), 3.89 (1H, d, *J* = 3.7 Hz, H-3), 4.12–4.28 (4H, m, -OC*H*$_2$CH$_3$); ^{13}C-NMR ($CDCl_3$) δ 8.8 (q), 12.7 (q), 14.3 (q), 14.4 (q), 17.5 (q), 19.7 (q), 31.0 (d), 33.1 (t), 60.9 (t), 60.95 (d), 60.96 (t), 66.7 (s), 160.8 (s), 164.4 (s); HRMS *m/z* calcd for $C_{14}H_{27}N_2O_2S$ $(M+H)^+$ 287.1794, found 287.1789.

(3*S*,6*S*)-2,5-Diethoxy-3,6-dihydro-3,6-diisopropyl-6-methylsulfanylpyrazine 7a: oil; $[\alpha]_D^{25}$ +59.0 (c 0.40, EtOH); IR (liquid film) ν_{max} 1681 (C=C) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.75 (3H, d, *J* = 6.9 Hz, 6-*i*Pr-C*H*$_3$), 0.76 (3H, d, *J* = 6.9 Hz, 6-*i*Pr-C*H*$_3$), 1.10 (3H, d, *J* = 6.9 Hz, 3-*i*Pr-C*H*$_3$), 1.10 (3H, d, *J* = 6.9 Hz, 3-*i*Pr-C*H*$_3$), 1.29 (3H, t, *J* = 7.1 Hz, -OC*H*$_2$CH$_3$), 1.31 (3H, t, *J* = 7.1 Hz, -OC*H*$_2$CH$_3$), 2.01 (3H, s, -SC*H*$_3$), 2.32 (1H, sept, *J* = 6.9 Hz, 6-C*H*(CH_3)$_2$), 2.35 (1H, sept d, *J* = 6.9, 3.7 Hz, 3-C*H*(CH_3)$_2$), 3.84 (1H, d, *J* = 3.7 Hz, H-3), 4.11–4.27 (4H, m, -OC*H*$_2$CH$_3$); ^{13}C-NMR ($CDCl_3$) δ 13.2 (q), 14.3 (q), 14.4 (q), 16.1 (q), 17.5 (q), 17.8 (q), 19.7 (q), 30.8 (d), 35.8 (d), 60.5 (d), 60.87 (t), 60.9 (t), 70.1 (s), 161.3 (s), 164.2 (s); HRMS *m/z* calcd for $C_{15}H_{29}N_2O_2S$ $(M+H)^+$, 301.1950, found 301.1950.

*Minor product **6b** or **7b** could not be isolated due to instability during the purification by silica gel chromatography or preparative TLC.

(3*S*,6*S*)-2,5-Diethoxy-3,6-dihydro-3-isopropyl-6-piperonyl-6-methylsulfanylpyrazine 8a: oil; $[\alpha]_D^{25}$ –9.2 (c 0.33, $CHCl_3$); IR (liquid film) ν_{max} 1646 (C=C) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.68 (3H, d, *J* = 6.9 Hz, *i*Pr-C*H*$_3$), 0.97 (3H, d, *J* = 6.9 Hz, *i*Pr-C*H*$_3$), 1.29 (3H, t, *J* = 7.1 Hz, -OCH$_2$C*H*$_3$), 1.37 (3H, t, *J* = 7.1 Hz, -OCH$_2$C*H*$_3$), 2.11 (3H, s, -SC*H*$_3$), 2.21 (1H, sept d, *J* = 6.9, 3.7 Hz, -C*H*(CH_3)$_2$), 3.01 (1H, d, *J* = 12.8 Hz, ArCH*H*-), 3.20 (1H, d, *J* = 3.7 Hz, H-3), 3.32 (1H, d, *J* = 12.8 Hz, ArC*H*H-), 4.06–4.30 (4H, m, -OC*H*$_2$CH$_3$), 5.89 (1H, d, *J* = 1.6 Hz, -OCH*H*O-), 5.90 (1H, d, *J* = 1.6 Hz, -OC*H*HO-), 6.52 (1H, dd, *J* = 7.8, 1.6 Hz, Ar-H), 6.55 (1H, d, *J* = 1.6 Hz, Ar-H), 6.62 (1H, d, *J* = 7.8 Hz, Ar-H); ^{13}C-NMR ($CDCl_3$) δ 12.8 (q), 14.4 (q), 14.5 (q), 17.2 (q), 19.5 (q), 30.6 (d), 45.6 (t), 60.4 (d), 60.9 (t), 61.0 (t), 67.3 (s), 100.7 (t), 107.7 (d), 110.5 (d), 123.3 (d), 129.9 (s), 146.2 (s), 146.9 (s), 159.7 (s), 164.5 (s); HRMS *m/z* calcd for $C_{20}H_{28}N_2O_4S$ $(M)^+$ 392.1769, found 392.1765.

Ethanolysis of 6-methylsulfanyl-bislactim ether

General procedure (Scheme 5): Compound **3a** (19.3 mg, 0.061 mmol) was dissolved in 0.2 M TFA

solution in ethanol (1.22 mL). After stirring for 6 days at rt, the reaction mixture was evaporated directly to afford a crude residue that was purified by preparative TLC (solvent: hexane:EtOAc = 10:1) to give **9** (15.7 mg, 86%).

6-Benzyl-2,5-diethoxy-3-isopropylpyrazine 9: oil; IR (liquid film) ν_{max} 1636 (C=C), 1495 (C=C) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.18 (6H, d, *J* = 6.9 Hz, ArCH(C*H*$_3$)$_2$), 1.33 (3H, t, *J* = 7.1 Hz, -OCH$_2$C*H*$_3$), 1.35 (3H, t, *J* = 7.1 Hz, -OCH$_2$C*H*$_3$), 3.22 (1H, sept, *J* = 6.9 Hz, ArC*H*(CH$_3$)$_2$), 3.99 (2H, s, PhC*H*$_2$-), 4.30 (2H, q, *J* = 7.1 Hz, -OC*H*$_2$CH$_3$), 4.32 (2H, q, *J* = 7.1 Hz, -OC*H*$_2$CH$_3$), 7.17 (1H, t, *J* = 7.1 Hz, Ar-H), 7.25(1H, t, *J* = 7.1 Hz, Ar-H), 7.35 (1H, t, *J* = 7.1 Hz, Ar-H); ^{13}C-NMR ($CDCl_3$) δ 14.7 (q), 14.8 (q), 20.7 (q), 28.8 (d), 37.8 (t), 61.7 (t), 61.8 (t), 125.9 (d), 128.1 (d), 129.2 (d), 136.1 (s), 139.5 (s), 143.9 (s), 151.3 (s), 151.9 (s); HRMS *m/z* calcd for $C_{18}H_{24}N_2O_2$ $(M)^+$ 300.1837, found 300.1834.

2,5-Diethoxy-3-isopropyl-6-methylpyrazine 10: oil; IR (liquid film) ν_{max} 1637 (C=C) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.20 (6H, d, *J* = 6.9 Hz, ArCH(C*H*$_3$)$_2$), 1.35 (3H, t, *J* = 7.1 Hz, -OCH$_2$C*H*$_3$), 1.36 (3H, t, *J* = 7.1Hz, -OCH$_2$C*H*$_3$), 2.32 (3H, s, 6-C*H*$_3$), 3.25 (1H, sept, *J* = 6.9Hz, ArC*H*(CH$_3$)$_2$), 4.30 (2H, q, *J* = 7.1Hz, -OC*H*$_2$CH$_3$), 4.34 (2H, q, *J* = 7.1 Hz, -OC*H*$_2$CH$_3$); ^{13}C-NMR ($CDCl_3$) δ 14.8 (q), 14.9 (q), 18.0 (q), 20.8 (q), 28.7 (d), 61.7 (t), 61.8 (t), 134.4 (s), 143.0 (s), 151.1 (s), 152.4 (s); HRMS *m/z* calcd for $C_{12}H_{20}N_2O_2$ $(M)^+$ 224.1524, found 224.1523.

2,5-Diethoxy-6-ethyl-3-isopropylpyrazine 11: oil; IR (liquid film) ν_{max} 1635 (C=C) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.20 (6H, d, *J* = 6.9 Hz, ArCH(C*H*$_3$)$_2$), 1.22 (3H, t, *J* = 7.6 Hz, ArCH$_2$C*H*$_3$), 1.356 (3H, t, *J* = 7.1Hz, -OCH$_2$C*H*$_3$), 1.358 (3H, t, *J* = 7.1Hz, -OCH$_2$C*H*$_3$), 2.68 (2H, q, *J* = 7.6 Hz, ArC*H*$_2$CH$_3$), 3.25 (1H, sept, *J* = 6.9Hz, ArC*H*(CH$_3$)$_2$), 4.33 (2H, q, *J* = 7.1Hz, -OC*H*$_2$CH$_3$), 4.34 (2H, q, *J* = 7.1 Hz, -OC*H*$_2$CH$_3$); ^{13}C-NMR ($CDCl_3$) δ 11.8 (q), 14.8 (q), 20.8 (q), 24.5 (t), 28.7 (d), 61.6 (t), 61.7 (t), 134.4 (s), 139.0 (s), 142.7 (s), 151.2 (s), 151.9 (s); HRMS *m/z* calcd for $C_{13}H_{22}N_2O_2$ $(M)^+$ 238.1681, found 238.1684.

2,5-Diethoxy-3,6-diisopropylpyrazine 12: oil; IR (liquid film) ν_{max} 1635 (C=C) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.20 (12H, d, *J* = 6.9 Hz, ArCH(C*H*$_3$)$_2$), 1.35 (6H, t, *J* = 7.1Hz, -OCH$_2$C*H*$_3$), 3.24 (1H, sept, *J* = 6.9Hz, ArC*H*(CH$_3$)$_2$), 4.34 (4H, q, *J* = 7.1 Hz, -OC*H*$_2$CH$_3$); ^{13}C-NMR ($CDCl_3$) δ 14.9 (q), 20.9 (q), 28.7 (d), 61.5 (t), 142.4 (s), 151.1 (s); HRMS *m/z* calcd for $C_{14}H_{24}N_2O_2$ $(M)^+$ 252.1837, found 252.1834.

2,5-Diethoxy-3-isopropyl-6-piperonylpyrazine 13: oil; IR (liquid film) ν_{max} 1635 (C=C), 1504 (C=C) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.18 (6H, d, *J* = 6.9 Hz, ArCH(C*H*$_3$)$_2$), 1.34 (3H, t, *J* = 6.8 Hz, -OCH$_2$C*H*$_3$), 1.36 (3H, t, *J* = 6.8 Hz, -OCH$_2$C*H*$_3$), 3.23 (1H, sept, *J* = 6.9 Hz, ArC*H*(CH$_3$)$_2$), 3.89 (2H, s, -C*H*$_2$Ar), 4.31 (2H, q, *J* = 6.8 Hz, -OC*H*$_2$CH$_3$), 4.33 (2H, q, *J* = 6.8 Hz, -OC*H*$_2$CH$_3$), 6.73 (1H, d, *J* = 8.0 Hz, Ar-H), 6.81 (1H, dd, *J* = 8.0, 1.6 Hz, Ar-H), 6.87 (1H, d, *J* = 1.6 Hz, Ar-H); ^{13}C-NMR ($CDCl_3$) δ 14.77 (q), 14.84 (q), 20.7 (2x q), 28.8 (d), 37.4 (t), 61.75 (t), 61.78 (t), 100.7 (t), 107.9 (d), 109.7 (d), 122.0 (d), 133.3 (s), 136.1 (s), 144.0 (s), 145.7 (s), 147.3 (s), 151.3 (s), 151.8 (s); HRMS *m/z* calcd for

$C_{19}H_{24}N_2O_4$ $(M)^+$ 344.1736, found 344.1739.

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