

SYNTHESIS OF OPC-15161

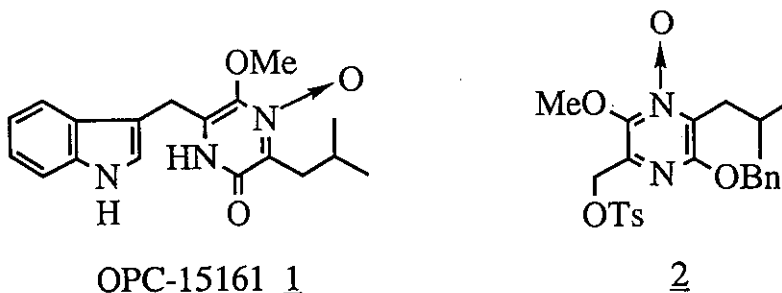
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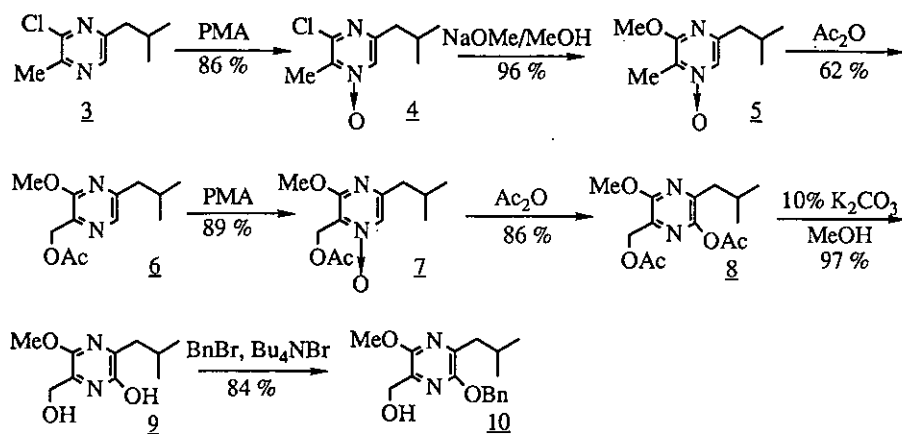
Abstract --- OPC-15161 (1), an inhibitor of superoxide anion generation by guinea pig macrophages, was synthesized from 5-chloro-3-isobutyl-6-methylpyrazine in several steps.

Some natural compounds, such as astechrome, *Cypridina* luciferin and OPC-15161 (1), consist of indole and pyrazine rings.¹⁻³ OPC-15161 (1), an inhibitor of superoxide anion generation by guinea pig macrophages, was recently obtained as a major degradation product of OPC-15160, which was isolated from the culture broth of the fungus *Thielavia minor* OFR-1561.³ This substance had been previously synthesized by Kita *et al.*⁴ from tryptophan methyl ester and by Ito *et al.*⁵ from 2-(hydroxyimino)-4-methyl pentanoic acid and ethyl aminocynoacetate.



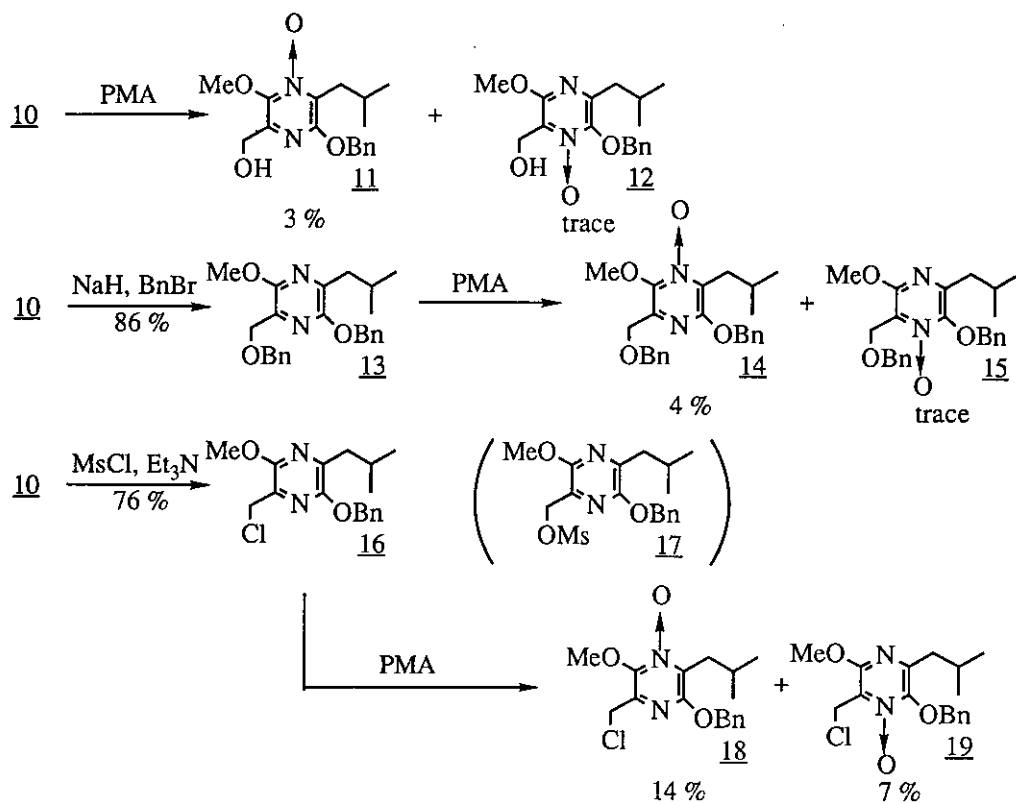
We were interested in the synthesis of these compounds and recently reported the coupling reaction⁶ between indolylmagnesium bromide and tosyloxymethylpyrazines. To apply the reported method⁶ to the synthesis of 1, the synthesis of 2-benzyloxy-3-isobutyl-5-methoxy-6-tosyloxymethylpyrazine 4-oxide (2) was attempted. However, the synthesis of 2 was unsuccessful. In this report, we describe a third method for synthesizing OPC-15161 from 5-chloro-3-isobutyl-6-methylpyrazine (3)⁷ as the starting material *via* 2-benzyloxy-

6-iodomethyl-3-isobutyl-5-methoxy-pyrazine 4-oxide (20).



Scheme 1

Compound 3⁷ was oxidized with permaleic acid (PMA) to produce the corresponding 1-oxide (4). The position of the N-oxide group was determined on the basis of the ¹H-nmr spectra of the products.^{8,9} Replacement of the chlorine atom of 4 with sodium methoxide in absolute methanol produced 3-isobutyl-5-methoxy-6-methylpyrazine 1-oxide (5), which was then converted to 6-acetoxymethyl-3-isobutyl-5-methoxy-pyrazine (6) by reflux in acetic anhydride. In order to introduce a hydroxyl group into the pyrazine ring, 6 was oxidized with PMA to give 7, which was then converted to 2-acetoxy-6-acetoxymethyl-3-isobutyl-5-methoxy-pyrazine (8) by the reaction with acetic anhydride. After hydrolyzing 8 in 10% K₂CO₃, the product, 2-hydroxy-6-hydroxymethyl-3-isobutyl-5-methoxy-pyrazine (9) was selectively O-benzylated with benzyl bromide under phase transfer catalysis conditions to give 2-benzyloxy-6-hydroxymethyl-3-isobutyl-5-methoxy-pyrazine (10). The oxidation of 10 was then attempted. Direct oxidation with an oxidant, such as PMA or MCPBA, gave a mixture of the desired 2-benzyloxy-6-hydroxymethyl-3-isobutyl-5-methoxy-pyrazine 4-oxide (11) and the isomeric 1-oxide (12). Compounds (11) and (12) were separated from each other by column chromatography, but their yields were very poor. Therefore, we attempted oxidation of the benzyl ether (13), after protecting the hydroxyl group of 10, but with an even less satisfactory result (Scheme 2).



Scheme 2

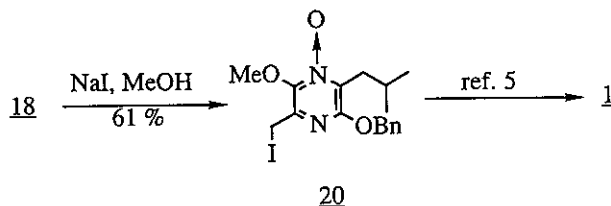
Compound (10) was treated with tosyl chloride in the presence of some bases, such as triethylamine, butyl lithium and sodium hydride. However, the starting material (10) was recovered in all cases. When 10 was treated with mesyl chloride in the presence of triethylamine, in the hope of producing the mesylated compound (17), the chlorinated substance (16) was obtained at a yield of 76%. Accordingly, the oxidation of 2-benzyloxy-6-chloro-methyl-3-isobutyl-5-methoxypyrazine (16) was studied under various reaction conditions and the results are shown in Table 1. The products, 4-oxide (18) and 1-oxide (19), were separable from each other by medium pressure liquid chromatography.

Table 1. The oxidation of 16 (Reaction Time : 8 h ; Reaction Temperature: reflux)

Entry	Oxidant	Solvent	Oxidant/ <u>16</u> (molar ratio)	Yield(%)	
				<u>18</u>	<u>19</u>
1	PMA	CHCl ₃	2.5	13	9
2	PMA	CHCl ₃	4	14	7
3	PMA	CHCl ₃	10	9	7
4	PMA	ClCH ₂ CH ₂ Cl	5	14	8
5	MCPBA	CHCl ₃	5	0	0

The coupling reaction between indole and 18 was then conducted by two methods, using indolylmagnesium bromide and indolylzinc chloride. However, both methods caused the formation of many products which could not be separated.

Consequently, 18 was converted to 2-benzyloxy-6-iodomethyl-3-isobutyl-5-methoxypyrazine 4-oxide (20) by treatment with sodium iodide under heating in methanol. Compound 20 is an intermediate for the synthesis of 1.⁵ Thus the formal synthesis of 1 was accomplished (Scheme 3).



Scheme 3

EXPERIMENTAL

The melting and boiling points are uncorrected. Distillation of the liquid products was conducted using a micro boiling apparatus (Sibata, Model G70-250RS). Medium-pressure column chromatography was conducted using a UVILOG ALPC-100 as the pump, UVILOG 5IIIa as the UV detector (Oyo Bunko Kiki Co. Ltd., Tokyo) and Kiesel gel 60 (Merck AG, Darmstadt) as the packing material.

$^1\text{H-Nmr}$ spectral data were obtained with a Varian Gemini-300 in CDCl_3 using TMS as the internal standard. Other spectral data were obtained using the following instruments. Ir spectra: Japan Spectroscopic Co. A-100; Ms: Hitachi M-80 spectrometer.

Oxidation of 5-Chloro-3-isobutyl-6-methylpyrazine (3): A solution of **3** (5.0 g, 27.2 mmol), 60% H_2O_2 (2.0 g, 35.1 mmol) and maleic anhydride (4.0 g, 40.8 mmol) in CHCl_3 (100 ml) was stirred overnight at room temperature. The reaction mixture was then washed successively with H_2O , 10% KHCO_3 and H_2O . The organic layer was worked up as usual to give a mixture, which was purified by silica gel column chromatography with hexane containing an increasing amount of AcOEt to produce **4** as colorless needles (from MeOH- H_2O); mp 62-63°C; yield: 4.7 g (86%); ms: m/z 200 (M^+); $^1\text{H-nmr}$: 0.98 (d, $J = 7$ Hz, 6H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.15 (m, 1H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.55 (d, $J = 7$ Hz, 2H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.59 (s, 3H, pyrazine CH_3), 7.95 (s, 1H, pyrazine H) ppm; Anal. Calcd for $\text{C}_9\text{H}_{13}\text{N}_2\text{OCl}$: C, 53.87; H, 6.53; N, 13.96. Found: C, 53.84; H, 6.52; N, 13.92.

Synthesis of 3-Isobutyl-5-methoxy-6-methylpyrazine 1-Oxide (5): In a NaOMe-MeOH solution, prepared from abs. MeOH (115 ml) and sodium (2.5 g, 108.7 mg atom), **4** (4.4 g, 21.8 mmol) was heated under reflux for 2 h. After the solvent was removed by distillation in vacuo, the residue was triturated with water and extracted with Et_2O . The extract was worked up as usual to give a crystalline mass, which was recrystallized from MeOH- H_2O to produce 4.1 g (96%) of **5** as colorless needles; mp 60-62°C; ms: m/z 196 (M^+); $^1\text{H-nmr}$: 0.94 (d, $J = 7$ Hz, 6H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$); 2.10 (m, 1H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.38 (s, 3H, pyrazine CH_3), 2.43 (d, $J = 6$ Hz, 2H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 3.98 (s, 3H, OCH_3), 7.67 (s, 1H, pyrazine H) ppm; Anal. Calcd for $\text{C}_{10}\text{H}_{16}\text{N}_2\text{O}_2$: C, 61.20; H, 8.22; N, 14.28. Found: C, 61.10; H, 8.17; N, 14.27.

Reaction of 3-Isobutyl-5-methoxy-6-methylpyrazine 1-Oxide (5) with Acetic Anhydride: A solution of **5** (1.9 g, 9.7 mmol) in Ac_2O (60 ml) was refluxed for 1 h and poured into ice-water. The solution was made alkaline with powdered K_2CO_3 and extracted with Et_2O . A standard work-up of the extract produced a dark-brown oil, which was purified by distillation to give 1.4 g (62%) of **6** as a colorless oil; bp 145-7°C/3 torr; ms: m/z 238 (M^+); ir (neat): 1750 (C=O) cm^{-1} ; $^1\text{H-nmr}$: 0.96 (d, $J = 7$ Hz, 6H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.14 (m, 1H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.16 (s, 3H, $\text{CH}_2\text{OCOCH}_3$), 2.55 (d, $J = 7$ Hz, 2H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 3.98 (s, 3H, CH_3O), 5.22 (s, 2H, $\text{CH}_2\text{OCOCH}_3$), 7.93 (s, 1H,

pyrazine H) ppm; Anal. Calcd for $C_{12}H_{18}N_2O_3$: C, 60.49; H, 7.61; N, 11.76. Found: C, 60.45; H, 7.62; N, 11.71.

Oxidation of 6-Acetoxyethyl-3-isobutyl-5-methoxypyrazine (6): A solution of 6 (800 mg, 3.4 mmol), 60% H_2O_2 (200 mg, 4.3 mmol), and maleic anhydride (600 mg, 6.6 mmol) in $CHCl_3$ (15 ml) was stirred overnight at room temperature. The reaction mixture was treated similarly to the oxidation of 3, and the product was purified by distillation to give 800 mg (89%) of 7 as a colorless oil; bp 150-160°C/1 torr; ms: m/z 254 (M^+); ir (neat): 1740 (C=O) cm^{-1} ; 1H -nmr: 0.96 (d, J = 7 Hz, 6H, $CH_2CH(CH_3)_2$), 2.09 (s, 3H, CH_2COCH_3), 2.17 (m, 1H, $CH_2CH(CH_3)_2$), 2.47 (d, J = 7 Hz, 2H, $CH_2CH(CH_3)_2$), 4.00 (s, 3H, CH_3O), 5.33 (s, 2H, CH_2OCOCH_3), 7.88 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_{12}H_{18}N_2O_4$: C, 56.68; H, 7.14; N, 11.02. Found: C, 56.70; H, 7.17; N, 11.01.

Reaction of 6-Acetoxyethyl-3-isobutyl-5-methoxypyrazine 1-Oxide (7) with Acetic Anhydride: A solution of 7 (100 mg, 0.4 mmol) in Ac_2O (2.5 ml) was treated similarly to the reaction of 5 with Ac_2O . The product was purified by distillation to produce 100 mg (86%) of 8 as a colorless oil; bp 155-165°C/1 torr; ms: m/z 296 (M^+); ir (neat): 1750 (C=O), 1780 (C=O) cm^{-1} ; 1H -nmr: 0.96 (d, J = 7 Hz, 6H, $CH_2CH(CH_3)_2$), 2.12 (s, 3H, CH_2OCOCH_3), 2.16 (m, 1H, $CH_2CH(CH_3)_2$), 2.34 (s, 3H, $OCOCH_3$), 2.49 (d, J = 7 Hz, 2H, $CH_2CH(CH_3)_2$), 3.98 (s, 3H, OCH_3), 5.15 (s, 2H, CH_2OCOCH_3) ppm; Anal. Calcd for $C_{14}H_{20}N_2O_5$: C, 56.75; H, 6.80; N, 9.45. Found: C, 56.59; H, 6.80; N, 9.33.

Hydrolysis of 2-Acetoxy-6-acetoxyethyl-3-isobutyl-5-methoxypyrazine (8): A solution of 8 (11.4 g, 38.5 mmol) in a mixture of 10% K_2CO_3 (115 ml) and MeOH (115 ml) was stirred for 0.5 h at room temperature, followed by removal of the solvent by distillation in vacuo. Water was added to the residue and the solution was extracted with Et_2O . After a standard work-up, the crude products were recrystallized from hexane to produce 8.0 g (97%) of 9 as colorless needles; mp 110-113°C; ms: m/z 212 (M^+); ir (KBr): 3100 (OH) cm^{-1} ; 1H -nmr: 0.94 (d, J = 6 Hz, 6H, $CH_2CH(CH_3)_2$), 2.17 (m, 1H, $CH_2CH(CH_3)_2$), 2.62 (d, J = 7 Hz, 2H, $CH_2CH(CH_3)_2$), 3.92 (s, 3H, OCH_3), 4.68 (s, 2H, CH_2OH) ppm; Anal. Calcd for $C_{10}H_{16}N_2O_3$: C, 56.59; H, 7.60; N, 13.20. Found: C, 56.30; H, 7.52; N, 13.12.

Benylation of 2-Hydroxy-6-hydroxyethyl-3-isobutyl-5-methoxypyrazine (9): Ten percent NaOH (120 ml) was added at room temperature to a mixture of 9 (3.0 g, 14.2 mmol), BnBr (1.9 ml, 15.7 mmol), and a catalytic amount of

tetrabutylammonium bromide in CH_2Cl_2 (120 ml). After ultrasound was applied to the reaction mixture for 3 h, the mixture was made acidic with 5% HCl and extracted with CH_2Cl_2 . The organic layer received a standard work-up followed by silica gel column chromatography with hexane containing an increasing amount of AcOEt, to give 3.6 g (84%) of 10; colorless prisms (from hexane); mp 55-57°C; ms: m/z 302 (M^+); ir (KBr): 3475 (OH) cm^{-1} ; $^1\text{H-nmr}$: 0.96 (d, J = 7 Hz, 6H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.19 (m, 1H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.65 (d, J = 7 Hz, 2H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 3.93 (s, 3H, OCH_3), 4.66 (s, 2H, CH_2OH), 5.36 (s, 2H, $\text{OCH}_2\text{C}_6\text{H}_5$), 7.26-7.45 (m, 5H, $\text{OCH}_2\text{C}_6\text{H}_5$) ppm; Anal. Calcd for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_3$: C, 67.53; H, 7.33; N, 9.29. Found: C, 67.37; H, 7.33; N, 9.19.

Oxidation of 2-Benzyloxy-6-hydroxymethyl-3-isobutyl-5-methoxypyrazine (10):

A solution of 10 (1.0 g, 3.3 mmol), 60% H_2O_2 (400 mg, 6.3 mmol) and maleic anhydride (600 mg, 6.3 mmol) in CHCl_3 (157 ml) was refluxed for 4 h, and then treated similarly to the oxidation of 3. The reaction mixture was purified by silica gel chromatography. Compounds 12 (trace) and 11 (31.5 mg, 3%) were successively eluted with hexane containing an increasing amount of AcOEt.

2-Benzyloxy-6-hydroxymethyl-3-isobutyl-5-methoxypyrazine 4-Oxide (11):

colorless prisms (from hexane- Et_2O); mp 65-66°C (lit.⁵; mp 68.0-69.2°C); The spectral data agreed with the previous report.⁵

2-Benzyloxy-6-hydroxymethyl-3-isobutyl-5-methoxypyrazine 1-Oxide (12): a

viscous oil; CI-ms: m/z 319 ($\text{M}^+ + 1$); $^1\text{H-nmr}$: 0.87 (d, J = 7 Hz, 6H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.11 (m, 1H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.43 (d, J = 7 Hz, 2H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 3.69 (s, 3H, OCH_3), 4.87 (s, 2H, CH_2OH), 5.31 (s, 2H, $\text{OCH}_2\text{C}_6\text{H}_5$), 7.36-7.40 (m, 5H, $\text{OCH}_2\text{C}_6\text{H}_5$) ppm.

Benylation of 2-Benzyloxy-6-hydroxymethyl-3-isobutyl-5-methoxypyrazine (10):

A solution of 10 (100 mg, 0.3 mmol) in dry THF (2 ml) was added to a suspension of NaH (15 mg, 0.4 mmol) in dry THF (1 ml). BnBr (0.04 ml, 0.4 mmol) was added after the solution had been stirred at room temperature for 1 h. The reaction mixture was stirred overnight at room temperature, washed with H_2O and dried over Na_2SO_4 . After a standard work-up of the organic layer, the product was purified by silica gel column chromatography, eluting with hexane containing an increasing amount of AcOEt, to produce 13 (100 mg, 86%) as a colorless oil; ms: m/z 392 (M^+); $^1\text{H-nmr}$: 0.93 (d, J = 7 Hz, 6H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.18 (m, 1H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.64 (d, J = 7 Hz, 2H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 3.91 (s, 3H, OCH_3), 4.47 (s, 2H, $\text{CH}_2\text{OCH}_2\text{C}_6\text{H}_5$), 4.60 (s, 2H, $\text{CH}_2\text{OCH}_2\text{C}_6\text{H}_5$),

5.37 (s, 2H, $\text{CH}_2\text{C}_6\text{H}_5$), 7.25-7.46 (m, 10H, $\text{CH}_2\text{OCH}_2\text{C}_6\text{H}_5$ and $\text{OCH}_2\text{C}_6\text{H}_5$) ppm.

Oxidation of 2-Benzyloxy-6-benzyloxymethyl-3-isobutyl-5-methoxy-pyrazine (13):

A solution of 13 (100 mg, 0.3 mmol), 60% H_2O_2 (32 mg, 0.6 mmol) and maleic anhydride (55.4 mg, 0.6 mmol) in CHCl_3 (6 ml) was refluxed for 4 h. The reaction mixture was then treated similarly to the oxidation of 3. The reaction mixture was applied to a silica gel column and 15 (trace) and 14 (4.9 mg, 4%) were successively eluted with hexane containing an increasing amount of AcOEt.

2-Benzyloxy-6-benzyloxymethyl-3-isobutyl-5-methoxy-pyrazine 4-Oxide (14): a viscous oil; CI-*ms*: *m/z* 409 ($\text{M}^+ + 1$); $^1\text{H-nmr}$: 0.94 (d, $J = 7$ Hz, 6H,

$\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.23 (m, 1H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.83 (d, $J = 7$ Hz, 2H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$),

4.02 (s, 3H, OCH_3), 4.59 (s, 2H, $\text{CH}_2\text{OCH}_2\text{C}_6\text{H}_5$), 4.66 (s, 2H, $\text{CH}_2\text{OCH}_2\text{C}_6\text{H}_5$),

5.40 (s, 2H, $\text{OCH}_2\text{C}_6\text{H}_5$), 7.32-7.44 (m, 10H, $\text{OCH}_2\text{C}_6\text{H}_5$ and $\text{CH}_2\text{OCH}_2\text{C}_6\text{H}_5$) ppm.

2-Benzyloxy-6-benzyloxymethyl-3-isobutyl-5-methoxy-pyrazine 1-Oxide (15):

$^1\text{H-nmr}$: 0.86 (d, $J = 7$ Hz, 6H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.17 (m, 1H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.42

(d, $J = 7$ Hz, 2H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 3.92 (s, 3H, OCH_3), 4.71 (s, 2H, $\text{CH}_2\text{OCH}_2\text{C}_6\text{H}_5$),

4.84 (s, 2H, $\text{CH}_2\text{OCH}_2\text{C}_6\text{H}_5$), 5.30 (s, 2H, $\text{OCH}_2\text{C}_6\text{H}_5$), 7.33-7.47 (m, 10H, $\text{OCH}_2\text{C}_6\text{H}_5$ and $\text{CH}_2\text{OCH}_2\text{C}_6\text{H}_5$) ppm.

Mesylation of 2-Benzyloxy-6-hydroxymethyl-3-isobutyl-5-methoxy-pyrazine (10):

A solution of 10 (1.0 g, 3.3 mmol), Et_3N (0.9 ml, 6.6 mmol) in dry CH_2Cl_2 (10 ml) was added to MsCl (0.3 ml, 3.4 mmol) at 0°C . After stirring at room temperature overnight, water was added to the reaction mixture. The organic layer was separated and the water layer was extracted with CH_2Cl_2 . The combined CH_2Cl_2 extract was worked up as usual to produce a crude product,

which was purified by silica gel column chromatography. Compound (16) (810 mg,

76%) was obtained; colorless needles (from hexane); mp $52-53^\circ\text{C}$; *ms*: *m/z* 320

(M^+); $^1\text{H-nmr}$: 0.95 (d, $J = 7$ Hz, 6H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.19 (m, 1H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$),

2.66 (d, $J = 7$ Hz, 2H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 3.97 (s, 3H, OCH_3), 4.65 (s, 2H, CH_2Cl),

5.36 (s, 2H, $\text{OCH}_2\text{C}_6\text{H}_5$), 7.25-7.48 (m, 5H, $\text{OCH}_2\text{C}_6\text{H}_5$) ppm; Anal. Calcd for

$\text{C}_{17}\text{H}_{21}\text{N}_2\text{O}_2\text{Cl}$: C, 63.64; H, 6.60; N, 8.73. Found: C, 63.69; H, 6.58; N, 8.88.

Oxidation of 2-Benzyloxy-6-chloromethyl-3-isobutyl-5-methoxy-pyrazine (16):

A solution of 16 (51 mg, 0.2 mmol), 60% H_2O_2 (44 mg, 0.8 mmol) and maleic anhydride (78 mg, 0.8 mmol) in CHCl_3 (2.5 ml) was refluxed for 8 h. The

reaction mixture was then treated similarly to the oxidation of 3. The crude

products were purified by silica gel column chromatography. Compounds (19) (3.7 mg, 7%) and (18) (7.3 mg, 14%) were successively eluted with hexane containing an increasing amount of AcOEt.

2-Benzyloxy-6-chloromethyl-3-isobutyl-5-methoxypyrazine 4-Oxide (18):

colorless prisms (from pentane); mp 61-63°C; CI-*ms*: *m/z* 337 ($M^+ + 1$), $^1\text{H-nmr}$: 0.94 (d, $J = 7$ Hz, 6H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.23 (m, 1H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.83 (d, $J = 7$ Hz, 2H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 4.12 (s, 3H, OCH_3), 4.60 (s, 2H, CH_2Cl), 5.40 (s, 2H, $\text{OCH}_2\text{C}_6\text{H}_5$), 7.32-7.48 (m, 5H, $\text{OCH}_2\text{C}_6\text{H}_5$) ppm; *Anal.* Calcd for $\text{C}_{17}\text{H}_{21}\text{N}_2\text{O}_3\text{Cl}$: C, 60.62; H, 6.28; N, 8.32. Found: C, 60.64; H, 6.23; N, 8.38.

2-Benzyloxy-6-chloromethyl-3-isobutyl-5-methoxypyrazine 1-Oxide (19): *ms*:

a viscous oil; *m/z* 336 (M^+); $^1\text{H-nmr}$: 0.87 (d, $J = 7$ Hz, 6H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.18 (m, 1H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.44 (d, $J = 7$ Hz, 2H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 3.98 (s, 3H, OCH_3), 4.86 (s, 2H, CH_2Cl), 5.35 (s, 2H, $\text{OCH}_2\text{C}_6\text{H}_5$), 7.34-7.47 (m, 5H, $\text{OCH}_2\text{C}_6\text{H}_5$) ppm.

Synthesis of 2-Benzyloxy-6-iodomethyl-3-isobutyl-5-methoxypyrazine 4-Oxide

(20): A solution of 18 (14.7 mg, 0.04 mmol), NaI (13 mg, 0.09 mmol) in MeOH (0.5 ml) was refluxed for 4 h. After evaporation of the solvent, water was added, and the mixture was extracted with Et_2O . The extract was worked up as usual and the residue was subjected to preparative TLC on silica gel (hexane: AcOEt 7:3) to produce 20 (11.4 mg, 61%) as a colorless needles (from hexane- Et_2O); mp 75-77°C (lit.⁵ 78.3-79.5°C). The spectral data agreed with the previous report.⁵

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