by dissolving in the minimum amount of EtOH and precipitation by ethyl acetate addition (0.76 g; 55%): mp 220 °C dec. Anal. Calcd for $C_{19}H_{12}NBrH_2O$: C, 64.78; H, 4.00; N, 3.97. Found: C, 63.60; H, 3.84; N, 4.07. Metathesis with HPF_6 (70%) yields the hexafluorophosphate, recrystallized from $EtOH/CH_3CN$: λ_{max} (EtOH) 260 (4.03), 274 (3.99), 410 (sh, 3.75), 448 (3.82), 460 (sh, 3.55). Anal. Calcd for $C_{19}H_{12}NPF_6$: C, 57.15; H, 3.03; N, 3.51. Found: C, 56.97; H, 3.05; N, 3.52.

2,3-Dimethylquinolizinium Hexafluorophosphate (6b). It has been prepared following ref 24: ^1H δ 9.21 (H_1), 8.37 (H_4), 8.38 (H_5), 8.25 (H_6), 7.99 (H_7), 9.13 (H_8); ^{13}C δ 135.1 (C_1), 134.7 (C_2), 150 (C_3), 125.2 (C_4), 140.8 (C_{4a}), 125.8 (C_5), 135.7 (C_6), 122.8 (C_7), 134 (C_8).

(24) Alvarez-Builla, J.; Gonzalez Trigo, G.; Ezquerra, J.; Fombella, M. E. *J. Heterocycl. Chem.* **1985**, *22*, 681.

Acknowledgment. We are grateful to Dr. G. Mousset (University of Clermont-Ferrand, France) for performing the EPR measurements and to Dr. R. Servin (HNI, AB, Malmö, Sweden) for ^{15}N NMR measurements. A. Politi (University P. and M. Curie, Paris, France) was of great help by performing the EPR simulations. The financial support of M.F. by the University of Copenhagen is gratefully acknowledged.

The First Total Synthesis of OPC-15161

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The first total synthesis of OPC-15161, a novel inhibitor of superoxide generation by guinea pig macrophages, has been accomplished via a convergent and efficient route exploiting the coupling of the fully functionalized pyrazine part with the indolyl group. 2-(Hydroxyimino)-4-methylpentanoic acid and ethyl aminocyanoacetate were condensed with DCC to afford the amide **3**, which was converted to pyrazinone *N*-oxide **4** via intramolecular cyclization between the oxime and cyano groups. O-Benzylation of **4** followed by reduction of the ethoxycarbonyl group by DIBALH gave the aminopyrazine alcohol **7**. The aryl chloride **8** was obtained by the direct substitutive deamination using isoamyl nitrite and copper salts. After protection of the hydroxyl group, the methoxy group was introduced at the 5-position via treatment of 2,5-bis(benzyloxy)pyrazine 4-oxide **10** with methoxide to afford **11**. The methoxy compound **11** was converted to benzylic iodide **14** via deprotection, mesylation, and iodination. The functionalized pyrazine skeleton **14** was coupled with the zinc salt of indole to produce **17**, which upon catalytic hydrogenolysis afforded OPC-15161.

Introduction

A new pyrazinone OPC-15161 (**1**) was isolated by Nakano et al. as a major degradation product of the natural compound OPC-15160, which was obtained from a fermentation broth of the fungus *Thielavia minor* OFR-1561.[1] OPC-15160 and OPC-15161 are novel inhibitors against superoxide anion generation by guinea pig macrophages, and the latter compound is 5 times more active than the parent OPC-15160. These compounds are therapeutically promising since recent studies suggest that inhibitors of superoxide generation are effective in protecting against tissue damage in vitro and in vivo in models of ischemia or inflammation.[2] The structure of OPC-15161 was established by X-ray crystallographic analysis to be 6-(1*H*-indol-3-ylmethyl)-3-isobutyl-5-methoxy-2(1*H*)-pyrazinone 4-oxide.[1] In addition to its therapeutic potential, OPC-15161 is of chemical interest in that it possesses a hitherto unknown highly functionalized skeleton. From a synthetic point of view, construction of such a highly functionalized pyrazine is challenging. Herein, we report the first total synthesis of OPC-15161.

OPC-15161 embodies a functionalized pyrazine ring and an indolyl group. Synthesis of indolyl derivatives often suffer from their instability, and this consideration led us to couple a correctly functionalized pyrazine moiety with indolylmetal at a late stage of the total synthesis to furnish OPC-15161 (Scheme I).

Scheme I

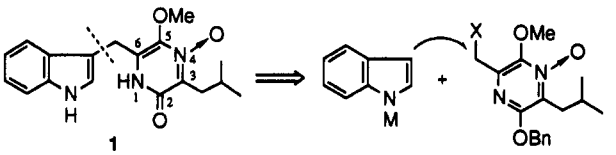

Table I. Substitutive Deamination of the Aminopyrazine Alcohol 7[a]

run	$CuCl_2$/7	CuCl/7	yield of 8,[b] %	yield of 15,[b] %
1	5	0	48	19
2	0	5	13	13
3	3	2	75	10

[a] Reactions were performed in acetonitrile at rt using 3 equiv of isoamyl nitrite. [b] Isolated yields by chromatography.

Synthesis of the Pyrazine Skeleton

The framework of the pyrazine moiety is a cyclodipeptide. To prepare this heterocycle, 2-(hydroxyimino)-4-methylpentanoic acid (**2**) and ethyl aminocyanoacetate[3] were condensed using DCC to afford the amide **3** (Scheme II). Following the procedure reported by Taylor et al.,[4] **3** was converted to the pyrazinone *N*-

(1) Nakano, Y.; Kawaguchi, T.; Sumitomo, J.; Takizawa, T.; Uetsuki, S.; Sugawara, M.; Kido, M. *J. Antibiot.* **1991**, *44*, 52.

(2) (a) Weiss, S. J. *Acta. Physiol. Scand.* **1986**, *548*, 9. (b) Badway, J. A.; Karnovsky, M. L. *Ann. Rev. Biochem.* **1980**, *49*, 695. (c) Freeman, B. A.; Crapo, J. D. *Lab. Invest.* **1986**, *47*, 412. (d) Ward, P. A.; Dugue, R. E.; Sulavik, M. C.; Johnson, K. T. *Am. J. Pathol.* **1983**, *110*, 297. (e) Taniguchi, M.; Urakami, M.; Takanaka, K. *Jpn. J. Pharmacol.* **1988**, *46*, 275.

(3) Logemann, F. I.; Shaw, G. *Chem. Ind.* **1980**, 541.

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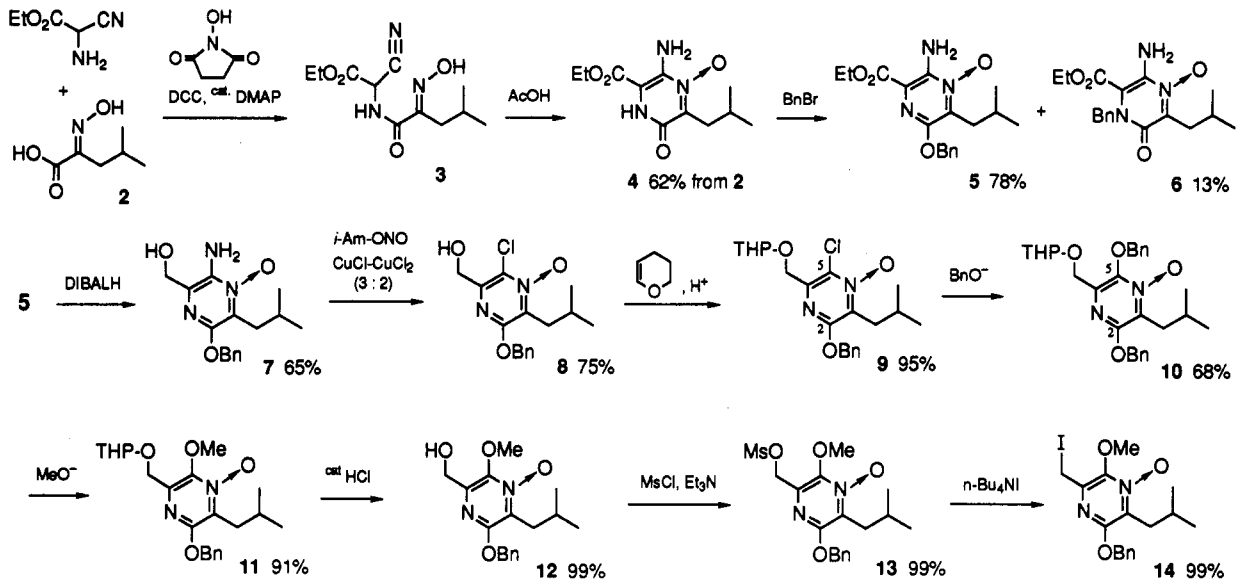
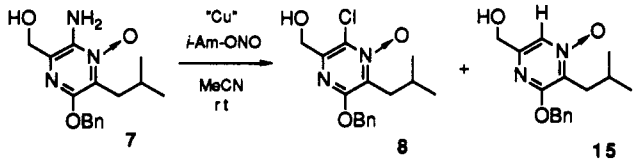
Scheme II



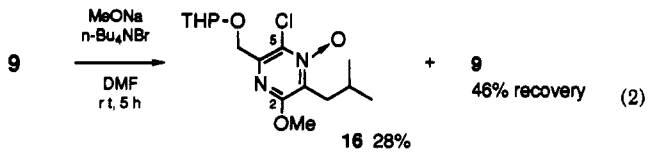
oxide 4 (62% from 2) via intramolecular cyclization of the oxime and cyano groups. Treatment of 4 with benzyl bromide and $KHCO_3$ in DMF gave the desired O-benzylated product 5 in 78% yield along with the N-benzylated 2-pyrazinone derivative 6 (13%). The ethoxycarbonyl group of 5 was selectively reduced by DIBALH to a benzylic primary hydroxyl group in the presence of the N-oxide moiety giving 7 in 65% yield.[5]

Replacement of the aromatic amino group of 7 with the methoxy group was next performed. The amino pyrazine alcohol 7 was converted to the corresponding chloride 8 by direct substitutive deamination using isoamyl nitrite and copper salts.[6] Of note was that the combined use of cupric chloride and cuprous chloride afforded the best yield of 8 (75%) with a minor amount of the reduced product 15 (10%) as shown in Table I. After protection of the



(1)

primary hydroxyl group of 8 as the tetrahydropyranyl ether, the introduction of the methoxy group on the 5-position of 9 was attempted. The direct substitution of the 5-chloro group with methoxy group was unsuccessful, however, because the 2-position of 9 was more reactive toward nucleophilic substitution than the 5-position, leading to the formation of the 2-methoxy-5-chloropyrazine derivative 16 in 28% yield along with recovered 9 (46%).



(2)

Therefore, 9 was converted to 2,5-bis(benzyloxy)pyrazine 4-oxide 10 (68%) prior to the introduction of the methoxy group. The reactivity of the benzyloxy group at the 5-position of 10 was much greater than that at the 2-position because of the adjacent *N*-oxide moiety.[7] Treatment of 10 with methoxide permitted the selective substitution of the benzyloxy group at the 5-position by the methoxy group to produce 11 in 91% yield. The methoxy compound 11 was then converted to the benzylic iodide 14, which is to be ultimately coupled with the indolyl group via deprotection of the tetrahydropyranyl ether (99%), mesylation of the resulting hydroxyl group (99%), and iodination (99%).

Table II. Coupling of Benzylic Iodide 14 with Indolylmetal

run	metal	solvent	conditions	yield of 17,[a] %	yield of 18,[a] %
1	Na	DMSO	rt, 90 min	0	73
2	Na	toluene	rt, 14 h	79	0
3	Li	toluene	−78 °C–rt, 6 h	35	0
4	K	toluene	0 °C–rt, 3 h	67	0
5	Sn(*n*-Bu)$_3$	toluene	80 °C, 14 h	74	0
6	ZnCl	toluene	rt, 1 h	91	0

[a] Isolated yields by chromatography.

Coupling of the Functionalized Pyrazine 14 with Indole

It has been reported that the magnesium salt of indole reacts with electrophiles at the 3-carbon, whereas alkali-metal salts react mainly at the nitrogen.[8] However, the functionalized pyrazine 14 decomposed on treatment with the magnesium salt of indole, giving the desired coupling product 17 in very low yield. The coupling reaction of the functionalized pyrazine skeleton 14 with indole was then studied using a variety of indolylmethyl reagents and solvents (Table II). The selective C-alkylation of 14 was accomplished by the use of the zinc salt of indole in toluene to produce 17 in 91% yield.

Catalytic hydrogenolysis removed the benzyl group to afford OPC-15161 (1) in quantitative yield. Synthetic 1 (mp 225.5–228.0 °C) was identical in all respects with an authentic sample.

(4) Taylor, E. C.; Perlman, K. L.; Sword, I. P.; Sequin-Frey, M.; Jacobi, P. A. *J. Am. Chem. Soc.* **1973**, *95*, 6407.

(5) Use of other reducing reagents such as $LiAlH_4$, $NaBH_4$, and $NaBH_4$–$CaCl_2$ for the reduction of the ester group gave the desired 7 in much lower yields along with several byproducts.

(6) Doyle, M. P.; Siegfried, B.; Dellaria, J. F., Jr. *J. Org. Chem.* **1977**, *42*, 2426.

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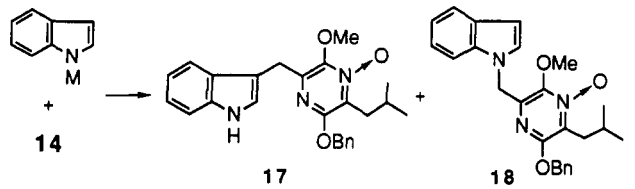
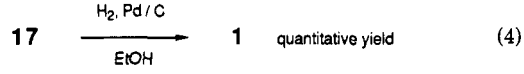


(3)



(4)

This convergent route to OPC-15161, which exploits the efficient coupling of the fully functionalized pyrazine with the indolyl group, affords a versatile and flexible synthetic pathway for the preparation of analogues. Hence, this approach offers the opportunity for evaluating other derivatives for their inhibitory activity against superoxide anion generation.

Experimental Section

General. Unless otherwise noted, materials were obtained from commercial sources and used without further purification. Dioxane was dried with molecular sieves (5A). Tetrahydrofuran (THF), diethyl ether, toluene, and benzene were distilled from $LiAlH_4$ and CH_2Cl_2, dimethylformamide, ethanol, methanol, and acetonitrile from CaH_2. Column chromatography was performed with silica gel 60 (E. Merck, Darmstadt), 230–400 mesh. Preparative thin-layer chromatography was performed with silica gel 60 PF_{254} (E. Merck, Darmstadt). ^1H and ^{13}C NMR spectra were recorded at 200 MHz for ^1H and 50.3 MHz for ^{13}C in chloroform-*d* unless otherwise noted. Carbon chemical shifts were recorded relative to chloroform-*d* (δ 77.0) and DMSO-d_6 (δ 39.5). $MgSO_4$ was used to dry organic layers after extraction in all reactions.

2-(Hydroxyimino)-4-methylpentanoic acid (**2**) was prepared quantitatively by condensation of sodium 4-methyl-2-oxopentanoate with hydroxylamine hydrochloride in methanol.

***N*-[Cyano(ethoxycarbonyl)methyl]-2-(hydroxyimino)-4-methylpentanamide (3).** To a mixture of 2-(hydroxyimino)-4-methylpentanoic acid (**2**, 19.5 g, 134 mmol) and *N*-hydroxysuccinimide (16.2 g, 141 mmol) in dioxane (200 mL) was added 1,3-dicyclohexylcarbodiimide (29.1 g, 141 mmol) in dioxane (50 mL) over 5 min at 0 °C under nitrogen. After the mixture was stirred at rt for 20 min, ethyl aminocyanoacetate[9] (22.0 g, 172 mmol) and 4-(dimethylamino)pyridine (1.64 g, 13.4 mmol) were added and the mixture was heated at 50 °C for 14 h. The precipitated urea was filtered off, and the filtrate was evaporated. The residue was diluted with AcOEt, washed (H_2O, 10% HCl, H_2O, saturated $NaHCO_3$, saturated NaCl), dried, and concentrated in vacuo to give the crude **3** (35.0 g) as brown oil, which was used in the next step without purification: IR (neat) 3358, 2265, 1756, 1673 cm^{-1}, ^1H NMR δ 0.91 (d, J = 7.0 Hz, 6 H), 1.36 (t, J = 7.0 Hz, 3 H), 2.04 (sept, J = 7.0 Hz, 1 H), 2.53 (d, J = 7.0 Hz, 2 H), 4.36 (q, J = 7.0 Hz, 2 H), 5.51 (d, J = 8.0 Hz, 1 H), 7.49 (d, J = 8.0 Hz, 1 H), 7.80 (br s, 1 H).

5-Amino-6-(ethoxycarbonyl)-3-isobutyl-2(1*H*)-pyrazinone 4-Oxide (4). The crude amide (**3**, 35.0 g) was heated at 70 °C for 1 h in acetic acid (400 mL), which was then removed in vacuo. The residue was washed with ethanol and subjected to column chromatography on silica gel (AcOEt:*n*-hexane = 1:1) to give **4** (21.3 g, 62% from **2**): mp 179–181 °C (EtOH); IR (KBr) 3465, 3324, 1714, 1650, 1624, 1244 cm^{-1}; ^1H NMR δ 0.98 (d, J = 7.0 Hz, 6 H), 1.40 (t, J = 7.0 Hz, 3 H), 2.33 (sept, J = 7.0 Hz, 1 H), 2.93 (d, J = 7.0 Hz, 2 H), 4.42 (q, J = 7.0 Hz, 2 H), 6.67 (br s, 2 H), 9.50 (br s, 1 H); ^{13}C NMR (DMSO-d_6) δ 14.23, 22.57, 25.38 33.46, 61.06, 114.39, 137.54, 145.46, 150.12, 165.54. Anal. Calcd for $C_{11}H_{17}N_3O_4$: C, 47.68; H, 4.94; N, 6.54. Found: C, 47.88; H, 4.88; N, 6.54.

5-Amino-2-(benzyloxy)-6-(ethoxycarbonyl)-3-isobutylpyrazine 4-Oxide (5). A mixture of **4** (1.00 g, 3.92 mmol), benzyl bromide (932 μL, 7.84 mmol), and $KHCO_3$ (1.18 g, 11.8 mmol) in DMF (20 mL) was stirred at rt for 16 h under nitrogen. The resultant mixture was diluted with AcOEt, washed with H_2O, dried, and evaporated. Recrystallization of the residue from *n*-hexane afforded **5** as pale yellow needles. Column chromatography on silica gel (AcOEt:*n*-hexane = 2:3) of the mother liquor permitted the isolation of the remaining **5** and **6**. **5** (1.06 g, 78% total): mp 114.5–115.5 °C (EtOH); IR (KBr) 3450, 3334, 1694, 1509, 1151 cm^{-1}; ^1H NMR δ 0.94 (d, J = 7.0 Hz, 6 H), 1.47 (t, J = 7 Hz, 3 H), 2.28 (sept, J = 7.0 Hz, 1 H), 2.91 (d, J = 7.0 Hz, 2 H), 4.44 (q, J = 7.0 Hz, 2 H), 5.36 (s, 2 H), 6.97 (br s, 2 H), 7.30–7.40 (m, 3 H), 7.45–7.55 (m, 2 H); ^{13}C NMR δ 14.18, 22.71, 25.87, 33.56, 61.51, 68.17, 127.87, 128.17, 128.48, 136.64, 138.74, 146.27, 149.42, 166.22. Anal. Calcd for $C_{18}H_{23}N_3O_4$: C, 62.59; H, 6.71; N, 12.17. Found: C, 62.42; H, 6.58; N, 12.12. **6** (178 mg, 13%): ^1H NMR δ 1.00 (d, J = 7.0 Hz, 6 H), 1.19 (t, J = 7.0 Hz, 3 H), 2.34 (sept, J = 7.0 Hz, 1 H), 3.00 (d, J = 7.0 Hz, 2 H), 4.24 (q, J = 7.0 Hz, 2 H), 5.57 (s, 2 H), 6.45 (br s, 2 H), 7.00–7.10 (m, 2 H), 7.20–7.40 (m, 3 H).

5-Amino-2-(benzyloxy)-6-(hydroxymethyl)-3-isobutylpyrazine 4-Oxide (7). To a CH_2Cl_2 solution (14 mL) of **5** (670 mg, 1.94 mmol) was added a *n*-hexane solution of DIBALH (4.7 mL, 4.7 mmol) at −35 °C over 5 min under nitrogen. After the mixture was stirred for 40 min at −30 °C, H_2O (1 mL) was added. The mixture was warmed to rt, diluted with 2% HCl, extracted with CH_2Cl_2, and the extracts were dried and evaporated. The residue was subjected to column chromatography on silica gel (MeOH:CH_2Cl_2 = 7:93) to give **7** (385 mg, 65%): mp 129.0–131.3 °C (benzene); IR (KBr) 3366, 3270, 1140, 1026 cm^{-1}; ^1H NMR δ 0.94 (d, J = 7.0 Hz, 6 H), 2.24 (sept, J = 7.0 Hz, 1 H), 2.86 (d, J = 7.0 Hz, 2 H), 4.69 (s, 2 H), 5.30 (s, 2 H), 7.30–7.50 (m, 5 H); ^{13}C NMR δ 22.64, 26.11, 32.97, 63.69, 68.10, 127.58, 127.73, 128.29, 132.50, 133.27, 136.75, 141.14, 150.62. Anal. Calcd for $C_{16}H_{21}N_3O_3$: C, 63.35; H, 6.98; N, 13.85. Found: C, 63.36; H, 6.97; N, 13.79.

2-(Benzyloxy)-5-chloro-6-(hydroxymethyl)-3-isobutylpyrazine 4-Oxide (8). To a mixture of **7** (2.17 g, 7.15 mmol), $CuCl_2$ (2.89 g, 21.5 mmol), and CuCl (1.42 g, 14.3 mmol) in MeCN (22 mL) was added isoamyl nitrite (2.88 mL, 21.4 mmol) at rt under nitrogen. After being stirred for 30 min, the mixture was diluted with 2% HCl and extracted with ether, and the extracts were dried and evaporated. The residue was subjected to column chromatography on silica gel (AcOEt:*n*-hexane = 5:5 increased to 7:3) to afford **8** (1.73 g, 75%) along with the reduced product (**15**, 210 mg, 10%). **8**: mp 85.0–88,0 °C (*n*-hexane–ether); IR (KBr) 3432, 1170, 1158 cm^{-1}; ^1H NMR δ 0.94 (d, J = 7.0 Hz, 6 H), 2.23 (sept. J = 7.0 Hz, 1 H), 2.86 (d, J = 7.0 Hz, 2 H), 3.31 (t, J = 5.0 Hz, 1 H), 4.70 (d, J = 5.0 Hz, 2 H), 5.43 (s, 2 H), 7.30–7.45 (m, 5 H); ^{13}C NMR δ 22.78, 25.84, 33.34, 61.21, 69.41, 127.75, 128.38, 128.70, 135.85, 136.45, 147.35, 150.43. Anal. Calcd for $C_{16}H_{19}ClN_2O_3$: C, 59.54; H, 5.93; N, 8.68. Found: C, 59.59; H, 5.76; N, 8.54. **15**: ^1H NMR δ 0.91 (d, J = 7.0 Hz, 6 H), 2.20 (sept, J = 7.0 Hz, 1 H), 2.81 (d, J = 7.0 Hz, 2 H), 3.49 (br s, 1 H), 4.62 (br s, 2 H), 5.38 (s, 2 H), 7.30–7.45 (m, 5 H), 7.89 (s, 1 H).

2-(Benzyloxy)-5-chloro-3-isobutyl-6-[(tetrahydropyran-2-yloxy)methyl]pyrazine 4-Oxide (9). A mixture of **8** (65 mg, 0.20 mmol), 3,4-dihydro-2*H*-pyran (40 μL, 0.44 mmol), and *p*-TsOH·H_2O (4 mg, 0.02 mmol) in CH_2Cl_2 (2 mL) was stirred at rt for 1 h, washed with saturated $NaHCO_3$, dried, and evaporated. The residue was subjected to preparative TLC on silica gel (AcOEt:*n*-hexane = 1:3) to afford **9** (78 mg, 95%): IR (neat) 1162, 1121, 1075, 1028 cm^{-1}; ^1H NMR δ 0.93 (d, J = 7.0 Hz, 6 H), 1.50–1.90 (m, 6 H), 2.23 (sept, J = 7.0 Hz, 1 H), 2.85 (d, J = 7.0 Hz, 2 H), 3.50–3.60 (m, 1 H), 3.90–4.00 (m, 1 H), 4.64 (d, J = 12.0 Hz, 1 H), 4.83 (d, J = 12.0 Hz, 1 H), 4.83 (br t, J = 3 Hz, 1 H), 5.42 (s, 2 H), 7.30–7.45 (m, 5 H); ^{13}C NMR δ 18.77, 22.64, 25.19, 25.60, 30.10, 33.33, 61.77, 66.93, 68.76, 98.50, 127.88, 128.02, 128.32, 132.77, 135.93, 136.65, 146.04, 158.16; HRMS calcd for $C_{21}H_{27}ClN_2O_4$ m/z 406.1659, found m/z 406.1679.

2,5-Bis(benzyloxy)-3-isobutyl-6-[(tetrahydropyran-2-yloxy)methyl]pyrazine 4-Oxide (10). To a mixture of **9** (170 mg, 0.42 mmol), Bu_4NBr (72 mg, 0.22 mmol), and benzyl alcohol (230 μL, 2.22 mmol) in DMF (1.5 mL) was added sodium hydride in mineral oil (60%, 42.5 mg, 1.1 mmol) at rt under nitrogen. After being stirred for 40 min, the mixture was diluted with Et_2O, washed with H_2O, dried with $MgSO_4$, and evaporated. The residue was subjected to preparative TLC on silica gel (AcOEt:benzene = 1:9) to afford **10** (136 mg, 68%): IR (neat) 1600, 1500, 1152, 1028 cm^{-1}; ^1H NMR δ 0.94 (d, J = 7.0 Hz, 6 H), 1.45–1.90 (m, 6 H), 2.28 (sept, J = 7.0 Hz, 1 H), 2.85 (d, J = 7.0 Hz, 2 H), 3.45–3.55

(m, 1 H), 3.85–3.95 (m, 1 H), 4.43 (d, J = 11.0 Hz, 1 H), 4.62 (d, J = 11.0 Hz, 1 H), 4.72 (br t, J = 3 Hz, 1 H), 5.30 (d, J = 10.0 Hz, 1 H), 5.36 (d, J = 10.0 Hz, 1 H), 5.38 (s, 2 H), 7.30–7.50 (m, 10 H); ^{13}C NMR δ 18.94, 22.68, 25.23, 25.77, 30.25, 32.87, 61.72, 64.77, 68.35, 74.22, 98.21, 127.81, 127.83, 128.29, 128.35, 128.51, 128.89, 135.65, 136.13, 136.46, 139.54, 148.79, 155.84; HRMS calcd for $C_{28}H_{34}N_2O_5$ m/z 478.2468, found m/z 478.2463.

2-(Benzyloxy)-3-isobutyl-5-methoxy-6-[(tetrahydropyran-2-yloxy)methyl]pyrazine 4-Oxide (11). To a mixture of **10** (65 mg, 0.14 mmol), Bu_4NBr (22 mg, 0.07 mmol), and methanol (55 μL, 1.4 mmol) in DMF (0.65 mL) was added sodium hydride in mineral oil (60%, 11 mg, 0.28 mmol) at rt under nitrogen. After being stirred for 40 min, the mixture was diluted with Et_2O, washed with H_2O, dried, and evaporated. The residue was subjected to preparative TLC on silica gel (AcOEt:n-hexane = 3:7) to afford **11** (50 mg, 91%): IR (neat) 1454, 1368, 1152, 1028 cm^{-1}; ^{1}H NMR δ 0.93 (d, J = 7.0 Hz, 6 H), 1.50–1.90 (m, 6 H), 2.22 (sept, J = 7.0 Hz, 1 H), 2.82 (d, J = 7.0 Hz, 2 H), 3.50–3.60 (m, 1 H), 3.90–4.00 (m, 1 H), 4.05 (s, 3 H), 4.53 (d, J = 11.0 Hz, 1 H), 4.76 (d, J = 11.0 Hz, 1 H), 4.83 (br t, J = 3 Hz, 1 H), 5.39 (s, 2 H), 7.30–7.50 (m, 5 H); ^{13}C NMR δ 18.86, 22.64, 25.22, 25.87, 30.24, 32.78, 60.37, 61.63, 65.12, 68.32, 98.27, 127.80, 128.26, 136.21, 136.43, 138.95, 150.21, 155.76; HRMS calcd for $C_{22}H_{30}N_2O_5$ m/z 402.2155, found m/z 402.2136.

2-(Benzyloxy)-6-(hydroxymethyl)-3-isobutyl-5-methoxypyrazine 4-Oxide (12). To a solution of **11** (80 mg, 0.20 mmol) in methanol (1 mL) was added a drop of concd HCl at rt. After being stirred for 30 min, the mixture was diluted with Et_2O, washed with saturated $NaHCO_3$, dried, and evaporated. The residue was subjected to preparative TLC on silica gel (AcOEt:n-hexane = 1:1) to give **12** (63 mg, 99%): mp 68.0–69.2 °C (n-hexane–ether); IR (KBr) 3375, 1482, 1254, 1154 cm^{-1}; ^{1}H NMR δ 0.94 (d, J = 7.0 Hz, 6 H), 2.22 (sept, J = 7.0 Hz, 1 H), 2.83 (d, J = 7.0 Hz, 2 H), 3.02 (t, J = 6.0 Hz, 1 H), 4.03 (s, 3 H), 4.68 (d, J = 6.0 Hz, 1 H), 5.39 (s, 2 H), 7.30–7.50 (m, 5 H); ^{13}C NMR δ 22.59, 25.90, 32.64, 59.62, 59.98, 68.66, 127.53, 127.98, 128.42, 135.56, 136.18, 140.29, 148.14, 155.86. Anal. Calcd for $C_{17}H_{22}N_2O_4$: C, 64.13; H, 6.97; N, 8.80. Found: C, 64.23; H, 6.86; N, 8.76.

2-(Benzyloxy)-3-isobutyl-6-[(methanesulfonyloxy)methyl]-5-methoxypyrazine 4-Oxide (13). To a solution of **12** (210 mg, 0.66 mmol) and Et_3N (184 μL, 1.32 mmol) in CH_2Cl_2 (2 mL) was added methanesulfonyl chloride (52 μL, 0.67 mmol) at 0 °C under nitrogen. After being stirred for 30 min, the mixture was diluted with Et_2O, washed with H_2O, dried, and evaporated. The residue was subjected to preparative TLC on silica gel (AcOEt:n-hexane = 1:1) to give **13** (260 mg, 99%): IR (neat) 1605, 1454, 1407, 1357, 1174 cm^{-1}; ^{1}H NMR δ 0.94 (d, J = 7.0 Hz, 6 H), 2.23 (sept, J = 7.0 Hz, 1 H), 2.84 (d, J = 7.0 Hz, 2 H), 3.01 (s, 3 H), 4.09 (s, 3 H), 5.24 (s, 2 H), 5.38 (s, 2 H), 7.30–7.50 (m, 5 H); ^{13}C NMR δ 22.33, 25.51, 32.50, 37.32, 60.30, 66.64, 68.31, 127.47, 127.63, 128.02, 133.88, 135.77, 137.53, 150.15, 155.66; HRMS calcd for $C_{18}H_{24}N_2O_6S$ m/z 396.1355, found m/z 396.1358.

2-(Benzyloxy)-6-(iodomethyl)-3-isobutyl-5-methoxypyrazine 4-Oxide (14). A mixture of **13** (140 mg, 0.35 mmol) and n-Bu_4NI (200 mg, 0.54 mmol) in benzene (7 mL) was stirred in the dark at rt for 90 min and filtered through short column of silica gel (AcOEt:n-hexane = 3:7). Evaporation of the filtrate afforded **14** (150 mg, 99%): mp 78.3–79.5 °C (n-hexane–ether); IR (KBr) 1460, 1367, 1248, 1152 cm^{-1}; ^{1}H NMR δ 0.92 (d, J = 7.0 Hz, 6 H), 2.21 (sept, J = 7.0 Hz, 1 H), 2.79 (d, J = 7.0 Hz, 2 H), 4.14 (s, 3 H), 4.34 (s, 2 H), 5.36 (s, 2 H), 7.30–7.50 (m, 5 H); ^{13}C NMR δ –0.86, 22.65, 25.85, 32.86, 58.90, 68.51, 127.92, 127.99, 128.29, 136.14, 136.47, 139.79, 148.35, 155.42. Anal. Calcd for $C_{17}H_{21}IN_2O_3$: C, 47.68; H, 4.94; N, 6.54. Found: C, 47.88; H, 4.88; N, 6.54.

2-(Benzyloxy)-6-(1*H*-indol-3-ylmethyl)-3-isobutyl-5-methoxypyrazine 4-Oxide (17). To a lithium salt of indole, prepared from indole (352 mg, 3.0 mmol) and n-BuLi (2.1 mL in n-hexane, 3.0 mmol) in THF (3 mL) under nitrogen, was added $ZnCl_2$ (409 mg, 3.0 mmol) at rt, and the mixture was stirred for 80 min. Then solvent was removed in vacuo, and toluene (5 mL) was added. The toluene solution of zinc salt of indole thus formed was added to a toluene solution (15 mL) of **14** (428 mg, 1.0 mmol). The mixture was stirred for 1 h at rt, diluted with ether, washed with H_2O, dried, and evaporated. The residue was subjected to column chromatography on silica gel (AcOEt:n-hexane = 1:1) to give **17** (382 mg, 91%): mp 139.6–141.9 °C (n-hexane–ether); IR (KBr) 3276, 1600, 1154, 1050 cm^{-1}; ^{1}H NMR δ 0.91 (d, J = 7.0 Hz, 6 H), 2.19 (sept, J = 7.0 Hz, 1 H), 2.77 (d, J = 7.0 Hz, 2 H), 3.93 (s, 3 H), 4.17 (s, 2 H), 5.36 (s, 2 H), 7.03 (d, J = 2.4 Hz, 1 H), 7.10 (d, J = 7.6 Hz, 1 H), 7.18 (t, J = 7.8 Hz, 1 H), 7.30–7.40 (m, 6 H), 7.75 (d, J = 7.8 Hz, 1 H), 8.01 (br s, 1 H); ^{13}C NMR δ 22.68, 26.01, 28.37, 32.79, 59.73, 68.27, 111.21, 111.76, 119.05, 119.12, 121.67, 122.83, 127.18, 127.76, 128.27, 134.37, 136.16, 136.60, 142.94, 149.00, 155.44. Anal. Calcd for $C_{25}H_{27}N_3O_3$: C, 71.92; H, 6.52; N, 10.06. Found: C, 71.96; H, 6.54; N, 10.00.

6-(1*H*-Indol-3-ylmethyl)-3-isobutyl-5-methoxy-2(1*H*)-pyrazinone 4-Oxide (1). The coupling product **17** (5.0 mg, 0.011 mmol) was treated with 10% Pd–C (2 mg) in EtOH (0.5 mL) under hydrogen at rt for 30 min. Preparative TLC on silica gel (MeOH:CH_2Cl_2 = 7:93) afforded **1** (3.9 mg, quant), which was identical in all respects with an authentic sample (^{1}H NMR, ^{13}C NMR, MS, IR, TLC, mp).[1]

Supplementary Material Available: ^{13}C NMR spectra for **9**–**11** and **13** (4 pages). Ordering information is given on any current masthead page.