# FIRST SYNTHESIS OF (+)-SEPTORINE

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**Abstract**——(+)-Septorine, a metabolite of Septoria nodorum, was synthesized via alanyl-isoleucyl anhydride (2) from L-isoleucine at the first time. Compound (2) was led to a pyrazine-carboxaldehyde (13), which was treated with p-methoxymethoxy-phenylmagnesium bromide to afford an alcohol (14) in a quantative yield. The alcohol (14) was oxidized to a ketone (16), which was subjected to the Pummerer reaction and the following hydrolysis to give (+)-septorine.

Septorine (1), a metabolite of Septoria nodorum, has a pyrazine skeleton.[1] While coducting a study on pyrazine chemistry, the authors became interested in the synthesis of this compound and the method for doing so from L-isoleucine is presented in this paper.

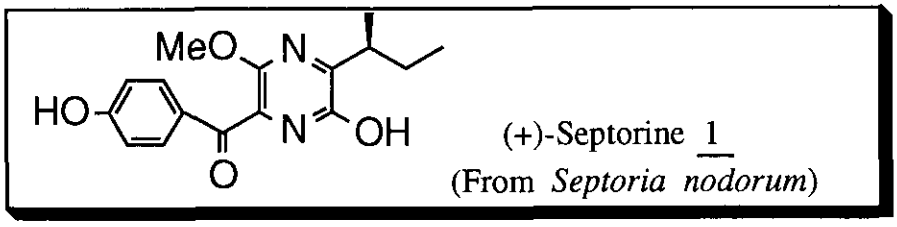
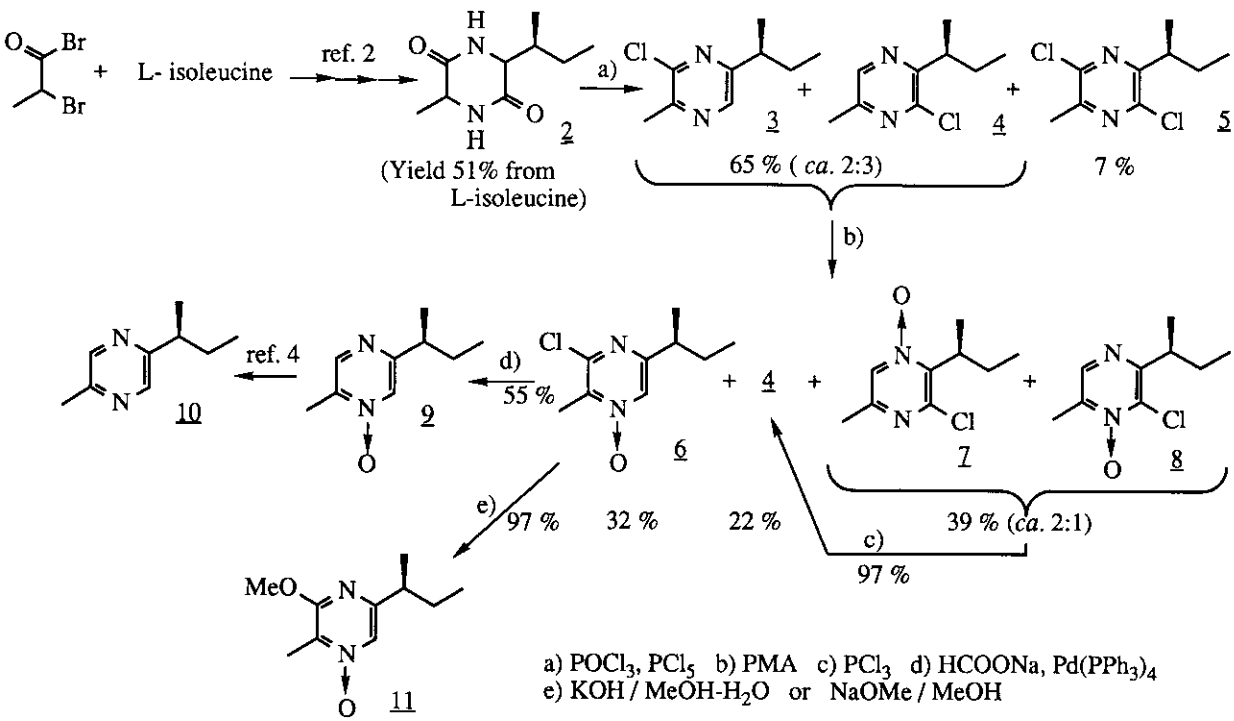



Figure 1

In accordance with the method previously reported,[2] alanyl-isoleucyl anhydride (2) was prepared starting from L-isoleucine. Compound (2),

a mixture of diastereoisomers, was employed in the following reaction without separation, because the chirality of C-3 and C-6 of three asymmetric carbons should disappear in the following aromatization step. Compound (2) was heated with a mixture of phosphoryl chloride and a small amount of phosphorus pentachloride in a sealed tube at 140°C, to give a mixture of (S)-(+)-6-sec-butyl-2-chloro-3-methylpyrazine (3), (S)-(+)-6-sec-butyl-5-chloro-3-methylpyrazine (4) and (S)-(+)-6-sec-butyl-2,5-dichloro-3-methylpyrazine (5). A hexane solution of the mixture was shaken with conc. hydrochloric acid to extract 3 and 4. The extract was made alkaline with potassium carbonate, followed by further extraction with ether to give a mixture. The $^1$H-nmr spectrum of the mixture indicated two pairs of singlets due to pyrazine ring protons (8.21 and 8.33 ppm) and methyl protons (2.51 and 2.61 ppm). In the molecules of 3 and 4, N-4 of 3 may be most oxidizable by peracid, being for less sterically hindered.




Scheme 1

The mixture was thus treated with *permaleic acid* (PMA). The reaction mixture was chromatographyed on silica gel to give the following products; 4, (S)-(+)-6-sec-butyl-2-chloro-3-methylpyrazine 4-oxide (6) and a mixture of (S)-(+)-6-sec-butyl-5-chloro-3-methylpyrazine 1-oxide (7) and (S)-(+)-6-sec-butyl-5-*chloro*-3-*methylpyrazine* 4-oxide (8). Compound (6) was reacted with sodium formate and tetrakis(triphenylphosphine)palladium,[3] giving (S)-(+)-5-sec-butyl-2-methylpyrazine 1-oxide (9). This compound was reacted with phosphorus trichloride to give (S)-(+)-5-sec-butyl-2-*methylpyrazine* (10)[4] (Scheme 1).

Signals of the α-carbons of an N-oxide group of pyrazine N-oxides are known to appear in a field higher than those of the corresponding protons of the mother amines and those of the ß-carbons in a slightly lower field.[5] Based *on analysis of* the spectra of 9 and 10 by the LSPD method, assignment was made for all the carbon atoms of the pyrazine ring, consequently clarifying the structure of 9 (Figure 2).

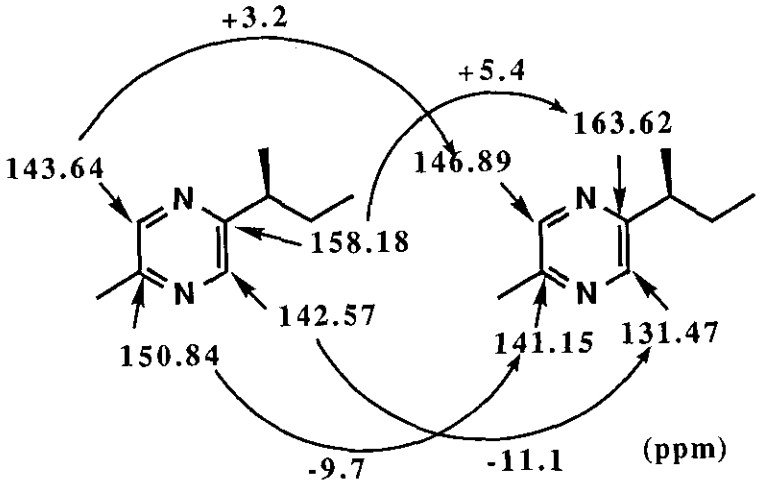



**Figure 2 $^{13}$C-Nmr data of 9 and 10**

Compound (6) was heated in a mixture of 10% potassium *hydroxide-methanol* (1:1), anticipating that a hydroxamic acid might possibly be obtained under alkaline conditions,[6] if a chlorine atom is situated adjacent to an N-oxide group. Actually, however, a methoxyl compound, (S)-(+)-6-sec-butyl-

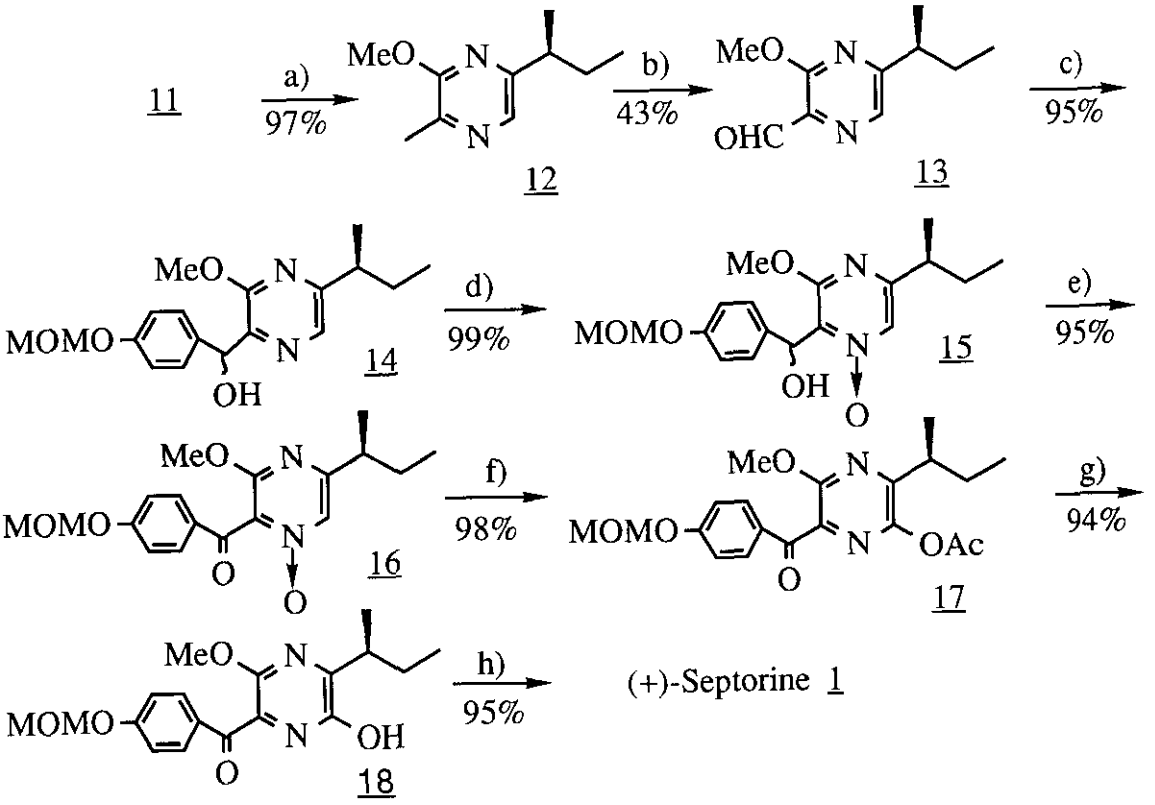
2-methoxy-3-methylpyrazine 4-oxide (11) was obtained, indicating no possibility that chlorine atom is present adjacent to the N-oxide group. Compound (6) was deoxygenated with phosphorus tribromide to give 3, so that the structure of 4 could be deductively determined.

Although a mixture of 7 and 8 showed one spot on a tlc plate, its $^1$H-nmr spectrum indicated two siganals due to pyrazine ring protons (7.90 and 8.30 ppm) and methyl protons (2.40 and 2.46 ppm) for these two compounds. The mixture thus appeared to contain two substances. This mixture was reacted with phosphorus tribromide, giving 4 as the sole product. The mixture was thus confirmed to be comprised of 7 and 8.

The chlorine atom of 6 was replaced with a methoxyl group by reaction with sodium methoxide in methanol, giving 11, which was deoxygenated with phosphorus tribromide to give (S)-(+)-6-sec-butyl-2-methoxy-3-methylpyrazine (12). Oxidation of the methyl group of 12 with benzeneseleninic anhydride (BSA)[7] yielded the aldehyde (13). The Grignard reaction of 13 with p-methoxymethoxyphenylmagnesium bromide in tetrahydrofuran-ether (1:1) afforded the alcohol (14), which was a mixture of diastereoisomers. Without separating the diastereoisomers, compound (14) was then oxidized with PMA to give the N-oxide (15). The $^1$H-nmr spectrum of 15 indicated a pyrazine ring proton (7.54 ppm) in a field higher than that (7.91 ppm) of 14 and a proton on the methine group between the benzene and pyrazine rings (6.10 ppm) in a field lower than that (5.83 ppm) of 14. It is thus evident that the N-oxidation of 14 occurs at N-4, as shown in the Scheme 2. The alcoholic group of 15 was oxidized to a keto group with Collins reagent, to afford 16, which was then heated with acetic anhydride. The ir spectrum of the sole product (17) indicated an acetoxyl carbonyl band at 1780 $cm^{-1}$ and the $^1$H-nmr spectrum of 17 did not show any signal in response to the pyrazine ring proton, thus demonstrating acetoxylation to occur on the pyrazine ring.

The acetate (17) was hydrolyzed under alkaline conditions to give the hydroxylpyrazine (18). To remove the methoxymethyl group, 18 was treated with a hydrochloric acid-methanol solution to give (+)-septorine (1) as

a yellow crystalline mass, which was proved to be identical with an authentic specimen by comparison of their $^1$H-nmr and ir spectra.




a) $PBr_3$ b) BSA c) MOMO—C$_6$H$_4$—MgBr / THF-$Et_2O$ d) PMA e) Collins reagent f) $Ac_2O$ g) $OH^-$ h) $H^+$

Scheme 2

**EXPERIMENTAL**

No correction was made for melting or boiling points. $^1$H-Nmr spectral data were obtained with a Varian EM-360, EM-390 or Brucker AM-400 in $CDCl_3$ using TMS as the internal standard. In the silica gel column chromatography, Wako gel C-200 (Wako Pure Chemical Ind., Ltd., Tokyo) was served as the

packing material. 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. Other spectral data were obtained using the following; Ir spectra, Japan Spectroscopic Co. A-100; Ms, Hitachi M-80B spectrometer; Optical Rotation, Japan Spectroscopic Co. DIP-360.

Synthesis of Alanyl-isoleucyl Anhydride (2)

To a mixture of 2N aq. NaOH. (500 ml) and L-isoleucine (122 g, 0.93 mol), α-bromopropionyl bromide (102 ml, 0.96 mol) and 2N aq. NaOH (500 ml) were added dropwise simultaneously at 0°C. The mixture was stirred for 1 h keeping the temperature. After the reaction mixture was acidified with 5N aq. HCl, precipitates were collected by suction, and dried to give an amide (yield 70 %, colorless crystals, mp 153°-155°C). Without further purification, the product was employed in the next reaction. The mixture of the amide (172 g, 0.65 mol) and conc. $NH_4OH$ (1000 ml) was allowed to stand being sealed tightly for 7 days. The solvent was evaporated to dryness. After addition of phenol (1000 g) to the residue, the resulting mixture was heated at 140°-150°C for 2 h. Phenol was removed in vacuo, the residue was washed with $H_2O$, and subsequently with $Et_2O$ to afford 2 (yield 73 %, colorless crystals from MeOH, mp 259°-260°C). Compound (2), which was a mixture of stereoisomers, was employed in the following reaction without further purification.

Reaction of Alanyl-isoleucyl Anhydride (2) with a Mixture of $POCl_3$ and $PCl_5$

A mixture of 2 (20 g, 110 mmol), $POCl_3$ (40 ml, 429 mmol) and $PCl_5$ (ca. 5 g) was heated at 140°C for 1.5 h in a sealed tube. After being cooled, the reaction mixture was poured into ice-water. The resulting mixture was made alkaline with powdered $K_2CO_3$ and extracted with $Et_2O$. The $Et_2O$ layer was dried with $Na_2SO_4$ and the solvent was removed by distillation to give a brown oil, subsequently dissolved in hexane. The hexane solution was extracted with conc. HCl. The HCl layer was made alkaline with powdered

$K_2CO_3$ and extracted with $Et_2O$ to give a mixture (colorless oil; yield: 65%; bp 89-90°C/7 torr; ms: 184) of 3 and 4. The hexane layer gave 5.

(S)-(+)-6-sec-Butyl-2,5-dichloro-3-methylpyrazine (5); Colorless oil; bp 78°C/2 torr; yield: 7%; ms: m/z 218 ($M^+$); $[\alpha]_D^{20}$ +32.6° (c = 1.05, $CHCl_3$); $^1$H-nmr (60 MHz): δ 0.86 (t, J = 7 Hz, 3H, $CH(CH_3)CH_2C\underline{H}_3$), 1.26 (d, J = 7 Hz, 3H, $CH(C\underline{H}_3)CH_2CH_3$), 1.43-2.10 (m, 2H, $CH(CH_3)C\underline{H}_2CH_3$), 2.60 (s, 3H, $CH_3$), 3.03-3.40 (m, J = 7 Hz, 1H, $C\underline{H}(CH_3)CH_2CH_3$) ppm; Anal. Calcd for $C_9H_{12}N_2Cl_2$: C, 49.33; H, 5.52; N, 12.79. Found: C, 49.18; H, 5.55; N, 12.77.

Isolation of (S)-(+)-6-sec-Butyl-2-chloro-3-methylpyrazine 4-Oxide (6)

To a solution of a mixture (1.84 g, 10 mmol) of 3 and 4 in $CHCl_3$ (40 ml), 60% $H_2O_2$ (0.68 g, 12 mmol) and maleic anhydride (1.18 g, 12 mmol) were added. After standing overnight at room temperature, the reaction mixture was refluxed for 1 h and then washed with $H_2O$, 10% $KHCO_3$ and $H_2O$, successively. The organic layer was worked up as usual to give a pale yellow oil (ca. 2 g), which was submitted to medium-pressure chromatography. Elution with hexane-$Et_2O$ (7:3) gave 4, 6 and a mixture of 7 and 8 (781 mg, 39%), in this order.

(S)-(+)-6-sec-Butyl-5-chloro-3-methylpyrazine (4); Colorless oil; bp 93°C/8 torr; yield: 70%; ms: m/z 184 ($M^+$); $[\alpha]_D^{20}$ +20.7° (c = 1.04, $CHCl_3$); $^1$H-nmr (60 MHz): δ 0.86 (t, J = 7 Hz, 3H, $CH(CH_3)CH_2C\underline{H}_3$), 1.25 (d, J = 7 Hz, 3H, $CH(C\underline{H}_3)CH_2CH_3$), 1.38-2.01 (m, 2H, $CH(CH_3)C\underline{H}_2CH_3$), 2.60 (s, 3H, $CH_3$), 3.09-3.50 (m, J = 7 Hz, 1H, $C\underline{H}(CH_3)CH_2CH_3$) ppm; Anal. Calcd for $C_9H_{13}N_2Cl$: C, 58.53; H, 7.10; N, 15.17. Found: C, 58.33; H, 7.00; N, 15.17.

(S)-(+)-6-sec-Butyl-2-chloro-3-methylpyrazine 4-Oxide (6); Colorless needles (hexane); mp 37-38°C; yield: 38%; ms: m/z 200 ($M^+$); $[\alpha]_D^{20}$ +28.9° (c = 1.07, $CHCl_3$); $^1$H-nmr (90 MHz): δ 0.79 (t, J = 7 Hz, 3H, $CH(CH_3)CH_2C\underline{H}_3$), 1.19 (d, J = 7 Hz, 3H, $CH(C\underline{H}_3)CH_2CH_3$), 1.42-1.86 (m, 2H, $CH(CH_3)C\underline{H}_2CH_3$), 2.47 (s, 3H, $CH_3$), 2.47-2.79 (m, 1H, $C\underline{H}(CH_3)CH_2CH_3$), 7.89 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_9H_{13}N_2OCl$: C, 53.87; H, 6.53; N, 13.96. Found: C, 53.84; H, 6.49; N, 14.07.

Deoxygenation of (S)-(+)-6-sec-Butyl-2-chloro-3-methylpyrazine 4-Oxide (6)

A mixture of 6 (595 mg, 2.97 mmol) and $PCl_3$ (5 ml, 57.4 mmol) was heated in a sealed tube at 100°C for 1 h. The reaction mixture was poured into ice-water, made alkaline with powdered $K_2CO_3$ and extracted with $Et_2O$. The $Et_2O$ extract was dried over $Na_2SO_4$ and the solvent was evaporated to give a colorless oil, subsequently purified by distillation to give 3 as a colorlerss oil (302 mg, 55%), bp 70-75°C/6 torr. Ms: m/z 184 ($M^+$); $[\alpha]_D^{20}$ +30.3° (c = 0.93, $CHCl_3$); $^1$H-nmr (60 MHz): δ 0.87 (t, J = 7 Hz, 3H, $CH(CH_3)CH_2\underline{CH}_3$), 1.30 (d, J = 7 Hz, 3H, $CH(\underline{CH}_3)CH_2CH_3$), 1.52-1.98 (m, 2H, $CH(CH_3)\underline{CH}_2CH_3$), 2.63 (s, 3H, $CH_3$), 2.62-3.02 (m, J = 7 Hz, 1H, $\underline{CH}(CH_3)CH_2CH_3$), 8.23 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_9H_{13}N_2Cl$: C, 58.33; H, 7.10; N, 15.17. Found: C, 58.59; H, 7.09; N, 15.28.

Deoxygenation of a Mixture of (S)-(+)-6-sec-Butyl-5-chloro-3-methylpyrazine 1-Oxide (7) and (S)-(+)-6-sec-Butyl-5-chloro-3-methylpyrazine 4-Oxide (8)

A solution of the mixture of 7 and 8 (400 mg, 2 mmol) and $PBr_3$ (1.8 ml, 10 mmol) in $CH_2Cl_2$ (5 ml) was stirred overnight at room temperature and then refluxed for 2 h. The reaction mixture was poured into ice-water and the system was made alkaline with powdered $K_2CO_3$, followed by extraction with $Et_2O$. The $Et_2O$ extract was worked up as usual to give an oil, which was purified by medium-pressure chromatography with hexane-$Et_2O$ (20:1) to give 4 (363 mg, 98%).

Synthesis of (S)-(+)-5-sec-Butyl-2-methylpyrazine 1-Oxide (9)

A solution of 6 (1.00 g, 5 mmol), $Pd(PPh_3)_4$ (297 mg, 0.26 mmol) and HCOONa (516 mg, 7.6 mmol) in dry DMF (20 ml) was heated at 100°C for 3 h under stirring. The reaction mixture was acidified with conc. HCl and the solvent was evaporated in vacuo. The residue was triturated with $H_2O$, made alkaline with powdered $K_2CO_3$ and extracted with $Et_2O$ to give 9, which was purified by distillation. Colorless oil; bp 155-160°C/12 torr; yield; o.457 g, 55%; ms: m/z 166 ($M^+$); $[\alpha]_D^{20}$ +29.0° (c = 0.87, $CHCl_3$); $^1$H-nmr (60 MHz): δ 0.86 (t, J = 7 Hz, 3H, $CH(CH_3)CH_2\underline{CH}_3$), 1.26 (d, J = 7 Hz, 3H, $CH(\underline{CH}_3)CH_2CH_3$),

1.57-1.80 (m, 2H, $CH(CH_3)C\underline{H}_2CH_3$), 2.43 (s, 3H, $CH_3$), 2.66-2.75 (m, 1H, $C\underline{H}(CH_3)CH_2CH_3$), 7.83 (s, 1H, pyrazine H), 8.37 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_9H_{14}N_2O$: C, 65.03; H, 8.49; N, 16.85. Found: C, 64.80; H, 8.50; N, 16.79.

Synthesis of (S)-(+)-6-sec-Butyl-2-methoxy-3-methylpyrazine 4-Oxide (11)

1) A mixture of 6 ( 179 mg, 0.9 mmol), 10% KOH (5 ml, 9 mmol) and MeOH (5 ml) was refluxed for 1 h. MeOH was removed by distillation in vacuo and the residue was extracted with $Et_2O$. A usual work-up of the $Et_2O$ extract gave 11, as a colorless oil. (yield: 155 mg, 88%)

2) A mixture of 6 (2.08 g, 10 mmol) and NaOMe, prepared from Na (1.14 g, 49 mg atoms) and MeOH (20 ml), was refluxed for 3 h. After removing the solvent in vacuo, the residue was triturated with $H_2O$ (20 ml) and extracted with $Et_2O$. The $Et_2O$ extract was worked up as usual to give 11, which was purified by distillation. Colorless oil; bp 115°C/3 torr; yield: 1.85 g, 95%; ms: m/z 196 ($M^+$), 179 ($M^+$-OH); $[\alpha]_D^{20}$ +22.9° (c = 1.06, $CHCl_3$); $^1$H-nmr (60 MHz): δ 0.80 (t, J = 7.5 Hz, 3H, $CH(CH_3)CH_2C\underline{H}_3$), 1.26 (d, J = 7.5 Hz, 3H, $CH(C\underline{H}_3)CH_2CH_3$), 1.38-1.91 (m, 2H, $CH(CH_3)C\underline{H}_2CH_3$), 2.41 (s, 3H, $CH_3$), 2.32-2.78 (m, 1H, $C\underline{H}(CH_3)CH_2CH_3$), 4.03 (s, 3H, $OCH_3$), 7.69 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.28. Found: C, 61.12; H, 8.31; N, 14.20.

Synthesis of (S)-(+)-6-sec-Butyl-2-methoxy-3-methylpyrazine (12)

To a solution of 11 (3.0 g, 15.3 mmol) in dry $CHCl_3$ (30 ml), $PBr_3$ (1.5 ml, 16.8 mmol) was added at once under ice-cooling and stirring. Stirring was continued for 2 h at room temperature and the reaction mixture was poured into ice-water. The solution thus obtained was made alkaline with powdered $K_2CO_3$ and extracted with $CHCl_3$. The $CHCl_3$ layer was worked up as usual to give 12, which was purified by distillation. colorless oil; bp 100°C/2 torr; yield: 2.67 g, 97%; ms: m/z 180 ($M^+$), 165 ($M^+$-$CH_3$); $[\alpha]_D^{20}$ +26.1° (c = 1.16, $CHCl_3$); $^1$H-nmr (90 MHz): δ 0.81 (t, J = 7 Hz, 3H, $CH(CH_3)CH_2C\underline{H}_3$), 1.23 (d, J = 7 Hz, 3H, $CH(C\underline{H}_3)CH_2CH_3$), 1.47-1.97 (m, 2H, $CH(CH_3)C\underline{H}_2CH_3$), 2.40 (s, 3H, $CH_3$), 2.53-2.90 (m, 1H, $C\underline{H}(CH_3)CH_2CH_3$), 3.96

(s, 3H, $OCH_3$), 7.80 (s, 1H, pyrazine H) ppm; High resolution mass Calcd for $C_{10}H_{16}N_2O$: 180.1262. Found: 180.1286.

Synthesis of (S)-(+)-6-sec-Butyl-3-formyl-2-methoxypyrazine (13)

A solution of 12 (2.47 g, 13.7 mmol) and benzeneseleninic anhydride (1.64 g, 4.5 mmol) in chlorobenzene (30 ml) was refluxed for 6 h. After cooling, the reaction mixture was diluted with hexane, chromatographed on silica gel and eluted with hexane of increasing $Et_2O$ content. The fractions eluted with hexane gave chlorobenzene while the hexane-$Et_2O$ fractions gave a mixture of 12 and 13 as a pale yellow oil. These were subsequently separated by medium-pressure column chromatography using hexane-$Et_2O$. bp 92°C/0.005 torr (bath temp.); yield: 1.14 g, 43% (0.96 g, 39% recovery); ms: m/z 194 ($M^+$), 179 ($M^+$-$CH_3$); ir (neat): 1720 (CHO) $cm^{-1}$; $[\alpha]_D^{20}$ +35.9° (c = 1.07, $CHCl_3$); $^1$H-nmr (90 MHz): δ 0.81 (t, J = 7 Hz, 3H, $CH(CH_3)CH_2\underline{CH_3}$), 1.27 (d, J = 7 Hz, 3H, $CH(\underline{CH_3})CH_2CH_3$), 1.50-1.82 (m, 2H, $CH(CH_3)\underline{CH_2}CH_3$), 2.66-3.04 (m, 1H, $\underline{CH}(CH_3)CH_2CH_3$), 4.03 (s, 3H, $OCH_3$), 8.13 (s, 1H, pyrazine H), 10.17 (s, 1H, CHO) ppm; High resolution mass Calcd for $C_{10}H_{14}N_2O_2$: 194.1055. Found: 194.1076.

Synthesis of (S)-(+)-6-sec-Butyl-3-(α-hydroxy-p-methoxymethoxybenzyl)-2-methoxypyrazine (14)

A solution of 4-methoxymethoxybromobenzene (648 mg, 3 mmol) in a mixture of dry $Et_2O$ (4 ml) and THF (4 ml) was added to a mixture of Mg (72 mg, 3 mg atoms) and a catalytic amount of $I_2$ and the system was refluxed for 30 min. It was then added slowly to a solution of 13 (194 mg, 1 mmol) in a mixture of dry $Et_2O$ (2 ml) and THF (2 ml) under ice-cooling followed by stirring for 6 h at room temperature. After the solvent was removed by distillation, the residue was triturated with 5% $NH_4Cl$ (10 ml) and extracted with $Et_2O$. A usual work-up of the $Et_2O$ extract gave 14, which was purified by medium-pressure column chromatography, eluting with hexane-$Et_2O$ (4:1). Colorless oil; bp 178°C/0.002 torr (bath temp.); yield: 0.315 g, 95%; ms: m/z 332 ($M^+$); ir (neat): 3450 (OH) $cm^{-1}$; $[\alpha]_D^{20}$ +17.7° (c = 1.30, $CHCl_3$); $^1$H-nmr (90 MHz): δ 0.81 (t, J = 7 Hz, 3H, $CH(CH_3)CH_2\underline{CH_3}$),

1.32 (d, J = 7 Hz, 3H, $CH(C\underline{H}_3)CH_2CH_3$), 1.47-1.83 (m, 2H, $CH(CH_3)C\underline{H}_2CH_3$), 2.51-2.89 (m, 1H, $C\underline{H}(CH_3)CH_2CH_3$), 3.41 (s, 3H, $CH_2OC\underline{H}_3$), 3.89 (s, 3H, $OCH_3$), 4.80 (br s, 1H, OH), 5.11 (s, 2H, $C\underline{H}_2OCH_3$), 5.83 (br s, 1H, C<u>H</u>OH), 6.96 (d, J = 9 Hz, 2H, benzene H), 7.30 (d, J = 9 Hz, 2H, benzene H), 7.91 (s, 1H, pyrazine H) ppm; <u>High resolution mass</u> Calcd for $C_{18}H_{24}N_2O_4$: 332.1735. Found: 332.1749.

<u>Synthesis of (S)-(+)-6-sec-Butyl-3-(α-hydroxy-p-methoxymethoxybenzyl)-2-methoxypyrazine 4-Oxide (15)</u>

A solution of 90% $H_2O_2$ (79 mg, 2.1 mmol) and maleic anhydride (206 mg, 2.1 mmol) in $CHCl_3$ (40 ml) was refluxed for 5 min and to which, after cooling, <u>14</u> (233 mg, 0.70 mmol) was added. The reaction mixture, after standing overnight, was worked up as described for the synthesis of <u>6</u> to give <u>14</u>. Colorless viscous oil; yield: 0.239 g, 98%; ms: m/z 331 ($M^+$-OH); ir (neat): 3450 (OH) $cm^{-1}$; $[\alpha]_D^{20}$ +14.5° (c = 0.52, $CHCl_3$); $^1$H-nmr (90 MHz): δ 0.82 (t, J = 7 Hz, 3H, $CH(CH_3)CH_2C\underline{H}_3$), 1.19 (d, J = 7 Hz, 3H, $CH(C\underline{H}_3)CH_2CH_3$), 1.46-1.82 (m, 2H, $CH(CH_3)C\underline{H}_2CH_3$), 2.46-2.83 (m, 1H, $C\underline{H}(CH_3)CH_2CH_3$), 3.39 (s, 3H, $CH_2OC\underline{H}_3$), 4.00 (s, 3H, $OCH_3$), 5.09 (s, 2H, $C\underline{H}_2OCH_3$), 6.10 (br s, 1H, C<u>H</u>OH), 6.49 (d, J = 9 Hz, 2H, benzene H), 7.38 (d, J = 9 Hz, 2H, benzene H), 7.54 (s, 1H, pyrazine H) ppm; <u>High resolution mass</u> Calcd for $C_{18}H_{22}N_2O_4$ ($M^+$-$H_2O$): 330.1578. Found: 330.1585.

<u>Synthesis of (S)-(+)-6-sec-Butyl-2-methoxy-3-(p-methoxymethoxybenzoyl)-pyrazine 4-Oxide (16)</u>

A solution of <u>11</u> (305 mg, 0.88 mmol) in dry $CH_2Cl_2$ (5 ml) was added slowly to a suspension of the Collins reagent (1.33 g, 5.2 mmol) in dry $CH_2Cl_2$ (30 ml) under ice-cooling. The reaction mixture was stirred for 3 h at room temperature. The supernatant liquid was decanted and the solvent was removed by distillation. The residue was purified by medium-pressure column chromatography, eluting with hexane containing an increasing amount of $Et_2O$ to give <u>16</u> as a colorless viscous oil. bp 200°C/0.005 torr (bath temp.); yield: 301 mg, 99%; ms (CI): m/z 347 ($M^+$+1); ir (neat): 1680 (CO) $cm^{-1}$; $[\alpha]_D^{20}$ +15.7° (c = 0.50, $CHCl_3$); $^1$H-nmr (90 MHz): δ 0.90 (t, J = 7

Hz, 3H, $CH(CH_3)CH_2C\underline{H}_3$), 1.28 (d, J = 7 Hz, 3H, $CH(C\underline{H}_3)CH_2CH_3$), 1.50-1.97 (m, 2H, $CH(CH_3)C\underline{H}_2CH_3$), 2.47-2.86 (m, 1H, $C\underline{H}(CH_3)CH_2CH_3$), 3.44 (s, 3H, $CH_2OC\underline{H}_3$), 3.93 (s, 3H, $OCH_3$), 5.21 (s, 2H, $C\underline{H}_2OCH_3$), 7.07 (d, J = 9 Hz, 2H, benzene H), 7.68 (s, 1H, pyrazine H), 7.81 (d, J = 9 Hz, 2H, benzene H) ppm; High resolution mass Calcd for $C_{18}H_{22}N_2O_4$ ($M^+$-O): 330.1578. Found: 330.1585.

Synthesis of (S)-(+)-5-Acetoxy-6-sec-butyl-2-methoxy-3-(p-methoxymethoxybenzoyl)pyrazine (17)

A solution of 16 (169 mg, 0.49 mmol) in $Ac_2O$ (3 ml, 31.8 mmol) was refluxed for 6 h. The reaction mixture was then poured into ice-water. The resulting solution was made alkaline with powdered $K_2CO_3$ and extracted with $Et_2O$. The $Et_2O$ extract was worked up as usual to give 11 as a viscous oil, which showed only one spot on a tlc plate. So unstable was this substance that its purification was not possible. Yield: 183 mg, 97%; ir (neat): 1780 ($OCOCH_3$), 1680 (CO) $cm^{-1}$; $[\alpha]_D^{20}$ +17.4° (c = 0.52, $CHCl_3$); $^1$H-nmr (90 MHz): δ 0.80 (t, J = 7 Hz, 3H, $CH(CH_3)CH_2C\underline{H}_3$), 1.20 (d, J = 7 Hz, 3H, $CH(C\underline{H}_3)CH_2CH_3$), 1.47-1.87 (m, 2H, $CH(CH_3)C\underline{H}_2CH_3$), 2.27 (s, 3H, $COCH_3$), 2.63-3.00 (m, 1H, $C\underline{H}(CH_3)CH_2CH_3$), 3.40 (s, 3H, $CH_2OC\underline{H}_3$), 3.93 (s, 3H, $OCH_3$), 5.14 (s, 2H, $C\underline{H}_2OCH_3$), 7.00 (d, J = 9 Hz, 2H, benzene H), 7.87 (d, J = 9 Hz, 2H, benzene H) ppm.

Synthesis of (S)-(+)-6-sec-Butyl-5-hydroxy-2-methoxy-3-(p-methoxymethoxybenzoyl)pyrazine (18)

A solution of 17 (189 mg, 0.48 mmol), 10% $K_2CO_3$ (3 ml, 2.2 mmol) and MeOH (3 ml) was gently refluxed for 30 min, followed by the removal of MeOH by distillation in vacuo. The resulting solution was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with sat. NaCl and worked up as usual. Yellow viscous oil; yield: 164 mg, 99%; ms: m/z 346 ($M^+$); ir (neat): 1660 (CO) $cm^{-1}$; $[\alpha]_D^{20}$ +27.5° (c = 0.57, $CHCl_3$); $^1$H-nmr (90 MHz): δ 0.85 (t, J = 7 Hz, 3H, $CH(CH_3)CH_2C\underline{H}_3$), 1.20 (d, J = 7 Hz, 3H, $CH(C\underline{H}_3)CH_2CH_3$), 1.34-1.98 (m, 2H, $CH(CH_3)C\underline{H}_2CH_3$), 3.08-3.33 (m, 1H, $C\underline{H}(CH_3)CH_2CH_3$), 3.44 (s, 3H, $CH_2OC\underline{H}_3$), 3.79 (s, 3H, $OCH_3$), 5.18 (s, 2H, $C\underline{H}_2OCH_3$), 6.93 (d, J = 9 Hz,

2H, benzene H), 7.81 (d, J = 9 Hz, 2H, benzene H), 9.18 (br s, 1H, NH or OH) ppm; High resolution mass Calcd for $C_{18}H_{22}N_2O_5$: 336.1527. Found: 336.1518.

Synthesis of (+)-Septorine (1)

After stirring a solution of 18 (129 mg, 0.37 mmol) in a mixture of MeOH (2 ml) and conc. HCl (0.1 ml) for 8 h at room temperature, the solvent was removed by distillation in vacuo. The residue was triturated with $H_2O$ and extracted with AcOEt. The AcOEt extract was worked up as usual to give a viscous mass, which was triturated with $CCl_4$ to give a yellow powder. mp 163-167°C (lit., amorphous); yield: 106 mg, 95%; ms: m/z 302 ($M^+$); ir (KBr): 3200 (OH), 1640 (CO) $cm^{-1}$; $[\alpha]_D^{20}$ + 17.8° (c = 0.89, MeOH) (lit., $[\alpha]_D^{20}$ + 19° (MeOH)); $^1$H-nmr (400 MHz): δ 0.90 (t, J = 7.4 Hz, 3H, $CH(CH_3)CH_2C\underline{H}_3$), 1.23 (d, J = 7 Hz, 3H, $CH(C\underline{H}_3)CH_2CH_3$), 1.53-1.63 and 1.81-1.91 (m, 2H, $CH(CH_3)C\underline{H}_2CH_3$), 3.28-3.33 (m, 1H, $C\underline{H}(CH_3)CH_2CH_3$), 3.82 (s, 3H, $OCH_3$), 6.80 (d, J = 9 Hz, 2H, benzene H), 7.59 (d, J = 9 Hz, 2H, benzene H) ppm; High resolution mass Calcd for $C_{18}H_{18}N_2O_4$: 302.1265. Found: 302.1226.

**ACKNOWLEDGEMENT**

The authors are sincerely grateful to Dr. M. Devys, Institut de Chimie des Substances Naturelles, France, for providing the septorine.

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Received, 29th January, 1991