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A new route to Septorin via controlled metalations of pyrazines. Diazines XXX

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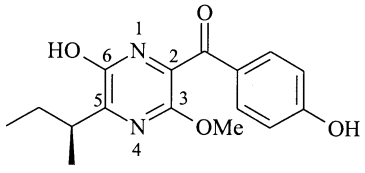
Abstract—The metalation of 2-chloro-3-(1-hydroxy-4-alkoxyphenylmethyl)pyrazines with LTMP in tetrahydrofuran has been studied and afforded regioselectively functionalized compounds at C_6. This regioselectivity was established by application of gradient enhanced HMBC sequence for the observation of long range $^{1}H-^{15}N$ heteronuclear couplings at natural abundance and by X-ray diffraction. Associated with the regioselective metalation at C_6, the transition metal catalyzed cross coupling reaction provides a new pathway to Septorin. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

A previous study of the metalation of 2-fluoropyrazine[1] has highlighted the fact that it is possible to control the regioselectivity of the metalation of 2-fluoro-3-substituted pyrazines at C_5 or C_6.

These results could be used to perform regioselective syntheses of polysubstituted pyrazines; a good example could be the synthesis of Septorin (**1**) which is the main agent of a wheat disease impeding growth.



1

The first synthesis of a close precursor of **1** (6-acetoxy and methylated on phenol) was performed by Barbier,[2,3] however with very low yield. The first complete synthesis of **1** was achieved by Ohta[4] starting from L-isoleucine. An overall yield of 1% was obtained over twelve steps.

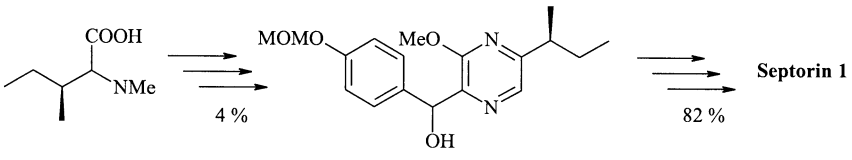
The enantioselective synthesis of (+)-Septorin has been described.[4] The main drawback of this synthesis was in the initial chlorination step which gave a mixture of three products and led to difficult isolation of the required compound via N-oxidation. Under these conditions, intermediate **2** was obtained with a low overall yield of 4% (Scheme 1).

The remainder of the Ohta's synthesis[4] from intermediate **2** to Septorin **1** was very efficient and gave an 82% yield in five steps.

Our expertise in metalation and cross coupling reactions of pyrazines allowed us to synthesize intermediate **2** from the commercially available 2-chloropyrazine **3**.

2. Results and discussion

The functionalization of 2-chloropyrazine **3** via the



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Scheme 1.

Keywords: Septorin; pyrazine; metalation; regioselectivity; cross coupling reaction.
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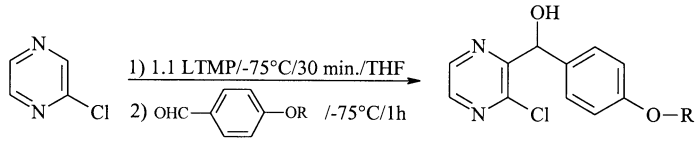


3 **4** R = Me 89 %
5 R = MOM 57 %

Scheme 2.

metalation reaction has been previously described[5] with good yields. The lithio derivative was reacted with 4-methoxy and 4-methoxymethoxybenzaldehyde as the electrophiles affording the 2,3-disubstituted pyrazines **4**, **5** (Scheme 2).

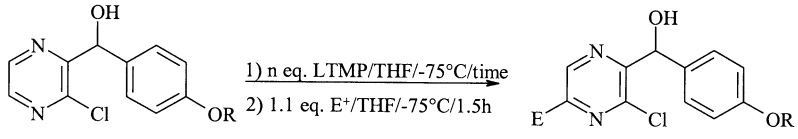
The lower yield in the case of **5** might result from a partial cleavage of the methoxymethoxy group during purification by flash chromatography on silica gel.

The next step was the introduction of the *sec*-butyl group in the 6 position. As we planned to introduce a substituent at this position by metalation, it was necessary to test the regioselectivity of this reaction. So, a preliminary study has been performed with compound **4** which was obtained in better yield than **5**. The usual aldehydes (acetaldehyde and benzaldehyde) were used as electrophiles, then hexachloroethane and iodine were chosen to introduce an halogen atom allowing further substitutions or cross coupling reactions (Scheme 3, Table 1).

In all cases only one isomer was obtained with functionalization at C_6. In spite of an excess of metalating agent (3.1 or 4.1 equiv., entries 4,5) and a longer reaction time (entries 3,4), some starting material was always recovered. In order to verify that the metalation took place at C_6, another regioselective synthetic route was used. Thus 2,6-dichloro-3-(4-methoxyphenyl-1-hydroxymethyl)pyrazine **8** was prepared regioselectively by metalation of 2,6-dichloropyrazine **11** and reaction with 4-methoxybenzaldehyde (Scheme 4).

The so-obtained compound presented physicochemical properties, as well as IR and NMR spectra identical to those of compound **8** previously obtained, thus proving that the metalation of pyrazines **4** and **5** occurred at C_6. It may thus be assumed that compounds **6** and **7** (entries 1,2) are also 2,3,6-trisubstituted pyrazines.

When iodine was used as the electrophile (entries 6–8), the structure of iodo compounds **9** and **10** was not so clear since some halogen dance reactions during the metalation and reaction with electrophile, as previously described, could occur.[6] Structure elucidation of compounds **9** and **10** was



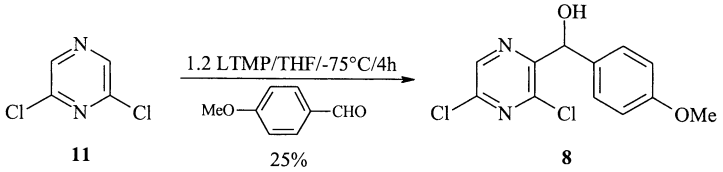
R = Me **4**
R = MOM **5**

R = Me **6 - 9**
R = MOM **10**

Scheme 3.

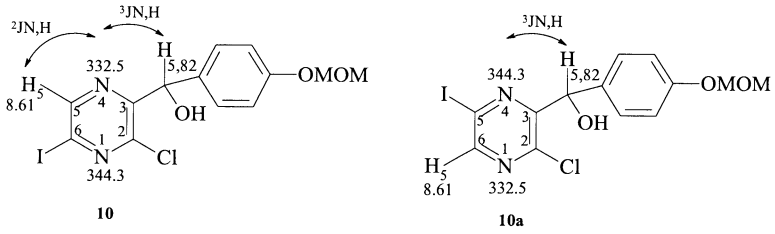
Table 1. Metalation of compounds **4** and **5**

Entry	R	*n* equiv. LTMP	Time (min)	E	Compound number	Yield (%)	Starting material (%)
1	Me	3.1	15	$CH_3CH(OH)$	**6**	56	33
2	Me	3.1	15	Ph-CH(OH)	**7**	52	30
3	Me	3.1	15	–Cl	**8**	61	16
4	Me	3.1	60	–Cl	**8**	60	12
5	Me	4.1	15	–Cl	**8**	69	10
6	Me	3.1	15	–I	**9**	64	22
7	MOM	3.1	15	–I	**10**	52	21
8	MOM	4.1	15	–I	**10**	50	11

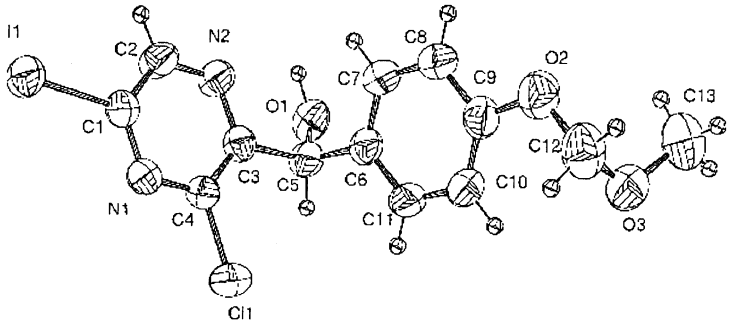


11 **8**

Scheme 4.



Scheme 5.



Scheme 6.

performed by applying gradient-enhancement HMBC sequence optimized on long range $^{1}H-^{15}N$ heteronuclear couplings at natural abundance[7] with low-pass J-filter to suppress one-bond correlations. The unequivocal identification of ^{15}N chemical shifts was based on $^{2}J_{1H-15N}$ interactions in the proton-coupled nitrogen spectrum which were only present in the spectrum of **10** (Scheme 5).

Finally an X-ray diffraction spectrum was performed on **10**, allowing confirmation of the presence of the iodine atom at C_6 (Scheme 6).

Having established that metalation took place at C_6 and that all electrophiles including iodine atom were introduced at this position, the pending question is: why is metalation regioselective at C_6? The compound which was actually metalated was not **4** or **5** but a lithium complex resulting from the abstraction of the labile hydrogen of the alcohol moiety. The lithium atom forms a chelate between the oxygen of the alcoholate and the neighboring nitrogen as indicated by semi empiric Li/PM3 calculations.[8] Moreover, the lithio derivative of **4** at C_6 (**4a**) may coordinate with the free N_1, whereas the lithio derivative at C_5 (**4b**) cannot be coordinated with N_4 which is already chelated (Scheme 7).

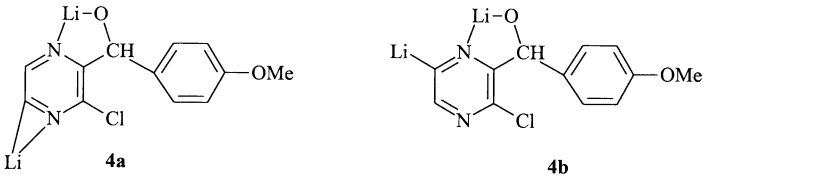
This assumption is in agreement with the calculation of the heat of formation of the two lithio derivatives by Li/PM3 (Scheme 7), the 6-lithio derivative **4a** being more stable than the 5-lithio derivative (**4b**) with a difference of heat of formation $\Delta\Delta Hf=6.8$ kcal mol^{-1}.

To return to the synthesis of **2**, the most straightforward way of introducing the *sec*-butyl moiety was to react 2-iodobutane with the C_6 lithio derivative of **4**. Both 2-iodobutane and iodoethane were tested without success.

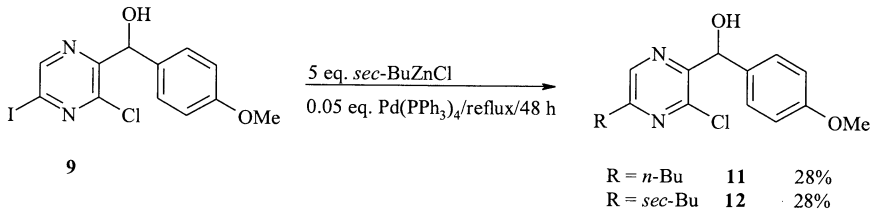
Another route envisioned was by way of an addition reaction of *sec*-BuLi on the 1–6 carbon–nitrogen bond, no addition–elimination product could be isolated and as usual an increase of temperature led to degradation.

The coupling reaction with organozinc derivatives was then studied: the first experiment was the metalation of **4** with LTMP followed by a transmetallation reaction with $ZnCl_2$[9] and cross coupling with iodoethane. Unfortunately this reaction failed to give the desired product. Thereafter, we tested the cross coupling reaction of iodo derivative **9** with *sec*-butylzinc chloride (Scheme 8).

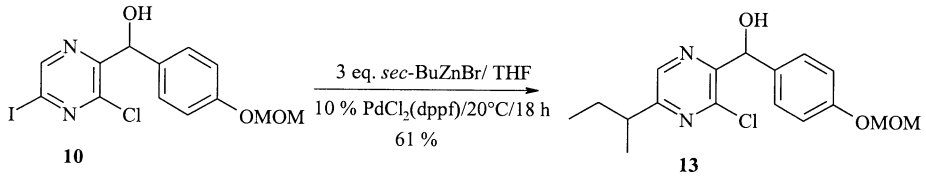
Compound **12** was obtained with a modest yield (28%), isomerization leading to *n*-butyl derivative **11** accounting for also 28% yield. This isomerization could be avoided by the choice of a suitable catalyst[10–12] under the right experimetal conditions. It has been highlighted that $PdCl_2$



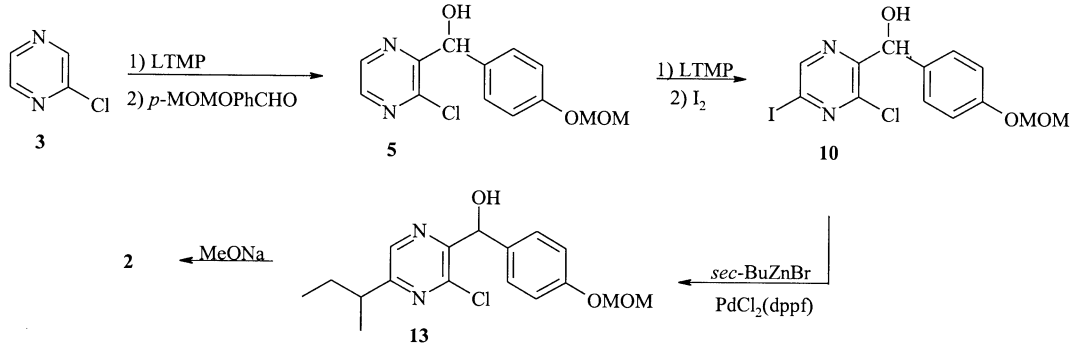
Scheme 7.



Scheme 8.



Scheme 9.



Scheme 10.

(dppf) was a very selective catalyst. So we tested this reaction directly on the OMOM substituted compound **10** (Scheme 9).

After optimization of the experimental conditions, a 61% yield of **13** as the sole compound was obtained unaccompanied by any isomerization product.

In a last step, the chlorine atom of **13** was substituted by a methoxy group by reaction of sodium methoxide at the reflux temperature of methanol for 48 h. Under these conditions **2** was obtained in 70% yield together with a small amount of starting material **13** (17%).

The complete synthetic pathway is summarized in Scheme 10).

Starting from 2-chloropyrazine, we have prepared the intermediate **2** in four steps with an overall yield of 14%.

This intermediate **2** can be used, following Ohta's method,[4] to access racemic Septorin in five steps and 82% yield. In this way, it should be possible to prepare racemic Septorin from commercial 2-chloropyrazine in nine steps with an overall yield of 11.5%.

3. Experimental

3.1. General

IR spectra were obtained from potassium bromide pellets with a Perkin–Elmer FMR 1650 spectrophotometer. The NMR spectra were recorded on a Bruker AC 200F (200 MHz), Bruker Avance (300 MHz) or Bruker ARX (400 MHz) spectrometer. All NMR spectra were carried out with deuteriochloroform solutions and δ are given in ppm. Chemical shifts in $CDCl_3$ were reported downfield from TMS (=0) for ^1H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to $CHCl_3$ (77.0 ppm for ^{13}C NMR) as an external reference. Microanalyses were performed with a Carlo Erba 1106 apparatus. Melting points were determined with a Kofler hot-stage apparatus and were uncorrected.

Metalations were carried out in dry solvents under an argon atmosphere. Reagents were handled with syringes through septa. Tetrahydrofuran (THF) was distilled from benzophenone sodium and used immediately (water content <60 ppm). Column chromatography was performed with silica gel Merck (70–230 mesh ASTM).

3.2. General procedures for metalation

3.2.1. Method A. A solution of *n*-butyllithium (1.6 or 2.5 M in hexane) was added to cold (−75°C), stirred, anhydrous THF (15 mL) under an atmosphere of dry argon, then 2,2,6,6-tetramethylpiperidine was added and the mixture was warmed to 0°C and kept at this temperature for 15 min in order to achieve a complete formation of the amide. The solution was cooled to −75°C and a solution of reagent (*x* mmol) in 5 mL of THF was added and the mixture was stirred for *t* min at −75°C. Then the electrophile (1.2 equiv. mmol) was added dropwise and stirring was continued for *t* min at −75°C. Hydrolysis was then carried out at −75°C using a mixture of ethanol (1 mL) and THF (1 mL). The solution was gently warmed to 0°C and the solvent was evaporated under reduced pressure. The residue was extracted with dichloromethane (4×25 mL). The organic extract was dried with $MgSO_4$ and evaporated. The crude product was purified by column chromatography on silica gel.

3.2.2. Method B (in situ trapping method). A solution of *n*-butyllithium (1.6 or 2.5 M in hexane) was added to cold (−75°C), stirred, anhydrous THF (15 mL) under an atmosphere of dry argon, then 2,2,6,6-tetramethylpiperidine was added and the mixture was warmed to 0°C and kept at this temperature for 15 min in order to achieve a complete formation of the amide. The solution was cooled to −75°C and a mixture of the reagent (*x* mmol) and the electrophile (1.2 equiv. mmol) in 5 mL of THF was added slowly and the mixture was stirred for 2 h at −75°C. Hydrolysis was then carried out at −75°C using a mixture of ethanol (1 mL) and THF (1 mL). The solution was gently warmed to 0°C and the solvent was evaporated under reduced pressure. The residue was extracted with dichloromethane (4×25 mL). The organic extract was dried with $MgSO_4$ and evaporated. The crude product was purified by column chromatography on silica gel.

3.3. Synthesis of the Septorin precursor

3.3.1. 6-*sec*-Butyl-3-(1-hydroxy-4-methoxymethoxyphenylmethyl)-2-methoxypyrazine (2). To a solution of **13** (0.075 g, 0.22 mmol) in methanol (10 mL) was added sodium methoxide (anhydrous powder) (0.060 g, 1.1 mmol) by fractions. The resulting mixture was warmed at reflux during 48 h. The reaction mixture was again cooled down to room temperature and was hydrolysed with 1 mL of water. Methanol was evaporated under vacuum and the aqueous layer was extracted with methylene chloride (6×15 mL). The resulting organic phase was dried over magnesium sulphate and evaporated. A flash chromatography on silica gel (ether petroleum/ethyl acetate=4:1) gave **2** (0.051 g, 70%) as a colorless oil: IR (KBr) ν 3438, 2961, 2932, 2874, 1610, 1545, 1509, 1460, 1320, 1234, 1173, 1153, 1080, 1005 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.76 (t, $J_{CH2,CH3}$=7.3 Hz, 3H, CH_2CH_3), 1.17 (dd, $J_{CH,CH3}$=6.8 Hz, 3H, $CHCH_3$), 1.50–1.65 (m, $J_{CH2,CH3}$=7.3 Hz, 2H, CH_2), 2.63 (m, $J_{CH,CH3}$=6.8 Hz, 1H, CH), 3.38 (s, 3H, CH_2OCH_3), 3.83 (s, 3H, OCH_3), 4.76 (d, $J_{CH,OH}$=7.2 Hz, 1H, OH), 5.07 (s, 2H, OCH_2O), 5.75 (d, $J_{CH,OH}$=7.2 Hz, 1H, CH), 6.88 (d, *J*=8.6 Hz, 2H, $H_{Ph3,5}$), 7.22 (d, *J*=8.6 Hz, 2H, $H_{Ph2,6}$), 7.85 (s, 1H, H_5); ^{13}C NMR ($CDCl_3$) δ 12.4 (CH_3), 20.2 (CH_3), 29.7 (CH_2), 40.6 (CH), 53.6 (OCH_3), 56.4 (CH_2OCH_3), 70.6 (CH), 94.8 (OCH_2O), 116.3 ($C_{Ph3,5}$), 128.6 ($C_{Ph2,6}$), 132.8 (C_5), 136.0 (C_{Ph1}), 146.8 (C_3), 152.0 (C_6), 155.6 (C_2), 157.8 (C_{Ph4}); Anal. Calcd for $C_{18}H_{24}N_2O_4$: C, 65.04; H, 7.28; N, 8.43. Found: C, 65.23; H, 7.14; N, 8.37.

3.4. Synthesis of substituted pyrazines via metalation reaction

3.4.1. 2-Chloro-3-(1-hydroxy-4-methoxyphenylmethyl)-pyrazine (4). Metalation of chloropyrazine **3** (0.78 mL, 8.7 mmol) according to the general procedure (method A) with *n*-butyllithium 1.6 M (6.0 mL, 9.6 mmol) and 2,2,6,6-tetramethylpiperidine (1.8 mL, 10.5 mmol), *t*=30 min, then reaction with *para*-anisaldehyde (1.3 mL, 10.5 mmol), *t*=60 min gave, after purification by column chromatography on silica gel (ether petroleum/ethyl acetate=7:3), **4** (1.950 g, 89%) as a cream oil: IR (KBr) ν 3412, 3005, 2958, 2935, 2837, 1610, 1511, 1370, 1029, 757 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.70 (s, 3H, OCH_3), 4.85 (d, *J*=6.0 Hz, 1H, OH), 5.97 (d, *J*=6.0 Hz, 1H, CH), 6.80 (d, *J*=9.0 Hz, 2H, H_{Ph}), 7.23 (d, *J*=9.0 Hz, 2H, H_{Ph}), 8.20 (d, $J_{H5,H6}$=2.0 Hz, 1H, H_5), 8.42 (d, $J_{H5,H6}$=2.0 Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$) δ 55.6 (OCH_3), 72.0 (*C*H(OH)), 114.4 ($C_{Ph3,5}$), 129.2 ($C_{Ph2,6}$), 132.9 (C_{Ph1}), 141.5 (C_5), 143.3 (C_6), 147.9 (C_3), 155.4 (C_2), 158.4 (C_{Ph4}); Anal. Calcd for $C_{12}H_{11}ClN_2O_2$: C, 57.50; H, 4.42; N, 11.17. Found: C, 57.78; H, 4.78; N, 10.93.

3.4.2. 4-Methoxymethoxybenzaldehyde. To a solution of 4-hydroxybenzaldehyde (2.442 g, 20 mmol) in acetone (30 mL) was added dry K_2CO_3 (5.530 g, 40 mmol). This solution was allowed to stir for 15 min at room temperature (orange color). To this solution, MOMCl (1.60 mL, 21 mmol) was added slowly by syringe through a septum. After complete addition, the reaction mixture was warmed up to reflux during 2 h. Again, the reaction mixture was cooled down to room temperature. After filtration of excess K_2CO_3 on a Buchner funnel, solvent was evaporated under reduced pressure to give 4-methoxymethoxy-benzaldehyde (3.318 g, 100%) as an orange visquous liquid. IR (KBr) ν 3368, 2958, 2903, 2829, 2741, 1695, 1600, 1579, 1508, 1241, 1215, 1152, 1082, 986, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.42 (s, 3H, OCH_3), 5.19 (s, 2H, OCH_2), 7.06 (d, *J*=8.8 Hz, 2H, $H_{Ph3,5}$), 7.79 (d, *J*=8.8 Hz, 2H, $H_{Ph2,6}$), 9.82 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$) δ 56.4 (OCH_3), 94.3 (OCH_2), 116.5 ($C_{Ph3,5}$), 130.9 (C_{Ph1}), 132.0 ($C_{Ph2,6}$), 162.4 (C_1), 191.0 (CHO); Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 64.94; H, 5.89.

Caution: methoxymethyl chloride is very toxic and should be handled with care.

3.4.3. 2-Chloro-3-(1-hydroxy-4-methoxymethoxyphenylmethyl)pyrazine (5). Metalation of chloropyrazine **3** (4.5 mL, 50 mmol) according to the general procedure (method A) with *n*-butyllithium 2.5 M (22 mL, 55 mmol) and 2,2,6,6-tetramethylpiperidine (9.3 mL, 55 mmol), *t*=30 min, then reaction with 4-methoxymethoxybenzaldehyde (9.97 g, 60 mmol), *t*=60 min gave, after purification by column chromatography on silica gel (ether petroleum/ethyl acetate=3:2), **5** (8.002 g, 57%) as an orange oil: IR (KBr) ν 3401, 2958, 2827, 1609, 1509, 1236, 1152, 1081,

1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.39 (s, 3H, OCH_3), 4.81 (d, $J_{CH,OH}$=6.0 Hz, 1H, OH), 5.11 (s, 2H, OCH_2), 6.06 (d, $J_{CH,OH}$=6.0 Hz, 1H, CH), 6.98 (d, J=9.0 Hz, 2H, $H_{Ph3,5}$), 7.30 (d, J=9.0 Hz, 2H, $H_{Ph2,6}$), 8.24 (d, $J_{H5,H6}$=2.0 Hz, 1H, H_5), 8.46 (d, $J_{H5,H6}$=2.0 Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$) δ 56.3 (OCH_3), 71.9 (*C*H(OH)), 94.5 (OCH_2), 116.6 ($C_{Ph3,5}$), 129.1 ($C_{Ph2,6}$), 134.2 (C_{Ph1}), 141.8 (C_5), 143.2 (C_6), 147.7 (C_3), 155.4 (C_2), 157.4 (C_{Ph4}); ^{15}N NMR ($CDCl_3$) δ 326 (d, J=10.5 Hz, N_1), 331 (d, J=10.5 Hz, N_4); Anal. Calcd for $C_{13}H_{13}ClN_2O_3$: C, 55.62; H, 4.67; N, 9.98. Found: C, 55.51; H, 4.82; N, 10.09.

3.4.4. 2-Chloro-3-(1-hydroxy-4-methoxyphenylmethyl)-6-(1-hydroxyethyl)pyrazine (6). Metalation of **4** (0.300 g, 1.2 mmol) according to the general procedure (method A) with *n*-butyllithium 1.6 M (2.3 mL, 3.7 mmol) and 2,2,6,6-tetramethylpiperidine (0.65 mL, 3.8 mmol), *t*=15 min, then reaction with acetaldehyde (0.4 mL, 7.1 mmol), *t*=45 min gave, after purification by column chromatography on silica gel (cyclohexane/ethyl acetate=1:1), **6** (0.200 g, 56%) as a yellow oil: IR (KBr) ν 3401, 2977, 2934, 2837, 1702, 1610, 1512, 1251, 1175, 1083, 1033, 756 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.49 (d, $J_{CH,CH3}$=6.8 Hz, 3H, 1dia, CH_3), 1.50 (d, $J_{CH,CH3}$=6.8 Hz, 3H, 1dia, CH_3), 2.70 (p, 1H, OH), 3.70 (s, 3H, OCH_3), 4.60 (p, 1H, OH), 4.89 (q, $J_{CH,CH3}$=6.8 Hz, 1H, CH), 5.90 (s, 1H, CH), 6.77 (d, J=8.7 Hz, 2H, $H_{Ph3,5}$), 7.18 (d, J=8.7 Hz, 2H, $H_{Ph2,6}$), 8.56 (s, 1H, 1dia, H_5), 8.57 (s, 1H, 1dia, H_5); ^{13}C NMR ($CDCl_3$) δ 24.11 (CH_3, 1dia), 24.15 (CH_3, 1dia), 55.7 (OCH_3), 68.42 (*C*H(CH_3), 1dia), 68.46 (*C*H(CH_3), 1dia), 72.0 (*C*H(OH)), 114.4 ($C_{Ph3,5}$), 129.1 ($C_{Ph2,6}$), 132.94 (C_6, 1dia), 132.98 (C_6, 1dia), 138.6 (C_5), 153.4 (C_2), 158.53 (C_3, 1dia), 158.57 (C_3, 1dia), 159.9 (C_{Ph4}); Anal. Calcd for $C_{14}H_{15}ClN_2O_3$: C, 57.06; H, 5.19; N, 9.50. Found: C, 56.87; H, 5.55; N, 9.39.

3.4.5. 2-Chloro-3-(1-hydroxy-4-methoxyphenylmethyl)-6-(1-hydroxyphenylmethyl) pyrazine (7). Metalation of **4** (0.200 g, 0.8 mmol) according to the general procedure (method A) with *n*-butyllithium 1.6 M (1.6 mL, 2.5 mmol) and 2,2,6,6-tetramethylpiperidine (0.44 mL, 2.6 mmol), *t*=15 min, then reaction with benzaldehyde (0.1 mL, 1.0 mmol), *t*=60 min gave, after purification by column chromatography on silica gel (cyclohexane/ethyl acetate=7:3), **7** (0.148 g, 52%) as a yellow oil: ^1H NMR ($CDCl_3$) δ 3.36 (p, 1H, OH), 3.50 (p, 1H, OH), 3.75 (s, 3H, OCH_3), 5.61 (s, 1H, CH), 5.92 (s, 1H, CH), 6.82 (d, J=8.7 Hz, 2H, $H_{Ph3,5}$), 7.30 (d, J=8.7 Hz, 2H, $H_{Ph2,6}$), 8.60 (s, 1H, H_5); Anal. Calcd for $C_{19}H_{17}ClN_2O_3$: C, 63.96; H, 4.80; N, 7.85. Found: C, 64.20; H, 4.67; N, 7.71.

3.4.6. 2,6-Dichloro-3-(1-hydroxy-4-methoxyphenylmethyl)pyrazine (8). *1st method*: Metalation of **4** (0.330 g, 1.3 mmol) according to the general procedure (method A) with *n*-butyllithium 1.6 M (2.5 mL, 4.0 mmol) and 2,2,6,6-tetramethylpiperidine (0.71 mL, 4.2 mmol), *t*=15 min, then reaction with hexachloroethane (0.380 g, 1.6 mmol), *t*=60 min gave, after purification by column chromatography on silica gel (cyclohexane/ethyl acetate=3:2), **8** (0.250 g, 61%) as a yellow oil which crystallized. *2nd method*: Metalation of 2,6-dichloropyrazine **11** (0.150 g, 1.0 mmol) according to the general procedure (method B) with *n*-butyllithium 2.5 M (0.44 mL, 1.1 mmol) and 2,2,6,6-tetramethylpiperidine (0.13 mL, 1.1 mmol), *para*-anisaldehyde (0.13 mL, 1.1 mmol), *t*=4 h gave, after purification by column chromatography on silica gel (cyclohexane/ethyl acetate=3:2), **8** (0.040 g, 25%) as a yellow oil which crystallized: mp=107°C (CH_2Cl_2); IR (KBr) ν 3423, 3002, 2934, 2836, 1609, 1511, 1305, 1251, 1174, 1156, 1032, 836 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.76 (s, 3H, OCH_3), 4.29 (d, $J_{CH,OH}$=6.9 Hz, 1H, OH), 5.98 (d, $J_{CH,OH}$=6.9 Hz, 1H, CH), 6.85 (d, J=8.7 Hz, 2H, $H_{Ph3,5}$), 7.24 (d, J=8.7 Hz, 2H, $H_{Ph2,6}$), 8.54 (s, 1H, H_5); ^{13}C NMR ($CDCl_3$) δ 55.1 (OCH_3), 71.3 (CH), 114.0 ($C_{Ph3,5}$), 128.5 ($C_{Ph2,6}$), 131.9 (C_{Ph1}), 140.9 (C_5), 145.2 (C_6), 146.1 (C_3), 153.0 (C_2), 159.4 (C_{Ph4}); MS 284 (M^+), HRMS 284.0119; Anal. Calcd for $C_{12}H_{10}Cl_2N_2O_2$: C, 50.55; H, 3.54; N, 9.82. Found: C, 50.48; H, 3.66; N, 9.75.

3.4.7. 2-Chloro-3-(1-hydroxy-4-methoxyphenylmethyl)-6-iodopyrazine (9). Metalation of **4** (0.210 g, 0.8 mmol) according to the general procedure (method A) with *n*-butyllithium 2.5 M (1.0 mL, 2.5 mmol) and 2,2,6,6-tetramethylpiperidine (0.44 mL, 2.6 mmol), *t*=15 min, then reaction with iodine (0.240 g, 0.9 mmol), *t*=120 min gave, after purification by column chromatography on silica gel (cyclohexane/ethyl acetate=3:2), **9** (0.200 g, 64%) as a red oil: IR (KBr) ν 3412, 3004, 2956, 2932, 2836, 1610, 1509, 1305, 1251, 1175, 1117, 1035, 832, 756 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.76 (s, 3H, OCH_3), 4.28 (d, $J_{CH,OH}$=7.5 Hz, 1H, OH), 5.92 (d, $J_{CH,OH}$=7.5 Hz, 1H, CH), 6.87 (d, J=8.7 Hz, 2H, $H_{Ph3,5}$), 7.27 (d, J=8.7 Hz, 2H, $H_{Ph2,6}$), 8.78 (s, 1H, H_5); ^{13}C NMR ($CDCl_3$) δ 55.3 (OCH_3), 71.3 (CH), 111.5 (C_6), 114.0 ($C_{Ph3,5}$), 128.6 ($C_{Ph2,6}$), 131.9 (C_{Ph1}), 146.4 (C_3), 149.5 (C_5), 153.6 (C_2), 159.6 (C_{Ph4}); Anal. Calcd for $C_{12}H_{10}ClIN_2O_2$: C, 38.27; H, 2.68; N, 7.44. Found: C, 38.45; H, 2.76; N, 7.21.

3.4.8. 2-Chloro-3-(1-hydroxy-4-methoxymethoxyphenylmethyl)-6-iodopyrazine (10). Metalation of **5** (2.873 g, 10 mmol) according to the general procedure (method A) with *n*-butyllithium 2.5 M (12.4 mL, 31 mmol) and 2,2,6,6-tetramethylpiperidine (5.2 mL, 31 mmol), *t*=15 min, then reaction with iodine (2.793 g, 11 mmol), *t*=120 min gave, after purification by column chromatography on silica gel (ether petroleum/ethyl acetate=7:3), **10** (2.114 g, 52%) as an orange oil which crystallized: mp=66°C (CH_2Cl_2); IR (KBr) ν 3478, 2954, 2897, 1607, 1509, 1415, 1388, 1306, 1229, 1004, 834 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.33 (s, 3H, OCH_3), 4.64 (p, 1H, OH), 5.04 (s, 2H, OCH_2O), 5.87 (s, 1H, CH), 6.88 (d, J=9.1 Hz, 2H, $H_{Ph3,5}$), 7.18 (d, J=9.1 Hz, 2H, $H_{Ph2,6}$), 8.65 (s, 1H, H_5);^{13}C NMR ($CDCl_3$) δ 56.3 (OCH_3), 71.7 (CH), 94.5 (OCH_2O), 113.1 (C_6), 116.6 ($C_{Ph3,5}$), 128.9 ($C_{Ph2,6}$), 133.7 (C_{Ph1}), 146.7 (C_2), 150.1 (C_5), 154.2 (C_3), 157.5 (C_{Ph4}); ^{15}N NMR ($CDCl_3$) δ 328.8 (s, N_1), 330.1 (d, J=10.5 Hz, N_4); Anal. Calcd for $C_{13}H_{12}ClIN_2O_2$: C, 38.40; H, 2.97; N, 6.89. Found: C, 38.67; H, 3.14; N, 7.28.

3.5. Synthesis of alkylpyrazines via cross-coupling reaction with organozinc reagent

3.5.1. 6-*n*-Butyl-2-chloro-3-(1-hydroxy-4-methoxyphenylmethyl)pyrazine (11) and 6-*sec*-butyl-2-chloro-3-(1-hydroxy-4-methoxyphenylmethyl)pyrazine (12). A solution containing 12.5 equiv. of zinc chloride (0.885 g, 6.5 mmol) (previously dried under vaccum with a flameless heat gun) dissolved in 5 mL of THF under an atmosphere of

dry nitrogen was added to 5.0 equiv. of *sec*-butyllithium 1.3 M (2.0 mL, 2.6 mmol) at −75°. The mixture was then gently warmed to room temperature. A solution containing 5 mol% tetrakis(triphenylphosphine)palladium[13] (0.031 g, 0.026 mmol) and 2-chloro-3-(1-hydroxy-4-methoxyphenylmethyl)-6-iodopyrazine **9** (0.200 g, 0.53 mmol) dissolved in 5 mL of THF was added to the organozinc derivative and the mixture was warmed at reflux during 48 h. The reaction mixture was then hydrolysed with a solution containing 12.5 equiv. of ethylenediamine tetraacetic acid and 15 mL of water. THF was evaporated under vacuum and the aqueous layer was extracted with methylene chloride (4×15 mL). The resulting organic layer was dried over magnesium sulphate and evaporated. After a flash chromatography on silica gel (ether petroleum/ethyl acetate=7:3), a mixture (50/50) (0.090 g, 55%) of products **11** and **12** was isolated as an orange oil: IR (KBr) ν 3426, 2959, 2931, 2872, 2837, 1610, 1511, 1462, 1250, 1175, 1034, 806 cm^{-1}; ^1H NMR (**11**) ($CDCl_3$) δ 0.95 (t, 3H, CH_3), 1.34 (m, 2H, CH_2), 1.72 (m, 2H, CH_2), 2.80 (t, $J_{CH2,CH2}$=7.7, 2H, CH_2), 3.78 (s, 3H, OCH_3), 4.60 (d, $J_{CH,OH}$=7.4 Hz, 1H, OH), 5.95 (d, $J_{CH,OH}$=7.4 Hz, 1H, CH), 6.84 (d, J=8.6 Hz, 2H, $H_{Ph3,5}$), 7.27 (d, J=8.6 Hz, 2H, $H_{Ph2,6}$), 8.36 (s, 1H, H_5); ^1H NMR (**12**) ($CDCl_3$) δ 0.86 (t, $J_{CH2,CH3}$=7.5 Hz, 3H, CH_2CH_3), 1.28 (dd, $J_{CH,CH3}$=7.5 Hz, 3H, $CHCH_3$), 1.50–1.65 (m, 2H, CH_2), 2.80 (m, $J_{CH,CH3}$=7.5 Hz, 1H, CH), 3.78 (s, 3H, OCH_3), 4.60 (d, $J_{CH,OH}$=7.4 Hz, 1H, OH), 5.95 (d, $J_{CH,OH}$=7.4 Hz, 1H, CH), 6.84 (d, J=8.6 Hz, 2H, $H_{Ph3,5}$), 7.27 (d, J=8.6 Hz, 2H, $H_{Ph2,6}$), 8.37 (s, 1H, H_5); ^{13}C NMR (**11**) ($CDCl_3$) δ 14.2 (CH_3), 22.7 (CH_2), 31.8 (CH_2), 34.8 (CH_2), 56.6 (OCH_3), 71.8 (CH), 114.3 ($C_{Ph3,5}$), 129.1 ($C_{Ph2,6}$), 133.4 (C_6), 140.7 (C_5), 146.7 (C_{Ph1}), 151.9 (C_3), 157.5 (C_2), 159.8 (C_{Ph4}); ^{13}C NMR (**12**) ($CDCl_3$) δ 12.3 (CH_3), 20.07 (1dia, CH_3), 20.13 (1dia, CH_3), 29.8 (CH_2), 40.92 (1dia, CH), 40.96 (1dia, CH), 55.6 (OCH_3), 71.8 (CH), 114.3 ($C_{Ph3,5}$), 129.0 ($C_{Ph2,6}$), 133.36 (1dia, C_6), 133.39 (1dia, C_6), 140.0 (1dia, C_5), 140.1 (1dia, C_5), 146.7 (C_{Ph1}), 151.98 (1dia, C_3), 152.0 (1dia, C_3), 157.6 (C_2), 159.8 (C_{Ph4}); MS 306 (MH^+) *m/z* 137; Anal. Calcd for $C_{16}H_{19}ClN_2O_2$: C, 62.64; H, 6.24; N, 9.13. Found: C, 62.82; H, 6.19; N, 9.33.

3.5.2. 6-*sec*-Butyl-2-chloro-3-(1-hydroxy-4-methoxymethoxyphenylmethyl)pyrazine (13). *Sec*-butylzinc bromide 0.5 M (3.0 mL, 1.5 mmol) was added to a solution containing 10 mol% dichloro[1,1′-bis(diphenylphosphino)-ferrocene]palladium (II)[11] (0.041 g, 0.05 mmol) in 10 mL of THF at −75°C. A solution containing 2-chloro-3-(1-hydroxy-4-methoxymethoxyphenylmethyl)-6-iodopyrazine **10** (0.203 g, 0.50 mmol) dissolved in 5 mL of THF was added to the organozinc derivative and the mixture was then gently warmed to room temperature. The reaction mixture was stirred at room temperature during 18 h and was then hydrolysed with 10 mL of water. The emulsion was eliminated by filtration under vacuum. THF was evaporated under reduced pressure and the aqueous layer was extracted with methylene chloride (4×15 mL). The resulting organic layer was dried over magnesium sulphate and evaporated. A flash chromatography on silica gel (ether petroleum/ethyl acetate=3:2) gave **13** (0.103 g, 61%) as a pale yellow oil: ^1H NMR ($CDCl_3$) δ 0.78 (t, $J_{CH2,CH3}$=7.3 Hz, 3H, CH_2CH_3), 1.22 (dd, $J_{CH,CH3}$=6.8 Hz, 3H, $CHCH_3$), 1.57–1.67 (m, 2H, CH_2), 2.72–2.80 (m, 1H, CH), 3.37 (s, 3H, OCH_3), 4.52 (d, $J_{CH,OH}$=7.5 Hz, 1H, OH), 5.07 (s, 2H, OCH_2O), 5.87 (d, $J_{CH,OH}$=7.5 Hz, 1H, CH), 6.90 (d, J=8.7 Hz, 2H, $H_{Ph3,5}$), 7.20 (d, J=8.7 Hz, 2H, $H_{Ph2,6}$), 8.28 (s, 1Hdia, H_5), 8.29 (s, 1Hdia, H_5); ^{13}C NMR ($CDCl_3$) δ 12.4 ($CH_3(CH_2)$), 20.07 (CH_3, 1dia), 20.13 (CH_3, 1dia), 29.8 (CH_2), 40.93 (CH, 1dia), 40.97 (CH, 1dia), 56.4 (OCH_3), 71.8 (CH(OH)), 94.7 (OCH_2O), 116.3 ($C_{Ph3,5}$), 129.1 ($C_{Ph2,6}$), 134.6 (C_{Ph1}), 140.0 (C_5, 1dia), 140.1 (C_5, 1dia), 146.85 (C_2, 1dia), 146.92 (C_2, 1dia), 151.9 (C_3), 157.4 (C_{Ph4}), 161.46 (C_6, 1dia), 161.53 (C_6, 1dia); MS 337 (MH^+) *m/z* 319, HRMS 337.1288; Anal. Calcd for $C_{17}H_{21}ClN_2O_3$: C, 60.57; H, 6.23; N, 8.31. Found: C, 60.65; H, 6.39; N, 8.45.

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