

## Research Article

# Preparation of labelled 2-methoxy-3-alkylpyrazines: synthesis and characterization of deuterated 2-methoxy-3-isopropylpyrazine and 2-methoxy-3-isobutylpyrazine

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## Summary

Efficient synthetic routes for a number of deuterated analogues of 2-methoxy-3-isopropylpyrazines and 2-methoxy-3-isobutylpyrazines have been developed involving the condensation of glyoxal with an  $\alpha$ -amino acid amide followed by methylation with iodomethane. In this way [ $^2\text{H}_3$ ]2-methoxy-3-isopropylpyrazine, 2-methoxy-3-isopropyl-[ $^2\text{H}_2$ ]pyrazine, [ $^2\text{H}_3$ ]2-methoxy-3-isopropyl-[ $^2\text{H}_2$ ]pyrazine, [ $^2\text{H}_3$ ]2-methoxy-3-isobutylpyrazine; 2-methoxy-3-isobutyl-[ $^2\text{H}_2$ ]pyrazine and [ $^2\text{H}_3$ ]2-methoxy-3-isobutyl-[ $^2\text{H}_2$ ]pyrazine were prepared and characterized by NMR and MS. Copyright © 2002 John Wiley & Sons, Ltd.

**Key Words:** pyrazines; synthesis; regiospecific deuterium label

## Introduction

Certain members of the pyrazine family of heterocycles are well known to be powerful, odorous compounds.<sup>1</sup> Ironically, while some

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2-methoxy-2-alkylpyrazines are desirable flavour components in wines such as cabernet-sauvignon and cabernet-franc,<sup>2</sup> they also comprise a group of unpleasant, musty-tasting chemicals found in water.

Threshold values in drinking water for the two major odour-causing chemicals, 2-methoxy-3-isopropylpyrazine (**1**, Figure 1) and 2-methoxy-3-isobutyl pyrazine (**2**), were recently reported to be  $2 \text{ ng l}^{-1}$  by Bruchet and Malleret.<sup>3</sup> Quantification at these levels is difficult to achieve due to losses in the extraction process. Spiking samples with the same compound, carrying isotopic labels, allows the analyst to determine more accurately the concentrations of analytes, since both the analytes and the labelled compounds should behave identically in the extraction process. In addition, interest has also been shown in the biological activity possessed by certain pyrazines. In a recent study,<sup>4</sup> the effect of 2-methoxy-3-isobutylpyrazine on leghorn chickens reportedly increased the mass of their eggs by 5–10%. The effect was reversible. Although the mechanism for this increase in mass is not well understood, the studies seem to indicate that pyrazines affect the endocrine systems of these vertebrates.

Synthetic routes to pyrazines isotopically labelled in various positions are needed in order to help facilitate these analytical and biological studies. Methods for the production of 2-methoxy-3-isopropylpyrazine incorporating deuterium have been reported;<sup>5</sup> however, a more general, *de novo* synthesis was developed in order to allow for the preparation of a variety of isotopic analogues of 2-methoxy-3-alkylpyrazines labelled at multiple positions. This approach, illustrated in Scheme 1, permitted

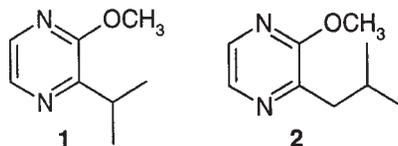
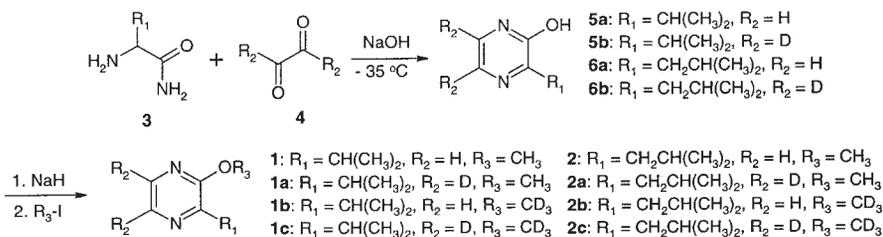


Figure 1.



Scheme 1.

the greatest flexibility and best suited our requirements.<sup>6</sup> First described by Jones, then later modified by Karmas and Spoerri,<sup>7</sup> formation of the 2-hydroxy-3-alkyl-pyrazine unit is achieved *via* the condensation of an  $\alpha$ -amino acid amide (**3**) and a 1, 2-dicarbonyl **4** (in the present case, glyoxal). Methylation to the described compounds can proceed either *via* treatment with diazomethane or methyl iodide. This simple, two-step, three component synthesis allows for the inclusion of an isotopic label within either the alkyl side chain ( $R_1$ ), the aromatic core ( $R_2$ ) or the methoxy group ( $R_3$ ) by using the appropriately labelled reagent. We are currently developing new methodologies for the preparation of isotopically labelled  $\alpha$ -amino acid amides and the present paper focuses on our work using  $d_2$ -glyoxal and  $d_3$ -methyl iodide as a means to incorporating deuterium.

## Results and discussion

Optimization of the chemistry required was carried out during the syntheses of the non-labelled compounds. The Karmas–Spoerri method proved to be an efficient route to the pyrazine ring system. Condensation of glyoxal with either valinamide or leucinamide allowed for the production of 2-hydroxy-3-isopropyl-pyrazine (**5a**) and 2-hydroxy-3-isobutyl-pyrazine (**6a**), respectively, in higher yields than those originally reported, with only minor modifications to the reaction conditions (that included lower reaction temperature and slightly higher amounts of glyoxal). The reaction used can easily be modified to use other amino acid amides, provided they do not have interfering functional groups. Exploratory experiments revealed that capping of the free hydroxyl to provide the methoxy ether was best achieved using 1.1 equivalents of sodium hydride and 1.1 equivalents of iodomethane. Using these methods, samples of 2-methoxy-3-isopropyl-pyrazine (**1**) and 2-methoxy-3-isobutyl-pyrazine (**2**) were prepared and fully characterized.

Efforts were then directed towards the synthesis of the deuterated analogues using labelled glyoxal and/or labelled iodomethane. Among the preparative routes to glyoxal described in the literature (including those involving the oxidation of ethylene with selenium oxide<sup>8</sup> or the ozonolysis of benzene<sup>9</sup>), the method described by Ramesh proved particularly amenable.<sup>10</sup> In this way,  $d_2$ -glyoxal was synthesized under relatively mild conditions from diethyl oxalate and lithium aluminum

deuteride. An aqueous solution of  $d_2$ -glyoxal could be used directly in the pyrazine synthesis or converted to its bisulphate salt by treating the aqueous glyoxal with a solution of sodium bisulfate in 40% ethanol in water. Condensation of  $d_2$ -glyoxal with either valinamide or leucinamide allowed for the 2-hydroxy-3-isopropyl- $d_2$ -pyrazine (**5b**) and 2-hydroxy-3-isobutyl- $d_2$ -pyrazine (**6b**), respectively. While these compounds showed the expected NMR and MS characteristics, integration of  $^1\text{H-NMR}$  revealed that deuterium incorporation was lower than expected (only about 60%).

Using the methylation chemistry developed above, 2-methoxy-3-isopropyl- $^2\text{H}_2$ pyrazine (**1a**) and 2-methoxy-3-isobutyl- $^2\text{H}_2$ pyrazine (**2a**) were synthesized and fully characterized by NMR and MS. Utilization of  $d_3$ -iodomethane worked equally as well and when employed with 2-hydroxy-3-isopropyl-pyrazine (**5a**) and 2-hydroxy-3-isobutyl-pyrazine (**6a**), the analogues containing the deuterated methyl group, **1b** and **2b**, were easily accessed. Deuterium incorporation in these latter samples (**1b** and **2b**) was shown to be greater than 99% and showed the expected spectroscopic characteristics. Finally, treatment of the deuterated hydroxypyrazines with  $d_3$ -iodomethane yielded the pentadeutero compounds **1c** and **2c**.

Several of the unusual features in the mass spectra of the compounds deserve comment (see Figure 2).<sup>11</sup> 2-Methoxy-isobutyl-pyrazine (**2**) shows a molecular ion at  $m/z = 166$  (169 for **2b**) and a loss of  $\text{CH}_3$  leading to a mass at 151. Incorporation of  $\text{CD}_3$  in **2b** and examination of its mass spectrum reveals that this methyl loss can either come from the methoxy methyl group (giving rise to  $m/z = 151$ ) or the alkyl side chain (giving rise to  $m/z = 154$ ). McLafferty rearrangement leads to the base peak at 127 for **2b** (124 for **2**), clearly indicating that the deuterium label was still incorporated in the species. Similarly, 2- $d_3$ -methoxy-3-isopropylpyrazine (**1b**) showed a base peak at  $m/z = 127$  [ $\text{M}-28$ ] (in contrast to its none-labelled analogue **1** which had a base peak at 137 [ $\text{M}-15$ ] and a less prominent peak at 124 [ $\text{M}-28$ ]). The mechanism responsible for the production of the base peak in **1b** clearly cannot be a McLafferty rearrangement. Furthermore, HRMS shows that the exact mass corresponds to an elemental composition of  $\text{C}_6\text{H}_5\text{D}_3\text{N}_2\text{O}$ , indicating a loss of  $\text{C}_2\text{H}_2$  and not  $\text{CO}$  from the molecular ion. While a number of possible mechanisms can be postulated, further work is required in order to ascertain the exact nature of the rearrangement. Overall, however, the MS studies of the compounds demonstrated that **1b** and **2b** are ideally suited for use as isotopic

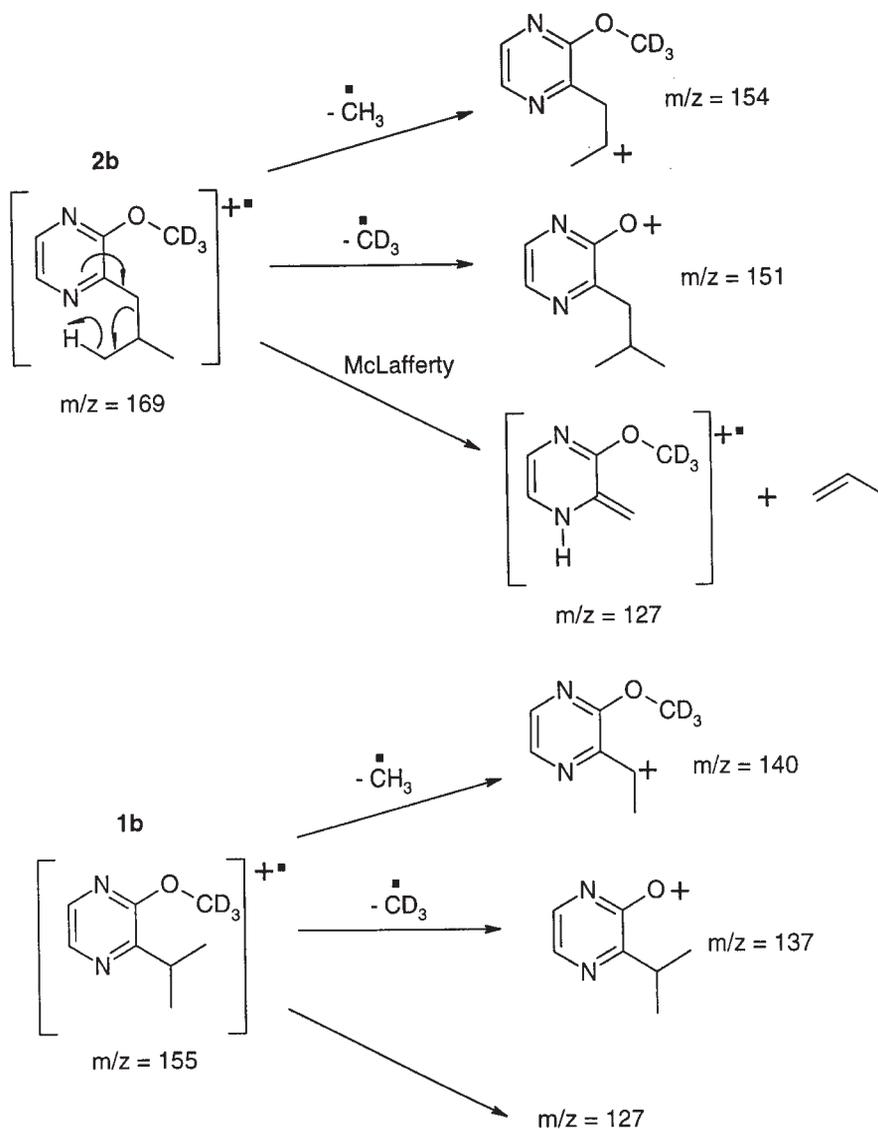


Figure 2.

dilution tracers since the deuterium label remains incorporated in their respective base peaks.

## Conclusions

The chemistry developed above provides rapid access to a number of deuterated analogues of 2-methoxy-3-isobutylpyrazine and 2-methoxy-

3-isobutylpyrazine. The approach allows for selective incorporation of the deuterium label at multiple sites and its general applicability should also allow for the inclusion of other isotopic labels ( $^{13}\text{C}$ ,  $^3\text{H}$  for example). Isotopic dilution studies involving the compounds prepared are currently underway and will be reported in due course.

## Experimental

Starting materials were purchased from Aldrich Chemical Co. and used without further purification.  $^1\text{H}$ -NMR and  $^{13}\text{C}$ -NMR spectra were obtained by using a Bruker Advance DP/RX 300 MHz Digital FT-NMR with chloroform- $d$  as the solvent and internal reference unless otherwise noted. Mass spectra were obtained in electron ionization (EI) mode using a Kratos Concept 1S double focusing mass spectrometer interfaced to a Kratos DART acquisition system optically linked to a SUN SPARC workstation. Silica gel used for column chromatography (5.0% of 100 mesh up; 47.6% of 100–200 mesh and 47.4% of 200 mesh down) was purchased from Aldrich. Silica gel 60 F<sub>254</sub> (E. Merck Co.) plates of 0.2 mm thickness were used for analytical thin layer chromatography (TLC).

### *Synthesis of [ $^2\text{H}_2$ ]-Glyoxal (4 with $R_2=D$ )*

The procedure used was a modification of that described by Ramesh.<sup>10</sup> To a suspension of lithium aluminum deuteride (100 mg, 2.5 mmol) in ether (40 ml) cooled to 0°C was added a solution of diethyl oxalate (1.46 g, 10 mmol) in ether (40 ml) over a 30 min period. The temperature was maintained for an additional 30 minutes before the reaction was allowed to warm to room temperature. Water (100 ml) was then added, the organic layer separated and the aqueous layer washed with ether (2 × 40 ml). Glyoxal formation was confirmed by  $^{13}\text{C}$ -NMR which showed expected aldehyde peak at 215.7 ppm. The aqueous solution of [ $^2\text{H}_2$ ]-glyoxal could be used directly in the pyrazine synthesis or converted to its bisulphate salt by treating the aqueous glyoxal with a solution of sodium bisulfate in 40% ethanol in water. The resultant mixture is stirred for 3 h at which time the precipitated [ $^2\text{H}_2$ ]-glyoxal bisulfate was filtered and washed with ethanol (2 × 15 ml) ether (2 × 15 ml). The yield was 40% based on the mass of [ $^2\text{H}_2$ ]-glyoxal bisulfate.

*Synthesis of 2-Hydroxy-3-isopropyl-pyrazine (5a)*

A modification of the procedure described by Karmas and Spoerri<sup>7</sup> was employed. A solution of valinamide hydrochloride (1.52 g, 10 mmol) in methanol (20 ml) was cooled to  $-35^{\circ}\text{C}$ . Glyoxal (1.74 g of a 40% aqueous solution of glyoxal, 12 mmol) was added with rapid stirring. This was followed by dropwise addition of 12 M sodium hydroxide solution (2.0 ml) over 20 min while the temperature was maintained at  $-35^{\circ}\text{C}$ . After 30 min, the reaction was allowed to warm to room temperature and stirred for an additional 2 h. The reaction flask was then cooled to  $0^{\circ}\text{C}$  and 12 M hydrochloric acid (2.0 ml) was added, followed by sodium bicarbonate (2.0 g). The reaction mixture was filtered. To the filtrate, water (20 ml) was added and the methanol removed by evaporation under a reduced pressure. The product was extracted with dichloromethane ( $3 \times 50$  ml) and dried with  $\text{MgSO}_4$ . The evaporation of the solvent yielded the product **5a** in 75% (1.04 g, 7.54 mmol) and showed: TLC  $R_f=0.21$  (4% methanol in dichloromethane);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  1.23 (6 H, d,  $\text{CH}_3$ ), 3.44 (1 H, m, CH), 7.01 (1 H, d, CH), 7.27 (1 H, d, CH);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  19.9, 30.1, 123.4, 124.1, 157.5, 165.0; EIMS  $m/z$  (RI%): 138 (66), 123 (100), 110 (37), 95 (38); HRMS for  $\text{C}_7\text{H}_{10}\text{N}_2\text{O}$ , calculated 138.1688, observed 138.1674.

*Synthesis of 2-Hydroxy-3-isopropyl- $[\text{}^2\text{H}_2]$ -pyrazine (5b)*

The procedure described above for **5a** was employed using an aqueous solution of the  $[\text{}^2\text{H}_2]$ -glyoxal. **5b** (64% yield) showed: TLC  $R_f=0.21$  (4% methanol in dichloromethane);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  1.26 (6 H, d,  $\text{CH}_3$ ), 3.42 (1 H, m, CH).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  20.3, 30.5, 123.2, 124.5, 157.8, 165.3; EIMS  $m/z$  (RI%): 140 (65), 125 (100), 112 (36), 97 (37); HRMS for  $\text{C}_7\text{H}_8\text{D}_2\text{N}_2\text{O}$ , calculated 140.1529, observed 140.1604.

*Synthesis of 2-Hydroxy-3-isobutyl-pyrazine (6a)*

The procedure for the preparation of **5a** was employed with leucinamide hydrochloride used in place of the valinamide hydrochloride to yield **6a** in 90%. The product showed: TLC  $R_f=0.23$  (4% methanol in dichloromethane);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  0.82 (6 H, d,  $\text{CH}_3$ ), 2.08 (1 H, m, CH), 2.55 (2 H, d,  $\text{CH}_2$ ), 7.04 (1 H, d, CH), 7.29 (1 H, d,

CH);  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  22.3, 26.3, 41.5, 123.4, 123.9, 157.8, 160.1; EIMS  $m/z$  (RI%): 152 (12), 137 (25), 110 (100), 81 (15); HRMS for  $\text{C}_8\text{H}_{12}\text{N}_2\text{O}$ , calculated 152.0950, observed 154.0956.

#### *Synthesis of 2-Hydroxy-3-isobutyl-[ $^2\text{H}_2$ ]-pyrazine (6b)*

The procedure described above for **6a** was employed using an aqueous solution of the [ $^2\text{H}_2$ ]-glyoxal to **6b** in 69% yield. The product showed: TLC  $R_f$ =0.23 (4% methanol in dichloromethane);  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  1.04 (6H, d,  $\text{CH}_3$ ), 2.18 (1H, m, CH), 2.68 (2H, d  $\text{CH}_2$ );  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  20.1, 27.4, 42.4, 123.8, 124.5, 158.3, 166.8; EIMS  $m/z$  (RI%): 154 (10), 139 (24), 112 (100), 86 (24); HRMS for  $\text{C}_8\text{H}_{12}\text{D}_2\text{N}_2\text{O}$ , calculated 154.1786, observed 154.1834

#### *Synthesis of 2-Methoxy-3-isopropylpyrazine (1)*

Sodium hydride (320 mg of a 60% dispersion in mineral oil, 8.00 mmol) was washed with  $3 \times 5$  ml dry hexane. The sodium hydride was then suspended in 5 ml of dry THF and the reaction flask cooled to 0 °C before addition of 2-hydroxy-3-isopropylpyrazine (**5a**, 1.00 g, 7.24 mmol). The reaction mixture was stirred for 30 min at which time iodomethane (1.14 g, 8.00 mmol) was added. The reaction was stirred at room temperature for 48 h before the contents of the flask were diluted with water (30 ml). THF was removed by evaporation under a reduced pressure and the remaining aqueous solution was extracted with dichloromethane ( $3 \times 50$  mL). The organic layers were combined, washed with a 5% aqueous solution of sodium thiosulfate ( $2 \times 20$  mL) and dried over  $\text{MgSO}_4$ . The solvent was removed by evaporation under a reduced pressure and the crude product purified on a silica gel column (using 4% methanol in dichloromethane as the eluent) to give **1** in 89% yield (0.98 g, 6.45 mmol). The product showed: TLC  $R_f$ =0.89 (4% methanol in dichloromethane);  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  1.19 (6H, d,  $\text{CH}_3$ ), 3.39 (1H, m, CH), 5.24 (3H, s,  $\text{CH}_3$ ), 7.10 (1H, d, CH), 7.38 (1H, d, CH);  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  19.9, 30.0, 43.3, 123.4, 124.1, 157.5, 164.9; EIMS  $m/z$  (RI%): 152 (52), 137 (100), 124 (22), 105 (12), 95 (6); HRMS for  $\text{C}_8\text{H}_{12}\text{N}_2\text{O}$ , calculated 152.1927, observed 152.1874.

*Synthesis of 2-Methoxy-3-isopropyl-[<sup>2</sup>H<sub>2</sub>]-pyrazine (1a)*

The procedure described above for **1** was employed utilizing 2-hydroxy-3-isopropyl-[<sup>2</sup>H<sub>2</sub>]-pyrazine (**5b**) to give **1a** in 83% yield. The product showed: TLC  $R_f$ =0.87 (4% methanol in dichloromethane); <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  1.23 (6 H, d, CH<sub>3</sub>), 3.32 (1 H, m, CH), 3.23 (3 H, s, CH<sub>3</sub>); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  20.3, 30.5, 43.3, 123.5, 124.5, 157.2, 165.3; EIMS  $m/z$  (RI%): 154 (56), 139 (100), 126 (23), 111 (13), 98 (5); HRMS for C<sub>8</sub>H<sub>10</sub>D<sub>2</sub>N<sub>2</sub>O, calculated 154.1788, observed 154.1801.

*Synthesis of 2-[<sup>2</sup>H<sub>3</sub>]-Methoxy-3-isopropylpyrazine (1b)*

The procedure described above for **1** was employed using [<sup>2</sup>H<sub>3</sub>] -iodomethane to give **1b** in 87% yield. The product showed: TLC  $R_f$ =0.62 (4% methanol in dichloromethane); <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  1.21 (6 H, d, CH<sub>3</sub>), 3.48 (1 H, m, CH), 6.98 (1 H, d, CH), 7.22 (1 H, d, CH); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  19.9, 30.3, 46.5, 121.6, 127.9, 155.8, 164.7; EIMS  $m/z$  (RI%): 155 (97), 140 (69), 137 (57), 127 (100), 112 (82); HRMS for C<sub>8</sub>H<sub>9</sub>D<sub>3</sub>N<sub>2</sub>O, calculated 155.1689, observed 155.1834.

*Synthesis of 2-[<sup>2</sup>H<sub>3</sub>]-Methoxy-3-isopropyl-[<sup>2</sup>H<sub>2</sub>]-pyrazine (1c)*

The procedure described above for **1** was employed utilizing 2-hydroxy-3-isopropyl-[<sup>2</sup>H<sub>2</sub>]-pyrazine (**5b**) and [<sup>2</sup>H<sub>3</sub>]-iodomethane to give **1c** in 89% yield. The product showed: TLC  $R_f$ =0.87 (4% methanol in dichloromethane); <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  1.19 (6 H, d, CH<sub>3</sub>), 3.40 (1 H, m, CH); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  20.4, 30.3, 43.3, 122.3, 123.6, 157.4, 165.8; EIMS  $m/z$  (RI%): 157 (93), 142 (62), 139 (55), 129 (100), 114 (80); HRMS for C<sub>8</sub>H<sub>8</sub>D<sub>5</sub>N<sub>2</sub>O, calculated 157.1629, observed 157.1687.

*Synthesis of 2-Methoxy-3-isobutylpyrazine (2)*

The procedure described above for **1** was employed using 2-hydroxy-3-isobutyl-pyrazine (**6a**) to give **2** in 89% yield. The product showed: TLC  $R_f$ =0.94 (4% methanol in dichloromethane); <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  0.89 (6 H, d, CH<sub>3</sub>), 2.15 (1 H, m, CH), 2.62 (2 H, d CH<sub>2</sub>), 3.45 (3 H, s, CH<sub>3</sub>), 6.96 (1 H, d, CH), 7.15 (1 H, d, CH); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  22.5, 26.4, 37.0, 42.0, 122.3, 127.6, 156.5, 160.2;

EIMS  $m/z$  (RI%): 166 (8), 151 (23), 139 (6), 124 (100), 109 (6), 94 (17); HRMS for  $C_9H_{14}N_2O$ , calculated 166.2186, observed 166.2068.

#### *Synthesis of 2-Methoxy-3-isobutyl-[ $^2H_2$ ]-pyrazine (2a)*

The procedure described above for **1** was employed using 2-hydroxy-3-isobutyl-[ $^2H_2$ ]-pyrazine (**6b**) to give **2a** in 92% yield. The product showed: TLC  $R_f$ =0.92 (4% methanol in dichloromethane);  $^1H$ -NMR ( $CDCl_3$ , 300 MHz)  $\delta$  1.26 (6 H, d,  $CH_3$ ), 2.38 (1 H, m, CH), 2.62 (2 H, d  $CH_2$ ), 3.87 (3 H, s,  $CH_3$ );  $^{13}C$ -NMR ( $CDCl_3$ , 75 MHz)  $\delta$  22.8, 27.7, 41.6, 53.3, 135.8, 138.2, 147.9, 159.0; EIMS  $m/z$  (RI%): 168 (9), 153 (22), 141 (7), 126 (100), 109 (3), 96 (12); HRMS for  $C_9H_{12}D_2N_2O$ , calculated 168.2068, observed 168.2109.

#### *Synthesis of 2-[ $^2H_3$ ]-Methoxy-3-isobutylpyrazine (2b)*

The procedure described above for **1** was employed using 2-hydroxy-3-isobutyl-pyrazine (**6a**) and [ $^2H_3$ ]-iodomethane to give **2b** in 89% yield. The product showed: TLC  $R_f$ =0.66 (4% methanol in dichloromethane);  $^1H$ -NMR ( $CDCl_3$ , 300 MHz)  $\delta$  0.92 (6 H, d,  $CH_3$ ), 2.20 (1 H, m, CH), 2.66 (2 H, d  $CH_2$ ), 6.97 (1 H, d, CH), 7.19 (1 H, d, CH);  $^{13}C$ -NMR ( $CDCl_3$ , 75 MHz)  $\delta$  22.5, 26.4, 36.4, 42.0, 122.2, 127.5, 156.5, 160.3; EIMS  $m/z$  (RI%): 169 (32), 154 (33), 151 (33), 127 (100), 98 (22); HRMS for  $C_9H_{11}D_3N_2O$ , calculated 169.1945, observed 169.1941.

#### *Synthesis of 2-[ $^2H_3$ ]-Methoxy-3-isobutyl-[ $^2H_2$ ]-pyrazine (2c)*

The procedure described above for **1** was employed using 2-hydroxy-3-isobutyl-[ $^2H_2$ ]-pyrazine (**6b**) and [ $^2H_3$ ]-iodomethane to give **2c** in 93% yield. The product showed: TLC  $R_f$ =0.91 (4% methanol in dichloromethane);  $^1H$ -NMR ( $CDCl_3$ , 300 MHz)  $\delta$  1.25 (6 H, d,  $CH_3$ ), 2.43 (1 H, m, CH), 2.68 (2 H, d  $CH_2$ );  $^{13}C$ -NMR ( $CDCl_3$ , 75 MHz)  $\delta$  21.9, 27.8, 41.6, 53.7, 135.3, 137.2, 147.4, 158.5; EIMS  $m/z$  (RI%): 171 (31), 156 (32), 153 (31), 129 (100), 94 (24); HRMS for  $C_9H_{11}D_3N_2O$ , calculated 171.1786, observed 171.1674.

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