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Total chemical synthesis of 2-ethenyl-3,5-dimethylpyrazine and 3-ethenyl-2,5-dimethylpyrazine

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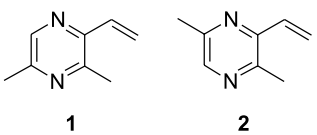
Abstract—The aroma compounds 2-ethenyl-3,5-dimethylpyrazine **1** and 3-ethenyl-2,5-dimethylpyrazine **2** were synthesized via a new chemical route. The key steps of the synthesis involve cyclocondenzation of 1-[bicyclo[2.2.1]5-hepten-2-yl]-1,2-propanedione and 1,2-propanediamine, aromatization of the resulting 5,6-dihydropyrazines, and subsequent Retro-Diels–Alder reaction to generate pyrazines **1** and **2**. Pyrazine **1**, a powerful odorant, was obtained in large excess (8:2) when *endo*-1-[bicyclo[2.2.1]5-hepten-2-yl]-1,2-propanedione was used as intermediate substrate.

1. Introduction

Pyrazines are heterocycles which exhibit nutty, roasted, or earthy flavor tonalities. Two particularly interesting pyrazines with earthy aroma characteristics and low odor thresholds are 2-ethenyl-3,5-dimethylpyrazine **1** and 3-ethenyl-2,5-dimethylpyrazine **2** (Scheme 1).[1] Pyrazine **1** was identified in freshly roasted and ground Brazilian and Columbian coffee,[2] coffee powder and coffee brew,[3] and roasted seeds of wild mango,[4] while pyrazine **2** was found among the aroma volatiles of roasted peanut,[5] Corn Tortilla Chips,[6] and green kohlrabi.[7] Two synthetic routes to produce ethenylpyrazines have been described in literature. The synthesis of 2-ethenyl-3-ethyl-5-methylpyrazine and 3-ethenyl-2-ethyl-5-methylpyrazine was done by bromination of 2,3-diethyl-5-methylpyrazine followed by elimination of hydrogen bromide with total yields lower than 1%.[8] In another study, compound **1** was produced with 5% yield from 2,6-dimethylpyrazine and vinyl magnesium bromide via Grignard reaction.[9] Herein, we describe a novel and efficient total synthesis of pyrazines **1** and **2**.



1 **2**

Scheme 1. Molecular structure of 2-ethenyl-3,5-dimethylpyrazine **1** and 3-ethenyl-2,5-dimethylpyrazine **2**.

2. Results and discussion

Ethenylpyrazines **1** and **2** were synthesized as described in Scheme 2. The first two steps, the condensation of 5-norbornen-2-carboxaldehyde **3** with acetaldehyde and the oxidation of the produced pair of acyloins **4** and **5**, were performed as described in the literature.[10,11] The experimental procedure was slightly modified, notably by the addition of acetaldehyde at several time points, in order to increase the yield (40%). The resulting diketone **6**, identified as a mixture of *endo* and *exo* isomers in a ratio of 3:7 by comparison of ^{1}H NMR data with those of the literature,[11] was then reacted with 1,2-propanediamine to yield 5,6-dihydropyrazines **7** and **8** which were subsequently oxidized to pyrazines **9** and **10** in the presence of MnO_2. The last two steps were achieved in an overall yield of 41%. By interpretation of ^{1}H NMR data of the mixture of pyrazines **9** and **10**, the ratio between the *endo* and *exo* isomers was determined as 3:7. The *endo* isomers (*endo*-**9** and *endo*-**10**) were separated from the *exo* isomers (*exo*-**9** and *exo*-**10**) by preparative chromatography on silica gel. Further ^{1}H NMR analysis of the respective fractions indicated that the *exo* fraction consisted of an equimolar mixture of **9** and **10**, while the *endo* fraction was composed of *endo*-**9** and *endo*-**10** in a molar ratio of 8:2. The stereochemistry of the major compound (*endo*-**9**) was further validated by HMBC NMR analysis. As shown in Scheme 3, the aromatic hydrogen at position 6 of the pyrazine ring correlated intensely with the

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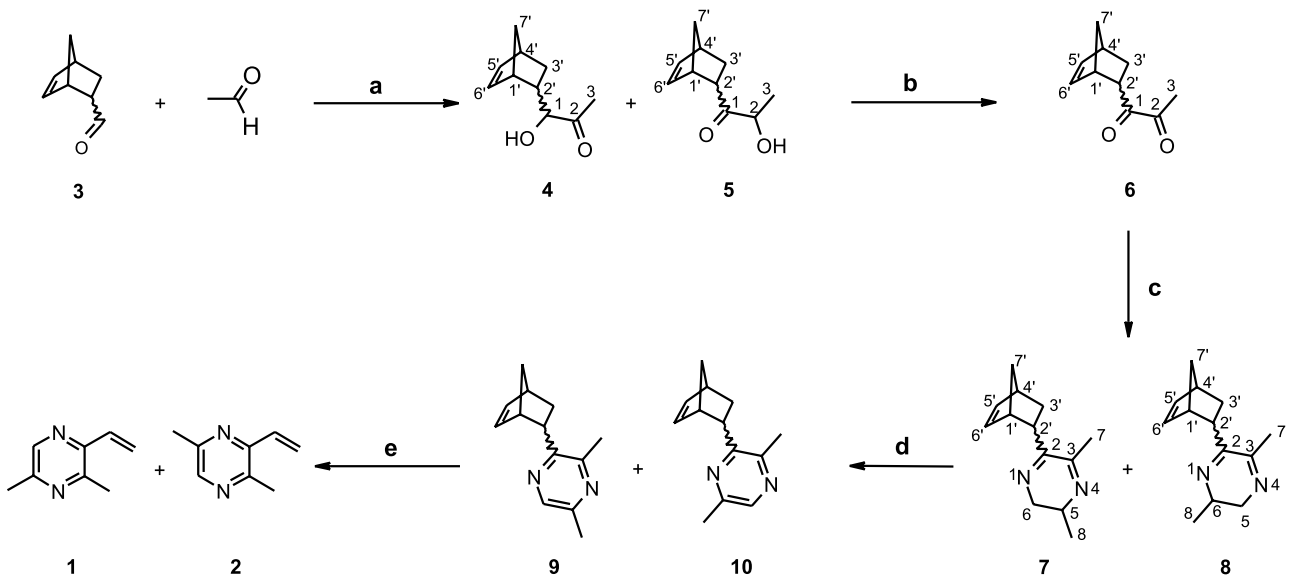


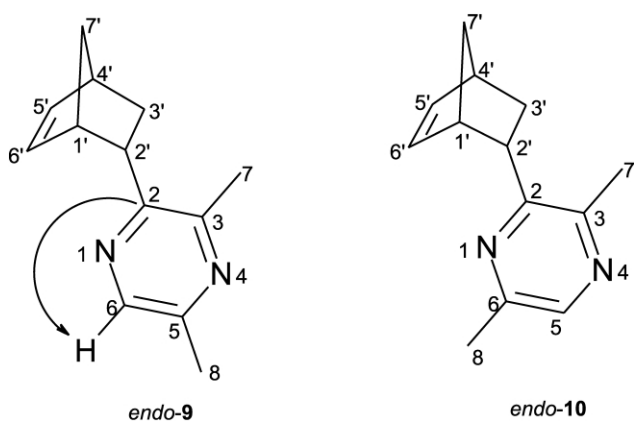
Scheme 2. Synthetic route to 2-ethenyl-3,5-dimethylpyrazine **1** and 3-ethenyl-2,5-dimethylpyrazine **2**. (a) EtOH, thiazolium catalyst, triethylamine; (b) Ethoxyethanol, AcOH, Bi_2O_3; (c) 1,2-Propanediamine, diethyl ether; (d) EtOH, KOH, MnO_2; (e) Pyrolysis (600°C, 1–2 Pa).

norbornenyl substituted carbon at position 2, whereas a comparable correlation could not be found for the other regio isomer (*endo*-**10**).

The Retro-Diels–Alder reaction of the mixture of *exo*-**9** and *exo*-**10** resulted in the formation of pyrazines **1** and **2** in an equimolar ratio, while that of the *endo* isomers gave **1** and **2** in a ratio of 8:2. In both pyrolysis reactions, pyrazines **1** and **2** were obtained in 85% yield.

^{1}H NMR, MS and Retention Index (RI) data of compound **1** were in agreement with those reported in the literature.[12]

In conclusion, 2-ethenyl-3,5-dimethylpyrazine **1** and 3-ethenyl-2,5-dimethylpyrazine **2** were produced in five steps with a global yield of 14%. The more aroma-active pyrazine **1** was obtained as major compound when the pyrolysis was performed on the mixture of the *endo*-**9** and *endo*-**10** isomers. The approach described here could be used to synthesize other alkenylpyrazines.



Scheme 3. *endo*-2-[Bicyclo[2.2.1]5-hepten-2-yl]-3,5-dimethylpyrazine **9** and **10**.

3. Experimental

3.1. General methods

5-Norbornen-2-carboxaldehyde (a mixture of isomers *endo* and *exo*) was purchased from Lancaster Synthesis (Strasbourg, France). All other chemicals were from Sigma Aldrich Chemical Co (Buchs, Switzerland).

NMR spectra were recorded at 400 MHz for ^{1}H and 100 MHz for ^{13}C on a Bruker AC 400 spectrometer. GC-MS analyses were performed on a Finnigan MAT-8430 mass spectrometer combined with an HP 5890 gas chromatograph equipped with a DB-1 capillary column (30 m×0.25 mm, film thickness 0.25 μm, J & W Scientific), a splitless injector, and using helium as carrier gas (1.5 mL min^{-1}). The MS-EI spectra were generated at 70 eV and MS-CI spectra at 150 eV with ammonia as reagent gas. High-resolution mass spectra were acquired on a Micromass QToF-2 instrument (Micromass, Manchester, UK). Data acquisition and data evaluation were performed using the Micromass MassLynx 4.0 software. Survey mass spectra were acquired by directly infusing sample dissolved in methanol/water (1:1, v/v) into the electrospray ion source of the instrument at a flow rate of 5 μl/min. The electrospray (needle) voltage was set at 3 kV, and the ion source block temperature at 120°C. The cone gas (nitrogen) was set to a flow rate of 50 l/min and the desolvation gas to 300 l/min with a temperature of 140°C. Accurate mass measurements were realized by mixing the respective samples obtained with a calibrant solution (1 mg/ml NaI, 0.05 mg/ml CsI in water/propanol-2, 60:40, v/v) and infused as described above. Under these conditions, all compounds showed up as both the $[M+H]^+$ and $[M+Na]^+$ ion. About 20 scans were averaged at different cone voltages (1 min total acquisition time at ca. 1 scan/s), and accurate mass data were obtained using a suitable lockmass from the calibrant. The elemental composition of the $[M+H]^+$ and $[M+Na]^+$ peaks was calculated using a software developed in-house as described

elsewhere.[13] Measured values and calculated composition matched in all cases with +/−2.2 mmu or better.

3.2. Synthesis of ethenylpyrazines

3.2.1. 1-[Bicyclo[2.2.1]5-hepten-2-yl]-2-hydroxy-1-propanone 4 and 1-[bicyclo[2.2.1]5-hepten-2-yl]-1-hydroxy-2-propanone 5. The acyloin condensation of 5-norbornen-2-carboxaldehyde **3** and acetaldehyde was realized according to the protocol described by Stetter and Dämbkes.[10] The procedure was slightly modified in order to increase the yields, notably by the addition of excesses of acetaldehyde at several time points. To 75.3 g (0.616 mol) of compound **3** in 158 ml EtOH, were added 104 ml (1.85 mol) of acetaldehyde and 37.8 g of 3,4-dimethyl-5-(2-hydroxyethyl)-thiazolium iodide (0.616 mol). 49.3 ml (0.355 mol) of triethylamine were added dropwise under an argon atmosphere and stirring and the reaction mixture was heated to 65°C. After 4 and 8 h, respectively, further excesses of acetaldehyde (51.8 mL, 0.927 mol) were added and after 24 h, the mixture was cooled to room temperature, poured onto ice (250 mL), and extracted with CH_2Cl_2 (3×75 mL). The combined organic phases were washed with an aqueous solution of 1 M HCl (100 mL) and with a saturated aqueous solution of $NaHCO_3$ (100 mL). The organic phase was dried over $MgSO_4$, the solvent was evaporated, and the residue was distilled under reduced pressure (76–84°C/6 Pa). 101,4 g of a yellow oil (49%) was obtained and characterized as a mixture of isomers **4** (*endo*+*exo*) and **5** (*endo*+*exo*).

Compounds **4** *and* **5**. ^{1}H NMR ($CDCl_3$) δ 4.42, 4.37, 4.30, and 4.19 (each q, 1H, J=7 Hz, H_2 (**5**), 4.11, 3.73 and 3.55 (each d, 1H, H_1 (**4**)), 3.60 (br s, 1H, OH), 3.25–3.45 (m, 3H), 2.26, 2.24 and 2.19 (each s, 3H, H_3 (**4**)), 2.20–0.95 (m, 4H), 1.44, 143, 1.40, and 1.37 (each d, 3H, H_3 (**5**)).

3.2.2. 1-[Bicyclo[2.2.1]5-hepten-2-yl]-1,2-propanedione 6 (*endo*+*exo*). The synthesis of the protected diketone **6** was realized according to the protocol described by Stetter and Dämbkes.[10] 50 g (0.3 mol) of the protected acyloins **4** and **5** were dissolved in 250 ml of ethoxyethanol and 75 mL of acetic acid were added. The mixture was heated to 105°C and 50 g (0.107 mol) of Bi_2O_3 were added under agitation. After 5 h the reaction mixture was cooled to room temperature, filtered, and the filtrate was washed several times with CH_2Cl_2 (100 mL). The washed filtrate was concentrated under reduced pressure (1.3 kPa) and the diketone **6** was distilled (55–65°C under 6 Pa). 40.4 g (0.256 mol) of a yellow oil were obtained (70% *exo* and 30% *endo*), corresponding to a yield of 40% based on the amount of norbornen-2-carboxaldehyde used. ^{1}H NMR was compared with literature data.[11]

^{1}H NMR ($CDCl_3$) δ 6.19 (m, 1H, *endo* $H_{5'}$, *exo* $H_{5'}$ and *exo* $H_{6'}$), 5.77 (dd, 1H, J=2.8, 5.6 Hz, *endo* $H_{6'}$), 3.66 (dt, 1H, J=3.8, 9.8 Hz, *endo* $H_{2'}$), 3.28 (m, 1H, *endo* $H_{1'}$), 3.05 (dd, 1H, J=5.1, 9.3 Hz, *exo* $H_{1'}$), 2.95 (m, 2H, $H_{4'}$ and *exo* $H_{1'}$), 2.38 (s, 3H, *exo* CH_3), 2.31 (s, 3H, *endo* CH_3), 1.84 (m, 1H, $H_{3'b}$), 1.5–1.2 (m, 3H, $H_{3'a}$ and H_7).

3.2.3. 2-[Bicyclo[2.2.1]5-hepten-2-yl]-3,5-dimethyl-5,6-dihydropyrazine 7 and 3-[bicyclo[2.2.1]5-hepten-2-yl]-2,5-dimethyl-5,6-dihydropyrazine 8 (*endo*+*exo* isomers). 3 g (40.5 mmol) of 1,2-propanediamine were added to 5.0 g (30.5 mmol) of 1-[bicyclo[2.2.1]5-hepten-2-yl]-1,2-propanedione **6** in 100 mL dried diethyl ether. The reaction was performed at ambient temperature until the complete consumption of the diketone (16 h). After dilution with 100 ml diethyl ether, the reaction mixture was washed with 100 ml brine, dried over $MgSO_4$ and the organic phase was concentrated under reduced pressure. The crude mixture of 2-[bicyclo[2.2.1]5-hepten-2-yl]-3,5-dimethyl-5,6-dihydropyrazine **7** and 3-[bicyclo[2.2.1]5-hepten-2-yl]-2,5-dimethyl-5,6-dihydropyrazine **8** was directly used in further reactions without purification. Meanwhile, the mixture was analyzed by GC–MS using a DB-1 capillary column. The temperature program was 5 min isothermal at 40°C, then raised to 260°C at 4°C min^{-1}, and kept at 260°C for 5 min. These new compounds were tentatively identified on the basis of their NMR (^{1}H and ^{13}C), MS, IR and HRMS data analysis.

Compounds **7** *and* **8**. ^{1}H NMR ($CDCl_3$) δ 6.1–5.5 (series of m, 2H, $H_{5'}$ and $H_{6'}$), 3.6–2.15 (series of m, 6H, $H_{1'}$, $H_{2'}$, $H_{4'}$, H_5 and H_6), 2.09–1.96 (series of s, 3H, H_7), 2.1–1.0 (series of m, 4H, $H_{3'}$ and $H_{7'}$), 1.2–1.1 (series of d, 3H, H_8). ^{13}C NMR ($CDCl_3$) δ 164.7, 164.3, 163.1, 162.8, 162.3, 161.7, 160.0, 159.8, 159.6, 159.3, 159.0 and 158.8 (C_2 and C_3), 138.8, 138.3, 137.1, 136.8, 136.3, 136.2, 135.9, 135.8, 135.5, 133.4, 130.9 and 130.8 ($C_{5'}$ and $C_{6'}$), 51.5, 51.4, 51.3, 51.2, 49.9, 49.8, 49.7, 49.6, 49.5, 49.4, 49.3, 49.2 and 49.0 (C_5 and C_6), 45.9, 45.7, 45.6, 45.4, 45.2, 45.0, 44.8, 44.7, 44.2, 44.1, 43.2, 42.9, 42.7, 42.3 and 42.0 ($C_{1'}$, $C_{2'}$, $C_{4'}$, and $C_{7'}$), 31.0, 30.8, 29.8, 29.4, 29.2, 28.7, 27.1, 27.0 ($C_{3'}$), 23.2, 23.0, 22.9, 19.1, 19.0, 18.9, 18.8, 18.7 and 18.4 (C_7 and C_8). IR (neat) 3056, 2966, 2870, 1646, 1590, 1570, 1439, 711 cm$_{-1}$. HRESIMS *m*/*z* 203.1530 $[M+H]^+$ (calcd for $C_{13}H_{19}N_2$, 203.1548); *m*/*z* 225.1350 $[M+Na]^+$ (calcld for $C_{13}H_{18}N_2Na$, 225.1368).

Compound **7**. MS-EI, *m*/*z* (relative intensity): 202 (100) $[M]^+$, 187 (88), 161 (43), 137 (55), 121 (60), 80 (15), 66 (35), 54 (18), 42 (40).

Compound **8**. MS-EI, *m*/*z* (relative intensity): 202 (100) $[M]^+$, 187 (88), 161 (30), 137 (52), 121 (47), 80 (17), 66 (32), 54 (21), 42 (38).

3.2.4. 2-[Bicyclo[2.2.1]5-hepten-2-yl]-3,5-dimethylpyrazine 9 and 3-[bicyclo[2.2.1]5-hepten-2-yl]-2,5-dimethylpyrazine 10. The crude mixture of 2-[bicyclo[2.2.1]5-hepten-2-yl]-3,5-dimethyl-5,6-dihydropyrazine **7** and 3-[bicyclo[2.2.1]5-hepten-2-yl]-2,5-dimethyl-5,6-dihydropyrazine **8** was dissolved in 100 mL EtOH containing 1.9 g (33.5 mmol) KOH, and 8.0 g of MnO_2 (92 mmol) were added. The mixture was refluxed until the completion of the reaction (10 h). The reaction mixture was cooled to room temperature and filtered. The solvent was evaporated under reduced pressure and the residue (41%) was purified by column chromatography (eluent: cyclohexane/EtOAc, 9/1). A first fraction (1.75 g) corresponded to an equimolar mixture of *exo*-2-[bicyclo[2.2.1]5-hepten-2-yl]-3,5-dimethylpyrazine **9** and *exo*-3-[bicyclo[2.2.1]5-hepten-2-yl]-2,5-dimethylpyrazine **10**. A second fraction (0.75 g) corresponded to the *endo*-pyrazines with a ratio of 80:20 in

favor of the 3,5-dimethylpyrazine regioisomer. Both fractions were isolated as pale yellow oils.

endo-**9** and *endo*-**10**. ^{1}H NMR ($CDCl_3$) δ 8.04 (s, 1H, H_6 (**9**)), 7.98 (s, 1H, H_5 (**10**)), 6.14 (m, 1H, $H_{5'}$ (**9**)), 6.05 (m, 1H, $H_{5'}$ (**10**)), 5.69 (m, 1H, $H_{6'}$ (**10**)), 5.62 (m, 1H, $H_{6'}$ (**9**)), 3.50 (m, 1H, $H_{2'}$), 3.18 (m, 1H, $H_{1'}$), 2.89 (m, 1H, $H_{4'}$), 2.53 (s, 3H, H_7 (**9**)), 2.49 (s, 3H, H_7 (**10**)), 2.37 (s, 3H, H_8 (**9**)), 2.34 (s, 3H, H_8 (**10**)), 2.00 (m, 1H, $H_{3'a}$), 1.63 (m, 1H, $H_{3'b}$), 1.44 (m, 2H, $H_{7'}$). ^{13}C NMR ($CDCl_3$) δ 155.4, 153.7 (C_2 (**9**)), 151.4 (C_3 (**9**)), 149.0 (C_5 (**9**)), 139.9 (C_6 (**9**)), 139.6 (C_5 (**10**)), 136.7 ($C_{5'}$ (**9**)), 136.1 ($C_{5'}$ (**10**)), 132.9 ($C_{6'}$ (**10**)), 132.4 ($C_{6'}$ (**9**)), 50.2 ($C_{7'}$ (**9**)), 49.8 ($C_{7'}$ (**10**)), 46.5 ($C_{1'}$ (**9**)), 46.2 ($C_{1'}$ (**10**)), 43.0 ($C_{2'}$ (**10**)), 42.9 ($C_{4'}$ (**9**)), 42.8 ($C_{4'}$ (**10**)), 42.3 ($C_{2'}$ (**9**)), 30.7 ($C_{3'}$ (**9**)), 30.6 ($C_{3'}$ (**10**)), 21.9 (C_8 (**9**)), 21.4 (C_8 (**10**)), 21.1 (C_7 (**10**)), 20.9 (C_7 (**9**)).

Remarks. For ^{1}H NMR, when the compound is not mentioned means that the signals are merged. For ^{13}C NMR, only one signal has been detected at 155.4 for all the quaternary carbons of compound **10**. The signals detected at 43.0, 42.8, 21.4 and 21.1 are tentatively attributed.

IR (neat) 3057, 2967, 2866, 1570, 1531, 1444, 716 cm^{-1}. MS-EI, *m/z* (relative intensity): 200 (100) $[M]^+$, 185 (73), 159 (35), 146 (30), 133 (90), 122 (78), 66 (58), 54 (28), 42 (26). HRESIMS *m/z* 201.1370 $[M+H]^+$ (calcd for $C_{13}H_{17}N_2$, 201.1392); *m/z* 223.1200 $[M+Na]^+$ (calcld for $C_{13}H_{16}N_2Na$, 223.1211).

exo-**9** and *exo*-**10**. ^{1}H NMR ($CDCl_3$) δ 8.20 and 8.10 (each s, 1H, H_6 (**9**) and H_5 (**10**)), 6.25 (m, 2H, $H_{5'}$ and $H_{6'}$), 3.00–2.92 (m, 2H, $H_{1'}$ and $H_{4'}$), 2.85 (m, 1H, $H_{2'}$), 2.55, 2.53, 2.49 and 2.47 (each s, 3H, H_7 and H_8), 2.15 and 2.05 (each m, 1H, $H_{3'a}$), 1.79 (m, 1H, $H_{7'a}$), 1.53 (m, 1H, $H_{3'b}$), 1.40 (m, 1H, $H_{7'b}$). ^{13}C NMR ($CDCl_3$) δ 157.2, 155.2, 151.4, 149.4, 149.0 and 148.9 (C_2, C_3, C_5 (**9**) and C_6 (**10**)), 140.2 and 139.6 (C_6 (**9**) and C_5 (**10**)), 138.4, 136.7 ($C_{5'}$ and $C_{6'}$), 47.3 and 47.1 ($C_{2'}$ and/or $C_{4'}$ and/or $C_{1'}$), 45.6, 45.5 ($C_{7'}$), 42.2 and 41.9 ($C_{2'}$ and/or $C_{4'}$ and/or $C_{1'}$), 31.5 and 31.1 ($C_{3'}$), 21.8, 21.3, 21.2 and 20.8 (C_7 and C_8).

Remark. The ^{1}H and ^{13}C NMR signals are tentatively attributed.

IR (neat) 3056, 2969, 2869, 1568, 1531, 1442, 699 cm_{-1}. MS-EI, *m/z* (relative intensity): 200 (100) $[M]^+$, 185 (75), 159 (20), 146 (40), 133 (93), 122 (60), 66 (63), 54 (13), 42 (35). HRESIMS *m/z* 201.1370 $[M+H]^+$ (calcd for $C_{13}H_{17}N_2$, 201.1392); *m/z* 223.1190 $[M+Na]^+$ (calcld for $C_{13}H_{16}N_2Na$, 223.1211).

3.2.5. 2-Ethenyl-3,5-dimethylpyrazine 1 and 3-ethenyl-2,5-dimethylpyrazine 2. Retro-Diels–Alder reaction of 1 g (5 mmol) of the mixture of 2-[bicyclo[2.2.1]5-hepten-2-yl]-3,5-dimethylpyrazine **9** and 3-[bicyclo[2.2.1]5-hepten-2-yl]-2,5-dimethylpyrazine **10** was performed by gas phase pyrolysis at 600°C and 1–2 Pa, according to Kramme et al.[11] The compounds were vaporized by heat treatment to 80°C. The vapors penetrated in a quartz tube that had been heated to 600°C. After pyrolysis, the products were collected in traps that were connected to the quartz tube. The first trap, cooled with solid carbon dioxide (−78°C), contained an lightly amber oil with pronounced odor, while, in the second trap, which was cooled with liquid nitrogen, cyclopentadiene condensed. 570 mg (4.25 mmol) of a mixture of 2-ethenyl-3,5-dimethylpyrazine **1** and 3-ethenyl-2,5-dimethylpyrazine **2** were isolated (85%).

Compounds **1** *and* **2**. ^{1}H NMR ($CDCl_3$) δ 8.1–8.2 (s, 2H, H_6), 6.8–6.9 (m, 2H, H_7), 6.2–6.4 (m, 2H, H_8 *trans*), 5.4–5.55 (m, 2H, H_8 *cis*), 2.4–2.5 (s, 12H, CH_3).

Compound **1**. MS-EI, *m/z* (relative intensity): 134 (90) $[M]^+$, 133 (100), 66 (10), 54 (48), 42 (28), 39 (22). RI on DB-Wax column: 1531.

Compound **2**. MS-EI, *m/z* (relative intensity): 134 (98) $[M]^+$, 133 (100), 66 (15), 54 (23), 42 (54), 39 (23). RI on DB-Wax column: 1513.

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