Cycloisomerisations in Pd-Catalysed Spiroannulations onto Chiral Pyrazine Derivatives

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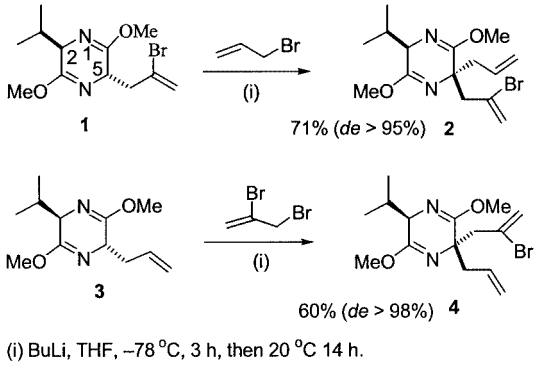
A method for 5-*exo*-*trig*-spiroannulations is described which uses the Pd complex *trans*-bis(μ-acetato)bis[*o*-(di-*o*-tolylphosphanyl)benzyl]dipalladium(II) as catalyst in cyclisation reactions of dienes with the chiral auxiliary (2*R*)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine. Extensive NMR assignments are described and used in structure determinations. Isomer identification has been verified by a separate unequivocal synthesis. Nickel catalysis with MeMgBr was compatible with cross-coupling in the spiroannulated chiral auxiliary.

Introduction

In previous reports we have described methods for the preparation of heterocyclic spiranes by palladium-catalysed cycloisomerisation reactions,[1] or by ruthenium-catalysed ring-closing metathesis reactions.[2−4] The substrates for these transformations were appropriate dienes, enynes, or homologues derived from the chiral auxiliary (2*R*)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine. On subsequent hydrolysis, the pyrazino-spirane products provide the corresponding rigid cyclic α-amino acids with the quaternary α-carbon atom being part of the ring structures.[1,2] This is a convenient method for the preparation of cyclic members of an important family of quaternary α-amino acids.[5,6]

Results and Discussion

In the Pd-catalysed cycloisomerisation, product isomers may be formed either by *exo-trig* or *endo-trig* reaction routes. This report describes cyclisations by the 5-*exo-trig* pathway. The products are spiroannulated five-membered ring derivatives of pyrazine, as shown in Scheme 2. Appropriate substrates for the cyclisation reactions were prepared according to Scheme 1.



Scheme 1

The substrate **1** was produced by alkylation of the Schöllkopf chiron (*R*)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine with 2,3-dibromopropene.[7] Lithiation of substrate **1** at −78 °C and alkylation with allyl bromide provided the 5,5-dialkenylated bromide **2**. Only one stereoisomer was observed. For the cycloisomerisation studies (Scheme 2), the diastereomer **4** with the opposite configuration at C-5 was required. Synthesis of this, in stereochemically pure form, was effected by allylation of the Schöllkopf chiron[8] and subsequent reaction with 2,3-dibromopropene, as above. In the palladium-mediated cyclisation reactions, under the conditions studied with compound **2** as substrate, intramolecular Heck products furnished the expected 5-*exo-trig*-3′,4′-bis(methylene)cyclopentane **5**, as well as the 3′-methyl isomer **6**. The modified palladacycle system *trans*-bis(μ-acetato)bis[*o*-(di-*o*-tolylphosphanyl)benzyl]-dipalladium(II) of Herrmann was used as the catalyst.[9,10] The product isomer ratio **5**/**6** was 1:1.1 under these conditions. The cycloisomerisation proceeded in the same manner with the diastereomer **4**. The isomeric products **5** and

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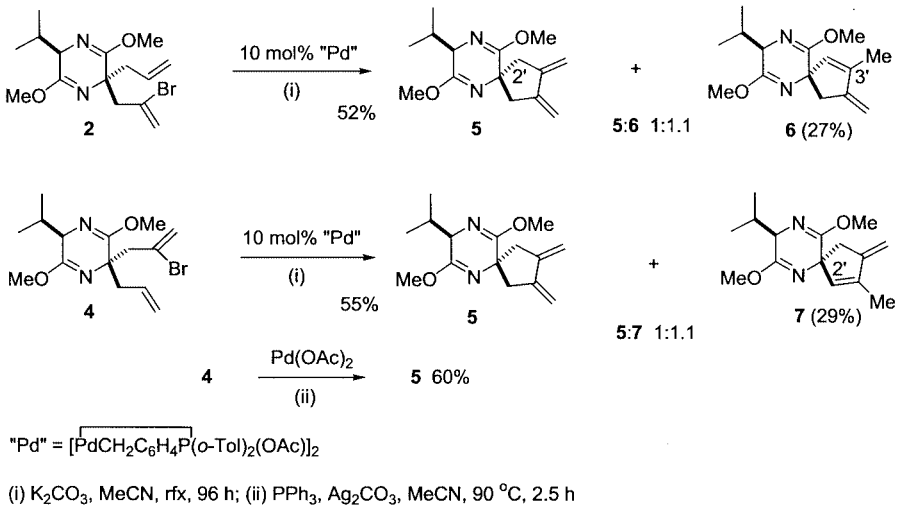
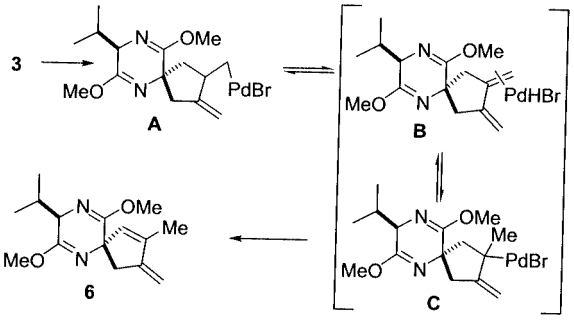


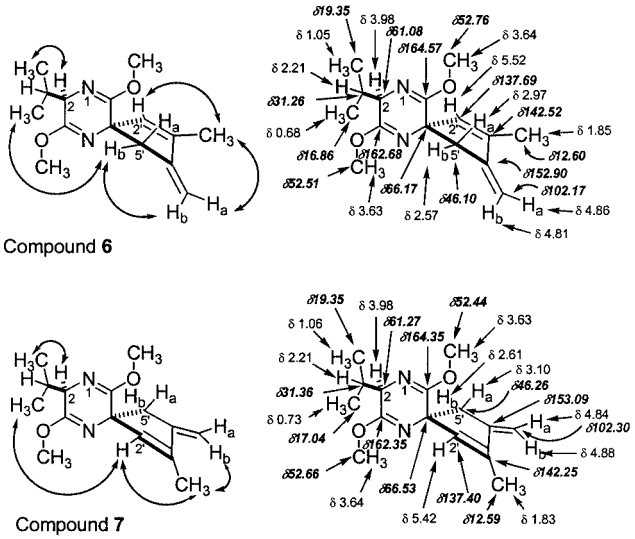
Scheme 2

7 were formed in similar yields and with the same isomer distribution. However, when using palladium acetate and triphenylphosphane together with silver carbonate in acetonitrile, the bis(methylene) product **5** was obtained free of its methyl isomer **7**. Under these conditions a small amount of the 6-*endo*-*trig*-spiroannulated product was observed. This was readily removed by flash chromatography.

An attempt to rationalise the reaction pathway is shown in Scheme 3. The bis(methylene) product **5** is formed by the usual pathway, which involves addition of the organopalladium moiety to the double bond as in structure **A** (Scheme 3) followed by an elimination reaction. Attempts to rationalise the formation of the methyl product as an isomerisation of compound **5**, the first product formed under these reaction conditions, were not successful. In separate experiments, the bis(methylene) isomer **5** was not isomerised to the methyl isomer **6** under the conditions of the reaction. A catalytic cycle involving the oxidation of $Pd^{II} \rightarrow Pd^{IV}$ could offer an explanation for the outcome of the reaction.[11,12] Most recent evidence, however, favours a $Pd^{0} \rightarrow Pd^{II}$ cycle.[13] It seems most likely that formation of the methyl product starts with the usual cycloadduct formation indicated by structure **A** in Scheme 3. Hydridopalladium elimination then leads, initially, to the complex **B**, which may further dissociate to furnish the bis(methylene) product **5**. If, however, the hydridopalladium remains coordinated to the double bond for some time, readdition can occur with the opposite regiochemistry. The new adduct is formulated as structure **C**. A new hydridopalladium elimination can then take place in an endocyclic manner, thereby providing the methyl derivative **6**.



Scheme 3

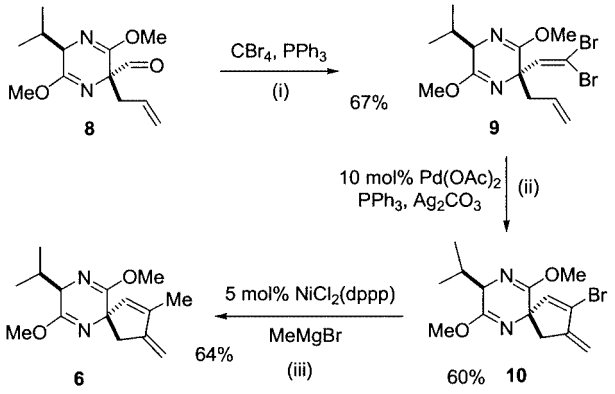


Scheme 4

The structures of the isomeric products **5**−**7** were assigned from their NMR spectra. In Scheme 4 complete chemical shift assignments for the two isomeric methyl derivatives **6** and **7** are shown. Diagnostic NOE correlations are also indicated. In compound **6** an NOE correlation is observed between the high-field methyl group in the 2-isopropyl substituent and the 5-methylene protons. Hence the methylene group has a *cis* relationship to the 2-isopropyl group with respect to the pyrazine ring plane. This interaction is with both methylene protons. It is drawn for one of them, namely 5′-H_b. The two methyl groups of the isopropyl substituents resonate at different field values. Only the high-field methyl group in the isopropyl substituent is involved in the interaction. This is also the case for the other

spiroannulated derivatives. An interaction is also seen between the terminal olefinic proton and the 5′-methylene protons. In the isomeric structure **7**, an NOE correlation is observed between the high-field methyl protons in the isopropyl substituent and the 2′-H olefinic proton. These, therefore, have a *cis* relationship. There is no interaction between the 5′-methylene protons and the protons in the isopropyl substituent. An interaction is also seen between 2′-H and the 3′-methyl substituent. In the 3′,4′-bis(methylene) product **5**, an NOE interaction occurs between the high-field methyl protons in the isopropyl substituent and the *cis*-methylene protons, whereas no interaction is observed with the *trans*-methylene protons. The data from the NMR measurement are all in agreement with the regiochemistry for the double bond as drawn in the structures discussed.

Finally, a method has been developed for the synthesis of the 3′-methyl derivative **6** as a pure isomer, as shown in Scheme 5. The formyl substrate **8** was produced by a hydroxymethylation reaction of the lithiated allyl substrate **3** followed by a Swern oxidation.[14] For the palladium-catalysed cyclisation the dibromide **9** was prepared by a Wittig-type reaction between the formyl derivative **8** and tetrabromomethane. The desired bromide **10** was formed in 60% yield using the catalyst system $Pd(OAc)_2$ and triphenylphosphane, with silver carbonate as base. The relatively high yield of the cyclic product **10** indicates stereoisomerisation at the terminal dibromomethylene carbon atom, subsequent to the palladation reaction, in order to arrive at the *cis* configuration at the reactive center. This configuration is necessary for cyclisation to occur. Various methods were tried for methyl displacement of the 3′-bromo substituent in intermediate **10**. Reductive debromination was a side-reaction in most cases. With a methyl Grignard reagent and Ni catalysis, however, alkylation was effected in a satisfactory yield with formation of the desired product **6**.



Scheme 5

In conclusion, we have described Pd-catalysed cycloisomerisation reactions as a method for spiroannulation onto the chiral auxiliary (2*R*)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine in the 5-position. The reaction proceeds by the *exo-trig* pathway. Nickel catalysis with a Grignard reagent is compatible with cross-coupling in the spiroannulated chiral auxiliary.

Experimental Section

General: IR spectra were recorded with a Nicolet Magna FT-IR 550 spectrophotometer. ^1H NMR spectra were recorded in $CDCl_3$ at 500 or 300 MHz with a Bruker DPX 500 or DPX 300; ^{13}C NMR spectra were recorded in $CDCl_3$ at 75 MHz or 50 MHz; chemical shifts are reported in ppm with residual $CHCl_3$ (δ = 7.24 ppm) and $CDCl_3$ (δ = 77 ppm) as references; *J* values are given in Hz; COSY, NOESY and ROESY were used for homonuclear assignments of ^1H-shifts; XHCORR and COLOC were used for heteronuclear ^{13}C detected 2D spectroscopy. Mass spectra (MS) under electron-impact conditions (EI) were recorded at 70 eV ionizing potential; the spectra are presented as *m*/*z* (% rel. int). Dry THF was distilled from sodium/benzophenone under argon. Solvents were degassed by bubbling argon through them. For reasons of consistency, the atom numbering in the formulae and names might not be in accordance with nomenclature rules.

(2*R*,5*R*)-5-Allyl-5-(2-bromoallyl)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine (2): *n*-Butyllithium (1.45 mL, 3.63 mmol, 2.5 M in heptane) was added dropwise to a solution of (2*R*,5*S*)-5-(2-bromoallyl)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine (**1**)[7] (1.00 g, 3.30 mmol) in dry THF (30 mL) under argon at −60 °C. The solution was cooled to −78 °C. After 45 min, a precooled (−78 °C) solution of allyl bromide (1.20 g, 9.90 mmol) in THF (3 mL) was added. The mixture was stirred at −78 °C for 3 h and left to reach ambient temperature overnight before 10% aqueous ammonium chloride was added. The mixture was extracted with diethyl ether. The diethyl ether solution was dried ($MgSO_4$) and the solvents were evaporated at reduced pressure. The residual product was purified by flash chromatography on silica gel using CH_2Cl_2/hexane (2:1); yield 0.80 g (71%, *de* > 95%) of a colourless oil. $[\alpha]_D^{20}$ = −49.4 (*c* = 0.0248 in $CHCl_3$). IR (film): $\tilde{\nu}$ = 3077 (w), 2970 (m), 2943 (m), 2871 (w), 1694 (s), 1624 (m), 1436 (m), 1308 (m), 1240 (s), 1196 (m), 1160 (s), 1013 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.68, 1.05 [2 × d, *J* = 6.9 Hz, 6 H, $CH(CH_3)_2$], 2.27 [dsept, *J* = 3.4 and *J* = 6.9 Hz, 1 H, $CH(CH_3)_2$], 2.28, 2.46 (2 × dd, *J* = 7.3 and *J* = 13.1 Hz, 2 H, $CH_2CH{=}CH_2$), 2.72, 3.05 (2 × d, *J* = 14.0 Hz, 2 H, $CH_2CBr{=}CH_2$), 3.64 (s, 3 H, OCH_3), 3.68 (s, 3 H, OCH_3), 3.79 [d, *J* = 3.4 Hz, 1 H, $CHCH(CH_3)_2$], 4.97 (dd, *J* = 1.1, 13.5 Hz, 1 H, $=CH_2$*cis*), 5.01 (dd, *J* = 1.1, 14.6 Hz, 1 H, $=CH_2$ *trans*), 5.42 (d, *J* = 1 Hz, 1 H, $CBr{=}CH_2$), 5.50 (dddd, *J* = 7.3, *J* = 7.3, J_{cis} = 13.5 Hz and J_{trans} = 14.6 Hz, 1 H, $CH{=}CH_2$), 5.53 (d, *J* = 1 Hz, 1 H, $CBr{=}CH_2$) ppm. ^{13}C NMR ($CDCl_3$): δ = 16.6, 19.6 [$CH(CH_3)_2$], 30.3 [$CH(CH_3)_2$], 45.2 ($CH_2CH{=}CH_2$), 49.9 ($CH_2CBr{=}CH_2$), 51.8 (6-OCH_3), 52.4 (3-OCH_3), 60.7 [$(CH_3)_2CHCH$N], 62.2 (NCC=N), 118.7 ($CH{=}CH_2$), 121.1 ($CBr{=}CH_2$), 128.2 ($CBr{=}CH_2$), 132.7 ($CH{=}CH_2$), 162.0 (C-6), 162.9 (C-3) ppm. MS(EI): *m*/*z* (%) = 344/342 (1/1) [M^+], 329/327 (3/3), 303/301 (52/52), 301/299 (19/19), 287/285 (1/1), 272/270 (1/1), 263 (11), 261/259 (94/100), 223 (81), 181 (85), 166 (7), 165 (10), 164 (10). HRMS: calcd. for $C_{14}H_{20}BrN_2O_2$ [M − CH_3] 327.0708/329.0688; found 327.0707/329.0701.

(2*R*,5*S*)-5-Allyl-5-(2-bromoallyl)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine (4): *n*-Butyllithium (6.54 mL, 10.13 mmol, 1.55 M in hexane) was added dropwise to a solution of (2*R*,5*S*)-5-allyl-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine[8] (**3**) (2.07 g, 9.21 mmol) in dry THF (60 mL) under argon at −60 °C. The solution was cooled to −78 °C, stirred at this temperature for 45 min

and then treated with a precooled (−78 °C) solution of 2,3-dibromopropene (5.52 g, 27.63 mmol) in THF (6 mL). The mixture was stirred at −78 °C for 3 h and left to reach ambient temperature overnight before 10% aqueous ammonium chloride was added. The mixture was extracted with diethyl ether. The diethyl ether solution was dried ($MgSO_4$) and the solvents were evaporated under reduced pressure. The residual product was purified by flash chromatography on silica gel using CH_2Cl_2/hexane (2:1); yield 1.90 g (60%, *de* > 98%) of a colourless oil. $[\alpha]_D^{20} = +31.2$ (*c* = 0.0120 in $CHCl_3$). IR (film): $\tilde{\nu}$ = 3077 (w), 2960 (m), 2943 (m), 2870 (w), 1694 (s), 1623 (m), 1436 (m), 1308 (m), 1240 (s), 1196 (m), 1160 (s), 1013 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.63, 1.04 [2 × d, *J* = 6.8 Hz, 6 H, $CH(CH_3)_2$], 2.28 [dsept, *J* = 3.3, 6.8 Hz, 1 H, $CH(CH_3)_2$] 2.34 (dd, *J* = 7.4, 13.1 Hz, 1 H, $CH_2CH{=}CH_2$), 2.51 (dd, *J* = 7.2, 13.1 Hz, 1 H, $CH_2CH{=}CH_2$), 2.65, 2.91 (2 × d, *J* = 14.0 Hz, 2 H, $CH_2CBr{=}CH_2$), 3.64 (s, 3 H, OCH_3), 3.67 (s, 3 H, OCH_3), 3.89 [d, *J* = 3.3 Hz, 1 H, $CHCH(CH_3)_2$], 4.97 (dd, *J* = 1.1, 10.0 Hz, 1 H, $=CH_2$ *cis*), 5.00 (dd, *J* = 1.1, 17.2 Hz, 1 H, $=CH_2$ *trans*), 5.43, 5.44 (2 × d, *J* = 1 Hz, 2 H, $CBr{=}CH_2$), 5.61 (dddd, *J* = 7.2, *J* = 7.4, J_{cis} = 10.0 Hz and J_{trans} = 17.2 Hz, 1 H, $CH{=}CH_2$) ppm. ^{13}C NMR ($CDCl_3$): δ = 17.2, 19.5 [$CH(CH_3)_2$], 30.4 [$CH(CH_3)_2$], 45.1 ($CH_2CH{=}CH_2$), 50.4 ($CH_2CBr{=}CH_2$), 51.9, 52.3 (2 × OCH_3), 60.8 [$(CH_3)_2CHCHN$], 62.1 (N*C*C=N), 118.0 ($CH{=}CH_2$), 120.8 ($CBr{=}CH_2$), 128.1 (*C*Br=CH_2), 133.8 ($CH{=}CH_2$), 162.0 (C-6), 163.2 (C-3) ppm. MS(EI): *m*/*z* (%) = 344/342 (1/1) [M^+], 329/327 (1/1), 303/301 (12/12), 301/299 (9/9), 287/285 (1/1), 272/270 (1/1), 263 (4), 261/259 (26/27), 223 (74), 181 (100), 166 (5), 165 (6), 164 (4). $C_{15}H_{23}BrN_2O_2$ (343.26): calcd. C 52.48, H 6.75; found C 52.26, H 6.90.

(2*R*)-2,5-Dihydro-2-isopropyl-3,6-dimethoxy-3′,4′-bis(methylene)-pyrazine-5-spirocyclopentane (5) and (2*R*,5*S*)-2,5-Dihydro-2-isopropyl-3,6-dimethoxy-3′-methyl-4′-methylenepyrazine-5-spirocyclopent-2′-ene (6): (2*R*,5*R*)-5-Allyl-5-(2-bromoallyl)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine (**2**) (102.6 mg, 0.2989 mmol) in dry acetonitrile (5 mL) was added to a stirred suspension of the palladacycle ($[Pd\{C_6H_4CH_2P(o\text{-}Tol)_2\}\cdot OAc]_2$)[9,15] (28.0 mg, 0.0299 mmol) and K_2CO_3 (82.6 mg, 0.5978 mmol) in dry acetonitrile (30 mL) under argon. The reaction mixture was heated slowly to 88 °C and stirred at this temperature until GLC showed that all the starting material had disappeared (96 h). GLC analysis showed the products **5** and **6** to be present in a 1:1.1 ratio. The solvent was evaporated under reduced pressure and the residue was dissolved in diethyl ether. The diethyl ether solution was washed twice with 10% aqueous ammonium chloride, dried ($MgSO_4$), and the solvents were evaporated. The products were separated and purified by flash chromatography on silica gel using hexane/EtOAc (20:1) as eluent. The yield of compound **6** was 21.2 mg (27%). Physical data for the products are given below.

(2*R*)-2,5-Dihydro-2-isopropyl-3,6-dimethoxy-3′,4′-bis(methylene)-pyrazine-5-spirocyclopentane (5): (2*R*,5*S*)-5-Allyl-5-(2-bromoallyl)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine (**4**) (134.7 mg, 0.3924 mmol) in dry, deoxygenated acetonitrile (10 mL) was added to a stirred mixture of $Pd(OAc)_2$ (8.8 mg, 0.0392 mmol), PPh_3 (23.7 mg, 0.0903 mmol), and Ag_2CO_3 (129.8 mg, 0.4709 mmol) in a screw cap Pyrex bottle under argon. The sealed bottle was heated to 90 °C for 2.5 h. The reaction mixture was cooled to ambient temperature and filtered. GLC analysis showed full conversion of the starting material. The filtrate was concentrated under vacuum to approximately 1 mL and the residual product was purified by flash chromatography on silica gel using hexane/EtOAc (9:1); yield 61.8 mg (60%) of a colourless oil. $[\alpha]_D^{20} = -47.3$ (*c* = 0.013 in $CHCl_3$). IR (film): $\tilde{\nu}$ = 3080 (w), 2959 (m), 2945 (m), 2871 (w), 1690 (s), 1436 (m),1308 (m), 1292 (s), 1227 (s), 1201 (m), 1032 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.67, 1.04 [2 × d, *J* = 6.9 Hz, 6 H, $CH(CH_3)_2$], 2.21 [dsept, *J* = 3.5, 6.9 Hz, 1 H, $CH(CH_3)_2$], 2.37 (dd, *J* = 1.8 and 16 Hz, 1 H, 5′-H_b), 2.41 (dd, *J* = 1.8 and 16 Hz, 1 H, 2′-H_b), 2.98 (ddd, *J* = 2.4, 2.7, and 16 Hz, 1 H, 5′-H_a), 3.04 (ddd, *J* = 2.4, 2.7, and 16 Hz, 1 H, 2′-H_a), 3.59 (s, 3 H, OCH_3), 3.65 (s, 3 H, OCH_3), 3.96 (d, *J* = 3.5 Hz, 1 H, 2-H), 4.85 (dd, *J* = 1.8, 2.1 Hz, 2 H, 3′ =CH_aH_b and 4′ =CH_aH_b), 5.40 (dd, *J* = 2.1, 2.4 Hz, 2 H, 3′ =CH_aH_b and 4′ =CH_aH_b) ppm. ^{13}C NMR ($CDCl_3$): δ = 16.9, 19.3 [$CH(CH_3)_2$], 31.2 [$CH(CH_3)_2$], 47.7 (C-5′),47.8 (C-2′), 52.2, 52.4 (2 × OCH_3), 61.0 (C-2), 61.8 (spiro *C*), 103.9, 104.0 (2 × $=CH_2$), 146.9 (C-4′), 147.0 (C-3′), 161.4 (C-3), 164.8 (C-6) ppm. MS(EI): *m*/*z* (%) = 262 (38) [M^+], 247 (16), 231 (4), 219 (100), 205 (12), 204 (11), 190 (10), 189 (8), 176 (6), 162 (5). HRMS for $C_{15}H_{22}N_2O_3$: 262.1681; found 262.1666.

(2*R*)-2,5-Dihydro-2-isopropyl-3,6-dimethoxy-3′,4′-bis(methylene)-pyrazine-5-spirocyclopentane (5) and (2*R*,5*R*)-2,5-Dihydro-2-isopropyl-3,6-dimethoxy-3′-methyl-4′-methylenepyrazine-5-spirocyclopent-2′-ene (7): (2*R*,5*S*)-5-Allyl-5-(2-bromoallyl)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine (**4**) (295 mg, 0.859 mmol) in dry acetonitrile (15 mL) was added to a stirred suspension of the palladacycle ($[Pd(C_6H_4CH_2P(o\text{-}Tol)_2\cdot OAc]_2$)[9,15] (80.6 mg, 0.0859 mmol) and K_2CO_3 (238 mg, 1.718 mmol) in dry acetonitrile (85 mL) under argon. The reaction mixture was heated slowly to 88 °C and stirred at this temperature until GLC showed full conversion of the starting material (96 h). GLC analysis showed the product ratio **5**/**7** to be 1:1.1. The solvent was evaporated under reduced pressure and the residue was dissolved in diethyl ether. The solution was washed twice with 10% aqueous ammonium chloride, dried ($MgSO_4$), and the solvents evaporated. The products were separated and purified by flash chromatography on silica gel using hexane/EtOAc (20:1) as eluent; yield of compound **7** was 65 mg (29%). MS(HR): $[\alpha]_D^{20} = -75.0$ (*c* = 0.006 in $CHCl_3$). IR (film): $\tilde{\nu}$ = 3082 (w), 2959 (m), 2944 (m), 2872 (w), 1686 (s), 1622 (w), 1436 (m), 1290 (m), 1237 (s), 1225 (s), 1195 (m), 1029 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.73, 1.06 [2 × d, *J* = 6.8 Hz, 6 H, $CH(CH_3)_2$], 1.83 (d, *J* = 1.3 Hz, 3 H, CH=C-CH_3) 2.21 [dsept, *J* = 3.7, 6.8 Hz, 1 H, $CH(CH_3)_2$], 2.61 (ddd, *J* = 2.2, 2.2, 16.3 Hz, 1 H, 5′-H_b), 3.10 (ddd, *J* = 1.8, 1.8, 16.3 Hz, 1 H, 5′-H_a), 3.63 (s, 3 H, OCH_3), 3.64 (s, 3 H, OCH_3), 3.98 [d, *J* = 3.5, 1 H, $CHCH(CH_3)_2$], 4.84 (dd, *J* = 1.8, 2.2 Hz, 1 H, =CH_aH_b), 4.88 (dd, *J* = 1.8, 2.2 Hz, 1 H, =CH_aH_b), 5.42 (s, 1 H, 2′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 12.6 ($CH{=}CCH_3$), 17.0, 19.4 [$CH(CH_3)_2$], 31.4 [$CH(CH_3)_2$], 46.3 (C-5′), 52.4, 52.7 (2 × OCH_3), 61.3 [$(CH_3)_2CHCHN$], 66.5 (spiro *C*), 102.3 ($=CH_2$), 137.40 (C-2′), 142.3 (C-3′), 153.1 (C-4′), 162.4 (C-3), 164.4 (C-6) ppm. MS(EI): *m*/*z* (%) = 262 (23) [M^+], 247 (100), 231 (3), 219 (90), 205 (11), 204 (8), 190 (66), 173 (4), 162 (6), 134 (23). HRMS: calcd. for $C_{15}H_{22}N_2O_2$ 262.1681; found 262.1662.

(2*R*,5*S*)-2,5-Dihydro-2-isopropyl-3,6-dimethoxy-3′-methyl-4′-methylenepyrazine-5-spirocyclopent-2′-ene (6): Methylmagnesium bromide (1.22 mL, 3.6672 mmol, 3 M in diethyl ether) was added dropwise to a solution of (2*R*,5*S*)-3′-bromo-2,5-dihydro-2-isopropyl-3,6-dimethoxy-4′-methylenepyrazine-5-spirocyclopent-2′-ene (**10**; 200 mg, 0.611 mmol) and Ni(dppp)Cl_2 (16.6 mg, 0.031 mmol) in THF (15 mL) under argon at 0 °C. The reaction mixture was stirred at ambient temperature for 20 h, diluted with diethyl ether and quenched by adding 10% aqueous ammonium chloride. The aqueous phase was extracted with diethyl ether. The combined organic solutions were dried ($MgSO_4$) and the solvents were evaporated under reduced pressure. The residual product was purified by flash chromatography on silica gel using hexane/EtOAc (9:1); yield 102 mg (64%) of a colourless oil. $[\alpha]_D^{20} = -7.9$ (*c* =

0.050 in $CHCl_3$). IR (film): $\tilde{\nu}$ = 3083 (w), 2960 (m), 2945 (m), 2872 (w), 1686 (s), 1624 (m), 1437 (m), 1292 (s), 1237 (s), 1225 (s), 1196 (m), 1029 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.68, 1.05 [2 × d, *J* = 6.8 Hz, 6 H, $CH(CH_3)_2$], 1.85 (d, *J* = 1.4 Hz, 3 H, $CH{=}C{-}CH_3$) 2.21 [dsept, *J* = 3.5, 6.8 Hz, 1 H, $CH(CH_3)_2$], 2.57 (ddd, *J* = 2.1, 2.1, 16.4 Hz, 1 H, 5′-H_b), 2.97 (ddd, *J* = 1.9, 1.9 Hz and 16.4 Hz, 1 H, 5′-H_a), 3.63 (s, 3 H, OCH_3), 3.64 (s, 3 H, OCH_3), 3.98 (d, *J* = 3.5 Hz, 1 H, 2-H), 4.81 (dd, *J* = 1.9, 2.1 Hz, 1 H, $=CH_aH_b$), 4.86 (dd, *J* = 1.9, 2.1 Hz, 1 H, $=CH_aH_b$), 5.52 (s, 1 H, 2′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 12.6 ($CH{=}CCH_3$), 16.9, 19.4 [$CH(CH_3)_2$], 31.3 [$CH(CH_3)_2$], 46.1 (C-5′), 52.5, 52.8 (2 × OCH_3), 61.1 (C-2), 66.2 (spiro *C*), 102.2 ($=CH_2$), 137.7 (C-2′), 142.5 (C-3′), 152.9 (C-4′), 162.7 (C-3), 164.6 (C-6) ppm. MS(EI): *m*/*z* (%) = 262 (16) [M^+], 247 (100), 231 (2), 219 (86), 205 (12), 204 (9), 190 (81), 173 (3), 162 (7), 134 (48). HRMS: calcd. for $C_{15}H_{22}N_2O_2$ 262.1681; found 262.1679.

(2*R*,5*S*)-5-Allyl-5-(2′,2′-dibromoethenyl)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine (9): A solution of tetrabromomethane (5.22 g, 15.75 mmol) in dry dichloromethane (30 mL) was added dropwise to a solution of triphenylphosphane (8.26 g, 31.49 mmol) in dry dichloromethane (20 mL) under argon at 0 °C. Stirring was continued for 30 min before a solution of (2*R*,5*S*)-5-allyl-2,5-dihydro-5-formyl-2-isopropyl-3,6-dimethoxypyrazine[14] (**8**) (1.98 g, 7.87 mmol) in dry dichloromethane (30 mL) was added dropwise. Stirring was then continued at 0 °C for 5 h. The reaction mixture was added to pentane (600 mL), with stirring, then left to stand overnight. The mixture was filtered and the solvents were evaporated from the filtrate under reduced pressure. The residual product was purified by flash chromatography on silica gel using CH_2Cl_2/hexane (2:1); yield 2.17 g (67%) of a colourless oil. ^1H NMR ($CDCl_3$): δ = 0.68, 1.07 [2 × d, *J* = 6.8 Hz, 6 H, $CH(CH_3)_2$], 2.35 [dsept, *J* = 3.5, 6.8 Hz, 1 H, $CH(CH_3)_2$], 2.50 (ddt, *J* = 1.1, 6.9 Hz and 13.3 Hz, 1 H, $CH_2CH{=}CH_2$), 2.59 (dd, *J* = 7.7, 13.3 Hz, 1 H, $CH_2CH{=}CH_2$), 3.66 (s, 3 H, OCH_3), 3.68 (s, 3 H, OCH_3), 3.89 [d, *J* = 3.5, 1 H, $(CH_3)_2CHCH$N], 5.07 (dd, *J* = 1.1 Hz and J_{cis} = 10.4 Hz, 1 H, $CH{=}CH_2$ *cis*), 5.08 (dd, *J* = 1.1 Hz and J_{trans} = 16.9 Hz, 1 H, $CH{=}CH_2$ *trans*), 5.70 (dddd, *J* = 6.9, 7.7, J_{cis} = 10.4, J_{trans} = 16.9 Hz, 1 H, $CH{=}CH_2$), 6.73 (s, 1 H, $CH{=}CBr_2$) ppm. ^{13}C NMR ($CDCl_3$): δ = 17.7, 19.6 [$CH(CH_3)_2$], 30.5 [$CH(CH_3)_2$], 46.5 ($CH_2CH{=}CH_2$), 52.7, 52.7 (2 × OCH_3), 61.2 [$(CH_3)_2CHCH$N], 62.4 (N*C*C=N), 91.8 ($CH{=}CBr_2$), 119.2 ($CH{=}CH_2$), 132.9 ($CH{=}CH_2$), 139.3 ($CH{=}CBr_2$), 160.0 (C-6), 163.9 (C-3) ppm. MS(CI): *m*/*z* (%) = 411/409/407 (37/73/45) [M^+ + 1], 383/381/379 (18/31/25), 369/367/379 (18/31/25), 369/367/365 (34/63/42), 341/339/337 (17/23/13), 329/327 (18/18), 327/325/323 (20/34/21), 302/300 (19/19), 287/285 (27/27), 249/247 (16/16), 248 (20), 223 (72), 221 (40), 181 (31), 58 (100).

(2*R*,5*S*)-3′-Bromo-2,5-dihydro-2-isopropyl-3,6-dimethoxy-4′-methylenepyrazine-5-spirocyclopent-2′-ene (10): A solution of (2*R*,5*S*)-5-allyl-5-(2′,2′-dibromoethenyl)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine (**9**)[8] (900 mg, 2.205 mmol) in dry acetonitrile (50 mL) was added to a suspension of $Pd(OAc)_2$ (49.5 mg, 0.220 mmol), PPh_3 (133 mg, 0.507 mmol) and Ag_2CO_3 (730 mg, 2.650 mmol) in dry acetonitrile (100 mL) under argon at 50 °C. The reaction mixture was stirred at 60 °C for 2 h, cooled to ambient temperature and filtered. The filtrate was concentrated under reduced pressure to a small volume (not dryness!) and the residual product was purified by flash chromatography on silica gel using hexane/EtOAc (9:1); yield 433 mg (60%) of a white solid. $[\alpha]_D^{20}$ = +5.6 (*c* = 0.036 in $CHCl_3$). IR (film): $\tilde{\nu}$ = 2960 (m), 2945 (m), 2871 (w), 1688 (s), 1436 (m), 1291 (m), 1238 (s), 1216 (m), 1030 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.67, 1.04 [2 × d, *J* = 6.8 Hz, 6 H, $CH(CH_3)_2$], 2.22 [dsept, *J* = 3.5, 6.8 Hz, 1 H, $CH(CH_3)_2$], 2.65 (ddd, *J* = 2.0, 2.0, 16.2 Hz, 1 H, 5′-H_b), 3.02 (ddd, *J* = 1.9, 1.9 H and 16.2 Hz, 1 H, 5′-H_a), 3.64 (s, 6 H, 2 × OCH_3), 3.98 (d, *J* = 3.5 Hz, 1 H, 2-H), 4.96 (dd, *J* = 1.9, 2.0 Hz, 1 H, $=CH_aH_b$), 5.17 (dd, *J* = 1.9, 2.0 Hz, 1 H, $=CH_aH_b$), 5.95 (s, 1 H, 2′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 16.8, 19.3 [$CH(CH_3)_2$], 31.2 [$CH(CH_3)_2$], 44.4 (C-5′), 52.6, 52.9 (2 × OCH_3), 61.1 (C-2), 66.4 (spiro *C*), 106.8 ($=CH_2$), 127.1 (C-3′), 140.8 (C-2′), 148.6 (C-4′), 163.0 (C-6), 163.4 (C-3) ppm. MS(EI): *m*/*z* (%) = 328/326 (46/46) [M^+], 313/311 (96/100), 297/295 (8/8), 285/283 (99/99), 271/269 (23/25), 256/256 (96/99), 247 (2), 239/237 (5/4), 200 (29), 119 (37), 112 (28). HRMS: calcd. for $C_{14}H_{19}BrN_2O_2$ 328.0609, 326.0629; found 328.0598, 326.0621.

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