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Chemoselective rhodium(II)–carbenoid cyclisation reactions in the stereoselective construction of rigidified cyclic α-amino acid derivatives

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Abstract—Intramolecular rhodium(II)-catalysed reactions in geminally disubstituted derivatives of the chiron (*R*)-2-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine occurred with complete chemoselectivity at the adjacent annular nitrogen in preference to carbon–carbon double bond additions or C–H insertions. The products were four- and five-membered annulated rings, azetidin-3-one and pyrrolidin-3-one derivatives. The latter are valuable substrates for the preparation of quaternary cyclic α-amino acid derivatives where both the α-quaternary carbon and the amino nitrogen are embedded in a pyrrolidine ring thus providing novel α-quaternary proline derivatives. Five-membered ring formation in the cyclisation reactions has been verified by a single crystal X-ray analysis, and the four-membered ring products by NMR.

1. Introduction

In recent reports we have described methods for the preparation of cyclic rigidified α-quaternary amino acids with the α-carbon embedded in the ring structure.[1–4] This work was initiated because it had been established that rigidified α-carbosubstituted α-amino acids play an important role in drug design and development, which involves small peptides and peptidomimetics.[5] The cyclic structures prepared are members of an important family of quaternary α-amino acids.[6,7] The rigid amino acid analogues affect conformational freedom, and thereby bioactivity, when incorporated into peptides, and the construction of peptidomimetics in searches for useful medicines. Using the chiron (*R*)-2-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine,[8] for stereoselective transformations, we herein report work towards the construction of quaternary cyclic α-amino acid derivatives where both the α-quaternary carbon and the amino nitrogen are embedded in the ring structure, in which the key transformation was effected by rhodium(II)-catalysed cyclisation reactions.

2. Results and discussion

The cyclisation reactions in Schemes 3 and 4 were carried out on diazomethyl ketones using dirhodium tetraacetate as catalyst. The synthesis of the appropriate diazo substrates for the ring formation is shown in Scheme 2 and their precursors in Scheme 1. Stepwise bisalkylation of chiron **1** provided substrates with two different *gem*-substituents (Scheme 1). The first alkylation step was effected by lithiation at −78 °C using methyl bromoacetate or iodomethane. Chemoselective LAH reduction of the ester group in the major diastereomer **2b** provided alcohol **3**, which was transformed to the methyl ether **4** with methyl iodide. The monoalkylated intermediates **2a** and **4** were all lithiated at −78 °C and treated with acetaldehyde to furnish the ethanol derivatives **5a** and **5b**. Once lithiated for the second time, the stereochemistry at the initial alkylating site is lost. Hence the substrate can be an epimeric mixture at this carbon. The second metallation is fully regioselective because the branching of the isopropyl group at its α-carbon leads to full shielding of its site of attachment in the ring. The second alkylating agent then approaches the reactive carbanionic site from the side of the ring opposite to the isopropyl group. The diastereomeric excess of products **5a** and **5b** after the second alkylation step was excellent, in excess of 90%; the chemical yields were in the range of 70%. However the steric induction

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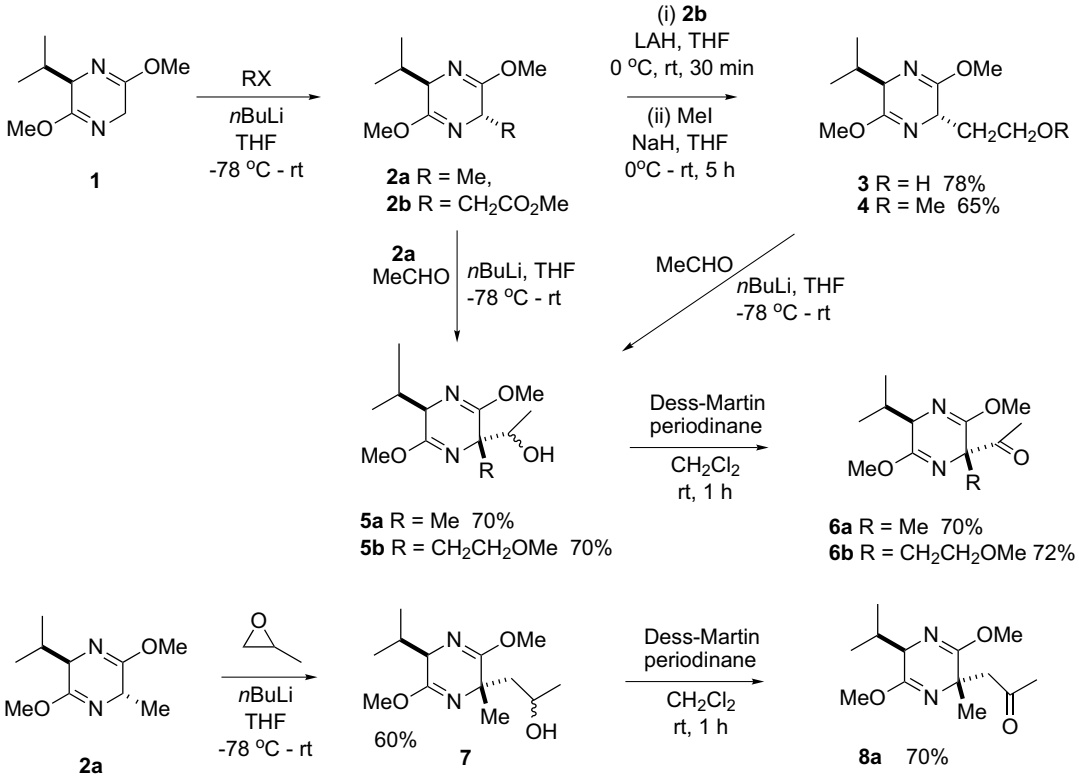
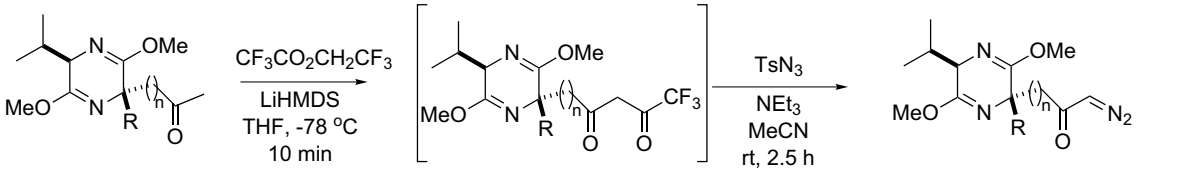


Scheme 1.

at the carbonyl carbon was low. The epimeric ratios at the alcohol carbon were 2:3 for **5a**, and 4:1 for **5b**. For analytical purposes, the alcohol diastereomers were separated by flash chromatography on silica gel, but the alcohol configuration was not determined since both stereoisomers under oxidation under Dess–Martin conditions provided the same methyl ketones **6** in about 70% yield.

For the second series of keto substrates, a methylene group was inserted between the ring and the carbonyl group as in structure **8a**. Alcohol intermediate **7** was prepared from racemic propylene oxide resulting in high diastereoselectivity at the pyrazine 2-position. At the alcohol carbon, however, the epimer ratio was 1:1. Structure **7** was isolated after flash chromatography on silica gel and converted into the methyl ketone **8a** in a Dess–Martin reaction. Allyl analogue **8b** (Scheme 2) was prepared in a similar reaction.[1]

For diazo transfer in the formation of diazoketones **12** and **13**, the methyl group in ketones **6** and **8** (Scheme 2) was activated. The lithiated species of the ketones were reacted with 2,2,2-trifluoroethyl trifluoroacetate (TFEA) by analogy to methodology described by Danheiser et al.[9,10] The acylation was carried out with 1 equiv of base in a reaction with TFEA at −78 °C for 5–10 min. The diazo transfer was effected by tosyl azide on the crude 1,3-diketones **9** and **10** at ambient temperature. The crude α-trifluoroacetyl ketone was treated with tosyl azide in acetonitrile containing water and triethylamine at room temperature for 2.5 h to provide α-diazo ketones **12** and **13** in moderate overall chemical yields, in the range of 42–53%.



6a n = 0, R = Me
6b n = 0, R = CH_2CH_2OMe
6c n = 0, R = $CH_2CH{=}CH_2$
8a n = 1, R = Me
8b n = 1, R = $CH_2CH{=}CH_2$

9 n = 0
10 n = 1

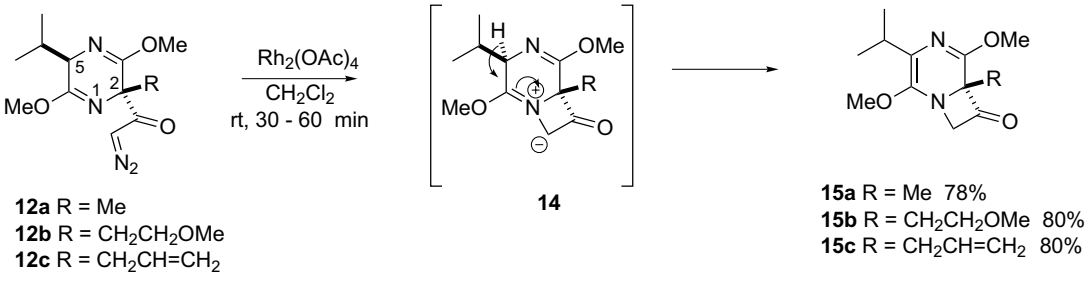
12a n = 0, R = Me 44%
12b n = 0, R = CH_2CH_2OMe 53%
12c n = 0, R = $CH_2CH{=}CH_2$ 42%
13a n = 1, R = Me 52%
13b n = 1, R = $CH_2CH{=}CH_2$ 50%

Scheme 2.

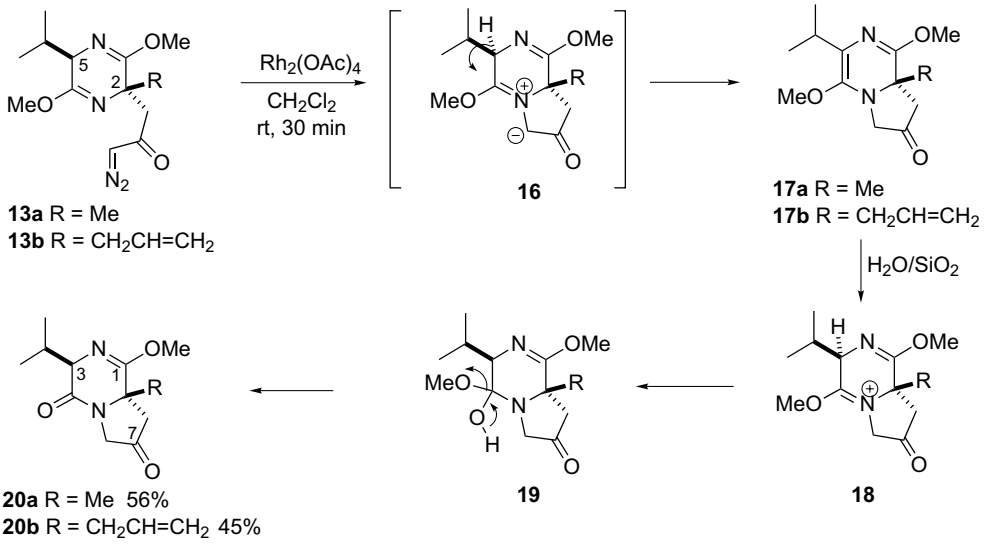
The carbenoid insertions in Scheme 3 were carried out using 5 mol% dirhodium tetraacetate in dichloromethane at ambient temperature for 30–60 min under an argon atmosphere. In substrates **12**, several opportunities for carbenoid insertions are present. There was no significant addition to the double bond in the allylic substrate **12c**. Ample opportunities were present for C–H insertions. The frequently favoured five-membered ring formation, by insertion in the appropriate methylene group in substrate **12b**, was not observed.[11,12] Insertion might have been expected since this methylene group is also activated by the attached ether oxygen.[13] Instead the highly electrophilic nature of the rhodium carbenoids led to adduct formation with the adjacent annular nitrogen. Perhaps surprisingly, highly strained four-membered ring annulated azetidin-3-ones **15** were obtained in high yields (78–80%), rather than C–H insertion to the more favoured ring sizes. Their formation can be rationalised by the initial generation of ylide **14** as shown in Scheme 3. A subsequent 1,4-hydrogen shift provides the neutral species **15**.

The strained four-membered ring products were of low chemical stability but could be purified by flash chromatography on silica gel. The products could not be obtained in a crystalline state useful for X-ray analysis. Neither did we succeed in converting these structures into crystalline derivatives. However, their structures were deduced by NMR experiments. Most important, the H-5 proton of substrates **12** was absent in the ^{1}H NMR spectra of products **15**. In the NMR spectra of allyl derivative **15c**, the methine proton of the isopropyl group appeared as a septet at δ 2.25 ppm with $J = 6.8$ Hz. The methylene protons in the four-membered ring appeared at 4.42 and 4.49 with *gem* coupling constant $J = 12.3$ Hz. In the ^{13}C NMR spectrum, the signal for C-5 had been shifted from 60.29 ppm in substrate **12c** to 117.05 ppm in the product, which is in agreement with a change from sp^3-hybridisation to sp^2-hybridisation in structure **15c**. The two-dimensional ^{1}H,^{15}N-correlated spectrum of **15c** recorded by the gs-HMBC (gradient selected-heteronuclear multiple bond correlation) method, showed a correlation peak for C*H*(CH$_3$)$_2$ and N-4. In the case of N-1, there were correlation peaks with 2-C*H*$_2$–CH=CH$_2$, and N–C*H*$_2$–CO of the four-membered ring. The stereogenic centre at the quaternary carbon at the 2-position in substrates **12** was not affected by the carbenoid reaction. Only the stereochemistry at the 5-position was lost. As a result, products **15** are pure (*R*)-enantiomers.

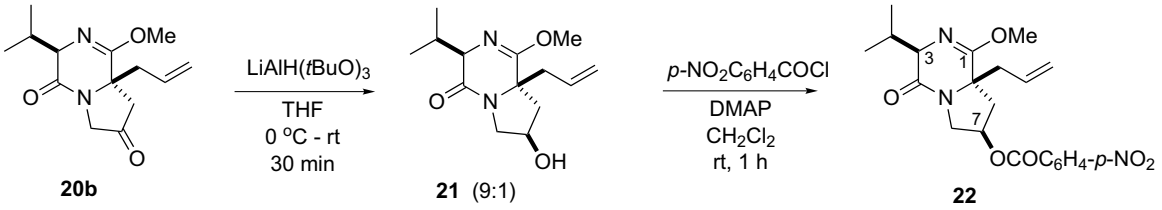
In the homologous diazoketone series **13** in Scheme 4, carbenoid addition to the annular nitrogen would provide a highly favoured five-membered ring. No racemisation



Scheme 3.



Scheme 4.



Scheme 5.

in the carbenoid reactions can take place at the quaternary 2-carbon in substrate **13**. Proton abstraction and re-addition at C-5 would be expected to epimerise the structure in this position thereby forming a diastereomeric mixture. Chromatography and NMR showed that the product isolated was a single diastereomer. Single crystal X-ray structure analysis (vide infra) of its derivative **22** (Scheme 5) showed that the stereochemistry at the position for the isopropyl carbon, the 3-position in products **20**, was unchanged. Hence it would appear that there was no significant proton exchange in the 5-position in the substrates **13**. The methoxy group adjacent to the annular nitrogen, however, had been replaced by an oxo group as in structures **20**. The generation of different products during the four-membered **15** and five-membered ring annulations **20** led us to monitor the latter reaction sequence in an NMR tube. The study revealed that the reaction path was the same in both cases. The disappearance of proton signals and chemical shift changes corresponded to the formation of structures **17** as the initial product in the reaction mixture. The cyclisation reaction was clean corresponding to an almost quantitative yield of annulated products **17**. This transformation was subsequently repeated on a small preparative scale.

When a small amount of silica gel was added to the NMR tube, a chemical transformation took place. The reaction mixture went from pale green to a brown colour. The new NMR spectra were the same as recorded for isolated products **20**. The purification of the crude reaction product, as first prepared, was carried by flash chromatography on silica gel, which contained some water. During chromatography a chemical reaction took place with the formation of isolated products **20**. The intermediate products **17** are both an enol ether and a vinylamine. The β-carbon is therefore highly activated for protonation. Subsequent water addition to the immonium ion intermediate **18** is followed by the elimination of methanol to provide oxo products **20**. This mechanistic path would be expected to yield a diastereomeric mixture. However only one major product was isolated, which had a (5*R*)-configuration of the original substrate **13**. The mechanism for this transformation has not been further studied. Steric interactions between the substituents presumably direct the stereoselectivity in the protonation and hydrolysis. The isolated yields in the preparative work were moderate, 45% and 56%, whereas the NMR studies indicated a clean, high yielding process suggesting extensive loss of material in the silica gel column.

For the five-membered ring series **20**, the assigned structure was established by single crystal X-ray analysis of the allylic derivative **20b**. The latter was converted into the suitable crystalline ester **22**. Initially, the keto group in structure **20b** was chemoselectively reduced with the bulky lithium tri(*tert*-butoxy)aluminium hydride to favour formation of one of the hydroxy forms. Considerable stereoselectivity was achieved by preferential hydride attack at the less shielded face, opposite to the isopropyl and allyl substituents, diastereomer ratio 9:1. The crude mixture was subsequently esterified and the major nitrobenzoyl ester **22** isolated in a pure crystalline state after simple chromatography. The ORTEP plot of the X-ray structure in Figure 1 shows the product to have structure **22**.

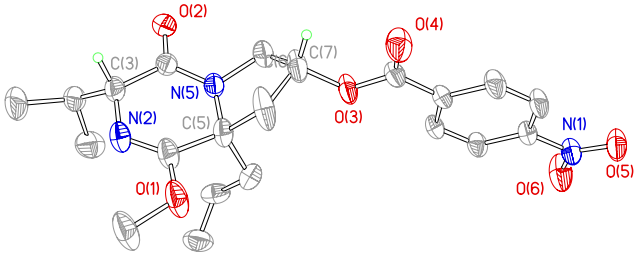
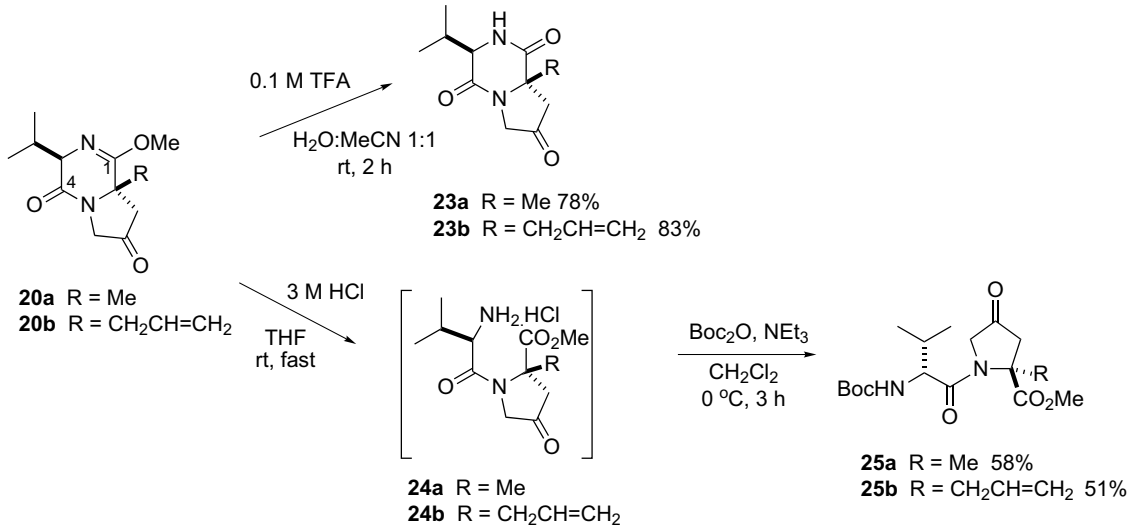


Figure 1. The ORTEP plot of compound **22**. Ellipsoids are shown at 50% probability. For clarity only the hydrogen at the stereogenic centres C3 and C7 are shown.

Hydrolytic reactions are shown in Scheme 6. Inspection of structures **20** in Scheme 6 shows a lactam function at the 4-position and an iminoether function at the 1-position. The former is highly resistant towards acid hydrolysis while the latter is very acid sensitive.

Mild acidic conditions using 0.1 M TFA led to the formation of the corresponding diketopiperazines **23**, which were isolated in ca. 80% yield. Cleavage of the cyclic peptides **23**, as diketopiperazine derivatives, to amino acid constituents would require strong hydrolytic acidic conditions. Hydrolysis of the monolactim ethers **20** with 3 M hydrochloric acid at room temperature, gave the hydrochlorides **24**, which were further treated with triethylamine and di-*tert*-butyl dicarbonate (Boc_2O) to furnish the protected dipeptides **25a** and **25b** (Scheme 6).

The importance of proline and many of its derivatives is expressed by a number of syntheses of α-substituted prolines either with proline or its derivatives as a sub-



Scheme 6.

strate for alkylation reactions, or via the use of appropriate chirons, and by enzymatic operations.[14]

3. Conclusion

In conclusion we have shown that intramolecular rhodium(II)-catalysed reactions in geminally disubstituted derivatives of the chiron (*R*)-2-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine provide valuable substrates for the preparation of quaternary cyclic α-amino acid derivatives, where both the α-quaternary carbon and the amino nitrogen are to be embedded in a pyrrolidine ring. Complete chemoselectivity was seen in the rhodium(II) carbenoid reactions, which occurred at the adjacent annular nitrogen in preference to carbon–carbon double bond additions or C–H insertions. The products are four- and five-membered annulated rings, azetidin-3-one and pyrrolidin-3-one derivatives. The five-membered products are stable and can be hydrolysed to α-quaternary derivatives of the amino acid proline.

4. Experimental

^{1}H NMR spectra were recorded in $CDCl_3$ at 500, 300 or 200 MHz with Bruker DPX 500, DPX 300 or DPX 200. The ^{13}C spectra were recorded in $CDCl_3$ at 125 MHz with a Bruker DPX 500, at 75 MHz with DPX 300 and at 50 MHz with a Bruker DPX 200 instrument. NMR techniques such as DEPT, COSY, HETCOR, COLOC, gs-HMBC, ^{1}H,^{15}N correlation with gs-HMBC were used. Chemical shifts are reported in parts per million with residual $CHCl_3$ (7.24 ppm) and $CDCl_3$ (77 ppm) as references. *J* values are given in hertz. Mass spectra under electron-impact conditions (EI) were recorded at 70 eV ionising potential, methane was used for chemical ionisation (CI). The spectra are presented as *m*/*z* (% rel int). IR spectra were measured either on a Perkin–Elmer 1310 infrared spectrophotometer or a Nicolet Magna 550 spectrometer using ATR (attenuated total reflectance). Specific rotation values are given in 10^{-1} deg cm^2 g^{-1}. Dry THF was distilled from sodium and benzophenone under argon.

4.1. X-ray crystallographic analysis for compound 22

Supplementary crystallographic data have been passed to the Cambridge Crystallographic Data Centre. Summary of Data CCDC 222197: X-ray data were collected on a Siemens SMART CCD diffractometer[15] using graphite monochromated MoKα radiation ($\lambda = 0.71073$ Å). Data collection method: ω-scan, range 0.6°, crystal to detector distance 5 cm. Data reduction and cell determination were carried out with the SAINT and XPREP programs.[15] Absorption corrections were applied by the use of the SADABS program.[16] The structure was determined and refined using the SHELXTL program package.[17] The non-hydrogen atoms were refined with anisotropic thermal parameters; hydrogen atoms were located from difference Fourier maps and refined with isotropic thermal parameters. Crystal data for $C_{21}H_{25}N_3O_6$ **22** $M = 415.44$, monoclinic, $P2_1$, $a = 10.535(1)$, $b = 7.172(1)$, $c = 13.926(1)$ Å, $\beta = 99.63(1)°$, $V = 1073.4(1)$ Å^3, $Z = 2$, $D_x = 1.330$ Mg m^{-3}, $\mu = 0.098$ mm^{-1}, $T = 168(2)$ K, measured 14,841 reflections in 2θ range 5.3–56.7°, $R_{int} = 0.028$; 343 parameters refined against 5123 F^2, $R = 0.036$ for $I_o > 2\sigma(I_o)$ and 0.042 for all data.

4.2. (2′*S*,5′*R*)-2-(5-Isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)acetic acid methyl ester 2b

A solution of (2*R*)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine **1** (3.00 g, 16.29 mmol) in THF (40 mL) under argon was lithiated by the addition of *n*-BuLi (11.2 mL, 17.92 mmol, 1.6 M in hexane) at −78 °C. The mixture was stirred at this temperature for 30 min and a solution of methyl bromoacetate (3.06 g, 1.8 mL, 20.0 mmol) in THF (15 mL) added dropwise. The

resultant mixture was stirred at −78 °C and allowed to reach ambient temperature overnight. The reaction was terminated by the addition of a phosphate buffer pH 7 (25 mL) and extracted with diethyl ether (3×20 mL). The extracts were dried over $MgSO_4$ and the solvent distilled off. The residue was subjected to flash chromatography on silica gel using 10% EtOAc in hexane. R_f 0.1. The product was a colourless oil; yield 2.12 g (51%). Found: C, 55.9; H, 7.7. $C_{12}H_{20}N_2O_4$ requires C, 56.2; H, 7.9. HRMS: M 256.1431. $C_{12}H_{20}N_2O_4$ requires 256.1423. ν_{max} (film/cm^{-1}) 2957, 2872, 1747, 1698, 1463, 1436, 1241, 1196, 1168; δ_H ($CDCl_3$) 0.66 and 0.99 (6H, 2d, *J* 6.8, $CH(CH_3)_2$), 2.16–2.22 (1H, m, $CH(CH_3)_2$), 2.60 (1H, dd, *J* 15.2, 7.2, $CHCO_2CH_3$), 2.80 (1H, dd, *J* 15.2, 7.2, $CHCO_2CH_3$), 3.60, 3.66, 3.77 (9H, 3s, 2×OCH_3 and CO_2CH_3), 3.94 (1H, t, *J* 3.6, H-5), 4.26–4.32 (1H, m, H-2); δ_C ($CDCl_3$) 16.8 and 18.9 ($CH(CH_3)_2$), 32.0 ($CH(CH_3)_2$), 39.4 ($CH_2CO_2CH_3$), 51.5 (CO_2CH_3), 52.4 (C-2), 52.4 and 52.5 (2×OCH_3), 61.3 (C-5), 162.5 and 164.4 (2×C=N), 171.6 (CO_2CH_3); *m*/*z* (EI) 256 (M^+, 5%), 241 (4), 225 (7), 214 (11), 213 (91), 184 (6), 183 (21), 154 (10), 153 (100), 141 (21), 140 (15), 123 (8).

4.3. (2′*S*,5′*R*)-2-(5-Isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)ethanol 3

LAH (0.343 g, 8.78 mmol) was added in portions to a solution of (2′*S*,5′*R*)-2-(5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)acetic acid methyl ester **2b** (1.5 g, 5.85 mmol) in THF (20 mL) under argon at 0 °C. The mixture was stirred at this temperature for 30 min and at room temperature for 3 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl. The mixture was extracted with diethyl ether (3×10 mL), the combined organic extracts dried over $MgSO_4$ and evaporated. The residue was subjected to flash chromatography on silica gel using hexane–EtOAc 5:1. R_f 0.1. The product was an oil; yield 1.00 g (78%). HRMS: M 228.1470. $C_{11}H_{20}N_2O_3$ requires 228.1473. ν_{max} (film/cm^{-1}) 3368, 2961, 2946, 2872, 1694, 1463, 1436, 1239, 1196, 1009; δ_H ($CDCl_3$) 0.69 and 0.99 (6H, 2d, *J* 6.8, $CH(CH_3)_2$), 1.71–1.99 (1H, m, $CHCH_2OH$), 2.13–2.22 (2H, m, $CH(CH_3)_2$ and $CHCH_2OH$), 3.62 and 3.68 (6H, 2s, 2×OCH_3), 3.83–3.91 (2H, m, CH_2CH_2OH), 3.94–3.96 (1H, t, *J* 3.6, H-5), 4.00–4.08 (1H, m, H-2), 4.7 (1H, br s, OH); δ_C ($CDCl_3$) 16.8 and 18.9 ($CH(CH_3)_2$), 32.2 ($CH(CH_3)_2$), 35.7 (CH_2CH_2OH), 52.6 (2×OCH_3), 56.5 (C-2), 60.8 (C-5), 62.7 (CH_2CH_2OH), 163.0 and 164.3 (2×C=N); *m*/*z* (EI) 228 (M^+, 9%), 198 (6), 197 (8), 196 (24), 185 (15), 181 (23), 183 (18), 167 (18), 154 (27), 153 (100), 141 (22), 125 (23), 110 (22).

4.4. (2*R*,5*S*)-2-Isopropyl-3,6-dimethoxy-5-(2-methoxyethyl)-2,5-dihydropyrazine 4

NaH (0.210 g, 8.77 mmol) was added in portions to a solution of (2′*S*,5′*R*)-2-(5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)ethanol **3** (1.00 g, 4.38 mmol) in THF (15 mL) under argon at 0 °C. The mixture was stirred at this temperature for 30 min and a solution of methyl iodide (0.545 mL, 8.76 mmol) in THF (5 mL) added dropwise. The mixture was stirred at ambient temperature for 5 h, the reaction stopped by the addition of saturated aqueous ammonium chloride (5 mL), extracted with diethyl ether (3×10 mL), the ether solution dried over $MgSO_4$ before evaporation and the residual material subjected to flash chromatography on silica gel using hexane–EtOAc 5:1. R_f 0.15. The product was a colourless oil; yield 0.689 g (65%). Found: C, 59.5; H, 9.1. $C_{12}H_{22}N_2O_3$ requires C, 59.5; H, 9.15. HRMS: M 242.1629. $C_{12}H_{22}N_2O_3$ requires 242.1630. ν_{max} (film/cm^{-1}) 2961, 2872, 2830, 2810, 1694, 1462, 1436, 1239, 1195, 1124, 1011; δ_H ($CDCl_3$) 0.66 and 1.02 (6H, 2d, *J* 6.8, $CH(CH_3)_2$), 1.75–1.83 (1H, m, $CHCO_2CH_3$), 2.13–2.22 (2H, m, $CH(CH_3)_2$ and $CHCO_2CH_3$), 3.29 (3H, s, OCH_3), 3.32–3.41 (1H, m, CH_2CHOCH_3), 3.49–3.53 (1H, m, CH_2CHOCH_3), 3.64 and 3.66 (6H, 2s, 2×OCH_3), 3.90 (1H, t, *J* 3.6, H-2), 4.00–4.06 (1H, m, H-5); δ_C ($CDCl_3$) 16.6 and 19.0 ($CH(CH_3)_2$), 31.8 ($CH(CH_3)_2$), 34.1 ($CH_2CH_2OCH_3$), 52.3, 52.4 (2×OCH_3), 52.6 (C-5), 58.6 (CH_2OCH_3), 60.7 (C-2), 69.0 (CH_2OCH_3), 163.5 and 163.8 (2×C=N); *m*/*z* (EI) 242 (M^+, 15), 227 (35), 199 (8), 183 (22), 167 (94), 141 (100), 55 (16), 45 (3), 43 (11).

4.5. (2′*S*,5′*R*)-1-(5-Isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydropyrazin-2-yl)ethanol 5a

A solution of (2*R*,5*SR*)-2,5-dihydro-2-isopropyl-3,6-dimethoxy-5-methylpyrazine **2a**[18] (2.05 g, 10.35 mmol) in THF (50 mL) under argon was lithiated by the addition of *n*-BuLi (7.34 mL, 11.38 mmol, 1.55 M in hexane) at −78 °C, the mixture stirred at this temperature for 30 min and a solution of acetaldehyde (0.91 g, 1.155 mL, 20.7 mmol) in THF (20 mL) added dropwise. The resultant mixture was stirred at −78 °C for 1 h, allowed to reach ambient temperature and the reaction terminated by the addition of phosphate buffer pH 7 (30 mL). The mixture was extracted with diethyl ether (3×20 mL), the extracts dried ($MgSO_4$) and the solvent evaporated off. The residue was subjected to flash chromatography on silica gel using EtOAc–hexane 3:7. The product was a colourless oil and consisted of two alcohol epimers in the ratio 2:3; yield 1.75 g (70%). The epimer mixture was used as such in the subsequent reaction. For analytical purposes the epimers were separated by repetition of the chromatography as above.

Major epimer: R_f 0.21. Found: C, 59.55; H, 9.2. $C_{12}H_{22}N_2O_3$ requires C, 59.5; H, 9.15. HRMS: M 242.1632. $C_{12}H_{22}N_2O_3$ requires 242.1630. ν_{max} (film/cm^{-1}) 3435, 2971, 2944, 2875, 1695, 1470, 1455, 1289, 1242; δ_H ($CDCl_3$) 0.65 and 1.07 (6H, 2d, *J* 6.8, $CH(CH_3)_2$), 1.14 (3H, d, *J* 6.3, $CHOHCH_3$), 1.28 (3H, s, CH_3), 2.10 (1H, d, *J* 9.2, $CHOHCH_3$), 2.15–2.27 (1H, m, $CH(CH_3)_2$), 3.63 and 3.67 (6H, 2s, 2×OCH_3), 3.74–3.84 (1H, m, $CHOHCH_3$), 3.91 (1H, d, *J* 3.4, H-5); δ_C ($CDCl_3$) 16.9, 17.4, 19.3 and 24.3 ($CH(CH_3)_2$, CH_3, $COCH_3$), 31.0 ($CH(CH_3)_2$), 52.2 and 52.4 (2×OCH_3), 61.0 (C-5), 61.6 (C-2), 73.2 (CHOH), 163.2 and 164.2 (2×C=N); *m*/*z* (EI) 242 (M^+, 2%), 198 (4), 197 (10), 181 (7), 155 (100), 43 (4).

Minor epimer: R_f 0.33; δ_H ($CDCl_3$) 0.65 and 1.02 (6H, 2d, J 6.8, $CH(CH_3)_2$), 0.82 (3H, d, J 6.2, $CHOHCH_3$), 1.36 (1H, s, CH_3), 2.16–2.20 (1H, m, $CH(CH_3)_2$), 2.77 (1H, d, J 9.1, $CHOHCH_3$), 3.59 and 3.62 (6H, 2s, $2\times OCH_3$), 3.84–3.89 (1H, m, $CHOHCH_3$), 3.91 (1H, d, J 3.4, H-5); δ_C ($CDCl_3$) 17.0, 18.8, 19.3 and 25.1 ($CH(CH_3)_2$, CH_3, $COCH_3$), 31.2 ($CH(CH_3)_2$), 52.2 and 52.3 ($2\times OCH_3$), 60.9 (C-2), 61.2 (C-5), 71.4 ($CHOH$), 163.5 and 164.4 ($2\times C{=}N$).

4.6. (2′*S*,5′*R*)-1-(5-Isopropyl-3,6-dimethoxy-2-(2-methoxyethyl)-2,5-dihydropyrazin-2-yl)ethanol 5b

Compound **5b** was prepared from (2*R*,5*S*)-2-isopropyl-3,6-dimethoxy-5-(2-methoxyethyl)-2,5-dihydropyrazine **4** (0.400 g, 1.66 mmol) and acetaldehyde (0.146 g, 1.19 mL, 3.32 mmol) as above. The crude product was purified by flash chromatography on silica gel using EtOAc–hexane 2:3. The product was a colourless oil and consisted of the two alcohol epimers in the ratio 4:1; yield 0.332 g (70%). The epimer mixture was used as such in the subsequent reaction. For analytical purposes, the major epimer was separated by repetition of the chromatography as above. R_f 0.22. Found: C, 58.6; H, 9.1. $C_{14}H_{26}N_2O_4$ requires C, 58.7; H, 9.15. HRMS: M+H 287.1974. $C_{14}H_{26}N_2O_4$+H requires 287.1970. ν_{max} (film/cm^{-1}) 3442, 2971, 2944, 2872, 1694, 1680, 1462, 1436, 1240, 1197, 1140, 1118; δ_H ($CDCl_3$) 0.64 and 1.06 (6H, 2d, J 6.8, $CH(CH_3)_2$), 1.05 (3H, d, J 6.2, $CHOHCH_3$), 2.01–2.06 (2H, m, $CHHCH_2OCH_3$ and $CHOH$), 2.19–2.32 (2H, m, $CH(CH_3)_2$ and $CHHCH_2OCH_3$), 3.23–3.31 (2H, m, $CH_2CH_2OCH_3$), 3.24 (3H, s, OCH_3), 3.66 and 3.69 (6H, 2s, $2\times OCH_3$), 3.68–3.75 (1H, m, $CHOH$), 3.87 (1H, d, J 3.6, H-5); δ_C ($CDCl_3$) 16.5 and 19.3 ($CH(CH_3)_2$), 17.0 ($CHOHCH_3$), 30.3 ($CH(CH_3)_2$), 34.7 ($CH_2CH_2OCH_3$), 52.0, 52.2 ($2\times OCH_3$), 58.1 (CH_2OCH_3), 60.3 (C-5), 63.5 (C-2), 69.0 (CH_2OCH_3), 72.7 ($CHOH$), 162.5 and 163.5 ($2\times C{=}N$); m/z (CI) 287 (M^++H, 100%), 269 (13), 255 (15), 243 (22), 241 (24), 199 (71), 167 (31).

4.7. (2′*R*,5′*R*)-1-(5-Isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydropyrazin-2-yl)ethanone 6a

A solution of (2′*S*,5′*R*)-1-(5-isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydropyrazin-2-yl)ethanol **5a** (1.00 g, 4.13 mmol) in dichloromethane (20 mL) was added to a solution of Dess–Martin reagent (2.12 g, 5.00 mmol) in dichloromethane (20 mL) under argon at ambient temperature, and the mixture stirred for 1 h. NaOH (30 mL, 1.3 M) and diethyl ether (30 mL) were added, the resultant mixture stirred for 10 min before extraction with NaOH (20 mL) and washing with water (20 mL). The ether phase was dried over $MgSO_4$, evaporated and residual material subjected to flash chromatography on silica gel using EtOAc in hexane 1:4. R_f 0.32. The product was a colourless oil; yield 0.694 g (70%). Found: C, 60.1; H, 8.2. $C_{12}H_{20}N_2O_3$ requires C, 60.0; H, 8.4. HRMS: M 240.1468. $C_{12}H_{20}N_2O_3$ requires 240.1474. ν_{max} (film/cm^{-1}) 2961, 2947, 2873, 1736, 1690, 1438, 1287, 1247; δ_H ($CDCl_3$) 0.69 and 1.06 (6H, 2d, J 6.8, $CH(CH_3)_2$), 1.42 (3H, s, CH_3), 2.03 (3H, s, $COCH_3$), 2.23–2.32 (1H, m, $CH(CH_3)_2$), 3.64 and 3.66 (6H, 2s, $2\times OCH_3$), 4.03 (1H, d, J 3.4, H-5); δ_C ($CDCl_3$) 17.0 and 19.4 ($CH(CH_3)_2$), 22.9 and 24.4 (CH_3 and $COCH_3$), 31.2 ($CH(CH_3)_2$), 52.7 and 52.8 ($2\times OCH_3$), 61.2 (C-5), 67.3 (C-2), 161.9 and 164.1 ($2\times C{=}N$), 202.9 (CO); m/z (EI) 240 (M^+, 5%), 197 (64), 181 (10), 170 (18), 155 (100), 140 (9), 43 (45).

4.8. (2′*R*,5′*R*)-1-[5-Isopropyl-3,6-dimethoxy-2-(2-methoxyethyl)-2,5-dihydropyrazin-2-yl]ethanone 6b

Compound **6b** was prepared as above from (2′*S*,5′*R*)-1-[5-isopropyl-3,6-dimethoxy-2-(2-methoxyethyl)-2,5-dihydropyrazin-2-yl]ethanol **5b** (0.500 g, 1.74 mmol) and the Dess–Martin reagent (0.815 g, 1.92 mmol). The crude product was purified by flash chromatography on silica gel using EtOAc–hexane 1:5. R_f 0.23. The product was a colourless oil; yield 0.355 g (72%). Found: C, 59.2; H, 8.5. $C_{14}H_{24}N_2O_4$ requires C, 59.1; H, 8.5. HRMS: M+H, 285.1809. $C_{14}H_{24}N_2O_4$+H requires 285.1814. ν_{max} (film/cm^{-1}) 2971, 2946, 2872, 1728, 1689, 1437, 1247, 1117; δ_H ($CDCl_3$) 0.68 and 1.08 (6H, 2d, J 6.8, $CH(CH_3)_2$), 2.02 (3H, s, $COCH_3$), 2.24 (2H, t, J 7.8, $CH_2CH_2OCH_3$), 2.28–2.39 (1H, m, $CH(CH_3)_2$), 3.23 (3H, s, OCH_3), 3.24–3.34 (2H, m, $CH_2CH_2OCH_3$), 3.66 and 3.69 (6H, 2s, $2\times OCH_3$), 3.96 (1H, d, J 4.8, H-5); δ_C ($CDCl_3$) 16.9 and 19.5 ($CH(CH_3)_2$), 24.9 ($COCH_3$), 30.7 ($CH(CH_3)_2$), 34.5 ($CH_2CH_2OCH_3$), 52.8 ($2\times OCH_3$), 58.4 (CH_2OCH_3), 60.7 (C-5), 68.6 (CH_2OCH_3), 69.6 (C-2), 160.2 and 164.5 ($2\times C{=}N$), 202.6 (CO); m/z (CI) 285 (M^++H, 100%), 253 (34), 241 (57), 211 (9), 199 (50), 183 (6), 167 (30).

4.9. (2′*S*,5′*R*)-1-(5-Isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydropyrazin-2-yl)propan-2-ol 7

A solution of (2*R*,5*S*)-2-isopropyl-3,6-dimethoxy-5-methyl-2,5-dihydropyrazine **2a** (2.00 g, 10.10 mmol) in THF (40 mL) under argon was lithiated by the addition of *n*-BuLi (6.95 mL, 11.11 mmol, 1.6 M in hexane) at −78 °C, the mixture stirred at this temperature for 30 min and a solution of propylene oxide (1.05 mL, 0.878 g, 15.15 mmol) in THF (20 mL) added dropwise. The resultant mixture was stirred and allowed to reach ambient temperature over 1 h. The reaction was terminated by addition of phosphate buffer pH 7 (35 mL). The mixture was extracted with diethyl ether (3×20 mL), the extracts dried over $MgSO_4$ and the solvent evaporated off. The residue was subjected to flash chromatography on silica gel using EtOAc–hexane 3:7. The product was a colourless oil that consisted of the two alcohol epimers in ratio 1:1. R_f 0.20; yield 1.551 g (60%). Found: C, 61.05; H, 9.3. $C_{13}H_{24}N_2O_3$ requires C, 60.9, H, 9.4. HRMS: M 256.1781. $C_{13}H_{24}N_2O_3$ requires 256.1786. ν_{max} (film/cm^{-1}) 3427, 2969, 2945, 2872, 1690, 1461, 1436, 1241, 1201, 1143; δ_H ($CDCl_3$) 0.67 and 1.03 (6H, 2d, J 6.8, $CH(CH_3)_2$), 0.70 and 1.10 (6H, 2d, 6H, J 6.8, $CH(CH_3)_2$), 1.19 and 1.24 (6H, 2d, J 6.4, $2\times CHOHCH_3$), 1.29 and 1.38 (6H, 2s, $2\times CH_3$), 1.43–1.78 (4H, m, $2\times CH_2CHOH$), 2.12–2.30 (2H, m,

2×C*H*(CH_3)$_2$), 3.12 (1H, br s, CHO*H*), 3.60, 3.62, 3.63 and 3.64 (12H, 4s, 4×OCH_3), 3.69–3.75 (m, 1H, C*H*OHCH$_3$), 3.80 and 3.92 (2H, 2d, *J* 4.0 Hz, 2×H-5), 4.18–4.30 (1H, m, C*H*OHCH$_3$), 5.38 (1H, br s, CHO*H*); δ_C ($CDCl_3$) 17.1, 17.5, 19.3 and 19.5 (2×CH(*C*H$_3$)$_2$), 23.4 and 23.6 (2×CHOH*C*H$_3$), 25.9 and 29.8 (2×CH_3), 31.1 and 31.4 (2×*C*H(CH_3)$_2$), 47.6 and 49.0 (2×*C*H$_2$CHOH), 52.2, 52.3, 52.4 and 52.5 (4×OCH_3), 58.2 and 58.6 (2×C-2), 60.5 and 61.5 (2×C-5), 64.6 and 65.8 (2×*C*HOH), 162.4, 164.2, 164.9 and 162.4 (4×C=N); *m*/*z* (EI) 256 (M^+, 4%), 241 (11), 224 (10), 212 (18), 198 (11), 197 (43), 184 (8), 182 (15), 167 (19), 156 (14), 155 (100), 140 (17), 139 (29).

4.10. (2′*S*,5′*R*)-1-(5-Isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydropyrazin-2-yl)propan-2-one 8a

A solution of (2′*S*,5′*R*)-1-(5-isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydropyrazin-2-yl)propan-2-ol **6** (1.300 g, 5.07 mmol) in dichloromethane (25 mL) was added to a solution of the Dess–Martin reagent (2.583 g, 6.09 mmol) in dichloromethane (15 mL) under argon at ambient temperature and the mixture stirred for 30 min. Diethyl ether (30 mL) and 1.3 M NaOH (30 mL) were added, the resultant mixture stirred for 10 min before extraction with NaOH (20 mL) and washing with water (15 mL). The ether phase was dried over $MgSO_4$, evaporated and the residual material subjected to flash chromatography on silica gel using EtOAc in hexane 1:4. R_f 0.27. The product was a colourless oily material; yield 0.901 g (70%). Found: C, 61.5; H, 8.55. $C_{13}H_{22}N_2O_3$ requires C, 61.4; H, 8.7. HRMS: M 254.1625. $C_{13}H_{22}N_2O_3$ requires 254.1630. ν_{max} (film/cm^{-1}) 2970, 2946, 2871, 1723, 1698, 1436, 1245, 1205, 1136; δ_H ($CDCl_3$) 0.67 and 1.03 (6H, 2d, *J* 6.8, CH(C*H*$_3$)$_2$), 1.29 (3H, s, CH_3), 2.01 (3H, s, $COCH_3$), 2.21–2.30 (1H, m, C*H*(CH_3)$_2$), 2.70 and 2.88 (2H, 2d, *J* 15.5, C*H*$_2$CO), 3.57 and 3.66 (6H, 2s, 2×OC*H*$_3$), 3.99 (1H, d, *J* 3.4, H-5); δ_C ($CDCl_3$) 17.6 and 19.9 (CH(*C*H$_3$)), 29.5 and 31.3 ($COCH_3$ and CH_3), 31.7 (*C*H(CH_3)$_2$), 52.6 and 52.7 (2×OCH_3), 53.8 (*C*H$_2$COCH$_3$), 56.7 (C-2), 61.78 (C-5), 162.7 and 163.3 (2×C=N), 206.7 (CO); *m*/*z* (EI) 254 (M^+, 22%), 239 (13), 227 (10), 212 (23), 211 (100), 197 (65), 182 (24), 169 (35), 155 (56), 154 (27), 140 (9), 137 (17).

4.11. (2′*R*,5′*R*)-2-Diazo-1-(5-isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydropyrazin-2-yl)ethanone 12a

n-BuLi (2.12 mL, 3.3 mmol, 1.55 M in hexane) was added to a solution of HMDS (0.516 mL, 3.3 mmol) in THF (10 mL) under argon at 0 °C. After stirring for 10 min, the solution was cooled to −78 °C and a solution of (2′*S*,5′*R*)-1-(5-isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydropyrazin-2-yl)ethanone **6a** (0.720 g, 3.00 mmol) in THF (15 mL) added dropwise over 15 min. The mixture was stirred at −78 °C for 30 min before TFEA (0.446 mL, 3.3 mmol) was rapidly injected. The reaction mixture was stirred for 10 min, transferred to a separating funnel containing 5% aqueous HCl (20 mL) and diethyl ether (15 mL). The funnel was shaken, the layers separated, the aqueous layer extracted with diethyl ether (2×10 mL), the combined organic solutions washed with saturated aqueous NaCl (20 mL) and the solution evaporated. The residual oil was dissolved in MeCN (20 mL), and transferred to a three-necked flask. Subsequently, water (0.054 mL, 3.00 mmol) and triethylamine (0.626 mL, 4.5 mmol) were added followed by the dropwise addition of a solution of tosyl azide (0.886 g, 4.5 mmol) in MeCN (5 mL) over 10 min. The resultant reaction mixture was stirred at ambient temperature for 2.5 h, the solvent distilled off, the residue dissolved in diethyl ether (15 mL) and the ether solution shaken with 5% aqueous NaOH (20 mL), and aqueous saturated NaCl (20 mL). The solution was dried over $MgSO_4$, evaporated and the residual material subjected to flash chromatography on silica gel using EtOAc in hexane 1:4. R_f 0.20. The product was a yellow oily material; yield 0.351 g (44%). HRMS: M 266.1368. $C_{12}H_{18}N_4O_3$ requires 266.1379. ν_{max} (film/cm^{-1}) 2960, 2946, 2109, 1689, 1671, 1438, 1350, 1247; δ_H ($CDCl_3$) 0.67 and 1.05 (6H, 2d, *J* 6.8, CH(C*H*$_3$)$_2$), 1.5 (3H, s, CH_3), 2.26–2.32 (1H, m, C*H*(CH_3)$_2$), 3.66 and 3.69 (6H, 2s, 2×OCH_3), 3.99 (1H, d, *J* 3.4, H-5), 5.27 (1H, s, C*H*=N$_2$); δ_C ($CDCl_3$) 16.9 and 19.4 (CH(*C*H$_3$)$_2$), 24.0 (*C*H$_3$), 31.1 (*C*H(CH_3)$_2$), 52.7 and 53.0 (2×OCH_3), 53.3 (CH=N$_2$), 60.9 (C-5), 65.8 (C-2), 161.3 and 164.1 (2×C=N), 191.4 (CO); *m*/*z* (EI) 266 (M^+, 2%), 238 (7), 197 (45), 155 (100), 140 (10), 69 (7), 43 (14).

4.12. (2′*R*,5′*R*)-2-Diazo-1-[5-isopropyl-3,6-dimethoxy-2-(2-methoxyethyl)-2,5-dihydropyrazin-2-yl]ethanone 12b

Compound **12b** was prepared as above from (2′*S*,5′*R*)-1-[5-isopropyl-3,6-dimethoxy-2-(2-methoxyethyl)-2,5-dihydropyrazin-2-yl]ethanone **6b** (0.233 g, 0.82 mmol), TFEA (0.121 mL, 0.90 mmol) and tosyl azide (0.242 g, 1.23 mmol). The product was isolated after flash chromatography on silica gel using EtOAc–hexane 3:7. R_f 0.22. The product was a yellow oily material; yield 0.134 g (53%). HRMS: M+H 311.1712. $C_{14}H_{22}N_4O_4$+H require 311.1719. ν_{max} (film/cm^{-1}) 2947, 2873, 2107, 1748, 1689, 1670, 1586, 1462, 1438, 1347, 1243, 1196, 1139; δ_H ($CDCl_3$) 0.65 and 1.06 (6H, 2d, *J* 6.8, CH(C*H*$_3$)$_2$), 2.17–2.33 (3H, m, C*H*$_2$CH$_2$OCH$_3$ and C*H*(CH_3)$_2$), 3.20 (3H, s, OCH_3), 3.31 (2H, t, *J* 7.0, CH$_2$CH$_2$OCH$_3$), 3.64 and 3.68 (6H, 2s, 2×OCH_3), 3.90 (1H, d, *J* 3.4, H-5), 5.34 (1H, s, CHN_2); δ_C ($CDCl_3$) 16.6 and 19.3 (CH(*C*H$_3$)$_2$), 30.6 (*C*H(CH_3)$_2$), 35.4 (*C*H$_2$CH$_2$OCH$_3$), 52.8 and 53.0 (2×OCH_3), 53.2 (CHN_2), 58.3 (CH$_2$O*C*H$_3$), 60.3 (C-5), 67.7 (C-2), 68.5 (*C*H$_2$OCH$_3$), 159.6 and 164.6 (2×C=N), 190.8 (CO); *m*/*z* (CI) 311 (M^++H, 100%), 283 (27), 279 (33), 255 (4), 251 (15), 241 (65), 209 (18), 199 (82), 167 (31), 69 (9), 45 (44).

4.13. (2′*R*,5′*R*)-1-(2-Allyl-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)-2-diazoethanone 12c

n-BuLi (1.60 mL, 2.48 mmol, 1.55 M in hexane) was added to a solution of HMDS (0.516 mL, 2.48 mmol) in THF (10 mL) under argon at 0 °C. The solution was

cooled to −78 °C after stirring for 10 min and a solution of (2′*R*,5′*R*)-1-(2-allyl-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)ethanone **6c** (0.600 g, 2.25 mmol) in THF (15 mL) added dropwise over 15 min. The mixture was stirred at −78 °C for 30 min before TFEA (0.348 mL, 2.48 mmol) was rapidly injected. The reaction mixture was stirred for 10 min, transferred to a separating funnel containing 5% aqueous HCl (20 mL) and diethyl ether (15 mL). The funnel was shaken, the layers separated, the aqueous layer extracted with diethyl ether (2×10 mL), the combined organic solutions washed with saturated aqueous NaCl (20 mL) and the solution evaporated. The residual oil was dissolved in acetonitrile (20 mL), and transferred to a three-necked flask. Subsequently, water (0.044 mL, 2.48 mmol) and triethylamine (0.517 mL, 3.72 mmol) were added followed by the dropwise addition over 10 min of a solution of tosyl azide (0.732 g, 3.72 mmol) in acetonitrile (5 mL). The resultant reaction mixture was stirred at ambient temperature for 2.5 h, the solvent distilled off, the residue dissolved in diethyl ether (15 mL) and the ether solution shaken with 5% aqueous NaOH (20 mL), and aqueous saturated NaCl (20 mL). The solution was dried over $MgSO_4$, evaporated and the residual material subjected to flash chromatography on silica gel using EtOAc–hexane 1:5. R_f 0.27. The product was a yellow oily material; yield 0.276 g (42%). HRMS: M 292.1548. $C_{14}H_{20}N_4O_3$ requires 292.1535. ν_{max} (film/cm^{-1}) 2982, 2944, 2875, 2108, 1685, 1643, 1438, 1350, 1302, 1247; δ_H ($CDCl_3$) 0.63 and 1.05 (6H, 2d, *J* 7.0, CH(C*H*$_3$)$_2$), 2.30–2.35 (1H, m, C*H*(CH$_3$)$_2$), 2.67–2.69 (1H, m, C*H*HCH=CH$_2$), 2.77–2.81 (1H, m, CH*H*CH=CH$_2$), 3.66 and 3.69 (6H, 2s, 2×OCH$_3$), 3.92 (1H, d, *J* 3.4, H-5), 4.95–5.06 (2H, m, CH=C*H*$_2$), 5.35 (1H, s, CH=N$_2$), 5.50–5.54 (1H, m, C*H*=CH$_2$); δ_C ($CDCl_3$) 17.0 and 19.5 (CH(*C*H$_3$)$_2$), 30.5 (*C*H(CH$_3$)$_2$), 40.6 (*C*H$_2$CH=CH$_2$), 52.8 and 52.9 (2×OCH$_3$), 53.2 (CH=N$_2$), 60.3 (C-5), 69.4 (C-2), 118.6 (CH=*C*H$_2$), 133.1 (*C*H=CH$_2$), 159.4 and 164.4 (2×C=N), 190.9 (CO); *m*/*z* (EI) 292 (M$^+$, 2%), 264 (7), 223 (16), 223 (75), 221 (9), 182 (17), 181 (100), 179 (6), 166 (8).

4.14. (2′*S*,5′*R*)-1-Diazo-3-(5-isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydropyrazin-2-yl)propan-2-one 13a

n-BuLi (2.28 mL, 3.66 mmol, 1.6 M in hexane) was added to a solution of HMDS (0.763 mL, 3.66 mmol) in THF (15 mL) under argon at 0 °C. After stirring for 10 min, the solution was cooled to −78 °C and a solution of (2′*S*,5′*R*)-1-(5-isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydropyrazin-2-yl)propan-2-one **8a** (0.800 g, 3.15 mmol) in THF (20 mL) added dropwise over 15 min. The mixture was stirred at −78 °C for 30 min before TFEA (0.500 mL, 3.66 mmol) was rapidly injected. The reaction mixture was stirred for 10 min, transferred to a separating funnel containing 5% aqueous HCl (25 mL) and diethyl ether (15 mL). The funnel was shaken, the layers separated, the aqueous layer extracted with diethyl ether (2×15 mL), the combined organic solutions washed with saturated aqueous NaCl (25 mL) and the solution evaporated. The residual oil was dissolved in acetonitrile (20 mL), and transferred to a three-necked flask. Water (0.057 mL, 3.15 mmol) and triethylamine (0.657 mL, 4.72 mmol) were then added followed by the dropwise addition of a solution of tosyl azide (0.929 g, 4.72 mmol) in acetonitrile (10 mL) over 10 min. The resultant reaction mixture was stirred at ambient temperature for 2.5 h, the solvent distilled off, the residue dissolved in diethyl ether (25 mL) and the ether solution shaken with 5% aqueous NaOH (25 mL), and aqueous saturated NaCl (25 mL). The solution was dried over $MgSO_4$, evaporated and the residual material subjected to flash chromatography on silica gel using EtOAc–hexane 1:5. R_f 0.16. The product was a yellow oily material; yield 0.458 g (52%). HRMS: M+H 281.1599. $C_{13}H_{20}N_4O_3$+H require 281.1613. ν_{max} (film/cm^{-1}) 2960, 2946, 2872, 2109, 1689, 1671, 1438, 1350, 1247; δ_H ($CDCl_3$) 0.65 and 1.03 (6H, 2d, *J* 6.8, CH(C*H*$_3$)$_2$), 1.32 (3H, s, CH$_3$), 2.19–2.28 (1H, m, C*H*(CH$_3$)$_2$), 2.55 and 2.80 (2H, 2d, *J* 13.9, C*HH*CO), 3.61 and 3.66 (6H, 2s, 2×OCH$_3$), 3.95 (1H, d, *J* 3.4, H-5), 5.15 (1H, s, CHN$_2$); δ_C ($CDCl_3$) 17.0 and 19.4 (CH(C*H*$_3$)$_2$), 29.0 (CH$_3$), 30.8 (*C*H(CH$_3$)$_2$), 51.3 (*C*H$_2$CO), 52.3 and 52.4 (2×OCH$_3$), 55.1 (CH=N$_2$), 57.1 (C-2), 61.1 (C-5), 162.9 and 163.8 (2×C=N), 192.0 (CO); *m*/*z* (CI) 281 (M$^+$+H, 100%), 253 (93), 252 (35), 237 (15), 231 (27), 209 (45), 197 (43), 181 (7), 167 (22), 155 (36).

4.15. (2′*S*,5′*R*)-3-(2-Allyl-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)-1-diazopropan-2-one 13b

Compound **13b** was prepared as above from (2′*S*,5′*R*)-1-(2-allyl-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)propan-2-one **8b** (0.450 g, 1.60 mmol), TFEA (0.237 mL, 1.76 mmol) and tosyl azide (0.472 g, 2.4 mmol). The product was isolated after flash chromatography on silica gel using EtOAc–hexane 1:5. R_f 0.20. The product was a yellow oil; yield 0.244 g (50%). HRMS: M 306.1698. $C_{15}H_{22}N_4O_3$ requires 306.1691. ν_{max} (film/cm^{-1}) 2959, 2944, 2871, 2103, 1697, 1640, 1436, 1367, 1237; δ_H ($CDCl_3$) 0.60 and 1.04 (6H, 2d, *J* 7.0, CH(C*H*$_3$)$_2$), 2.23–2.28 (1H, m, C*H*(CH$_3$)$_2$), 2.30–2.78 (signals overlapp, 4H, m, C*H*$_2$CH=CH$_2$ and CH$_2$CO), 3.64 and 3.66 (6H, 2s, 2×OCH$_3$), 3.92 (1H, d, *J* 3.4, H-5), 4.96–5.11 (2H, m, CH=C*H*$_2$), 5.12 (1H, s, CHN$_2$), 5.52–5.69 (1H, m, C*H*=CH$_2$); δ_C ($CDCl_3$) 17.3 and 19.5 (CH(*C*H$_3$)$_2$), 30.3 (*C*H(CH$_3$)$_2$), 45.3 (*C*H$_2$CH=CH$_2$), 49.9 (*C*H$_2$CO), 52.1 and 52.2 (2×OCH$_3$), 55.0 (CH=N$_2$), 60.2 (C-2), 60.6 (C-5), 118.1 (CH=*C*H$_2$), 133.5 (*C*H=CH$_2$), 162.1 and 163.4 (2×C=N), 191.8 (CO); *m*/*z* (EI) 306 (M$^+$, 1%), 278 (3), 265 (5), 237 (26), 235 (100), 223 (20), 195 (60), 181 (52), 167 (22), 153 (26), 123 (12).

4.16. (6*R*)-3-Isopropyl-2,5-dimethoxy-6-methyl-1,4-diazabicyclo[4.2.0]octa-2,4-dien-7-one 15a

A solution of (2′*R*,5′*R*)-2-diazo-1-(5-isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydropyrazin-2-yl)ethanone **12a** (0.260 g, 0.97 mmol) in dry dichloromethane (20 mL) was added dropwise to a solution of $Rh_2(OAc)_4$ (0.022 g, 0.048 mmol) in dry dichloromethane (20 mL)

under argon at ambient temperature. The mixture was stirred at ambient temperature for 20 min and the solution evaporated to dryness at reduced pressure. The residual material was subjected to flash chromatography on silica gel using EtOAc–hexane 2:3. R_f 0.36. The product was a yellow, unstable oily material; yield 0.180 g (78%). $[\alpha]_D = +13.6$ (c 1.0, $CHCl_3$). HRMS: M 238.1310. $C_{12}H_{18}N_2O_3$ requires 238.1317. ν_{max} (film/cm^{-1}) 2953, 2930, 2860, 1755, 1683, 1395, 1235; δ_H ($CDCl_3$) 0.95 and 1.07 (6H, 2d, J 6.8, $CH(CH_3)_2$), 1.43 (3H, s, CH_3), 2.80–2.85 (1H, sept, J 6.8, $CH(CH_3)_2$), 3.55 and 3.74 (6H, 2s, $2\times OCH_3$), 4.50 and 4.52 (2H, 2d, J 12.3, CH_2CO); δ_C ($CDCl_3$) 20.5, 20.9 and 21.3 ($CH(CH_3)_2$ and CH_3), 26.8 ($CH(CH_3)_2$), 54.2 (5-OCH_3) and 57.7 (2-OCH_3), 77.1 (CH_2CO), 86.7 (C-6), 117.8 (C-3), 140.5 (C-2) and 148.9 (C-5), 196.1 (CO); m/z (EI) 238 (M^+, 8%), 210 (20), 196 (25), 195 (100), 181 (25), 155 (24), 125 (20), 56 (32), 43 (30).

4.17. (6*R*)-3-Isopropyl-2,5-dimethoxy-6-(2-methoxyethyl)-1,4-diazabicyclo[4.2.0]octa-2,4-dien-7-one 15b

Compound **15b** was prepared as above from (2′*R*,5′*R*)-2-diazo-1-[5-isopropyl-3,6-dimethoxy-2-(2-methoxyethyl)-2,5-dihydropyrazin-2-yl]ethanone **12b** (0.100 g, 0.32 mmol) using $Rh_2(OAc)_4$ (0.007 g, 0.016 mmol). The product was isolated after flash chromatography on silica gel using EtOAc–hexane 3:7. R_f 0.43. The product was an unstable yellow oil; yield 0.072 g (80%). $[\alpha]_D = +23.3$ (c 0.45, $CHCl_3$). HRMS: M 282.1584. $C_{14}H_{22}N_2O_4$ requires 282.1580. ν_{max} (film/cm^{-1}) 2950, 2866, 1755, 1687, 1593, 1395, 1205; δ_H ($CDCl_3$) 0.94 and 1.05 (6H, 2d, J 6.8, $CH(CH_3)_2$), 1.84–1.98 (1H, m, $CHHCH_2OCH_3$), 2.20–2.32 (1H, m, $CHHCH_2OCH_3$), 2.81 (1H, sept, J 6.8, $CH(CH_3)_2$), 3.25 (3H, s, OCH_3), 3.26–3.43 (2H, m, $CH_2CH_2OCH_3$), 3.56 and 3.71 (6H, 2s, $2\times OCH_3$), 4.51 and 4.54 (2H, 2d, J 12.3, CH_2CO); δ_C ($CDCl_3$) 21.0 and 21.3 ($CH(CH_3)_2$), 26.8 ($CH(CH_3)_2$), 34.1 ($CH_2CH_2OCH_3$), 54.2 (5-OCH_3) and 57.7 (2-OCH_3), 58.8 ($CH_2CH_2OCH_3$), 67.5 ($CH_2CH_2OCH_3$), 77.4 (CH_2CO), 88.3 (C-6), 117.5 (C-3), 140.8 (C-2) and 148.0 (C-5), 194.7 (CO); m/z (EI) 282 (M^+, 6%), 257 (9), 207 (24), 195 (100), 167 (33), 125 (16), 83 (24), 68 (20), 43 (21).

4.18. (6*R*)-6-Allyl-3-isopropyl-2,5-dimethoxy-1,4-diazabicyclo[4.2.0]octa-2,4-dien-7-one 15c

A solution of (2′*R*,5′*R*)-1-(2-allyl-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)-2-diazoethanone **12c** (0.250 g, 0.85 mmol) in dry dichloromethane (20 mL) was added dropwise to a solution of $Rh_2(OAc)_4$ (0.020 g, 0.043 mmol) in dry dichloromethane (20 mL) under argon at ambient temperature. The mixture was stirred at ambient temperature for 30 min and the solution evaporated to dryness at reduced pressure. The residual material was subjected to flash chromatography on silica gel using EtOAc in hexane 1:4 R_f 0.57. The product was a yellow unstable oily material; yield 0.180 g (80%). $[\alpha]_D = +10.2$ (c 1.0, MeOH). HRMS: M 264.1471. $C_{14}H_{20}N_2O_3$ requires 264.1473. ν_{max} (film/cm^{-1}) 2954, 2931, 2758, 1725, 1685, 1455, 1358, 1241, 1190; δ_H ($CDCl_3$) 0.90 and 1.03 (6H, 2d, J 6.8, $CH(CH_3)_2$), 2.38–2.59 (2H, m, $CH_2CH{=}CH_2$), 2.71–2.81 (1H, sept, J 6.8, $CH(CH_3)_2$), 3.52 and 3.71 (6H, 2s, $2\times OCH_3$), 4.42 and 4.49 (2H, 2d, J 12.3, $CHHCO$), 5.02–5.13 (2H, m, $CH{=}CH_2$), 5.52–5.69 (1H, m, $CH{=}CH_2$); δ_C ($CDCl_3$) 20.2 and 20.6 ($CH(CH_3)_2$), 26.2 ($CH(CH_3)_2$), 38.4 ($CH_2CH{=}CH_2$), 53.5 (5-OCH_3) and 57.1 (2-OCH_3), 76.9 (CH_2CO), 89.1 (C-6), 117.1 (C-3), 119.3 ($CH{=}CH_2$), 130.2 ($CH{=}CH_2$), 140.4 (C-2) and 146.9 (C-5), 194.5 (CO); m/z (EI) 264 (M^+, 19%), 236 (14), 223 (61), 221 (50), 207 (23), 195 (100), 165 (7), 151 (21), 139 (9), 125 (14), 114 (12).

4.19. NMR studies in the formation of the intermediate: 3-isopropyl-1,4-dimethoxy-8a-methyl-8,8a-dihydropyrrolo-[1,2-α]pyrazin-7-one 17a

$Rh_2(OAc)_4$ (0.004 g, 0.01 mmol) was added to a solution of (2′*S*,5′*R*)-1-diazo-3-(5-isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydropyrazin-2-yl)propan-2-one **13a** (0.028 g, 0.1 mmol) in $CDCl_3$ (1 mL) at room temperature. The mixture was stirred for 5 min when all the substrate had reacted. According to NMR measurements (vide infra) only one product was formed in the reaction. The NMR spectra of the crude reaction mixture were recorded: δ_H ($CDCl_3$) 0.95 and 1.09 (6H, 2d, J 6.8, $CH(CH_3)_2$), 1.20 (3H, s, CH_3), 2.39 (1H, d, J 19.0, $CHHCO$), 2.85 (1H, sept, J 6.8, $CH(CH_3)_2$), 3.15 and 3.19 (2H, 2d, J 19 and 18.7, $CHHCO$ and $NCHHCO$), 3.57 (1H, s, OCH_3), 3.68 (1H, d, J 18.7, $NCHHCO$), 3.71 (1H, s, OCH_3); δ_C ($CDCl_3$) 20.9 and 21.0 ($CH(CH_3)_2$), 22.9 (CH_3), 26.4 ($CH(CH_3)_2$), 45.5 (CH_2CO), 53.8 (OCH_3), 57.21 (NCH_2CO), 58.1 (OCH_3), 60.3 (C-8a), 118.9 (C-3), 139.5 (C-4), 155.6 (C-1), 210.8 (CO-7).

Further transformation of compound **17a** into (3*R*,8a*S*)-3-isopropyl-1-methoxy-8a-methyl-8,8a-dihydro-3*H*-pyrrolo[1,2-*a*]pyrazine-4,7-dione **20a** in an NMR tube was effected by the addition of some silica gel and the tube shaken occasionally with NMR monitoring. The originally green solution turned brown on the addition of silica gel indicating destruction of the catalyst. The NMR spectra (vide infra) recorded after 1 h showed that the dione **20a** was the only product.

4.20. NMR studies in the formation of the intermediate: 8a-allyl-3-isopropyl-1,4-dimethoxy-8,8a-dihydropyrrolo-[1,2-α]pyrazin-7-one 17b

Compound **17b** was prepared as above from (2′*S*,5′*R*)-1-diazo-3-[2-allyl-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl]propan-2-one **13b** (0.030 g, 0.1 mmol) and $Rh_2(OAc)_4$ (0.004 g, 0.01 mmol) and the NMR spectra recorded after 5 min. δ_H ($CDCl_3$) 0.96 and 1.09 (6H, 2d, J 6.8, $CH(CH_3)_2$), 2.23–2.25 (2H, m, CH_2-$CH{=}CH_2$), 2.55 (1H, d, J 19.2, $CHHCO$), 2.85 (1H, sept, J 6.8, $CH(CH_3)_2$), 3.04 (1H, d, J 19.2, $CHHCO$), 3.25 (1H, d, J 18.0, $NCHHCO$), 3.56 (1H, s, OCH_3), 3.65 (1H, d, J 18.0, $NCHHCO$), 3.69 (1H, s, OCH_3), 5.03–5.12 (2H, m,

CH=CH_2), 5.63–5.78 (1H, m, CH=CH$_2$); δ_C ($CDCl_3$) 20.9 and 21.0 (CH(CH_3)$_2$), 26.4 (CH(CH$_3$)$_2$), 39.3 (CH_2CH=CH$_2$), 42.5 (CH_2CO), 53.7 (OCH$_3$), 57.1 (NCH_2CO), 58.5 (OCH$_3$), 63.3 (C-8a), 117.9 (C-3), 119.6 (CH=CH$_2$), 131.8 (CH=CH$_2$), 139.2 (C-4), 154.1 (C-1), 210.4 (CO-7).

Further transformation of compound **17b** into (3*R*,8a*S*)-8a-allyl-3-isopropyl-1-methoxy-8,8a-dihydro-3*H*-pyrrolo-[1,2-*a*]pyrazine-4,7-dione **20b** in an NMR tube was effected as above by addition of some silica to the tube. The originally green solution turned brown. The NMR spectra (vide infra) were recorded after 1 h and showed that the dione **20b** was the only product.

4.21. (3*R*,8a*S*)-3-Isopropyl-1-methoxy-8a-methyl-8,8a-dihydro-3H-pyrrolo[1,2-*a*]pyrazine-4,7-dione 20a

A solution of (2′*S*,5′*R*)-1-diazo-3-(5-isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydropyrazin-2-yl)propan-2-one **13a** (0.340 g, 1.21 mmol) in dry dichloromethane (25 mL) was added dropwise to a solution of $Rh_2(OAc)_4$ (0.027 g, 0.060 mmol) in dry dichloromethane (10 mL) under argon at ambient temperature. The mixture was stirred at ambient temperature for 30 min and the solution evaporated to dryness at reduced pressure. The residual material was subjected to flash chromatography on silica gel using EtOAc–hexane 2:3. R_f 0.16. The product was a colourless oil; yield 0.162 g (56%). $[\alpha]_D = -20.1$ (*c* 1.0, $CHCl_3$). HRMS: M+H 239.1405. $C_{12}H_{18}N_2O_3$+H require 239.1395. ν_{max} (film/cm^{-1}) 2963, 2873, 1767, 1698, 1655, 1464, 1428, 1248, 1186; δ_H ($CDCl_3$) 0.92 and 1.10 (6H, 2d, *J* 6.7, CH(CH_3)$_2$), 1.51 (3H, s, CH_3), 2.15–2.23 (1H, m, CH(CH$_3$)$_2$), 2.51 and 2.73 (2H, 2d, *J* 17.5, CHHCO), 3.73 (3H, s, OCH$_3$), 3.55 and 4.46 (2H, 2d, *J* 19.7, NCHHCO), 4.01 (1H, d, *J* 5.4, H-3); δ_C ($CDCl_3$) 18.6 and 19.9 (CH(CH_3)$_2$), 26.4 (CH_3), 33.1 (CH(CH$_3$)$_2$), 49.6 and 50.1 (CH_2CO and NCH_2CO), 53.3 (OCH$_3$), 61.1 (C-8a), 65.6 (C-3), 160.1 (C=N), 168.3 (4-CO), 207.4 (7-CO); *m*/*z* (CI) 239 (M$^+$+H, 100), 223 (10), 196 (43), 181 (11), 167 (8), 154 (21), 98 (7).

4.22. (3*R*,8a*S*)-8a-Allyl-3-isopropyl-1-methoxy-8,8a-dihydro-3H-pyrrolo[1,2-*a*]pyrazine-4,7-dione 20b

Compound **20b** was prepared as above from (2′*S*,5′*R*)-3-(2-allyl-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)-1-diazidopropan-2-one (0.140 g, 0.46 mmol) **13b** and $Rh_2(OAc)_4$ (0.011 g, 0.023 mmol). The product was isolated after flash chromatography on silica gel using EtOAc–hexane 2:3. R_f 0.18. The product was a colourless oil; yield 0.055 g (45%). $[\alpha]_D = -179.6$ (*c* 1.34, $CHCl_3$). Found: C, 63.5; H, 7.5. $C_{14}H_{20}N_2O_3$ requires C, 63.6; H, 7.6. HRMS: M+H 265.1558. $C_{14}H_{20}N_2O_3$+H requires 265.1552. ν_{max} (film/cm^{-1}) 2963, 2873, 1767, 1698, 1655, 1470, 1428, 1248, 1186; δ_H ($CDCl_3$) 0.97 and 1.10 (6H, 2d, *J* 6.7, CH(CH_3)$_2$), 2.03–2.11 (1H, sept, *J* 6.8, CH(CH$_3$)$_2$), 2.51–2.58 (2H, m, CH_2CH=CH$_2$), 2.60 and 2.73 (2H, 2d, *J* 17.8, CH_2CO), 3.70 (3H, s, OCH$_3$), 3.52 and 4.38 (2H, 2d, *J* 19.8, NCH$_2$CO), 3.89 (1H, d, *J* 6.8, H-3), 5.10–5.16 (2H, m, CH=CH_2), 5.62–5.75 (1H, m, CH=CH$_2$); δ_C ($CDCl_3$) 19.5 and 20.1 (CH(CH_3)$_2$), 33.6 (CH(CH$_3$)$_2$), 44.8 (CH_2CH=CH$_2$), 47.2 (CH_2CO), 51.8 (NCH_2CO), 53.2 (OCH$_3$), 64.3 (C-8a), 65.8 (C-3), 121.7 (CH=CH_2), 130.5 (CH=CH$_2$), 159.4 (C=N), 169.0 (4-CO), 207.3 (7-CO); *m*/*z* (CI) 265 (M$^+$+H, 100%), 237 (2), 223 (20), 195 (13), 181 (10), 167 (5), 163 (7).

4.23. (3*R*,7*R*,8a*S*)-8a-Allyl-7-hydroxy-3-isopropyl-1-methoxy-6,7,8,8a-tetrahydro-3H-pyrrolo[1,2-*a*]pyrazin-4-one 21

LiAlH(*t*-BuO)$_3$ (0.124 g, 0.48 mmol) was added to a solution of (3*R*,8a*S*)-8a-allyl-3-isopropyl-1-methoxy-8,8a-dihydro-3*H*-pyrrolo[1,2-*a*]pyrazine-4,7-dione **20b** (0.100 g, 0.37 mmol) in THF (5 mL) at 0 °C. The reaction mixture was stirred at this temperature for 30 min and at ambient temperature for 2.5 h before the reaction was quenched by addition of saturated aq NH_4Cl. The mixture was extracted with diethyl ether (3×10 mL), the combined organic extracts dried over $MgSO_4$ and evaporated to give product **21** as an oil. The NMR spectra of the crude product showed a stereoisomeric mixture of hydroxy derivatives in ratio 9:1. δ_H ($CDCl_3$) 0.97 and 1.07 (6H, 2d, *J* 6.8, CH(CH_3)$_2$), 1.97–2.22 (3H, m, CH(CH$_3$)$_2$ and CH_2CHOH), 2.20 (1H, d, *J* 14.0, CHOH), 2.62–2.77 (2H, m, CH_2CH=CH$_2$), 3.70 (3H, s, OCH$_3$), 3.18–3.22 (1H, m, NCHHCHOH), 4.43–4.48 (1H, m, NCHHCHOH), 3.71–3.78 (2H, m, H-3 and CHOH), 5.03–5.09 (2H, m, CH=CH_2), 5.67–5.74 (1H, m, CH=CH$_2$); δ_C ($CDCl_3$) 19.7 and 20.3 (CH(CH_3)$_2$), 33.7 (CH(CH$_3$)$_2$), 42.8 (CH_2CH=CH$_2$), 44.1 (CH_2CHOH), 51.8 (NCH_2CHOH), 53.05 (OCH$_3$), 65.4 (C-8a), 66.7 (C-3), 67.5 (CHOH), 119.0 (CH=CH_2), 133.1 (CH=CH$_2$), 160.8 (C=N), 169.0 (4-CO).

4.24. 4-Nitrobenzoic acid (3*R*,7*R*,8a*S*)-8a-allyl-3-isopropyl-1-methoxy-3,4,6,7,8,8a-tetrahydropyrrolo[1,2-*a*]pyrazin-7-yl ester 22

p-Nitrobenzoyl chloride (0.118 g, 0.64 mol) was added to a solution of (3*R*,7*R*,8a*S*)-8a-allyl-7-hydroxy-3-isopropyl-1-methoxy-6,7,8,8a-tetrahydro-3*H*-pyrrolo[1,2-*a*]-pyrazin-4-one **21** (0.085 g, 0.32 mmol) and DMAP (0.078 g, 0.64 mmol) in dry dichloromethane (10 mL) and the mixture stirred at room temperature. The progress of the reaction was monitored by TLC. The reaction was complete after 1 h when the solvent was distilled off and the crude product purified by flash chromatography on silica gel using EtOAc–hexane 2:3. R_f 0.16. The product was a pale yellow crystalline solid 0.050 g (38%), mp 137–139 °C (Et_2O). Found: C, 60.4; H, 6.25; $C_{21}H_{25}N_3O_6$ requires C, 60.7; H, 6.1. HRMS: M+H 416.1820. $C_{21}H_{25}N_3O_6$+H require 416.1822. ν_{max} (film/cm^{-1}) 2961, 2867, 1727, 1687, 1655, 1608, 1529, 1430, 1250, 1276; δ_H ($CDCl_3$) 0.98 and 1.11 (6H, 2d, *J* 6.7, CH(CH_3)$_2$), 2.01–2.07 (1H, m, CH(CH$_3$)$_2$), 2.29–2.50 (2H, m, CH_2CHO–), 2.60–2.68 (2H, m, CH_2CH=CH$_2$), 3.40–3.45 (1H, m, NCHHCHO–), 3.70 (3H, s, OCH$_3$), 3.82 (1H, d, *J* 4.8, H-3), 4.71–4.78 (1H,

m, NC*H*HCHO–), 4.94–5.08 (2H, m, CH=CH_2), 5.49–5.52 (1H, m, CHOCO), 5.72–5.78 (1H, m, C*H*=CH_2); 8.17 (2H, d, *J* 8.8, arom.), 8.30 (2H, d, *J* 8.8, arom.) δ_C ($CDCl_3$) 20.1 and 20.7 (CH(*C*H_3)$_2$), 34.2 (*C*H(CH_3)$_2$), 41.7 (*C*H_2CHO), 43.3 (*C*H_2CH=CH_2), 50.8 (N*C*H_2CHO), 53.3 (OCH_3), 65.5 (C-8a), 67.2 (C-3), 72.4 (CHO) 119.8 (CH=*C*H_2), 124.2 (2×CH_{ar}), 131.1 (2×CH_{ar}), 132.9 (*C*H=CH_2), 135.3 and 151.2 (2×C_{ar}), 160.5 (C=N), 164.4 (CO-ester), 169.4 (4-CO); *m*/*z* (CI) 416 (M^++H, 100%), 402 (10), 386 (9), 249 (5), 207 (55), 193 (6), 179 (17), 153 (6).

4.25. (3*R*,8a*S*)-3-Isopropyl-8a-methyltetrahydropyrrolo-[1,2-α]pyrazine-1,4,7-trione 23a

A solution of (3*R*,8a*S*)-3-isopropyl-1-methoxy-8a-methyl-8,8a-dihydro-3*H*-pyrrolo[1,2-*a*]pyrazine-4,7-dione **20a** (0.100 g, 0.42 mmol) and trifluoroacetic acid (0.2 M, 21 mL, 4.2 mmol) in acetonitrile (21 mL) was stirred at ambient temperature for 2 h. The solvent was distilled off at reduced pressure, water (8 mL) and dichloromethane (15 mL) added, the aqueous layer made alkaline (pH 10) by addition of concd ammonia, the mixture extracted with dichloromethane (2×15 mL), the combined organic layers dried over $MgSO_4$, concentrated and the product isolated by flash chromatography using as the eluent methanol in dichloromethane (1:20); R_f 0.52; yield 0.074 g (78%) of a solid material; mp 181–183 °C; $[\alpha]_D = -211.3$ (*c* 0.85, CH_2Cl_2). Found: C, 59.2; H, 6.9. $C_{11}H_{16}N_2O_3$ requires C, 58.9; H, 7.2. HRMS: M+H 225.1236. $C_{11}H_{16}N_2O_3$+H require 225.1239. ν_{max} (film/cm^{-1}) 3219, 2966, 2930, 1766, 1663, 1439, 1193; δ_H ($CDCl_3$) 1.02 and 1.08 (6H, 2d, *J* 6.7, CH(CH_3)$_2$), 1.62 (1H, s, CH_3), 2.22–2.28 (1H, m, C*H*(CH_3)$_2$), 2.65 and 2.88 (2H, 2d, *J* 17.8, CH_2CO), 3.65 and 4.43 (2H, 2d, *J* 19.7, NCH_2CO), 3.82–3.86 (1H, dd, *J* 5.7, 3.3, CH), 7.07 (1H, br s, NH); δ_C ($CDCl_3$) 18.1 and 19.2 (CH(*C*H_3)$_2$), 26.8 (CH_3), 33.0 (*C*H(CH_3)$_2$), 49.5 (*C*H_2CO), 51.3 (N*C*H_2CO), 62.4 (CH), 62.7 (C-8a), 164.2 and 167.0 (4-CO and 1-CO), 206.0 (7-CO); *m*/*z* (CI) 225 (M^++H, 100%), 183 (6), 182 (81), 181 (9), 167 (12), 153 (8), 98 (24).

4.26. (3*R*,8a*S*)-8a-Allyl-3-isopropyltetrahydropyrrolo-[1,2-α]pyrazine-1,4,7-trione 23b

A solution of (3*R*,8a*S*)-8a-allyl-3-isopropyl-1-methoxy-8,8a-dihydro-3*H*-pyrrolo[1,2-*a*]pyrazine-4,7-dione **20b** (0.080 g, 0.30 mmol) and trifluoroacetic acid (0.2 M, 15 mL, 3.0 mmol) in acetonitrile (15 mL) was stirred at ambient temperature for 2 h. The solvent was distilled off at reduced pressure, water (5 mL) and dichloromethane (10 mL) added, the aqueous layer made alkaline (pH 10) by addition of concd ammonia, the mixture extracted with dichloromethane (2×10 mL), the combined organic layers dried over $MgSO_4$, concentrated and the product isolated after flash chromatography using methanol in dichloromethane (1:20); R_f 0.37; yield 0.062 g (83%) of a solid material; mp 162–163 °C; $[\alpha]_D = -104.3$ (*c* 0.72, $CHCl_3$). Found: C, 62.2; H, 7.0. $C_{13}H_{18}N_2O_3$ requires C, 62.4; H, 7.25. HRMS: M+H 251.1386. $C_{13}H_{18}N_2O_3$+H require 251.1395. ν_{max} (film/cm^{-1}) 3234, 3079, 2965, 2926, 2875, 1766, 1675, 1434, 1183; δ_H ($CDCl_3$) 1.05 and 1.10 (6H, 2d, *J* 6.7, CH(CH_3)$_2$), 2.15–2.28 (1H, m, C*H*(CH_3)$_2$), 2.60–2.68 (2H, m, CH_2CH=CH_2), 2.73 and 2.87 (2H, 2d, *J* 18.3, CH_2CO), 3.65 and 4.36 (2H, 2d, *J* 19.8, NCH_2CO), 3.70–3.79 (1H, dd, *J* 7, 3.3, CH), 5.19–5.25 (2H, m, CH=CH_2), 5.69–5.78 (1H, m, CH=CH_2), 6.94 (1H, br s, NH); δ_C ($CDCl_3$) 18.9 and 19.5 (CH(*C*H_3)$_2$), 33.3 (*C*H(CH_3)$_2$), 45.1 (*C*H_2CH=CH_2), 46.9 (*C*H_2CO), 53.1 (N*C*H_2CO), 62.6 (CH), 65.9 (C-8a), 122.5 (CH=*C*H_2), 129.8 (*C*H=CH_2), 164.9 and 169.3 (4-CO and 1-CO), 206.0 (7-CO); *m*/*z* (CI) 251 (M^++H, 100%), 238 (5), 224 (6), 210 (12), 209 (75), 181 (43), 153 (27).

4.27. (2*S*,2′*R*)-1-(2-*tert*-Butoxycarbonylamino-3-methylbutyryl)-2-methyl-4-oxopyrrolidine-2-carboxylic acid methyl ester 25a

Hydrochloric acid (3 M, 8 mL) was added to a solution of (3*R*,8a*S*)-3-isopropyl-1-methoxy-8a-methyl-8,8a-dihydro-3*H*-pyrrolo[1,2-*a*]pyrazine-4,7-dione **20a** (0.13 g, 0.54 mmol) in THF (5 mL). The solution was subsequently evaporated to dryness at reduced pressure. The resulting solid residue was dipeptide **24a**. The latter was isolated as a Boc-derivative. For this purpose dichloromethane (4 mL), di-*tert*-butyldicarbonate (0.152 g, 0.7 mmol), and a solution of triethylamine (0.14 mL, 1 mmol) in dichloromethane (3 mL) were added at 0 °C. The mixture was stirred at this temperature for 3 h and allowed to reach room temperature. Water (4 mL) was added, the two layers separated. The water phase was extracted with dichloromethane (4×4 mL). The organic phase and the extracts were combined, dried over $MgSO_4$, and the solvent was removed in vacuo. The *N*-Boc-dipeptide **25a** was isolated after flash chromatography on silica gel using Et_2O–hexane 1:1. R_f 0.31; yield 0.111 g (58%); $[\alpha]_D = -9.3$ (*c* 1.0, CH_2Cl_2). HRMS: M+H 357.2015. $C_{17}H_{28}N_2O_6$+H require 357.2025. ν_{max} (film/cm^{-1}) 3339, 2968, 2928, 1767, 1751, 1705, 1655, 1507, 1419, 1367, 1170; δ_H ($CDCl_3$) 0.92 and 0.94 (6H, 2d, *J* 6.4, CH(CH_3)$_2$), 1.41 (9H, s, C(CH_3)$_3$), 1.64 (3H, s, CH_3), 1.88–1.95 (1H, m, C*H*(CH_3)$_2$), 2.53 and 2.88 (2H, 2d, *J* 18.6, CH_2CO), 3.70 (3H, s, CO_2CH_3), 4.04 and 4.52 (2H, 2d, *J* 17.9, NCH_2CO), 3.97–4.02 (1H, dd, *J* 5.7, 8.8, CH), 5.03 (1H, d, *J* 8.8, NH); δ_C ($CDCl_3$) 17.8 and 19.2 (CH(*C*H_3)$_2$), 22.2 (CH_3), 28.3 (C(*C*H_3)$_3$), 31.2 (*C*H(CH_3)$_2$), 49.1 (*C*H_2CO), 52.7 (CO_2CH_3), 53.9 (N*C*H_2CO), 57.5 (CH), 63.6 (C-2), 79.8 (*C*(CH_3)$_3$), 155.9 (*C*O_2C(CH_3)$_3$), 171.9 and 172.6 (*C*O_{ester} and *C*O_{amide}), 206.0 (4-CO); *m*/*z* (CI) 357 (M^++H, 29%), 301 (44), 283 (12), 269 (20), 257 (79), 172 (39), 158 (17), 156 (11), 116 (72), 98 (23), 72 (100), 57 (55).

4.28. (2*S*,2′*R*)-2-Allyl-1-(2-*tert*-butoxycarbonylamino-3-methylbutyryl)-4-oxopyrrolidine-2-carboxylic acid methyl ester 25b

Hydrochloric acid (3 M, 8 mL) was added to a solution of (3*R*,8a*S*)-8a-allyl-3-isopropyl-1-methoxy-8,8a-dihydro-3*H*-pyrrolo[1,2-*a*]pyrazine-4,7-dione **20b** (0.150 g,

0.56 mmol) in THF (5 mL). The solution was subsequently evaporated to dryness at reduced pressure. The resulting solid residue was dipeptide **24b**. The latter was isolated as a Boc-derivative. For this purpose dichloromethane (4 mL), di-*tert*-butyldicarbonate (0.152 g, 0.7 mmol), and a solution of triethylamine (0.14 mL, 1 mmol) in dichloromethane (3 mL) were added at 0 °C. The mixture was stirred at this temperature for 3 h and allowed to reach room temperature. Water (4 mL) was added resulting in two layers separating. The water phase was extracted with dichloromethane (4×4 mL). The organic phase and the extracts were combined, dried over $MgSO_4$, and the solvent was removed in vacuo. The *N*-Boc-dipeptide **25b** was isolated after flash chromatography on silica gel using Et_2O–hexane 1:1. R_f 0.25; yield 0.109 g (51%); $[\alpha]_D = +21.5$ (*c* 1.0, $CHCl_3$). HRMS (electrospray): [M+Na] 405.2005. $C_{19}H_{30}N_2O_6$+Na require 405.1996. ν_{max} (film/cm^{-1}) 3341, 2964, 2926, 1768, 1748, 1707, 1656, 1511, 1417, 1367, 1260, 1170; δ_H ($CDCl_3$) 0.90 and 0.95 (6H, 2d, *J* 6.6, $CH(CH_3)_2$), 1.40 (9H, s, $C(CH_3)_3$), 1.88–1.94 (1H, m, $CH(CH_3)_2$), 2.64–2.78 (3H, m, CH_2CO and $CHHCH{=}CH_2$), 3.12–3.16 (1H, m, $CHHCH{=}CH_2$), 3.69 (3H, s, CO_2CH_3), 3.83 and 4.46 (2H, 2d, *J* 17.8, NCH_2CO), 4.02–4.07 (1H, dd, *J* 5.7, 9.0, CH), 5.10 (1H, d, *J* 9.0, NH), 5.13–5.18 (2H, m, $CH{=}CH_2$), 5.52–5.70 (1H, m, $CH{=}CH_2$); δ_C ($CDCl_3$) 17.3 and 19.7 ($CH(CH_3)_2$), 28.3 ($C(CH_3)_3$), 30.7 ($CH(CH_3)_2$), 38.3 ($CH_2CH{=}CH_2$), 45.9 (CH_2CO), 52.7 (CO_2CH_3), 54.7 (NCH_2CO), 57.5 (CH), 66.2 (C-2), 79.8 ($C(CH_3)_3$), 121.7 ($CH_2CH{=}CH_2$), 131.1 ($CH_2CH{=}CH_2$), 155.9 ($CO_2C(CH_3)_3$), 171.8 and 172.3 (CO_{amide} and CO_{ester}), 205.9 (4-CO); *m*/*z* (CI) 383 (M^++H, 3%), 327 (12), 309 (7), 295 (14), 283 (32), 184 (18), 172 (30), 142 (7), 124 (14), 116 (75), 98 (3), 72 (100), 57 (66).

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