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Rh(II)-catalysed carbenoid cyclisations in a stereoselective approach to α-quaternary pipecolic acid derivatives

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Abstract—Preparation of α-quaternary pipecolic acid derivatives has been carried out by intramolecular rhodium(II)-carbenoid cyclisation reactions with diazoketones in the geminally disubstituted chiron (*R*)-2-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine. Both enantiomeric pairs of the pipecolic acid derivatives have been prepared from the same chiron. Exclusive chemoselectivity was seen in the rhodium(II)-carbenoid reactions, which occurred at the adjacent annular nitrogen. Controlled acid hydrolysis provided either the corresponding diketopiperazine or the corresponding valyl-pipecolic acid dipeptide. Single crystal X-ray structure analysis has been used to establish regiochemistry and relative stereochemistry.

1. Introduction

Cyclic α-amino acids with the α-carbon imbedded in the ring have restricted conformational freedom compared to the corresponding acyclic amino acids and can thus be regarded as belonging to a subclass of α-quaternary amino acids. We have previously reported several methods for the preparation of cyclic quaternary amino acids.[1–3] Herein we report on target molecules, which are derivatives of pipecolic acid. The α-alkylated pipecolic acid derivatives are an α-quaternary α-amino acid with the α-amino group imbedded within a six-membered ring.

Recently various cyclisation methods have been reported for the synthesis of pipecolic acid derivatives.[4] Such reactions include the preparation of α-alkylpipecolic acid derivatives,[5] alkylations of the Seebach chiron *tert*-butyl (*S*)-2-*tert*-butyl-3-methyl-4-oxo-imidazolidinecarboxylate[6] and synthesis of (*R*)-3-methyltetrahydroisoquinolinone-3-carboxylic acid via the Schöllkopf cyclo(L-Val-Ala-) chiron.[7] Further syntheses of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid include the use of 3,6-dihydro-2*H*-1,4-oxazin-2-one as a chiron.[8] Diastereoselective alkylation of Schiff bases of amino acids have been used in preparing methyl esters of (*S*)-α-alkylpipecolic acid.[9] Highly functionalised derivatives of α-alkylpipecolic acid are available from reactions between sugar aldehyde and amino acids.[10] L-α-Methyl-α-allylglycine has previously been used as a substrate in ruthenium-catalysed ring-closing olefin metathesis for the preparation of α-methylpipecolic acid derivatives.[11] Herein we report on the rhodium(II)-catalysed cyclisation of geminally disubstituted derivatives of the Schöllkopf chiron. The targets are enantiomerically pure (*S*)- and (*R*)-δ-oxo derivatives of α-alkylpipecolic acid dipeptides.

2. Results and discussion

Pipecolic acid intermediates were formed in cyclisation reactions as shown in Scheme 2. The substrates were diazoketones and the cyclisations were effected with dirhodium tetraacetate as catalyst. The synthesis of the appropriate diazoketones is shown in Scheme 1. For the geminal alkylation of chiral substrate **1**, the latter was lithiated at −78 °C and treated with 4-bromo-1-butene to furnish the 2-*gem*-dialkyl derivatives **2** in about 80% yield and diastereomeric excess (de) >95%. Once lithiated, the original stereochemistry at the 2-carbanionic site is lost. The metallation is fully regioselective because the branching at the α-carbon of the isopropyl group leads to full shielding of its site of attachment in the ring. The new alkylating agent then approaches the carbanionic site in a *trans* manner with respect to the isopropyl group.

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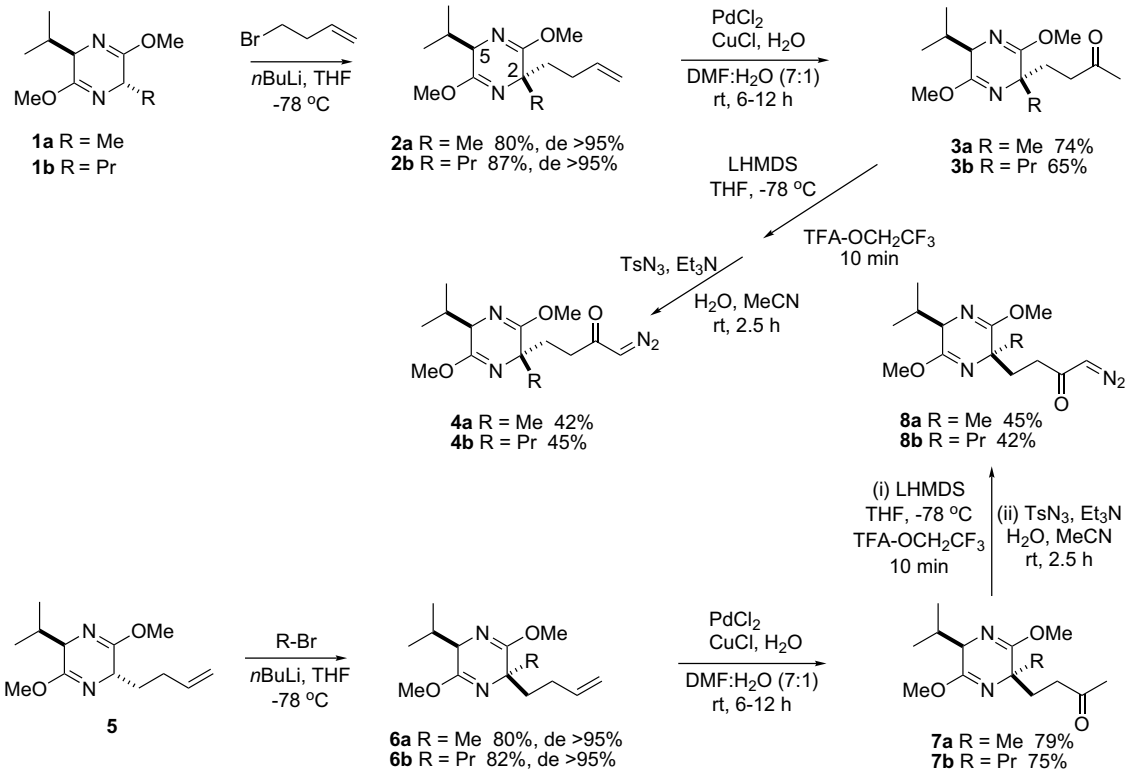


Scheme 1.

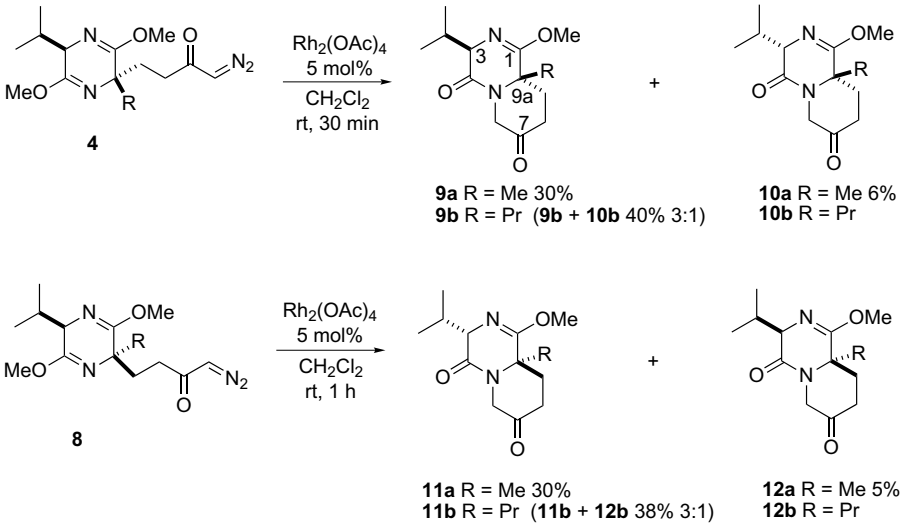
Chemoselective oxidation of the alkene double bond was effected under Wacker conditions with the formation of ketones **3** in high yields. Under the conditions of the Wacker oxidation, there was no significant interference from the functionalities in the heterocycle. The keto methyl group was activated as an α-trifluoroacetyl derivative before introduction of the diazo function. Thus the methyl ketone moiety was lithiated and reacted with 2,2,2-trifluoroethyl trifluoroacetate (TFEA) at −78 °C for 10 min by analogy to a methodology described by Danheiser et al. and Doyle et al.[12,13] The product was the corresponding α-trifluoroacetyl ketone, which was reacted further in situ with tosyl azide in acetonitrile containing water and triethylamine at room temperature. The products were diazoketones **4** in moderate overall chemical yields, in the range 42–45%.

The stereochemistry at the α-position of the new amino acid can be inverted by changing the order of the alkylations of the Schöllkopf chiron. This is demonstrated with the butenyl derivative **5**, which was converted by alkylations into the *gem*-dialkylated product **6**. Scheme 1 shows that **2a** and **6a** are diastereomers, which differ in the configuration at C-2 and therefore, after hydrolysis, would yield enantiomeric α-quaternary-α-amino acids. With butenyl substrates **6**, Wacker oxidation and diazo transfer proceeded as above to provide diazoketones **8** in the same manner. The diazomethyl ketones **4** and **8** are pairwise diastereomers, which differ only in the configuration at C-2.

The carbenoid cyclisations in Scheme 2 were effected using 5 mol% dirhodium tetraacetate in dichloromethane under an argon atmosphere at ambient temperature for 30 min. No racemisation took place at the quaternary 2-carbon in substrate **4** during the carbenoid reactions. Two products were formed in the reaction and were identified as diastereomer **9** as the major product and diastereomer **10** as the minor product. Since the configuration at C-2 is fixed, isomerisation must arise by proton abstraction and re-addition at C-5. Besides the annulation reactions, it can be seen that the 6-methoxy group on substrates **4** and **8** is replaced by an oxo group at the 4-position in products **9**–**12**. The structure of **9a** was verified indirectly by single crystal X-ray analysis of the diketopiperazine product **18a** (Scheme 4) after a further hydrolytic reaction. The structures of the other products were assigned after NMR correlations. The two-dimensional $^{1}H,^{15}N$-correlated spectrum of **9a** and **10a** recorded by the gs-HMBC method, showed a correlation peak for $CH(CH_3)_2$ and N-2. In the case of N-5 there were correlation peaks with CH_3, NCH_2CO and CH_2CH_2CO.

Intramolecular rhodium carbenoid C–H insertion reactions favour five-membered ring formation in the absence of an activating heteroatom moiety.[14,15] In substrates **4** and **8**, the smallest ring formation possible is a six-membered ring either by C–H insertion at the α-carbon on the R-substituent, or by adduct formation with the annular adjacent nitrogen. Only the latter pathway was observed. An attempt has been made to rationalise the course of the transformations in Scheme 3.

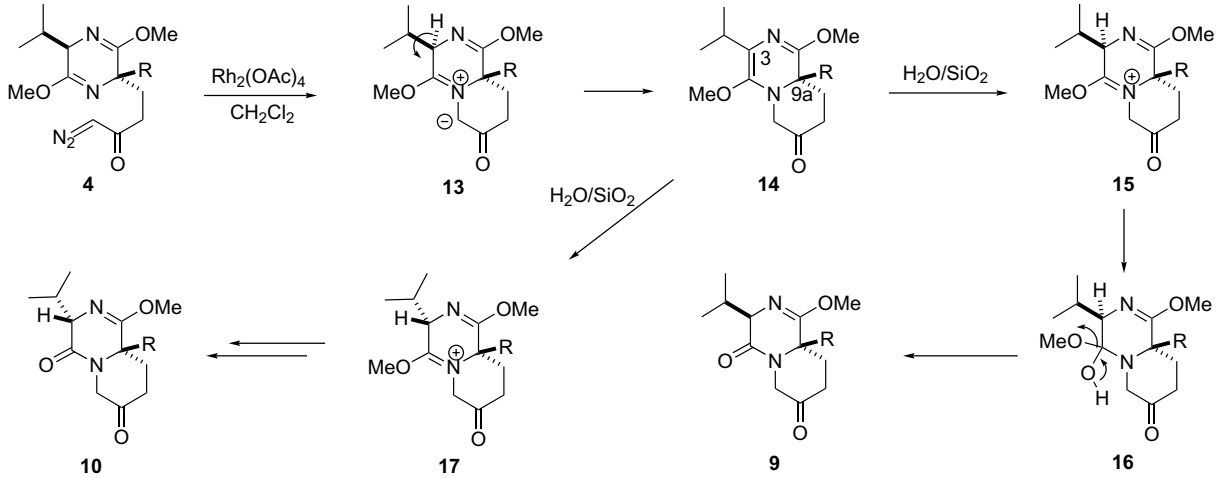
The initial product was assigned as ylide structure **13**. Monitoring the course of the reaction by NMR showed



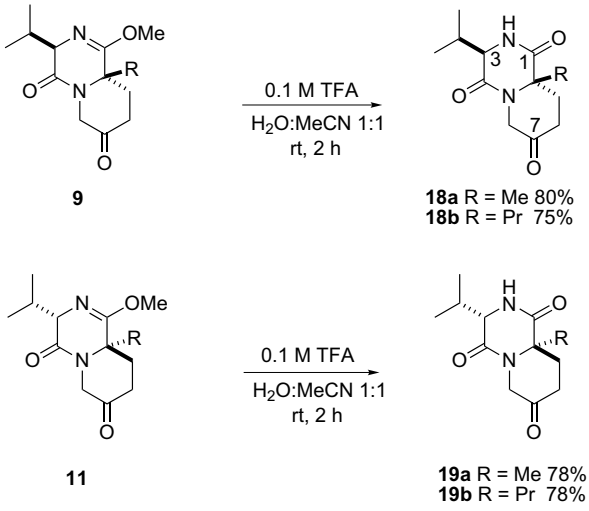
Scheme 2.

changes in the spectra in accordance with formation of structure **14**. The stereochemistry at C-3 was lost by the introduction of a double bond at this position of the new product. The NMR studies indicated a clean insertion with complete transformation into the annulated product **14**. The work-up of the reaction mixture involved chromatography on silica gel. Under these conditions, the nucleophilic 3,4-double bond presumably becomes protonated and forms adduct **16** with water present in the silica gel. Subsequent elimination of methanol from adduct **16** provided products **9** and **10** as isolated from the reaction. This mechanistic path rationalises formation of a diastereomeric mixture. Protonation of the initial reaction product **14** is reversible. Water addition can occur from either side of the dihydropiperazine ring. Addition at the imino carbon in the protonated species **15** *trans* to the R-group furnishes the major product **9**. The protonated species **17** yields the minor isomer **10**. Steric interactions favour the formation of structure **9**, which has the same stereochemistry at C-3 as in the corresponding position in substrate **4**. The preference is affected by the R-substituent in that the methyl diastereomers **9a** and **10a** were obtained in the ratio 5:1, and the propyl homologues **9b** and **10b** in the ratio 3:1. The mechanism for this transformation was not further studied. In a related five-membered ring formation, only one stereomer was obtained.[16]

Support for the above interpretation became available by working with substrate **8**. Substrates **4** and **8** have an opposite configuration at C-2. When substrate **8** was subjected to the rhodium-carbenoid reaction, the configuration of the isopropyl group C-3 on the major product **11** was changed from its configuration in the substrate **8**. In both the major products **9** and **11**, the isopropyl group was *cis* with respect to the R-group. The isomeric ratios **9a**/**10a** and **11a**/**12a** are almost the same. Structures **9** and **11** are enantiomeric. The same is true for the minor isomers **10** and **12**. The specific rotations in chloroform were positive in the **9**- and **10**-series and negative in the **11**- and **12**-series; however the numerical values were pairwise the same.



Scheme 3.



Scheme 4.

Treatment of the major isomers **9** and **11** with 0.1 M TFA provided the diketopiperazines **18** and **19** in high yields (Scheme 4). Compound **18a** was a crystalline solid, which was subjected to single crystal X-ray analysis. The ORTEP plot of the X-ray structure of compound **18a** is shown in Figure 1. The X-ray structure confirmed the regiochemistry and the relative stereochemistry in the transformations described (vide supra).

The iminoether moiety at C-1 in substrates **9** and **11** is sensitive to acid cleavage whereas the lactam function at C-4 is highly acid stable and would require a high concentration of acid for cleavage to occur. With 3 M hydrochloric acid at room temperature for a few minutes, chemoselective opening of the iminoether function in substrates **9** and **11** yielded dipeptides **20** and **22** as hydrochloride salts. The products were purified and isolated as the Boc-derivatives **21** and **23** after treatment of the hydrochlorides with triethylamine and di-*tert*-butyl dicarbonate (Scheme 5).

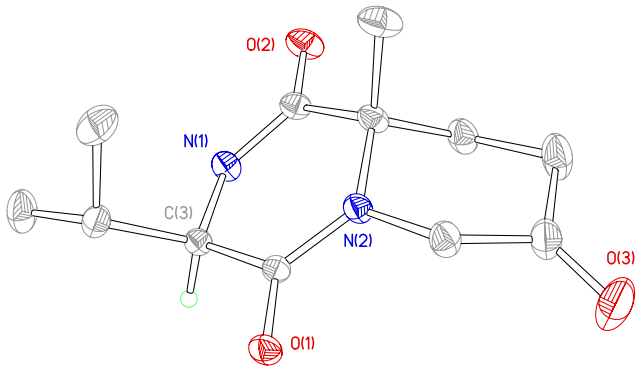
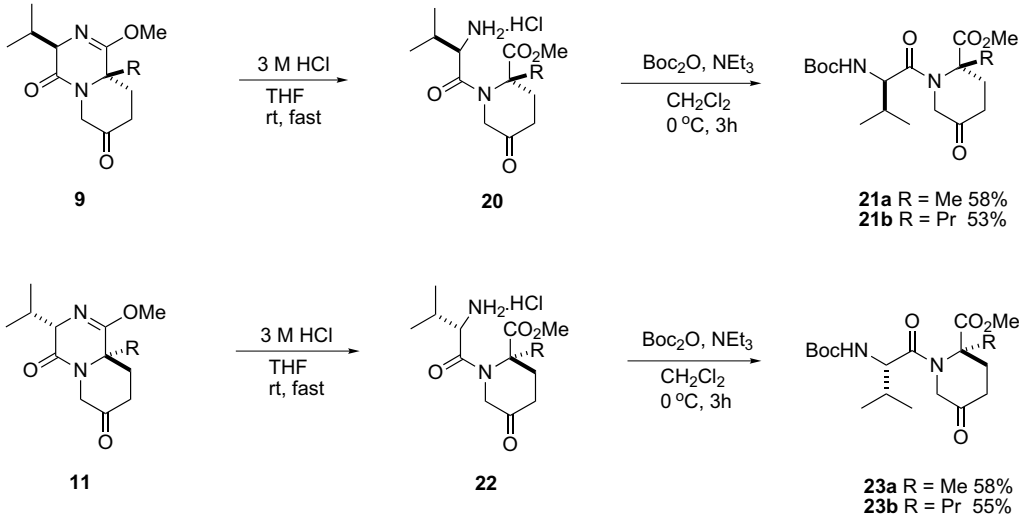


Figure 1. ORTEP plot of compound **18a**. Ellipsoids are shown at 50% probability. For clarity, only the hydrogen atom at the stereogenic centre at C-3 is shown.

Substrates **9** and **11** are enantiomers, hence the protected dipeptides **21** and **23** are also enantiomers. Additional confirmation is available from the specific rotations of the respective pairs **21**/**23**. The experimental numerical values were the same but of opposite sign.

3. Conclusion

In conclusion we have shown that intramolecular rhodium(II)-catalysed cyclisations with diazoketones in geminally disubstituted chiron (*R*)-2-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine may be used for the preparation of cyclic α-quaternary α-amino acids as derivatives of pipecolic acid. Chemo- or regioselective addition of the rhodium(II)-carbenoid function occurred at the adjacent annular nitrogen. Hydrolytic reactions can be controlled for the preparation of the corresponding diketopiperazine derivatives or the valyl dipeptides of the quaternary pipecolic acid derivatives.



Scheme 5.

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. ^{13}C NMR 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 ppm with residual $CHCl_3$ (7.24 ppm) and $CDCl_3$ (77 ppm) as references. *J* values are given in Hz. 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 on a Perkin–Elmer 1310 infrared spectrophotometer or a Nicolet Magna 550 spectrometer using ATR (attenuated total reflectance). Optical 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 18a

X-ray data were collected on a Siemens SMART CCD diffractometer[17] 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.[17] Absorption corrections were applied by the use of the SADABS program.[18] The structure was determined and refined using the SHELXTL program package.[19] The non-hydrogen atoms were refined with anisotropic thermal parameters; hydrogen atoms were located from difference Fourier maps and refined with isotropic thermal parameters.

4.2. Crystal data for $C_{12}H_{18}N_2O_3$ 18a

$M = 238.28$, orthorhombic, $P2_12_12_1$, $a = 8.196(1)$, $b = 10.028(1)$, $c = 14.946(1)$ Å, $V = 1228.43(5)$ Å^3, $Z = 4$, $D_x = 1.288$ Mg m^{-3}, $\mu = 0.093$ mm^{-1}, $T = 105(2)$ K, measured 30,020 reflections in θ range 2.5–40.3°, $R_{int} = 0.029$, 226 parameters refined against 7580 F^2, $R = 0.038$ for $I_o > 2\sigma(I_o)$ and 0.043 for all data. Crystallographic data (excluding structure factors) for the structure herein have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 229929.

4.3. (2*R*,5*S*)-2,5-Dihydro-2-isopropyl-3,6-dimethoxy-5-propylpyrazine 1b

n-BuLi (11.2 mL, 17.9 mmol, 1.6 M in hexane) was added to a solution of (*R*)-2-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine (3.00 g, 16.3 mmol) in THF (40 mL) under argon at −78 °C. The mixture was stirred at this temperature for 15 min and a solution of 1-bromopropane (2.205 g, 1.63 mL, 17.9 mmol) in THF (20 mL) then added dropwise. The solution was allowed to reach room temperature overnight. The reaction was quenched by the addition of 0.1 M phosphate buffer (pH 7, 30 mL), the aqueous phase extracted with diethyl ether (3×20 mL), the combined organic extracts dried over $MgSO_4$, evaporated and the crude product purified by flash chromatography on silica gel using 5% diethyl ether in hexane; yield 2.850 g (77%, de 80%) of a colourless oil. The product was used as such for the subsequent alkylation reaction, whereas for analytical purposes the major diastereomer was isolated by repetition of the chromatographic operation. R_f 0.38; HRMS (EI): M 226.1682. $C_{12}H_{22}N_2O_2$ requires: 226.1681; δ_H ($CDCl_3$): 0.65 and 1.03 (6H, 2d, *J* 6.8, CH(CH_3)$_2$), 0.85–0.90 (3H, t, *J* 6.7, CH_3), 1.19–1.29 (2H, m, $CH_2CH_2CH_3$), 1.61–1.76 (2H, m, $CH_2CH_2CH_3$), 2.20–2.25 (1H, m, CH(CH$_3$)$_2$), 3.65 (3H, s, OCH_3), 3.66 (3H, s, OCH_3), 3.89–3.92 (1H, m, H-2), 3.99–4.04 (1H, m, H-5); δ_C ($CDCl_3$): 14.0 (CH_3), 16.5 and 19.1 (CH(CH_3)$_2$), 17.8 ($CH_2CH_2CH_3$), 31.6 (CH(CH$_3$)$_2$), 36.4 ($CH_2CH_2CH_3$), 52.25 (2×OCH_3), 55.4 (C-5), 60.65 (C-2), 163.4 and 164.0 (2×C=N); MS (EI): 226 (M^+, 27%), 211 (20), 183 (100), 154 (5), 141 (61), 55 (11).

4.4. (2*S*,5*R*)-2-(But-3-enyl)-5-isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydropyrazine 2a

n-BuLi (8.89 mL, 14.22 mmol, 1.6 M in hexane) was added to a solution of (2*R*,5*RS*)-2,5-dihydro-2-isopropyl-3,6-dimethoxy-5-methylpyrazine[20] (2.600 g, 12.93 mmol) in dry THF (40 mL) under argon at −78 °C. The mixture was stirred at this temperature for 30 min, 4-bromo-1-butene (1.44 mL, 1.919 g, 14.22 mmol) in THF (15 mL) then added dropwise and the solution left to reach room temperature overnight. The reaction was quenched by the addition of 0.1 M phosphate buffer (pH 7, 30 mL), the phases separated, the aqueous phase extracted with diethyl ether (3×20 mL), the combined organic extracts dried over $MgSO_4$, evaporated and the crude product purified by flash chromatography on silica gel using 5% diethyl ether in hexane. R_f 0.22; yield 2.6 g (80%, de >95%) of a colourless oil; HRMS (CI): [M^+H] 253.1903. $C_{14}H_{24}N_2O_2$+H requires: 253.1910. (Found: C, 66.59; H, 9.35. $C_{14}H_{24}N_2O_2$ requires: C, 66.63; H, 9.59); ν_{max} (film/cm^{-1}) 2972, 2945, 2871, 1694, 1642, 1462, 1436, 1257, 1240, 1199, 1006; δ_H ($CDCl_3$): 0.64 and 1.03 (6H, 2d, *J* 6.8, CH(CH_3)$_2$), 1.29 (3H, s, CH_3), 1.56–1.88 (4H, m, CH_2CH_2), 2.18–2.25 (1H, m, CH(CH$_3$)$_2$), 3.61 (3H, s, OCH_3), 3.62 (3H, s, OCH_3), 3.88 (1H, d, *J* 3.2, H-5), 4.82–4.93 (2H, m, CH=CH_2), 5.64–5.76 (1H, m, CH=CH$_2$); δ_C ($CDCl_3$): 16.8 and 19.3 (CH(CH_3)$_2$), 28.6 (CH_3), 29.0 (CH_2CH_2), 30.9 (CH(CH$_3$)$_2$), 40.5 (CH_2CH_2), 52.0 and 52.1 (2×OCH_3), 58.1 (C-2), 61.2 (C-5), 114.0 (CH=CH_2), 138.5 (CH=CH$_2$), 161.9 and 165.2 (2×C=N); MS (CI): 253 (100, M^++H), 237 (56), 221 (23), 210 (31), 209 (29), 197 (19), 195 (21), 180 (26), 155 (22).

4.5. (2*S*,5*R*)-2-(But-3-enyl)-5-isopropyl-3,6-dimethoxy-2-propyl-2,5-dihydropyrazine 2b

Compound **2b** was prepared as above from (2*R*,5*S*)-2,5-dihydro-2-isopropyl-3,6-dimethoxy-5-propylpyrazine **1b** (2.850 g, 12.61 mmol), *n*-BuLi (1.6 M in hexane,

8.66 mL, 13.87 mmol) and 4-bromo-1-butene (1.4 mL, 1.87 g, 13.87 mmol). The crude product was purified by flash chromatography on silica gel using 10% EtOAc in hexane. R_f 0.48; yield 3.050 g (87%, de >95%) of a colourless oil; HRMS (CI): M^++H 281.2239. $C_{16}H_{28}N_2O_2$+H requires: 281.2229. (Found: C, 68.26; H, 10.31. $C_{16}H_{28}N_2O_2$ requires: C, 68.53; H, 10.06); ν_{max} (film/cm^{-1}) 2959, 2944, 2872, 1690, 1641, 1463, 1436, 1302, 1236, 1197; δ_H ($CDCl_3$): 0.64 and 1.04 (6H, 2d, *J* 6.8, CH(CH_3)$_2$), 0.79–1.24 (5H, m, $CH_2CH_2CH_3$), 1.40–1.83 (6H, m, 3×CH_2), 2.29–2.33 (1H, m, CH(CH_3)$_2$), 3.62 (3H, s, OCH_3), 3.64 (3H, s, OCH_3), 3.85 (1H, d, *J* 3.3, H-5), 4.83–4.94 (2H, m, CH=CH_2), 5.66–5.75 (1H, m, CH=CH_2); δ_C ($CDCl_3$): 14.4 ($CH_2CH_2CH_3$), 17.0 and 19.6 (CH(CH_3)$_2$), 18.0 ($CH_2CH_2CH_3$), 28.5 (CH_2CH_2CH=CH_2), 30.6 (CH(CH_3)$_2$), 40.3 (CH_2CH_2CH=CH_2), 42.7 ($CH_2CH_2CH_3$), 52.0 and 52.1 (2×OCH_3), 60.8 (C-5), 61.9 (C-2), 114.0 (CH=CH_2), 138.5 (CH=CH_2), 162.4 and 164.2 (C=N); MS (CI): 281 (M^++H, 58%), 279 (8), 265 (8), 249 (29), 237 (27), 225 (72), 195 (100), 183 (62).

4.6. (2′*S*,5′*R*)-4-(5-Isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydropyrazin-2-yl)butan-2-one 3a

Palladium dichloride (0.196 g, 1.11 mmol) and copper chloride (1.100 g, 11.11 mmol) were stirred together in water (2.00 mL) and DMF (14.00 mL) at room temperature for 1 h before (2*S*,5*R*)-2-(but-3-enyl)-5-isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydropyrazine **2a** (2.800 g, 11.11 mmol) was added. The black solution was stirred under oxygen at room temperature for 6 h, extracted with diethyl ether, the ether solutions dried over $MgSO_4$ and the solvent distilled off. The crude product was purified by flash chromatography on silica gel using hexane/EtOAc 5:1. R_f 0.23; yield 2.185 g (74%) of a colourless oil; HRMS (EI): M 268.1780. $C_{14}H_{24}N_2O_3$ requires: 268.1786. (Found: C, 62.49; H, 9.32. Calcd for $C_{14}H_{24}N_2O_3$: C, 62.66; H, 9.01); ν_{max} (film/cm^{-1}) 2969, 2945, 2872, 1719, 1691, 1461, 1437, 1242, 1200, 1134, 1001; δ_H ($CDCl_3$): 0.63 and 1.02 (6H, 2d, *J* 6.8, CH(CH_3)$_2$), 1.29 (3H, s, CH_3), 1.77–1.85 (1H, m, CHHCH$_2$CO), 1.99–2.05 (1H, m, CHHCH$_2$CO), 2.07 (3H, s, $COCH_3$), 2.08–2.22 (3H, m, CH(CH_3)$_2$ and CH_2CO), 3.58 (3H, s, OCH_3), 3.61 (3H, s, OCH_3), 3.91 (1H, d, *J* 3.4, H-5′); δ_C ($CDCl_3$): 16.8 and 19.3 (CH(CH_3)$_2$), 28.3 (CH_3), 29.8 ($COCH_3$), 31.0 (CH(CH_3)$_2$), 35.3 and 39.2 (2×CH_2), 52.1 and 52.3 (2×OCH_3), 57.6 (C-2′), 61.1 (C-5′), 162.2 and 164.9 (2×C=N), 208.5 (C=O); MS (EI): 268 (M^+, 13%), 253 (16), 226 (9), 225 (22), 211 (14), 197 (82), 155 (100), 151 (26), 140 (7), 124 (8), 113 (11), 97 (18).

4.7. (2′*S*,5′*R*)-4-(5-Isopropyl-3,6-dimethoxy-2-propyl-2,5-dihydropyrazin-2-yl)butan-2-one 3b

Compound **3b** was prepared as above from palladium dichloride (0.189 g, 1.071 mmol), copper chloride (1.060 g, 10.71 mmol) and (2*S*,5*R*)-2-(but-3-enyl)-5-isopropyl-3,6-dimethoxy-2-propyl-2,5-dihydropyrazine **2b** (3.000 g, 10.71 mmol) in water (2.00 mL) and DMF (14.00 mL). The resulting black solution was stirred under oxygen at room temperature for 12 h and then worked up as above. The crude product was purified by flash chromatography on silica gel using hexane/EtOAc 9:1. R_f 0.23; yield 2.060 g (65%) of a colourless oil; HRMS (EI): M 296.2086. $C_{16}H_{28}N_2O_3$ requires: 296.2099. (Found: C, 64.59; H, 9.71. $C_{16}H_{28}N_2O_3$ requires: C, 64.83; H, 9.52); ν_{max} (film/cm^{-1}) 2958, 2945, 2872, 1718, 1691, 1648, 1462, 1437, 1301, 1237, 1197, 1008; δ_H ($CDCl_3$): 0.63 and 1.05 (6H, 2d, *J* 6.8, CH(CH_3)$_2$), 0.78–1.23 (5H, m, $CH_2CH_2CH_3$), 1.42–1.50 (1H, m, CHHCH$_2$CH$_3$), 1.69–1.78 (1H, m, CHHCH$_2$CH$_3$), 1.85–2.13 (4H, m, CH_2CH_2CO), 2.05 (3H, s, $COCH_3$), 2.18–2.32 (1H, m, CH(CH_3)$_2$), 3.61 (6H, s, 2×OCH_3), 3.86 (1H, d, *J* 3.4, H-5′); δ_C ($CDCl_3$): 14.3 ($CH_2CH_2CH_3$), 17.0 and 19.5 (CH(CH_3)$_2$), 17.9 ($CH_2CH_2CH_3$), 29.8 ($CH_2CH_2CH_3$), 30.7 (CH(CH_3)$_2$), 34.9 ($COCH_3$), 38.9 and 42.4 (CH_2CH_2CO), 52.1 and 52.2 (2×OCH_3), 60.7 (C-5′), 61.3 (C-2′), 162.6 and 163.9 (2×C=N), 208.4 (C=O); MS (EI): 296 (M^+, 15%), 281 (25), 267 (7), 254 (22), 253 (83), 239 (16), 226 (18), 225 (64), 224 (22), 212 (10), 211 (75), 183 (100), 179 (18), 167 (12), 153 (15).

4.8. (2′*S*,5′*R*)-1-Diazo-4-(5-isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydropyrazin-2-yl)butan-2-one 4a

n-BuLi (3.84 mL, 6.15 mmol, 1.6 M in hexane) was added to a solution of HMDS (1.28 mL, 6.15 mmol) in THF (15 mL) under argon at 0 °C, the solution stirred at 0 °C for 10 min, cooled to −78 °C and a solution of (2*S*,5*R*)-4-(5-isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydropyrazin-2-yl)butan-2-one **3a** (1.500 g, 5.59 mmol) in THF (20 mL) added dropwise over 15 min. The mixture was stirred at −78 °C for 30 min before TFEA (0.831 mL, 6.15 mmol) was rapidly injected by means of a syringe. The reaction mixture was stirred for 10 min at this temperature, transferred to a separating funnel containing 5% aqueous HCl (30 mL) and diethyl ether (25 mL). The funnel was shaken, the layers separated, the aqueous layer extracted with diethyl ether (2×20 mL), the combined organic solutions washed with saturated aqueous NaCl (30 mL) and the solution evaporated. The residual oil was dissolved in MeCN (20 mL), and transferred to a three-necked flask. Subsequently, water (0.1 mL, 5.59 mmol) and triethylamine (1.16 mL, 8.38 mmol) were added followed by dropwise addition over 10 min of a solution of tosyl azide (1.6 g, 8.38 mmol) in MeCN (10 mL). The resulting 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 then with 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 20% EtOAc in hexane. R_f 0.12. The product was a yellow oily material, yield 0.690 g (42%); HRMS (CI): [M^++H], 295.1762. $C_{14}H_{22}N_4O_3$+H require: 295.1770. ν_{max} (film/cm^{-1}) 3089, 2970, 2945, 2872, 2103, 1690, 1651, 1437, 1367, 1242,

1203, 1143, 1003; δ_H ($CDCl_3$): 0.64 and 1.04 (6H, 2d, *J* 6.8, $CH(CH_3)_2$), 1.30 (3H, s, CH_3), 1.80–1.86 (1H, m, $CHHCH_2$), 2.00–2.10 (3H, m, $CHHCH_2$), 2.15–2.23 (1H, m, $CH(CH_3)_2$), 3.60 and 3.62 (6H, 2s, $2\times OCH_3$), 3.90 (1H, d, *J* 3.4, H-5′), 5.13 (1H, br s, $CH{=}N_2$); δ_C ($CDCl_3$): 16.9 and 19.3 ($CH(CH_3)_2$), 28.3 (CH_3), 31.1 ($CH(CH_3)_2$), 36.4 and 36.8 ($2\times CH_2$), 52.2 and 52.3 ($2\times OCH_3$), 53.3 ($CH{=}N_2$), 58.0 (C-2′), 61.2 (C-5′), 162.3 and 164.8 ($2\times C{=}N$), 194.6 (CO); *m*/*z* (CI) 295 (M^++H, 100%), 269 (42), 267 (84), 251 (37), 235 (59), 223 (61), 209 (17), 197 (59), 195 (27), 181 (22), 155 (63), 154 (33).

4.9. (2′*S*,5′*R*)-1-Diazo-4-(5-isopropyl-3,6-dimethoxy-2-propyl-2,5-dihydropyrazin-2-yl)butan-2-one 4b

n-BuLi (4.29 mL, 6.87 mmol, 1.6 M in hexane) was added to a solution of HMDS (1.43 mL, 6.87 mmol) in THF (20 mL) under argon at 0 °C. The mixture was stirred at this temperature for 10 min, cooled to −78 °C and a solution of (2′*S*,5′*R*)-4-(5-isopropyl-3,6-dimethoxy-2-propyl-2,5-dihydropyrazin-2-yl)butan-2-one **3b** (1.850 g, 6.25 mmol) in THF (20 mL) added dropwise over 15 min. The mixture was stirred at −78 °C for 30 min before TFEA (0.93 mL, 6.87 mmol) was rapidly injected by means of a syringe. The reaction mixture was stirred for 10 min, transferred to a separating funnel containing 5% aqueous HCl (40 mL) and diethyl ether (25 mL). The funnel was shaken, the layers separated, the aqueous layer extracted with diethyl ether (2×20 mL), the combined organic solutions washed with saturated aqueous NaCl (30 mL) and the solution evaporated. The residual oil was dissolved in MeCN (20 mL), and transferred to a three-necked flask. Subsequently, water (0.123 mL, 6.87 mmol) and triethylamine (1.30 mL, 9.37 mmol) were added followed by the dropwise addition over 10 min of a solution of tosyl azide (1.837 g, 9.37 mmol) in MeCN (10 mL). The resulting 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 then with aqueous saturated NaCl (25 mL). The solution was dried over $MgSO_4$, evaporated and residual material subjected to flash chromatography on silica gel using 20% EtOAc in hexane. R_f 0.22. The product was a yellow oily material; yield 0.905 g (45%); HRMS (CI) [M^++H] 323.2079; $C_{16}H_{26}N_4O_3$+H require: 323.2083. ν_{max} (film/cm^{-1}) 2970, 2945, 2872, 2104, 1690, 1650, 1437, 1367, 1242, 1203, 1143; δ_H ($CDCl_3$): 0.62 and 1.03 (6H, 2d, *J* 6.8, $CH(CH_3)_2$), 0.79–1.19 (5H, m, $CH_2CH_2CH_3$), 1.49–1.59 (1H, m, $CHHCH_2CH_3$), 1.65–1.76 (1H, m, $CHHCH_2CH_3$), 1.80–2.15 (4H, m, CH_2CH_2), 2.19–2.32 (1H, m, $CH(CH_3)_2$), 3.62 (6H, s, $2\times OCH_3$), 3.85 (1H, d, *J* 3.4, H-5′), 5.12 (1H, br s, $CH{=}N_2$); δ_C ($CDCl_3$) 14.2 ($CH_2CH_2CH_3$), 17.0 and 19.5 ($2\times CH(CH_3)_2$), 17.9 ($CH_2CH_2CH_3$), 30.7 ($CH(CH_3)_2$), 35.9 ($CH_2CH_2CH_3$), 36.5 and 42.3 (CH_2CH_2CO), 52.1 and 52.2 ($2\times OCH_3$), 54.3 ($CH{=}N_2$), 60.7 (C-5′), 61.4 (C–2′), 162.6 and 163.8 ($2\times C{=}N$), 194.5 (CO).

4.10. (2*R*,5*R*)-2-(But-3-enyl)-5-isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydropyrazine 6a

n-BuLi (9.24 mL, 14.78 mmol, 1.6 M in hexane) was added to a solution of (2*S*,5*R*)-2-(but-3-enyl)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine[21] **5** (3.2 g, 13.44 mmol) in dry THF (40 mL) under argon at −60 °C. The mixture was stirred for 30 min at this temperature, cooled to −78 °C and iodomethane (0.92 mL, 14.78 mmol) in THF (15 mL) added dropwise. The solution was left to reach ambient temperature overnight. The reaction was quenched by the addition of 0.1 M phosphate buffer (pH 7, 30 mL), the two phases separated, the aqueous phase extracted with diethyl ether (3×20 mL), the combined organic extracts dried over $MgSO_4$, evaporated and the crude product purified by flash chromatography using 5% diethyl ether in hexane. R_f 0.21; yield 2.7 g (80%, de >95%) of a colourless oil; HRMS (EI): M 252.1837. $C_{14}H_{24}N_2O_2$ requires: 252.1837. (Found: C, 66.50; H, 9.38. $C_{14}H_{24}N_2O_2$ requires: C, 66.63; H, 9.59); ν_{max} (film/cm^{-1}) 2971, 2960, 2845, 2873, 1691, 1436, 1242, 1203, 1180, 1006; δ_H ($CDCl_3$): 0.64 and 1.06 (6H, 2d, *J* 6.8, $CH(CH_3)_2$), 1.25 (3H, s, CH_3), 1.59–1.90 (4H, m, CH_2CH_2), 2.28–2.34 (1H, m, $CH(CH_3)_2$), 3.63 (3H, s, OCH_3), 3.64 (3H, s, OCH_3), 3.87 (1H, d, *J* 3.2, H-5), 4.86–4.98 (2H, m, $CH{=}CH_2$), 5.71–5.82 (1H, m, $CH{=}CH_2$); δ_C ($CDCl_3$): 16.9 and 19.5 ($CH(CH_3)_2$), 28.6 (CH_3), 29.3 (CH_2CH_2), 30.5 ($CH(CH_3)_2$), 39.8 (CH_2CH_2), 52.2 ($2\times OCH_3$), 58.0 (C-2), 60.3 (C-5), 114.0 ($CH{=}CH_2$), 138.9 ($CH{=}CH_2$), 161.9 and 165.5 ($2\times C{=}N$); MS (EI): 252 (M^+, 5%), 237 (100), 221 (13), 209 (28), 195 (24), 180 (44), 155 (93), 140 (12).

4.11. (2*R*,5*R*)-2-(But-3-enyl)-5-isopropyl-3,6-dimethoxy-2-propyl-2,5-dihydropyrazine 6b

Compound **6b** was prepared as above from (2*S*,5*R*)-2-(but-3-enyl)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine[19] **5** (794 mg, 3.34 mmol), *n*-BuLi (2.29 mL, 3.67 mmol, 1.6 M in hexane) and 1-bromopropane (0.34 mL, 3.68 mmol) in dry THF (25 mL). The crude product was purified by flash chromatography using 5% diethyl ether in hexane as eluent. R_f 0.42; yield 766 mg (82%, de >95%) of a colourless oil. HRMS (EI): M 280.2157. $C_{16}H_{28}N_2O_2$ requires: 280.2150. (Found: C, 68.40; H, 9.80. $C_{16}H_{28}N_2O_2$ requires: C, 68.53; H, 10.06). ν_{max} (film/cm^{-1}) 2959, 2944, 2872, 1694, 1641, 1463, 1436, 1381, 1300, 1237; δ_H ($CDCl_3$): 0.63 and 1.04 (6H, 2d, *J* 6.8, $CH(CH_3)_2$), 0.79–1.01 (5H, m, $CH_2CH_2CH_3$), 1.40–1.53 (1H, m, $CHHCH_2CH_3$), 1.63–1.72 (3H, m, $CHHCH_2CH_3$ and $CH_2CH_2CH{=}CH_2$), 1.86–1.89 (2H, m, $CH_2CH_2CH{=}CH_2$), 2.30–2.35 (1H, m, $CH(CH_3)_2$), 3.63 (3H, s, OCH_3), 3.64 (3H, s, OCH_3), 3.86 (1H, d, *J* 3.1, H-5), 4.86–4.97 (2H, m, $CH{=}CH_2$), 5.70–5.81 (1H, m, $CH{=}CH_2$); δ_C ($CDCl_3$): 14.1 ($CH_2CH_2CH_3$), 16.9 and 19.5 ($CH(CH_3)_2$), 17.2 ($CH_2CH_2CH_3$), 29.1 ($CH_2CH_2CH{=}CH_2$), 30.5 ($CH(CH_3)_2$), 39.4 ($CH_2CH_2CH{=}CH_2$), 43.4 ($CH_2CH_2CH_3$), 52.1 and 52.2 ($2\times OCH_3$), 60.6 (C-5), 61.8 (C-2), 114.0 ($CH{=}CH_2$), 139.0 ($CH{=}CH_2$), 162.5 and 164.2 (C=N); MS (EI): 280

(M^+, 4%,), 279 (9), 265 (24), 237 (100), 225 (9), 195 (65), 183 (46), 153 (10).

4.12. (2′*R*,5′*R*)-4-(5-Isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydropyrazin-2-yl)butan-2-one 7a

Palladium dichloride (0.143 g, 0.813 mmol) and copper chloride (0.805 g, 8.13 mmol) in water (2.00 mL) and DMF (14.00 mL) were stirred together at room temperature for 1 h before (2*R*,5*R*)-2-(but-3-enyl)-5-isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydropyrazine **6a** (2.050 g, 8.13 mmol) was added and the black solution stirred under oxygen at room temperature for 6 h. The mixture was extracted with diethyl ether, the organic layer dried over $MgSO_4$ and evaporated at reduced pressure. The crude product was purified by flash chromatography using hexane/EtOAc 5:1. R_f 0.29; yield 1.750 g (80%) of a colourless oil; HRMS (EI): M 268.1789. $C_{14}H_{24}N_2O_3$ requires: 268.1786. (Found: C, 62.43; H, 9.38. $C_{14}H_{24}N_2O_3$ requires: C, 62.66; H, 9.01). ν_{max} (film/cm^{-1}) 2970, 2945, 2871, 1719, 1690, 1462, 1436, 1244, 1204, 1134, 1004; δ_H ($CDCl_3$): 0.64 and 1.05 (6H, 2d, *J* 6.8, $CH(CH_3)_2$), 1.22 (3H, s, CH_3), 1.80–1.86 (1H, m, $CHHCH_2CO$), 1.99–2.03 (1H, m, $CHHCH_2CO$), 2.07 (3H, s, $COCH_3$), 2.12–2.32 (3H, m, $CH(CH_3)_2$ and CH_2CO), 3.59 (3H, s, OCH_3), 3.61 (3H, s, OCH_3), 3.84 (1H, d, *J* 3.2, H-5′); δ_C ($CDCl_3$): 16.7 and 19.5 ($CH(CH_3)_2$), 28.0 (CH_3), 29.8 ($COCH_3$), 30.4 ($CH(CH_3)_2$), 39.4 (CH_2–CH_2–CO), 43.8 (CH_2CH_2CO), 52.2 and 52.2 ($2\times OCH_3$), 57.3 (C–2′), 60.3 (C-5′), 162.2 and 165.2 (2×C=N), 208.7 (C=O); MS (EI): 268 (M^+, 7%), 253 (70), 241 (14), 226 (35), 225 (66), 211 (68), 197 (73), 155 (100), 151 (42), 140 (16), 126 (22), 113 (18), 97 (29).

4.13. (2′*R*,5′*R*)-4-(5-Isopropyl-3,6-dimethoxy-2-propyl-2,5-dihydropyrazin-2-yl)butan-2-one 7b

Compound **7b** was prepared as above from palladium dichloride (0.092 g, 0.518 mmol), copper chloride (0.513 g, 5.18 mmol), (2*R*,5*R*)-2-(but-3-enyl)-5-isopropyl-3,6-dimethoxy-2-propyl-2,5-dihydropyrazine **6b** (1.450 g, 5.18 mmol) in a solution of water (2.00 mL) and DMF (14.00 mL). The mixture was stirred under oxygen at room temperature for 10 h and the reaction worked up as above. Purification was by flash chromatography using hexane/EtOAc 9:1. R_f 0.30; yield 1.15 g (75%) of a colourless oil. HRMS (EI): M 296.2095. $C_{16}H_{28}N_2O_3$ requires: 296.2099. (Found: C, 64.55; H, 9.36. $C_{16}H_{28}N_2O_3$ requires: C, 64.83; H, 9.52). ν_{max} (film/cm^{-1}) 2959, 2945, 2873, 1720, 1691, 1463, 1437, 1237, 1197, 1008; δ_H ($CDCl_3$): δ 0.65 and 1.05 (6H, 2d, *J* 6.8, $CH(CH_3)_2$), 0.80 (3H, t, *J* 7.0, CH_2CH_3), 0.96–1.06 (2H, m, $CH_2CH_2CH_3$), 1.39–1.47 (1H, m, $CHHCH_2CH_3$), 1.65–1.68 (1H, m, $CHHCH_2CH_3$), 1.85–1.91 (1H, m, $CHHCH_2CO$), 1.94–2.01 (1H, m, $CHHCH_2CO$), 2.08 (3H, s, $COCH_3$), 2.10–2.32 (3H, m, $CH(CH_3)_2$ and CH_2CO), 3.60 (6H, s, $2\times OCH_3$), 3.85 (1H, d, *J* 3.3, H-5′); δ_C ($CDCl_3$): 14.0 (CH_2CH_3), 16.8 and 19.5 ($CH(CH_3)_2$), 17.3 (CH_2CH_3), 29.8 (CH_2), 30.5 ($CH(CH_3)_2$), 34.1 (CH_3CO), 39.4 (CH_2), 42.9 (CH_2), 52.2 and 52.2 ($2\times OCH_3$), 60.7 (C-5′), 61.1 (C-2′), 162.7 and 163.9 (2×C=N), 208.9 (C=O); MS (EI): 296 (M^+, 8%), 253 (75), 225 (60), 211 (100), 153 (25), 43 (30).

4.14. (2′*R*,5′*R*)-1-Diazo-4-(5-isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydropyrazin-2-yl)butan-2-one 8a

n-BuLi (3.84 mL, 6.15 mmol, 1.6 M in hexane) was added to a solution of HMDS (1.28 mL, 6.15 mmol) in THF (15 mL) under argon at 0 °C. The solution was stirred for 10 min at 0 °C, cooled to −78 °C and a solution of (2′*R*,5′*R*)-4-(5-isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydropyrazin-2-yl)butan-2-one **7a** (1.500 g, 5.59 mmol) in THF (20 mL) added dropwise over 15 min. The mixture was stirred at −78 °C for 30 min before TFEA (0.831 mL, 6.15 mmol) was rapidly injected. The reaction mixture was stirred for 10 min, transferred to a separating funnel containing 5% aqueous HCl (30 mL) and diethyl ether (25 mL). The funnel was shaken, the layers separated, the aqueous layer extracted with diethyl ether (2×20 mL), the combined organic solutions washed with saturated aqueous NaCl (30 mL) and the solution evaporated. The residual oil was dissolved in MeCN (20 mL), and transferred to a three-necked flask. Subsequently, water (0.1 mL, 5.59 mmol) and triethylamine (1.16 mL, 8.38 mmol) were added followed by dropwise addition over 10 min of a solution of tosyl azide (1.6 g, 8.38 mmol) in MeCN (10 mL). The resulting 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 then with aqueous saturated NaCl (20 mL). The solution was dried over $MgSO_4$, evaporated and residual material subjected to flash chromatography on silica gel using 20% EtOAc in hexane. R_f 0.17. The product was a yellow oily material, yield 0.740 g (45%); HRMS (CI): [M^++H] 295.1763. $C_{14}H_{22}N_4O_3$+H requires: 295.1764; ν_{max} (film/cm^{-1}) 2970, 2945, 2873, 2103, 1690, 1647, 1436, 1364, 1340, 1244, 1203, 1140, 1003; δ_H ($CDCl_3$): 0.62 and 1.03 (6H, 2d, *J* 6.8, $CH(CH_3)_2$), 1.26 (3H, s, CH_3), 1.87–1.93 (1H, m, $CHHCH_2$), 2.00–2.13 (3H, m, $CHHCH_2$), 2.27–2.33 (1H, m, $CH(CH_3)_2$), 3.60 and 3.62 (6H, 2s, $2\times OCH_3$), 3.86 (1H, d, *J* 3.4, H-5′), 5.16 (1H, br s, $CH=N_2$); δ_C ($CDCl_3$): 16.7 and 19.4 ($CH(CH_3)_2$), 28.1 (CH_3), 30.3 ($CH(CH_3)_2$), 35.5 and 36.8 ($2\times CH_2$), 52.2 and 52.3 ($2\times OCH_3$), 53.3 ($CH=N_2$), 57.5 (C-2′), 60.3 (C-5′), 162.3 and 165.1 (2×C=N), 194.9 (CO); *m*/*z* (CI) 295 (M^++H, 39%), 267 (52), 251 (23), 223 (100), 209 (17), 197 (37), 195 (34), 181 (13), 155 (85), 154 (33).

4.15. (2′*R*,5′*R*)-1-Diazo-4-(5-isopropyl-3,6-dimethoxy-2-propyl-2,5-dihydropyrazin-2-yl)butan-2-one 8b

n-BuLi (4.87 mL, 7.8 mmol, 1.6 M in hexane) was added to a solution of HMDS (1.6 mL, 7.8 mmol) in THF (15 mL) under argon at 0 °C. The solution was stirred for 10 min, cooled to −78 °C and a solution of (2′*R*,5′*R*)-4-(5-isopropyl-3,6-dimethoxy-2-propyl-2,5-dihydropyrazin-2-yl)butan-2-one **7b** (2.1 g, 7.09 mmol) in THF (25 mL) was added dropwise over 15 min. The mixture

was stirred at −78 °C for 30 min before TFEA (1.054 mL, 7.8 mmol) was rapidly injected. The resulting mixture was stirred for 10 min, transferred to a separating funnel containing 5% aqueous HCl (30 mL) and diethyl ether (25 mL). The funnel was shaken, the layers separated, the aqueous layer extracted with diethyl ether (2×20 mL), the combined organic solutions washed with saturated aqueous NaCl (30 mL) and the solution evaporated. The residual oil was dissolved in MeCN (20 mL) and transferred to a three-necked flask. Subsequently, water (0.127 mL, 7.09 mmol) and triethylamine (1.47 mL, 10.63 mmol) were added followed by the dropwise addition over 10 min of a solution of tosyl azide (2.095 g, 10.63 mmol) in MeCN (10 mL). The resulting reaction mixture was stirred at ambient temperature for 2.5 h, the solvent distilled off, the residue dissolved in diethyl ether (20 mL) and the ether solution shaken with 5% aqueous NaOH (20 mL) and then with 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 20% EtOAc in hexane. R_f 0.22. The product was a yellow oily material; yield 0.950 g (42%); HRMS (CI): [M+H] 323.2074. $C_{16}H_{26}N_4O_3$+H require: 323.2083. ν_{max} (film/cm^{-1}) 2959, 2944, 2867, 2103, 1691, 1643, 1380, 1337, 1197, 1143; δ_H ($CDCl_3$): 0.62 and 1.03 (6H, 2d, *J* 6.8, CH(C*H*$_3$)$_2$), 0.77–1.06 (5H, m, CH$_2$C*H*$_2$C*H*$_3$), 1.4–1.55 (1H, m, C*H*HCH$_2$CH$_3$), 1.62–1.8 (1H, m, CH*H*CH$_2$CH$_3$), 1.87–1.93 (1H, m, C*H*H–CH$_2$CO), 2.00–2.18 (3H, m, CH*H*C*H*$_2$CO), 2.27–2.33 (1H, m, C*H*(CH$_3$)$_2$), 3.61 and 3.62 (6H, 2s, 2×OCH$_3$), 3.84 (1H, d, *J* 3.4, H-5′), 5.15 (1H, br s, CH=N$_2$); δ_C ($CDCl_3$): 14.0 (CH_3), 16.8 and 19.5 (CH(*C*H$_3$)$_2$), 17.2 (CH_2), 30.4 (*C*H(CH$_3$)$_2$), 35.2 and 36.6 (2×CH$_2$), 42.9 (CH_2), 52.2 and 52.3 (2×OCH$_3$), 54.1 (CH=N$_2$), 60.6 (C-5′), 61.3 (C-2′), 162.9 and 163.8 (2×C=N), 195.0 (CO); *m*/*z* (CI) 323 (M$^+$+H, 39%,), 295 (53), 279 (19), 263 (19), 253 (12), 251 (50), 237 (8),225 (21), 209 (100), 183 (53), 182 (31), 167 (10).

4.16. (3*R*,9a*S*)-3-Isopropyl-1-methoxy-9a-methyl-3,8,9,9a-tetrahydropyrido[1,2-*a*]pyrazine-4,7-dione 9a and (3*S*,9a*S*)-3-isopropyl-1-methoxy-9a-methyl-3,8,9,9a-tetrahydropyrido[1,2-*a*]pyrazine-4,7-dione 10a

A solution of (2′*S*,5′*R*)-1-diazo-4-(5-isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydropyrazin-2-yl)butan-2-one **4a** (0.294 g, 1.00 mmol) in dry dichloromethane (25 mL) was added dropwise to a solution of $Rh_2(OAc)_4$ (0.022 g, 0.05 mmol) in dry dichloromethane (20 mL) under argon at room temperature. The mixture was stirred at room 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/CH_2Cl_2 1:6. The first compound eluted was **10a**. R_f 0.28; yield 0.015 g (6%); $[\alpha]_D = -169.8$ (*c* 1.00, $CHCl_3$); HRMS (CI): [M$^+$+H] 253.1540; $C_{13}H_{20}N_2O_3$+H require 253.1552; ν_{max} (film/cm^{-1}) 3292, 2962, 2932, 2873, 1726, 1708, 1654, 1461, 1437, 1261; δ_H ($CDCl_3$): 0.68 and 1.10 (6H, 2d, *J* 6.8, CH(C*H*$_3$)$_2$), 1.51 (3H, s, CH_3), 2.13–2.19 (1H, m, C*H*HCH$_2$CO), 2.36–2.42 (1H, m, CH*H*CH$_2$CO), 2.44–2.50 (2H, m, CH$_2$C*H*$_2$CO), 2.50–2.59 (1H, m, C*H*(CH$_3$)$_2$), 3.53 (1H, d, *J* 19.2, NC*H*HCO), 3.73 (3H, s, OCH$_3$), 3.94 (1H, d, *J* 3.6, H-3), 4.95 (1H, d, *J* 19.2, NCH*H*CO); δ_C ($CDCl_3$): 16.4 and 19.7 (CH(*C*H$_3$)$_2$), 22.5 (CH_3), 31.3 (*C*H(CH$_3$)$_2$), 32.3 and 34.9 (2×CH$_2$), 48.3 (N*C*H$_2$CO), 53.2 (OCH$_3$), 56.7 (C-9a), 62.7 (C-3), 160.5 (C-1) and 168.8 (CON), 204.7 (CO); *m*/*z* (CI) 253 (M$^+$+H, 100%), 237 (5), 210 (45), 197 (14), 195 (12), 181 (6), 170 (20), 126 (6), 112 (7).

The second eluated compound was **9a**. R_f 0.21; yield 0.076 g (30%) of a white solid; mp 92–94 °C; $[\alpha]_D = -69.7$ (*c* 1.00, $CHCl_3$); HRMS (EI): M 252.1470; $C_{13}H_{20}N_2O_3$ requires 252.1473; ν_{max} (film/cm^{-1}) 3305, 2960, 2928, 2873, 1727, 1708, 1651, 1463, 1418, 1263, 1239; δ_H ($CDCl_3$): 0.73 and 1.09 (6H, 2d, *J* 6.8, CH(C*H*$_3$)$_2$), 1.58 (3H, s, CH_3), 2.21–2.33 (2H, m, C*H*$_2$CH$_2$CO), 2.39–2.45 (1H, m, C*H*(CH$_3$)$_2$), 2.50–2.55 (2H, m, CH$_2$C*H*$_2$CO), 3.50 (1H, d, *J* 19.2, NC*H*HCO), 3.72 (3H, s, OCH$_3$), 4.05 (1H, d, *J* 3.6, H-3), 5.07 (1H, d, *J* 19.2, NCH*H*CO); δ_C ($CDCl_3$): 17.2 and 19.7 (CH(*C*H$_3$)$_2$), 22.9 (CH_3), 32.3 (*C*H(CH$_3$)$_2$), 33.2 and 34.9 (2×CH$_2$), 48.2 (N*C*H$_2$CO), 53.10 (OCH$_3$), 56.5 (C-9a), 63.7 (C-3), 160.0 (C-1) and 168.2 (CON), 204.2 (CO); *m*/*z* (EI) 252 (M$^+$, 20%), 237 (25), 210 (100), 197 (8), 195 (43), 181 (12), 126 (3), 112 (7).

4.17. (3*R*,9a*S*)-3-Isopropyl-1-methoxy-9a-propyl-3,8,9,9a-tetrahydropyrido[1,2-*a*]pyrazine-4,7-dione 9b and (3*S*,9a*S*)-3-isopropyl-1-methoxy-9a-propyl-3,8,9,9a-tetrahydropyrido[1,2-*a*]pyrazine-4,7-dione 10b

Compounds **9b** and **10b** were prepared as above from (2′*S*,5′*R*)-1-diazo-4-(5-isopropyl-3,6-dimethoxy-2-propyl-2,5-dihydropyrazin-2-yl)butan-2-one **4b** (0.400 g, 1.24 mmol) and $Rh_2(OAc)_4$ (0.028 g, 0.06 mmol). The crude product was subjected to flash chromatography on silica gel using EtOAc/CH_2Cl_2 1:6. The product consisted of two diastereomers **9b** and **10b** in the ratio 3:1; yield 0.139 g (40%). For analytical purposes the diastereomers were separated by repetition of the chromatography as above. The major diastereomer vas **9b**: R_f 0.26; $[\alpha]_D = -111.8$ (*c* 1.00, $CHCl_3$); HRMS (CI): [M$^+$+H], 281.1862. $C_{15}H_{24}N_2O_3$+H require: 281.1865. (Found: C, 64.52; H, 8.46. $C_{15}H_{24}N_2O_3$ requires: C, 64.26; H, 8.63). ν_{max} (film/cm^{-1}); 3292, 2968, 2875, 1726, 1708, 1654, 1460, 1437, 1420, 1260; δ_H ($CDCl_3$): 0.70 and 1.05 (6H, 2d, *J* 6.8, CH(C*H*$_3$)$_2$), 0.82–0.90 (3H, m, CH$_2$CH$_2$C*H*$_3$), 1.03–1.14 (2H, m, CH$_2$C*H*$_2$CH$_3$), 1.70–2.24 (4H, m, C*H*$_2$CH$_2$CO and C*H*$_2$CH$_2$CH$_3$), 2.39–2.54 (3H, m, C*H*(CH$_3$)$_2$ and CH$_2$C*H*$_2$CO), 3.35 (1H, d, *J* 19.2, NC*H*HCO), 3.66 (3H, s, OCH$_3$), 3.92 (1H, d, *J* 3.6, H-3), 5.15 (1H, d, *J* 19.2, NCH*H*CO); δ_C ($CDCl_3$): 13.9 (CH$_2$CH$_2$*C*H$_3$), 17.3 and 19.9 (CH(*C*H$_3$)$_2$), 17.9 (CH_2), 31.4 (*C*H(CH$_3$)$_2$), 33.7, 34.8 and 35.5 (3×CH$_2$), 48.4 (N*C*H$_2$CO), 52.9 (OCH$_3$), 60.4 (C-9a), 62.90 (C-3), 158.8 (C-1) and 168.5 (CON), 204.7 (CO); *m*/*z* (CI) 281 (M$^+$+H, 100%), 265 (6), 253 (8), 238 (45), 180 (4), 181 (12), 126 (24), 112 (9).

The first compound eluted was the minor diastereomer **10b**. R_f 0.32; $[\alpha]_D = -185.7$ (*c* 1.00, $CHCl_3$); HRMS (CI)

[M^++H] 281.1857; $C_{15}H_{24}N_2O_3$+H require 281.1865; δ_H ($CDCl_3$): 0.65 and 1.09 (6H, 2d, *J* 6.8, CH(CH_3)$_2$), 0.82–0.90 (3H, m, $CH_2CH_2CH_3$), 1.03–1.15 (2H, m, $CH_2CH_2CH_3$), 1.75–1.81 (2H, m, $CH_2CH_2CH_3$), 2.12–2.40 (2H, m, CH_2CH_2CO), 2.41–2.60 (3H, m, CH(CH$_3$)$_2$ and CH_2CH_2CO), 3.37 (1H, d, *J* 19.2, NCHHCO), 3.70 (3H, s, OCH_3), 3.97 (1H, d, *J* 3.6, H-3), 4.96 (1H, d, *J* 19.2, NCHHCO); δ_C ($CDCl_3$): 13.6 ($CH_2CH_2CH_3$), 16.4 and 19.6 (CH(CH_3)$_2$), 17.2 (CH_2), 31.7 (CH(CH$_3$)$_2$), 32.7, 34.8 and 36.6 (3×CH_2), 48.4 (NCH_2CO), 53.0 (OCH_3), 60.4 (C-9a), 62.90 (C-3), 159.0 (C-1) and 169.1 (CON), 204.7 (CO). *m*/*z* (CI) 281 (M^++H, 100%), 265 (4), 238 (23), 209 (22), 195 (9), 167 (5).

4.18. (3*S*,9a*R*)-3-Isopropyl-1-methoxy-9a-methyl-3,8,9,9a-tetrahydropyrido[1,2-*a*]pyrazine-4,7-dione 11a and (3*R*,9a*R*)-3-isopropyl-1-methoxy-9a-methyl-3,8,9,9a-tetrahydropyrido[1,2-*a*]pyrazine-4,7-dione 12a

Compounds **11a** and **12a** were prepared as above from (2′*R*,5′*R*)-1-diazo-4-(5-isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydropyrazin-2-yl)butan-2-one **8a** (0.294 g, 1.00 mmol) and $Rh_2(OAc)_4$ (0.022 g, 0.05 mmol). The crude product was subjected to flash chromatography on silica gel using EtOAc/CH_2Cl_2 1:6. The first eluted compound was **12a**. R_f 0.28; yield 0.013 g (5%); $[\alpha]_D = +170.5$ (*c* 1.00, $CHCl_3$); MS, IR and NMR spectra were the same as the spectra of **10a**.

The second eluated compound was **11a**. R_f 0.21; yield 0.076 g (30%) of a white solid; mp 92–94 °C; $[\alpha]_D = +72.5$ (*c* 1.0, $CHCl_3$); MS, IR and NMR spectra were the same as the spectra of **9a**.

4.19. (3*S*,9a*R*)-3-Isopropyl-1-methoxy-9a-propyl-3,8,9,9a-tetrahydropyrido[1,2-*a*]pyrazine-4,7-dione 11b and (3*R*,9a*R*)-3-isopropyl-1-methoxy-9a-propyl-3,8,9,9a-tetrahydropyrido[1,2-*a*]pyrazine-4,7-dione 12b

Compounds **11b** and **12b** were prepared as above from (2′*R*,5′*R*)-1-diazo-4-(5-isopropyl-3,6-dimethoxy-2-propyl-2,5-dihydropyrazin-2-yl)butan-2-one **8b** (0.400 g, 1.24 mmol) and $Rh_2(OAc)_4$ (0.028 g, 0.06 mmol). The crude product was subjected to flash chromatography on silica gel using EtOAc/CH_2Cl_2 1:6. The product consisted of two diastereomers **11b** and **12b** in the ratio 3:1; yield 0.139 g (40%). For analytical proposes the diastereomers were separated by repetition of the chromatography as above. **11b**: R_f 0.26; $[\alpha]_D = +112.5$ (*c* 0.90, $CHCl_3$); **12b**: R_f 0.30; $[\alpha]_D = +184.2$ (*c* 1.00, $CHCl_3$). The MS, IR and NMR spectra were pairwise the same as the spectra of **9b** and **10b**, respectively.

4.20. (3*R*,9a*S*)-3-Isopropyl-9a-methyl-3,8,9,9a-tetrahydropyrido[1,2-σ]pyrazine-1,4,7-trione 18a

A solution of (3*R*,9a*S*)-3-isopropyl-1-methoxy-9a-methyl-3,8,9,9a-tetrahydropyrido[1,2-*a*]pyrazine-4,7-dione **9a** (0.100 g, 0.39 mmol) and trifluoroacetic acid (0.2 M, 19.5 mL, 3.9 mmol) in acetonitrile (19.5 mL) was stirred at ambient temperature for 2 h. The solvent was distilled off at reduced pressure, water (10 mL) and dichloromethane (15 mL) then added, the aqueous layer made alkaline (pH 10) by the 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 MeOH/CH_2Cl_2 1:20. R_f 0.30. The product was a white solid, mp 172–175 °C; yield 0.073 g (80%); $[\alpha]_D = -36.6$ (*c* 0.72, $CHCl_3$); HRMS (EI): M 238.1311; $C_{12}H_{18}N_2O_3$ requires 238.1317; ν_{max} (film/cm^{-1}) 3221, 2965, 2929, 1732, 1675, 1464, 1428, 1372, 1295, 1152; δ_H ($CDCl_3$): 0.91 and 1.03 (6H, 2d, *J* 6.8, CH(CH_3)$_2$), 1.63 (3H, s, CH_3), 2.19–2.24 (1H, m, CHHCH$_2$CO), 2.35–2.39 (1H, m, CH(CH$_3$)$_2$), 2.46–2.58 (3H, m, CH_2CH_2CO and CHHCH_2CO), 3.53 (1H, d, *J* 19.0, NCHHCO), 3.94 (1H, dd, *J* 4.0, 2.6, H-3), 5.01 (1H, d, *J* 19.0, NCHHCO), 6.99 (1H, br s, NH); δ_C ($CDCl_3$): 16.9 and 18.9 (CH(CH_3)$_2$), 23.7 (CH_3), 32.6 (CH(CH$_3$)$_2$), 33.2 and 35.1 (2×CH_2), 48.9 (NCH_2CO), 58.9 (C-9a), 60.9 (C-3), 164.7 and 170.5 (1-CO and 4-CO), 203.9 (7-CO); *m*/*z* (EI) 238 (M^+, 16%), 197 (10), 196 (100), 195 (17), 181 (23), 167 (18), 153 (6), 139 (12), 112 (52).

4.21. (3*R*,9a*S*)-3-Isopropyl-9a-propyl-3,8,9,9a-tetrahydropyrido[1,2-σ]pyrazine-1,4,7-trione 18b

Compound **18b** was prepared as above from (3*R*,9a*S*)-3-isopropyl-1-methoxy-9a-propyl-3,8,9,9a-tetrahydropyrido[1,2-*a*]pyrazine-4,7-dione **9b** (0.100 g, 0.35 mmol). The product was isolated after flash chromatography using MeOH/CH_2Cl_2 1:20. R_f 0.27; yield 0.070 g (75%); mp 191–194 °C; $[\alpha]_D = -34.8$ (*c* 1.00, $CHCl_3$); HRMS (EI): M 266.1622; $C_{14}H_{22}N_2O_3$ requires 266.1630; ν_{max} (film/cm^{-1}) 3219, 2965, 2930, 1770, 1663, 1464, 1439, 1193; δ_H ($CDCl_3$): 0.88–0.94 (6H, CH(CH_3)$_2$ and $CH_2CH_2CH_3$), 1.04 (3H, d, *J* 6.8, CH(CH_3)$_2$), 1.15–1.26 (2H, m, $CH_2CH_2CH_3$), 1.70–1.86 (1H, m, CHHCH_2CH_3), 2.05–2.14 (1H, m, CHHCH$_2$CH$_3$), 2.18–2.28 (1H, m, CHHCH$_2$CO), 2.32–2.39 (1H, m, CHHCH_2CO), 2.46–2.58 (3H, m, CH_2CH_2CO and CH(CH$_3$)$_2$), 3.42 (1H, d, *J* 19.0, NCHHCO), 3.98 (1H, dd, *J* 3.5, 1.6, H-3), 5.13 (1H, d, *J* 19.0, NCHHCO), 6.49 (1H, br s, NH); δ_C ($CDCl_3$): 13.9 ($CH_2CH_2CH_3$), 16.7 and 19.0 (CH(CH_3)$_2$), 17.9 (CH_2), 31.6 (CH(CH$_3$)$_2$), 33.3, 35.0 and 36.8 (3×CH_2), 49.2 (NCH_2CO), 60.3 (C-3), 62.7 (C-9a), 164.9 and 169.3 (1CO and 4-CO), 204.0 (7-CO); *m*/*z* (EI) 266 (M^+, 32%), 224 (30), 223 (95), 213 (14), 196 (12), 195 (100), 181 (16), 167 (20), 153 (12).

4.22. (3*S*,9a*R*)-3-Isopropyl-9a-methyl-3,8,9,9a-tetrahydropyrido[1,2-σ]pyrazine-1,4,7-trione 19a

Compound **19a** was prepared as above from (3*S*,9a*R*)-3-isopropyl-1-methoxy-9a-methyl-3,8,9,9a-tetrahydropyrido[1,2-*a*]pyrazine-4,7-dione **11a** (0.073 g, 0.39 mmol). The crude product was subjected to flash chromatography on silica gel using MeOH/CH_2Cl_2 1:20. R_f 0.37. The product was a white solid, mp 172–175 °C; yield 0.072 g (78%); $[\alpha]_D = +35.9$ (*c* 0.72, $CHCl_3$); MS, IR and NMR spectra were the same as the spectra of **18a**.

4.23. (2*S*,9a*R*)-3-Isopropyl-9a-propyl-3,8,9,9a-tetrahydropyrido[1,2-σ]pyrazine-1,4,7-trione 19b

Compound **19b** was prepared as above from (3*S*,9a*R*)-3-isopropyl-1-methoxy-9a-propyl-3,8,9,9a-tetrahydropyrido[1,2-*a*]pyrazine-4,7-dione **11b** (0.100 g, 0.35 mmol). The product was isolated by flash chromatography using MeOH/CH_2Cl_2 1:20. R_f 0.27; yield 0.073 g (78%); $[\alpha]_D = +35.3$ (*c* 1.00, $CHCl_3$); MS, IR and NMR spectra were the same as the spectra of **18b**.

4.24. (2*S*,2′*R*)-1-(2-*tert*-Butoxycarbonylamino-3-methyl-butyryl)-2-methyl-5-oxo-piperidine-2-carboxylic acid methyl ester 21a

Hydrochloric acid (3 M, 8 mL) was added to a solution of (3*R*,9a*S*)-3-isopropyl-1-methoxy-9a-methyl-3,8,9,9a-tetrahydropyrido[1,2-*a*]pyrazine-4,7-dione **9a** (0.126 g, 0.5 mmol) in THF (5 mL). The solution was subsequently evaporated to dryness at reduced pressure. The resulting solid residue was the dipeptide **20a**. The latter was isolated as a Boc-derivative. For this purpose dichloromethane (5 mL), di-*tert*-butyl dicarbonate (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 and the two layers separated. The water was extracted with dichloromethane (4×4 mL). The organic phase and the extracts were combined, dried over $MgSO_4$, and the solvent removed in vacuo. The *N*-Boc-dipeptide **21a** was isolated after flash chromatography on silica gel using EtOAc/hexane 2:3. R_f 0.23; yield 0.107 g (58%); mp 53–54 °C; $[\alpha]_D = -32.7$ (*c* 0.66, $CHCl_3$); HRMS (CI): [M+H] 371.2169; $C_{18}H_{30}N_2O_6$+H require 371.2182; ν_{max} (film/cm^{-1}) 3340, 2968, 2928, 1767, 1748, 1705, 1655, 1417, 1260, 1170; δ_H ($CDCl_3$): 0.81 and 0.92 (6H, 2d, *J* 6.8, $CH(CH_3)_2$), 1.39 (9H s, $C(CH_3)_3$), 1.55 (3H, s, CH_3), 1.80–1.72 (1H, m, $CH(CH_3)_2$), 1.92–2.02 (1H, m, $CHHCH_2CO$), 2.17–2.24 (1H, m, $CHHCH_2CO$), 2.37–2.44 (1H, m, CH_2CHHCO), 2.70–2.86 (1H, m, CH_2CHHCO), 3.69 (3H, s, CO_2CH_3), 3.90 (1H, d, *J* 17.8, $NCHHCO$), 4.29-4.38 (2H, $NHHCO$ and 2′-H), 5.16 (1H, d, *J* 8.9, NH); δ_C ($CDCl_3$): 16.8 and 19.5 ($CH(CH_3)_2$), 21.0 (CH_3), 28.25 ($C(CH_3)_3$), 31.0 ($CH(CH_3)_2$), 31.5 and 34.3 (CH_2CH_2CO), 52.2 (NCH_2CO), 52.4 (CO_2CH_3), 55.5 (2′-C), 59.9 (2-C), 79.6 ($C(CH_3)_3$), 155.8 (OCONH), 171.6 and 173.0 (CO_{ester} and CO_{amide}), 204.4 (5-CO); *m*/*z* (CI) 371 ($M+H^+$, 18), 315 (14), 283 (23), 271 (27), 172 (40), 170 (40), 116 (41), 112 (14), 72 (61), 57 (100).

4.25. (2*S*,2′*R*)-1-(2-*tert*-Butoxycarbonylamino-3-methyl-butyryl)-5-oxo-2-propyl-piperidine-2-carboxylic acid methyl ester 21b

Compound **21b** was prepared as above from (3*R*,9a*S*)-3-isopropyl-1-methoxy-9a-propyl-3,8,9,9a-tetrahydropyrido[1,2-*a*]pyrazine-4,7-dione **9b** (0.140 g, 0.5 mmol). The product was isolated after flash chromatography on silica gel using EtOAc/hexane 2:3. R_f 0.32; yield 0.105 g (53%); mp 64–65 °C; $[\alpha]_D = -39.9$ (*c* 1.00, $CHCl_3$); HRMS (electrospray): [M+Na] 421.2291; $C_{20}H_{34}N_2O_6$+Na require 421.2309; ν_{max} (film/cm^{-1}) 3341, 2968, 2928, 1765, 1746, 1705, 1655, 1421, 1260; δ_H ($CDCl_3$): 0.80 (3H, d, *J* 6.8, $CH(CH_3)_2$), 0.87–0.95 (6H, $CH(CH_3)_2$ and $CH_2CH_2CH_3$), 1.22–1.36 (2H, m, $CH_2CH_2CH_3$), 1.39 (9H, s, $C(CH_3)_3$), 1.80–1.89 (2H, m, $CH(CH_3)_2$ and $CHHCH_2CH_3$), 2.00–2.12 (1H, m, $CHHCH_2CO$), 2.15–2.21 (1H, m, $CHHCH_2CO$), 2.22–2.29 (1H, m, $CHHCH_2CH_3$), 2.32–2.40 (1H, m, CH_2CHHCO), 2.75–2.83 (1H, m, CH_2CHHCO), 3.67 (3H, s, CO_2CH_3), 3.80 (1H, d, *J* 17.8, $NCHHCO$), 4.37–4.43 (2H, $NCHHCO$ and H-2′), 5.16 (1H, d, *J* 8.9, NH); δ_C ($CDCl_3$): 14.2 ($CH_2CH_2CH_3$), 16.4 and 19.8 ($CH(CH_3)_2$), 16.8 ($CH_2CH_2CH_3$), 28.00 (CH_2), 28.2 ($C(CH_3)_3$), 30.6 ($CH(CH_3)_2$), 34.4 and 36.2 (2×CH_2), 52.3 (CO_2CH_3), 53.4 (NCH_2CO), 55.7 (2′-C), 62.4 (2-C), 79.6 ($C(CH_3)_3$), 155.8 (OCONH), 171.4 and 172.9 (CO_{ester} and CO_{amide}), 204.5 (5-CO); *m*/*z* (CI) 399 (M^++H, 17%), 357 (7), 343 (23), 325 (16), 311 (74), 299 (44), 200 (31), 198 (39), 172 (43), 140 (42), 116 (85), 72 (199), 57 (63).

4.26. (2*R*,2′*S*)-1-(2-*tert*-Butoxycarbonylamino-3-methyl-butyryl)-2-methyl-5-oxo-piperidine-2-carboxylic acid methyl ester 23a

Compound **23a** was prepared as above from (3*S*,9a*R*)-3-isopropyl-1-methoxy-9a-methyl-3,8,9,9a-tetrahydropyrido[1,2-*a*]pyrazine-4,7-dione **11a** (0.126 g, 0.5 mmol). The product was isolated after flash chromatography using EtOAc/hexane 2:3. R_f 0.23; yield 0.107 g (58%); $[\alpha]_D = +31.9$ (*c* 0.66, $CHCl_3$); MS, IR and NMR spectra were the same as the spectra for **21a**.

4.27. (2*R*,2′*S*)-1-(2-*tert*-Butoxycarbonylamino-3-methyl-butyryl)-5-oxo-2-propyl-piperidine-2-carboxylic acid methyl ester 23b

Compound **23b** was prepared as above from (3*S*,9a*R*)-3-isopropyl-1-methoxy-9a-propyl-3,8,9,9a-tetrahydropyrido[1,2-*a*]pyrazine-4,7-dione **11b** (0.140 g, 0.5 mmol). The product was isolated after flash chromatography using EtOAc/hexane 2:3. R_f 0.32; yield 0.110 g (53%); $[\alpha]_D = +39.2$ (*c* 1.00, $CHCl_3$); MS, IR and NMR spectra were the same as the spectra of **21b**.

References and notes

1. Andrei, M.; Undheim, K. *Tetrahedron: Asymmetry* **2004**, *15*, 53–63.
2. (a) Møller, B.; Undheim, K. *Eur. J. Org.* **2003**, 332–336; (b) Hammer, K.; Undheim, K. *Tetrahedron* **1997**, *53*, 10603–10614; (c) Hammer, K.; Undheim, K. *Tetrahedron: Asymmetry* **1998**, *9*, 2359–2368.
3. (a) Hoven, G. B.; Efskind, J.; Römming, C.; Undheim, K. *J. Org. Chem.* **2002**, *67*, 2459–2463; (b) Efskind, J.;

Römming, C.; Undheim, K. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2697–2703.
4. For a review, see: Park, K.-Ho.; Kurth, M. J. *Tetrahedron* **2002**, *58*, 8629–8659.
5. For a review, see: Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645–732.
6. Seebach, D.; Dziadulewicz, E.; Behrendt, L.; Cantoreggi, S.; Fitzi, R. *Liebigs Ann. Chem.* **1989**, 1215–1232.
7. Schöllkopf, U.; Hinrichs, R.; Lonsky, R. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 143–145.
8. Chinchilla, R.; Galindo, N.; Nájera, C. *Synthesis* **1999**, 704–717.
9. El Achquar, A.; Boumzebra, M.; Roumestant, M.-L.; Viallefont, P. *Tetrahedron* **1988**, *44*, 5319–5332.
10. Grandel, R.; Kazmaier, U.; Rominger, F. *J. Org. Chem.* **1998**, *63*, 4524–4528.
11. (a) Rutjes, P. J. T.; Schoemaker, H. E. *Tetrahedron Lett.* **1997**, *38*, 677–680; (b) Osipov, S. N.; Bruneau, C.; Picquet, M.; Kolomiets, A. F.; Dixneuf, P. H. *J. Chem. Soc., Chem. Commun.* **1998**, 2053–2054.
12. Danheiser, R. L.; Miller, R. F.; Brisbois, R. G. *Org. Synth.* **1996**, *73*, 134–143.
13. Doyle, M. P.; Mckervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds. From Cyclopropanes to Ylides*; Wiley-Interscience: New York, 1998; pp 15–17.
14. Taber, D. F.; Petty, E. H.; Ramon, K. *J. Am. Chem. Soc.* **1985**, *107*, 196–199; Taber, D. F.; Petty, E. H. *J. Org. Chem.* **1982**, *47*, 4808–4809.
15. Adams, J.; Spero, D. M. *Tetrahedron* **1991**, *47*, 1765–1808; Wang, P.; Adams, J. *J. Am. Chem. Soc.* **1994**, *116*, 3296–3305.
16. Andrei, M.; Efskin, J.; Viljugrein, T.; Römming, C.; Undheim, K. *Tetrahedron: Asymmetry* **2004**, *15*, in this issue. doi:10.1016/j.tetasy.2004.03.001.
17. SMART and SAINT Area Detector Control and Integration Software Version 5.054. Bruker Analytical X-ray Instruments Inc., Madison, Wisconsin, USA, 1998.
18. Sheldrick, G. M. SADABS Version 2.01. Program for Empirical Correction of Area Detector Data, University of Göttingen, Germany, 2000.
19. Sheldrick, G. M. SHELXTL, Structure Determination Programs Version 5.10. Bruker Analytical X-ray Instruments Inc., Madison, Wisconsin, USA, 1997.
20. Lange, M.; Undheim, K. *Tetrahedron* **1998**, *54*, 5337–5344.
21. Hammer, K.; Undheim, K. *Tetrahedron* **1997**, *53*, 5925–5936.