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Stereoselective synthesis of functionalised cycloalkene α-quaternary α-amino acid derivatives

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Abstract—A route for the preparation of unsaturated cyclic α-quaternary α-amino acid derivatives is described. Stepwise and stereocontrolled alkylations of the chiron (*R*)-2-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine provided *gem*-disubstituted derivatives with an alkene and an alkoxo substituent. The Wacker oxidation was compatible for chemoselective oxidation of the alkene function. Formation of a methyl ketone or an aldehyde was substrate dependent. Spiroannulation in the dioxo substrates was effected with caesium carbonate in acetonitrile by intramolecular aldol condensations. The regiochemistry was substrate dependent. Cleavage of the heterospiranes under mild acidic conditions provided cyclic α-quaternary α-amino acid derivatives.
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1. Introduction

Cyclic α-quaternary α-amino acids are conformationally constrained. When incorporated into peptidic material the conformational freedom of the peptidic material will be significantly affected. Hence the preparation and studies of the bioproperties of this class of compounds have attracted great attention.[1,2] Our efforts to develop methodologies for the construction of cyclic α-quaternary α-amino acids can be summarised as in Scheme 1.

Group **A** structures are available from ruthenium-catalysed ring-closing metathesis (RCM) reactions on appropriately substituted (2*R*)- or (2*S*)-2-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine as a chiron. The ring sizes can be varied from five- to seven-membered rings and the products are 1-aminocycloalkene-1-carboxylic acids and hydroxylated analogues.[3] Group **B** structures in the same way are conjugated vinyl derivatives with one of the double bonds exocyclic.[3] The complementary alkylidene derivatives **C**, **D** and **E** are available from palladium-catalysed cycloisomerisation reactions.[4] Oxo derived analogues **F** are available by the RCM Ru(II)-catalysed route.[5]

In the present work the target molecules were oxo-functionalised cyclic α-quaternary α-amino acids shown in the structures **G**, **H** and **I** in Scheme 1.

2. Results and discussion

The chiron (*R*)-2-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine was lithiated and alkylated to provide the substrate **1**.[3c] The aldols **2a** and **2b** were obtained in reactions between the lithiated species of substrate **1** and acetaldehyde. The new stereogenic centre in the heterocyclic 2-position was formed with high *trans*-selectivity. The *trans*-product was isolated after chromatography. Low diastereoselectivity, ratio 4:1 for **2a** and 7:1 for **2b**, was observed at the aldehyde carbon in the aldol formation. The aldol isomers could be separated by chromatography, but the configuration at the alcohol carbon was not determined. The mixture was used as a substrate for the subsequent oxidation by the Dess–Martin procedure.[6] The oxidation provided the corresponding ketones in the range 70–80% yield. The ketones **3a** and **3b** have the oxo group next to the quaternary spirocentre. In a second series illustrated by structures **3c** and **3d**, the oxo group has been moved one carbon unit away from the spirocentre and is thus less sterically shielded. Substrate **1** was used for their preparation with racemic propylene oxide as the alkylating reagent to provide the alcohols **2c** and **2d**. High *trans*-diastereoselectivity was observed at the heterocyclic

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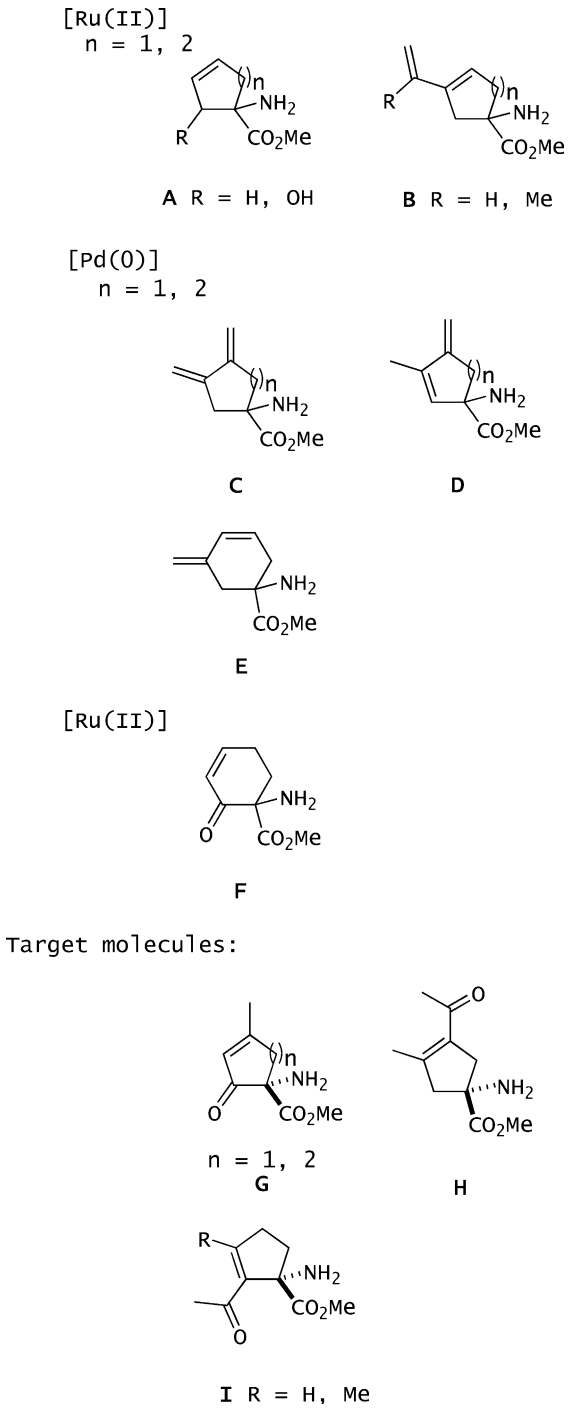


Scheme 1.

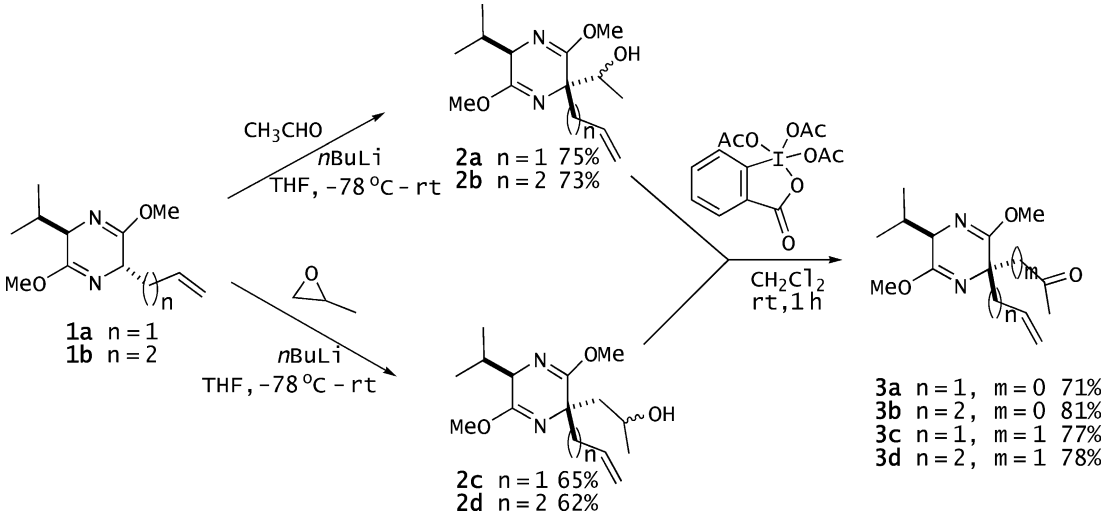
2-position. The *trans*-product was isolated after chromatography. The expected 1:1 ratio of epimeric isomers at the alcohol carbon was observed. The subsequent Dess–Martin oxidation proceeded well to provide the desired ketones **3c** and **3d** (Scheme 2).

The oxo-alkylidene derivatives **3** were to be investigated as substrates for introduction of a second oxo function by the Wacker type oxidation procedure. Chemoselectivity for oxidation of the carbon–carbon double bond in the heterocyclic substrates **3** was essential. Therefore Wacker oxidation was attempted and found to provide a direct synthesis of methyl ketones. In the Wacker oxidation, however, it is known that from some substrates aldehydes may be formed alone or in mixture with the methyl ketone. One reason for aldehyde formation may be steric hindrance, which may affect the relative rate of olefin oxidation.[7] Coordination to heteroatoms may also retard oxidation leading to a reversal of the regiochemistry in Wacker type oxidations.[8]

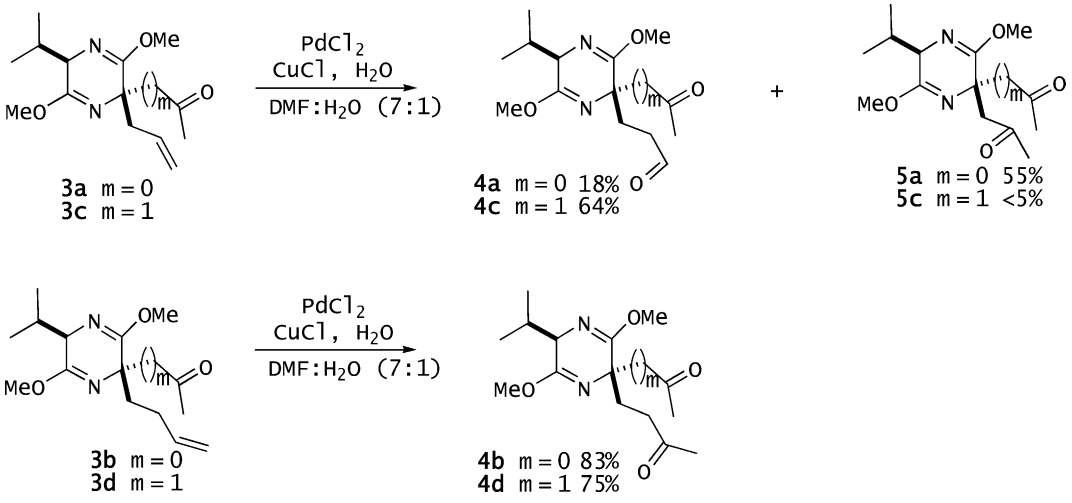
In the heterocyclic substrates **3b** and **3d**, which carry a C_4-olefin substituent, the Wacker oxidation in an aqueous medium proceeded well with formation of the methyl ketones **4b** and **4d** in high yields. Steric effects, or perhaps heteroatom coordination effects, become more important in the propene substrates **3a** and **3c** resulting in coformation, or a dominating formation, of aldehyde. With the acetyl substituent at the spirocentre **3a**, the ratio between aldehyde **4a** and ketone **5a** formation was 1:3. With an acetonyl substituent at the spirocentre **3c**, by far the major product was the aldehyde **4c** (Scheme 3).

In Scheme 4 spiroannulation reactions are shown. In a search for procedures to effect internal aldol condensations under mild alkaline conditions, the most satisfactory results were obtained with caesium carbonate as base.[9] The aldol reactions were run in acetonitrile under reflux conditions using 1–1.5 equiv of caesium carbonate. The acetyl oxo group in the substrates **4a**, **4b** and **5a** is attached directly to a quaternary centre and is sterically shielded. Enolate addition to this carbonyl group is slower than enolate addition to the less shielded oxo group in the other *gem*-substituent further away from the quaternary centre. Enolisation of the acetyl methyl group in substrate **4a** therefore leads preferentially to six-membered ring spiroannulation and formation of the heterospirane **6**. The acetonyl substrate **5a**, as well as the higher 2-butanoyl homologue **4b**, react regioselectively with formation of the five- and six-membered heterospiranes **7a** and **7b**, respectively. In the acetonyl substrates **4c** and **4d**, the carbonyl group is located one carbon unit further away from the quaternary centre. Enolisation can take place in either *gem*-dicarbonyl substituent in the heterocycle. Competitive internal enolisations in the aldehyde **4c** led to a mixture of the isomeric five-membered spiroannulated structures **7c** and **8c**, almost in ratio 1:1. Seven-membered ring formation, after enolisation in the methyl group, was not seen. A similar product ratio resulted in the cyclocondensation of the diketone **4d** with formation of the isomeric heterospiranes **7d** and **8d**. Enolisation in the methyl groups was not an important pathway for product formation.

Mild acid hydrolysis using 0.1 M TFA in aqueous acetonitrile was used to effect hydrolytic cleavage of the pyrazine ring. The ketospirane substrates in Scheme 5 are pure diastereomers after chromatographic purification procedures. Hydrolysis does not affect the α-quaternary carbon in the new α-amino acid. Hence the amino acid derivatives in Scheme 5 are assumed to be pure enantiomers.



Scheme 2.

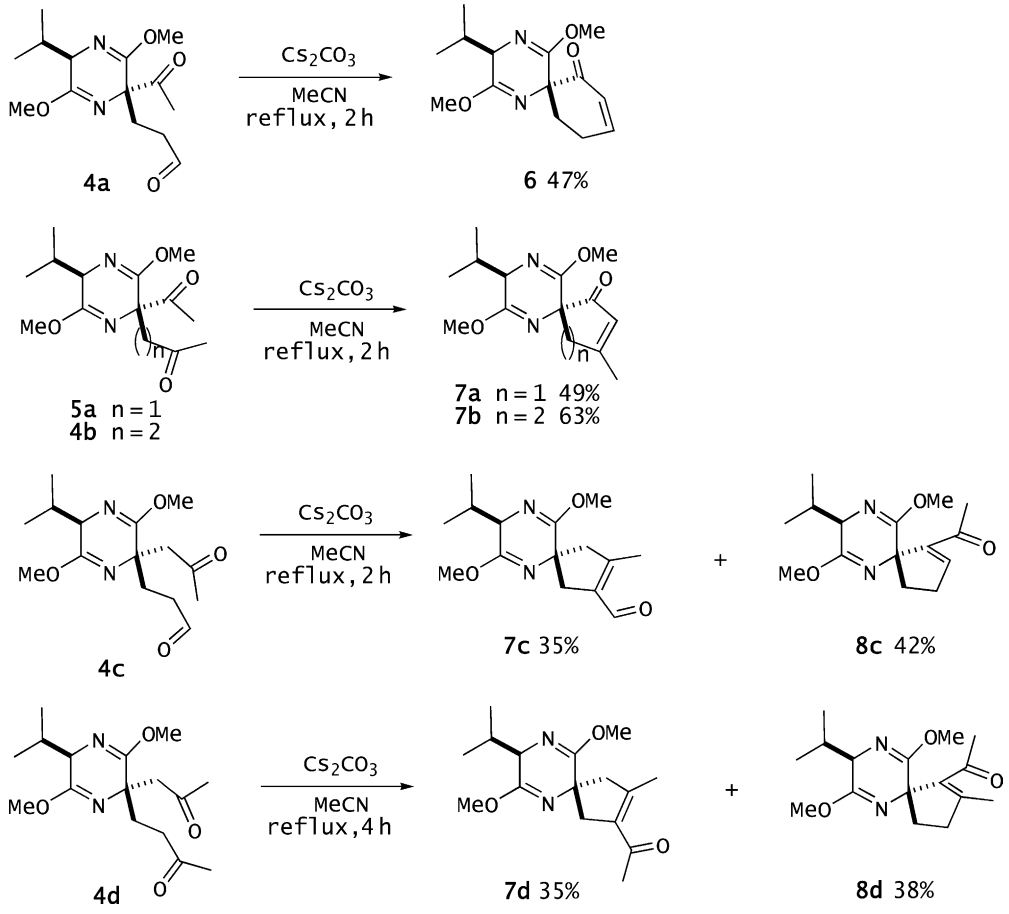


Scheme 3.

Acid hydrolysis next to the spirocentre was slow, and the reaction was run at ambient temperature over 3 days when TLC-monitoring showed the absence of the substrate. Strongly acidic conditions during hydrolysis is to be avoided since the reaction then proceeds via the corresponding 2,5-diketopiperazine, which requires forcing acidic conditions for further cleavage into its amino acid components.[10] Under mild acidic conditions, cleavage takes another course providing the amino acid components as esters, which can be readily separated.[11] This reaction pathway, however, is sensitive to steric interactions as is evident in the spiro substrates in Scheme 5. The 1-oxospiranes **6a** and **6b** furnished the corresponding cyclic amino acid esters **9a** and **9b** in moderate yields. The 1-acetyl derivative **9c** was cleaved in a similar manner to the functionalised cyclic amino ester **9c**. The formyl spirane derivative **7c** (Scheme 4) was unstable under the reaction conditions and the corresponding amino acid could not be prepared. The spirane **7d** provided the desired amino acid ester **11** in a moderate yield together with the valine dipeptide **12** in low yield. Formation of the latter is ascribed to initial cleavage in the piperazine ring between the nitrogen adjacent to the spirocentre and the corresponding enol ether carbon. Cleavage of the second iminoether function would subsequently provide the peptide bond. The same course of the reaction was seen with the heterospirane **8d** and formation of the cyclic amino ester **13** and the valine dipeptide **14**.

3. Conclusions

We have developed a route for the preparation of unsaturated cyclic α-quaternary α-amino acid derivatives. Stepwise and stereocontrolled alkylations of the chiron (*R*)-2-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine provided *gem*-disubstituted derivatives with an



Scheme 4.

alkene and an ethanol or propanol substituent. The epimeric alcohols were oxidised by the Dess–Martin methodology to the corresponding acetyl or acetonyl derivatives. The Wacker oxidation was compatible for chemoselective oxidation of the alkene function. Formation of a methyl ketone or an aldehyde was substrate dependent. The products were dioxo derivatives. Spiroannulation in the dioxo substrates was effected with caesium carbonate in acetonitrile by intramolecular aldol condensations. The regiochemistry was substrate dependent. The heterospiranes were cleaved under mild acidic conditions to cyclic α-quaternary α-amino acid derivatives.

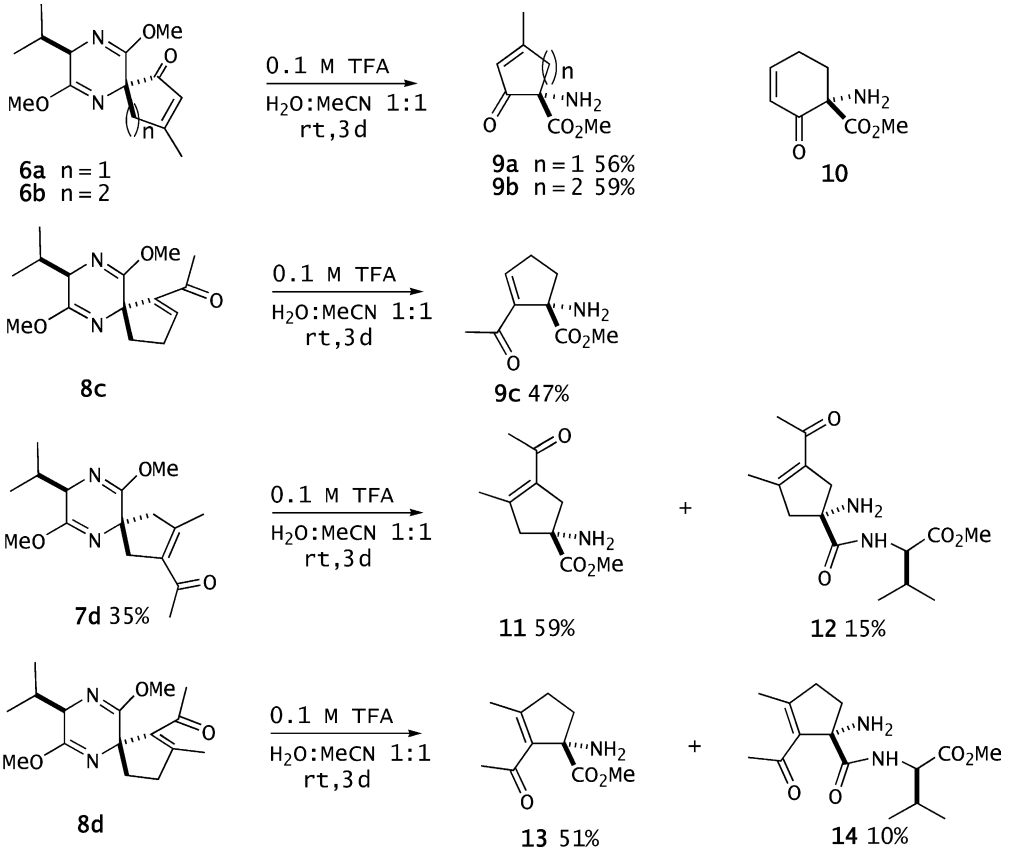
4. Experimental

^{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 on a Bruker DPX 500, at 75 MHz with DPX 300 and at 50 MHz on a Bruker DPX 200 instrument. NMR techniques such as DEPT, COSY, HETCOR, COLOC, 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 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 on a Perkin–Elmer 1310 infrared spectrophotometer or a Nicolet Magna 550 spectrometer using attenuated total reflectance (ATR).

Dry THF was distilled from sodium and benzophenone under argon. Dry dichloromethane was distilled from calcium hydride under argon.

4.1. (2′*S*,5′*R*)-1-(2-Allyl-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)ethanol 2a

A solution of (2*S*,5*R*)-2-allyl-2,5-dihydro-5-isopropyl-3,6-dimethoxypyrazine **1a** (2.00 g, 8.92 mmol) in THF (30 mL) under argon was lithiated by the addition of *n*-BuLi (6.13 mL, 9.81 mmol, 1.6 M in hexane) at −78 °C. The mixture was stirred at this temperature for 30 min and a solution of acetaldehyde (0.784 g, 1.0 mL, 17.84 mmol) in THF (15 mL) added dropwise. The resultant mixture was stirred at −78 °C for 1 h, allowed to reach ambient temperature and the reaction terminated by addition of phosphate buffer pH 7 (25 mL). The mixture was extracted with diethyl ether (3 × 20 mL), the extracts dried ($MgSO_4$) and the solvent evaporated.



Scheme 5.

The residual material was subjected to flash chromatography on silica gel using EtOAc/hexane 1:4. The product was a colourless oil and consisted of two alcohol epimers in the ratio 1:4; yield 1.800 g (75%). The epimer mixture was used as such in the subsequent reaction. For analytical purposes the epimers were separated by repetition of the chromatographic conditions as above.

Major epimer: R_f 0.24 (Found: C, 62.39; H, 8.85. $C_{14}H_{24}N_2O_3$ requires C, 62.66; H, 9.01%); HRMS: M 268.1783; $C_{14}H_{24}N_2O_3$ requires 268.1787; ν_{max} (film/cm^{-1}) 3416, 2971, 2945, 2872, 1694, 1670, 1432, 1289, 1237; δ_H ($CDCl_3$) 0.63 and 1.05 (6H, 2d, *J* 6.8, $CH(CH_3)_2$), 1.08 (3H, d, *J* 6.2, $CHOHCH_3$), 2.07–2.10 (1H, d, *J* 8.9, $CHOHCH_3$), 2.28–2.34 (1H, m, $CH(CH_3)_2$), 2.35–2.41 (1H, m, $CHHCH{=}CH_2$), 2.57–2.64 (1H, m, $CHHCH{=}CH_2$), 3.65 and 3.66 (6H, 2s, $2\times OCH_3$), 3.74–3.79 (1H, m, $CHOHCH_3$), 3.86 (1H, d, *J* 3.4, H-5), 4.92–5.03 (2H, m, $CH{=}CH_2$), 5.50–5.6 (1H, m, $CH{=}CH_2$); δ_C ($CDCl_3$) 17.2, 17.6 and 19.6 ($CH(CH_3)_2$ and CH_3), 30.5 ($CH(CH_3)_2$), 40.2 ($CH_2CH{=}CH_2$), 52.2 and 52.4 ($2\times OCH_3$), 60.6 (C-5), 65.6 (C-2), 72.9 (CHOH), 117.7 ($CH{=}CH_2$), 134.2 ($CH{=}CH_2$), 162.4 and 163.6 ($2\times C{=}N$); *m*/*z* (EI) 268 (M^+, 1%), 224 (19), 223 (10), 183 (7), 182 (11), 181 (100), 141 (14), 41 (8).

Minor epimer: R_f 0.33; HRMS: M 268.1790; $C_{14}H_{24}N_2O_3$ requires 268.1787; δ_H ($CDCl_3$) 0.66 and 1.05 (6H, 2d, 6H, *J* 6.8, $CH(CH_3)_2$), 0.87 (3H, d, *J* 6.2, $CHOHCH_3$), 2.24–2.30 (1H, m, $CH(CH_3)_2$), 2.63–2.69 (3H, m, $CH_2CH{=}CH_2$ and $CHOHCH_3$), 3.62 and 3.67 (6H, 2s, $2\times OCH_3$), 3.84–3.90 (2H, m, $CHOHCH_3$ and H-5), 4.90–5.01 (2H, m, $CH{=}CH_2$), 5.47–5.62 (1H, m, $CH{=}CH_2$); δ_C ($CDCl_3$) 17.6, 18.8 and 19.6 ($CH(CH_3)_2$ and CH_3), 30.8 ($CH(CH_3)_2$), 41.4 ($CH_2CH{=}CH_2$), 52.1 and 52.5 ($2\times OCH_3$), 60.9 (C-5), 65.1 (C-2), 71.8 (CHOH), 117.7 ($CH{=}CH_2$), 134.5 ($CH{=}CH_2$), 162.5 and 164.4 ($2\times C{=}N$); *m*/*z* (EI) 268 (M^+, 1%), 224 (4), 223 (4), 207 (6), 182 (7), 181 (100), 179 (13), 167 (8), 166 (5), 141 (8), 45 (20), 43 (22).

4.2. (2′*S*,5′*R*)-1-[2-(3-Butenyl)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl]ethanol 2b

Compound **2b** was prepared as above from (2*S*,5*R*)-2-(3-butenyl)-2,5-dihydro-5-isopropyl-3,6-dimethoxypyrazine **1b**[4] (2.00 g, 8.40 mmol) in THF (30 mL) under argon. Lithiation was effected with *n*-BuLi (5.77 mL, 9.24 mmol, 1.6 M in hexane) at −78 °C. Dropwise addition of acetaldehyde (0.740 g, 0.94 mL, 16.80 mmol) in THF (15 mL) gave the adduct. The crude product was subjected to flash chromatography on silica gel using EtOAc/hexane 1:4. The product was a colourless oil and consisted of two alcohol epimers in the ratio 1:7; yield 1.720 g (73%). 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 0.30 (Found: C, 63.46; H, 9.24. $C_{15}H_{26}N_2O_3$ requires C, 63.80; H, 9.28%); HRMS: $[M^+ + H]$ 283.2015; $C_{15}H_{26}N_2O_3 + H$ requires 283.2021; ν_{max} (film/cm^{-1}) 3460, 2971, 2943, 2871, 1694, 1641, 1462, 1436, 1241, 1197; δ_H ($CDCl_3$) 0.65 (3H, d, *J* 6.7, $CH(CH_3)_2$), 1.07 (6H, 2d, $CH(CH_3)_2$ and $CHOHCH_3$), 1.66–1.92 (4H, m, $2\times CH_2$), 2.00 (1H, d, *J* 9.2, $CHOHCH_3$), 2.30–2.47 (1H, m, $CH(CH_3)_2$), 3.65 and 3.67 (6H, 2s, $2\times OCH_3$), 3.69–3.78 (1H, m, $CHOHCH_3$), 3.88 (1H, d, *J* 3.4, H-5), 4.87–4.99 (2H, m, $CH{=}CH_2$), 5.69–5.83 (1H, m, $CH{=}CH_2$); δ_C ($CDCl_3$) 17.0 and 19.5 ($CH(CH_3)_2$), 17.5 ($CHOHCH_3$), 28.8 (CH_2), 30.5 ($CH(CH_3)_2$), 34.6 (CH_2), 52.2 and 52.3 ($2\times OCH_3$), 60.6 (C-5), 65.3 (C-2), 73.0 (CHOH), 114.2 ($CH{=}CH_2$), 138.7 ($CH{=}CH_2$), 162.7 and 163.7 ($2\times C{=}N$); *m/z* (CI–CH_4) 283 ($M^+ + H$, 72%), 265 (15), 251 (8), 239 (30), 238 (31), 237 (100), 223 (18), 211 (27), 197 (23), 195 (99), 169 (25), 153 (5).

Minor epimer: R_f 0.22; δ_H ($CDCl_3$) 0.65 and 1.05 (6H, 2d, *J* 6.8, $CH(CH_3)_2$), 0.85 (3H, d, *J* 6.2, $CHOHCH_3$), 1.62–1.98 (4H, m, $2\times CH_2$), 2.26–2.37 (1H, m, $CH(CH_3)_2$), 2.55 (1H, d, *J* 9.8, $CHOHCH_3$), 3.61 and 3.65 (3H, 2s, $2\times OCH_3$), 3.79–3.87 (2H, m, $CHOHCH_3$ and H-5), 4.84–4.95 (2H, m, $CH{=}CH_2$), 5.67–5.78 (1H, m, $CH{=}CH_2$); δ_C ($CDCl_3$) 17.2 and 19.5 ($CH(CH_3)_2$), 18.7 ($CHOHCH_3$), 29.2 (CH_2), 30.7 ($CH(CH_3)_2$), 35.6 (CH_2), 52.1 and 52.5 ($2\times OCH_3$), 60.8 (C-5), 64.9 (C-2), 72.3 (CHOH), 114.1 ($CH{=}CH_2$), 138.5 ($CH{=}CH_2$), 162.7 and 164.4 ($2\times C{=}N$).

4.3. (2′*S*,5′*R*)-1-(2-Allyl-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)propan-2-ol 2c

A solution of (2*S*,5*R*)-2-allyl-2,5-dihydro-5-isopropyl-3,6-dimethoxypyrazine **1b** (1.5 g, 6.7 mmol) in THF (30 mL) under argon, was lithiated by the addition of *n*-BuLi (4.60 mL, 7.37 mmol, 1.6 M in hexane) at −78 °C, the mixture stirred at this temperature for 30 min and a solution of propylene oxide (0.70 mL, 0.583 g, 10.05 mmol) in THF (15 mL) added dropwise. The resultant mixture was stirred at −78 °C for 1 h, allowed to reach ambient temperature and the reaction terminated by addition of phosphate buffer pH 7 (25 mL). The mixture was extracted with diethyl ether (3×20 mL), the extracts dried ($MgSO_4$) and the solvent evaporated. The crude product was purified by flash chromatography on silica gel using EtOAc/hexane 3:7. The product was a colourless oil consisting of the two alcohol epimers 1:1; R_f 0.22; yield 1.228 g (65%) (Found: C, 63.56; H, 9.12. $C_{15}H_{26}N_2O_3$ requires C, 63.80; H, 9.28%); HRMS: M 282.1944; $C_{15}H_{26}N_2O_3$ requires 282.1943; ν_{max} (film/cm^{-1}) 3406, 2944, 2872, 1694, 1462, 1437, 1237; δ_H ($CDCl_3$) 0.63 and 1.02 (6H, 2d, *J* 6.8, $CH(CH_3)_2$), 0.67 and 1.10 (6H, 2d, *J* 6.8, $CH(CH_3)_2$), 1.12 and 1.15 (6H, 2d, *J* 6.4, $2\times CHOHCH_3$), 1.55–2.07 (4H, m, $2\times CH_2CHOH$), 2.12–2.28 (2H, m, $2\times CH(CH_3)_2$), 2.30–2.56 (4H, m, $2\times CH_2CH{=}CH_2$), 2.90 (1H, br s, CHO*H*), 3.60–3.64 (12H, 4s, $4\times OCH_3$), 3.79–3.95 (signals overlap, 3H, $CHOHCH_3$ and $2\times$H-5), 4.10–4.25 (1H, m, $CHOHCH_3$), 4.80 (1H, br s, CHO*H*), 4.92–5.03 (4H, m, $2\times CH{=}CH_2$), 5.50–5.60 (2H, m, $2\times CH{=}CH_2$); δ_C ($CDCl_3$) 17.4, 17.6, 19.5 and 19.6 ($2\times CH(CH_3)_2$), 23.5 and 23.7 ($2\times CHOHCH_3$), 30.6 and 31.0 ($2\times CH(CH_3)_2$), 42.2 and 46.1 ($2\times CH_2CH{=}CH_2$), 47.6 and 47.8 ($2\times CH_2CHOH$), 52.2, 52.3, 52.4 and 52.8 ($4\times OCH_3$), 60.1 and 60.9 ($2\times$C-5), 61.6 ($2\times$C-2), 64.6 and 65.5 ($2\times CHOH$), 117.9 and 118.0 ($2\times CH{=}CH_2$), 133.7 and 134.1 ($2\times CH{=}CH_2$), 163.1, 163.3, 163.6 and 164.3 ($4\times C{=}N$); *m/z* (EI) 282 (M^+, 1%), 241 (21), 209 (7), 198 (13), 197 (100), 181 (52), 155 (14).

4.4. (2′*S*,5′*R*)-1-[2-(3-Butenyl)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl]propan-2-ol 2d

Compound **2d** was prepared as above from (2*S*,5*R*)-2-(3-butenyl)-2,5-dihydro-5-isopropyl-3,6-dimethoxypyrazine **1b** (2.00 g, 8.40 mmol) in THF (30 mL), under argon, *n*-BuLi (5.77 mL, 9.24 mmol, 1.6 M in hexane) and a solution of propylene oxide (0.803 g, 0.97 mL, 13.86 mmol) in THF (15 mL). The reaction product was subjected to flash chromatography on silica gel using EtOAc/hexane 3:7; R_f 0.32. The product consisted of two alcohol epimers, in an inseparable mixture, in the ratio 1:1; yield 1.720 g (62%). The epimer mixture was used in the subsequent reaction. HRMS (electrospray): $[M^+ + H]$ 297.2180; $C_{16}H_{28}N_2O_3 + H$ requires 297.2172; ν_{max} (film/cm^{-1}) 3383, 2969, 2944, 2871, 1694, 1654, 1642, 1460, 1437, 1381, 1230, 1198, 1144; δ_H ($CDCl_3$) 0.64–0.69 (6H, 2d overlap, $2\times CH(CH_3)_2$), 1.05–1.09 (9H, 3d overlap, $2\times CH(CH_3)_2$ and $CHOHCH_3$), 1.50–2.08 (12H, m, $6\times CH_2$), 2.18–2.42 (2H, m, $2\times CH(CH_3)_2$), 2.77 (1H, br s, OH), 3.63–3.71 (13H, 4s and 1m, $4\times OCH_3$ and $CHOHCH_3$), 3.89 (1H, d, *J* 3.4, H-5), 3.95 (1H, d, *J* 3.4, H-5), 4.09–4.23 (1H, m, $CHOHCH_3$), 4.71 (1H, br s, OH), 4.87–4.94 (4H, m, $2\times CH{=}CH_2$), 5.69–5.80 (2H, m, $2\times CH{=}CH_2$); δ_C ($CDCl_3$) 17.1, 17.4 and 19.5, 19.6 ($2\times CH(CH_3)_2$), 23.6 and 23.6 ($2\times CHOHCH_3$), 28.6 and 29.2 ($2\times CH_2$), 30.5 and 30.9 ($2\times CH(CH_3)_2$), 36.5, 40.5, 48.3 and 48.4 ($4\times CH_2$), 52.3 and 52.4 ($4\times OCH_3$), 60.1 and 60.9 ($2\times$C-5), 60.3 ($2\times$C-2), 64.6 and 65.5 ($2\times CHOH$), 114.3 and 114.4 ($2\times CH{=}CH_2$), 138.3 and 138.4 ($2\times CH{=}CH_2$), 163.3, 163.6, 163.8 and 164.3 ($4\times C{=}N$); *m/z* (CI–CH_4) 297 ($M^+ + H$, 64%), 281 (8), 279 (6), 265 (17), 238 (8), 237 (56), 223 (11), 209 (7), 197 (13), 195 (100), 181 (16), 167 (6), 139 (7).

4.5. (2′*R*,5′*R*)-1-(2-Allyl-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)ethanone 3a

A solution of (2′*S*,5′*R*)-1-(2-allyl-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)ethanol **2a** (0.850 g, 3.17 mmol) in dry dichloromethane (25 mL) was added with stirring to a solution of the Dess–Martin reagent (1.61 g, 3.8 mmol) in dry dichloromethane (20 mL) at ambient temperature. The homogeneous reaction mixture was diluted with diethyl ether (50 mL) after 1 h, and the resulting suspension added to 1.3 M NaOH (30 mL). The mixture was stirred for 10 min, the ether layer extracted with 1.3 M NaOH (25 mL) and water (25 mL). The ether phase was dried ($MgSO_4$), evaporated and

residual material subjected to flash chromatography on silica gel using EtOAc/hexane 1:4; R_f 0.46. The product was a colourless oil; yield 0.600 g (71%) (Found: C, 63.05; H, 8.12. $C_{14}H_{22}N_2O_3$ requires C, 63.13; H, 8.33%); HRMS: M 266.1620; $C_{14}H_{22}N_2O_3$ requires 266.1630; ν_{max} (film/cm^{-1}) 2970, 2945, 2871, 1716, 1694, 1670, 1437, 1245; δ_H ($CDCl_3$) 0.65 and 1.08 (6H, 2d, J 6.8, CH(CH_3)$_2$), 2.03 (3H, s, COCH_3), 2.31–2.36 (1H, m, CH(CH$_3$)$_2$), 2.58–2.65 (1H, m, CHHCH=CH$_2$), 2.74–2.81 (1H, m, CHHCH=CH$_2$), 3.64 and 3.68 (6H, 2s, 2×OCH$_3$), 3.98 (1H, d, J 3.4, H-5), 4.94–5.05 (2H, m, CH=CH_2), 5.48–5.60 (1H, m, CH=CH$_2$); δ_C ($CDCl_3$) 17.3 and 19.6 (CH(CH$_3$)$_2$), 25.1 (COCH$_3$), 30.6 (CH(CH$_3$)$_2$), 39.4 (CH$_2$CH=CH$_2$), 52.7 and 52.8 (2×OCH$_3$), 60.6 (C-5), 71.3 (C-2), 118.3 (CH=CH$_2$), 133.5 (CH=CH$_2$), 159.8 and 164.2 (2×C=N), 202.9 (CO); m/z (EI) 266 (M$^+$, 1%), 223 (25), 182 (11), 181 (100), 68 (5), 43 (54).

4.6. (2′*R*,5′*R*)-1-[2-(3-Butenyl)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl]ethanone 3b

Compound **3b** was prepared as above from (2′*S*,5′*R*)-1-[2-(3-butenyl)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl]ethanol **2b** (1.500 g, 5.31 mmol) in dry dichloromethane (25 mL) and the Dess–Martin reagent (2.819 g, 6.64 mmol) in dry dichloromethane (20 mL) at ambient temperature. The homogeneous reaction mixture was diluted with diethyl ether (50 mL) and subsequently treated with 1.3 M NaOH (30 mL). The mixture was stirred for 10 min, the ether layer extracted with 1.3 M NaOH (25 mL) and water (25 mL). The crude product was purified by flash chromatography on silica gel using EtOAc/hexane 1:4; R_f 0.46. The product was a colourless oil; yield 1.200 g (81%); HRMS: [M$^+$+H] 281.1854; $C_{15}H_{24}N_2O_3$+H requires 281.1865; ν_{max} (film/cm^{-1}) 2971, 2961, 2946, 2872, 2846, 1728, 1686, 1641, 1438, 1383, 1246, 1146; δ_H ($CDCl_3$) 0.68 and 1.09 (6H, 2d, J 6.7, CH(CH_3)$_2$), 1.66–1.99 (2H, m, CH_2–CH$_2$), 2.00–2.15 (2H, m, CH$_2$–CH_2), 2.05 (3H, s, COCH_3), 2.28–2.41 (1H, m, CH(CH$_3$)$_2$), 3.67 and 3.69 (6H, 2s, 2×OCH$_3$), 3.98 (1H, d, J 3.4, H-5), 4.84–5.03 (2H, m, CH=CH_2), 5.68–5.88 (1H, m, CH=CH$_2$); δ_C ($CDCl_3$) 17.0 and 19.5 (CH(CH$_3$)$_2$), 25.1 (COCH$_3$), 28.5 (CH$_2$–CH$_2$), 30.6 (CH(CH$_3$)$_2$), 34.2 (CH$_2$–CH$_2$), 52.8 (2×OCH$_3$), 60.6 (C-5), 71.3 (C-2), 114.5 (CH=CH$_2$), 138.3 (CH=CH$_2$), 160.1 and 164.4 (2×C=N), 203.12 (CO); m/z (CI–CH$_4$) 281 (M$^+$+H, 100%), 253 (9), 238 (13), 237 (56), 236 (12), 211 (14), 195 (28), 169 (6), 153 (3).

4.7. (2′*S*,5′*R*)-1-(2-Allyl-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)propan-2-one 3c

Compound **3c** was prepared as above from a solution of (2′*S*,5′*R*)-1-(2-allyl-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)propan-2-ol **2c** (0.600 g, 2.12 mmol) and Dess–Martin reagent (1.030 g, 2.43 mmol). The product was isolated after flash chromatography on silica gel using EtOAc/hexane 1:4; R_f 0.30. The product was a colourless oily material; yield 0.457 g (77%) (Found: C, 64.29; H, 8.55. $C_{15}H_{24}N_2O_3$ requires C, 64.26; H, 8.63%); HRMS: M 280.1784; $C_{15}H_{24}N_2O_3$ requires 280.1787; ν_{max} (film/cm^{-1}) 2969, 2945, 2867, 1726, 1697, 1436, 1235; δ_H ($CDCl_3$) 0.61 and 1.02 (6H, 2d, J 6.8, CH(CH$_3$)$_2$), 1.96 (3H, s, COCH$_3$), 2.21–2.30 (1H, m, CH(CH$_3$)$_2$), 2.31–2.42 (2H, m, CH_2CH=CH$_2$), 2.68 and 2.79 (2H, 2d, J 15.6, CH$_2$CO), 3.54 and 3.58 (6H, 2s, 2×OCH$_3$), 3.92 (1H, d, J 3.4, H-5), 4.92–4.98 (2H, m, CH=CH_2), 5.52–5.60 (1H, m, CH=CH$_2$); δ_C ($CDCl_3$) 17.6 and 19.7 (CH(CH$_3$)$_2$), 30.5 (COCH$_3$), 31.4 (CH(CH$_3$)$_2$), 45.6 (CH$_2$CH=CH$_2$), 51.8 (CH$_2$COCH$_3$), 52.3 (2×OCH$_3$), 59.4 (C-2), 61.0 (C-5), 118.2 (CH=CH$_2$), 133.7 (CH=CH$_2$), 162.5 and 163.6 (2×C=N), 206.2 (CO); m/z (EI) 280 (M$^+$, 4%), 239 (33), 237 (7), 223 (6), 197 (100), 195 (12), 181 (6), 155 (6), 154 (9).

4.8. (2′*S*,5′*R*)-1-[2-(3-Butenyl)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl]propan-2-one 3d

The reaction was carried out as above from (2′*S*,5′*R*)-1-[2-(3-butenyl)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl]propan-2-ol **2d** (1.5 g, 5.06 mmol) and the Dess–Martin reagent (2.58 g, 6.07 mmol). The product was isolated after chromatography on silica gel using EtOAc/hexane 1:4. The product thus obtained was a colourless oil; yield 1.16 g (78%); R_f 0.29; HRMS (electrospray): [M$^+$+H] 295.2005; $C_{16}H_{26}N_2O_3$ (M+H) requires 295.2016; ν_{max} (film/cm^{-1}) 2958, 2945, 2929, 2871, 1726, 1697, 1645, 1462, 1437, 1364, 1243, 1223, 1146; δ_H ($CDCl_3$) 0.65 and 1.07 (6H, 2d, J 6.8, CH(CH_3)$_2$), 1.63–1.92 (4H, m, CH$_2$CH$_2$), 2.29–2.35 (1H, m, CH(CH$_3$)$_2$), 2.00 (3H, s, COCH$_3$), 2.71 and 2.82 (2H, 2d, J 15.4, CHHCO), 3.59 and 3.63 (6H, 2s, 2×OCH$_3$), 3.96 (1H, d, J 3.4, H-5), 4.87–4.97 (2H, m, CH=CH_2), 5.68–5.78 (1H, m, CH=CH$_2$); δ_C ($CDCl_3$) 17.3 and 19.6 (CH(CH$_3$)$_2$), 28.41 (CH$_2$CH$_2$), 30.3 (CH(CH$_3$)$_2$), 31.4 (COCH$_3$), 39.9 (CH$_2$$CH_2$), 52.2 ($CH_2$CO), 52.4 (2×OCH$_3$), 59.3 (C-2), 60.9 (C-5), 114.3 (CH=CH$_2$), 138.3 (CH=CH$_2$), 162.4 and 163.8 (2×C=N), 206.09 (CO); m/z (CI–CH$_4$) no molecular ion, 239 (18), 237 (100), 223 (7), 195 (71), 55 (3).

4.9. (2′*R*,5′*R*)-3-(2-Acetyl-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)propionaldehyde 4a

Palladium dichloride (0.066 g, 0.375 mmol) and copper(I) chloride (0.371 g, 3.75 mmol) in water (2 mL) and DMF (14 mL) were stirred together at room temperature for 1 h before (2′*R*,5′*R*)-1-(2-allyl-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)ethanone **3a** (1.00 g, 3.75 mmol) was added. The black solution was stirred under an oxygen atmosphere at room temperature and the progress of the reaction monitored by TLC. The reaction was essentially complete after 10 h. The resulting solution was poured into water (10 mL), extracted with diethyl ether (3×20 mL) and the combined organic extracts dried ($MgSO_4$), and evaporated at reduced pressure. The product was isolated after flash chromatography on silica gel using EtOAc/hexane 1:5 and was a colourless oil; yield 0.190 g (18%); R_f 0.20; HRMS: M

282.1588; $C_{14}H_{22}N_2O_4$ requires 282.1579; ν_{max} (film/cm^{-1}) 2960, 2873, 2789, 1725, 1690, 1670, 1461, 1439, 1354, 1311, 1247, 1184, 1145; δ_H ($CDCl_3$) 0.68 and 1.07 (6H, 2d, *J* 6.8, CH(CH_3)$_2$), 2.00 (3H, s, CH_3), 2.13–2.19 (1H, m, C*H*HCH$_2$), 2.29–2.43 (4H, m, CH*H*CH_2 and C*H*(CH$_3$)$_2$), 3.64 (6H, s, 2×OCH$_3$), 3.98 (1H, d, *J* 3.4, H-5), 9.67 (1H, t, *J* 1.7, CHO); δ_C ($CDCl_3$) 16.9 and 19.5 (CH(*C*H$_3$)$_2$), 25.0 (CO*C*H$_3$), 28.1 (CH$_2$), 30.78 (*C*H(CH$_3$)$_2$), 39.0 (CH$_2$), 52.9 and 54.0 (2×OCH$_3$), 60.8 (C-5), 70.3 (C-2), 159.9 and 165.0 (2×C=N), 202.1 and 202.4 (2×CO); *m*/*z* (EI) 282 (M$^+$, 2%), 255 (39), 240 (10), 239 (63), 213 (30), 198 (11), 197 (100), 195 (43), 182 (16), 167 (25), 153 (42).

4.10. (2′*R*,5*R*)-1-(2-Acetyl-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)butan-3-one 4b

Compound **4b** was prepared as above from (2′*R*,5′*R*)-1-[2-(3-butenyl)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl]ethanone **3b** (1.150 g, 4.10 mmol), palladium dichloride (0.072 g, 0.41 mmol) and copper(I) chloride (0.406 g, 4.10 mmol). The product was a colourless oil after flash chromatography on silica gel using EtOAc/hexane 1:4; yield 1.00 g (83%); HRMS: [M+1] 297.1803; $C_{15}H_{24}N_2O_4$+1 requires 297.1814; ν_{max} (film/cm^{-1}) 2961, 2948, 2873, 1720, 1689, 1461, 1438, 1366, 1247, 1202; δ_H ($CDCl_3$) 0.68 and 1.06 (6H, 2d, *J* 6.8, CH(CH_3)$_2$), 1.90–2.08 (1H, m, C*H*HCH$_2$), 1.99 (3H, s, COCH$_3$), 2.06 (3H, s, COCH$_3$), 2.11–2.41 (4H, m, CH*H*CH_2 and C*H*(CH$_3$)$_2$), 3.63 and 3.65 (6H, 2s, 2×OCH$_3$), 3.96 (1H, d, *J* 3.4, H-5); δ_C ($CDCl_3$) 17.0 and 19.5 (CH(*C*H$_3$)$_2$), 25.1 (CO*C*H$_3$), 29.4 (CO*C*H$_3$), 29.8 (CH$_2$), 30.8 (*C*H(CH$_3$)$_2$), 38.7 (CH$_2$), 52.8 and 52.9 (2×OCH$_3$), 60.8 (C-5), 70.3 (C-2), 160.2 and 164.7 (2×C=N), 202.69 (CO), 208.9 (CO); *m*/*z* (CI–CH$_4$) 297 (M$^+$+H, 100%), 255 (6), 254 (16), 253 (66), 227 (8), 211 (34), 197 (4), 153 (8).

4.11. (2′*S*,5′*R*)-3-[5-Isopropyl-3,6-dimethoxy-2-(2-oxopropyl)-2,5-dihydropyrazin-2-yl]propionaldehyde 4c

Compound **4c** 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 **3c** (1.00 g, 3.57 mmol), palladium dichloride (0.063 g, 0.357 mmol) and copper(I) chloride (0.353 g, 3.57 mmol). The product was obtained as a colourless oil after flash chromatography on silica gel using EtOAc/hexane 1:4; yield 0.676 g (64%); R_f 0.11; HRMS: M 296.1745; $C_{15}H_{24}N_2O_4$ requires 296.1736; ν_{max} (film/cm^{-1}) 2959, 2946, 2871, 1724, 1697, 1472, 1437, 1364, 1308, 1242, 1201; δ_H ($CDCl_3$) 0.66 and 1.07 (6H, 2d, *J* 6.8, CH(CH_3)$_2$), 1.97–2.09 (5H, m and 1s, CH_3 and CH$_2$), 2.22–2.34 (3H, m, CH$_2$ and C*H*(CH$_3$)$_2$), 2.72 and 2.84 (2H, 2d, *J* 15.9, C*HH*COCH$_3$), 3.56 and 3.62 (6H, 2s, 2×OCH$_3$), 3.99 (1H, d, *J* 3.4, H-5), 9.66 (1H, t, *J* 1.6, CHO); δ_C ($CDCl_3$) 17.3 and 19.6 (CH(*C*H$_3$)$_2$), 30.3 (CO*C*H$_3$), 31.4 (*C*H(CH$_3$)$_2$), 33.1 and 38.9 (2×CH$_2$), 51.7 (*C*H$_2$COCH$_3$), 52.4 and 52.5 (2×OCH$_3$), 58.6 (C-2), 60.9 (C-5), 161.9 and 164.5 (2×C=N), 201.9 (CHO), 205.7 (*C*OCH$_3$); *m*/*z* (EI) 296 (M$^+$, 3%), 269 (63), 255 (39), 253 (32), 239 (40), 197 (100), 195 (24), 167 (18), 155 (24), 43 (69).

4.12. (2′*S*,5′*R*)-4-[5-Isopropyl-3,6-dimethoxy-2-(2-oxopropyl)-2,5-dihydropyrazin-2-yl]butan-2-one 4d

Compound **4d** was prepared as above from (2′*S*,5′*R*)-1-[2-(3-butenyl)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl]propan-2-one **3d** (1.00 g, 3.40 mmol), palladium dichloride (0.060 g, 0.34 mmol) and copper(I) chloride (0.337 g, 3.40 mmol). The product was a colourless oil after flash chromatography using EtOAc/hexane 1:4; yield 0.790 g (75%); R_f 0.18; HRMS: [M$^+$+H] 311.1970; $C_{16}H_{26}N_2O_4$+H requires 311.1970; ν_{max} (film/cm^{-1}) 2959, 2946, 2871, 1719, 1694, 1462, 1437, 1357, 1308, 1243, 1200; δ_H ($CDCl_3$) 0.65 and 1.05 (6H, 2d, *J* 6.8, CH(CH_3)$_2$), 1.83–2.08 (8H, m+2s, CH_2CH$_2$ and 2×COCH$_3$), 2.11–2.35 (3H, m, CH$_2$CH_2 and C*H*(CH$_3$)$_2$), 2.68 and 2.81 (2H, 2d, *J* 15.5, C*HH*CO), 3.54 and 3.59 (6H, 2s, 2×OCH$_3$), 3.96 (1H, d, *J* 3.4, H-5); δ_C ($CDCl_3$) 17.3 and 19.5 (CH(*C*H$_3$)$_2$), 29.8 (CO*C*H$_3$), 30.2 (*C*H(CH$_3$)$_2$), 31.4 (CO*C*H$_3$), 34.4 and 38.6 (*C*H$_2$*C*H$_2$), 51.8 (*C*H$_2$CO), 52.2 and 52.3 (2×OCH$_3$), 58.5 (C-2), 60.9 (C-5), 162.1 and 164.1 (2×C=N), 205.8 (CO), 208.07 (CO); *m*/*z* (CI–CH$_4$) 311 (M$^+$+H, 100%), 310 (8), 268 (7), 267 (28), 253 (23), 252 (9), 239 (7), 211 (5), 197 (9).

4.13. (2′*R*,5′*R*)-1-(2-Acetyl-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)propan-2-one 5a

The diketone **5a** was the second product eluted from the flash chromatography column in the experiment described for the preparation of propionaldehyde **4a** (vide supra); yield 0.581 g (55%) of an oily material; R_f 0.16; HRMS: [M$^+$+H] 283.1643; $C_{14}H_{22}N_2O_4$+H requires 283.1657; ν_{max} (film/cm^{-1}) 2960, 2947, 2872, 1722, 1691, 1666, 1462, 1437, 1356, 1300, 1249; δ_H ($CDCl_3$) 0.72 and 1.08 (6H, 2d, *J* 6.7, CH(CH_3)$_2$), 2.02 and 2.05 (6H, 2s, 2×COCH_3), 2.28–2.40 (1H, m, C*H*(CH$_3$)$_2$), 3.03 (1H, d, *J* 16.0, C*H*HCO), 3.18 (1H, d, *J* 16.0, CH*H*CO), 3.63 (6H, s, 2×OCH$_3$), 3.95 (1H, d, *J* 3.4, H-5); δ_C ($CDCl_3$) 16.9 and 19.6 (CH(*C*H$_3$)$_2$), 24.9 (CO*C*H$_3$), 30.6 (*C*H(CH$_3$)$_2$), 31.2 (CH$_2$CO*C*H$_3$), 48.3 (CH$_2$), 52.9 and 53.1 (2×OCH$_3$), 60.91 (C-5), 69.7 (C-2), 159.2 and 165.0 (2×C=N), 201.9 and 205.1 (2×CO); *m*/*z* (CI–CH$_4$) 283 (M$^+$+H, 100%), 265 (3), 251 (6), 241 (12), 239 (33), 197 (41).

4.14. (3*R*,6*S*)-3-Isopropyl-2,5-dimethoxy-1,4-diazaspiro[5.5]undeca-1,4,8-trien-7-one 6

Caesium carbonate (0.194 g, 0.59 mmol) was added to a solution of (2′*R*,5′*R*)-3-(2-acetyl-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)propionaldehyde **4a** (0.150 g, 0.59 mmol) in acetonitrile (5 mL). The suspension was stirred under reflux. TLC monitoring showed the reaction to be complete after 2 h. The mixture was filtered through a short silica gel column, the filtrate evaporated and the residual material subjected to flash

chromatography on silica gel using EtOAc/hexane 3:7. The product was a colourless oil; yield 0.073 g (47%); R_f 0.47.

The spectroscopic data were in agreement with the spectroscopic data reported in the literature for this compound.[5b]

4.15. (5*R*,8*R*)-8-Isopropyl-7,10-dimethoxy-3-methyl-6,9-diazaspiro[4.5]deca-2,6,9-trien-1-one 7a

Caesium carbonate (0.575 g, 1.77 mmol) was added to a solution of (2′*R*,5′*R*)-1-(acetyl-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)propan-2-one **5a** (0.500 g, 1.77 mmol) in acetonitrile (15 mL). The resulting suspension was stirred under reflux, and the progress of the reaction monitored by TLC. The reaction was complete after 2 h when the mixture was filtered through a short silica gel column and the filtrate evaporated. The product was isolated from the residual material after flash chromatography on silica gel using EtOAc/hexane 3:7. The product was a colourless oil; yield 0.229 g (49%); R_f 0.22; HRMS: M 264.1477; $C_{14}H_{20}N_2O_3$ requires 264.1473; ν_{max} (film/cm^{-1}) 2959, 2947, 2871, 1721, 1693, 1672, 1635, 1437, 1300, 1288, 1238, 1198, 1144; δ_H ($CDCl_3$) 0.62 and 1.01 (6H, 2d, *J* 6.8, CH(C*H*$_3$)$_2$), 2.13 (3H, s, CH_3), 2.20–2.26 (1H, m, C*H*(CH$_3$)$_2$), 2.53 (1H, d, *J* 18.1, C*H*H), 2.98 (1H, d, *J* 18.1, CH*H*), 3.58 (6H, s, 2×OCH$_3$), 4.10 (1H, d, *J* 3.2, H-8), 5.92 (1H, s, CH); δ_C ($CDCl_3$) 16.3, 19.2 and 19.4 (*C*H$_3$ and CH(*C*H$_3$)$_2$), 30.8 (*C*H(CH$_3$)$_2$), 48.3 (CH_2), 52.6 (2×OCH$_3$), 60.9 (C-8), 66.5 (C-5), 127.6 (*C*H=), 160.3 and 164.8 (2×C=N), 178.1 (C=), 204.2 (CO); *m*/*z* (EI) 264 (M^+, 45%), 249 (11), 222 (27), 221 (100), 297 (14), 193 (21), 192 (43), 178 (8), 153 (11).

4.16. (3*R*,6*R*)-3-Isopropyl-2,5-dimethoxy-9-methyl-1,4-diazaspiro[5.5]undeca-1,4,8-trien-7-one 7b

Compound **7b** was prepared as above from (2′*R*,5′*R*)-1-(2-acetyl-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)butan-3-one **4b** (0.950 g, 3.2 mmol) and caesium carbonate (1.043 g, 3.2 mmol) by heating under reflux for 2 h. The product was a colourless oil after flash chromatography on silica gel using EtOAc/hexane 1:4; yield 0.560 g (63%); R_f 0.4; HRMS: M 278.1632; $C_{15}H_{22}N_2O_3$ requires 278.1630; $[\alpha]_D$ −23.6 (*c* 1.28, $CHCl_3$); ν_{max} (film/cm^{-1}) 2957, 2946, 2871, 1697, 1677, 1636, 1461, 1436, 1381, 1241, 1214, 1200; δ_H ($CDCl_3$) 0.64 and 1.06 (6H, 2d, *J* 6.8, CH(C*H*$_3$)$_2$), 1.78–1.85 (1H, m, C*H*HCHH), 1.98 (3H, s, CH_3), 2.13–2.22 (1H, m, CHHC*H*H), 2.25–2.30 (1H, m, C*H*(CH$_3$)$_2$), 2.55–2.60 (1H, m, CH*H*CHH), 2.70–2.89 (1H, m, CHHCH*H*), 3.59 and 3.65 (6H, 2s, 2×OCH$_3$), 4.05 (1H, d, *J* 3.2, H-3), 5.85 (1H, s, C=CH); δ_C ($CDCl_3$) 16.6 and 19.3 (CH(*C*H$_3$)$_2$), 24.5 (CH_3), 27.6 (CH_2*C*H$_2$), 30.6 (*C*H(CH$_3$)$_2$), 34.1 (*C*H$_2$CH$_2$), 52.4 and 52.5 (2s, 2×OCH$_3$), 60.7 (C-3), 63.9 (C-6), 124.3 (C=*C*H), 161.4 (C=N), 163.6 (*C*=CH), 164.3 (C=N), 193.6 (CO); *m*/*z* (EI) 278 (M^+, 30%), 236 (21), 235 (100), 209 (9), 207 (31), 196 (10), 154 (26), 153 (56), 123 (10), 82 (23).

4.17. (5*R*,8*R*)-8-Isopropyl-7,10-dimethoxy-3-methyl-6,9-diazaspiro[4.5]deca-2,6,9-triene-2-carbaldehyde 7c

Compound **7c** was obtained as above from (2′*S*,5′*R*)-3-[5-isopropyl-3,6-dimethoxy-2-(2-oxo-propyl)-2,5-dihydropyrazin-2-yl]propionaldehyde **4c** (0.600 g, 2.02 mmol) and caesium carbonate (0.666 g, 2.02 mmol). The reaction was run under reflux for 2 h. The product was isolated as a colourless oil after flash chromatography on silica gel using EtOAc/hexane 3:7; yield 0.196 g (35%); R_f 029; HRMS: M 278.1627; $C_{15}H_{22}N_2O_3$ requires 278.1630; $[\alpha]_D$ −70.2 (*c* 1.00, $CHCl_3$); ν_{max} (film/cm^{-1}) 2959, 2946, 2872, 2844, 1690, 1667, 1644, 1438, 1382, 1349, 1305, 1238; δ_H ($CDCl_3$) 0.65 and 1.01 (6H, 2d, *J* 6.8, CH(C*H*$_3$)$_2$), 1.12–2.23 (4H, m+1s, CH_3 and C*H*(CH$_3$)$_2$), 2.55–2.60 (2H, 2d, 2×C*H*H), 2.99 (1H, d, *J* 16.2, CH*H*), 3.20 (1H, d, *J* 18.8, CH*H*), 3.58 and 3.63 (6H, 2s, 2×OCH$_3$), 3.95 (1H, d, *J* 3.4, H-8), 9.96 (1H, s, CHO); δ_C ($CDCl_3$) 14.5 (CH_3), 17.3 and 19.7 (CH(*C*H$_3$)$_2$), 31.7 (*C*H(CH$_3$)$_2$), 47.0 (CH_2), 52.7 and 53.0 (2×OCH$_3$), 56.1 (CH_2), 60.9 (C-5), 61.6 (C-8), 135.9 (C-3), 159.5 (C-2), 162.5 and 165.2 (2×C=N), 188.2 (CHO); *m*/*z* (EI) 278 (M^+, 17%), 277 (12), 251 (31), 235 (73), 207 (13), 197 (100), 195 (15), 167 (17), 153 (24).

4.18. (*5R,8R*)-1-(8-Isopropyl-7,10-dimethoxy-3-methyl-6,9-diazaspiro[4.5]deca-2,6,9-trien-2-yl)ethanone 7d

Compound **7d** was prepared as above from (2′*S*,5,*R*)-4-[5-isopropyl-3,6-dimethoxy-2-(2-oxo-propyl)-2,5-dihydropyrazin-2-yl]butan-2-one **4d** (0.600 g, 1.93 mmol) and caesium carbonate (0.945 g, 2.9 mmol). The reaction mixture was heated under reflux for 4 h. The product was isolated as a colourless oil after flash chromatography on silica gel using EtOAc/hexane 3:7; yield 0.197 g (35%); R_f 0.36; HRMS: [M^++H] 293.1852; $C_{16}H_{24}N_2O_3$+H requires 293.1865; $[\alpha]_D$ −57.3 (*c* 1.00, $CHCl_3$); ν_{max} (film/cm^{-1}) 2958, 2954, 2872, 2843, 1690, 1657, 1635, 1619, 1462, 1437, 1365, 1305, 1227, 1200; δ_H ($CDCl_3$) 0.67 and 1.03 (6H, 2d, *J* 6.8, CH(C*H*$_3$)$_2$), 2.09 (3H, s, CH_3), 2.15–2.23 (4H, m and 1s, $COCH_3$ and C*H*(CH$_3$)$_2$), 2.51 (1H, d, *J* 17.8, C*H*H-4), 2.62 (1H, d, *J* 15.0, C*H*H-1), 3.13–3.19 (2H, 2d, CH*H*-4 and CH*H*-1), 3.60 and 3.66 (6H, 2s, 2×OCH$_3$), 3.96 (1H, d, *J* 3.4, H-8); δ_C ($CDCl_3$) 16.7 (CH_3), 16.9 and 19.3 (CH(*C*H$_3$)$_2$), 30.4 (CO*C*H$_3$), 31.3 (*C*H(CH$_3$)$_2$), 50.2 (C-1), 52.4 and 52.6 (2s, 2×O*C*H$_3$), 56.2 (C-4), 60.2 (C-5), 61.1 (C-8), 133.1 (C-3), 150.9 (C-2), 161.8 and 165.0 (2×C=N), 197.3 (CO); *m*/*z* (CI–CH_4) 293 (M^++H, 61%), 292 (20), 265 (8), 250 (18), 249 (100), 207 (18), 192 (6).

4.19. (5*S*,8*R*)-1-(8-Isopropyl-7,10-dimethoxy-6,9-diazaspiro[4.5]deca-1,6,9-trien-1-yl)ethanone 8c

The diketone **8c** was the second product eluted from the flash chromatography column in the experiment

described for the preparation of the carbaldehyde **7c** (vide supra) The product was obtained as an oily material; yield 0.235 g (42%); HRMS: M 278.1642; $C_{15}H_{22}N_2O_3$ requires 278.1630; $[\alpha]_D$ +30.7 (*c* 1.55, $CHCl_3$); ν_{max} (film/cm^{-1}) 2957, 2946, 2867, 1694, 1674, 1436, 1367, 1303, 1241, 1170; δ_H ($CDCl_3$) 0.67 and 1.05 (6H, 2d, *J* 6.8, $CH(CH_3)_2$), 1.93–2.01 (1H, m, $CHHCH_2$), 2.22–2.35 (5H, m+1s, $CH(CH_3)_2$, $CHHCH_2$ and $COCH_3$), 2.55–2.68 (2H, m, $CHHCH_2$), 3.56 and 3.59 (6H, 2s, 2×OCH_3), 4.09 (1H, d, *J* 5.2, H-8), 6.89 (1H, t, *J* 3.4, CH=); δ_C ($CDCl_3$) 17.0 and 19.4 ($CH(CH_3)_2$), 27.1 ($COCH_3$), 30.8 ($CH(CH_3)_2$), 31.5 and 39.9 (2×CH_2), 52.3 and 52.5 (2×OCH_3), 61.1 (C-8), 68.33 (C-5), 146.7 (C-1 and C-2), 163.3 (2×C=N), 194.8 ($COCH_3$); *m*/*z* (EI) 278 (M^+, 100%), 263 (61), 253 (18), 247 (23), 239 (99), 235 (91), 206 (57), 197 (60), 193 (21).

4.20. (5*S*,8*R*)-1-(8-Isopropyl-7,10-dimethoxy-2-methyl-6,9-diaza-spiro[4.5]deca-1,6,9-trien-1-yl)ethanone 8d

Compound **8d** was the second product eluted from the flash chromatography column in the reaction above with **4d** as substrate with formation of the methyl ketone **7d** (vide supra); yield of colourless oily material 0.214 g (38%); R_f 0.28; HRMS: $[M^+ + H]$ 293.1863; $C_{16}H_{24}N_2O_3$+H requires 293.1865; $[\alpha]_D$ −46.4 (*c* 1.00, $CHCl_3$); ν_{max} (film/cm^{-1}) 2959, 2945, 2871, 2843, 1686, 1619, 1461, 1435, 1358, 1305, 1285, 1241, 1097; δ_H ($CDCl_3$) 0.69 and 1.05 (6H, 2d, *J* 6.8, $CH(CH_3)_2$), 1.8–1.95 (1H, m, $CHHCH_2$), 2.02 (3H, s, CH_3), 2.11 (3H, s, $COCH_3$), 2.12–2.30 (2H, m, $CHHCH_2$ and $CH(CH_3)_2$), 2.52–2.7 (2H, m, $CHHCH_2$), 3.57 and 3.62 (6H, 2s, 2×OCH_3), 4.04 (1H, d, *J* 3.4, H-8); δ_C ($CDCl_3$) 17.2 and 19.4 ($CH(CH_3)_2$), 17.5 (CH_3), 29.8 ($COCH_3$), 31.2 ($CH(CH_3)_2$), 38.6 (C-3), 39.1 (C-4), 52.5 and 52.7 (2×OCH_3), 61.3 (C-8), 70.6 (C-5), 139.4 (C-2), 156.7 (C-1), 163.1 and 164.6 (2×C=N), 197.2 (CO); *m*/*z* (CI–CH_4) 293 (M^++H, 100%), 292 (53), 277 (36), 261 (13), 250 (9), 249 (38), 220 (26), 207 (5), 197 (8).

4.21. Hydrolytic formation of cyclic α-amino acid esters

The bicyclic products **7a**–**d** and **8c**,**d** (0.50 mmol) were separately stirred with trifluoroacetic acid (25 mL, 5.0 mmol, 0.2 M) in acetonitrile (25 mL) at ambient temperature for 3 d. The solution was evaporated almost to dryness at reduced pressure, water (10 mL) and dichloromethane (20 mL) were added and the aqueous layer made alkaline (pH 10) by addition of concd aq ammonia. The mixture was extracted with dichloromethane (2×20 mL), the combined organic layers dried ($MgSO_4$), evaporated and the product isolated from the residual material after flash chromatography on silica gel using MeOH/CH_2Cl_2 1:20.

4.22. (1*S*)-1-Amino-4-methyl-2-oxo-cyclopent-3-enecarboxylic acid methyl ester 9a

Compound **9a** was a colourless oil; yield 0.047 g (56%); R_f 0.25; HRMS: M 169.0742; $C_8H_{11}NO_3$ requires 169.0738; $[\alpha]_D$ +34.2 (*c* 0.77, CH_2Cl_2); ν_{max} (film/cm^{-1}) 3368, 3306, 2959, 2923, 1744, 1705, 1621, 1435, 1255, 1204, 1149, 1067; δ_H ($CDCl_3$) 1.96–2.04 (2H, br s, NH_2), 2.06 (3H, s, CH_3), 2.52 (1H, d, *J* 18.3, CHH), 3.09 (1H, d, *J* 18.3, CHH), 3.69 (3H, s, CO_2CH_3), 5.95 (1H, s, CH); δ_C ($CDCl_3$) 19.5 (CH_3), 47.2 (CH_2), 52.9 (CO_2CH_3), 66.1 (C-1), 127.2 (CH=), 174.6 (CO_2CH_3), 178.3 (C=), 204.2 (CO); *m*/*z* (EI) 169 (M^+, 10%), 154 (6), 149 (7), 126 (5), 111 (19), 110 (100), 82 (17).

4.23. (1*S*)-1-Amino-4-methyl-2-oxo-cyclohex-3-enecarboxylic acid methyl ester 9b

The product **9b** was a colourless oil; yield 0.054 g (59%). R_f 0.26; HRMS: $[M^+ + H]$ 184.0973; $C_9H_{13}NO_3$+H requires 184.0973; $[\alpha]_D$ −39.8 (*c* 1.28, $CHCl_3$); ν_{max} (film/cm^{-1}) 3383, 3314, 2954, 2925, 2851, 1735, 1670, 1633, 1435, 1381, 1247, 1172. δ_H ($CDCl_3$) 1.94 (3H, s, CH_3), 1.89–2.05 (3H, m, NH_2 and $CHHCH_2$), 2.35–2.49 (3H, m, $CHHCH_2$), 3.68 (3H, s, OCH_3), 5.90 (1H, s, CH); δ_C ($CDCl_3$) 24.7 (CH_3), 29.0 (CH_2CH_2), 33.9 (CH_2CH_2), 53.1 (OCH_3), 63.7 (C-1), 125.0 (C=*C*H), 163.6 (*C*=CH), 173.6 (C=N), 193.6 (CO_2Me), 195.3 (CO); *m*/*z* (CI–CH_4) 184 (M^++H, 100%), 167 (8), 166 (13), 135 (10), 124 (74), 96 (14), 82 (24).

4.24. (1*S*)-2-Acetyl-1-amino-cyclopent-2-enecarboxylic acid methyl ester 9c

The product **9c** was a colourless oil; yield 0.043 g (47%). R_f 0.2; HRMS (electrospray): $[M^+ + H]$ 184.0977; $C_9H_{13}NO_3$+H requires 184.0968; $[\alpha]_D$ +74.2 (*c* 1.00, CH_2Cl_2); ν_{max} (film/cm^{-1}) 3367, 3302, 2953, 1735, 1674, 1651, 1593, 1437, 1378, 1276, 1258, 1178, 1086; δ_H ($CDCl_3$) 1.88–1.94 (1H, m, $CHHCH_2$), 2.06 (2H, br s, NH_2), 2.24–2.31 (4H, m+1s, $COCH_3$ and $CHHCH_2$), 2.61–2.9 (2H, m, $CHHCH_2$), 3.63 (3H, s, CO_2CH_3), 6.85 (1H, t, *J* 2.6, CH=); δ_C ($CDCl_3$) 26.6 ($COCH_3$), 31.5 and 38.3 (2×CH_2), 52.4 (CO_2CH_3), 68.4 (C-1), 147.0 (C-3), 147.4 (C-2), 176.7 (CO_2CH_3), 195.8 ($COCH_3$); *m*/*z* (CI–CH_4) 184 (M^++H, 7%), 135 (17), 124 (100), 72 (82).

4.25. (1*R*)-3-Acetyl-1-amino-4-methylcyclopent-3-enecarboxylic acid methyl ester 11

The product **11** was a colourless oil; yield 0.057 g (58%). R_f 0.23; HRMS: $[M^+ + H]$ 198.1120; $C_{10}H_{15}NO_3$+H requires 198.1130; $[\alpha]_D$ +40.0 (*c* 1.00, CH_2Cl_2); ν_{max} (film/cm^{-1}) 3368, 3301, 2954, 2923, 1732, 1678, 1650, 1631, 1617, 1434, 1361, 1221, 1064; δ_H ($CDCl_3$) 1.82 (2H, br s, NH_2), 2.08 (3H, s, CH_3), 2.22 (3H, s, $COCH_3$), 2.40 (1H, d, *J* 17.5, CHH-5), 2.61 (1H, d, *J* 14.7, CHH-2), 3.15–3.26 (2H, 2d, CHH-5 and CHH-2), 3.70 (3H, s, CO_2CH_3); δ_C ($CDCl_3$) 16.7 (CH_3), 30.3 ($COCH_3$), 48.0 (C-2), 52.5 (CO_2CH_3), 53.7 (C-5), 61.0 (C-1), 132.9 (C-4), 150.1 (C-3), 176.3 (CO_2CH_3), 196.9 ($COCH_3$); *m*/*z* (CI–CH_4) 198 (M^++H, 9%), 181 (6), 154 (6), 149 (11), 139 (12), 138 (199), 96 (12), 95 (7), 94 (8).

4.26. (1′*R*,2*R*)-2-[(3-Acetyl-1-amino-4-methylcyclopent-3-enecarbonyl)amino]-3-methylbutyric acid methyl ester 12

The dipeptide **12** was formed by partial hydrolysis in the above reaction from the bicyclic substrate **7d**, and was the first product eluted from the flash chromatography column in the above reaction. The dipeptide **11** thus obtained was an oily material; yield 0.022 g (15%); R_f 0.33; HRMS: [M$^+$+H] 297.1816; $C_{15}H_{24}N_2O_4$+H requires 297.1814; $[\alpha]_D$ +41.3 (*c* 1.00, CH_2Cl_2); ν_{max} (film/cm^{-1}) 3362, 2964, 2933, 2876, 1740, 1713, 1674, 1616, 1509, 1466, 1437, 1371, 1312, 12611211; δ_H ($CDCl_3$) 0.88–0.93 (6H, 2d, CH(C*H*$_3$)$_2$), 1.80 (2H, br s, NH_2), 2.08 (3H, s, CH_3), 2.12–2.22 (4H, s+m, $COCH_3$ and C*H*(CH$_3$)$_2$), 2.29 (1H, d, *J* 18.4, C*H*H-5), 2.53 (1H, d, *J* 15.9, C*H*H-2), 3.31–3.47 (2H, 2d, CH*H*-5 and CH*H*-2), 3.70 (3H, s, CO_2CH_3), 4.44–4.49 (1H, dd, *J* 4.7, *J* 8.9, C*H*NH), 8.10 (2H, d, *J* 8.9, NH); δ_C ($CDCl_3$) 16.8 (CH_3), 17.7 and 19.1 (CH(*C*H$_3$)$_2$), 30.3 (CO*C*H$_3$), 31.1 (*C*H(CH$_3$)$_2$), 49.3 (C-2), 52.0 (CO_2CH_3), 55.0 (C-5), 57.2 (NHCH), 61.9 (C-1), 132.6 (C-4), 150.7 (C-3), 172.4 (CONH), 175.7 (*C*O$_2$CH$_3$), 197.3 (*C*OCH$_3$); *m*/*z* (CI–CH_4) 297 (M$^+$+H, 24%), 280 (25), 269 (8), 149 (11), 138 (100), 137 (17), 132 (12), 111 (8), 110 (29), 96 (14), 72 (8).

4.27. (1*S*)-2-Acetyl-1-amino-3-methyl-cyclopent-2-enecarboxylic acid methyl ester 13

The product **13** was a colourless oil; yield 0.057 g (51%). R_f 0.18; HRMS: [M+H] 198.1137; $C_{10}H_{15}NO_3$+H requires 198.1130; $[\alpha]_D$ +81.9 (*c* 0.76, CH_2Cl_2); ν_{max} (film/cm^{-1}) 3368, 3304, 2953, 1736, 1673, 1651, 1593, 1434, 1378, 1367, 1276, 1259, 1178, 1086; δ_H ($CDCl_3$) 1.75–1.81 (1H, m, C*H*HCH$_2$), 2.07–2.18 (4H, m + s, CH*H*CH$_2$ and C*H*$_3$), 2.20–2.41 (5H, br s + s, NH_2 and $COCH_3$), 2.50–2.63 (1H, m, CHHC*H*H), 2.71–2.83 (1H, m, CHHCH*H*), 3.65 (3H, s, CO_2CH_3); δ_C ($CDCl_3$) 17.5 (CH_3), 30.5 (CO*C*H$_3$), 36.2 (CH$_2$*C*H$_2$), 39.4 (*C*H$_2$CH$_2$), 52.4 (CO_2CH_3), 71.2 (C-1), 140.9 (C-3), 156.4 (C-2), 177.1 (*C*O$_2$CH$_3$), 196.9 (CO); *m*/*z* (CI–CH_4) 198 (M$^+$+H, 5%), 181 (5), 152 (9), 149 (22), 138 (100), 96 (18), 72 (9).

4.28. (1′*S*,2*R*)-2-[(2-Acetyl-1-amino-3-methylcyclopent-2-enecarbonyl)amino]-3-methylbutyric acid methyl ester 14

The dipeptide **14** was formed by partial hydrolysis in the above reaction from the bicyclic substrate **8d**, and was the first product eluted from the flash chromatography column in the above reaction. The dipeptide **13** thus obtained was an oily material; yield 0.015 g (10%); R_f 0.25; HRMS: [M$^+$+H] 297.1808; $C_{15}H_{24}N_2O_4$+1 requires 297.1814; $[\alpha]_D$ +52.8 (*c* 0.50, CH_2Cl_2); ν_{max} (film/cm^{-1}) 3368, 2963, 2930, 2875, 1740, 1671, 1655, 1510, 1436, 1371, 1267, 1154; δ_H ($CDCl_3$) 0.85–0.91 (6H, 2d, CH(C*H*$_3$)$_2$), 1.75–1.81 (1H, m, C*H*HCH$_2$), 2.02 (3H, s, CH_3), 2.03–2.30 (4H, m, CH*H*CH$_2$, NH_2 and C*H*(CH$_3$)$_2$), 2.33 (3H, s, $COCH_3$), 2.58–2.63 (2H, m, CHHC*H*$_2$), 3.72 (3H, s, CO_2CH_3), 3.73–3.49 (1H, dd, *J* 4.8, *J* 9.0, C*H*NH), 7.74 (1H, d, *J* 9.0, CHN*H*); δ_C ($CDCl_3$) 17.6 (*C*H$_3$), 17.7 and 19.0 (CH(*C*H$_3$)$_2$), 30.8 (CO*C*H$_3$), 31.4 (*C*H(CH$_3$)$_2$), 35.8 (CH$_2$*C*H$_2$), 38.9 (*C*H$_2$CH$_2$), 52.1 (CO_2CH_3), 57.1 (NHCH), 72.8 (C-1), 141.5 (C-3), 154.3 (C-2), 172.3 (CONH), 174.3 (*C*O$_2$CH$_3$), 198.0 (*C*OCH$_3$); *m*/*z* (CI–CH_4) 297 (17), 289 (10), 198 (6), 139 (10), 138 (100), 96 (10).

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