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A stereoselective synthesis of a spiro-bridged bis(α-amino acid) derivative based on Ru(II)-catalysed RCM reactions

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Abstract—Methodology for a stereoselective synthesis of a member of a novel family of spiro-bridged bis(α-amino acid) derivatives is described. The key step in the construction is a spirane annulation reaction effected by a Ru(II)-catalysed ring-closing metathesis (RCM) reaction of an appropriately substituted tetraene. The latter became available after stereocontrolled allylations of 3,3-bis[2-((2*S*,5*R*)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)ethyl]-1,4-pentadiene, which was prepared in several reaction steps from (2*R*)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine as a chiral starting material.
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1. Introduction

Cystine is a central structural element in peptide and protein architecture widely distributed in living matter, which can be regarded as a four-atom bridged bis(α-glycine).

When cystine exerts mainly a skeletal, structural function, isosteric structures may be envisaged to take its place where the natural $-CH_2S_2CH_2-$bridged has been replaced with an all-carbon C_4-bridge, a dicarba analogue.[1] In some cases it may also be desirable to replace cystine with a non-reducible isosteric analogue. Besides reports on the preparation of cystine dicarba analogues, the literature provides several reports on the preparation of C_3-bridged glycines because members of the C_3-bridge family naturally occur in certain microorganisms and higher order plants.[2] Reports on additions to C_1-bridged derivatives,[3] to C_2-bridged derivatives,[4] a C_5-bridged structure,[5] and higher member functionalised bridges have been described.[6]

As a general rule, substitution at the α-carbon results in a more highly constrained α-amino acid. The resultant conformationally constrained α-quaternary α-amino acid, when incorporated into peptides, will affect secondary and tertiary peptide structures and thereby provide useful information about structural requirements for bioactivity.[7] Conformational restriction is especially pronounced in α-quaternary α-amino acids,[8] and in particular when the α-carbon of the amino acid is imbedded in a cyclic structure.[9] In another group of α-quaternary α-amino acids, the amino nitrogen is imbedded in the ring with the α-substituent and the carboxy group situated at the same adjacent vicinal ring carbon.[10]

Stereocontrolled constructions of rigid *as*-indacene-bridged bis(α-amino acid) and higher ring homologues have recently been described and are illustrated by structure **A** in Figure 1.[11,12] In the indacenes, the amino and carboxy groups are attached to a quasiplanar bridge. In the (*R*,*R*)-configuration as drawn in Figure 1, the amino and the carboxy groups have a trans relationship. In spiranes, the amino and carboxy groups as well as the two spirane rings are fixed in an orthogonal relationship. A unique family of novel spiro-bridged bis(α-amino acid) derivatives thereby becomes accessible. A literature search revealed no members of this family of amino acids.

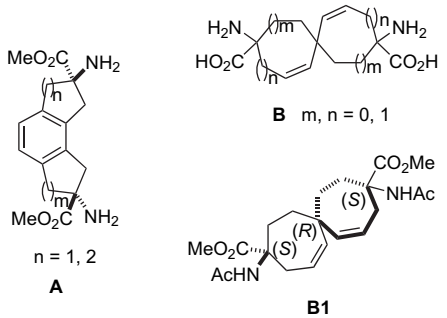

Figure 1. Rigidified substitutes for cystine.

Keywords: Cystine substitutes; Cystine carba analogues; Spiro-bridged bis(α-amino acids); RCM in spirane formation; Stereoselective synthesis.
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2. Results and discussion

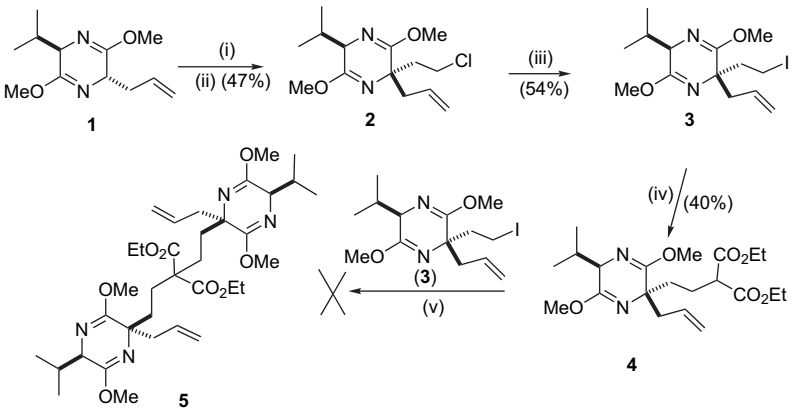
We herein describe the preparation of the first member of a spiro-bridged bis(amino acid) derivative. The key step in the methodology involves a Ru(II)-catalysed ring-closing metathesis (RCM) reaction of an appropriate tetraene substrate (Scheme 4). Hence the spirane products are dienes, which can be further manipulated by reactions of the double bonds in the spirane; hydrogenation would provide the saturated spirane analogue. But the RCM methodology limits the ring sizes in the spirane to five-, six- and seven-membered rings. Within this limit, equal or unequal rings constituting the two-ring spirane can in principle be constructed depending on the symmetry of the tetraene substrate. We report on the synthesis of spirane with an equal ring size, viz. a spiro-[6,6]trideca-5,12-diene, structure **B** (m=n=1) in Figure 1.

The stereochemistry at the α-amino carbons was controlled by the use of (2*R*)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine as a chiral starting material. Little or no control of the stereochemistry at the new stereogenic spirocarbon was expected with this methodology. A diastereomeric mixture of the two possible spiranes is formed (vide infra), which subsequently would require a separation step.

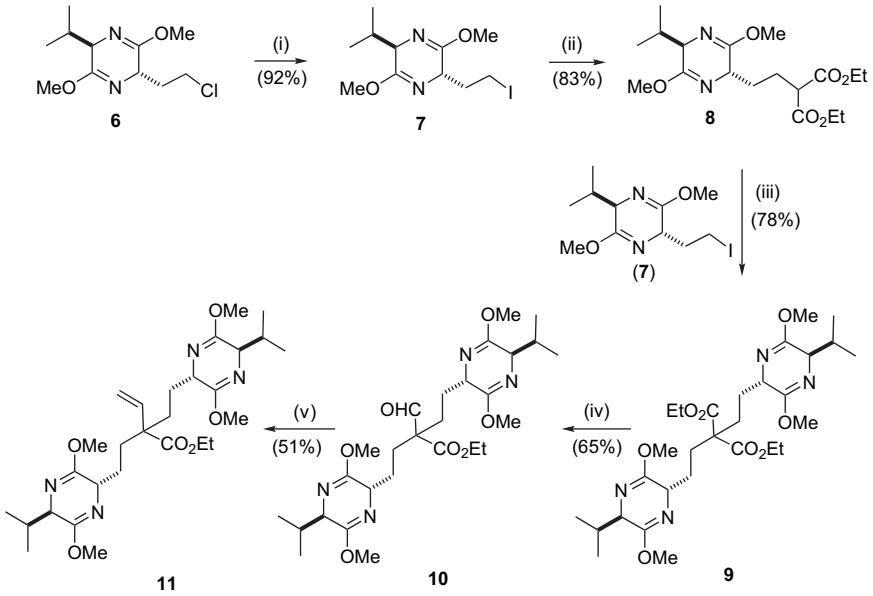
A successful synthesis of a tetraene, as a substrate for the RCM reaction, is outlined in Scheme 3. Scheme 1 shows an initial synthetic failure. The chiral starting material, the bislactim ether (2*R*)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine, was allylated to provide substrate **1**.[13] The configuration at the valine α-carbon also controls the steric induction during the *gem*-dialkylation at the α-glycine carbon, which is to become the α-quaternary carbon in the new α-amino acid derivative. Once the new α-amino acid carbon has become quaternary, racemisation at this carbon cannot occur. The *gem*-dialkylation of the allyl derivative **1** was run at −78 °C in THF using *n*-BuLi as a base and an excess of 1-bromo-2-chloroethane as the alkylating reagent. The new alkylating agent will approach the carbanion site in a trans manner with respect to the isopropyl group. The diastereoselectivity in the second alkylation step is high. When the monoalkylated product is lithiated for a second alkylation, the original stereochemistry at the glycyl carbon as an anionic site is lost. The chloroethyl electrophile becomes attached trans to the isopropyl group (de 85%) in structure **2**. Schöllkopf has also reported high diastereoselectivity in *gem*-dialkylations.[14] In selected cases from our analogous earlier work, the stereochemical course has been verified by X-ray analyses.[15] The analyses include bridged structures with some resemblance to structure **15** in Scheme 3.[11,12] Furthermore, the ^{1}H and ^{13}C NMR spectra of the bridged compounds are consistent with C_2-symmetry. Therefore the new chiral quaternary sites (compound **15**) have the same configuration.

The chloro derivative **2** was converted into the corresponding iodo compound **3** by a Finkelstein reaction. A malonate synthesis provided the alkylated malonate **4**, which was to act as a substrate for a second alkylation thereby providing the malonate-bridged structure **5**. We were not able to effect the second alkylation in a satisfactory yield, presumably because of steric interactions. Therefore the allyl group has to be introduced after the malonate-bridge forming reaction in substrate **14** in Scheme 3. The new substrate was the chloroethyl derivative **6**, which was available from the lithiated chiron at −78 °C and 1-bromo-2-chloroethane (Scheme 2).

A Finkelstein reaction provided the more reactive iodo electrophile **7** for the malonate alkylation, which subsequently proceeded well with NaH as base in THF. Under these conditions no proton abstraction at the pyrazine ring system takes place. In contrast to the reactions given in Scheme 1, the second alkylation of the malonate **8** proceeded to give the dialkylated malonate **9** in 78% yield. Reduction of the malonate diester **9** with DIBAL in toluene at −78 °C led to selective reduction of only one of the ester groups. The monoaldehyde **10** was isolated in 65% yield. The formyl function was required for a Wittig reaction to provide a vinyl group for a subsequent Ru(II)-catalysed RCM spirane annulation. The Wittig reaction proceeded as planned with the aldehyde **10** as substrate to provide the olefin **11**. The selective aldehyde formation and subsequent olefination provide an intermediate **11** suitable for conversion into an unsymmetrical diene, after transforming the remaining ester group into a formyl group, followed by olefination (vide infra). In this work, however, the aim was to prepare a symmetrical spirane, and the transformation of both ester groups to formyl groups was effected in the same two-step process (Scheme 3).

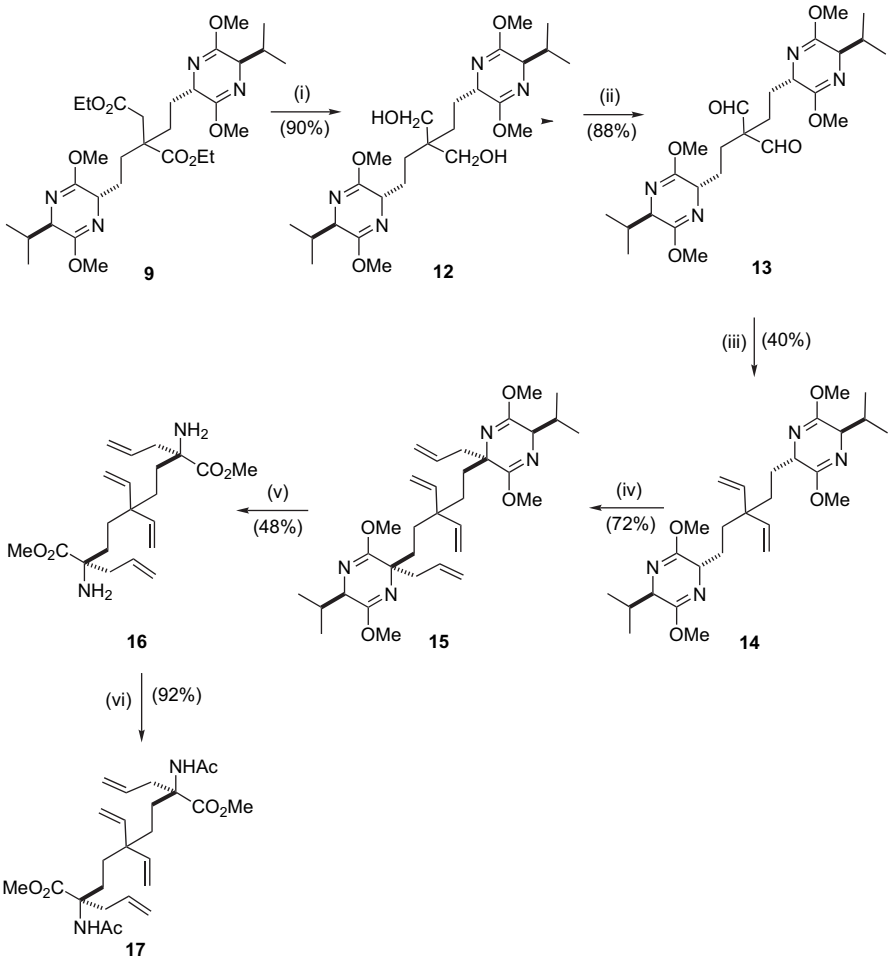


Scheme 1. Reagents and conditions: (i) *n*-BuLi, THF, −78 °C, 0.5 h; (ii) $BrCH_2CH_2Cl$, −78 °C to rt, 5 h; (iii) NaI, DMF, 78 °C, 40 h; (iv) NaH, THF, $CH_2(CO_2Et)_2$, reflux, 24 h; (v) NaH, THF.



Scheme 2. Reagents and conditions: (i) NaI, acetone, reflux, 24 h; (ii) NaH, THF, $CH_2(CO_2Et)_2$, reflux, 12 h; (iii) NaH, THF, reflux, 24 h; (iv) DIBAL, toluene, −78 °C, 30 min; (v) $MePPh_3$-Br, $NaNH_2$, THF, rt, 1 h.

The malonate **9** in Scheme 3 could be reduced to the corresponding diol **12** by LAH in THF in the cold in excellent yield (90%). A subsequent oxidation with the Dess–Martin periodinane reagent,[16] provided the dialdehyde **13** in a similar yield. The latter, however, was chemically unstable and was therefore reacted further as a crude substrate with



Scheme 3. Reagents and conditions: (i) LAH, THF, 0 °C to rt, 3 h; (ii) Dess–Martin periodinane reagent, CH_2Cl_2, rt, 1 h; (iii) $MePPh_3$-Br, $NaNH_2$, THF, 0 °C, 1 h; (iv) (a) *n*-BuLi, THF, −50 °C, 1 h; (b) allyl-Br, −78 °C to rt, 14 h; (v) 0.1 M TFA, MeCN, H_2O, rt, 5 d; (vi) Ac_2O, DMAP, CH_2Cl_2, rt, 3 h.

commercially available Wittig methyl reagent, a 1:1 mixture of methyl(triphenyl)phosphonium bromide and sodium amide. The overall yield was 40% for the purified divinylated product **14** after the two steps from substrate **12**.

Introduction of the second pair of carbon double bonds was effected by allylation. The substrate **14** was very sensitive to the reaction conditions. It was important to secure complete dilithiation of the substrate, which was achieved with *n*-BuLi in THF between −50 and −60 °C. The bis-allylation procedure provided the product **15** in 72% yield. The first alkylation involves the lithiated species **14**, whereas the first formed product is the substrate for the second alkylation. Furthermore, the allylation in both reactions appears to be stereochemically clean in that only one dialkylated product was detected by NMR spectroscopy and TLC. In this process, the configuration at the pyrazine 2-position becomes inverted because the allyl electrophile adds in a trans manner to the isopropyl group. However, both centres in the substrate and the product are assigned a (*S*)-configuration based on the priority rule in describing such configurations. The NMR spectra exhibit C_2-symmetry inferring that the configuration is identical in both stereogenic heterocyclic centres.

Attempts to apply the Ru(II)-catalysed RCM reaction with the Grubbs-I catalyst, bis(tricyclohexylphosphine)benzylidene ruthenium dichloride, to the tetraene **15** for spirane annulation (structure **18** in Scheme 4) were unsatisfactory. The failure is ascribed mainly to a sterically congested substrate. The more reactive Grubbs-II catalyst also failed to effect spiroannulation.[17]

Therefore, to decrease the steric bulkiness, the bislactim heterocycle was cleaved under weakly acidic conditions. The use of 0.1 M TFA in aqueous acetonitrile at ambient temperature provided the dimethyl ester of the highly functionalised bis(α-amino acid) **16** (Scheme 3). The hydrolysis was slow and was accompanied by partially hydrolysed products. Strongly acidic conditions should be avoided, however, since the hydrolysis leads to an undesirable pathway.[18]

Before the Ru(II)-catalysed RCM reactions, the bis(amino acid) ester **16** was N-protected as the diacetyl derivative **17**. The less bulky acyclic bis(amino) acid **17** was a good substrate for the RCM reaction, which proceeded in toluene at 85 °C over 4 h, using 10 mol % catalyst. The spiranes **19** and **20** were isolated in 73% yield as a mixture of the two diastereomers in a ratio 3:2 (Scheme 4) as indicated by NMR. The isomers were separated by repeated flash chromatography. Both diastereomers were strongly levorotatory in CH_2Cl_2 at room temperature with specific rotation for major isomer: $[\alpha]_D$ −99.5 (CH_2Cl_2) and for the minor isomer: $[\alpha]_D$ −144.3 (CH_2Cl_2). For comparison, the specific rotation for the acyclic precursor amino acid derivative **17** was $[\alpha]_D$ +9.6 (CH_2Cl_2). Both the ^1H and ^{13}C NMR spectra were clearly different for the two isomers, but so far attempts to assign the respective configuration to the spiro centre by NOE at ordinary or higher temperatures have failed. Unfortunately, the microcrystalline states of the products have precluded X-ray analysis for configurational assignments at the spiro centre.

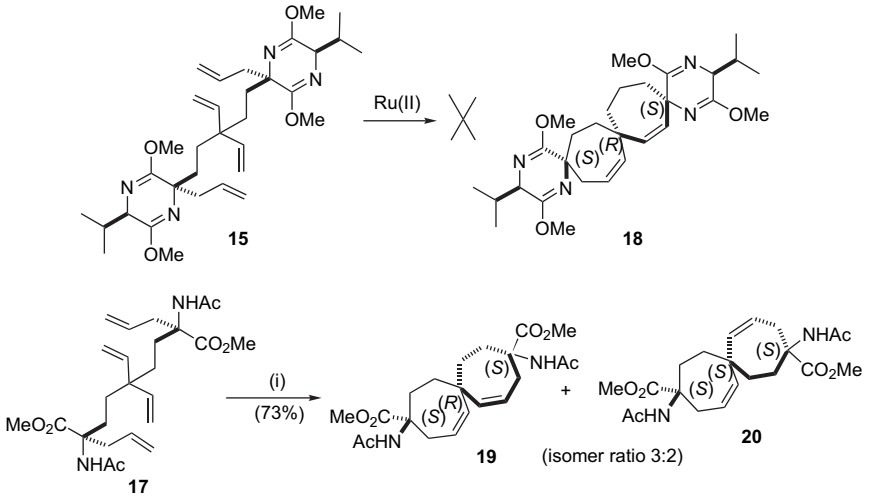
3. Conclusion

A stereoselective synthesis of a member of a novel family of spiro-bridged bis(α-amino acid) derivatives has been achieved from (2*R*)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine as a chiral starting material. The spirane skeleton was constructed by an annulation, which was effected by a Ru(II)-catalysed RCM reaction of an appropriately substituted tetraene. The latter became available after stereocontrolled allylations of 3,3-bis[2-((2*S*,5*R*)-2-allyl-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)ethyl]-1,4-pentadiene as an intermediate. The target molecules are cystine substitutes, which could bridge a peptide, or peptide like structures, in an orthogonal manner.

4. Experimental

4.1. General

^1H 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 NMR spectra were recorded in $CDCl_3$ at 125, 75



Scheme 4. Reagents and conditions: (i) 10% Ru(II), toluene, 85 °C, 4 h.

or 50 MHz. Chemical shifts are reported in parts per million with residual $CHCl_3$ (7.24 ppm) and $CDCl_3$ (77 ppm) as references. *J* values are given in Hertz. Mass spectra under electron-impact condition (EI) were recorded at 70 eV ionising potential; methane was used for chemical ionisation (CI). IR spectra were recorded on a Perkin–Elmer 1310 infrared spectrophotometer or a Nicolet Magna FTIR 550 spectrophotometer with attenuated total reflectance (ATR spectra). Specific rotation values are given in 10^{-1} deg cm^2 g^{-1}.

Dry THF was distilled from sodium and benzophenone under argon. Argon was bubbled through toluene to remove any oxygen.

4.1.1. (2*S*,5*R*)-2-Allyl-2-(2-chloroethyl)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine (2). A solution of *n*-BuLi in hexane (1.38 M, 0.71 mL, 0.98 mmol) was added via a syringe over 5 min to a solution of (2*S*,5*R*)-2-allyl-2,5-dihydro-3,6-dimethoxy-5-isopropylpyrazine[13] (0.200 g, 0.89 mmol) in dry THF (3 mL) at −78 °C, under argon. The mixture was stirred for 30 min before a solution of 1-bromo-2-chloroethane (0.382 mg, 0.22 mL, 2.67 mmol) in dry THF (2.5 mL) was added dropwise over 5 min. The solution was stirred at −78 °C for 5 h and the reaction quenched by the addition of phosphate buffer of pH 7 (5 mL). The mixture was extracted with diethyl ether (3×10 mL), the combined organic extracts were dried ($MgSO_4$) and the solvent distilled off. The product was further purified by flash chromatography using hexane/Et_2O 20:1, R_f 0.45; yield 0.120 g (47%) of a colourless oily material. HRMS (CI) M+H: 287.1330; calcd for $C_{14}H_{23}O_2N_2$ Cl+H: 287.1340; ν_{max} (film/cm^{-1}): 2960, 2945, 2871, 1691, 1461, 1437, 1308, 1239, 1197; δ_H ($CHCl_3$): 0.65 and 1.06 (6H, 2d, *J* 6.9 Hz, CH(C*H*$_3$)$_2$), 1.97–2.06 (1H, m, C*H*HCH$_2$Cl), 2.10–2.32 (2H, m, CH*H*CH$_2$Cl and C*H*(CH$_3$)$_2$), 2.34–2.39 (1H, m, C*H*HCH=CH$_2$), 2.45–2.55 (1H, m, CH*H*CH=CH$_2$), 3.21–3.38 (2H, m, CH$_2$C*H*$_2$Cl), 3.64 (6H, s, 2×OC*H*$_3$), 3.87 (1H, d, *J* 3.4 Hz, H-5), 4.96–5.03 (2H, m, CH=C*H*$_2$), 5.67–5.69 (1H, m, C*H*=CH$_2$); δ_C ($CDCl_3$): 17.3 and 19.5 (CH(*C*H$_3$)$_2$), 30.7 (*C*H(CH$_3$)$_2$), 40.3 and 42.6 (*C*H$_2$*C*H$_2$Cl), 45.05 (*C*H$_2$CH=CH$_2$), 52.3 and 52.4 (2×OCH$_3$), 60.65 (C-5) and 60.7 (C-2), 118.0 (CH=*C*H$_2$), 133.7 (*C*H=CH$_2$), 162.9 and 163.0 (2×C=N); *m*/*z* (EI): 286 (M$^+$, 5%), 285 (15), 275 (6), 259 (14), 245 (100), 243 (64), 239 (21), 218 (24), 196 (37), 181 (32).

4.1.2. (2*S*,5*R*)-2-Allyl-2-(2-iodoethyl)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine (3). A solution of (2*S*,5*R*)-2-allyl-2-(2-chloroethyl)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine (**2**) (0.370 g, 1.3 mmol) and NaI (0.975 g, 6.5 mmol) in DMF (5 mL) was stirred at 78 °C under argon for 40 h. The solvent was removed and the residual material shaken with water (10 mL) and diethyl ether (10 mL). The layers were allowed to separate, the water layer extracted twice with diethyl ether (10 mL), the combined ether extracts were dried ($MgSO_4$) and the ether distilled off. The crude product was purified by flash chromatography on silica gel using hexane/Et_2O 20:1, R_f 0.52; yield 0.265 g (54%) of a colourless oil. HRMS (EI) M: 378.0805. Calcd for $C_{14}H_{23}O_2N_2I$: 378.0804; ν_{max} (film/cm^{-1}): 2960, 2947, 2871, 1690, 1462, 1437, 1238, 1196; δ_H ($CHCl_3$): 0.64 and 1.04 (6H, 2 d, *J* 7.2 Hz, CH(C*H*$_3$)$_2$), 2.14–2.45 (5H, m, C*H*$_2$CH$_2$I, C*H*(CH$_3$)$_2$ and C*H*$_2$CH=CH$_2$), 2.77–2.89 (2H, m, CH$_2$C*H*$_2$I), 3.64 (6H, s, 2×OC*H*$_3$), 3.86 (1H, d, *J* 3.5 Hz, H-5), 4.94 and 5.04 (2H, m, CH=C*H*$_2$), 5.53–5.62 (1H, m, C*H*=CH$_2$); δ_C ($CDCl_3$): 1.00 (CH$_2$*C*H$_2$I), 17.3 and 19.5 (CH(*C*H$_3$)$_2$), 30.7 (*C*H(CH$_3$)$_2$), 44.6 and 44.7 (*C*H$_2$CH$_2$I and *C*H$_2$CH=CH$_2$), 52.3 and 52.4 (2×OCH$_3$), 60.8 (C-5) and 63.3 (C-2), 118.0 (CH=*C*H$_2$), 133.7 (*C*H=CH$_2$), 163.15 (2×C=N); *m*/*z* (EI): 378 (M$^+$, 1%), 338 (13), 337 (98), 295 (100), 251 (5), 223 (14), 181 (38), 167 (45).

4.1.3. (2*R*,5*R*)-2-[2-(2-Allyl-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)ethyl]malonic acid diethyl ester (4). A flask containing a suspension of NaH (0.034 g of a 57% suspension in mineral oil, 0.8 mmol) in dry THF (5 mL) was cooled in an ice-bath while diethyl malonate (0.11 g, 0.1 mL, 0.74 mmol) was added dropwise under argon. The mixture was stirred at room temperature for 30 min before a solution of (2*S*,5*R*)-2-allyl-2-(2-iodoethyl)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine (**3**) (0.280 g, 0.74 mmol) in dry THF (5 mL) was added dropwise over 5 min. The mixture was heated at reflux for 24 h, cooled at 0 °C and 5% aqueous HCl was added cautiously (pH 7). The water layer was washed with diethyl ether (3×10 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent distilled off. The product was further purified by flash chromatography using hexane/EtOAc 9:1, R_f 0.28; yield 0.110 g (40%) of an oily material. HRMS (EI) M: 410.2405. Calcd for $C_{21}H_{34}O_6N_2$: 410.2416; ν_{max} (film/cm^{-1}): 2981, 2871, 1735, 1729, 1694, 1461, 1438, 1308, 1239, 1197; δ_H ($CDCl_3$): 0.62 and 1.03 (6H, 2 d, *J* 6.8 Hz, CH(C*H*$_3$)$_2$), 1.23 (6H, t, *J* 7.1 Hz, 2×OCH$_2$C*H*$_3$), 1.50–1.76 (4 H, m, C*H*$_2$C*H*$_2$CH(CO$_2$Et)$_2$), 2.20–2.34 (2H, m, C*H*(CH$_3$)$_2$ and C*H*HCH=CH$_2$), 2.44–2.58 (1H, m, CH*H*CH=CH$_2$), 3.20 (1H, t, *J* 7.0 Hz, C*H*(CO$_2$Et)$_2$), 3.63 and 3.64 (6H, s, 2×OC*H*$_3$), 3.88 (1H, d, *J* 3.6 Hz, H-5), 4.14 (4 H, q, *J* 7.1 Hz, 2×OC*H*$_2$CH$_3$), 4.91–5.03 (2H, m, CH=C*H*$_2$), 5.55–5.63 (1H, m, C*H*=CH$_2$); δ_C ($CDCl_3$): 14.0 (2×OCH$_2$*C*H$_3$), 17.2 and 19.5 (CH(*C*H$_3$)$_2$), 30.5 (*C*H(CH$_3$)$_2$), 37.6 and 41.6 (*C*H$_2$*C*H$_2$CH(CO$_2$Et)$_2$), 44.9 (*C*H$_2$CH=CH$_2$), 51.8 (*C*H(CO$_2$Et)$_2$), 52.1 and 52.3 (2×OCH$_3$), 60.6 (C-2) and 61.2 (2×O*C*H$_2$CH$_3$), 61.5 (C-5), 117.5 (CH=*C*H$_2$), 134.3 (*C*H=CH$_2$), 162.7 and 163.2 (2×C=N), 166.6 and 169.2 (2×*C*O$_2$Et); *m*/*z* (EI): 410 (M$^+$, 4%), 370 (21), 369 (100), 365 (15), 235 (20), 223 (10), 181 (16), 167 (12).

4.1.4. (2*S*,5*R*)-2-(2′-Chloroethyl)-2,5-dihydro-3,6-dimethoxy-5-isopropylpyrazine (6). 1-Bromo-2-chloroethane (7.00 g, 4 mL, 48.8 mmol) in THF (15 mL) was added with stirring to a solution prepared from (2*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (3.00 g, 16.29 mmol), THF (50 mL) and *n*-BuLi (13 mL, 17.92 mmol, 1.38 M in hexane) under argon at −78 °C. Stirring was continued at −78 °C for 5 h and the mixture left to reach room temperature overnight. The reaction was quenched by addition of phosphate buffer of pH 7 (35 mL). The mixture was extracted with diethyl ether (3×30 mL), the extracts were dried ($MgSO_4$) and the solvent evaporated. The crude product was purified by flash chromatography on silica gel using hexane/Et_2O 20:1, R_f 0.38; yield 3.1 g (78%, de 85%). The minor isomer was removed by flash chromatography. The title compound was a colourless oil. HRMS (EI) M: 246.1138. Calcd for $C_{11}H_{19}O_2N_2Cl$: 246.1135; ν_{max} (film/cm^{-1}): 2961, 2946, 2872, 1694, 1462, 1437, 1304, 1242, 1196; δ_H

($CDCl_3$): 0.67 and 1.02 (6H, 2d, *J* 6.9 Hz, $CH(CH_3)_2$), 1.93–2.01 (1H, m, $CHHCH_2Cl$), 2.13–2.25 (1H, m, $CH(CH_3)_2$), 2.26–2.39 (1H, m, $CHHCH_2Cl$), 3.59–3.73 (2H, m, CH_2CH_2Cl), 3.66 and 3.68 (6H, 2s, 2×OCH_3), 3.93 (1H, t, *J* 3.6 Hz, H-5), 4.05–4.11 (1H, m, H-2); δ_C ($CDCl_3$): 16.8 and 19.0 ($CH(CH_3)_2$), 32.0 ($CH(CH_3)_2$), 37.3 and 41.5 (CH_2CH_2Cl), 52.4 and 52.5 (2×OCH_3), 52.9 (C-2), 60.9 (C-5), 163.2 and 164.0 (2×C=N); *m*/*z* (EI): 246 (M^+, 15%), 205 (34), 204 (14), 203 (100), 183 (9), 174 (6), 167 (25), 152 (5), 141 (36).

4.1.5. (2*S*,5*R*)-2,5-Dihydro-3,6-dimethoxy-2-(2′-iodoethyl)-5-isopropylpyrazine (7). (2*S*,5*R*)-2-(2-Chloroethyl)-2,5-dihydro-3,6-dimethoxy-5-isopropylpyrazine (**6**) (2.300 g, 9.34 mmol) and NaI (7.00 g, 46.72 mmol) in acetone (50 mL) was stirred under reflux under argon for 24 h. The solvent was removed and the residual material shaken with water (25 mL) and diethyl ether (25 mL). The layers were allowed to separate, the water layer extracted twice with diethyl ether (20 mL), the combined ether extracts were dried ($MgSO_4$) and the ether distilled off. The crude product was purified by flash chromatography on silica gel using hexane/Et_2O 20:1, R_f 0.45; yield 2.90 g (92%) of a colourless oil. HRMS (EI) M: 338.0481. Calcd for $C_{11}H_{19}O_2N_2I$: 338.0491; ν_{max} (film/cm^{-1}): 2960, 2944, 2871, 1694, 1461, 1436, 1299, 1239, 1195; δ_H ($CDCl_3$): 0.68 and 1.02 (6H, 2d, *J* 6.9 Hz, $CH(CH_3)_2$), 2.00–2.13 (1H, m, $CHHCH_2I$), 2.15–2.29 (1H, m, $CH(CH_3)_2$), 2.30–2.45 (1H, m, $CHHCH_2I$), 3.17–3.30 (2H, m, CH_2CH_2I), 3.65 and 3.67 (6H, 2s, 2×OCH_3), 3.91 (1H, t, *J* 3.6 Hz, H-5), 3.95–3.99 (1H, m, H-2); δ_C ($CDCl_3$): 2.01 (CH_2CH_2I), 16.7 and 19.0 ($CH(CH_3)_2$), 32.0 ($CH(CH_3)_2$), 38.4 (CH_2CH_2I), 52.5 and 52.6 (2×OCH_3), 55.8 (C-2), 61.0 (C-5), 162.8 and 164.0 (2×C=N); *m*/*z* (EI): 338 (M^+, 69%), 323 (6), 295 (100), 266 (6), 211 (7), 183 (44), 167 (21), 155 (12), 141 (83).

4.1.6. (2′*S*,5′*R*)-2-[2-(5-Isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)ethyl] malonic acid diethyl ester (8). A flask containing NaH (0.197 g of a 57% suspension in mineral oil, 4.88 mmol) in dry THF (25 mL) was cooled in an ice-bath while diethyl malonate (0.780 g, 0.74 mL, 4.88 mmol) was added dropwise under argon. The mixture was stirred at room temperature for 30 min before a solution of (2*S*,5*R*)-2,5-dihydro-3,6-dimethoxy-2-(2-iodoethyl)-5-isopropylpyrazine (**7**) (1.5 g, 4.43 mmol) in dry THF (15 mL) was added dropwise over 5 min. The mixture was heated under reflux for 12 h, cooled to 0 °C and 5% aqueous HCl added slowly (pH 7). The water layer was washed with diethyl ether (3×10 mL), the combined organic extracts dried ($MgSO_4$) and the solvent distilled off. The product was further purified by flash chromatography on silica gel using hexane/EtOAc 5:1, R_f 0.39; yield 1.360 g (83%) of an oily material. HRMS (EI) M: 370.2121. Calcd for $C_{18}H_{30}O_6N_2$: 370.2103. ν_{max} (film/cm^{-1}): 2974, 2946, 2872, 1752, 1734, 1695, 1464, 1438, 1368, 1239, 1196; δ_H ($CDCl_3$): 0.65 and 1.01 (6H, 2d, *J* 6.9 Hz, $CH(CH_3)_2$), 1.23 (6H, t, *J* 7.1 Hz, 2×OCH_2CH_3), 1.67–1.93 (4H, m, CH_2CH_2), 2.20–2.25 (1H, m, $CH(CH_3)_2$), 3.33 (1H, t, *J* 7.3 Hz, $CH(CO_2Et)_2$), 3.65 and 3.66 (6H, 2s, 2×OCH_3), 3.90–3.94 (1H, t, *J* 3.6 Hz, H-5), 3.93–4.01 (1H, m, H-2), 4.16 (4H, q, *J* 7.1 Hz, 2×OCH_2CH_3); δ_C ($CDCl_3$): 14.0 (2×OCH_2CH_3), 16.6 and 19.0 ($CH(CH_3)_2$), 24.2 and 31.6 (CH_2CH_2), 31.8 ($CH(CH_3)_2$), 51.8 ($CH(CO_2Et)_2$), 52.4 (2×OCH_3), 54.9 (OCH_2CH_3), 60.8 (C-2), 61.2 (C-5), 163.2 and 163.8 (2×C=N), 169.4 (2×CO); *m*/*z* (EI): 370 (M^+, 2%), 327 (100), 325 (22), 281 (10), 235 (62), 183 (15), 167 (7), 141 (21).

4.1.7. 2,2-Bis-[(2′*S*,5′*R*)-2-(5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)ethyl]malonic acid diethyl ester (9). A flask containing NaH (0.142 g of a 57% suspension in mineral oil, 3.51 mmol) in dry THF (25 mL) was stirred at room temperature while (2*S*,5*R*)-2-[2-(5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)ethyl]malonic acid diethyl ester (**8**) (1.300 g, 3.51 mmol) in dry THF (10 mL) was added dropwise under argon. The mixture was stirred at room temperature for 1 h before a solution of (2*S*,5*R*)-2,5-dihydro-3,6-dimethoxy-2-(2-iodoethyl)-5-isopropylpyrazine (**7**) (1.185 g, 3.51 mmol) in dry THF (10 mL) was added dropwise over 5 min. The mixture was heated under reflux for 24 h, cooled to 0 °C and 5% aqueous HCl was added slowly (pH 7). The water layer was washed with diethyl ether (3×25 mL), the combined organic extracts were dried ($MgSO_4$) and the solvent distilled off. The product was further purified by flash chromatography on silica gel using hexane/EtOAc 4:1, R_f 0.28; yield 1.585 g (78%) of a solid material with mp 79–80 °C. HRMS (EI) M: 580.3489. Calcd for $C_{29}H_{48}O_8N_4$: 580.3472; ν_{max} (film/cm^{-1}): 2960, 2944, 2871, 1729, 1692, 1460, 1436, 1364, 1305, 1235, 1193; δ_H ($CHCl_3$): 0.67 and 1.02 (12H, 2d, *J* 6.9 Hz, 2×$CH(CH_3)_2$), 1.20 (6H, t, *J* 7.1 Hz, 2×OCH_2CH_3), 1.53–1.86 (8H, m, 2×CH_2CH_2), 2.19–2.27 (2H, m, 2×$CH(CH_3)_2$), 3.64 (12H, s, 4×OCH_3), 3.91–4.03 (4H, m, 2×H-5 and 2×H-2), 4.13 (4H, q, *J* 7.1 Hz, 2×OCH_2CH_3); δ_C ($CDCl_3$): 14.1 (2×OCH_2CH_3), 16.6 and 19.0 (2×$CH(CH_3)_2$), 26.4 and 28.1 (2×CH_2CH_2), 31.9 (2×$CH(CH_3)_2$), 52.3 (2×OCH_3), 52.4 (2×OCH_3), 54.8 (2×OCH_2CH_3), 56.6 ($C(CO_2Et)_2$), 60.9 (2×C-2), 61.0 (2×C-5), 163.2 and 163.8 (4×C=N), 171.6 (2×CO); *m*/*z* (EI): 580 (M^+, 5%), 537 (100), 535 (7), 397 (6), 247 (5), 167 (5), 141 (12).

4.1.8. 2-Formyl-4-[(2*S*,5*R*)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl]-2-[2-((2*S*,5*R*)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)ethyl]butyric acid ethyl ester (10). A solution of 2,2-bis-[(2′*S*,5′*R*)-2-(5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)ethyl]malonic acid diethyl ester (**9**) (1.160 g, 2.0 mmol) in toluene (10 mL) under nitrogen was stirred, cooled to −78 °C and a 1.5 M solution of DIBAL in toluene (3.3 mL, 5 mmol) was added dropwise with a syringe. The reaction mixture was quenched after 30 min by addition of aqueous ammonium chloride. Additional water was added and the mixture extracted with ethyl acetate (3×20 mL). The organic layer was washed with water and brine, dried ($MgSO_4$) and the solvent distilled off. The product was further purified by flash chromatography on silica gel using hexane/EtOAc 4:1, R_f 0.12; yield 0.696 g (65%) of an oily material. HRMS (electrospray) M+H^+: 537.3264. Calcd for $C_{27}H_{44}O_7N_4$+H^+: 537.3282. ν_{max} (film/cm^{-1}): 2960, 2945, 2871, 1747, 1722, 1695, 1460, 1436, 1307, 1239, 1195; δ_H ($CHCl_3$): 0.65 and 1.01 (12H, 2d, *J* 6.8 Hz, 2×$CH(CH_3)_2$), 1.22 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.51–1.86 (8H, m, 2×CH_2CH_2), 2.18–2.27 (2H, m, 2×$CH(CH_3)_2$), 3.65 (12H, s, 4×OCH_3), 3.90–4.02 (4H, m, 2×H-5 and 2×H-2), 4.19 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 9.68 (1H, s, CHO); δ_C

($CDCl_3$): 14.1 (OCH_2CH_3), 16.6 and 19.0 (2×$CH(CH_3)_2$), 26.6 and 28.2 (2×CH_2CH_2), 31.9 (2×$CH(CH_3)_2$), 52.3 (2×OCH_3), 52.4 (2×OCH_3), 54.9 (2×OCH_2CH_3), 60.2 (C-2), 60.9 (2×C-2′), 61.25 (2×C-5′), 163.1 and 163.8 (4×C=N), 175.1 (CO_2Et), 199.4 (CHO); *m/z* (EI): 536 (M^+, 5%), 493 (100), 465 (51), 326 (5), 311 (10), 183 (11), 154 (8), 141 (25).

4.1.9. 2,2-Bis-[2-((2*S*,5*R*)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)ethyl]but-3-enoic acid methyl ester (11). The commercial Wittig methyl reagent, a 1:1 mixture of methyl(triphenyl)phosphonium bromide and sodium amide (0.585 g, 1.4 mmol), in freshly distilled dry THF (5 mL) was stirred at room temperature until a bright yellow colour was obtained (30 min). 2-Formyl-4-[(2*S*,5*R*)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl]-2-[2-((2*S*,5*R*)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)ethyl]butyric acid ethyl ester (**10**) (0.500 g, 0.93 mmol) in dry THF (10 mL) was added and the reaction mixture stirred at room temperature for 1 h. The mixture developed a dark yellow colour during the reaction. The reaction was quenched with saturated aqueous ammonium chloride solution, the two layers separated, the aqueous phase extracted with diethyl ether (2×10 mL) and the combined extracts and the organic layer dried ($MgSO_4$). Evaporation of the solution left the product as a yellow oil, which was further purified by flash chromatography on silica gel using hexane/EtOAc 4:1, R_f 0.23; yield 0.253 g (51%) of a colourless oily material. HRMS (electrospray) M+H^+: 535.3495. Calcd for $C_{28}H_{46}O_6N_4$+H^+: 535.3490. ν_{max} (film/cm^{-1}): 2960, 2944, 2871, 1731, 1695, 1462, 1436, 1307, 1238, 1195; δ_H ($CHCl_3$): 0.65 and 1.02 (12H, 2d, *J* 6.8 Hz, 2×$CH(CH_3)_2$), 1.22 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.50–1.86 (8H, m, 2×CH_2CH_2), 2.18–2.25 (2H, m, 2×$CH(CH_3)_2$), 3.65 (12H, s, 4×OCH_3), 3.90–3.97 (4H, m, 2×H-5 and 2×H-2), 4.10 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 5.01–5.16 (2H, m, CH=CH_2), 5.83–5.98 (1H, m, CH=CH_2); δ_C ($CDCl_3$): 14.2 (OCH_2CH_3), 16.6 and 19.0 (2×$CH(CH_3)_2$), 28.5 and 30.3 (2×CH_2CH_2), 31.8 (2×$CH(CH_3)_2$), 51.1 (C-2), 52.2 (2×OCH_3), 52.35 (2×OCH_3), 55.1 (2×OCH_2CH_3), 60.5 (2×C-2′), 60.7 (2×C-5′), 114.6 (CH=CH_2), 139.8 (CH=CH_2), 163.5 and 163.6 (4×C=N), 175.1 (CO_2Et); *m/z* (EI): 534 (M^+, 3%), 492 (29), 491 (100), 465 (4), 324 (3), 183 (4), 154 (3), 141 (15).

4.1.10. 2,2-Bis-[2-((2*S*,5*R*)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)ethyl]propane-1,3-diol (12). LAH (0.345 g, 9 mmol) was added in small portions to a solution of 2,2-bis-[(2′*S*,5′*R*)-2-(5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)ethyl]malonic acid diethyl ester (**9**) (1.500 g, 2.58 mmol) in THF (30 mL) at 0 °C. The reaction mixture was stirred at this temperature for 30 min and at room temperature for 2.5 h before the reaction was quenched by addition of saturated aqueous NH_4Cl. The mixture was extracted with diethyl ether (3×20 mL), the combined organic extracts were dried ($MgSO_4$) and evaporated to give the product as a viscous oil; yield 1.150 g (90%). The crude product was used in the subsequent reaction step without further purification. HRMS (EI) M: 496.3277. Calcd for $C_{25}H_{44}O_6N_4$: 496.3260. ν_{max} (film/cm^{-1}): 3351, 2959, 2945, 2871, 1694, 1462, 1436, 1309, 1237, 1195; δ_H ($CHCl_3$): 0.68 and 1.01 (12H, 2d, *J* 6.8 Hz, 2×$CH(CH_3)_2$), 1.15–1.32 (4H, m, 2×CH_2CH_2), 1.52–1.68 (2H, m, 2×$CHHCH_2$), 1.75–1.93 (2H, m, 2×$CHHCH_2$), 2.15–2.24 (2H, m, 2×$CH(CH_3)_2$), 3.28 (2H, t, *J* 5.7 Hz, 2×CH_2OH), 3.48 (4H, d, *J* 5.7 Hz, 2×CH_2OH), 3.66 (6H, s, 2×OCH_3), 3.67 (6H, s, 2×OCH_3), 3.93–3.99 (4H, m, 2×H-5 and 2×H-2); δ_C ($CDCl_3$): 16.8 and 19.0 (2×$CH(CH_3)_2$), 24.5 and 26.8 (2×CH_2CH_2), 32.0 (2×$CH(CH_3)_2$), 41.3 ($C(CH_2OH)_2$), 52.4 (2×OCH_3), 52.6 (2×OCH_3), 55.2 (2×C-2), 61.2 (2×C-5), 68.3 (2×CH_2OH), 163.5 and 164.8 (4×C=N); *m/z* (EI): 496 (M^+, 11%), 454 (29), 453 (100), 423 (15), 421 (27), 405 (6), 393 (8), 313 (7), 197 (6), 183 (10), 167 (7), 141 (34).

4.1.11. 2,2-Bis[2-((2*S*,5*R*)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)ethyl]malonaldehyde (13). A solution of 2,2-bis-[2-((2*S*,5*R*)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)ethyl]propane-1,3-diol (**12**) (1.00 g, 2.0 mmol) in dichloromethane (20 mL) was added to a solution of the Dess–Martin periodinane reagent (2.12 g, 5.00 mmol) in dichloromethane (20 mL) under argon at room temperature and the mixture stirred at this temperature for 1 h. Subsequently 1.3 M NaOH (30 mL) and diethyl ether (30 mL) were added, the resultant mixture stirred for 10 min, shaken with NaOH (20 mL) and water (20 mL). The ether phase was separated, dried ($MgSO_4$), and evaporated to give the product as a yellow oily material; yield 0.866 g (88%). The crude product was used in the subsequent reaction step without further purification. HRMS (electrospray) M+H^+: 493.2993. Calcd for $C_{25}H_{40}O_6N_4$+H^+: 493.3020. ν_{max} (film/cm^{-1}): 2959, 2867, 1736, 1693, 1437, 1309, 1238, 1196; δ_H ($CHCl_3$): 0.66 and 1.0 (12H, 2d, *J* 6.8 Hz, 2×$CH(CH_3)_2$), 1.52–1.62 (2H, m, 2×CH_2CHH), 1.74–1.80 (4H, m, 2×CH_2CH_2), 2.18–2.26 (4H, m, 2×$CH(CH_3)_2$ and 2×CH_2CHH), 3.64 (6H, s, 2×OCH_3), 3.65 (6H, s, 2×OCH_3), 3.90–3.99 (4H, m, 2×H-5 and 2×H-2), 9.60 (2H, s, 2×CHO); δ_C ($CDCl_3$): 16.7 and 19.0 (2×$CH(CH_3)_2$), 24.9 and 27.8 (2×CH_2CH_2), 32.0 (2×$CH(CH_3)_2$), 52.4 (2×OCH_3), 52.5 (2×OCH_3), 54.8 (2×C-2), 61.0 (2×C-5), 64.8 ($C(CHO)_2$), 162.9 and 164.1 (4×C=N), 201.2 (2×CHO); *m/z* (EI): no molecular ion, 449 (15), 421 (100), 393 (35), 387 (15), 248 (8), 211 (11), 197 (24), 183 (19), 167 (8), 141 (61).

4.1.12. 3,3-Bis[2-((2*S*,5*R*)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)ethyl]-1,4-pentadiene (14). The commercial Wittig methyl reagent, a 1:1 mixture of methyl(triphenyl)phosphonium bromide and sodium amide (2.375 g, 5.7 mmol), in freshly distilled dry THF (10 mL) was stirred at room temperature until a bright yellow colour resulted (30 min). Subsequently, a solution of 2,2-bis[2-((2*S*,5*R*)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)ethyl]malonaldehyde (**13**) (800 mg, 1.62 mmol) in dry THF (10 mL) was added and the reaction mixture stirred at room temperature for 1 h. The reaction medium gradually developed a dark yellow colouration. The reaction was quenched by addition of saturated aqueous ammonium chloride solution. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2×15 mL), the extracts were combined with the original organic layer and dried ($MgSO_4$). The dried solution was evaporated to give the crude product as a yellow oil. The product was further purified by flash chromatography on silica gel using hexane/EtOAc 9:1, R_f 0.32; yield 317 mg (40%) of a colourless oily material. HRMS (EI) M: 488.3340. Calcd for $C_{27}H_{44}O_4N_4$: 488.3362. ν_{max} (film/cm^{-1}): 2969, 2945, 2871, 1694, 1462, 1437, 1309, 1237, 1196, 1008; δ_H

($CHCl_3$): 0.65 and 1.01 (12H, 2d, *J* 6.8 Hz, 2×CH(CH_3)$_2$), 1.22–1.35 (4H, m, 2×CH_2CH_2), 1.55–1.80 (4H, m, 2×CH_2CH_2), 2.18–2.26 (2H, m, 2×CH(CH_3)$_2$, 3.64 (12H, s, 4×OCH_3), 3.90 (2H, t, *J* 3.2 Hz, 2×H-5), 3.95–3.99 (2H, m, 2×H-2), 4.89–5.03 (4H, m, 2×CH=CH_2), 5.59–5.68 (2H, m, 2×CH=CH_2); δ_C ($CDCl_3$): 16.5 and 19.0 (2×CH(CH_3)$_2$), 28.4 and 31.4 (2×CH_2CH_2), 31.7 (2×CH(CH_3)$_2$), 45.0 (C(CH=CH_2)$_2$), 52.2 (2×OCH_3), 52.3 (2×OCH_3), 55.4 (2×C-2), 60.7 (2×C-5), 113.1 (2×CH=CH_2), 144.3 (2×CH=CH_2), 163.5 and 163.8 (4×C=N); *m/z* (EI): 488 (M^+, 5%), 447 (9), 446 (28), 445 (100), 419 (12), 405 (7), 278 (8), 277 (11), 197 (13), 183 (7), 141 (26).

4.1.13. 3,3-Bis[2-((2*S*,5*R*)-2-allyl-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)ethyl]-1,4-pentadiene (15). A solution of 3,3-bis[2-((2*S*,5*R*)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)ethyl]-1,4-pentadiene (**14**) (250 mg, 0.51 mmol) in THF (10 mL) under argon was lithiated by the addition of *n*-BuLi (1.6 M in hexane, 0.70 mL, 1.12 mmol) at −50 °C. The mixture was stirred at −50 °C for 1 h, cooled to −78 °C and a solution of allyl bromide (136 mg, 0.1 mL, 1.12 mmol) in THF (2 mL) added dropwise. The resultant mixture was allowed to reach room temperature overnight. The reaction was terminated by addition of phosphate buffer of pH 7 (10 mL) and the mixture extracted with diethyl ether (3×10 mL), the extracts dried ($MgSO_4$) and the solvent distilled off. The residue was subjected to flash chromatography on silica using hexane/EtOAc 9:1, R_f 0.42. The product was a colourless oil; yield 210 mg (72%). HRMS (electrospray) M^++H: 569.4086. Calcd for $C_{33}H_{52}O_4N_4$+H^+: 569.4061. ν_{max} (film/cm^{-1}): 2971, 2942, 2872, 1689, 1459, 1438, 1291, 1254, 1167, 1002; δ_H ($CHCl_3$): 0.66 and 1.06 (12H, 2d, *J* 6.8 Hz, 2×CH(CH_3)$_2$), 1.03–1.08 (2H, m, 2×CH*H*CH_2), 1.19–1.24 (2H, m, 2×C*H*HCH_2), 1.39×1.45 (2H, m, 2×CH_2C*H*H), 1.70–1.83 (2H, m, CH_2CH*H*), 2.19–2.25 (2H, m, 2×CH*H*CH=CH_2), 2.25–2.229 (2H, m, 2×CH(CH_3)$_2$, 2.31–2.40 (2H, m, 2×C*H*HCH=CH_2), 3.64 (12H, s, 4×OCH_3), 3.80 (2H, d, *J* 3.3 Hz, 2×H-5), 4.82–4.99 (8H, m, 4×CH=CH_2), 5.40–5.62 (4H, m, 4×CH=CH_2); δ_C ($CDCl_3$): 17.1 and 19.5 (2×CH(CH_3)$_2$), 30.6 (2×CH(CH_3)$_2$), 31.3 and 33.7 (2×CH_2CH_2), 45.0 (C(CH=CH_2)$_2$), 45.5 (CH_2CH=CH_2), 51.9 (2×OCH_3), 52.3 (2×OCH_3), 60.6 (2×C-2), 62.1 (2×C-5), 112.7 (2×CH=CH_2), 118.1 (2×CH_2CH=CH_2), 133.5 (2×CH_2CH=CH_2), 144.8 (2×CH=CH_2), 162.7 and 163.7 (4×C=N); *m/z* (EI): 568 (M^+, 2%) 529 (6), 528 (34), 527 (100), 443 (5), 210 (3), 201 (3), 181 (8).

4.1.14. (2*S*,8*S*)-2,8-Diallyl-2,8-diamino-5,5-divinylnonanedioic acid dimethyl ester (16). TFA (0.2 M, 7.00 mmol, 35 mL) was added to a solution of 3,3-bis[2-((2*S*,5*R*)-2-allyl-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)-ethyl]-1,4-pentadiene (**15**) (200 mg, 0.35 mmol) in MeCN (35 mL) and the mixture stirred at ambient temperature for 5 d. The solution was then concentrated to about 30 mL under reduced pressure, brought to pH 10 using concd aqueous ammonia, extracted with dichloromethane (3×15 mL), the combined organic extracts were dried ($MgSO_4$) and evaporated. The product was isolated from the residual material after flash chromatography using MeOH/CH_2Cl_2 1:20, R_f 0.22. The product was a colourless oily material; yield 63 mg (48%). HRMS (CI) M+1: 379.2608. Calcd for $C_{21}H_{34}O_4N_2$+H: 379.259. ν_{max} (film/cm^{-1}): 3424, 3081, 2953, 1732, 1640, 1446, 1216, 1171; δ_H ($CHCl_3$): 1.22–1.71 (12H, m, 2×CH_2CH_2 and 2×NH_2), 2.18–2.24 (2H, m, 2×C*H*HCH=CH_2), 2.44–2.50 (2H, m, CH*H*CH=CH_2), 3.68 (6H, s, 2×COOCH_3), 4.88–5.12 (8H, m, 2×CH_2CH=CH_2 and 2×CH=CH_2), 5.51–5.68 (4H, m, 2×CH_2C*H*=CH_2 and 2×C*H*=CH_2); δ_C ($CDCl_3$): 31.3 and 34.0 (2×CH_2CH_2), 44.2 (CH_2CH=CH_2), 45.0 (C-5), 52.0 (2×COOCH_3), 60.7 (C-2 and C-8), 114.0 (CH=CH_2), 119.5 (CH_2CH=CH_2), 132.6 (CH_2CH=CH_2), 143.3 (CH=CH_2), 177.0 (COOCH$_3$); *m/z* (EI): 378 (M+, 1%), 337 (100), 319 (71), 304 (8), 279 (24), 250 (25), 223 (8).

4.1.15. (2*S*,8*S*)-2,8-Diacetylamino-2,8-diallyl-5,5-divinylnonanedioic acid dimethyl ester (17). A solution of acetic anhydride (51 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) was added to a solution of (2*S*,8*S*)-2,8-diallyl-2,8-diamino-5,5-divinylnonanedioic acid dimethyl ester (**16**) (80 mg, 0.21 mmol) and DMAP (65 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) and the mixture stirred at room temperature for 3 h. The reaction was quenched by addition of aqueous saturated ammonium chloride solution. The phases were separated, the aqueous phase extracted with dichloromethane, the combined extracts and the organic solution were dried ($MgSO_4$) and evaporated at reduced pressure. The residual material was subjected to flash chromatography on silica gel using MeOH/CH_2Cl_2 1:20, R_f 0.31. The product was a colourless oily material; yield 90 mg (92%). $[\alpha]_D$ +9.6 (*c* 0.772, CH_2Cl_2). HRMS (CI) M+1: 463.2786. Calcd for $C_{25}H_{38}O_6N_2$+H: 463.2808; ν_{max} (film/cm^{-1}): 3408, 3075, 2952, 1738, 1654, 1542, 1447, 1437, 1373, 1223; δ_H ($CHCl_3$): 0.92–1.10 (2H, m, 2×CHHCH*H*), 1.30–1.48 (2H, m, 2×CHHC*H*H), 1.55–1.70 (2H, m, 2×CH*H*CHH), 1.98 (6H, s, 2×COCH_3), 2.17–1.31 (2H, m, 2×C*H*HCHH), 2.43–2.54 (2H, m, 2×CH*H*CH=CH_2), 3.01–3.12 (2H, m, 2×C*H*HCH=CH_2), 3.73 (6H, s, 2×$COOCH_3$), 4.83–5.09 (8H, m, 2×CH_2CH=CH_2) and 2×CH=CH_2), 5.47–5.64 (4H, m, 2×CH_2C*H*=CH_2 and 2×C*H*=CH_2), 6.37 (2H, br s, 2×N*H*COCH$_3$); δ_C ($CDCl_3$): 23.9 (2×NHCO*C*H$_3$), 29.6 and 31.4 (2×CH_2CH_2), 39.4 (2×CH_2CH=CH_2), 44.6 (2×C-5), 52.6 (2×CO_2CH_3), 64.2 (C-2 and C-8), 113.95 (CH=CH_2), 118.9 (CH_2CH=CH_2), 132.45 (CH_2CH=CH_2), 143.05 (CH=CH_2), 169.2 (2×NH*C*OCH$_3$), 173.9 (CO_2CH_3); *m/z* (EI): 462 (M+, 5%), 460 (23), 421 (100), 403 (67), 389 (36), 379 (24), 361 (31), 353 (11), 330 (20), 198 (74), 171 (49).

4.1.16. 3,10-Diacetylaminospiro[6.6]trideca-5,12-diene-3,10-dicarboxylic acid dimethyl esters [19-(3*S*,7*S*(*R*),10*S*)] and [20-(3*S*,7*R*(*S*),10*S*)]. A solution of (2*S*,8*S*)-2,8-diacetylamino-2,8-diallyl-5,5-divinylnonanedioic acid dimethyl ester (**17**) (80 mg, 0.17 mmol) in degassed toluene (3 mL) and benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium (14 mg, 0.017 mmol) was heated at 85 °C for 4 h. The solvent was distilled off at reduced pressure and the residual material subjected to flash chromatography on silica gel using MeOH/CH_2Cl_2 1:20. The product was a mixture of the two diastereomers **19** and **20** in the ratio 3:2; yield 50 mg (73%). For analytical purposes the two diastereomers were separated by repeated flash chromatography on silica gel using MeOH/CH_2Cl_2 1:20. The major component was first eluted (R_f 0.15). Specific rotation at room temperature for the major isomer: $[\alpha]_D$ −99.5 (*c* 0.86, CH_2Cl_2) and

for the minor isomer: $[\alpha]_D$ −144.3 (*c* 0.45, CH_2Cl_2). HRMS (electrospray) M+Na^+: 429.2012. Calcd for $C_{21}H_{30}O_6N_2$+Na: 429.1996. ν_{max} (film/cm^{-1}): 3435, 3381, 2952, 1733, 1652, 1540, 1435, 1373, 1304, 1226; δ_H ($CHCl_3$): 1.66–1.70 (4H, m, 2×CH*H*CH*H*), 1.96 (6H, s, 2×NHCOCH_3), 2.19–2.22 (4H, m, 2×C*H*HC*H*H), 2.50–2.57 (2H, m, 2×CH*H*CH=CH), 2.64–2.78 (2H, m, 2×C*H*HCH=CH), 3.70 (6H, s, 2×CO_2CH_3), 5.41–5.47 (2H, m, 2×CH_2C*H*=CH), 5.62 (2H, br s, 2×N*H*$COCH_3$), 5.70 (2H, d, *J* 10.7 Hz, 2×CH_2CH=C*H*); δ_C ($CDCl_3$): 23.2 (2×NHCO*C*H_3), 29.5 and 30.9 (2×*C*H_2*C*H_2), 33.8 (2×*C*H_2CH=CH), 46.0 (C-7), 52.6 (2×CO_2*C*H_3), 60.4 (C-3 and C-10), 122.0 (CH=*C*H), 143.3 (*C*H=CH), 169.4 (NH*C*OCH_3), 173.9 (CO_2CH_3); *m*/*z* (EI): no molecular ion, 347 (14), 296 (5), 256 (14), 214 (100), 209 (44), 169 (9), 157 (12), 133 (35), 132 (39).

The second compound eluted was the minor isomer, R_f 0.10. HRMS (electrospray) M+Na^+: 429.1975. Calcd for $C_{21}H_{30}O_6N_2$+Na: 429.1996; δ_H ($CHCl_3$): 1.42–1.58 (2H, m, 2×CHHCH*H*), 1.68–1.74 (2H, m, CH*H*CHH), 1.96 (6H, s, 2×NHCOCH_3), 2.18–2.28 (2H, m, 2×CHHC*H*H), 2.30–2.41 (2H, m, 2×C*H*HCHH), 2.43–2.55 (2H, m, 2×CH*H*CH=CH), 2.64×2.75 (2H, m, 2×C*H*HCH=CH), 3.69 (6H, s, 2×COOCH_3), 5.42–5.50 (2H, m, 2×CH_2C*H*=CH), 5.67 (2H, br s, 2×N*H*$COCH_3$), 5.93 (2H, d, *J* 11.2 Hz, 2×CH_2CH=C*H*); δ_C ($CDCl_3$): 23.1 (2×NHCO*C*H_3), 30.7 and 33.65 (2×*C*H_2*C*H_2), 34.0 (2×*C*H_2CH=CH), 45.0 (C-7), 52.55 (2×CO_2*C*H_3), 60.1 (C-3 and C-10), 122.5 (CH=*C*H), 139.4 (*C*H=CH), 169.5 (NH*C*OCH_3), 174.1 (CO_2CH_3).

References and notes

1. Undheim, K.; Efskind, J.; Hoven, G. B. *Pure Appl. Chem.* **2003**, *75*, 279–292.
2. (a) Bold, G.; Allmendinger, T.; Herold, P.; Moesch, L.; Schär, H.-P.; Duthaler, R. O. *Helv. Chim. Acta* **1992**, *75*, 865–882; (b) Williams, R. M.; Yan, C. *J. Org. Chem.* **1992**, *57*, 6519–6527; (c) Baldwin, J. E.; Lee, V.; Schofield, C. J. *Synlett* **1992**, 249–251.
3. Belokon, Yu. N.; Chernoglazova, N. I.; Batsanov, A. S.; Garbalinskaya, N. S.; Bakhmuhtov, V. I.; Struchkov, Yu. T.; Belikov, V. M. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1987**, 852–857; *Chem. Abstr.* **1988**, *108*, 132255v.
4. (a) Lange, M.; Undheim, K. *Tetrahedron* **1998**, *54*, 5337–5344; (b) Neset, S.; Hope, H.; Undheim, K. *Tetrahedron* **1997**, *53*, 10459–10470; (c) Bhatnagar, P. K.; Agner, E. K.; Alberts, D.; Arbo, B. E.; Callahan, J. F.; Cuthbertson, A. S.; Engelsen, S. J.; Fjerdingstad, H.; Hartmann, M.; Heerding, D.; Hiebl, J.; Huffman, W. F.; Hysben, M.; King, A. G.; Kremminger, P.; Kwon, C.; LoCastro, S.; Lövhaug, D.; Pelus, L. M.; Petteway, S.; Takata, J. S. *J. Med. Chem.* **1996**, *39*, 3814–3819.
5. (a) Mueller, R.; Revesz, L. *Tetrahedron Lett.* **1994**, *35*, 4091–4092; (b) Lombart, H.-G.; Lubell, W. D. *J. Org. Chem.* **1994**, *59*, 6147–6149.
6. Rödbotten, S.; Benneche, T.; Undheim, K. *Acta Chem. Scand.* **1997**, *51*, 873–880.
7. (a) Liskamp, R. M. J. *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 1–19; (b) Goodman, M.; Shao, H. *Pure Appl. Chem.* **1996**, *68*, 1303–1308.
8. Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517–3599.
9. Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645–732.
10. (a) Andrei, M.; Efskind, J.; Viljugrein, T.; Römming, C.; Undheim, K. *Tetrahedron: Asymmetry* **2004**, *15*, 1301–1313; (b) Andrei, M.; Römming, C.; Undheim, K. *Tetrahedron: Asymmetry* **2004**, *15*, 1359–1370.
11. Hoven, G. B.; Efskind, J.; Römming, C.; Undheim, K. *J. Org. Chem.* **2002**, *67*, 2459–2463.
12. Efskind, J.; Römming, C.; Undheim, K. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2697–2703.
13. Rose, J. E.; Leeson, P. D.; Gani, D. *J. Chem. Soc., Perkin Trans. 1* **1995**, 157–165.
14. (a) Groth, U.; Chiang, Y.-C.; Schöllkopf, U. *Liebigs Ann. Chem.* **1982**, 1756–1757; (b) Schöllkopf, U. *Pure Appl. Chem.* **1983**, *55*, 1799–1806.
15. (a) Krikstolaityté, S.; Sackus, A.; Rømming, C.; Undheim, K. *Tetrahedron: Asymmetry* **2001**, *12*, 393–398; (b) Andrei, M.; Rømming, C.; Undheim, K. *Tetrahedron: Asymmetry* **2004**, *15*, 2711–2717.
16. (a) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899; (b) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537–4538.
17. Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783–3784.
18. Bull, S. D.; Davies, S. G.; Epstein, S. W.; Leech, M. A.; Ouzman, J. V. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2321–2330.