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Stereoselective Synthesis of Alkenyl α,α′-Bridged Bis(glycines) using Palladium Promoted Substitution in the Bridge

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Conformationally constrained cystine analogues have been synthesized which have an unsaturated four-carbon backbone-chain as a bridge between the α,α′-positions in two glycine units. Stereoselective synthesis of the *cis* and *trans* isomers of bis(glycines) with a 2′-butene bridge, and their 2′-bromo derivatives, is described. Palladium mediated coupling between the bromides and stannanes provided for carbo-substitution at the olefinic carbon in the bridge. *N*-Methyl-2-pyrrolidinone was an excellent solvent for this reaction when triphenylarsine was the ligand for palladium. Mild hydrolytic conditions furnished the methyl esters of the C_4-bridged bis(glycine) derivatives.

The present great interest in peptidomimetic building blocks such as rigidified α-amino acids is largely due to their potential importance in the design and development of drugs.[1] We and others have been interested in finding substitutes for cystine in immunoactive peptides.[2,3]

In our program for the preparation of isosteric analogues of cystine, the latter is regarded as a dimeric amino acid composed of two glycine units connected at the glycine α-position by the $-CH_2SSCH_2-$ bridge. We have confined our efforts mainly to the construction of C_4-bridges to replace the four-atom $-CH_2SSCH_2-$ bridge in cystine.[4–6] Other dimeric amino acids with bridges of different sizes and types are known.[7]

When all the carbons of a C_4-bridge in isosteric analogues of cystine are part of an aromatic ring, an exceptionally rigid amino acid structure results;[4] less conformational constraint is likely only when the two carbons corresponding to the disulfide unit is part of an aromatic or heteroaromatic ring structure.[5] Conformational constraint is also to be found in our recently described acyclic C_4-bridged bisglycines in which the two central carbon atoms of the C_4-bridge were replaced by two methylene groups.[6] This report describes isosteric analogues of cystine where a carbon–carbon double bond has been substituted for the disulfide unit; both *cis* and *trans* structures are described.

Several chiral auxiliaries are available for amino acid constructions.[8] In this report we have adapted the Schöllkopf 'bislactim ether' procedure for the preparation of isosteric cystine analogues.[9]

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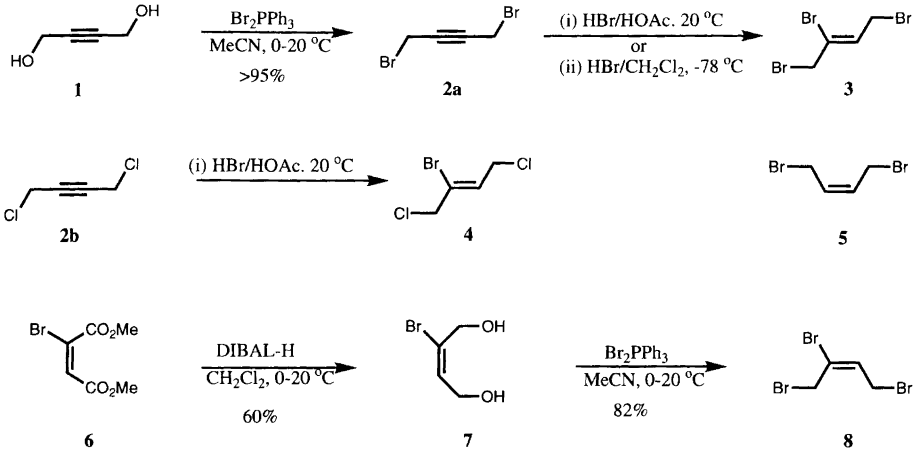
Results and discussion

The close structural analogy of the target molecules **B** to the structure of (*R*)-cystine (**A**) is shown in Fig. 1. The steric crowding around the double bonds was further increased and controlled by carbo-substitution at the double bond. For this purpose sp^2-brominated derivatives were synthesized and carbo-substitution effected by palladium-catalyzed coupling reactions with stannanes (*vide infra*).

The bridge was formed in a stereoselective dialkylation reaction between 1,4-dibromo-2-alkenes and the chiral auxiliary (2*S*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (**9**; Scheme 2). The synthesis of the appropriate diallylic bromides or chlorides, which were to be used for the alkylation reactions, are outlined in Scheme 1. The vinyl bromides **3** and **4** were prepared from the corresponding alkynes by HBr addition. The substrate 1,4-dibromo-2-butyne (**2a**) for this reaction was best obtained from 2-butyne-1,4-diol (>95% yield) by bromination with bromine–triphenylphosphine; the reagent was generated *in situ* in acetonitrile. Phosphorus tribromide has previously been described for this reaction, but in our hands this reagent gave inferior product quality.[10]

The bromine–triphenylphosphine reagent in aceto-

Fig. 1.



Scheme 1.

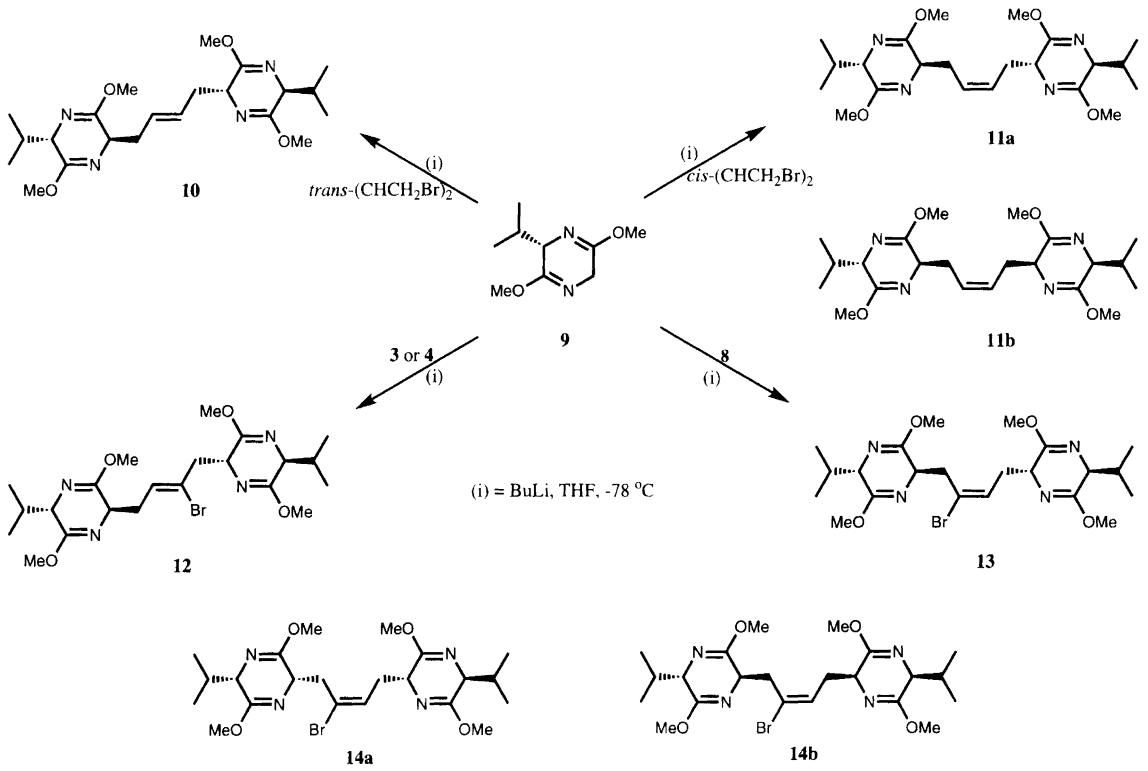
nitrile was also used to convert (*Z*)-2-butene-1,4-diol into the dibromide **5**. The conditions used in this reaction did not affect the stereochemistry of the double bond, the yield of **5** being of the order 95%. In the preparation of (*Z*)-1,2,4-tribromo-2-butene (**3**) from the neat diol **1** with HBr we failed to reproduce the high yields reported for this reaction.[11] A convenient modification was to treat the 1,4-dibromo substrate **2a** with an excess of HBr in acetic acid at ambient temperature; high yields of the tribromide **3** were obtained. The stereochemistry is consistent with the reported assignment based on NMR studies.[12] The analogue, (*Z*)-2-bromo-1,4-dichloro-2-butene (**4**) was available in an excellent yield by the same reaction from 1,4-dichloro-2-butyne. This method was superior to a procedure involving addition of chlorine to 2-bromo-1,3-butadiene.[13]

An attempt to prepare (*E*)-1,2,4-tribromo-2-butene (**8**) by the addition of HBr in dichloromethane to a solution of 1,4-dibromo-2-butyne (**2a**) at −78 °C, led to stereoisomer **3** as the main product; the conditions described were those used to effect *cis* addition of HBr to double bonds.[13,14] The *E*-bromide **8**, however, was readily prepared by bromination of (*E*)-2-bromo-2-butene-1,4-diol (**7**). The latter was available by DIBAL-H reduction of dimethyl bromomaleate (**6**). In the isolation of the product, the complexation of the diol with aluminium salts was weakened by pouring the reaction mixture into 10% methanol in dichloromethane with ammonium chloride present, in which case the diol **7** was isolated in 60% yield. The bromomaleate **6** was a better substrate than bromomaleic anhydride for the reduction; the anhydride was the precursor of the ester **6**.[15]

For the preparation of the *trans*- and *cis*-olefin-bridged amino acids **10** and **11** (Scheme 2), lithiated (*2S*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (**9**) was alkylated in THF at −78 °C with (*E*)- and (*Z*)-1,4-dibromo-2-butene. The alkylation with the *E*-reagent was characterized by high diastereoselectivity; in most cases only one stereoisomer was seen by NMR and chromatography. It is noteworthy that high stereoselectivity results after two separate alkylation steps where, in principle, two different alkylating agents are involved in the formation of the product **10**. If the second isomer was detectable in a preparation, it was easily removed by flash chromatograpy or recrystallization from acetonitrile; we define diastereomeric excess (d.e) >95% when we failed to see the second isomer. The chemical yield of isolated and purified material was about 80%. The products in this report all contain more than one stereochemical center. The main stereochemical information on the homogeneity of a product formed, was gained from ^{13}C and ^{1}H NMR spectroscopy (*vide infra*). Additional information was provided by chromatography.

The diastereoselectivity was significantly lower in the preparation of the *cis* analogue **11a**. The reactions were run at −78 °C either using addition of the alkylating agent or the reverse to the lithiated bislactim ether. The order of addition had no significant effect on either yields or stereoselectivity. Both the dichloride and the dibromide were used for alkylation but no significant difference was observed. *N,N'*-Dimethyl-*N,N'*-propyleneurea (DMPU) as a cosolvent, however, increased the chemical yield from 60 to 83% but the d.e. was decreased from 67 to 58%. We found the addition of DMPU to be advantageous, however, because he higher chemoselectivity simplified the isolation of the desired compound **11a** from the product mixture. In the preparation of the *trans* derivative **10** (*vide supra*) the effect of DMPU was to increase the yield by about 8%.

In addition to **11a**, its stereoisomer **11b** with *S*-stereochemistry at C-5 of one of the pyrazine rings, was isolated in 17% yield after chromatographic separation from **11a**. Hydrolysis of **11b** would have yielded the *meso* analogue of the amino acid ester **21a** (Scheme 5). The symmetry of **11a** is lost in **11b** which is clearly shown in their NMR spectra., e.g. **11a** in its ^{1}H NMR spectrum has two signals for the two different methoxy groups and two signals for the two methyl groups of the isopropyl group. The isomer **11b** shows three or four signals in each case.This phenomenon was even more



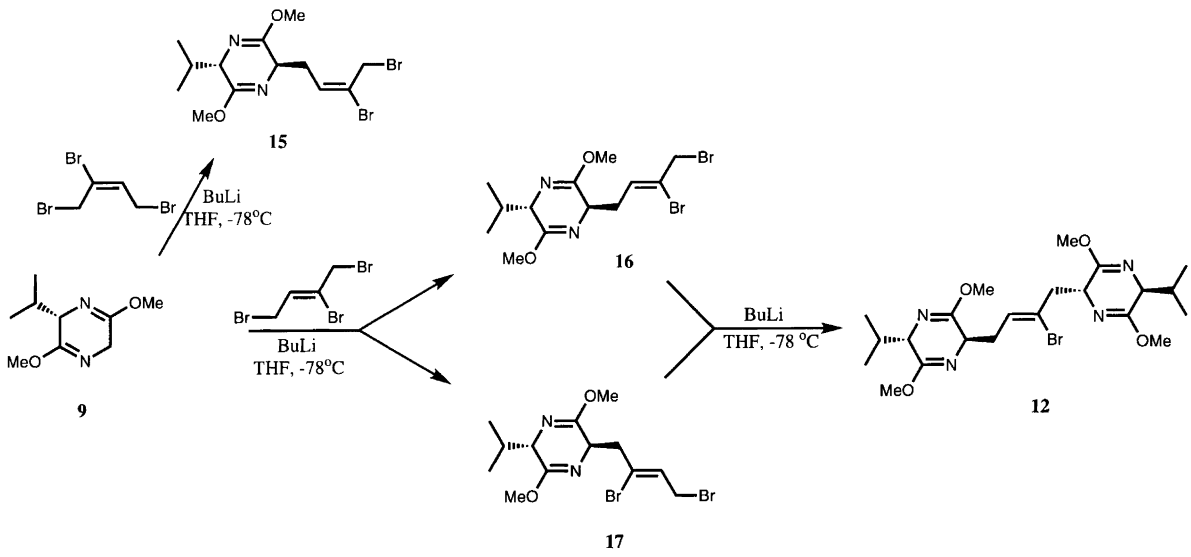
Scheme 2.

clearly demonstrated in the ^{13}C NMR spectra at higher resolution which gave two and four signals for the respective isomers.

Stereoselectivity in the dialkylation reaction with the (*Z*)-2-bromo-1,4-dihalogeno-2-butenes **3** and **4,** which have a *trans* relationship between the halogenomethylene groups, was reduced from the high d.e. (>99%) of the parent compound **10** to a d.e. of 80% (56% yield) for the bromo compound **12** irrespective of whether the alkylating agent was the 1,4-dibromo or the 1,4-dichloro reagent. The presence of DMPU did not affect significantly the course of these reactions. Reaction with the *E*-reagent **8,** which has a *cis* relationship between the halogenomethylene groups, was more difficult. Dialkylation gave a mixture of the desired product **13** and one of its diastereomeric analogues, either **14a** or **14b**. The isomers were separated by flash chromatography; the yield of **13** was 30%, the other isomer was obtained in 20% yield. A monoalkylated product was also isolated in 6% yield; it was assigned structure **15** (Scheme 3). The structure assignment was based on ^{1}H, ^{13}C and COSY NMR analyses. The allylic methylene protons at the site of the allylic bromide showed geminal coupling, *J* 14.5 Hz. A COSY spectrum confirmed that there was no other detectable coupling to these methylene protons. The COSY spectrum also showed that the olefinic proton was coupled to the other methylene protons which were further coupled to an adjacent methine proton on the carbon attached to the ring structure.

The isolation of the monoalkylated product **15** (*vide supra*) led to attempts to isolate either of the monoalkylated intermediates **16** and **17** in the dialkylation leading to product **12** (Scheme 3). Inverse addition was used; lithiated bislactim ether at −78 °C was added dropwise to an excess of the alkylating agent at −78 °C. NMR spectroscopy of the product mixture showed the presence of an almost 1 : 1 ratio of the two regioisomers **16** and **17**. Attempts to effect separation by chromatography were not successful. The relative amounts of **16** and **17**, however, varied slightly between different runs. This allowed the NMR signals to be assigned to the respective isomers in the mixture. No stereoisomers of **16** and **17** were detected which indicates that relatively low stereoselectivity in the second alkylation step is responsible for the low d.e. (80%) of the overall reaction in the formation of the dialkylated product **12**.

Each one of the olefinic bromo derivatives **12** and **13** was to serve as a common substrate in the respective stereoisomeric series for the introduction of carbo-substituents into preformed bridge systems (Scheme 4). The strategy called for a palladium-catalyzed coupling reaction with an appropriate organometallic derivative; organostannanes were used.[16] 2-Thienyl(tributyl)-stannane,[17] β-styryl(tributyl)stannane,[18] and phenylethynyl(tributyl)stannane[19] were prepared essentially as described. Vinyl(tributyl)stannane was commercially available. Initial attempts to effect the coupling between the 2-thienyl(tributyl)stannane and the bromoalkene **12** using tripenylphosphine for ligation of palladium met



Scheme 3.

with little success. Nor did addition of CuI have any significant effect on the reactivity in the coupling reaction. The transmetallation step, the transfer of the reactive residue from the stannane to the palladium complex, is the rate determining step in these reactions.[20] The σ-donor triphenylphosphine is relatively strongly coordinated to Pd^{II} whereas the more electron deficient triphenylarsine is more loosely coordinated to the metal which facilitates dissociation to a more reactive species for the transmetallation reaction to occur. Triphenylarsine was used as a ligand for palladium in the subsequent reactions. The catalyst was generated *in situ* from $Pd_2(dba)_3 \cdot CHCl_3$ by addition of 8 mol equiv. of triphenylarsine.[21]

The coupling between the 2-thienyl(tributyl)stannane and the (*Z*)-olefinic bromide **12** with a *trans*-relationship between the methylene groups, failed on heating in THF. Low stability of the Pd-catalyst to heating in 1,2-dichloroethane was a major problem; only 35% of the substrate could be transformed before the catalyst decomposed. Addition of more catalyst after an initial reaction period increased the yield to 65%, with substrate still unreacted.

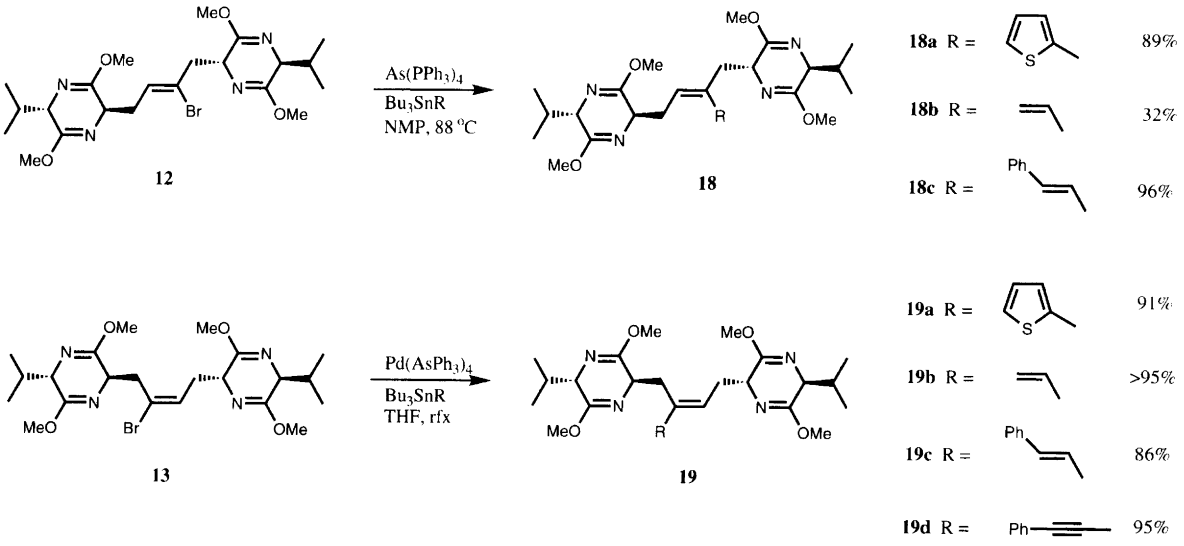
It has been reported that certain aprotic solvents such as HMPA or DMF may stabilize Pd-catalysts and prevent precipitation of metallic palladium from the reaction.[22] We have found *N*-methyl-2-pyrrolidinone (NMP) to be an excellent stabilizing solvent for the execution of the desired reaction. Its stabilizing effect may be attributed to weak coordination to the metal resulting in slow decomposition of the catalyst. The increased survival time for the catalyst may allow the reaction to proceed almost to completion as in the case of **18a** and **18c** (Scheme 4). Heating was necessary; the reactions were run at 88 °C. The thienyl derivative **18a** and the styryl derivative **18c** were isolated in 89 and 96%, respectively. The *cis*:*trans* ratio 1:9 in the styryl double bond in **18c** was unchanged from that of the β-styryl(tributyl)stannane reagent. The yield of the vinyl derivative **18b** was only 32%; decreased rate of the coupling reaction and extensive decomposition of the catalyst were observed.

The coupling proceeded more readily for the bromoalkene **13** with the *E*-configuration, where the methylene groups of the bridge have a *cis*-relationship. The bromine substituent in this substrate is probably more exposed than in *Z*-isomer **12** allowing for milder reaction conditions than for the more sterically crowded isomer **12**. The reactions with triphenylarsine as ligand ran very well on heating in THF; yields were in the range 86–95%.

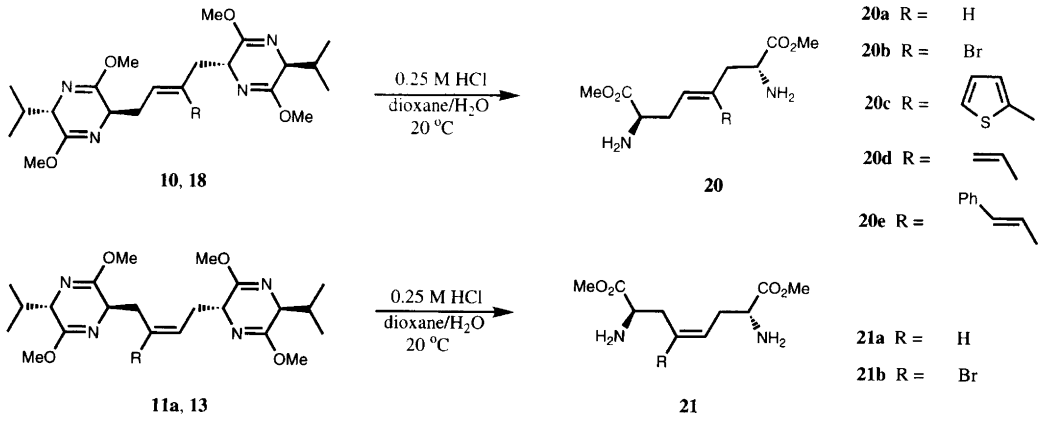
Hydrolysis of some of the bislactim ethers, *viz.* **10**, **11a**, **12**, **13**, **18a**, **18b** and **18c** to the corresponding amino acid methyl esters **21**, **22**, **23** (Scheme 5) was effected at ambient temperature in a solution of 0.25 M HCl in dioxane–water 1:1 adhering to the experimental procedure provided by Schöllkopf and coworkers.[23] The desired amino acid ester was isolated from the hydrolysates after initial removal of valine methyl ester had been effected by bulb-to-bulb distillation at ambient temperature and reduced pressure. The amino acid methyl esters were purified by flash chromatography on silica; yields were in the range 77–95%.

Experimental

The ^1H NMR spectra were recorded at 200 MHz with a Varian Gemini 200 or a Bruker DPX 200 instrument; for 300 MHz spectra a Bruker DPX 300 was used. The 500 MHz spectra were recorded on a Bruker DPX 500. The ^{13}C NMR spectra were recorded at 50 MHz with a Gemini 200 or a Bruker DPX 200, at 75 MHz with DPX 300, and 125 MHz on a Bruker DPX 500 instrument. NMR techniques such as DEPT, COSY, INVERSE COSY, HETCOR, INVERSE LONG RANGE



Scheme 4.



Scheme 5.

HETCOR and proton–proton decoupling techniques were used. The mass spectra under electron impact conditions (EI) were recorded at 70 eV ionizing potential, and ammonia was used for chemical ionization (CI); the spectra are presented as *m/z* (% rel. int.). Dry THF was distilled from sodium and benzophenone.

1,4-Dibromo-2-butyne (**2a**). Bromine (4.54 ml, 88.60 mmol) was added dropwise to a suspension of triphenylphosphine (23.23 g, 88.60 mmol) in acetonitrile (120 ml) under nitrogen at 0 °C. 2-Butyne-1,4-diol was then added all at once and the mixture was stirred at ambient temperature for 1 h. The precipitated triphenylphosphine oxide was filtered off and the solution evaporated to a small volume. Additionally precipitated triphenyl phosphine oxide was removed by filtration and washed with diethyl ether, and the ether washings and the filtrate were combined, evaporated to dryness and the residual oil dissolved in EtOAc–hexane (1:4). The resultant solution was filtered through a plug of silica to remove any further precipitated triphenylphosphine oxide and the filtrate evaporated to leave the title compound as a yellow oil which was used in the subsequent reactions without any further purification; yield 8.60 g (95%). ^{1}H NMR ($CDCl_3$): δ 3.94 (4 H, s, 2 × CH_2). ^{13}C NMR ($CDCl_3$): δ 15.52 (2 × CH_2), 82.44 (C=C).

(Z)-1,2,4-Tribromo-2-butene (**3**). 1,4-Dibromo-2-butyne (3.50 g, 16.50 mmol) was added to HBr in AcOH (40.2 ml, 165 mmol) and the mixture stirred at ambient temperature for 12 h before the acetic acid was removed at reduced pressure. The residual material was dissolved in dichloromethane (20 ml), the solution shaken with a saturated aqueous solution of sodium hydrogen carbonate and with water, and the organic phase dried ($MgSO_4$). Removal of the solvent by distillation left the title compound as a yellow oil which was used in subsequent reactions without further purification; yield 4.59 g (95%). ^{1}H NMR ($CDCl_3$): δ 4.02 (2 H, d, $\underline{CH_2}$CH=CBr, *J* 7.8 Hz), 4.23 (2 H, d, CH_2CBr=C, *J* 0.82 Hz), 6.37 (1 H, tt, CH=CBr, *J* 0.82 Hz). ^{13}C NMR ($CDCl_3$): δ 28.84/37.17(CH_2), 127.11 ($\underline{C}$Br=C), 129.11 ($\underline{C}$H=CBr).

(Z)-2-Bromo-1,4-dichloro-2-butene (**4**) was prepared from 1,4-dichloro-2-butyne as described above for the bromo derivative **3**; yield 95%. ^{1}H NMR ($CDCl_3$): δ 4.17 (2 H, d, *J* 7.2 Hz, $\underline{CH_2}CH{=}CBr$), 4.28 (2 H, d, $CH_2CBr{=}\underline{C}$, *J* 1.1 Hz), 6.34 (1 H, tt, $\underline{CH}{=}CBr$, *J* 1.1, 7.2 Hz) ^{13}C NMR ($CDCl_3$): δ 41.86 ($\underline{C}H_2CH{=}CBr$), 49.23 ($\underline{C}H_2CBr{=}C$), 125.82 ($\underline{C}Br{=}C$),128.57 ($\underline{C}H{=}CBr$).

(Z)-1,4-Dibromo-2-butene (**5**) was prepared from (*Z*)-2-butene-1,4-diol as described for the synthesis of the dibromide **2a**; yield 95% of a yellow oil. ^{13}C NMR ($CDCl_3$): δ 24.46 (2 × CH_2), 129.80 (2 × CH=C).

(E)-2-Bromo-2-butene-1,4-diol (**7**). A solution of dimethyl 2-bromomaleate (2.20 g, 9.90 mmol) in dichloromethane (23 ml), was added to DIBAL-H in hexane (50 ml, 1.0 M, 50 mmol) under nitrogen and the mixture stirred at ambient temperature for 4 h before the reaction was stopped by transferring the reaction mixture to a solution of 10% MeOH in dichloromethane (1.0 l). Aqueous ammonium chloride was subsequently added and the mixture was stirred for 10 min and filtered. The solid on the filter was washed with 10% MeOH in dichloromethane and the combined washings and filtrate were evaporated. The residue was dissolved in acetonitrile and the solution filtered through a cotton plug. Evaporation of the solution left the the oily product which was used in the subsequent reaction without further purification; yield 0.97 g (60%). ^{1}H NMR ($CDCl_3$): δ 4.04 (2 H, d, $\underline{CH_2}CH{=}CBr$, *J* 6.96 Hz), 4.19 (2 H, s, $CH_2CBr{=}\underline{C}$), 6.10 (1 H, t, $\underline{CH}{=}CBr$, *J* 6.96 Hz). ^{13}C NMR ($CDCl_3$): δ 59.36 (CH_2) and 63.35 (CH_2), 128.52 ($\underline{C}H{=}C$), 135.00 ($\underline{C}Br{=}C$).

(E)-1,2,4-Tribromo-2-butene (**8**). Bromine (0.73 ml, 14.2 mmol) was added dropwise to a suspension of triphenylphosphine (3.73 g, 14.2 mmol) in acetonitrile (20 ml) under nitrogen at 0 °C. Subsequently, a solution of (*E*)-2-bromo-2-butene-1,4-diol (1.13 g, 6.77 mmol) in acetonitrile (2 ml) was added dropwise and the mixture stirred at ambient temperature for 1 h before the solvent was distilled off. The residue was extracted with diethyl ether, insoluble triphenylphosphine oxide removed by filtration and subsequent filtration through a plug of silica. The filtrate was evaporated to leave the title compound as a yellow oil which was used as such in the subsequent reaction; yield 1.62 g, 82%. ^{1}H NMR ($CDCl_3$): δ 3.90 (2 H, d, $\underline{CH_2}CH{=}CBr$, *J* 8.83 Hz), 4.27 (2 H, s, $CH_2CBr{=}\underline{C}$, 6.31 (1 H, t, $\underline{CH}{=}CBr$, *J* 8.83 Hz). MS (EI): 296/294/292/290 (3/8/8/3, M^+), 215 (49), 213 (100), 211 (61), 134 (15), 133 (22), 132 (27), 131 (18), 105 (11), 85 (12), 71 (19).

(2S)-2,5-Dihydro-3,6-dimethoxy-2-isopropylpyrazine (**9**) was prepared as described.[24]

(E)-1,4-Bis[(2S5R)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-pyrazinyl]-2-butene (**10**). A solution of (*2S*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (1.07 g, 5.81 mmol) in anhydrous THF (12.0 ml) at −78 °C was lithiated by the addition of a solution of BuLi in hexane (2.90 ml, 2.20 M, 6.39 mmol). The solution was stirred at −78 °C for 30 min, a precooled solution of (*E*)-1,4-dibromo-2-butene (0.607 g, 2.84 mmol) in THF (6.0 ml) was added dropwise with stirring and the resultant mixture was allowed to reach ambient temperature overnight. After hydrolysis with phosphate buffer (pH 7), the mixture was extracted with diethyl ether, the organic layer was washed with water and brine and then dried ($MgSO_4$) and the solvent distilled off. The residual product contained 0–3% of the wrong isomer, and was obtained isomer-pure by flash chromatography on silica gel (hexane–EtOAc 4:1); yield 0.866 g (71%), d.e. >99%. Anal. $C_{22}H_{36}N_4O_4$: C, H.[1] H NMR ($CDCl_3$): δ 0.62/0.99 (12 H, d, 4 × $CH\underline{Me_2}$, *J* 6.9 Hz), 2.16–2.21 (2 H, m, $C\underline{H}Me_2$), 2.37–2.41 (4 H, m, 2 × $\underline{CH_2}$), 3.60 (12 H, s, 4 × OMe), 3.60–3.65 (2 H, m, H-2, H-2′), 3.85–3.99 (2 H, m, H-5, H-5′), 5.26–5.29 (2 H, m, 2 × CH_2 $\underline{CH}{=}C$). ^{13}C NMR ($CDCl_3$): δ 16.42/19.01 (2 × $CH\underline{Me_2}$), 31.50 (2 × $\underline{C}HMe_2$), 37.05 ($\underline{C}H_2$), 52.02/52.24 (2 × OMe, 55.58 (C-5, C-5′), 60.49 (C-2, C-2′), 128.42 ($\underline{C}H{=}C$), 163.80/163.62 (C-3, C-3′).

(Z)-1,4-Bis[(2S,5R)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-pyrazinyl]-2-butene (**11a**). A solution of (*2S*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (0.542 g, 2.94 mmol) in anhydrous THF (6.0 ml) and DMPU (1.44 ml, 12 mmol) was lithiated by the addition of a solution of BuLi in hexane (1.44 ml, 2.25 M, 3.23 mmol). The solution was stirred at −78 °C for 30 min before the dropwise addition of a solution of (*Z*)-1,4-dichloro-2-butene (0.300 g, 1.42 mmol) in THF (1.50 ml). The reaction mixture was stirred at −78 °C for 3 h before being allowed to reach ambient temperature overnight. After hydrolysis with phosphate buffer (pH 7), the mixture was extracted with diethyl ether, the organic extracts were dried ($MgSO_4$) and the solvent was removed by distillation. The stereoisomers were separated by flash chromatography on silica gel using hexane–EtOAc (9:1); yield 388 mg (66%), d.e. >95%. The other stereoisomer was also isolated; yield 102 mg (17%). Title compound: Found: *M* 420.2728. Calc. for $C_{22}H_{36}N_4O_4$. 420.2737. ^{1}H NMR ($CDCl_3$): δ 0.62/0.99 (12 H, d, 4 × $CH\underline{Me_2}$, *J* 6.9 Hz), 2.18–2.23 (2 H, m, $C\underline{H}Me_2$), 2.45–2.58 (4 H, m, 2 × $\underline{CH_2}$), 3.61/3.63 (12 H, s, 4 × $O\underline{Me}$), 3.86 (2 H, t, H-2, H-2′, *J* 3.9 Hz), 4.03–3.99 (2 H, m, H-5, H-5′), 5.33 (2 H, m, 2 × $CH_2\underline{CH}{=}C$). ^{13}C NMR ($CDCl_3$): δ 16.46/19.00 (2 × $CH\underline{Me_2}$), 31.53 (2 × $\underline{C}HMe_2$), 31.97 (CH_2), 52.19/52.78 (2 × OMe), 55.42 (C-5, C-5′), 60.63 (C-2, C-2′), 127.30 ($\underline{C}H{=}C$), 163.18/163.63 (C-6, C-6′). MS (EI) : 420 (2, M^+), 377 (40), 238 (8), 237 (9), 184 (21), 183 (29), 141 (100), 140 (5), 126 (4).

(Z)-1-[(2S,5R)-2,5-Dihydro-3,6-dimethoxy-2-isopropyl-5-pyrazinyl]-4-[(2S,5S)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-pyrazinyl]-2-butene (**11b**) was isolated from its mixture with the isomer **11a** by flash chromatography in 17% yield as described above. ^{1}H NMR ($CDCl_3$): δ 0.63/0.69 (6 H, d, 2 × $CH\underline{Me_2}$, *J* = 6.8 Hz), 0.98–1.03 (6 H, m,

2 × $CHMe_2$), 2.14–2.30 (2 H, m, 2 × $CHMe_2$), 2.34–2.64 (4 H, m, 2 × CH_2), 3.60/3.62/3.67 (12 H, s, 4 × OMe), 3.85–3.88 (2 H, m, H-5, H-5′), 3.96–4.07 (2 H, m, H-2, H-2′), 5.30–5.40 (1 H, m, C=CH), 5.50–5.60 (1 H, m, C=CH). ^{13}C NMR ($CDCl_3$): δ 16.91/17.96/19.44/19.98 (4 × $CHMe_2$), 31.58/31.96 (2 × $CHMe_2$), 32.43/33.53 (2 × CH_2), 52.54/52.62/52.71 (4 × OMe), 55.88/56.16 (C-5, C-5′), 61.11/61.22 (C-2, C-2′), 127.00/129.00 (2 × C=CH), 163.48/163.59/163.65/164.15 (C-3, C-3′, C-6, C-6′).

(Z)-1,4-Bis[(2S,5R)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-pyrazinyl]-2-bromo-2-butene (**12**). A solution of (*2S*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (2.52 g, 13.60 mmol) in anhydrous THF (25 ml) under nitrogen was lithiated by the addition of a solution of BuLi in hexane (12.5 ml, 1.2 M, 15.00 mmol). The solution was stirred at −78 °C for 15 min before being transferred through Teflon tubing to a precooled and stirred solution of (*Z*)-1,2,4-tribromo-2-butene (2.00 g, 6.83 mmol) in THF (6.8 ml) under nitrogen at −78 °C. The reaction mixture was allowed to reach ambient temperature overnight, phosphate buffer (pH 7, 5.0 ml) and water (5 ml) were added, the mixture was shaken with diethyl ether (10 ml) and the phases separated. The aqueous phase was extracted with diethyl ether (2 × 20 ml), the combined ether solutions were dried ($MgSO_4$) and evaporated. The d.e. of the crude product was 80%. The crude product was purified by flash chromatography on silica using EtOAc–hexane (1:9), which also removed the diastereomeric isomers; yield 1.91 g (56%) of a yellow oily material. ^{1}H NMR ($CDCl_3$): δ 0.67/0.68/1.03/1.04 (12 H, d, 4 × $CHMe_2$, *J* 6.8 Hz), 2.21–2.30 (2 H, m, 2 × $CHMe_2$), 2.50–2.82 (3 H, m, CHH, CH_2), 2.95 (1 H, dd, CHH, *J* 3.6 Hz), 3.66/3.68/3.68 (12 H, s, 4 × OMe), 3.91–3.97 (2 H, m, H-2, H-2′), 4.03–4.08/4.18–4.25 (2 H, m, H-5, H-5′), 5.61 (1 H, t, CH=CBr, *J* 6.6 Hz). ^{13}C NMR ($CDCl_3$): δ 17.04/17.20/19.48/19.67 ($CHMe_2$), 32.10/32.29 (2 × $CHMe_2$), 36.97 (CH_2CH=CBr), 46.03 (CH_2CBr=), 52.62 (4 × OMe), 54.76 (C-2, C-2′), 60.8 (C-5, C-5′), 124.1 (CH=CBr), 126.9 (CBr=CH), 161.37/162.00/162.88/163.00 (C-3, C-3′, C-6, C-6′). MS (CI): 501/499 (91/100, *M*+1), 419 (43), 183 (22).

(E)-1,4-Bis[(2S,5R)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-pyrazinyl]-2-bromo-2-butene (**13**). A solution of (*2S*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (0.57 g, 3.09 mmol) in anhydrous THF (6 ml) under nitrogen was lithiated by the addition of a solution of BuLi in hexane (0.88, 1.6 M, 1.42 mmol). The solution was stirred at −78 °C for 20 min before being transferred through Teflon tubing to a precooled and stirred solution of (*E*)-1,2,4-tribromo-2-butene (0.36 g, 1.29 mmol) in THF (1.3 ml) under nitrogen at −78 °C. The reaction mixture was allowed to reach ambient temperature overnight, phosphate buffer (pH 7, 4.0 ml) and water (4 ml) were added, the mixture was shaken with diethyl ether (10 ml) and the phases separated. The aqueous phase was extracted with diethyl ether (2 × 20 ml) and the combined ether solutions were dried ($MgSO_4$) and evaporated. The title compound was isolated from the reaction products by flash chromatography on silica gel using EtOAc–hexane (1:9). The product thus obtained was a mixture of the diastereoisomers of dialkylated product. The isomers were separated by a second flash chromatographic operation on silica gel using 7% EtOAc in CH_2Cl_2. The title compound was isolated in 30% yield (0.193 g); the second component isolated was one or both of its diastereoisomers **14a** or **14b** in 20% yield (0.128 g), and the third product was the monoalkylated derivative **15** in 9% yield (0.046 g). All products were yellow oils. Spectroscopic data for the title compound: ^{1}H NMR ($CDCl_3$): δ 0.62/0.64/1.00/1.01 (12 H, d, 4 × $CHMe_2$, *J* 6.8 Hz), 2.14–2.30 (2 H, m, $CHMe_2$, *J* 6.8, 3.4 Hz), 2.36–2.68 (2 H, m, CH_2), 2.78 (H, CHH, dd, *J* 14.3, 7.8 Hz), 2.92 (1 H, dd, CHH, *J* 14.3, 4.3 Hz), 3.63/3.64/3.68 (12 H, s, 4 × OMe), 3.93 (2 H, m, H-5, H-5′), 4.00–4.21 (2 H, m, H-2, H-2′). 5.91 (1 H, t, CH=CBr, *J* 7.7 Hz). ^{13}C NMR ($CDCl_3$): δ 16.59/16.68/19.01/19.06 ($CHMe_2$), 31.74 (2 × $CHMe_2$), 34.43 (CH_2CH=CBr), 40.47 (CH_2CBr=), 52.36/52.44 (4 × OMe), 54.34 /54.87 (C-2, C-2′), 60.80 (C-5, C-5′), 123.22 (CH=CBr), 130.48 (CBr=CH), 162.63/162.74/163.78/164.11 (C-3, C-3′, C-6, C-6′). MS (CI): 501/499 (34/32, *M*+1), 445 (10), 367 (63), 373 (12), 372 (16). 356 (10), 355 (12), 299 (18), 298 (26), 281 (14), 215 (14), 184 (12), 183 (100), 140 (35), 132 (36).

(E)-1,4-Bis[(2R)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-pyrazinyl]-2-bromo-2-butene (**14**). The product was isolated in 20% yield by chromatograpic separation of the product mixture in the preparation of **13** (*vide supra*). ^{1}H NMR ($CDCl_3$): δ 0.70/0.82/1.06/1.11 (12 H, d, 4 × $CHMe_2$, *J* 6.8 Hz), 2.17–2.30 (2 H, m, 2 × $CHMe_2$, *J* 6.8, 3.4 Hz), 2.35–2.69 (2 H, m, CH_2), 2.77 (1 H, CHH, dd, *J* 14.3, 8.8 Hz), 2.96 (1 H, dd, CHH, *J* 14.3, 4.7 Hz), 3.68/3.70/3.71 (12 H, s, 4 × OMe), 3.98 (2 H, m, H-5, H-5′), 4.06–4.33 (2 H, m, H-2, H-2′), 5.96 (1 H, t, CH=CBr, *J* 7.1 Hz). ^{13}C NMR ($CDCl_3$): δ 16.56/17.34/18.99/19.48 (4 × $CHMe_2$), 31.34/31.70 (2 × $CHMe_2$), 34.46 (CH_2CH=CBr), 41.96 (CH_2CBr=), 52.39 (4 × OMe), 54.37/54.87 (C-2, C-2′), 60.78/60.87 (C-5, C-5′), 123.63 (CH=CBr), 130.02 (CBr=CH), 162.65/163.94/164.10 (C-3, C-3′, C-6, C-6′).

(E)-1-[(2S,5R)-2,5-Dihydro-3,6-dimethoxy-2-isopropyl-5-pyrazinyl]-3,4-dibromo-2-butene (**15**). The monoalkylated product **15** was isolated in 9% yield on flash chromatography of the product mixture obtained in the preparation of **14** (*vide supra*). ^{1}H NMR ($CDCl_3$): δ 0.65/0.99 (6 H, d, 2 × $CHMe_2$, *J* 6.8 Hz), 2.17–2.25 (1 H, m, $CHMe_2$), 2.52–2.61 (2 H, m, CH_2), 3.6/3.67 (6 H, s, 2 × OMe), 3.92 (1 H, m, t, H-2, *J* 3.5 Hz), 4.04–4.11 (1 H, m, H-5), 4.23 (1 H, d, BrCHH–CBr, *J* 14.5 Hz), 4.28 (1 H, d, Br–CHH–CBr, *J* 14.5 Hz), 5.94 (1 H, t, CH_2CH=C, *J* 8.0 Hz). ^{13}C NMR ($CDCl_3$): δ 16.27/19.28 ($CHMe_2$), 32.15 ($CHMe_2$), 33.16

($\underline{C}H_2CH{=}CBr$), 34.54 ($BrCH_2CBr{=}\underline{C}$), 52.71 ($2\times OMe$), 54.34 (C-5), 61.05 (C-2), 121.24 ($CH_2\underline{C}Br{=}CH$), 133.01 ($CH_2\underline{C}H{=}C$), 161.68/164.0.7 (C-3, C-6). MS (CI): 399/397/395 (11/22/11, $M+1$), 319 (5), 317 (8), 238 (14), 237 (100), 183 (10), 141 (10).

(Z)-1-[(2S,5R)-2,5-Dihydro-3,6-dimethoxy-2-isopropyl-5-pyrazinyl]-3,4-dibromo-2-butene (**16**) *and (Z)-1-[(2S5R)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-pyrazinyl]-2,4-dibromo-2-butene* (**17**). A solution of (*2S*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (300 mg, 1.63 mmol) in anhydrous THF (3.5 ml) under nitrogen was lithiated by the addition of a solution of BuLi in hexane (0.80 ml, 2.2 M, 1.76 mmol). The solution was stirred at −78 °C for 20 min before being transferred through Teflon tubing to a precooled and stirred solution of (*Z*)-1,2,4-tribromo-2-butene (1.90 g, 6.51 mmol) in THF (6.8 ml) under nitrogen at −78 °C. The reaction mixture was allowed to reach ambient temperature overnight, phosphate buffer (pH 7, 3.0 ml) and water (3 ml) were added and the mixture was shaken with diethyl ether (10 ml). The phases were separated, the aqueous phase extracted with diethyl ether (2×20 ml), and the combined ether solutions were dried ($MgSO_4$) and evaporated. The major reaction products consisted of a mixture of the two regioisomeric monoalkylated compounds **16** and **17**. The isomers were isolated as a pure isomer mixture after flash chromatography on silica using EtOAc–hexane (1:9). The title compounds were obtained as a yellow oil. MS (EI): 398/396/394 (11/22/11, M^+), 353 (2) (5), 317 (7), 183 (59), 141 (100); MS (CI): 399/397/395 (11/22/11, $M+1$), 319 (5), 317 (8), 238 (14), 237 (100), 183 (10), 141 (10).

Isomer **16**: ^{1}H NMR ($CDCl_3$): δ 0.65/1.00 (6 H, d, $4\times CHMe_2$, *J* 6.8 Hz), 2.17 –2.34 (1 H, m, $CHMe_2$), 2.76 (1 H, dd, CHH, *J* 7.3, 14.3 Hz), 3.02 (1 H, dd, CHH, *J* 4.6, 14.3 Hz), 3.65/3.68 (6 H, s, $2\times OMe$), 3.91–3.95 (1 H, m, H-2), 4.02 (2 H, d, $CBr{=}CH{-}C\underline{H}_2Br$, *J* 7.9 Hz), 4.20–4.29 (1 H, m, H-5), 5.98 (1 H, t, $CH_2\underline{C}H{=}C$, *J* 7.9 Hz). ^{13}C NMR ($CDCl_3$): δ 16.61/19.04 ($CH\underline{M}e_2$), 30.01 ($\underline{C}HMe_2$), 31.65 ($\underline{C}H_2CH{=}CBr$), 45.78 ($BrCH_2CBr{=}\underline{C}$), 52.57 ($2\times OMe$), 54.07 (C-5), 60.73 (C-2), 127.45 ($CH_2\underline{C}H{=}CBr$), 130.79 ($CH_2\underline{C}Br{=}CH$), 162.04/163.93 (C-6, C-3).

Isomer **17**: ^{1}H NMR ($CDCl_3$): δ 0.65/1.01 (6 H, d, $4\times CHMe_2$, *J* 6.8 Hz), 2.17–2.34 (1 H, m, $2\times CHMe_2$), 2.50–2.80 (2 H, m, CH_2), 3.65/3.68 (3 H, s, OMe), 3.91–3.95 (1 H, m, H-2) 4.05–4.15 (1 H, m, H-5), 4.20 (2 H, s, $CH{=}CBrC\underline{H}_2Br$), 6.06 (1 H, t, $CH_2CH{=}CBr$, *J* 7.3 Hz). ^{13}C NMR ($CDCl_3$): δ 16.61/19.04 ($CH\underline{M}e_2$), 31.81 ($\underline{C}HMe_2$), 36.76/38.91 ($2\times CH_2$), 52.38 ($2\times OMe$), 54.30 (C-5), 60.87 (C-2), 124.26 ($CH_2\underline{C}H{=}CBr$), 129.28 ($CH_2\underline{C}Br{=}CH$), 162.67/164.18 (C-6, C-3).

General procedure for the Pd-catalyzed coupling reactions in the formation of **18**. The catalyst $Pd(AsPh_3)_4$ was prepared *in situ* by adding dry degassed NMP (3.0 ml) to a mixture of $Pd_2(dba)_3\cdot CHCl_3$ (0.013 mmol) and triphenylarsine (0.107 mmol) under argon. The mixture was stirred at ambient temperature for 10 min after which a yellow solution resulted. A solution of (*Z*)-1,4-bis[(2*S*,5*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-pyrazinyl]-2-bromo-2-butene (0.263 mmol) in dry and degassed NMP (1 ml) was added, and the mixture was stirred at ambient temperature for 10 min before a solution of the (tributyl)stannyl derivative (0.657 mmol) in dry and degassed NMP (1.0 ml) was added dropwise. The mixture was stirred for 10 min at ambient temperature, heated slowly to 88 °C and maintained at this temperature for 12 h. The solvent was then removed at reduced pressure and the product isolated after flash chromatography on silica gel using Et_2O–CH_2Cl_2 (1:10). The products were obtained as oily materials.

(Z)-1,4-Bis[(2S,5R)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-pyrazinyl]-2-(2-thienyl)-2-butene (**18a**) The product was obtained in 83% yield by coupling **12** with tributyl(2-thienyl)stannane. MS: *M* 502.2609. Calc. for $C_{26}H_{38}N_4O_4S$: 502.2613. ^{1}H NMR ($CDCl_3$): δ 0.58/0.65/0.97/1.01 (12 H, d, $4\times CHMe_2$, *J* 6.8 Hz), 2.14–2.30 (2 H, m, $2\times CHMe_2$), 2.64–2.80 (3 H, m, CHH, CH_2), 2.94 (1 H, dd, CHH, *J* 4.6, 13.7 Hz), 3.41/3.52/3.62/3.63 (12 H, s, $4\times OMe$), 3.76/3.93 (2 H, t, H-5, H-5′, *J* 7.5 Hz), 4.02/4.10 (2 H, m, H-2, H-2′). 5.39 (1 H, t, CH=C, *J* 7.0 Hz), 6.91 (2 H, m, thienyl H), 7.18 (1 H, dd, *J* 5.0, 1.1 Hz, thienyl-H). ^{13}C NMR ($CDCl_3$): δ 15.45/15.60/18.04 ($CH\underline{M}e_2$), 30.31/30.76 ($\underline{C}HMe_2$), 33.01/43.09 ($2\times\underline{C}H_2$), 50.85/51.16/51.26/51.42 ($4\times OMe$), 54.26/54.54 (C-2, C-2′), 59.43/59.75 (C-5, C-5′), 123.24/124.77/125.34 (thienyl–C), 126.84 ($CH_2\underline{C}H{=}C$), 130.30 (thienyl-C), 141.98 ($CH_2CH{=}\underline{C}$), 161.58/162.15/162.80 (C-3, C-3′, C-6, C-6′). MS (EI): 502 (2, M^+), 461 (3), 460 (9), 459 (33), 320 (6), 319 (28), 305 (3), 184 (23), 183 (23), 141 (100).

(Z)-1,4-Bis[(2S5R)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-pyrazinyl]-2-vinyl-2-butene (**18b**). The product was obtained in 32% yield by coupling **12** with tributyl(vinyl)stannane. MS: *M* 446.2895. Calc. for $C_{24}H_{38}N_4O_4S$ 446.2893. ^{1}H NMR ($CDCl_3$): δ 0.57/0.59/0.95/0.96 (12 H, d, $4\times CHMe_2$, *J* 6.8 Hz), 2.14–2.29 (2 H, m, $2\times CHMe_2$), 2.34 (1 H, dd, CHH, *J* 13.8, 6.6 Hz), 2.60 (2 H, m, CH_2), 2.72 (1 H, dd, CHH, *J* 13.8, 4.1 Hz), 3.55/3.58/3.358/3.58 (12 H, s, $4\times OMe$), 3.77/3.86 (2 H, t, H-5, H-5′, *J* 3.4 Hz), 4.02/4.05 (2 H, m, H-2, H-2′), 5.01 (1 H, d, CHH=CH, *J* 11.0 Hz), 5.21 (1 H, d, C=CH, *J* 7.6 Hz), 5.29 (1 H, d, CHH=CH, *J* 17.5 Hz), 6.62 (1 H, dd, CH_2=CH, *J* 11.0, 17.5 Hz). ^{13}C NMR ($CDCl_3$): δ 16.45/16.57/19.06/19.13 ($CH\underline{M}e_2$), 31.28/31.34 ($\underline{C}HMe_2$), 32.21/37.40 ($2\times\underline{C}H_2$), 51.95/52.18/52.26/52.33 ($4\times OMe$), 55.39/55.59 (C-2, C-2′), 60.33/60.69 (C-5, C-5′), 113.88 ($\underline{C}H_2{=}C$), 127.94 ($CH_2\underline{C}H{=}C$), 133.44 ($\underline{C}H{=}CH_2$), 135.20 ($CH_2CH{=}\underline{C}$), 162.89/163.17/163.87 (C-3, C-3′, C-6, C-6′). MS (EI): 446 (3, M^+), 404 (12), 403 (49), 264 (21), 263 (93), 250 (6), 249 (6), 184 (6), 183 (17), 142 (7), 141 (100), 139 (7).

(Z)-1,4-Bis[(2S,5R)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-pyrazinyl]-2-(β-styryl)-2-butene (**18c**). The product was obtained in 96% yield by coupling **12** with tributyl(β-styryl)stannane. MS: *M* 522.3215. Calc. for $C_{30}H_{42}N_4O_4$: 522.3206. ^{1}H NMR ($CDCl_3$): δ 0.61/0.64/1.00/1.01 (12 H, d, 4 × $CHMe_2$, *J* 6.8 Hz), 2.18–2.29 (2 H, m, 2 × $CHMe_2$), 2.55 (1 H, dd, CHH, *J* 13.9, 6.3 Hz), 2.88 (2 H, m, CH_2), 2.89 (1 H, dd, CHH, *J* 13.9, 4.2 Hz), 3.55/3.58/3.618/3.63 (12 H, s, 4 × OMe), 3.84/3.93 (2 H, t, H-5, H-5′, *J* 3.5 Hz), 4.11–4.18 (2 H, m, H-2, H-2′), 5.32 (1 H, t, CH_2CHCH, *J* 7.9 Hz), 6.71 (1 H, d, CH=CHPh, *J* 16.2 Hz), 7.14 (1 H, d, CH=CHPh, *J* 16.2 Hz), 7.17–7.42 (5 H, m, PhH). ^{13}C NMR ($CDCl_3$): δ 16.42/16.56/19.06/19.11 ($CHMe_2$), 31.28/31.64 ($CHMe_2$), 32.35/37.62 (2 × CH_2), 51.99/52.16/52.22/52.28 (4 × OMe), 55.46/55.92 (C-2, C-2′), 60.31/60.68 (C-5, C-5′), 125.91 (PhCH=), 126.31/127.08/128.54 (Ph), 128.64 (CH_2CH=C), 128.73 (PhCH=CH,), 135.22 (CH_2CH=C), 138.10 (*ipso*-Ph), 162.73/162.83/163.25/163.99 (C-3, C-3′, C-6, C-6′). MS (EI): 522 (6, M^+), 480 (6), 479 (25), 440 (8), 439 (28), 184 (20), 183 (20), 167 (5), 141 (100), 97 (8).

General procedure for the Pd-catalyzed coupling reactions in the formation of **19**. The catalyst $Pd(AsPh_3)_4$ was prepared *in situ* by adding $Pd_2(dba)_3 \cdot CHCl_3$ (0.012 mmol) and triphenylarsine (0.103 mmol) to dry degassed THF (3 ml) under argon. The mixture was stirred at ambient temperature for 10 min after which a yellow solution resulted. A solution of (*E*)-1,4-bis[(2*S*,5*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-pyrazinyl]-2-bromo-2-butene (0.244 mmol) in dry and degassed THF (1 ml) was added, and the mixture was stirred at ambient temperature for 10 min before a solution of the tributylstannyl derivative (0.488 mmol) in dry and degassed THF (1.0 ml) was added dropwise. The mixture was stirred for 10 min at ambient temperature, heated slowly to 45–50 °C and maintained at this temperature for 12 h. The solvent was then distilled off and the product isolated after flash chromatography on silica gel using Et_2O–CH_2Cl_2 (1:10). The products were obtained as oily materials.

(E)-1,4-Bis[(2S,5R)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-pyrazinyl]-2-(2-thienyl)-2-butene (**19a**) The product was obtained in 91% yield by coupling **13** with tributyl(2-thienyl)stannane. MS: *M* 502.2630. Calc. for $C_{26}H_{38}N_4O_4S$: 502.2613. ^{1}H NMR ($CDCl_3$): δ 0.60/0.66/0.98/1.00 (12 H, d, 4 × $CHMe_2$, *J* 6.8 Hz), 2.18–2.24 (2 H, dsept, 2 × $CHMe_2$, *J* 3.4, 6.8 Hz), 2.64–2.68 (1 H, m, CH_2), 2.73–2.78 (2 H, m, CHH), 3.09 (1 H, dd, CHH, *J* 4.1, 13.9 Hz), 3.50/3.62/3.65/3.66 (12 H, s, 4 × OMe), 3.83/3.88 (2 H, t, H-5, H-5′, *J* 3.4 Hz), 4.10–4.17 (2 H, m, H-2, H-2′). 5.89 (1 H, t, CH_2CH=C, *J* 7.5 Hz), 6.88–6.90 (1 H, m, thienyl-H), 6.94–6.96 (1 H, m, thienyl-H). 7.02–7.04 (1 H, m, thienyl-H).^{13}C NMR ($CDCl_3$): δ 16.55/16.65/19.04/19.08 ($CHMe_2$), 31.34/31.70 ($CHMe_2$), 33.64/35.52 (2 × CH_2), 52.23/52.27/52.37 (4 × OMe), 55.54/55.60 (C-2, C-2′), 60.57/60.83 (C-5, C-5′), 122.76/122.96/126.92 (thienyl-C), 126.17 (CH=C), 132.52 (CH=C), 147.51 (thienyl-C), 163.22/163.32/163.96 (C-3, C-3′, C-6, C-6′). MS (EI): 502(3, M^+), 460 (10), 459 (37), 403 (4), 319 (29), 305 (4), 184 (23), 183 (32), 183 (24), 141 (100).

(E)-1,4-Bis[(2S,5R)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-pyrazinyl]-2-vinyl-2-butene (**19b**). The product was obtained in >95% yield by coupling **13** with tributyl(vinyl)stannane. MS: *M* 446.2893. Calc. for $C_{24}H_{38}N_4O_4S$: 446.2893. ^{1}H NMR ($CDCl_3$): δ 0.63/0.64/1.00/1.01 (12 H, d, 4 × $CHMe_2$, *J* 6.8 Hz), 2.12–2.27 (2 H, dsept, 2 × $CHMe_2$, *J* 3.4, 6.8 Hz), 2.42 (1 H, dd, CHH, *J* 13.7, 8.8 Hz), 2.62–271 (2 H, m, CH_2), 2.85 (1 H, dd, CHH, *J* 13.7, 3.7 Hz), 3.62/3.63/3.67 (12 H, s, 4 × OMe), 3.87 (2 H, t, H-5, H-5′, *J* 3.4 Hz), 4.04–4.09 (2 H, m, H-2, H-2′), 4.91 (1 H, d, CHH=CH, *J* 11.0 Hz), 5.20 (1 H, d, CHH=C, *J* 17.5. Hz), 5.54 (1 H, d, C=CH, *J* 7.4 Hz), 6.26 (1 H, dd, CH_2=CH, *J* 11.0, 17.5 Hz). ^{13}C NMR ($CDCl_3$): δ 16.53/19.01/19.09 ($CHMe_2$), 31.41 ($CHMe_2$), 31.60 (CH_2), 31.65 (2 × $CHMe_2$), 33.47 (CH_2), 52.25/52.32/52.37 (4 × OMe), 55.37 (C-2, C-2′), 60.52/60.70 (C-5, C-5′), 113.31 (CH_2=CH), 130.42 (CH_2CH=C), 137.17 (CH_2C=CH), 140.34 (CH=CH_2), 163.18/163.78 (C-3, C-3′, C-6, C-6′). MS (EI): 446 (4, M^+), 404 (11), 403 (49), 264 (15), 263 (69), 250 (6), 249 (7), 184 (15), 183 (16), 167 (6), 141 (100), 126 (5).

(E)-1,4-Bis[(2S,5R)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-pyrazinyl]-2-(β-styryl)-2-butene (**19c**). The product was obtained in 96% yield by coupling **13** with tributyl(β-styryl)stannane. ^{1}H NMR ($CDCl_3$): δ 0.63/0.66/1.02 (12 H, d, 4 × $CHMe_2$, *J* 6.8 Hz), 2.16–2.27 (2 H, m, 2 × $CHMe_2$), 2.50–2.79 (3 H, m, CHH, CH_2), 2.99 (1 H, dd, CHH, *J* 13.9, 3.7 Hz), 3.61/3.65/3.66/3.71 (12 H, s, 4 × OMe), 3.89–3.92 (2 H, m H-5, H-5′), 4.08–4.18 (2 H, m, H-2, H-2′), 5.68 (1 H, t, CH_2CH=CH, *J* 7.5 Hz), 6.57 (1 H, d, CH=CHPh, *J* 16.3 Hz), 6.73 (1 H, d, CH=CHPh, *J* 16.3 Hz), 7.11–7.40 (5 H, m, PhH). ^{13}C NMR ($CDCl_3$): δ 16.57/19.03/19.10 ($CHMe_2$), 31.43/31.70 ($CHMe_2$), 32.12/37.71 (2 × CH_2), 52.29/52.32/52.40/52.46 (4 × OMe), 55.47/55.64 (C-2, C-2′), 60.59/60.77 (C-5, C-5′), 126.31 (PhCH=), 126.20/126.85/128.48 (Ph), 131.20 (CH_2CH=C), 132.92 (PhCH=CH), 137.14 (CH_2CH=C), 137.96 (*ipso*-Ph), 163.21/163.30/163.67/163.86 (C-3, C-3′, C-6, C-6′).

(E)-1,4-Bis[(2S,5R)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-pyrazinyl]-2-(2-phenylethynyl)-2-butene (**19d**). The product was obtained in 95% yield by coupling **13** with tributyl(2-phenylethynyl)stannane. MS: *M* 520.3062. Calc. for $C_{30}H_{42}N_4O_4$: 520.3050. ^{1}H NMR ($CDCl_3$): δ 0.66/0.67/1.02 /1.03 (12 H, d, 4 × $CHMe_2$, *J* 6.8 Hz), 2.21–2.26 (2 H, m, 2 × $CHMe_2$), 2.54–2.85 (4 H, m, 2 × CH_2), 3.62/3.66/3.67/3.68 (12 H, s, 4 × OMe), 3.93–3.99 (2 H, m H-5, H-5′), 4.05–4.32 (2 H, m, H-2, H-2′), 5.98 (1 H, t, CH_2CH=C, *J* 7.5 Hz), 7.25 (3 H, Ph,), 7.38 (2 H, m, PhH). ^{13}C NMR ($CDCl_3$):

δ 16.59/16.61/19.00/19.10 ($CHMe_2$), 31.40/31.77 ($2\times CHMe_2$), 33.41/35.53 ($2\times CH_2$), 52.37/52.45 ($4\times OMe$), 55.13/55.16 (C-2, C-2'), 60.52/60.83 (C-5, C-5'), 86.81/91.75 (CC), 121.53 (CH=C), 123.86 (*ipso*-Ph), 127.61/128.10/131.39 (Ph), 136.25 (CH_2C=CH), 162.99/163.06/163.83/163.98 (C-3, C-3', C-6, C-6'). MS (EI): 520 (3, M^+), 478 (14), 477 (48), 440 (8), 375 (5), 338 (10), 337 (33), 277 (4), 184 (19), 183 (30), 167 (12), 141 (100).

General procedure for the preparation of dimethyl 2,7-diamino-4-octenedioate derivatives **20** *and* **21**. Aqueous HCl (2.88 ml, 1.0 M, 2.88 mmol) was added to a solution of the 1,4-bis[(2*S*,5*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-pyrazinyl]-2-butene **10**, **11**, **13** or **18** (0.686 mmol) in dioxane (5.75 ml) and water (2.88 ml), the mixture was stirred at ambient temperature for 5 h, and the pH adjusted to 10 by addition of conc. aq. ammonia. The mixture was extracted with dichloromethane (3 × 10 ml), the combined organic extracts were dried ($MgSO_4$) and the solvent was removed by distillation. The methyl valine ester in the product was removed by slow (3 h) bulb-to-bulb distillation at 50 °C/0.25 mmHg). The remaining oily material was essentially the desired, pure amino acid methyl ester.

(E)-Dimethyl (2R,7R)-2,7-diamino-4-octenedioate (**20a**). A solution of (*E*)-1,4-bis[(2*S*,5*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-pyrazinyl]-2-butene (0.420 g, 1.0 mmol) in dioxane (8.40 ml) and HCl (4.20 mmol, 1.0 M, 4.20 ml) in water (4.20 ml) was stirred at ambient temperature for 5 h. The pH of the solution was adjusted to 10 with aqueous conc. ammonia, and the mixture was extracted with dichloromethane (3 × 15 ml). The dried ($MgSO_4$) organic solution was evaporated and the valine methyl ester removed from the residual material by slow bulb-to-bulb distillation at 0.04 Torr/50 °C; yield 0.208 g (91%). MS: *M* 230.1276. Calc. for $C_{10}H_{18}N_2O_4$: 230.1267. ^{1}H NMR ($CDCl_3$): δ 1.55 (4 H, s, NH_2), 2.17–2.45 (4 H, m, $2\times CH_2$), 3.34–3.38 (2 H, m, $2\times CH$), 3.56 (6 H, s, $2\times OMe$), 5.31–5.34 (2 H, m, $2\times CH$=C). ^{13}C NMR ($CDCl_3$): δ 37.62 ($2\times CH_2$), 51.64 ($2\times OMe$), 53.76 ($2\times CH$), 128.81 ($2\times CH$=C), 175.27 ($2\times CO_2Me$). MS (EI): 230 (0.18, M^+), 171 (40), 143 (53), 111 (14), 89 (30), 88 (100).

(Z)-Dimethyl (2R,7R)-2,7-diamino-4-bromo-4-octenedioate (**20b**) was prepared from **12** in 95% yield. Anal. $C_{14}H_{20}N_2O_4$: C, H. MS: *M* 312.1140. Calc. for $C_{14}H_{20}N_2O_4$: 312.1144 . ^{1}H NMR ($CDCl_3$): δ 1.59 (4 H, s, NH_2), 2.38–2.56 (3 H, m, CHH, CH_2), 2.81 (1 H, dd, CHH, *J* 14.1, 4.5 Hz), 3.45–3.49 (1 H, m, $CHCO_2Me$), 3.61/3.62(6 H, s, $2\times OMe$), 3.66–3.72 (1 H, m, $CHCO_2Me$), 5.74 (1 H, t, CH=C, *J* 7.0 Hz). ^{13}C NMR ($CDCl_3$): 35.71/45.94 ($2\times CH_2$), 51.20 ($2\times OMe$), 51.56/52.56 ($2\times CHCO_2Me$), 125.00 (CBr=C), 127.03 (CH=CBr), 173.72/174.40 ($2\times CO_2Me$).

(Z)-Dimethyl (2R,7R)-2,7-diamino-4-(2-thienyl)-4-octenedioate (**20c**) was prepared from **18a** in 77% yield. MS: *M* 312.1140. Calc. for $C_{14}H_{20}N_2O_4$: 312.1144. ^{1}H NMR ($CDCl_3$): δ 1.70 (4 H, s, NH_2), 2.53–2.68 (3 H, m, CHH, CH_2), 2.69 (1 H, dd, CHH, *J* 13.74.3 Hz), 3.52–3.61 (2 H, m, $2\times CHCO_2Me$), 3.64/3.73 (6 H, s, $2\times OMe$), 5.61 (1 H, t, CH=C, *J* 7.3 Hz), 6.96–7.04 (2 H, m, thienyl-H), 7.27–7.31 (1 H, m, thienyl-H). ^{13}C NMR ($CDCl_3$): δ 28.67/33.52 ($2\times CH_2$), 50.90/51.07 ($2\times OMe$), 52.04/53.35 ($2\times CHCO_2Me$), 124.27/125.60/125.94 (thienyl-C), 127.04 (CH_2CH=C), 131.24 (thienyl-C), 139.23 (CH_2C=CH), 175.28/175.53 ($2\times CO_2Me$). MS (EI): 312 (11, M^+), 253 (8), 225 (32), 210 (9), 166 (7), 150 (11), 149 (12), 138 (12), 137 (22), 89 (18), 88 (100).

(Z)-Dimethyl (2R,7R)-2,7-diamino-4-vinyl-4-octenedioate (**20d**) was prepared from **18b** in 89% yield. MS: *M* 256.1432. Calc. for $C_{12}H_{20}N_2O_4$: 256.1423. ^{1}H NMR ($CDCl_3$): δ 1.70 (4 H, s, NH_2), 2.29 (1 H, dd, CHH, *J* 8.6, 13.7 Hz), 2.47–2.64 (2 H, m, CH_2), 2.78 (1 H, dd, CHH, *J* 13.7, 4.7 Hz), 3.52 (1 H, t, $CHCO_2Me$, *J* 6.2 Hz), 3.59–3.62 (1 H, m, $CHCO_2Me$), 3.67 (6 H, s, $2\times OMe$), 5.17 (1 H, d, C=CH_2, *J* 11.1 Hz), 5.32 (1 H, d, CH=CH_2, *J* 2 17.6 Hz), 5.42 (1 H, t, CH_2CH=C, *J* 7.8 Hz), 6.60 (1 H, dd, C=CH_2, *J* 17.6, 11.1 Hz). ^{13}C NMR ($CDCl_3$): δ 32.76/39.57 ($2\times CH_2$), 51.88/52.00 ($2\times OMe$), 53.38/54.45 ($2\times CHCO_2Me$), 115.32 (CH=CH_2), 127.90 (CH_2CH=C), 131.78 (C–CH=CH_2), 136.65 (CH_2C=CH), 175.74 ($2\times CO_2Me$). MS (EI): 256 (4, M^+), 197 (11), 169 (22), 168 (14), 120 (4), 110 (14), 94 (11), 88 (100), 74 (8).

(Z)-Dimethyl (2R,7R)-2,7-diamino-4-(β-styryl)-4-octenedioate (**20e**) was prepared from **18c** in 90% yield. MS: *M* 332.1731. Calc. for $C_{12}H_{20}N_2O_4$: 332.1736. ^{1}H NMR ($CDCl_3$): δ 1.76 (4 H, s, NH_2), 2.41 (1 H, dd, CHH, *J* 8.5, 13.7 Hz), 2.58–2.69 (2 H, m, CH_2), 2.89 (1 H, dd, CHH, *J* 13.7, 4.7 Hz), 3.51–3.61 (2 H, m, $2\times CHCO_2Me$), 3.67/3.68 (6 H, s, $2\times OMe$), 5.84 (1 H, t, CH_2CH=C, *J* 7.7 Hz), 6.65 (1 H, d, CH=CHPh, *J* 16.3 Hz), 7.07 (1 H, CH=CHPh, d, *J* 16.3 Hz), 7.21–7.49 (5 H, m, PhH). ^{13}C NMR ($CDCl_3$): δ 32.94/39.98 ($2\times CH_2$), 51.88/51.95 ($2\times OMe$), 53.50/54.47 ($2\times CHCO_2Me$), 123.78 (CH=CHPh), 126.50/127.70/128.31/128.58 (5 H, PhH), 129.81 (CH_2CH=C), 135.30 (CH=CHPh), 137.24 (CH_2C=CH), 175.49 ($2\times CO_2Me$). MS (EI): 332 (18, M^+), 279 (4), 273 (10), 246 (6), 245 (35), 234 (14), 230 (7), 186 (8), 167 (9), 157 (20), 89 (13), 88 (100).

(Z)-Dimethyl (2R,7R)-2,7-diamino-4-octenedioate (**21a**). A solution of (*Z*)-1,4-bis[(2*S*,5*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-pyrazinyl]-2-butene (0.250 g, 0.595 mmol) in dioxane (4.76 ml) and HCl (2.38 mmol, 1.0 M, 2.38 ml) in water (2.38 ml) was stirred at ambient temperature for 5 h. Aqueous conc. ammonia was added dropwise to the solution until pH 10 was reached and the mixture was extracted with dichloromethane (3 × 10 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated and the residue was subjected

to flash chromatography on silica using EtOH–dichloromethane: NH_3 (20:90:1), yield: 0.127 g (85%). MS: *M* 230.1249. Calc. for $C_{10}H_{18}N_2O_4$: 230.1267. ^{1}H NMR ($CDCl_3$): δ 1.97 (4 H, s, 2 × NH_2), 2.3–2.5 (4 H, m, 2 × CH_2), 3.4–3.6 (2 H, m, CH), 3.64 (6 H, s, 2 × OMe), 5.45–5.49 (2 H, m, 2 × CH=C). ^{13}C NMR ($CDCl_3$): δ 32.24 (2 × CH_2), 51.94 (2 × OMe), 53.89 (2 × CH), 127.85 (CH=C), 175.32 (2 × CO_2Me). MS (EI): 230 (0.26, M^+), 171 (6), 154 (15), 143 (46), 128 (343), 122 (6), 111 (6), 94 (20), 88 (100).

(E)-Dimethyl (2R,7R)-2,7-diamino-4-bromo-4-octenedioate (**21b**) was prepared from **13** in 85% yield. ^{1}H NMR ($CDCl_3$): δ 1.55 (4 H, s, NH_2), 2.23–2.48 (2 H, m, CH_2), 2.69 (2 H, d, CHH, *J* 6.9 Hz), 3.42–3.56 (1 H, m, $CHCO_2$Me), 3.62/3.63 (6 H, s, 2 × OMe), 3.69 (1 H, t, $CHCO_2$Me), 5.94 (1 H, t, *J* 6.9 Hz, CH=C, *J* 7.8 Hz). ^{13}C NMR ($CDCl_3$): δ 34.29/40.42 (2 × CH_2), 51.97/52.00 (2 × OMe), 52.65/53.48 (2 × $CHCO_2$Me), 123.37 (CBr=C), 130.86 (CH=CBr), 174.68/174.90 (2 × CO_2Me).

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