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Ruthenium(II) in Ring Closing Metathesis for The Stereoselective Preparation of Cyclic 1-Amino-1-Carboxylic Acids.

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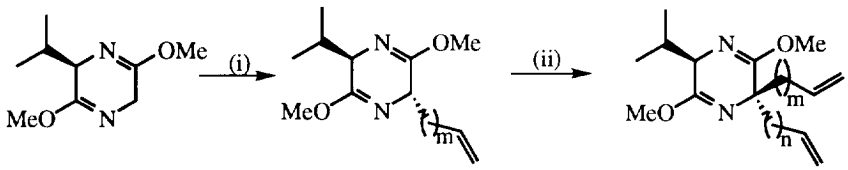
Abstract: Stereoselective synthesis of α-amino acids where the α-carbon of the amino acid is incorporated into a five-, six- or seven-membered ring is described. The stereoselective control results from stepwise bisalkenylation of (*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine. Ring closing metathesis was effected by ruthenium(II)-catalysis. The spiro-cycloalkene intermediates were further transformed into 1-aminocycloalkene-1-carboxylic acid derivatives by mild acid hydrolysis. © 1997, Elsevier Science Ltd. All rights reserved.

The preparation of rigidified α-amino acids to effect conformational constraints in peptides has assumed an important role in drug design and development.[1] We have reported on replacement of the disulfide bridge in cystine with constraining carbon bridges.[2] Replacement of the α-hydrogen in α-amino acids with a carbosubstituent constrains the conformation of the amino acid unit as exemplified in simple α-methyl and higher α-alkyl derivatives which may be achiral, or chiral in the form of a racemate, or in a stereochemically pure form from the resolution of a racemate or from stereoselective syntheses.[3] When substitution at the nitrogen of the α-amino group is tolerated, rigid amino acid structures arise where the amino group is part of a heterocyclic five- or higher-membered ring, particularly when fused into bicyclic or tricyclic derivatives of phenylalanine, tyrosine or tryptophane.[4]

Steric constraints are further increased on going from α-methyl α-amino acids to cyclic structures involving the α-carbon of the amino acid such as in 1-aminocycloalkyl-1-carboxylic acids and hetero analogues. Symmetrical 1-aminocycloalkyl-1-carboxylic acids derivatives or racemates,[5] chemically or enzymatically resolved racemates,[6] and optically pure stereoisomers prepared by stereoselective syntheses,[7] have very recently been reported. Derivatives of the simplest member of the cycloalkyl series, *viz.* 1-amino-1-cyclopropanecarboxylic acid, have been reported using the Schöllkopf bislactim ether reagent, (2*S*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine,[8] which is the enantiomer of the chiral auxiliary used as substrate in the present work (*vide infra*).

The very important advancement in effecting ring closing reactions recently reported by Grubbs using late transition metal,[9] led us to apply such reactions for the preparation of cyclic amino acids of the 1-amino-1-carboxylic type. The substrates for the ring closing metathesis (RCM) reactions were to be α,α-disubstituted glycine derivatives with the desired stereochemistry already built into the stereogenic center. This report deals with the preparation of unique and conformationally constrained α-amino acids available by this approach.[10]

Carbenoid ruthenium(II) complexes are excellent catalysts in RCM reactions.[9,11] More reactive, but less selective molybdennum complexes, were initially studied.[9a,12] Tungsten complexes also effect RCM reactions.[13] In our amino acid synthesis we have combined the Grubbs RCM methodology using ruthenium(II) complexes with stereoselective alkylation reactions using the Schöllkopf methodology for amino acid construction which involves the chiral auxiliary (2*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine.[14] This constitutes a powerful method for the preparation of 1-aminocycloalkene-1-carboxylic acid methyl esters. The cyclic structures prepared consist of five- to seven-membered rings carrying a double bond which may be used for further chemical modifications.



1		Yield%	d.e.%			Yield%	d.e.%
2a	m = 1	83	96	**3a**	m = n = 1	81	
2b	m = 2	92	75	**3b**	m = 1, n = 2	87	>95
2c	m = 3	80	82	**3c**	m = 2, n = 1	76	>95
				3d	m = n = 2	73	
				3e	m = 3, n = 1	65	>95
				3f	m = 2, n = 3	66	>95

(i) nBuLi/THF/-78 °C

$(CH_2)_mBr$/-78 - 20 °C

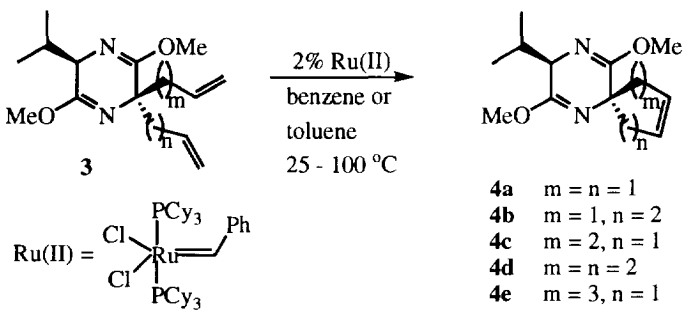
(ii) nBuLi/THF/-50 °C

$(CH_2)_nBr$/-78 - 20 °C

Scheme 1

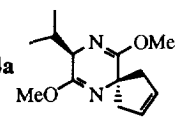
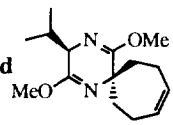
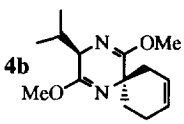
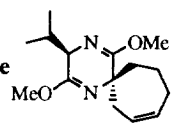
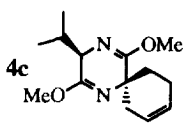
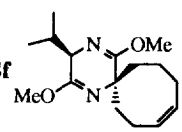
The substrates for the RCM reactions were to be geminal diolefins **3** derived from (2*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (**1**). Bisalkylation of the latter was to be effected in a stepwise manner which allows for the introduction of two different alkenes. The first alkylation step was effected by lithiation at -78 °C using allyl, 4-bromo-1-butene and 5-bromo-1-pentene. The yields of the monoalkylated products **2** were in the range 80 - 92%, the diastereomeric excess (d.e.) in the range 75 - 96%. The minor isomer can be removed and isolated by flash chromatography, but separation is not necessary since the overall stereochemistry in the reaction sequence is determined during the second alkylation step. The lithiation of the monalkylated products is slower than before the first alkylation, and was effected at - 50 °C. The lithiated species were subsequently cooled to -78 °C and the second alkylating agent added. Once lithiated the second time, the stereochemistry at the initial alkylating site is lost. The new alkylating agent will approach the reactive carbanionic center at the 5-position from the side of the ring opposite to the isopropyl group. The d.e. of the product **3** after the second alkylation step was excellent, as seen when different alkylating agents were used in the two steps (**3b**, **3c**, **3e**, **3f**), in excess of 95%; the chemical yields were in the range 65 - 87%.

The RCM reactions were effected by adding catalytic amounts of bis(tricyclohexylphosphine)-benzylidine ruthenium dichloride, usually 2%, to a solution of the bis-olefin **3** in benzene or toluene. The progress of the reaction was monitored by GLC or TLC. The time and temperature varied for the reaction to go to completion; the rate was monitored by the disappearnce of the substrate. The results from the RCM experiments are shown in Table 1. The catalyst complex seems sensitive to steric interaction from the isopropyl group of the substrate. An allyl group *cis* to the isopropyl group seems to be less reactive than in the *trans* position, and when the double bond is further removed by extension of the alkene; the formation of the six-membered ring structure **4b** proceeded more readily than the formation of its isomer **4c**. Support was further found in the relative ease of formation of the seven-membered ring structure **4d** wheras formation of the five-membered ring structure **4a** proceeded less readily from its diallyl precursor by RCM. Further conclusions are difficult to draw because of the relative ring-size preferences in RCM reactions.[9,11] In the



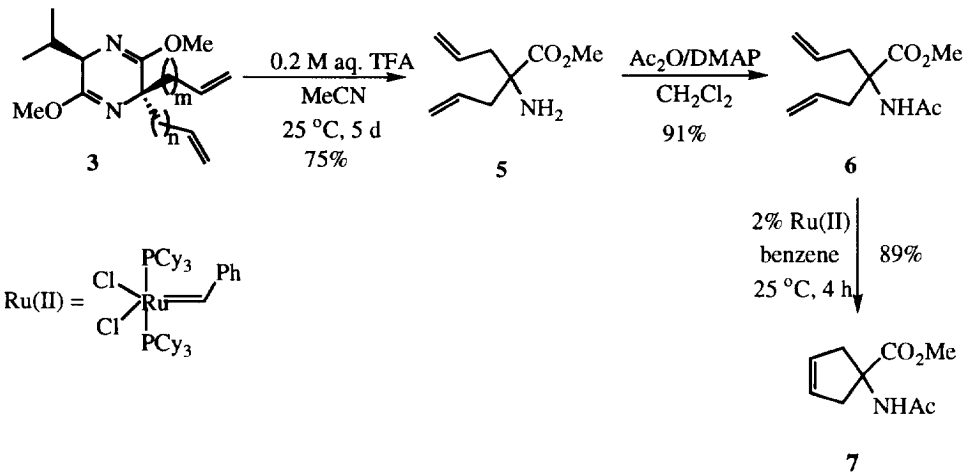
Scheme 2

Table 1. Formation of Cycloalkenes in Ru(II)-Catalyzed RCM Reactions.

	Temp./°C	Time/h	Yield%		Temp./°C	Time/h	Yield%
4a 	100	18	53	**4d** 	20	23	90
4b 	60	5	95	**4e** 	80	8	60
4c 	20	23	99	**4f** 	20 - 80	24	0

Solvent: **4a** toluene; **4b** - **4d** benzene.

slow reaction for the formation of the five-membered ring structure **4a**; the rection was effected in toluene at 100 °C. The catalyst under these conditions became inactive after a few hours and a second 2% portion of the catalyst was added after 4 hours; 53% yield was obtained after 18 hours. The diolefin substrate **3f** failed to yield any significant amount of the eight-membered ring derivative **4f**, even after prolonged heating and additional amounts of catalyst complex.



Scheme 3

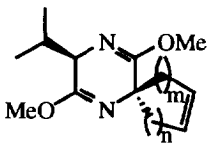
The low reactivity of the bisallyl derivative **3a** in the formation of its RCM five-membered ring product **4a** led to an alternative approach for the preparation of the amino acid target **8**. The bisallyl derivative **3a** was hydrolyzed under mild acid conditions with trifluoroacetic acid in acetonitrile at room temperature over 5 days. Mild conditions were necessary to avoid alternative reaction paths which lead to dipeptides. Prior to the RCM reaction the amino group was protected by acetylation. There was a very significant change in the ease

of the RCM reaction for the acyclic amino acid **6** and its precursor **3a**; the RCM reaction for **3a** gave 89% of the cyclic amino acid **7** after 4 hours at ambient temperature.

The Schöllkopf bislactim ethers are generally hydrolyzed by acid under mild conditions, 0.25 - 0.50 M HCl, to furnish their respective amino acid methyl esters. For the cyclic products **4**, however, hydrolysis was slow under these conditions and the formation of dipeptides was a problem. Better results were obtained using 0.2 M trifluoroacetic acid in acetonitrile allowing the reaction to proceed at ambient temperature for several days.

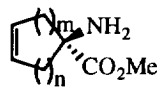
According to NMR and GLC the RCM products **4b**, **4c** and **4e** were diastereomerically pure. Accordingly the specific rotations of the enantiomeric pairs **8b** and **8c** after acid hydrolysis were found to be approximately the same with opposite rotational sign (Scheme 4). Only one of the enantiomeric seven-membered rings, *viz.* **8e**, was prepared. The other enantiomer would be available by changing the order of the stepwise alkylation used in the preparation of the intermediate substrate **3**, or by using the chiral auxiliary **1** with the opposite (2*S*)-configuration and retaining the order of the stepwise alkylation.

We have in this work found a new and convenient route for stereoselective preparation of unsaturated cyclic amino acids.

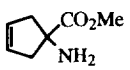
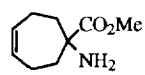
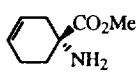
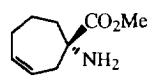
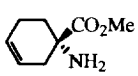


4

0.2 M aq. TFA
MeCN
25 °C, 3-8 d



8 + (*R*)-Val-OMe

		Yield%	$[\alpha]_D$			Yield%	$[\alpha]_D$
8a		45		**8d**		69	
8b		58	-19.2°	**8e**		73	-12.8°
8c		42	+19.5°				

Scheme 4

EXPERIMENTAL

^{1}H NMR spectra were recorded in $CDCl_3$ at 300 MHz or 200 MHz with Bruker DPX 300 or DPX 200. The ^{13}C NMR spectra were recorded in $CDCl_3$ at 75 MHz or 50 MHz. Chemical shifts are reported in ppm using residual $CHCl_3$ (7.24 ppm) and $CDCl_3$ (77.00 ppm) as references. The mass spectra under electron impact conditions (EI) were recorded at 70 eV ionizing potential; isobutane was used for chemical ionization (CI). The spectra are presented as *m/z* (% rel. int.). Dry THF, benzene and toluene were distilled from sodium and benzophenone. Benzene and toluene were degassed by bubbling argon through the solvents. Bis(tricyclohexylphosphine)benzylidine ruthenium dichloride was purchased from Strem Chemicals Inc., 7 Mulliken Way, Newburyport, MA.

(2*R*,5*S*)-5-Allyl-3,6-dimethoxy-2,5-dihydro-2-isopropylpyrazine (**2a**).[15]

(2*R*,5*S*)-5-(3-Butenyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (**2b**) and (2*R*,5*R*)-5-(3-butenyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine. nBuLi (5.30 ml, 11.13 mmol, 2.1 M in hexane) was added to a solution of (*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (2.00 g, 10.86 mmol) in THF (20 ml) under argon at -78 °C. After 25 min, 4-bromo-1-butene (1.10 ml, 11.00 mmol) in THF (5 ml) was added dropwise over 20 min. The mixture was left to reach ambient temperature overnight before the reaction was quenched by addition of 0.1 M phosphate buffer (pH 7, 15 ml). The aqueous layer was extracted with dichloromethane (3 x 20 ml). The combined organic layers were dried ($MgSO_4$) and evaporated to dryness. The residual

product was purified by flash chromatography using 3% and 5% ethyl acetate in hexane as eluents; yield 1.36 g (92%, d.e. 75%) of a colourless oil. Found: C, 65.22; H, 9.09. Calc. for $C_{13}H_{22}N_2O_2$: C, 65.51; H, 9.30%. $[\alpha]_D$ = +6.9° (c = 1.04, $CHCl_3$). ^1H NMR (300 MHz): δ 0.64 (d, *J* 7 Hz, 3H, CH_3), 0.82 (d, *J* 7 Hz, 3H, CH_3), 1.69--2.25 (m, 5H, CH, 2 x CH_2), 3.64 (s, 3H, CH_3O), 3.65 (s, 3H, CH_3O), 3.88 (m, 1H, H-2), 3.99 (m, 1H, H-5), 4.95 (m, 2H, CH_2=), 5.75 (m, 1H, CH=). ^{13}C NMR (75 MHz): δ 16.50 (CH_3), 19.00 (CH_3), 28.92 (CH_2), 31.63 (CH), 33.35 (CH_2), 52.22 (2 x CH_3O), 54.85 (C-5), 60.71 (C-2), 114.40 (CH_2=), 138.36 (CH=), 163.46 (C), 163.68 (C). MS(EI): 238 (8, M^+), 223 (41), 196 (29), 195 (100), 183 (17), 166 (16), 153 (64), 141 (95). MS(EI): *M* 238.1674. Calc. for $C_{13}H_{22}N_2O_2$: 238.1681.

The slower moving component isolated after flash chromatography was (2*R*,5*R*)-5-(3-butenyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine: Colourless oil. $[\alpha]_D$ = -82.2° (c = 1.03, $CHCl_3$). ^1H NMR (300 MHz): δ 0.68 (d, *J* 7 Hz, 3H, CH_3), 1.02 (d, *J* 7 Hz, 3H, CH_3), 1.49-2.23 (m, 5H, CH, 2 x CH_2), 3.62 (s, 3H, CH_3O), 3.63 (s, 3H, CH_3O), 3.87-3.97 (m, 2H, H-2, H-5), 4.97 (m, 2H, CH_2=), 5.82 (m, 1H, CH=). ^{13}C NMR (75 MHz): δ 17.35 (CH_3), 19.48 (CH_3), 30.18 (CH_2), 31.16 (CH), 34.75 (CH_2), 52.09 (2 x CH_3O), 55.05 (C-5), 60.81 (C-2), 114.61 (CH_2=), 138.35 (CH=), 162.91 (C), 163.63 (C).

(2*R*,5*S*)-2,5-Dihydro-3,6-dimethoxy-2-isopropyl-5-(4-pentenyl)pyrazine (**2c**) and (2*R*,5*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-(4-pentenyl)pyrazine. nBuLi (2.6 ml, 5.46 mmol, 2.1 M in hexane) was added dropwise to a solution of (*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (971 mg, 5.27 mmol) in dry THF (15 ml) under argon at -78 °C. After 20 min, 5-bromo-1-pentene (0.65 ml, 5.46 mmol) in THF (2 ml) was added dropwise with stirring, the mixture allowed to reach ambient temperature overnight, 0.1 M phosphate buffer (pH 7, 10 ml) added, the phases separated and the aqueous phase extracted with dichloromethane (3 x 20 ml). The combined organic extracts were dried ($MgSO_4$), evaporated and the two residual isomers separated by flash chromatography using 3% and then 5% ethyl acetate in hexane as eluents; yield 1.07 g (80%, d.e. 82%). The product was a colourless oil. Found: C, 66.49; H, 9.49. Calc. for $C_{14}H_{24}N_2O_2$: C, 66.23; H, 9.59%. $[\alpha]_D$ = +6.1° (c = 1.45, $CHCl_3$). ^1H NMR (300 MHz): δ 0.63 (d, *J* 7 Hz, 3H, CH_3), 0.98 (d, *J* 7 Hz, 3H, CH_3), 1.31 (m, 2H, CH_2), 1.71 (m, 2H, CH_2), 1.95 (m, 2H, CH_2), 2.19 (m, 1H, CH), 3.61 (s, 3H, CH_3O), 3.62 (s, 3H, CH_3O), 3.87 (m, 1H, H-2), 3.96 (m, 1H, H-5), 4.89 (m, 2H, CH_2=), 5.73 (m, 1H, CH=). ^{13}C NMR (75 MHz): 16.44 (CH_3), 18.99 (CH_3), 23.80 (CH_2), 31.55 (CH), 33.52 (CH_2), 33.62 (CH_2), 52.17 (2 x CH_3O), 55.27 (C-5), 60.61 (C-2), 114.28 (CH_2=), 138.66 (CH=), 163.36 (C), 163.75 (C). MS (EI): 252 (34, M^+), 209 (58), 184 (11), 183 (100), 153 (26), 141 (45). The second product eluated on flash chromatography was (2*R*,5*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-(4-pentenyl)pyrazine: Colourless oil. $[\alpha]_D$ = -88.6° (c = 0.57, $CHCl_3$). ^1H NMR (300 MHz): δ 0.70 (d, *J* 7 Hz, 3H, CH_3), 1.03 (d, *J* 7 Hz, 3H, CH_3), 1.45-2.16 (m, 6H, 3 x CH_2), 2.18 (m, 1H, CH), 3.63 (s, 3H, CH_3O), 3.64 (s, 3H, CH_3O), 3.93 (m, 2H, H-2, H-5), 4.95 (m, 2H, CH_2=), 5.80 (m, 1H, CH=). ^{13}C NMR (75 MHz): δ 17.52 (CH_3), 19.57 (CH_3), 25.31 (CH_2), 31.32 (CH), 33.60 (CH_2), 35.00 (CH_2), 52.19 (2 x CH_3O), 55.69 (C-5), 60.89 (C-2), 114.34 (CH_2=), 138.78 (CH=), 162.99 (C), 163.79 (C).

(2*R*)-5,5-Diallyl-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (**3a**). nBuLi (2.7 ml, 5.94 mmol, 2.2 M in hexane) was added to a solution of (*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (1.00 g, 5.43 mmol) in dry THF (10 ml) under nitrogen at -78 °C. After 20 min, a solution of allyl bromide (0.51 ml, 5.97 mmol) in THF (2 ml) was added dropwise with stirring. The reaction mixture was left overnight to reach ambient

temperature. The mixture was subsequently cooled to -78 °C, and nBuLi (2.7 ml, 5.94 mmol, 2.2 M in hexane) added. After 20 min, a solution of allyl bromide (0.51 ml, 5.97 mmol) in dry THF (2 ml) was added. The mixture was stirred at -78 °C for 3 h, the cold bath removed and the mixture stirred for 1 h at ambient temperature before 0.1 M phosphate buffer (pH 7, 20 ml) was added. The phases were separated, the aqueous phase extracted with dichloromethane (3 x 20 ml) and the combined organic phases dried ($MgSO_4$), evaporated and the residual product purified by flash chromatography using 2% ethyl acetate in hexane as eluent; yield 1.16 g (81%) of a colourless oil. Found: C, 67.95; H, 8.78. Calc. for $C_{15}H_{24}N_2O_2$: C, 68.15; H, 9.15%. $[\alpha]_D$ = -28.4° (c = 0.62, $CHCl_3$). ^1H NMR (200 MHz): δ 0.61 (d, *J* 6.8 Hz, 3H, CH_3), 1.03 (d, *J* 6.8 Hz, 3H, CH_3), 2.19-2.28 (m, 5H, CH, 2 x CH_2), 3.61 (s, 3H, CH_3O), 3.63 (s, 3H, CH_3O), 3.79 (d, *J* 3.3 Hz, 1H, H-2), 4.90-5.02 (m, 4H, 2 x CH_2=), 5.39-5.67 (m, 2H, 2 x CH=). ^{13}C NMR (50 MHz): δ 17.08 (CH_3), 19.49 (CH_3), 30.45 (CH), 44.46 (CH_2), 44.74 (CH_2), 51.96 (CH_3O), 52.21 (CH_3O), 60.54 (C-2), 62.02 (C-5), 117.39 (CH_2=), 118.12 (CH_2=), 133.40 (CH=), 134.48 (CH=), 162.60 (C), 163.31 (C). MS(EI): 264 (0.3, M^+), 223 (59), 182 (11) 181 (100).

(2*R*,5*R*)-5-Allyl-5-(3-butenyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (**3b**). nBuLi (1.10 ml, 2.31 mmol, 2.1 M in hexane) was added to a solution of (2*R*,5*S*)-5-allyl-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (514 mg, 2.29 mmol) in dry THF (15 ml) under argon at -50 °C After 30 min, the mixture was cooled to -78 °C and 4-bromo-1-butene (0.25 ml, 2.40 mmol) in THF (1 ml) added dropwise. The solution was left to reach ambient temperature overnight, 0.1 M phosphate buffer (pH 7, 10 ml) added, the phases separated, the aqueous phase extracted with dichloromethane (2 x 15 ml), the combined organic extracts dried ($MgSO_4$), evaporated and the crude product purified by flash chromatography using 2% ethyl acetate in hexane as eluent; yield 554 mg (87%, d.e. >95%) of a colourless oil. $[\alpha]_D$ = -32.8 ° (c = 1.27, $CHCl_3$). Found: C, 68.61; H, 9.43. Calc. for $C_{16}H_{26}N_2O_2$: C, 69.03; H, 9.41%. ^1H NMR (200 MHz): δ 0.63 (d, *J* 7 Hz, 3H, CH_3), 1.05 (d, *J* 7 Hz, 3H, CH_3), 1.59--2.56 (m, 7H, CH, 3 x CH_2), 3.62 (s, 3H, CH_3O), 3.63 (s, 3H, CH_3O), 3.81 (d, *J* 3 Hz, 1H, H-2), 4.81--5.01 (m, 4H, 2 x CH_2=), 5.50--5.77 (m, 2H, 2 x CH=). ^{13}C NMR (50 MHz): δ 17.21 (CH_3), 19.56 (CH_3), 28.61 (CH_2), 30.54 (CH), 39.54 (CH_2), 45.09 (CH_2), 52.03 (CH_3O), 52.18 (CH_3O), 60.75 (C-2), 61.73 (C-5), 114.13 (CH_2=), 117.35 (CH_2=), 134.56 (CH=), 138.32 (CH=), 162.47 (C), 163.65 (C). MS (EI): 278 (1, M^+), 237 (23), 235 (30), 223 (17), 196 (18), 195 (100), 153 (39), 141 (35), 123 (10). MS (EI): *M* 278.1981. Calc. for $C_{16}H_{26}N_2O_2$: 278.1994.

(2*R*,5*S*)-5-Allyl-5-(3-butenyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (**3c**). nBuLi (1.20 ml, 2.52 mmol, 2.1 M in hexane) was added dropwise to a solution of (2*R*,5*S*)-5-(3-butenyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine and (2*R*,5*R*)-5-(3-butenyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (578 mg, 2.43 mmol) in THF under argon (15 ml) at -50 °C. After 30 min, the solution was cooled to -78 °C, allyl bromide (0.21 ml, 2.52 mmol) in THF (2 ml) added dropwise with stirring, the mixture allowed to reach ambient temperature overnight, phosphate buffer (pH 7, 10 ml) added, the two phases separated and the aqueous phase extracted with dichloromethane (3 x 20 ml). The combined organic extracts were dried ($MgSO_4$), evaporated and the residual product purified by flash chromatography using 2% ethyl acetate in hexane as eluent; yield 516 mg (76%, d.e. >95 %) of a colourless oil. Found: C, 69.30; H, 9.27. Calc. for $C_{16}H_{26}N_2O_2$: C, 69.03; H, 9.41%. $[\alpha]_D$ = -20.5° (c = 1.00, $CHCl_3$). ^1H NMR (300 MHz): δ 0.63 (d, *J* 7 Hz, 3H, CH_3), 1.05 (d, *J* 7 Hz, 3H, CH_3), 1.61-2.47 (m, 7H, 3 x CH_2, CH), 3.63 (s, 3H, CH_3O), 3.64 (s, 3H,

CH_3O), 3.81 (d, *J* 3 Hz, 1H, H-2), 4.96 (m, 4H, 2 x CH_2=), 5.43--5.82 (m, 2H, 2 x CH=). ^{13}C NMR (75 MHz): δ 16.91 (CH_3), 19.52 (CH_3), 29.11 (CH_2), 30.49 (CH), 38.98 (CH_2), 45.37 (CH_2), 52.06 (CH_3O), 52.26 (CH_3O), 60.66 (C-2), 61.87 (C-5), 114.08 (CH_2=), 118.16 (CH_2=), 133.40 (CH=), 138.77 (CH=), 162.88 (C), 163.57 (C). MS(EI): 278 (1, M^+), 237 (51), 235 (23), 196 (12), 195 (100), 181 (12), 153 (27). MS(EI): *M* 278.1978. Calc. for $C_{16}H_{26}N_2O_2$: 278.1994.

(2*R*)-5,5-Bis(3-butenyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (**3d**). nBuLi (1.10 ml, 2.31 mmol, 2.1 M in hexane) was added dropwise to a solution of (2*R*,5*S*)-5-(3-butenyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine and (2*R*,5*R*)-5-(3-butenyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (529 mg, 2.22 mmol) in THF (15 ml) under argon at -50 °C. After 30 min, the solution was cooled to -78 °C, 4-bromo-1-butene (0.25 ml, 2.31 mmol) in THF (2 ml) added dropwise with stirring, the reaction mixture allowed to reach ambient temperature overnight, 0.1 M phosphate buffer (pH 7, 10 ml) added, the two phases separated, the aqueous phase extracted with dichloromethane (3 x 20 ml), the combined organic extracts dried ($MgSO_4$), evaporated and the residual product purified by flash chromatography using 2% ethyl acetate in hexane as eluent, yield 475 mg (73%) of a colourless oil. Found: C, 69.47; H, 9.41. Calc. for $C_{17}H_{28}N_2O_2$: C, 69.82; H, 9.65%. $[\alpha]_D$ = -26.0° (c = 1.09, $CHCl_3$). ^1H NMR (300 MHz): δ 0.65 (d, *J* 7 Hz, 3H, CH_3), 1.07 (d, *J* 7 Hz, 3H, CH_3), 1.61-1.90 (m, 8H, 4 x CH_2), 2.32 (m, 1H, CH), 3.64 (s, 3H, CH_3O), 3.65 (s, 3H, CH_3O),3.85 (d, *J* 3 Hz, 1H, H-2), 4.90 (m, 4H, 2 x CH_2=), 5.74 (m, 2H, CH=). ^{13}C NMR (75 MHz): δ 16.99 (CH_3), 19.56 (CH_3), 28.53 (CH_2), 29.07 (CH_2), 30.55 (CH), 39.51 (CH_2), 40.15 (CH_2), 52.12 (CH_3O), 52.22 (CH_3O), 60.79 (C-2), 61.50 (C-5), 114.05 (CH_2=), 114.11 (CH_2=), 138.38 (CH=), 138.84 (CH=), 162.65 (C), 163.89 (C). MS(EI): 292 (1, M^+), 277 (14), 249 (10), 237 (36), 196 (13), 195 (100), 153 (14). MS(EI): *M* 292.2163. Calc. for $C_{17}H_{28}N_2O_2$: 292.2151

(2*R*,5*S*)-5-Allyl-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-(4-pentenyl)pyrazine (**3e**). nBuLi (1.30 ml, 2.73 mmol, 2.1 M in hexane) was added to a solution of (2*R*,5*S*)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-(4-pentenyl)pyrazine and (2*R*,5*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-(4-pentenyl)pyrazine (622 mg, 2.46 mmol) in dry THF (20 ml) under argon at -50 °C. After stirring for 1 h, the solution was cooled to -78 °C, allyl bromide (0.25 ml, 2.89 mmol) in THF (2 ml) added dropwise with stirring, the mixture left to reach ambient temperature overnight, 0.1 M phosphate buffer (pH 7, 10 ml) added, the phases separated, the aqueous phase extracted with dichloromethane (3 x 20 ml) and the combined organic extracts dried ($MgSO_4$), evaporated and the residual product purified by flash chromatography using 2% ethyl acetate as eluent; yield 466 mg (65%, d.e. >95%) of a colourless oil. Found: C, 69.47; H.9.81 Calc. for $C_{17}H_{28}N_2O_2$: C, 69.82; H, 9.65%. $[\alpha]_D$ = -13.6° (c = 0.96, $CHCl_3$). ^1H NMR (300 MHz): δ 0.62 (d, *J* 7Hz, 3H, CH_3), 1.04 (d, *J* 7Hz, 3H, CH_3), 1.07-2.45 (m, 9H, 4 x CH_2, CH), 3.61 (s, 3H, CH_3O), 3.62 (s, 3H, CH_3O), 3.79 (d, *J* 3 Hz, 1H, H-2), 4.90 (m, 4H, 2 x CH_2=), 5.50 (m, 1H, CH=), 5.70 (m, 1H, CH=). ^{13}C NMR (75 MHz): δ 16.88 (CH_3), 19.50 (CH_3), 23.86 (CH_2), 30.49 (CH), 33.67 (CH_2), 39.24 (CH_2), 45.41 (CH_2), 51.96 (CH_3O), 52.16 (CH_3O), 60.63 (C-2), 62.10 (C-5), 114.11 (CH_2=), 118.00 (CH_2=), 133.47 (CH=), 138.73 (CH=), 162.68 (C), 163.70 (C). MS(EI): 292 (10, M^+), 252 (19), 251 (100), 209 (62), 195 (20). MS(EI): *M*: 292.2152. Calc. for $C_{17}H_{28}N_2O_2$: 292.2151.

(2*R*,5*S*)-5-(3-Butenyl)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-(4-pentenyl)pyrazine (**3f**). nBuLi (1.90 ml, 3.99 mmol, 2.1 M in hexanes) was added to a solution of (2*R*,5*S*)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-(4-pentenyl)pyrazine and (2*R*,5*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-(4-pentenyl)pyrazine (980 mg, 3.88 mmol) in dry THF (10 ml) at -50 °C under argon. After 30 min, the solution was cooled to -78 °C and 4-bromo-1-butene (0.41 ml, 3.99 mmol) in THF (2 ml) was added dropwise with stirring. The mixture was left to reach ambient temperature overnight, 0.1 M phosphate buffer (pH 7, 10 ml) added, the two phases separated, the aqueous phase extracted with dichloromethane (3 x 20 ml), the combined organic phases dried ($MgSO_4$), evaporated and the residual product purified by flash chromatography using 2% ethyl acetate as eluent; yield 781 mg (66%, d.e. >95%) of a colourless oil. Found: C, 69.94; H, 9.66. Calc. for $C_{18}H_{30}N_2O_2$: C, 70.55; H, 9.87%. $[\alpha]_D$ = -21.7 °. ^{1}H NMR (300 MHz): δ 0.65 (d, *J* 7 Hz, 3H, CH_3), 1.07 (d, *J* 7 Hz, 3H, CH_3), 1.11-2.01 (m, 10, 5 x CH_2), 2.31 (m, 1H, CH), 3.63 (s, 3H, CH_3O), 3.64 (s, 3H, CH_3O), 3.84 (d, *J* 3 Hz, 1H, H-2), 4.87 (m, 4H, 2 x CH_2=), 5.72 (m, 2H, 2 x CH=). ^{13}C NMR (75 MHz): δ 17.00 (CH_3), 19.56 (CH_3), 23.82 (CH_2), 28.54 (CH_2), 30.59 (CH), 33.72 (CH_2), 39.81 (CH_2), 40.20 (CH_2), 52.07 (CH_3O), 52.17 (CH_3O), 60.79 (C-2), 61.73 (C-5), 114.05 (CH_2=), 114.12 (CH_2=), 138.43 (CH=), 138.82 (CH=), 162.57 (C), 164.07 (C). MS(EI): 306 (12, M^+), 291 (16), 265 (23), 263 (19), 251 (21), 209 (46), 195 (100), 153 (11). MS(EI): *M* 306.2300. Calc. for $C_{18}H_{30}N_2O_2$: 306.2307.

(2*R*)-2,5-Dihydro-3,6-dimethoxy-2-isopropylpyrazine-5-spiro(3-cyclopentene)(**4a**). Bis(tricyclohexylphosphine)benzylidine ruthenium dichloride (24 mg, 0.029 mmol) in dry toluene (1 ml) was added to a solution of (2*R*)-5,5-diallyl-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (193 mg, 0.73 mmol) in dry toluene (10 ml) under argon, the mixture heated at 100 °C for 4 h when another portion of bis(tricyclohexylphosphine)benzylidine ruthenium dichloride (24 mg, 0.029 mmol) in dry toluene (1 ml) was added. The solution was heated under argon at 100 °C with stirring overnight, the solvent evaporated at reduced pressure and the product isolated from the residual material by flash chromatography using 2% ethyl acetate in hexane as eluent; yield 92 mg (53%) of a colourless oil. Found: C, 65.88; H, 8.44. Calc. for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53%. $[\alpha]_D$ = -43.2° (c = 0.47, $CHCl_3$). ^{1}H NMR (300 MHz): δ 0.66 (d. *J* 7 Hz, 3H, CH_3), 1.03 (d, *J* 7 Hz, 3H, CH_3), 2.17 (m, 1H, CH), 2.27 (m, 2H, CH_2), 2.85 (m, 2H, CH2), 3.61 (s, 3H, CH_3O), 3.67 (s, 3H, CH_3O), 3.96 (d, *J* 3 Hz, 1H, H-8), 5.65 (m, 2H, 2 x CH=). ^{13}C NMR (75 MHz): δ 16.80 (CH_3), 19.25 (CH_3), 31.21 (CH), 48.95 (CH_2), 49.09 (CH_2), 52.23 (CH_3O), 52.48 (CH_3O), 61.06 (C-8), 62.45 (C-5), 127.73 (CH=), 128.26 (CH=), 161.35 (C), 165.96 (C). MS(EI): 236 (10, $M^{+\cdot}$), 221 (8), 194 (19), 193 (100), 179 (11), 178 (14). MS(EI): *M* 236.1504. Calc. for $C_{13}H_{20}N_2O_2$: 236.1525.

(2*R*,5*R*)-2,5-Dihydro-3,6-dimethoxy-3-isopropylpyrazine-5-spiro(3-cyclohexene) (**4b**). Bis(tricyclohexylphosphine)benzylidine ruthenium dichloride (17 mg, 0.020 mmol) in dry degassed benzene (1 ml) was added to a solution of (2*R*,5*R*)-5-allyl-5-(3-butenyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (291 mg, 1.05 mmol) in dry degassed benzene (30 ml) under argon at 60 °C. After 5 h, the solvent was evaporated and the product purified by flash chromatography using 2% ethyl acetate in hexane as eluent; yield 249 mg (95%) of a colourless oil. Found: C, 66.89; H, 8.61. Calc. for $C_{14}H_{22}N_2O_2$: C, 67.17; H, 8.86%. $[\alpha]_D$ = +24.6° (c = 0.82, $CHCl_3$). ^{1}H NMR (300 MHz): δ 0.68 (d, *J* 7 Hz, 3H, CH_3), 1.04 (d, *J* 7 Hz, 3H, CH_3), 1.41-2.71 (m, 7H, 3 x CH_2, CH), 3.61 (s, 3H, CH_3O), 3.64 (s, 3H, CH_3O), 3.92 (d, *J* 3 Hz, H-3), 5.59 (m, 1H, CH=), 5.75 (m, 1H, CH=). ^{13}C NMR (75 MHz): δ 16.96 (CH_3), 19.33 (CH_3), 21.35 (CH), 32.75 (CH_2), 36.47 (CH_2),

52.01 (CH_3O), 52.36 (CH_3O), 55.83 (C-6), 60.58 (C-3), 123.66 (CH=), 126.28 (CH=), 161.17 (C), 166.34 (C). MS(EI): 250 (54, M^+), 208 (13), 207 (100), 154 (21), 153 (40). MS(EI): *M* 250.1681. Calc. for $C_{14}H_{22}N_2O_2$: 250.1681.

(2*R*,5*S*)-2,5-Dihydro-3,6-dimethoxy-3-isopropylpyrazine-5-spiro(3-cyclohexene) (**4c**). Bis(tricyclohexylphosphine)benzylidine ruthenium dichloride (10 mg, 0.013 mmol) in dry degassed benzene (1 ml) was added to a solution of (2*R*,5*S*)-5-allyl-5-(3-butenyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (175 mg, 0.63 mmol) in dry degassed benzene (15 ml). The mixture was stirred under argon for 23 h at ambient temperature, the solvent evaporated and the product purified by flash chromatography using 5% ethyl acetate in hexane as eluent; yield 156 mg (99%) of a colourless oil. Found: C, 66.99; H, 8.40. Calc. for $C_{14}H_{22}N_2O_2$: C, 67.17; H, 8.865. $[\alpha]_D$ = -102.3° (c = 1.45, $CHCl_3$). ^1H NMR (300 MHz): δ 0.65 (d, *J* 7 Hz, 3H, CH_3), 1.05 (d, *J* 7 Hz, 3H, CH_3), 1.40-2.66 (m, 7H, 3 x CH_2, CH), 3.59 (s, 3H, CH_3O), 3.63 (s, 3H, CH_3O), 3.93 (d, *J* 3 Hz, 1H, H-3), 5.58 (m, 1H, CH=), 5.72 (m, 1H, CH=). ^{13}C NMR (75 MHz): δ 16.88 (CH_3), 19.34 (CH_3), 21.56 (CH_2), 30.82 (CH), 32.71 (CH_2), 36.65 (CH_2), 51.94 (CH_3O), 52.26 (CH_3O), 55.82 (C-6), 60.51 (C-3), 123.57 (CH=), 126.17 (CH=), 160.96 (C), 166.15 (C). MS(EI): 250 (50, M^+), 208 (13), 207 (100), 196 (11), 154 (36), 153 (61), 123 (11). MS(EI): *M* 250.1679. Calc. for $C_{14}H_{22}N_2O_2$: 250.1681.

(2*R*)-2,5-Dihydro-3,6-dimethoxy-2-isopropylpyrazine-5-spiro-(4-cycloheptene) (**4d**). Bis(tricyclohexylphosphine)benzylidine ruthenium dichloride (13 mg, 0.015 mmol) in dry degassed benzene (1 ml) was added to a solution of (2*R*)-5,5-bis(3-butenyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (230 mg, 0.79 mmol) in dry degassed benzene (20 ml) under argon at ambient temperature. The solution was stirred for 23 h, the solvent evaporated and the residual product purified by flash chromatography using 2% ethyl acetate in hexane as eluent; yield 186 mg (90%) of a colourless oil. Found: C, 68.21; H, 8.95. Calc. for $C_{15}H_{24}N_2O_2$: C, 68.15; H, 9.15%. ^1H NMR (300 MHz): 0.62 (d, *J* 7 Hz, 3H, CH_3), 1.04 (d, *J* 7 Hz, 3H, CH_3), 1.52 (m, 2H, CH_2), 2.02 (m, 4H, 2 x CH_2), 2.21 (m, 1H, CH), 2.59 (m, 2H, CH_2), 3.63 (s, 3H, CH_3O), 3.66 (s, 3H, CH_3O), 3.88 (d, *J* 3 Hz, 1H, H-3), 5.74 (m, 2H, 2 x CH=). ^{13}C NMR (75 MHz): 16.89 (CH_3), 19.37 (CH_3), 23.03 (CH_2), 23.25 (CH_2), 30.87 (CH), 38.30 (CH_2), 38.45 (CH_2), 52.03 (CH_3O), 52.23 (CH_3O), 59.88 (C-6), 60.34 (C-3), 131.86 (2 x CH=), 160.14 (C), 167.05 (C). MS(EI): 264 (25, M^+), 249 (26), 222 (18), 221 (100), 193 (40), 153 (21). MS(EI): *M* 264.1849. Calc. for $C_{15}H_{24}N_2O_2$: 264.1838.

(2*R*,5*S*)-2,5-Dihydro-3,6-dimethoxy-2-isopropylpyrazine-5-spiro(3-cycloheptene) (**4e**). Bis(tricyclohexylphosphine)benzylidine ruthenium dichloride (11 mg, 0.013 mmol) in dry benzene (1ml) was added to a solution of (2*R*,5*S*)-5-allyl-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-(4-pentenyl)pyrazine (188 mg, 0.64 mmol) in benzene (10 ml) at 80 °C. The mixture was refluxed for 8 h, the solvent evaporated and the residual product purified by flash chromatography using 2% ethyl acetate in hexane as eluent; yield 101 mg (60%) of a colourless oil. Found: C, 68.38; H, 8.97. Calc. for $C_{15}H_{24}N_2O_2$: C, 68.15; H, 9.15%. $[\alpha]_D$ = -79.8° (c = 0.5, $CHCl_3$). ^1H NMR (200 MHz): δ 0.64 (d, *J* 7 Hz, 3H, CH_3), 1.04 (d, *J* 7 Hz, 3H, CH_3), 1.49-2.75 (m, 9H, 4 x CH_2, CH), 3.60 (CH_3O), 3.64 (CH_3O), 3.88 (d, *J* 3 Hz, H-3), 5.50 (m, 1H, CH=), 5.78 (m, 1H, CH). ^{13}C NMR (50 MHz): δ 16.96 (CH_3), 19.35 (CH_3), 20.37 (CH_2), 29.21 (CH_2), 30.93 (CH), 38.73 (CH_2), 42.05 (CH_2), 52.01 (CH_3O), 52.27 (CH_3O), 58.50 (C-6), 60.32 (C-3), 126.65 (CH=), 131.56 (CH=), 159.99 (C),

167.04 (C). MS(EI): 264 (21, M^+), 249 (11), 222 (17), 221 (100), 207 (12), 196 (26). MS(EI): *M* 264.1823. Calc. for $C_{15}H_{24}N_2O_2$: 264.1838.

Methyl 2-allyl-2-amino-4-pentenoate (**5**). A solution of (2*R*)-5,5-diallyl-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (1.30 g, 4.92 mmol) in MeCN (40 ml) and 0.2 M TFA (250 ml, 50.00 mmol) was stirred at ambient temperature for 5 d, the solution evaporated almost to dryness at reduced pressure and water (20 ml) and dichloromethane (40 ml) added. The phases were separated, the aqueous layer brought to pH 10 by addition of conc. aq. ammonia, the aqueous mixture extracted with dichloromethane (3 x 50 ml), the combined dichloromethane extracts dried ($MgSO_4$), evaporated and the product isolated by flash chromatography using dichloromethane/diethyl ether 2:1 as eluent; yield 0.59 g (75%) of a colourless oil. Found: C, 64.37; H, 8.75. Calc. for $C_9H_{15}NO_2$: C, 63.88; H, 8.93%. ^{1}H NMR (200 MHz): δ 1.57 (s, 2H, NH_2), 2.12, 2.19 and 2.42, 2.49 (2 x dd, *J* 8 Hz and 6 Hz, 4H, 2 x CH_2), 3.61 (s, 3H, CH_3O), 5.05 (m, 4H, 2 x CH_2=), 5.57 (m, 2H, CH=). ^{13}C NMR (50 MHz): δ 43.89 (2 x CH_2), 51.88 (CH_3O), 60.43 (C), 119.25 (2 x CH_2=), 132.40 (2 x CH=), 176.50 (C=O). MS(CI-CH_4): 170 (65, *M* + 1), 128 (100), 110 (40).

Methyl 2-acetamido-2-allyl-4-pentenoate (**6**). A solution of (2*R*)-5,5-diallyl-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (229 mg, 0.87 mmol) in 0.2 M TFA (43.5 ml, 8.70 mmol) and MeCN (10 ml) was stirred at ambient temperature for 5 d, the solution concentrated to about 10 ml under reduced pressure, brought to pH 10 using conc. aq. ammonia, extracted with dichloromethane (3 x 20 ml), the combined organic extracts dried ($MgSO_4$) and evaporated. The residual mixture was dissolved in dichloromethane (5 ml), *N,N*-dimethyl-4-aminopyridine (244 mg, 2.00 mmol) and acetic anhydride (0.20 ml, 2.00 mmol) added, the mixture stirred at ambient temperature overnight, the solution evaporated and the residual mixture subjected to flash chromatography. The desired product was isolated using dichloromethane/diethyl ether 9:1 and 4:1 as eluents; yield 144 mg (81%); white needles, m.p. 60 °C. Found: C, 62.96; H, 8.03. Calc. for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11%. ^{1}H NMR (200 MHz): δ 1.97 (s, 3H, CH_3), 2.45, 2.52 and 3.11, 3.17 (2 x dd, *J* 7 Hz, 4H, 2 x CH_2), 3.72 (s, 3H, CH_3O), 4.99 (m, 4H, 2 x CH_2=), 5.45-5.59 (m, 2H, 2 x CH=), 6.25 (s, 1H, NH). ^{13}C NMR (50 MHz): δ 23.74 (CH_3), 38.78 (2 x CH_2), 52.51 (CH_3O), 64.04 (C), 118.87 (2 x CH_2=), 132.12 (2 x CH=), 169.13 (C=O), 173.29 (C=O). MS(CI-iBu): 212 (100, *M*+1), 196 (10), 184 (6). MS(EI): *M* 211.1194. Calc. for $C_{11}H_{17}NO_3$: 211.1208.

Methyl 1-acetamido-3-cyclopentene-1-carboxylate (**7**). Bis(tricyclohexylphosphine)benzylidine ruthenium dichloride (13 mg, 0.016 mmol) in dry degassed benzene (1 ml) was added to a solution of methyl 2-acetamido-2-allyl-4-pentenoate (166 mg, 0.79 mmol) in dry degassed benzene (20 ml) under argon, the mixture stirred for 4 h at ambient temperature, the solvent evaporated and the residual product purified by flash chromatography using dichloromethane/diethyl ether 1:1 as eluent, yield 127 mg (89%), white solid material, m.p. 155 °C. Found: C, 59.31; H, 7.02. Calc. for $C_9H_{13}NO_3$: C, 59.00; H, 7.15%. ^{1}H NMR (300 MHz): δ 1.95 (s, 3H, CH_3), 2.61, 3.04 (2 x d, *J* 14 Hz, 4H, H-2 and H-5), 3.71 (s, 3H, CH_3O), 5.63 (s, 2H, H-3 and H-4), 6.15 (s, 1H, NH). ^{13}C NMR (75 MHz): δ 23.13 (CH_3), 44.48 (C-2 and C-5), 52.70 (CH_3O), 64.10 (C-1), 127.77 (C-3 and C-4), 169.82 (C=O), 174.20 (C=O). MS(CI-iBu): 184 (100, *M*+1), 152 (12). MS(EI): *M* 183.0909. Calc. for $C_9H_{13}NO_3$: 183.0895.

Methyl 1-amino-3-cyclopentene-1-carboxylate (**8a**). A solution of (2*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine-5-spiro(3-cyclopentene) (98 mg, 0.42 mmol) in TFA (21 ml, 4.20 mmol, 0.2 M) and MeCN (5 ml) was left at ambient temperature for 8 d, the solution concentrated to about 10 ml and dichloromethane (20 ml) added. The two phases were separated, the pH of the aqueous solution brought to 10 by adding conc. aq. ammonia, the mixture extracted with dichloromethane (3 x 15 ml), the organic solution dried ($MgSO_4$), evaporated and the product isolated by flash chromatography using 3% methanol in dichlormethane as eluent; yield 26 mg (45%) of a colourless oil. Found: C, 61.20; H, 8.14. Calc. for $C_7H_{11}NO_2$: C, 59.99; H, 7.85%. ^1H NMR (200 MHz): δ 1.40 (s, 2H, NH_2), 2.29, 2.97 (dd, *J* 16 Hz, 4H, 2 x CH_2), 3.72 (s, 3H, CH_3O), 5.68 (s, 2H, 2 x CH=). ^{13}C NMR (50 MHz): δ 47.16 (C-2, C-5), 52.39 (CH_3O), 63.36 (C-1), 127.80 (C-3, C-4), 177.76 (C=O). MS(EI): 115 (7), 112 (4), 82 (M^+- ·CO_2CH_3, 100), 81 (7), 80 (15).

(*R*) Methyl 1-amino-3-cyclohexene-1-carboxylate (**8b**). A solution of (2*R*, 5*R*)-2,5-dihydro-3,6-dimethoxy-3-isopropylpyrazine-5-spiro(3-cyclohexene) (177 mg, 0.71 mmol) in TFA (36 ml, 7.20 mmol, 0.2 M) and MeCN (36 ml) was stirred at ambient temperature for 3 d, the solution concentrated to about 10 ml and dichloromethane (20 ml) added. The aqueous phase was separated and brought to pH 10 with conc. aq. ammonia, the mixture extracted with dichloromethane (2 x 20 ml), the combined organic solutions dried ($MgSO_4$), evaporated and most of the methyl valinate removed from the residual material by bulb to bulb distillation, 25 °C/0.6 mmHg (10 min). The residual product was purified by flash chromatography using 3% methanol in dichloromethane as eluent; yield 64 mg (58%) of a colourless oil. Found: C, 60.72; H, 8.18. Calc. for $C_8H_{13}NO_2$: C, 61.91; H, 8.44%. $[\alpha]_D$ = -19.2° (c = 0.50, $CHCl_3$). ^1H NMR (300 MHz): δ 1.61-2.61 (m, 8H, 3 x CH_2, NH_2), 3.69 (s, 3H, CH_3O), 5.58-5.71 (m, 2H, 2 x CH=). ^{13}C NMR (50 MHz): δ 21.73 (CH_2), 31.13 (CH_2), 35.27 (CH_2), 52.11 (CH_3O), 55.58 (C-1), 123.54 (CH=), 125.87 (CH=), 177.19 (C=O). MS(EI): 155 (1, M^+), 101 (29), 95 (100), 79 (22). MS(EI): *M* 155.0941. Calc. for $C_8H_{13}NO_2$: 155.0946.

(*S*) Methyl 1-amino-3-cyclohexene-1-carboxylate (**8c**). A solution of (2*R*, 5*S*)-2,5-dihydro-3,6-dimethoxy-3-isopropylpyrazine-5-spiro(3-cyclohexene) (118 mg, 0.47 mmol) in TFA (23.5 ml, 4.70 mmol, 0.2 M) and MeCN (23.5 ml) was kept at ambient temperature for 3 d, the solution evaproated almost to dryness at reduced pressure, water (5 ml) and dichloromethane (10 ml) added and the two layers separated. The aqueous solution was brought to pH 10 by addition of conc. aq. ammonia, the mixture extracted with dichloromethane (3 x 20 ml), the organic extracts dried ($MgSO_4$), evaporated and the product isolated by flash chromatography using 3% methanol in dichloromethane as eluent; yield 31 mg (42%) of a colourless oil. $[\alpha]_D$ = +19.5° (c = 0.62, $CHCl_3$). ^1H NMR (300 MHz): δ 1.61-2.61 (m, 8H, 3 x CH_2, NH_2), 3.69 (s, 3H, CH_3O), 5.58-5.71 (m, 2H, 2 x CH=). ^{13}C NMR (75 MHz): δ 21.82 (CH_2), 31.24 (CH_2), 35.39 (CH_2), 52.18 (CH_3O), 55.67 (C), 123.63 (CH=), 125.96 (CH=), 177.30 (C=O). MS(EI): 101 (28), 96 (100), 79 (31). MS(EI): *M* 155.0956. Calc. for $C_8H_{13}NO_2$: 155.0946.

Methyl 1-amino-4-cycloheptene-1-carboxylate (**8d**). A solution of (2*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine-5-spiro(4-cycloheptene) (186 mg, 0.70 mmol) in MeCN (35 ml) and TFA (35 ml, 7.00 mmol, 0.2 M) was stirred at ambient temperature for 3 d, the solution concentrated to about 10 ml and dichloromethane (20 ml) added. The two phases were separated, the aqueous phase brought to pH 10 by

addition of conc. aq. ammonia, extracted with dichloromethane (3 x 20 ml), the solvent removed by distillation, and most of the methyl valinate removed from the residue by careful bulb to bulb distillation at 25 °C/0.05 mmHg (45 min). The residual product was purified by flash chromatography using 3% methanol in dichloromethane as eluent; yield 83 mg (69%) of a colourless oil. Found: C, 62.61; H, 8.39. Calc. for $C_9H_{15}NO_2$: C, 63.88; H, 8.94%. ^1H NMR (300 MHz): δ 1.53-2.30 (m, 10H, 4 x CH_2, NH_2), 3.67 (s, 3H, CH_3O), 5.66 (m, 2H, 2 x CH=). ^{13}C NMR (75 MHz): δ 23.45 (2 x CH_2), 36.50 (2 x CH_2), 52.07 (CH_3O), 60.71 (C), 131.13 (2 x CH=), 178.13 (C=O). MS(EI): 169 (1, M^+), 110 (100), 93 (11). MS(EI): *M* 169.1101. Calc. for $C_9H_{15}NO_2$: 169.1103.

(*S*) Methyl 1-amino-3-cycloheptene carboxylate (8e). A solution of (3*R*,6*S*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine-5-spiro(3-cycloheptene) (100 mg, 0.38 mmol) in MeCN (19 ml) and 0.2 M TFA (19 ml, 3.70 mmol) was stirred for 5 d at ambient temperature. The solution was concentrated to about 10 ml, dichloromethane (10 ml) added, the layers separated, the aqueous solution brought to pH 10 by addition of conc. aq. ammonia, the mixture extracted with dichloromethane (3 x 10 ml), the organic extracts dried ($MgSO_4$), evaporated and the methyl valinate removed from the residual material by bulb to bulb distillation at 25 °C/0.05 mmHg (10 min). The residual product was purified by flash chromatography using 3% methanol in dichloromethane as eluent; yield 46 mg (73%) of a colourless oil. $[\alpha]_D$ = -12.8° (c = 0.78, $CHCl_3$). ^1H NMR (200 MHz): δ 1.46-2.58 (m, 10H, 4 x CH_2, NH_2), 3.65 (s, 3H, CH_3O), 5.57 (m, 1H, CH=), 5.90 (m, 1H, CH=). ^{13}C NMR (50 MHz): δ 21.54 (CH_2), 28.30 (CH_2), 37.27 (CH_2), 41.51 (CH_2), 51.97 (CH_3O), 57.81 (C-1), 126.31 (CH=), 134.49 (CH=), 176.97 (C=O). MS(EI): 154 (8, M^+-Me), 114 (28), 110 (100).

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