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Cyclic α-Amino Acids by Pd-mediated Cycloisomerization and Coupling Reactions

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Abstract: Stereoselective syntheses of cyclic α-amino acids are described. The α-carbon of the amino acid is incorporated into a five- or six-membered vicinal dimethylenecycloalkane or conjugated methylenecycloalkene. Palladium-catalysis was used for cycloisomerization of intermediate enynes and intramolecular Heck type cyclizations of bromodienes. A stereoselective elimination from a homoallylic Pd-intermediate is described. Enantiomerically pure substrates for the cyclization reactions were available by stepwise alkylations of the chiral auxiliary (*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine with bromo-alkenes and -alkynes.

In recent reports we have described methods for the preparation of conformationally restricted α-amino acids by stereoselective α,α-dialkylation of glycine to yield cyclic structures of potential interest as bioorganics.[1] Ring formation was effected from geminal alkenyl or alkynyl derivatives of Schöllkopf's chiral auxiliary (2*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine using Grubbs methodology with a carbenoid ruthenium(II) complex as catalyst to effect the ring closing metathesis reaction.[2,3] Cyclic amino acids available by this approach are shown in Fig. 1. Group **A** structures comprise five-, six- and seven-membered 1-aminocycloalkene-1-carboxylic acids and their hydroxylated analogues; group **B** in the same way are conjugated vinyl derivatives with the one double bond *exo*-cyclic. The target molecules in the present work were to be complimentary alkylidene derivatives (**C**). Besides being target molecules, these unsaturated amino acid derivatives and their heterospirane precursors may serve as intermediates for further manipulations with special emphasis on dienes and in particular on the adduct forming properties of vicinal cycloalkanedimethylenes (**C**).

A R = H, OH **B** R = H, Me **C**

Figure 1

To effect the synthesis of the complimentary and isomeric structures **C** (Fig. 1) palladium mediated cyclizations were used. The diene and enyne substrates for the cyclizations were available by alkylation

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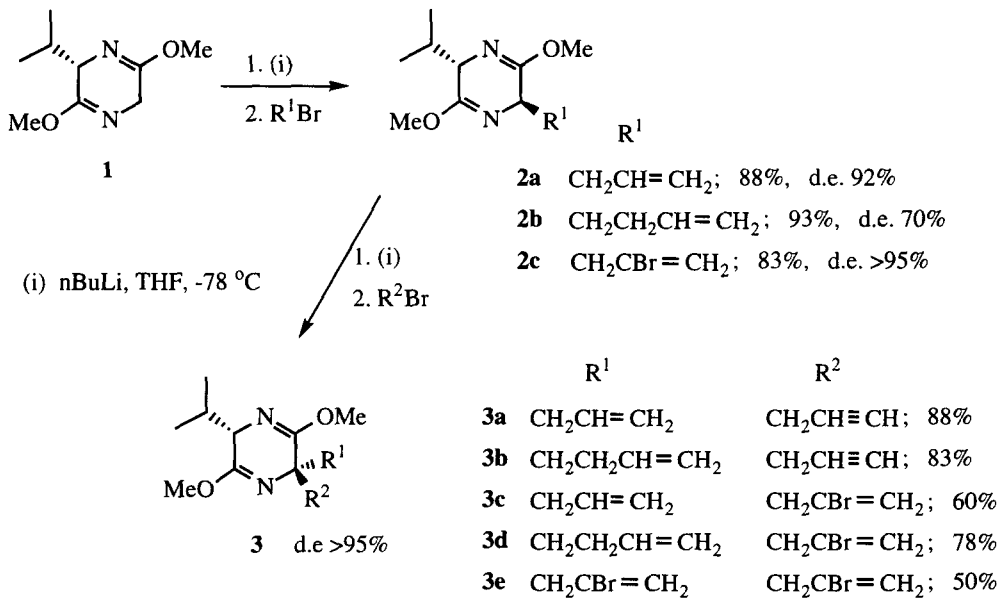
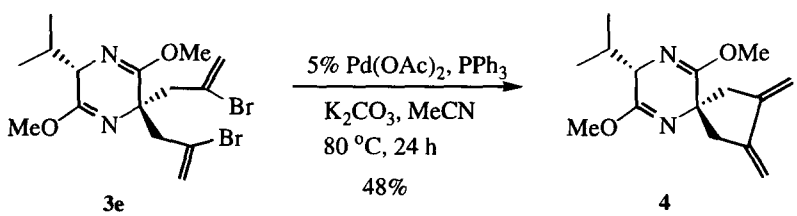


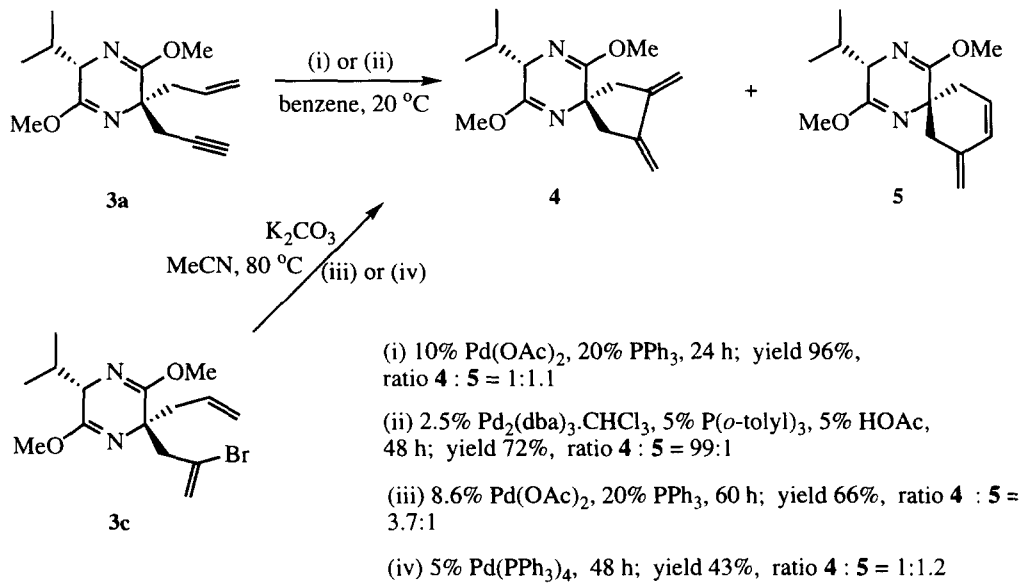
Scheme 1

reactions of (2*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (Scheme 1). The diastereomeric excess (d.e.) in the first alkylation step of the bislactim ether **1** was variable. The stereochemical yield in this step, however, is of little importance in this context since the stereochemistry at C-5 in the initial products **2** is lost when the monoalkylated species are metalated again for the second alkylation. The stereoselectivity in the second alkylation step is almost exclusively *trans* with respect to the incoming electrophile. In most cases only one stereoisomer was seen (GLC, TLC, NMR). This parallels previous findings in dialkylations with ω-bromo-1-alkenes and -alkynes.[1] The bromine at the olefinic carbon in 2,3-dibromopropene slows down the alkylating process. The lowest yield in the alkylation was observed for the dibromo derivative **3e**, which in part can be rationalized as due to competitive metal-bromine exchange on sp^2-hybridized carbon which becomes more important when the alkylation is slow.



Scheme 2

The dibromide **3e** was prepared to circumvent the problem of regioselectivity in the subsequent Heck reactions (*vide infra*) for the selective preparation of the 3,4-dimethylene derivative **4**. The conditions used, 5 mol% $Pd(OAc)_2$ with triphenylphosphine and anhydrous potassium carbonate were the same as used by us for the successful intermolecular homocoupling of the corresponding monobromide **2c** which gave bridged bisamino acids.[4] The coupling protocol is due to Grigg *et al.* from their studies of Pd-catalyzed cyclization of simple 2,6-dibromo-1,6-dienes.[5] Yields of cyclic products varied both with concentration and nature of the triarylphosphine ligand as reported by Grigg *et al.* in their work; our best condition is given in Scheme 2. An additional problem in the present case, is the sensitivity of the bislactim ether ring system towards acidic conditions. The reaction may proceed by a Heck mechanism, with Pd-Br elimination from the homoallylic intermediate to regenerate the double bond;[5] or by metal insertion into both C-Br bonds, disproportionation and elimination of $PdBr_2$, and finally reductive elimination from the intermediate metalacycle yielding the dimethylene product **4**.

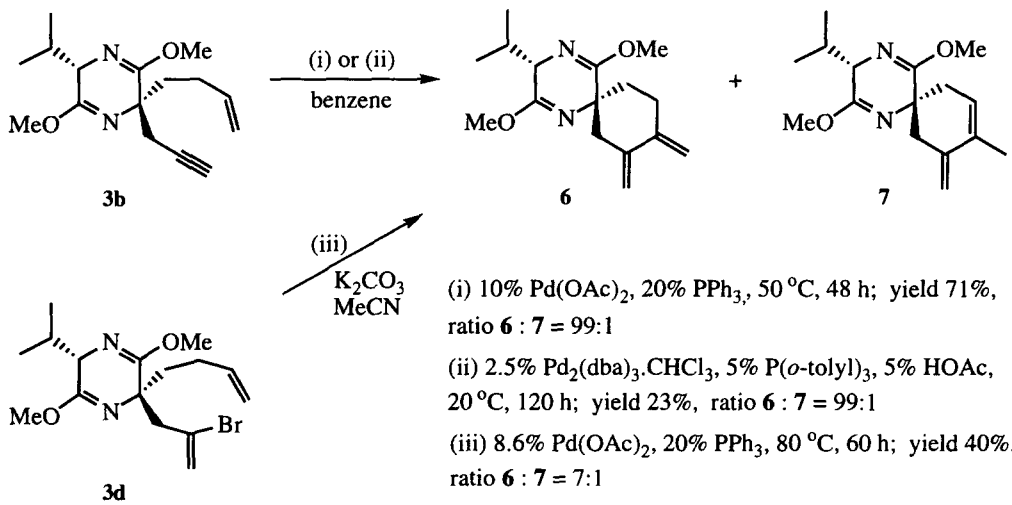


Scheme 3

In the intramolecular Heck reaction, products from both 5-*exo* and 6-*endo* cyclizations were formed, *i.e.* the 3,4-dimethylenecyclopentane **4** and the 5-methylenecyclohex-3-ene **5**, respectively. The relative yields of the two products were dependent on reaction conditions. Isomeric product formations are frequently encountered in intramolecular Heck reactions.[6] When the enyne **3a** was treated with $Pd(OAc)_2$ and PPh_3 in benzene the isomers **4** and **5** were formed almost in equimolar quantities in high yield. The reaction conditions are an adaption of the protocol used by Trost *et al.* for enyne cycloisomerizations which gave exclusively 1,3-dienes such as dimethylenecyclopentanes from simple 1,6-enynes.[7]

The combination of $(dba)_3Pd_2{\cdot}CHCl_3$ and a carboxylic acid has been found to effectively catalyze cyclization of 1,6-enynes.[8] In the present case, the isomer distribution was drastically changed from that of the former conditions on use of the catalyst system 2.5 mol% $Pd_2(dba)_3{\cdot}CHCl_3$ tri-*o*-tolylphoshine and 5 mol% acetic acid. Almost exclusive formation of the 5-membered ring product **4** resulted.

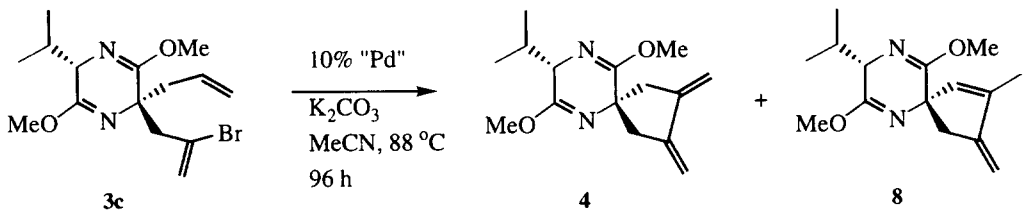
The initial step in the enyne cycloisomerization reactions is a hydropalladation of the triple bond. The same intermediate should in principle arise by palladium insertion into the C-Br bond in bromide **3c** except for the counterion generated on palladium which may well affect the catalytic course of the reaction. Under conditions similar to those used to effect cyclization of the dibromide **3e**, which gave the dimethylenecyclopentane **4** as the sole isolatable product, the preference for *exo*-trig addition was retained in that the ratio of the isomers **4**:**5** was 3.7:1. With the tetrakis(triphenylphospine)palladium catalyst system in the absence of acetate, the isomer ratio was closer to unity. Small changes in the catalyst concentration and base have previously been reported to change the course of reaction and regioselectivity in simpler but related substrates.[9] The enyne reactions were run at ambient temperature whereas the Heck reaction had to be heated at 80 °C. In the latter case the isolated yield was lowered in part because of the increased tendency for Diels-Alder reactions with the reactive dimethylene derivative **4** serving both as a diene and as an ene substrate.

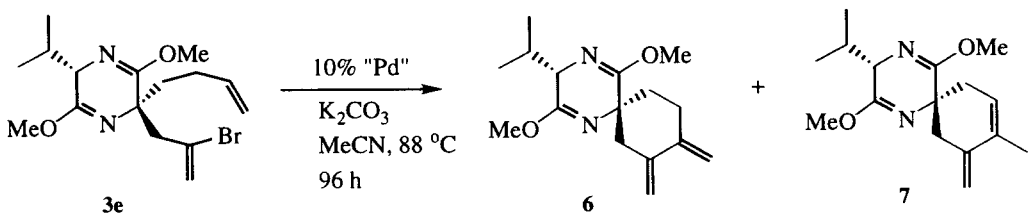


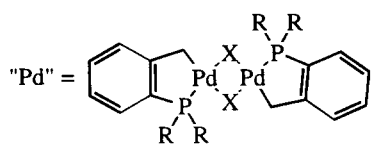
Scheme 4

In Scheme 4 the substrates **3b** and **3d** carry a butenyl alkene substituent instead of the allyl substituent in the substrates **3a** and **3c** (*vide supra*). This opens for competitive 6-*exo* and 7-*endo* Heck reactions. Exclusive six-membered ring formation was observed. Use of the previous conditions for enyne cycloisomerization gave almost exclusively the 3,4-dimethylenecyclohexane **6** with the *endo*-olefinic product **7** barely detectable. The palladium insertion reaction on the bromide **3d** would result in a similar hydropalladated intermediate as formed from hydropalladation of the enyne **3b** except for the counterion on palladium; the relative amounts of *endo*-double bond product was increased in this reaction. It was difficult to

effect full conversion of the substrate in these reactions. Reaction conditions were chosen to balance the rate of cyclization and the rate of polymerization of the desired products.







where R = *o*-tolyl; X = OAc

Scheme 5

The relative amount of the *endo*-double bond product **7** has been increased, to almost equimolar amounts of the isomers **6** and **7**, by using a recent Pd-catalyst system due to Herrmann *et al.*[10] This palladacycle system has been recommended for Heck reactions because of good thermal tolerance and high activity with the possibility for the operation of an alternative catalytic cycle involving a Pd(II) --->Pd(IV) process.[10] The acetate-bridged palladacycle is available by treatment of $Pd(OAc)_2$ with *tri-o*-tolylphosphane in toluene and becomes catalytically active at about 80 °C. We ran our reactions successfully at 88 °C. 10 Mol% of the palladacycle catalyst with anhydrous potassium carbonate in acetonitrile converted the bromide **3c** into an almost equimolar amount of the 3,4-dimethylenecyclopentane **4** and the isomeric 4-methylenecyclopent-2-ene **8**. The latter product, with an *endo*-cyclic double bond, had not been observed when using the catalytic systems previously discussed for the formation of **4**. The six-membered ring structure **5** was not seen.

Formation of the cycloisomer **8** could be rationalized by partial isomerization of the dimethylenecyclopentane **4** as the kinetic product to the thermodynamically more stable cycloisomer **8**. This postulate would harmonize with observations and explanations offered in the literature for similar

phenomenon.[7a,11] Our attempts to effect isomerization of the dimethylene derivative **4** by simulation of the reaction conditions for its formation, however, failed to yield any of the cycloisomer **8**.

Any isomerization reaction of the dimethylene derivative **4** would be expected to yield either the product **8** or its diastereoisomer arizing from isomerization of the other methylene group. In the dimethylene spiro structure **4** one of the cyclopentane faces is shielded by the 6-methoxy group in the pyrazine ring. A slight differential shielding of the 2′- and 3′-methylene groups is expected from the distant isopropyl group, which has a *quasi cis*- and *trans*-relationship to the methylene groups in the semiplanar pyrazine ring. Whether the differential shielding is sufficient for the control of the regiochemistry in any isomerization reaction seems doubtful. Regiocontrolled isomerization is a requirement since both the ^{1}H and ^{13}C NMR spectra are consistent with a stereochemically homogenous product in that no dublication of the signals corresponding to two diastereoisomers was seen. GLC and HPLC were also consistent with the formation of one isomer.

In the reactions of the butenyl derivatives **3b** and **3d** (Schemes 4 and 5) the apparent isomerization reaction is also regioselective. The NMR spectra were charaterized by one set of ^{1}H- and ^{13}C-signals and GLC and TLC were consistent with a single product being formed. It seems unlikely that the vicinal dimethylenecyclohexane **6** is an intermediate in the formation of the cyclohexene **7** by a regioselective rearrangement process involving only one of the methylene groups.

The heterospiranes were cleaved under mild acid conditions to the corresponding cyclic amino acid methyl esters **9** - **12** (Scheme 6). The second product in these reactions is methyl valinate. In work on gram scale the valine ester can frequently be removed by a distillation process, in small scale work flash chromatography on dry packed columns serves to separate the products. For the separation of the vicinal dimethylene esters **9** and **10**, wet packed columns with CH_2Cl_2:MeOH (40:1) were used. Substantial amounts of these unstable products, however, were lost in the isolation procedure.

The amino acid derivative from **8** was optically active with specific rotation $[\alpha]_D$ +17.2° whereas its amino acid isomer **9** is achiral. The assignment of structure **8** to the double bond isomeric cyclization product is based on NMR data. Complete assignments of the NMR resonances were carried out by GS-HMQC and GS-COSY NMR spectroscopy. Support for assignments and analyses was sought by including in the study the structurally close analogues **4** and **5** with known structures. Chemical shifts are given and correlations are expressed by double headed arrows in Fig. 2. The NOESY spectrum of compound **4** is consistent with an envelope conformation of the five-membered ring. In the 1′-position in compound **4** only H_b was correlated to protons in one of the isopropyl methyl groups. The other proton, H_a-1′ was correlated with the methoxy group at C-6. The envelope coformation was further supported by a correlation between the 3-methoxy protons and H_b-4′, but not with H_a-4′. The NOESY spectrum showed the 6-methoxy group to be oriented in space between the two isopropyl methyl groups. There was also interaction between the 3-methoxy group and one of the isopropyl methyl groups, the one which was correlated to H_b-1′.

Analysis of the NOESY spectrum of the six-membered ring analogue **5** showed a similar conformational preference. H_b-1′, but not H_a-1′, was correlated with the isopropyl methyl protons. H_b-5′was strongly correlated with H_b-6′, while H_a-5′ was not affected. H_a-6′was only correlated with H_a-3′.

In the compound eventually assigned structure **8**, the isopropyl group and the olefinic proton in the cyclopentene ring have a *cis*-relationship in the pyrazine ring. The NOESY spectrum with optimized mixing time (d8) of 1.7 s showed strong correlation between the vinyl proton H-1′and the isopropyl methyl protons.

No correlation was observed between the methylene protons H_a-4′or H_b-4′ and the isopropyl protons. This confirms that the double bond in the five-membered ring and the isopropyl group must have a *cis*-relationship in the pyrazine ring, and this is expressed in structure **8**. On the basis of the above evidence, we conclude that it is unlikely that the cycloisomer **8** originates from the vicinal dimethylenecyclopentane **4** by an isomerization reaction.

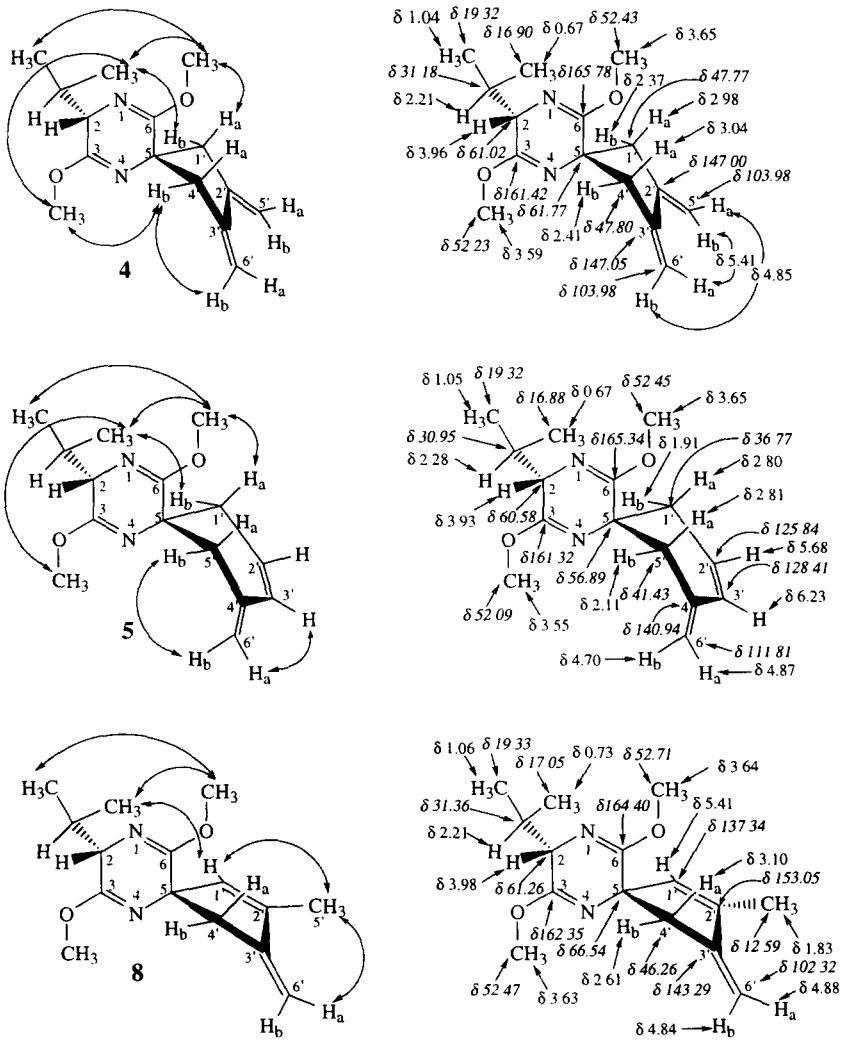
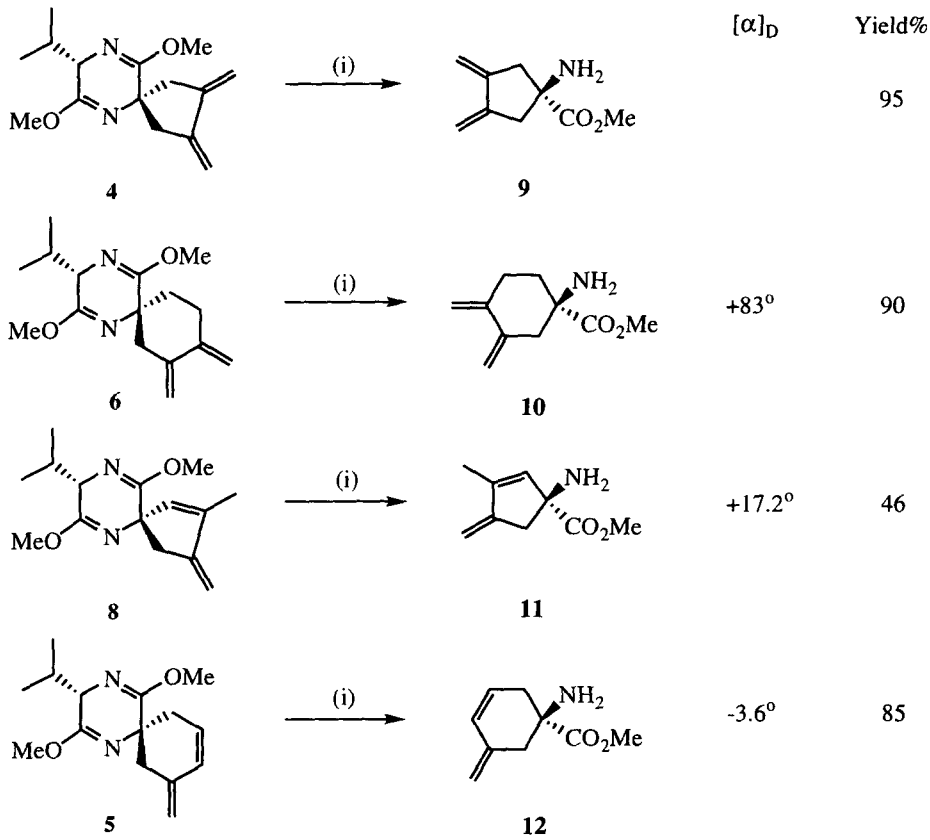


Fig. 2. Assignments and Correlations in ^{1}H and ^{13}C NMR Spectra



(i) 0.2 M TFA, MeCN, 20 °C, 16 h (**6**; 24 h)

Scheme 6

Presumably the homoallylic palladium intermediate in the reactions of **3c** is common for both reaction paths. β-Hydridopalladium elimination yields the dimethylene product **4**. For the stereochemistry to be retained in the formation of the product **8**, it may be that the hydridopalladium complex after elimination remains attached to the double bond generated and subsequently adds to the double bond in the reverse regiosense. The strength of binding to the double bond may be a function of the electrophilic character of the particular palladium catalyst. β-Hydridopalladium elimination may subsequently lead to either *endo*- (**8**) or *exo*- (**4**) cyclic double bond formation. This implies that the other methylene group has little influence on this process.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded at 500 MHz with a Bruker Avance DRX 500 instrument, at 300 MHz with a Bruker Avance DPX 300, or at 200 MHz with a Bruker Avance DPX 200 instrument with 5 mm QNP, BBO and TXI probes. The ^{13}C NMR spectra were recorded at 125, 75 or 50 MHz using instruments mentioned above with 5 mm QNP or BBO probes. Chemical shifts (δ) are given in ppm downfield from

tetramethylsilane. Gradient accelerated (z gradient) ^{1}H ^{13}C HMBC and ^{1}H {^{13}C} HMQC spectra were recorded with the Bruker Avance DRX 500 spectrometer equipped with a 5 mm triple resonance (^{1}H, ^{13}C, ^{15}N) inverse detection probe (TXI) using the Bruker pulse programs; inv4gslplrnd (HMBC) and inv4gs (HMQC). The GS-COSY spectra were recorded with the sweep optimized pulse program cosygssw. The NOESY spectra were recorded at 500 MHz using the Bruker pulse program noesytp (phase sensitive, TPPI), the mixing time (d8) were optimized with the program tlirld (T1 invention recovery pulse program).

Mass spectra were recorded with a VG Prospec instrument under electron impact conditions at 70 eV (EI). CH_4 was used for chemical ionization (CI). The spectra are presented as *m/z* (% rel. int.).

Silica gel for flash chromatography was purchased from Merck, Darmstadt, Germany (Merck No. 9385). THF and benzene were distilled from sodium/benzophenone and acetonitrile from CaH_2.

(2*S*,5*R*)-5-Allyl-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (***2a***).[12]

(2*S*,5*R*)-5-(3-Butenyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (***2b***). *n*-Butyllitium (6.96 ml, 15.32 mmol, 2.2 M in hexane) was added dropwise to a solution of (*S*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (2.57 g, 13.93 mmol) in dry THF (40 ml) under argon at -78 °C. The mixture was stirred for 30 min before addition of a solution of 4-bromo-1-butene (2.44 g, 1.85 ml, 18.11 mmol) in THF (3 ml) which was precooled to -78 °C. The mixture was stirred at -78 °C for 3 h and left to reach ambient temperature overnight. The solvent was evaporated at reduced pressure, the residue dissolved in diethyl ether (150 ml), the ether solution washed with 10% aqueous ammonium chloride (2 x 30 ml), dried ($MgSO_4$), evaporated and the residual product purified by flash chromatography on silica gel using hexane:ethyl acetate (9:1); yield 3.08 g (93%, d.e. 70%). The minor isomer was removed by flash chromatography on silica gel using dichloromethane for elution. The title compound was a colourless oil. Found: C, 66.21; H, 9.41. Calc. for $C_{13}H_{22}N_2O_2$: C, 65.51; H, 9.49. MS(HR): Found for *M*: 238.1676. Calc. for $C_{13}H_{22}N_2O_2$: 238.1681. $[\alpha]_D$ -8.9° (c = 0.280, $CHCl_3$) ^{1}H NMR ($CDCl_3$): δ 0.61, 0.97 [2 d, *J* 6.8 Hz, 6H, $CH(\underline{CH_3})_2$], 1.6-1.9 (m, 2H, $\underline{CH_2}CH_2$-CH=), 1.9-2.05 (m, 2H, $CH_2\underline{CH_2}$-CH=), 2.19 [dsept, *J* 3.3 Hz and *J* 6.8 Hz, 1H, $\underline{CH}(CH_3)_2$], 3.60 (s, 3H, OCH_3), 3.61 (s, 3H, OCH_3), 3.85 [dd, *J* 3.3 Hz and *J* 3.5 Hz, 1H, $\underline{CH}$-$CH(CH_3)_2$], 3.96 (ddd, *J* 3.5 Hz, *J* 3.9 Hz and *J* 6.4 Hz, 1H, $\underline{CH}$-CH_2CH_2), 4.86 (ddt, *J* 1.2 Hz, *J* 2.0 Hz and *J* 10.2 Hz, 1H, =$\underline{CH_2}$cis), 4.93 (ddt, *J* 1.5 Hz, *J* 2.0 Hz and *J* 17.1 Hz, 1H, =$\underline{CH_2}$trans), 5.74 (ddt, *J* 6.3 Hz, J_{cis}10.2 Hz and J_{trans} 17.1 Hz, 1H, $\underline{CH}$=CH_2). ^{13}C NMR ($CDCl_3$): δ 16.51, 19.01 [$CH(\underline{CH_3})_2$], 28.92 ($CHCH_2\underline{CH_2}$-CH=), 31.64 [$\underline{CH}(CH_3)_2$], 33.35 ($CH\underline{CH_2}CH_2$-CH=), 52.24 (2x OCH_3), 54.86 ($\underline{CH}CH_2CH_2$-CH=), 60.71 [$(CH_3)_2CH$-$\underline{CH}$-N], 114.41 (=$\underline{CH_2}$), 138.37 (-$\underline{CH}$=), 163.48, 163.69 (2x $\underline{C}$-OCH_3). MS(EI): 238 (14, M^+), 223 (37), 207 (5), 195 (100), 183 (15), 181 (6), 166 (14), 153 (48), 141 (82), 123 (8).

(2*S*,5*S*)-5-(3-Butenyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine; the minor isomer. MS(HR): Found for *M*: 238.1670. Calc. for $C_{13}H_{22}N_2O_2$: 238.1681. $[\alpha]_D$ +72.5° (c = 0.400, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.72, 1.04 [2d, *J* 6.9 Hz, 6H, $CH(\underline{CH_3})_2$], 1.55 (ddt, *J* 6 Hz, *J* 9 Hz and *J* 16 Hz, 1H, $\underline{CH_2}CH_2$-CH=), 1.96 (ddt, *J* 4 Hz, *J* 7 Hz and *J* 16 Hz, 1H, $\underline{CH_2}CH_2$-CH=), 2.14-2.25 [m, 3H, $CH_2\underline{CH_2}$-CH= and $\underline{CH}(CH_3)_2$], 3.65 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.93 [d, *J* 3.9 Hz, 1H, $\underline{CH}$-$CH(CH_3)_2$], 3.99 (dd, *J* 4 Hz and *J* 9 Hz, 1H, $\underline{CH}$-CH_2CH_2), 4.95 (d, *J* 10 Hz, 1H, =$\underline{CH_2}$cis), 5.03 (dd, *J* 1.7 Hz and *J* 17 Hz, 1H, =$\underline{CH_2}$trans), 5.84 (ddt, *J* 6.7 Hz, J_{cis}10 Hz and J_{trans} 17 Hz, 1H, $\underline{CH}$=CH_2). ^{13}C NMR ($CDCl_3$): δ 17.50, 19.54 [$CH(\underline{CH_3})_2$], 30.24 ($CHCH_2\underline{CH_2}$-CH=), 31.30 [$\underline{CH}(CH_3)_2$], 34.80 ($CH\underline{CH_2}CH_2$-CH=), 52.30 (2x OCH_3), 55.13 ($\underline{CH}CH_2CH_2$-

CH=), 60.89 [$(CH_3)_2$CH-CH-N], 114.71 (=CH_2), 138.42 (-CH=), 163.11, 163.80 (2x C-OCH_3). MS(EI): 238 (3, M^+), 223 (19), 207 (6), 195 (100), 183 (4), 166 (22), 153 (45), 141 (74), 123 (9).

(2*S*,5*R*)-5-(2-Bromoallyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (**2c**).[4]

(2*S*,5*R*)-5-Allyl-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-propargylpyrazine (***3a***). *n*-Butyllitium (2.90 ml, 6.38 mmol, 2.2 M in hexane) was added dropwise to a solution of (2*S*,5*R*)-5-allyl-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (1.30 g, 5.80 mmol) in dry THF (25 ml) under argon at -60 °C. The solution was cooled to -78 °C after 1 h and a precooled (-78 °C) solution of propargyl bromide (2.07 g, 17.39 mmol) in THF (2 ml) was added. The mixture was stirred at -78 °C for 2 h and left to reach ambient temperature overnight. The solvent was evaporated at reduced pressure, and the residue dissolved in diethyl ether (100 ml). The ether solution was washed twice with 10% aqueous ammonium chloride, dried ($MgSO_4$), evaporated and the product purified by flash chromatography on silica gel using dichloromethane:hexane (4:1); yield 1.34 g (88%, d.e. >95%) of a colourless oil. Found: C, 68.35; H, 8.27. Calc. for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45%. $[\alpha]_D$ 30.6° (c = 0.808, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.61, 1.05 [2d, *J* 6.9 Hz, 6H, CH(CH_3)$_2$], 1.83 (t, *J* 2.5 Hz, 1H, ≡CH), 2.28 [dsept, *J* 3.3 Hz and *J* 6.9 Hz, 1H, CH(CH_3)$_2$], 2.32, 2.49 (2 dd, *J* 7.3 Hz and *J* 13.3 Hz, 2H, CH_2-CH=), 2.39, 2.59 (2 dd, *J* 2.5 Hz and *J* 16.3 Hz, 2H, CH_2-C≡CH), 3.65 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.97 [d, *J* 3.3 Hz, 1H, CH-CH(CH_3)$_2$], 4.95 (dd, *J* 2 Hz and *J* 10.1 Hz, 1H, =CH_2cis), 4.99 (dd, *J* 2 Hz and *J* 17.1 Hz, 1H, =CH_2trans), 5.59 (dddd, *J* 7.3 Hz, *J* 7.3, J_{cis} 10.1 Hz and J_{trans} 17.1 Hz, 1H, CH=CH_2). ^{13}C NMR ($CDCl_3$): δ 17.07, 19.50 [CH(CH_3)$_2$], 30.49 [CH(CH_3)$_2$], 31.05 (CH_2-C≡), 44.00 (CH_2-CH=), 52.26, 52.38 (2x OCH_3), 60.80 [$(CH_3)_2$CH-CH-N], 61.45 (N-C-C=N), 70.08 (-C≡CH), 80.40 (-C≡CH), 117.90 (=CH_2), 133.92 (-CH=), 162.31, 163.68 (2x C-OCH_3). MS(EI): 262 (3, M^+), 247 (8), 231 (1), 223 (58), 221 (46), 219 (26), 204 (4), 189 (3), 181 (100), 179 (68), 166 (9), 164 (17).

(2*S*,5*R*)-5-(3-Butenyl)-5-(propargyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (***3b***) was prepared as above from (2*S*,5*R*)-5-(3-butenyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (4.20 mmol) and propargyl bromide (12.60 mmol). The product was purified by flash chromatography on silica gel using dichloromethane:hexane (4:1); yield 83%, d.e. >95% of a colourless oil. Found: C, 70.05; H, 8.87. Calc. for $C_{16}H_{24}N_2O_2$: C, 69.53; H, 8.75%. MS(HR): Found for *M*: 276.1899. Calc. for $C_{16}H_{24}N_2O_{22}$: 276.1838. $[\alpha]_D$ +17.1° (c = 0.510, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.64, 1.08 [2 d, *J* 6.8 Hz, 6H, CH(CH_3)$_2$], 1.61 - 1.75, 1.86 - 1.91 (2 m, 4H, CH_2CH_2), 1.84 (t, *J* 2.6 Hz, 1H, ≡CH), 2.33 [dsept, *J* 3.3 Hz and *J* 6.8 Hz, 1H, CH(CH_3)$_2$], 2.39, 2.59 (2 dd, *J* 2.6 Hz and *J* 16.2 Hz, 2H, CH_2-C≡), 3.676 (s, 3H, OCH_3), 3.679 (s, 3H, OCH_3), 4.00 [d, *J* 3.3 Hz, 1H, CH-CH(CH_3)$_2$], 4.89 (dd, *J* 1.6 Hz and *J* 9.8 Hz, 1H, =CH_2cis), 4.94 (dd, *J* 1.6 Hz and *J* 17.1 Hz, 1H, =CH_2trans), 5.75 (dddd, *J* 6.2 Hz, *J* 6.2, J_{cis} 9.8 Hz and J_{trans} 17.1 Hz, 1H, CH=CH_2). ^{13}C NMR ($CDCl_3$): δ 16.92, 19.53 [CH(CH_3)$_2$], 29.10 (CH_2CH_2-CH=), 30.51 [CH(CH_3)$_2$], 31.67 (CH_2-C≡), 38.56 (CH_2CH_2-CH=), 52.35, 52.44 (2x OCH_3), 60.93 [$(CH_3)_2$CH-CH-N], 61.34 (N-C-C=N), 70.02 (-C≡CH), 80.39 (-C≡CH), 114.32 (=CH_2), 138.36 (-CH=), 162.49, 164.03 (2x C-OCH_3). MS(EI): 276 (3, M^+), 261 (16), 245 (2), 237 (92), 233 (51), 195 (100), 179 (22), 164 (6), 153 (32), 123 (10).

(2*S*,5*R*)-5-Allyl-5-(2-bromoallyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (***3c***) was prepared as above from (2*S*,5*R*)-5-allyl-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (1.78 mmol) and 2,3-

dibromopropene (5.35 mmol). The product was purified by flash chromatography on silica gel using dichloromethane:hexane (2:1); yield 60%, d.e. >98% of a colourless oil. MS(HR): Found for *M* 342.0951, 344.0965. Calc. for $C_{15}H_{25}BrN_2O_2$ 342.0943, 344.0922. $[\alpha]_D$ -31.8° (c = 0.776, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.64, 1.05 [2 d, *J* 6.9 Hz, 6H, CH(C<u>H</u>$_3$)$_2$], 2.29 [dsept, *J* 3.3 Hz and *J* 6.9 Hz, 1H, C<u>H</u>(CH$_3$)$_2$] 2.35, 2.52 (2 dd, *J* 7.2 Hz and *J* 13.2 Hz, 2H, C<u>H</u>$_2$CH=CH$_2$), 2.66, 2.92 (2 d, *J* 14.0 Hz, 2H, C<u>H</u>$_2$CBr=CH$_2$), 3.65 (s, 3H, OCH$_3$), 3.68 (s, 3H, OCH$_3$), 3.90 [d, *J* 3.3 Hz, 1H, C<u>H</u>-CH(CH$_3$)$_2$], 4.97 (dd, *J* 1.1 Hz and *J* 10.1 Hz, 1H, =C<u>H</u>$_2$cis), 5.01 (dd, *J* 1.1 Hz and *J* 17.1 Hz, 1H, =C<u>H</u>$_2$trans), 5.44, 5.45 (2 d, *J* 1 Hz, 2H, CBr=C<u>H</u>$_2$), 5.62 (dddd, *J* 7.2 Hz, *J* 7.2, J_{cis} 10.1 Hz and J_{trans} 17.1 Hz, 1H, C<u>H</u>=CH$_2$). ^{13}C NMR ($CDCl_3$): δ 17.26, 19.52 [CH(<u>C</u>H$_3$)$_2$], 30.47 [<u>C</u>H(CH$_3$)$_2$], 45.08 (<u>C</u>H$_2$CH=CH$_2$), 50.44 (<u>C</u>H$_2$-CBr=CH$_2$), 51.93, 52.33 (2x OCH$_3$), 60.79 [(CH$_3$)$_2$CH-<u>C</u>H-N], 62.08 (N-<u>C</u>-C=N), 118.01 (CH=<u>C</u>H$_2$), 120.84 (CBr=<u>C</u>H$_2$), 128.10 (<u>C</u>Br=CH$_2$), 133.86 (<u>C</u>H=CH$_2$), 162.00, 163.20 (2x <u>C</u>-OCH$_3$). MS(EI): 344/342 (1/1, M^+), 329/327 (1/1), 303/301 (14/14), 301/299 (10/10), 287/285 (1/1), 272/270 (1/1), 263 (5), 261/259 (30/33), 223 (81), 181 (100), 166 (6), 165 (7), 164 (5).

<u>(2*S*,5*R*)-5-(2-Bromoallyl)-5-(3-butenyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (*3d*)</u> was prepared as above from (2*S*,5*R*)-5-(3-butenyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (1.68 mmol) and 2,3-dibromopropene (5.04 mmol). The product was purified by flash chromatography on silica gel using dichloromethane:hexane (2:1); yield 78%, d.e. >98% of a colourless oil. MS(HR): Found for *M*: 356.1085, 358.1111. Calc. for $C_{16}H_{25}BrN_2O_2$: 356.1099, 358.1079. $[\alpha]_D$ -26.9° (c = 1.468, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.65, 1.07 [2 d, *J* 6.9 Hz, 6H, CH(C<u>H</u>$_3$)$_2$], 1.60 - 1.96 (m, 4H, C<u>H</u>$_2$C<u>H</u>$_2$), 2.33 [dsept, *J* 3.3 Hz and *J* 6.9 Hz, 1H, C<u>H</u>(CH$_3$)$_2$], 2.65, 2.91 (2 d, *J* 13.9 Hz, 2H, C<u>H</u>$_2$CBr=CH$_2$), 3.66 (s, 3H, OCH$_3$), 3.69 (s, 3H, OCH$_3$), 3.91 [d, *J* 3.3 Hz, 1H, C<u>H</u>-CH(CH$_3$)$_2$], 4.90 (dd, *J* 1.6 Hz and *J* 10.9 Hz, 1H, =C<u>H</u>$_2$cis), 4.96 (dd, *J* 1.6 Hz and *J* 17.4 Hz, 1H, =C<u>H</u>$_2$trans), 5.44 (s, 2H, CBr=C<u>H</u>$_2$), 5.70-5.81 (m, 1H, C<u>H</u>=CH$_2$). ^{13}C NMR ($CDCl_3$): δ 17.07, 19.54 [CH(<u>C</u>H$_3$)$_2$], 28.81 (CH$_2$<u>C</u>H$_2$CH=), 30.48 [<u>C</u>H(CH$_3$)$_2$], 39.55 (<u>C</u>H$_2$CH$_2$CH=), 51.13 (<u>C</u>H$_2$-CBr=CH$_2$), 52.01, 52.36 (2x OCH$_3$), 60.90 [(CH$_3$)$_2$CH-<u>C</u>H-N], 62.07 (N-<u>C</u>-C=N), 114.33 (CH=<u>C</u>H$_2$), 120.95 (CBr=<u>C</u>H$_2$), 127.99 (<u>C</u>Br=CH$_2$), 138.45 (<u>C</u>H=CH$_2$), 162.11, 163.59 (2x <u>C</u>-OCH$_3$). MS(EI): 358/356(1/1, M^+), 315/313 (61/61), 286/284 (2/2), 277 (63), 261/259 (15/16), 237 (76), 195 (100), 180 (10), 179 (11), 153 (49), 123 (15).

<u>(2*S*,5*R*)-5,5-Bis(2-bromoallyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (*3e*)</u> was prepared as above from (2*S*,5*R*)-5-(2-bromoallyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (2.43 mmol) and 2,3-dibromopropene (7.30 mmol). The product was purified by flash chromatography on silica gel using hexane:ethyl acetate (20:1); yield 0.51 g (50%). MS(HR): Found for *M*: 420.0005, 421.9893, 423.9951. Calc. for $C_{15}H_{22}Br_2N_2O_2$: 420.0048, 422.0027, 424.0007. $[\alpha]_D$ -5.7° (c = 0.954, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.70, 1.06 [2 d, *J* 6.9 Hz, 6H, CH(C<u>H</u>$_3$)$_2$], 2.29 [dsept, *J* 3.4 Hz and *J* 6.9 Hz, 1H, C<u>H</u>(CH$_3$)$_2$], [bromoallyl trans isopropyl: 2.67, 2.93 (2 d, *J* 13.8 Hz, 2H, C<u>H</u>$_2$-CBr), 5.47 (s, 1H, BrC=C<u>H</u>$_2$cisBr), 5.48 (s, 1H, BrC=C<u>H</u>$_2$transBr)], [bromoallyl cis isopropyl: 2.72, 3.04 (2 d, *J* 13.9 Hz, 2H, C<u>H</u>$_2$-CBr), 5.47 (s, 1H, BrC=C<u>H</u>$_2$cisBr), 5.57 (s, 1H, BrC=C<u>H</u>$_2$transBr)], 3.67 (s, 3H, OCH$_3$), 3.72 (s, 3H, OCH$_3$), 3.89 [d, *J* 3.4 Hz, 1H, C<u>H</u>-CH(CH$_3$)$_2$]. ^{13}C NMR ($CDCl_3$): δ 16.73, 19.63 [CH(<u>C</u>H$_3$)$_2$], 30.26 [<u>C</u>H(CH$_3$)$_2$], [bromoallyl cis isopropyl: 50.37 (<u>C</u>H$_2$-CBr), 121.77 (BrC=<u>C</u>H$_2$)], [bromoallyl trans isopropyl: 50.70 (<u>C</u>H$_2$-CBr), 121.50 (BrC=<u>C</u>H$_2$)], 51.75, 52.48 (2x OCH$_3$), 60.92 [<u>C</u>H-CH(CH$_3$)$_2$], 62.43 (N-<u>C</u>-CH$_2$), 127.17, 127.29, (2x

C=CH_2), 160.54, 163.52 (2x C-OCH_3). MS(EI): 424/422/420 (0.06/0.1/0.06, M^+), 409/407/405 (0.2/0.4/0.2), 397/395/393 (0.3/0.6/0.4), 381/379/377 (14/28/15), 352/350/348 (0.3/0.5/0.3), 343/341 (14/14), 303/301 (39/40), 277/275 (4/4), 261/259 (97/100), 221/219 (3/4), 181 (5), 180 (5), 179 (29), 165 (11), 164 (15).

(2*S*)-2,5-Dihydro-3,6-dimethoxy-2-isopropylpyrazine-5-spiro(2',3'-bismethylenecyclopentane) (**4**) by intramolecular coupling. A suspension of $Pd(OAc)_2$ (25.5 mg, 0.114 mmol), PPh_3 (224 mg, 0.853 mmol) and anhydrous K_2CO_3 (393 mg, 2.845 mmol) in dry acetonitrile (50 ml) was stirred at 50 °C under argon for 5 min, (2*S*,5*R*)-5,5-bis(2-bromoallyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (240 mg, 0.569 mmol) in dry acetonitrile (2 ml) added, and the reaction mixture heated at 80 °C until GLC showed full conversion (24 h) of starting material. The solvent was removed by evaporation at reduced pressure, and the residue dissolved in diethyl ether (30 ml). The ether solution was washed twice with 10% aqueous ammonium chloride, dried ($MgSO_4$), evaporated and the product isolated by flash chromatography on silica gel using dichloromethane as eluent; yield: 72 mg (48%) of a slightly yellow oil. MS(HR): Found for *M*: 262.1686. Calc. for $C_{15}H_{22}N_2O_2$: 262.1681. $[\alpha]_D$ +27.7° (c = 0.614, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.67, 1.04 [2 d, *J* 6.8 Hz, 6H, CH(CH_3)$_2$], 2.21 [dsept, *J* 3.4 Hz and *J* 6.8 Hz, 1H, CH(CH_3)$_2$], 2.37 (dd, *J* 1.8 Hz and *J* 16 Hz, 1H, H_b-1'), 2.41 (dd, *J* 1.8 Hz and *J* 16 Hz, 1H, H_b-4'), 2.98 (ddd, *J* 2.2 Hz , *J* 2.6 Hz and *J* 16 Hz, 1H, H_a-1'), 3.04 (ddd, *J* 2.2 Hz, *J* 2.6 Hz and *J* 16 Hz, 1H, H_a-4'), 3.59 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.96 (d, *J* 3.4 Hz, 1H, H-2), 4.85 (dd, *J* 1.8 Hz and *J* 1.9 Hz, 2H, H_a-5' and H_b-6'), 5.41 (dd, *J* 1.9 Hz and *J* 2.2 Hz, 2H, H_b-5' and H_a-6'). ^{13}C NMR ($CDCl_3$): δ 16.90, 19.32 [CH(CH_3)$_2$], 31.18 [CH(CH$_3$)$_2$], 47.77 (C-1'), 47.80 (C-4'), 52.23, 52.43 (2x OCH_3), 61.02 (C-2), 61.77 (spiro C), 103.98 (2x =CH_2), 147.00 (C-2'), 147.05 (C-3'), 161.42 (C-3), 165.78 (C-6). MS(EI): 262 (38, M^+), 247 (14), 231 (4), 219 (100), 205 (12), 204 (9), 190 (10), 189 (8), 176 (6), 162 (5).

(2*S*)-2,5-Dihydro-3,6-dimethoxy-2-isopropylpyrazine-5-spiro(2',3'-bismethylenecyclopentane) (**4**) and (2*S*,5*R*)-2,5-Dihydro-3,6-dimethoxy-2-isopropylpyrazine-5-spiro(4'-methylenecyclohex-2'-ene) (**5**) by Enyne Cycloisomerization. Method (i): (2*S*,5*R*)-5-Allyl-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-propargylpyrazine (460 mg, 1.753 mmol) in dry benzene (10 ml) was added to a solution of $Pd(OAc)_2$ (39.3 mg, 0.175 mmol) and PPh_3 (92 mg, 0.351 mmol) in dry benzene (180 ml) under argon. The reaction mixture was stirred at ambient temperature until GLC showed completion of the reaction (24 h). GLC showed that the cyclization products **4** and **5** were formed in a total yield of 96%, ratio 1:1.1. The solvent was removed by evaporation at reduced pressure, and the crude product purified by flash chromatography on silica gel using dichloromethane:hexane (2:1). The products are highly unstable and were partially lost during the purification. There was isolated 103 mg of product **4** and 108 mg of product **5**; total yield 211 mg (46%).

(2*S*,5*R*)-2,5-Dihydro-3,6-dimethoxy-2-isopropylpyrazine-5-spiro(4'-methylenecyclo-hex-2'-ene) (**5**): MS(HR): Found or *M*: 262.1671. Calc. for $C_{15}H_{22}N_2O_2$: 262.1681. $[\alpha]_D$ -48.9° (c = 0.880, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.67, 1.05 [2 d, *J* 6.8 Hz, 6H, CH(CH_3)$_2$], 1.91 (dd, *J* 5.2 Hz and *J* 17.8 Hz, 1H, H_b-1'), 2.11 (d, *J* 14.4 Hz, 1H, H_b-5'), 2.28 [dsept, *J* 3.4 Hz and *J* 6.8 Hz, 1H, CH(CH$_3$)$_2$], 2.80 (dd, *J* 2.5 Hz and *J* 17.8 Hz, 1H, H_a-1'), 2.81 (d, *J* 14.3 Hz, 1H, H_a-5'), 3.55 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.93 (d, *J* 3.4 Hz, 1H, H-2), 4.70 (s, 1H, H_b-6'), 4.87 (s, 1H, H_a-6'), 5.68 (ddd, *J* 2.5 Hz, *J* 5.2 Hz and *J* 10.1 Hz, 1H, H-2'), 6.23 (d, *J* 10.1 Hz, 1H, H-3'). ^{13}C NMR ($CDCl_3$): δ 16.88, 19.32 [CH(CH_3)$_2$], 30.95 [CH(CH$_3$)$_2$], 36.77 (C-1'), 41.43 (C-5'), 52.09, 52.45 (2x OCH_3), 56.89 (spiro C), 60.58 (C-2), 111.81 (C-6'), 125.84 (C-2'), 128.41

(C-3'), 140.94 (C-4'), 161.32 (C-3), 165.34 (C-6). MS(EI): 262 (25, M^+), 247 (6), 236 (3), 231 (3), 230 (3), 219 (100), 205 (8), 204 (7), 190 (6), 153 (14).

Method (ii): Acetic acid (1.7 mg, 0.0286 mmol) was added to a solution of $(dba)_3Pd_2{\cdot}CHCl_3$ (14.8 mg, 0.0143 mmol) and (*o*-tolyl)$_3$P (8.7 mg, 0.0286 mmol) in dry benzene (10 ml) under argon. The catalyst mixture was stirred for 30 min, diluted with benzene (30 ml) before (2*S*,5*R*)-5-allyl-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-propargylpyrazine (150.0 mg, 0.5717 mmol) in benzene (10 ml) was added. The mixture was stirred at ambient temperature until GLC monitoring showed the absence of starting material (48 h). GLC showed the product **4** (78%) to contain about 1% of the isomer **5**. The latter was removed by evaporation of the solution at reduced pressure and flash chromatography of the residual material on silica gel using hexane:ethyl acetate (20:1). Partial loss, because of low stability, reduced the yield of isolated product **4** to 85.5 mg (57%).

(2*S*)-2,5-Dihydro-3,6-dimethoxy-2-isopropylpyrazine-5-spiro(2',3'-bismethylenecyclopentane) (**4**) and (2*S*,5*R*)-2,5-Dihydro-3,6-dimethoxy-2-isopropylpyrazine-5-spiro(4'-methylenecyclohex-2'-ene) (**5**) by intramolecular Heck reaction. (2*S*,5*R*)-5-Allyl-5-(2-bromoallyl)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-pyrazine (291 mg, 0.848 mmol) in dry acetonitrile (2 ml) was added to a stirred suspension of $Pd(OAc)_2$ (16.4 mg, 0.073 mmol), PPh_3 (44.4 mg, 0.170 mmol) and K_2CO_3 (234 mg, 1.696 mmol) in dry acetonitrile (100 ml) under argon. The reaction mixture was heated at 80 °C until GLC showed full conversion of the starting material (60 h). GLC analysis showed that the products were formed to the extent of 66%; the isomer ratio was **4:5** = 3.7:1. The solvent was evaporated at reduced pressure, and the residue dissolved in diethyl ether. The solution was washed twice with 10% aqueous ammonium chloride, dried ($MgSO_4$) and evaporated. The products were purified by flash chromatography on silica gel using dichloromethane:hexane (2:1) as eluent; yield: 69 mg (31 %), isomer ratio **4:5** = 3.3:1.

(2*S*,5*R*)-2,5-Dihydro-3,6-dimethoxy-2-isopropylpyrazine-5-spiro(2',3'-bismethylenecyclohexane) (**6**) by Enyne Cycloisomerization. (2*S*,5*R*)-5-(3-Butenyl)-5-(propargyl)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-pyrazine (123 mg, 0.444 mmol) in dry benzene (2 ml) was added to a solution of $Pd(OAc)_2$ (10.0 mg, 0.044 mmol) and PPh_3 (23.2 mg, 0.089 mmol) in dry benzene (50 ml) under argon. The reaction mixture was monitored at 50 °C by GLC until the reaction was complete (48 h). GLC showed the presence of product **6** in 71% containing about 1% of (2*S*,5*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine-5-spiro(3'-methyl-4'-methylenecyclohex-2'-ene), the isomer **7** (*vide infra*). The latter was removed by evaporation of the solution at reduced pressure and subsequent flash chromatography of the residual material on silica gel using hexane:ethyl acetate (20:1). Because of instability, the yield of isolated product was reduced to 51.7 mg (42%). ^{1}H NMR ($CDCl_3$): δ 0.65, 1.05 [2 d, *J* 6.8 Hz, 6H, $CH(\underline{CH_3})_2$] 1.45-1.57 (m, 1H, $\underline{CH_2}CH_2C$=), 2.02-2.11 (m, 1H, N-C-$\underline{CH_2}$C=), 2.06-2.16 (m, 1H, $\underline{CH_2}CH_2C$=), 2.24 [dsept, *J* 3.4 Hz and *J* 6.8 Hz, 1H, $\underline{CH}(CH_3)_2$] 2.16-2.28 (m, 1H, $CH_2\underline{CH_2}C$=), 2.65-2.85 [m, 2H, (N-C-$\underline{CH_2}$C=) and ($CH_2\underline{CH_2}C$=)], 3.59 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 3.93 [d, *J* 3.4 Hz, 1H, $\underline{CH}$-$CH(CH_3)_2$], 4.54, 5.00 (2 dd, *J* 2.2 Hz and *J* 2.2 Hz, 2H, =$\underline{CH_2}$), 4.68, 4.98 (2 dd, *J* 2.3 Hz and *J* 2.3 Hz, 2H, =$\underline{CH_2}$). ^{13}C NMR ($CDCl_3$): δ 16.85, 19.33 [$CH(\underline{CH_3})_2$], 29.47 ($CH_2\underline{CH_2}C$=), 30.09 [$\underline{CH}(CH_3)_2$], 36.43 ($\underline{CH_2}CHC$=), 45.35 (N-C-$\underline{CH_2}$-C=), 52.23, 52.36 (2x OCH_3), 58.02 (spiro $\underline{C}$), 60.43 [-$\underline{CH}$-$CH(CH_3)_2$], 107.83, 109.52 (2x C=$\underline{CH_2}$), 145.84, 148.38 (2x

C=CH_2), 160.50 (C-3), 165.28 (C-6). MS(EI): 276 (44, M^+), 261 (8), 245 (4), 244 (1), 233 (100), 218 (11), 204 (10), 195 (6), 176 (6), 153 (27).

(2*S*,5*R*)-2,5-Dihydro-3,6-dimethoxy-2-isopropylpyrazine-5-spiro(2',3'-bismethylenecyclohexane) (**6**) and (2*S*,5*R*)-2,5-Dihydro-3,6-dimethoxy-2-isopropylpyrazine-5-spiro(3'-methyl-4'-methylenecyclohex-2'-ene) (**7**) by intramolecular Heck reaction. (2*S*,5*R*)-5-(2-Bromoallyl)-5-(3-butenyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (319 mg, 0.892 mmol) in dry acetonitrile (2 ml) was added to a stirred suspension of $Pd(OAc)_2$ (17.2 mg, 0.077 mmol), PPh_3 (46.8 mg, 0.178 mmol) and K_2CO_3 (247 mg, 1.784 mmol) in dry acetonitrile (100 ml) under argon. The reaction mixture was monitored at 80 °C until GLC showed full disappearance of the starting material (60 h). GLC analysis showed 40% yield of the products **6** and **7** ; isomer ratio **6**:**7** = 7:1. The solvent was evaporated at reduced pressure, and the residue dissolved in diethyl ether. The solution was washed twice with 10% aqueous ammonium chloride, dried ($MgSO_4$) and evaporated. The products were separated and purified by flash chromatography on silica gel using dichloromethane:hexane (2:1) as eluent; isolated yield 54 mg of compound **6** (*vide supra*) and 8 mg of compound **7** (*vide infra*).

(2*S*,5*R*)-2,5-Dihydro-3,6-dimethoxy-2-isopropylpyrazine-5-spiro(3'-methyl-4'-methylenecyclohex-2'-ene) (**7**) and (2*S*,5*R*)-2,5-Dihydro-3,6-dimethoxy-2-isopropylpyrazine-5-spiro(2',3'-bismethylenecyclohexane) (**6**) using a Palladacycle Catalyst. (2*S*,5*R*)-5-(2-Bromoallyl)-5-(3-butenyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (174 mg, 0.487 mmol) in dry acetonitrile (10 ml) was added to a stirred suspension of palladacycle ($[Pd(C_6H_4CH_2P(o\text{-}Tol)_2\cdot OAc]_2$)[10] (4.6 mg, 0.049 mmol) and K_2CO_3 (134 mg, 0.974 mmol) in dry acetonitrile (45 ml) under argon. The reaction mixture was heated slowly to 88 °C and stirred at this temperature until all the starting material had disappeared (96 h). GLC analysis of the reaction mixture showed 40% of the product isomers **7** and **6** in the ratio 1:1.2. The solution of the reaction products was evaporated at reduced pressure, the residue dissolved in diethyl ether, the solution washed twice with 10% aqueous ammonium chloride, dried ($MgSO_4$) and evaporated. The products were separated and purified by flash chromatography on silica gel using dichloromethane:hexane (2:1) as eluent; yield: 16.5 mg (12 %) of product **7** and 20 mg (15 %) of the isomer **6**. The products were yellow oils.

(2*S*,5*R*)-2,5-Dihydro-3,6-dimethoxy-2-isopropylpyrazine-5-spiro(3'-methyl-4'-methyl-enecyclohex-2'-ene) (**7**): MS(HR): Found for *M*: 276.1858. Calc. for $C_{16}H_{24}N_2O_2$: 276.1838. ^{1}H NMR ($CDCl_3$): δ 0.68, 1.04 [2 d, *J* 6.8 Hz, 6H, CH(CH_3)$_2$], 1.86 (s, 3H, CH=C-CH_3), 1.92 (dd, *J* 5.6 Hz and *J* 18 Hz, 1H, C-CH_2-CH=), 2.12 (d, *J* 14 Hz, 1H, C-CH_2-C=), 2.21 [dsept, *J* 3.4 Hz and *J* 6.8 Hz, 1H, CH(CH$_3$)$_2$], 2.82 (dd, *J* 2 Hz and *J* 18 Hz, 1H, C-CH_2-CH=), 2.83 (d, *J* 14 Hz, 1H, C-CH_2-C=), 3.55 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.94 [d, *J* 3.4 Hz, 1H, CH-CH(CH$_3$)$_2$], 4.68, 4.94 (2 s, 2H, =CH_2), 5.49 (dd, *J* 2 Hz and *J* 5.6 Hz, 1H, CH_2-CH=). ^{13}C NMR ($CDCl_3$): δ 16.92 [CH(CH_3)$_2$], 19.25 (CH=C-CH_3), 19.32 [CH(CH_3)$_2$], 31.00 [CH(CH$_3$)$_2$], 37.64 (C-CH_2CH=), 42.90 (C-CH_2-C=), 52.09, 52.53 (2x OCH_3), 57.34 (spiro C), 60.61 [-CH-CH(CH$_3$)$_2$], 109.10 (C=CH_2), 131.96 (CH=C-CH$_3$), 142.21 (C=CH$_2$), 161.25 (C-3), 165.51 (C-6). MS(EI): 276 (28, M^+), 261 (23), 245 (2), 244 (2), 233 (100), 218 (6), 201 (8), 195 (6), 153 (47).

(2*S*,5*S*)-2,5-Dihydro-3,6-dimethoxy-2-isopropylpyrazine-5-spiro(2'-methyl-3'-methylenecyclopent-1'-ene) (**8**) and (2*S*)-2,5-Dihydro-3,6-dimethoxy-2-isopropylpyrazine-5-spiro(2',3'-bismethylenecyclopentane) (**4**).

(2*S*,5*R*)-5-Allyl-5-(2-bromoallyl)-2,5 dihydro-3,6-dimethoxy-2-isopropylpyrazine (220 mg, 0.641 mmol) in dry acetonitrile (10 ml) was added to a stirred suspension of palladacycle ($[Pd(C_6H_4CH_2P(o\text{-}Tol)_2\cdot OAc]_2$)[10] (6 mg, 0.064 mmol) and K_2CO_3 (177 mg, 1.281 mmol) in dry acetonitrile (55 ml) under argon. The reaction mixture was heated slowly to 88 °C and stirred at this temperature until GLC showed that all the starting material had disappeared (96 h). GLC analysis showed 51% yield of products **8** and **4** in the ratio 1.1:1. The solvent was evaporated at reduced pressure, and the residue dissolved in diethyl ether. The solution was washed twice with 10% aqueous ammonium chloride, dried ($MgSO_4$) and evaporated. The products were separated and purified by flash chromatography on silica gel using dichloromethane as eluent; yield of compound **8** was 45 mg. MS(HR): Found for *M*: 262.1663. Calc. for $C_{15}H_{22}N_2O_2$: 262.1681. $[\alpha]_D$ +48.0° (c = 0.175, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.73, 1.06 [2 d, *J* 6.8 Hz, 6H, $CH(\underline{CH_3})_2$], 1.83 (s, 3H, =C-$\underline{CH_3}$), 2.21 [dsept, *J* 3.7 Hz and *J* 6.8 Hz, 1H, $\underline{CH}(CH_3)_2$], 2.61 (ddd, *J* 2.2 Hz, *J* 2.2 Hz and *J* 16.4 Hz, 1H, H_b-4'), 3.10 (ddd, *J* 1.8 Hz, *J* 1.8 Hz and *J* 16.4 Hz, 1H, H_a-4'), 3.63 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 3.98 (d, *J* 3.7 Hz, 1H, H-2), 4.84 (dd, *J* 1.8 Hz and *J* 2.2 Hz, 1H, H_b-6'), 4.88 (dd, *J* 1.8 Hz and *J* 2.2Hz, 1H, H_a-6'), 5.41 (s, 1H, H-1'). ^{13}C NMR ($CDCl_3$): δ 12.59 (CH=C-$\underline{CH_3}$), 17.05, 19.33 [$CH(\underline{CH_3})_2$], 31.36 [$\underline{CH}(CH_3)_2$], 46.26 (C-4'), 52.47, 52.71 (2x OCH_3), 61.26 (C-2), 66.54 (spiro $\underline{C}$), 102.32 (C-6'), 137.34 (C-1'), 143.29 (C-3'), 153.05 (C-2'), 162.35 (C-3), 164.40 (C-6). MS(EI): 262 (34, M^+), 247 (100), 231 (3), 219 (82), 205 (10), 204 (7), 190 (70), 173 (3), 162 (5), 134 (24).

General procedure for hydrolysis leading to the cyclic amino acid methyl esters **9** -**12**. 0.1 M TFA (5 ml, 0.50 mmol) was added dropwise to a stirred solution of the spiro compounds **4** -**7** (0.164 mmol) in acetonitrile (1.5 ml). The mixture was stirred at ambient temperature for 24 h before the pH was adjusted to 10 with conc. aqueous ammonia. The aqueous solution was extracted with dicloromethane (3x10 ml), the organic solution dried ($MgSO_4$), evaporated and the residual product purified by flash chromatography on silica gel (wet packed). The products did not crystallize.

Methyl 1-amino-3,4-bismethylenecyclopentane-1-carboxylate (**9**). CH_2Cl_2:MeOH (40:1) was used for the flash chromatography; yield: 59 %. MS(HR): Found for *M*: 167.0922. Calc. for $C_9H_{13}NO_2$: 167.0946. ^1H NMR ($CDCl_3$): δ 1.58 (s, 2H, NH_2), 2.40 (d, *J* 15.9 Hz, 2H, 2x $\underline{CH_2}$-C=), 2.97 (d, *J* 15.9 Hz, 2H, 2x $\underline{CH_2}$-C=), 3.72 (s, 3H, OCH_3), 4.95 (d, *J* 1.8 Hz, 2H, 2x =$\underline{CH_2}$), 5.45 (d, *J* 1.8 Hz, 2H, 2x =$\underline{CH_2}$). ^{13}C NMR ($CDCl_3$): δ 46.12 (2x $\underline{CH_2}$-C=), 52.38 (OCH_3), 61.67 (spiro $\underline{C}$), 106.06 (2x C=$\underline{CH_2}$), 145.19 (2x $\underline{C}$=CH_2), 176.65 (C=O). MS(EI): 167 (1, M^+), 152 (2), 150 (1), 135 (1), 134 (1), 120 (1), 108 (100), 107 (5), 106 (7), 93 (14), 91 (8), 81 (6), 79 (6).

Methyl (*R*)-1-amino-3,4-bismethylenecyclohexane-1-carboxylate (**10**). CH_2Cl_2:MeOH (20:1) was used for the flash chromatography; yield 90 %. MS(HR): Found for *M*: 181.1103. Calc. for $C_{10}H_{15}NO_2$: 181.1103. $[\alpha]_D$ +82.9° (c=0.625, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.65-2.05 (m, 2H, $\underline{CH_2}$-CH_2-C=), 1.68 (s, 2H, NH_2), 2.28 (d, *J* 13.5 Hz, 1H, C-$\underline{CH_2}$-C=), 2.26-2.57 (m, 2H, CH_2-$\underline{CH_2}$-C=), 2.71 (d, *J* 13.5 Hz, 1H, C-$\underline{CH_2}$-C=), 3.72 (s, 3H, OCH_3), 4.71, 4.99 [2 s, 2H, $\underline{H_2C}$=(C-4)], 4.74, 5.08 [2 s, 2H, $\underline{H_2C}$=(C-3)]. ^{13}C NMR ($CDCl_3$): δ 29.60 (CH_2-$\underline{CH_2}$-C=), 34.75 ($\underline{CH_2}$-CH_2-C=), 43.98 (C-$\underline{CH_2}$-C=), 52.36 (OCH_3), 57.52 (spiro $\underline{C}$), 109.15 [$\underline{H_2C}$=(C-4)], 111.82 [$\underline{H_2C}$=(C-3)], 144.52 (C-4), 146.73 (C-3), 176.66 (C=O). MS(EI): 181 (5, M^+) 166 (2), 164 (2), 149 (1), 122 (100), 121 (6), 120 (6), 114 (4), 105 (13), 95 (11), 79 (8).

Methyl (*S*)-1-amino-3-methyl-4-methylenecyclopent-2-ene-1-carboxylate (**11**). The hydrolysis was run on a 0.05 mmol scale of compound **8**. The residual material after evaporation of the organic extracts was subjected to preparative TLC chromatography on silica gel using CH_2Cl_2:MeOH (20:1); yield: 46 %. MS(HR): Found for *M*: 167.0953. Calc. for $C_9H_{13}NO_2$: 167.0946. $[\alpha]_D$ +17.2° (c= 0.070, MeOH). ^1H NMR ($CDCl_3$): δ 1.70 (s, 2H, NH_2), 1.73 (s, 3H, =C-CH_3), 2.49 (ddd, *J* 2.3 Hz, *J* 2.3 Hz and *J* 16.9 Hz, 1H, CH_2-C=), 3.15 (ddd, *J* 1.8 Hz, *J* 1.8 Hz and *J* 16.9 Hz, 1H, CH_2-C=), 3.58 (s, 3H, OCH_3), 4.82 (dd, *J* 1.8 Hz and *J* 2.3 Hz, 1H, =CH_2), 4.87 (dd, *J* 1.8 Hz and *J* 2.3 Hz, 1H, =CH_2), 5.62 (s, 1H, CH=C-CH_3). MS(EI): 167 (1, M^+), 152 (1), 150 (1), 110 (1), 108 (100), 107 (4), 106 (5), 93 (19), 19 (5), 81 (3), 79 (3).

Methyl (*R*)-1-amino-5-methylenecyclohex-3-ene-1-carboxylate (**12**). CH_2Cl_2:MeOH (40:1) was used for the flash chromatography; yield: 85 %. MS(HR): Found for *M*: 167.0950. Calc. for $C_9H_{13}NO_2$: 167.0946. $[\alpha]_D$ -3.5° (c=0.115, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.59 (s, 2H, NH_2), 2.15 (dd, *J* 5 Hz and *J* 17.8 Hz, 1H, CH_2-CH=), 2.37 (d, *J* 14.5 Hz, 1H, CH_2-C=CH_2), 2.70 (dd, *J* 1.8 Hz and *J* 17.8 Hz, 1H, CH_2-CH=), 2.74 (d, *J* 14.5 Hz, 1H, CH_2-C=CH_2), 3.72 (s, 3H, OCH_3), 4.89, 4.98 (2 s, 2H, =CH_2), 5.72 (ddd, *J* 1.8 Hz, *J* 5.0 Hz and *J* 9.9 Hz, 1H, CH_2CH=CH), 6.20 (d, *J* 9.9 Hz, 1H, CH_2CH=CH). ^{13}C NMR ($CDCl_3$): δ 36.10 (C-CH_2-CH=), 40.44 (C-CH_2-C=), 52.37 (OCH_3), 56.58 (spiro C), 114.61 (C=CH_2), 125.93 (CH_2CH=CH-C=), 128.68 (CH_2CH=CH-C=), 139.29 (C=CH_2), 176.40 (C=O). MS(EI): 167 (2, M^+), 152 (3), 150 (3), 135 (1), 134 (1), 120 (1), 108 (100), 107 (9), 106 (12), 101 (3), 93 (13), 91 (19), 81 (12), 79 (8).

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