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Ru(II)-Catalyzed Ring Closing Metathesis in Stereoselective Spiroannulations and Cascade Reactions of Cyclic Dipeptide Substrates

Kjell Undheim* and Jon Efskind

Department of Chemistry, University of Oslo, P.O Box 1033, N-0315 Oslo, Norway

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Abstract—Several Ru(II)-catalyzed ring closing metathesis (RCM) reactions have been reviewed where the substrates were diene or enyne geminally disubstituted cyclic dipeptide derivatives. The RCM reactions are highly useful for the preparation of spiroannulated cyclic dipeptides as precursors for conformationally restricted cyclic α-amino acid derivatives. Five-, six- and seven-membered rings can be formed. Six- and seven-membered rings were formed most readily from dienes, five- and six-membered rings from enynes. Cascade reactions of diene substrates, which were connected by an alkynyl bridge between the two cyclic dipeptide units, yielded bis(cyclic α-amino acid) as precursors for cystine analogues. © 2000 Published by Elsevier Science Ltd.

The Grubbs ring closing metathesis (RCM) methodology using as catalyst bis(tricyclohexylphosphine)benzylidene ruthenium dichloride has become a key step in our preparation of rigidified α-amino acids as exemplified by the structure **A** in Scheme 1.[1–7] The combination of the Grubbs RCM methodology with ruthenium(II) catalysis,[8,9] and stereoselective alkylation reactions with the Schöllkopf chiral auxiliary (2*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (**45**, Scheme 8) for amino acid construction,[10] has in fact been found to be a powerful method for the preparation of 1-aminocycloalkene-1-carboxylic acid derivatives **A**. The amino acid products are expected to confer conformational constraints onto peptides when incorporated.

The Ru(II) catalyst system has proven highly compatible with bislactim ether substrates, e.g. substrate **1** (Scheme 1). Catalytically more active carbenoid systems can in principle be used for RCM reactions as exemplified with molybdenum complexes, if reduced chemoselectivity is acceptable.[8,9]

The spiroannulated cycloalkenes **2**–**6** (Scheme 1), consisting of unsaturated five- to seven-membered rings, may be used for further chemical modifications. The ring sizes available are in the main limited to five-, six- and seven-membered rings due to the reversible nature of metathesis reactions. Thermodynamic factors will largely control whether oligomerization or cyclization can occur. Because of the strain of three-, four-, and eight- to eleven-membered rings, these will be difficult to prepare by metathesis. Larger ring structures are expected to be available,[11] but their chemistry has not been explored in the present system.

The influence of ring size on the yields in the RCM reactions leading to cyclic amino acid precursors is illustrated by the formation of the spiroannulated cyclic dipeptides **2**–**6**. The amino acid precursors **2**–**6** will on hydrolysis furnish 1-aminocycloalkyl-1-carboxylic acid derivatives **A**. The substrates for the RCM reactions are α,α-disubstituted glycine derivatives with the desired stereochemistry already built into the stereogenic center at C-5 by stereoselective and stepwise bisalkenylation reactions of (*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (vide infra). In this manner two different unsaturated alkane substituents can be introduced in a controlled manner. The stereochemistry is determined by the second alkylation reaction.[1–7]

In the RCM reactions throughout this work bis(tricyclohexylphosphine)benzylidene ruthenium dichloride was used as the precursor catalyst. The time and conditions for effecting the RCM reaction varied with the substrates. Formation of the spiroannulated six- and seven-membered rings **3**–**6** proceeded readily in remarkable high yields. As expected (vide supra), eight-membered ring formation (**7**) was not seen. Formation of the five-membered ring structure **2** was most difficult to effect. When the substrate for five-membered ring formation was substituted by an α-hydroxy group, no RCM reaction was seen whereas formation of six- and seven-membered rings proceeded readily (Scheme 2). The reluctance towards five-membered ring formation is attributed to steric interactions. Indirectly this was

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* Corresponding author. Tel.: +47-22855521; fax: +47-22855507; e-mail: kjell.undheim@kjemi.uio.no

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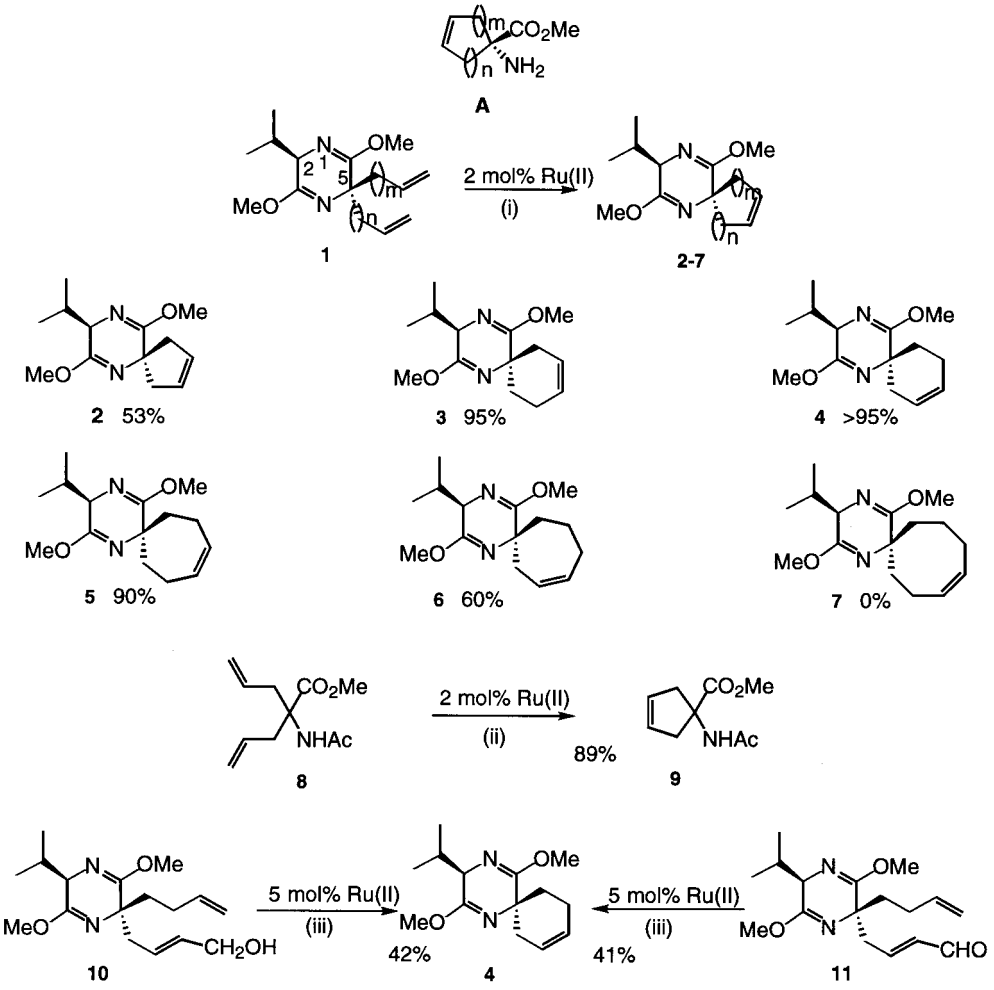
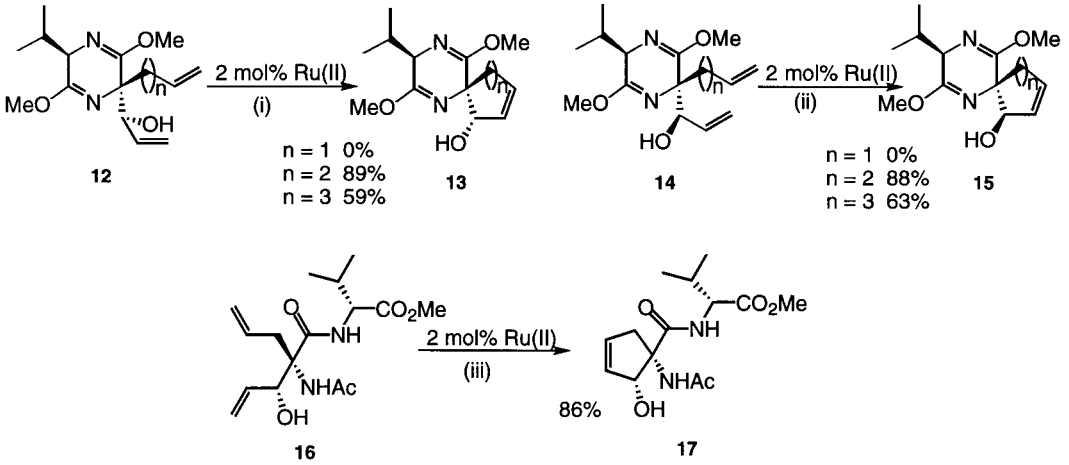


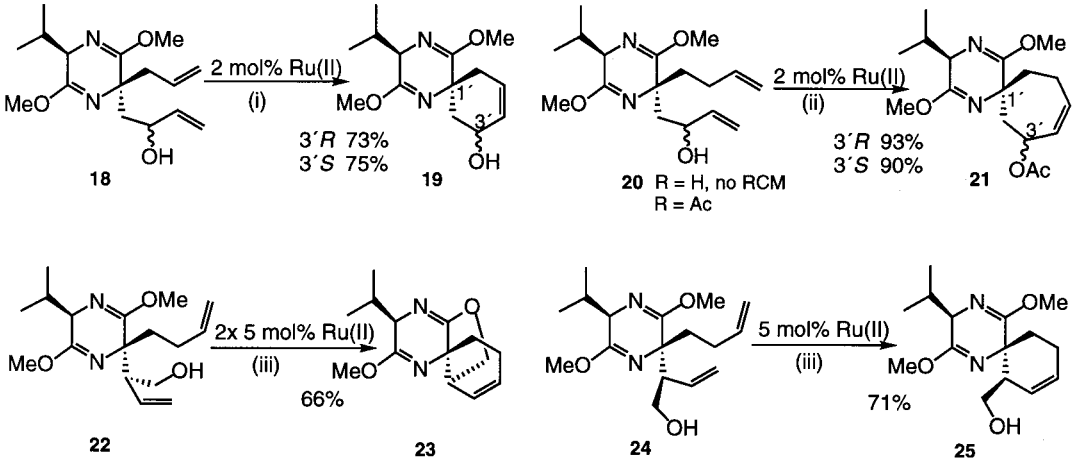
Scheme 1. (i) Benzene/toluene, 20–100°C, 5–24 h; (ii) benzene, 25°C, 4 h; (iii) toluene, 60°C, 16–18 h (Ru(II): $PhCH{=}RuCl_2(Pcy_3)_2$).

overcome by hydrolysis of substrate **1** ($m{=}n{=}1$) to the corresponding amino acid ester followed by *N*-protection. The new *N*-protected substrate **8** reacted readily under RCM conditions to form the cyclic amino acid derivative **9**. In general, cyclic α-amino acids are expected to become available by this methodology from appropriately substituted amino acids.

Generally, ruthenium based catalysts are used to effect RCM reactions on olefins bearing no substituent at the terminal carbon. RCM reactions with the terminal hydroxymethyl derivative **10**, however, proceeded at elevated temperature with expulsion of the hydroxymethylene group together with the terminal olefin carbon to yield the spirocyclohexene **4**. The yield was lower than from the



Scheme 2. (i) Benzene, 20°C, 14 h–3 days; (ii) DCE, rfx, 14–17 h; (iii) CH_2Cl_2, 20°C, 1 h.



Scheme 3. (i) DCE, 60°C, 8–24 h; (ii) DCE, 40°C, 16 h; (iii) DCE, 60°C, 6–18 h.

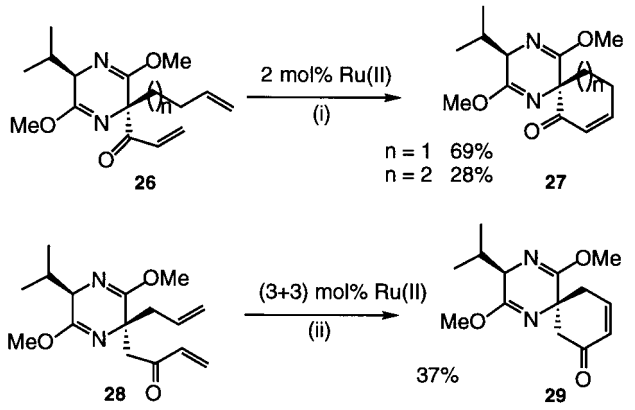
parent olefin without terminal substitution.[5] Even the α,β-unsaturated carbonyl derivative **11**, which has a formyl group at the terminal olefin carbon, underwent the RCM reaction at about the same rate and in yields comparable with the hydroxymethyl substrate **10**. Allyl alcohol and acrolein are probably the expulsion products in these cyclization reactions. Previously it has been reported that another ruthenium precatalyst system could be used to effect an RCM reaction under relatively vigorous conditions using as substrate a terminal olefin carbon which was substituted by a carboxylic ester group.[12]

In the α-hydroxylated series, the RCM reactions were effected in benzene solution without protection of the hydroxyl group in the substrates **12** and **14**, which differ only by the configuration at the epimeric alcohol carbon.[2] The six-membered ring structures **13** (n=2) and **15** (n=2) were formed in similar high yields, but the α-(*S*)-isomer **12** (n=2) reacted significantly faster than the (*R*)-isomer **14** (n=2). Perhaps the alkenyl groups in the former are held more closely together by hydrogen bonding between the hydroxy and the 6-methoxy groups facilitating coordination with the catalyst, which is a necessary prerequisite for the RCM reaction to take place. The seven-membered ring compounds **13** (n=3) and **15** (n=3), were also formed in similar but lower yields than in the six-membered series. Five-membered ring formation was not observed from either substrate. Again this was assumed to be caused by steric interactions which disfavor conformations required for the RCM reaction to take place. Support for steric interference is forthcoming from the dipeptide **16**, which was available by a hydrolytic reaction of substrate **14** (n=1) followed by *N*-protection. The RCM reaction proceeded smoothly at ambient temperature in dichloromethane to yield the five-membered serine analogue as the dipeptide **17** in high yield. Furthermore, this reaction shows that the RCM reaction can be applied to appropriate amino acid substrates when incorporated into peptides. Additional examples from peptide applications are found in the preparation of ethylenic pseudodipeptides by the RCM methodology.[13]

In the subsequent work the hydroxyl group was moved one carbon atom further away from the 5-position in the dihydropyrazine as shown in structure **18**.[4] Both epimeric alcohols were prepared enantiomerically pure and reacted separately under RCM conditions. Six-membered ring formation **19** proceeded readily and in similar yields from both alcohol epimers. In the corresponding butenyl alcohol series **20** no reaction took place. After protection of the free hydroxyl groups as an acetate, however, the RCM reaction proceeded readily to furnish the seven-membered ring products **21** in very high yields. The RCM transformation in this case has gone from a zero reaction to a 90–93% yield reaction. It is remarkable that the free hydroxyl group is compatible in the RCM reactions that lead to six-membered ring formation whereas the corresponding reaction is completely blocked for seven-membered ring formation. It will be recalled that in the α-hydroxy series (Scheme 2) there was no significant interaction from the hydroxy group in the seven-membered ring formation. Perhaps the lack of reactivity for seven-membered ring formation may be ascribed to hydrogen bonding resulting in strongly populated conformations where the alkenyl groups are held too far apart for the RCM reaction to take place. Alternatively, the difference in behavior may depend on geometry and distance for interaction between the heteroatom and the metal center making the catalytic system less reactive.[11]

In a second series of cyclic homoserine analogues, the hydroxyl group was exocyclic in the form of a hydroxymethyl substituent.[5] The precursors for the RCM reactions were the substrates **22** and **24** with free hydroxyl groups. The product from the substrate **22** was the tricyclic spirane **23**. Formation of the tricyclic product **23** requires that the hydroxymethyl substituent is located in the vicinity of the lactim carbon at C-6. Under the conditions of the reaction transesterification occurs with expulsion of methanol. Lewis catalyzed interchange of the alcoholic group as in the case of the other isomer **24** is excluded for steric reasons. The product was the hydroxymethyl spirane **25**. The analogue **18** (3′*R*), where the hydroxyl group is located in the ring, did not participate in five-membered ring formation by this alcohol exchange reaction under the conditions of the RCM reaction. The yields in the cyclization of both stereoisomers **22** and **24** were closely similar.

Dienes with an electron-withdrawing group attached to the

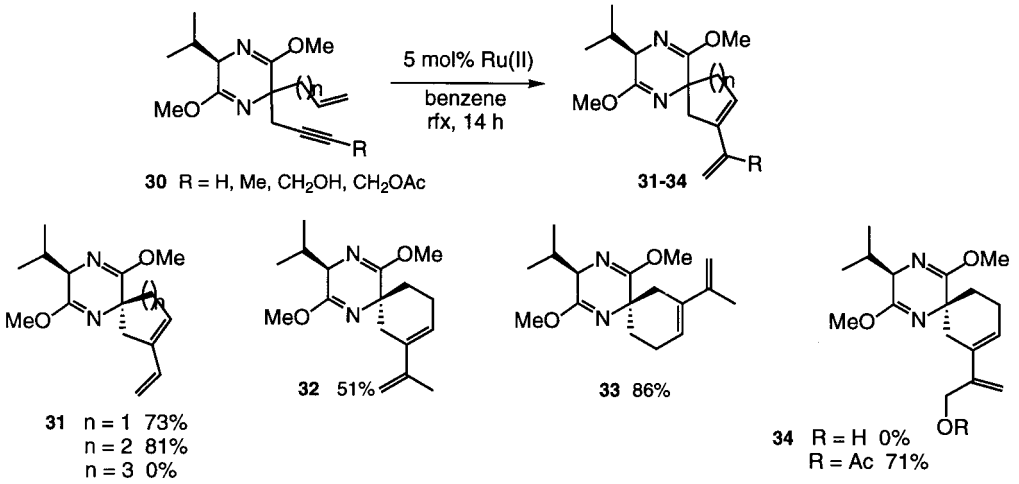


Scheme 4. (i) DCE; **24**, 40°C, 4 h; **25**, 80°C, 22 h; (ii) benzene, 70°C, 4 days.

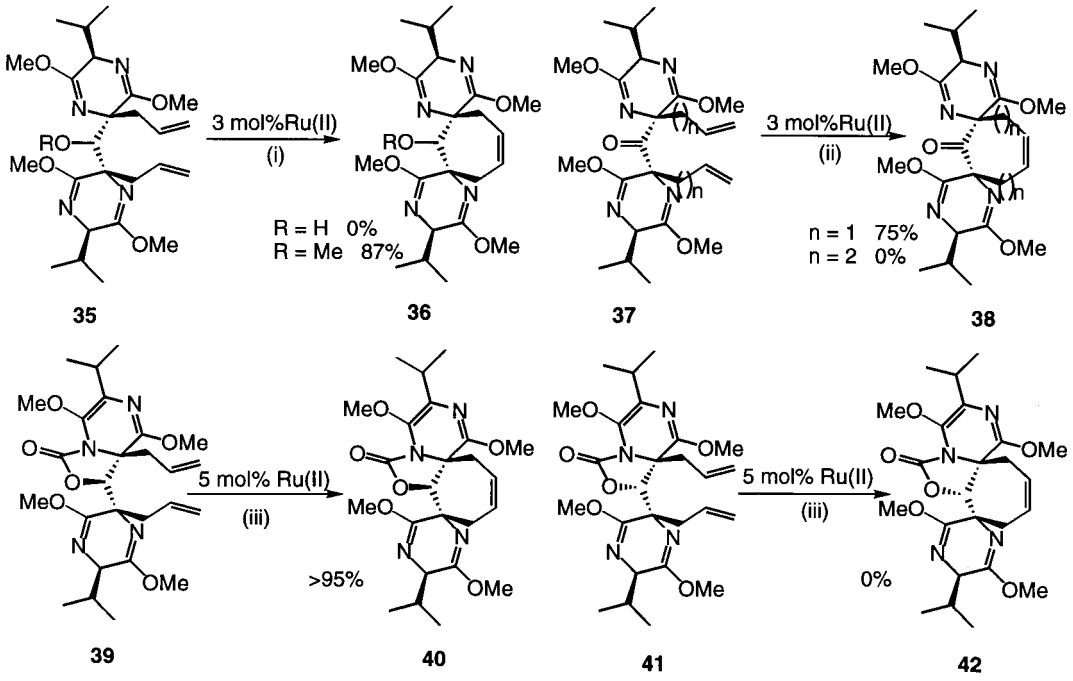
inner olefinic carbon react sluggishly under RCM conditions either for steric reasons, or because of electron withdrawal from the double bond.[14] Steric effects are minimized in an α,β-unsaturated ketone. The ketones **26** possess a strongly electrophilic double bond with low steric effects. Six-membered ring formation **27** (n=1) proceeded readily.[6,7] A significantly lower RCM transformation was observed in seven-membered ring **27** (n=2) formation. In RCM reactions of the parent allylic alcohols **12** and **14** under similar conditions six-membered ring allylic products were formed in ca. 90% yield from both epimeric alcohols, and seven-membered ring allylic products in ca. 60% yield (Scheme 2). The cyclohexenone spirane **29** was isolated in a 37% yield after running the RCM reaction of the α,β-unsaturated ketone substrate **28** at 70°C for 4 days (Scheme 4). The slow reaction rate in this case stands in contrast to the ready RCM reaction of the allylic alchols **18** (Scheme 3). The findings in general are best rationalized in terms of rates controlled by conformational populations biased for cyclization that again may be influenced by the tethering system used. The conformational factor, rather than the electronic state of the double bond, seems more important for the control of the rate of the RCM reaction. Furthermore, it seems most likely that the RCM reaction is initiated by attack from the carbenoid catalyst on the more electron rich double bond, or for steric reasons sometimes on the less substituted double bond. Once the initial adduct has been formed, the electronic state of the second double bond becomes less important. The conformational accessibility of the second double bond will be an important factor for the catalyst in the metathetic operation.

Enynes **30** have been studied as substrates for the construction of amino acid precursors where the α-carbon of the amino acid is incorporated into a cycloalkene which has the structure of a conjugated diene **31**–**34** with one exocyclic double bond (Scheme 5).[3] Several recent reports describe metal-catalyzed formation of 1-vinylcycloalkenes from enyne substrates by intramolecular reactions, in particular five-membered ring compounds.[15] In the enyne RCM reactions shown in Scheme 5, the Ru(II)-catalyst has also been found highly useful for intramolecular metathesis reactions. Mechanistically the enyne reactions differ from the diene RCM reactions. In the RCM reactions of bisalkenes the terminal methylenes are expelled as ethylene during the ring closure. In the enyne reactions the terminal alkylidene moiety of the alkene is transferred onto the alkyne carbon in the formation of the cyclic diene.[16] In this manner the 1-vinylcyclohexenyl derivative **31** (n=2) was formed in 81% and the five-membered ring derivative **31** (n=1) in 73% yield. The ready formation of the cyclopentenyl derivative **31** contrasts the results from studies on RCM reactions of dienes where formation of five-membered spirane rings was difficult to effect (Schemes 1 and 2). Another important difference was the failure to form the seven-membered ring product **31** (n=3) whereas this ring size was readily formed from dienes (Schemes 1–3). Also it has been reported that heterocyclic rings such as an azacycloheptene are formed under similar conditions.[16] The difference in behavior of the ruthenium catalyst towards dienes and enynes indicates two mechanistically different pathways (vide supra).

The enyne with a terminal methyl group on the acetylenic carbon (*S*)-**30** (R=Me) gave the cyclic product (5*S*)-**32** in medium yield whereas the product (*R*)-**33** from the (5*R*)-substrate **30** (R=Me), was obtained in high yield. The difference in product formation may be caused by different



Scheme 5.



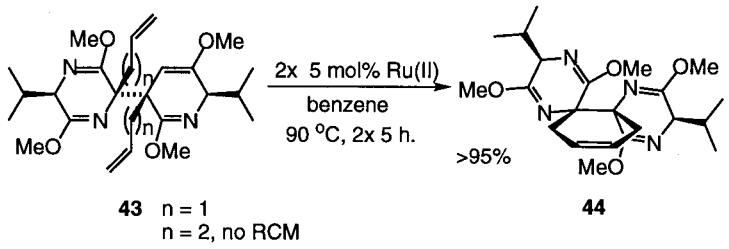
Scheme 6. (i) Benzene, rfx, 4 h; (ii) benzene, rfx, 14 h; (iii) benzene, rfx, 3 h.

non-bonded interactions in the formation of the two diastereomers **32** and **33**. If desirable, a more efficient process for the generation of **32** can be effected by changing the configuration at C-2 in the chiral bislactim auxiliary, which is used to generate the enyne substrate. The hydroxymethyl enyne **30** (R=CH_2OH) failed to undergo the skeletal rearrangement metathesis reaction. In contrast, it will be recalled that the allylic alcohols **13** and **14** (Scheme 2) were compatible in the diene RCM reaction using the same catalyst. After protection of the hydroxyl group as the acetyl derivative **30** (R=CH_2OAc), however, 71% yield of the RCM product **34** (R=Ac) was obtained.

It is appropriate to mention that complimentary diene spiroannulated cyclic dipeptides, and subsequently their corresponding enantiomerically pure cyclic amino acids, are available using palladium mediated catalysis in reactions from similar enyne substrates as shown in Scheme 5.[17] Preparation of racemic cyclic dienes from enyne amino acids using Schrock's molybdenum catalyst has recently been described.[18]

Scheme 6 shows that sterically highly crowded dienes may undergo RCM reactions to furnish heterocyclic bispiranes from high to quantitative yields.[19] For the RCM reactions to take place, it is essential that conformations biased towards closeness of the two ene groups are available. In crowded molecules we therefore expected to find high yield or very low yield transformations resulting from what might appear superficially to be subtle changes in the structures of the substrates. These differences, however, could cause significant changes in the conformational preferences of the substrates and hence affect reactivities. The two ene functionalities in the ketones **37** (Scheme 6) would be expected to be able to assume conformations with pseudo parallelism of the two ene chains suitable for the catalyst to effect the ring closing operation. The RCM reaction for the propenyl derivative **37** (n=1) proceeded very readily to furnish the spiroannulated cycloheptenone **38** (n=1). In accordance with previous statements (vide supra), the butenyl analogue failed to yield any nine-membered ring product **38** (n=2). The corresponding hydroxyl substrate **35** (R=H) did not show any sign of the RCM reaction even though the X-ray structures of the unreactive hydroxy compound **35** and the highly reactive ketone **37** (n=1) showed no marked differences in the crystalline state that could be used to suggest conformational differences of importance for the outcome of the RCM reaction in solution. In the crystalline state both the heterocyclic rings were held in a sandwich like pseudoparallel structure with the alkenyl groups protruding in opposite directions. In solution the molecules must assume different conformations closer to alignment of the alkene groups for the RCM reaction to occur. On the other hand, when the hydroxy group was protected as the *O*-methyl derivative **35** (R=Me), a high yield of the RCM product **36** (R=Me) was obtained reminiscent of the reaction of the ketone **37**.

The tricyclic structures **39** and **41** are epimeric at the hydroxy bridge carbon between the two dihydropyrazine rings. Hence the arrangements of the propenyl groups are fixed by the configuration at the hydroxy carbon. In the crystalline (*S*)-isomer **41**, the propenyl groups are pointing in the opposite directions and are prevented from assuming a conformation which has the propenyl groups in a pseudoparallel arrangement. No RCM product **42** was formed from this substrate. According to molecular models, the (*R*)-isomer **39** has the propenyl groups lined up in a parallel fashion for the RCM reaction to take place. This arrangement for the (*R*)-isomer was expressed in close to quantitative yield of the cyclic product **40**.



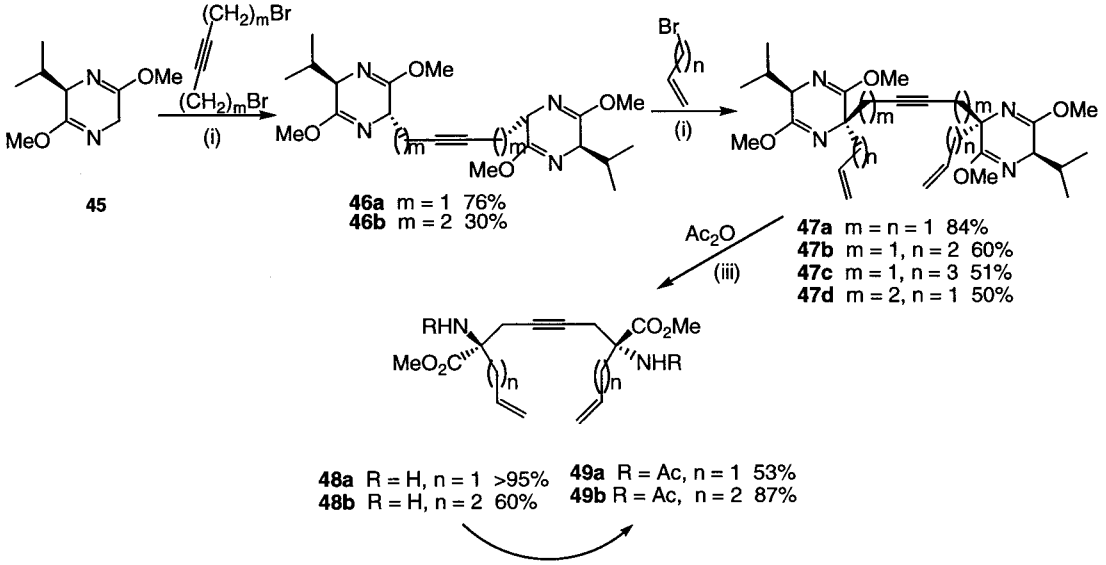
Scheme 7.

Perhaps an even more congested molecule has been constructed in structure **43** where two (2*R*)-5-alkenyl-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine rings are directly attached to one another without any interconnecting carbon bridge (Scheme 7).[20] The Ru(II)-catalyzed ring closure proceeded in close to quantitative yield for six-membered ring **43** (n=1) formation, but failed for eight-membered ring formation from substrate **43** (n=2), not unexpected (vide supra). 5 mol% catalyst was added twice to effect an almost quantitative yield of the RCM product **44** at reflux temperature. No reaction was observed at ambient temperature. The Ru(II)-catalyst system suffers from thermolytic decomposition. Therefore, when running relatively slow reactions at elevated temperature, additional catalyst may have to be added at time intervals.[21]

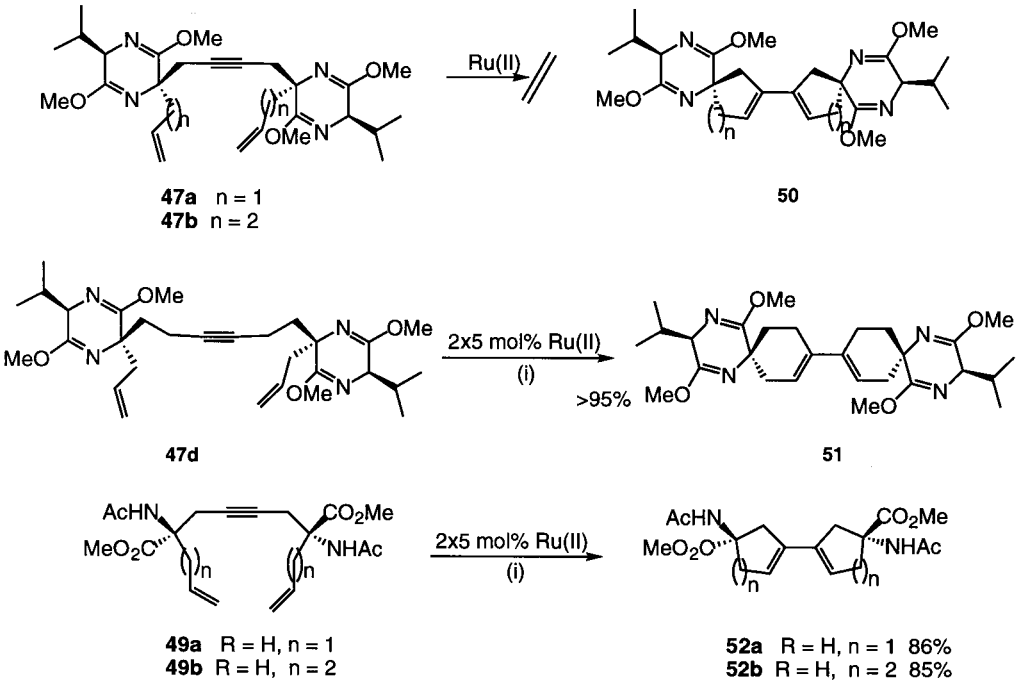
In our subsequent work, attention was turned to Ru(II)-catalyzed cascade reactions which were to provide two-ring amino acid structures interconnected by C_4–C_6 bridges (Scheme 9). The target molecules, or hydrolysis products thereof, can be regarded as analogues of the amino acid cystine. We have previously reported several other conformationally constrained cystine analogues.[22]

Scheme 8 shows the routes for the preparation of intermediates to be used as substrates for the RCM reactions of 'dimeric' structures (Scheme 9). Alkylation of lithiated (2*R*,5*S*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (**45**) with a symmetrical dihalogenoalkyne provided the alkyne bridged bislactim ethers **46**. The reaction proceeded readily for 1,4-dichloro- or 1,4-dibromo-butyne.[22] For the corresponding 1,6-dibromo-3-hexyne competitive elimination of HBr after monalkylation also leads to a product with a conjugated enyne 5-substituent (NMR). The bridged structures **46** were subsequently lithiated and dialkylated to furnish the dienynes **47**. Only one stereoisomer was observed in the alkylation reactions as previously reported from related cases.[1–7] Subsequent hydrolysis under mild conditions using 0.1 M TFA in aqueous acetonitrile furnished the amino acid esters **48a** and **48b**. The yield of the hydrolysis product was lower for the butenyl **48b** than for the allyl **48a** derivative, and the pentenyl substrate **47d** did not undergo hydrolysis under these reaction conditions. The hexyne bridged **47d** was used directly in the RCM reaction and was therefore not subjected to hydrolysis. The diamines **48a** and **48b** were subsequently *N*-protected before the RCM reactions.

The RCM reactions shown in Scheme 9 were run by heating in toluene at 85–90°C. Below this temperature the reaction rate was slow. The catalyst was gradually deactivated at the temperature, which was required to effect the cascade reaction. 5 mol% catalyst was originally added, and the same amount of catalyst was added after 5 h. The C_4-bridged substrates **47a** and **47b** failed to furnish any of the RCM product **50**. When the distance between the bislactim rings



Scheme 8. (i) *n*-BuLi, THF, −78 to −20°C, 17 h; (ii) DMAP, CH_2Cl_2, 20°C, 5 h; (iii) 0.1 M TFA, $MeCNIH_2O$, 20°C, 4–6 days.



Scheme 9. (i) Toluene, 85°C, 2×5 h (Ru(II): $PhCH{=}RuCl_2(Pcy_3)_2$).

was extended to a C_6-bridge, an almost quantitative yield of the RCM product **51** resulted. The failure of the C_4-bridged substrates to react, whereas the C_6-bridged substrate gave very high conversion, is attributed to severe steric interactions between the two bislactim ether moieties in the C_4-bridged derivatives.

The failure of the dienynes **47a** and **47b** to undergo the cascade reaction has been overcome indirectly by initial hydrolysis and *N*-protection of the hydrolysis products to form the bisamino acid derivatives **49** (Scheme 8). The RCM reactions of the substrates **49** proceeded readily. From these results it becomes apparent that the RCM cascade reaction can be applied to appropriately substituted amino acid derivatives, and probably also when such amino acids are incorporated into peptides.

In conclusion it has been demonstrated that the Ru(II)-catalyzed RCM reaction is highly useful for the preparation of spiroannulated cyclic dipeptides as precursors for conformationally restricted cyclic α-amino acid derivatives. Five-, six- and seven-membered rings can be formed. In diene RCM reactions, six-and seven-membered rings are formed. Five-membered ring formation occurs less readily and is sensitive to substitution at the α-carbon in the spiroannulated cycloalkene. In conformationally flexible amino acids, five-membered ring formation occurs readily. Free hydroxyl groups may be incompatible, but were compatible in most cases. The most dramatic effect of a free hydroxyl interaction was in a reaction which gave no conversion for a substrate with a free hydroxyl group but resulted in >95% yield of RCM product after *O*-methylation. In enyne RCM reactions, five- and six-membered rings are most readily formed, seven-membered rings with difficulty. In highly congested systems, the RCM cyclization may result in >95% yield of cyclic product, or no RCM cyclization at all. These findings are rationalized as due to steric influences on conformational preferences which may affect the catalyst coordination. Cascade reactions could not be affected for dienyne spiroannulated cyclic dipeptides from dimeric structures interlinked by a C_4-alkynyl bridge, but the RCM reaction proceeded to give >95% yield when the bridge was extended to a six-carbon chain. In the former case, hydrolysis, *N*-protection and subsequent RCM reactions readily furnished bis(amino acid) derivatives by cascade reactions. The products can be regarded as analogues of the amino acid cystine.[22]

Experimental

^1H NMR spectra were recorded in $CDCl_3$ at 300 or 200 MHz with Bruker DPX 300 or DPX 200. The ^{13}C 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 ppm) as references. The mass spectra under electron impact conditions (EI) were recorded at 70 eV ionizing potential; methane was used for chemical ionization (CI). The spectra are presented as *m/z* (% rel. int.).

Dry THF was distilled from sodium and benzophenone under argon. Solvents were degassed by bubling argon through. Bis(tricyclohexylphosphine)benzylidene ruthenium dichloride was purchased from Strem Chemicals Inc., 7 Mulliken Way, Newburyport, MA.

1,4-Bis[(2*R*,5*S*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazin-5-yl]but-2-yne (46a).[23] A solution of (2*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (1.192 g, 6.48 mmol) in anhydrous THF (11 ml) was lithiated by the addition of a solution of *n*-BuLi in hexane (4.95 ml, 1.44 M, 7.13 mmol) at −78°C. The mixture was stirred at this

temperature for 30 min before a precooled (−78°C) solution of 1,4-dichlorobut-2-yne (0.40 g, 3.24 mmol) in THF (5 ml) was added through a Teflon tube. The reaction mixture was stirred at −78°C for 3 h and was then allowed to reach ambient temperature overnight. The reaction was quenched by addition of phosphate buffer (pH 7) and water. The mixture was extracted with CH_2Cl_2 and the combined organic solution was dried ($MgSO_4$), the solvent distilled off and the product purified by flash chromatography on silica gel using EtOAc/hexane 10:90; yield 1.025 g (76%) of a noncrystalline solid. HRMS: Found *M* 418.2587. Calcd for $C_{22}H_{34}N_4O_4$ 418.2580. IR (film): ν_{max} cm^{-1} 2945 (s), 2871 (s), 2844 (m), 1683 (s), 1462 (s), 1436 (s), 1310 (s), 1223 (s), 1142 (s), 1108 (s), 1017 (s). ^1H NMR (300 MHz, $CDCl_3$): δ 0.64/1.07 (12H, d, *J*= 6.8 Hz, 2×CH*Me*$_2$), 2.28 (6H, ds, 2×C*H*Me$_2$), 2.52–2.83 (4H, m, 2×C*H*$_2$), 3.70/3.71 (12H, s, 4×OMe), 4.00–4.11 (4H, m, H-2, H-2′, H-5 and H-5′). ^{13}C NMR ($CDCl_3$): δ 16.45/19.12 (2×CH*Me*$_2$), 25.24 (2×CH$_2$), 31.52 (2×*C*HMe$_2$), 52.35/54.42 (4×OMe), 60.59 (C-2 and C-2′, C-5 and C-5′), 77.57 (2×*C*C), 161.50/164.96 (C-3, C-3′, C-6 and C-6′). MS(EI): 418 (M^+, 18%), 375 (7), 237 (8), 236 (54), 184 (33), 183 (73), 141 (100), 140 (8), 126 (6).

1,6-Bis[2*R*,5*S*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazin-5-yl]hex-3-yne (46b). A solution of (2*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (**45**) (1.89 g, 10.03 mmol) in anhydrous THF (20 ml) was lithiated by the addition of a solution of *n*-BuLi in hexane (7.66 ml, 1.44 M, 11.03 mmol). The solution was stirred at −78°C for 1.5 h before a precooled solution (−78°C) of 1,6-dibromohex-3-yne (1.18 g, 4.91 mmol) in THF (10 ml) was added through a Teflon tube. The reaction mixture was stirred at this temperature for 3 h and then allowed to reach ambient temperature overnight. The reaction was quenched by addition of phosphate buffer (pH 7) and water. The aqueous phase was extracted with dichloromethane and the combined organic solution was dried ($MgSO_4$). The solvent was distilled off at reduced pressure and the product was isolated by flash chromatography on silica gel using EtOAc/hexane 10:90; yield 0.670 g (30%) of a colorless oil. HRMS (electrospray): Found *M* 447.2965. Calcd for $C_{24}H_{39}N_4O_4$ 447.2966. IR (film): ν_{max} cm^{-1} 2959 (m), 2944 (m), 1694 (s), 1436 (m), 1234 (s), 1195 (m), 1013 (m). ^1H NMR (300 MHz, $CDCl_3$): δ 0.66/1.00 (12H, d, *J*= 6.8 Hz, 2×CH*Me*$_2$), 1.72–1.85 (2H, m, 2×C*H*$_2$), 1.95–2.26 (6H, m, CH$_2$ and 2×C*H*Me$_2$), 3.63/3.65 (12H, s, 4×OMe), 3.89 (2H, m, H-2 and H-2′), 3.91–4.02 (2H, m, H-5 and H-5′). ^{13}C NMR ($CDCl_3$): δ 14.55 (2×*C*H$_2$–CH$_2$–CC), 16.23/19.02 (2×CH*Me*$_2$), 31.78 (2×*C*HMe$_2$), 33.76 (2×CH$_2$ *C*H$_2$–CC), 52.36 (4×OMe), 54.40 (C-2 and C-2′), 60.80 (C-5 and C-5′), 79.73 (2×CC), 163.44/163.71 (C-3, C-3′, C-6 and C-6′). MS(EI): 446 (M^+, 2%), 431 (7), 404 (24), 403 (100), 207 (6), 181 (5), 141 (9).

1,4-Bis[(2*R*,5*R*)-5-allyl-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazin-5-yl]but-2-yne (47a). A solution of 1,4-bis[(2*R*,5*S*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazin-5-yl]but-2-yne (**46a**) (1.148 g, 2.75 mmol) in anhydrous THF (10 ml) was lithiated by the addition of a solution of *n*-BuLi in hexane (3.90 ml, 1.55 M, 6.04 mmol) at −78°C. The resultant solution was stirred at −78°C for 1 h before a solution of precooled (−78°C) allyl bromide (0.83 g, 6.86 mmol) in THF (7 ml) was added through a Teflon tube. The reaction mixture was stirred at −78°C for 3 h and allowed to reach ambient temperature overnight. The reaction was quenched by addition of phosphate buffer (pH 7) and the mixture diluted with water. The aqueous phase was extracted with dichloromethane, the combined organic solution dried ($MgSO_4$), the solution evaporated at reduced pressure and the residual material subjected to flash chromatography on silica gel using EtOAc/hexane 7:93; yield 1.150 g (84%) of a colorless oil. Found: C, 67.44; H, 8.49. Calcd for $C_{28}H_{42}N_4O_4$: C, 67.59; H, 8.79%. HRMS: Found *M* 498.3204. Calcd for $C_{28}H_{42}H_4O_4$ 498.3206. IR (ATR plate): ν_{max} cm^{-1} 3077 (w), 3009 (w), 2944 (m), 2870 (w), 1697 (s), 1436 (m), 1308 (m), 1239 (s), 1198 (m 1143 (m). ^1H NMR ($CDCl_3$): δ 0.70/1.07 (12H, d, 2×CH*Me*$_2$, *J*= 6.8 Hz), 2.17–2.60 (10H, m, 4×C*H*$_2$ and 2×C*H*Me$_2$), 3.63 (12H, s, 4×OMe), 3.81 (2H, d, H-2 and H-2′, *J*= 3.3 Hz), 4.90–4.98 (4H, m, 2×CH=C*H*$_2$), 5.48–5.62 (2H, m, 2×C*H*=CH$_2$). ^{13}C NMR ($CDCl_3$): δ 17.04/19.58 (2×CH*Me*$_2$), 30.54 (2×*C*HMe$_2$), 31.06/44.35 (4×*C*H$_2$), 52.14/52.30 (4×OMe), 60.70 (C-2 and C-2′), 61.66 (C-5 and C-5′), 78.63 (2×CC), 118.32 (*C*H$_2$=CH), 133.18 (CH$_2$=*C*H), 162.71/162.95 (C-3, C-3′, C-6, C-6′). MS(EI): 498 (M^+, 2%), 458 (14), 457 (48), 456 (11), 455 (36), 224 (12), 223 (72) 182 (11), 181 (100), 153 (10).

1,4-Bis[(2*R*,5*R*)-5-(3-butenyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazin-5-yl]but-2-yne (47b). It was prepared as above from 1,4-bis[(2*R*,5*S*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazin-5-yl)]but-2-yne (**46a**) (0.359 g, 0.857 mmol), *n*-BuLi in hexane (1.17 ml, 1.55 M, 1.80 mmol) 4-bromo-1-butene (0.255 g, 1.80 mmol) in THF. The reaction mixture was work-up as above and the product isolated after flash chromatography using EtOAc/hexane 5:95; yield 0.272 g (60%) of colorless oil. HRMS: Found *M* 526.3540. Calcd for $C_{30}H_{46}N_4O_4$ 526.3519. IR (film): ν_{max} cm^{-1} 2994 (m), 2361 (w), 1694 (s), 1463 (m), 1308 (m), 1239 (s), 1197 (m), 1143 (m), 911 (m). ^1H NMR ($CDCl_3$): δ 0.71/1.07 (12H, d, 2×CH*Me*$_2$, *J*= 6.8 Hz), 1.58–1.84 (8H, m, 4×C*H*$_2$), 2.21–2.60 (6H, m, 2×C*H*$_2$ and 2×C*H*Me$_2$), 3.62 (12H, s, 4×OMe), 3.83 (2H, d, H-2 and H-2′, *J*= 3.4 Hz), 4.81–4.94 (4H, m, 2×CH=C*H*$_2$), 5.59–5.78 (2H, m, 2×C*H*=CH$_2$). ^{13}C NMR ($CDCl_3$): δ 17.16/19.62 (2×CH*Me*$_2$), 28.57 (2×*C*H$_2$), 30.60 (2×*C*HMe$_2$), 31.64/39.28 (4×*C*H$_2$), 52.20/52.26 (4×OMe), 60.87 (C-2 and C-2′), 61.38 (C-5 and C-5′), 78.54 (2×CC), 114.23 (2×*C*H$_2$–CH), 138.12 (2×CH$_2$=*C*H), 162.81/162.97 (C-3, C-3′, C-6, C-6′). MSEI): 526 (M^+, 2%), 483 (24), 471 (7), 430 (13), 429 (50), 289 (25), 238 (13) 237 (84), 196 (12), 195 (100), 153 (23), 123 (6).

1,4-Bis[(2*R*,5*R*)-5-(4-pentenyl)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazin-5-yl]but-2-yne (47c). A solution of 1,4-bis[(2*R*,5*S*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazin-5-yl)]but-2-yne (0.439 g, 1.05 mmol) in anhydrous THF (5 ml) was lithiated by the addition of a solution of *n*-BuLi in hexane (1.42 ml, 1.55 M, 2.20 mmol). The solution was stirred at −78°C for 1 h before a precooled (−78°C) solution of 5-bromo-1-pentene (0.39 g, 2.62 mmol) in THF (3 ml) was added through a Teflon tube. The mixture was stirred at −78°C for 3 h and allowed to reach ambient temperature overnight. Phosphate buffer (pH 7) and water were then added, the mixture extracted with

dichloromethane, the combined organic solutions dried ($MgSO_4$), the solvent distilled off and the residual material subjected to flash chromatography using EtOAc/hexane 6:94; yield 0.299 g (51%) of a colorless oil. HRMS (EI, 70 eV): Found *M* 554.3804. Calcd for $C_{32}H_{50}N_4O_4$ 554.3832. IR (film): ν_{max} cm^{-1} 3076 (w), 2944 (s), 2870 (m), 1694 (s), 1436 (m), 1237 (s), 1197 (m), 1143 (m). ^1H NMR ($CDCl_3$): δ 0.71/1.08 (12H, d, 2×CH*Me*$_2$, *J*=6.8 Hz), 0.95–1.23 (4H, m, 2×CH_2), 1.40–1.77 (4H, m, 2×C*H*$_2$), 1.88–1.99 (4H, m, 2×C*H*$_2$), 2.25–2.55 (2×CH_2 and 2×C*H*Me$_2$), 3.63 (12H, s, 4×OMe), 3.84 (2H, d, H-2 and H-2′, *J*=3.3 Hz), 4.85–4.96 (4H, m, 2×CH=C*H*$_2$), 5.59–5.76 (2H, m, 2×C*H*=CH_2). MS(EI): 554 (M^+, 0.7%), 304 (7), 252 (17), 251 (100), 209 (28), 195 (10), 153 (6).

1,6-Bis[(2*R*,5*S*)-5-allyl-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazin-5-yl]hex-3-yne (47d). *n*-BuLi in hexane (2.29 ml, 1.44 M, 3.30 mmol) was added to a solution of 1,6-bis[(2*R*,5*S*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazin-5-yl)]hex-3-yne (**46b**) (0.670 g, 1.50 mmol) in anhydrous THF (4 ml) at −78°C. The solution was stirred at −78°C for 1 h before a precooled (−78°C) solution of allyl bromide (0.457 g, 3.77 mmol) in THF (4 ml) was added through a Teflon tube. The reaction mixture was stirred at this temperature for 3 h and allowed to reach ambient temperature overnight. The reaction was quenched by addition of phosphate buffer (pH 7) and water. The aqueous phase was extracted with diethyl ether and the combined organic solution dried ($MgSO_4$) and the solvent distilled off. The residual material was subjected to flash chromatography using EtOAc/hexane 7:93; yield 0.400 g (50%) of a colorless oil. HRMS (electrospray): Found *M* 527.3583. Calcd for $C_{30}H_{47}N_4O_4$ 527.3591. IR (film): ν_{max} cm^{-1} 2969 (m), 2943 (m), 1691 (s), 1436 (m), 1239 (s), 1195 (m), 1144 (m). ^1H NMR ($CDCl_3$): δ 0.60/1.04 (12H, d, 2×CH*Me*$_2$, *J*=6.8 Hz), 1.76–2.11 (8H, m, 4×C*H*$_2$), 2.21 (2H, dd, *J*=7.4, 13.2 Hz, 2×C*H*H–CC), 2.29 (2H, ds, *J*=3.3, 6.8 Hz, 2×C*H*Me$_2$), 2.41 (2H, dd, *J*=7.4, 13.2 Hz, 2×CH*H*–CC), 3.62/3.63 (12H, s, 4×OMe), 3.79 (2H, d, H-2 and H-2′, *J*=3.3 Hz) 4.92–4.97 (4H, m, 2×CH=C*H*$_2$), 5.43–5.53 (2H, m, 2×C*H*=CH_2). ^{13}C NMR ($CDCl_3$): δ 14.56 (2×*C*H$_2$CH$_2$–CC), 16.81/19.48 (2×CH*Me*$_2$), 30.47 (2×*C*HMe$_2$), 39.14/45.08 (4×*C*H$_2$), 52.14/52.32 (4×OMe), 60.62 (C-2 and C-2′), 61.55 (C-5 and C-5′), 79.87 (2×CC), 118.37 (2×*C*H$_2$=CH), 133.16 (2×CH$_2$=*C*H), 163.3 (C-3, C-3′, C-6, C-6′). MS(EI): 526 (M^+, 1%), 512 (7), 511 (22), 486 (23), 485 (81), 484 (31), 483 (100), 443 (8), 401 (13), 359 (10), 303 (11), 221 (20), 181 (35).

Dimethyl (2*R*,7*R*)-2,7-diallyl-2,7-diamino-4-octynedioate (48a). Trifluoroacetic acid (20 ml, 0.2 M) was added to a solution of 1,4-bis[(2*R*,5*R*)-5-allyl-2-dihydro-3,6-dimethoxy-2-isopropylpyrazin-5-yl)]but-2-yne (**47a**) (0.359 g, 0.857 mmol) in MeCN (20 ml) and the mixture stirred at ambient temperature for 4 days. Aqueous conc. ammonia was added dropwise to the solution until pH 10, the mixture extracted with dichloromethane and the combined organic extracts dried ($MgSO_4$) and evaporated. The valine ester in the mixture was removed by slow distillation under high vacuum at ambient temperature. The residual crude product was acetylated (vide infra) without further purification; yield 0.125 g (>95%) of an oily material. HRMS: Found *M* 308.1733. Calcd for $C_{16}H_{24}N_2O_4$ 308.1736. IR (film): ν_{max} cm^{-1} 3075 (w), 3009 (w), 2959 (m), 2945 (m), 2869 (w), 2839 (w), 2352 (w), 1697 (s), 1462 (m), 1436 (m), 1309 (m) 1239 (s), 1198 (m), 1144 (m), 1012 (m), 917 (m). ^1H NMR ($CDCl_3$): δ 1.76 (4H, s, 2×N*H*$_2$), 2.14–2.62 (8H, m, 4×C*H*$_2$), 3.64 (6H, s, 2×OMe), 4.96–5.11 (4H, m, 2×CH=C*H*$_2$), 5.43–5.70 (2H, m, 2×C*H*=CH_2). ^{13}C NMR ($CDCl_3$): δ 29.85/43.24 (4×*C*H$_2$), 52.23 (2×OMe), 60.49 (2×MeO– (CO)– *C*–NH$_2$), 78.43 (2×CC), 119.52 (2×*C*H$_2$=CH), 138.02 (2×CH$_2$=*C*H), 175.60 (*C*O–OMe). MS(EI): 308 (M^+, 0.2%), 276 (9), 267 (45), 249 (28), 232 (21), 181 (23), 140 (72), 128 (20), 122 (72), 112 (20), 80 (25), 68 (81), 41 (100).

Dimethyl (2*R*,7*R*)-2,7-diamino-2,7-di(3-butenyl)-4-octynedioate (48b). Trifluoroacetic acid (84 ml, 0.2 M) was added to a solution of 1,4-bis[(2*R*,5*R*)-5-(3-butenyl)-2-dihydro-3,6-dimethoxy-2-isopropylpyrazin-5-yl)]but-2-yne (**47b**) (0.889 g, 1.69 mmol) in MeCN (84 ml) and the mixture stirred at ambient temperature for 6 days. Aqueous conc. ammonia was then added dropwise to the solution until pH 10, the mixture extracted with dichloromethane and the combined organic extracts dried ($MgSO_4$) and evaporated and the residual material subjected to flash chromatography using MeOH/CH_2Cl_2 3:97; yield 0.344 g (60%). HRMS: Found *M* 336.2053. Calcd for $C_{18}H_{28}N_2O_4$ 336.2049. IR (film): ν_{max} cm^{-1} 3377 (w), 3077 (w), 2998 (w), 2951 (m), 2921 (m), 2849 (w), 2354 (w), 1735 (s), 1641 (m), 1600 (m), 1436 (m), 1207 (s), 912 (m). ^1H NMR ($CDCl_3$): δ 1.52–2.18 (8H, m, 4×C*H*$_2$), 1.82 (4H, s, 2×N*H*$_2$), 2.35 (2H, d, 2×C*H*H, *J*= 14.3 Hz), 2.60 (2H, d, 2×C*H*H, *J*= 14.3 Hz), 3.69 (6H, s, 2×OMe), 4.88–5.01 (4H, m, 2×CH=C*H*$_2$), 5.61–5.78 (2H, m, 2×C*H*=CH_2). ^{13}C NMR ($CDCl_3$): δ 28.43/30.42/38.36 (6×*C*H$_2$), 52.36 (2×OMe), 60.69 (2×MeO– (CO)– *C*–NH$_2$), 78.50 (2×CC), 115.07 (2×*C*H$_2$=CH), 137.41 (2×CH$_2$=*C*H), 176.03 (*C*O–OMe). MS(EI): 336 (M^+, 0.2), 281 (5), 278 (20), 277 (100), 196 (21), 195 (59), 194 (18), 142 (86), 136 (78), 119 (14), 109 (22), 101 (11), 95 (10), 82 (81), 81 (18), 80 (15), 79 (11).

Dimethyl (2*R*,7*R*)-2,7-diacetamido-2,7-diallyl-4-octynedioate (49a). A solution of acetic acid anhydride (0.185 g, 3.63 mmol) in dichloromethane (6 ml) was added dropwise to a solution of dimethyl (2*R*,7*R*)-2,7-diallyl-2,7-diamino-4-octynedioate (**48a**) (0.233 g, 0.756 mmol) and DMAP (0.231 g, 3.78 mmol) in dichloromethane (12 ml) at 0°C. The reaction mixture was stirred at ambient temperature for 3 h before the reaction was stopped by addition of saturated aqueous ammonium chloride. The phases were separated, the aqueous phase extracted with dichloromethane and the combined organic extracts dried ($MgSO_4$) before the solvent was distilled off at reduced pressure. The residual material was subjected to flash chromatography using MeOH/CH_2Cl_2 4:96; yield: 157 mg (53%) of a viscous oily material. HRMS (electrospray): Found *M* 393.2019. Calcd for $C_{20}H_{29}N_2O_6$: 393.2020. IR (film): ν_{max} cm^{-1} 3284 (m), 3076 (m), 2952 (m), 1724 (s), 1656 (s), 1547 (s), 1438 (s), 1335 (s), 1221 (s), 925 (m). ^1H NMR ($CDCl_3$): δ 1.99 (6H, s, CO*Me*), 2.40–3.17 (8H, m, 4×C*H*$_2$), 3.71 (6H, s, 2×OMe), 4.99–5.08 (4H, m, 2×CH=C*H*$_2$), 5.47–5.61 (2H, m, 2×C*H*=CH_2), 6.37 (2H, s, 2×N*H*). ^{13}C NMR ($CDCl_3$): δ 23.69 (2×*Me*CO–), 25.44/38.57 (4×*C*H$_2$), 52.85 (2×OMe), 63.10 (2×MeO–(CO)–*C*–NH), 77.69 (2×CC), 119.38

(2×*C*H_2=CH), 131.67 (2×CH_2=*C*H), 169.52/172.56(*C*O). MS(CI): *m*/*z* 393 (M^++1, 100%), 351 (19), 333 (14), 292 (8), 222 (11), 184 (34), 128 (17).

Dimethyl (2*R*,7*R*)-2,7-diacetamido-2,7-di(3-butenyl)-4-octynedioate (49b). A solution of acetic acid anhydride (0.251 g, 2.46 mmol) in dichloromethane (9 ml) was added dropwise to a solution of dimethyl (2*R*,7*R*)-2,7-di(3-butenyl)-2,7-diamino-4-octynedioate (**48b**) (0.344 g, 1.02 mmol) and DMAP (0.313 g, 2.56 mmol) in dichloromethane (9 ml). The reaction mixture was stirred at ambient temperature for 5 h before addition of saturated aqueous ammonium chloride. The mixture was extracted with dichloromethane, the combined organic extracts dried ($MgSO_4$), the solvent distilled off and the residual material subjected to flash chromatography using MeOH/CH_2Cl_2 5:95; yield 347 mg (87%) of a viscous oily material. HRMS: Found (electrospray) *M* 420.2248. Calcd for $C_{22}H_{32}N_2O_6$: 420.2260. IR (film): ν_{max} cm^{-1} 3584 (w), 3288 (m), 3074 (m), 2951 (m), 2852 (w), 1741 (s), 1655 (s), 1541 (s), 1435 (s), 1372 (m), 1211 (s), 914 (w). ^{1}H NMR ($CDCl_3$): δ 1.71–2.17 (6H, m, 2×C*H*$_2$CH$_2$–CH=CH$_2$, CH$_2$C*H*–CH=CH$_2$), 1.99 (6H, s, CO*Me*), 2.34–2.42 (2H, m, 2×CH$_2$CH*H*–CH=CH$_2$), 2.57 (2H, app. d, *J*= 16.3 Hz, C*H*H–CC), 3.15 (2H, app. d, *J*= 16.3 Hz, C*H*H-CC), 3.70 (6H, s, 2×OMe), 4.86–4.96 (4H, m, 2×CH=C*H*$_2$), 5.60–5.69 (2H, m, 2×C*H*=CH$_2$), 6.44 (2H, s, 2×N*H*). ^{13}C NMR ($CDCl_3$): δ 23.74 (2×*C*H$_2$CH$_2$–CH=CH$_2$), 25.70 (2×*Me*CO–), 28.40 (2×CH$_2$*C*H$_2$–CH=CH$_2$), 33.82 (2×*C*H$_2$–CC), 52.83 (2×OMe), 63.17 (2×MeO–(CO)–*C*–NH), 77.42 (2×*C*C), 115.22 (2×*C*H$_2$=CH), 136.87 (2×CH$_2$=*C*H), 169.36/173.00 (2×*C*O). MS(EI): 420 (M^+, 0.5), 361 (28), 346 (17), 319 (15), 302 (15), 287 (16), 237 (61), 236 (81), 184 (18), 183 (17), 178 (27), 144 (18), 142 (100), 136 (14), 119 (14), 92 (18), 91 (31), 82 (52).

3,3′,4,4′,5,5′,6,6′-Octahydro-4,4′-dispiro[(2*R*,5*S*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazin-5-yl]biphenyl (51). Bis(tricyclohexylphosphine)benzylidene ruthenium dichloride (15 mg, 0.0175 mmol) was added to a solution of 1,6-bis[(2*R*,5*S*)-5-allyl-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazin-5-yl)]hex-3-yne (**47d**) (0.185 g, 0.35 mmol) in dry degassed toluene (15 ml) under argon. The reaction mixture was kept at 85°C for 5 h before addition of another portion of the catalyst (15 mg, 0.0175 mmol). The stirring was continued for another 5 h, the solvent distilled off and the product isolated after flash chromatography using EtOAc/hexane 7:93; yield (>95%) of a white solid, mp 128–132°C. Found: C, 67.59; H, 8.79. Calcd for $C_{28}H_{42}N_4O_4$: C, 67.44; H, 8.49%. HRMS: Found *M* 498.3211. Calcd for $C_{28}H_{42}N_4O_4$: 498.3206. IR (film): ν_{max} cm^{-1} 2943 (s), 2870 (s), 1690 (s), 1461 (m), 1434 (s), 1297 (s), 1228 (s), 1109 (m), 1031 (m). ^{1}H NMR ($CDCl_3$): δ 0.74/1.12 (12H, d, 2×CH*Me*$_2$, *J*= 6.8 Hz), 1.56–1.63 (2H, m, C*H*H–CH$_2$), 1.96 (2H, dd, *J*= 4.4, 17.8 Hz, C*H*H–CH=C), 2.05–2.39 (8H, m, 4×C*H*H and 2×C*H*Me$_2$), 2.49–2.68 (2H, m, 2×CH*H*), 2.85 (2H, d, *J*= 17.8 Hz, CH*H*–CH=C) 3.63/3.71 (12H, s, 4×OMe), 4.00 (2H, d, H-2 and H-2′, *J*= 3.4 Hz), 5.68–5.76 (2H, m, 2×C*H*=C), 5.43–5.53 (2H, m, 2×C*H*=CH$_2$). ^{13}C NMR ($CDCl_3$): δ 16.93/19.37 (2×CH*Me*$_2$), 21.89 (2×*C*H$_2$–CH$_2$), 30.87 (2×*C*HMe$_2$), 33.41 (2×CH$_2$–*C*H$_2$), 37.38 (2×–*C*H$_2$–CH=C), 51.95/52.33 (4×OMe), 55.80 (C-5 and C-5′), 60.54 (C-2 and C-2′), 117.56 (2×C=*C*H), 136.10 (2×*C*=CH), 160.96/166.35 (C-3, C-3′, C-6, C-6′). MS(EI): 498 (M^+, 100), 465 (9), 456 (17), 455 (60), 423 (8), 302 (10), 259 (34), 197 (12).

Dimethyl (3*R*,3′*R*)-3,3′-bis(1-acetamido-3-cyclopentene-1-carboxylate) (52a). Bis(tricyclohexylphosphine)benzylidene ruthenium dichloride (213 mg, 0.543 mmol) was added to a solution of dimethyl (2*R*,7*R*)-2,7-diacetamido-2,7-diallyl-4-octynedioate (**49a**) (0.460 g, 1.17 mmol) in dry degassed toluene (20 ml) under argon. The reaction mixture was stirred at 90°C for 5 h before another portion of the catalyst (213 mg, 0.543 mmol) was added. The mixture was stirred for an additional 5 h before the solvent was distilled off. The product was isolated after flash chromatography using MeOH/CH_2Cl_2 5:95; yield 0.169 g (86%) of a white solid material. HRMS (electrospray): Found *M* 365.1709. Calcd for $C_{18}H_{25}N_2O_6$ 365.1707. IR (film): ν_{max} cm^{-1} 3346 (s), 3269 (s), 3061 (m), 2996 (m), 2950 (m), 2927 (m), 1739 (s), 1659 (s), 1541 (s), 1432 (s), 1327 (s), 1217 (s), 1036 (s). ^{1}H NMR ($CDCl_3$): δ 1.99 (6H, s, CO*Me*), 2.68–2.84 (4H, m, 2×C*H*$_2$), 3.07–3.24 (4H, m, 2×C*H*$_2$), 3.73 (6H, s, 2×OMe), 5.45 (2H, s, 2×C*H*=C), 6.19 (N*H*). ^{13}C NMR ($CDCl_3$): δ 23.63 (2×*Me*CO–), 44.56/45.19 (4×*C*H$_2$), 53.25 (2×OMe), 64.61 (2×–*C*–CO$_2$Me), 124.25 (2×*C*H=C), 136.99 (2×CH=*C*), 170.27/174.44 (*C*O). MS: no molecular ion.

Dimethyl (3*R*,3′*R*)-3,3′-bis(1-acetamido-3-cyclohexene-1-carboxylate) (52b). Bis(tricyclohexylphosphine)benzylidene ruthenium dichloride (213 mg, 0.543 mmol) was added to a solution of dimethyl (2*R*,7*R*)-2,7-diacetamido-2,7-diallyl-4-octynedioate (**49b**) (0.335 g, 0.854 mmol) in dry degassed toluene (30 ml) under argon. The reaction mixture was kept at 90°C for 5 h before another portion of the catalyst (0.335 g, 0.854 mmol) was added, and the stirring was continued for another 5 h. The mixture was filtered, the solvent distilled off and the product isolated after flash chromatography using MeOH/CH_2Cl_2 5:95; yield 0.263 g (85%) of a white solid foam. HRMS (elektrospray): Found *M* 393.2017. Calcd for $C_{20}H_{29}N_2O_6$ 393.2020. IR (ATR plate): ν_{max} cm^{-1} 3296 (m), 3055 (m), 2950 (m), 1739 (s), 1653 (s), 1538 (s), 1435 (m), 1254 (m). ^{1}H NMR ($CDCl_3$): δ 1.78–1.92 (4H, m, 2×C*H*$_2$CH$_2$–CH=C), 1.95 (6H, s, CO*Me*), 2.14–2.30 (4H, m, 2×CH$_2$C*H*$_2$–CH=C), 2.50 (2H, d, *J*= 17.0 Hz, 2×CH*H*–C=CH), 2.68 (2H, d, *J*= 17.0 Hz, 2×CH*H*–C=CH), 3.72 (6H, s, 2×OMe), 5.48 (2H, s, NH-Ac), 5.66–5.74 (2H, m, 2×C*H*=C). ^{13}C NMR ($CDCl_3$): δ 22.00 (2×*C*H$_2$CH$_2$–CH=CH$_2$), 23.16 (2×*Me*CO–), 26.94 (2×CH$_2$*C*H$_2$–CH=CH$_2$), 33.93 (2×*C*H$_2$–C=CH), 52.50 (2×OMe), 57.57 (2×MeO– (CO)– *C*–NH), 121.27 (2×*C*H=C), 132.09 (2×CH$_2$=*C*H), 169.86/174.03 (2×*C*O). MS: no molecular ion.

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