

The Schöllkopf chiron and transition metal mediated reactions, a powerful combination for stereoselective construction of cyclic α -quaternary- α -amino acid derivatives

Review Article

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Summary. The focus has been on the development of methodology for stereoselective preparation of spiroannulated intermediates of the Schöllkopf chiron and further transformations to cyclic α -amino acids. The spiroannulations are effected by Ru(II)-catalysed ring-closing metathesis reactions, by Ru(II)- and Pd(0)-catalysed cycloisomerisations, by Rh(II)-carbenoid cyclisation reactions and by intramolecular aldol condensations. Hydrolytic reactions of the spirane intermediates have provided several groups of highly novel and functionalised five-, six- and seven-membered cyclic α -quaternary- α -amino acid derivatives as well as alicyclic derivatives. The novel cyclic amino acid derivatives can be regarded as cyclic constrained analogues of corresponding common amino acids, or in some cases as intermediates for further preparation of such amino acids. Some emphasis has been on the preparation of cyclic serine analogues. Major efforts have been on the preparation of cyclic α -quaternary bis(α -amino acid) derivatives as conformationally constrained dicarba-analogues of cystine.

Keywords: Schöllkopf chiron – Stereoselective *gem*-dialkenylations – Transition metal promoted cyclisations – α -quaternary- α -amino acids – Spiroannulation

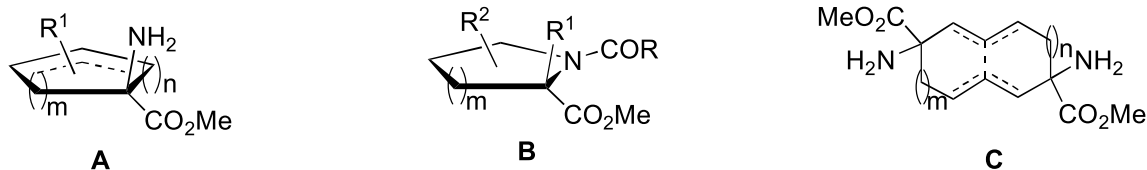
1. Introduction

Incorporation of conformationally constrained non-coded amino acids into peptides will affect secondary and tertiary peptide structures and thereby provide useful information about structural requirements for bioactivity [1–3]. Cyclic α -quaternary- α -amino acids are conformationally constrained. When incorporated into peptidic material the conformational freedom of the peptidic material will be significantly affected. Hence preparation and studies of bioproperties of α -quaternary- α -amino acids have attracted great attention [4–6]. In this paper we have reviewed

efforts to develop methodologies for the construction of five-, six- and seven-membered cyclic α -quaternary- α -amino acids. The families of target molecules are shown in Fig. 1.

Several chiral auxiliaries are available for amino acid constructions [7–11]. Most chiral auxiliaries are small heterocyclic compounds which rely on sterically demanding functional groups to control the conformation of their ring systems. Under ideal circumstances, the conformation of an auxiliary should be constrained to ensure that its pro-chiral center reacts with a reagent *via* diastereomeric transition states which are sufficiently different in energy to ensure that only a single diastereomer is formed as product [12]. Alkylation of the enolates of the Seebach imidazolidinone, or the Schöllkopf bislactim ether auxiliary are controlled *via* 1,3- and 1,4-asymmetric induction, respectively [12]. In the work herein presented, almost all amino acids have been prepared by the Schöllkopf bislactim ether route. In most of the work, the chiron (*2R*)-2-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine (**1**), the dimethyl ether of cyclo(-Val-Gly-), has been used (Scheme 1). In a minor part of the work, the (*S*)-enantiomer **1-(S)** was employed.

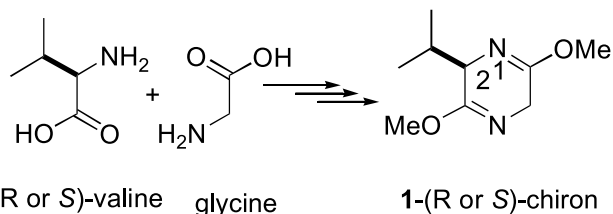
The configuration at the valine α -carbon controls the steric induction during the *gem*-dialkylation at the α -glycine carbon which is to become the α -quaternary carbon in the new α -amino acid derivative. Once the new α -amino acid carbon has become quaternary, racemisation at this carbon cannot occur. The alkylated products are diastereomers and



Five-, six- or seven-membered rings $R^1 = \text{OR}$, oxo, acyl, alkyl, alkenyl or aryl

Five-, or six-member rings. $R^1 = \text{alkyl}$ or alkenyl, $R^2 = \text{OR}$, oxo

Fig 1. Cyclic α -quarternary- α -amino acid families as target molecules



Scheme 1. Schöllkopf bislactim ether **1**

have so far been readily purified and separated by simple column chromatography on silica gel. Hydrolysis by ring-opening of the piperazine diastereomer will thus provide a pure enantiomer. Since our purity criteria are based on chromatographic purification of the diastereomer precursor in combination with NMR spectroscopy, a stereochemically pure product in our hands is expressed as $>95\%$, about the limit for detection of its stereomer in ^1H NMR.

In selected cases, the relative configuration in the diastereomers has been determined by X-ray analyses. These analyses have also confirmed the chemoselectivity in the reactions reported. In these derivatives the absolute configuration at the valine α -carbon in the chiron is known. Therefore, a combination of the absolute configuration of the chiron and the relative stereochemistry from the X-ray analyses, allows assignment of the absolute configuration at the new stereogenic centers. Once a reference has been established, NMR spectroscopy will provide additional correlations.

2. Discussion

2.1 Stereoselective alkylations in the Schöllkopf chiron

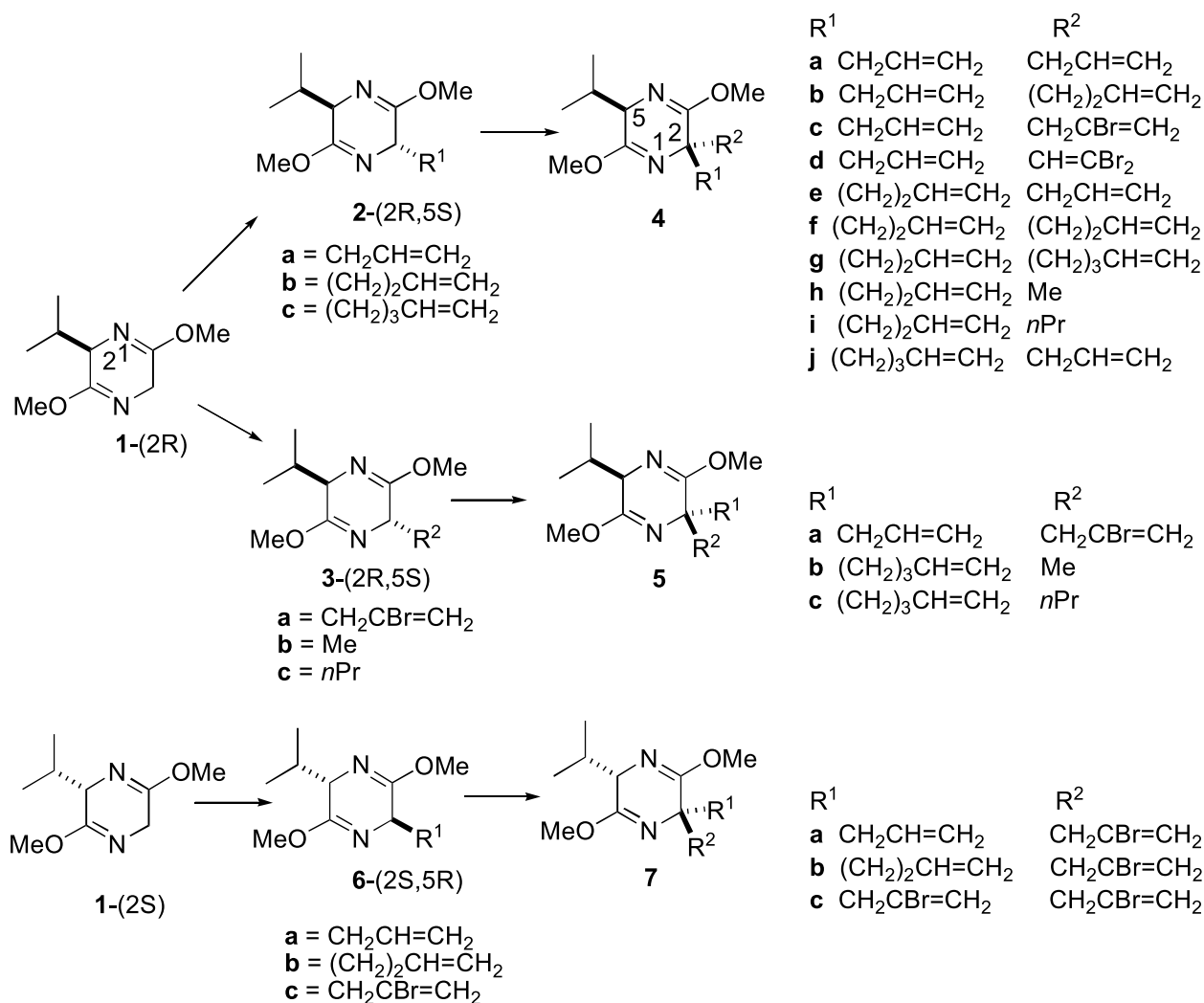
Ring-closing metathesis (RCM) reactions, cycloisomerisation reactions, insertion reactions and condensation reactions leading to highly functionalised heterospirane intermediates for the amino acid syntheses are shown in Schemes 17–25 (Ru), Schemes 27–30 (Pd), Schemes 31–35 (Rh), Scheme 36 (Co), and Scheme 37 aldol con-

densations. The subsequent hydrolytic reactions leading to α -quarternary- α -amino acid derivatives are shown in Schemes 43–46, 48, 49, 51–54, 57, 58, 60, 61, 64. Schemes 47, 50, 55, 59, 62, 63 present five- and six-membered cyclic α -amino acid derivatives which have been prepared by alternative methodologies.

The substrates for the ring-closing reactions are all 5,5-disubstituted derivatives of the chiron **1** where the substituents are variously functionalised. The preparation involves a 5:5-*gem*-dialkylation of the chiron in a two-step process (Schemes 2–15).

In Scheme 2, the chiron **1**-(2*R*) is lithiated at -78°C and treated with an ω -bromo-1-alkene to furnish the 2-alkyl derivatives **2a** [13], **2bc** [14], **3a** [15] and **3bc** [16] in high yields. In the same way compounds **6abc** [17] become available from the **1**-(*S*)-chiron. The diastereomeric excess (*de*) is significantly affected by the nature of the carbon electrophile. However, when the first formed monoalkylated product is lithiated for a second alkylation, the original stereochemistry at the glycylic carbon, as an anionic site, is lost. The metallation is fully regioselective in the absence of branching at the α -carbon in the monoalkyl substituent. The branching at the α -carbon of the valine isopropyl group leads to full shielding of its site of attachment in the ring. The new alkylating agent will approach the carbanion site in a *trans* manner with respect to the isopropyl group. The diastereoselectivity in the second alkylation step is high. In most cases only one product is observed.

Previously Schöllkopf had observed very high high stereoselectivity in the second *gem*-dialkylations. Thus in the alkylation of (2*S*,5*S*/*R*)-2-isopropyl-3,6-dimethoxy-5-methyl-2,5-dihydropyrazine with chloromethyl benzyl ether, the (5*R*)-adduct was obtained in 95% chemical yield with *de* 95% or more, since only one isomer was detected by ^1H and ^{13}C NMR spectroscopy [18]. With other electrophiles such as alkyl, benzyl, allyl, and propargyl halides, virtually complete asymmetric inductions were observed in the formation of the (2*R*)-addition



Scheme 2. Refs: **2a** [13]; **2bc** [14]; **3a** [15]; **3b** [16]; **3c** [21]; **4abdefgj** [14]; **4d** [17]; **4hi** [20]; **5a** [20]; **5bc** [22]; **6abc** [17]; **7abc** [17]

products. In the ¹H NMR spectra, only the (6*S*,2*R*)-diastereomers were detected. Capillary GLC analysis revealed diastereomer ratios of the order >98:2. Acid hydrolysis liberates α-methyl amino acid methyl esters which were enantiomerically pure by ¹H NMR-standard [19].

When a second product is obtained in the *gem*-alkylation, it is readily removed by simple flash chromatography. As a routine, all products have been subjected to purification by flash chromatography. The pure diastereomers **4ab** [14], **4cd** [20], **4efg** [14], **4hi** [21], **4j** [14], **5a** [20], **7abc** [17] have been used in the subsequent reactions.

In the alkylation reactions, when the monoalkylated product **2-(2*R*,5*S*)** (Scheme 2) is the substrate for a second alkylation involving lithiation, the relative stereochemistry of the R¹-substituent is changed from a *trans*- to a *cis*-relationship with respect to the isopropyl group. The new R² group has a *trans*-relationship. When the order of

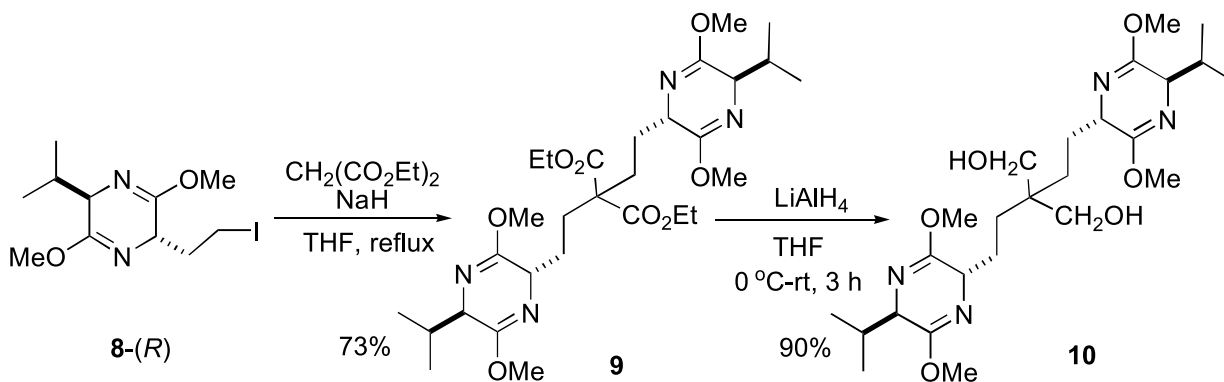
alkylation is interchanged, the opposite configuration will be generated at the C-2 carbon in the structure **4**. Thus the isomeric structures **4c** and **5a** are diastereomers and differ solely in the configuration at C-2. A similar configurational relationship exists between the structures **4h** and **5b**, and between structures **4i** and **5c**. An important conclusion becomes evident. Either the (*R*)- or the (*S*)-configuration can be generated at C-2 from the same chiron depending only on the order of the *gem*-dialkylation. In a further correlation, it is apparent that alkylation of the **1-(2*S*)** chiron in the **1**→**7** order provides the same configuration at C-2 as when the other sequence was used in the alkylation of **1-(2*R*)** furnishing the diastereomer products **5a** and **7a**. Hydrolysis will provide the same α-quaternary-α-amino acid.

Hydrolysis of the 5,5-*gem*-dialkylated products in Scheme 2, and corresponding products in a number of the

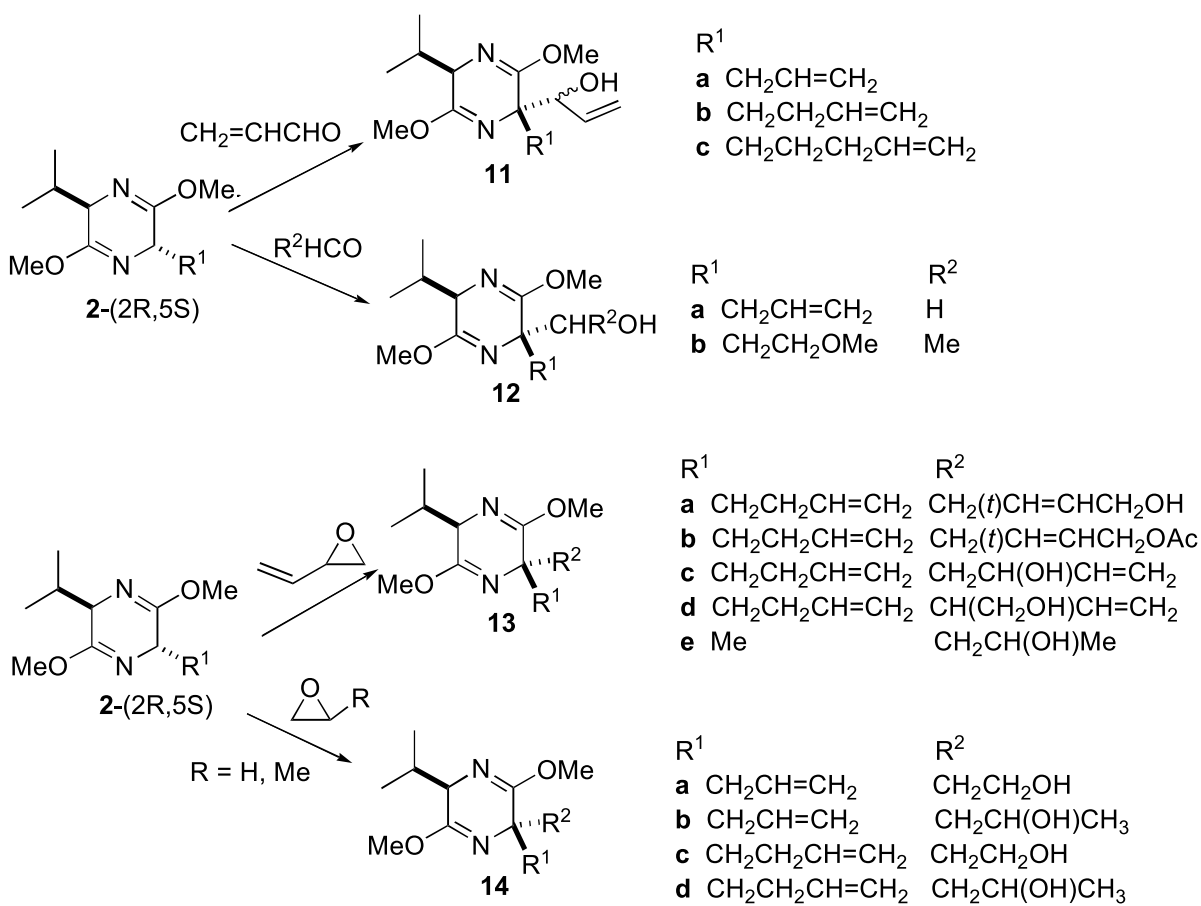
subsequent schemes, will provide corresponding non-cyclic α -quaternary- α -amino acid derivatives. The present review is limited to cyclic α -quaternary- α -amino acid derivatives with a few exceptions of highly novel products.

The alkylations leading up to structure **9** in Scheme 3 represent the first part of a synthesis of a novel quaternary spirane-bridged bis(α -amino acid) derivative **75** as carba

analogues of the amino acid cystine (Scheme 23). The substrate **8** is prepared by alkylation of lithiated **1**-(2*R*) with 1-bromo-2-chloroethane. The 2-chloroethyl product is subsequently subjected to a Finkelstein reaction to provide the iodide **8**. The latter is the alkylating reagent in a diethyl malonate *gem*-dialkylation synthesis. The bridged product **9** is obtained in a satisfactory yield. A subsequent



Scheme 3. Refs: **9**, **10** [23]

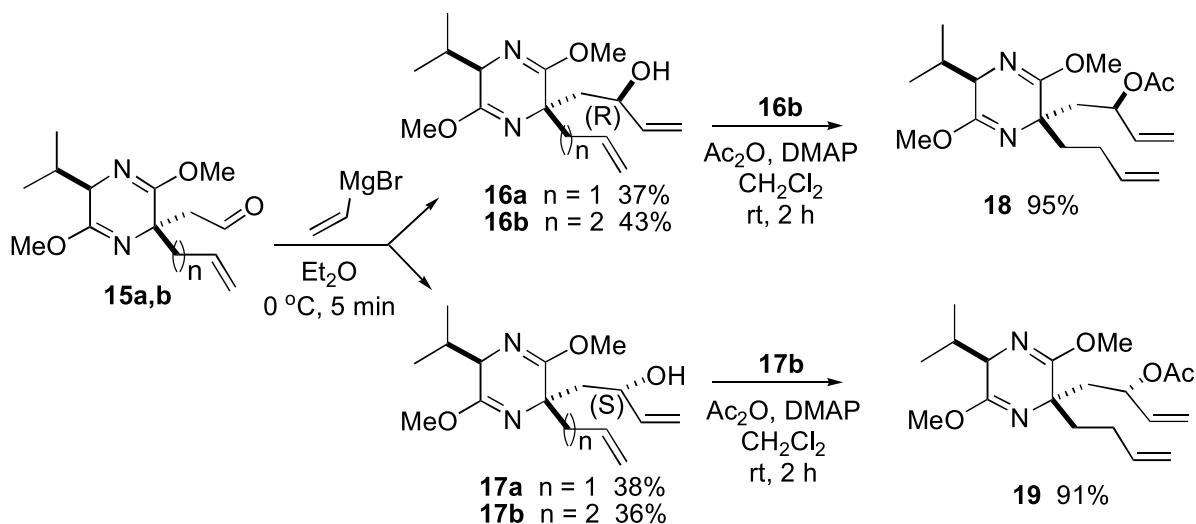


Scheme 4. Refs: **11abc** [24]; **12a** [25]; **12b** [32], **13abc** [27], **13d** [27]; **13e** [32]; **14ac** [26]; **14bd** [31]

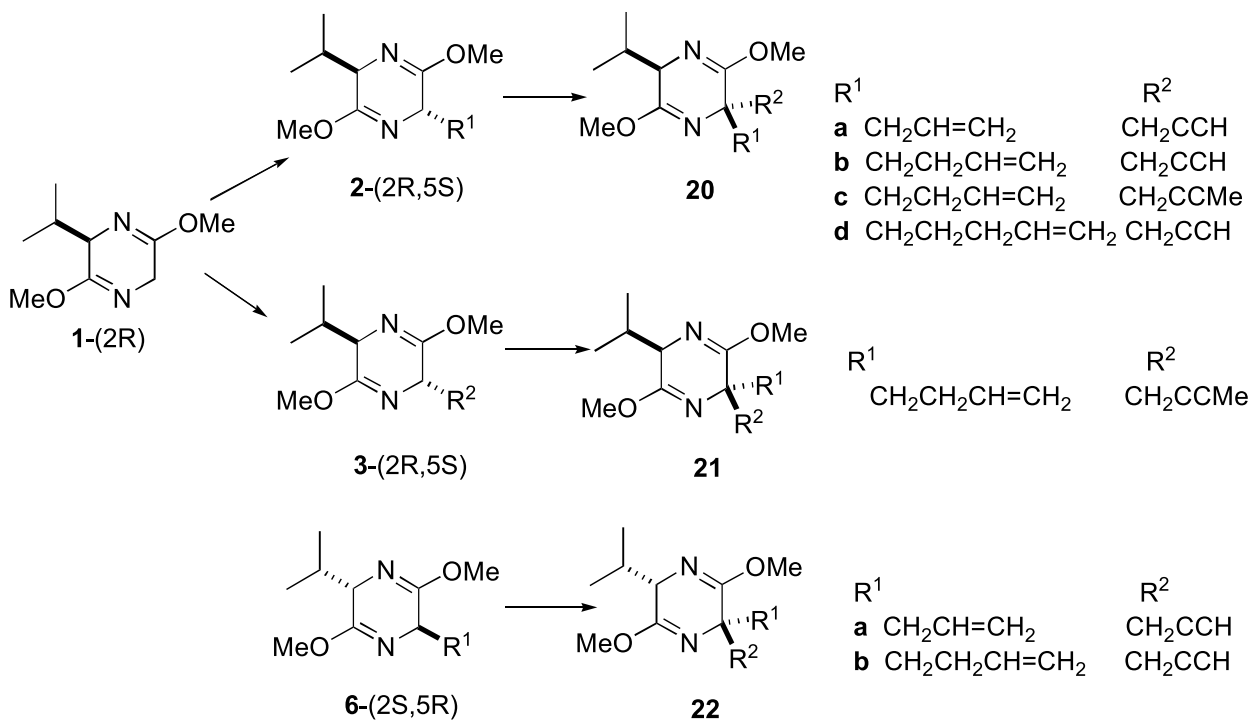
LAH reduction proceeds very well to provide the diol **10** [23].

In the preparation of α -hydroxy derivatives in the side-chain, the hydroxy group is introduced in the second step in a *gem*-dialkylation reaction by adduct formation with an oxo derivative. When acolein is the addend to the lithiated chiron **2**, exclusive 1,2-addition is observed [24]. The reaction proceeds with high diastereoselectivity

in the heterocycle, but with low diastereoselectivity at the hydroxyl carbon. However, the alcohol epimers **11** can be separated by flash chromatography and characterised. With paraformaldehyde, the primary alcohol **12a** is formed in high yield [25]. β -Hydroxy derivatives are available by a reaction of the lithiated species of **2**-(2*R*,5*S*) with ethylene oxide to provide the ethanol derivatives **14** with high diastereoselectivity at C-2 [26]. When the epoxide of



Scheme 5. Refs: **16ab**, **17ab**, **18**, **19** [26]



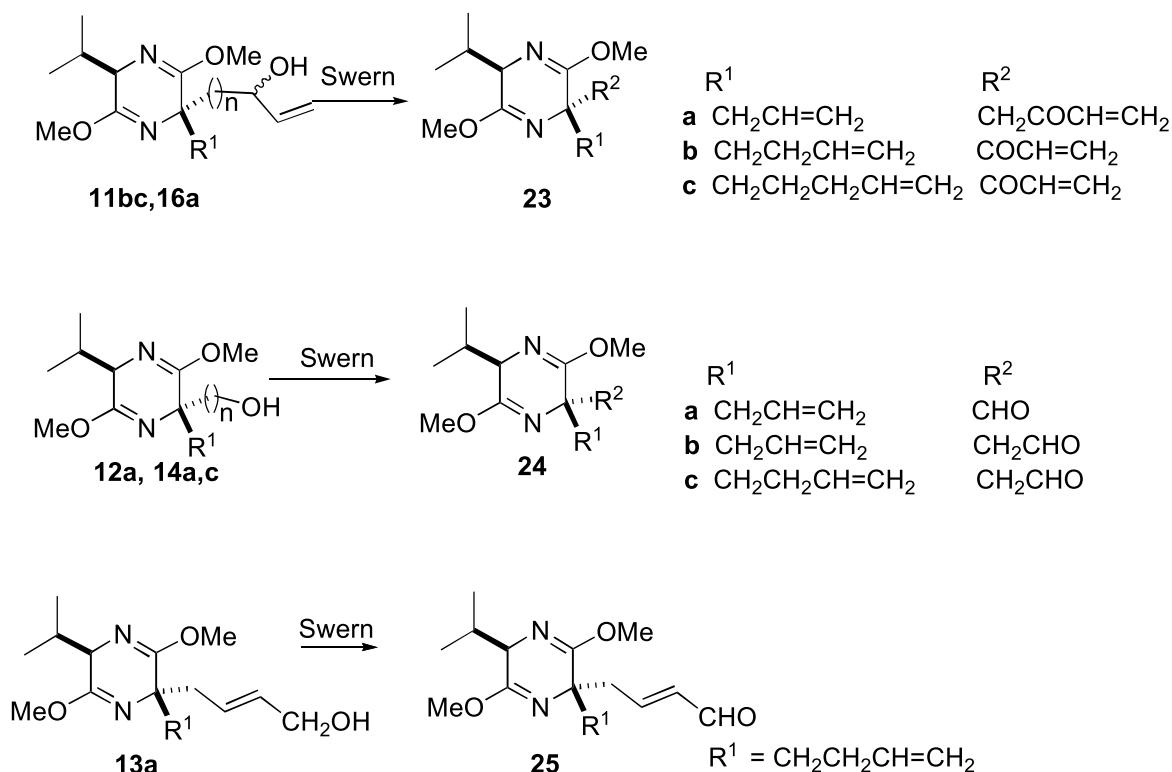
Scheme 6. Refs: **20abcd**, **21** [28]; **22ab** [17]

1,3-butadiene is used, a mixture of hydroxy derivatives **13** is produced. The major product is formed by conjugate addition to the double bond of the epoxide followed by epoxide ring opening. The product is the *trans*-allylic alcohol **13a**. Attack at the terminal epoxide carbon explains the formation of secondary alcohol **13c**, and attack at the other epoxide carbon the formation of the hydroxymethyl derivative **13d** [27]. With propylene oxide, the product is the corresponding secondary alcohol **13e** [32].

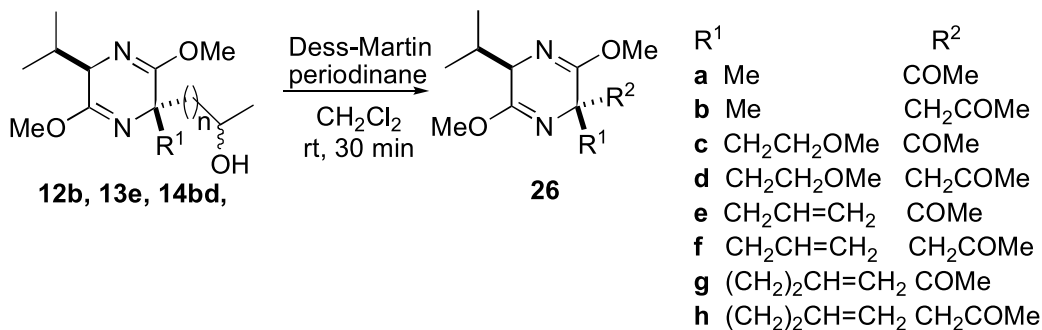
β -Hydroxy allylic alcohols become available by a Grignard reaction between vinylmagnesium bromide and the β -aldehyde **15**, which itself is prepared from the cor-

responding ethanol by oxidation as shown in Scheme 7. The mixtures, epimeric at the alcohol carbon, can be separated by chromatography and acetyl protected for a subsequent RCM reaction (*vide infra*) [26].

The substrates for the alkynyl derivatives **20** in Scheme 6 are the corresponding monoalkenyl compounds **2**-(*2R,5S*) [28]. When the monoalkenyl derivative **3** is the substrates for the second alkenylation reaction, the configuration at C-2 is changed. The change is apparent by a comparison of structures **20c** and **21** [28]. By analogy, substrate **6**-(*2S,5R*) can be prepared and alkynylated in the same manner to furnish compounds **22** [17].



Scheme 7. Refs: **23a** [41]; **23bc** [30]; **24a** [20, 25]; **24bc** [26]; **25** [27]



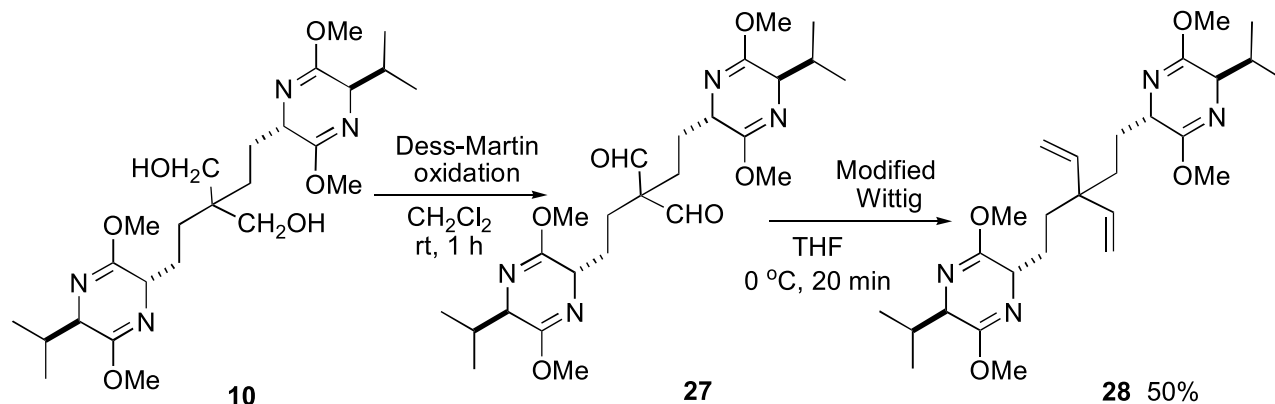
Scheme 8. Refs: **26abcde**; [32]; **26efgh** [31]

Oxo derivatives become available by chemoselective oxidations of corresponding hydroxyl derivatives. Both the Swern and the Dess-Martin periodinane methodologies lead to high yield processes for the preparation of oxo compounds. Examples from the Swern oxidation are given in Scheme 7. Both α - and β -oxo derivatives become available as expressed in the ketones **23** [30, 41, 51] and the aldehydes **24** [20, 25, 26]. This route is recommendable for the preparation of α -formyl derivatives expressed by

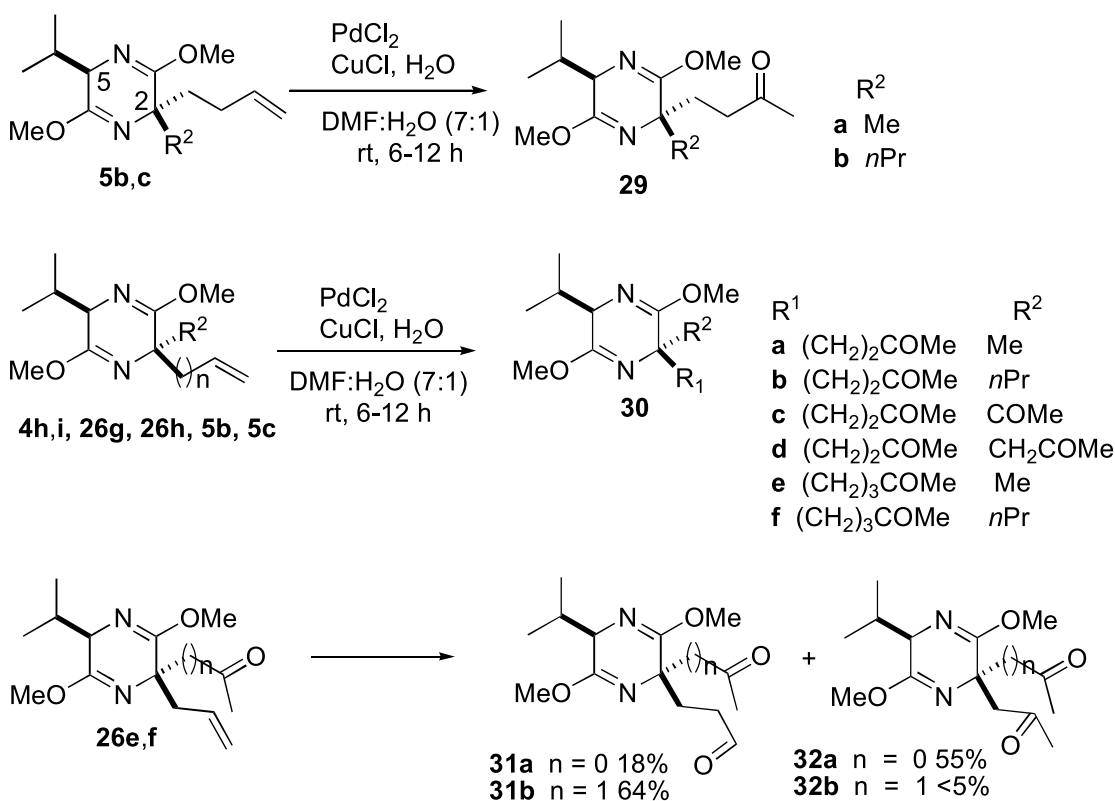
structure **24a** [25]. The terminal allylic alcohol **13a** is also chemoselectively converted to the conjugated aldehyde **25** under the Swern conditions [27].

Alternatively, related oxidations of hydroxyl compounds can be effected by the Dess-Martin periodinane reagent in a chemoselective manner to provide the ketones **26** (Scheme 8) [31, 32].

With the bridged diol **10**, the Dess-Martin reaction provides the dialdehyde **27** (Scheme 9). The latter was chemi-



Scheme 9. Refs: 27, 28 [23]



Scheme 10. Refs: 29ab, 30ab [21]; 30cd, 31ab, 32ab [31]; 30ef [22]

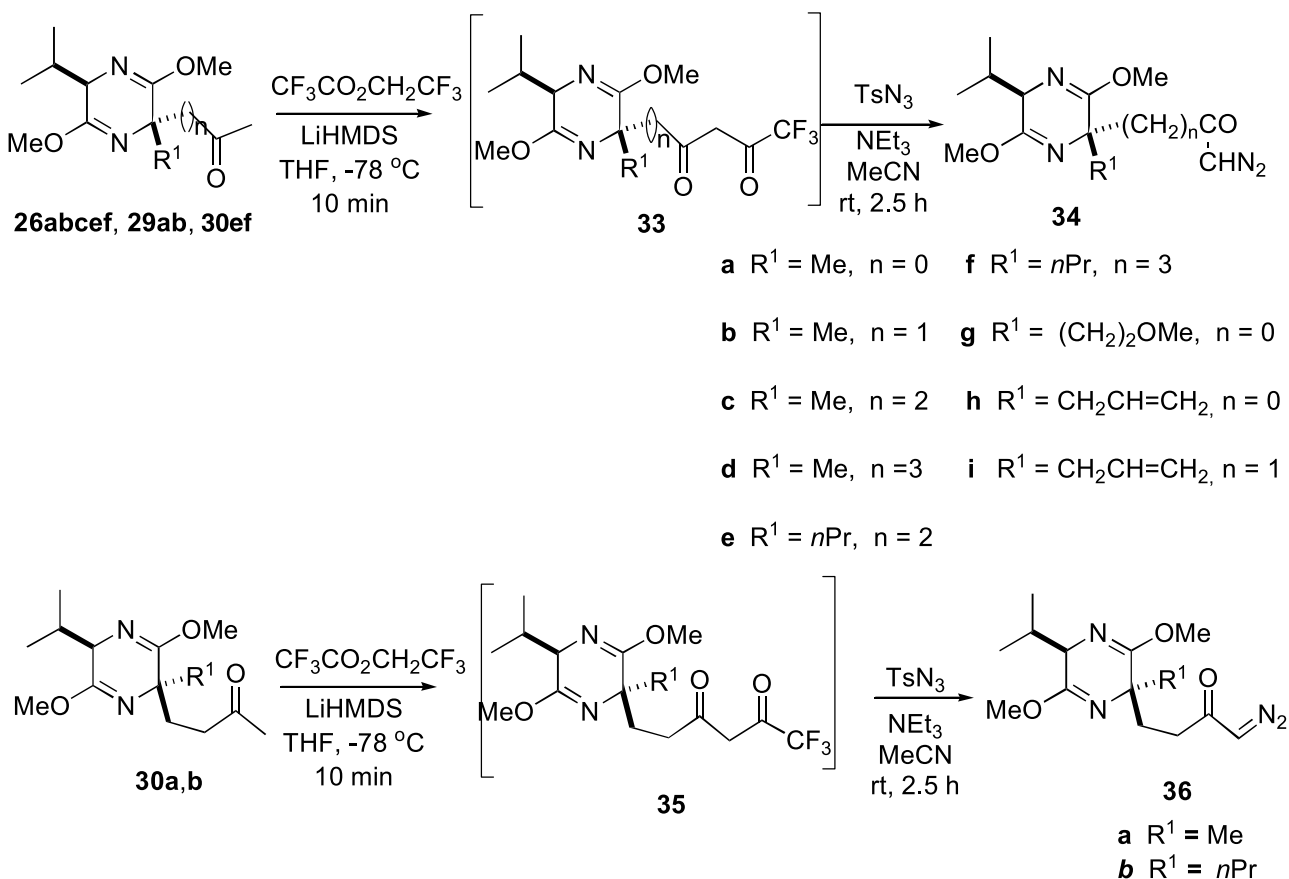
cally somewhat unstable, and the crude product is therefore used as a substrate for the subsequent divinylolation reaction under modified Wittig conditions to furnish the diene **28** in 50% overall yield [23].

The use of hydroxy derivatives as intermediates for oxo products, can be circumvented by Wacker type oxidations. The Wacker oxidations have been explored since carbon-carbon double bonds would provide convenient substrate moieties. These reactions turned out to be fully chemoselective for oxidation of the carbon-carbon double bond in high yielding processes. In the heterocyclic substrates **4** and **5** in Scheme 10, oxidation in aqueous medium under the Wacker conditions proceed well with formation of the methyl ketones **29** and **30** in high yields [21, 22, 31]. Methyl ketones are normally the products in the Wacker oxidation, but from some substrates aldehydes may be formed alone or in mixture with the methyl ketone, because of steric interactions or heteroatom interactions. In the propene substrates **26**, minor coformation or a dominating formation of aldehyde was observed. With the acetyl group at the spirocenter **26e**, the ratio between aldehyde **31a** and ketone **32a** formation was 1:3. With an

acetyl substituent at the spirocenter **26f**, by far the major product was the aldehyde **31b** [31].

The rhodium(II)-catalysed cycloinsertion reaction in Schemes 31–35 requires diazomethyl ketones as substrates. Preparation of appropriate diazoketone substrates **34** and **36** is shown in Scheme 11. Compounds **34c** and **36a** as well as **34e** and **36b** are pairwise diastereomers that differ only in the configuration at C-2. The respective ketone substrates (**26**, **29**, **30**) were activated in the methyl group for regioselective introduction of the diazo function by way of a trifluoroacetyl derivative **33** or **35** as a 1,3 diketone. Activation is effected by lithiation and reaction with 2,2,2-trifluoroethyl trifluoroacetate (TFEA) at -78°C for 10 min by analogy to methodology described by Danheiser and Doyle [33, 34]. The product is the corresponding α -trifluoroacetyl ketone which is reacted further *in situ* with tosyl azide in acetonitrile containing water and triethylamine, at room temperature. The products are the diazomethyl ketones **34** and **36** in moderate overall chemical yields, in the range 42–45% [21, 22, 34].

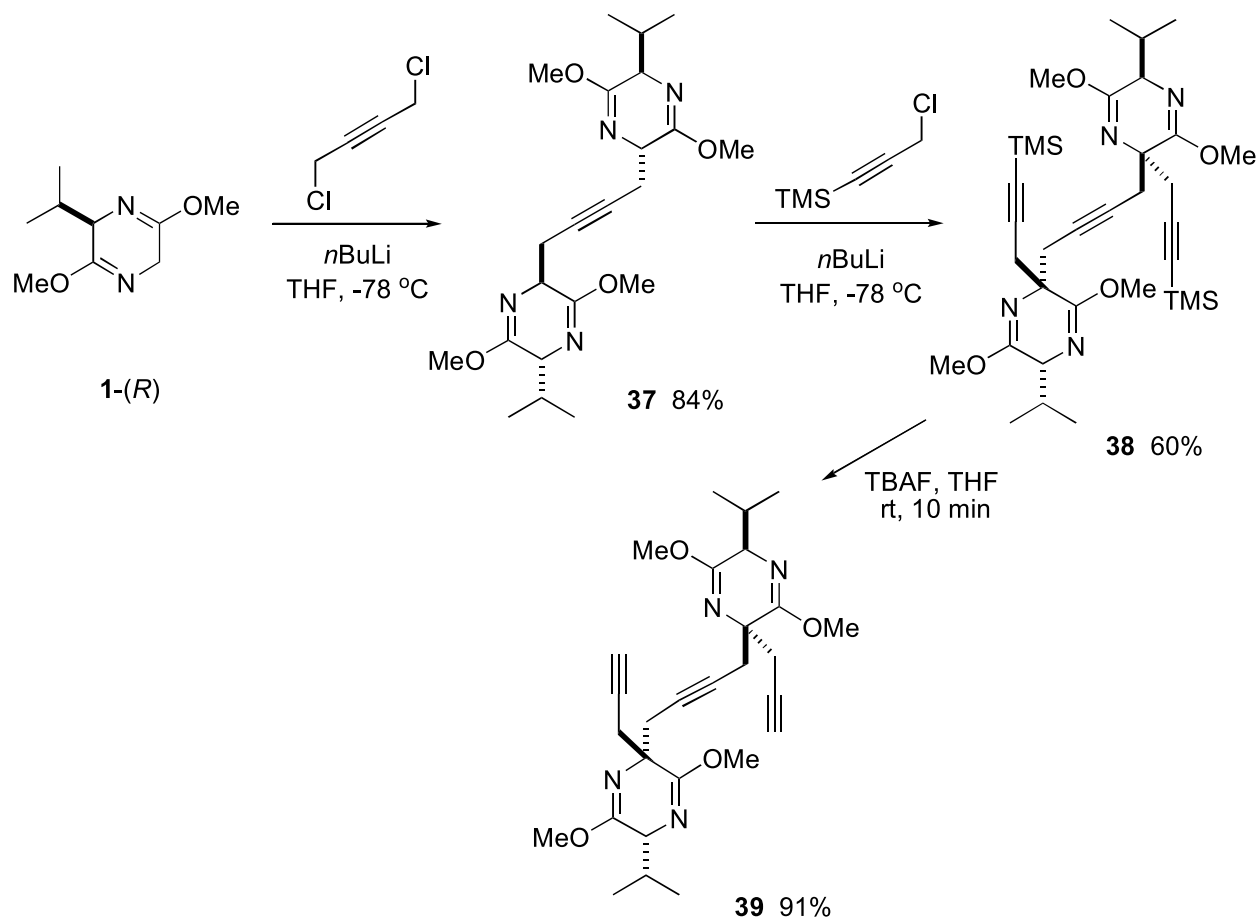
A C_4 -alkyne bridge can be introduced by bisalkynylation of the lithiated species derived from the chiron **1-(R)**



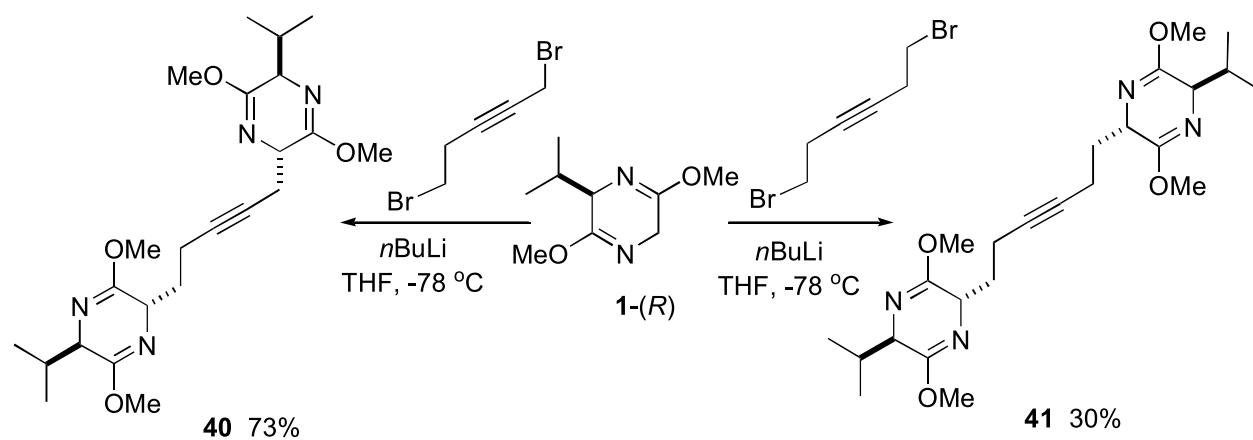
Scheme 11. Refs: **34abghi** [32]; **34ce** [21]; **34df** [22]; **36ab** [21]

with 1,4-dichloro- or 1,4-dibromo-2-butyne [35]. The reaction is stepwise. The first formed monoalkynylated product becomes the substrate for the second alkylation reaction. Despite the two different reaction steps, high yields and high diastereoselectivity are obtained in the

formation of the bridged product **37**. The subsequent two-step alkylation reaction is highly stereoselective in that the electrophile enters the heterocycle *trans* to the isopropyl group. Only one stereoisomer is observed. The acidic terminal acetylenic hydrogen is removed by silyl



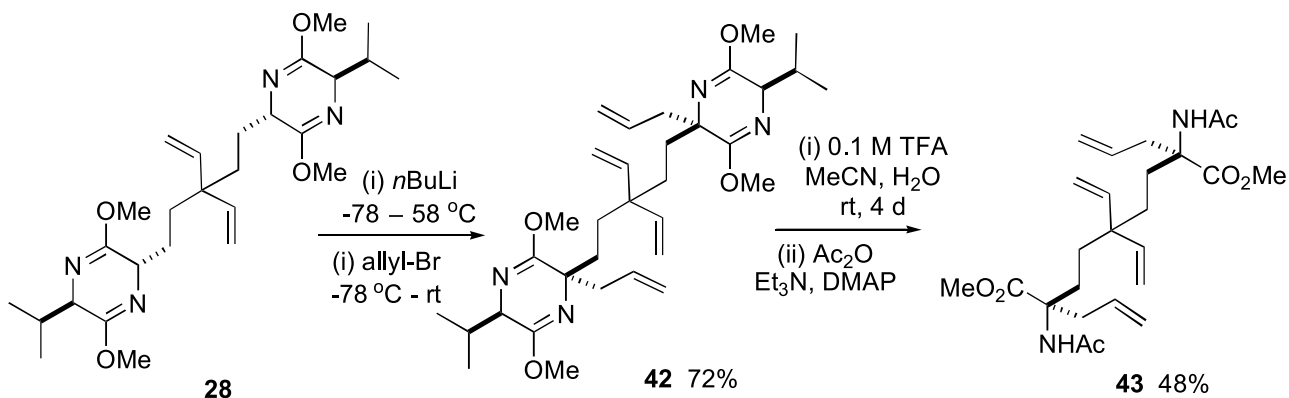
Scheme 12. Refs: **37** [35]; **38**, **39** [29]



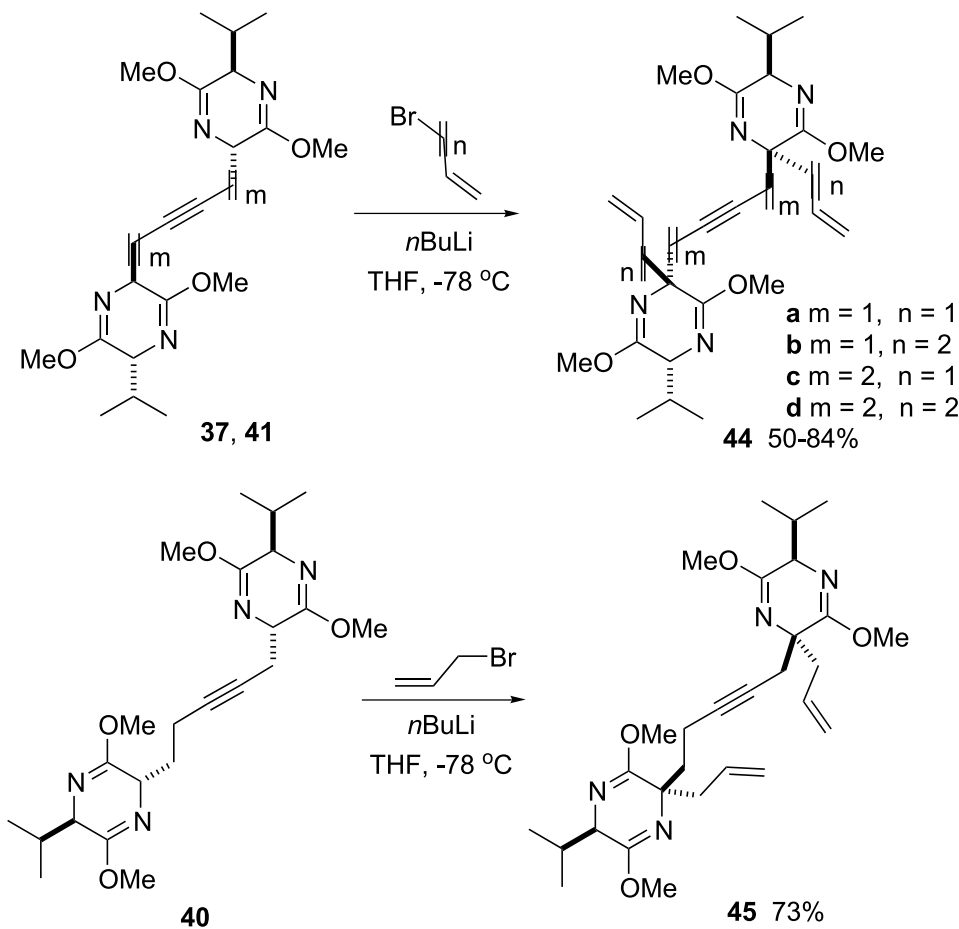
Scheme 13. Refs: **40** [36]; **41** [35]

protection, the reagent being a silylpropargyl chloride. The bisalkynylated product **38** becomes available in 60% yield. The deprotected triyne **39** is subsequently prepared by removal of the TMS-protection by treatment of compound **38** with tetrabutylammonium fluoride (TBAF) [29].

With 1,5-dibromo-3-pentyne (Scheme 13), competitive elimination of HBr occurs after monoalkylation at the propargylic carbon leading to a product with a conjugated enyne 5-substituent(NMR). But the major product, 73%, is the bridged structure **40** [36].



Scheme 14. Refs: **42**, **43** [23]



Scheme 15. Refs: **44abcd** [35]; **45** [36]

The symmetrically bridged ynedienes **44** in Scheme 15 are available from the bridged substrates **37** and **41** which are lithiated and alkenylated in high yields and high diastereoselectivity [35]. The C₅-bridged product **45** in the same way is prepared from the alkyne-bridged substrate **40** by an allylic alkylation of the dilithiated species [36]. The products are purified by flash chromatography. The pure stereoisomers are used as substrates in the subsequent reactions.

The poor yields in the domino RuCl₂(CHPh)(PCy₃)₂ catalysed RCM reactions with the substrates **44** and **45** (*vide infra*), can be circumvented by prior hydrolysis and ring-opening of the bulky chiron moieties. Mild acidic conditions are used, such as 0.1 M TFA in aqueous acetonitrile. The products in Scheme 16 are the bridged amino acids which are isolated as the C₄-bridged diacetamide **46** [35], and the C₅-bridged diacetamide **47** [36], in yields 60–95%. Free amino groups are not compatible with the ruthenium catalyst, and the amino acid esters are therefore converted into amides by means of acetic anhydride in the presence of DMAP. The acetyl group was chosen as the most convenient protection group for use in the subsequent development of cyclisation studies. Other compatible protecting groups for peptide work are expected to be equally applicable. The triyne **39** in the same manner can be converted to the *N*-acetylated bridged amino acid **48** for use in cycloisomerisation reactions [29].

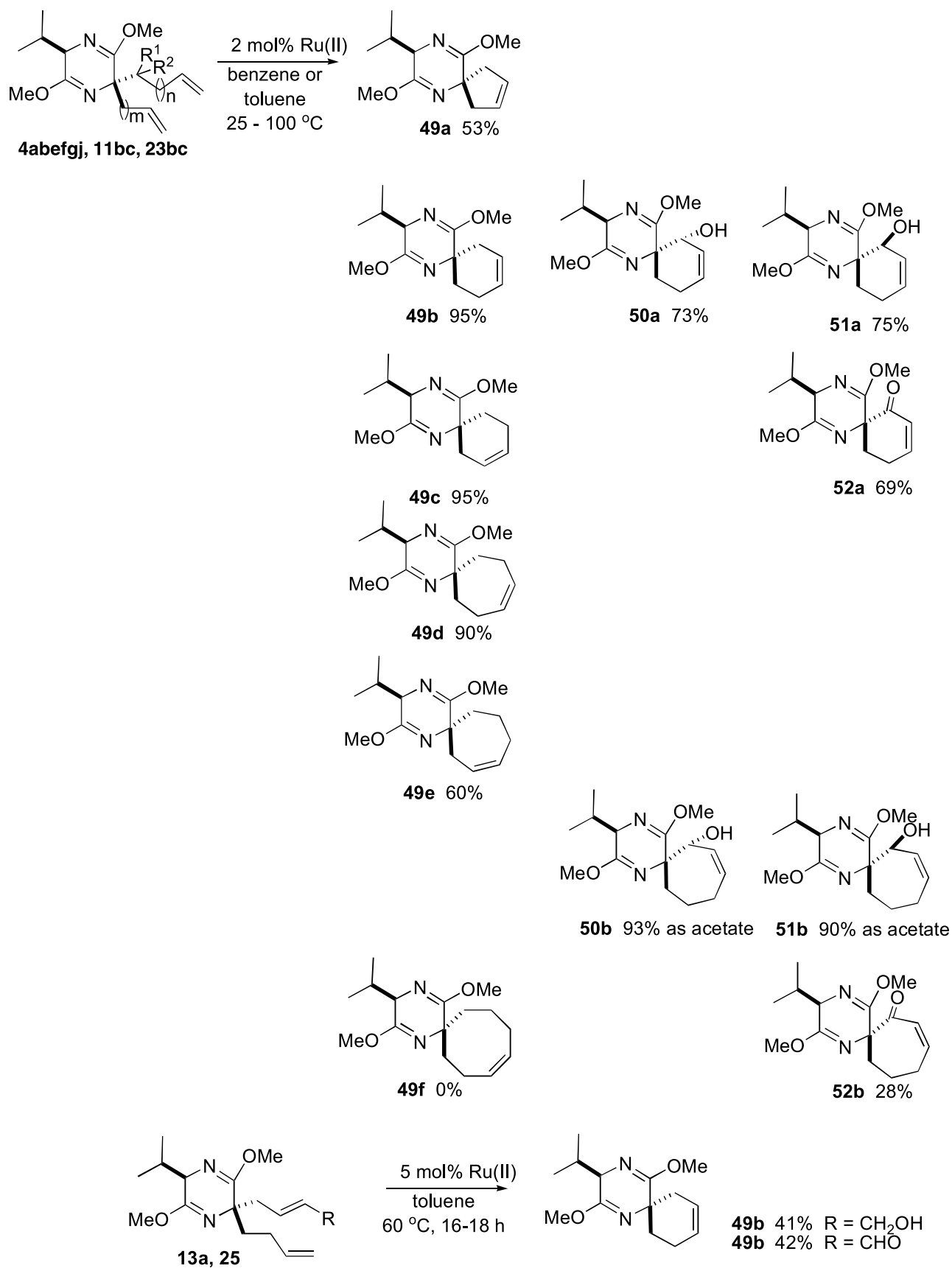
2.2 Cyclisation reactions

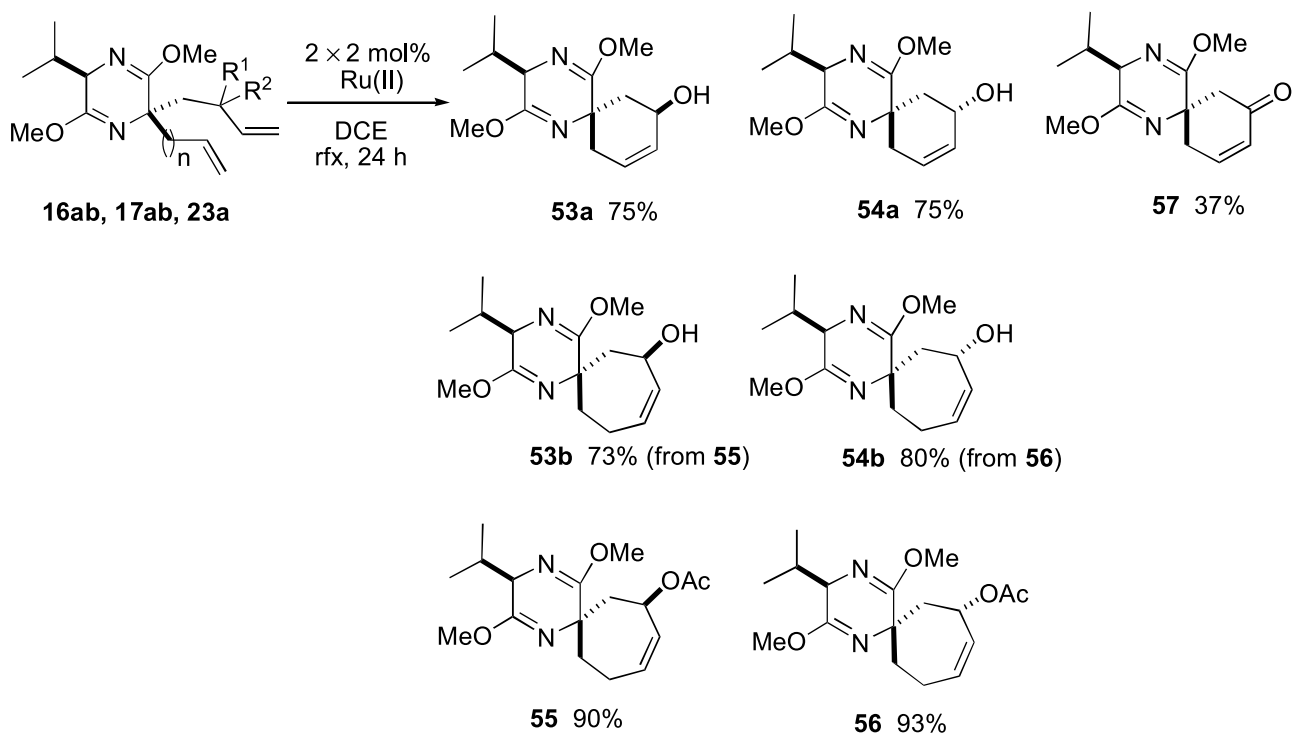
2.2.1 Ruthenium catalysed cyclisations by RCM and cycloisomerisation reactions

The Grubbs ring-closing metathesis (RCM) methodology [37, 38] using as catalyst bis(tricyclohexylphosphine)benzylidene ruthenium has proven highly compatible with bislactim ether substrates as seen in the preparation of the heterocyclic spiranes in Scheme 17, generally in high yields. The spiroannulated cycloalkenes **49** are restricted in ring-size to unsaturated five- to seven-membered rings, presumably because of the reversible nature of metathesis reactions. Thermodynamic factors will largely control whether oligomerisation or cyclisation can occur which disfavour three-, four- and eight-member rings. In the present system no cyclisation was observed in an attempted preparation of the all carbon eight-member structure **49f**. Heteroatoms incorporated into an eight-member ring, however, may be prepared by this methodology [39, 40]. Larger ring structures are within reach, but their chemistry has not been explored in the present system. Formation

of the spiroannulated six- and seven-membered rings **49b–49e** proceeds readily in remarkably high yields. Formation of the five-membered ring structure **49a** requires higher temperature and longer heating time and the yield is significantly lower than for the six- and seven-membered ring structures [14]. When the substrate for five-membered ring formation is substituted by an α -hydroxy group, no RCM reaction was seen. However, formation of six- and seven-membered rings, **50ab**, proceeds readily [24]. The reluctance towards five-membered ring formation is attributed to steric interactions. Indirectly, this is overcome by prior hydrolysis of the appropriately substituted chiron to the corresponding amino acid ester followed by *N*-protection. On the other hand, the new *N*-protected substrates, **61** and **63** in Scheme 20, react readily under RCM conditions to form the cyclic amino acid **62** [14], and the dipeptide **64** [24]. In general, cyclic α -amino acids are expected to become available by this methodology from appropriately substituted amino acids. In the α -hydroxylated series, the RCM reactions are effected in benzene solution without protection of the hydroxyl group in the substrates leading to the heterospiranes **50** and **51** (Scheme 17). The latter products differ only by the configuration at the epimeric hydroxyl carbon. The six-member structures **50a** and **51a** are formed in similar high yields, but the α -(*S*)-isomer **11b** (Scheme 4) reacts significantly faster than the (*R*)-isomer **11b**. 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 **50b** and **51b**, are also formed from **11c** in similar reactions but in lower yields than in the six-membered series. Five-membered ring formation was not observed from either hydroxy substrate **11a** (Scheme 4). Again this is assumed to be caused by steric interactions which disfavour conformations required for the RCM reaction to take place.

Dienes with an electron-withdrawing group attached to the inner olefinic carbon, reacts sluggishly under RCM conditions, either for steric reasons, or because of electron withdrawal from the double bond. Steric effects are minimised in an α,β -unsaturated ketone. The ketones **23** possess a strongly electrophilic double bond with low steric effects. Six-membered ring formation **52a** proceeds readily. A significantly lower RCM transformation is observed in seven-membered ring **52b** formation. For comparison, in RCM reactions leading to the corresponding allylic alcohols **50** and **51** under similar conditions, six-membered

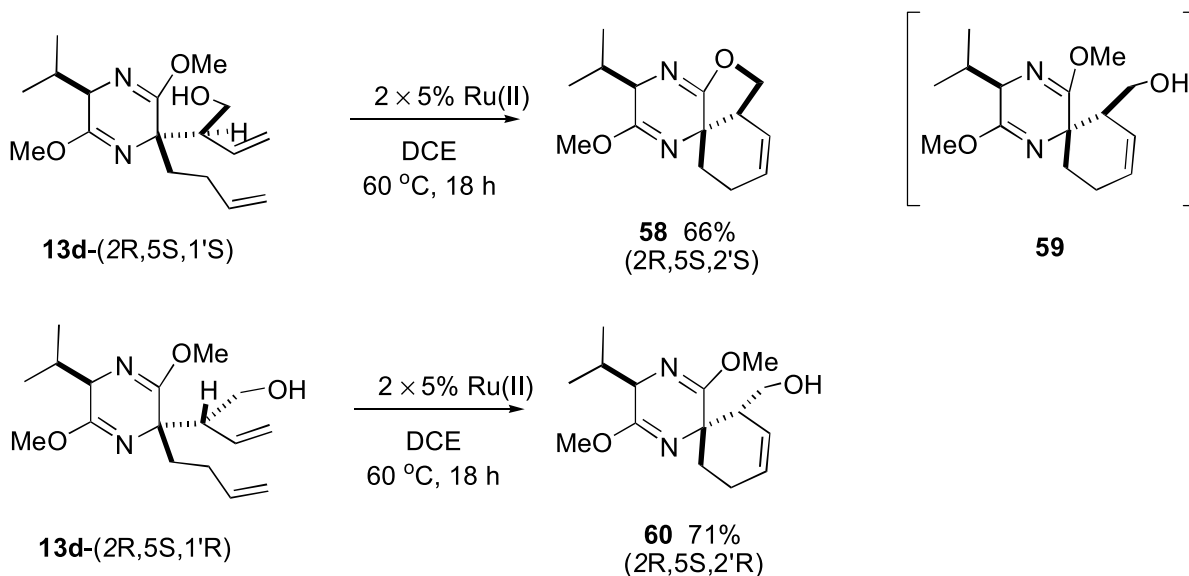
Scheme 17. Refs: **49abcdef** [14]; **50ab, 51ab** [24]; **52ab** [30]

Scheme 18. Refs: **53ab**, **54ab**, **55**, **56** [26]; **57** [41]

ring allylic products are formed in *ca.* 75% yield from both epimeric alcohols, and seven-member ring allylic products in *ca.* 90% yield.

The hydroxy group in the compounds in Scheme 18 has been moved one carbon atom further away from the 5-position in the dihydropyrazine. The epimeric six-membered ring alcohol isomers are both produced in *ca.* 75%

yield. In the corresponding butenyl alcohol series, which should yield the seven-membered ring structures **53b** and **54b**, no reaction took place. After protection of the free hydroxy groups as acetates, however, the RCM proceeds readily to furnish the seven-membered ring products **55** and **56** in *ca.* 90% yields [26]. It is remarkable that the free hydroxy group is compatible in the RCM

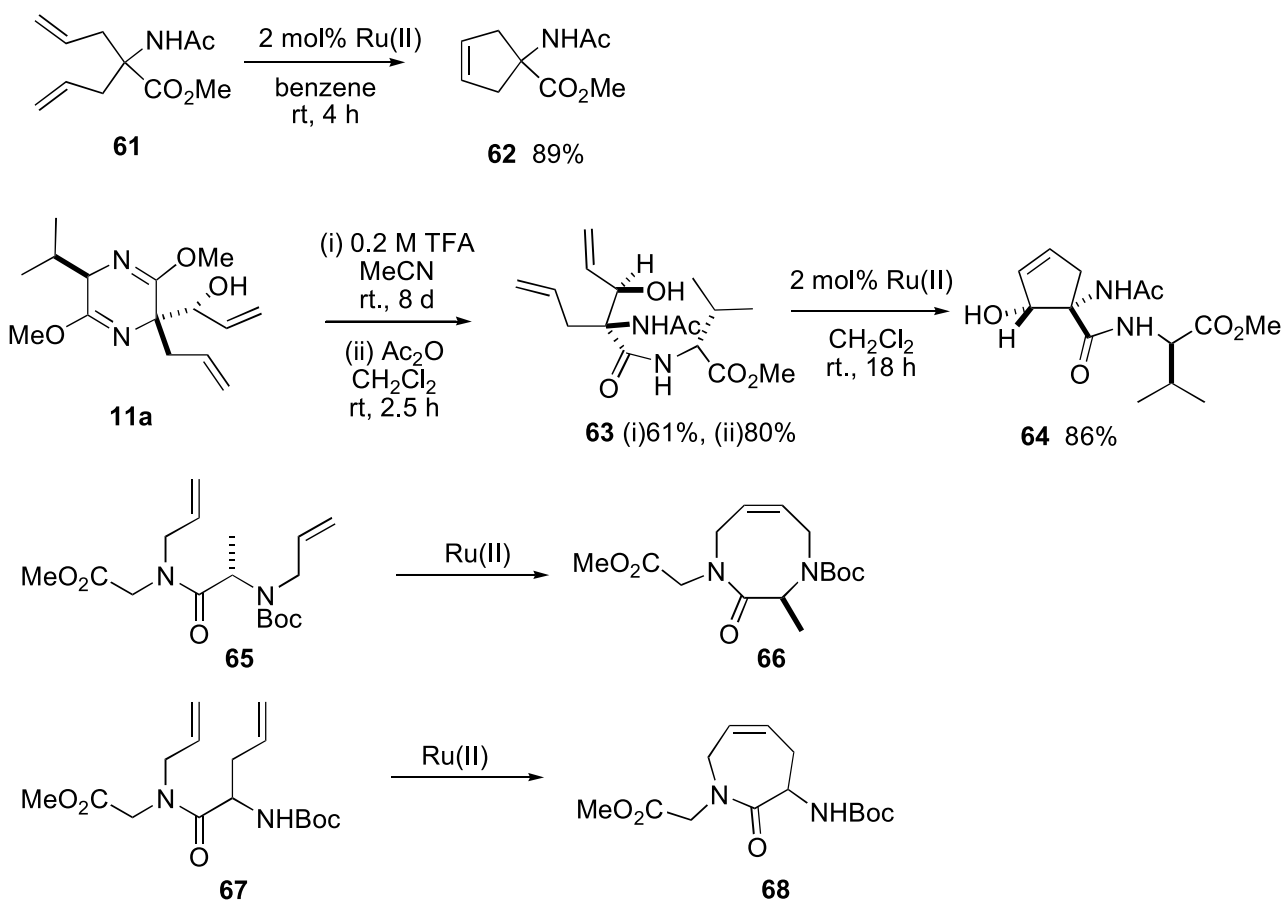
Scheme 19. Refs: **58**, **59**, **60** [27]

reaction that leads to six-member ring formation, whereas the corresponding reaction is completely blocked for seven-membered ring formation. It will be recalled that in the α -hydroxy series, 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 in strongly populated conformations where the alkenyl groups are held too far apart for the RCM reaction to take place. Alternatively, the difference in behaviour may depend on the geometry and distance for interaction between the heteroatom and the metal center making the catalytic system less reactive.

The rate reducing effect of an oxo group is also apparent in the RCM reaction of the α,β -unsaturated substrate **23a** in the formation of the cyclic α,β -unsaturated ketone **57** which was obtained in 37% yield after heating at 70 °C for 4 days [41]. The low reaction rate stands in contrast to the ready RCM reaction of the corresponding allylic alcohol **16a** and **17a**.

In the series of cyclic homoserine analogues in Scheme 19, the hydroxy group is exocyclic in the form of a hydroxymethyl substituent. The precursors for the RCM reactions are the stereoisomers **13d** with a free hydroxy group. The tricyclic spirane **58** is formed from compound **13d**-(2*R*,5*S*,1'*S*), which requires that the hydroxymethyl substituent is located in the vicinity of the lactim ether carbon at C-6. Under the conditions of the reaction, transesterification in the bislactim moiety occurs with expulsion of methanol. Lewis acid catalysed interchange of the alcoholic group is excluded for steric reasons in the other isomer **13d**-(2*R*,5*S*,1'*R*). The product is the hydroxymethyl spirane **60**. The yields are similar in both cyclisations [27]. When the hydroxy group is located in the ring, no ring closure with loss of methanol is observed (*vide supra*).

RCM reactions proceed readily with appropriate amino acid dienes as in the case of the *N*-protected diallyl substrate **61** in Scheme 20 [14]. In a second example, the RCM reaction is also exemplified in the preparation of a



Scheme 20. Refs: **62** [14]; **64** [24]; **66**, **68** [39]

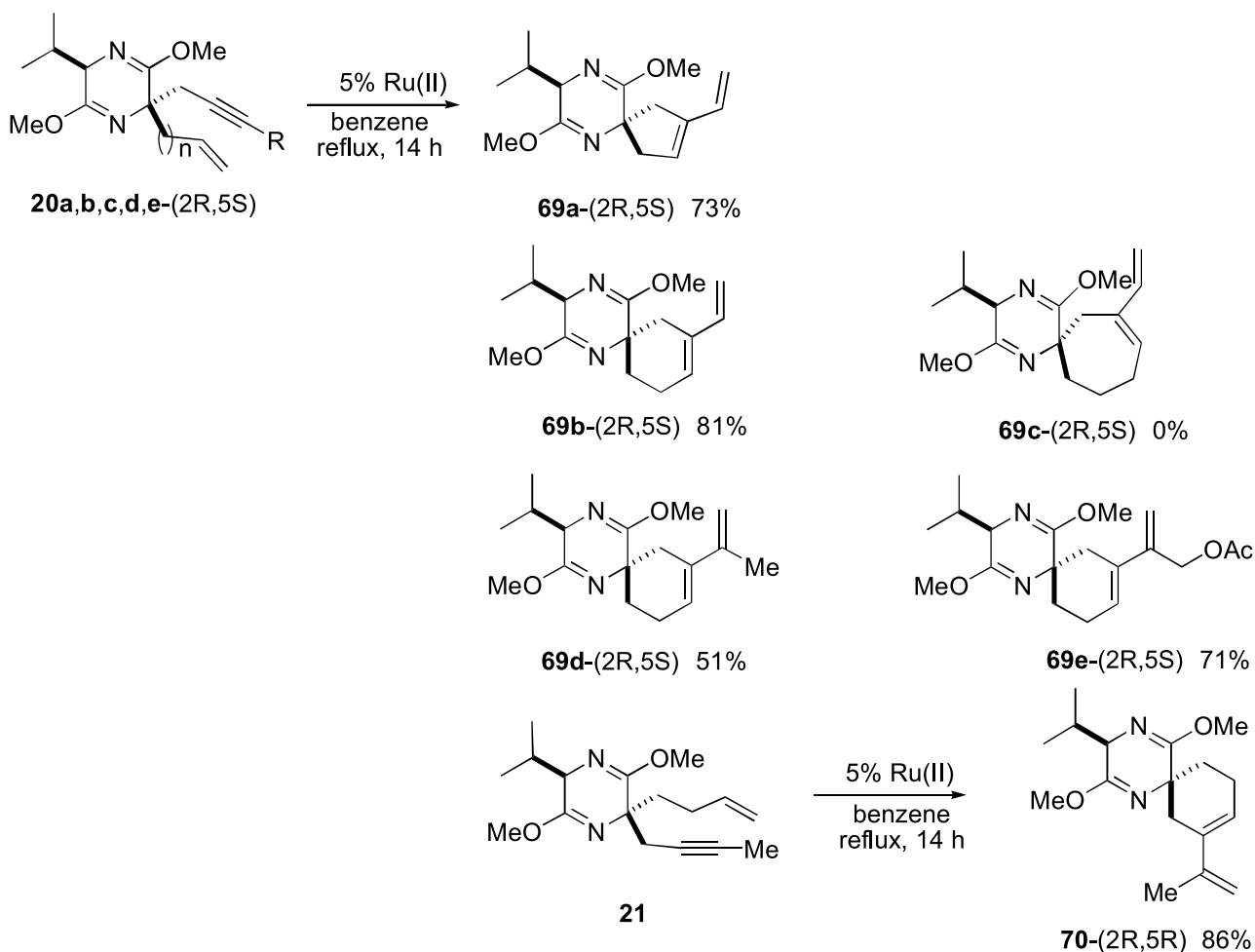
dipeptide **64**. Its precursor **11a** does not undergo the RCM reaction under standard conditions involving formation of a five-membered spirane (*vide supra*). After hydrolysis of the heterocyclic ring and *N*-protection, the RCM reaction proceeds from the protected dipeptide **63** in high yield to furnish the five-membered ring dipeptide **64**. This finding suggests that in general RCM reactions can be effected in appropriately dienyl substituted peptides [24].

For comparison, a diaza eight-membered ring **66** has been described where the dipeptide **65** was initially prepared for the RCM reaction [39, 40]. In another example, the molecule is a constrained Ala-Gly surrogate dipeptide **67**. The RCM product is an azepine derivative **68** [42].

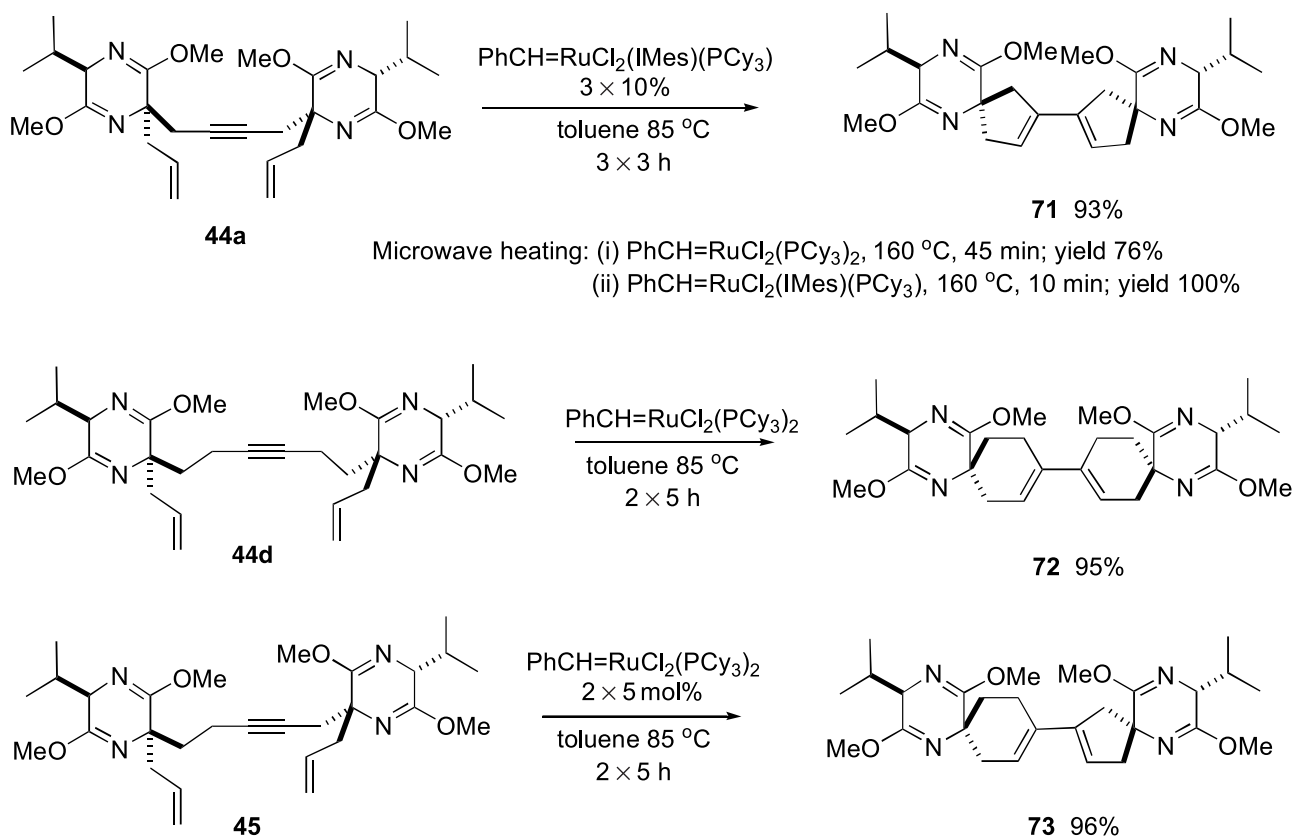
Enynes **20** in Scheme 21 have been studied as substrates for the construction of amino acid conjugated diene precursors **69** with one exocyclic double bond. Mechanistically, the enyne reactions differ from the RCM reactions. In the dienes, the terminal methylenes are expelled as ethylene during the ring closure. In the enyne reactions,

the terminal alkylidene moiety of the alkene is transferred onto the alkyne carbon in the formation of cyclic diene. In this manner the 1-vinylcyclohexenyl derivative **69b** is formed in 81% yield and the five-membered derivative **69a** in 73% yield. The ready formation of the cyclopentenyl derivative **69a** differs from reactions of dienes where spirane five-membered rings were difficult to effect. Another important difference was the failure to form the seven-membered ring product **69c** whereas this ring size was readily formed from dienes. Also, it has been reported that heterocyclic rings such as azacycloheptene are formed under similar conditions. The difference in behaviour of the ruthenium catalyst towards dienes and enynes supports two mechanistically different pathways (*vide supra*).

The enyne **20d**, with a terminal methyl group, provides the cyclic product **69d** in medium yield whereas the product **70**, from the (*2R*)-**21** substrate, is obtained in high yield. The difference in product formation may be caused



Scheme 21. Refs: **69abcde**, **70** [28]



Scheme 22. Refs: **71** [36, 43]; **72** [35]; **73** [36]

by different non-bonded interactions in the formation of the two diastereomers **69d** and **70**. If desirable, a more efficient process for the generation of **69d** can be effected by changing the configuration of the chiron. Finally, the alkyne substrate can carry a hydroxymethyl group at the terminal alkyne carbon after protection as an acetate. The hydroxylated product **69e** is obtained in a good yield [28].

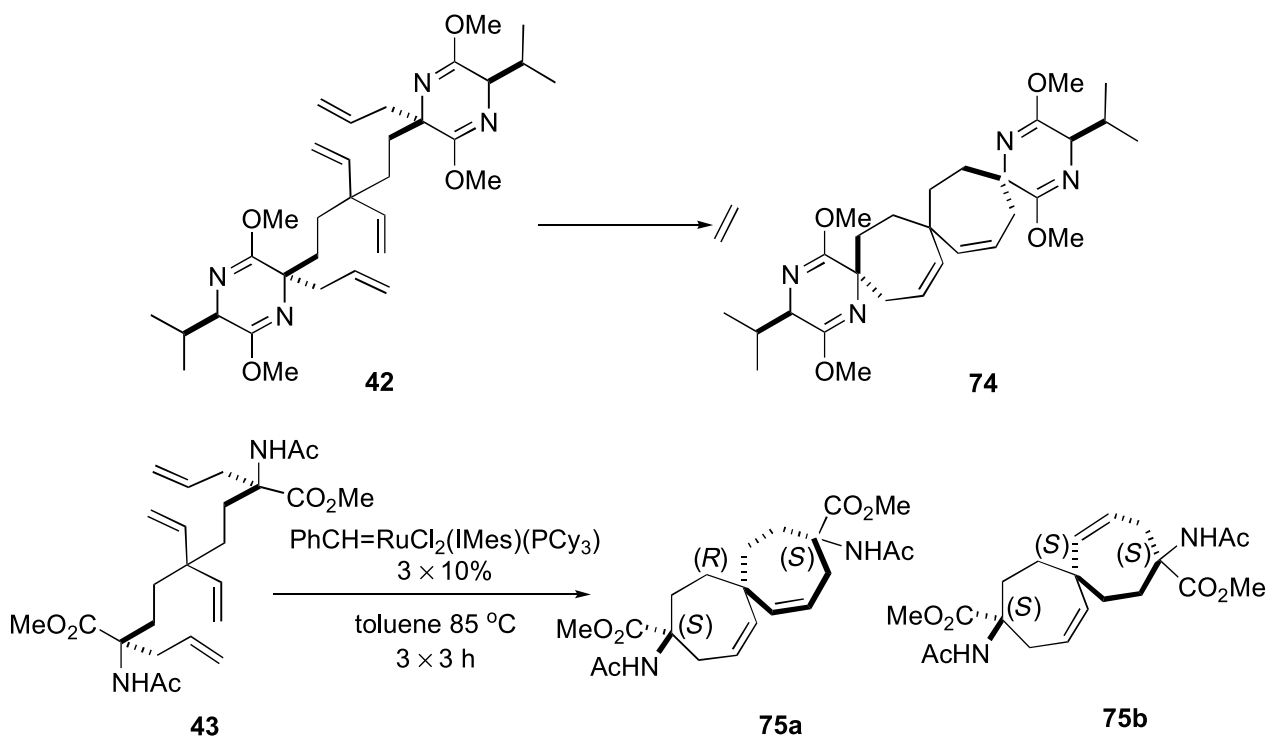
Scheme 22 shows attempts to construct dicarba analogues of cystine precursors by cyclisation of the butyne **44a**, the pentyne **45** and the hexyne **44d** which are bridged and dialkenylated bis(chirons). The RCM reaction of the butyne substrate **44a** with the original Grubbs catalyst, provides the RCM product in 10–20% after prolonged heating at 85°C . The reaction proceeds readily, however, when the distance between the chiron moieties is increased from four to five or six carbon units [35, 36]. In fact, the change in the bridge length from four to six carbon units changes the yield of the reaction from *ca.* 10% (**71**) to *ca.* 95% (**72** and **73**). In these experiments the RCM reactions are run by heating in toluene at 85 – 90°C . Below this temperature the reaction rate is slow. The Grubbs-I catalyst is gradually deactivated at the tem-

perature which is required to effect the cascade reaction. 5 mol% catalyst was originally added, and the same amount of catalyst is added after 5 hours. It is suggested that steric congestion is responsible for the failure in the former cases.

With the more active Grubbs-II catalyst system, $\text{PhCH}=\text{RuCl}_2(\text{IMes})(\text{PCy}_3)$, the RCM reaction for the most crowded substrate **44a** was repeated. The reaction was run in toluene at 85°C . with 10 mol% catalyst added at three hours intervals three times which provides the cascade product in very high yield, 93% [36].

The thermal instability of ruthenium(II)-catalyst systems under prolonged heating at 85°C in cycloisomerisation reactions has been circumvented by working under microwave conditions. The temperature is increased to 160°C , and the reaction time reduced to minutes. Sufficient catalyst survives heating at a high temperature for a short time, and the product yield is much improved. The ruthenium-catalysed domino-reaction of the diyne substrate **44a** is run in an inert atmosphere. The IMes-ligated Grubbs-II catalyst was the better [43].

The crowded C_5 -bridged tetraene **42** in Scheme 23 is unreactive towards catalysis by the original Grubbs-I sys-



Scheme 23. Ref: 75ab [23]

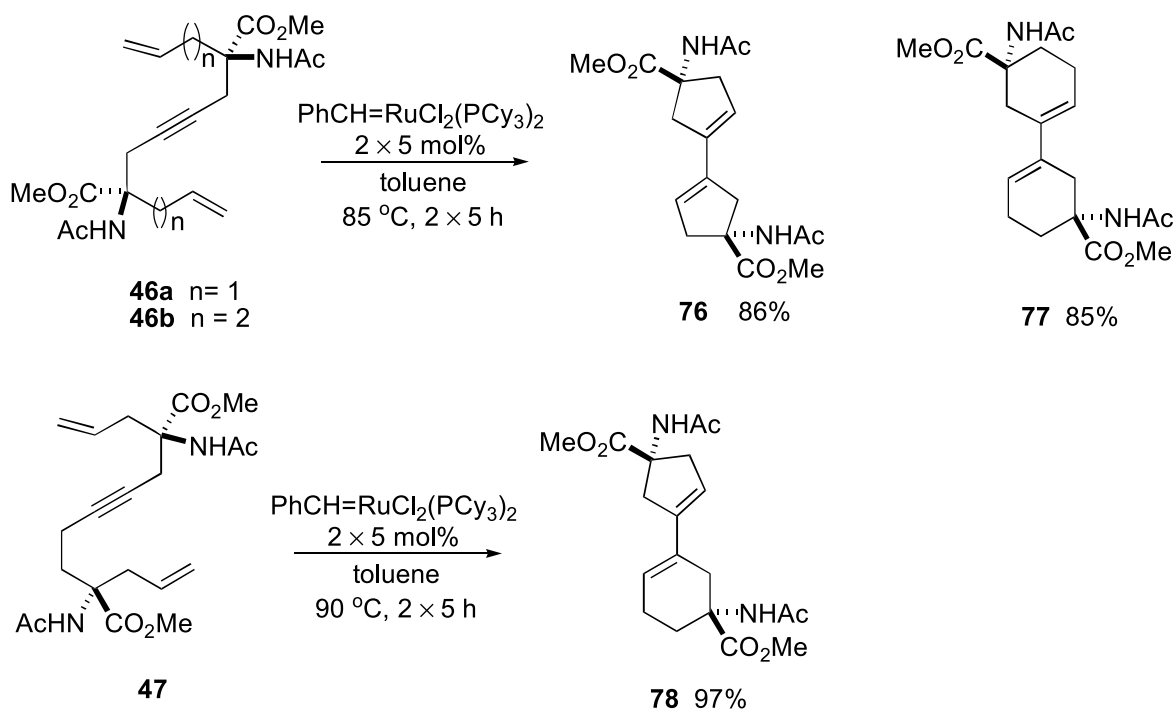
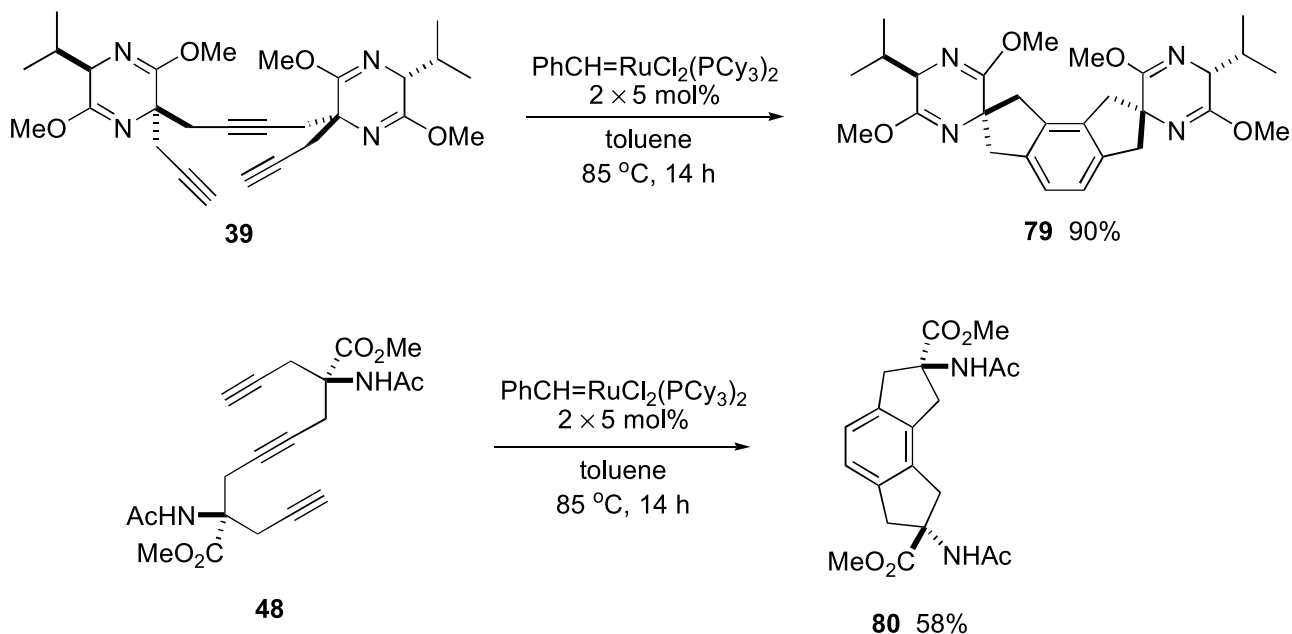
tem, nor did it react in the presence of the more active Grubbs-II catalyst system. Hence the pyrazine units have been hydrolytically cleaved. The product **43** is subsequently subjected to the Grubbs-II catalyst at 85 °C in toluene. The RCM reaction leads to formation of the spiroane-bis(amino acid) derivative **75** as a diastereomer mixture. In the spiroannulation, a new stereogenic center is formed at the spirocenter. The two rotational isomers are formed in the ratio 2:3. The diastereomers can be separated by flash chromatography on a silica gel column [23].

Scheme 24 shows series of cascade reactions of ynediene substrates with the formation of bridged bis(α -amino acid) derivatives. The substrates are hydrolytic products from the bridged bislactim ethers previously discussed. Dicyclopentenyl and dicyclohexenyl bis(α -amino acid) derivatives, **76** and **77**, are obtained in high yields from the symmetrically bridged substrates [35]. With the unsymmetrical ynediene bridged structure **47**, the RCM product **78** can be isolated in almost quantitative yield, 97%.

The preparation of highly rigidified dicarba analogues **80** of cystine involves methodology for the construction of *as*-indacene-bridged bis(α -amino acid) derivatives by a Ru(II)-effected cascade RCM reaction with an appropriate triyne as substrate (Scheme 25). The amino-protected triyne **48** can be cycloisomerised to the *as*-indacene-bridged

bis(α -amino acid) derivative **80** by a Ru(II)-mediated cascade RCM reaction. The cascade reaction of the congested triyne **39** in toluene at 85 °C gives the bis-spiro-pentacyclic product **79** in high yield, 90%. At lower temperature, there is no reaction, or the reaction is very slow. Catalyst (5 mol%) is added twice. A second addition of catalyst is necessary to compensate for thermal instability of the catalyst at the temperature of the reaction. It will be recalled that when the same catalyst and reaction conditions are used with the analogous ynediene substrate **44a** (Scheme 22), hardly any cascade reaction is observed, unless the more active catalyst system is used. With microwave heating, an almost quantitative conversion is achieved in the course of minutes. For the triyne substrate **39**, the reaction with the Grubbs-II catalyst is inferior to reactions with the standard Grubbs-I catalyst [43].

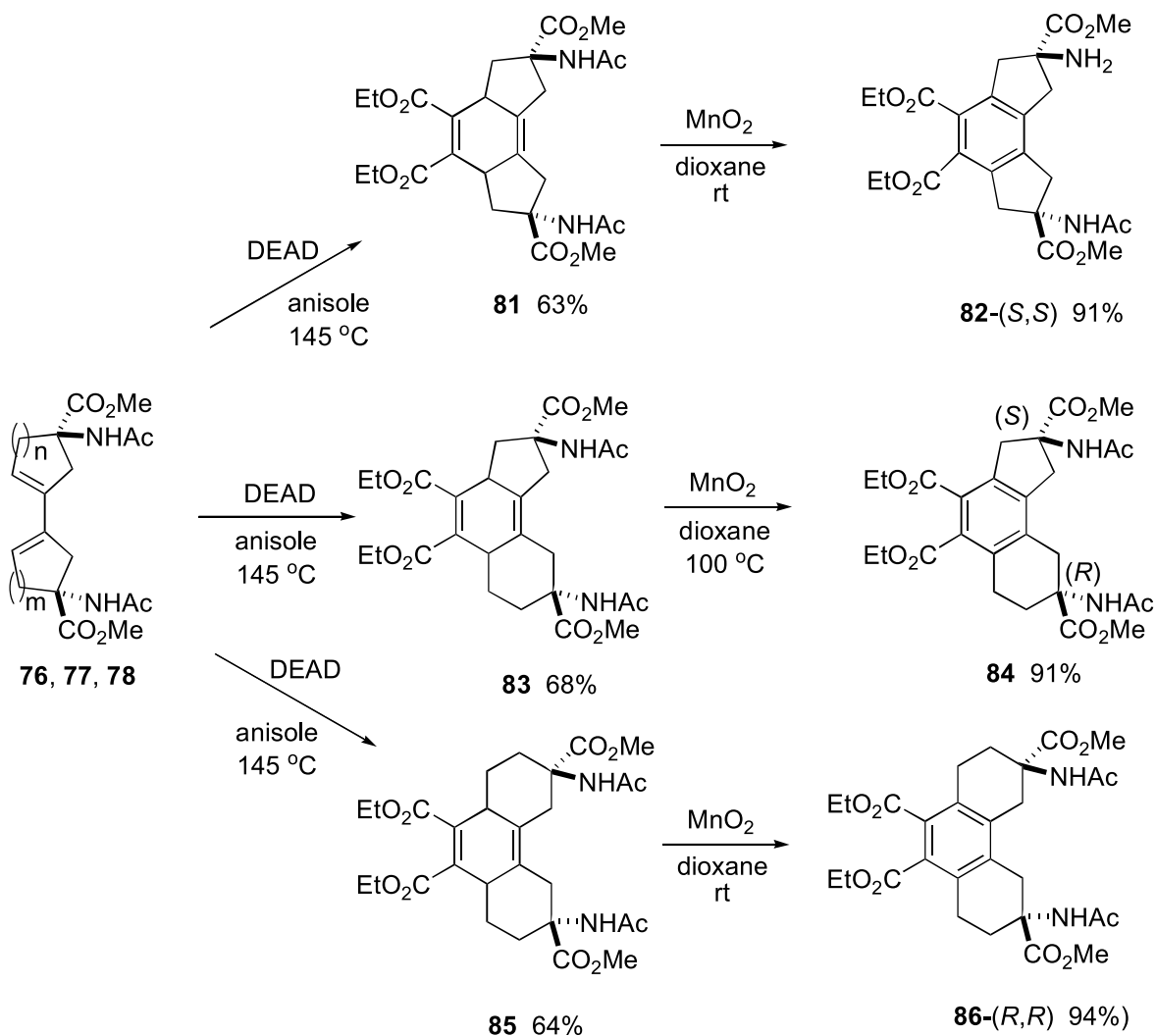
A more flexible way for varying the size of the annulated rings is indicated in Scheme 26 in the structures **82**, **84** and **86** or possibly their dihydro precursors. Diels-Alder reactions are run in anisole at 145 °C with the appropriately substituted dienes **76**–**78**. For simplicity, a symmetrical and highly reactive dienophile, diethyl acetylenedicarboxylate (DEAD), are used to demonstrate the methodology. In the bis(cyclopentenyl)diene substrate **76**, a mixture of the cycloadduct **81** and its aromatised

Scheme 24. Refs: **76**, **77** [35]; **78** [36]Scheme 25. Refs: **79** [29, 43], **80** [29]

benzene analogue **82** are obtained in a total yield of 63%. The product mixture, when treated with manganese dioxide, provides the benzo derivative in a yield of 91%. The other isomers react similarly. Both the symmetrical **82** and **86**, and unsymmetrical **84** derivatives become available by this approach [36].

2.2.2 Palladium catalysed cycloisomerisation reactions

Some cycloisomerisation reactions mediated by Pd(0)-catalysis are shown in Scheme 27. Palladium-catalysed cycloisomerisation of enynes has been developed extensively by Trost [44]. An adaption of cycloisomerisation of



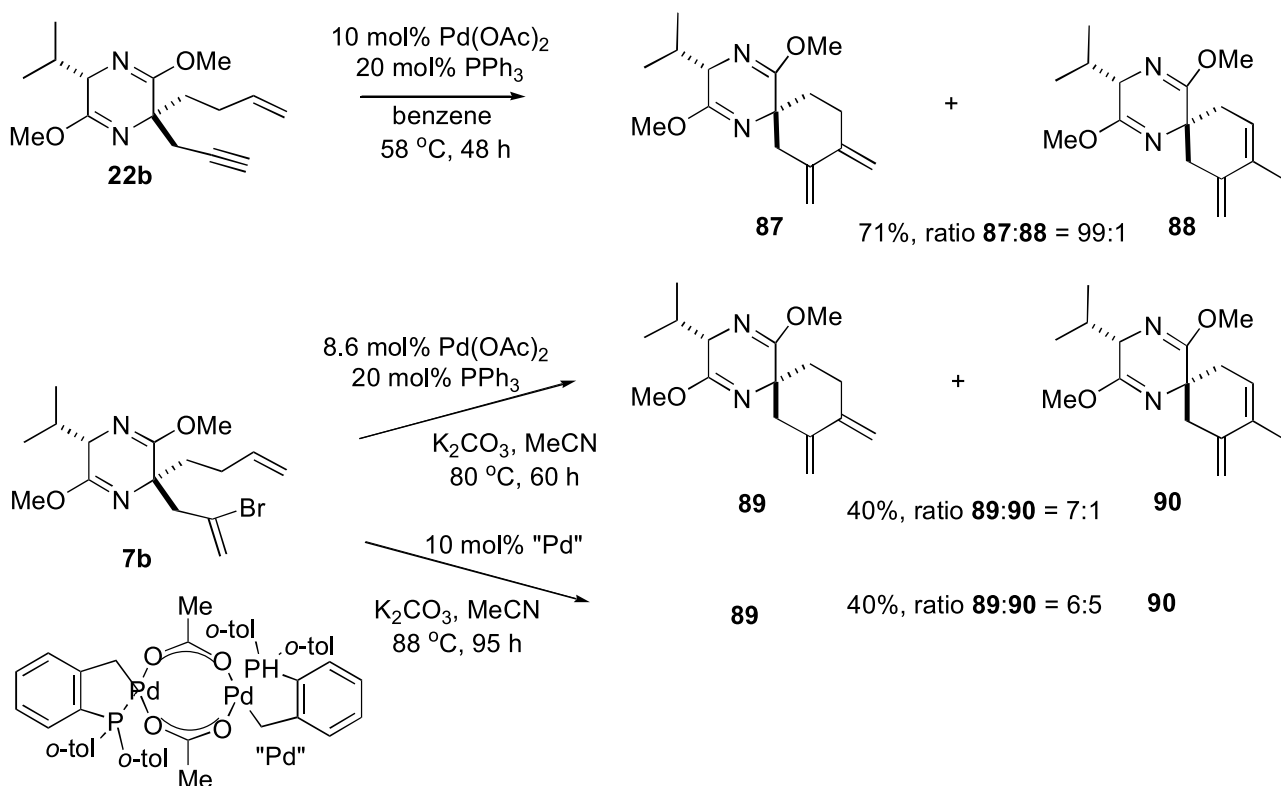
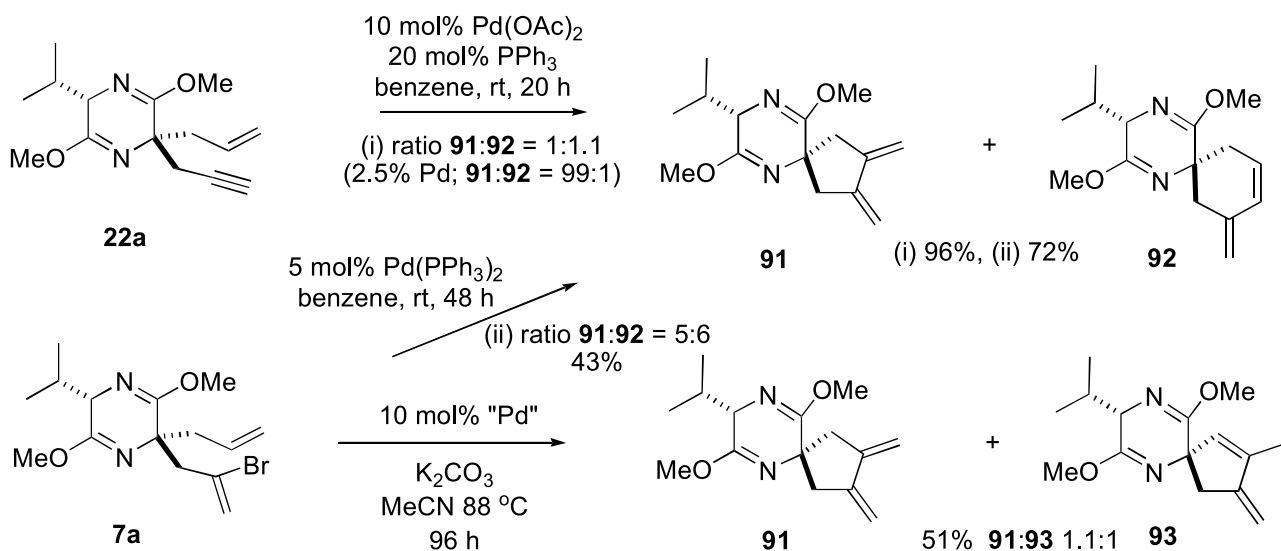
Scheme 26. Refs: 82, 84, 86 [36]

an 1,7-enyne is shown in the preparation of cyclic α -amino acid precursors in Scheme 27. Mechanistically, the Pd(0)-catalyst system will react with an acid to form a Pd(II)-hydride which adds to the triple bond. The metal becomes attached to the inner carbon triple bond and becomes coordinated to the double bond. 6-*Exo-trig* addition leads to the 3,4-dimethylene product **87** and its endo-olefinic isomer **88**, isomer ratio 99:1. No product from *endo-trig* addition with seven-membered ring formation was observed. The isomer ratio varies with the solvent used. In THF the ratio is 10:1. The nature of the catalyst system seems less important except for the Herrmann catalyst (*vide infra*) which produced an isomer ratio 1.2:1. The same products **89** and **90** are formed from the corresponding bromovinyl substrate **7b** in a ratio 7:1. With the Herrmann palladacycle, which has been recommended for

Heck reactions because of good thermal stability and high activity, the ratio becomes 6:5. In no case was formation of a seven-membered ring detected [17].

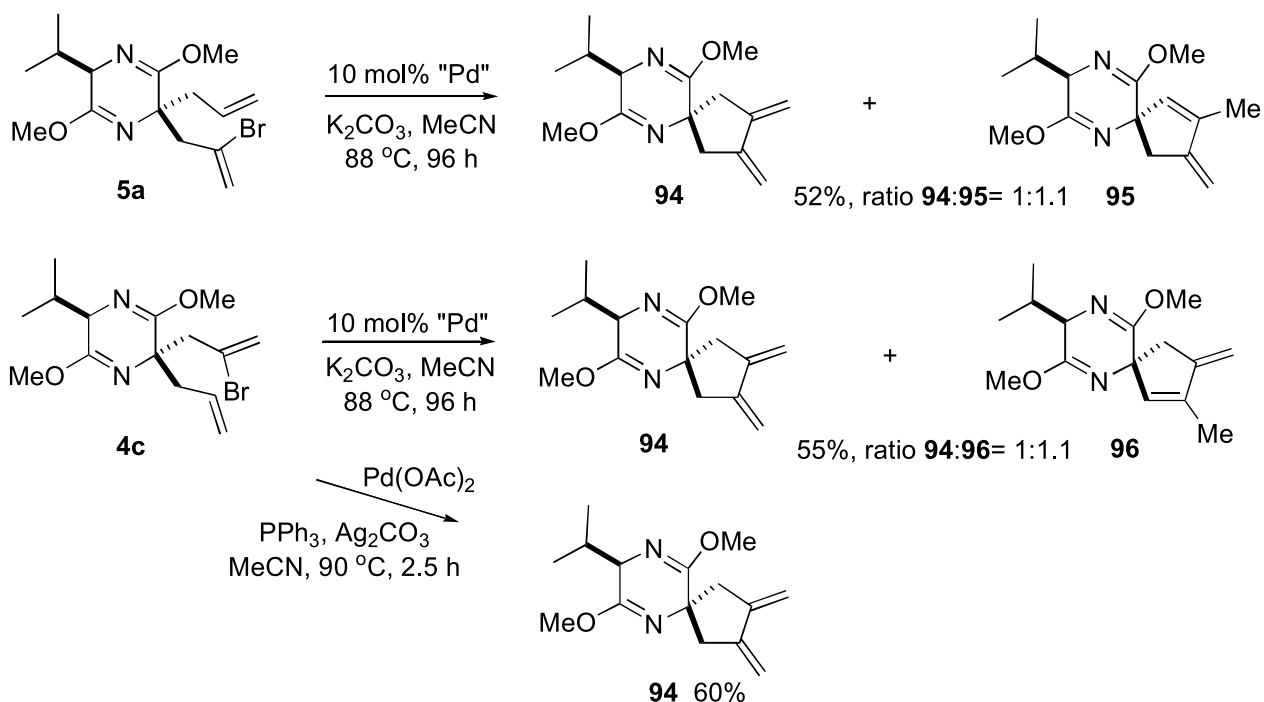
In the cycloisomerisation of the 1,6-enyne **22a** in Scheme 28 both the five- and six-membered ring structures **91** and **92** are formed. The product ratio varies with changes in the ligands and palladium catalyst system. In the example given, the product ratio was almost 1:1. The ratio can be changed by variation in the catalyst system. Mechanistically, 5-*exo-trig* addition leads to the five-membered ring product **91**, 6-*endo-trig* to the six-membered product **92**. In the intramolecular Heck reaction from the corresponding bromovinyl substrate **7a**, a similar ratio of products **91** and **93** results [17].

With the palladacycle catalyst system in the Heck reaction in Scheme 29, the products are two five-membered

Scheme 27. Refs: **87**, **89**, **90** [17]Scheme 28. Refs: **91**, **92**, **93** [17]

ring systems **94** and **95** which are formed in almost equivalent amounts. The latter product, with one endo-cyclic double bond had not been observed with the previous catalyst systems. Formation of the cycloisomer **95** could

not be rationalised by partial isomerisation of the dimethylenecyclopentane **94**, as the kinetic product, to the thermodynamically more stable cycloisomer **95**. Attempts to effect isomerisation of the double bond in isomer **94**

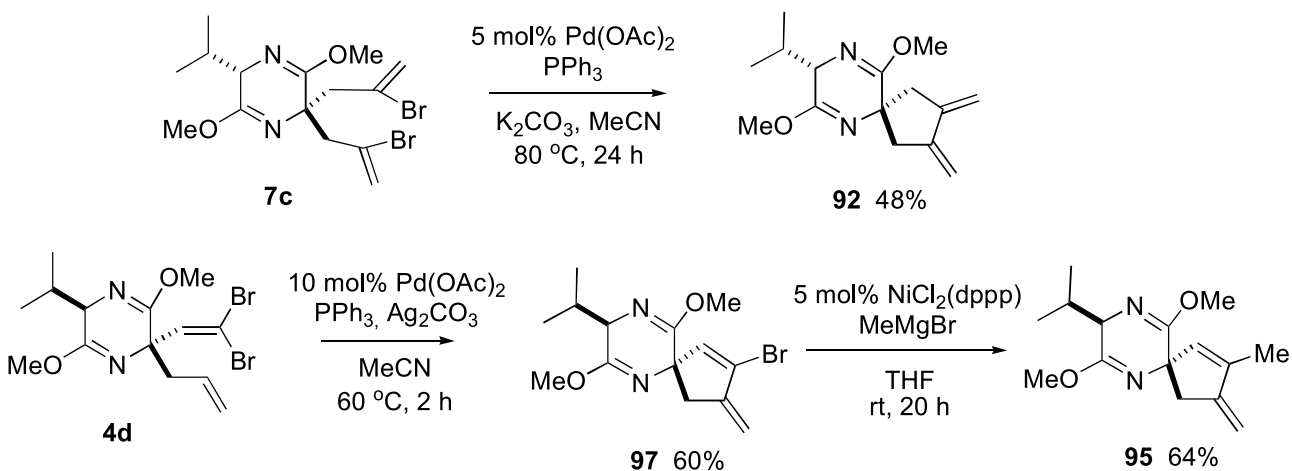
Scheme 29. Refs: **94**, **95**, **96** [20]

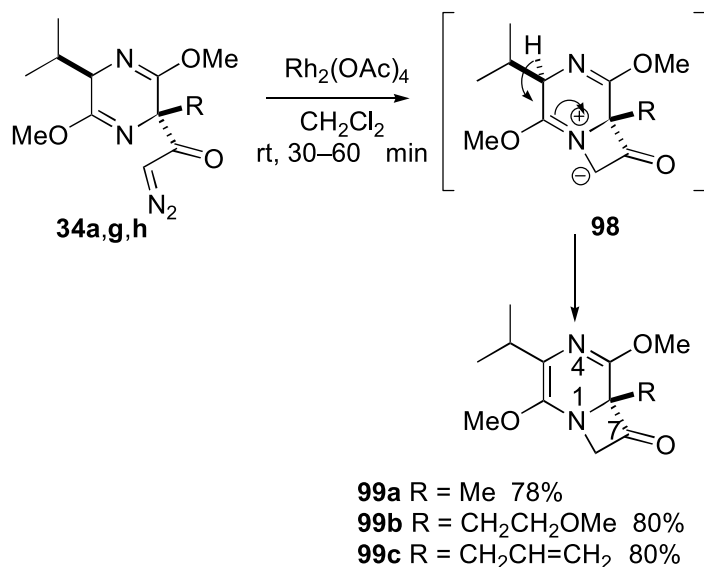
under the reaction conditions have failed to yield any cycloisomer **95**. The reaction has subsequently been repeated for the diastereomeric substrate **4c**. The reactions proceed in the same manner to furnish the diastereomer products **94** and **96** in the same ratio as previously, in about equivalent amounts. A change of the palladium catalyst by coupling in the presence of silver carbonate, provides only the 3,4-dimethylene product **94**.

It seems most likely that both isomers are formed from the same initial intermediate. Hydridopalladium elimina-

tion leads initially to a complex which may further dissociate into the bis(methylene)-product. If, however, the hydridopalladium remains coordinated to the double bond for some time, readdition can occur with the opposite regiochemistry. A subsequent hydridopalladium elimination in an *endo*-cyclic manner from the new adduct generates structure **96** [20].

The structure of the bis(methylene)cyclopentane product **92** has been verified by a palladium mediated homocoupling from the bis(2-bromoallyl) substrate **7c** in

Scheme 30. Refs: **92** [17]; **95**, **97** [20]

Scheme 31. Refs: **99abc** [32]

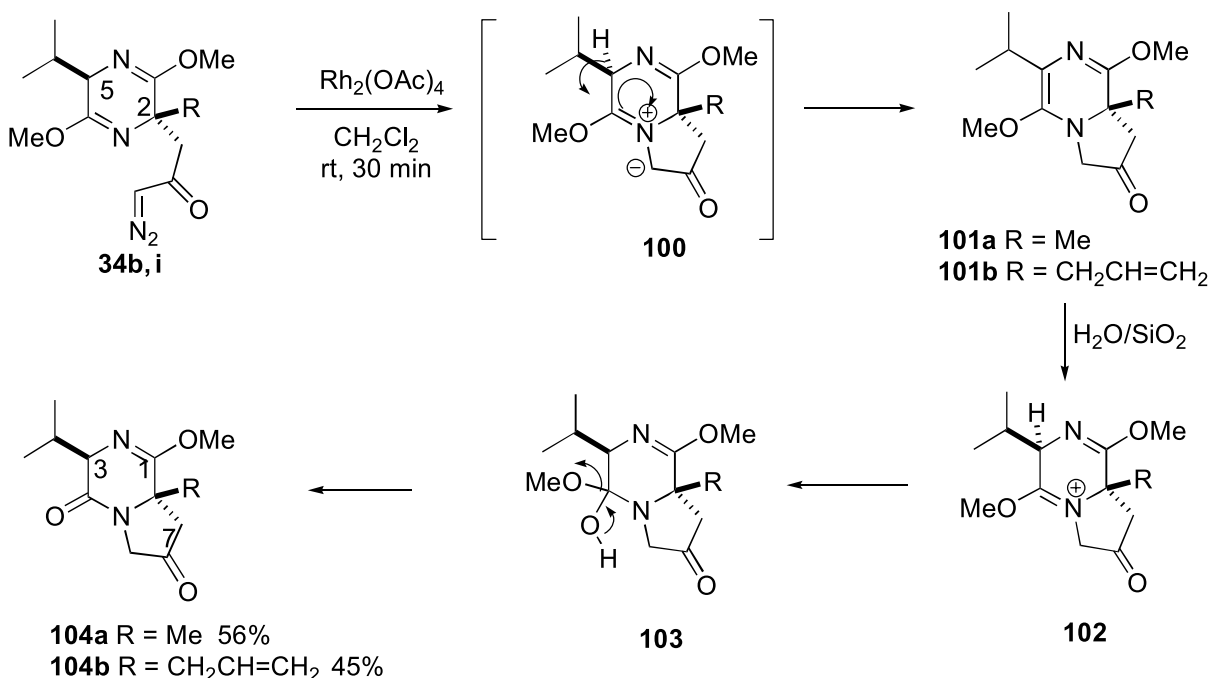
Scheme 30. The other cycloisomer **95** becomes available after a series of reactions steps. The formyl substrate is itself prepared from the allyl derivative **2a** by metallation and treatment with paraformaldehyde in an aldol reaction **12a**. Swern oxidation provides the aldehyde **24a**. A Wittig type reaction with tetrabromomethane will furnish the terminal dibromolefin **4d**. An intramolecular Heck reaction yields the desired bromocyclopentene **97**. Attempts to effect methylation with lithium dicuprate, methyl lithium or various palladium conditions favoured reductive debromination. With the nickel catalyst, NiCl₂(dppp), and methylmagnesium bromide as Grignard reagent, however, the coupling reaction is effected in satisfactory yield to provide the methyl derivative **95** [20].

2.2.3 Rhodium catalysed cyclisation reactions

In the subsequent treatment, Rh(II)-carbenoid insertion reactions are to be discussed. Substrates for the rhodium carbenoid reactants are diazomethyl ketones **34**. The carbenoid reactions in Scheme 31 can be effected using 5 mol% dirhodium tetraacetate in dichloromethane at ambient temperature for 30–60 min under an atmosphere of argon. In the substrates **34**, there exist opportunities for carbenoid C–H insertions by an attack at the α -carbon of the methyl or propyl group with formation of a six-membered ring, or by insertion in the carbon–carbon double bond in the allyl substrate **34h** with formation of an annulated five-membered ring. When possible, five-membered ring formation is greatly favoured, in most cases over the reactivity order methine > methylene > methyl. On the other hand, a heteroatom such as oxygen in an ether,

can activate an adjacent C–H bond for insertion with preference over five-membered ring formation [45–47]. In the methyl ethyl ether substrate **34g**, insertion at the adjacent carbon to the ether oxygen would have provided a five-membered ring structure carrying a methoxy substituent at the carbon where insertion occurred. No such compound was detected. Instead the highly electrophilic nature of the rhodium carbenoids leads to adduct formation with the adjacent annular nitrogen atom. Perhaps surprising, in the case of the ethanone series, highly strained four-membered ring annulated azetidines **99** are obtained in high yields, 78–80%, rather than C–H insertion to more favoured ring sizes. The four-membered ring products gradually decompose. Attempts to derivatise these structures for conversion into solid crystalline materials have proven difficult. However, their molecular structures can be deduced by NMR experiments. Most important, the H-5 proton of the substrates is absent in the ¹H NMR spectra of the products, and the methine proton of the isopropyl group in **3c** resonates as a heptet at δ 2.25 ppm with $J = 6.8$ Hz. No racemisation in the carbenoid reactions can take place at the quaternary 2-carbon in substrate **34a**. The products therefore, have the same (*R*)-configuration as in their substrates **34** [32].

The carbenoid insertion reaction with substrates **34bi** in Scheme 32 could yield a five-membered structure **100** on carbenoid addition to the nitrogen. An X-ray analysis of a derivative of **104b** has shown that the product has structure **104** in which the original stereochemistry at the isopropyl attached carbon has been retained [32]. NMR monitoring in this case was consistent with full conversion to the dihydropyrazine **101** which upon work-up of the

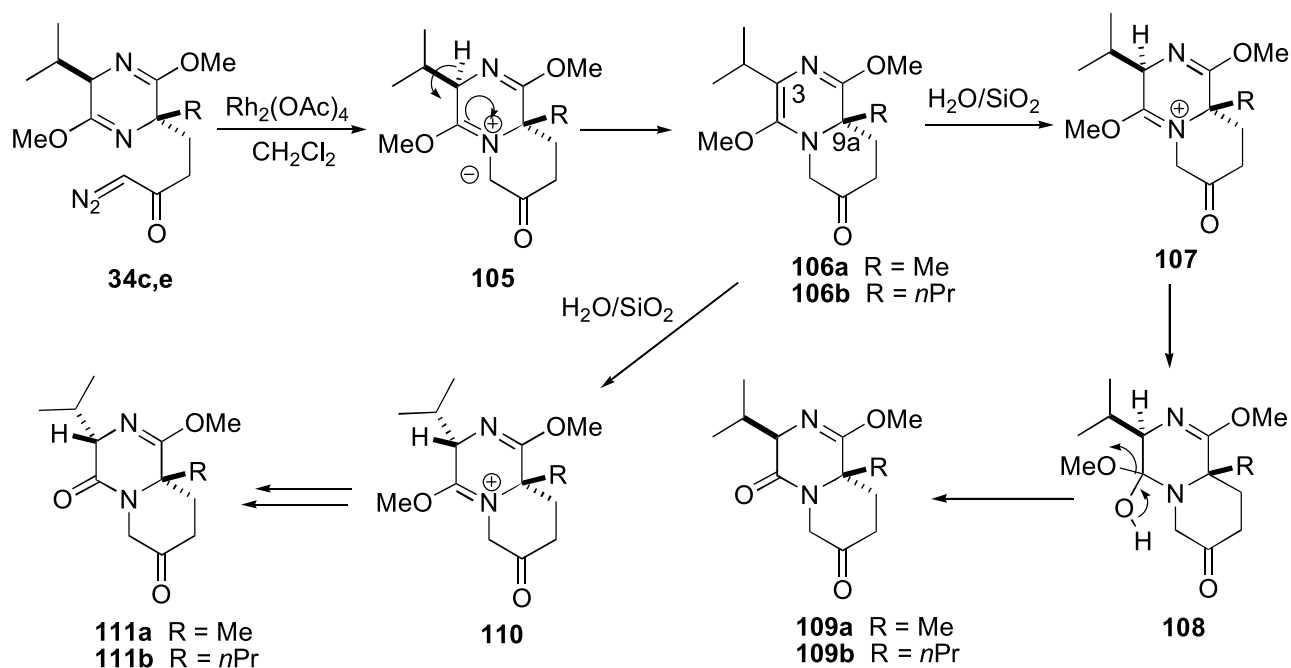
Scheme 32. Refs: **104ab** [32]

reaction by column chromatography produced the structure **104**. Although NMR monitoring showed that the first reaction product **101** is formed in quantitative yield, the final products **104a** and **104b** are only isolated in moderate yields, 56 and 45%, respectively. The methoxy group adjacent to the annular nitrogen, has been replaced by a 4-oxo group in structure **104**. The reaction sequence can be monitored in an NMR tube. Disappearance of proton signals and chemical shift changes occur which correspond to formation of **101** as the initial product in the reaction mixture. The insertion reaction resulted in an almost quantitative yield of annulated products **101**. When a small amount of silica gel is added to the NMR tube, a chemical transformation takes place. The reaction mixture goes from pale green to a brown colour. The purification of the crude reaction product, as first prepared, had been by flash chromatography on silica gel. Silica gel will contain some water. During chromatography a chemical reaction takes place with formation of the isolated products **104**. The intermediate products **101** are structurally both an enol ether and a vinylamine. The β -carbon in position 5 is therefore highly activated for protonation. A subsequent water addition to the immonium ion intermediates **102**, is followed by elimination of methanol to provide the oxo products **104**. The (5*R*)-configuration of the original substrate **34** is retained. Water addition to either face would yield a mixture of diastereomeric products. Only one product was obtained in which the con-

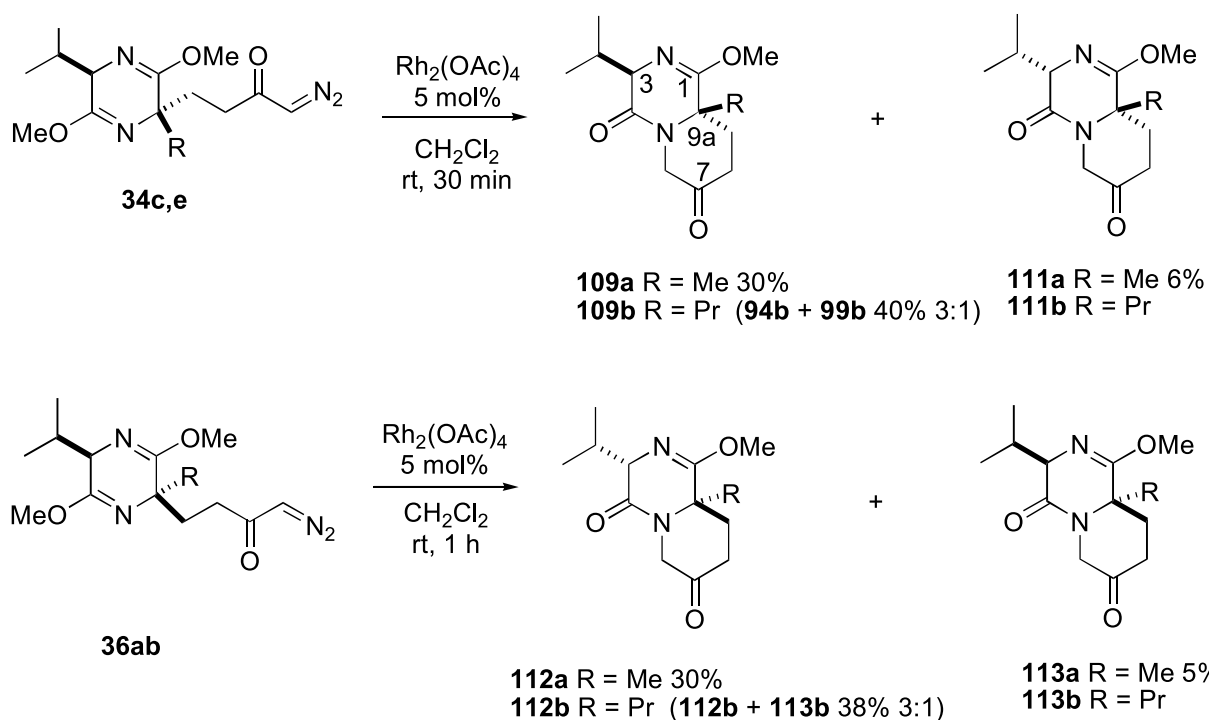
figuration at the isopropyl hinged carbon is the same both in the substrate and the product. The substituent at the bridgehead carbon in the product is *cis* to the isopropyl group and *trans* to the annulated six-membered ring. Presumably the repulsion between the annulated ring and the isopropyl group is the more important and leads to the thermodynamically more stable products **104** as the major isomer. The isolated yields in the preparative work have been moderate, *ca.* 45 and 56%, whereas the NMR studies indicate a clean, high yielding processes. The regiochemistry and the stereochemistry in this process have been established by an X-ray analysis of a *p*-nitrobenzoate of a hydroxyl derivative **130** (Scheme 39) [32].

Cyclisation of the substrates **34c** and **34e** onto the annular nitrogen atom (Scheme 33) would lead to six-membered ring formation. Proton abstraction and readdition at C-3 in an intermediate **106**, would be expected to epimerise the structure in this position thereby forming a diastereomeric mixture. Chromatography and NMR show that the product isolated is a diastereomeric mixture in the ratio range 3:1. A single crystal X-ray structure analysis (*vide infra*) of a further derived structure **138a** in Scheme 42, showed that the stereochemistry was unchanged for the major isomer at the position for the isopropyl carbon. The products **109** and **111** were isolated after extensive loss of material on the silica gel column [21].

Support for the above interpretation has become available by a comparison of the products obtained from reac-



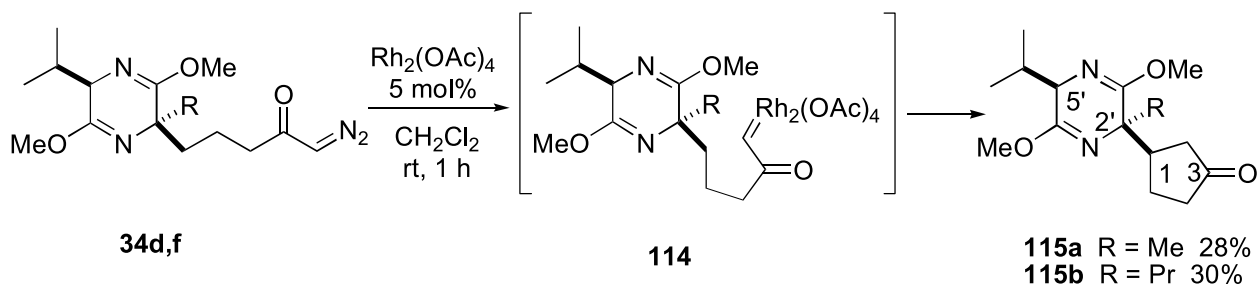
Scheme 33. Refs: 111ab [21]



Scheme 34. Refs: 109ab, 110ab, 112ab, 113ab [21]

tions with the diastereomeric substrates **34c** and **34e** in Scheme 34. Compared with the substrates **36a** and **36b**, they differ only in the configuration at C-2. When **34c** and **34e** are subjected to the rhodium-carbenoid reaction, the

configuration of the isopropyl group C-3 in the major product **109** remains unchanged whereas the configuration in the minor product has been changed. In substrates **36a** and **36b**, however the configuration in the major product



Scheme 35. Ref: 115ab [22]

112 is changed from its configuration in the substrate **36a** and **36b**. The minor product has retained the original configuration at this carbon. In both the major products **109** and **112**, the isopropyl group is *cis* with respect to the R-group. The isomer ratios **109a**:**111a** and **112a**:**113a** are almost the same. Structures **109** and **112** are enantiomeric. The same is true for the minor isomers **111** and **113**. The specific rotation in chloroform is positive in the **109**- and **111**-series, and negative in the **112**- and **113**-series, but the numerical values are pairwise the same [21].

Three methylene carbons have been inserted between the diazoketone moiety and the heterocycle in the substrates **34d** and **34f** in Scheme 35. In these substrates, carbenoid addition to the heterocyclic nitrogen would form an unfavourable seven-membered ring. No such product has been seen. Instead C–H insertion results in formation of a five-membered ring structure **115** in *ca.* 30% yield. A new stereogenic center is generated in the cyclopentanone ring, marked as 1-position, and hence a diastereomeric mixture was to be expected. However, only one product is seen and isolated. The propyl derivative **115b** is a crystalline solid. An X-ray analysis was in accord with the stereochemistry shown [22].

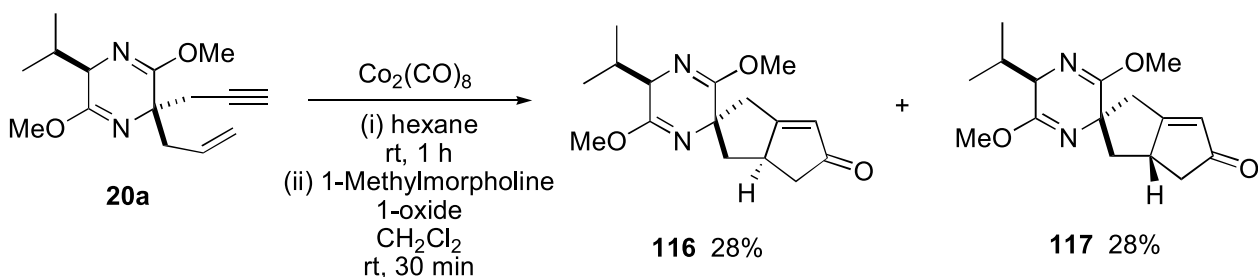
2.2.4 Cobalt effected cyclisation reactions

The combination of intramolecular Pauson-Khand methodology for $\text{Co}_2(\text{CO})_8$ mediated cyclisation, and the Schöllkopf chiron for stereoselective preparation of ap-

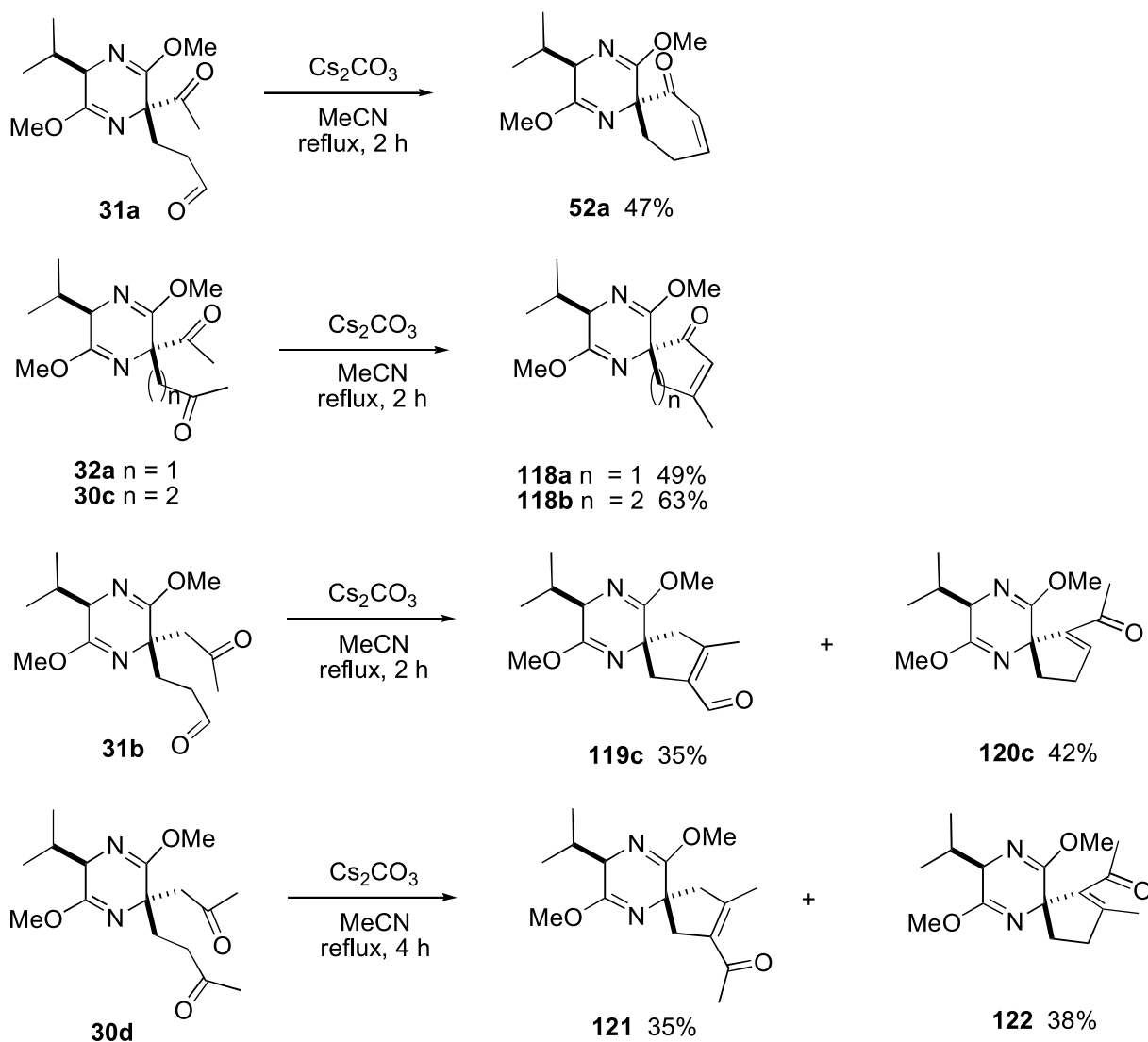
propriate 1,6-heptynynes in Scheme 36, constitutes a powerful method for the preparation of rigidified bicyclic α -amino acids [48]. The Pauson-Khand reaction is a formal [2 + 2 + 1] cyclisation which is highly useful for the construction of bicyclic annulated cyclopentenone derivatives [49, 50]. The intramolecular Pauson-Khand reaction can be effected with the 4,4-disubstituted 1,6-enyneheptane **20a** under conditions with stoichiometric amounts of dicobaltoctacarbonyl in the presence of an *N*-oxide to promote the reaction at low temperature to avoid decomposition of the bislactim moiety. The enyne complex with dicobalthexacarbonyl is formed from the substrate **20a** and dicobaltoctacarbonyl in hexane at room temperature. A subsequent addition of excess of *N*-methylmorpholine *N*-oxide provides the spiroannulated Pauson-Khand products **116** and **117** in a 1:1 mixture. The isomers are readily separated by flash chromatography. Both products are crystalline solids, and both structures have been confirmed by an X-ray analysis [48].

2.2.5 Intramolecular aldol condensations

Spiroannulation by intramolecular Aldol condensation reactions is shown in Scheme 37 [31]. The aldol condensation has been effected in acetonitrile under reflux conditions using 1–1.5 eq of cesium carbonate. The oxo group in the acetyl substrates **31a**, **32a** and **30c** is attached directly to a quaternary center and is sterically shielded. Enolate addition to this carbonyl group is slower than



Scheme 36. Ref: 116, 117 [48]

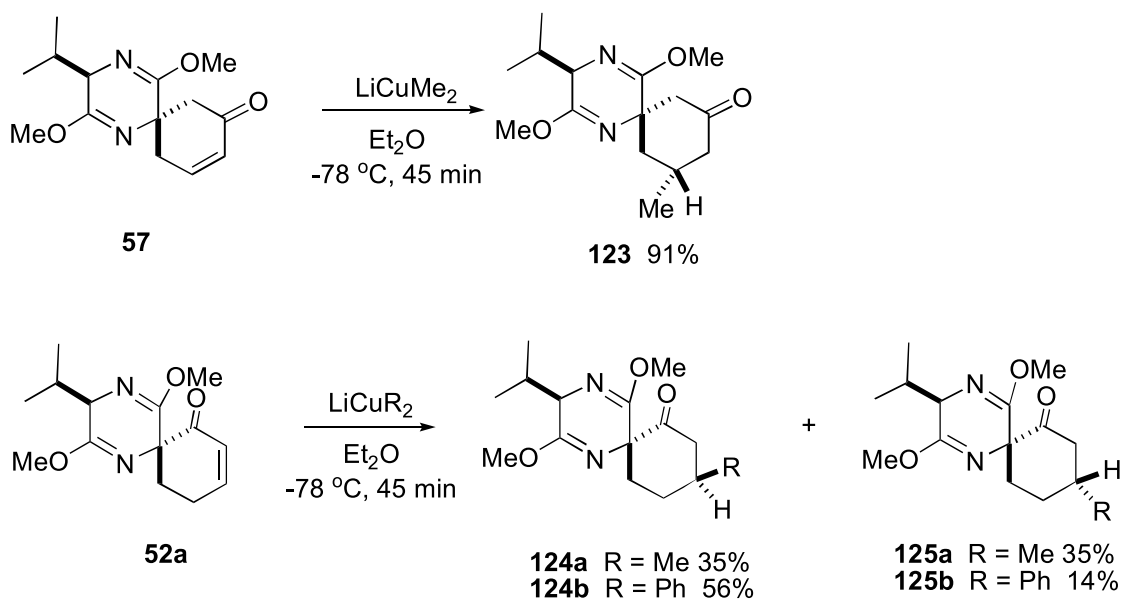
Scheme 37. Refs: **52a**, **118ab**, **119c**, **120c**, **121**, **122** [31]

enolate addition to the less shielded oxo group in the other *gem*-substituent further away from the quaternary center. Enolisation in the acetyl methyl group in substrate **31a** therefore leads preferentially to six-membered ring spiroannulation and formation of the heterospirane **52a**. The acetyl derivative **32a**, as well as the higher 2-butanoyl homologue **30c**, react regioselectively with formation of the five- and six-membered heterospiranes **118a** and **118b**, respectively. In the acetyl substrates **31b** and **30d**, respectively, the carbonyl group is located one carbon unit further away from the quaternary center. Enolisation can take place in either *gem*-dicarbonyl substituent in the heterocycle. Competitive internal enolisations in the aldehyde **31b** lead to a mixture of the isomeric five-membered spiroannulated structures **119** and **120**, almost in ratio 1:1. Seven-

membered ring formation, after enolisation in the methyl group, was not seen. A similar product ratio resulted from the cyclocondensation of the diketone **30d** with formation of the isomeric heterospiranes **121** and **122**. Enolisation in the methyl groups is not an important pathway for the product formation [31].

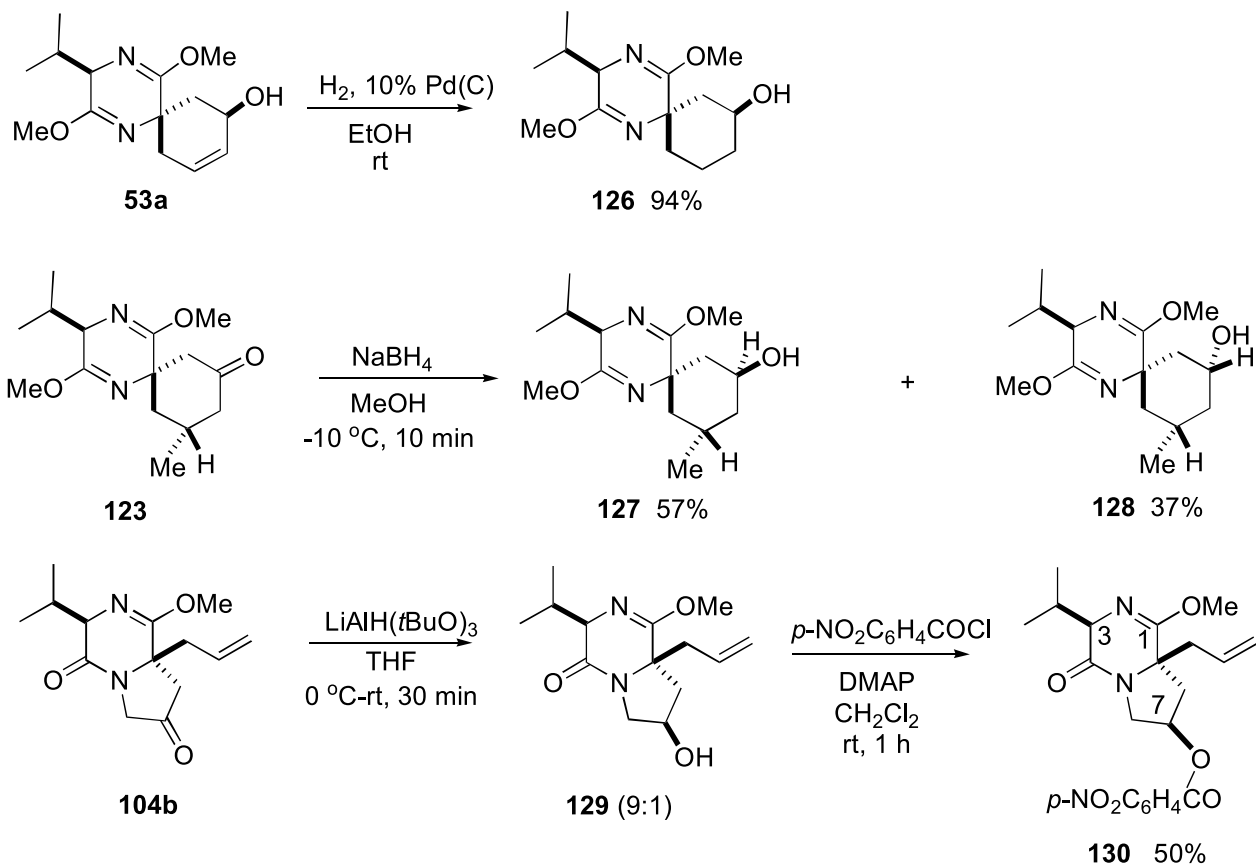
2.3 Chemical modifications after heterospirane annulations

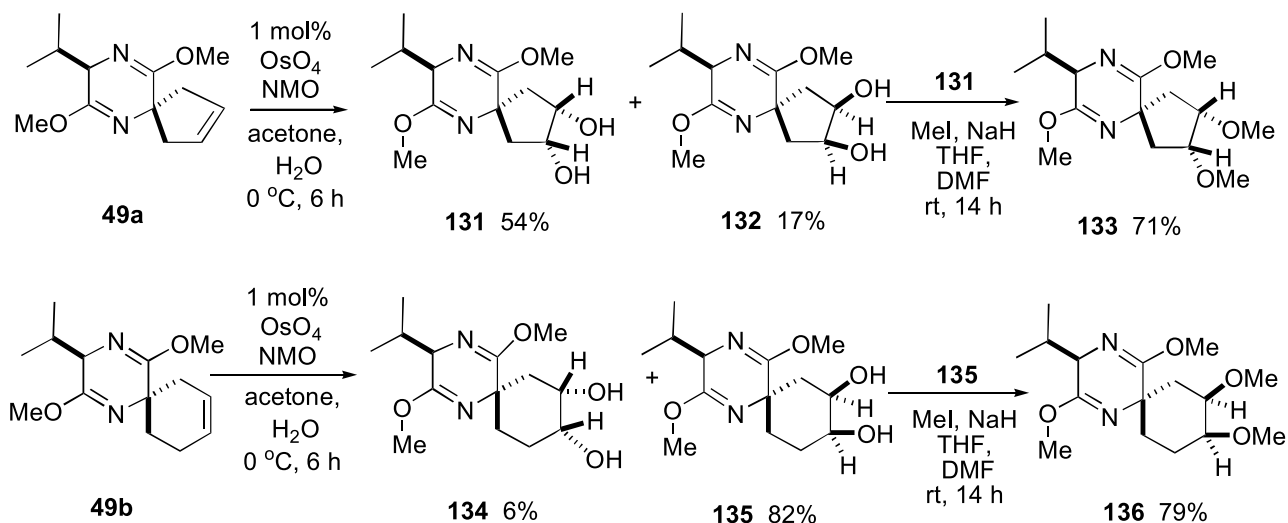
Conjugate addition of lithium dimethylcuprates to the β -oxo conjugated cyclohexenone **57** in diethyl ether at -78°C provides the isomerically pure adduct **123** in 91% yield (Scheme 37) [41]. An X-ray structure analysis of the cyclohexenone substrate **57** shows a conformational

Scheme 38. Refs: **123** [41]; **124ab**, **125ab** [51]

preference of the cyclohexenone to minimise steric interactions with the overlying 6-methoxy group of the orthogonal pyrazine ring. No serious interaction is seen

at the other face of the cyclohexenone ring. Hence the high diastereoselectivity is attributed to the difference in shielding of the two faces providing stereoisomer **123**.

Scheme 39. Refs: **126** [26]; **127**, **128** [41]; **129**, **130** [32]



Scheme 40. Refs: 131, 132, 133, 134, 135, 136 [52]

In the α -oxo conjugated cyclohexenone **52a**, the environmental interactions are different. Low diastereoselectivity is observed in the addition of lithium dimethyl- and diphenylcuprates in diethyl ether at -78°C . The methylated adducts **124a** and **125a** are obtained in almost equivalent amounts. In the phenylated products, the isomer ratio **124b**:**125b** was 4:1. The diastereomers are readily separated before hydrolysis to their respective amino acid derivatives [51].

Catalytic hydrogenation of the carbon–carbon double bond in the allylic alcohol **53a** in Scheme 39 proceeds chemoselectively to furnish the saturated alcohol **126** in high yield [26]. Oxo groups are chemoselectively reduced by metal hydrides. Low diastereoselectivity is observed in a simple sodium borohydride reduction of the saturated ketone **123**, the products being **127** and **128** [41]. In the annulated pyrrolidinone **104**, stereoselectivity was desired in a reduction of the oxo group to form the corresponding alcohol. The bulky tri(butoxy)aluminum hydride reagent was employed in THF at 0°C when the isomer **129** is the major product as a result of preferential attack by the bulky metal hydride at the less shielded face of the

ketone. The epimeric alcohols are formed in the ratio 9:1. The alcohol **129** has subsequently been converted into the crystalline ester **130** for an X-ray analysis [32].

Vicinal dihydroxylation, using a combination of osmium tetroxide and *N*-methylmorpholine *N*-oxide, is shown in Scheme 40. From the cyclopentene spirane **49a**, the *cis*-diol isomer ratio **131**:**132** was *ca.* 3:1. In the hexene homologue, the ratio **134**:**135** was *ca.* 1:14 where the vicinal hydroxyl groups in the major product has a *cis*-relationship to the overlying orthogonal methoxy group. The major isomers were *O*-methylated before conversion to amino acid derivatives [52].

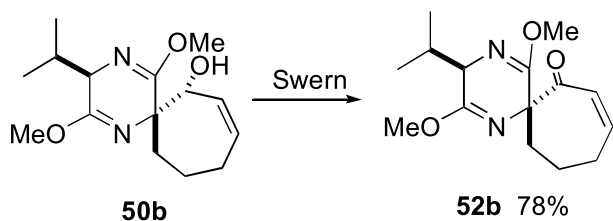
Scheme 41 shows an oxidation reaction in a spirane. Under Swern conditions the allylic seven-membered ring spirane **50b** is converted into the corresponding cycloheptenone **52b** in high yield [30].

2.4 Hydrolytic reactions and amino acid formation

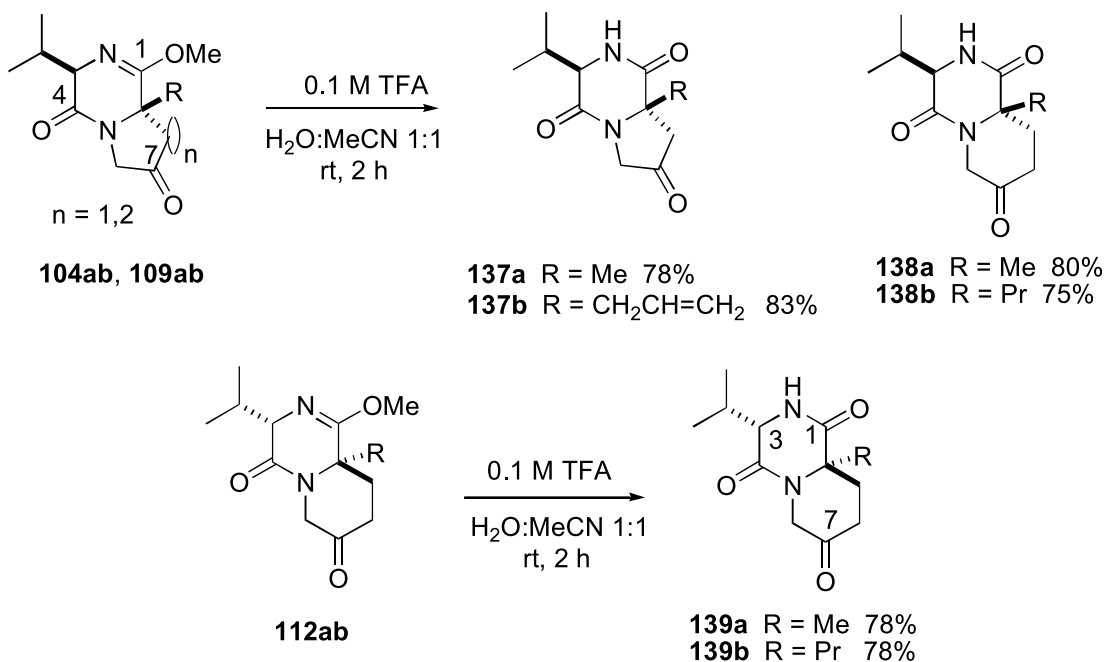
2.4.1 Chemoselective hydrolysis

Hydrolytic reactions are shown in Scheme 42. An inspection of structures **104** and **109** shows a lactam function in the 4-position and an iminoether function in the 1-position. The former is highly resistant towards acid hydrolysis, the latter is acid sensitive.

Therefore mild acid conditions using 0.1 M TFA leads to formation of the corresponding diketopiperazines **137** [32] and **138** [21], which are isolated in *ca.* 80% yield. The corresponding cyclohexane annulated triones **139** are formed in similar yields from the corresponding



Scheme 41. Ref: 52b [30]



Scheme 42. Refs: **137ab** [32]; **138ab, 139ab** [21]

precursors **112a** and **112b** [21]. Further cleavage of the diketopiperazine cyclic peptides **137–139** to amino acid constituents would require strongly hydrolytic acidic conditions.

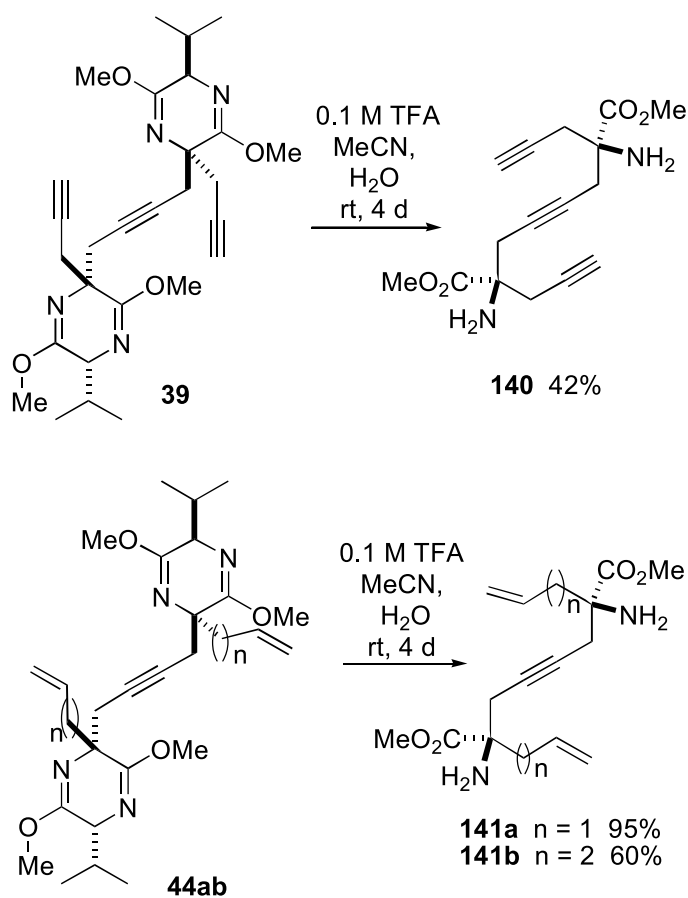
2.4.2 Hydrolysis with formation of amino acid derivatives

Hydrolysis of the cyclic dipeptide products to their amino acid components may sometimes cause problems because the preferential course of the hydrolysis is sensitive to non-bonded interactions. Under mild acidic conditions, the iminoether function can be cleaved in such a way that the amino group and the methyl ester group are liberated thereby providing opening of the ring at this point. When this reaction path also occurs at the second iminoether function, the two amino acids are set free and can be separated, frequently by flash chromatography. The valine methyl ester is fairly volatile and it may be advantageous to remove most of the valine by slow bulb-to-bulb distillation at reduced pressure at ambient temperature before the final purification step. This pathway is sensitive to interference from the adjacent substituents R^1 and R^2 . The hydrolytic reaction normally is carried out at ambient temperature. Schöllkopf has recommended low acid concentrations for this desired pathway, 0.2 M HCl and in particular 0.1 M TFA in aqueous acetonitrile [53, 54]. Heat, or strong acids, changes the course of the reaction

since cleavage of the iminoether function takes a different course. One path leads to generation of a cyclic amide, which requires very strong acidic conditions for further hydrolysis, especially if the intermediate reacts further to a diketopiperazine. More often an acyclic dipeptide is formed. Ring-opening can occur at either iminoether function, more often at the less shielded valine carbonyl function.

The hydrolytic products **140** and **141** in Scheme 43 are acyclic α -quaternary- α -amino acid derivatives highly triple- and double-bond functionalised dicarba analogues of the amino acid cystine. The same compounds are key intermediates in cycloisomerisation and RCM reactions in the construction of heterospiranes as precursors for cyclic target molecules (Schemes 23–25). Hydrolysis of the triyne **39** under mild acidic conditions can be effected in 0.1 M TFA in aqueous acetonitrile at room temperature. In sterically crowded substrates such as the triyne **39**, the hydrolysis is slow and is accompanied by partially hydrolysed products. Hydrolysis under forcing conditions takes another course with formation of the corresponding diketopiperazines. After running the reaction at ambient temperature for 4 days, 35% yield of the bridged amino acid **140** can be isolated [29]. Hydrolysis of the ynedienes **44** is a cleaner reaction which provides the bisamino acid esters **141a** and **141b** in 95 and 60% yield, respectively.

The substrates **49** in Scheme 44 are available by Ru(II)-catalysed RCM reactions as shown in Scheme 17. Under

Scheme 43. Refs: **140** [29]; **141ab** [35]

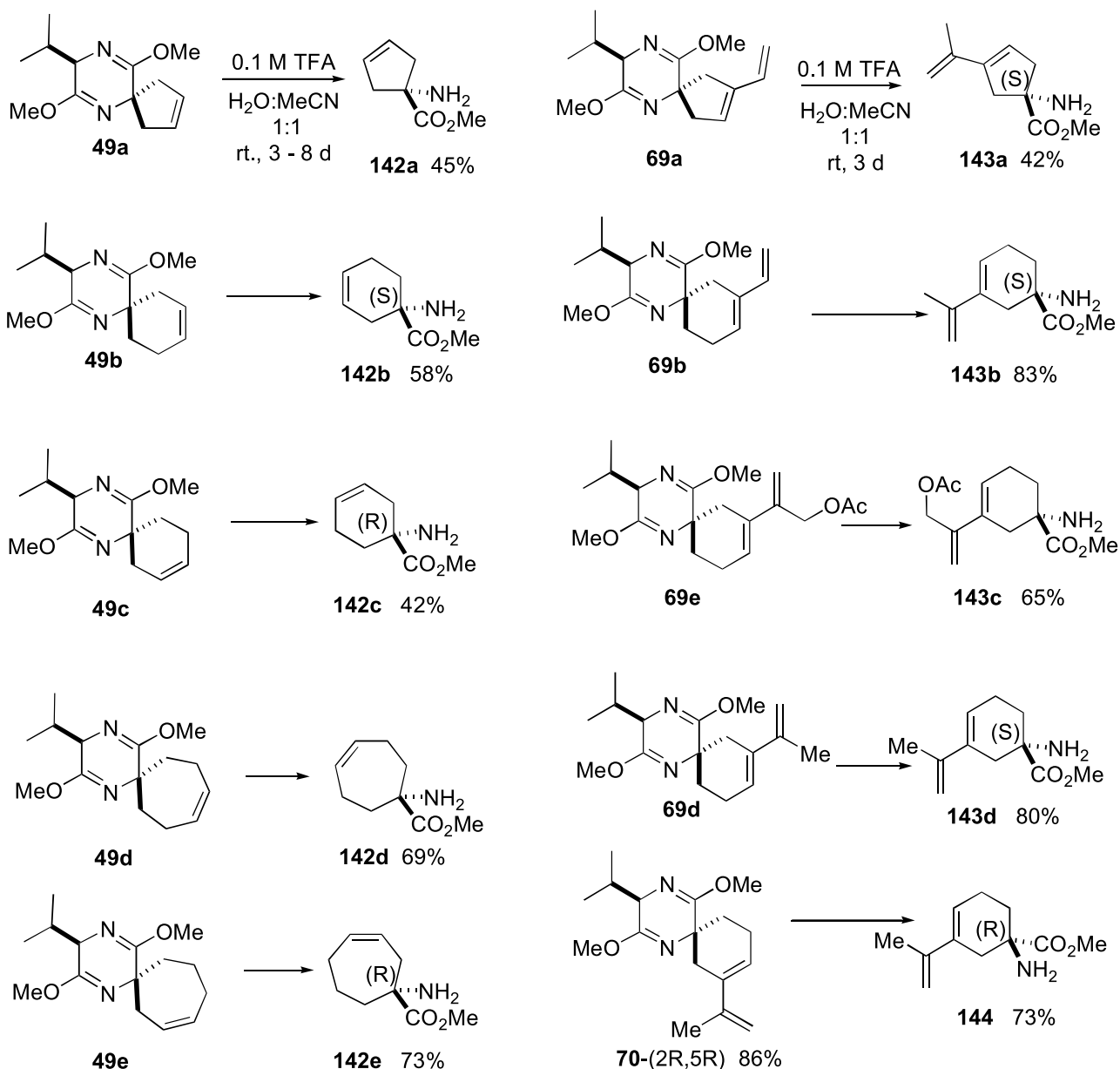
mild acid conditions, slow hydrolysis provides cycloalkenyl- α -amino acids **142** in variable yields which are affected by steric factors. Compounds **142b** and **142c** are cyclohexenyl double bond regioisomers, and **142d** and **142e** are cycloheptenyl double bond regioisomers. The cyclopentenyl and cycloheptenyl products **142a** and **142d** are symmetrical.

The novel diene substrates **69**, from the ruthenium(II)-cycloisomerisation of enyne substrates shown in Scheme 21, under mild hydrolysis conditions provide novel conjugated diene cyclic amino acids **143** with one exocyclic and one endocyclic double bond. Substrates **69d** and **70** are diastereomers which differ in the configuration at the spirocarbon. Hence hydrolysis provides the enantiomer pairs **143d** and **144**.

The substrates in Scheme 45 are available by the palladium catalysed cycloisomerisation reactions shown in Schemes 27–30. The cyclopentylidimethylene substrate **91** and the higher homologue **89** are hydrolysed to cyclic amino acids where both the conjugated double bonds are exocyclic, **145** and **147**, respectively. Substrates **93** and **92** yield cyclic amino acid products **146** and **148** where one of the conjugated bonds is exocyclic, the other endocyclic.

Scheme 46 shows preparation of various cyclic serine analogues with the hydroxy group attached to the ring [24]. The α -hydroxy spirane substrates **50** and **51** are provided by the ruthenium-catalysed RCM reactions in Scheme 18. The series **149** and **150** are pairwise diastereomeric because of the opposite configuration of the hydroxyl group in the two series. Hydrolytic conditions for cleavage of the cycloheptenol **50b** to provide its amino acid ester **149b** also yield the dipeptides **151** and **152** in almost equivalent amounts. The former arises by opening of the pyrazine ring at C-6 next to the isopropyl group, and the valyl dipeptide **152** by opening of the pyrazine ring at C-3.

Some alternative routes for the preparation of cyclic serine analogues are shown in Scheme 47. The saturated cyclopentyl serine analogue **155** was prepared via the (*S*)-phenylalanine ester of 2-hydroxycyclopentanone **153**, which was cyclised under acidic conditions, reacted with trimethylsilyl cyanide to provide diastereomeric amino nitriles in the ratio 98:2; the major isomer **154** is shown. Mild oxidation and a subsequent hydrolytic reaction under vigorous acidic conditions provided the (1*S*,2*R*)-1-amino-

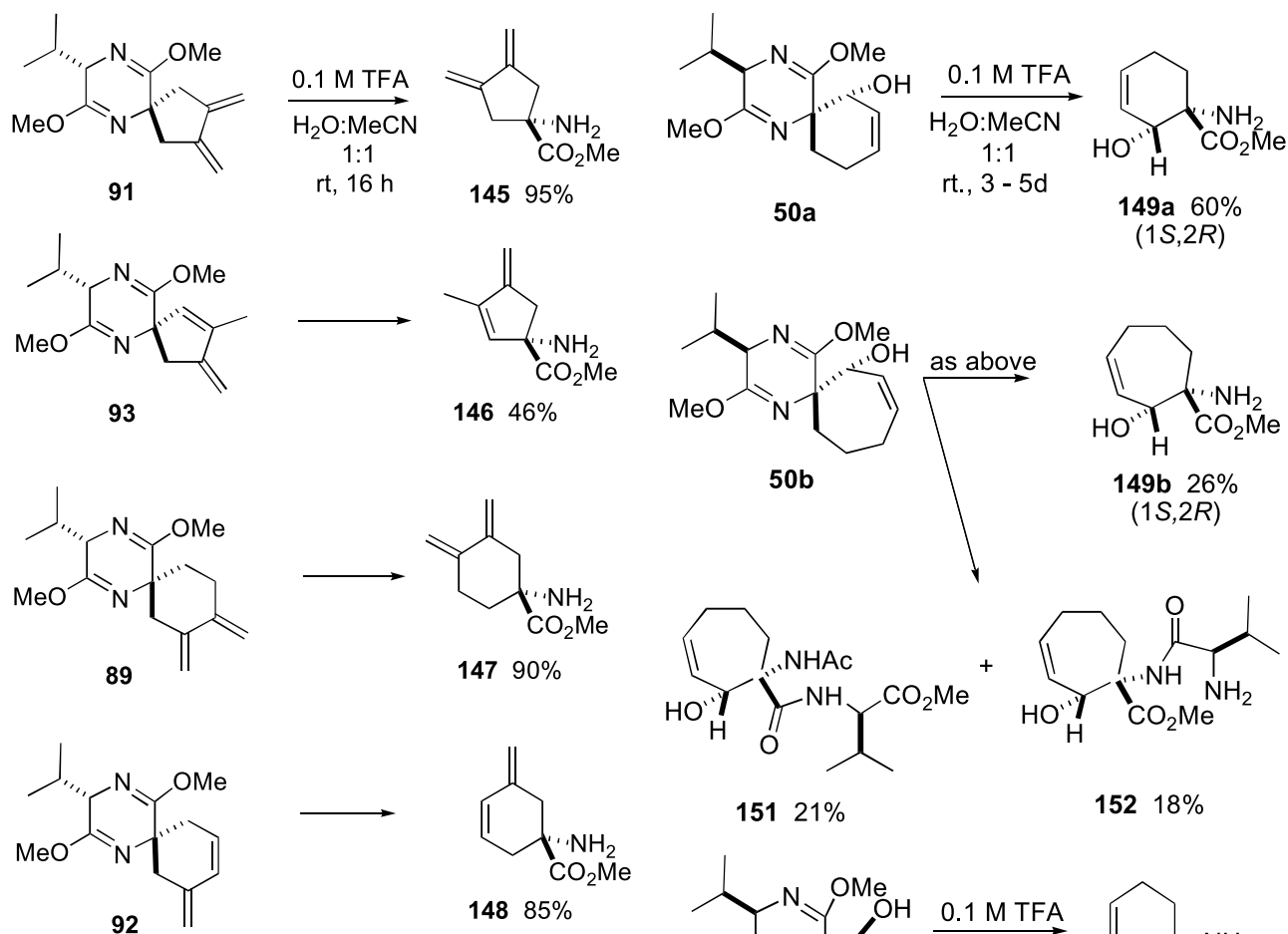


Scheme 44. Refs: **142abcde** [14]; **143abcd**, **144** [28]

2-hydroxycyclopentanecarboxylic acid **155** [56]. The enantiomer was prepared from (*R*)-phenylalanine. Essentially the same reaction sequences from corresponding cyclohexane substrates have been used to prepare the cyclohexane analogues **159** and **161** [56]. Scheme 47 also shows a route for the preparation of the four stereomeric 1-amino-2-hydroxycyclohexanecarboxylic acids **158–161** [57]. The *cis*- and *trans*-cyclohexane serine analogues were synthesised separately as racemates. A Diels-Alder reaction between methyl 2-benzamidoacrylate and the Danishefsky diene or 1-methoxy-1,3-butadiene, provided the adducts. Optical resolution was effected by preparation of diaster-

eomeric dipeptides with (*S*)-2-acetoxypropane in the *cis*-series **156** and (*S*)-phenylalaninecyclohexylamide **157** in the *trans*-series. The diastereomers in each series were separated by chromatography on silica gel. The double bond in the Diels-Alder adduct in the *trans* series **157** was saturated before the optical resolution, in the *cis*-series **156** after resolution. Vigorous acidic conditions have to be used to hydrolyse the separated diastereomers into the respective amino acid enantiomers [57].

Scheme 48 shows a series of six- and seven-membered cyclic analogues of homoserine. The substrates are available by Ru(II)-catalysed RCM reactions as shown in



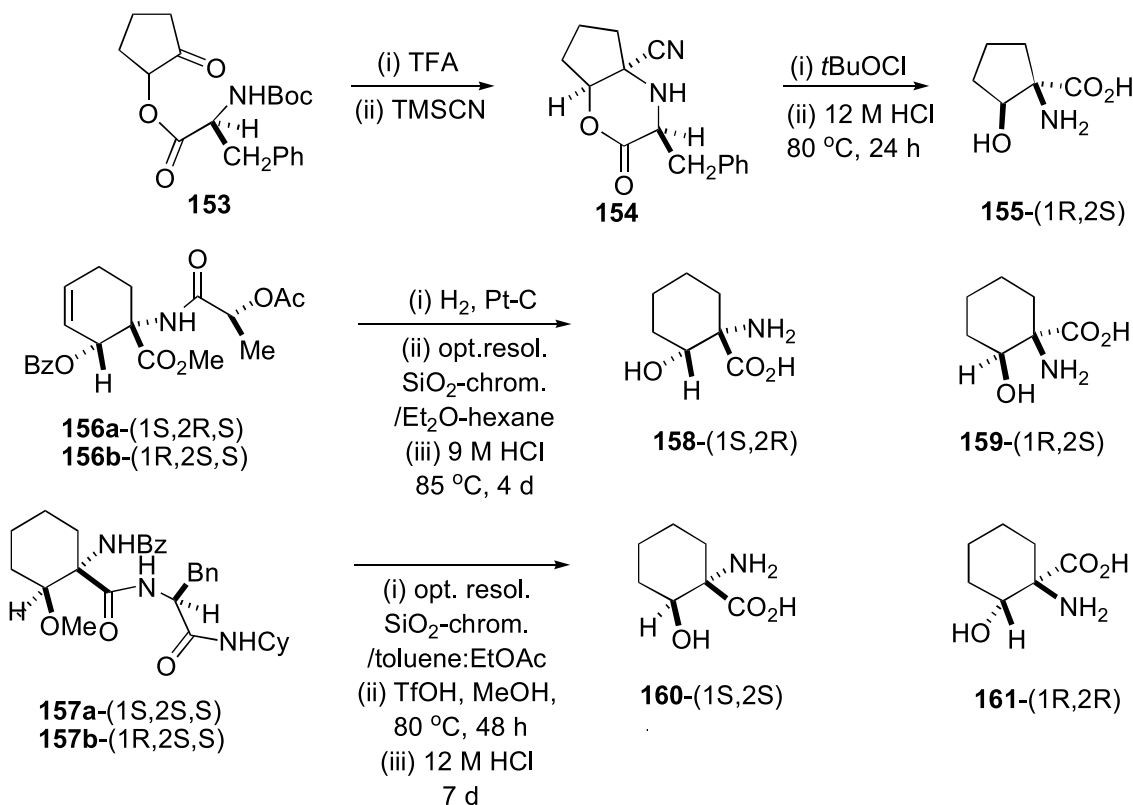
Scheme 45. Refs: 145, 146, 147, 148 [17]

Scheme 18 and the reductive reactions in Scheme 39. The rate of hydrolysis in the preparation of compounds **162a** and **162b** was very low and the amino acids were isolated in low yields. In the isomer **53a**, which has the opposite stereochemistry at the hydroxyl carbon, the hydrolytic rate was slightly improved. From the reaction of the cycloheptenol **53b**, the amino acid lactone **164** is obtained in 63% yield. Lactone formation requires that the hydroxyl group and the carboxy group have a *cis*-relationship. No lactone formation was seen in its hydroxyl isomer **162b**. This observation can be used for the configurational assignments of the hydroxy group in the series. In the saturated hydroxy spirane **126**, hydrolytic ring opening yields the amino acid **165** as well as some of its lactone **166** in accordance with a *cis*-relationship between the hydroxy and the carboxy groups. The dipeptide **167** is the third product, and is formed by opening of the pyrazine ring at the less shielded 6-position.

Preparation of cyclic homoserine analogues with an additional methyl group in the 5-position is shown in

Scheme 46. Refs: 149ab, 150ab, 151, 152 [24]

Scheme 49. The substrates are available as shown in Scheme 39 [41]. The spiranes **127** and **128** are diastereomers because of the different configuration at the hydroxy carbon. With *cis*-hydroxy and- methyl groups **128**, mild acid hydrolysis will furnish the target cycloamino acid derivative **169**. In the *trans*-isomer **127**, both faces of the cyclohexane ring are shielded. Only the dipeptide **168**



Scheme 47. Refs: **155** [56]; **158–161** [57]

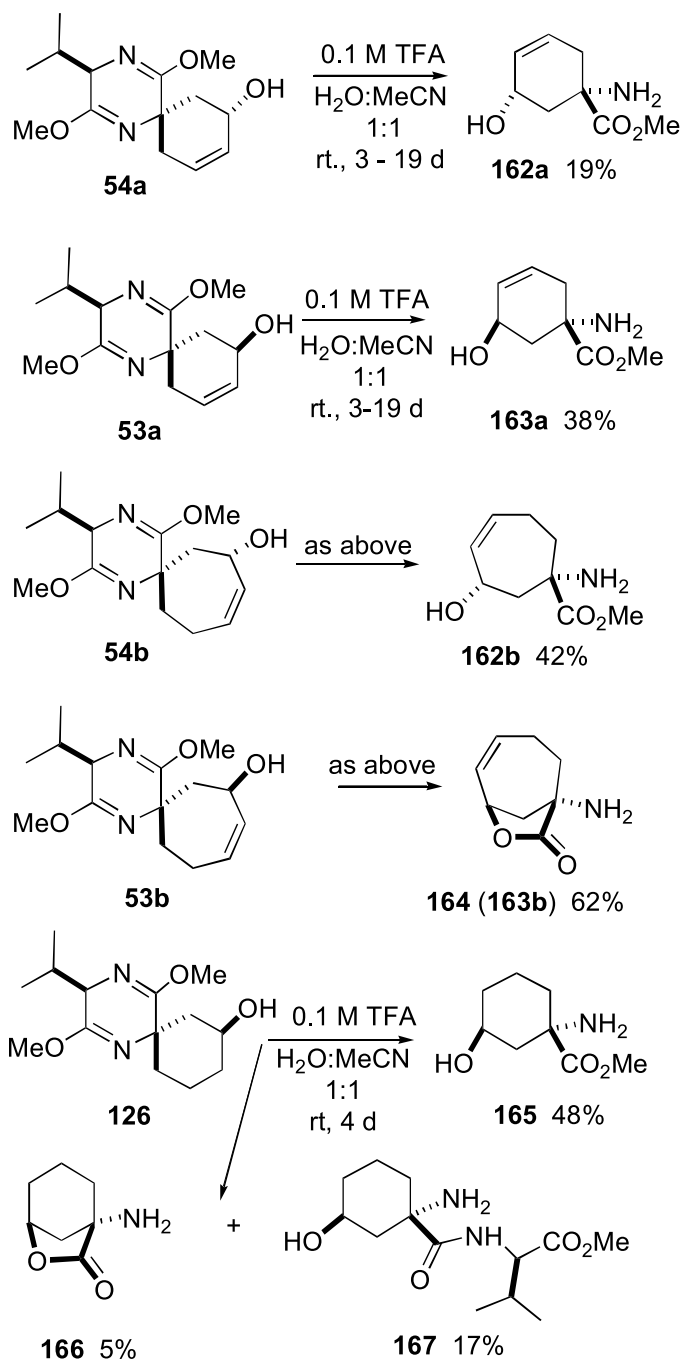
could be isolated. The opening of the pyrazine ring was at the less shielded 6-position.

Some alternative routes for the preparation of cyclic α -quaternary homoserine analogues are shown in Scheme 50. The cyclohexyl analogue **172**-(1*S*,3*R*) has been prepared from a Diels-Alder adduct **170** which was available from (–)-8-phenylmenthyl α,β -didehydroalaninate and 1,3-butadiene in a diastereofacial selective reaction. Direct hydroxylation with a *syn* relationship to the amide group, was effected with *N*-iodosuccinimide. The product from the reaction is a dihydro-1,3-oxazine intermediate **171**. Tributyltin hydride was used for hydrogenolysis of the iodo substituent. TFA is used to hydrolyse the oxazine, and reflux in 6M HCl liberates the amino acid **172** [58]. In the second approach, Diels-Alder reactions between (*E*)-2-cyanocinnamic esters of the chiral auxiliary (*R*)-pantolactone as dienophiles and 1,2-butadiene, provided stereoselectively the substrate **173**. Hydroxylation of the double bond in the Diels-Alder adducts gave enantiomerically pure α -amino- γ -hydroxy acids. Initially the adduct **173**-(1*R*,6*S*,*S*) was converted into the carbamoyl methyl ester **174**. After a series of reaction steps initiated by iodination and hydroxylation methodology as above, followed by a Hofmann type degradation converted the carbamoyl

group into an amino function. Finally acid hydrolyses with 3M HCl and TFA under reflux furnished the amino acid **175**-(1*S*,3*S*,6*S*). The (1*R*,3*R*,6*R*)-enantiomer was similarly obtained when the (*E*)-2-cyanocinnamate of (*S*)-ethyl lactate was a reactant in the Diels-Alder adduct formation [59].

Hydrolytic preparation of vicinal dimethoxy-cycloalkanyl amino acid derivatives is shown in Scheme 51. Both substrates **133** and **136** are *cis*-dimethoxy derivatives available from their precursor vicinal dihydroxy compounds (Scheme 40). Both substrates were cleaved with formation of the corresponding amino acids **176** and **177** [52].

Preparation of homoserine analogues with the hydroxy group as a substituent in the ring was shown in Scheme 48. Scheme 52 provides examples where the hydroxy group in the substrates is located exocyclic in the form of a hydroxymethyl substituent **60** or in the form of a cyclic oximine structure **58**. In the latter, the original hydroxymethyl substituent was located in a position for an ester exchange to take place by expulsion of methanol (Scheme 19). This arrangement leads to shielding of the 3-position, the hydrolytic product being the dipeptide **178** which is formed by opening of the hydrazine ring in the 6-position. In the hydroxymethyl stereomer **60**, both



Scheme 48. Refs: 162ab, 163ab, 164, 165, 166, 167 [26]

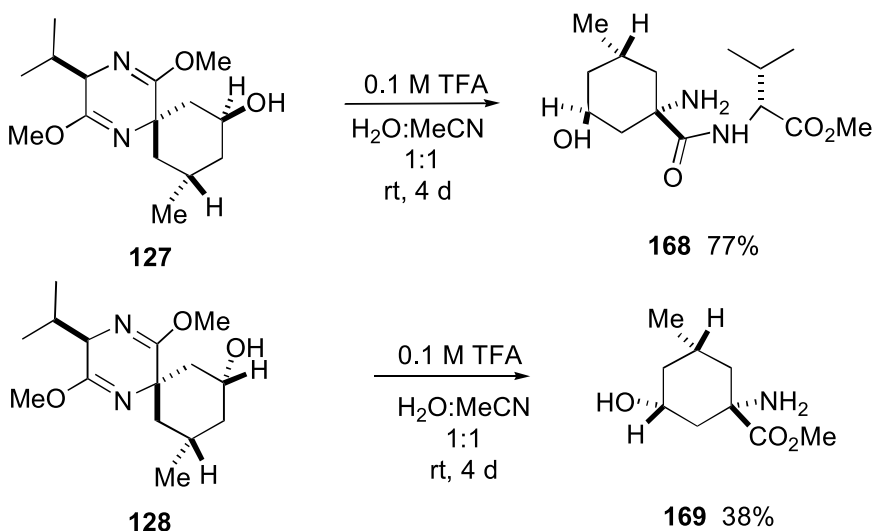
dipeptides **179** and **180** are formed. The major peptide **179** comes from opening of the pyrazine ring in the less shielded 6-position [27].

The α,β -unsaturated cyclohexenone and -heptenone spiranes **52a** and **52b** in Scheme 53 are available from the products in Ru(II)-catalysed RCM reactions (Scheme 17). Hydrolysis to the novel α,β -unsaturated cyclic amino acid derivatives **181a** and **181b** produces acceptable yields for this reaction [30, 51]. Perhaps the α,β -unsaturated carbo-

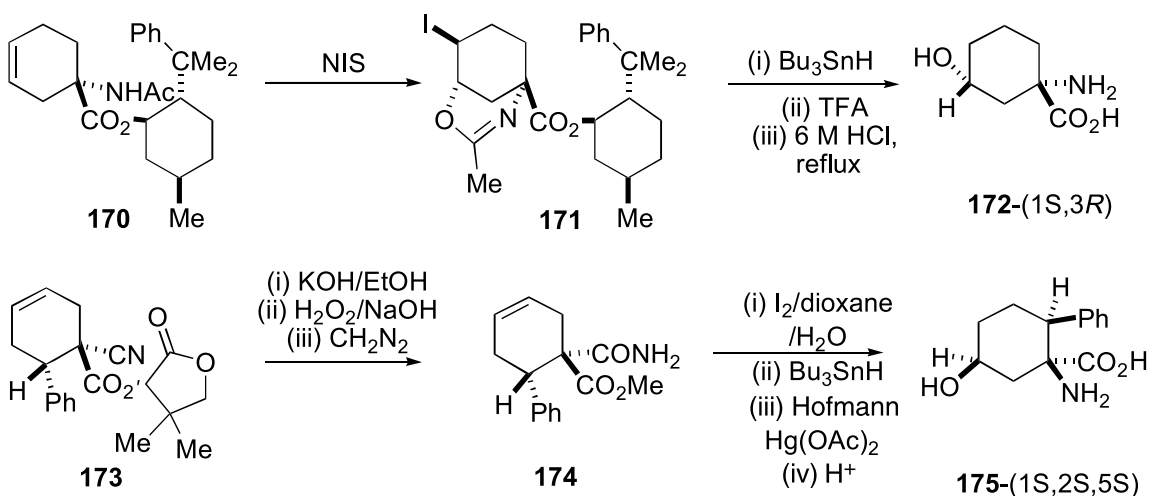
nyl ring moiety exerts a less shielding effect at the 3- and 6-positions than in previous examples.

The methyl substituted substrate analogues **118a** and **118b** are available by aldol condensation reactions as described in Scheme 37. The unique cyclic α,β -unsaturated keto amino acid derivatives **182a** and **182b** are obtained in reasonable yields after mild acid hydrolysis [31].

The cyclohexanone spirane substrates **124ab**, and **125a** from Scheme 38 can all be hydrolytically cleaved as



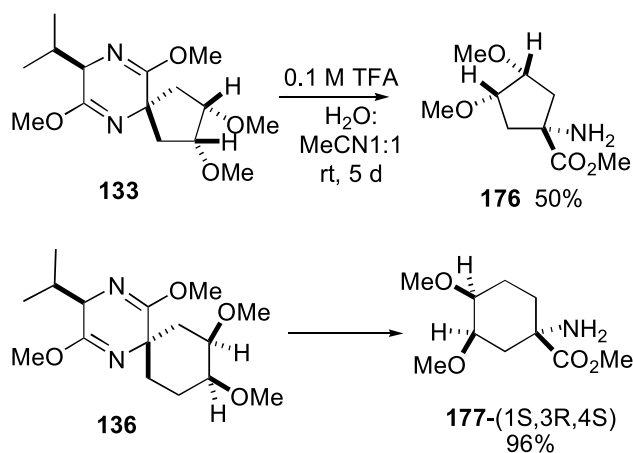
Scheme 49. Refs: 168, 169 [41]



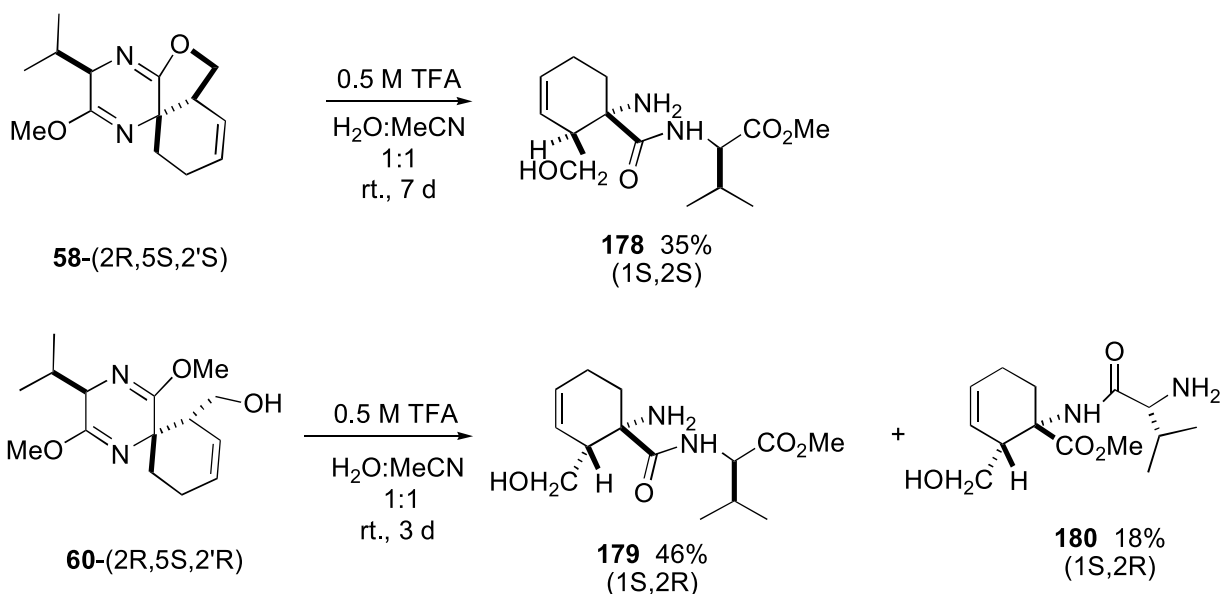
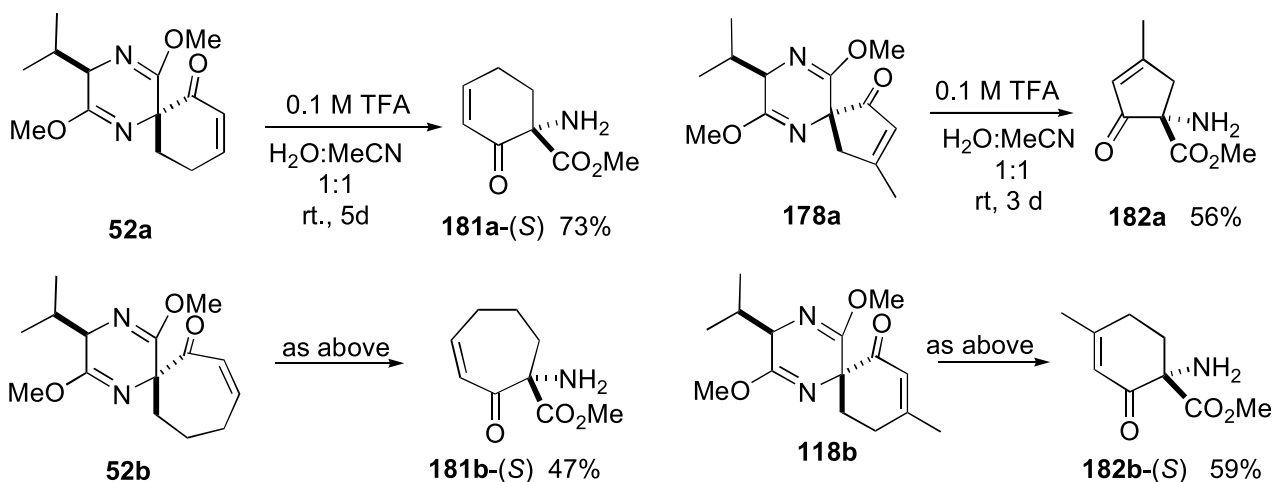
Scheme 50. Refs: 172 [58, 59]; 174, 175 [59]

shown in Scheme 54 to the corresponding cyclohexanone amino acid derivatives **183a**, **183b** and **184** in 41–50% yield.

In an alternative method for the preparation of β -phenylated α -quaternary- α -amino acid derivatives, a Diels-Alder reaction between (*E*)-2-cyanocinnamate ester and (*S*)-ethyl lactate or (*R*)-pantolactone **185** as dienophiles and 1,3-butadiene provided a *cis*- and a *trans*-series of adducts (Scheme 55) [60]. The two major stereoisomers **186** and **187** in the two series could be isolated. Subsequent elaborations by a series of alternative and complimentary degradation reactions including vigorous acidic hydrolysis in the final reaction step furnished the four enantiomerically pure 1-amino-2-phenylcyclohexanecarboxylic acids **188–191** [60].



Scheme 51. Refs: 176, 177 [52]

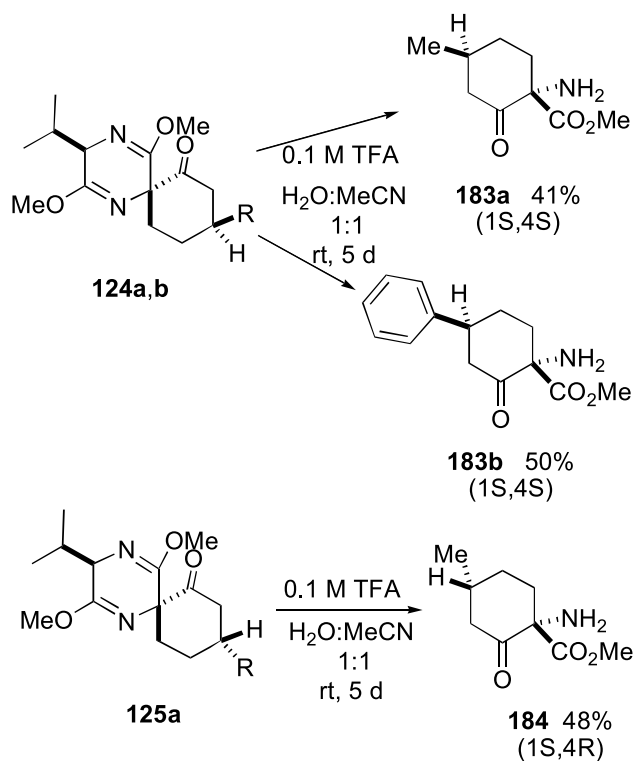
Scheme 52. Refs: **178**, **179**, **180** [27]Scheme 53. Refs: **181ab** [30, 51]; **182ab** [31]

The Strecker or Bucherer-Bergs reactions are frequently used methods to prepare families of amino acid derivatives from a cyclopentane ring. In this way the four stereoisomers of 1-aminocyclopentane-1,3-dicarboxylic acid have been prepared (Scheme 56). The products are regarded as conformationally constrained analogues of glutamic acid. (*R*)-3-Oxocyclopentanecarboxylic acid (**192**) when reacted under Strecker conditions provides diastereomeric hydantoins **193**. The diastereomers were separated by fractional crystallisation and cleaved by acid hydrolysis to the enantiomeric amino acids **194** and **195**. The (1*R*,2*S*)- and the (1*S*,2*S*)-stereoisomers were obtained in the same way from (*S*)-3-oxocyclopentane carboxylic acid [61]. A similar

approach has been used in the synthesis of the enantiomers of 1-aminocyclopentane-1,3,4-tricarboxylic acid [62].

Cis- and *trans*-1-aminocyclopentane-1,3-dicarboxylic acids have been optically resolved by simple ion exchange chromatography of their α -boroxazolidone- γ -phenylethylamides or - γ -phenylethanolamides **197** and hydrolysed to the amino acids by 6 M HCl [63].

Racemic *cis*-1-aminocyclohexane-1,3-dicarboxylic acid **198** has been optically resolved as a γ -phenylethanolamide **199**. The α -carboxy group together with the amino group were protected as an α -boroxazolidone by a reaction with triethylborane and a subsequent coupling with (*R*)-phenylglycinol. The diastereomers were separated by

Scheme 54. Refs: **183ab**, **184** [51]

ion exchange chromatography and subsequently hydrolysed under acidic conditions to the respective amino acid enantiomers **200** and **201** [64].

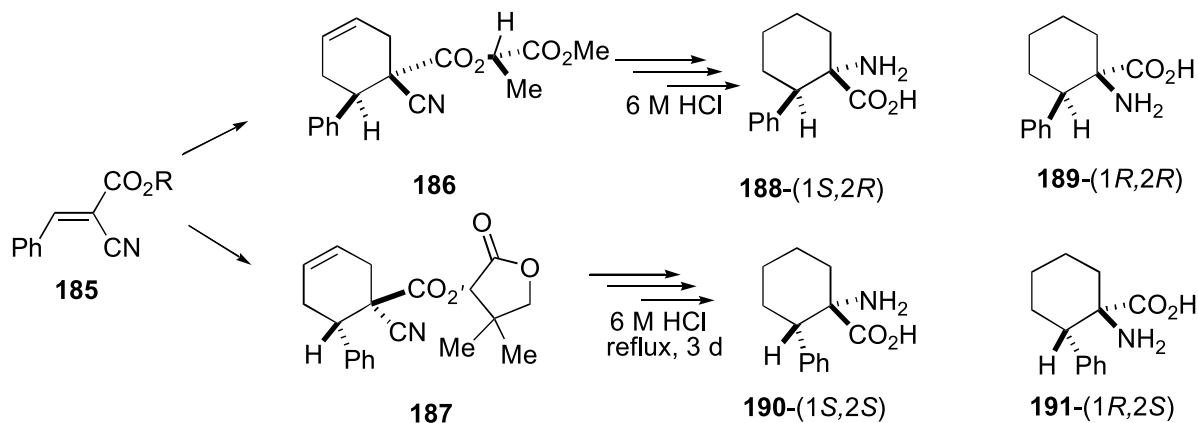
The racemic unsaturated cyclic analogue of glutamic acid, 1-amino-2-cyclohexene-1,3-dicarboxylic acid as the dibenzyl ester **202** when coupled with (*S*)-leucine yielded a mixture of dipeptide diastereomers which were resolved by anion exchange chromatography and the peptides hydrolysed under acidic conditions. The racemic material was available from 3-carboxy-4-cyclohexanone by a Bucherer-Bergs reaction [65].

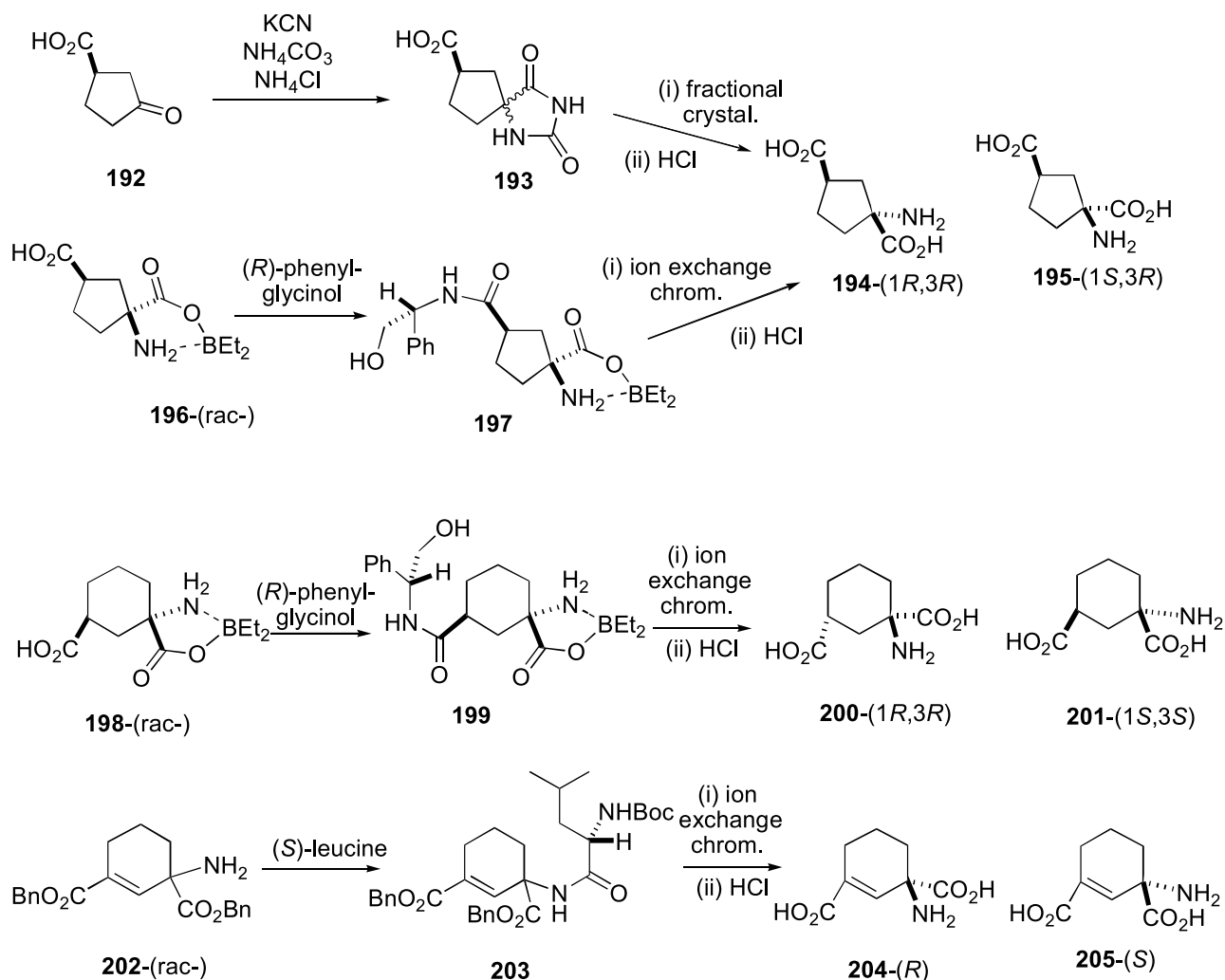
Spiranes **120c**, **121** and **122** in Scheme 57 are α,β -unsaturated carbonyl systems where the carbon–carbon double bond is endocyclic and the carbon–oxygen bond is exocyclic. They can be prepared by aldol condensation reactions according to Scheme 37. Mild acid hydrolysis provides novel, highly functionalized α,β -unsaturated keto derivatives of cyclic α -amino acids **206**, **207** and **209** in 47–59% yield [31]. In the case of the α -acetyl-substrate **122** with a vicinal methyl group, the dipeptide **208** can be isolated in 10% yield after hydrolytic opening of the pyrazine ring in the less shielded 6-position. A shift of the acetyl substituent one carbon unit away from the spiro center has little effect on the outcome of the hydrolytic reaction. Besides the amino acid derivative **209**, the dipeptide **210** is isolated in 15% yield after opening of the pyrazine ring in the 6-position.

The substrates **116** and **117** in Scheme 58 are diastereomers which are available from the Pausson-Khand reaction in Scheme 36. The hydrolytic products **211** and **212** are rigid bicyclic α -amino acid derivatives. Absolute stereochemistry was assigned to the substrates by way of X-ray analyses. Hence the stereochemistry in the amino acid products **211** and **212** is known [48].

An alternative approach for preparing cyclic quaternary amino acids in this field relies on optical resolution. The conformationally constrained 3-aminobicyclo[3.3.0]octane-1,3-dicarboxylic acids **215** and **216** in Scheme 59 have been obtained from the corresponding spirohydantoin diastereomers **214** which could be readily separated, and resolved by fractional crystallisation of the (*S*)-brucine-spirohydantoin diastereomeric salts. The spirohydantoin **214** were prepared by a Bucherer-Bergs reaction from the corresponding ketone [66].

The cyclopentanones **115a** and **115b** in Scheme 60 are difficult to convert into their corresponding amino acid

Scheme 55. Refs: **188**–**191** [60]



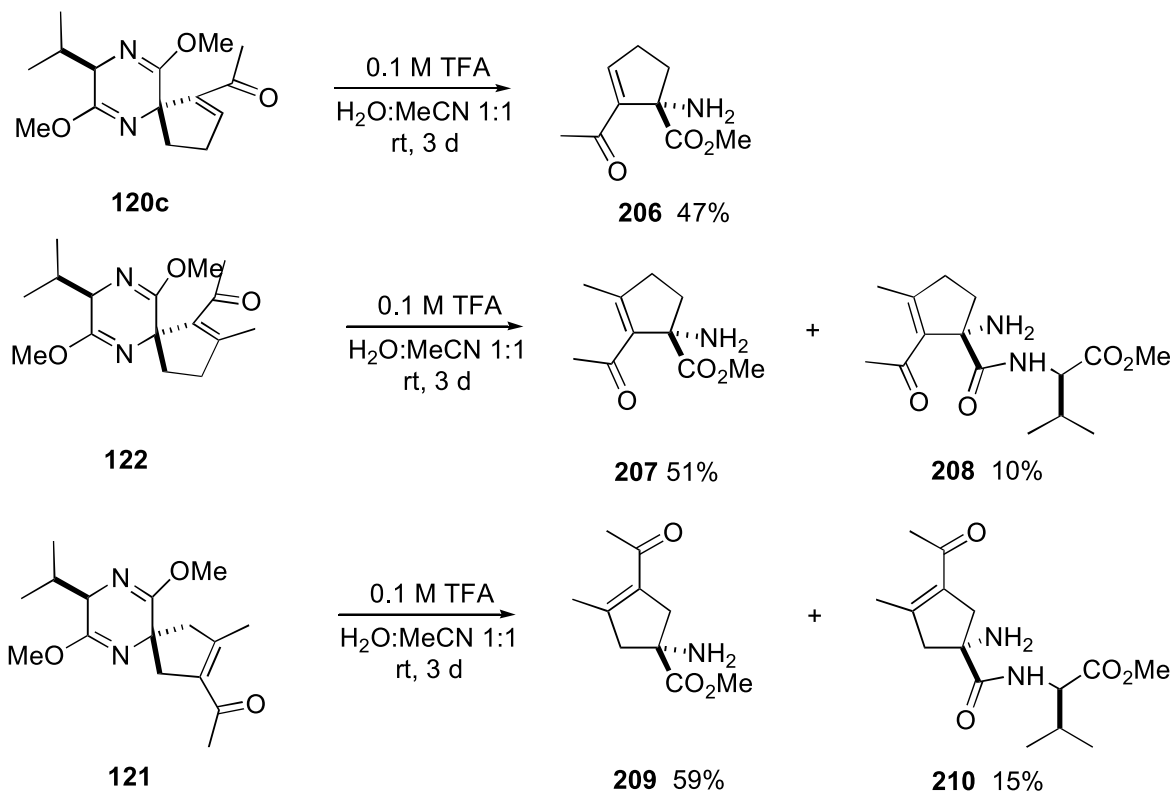
Scheme 56. Refs: **194, 195** [61, 64]; **200, 201** [64]; **204, 205** [65]

derivatives. A cyclic 2-substituent, such as the cyclopentanone moiety together with a second substituent in the pyrazine 2-position, largely prevents the desired hydrolytic cleavage of the pyrazine ring. Under mild acidic conditions, a low yield of the valine dipeptide **217** can be obtained. In strong acid solution, the product is a mixture of the diketopiperazine **218** and the amino acid **219** [22].

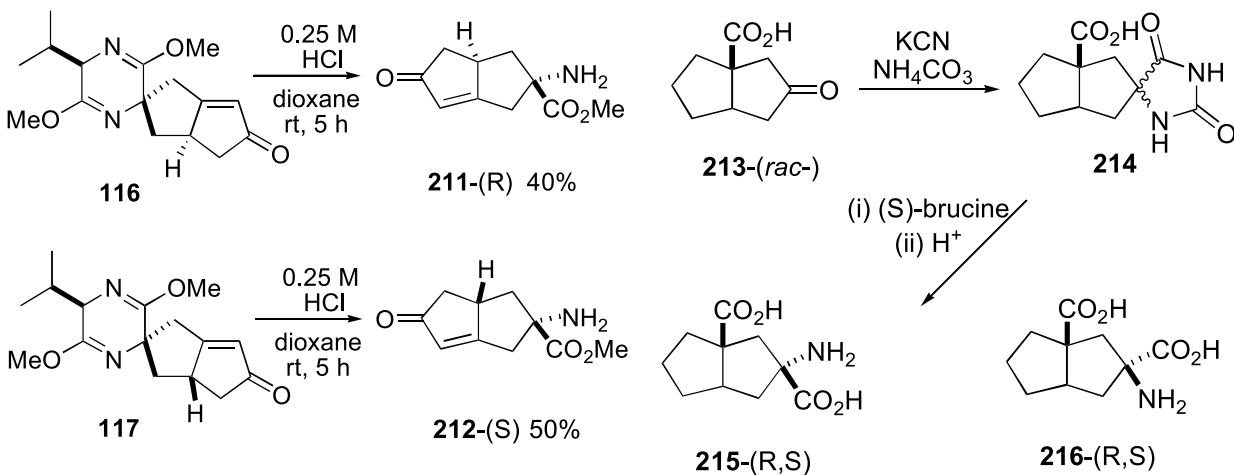
An inspection of structures **104** in Scheme 61 shows a lactam function in the 4-position and an iminoether function in the 1-position. The former is highly resistant towards acid hydrolysis, the latter is acid sensitive. Under mild acid conditions using 0.1 M TFA the corresponding diketopiperazines **137** and **138** are formed in high yields (Scheme 42). The substrates are prepared according to Schemes 32 and 33. Cleavage of the diketopiperazine derivatives to amino acid constituents would require strong

hydrolytic acidic conditions. Hydrolysis of the monolactam ethers **104** with 3 M hydrochloric acid at room temperature, provides the hydrochlorides **220** after opening of the ring in the more reactive 1-position. The amines can be isolated as the Boc-protected dipeptides **221a** and **221b** after treatment with triethylamine and di-*t*-butyl dicarbonate (Boc₂O) [32]. The homologue cyclohexanone substrates **109** react in a similar manner under mild acidic conditions with ring-opening in the 1-position to provide the dipeptides **222**. The cyclohexanone diastereomers **113** react under hydrolytic conditions in the same manner to form the corresponding dipeptides **223** in almost the same yields [21]. The product can be regarded as an α -quaternary pipecolic acid derivative [67].

RCM-reactions effected by Ru(II)-catalysis have been applied directly to appropriate amino acid derivatives for the construction of partially reduced azines as shown in



Scheme 57. Refs: 206, 207, 208, 209, 210 [31]



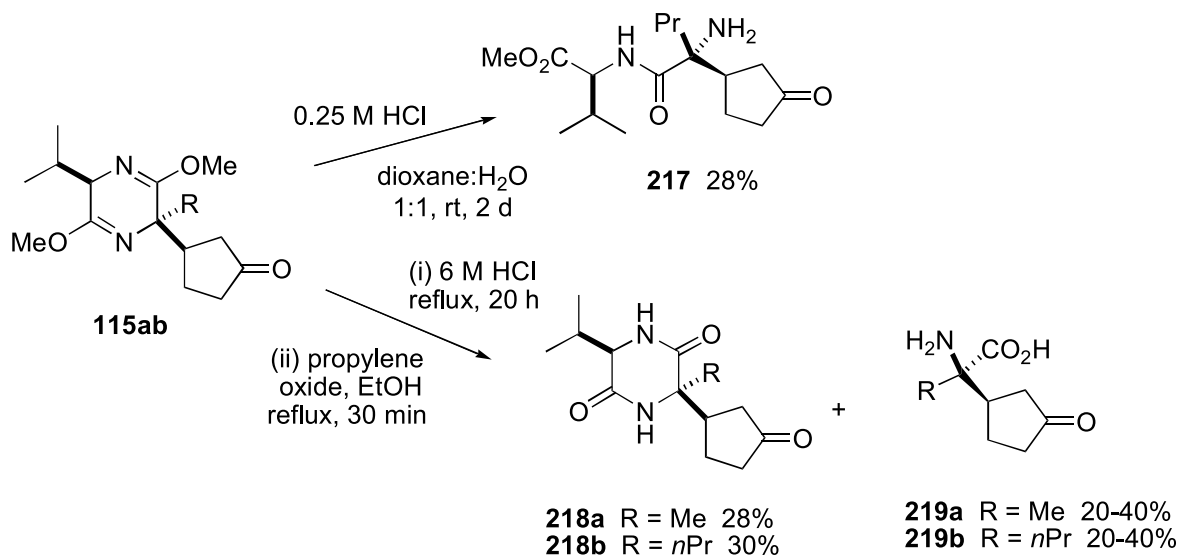
Scheme 58. Refs: 211, 212 [48]

Scheme 59. Refs: 214, 215, 216 [66]

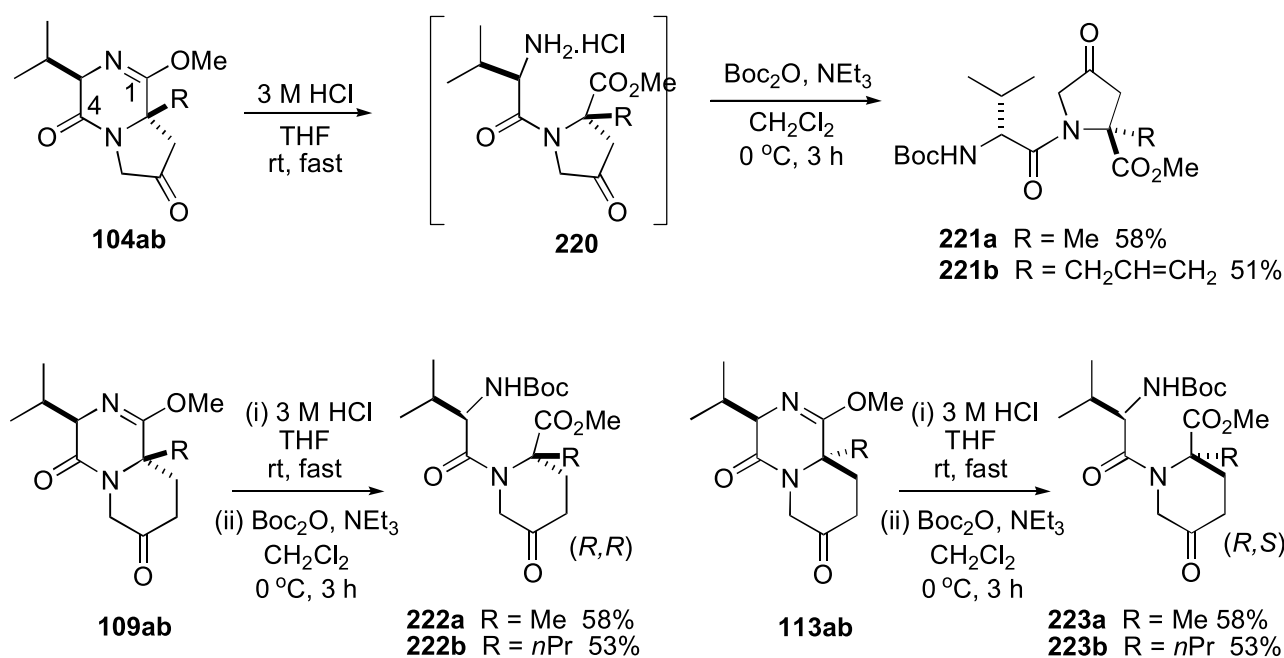
Scheme 62. Thus (S)- α -methyl- α -allylglycine is a substrate for the synthesis of α -methylproline derivatives by ruthenium-catalysed ring closing olefin metathesis [68]. In this reaction sequence, α -allylated alanine **224** was converted into its *N*-4-methoxybenzyl (PMB) derivative and *N*-allylated. The resulting diene **225**, when subjected to the RCM reaction under the influence of Ru(II)-catalysis, afforded the α -quaternary didehydro

proline derivative **226**. The diene **227** was available from the corresponding *N*-acryloyl derivative, and after the RCM reaction yielded the oxo analogue **228**.

The importance of proline and many of its derivatives is expressed by a number of syntheses of α -substituted prolines. The Seebach procedure has most often been used in the preparation of α -alkylprolines in a stereocontrolled manner [69]. Enantiomerically pure proline is condensed



Scheme 60. Refs: 217, 218ab, 219ab [22]

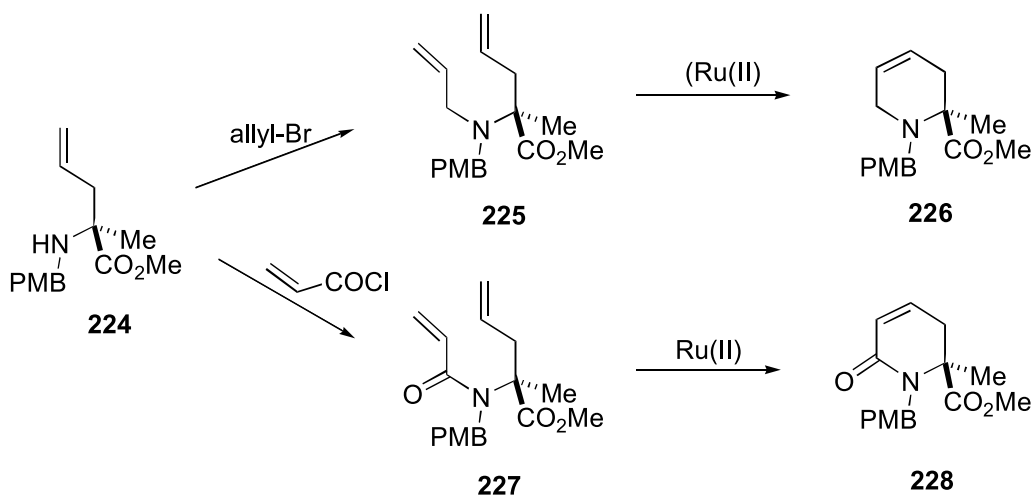


Scheme 61. Refs: 221ab [32]; 222ab, 223ab [21]

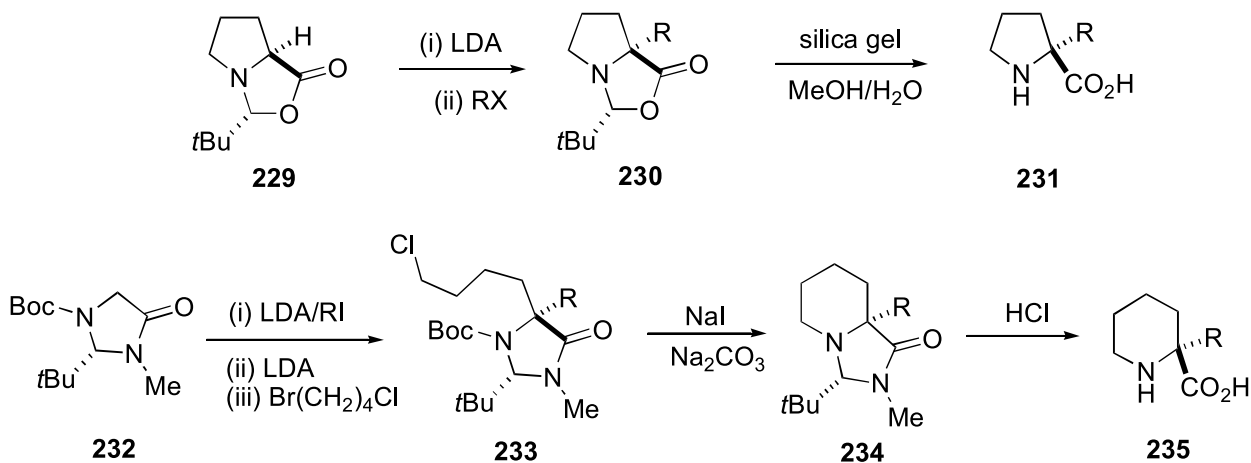
with pivaldehyde to provide mainly a single stereoisomer of 2-*tert*-butyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one **229**. Deprotonation with LDA and treatment with an alkyl halide produce a single diastereomer **230**. The products are fairly acid resistant but can be cleaved to the corresponding proline amino acid **231** under strongly acidic conditions. Mild conditions for hydrolysis, however, have been claimed using a suspension of silica gel in methanol-water [70]. A substituent in any other position would

require the corresponding proline as a substrate for the α -alkylation as in the synthesis of 2-alkyl-4-hydroxyprolines from (2*S*,4*R*)-4-hydroxyproline [71].

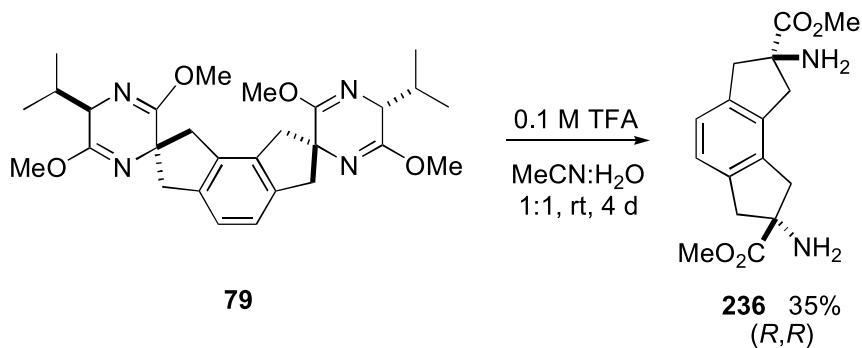
Asymmetric syntheses of α -alkylpiperidic acid are based on the construction of the heterocyclic ring by intramolecular cyclisation of a geminally disubstituted glycine equivalent carrying an appropriate leaving group on the side chain as in the case of the reaction shown for the Seebach chiron **232**. The latter is dialkylated in a stepwise manner,



Scheme 62. Refs: 225–228 [68]



Scheme 63. Refs: 231 [70]; 235 [72]



Scheme 64. Refs: 236 [29]

cyclised by intramolecular alkylation and the product **234** hydrolysed under strongly acidic conditions to the piperidine derivative **235** [72].

Hydrolytic cleavage of the congested bis-spiro pentacyclic substrate **79** under mild conditions using 0.1 M TFA

at ambient temperature provides the rigid bis(α -amino acid) **236**. The reaction is slow and only partially completed when the reaction was stopped after 4 days, yield 35% of the target compound, the *as*-indacine bridged amino acid **236** [29].

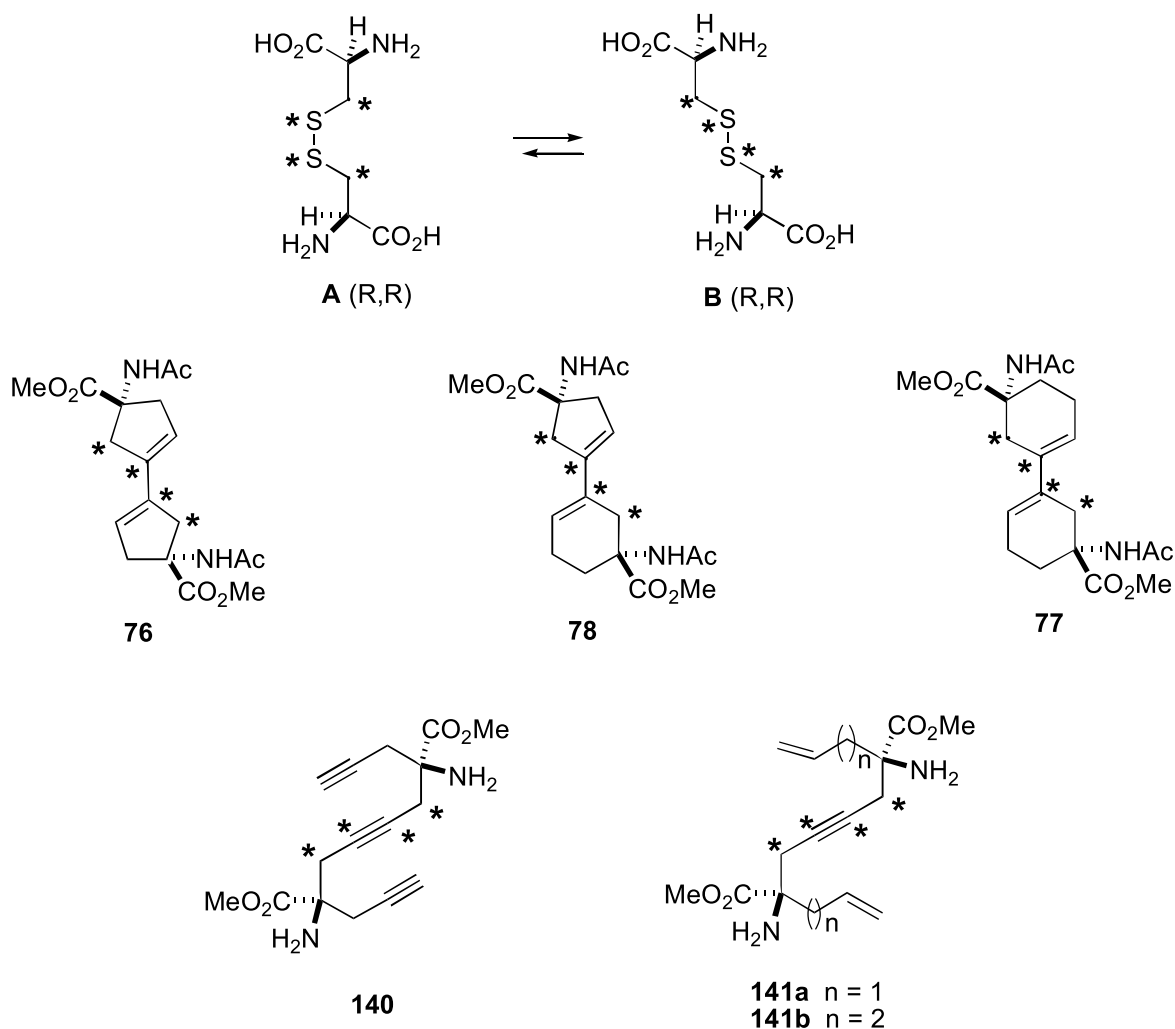


Fig. 2. C₄-Bridged conformationally constrained carba-analogues of cystine

Structure confirmations: Assignments of configurations and regiochemistry for the compounds generated under the title of the review have been greatly assisted by single crystal X-ray analyses. Structure data have been reported for the following compounds: **57** [41], **73** [36], **79** [29], **115b** [22], **116** [48], **117** [48], **123** [41], **124b** [51], **126** [26], **127** [41], **130** [32], **131** [52], **136** [52], **138a** [21].

Cystine, carba analogues: To provide a structural overview of rigidly bridged bis-(α-amino acid) derivatives, the highly novel structures have been summarised in Figs. 2 and 3 [73]. The cystine –CH₂SSCH₂–bridge between the α-glycyl carbons consists of four atoms. The structures in Fig. 2 may be regarded as quaternary C₄-carba analogues of cystine, which itself is drawn as two conformers **A** and **B**. The starred four carbon atoms constitute a C₄-bridge between the α-glycyl carbon atoms. In the cystine carba analogues **76**, **77**, and **78** the two rings are connected by a central single bond. The

central connection in the alicyclic compounds **140**, **141a** and **141b** consists of a triple bond.

In Fig. 3 the α-glycyl carbons are connected through a rigid, fused three-membered ring system where the amino acid functions are fixed in a *cis-trans* relationship with respect to the planar ring system. The distance between the α-glycyl carbons, as starred in the structures, still indicates that the structures can be regarded as C₄-carba analogues. In the rigid spiranes **75**, however, five-bridge carbons separate the α-glycyl carbons. The amino acid moieties in a spirane have an orthogonal relationship, as have the spirane annulated rings. The distance between the amino acid functions in the spirane is less than in a corresponding planar structure and therefore only the ring carbons in the spirane have been starred for indicating the bridge distance between the α-glycyl carbons.

Conclusion: Methodologies for the preparation of several novel structural groups of α-quaternary-α-amino

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