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# Stereocontrolled construction of conformationally constrained and rigid bis(α-amino acid) derivatives*

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*Abstract*: Cystine is regarded as a four-atom bridged bis(α-amino acid). The bridge between the two glycine moieties in cystine has been replaced with all-carbon $C_4$-bridges between the α-carbon of the glycines. The products are dicarba analogs of cystine. Conformational constraints have been conferred on these molecules by insertion of *cis*- and *trans*- double bonds in the bridge, by alkylidene substituents, by insertion of a triple bond, by insertion of aromatic or heteroaromatic rings, or otherwise by ring formation. Particularly rigidified dicarba analogs of cystine have been prepared where the α-amino acid carbon is quaternary and part of tricyclic ring structures. Ru(II)-catalyzed ring-closing metathesis (RCM) reactions have been widely used in the preparation of cyclic amino acids. Conformational constraints in acyclic structures result from substitution by simple alkyl, alkenyl, or alkynyl groups at the α-amino acid carbon in the formation of α-quaternary amino acid derivatives.

## INTRODUCTION

The introduction of conformational constraints that affect secondary and tertiary peptide structures by incorporation of noncoded amino acids may provide useful information and understanding of structural requirements for bioactivity [1]. Access to appropriate conformationally restricted or stiffened amino acid analogs is essential for these studied. In this paper, we have summarized some of our work on the preparation of dicarba analogs of cystine.

Cystine residues are a main structural element in peptide and protein architectures through the disulfide bonding. When cystine exerts mainly a skeletal, structural function, isosteric structures may be envisaged to take its place. In some cases, it may also be desirable to replace cystine with a nonreducible cystine isosteric analog. In the structurally simplest case, when the $–CH_2–S–S–CH_2$-bridge between the two glycine α-carbons in cystine is replaced by an all-carbon $–(CH_2)_4$-bridge, the new $C_4$-bridge amino acid (*S*,*S*)-2,7-diaminosuberic acid [(*S*,*S*)-2,7-diaminooctanedioic acid], is a nonreducible isosteric dicarba analog of cystine. Early studies of the replacement of cystine by (*S*,*S*)-2,7-diaminosuberic acid in essential peptides include peptides such as oxytocin, calcitonin, and somatostatin.[2].

Replacement of the disulfide linkage with its conformational preferences with an ethylene substitute will increase the conformational freedom of the bridged amino acid as compared to cystine. Substitution in the dicarba analog, however, will increase conformational constraints and may be explored for subtle-tuning of conformational constraints in the amino acid and its derived peptides. We have for some time been involved in the preparation of conformationally constrained α-amino acids.

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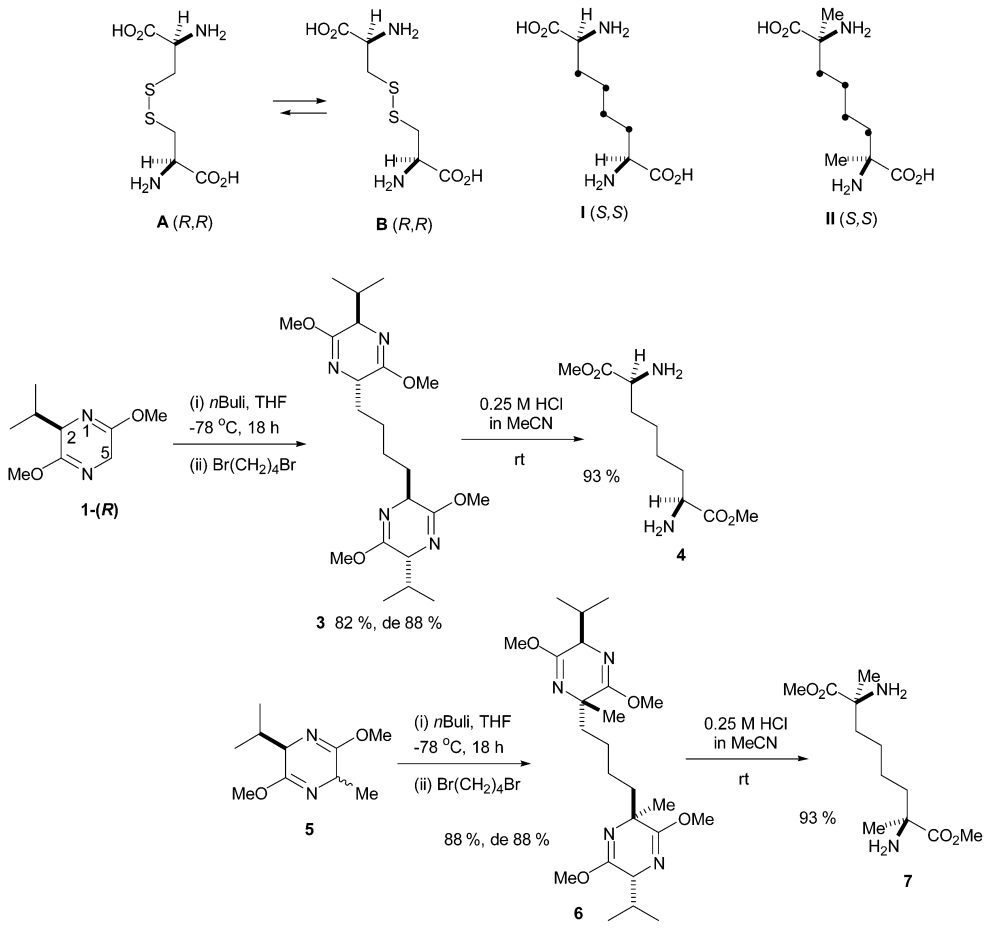
From these studies, we have reported on cystine analogs by insertion of a double or triple bond in the $C_4$-bridge, by insertion of aryl or heteroaryl groups, or by preparing appropriate annulated structures (vide infra). The conformational constraints in $C_4$-bridged molecules have been additionally increased by carbosubstitution at the α-carbon of the α-amino acid (vide infra).

Besides the dicarba cystine analogs, major emphasis has been reported on the preparation of $C_3$-bridged glycines because members of this family are naturally occurring in certain microorganisms and higher plants [3]. References are also made to a $C_1$-bridge [4], to $C_2$-bridges [5,6], a $C_5$-bridge [7], and higher-member functionalized bridges [8].

Several chiral auxiliaries are available for amino acid constructions [9]. We have used extensively the Schöllkopf "bislactim ether" chiron in our bridge-forming reactions with lithiated 2(*R*)- or 2(*S*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine [10].

## DISCUSSION

In Scheme 1, cystine has been drawn in a *cisoid* form **A** and an extended *transoid* form **B**. The dicarba analogs **I** and **II** are drawn in an extended form. The methyl ester **4** of the parent compound was prepared by a double alkylation of the Schöllkopf **1**-(*R*) chiron. Both enantiomeric forms of the Schöllkopf bislactim ether have been used as substrates in this work.



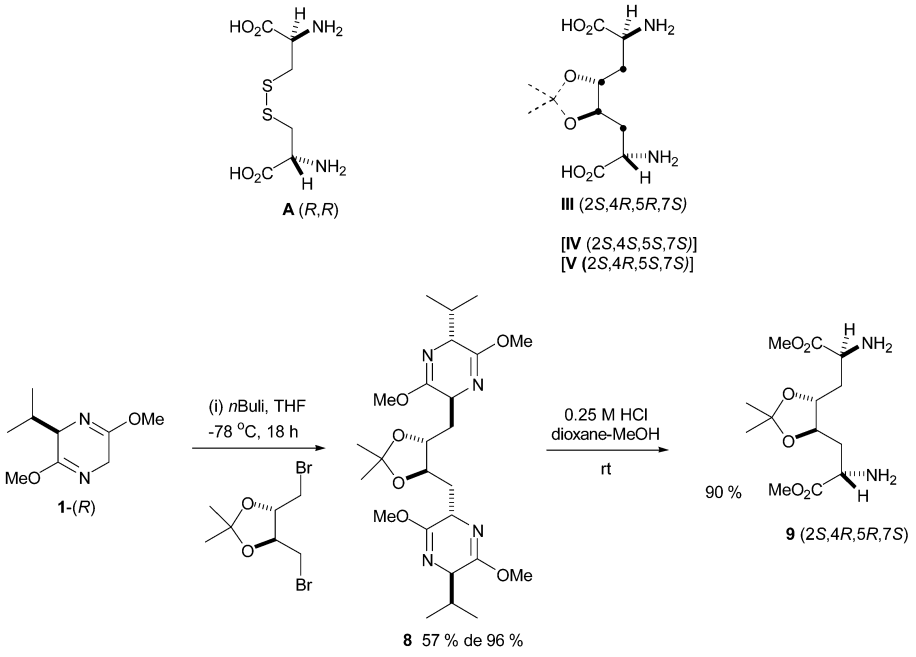

**Scheme 1**

Metallation is normally effected by butyllithium at –78 °C, and the electrophile adds preferentially in a *trans* manner with respect to the isopropyl group. The first formed product is the alkylating agent in the next step with another species of lithiated bislactim ether **1**. The product is the bridged structure **3**, which was formed in high yield [5,11]. The diastereomeric access (de) for the two steps was 88 %, which would correspond to about 94 % de in each separate step. Fortunately, in almost all cases encountered so far (vide infra), separation or purification of the diastereomeric products is readily effected by flash chromatography on silica gel. Hydrolysis of the bridged compound to provide the dicarba cystine analog **4** was effected under weakly acidic conditions as advised by Schöllkopf in his work [12]. The coformed methyl ester of valine is normally removed by slow distillation with a minimum of heating before an additional purification step by chromatography. Final purification may be by recrystallization. Hydrolysis under forcing conditions takes another course with formation of the corresponding diketopiperazines. Strongly acidic conditions are required for hydrolysis of diketopiperazines. The dicarba analog of cystine was first prepared as a stereochemical mixture by the Gabriel synthesis from octanedioic acid [13]. In its optically active form, the dicarba analog was first prepared from appropriately protected glutamic acid by electrochemical Kolbe synthesis [14]. Preparation by this method has since been investigated in some detail and greatly improved with inclusion of a variety of protecting groups, but yields are moderate [15]. The dicarba cystine analog has $C_2$-symmetry and will react as such under peptide-forming conditions. For the construction of unsymmetrical peptides, a method has been developed with **4** as substrate to prepare a differentially protected dicarba analog of cystine [16].

Substitution at the α-carbon in α-amino acids leads to conformational constraints. The α-amino acid carbon becomes quaternary. A number of both acyclic and cyclic quaternary α-amino acids have been prepared and studied inter alia for conformational preferences and ability to impart well-defined conformational constraints to a peptide backbone [17]. The dimethyl ester of the bridged α,α′-dimethyl dicarba cystine analog **II** in Scheme 1 represents the structurally simplest member in our series.

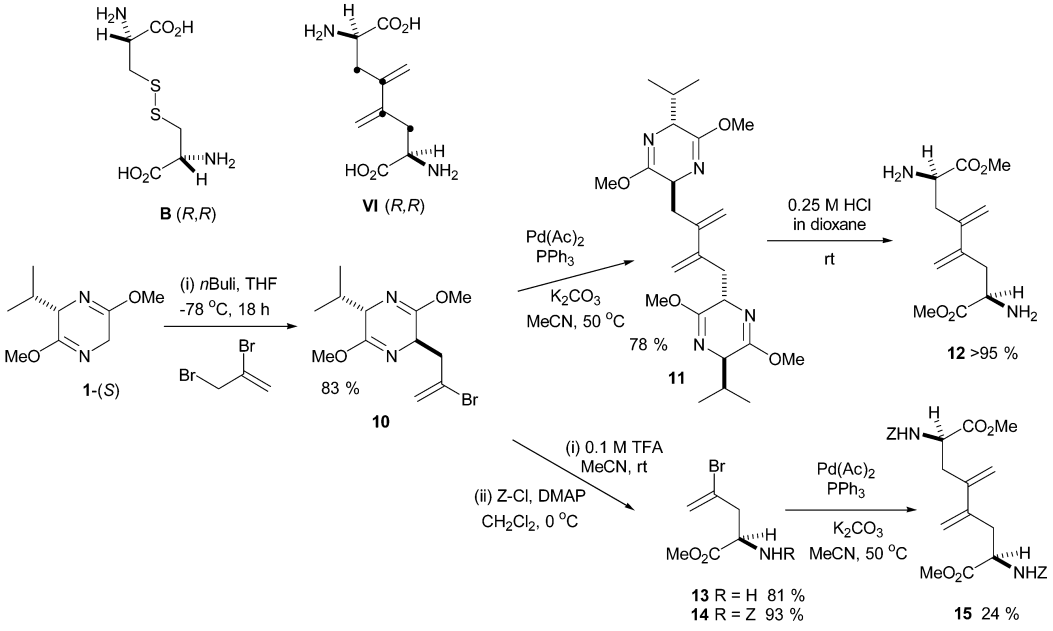
The stereochemistry at C5 in the bislactim ether ring is of little interest in the methyl-substituted substrate **5** because either stereoisomer of the bislactim ether will furnish the same carbanion. Stereoselectivity in the second alkylation is *trans* with respect to the isopropyl group. Whereas stereoselectivity in the first alkylation may be variable, the second alkylation is generally highly stereoselective (vide infra). With the small methyl group, however, diastereoselectivity was only 88 %, about the same as in the parent compound **3**. Since the configuration at C5 is controlled by the configuration of the isopropyl group in the cyclic valine residue, choice of the chiron will provide either configuration of the new amino acid. But it will be recalled that the stereochemistry in dialkylation reactions is controlled by the second alkylation alone. Hence, either stereoisomer at C5 can be prepared from the same configurational chiron by changing the order of the two alkylation reactions (vide infra). The potential bridge was the alkylating agent in the preparation of the dimethyl derivative **6**. Hence, the product **6** must have the (*S*,*S*)-configuration. Mild acid hydrolysis furnished the amino acid dimethyl ester **7**.

In the second series of compounds, rotational freedoms in the bridge have been greatly restricted by introduction of two hydroxy groups. The two hydroxy groups have been fixed as an acetal into a five-membered ring shown in the structures **III**–**V** that become available from the respective $C_3$-sugar alcohols in Scheme 2. The preparative reactions are shown for the acetonide protected sugar alcohol (2*R*,3*R*)-2,3-*O*-isopropylidenethreitol derived product **III**. Acetonide-protected (2*R*,3*R*)-2,3-*O*-threitol was initially brominated to provide the corresponding (2*S*,3*S*)-dibromo alkylating agent. Reaction with this bulky substance gave a moderate yield of the bridged structure **8** with high diastereoselectivity. Chemoselective cleavage of the dihydropyrazine rings under mild acid conditions provided the bridged bisamino acid **9** in 90 % yield. For incorporation into peptides by the solid-phase technique, the methyl ester groups were selectively hydrolyzed using 1 M lithium hydroxide. The product is the amino acid **III** in Scheme 2 that was subsequently protected as a 9-fluorenemethyloxycarbonyl (Fmoc) derivative for peptide work [18].




**Scheme 2**

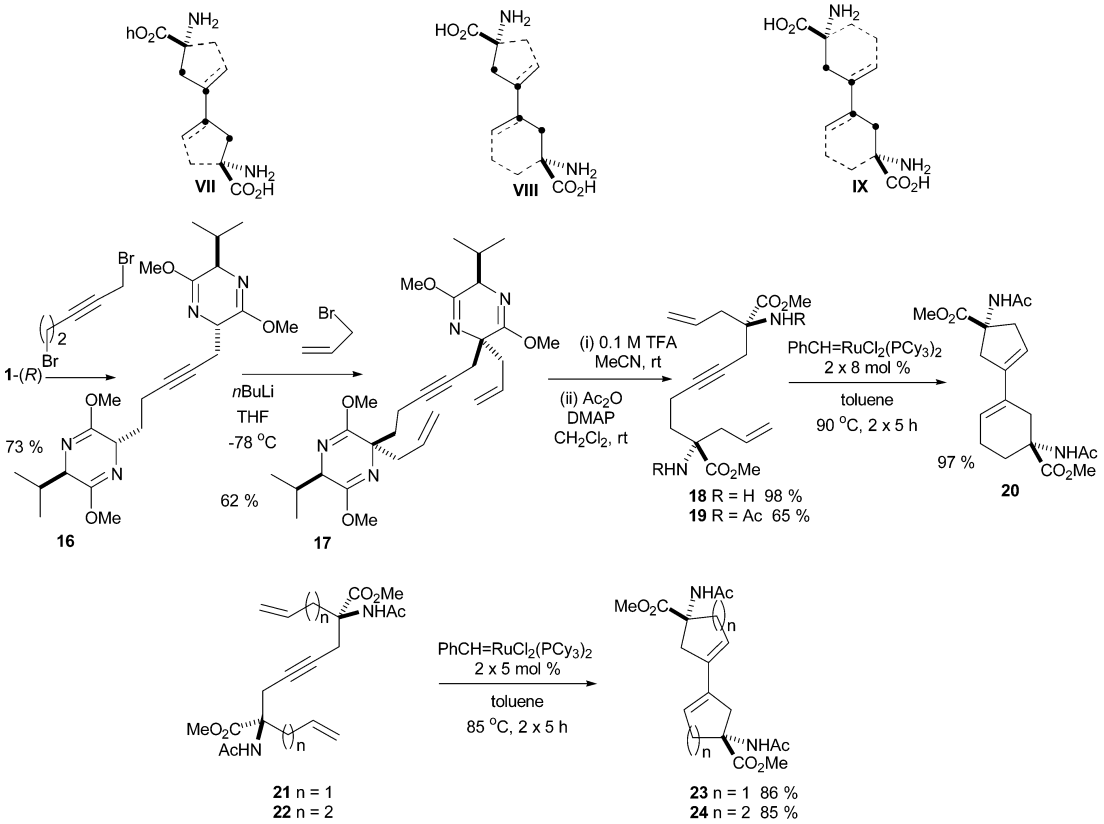
In Scheme 3, the alkylidene amino acid **VI** can be regarded as an analog of cystine **B** conformer in that the π-electrons of the double bonds may possess properties comparable to the sulfur lone pair of electrons in cystine. In this case, the bridge has been constructed by a cross-coupling reaction between two monomeric species **10**. The latter were prepared from the **1**-(*S*) chiron by lithiation and reaction with 2,3-dibromopropene. High diastereoselectivity in the alkylation is attributed to the relative bulki-




**Scheme 3**

ness of the 2-bromo substituent [19]. The (*S*)-isomer has been prepared similarly [20]. Several attempts were made to find a high-yielding cross-coupling reaction for the preparation of the bridged structure **11**. Our best conditions with palladium acetate and excess triphenylphoshine in the presence of a base provided 78 % yield of the coupling product **11**. Subsequently, mild hydrolytic conditions yielded the dimethyl ester of the bridged amino acid **12**. Alternatively, the initial alkylation product **10** was hydrolyzed to the amino acid methyl ester **13** that was protected for the coupling reaction as a benzyloxycarbonyl (Z) derivative **14**. The Pd-catalyzed cross-coupling reaction in this case was less satisfactory. Moderate yield of the coupling product **15** resulted.

The same concept lies behind the structures **VII**–**IX** in Scheme 4 where the double bond has been incorporated into five- and six-membered rings [21]. The amino acid products are also intermediates for the preparation of the highly rigidified amino acids shown in Schemes 11 and 12.

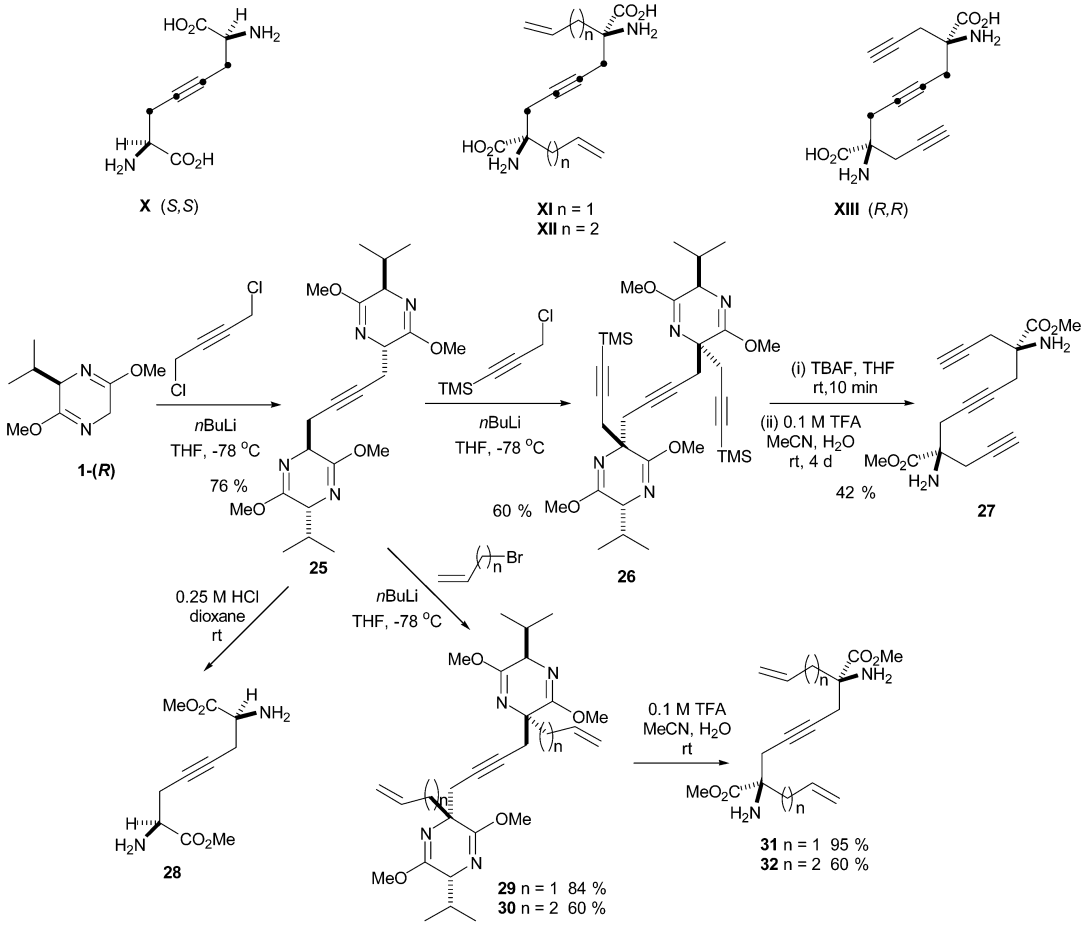



**Scheme 4**

The amino acids **VII**–**IX** are all quaternary α-amino acids where the α-carbon of the amino acid has become part of the ring structure. The derivative **20** corresponding to the unsymmetrical structure **VIII** was prepared from the **1**-(*R*) chiron that was initially alkylated with 1,5-dibromo-2-pentyne in 73 % yield. In competition with the alkylation reaction, a minor product formed was due to monoalkylation and a subsequent HBr elimination in preference to a second alkylation, showing that at least in this case reaction at allylic carbon was faster than at alkyl carbon. Lithiation and alkylation with allyl bromide provided the dienyne **17** in 62 % yield after two alkylation steps. The reaction is stereoselective in that the electrophile becomes attached *trans* to the isopropyl group. Only one stereoisomer **17** was seen from the allylation reactions. Mild acid hydrolysis with 0.1 M tetrahydrofuran (TFA), and protection of the amino group by acetylation, gave the products **18** and **19** in 98 % and 65 % yield, re-

spectively. Formation of the bicyclic amino acid derivative **20** was effected by use of the Grubbs's bis(tricyclohexylphosphine)benzylideneruthenium dichloride catalyst system in a ring-closing metathesis (RCM) reaction [22]. We have used extensively this catalyst system for the preparation of cyclic α-quaternary α-amino acids [23]. In this case, the RCM reaction was effected in two steps. After 5 h at 90 °C, the same amount of catalyst was added once more and the heating at this temperature was continued for another 5 h when close to quantitative yield of the cascade bridged structure **20** was obtained. The catalyst was added in two portions because of low chemical stability and gradual destruction of the catalyst in slow reactions.

The symmetrical amino acid substrates **21** and **22** were available by *N*-acetylation of the amino acid esters **31** and **32** that were prepared as shown in Scheme 5. Also in these cases, the cascade reactions under Ru(II)-catalysis proceeded extremely well with formation of the bicyclic amino acid derivatives **23** and **24** [24].



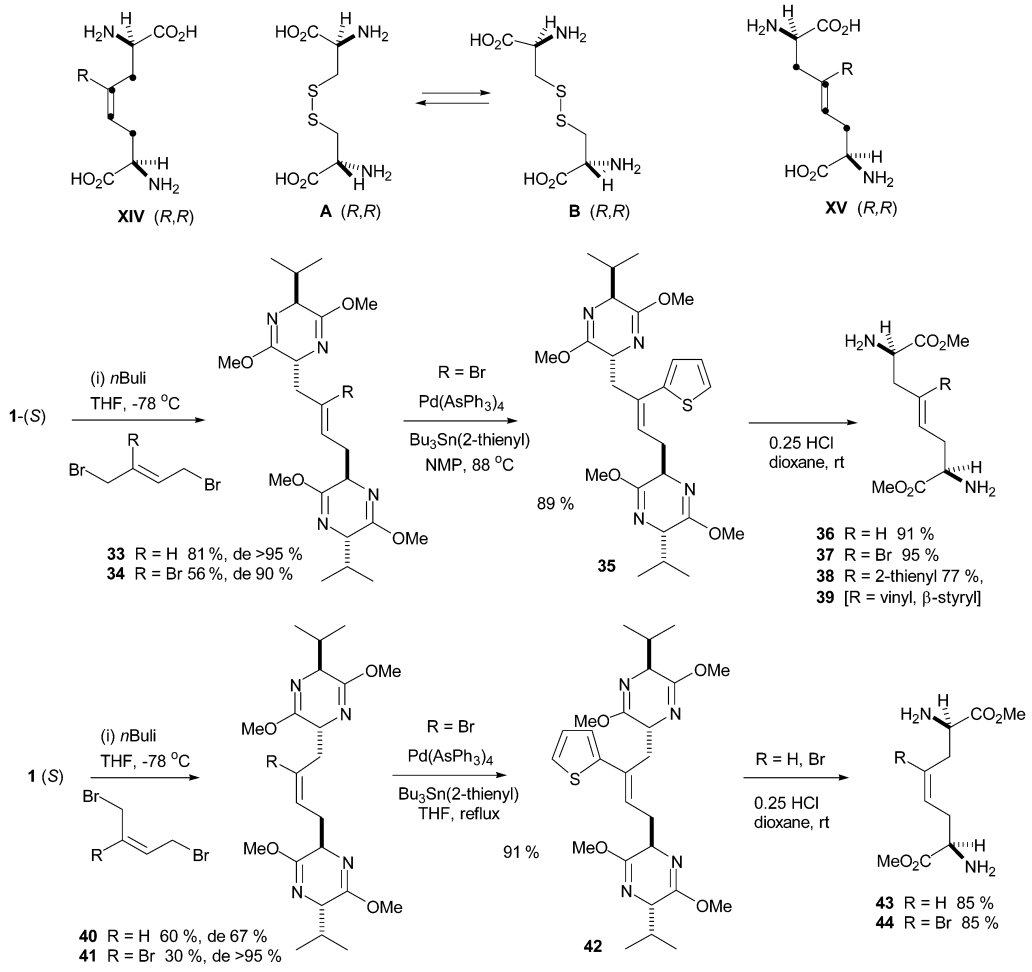

**Scheme 5**

Scheme 5 shows an extended dicarba cystine analog **X** with a triple bond in the middle of the $C_4$-bridge, and α-quaternary homologs with a triple bond **XIII** and a double bond **XI** and **XII** in the α,α′-substituents. Alkylation of the **1**-(*R*) chiron was with 1,4-dibromo-2-butyne or the dichloro analog [24]. Mild acid hydrolysis provided the parent amino acid dimethyl ester **28** [11]. For the triyne amino acid **XIII** derivatives, the bridged substrate **25** was lithiated and alkylated with silyl-protected propar-

gyl chloride. The propargyl group enters *trans* to the isopropyl group. Only stereoisomer **26** was seen and was obtained in 60 % yield.

Tetrabutylammonium fluoride (TBAF) was used to remove the silyl protection, and the product was hydrolyzed to the triyne amino acid diester **27** under mild acid conditions [25]. For the alkenyl reactions of the bridged substrate **25**, the corresponding bromo alkylating agents were used. In each case, only one diastereoisomer was seen. Mild acid hydrolysis provided the quaternary dienyne amino acid diesters **31** and **32** [24].

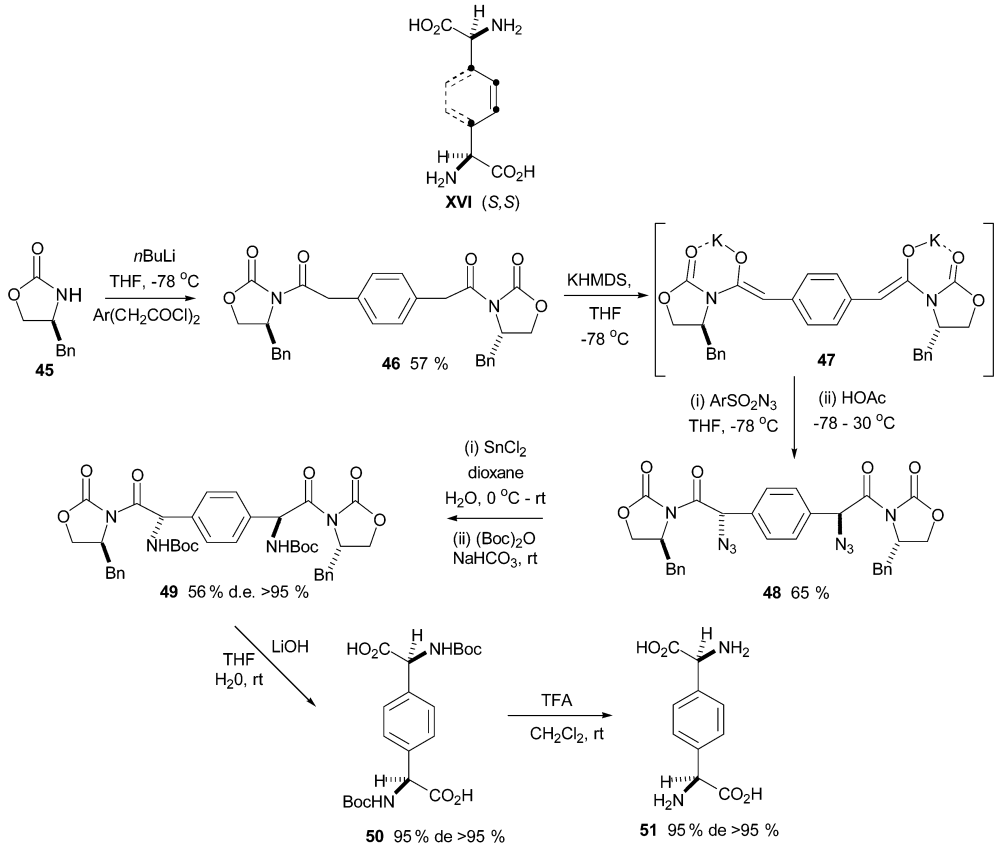
In the series of compounds shown in Scheme 6, conformational constraints have been achieved by insertion of a double body in the middle of the $C_4$-bridge. The *cis*-derivatives **XIV** can be compared with the *cisoid* form **A** of cystine, the *trans*-derivatives **XV** with the *transoid* form **B**. Substrate **1**-(*S*) was the chiron used in the series shown. Alkylation of the lithiated species **1**-(*S*) with *trans*-1,4-dibromo-2-butene provided the bridged structure **33** in high yield. But the reaction is especially remarkable in that very high diastereoselectivity was repeatedly obtained, in excess of 95 % after two stereocontrolled bond-forming steps. On the other hand, with *cis*-1,4-dibromo-2-butene as alkylating agent, the diastereoselectivity was only 67 % in product **40**. With a bromine atom attached to one of the olefinic carbons, alkylations were more difficult. Low yields resulted of the products **34** and **41**, but the diastereoselectivity was good. Subsequently, the bromo derivatives were to be substrates for the intro-




**Scheme 6**

duction of additional carba-substituents by palladium-mediated cross-coupling reactions. The reactions are shown for the introduction of a 2-thienyl substituent. Other examples are given by the vinyl and β-styryl derivatives **39**. The bromo substrates appear to be highly crowded, making it difficult for the metal of the catalyst to access the bromine substituent. Little or no reaction occurred with triphenylphosphine-ligated palladium. Ligation with the less nucleophilic triphenylarsine, however, led to coupling reactions. In the *trans*-substrate **34**, the Stille coupling required heating in 1-methyl-2-pyrrolidinone (NMP) at 88 °C. Around this temperature, the reaction was turned on. In the *cis*-substrate **41**, the reaction proceeded well under reflux conditions in THF, indicating that the bromo substituent is more accessible in the *cis*-substrate. Under these conditions, both the 2-thienyl products **35** and **42** were obtained in high yields, 89 and 91 % respectively. Some of the products were subjected to acid-catalyzed hydrolysis to provide the corresponding amino acid diesters **36**–**39** and **43**–**44** [26].

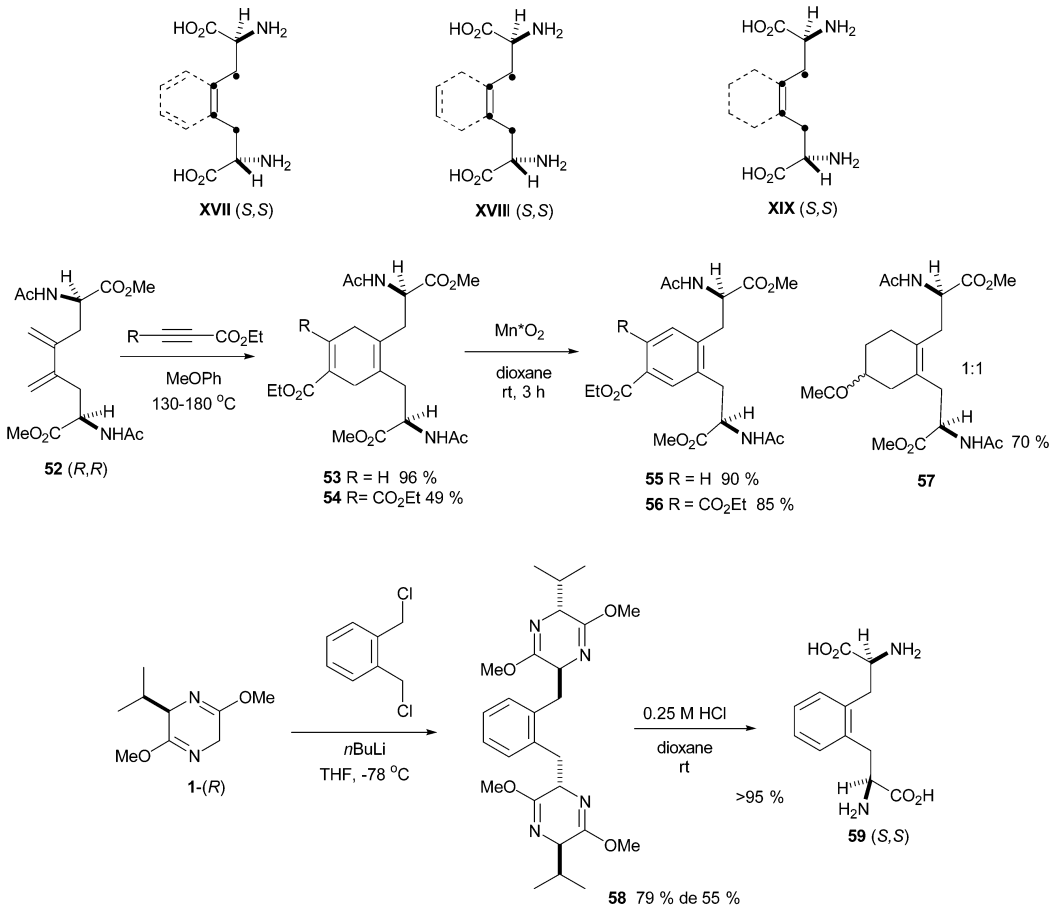
In Scheme 7, a phenyl ring carrying the glycine functionalities in the 1,4-positions constitutes the $C_4$-bridge. Thus, structure **XVI** corresponds to the *cisoid*-form **A** of cystine. The bislactim ether approach (vide supra) requires an electrophilic arene. This excludes direct arylation unless the aryl group is made strongly electrophilic by appropriate substitutions or by metal complexation. For this reason, the Evans chiral carboximide approach, where the nitrogen is introduced as an electrophile on chiral phenylacetamide derivatives, was adapted for our purpose [27]. Preparation of the target molecule **51** is shown in Scheme 7 [28]. 1,4-Benzenediacetyl dichloride was used for acylation of lithiated (*S*)-4-benzyl-2-oxazolidinone to form the diacetamide **46**. Introduction of electrophilic nitrogen was effected by 2,4,6-triisopropylbenzenesulfonyl azide after initial enolization of the bisacetamide **46** at both α-car-




**Scheme 7**

bons by addition of a slight excess of potassium hexamethyldisilazide at 78 °C. The stereochemical course can be rationalized with the presence of a pseudo-bicyclic intermediate **47** that is preferentially attacked by the electrophile at the less shielded *trans*-face to the benzyl substituent. The initially formed triazene in the azidolysis was cleaved to the diazide **48** on treatment with acetic acid in the cold. Reduction with tin(II) chloride was the preferred method for reduction of the azido to amino groups. It was difficult to isolate the desired diamine from the complex reaction mixture. The diamine was, therefore, converted in situ to the *tert*-butyloxycarbonyl (Boc) derivative **49** before isolation by extraction and chromatography. Aqueous lithium hydroxide was used for hydrolysis of the methyl ester groups to form the *N*-Boc amino acid **50**. The Boc-protecting groups were removed by treatment with TFA to provide (*S*,*S*)-benzene-1,4-bis(glycine) (**51**). The reaction sequence described (vide supra) worked equally well for the preparation of the regioisomeric benzene-1,3-bis(glycine). The latter can be regarded as a $C_3$-bridged bis(α-amino acid) derivative [28].

Vicinal bis(alanine) substituted ring systems can also be regarded as dicarba analogs of cystine as indicated by the *ortho*-disubstituted benzene derivative **XVII** in Scheme 8. From the methods envisaged for the preparation of this family of amino acids, two approaches are shown in Scheme 8. In the first case, an appropriately substituted diene is reacted with an alkyne under Diels–Alder conditions [29]. The diene **52** was prepared by acetylation of the corresponding amino acid dimethyl ester **12**, which was available from the cross-coupling reaction between two monomeric structures as described in



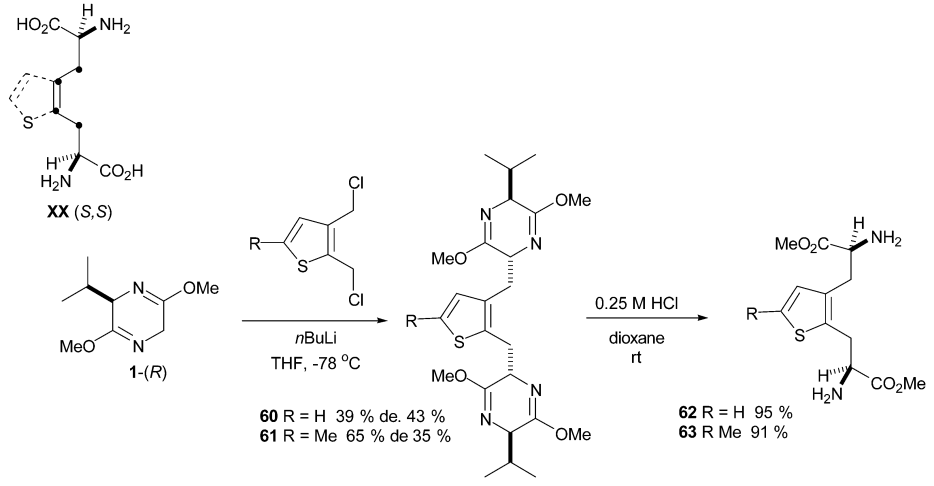

**Scheme 8**

Scheme 3. Adduct formation with the ethyl esters of either acetylene carboxylic acid or acetylenedicarboxylic acid was effected on heating in anisole.

The adducts **53** and **54** belong to a family of 1,4-dihydrobenzenes as dicarba analogs **XVIII** of cystine. Treatment of the adducts with manganese dioxide provided the benzene-bridged target molecules **55** and **56**. Similarly, when the diene **52** was reacted with methyl vinyl ketone under similar conditions, a tetrahydrobenzene-bridged amino acid derivative **57** was obtained, a member of a dicarba analog series based on structure **XIX**.

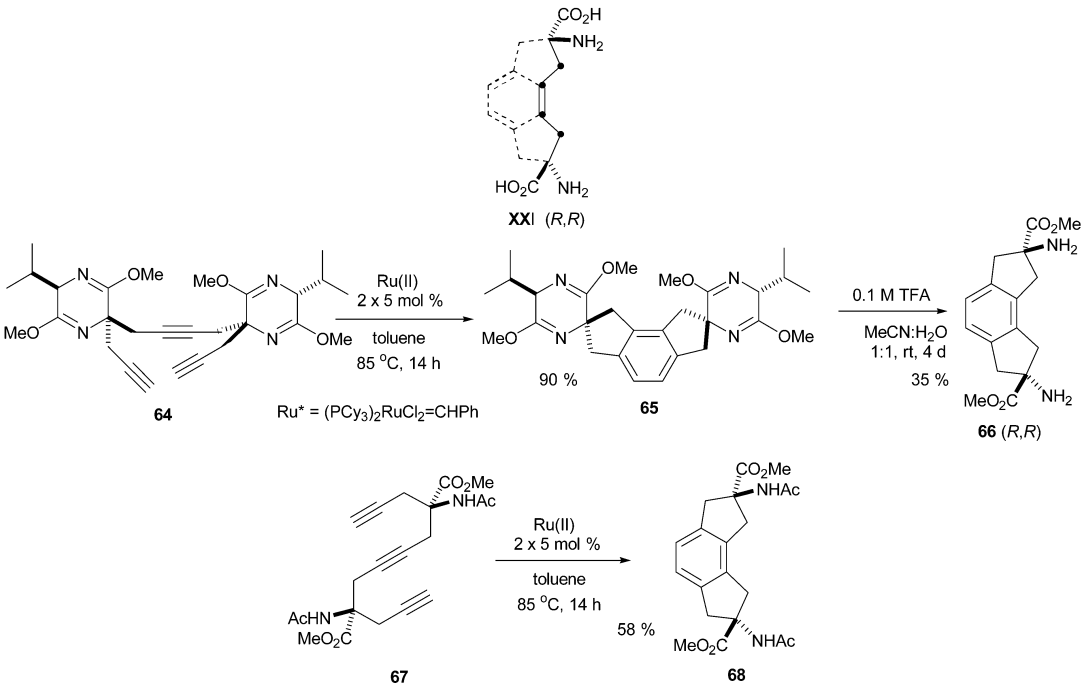
In the alternative approach for the direct preparation of aromatic derivatives, lithiated Schöllkopf **1**-(*R*) chiron was reacted with 1,2-di(bromomethyl)benzene. The *o*-xylene-bridged product **58** was formed in good yield, but the diastereoselectivity was only 55 %. In other cases, we have also observed low stereoselectivity in reactions with vicinal dialkylating agents. Acid hydrolysis provided the amino acid target structure **59** [30]. The latter was first described from a synthesis with lithiated Seebach chiron (*S*)-2-*t*-butyl-1-*t*-butyloxycarbonyl-3-methyl-4-imidazolidinone and α,α′-dibromo-1,2-xylene. High yield and diastereoselectivity were obtained [31]. However, the vigorous acidic conditions required for hydrolytic cleavage of the alkylation product to liberate the free amino acid, limits the application of this methodology to acid-stable products.

Conceptionally, the same type of product is based on the thiophene structure **XX** in Scheme 9. The alkylating agent was a vicinal di(halomethyl) reagent, and low diastereoselectivity was observed as for the *o*-benzene alkylating agent in Scheme 8. With easily metallated heterocycles like thiophene, metal-proton exchange can occur with the heterocycle. In slow alkylation, this results in low-yield processes and undesirable side-reactions. Thus, the thienyl derivative **60** was isolated in only 39 %, whereas the 5-methylthienyl derivative, where the α-thienyl position is blocked, was isolated in 65 % yield. Significant amounts of monoalkylated products were obtained. When both the acidic *o*-positions in thiophene were blocked, as in 2,5-di(chloromethyl)thiophene, formation of the corresponding thiophene-bridged alkylation product was raised to 75 % yield with 96 % de [30].




**Scheme 9**

In the next Schemes 10–12, preparations of highly rigidified dicarba analogs of cystine are shown. In structure **XXI** in Scheme 10, a methylene carbon has been inserted to form a ring between the α-amino carbon and a vicinal benzene position. Thereby, the rotational freedom of the aniline moiety in the benzene-bridged structure **59** (Scheme 8) is lost. In Scheme 10, we have described methodology developed 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. The cascade reaction was effected using Grubbs's versatile RCM conditions with the precatalyst system bis(tricyclohexylphosphine)ben-



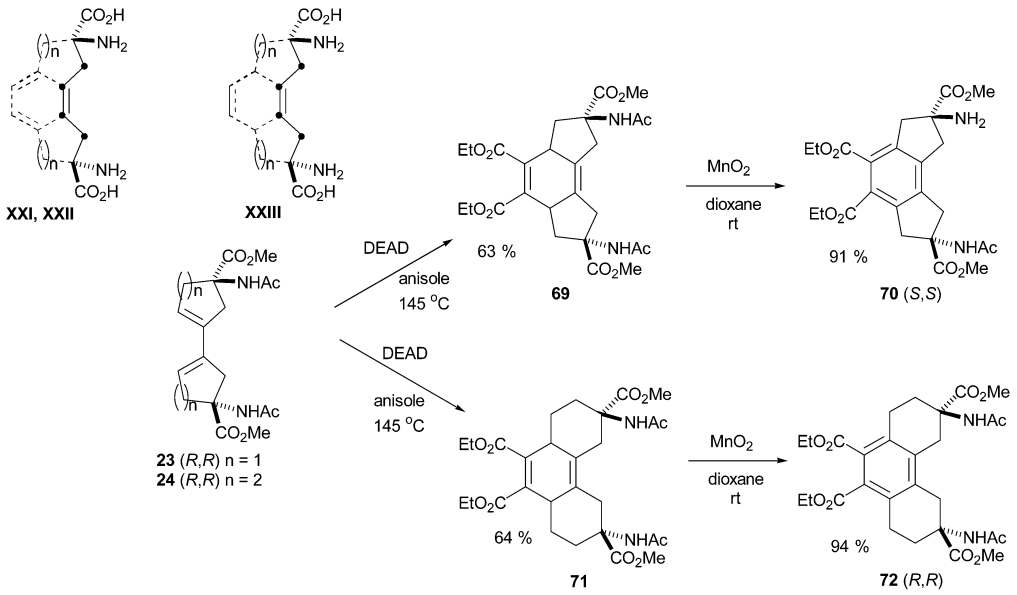

**Scheme 10**

zylideneruthenium dichloride [22]. The strategy was adapted from a recent report on ruthenium-catalyzed cascade conversion of triynes to benzene derivatives [32]. The Ru(II)-catalyzed RCM reaction is strongly affected by sterical factors. Thus, highly congested molecules may react with close to quantitative conversion, while apparently subtle changes in such molecules may result in almost no conversion [24,33]. The substrate **64** was available from the silyl-protected triple bond derivative **26** (Scheme 5) by deprotection with TBAF. The cascade reaction of the congested triyne **64** in toluene at 85 °C gave the *bis*-spiro pentacyclic product **65** in high yield (90 %). At lower temperature, there was no reaction, or the reaction was very slow. Catalyst (5 mol %) was added twice. A second addition of catalyst was necessary to compensate for the thermal instability of the catalyst at the temperature of the reaction. The high overall yield seems remarkable in view of the number of steps involved. A rationale for the course of the reaction has been published [25].

The cascade reaction with the *N*-protected alkyne-bridged bis(α-amino acid) derivative **67** also proceeded well. The *as*-indacene-bridged bis(α-amido acid) derivative **68** was isolated in 58 % yield under the same conditions as above. The product **66** with free amino groups was obtained by hydrolytic cleavage of the congested bis-spiro pentacyclic product **65**. The hydrolysis was slow and only partially completed after four days. Unfortunately, forcing conditions would yield the corresponding diketopiperazine as previously discussed.

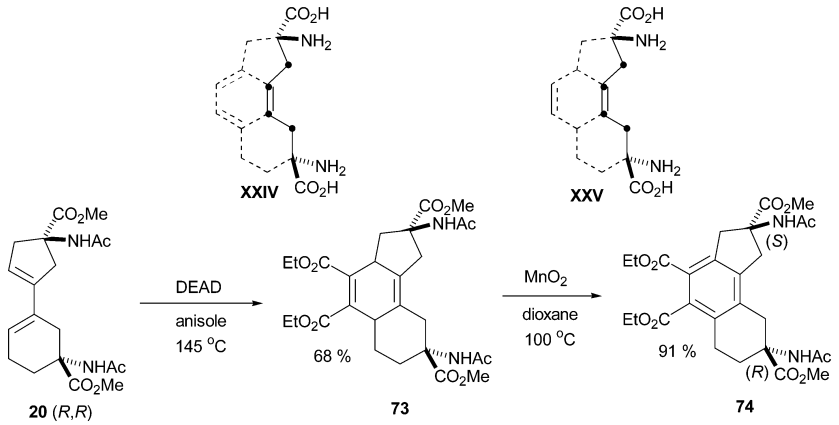
A more versatile method for varying the size of the annulated rings is indicated in structures **XXI**–**XXIII** in Scheme 11. Diels–Alder reactions were run in anisole at 145 °C on the appropriately substituted dienes **23** and **24** that were available by RCM reactions as shown in Scheme 4 [21].

For simplicity, the symmetrical and highly reactive dienophile diethyl acetylenedicarboxylate (DEAD) was used. In the bis(cyclopentenyl)diene substrate **23**, a mixture of the cyclodiene adduct **69** and its aromatized benzene analog **70** was obtained in a total yield of 63 %. The product mixture, when treated directly with manganese dioxide, the benzo derivative **70**. The Diels–Alder adduct **71** from the bis(cyclohexene) substrate **24** was obtained in 64 % yield. The adduct **71** was aromatized in almost quantitative yield to the benzo derivative **72** when reacted with manganese dioxide [21].




**Scheme 11**

Unsymmetrically bridged structures **XXIV** and **XXV** are available as shown in Scheme 12. Members of these series were prepared as Diels–Alder adducts from the unsymmetrical diene, the cyclopentenyl-cyclohexenyl diene **20**. The cyclohexadiene adduct **73** and its aromatized analog **74** were obtained as a mixture, ratio 1:1 in 68 % overall yield. The mixture was fully aromatized as above by the use of manganese dioxide. The aromatization could also be effected with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) [21].




**Scheme 12**

In conclusion, we have described methods for the preparation of all-carbon $C_4$-bridged analogs of cystine. The conformational constraints in the analogs vary from almost free rotation through gradual stiffening of the skeleton, and to highly rigidified dicarba analogs.

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