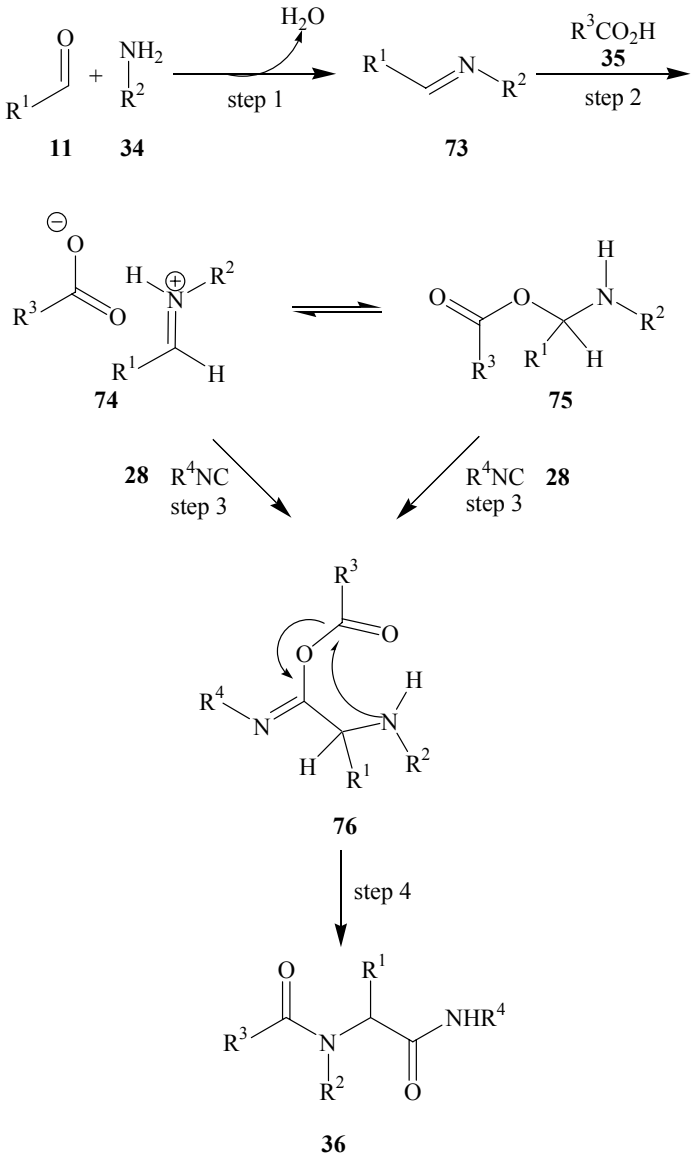
4 Ugi Four-component reactions (U-4CR) with siloxycyclopropanes

In 1959, Ugi et al. described the most frequently employed variants of the four-component condensation, the U-4CRs. It was postulated that the reaction involved a sequence of:

a) imine formation (step 1),
b) protonation of the imine by acid thus strongly increasing the electrophilicity of the C=N bond (step 2),
c) α-addition of the electrophilic iminium cation and the nucleophilic carboxylate anion to isocyanide (step 3) and
d) intramolecular acyl-transfer (step 4) (Scheme 32).[81]

α-Acylaminoamides **36** were formed, compounds which could be involved in a variety of important biological activities.

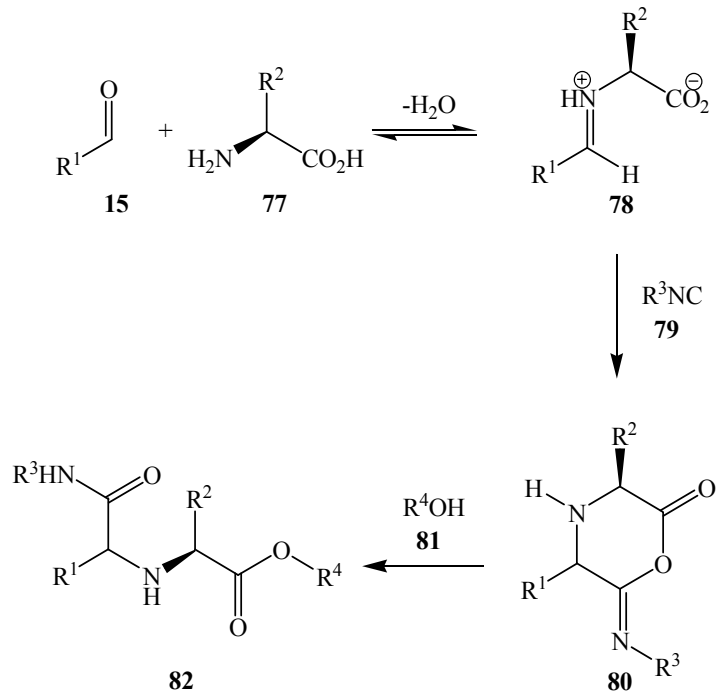


Scheme 32. Mechanism of U- 4CR

The α-adduct **76** formed in step 3 can be regarded as hetero analogue of an acid anhydride in which an *exo*-oxygen atom has been substituted by an N-R^4 group and thus as strong acylating agent. The closest nucleophilic atom is the nitrogen of the former amine and therefore the stable Ugi product is obtained after an intramolecular acylation and subsequent rearrangement to an amide. This type of intramolecular acylation was first described in 1910 by Mumm and was afterwards called Mumm rearrangement.[82, 83] All elementary steps of this reaction sequence are equilibria; however, the rearrangement to the stable α-acylaminoamide **36** lies exclusively on the product side. The overall driving force is the conversion of a high-energy isocyanide carbon atom into the tetravalent amide carbon atom. The reaction is versatile in the starting materials, comprising both aliphatic and aromatic compounds. The reaction is ecologically gentle, since only one molecule of water is lost in an entire process creating new four chemical bonds.

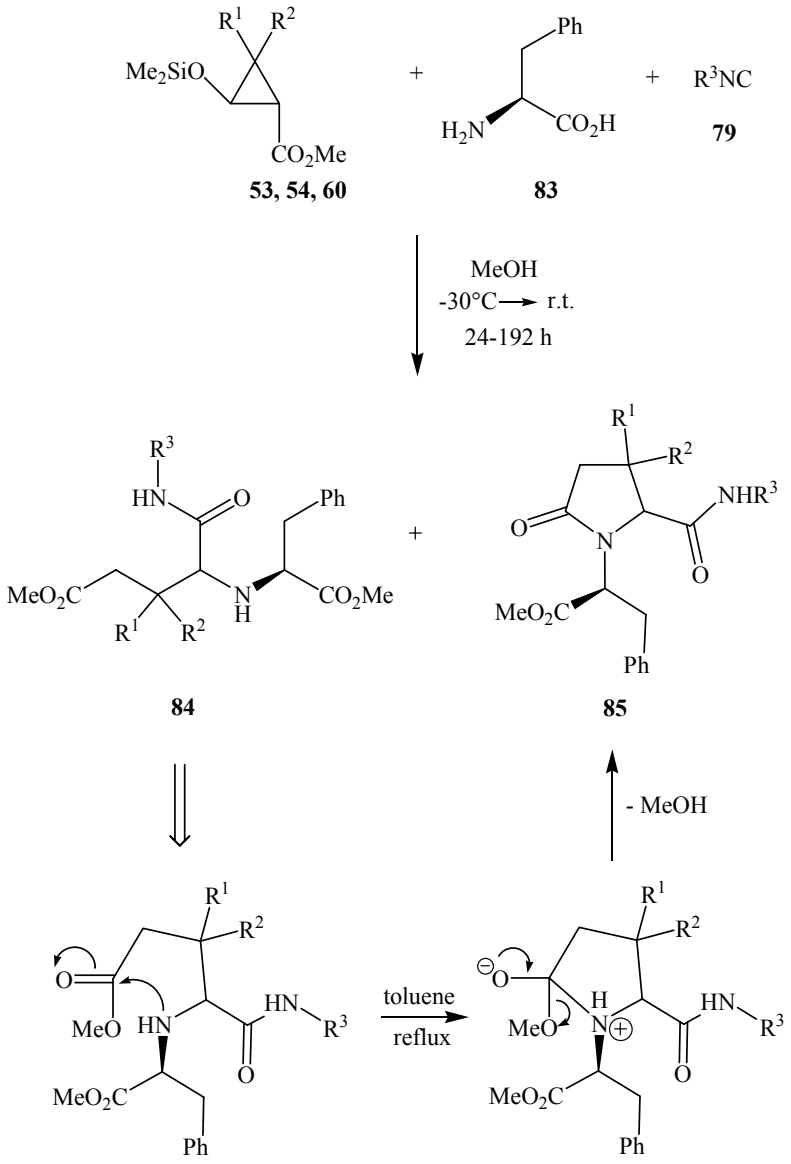
4.1 Ugi Five-center four-component reaction (U5-4CR)

α-Amino acids **77** may also be employed as amine component and by use of alcohol **81** as solvent the Ugi-4CR could be extended to an Ugi 5-center-4-component reaction (U5-4CR) providing functionalized α-amino diacid derivatives **82** *via* the iminium ion **78** and elusive cyclic intermediate O-acylamide **80**. A new stereocenter is created at the initially carbonyl carbon atom of the aldehyde. Its preferred absolute configuration is induced by the chiral amino acid employed. Apart from cysteine, all known natural and many unnatural α-amino acids can undergo this reaction.[84]



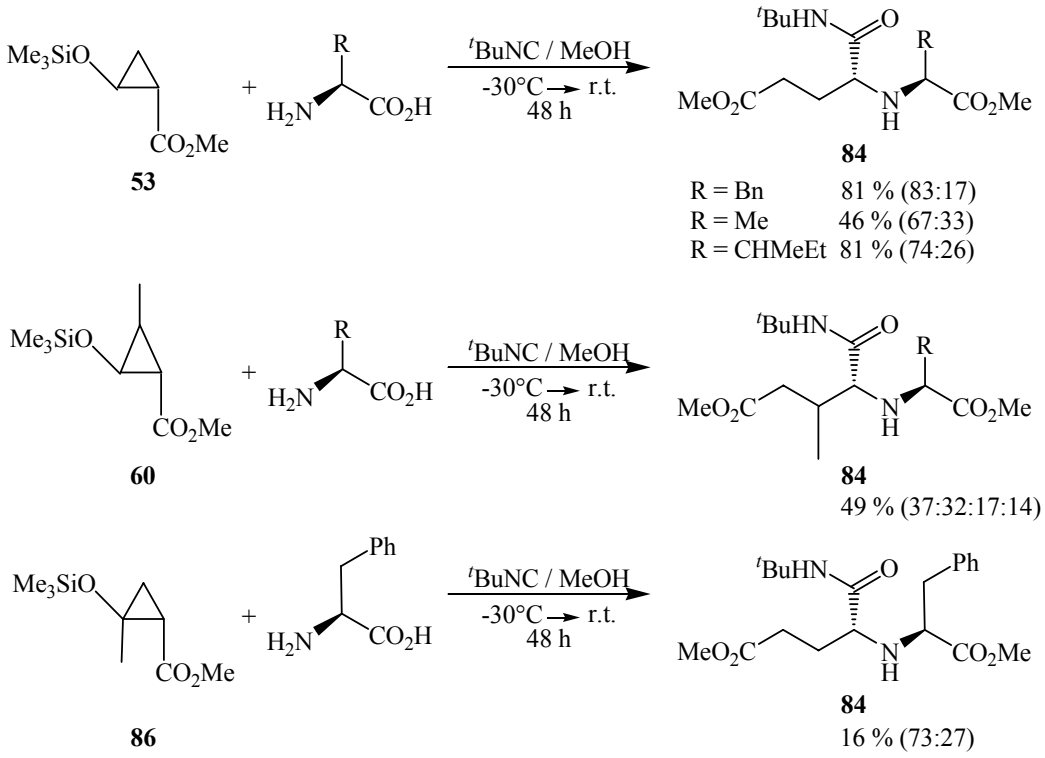
Scheme 33. Mechanism of U5-4CR

The Ugi-reaction with methyl 2-siloxycyclopropanecarboxylates as masked carbonyl compounds, the α-amino acid L-phenylalanine and several isocyanides generated in moderate to good yields functionalized α-amino diacid derivatives **84** and pyrrolidinones **85**, which represent interesting peptidomimetics.[2] 2-Siloxycyclopropanecarboxylates may directly be introduced as precursor compounds since under protic conditions as employed for this reaction, they undergo smooth cleavage to furnish γ-oxocarboxylates. The reaction temperature was allowed to rise from –30°C to room temperature. The solvent was evaporated and the residue was purified by column chromatography and in some cases by HPLC.[40] Primary adducts **84** undergo cyclization to pyrrolidinones **85** under the reaction conditions employed, as depicted in Scheme 34.



Scheme 34. U5-4CR

The concept to apply methyl 2-siloxycyclopropanecarboxylates in U5-4CR was first introduced by Zimmer et al.[40] They reacted methyl 2-siloxycyclopropanecarboxylates **53** and **60** and three α-amino acids with *tert*-butylisocyanide to obtain primary Ugi adducts in moderate to good yields. They have also introduced methyl 2-methyl-2-siloxycyclopropanecarboxylate **86**, which is equivalent to methyl levinulate, into this modification of Ugi reaction, but this reaction was inefficient under standard conditions and only 16% of the corresponding adduct containing a quaternary center were isolated (Scheme 35).



Scheme 35: Results of U5-4CR performed by Zimmer et al.

For further exploration of this reaction methyl 2-siloxycyclopropanecarboxylates **53**, **54** and **60** have been reacted with L-phenylalanine and five isocyanides in methanol. The results of these reactions are listed in Table 1.

Table 1. Results of the U5-4CR according to Scheme 28 (experiments: E2-E6, E8, E9, E11, E12)

Entry	Starting material	R^1	R^2	R^3	R. Time (h)	Product	Yield (%)	diastereomer ratio	Product	Yield (%)	diastereomer ratio
1	**53**	H	H	$PhCH_2$	96	**84a**	32	82:18	/	/	/
2	**53**	H	H	*n*- Bu	54	**84b**	22	83:17	**85b**	4	> 95:5
3	**53**	H	H	MeO_2C-CH_2	118	**84c**	12	56:44	/	/	/
4	**60**	Me	H	$PhCH_2$	24	**84d**	10	84:16	**85d**	13	53:47
5	**54**	Me	Me	$PhCH_2$	88	**84e**	32	80:20	**85e**	39	86:14
6	**54**	Me	Me	*n* -Bu	89	**84f**	17	82:18	**85f**	34	> 95:5
7	**54**	Me	Me	MeO_2C-CH_2	118	**84g**	4	81:19	**85g**	6	> 95:5
8	**54**	Me	Me	*p* -Methoxyphenyl	111	**84h**	38	92:8	**85h**	32	> 95:5
9	**54**	Me	Me	Cyclohexenyl	208	/	/	/	**85i**	27	> 95:5

When reacted with benzylisocyanide and methyl cyanoacetate, siloxyclopropane **53** afforded only α-amino diacid derivatives **84a** and **84c**, respectively, and no cyclic compounds were isolated. On the contrary, siloxycyclopropane **54** in reaction with cyclohexenylisocyanide gave only cyclic compound **85i**.

Siloxycyclopropanes **53** and **54** afforded after cleavage achiral aldehydes which reacted in the Ugi-reaction. In these examples only two diastereoisomers of the product were observed. The diastereoselectivity induced by the stereogenic center of the amino acid is moderate to good (ca. 4:1 to 12:1; in entries 2, 6, 7, 8 and 9 corresponding pyrrolidinones were obtained as a single diastereoisomers), except in entry 4 where a mixture of approximately 1:1 of diastereoisomers was obtained.

When siloxycyclopropane **60** was used, *in situ* generated β-formyl ester **61** is chiral but racemic. Compounds **84d** and **85d** were also isolated as mixtures of only two diastereoisomers, although four diastereoisomers could be expected in this case (entry 4).

The reaction is general for both aliphatic and aromatic isocyanides. Yields ranged between 12 and 71%. It was observed that yields depended on the nature of the aldehyde component: 3,3 dimethyl substituted 2-siloxycyclopropane gave the best yields. Among isocyanides, aromatic isocyanides (phenyl- and *p*-methoxyphenylisocyanide) gave better results than aliphatic isocyanides.
It can be concluded that most promising reactions were generally observed with 3,3-dimethyl-substituted siloxycyclopropane **54** and benzylisocyanide (71%, Table 1, entry 5), and *p*-methoxyphenylisocyanide (70%, Table 2, entry 8).

4.1.1 NMR and IR data of compounds 84 and 85

Characteristics in the ^{1}H NMR spectra of phenylalanine derived primary Ugi adducts are the signals of the benzyl group of the amino acid moiety in the range of δ = 2.7 to 3.3 ppm as multiplets, of the methyl ester in the range of δ = 3.5 to 3.8 ppm as singlets and of amide NH in the range of δ = 6.2 to 8.7 ppm as broad singlets.

Table 2. Characteristic ^{1}H chemical shifts of primary Ugi adducts **84a-h**; δ(ppm) ($CDCl_3$)

Primary Ugi adduct	CH_2-Ph	amide NH
84a	2.98-3.33	6.77[a]; 7.50
84b	2.81-3.22 / 2.91-3.08[a]	7.12-7.34; 6.36[a]
84c	2.98-3.14	6.69; 7.55[a]
84d	2.93-3.14	6.67[a]; 7.02
84e	2.70-2.89	6.97-7.29
84f	3.18-3.27	6.23[a]; 6.71
84g	2.95-3.10	6.60[a]; 7.39
84h	2.83-3.06 / 2.66-2.75[a]	8.17[a]; 8.86

[a] minor isomer

The most significant signal in the ^{1}H NMR spectra of pyrrolidinones **85** is the proton at position 2 in the pyrrolidinone ring which appears at δ ≈ 3 ppm. Further characteristics are the signals of the α-proton of the amino acid moiety as a doublet of doublet with coupling constants 5 Hz to 6 Hz and 10 Hz to 11 Hz at δ = 3.9 to 4.2 ppm and the protons at position 4 in the pyrrolidinone ring, which in 3,3-disubstituted pyrrolidinone rings appear as doublets with coupling constant ≈ 17 Hz at δ = 1.9 to 2.4 ppm.

Table 3. Characteristic ^{1}H chemical shifts of pyrrolidinones **85b-i**; δ(ppm) and *J*(Hz) ($CDCl_3$)

Pyr.	2-H	NCH	^3J	4-H	^2J	OMe	NH
85b	2.97-3.08	3.86-3.91		2.15-2.46		3.90	8.06
85d	2.89-3.15	3.86-3.99		1.82-2.62		3.64	8.02; 8,12[a]
85e	3.02[a]; 3.08	4.02	10.1; 6.0	1.97[a]; 2.28[a] / 2.00; 2.26	16.9[a] /16.7	3.58[a]; 3.60	7.80
85f	3.12	4.07-4.19		2.06/2.32	16.8	3.82	7.59
85g	3.22	3.88-4.15		2.06/2.37	16.7	3.71; 3.79	8.08
85h	3.12	4.18	10.8; 5.5	2.10/2.37	16.8	3.78; 3.90	9.47
85i	3.01	4.11	10.2; 5.9	2.05/2.32	16.9	3.85	8.30

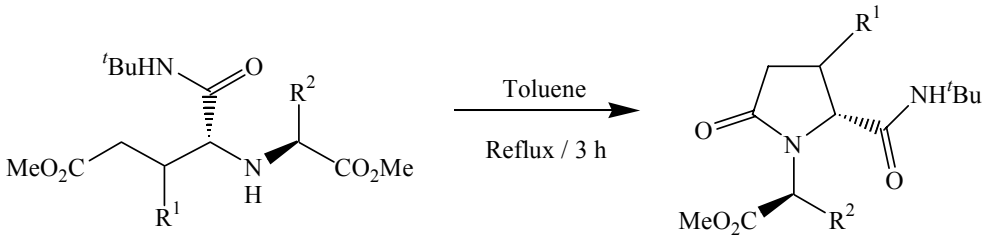
[a] minor isomer

In the ^{13}C NMR spectra, characteristic for compounds **85** are chemical shifts of C-3, which range between δ = 31.0 to 36.7 ppm, chemical shifts for α-carbon of the amino acid moiety at δ = 58.1 to 59.4 ppm and of C-2 at δ = 64.0 to 74.9 ppm.

IR spectra (KBr) of the compounds **85b** - **85i** show characteristic bands at 1740-1745 [ν(C=O) (ester)] and 1665-1700 cm^{-1} [ν(C=O) (amide)].

4.2 Lactam formation

Primary adducts **84** could efficiently be cyclized by heating in toluene for 3 hours providing the desired pyrrolidinone derivatives **85** in good to excellent yields, as had been shown in previous work of Zimmer et al. (Scheme 36)[40]:

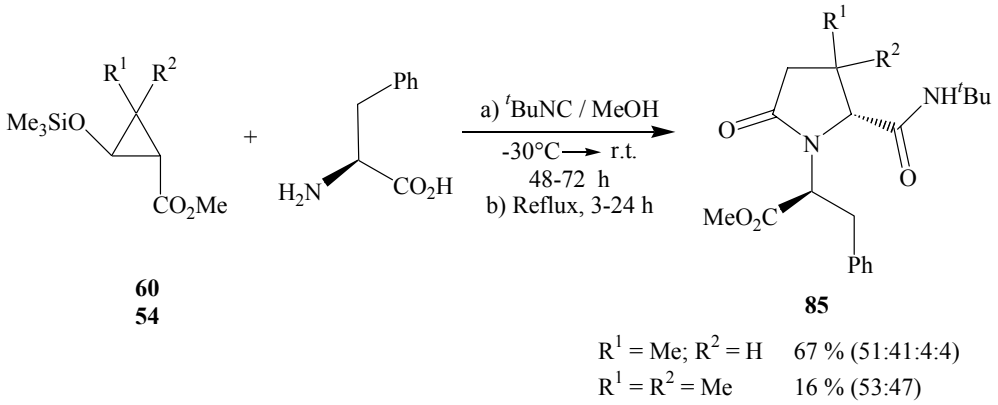


84 **85**

R^1 = Me; R^2 = Bn	81 % (50:42:4:4)
R^1 = Me; R^2 = CH_2Indolyl	69 % (52:42:3:3)
R^1 = Me; R^2 = Me	71 % (34:22:22:22)
R^1 = H; R^2 = Bn	98 % (90:10)
R^1= H; R^2 = Me	86 % (64:36)
R^1 = H; R^2 = CHMeEt	82 % (79:21)

Scheme 36: Cyclizations of the primary Ugi adducts **84** to **85**

Zimmer et al. also attempted a one-pot protocol from siloxycyclopropanes to pyrrolidinones.[40] With siloxycyclopropane **60** a one-pot protocol was successfully performed and corresponding pyrrolidinone was obtained in 67 % overall yield. However, it seemed that for 3,3-dimethyl-2-trimethylsiloxycyclopropane **54**, which is the precursor of β-dimethyl-substituted β-formyl ester **59**, the steric hinderance exhibited by the two methyl groups hamper the Ugi reaction considerably and the corresponding pyrrolidinone derivative was isolated in only 16 % yield and negligible diastereoselectivity (Scheme 37).



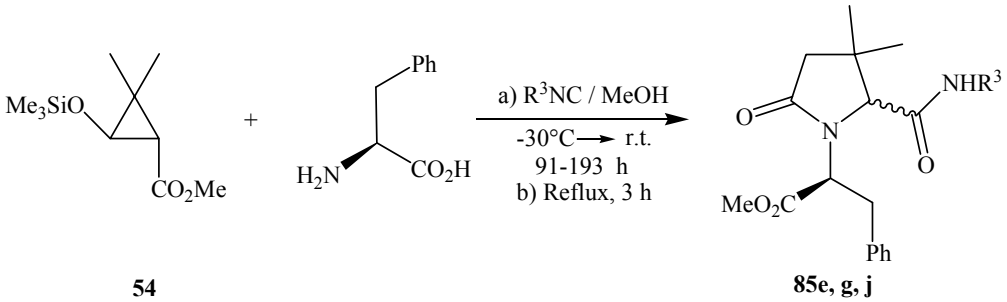
60
54

85

R^1 = Me; R^2 = H 67 % (51:41:4:4)
R^1 = R^2 = Me 16 % (53:47)

Scheme 37: One-pot synthesis of substituted pyrrolidinones **85**

Following these initial experiments the one-pot protocol was attempted with siloxycyclopropane **54**, three isocyanides and L-phenylalanine and pyrrolidinones **85e, g, j** were successfully obtained (Scheme 38). The crude product from U5-4CR was dissolved in *p*-xylene and refluxed for 3 hours. The solvent was evaporated and the residue was purified by column chromatography.[40] The overall transformation may be classified as 6-center 4-component reaction (6-C 4CR).



54

85e, g, j

85e R^3 = $PhCH_2$[a] 68 % (86:14)
85g R^3 = MeO_2C-CH_2 78 % (>95:5)
85j R^3 = 1,1,3,3-Tetramethylbutyl 64 % (73:27)

[a] 6% of **84e** was also isolated

Scheme 38. One-pot synthesis of substituted pyrrolidinones (experiments: E7, E10, E13)

These experiments have shown that even with sterically hindered siloxycyclopropane **54** satisfactory results could be obtained in a one-pot protocol. The described one-pot protocol proved to be the more favorable method for synthesis of compound **85g** compared to the previously described U5-4CR. Thus, only 10% overall yield was obtained (Table 1, entry 7)

under normal Ugi conditions, while latter experiment including refluxing in *p*-xylene afforded 78% of cyclic compound. The reaction involving benzylisocyanide was also slightly improved: 74% towards 71% in typical U5-4CR (Table 1, entry 5). Experiment with 1,1,3,3-tetramethylbutylisocyanide was performed only as one-pot protocol for obtaining cyclic compound **85j**.

Compounds **85e** and **j** were isolated as mixtures of two diastereoisomers. The ratio of diastereoisomers for compound **85e** was exactly the same as in the previous experiment, although under the rather harsh cyclization conditions isomerization at the stereogenic center α to the carbonyl group might occur to some extend. This seems to happen with compound **84e** which has been isolated in this experiment with a ratio of diastereoisomers of 85:15 compared to 80:20 in the previous experiment. Compound **85g** was isolated as only one diastereoisomer as in the previous experiment (Table 1, entry 7). It was possible to grow suitable crystals from the major diastereoisomer of **85j**, which could be analyzed by an X-ray crystallography (Figure 1).

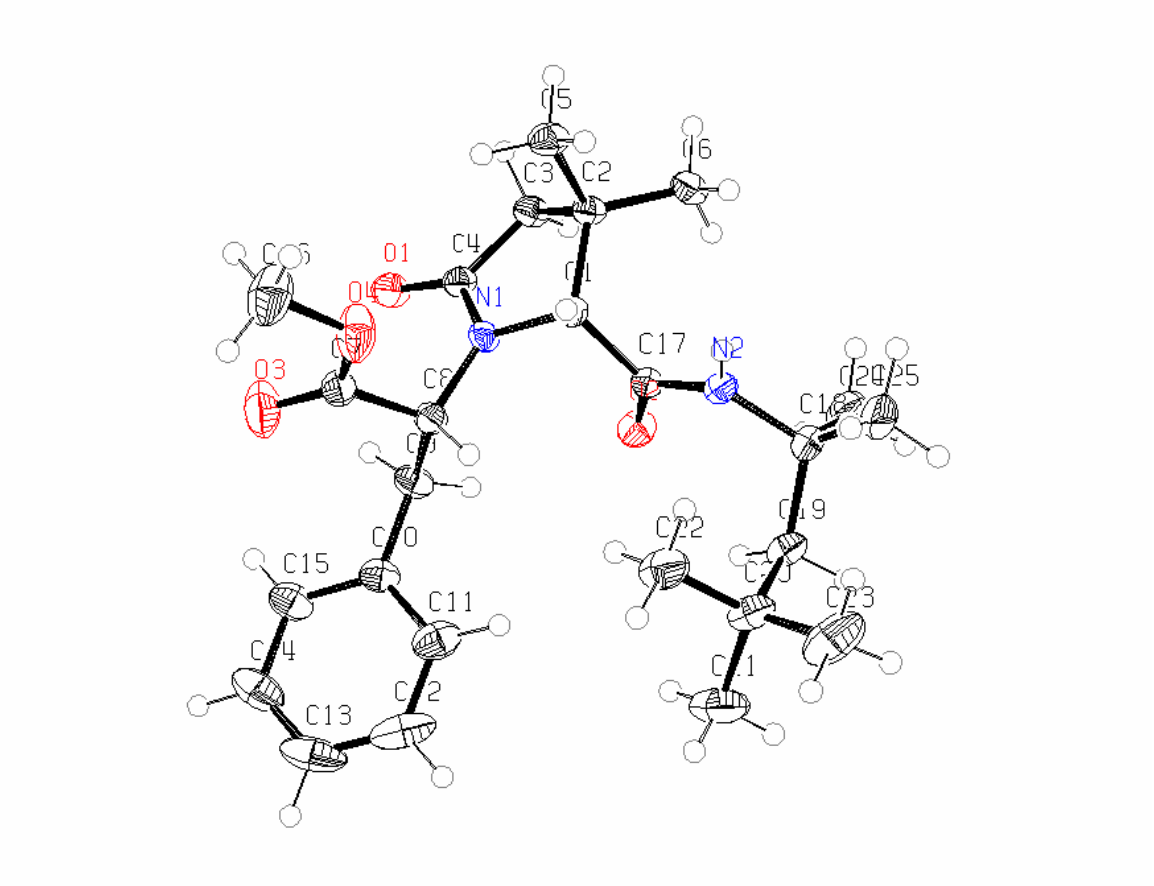
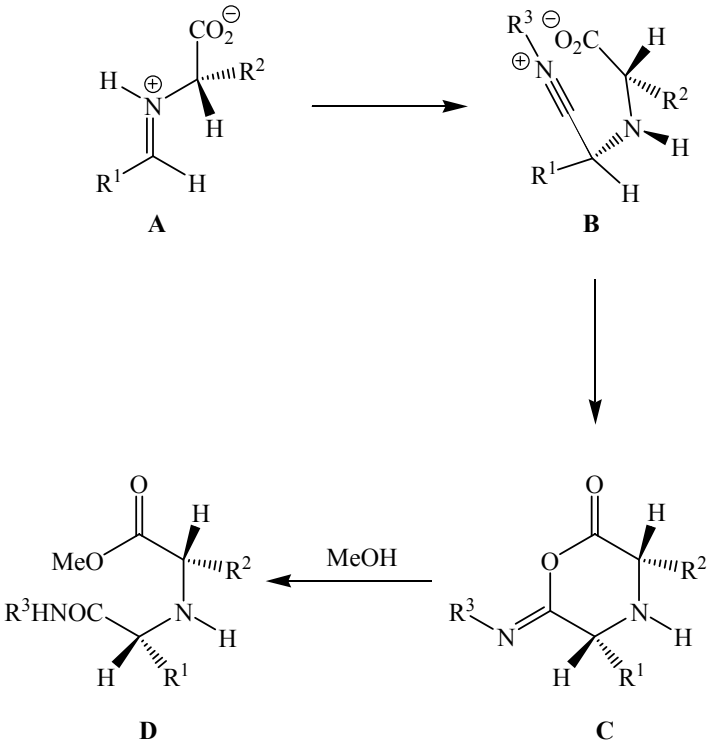


Figure 1 Structure of compound **85j** determined by X-ray crystallography

This measurement established the *R*-configuration of the major diastereoisomer at the pyrrolidine ring, which is in accordance with the configuration of a product in related examples.[40, 85] On this basis it could be suggested that the preferred attack of the isocyanide to the intermediate iminium ion **A** formed from the aldehyde and the amino acid proceeds from the front side giving a nitrilium ion **B** (Scheme 39). Cyclic intermediate **C** is formed, then ring-opened by methanol to afford the isolated product **D**. The front side attack is more favoured and hence the diastereoselectivity higher if substituent R^2 is larger.[40]



Scheme 39.

From the X-ray crystallography results it was also possible to observe an intermolecular hydrogen bonding between the amide hydrogen of one molecule and the carbonyl oxygen of the other molecule of the compound **85j** (Figure 2).

In the crystal two crystallographically distinct molecules are associated into chains through hydrogen bonds (N2 – H2 ··· O1: 0.857 and 2.052 Å) with an N ··· O separation of 2.899 Å.

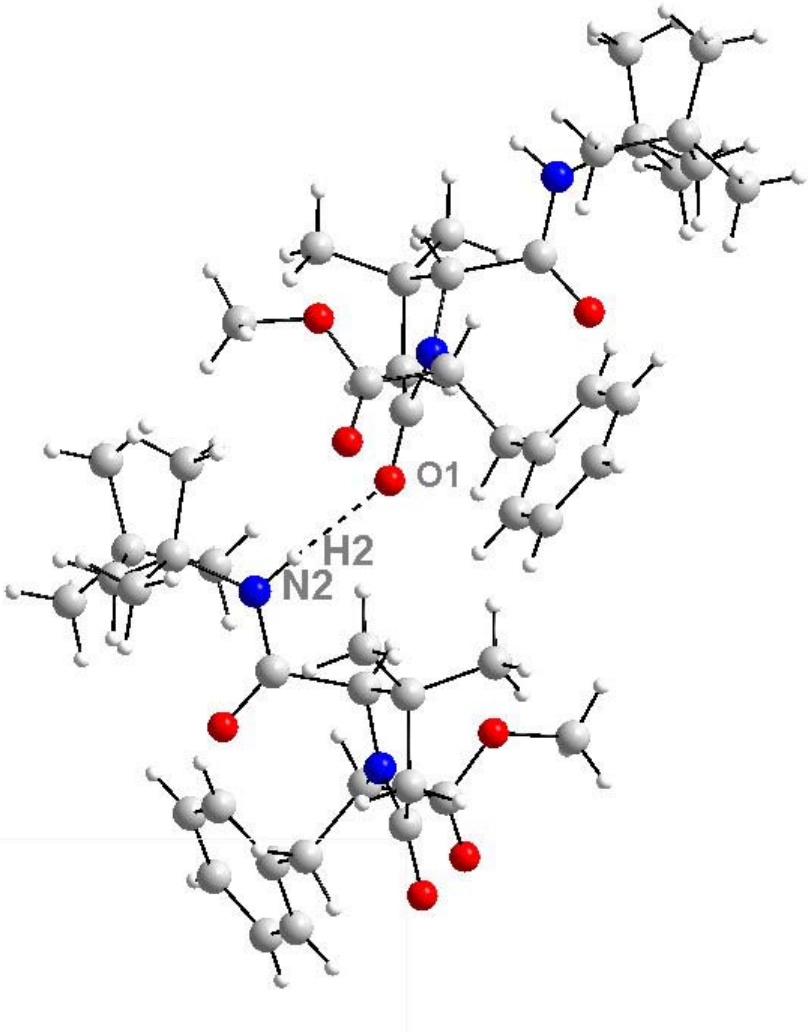
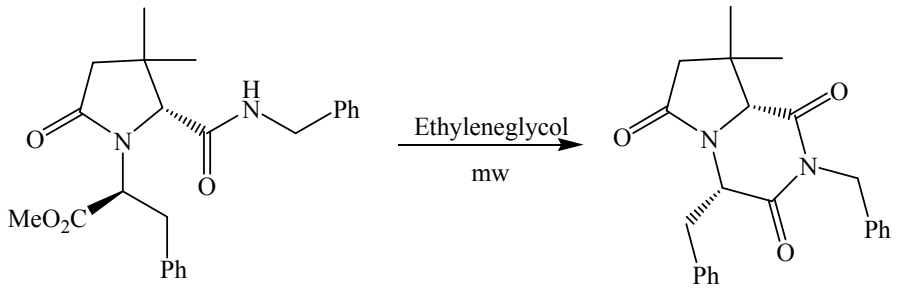


Figure 2 – Intermolecular hydrogen bonds

4.3 Microwave assisted cyclization

The use of microwaves as an energy source for chemical reactions and processes has been extensively investigated during recent years, but the experimental details and the microwave systems used are still insufficiently described.[86] Microwave techniques in synthetic chemistry often elicit a dramatic increase of the reaction rate and yields. There are reports which suggest that such dramatic improvements can be regarded as a consequence of increased temperatures caused by superheating or concentration effects. In microwave dielectric heating, the microwave energy is introduced into the chemical reactor remotely and direct access by the energy source to the reaction vessel is obtained. The microwave radiation passes through the walls of the vessel and heats only the reactants and solvent, not the reaction vessel itself. If the apparatus is properly designed, the temperature increase will be uniform throughout the sample, which can lead to the less by-products and/or decomposition products. In pressurized systems, it is possible to rapidly increase the temperature far above the conventional boiling point of the solvent used.[87, 88]

Attempts to cyclize compound **85e**, used as a mixture of two diastereoisomers, by refluxing in toluene have failed and starting material was recovered in this experiments. Microwave-assisted (power of 1000 W) cyclization in ethylene glycol afforded bicyclic compound **86** as a single diastereoisomer in 37% yield after extraction and purification by column chromatography.

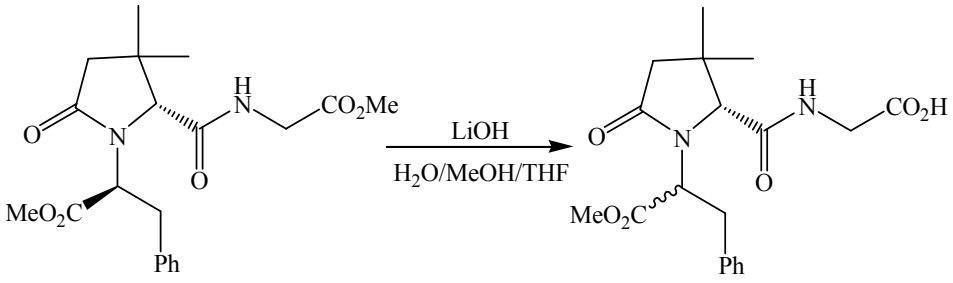


85e **86**
37%

Scheme 40. Microwave-assisted cyclization reaction of **85e** to the bicyclic compound **86** (experiment: E14)

4.4 Ester hydrolysis

In order to obtain free carboxylic acid **87**, hydrolysis of pyrrolidinone **85g** with 3 equivalents of LiOH in H_2O/MeOH/THF mixture was performed.[89] The reaction mixture was stirred over night at room temperature and after acidic workup monoacid derivative **87** was obtained in 59% yield as a mixture of two diastereoisomers in a ratio 71:29. Although starting compound **85g** was used as a single diastereoisomer under the reaction conditions applied for this reaction epimerization occurred and the product was isolated as a mixture of two diastereoisomers (Scheme 41).

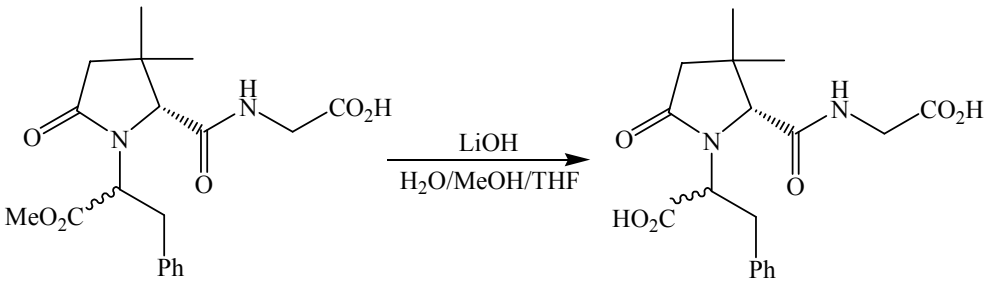


85g **87**

59% (71:29)

Scheme 41. Base-mediated hydrolysis of **85j** (experiment: E15)

To obtain diacid compound **88**, monoacid **87** was subjected to further hydrolysis as a mixture of diastereoisomers. After stirring with another 3 equivalents of LiOH in H_2O/MeOH/THF mixture at room temperature over 12 hours,[89] diacid **88** was obtained in 92% yield, ratio of diastereoisomers is 84:16 (Scheme 42).

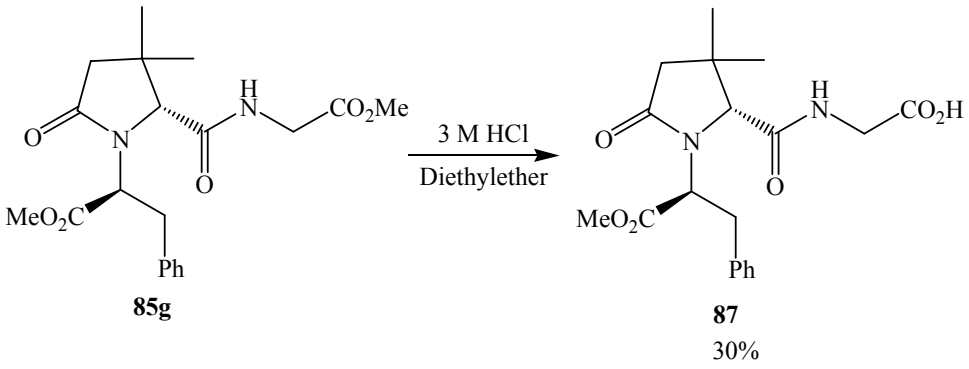


87 **88**

92%

Scheme 42. Base-mediated hydrolysis of **87** to diacid **88** (experiment: E16)

To preserve configuration hydrolysis under acidic conditions has been attempted. Compound **85g** as a single diastereoisomer was dissolved in diethyl ether, than 3 M HCl solution was added and the reaction mixture stirred at room temperature over night. Compound **87** was isolated after workup in 30% yield as only one diastereoisomer. The significantly lower yield in this reaction is understandable since acid-catalyzed ester hydrolysis is an equilibrium reaction without a way of shifting the equilibrium to the right. Compound **85g** was reisolated in 52 % yield (Scheme 43).



85g **87** 30%

Scheme 43. Acid-catalyzed hydrolysis (experiment: E17)

4.5 Conclusion

In conclusion, these findings extend the previously published application of methyl 2-siloxycyclopropanecarboxylates in the Ugi 5-center 4-component reaction to new inputs. The primary products **84** are interesting because the four functional groups provide many possibilities for further transformations; compounds of this type also may possess biological activity. The cyclized products **85**, which are highly functionalized pyrrolidinones and therefore interesting peptidomimetics, can be obtained either under standard conditions of U5-4CR, or, in higher yields, in a one-pot sequence which can be classified as a 6-center 4-component reaction. The compounds **85** can be further modified to yield interesting bicyclic compounds as **86** or mono- and diacid derivatives such as **87** and **88**. Since precursor cyclopropanes are easily available in many structural variations, this modification of Ugi reaction should enable synthesis of highly diverse libraries of compounds **84** and **85**. The diastereoselectivity of the reactions is moderate to good.