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CARBOHYDRATES AS CHIRAL TEMPLATES: ASYMMETRIC UGI-SYNTHESIS OF ALPHA-AMINO ACIDS USING GALACTOSYLAMINES AS THE CHIRAL MATRICES

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Abstract: In the presence of Lewis acid catalysts O-acetyl- (1) and O-pivaloyl- (2) protected ß-D-galactopyranosylamines react with aldehydes, isocyanides and carboxylic acids in Ugi-four-component-condensations to give the corresponding N-galactosyl-amino acid amide derivatives 3, 5 in almost quantitative yields. Zinc chloride is the most effective Lewis acid catalyst. At 0°C or even at room temperature the (2R,ß-D)-diastereomers of the amino acid derivatives 3, 5 are formed with high diastereoselectivity. If the sterically more demanding O-pivaloyl galactosylamine 2 is used at -78°C to -25°C the stereoselectivity often exceeds 20:1 favouring the (2R,ß-D) diastereomers 5. After one recrystallisation pure (R)-amino acid derivatives 5 are obtained in yields of 80-95%. In addition to the high yields and stereoselectivity the amino acid synthesis discribed here has the further advantage that it neither requires organometallic reagents and intermediates nor exclusion of oxygen and moisture. Two step acid hydrolysis of the N-galactosylamino acid amide derivatives 5 delivers the enantiomerically pure (R)-amino-acids 8 in high yields.

Introduction

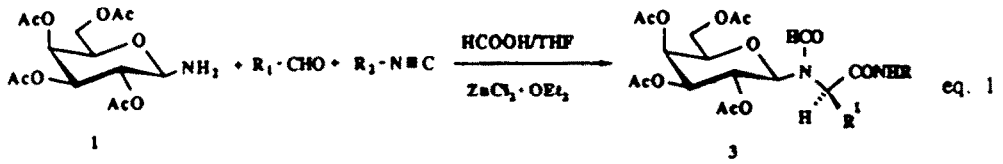
Proteinogenic and non-proteinogenic α-amino acids are valuable starting materials for the construction of biologically selective and degradable drugs.[1] Consequently, intensive research efforts are directed towards the development of stereoselective syntheses of these compounds. Among the advances recently reported in this field, most are based on the alkylation of chiral glycine enolates[2] or on the electrophilic amination of amide-[3]or ester-enolates.[4] A similar route consists in the asymmetric halogenation of enolates followed by nucleophilic substitution of the halogen.[5] These methods have the common feature that organometallic intermediates sensitive to oxygen and moisture are formed during the process.

Therefore, both the stereoselective Strecker synthesis[6,7]and the Ugi-four-component-condensation[8] are interesting from an economical viewpoint, because they circumvent the application of organometallic compounds. In these reactions α-aryl alkylamines have been used as the chiral auxiliaries.[6-8] However the chirality of these compounds is destroyed during hydrogenolytic[6,8] or oxidative[7] removal from the amino acid derivative. In addition, phenylglycine derivatives and amino acids with alkene- or sulfur- containing side chains are sensitive to hydrogenation or oxidation and cannot be obtained by these methods.

The Ugi reaction as well as the Strecker synthesis proceed via aldimines as intermediates. We now report on the stereochemical control of the Ugi reaction with carbohydrate derived amines[9,10] as the chiral templates. Carbohydrates constitute a class of inexpensive natural products of high chiral content. Apart from chiral pool syntheses and some complex hydride reagents, carbohydrate derivatives have been used only in a few cases in asymmetric synthesis.[11] From the chemical synthesis of glycopeptides[12] we learned that carbohydrates, which play central roles in the posttranslational biological selectivity[13], also exhibit considerable complexing abilities toward cations. We concluded that this complexation together with the high chirality of the carbohydrates should be useful for the stereochemical control in asymmetric synthesis.[14] In Strecker syntheses of α-amino nitrile derivatives galactosyl amines proved to be most effective auxiliaries.[10,15] However in further studies we found that the Ugi-synthesis described here is even more effective.

Results and Discussion

The carbohydrate auxiliaries 2,3,4,6-tetra-O-acetyl-(1) and 2,3,4,6-tetra-O-pivaloyl-ß-D-galactopyranosylamine 2 are easily accessible even in large amounts in three straightforward steps starting from peracylated galactopyranoses.[10,15] Our first Ugi reactions were carried out with the tetra-O-acetyl derivative 1. Surprisingly, even at room temperature in tetrahydrofurane the galactosylamine 1 does not react with aldehydes, isocyanides and carboxylic acids. However, the reaction is complete in a few minutes after addition of equimolar amounts of a Lewis acid. Among a variety of Lewis acids investigated zinc chloride proved to be most effective. Most favourably the reactions (eq. 1) are carried out at -20°C in a simple one-pot-procedure and they are complete after 2 to 4 hours. The results are shown in table 1.



eq. 1

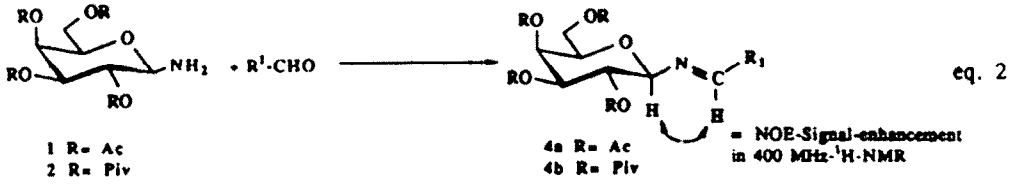
Table 1: Diastereoselective Ugi-Synthesis of N-Galactosyl Amino Acids Using 2,3,4,6-tetra-O-acetyl-ß-D-galactopyranosylamine 1 (eq. 1) at - 20°C.[f]

product	R_1	reaction time (h)	kinetic ratio[a] (2R : 2S)	yield of pure (2R)-3 (%)	m.p. (°C)	$[\alpha]_D^{20}$ $CHCl_3$ (c = 1)
3a	Ph	2.5	90 :10	80	75[b]	-57.5°
3b	p-Cl-Ph	2	93 : 7	82	156-8[c]	-65.3°
3c	t-Bu	4	91 : 9	83	180-1[d]	- 8.3°
3d	i-Prop	2	91 : 9	43[e]	140	- 0.5°[g]

[a] HPLC (diode array detection) directly taken from the reaction mixture. [b] After flash chromatography on silica gel with ethyl acetate/light petroleum ether (1 : 2), [c] Recrystallised from CH_2Cl_2/heptane ; [d] Recrystallised from MeOH/water; [e] After two recrystallisations; [f] In all cases the yields of the diastereomeric mixture 2R/2S -3 is almost quantitative; [g] (c = 4).

The diastereomeric ratio of the Ugi-adducts 3 cannot be easily determined by ^{1}H-NMR. Due to the hindered rotation of the N-formyl group the pure diastereomers of 3 exist in two rotamers showing different NMR signals. Effective analysis of the diastereoselectivity is achieved by analytical HPLC of samples directly taken from the reaction mixture. The assignment of the absolute configuration of the newly formed chiral center was based on the transformation of the derivatives 3 into the corresponding amino acids. In all cases (eq. 1) the (R)-amino acid derivatives 3 are formed preferably.

NMR experiments on the aldimines 4 formed from the 2,3,4,6-tetra-O-acyl-galactosylamines 1 (and 2) with aldehydes allow a mechanistic interpretation of the stereocontrol observed in these reactions.[10] A strong NOE between the anomeric and the aldimine proton shows that the Schiff bases prefer the conformation depicted in eq 2.



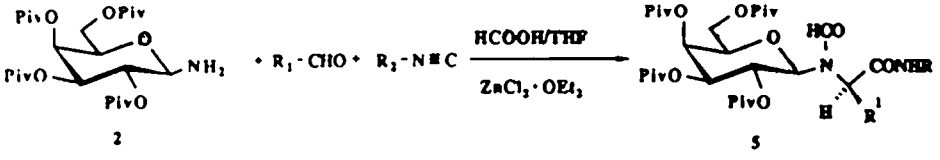
eq. 2

The isocyanide obviously attacks the aldimine 4a from the Si-side, i.e., from the side of the pyranose oxygen. The Re-side of the aldimine is shielded by the 2- and 3-O-acyl substituent adjacent to the imino group and, presumably, by their coordination to the zinc catalyst.

Following this interpretation the diastereoselectivity of this process should be enhanced if the O-acyl groups of 1 are substituted by sterically more demanding groups. Recently, we could show that glycosylation reactions can be directed more effectively by switching from acetyl protected to pivaloyl protected carbohydrate derivatives.[16] The O-pivaloyl group has the further advantage that it is stable to acid- and base-catalysed acyl migrations and transesterifications. In contrast to the O-acetyl groups in 3, the corresponding O-pivaloyl groups should be stable under the acidic conditions applied during the removal of the carbohydrate from the newly formed amino acid.

Consequently 2,3,4,6-tetra-O-pivaloyl-ß-D-galactosyl-amine 2[10,15,17] was subjected to Ugi-reactions under the conditions described above. In comparison to 1 somewhat longer reaction times are required: at -25°C about 24h; at -78°C and with sterically demanding aldehydes about 3 days. However, the diastereoselectivity of the process (eq. 3) increases to 15-35:1 in favour of the (2R,ß-D)-isomer of 5.[9]

In particular, the (R)-diastereomer of the tert-leucine derivative 5c (table 2) is formed exclusively from pivalaldehyde at -78°C. The other diastereomer cannot be detected even by 400 MHz-proton-NMR and by analytical HPLC. After one simple recrystallisation either from heptane or dichloromethane/heptane the pure (2R,ß-D)-diastereomers 5 are obtained in yields of 75-95 % (see table 2). Only in the cases of 5a and 5b flash chromatography is required for purification.



eq.3

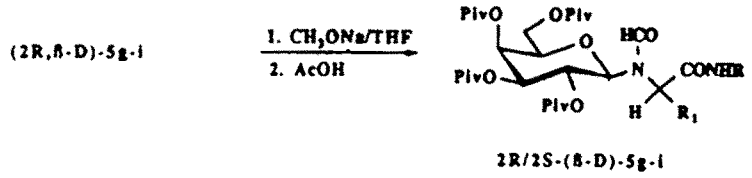
Table2: Diastereoselective Ugi-Synthesis of N-Galactosyl Amino Acid Derivatives 5, Using 2,3,4,6-Tetra-O-pivaloyl-ß-D-galactosylamine 2 (eq. 3)

pro-duct	R_1	reaction cond. °C/time	kinetic ratio (2R:2S)a	yield of pure 2R(%)	m.p. (°C)	$[\alpha]_D^{20}$ $CHCl_3$ (c = 1)
5a	n-C_3H_7	-78/2d	94 : 6	80	98-100[c]	-4,1[e]
5b	i-C_3H_7	-78/2d	95 : 5	86	amorphous[c]	-1.2[e]
5c	t-C_4H_9	-25/3d	96 : 4[b]	80	162-3	-8,6[e]
5d	Ph-	-25/24h	95 : 5	80	88-90	-13,7
5e	2-Furyl	-25/24h	95 : 5	90	122-4	-33,9
5f	2-Thienyl	-25/24h	96 : 4	93	124	-29,7
5g	Ph	0/8h	91 : 9	81	144	-37,4
5h	p-Cl-Ph	-25/24h	97 : 3	92	133	-38,6
5i	p-NO_2-Ph	0/4h	94 : 6	91	138	-35,6
5j	Styryl	-25/24h	95 : 5	75	148-50	-24,9
5k[d]	γ-Cyano-propyl	-25/24h	93 : 7	80	176-8	-11,4

[a]HPLC (diode array detection) directly taken from the reaction mixture; [b]At -78°C: (2R:2S) >100:1; [c]Separated by flash chromatography; [d]Phenylisocyanide was used; [e]c=2 in $CHCl_3$.

Table 2 illustrates that the Ugi reaction using the pivaloyl protected galactosylamine 2 as the chiral template offers a very effective access to (R)-amino acid derivatives having quite different side chains. Sterically demanding (5c) as well as unbranched (5a), benzylic (5d), aromatic (5g, 5h), heteroaromatic (5e, 5f), unsaturated (5j) and functionalized (5k) amino acid derivatives are available stereoselectively in high yields. In particular the efficiency of this method becommes evident in the stereoselective formation of the (R)-p-nitrophenylglycine derivative 5i prone to racemisation.

In the cases of the phenylglycine derivatives 5g-5i the (S)-diastereomers (2S,ß-D)-5 can be separated and identified. In order to prove their structure, they can be obtained even in preparative yield after epimerisation of the pure (2R,ß-D)-isomers 5 with catalytic amounts of sodium methoxide in tetrahydrofurane and subsequent separation by flash chromatography (eq. 4 and table 3).



2R/2S-(ß-D)-5g-i

eq.4

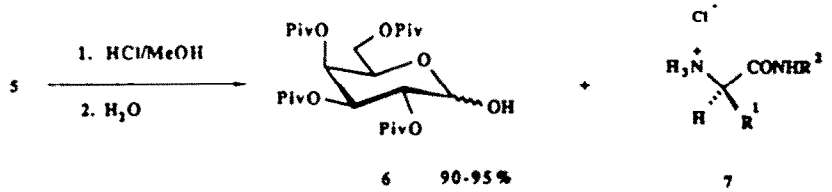
Table3: Formation of the (2S,ß-D)-Diastereomers of N-Galactosyl Phenylglycine Amides From Pure (2R,ß-D)-5 Isomers (eq. 4)[c].

2R,ß-D-5	diastereomeric ratio[a] (2R : 2S)	R_f[b] R	S	m.p.	2S,ß-D-5 $[\alpha]_D^{20}$(c=1,$CHCl_3$)
5g	3 : 1	0,66	0,40	224	+48,9
5h	3 : 2	0,58	0,47	174	+36,7
5i	3 : 2	0,42	0,32	208	+16,6

[a]After reprotonation; [b]On silica gel with ethyl acetate/light petroleum ether(1:3); [c]Equilibration time was 3 days at room temp.

The results summarized in table 3 suggest that the enolates of 5 are reprotonated diastereoselectively to give preferably the (2R)-diastereomers 5.

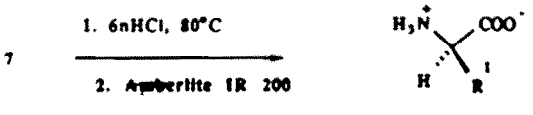
The N-galactosyl-amino acid derivatives 3 and 5 are starting materials for the synthesis of a broad range of valuable chiral products, e.g. ß-amino alcohols and 1,2-diamines. The most interesting ones are the R-amino acids themselves. Since the N-formyl amino acid amides 5 are stable toward aqueous acids their cleavage cannot be achieved in a single step. Therefore, the N-formyl group is first removed using hydrogen chloride in methanol. Then the N-glycosidic bond is cleaved by addition of water.



6 90-95%

7

eq. 5



8

The O-pivaloyl galactose 6 can be reisolated in yields of 90-95%. It can easily be converted into the starting auxiliary 2. Finally, the amino acid amides 7 are hydrolysed in aqueous hydrochloric acid. Subsequent deprotonation delivers the free enantiomerically[17] pure R-amino acids 8 (see table 4).

Table 4: Hydrolysis of N-Galactosyl Amino Acid Amides 5.

product	R_1	overall yield (%)	$[\alpha]_D^{22}$
8a	t-C_4H_9	90	-8,8°(c=2, 1,5n HCl); $[\alpha]_D^{20}$= -7° (c=5, 5n HCl)[19]
8b	Ph-CH_2	82	+6,5° (c=1, 1,5n HCl) $[\alpha]_D^{25}$= +7,07° (c=1, 1nHCl)[20]
8c	Ph	85	-157° (c=1, 1n HCl) $[\alpha]_D^{20}$= -155° (c=1, 1n HCl)[21]
8d	p-Cl-Ph	90	-140° (c=0,5, 1n HCl)[21] $[\alpha]_D^{20}$= -138,7° (c=1, 1n HCl)[21]
8e	HOOC-$(CH_2)_3$-	87	-21,5° (c=0,7, 2n HCl) $[\alpha]_D^{16}$= -25 (c=0,7, 6n HCl)[22]

The optical purity of the (R)-amino acids is checked by t.l.c. using "chiral plate" [18].

In conclusion, the Ugi-reaction using the galactosylamines 1 and 2 as the chiral auxiliaries provides an efficient route to (R)-amino acids of quite different structure. It proceeds in a simple one-pot-procedure. High stereoselectivity is achieved. The pure diastereomers 3 and 5 are easily obtained in high yields by recrystallisation or chromatography. Furthermore, organometallic reagents or intermediates and exclusion of oxygen are not required.

Experimental

General: 400 MHz-^{1}H-NMR-spectra were recorded on Bruker AM-400 in $CDCl_3$; optical rotations were measured with a Perkin-Elmer 241 polarimeter; analytical HPLC was carried out with LKB-equipment including diode array detection (190-370 nm) on reversed phase columns (100x4 mm ID, 120-3 C_{18}) with methanol/water mixtures as eluent.

N-Formyl-N-Galactosyl-Amino Acid-N'-tert-Butylamides 3 / 5. General procedure.

A solution of 4 mmol of 2,3,4,6-tetra-O-acetyl-ß-D-galactopyranosylamine 1 or 2,3,4,6-tetra-O-pivaloyl-ß-D-galactopyranosylamine 2, 4,1 mmol of the respective aldehyde (see table 1 and 2), 4,4 mmol formic acid and 4,2 mmol t-butylisocyanide in 30 ml tetrahydrofurane is cooled to the temperature given in table 1 or 2. 4 mmol zinc chloride (as a 2,2 molar solution of the diethylether complex in dichloromethane) is added and the reaction is monitored by t.l.c. (ethyl acetate/light petroleum ether 1:1 or 1:3 respectively). After complete consumption of the starting material (1, 2 or aldimines 4) the solvent is evaporated in vacuo. The residue is dissolved in 50 ml of dichloromethane, extracted twice with 100 ml saturated aqueous sodium bicarbonate and twice with water. The organic layer is dried over $MgSO_4$, filtered and evaporated in vacuo to give the mixture of diastereomers 3/5 in almost quantitative yield. The pure (2R)-diastereomers are obtained by recrystallisation from heptane, dichloromethane/heptane or by flash chromatography. Results and physical data of the compounds 3 and 5 are summarized in tables 1 and 2. For nomenclature, elemental analysis and typical ^{1}H-NMR-signals see tables 5 and 6.

Table 5: 400 MHz-^{1}H-NMR-Signals (two rotamers) and Elemental Analysis of N-Formyl-N-(2,3,4,6-tetra-O-acetyl-ß-D-galactopyranosyl)-(R)-amino-acid-N'-tert-butyl-amides 3[a].

product	amino acid	^{1}H-NMR δ (ppm) H-1 (d, J)	CHO (s)	αCH (s)	elemental analysis	C	H	N
3a	phenylglycine[a]	4,69 (9,6 Hz)*	8,60*	5,45*	calc.:	57,42	6,43	4,96
		5,85 (9,4 Hz)	8,22	5,39	found :	57,46	6,73	4,64
3b	p-chlorophenyl-glycine[a]	4,75 (9,6 Hz)*	8,57*	5,65*		54,11	5,89	4,68
		5,83 (9,3 Hz)	8,21	5,85		53,87	5,91	4,47
3c	tert-leucine[a,b]	5,82 (8,7 Hz)*	8,60*	4,70*		55,12	7,41	5,15
			55,01	7,33		5,08		
3d	valine[a,b]	5,34 (9,6 Hz)*	8,50*	4,05*		54,33	7,22	5,28
						54,28	7,33	5,18

*Major rotamer; [a] Full name is formed by inserting the name of the amino acid into the headline denomination. [b] Minor rotamer less than 10%.

Epimerisation of (2R,ß-D)-Isomers of N-Galactosyl-Phenylglycine-Amides 5 (General procedure).

The (2R)-diastereomers of 5g, 5h or 5i (2 mmol) are dissolved in 50 ml of dry tetrahydrofurane. Sodium methoxide (20 mg, 0,2 eq.) is added, and the suspension is stirred for 3 d at room temperature. The formation of the (2S)-epimer is monitored by t.l.c. and HPLC. After addition of 0,1 ml of acetic acid the solvent is evaporated in vacuo. The diastereomers (2R,ß-D)-5 and (2S,ß-D)-5 are separated by flash-chromatography on silica gel using ethylacetate/light petroleum ether (1:4) as the eluent. The results and the characterisation of the (S)-amino acid derivatives are shown in table 3 and 6.

Hydrolysis of N-Galactosyl Amino-Acid-Amides 5-Synthesis of (R)-Amino Acid 8 (General procedure).

To a solution of 2 mmol of 5 in 10 ml of dry methanol at 0°C 3 ml of saturated hydrogen chloride in methanol are added. The mixture is stirred 1h at 0°C and 3h at room temperature. After the starting material has disappeared (t.l.c. control) 2 ml water are added and the mixture is stirred for 12h. The methanol is evaporated in vacuo, the residue taken up in 20 ml water and extracted twice with 10 ml of n-pentane. After drying with $MgSO_4$ the 2,3,4,6-tetra-O-pivaloyl-D-galactopyranose 6 is isolated from the organic layer in almost quantitative yield.

The aqueous layer is also evaporated in vacuo to yield the amino acid amides 7 as the hydrochlorides almost quantitatively. They are treated with 10 ml of 6n hydrochloric acid at 80°C until the compounds 7 are completely hydrolysed (t.l.c. control, about 24-48h). After evaporation in vacuo the remaining crystalline residue is dried by codistillation with toluene (10 ml) from it. Then it is dissolved in water and deprotonated by passing through a column of ion exchange resin (Amberlite IR 200). The resin is washed until the eluent becomes neutral. Then the amino acid 8 is liberated from the resin by elution with 3% aqueous ammonia. After evaporation of the eluate in vacuo the free (R)-amino acids are obtained as colorless crystalline residues. The results and characterisations are shown in table 4.

Table 6: 400 MHz-^{1}H-NMR-Signals (two rotamers) and Elemental Analysis of N-Formyl-N-(2,3,4,6-tetra-O-pivaloyl-β-D-galactopyranosyl)-(R)-Amino Acid-N'-tert-Butyl-Amides[5c]

product	amino acid	^{1}H-NMR δ (ppm) H-1 (d, J)	CHO (s)	αCH (s)	elemental analysis calc.: found:	C	H	N
5a	(R)-α-amino-butyric acid	5,90 (9,2 Hz)*	8,29*	--[a]		61,87	8,94	4,00
		4,00 (8,9 Hz)	8,61	--[a]		61,91	8,91	3,86
5b	(R)-valine	5,95 (8,9 Hz)*	8,32*	3,90*		61,87	8,94	4,00
		--[a]	8,65	--[a]		62,07	9,04	3,84
5c	(R)-tert-leucine	6,17 (9,5 Hz)*	8,50*	4,96*		62,33	9,05	3,93
		6,04 (8,8 Hz)	8,73	3,50		62,45	9,02	3,90
5d	(R)-phenyl-alanine	5,90 (9,2 Hz)*	8,77*	3,15*		64,32	8,37	3,75
		5,38 (9,5 Hz)	8,39	--[a]		64,54	8,14	3,68
5e	(R)-(2-furyl)-glycine	5,90 (9,3 Hz)*	8,42*	5,36*		61,48	8,09	3,88
		--[a]	8,40	5,08		61,65	8,19	4,09
5f	(R)-(2-thienyl)-glycine	5,92 (9,4 Hz)*	8,38*	5,20*		60,14	7,91	3,79
		--[a]	8,34	5,29		60,22	7,79	3,73
5g	(R)-phenyl-glycine	5,95 (9,4 Hz)*	8,19*	5,08*		63,91	8,25	3,82
		--[a]	8,42	5,53		63,97	8,19	3,89
	(S)-phenyl-glycine	6,00 (9,5 Hz)*	8,15*	4,84*		63,91	8,25	3,82
		4,71 (9,6 Hz)	8,46	5,26		64,02	8,22	3,80
5h	(R)-p-chloro-phenylglycine	5,93 (9,3 Hz)*	8,20*	5,01*		61,04	7,75	3,65
		5,06 (9,4 Hz)	8,36	5,32		60,95	7,62	3,86
	(S)-p-chloro-phenylglycine	5,99 (9,4 Hz)*	8,13*	4,79*		61,04	7,75	3,65
		4,83 (9,6 Hz)	8,40	5,14		61,38	7,98	3,75
5i	(R)-p-nitro-phenylglycine	5,96 (9,0 Hz)*	8,29*	5,10*		60,22	7,65	5,40
		5,12 (9,3 Hz)	8,33	5,21		59,83	7,34	5,69
	(S)-p-nitro-phenylglycine	6,02 (9,4 Hz)*	8,16*	4,92*		60,22	7,65	5,40
		5,03 (9,3 Hz)	8,38	5,11		60,19	7,71	5,47
5j	(R)-α-amino-4-phenyl-3-butenoic acid	5,00 (9,4 Hz)*	8,28*	4,60*		64,88	8,23	3,69
		5,91 (9,4 Hz)	8,43	4,57		64,95	8,22	3,77
5k[b]	(R)-α-amino-5-cyano-pentanoic acid	4,97 (9,3 Hz)*	8,32*	4,28*		62,97	7,72	5,65
		5,96 (9,5 Hz)	8,56	--[a]		62,86	7,56	5,38

*Major rotamer; [a]Signal can not be identified; [b] This compound is formed as the N'-phenylamide obtained from phenylisocyanide, [c] Full name is formed by inserting the name of the amino acid into the headline denomination.

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