O-Alkyl-D-glucopyranosylamines and Their Derivatives

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Dedicated to Professor H.J. Bestmann in recognition of his contribution to science as Editor of Synthesis

O-Alkyl-D-glucopyranosylamines are prepared by alkylation of glucose and subsequent exchange of the 1-hydroxy group by an amino group. The title compounds are being tested as chiral templates, in particular for peptide syntheses by asymmetric four-component condensations.

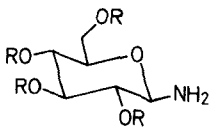
The four-component condensation (4CC, Ugi reaction)[1-3] is a widely usable principle of synthesis. The 4CC permits the preparation of a great variety of compounds by a simple one-pot reaction. In the synthesis of peptides the 4CC offers particular advantages.[4] Since the discovery of the 4CC's,[1] methods for the synthesis of peptides via this reaction have been developed, and particular attention is devoted to the synthesis of peptide segments by asymmetrically induced 4CC's.[4,5]

In this endeavor the main attention is devoted to the asymmetrically inducing chiral amine component, because the success of the synthesis depends largely on the choice of the latter. A chiral amine component of peptide syntheses by asymmetric 4CC must have good asymmetric inducing power under suitable reaction conditions, it must yield 4CC products with a cleavable auxiliary group, and it must be readily available.[4]

Until recently the α-ferrocenyl alkylamines were the only amine components that met these requirements.[3-6] In 1988 Kunz and Pfrengle[7] reported that 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine undergoes 4CC in excellent yield and with a high degree of stereoselectivity in tetrahydrofuran at −78 to 0°C in the presence of anhydrous zinc chloride. In a later communication, the use of the complementary arabinose derivative as amine component in such 4CC is described.[8]

The resulting 4CC products can be cleaved to yield α-amino acids. This synthesis is restricted to α-amino acids, because under the required cleavage conditions (HCl/MeOH/H_2O, 0°C, 1 h, then, r.t., 15 h) peptides are destroyed.

The amine components of Kunz and Pfrengle correspond to "disarmed" carbohydrate derivatives. In order to facilitate the cleavage of the 4CC products, we introduce the *O*-alkyl-1-amino-D-glucoses as "armed" amine components.[9] In this article we describe the synthesis of the 2,3,4,6-tetra-*O*-alkyl-β-D-glucopyranosylamines **5a–c** that are tested as amine components for peptide syntheses.



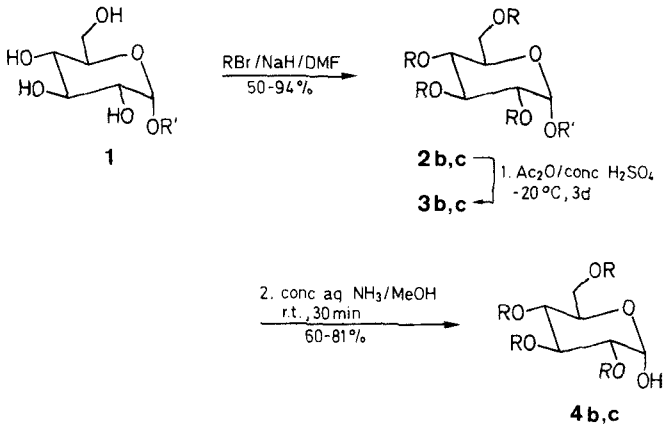
5

5	a	b	c	d
R	Me	Et	$Me_2CHCH_2CH_2$[a]	$PhCH_2$

[a] *i*-Am.

The glucose derivatives **5a–c** are new compounds. The only known close analog of **5a–c** is **5d**.[10]

2,3,4,6-Tetra-*O*-methyl-β-D-glucopyranosylamine (**5a**) is obtained in 62% yield from the readily available 2,3,4,6-tetra-*O*-methyl-D-glucopyranose[11a] (**4a**) by mesylation and subsequent treatment with gaseous ammonia in a one-pot reaction, in analogy to the procedure of Vasella et. al.[10]

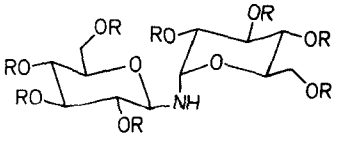


Compound	R	R'	4	R
2b	Et	Me	**a**	Me
2c	*i*-Am	Me	**b**	Et
3b	Et	Ac	**b**	Et
3c	*i*-Am	Ac	**c**	*i*-Am

Scheme 1

The glucopyranosides **2b** and **2c** are prepared from methyl α-D-glucopyranoside (**1**) by alkylation; the procedure of Brimacombe et. al.[12] serves well. Subsequent acetolysis of **2** to yield **3**, followed by ammonolysis, leads to **4b** and **4c** respectively. The yields of compounds **2b** and **4b** are thus quite improved compared to the only previously known synthetic route (94 vs. 39% for **2b**).[11b]

The amines **5b** and **5c** are prepared in analogy to the procedure for **4a** to **5a**, and have a pronounced tendency to undergo self-condensation yielding secondary amines of the type **6**.



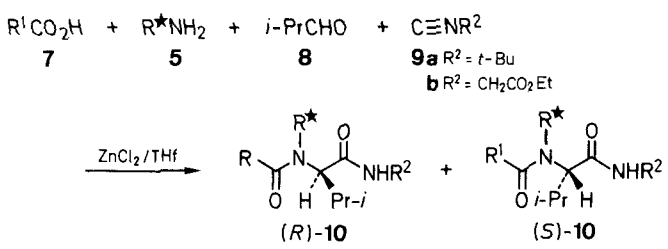
6 R = Me, Et, *i*-Am

Table 1. Formation of α-Acylamino Acid Derivatives **10** by 4CC with Isobutyraldehyde (**8**) and *tert*-Butyl Isocyanide (**9a**) or Ethyl 2-Isocyanoacetate (**9b**)

Amine R^*NH_2	Acid **7** R^1CO_2H	Isocyanide	Temp. (°C)/ Time (h)	Product	Yield (%)[a]	de[b] (%)
5a	$ClCH_2CO_2H$	**9a**	0/4	**10a**	78	74
5a	CF_3CO–Gly–OH	**9a**	−50/48	**10b**	70	69
5a	Pht–Gly–OH	**9a**	0/4	**10c**	64	66
5a	$PhCO_2H$	**9a**	0/4	**10d**	70	59
5b	$PhCO_2H$	**9a**	0/4	**10e**	77	74
			−50/72		80	68
5b	CF_3CO–Gly–OH	**9a**	0/4	**10f**	87	74
			−50/72		79	85
5b	CF_3CO–Gly–OH	**9b**	0/4	**10g**	76	71
5b	$PhSCH_2CO_2H$	**9a**	0/4	**10h**	86	72
5c	CF_3CO–Gly–OH	**9a**	0/4	**10i**	80[c]	98

[a] Total yield of all diastereomers.
[b] (β,*R*)%-(β,*S*)%-isomer, the β refers to the configuration at C-atom 1 of the glucose moiety and *R* to the configuration of the valine unit. The relative amounts of the diastereomers were determined by GC/MS with a Carlo Erba 4160 capillary (25 m) GC/Varian MAT 112 coupled instrument.
[c] Yield of pure (Glc-β-D,*R*-Val) diastereomer was 35%, not optimized.

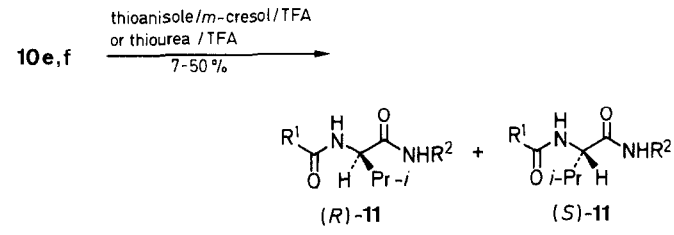
The amines **5a–c** have been tested as chiral amine components in various model 4CCs (see Scheme **2** and Table 1).



Scheme **2**

According to their high resolution ^{1}H-NMR spectra (Table 3), the major diastereomers of the 4CC products **10b,e,f,i** have the (Glc-βD,*R*-Val) configuration; the observed double septets of the side-chain methine protons in the valine residue are thus best explained. The spectra of the other compounds of type **10** have similar essential features; accordingly these probably also have the (Glc-β,D,*R*-Val)-configuration.

The 4CC products **10** were used as model compounds for acidolytic cleavages to form **11**. Trifluoroacetic acid in combination with a soft base gave the best results (see Table 2). A "push-pull" mechanism as described by Yajima et. al.[13] is likely.



Scheme **3**

Table 2. The Acidolytic Cleavage of **10** into **11**

Substrate	Solvent/ Reagent[a]	Temp. (°C)/ Time	% Reacted[b]	Product	Yield (%)	Major Isomer
10e	A	90/1 h	–[c]	**11e**	10	*R*[f]
10e	A	50/23 h	–[c]	**11e**	7	*R*[f]
10f	A	50/3 h	–[c]	**11f**	11	*R*
10f	A	70/2 h	40[d]	**11f**	20	*R*
10f	A	70/1 h	36[d]	**11f**	11	*R*[g]
10f	B	80/20 h	50[e]	**11f**	50[e]	*R*
10f	B	20/6 d 80/4 h	33[e]	**11f**	33[e]	*R*

[a] Solvent/reagent were as follows: A: 10 (1.0 g) in a solution of thioanisole (12 mL), *m*-cresol (2.0 mL) and TFA (20 mL). B: 10 (0.5 g) in solution of thiourea (3.16 g) and TFA (40 mL).
[b] After evaporation of TFA under reduced pressure, neutralization ($NaHCO_3$) and extraction (EtOAc).
[c] Not determined.
[d] Determined by ^{1}H-NMR (360 MHz) after silica gel gradient filtration (hexane → Et_2O).
[e] Determined by ^{1}H-NMR (360 MHz) after evaporation of the solvent.
[f] Checked by chiral TLC; comparison with an authentic sample.[15]
[g] Determined by chiral TLC; comparison of cleaved diastereomer mixture vs. cleaved pure (Glc-β-D,*R*-Val) diastereomer (obtained by destructively selective[16] precleavage of the diastereomer mixture); eluent MeOH/H_2O/MeCN (5 : 5 : 3); R_f[(*R*)-**11f**] = 0.25; R_f[(*S*)-**11f**] = 0.37.

The present results indicate that as chiral amine components of asymmetric 4CC's, the 2,3,4,6-tetra-*O*-alkyl-β-D-glucopyranosylamines **5** are as favorable as the *O*-acyl-aldopyranosylamides of Kunz et. al.[7,8] The yields as well as the degree of stereoselectivity are comparable. The *O*-*i*-Am derivatives seem to be particularly well suited for peptide syntheses by stereoselective 4CC's. As expected, the acidolysis of the *O*-alkyl compounds proceeds under much milder conditions than the corresponding cleavage of the *O*-acyl products. The presence of the thio-compounds as soft bases facilitates the acidolysis greatly.

In our future work in this field we shall primarily concentrate on systems that enable to remove the auxiliary group from the peptides effectively and under mild conditions.

Alkylated Glucopyranosides 2; General Procedure:
A solution of methyl α-D-glucopyranoside (**1**, 15 g, 77.2 mmol) in dry DMF (360 mL) is stirred vigorously at r.t. under an inert gas blanket. NaH (12 g, 500 mmol, 1.6 equiv.) is carefully added, and after 20 min at r.t. the suspension is cooled to 0 °C. After another 20 min of continued stirring, the alkylating agent, *i*-AmBr or EtBr, (310 mmol, 2.0 equiv) is added dropwise to the now pasty suspension that is shaken periodically. After adding all of the alkyl bromide, the paste is slowly allowed to warm to r.t., resulting in a stirrable, usually clear solution (~ 22 h). In the case of **2c**, stirring is continued at 40 °C for 14 d. The reaction is quenched by addition of MeOH (50 mL). The solution is evaporated in vacuo to yield a syrup. This is diluted with H_2O (150 mL) and extracted with either $CHCl_3$ (4 × 120 mL, **2b**) or hexane (3 × 150 mL, **2c**). The combined organic layers are washed with H_2O (2 × 100 mL), dried (Na_2SO_4), and evaporated in vacuo. The residue is either distilled, **2b**, or used directly for acetolysis.

Compound **2b**: yield 94%; bp 146–8 °C/0.45 Torr (Lit.[11b] 94–6 °C/0.15 Torr); $[\alpha]_D^{20}$ + 116.9° (*c* = 2.6, $CHCl_3$) (Lit.[11b] $[\alpha]_D$ + 76.5° (*c* = 5, EtOH)).

Table 3. Compounds **10** and **11** Prepared

Compound	Molecular Formula[a]	IR[b] ν (cm^{-1})	MS (70 eV)[c] m/z (%)	^{1}H-NMR ($CDCl_3$)[d] δ, J (Hz)
10a	$C_{21}H_{39}ClN_2O_7$ (467.1)	1660, 1540	366 (M − 100, 6), 88 (100)	0.83 (d, 3H, J = 6.6, Me–Val), 0.95 (d, 3H, J = 6.6, Me–Val), 2.73 (m, 1H, CH–Val), 4.08 (d, 1H, J = 12.9, CHCl), 4.32 (d, 1H, J = 12.9, CHCl), 4.58 (d, 1H, J = 8.8, β-H_1)
10b	$C_{23}H_{40}F_3N_3O_8$ (543.7)	1650, 1510	453 (M − 100, 1), 88 (100), 544 (M + 1, 100)	0.79 (d, 3H, J = 6.6, Me–Val), 0.95 (d, 3H, J = 6.6, Me–Val), 2.71 (d sept 1H, J_1 = 6.3, J_2 = 11.3, CH–Val), 4.21 (dd, 1H, J_{HF} = 4.4, J_2 = 17.6, CH–Gly), 4.29 (dd, 1H, J_{HF} = 3.5, J_2 = 17.6), 4.42 (d, 1H, J = 8.7, β-H_1)
10c	$C_{29}H_{43}N_3O_9$ (577.7)	1770, 1715, 1660, 1540	477 (M − 100, 6), 88 (100), 578 (M + 1, 100)	0.85 (d, 3H, J = 6.6, Me–Val), 0.92 (d, 3H, J = 6.6, Me–Val), 2.70 (m, 1H, CH–Val), 4.51 (d, 1H, J = 16.2, CH–Gly), 4.63 (d, 1H, J = 8.6, β-H_1, 4.81 (d, 1H, J = 16.2, CH–Gly)
10d	$C_{26}H_{42}N_2O_7$ (494.7)	1630, 1510	394 (M − 100, 20), 187 (100), 495 (M + 1, 100)	0.97 (d, 3H, J = 6.6, Me–Val), 1.04 (d, 3H, J = 6.6, Me–Val), 2.45 (m, 1H, CH–Val), 4.52 (d, 1H, J = 8.91, β-H_1)
10e	$C_{30}H_{50}N_2O_7$ (550.8)	1655, 1510	450 (M − 100, 8), 116 (100)	0.91 (d, 3H, J = 6.6, Me–Val), 0.97 (d, 3H, J = 6.6, Me–Val), 2.76 (d sept, 1H, J_1 = 6.6, J_2 = 11.0, CH–Val), 3.37 (d, 1H, J = 11.0, NCHCO), 4.55 (d, 1H, J = 8.9, β-H_1)
10f	$C_{27}H_{48}F_3N_3O_8$ (599.8)	1720, 1655, 1540	499 (M − 100, 1), 116 (100), 600 (M + 1, 100)	0.80 (d, 3H, J = 6.6, Me–Val), 0.98 (d, 3H, J = 6.6, Me–Val), 2.68 (d sept, 1H, J_1 = 6.7, J_2 = 11.2, CH–Val), 4.24 (dd, 1H, J_{HF} = 3.9, J_2 = 17.4, CH–Gly), 4.38 (dd, 1H, J_{HF} = 3.1, J_2 = 17.4, CH–Gly), 4.46 (d, 1H, J = 8.8, β-H_1)
10g	$C_{27}H_{46}F_3N_3O_{10}$ (629.7)	1720, 1660, 1530	584 (M − 46, 0.2), 116 (100), 630 (M + 1, 59), 229 (100)	0.84 (d, 3H, J = 6.6, Me–Val), 2.89 (m, 1H, CH–Val), 4.27 (dd, 1H, J_{HF} = 5.2, J_2 = 17.3), 4.37 (dd, 1H, J_{HF} = 3.5, J_2 = 17.3), 2 × CH–Gly), 4.46 (d, 1H, J = 8.6, β-H_1)
10h	$C_{31}H_{52}N_2O_7S$ (596.2)	1665, 1540	596 (M^+, 1.4), 116 (100)	0.68 (d, 3H, J = 6.6, Me–Val), 0.84 (d, 3H, J = 6.6, Me–Val), 2.65 (m, 1H, CH–Val), 3.82 (d, 1H, J = 14.8, CHS), 3.94 (d, 1H, J = 14.8, CHS), 4.65 (d, 1H, J = 8.9, β-H_1)
10i[e]	$C_{39}H_{72}F_3N_3O_8$ (768.1)	3290, 1730, 1665, 1550	680 (M − 88, 0.4), 71 (100), 768 (M + 1, 100)	0.84 (d, 3H, J = 6.6, Me–Val), 0.96 (d, 3H, J = 6.6, Me–Val), 2.69 (d sept, 1H, J_1 = 6.4, J_2 = 11.3), 4.20 (dd, 1H, J_{HF} = 3.9, J_2 = 17.6, CH–Gly), 4.39 (dd, 1H, J_{HF} = 3.7, J_2 = 17.6, CH–Gly), 4.44 (d, 1H, J = 8.7, β-H_1)
11f[f]	$C_{13}H_{22}F_3N_3O_3$ (325.4)	3310, 1710, 1640, 1545	226 (M − 99, 22), 72 (100), 326 (M + 1, 100)	0.81 (d, 3H, J = 6.9, Me–Val), 0.83 (d, 3H, J = 6.9, Me–Val), 1.88 (oct. 1H, J = 6.8, CH–Val), 3.85 (dd, 1H, J_{HF} = 5.9, J_2 = 16.5), 3.91 (dd, 1H, J_{HF} = 5.9, J_2 = 16.5, 2 × GlyH)
(*R*)-**11e**[g]	–	1630, 1510	176 (M − 100, 17), 105 (100), 277 (M + 1, 100)	–

[a] All new compounds gave satisfactory microanalytical data: C ±0.40, H ±0.30, N ±0.36; except **10d**: N −0.64, **10g**: C −0.55.
[b] Recorded on a Perkin-Elmer 257 spectrophotometer; compounds **10f**, **10k** and **11f** were recorded as KBr discs, **10c** in $CHCl_3$ solution and all other compounds as Nujol mulls.
[c] Recorded on a Varian MAT 112 instrument, chemical ionization with isobutane.
[d] Selected data, recorded on a Bruker AM 360 spectrometer (360 MHz); full ^{1}H- and ^{13}C-NMR data is available from the authors on request.
[e] mp 118–120 °C; $[\alpha]_D^{25}$ −11.9° (c = 0.94, MeOH).
[f] NMR experiment recorded in DMSO-d_6.
[g] mp of amorphons material (purified by preparative TLC) 226–228 °C (Lit.[12] mp 228–231 °C); $[\alpha]_D^{20}$ +60.3° (c = 2.1, AcOH/$CHCl_3$ 1:1) (Lit.[14] $[\alpha]_D^{22}$ +61.4° (c = 2.1, AcOH/$CHCl_3$ 1:1)).

Alkylated Glucopyranoses 4; General Procedure:
Conc. H_2SO_4 (1 mL) is added to a solution of **2b** or **2c** (65.3 mmol) in Ac_2O (150 mL) under an inert gas blanket, and the flask is allowed to stand for 3 d at −20 °C. The resulting dark olive solution is poured into a vigorously stirred ice-cold mixture of either CH_2Cl_2 (400 mL, **4b**) or hexane (400 mL, **4c**) and H_2O (200 mL); it is stirred for 5 min. The layers are separated; the organic layer is washed first with H_2O (5 × 400 mL), then sat. aq $NaHCO_3$ solution (2 × 250 mL). Evaporation of the solvent containing $NaHCO_3$ powder (≈ 2 g) leads to a sirupy residue which is taken up in MeOH (150 mL). Conc. aq NH_3 (150 mL) is added gradually to this cooled and stirred solution; the clear solution is stirred for another 30 min. Then H_2O (200 mL) is added and the mixture extracted with either CH_2Cl_2 (4 × 200 mL, **4b**) or hexane (4 × 200 mL, **4c**). The combined organic layers are washed with H_2O (200 mL), dried (Na_2SO_4), and the solvent is evaporated in vacuo. The oily residue is either used directly for amination, **4c**, or crystallized by addition of pentane (50 mL) and subsequent cooling to −20 °C, **4b**. Three to four fractions of crystalline **4b** can thus be obtained.

Compound **4b**: yield (4 fractions) 60%; mp 80.5–82 °C (Lit.[11b] mp 80–82 °C); $[\alpha]_D^{20}$ +79.1° (c = 0.5, $CHCl_3$) (Lit.[11b] $[\alpha]_D$ +95.9° (c = 2, EtOH)).

Alkylated Glucopyranosylamines 5; General Procedure:
Mesyl chloride (6.5 mL, 1.9 equiv) in dry CH_2Cl_2 (50 mL) is added dropwise to a stirred solution of **4** (44.3 mmol) and dry Et_3N (16 mL, 2.6 equiv) in dry CH_2Cl_2 (260 mL) at −20 °C within 15 min. After continued stirring (30 min) the mixture is cooled to −30 °C. Dry gaseous NH_3 is bubbled through the solution for 1 h. The suspension is gradually allowed to warm to r.t. and stirred for 23 h. After this time, the precipitate is removed by filtration. The solution is washed with H_2O (3 × 40 mL), dried (Na_2SO_4), and the solvent is evaporated in vacuo. The crystalline residue is either recrystallized from hexane, **5a,b**, or reprecipitated from MeOH/H_2O.

Diastereoselective Model 4CC's; General Procedure:
Under an inert gas blanket a solution of the amine **5** (20.6 mmol) in dry THF (90 mL) is added dropwise in the course of 20 min to a

Table 4. Compounds **2c**, **4c**, **5a–c** Prepared

Compound	Yield (%)	mp (°C) bp (°C)/Torr	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)	Molecular[a] Formula	IR[b] ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[c] δ, *J* (Hz)	MS (70 eV)[d] *m/z* (%)
2c	50	234–236/0.9	+70.8 (0.43)	$C_{27}H_{54}O_6$ (474.8)	2950, 2920, 2870, 1465, 1370, 1100	0.79 (m, 24H, 8 × Me), 1.37 (m, 8H, 4 × CH_2), 1.58 (m, 4H, 4 × CH), 4.67 (d, 1H, J = 3.5, H_1)	355 (M − 119, 0.6), 71 (100), 443 (M + 1–32, 15), 355 (100)
4c	81	–[e]	+35.9 (0.43)	$C_{26}H_{52}O_6$ (466.8)	3400, 2950, 2920, 2870, 1465, 1370, 1100	0.90 (m, 24H, 8 × Me), 1.47 (m, 8H, 4 × CH_2), 1.67 (m, 4H, 4 × CH), 4.56 (d, 1H, J = 7.7, β-H_1), 5.27 (d, 1H, J = 3.3, α-H_1), (α/β = 2 : 1)	442 (M − 18, 0.4), 71 (100)
5a	62	72–73[f]	+83.3 (0.25)	$C_{10}H_{21}NO_5$ (235.3)	3390, 3360, 1625, 1460, 1390, 1100	3.41 (s, 3H, MeO), 3.53 (s, 3H, MeO), 3.62 (s, 3H, MeO), 3.66 (s, 3H, MeO), 3.95 (d, 1H, J = 8.7, β-H_1), 5.04 (d, 1H, J = 4.7, α-H_1), (α/β = 12 : 88)	203 (M − 32, 4), 88 (100), 236 (M + 1, 100)
5b	79 (45)[g]	92–93[h]	+36.5 (0.4)	$C_{14}H_{29}NO_5$ (291.4)	3370, 3340, 1480, 1440, 1375, 1100	1.20 (m, 12H, 4 × Me), 1.88 (br s, 2H, NH_2), 3.97 (d, 1H, J = 8.7, β-H_1), 5.00 (d, 1H, J = 4.8, α-H_1), ($\alpha \ll 10\%$)	216 (M − 75, 3), 116 (100), 292 (M + 1, 100)
5c	92 (37)[g]	50–51[i]	+17.8 (0.14)	$C_{26}H_{53}NO_5$ (459.8)	3370, 3330, 1460, 1370, 1100	0.83 (m, 24H, 8 × Me), 1.41 (m, 8H, 4 × CH_2), 1.61 (m, 4H, 4CH), 1.82 (b s, 2H, NH_2), 3.88 (d, 1H, J = 8.7, β-H_1), 4.94 (d, 1H, J = 4.7, α-H_1), ($\alpha \ll 10\%$)	460 (M + 1, 100)

[a] Satisfactory microanalysis obtained: C ±0.31, H ±0.29, N ±0.40; except **4c**: C −0.64, **5c**: N −0.75.
[b] See Table 3 for instrument details; compounds **5a, b** were recorded as KBr discs, **5c** as a Nujol mull, and **2c**, **4c** as films.
[c] See Table 3 for instrument details; full ^{1}H- and ^{13}C-NMR is available from the authors on request.
[d] See Table 3 for instrument details, chemical ionization with isobutane.
[e] Oil, decomposed on distillation.
[f] From petroleum ether (bp 40–80 °C/Et_2O).
[g] Total yield of amine from **1**.
[h] From hexane.
[i] Reprecipitated from MeOH/H_2O.

stirred solution of isobutyraldehyde (**8**, 1.9 mL, 20.9 mmol, 1.02 equiv) and anhydrous $ZnCl_2$ (1 M solution in Et_2O, 21 mL, 21 mmol, 1.02 equiv) in dry THF (150 mL), containing molecular sieves (11.4 g, 3 Å, 1.7–2.4 mm beads). Stirring is continued at r.t. for another 20 h. Then the suspension is cooled to the temperature given in Table 1. The respective isocyanide **9** (21.2 mmol, 1.03 equiv) is added, and stirring is continued for another 15 min. A solution of the respective acid **7** (21.0 mmol, 1.02 equiv) in THF (90 mL) is added dropwise. Stirring is continued for the time indicated in Table 1; the reaction is monitored by TLC ($CHCl_3$/MeOH 9:1, ninhydrine). After the starting material has disappeared, the suspension is filtered over a Celite bed and evaporated in vacuo. The oily residue is taken up in CH_2Cl_2 (100 mL), washed with 3.5% aq tartaric acid (100 mL) and sat. aq. $NaHCO_3$ solution (100 mL). The organic phase is then stirred for 15 h (r.t.) with a sat. aq $NaHSO_3$ solution (200 mL), washed with H_2O (75 mL), dried (Na_2SO_4), and evaporated in vacuo. The product **9i** is obtained as a crystalline solid, **9b,c,f** as amorphous foams and the others as gums. The (Glc-βD,*R*-Val) diastereomers of **9e,i** are purified by either recrystallization from MeOH/H_2O, **9i**, or prep TLC (EtOAc/hexane 3:7), **9e**, the other compounds **9** are characterized as mixtures of diastereomers (Tables 1 and 3).

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(1) Ugi, I.; Meyr, R.; Fetzer, U.; Steinbrückner, C. *Angew. Chem.* **1959**, *71*, 386.
(2) Ugi, I. *Angew. Chem.* **1962**, *74*, 9.
(3) Ugi, I.; Lohberger, S.; Karl, R. in: *Comprehensive Organic Synthesis: Selectivity for Synthetic Efficiency*, Trost, B.M., Heathcock, C.H. (eds.), Pergamon, Oxford, 1991, Vol. 2, Ch. 4.6, in Press.
(4) Ugi, I.; Marquarding, D.; Urban, R. in: *Chemistry and Biochemistry of Amino Acids, Peptides and Proteins*, Weinstein, B. (ed.), Marcel Dekker, New York, 1982, Vol. 6, p. 245.
(5) (a) Dugundji, J.; Kopp, R.; Marquarding, D.; Ugi, I. *Top. Curr. Chem.* **1978**, *75*, 165.
(b) Ugi, I. *Chimia* **1986**, *40*, 340.
(6) (a) Herrmann, R.; Hübener, G.; Siglmüller, F.; Ugi, I. *Liebigs Ann. Chem.* **1986**, 251.
(b) Siglmüller, F.; Herrmann, R.; Ugi, T. *Tetrahedron* **1986**, *42*, 5931
(c) Westinger, B.; Ugi, I. in: *Chemistry of Peptides and Proteins*, Proc. of the German-Soviet Peptide Symposium 1987 Hamburg, Sept. 1987, König, W. (ed.), Attempto-Verlag, Tübingen, 1989, Vol. 4, p. 107.
(d) Ugi, I.; Gruber, B.; Stein, N.; Demharter, A. *J. Chem. Inf. Comput. Sci.* **1990**, *30*, 485.
(7) Kunz, H.; Pfrengle, W. *Tetrahedron* **1988**, *44*, 5487.
Kunz, H.; Pfrengle, W. *J. Am. Chem. Soc.* **1988**, *110*, 651.
(8) Kunz, H.; Pfrengle, W.; Sager, W. *Tetrahedron Lett.* **1989**, *30*, 4109.
(9) Fraser-Reid, B.; Wu, E.; Udong, U.E.; Ottoson, H. *J. Org. Chem.* **1990**, *55*, 6068.
Waldmann, H. *Nachr. Chem. Tech. Lab.* **1991**, *39*, 675 and references therein.
(10) Aebischer, B.M.; Hanssen, H.W.; Schweizer, W.B.; Vasella, A.T. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2139 and references therein.
(11) (a) West, E.; Holden, R. *J. Am. Chem. Soc.* **1934**, *58*, 930.
(b) Degerig, E.F.; Brinkley, W.W.; Sprang, C.A. *Proc. Indiana Acad. Sci.* **1940**, *50*, 102; *C.A.* **1941**, *35*, 58607.
(12) Brimacombe, J.S.; Jones, B.D.; Stacey, M.; Willard, J.J. *Carbohydr. Res.* **1966**, *2*, 167.
(13) Fujii, N.; Funakoshi, S.; Sasaki, T.; Yajima, H. *Chem. Pharm. Bull. (Tokyo)* **1977**, *25*, 3096.
(14) Marquarding, D.; Hoffmann, P.; Heizer, H.; Ugi, I. *J. Am Chem. Soc.* **1970**, *92*, 1969.
(15) See brochure "Chiral Plate", Machery & Nagel, Düren, Fed Rep. Germany, 1985.
(16) Brandt, J.; Jochum, C.; Ugi, I.; Jochum, P. *Tetrahedron* **1977** *33*, 1353.