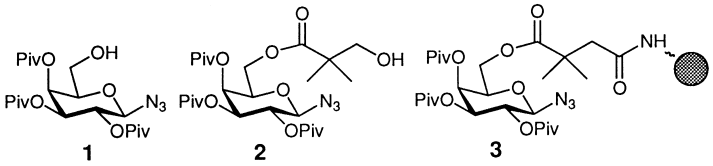
Stereoselective Combinatorial Ugi-Multicomponent Synthesis on Solid Phase**

Kai Oertel, Gernot Zech, and Horst Kunz*

Dedicated to Professor Rudolf Mengel on the occasion of his 60th birthday



The search for new drugs has been influenced decisively by combinatorial chemistry. To prevent false results in biological evaluations of combinatorial libraries, nowadays the parallel synthesis of sets of single compounds is strongly preferred. These parallel syntheses are more readily achieved even in an automated fashion, if the reactions are carried out with substrates immobilized on a solid phase.[1] As a consequence and according to the prototype of solid-phase peptide synthesis,[2] numerous reactions known from solution chemistry have been transferred to the solid phase. Although it has generally long-been agreed that the preparation of enantiomerically pure compounds is indispensable for drug development, only a few asymmetric syntheses on solid phase have been reported so far.[3]

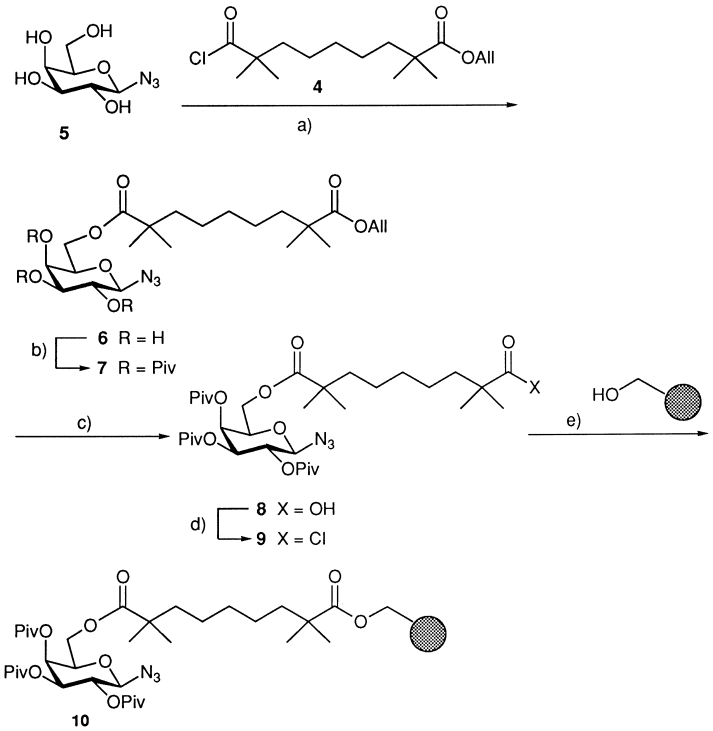
Multicomponent reactions play an important role in combinatorial chemistry. This holds true, in particular, for the Ugi four-component condensation, because this one-pot reaction offers great potential in the generation of molecular diversity.[4] Combinatorial Ugi reactions have successfully been carried out on solid phase, however, hitherto exclusively yielding racemic mixtures.[5]

We here report on the first stereoselective Ugi reactions on solid phase. To accomplish the desired stereodifferentiation, the O-pivaloylated galactosylamine[6] as an equivalent of "asymmetric ammonia" was linked to a polymeric support.

A number of problems had to be solved during this development: a) A reversible anchoring of the galactosylamine on the polymer had to be found, which would enable a direct determination of the ratios of diastereomers for the carbohydrate-linked amino acid amides. b) The galactosyl azide precursor of the galactosylamine should be immobilized first, to prevent multiple protecting group manipulations and accompanying anomerizations. The conversion of the galactosyl azide into the galactosylamine on solid phase is a prerequisite for this strategy. Heterogeneous hydrogenations[6] are unsuitable in this context. c) The anchor as well as the structure of the spacer should not interfere with the zinc chloride catalyzed Ugi reaction to be carried out on solid phase.

The coupling of the model galactosyl azides **1** and **2** (Piv = pivaloyl, *t*BuCO) through polymer-linked silyl ethers[7] failed because their hydroxy groups did not react with the corresponding silylation reagents. The polymer-linked galactosylamine **3**, synthesized from **1** by treatment with 4-allyl 2,2-dimethylsuccinate and subsequent reduction of the azide, only sluggishly reacted with the other components in the Ugi reaction. The amide structure of the spacer disturbs the activation of the *N*-galactosyl imine by $ZnCl_2$ in the Ugi reaction.

These only partly outlined difficulties could be solved by applying $\alpha,\alpha,\alpha',\alpha'$-tetramethyl azelaic acid[8] as the spacer between the galactosylamine and the polymer-linked anchor. To this end, tetramethyl azelaic acid was converted into its monoallyl ester which was then transformed to the monoacid chloride **4** by treatment with oxalic dichloride. The regioselective acylation of the galactopyranosyl azide **5** with **4** in pyridine furnished **6**, which was acylated at the secondary hydroxy groups using pivaloyl chloride in pyridine at 60 °C (Scheme 1). After palladium(0)-catalyzed removal of the allyl



Scheme 1. a) Pyridine, 60 °C, 18 h, 61 %; b) pyridine/$(CH_3)_3CCOCl$, 60 °C, 6 d, 71 %; c) cat. $[Ph_3P]_4Pd$, THF, morpholine (10 equiv), 3 d, 68 %; d) $(COCl)_2$, CH_2Cl_2; e) Wang resin, DMAP, CH_2Cl_2, pyridine, loading 0.257 mmol g^{-1}.

ester **7**,[10] the terminal carboxylic function of **8** was converted into the acid chloride **9**. For the loading, polystyrene equipped with Wang anchor[11] was treated with **9** in dichloromethane/pyridine in the presence of catalytic amounts of 4-dimethylaminopyridine (DMAP).[12] The loading of resin **10** was monitored by IR spectroscopy ($\tilde{\nu} = 2116$ cm^{-1}) and quantified by elemental analysis to 0.257 mmol g^{-1}.

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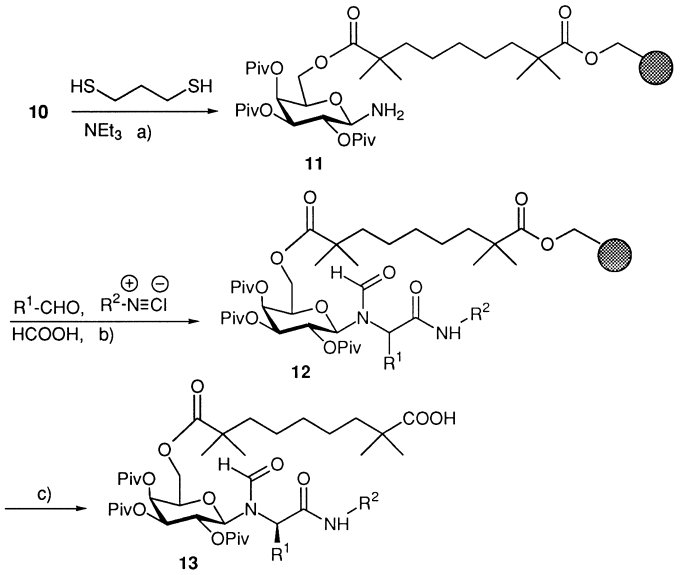
The reduction of the polymer-linked galactosyl azide **10** with complex hydrides was not successful. Under the conditions of the Staudinger reaction[13] extended anomerization occurred. However, the reaction of **10** with five equivalents each of propane-1,3-dithiol and triethylamine in dimethylformamide proved efficient for the formation of the solid-phase-linked galactosylamine **11** (Scheme 2). The reduction evidently proceeded quantitatively and without anomerization (IR spectrum, elemental analysis).



Scheme 2. a) DMF, 2 d, room temperature; b) $ZnCl_2 \cdot Et_2O$, THF, $-40\,^{\circ}C \rightarrow 0\,^{\circ}C$, 24 h; c) TFA/$CH_2Cl_2$ (1:9), anisole, 12 h, Table 1.

For performing the stereoselective Ugi reactions the immobilized galactosylamine **11** was swollen in tetrahydrofuran. At room temperature the corresponding aldehyde (5 equivalents) and after 1 h at $-40\,^{\circ}C$ the isonitrile, formic acid (5 equivalents of each) and zinc chloride etherate (1 equivalent of a 2.2 M solution in dichloromethane) were added. After 24 h at $0\,^{\circ}C$, the polymer **12** was washed with dichloromethane, tetrahydrofuran, and diethyl ether (Scheme 2).

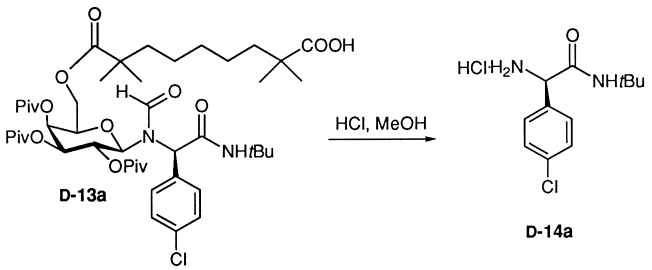
To detach the stereoselectively formed amino acid derivatives **13**, the Wang anchor of **12** was cleaved with trifluoroacetic acid (TFA)/dichloromethane (1:9) in the presence of anisole. After evaporation of the organic detachment and washing solutions followed by hydrolysis, the diastereomeric ratios of the crude products were determined directly (Table 1). The yields quoted in Table 1 refer to pure diastereomers which have been isolated after three steps (reduction of the azide, Ugi reaction, and detachment) and after separation by preparative HPLC.

Table 1. Stereoselective solid-phase Ugi synthesis of *N*-galactosyl amino acid amides according to Scheme 2.

Compound	R^1	R^2	d.r. (D:L)	Yield (D) [%]	Yield (L) [%][a]
13a	4-Cl-Ph	*t*Bu	10:1	37	4.4
13b	4-NO_2-Ph	*t*Bu	15:1	38	7
13c	4-MeO-Ph	*t*Bu	6:1	35	8
13d	Ph	*t*Bu	12:1	35	8
13e	4-Cl-Ph	cHex	9:1	37	5
13f	4-Cl-Ph	*n*Bu	14:1	20	3
13g	*i*Pr	*t*Bu	9:1	59	4

[a] Isolated product.

Using a set of five aldehydes, among which one was allowed to react with three different isonitriles, the corresponding D-amino acid amide derivatives **13** were obtained in diastereomeric ratios of 10:1 – 15:1. Of course, any other carboxylic acid instead of formic acid can be applied to these reactions if sets of single compounds or libraries at the stage of compounds **13** should be obtained. Formic acid was used in the synthesis described here, because the formyl group can be removed readily from **13** by treatment with HCl in methanol (Scheme 3). Only after removal of the formyl group, the



Scheme 3.

cleavage of the *N*-glycosidic bond and, thus, the liberation of the enantiopure amino acid derivatives is possible.[6] The data of the 4-chlorophenylglycine amide **14a** obtained by this procedure from D-**13a** (Table 1) proved identical with those of the compound synthesized previously in solution.[6] This confirms the D configuration of the major diastereomer **13a**.

As an alternative to the coupling through a cleavable anchor (**10**), the carbohydrate auxiliary was directly linked to a hydroxymethyl-substituted polystyrene (Merrifield resin, 0.6 mmol g^{-1}) by analogous reaction of the acid chloride **9** (see, Scheme 1). The resulting immobilized auxiliary **15** (loading 0.17 mmol g^{-1}) was subjected to reduction of the azide with propane-1,3-dithiol and subsequent Ugi reaction under identical conditions to those given for **10** (Scheme 4). Monitoring by IR spectroscopy revealed that the conversions proceeded more slowly because of the absence of the spacer effect exhibited by the anchor.

After swelling in dichloromethane, the polymer-linked Ugi products **16** were treated with HCl in methanol which resulted in successive cleavage of the *N*-formyl and the *N*-glycosidic bonds. The galactose auxiliary remained completely linked to the polymer **17**, which showed an intensive ester carbonyl ($\tilde{\nu} =$ 1739 cm^{-1}), but no amide band in the FT-IR spectrum. The detachment solutions dissolved in water were extracted with *n*-pentane. After evaporation of the aqueous solutions, the amino acid amide hydrochlorides **18** were isolated. The yields are lower than those given in Table 1 for the reactions of **10**, because of the slower conversions (three steps) on the non-modified Merrifield resin. However, the stereoselectivity of the Ugi reaction remains unchanged as was shown by comparison of the data of the *p*-nitrophenylglycine amide derivative with those of the *p*-nitrophenylglycine amide **18a** obtained from the *N*-galactosyl precursor **13b** (Scheme 4).[14]

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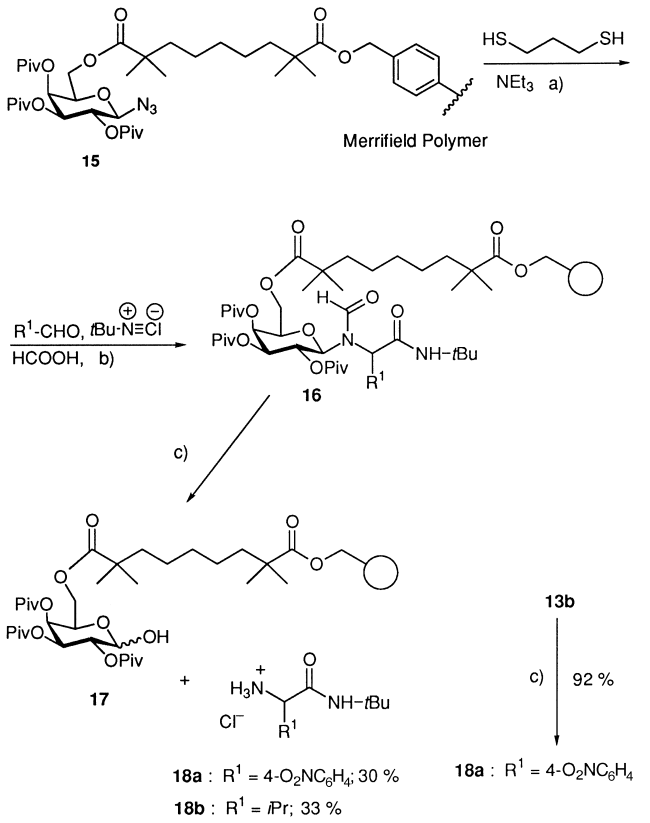

Scheme 4. a) DMF, 2 d, room temperature; b) $ZnCl_2 \cdot Et_2O$, THF, $-40\,^{\circ}C \rightarrow 0\,^{\circ}C$, 24 h; c) CH_2Cl_2/HCl (saturated) in MeOH (3:1), 12 h, then a little H_2O.

The potential of this stereodifferentiating synthesis on solid phase becomes evident, if one keeps in mind that the corresponding L-amino acid derivatives are available by analogous use of the D-arabinopyranosylamine,[15] that combinatorial reactions with phosphites give α-aminophosphonic acid derivatives,[16] those with silyl ketene acetals yield β-amino acid derivatives[17] or with silyl dienol ethers furnish mono- and bicyclic chiral nitrogen heterocycles.[18, 19] Thus, the stereodifferentiating effect of solid-phase-linked glycosylamines of type **11** provides a versatile combinatorial access to chiral products of diverse structure.

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Ring-Opening Metathesis Polymerization: Access to a New Class of Functionalized, Monolithic Stationary Phases for Liquid Chromatography

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Michael Rudolf Buchmeiser*

Monolithic separation media for liquid chromatograpy were described as early as the 1960s and 1970s.[1, 2] The introduction of compressed, continuous supports by Hjertén et al. initiated an intense research activity in this field of materials science.[3, 4] Compared to classical, packed columns, continuous stationary phases offer a series of advantages. On one hand, the time-consuming procedures of particle syn-

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