[9] Tetra-n-butylammonium fluoride/THF resulted in destruction of the butenolide, whereas HNOAc/aq. THF gave no reaction at room temperature. At higher temperatures (60 °C) desilylation was accompanied by partial hydrolysis of the acid-sensitive 2-deoxyglycoside linkages.

**Unichemo Protection: A Concept for Chemical Synthesis**
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Chemical synthesis is a powerful method for creating complex molecules with tailored biological and physical properties for drug discovery, engineering, nanotechnology, and the investigation of biological processes. However, the applicability of chemical synthesis to peptides, oligosaccharides, and other organic molecules is limited and inherently complicated using the existing functional-group protecting strategies. The differential protection of functional groups of similar reactivity in chemical synthesis is a major challenge with conventional protecting-group strategies, namely orthogonal protection and modulated lability. In particular, the development of effective protective schemes for polyfunctional molecules is not trivial. The number and type of protecting groups influences the length, efficiency, and complexity of a given synthesis, and is often responsible for its success or failure.

Herein, a new concept, termed unichemo protection (UCP), illustrated in Figure 1, is introduced. This strategy only requires a single chemical process for all deprotection reactions. The UCP protecting groups are derived from a repetitive unit that permits their controlled and efficient stepwise removal. Functional site selectivity is achieved by varying the degree of oligomerization at each site, and, after each deprotection cycle, only the newly liberated functional site is available for derivatization.

In principle, the UCP strategy does not impose a restriction on the possible number of selectively protected sites in a molecule. This method should be particularly useful in areas including the combinatorial synthesis of highly substituted scaffolds, peptide synthesis, template-assisted synthetic proteins (TASP), automated oligosaccharide synthesis, and the general goal of automated organic synthesis.

The effectiveness of the UCP chemistry was demonstrated by the controlled derivatization of a pentalysine-based amino-functionalized scaffold on the solid support. To facilitate this, a N-sec-butyrglycyl-based protecting-group unit was devised for the protection of amino groups. With conventional protection strategies, the controlled derivatization of five or more otherwise identical amino groups on the solid-support is a difficult challenge. Here, this problem was solved by using the UCP concept in the form of N-oligo(N-sec-butyrglycyl) protected lysine building blocks for the assembly of scaffold 1 (see Figure 3).

In its present form the UCP concept takes advantage of large reactivity differences between primary amino functional groups and the otherwise similar protecting groups. The use of oligomeric N-sec-butyrglycyl protecting groups exploits the relatively high degree of steric hindrance around the secondary amino terminus to differentiate between deprotection and derivatization processes. High yields of oligomeric N-sec-butyrglycyl protecting groups are readily obtained using strong activation during amide-bond formation on the solid support. Importantly, the oligomers were completely inert to less activated carboxylic derivatives, such as readily prepared para-nitrophenyl (ONp) and succinimide (OSu) esters (Figure 2). The inert character of the UCP secondary amine protecting groups under acylation conditions thus allows for the chemoselective derivatization of newly liberated primary amino group with nitrophenyl esters. That is, chemical selectivity against the secondary amino terminus of the protecting groups is employed to distinguish between derivatization and removal steps.

For deprotection cycles, efficient stepwise removal of terminal protecting group units is facilitated by a reliable two-step procedure originally developed by Edman for protein sequencing. In the first step, phenylisothiocyanate (PITC) reacts quantitatively at pH 8 with the terminal unit of the oligomeric protecting group (Figure 2). In the second step, a quantitative cyclization and elimination reaction occurs at

![Image](http://www.angewandte.com)
acidic pH, to give the shortened protecting group by the expulsion of a phenylthiohydantoin derivative.

Accordingly, following assembly of scaffold 1 each of the five primary amino groups on the scaffold was successively liberated with PITC/TFA (TFA = trifluoroacetic acid) deprotection cycles (Figure 3).[15] Each newly exposed amino group was then acylated with a given carboxylic acid derivative. After five deprotection–derivatization cycles, cleavage from the solid support afforded 2, in good purity and yield.[16] Molecular dynamics simulations indicate that low-energy conformers of N-sec-butyrglycyl protecting-group oligomers are generally flexible, extended, and hydrophobic, which agrees well with experimental observations in terms of accessibility and solubility in organic solvents.

The advantage of UCP is its conceptual and practical simplicity. In contrast, orthogonal protection requires the identification, availability, and interplay of a range of sufficiently different orthogonal protecting groups and a multitude of unique chemical conditions for the removal of each individual protecting group in a selective and efficient manner.[17] This may create a problem particularly in the case of polyfunctional molecules because the cleavage of one protecting group strictly requires not only the stability of all the other protecting groups, but also of the masked molecule itself under a multitude of reaction conditions.[18–20] At the core of the problem is the limited availability of fully orthogonal protecting groups that work well together.

UCP effectively facilitates an orthogonal process that is not dependent on a range of finely tuned and differently compatible processes. Moreover, since UCP is based on uniform deprotection reactions, the requirement of reaction compatibility with other parts of a molecule only increases linearly with the degree of polyfunctionalization (Figure 4 and 5). That is, after the initial requirement of parent-molecule stability is satisfied, only the sequential requirements towards each newly introduced group is an issue. In contrast, a quadratic increase in complexity with respect to the number of protected functional groups, even in the simplest cases, accompanies existing orthogonal protection strategies.

In the implementation of the strategy described here, a highly efficient PITC/TFA cycloelimination process, which enabled the differential protection of five otherwise identical amino groups, was employed. Differential derivatization of five or more amino groups in a single molecule would be an extraordinary challenge for conventional protection strategies. With UCP chemistry, the number of a given functional group that can be successfully protected and sequentially assessed may exceed twenty. The UCP concept should be amenable to the protection of many other types of functional groups, such as hydroxyls, thiols, and carboxylates. A host of different UCP units may be devised from other sequential cleavage processes. However, several issues need to be considered for their development, these include: 1) the
ease and cost of assembling the protecting group; 2) the practicality, and particularly, the efficiency of the step-wise degradation method; 3) the inertness of the protecting group towards the expected synthesis conditions and reagents for a given application. In this regard, a three-step UCP process in which the UCP protection group is fully protected during derivatization would be advantageous.

UCP complements existing orthogonal protection strategies, and both approaches together will enable the synthesis of more elaborate and novel molecular structures. The experiments reported here show that it is possible to synthesize and derivatize polyfunctional molecules in a simple and effective fashion, without the need for complicated protection chemistry. One outcome of the simplification of both design and chemical requirements is the relative ease of using combinatorial techniques and automating the entire synthesis.

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[3] a) An orthogonal system is defined as a set of completely independent classes of protecting groups.[31] In a system of this kind, each class of group can be removed in any order, and in the presence of all other classes and functional groups. Modulated lability strategies rely on the precise graduation of chemical conditions, such as acidity, for selectivity. b) G. Barany, R. B. Merrifield, J. Am. Chem. Soc. 1977, 99, 7363 – 7365.


[8] Although elegant and widely applicable, the N-sec-butylglycyl-based protecting group reported here should be considered as a preliminary system to demonstrate the UCP concept. Forthcoming innovations and refinements of UCP protecting group units should produce more robust, practical, and applicable protection chemistry.


[10] See supporting information for experimental details for the construction of the UCP protected pentylsine scaffold.


[16] See supporting information for experimental details for the product.

[17] This demand for selective deprotection conditions is counteracted by the intrinsic lack of diverse and yet compatible reaction conditions for the clean and efficient removal of one protecting group over another. In general, the conditions available are protonation, deprotonation, electrophilic and nucleophilic reactions, reductions, oxidations, rearrangements, photolysis, and other cleavage reactions.

