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From Synthetic Methods to γ-Peptides – From Chemistry to Biology

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Abstract: The research activities of our group are demonstrated by examples in the following fields: (i) TADDOL auxiliary system (combinatorial synthesis, a chiral hydroperoxide, immobilization on controlled-pore glass silica gel); (ii) a geminally diphenyl-substituted 4-isopropyl-1,3-oxazolidinone as a superior Evans-type auxiliary (for enantioselective enolate alkylation, aldol addition, Michael addition, and Diels-Alder reactions); (iii) enantioselective reactivity umpolung (with a lithiated methylthiomethyl derivative of an oxazolidinone), and (iv) chemical and biological investigations of γ-peptides (folding to helices and turns, stability against peptidases). The impact of biology on the projects of a synthetic organic group is discussed.

Keywords: Chiral formyl-anion equivalent · β-Peptides · γ-Peptides · Polyhydroxyalkanoates · TADDOL

Introduction

When our group moved from Giessen to Zürich almost 25 years ago it was totally devoted to synthetic methodology [1] and its applications to natural product synthesis [2]. At ETH there was a shift of interest towards mechanistic and structural investigations of synthetic reagents [3], and towards biological chemistry [4]. Since we have extensively reviewed in recent years the results in the fields of the TADDOL auxiliary system [5–7], chiral dendrimers [8], the biopolymer PHB [4][6][9], and the chemistry and biology of β-peptides [6][9][10], we will exemplify our research on the following pages by presenting a new chiral oxazolidinone auxiliary, the stoichiometric use and immobilization on silica of TADDOL derivatives, and the γ-peptides.

Some may argue that shift of interest from synthetic methodology to biology is a sign of old age of the senior author. Others may interpret this shift as the move from what might have become a matter of (synthetic) engineering to the front of natural sciences.

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Synthetic Methods – The TADDOL System – Reactions, Materials, and Catalysis

In a recent review article we used the term *chiral auxiliary system* [7] for TADDOL and its derivatives, see the glorifying presentation in Fig. 1; among the chiral auxiliaries, defined in the broadest possible sense, these compounds can be prepared in a combinatorial fashion by variation of the substituents on the acetal/ketal center, of the aryl groups and of the heteroatoms on the diarylmethylene carbon. Modifications of the parent TADDOL (with methyl groups on the dioxolane ring and four simple phenyl groups in the exocyclic positions) are shown in Fig. 2. The range of heteroatoms goes from nitrogen through oxygen, fluorine, phosphorous, sulfur, all the way to chlorine and bromine; the range of pK_a values of the HX-derivatives spans from above 34 (NH_2) to below 6 ($NHSO_2CF_3$); and the organometallic complexes (mostly chelates) include a wide variety of metal centers, such as Li, Na, Mg, B, Al, Si, Sn, Ti, Zr, Cr, Mo, Rh, Ir, Pd, Cu, Zn, and Ce. TADDOLs can also be used as chiral NMR shift reagents, as chiral dopants for liquid crystals, and as chiral hosts in inclusion compounds. Finally, the ready access to and the easy recovery of TADDOLs allows their use as stoichiometric additives or reagents. Thus, we have recently prepared a hydroperoxide, TADOOH, which can be used for enantioselective and enantiomer-differentiating oxidations, with better results than any other previously tested chiral hydroperoxide [11][12] (Scheme 1).

Despite the fact that TADDOLs (having high melting points, a pronounced tendency to crystallize, low volatility, good solubility in non-polar solvents, large R_f values on silica chromatography) are easily separated from reaction products, it was desirable to have immobilized derivatives for multiple applications. These were first prepared by cross-linking suspension polymerization of styrene with styryl-substituted (also dendritic) TADDOLs [5-7][8][13][14]. Beads with dendritically incorporated TADDOLs [14] turned out to have constant swelling and to give reproducible rates and enantioselectivities in titanate-mediated transformations, over dozens of cycles. Still, we also explored the inorganic support silica gel which has the obvious advantage of not being dependant upon swelling, of being chemically inert, and amenable to high-pressure and low or high temperature in its applications. We used the controlled-pore glass (CPG, by the Grace Co.), with a surface of up to 320 $m^2\ g^{-1}$,

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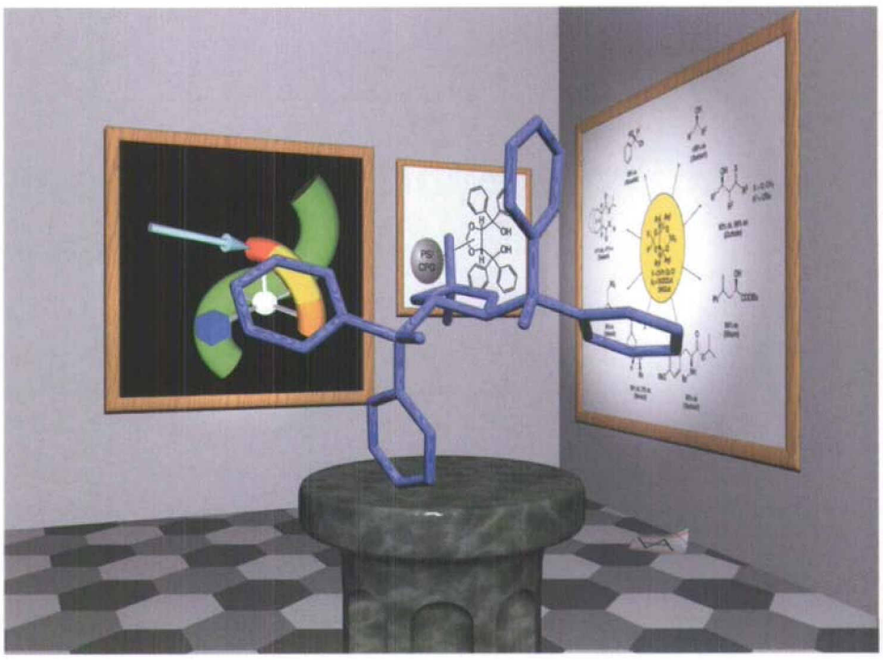


Fig. 1. 'Pictures at a TADDOL-Exhibition' (*cf.* the name of Mussorgsky's piano cycle). A model of the original TADDOL, the α, α, α', α'-tetraphenyl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanol, is shown on a pedestal, in front of an artistic presentation of the general stereochemical course of reactions involving Ti-TADDOLates and chelating electrophiles (chiral Lewis acid catalysis) (left), a *formula* of TADDOL immobilized on silica (controlled-pore glass, CPG) (center), and a flow sheet demonstrating the broad applicability of X_2Ti-TADDOLates in directing nucleophilic additions enantioselectively (right). For details, see the review articles [7].

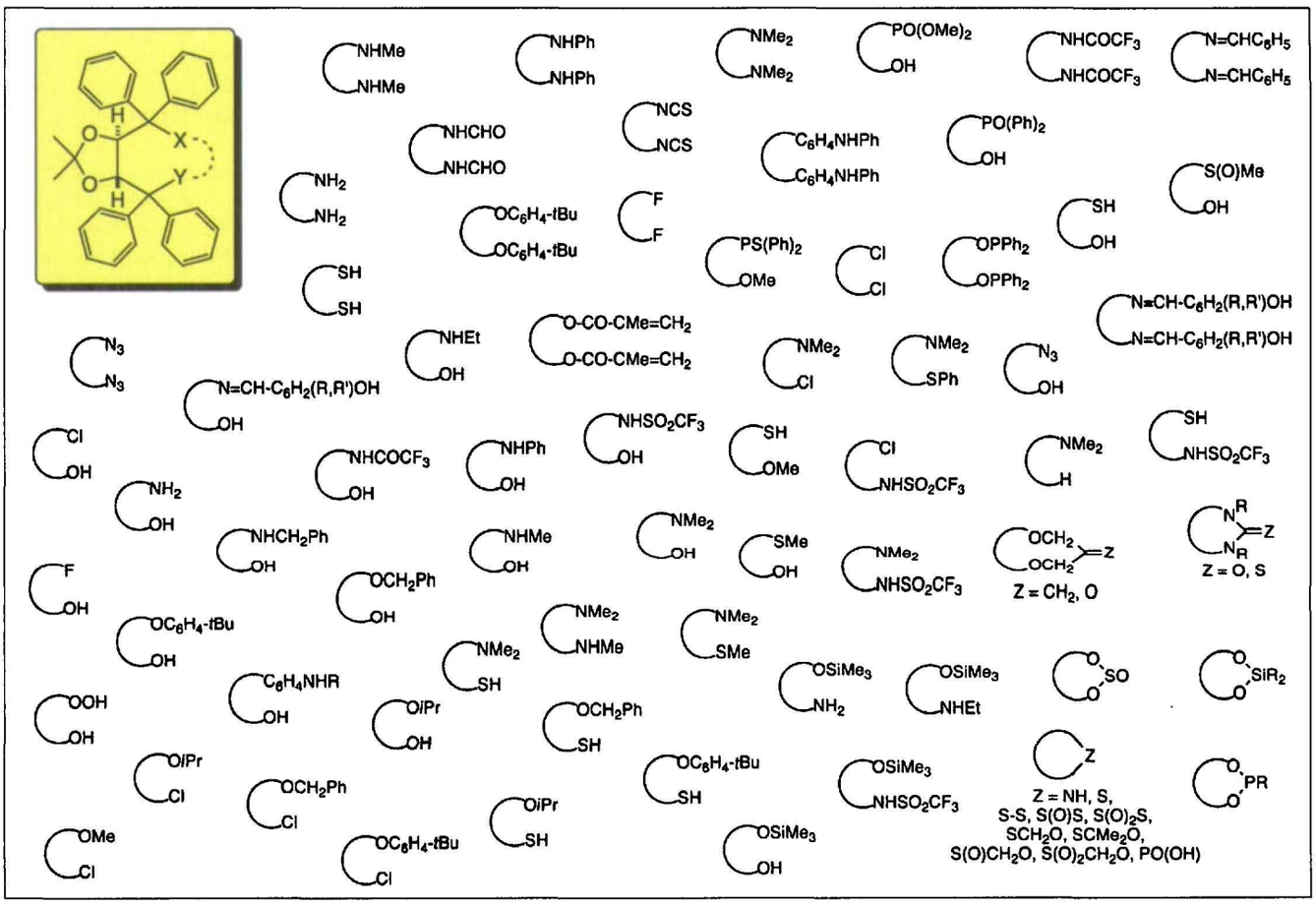
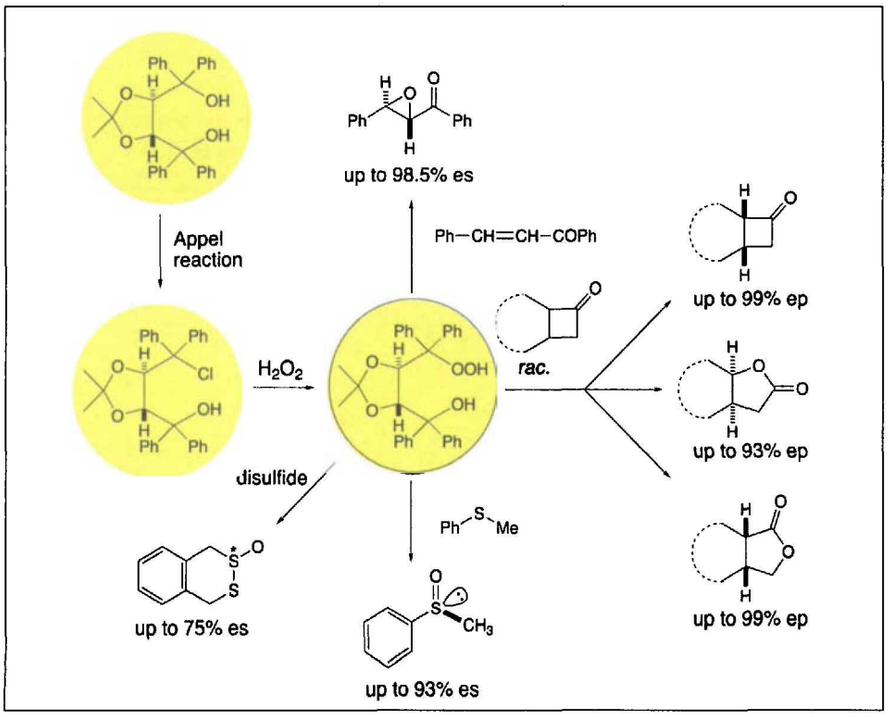


Fig. 2. Patchwork presentation of TADDOL derivatives obtained by derivatization or replacement of one or both TADDOL OH-groups. The oxygen(s) may be derivatized with the formation of alkyl, aryl or silyl ethers, phosphonites, sulfites or phosphoric acid esters or replaced by other heteroatoms or functionalities, such as N, P, OOH, S, F, Cl, Br, with and without formation of five-, six-, and seven-membered rings. Almost half of the compounds, schematic *formulae* of which are shown here, have first been prepared by one graduate student (A. Pichota) at ETH Zürich; for references, see Fig. 2 in [7a]. The pK_a values of the derivatives shown here range from >30 (NH_2/NH_2) through *ca.* 17 (OH/OR), >11 (OH/OH), 11 (OH/$NHCOCF_3$), 9 (SH/OH), all the way down to 5.7 (SH/$NHSO_2CF_3$). The various heteroatoms can be exploited for specific binding to particular metal centers, and thus for enantioselective organometallic catalysis [4–7].



Scheme 1. Example for the stoichiometric use of a TADDOL derivative for enantioselective transformations: oxidations by the hydroperoxide TADOOH (M. Aoki) [11]. Oxygen atoms may be transferred enantioselectively to enones (→ epoxides), cyclic ketones (→ lactones), thioethers (→ sulfoxides), and disulfides (→ thiosulfinates), also with kinetic resolution. The enantioselectivities, with which products are formed, and the enantiopurities, with which unreacted enantiomers are recovered in kinetic resolutions may be up to 99%. TADOOH is readily available from TADDOL in two steps, which involve an Appel reaction (CCl_4/PPh_3) and treatment of the resulting monochloride with the H_2O_2·urea complex. The oxidation of the cyclic disulfide was carried out by S. Bräutigam (ETH Zürich, 2001).

grafted TADDOL on it (loading up to 0.4 mmol g^{-1}) and hydrophobized ('capped') the unreacted OH groups by trimethylsilylation [15]. In a more flexible approach, an appropriately functionalized tartrate ester acetal was grafted on CPG, and subsequently the diarylmethanol moieties of the desired immobilized TADDOL were generated by addition of excess aryl Grignard reagents (Scheme 2) [16]. The performance of the materials, thus obtained, in enantioselective, titanate-mediated organometallic reactions (R_2Zn + R'CHO) and [3 + 2] cycloadditions was excellent, giving the same selectivities as in solution. The CPG particles could even be washed (more than once!) with HCl/H_2O/acetone, without loss of their high performance in subsequent applications: both the grafted TADDOL units, and the Me_3SiO groups are stable and survive the acidic removal of impurities or side products (such as oxide and salt deposits).

A Valine-Derived Diphenyloxazolidinone Auxiliary – A Most Successful Excursion into the Past

For many years, we had not worked on the systematic development of new or improved reagents. The investigation of TADDOLs made us realize that *geminal* diaryl groups provide a number of special effects when incorporated in a molecule: they enhance the rates of cyclization (*cf.* the Thorpe-Ingold effect), and thus also the stability of the cyclic products formed; in chiral molecules the two *geminal* aryl groups are diastereotopic and may cause a pronounced preference for one of two regioisomeric or diastereomeric reaction trajectories; the aryl groups can exert a buttressing effect on the formation of otherwise conformationally flexible groups; they can sterically block access to reactive centers and thus provide functional group selectivity (sometimes referred to as 'chemoselectivity'); last but not least, introduction of *geminal* aryl groups into a molecule leads to compounds of greatly enhanced crystallization tendency (*cf.* easy purification of products and ready recovery of an auxiliary!). These assets of diphenyl- or diarylmethylene groups have led to their widespread use (Fig. 19 in reference [7a]) in enantioselective synthesis, and an example from our own laboratory is described in the following section.

To demonstrate the usefulness of a diphenylmethylene group, we chose four years ago [17][18] the probably most frequently used chiral auxiliaries, the amino acid or ephedrine-derived Evans oxazolidinones [19]. Our modified version is the diphenyl-substituted, valine-derived oxazolidinone shown in Scheme 3. It is now sold by a Japanese company as (*S*)-DIOZ [20] (5,5-diphenyl-4-isopropyl-1,3-oxazolidin-2-one). The compound had been mentioned before in a patent [21a], and it was published simultaneously with [21b], and somewhat after [21c, d] our report [18] by three other groups. In one of these papers [21d] DIOZ and analogous derivatives of other amino acids were hydrogenolytically cleaved to chiral primary amines carrying a diphenylmethylene group [21e]. The real beauty of this compound, however, was not recognized until we employed it as chiral auxiliary in the standard transformations first elaborated with the classical oxazolidinones by Evans and his associates: enolate alkylations, aldol additions, Michael additions, Diels-Alder reactions *et cetera*. The superiority of the diphenyl-substituted oxazolidinone is evident from the features outlined in Scheme 3, and specific examples for its use are collected in Fig. 3 [16–18][22]. Similar selectivities as with the *tert*-leucine-derived auxiliary are obtained, almost all products are crystalline, their purification requires no chromatography, and the auxiliary is cleaved without H_2O_2 – great advantages for large-scale applications!

Along a totally different line of work, leading even further back to past activities of our group (umpolung with sulfur derivatives, including dithianes), we have recently studied the lithiated 3-methylthiomethyl oxazolidinone (Scheme 3, right hand side). It adds diastereoselectively to aldehydes, ketones, imines, and enones, providing the types of products shown in Scheme 4, after cleavage (with recovery) of the auxiliary [23][24]. Thus, the lithiated compound is a reagent equivalent to chiral nucleophilic hydroxyalkyl, formyl, and methoxycarbonyl synthons. Again, the protection of the oxazolidinone C=O group by the *geminal* phenyl rings allows direct metalation with BuLi, and the conformational fixation of the isopropyl group (*plus* a stereoelectronic effect, $\sigma_{C\text{-}Li} \rightarrow \sigma^*_{S\text{-}C}$) secures diastereotopic bias in the nucleophilic addition reactions. Almost two dozen X-ray crystal structures

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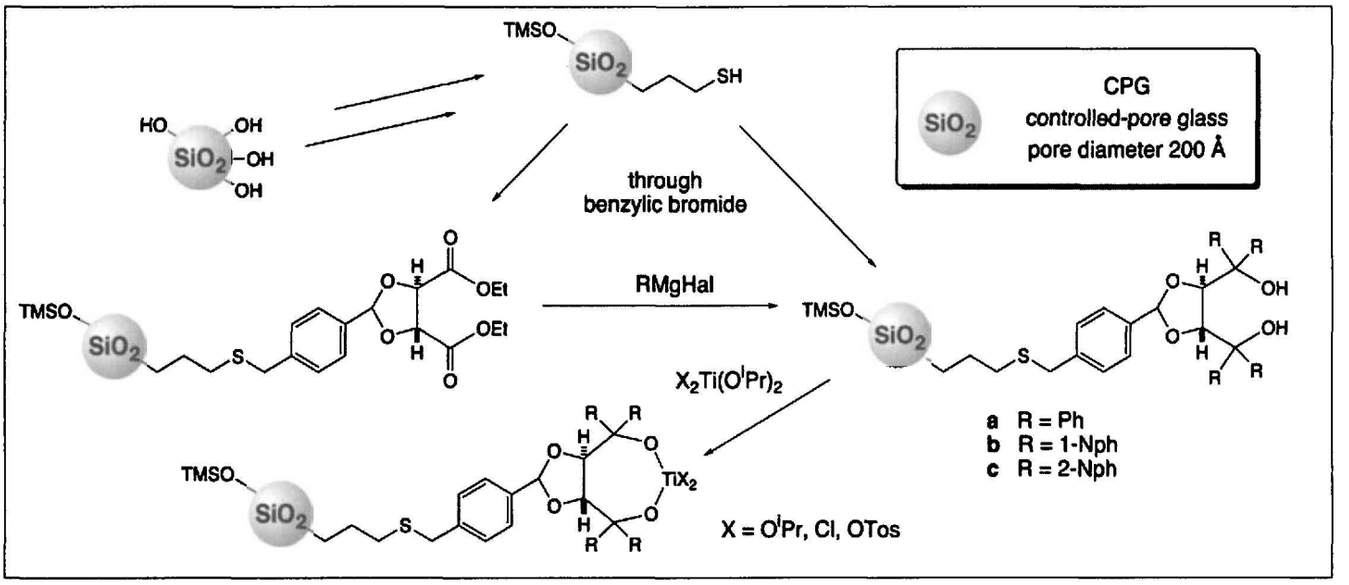
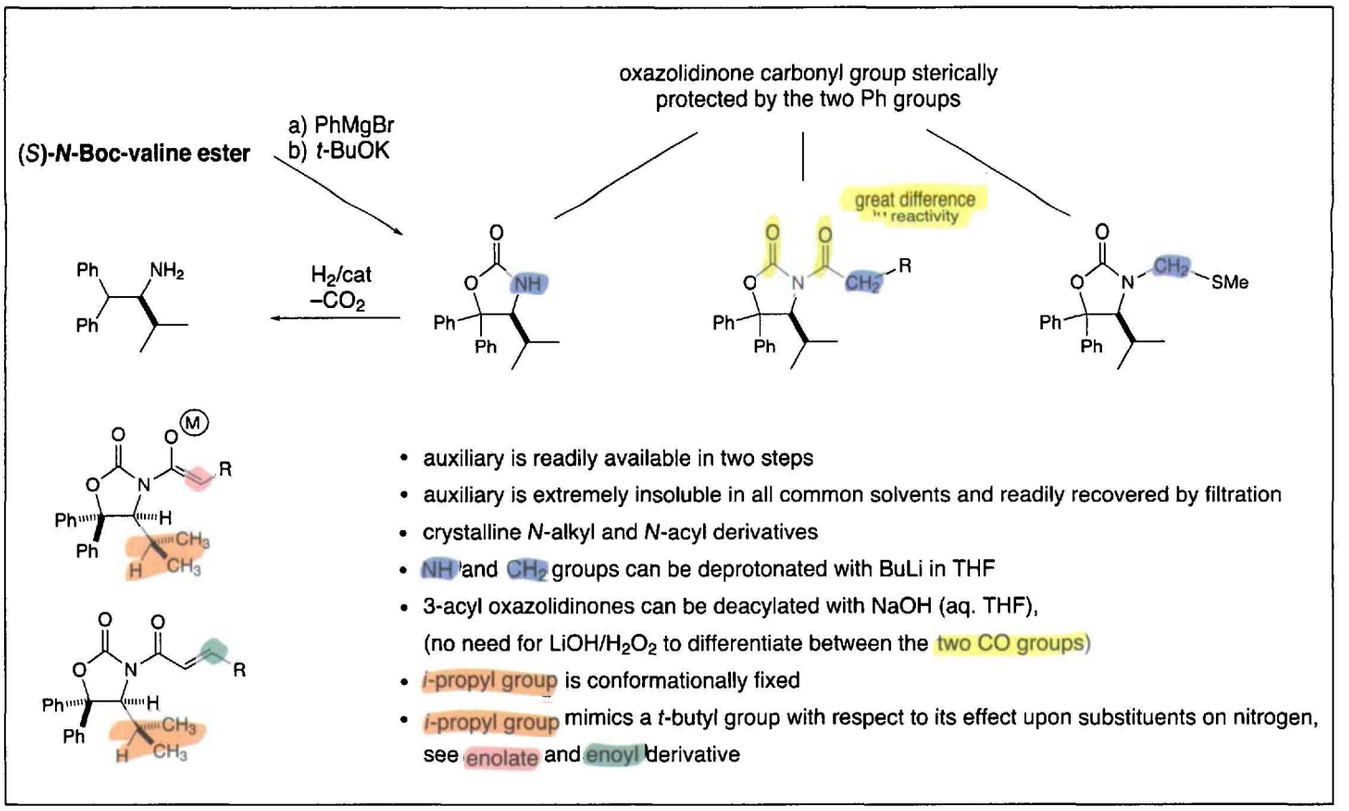


Scheme 2. TADDOLs immobilized on CPG, a highly porous silica gel [15][16]. The silica (surface *ca.* 320 $m^2\ g^{-1}$) is mercaptopropylated (with $(MeO)_3Si(CH_2)_3S$-R), free OH-groups are capped (N-trimethylsilyl-imidazole), and a tartrate ester acetal or a TADDOL with bromobenzyl substitution is used to form a thioether linkage. The diester acetal can be converted to a TADDOL moiety by reaction with an aryl-Grignard reagent on the solid support. The immobilized chiral Lewis acids obtained by titanation of the TADDOL unit have useful properties: unlike the situation with polystyrene-bound reagents and catalysts their performance does not depend on swelling properties of a polymer; CPG-immobilized ligands and complexes may be used at high pressure, at high and low temperatures, and the material may be washed with aqueous acid for removal of inorganic deposits (without loss of activity or performance!).



Scheme 3. A superior Evans oxazolidinone auxiliary, the 4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one, prepared in two steps from *N*-Boc-valine ester and a phenyl-Grignard reagent. The major advantages over previously used chiral oxazolidinones of this type are (i) better functional-group selectivity between the CO groups of 3-acyl-derivatives, (ii) higher crystallization tendency of all derivatives and of the auxiliary heterocycle (no chromatography, easy recovery of the auxiliary), (iii) steric effects of the isopropyl group similar to those of a *t*-Bu group by the buttressing effect of the phenyl groups. Disadvantages are (i) the higher molecular weight of the auxiliary and (ii) the labile Ph_2C-O bond, under conditions of catalytic hydrogenation.

of products [16] formed in the addition reaction of the new lithium reagent to electrophiles, as well as sophisticated NMR, IR and computational investigations on the lithium compound [24] provide information about its structure and about the stereochemical course of its reactions. Again, the crystallinity of the products is an inherent advantage of this diphenyloxazolidinone-based nucleophilic *umpolung* reagent (for other chiral formyl-anion reagents we have to refer to the literature [25]).

Homologation of Peptides – From Chemistry to Biology

For almost 20 years our group has been involved in investigations of the biopolymer PHB (polyhydroxybutyrate) [4b], (i) because this microbial storage material was a source of (*R*)-3-hydroxybutanoic acid, a welcome chiral building block for organic synthesis; (ii) because this polymer is fully biodegradable, and the copolymer with the analogous valerate (PHB/PHV) can be used as plastic material; (iii) because we discovered, together with R. Reusch, that a short-chain variety of *ca.* 150 HB residues is ubiquitous in all living cells and organisms, forming, for instance, ion channels through cell walls [26]; (iv) and finally because we were intrigued by the fact that this simple biopolymer does not have

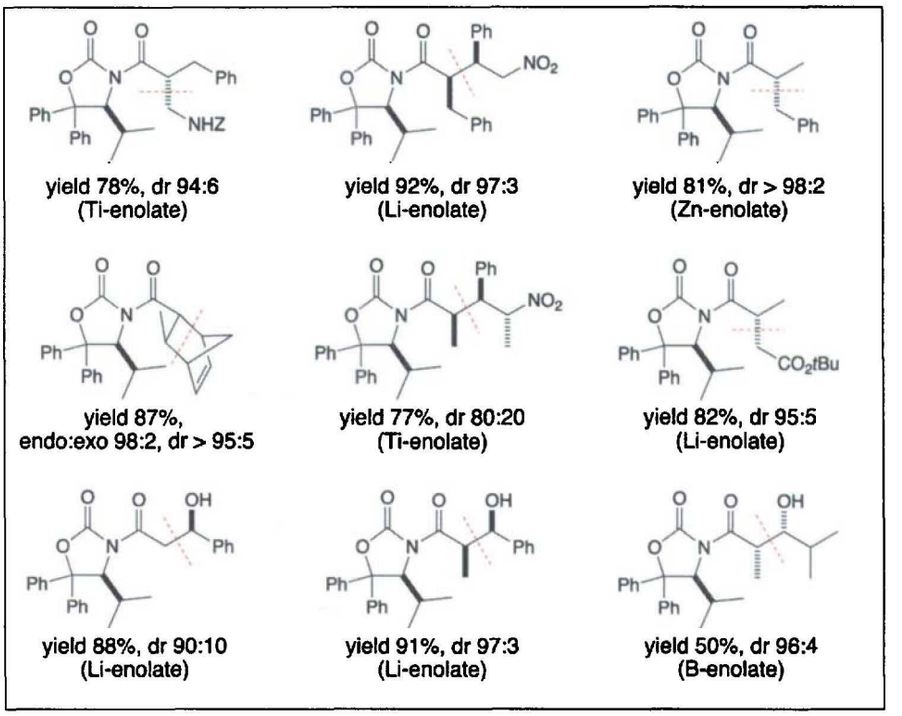
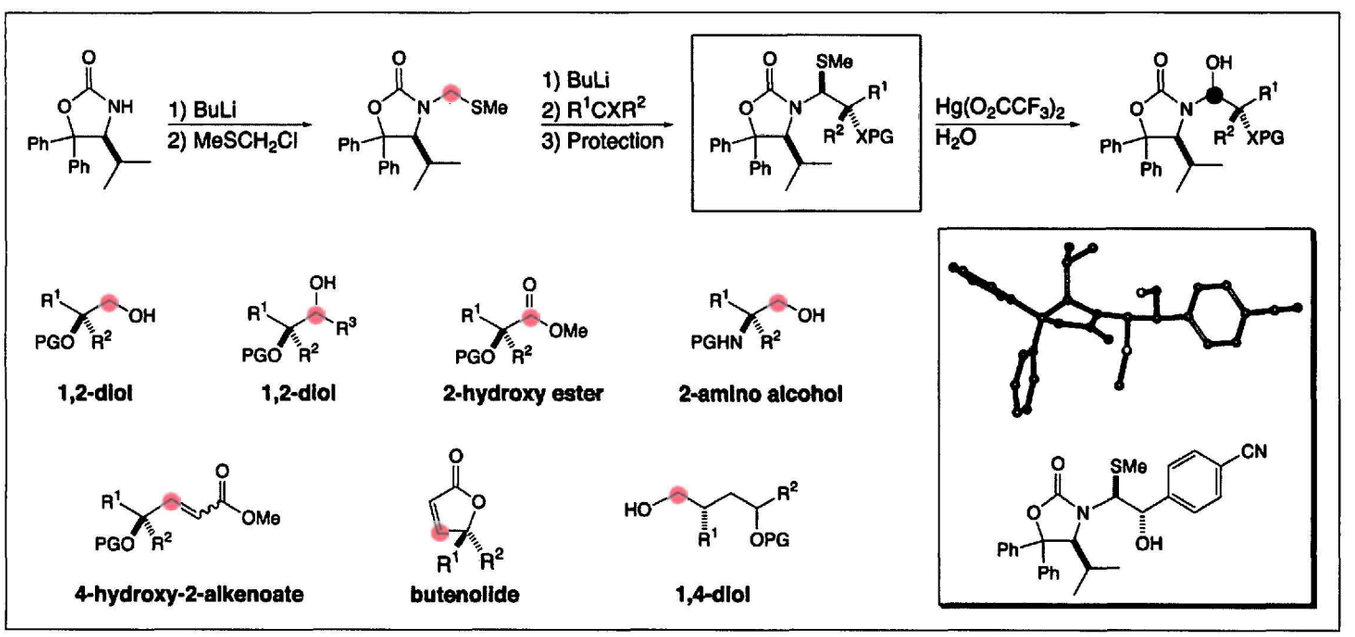


Fig. 3. Products of C,C-bond-forming reactions of the *N*-acyl-4-isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one with electrophiles and with a nucleophile (cyclopentadiene). Yields and diastereoisomer ratios obtained with Li, B, Zn, and Ti enolates of the corresponding acyl-oxazolidinones are given. All products are crystalline [17][18][22]. The products of aminomethylation (Mannich reaction) and of carbalkoxymethylation are useful precursors to β^2-amino acids and to β^2- or β^3-amino acids (Curtius degradation!), respectively. The products of Michael addition to nitroolefins are converted to γ-lactams and γ-amino acids. Thus, the new auxiliary is a welcome tool in our work on β- and γ-amino acids (*cf.* Fig. 4 and 5). The product shown in the center of this figure contains four stereocenters (three newly formed ones); only two diastereoisomers are isolated, which are epimeric at the NO_2-substituted center (the configurational assignment was made at the stage of the corresponding lactam).



Scheme 4. Lithiated 4-isopropyl-3-methylthiomethyl-5,5-diphenyl-1,3-oxazolidin-2-one – a chiral nucleophilic hydroxyalkylating, formylating, or carbalkoxylating reagent [23][24]. The marked carbon atoms in the structures are derived from the CH_2 group of the methylthiomethyl-oxazolidinone. Additions to C=O, C=N, and C=C bonds occur diastereoselectively, the products are crystalline, the chiral auxiliary is readily recovered (*cf.* Scheme 3 and Fig. 3). The crystal structure of the adduct of the lithiated methylthiomethyl-oxazolidinone to 4-cyanobenzaldehyde is shown in the right-hand corner, demonstrating the buttressing effect of the phenyl groups.

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a defined secondary structure: its backbone is extremely flexible, and numerous NMR measurements and modeling studies have produced no evidence for a preferred conformation (secondary structure) of the polyester chain in solution [27] – how could it have a biological function?; all other biopolymers (proteins, nucleic acids, polysaccharides) have well-defined complex structures, which determine their functions.

In stretched fibers and in lamellar crystallites PHB has been found to be folded to a 2_1 helix, and crystals of cyclic oligohydroxybutyrates (oligolides) contain 3_1-helical substructures. It occurred to us that these may be stabilized by exchanging the chain-bound oxygens by NH, *i.e.* by going from oligomers of 3-hydroxy carboxylic acids to oligomers of 3-amino carboxylic acids (β-peptides, see Fig. 4) [10]. Indeed, such β-peptides, consisting of the homologated proteogenic α-amino acids, form helices and hair-pin turns with as few as six residues in pyridine, methanol, and water. These secondary structures can be produced by design and are 'generated' by molecular dynamics calculations. Almost all of their properties differ drastically from those of the parent α-peptides.

Since 1996 we have published 60 papers on these fascinating new peptide analogs; research moved more and more into biology: Are β-peptides interacting with α-peptides and proteins? Are β-peptides cleaved by peptidases? Are they biodegradable in natural environments? Are there β-proteins with tertiary structures and catalytic activities? How do β-peptides interact with the mammalian immune system? Is there a specific binding with RNA and DNA? Will there be β-peptidic drugs? Why did nature use α-, rather than β-amino acids for the construction of proteins?

All these questions have been or are being addressed [4c][9][10][28][29], and investigations of the doubly homologated α-amino acids, the γ-amino acids, and their oligomers, the γ-peptides have ensued [16][22][30–33]. There is, of course, much more structural and synthetic variety with γ-amino acids; three stereogenic centers may be present; additional heteroatoms (including NH_2, OH, SH, halogen) can sit on two backbone carbons; a myriad of synthetic methods is available for constructing enantiopure γ-amino acids (*cf.* γ-lactones or pyrrolidinones). On the other hand, predictions about the conformation of γ-peptidic backbones are easier to make, based on first principles of classical conformational analysis in organic

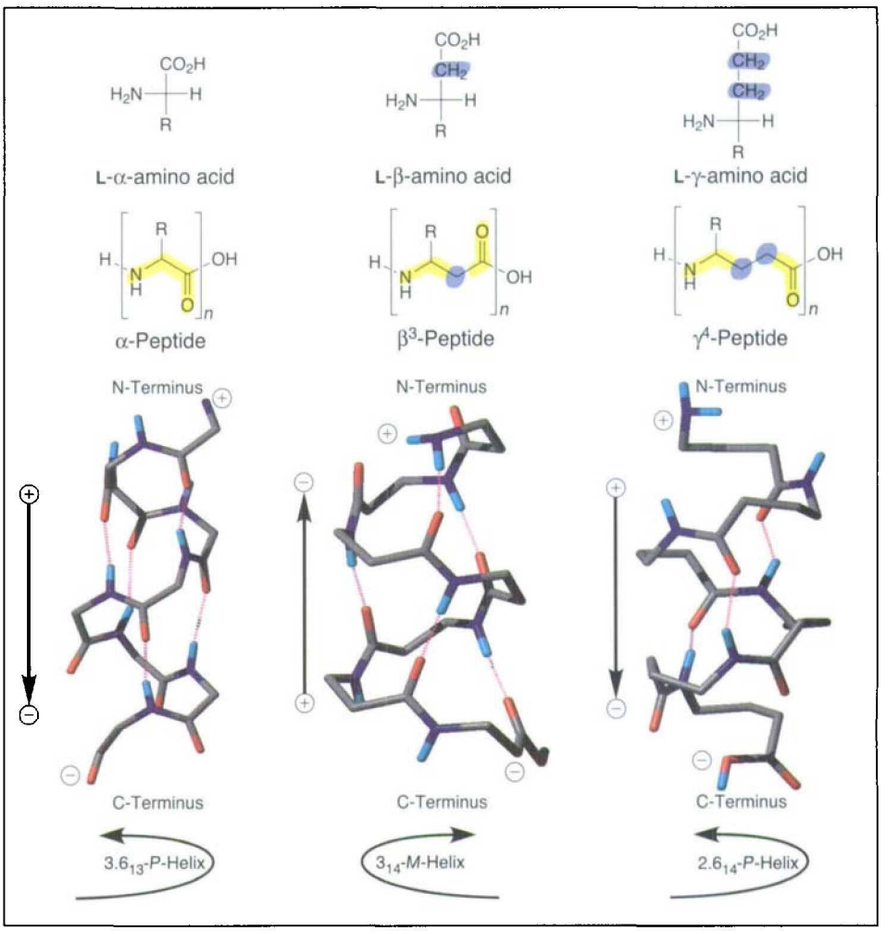

Fig. 4. From α- to β- to γ-amino acids and –peptides – homologation of the oligomers of α-amino acids. Contrary to the predictions of those knowledgeable in the field of the natural, proteogenic peptides and proteins, the tendency to form secondary structures, such as helices, pleated sheets, or turns increases upon homologation (insertion of CH_2 groups in the backbone of *all* amino acid residues of the oligomers). It is beautiful to see that the handedness (right, left, right), the polarity (N→C, C→N, N→C) and the stability (increasing from the 3.6_{13}-α- to the 3_{14}-β- to the 2.6_{14}-γ-helix) of the helices change upon homologation of the residues (with retention of the configuration!).

chemistry: there are *two* ethane bonds in a γ-amino acid (one in a β- and *none* in an α-amino acid!); a γ-peptidic oligomer chain with its substituents can be modeled into a diamond lattice ('the poor man's computer', according to Vlado Prelog), with maximum avoidance of 'diaxial' interactions ($A^{1,3}$-strain or 1,5-repulsion, or Newman strain [34]), to find the preferred conformation [35]. Thus, it may not be surprising that a stable helix conformation is found in methanol solution of a γ^4-tetrapeptide while it takes six residues to observe (by NMR spectroscopy) such a helix of a β^3-peptide under the same conditions, and many more in the case of an α-peptide (Fig. 4). Also, a turn superimposable with an α-peptidic, so-called βII' turn, can be observed in solution with a simple acetyl-γ-dipeptide-amide [33] while four [28] or more [36] β-amino acid moieties are required to mimic a classical peptide turn (see α-peptidic hair-pins [37]) (Fig. 5). It is likely that we will soon have simple, turn-mimicking γ-peptides for probing suitable receptors, such as the somatostatin-binding proteins sst 1-5. A recent thorough investigation of 15 different proteases, peptidases, amidases, and β-lactamases with β-and γ-peptides of broad structural variety has revealed that the γ-peptides (like their lower homologs, the β-peptides) are absolutely stable, *i.e.* no cleavage occurs in 48 h [29], see Fig. 6. Thus, whatever physiological and biological activity they may have, γ-peptides will do their work without being threatened by peptidases!

Conclusion and Outlook

Studying PHB and the homologs of peptides has led us deep into biology, away from chemistry. After the group has

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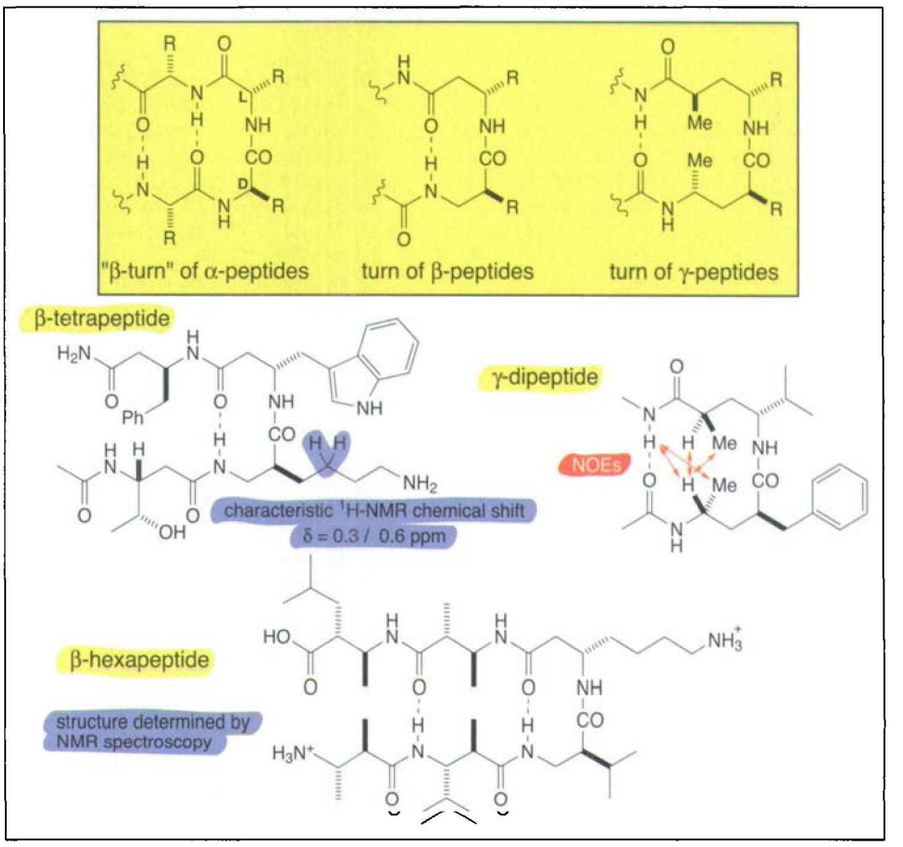

Fig. 5. Turn or hair-pin structures of α-, β-, and γ-peptides. The degree of rational design increases and the minimum number of residues decreases as we go along the homologous series of amino acid building blocks. On the other hand, the geometry of the turn section –CHR–NH–CO–CHR'– is identical in the three turn structures, so that the unnatural β- and γ-peptides mimic the natural α-peptide. Since the turn motif is often decisive for peptide-protein (*cf.* hormone-receptor) interaction and binding affinity, there is a possibility of developing low-molecular-weight inhibitors or activators as drugs, consisting entirely of the proteolytically stable (*cf.* Fig. 6) β- or γ-peptides.

spent 30 years on synthesis, the core of organic chemistry [38], the excitement has moved from inventing new reactions and transformations, from understanding mechanistic details, from structure determination, and from total synthesis to supramolecular structures (secondary/tertiary structures), microbial storage materials, non-proteinaceous ion channels, peptide homologs and mimics, biodegradation, peptide-hormone to protein-receptor affinity, transport systems in the brush-border membrane (Caco-2 cells), antibiotic, antiproliferic, hemolytic, and cytotoxic activities, and so forth. Synthetic methods have become a hobby, maybe a nostalgic pastime in our group.

The senior author has experienced it as a shock to realize what had happened when a collaborator reported a low yield in one of the steps leading to a β-peptide: there was no sitting down and discussing what the reason for the poor yield might be, and how the situation could possibly be improved; rather the comment was: 'Get going and prepare a few milligrams of the desired compound in HPLC-pure form, so that we can proceed and determine the folding and the biological activity of the compound!' Times have changed; synthesis as the core of chemistry may not be at the frontier of natural sciences any more. However, chemistry as such remains – by definition – the central science of all matter, living or not living!

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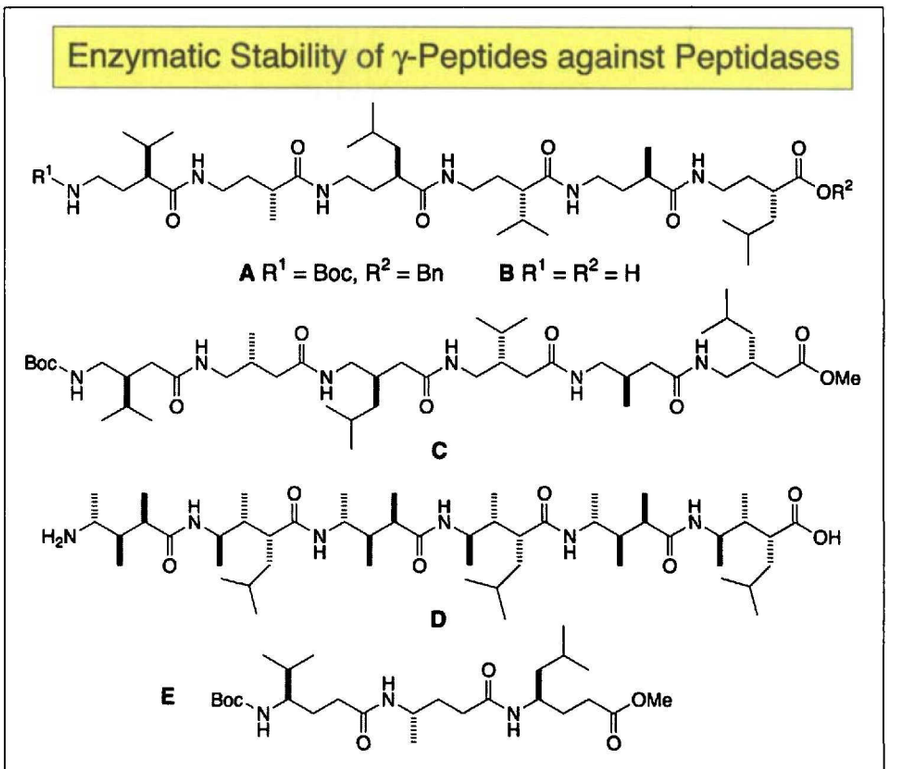

Enzymes used for degradation studies with γ-peptides **A-D**: pronase, proteinase K, penicillin amidase, β-lactamase; in addition, the γ-peptide **A** was also tested with: pepsin, chymotrypsin, elastase, trypsin, carboxypeptidase A, leucyl aminopeptidase, proteinase, peptidase, pronase E, amidase.

Fig. 6. Stability of γ-peptides against peptide-cleaving enzymes. Like all types of β-peptides, the γ-peptides shown are absolutely stable for 48 h towards cleavage by peptidases [29]. The enzymes used for the tests are endo- or exo-peptidases and belong to the classes of serine and threonine proteases, aspartic peptidases, metallopeptidases, or β-lactamases. Note that the γ-peptides used in this series of tests include γ^{2}-, γ^{3}-, γ^{4}-, and $\gamma^{2,3,4}$-peptides consisting of three or six residues.

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