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Sugars, Alkaloids, and Heteroaromatics: Exploring Heterocyclic Chemistry with Alkoxyallenes†

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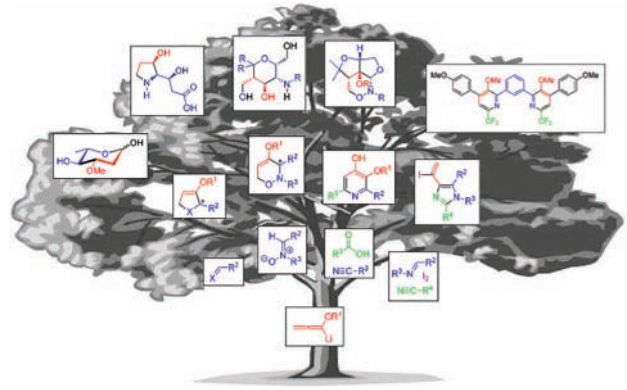
CONSPECTUS



As master craftsmen, modern synthetic chemists are challenged to achieve remarkable feats of efficiency and elegance toward molecular targets. The nature of this pursuit necessitates the collection of synthetic repertoires that are tried and true. With methodologies and pathways increasingly scrutinized, the adept chemist must seek out propitious tools to incorporate into the arsenal. With this in mind, this Account highlights the versatility of alkoxyallenes as precursors to valuable heterocyclic building blocks for such efforts as natural product synthesis.

Accessed by the etherification of either propargyl alcohols or propargylic halides, alkoxyallenes are obtained after base-catalyzed isomerizations of the propargylic ethers. A host of umpolung synthons are available through this scheme after metalation, generating C_3 nucleophiles synthetically equivalent to vital anionic and zwitterionic synthons. Reactions with a diverse set of heteroatomic electrophiles yield carbohydrates, spiroketals, alkaloids, and heteroaromatics via [3 + 2] or [3 + 3] cyclizations. By employing lithiated alkoxyallenes into transformation routes, the natural product chemist can utilize this methodology as a viable resource in stereoselective synthesis.

A survey of our own utilization of alkoxyallenes along synthetic pathways toward natural product targets reveals their suitability for generating advantageous precursors. A set of four stereoisomeric 2,6-dideoxyhexoses were stereoselectively obtained after an initial lithiated alkoxyallene and lactaldehyde cyclization, followed by the oxidative ring opening of the dihydrofurans. Through the addition of a lithiated alkoxyallene to a functionalized benzaldehyde, an essential spiroketal diastereomer was rapidly achieved in a few steps. We greatly benefitted from alkoxyallenes in the construction of complex nitrogen-containing synthetic targets, whether pyrrolidine alkaloids, substituted imidazole derivatives, or functionalized pyridines. A pinnacle example of their utility came from the coupling of alkoxyallenes to nitrones affording 1,2-oxazines, which served as a gateway to an array of novel polyfunctionalized compounds such as aminopolyols, hydroxylated pyrrolidines, or carbohydrate mimetics.

Alkoxyallenes have proven themselves to be powerful C_3 building blocks toward complex molecular targets, revealing novel pathways to a variety of desirable highly functionalized heterocycles. In our view, the full extent of their synthetic utility has yet to be truly realized.

Introduction

Allenes have fascinated generations of chemists and we have witnessed extensive research activity devoted to this compound class, including numerous applications in natural product synthesis.[1] Among the different classes of allenes, alkoxy-substituted allenes constitute a distinct and synthetically particularly useful genus. Alkoxyal-

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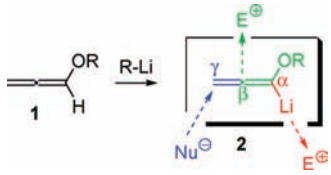
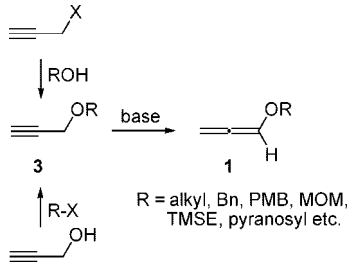
lenes **1** are characterized by a unique triple reactivity pattern (Scheme 1): Whereas the γ-carbon is susceptible to nucleophilic attack (i), the central carbon (β-position) displays typical enol ether reactivity (ii). Most importantly, the α-hydrogen is easily abstracted by bases such as alkyllithiums[2] generating highly reactive C_3-nucleophiles **2** (iii), which undergo substitutions at C-1 leading to a multitude of synthetically versatile intermediates with an alkoxyallenyl moiety.

SCHEME 1. Reactivity Pattern of Lithiated Alkoxyallenes **2**



A variety of alkoxyallenes **1** are accessible by base-catalyzed rearrangement of the corresponding propargylic ethers **3** (Scheme 2),[3] which are easily prepared either from propargylic alcohols or halides by Williamson ether syntheses.[4]

SCHEME 2. Generation of Alkoxyallenes **1**[a]



[a] TMSE = $CH_2CH_2SiMe_3$; PMB = 4-methoxybenzyl.

In continuation of Arens' pioneering work,[5] lithiated alkoxyallenes have been recognized as versatile synthetic equivalents for important synthons, some of which are displayed in Figure 1; they represent acyl anion synthons such as **a** or **d**, zwitterionic synthons like **b** and **c**, or homoenolate synthon **e**. All synthons involve an umpolung of regular reactivity.[6]

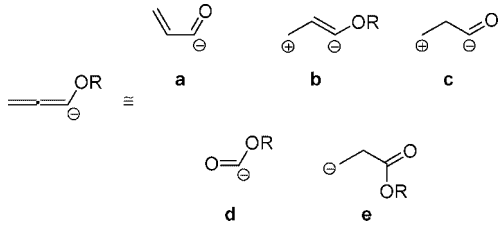


FIGURE 1. Synthons **a**–**e** derived from metalated alkoxyallenes.

More remarkable, syntheses of carbocycles and heterocycles with allene precursors have recently seen a refit by transition metal catalysis.[1a,7] Palladium- and gold-mediated transformations have been extended to alkoxyallene methodology[8] and new developments can be expected in this field.

While comprehensive overviews on the chemistry of alkoxyallenes have appeared in the past,[9] this Account primarily focuses on their recent applications to the synthesis of heterocyclic compounds, including natural products. Consequently, the manuscript is organized around the distinct compound classes. It reflects our research toward the synthesis of carbohydrates, spiroketals, alkaloids, and heteroaromatics. Each section begins with an introduction to methodology essentials, followed by a discussion of key transformations of the primary allenyl intermediates and rationalization of the observed reactivity and selectivity.

Synthesis of Deoxysugars

Deoxysugars, that is 2,6-dideoxysugars, are essential constituents of a large number of biologically active natural glycosides.[10] The limited availability of these "rare" materials from microbial sources renders their *de novo* synthesis a topic of continuous interest.[11] As part of a total synthesis of heliquinomycin, we conceived an allene-based synthesis of the 2,6-dideoxy-3-*O*-methyl hexose L-cymarose (**4**) and its stereoisomers **5**–**7** (Figure 2).

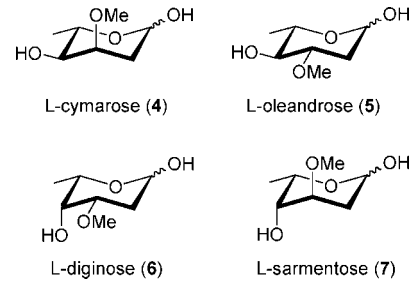
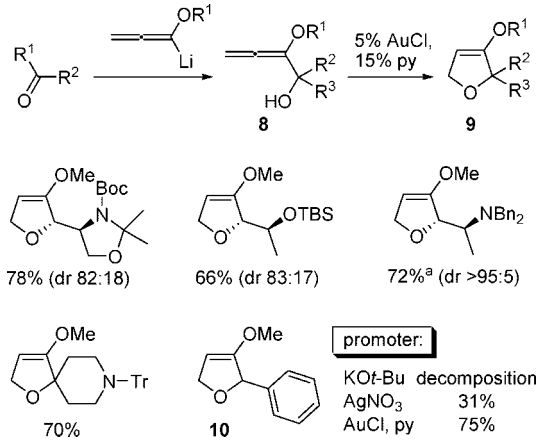


FIGURE 2. Rare sugars: four 2,6-dideoxy-3-*O*-methyl hexoses.

Two synthetic methods emerged as keys for a generalized approach to **4** and related sugars: (i) the two-step preparation of 3-alkoxy-2,5-dihydrofurans from alkoxyallenes and carbonyl compounds and (ii) an oxidative aromatization–cleavage reaction leading to α,β-unsaturated keto aldehydes.

The addition of lithiated alkoxyallenes to aldehydes and ketones quantitatively furnishes alcohols **8**. With α-chiral carbonyl compounds, the addition proceeds via the Felkin–Anh mode, and good to excellent levels of diastereocontrol are observed (Scheme 3).[8e,12] Products **8** are sensitive to purification and therefore employed in subsequent reactions as crude materials, one option being the 5-*endo-trig* cyclization to 2,5-dihydrofurans **9**. The choice of promoter is crucial for this transformation. While Arens' strongly basic conditions (KO*t*-Bu in DMSO)[13] and electrophilic activation with silver(I) sources[14] give satisfactory results in simple cases, catalytic amounts of gold(I) chloride and pyridine emerged as the most general and reliable reagent system (see compound **10** as example, Scheme 3).[8e,15]

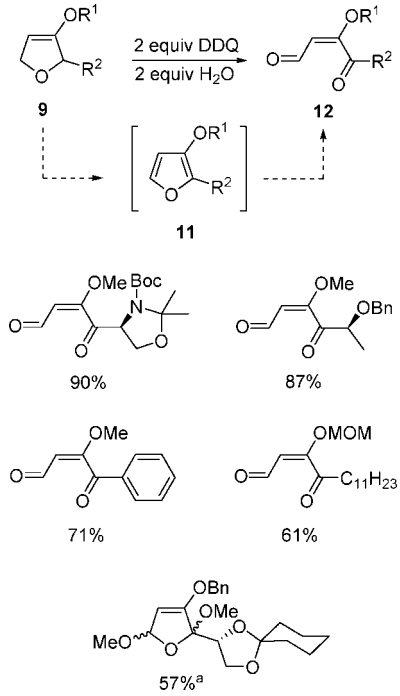
SCHEME 3. Two-Step Protocol for Preparation of 3-Alkoxy-2,5-dihydrofurans **9**



[a] Superscript "a" indicates cyclization with KO*t*-Bu/DMSO. py = pyridine.

The 3-alkoxy-substituted dihydrofurans can be utilized in oxidative transformations. Upon treatment with DDQ and water or alcohols, they undergo a rapid oxidative cleavage to α,β-unsaturated γ-keto aldehydes **12** (Scheme 4). This protocol involves *in situ* aromatization to the short-lived furan intermediate **11**, which is further oxidized to 1,4-dicarbonyl compound **12**.[16] The reaction is fairly general, and the second step is similar to the Achmatowicz reaction (oxidation of α-furyl alcohols to 4-enuloses), a well-known method in carbohydrate chemistry.[17]

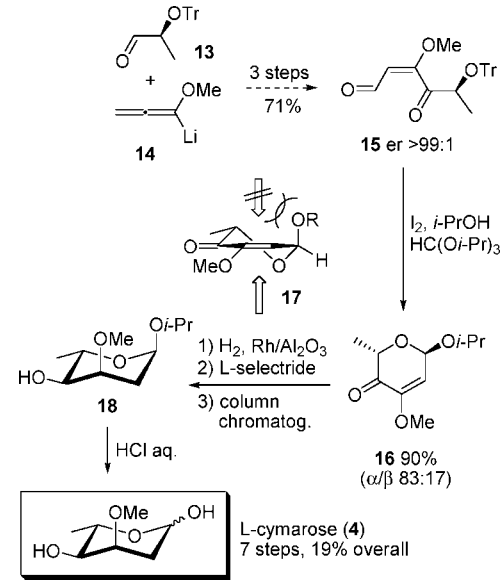
SCHEME 4. Oxidative Cleavage of Dihydrofurans **9** to Conjugated γ-Keto Aldehydes **12**



[a] Superscript "a" indicates MeOH used instead of H_2O.

Utilizing this strategy, L-cymarose (**4**) was synthesized in only seven steps (Scheme 5).[18] Lactaldehyde derivative **13** and lithiated methoxyallene **14** were converted into enantiopure γ-keto aldehyde **15**, which, after deprotection and acetalization, furnished α-configured pyranoside **16**. Face-selective hydrogenation of this material (presumably via half-chair conformation **17**), followed by diastereoselective reduction of the carbonyl group gave *ribo*-configured pyranoside **18**, the immediate precursor to sugar **4**.

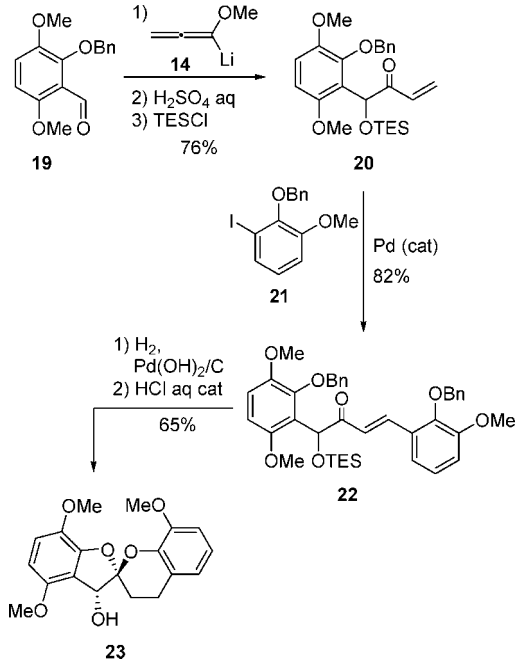
SCHEME 5. Efficient *de Novo* Synthesis of L-Cymarose (**4**)



Access to Benzannulated Spiroketals

For the synthesis of DNA helicase inhibitor heliquinomycin,[19] a flexible method for the construction of the central spiroketal motif was essential. In model studies, we examined an approach relying on the addition of lithiated methoxyallene **14** to functionalized aldehydes such as **19** (Scheme 6). After hydrolysis of the enol ether moiety of the primary addition product and hydroxyl protection, a Heck reaction of enone **20** with aryl iodide **21** provided substituted enone **22**. Finally, hydrogenolysis of **22** and acid-promoted acetalization generated bisbenzannulated spiroketal **23** in good yield and as a single diastereoisomer.[20] In this sequence, lithiated methoxyallene **14** served as equivalent of the unsaturated acyl anion synthon **a** (Figure 1),[21] and compounds like **23** could potentially be prepared enantiopure using auxiliary-substituted allenic precursors (see below).[22]

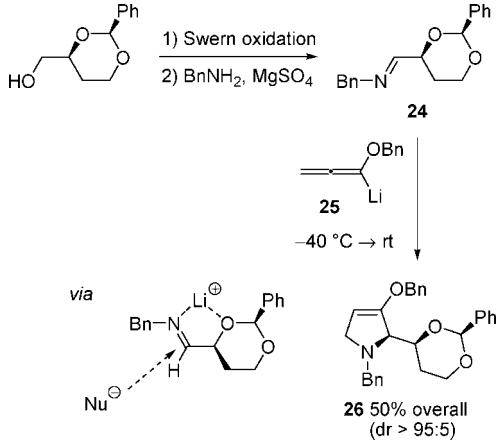
SCHEME 6. Synthesis of Spiroketal **23** as Heliquinomycin Model Compound



A Quest for Pyrrolidine Alkaloids

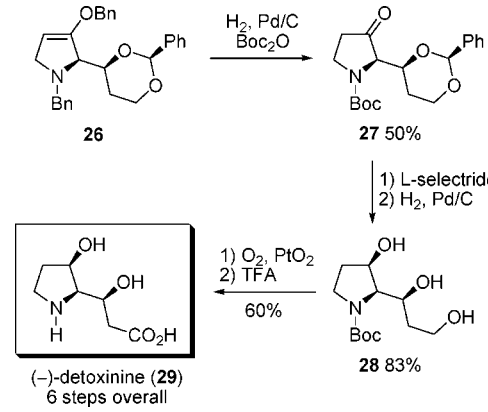
1,2-Additions of lithiated alkoxyallenes to imines (or imine precursors) lead to α-allenyl amines, which readily undergo cyclizations to functionalized 2,5-dihydropyrrole derivatives.[23] This methodology was broadly investigated in our group and consequently exploited in the synthesis of diverse bioactive pyrrolidine alkaloids. As shown in Scheme 7, excellent diastereoselectivities may result when employing α-chiral imines such as **24** in the addition step. Electron-donating protecting groups at nitrogen favor a chelation-controlled reaction (in contrast to α-chiral aldehydes) and spontaneous 5-*endo-trig* ring closure occurs upon warming the reaction mixture to room temperature.[24]

SCHEME 7. Preparation of Diastereomerically Pure Dihydropyrrole **26**



Dihydropyrrole **26** was converted into polyhydroxylated γ-amino acid (−)-detoxinine (**29**) within five steps (Scheme 8). Catalytic hydrogenation under well-balanced conditions in the presence of Boc-anhydride furnished *N*-carbamoyl-protected pyrrolidinone **27**. Diastereoselective reduction of the keto group and reductive acetal cleavage gave triol **28**. Oxidation of the primary hydroxyl group and deprotection with acid completed the concise and highly stereoselective sequence toward target compound **29**.[24]

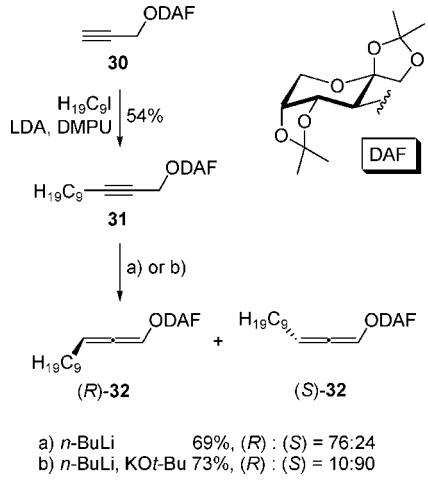
SCHEME 8. Route to (−)-Detoxinine (**29**)



Where prochiral imines are employed, induction of chirality can be achieved with auxiliary-substituted alkoxyallenes, a concept introduced and explored by Goré for aldehydes as electrophiles.[22] Monosubstituted chiral alkoxyallenes are accessible by *O*-alkylation of carbohydrate derivatives and other chiral alcohols employing propargylic halides followed by isomerization.[25] We also developed a new protocol for the stereodivergent preparation of diastereomerically pure 1,3-disubstituted allenes such as D-fructose-derived allene **32** (Scheme 9). Alkylation at the C-terminus of propargyl ether **30** furnished alkyne **31**, which was isomerized to allene **32** either with *n*-butyllithium or under "superbasic" conditions,[26] selectively yielding either (*R*)-**32** or (*S*)-**32**, with fair to good stereocontrol.[27]

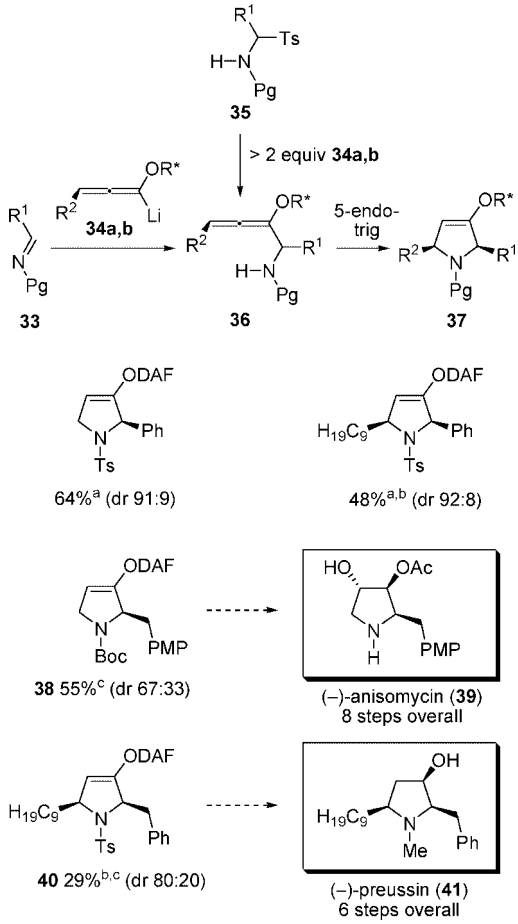
Reactions of lithiated D-fructose-derived allenes **34**(**34a**, R^2 = H; **34b**, $R^2 = C_9H_{19}$, used in excess) with imines **33** or imine precursors **35** proceed with moderate to high facial selectivity (Scheme 10). Cyclization of the *N*-Boc or *N*-Tosyl protected α-allenyl amines **36** can be induced using either KO*t*-Bu or silver(I) salts.[23,28]Dihydropyrroles **38** and **40** were key intermediates in total syntheses of antibiotics (−)-anisomycin (**39**) and (−)-preussin (**41**), two targets that were accessed via this methodology in only eight and six steps.[27b,29] Applying a similar strategy, the pentasubstituted pyrrolidine alkaloid codonopsinine has been prepared as racemate.[30]

SCHEME 9. Stereodivergent Preparation of D-Fructose-Derived 1,3-Disubstituted Allene **32**[a]



[a] Conditions: (a) 3.0 equiv of *n*-BuLi, THF, −85 °C, then H_2O; (b) 1.2 equiv of *n*-BuLi, −30 °C, then 1.2 equiv of KO*t*-Bu, −85 °C, then H_2O. DAF = diacetone-D-fructose.

SCHEME 10. Auxiliary-Assisted Synthesis of Enantiopure 2,5-Dihydropyrroles



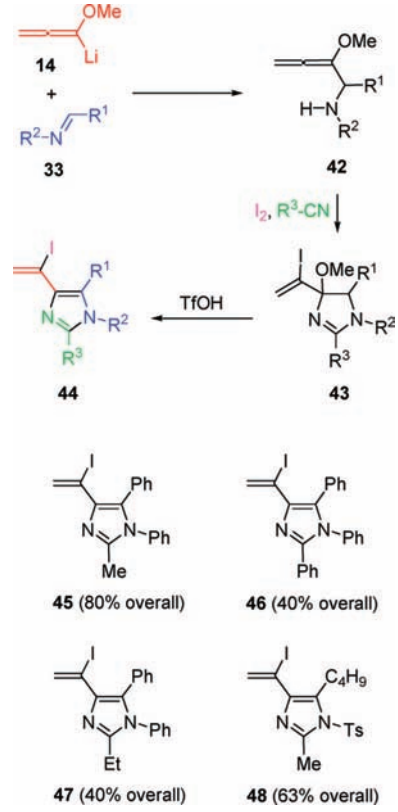
[a] Superscript "a" indicates cyclization with KO-*t*Bu. Superscript "b" indicates that yields refer to main isomers after two steps and separation. Superscript "c" indicates cyclization with $AgNO_3$. PMP = 4-methoxyphenyl.

Novel Multicomponent Syntheses of Heteroaromatic Compounds

Heteroaromatic compounds such as imidazoles and pyridines play an important role in synthetic and medicinal chemistry but have also found applications in material-oriented research.[31] Hence, the development of new synthetic methods aimed at rapid and flexible construction of these classes of heterocycles are of high interest, and multicomponent reactions have proven particularly useful in this context.[32] By mere serendipity, we discovered two novel and powerful protocols for the synthesis of functionalized imidazole and pyridine derivatives, alkoxyallenes and nitriles being the key precursors in both reaction sequences.

During our cyclization studies toward five-membered heterocycles (see above), we investigated the ring closure of α-allenyl amines **42** with various electrophiles. Contrary to the cyclization applying transition metals (Ag^I, Au^I, Pd^{II}), treatment of α-allenyl amines **42** with iodine in acetonitrile did not lead to the expected dihydropyrroles but furnished iodovinyl-substituted dihydroimidazoles **43** (Scheme 11).[33] Subsequent elimination of methanol by treatment of **43** with trifluoromethane sulfonic acid afforded imidazoles **44**. The key step in this sequence is similar to the Ritter reaction: After α-iodi-

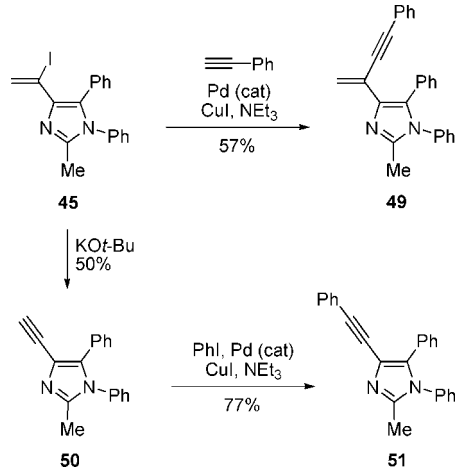
SCHEME 11. Four-Component Synthesis (Alkoxyallene + Imine + Iodine + Nitrile) of Highly Substituted Imidazole Derivatives **44**



nation of the enol ether moiety of **42**, nucleophilic attack of the nitrile onto the allyl cation occurs, followed by ring closure of the resulting nitrilium species to dihydroimidazoles **43**. This new four-component reaction (alkoxyallene + imine + iodine + nitrile) proved to be generally applicable, and by change of either the imine or the nitrile component, a whole series of 4-iodovinyl-substituted imidazoles **45**–**48** was prepared.

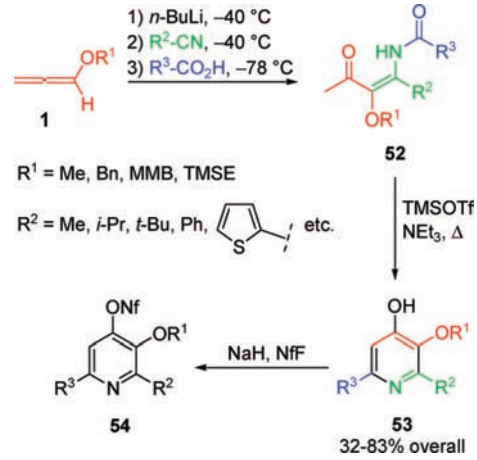
The primarily obtained imidazole products can be further functionalized by means of exploiting their iodovinyl group in palladium-catalyzed C–C couplings (Scheme 12).[34] Sonogashira reaction of compound **45** with phenyl acetylene led to enyne **49**, or after dehydroiodination of **45**, coupling of alkyne **50** with iodobenzene furnished compound **51**.

SCHEME 12. Palladium-Catalyzed Reactions of Imidazole **45**



Direct combination of lithiated alkoxyallenes with nitriles led to the discovery of a second multicomponent protocol with carboxylic acids being the third reaction partner to deliver functionalized pyridines.[35] The initial observation toward this remarkable process was the formation of enamides **52**, which are produced upon addition of lithiated alkoxyallenes to nitriles followed by reaction with a carboxylic acid (Scheme 13). The proposed mechanism for formation of these enamides is unique though straightforward.[35] Treatment of enamides **52** with trimethylsilyl triflate and base causes intramolecular aldol condensations (involving amides!) and affords 4-hydroxypyridine derivatives **53**. The hydroxyl group can be exploited for subsequent palladium-catalyzed derivatization, for example, after conversion into nonaflates **54**. A broad range of highly substituted pyridinols **53** and nonaflates **54** could be prepared efficiently by this novel three-component reaction (alkoxyallenes + nitriles + carboxylic acids).[36]

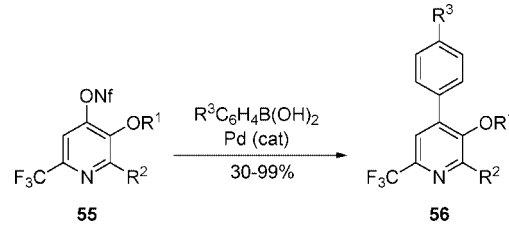
SCHEME 13. Three-Component Synthesis (Alkoxyallenes + Nitriles + Carboxylic Acids) of 4-Hydroxypyridine Derivatives **53**[a]

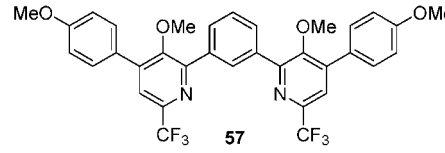


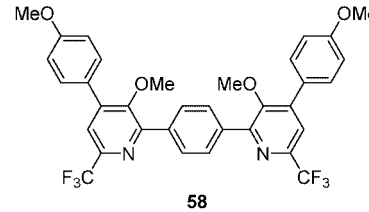
[a] MMB = 3-methoxybenzyl; Nf = $SO_2C_4F_9$.

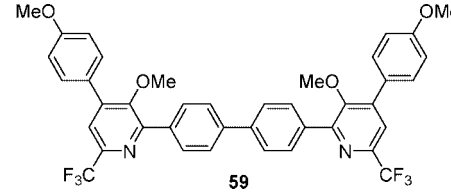
Nonaflates **54** served as playground for further diversity-oriented synthesis. Suzuki reactions of compounds such as **55** gave aryl-substituted pyridine derivatives **56** in yields of 30–99%.[35,36] We also introduced aromatic dinitriles as precursors in the three-component pyridine synthesis and the subsequently prepared bisnonaflates were subjected to similar couplings with *p*-methoxyphenyl boronic acid. Poly(het)ar-

SCHEME 14. Suzuki Reactions of Pyridines **55** Leading to **56** and Structures of Poly(het)aryls **57**–**59**





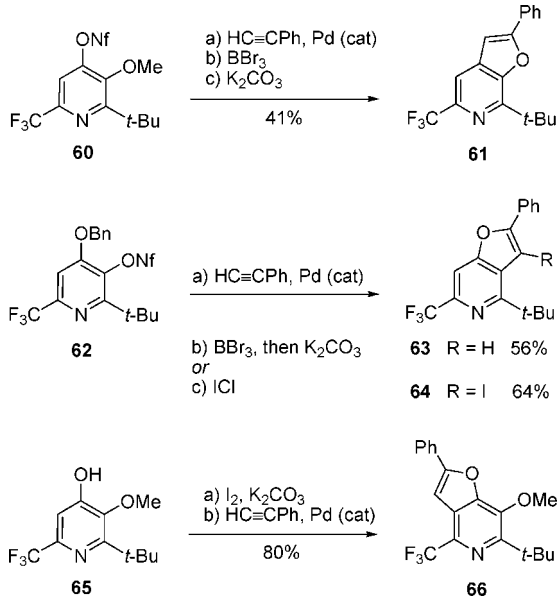




yls with extended π-systems such as **57**, **58**, and **59** are accessible in a short and flexible route (Scheme 14). It should be noted that 10 new C−N and C−C bonds are generated during preparation of these compounds.[36]

The conversion of pyridines **60**, **62**, and **65** into regioisomeric furopyridines represents another useful application (Scheme 15). Furopyridine **61** was prepared in a straightforward manner by Sonogashira coupling of pyridyl nonaflate **60** with phenyl acetylene, boron tribromide-promoted demethylation, and 5-*endo-dig* cyclization under basic conditions.[37] Preparation of regioisomer **63** was possible starting from substrate **62** bearing the nonaflated hydroxyl group in 3-position. Alternatively to these cyclizations, ring closure could also be performed by iodine monochloride treatment of the intermediate alkyl-substituted pyridinol leading to iodo-substituted furopyridine **64**. Finally, pyridinol **65** was elaborated to compound **66** via iodination and coupling of the free 5-iodopyridinol intermediate with phenyl acetylene.

SCHEME 15. Furopyridines with Differing Ring Junction via Sonogashira Couplings and Subsequent 5-*endo-dig* Cyclizations

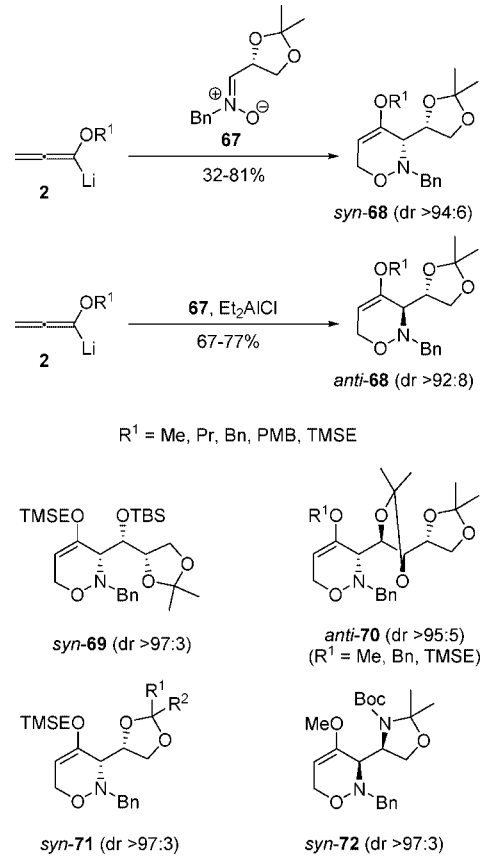


Amino Polyols, Novel Carbohydrate Mimetics, and More from 1,2-Oxazines

The addition of lithiated alkoxyallenes to nitrones as electrophiles delivered exceptionally useful products: 1,2-oxazines![38,39] This novel [3 + 3] cyclization allowed for the preparation of precursors to a multitude of biologically active target compounds, from amino alcohols to α-amino-β-hydroxy esters,[40] neuramic acid derivatives,[41] polyhydroxylated pyrrolidines, and azetidines. Moreover, carbohydrate and peptide mimetics could be accessed via novel skeletal rearrangements of 1,2-oxazines leading to bicyclic compounds as key intermediates.

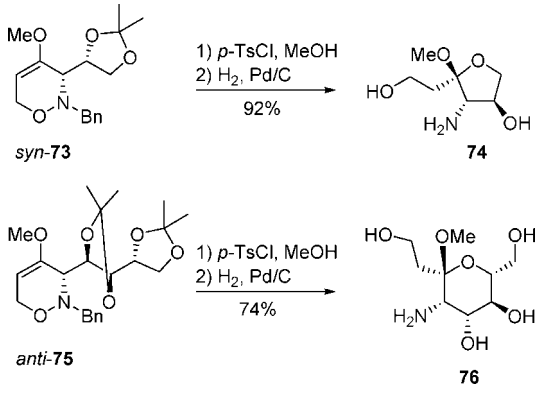
The substrate-controlled highly diastereoselective addition of lithiated alkoxyallenes **2** to chiral aldonitrones furnishes allenyl hydroxylamines as transient primary products, which immediately cyclize to give enantiopure 3,6-dihydro-2*H*-1,2-oxazines in high yields via the aforementioned [3 + 3] 6-*endo-trig* cyclization (Scheme 16).[38,39] Most gratifyingly, (*R*)-glyceraldehyde-derived nitrone **67** allows for a highly selective and stereodivergent synthesis of dioxolanyl-substituted 1,2-oxazines *syn*- and *anti*-**68**. Reaction of **2** with **67** in tetrahydrofuran as solvent results in excellent *syn*-selectivity, whereas precomplexation of **67** with diethylaluminum chloride as Lewis acid in diethyl ether leads to *anti*-**68** with very high preference (Scheme 16). This perfect stereochemical switch is in agreement with Dondoni's results,[42] who studied the addition of C-2 metalated thiazoles to nitrone **67**. Starting from different carbohydrate, ascorbic acid, or α-amino acid derived nitrones, *syn*-1,2-oxazines such as *syn*-**69**, *syn*-**71**, and *syn*-**72** or *anti*-**70** were prepared in good yields and diastereoselectivities. In only a few cases, the primarily formed allenyl hydroxylamine derivatives could be isolated, which slowly cyclize to the corresponding 1,2-oxazine derivatives.[43]

SCHEME 16. Stereoselective Preparation of 1,2-Oxazines **68**−**72** from Lithiated Alkoxyallenes **2** and Aldonitrones via [3 + 3]-Cyclization



The synthetic value of 1,2-oxazines depicted in Scheme 16 may be illustrated by the two-step conversion into enantiopure new dideoxyamino carbohydrates (Scheme 17).[44] Acid-induced acetal cleavage of *syn*-**73** or *anti*-**75** and subsequent cyclization generated the furan or pyran ring. Hydrogenolysis removed the *N*-benzyl group and cleaved the N−O bond giving products **74** and **76**. Use of samarium diiodide for the reduction would just open the 1,2-oxazine ring without removal of the benzyl group. Analogous transformations were executed with the *anti*-diastereomer of **73** and the corresponding enantiomers. Thus, a complete set of four stereoisomers of 4-amino-1,4-dideoxy-hex-3-ulose was smoothly prepared.[44]

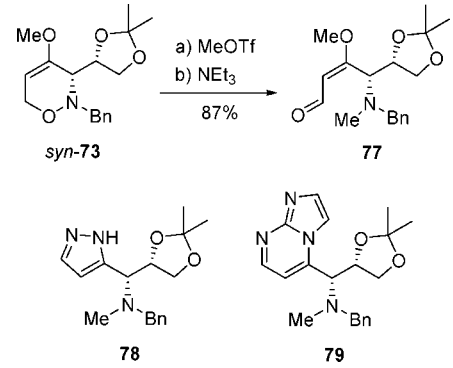
SCHEME 17. Acid-Promoted Formation of Dideoxyamino Sugar Derivatives **74** and **76**



Cleavage of their weak N−O bonds is one of the most suitable transformations of 1,2-oxazine and isoxazole derivatives making these heterocycles valuable amino alcohol precursors.[45] With the two 3,6-dihydro-2*H*-1,2-oxazines *syn*-**73** and *anti*-**73**, we discovered an interesting stereodivergent behavior when they were subjected to different reduction conditions leading to a set of four diastereomeric amino alcohol derivatives.[46] An alternative cleavage mode of 3,6-dihydro-2*H*-1,2-oxazines is depicted in Scheme 18 with *syn*-**73** as an exemplary substrate. Based on Murahashi's method developed for isoxazolidines,[47] the heterocycle is *N*-alkylated and treated with base, which, under N−O bond cleavage, furnished the unsaturated aldehyde **77**.[48] These compounds serve as intermediates for the preparation of heterocycles such as **78** and **79**, generated by simple condensation reactions of the masked keto aldehyde function either with hydrazine or with 2-aminoimidazole.

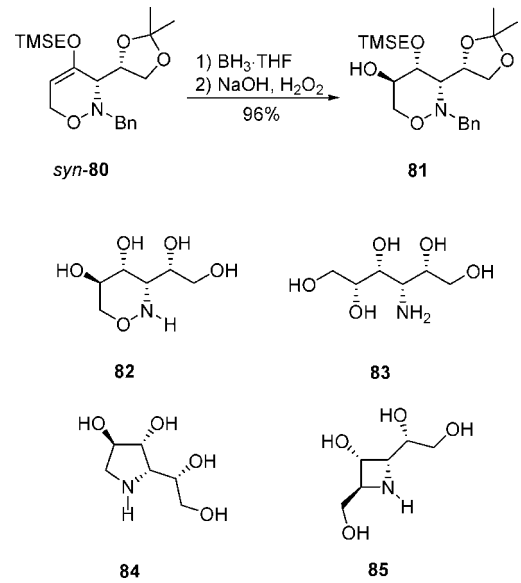
So far the enol ether moiety of 3,6-dihydro-2*H*-1,2-oxazines was not exploited for introduction of additional substituents or functional groups. Many options arise from the use of this activated double bond. Cyclopropanation with dihalocarbenes led to enantiopure 1,2-oxazepine derivatives[49] and

SCHEME 18. Cleavage of *syn*-**73** to **77** and Subsequent Condensations Furnishing Heterocycles **78** or **79**



reactions with NBS stereoselectively delivered 5-bromo-1,2-oxazin-4-one derivatives,[50] which also undergo a broad range of subsequent reactions. The regio- and stereoselective hydroboration of 3,6-dihydro-2*H*-1,2-oxazines introduced a hydroxyl group at position 5 and allowed the preparation of interesting polyhydroxylated compounds.[51] In Scheme 19, the hydroboration of *syn*-**80** serves as an example for this strategy. The TMSE (trimethylsilylethyl) group was selected because it can easily be removed under mild (and orthogonal) conditions. Hydroboration product **81** was transformed in straightforward reactions either into fully deprotected 1,2-oxazine derivative **82**,[52] into its ring-cleaved amino polyol counterpart **83**, into polyhydroxylated pyrrolidine derivative **84**[51] (a known L-fucosidase inhibitor)[53] or into azetidine derivative **85**.[52] It is obvious that stereoisomers of *syn*-**80** would open access to diastereomers or enantiomers of compounds **82**−**85**. The examples assembled in Scheme 19 demonstrate

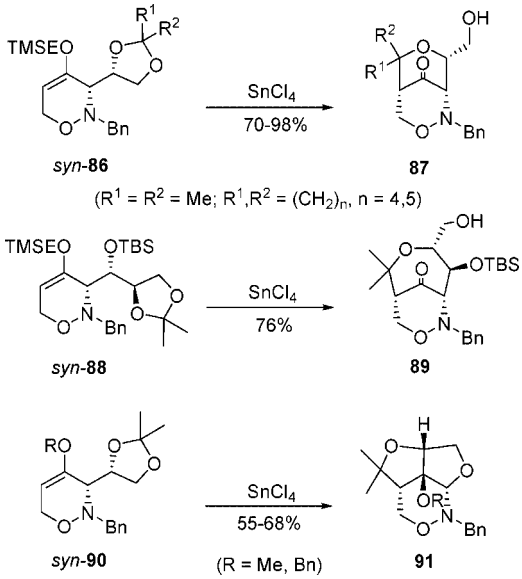
SCHEME 19. Structurally Diverse Products **82**−**85** Accessible from Hydroboration Product **81**



the synthetic versatility and flexibility of selectively protected amino polyol precursors such as **81**.

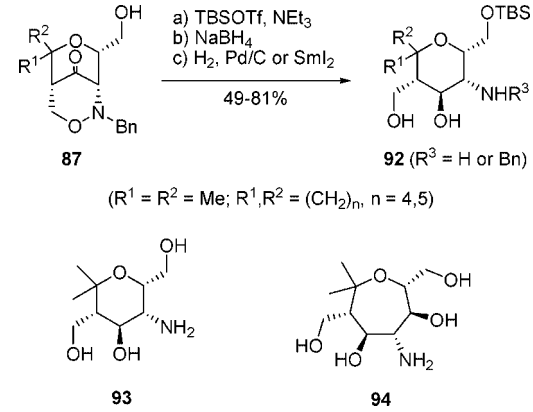
During attempts to selectively deprotect 1,2-oxazine derivative *syn*-**80**, we discovered an unanticipated Lewis-acid-promoted C−C bond forming reaction, leading to functionalized amino-substituted pyran derivatives in a stereoselective fashion.[54] Again, serendipity helped us to discover a new playground, now for the synthesis of carbohydrate mimetics. Scheme 20 presents typical examples and also a more complicated case. Treatment of the TMSEO-substituted 1,2-oxazines *syn*-**86** and *syn*-**88** with tin tetrachloride afforded products **87** and **89** in good yields, where the 1,2-oxazine ring is incorporated into bicyclo[3.3.1]- or bicyclo[4.3.1]-skeletons. As mechanism, we suggest coordination of the Lewis acid at the "external" oxygen of the dioxolane ring, formation of a carbenium ion, which intramolecularly attacks the enol ether moiety of the 1,2-oxazine ring. The fast fragmentation of the TMSE group into ethylene and a Me_3SiX species was proven and seems to be essential for this multistep process. The crucial new C−C bond-forming reaction is related to a Lewis-acid-promoted aldol-type reaction of a ketal with an enol ether as nucleophile. In contrast, when 1,2-oxazines such as *syn*-**90** (R = methyl or benzyl instead of TMSE) were exposed to similar reaction conditions, the fragmentation appears to be considerably slower, and for these two compounds, an additional ring-contracting reaction to generate tricyclic skeleton **91** was observed.[55]

SCHEME 20. Lewis-Acid Mediated Rearrangements of 1,2-Oxazines Leading to Polycyclic Compounds **87**, **89**, and **91**



Compounds such as **87** are selectively protected pyran derivatives, which allow conversion into products resembling amino pyranoses. Scheme 21 summarizes protection and reduction steps transforming **87** into pyran intermediate **92**.[54] The geminally dimethylated compound was fully deprotected affording carbohydrate mimetic **93**, which was used as a key component for the synthesis of a highly potent L-selectin ligand.[56] By similar reduction protocols, bicyclic precursor **89** was stereoselectively transformed into oxepine derivative **94**, which can be regarded as a unique heptanose analogue.[54]

SCHEME 21. Routes to New Carbohydrate Mimetics: Amino-Substituted Pyrans **92** and **93** and Oxepane **94**



Compounds such as **87** were appropriately functionalized for synthesis of disaccharide mimetics by click chemistry, but they could also be converted into novel enantiopure β- or γ-amino acids. Simple peptides incorporating these uncommon amino acids derived from 1,2-oxazines have been prepared.[57]

Conclusions

In this Account, we collected results from our group demonstrating the tremendous versatility of lithiated alkoxyallenes in organic synthesis.[58] Five- and six-membered heterocycles are easily constructed in [3 + 2] and [3 + 3] cyclization modes starting from different electrophiles and lithiated alkoxyallenes as nucleophilic C_3 building blocks being equivalents of 1,3-zwitterionic synthons **b** or **c** (Figure 1). The resulting functionalized heterocycles were employed for the stereoselective synthesis of different classes of natural products in a straightforward manner. The preparation of spiroketals employs lithiated alkoxyallene as unsaturated acyl anion synthon **a**. The equivalency of lithiated alkoxyallenes to formyl anion synthon **d** or homoenolate **e** has been demonstrated earlier.[40,59,60] To our great delight, we also detected less obvious novel synthons, which guided us in unexpected directions (Figure 3). The oxidative ring opening of dihydrofurans as described in Scheme 4 demonstrates that lithiated alkoxyallenes are equivalent to the unusual malondialdehyde anion

f. By mere serendipity, we discovered tripolar synthons such as **g**, **h**, and **i** (Figure 3), which are introduced into functionalized heterocycles via alkoxyallene chemistry. The Lewis-acid promoted rearrangement of 1,2-oxazines leads to bicyclic compounds containing an allene-derived C_3 moiety with the formal charge distribution **g** (Scheme 21). The unique synthesis of pyridinol derivatives (Scheme 13) incorporates alkoxyallenes as tripolar unit **h**, while the iodovinyl-substituted imidazoles of Scheme 11 contain a C_3 fragment with a formal charge pattern **i**.

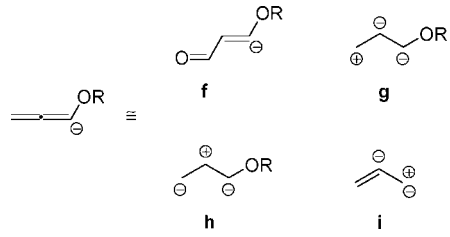


FIGURE 3. Novel synthons **f**–**i** derived from metalated alkoxyallenes.

All these compounds derived from lithiated alkoxyallenes and different electrophiles contain at least one substructure containing O- or N-atoms at neighbored carbons, this synthetically valuable 1,2-relationship being generally established by the above-mentioned umpolung of reactivity. In our recent original reports and in this Account, we could demonstrate that even more complex and synthetically valuable functional group arrangements can be incorporated into heterocyclic and acyclic products. In addition, novel highly conjugated π-systems with almost unlimited variations are accessible. With the already existing methodology a variety of biologically active natural products, in particular carbohydrate and alkaloid derivatives, may efficiently be prepared in the future, and new heterocycles for material science syntheses will be available. The tree with many branches is still growing!

The results of our group were obtained by a number of very talented and engaged young colleagues whose names are found in the references. We are grateful to their important intellectual contributions and skillful experimental work. The authors also thank the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and Bayer Schering AG for continuous and generous support during the last years.

BIOGRAPHICAL INFORMATION

Malte Brasholz, born 1978, received his Ph.D. degree from Freie Universität Berlin in 2007 under the guidance of Prof. Hans-Ulrich Reissig. Thereafter, he visited the group of Prof. Hisashi Yamamoto at the University of Chicago as a short-term research scholar. Currently, he stays at the University of Cambridge for postdoctoral studies under the guidance of Prof. Steven V. Ley.

Hans-Ulrich Reissig, born 1949, received his Ph.D. degree from Ludwig-Maximilians-Universität München in 1978 under the guidance of Prof. Rolf Huisgen. He did postdoctoral research with Prof. Edward Piers at the University of British Columbia, Vancouver, and had academic positions at the Universität Würzburg, Technische Universität Darmstadt, Technische Universität Dresden, and finally at the Freie Universität Berlin. He is interested in organic synthesis, in particular in synthetic methodology and its application to natural product synthesis, and has published more than 300 publications.

Reinhold Zimmer, born 1959, received his Ph.D. degree from Technische Universität Darmstadt in 1990 under the guidance of Prof. Hans-Ulrich Reissig. Thereafter, he did postdoctoral research as Karl-Landsteiner fellow at the Sandoz Research Institute in Vienna. Since 1994, he has been a permanent research associate with Prof. Reissig.

FOOTNOTES

†Dedicated to Professor Ekkehard Winterfeldt.

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