Heterocycles in organic synthesis: thiazoles and triazoles as exemplar cases of synthetic auxiliaries

Alessandro Dondoni*

Received 5th February 2010, Accepted 12th May 2010
First published as an Advance Article on the web 26th May 2010
DOI: 10.1039/c002586k

This Perspective article illustrates the key role of thiazole and triazole in the work carried out in the author's laboratory over three decades and deals with the synthesis of carbohydrate-based bioactive molecules. The first part reports on the development of synthetic strategies exploiting the use of various thiazole-based reagents and the ready conversion of thiazole into the formyl group. After describing the chain elongation of monosaccharides into higher-carbon homologues, the synthesis of target natural and non-natural carbohydrates, or their ultimate precursors, is presented. These include some sphingoids, neuraminic and destomic acids, lincosamine, various 3-deoxy-2-ulosonic acids (KDO, KDN, iso-Neu4Ac), iminosugars (nojirimycin, mannojirimycin, galactostatin) and homoazasugars. Also prepared were the disaccharide subunit of bleomycin A_2 and the side-chain of taxol and taxotere.® The use of 1,2,3-triazole is discussed in the second part of the paper. The service of this heterocycle that is easily formed by the Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC) is considered in light of its use as a robust linker (a sort of keystone) of complex and diverse molecular architectures. Thus, the assembly of triazole-linked glycosyl amino acids, non-natural nucleotides, 1,6-oligomannosides, sialoside clusters on calixarene platfom *via* CuAAC is described and the biological relevance of these compounds is discussed in brief.

Introduction

In 1974 Albert (Al) I. Meyers published a monograph entitled "*Heterocycles in Organic Synthesis*" in which he discussed the service of some common heterocycles as useful auxiliaries in synthetic methodologies.[1] A synthetic auxiliary was intended to be a compound acting either as a precursor, reagent or vehicle for formation of non-heterocyclic material. Professor Meyers used not only the content of his book but also the results from his intense research activity to "stimulate the imagination of investigators into looking at a heterocyclic system with the renewed interest in its potential synthetic utility".[1] Hence I have used the title of Al's book in this article as well because I thought that no title was more appropriate for introducing the role played by two simple five-membered heterocycles, thiazole and triazole, in research carried out over the last three decades in my laboratory. I am sure that Al, a generous friend and distinguished colleague, would forgive me for the plagiarism. Curiously there is a great assonance in the terms thiazole and triazole as they differ only by one consonant. However, their ways of operating as synthetic auxiliaries are quite different because thiazole serves as a masked functional group *via* a fragmentation process while triazole behaves as a chemical keystone locking molecular fragments in a single and highly stable architecture. Accordingly, I will report in this paper a harvest of data from our own research to demonstrate the key role of thiazole as a formyl group equivalent[2] and triazole as a robust linker in synthetic routes to bioactive molecules such as carbohydrates and their conjugates. As it is well established that carbohydrates play a crucial role in a multitude of events—some of which are beneficial while some other are detrimental—occurring in living organisms,[3] the synthesis of carbohydrate-based molecules in a pure form and composition followed by the use as probes or/and leads for the development of new drugs are at the forefront of research in chemistry, biochemistry and medicine.

Dipartimento di Chimica, Laboratorio di Chimica Organica, Università di Ferrara, Via L. Borsari 46, I-44100 Ferrara, Italy. E-mail: adn@unife.it; Fax: +39 0532 240709; Tel: +39 0532 455176

Alessandro Dondoni

Alessandro Dondoni has been Professor of Organic Chemistry at the University of Ferrara from 1975 to 2008. At present he is Senior Scientist in the same University. He has been the recipient of several awards including the A. Mangini Gold Medal by the Italian Chemical Society (1996); the Avogadro–Minakata Lectureship Award of the Chemical Society of Japan (1999); the Ziegler–Natta Lectureship Award of the German Chemical Society (1999); the Lincei National Academy Prize in Chemistry (1999). His present research interests are in new synthetic methods, organocatalysis, and carbohydrate chemistry. He recently started a new program dealing with the use of free-radical thiol–ene coupling as a click ligation tool for peptide and protein modification. A large part, if not all, of his chemistry is being developed with the aim of providing new products for biochemical studies, pharmaceutical and biomedical applications.

Thiazole as a masked formyl group

Very likely thiazole is mainly known to the majority of chemists for its role in the form of a thiazolium ion as a catalyst in carbon–carbon bond forming reactions such as the benzoin condensation[4] and the Stetter reaction.[5] On the other hand, biologists are likely to be familiar with thiazole for its key role in the catalytic activity of thiamine pyrophosphate (TPP), a coenzyme important in respiration in the Krebs cycle[6] (Fig. 1). It has been demonstrated by Breslow that in all cases the actual catalyst is a thiazolium 2-ylide[7] that triggers the whole process by transformation of the electrophilic carbonyl compound, such as aldehyde and pyruvic acid, into a highly reactive nucleophilic species (umpolung). The thiazole ring, moreover, is a key structural motif that is present in numerous natural bioactive compounds. Epothilones[8] (Fig. 1) and the large family of macrocyclic thiopeptide antibiotics, the prototype of which is thiostrepton[9] (Fig. 1), are well known examples of thiazole containing biomolecules. Another remarkable example of thiazole containing natural product is micrococcin P_1 (Fig. 1), a thiopeptide antibiotic active against microorganisms resistant even to vancomycin and whose correct structure was established by total synthesis some sixty years after its isolation.[10]

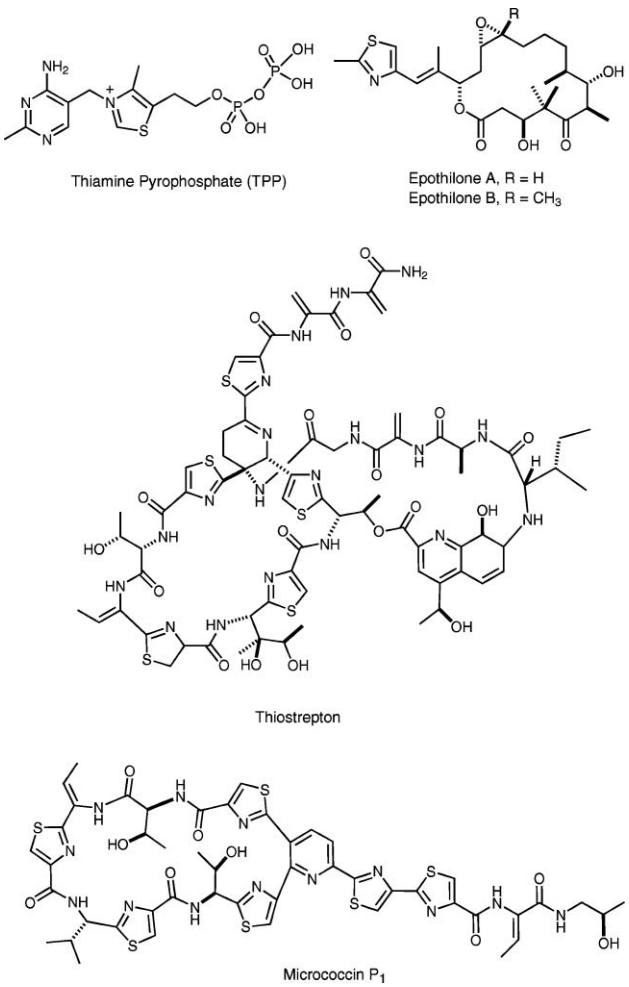
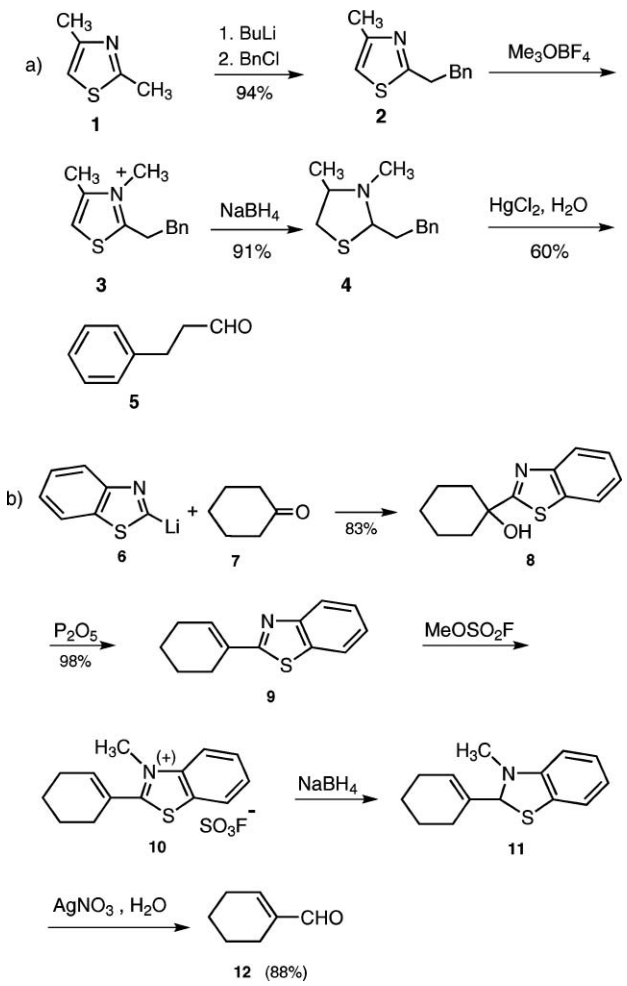


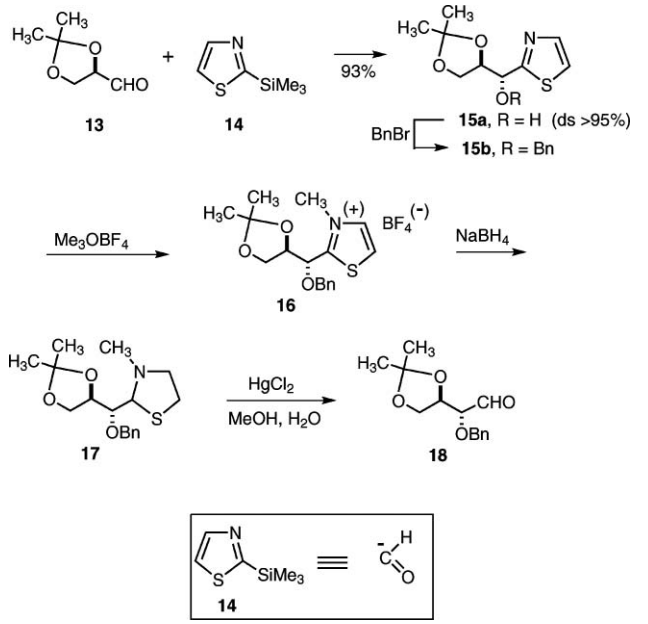
Fig. 1 Examples of thiazole-containing bioactive natural products.

While in the past most of thiazole chemistry was centered on the functionalization of the ring,[11] Altmann and Richheimer in 1971 focused their attention on a neglected aspect.[12] This involved the cleavage of the thiazole ring *via* a one-pot reaction sequence constituted of *N*-alkylation by trimethyloxonium fluoroborate, Me_3OBF_4, reduction of the C=C and C=N bonds of the thiazolium salt by $NaBH_4$, and hydrolysis of the thiazolidine thus formed by $HgCl_2$ in MeOH–H_2O. In this way 2,4-dimethyl thiazole **1** was transformed into phenyl propanal **5** (Scheme 1, eq. a). The publication by Altmann and Richheimer was followed some years later by a paper by Corey and Boger[13] who described the transformation of 2-substituted benzothiazoles into aldehydes *via* a reaction sequence constituted of alkylation–reduction–hydrolysis. For example compound **8** obtained from lithiobenzothiazole **6** and cyclohexanone **7** was transformed into the α,β-unsaturated aldehyde **12** (Scheme 1, eq. b). Thus, the reactions in Scheme 1 laid the classical foundation of the thiazole to formyl equivalence in synthetic methodology. The importance of this concept is evident when considering that the synthesis of complex aldehydes may require the presence of the formyl group in a protected form. The thiazole ring appears to be well qualified to serve as a masked formyl group owing to its stability and tolerance to a wide range of reaction conditions while the latter can be easily revealed by thiazole cleavage under almost neutral conditions *via* the above alkylation–reduction–hydrolysis sequence.



Scheme 1 Early examples of thiazole and benzothiazole acting as masked formyl groups.

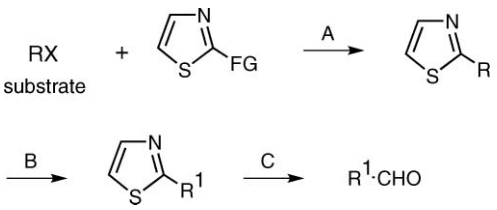
After the above reports, however, the thiazole-to-formyl equivalence did not attract much attention by researchers for almost two decades probably because of the high popularity of more traditional masked formyl groups such as 1,3-dithiane and 1,3-dithiolane. In 1985 we reported[14] the first thiazole-based synthesis of a chiral aldehyde, the protected D-erythrose **18**, by one-carbon homologation of 2,3-*O*-isopropylidene-D-glyceraldehyde **13** (Scheme 2). The key reagent in this transformation was 2-(trimethylsilyl)thiazole (2-TST, **14**), a stable and readily available organometal prepared for the first time in our laboratory. 2-TST **14** reacted with **13** under fluoride-free conditions to yield the alcohol **15** in high yield and diastereoselectivity (ds >95%)). The cleavage of the thiazole ring by the Altmann and Richheimer methylation–reduction–hydrolysis protocol afforded the tetrose **18**, a product of the formal addition of the formyl anion to the triose **13**. Thus, it appeared that in the whole process 2-TST **14** served as a formyl anion equivalent.



Scheme 2 2-(Trimethylsilyl)thiazole **14** as formyl anion equivalent.

The thiazole–aldehyde synthesis

Inspired by the model system shown in Scheme 2, we formulated a general synthetic strategy that we coined *Thiazole–Aldehyde Synthesis*, which entailed the transformation of a given substrate into an aldehyde through thiazole-based intermediates (Scheme 3). This occurred through three sequential operations : **A**, introduction of the thiazole ring in a substrate RX by reaction with a C-2-functionalized thiazole FGTh (*coupling*); **B**, transformation of the resulting C-2-substituted thiazole RTh into R^1Th by synthetic elaboration of the group R (*elaboration*); **C**, liberation of the target aldehyde R^1CHO from R^1Th by cleavage of the thiazole ring (*unmasking*).



Scheme 3 The thiazole–aldehyde synthesis: A, coupling; B, elaboration; C, unmasking.

In order to broaden the scope of the above synthetic strategy and provide a number of potential routes for performing the coupling step **A**, a set of reagents FGTh was prepared displaying a variety of reactive functional groups FG (Fig. 2). All reagents were easily prepared in multigram scale since the commercially available 2-bromothiazole **19** was the progenitor of all of them. A broad range of elaborations of RTh in step **B** were expected to be feasible owing to the inertness of the thiazole ring under a variety of reaction conditions. Finally, the unmasking step **C** was improved by using efficient alkylating agents and various thiophilic metals. Specifically, methylation with methyl triflate (CF_3SO_3Me) at room temperature reduced to a few minutes the long reaction time required with MeI, and thiazolidine hydrolysis promoted by $CuCl_2$·CuO or $AgNO_3$ was quite efficient while avoiding the use of the noxious $HgCl_2$. Notably, the almost neutral conditions of the unmasking sequence ensured that delicate functional groups and stereocenters that were present in the aldehyde residue remained unaltered.

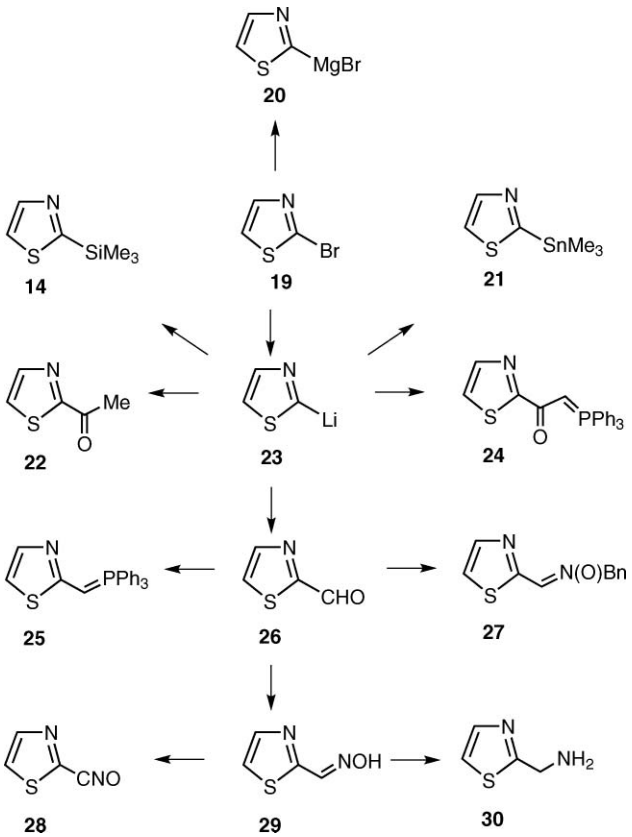
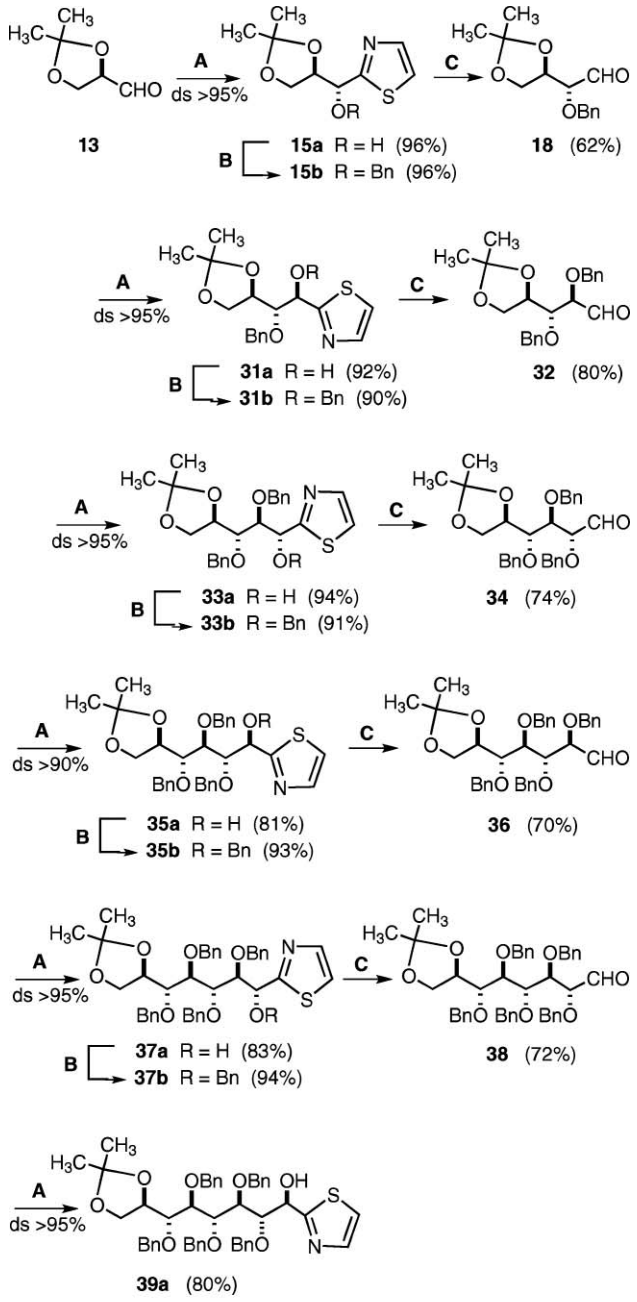


Fig. 2 The tool box of C2 functionalized thiazoles.

Synthesis of higher sugars

Having demonstrated that 2-TST **14** served as an efficient formyl anion equivalent in the stereoselective one-carbon chain elongation of *aldehydo* D-glyceraldehyde **13** (Scheme 2), the

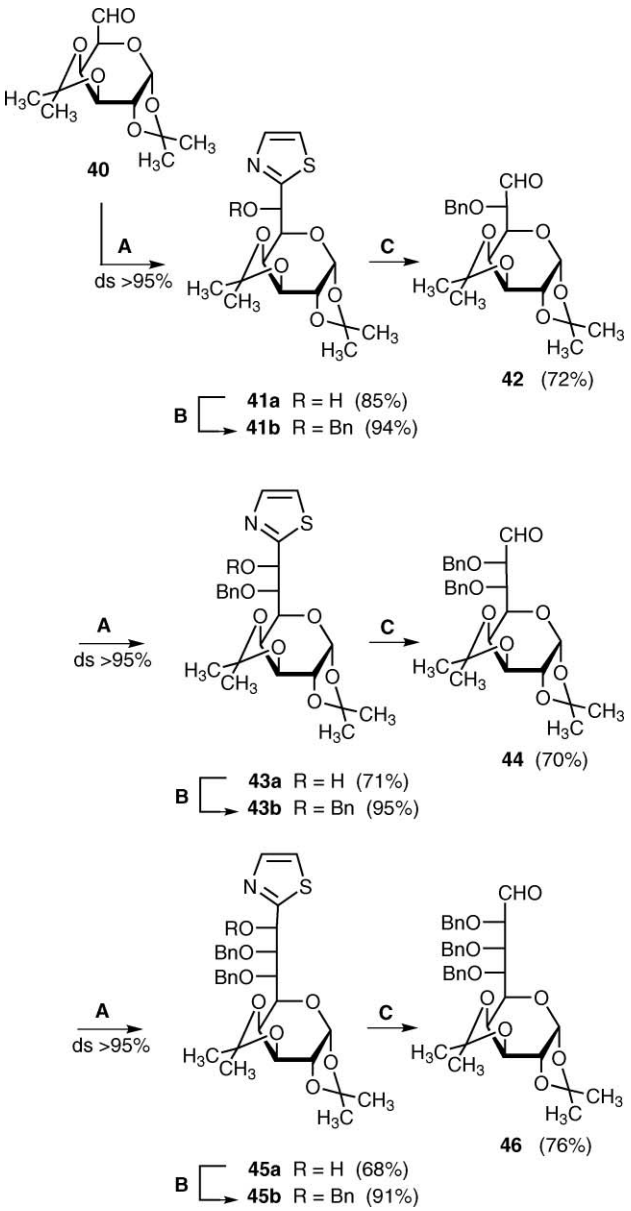
same coupling–elaboration–unmasking sequence was repeated over several consecutive cycles[15] to give a series of one-carbon higher homologues up to the octose **38** (Scheme 4). The *anti*-diastereoselectivity of the addition of 2-TST **14** to each *aldehydo* sugar was demonstrated by transformation of the thiazole D-octose **37a** into a *meso*-octitol. The same iterative chain-elongation methodology was successfully applied to 4-*O*-benzyl-2,3-*O*-isopropylidene-L-threose, thus affording a series of non-natural *aldehydo* L-sugars up to a seven-carbon atom member.[16]



Key: **A**, coupling with 2-TST **14**; **B**, elaboration (BnBr, NaH); **C**, unmasking (MeI, then $NaBH_4$, then $HgCl_2$, H_2O).

Scheme 4 Homologation of D-glyceraldehyde to higher sugars by 2-(trimethylsilyl)thiazole **14**.

The above 2-TST-based one-carbon homologation strategy was applied to dialdoses[16,17] with the aim of obtaining higher-carbon derivatives as potential building blocks for biologically active compound synthesis. In fact, the introduction of stereochemically well defined polyhydroxylated carbon chains at C5 of pyranose ring was an important operation[18] because the resulting higher sugars were the constituents of various natural antibiotics, such as hikizimycin[19] and tunicamycin.[20] Thus, starting from the protected α-D-*galacto*-hexodialdo-1,5-pyranose **40**, the iterative thiazole–aldehyde synthesis over three consecutive cycles furnished[16] the nine carbon-atom dialdogalactopyranoside **46** (Scheme 5). It is noteworthy that also in this homologative sequence the coupling

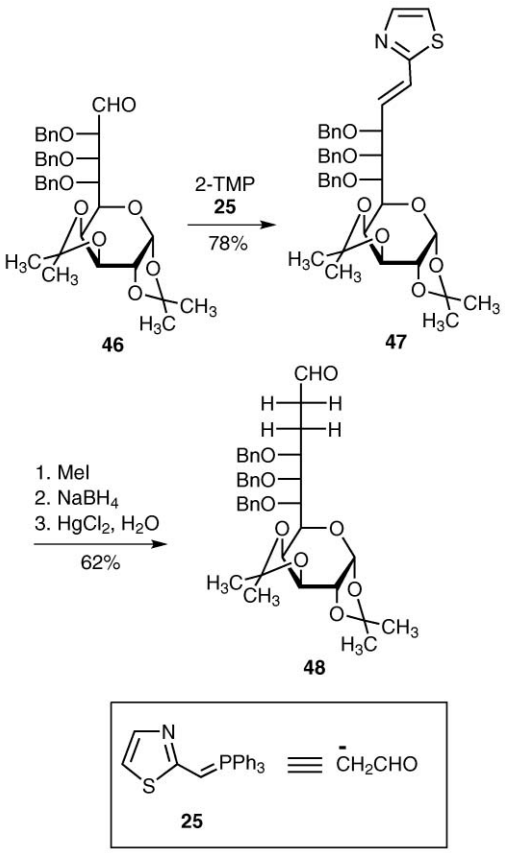


Key: **A**, coupling with 2-TST **14**; **B**, elaboration (BnBr, NaH); **C**, unmasking (MeI, then $NaBH_4$, then $HgCl_2$, H_2O).

Scheme 5 Homologation of dialdose **40** to higher sugars by 2-(trimethylsilyl)thiazole **14**.

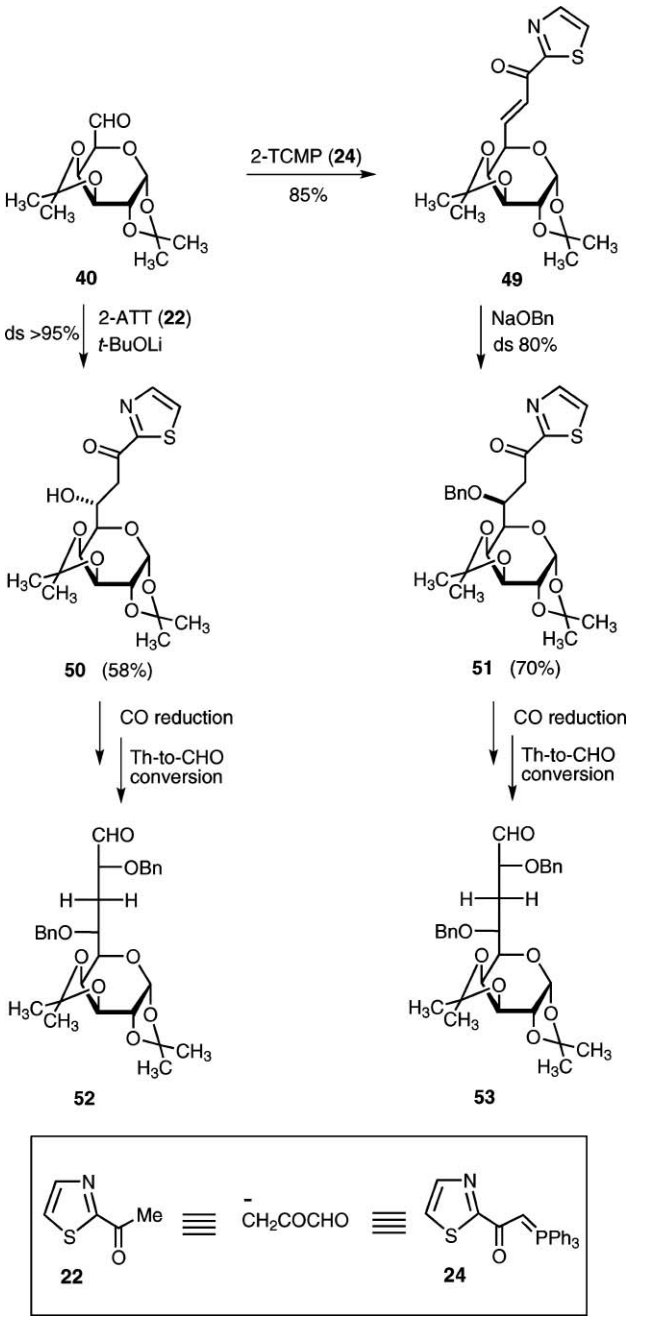
between 2-TST **14** and each sugar aldehyde occurred with high diastereoselectivity to give exclusively the *anti*-adduct in high yield.

The synthesis of higher dialdoses was more rapidly performed *via* two- and three-carbon chain elongation strategies using suitable thiazole bearing reagents. Thus, the Wittig reaction of dialdose **46**—obtained from **40** as described in Scheme 5—by the phosphorous ylide 2-thiazolylmethylene triphenylphosphorane (2-TMP, **25**), a two-carbon synthon equivalent, furnished the *E*-olefin **47** (Scheme 6).[21] From this key intermediate, the thiazole-to-formyl unmasking and concomitant reduction of the carbon–carbon double bond afforded the dideoxy undecadialdose **48**.



Scheme 6 Homologation of dialdose **46** by thiazolyl phosphorane **25**.

The three-carbon chain elongation of dialdose **40** was carried out by the use of two reagents, namely 2-acetylthiazole (2-ATT, **22**) and triphenyl(thiazol-2-yl-carbonylmethylene)phosphorane (2-TCMP, **24**). The reaction of **40** with the lithium enolate of **22** afforded the the β-hydroxy ketone **50** while the reaction with the phosphorane **24** yielded the *E*-configured α,β-enone **49** (Scheme 7).[22] The latter compound underwent a stereoselective Michael addition by sodium benzyl oxide to give the β-benzyloxy ketone **51** as major product. The reduction of the carbonyl of **50** and **51** with suitable hydride releasing reagents and then application of the standard thiazole-to-formyl unmasking protocol afforded the two epimers 7-deoxynonodialdoses **52** and **53**.



Scheme 7 Homologation of dialdose **40** by thiazolyl phosphorane **24** and acetylthiazole **22.**

Synthesis of the disaccharide subunit of bleomycin A_2

The biological importance of the so-called uncommon or rare sugars is due to their presence in the glycidic subunit of natural antibiotics. They affect the pharmacokinetic and pharmacodynamic properties of these bioactive compounds. In many cases the chemical synthesis of these sugars is by far a non-trivial task. A typical case is represented by the D-Man-L-Gul disaccharide subunit of bleomycin A_2, the major constituent of a family of glycopeptide antibiotics[23] capable of mediating the cleavage of DNA and RNA by a metal dependent oxidative process. This disaccharide is constituted of L-gulose coupled at C2 through an α-glycosidic linkage with 3-*O*-carbamoyl-D-mannose (Fig. 3). The synthesis of this sugar moiety and its introduction in the aglycon of bleomycin A_2 was reported in 1994 by Boger and Honda.[24] This synthesis required numerous steps as just the preparation of the

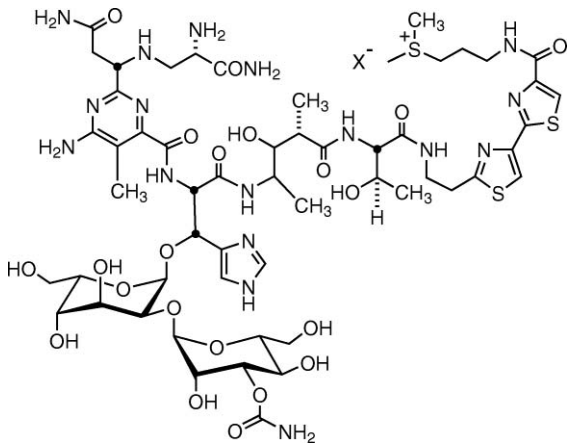
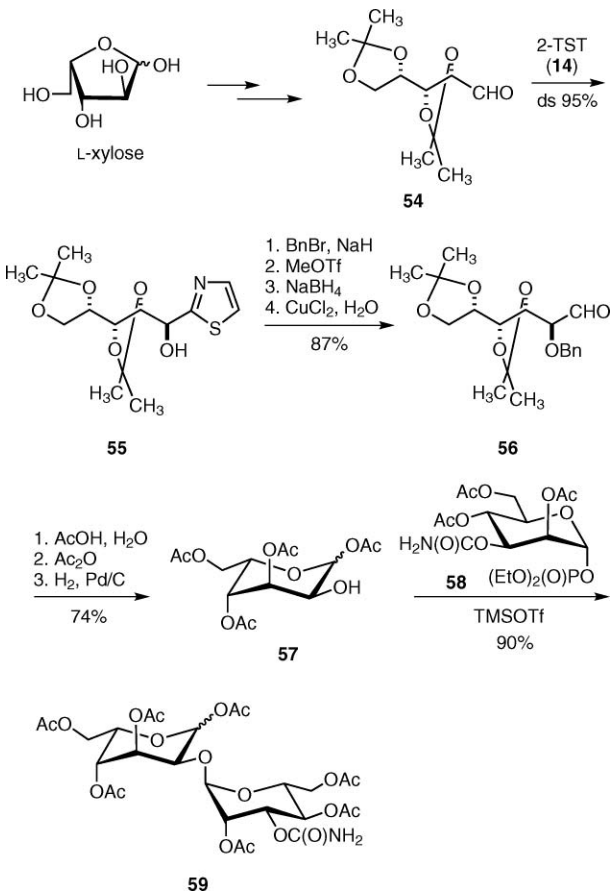


Fig. 3 The antitumor antibiotic bleomycin A_2.

L-gulose residue from benzyl α-D-mannopyranoside was carried out in nine steps and 12.5% yield.

We have performed a concise synthesis of the disaccharide subunit of bleomycin A_2 *via* a thiazole-based strategy[25] (Scheme 8). At first, the partially acetylated hexasaccharide L-gulose **57** was prepared by diastereoselective addition of 2-TST **14** to *aldehydo*-L-xylose diacetonide **54**. Then, the monosaccharide **57** was glycosylated by the mannopyranosyl phosphate **58** to give the peracetylated target disaccharide **59** in a rewarding overall yield

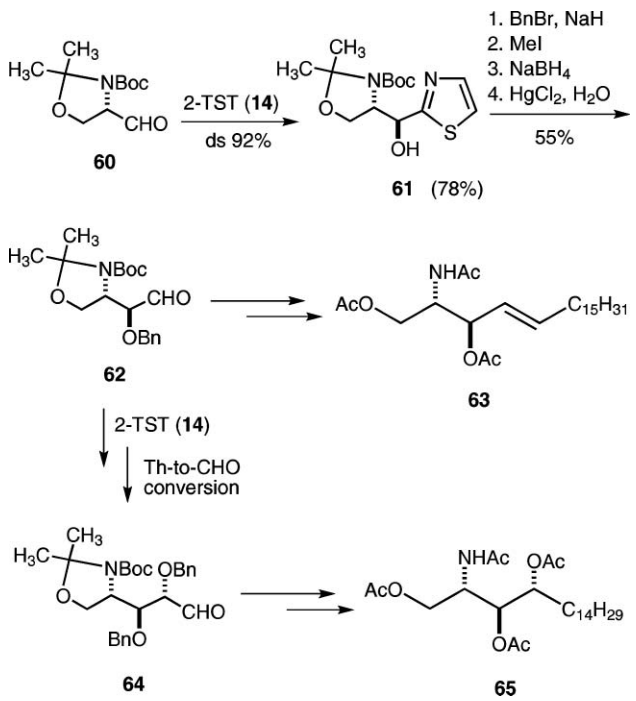


Scheme 8 Synthesis of the sugar moiety of bleomycin A_2.

of 23.5% from L-xylose. Compound **59** is the precisely activated sugar donor that is required for the conjugation with the aglycon of bleomycin A_2.

Synthesis of sphingoids

The homologation of the configurationally stable amino aldehyde *N*-Boc L-serinal acetonide **60** using 2-TST **14** as the formyl anion equivalent afforded[26] the *O*- and *N*-protected amino sugar **62** (L-*erythro*). This was transformed by the same strategy into the one-carbon higher homologue **64** (L-*ribo*) (Scheme 9). These aldehydo sugars served as building blocks, *via* Wittig olefination with suitable alkyl phosphoranes, for the synthesis of sphingoids, *i.e.* long chain aliphatic amino alcohols that form the backbone of all glycosphingolipids. Hence, the peracetylated D-*erythro*-C_{20}-sphingosine **63** and D-*ribo*-C_{18}-phytosphingosine **65** were prepared from **62** and **64**, respectively. At the same time of our first report on this topic,[26a] other syntheses of sphingosines *via* addition of metal acetylides to the amino aldehyde **60** were reported by four independent groups.[27] The advantage of our approach employing more advanced intermediates such as the aldehydes **62** and **64** was that the stereochemistry of the whole hydrophilic head of the sphingosine under construction was already established in those intermediates. Nevertheless, the low yield of the Wittig olefination induced us to reconsider the synthesis of sphingosines some years later using an *O*-silyl-protected analogue of **62** as a substrate for the Wittig olefination.[28] Unfortunately this carbon–carbon bond forming reaction turned out to be scarcely stereoselective as it afforded a mixture of *Z*- and *E*-alkenes in almost equal amounts. Therefore the required *E*-configuration of the double bond was achieved by photoisomerization of the reaction mixture.

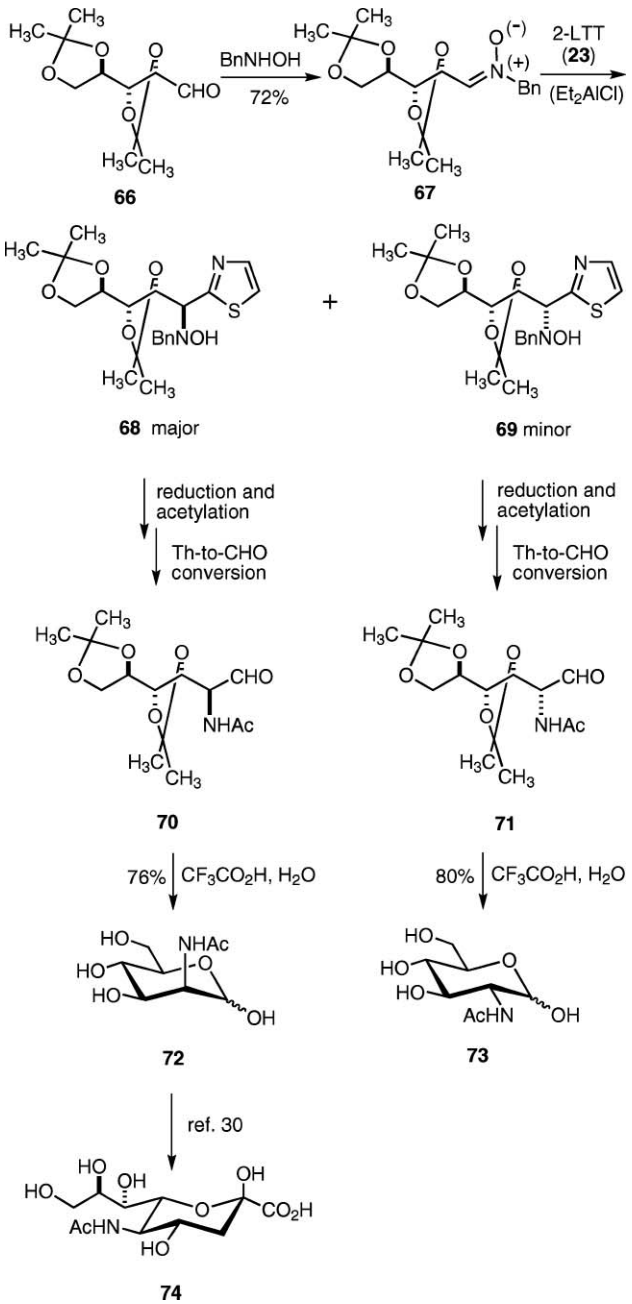


Scheme 9 Synthesis of key precursors of C_{20}-sphingosine **63** and C_{18}-phytosphingosine **65**.

Formal synthesis of neuraminic acid, destomic acid, and lincosamine

We have developed a wide-scope version of the thiazole–aldehyde synthesis that allowed performing the one carbon homologation of aldoses and at the same time introducing an α-amino group (aminohomologation). This new methodology entailed the aldose to nitrone transformation followed by Lewis acid catalyzed addition of 2-lithiothiazole (2-LTT, **23**) to the latter. The 2-thiazolyl hydroxylamine thus generated was converted to the target amino sugar by reduction ($TiCl_3$) of the hydroxylamino group to amino group and thiazole-to-formyl unmasking. As an example of this strategy, the aminohomologation of the *aldehydo*-D-arabinose diacetonide **66** into *N*-acetyl-D-mannosamine **72** (major product) and the D-glucosamine epimer **73** (minor product) was reported[29] (Scheme 10). It has to be noted, however, that the synthesis of these amino sugars was achieved through a scarcely diastereoselective process rather than two stereocontrolled reactions. Nevertheless, the main route in Scheme 10 represented a formal synthesis of *N*-acetyl-neuraminic acid **74**, the prototypical sialic acid, because this can be obtained from **72** according to Vasella and co-workers.[30]

A truly stereodivergent aminohomologation of the dialdose **40** was performed[29] by Lewis acid stereocontrolled addition of 2-lithiothiazole **23** to the nitrone intermediate **75** (Scheme 11). The complexation of this nitrone with two different Lewis acids such as $ZnBr_2$ and Et_2AlCl induced substantial diastereoselectivity but in opposite senses so that the two epimer *N*-benzyl hydroxylamines **76** and **77** were obtained as the major products in high yields. The elaboration of these adducts *via* reduction of the hydroxylamino group and thiazole-to-formyl unmasking afforded the corresponding amino aldehydes **78** and **79**. This scheme represented a formal synthesis of the polyhydroxylated ε-amino acid destomic acid **80**, a component of the antibiotic natural product destomycin,[31] and the amino sugar lincosamine **81**, a component of the commercially important antibiotic lincomycin.[32] Indeed, compounds **78** and **79** can be considered as advanced intermediates for the synthesis of destomic acid and lincosamine, respectively.[33,34]

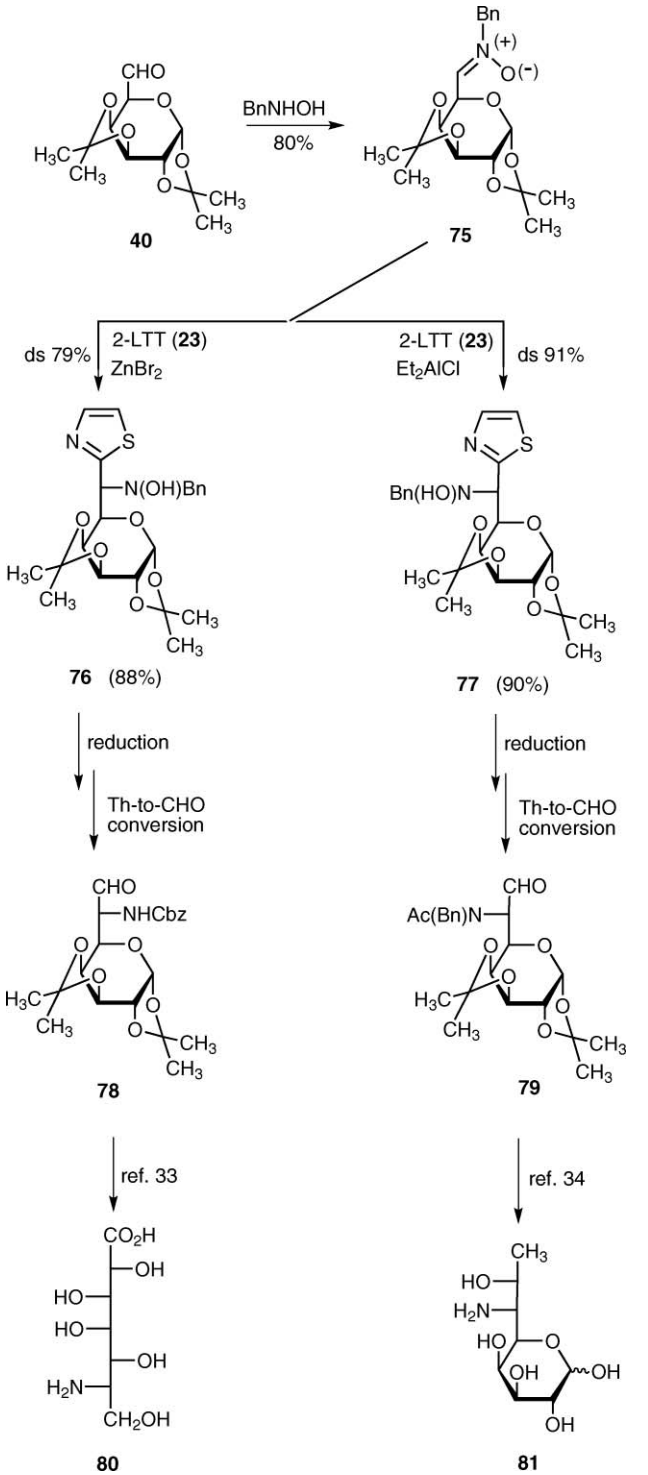


Scheme 10 Aminohomologation of *aldehydo*-D-arabinose **66** and formal synthesis of *N*-acetyl-neuraminic acid **74**.

Synthesis of 3-deoxy-2-ulosonic acids

The easy oxidation of the formyl group to carboxyl allowed to broaden the scope of the thiazole–aldehyde synthesis toward the preparation of natural 3-deoxy-2-ulosonic acids and unnatural epimers. A great deal of interest has been focused over the years on enzymatic and chemical synthesis of these carbohydrates in pure form and well defined structure because of their potential as building blocks for complex glycoconjugates and use as probes for the clarification of biological pathways. Some common natural members are shown in Fig. 4. The 7-phosphate of the seven-carbon compound 3-deoxy-D-*arabino*-2-heptulosonic acid (DAH, **82**) is a key intermediate in the biosynthesis of aromatic amino acids from glucose in microorganisms and plants (shikimate pathway);[35] the well known eight-carbon compound 3-deoxy-D-*manno*-2-octulosonic acid (KDO, **83**) occurs in the lipopolysaccharide region of the cell surface of all Gram-negative bacteria and is an essential component for their replication;[36] the nine-carbon compound 3-deoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid (KDN, **84**) has been isolated from polysialoglycoproteins of rainbow trout eggs, and its presence is thought to allow these proteins to perform some important functions in egg activation;[37] finally, the aminated analogue of **84**, namely the above mentioned *N*-acetyl-neuraminic acid (Scheme 10) *i.e.* 5-acetamido-3,5-dideoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid (Neu5Ac,**74**) is the most common member of a large family of aminononulosonic acids (sialic acids)[38] which are incorporated at the terminal positions of glycoproteins, glycolipids, and oligosaccharides. These largely diffused 2-ulosonic acids play an essential role in biological molecular recognition processes, such as cell adhesion and differentiation phenomena.[39]

We have carried out the synthesis of 2-ulosonic acids starting from simple *aldehydo* sugars employing 2-ATT **22** and 2-TCMP **24** as three-carbon chain elongating reagents. These reagents turned



Scheme 11 Stereodivergent aminohomologation of dialdose **40** and formal synthesis of destomic acid **80** and lincosamine **81**.

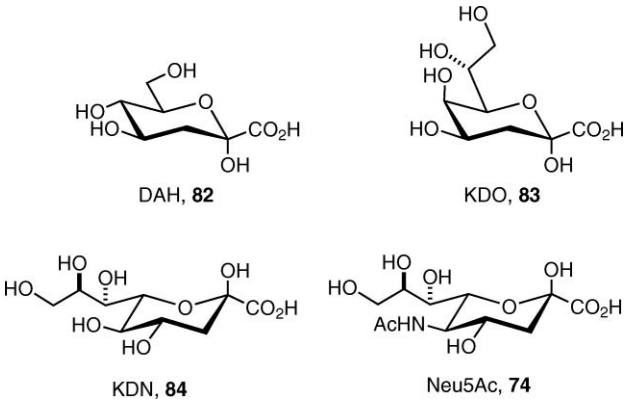
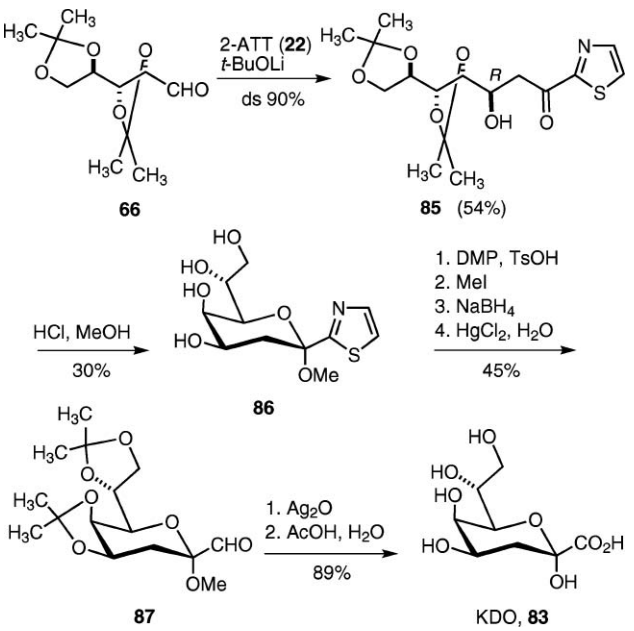


Fig. 4 Some common naturally occurring 3-deoxy-2-ulosonic acids.

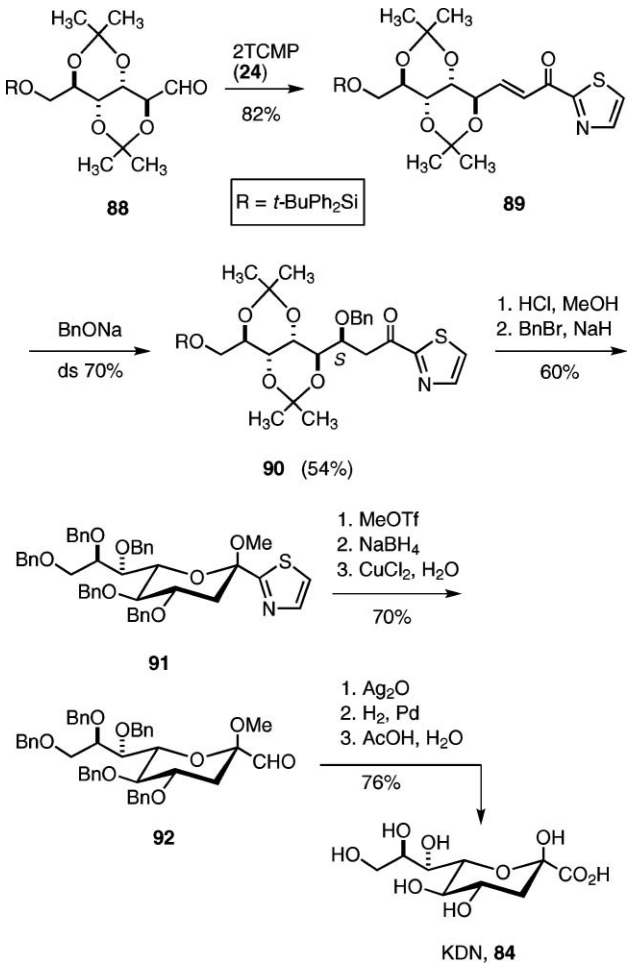


Scheme 12 Synthesis of KDO **83** from *aldehydo*-D-arabinose diacetonide **66** by means of 2-acetylthiazole **22**.

out to be complementary for achieving a full control of the configuration at C4 in the target product. For example, a concise synthesis of KDO **83** was performed[40] by *anti*-diastereoselective addition of the lithium enolate of 2-ATT **22** to the *aldehydo*-D-arabinose diacetonide **66** to give the *R*-configured β-hydroxy ketone **85** (Scheme 12). From this key intermediate, the synthesis proceeded by a further three steps, namely intramolecular hemiketalization, thiazole-to-formyl conversion and oxidation of the aldosulose **87** to the target KDO **83**.

On the other hand the total synthesis of KDN **84** was performed[41] by the use of the stabilized phosphorane 2-TCMP **24**. This reagent transformed the protected *aldehydo*-D-mannose **88** into the α,β-enone **89** which in turn underwent a *syn*-diastereoselective Michael addition of benzyloxide anion to give the *S*-configured alkoxy ketone **90** (Scheme 13). This compound represented a masked form of KDN **84**. Indeed, the synthesis was completed just by functional group manipulation, i. e.: a) hemiketalization to give **91**, b) formyl group unmasking to give aldosulose **92**, and c) formyl group oxidation to give the target nonulosonic acid KDN **84**.

The scope of the 2-TCMP-based synthesis of ulosonic acids was broadened by using nitrogenated nucleophiles in the Michael addition step. Following this approach the synthesis of the previously unreported 4-acetamido-3,4-dideoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid (iso-Neu4Ac, **100**), a positional isomer of Neu5Ac **74**, was performed[42] (Scheme 14). Given the essential role of **74** in the biological activity of various glycoconjugates, some

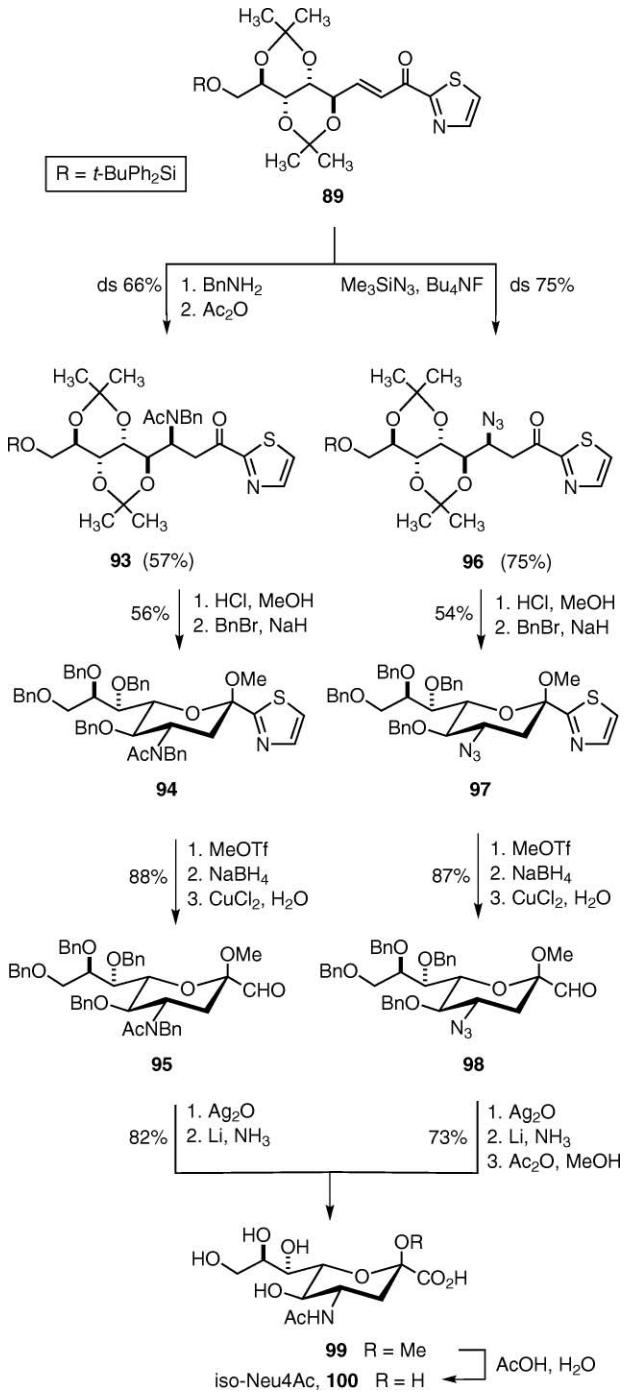


Scheme 13 Synthesis of KDN **84** from *aldehydo*-D-mannose **88** by means of thiazolyl phosphorane **24**.

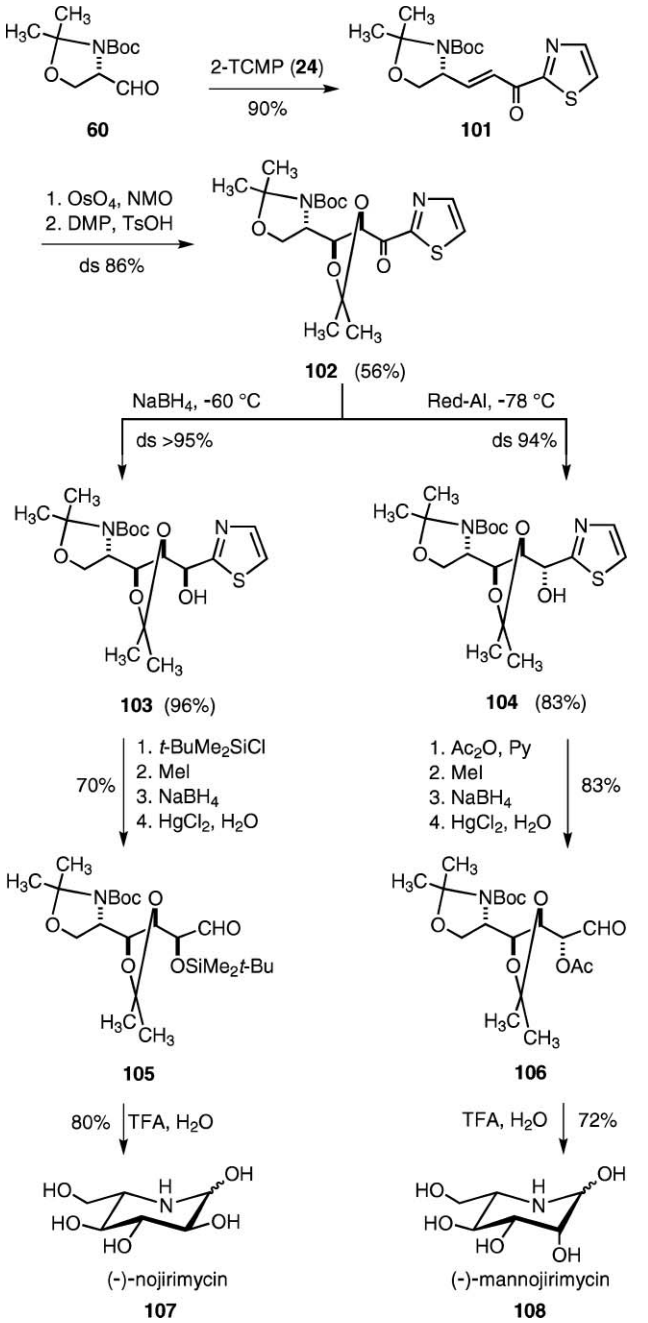
of which are detrimental to living organisms, it was important to prepare sialic acid analogues as potential inhibitors. The synthesis of iso-Neu4Ac **100** was approached by two different routes employing benzylamine ($BnNH_2$) and trimethylsilyl azide (Me_3SiN_3) as nitrogen nucleophiles reacting with the α,β-enone **89**. This starting compound was obtained as shown in Scheme 13 *via* olefination of protected D-mannose **88** by the phosphorane 2-TCMP **24**. The 1,4-conjugate additions of $BnNH_2$ and Me_3SiN_3 to **89** were both moderately *syn*-selective. The benzylamine route, however, turned out to be scarcely efficient because of the difficulty of *N*-benzyl group removal in compound **95**. Therefore an impure sample of **100** was obtained by this route. Fortunately, a similar problem did not occur with the aldosulose **98** as the complete reduction of the azido group and acetylation of the amino group thus formed did not present any problem. Therefore a pure sample of **100** was prepared by this route.

Synthesis of iminosugars

These compounds, also referred to as azasugars, display a nitrogen atom in a polyhydroxylated n-carbon atom ring. Therefore most of them are polyhydroxylated pyrrolidines and piperidines. Iminosugars have attracted and still do attract great interest because of a remarkable activity as glycosidase inhibitors.[43] Consequently they have considerable medicinal potential as antiviral, antimetastatic, antibacterial, antiadhesive, and antihyperglycemic agents. Although some of them are natural products,[44] their synthesis has been pursued by numerous different approaches in the last three decades. Accordingly iminosugars did not escape our attention as targets *via* thiazole–aldehyde synthesis. Scheme 15 shows two stereodivergent routes[45] that starting from the well known protected serinal **60** led to the C2 epimer azahexoses nojirimycin **107** and mannojirimycin **108**. The key intermediate ketone **102** was prepared by two simple operations involving the Wittig



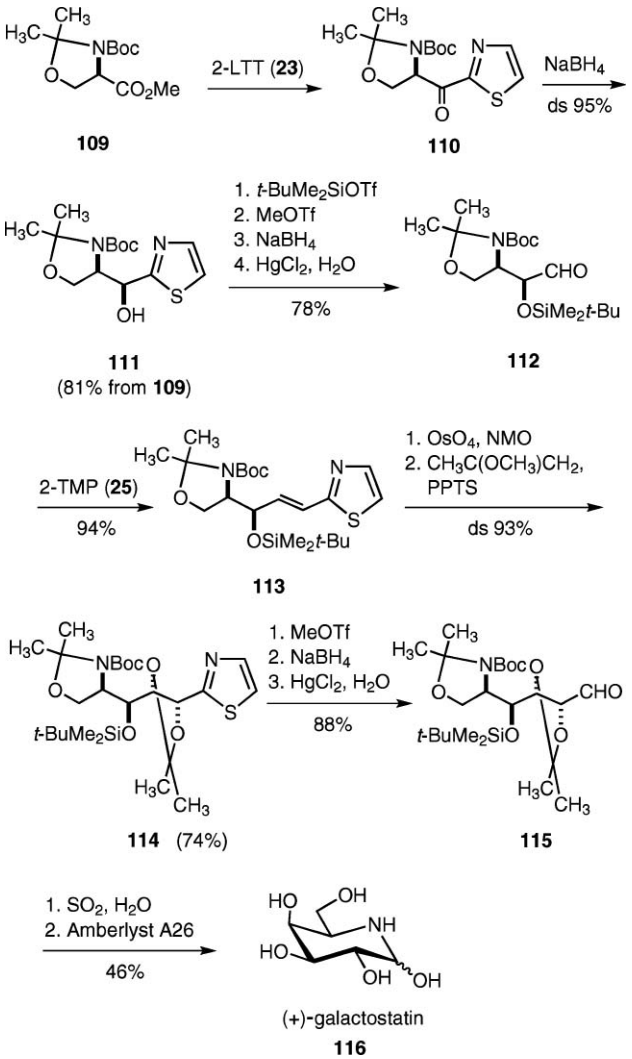
Scheme 14 Synthesis of iso-neuraminic acid iso-Neu4Ac **100** by means of thiazolyl phosphorane **24**.



Scheme 15 Synthesis of (–)-nojirimycin **107** and (–)-mannojirimycin **108** by means of phosphorane 2-TCMP **24**.

olefination of **60** by the phosphorane 2-TCMP **24**, followed by the *cis*-hydroxylation of the formed enone **101** by catalytic osmium tetroxide in the presence of *N*-methylmorpholine *N*-oxide as a reoxidant. The stereoselective reduction of ketone **102** with two different hydride releasing reagents such as $NaBH_4$ and Red-Al (sodium bis(2-methoxyethoxy)aluminiumhydride) furnished the alcohol **103** and the epimer **104**, respectively. The opposite stereochemical outcome of the carbonyl reduction of **102** was interpreted by different models of hydride transfer from the reducing agent to the carbonyl. Specifically, the sense of stereoselectivity from the $NaBH_4$ reduction was consistent with the open-chain Felkin–Anh model of asymmetric induction while that from the Red-Al reduction was explained by an α-chelate model resulting from the coordination of aluminium to alkoxy and carbonyl oxygens. The two iminosugars (–)-nojirimycin **107** and (–)-mannojirimycin **108** were obtained from the intermediates **103** and **104** by thiazole-to-formyl conversion and intramolecular hemiaminal formation. These products are the antipodes of the natural (+)-isomers which, however, can in principle be synthesized by the same versatile approach starting from the enantiomer of the aldehyde **60** which in turn can be prepared in a similar way from D-serine.

The synthesis of another naturally occurring azasugar, (+)-galactostatin **116** (Scheme 16) involved the use of two thiazole-based reagents in a sequence of two thiazole-to-aldehyde syntheses.[46] Given the recent isolation of **116** from natural sources,[47] only a few syntheses from carbohydrate precursors were available at the time of our work.[48] Our synthesis began with the reaction of the highly stable protected D-serine methyl ester **109** with lithio thiazole (2-LTT, **23**) to give the thiazolyl ketone **110**. The selective replacement of the methoxy group by thiazole in the ester **109** is noteworthy. In analogy to Chikashita's work with lithio benzothiazole,[49] it was suggested that the stabilization of the ketone **110** as a lithium complex avoided the formation of a



Scheme 16 Synthesis of (+)-galactostatin **116** by means of 2-lithiothiazole **23** and thiazolyl phosphorane **25**.

bis-adduct arising from the addition of **23** to the carbonyl. The highly stereoselective reduction of ketone **110** by $NaBH_4$ afforded the alcohol **111** from which the aldehyde **112** was liberated by the thiazole-to-formyl protocol. The second thiazole-to-aldehyde synthesis involved the olefination of the aldehyde **112** by the thiazolyl phosphorane **25** followed by a *cis*-hydroxylation of the *E*-alkene **113** thus formed to give the thiazole derivative **114**. Application of the standard thiazole-to-formyl unmasking protocol to the latter intermediate afforded the aldehyde **115** from which the target iminosugar (+)-galactostatin **116** was obtained by the intramolecular hemiaminal formation that followed the *O*- and *N*-protecting group removal.

The thiazole–aldehyde synthesis enabled us to prepare a special class of azasugars displaying a hydroxymethyl group at the anomeric position. These one-carbon higher homologues of the natural azasugars are known as homoazasugars or aza-*C*-glycosides.[50] Homoazasugars have attract great attention because they have been found to retain the same type of biological activity of the parent azasugars while exhibiting higher selectivity and potency. Moreover, they have great stability toward chemical and enzymatic degradation, a drawback of the parent azasugars due to the labile *O*,*N*-acetal function. Typical compounds **117**–**119** of the pyrrolidine family that have been prepared in our laboratory[51] are shown in Fig. 5 while the synthesis of one of them is described in Scheme 17. This consisted of the above mentioned thiazole-based aminohomologation route starting from the per-benzylated D-arabinofuranose **123**. This aldose was transformed into the nitrone **125** from which the formyl aza-*C*-glycoside **128** was obtained *via* one carbon-chain elongation by 2-LTT **23**, intramolecular nucleophilic substitution, and thiazole-to-formyl conversion. Reduction of the formyl group of **128** afforded the target pyrrolidine homoazasugar **129** (2,5-dideoxy-2,5-imino-D-glucitol). The scope of this strategy was broadened by the synthesis of homoazasugars **120**–**122** of the piperidine family starting from pyranoses[52] (Fig. 5). In this case the key process consisting of the introduction of the thiazole fragment into the masked nitrone intermediate was effectively accomplished by the use of 2-thiazolylmagnesium bromide **20** instead of 2-LTT **23**.

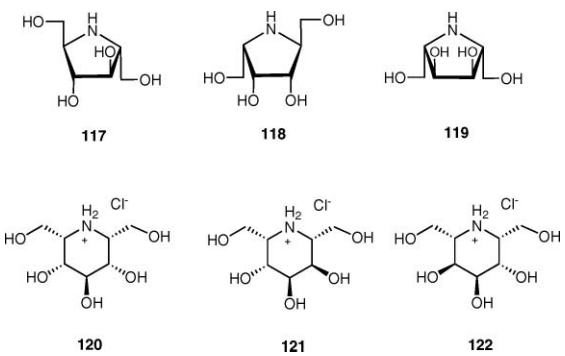
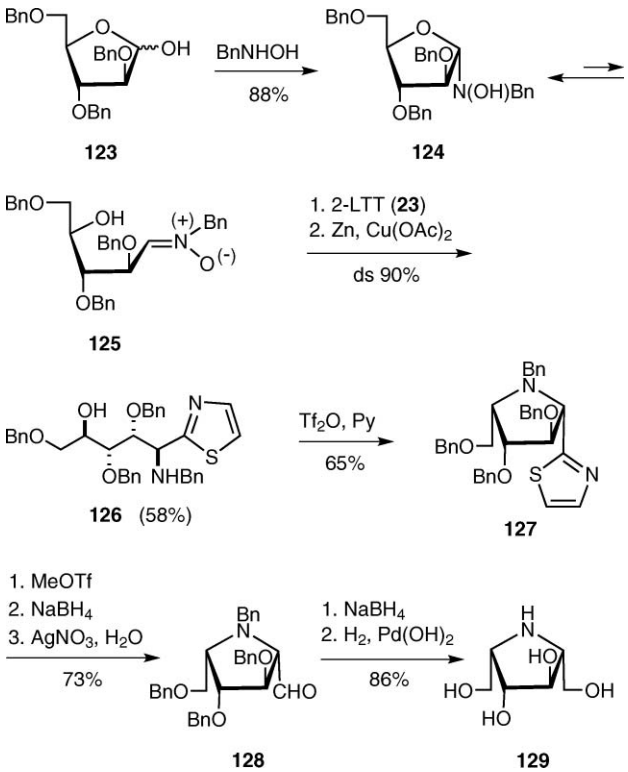


Fig. 5 Typical homoazasugars of the pyrrolidine and piperidine families.

Synthesis of the C13 side-chain of taxol and taxotere®

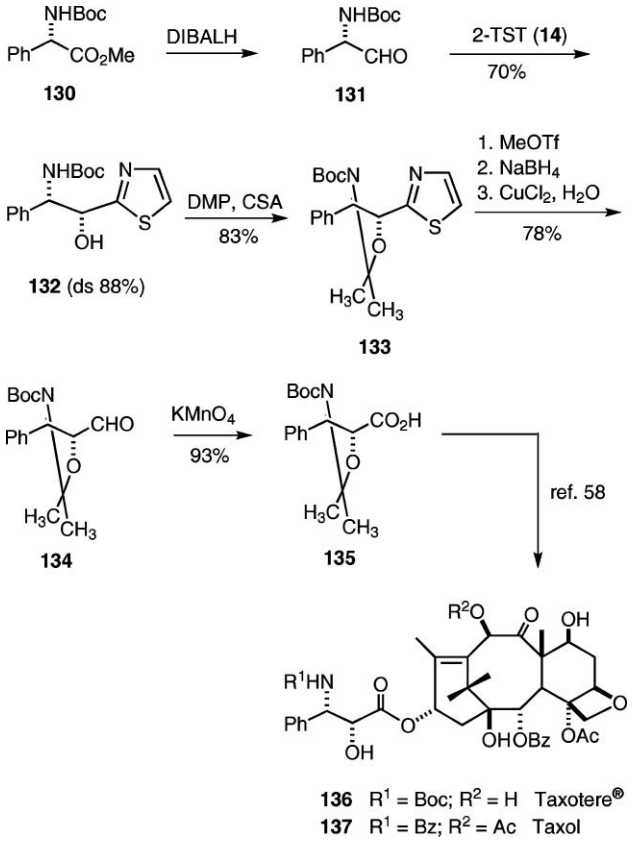
As shown in previous schemes the thiazole–aldehyde synthesis can be followed by an oxidative process to give a carboxylic acid. This synthetic potential was conveniently exploited in our laboratory for the preparation of a simple yet very important β-amino-α-hydroxy acid[53] such as the protected 3-phenylisoserine **135** (Scheme 18). This compound (Boc = *t*-BuOCO) and the *N*-Bz derivative (Bz = C_6H_5CO) constitute the C13 side chains of taxotere®[54] **136** and natural product taxol[55] **137**, respectively. The highly promising therapeutic application of taxol and taxotere® as anticancer agents and the limited availability of the former from natural sources have stimulated in the second half of the last century the development of semisynthetic routes to these compounds employing baccatin III and 3-phenylisoserine as building blocks. Hence, various syntheses of this amino acid have been reported.[53,56] Our thiazole-based synthesis consisted of the one-carbon chain elongation of the *N*-Boc phenylglycine derived aldehyde **131** using 2-(trimethylsilyl)thiazole **14** as a formyl anion equivalent. As expected on the basis of previous work from our laboratory,[57] the addition of **14** to the *N*-monoprotected α-amino aldehyde **131** was *syn*-selective, thus providing the amino alcohol **132** with the desired *R*-configuration at C1. Next, **132** was transformed into the acetonide derivative **133** and this was subjected to thiazole-to-formyl conversion to give the chiral β-amino-α-hydroxy aldehyde **134**. Oxidation of **134** under neutral conditions afforded the target carboxylic acid **135** in good enantiomeric purity (90%). In a similar way was the *N*-Bz derivative (not shown) prepared starting from *N*-Bz phenylglycine. The coupling of **135** with suitable baccatin III derivatives was reported[58] by Commerçon and co-workers in a semisynthetic route to both taxol and taxotere.®



Scheme 17 Model synthesis of the homoazasugar **129** *via* aminohomologation of D-arabinose **123**.

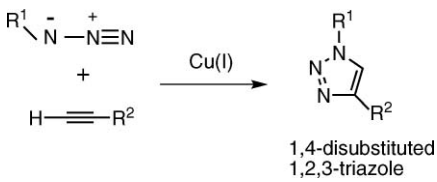
Triazole as a molecular keystone

The main objective of organic synthesis deals with the assembly of molecular fragments by robust connectors to give target molecular



Scheme 18 Synthesis of 3-phenylisoserine derivative **135**.

architectures. In a figurative manner, the linkers can be viewed as chemical keystones because they lock two separate residues in a stable single construction. It is in this context that the formation of the 1,2,3-triazole ring as a ligation tool in new synthetic methods has met with great success. In a few years this highly nitrogenated five-membered heterocycle which in the past attracted little attention, very likely because of the lack of convenient access to each disubstituted regioisomers, gained great popularity among many researchers. Two main aspects have to be mentioned. The triazole ring is endowed with great chemical stability under a variety of reaction conditions and over all 1,4-disubstituted derivatives can be constructed by one of the most efficient coupling reactions so far discovered such as the Cu(I)-catalyzed cycloaddition of azides with terminal alkynes[59] (Scheme 19). This reaction is so well performing that it is considered the quintessential of a "click process" as defined by Sharpless and his colleagues in 2001.[60] Actually, the copper catalyzed azide–alkyne cycloaddition (CuAAC) represents a substantial improvement of the thermal process that was included by Rolf Huisgen in early 1960s in the rich class of concerted 1,3-dipolar cycloadditions.[61] While the thermal process was almost



Scheme 19 The Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC).

neglected because of the low efficiency and lack of selectivity, the numerous applications of CuAAC (about one thousand so far)[62] in the most disparate fields of chemistry, biology, and material science highlight the great impact that this new methodology is having in modern basic and applied research. In fact, the chemoselectivity of CuAAC, i.e. the selective reactivity of azides and alkynes only with each other, and the absence of the azido and ethynyl groups in biological systems have made this reaction one of the most convenient bioorthogonal ligation tools for biological studies and medicinal applications.[63] We have exploited the fortunate event combining the high efficiency of the CuAAC with the stability of the triazole ring thus formed, in the context of our research interest in carbohydrate chemistry and I will describe below the main achievements of our synthetic endeavours. We and others, moreover, have previously reported extended accounts on the applications of the CuAAC in carbohydrate chemistry.[64]

Synthesis of non-natural *C*-glycosyl amino acids

As more than 50% of proteins in all eukaryotes are glycosylated, modern glycomics is posing a great demand for synthetic glycopeptide mimics with a well defined structure and composition. These unnatural compounds can serve both as probes in studies of carbohydrate-based metabolic processes or as potential leads in new drug discovery. A simple yet important modification of unnatural glycopeptides consists of the attachment of the carbohydrate residues to the peptide chain by chemical and enzyme resistant carbon–carbon or carbon–sulfur anomeric bonds.[65] This structural feature can be introduced by a co-translational peptide modification using carbon- and sulfur-linked glycosyl amino acids as building blocks.[66] Hence, given our earlier synthetic approaches to non-natural glycosyl amino acids[67] (Fig. 6), we set out to develop a research program based on the idea of assembling carbon-linked glycosyl amino acids through the efficient formation of nitrogenated heterocyclic rings.[68] Among the various approaches that were envisaged toward this goal, the formation of the triazole ring *via* click chemistry was the first to be successfully employed. Thus, the regioselective 1,4-disubstituted triazole formation by the Cu(I)-catalyzed cycloaddition of the ethynyl glucoside **138** with the azido alaninate **139** furnished the triazole-tethered *C*-glucosyl amino ester **141** (Scheme 20).[69] On the other hand the regioisomer **140** featuring the 1,5-disubstituted triazole ring as a tether was obtained as the sole product by using a Ru complex as a catalyst[68] according to Fokin and co-worker's recent studies.[70] Similar results, *i.e.* high yields and regioselectivity, were obtained using an ethynyl galactoside as cycloaddition partner. The use of these amino acids for the synthesis of glycopeptides is noteworthy because the triazole ring can act not only as a robust linker but also as a site of interaction with biological targets through hydrogen bonding and dipolar interactions. For these reasons the preparation of the 1,4- and 1,5-disubstituted regioisomers was quite important because the different substitution pattern of the triazole ring constitutes an element of diversity that may be crucial in molecular recognition processes.

Synthesis of potential antisense oligonucleotides

While deoxyribonucleic acid (DNA) is the genetic code which ensures that daughter cells inherit the same characteristics as the

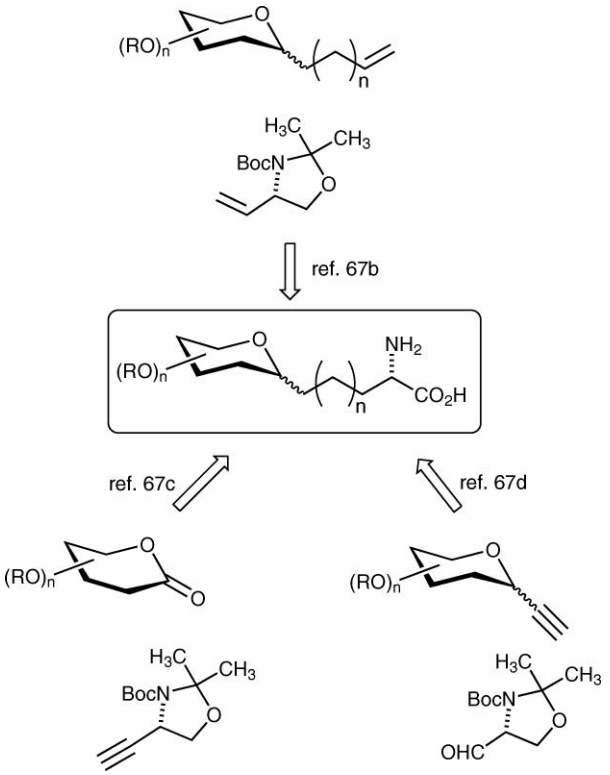
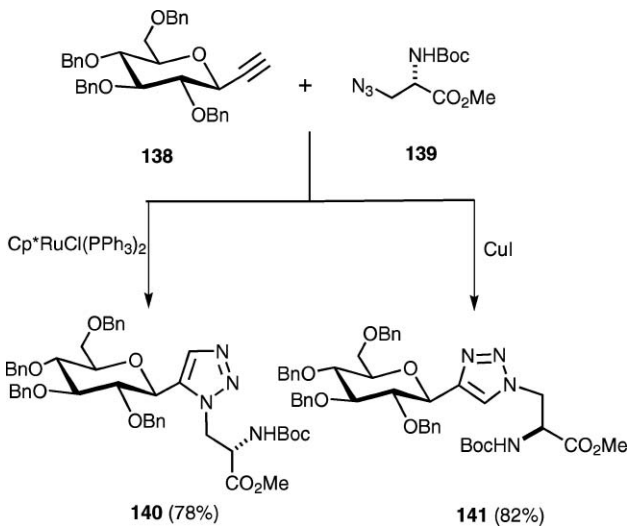


Fig. 6 Earlier approaches to *C*-glycosyl α-amino acids from the Dondoni laboratory.



Scheme 20 Catalyst-controlled regioselective azide-alkyne cycloadditions.

parent cells, natural oligonucleotides can be hardly used for the development of potential drugs because of the low stability toward cellular nucleases due to the easy cleavage of the phosphodiester group and poor cell penetration. For these reasons intense research has been carried out especially in pharmaceutical company laboratories to develop synthetic oligodeoxyribonucleotides in which non-natural internucleoside linkages replace the native phosphodiester group (Fig. 7). The great interest in these non-natural nucleotides stemmed from the Zamecnik and Stephenson discovery in the late 1970s on the antisense effect of a synthetic

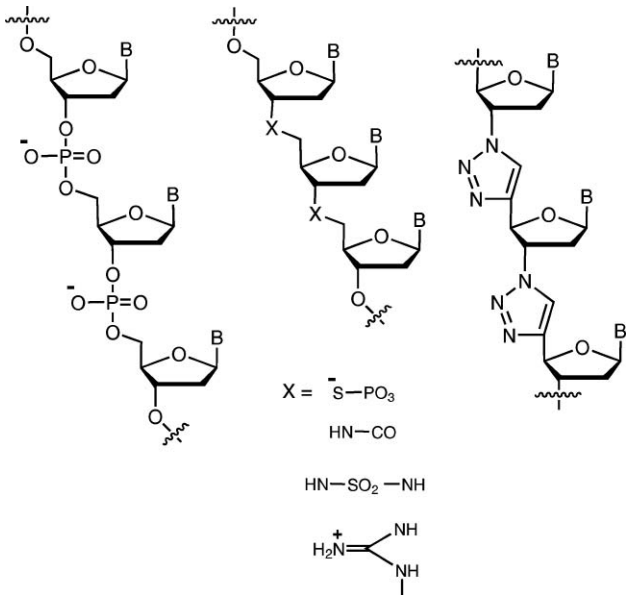
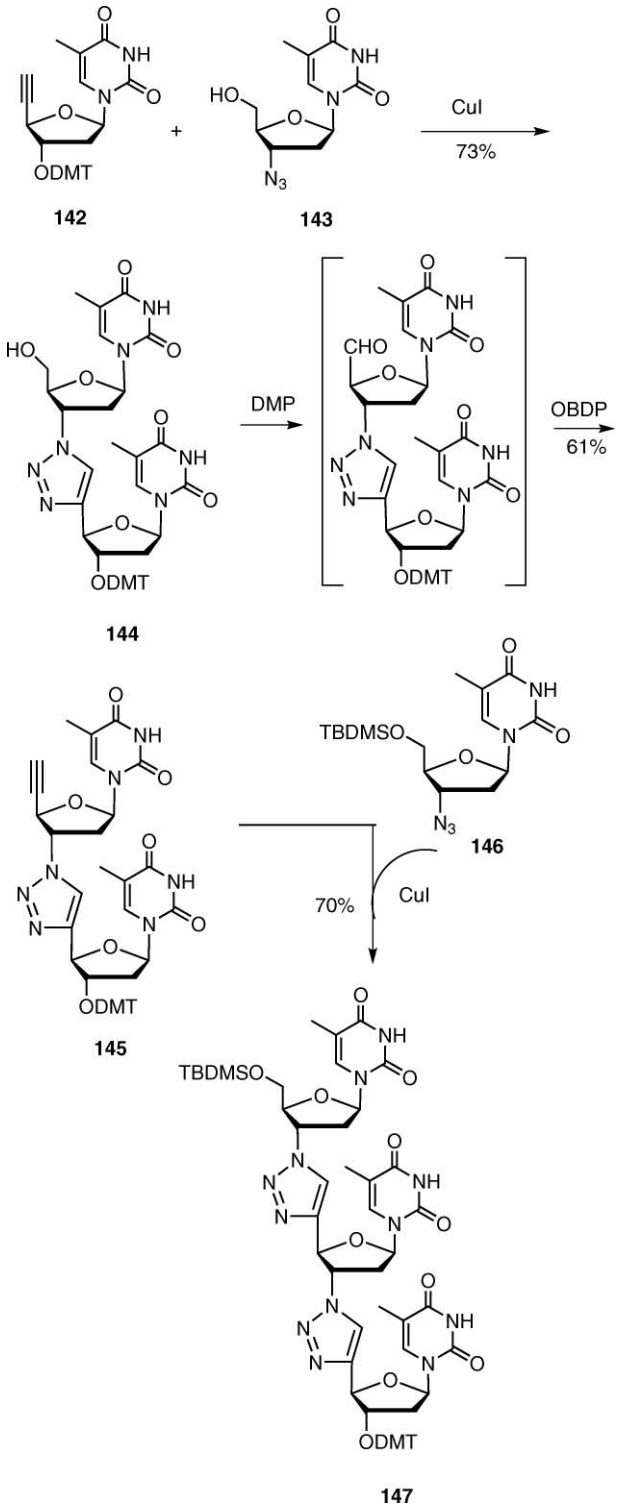


Fig. 7 Natural (left) and non-natural (center) oligodeoxyribonucleotides as well as target triazole-linked derivatives (right).

oligonucleotide sequence that inhibited viral replication in cell culture.[71] The use of antisense agents is a topic of intense research because they can, in principle, act as inhibitors of any deleterious genes (gene silencing) whose expression is responsible for a variety of diseases such as cancer growth, viral infection, inflammation. In this context nucleotides featuring various azoles (isoxazole and isoxazoline,[72] tetrazole,[73] and triazole[74]) have been prepared. Both 1,4- and 1,5-disubstitued triazole-linked nucleotides have been considered of special interest because the triazole ring constitutes a tether between the two deoxyribose fragments of comparable length to that of natural products. Moreover the presence of triazole as a densely nitrogenated heterocyle may allow to evaluate the influence of polarity and/or basicity of the modified backbone structure on RNA binding affinity. As only triazole-linked thymidine dinucleotides have been prepared, most of which before the discovery of the click CuAAC, we have developed a linear iterative methodology based on the formation of the triazole ring *via* CuAAC chemistry for the production of higher oligomers.[75]

As shown in Scheme 21 the initial Cu-catalyzed coupling reaction was carried out between the 5′-ethynylnucleoside **142** and the commercially available 3′-azidonucleoside AZT **143**. In this way only the 1,4-disubstituted triazole ring was formed as the interglycosidic linker in the thymidine dinucleotide **144** thus obtained. The protection of the 3′-hydroxyl group of the latter as 4,4′-dimethoxytrityl (DMT) derivative was introduced in view of the insertion of the oligomers thus prepared in more complex DNA strands by the standard automatic oligonucleotide synthesis. In order to perform the second CuAAC, the ethynyl group was introduced into the dinucleotide **144** by one-pot oxidation of the free primary alcohol to aldehyde by Dess–Martin periodinane (DMP) and ethynylation by the Ohira–Bestmann diazophosphonate (OBDP). The alkyne **145** thus formed reacted with the azidonucleoside **146** in the presence of CuI to give the target thymidine trinucleotide **147**. It is worth noting that the 5′-hydroxyl in this product was protected as the *tert*-butyldiphenylsilyl



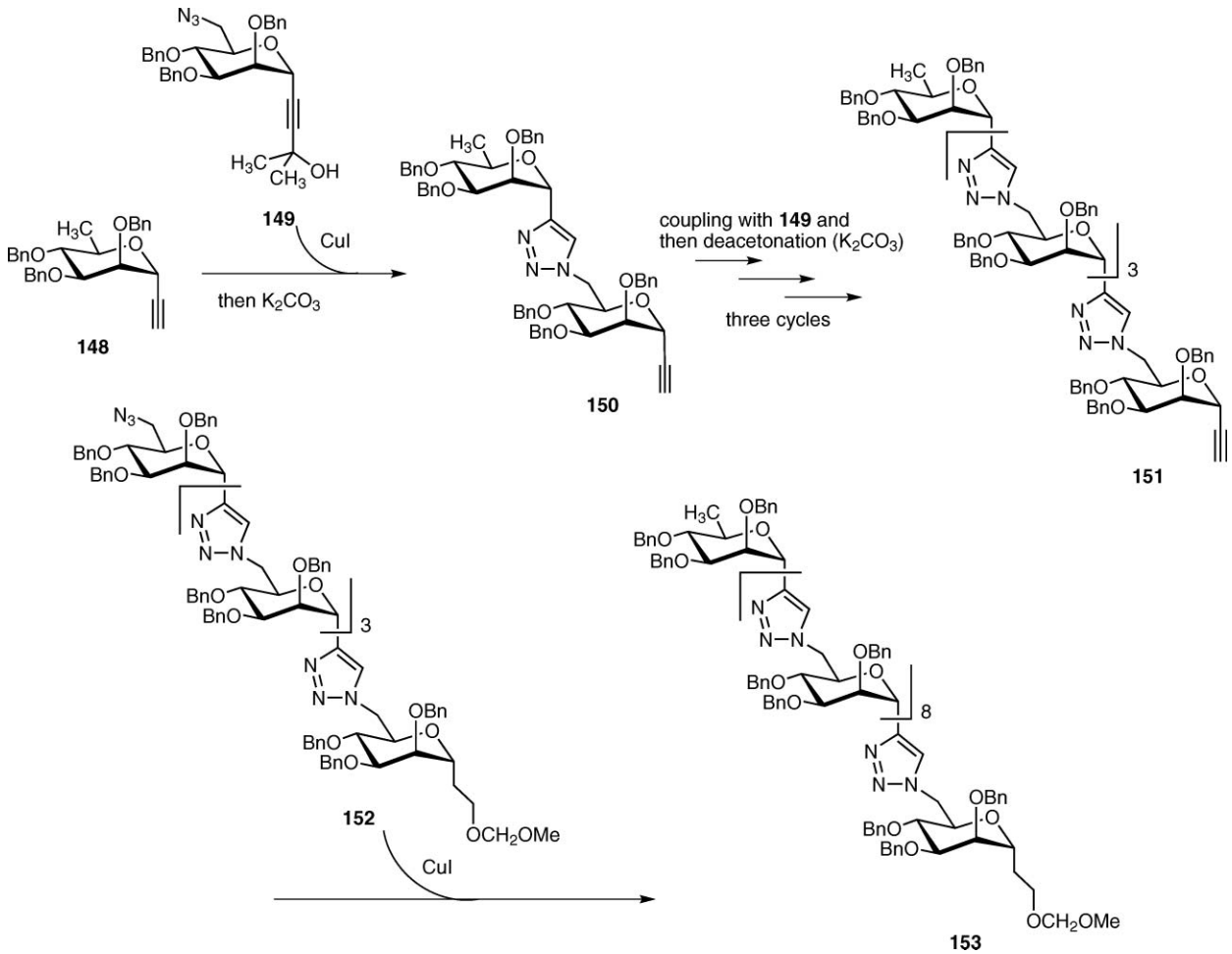
Scheme 21 Synthesis of triazole-linked thymidine dinucleotide **144** and trinucleotide **147** *via* iterative azide–alkyne cycloaddition.

(TBDPS) derivative to facilitate the isolation procedure. Moreover this orthogonal protection strategy enabled chemoselective transformations to be carried out toward the preparation of DNA chimeric oligonucleotides. Thus, one and two units of T-triazole-T **144** were introduced in a natural oligonucleotide T_{12} and the Tms (Tm corresponds to the temperature at which half of the strand is in a double strand and half as a single strand) with a complementary $C_2A_{12}C_2$ sequence were determined.[76] As a decrease in stability of 10 °C per modification was observed, it appeared that these hybrids cannot be used for antisense strategy. It is suggested that the additive destabilization of these duplexes is due to the fact that the triazole tether features one atom less that the native phosphodiester linkage, thus yielding an unfavourable constraint into the duplexes.

Synthesis of triazole-linked 1,6-α-D-oligomannosides

The recrudescence of tuberculosis (TB) in many parts of the world, including Western countries,[77] and the widespread antibiotic resistance have strengthened the need for rapid development of new antitubercular drugs targeting essential functions of its etiological agent, *Mycobacterium tuberculosis* (Mtb). As this bacterium invades and colonizes macrophage cells, its ability to survive within this inhospitable environment has been attributed to its robust cell wall.[78] Therefore an ideal TB drug target is the biosynthesis of the mycobacterial cell envelope. This is composed of various glycophospholipids[79] such as phosphatidylinositol mannosides (PIMs)[80] that in addition to being important in their own right may also be hyperglycosylated to form other wall components such as lipomannans (LMs) and lipoarabinomannans (LAMs).[81] These glycolipids all contain a common α-1,6-linked mannoside core as shown, for example, in LM (Fig. 8). Synthetic approaches to oligomannan fragments of the Mtb cell wall have been reported in various instances.[82] On the other hand, in order to avoid the construction of these high mannoside residues promoted by the abundant α-1,6-mannosyltransferases in mycobacteria, Watt and Williams prepared a series of hydrophobic octyl 6-deoxy α-1,6-linked oligomannosides up to a tetramer *via* iterative glycosylation.[83] The rationale behind this synthetic effort was that deoxygenation of the 6-position of the oligomannosyl chain should prevent these compounds acting as substrates for the α-1,6-mannosyltransferases. Oligomannosides prepared by Watt and Williams featured the natural *O*-glycosidic anomeric linkage and therefore were prone to undergo a facile cleavage by hydrolases. Moreover the chain lengths of these compounds might be too short for an efficient mimicry of the oligomannoside chains of LMs and LAMs. Hence we developed a new approach to more stable 6-deoxy 1,6-α-D-oligomannosides featuring robust anomeric carbon–carbon bonds and inert 1,4-disubstituted triazole rings as interglycosidic linkers (Fig. 8). We thought that also in these compounds the triazole ring could play an additional role as it can participate in hydrogen-bonding and dipole interactions, thereby favoring molecular recognition processes and improving solubility.[84]

We planned the preparation of mannose–triazole hybrids by a linear oligomerization strategy based on the construction of the triazole ring by iterative click CuAAC. After an initial exploratory work demonstrating the feasibility of our program,[85] we carried out the synthesis of the triazole-tethered oligomannosides shown in Fig. 8 in the following way[86] (Scheme 22). The first cycle involved the CuI-catalyzed cycloaddition between ethynyl 6-deoxymannoside **148** and 6-azidomannoside **149**. The latter featured a protected ethynyl group as a formal adduct to acetone. The coupling product was subjected to acetone removal to give the triazole-linked dimannoside **150** featuring the free ethynyl group.



Scheme 22 Synthesis of triazole-linked decamannoside **153** by iterative CuAAC.

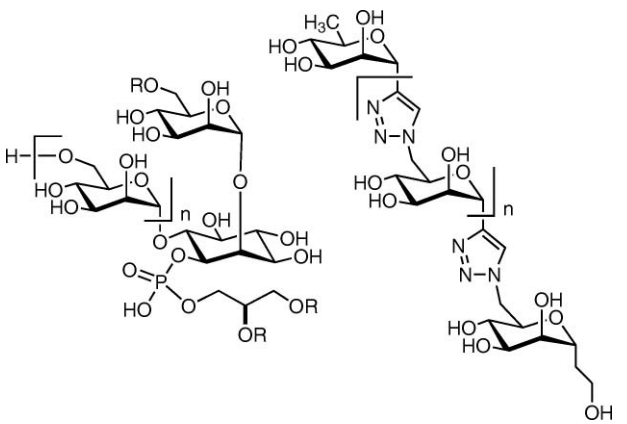


Fig. 8 Structures of lipomannan (LM) of Mtb cell wall (left) and designed triazole-tethered oligomannoside (right) featuring a capping 6-deoxymannose fragment.

Starting from this oligomer, the repetition of the two operations detailed above (cycloaddition with **149** and deacetonation) over three more consecutive cycles afforded the pentamannoside **151**. At this stage the synthesis of a decamannoside was pursued by a convergent approach. To this end the pentamannoside **151** exhibiting a terminal ethynyl group was reacted with the azide-functionalized oligomer **152** which was obtained by a simple manipulation of the triazole-linked pentamannoside that was earlier prepared in our laboratory.[85] The fidelity of the CuAAC was confirmed in this operation as well so that the decamannoside **153** was obtained in a rewarding isolated yield of 93%. The benzyl groups of **153** were removed to give compound **154** suitable for testing against Mbt cell wall biosynthesis (Fig. 9). Moreover, as cell-wall constituents of Mbt possess high oligomannose cores constituted of *ca.* 20 sugar units, in order to mimic such a structural feature, we have also synthesized the triazole-linked hexadecamannoside **155** (Fig. 9) by a convergent oligomerization strategy based on the CuAAC chemistry as well.[87] Competitive inhibition tests were performed with these compounds using the Besra protocol.[88] To our great delight these experiments showed that both oligomers at two different concentrations (1 and 2 mM) interrupted the biosynthetic mannosylation pathway of a model oligomannoside, thus indicating that both compounds acted as inhibitors of 1,6-mannosyltransferase catalyst.

Synthesis of triazole-linked glycocluters on calix[4]arene scaffolds

The high synthetic value of triazole as a linker, combining the ease of formation with good chemical stability, was exploited in our laboratory for the synthesis of a special class of biomolecules

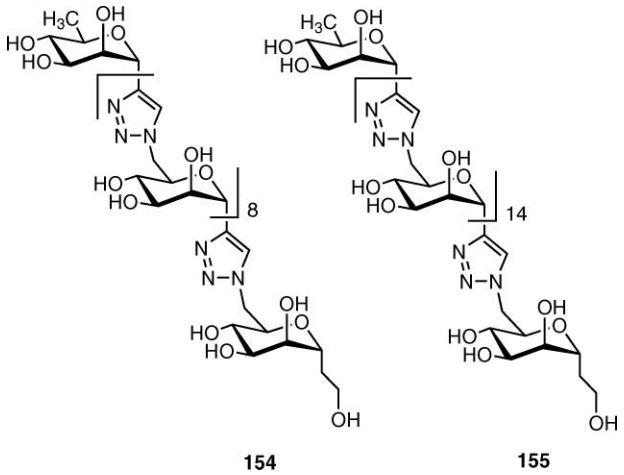
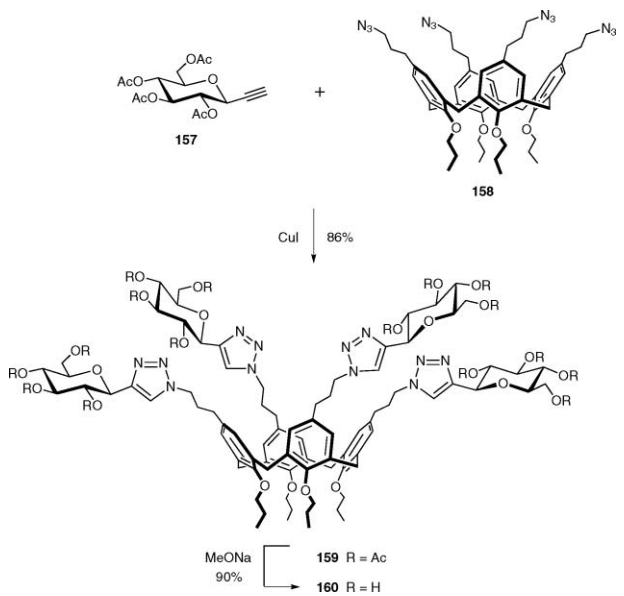


Fig. 9 Triazole-linked oligomannosides that acted as inhibitors of 1.6-mannosyltransferase.

such as calix[4]arene glycoconjugates (calixsugars). When these hybrid compounds are constituted of more than one carbohydrate residue, they can be viewed as glycoclusters anchored on a conformationally rigidified platform. It derives that these systems are interesting substrates for the assessment of the so-called glycoside cluster effect[89] in, for example, carbohydrate–protein interaction. The existence of such an effect relies on the observation that when a set of multivalent saccharides are clustered together with the right structure and spatial disposition, the association to a protein becomes stronger than would be expected on the basis of the increased carbohydrate local concentration. While various kind of approaches have been used for the preparation of calix[4]arene-based glycoclusters,[90] the approach relying on the triazole ring formation *via* CuAAC is very likely to be the most suitable for simplicity of execution and robustness of the tether thus formed. The synthesis of one of these glycoconjugates *via* CuAAC chemistry[91] is presented in Scheme 23. The tetra-azidopropyl calix[4]arene **158** and the ethynyl *C*-glucoside **157** were selected



Scheme 23 Synthesis of calix[4]arene-based glycocluster **160** *via* CuAAC.

as cycloaddition partners. Notably, the latter reagent featured an anomeric carbon–carbon bond in order to establish this robust linkage in the target glycoconjugate. Given the tetravalency of the azidocalix[4]arene **158**, this platform was expected to undergo four concomitant cycloadditions with the alkyne **157**. To this aim two equivalents of the latter per azido group of the former were employed. Thus, the CuI-catalyzed cycloaddition of these reagents afforded the expected calix[4]arene-based tetravalent *C*-glycocluster **159** featuring the triazole ring as a tether. The excellent yield (86%) of this isolated product indicated that each azido group of calix[4]arene **158** reacted with the sugar alkyne **157** in nearly quantitative manner. Moreover, the absence of products arising from partial coupling of the sugar acetylene with the macrocycle suggested that once the first triazole ring was formed, subsequent coupling reactions occurred much more readily, very likely due to the formation of Cu(I)-triazolide–ethynyl complexes. Finally, the easily removable *O*-acetyl groups by transesterification was key to the transformation of calixsugar **159** into the deprotected derivative **160** suitable for bioassays.

Calixsugar–oligonucleotide hybrids were prepared with the aim of evaluating their affinity to galactose recognizing lectins.[92] Compound **161** shown in Fig. 10 is an example of these hybrid molecules. This displayed two calixarene-based galactoclusters linked to an oligonucleotide chain. The key role of triazole rings as molecular keystones in various sectors of this complex molecular architecture is quite significant. Binding tests of **161** with *Pseudomonas aeruginosa* lectin (PA-IL) and *Ricinus communis* agglutinin (RCA 120) were carried out. IC_{50} values, *i.e.* the concentration of lactose required for the removal of 50% of RCA 120 bound to the immobilized glycoconjugates, were determined and compared with those obtained for linear monovalent and trivalent galactoside conjugates. These tests showed that the affinity per galactose residue of **161** to RCA 120 was only five and seven times higher than that of the monovalent conjugate. The lack of a substantial glycoside cluster effect was attributed to the absence of a suitable spatial arrangement of the glycoclusters.

Triazole-linked sialylated calix[4]arenes were prepared *via* CuAAC with the aim of obtaining efficient antiviral agents. It is in fact well known that sialic acids, due to their peculiar position within cell-surface glycoproteins and glycolipids, are exposed to the external environment and involved in numerous physiological and pathological recognition phenomena such as adhesion of bacteria and viruses to human cells. In fact single-stranded RNA viruses, such as the influenza A type virus that is responsible for annual flu epidemics in humans, carry a surface glycoprotein called hemagglutinin that recognizes sialic acid. In this way the hemagglutinin mediates the adhesion of the virus to the cell. This primary event is followed by the fusion of viral and cell membranes. Similar adhesion phenomena occur with the BK virus, a human polyomavirus known to be the etiological agent of a severe form of nephropathy. Therefore, designed molecules that bind more strongly than the natural ligands to these viruses can be, in principle, good antiviral agents. Based on these simple arguments we expected that multivalent sialoclusters anchored to the rigidified calix[4]arene platform could interact efficiently with viral lectins and, hopefully, display a glycoside cluster effect.[89] As a proof-of-principle, we prepared the tetra- and octavalent sialoside clusters **162** and **163** (Fig. 11) *via* multiple Cu(I)-catalyzed cycloaddition of *S*-propargyl sialoside

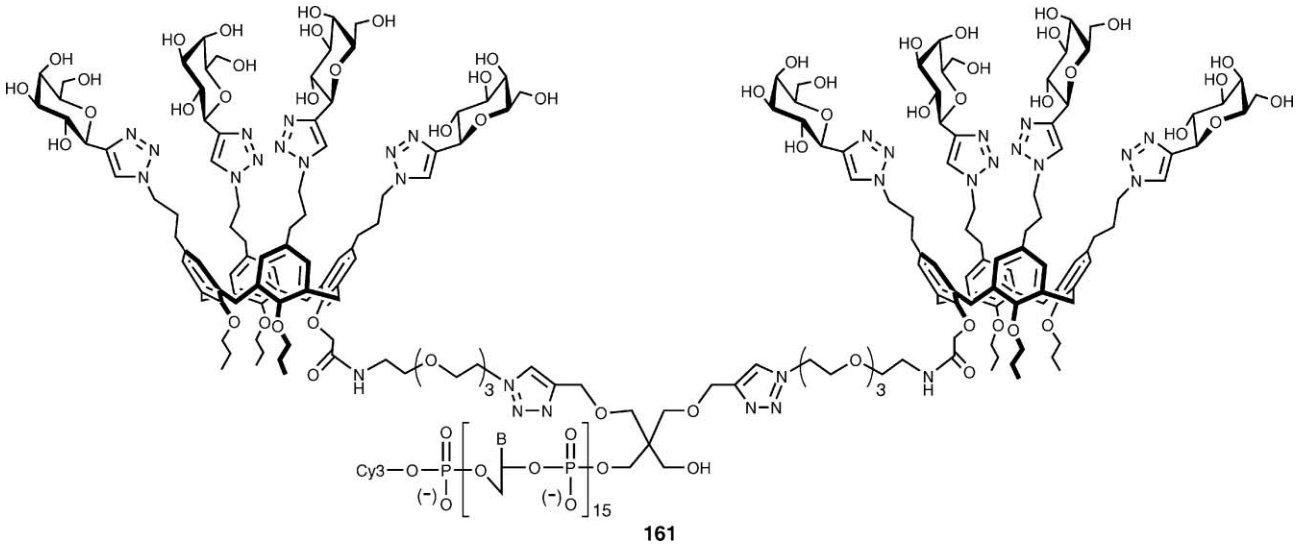


Fig. 10 Structure of a multivalent calixsugar–oligonucleotide hybrid for lectin recognition.

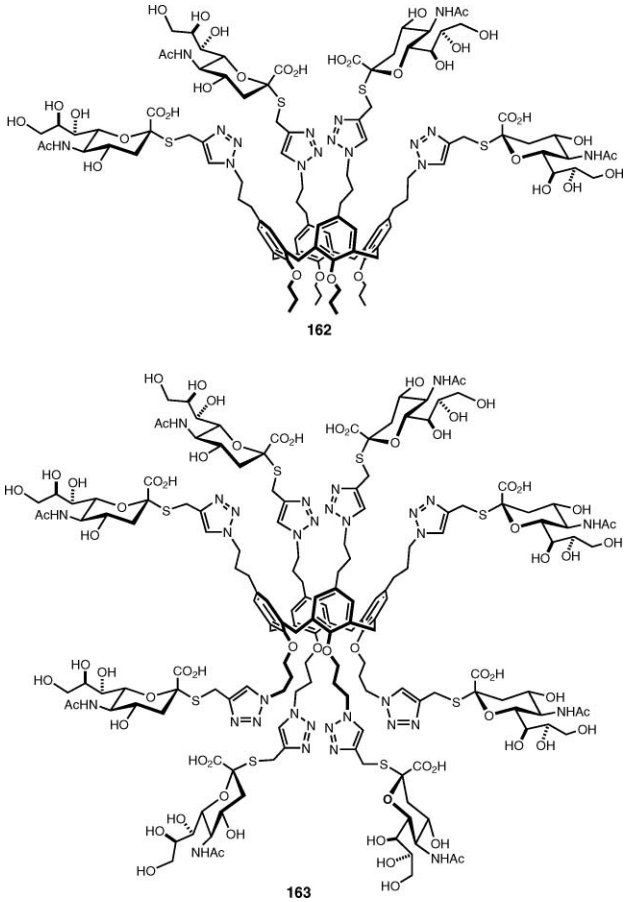


Fig. 11 Tetra- and octavalent sialoside clusters prepared.

with tetra- and octaazidated calix[4]arenes.[93] Notably the clustered sialyl residues in these compounds all featured a C–S bond at the anomeric position, thus providing high stability toward enzymatic degradation. Of course the presence of triazole rings locking the sugars to the macrocyclic platform rigidified in the cone conformation contributed to establishing an ordered architecture. It is also worth noting that compound **163** featuring sialoside clusters at both sides of the calix[4]arene cavity could, in principle, bind simultaneously to a couple of lectins located onto a single viron or two distinct viral particles. Hence compounds **162** and **163** were tested for their capabilities to bind BK and influenza A viruses using the hemagglutination inhibition assay. In both cases the compounds appeared to exhibit inhibitor activity at submillimolar concentrations while a moderate glycoside cluster effect was observed with both compounds **162** and **163**. The activity of the latter was close to that of the former, indicating that only one of the two sets of sialic acid units linked at both calixarene rims was involved in the interaction with the viral hemagglutinin. Nevertheless, in order to further assess the ability of these sialosides to bind the above viruses, neutralization assays of virus infectivity were performed by determination of the cytopathic effect (CPE). It was observed that CPE was present in cells infected with the viruses while it was absent when the same cultures were pretreated with the above sialoside clusters.

The valuable service of the triazole ring as a linker was further demonstrated in the construction of a tetravalent sialoside cluster immobilized on TiO_2 nanoparticles (Fig. 12).[94] Glyconanoparticles are of special relevance in glycobiology because they constitute a good biomimetic model of carbohydrate presentation at the cell surface. The direct installation of sialyl residues on the TiO_2 surface appeared to us a very difficult task. On the other hand the construction of the simple yet attractive architecture shown in Fig. 12 appeared more feasible. The orthogonally functionalized calix[4]arene unit displaying azido and carboxyl groups at the upper and lower rim, respectively, served as an ideal platform. It acted as a tetrapodal ligand for anchoring on the TiO_2 surface through the carboxyl groups while it exposed on the other side the azido groups for the installation of the four sialyl fragments *via* CuAAC chemistry. In this way the tetravalent sialoside cluster was assembled through the formation of the triazole ring, once again needless to say, acting as a robust molecular keystone of the whole architecture.

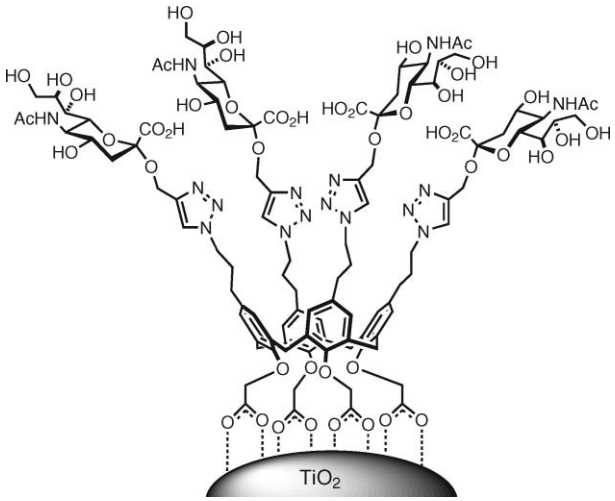


Fig. 12 TiO_2-based sialonanoparticle.

Conclusions

The chemistry presented in this article bears testimony to the key role played by thiazole and triazole as synthetic auxiliaries in a wide range of carbohydrate related topics. Thiazole embedded in various carbon–carbon bond forming reagents served as a convenient formyl group equivalent while triazole acted as a robust linker of molecular fragments in complex architectures. New synthetic methods have been developed based on the great potential of these heterocycles to serve as synthetic auxiliaries. Moreover, triazole was not used only because of the ease of formation and high stability but also for some special structural and chemical properties that it might confer to the assembled molecules. While the use of triazole as a ligation tool has been demonstrated in many fields of material and life science, we have to notice that the use of thiazole as a masked functionality has met with less success outside of our laboratory. Thus, it is hoped that the thiazole-based synthetic approaches illustrated in this Perspective will be taken as examples and models for the invention of new chemistry along the line established by Professor Albert I. Meyers about forty years ago.

Acknowledgements

I am indebted to all those who have collaborated to the development of this chemistry by their experimental and intellectual contribution. Their names appear in the author list of the papers thus published. Special thanks are due to my colleagues Prof. Alberto Marra and Dr Alessandro Massi who have actively participated in the recent journey across triazole-based synthetic pathways. I am also grateful to all agencies and institutions which have provided financial support and without which our research would have not been possible.

Notes and references

1 A. I. Meyers, *Heterocycles in Organic Synthesis*, Wiley, New York, 1974.
2 For a comprehensive review, see: A. Dondoni and A. Marra, *Chem. Rev.*, 2004, **104**, 2557–2600.
3 *Essential of Glycobiology*, ed. A. Varki, R. Cummings, J. Esko, H. Freeze, G. Hart and J. Marth, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, USA, 1999.
4 (*a*) T. Ukai, R. Tanaka and T. Dokawa, *J. Pharm. Soc. Jpn.*, 1943, **63**, 296–300; (*b*) J. C. Sheehan and T. Hara, *J. Org. Chem.*, 1974, **39**, 1196–1199; (*c*) C. A. Dvorak and V. H. Rawal, *Tetrahedron Lett.*, 1998, **39**, 2925–2928; (*d*) M. J. White and F. J. Leeper, *J. Org. Chem.*, 2001, **66**, 5124–5131.
5 (*a*) H. Stetter, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 639–647; (*b*) H. Stetter and H. Kuhlmann, in *Organic Reactions*, ed. L. A. Paquette, 1991, **40**, 407-496; (*c*) J. A. Murry, D. E. Frantz, A. Soheili, R. Tillyer, E. J. J. Grabowski and P. J. Reider, *J. Am. Chem. Soc.*, 2001, **123**, 9696–9697.
6 D. Voet and J. G. Voet, *Biochemistry*, John Wiley & Sons, London, 2004.
7 (*a*) R. Breslow, *Chem. Ind. (London)*, 1957, 893–894; (*b*) R. Breslow, *J. Am. Chem. Soc.*, 1958, **80**, 3719–3726.
8 (*a*) K. C. Nicolaou, F. Roschangar and D. Vourloumis, *Angew. Chem., Int. Ed.*, 1998, **37**, 2014–2045; (*b*) I. Ojima, G. D. Vite and K. H. Altmann, *Anticancer Agents: Frontiers in Cancer Chemotherapy*, American Chemical Society, Washington, D. C., 2001.
9 W. L. Kelly, L. Pan and C. Li, *J. Am. Chem. Soc.*, 2009, **131**, 4327–4334.
10 (*a*) D. Lefranc and M. A. Ciufolini, *Angew. Chem., Int. Ed.*, 2009, **48**, 4198–4201; (*b*) M. A. Ciufolini, *Nat. Prod. Rep.*, 2010, **27**, 330–342.
11 A. Dondoni and P. Merino, in *Comprehensive Heterocyclic Chemistry II*, ed. A. R. Katritzky, C. W. Rees and E. F. V. Scriven, Elsevier, Oxford, 1996, vol. 3, ch. 6.
12 L. J. Altman and S. L. Richheimer, *Tetrahedron Lett.*, 1971, **12**, 4709–4711.
13 E. J. Corey and D. L. Boger, *Tetrahedron Lett.*, 1978, **19**, 5–8.
14 A. Dondoni, M. Fogagnolo, A. Medici and P. Pedrini, *Tetrahedron Lett.*, 1985, **26**, 5477–5480.
15 A. Dondoni, G. Fantin, M. Fogagnolo and A. Medici, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 835–837.
16 A. Dondoni, G. Fantin, M. Fogagnolo, A. Medici and P. Pedrini, *J. Org. Chem.*, 1989, **54**, 693–702.
17 A. Dondoni, G. Fantin, M. Fogagnolo and A. Medici, *Tetrahedron*, 1987, **43**, 3533–3539.
18 (*a*) S. J. Danishefsky and M. Barbachyn, *J. Am. Chem. Soc.*, 1985, **107**, 7761–7762; (*b*) S. J. Danishefsky and C. Maring, *J. Am. Chem. Soc.*, 1985, **107**, 7762–7764; (*c*) S. J. Danishefsky and M. P. DeNinno, *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 15–23.
19 K. Uchida, T. Ichikawa, Y. Shimauchi, T. Ishikura and A. Ozaki, *J. Antibiot.*, 1971, **24**, 259–262.
20 A. Takatsuki, K. Arima and G. Tamura, *J. Antibiot.*, 1971, **24**, 215–223.
21 A. Dondoni, G. Fantin, M. Fogagnolo and P. Merino, *J. Carbohydr. Chem.*, 1990, **9**, 735–744.
22 A. Dondoni, S. Ianelli, L. Kniezo, P. Merino and M. Nardelli, *Chem. Soc., Perkin Trans.*, 1994, 1231–1239.
23 (*a*) H. Umezawa, K. Maeda, T. Tackeuchi and Y. Okami, *J. Antibiot.*, 1966, **19**, 200–209; (*b*) H. Umezawa, *Pure Appl. Chem.*, 1971, **28**, 665–680; (*c*) T. Takita, Y. Muraoka, T. Nakatani, A. Fujii, Y. Umezawa, H. Naganawa and H. Umezawa, *J. Antibiot.*, 1978, **31**, 801–804.
24 D. L. Boger and T. Honda, *J. Am. Chem. Soc.*, 1994, **116**, 5647–5656.
25 (*a*) A. Dondoni, A. Marra and A. Massi, *Carbohydr. Lett.*, 1997, **2**, 367–370; (*b*) A. Dondoni, A. Marra and A. Massi, *J. Org. Chem.*, 1997, **62**, 6261–6267.
26 (*a*) A. Dondoni, G. Fantin, M. Fogagnolo and A. Medici, *J. Chem. Soc., Chem. Commun.*, 1988, 10–12; (*b*) A. Dondoni, G. Fantin, M. Fogagnolo and P. Pedrini, *J. Org. Chem.*, 1990, **55**, 1439–1446.
27 (*a*) P. Garner, J. M. Park and E. Malecki, *J. Org. Chem.*, 1988, **53**, 4395–4398; (*b*) S. Nimkar, D. Menaldino, A. H. Merrill and D. Liotta, *Tetrahedron Lett.*, 1988, **29**, 3037–3040; (*c*) H. E. Radunz, R. M. Devant and V. Eiermann, *Liebigs Ann. Chem.*, 1988, 1103–1105; (*d*) P. Herold, *Helv. Chim. Acta*, 1988, **71**, 354–362.
28 A. Dondoni, D. Perrone and E. Turturici, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2389–2394.
29 A. Dondoni, S. Franco, F. Junquera, F. L. Merchan, P. Merino, T. Tejero and V. Bertolasi, *Chem.–Eur. J.*, 1995, **1**, 505–520.
30 R. Csuk, M. Hugener and A. Vasella, *Helv. Chim. Acta*, 1988, **71**, 609–618.
31 (*a*) S. Kondo, K. Inuma, H. Naganawa, H. Shimura and Y. Sekizawa, *J. Antibiot.*, 1975, **28**, 79–82; (*b*) H. Shimura, Y. Sekizawa, K. Inuma, H. Naganawa and S. Kondo, *Agric. Biol. Chem.*, 1976, **40**, 611–618.

32 A. Golebiowski and J. Jurczak, in *Recent Progress in the Chemical Synthesis of Antibiotics*, ed. G. Lukacs, and M. Ohno, Springer, Berlin-Heidelberg, 1990, pp. 365-386.
33 A. Golebiowski, J. Kozak and J. Jurczak, *J. Org. Chem.*, 1991, **56**, 7344–7347.
34 T. Atsumi, T. Fukumaru, T. Ogawa and M. Matsui, *Agric. Biol. Chem.*, 1973, **37**, 2621–2626.
35 (*a*) B. Ganem, *Tetrahedron*, 1978, **34**, 3353–3383; (*b*) P. M. Dewick, *Nat. Prod. Rep.*, 1988, **5**, 73–97; (*c*) E. Haslam, *Shikimic Acid. Metabolism and Metabolites*, Wiley, New York, 1993.
36 *Bacterial Lipopolysaccharides : Structure, Synthesis and Biological Activities*, ed. L. Anderson and F. M. Unger, ACS Symposium Series 231, American Chemical Society, Washington, D. C., 1983.
37 (*a*) D. Nadano, M. Iwasaki, S. Endo, K. Kitajima, S. Inoue and Y. Inoue, *J. Biol. Chem.*, 1986, **261**, 11550–11557; (*b*) S. Inoue, S.-L. Lin, T. Chang, S.-H. Wu, C.-W. Yao, T.-Y. Chu, F. A. Troy and Y. Inoue, *J. Biol. Chem.*, 1998, **273**, 27199–27204.
38 *Sialic Acids Chemistry, Metabolism and Function*, in *Cell Biology Monographs*, ed. R. Schauer, Springer-Verlag, Wien-New York, 1982, vol. 10.
39 (*a*) E. J. McGuire, in *Biological Roles of Sialic Acids*, ed. R. A. Rosenberg and C. L. Schengrund, Plenum, New York, 1976, ch. 4; (*b*) R. Schauer, S. Kelm, G. Reuter, P. Roggentin and I. Shaw, in *Biology of the Sialic Acids*, ed. R. A. Rosenberg, Plenum, New York, 1995.
40 A. Dondoni and P. Merino, P., *J. Org. Chem.*, 1991, **56**, 5294–5301.
41 A. Dondoni, A. Marra and P. Merino, *J. Am. Chem. Soc.*, 1994, **116**, 3324–3336.
42 (*a*) A. Dondoni, A. Boscarato and A. Marra, *Tetrahedron: Asymmetry*, 1994, **5**, 2209–2212; (*b*) A. Dondoni, A. Marra and A. Boscarato, *Chem.–Eur. J.*, 1999, **5**, 3562–3572.
43 (*a*) G. C. Look, C. H. Fotsch and C.-H. Wong, *Acc. Chem. Res.*, 1993, **26**, 182–190; (*b*) *Iminosugars as Glycosidase Inhibitors. Nojirimycin and Beyond*, ed. A. E. Stütz, Wiley-VCH, Weinheim 1999.
44 N. Asano, R. J. Nash, R. J. Molyneux and G. W. J. Fleet, *Tetrahedron: Asymmetry*, 2000, **11**, 1645–1680.
45 A. Dondoni, P. Merino and D. Perrone, *Tetrahedron*, 1993, **49**, 2939–2956.
46 A. Dondoni and D. Perrone, *J. Org. Chem.*, 1995, **60**, 4749–4754.
47 (*a*) Y. Miyake and M. Ebata, *J. Antibiot.*, 1987, **40**, 122–123; (*b*) Y. Miyake and M. Ebata, *Agric. Biol. Chem.*, 1988, **52**, 153–158.
48 (*a*) H. Paulsen, Y. Hayauchi and V. Sinnwell, *Chem. Ber.*, 1980, **113**, 2601–2608; (*b*) G. Legler and S. Pohl, *Carbohydr. Res.*, 1986, **155**, 119–129; (*c*) S. Aoyagi, S. Fujimaki, N. Yamazaki and C. Kibayashi, *J. Org. Chem.*, 1991, **56**, 815–819; (*d*) N. Chida, T. Tanikawa, T. Tobe and S. Ogawa, *J. Chem. Soc., Chem. Commun.*, 1994, 1247–1248.
49 H. Chikashita, M. Ishibaba, K. Ori and K. Itoh, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 3637–3648.
50 O. R. Martin, in *Carbohydrate Mimics. Concepts and Methods*, ed. Y. Chapleur, Wiley-VCH, Weinheim, 1998, pp. 259–282.
51 A. Dondoni, P. P. Giovannini and D. Perrone, *J. Org. Chem.*, 2002, **67**, 7203–7214.
52 A. Dondoni and A. Nuzzi, *J. Org. Chem.*, 2006, **71**, 7574–7582.
53 A. Dondoni, D. Perrone and T. Semola, *Synthesis*, 1995, 181–186.
54 D. Guénard, F. Guéritte-Voegelein and P. Potier, *Acc. Chem. Res.*, 1993, **26**, 160–167.
55 K. C. Nicolaou, W.-M. Dai and R. K. Guy, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 15–44.
56 (*a*) C. Gennari, A. Vulpetti, M. Donghi, N. Mongelli and E. Vanotti, E., *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1723–1725; (*b*) B. M. Adger, J. V. Barkley, S. Bergeron, M. W. Cappi, B. E. Flowerdew, M. P. Jackson, R. McCague, T. C. Nugent and S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1997, 3501–3508; (*c*) R. Fernández, A. Ferrete, J. M. Lassaletta, J. M. Llera and E. Martín-Zamora, *Angew. Chem., Int. Ed.*, 2002, **41**, 831–833; (*d*) T. Mandai, T. Oshitari and M. Susowake, *Synlett*, 2002, 1665–1668.
57 A. Dondoni, D. Perrone and P. Merino, P., *J. Org. Chem.*, 1995, **60**, 8074–8080.
58 A. Commerçon, D. Bézard, F. Bernard and J. D. Bourzat, *Tetrahedron Lett.*, 1992, **33**, 5185–5188.
59 (*a*) V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2002, **41**, 2596–2599; (*b*) C. W. Tornøe, C. Christensen and M. Meldal, *J. Org. Chem.*, 2002, **67**, 3057–3062.
60 (*a*) H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2001, **40**, 2004–2021; (*b*) H. C. Kolb and K. B. Sharpless, *Drug Discovery Today*, 2003, **8**, 1128–1137.
61 (*a*) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, 1963, **2**, 565–598; (*b*) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, 1963, **2**, 633–645.
62 see: http://www.scripps.edu/chem/sharpless/click.html.
63 M. Meldal and C. W. Tornøe, *Chem. Rev.*, 2008, **108**, 2952–3015.
64 (*a*) A. Dondoni, *Chem.–Asian J.*, 2007, **2**, 700–708; (*b*) S. Dedola, S. A. Nepogodiev and R. A. Field, *Org. Biomol. Chem.*, 2007, **5**, 1006–1017; (*c*) F. Santoyo-Gonzalez and F. Hernandez-Mateo, *Chem. Soc. Rev.*, 2009, **38**, 3449–3462.
65 L. A. Marcaurelle and C. R. Bertozzi, *Chem.–Eur. J.*, 1999, **5**, 1384–1390.
66 (*a*) A. Dondoni and A. Marra, *Chem. Rev.*, 2000, **100**, 4395–4421; (*b*) K. Pachamuthu and R. R. Schmidt, *Chem. Rev.*, 2006, **106**, 160–187.
67 (*a*) A. Dondoni, G. Mariotti and A. Marra, *Tetrahedron Lett.*, 2000, **41**, 3483–3486; (*b*) A. Dondoni, P. P. Giovannini and A. Marra, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2380–2388; (*c*) A. Dondoni, G. Mariotti, A. Marra and A. Massi, *Synthesis*, 2001, 2129–2137; (*d*) A. Dondoni, G. Mariotti and A. Marra, *J. Org. Chem.*, 2002, **67**, 4475–4486.
68 A. Dondoni and A. Massi, *Asymmetric Synthesis and Application of a-Amino Acids*, ACS Symposium Series 1009, ed. V. A. Soloshonok and I. Kunisuke, American Chemical Society, Washington, DC, 2009, pp. 13–30.
69 A. Dondoni, P. P. Giovannini and A. Massi, *Org. Lett.*, 2004, **6**, 2929–2932.
70 (*a*) L. Zhang, X. Chen, P. Xue, H. H. Y. Sun, I. D. Williams, K. B. Sharpless, V. V. Fokin and G. Jia, *J. Am. Chem. Soc.*, 2005, **127**, 15998–15999; (*b*) B. C. Boren, S. Narayn, L. K. Rasmussen, L. Zhang, H. Zhao, Z. Lin, G. Jia and V. V. Fokin, *J. Am. Chem. Soc.*, 2008, **130**, 8923–8930.
71 P. C. Zamecnik and M. L. Stephenson, *Proc. Natl. Acad. Sci. U. S. A.*, 1978, **75**, 280–284.
72 (*a*) S. J. Kim, J. Y. Lee and B. H. Kim, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 1313–1316; (*b*) J. R. Kong, S. K. Kim, B. J. Moon, S. J. Kim and B. H. Kim, *Nucleosides, Nucleotides Nucleic Acids*, 2001, **20**, 1751–1760.
73 V. V. Filichev, A. A. Malin, V. A. Ostrovskii and E. B. Pedersen, *Helv. Chim. Acta*, 2002, **85**, 2847–2885.
74 (*a*) P. von Matt, T. Lochmann and K.-H. Altmann, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 1549–1552; (*b*) P. von Matt and K.-H. Altmann, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 1553–1556; (*c*) L. Zhou, A. Amer, M. Korn, R. Burda, J. Balzarini, E. De Clercq, E. R. Kern and P. F. Torrente, *Antiviral Chem. Chemother.*, 2005, **16**, 375–383; (*d*) R. Lucas, V. Neto, A. H. Bouazza, R. Zerrouki, R. Granet, P. Krausz and Y. Champavier, *Tetrahedron Lett.*, 2008, **49**, 1004–1007.
75 A. Nuzzi, A. Massi and A. Dondoni, *QSAR Comb. Sci.*, 2007, **26**, 1191–1199.
76 F. Morvan, Université Montpellier, France, personal communication.
77 (*a*) *The Return of the White Plague*, ed. M. Gaudy and A. Zumla, Verso, London, 2003; (*b*) F. Ryan, *The Forgotten Plague: How the Battle Against Tuberculosis Was Won - And Lost*, Back Bay Books, New York, 1994.
78 P. J. Brennan and D. C. Crick, *Curr. Top. Med. Chem.*, 2007, **7**, 475–488.
79 P. J. Brennan and H. Nikaido, *Annu. Rev. Biochem.*, 1995, **64**, 29–63.
80 Y. S. Morita, J. H. Patterson, H. Billman-Jacobe and M. J. McConville, *Biochem. J.*, 2004, **378**, 589–597.
81 (*a*) K. H. Khoo, A. Dell, H. R. Morris, P. J. Brennan and D. Chatterjee, *Glycobiology*, 1995, **5**, 117–127; (*b*) D. Chatterjee, S. W. Hunter, M. McNeil and P. J. Brennan, *J. Biol. Chem.*, 1992, **267**, 6228–6233.
82 (*a*) M. Joe, D. Sun, H. Taha, G. C. Completo, J. E. Croudace, D. A. Lammas, G. S. Besra and T. L. Lowary, *J. Org. Chem.*, 2006, **128**, 5059–5072; (*b*) K. N. Jayaprakash, S. R. Chaudhuri, C. V. S. R. Murty and B. Fraser-Reid, *J. Org. Chem.*, 2007, **72**, 5534–5545; (*c*) M. Joe, Y. Bai, R. C. Nacario and T. L. Lowary, *J. Am. Chem. Soc.*, 2007, **129**, 9885–9901; (*d*) L. J. Alderwick, H. L. Birch, A. K. Mishra, L. Eggeling and G. S. Besra, *Biochem. Soc. Trans.*, 2007, **35**, 1325–1328; (*e*) B. Fraser-Reid, S. R. Chaudhuri, K. N. Jayaprakash, J. Luì and C. V. S. Ramamurty, *J. Org. Chem.*, 2008, **73**, 9732–9743; (*f*) P. S. Patiland and S.-C. Hung, *Chem. Eur. J.*, 2009, **15**, 1091–1094.
83 J. A. Watt and S. J. Williams, *Org. Biomol. Chem.*, 2005, **3**, 1982–1992.
84 W. S. Horne, M. K. Yadav, C. D. Stout and M. R. Ghadiri, *J. Am. Chem. Soc.*, 2004, **126**, 15366–15367.
85 P. Cheshev, A. Marra and A. Dondoni, *Org. Biomol. Chem.*, 2006, **4**, 3225–3227.
86 M. Lo Conte, A. Chambery, A. Marra and A. Dondoni, *Synlett*, 2009, 2679–2681.
87 M. Lo Conte, A. Marra, G. S. Besra, and A. Dondoni, unpublished results.

88 Bioassays have been performed in the laboratory of Professor G. S. Besra, at the University of Birmingham, U. K.
89 (*a*) Y. C. Lee and R. T. Lee, *Acc. Chem. Res.*, 1995, **28**, 321–327; (*b*) J. J. Lundquist and E. J. Toone, *Chem. Rev.*, 2002, **102**, 555–578.
90 A. Dondoni and A. Marra, *Chem. Rev.*, 2010, **110**, DOI: 10.1021/cr100027b.
91 A. Dondoni and A. Marra, *J. Org. Chem.*, 2006, **71**, 7546–7557.
92 L. Moni, G. Pourceau, J. Zhang, A. Meyer, S. Vidal, E. Souteyrand, A. Dondoni, F. Morvan, Y. Chevolot, J.-J. Vasseur and A. Marra, *ChemBioChem*, 2009, **10**, 1369–1378.
93 A. Marra, L. Moni, D. Pazzi, A. Corallini, D. Bridi and A. Dondoni, *Org. Biomol. Chem.*, 2008, **6**, 1396–1409.
94 L. Moni, S. Rossetti, M. Scoponi, A. Marra and A. Dondoni, *Chem. Commun.*, 2010, **46**, 475–477.