Thiazole-Mediated Synthetic Methodology

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1. Introduction

The second half of last century has witnessed an enormous progress in organic synthesis as a consequence of the advent of innovative concepts with high predictable power and the development of new strategies and technologies culminating in the preparation of numerous natural and unnatural products of great complexity.[1] Formidable goals were achieved owing to the continuous efforts in the search of new reagents and methods, particularly those allowing one to assemble molecular building blocks via chemically efficient and stereoselective carbon−carbon bond-forming reactions. At present, research in this field is even more actively promoted by the interplay of organic chemistry and various disciplines of life science such as biology, pharmacology, and medicine that are posing a pressing demand for natural products and synthetic analogues in meaningful scale and high purity.[2] Although a great deal of new reagents and catalysts have been formulated as the result of profitable studies in organometallic chemistry, also members of classical families of organic compounds proved to serve as effective synthetic auxiliaries. This is the case of heterocyclic compounds whose utility in organic synthesis, although recognized in recent times, is now well established. The publication in 1974 of the Meyers book entitled *Heterocycles in Organic Synthesis*[3] describing the main transformations of various heterocycles into common functional groups highlighted the concept of heterocycle-functional group equivalence as a powerful tool in new synthetic programs. Reviews and articles dealing with the use of readily available and simple heterocycles were also reported. These include 1,3-dithianes,[4] oxazolines,[5] oxazoles,[6] thiophenes,[7] isoxazolines,[8] isoxazoles,[9] pyrrolidines,[10] 2-silyloxyfurans,[11] thiazoles,[12] benzotriazoles,[13] and various heteroaromatics such as pyrroles, furans, and imidazoles.[14] Since substantial research has been carried out over the last 20 years on the use of thiazole as synthetic auxiliary but only partial accounts were reported in various instances,[12,15] the aim of this paper is to review our and other's work dealing with the service of thiazole as latent formyl group in the assembly of a great variety of densely functionalized and chiral molecular systems. The thiazolyl to formyl equivalence was central to the chemistry involved in synthetic schemes of some complexity. In fact, while the high and multiform reactivity of the formyl group is widely exploited in synthetic endeavors toward complex molecular systems, a drawback of this functionality stems from its scarce compatibility with various reaction conditions. Consequently, it is convenient, if not necessary, to introduce in a substrate the formyl group in a stable masked form from which it can be liberated in the late stage of the synthesis. Hence, we will describe synthetic schemes leading to a wide variety of compounds and which are based on a general strategy consisting of the introduction of thiazole or a thiazole-containing residue in a substrate, followed by the elaboration of the moiety linked to the thiazole ring and the final conversion of the latter into the formyl group (*Thiazole−Aldehyde Synthesis*). The wide scope of this synthetic strategy relies on two main properties of the thiazole ring: first, its tolerance to a broad range of reaction conditions, thus allowing for the elaboration of the substrate in which it has been introduced, and, second, the easy transformation into the formyl group under almost neutral conditions, thus leaving unaltered stereocenters and acid- and base-sensitive functional groups which are present in the molecule. It is intended that this contribution provides testimony to the potential of the thiazole ring as a latent functional group in synthetic methodology, thereby stimulating further developments in this field. Other

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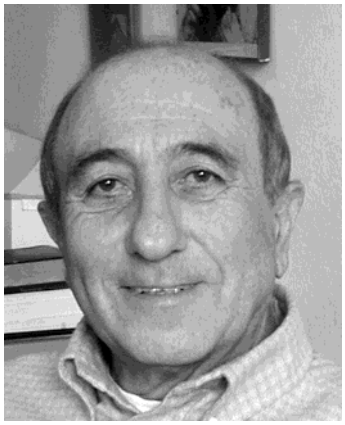


Alessandro Dondoni studied chemistry at the University of Bologna, where he graduated in Industrial Chemistry in 1960 under the guidance of Professor F. Montanari. He undertook postdoctoral work in the same place (1961) and then at the Illinois Institute of Technology in Chicago (1962–1963). In 1964 he was appointed Assistant Professor at the University of Bologna and joined the research group of Professor A. Mangini at the Department of Industrial Chemistry. For the teaching activity and research work carried out in that place he earned the 'habilitation' in Physical Organic Chemistry (1969). In 1970 he became Associate Professor at the University of Ferrara and in 1975 was promoted to the rank of Professor and appointed to the Chair of Organic Chemistry in the same University. His present research interests center on the invention of new reagents and the development of new synthetic methods that result in the preparation of biologically active compounds, largely carbohydrates, unnatural amino acids, and small peptides. Very recently he started new work on asymmetric multicomponent reactions. Professor Dondoni has held visitor professorships at the University of Rennes (1982), Hamburg (1983), Osaka (1988, JSPS Award), and Lyon (1994). In recognition of his many contributions he has been awarded the 1996 A. Mangini Gold Medal for creative work in organic chemistry sponsored by the Italian Chemical Society. In 1999 he obtained the Avogadro-Minakata Lectureship Award of the Chemical Society of Japan and the Ziegler–Natta Lectureship Award of the German Chemical Society. In the same year he was awarded the Lincei National Academy prize in Chemistry sponsored by the Italian Minister of Cultural Heritage and Activities. Professor Dondoni is a member of the advisory boards of international journals, including *Synthesis*, *Carbohydrate Letters*, *Tetrahedron Letters*, and *Tetrahedron*.

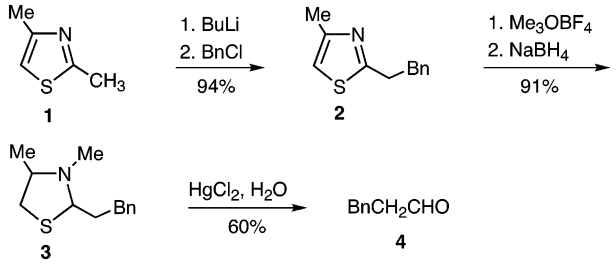
Alberto Marra graduated in Pharmaceutical Sciences from the University of Pisa in 1985 and obtained his Ph.D. degree in Organic Chemistry from the University Paris VI in 1989 under the supervision of Professor P. Sinaÿ. He spent one more year in Paris at the Ecole Normale Supérieure as Researcher of the French National Research Council. He was a Postdoctoral Research Associate at the University of Zurich with Professor A. Vasella (1991) and then moved to the University of Ferrara, where he joined the group of Professor A. Dondoni. He was appointed to a lectureship in Organic Chemistry at the Faculty of Engineering from 1992 to 1998 and was promoted to the position of Associate Professor in 1998 at the same university. As in the early activity, his present research interest centers on carbohydrate chemistry. Recent work is also dealing with the synthesis and properties of calixarene derivatives.

applications in the synthesis of thiazole derivatives, such as *N*-alkylthiazolium salts in the acyloin condensation[16] and the Stetter reaction[17] wherein the role of the heterocycle is to promoting the carbon−carbon bond formation between two reactants rather than participating as a masked functionality to the construction of the target molecule, will not be treated in this review.

2. Thiazole–Aldehyde Synthesis

Among the various syntheses of aldehydes[18] there are some methods based on the use of heterocyclic compounds. One of these methods was reported by Corey and Seebach[4] in 1965. They introduced substituents at C-2 of the 1,3-dithiane ring by reaction of 2-lithio-1,3-dithiane with *C*-electrophiles and then liberated the aldehyde by metal-assisted hydrolysis of the heterocycle. Another interesting method based on the use of 2-alkyl-dihydro-1,3-oxazines was reported a few years later by Meyers and co-workers.[19] In this case the 2-alkyl group linked to the heterocycle was elaborated via metalation and reaction with electrophiles, then the oxazine nucleus was completely reduced with sodium borohydride, and the resulting tetrahydro-1,3-oxazine was cleaved with dilute oxalic acid. These methods stimulated more research in the field. In fact, in analogy to the Meyers oxazine−aldehyde synthesis, Altman and Richheimer described[20] in 1971 the synthesis of an aldehyde, 3-phenylpropanal **4**, starting from 2,4-dimethylthiazole **1** (Scheme 1). This appears to be the first

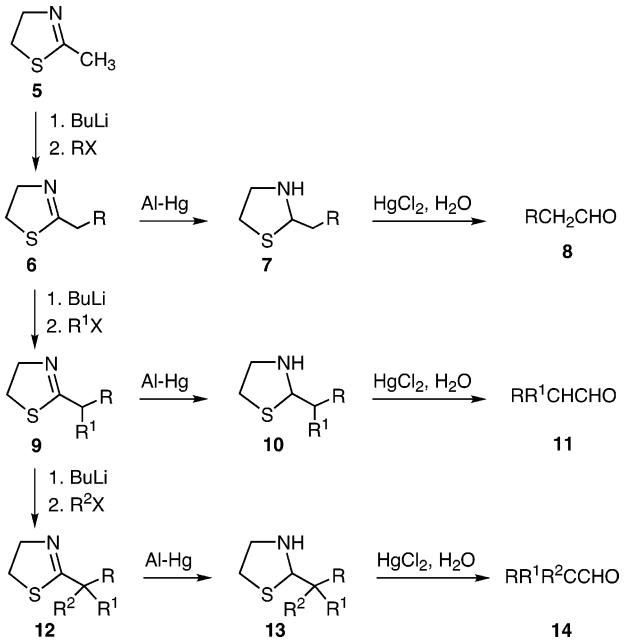
Scheme 1



registered aldehyde synthesis by the use of the thiazole nucleus as a formyl group equivalent. The method consisted of the chain elongation of the C-2 methyl group of **1** via selective metalation[21] and benzylation to give the 2-alkylthiazole **2**. The aldehyde **4** was liberated via a three-step reaction sequence constituted of *N*-methylation of the thiazole ring of **2**, reduction of the resulting *N*-thiazolium salt (not shown) to the thiazolidine **3**, and finally $HgCl_2$-promoted hydrolysis of the heterocyclic nucleus of **3**.

Very soon after the publication of Altman and Richheimer, Meyers introduced another approach to aliphatic aldehydes starting from 2-methyl-2-thiazoline **5** as the carrier of the latent formyl group[22] (Scheme 2). In this method too the first step consisted of the alkylation of the 2-methyl group of **5** via metalation and reaction with suitable electrophiles (alkyl, benzyl, allyl halides), whereas the

Scheme 2

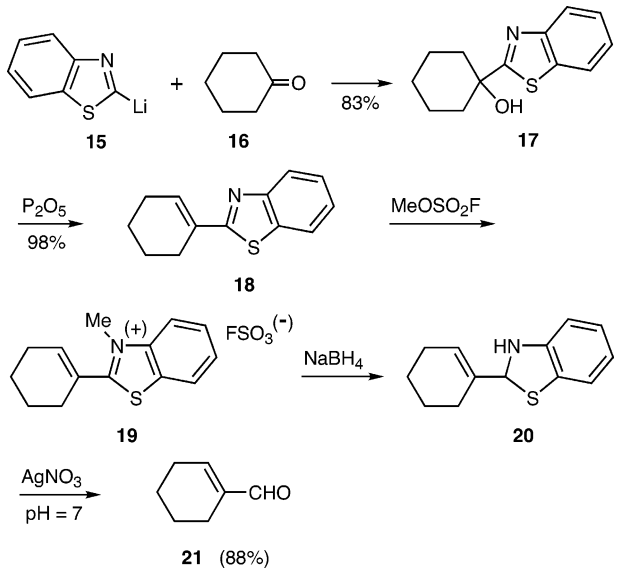


release of the aldehyde **8** was performed by reduction of the thiazoline **6** with aluminum amalgam in moist ether and then cleavage of the thiazolidine **7** using $HgCl_2$ in aqueous acetonitrile. This reaction sequence provided monoalkylated acetaldehydes in 30−70% overall yield. This process was repeated to produce dialkylated and trialkylated thiazolines **9** and **12** which in turn were transformed into di- and trialkylated acetaldehydes **11** and **14**, respectively.[23] Noteworthy is that the precursors to the substituted acetaldehydes, i.e., the thiazolidines **7**, **10**, and **13**, were transformed into products under neutral reaction conditions. It was emphasized that these conditions were crucial for the application of this aldehyde synthesis to acid-sensitive compounds. The Meyers 2-thiazoline method was also employed in the preparation of β-hydroxy aldehydes.[24]

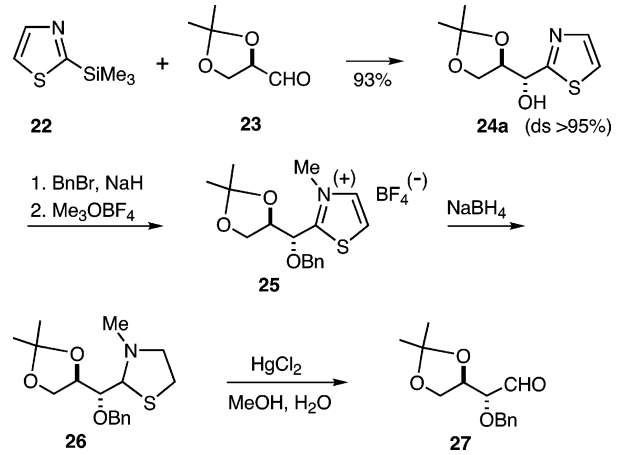
Other leading researchers became interested in thiazole derivatives as latent formyl group equivalents. In 1978 Corey and Boger reported on the synthesis of various aldehydes including unsaturated derivatives using 2-lithiobenzothiazole **15** as a formyl anion equivalent.[25] As illustrated in Scheme 3, the addition of **15** to cyclohexanone **16** afforded the tertiary benzothiazole carbinol **17** which was dehydrated (three methods were suggested) to give the vinyl benzothiazole **18**. This compound proved to be a masked form of the cyclohexene carboxaldehyde **21** which in fact was obtained by cleavage of the benzothiazole ring using a similar sequence to that employed by Altman and Richheimer,[20] i.e., *N*-methylation ($MeOSO_2F$), hydride reduction ($NaBH_4$), and metal-promoted hydrolysis ($AgNO_3$ in aqueous MeCN).

These methods did not receive a great deal of attention as the concept of utilizing thiazole or its derivatives as a latent functionality in organic synthesis was ignored for almost a decade. However, following earlier studies of the uncatalyzed reactions of a new metalated thiazole, 2-(trimethylsilyl)thiazole (2-TST, **22**),[26] with various carbon electrophiles[26,27] (ketenes, acyl chlorides, aldehydes, azaryl cations),

Scheme 3



Scheme 4



Dondoni and co-workers reported[28] in 1985 on the thiazole-based one-carbon homologation of 2,3-*O*-isopropylidene-D-glyceraldehyde **23** to protected D-erythrose **27**. This reaction sequence involved the stereoselective *anti*-addition of 2-TST **22** to **23** and the aldehyde releasing from the adduct **24a** by thiazole cleavage via *N*-methylation (Me_3OBF_4), reduction ($NaBH_4$), hydrolysis ($HgCl_2$ in MeOH−H_2O) (Scheme 4). Since the overall transformation of **23** to **27** corresponded to the addition of the formyl anion to the carbonyl of **23**, it became apparent that 2-TST **22** served in this methodology as the synthetic equivalent of this umpoled synthon.[29] The method was fairly efficient as the aldehyde **27** was isolated in 38% yield from **23**.[30] Noteworthy were two main features of the synthesis: first, the high level of stereoselectivity[31] (ds 95%) of the addition of 2-TST **22** to the chiral aldehyde **23**; second, the liberation of the formyl group from the thiazole ring without affecting the acid-sensitive isopropylidene protective group and stereocenters. This was the first example of a chiral aldehyde synthesis via thiazole-based methodology.

On the basis of this and the other processes which will be illustrated in the forthcoming sections, a general scheme can be formulated wherein an R′-substituted aldehyde can be obtained from a given substrate by three sequential operations: **A**, intro-

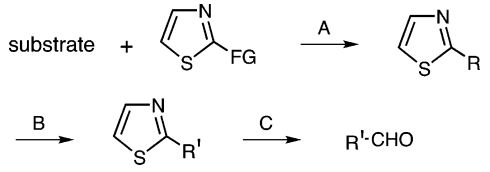
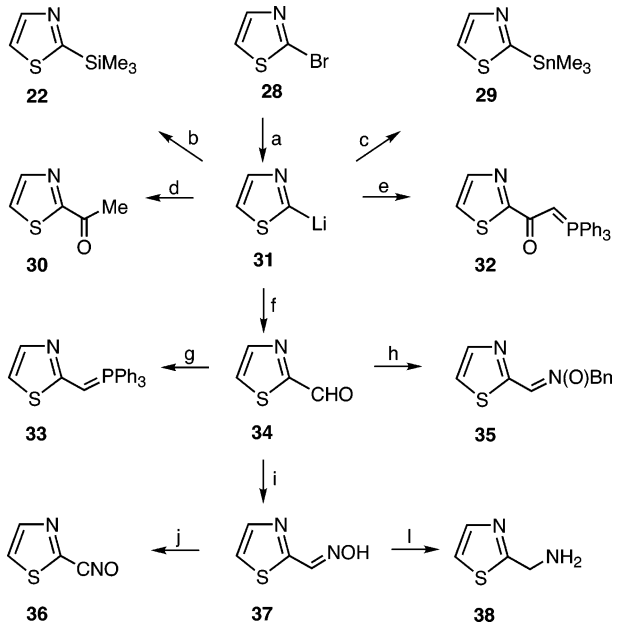


Figure 1. Thiazole−aldehyde synthesis: **A**, coupling; **B**, elaboration; **C**, unmasking.

duction of the thiazole ring in a substrate by reaction of a C-2-functionalized thiazole (FGTh) with a suitable functionality of the substrate (*coupling*); **B**, transformation of the resulting C-2-substituted thiazole RTh into R′Th by elaboration of the group R (*elaboration*); **C**, releasing of the target aldehyde R′CHO from R′Th by cleavage of the thiazole ring (*unmasking*) (Figure 1). This synthetic strategy leading to an aldehyde through a thiazole derivative was appropriately named 'thiazole−aldehyde synthesis'.[12b] Owing to the variety of reactive functional groups (FG) which can be introduced at C-2 of the thiazole nucleus, different types of thiazole-armed reagents (FGTh) can be prepared (see below). Hence, depending on the reagent employed in step **A**, one can install in the starting substrate the sole thiazole ring or a more complex residue containing this heterocycle. For example, the coupling of the substrate with metalated thiazoles (FG = Li, $SiMe_3$) results in the introduction of the thiazole nucleus, namely, the masked formyl group as shown in Scheme 4, whereas the coupling with thiazolylmethylene triphenylphosphorane ThCH=PPh_3 serves to introduce the fragment ThCH=, namely, the masked formylmethylene group. The scarce nucleophilicity and basicity of thiazole[21] and the inertness of its double bonds to undergo addition reactions make this heterocycle tolerant of a broad range of elaborations of the substituent R, so that convenient methods can be employed for the conversion of this group into the desired substituent R′ of the target aldehyde.

The key operation of the thiazole−aldehyde synthesis is carried out in step **C,** where the target aldehyde is released from its thiazole-masked equivalent R′Th by cleavage of the thiazole ring. This unmasking procedure was carried out under mild and neutral conditions in order to avoid side reactions of the resulting aldehyde and leave unaltered protective groups and stereocenters. As shown in Schemes 1, 3, and 4, the thiazole-to-formyl conversion consisted of a three-step reaction sequence involving *N*-methylation to *N*-methylthiazolium salt, then hydride reduction to thiazolidine[32] (or benzothiazoline, see Scheme 3), and finally metal-ion-assisted hydrolysis to aldehyde. Aiming at improving the conditions of the thiazolidine hydrolysis and particularly avoiding the use of the noxious $HgCl_2$, Dondoni and co-workers introduced[33] the mixture $CuCl_2$–CuO in acetonitrile−water as an efficient promoter. However, this system was scarcely effective with benzothiazolines. On the other hand, the use of $AgNO_3$ originally employed by Corey and Boger[25] (see Scheme 3) was found to be superior to $CuCl_2$–CuO and equally effective for the cleavage of thiazole and benzothiazole derivatives.[34] As it will be illustrated below, all variants of the thiazole-to-formyl unmasking protocol were compatible with commonly used hydroxyl and amino protective groups such as *O*-isopropylidene, *O*-silyl, *O*-benzyl, *N*-*tert*-butoxycarbonyl, and *N*-benzyloxycarbonyl as well as with a variety of functionalities. Overall yields of isolated aldehydes ranged between 60% and 90%. By contrast, this unmasking procedure gave poor results in the presence of free hydroxyl groups and was incompatible with *N*-alkylamino groups. Recent studies in the authors' laboratory (unpublished results), aiming at developing a fully automated unmasking protocol and simplifying the isolation of the target aldehyde in a satisfactory pure state, demonstrated that the hydride reduction of the thiazolium salt and the metal-promoted hydrolysis of the thiazolidine can be effectively carried out by use of polymer-supported reagents, namely, borohydride on Amberlite resin (IRA-400) and Amberlyst 15 (Ag^+ form).

Scheme 5[a]



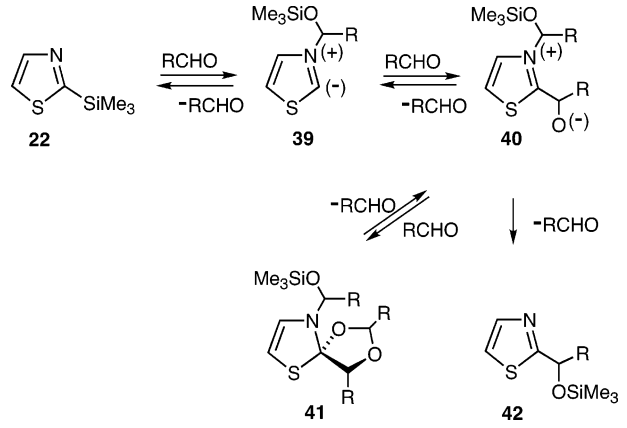
[a] Reagents: (a) BuLi; (b) Me_3SiCl; (c) Me_3SnCl, (d) AcOEt; (e) i. $BrCH_2CO_2Et$, ii. PPh_3, iii. NaOH; (f) DMF; (g) i. $NaBH_4$, ii. PPh_3-CCl_4, iii. PPh_3, iv. *t*-BuOK; (h) BnNHOH; (i) NH_2OH; (j) i. Cl_2, ii. Et_3N; (l) $LiAlH_4$.

The ease of introduction of a variety of reactive functional groups (FG) at C-2 of the thiazole ring led to the preparation of a collection of thiazole-based reagents (FGTh) allowing for the execution of step **A** via a great variety of carbon−carbon bond-forming reactions. These reagents are shown in Scheme 5. Although some of these compounds are commercially available, a synthetic route to each of them is indicated. 2-Bromothiazole **28** was the commercially available starting material whose halogen−metal exchange with butyllithium at low temperature (−70 °C) led to the in situ generation of 2-lithiothiazole[26] (2-LTT, **31**). This organometallic compound was used both as a reagent and precursor for the synthesis of other thiazole-based reagents via reaction with suitable electrophiles. Thus, quenching the ethereal solution of **31** with trimethylsilyl chloride and trimethylstannyl chloride afforded the corresponding organometallic 2-(trimethylsilyl)thiazole[26,27c] (2-TST, **22**) and 2-(trimethylstannyl)thiazole[35] **29**, respectively,

both stable at room temperature. Furthermore, the coupling reactions with *N*,*N*-dimethylformamide and ethyl acetate furnished 2-formylthiazole[36] **34** and 2-acetylthiazole[37] (2-ATT, **30**) in high yields. 2-LTT **31** was also the precursor to the stabilized thiazole-armed carbonyl phosphorane[38] (2-TCMP, **32**), although this compound was prepared in higher yield starting from 2-TST **22**. In both routes the common intermediate was 2-(bromoacetyl)thiazole, which was transformed into a phosphonium salt and then into the ylide **32** by treatment with sodium hydroxide. Other reactive functional groups were introduced starting from the aldehyde **34**. This compound was transformed through the alcohol and the iodo derivative into the thiazole-armed phosphorane, 2-thiazolylmethylene triphenylphosphorane[39] (2-TMP, **33**), and through the oxime **37** into the nitrile oxide[40] **36** and the amine[41] **38**. Finally, a direct conversion of the aldehyde **34** to the nitrone[42] **35** was carried out by treatment with *N*-benzyl hydroxylamine in the presence of a dehydrating agent. With the exception of the organometallic 2-LTT **31** and the nitrile oxide **36**, which must be generated in situ at low temperature, the other thiazole-armed reagents can be prepared in large quantities, isolated as pure materials, and adequately stored for a long time without appreciable decomposition. Such a variety of reactive functional groups linked at C-2 of the thiazole ring opened many opportunities for performing the coupling step **A** toward the formation of a great number of thiazole-containing systems RTh of variable complexity.

Among the reagents shown in Scheme 5, the organometallic 2-(trimethylsilyl)thiazole **22** which has been already introduced in Scheme 4 as a stable formyl anion equivalent, deserves some comments for its special reaction mechanism with carbon electrophiles.[26,27] This reagent shows the striking feature of reacting very rapidly with electrophiles under fluoride-free conditions, whereas other heteroaromatic silanes react more slowly or require suitable catalysts.[43] Of special importance for the numerous synthetic applications is the stereoselective addition of 2-TST **22** to chiral aldehydes to give secondary thiazolyl alcohols which are then transformed into α-hydroxy aldehyde homologues (see Scheme 4). This effective one-carbon homologation process has been applied to a variety of aldehydes containing groups R of variable complexity.[44] A reaction mechanism was proposed[15a,27] wherein the carbodesilylation process of **22** occurs through an activated intermediate, the thiazolium 2-ylide **39** (Scheme 6), i.e., a species postulated in chemical[16,17] (acyloin condensation, Stetter reaction) and biochemical[45] processes involving thiazole derivatives. It was suggested that the facile formation of the ylide **39** relied on the synergistic action of the three heteroatoms, i.e., nitrogen, sulfur, and silicon, linked to C-2 of the thiazole ring. Actually, this process involves the quaternization of the nitrogen atom by the aldehyde and the migration of the silyl group from C-2 to the oxygen atom of the *N*-alkyl group. The resulting negative charge at C-2 is stabilized by the adjacent sulfur atom (α-sulfur effect).[46] Some evidence supporting this mechanism was obtained from a kinetic study[47] and the observation by NMR in the early stage of the reaction of the 3:1 adduct **41** between the aldehyde and 2-TST

Scheme 6



22 and having the structure of spiro(thiazoline-2,4′-dioxolane). The conversion of **41** into the final product **42** should proceed through further reversible steps involving the loss of two molecules of aldehyde and transfer of the silyl group from the *N*-alkyl to the *C*-alkyl moiety. This reaction pathway was found to be in agreement with the results of a theoretical study based on ab initio calculations.[48] These calculations showed that the 2-ylide was formed via concerted nitrogen alkylation and silyl group migration without the formation of an initial betaine intermediate.

The hypothesis of the ylide **39** as a key intermediate in carbodesilylation reactions of 2-TST **22** was consistent with the finding that the addition of this organometallic compound to ketones was restricted to trifluoromethyl derivatives,[49] i.e., strong carbonyl electrophiles capable of giving the quaternization of the nitrogen atom of the thiazole ring. Aiming at extending the scope of the reaction to other ketones, Carcano and Vasella carried out the reaction in the presence of catalytic amount of aldehydes.[50] A fine kinetic study demonstrated that only highly electrophilic aldehydes, and particularly 2-fluorobenzaldehyde, increased the rate of addition of 2-TST **22** to electrophilic ketones, such as fluorinated acetophenones, whereas 2-methoxybenzophenone and benzophenone were unreactive in any case.

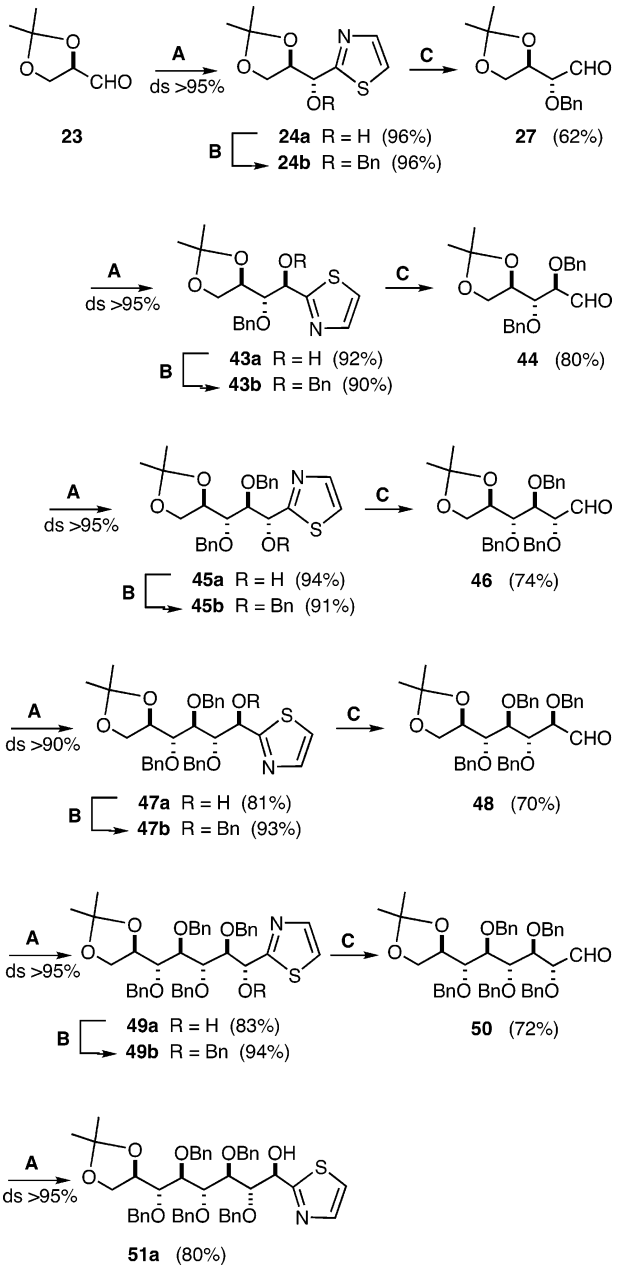
Having presented the strategy and some tools of the thiazole−aldehyde synthesis, examples will be reported in the following sections to illustrate the scope of the methodology in synthesis. In one case the use of benzothiazole instead of thiazole will be described as well because in this strategy the chemistry of the benzo derivative is qualitatively similar to that of the parent compound.

3. Synthesis of Mono- and Oligosaccharides

3.1. Higher Carbon Sugars

As shown in Scheme 4, the use of 2-TST **22** as a reagent in step **A** of the thiazole−aldehyde synthesis allowed for the transformation of an *aldehydo* sugar into one-carbon higher homologue in good yield and stereoselectivity. This is equivalent to the addition of the formyl anion to the lower isomer and is reminiscent of the classical Kiliani−Fischer cyanohydrin synthesis.[51] Hence, in order to test the efficiency of this new homologative method, the thiazole−aldehyde synthesis with **22** as a reagent was

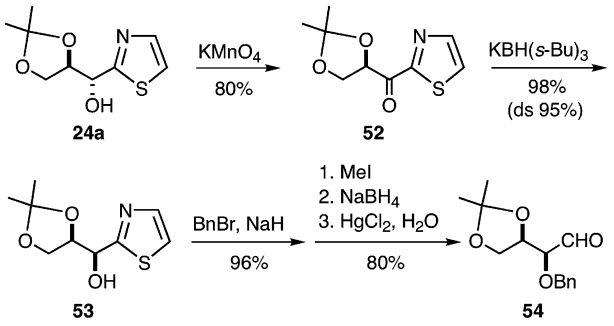
Scheme 7[a]



[a] Key: **A**, coupling with 2-TST **22**; **B**, elaboration (BnBr, NaH); **C**, unmasking (MeI, then $NaBH_4$, then $HgCl_2$, H_2O).

repeated over several consecutive cycles starting from 2,3-*O*-isopropylidene-D-glyceraldehyde **23**.[52] In this way the chain elongation of the triose **23** was brought up to the thiazole nonose **51a**[53] through a series of lower homologues, all exhibiting the *anti*-configuration in the 1,2-polyol units (Scheme 7). This structural feature was proved by X-ray analysis of the thiazole D-ribose **43a** and transformation of the thiazole D-octose **49a** into a *meso*-octitol. This sequential assembly of benzyloxymethylene groups did not appear to have been pushed to the limit of application, since high chemical yields and levels of diastereoselectivity were maintained in all steps **A** over the whole iterative sequence, and the unmasking protocol **C** proved to be equally efficient with short and long polyhydroxylated systems. The same iterative chain-elongation methodology was employed starting from 4-*O*-benzyl-2,3-*O*-isopropylidene-L-threose, thus affording a series of *aldehydo* L-sugars up to a seven-carbon-atom member.[52b]

Scheme 8

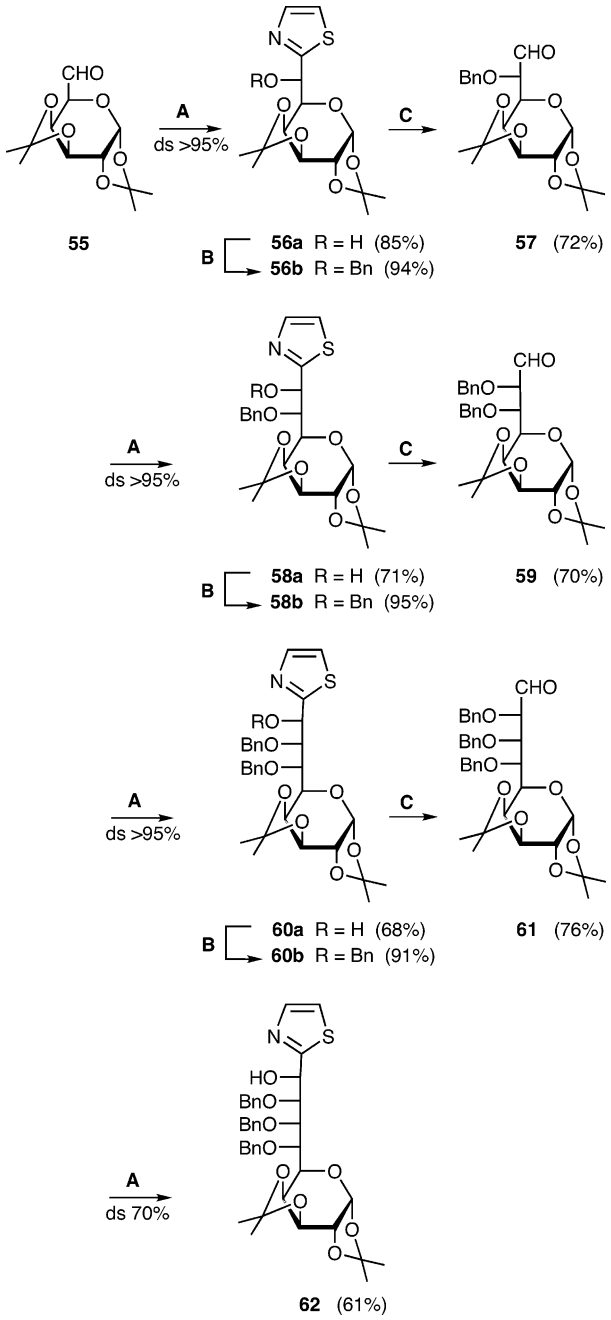


Extension of the scope of the methodology by a full stereocontrol in the addition sequence **A** in order to obtain either 1,2-*anti*- or 1,2-*syn*-diol units was hampered by the inherent *anti*-selectivity of the addition of 2-TST **22** to α,*β*-dialkoxy aldehydes. The control of the selectivity by the use of Lewis acids acting as chelating agents was also hindered by substantial decomposition of 2-TST **22**. This limitation was overcome by conversion of the *anti*-adduct into the *syn*-isomer via an oxidation−reduction sequence[54] as illustrated in Scheme 8. The secondary (*R*)-alcohol **24a** was oxidized to ketone **52** in dry dichloromethane with potassium permanganate partly solubilized with TDA-1 (tris[2-(2-methoxyethoxy)-ethyl]amine). It was proved that under these neutral nonaqueous oxidation conditions no appreciable racemization occurred via exchange of the proton at the secondary carbon α to the carbonyl. An alternative method of oxidation which proved to be quite effective in scaled up reactions,[55] was the Albright−Goldman oxidation using acetic anhydride/dimethyl sulfoxide. The hydride reduction[56] of the carbonyl of **52** with K-Selectride afforded the (*S*)-alcohol **53** in very high yield and stereoselectivity. Thus, the overall result of the oxidation−reduction sequence was the inversion of configuration of the α-carbon to the thiazole ring. Having the *syn*-adduct **53** in hand, the synthesis of the protected *aldehydo*-D-threose **54** was achieved through the usual steps **B** and **C** of the thiazole−aldehyde synthesis, i.e., elaboration of **53** by protection of the free hydroxyl group and formyl group unmasking.[57] Hence, the original triose D-glyceraldehyde **23** resulted to have been homologated into the two tetrose epimers, D-erythrose **27** and D-threose **54**.

In a similar way each of these tetroses was transformed in a pair of epimeric pentoses,[55] i.e., **27** in D-ribose and D-arabinose and **54** in D-xylose and D-lyxose. However, in the latter case the methodology was scarcely efficient because of the unusual *syn*-selectivity of the addition of 2-TST **22** to D-threose **54** to give the thiazole xylose as major product instead of the expected *lyxo* derivative. Nevertheless, the thiazole lyxose was obtained from the thiazole xylose by the oxidation−reduction sequence. In turn, all these thiazole sugars (*ribo*, *arabino*, *xylo*, and *lyxo*) were transformed into the corresponding *aldehydo* sugars by the usual thiazole-to-formyl unmasking reaction sequence.

The above one-carbon homologation scheme was applied to dialdoses[52b,57] with the aim of preparing

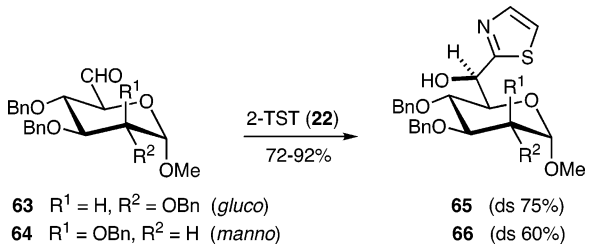
Scheme 9[a]



[a] Key: **A**, coupling with 2-TST **22**; **B**, elaboration (BnBr, NaH); **C**, unmasking (MeI, then $NaBH_4$, then $HgCl_2$, H_2O).

higher carbohydrates as potential building blocks for biologically active compounds. In fact, the building up of a stereochemically well-defined polyhydroxylated carbon chain at C-5 of a pyranose ring is an important operation[58] since the resulting higher sugars are present in various antibiotics, such as hikizimycin[59] and tunicamycin.[60] Thus, the iterative repetition of the thiazole−aldehyde synthesis (sequences **A**, **B**, and **C**) over four consecutive cycles starting from 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-hexodialdo-1,5-pyranose **55** (Scheme 9) provided[52b] a series of long-chain dialdogalactopyranosides in good chemical yields and diastereoselectivity up to 10 carbon atoms as shown in the thiazole sugar **62**. The configurational assignment[57] of the newly formed stereocenter in the adduct **56a** was supported by the

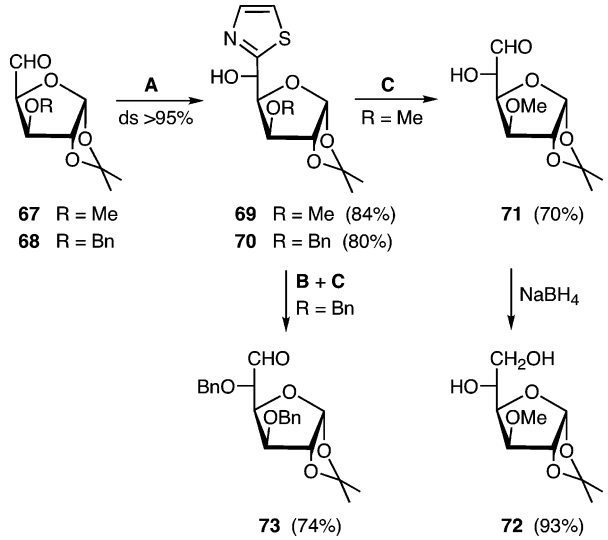
Scheme 10



identical physical properties of the D-*galacto*-hepto-dialdopyranoside **57** with the same compound prepared by the addition of other organometals[61] to the dialdohexose **55**. The stereochemical outcome of the first homologative cycle leading to **57** was confirmed by subsequent work of Aspinall and co-workers.[62] However, extension of the same method to other hexodialdo-1,5-pyranoses, such as the D-*gluco* and the D-*manno* derivatives **63** and **64** (Scheme 10), turned out to be scarcely efficient because the addition of 2-TST **22** to these dialdoses gave the corresponding 6-thiazolyl derivatives **65** and **66** and their C-6 epimers with very low selectivity. The configuration at C-6 of the major adducts **65** and **66** was found to be the opposite to that obtained by addition of 2-TST **22** to the D-*galacto* derivative **55**. These results led Aspinall to conclude[62] that the high level and sense of diastereoselectivity observed in the C-6 homologation of a hexodialdo-1,5-pyranose derivative using 2-TST **22** were restricted to the galactose series and that the stereochemical outcome of the addition was presumably controlled by the steric effect of the axial oxygen substituent at C-4.

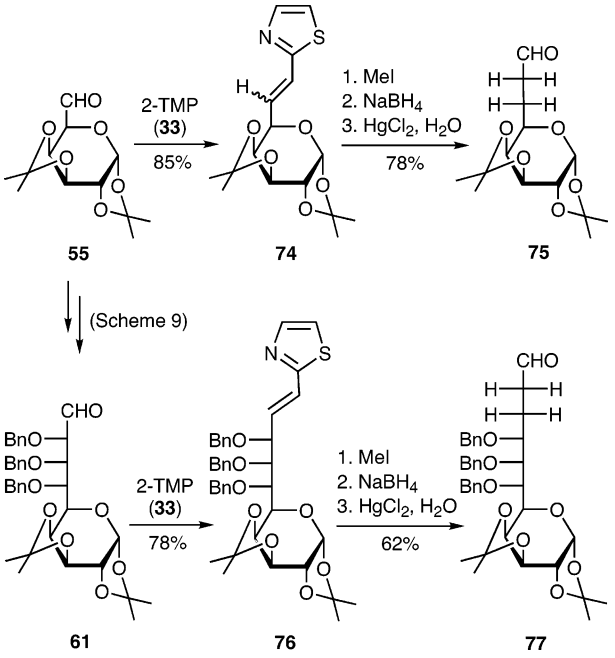
While the Aspinall work pointed out some problems regarding the stereoselectivity of the addition of 2-TST **22** to complex aldehydes, another example of efficient thiazole−aldehyde synthesis was reported.[57] This involved the one-carbon homologation of α-D-*xylo*-dialdofuranose 3-*O*-methyl and 3-*O*-benzyl ethers **67** and **68** (Scheme 11). The addition of **22** to these dialdoses showed high levels of stereoselectivity and

Scheme 11[a]



[a] Key: **A**, coupling with 2-TST **22**; **B**, elaboration (BnBr, NaH); **C**, unmasking (MeI, then $NaBH_4$, then $HgCl_2$, H_2O).

Scheme 12



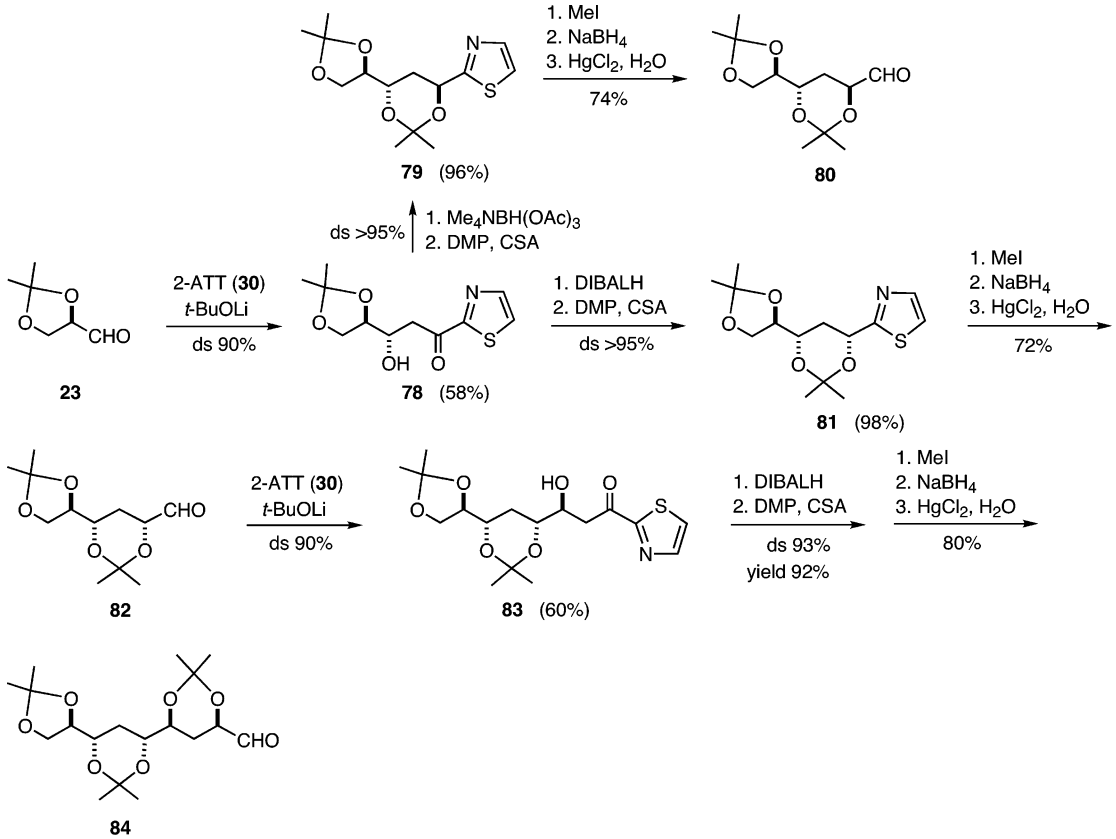
in the same sense observed in the addition to the dialdopyranose **55**. Both 5-thiazolyl adducts **69** and **70** were transformed into the corresponding α-D-*gluco*-dialdofuranoses **71** and **73**, respectively, by the usual unmasking protocol, and the structure of the former compound was confirmed by conversion into the known D-glucofuranose derivative **72**. Quite interestingly, the aldehyde **73** was employed by Momenteau and co-workers[63] in the synthesis of glycosylated porphyrins as new photosensitizers for the application in cancer photochemotherapy.

The above thiazole-based homologation of aldehydes was named after its principal inventor and was cited among a selection of classical and modern reactions of synthetic relevance.[64]

The two-carbon chain elongation of aldehydes was performed by use of the thiazole-armed ylide 2-TMP **33** (see Scheme 5) as a reagent in step **A** of the thiazole−aldehyde synthesis.[39,65] However, the resulting higher homologues were found to be saturated aldehydes instead of α,*β*-enals because of the concomitant reduction of the double bond of the 2-alkenylthiazole intermediates during the unmasking of the formyl group. For example, the coupling of the phosphorus ylide **33** with the α-D-*galacto*-dialdopyranose **55** afforded the olefin **74** (*E*,*Z* mixture), which when subjected to the formyl group unmasking protocol furnished the two-carbon higher dideoxy homologue **75** in good yield[66] (Scheme 12). In a similar way the coupling of **33** with the nine-carbon-atom dialdose **61** obtained from **55** via the iterative one-carbon homologation using 2-TST **22** gave the 2-alkenylthiazole **76** which was subsequently transformed into the dideoxy undecadialdose **77**. Scheme 12 illustrates quite well the sequential use of two thiazole-based reagents (2-TST **22** and 2-TMP **33**) in a reaction sequence leading to a densely functionalized alkyl chain linked to C-5 of a pyranose ring. Unfortunately the elaboration of the double bond of 2-alkenylthiazoles via addition reactions such hydroxylation, aminohydroxylation, and epoxidation was not examined.

The three-carbon chain elongation of *aldehydo* sugars and dialdoses using suitable thiazole-based reagents was also examined. 2-Acetylthiazole (2-ATT, **30**) was initially employed in the transformation of

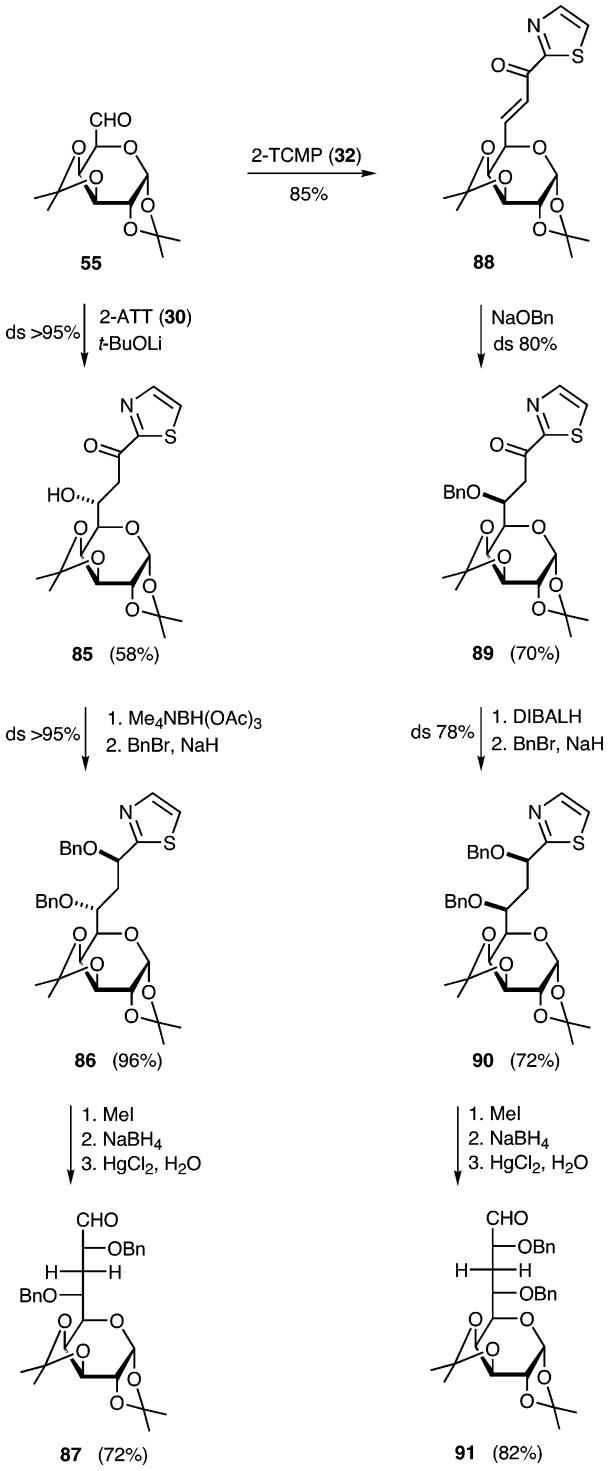
Scheme 13



aldehydo sugars into higher homologues containing *syn*- and *anti*-1,3-diol units.[67] For example, the aldol condensation of the lithium enolate[68] of 2-ATT **30** with 2,3-*O*-isopropylidene-D-glyceraldehyde **23** (Scheme 13) afforded the *anti*-adduct **78**, a *β*-hydroxy ketone. The elaboration of this product was carried out by reduction of the carbonyl with appropriate metal hydride reducing agents[69] in order to form *syn*- and *anti*-1,3-diol systems. In fact, treatment of **78** with tetramethylammonium triacetoxyborohydride (TETABH, $Me_4NBH(OAc)_3$) and acetonization furnished the *anti*-1,3-dioxane derivative **79**, whereas the use of diisobutylaluminum hydride (DIBALH) gave the *syn*-isomer **81**, in both cases with excellent diastereoselectivity. Then the application of the thiazole-to-formyl unmasking protocol to **79** and **81** provided the epimeric tetraalkoxy hexanals (3-deoxy-*aldehydo*-hexoses) **80** and **82** in good yield. The same thiazole-based scheme was followed for the three-carbon homologation of 4-*O*-benzyl-2,3-*O*-isopropylidene-L-threose (Mukaiyama aldehyde). Moreover, in order to further probe this homologation method for the synthesis of long chain polyalkoxy aldehydes, the sequence was repeated with the aldehyde **82**. The use of DIBALH as a reducing agent of the new *β*-hydroxy ketone **83** furnished another *syn*-1,3-diol system which, however, was anti to the existing one. Finally, the thiazole-to-formyl unmasking gave the polyalkoxy nonanal **84** featuring a sequence of 1,2- and 1,3-diol groups. As a conclusion, it was pointed out that the reduction of **83** with TETABH would give the epimer of **84** while the iterative homologation of **80** would lead to other stereoisomeric polyalkoxy aldehydes with predictable configuration at each newly formed stereocenter.

Another efficient implementation[70] of 2-ATT **30** based homologation is represented by the conversion of the α-D-*galacto*-hexodialdo-1,5-pyranose derivative **55** into the 7-deoxynonodialdose **87** (Scheme 14). Both asymmetric reactions in this scheme, i.e., the addition of **30** to **55** and the hydroxy-directed reduction of the *β*-hydroxy ketone **85** with TETABH, proceeded with high levels of stereoselectivity to give the protected *anti*-1,3-diol **86** whose structure was established by X-ray crystallography. The C-8 epimer (not shown) of **86** was in fact prepared by reduction of **85** with DIBALH. The opposite configuration at C-6 was obtained[70] by another homologative scheme employing triphenyl(thiazol-2-ylcarbonylmethylene)-phosphorane (2-TCMP, **32**) as an equivalent of a three-carbon synthon.[38] In this case the Wittig reaction between the aldehyde **55** and the stabilized ylide **32** afforded the *E*-configured α,*β*-enone **88**. This activated olefin treated with sodium benzyloxide at low temperature (−50 °C) underwent the Michael-type 1,4-addition giving rise to an 80:20 mixture of epimers in which the *β*-benzyloxy ketone **89** was the major product as proved also in this case by X-ray structure determination. Hence, it appeared that the aldol condensation route and the olefination−alkoxylation route allowed for the stereoselective installation of (*R*)-*β*-hydroxy- and (*S*)-*β*-benzyloxypropanoyl moieties at C-5 of the galactopyranosyl ring starting from the dialdose **55**. Then the reduction of **89** with DIBALH in the absence of the hydroxyl-directing group was scarcely selective. Nevertheless, the major

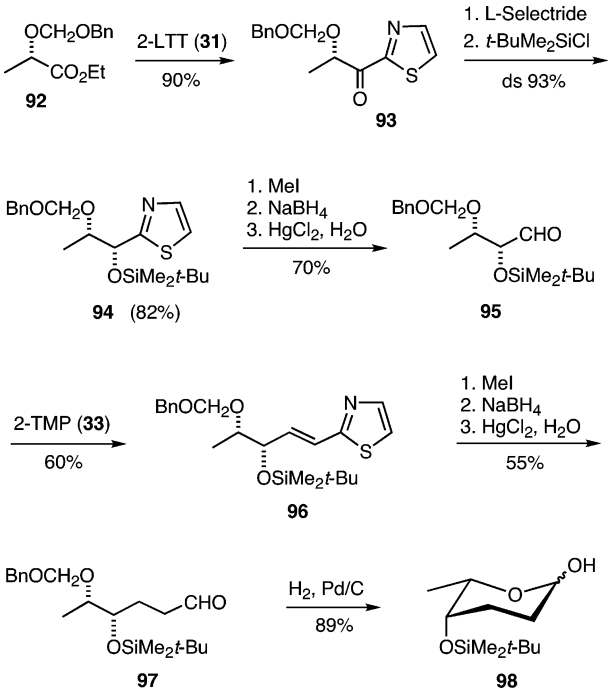
Scheme 14



product isolated after benzylation was the *syn*-isomer **90** (ds 78%), which when subjected to the standard thiazole-to-formyl unmasking protocol afforded the 7-deoxynonodialdose **91**, a C-6 epimer of **87**.

In conclusion, it has been shown that one-, two-, and three-carbon chain elongation of polyalkoxy aldehydes and dialdoses were carried out in good yield and stereoselectivity via the thiazole−aldehyde synthesis using four different thiazole-based reagents in the key coupling step, i.e., 2-TST **22**, 2-TMP **33**, 2-ATT **30**, and 2-TCMP **32**. These methods appear to be amenable to the construction of higher carbohydrates with high molecular diversity.

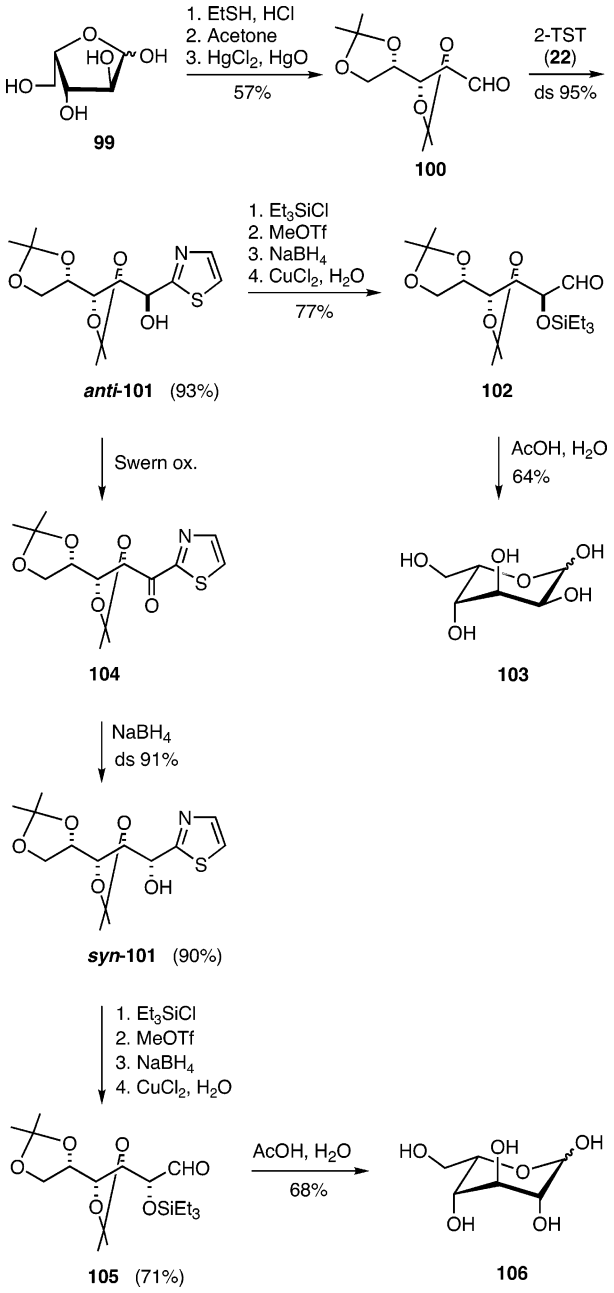
Scheme 15



3.2. Rare Sugars

The stepwise construction of densely functionalized carbon chains with orthogonal protection of the functional groups allowed selective transformations leading to products with a well-defined structure to be carried out. This tactic was exploited by the Dondoni group in the thiazole-based synthesis of the so-called uncommon or rare sugars whose importance stemmed from their presence in the glycidic subunits of bioactive compounds. The first target was 4-*O*-*tert*-butyldimethylsilyl (TBDMS) (−)-L-rhodinose **98** (Scheme 15),[71] whose desilylated parent compound is the constituent of various oligosaccharides which are present in the rhodomycin family of anthracycline antibiotics.[72] An earlier synthesis of **98** by Schlessinger and Graves from ethyl (*S*)-lactate in five steps (46% yield)[73] prompted Dondoni and co-workers to report their own synthesis from the same starting material using two different thiazole-based reagents. The first key intermediate (Scheme 15) was the 2-silyloxy-3-alkoxy butanal **95** featuring a *syn*-relationship between the two protected hydroxyl groups. This aldehyde, a 4-deoxy-L-threose derivative, was prepared starting from ethyl (*S*)-*O*-benzyloxymethyl-lactate **92** using 2-lithiothiazole (2-LTT, **31**) as the homologating agent and L-Selectride as the hydride donor for the *syn*-stereoselective carbonyl reduction[54] of the resulting thiazolyl ketone **93**. These reactions afforded the protected *syn*-1,2-diol **94** from which the aldehyde **95** was liberated by the thiazole-to-formyl unmasking protocol. The subsequent two-carbon chain elongation of **95** was carried out using the phosphorane 2-TMP **33**. The resulting 2-alkenylthiazole **96** subjected to the thiazole-to-formyl unmasking underwent the concomitant reduction of the exocyclic double bond,[39] leading to a saturated aldehyde, namely, *aldehydo*-rhodinose **97**. The selective removal of the benzyloxymethyl group by hydrogenolysis under mild conditions afforded the 4-*O*-

Scheme 16



TBDMS-(−)-L-rhodinose **98** in the exclusive pyranose form as a mixture of α- and *β*-anomers. The overall yield of **98** from **92** was 15%. The compound showed physical properties (mp and optical rotation) identical to those reported by Schlessinger and Graves,[73] while an accurate NMR analysis indicated a higher purity.

A concise and gram-scale synthesis of the rare sugars L-gulose **103** and L-idose **106** (Scheme 16) was reported by the Dondoni group in more recent years.[74] Since these hexoses are epimers at C-2, the 2-TST **22**-based one-carbon chain elongation strategy of a pentose[52] combined with the inversion of configuration at the newly formed stereocenter by an oxidation−reduction sequence[54,57] was employed for the preparation of both compounds. Succinctly, the *anti*-selective addition of **22** to *aldehydo*-L-xylose diacetonide **100** produced the (*R*)-configured alcohol *anti*-**101**, which when subjected to the improved[33] thiazole-to-formyl unmasking protocol afforded the *aldehydo*-

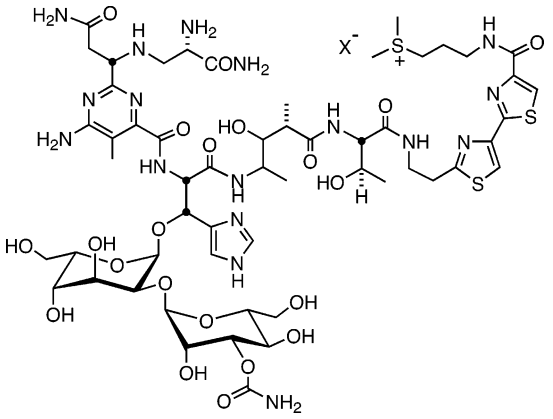
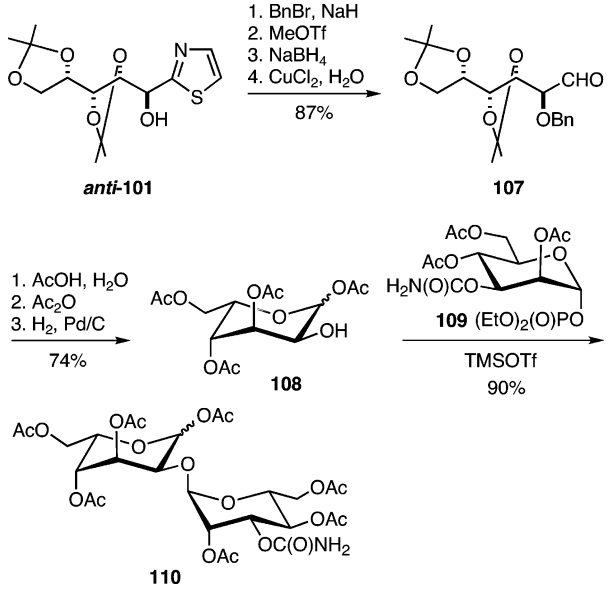


Figure 2. Antitumor antibiotic Bleomycin A2.

Scheme 17



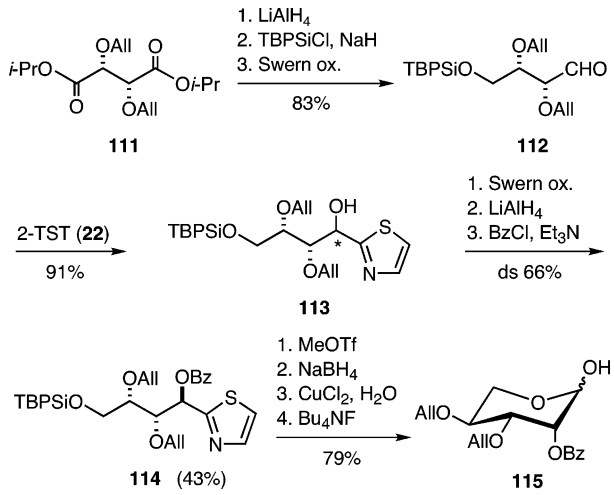
L-gulose derivative **102**. Instead, the Swern oxidation of *anti*-**101** and reduction ($NaBH_4$) of the resulting ketone **104** gave the (*S*)-configured alcohol *syn*-**101**, which was readily transformed into the *aldehydo*-L-idose derivative **105** by the usual thiazole-to-formyl unmasking protocol. It is noteworthy that all the above transformations occurred in good yields and the two asymmetric reactions were highly stereoselective. Both *aldehydo* sugars **102** and **105** were transformed into the free sugars **103** and **106**, respectively, the former existing mainly in the pyranose form as shown and the latter as a mixture of pyranoses and furanoses.

A significant example demonstrating the importance of L-gulose in a bioactive molecule is represented by the disaccharide subunit of bleomycin A_2 (Figure 2), the major constituent of a family of glycopeptide antibiotics[75] capable of mediating the cleavage of DNA and RNA by a metal-dependent oxidative process. This disaccharide is constituted of L-gulose coupled at C-2 through an α-glycosidic linkage with 3-*O*-carbamoyl-D-mannose.

A concise thiazole-based synthesis of a protected form of the disaccharide subunit of bleomycin A_2 is illustrated in Scheme 17. The chiral thiazolyl alcohol *anti*-**101** which was obtained in high yield by the addition of 2-TST **22** to *aldehydo*-L-xylose diacetonide **100** (see Scheme 16) proved to be a very convenient precursor[74] to the tetra-*O*-acetyl-L-gulopyranose **108** bearing a free hydroxyl group at C-2. This selectively protected L-gulose derivative served as glycosyl acceptor in the coupling with the mannopyranosyl donor **109** to give the peracetylated α-D-linked disaccharide **110** in a rewarding yield of 90% (23.5% from L-xylose in nine steps). An earlier synthesis of the disaccharide **110** and its use in the glycosylation of the aglycone of bleomycin A_2 was reported by Boger and Honda.[76] However, their synthesis was less efficient than that described above because of the higher number of steps employed for the preparation of the L-gulose acceptor (nine steps and 12.5% yield from benzyl α-D-mannopyranoside). Hence, this new synthesis of the disaccharide **110** is noteworthy because it provides an improvement of the total synthesis of bleomycin A_2.

The thiazole-based synthesis of another uncommon sugar suitably protected for use as a building block for a complex molecule such as everninomicin 13384−1 was reported by Nicolaou and co-workers.[77] The target molecule was L-lyxopyranose **115** (fragment G) (Scheme 18). In this case too the scheme

Scheme 18



which was employed consisted of the one-carbon chain homologation of a protected polyhydroxy aldehyde using 2-TST **22** as the formyl anion equivalent. After an abortive route due to the unsuccessful elaboration of a thiazole−aldehyde adduct, a satisfactory preparation was carried out as follows. The bisallylated diisopropyl L-tartrate **111** was reduced, monosilylated, and oxidized to the selectively protected hydroxy aldehyde **112**. This compound reacted very cleanly with **22** but unfortunately without any diastereoselectivity as the resulting alcohol **113** (91%) was a 1:1 mixture of diastereoisomers. Nevertheless, the synthesis was continued because the wrong *syn*-diastereoisomer was recycled by an oxidation−reduction sequence (see Scheme 8) into a 2:1 mixture in favor of the desired isomer, which was isolated as the *O*-benzoyl ester **114**. Completion of the sequence included only the unveiling of the aldehyde by the improved thiazole-to-formyl deblocking protocol[33] and desilylation to give the orthogonally protected L-sugar **115**. This compound activated as trichloroacetimidate

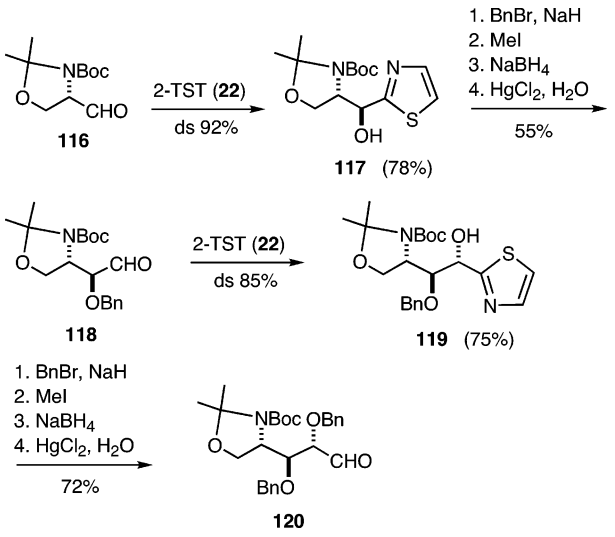
was used as a glycosyl donor in the coupling with another sugar (fragment F) for the assembly of the oligosaccharide portion of everninomicin 13384−1.

3.3. Amino Sugars

The stereoselective construction of polyhydroxy aldehydes bearing an amino group was performed through various schemes, all based on the thiazole−aldehyde synthesis. These procedures provided new entries to biologically active target molecules such as amino sugars[78] and to building blocks for other complex natural products such as sphingosines.[79]

An early approach[80] (Scheme 19) consisted of the

Scheme 19



2-TST **22** based homologation of amino aldehydes starting from the configurationally stable *N*-Boc L-serinal acetonide **116**, the so-called Garner aldehyde.[81] The execution of the methodology over two consecutive cycles afforded the *O*- and *N*-protected amino sugars **118** (L-*erythro*)[82] and **120** (L-*ribo*) in good overall yields. Hence, in both cycles the addition of **22** to the corresponding aldehyde was *anti*-diastereoselective[83] as shown by the structure of the alcohols **117** and **119**.

The scope of the homologation of the aldehyde **116** illustrated in Scheme 19 went beyond the synthesis of amino sugars[80] since the aldehydes **118** and **120** were convenient intermediates[84] via Wittig olefination with suitable phosphoranes for the synthesis of triacetyl D-*erythro*-C_{20}-sphingosine **121** and tetraacetyl D-*ribo*-phytosphingosine **122** (Figure 3).

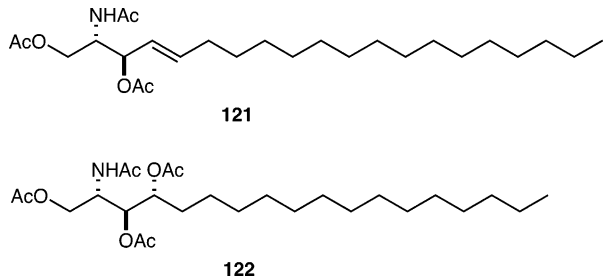
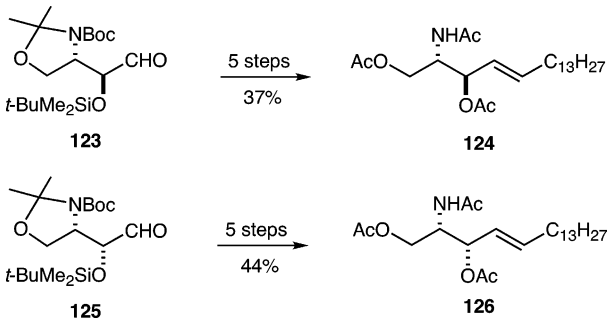


Figure 3. D-*Erythro*-C_{20} sphingosine **121** and D-*ribo* C_{18} phytosphingosine **122** prepared from the debenzylated analogue[80] of **118** and the amino sugar **120**, respectively.

Other syntheses of sphingosines via addition of metal acetylenes to the amino aldehyde **116** were reported in the same year 1988 by four independent groups.[85] The advantage of the synthesis employing a more advanced intermediate such as the aldehyde **118** was that the stereochemistry of the whole hydrophilic part of the sphingosine under construction was already established in that intermediate. However, the low yield of the Wittig olefination induced Dondoni and co-workers to reconsider the synthesis of sphingosines in more recent years[86] via the *O*-silyl-protected analogue of **118**, i.e., the aldehyde **123** (Scheme 20) and the C-2 epimer **125**. The required

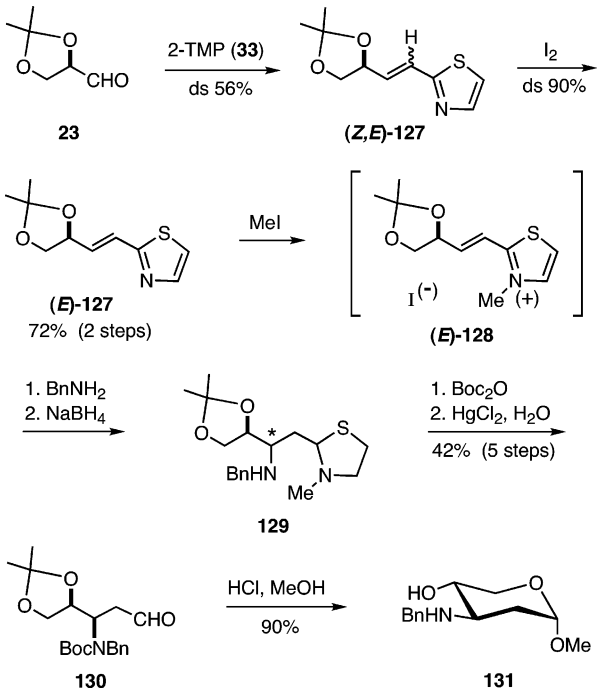
Scheme 20



E-configuration of the double bond of the target (*E*)-sphingosines was introduced by photoisomerization of the mixture of *Z*- and *E*-alkenes resulting from the Wittig olefination of **123** and **125**. In this way the *N*,*O*,*O*-triacetyl-D-*erythro* C_{18}-sphingosine **124** and the L-*threo* isomer **126** were prepared in 37−44% overall yield from the aldehydes **123** and **125**, respectively.

Another reaction scheme leading to amino sugars included as a key step the amination of 2-alkenylthiazoles derived from *aldehydo* sugars. This operation was carried out by a Michael-type 1,4-addition of nitrogen nucleophiles to the *N*-methylthiazolium salts derived from 2-alkenylthiazoles.[87] Hence, in this case the thiazole-based reagent employed in the coupling step **A** of the thiazole−aldehyde synthesis was the nonstabilized phosphorane 2-TMP **33** as illustrated in Scheme 21. The coupling between the model alkoxy aldehyde **23** and the ylide **33**, generated in situ (toluene, *t*-BuOK) from the corresponding phosphonium salt, was essentially unselective as the 2-alkenylthiazole **127** was obtained as a 1:1 mixture of *Z*- and *E*-isomers. The mixture was enriched in the isomer (*E*)-**127** (*E*:*Z* = 9:1) by refluxing in dichloroethane in the presence of iodine. The pure isomer (*E*)-**127** was isolated in 72% yield from the aldehyde **23**. While this olefin did not react with benzylamine, treatment of the *N*-methylthiazolium iodide (*E*)-**128** with the same amine and quenching with sodium borohydride afforded the aminated 2-alkyl *N*-methylthiazolidine **129** as a complex mixture of diastereomers. Protection of the benzylamino group of **129** as *N*-Boc derivative and completion of the unmasking protocol by $HgCl_2$-mediated hydrolysis of the thiazolidine ring afforded the *β*-amino aldehyde **130** and its C-3 epimer (not shown) in an 80:20 ratio. The stereochemistry of the major product **130** featuring the NBocBn and the adjacent alkoxy group in a *syn*-

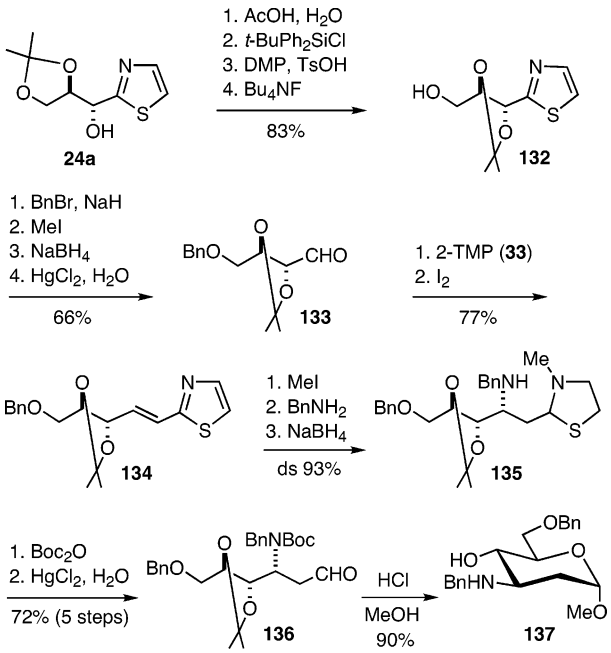
Scheme 21



relationship was assigned by NMR analysis of the pyranose derived therefrom. The NMR spectrum of this compound was in fact consistent with the methyl α-D-*threo*-pyranoside **131**. This demonstrated that the addition of benzylamine to (*E*)-**128** was *syn*-stereoselective with a ds of ca. 80%. Hence, this reaction scheme illustrated a new stereoselective amination strategy of chiral 2-alkenylthiazoles by combination of the thiazole-to-formyl unmasking protocol with the 1,4-conjugate addition of benzylamine.

A similar scheme was followed[88] in the two-carbon chain elongation and amination of the *aldehydo* tetrose 4-*O*-benzyl-2,3-*O*-isopropylidene-D-erythrose **133** (Scheme 22). This hitherto unknown stereoisomer of the four possible tetroses protected as 4-*O*-benzyl-2,3-*O*-isopropylidene derivatives was prepared starting from the alcohol **24a**, namely, the adduct of 2-TST **22** to D-glyceraldehyde acetonide **23** (see Scheme 4), by a protection−deprotection sequence of the hydroxyl groups and thiazole-to-formyl unmasking. Since also in this case the Wittig olefination of **133** with 2-TMP **33** gave a mixture of *E*- and *Z*-2-alkenylthiazoles in equal amounts, the almost complete conversion of the *Z*- into *E*-isomer **134** was carried out by refluxing the mixture in 1,2-dichloroethane containing iodine. Then the combined amination and aldehyde unmasking sequence was carried out. First, **134** was transformed into the *N*-methylthiazolium iodide, which upon treatment with benzylamine and quenching with sodium borohydride afforded the *syn* Michael-type adduct **135** with high selectivity. The completion of the formyl group unmasking by metal-assisted hydrolysis of the thiazolidine ring of **135** gave the protected chiral amino hexanal **136** in 72% overall yield. The stereochemistry of this product was demonstrated through the NMR spectrum of the methyl pyranoside **137** derived from it by treatment with hydrochloric acid in methanol. The structure of **137** corresponded to that of the 2-deoxy derivative of the amino sugar called kanosamine (3-amino-2,3-dideoxy-D-glucopyranose), which is one of the sugar fragments isolated from the natural product hikizimycin,[89] a potent anthelmintic agent.

Scheme 22

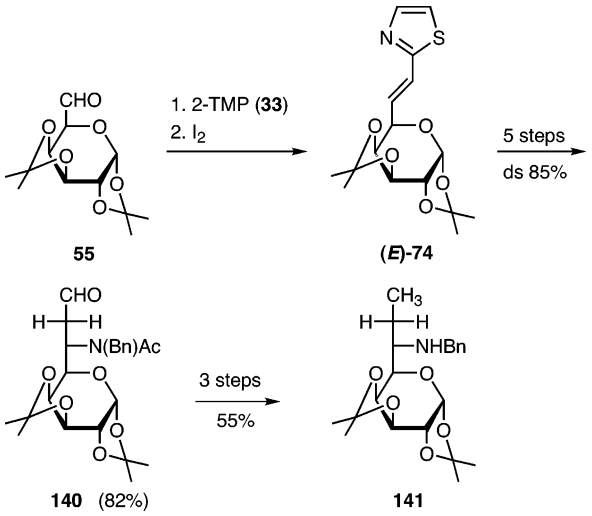


It was realized that the method illustrated above was also amenable to the construction of 3-amino-2,3,6-trideoxy-hexoses,[90] a class of simple amino sugars such as daunosamine, acosamine, ristosamine, and vancosamine, of great importance due to their presence in anthracycline antitumor antibiotics (adriamycin, daunomycin, daunorubicin).[91] Since it was known that stereochemical modifications of the amino sugar residue of these antibiotics provided some variations of their biological activity, 3-epi-D-daunosamine **139** (Scheme 23) was prepared[87] in good yield and stereoselectivity[92] by olefination of 4-deoxy-D-threose acetonide[93] **138** and amination as described above.

Scheme 23

A further example which is worth reporting on the application of the above methodology is that dealing with the transformation[87] of the α-D-*galacto*-hexodialdo-1,5-pyranose derivative **55** into the amino dialdooctose **140** (Scheme 24). In this case too the coupling step between **55** and 2-TMP **33** was scarcely stereoselective,[66] whereas the amination−unmasking sequence was both sufficiently stereoselective[92] and efficient as the amino sugar **140** was isolated in 82% yield from the 2-alkenylthiazole (*E*)-**74**. The formyl group of the *β*-amino aldehyde **140** was transformed via reduction to alcohol and dehydroxylation into a methyl group, thus producing an aminoalkyl chain linked to C-5 of the protected galactose ring. The resulting compound **141** featured some modifications

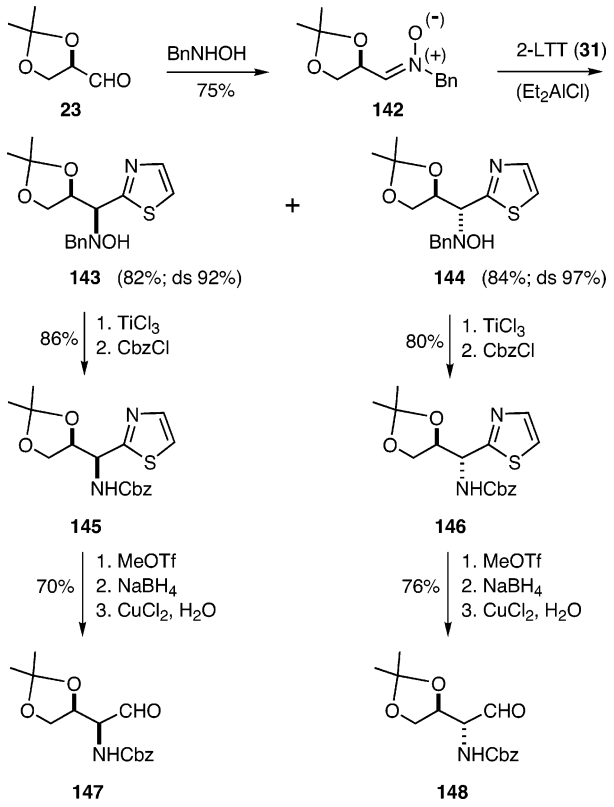
Scheme 24



in the C-5 aminated side chain with respect to the amino octose lincosamine, which is a component of the commercially important antibiotic lincomycin.[94]

A wide-scope thiazole-based synthetic methodology was developed by Dondoni and co-workers as a way of homologating aldehydes and at the same time introducing an α-amino group (aminohomologation).[95] This methodology entailed the coupling of aldonitrones with a 2-metalated thiazole followed by elaboration of the nitrogen-containing functionality in the adduct. When the initial aldehyde was an *aldehydo* sugar or a protected dialdose, a new entry to amino sugars was provided (see below). The choice of nitrones in this methodology was suggested by some advantages offered by these compounds, such as the ease of preparation[96] and stability and even more important the superior reactivity toward nucleophiles[97] with respect to other C=N derivatives of aldehydes such as imines. A model scheme of this new approach to α-amino aldehydes[95] is illustrated in Scheme 25. The (*Z*)-*N*-benzyl nitrone **142** derived from D-glyceraldehyde acetonide **23** treated with 2-lithiothiazole (2-LTT, **31**) generated in situ at low temperature afforded the 2-thiazolyl *N*-benzyl hydroxylamines **143** (*syn*-adduct) and **144** (*anti*-adduct) in good overall yield (82%) and 92:8 ratio.[98] On the other hand, the addition of diethyl aluminum chloride (or titanium tetrachloride) to the nitrone **142** before treatment with 2-LTT **31** gave the same *syn*- and *anti*-adduct **143** and **144** (84% overall yield) but in an opposite ratio (3:97). Each individual *N*-benzyl hydroxylamine **143** and **144** obtained as major product under the above conditions was transformed into the corresponding amine **145** and **146**, respectively, by a reductive dehydroxylation reaction using aqueous $TiCl_3$ at room temperature.[99] These reaction conditions were well tolerated by both the thiazole ring and the acid-sensitive acetonide protecting group, whereas the benzyl group was removed from nitrogen. Therefore, the resulting primary amine was protected again as *N*-Cbz derivative. Finally, the unmasking of the formyl group by the $CuCl_2$-based method[33] supplied the α-amino aldehyde **147** (2-amino-2-deoxy-D-threose) and the epimer **148** (2-amino-2-deoxy-D-erythrose).

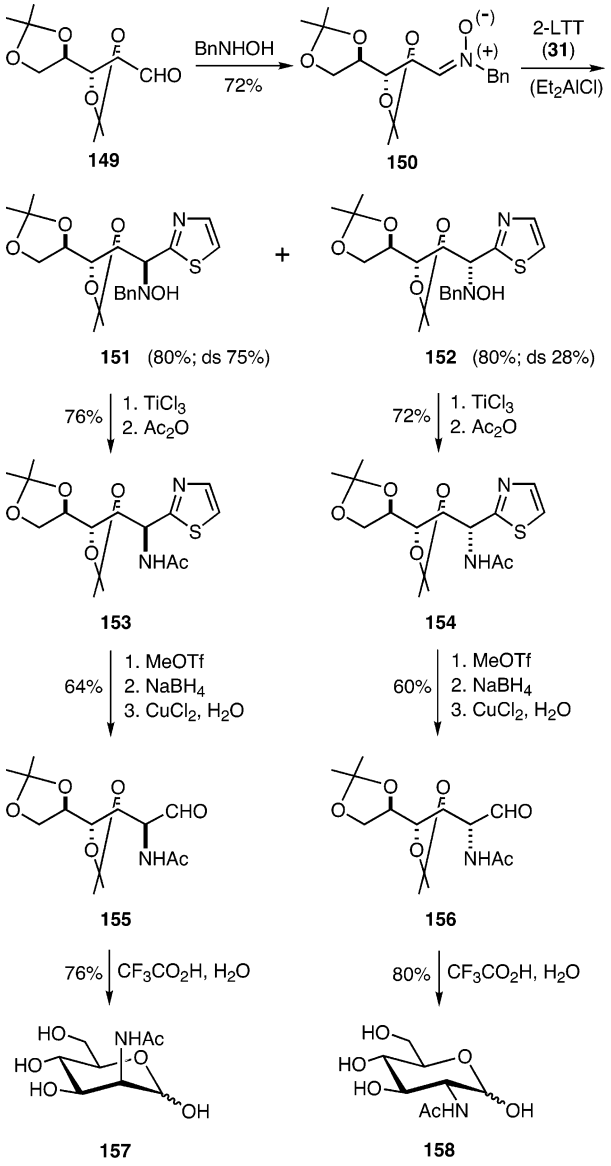
Scheme 25



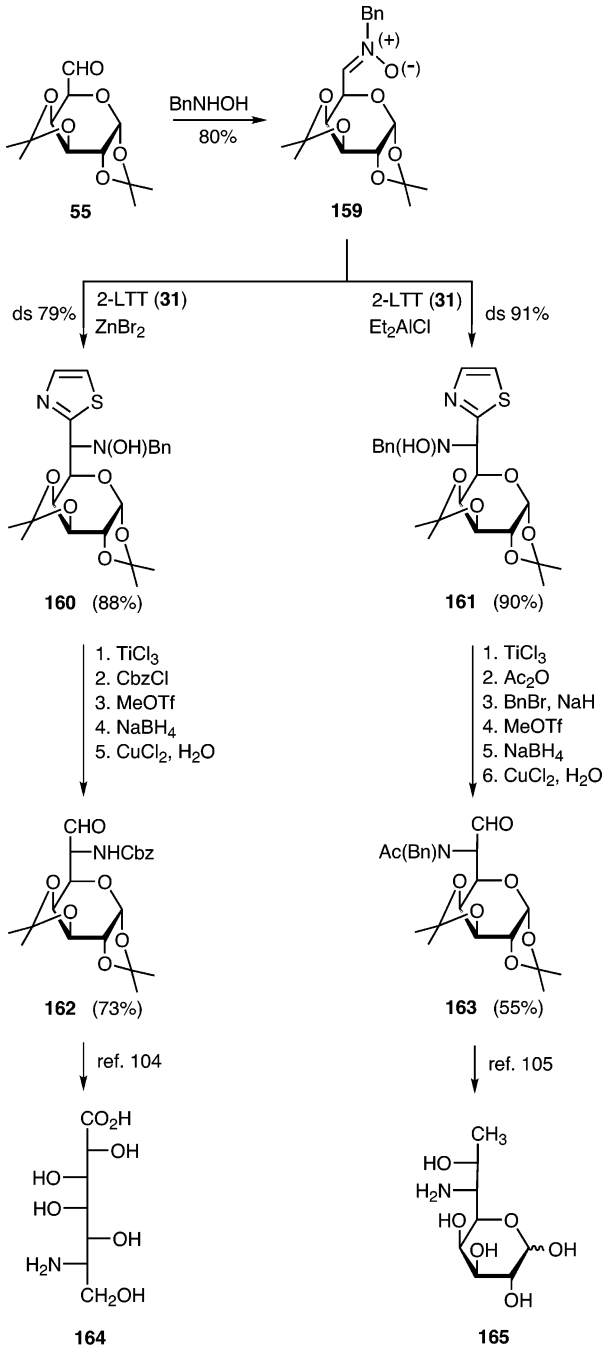
Addition reactions of 2-LTT **31** to nitrones derived from *aldehydo* sugars and dialdoses were carried out in the absence and presence of Lewis acids.[95] While mixtures of *syn*- and *anti*-adducts were obtained in good yields in all cases, the effect on stereoselectivity exerted by the precomplexation of the nitrone with Lewis acids was not as marked as shown in Scheme 25. In one case there was no change of selectivity at all. In fact, the addition of 2-LTT **31** to the nitrone **150** derived from *aldehydo*-D-arabinose diacetonide **149** (Scheme 26) was *anti*-selective either in the absence of a Lewis acid (ds 72%) or in the presence of Et_2AlCl (ds 75%). Hence, under both conditions the major product was the 2-thiazolyl *N*-benzyl hydroxylamine **151** and the minor product was the epimer **152**. The elaboration of these compounds via reductive dehydroxylation, protection of the amino group, and formyl group unmasking completed the two parallel aminohomologation sequences to give the *N*-acetyl-D-mannosamine diacetonide **155** and the *gluco* epimer **156**. Both compounds were readily transformed into the hydroxyl-free acetamido sugars **157** and **158**. It is worth noting that the amino sugar **155** was earlier prepared from D-gluconolactone (52%) and transformed into *N*-acetyl-neuraminic acid by Vasella and co-workers.[100]

The use of Lewis acids was crucial in the aminohomologation of the D-galacto-dialdose **55** because the addition of 2-LTT **31** to the *N*-benzyl nitrone **159** in the absence of complexing agents was essentially unselective.[95,101] Instead, the complexation of **159** with two different Lewis acids such as $ZnBr_2$ and Et_2AlCl induced substantial selectivity but in an opposite sense (Scheme 27). The isolation of the major products **160** and **161** and their elaboration afforded

Scheme 26



Scheme 27



the epimeric amino aldehydes **162** and **163**, respectively, thus completing the stereodivergent aminohomologation sequence of the aldehyde **55**. This scheme represented a formal stereoselective synthesis of the polyhydroxylated ϵ-amino acid **164** (destomic acid)[102] and amino sugar **165** (lincosamine).[103] In fact, synthetic routes leading to these natural products through compounds **162** and **163** as intermediates were previously reported.[104,105]

The wide scope of the aminohomologation of *aldehydo* sugars and dialdoses was further demonstrated by the synthesis of other pairs of diastereomeric amino sugars, some of which are shown in Figure 4.

3.4. 3-Deoxyulosonic Acids

The ease of oxidation of the formyl group to the carboxyl allowed exploitation of the thiazole-based methodology for the preparation of natural higher 3-deoxy-2-ulosonic acids and unnatural analogues. A great deal of interest has been focused over the years on enzymatic and chemical synthesis of these carbohydrates[106] due to their potential as building blocks for more complex glycoconjugates and use by glycobiologists in studies of their function in important biological processes as well as for the development of their inhibitors. Some common natural members of these sugar carboxylic acids are shown in Figure 5. The 7-phosphate of the seven-carbon compound 3-deoxy-D-*arabino*-2-heptulosonic acid (DAH) **170** is a key intermediate in the biosynthesis of aromatic amino acids from glucose in microorganisms and plants (shikimate pathway);[107] the well-known eight-carbon compound 3-deoxy-D-*manno*-2-octulosonic acid (KDO) **171** occurs in the lipopolysaccharide region of the cell surface of all Gram-negative bacteria and is an essential component for their replication;[108] the nine-carbon compound 3-deoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid (KDN) **172** has been isolated from polysialoglycoproteins of rainbow trout eggs, and its

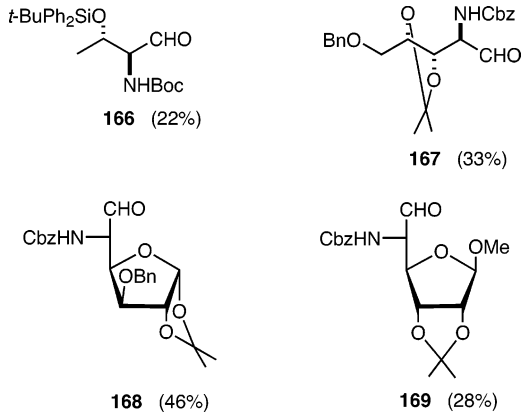


Figure 4. Amino sugars prepared by aminohomologation of the corresponding *aldehydo* sugars (the *C*-2 epimers are not shown).

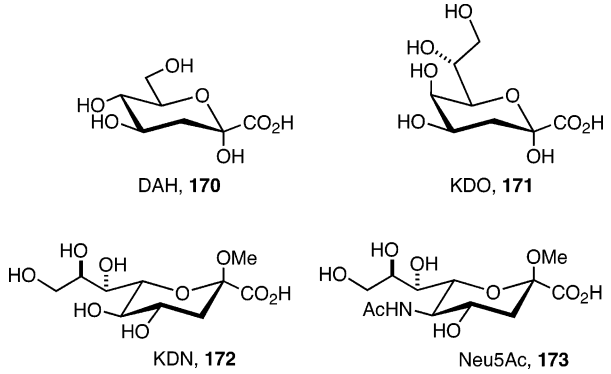
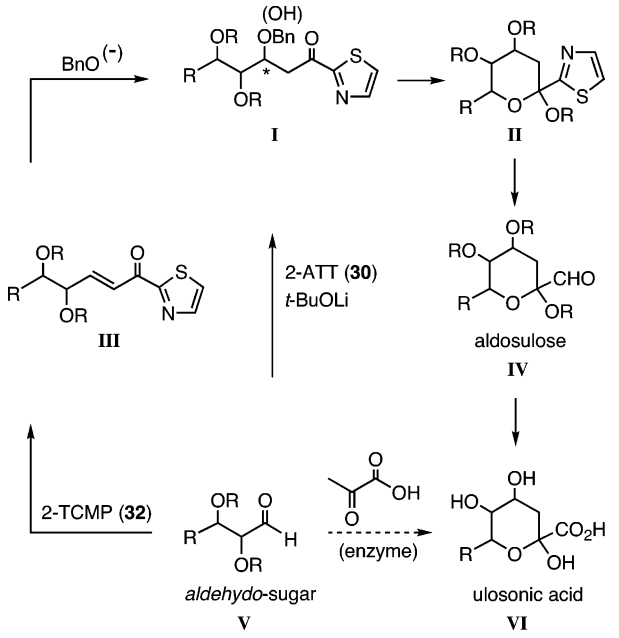


Figure 5. Naturally occurring 3-deoxy-ulosonic acids.

presence is thought to allow those polysialoglycoproteins to perform some important functions in egg activation;[109] finally, the aminated analogue of **172**, namely, 5-acetamido-3,5-dideoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid (*N*-acetyl-neuraminic acid, Neu5Ac or NANA) **173**, is the most common member of a large class of aminononulosonic acids (sialic acids)[110] which are incorporated at the terminal positions of glycoproteins, glycolipids, and oligosaccharides and play an essential role in biological molecular recognition processes, such as cell adhesion and differentiation phenomena.[111]

The most logical and simple synthetic approaches to 3-deoxy-2-ulosonic acids **VI** in general are those based on biomimetic pathways, i.e., the enzyme-catalyzed couplings of an *aldehydo* sugar **V** with a pyruvic acid derivative[112] or the chemical coupling of the same *aldehydo* sugar with a surrogate for the pyruvate unit (Scheme 28).[113] The Dondoni group developed two synthetic routes leading to these higher sugars based on the thiazole−aldehyde synthesis. These routes employed the thiazolyl ketone 2-ATT **30** and the phosphorane 2-TCMP **32** as synthetic equivalents of pyruvaldehyde. Crucial to the viability of these routes was the ready access to *R*- or *S*-configured *β*-hydroxy or *β*-alkoxy ketone **I**. In the most direct route, the *β*-hydroxy ketone **I** was obtained by aldol condensation of the *aldehydo* sugar **V** with the lithium enolate generated from 2-ATT **30** and a suitable base.[68] The other route was based on the Wittig olefination of **V** by 2-TCMP **32** to give the α,*β*-enone **III,** which in turn underwent the Michael-

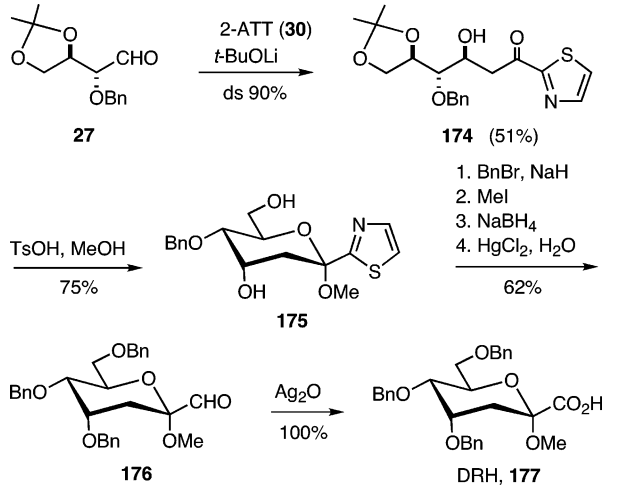
Scheme 28



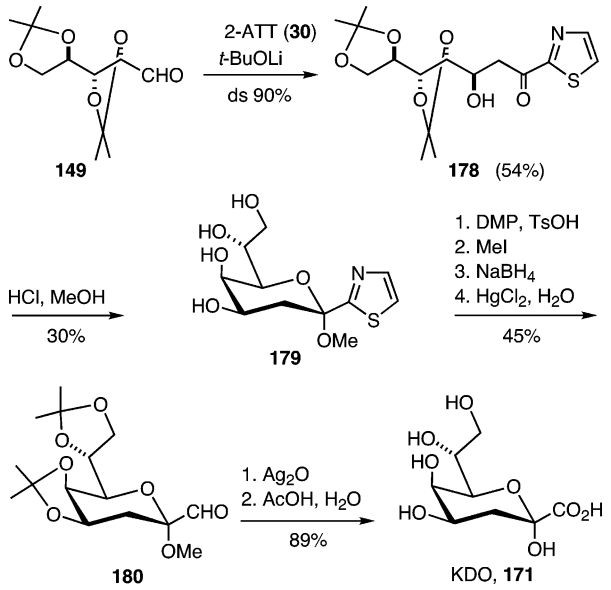
type addition of benzyl oxide anion to give the *β*-alkoxy ketone **I**. This intermediate furnished the aldosulose **IV**, a three-carbon higher homologue of the *aldehydo* sugar **V**, by intramolecular hemiketalization (formation of the thiazole masked precursor **II**) and formyl group unmasking. The conversion of **IV** to the target ulosonic acid **VI** occurred by the almost quantitative oxidation of CHO to CO_2H. A direct conversion of the intermediate **II** into **VI** appeared to be hampered by the lack of methods allowing for an effective conversion of the thiazole ring into the carboxyl group.[114] Some examples which serve to illustrate the two aforementioned synthetic routes in some detail are reported in the following schemes.

The aldol condensation route was first followed[37] for the synthesis of a heptulosonic acid starting from 2-*O*-benzyl-3,4-isopropylidene-D-erythrose **27** (Scheme 29). After searching for suitable conditions to generate the lithium enolate from 2-ATT **30**, the aldol condensation with **27** was carried out to give the *anti*-adduct **174**. The configuration of this *β*-hydroxy

Scheme 29



Scheme 30

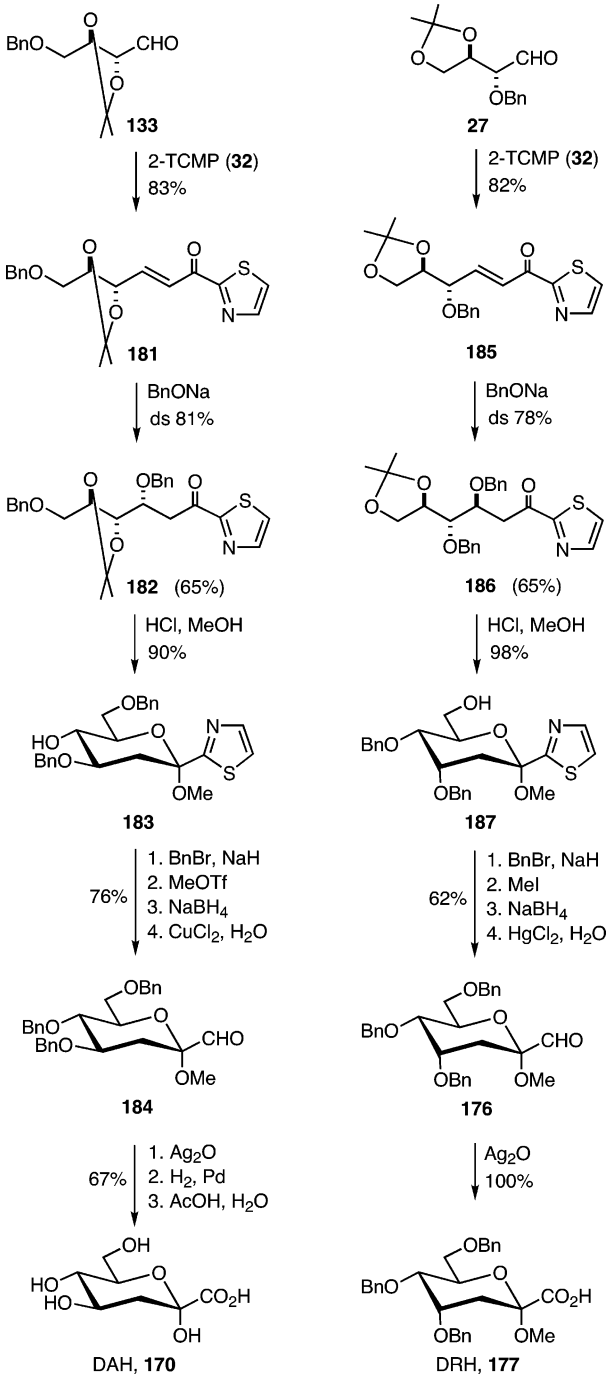


ketone was demonstrated by NMR analysis of the methyl pyranoside **175**, the precursor to the 3-deoxy-2-heptosulose **176** (*ribo* configuration). This aldehyde was transformed into the *O*-protected 3-deoxy-D-*ribo*-2-heptulosonic acid (DRH) **177** in virtually quantitative yield (24% from **174**). It is worth noting that DRH is the C-4 epimer of the naturally occurring product DAH **170** shown in Figure 5.

Having observed that the condensation of the lithium enolate of 2-ATT **30** with the alkoxy aldehyde **27** and with other polyalkoxy aldehydes[67] occurred with high levels of *anti*-selectivity (see Scheme 13), the synthesis of KDO **171** was carried out[37,115] starting from the *aldehydo*-D-arabinose diacetonide **149** (Scheme 30). As expected, the addition of a mixture of this aldehyde and 2-ATT **30** to the solution of *t*-BuOLi afforded the desired *anti*-aldol **178** with good diastereoselectivity (ds 90%) although in modest isolated chemical yield (54%). The formation of substantial amounts of side products explained the modest yield in this and other aldol condensations of the lithium enolate of 2-ATT **30** with *aldehydo* sugars. The synthesis was continued following the established scheme constituted of (a) intramolecular hemiketalization of **178** to **179**, (b) conversion of **179** into the aldosulose **180** by thiazole-to-formyl unmasking, and (c) oxidation of the latter to KDO[116] **171** in 6.5% overall yield from the protected D-arabinose **149**.

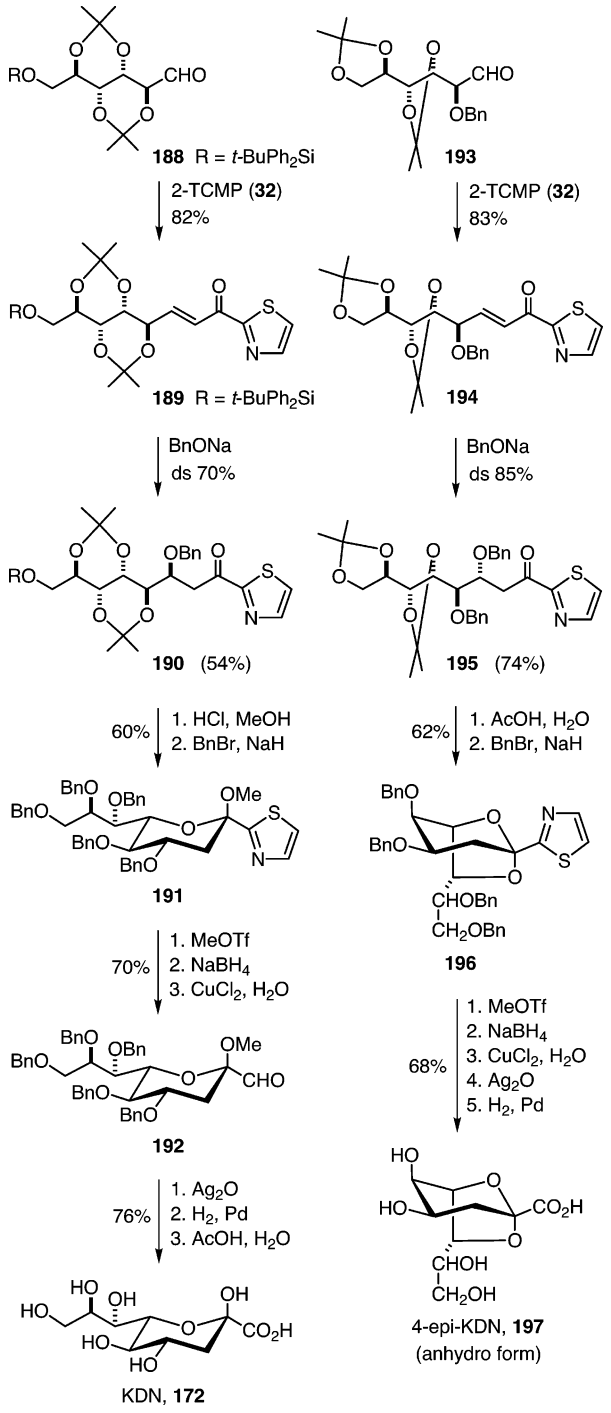
The addition of the lithium enolate of 2-ATT **30** to a set of *aldehydo* sugars confirmed high levels of *anti*-selectivity. On the other hand, initial studies[117] indicated that *syn*-adducts **I** were accessible by the Wittig−Michael route. In fact, the addition of benzyloxide anion to the α,*β*-enones derived from D-glyceraldehyde acetonide **23** and D-arabinose diacetonide **149** afforded the corresponding *β*-alkoxy ketones with high *syn*-selectivity. Hence, a formal synthesis of the C-4 epimer of KDO **171**, i.e., 3-deoxy-D-*gluco*-2-octulosonic acid was reported.[117] Also, the addition of benzyloxide anion to the α,*β*-enone **181** (Scheme 31) prepared via Wittig reaction of 2-TCMP **32** with 4-*O*-benzyl-2,3-*O*-isopropylidene-D-erythrose

Scheme 31



133 was *syn*-selective (ds 81%)[38] as it afforded the tetraalkoxy ketone **182** with the *arabino* configuration.[118] This ketone was transformed into DAH[119] **170** through the aldosulose **184**. Quite interestingly this synthetic work revealed the high dependence on the substrate structure of the stereochemical outcome of the 1,4-conjugate additions to these polyalkoxy α,*β*-enones. In particular, it appeared that the protection of the *γ*-hydroxyl group was critical in that respect. In fact, the addition of benzyloxide anion to compound **185** derived from the D-erythrose derivative **27**, an isomer of **133**, was essentially *anti*-selective (ds 78%) as proved by the conversion of the major adduct **186** featuring a *ribo* configuration into **187** which in turn was transformed into DRH, **177**.

Scheme 32

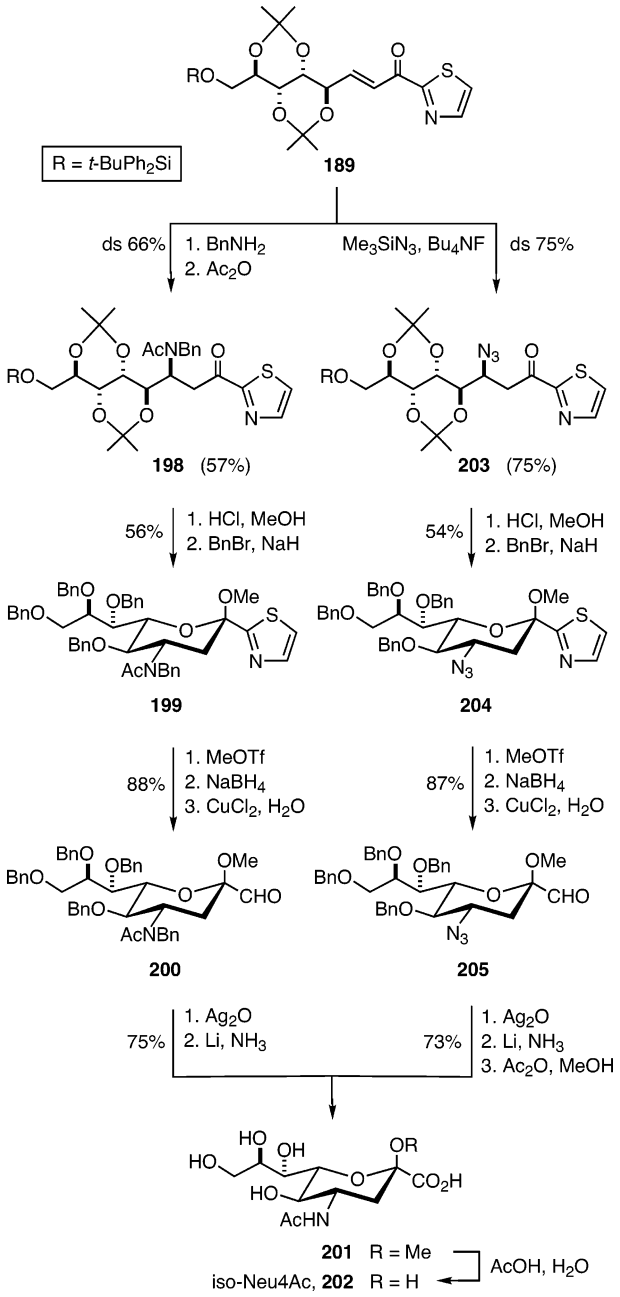


The same chemistry was extended[38,120] to prepare the 2-nonulosonic acids KDN **172** and the isomer 4-epi-KDN **197** (Scheme 32). The differentially protected *aldehydo*-D-mannoses **188** and **193** were employed as starting compounds in order to obtain via Wittig−Michael route two polyalkoxy ketones with opposite configuration at the carbon bearing the β-alkoxy group. In fact, under suitable conditions the addition of BnONa to the α,β-enones **189** and **194** was *syn*- (ds 70%) and *anti*-selective (ds 85%), respectively, leading to the diastereomeric ketones **190** and **195** in good isolated yields. The elaboration of **190** through the usual reaction sequence (hemiketalization, formyl group unmasking) afforded the aldosulose **192**, which was then transformed into KDN[121] **172** via oxidation and protective group removal. On the other hand, the hemiketalization of **195** was accompanied by a second ring closure via elimination of methanol. This reaction led to a 1,6-anhydro-pyranoside, which upon benzylation was isolated as the tetrabenzylated *C*-thiazolyl derivative **196**. The thiazole cleavage to formyl, oxidation of the latter to carboxyl, and reductive debenzylation afforded compound **197** which corresponded to the 2,7-anhydro form of 4-epi-KDN. Unfortunately the anhydro sugar **197** proved to be quite stable and resistant to the conversion to 4-epi-KDN even by treatment with aqueous trifluoroacetic acid.

It was realized that the use of nitrogen nucleophiles in the Wittig−Michael route shown in Scheme 28 would lead to ulosonic acids bearing a nitrogenated functionality at C-4. Hence, after an initial study[122] where conditions were searched to achieve a good level of *syn*-selectivity in the addition of benzylamine to a model α,β-enone,[123] a target compound was considered.[124] This was the hitherto unreported 4-acetamido-3,4-dideoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid **202** (Scheme 33), a positional isomer of *N*-acetylneuraminic acid (Neu5Ac) **173** (Figure 5). For this reason compound **202** was named iso-Neu4Ac. Given the essential role of Neu5Ac **173** and sialic acids in general in the biological activity of various glycoconjugates, it appeared important to prepare sialic acid analogues since these compounds are potential inhibitors of the above biological processes. Hence, an initial approach to iso-Neu4Ac **202** was carried out by addition of benzylamine to the thiazolyl α,β-enone **189** and acylation at low temperature. The reaction turned out to be poorly *syn*-selective (ds 66%) and afforded the required β-amino ketone **198** in 57% yield. The conversion of this compound into the aldosulose **200** was carried out without any problem via hemiketalization to **199** and thiazole-to-formyl unmasking. Also, the oxidation of the formyl group of **200** to carboxyl was effectively carried out by Ag_2O, whereas the removal of the *N*-benzyl group required harsh conditions such as the use of lithium in liquid NH_3. The methyl iso-Neu4Ac **201** obtained in this way was contaminated by small amounts of numerous side products whose removal proved to be unsuccessful. Consequently, the synthesis was interrupted at this point. A more effective synthesis was carried out by using trimethylsilyl azide ($TMSN_3$) as nitrogen nucleophile. One of the advantages of using this nucleophile was a more substantial *syn*-selectivity (ds 75%) in the 1,4-conjugate addition to the α,β-enone **189**, thus leading to the β-azido ketone **203** in 75% isolated yield. Then the synthesis was continued by the usual scheme to give in this case pure methyl iso-Neu4Ac **201** through the intermediates **204** and **205**. Finally, the removal of the methyl group from **201** by acid hydrolysis gave the target iso-Neu4Ac **202** in pure form. From this work it appeared that another common functional group such as the azido group was compatible with the thiazole-to-formyl unmasking protocol.

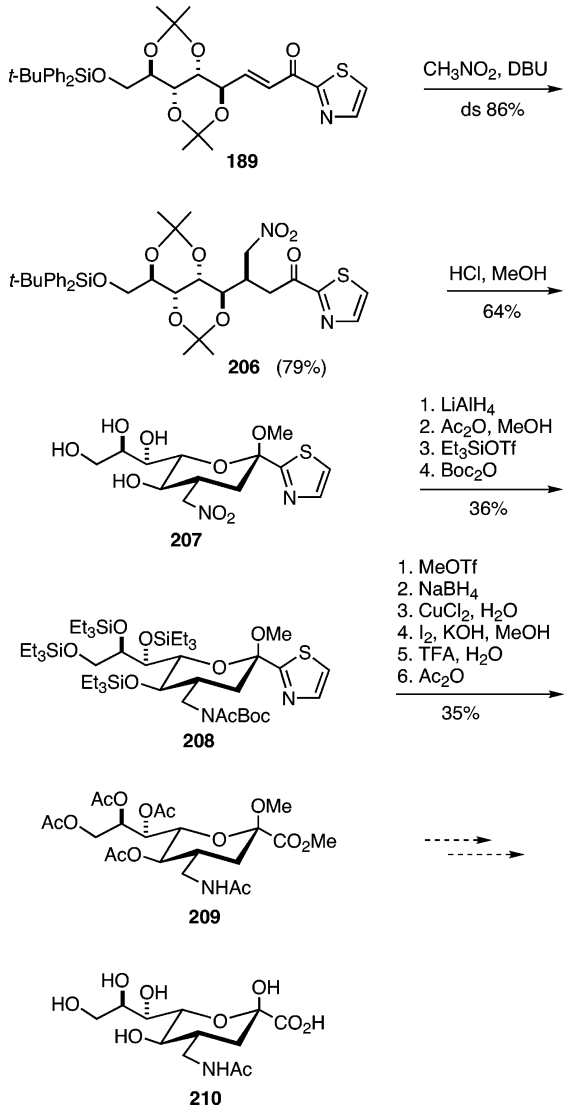
The carbanion of nitromethane was found to react readily[124b] with α,β-enones derived from *aldehydo* sugars by carbonylolefination with 2-TCMP **32**. Hence, the *syn*-stereoselective addition (ds 86%) of this

Scheme 33



carbon nucleophile to **189** leading to the ketone **206** (Scheme 34) was the key step in the preparation of a one-carbon higher homologue of iso-Neu4Ac **202**, which is the branched amino ulosonic acid **210** in which the acetamido group was attached to the pyranose ring through a methylene bridge. The interest for this type of ulosonic acid stemmed from the above-mentioned importance of preparing analogues of Neu5Ac. The hemiketalization of ketone **206** to methyl pyranoside **207** was carried out without any problem, whereas the elaboration of this compound was far for being a trivial operation. The nitro group was first reduced to amino group, and then this and the hydroxyl groups were protected as shown in the methyl pyranoside **208** in order to perform the formyl group unmasking and oxidation to carboxylic acid. The isolated compound **209** was a protected derivative of the target 4-*N*-acetylaminomethyl nonulosonic acid **210**.

Scheme 34

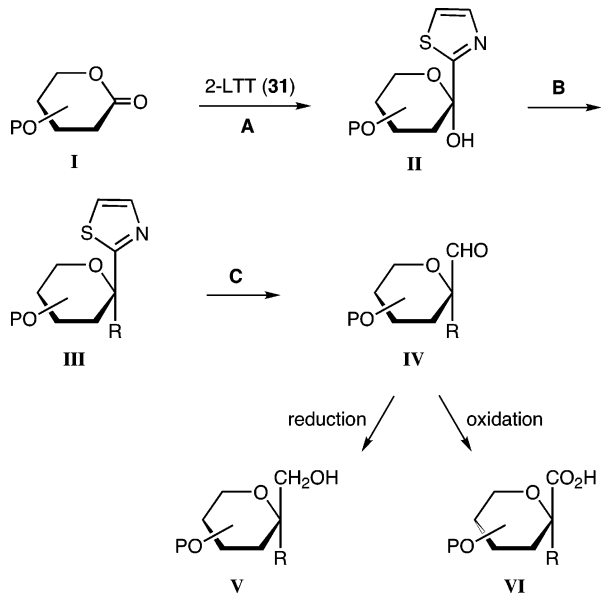


3.5. Ulosonides and Ketosides

A wide-scope thiazole-based synthetic methodology emerged from research in the Dondoni laboratory aiming at preparing formyl *C*-glycosides[125] (see section 4.1) as building blocks for more complex *C*-glycosides. The methodology relied on the coupling of the easily available sugar lactones **I** with 2-LTT **31** to give thiazolylketoses **II** (Scheme 35). The *O*-acetates of these adducts served as ketosyl donors toward various oxygen, nitrogen, phosphorus, and carbon nucleophiles[15e] to give glycosides **III,** which when subjected to the formyl unmasking afforded aldosulosides **IV**. Owing to the facile reduction and oxidation of the formyl group, the aldehydes **IV** were transformed into ketosides **V** and ulosonides **VI**, respectively.

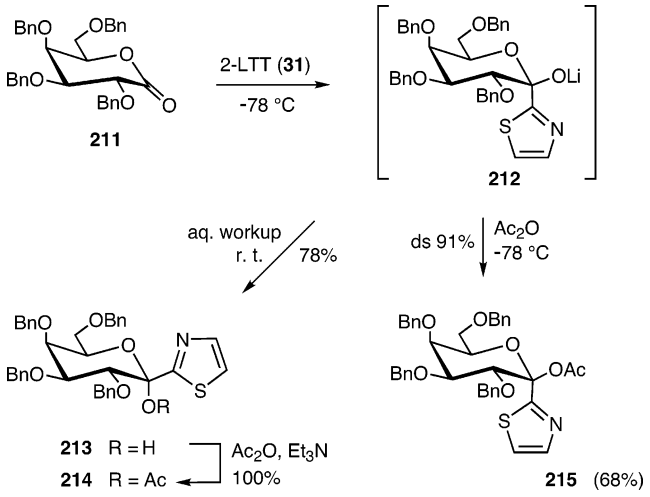
While thiazolylketoses **II** were inert as ketosyl donors, the activation as *O*-acetates transformed these compounds in very reactive species under polar glycosylation conditions.[15e] Hence, two reaction pathways were reported[125b] for the preparation of thiazolylketose acetates as pure α- or *β*-anomers. Typically, the reaction of 2,3,4,6-tetra-*O*-benzyl-D-galactonolactone **211** with 2-LTT **31**, generated in

Scheme 35



situ from 2-bromothiazole **28** and BuLi at −78 °C, followed by aqueous workup afforded the α-anomer thiazolylketose **213** in good isolated yield (78%) (Scheme 36). Treatment of this compound with Ac_2O

Scheme 36



and Et_3N in dry dichloromethane furnished the corresponding *O*-acetate **214** in essentially quantitative yield (method A). On the other hand, reacting **211** and **31** at −78 °C and then quenching the crude reaction mixture with Ac_2O, the *β*-anomer ketose acetate **215** was obtained as major isolated product (68%) (method B). Thus, it appeared that the acetylation at low temperature allowed for the efficient trapping of the lithioketose **212** whereas the aqueous workup of this product induced the conversion of the *β*- into the α-ketose **213**, the latter being the most stable isomer because of the anomeric effect. Given the availability of a large variety of pyrano- and furano-lactones, a collection of thiazolylketose acetates in either α- or *β*-form was prepared by the above methods A and B.[125] The compounds obtained as major isomers by the most employed method A are shown in Figure 6.

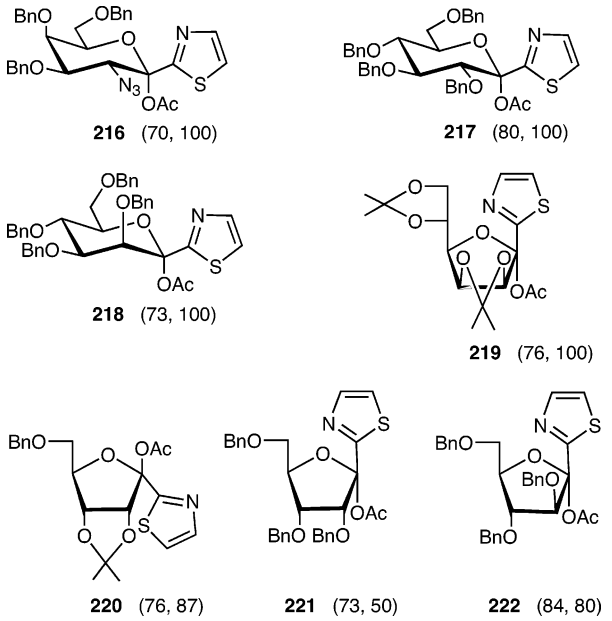
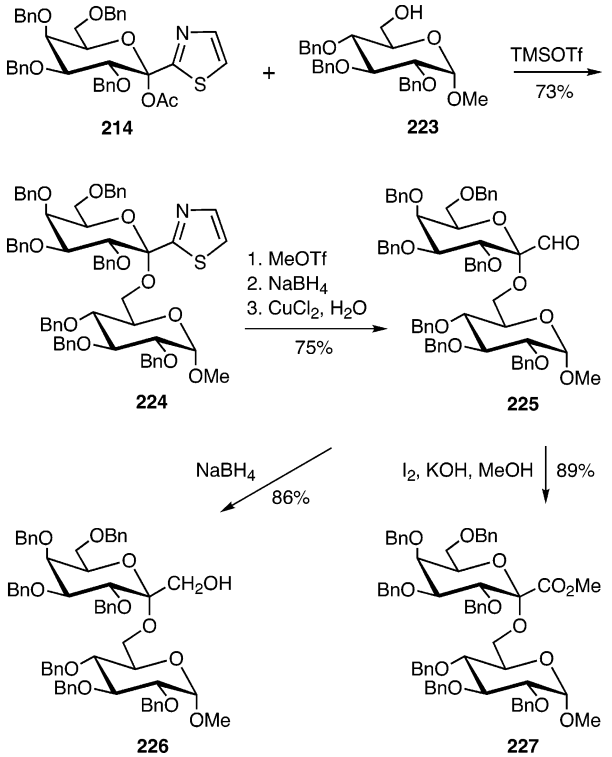


Figure 6. Thiazolylketose acetates prepared by method A (total yield % of isolated α and *β* anomers, and % of the major product that is shown).

The glycosidation of thiazolylketose acetates by primary and secondary sugar alcohols upon activation with trimethylsilyl triflate (TMSOTf) (*O*-glycosidation) was reported.[126] For example, the coupling between 1-*C*-(2-thiazolyl)-α-D-galactopyranosyl acetate **214** and methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **223** furnished exclusively the α-linked thiazolylketodisaccharide **224** in good isolated yield (73%) (Scheme 37). The same α-selectivity was observed using the *β*-anomer of **214** as ketosyl donor. This result was in agreement with the formation of a sugar oxycarbenium ion intermediate arising from

Scheme 37



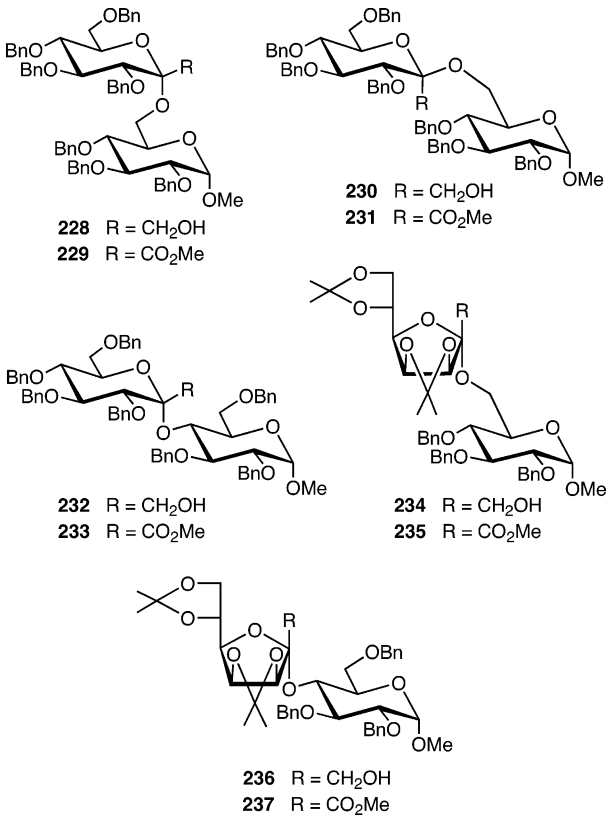


Figure 7. Disaccharides obtained by glycosidation with primary and secondary sugar alcohols.

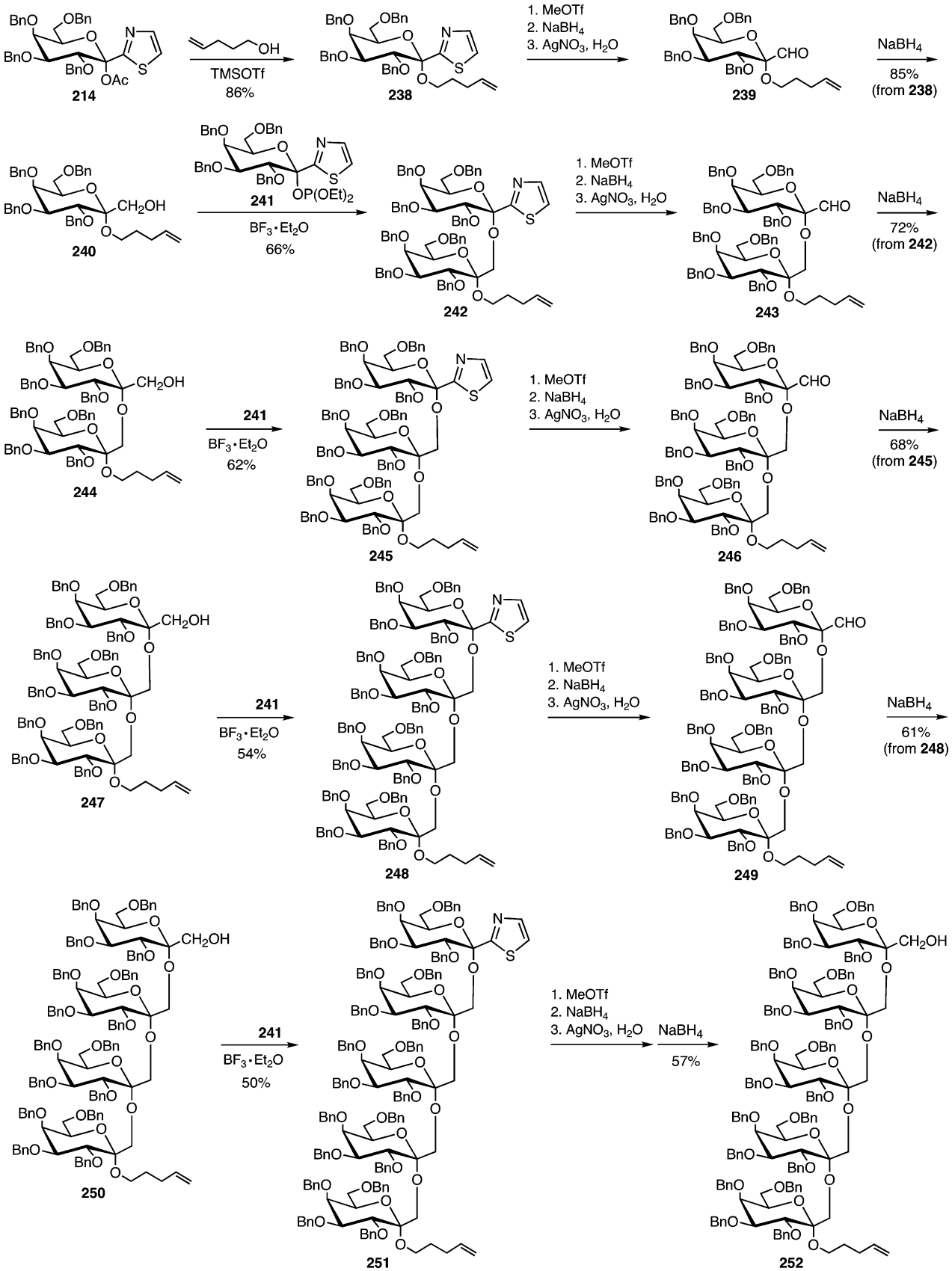
214 by removal of the acetoxy group followed by a sterically controlled nucleophilic addition according to the general mechanism of polar glycosidation reactions.[127] Hence, it appeared that thiazolylketose acetates as α- or *β*-anomers or their mixtures could be equally employed as ketosyl donors without affecting the stereochemical outcome of their glycosylation reactions. As a completion of the thiazole aldehyde synthesis according to Scheme 35, the thiazole ring of the ketodisaccharide **224** was transformed into the formyl group to give the aldehyde **225**. The easy reduction and oxidation of this compound afforded the *O*-ketoside **226**, a disaccharide of a ketose, and the *O*-ulosonide **227**, a disaccharide of an ulosonic acid, respectively. Similar *O*-ketosides and *O*-ulosonides which were prepared using other thiazolylketose acetates are collected in Figure 7. The synthesis of these functionalized disaccharides is noteworthy because of the well-known difficulties of *O*-glycosidation of ketoses and ulosonic acids.[128]

The ketosyl donor properties of **214** were exploited in the preparation of the alcohol **240**, which was designed to serve as ketosyl acceptor in a synthetic route to α-D-(2,1)-linked ketoside oligomers[129] (Scheme 38). In fact, the *O*-glycosidation of **214** with 4-penten-1-ol followed by thiazole-to-formyl transformation and reduction afforded the pentenyl hydroxymethylketoside **240** in very good overall yield (73%). It is worth noting that the *O*-pentenyl group was tolerant of the formyl group unmasking and its reduction conditions. The pentenyl hydroxymethylketoside **240** was glycosylated by the thiazolylketosyl phosphite **241**, which in turn was prepared in gram-scale quantities from the thiazolylketose **213** and ClP-$(OEt)_2$. The $BF_3{\cdot}Et_2O$-promoted coupling between **240** and **241** was quite stereoselective since it afforded exclusively the α-D-ketodisaccharide **242** in good isolated yield (66%). The application of the *O*-pentenyl compatible thiazole-to-formyl unmasking protocol furnished the aldehyde **243,** which was readily reduced to the hydroxymethyl ketodisaccharide **244** (48% overall yield from **240**). The repetition three more times of the same homologative cycle constituted of sequential α-selective glycosidation with **241** and generation of the hydroxymethyl group from the thiazole ring afforded the ketotrisaccharide **247** (42%), the ketotetrasaccharide **250** (33%), and the ketopentasaccharide **252** (28%), all exhibiting D-*galacto*-2-heptulopyranose units assembled through α-(2 → 1) linkages. There was only a slight decrease in yield from the first to the fourth cycle, which indicated that the assembly of longer oligoketosaccharidic chains should be possible. Furthermore, the thiazolyl ketosides **238**, **242**, **245**, **248**, and **251**, all bearing the *O*-pentenyl group, were considered as potential glycosyl donors via the Fraser−Reid pentenyl glycoside method[130] for preparing more complex oligosaccharides or glycoconjugates.

While the synthesis of the above linear ketoside oligomers highlighted the role of thiazole as synthetic auxiliary in multistep methodologies, the use of these compounds as biological probes was not investigated. On the other hand, their transformation into cyclic systems was considered[129] with the aim of preparing new molecular receptors similar to the so-called cyclofructins, the cyclic oligomers of D-fructofuranose produced by enzymatic degradation of inulin.[131] Accordingly, the intramolecular glycosidation of the ketotrisaccharide **247** under the Fraser−Reid activation conditions (*N*-iodosuccinimide and TMSOTf)[130] afforded the cyclic (α,α,α)-D-trisaccharide **253** whose highly symmetrical structure was consistent with ^1H and ^{13}C NMR spectra and was confirmed by X-ray analysis. Debenzylation of this compound by hydrogenolysis produced the hydroxy-free product **254**. The recognition ability in an organic solvent ($CHCl_3/CH_3CN$) of the benzylated cyclic trimer **253** was tested using neutral and charged species. The alkali metal cations lithium, sodium, potassium, calcium, and to a lesser extent magnesium formed stable complexes.

In relation to their interest on the construction of water-soluble chiral receptors by introduction of carbohydrate molecules at either rim of calixarenes,[132] Dondoni and co-workers exploited the good ketosyl donor properties of thiazolylketose acetates as a means for the installation of ketosyl and ulosonyl residues in calixarenes.[133] In particular, the reaction of the model D-*galacto* derivative **214** with the symmetrical calixarene diol **255** (Scheme 40) under the usual TMSOTf-promoted conditions afforded the bis-*O*-ketosyl calixarene derivative **256** in good isolated yield. It was firmly established by NMR analysis that both ketosyl moieties were linked with an α-D (axial) orientation and that the calixarene system retained the cone conformation as in the original diol **255**. The elaboration of the bis-ketoside **256** was carried out by the usual procedure, i.e., the unmasking of the dialdehyde **257** followed by the oxidation and protec-

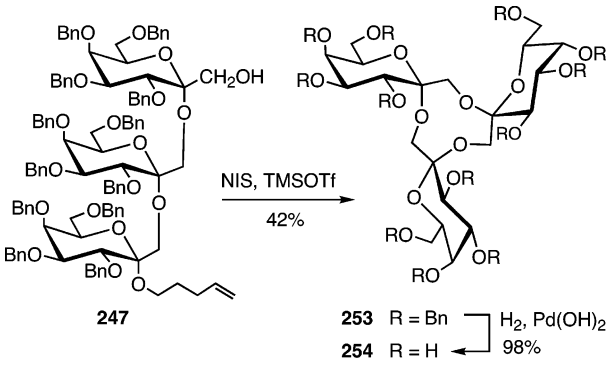
Scheme 38



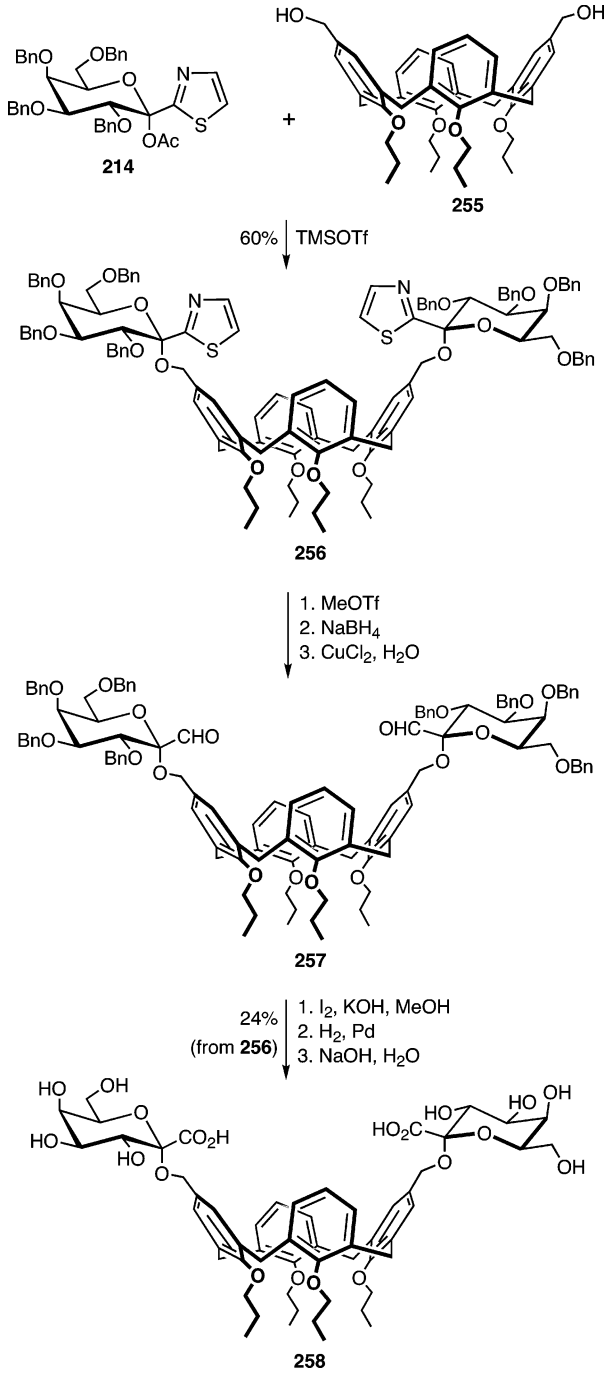
tive group removal to give the diacid **258**. This calixsugar exhibiting two heptulosonic acid residues represented the first member of a new class of calixsugars bearing charged functional groups at C-1 of the sugar moieties.

Glycosidation reaction of thiazolylketose acetates occurred readily also with trialkyl phosphites to give *P*-glycosides.[134] As illustrated in Scheme 41, a stereoselective reaction took place between the acetate **214** and triethyl phosphite to give the Arbusov-type

Scheme 39

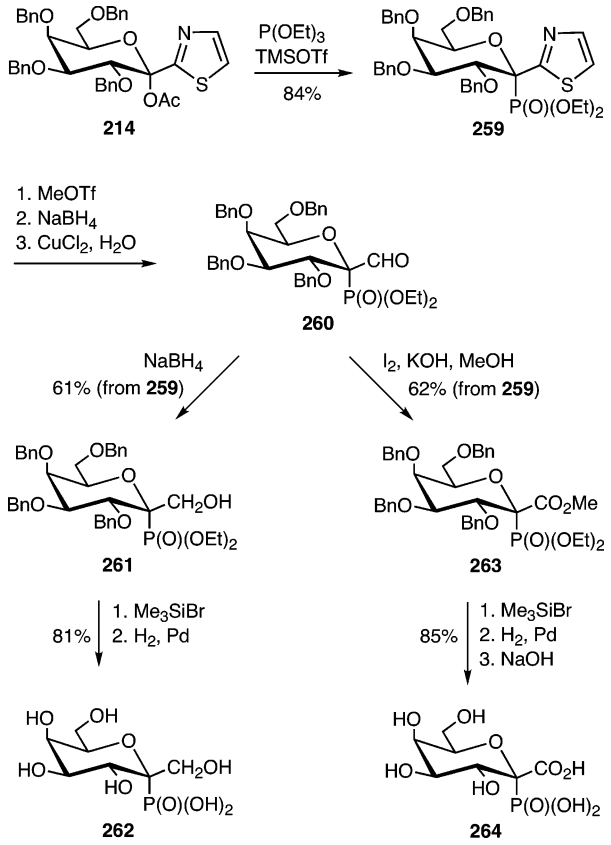


Scheme 40



product glycosyl phosphonate **259** as α-D-anomer in high isolated yield. The phosphonate group did not interfere with the thiazole-to-formyl transformation as the elaboration of **259** to the aldosulosyl phosphonate **260** by the copper-based protocol[33] was carried out in high yield (at least 90%). Then the reduction of this aldehyde to the alcohol **261** and oxidation to the ester **263** followed by the benzyl group removal and ester saponification afforded the ketosyl and ulosonyl phosphonic acids **262** and **264**, respectively. The same approach was successfully applied to other thiazolylketose acetates (see Figure 6), and therefore, a collection of ketosyl and ulosonyl phosphonates was prepared (Figure 8). It was pointed out that these *P*-glycosides were nonisosteric but isopolar analogues of glycosyl phosphates since the phosphono group was directly linked to the glycosyl residue. Hence, interest for these compounds[135] lacking the enzymatically susceptible ester linkage of phosphates stemmed from their potential activity as competitive inhibitors of glycosyltransferases and therefore from their use as lead structures in drug discovery against carbohydrate-based metabolic disorders.[136]

Scheme 41



Trimethylsilyl azide ($TMSN_3$) was found to be a suitable nitrogen nucleophile reacting with thiazolylketose acetates upon activation with TMSOTf to give the corresponding azido glycosides.[137] The first compound which was targeted through this glycosidation reaction was the peculiar azido acetaldehyde **276** sharing its central carbon atom with the D-ribofuranose ring (Scheme 42). The synthesis of **276** was carried out by addition of $TMSN_3$ to the thiazolyl-β-D-ribofuranose acetate **220** or its α-isomer. Both reactions furnished the β-azido glycoside **275** and its α-anomer (not shown) in a 3:1 ratio and 84% overall yield. Compound **275** was transformed into the target

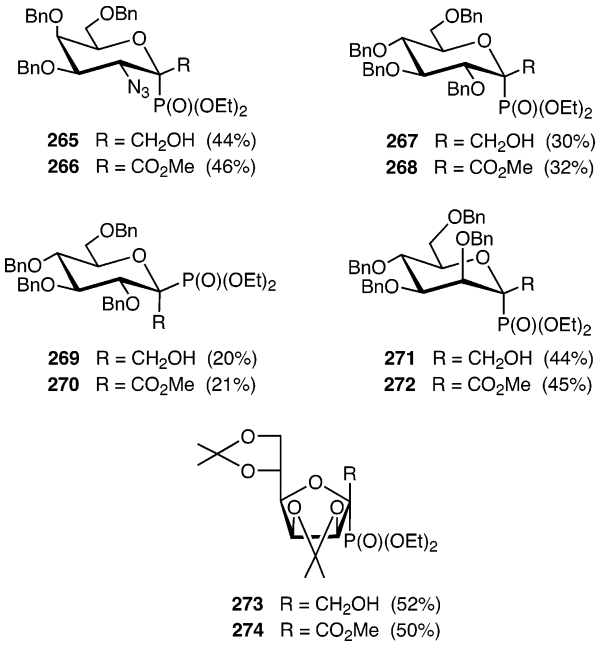
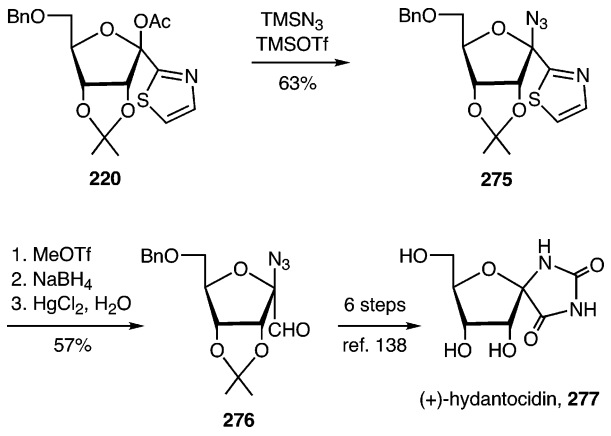


Figure 8. Protected ketosyl and ulosonyl phosphonates prepared from the corresponding thiazolylketose acetates.

Scheme 42



aldehyde **276** in satisfactory yield (57%) by the thiazole-to-formyl transformation protocol. In this case, the latter operation required some adjustments of the experimental conditions to avoid side reactions between the *N*-methylthiazolium ring, an intermediate of the unmasking sequence, and the adjacent azido group acting as a 1,3-dipolar partner of cycloaddition reaction. An earlier synthesis of **276** from D-fructose (seven steps, 34%) was reported by Mio and co-workers.[138] Then this aldehyde was converted into the herbicide and plant growth regulator (+)-hydantocidin **277**, a natural product produced by fermentation processes.

Given the facile reduction of the azido to the amino group and the oxidation of the formyl to carboxyl group, this method opened opportunities for preparing a special class of sugar amino acids called fused glycosyl glycines because the central carbon atom of the amino acid residue coincided with the anomeric carbon atom of a furanose or pyranose ring.[139] Compounds **278** and **279** shown in Figure 9 are two examples of these amino acids and were prepared by reaction of $TMSN_3$ with the corresponding thiazolylketose acetates **214** and **219**, respectively.[137] These glycosidation reactions occurred with high α-selectivity to give in each case a single azido glycoside in high yield (88% and 84%). Synthetic approaches to this special class of glycosyl amino acids and their use as precursors to biologically active compounds have been recently reviewed.[139]

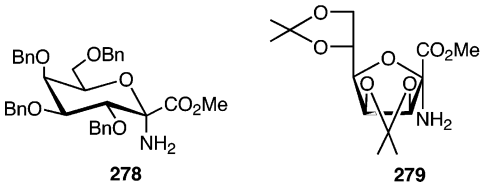


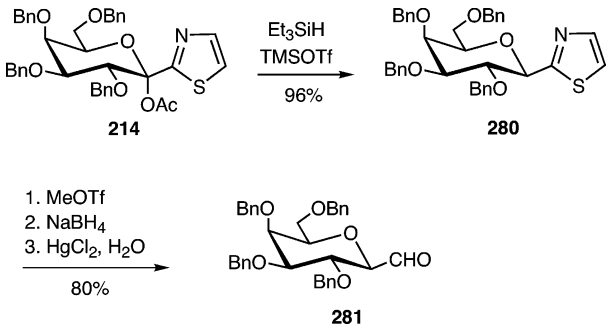
Figure 9. Fused glycosyl glycines prepared from thiazolylketose acetates.

4. Synthesis of Carbon-Linked Glycoconjugates

4.1. Formyl *C*-Glycosides

The preparation of compounds in which a glycosyl residue is linked to another sugar residue or to a nonsugar moiety (amino acid, ceramide, fatty acid) through an anomeric carbon−carbon bond instead of the native carbon−oxygen or carbon−nitrogen bond is a very important topic in modern carbohydrate chemistry.[140] The need for these compounds, particularly those which are true isosteres of natural products,[141] stems from their high stability toward chemical and enzymatic degradation. Therefore, these compounds can have application in medicinal chemistry as leads for new drug discovery or for improvement of known drugs acting as inhibitors of carbohydrate processing enzymes. Application can be also foreseen in glycobiology,[2a−c] the science dealing with studies of the role of carbohydrates in biological processes. However, while numerous *O*-glycosidation methods have been developed both in solution and the solid phase,[127] several difficulties can arise in *C*-glycosidation reactions, particularly in those cases directed toward the formation of complex systems. An alternative approach is to proceed stepwise by first introducing a simple yet reactive *C*-functional group at the anomeric center and then exploit suitable carbon−carbon or carbon−heteroatom bond-forming reactions of that functional group for the construction of a more complex residue. Following this leading concept, Dondoni and co-workers pointed to glycosyl aldehydes, namely, formyl *C*-glycosides **IV** (Scheme 35, R = H), as suitable compounds in a program directed to the synthesis of *C*-oligosaccharides and *C*-glycoconjugates. They reasoned that these anomeric sugar aldehydes could be obtained by reductive dehydroxylation of thiazolylketoses **II** via reaction of their acetates with a suitable hydride-releasing reagent followed by the formyl group unveiling from the thiazole ring. This methodology[125a,b] is illustrated in Scheme 43, showing the TMSOTf-promoted reduction of 1-*C*-(2-thiazolyl)-α-D-galactopyranosyl acetate **214** with triethylsilane (Et_3SiH) to give exclusively the β-linked thiazolyl *C*-glycoside **280**, which in turn was converted into the formyl *C*-galactopyranoside **281** in very good yield. The anomeric configuration of **280** was in agreement with

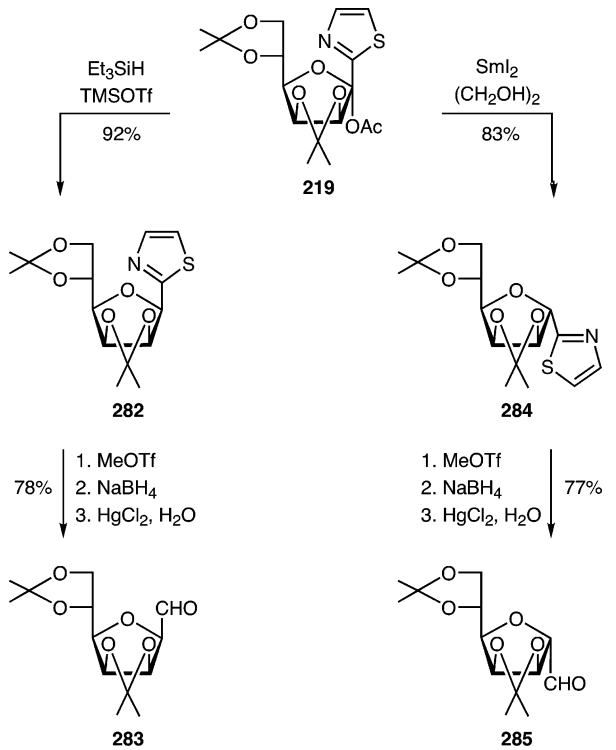
Scheme 43



a stereoselective addition of the hydride ion to a postulated sugar oxycarbenium intermediate.[127] The scope of this methodology was further broadened by the development of the SmI_2–$(CH_2OH)_2$ reductive dehydroxylation method of thiazolylketose acetates.[142] In fact, the reductive removal of the OAc group with the above samarium-based reagent afforded as a main product a thiazolyl *C*-glycoside exhibiting an opposite configuration to that obtained by the use of Et_3SiH. A thiazole-assisted two-electron reduction process was suggested to take place in the SmI_2-promoted reaction. The most significant example was provided by the reduction of the bis-acetonide-protected thiazolylmannofuranose acetate **219** which upon treatment with Et_3SiH−TMSOTf supplied[125b] the β-linked thiazolyl *C*-mannofuranoside **282** whereas with SmI_2–$(CH_2OH)_2$ afforded[142] the α-linked isomer **284**, in both cases in very good yields (Scheme 44). The subsequent application of the thiazole-to-formyl unmasking protocol to these compounds furnished the stereoisomeric formyl *C*-mannofuranosides **283** and **285**.[143]

In addition to those presented in Schemes 43 and 44, other formyl *C*-glycosides were prepared by the

Scheme 44



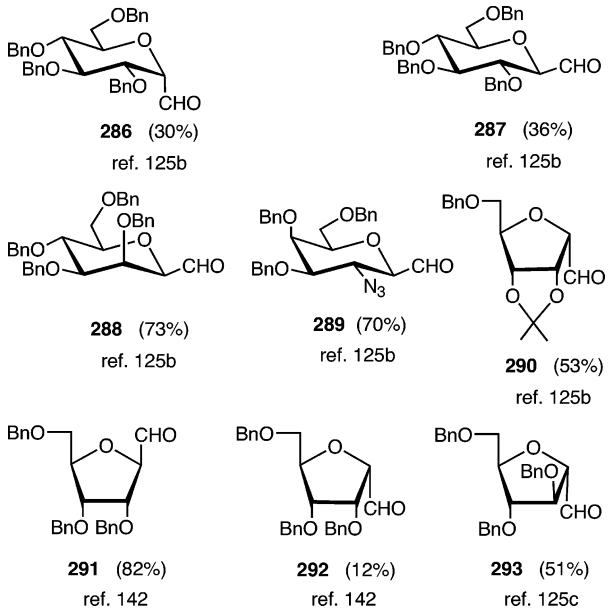
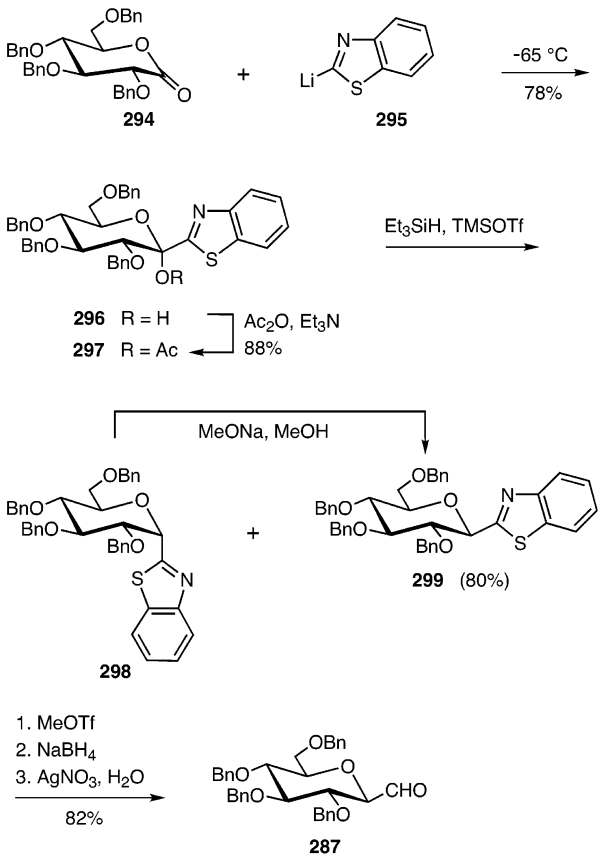


Figure 10. Formyl *C*-glycosides obtained from the corresponding thiazolylketose acetates (yield in parentheses).

above complementary methods (Figure 10). The lower yields which were registered in the case of the α- and β-D-gluco derivatives **286** and **287** with respect to the β-D-*galacto* and β-D-*manno* derivatives **281** and **288** were due to the unselective dehydroxylation of the thiazolylketose acetate **217** (see Figure 6), which afforded the two diastereomeric α- and β-linked thiazolyl *C*-glycosides in almost equal amounts.[125b] However, synthesis of the β-isomer **287** was carried out in very good yield and on a multigram scale by replacing thiazole with benzothiazole[144] as the masked formyl group (Scheme 45).[145] In fact, although the reductive dehydroxylation of the benzothiazolylketose acetate **297** by Et_3SiH−TMSOTf was unselective as well as it afforded the α- and the β-linked benzothiazolyl *C*-glycosides **298** and **299** in almost equal amounts, the β-isomer **299** was obtained in 80% yield from **297** by base-catalyzed isomerization of the α-isomer **298**. The same isomerization did not occur with the thiazole analogue of **298**. The synthesis of the β-linked formyl *C*-glucopyranoside **287** was completed by the $AgNO_3$-based thiazole-to-formyl unmasking protocol.

Although other syntheses of formyl *C*-glycosides have been reported over the years from various laboratories,[146] their generality was far from being demonstrated. On the other hand, a number of these compounds with a wide range of structural diversity were prepared via the thiazole-based methodology (Figure 10). Hence, in support to their view on the high potential of these anomeric sugar aldehydes as intermediates for the synthesis of more complex *C*-glycosides, Dondoni and co-workers reported several applications via different carbon−carbon bond-forming reactions (Figure 11). Thus, the α-(1 → 6)-carbon-linked pentasaccharide[147] **300** and the α-(1 → 5)-carbon-linked trisaccharide[125c] **301** were constructed by iterative Wittig reaction; the *C*-glycosyl amino acid[148] **302** was prepared by the Mukaiyama-type condensation; the *C*-glycosylated fulleropyrrolidine[149] **303** and the isoxazole[150] **304** were synthe-

Scheme 45



sized by cycloaddition of glycosylated 1,3-dipolar systems, namely, an azomethine ylide and a nitrile oxide, respectively, generated in situ; the *C*-nucleosides **305** and **306** were prepared by the multicomponent Biginelli[151] and Hantzsch[152] cyclocondensation reaction, respectively.

4.2. *C*-Glycosyl Amino Acids

Given the growing importance of unnatural amino acids in which the glycinyl moiety ($CH(NH_2)CO_2H$) is linked to the anomeric carbon of sugars by one or more carbon−carbon bonds,[139] the synthesis of *C*-glycosyl glycines via stereoselective aminohomologation of formyl *C*-glycosides was reported.[153] As discussed in section 3.3, this thiazole-based methodology involved as a carbon−carbon bond-forming reaction the addition of 2-lithiothiazole (2-LTT, **31**) to *N*-benzyl aldonitrones. The control of the stereoselectivity of this reaction was crucial to obtaining *R*- or *S*-configured α-amino aldehydes whose oxidation would lead to the corresponding carboxylic acids. This issue was addressed by the use of suitable Lewis acids capable of nitrone complexation. Accordingly, the addition of 2-LTT **31** to the *N*-benzyl nitrone **308** derived from formyl *C*-mannofuranoside diacetonide **283** showed opposite diastereoselectivity depending on whether the reaction was carried out with the free nitrone or its precomplexed derivative with Et_2AlCl (Scheme 46). Under the former conditions, the main product was the *N*-benzyl hydroxylamine **309** with *S*-configuration, whereas under the latter conditions the main product was the *R*-configured epimer **311**. Suitable elaboration of these products, i.e., reduction of the *N*-benzylhydroxylamino group to amino group

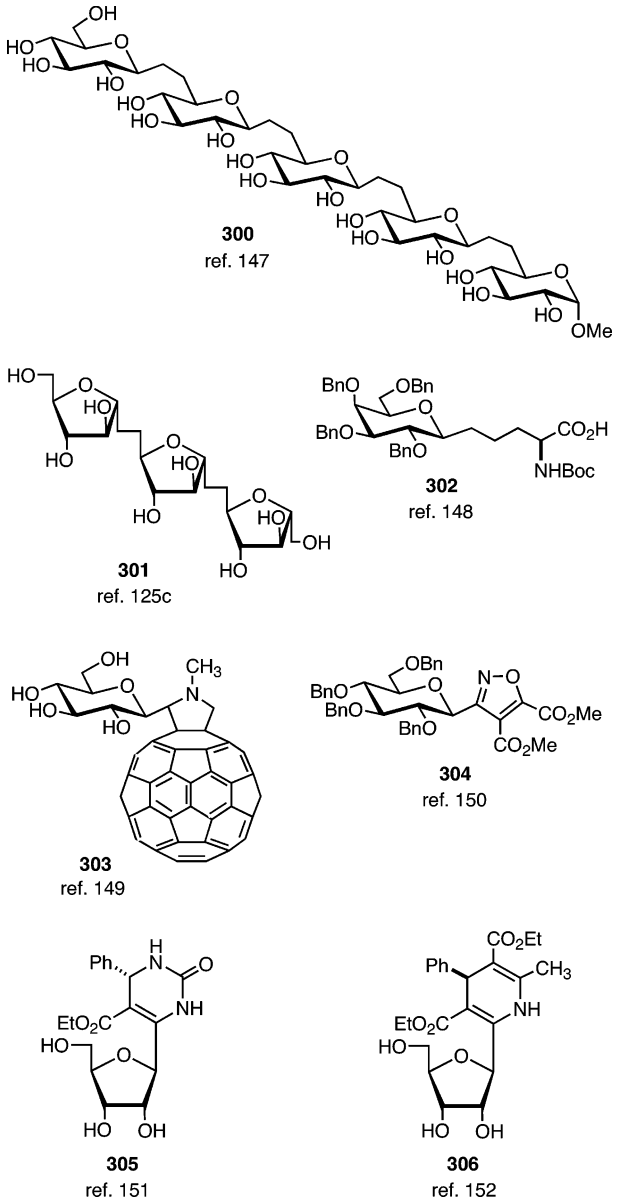
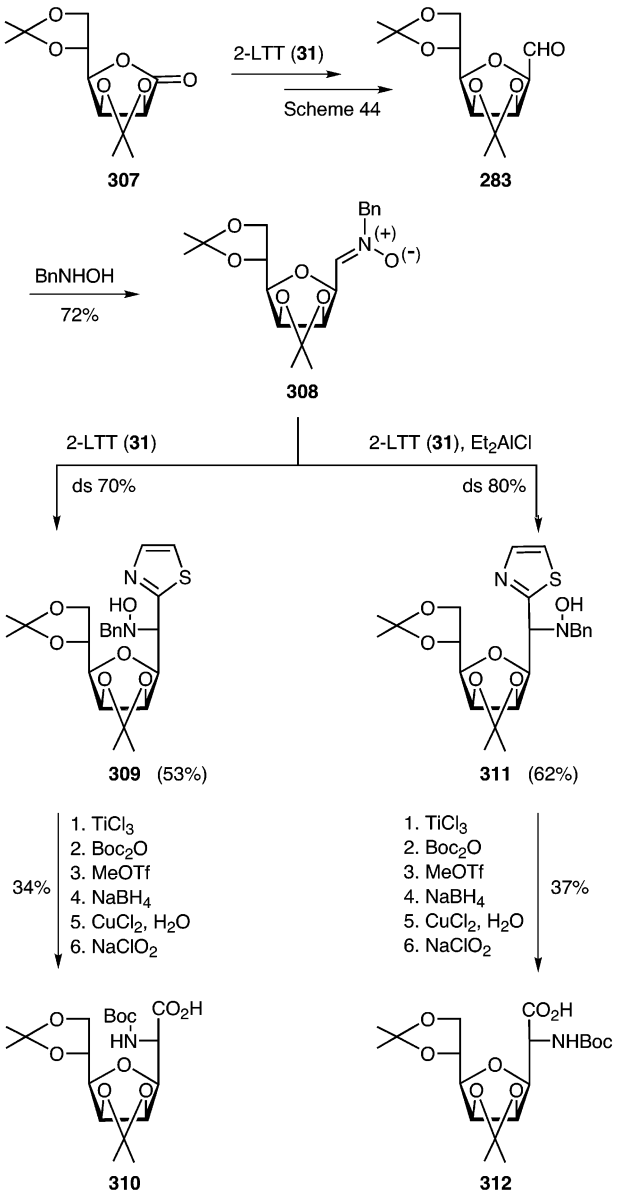


Figure 11. Selected examples of complex *C*-glycoconjugates prepared starting from formyl *C*-glycosides.

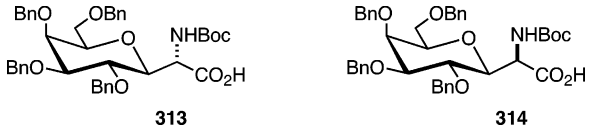
with $TiCl_3$ and protection as *tert*-butylcarbamate (Boc), then transformation of the thiazole ring to formyl (MeOTf, then $NaBH_4$, then $CuCl_2$, H_2O), and oxidation of the aldehyde with $NaClO_2$ afforded the pair of β-D-mannofuranosyl glycines as L- (compound **310**) and D-isomer (compound **312**). It was pointed out that unlike other syntheses of *C*-glycosyl glycines,[139] this method overcame the problem of controlling the stereochemistry at the anomeric center of the sugar moiety because this was already established in the original aldehyde **283**.

The same nitrone-based approach was employed[153] for the preparation of the epimeric β-D-galactopyranosyl glycines **313** and **314** (Figure 12) by the use of the *N*-benzyl nitrone derived from the formyl *C*-galactoside **281** as starting material (see Scheme 43). However, in this case the addition of 2-LTT **31** to either the free nitrone or its precomplexed derivative with Et_2AlCl afforded mixtures of diastereomeric *N*-benzylhydroxylamines in similar ratios. Nevertheless, separation and elaboration of these intermedi-

Scheme 46



ates as described above afforded the individual sugar glycines **313** and **314** as pure compounds.



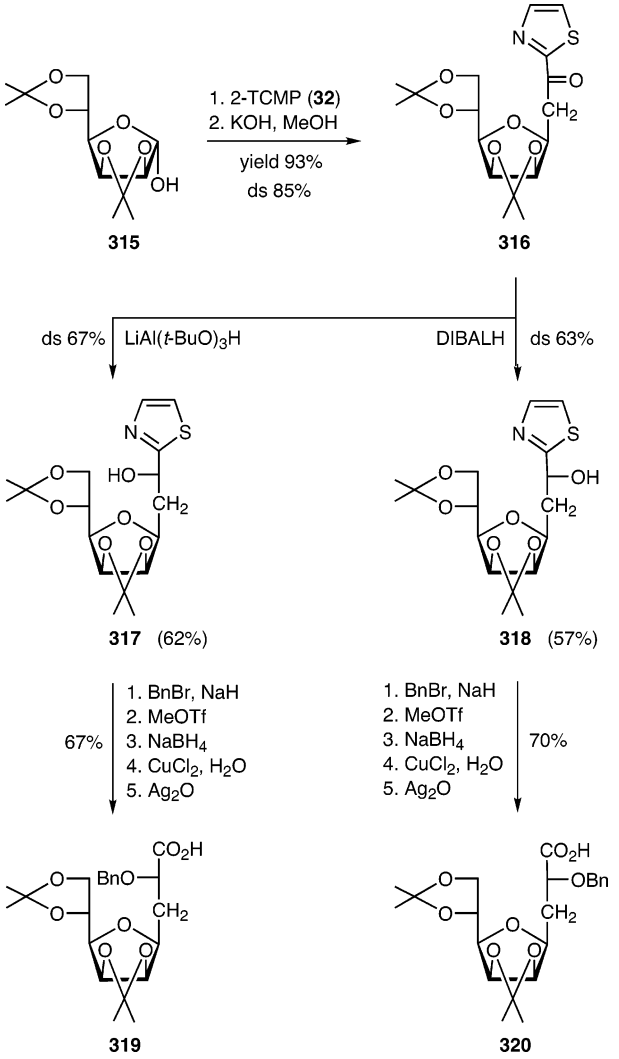
313 **314**

Figure 12. *C*-Galactosyl glycines obtained by amino-homologation of formyl *C*-galactoside **281**.

4.3. *C*-Glycosyl Hydroxy Acids

Other methods based on the thiazole−aldehyde synthesis were developed with the aim of introducing functionalized carbon chains at the anomeric center of carbohydrates. One of these approaches relied on a domino process constituted of a Wittig-type condensation of the anomerically unprotected sugar with the phosphorane 2-TCMP **32** followed by the spontaneous intramolecular cyclization (Michael-type addition) of the resulting alkene.[154] This reaction sequence furnished a mixture of α- and *β*-1-*C*-(2-

Scheme 47

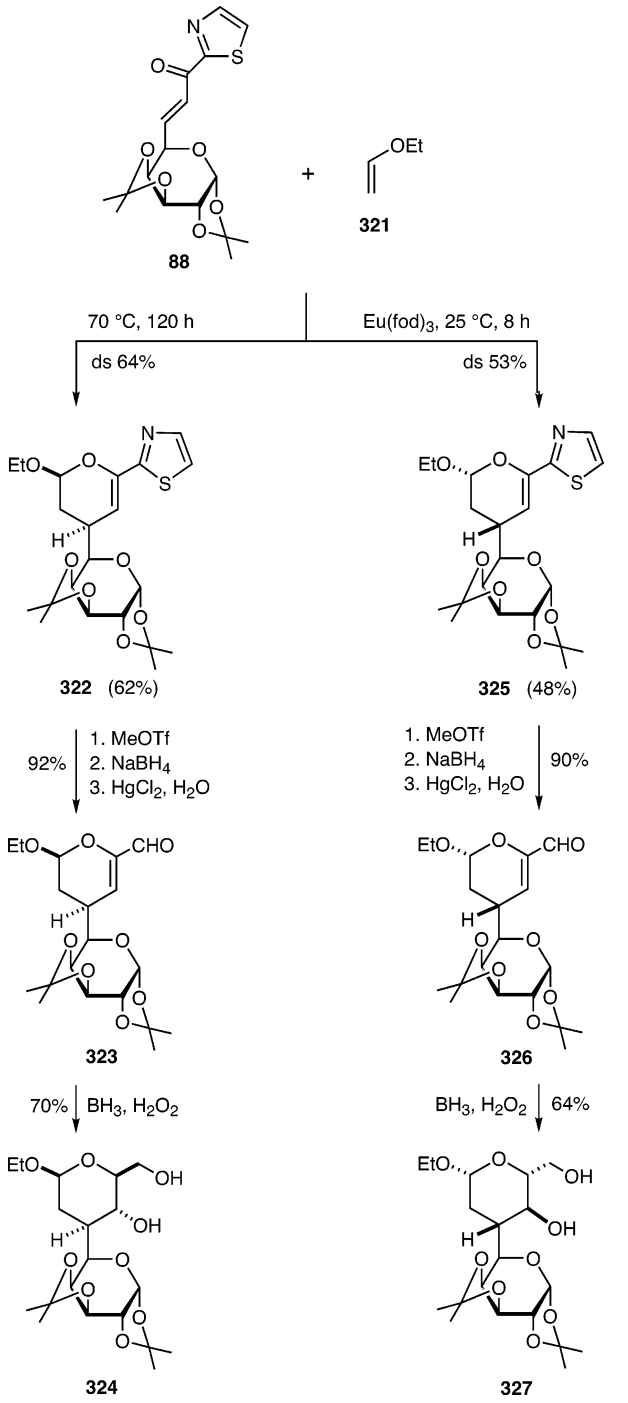


thiazolacyl)glycosides. In particular, the reaction mixture obtained from the *manno* derivative **315** (Scheme 47) upon basic treatment gave an α/*β* equilibrium ratio of 15:85. The major product *β*-*C*-glycosylmethyl ketone **316** was reduced with two different hydride-releasing reagents, i.e., LiAl(*t*-BuO)$_3$H and DIBALH which afforded as main products the alcohol **317** and the epimer **318**, respectively. The subsequent unveiling of the aldehydes from the *O*-benzyl derivatives of these compounds and oxidation furnished the *C*-glycosyl α-alkoxy propionic acids **319** and **320** in good yields. The same synthetic scheme could not be developed by use of the stabilized phosphorane $Ph_3P{=}CHC(O)CO_2Et$ because this reagent failed to react with furanoses. However, the use of 2-TCMP **32** was limited to furanoses because a pyranose such as 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose did not afford the corresponding *C*-glycoside.

4.4. Carbon-Linked Disaccharides

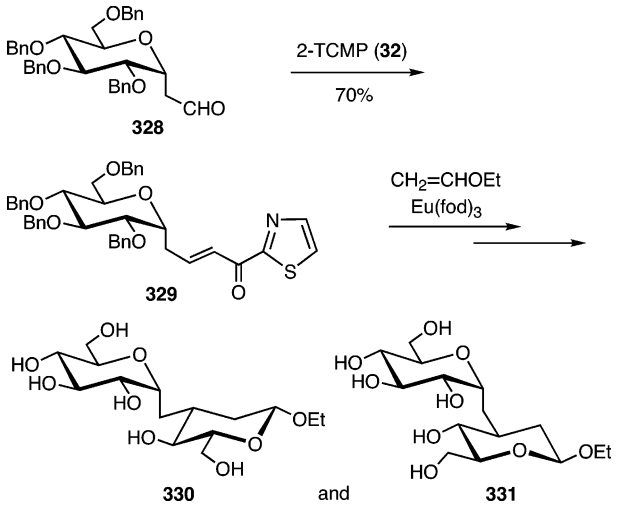
While in the last two decades a great deal of effort was made to find effective synthetic methods for preparing carbon-linked disaccharides in which a methylene group replaced the bridging oxygen of the natural glycosidic linkage,[155] there was also some interest on a special class of disaccharides in which

Scheme 48



two aldoses were directly linked through a carbon−carbon bond either at the anomeric or nonanomeric position.[156] Hence, a reaction scheme along the lines of the thiazole−aldehyde synthesis was developed in the Dondoni laboratory for building up a pyranose ring on an existing one.[157] This scheme was based on the hetero-Diels−Alder (HDA) reaction of ethyl vinyl ether **321** (Scheme 48) with the α,*β*-enone **88** which for that purpose was acting as an oxabutadiene system. This cycloaddition partner was readily available in high yield by carbonylolefination of the α-D-*galacto*-hexodialdo-1,5-pyranose derivative **55** with the thiazole-armed phosphorane 2-TCMP **32** (see Scheme 14). The reaction between **88** and **321** was moderately *endo* and face selective. Under thermal

Scheme 49



conditions the main product isolated was the *endo* cycloadduct **322** in low diastereomeric excess, whereas in the presence of Eu(fod)$_3$ (europium tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate) the product isolated in slight excess was compound **325**, which is an *endo* adduct as well but with opposite configuration at the newly formed stereocenters. The individual cycloadducts **322** and **325** were elaborated in an identical manner via aldehyde unmasking from the thiazole ring and hydroxylation of the double bond by hydroboration−oxidation. It is noteworthy that whereas the unmasking of the thiazole ring of 2-alkenylthiazoles occurred with concomitant reduction of the carbon−carbon double bond (see section 3.1), the same operation applied to compounds **322** and **325** did not affect their double bond and afforded the formyl-substituted dihydropyrans **323** and **326** in excellent yields. The inertness of the *N*-methyl thiazolium derivatives of **322** and **325** toward the hydride addition to the double bond of the dihydropyran ring was explained as being due to a captodative effect. The *cis*-selective hydroboration of **323** and **326** by BH_3 with concomitant reduction of the formyl group followed by introduction of a hydroxyl via addition of hydrogen peroxide proceeded smoothly, giving rise to the diastereomeric *C*-disaccharides **324** and **327**.

The same methodology described in Scheme 48 has been recently applied by Kniezo and co-workers[158] to the α-D-glucopyranosylacetaldehyde **328** (Scheme 49). In this case too the HDA reaction of the oxabutadiene **329** with ethyl vinyl ether **321** was *endo* selective but totally lacking of stereoselectivity. Hence, two cycloadducts were obtained in almost equal amounts. These compounds were elaborated as in Scheme 48 and transformed into the *C*-disaccharides **330** and **331** featuring a methylene bridge holding the two pyranose rings. Hence, these compounds can be considered as genuine methylene isosteres of (1 → 3)-*O*-disaccharides.

5. Synthesis of Azasugars

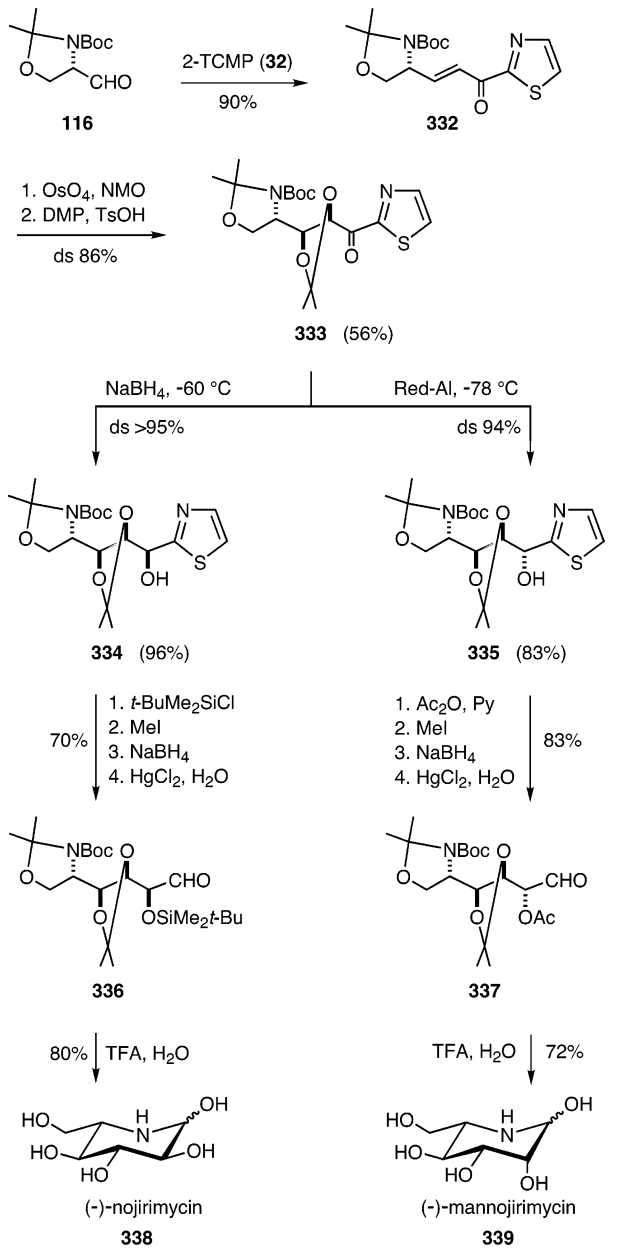
The search for selective and effective inhibitors of oligosaccharides processing enzymes has promoted

intense research over the last 20 years in the synthesis of stereochemically well-defined polyhydroxylated pyrrolidines and piperidines.[159] These compounds are called azasugars or more appropriately iminosugars since they are related to sugars by replacing the ring oxygen by the NH group. Iminosugars are known to be endowed with a remarkable therapeutic potential as antiviral, antimethastatic, antibacterial, antiadhesive, and antihyperglycemic agents. Hence, given the current interest in the development of new synthetic approaches to either natural azasugars[160] or analogues, the potential of the thiazole-based synthetic methodology was exploited in this field as well. In some cases two different thiazole-based reagents were sequentially employed in the de novo synthesis of these compounds from nonsugar precursors.

Wishing to exploit the atom array and chirality of serine for preparing polyhydroxylated δ-amino hexanals as precursors to azahexoses, Dondoni and coworkers described[161] the three-carbon-atom elongation of the L-serine-derived aldehyde[81b] **116** by Wittig reaction with the phosphorane **32** (Scheme 50). This reaction afforded the chiral α,β-enone **332** in excellent yield. The *cis*-hydroxylation of this compound with catalytic osmium tetroxide in the presence of *N*-methylmorpholine *N*-oxide as a reoxidant (OsO_4/NMO) followed by acetonization of the main 1,2-diol furnished the thiazolyl ketone **333** in 51% overall yield from the aldehyde **116**. The stereocontrolled reduction of the ketone **333** to an alcohol with either *R* or *S* configuration was envisaged as a route to C-2 epimeric azahexoses. Indeed, the reduction of **333** with two different hydride donors such as $NaBH_4$ and Red-Al [$NaAlH_2$·(OCH_2CH_2OMe)] occurred with high levels of selectivity but in opposite sense to give the alcohol **334** and the epimer **335**, respectively. The suitable protection of the hydroxyl group and the application of the standard thiazole-to-formyl deblocking protocol transformed these compounds into the aldehydes **336** and **337**. The removal of all protective groups from these compounds by acid treatment furnished the azahexose **338**, (−)-nojirimicyn, and the epimer **339**, (−)-mannojirimicyn. These products are the antipodes of the natural azasugars which, however, would be available through the same versatile method starting from the enantiomer of the aldehyde **116**, which in turn can be prepared from D-serine.

The use of 2-acetylthiazole (2-ATT, **30**) as the three-carbon chain elongating reagent of serinal **116** constituted the basis of a thiazole-based entry[161] to 3-deoxy derivatives of (−)-nojirimicyn **338** and (−)-mannojirimicyn **339** (Scheme 51). New azasugars featuring chemical modifications with respect to natural products are considered as interesting targets both for their potential biological activity and for studies in structure and enzyme−inhibitory activity relationships. Hence, the key intermediate β-hydroxy ketone **340** was prepared in good isolated yield by *anti*-stereoselective aldol condensation of the aldehyde **116** with the lithium enolate of 2-ATT **30**. In this case too two routes were opened by the stereocontrolled reduction of the carbonyl of **340**. This

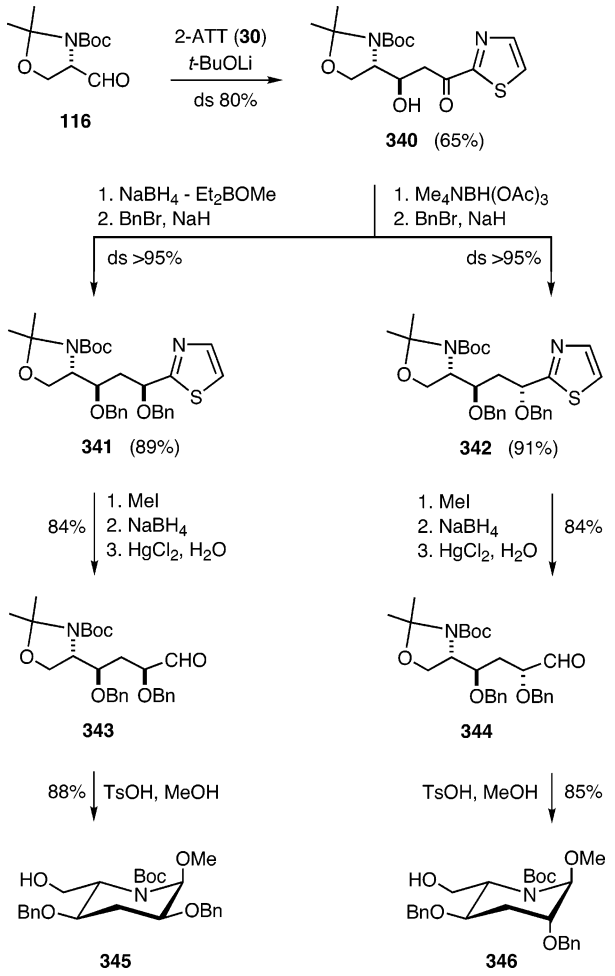
Scheme 50



operation was easily carried out owing to literature precedents on the stereoselective reduction of chiral β-hydroxy ketones. In fact, the reduction of **340** with sodium borohydride in the presence of diethylmethoxyborane[162] ($NaBH_4$·Et_2BOMe) afforded a *syn*-1,3-diol, which was isolated as the *O*-benzyl derivative **341**, whereas the use of tetramethylammonium triacetoxy borohydride[69] ($Me_4NBH(OAc)_3$) gave the *anti*-epimer, which was isolated as the *O*-benzyl derivative **342**. In both cases the diastereoselectivity of the reduction was higher than 95%. The two diastereoisomers **341** and **342** were easily transformed into the protected 3-deoxy azasugar **345** and the epimer **346** through the aldehydes **343** and **344**. It is worth noting that this transformation was carried out under different reaction conditions with respect to those employed in a preliminary communication[163] in order to avoid the formation of 1,6-anhydro derivatives.

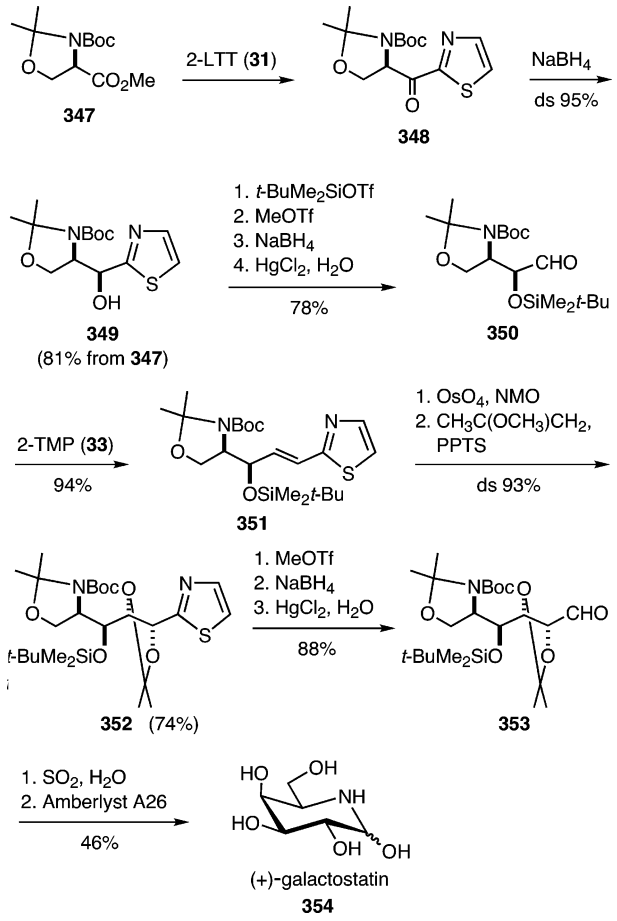
Guided by a retrosynthetic analysis, a reaction scheme involving two thiazole-based reagents was

Scheme 51



developed[36,164] for the totally chemical synthesis of the natural azasugar (+)-galactostatin **354** and its unnatural (−)-antipode from D- and L-serine, respectively (Scheme 52). Given the recent isolation of **354** from natural sources,[165] only a few syntheses of this compound were reported, all employing carbohydrate precursors.[166] Instead, the thiazole-based synthesis of **354** began by allowing 2-LTT **31** to react with the methyl ester of protected D-serine **347** to give the ketone **348**. This clean acylation of the thiazole ring at C-2 was expected on the basis of a similar reaction reported by Chikashita and co-workers between 2-lithiobenzothiazole and various esters and lactones.[167] According to Chikashita, the stabilization of the ketone **348** as a lithium complex of the hemiketalic intermediate avoids the formation of a bis adduct. The *syn*-stereoselective reduction of the carbonyl of **348** to give the desired alcohol **349** was expected on the basis of earlier studies on the reduction of 2-thiazolyl α-amino ketones.[168] After protection of the hydroxyl group of **349**, the aldehyde **350** was liberated by the standard thiazole-to-formyl unmasking protocol. Then a two-carbon chain elongation was carried out by reaction of this aldehyde with the unstabilized thiazolylphosphorane 2-TMP **33**. Quite luckily this olefination was very selective since it afforded almost exclusively the *E*-olefin **351**. The cis hydroxylation of this alkene by OsO_4/NMO was also an efficient and stereoselective reaction as it furnished a 1,2-diol, which was isolated as the

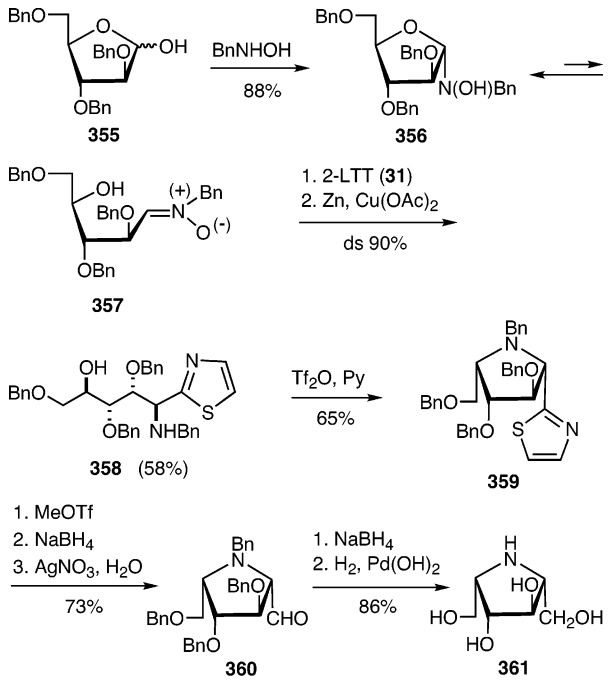
Scheme 52



acetonide derivative **352**. The application of the thiazole-to-formyl unmasking protocol to this compound afforded the second key intermediate aldehyde, namely, the amino- and hydroxy-protected 5-amino-5-deoxy-*aldehydo*-D-galactose **353**. This compound was transformed into the target (+)-galactostatin through its bisulfite adduct. The overall chemical yield (17.8% from **347**) of isolated **354** was higher than those registered (from 2.4% to 9.3%) in other approaches reported in the literature.[166] Another advantage of this thiazole-based synthesis is that the unnatural (−)-galactostatin antipode of **354** can be equally prepared starting from L-serine. Actually the synthesis of this compound was described in a preliminary communication,[164] although in low yield due to an unoptimized group protection strategy.

Considerable attention was given in recent years to a class of natural and synthetic azasugars of both pyrrolidine and piperidine families bearing a hydroxymethyl group or a polyhydroxylated carbon chain at the carbon atom adjacent to nitrogen, the anomeric carbon, so that they were called homoazasugars or aza-*C*-glycosides.[169] These compounds were found to retain the same type of biological activity of the parent azasugars and, in some cases, exhibit higher selectivity and potency. Moreover, they have great stability toward chemical and enzymatic degradation, a drawback of the parent azasugars as carbohydrate mimics due to the lability of the *O*,*N*-acetal function. Homoazasugars too were targeted via an appropriate thiazole-based methodology.[170]

Scheme 53



This was based on a variant of the aminohomologation strategy described in section 3.3 since it required an extra step constituted of an intramolecular substitution reaction as illustrated in Scheme 53. Starting materials were anomerically free aldofuranoses such as, for example, 2,3,5-tri-*O*-benzyl-D-arabinofuranose **355**. Treatment of this aldose with *N*-benzylhydroxylamine resulted in the formation of the corresponding arabinosyl hydroxylamine **356** (α-anomer only) very likely in equilibrium with the open-chain nitrone **357** (not detectable by NMR). In fact, subsequent addition of 2-LTT **31** afforded the formal adduct to **357**, i.e., an open-chain thiazolyl hydroxylamine (not shown), which by reduction of the N(OH)Bn group to NHBn furnished the secondary amine **358**. The activation as *O*-triflate of the free hydroxyl group which was present in the *N*-alkyl chain of this compound induced an intramolecular substitution reaction leading to the 2-thiazolylpyrrolidine **359**. A careful NMR analysis of this product allowed its structure as well as that of its precursor **358** (*anti*-adduct) to be established on the basis of the reasonable assumption that the ring closure had occurred via an S_N2-like mechanism. Finally, the unveiling of the formyl group from the thiazole ring afforded the 2-formyl pyrrolidine **360** (formyl aza-*C*-glycoside) as a stable compound. The reduction of the formyl and the removal of the benzyl protective groups furnished the target pyrrolidine homoazasugar **361** (2,5-dideoxy-2,5-imino-D-glucitol) in 21% overall yield from the aldose **355**. The scope of this methodology was broadened by the synthesis of three more pyrrolidine homoazasugars (Figure 13) including the natural product 2,5-dihydroxymethyl-3,4-dihydroxypyrrolidine (DMDP) **364** (2,5-dideoxy-2,5-imino-D-mannitol). Unfortunately this synthetic scheme could not be applied to aldopyranoses because their hydroxylamine−nitrone mixture did not react with 2-LTT **31**. It is of relevance to mention that owing to its sufficient stability the formyl aza-*C*-glycoside **360** served as a building block for aza-*C*-disaccharides via Wittig olefination with sugar phosphoranes.[170b]

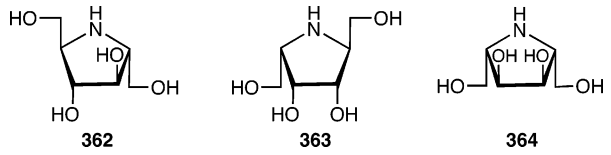


Figure 13. Homoazasugars prepared by aminohomologation of furanoses.

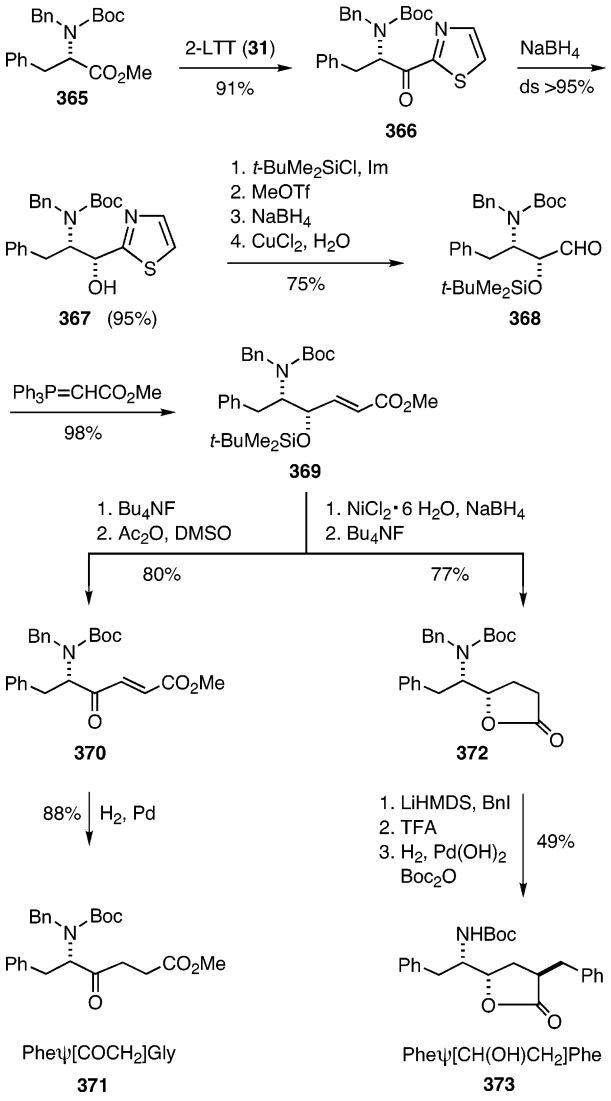
6. Synthesis of Peptide Mimetics

6.1. Dipeptide Isosteres

Definition, design, synthesis, and application of peptide mimetics, also called peptidomimetics, were reported in several specialized publications.[171] A wide class of peptidomimetics includes compounds featuring modification of the peptide backbone by isosteric or isoelectronic exchange of units in the peptide chain. Hence, a modern yet socially relevant field of research in which the thiazole-based synthetic methodology was successfully employed was that dealing with the synthesis of building blocks for protease inhibitors, especially peptide isosteres against two different aspartic protease enzymes, renin and human immunodeficiency virus (HIV) protease. Renin inhibitors may develop into drugs against hypertension,[172] and HIV inhibitors have been shown to be clinically useful in the control of AIDS.[173]

A communication[174a] appeared in 1992 from the Dondoni laboratory followed by a full report a few years later[174b] dealing with the synthesis of ketomethylene and hydroxyethylene isosteric dipeptides by thiazole-based homologation of L-phenylalanine and L-leucine. One of the routes went through thiazolyl amino ketones as intermediates. As illustrated in Scheme 54, the *N*,*N*-diprotected phenylalanine methyl ester **365** upon treatment with 2-LTT **31** was transformed into the amino ketone **366** in very high yield. The reasons for the highly selective monosubstitution reaction between esters and **31** have been commented on in section 5. The reduction of the carbonyl group of **366** afforded the expected[168] *syn*-amino alcohol **367** almost quantitatively, which after protection of the hydroxyl group was transformed into the aldehyde **368** by the copper-based thiazole-to-formyl unmasking protocol.[33] The Wittig olefination of this aldehyde with the stabilized (methoxycarbonylmethylene)triphenylphosphorane ($Ph_3P{=}CHCO_2Me$) furnished the (*E*)-enoate **369** in high isolated yield. This chiral unsaturated ester was the ultimate precursor to dipeptide isosteres incorporating the phenylalanine residue. Indeed, desilylation of **369** and oxidation of the resulting alcohol gave the (*E*)-enone **370**, whose ethylenic double bond was readily reduced with hydrogen over $Pd/BaSO_4$ to give the δ-amino-γ-ketoester **371**. This compound corresponded to the Phe-Gly ketomethylene dipeptide isostere, Pheψ[$COCH_2$]Gly, which was previously incorporated by Almquist and co-workers in various peptides to produce angiotensin-converting enzyme inhibitors.[175] Instead, the effective reduction of the

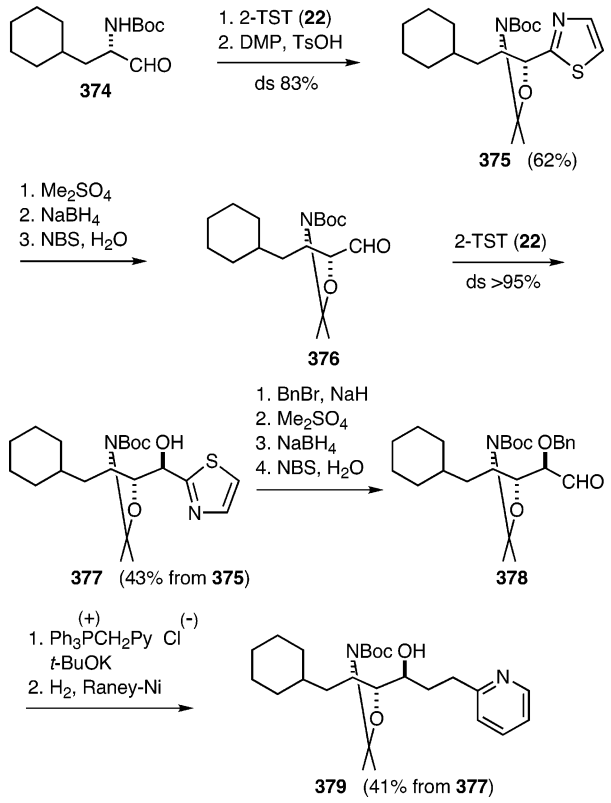
Scheme 54



ethylenic double bond of **369** using the scarcely exploited yet very convenient reagent nickel boride (from $NiCl_2$ hexahydrate and $NaBH_4$)[176] and the removal of the silyl protective group afforded the γ-lactone **372**. This compound was further elaborated by stereoselective benzylation at C-2 using lithium hexamethyldisilazide (LiHMDS) as a base and benzyl iodide as electrophile. Then, the removal of the *N*-benzyl group furnished compound **373** (24% overall yield from phenylalanine **365**), which corresponded to the lactone form of Phe-Phe hydroxyethylene dipeptide isostere, Pheψ[CH(OH)CH_2]Phe. This compound had been previously prepared by Merck researchers[177] from D-mannose (19% overall yield) and used as a precursor to potent and selective hydroxyethylene dipeptide isostere inhibitors of HIV-1 protease. The same synthetic route shown in Scheme 54 was followed for the synthesis of Leu-Leu analogue of **373**, i.e. Leuψ[CH(OH)CH_2]Leu, in 19% overall yield from leucine.[174b]

Aiming at improving the bioavailability of renin inhibitors by incorporation of suitable molecular residues containing polar groups, Hoechst researchers reported[178] on the synthesis of the protected amino diol **379** (Scheme 55), a dipeptide mimic

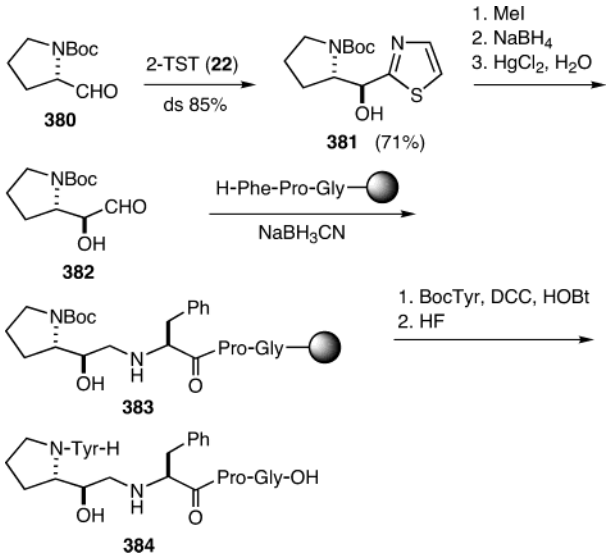
Scheme 55



bearing a pyridine ring at one terminal side of the carbon chain. The synthesis involved the iterative one-carbon homologation methodology of aldehydes using 2-TST **22** as the formyl anion equivalent (see section 3.1). Starting from the *N*-monoprotected cyclohexylalaninal **374**, the first homologative cycle via *syn*-stereoselective addition[83] of 2-TST **22** and thiazole-to-formyl unmasking furnished the aldehyde **376**. Application of the second homologative cycle to this aldehyde afforded the expected (see section 3.1) *anti*-adduct **377** from which the new one-carbon chain extended alkoxy aldehyde **378** was unveiled by cleavage of the thiazole ring. It is noteworthy that in both cycles the latter transformation was carried out by the use of *N*-bromosuccinimide (NBS) instead of mercury(II) chloride, thus demonstrating that the thiazole aldehyde synthesis can be an environmentally friendly methodology. The conversion of **378** into the target 2-pyridinyl derivative **379** was performed via Wittig olefination with a pyridine-armed phosphorus ylide and hydrogenation.

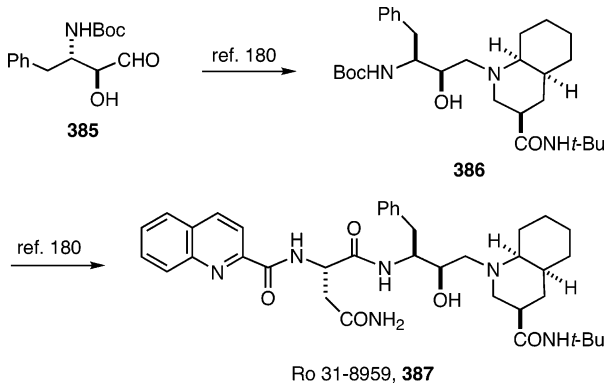
An interesting and practical application of β-amino-α-hydroxy aldehydes obtained via the thiazole–aldehyde synthesis was reported[179] by Tourwé and co-workers in a solid-phase synthesis procedure leading to hydroxyethylamine peptide isosteres. For example, the aldehyde **382** (Scheme 56) prepared by the 2-TST **22**-based stereoselective homologation of the *N*-Boc prolinal **380** was installed in a resin-bound peptide by reductive amination, thus creating an hydroxyethylamine dipeptide isostere, Proψ[CH(OH)-CH_2NH]Phe, in the peptide chain. After a further peptide synthesis by reaction of **383** with BocTyr, the pseudopeptide **384**, an hydroxyethylamine analogue of β-casomorphin-5, was cleaved from the resin and purified by HPLC for biological testing.

Scheme 56



The thiazole-based methodology was considered by a Hoffman-La Roche group[180] as a synthetic tool amenable to large-scale production of the hydroxyethylamine isosteric dipeptide **386** (Scheme 57) pre-

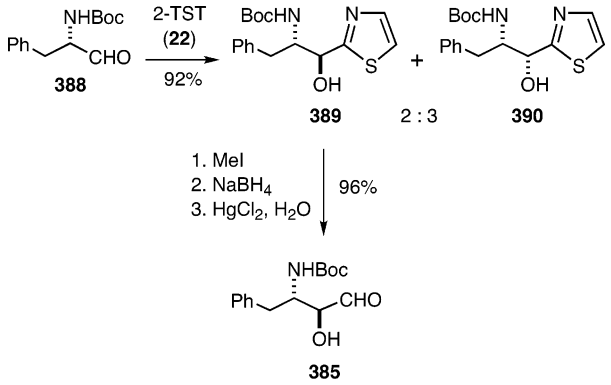
Scheme 57



cursor to the potent and selective HIV protease inhibitor Saquinavir **387** (Ro 31−8959). This compound was the first FDA-approved (1995) HIV protease inhibitor for the treatment of AIDS.[173a] The aldehyde **385** featuring a hydroxyl and amino group in an *anti*-relationship was considered a key building block for the dipeptide **386** via reductive amination with a decahydroisoquinoline derivative.

Notwithstanding an earlier report[80b] by Dondoni and co-workers showing that the addition of 2-TST **22** to *N*,*N*-diprotected α-amino aldehydes was *anti*-selective whereas the same reaction with *N*-monoprotected derivatives was *syn*-selective, the synthesis of **385** by the Hoffman-La Roche researchers was approached[180] by addition of **22** to the nitrogen singly protected *N*-Boc-L-phenylalaninal **388** (Scheme 58). This reaction furnished the desired anti amino alcohol **389** as minor product (ds 38%), which was isolated in a pure form in very low yield (13%). Hence, the target aldehyde **385** was obtained in low overall yield from **388**, a result which precluded performing an effective total synthesis of the dipeptide isostere **386**. Nevertheless, the planned synthesis of this compound by reductive amination of the aldehyde

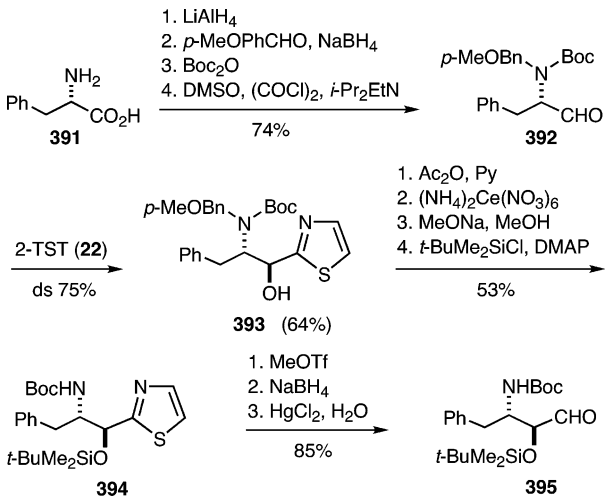
Scheme 58



385 with a decahydroisoquinoline derivative in the presence of sodium cyanoborohydride was demonstrated to occur in good yield.

An improved synthesis of the aldehyde **385** as the *O*-silyl derivative **395** was reported[181] by Dondoni and co-workers via homologation of the *N*,*N*-diprotected phenylalaninal **392** (Scheme 59). This aldehyde was

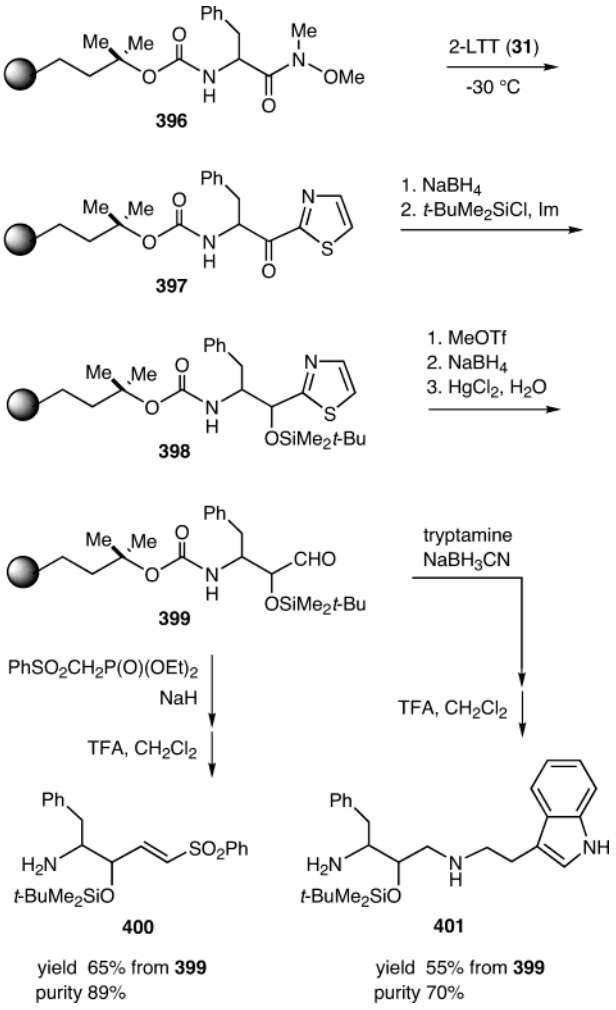
Scheme 59



obtained from L-phenylalanine **391** in good yield. The reaction of **392** with 2-TST **22** provided the expected anti amino alcohol **393** as a major product in 64% isolated yield. The oxidative removal of the *p*-methoxybenzyl group with cerium ammonium nitrate (CAN, $(NH_4)_2Ce(NO_3)_6$) and silylation furnished the compound **394**, which was transformed into the aldehyde **395** in excellent yield. Hence, given the previous report of the Hoffman-La Roche group,[180] a formal synthesis of the hydroxyethylamine isosteric dipeptide **386** was achieved in good yield from the aldehyde **392**.

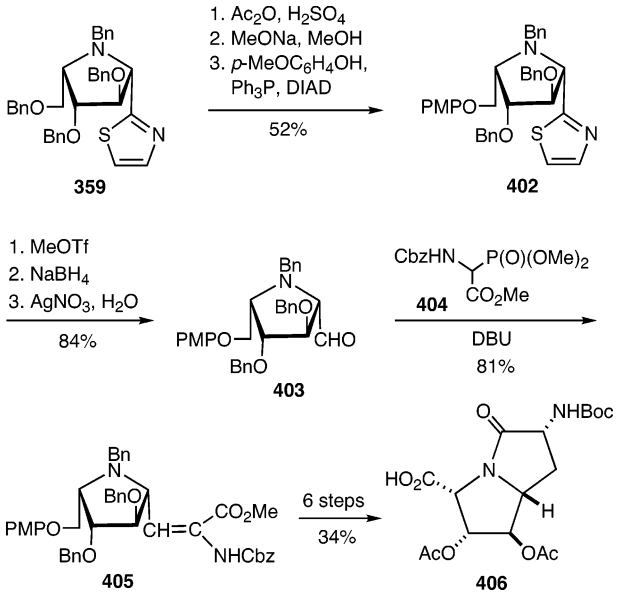
A wide-scope approach to two different classes of isosteric dipeptides, 2-hydroxy-1,3-propyldiamines and δ-amino-γ-hydroxy-vinyl sulfones, was recently reported by Jung and co-workers.[182] The novelty in this approach is that the key intermediates β-amino-α-hydroxy aldehydes were obtained by the hitherto unreported solid-phase thiazole-based homologation of *N*-terminal resin-bound α-amino acid Weinreb amides (Scheme 60). The successful transfer of the solution-phase thiazole−aldehyde synthesis to solid-phase chemistry provided a new and operatively

Scheme 60



simple manner by which this flexible methodology can be utilized. The selected α-amino acid, for example, phenylalanine, was anchored by its amine function to a carbamate resin, i.e., Boc-resin (loading ca. 0.7 mmol/g), and then transformed into the Weinreb amide **396**. This resin-bound substrate upon treatment with a THF solution of 2-LTT **31** at low temperature afforded the thiazolyl ketone **397**. Reduction of this ketone to alcohol and protection by silylation furnished racemic *O*-silyl ether **398**. These steps were followed on bead by FT-ATR−IR spectroscopy. Finally, application of the mercury-based thiazole to formyl unmasking protocol to **398** gave the *N*-terminal Boc-resin-bound *O*-*tert*-butyldimethylsilyl-protected *β*-amino-α-hydroxy aldehyde **399**. The generality of this solid-phase thiazole-based synthesis of functionalized aldehydes was demonstrated by using other α-amino acids (Val, Lys(Z), Leu, Ile) as starting material. The transformation of the resin-anchored aldehyde **399** into the hydroxyethylene peptide isosteres **400** (89% purity) and **401** (70% purity) was carried out via Horner−Emmons coupling with a phenylsulfonyl phosphonate and via reductive amination with tryptamine, respectively, followed by the cleavage of the products from the solid support using trifluoroacetic acid in dichloromethane. Unfortunately the chiral version of this methodology was not investigated, and therefore, no

Scheme 61



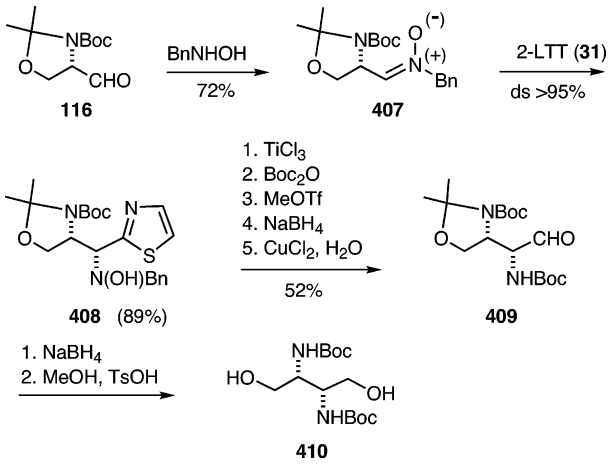
comparison can be made with the results of solution-phase approaches.

6.2. Conformationally Constrained Dipeptides

Research on peptidomimetics[171] has gained an enormous importance in recent years with the emergence of conformationally constrained systems that mimic certain structural features and therapeutic effects of natural peptides.[183] The efficient service of the thiazole−aldehyde synthesis was demonstrated in this field as well as it provided an effective entry[184] to the formyl *C*-iminosugar **403**. This aldehyde served as the key precursor to the 6,7-dihydroxylated azabicyclo[3.3.0]octan-2-one amino acid **406** (Scheme 61), which can be regarded as a conformationally restricted substitute for Ala-Pro dipeptide. There is increasing interest to develop synthetic methods of rigidified dipeptide surrogates since the incorporation of these systems into a peptide can provide a better understanding of the spatial requirements of its biological activity.[185] Moreover, these conformationally constrained systems can serve as rigid scaffolds onto which a variety of pharmacophores may be introduced by exploiting suitable reactions of the amino and carboxyl groups. Compound **406** offers in addition two hydroxyl groups as anchoring points for side chain moieties implicated in ligand−receptor interaction.[186]

The synthesis of the 2-formylpyrrolidine **403** (Scheme 61) exploited the readily available hydroxylated 2-thiazolylpyrrolidine **359** whose preparation from 2,3,5-tri-*O*-benzyl-D-arabinofuranose **355** was illustrated in Scheme 53. Compound **359** was first elaborated in order to establish an orthogonal protection of the hydroxyl groups. To this aim the 5-*O*-benzyl group was selectively removed by acetolysis, and the resulting free hydroxyl group was protected with *p*-methoxyphenol (PMP) via Mitsunobu reaction to give product **402**. The unveiling of the formyl group from thiazole of **402** by the silver-based procedure[129] afforded the aldehyde **403** in very good yield (84%). The construction of the second five-member ring

Scheme 62



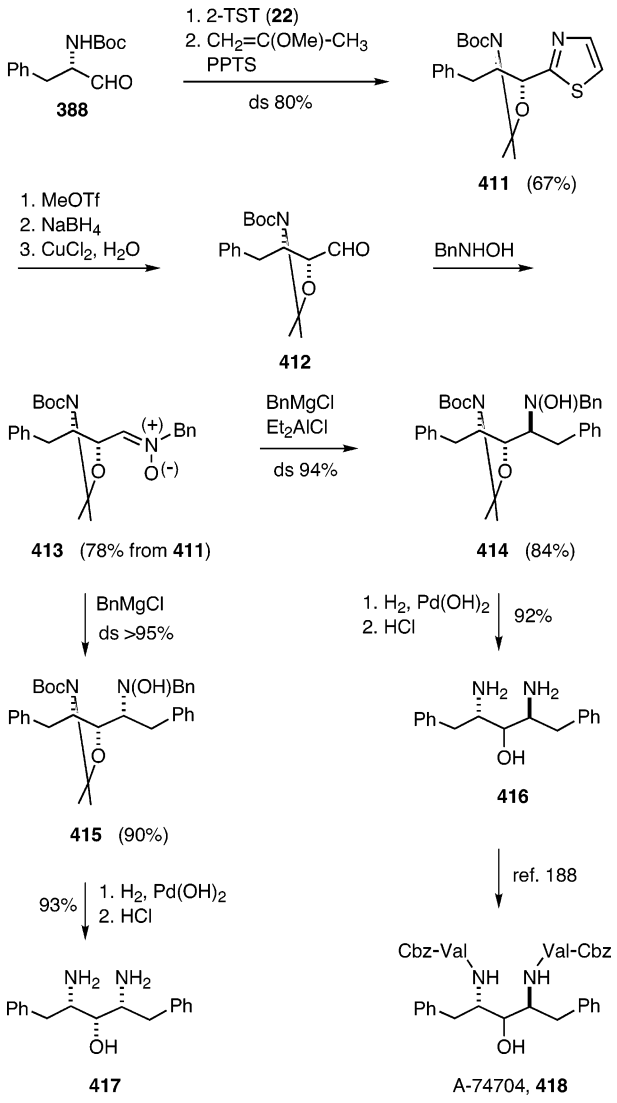
involved as a first step the chain elongation of the aldehyde **403** by Horner−Emmons olefination with the difunctionalized phosphonate **404**. The resulting olefin **405** was transformed into the target product **406** through a reaction sequence involving the reduction of the carbon−carbon double bond and the change of *O*- and *N*-protective groups, then intramolecular cyclization via amide formation, and finally deprotection of the primary alcohol and oxidation to carboxyl group. It was emphasized that compound **406** is the first member of a new class of conformationally constrained dipeptides featuring hydroxyl groups in one of the heterocyclic ring and that libraries of these compounds should be accessible by the same route employing stereoisomers[170] of the hydroxylated 2-thiazolylpyrrolidine **359** and analogues with different ring size.

7. Synthesis of Diamino Alcohols

Short chiral carbon chains containing amino and hydroxyl groups in a well-defined disposition are precious tools in organic and medicinal chemistry. They can be used as ligands for the preparation of organometallic catalysts or as chiral synthetic auxiliaries or can be an essential part of biologically active compounds.

A thiazole-based synthesis of 1,2-diamino diols via aminohomologation of *N*-Boc serine-derived aldehydes was reported.[187] It has been already illustrated in section 3.3 that aldehyde aminohomologation involves the transformation of the aldehyde into nitrone, addition of a 2-metalated thiazole, reduction of the hydroxylamino to amino group, unmasking of the formyl group from the thiazole ring. This reaction sequence was extended to transform the Garner aldehyde **116** into the homologue **409**, i.e., an *O*- and *N*-protected 2,3-diamino-4-hydroxybutanal, in 33% overall yield (Scheme 62). As expected, the addition of 2-LTT **31** to the nitrone **407** was *syn*-selective in analogy to the reaction of the same organometallic reagent with the nitrone **142** derived from D-glyceraldehyde acetonide **23** (see Scheme 25). Hence, the one-pot reduction of the aldehyde **409** to alcohol and deacetonization furnished the optically active *N*,*N*′-Boc *threo*-2,3-diaminobutane-1,4-diol **410** (yield not reported).[187] The epimer of this compound, i.e., the

Scheme 63



optically inactive *erythro* isomer, was prepared[187] by the same methodology starting from the *N*-benzyl nitrone of *O*-*tert*-butyldiphenylsilyl-*N*-*tert*-butoxycarbonyl L-serinal. In fact, the addition of 2-LTT **31** to this nitrone was *anti*-selective.

The synthesis of symmetrically substituted 1,3-diamino-2-propanols have elicited a great deal of interest because the chiral pseudo C_2-symmetric stereoisomers of this class of compounds were reported to be the key core unit of very potent and selective inhibitors of both protease activity and acute HIV-1 infection in vitro.[188] Hence, the thiazole-based synthesis of the four benzyl-substituted 1,3-diamino-2-propanol stereoisomers carried out by Dondoni and co-workers[189] is illustrated here (Scheme 63). To begin the synthesis, the one-carbon homologation of *N*-Boc L-phenylalaninal **388** was carried out by *syn*-stereoselective[83] addition of 2-TST **22** and cleavage of the thiazole ring of the intermediate **411**. Because of its scarce stability, the resulting protected β-amino-α-hydroxy-aldehyde **412** was transformed as a crude material into the stable and crystalline *N*-benzyl nitrone **413**. This served as a key intermediate in the preparation of two of the four possible stereoisomers by stereocontrolled addition of BnMgCl. In fact, the

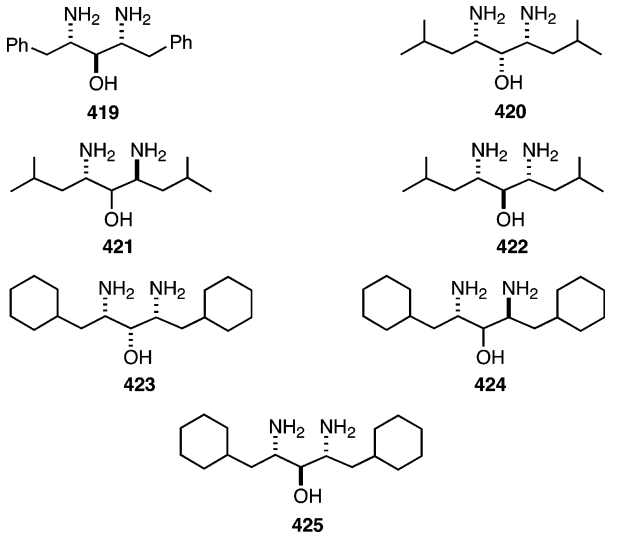


Figure 14. Other 1,3-diamino alcohols prepared.

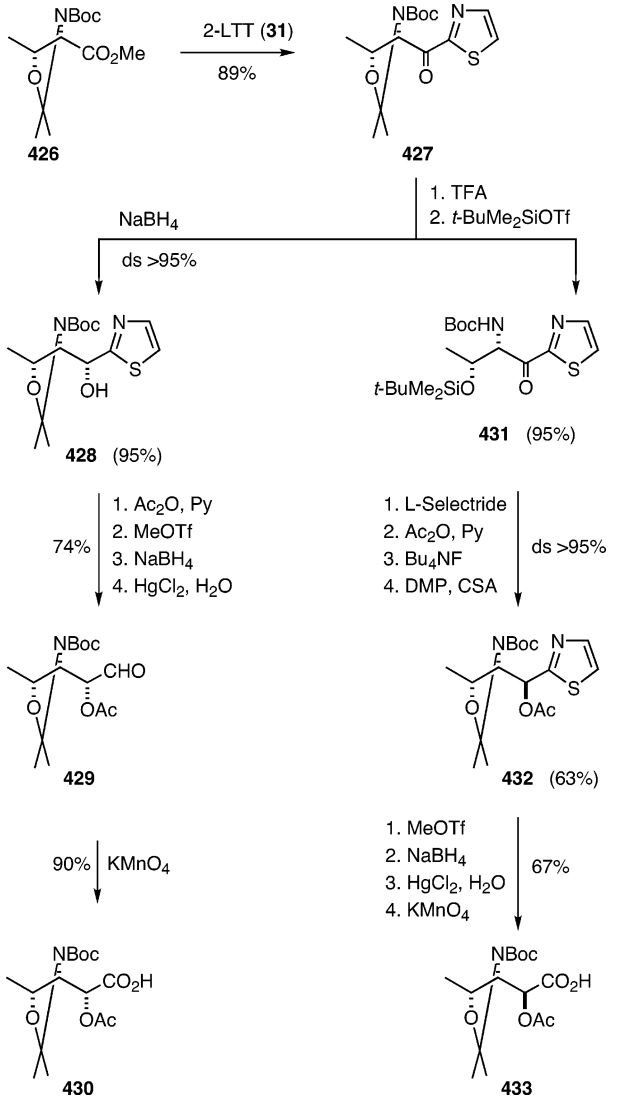
addition of this organometallic reagent to free **413** was *syn*-stereoselective and furnished the hydroxylamine **415**, whereas the addition of the same reagent to **413** precomplexed with Et_2AlCl was *anti*-stereoselective and afforded the hydroxylamine **414**. The products **415** and **414** were transformed into the *meso* compound **417** and the (*S*,*S*)-configured isomer **416**, respectively. The synthesis of the latter pseudo C_2-symmetric stereoisomer (23% overall yield from the phenylalaninal **388**) merits special attention because the *N*-ValCbz derivative A-74704, **418** developed by Abbott researchers,[188b] was shown to be a potent and very selective C_2-symmetric peptidic HIV-1 protease inhibitor.

While it was pointed out[189] that the (*R*,*R*)-configured stereoisomer, namely, the antipode of **416**, would be available through the same route starting from the (*R*)-enantiomer of **388**, the synthesis of the remaining fourth stereoisomer *meso* **419** (Figure 14) was carried out by *anti*-stereoselective addition of BnMgCl to the nitrone C-2 epimer of **413** precomplexed with Et_2AlCl. By the same methods were prepared the stereoisomers of other 1,3-diamino-2-propanols symmetrically substituted with the *i*-propyl group (from *N*-Boc leucinal) and cyclohexylmethyl group (from *N*-Boc cyclohexylalaninal) (Figure 14). This work was continued[189b] with the study of BnMgCl double addition to a chiral bis-nitrone incorporating a diol moiety, which led to symmetrically benzyl-substituted 1,4-diamino-2,3-butandiols. Also, these compounds were considered of great importance because they constituted the nonscissile core units of C_2-symmetric peptidic[190] and nonpeptidic[191] HIV protease inhibitors.

8. Synthesis of Hydroxylated Amino Acids

As it has been shown in sections 3.4 and 3.5, the ease of oxidation of the formyl to the carboxyl group under mild conditions allowed for the development of thiazole-based synthesis of sugar carboxylic acids. The same approach was followed to prepare nonprotein amino acids containing one or more hydroxyl

Scheme 64



groups, a rich class of compounds deserving special attention due to their presence in numerous natural and synthetic products of great biological relevance.[192] The synthesis of four pairs of C-2 epimer β-amino-α-hydroxy acids by one-carbon homologation of serine, threonine, phenylalanine, and leucine was reported.[193] The method is illustrated in Scheme 64. At first the thiazolyl amino ketone **427** was prepared by treating the threonine methyl ester **426** with 2-LTT **31**. This *N*,*N*-diprotected amino ketone was reduced[168] to the alcohol **428** by treatment with $NaBH_4$. The conversion of **427** into the *N*-monoprotected analogue **431** and reduction[168] with L-Selectride furnished the alcohol epimer of **428,** which was isolated as the *O*-acetyl derivative **432**. Compounds **428** and **432** were transformed into the C-2 epimer β-amino-α-hydroxy acids **430** and **433**, respectively, by formyl unmasking from the thiazole ring and oxidation of the resulting aldehydes. The other pairs of hydroxylated β-amino acids prepared are shown in Figure 15.

The thiazole-based synthesis of another simple yet very important β-amino-α-hydroxy acid such as 3-phenylisoserine was reported.[194] This amino acid was prepared as the *N*-Bz and *N*-Boc derivatives since these compounds correspond to the C-13 side chains

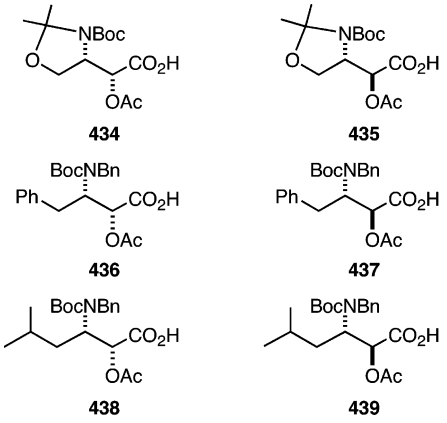
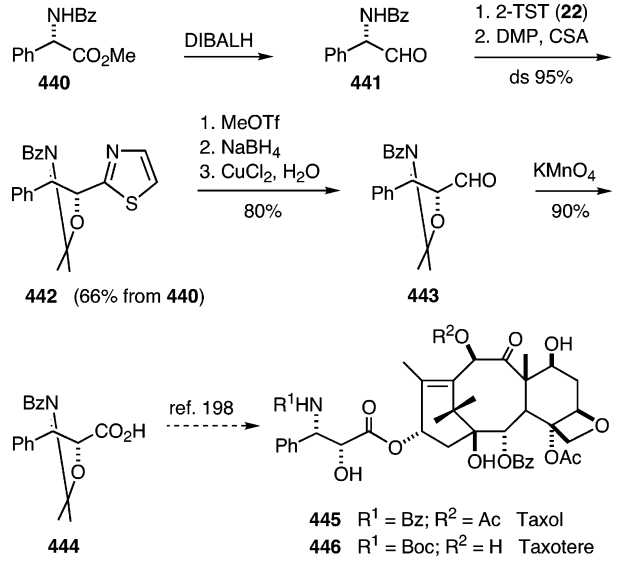


Figure 15. Other β-amino-α-hydroxy-acids prepared.

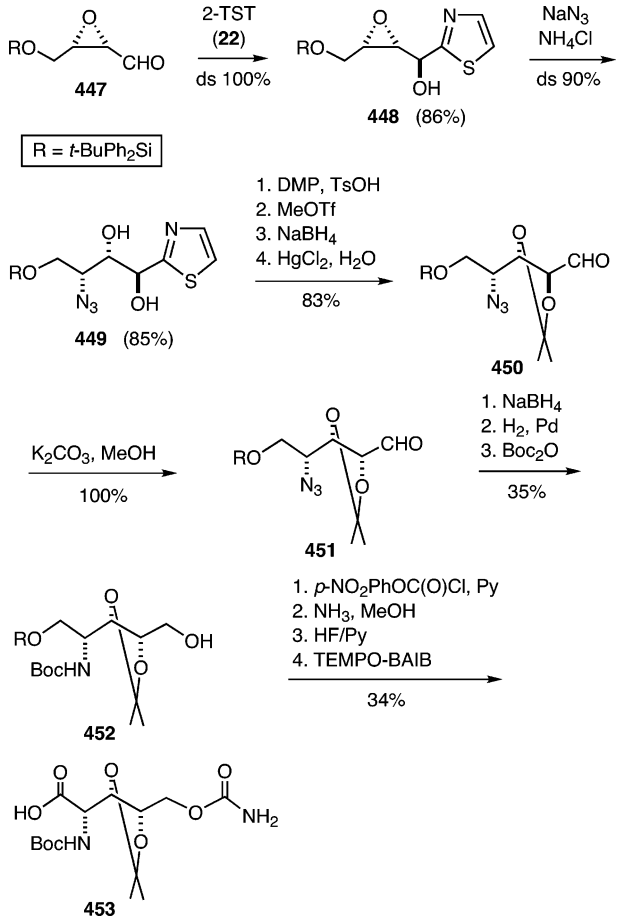
of taxol[195] and taxotere,[196] respectively. The highly promising therapeutic application of taxol and taxotere as anticancer agents and the difficulty of extraction of the former from the natural source have stimulated the development of semisynthetic routes to these compounds and their analogues employing baccatin III and phenylisoserine derivatives. Hence, because of the need of this amino acid building block, various syntheses have been reported over the years.[197] Unfortunately the route described in Scheme 64 could not be followed in this case because the *N*-Bn-*N*-Boc phenylglycine methyl ester upon treatment with 2-LTT **31** failed to give the corresponding thiazolyl amino ketone.[193] By contrast, *N*-benzoyl phenylglycinal **441** reacted[194] readily and stereoselectively with 2-TST **22**, affording a *syn*-amino alcohol as major product,[83] which upon acetonization was isolated as the oxazolidine **442** (Scheme 65). The thiazole-to-

Scheme 65



formyl unmasking transformed compound **442** into the aldehyde **443,** which was readily oxidized to the target 3-phenyl isoserine derivative **444**. This compound was established to have an enantiomeric purity of 84% due to some racemization of the amino aldehyde **441**. By the same route the *N*-Boc protected analogue (enantiomeric purity 90%) of **444** was prepared starting from *N*-Boc phenylglycinal. The

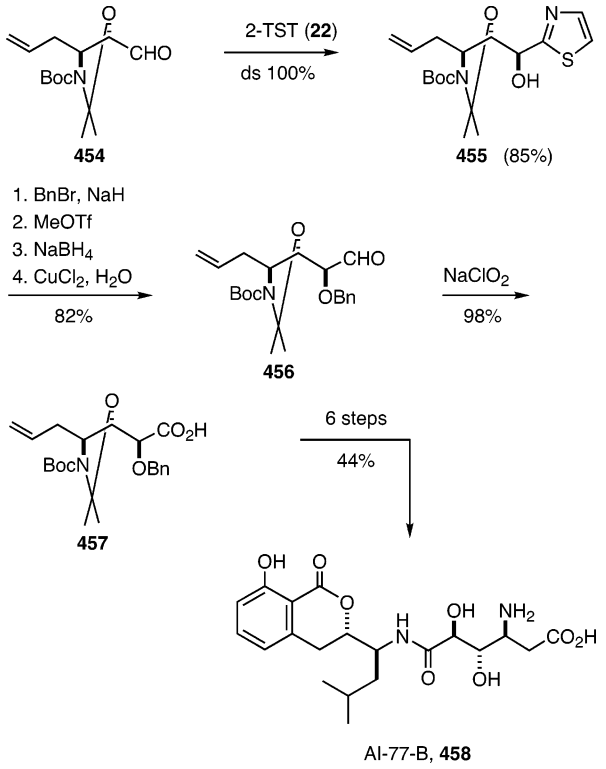
Scheme 66



coupling of suitable baccatin III derivatives with these amino acids prepared by another method was reported earlier by Commerçon and co-workers in a semisynthetic route to taxol and taxotere.[198]

An interesting example of thiazole-based synthesis of a polyhydroxylated amino acid such as 5-*O*-carbamoyl polyoxamic acid was recently reported by Baltas and co-workers.[199] This unusual amino acid represents the nonglycosidic part of several polyoxins, a class of peptidyl nucleosides antibiotics endowed with potent antifungal properties.[200] Although polyoxins are mainly used as agricultural antifungal agents, more recently considerable attention has been addressed to these compounds as inhibitors of opportunistic fungal infections in immunocompromised hosts such as AIDS victims and organ transplant patients. The Baltas synthesis of the protected 5-*O*-carbamoyl polyoxamic acid **453** (Scheme 66) included as a key operation the one-carbon homologation of the chiral epoxybutanal **447** into the functionalized aldehyde **450**. This transformation was effectively carried out by totally stereoselective *anti*-addition of 2-TST **22** to the aldehyde **447**, followed by stereo- and regioselective oxirane ring opening of the epoxy alcohol **448** by NaN_3/NH_4Cl, acetonization, and thiazole to formyl unmasking. Fortunately enough the aldehyde **450** under mild basic conditions epimerized quantitatively to the C-2 isomer **451**, thus establishing the correct configuration of all asymmetric carbons which were present in 5-*O*-carbamoylpolyoxamic acid. The final elaboration of **451** to the target amino

Scheme 67



acid **453** was based on a sequence of common functional group transformations such as the reduction of the formyl and azido groups, the carbamoylation of the primary alcohol, the removal of the *O*-silyl protective group, and oxidation. Curiously, among the numerous syntheses of 5-*O*-carbamoyl polyoxamic acid,[201] that reported by Dondoni and coworkers employed furan instead of thiazole as a synthetic auxiliary.[200a,202]

A very efficient synthesis of an unusual dihydroxyamino acid serving as a building block for the natural pseudopeptide microbial agent AI-77-B, **458** (Scheme 67), was reported by Ghosh and co-workers in 2001.[203] In this case too the key operation of the synthesis involved the chain elongation of an aldehyde, the formyl oxazolidine **454**, to the α-alkoxy homologue **456**. This transformation was carried out in the usual manner using 2-TST **22** as a formyl anion equivalent. The very good overall yield of isolated **456** (75%) was due to both the high stereoselectivity of the addition of **22** to **454** and the efficiency of the improved[33] thiazole-to-formyl unmasking protocol. The final oxidative step of the aldehyde **456** to the target amino acid **457** occurred in almost quantitative yield. The coupling of **457** with an isocumarine derivative bearing an aminated side chain and the conversion of the terminal alkene into carboxyl through an aldehyde intermediate furnished, after the removal of all protective groups, the natural product AI-77-B, **458**.

9. Conclusions

Review of synthetic schemes which have been developed in about 20 years of research by the use of thiazole-based methodology may serve to illustrate the potential of this approach in synthetic programs toward the construction of complex systems or special molecular fragments. The type and variety of the classes of compounds which were accessible by this methodology demonstrate its wide scope and utility. This was primarily due to a small arsenal of readily accessible thiazole-armed reagents and their effective carbon−carbon bond-forming reactions. Noteworthy among these reagents is the organometallic 2-(trimethylsilyl)thiazole (2-TST, **22**) (Scheme 5), which is now commercially available or can be easily prepared in multigram scale as described in a well-detailed procedure reported in *Organic Synthesis*.[26] The rapid diffusion of this new reagent in several laboratories is due to its use as an effective formyl anion equivalent for the stereoselective one-carbon homologation of alkoxy and amino aldehydes, an operation which happens to be carried out quite frequently in organic synthesis. In addition to the examples illustrated above, other stereoselective homologations of chiral alkoxy aldehydes using 2-TST **22** were reported as key steps in the synthesis of biologically active compounds.[204] Moreover, this reagent has been found to be a convenient mean in the preparation of thiazole-containing pharmaceutically interesting compounds[205] and for the rare yet synthetically useful carbon−sulfur bond formation at C-2 of the thiazole ring.[206] Another reagent which deserves special attention is the stabilized phosphorus ylide triphenyl(thiazol-2-ylcarbonylmethylene)phosphorane (2-TCMP, **32**) (Scheme 5) since this allows for the introduction of a three-carbon atom residue containing the thiazole-masked formyl group via Wittig-type coupling with aldehydes (Schemes 14, 31−34, 48, and 49). However, other thiazole-based reagents shown in Scheme 5 have been conveniently used. Hence, it may be concluded that although the major contribution in this field has so far given by the authors' group at the University of Ferrara, the synthetic utility of the thiazole-based methodology has been sufficiently established through the examples reported in this review and its scope should be expanded in the future. From the same examples it is apparent that the use of the thiazole ring as synthetic auxiliary allows a great deal of potential chemistry compatibility problems to be avoided, which may be a great obstacle to the execution of synthetic programs directed toward the preparation of densely functionalized chiral systems. In fact, the thiazole ring appears to be endowed with some properties which make it a very convenient tool in synthetic methodology. Specifically, it withstands a great deal of chemistry throughout the elaboration of the substrate in which it has been introduced, but it can be rapidly and efficiently immolated to give the formyl group by a procedure which is well tolerated by a wide variety of functional groups and does not affect existing stereocenters.

10. Acknowledgments

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11. References

(1) (a) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; Wiley: New York, 1989. (b) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weinheim, 1996. (c) In *Organic Synthesis Today & Tomorrow*; Trost, B. M., Hutchinson, C. R., Eds.; Pergamon: Oxford, 1981. (d) In *Current Trends in Organic Synthesis*; Nozaki, H., Ed.; Pergamon Press: Oxford, 1983. (e) Hanessian, S. *Total Synthesis of Natural Products. The Chiron Approach*; Pergamon Press: Oxford, 1983. (f) In *Strategies and Tactics in Organic Synthesis*; Lindberg, T., Ed.; Academic Press: Orlando, 1984. (g) In *Organic Synthesis Highlights*; Mülzer, J., Altenbach, H. J., Braun, M., Krohn, K., Reissig, H. U., Eds.; VCH: Weinheim, 1991. (h) Ho, T.-L. *Tactics of Organic Synthesis*; Wiley: New York, 1994. (i) In *Organic Synthesis Highlights II*; Waldmann, H., Ed.; VCH: Weinheim, 1995. (j) Smit, W. A.; Bochkov, A. F.; Caple, R. *Organic Synthesis. The Science behind the Art*; The Royal Society of Chemistry: Cambridge, 1998. (k) Fuhrhop, J.-H.; Li, G. *Organic Synthesis*; Wiley-VCH: Weinheim, 2003.

(2) (a) Varki, A. *Glycobiology* **1993**, *3*, 97. (b) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683. (c) In *Essential of Glycobiology*; Varki, A., Cummings, R., Esko, J., Freeze, H., Hart, G., Marth, J., Eds.; Cold Spring Harbor Laboratory Press: Cold Spring Harbor, 1999. (d) In *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinaÿ, P., Eds.; Wiley-VCH: Weinhein, 2000; Vol. 1.

(3) Meyers, A. I. In *Heterocycles in Organic Synthesis*; Taylor, E. C., Weissberger, A., Eds; Wiley: New York, 1974.

(4) (a) Corey, E. J.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 1075 and 1077. (b) Seebach, D. *Synthesis* **1969**, 17. (c) Yus, M.; Nájera, C.; Foubelo, F. *Tetrahedron* **2003**, *59*, 6147.

(5) (a) Meyers, A. I.; Mihelic, E. D. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 270. (b) Meyers, A. I.; Mihelic, E. D. *New Synthetic Methods*; Verlag Chemie: Weinhein, 1979; Vol. 5, p 105. (c) Reuman, M.; Meyers, A. I. *Tetrahedron* **1985**, *41*, 837. (d) Meyers, A. I. *J. Heterocycl. Chem.* **1998**, *35*, 991. (e) Cardillo, G.; Gentilucci, L.; Tolomelli, A. *Aldrichim. Acta* **2003**, *36*, 39.

(6) Wassermann, H. H.; McCarthy, K. E.; Prowse, K. S. *Chem. Rev.* **1986**, *86*, 845.

(7) Iddon, B. *Heterocycles* **1983**, *20*, 1127.

(8) (a) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410. (b) Kamimura, A. *J. Synth. Org. Chem. Jpn.* **1992**, *50*, 808.

(9) Baraldi, P. G.; Barco, A.; Benetti, S.; Pollini, G. P., Simoni, D. *Synthesis* **1987**, 857.

(10) Mukaiyama, T.; Asami, M. *Topics in Current Chemistry*; Springer-Verlag: 1985; Vol. 127, p 133.

(11) (a) Casiraghi, G.; Rassu, G. *Synthesis* **1995**, 607. (b) Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Chem. Soc. Rev.* **2000**, *29*, 109.

(12) (a) Iddon, B. *Heterocycles* **1995**, *41*, 533. (b) Dondoni, A. *Synthesis* **1998**, 1681. (c) Lopyrev, V. A.; Larina, L. I.; Voronkov, M. G. *Russ. J. Org. Chem.* **2001**, *37*, 149.

(13) (a) Katritzky, A. R.; Lan, X.; Fan, W.-Q. *Synthesis* **1994**, 445. (b) Katritzky, A. R.; Lan, X. *Chem. Soc. Rev.* **1994**, 363. (c) Katritzky, A. R.; Henderson, S. A.; Yang, B. Z. *J. Heterocycl. Chem.* **1998**, *35*, 1123. (d) Katritzky, A. R.; Lan, X.; Yang, J. Z.; Denisko, O. V. *Chem. Rev.* **1998**, *98*, 409.

(14) (a) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795 (b) Shipman, M. *Contemporary Org. Synth.* **1995**, *2*, 1.

(15) For previous partial surveys, see: (a) Dondoni, A. *Pure Appl. Chem.* **1990**, *62*, 643. Dondoni, A. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Verlag Helvetica Chimica Acta: Basel, 1992; p 377. (b) Dondoni, A. In *New Aspects of Organic Chemistry II*; Yoshida, Z., Ohshiro, Y., Eds.; Kodansha: Tokyo and VCH: Weinheim; 1992; p 105. (c) Dondoni, A.; Marra, A. In *Preparative Carbohydrate Chemistry*; Hanessian S., Ed.; Marcel Dekker: New York; 1997; p 173. (d) Dondoni, A.; Perrone, D. *Aldrichim. Acta* **1997**, *30*, 35. (e) Dondoni, A.; Marra, A. *Chem. Commun.* **1999**, 2133. (f) Dondoni, A. *Pure Appl. Chem.* **2000**, *72*, 1577.

(16) For selected articles with leading references, see: (a) discovery, Ugai, T.; Tanaka, S.; Dokawa, S. *J. Pharm. Soc. Jpn.* **1943**, *63*, 269. (b) kinetic and mechanism, Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719. Castells, J.; Lòpez-Calahorra, F.; Domingo, L. *J. Org. Chem.* **1988**, *53*, 4433. Castells, J.; Domingo, L.; Lòpez-Calahorra, F.; Martì, J. *Tetrahedron Lett.* **1993**, *34*, 517. Chen, Y.-T.; Barletta, G. L.; Haghjoo, K.; Cheng, J. T.; Jordan, F. *J. Org. Chem.* **1994**, *59*, 7714. Breslow, R.; Kim, R. *Tetrahedron Lett.* **1994**, *35*, 699. Breslow, R.; Schmuck, C. *Tetrahedron Lett.* **1996**, *37*, 8241. Motesharei, K.; Myles, D. C. *J. Am. Chem. Soc.* **1997**, *119*, 6674. White, M. J.; Leeper, F. J. *J. Org. Chem.* **2001**, *66*, 5124. (c) synthetic applications: Matsumoto, T.; Yamamoto, H.; Inoue, S. *J. Am. Chem. Soc.* **1984**, *106*, 4829. Matsumoto, T.; Ohishi, M.; Inoue, S. *J. Org. Chem.* **1985**, *50*, 603. Saimoto, H.; Shigemasa, Y. *J. Synth. Org. Chem. Jpn.* **1992**, *50*, 703. Teles, J. H.; Melder, J.-P.; Ebel, K.; Schneider, R.; Gehrer, E.; Harder, W.; Brode, S.; Enders, D.; Breuer, K.; Raabe, G. *Helv. Chim. Acta* **1996**, *79*, 61. Heck, R.; Henderson, H. P.; Kohler, B.; Retey, J.; Golding B. T. *Eur. J. Org. Chem.* **2001**, 2623.

(17) (a) Reviews: Stetter, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 639. Stetter, H.; Kuhlmann, H. *Org. React.* **1991**, *40*, 407. (b) Recent synthetic applications: Ciganek, E. *Synthesis* **1995**, 1311. Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. *Helv. Chim. Acta* **1996**, *79*, 1899. Woo, P. W. K.; Hartman, J.; Huang, Y.; Nanninga, T.; Bauman, K.; Butler, D. E.; Rubin, J. R.; Lee, H. T.; Huang, C. C. *J. Labeled Cmpd. Radiopharm.* **1999**, *42*, 121. Harrington P. E.; Tius, M. A. *Org. Lett.* **1999**, *1*, 649. Braun, R. U.; Zeitler, K.; Muller, T. J. *Org. Lett.* **2001**, *3*, 3297. Kobayashi, N.; Kaku, Y.; Higurashi, K.; Yamauchi, T.; Ishibashi, A.; Okamoto, Y. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1747.

(18) Brettle, R. In *Comprehensive Organic Chemistry*; Stoddart, J. F., Ed.; Pergamon Press: Oxford; 1979; Vol. 1, Chapter 5.

(19) (a) Meyers, A. I.; Nabeya, A.; Adickes, H. W.; Politzer, I. R. *J. Am. Chem. Soc.* **1969**, *91*, 763. (b) Meyers, A. I.; Nabeya, A.; Adickes, H. W.; Fitzpatrick, J. M.; Malone, G. R.; Politzer, I. R. *J. Am. Chem. Soc.* **1969**, *91*, 764. (c) Meyers, A. I.; Kovelesky, A. C. *J. Am. Chem. Soc.* **1969**, *91*, 5887.

(20) Altman, L. J.; Richheimer *Tetrahedron Lett.* **1971**, 4709.

(21) For an updated overview of the chemistry of thiazole, benzothiazole, and their reduced derivatives, see: Dondoni, A.; Merino, P. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier: Oxford; 1996; Vol. 3, Chapter 6.

(22) Meyers, A. I.; Munavu, R.; Durandetta, J. *Tetrahedron Lett.* **1972**, 3929.

(23) Meyers, A. I.; Durandetta, J. *J. Org. Chem.* **1975**, *40*, 2021.

(24) Meyers, A. I.; Durandetta, J.; Munavu R. *J. Org. Chem.* **1975**, *40*, 2025.

(25) Corey, E. J.; Boger, D. L. *Tetrahedron Lett.* **1978**, 5.

(26) In contrast to the procedure described in an organometallic manual (Brandsma, L.; Verkruijsse, H. *Preparative Polar Organometallic Chemistry 1*; Springer: Berlin, 1987; p 138), the synthesis of 2-TST **22** is more conveniently carried out starting from 2-bromothiazole than thiazole (see: Dondoni, A.; Merino, P. *Org. Synth.* **1995**, *72*, 21). The discovery and the first synthesis of this reagent were reported by Dondoni and coworkers much earlier (Medici, A.; Pedrini, P.; Dondoni, A. *J. Chem. Soc., Chem. Commun.* **1981**, 655) than in the above organometallic manual.

(27) (a) Medici, A.; Fantin, G.; Fogagnolo, M.; Dondoni, A. *Tetrahedron Lett.* **1983**, *24*, 2901. (b) Dondoni, A.; Dall'Occo, T.; Galliani, G.; Mastellari, A. R.; Medici, A. *Tetrahedron Lett.* **1984**, *25*, 3637. (c) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1988**, *53*, 1748.

(28) Dondoni, A.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Tetrahedron Lett.* **1985**, *26*, 5477.

(29) Dondoni, A.; Colombo, L. In *Advances in the Use of Synthons in Organic Chemistry*; Dondoni, A., Ed.; JAI: Greenwich, 1993; Vol. 1, p 1.

(30) This yield refers to that obtained in the procedure reported in *Organic Synthesis* cited in ref 26.

(31) We will use throughout this review the notation % ds instead of % de to quote the diastereoselectivity of a given transformation. The indicator % ds is defined as the percentage of a given diastereomer in a mixture of diastereomeric products (Thaisrivongs, S.; Seebach, D. *J. Am. Chem. Soc.* **1983**, *105*, 7407). For comments regarding the various stereochemical models by which the observed stereochemical outcomes can be interpreted, it is recommended to read the discussion in the original papers.

(32) The reduction of thiazolium salts to give thiazolidines by the use of sodium borohydride may be somewhat surprising considering that also the carbon−carbon double bond must undergo the borohydride attack. The mechanism of this process was carefully studied several years ago (Clarke, G. M.; Sykes, P. *J. Chem. Soc. (C)* **1967**, 1411). It has been demonstrated by the use of sodium borodeuteride in water and deuterium oxide that the reduction of the carbon−carbon bond of a 2-thiazoline intermediate occurs through the sequential addition of a proton at C-5 and a hydride ion at C-4. Such an activation of the carbon−carbon bond that allows for the addition of proton and hydride ions is due to the synergistic action of the adjacent heteroatoms.

(33) Dondoni, A.; Marra, A.; Perrone, D. *J. Org. Chem.* **1993**, *58*, 275.

(34) For a detailed description of the unmasking procedure using $AgNO_3$ in the final hydrolysis, see ref 129.
(35) Dondoni, A.; Mastellari, A. R.; Medici, A., Negrini, E.; Pedrini, P. *Synthesis* **1986**, 757.
(36) Dondoni, A.; Perrone, D. *J. Org. Chem*. **1995**, *60*, 4749.
(37) Dondoni, A.; Merino, P. *J. Org. Chem*. **1991**, *56*, 5294
(38) Dondoni, A.; Marra, A.; Merino, P. *J. Am. Chem. Soc.* **1994**, *116*, 3324.
(39) Dondoni, A.; Fantin G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Tetrahedron* **1988**, *44*, 2021.
(40) Dondoni, A.; Fantin G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Synthesis* **1987**, 998.
(41) Dondoni, A.; Merchan, F. L.; Merino, P.; Rojo, I.; Tejero, T. *Synthesis* **1996**, 641.
(42) Tejero, T.; Dondoni, A.; Rojo, I.; Merchan, F. L.; Merino, P. *Tetrahedron* **1997**, *53*, 3301.
(43) (a) 4-Methyl-2-(trimethylsilyl)oxazole (Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem*. **1987**, *52*, 3413). (b) 2-(trimethylsilyl)imidazole (Jutzi, P.; Sakriss, W. *Chem. Ber.* **1973**, *106*, 2815). (c) 2-(trimethylsilyl)pyridine (Effenberger, F.; Konig, J. *Tetrahedron* **1988**, *44*, 3281.
(44) An exceptional case has been recently reported by Marco-Contelles and co-workers in which the reaction of 2-TST **22** with α-iodo polyhydroxylated aldehyde derived from D-glucose gave in addition to the expected adduct in fair yield (60%) a formyl cyclopentane byproduct (7%) arising from an intramolecular alkylation in the aldehyde-2-TST adduct, see: (a) Marco-Contelles, J.; de Opazo, E. *Tetrahedron Lett.* **2000**, *41*, 5507. (b) Marco-Contelles, J.; de Opazo, E.; Arroyo, N. *Tetrahedron* **2001**, *57*, 4729. (c) Marco-Contelles, J.; de Opazo, E. *J. Carbohydr. Chem*. **2001**, *20*, 637.
(45) Pohl, M.; Lingen, B.; Müller, M. *Chem. Eur. J*. **2002**, *8*, 5288.
(46) Kwart, H.; King, K. G. *d-Orbitals in the Chemistry of Silicon, Phosphorus and Sulfur*; Springer-Verlag: Berlin, 1977.
(47) Dondoni, A.; Douglas, A. W.; Shinkai, I. *J. Org. Chem*. **1993**, *58*, 3196.
(48) Wu, Y.-D.; Lee, J. K.; Houk, K. N.; Dondoni, A. *J. Org. Chem*. **1996**, *61*, 1922.
(49) Dondoni, A.; Boscarato, A.; Formaglio, P.; Bégué, J.-P.; Benayoud, F. *Synthesis* **1995**, 654.
(50) Carcano, M.; Vasella, A. *Helv. Chim. Acta* **1998**, *81*, 889.
(51) For an overview of methods for the one-carbon homologation of sugars and leading references to higher carbohydrate synthesis, see ref 15c and Györgydeák, Z.; Pelyvás, I. F. *Monosaccharide Sugars: Chemical Synthesis by Chain Elongation, Degradation, and Epimerization*; Academic Press: San Diego, 1998; Chapter 1.
(52) (a) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 835. (b) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem*. **1989**, *54*, 693.
(53) By virtue of the thiazolyl-to-formyl equivalence, the polyhydroxyalkylthiazoles have been considered as 'thiazole sugars'. Hence, a simplified trivial name is given to these compounds by combining the word thiazole with that of the carbohydrate that is formed by formyl unmasking.
(54) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem*. **1989**, *54*, 702.
(55) Dondoni, A.; Orduna, J.; Merino, P. *Synthesis* **1992**, 201.
(56) Reviews on the hydride reduction of carbonyls: Oishi, Y.; Nakata, T. *Acc. Chem. Res.* **1984**, *17*, 338. See also: Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556. ApSimon, J. W.; Collier, T. L. *Tetrahedron* **1986**, *42*, 5157.
(57) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A. *Tetrahedron* **1987**, *43*, 3533.
(58) (a) Danishefsky, S. J.; Barbachyn, M. *J. Am. Chem. Soc.* **1985**, *107*, 7761. (b) Danishefsky, S. J.; Maring, C. *J. Am. Chem. Soc.* **1985**, *107*, 7762. (c) Danishefsky, S. J.; DeNinno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 15.
(59) Uchida, K.; Ichikawa, T.; Shimauchi, Y.; Ishikura, T.; Ozaki, A. *J. Antibiot.* **1971**, *24*, 259.
(60) Takatsuki, A.; Arima, K.; Tamura, G. *J. Antibiot.* **1971**, *24*, 215.
(61) Danishefsky, S. J.; Pearson, W. H.; Harvey, D. F.; Maring, C. G.; Springer, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1256.
(62) Khare, N. K.; Sood, R. K.; Aspinall, G. O. *Can. J. Chem*. **1994**, *72*, 237.
(63) Maillard, Ph.; Huel, C.; Momenteau, M. *Tetrahedron Lett.* **1992**, *33*, 8081.
(64) Hassner, A.; Stumer, C. *Organic Syntheses Based on Name Reactions*; Elsevier Science Ltd.: Oxford, 2002; p 92.
(65) Dondoni, A.; Merino, P.; Orduna, J.; Perrone, D. *Synthesis* **1993**, 277.
(66) Dondoni, A. Fantin, G.; Fogagnolo, M. Merino, P. *J. Carbohydr. Chem*. **1990**, *9*, 735.
(67) Dondoni, A.; Merino, P. *Synthesis* **1993**, 903.
(68) For a search of the conditions for a selective deprotonation of 2-ATT **30** leading to the lithium enolate and a trimethylsilyl enol ether as well as a study of the cross aldol condensation with various aldehydes including chiral alkoxy aldehydes, see ref 37.
(69) (a) Evans, D. A.; Chapman, K. T.; Carreira E. M. *J. Am. Chem. Soc*. **1988**, *110*, 3560. (b) Evans, D. A.; Hoveyda, A. H. *J. Org. Chem*. **1990**, *55*, 5190. (c) Evans, D. A.; Gauchet-Prunet, J. A.; Carreira, E. M.; Charette, A. B. *J. Org. Chem*. **1991**, *56*, 741.
(70) Dondoni, A.; Ianelli, S.; Kniezo, L.; Merino, P.; Nardelli, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1231.
(71) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Pedrini, P. *Tetrahedron* **1989**, *45*, 5141.
(72) Kennedy, J. F.; White, C. A. *Bioactive Carbohydrates*; Ellis Harwood: Chichester, 1983; Chapter 12.
(73) Schlessinger, R. H.; Graves, D. D. *Tetrahedron Lett.* **1987**, *28*, 4381.
(74) (a) Dondoni, A.; Marra, A.; Massi, A. *Carbohydr. Lett.* **1997**, *2*, 367. (b) Dondoni, A.; Marra, A.; Massi, A. *J. Org. Chem*. **1997**, *62*, 6261.
(75) (a) Umezawa, H. *Pure Appl. Chem*. **1971**, *28*, 665. (b) Takita, T.; Muraoka, Y.; Nakatani, T.; Fujii, A.; Umezawa, Y.; Naganawa, H.; Umezawa, H. *J. Antibiot.* **1978**, *31*, 801.
(76) Boger, D. L.; Honda, T. *J. Am. Chem. Soc.* **1994**, *116*, 5647.
(77) (a) Nicolaou, K. C.; Rodriguez, R. M.; Fylaktakidou, K. C.; Suzuki, H.; Mitchell, H. J. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3340. (b) Nicolaou, K. C.; Mitchell, H. J.; Fylaktakidou, K. C.; Rodriguez, R. M.; Suzuki, H. *Chem. Eur. J*. **2000**, *6*, 3116.
(78) (a) Horton, D.; Wander, J. D. In *The Carbohydrates Chemistry and Biochemistry*; Pigman, W., Horton, D., Eds.; Academic Press: New York, 1980; Vol. 1B, Chapter 16. (b) Collins, P.; Ferrier, R. *Monosaccharides. Their Chemistry and Their Roles in Natural Products*; Wiley: Chichester, 1995; pp 217−240.
(79) (a) Hakomori, S. In *Handbook of Lipid Research: Sphingolipid Biochemistry*; Kanfer, J. N., Hakomori, S., Eds.; Plenum Press: New York, 1983; Vol. 3, pp 1−150. (b) Kolter, T.; Sandhoff, K. *Angew. Chem., Int. Ed*. **1999**, *38*, 1532. (c) Vankar, Y. D.; Schmidt, R. R. *Chem. Soc. Rev*. **2000**, *29*, 201.
(80) (a) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A. *J. Chem. Soc., Chem. Commun*. **1988**, 10. (b) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Pedrini, P. *J. Org. Chem*. **1990**, *55*, 1439.
(81) (a) For a recent account on the synthetic application of this aldehyde, see: Liang, X.; Andersch, J.; Bols, M. *J. Chem. Soc., Perkin Trans 1* **2001**, 2136. (b) For an improved synthesis avoiding racemization, see: Dondoni, A.; Perrone, D. *Synthesis* **1997**, 527. Dondoni, A.; Perrone, D. *Org. Synth*. **1999**, *77*, 64.
(82) For an improved and detailed description of the addition of 2-TST **22** to the aldehyde **116**, see: Dondoni, A.; Perrone, D. *Org. Synth*. **1999**, *77*, 78.
(83) Parallel and further studies (see ref 181) on the addition of 2-TST **22** to α-amino aldehydes showed that the stereochemical outcome of the reaction can be controlled by the extent of substitution of the amino group, e.g., *N,N*-disubstituted compounds give *anti*-1,2-amino alcohols whereas *N*-monosubstituted derivatives give *syn*-products.
(84) The α-hydroxy-free aldehyde instead of the *O*-benzyl derivative **118** was employed in the Wittig reaction.
(85) (a) Garner, P.; Park, J. M.; Malecki, E. *J. Org. Chem*. **1988**, *53*, 4395. (b) Nimkar, S.; Menaldino, D.; Merril, A. H.; Liotta, D. *Tetrahedron Lett.* **1988**, *29*, 3037. (c) Radunz, H. E.; Devant, R. M.; Eiermann, V. *Liebigs Ann. Chem*. **1988**, 1103. (d) Herold, P. *Helv. Chim. Acta* **1988**, *71*, 354.
(86) Dondoni, A.; Perrone, D.; Turturici, E. *J. Chem. Soc., Perkin Trans 1* **1997**, 2389.
(87) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Merino, P. *Tetrahedron* **1990**, *46*, 6167.
(88) Dondoni, A.; Merino, P. *Synthesis* **1992**, 196.
(89) Ikemoto, N.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 9657.
(90) For a review on the synthesis of these amino sugars, see: Hauser, F. M.; Ellenberger, S. R. *Chem. Rev.* **1986**, *86*, 35.
(91) Arcamone, F. In *Anticancer Agents Based on Natural Product Models*; Cassay, J. M., Deouros, J. D., Eds.; Academic Press: New York, 1980; Medicinal Chemistry, Vol. 16, p 1.
(92) The indicated stereoselectivity under the arrow refers to the Michael-type addition of benzylamine to the 2-alkenylthiazolium salt.
(93) Servi, S. *J. Org. Chem*. **1985**, *50*, 5865.
(94) Review on the synthesis of lincomycin and precursors: Golebiowski, A.; Jurczak, J. In *Recent Progress in the Chemical Synthesis of Antibiotics*; Lukacs, G., Ohno, M., Eds., Springer: Berlin, 1990; p 366.
(95) Dondoni, A.; Franco, S.; Junquera, F.; Merchan, F. L.; Merino, P.; Tejero, T.; Bertolasi, V. *Chem. Eur. J*. **1995**, *1*, 505.
(96) Dondoni, A.; Franco, S.; Junquera, F.; Merchan, F. L.; Merino, P.; Tejero, T. *Synth. Commun*. **1994**, *24*, 2537.
(97) Lombardo, M.; Trombini, C. *Synthesis* **2000**, 759.
(98) A reversed ratio was quoted in a preliminary report by the same group (Dondoni, A.; Junquera, F.; Merchan, F. L.; Merino, P.; Tejero, T. *Tetrahedron Lett.* **1992**, *33*, 4221) due to the opposite, but incorrect, structural assignment to the major stereoisomer. For a prompt correction, see: Dondoni, A.; Franco, S.; Merchan, F. L.; Merino, P.; Tejero, T. *Tetrahedron Lett.* **1993**, *34*, 5475.

(99) (a) Murahashi, S.-I.; Kodera, Y. *Tetrahedron Lett.* **1985**, *26*, 4633. (b) Liebeskind, L. S.; Welker, M. E.; Fengl, R. W. *J. Am. Chem. Soc.* **1986**, *108*, 6328.

(100) Csuk, R.; Hugener, M.; Vasella, A. *Helv. Chim. Acta* **1988**, *71*, 609.

(101) Dondoni, A.; Franco, S.; Merchan, F. L.; Merino, P.; Tejero, T. *Synlett* **1993**, 78.

(102) Component of the antibiotic natural products destomycin (Kondo, S.; Inuma, K.; Naganawa, H.; Shimura, H.; Sekizawa, Y. *J. Antibiot.* **1975**, *28*, 79. Shimura, H.; Sekizawa, Y.; Inuma, K.; Naganawa, H.; Kondo, S. *Agric. Biol. Chem.* **1976**, *40*, 611) and hygromycin (Neuss, N.; Koch, K. F.; Molloy, B. B.; Day, W.; Huckstep, L. L.; Dorman, D. E.; Roberts, J. D. *Helv. Chim. Acta* **1970**, *53*, 2314).

(103) Component of the commercially important antibiotic lincomycin, see ref 94.

(104) The synthesis of destomic acid from **162** includes first the reduction ($NaBH_4$) to alcohol (Golebiowski, A.; Kozak, J.; Jurczak, J. *J. Org. Chem.* **1991**, *56*, 7344).

(105) For the synthesis of lincosamine from **163,** see: Atsumi, T.; Fukumaru, T.; Ogawa, T.; Matsui, M. *Agric. Biol. Chem.* **1973**, *37*, 2621.

(106) For recent reviews, see: (a) Baltas, M.; Ruland, Y. In *Targets in Heterocyclic Systems*; Attanasi, O. A., Spinelli, D., Eds.; Società Chimica Italiana: Roma, 2001; Vol 5, p 357. (b) Li, L.-S.; Wu, Y.-L. *Curr. Org. Chem.* **2003**, *7*, 447.

(107) (a) Ganem, B. *Tetrahedron* **1978**, *34*, 3353. (b) Dewick, P. M. *Nat. Prod. Rep.* **1988**, *5*, 73. (c) Haslam, E. *Shikimic Acid. Metabolism and Metabolites*; Wiley: New York, 1993.

(108) (a) Unger, F. M. *Adv. Carbohydr. Chem. Biochem.* **1981**, *38*, 323. (b) In *Bacterial Lipopolysaccharides: Structure, Synthesis and Biological Activities*; Anderson, L., Unger, F. M., Eds.; ACS Symposium Series 231; American Chemical Society: Washington, D.C., 1983.

(109) (a) Nadano, D.; Iwasaki, M.; Endo, S.; Kitajima, K.; Inoue, S.; Inoue, Y. *J. Biol. Chem.* **1986**, *261*, 11550. (b) Inoue, S.; Lin, S.-L.; Chang, T.; Wu, S.-H.; Yao, C.-W.; Chu, T.-Y.; Troy, F. A.; Inoue, Y. *J. Biol. Chem.* **1998**, *273*, 27199.

(110) Corfield, A. P.; Schauer, R. Sialic Acids. Chemistry, Metabolism, and Function. In *Cell Biography Monographs*; Schauer, R., Ed.; Springer-Verlag: Wien, 1982; Vol. 10.

(111) (a) McGuire, E. J. In *Biological Roles of Sialic Acids*; Rosenberg, R. A., Schengrund, C. L., Eds.; Plenum: New York, 1976; Chapter 4. (b) Schauer, R.; Kelm, S.; Reuter, G.; Roggentin, P.; Shaw, I. Biochemistry and Role of Sialic Acids. In *Biology of the Sialic Acids*; Rosemberg, A., Ed.; Plenum: New York, 1995.

(112) Selected references: (a) Augé, C.; David, S.; Gautheron, C. *Tetrahedron Lett.* **1984**, *25*, 4663. (b) Kim, M.-J.; Hennen, W. J.; Sweers, H. M.; Wong, C.-H. *J. Am. Chem. Soc.* **1988**, *110*, 6481. (c) Simon, E. S.; Bednarski, M. D.; Whitesides, G. M. *J. Am. Chem. Soc.* **1988**, *110*, 7159. (d) Draths, K. M.; Frost, J. W. *J. Am. Chem. Soc.* **1990**, *112*, 1657. (e) Kragl, U.; Gygax, D.; Ghisalba, O.; Wandrey, C. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 827. (f) Sugai, T.; Shen, G.-J.; Ichikawa, Y.; Wong, C.-H. *J. Am. Chem. Soc.* **1993**, *115*, 413. (g) Augé, C.; Delest, V. *Tetrahedron: Asymmetry* **1995**, *6*, 863. (h) Salagnad, C.; Goedde, A.; Ernst, B.; Kragl, U. *Biotechnol. Prog.* **1997**, *13*, 810.

(113) Selected references: (a) Schmidt, R. R.; Betz, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 430. (b) Shirai, R.; Ogura, H. *Tetrahedron Lett.* **1989**, *30*, 2263. (c) Kim, E.; Gordon, D. M.; Schmid, W.; Whitesides, G. M. *J. Org. Chem.* **1993**, *58*, 5500. (d) Chan, T.-H.; Lee, M.-C. *J. Org. Chem.* **1995**, *60*, 4228.

(114) The cleavage of the thiazole ring to amide via reaction with singlet oxygen has been occasionally reported (Matsuura, T.; Saito, I. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2973. Wasylyk, J. M.; Biskupiak, J. E.; Costello, C. E.; Ireland, C. M. *J. Org. Chem.* **1983**, *48*, 4445). This method appears to be rather unpractical and requires workup operations which are hardly compatible with the integrity of stereocenters and acid-sensitive protective groups in the substrate. For other attempts of oxidative cleavage, see note 17 in ref 38.

(115) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Merino, P. *Tetrahedron Lett.* **1990**, *31*, 4513.

(116) For earlier syntheses of KDO before 1994, see refs 37 and 38 and references therein. For recent syntheses, see: (a) Hu, Y. J.; Huang, X. D.; Yao, Z. J.; Wu, Y. L. *J. Org. Chem.* **1998**, *63*, 2456. (b) Schlessinger, R. H.; Pettus, L. H. *J. Org. Chem.* **1998**, *63*, 9089. (c) Brauer, N.; Kirschning, A.; Schaumann, E. *Eur. J. Org. Chem.* **1998**, 2729. (d) Reiner, M.; Schmidt, R. R. *Tetrahedron: Asymmetry* **2000**, *11*, 319. (e) Mlynarski, J.; Banaszek, A. *Tetrahedron: Asymmetry* **2000**, *11*, 3737. (f) Barton, D. H. R.; De Almeida, M. V.; Liu, W. H.; Shinada, T.; Jaszberenyi, J. C.; Dos Santos, H. F.; Le Hyaric, M. *Tetrahedron* **2001**, *57*, 8767. (g) Pathak, R.; Shaw, A. K.; Bhaduri, A. P. *Tetrahedron* **2002**, *58*, 3535. (h) Li, L. S.; Wu, Y. L. *Tetrahedron* **2002**, *58*, 9049.

(117) Dondoni, A.; Merino, P.; Orduna, J. *Tetrahedron Lett.* **1991**, *32*, 3247.

(118) An *O*-silylated analogue of the thiazolyl ketone **182**, prepared by addition of 2-LTT **31** to the corresponding Weinreb amide, was transformed into a protected DAH derivative via a reaction sequence similar to that shown in Scheme 31, see: Devianne, G.; Escudier, J.-M.; Baltas, M.; Gorrichon, L. *J. Org. Chem.* **1995**, *60*, 7343.

(119) For earlier syntheses of DAH before 1994, see ref 38 and references therein. For recent syntheses, see: (a) Garcia, F. S.; Cebrian, G. M. P.; Lopez, A. H.; Herrera, F. J. L. *Tetrahedron* **1998**, *54*, 6867. (b) Reiner, M.; Stolz, F.; Schmidt, R. R. *Eur. J. Org. Chem.* **2002**, 57. (c) Liu, K. G.; Hu, S. G.; Wu, Y. K.; Yao, Z. J.; Wu, Y. L. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1890.

(120) Dondoni, A.; Marra, A. *Carbohydr. Lett.* **1994**, *1*, 43.

(121) For earlier syntheses of KDN before 1994, see ref 38 and references therein. For recent syntheses, see: (a) Banwell, M.; De Savi, C.; Watson, K. *Chem. Commun.* **1998**, 1189. (b) Warwel, M.; Fessner, W. D. *Synlett* **2000**, 865. (c) Voight, E. A.; Rein, C.; Burke, S. D. *J. Org. Chem.* **2002**, *67*, 8489.

(122) Dondoni, A.; Boscarato, A.; Marra, A. *Synlett* **1993**, 256.

(123) A general observation which was made on the conjugate addition of *O*- and *N*-nucleophiles to thiazolyl α,β-enones of type III (see Scheme 28) was that the stereochemical outcome greatly depended on the reaction conditions, particularly the temperature, because the reactions were reversible and the selectivity can be under kinetic or thermodynamic control.

(124) (a) Dondoni, A.; Boscarato, A.; Marra, A. *Tetrahedron: Asymmetry* **1994**, *5*, 2209. (b) Dondoni, A.; Marra, A.; Boscarato, A. *Chem. Eur. J.* **1999**, *5*, 3562.

(125) (a) Dondoni, A.; Scherrmann, M.-C. *Tetrahedron Lett.* **1993**, *34*, 7319. (b) Dondoni, A.; Scherrmann, M.-C. *J. Org. Chem.* **1994**, *59*, 6404. (c) Dondoni, A.; Marra, A. *Tetrahedron Lett.* **2003**, *44*, 4067.

(126) Dondoni, A.; Marra, A.; Rojo, I.; Scherrmann, M.-C. *Tetrahedron* **1996**, *52*, 3057.

(127) (a) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155. (b) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212. (c) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380. (d) Seeberger, P. H.; Danishefsky, S. J. *Acc. Chem. Res.* **1998**, *31*, 685. (e) Osborn, H. M. I.; Khan, T. H. *Tetrahedron* **1999**, *55*, 1807. (f) Demchenko, A. V. *Synlett* **2003**, 1225.

(128) (a) Danishefsky, S. J.; DeNinno, M. P.; Chen, S. *J. Am. Chem. Soc.* **1988**, *110*, 3929. (b) Heskamp, B. M.; Veeneman, G. H.; van der Marel, G. A.; van Boeckel, C. A. A.; van Boom, J. H. *Tetrahedron* **1995**, *51*, 5657.

(129) Dondoni, A.; Marra, A.; Scherrmann, M.-C.; Bertolasi, V. *Chem. Eur. J.* **2001**, *7*, 1371.

(130) Fraser-Reid, B.; Madsen, R. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Dekker: New York, 1997; p 339.

(131) (a) Kawamura, M.; Uchiyama, T.; Kuramoto, T.; Tamura, Y.; Mizutani, K. *Carbohydr. Res.* **1989**, *192*, 83. (b) Sawada, M.; Tanaka, T.; Takai, Y.; Hanafusa, T.; Taniguchi, T.; Kawamura, M.; Uchiyama, T. *Carbohydr. Res.* **1991**, *217*, 7.

(132) (a) Marra, A.; Scherrmann, M.-C.; Dondoni, A.; Casnati, A.; Minari, P.; Ungaro, R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2479. (b) Dondoni, A.; Marra, A.; Scherrmann, M.-C.; Casnati, A.; Sansone, F.; Ungaro, R. *Chem. Eur. J.* **1997**, *3*, 1774. (c) Dondoni, A.; Kleban, M.; Hu, X.; Marra, A.; Banks, H. D. *J. Org. Chem.* **2002**, *67*, 4722.

(133) Marra, A.; Dondoni, F.; Sansone, F. *J. Org. Chem.* **1996**, *61*, 5155.

(134) Dondoni, A.; Daninos, S.; Marra, A.; Formaglio, P. *Tetrahedron* **1998**, *54*, 9859.

(135) Synthesis of nonisosteric glycosylphosphonates. Selected papers: (a) Dessinges, A.; Vasella, A. *Carbohydr. Res.* **1988**, *174*, 47. (b) Vasella, A.; Wyler, R. *Helv. Chim. Acta* **1991**, *74*, 451. (c) Müller, B.; Martin, T. J.; Schaub, C.; Schmidt, R. R. *Tetrahedron Lett.* **1998**, *39*, 509.

(136) Witczack, Z. J. *Curr. Med. Chem.* **1995**, *1*, 392.

(137) Dondoni, A.; Scherrmann, M.-C.; Marra, A.; Delépine, J.-L. *J. Org. Chem.* **1994**, *59*, 7517.

(138) Mio, S.; Kumagawa, Y.; Sugai, S. *Tetrahedron* **1991**, *47*, 2133.

(139) Dondoni, A.; Marra, A. *Chem. Rev.* **2000**, *100*, 4935.

(140) (a) Postema, M. H. D. *C-Glycoside Synthesis*; CRC Press: Boca Raton, 1995. (b) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Elsevier: Oxford, 1995. (c) Beau, J.-M.; Gallagher, T. *Top. Curr. Chem.* **1997**, *187*, 1. (d) Beau, J.-M.; Vauzeilles, B.; Skrydstrup, T. In *Glycoscience. Chemistry and Chemical Biology*; Fraser-Reid, B., Tatsuta, K., Thiem, J., Eds.; Springer-Verlag: Heidelberg, 2001; Vol. 3, p 2679.

(141) For some historical notes and an introduction to the concept of isosteric equivalence, see: Patani, G. A.; LaVoie, E. J. *Chem. Rev.* **1996**, *96*, 3147.

(142) Dondoni, A.; Formaglio, P.; Marra, A.; Massi, A. *Tetrahedron* **2001**, *57*, 7719.

(143) For a detailed description of the conversion of **284** into **285**, see ref 155.

(144) The use of benzothiazole instead of thiazole derivatives does not make any conceptual difference in the thiazole aldehyde synthesis as a strategy. Benzothiazole derivatives offer some advantages in terms of stability, crystallinity, and manipulability, while they are less reactive and the unmasking of the formyl

group can be in some cases rather difficult. Some differences in the chemistry of benzothiazole and thiazole derivatives have been observed, such as the conversion of vinylbenzothiazoles into α,β-unsaturated aldehydes reported by Corey and Boger (ref 25) and the isomerization of α- into β-linked benzothiazolyl *C*-glycoside shown in Scheme 45. Both processes do not occur with thiazole derivatives.

(145) Dondoni, A.; Marra, A. *Tetrahedron Lett.* **2003**, *44*, 13.

(146) (a) Ogawa, T.; Kikuchi, Y.; Matsui, M. Ohrui, H.; Kuzuhara, H.; Emoto, S. *Agric. Biol. Chem.* **1971**, *35*, 1825. (b) Trummlitz, G.; Moffat, J. G. *J. Org. Chem.* **1973**, *38*, 1841. (c) Horton, D.; Philips, K. D. *Carbohydr. Res.* **1973**, *30*, 367. (d) Albrecht, H.; Repke, D. B.; Moffatt, J. G. *J. Org. Chem.* **1973**, *38*, 1836. (e) Kobertz, W. R.; Bertozzi, C. R.; Bednarski, M. D. *Tetrahedron Lett.* **1992**, *33*, 737. (f) Bertozzi, C. R.; Bednarski, M. D. *Tetrahedron Lett.* **1992**, *33*, 3109. (g) Lasterra Sanchez, M. E.; Michelet, V.; Besnier, V.; Genét, J. P. *Synlett* **1994**, 705. (h) Labéguère, F.; Lavergne, J.-P.; Martinez, J. *Tetrahedron Lett.* **2002**, *43*, 7271.

(147) Dondoni, A.; Marra, A.; Mizuno, M.; Giovannini, P. P. *J. Org. Chem.* **2002**, *67*, 4186.

(148) Dondoni, A.; Marra, A.; Massi, A. *J. Org. Chem.* **1999**, *64*, 933.

(149) Dondoni, A.; Marra, A. *Tetrahedron Lett.* **2002**, *43*, 1649.

(150) Dondoni, A.; Giovannini, P. P. *Synthesis* **2002**, 1701.

(151) Dondoni, A.; Massi, S.; Sabbatini, S. *J. Org. Chem.* **2002**, *67*, 6979.

(152) Dondoni, A.; Massi, A.; Minghini, E.; Bertolasi, V. *Helv. Chim. Acta* **2002**, *85*, 3331.

(153) Dondoni, A.; Junquera, F.; Merchan, F. L.; Merino, P.; Schermann, M.-C.; Tejero, T. *J. Org. Chem.* **1997**, *62*, 5484.

(154) Dondoni, A.; Marra, A. *Tetrahedron Lett.* **1993**, *34*, 7327.

(155) Dondoni, A.; Zuurmond, H. M.; Boscarato, A. *J. Org. Chem.* **1997**, *62*, 8114 and references therein.

(156) (a) Danishefsky, S.; Barbachyn, M. *J. Am. Chem. Soc.* **1985**, *107*, 7761. (b) Lopez, J. C.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1989**, *111*, 3450. (c) Armstrong, R. W.; Teegarden, B. R. *J. Org. Chem.* **1992**, *57*, 915. (d) Eyrisch, O.; Fessner, W.-D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1639.

(157) (a) Dondoni, A.; Kniezo, L.; Martinkova, M. *J. Chem. Soc., Chem. Commun.* **1994**, 1963. (b) Dondoni, A.; Kniezo, L.; Martinkova, M.; Imrich, J. *Chem. Eur. J.* **1997**, *3*, 424.

(158) Stepánek, P.; Kniezo, L.; Dvoráková, H.; Vojtisek, P. *Synlett* **2003**, 963.

(159) (a) Look, G. C.; Fotsch, C. H.; Wong, C.-H. *Acc. Chem. Res.* **1993**, *26*, 182. (b) In *Iminosugars as Glycosidase Inhibitors. Nojirimycin and Beyond*; Stütz, A. E., Ed.; Wiley-VCH: Weinheim, 1999.

(160) For a review on natural azasugars, see: Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645.

(161) Dondoni, A.; Merino, P.; Perrone, D. *Tetrahedron* **1993**, *49*, 2939.

(162) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155.

(163) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Merino, P. *J. Chem. Soc., Chem. Commun.* **1990**, 854.

(164) Dondoni, A.; Merino, P.; Perrone, D. *J. Chem. Soc., Chem. Commun.* **1991**, 1576.

(165) (a) Miyake, Y.; Ebata, M. *J. Antibiot.* **1987**, *40*, 122. (b) Miyake, Y.; Ebata, M. *Agric. Biol. Chem.* **1988**, *52*, 153.

(166) Galactostatin **354** was prepared before isolation from the natural source: (a) Paulsen, H.; Hayauchi, Y.; Sinnwell, V. *Chem. Ber.* **1980**, *113*, 2601. (b) Legler, G.; Pohl, S. *Carbohydr. Res.* **1986**, *155*, 119. Synthesis after isolation: (c) Aoyagi, S.; Fujimaki, S.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1991**, *56*, 815. (d) Chida, N.; Tanikawa, T.; Tobe, T.; Ogawa, S. *J. Chem. Soc., Chem. Commun.* **1994**, 1247.

(167) Chikashita, H.; Ishibaba, M.; Ori, K.; Itoh, K. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3637.

(168) Various examples have been reported (see ref 193) wherein the hydride reduction of *N*,*N*-diprotected 2-thiazolyl α-amino ketones was *syn*-selective, whereas the same reaction with *N*-monoprotected derivatives was *anti*-selective. Tunable diastereoselectivity has also been observed in addition reactions of 2-metalated thiazoles to differentially protected α-amino aldehydes (refs 80, 83, and 181) and their nitrones (ref 187).

(169) Martin, O. R. In *Carbohydrate Mimics. Concepts and Methods*; Chapleur, Y., Ed.; Wiley-VCH: Weinheim, 1998; p 259.

(170) (a) Dondoni, A.; Perrone, D. *Tetrahedron Lett.* **1999**, *40*, 9375. (b) Dondoni, A.; Giovannini, P. P.; Perrone, D. *J. Org. Chem.* **2002**, *67*, 7203.

(171) (a) Spatola, A. F. In *Chemistry and Biochemistry of Amino Acids, Peptides, and Proteins*; Weinstein, B., Ed.; Marcel Dekker: New York, 1983; Vol. VII, p 267. (b) Olson, G. L.; Bolin, D. R.; Bonner, M. P.; Bös, M.; Cook, C. M.; Fry, D. C.; Graves, B. J.; Hatada, M.; Hill, D. E.; Kahn, M.; Madison, V. S.; Rusiecki, V. K.; Sarabu, R.; Sepinwall, J.; Vincent, G. P.; Voss, M. E. *J. Med. Chem.* **1993**, *36*, 3039. (c) Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699. (d) Babine, R.; Bender, S. L. *Chem. Rev.* **1997**, *97*, 1359. (e) Venkatesan, N.; Kim, B. H. *Curr. Med. Chem.* **2002**, *9*, 2243.

(172) (a) Lien, E. J.; Gao, H.; Lien, L. L. *Prog. Drug. Res.* **1994**, *43*, 43. (b) Dhanaraj, V. In *Drugs, Enzymes and Receptors of the Renin-Angiotensin System*; Husain, A., Graham, R. M., Eds.; Victor Chang Mol. Cardiol. Series 1; Harwood Academic: Amsterdam, 2000; p 283.

(173) (a) Ghosh, A. K.; Bilcer, G.; Schiltz, G. *Synthesis* **2001**, 2203. (b) Abdel-Rahman, H. M.; Al-karamany, G. S.; El-Koussi, N. A.; Youssef, A. F.; Kiso, Y. *Curr. Med. Chem.* **2002**, *9*, 1905.

(174) (a) Dondoni, A.; Perrone, D. *Tetrahedron Lett.* **1992**, *33*, 7259. (b) Dondoni, A.; Perrone, D.; Semola, M. T. *J. Org. Chem.* **1995**, *60*, 7927.

(175) Almquist, R. G.; Chao, W.-R.; Ellis, M. E.; Johnson, H. L. *J. Med. Chem.* **1980**, *23*, 1392.

(176) Brown, H. C.; Brown, C. A. *J. Am. Chem. Soc.* **1963**, *85*, 1003.

(177) Ghosh, A. K.; McKee, S. P.; Thompson, W. A. J. *J. Org. Chem.* **1991**, *56*, 6500.

(178) Wagner, A.; Mollath, M. *Tetrahedron Lett.* **1993**, *34*, 619.

(179) Tourwé, D.; Piron, J.; Defreyn, P.; Van Binst, G. *Tetrahedron Lett.* **1993**, *34*, 5499.

(180) Parkes, K. E. B.; Bushnell, D. J.; Crackett, P. H.; Dunsdon, S. J.; Freeman, A. C.; Gunn, M. P.; Hopkins, R. A.; Lambert, R. W.; Martin, J. A.; Merrett, J. H.; Redshaw, S.; Spurden, W. C.; Thomas, G. J. *J. Org. Chem.* **1994**, *59*, 3656.

(181) Dondoni, A.; Perrone, D.; Merino, P. *J. Org. Chem.* **1995**, *60*, 8074.

(182) Redemann, T.; Bandel, H.; Jung, G. *Mol. Diversity* **1998**, *4*, 191.

(183) (a) Peptide Secondary Structure Mimetics. In *Tetrahedron Symposia-in-Print* **1993**, *49*, 3433. (b) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789.

(184) Dondoni, A.; Marra, A.; Richichi, A. *Synlett* **2003**, 2345.

(185) (a) Gosselin, F.; Lubell, W. D. *J. Org. Chem.* **2000**, *65*, 2163. (b) Dietrich, E.; Lubell, W. D. *J. Org. Chem.* **2003**, *68*, 6988.

(186) (a) Polyak, F.; Lubell, W. D. *J. Org. Chem.* **2001**, *66*, 1171. (b) Feng, Z.; Lubell, W. D. *J. Org. Chem.* **2001**, *66*, 1181. (c) Artale, E.; Banfi, G.; Belvisi, L.; Colombo, L.; Colombo, M.; Manzoni, L.; Scolastico, C. *Tetrahedron* **2003**, *59*, 6241.

(187) Dondoni, A.; Merchan, F. L.; Merino, P.; Tejero, T.; Bertolasi, V. *J. Chem. Soc., Chem. Commun.* **1994**, 1731.

(188) (a) Erickson, J.; Neidhart, D. J.; VanDrie, J.; Kempf, D. J.; Wang, X. C.; Norbeck, D. W.; Plattner, J. J.; Rittenhouse, J. W.; Turon, M.; Wideburg, N.; Kohlbrener, W. E.; Simmer, R.; Helfrich, R.; Paul, D. A.; Knigge, M. F. *Science* **1990**, *249*, 527. (b) Kempf, D. J.; Norbeck, D. W.; Codacovi, L. M.; Wang, X. C.; Kohlbrener, W. E.; Wideburg, N. E.; Paul, D. A.; Knigge, M. F.; Vasavanonda, S.; Craig-Kennard, A.; Saldivar, A.; Rosenbrook, W., Jr.; Clement, J. J.; Plattner, J. J.; Erickson, J. *J. Med. Chem.* **1990**, *33*, 2687.

(189) (a) Dondoni, A.; Perrone, D. *Tetrahedron Lett.* **1997**, *38*, 499. (b) Dondoni, A.; Perrone, D.; Rinaldi, M. *J. Org. Chem.* **1998**, *63*, 9252.

(190) (a) Kempf, D. J.; Codacovi, L.; Wang, X. C.; Kohlbrener, W. E.; Wideburg, N. E.; Saldivar, A.; Vasavanonda, S.; Marsh, K. C.; Bryant, P.; Sham, H. L.; Green, B. E.; Betebenner, D. A.; Erickson, J. W.; Norbeck, D. W. *J. Med. Chem.* **1993**, *36*, 320. (b) Hosur, M. V.; Bhat, T. N.; Kempf, D. J.; Baldwin, E. T.; Liu, B.; Gulnik, S.; Wideburg, N. E.; Norbeck, D. W.; Appelt, K.; Erickson, J. W. *J. Am. Chem. Soc.* **1994**, *116*, 847.

(191) (a) Lam, P. Y. S.; Jadhav, P. K.; Eyermann, C. J.; Hodge, C. N.; Ru, Y.; Bacheler, L. T.; Meek, J. L.; Otto, M. J.; Rayner, M. M.; Wong, Y. N.; Chang, C.-H.; Weber, P. C.; Jackson, D. A.; Sharpe, T. R.; Erickson-Viitanen, S. *Science* **1994**, *263*, 380. (b) Rossano, L. T.; Lo, Y. S.; Anzalone, L.; Lee, Y.-C.; Meloni, D. J.; Moore, J. R.; Gale, T. M.; Arnett, J. F. *Tetrahedron Lett.* **1995**, *36*, 4967.

(192) (a) In *Chemistry and Biochemistry of the Amino Acids*; Barrett, G. C., Ed.; Chapman and Hall: London, 1985. (b) Wagner, I.; Musso, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 816.

(193) (a) Dondoni, A.; Perrone, D.; Merino, P. *J. Chem. Soc., Chem. Commun.* **1991**, 1313. (b) Dondoni, A.; Perrone, D. *Synthesis* **1993**, 1162.

(194) Dondoni, A.; Perrone, D.; Semola M. T. *Synthesis* **1995**, 181.

(195) Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15.

(196) Guénard, D.; Guéritte-Voegelein, F.; Potier, P. *Acc. Chem. Res.* **1993**, *26*, 160.

(197) For earlier syntheses of phenylisoserine before 1995, see ref 194 and references therein. For recent syntheses, see: (a) Gennari, C.; Vulpetti, A.; Donghi, M.; Mongelli, N.; Vanotti, E. *Angew. Chem., Int. Ed. Engl.* **1996**, *34*, 1723. (b) Adger, B. M.; Barkley, J. V.; Bergeron, S.; Cappi, M. W.; Flowerdew, B. E.; Jackson, M. P.; McCague, R.; Nugent, T. C.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3501. (c) Fernández, R.; Ferrete, A.; Lassaletta, J. M.; Llera, J. M.; Martín-Zamora, E. *Angew. Chem., Int. Ed.* **2002**, *41*, 831. (d) Mandai, T.; Oshitari, T.; Susowake, M. *Synlett* **2002**, 1665.

(198) Commerçon, A.; Bezard, D.; Bernard, F.; Bourzat, J. D. *Tetrahedron Lett.* **1992**, *33*, 5185.

(199) Dehoux, C.; Monthieu, C.; Baltas, M.; Gorrichon, L. *Synthesis* **2000**, 1409.
(200) For recent syntheses of polyoxin J as well as leading references to isolation, classification, and properties of polyoxins, see: (a) Dondoni, A.; Franco, S.; Junquera, F.; Merchán, F. L.; Merino, P.; Tejero, T. *J. Org. Chem*. **1997**, *62*, 5497. (b) Ghosh, A. K.; Wang, Y. *J. Org. Chem*. **1999**, *64*, 2789.
(201) See refs 199 and 200 and references therein.
(202) Dondoni, A.; Franco, S.; Merchán, F. L.; Merino, P.; Tejero, T. *Tetrahedron Lett.* **1993**, *34*, 5479.
(203) (a) Ghosh, A. K.; Bischoff, A.; Cappiello, J. *Org. Lett.* **2001**, *3*, 2677. (b) Ghosh, A. K.; Bischoff, A.; Cappiello, J. *Eur. J. Org. Chem*. **2003**, 821.
(204) (a) Nakashima, H.; Hirata, N.; Iwamura, T.; Yamagiwa, Y.; Kamikawa, T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2849. (b) Shimada, J.; Kwon, H. J.; Sawamura, M.; Schreiber, S. L. *Chem. Biol*. **1995**, *2*, 517. (c) Solladié, G.; Wilb, N.; Bauder, C.; Bonini, C.; Viggiani, L.; Chiummiento, L. *J. Org. Chem*. **1999**, *64*, 5447.
(205) (a) Yamaguchi, M.; Kamei, K.; Koga, T.; Akima, M.; Maruyama, A.; Kuroki, T.; Ohi, N. *J. Med. Chem*. **1993**, *36*, 4061. (b) Costanzo, M. J.; Maryanoff, B. E.; Hecker, L. R.; Schott, M. R.; Yabut, S. C.; Zhnag, H.-C.; Andrade-Gordon, P.; Kauffman, J. A.; Lewis, J. M.; Krishnan, R.; Tulinsky, A. *J. Med. Chem*. **1996**, *39*, 3039. (c) Akiyama, Y.; Tsutsumi, S.; Hatsushiba, E.; Ohuchi, S.; Okonogi, T. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 533. (d) D'Auria, M.; Mauriello, G.; Racioppi, R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 37.
(206) Munavalli, S.; Rohrbaugh, D. K.; Rossman, D. I.; Durst, H. D.; Dondoni, A. *Phosphorus, Sulfur, Silicon* **2002**, *177*, 2465.

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