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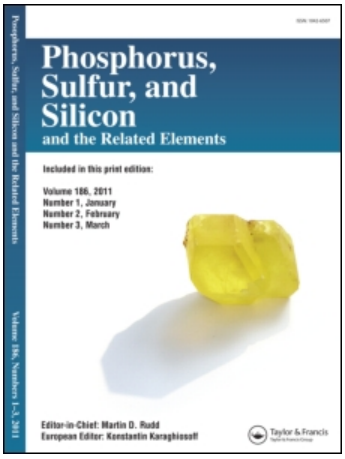

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Organic Synthesis with Sulfur Heterocycles (Thiazoles) as Auxiliaries. The Thiazole Route to Carbohydrates and Biologically Active Derivatives

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ORGANIC SYNTHESIS WITH SULFUR HETEROCYCLES (THIAZOLES) AS AUXILIARIES. THE THIAZOLE ROUTE TO CARBOHYDRATES AND BIOLOGICALLY ACTIVE DERIVATIVES*

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Dipartimento di Chimica, Laboratorio di Chimica Organica, Università, Ferrara, Italy

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ABSTRACT

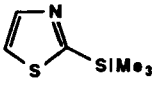
Functionally-substituted thiazoles at C-2, namely 2-trimethylsilylthiazole (2-TST), 2-thiazolylmethylenetriphenylphosphorane (2-TMP) and 2-thiazolylcarbonitrile N-oxide (2-TNO) serve as effective auxiliaries in new synthetic strategies for the stereoselective synthesis (THIAZOLE ROUTE) of long-chain protected polyhydroxyaldehydes, i.e. carbohydrate-like materials, starting from readily available precursors such as chiral hydroxy- and aminoaldehydes. These methodologies are based on two essential operations, both chemically and stereochemically very efficient : i) the coupling between the functionally-substituted thiazole and an appropriate substrate by a carbon-carbon bond forming reaction; ii) the aldehyde release in the resulting adduct by thiazole into formyl conversion. Some compounds obtained in this way are transformed by functional group elaborations into molecules of biological relevance such as deoxy- and aminosugars, and sphingosines.

INTRODUCTION

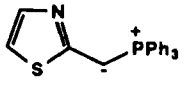
The element of sulfur in the form of various organosulfur compounds differing in the number and/or nature of ligands on sulfur, is currently employed as an auxiliary in organic synthesis.[1] Sulfur plays a pivotal role in many transformations, for instance as a chiral sulfoxide auxiliary, a powerful electron-withdrawing sulfone substituent, and a very effective metal radical scavenger thiocarbonyl group.[2] Despite the recent recognition that heterocycles can be used as convenient mediators of synthetic transformations[3] and the consequential widespread application of this concept in synthesis,[4] sulfur heterocycles are newcomers to this elite group of molecules. For instance acyclic syntheses via stereoselective carbon-carbon bond forming reactions based on 1,3-oxathianes,[5] 2,5-dihydrothiophene S,S-oxides,[6] and thiazolidine thiones[7] have recently been reported. Similarly, chiral thiazolines and thiazolidines are receiving increasing attention as precursors to new classes of biologically active compounds[8a] and thiocarbonyl-derived heterocycles are conveniently employed as key intermediates to macrocyclic lactones of biological relevance.[8b] The aim of this

*Dedicated to the memory of Professor A. Mangini, a pioneer of modern organic sulfur chemistry

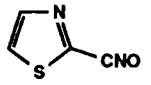
account is to introduce thiazoles[9] as auxiliaries for organic synthesis[10] since compounds bearing appropriate functionalities at C-2 can serve as reactants in carbon-carbon bond forming processes and as latent formyl group equivalents. I will illustrate synthetic strategies for long-chain polyhydroxyaldehydes, i.e. carbohydrate-like materials, based on three substituted thiazoles as auxiliaries (THIAZOLE ROUTE), i.e. a trimethylsilyl derivative, a phosphorus ylide, and a nitrile oxide (Fig. 1). These strategies are centred on two essential key operations : i) the coupling between the substituted thiazole and an appropriate reactant via a carbon-carbon bond forming reaction ; ii) the aldehyde release by thiazole into formyl conversion. There is ever-growing interest in the synthesis of rare and /or unnatural carbohydrates from nonsugar sources and in their use as chiral precursors to complex molecular systems of biological relevance.[11]



2-TST



2-TMP



2-TNO

Fig. 1

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THE THIAZOLE ROUTE TO CARBOHYDRATES

1. The Approach based on 2-TST

2-Trimethylsilylthiazole (2-TST) is a stable and storable organometal which can be prepared in multigram scale from commercially available starting materials and purified by distillation[12] (Fig 2). 2-TST serves as an excellent 2-thiazolyl anion equivalent since it undergoes rapid carbodemetalation reactions with various electrophiles (ketenes,[12] acyl chlorides,[12] aldehydes,[12] azolium ions[13]) to give the corresponding 2-substituted thiazoles in fairly good yields. Each type of reaction shows a remarkable degree of generality, thus giving access to a number of substituted thiazoles having manipulatable functionalities. Noteworthy in the context of the present account is the reaction of 2-TST with aldehydes (Fig. 3) which affords the corresponding O-trimethylsilyl alcohol as the result of the addition of the C-Si bond of 2-TST to the carbonyl of the aldehyde. The O-silylated alcohol can be either isolated and characterized, or desilylated in situ to the alfa-hydroxyalkylthiazole.

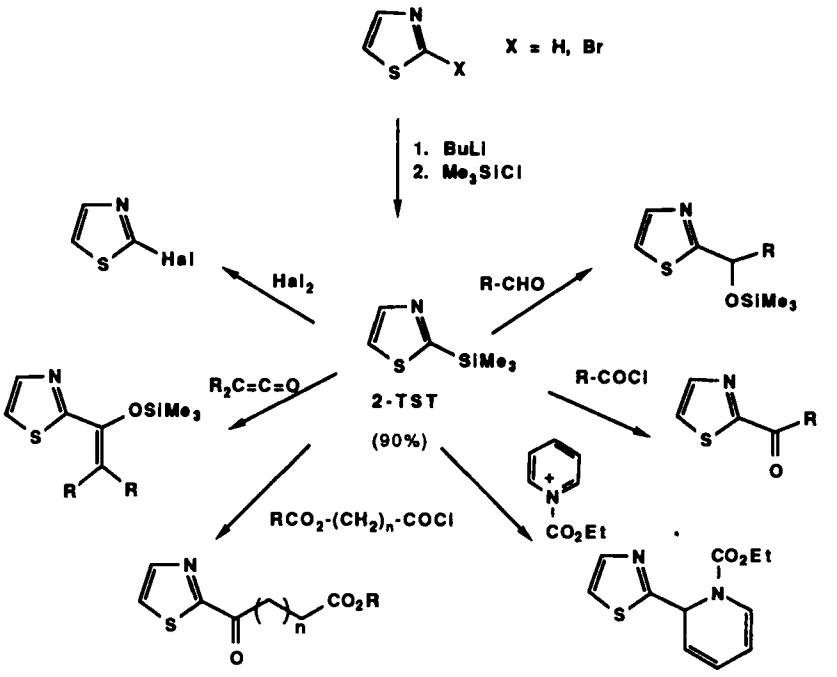

Fig. 2

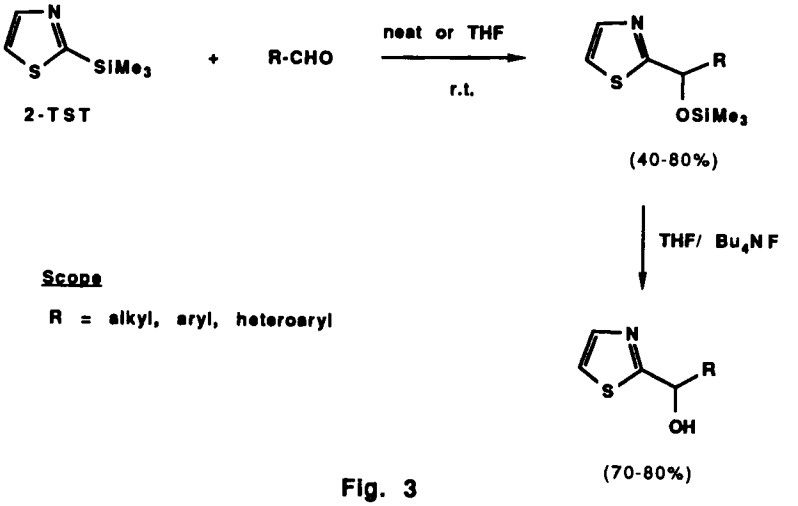

Fig. 3

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On the basis of various observations, it appears very likely that the reaction of 2-TST with aldehydes as well as with other C-electrophiles occurs by a multi-step mechanism involving the rate-determining formation of a thiazolium 2-ylide as an intermediate (Fig. 4). Sulfur and

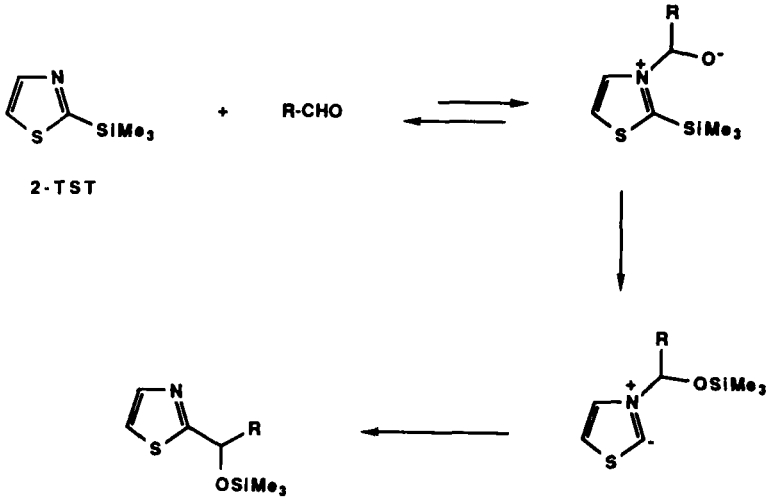

Fig. 4

silicon should play an important role in this process, the former by virtue of its ability to stabilize the negative charge on the vicinal carbon in the ylide (sulfur alfa-effect),[14] the latter through the formation of the stronger O-Si bond which amply compensates the cleavage of the weaker C-Si bond in the precursor N-thiazolium salt. Hence, 2-TST appears to be properly tailored for undertaking carbodesilylation reactions by the cascade contribution of the three heteroatoms, i.e. nitrogen, sulfur, and silicon!

The addition of 2-TST to chiral alfa-alkoxy- and alfa,beta-dialkoxyaldehydes (Fig.5) exhibits good to excellent levels of diastereoselectivity to form the corresponding *syn* - and *anti* -adducts respectively in high chemical yield.[15] As shown in Fig. 6 for the addition of 2-TST to D-glyceraldehyde acetonide (*anti* -adduct 90%, ds ≥ 95%), these stereochemical results are those expected on the basis of the Felkin-Ahn-Houk open-chain model for diastereoselectivity.[16] According to this model and the ylide mechanism described earlier, 2-TST should approach the aldehyde carbonyl from the less hindered side to form the carbon-nitrogen bond, and in such a way as to place the trimethylsilyl group close to oxygen in order to achieve silicon migration. 2-TST appears to be the metalate heterocycle of choice for achieving both chemical and stereochemical efficiency. In fact, the reaction of 2-lithiothiazole with D-glyceraldehyde acetonide proceeds without diastereofacial selectivity (*syn-anti* 1:1),[15] and that of 4-methyl-2-trimethylsilyloxazole with the same aldehyde shows a low degree of *anti*-selectivity (ds = 80%) and a rather poor chemical yield (65 %)[17].

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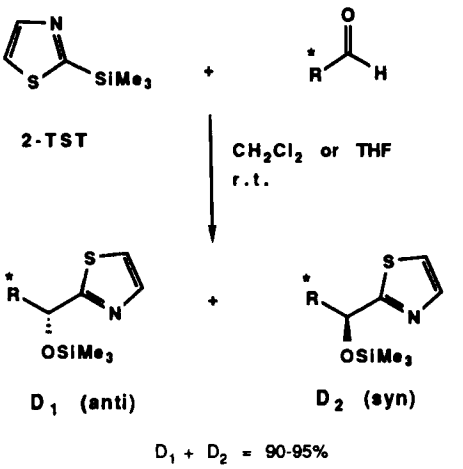

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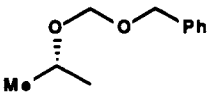
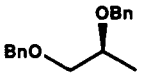
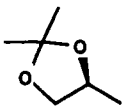
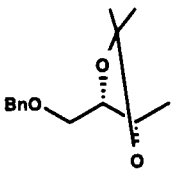
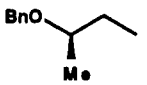
	33	67
	67	33
	≥95	
	90	10
	50	50

Fig. 5

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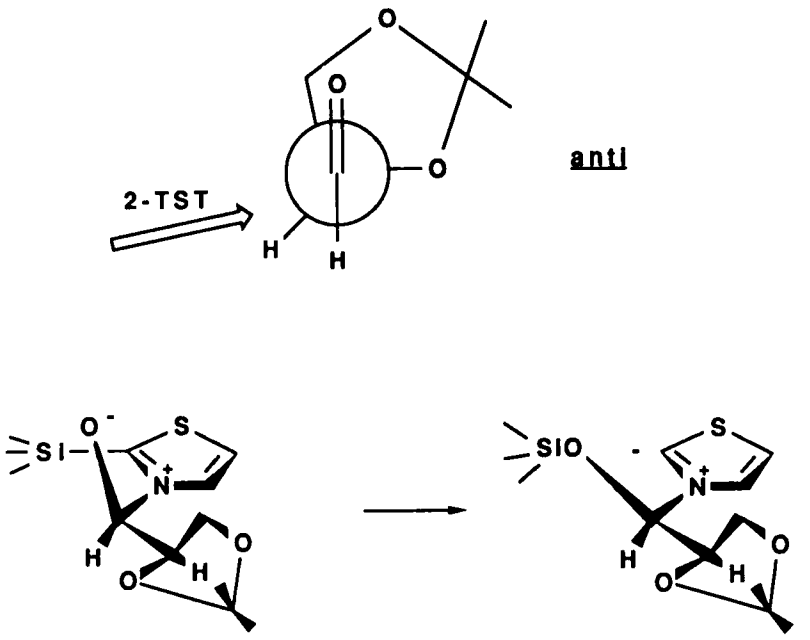

Fig. 6

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The protocol for the formyl deblocking from the thiazole ring in the adduct of 2-TST to D-glyceraldehyde acetonide[18] is shown in Fig. 7. This involves a sequence of simple and high yield reactions (OH-protection, N-methylation, reduction, hydrolysis) so that the unmasked aldehyde is isolated in very good chemical yield. It is also noteworthy that this extremely mild and neutral method of aldehydic release proceeds without noticeable racemization at the newly formed chiral hydroxymethylene center. Hence, it appears that the protected D-glyceraldehyde is converted into its upper homologue D-erythrose in good overall yield (ca. 72%) through the operations A and B, both involving the thiazole ring as an auxiliary, the first as a reactant (A : addition to the aldehyde), the second as a latent functionality (B : formyl unmasking) (Fig. 8). As a whole, 2-TST appears to serve as a reagent for the formyl anion synthon which, adding to the chiral aldehyde in a stereoselective manner, creates a new chiral hydroxymethylene center. We envisioned using iteratively this linear one-carbon-chain elongation methodology to construct higher *anti*-polyhydroxyaldehydes.

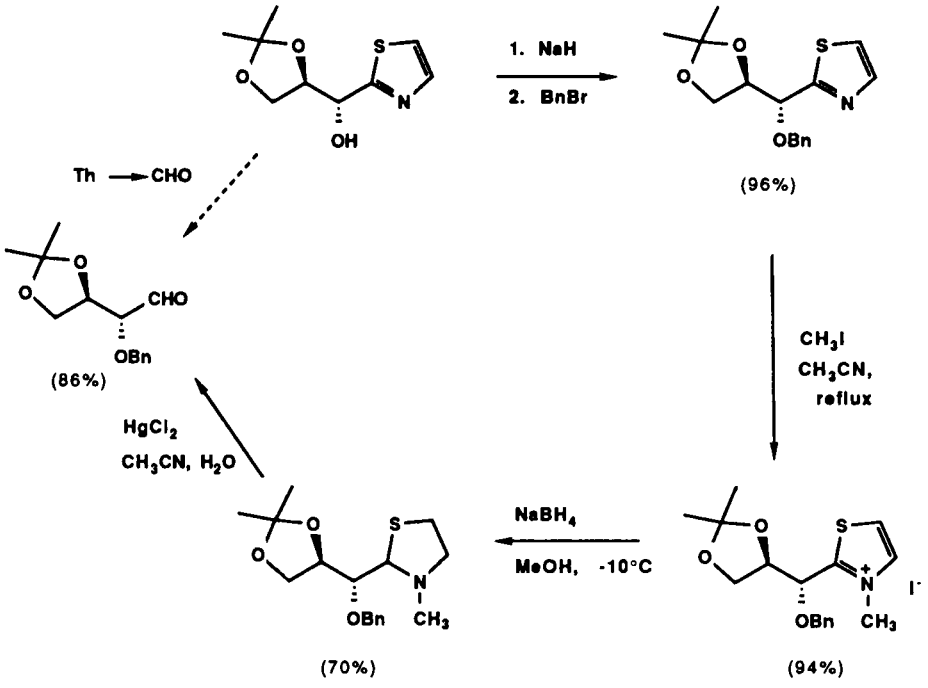

Fig. 7

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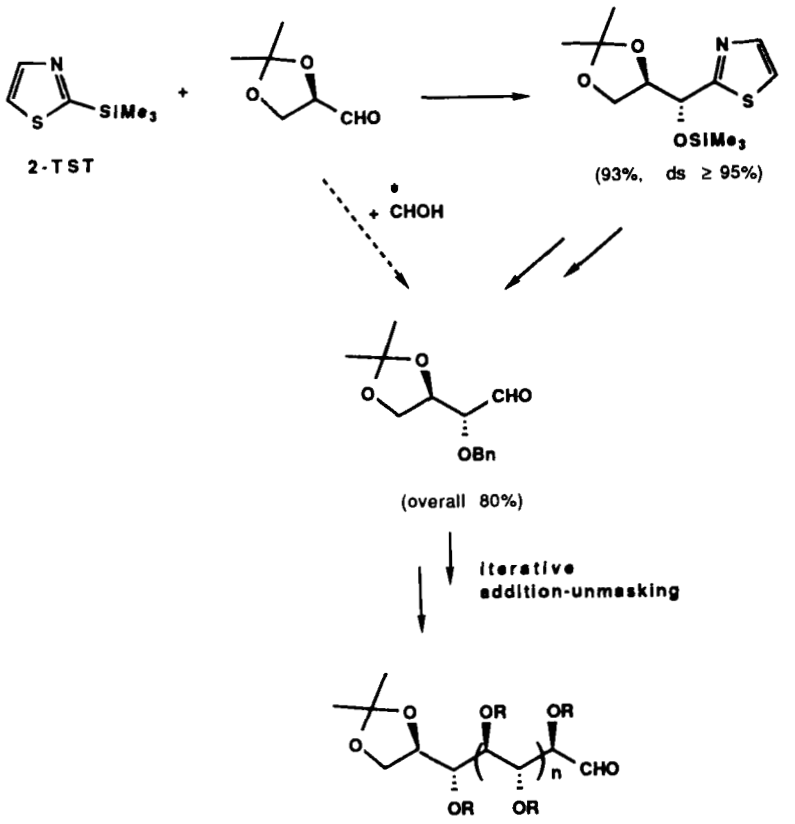

Fig. 8

As shown in Fig. 9, the application of this protocol over six consecutive cycles[15b,18] transforms D-glyceraldehyde acetonide into a series of higher homologues (D-sugars) up to the C-9 term (thiazole D-nonose). It is worth commenting that this does not appear to be the upper limit of the application of the method since high levels of stereoselectivity and good chemical yields are maintained with the increase of the length of the polyhydroxyalkyl chain. In a similar fashion, 4-benzyloxy L-threose 2,3-acetonide is homologated into a series of rare L-sugars up to the C-7 term[15b] and , even more significantly, the dialdose alfa-D-dialdogalactopyranose diacetonide is tranformed into higher homologues (carbon-carbon linked disaccarides) up to the thiazole masked C-10 term[15b,19] (Fig. 10). Hence a principle based on 2-TST as auxiliary for the homologation of alkoxyaldehydes and dialdoses into long-chain carbohydrates (THIAZOLE ROUTE) appears quite at hand.

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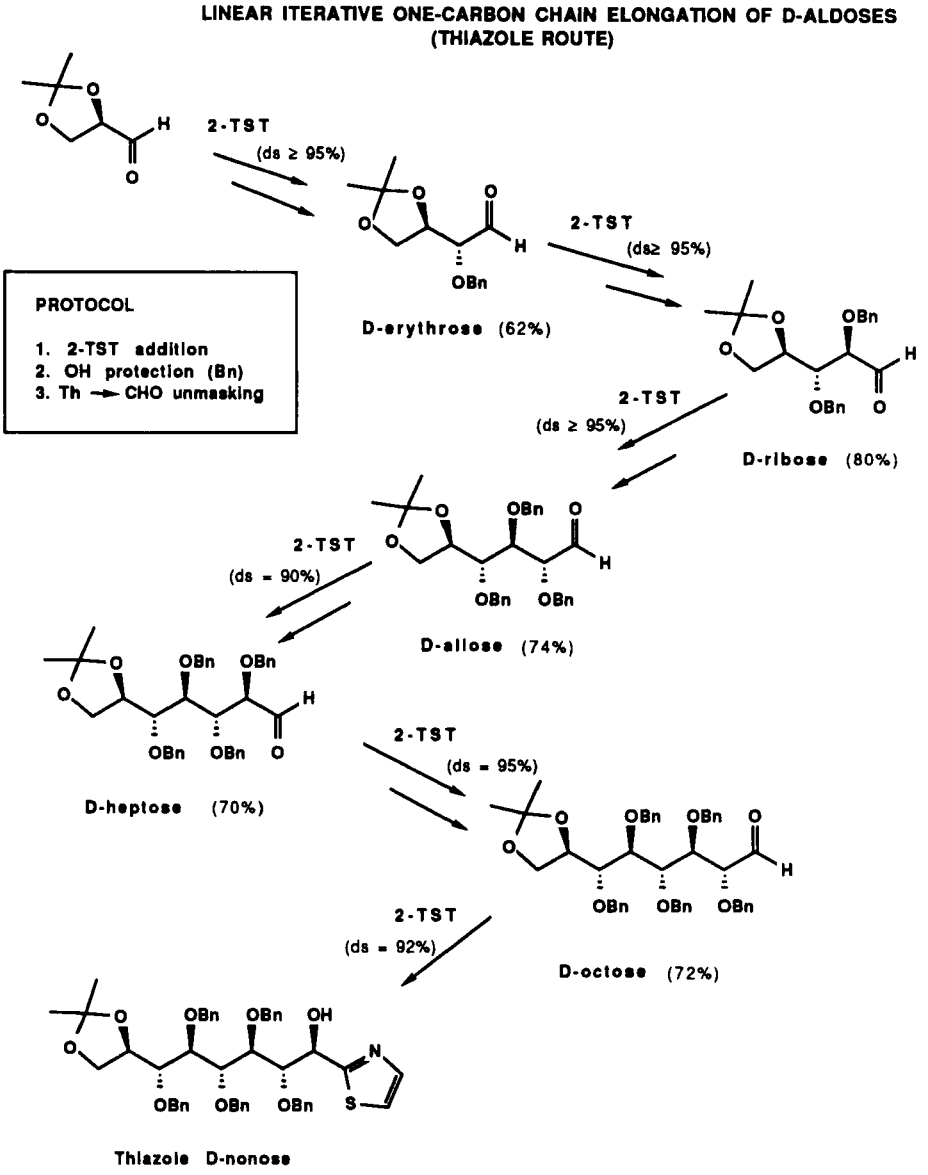

Fig. 9

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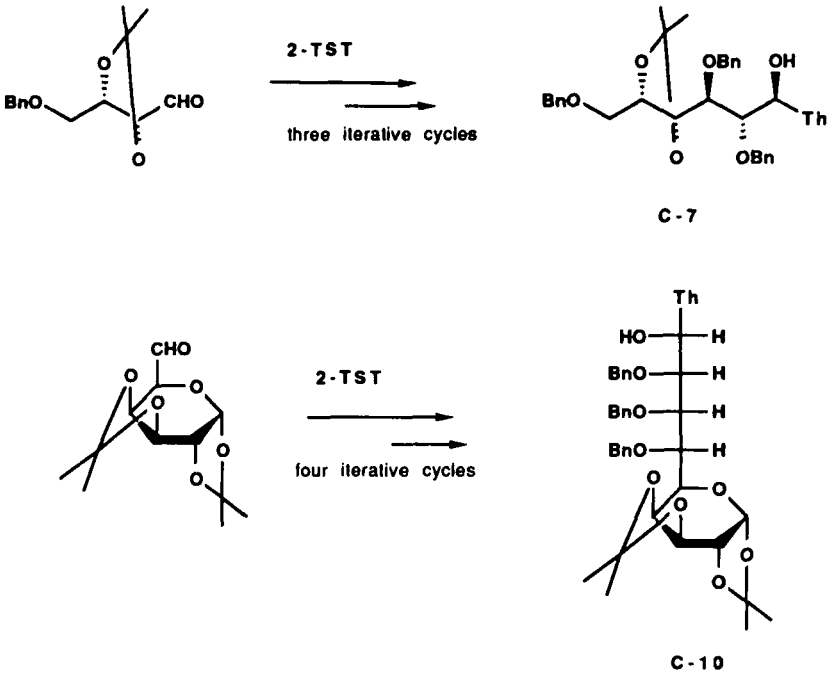

Fig. 10

The synthetic value of this new methodology for the construction of *anti* 1,2-polyol systems[20] may be found in the simplicity and efficiency, chemical and stereochemical, of the operations employed. Moreover, products appear to be suitable for selective elaborations by virtue of the different protections of the hydroxy groups which can be employed in the course of the construction of the polyol system. An application of this concept is illustrated in Fig. 11 by an expeditious synthesis[15b] of an important building block for natural product synthesis, i.e. 2,5-dideoxy D-ribose,[21] by selective hydroxy group removal in thiazole D-ribose.

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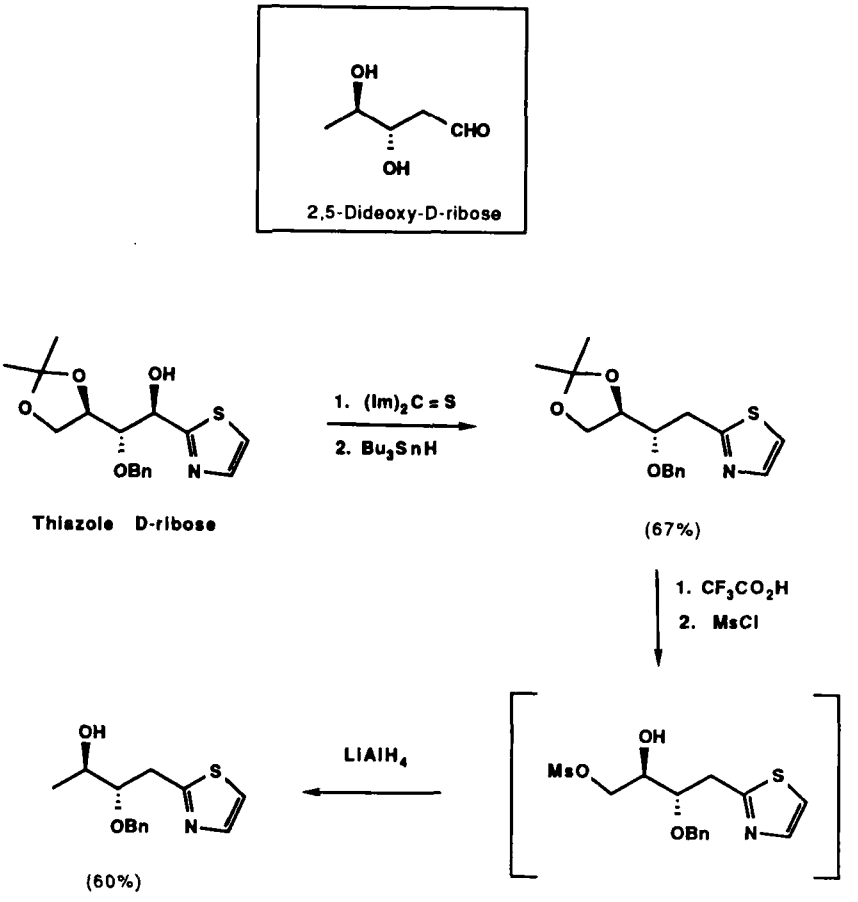

Fig. 11

Given the success that we registered in the 2-TST-mediated homologation of polyalkoxyaldehydes and dialdoses, we chose to examine the application of the principle to chiral alfa-aminoaldehydes. We intended to extend the Thiazole Route to L-aminosugars synthesis[22] from readily available L-aminoacids. As shown in the accompanying Fig. 12 , the L-serine derived aldehyde, N-Boc serinal acetonide, reacts with 2-TST to form mainly the *anti* -adduct with a high degree of selectivity (ds = 92 %) and very good chemical yield.[23] After separation from the *syn* -isomer, the *anti* -adduct is converted by the usual formyl-deblocking sequence into the homologue aldehyde, i.e. 3-deoxy-3-amino L-erythrose. This provides an example of a high degree of asymmetric induction in the addition of an organometal to an aminoaldehyde, and demonstrates that the aldehyde release tolerates the presence of a protected amino group.The addition of 2-TST to 3-deoxy-3-amino L-erythrose in a second one-carbon chain elongation sequence affords the two thiazole aminopentoses in good overall yield (75 %) and *anti*-selectivity

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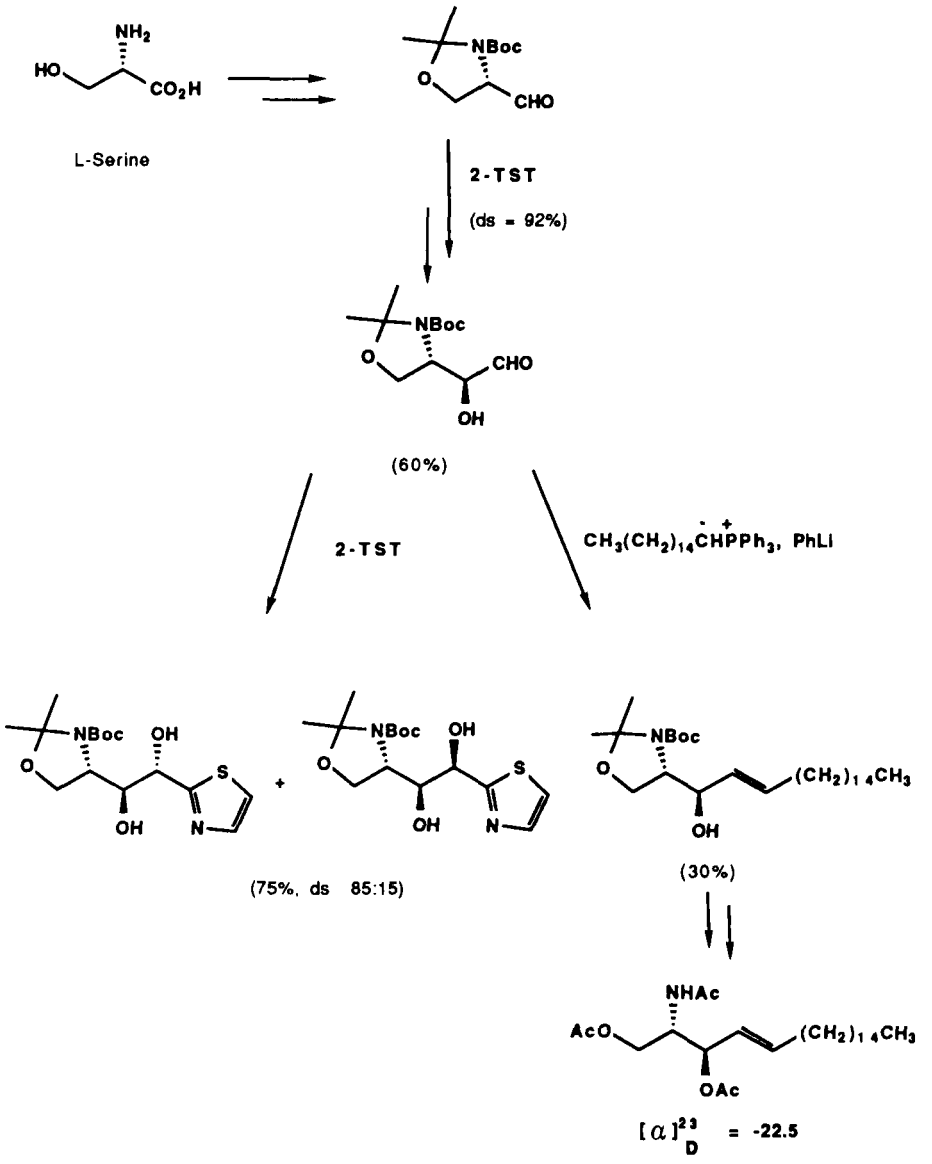

Fig. 12

in favor of the ribo-derivative (ds = 85 %). The scope of the Thiazole Route to aminosugars based on 2-TST as an auxiliary is extensible to other readily available and configurationally stable protected aminoaldehydes, i.e. N-Boc L-phenylalaninal and N-Boc L-threoninal acetonide.[24] Further to that , since 3-deoxy-3-amino L-erythrose appears to possess the correct substitution pattern and stereochemistry of the hydrophilic part of sphingosines and phitosphingosines,[25] the essential molecular fragments of sphingolipids which are the constituents

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of cell membranes, we planned synthetic applications in this direction. As shown in Fig. 12, the Wittig-type reaction of this aldehyde with hexadecanylidenetriphenylphosphorane in the presence of phenyllithium affords the C_{20}-*erythro*-sphingosine in 30 % yield. The potential of this very direct entry to phito- and homosphingosines from aminoacids is actively investigated in our laboratory using appropriate hydrophilic building blocks constructed by the Thiazole Route.

The profound *anti* -selectivity of the addition of 2-TST to chiral aldehydes and our unability to control the stereochemistry of this reaction make the construction of *syn* 1,2-diol and *syn*-1,2 aminoalcol fragments rather difficult. As shown in the accompanying Fig. 13 for L-serinal, this limitation can be overcome by a two operations sequence, i.e., i) $KMnO_4$-oxidation; ii) $NaBH_4$-reduction, which inverts the stereochemistry at the newly formed hydroxymethylene center and adjacent to the thiazole ring.[23] This oxidation-reduction protocol is rather general for alfa-hydroxyalkylthiazoles, including thiazole sugars, and can therefore be conveniently applied to convert an individual *anti*-adduct into the *syn*-isomer or to convert a mixture of these into the latter.[26] Thus, individual *anti*- and *syn*-1,2-diol and 1,2-aminoalcol fragments are equally available in gram scale. Hence the potential of the Thiazole Route to carbohydrates based on 2-TST as an auxiliary enriched by this new methodology may well be applied to the synthesis of an entire series of carbohydrates,[27] such as for instance, the

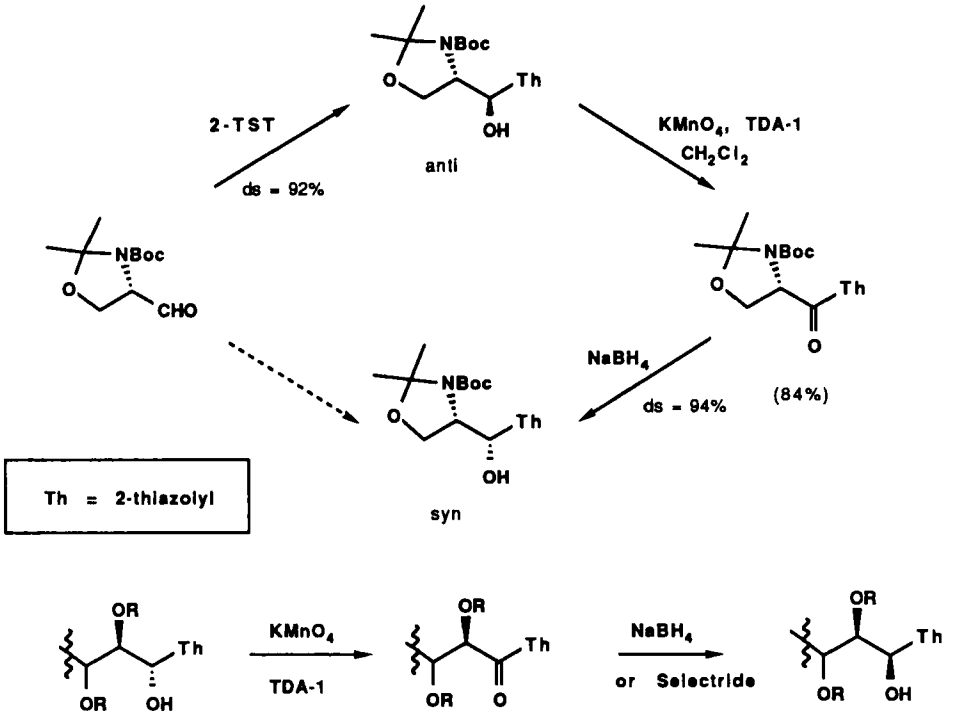

Fig. 13

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four possible D-pentoses, height D-hexoses, etc.

2. The Approach Based on 2-TMP

Having the formyl unmasking protocol from thiazole at hand, we designed the synthesis of 2-thiazolylmethylenetriphenylphosphorane (2-TMP) and its use through Wittig reactions as an auxiliary for the two-carbon chain-elongation of aldehydes[28] (Fig. 14). Actually this methodology leads to saturated aldehydes instead of the alfa,beta-unsaturated derivatives because of the concomitant reduction of the ethylenic double bond and the thiazole ring in the course of

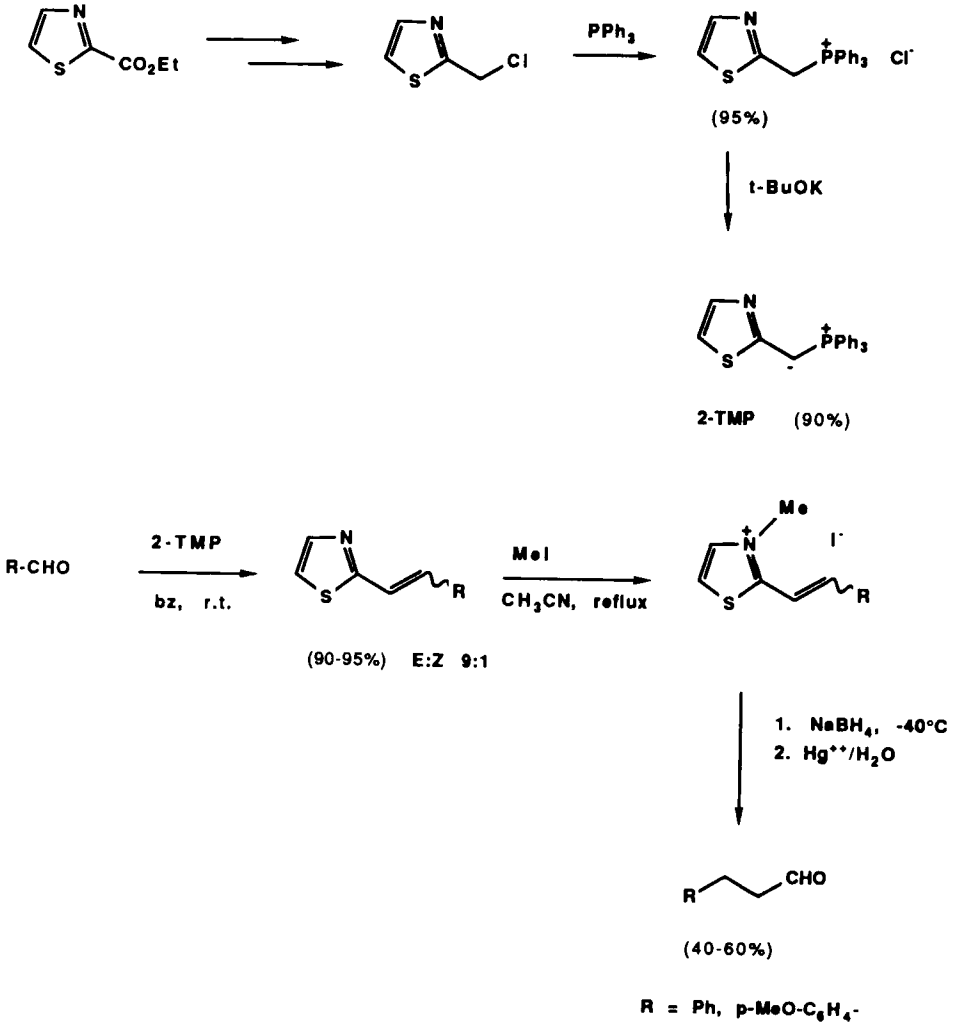

Fig. 14

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the formyl deblocking sequence. However, this does not appear to be an obstacle to the use of 2-TMP in the Thiazole Route to sugars since the high Michael-acceptor aptitude of the 2-vinyl N-methylthiazolium salt is conveniently exploited in new synthetic strategies to the 2,3,6-trideoxypyranose, L-Rhodinose (Fig. 15)[29] and 2,3,6-trideoxy-3-aminopyranoses, i.e. L-Daunosamine and L-Epiduanosamine[30] starting from (S)-ethyl lactate.

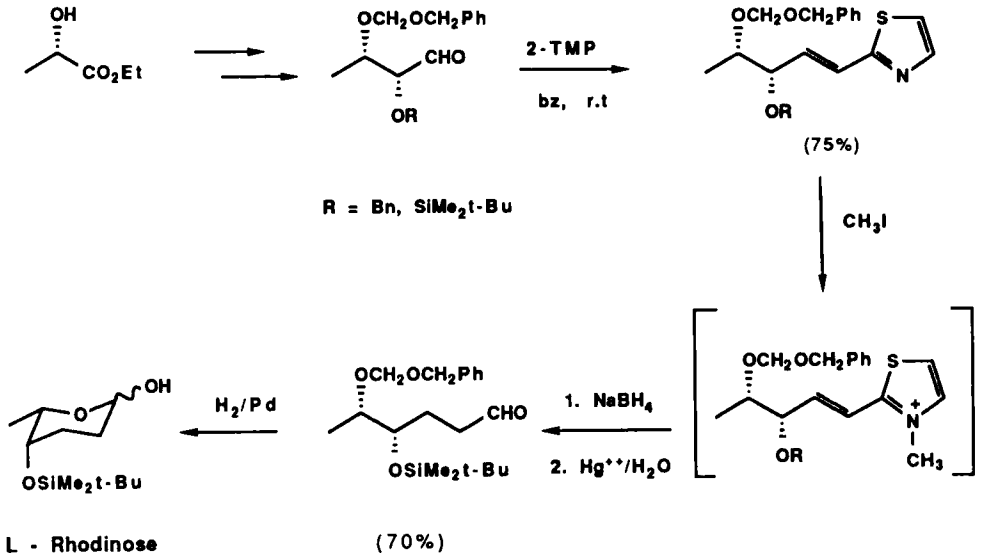

Fig. 15

A strategy based on the ethylenic double bond elaboration before the formyl unmasking is also under investigation in order to convert the E- and Z-vinylthiazoles derived from D-glyceraldehyde acetonide into the four possible diastereomeric D-pentoses (Fig. 16).[31] This involves as a key step a diastereoselective epoxidation followed by the hydrolytic cleavage of the oxirane ring. We intend to employ iteratively this two-carbon chain elongation methodology for the synthesis of long-chain sugars. It is noteworthy that the Wittig-type reaction of 2-TMP with a series of dialdoses obtained from dialdogalactopyranose by the 2-TST-mediated chain-lengthening approach, gives a series of thiazole-protected long-chain alkenyl sugars up to an eleven-carbon atoms term (Fig. 17).[32] Thus, the Thiazole Route to carbohydrates appears to possess one- and two-carbon chain extension methodologies which can be combined for the synthesis of a wide series of long-chain sugars.

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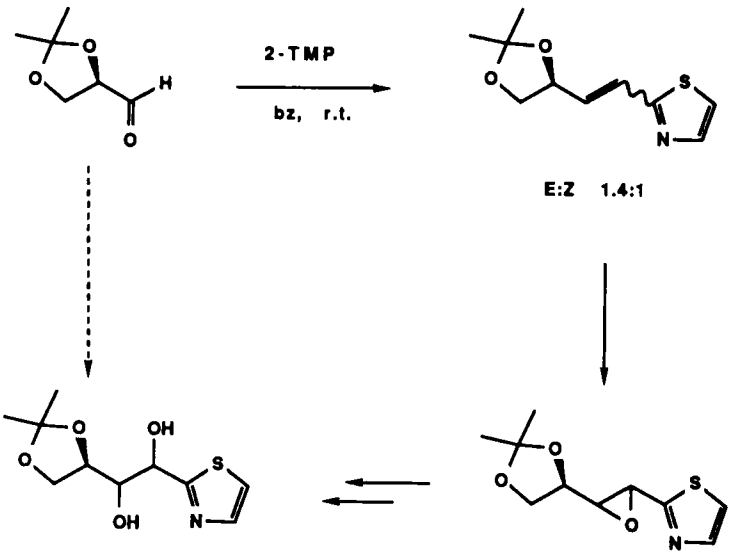
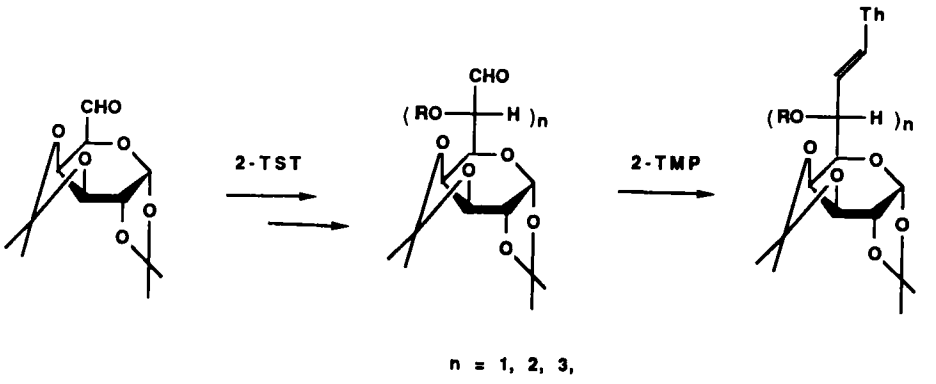


Fig. 16



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3. The Approach based on 2-TNO

Encouraged by the above results we decided to extend the concept of the thiazole mediated synthesis of carbohydrates to other strategies, and chose to examine 2-thiazolylcarbonitrile N-oxide (2-TNO) as a reactant in the 1,3-dipolar cycloaddition approach to aminosugars.[33] 2-TNO is a convenient masked equivalent to formylnitrile N-oxide, since once it is generated in situ in the presence of an excess of dipolarophile, i.e. an alkene or alkyne, it affords the corresponding isoxazoline and isoxazole in good isolated yields[34] (Fig. 18). These cycloadducts are precursors to functionally substituted aldehydes by virtue of the thiazole-formyl equivalence described earlier, and the various elaborations of the isoxazole and isoxazoline rings.[3]

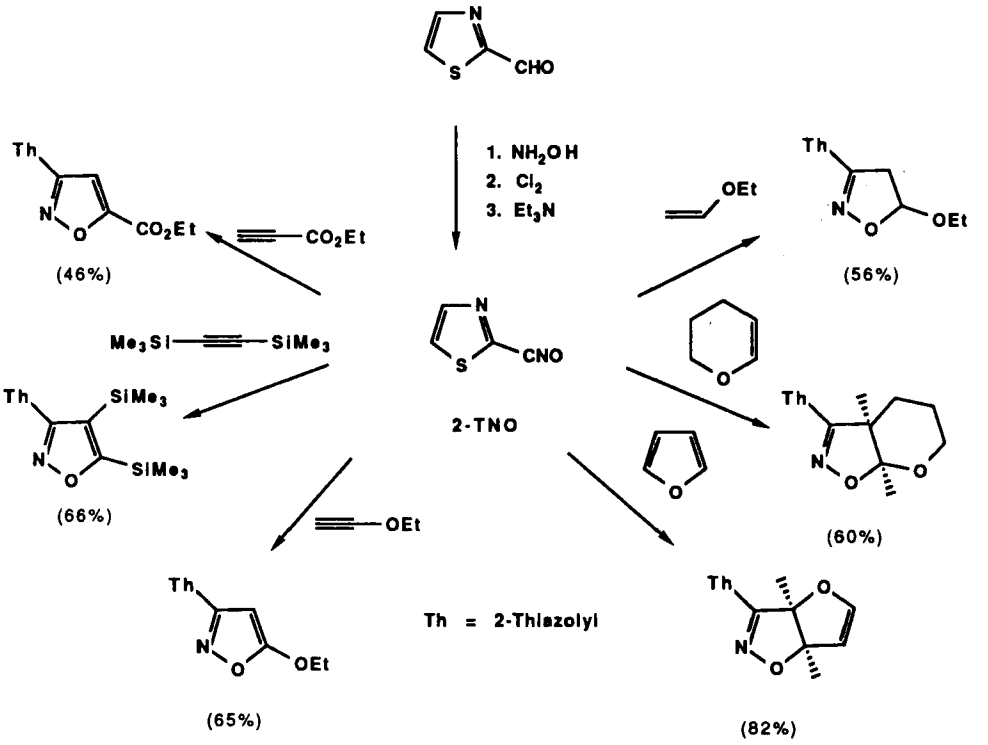

Fig. 18

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Accordingly, the furoisoxazoline obtained in 82% yield through the cycloaddition of 2-TNO to furan (Fig. 19) is transformed,[35] through a series of high yield and stereoselective operations (dihydrofuran dialkoxylation; isoxazoline reductive cleavage; thiazole into formyl deblocking), into the aminohexose 5-deoxy-5-amino-alfa-D-dialdoidofuranoside. 2-TNO offers several advantages over other protected formylnitrile N-oxides, which have been previously employed in the 1,3-dipolar cycloaddition approach to aminosugars[33] (Isoxazoline Route), since the thiazole ring combines the ability to activate the 1,3-dipolar reactivity of the nitrile oxide functionality with the ready conversion into the formyl group. While we are extending

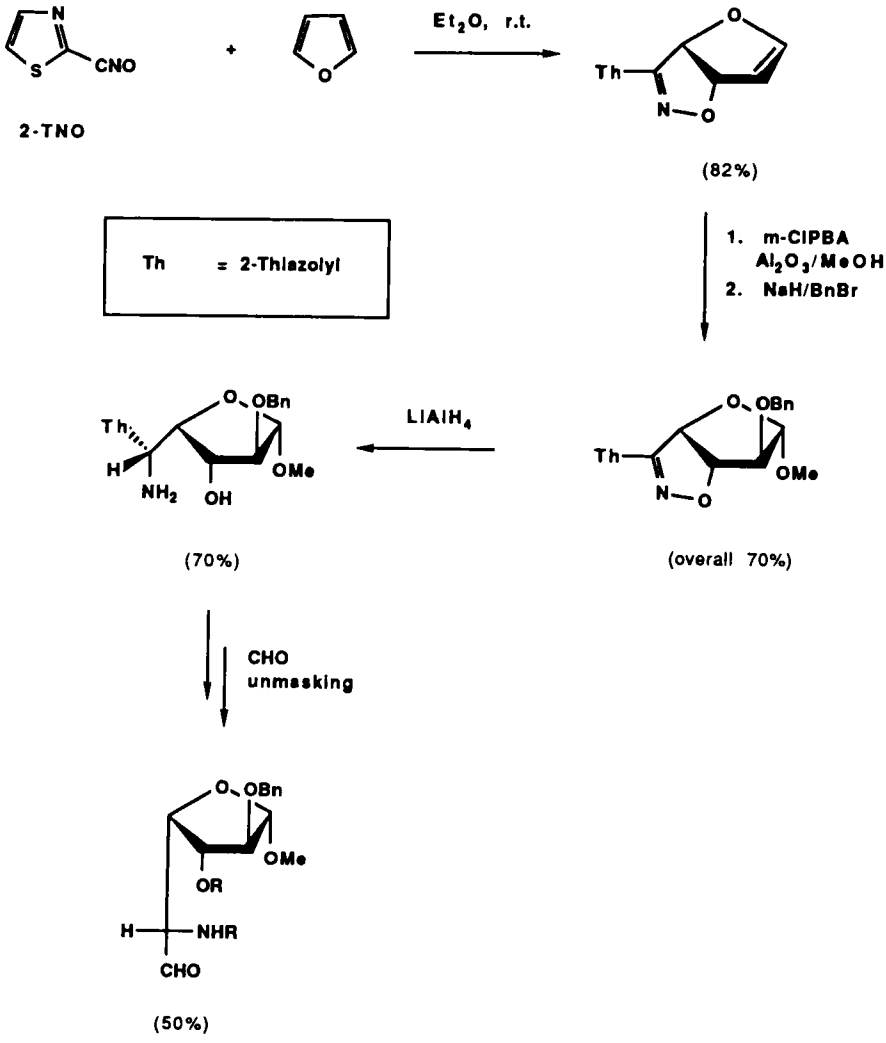

Fig. 19

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the scope of the Isoxazoline-Thiazole Route by investigating the cycloaddition of 2-TNO to other dipolarophiles, it is especially worthwhile noting that the aminodialdohexose of Fig. 19 is a stable yet reactive intermediate to long-chain aminosugars through the one- and two-carbon chain-elongation protocols based on 2-TST and 2-TMP as auxiliaries (Fig. 20). This Scheme summarizes quite well the concept on which we are developing the Thiazole Route to carbohydrates, which is the transformation of readily available substrates into long-chain polyalkoxyaldehydes in good chemical yield using Functionally-substituted Thiazoles (FST) as auxiliaries. The products obtained by this approach may be either target molecules or chiral precursors, i.e. chirons,[36] to more complex molecular systems of biological relevance. We are applying the same concept also to the synthesis of thiazole-containing natural products.[10]

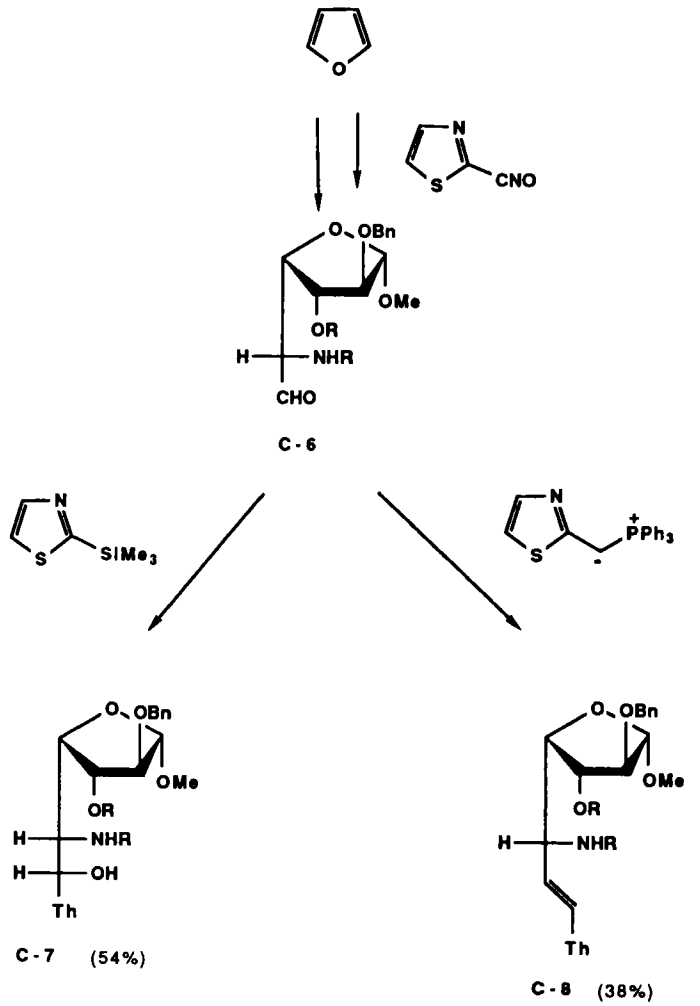

Fig. 20

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CONCLUSION

This account shows that three different FST at C-2 , i.e. the organometal 2-trimethylsilylthiazole (2-TST), the phosphorus ylide 2-thiazolylmethylenetriphenylphosphorane (2-TMP), and the 1,3-dipolar system 2-thiazolylcarbonitrile N-oxide (2-TNO), serve as convenient auxiliaries in synthetic approaches to long-chain polyalkoxyaldehydes, viz. carbohydrate-like materials. In all cases the thiazole ring plays an important role since it acts both as an activator of reactions at the functional group R at C-2 and as a precursor to the formyl group. There are several advantages associated with the use of the thiazole ring as a masked formyl group since it combines a high stability under a variety of conditions with the ready release of the formyl group under neutral conditions, which leave intact the asymmetric centres in the molecule. The special properties and reactivity of FST may well be associated with the ability of sulfur to behave both as an electron-donor and electron-acceptor center.

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