

New organometallic reagents. Use of 2-(trimethylsilyl)thiazole in acyclic stereoselective strategies

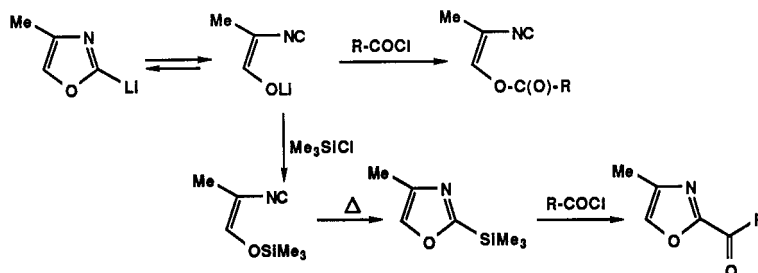
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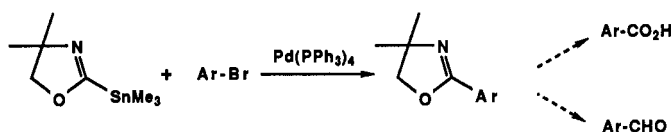
Abstract. 2-(Trimethylsilyl)thiazole (2-TST) is a member of a set of metalated heterocycles prepared in our laboratory for application as synthetic auxiliaries. 2-TST undergoes rapid and spontaneous carbodesilylation reactions with various C-electrophiles (ketenes, acyl chlorides, aldehydes, heteroaryl cations) producing the corresponding 2-substituted thiazoles in good yields. The addition of 2-TST to chiral aldehydes having a suitably protected asymmetric center adjacent to the carbonyl, occurs with high levels of anti-diastereoselectivity (90-95%) to give adducts which upon thiazole-to-formyl conversion liberate aldehydes having one-more carbon atom. This demonstrates the application of 2-TST as a formyl anion equivalent. The thiazole-addition-unmasking methodology (THIAZOLE ROUTE) is applied iteratively for the chain-elongation of *D*-glyceraldehyde acetonide, 4-*O*-benzyl-*L*-threose 2,3-acetonide, α -*D*-dialdogalactopyranose diacetonide, and *N*-Boc-*L*-serinal acetonide into series of higher homologues bearing all *anti*-1,2-diol units. Aldehyde homologues from protected *L*-serinal are employed as precursors to sphingosines and phytosphingosines. The synthesis of all possible pentoses and hexoses starting from *D*-glyceraldehyde acetonide is underway by combination of the *anti*-addition of 2-TST with an oxidation-reduction sequence providing the *syn*-adducts.

Applications of heteroaryl silanes and stannanes (ref. 1) to organic synthesis offer the opportunity for new synthetic strategies since these compounds can serve both as effective precursors to heteroaryl carbanions and as masked functional group equivalents. In one line of work (ref. 2), we have described the preparation of 2-(trimethylsilyl)- and 2-(trimethylstannyl)oxazoles and oxazolines and showed their superior synthetic utility with respect to the corresponding 2-lithio derivatives. For instance, treatment of 4-methyl-2-(trimethylsilyl)oxazole with acyl chlorides provides a direct entry to 2-acyl oxazoles, a class of oxazole derivatives which are unaccessible from lithiooxazoles (Scheme 1). Moreover, the

Scheme 1

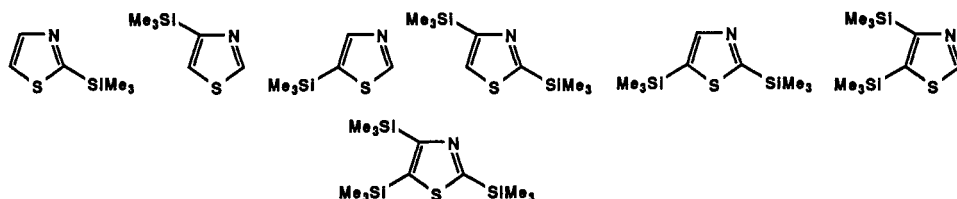


Scheme 2



cross-coupling reaction between 4,4'-dimethyl-2-(trimethylstannyl)oxazoline and aryl and heteroaryl bromides affords the corresponding 2-aryl substituted oxazolines (Scheme 2). These compounds can be considered as the precursors to carboxylic acids and aldehydes since the oxazoline ring can readily liberate these functionalities (ref. 3).

In another line of work we have reported (ref. 4) the preparation of all possible regioisomeric mono- and bis-(trimethylsilyl)thiazoles as well as the tris-(trimethylsilyl) derivative and investigated the reactivity and mechanism of their carbodesilylation reactions with various carbonyl compounds and heteroaryl cations.

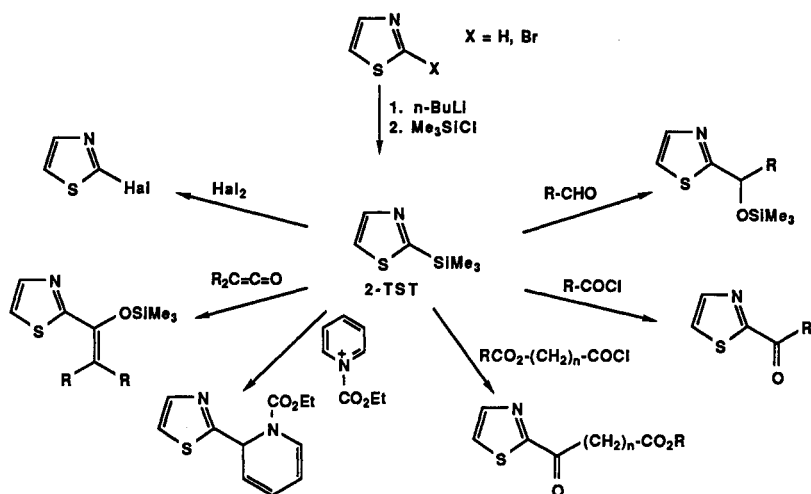


In this lecture I want to describe the extension of this work showing the use of 2-(trimethylsilyl)thiazole (2-TST) as an effective tetraorganosilicon reagent for the stereoselective synthesis of long-chain polyhydroxylated aldehydes starting from readily available material.

PREPARATION AND REACTIVITY OF 2-TST

2-TST is a readily accessible organometal which can be prepared in multigram scale by quenching 2-lithiothiazole (from thiazole or 2-bromothiazole and *n*-butyllithium) at -78°C with chlorotrimethylsilane (ref. 4) (Scheme 3). The compound, isolated and purified by distillation (b.p. $58-60^{\circ}\text{C}$ at 16 mmHg) is a colorless oil which can be indefinitely stored, eventually in a refrigerator, without substantial decomposition. However, upon treatment with diluted aqueous (5%) mineral acids it is desilylated to thiazole. Similarly, halo- and carbodesilylation reactions take place readily at room temperature without the need of any catalyst, to give the corresponding 2-substituted thiazoles in fair yield. The scope of these reactions has been proved to be quite large.

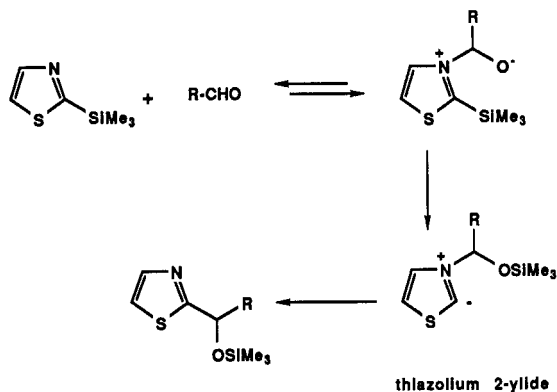
Scheme 3



The carbodesilylation in 2-TST occurs much more readily than in the 4- and 5-regioisomer (ref. 4) and in other 2-azaarylsilanes which in fact require more forcing conditions and catalysts (ref. 5). This and other observations led us to suggest (ref. 4) for reactions of 2-TST with C-electrophiles (Scheme 4 shows the case of aldehydes) a multi-step mechanism involving a thiazolium 2-ylide as an intermediate, i.e. an easily accessible species whose

occurrence has been postulated in other chemical (ref. 6) and biochemical transformations (ref. 7) involving thiazoles. In the present case, in addition to the stabilizing effect of sulfur, the formation of the ylide should be favored also by the ready cleavage of the carbon-silicon bond by inter- or intramolecular catalysis.

Scheme 4

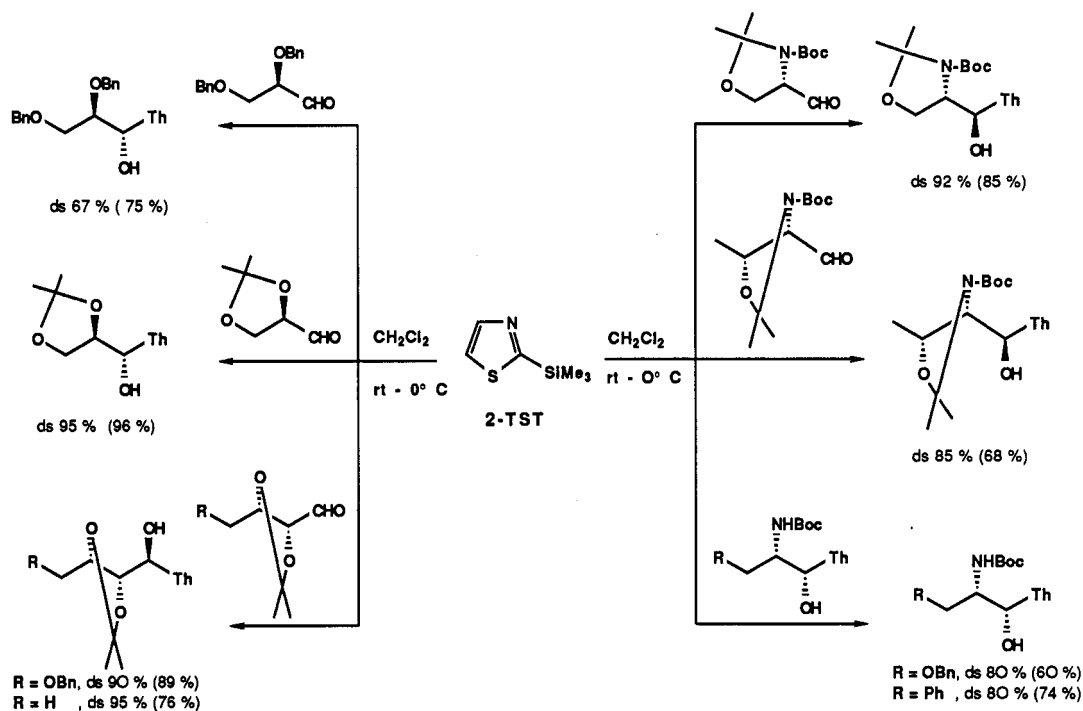


REACTIONS OF 2-TST WITH CHIRAL ALDEHYDES

Among the reactions of 2-TST presented in Scheme 3, that with aldehydes appeared particularly appealing in view of its extension to chiral compounds and the conversion of the resulting α -hydroxyalkylthiazole into a one-carbon higher homologue of the starting aldehyde by liberation of the formyl group from the thiazole ring (ref. 8).

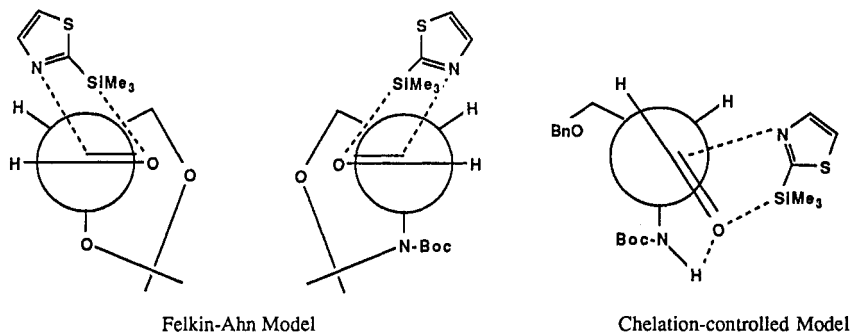
We first investigated the stereochemistry of the addition of 2-TST to chiral α , β -dialkoxyaldehydes and observed (ref. 9) high margins of *anti*-diastereoselectivity using suitably protected compounds such as *D*-glyceraldehyde acetonide, 4-*O*-benzyl-*L*-threose acetonide, and its 4-deoxy derivative (Scheme 5). The major products with diastereomeric ratios and

Scheme 5



isolated total yields are shown. More recently we have extended this stereochemical investigation to chiral *N*-protected α -amino aldehydes (ref. 10) and again we found an high *anti*-diastereofacial selectivity for reactions with *N*-Boc-*L*-serinal acetonide and *N*-Boc-*L*-threonal acetonide. This stereochemical outcome is that expected on the basis of the Felkin-Anh-Houk open-chain model for asymmetric induction (ref. 11). Hence, assuming this model and the stepwise mechanism proposed earlier (ref. 4), a schematic transition state for the addition to *D*-glyceraldehyde acetonide and to *N*-Boc-*L*-serinal acetonide is presented in Scheme 6. According to this model, 2-TST should approach the aldehyde carbonyl from the less

Scheme 6

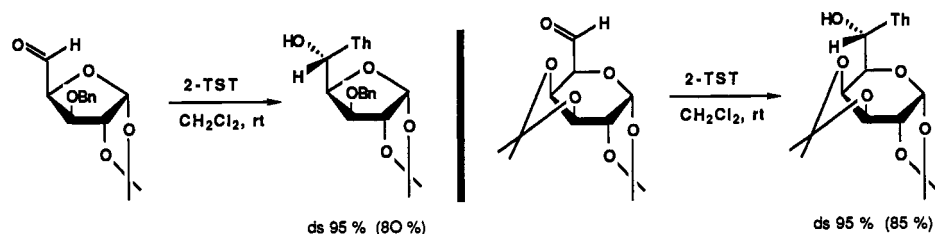


hindered face to form carbon-nitrogen bond and in such a way as to place the trimethylsilyl group close to oxygen in order to allow an intramolecular silicon migration from carbon to oxygen. The resulting tight transition state may considerably contribute to the high stereocontrol of the reaction. Aside from these mechanistic speculations, the trimethylsilyl group appeared to be the substituent of choice to ensure both chemical and stereochemical effectiveness to the process since we observed that the addition of 2-lithio-thiazole to *D*-glyceraldehyde acetonide was unselective and 2-(trimethylstannyl)thiazole was unreactive (ref. 7).

Other results in Scheme 5 show that the diastereoselectivity of the addition of 2-TST to α -amino aldehydes depends on the protection of the amino group. In fact, unlike that observed with the acetonide derivatives, the reactions with *O*-benzyl-*N*-Boc-*L*-serinal and *N*-Boc-*L*-phenylalaninal were mainly *syn*-diastereoselective. This reversal of diastereofacial selectivity should reflect some sort of chelation control in the transition state which can be explained on the basis of a proton-bridged Cram cyclic model (ref. 12) as shown in Scheme 6. This hypothesis is supported by a solvent effect study (in THF the *syn-anti* ratios were ca. 60:40) and the NMR spectra of the amino aldehydes (ref. 10). This result is important from the synthetic standpoint since, for instance, the commercially available amino acid *L*-serine can be transformed into *syn*- and *anti*-1,2-aminohydroxyl fragments by an appropriate protection of the amino group.

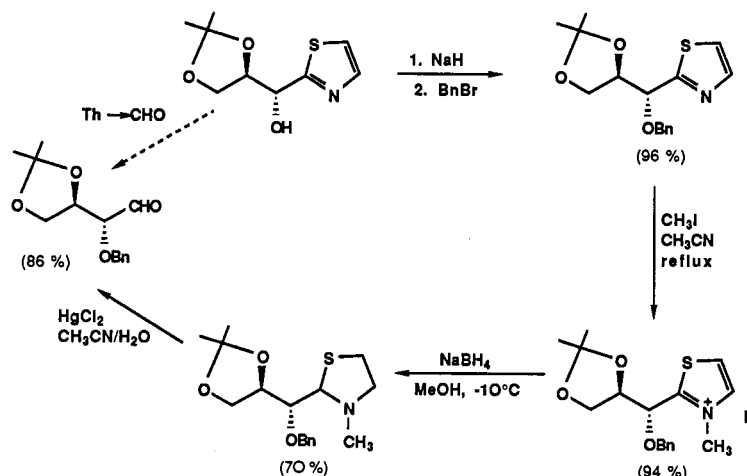
Following our general plan of studying the stereochemistry of the addition of 2-TST to more complex chiral aldehydes, we considered the reaction with dialdoses, i.e. monosaccharides having a free formyl group (ref. 13). As shown for the *O*-protected α -*D*-xylofuranose and α -*D*-galactopyranose (Scheme 7) the reactions proceed with high levels of diastereofacial selectivity to give essentially a single isomer whose stereochemistry is consistent with the non-chelate Felkin-Anh model for asymmetric induction (ref. 11). Specifically, the attack of 2-TST should occur on the aldehyde conformer implied in the indicated structures and opposite to the plane of the sugar moiety (*re* face).

Scheme 7



Having sufficiently demonstrated the effectiveness of 2-TST as a stereoselective reagent toward chiral aldehydes, we turned the attention to the second issue of our plan, that is the liberation of the aldehyde from the chiral α -hydroxyalkylthiazole by thiazole-to-formyl deblocking. The application of our protocol (ref. 9) to the adduct from D-glyceraldehyde acetonide is shown in Scheme 8. This involves a sequence of simple and high yield reactions (OH-protection; N-methylation; reduction; hydrolysis) which can be also conveniently carried out by a one-pot operation to give the aldehyde (D-erythrose) in 62% overall yield. This aldehyde-releasing sequence proceeds under almost neutral conditions which leave untouched the asymmetric centers in the chiral substrates. This simple procedure works equally well with the thiazole-dialdose adducts (ref. 13) and with the thiazole-serinal adduct (ref. 10) as well as with a thiazole aminofuranoside (ref. 14).

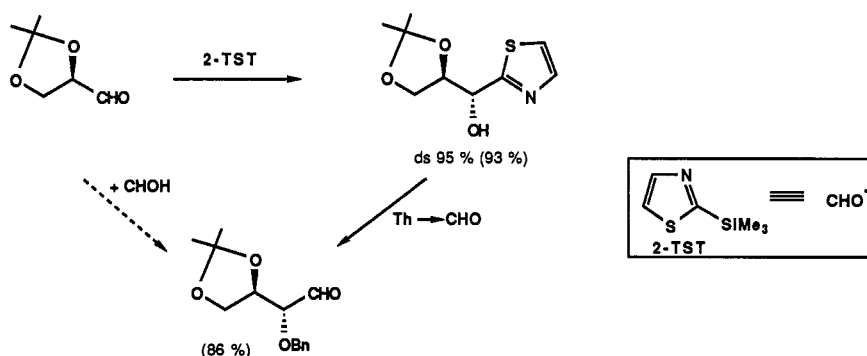
Scheme 8



LINEAR ITERATIVE HOMOLOGATION OF ALKOXY ALDEHYDES AND DIALDOSES

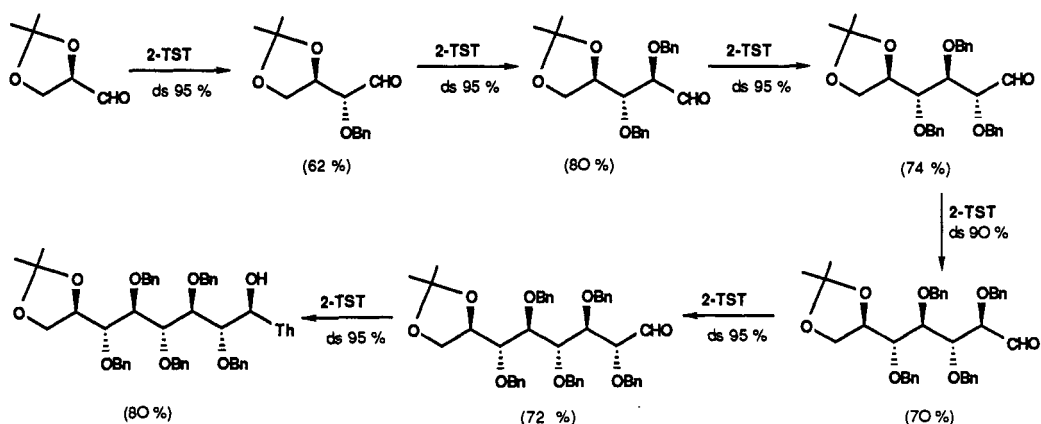
Considering the two main operations which have been described in the previous section (A, thiazole-addition; B, thiazole-to-formyl unmasking) one readily realizes that this sequence transforms effectively a chiral aldehyde into a higher term having one-more carbon atom. This homologation methodology is operatively simple, highly stereoselective, and chemically effective. For instance, D-glyceraldehyde acetonide is transformed into D-erythrose in 72% overall yield (Scheme 9). This is equivalent to using 2-TST as a reagent for the formyl anion synthon which adding to the aldehyde in a stereoselective manner, creates a new asymmetric hydroxymethylene center. We thought that the iterative repetition of operations

Scheme 9



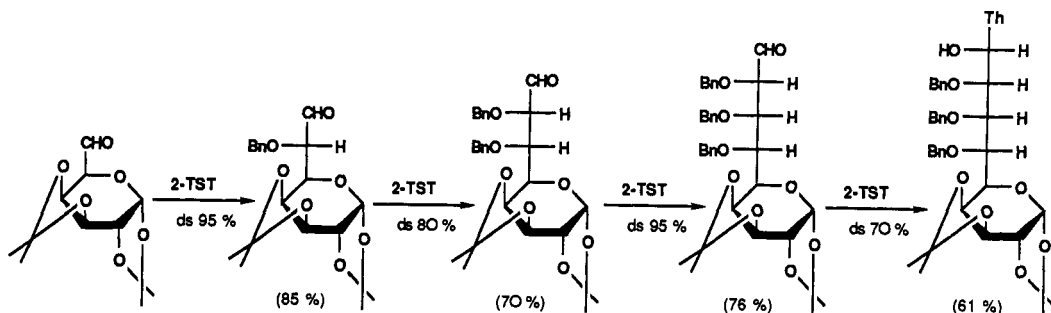
A (addition) and B (unmasking) could be employed for the construction of anti-1,2-polyhydroxyaldehyde units, i.e. higher carbohydrates. These compounds are important synthetic targets because of their potential biological activity (ref. 15) and/or their use as intermediates in the synthesis of natural products such as macrolides (ref. 16a) and antitumor (ref. 16b) antibiotics, and palytoxin-type compounds (ref. 16c). Thus, it was extremely gratifying to find (ref. 9 and 17) that the application of operations A and B over six consecutive cycles transforms D-glyceraldehyde acetonide into a series of higher homologues up to a nine carbon atoms term (Scheme 10). Very high degrees of facial diastereoselectivity and good chemical yields were maintained in each step. The all-anti configuration in the 1,2-polyol units was demonstrated by X-ray crystal structure determination of the thiazole-pentose and by transformation of the thiazole-octose into the meso-octitol.

Scheme 10



The validity of the linear iterative one-carbon chain-elongation methodology described above was confirmed by the homologation of 4-O-benzyl-L-threose acetonide into three higher homologues (ref. 10) and α -D-galactodialdopyranose acetonide into a series of homologues up to a ten carbon atoms term (ref. 10) (Scheme 11). The latter result is relevant in relation to the construction of stereochemically defined polyhydroxylated carbon-chains attached to a pyranose moiety since these structures (carbon linked disaccharides) are present in various biologically active natural products (linkosamine, neuraminic acid, hikosamine) (ref. 18).

Scheme 11



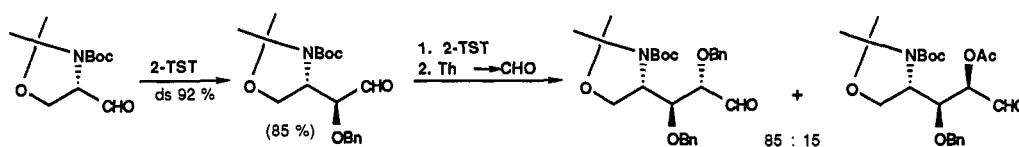
Hence, a principle based on the use of 2-TST as a formyl anion equivalent for the homologation of alkoxyaldehydes and dialdoses into long-chain carbohydrates (THIAZOLE ROUTE) (ref. 19) appears to be sufficiently demonstrated. Although various compounds are known to act as synthetic equivalents to the formyl anion synthon (ref. 20), there are several advantages which appear to be associated with the use of 2-TST. In fact, (i) it is a

relatively inexpensive and stable organometal; (ii) it reacts readily and stereoselectively under neutral conditions; (iii) it gives high yields of products which are stable to isolation and purification and nevertheless can be readily transformed into aldehydes. Some of these points stem from the intrinsic properties of the thiazole ring which associates a high degree of stability to a wide range of reaction conditions to the ability of yielding the aldehydic group under conditions that do not affect functional groups and asymmetric centers. Thus, our methodology (THIAZOLE ROUTE) appears to rank among the most useful procedures for the iterative homologation of aldehydes (ref. 21).

CHAIN-ELONGATION OF L-SERINAL. SYNTHESIS OF AMINOSUGARS AND SPHINGOSINES

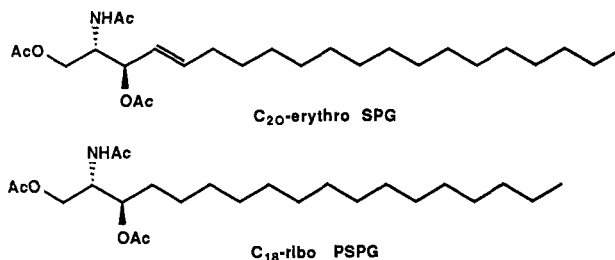
Having observed a high degree of diastereoselectivity and chemical yield in the addition of 2-TST to a L-serine derived aldehyde, i.e. N-Boc-L-serinal acetonide, and proved that the thiazole-to-formyl conversion is compatible with the N-Boc functionality, we chose to extend the above chain-elongation principle to the resulting protected α -hydroxy β -amino aldehyde (3-deoxy-3-amino-L-erythrose) (ref. 10b) (Scheme 12). This compound was transformed into two amino pentoses, the major one having the ribo and the minor the arabino configuration. Since this methodology appears to be extensible to other amino aldehydes, a new entry to L-amino sugars from amino acids should be at hand. The synthesis of amino sugars (ref. 15) as the glycosidic components of biologically active compounds is an issue of current interest.

Scheme 12



A straightforward synthetic application of the C_4 and C_5 aminoaldehydes of Scheme 12 was the conversion to a C_{20} -erythro-sphingosine and C_{18} -ribo-phytosphingosine respectively (Scheme 13) by Wittig reaction with the appropriate phosphoranes. Synthetic routes to these long-chain hydrocarbons bearing a hydrophilic moiety are important since these compounds are the essential parts of glycosphingolipids which are the constituents of cell membranes (ref. 22). The excellent agreement between the physical constants of the sphingosines prepared by

Scheme 13

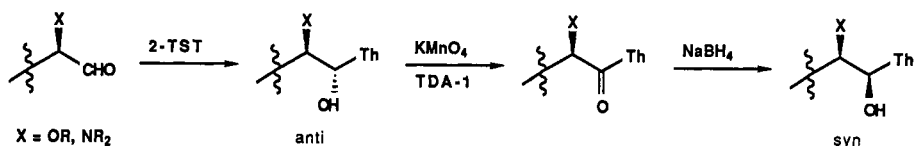


our methodology with their literature values served to characterize the products and indirectly to prove the stereochemistry assigned to their precursors. In conclusion, the synthesis of amino sugars and sphingolipid bases centered upon the use of 2-TST as a formyl anion equivalent for aldehyde homologation, illustrates an application of the THIAZOLE ROUTE to attractive molecules which exploits the 2S stereochemistry of L-serine as a chiral precursor.

AN EXTENSION OF THE SCOPE OF THE 2-TST-MEDIATED HOMOLOGATION OF ALDEHYDES

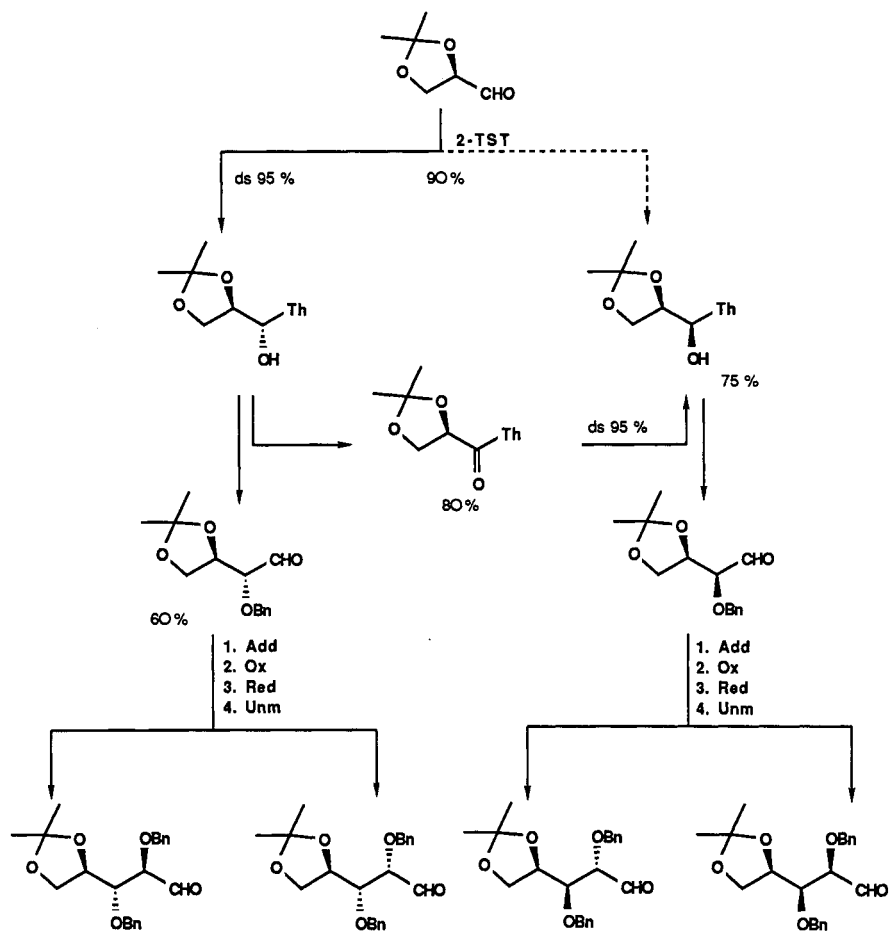
The synthetic utility of 2-TST as a formyl anion equivalent appeared somewhat limited by the profound anti-selectivity of the addition step and by our unsuccessful efforts to control the stereochemistry of the reaction in favor of the syn-selectivity using various chelating agents (ref. 23). Due to their acid nature, these catalysts interact with the thiazole ring rather than with the aldehyde and inhibit the reaction. This limitation has been overcome by a simple procedure which converts the anti-adduct into syn-isomer by inversion of the stereochemistry at the hydroxymethylene center adjacent to the thiazole ring (ref. 24). This involves two very efficient reactions, i.e. KMnO_4 -oxidation and NaBH_4 -reduction (Scheme 14).

Scheme 14



Since, this oxidation-reduction protocol turned out to be applicable to various α -hydroxyalkylthiazoles, it extends the potential of the THIAZOLE ROUTE to the synthesis of 1,2-polyhydroxyaldehyde units with syn- and anti-stereochemistry. The synthesis of the four D-pentoses (Scheme 15) and height D-hexoses from D-glyceraldehyde based on this principle is underway in our laboratory.

Scheme 15



CONCLUSION

In summary, 2-(trimethylsilyl)thiazole appears to be a useful metalated heterocycle which serves as a very effective formyl anion equivalent for the aldehyde homologation. The iterative repetition of this operation provides a methodology for the synthesis of useful chiral building blocks and higher carbohydrates. The value of 2-TST as a new organometallic reagent is under active investigation in our laboratory.

Acknowledgement

It is a pleasure to thank all individuals who have collaborated to develop the use of 2-TST to the present point and whose names appear in the references. The financial support by the Consiglio Nazionale delle Ricerche (Rome) is gratefully acknowledged.

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