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Stereoselective synthesis of acyclic natural products containing chiral vicinal diol

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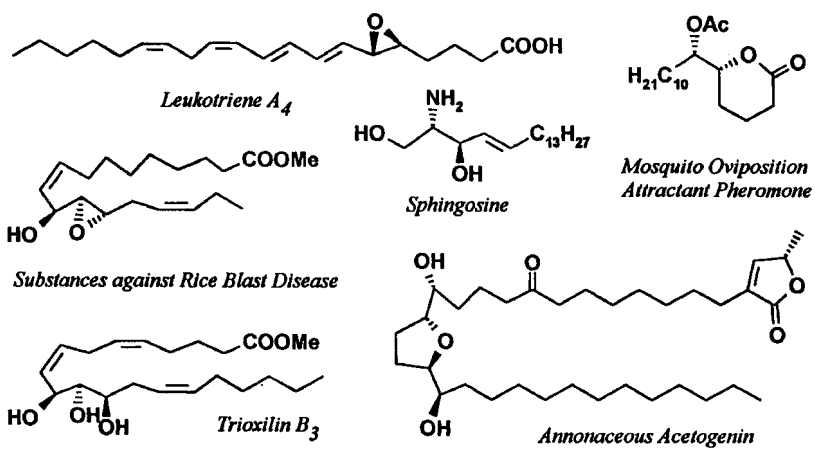
Abstract A series of acyclic natural products featuring with chiral vicinal diol have been stereoselectively synthesized from easily available carbohydrate or hydroxy acid. The *threo*-product has to be synthesized from corresponding *threo*-starting material or intermediate, however the *erythro*-product can be synthesized from either one of a pair of *erythro*-starting material or intermediate. In some special cases the *erythro*-product can also be synthesized from *threo*-precursor through a configuration conversion of lactol-acetonide.

There are a number of bio-active acyclic natural products, such as arachidonic acid metabolites, sphingosine, and substances against rice blast disease (Scheme 1), in which chiral vicinal diol, aminoalcohol, or their derivatives are the structurally characteristic moiety. Their biological significance and the challenge to chiral synthesis have stimulated many efforts[1]. Herewith we would like to report our recent progresses on their syntheses.

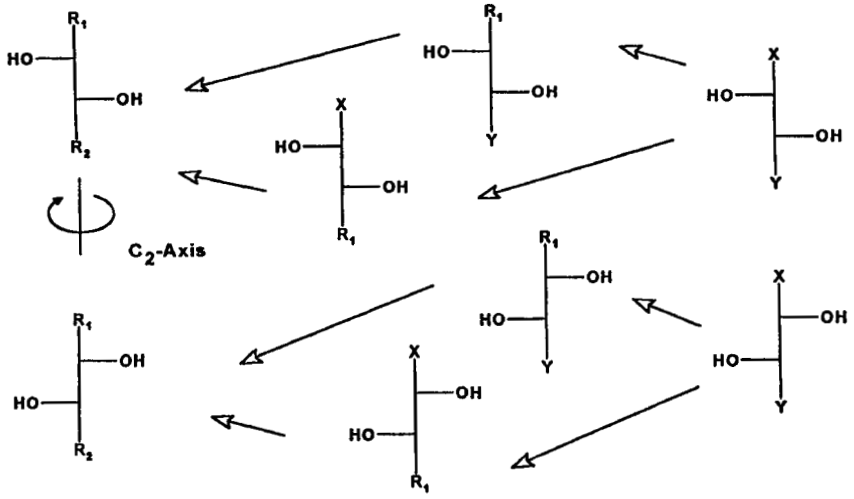
Scheme 1



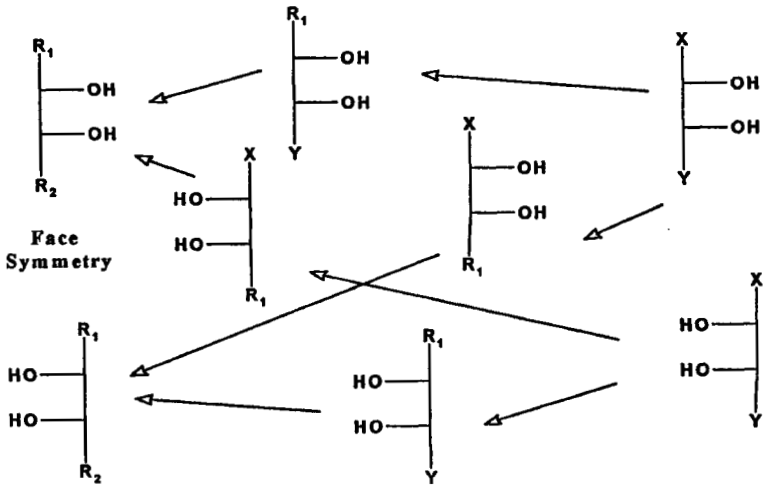
General consideration

Usually there are four stereoisomers for a chiral vicinal diol, two *threo* and two *erythro* isomers. Due to the C_2 symmetric property of *threo*-isomer, such kind of natural products have to be synthesized from the corresponding *threo*-intermediate prepared from chiral hydroxyl intermediate or by an asymmetric *threo*-selective reaction. In this respect, as shown in the scheme 2, the sequence and position of inducing two side chain has no influence to the last configuration of target molecule. On the other hand the *erythro*-isomer possesses a face symmetry, different introducing sequence or position will give different enantiotropic *erythro*-product (Scheme 3). In other word, an *erythro*-compound can be synthesized from either one of a pair of chiral *erythro*-starting material or intermediate just by changing the reaction sequence, an example is shown in the synthesis of mosquito oviposition attractant pheromone from both glyceraldehyde acetonide [2] (Scheme 4).

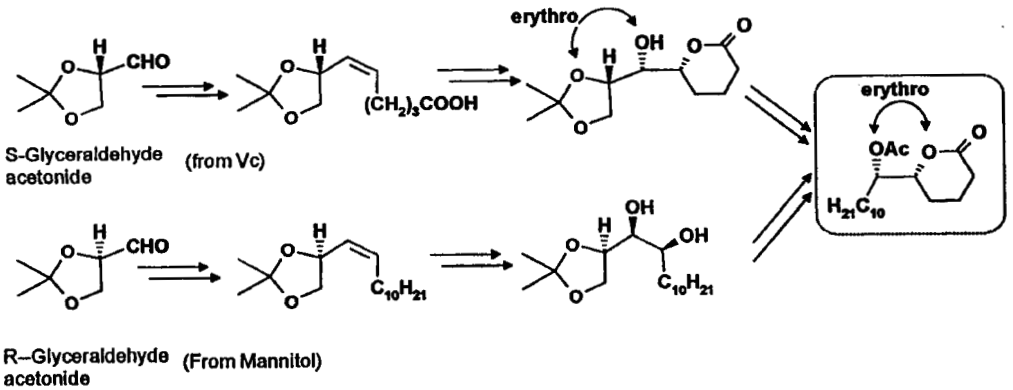
The chiral vicinal diol moiety could be directly taken from a monosaccharide by modification of its other part. It is preferred to utilize several common monosaccharides, such as glucose, mannose, xylose, as the chiral pool. Besides, different stereoisomers of chiral diol intermediates and then the corresponding target molecules could also be taken from altered moiety of an identical sugar. These chiral diol intermediates are also used as substrate of a diastereoselective reaction to induce a third consequent chiral hydroxyl group. Acyclic natural products containing chiral epoxide or aminoalcohol can be transformed to vicinal diol according to the retrosynthesis, so the same strategy and tactic can also be considered for their syntheses.



Scheme 2 Syntheses of threo-isomers



Scheme 3 Syntheses of erythro-isomers

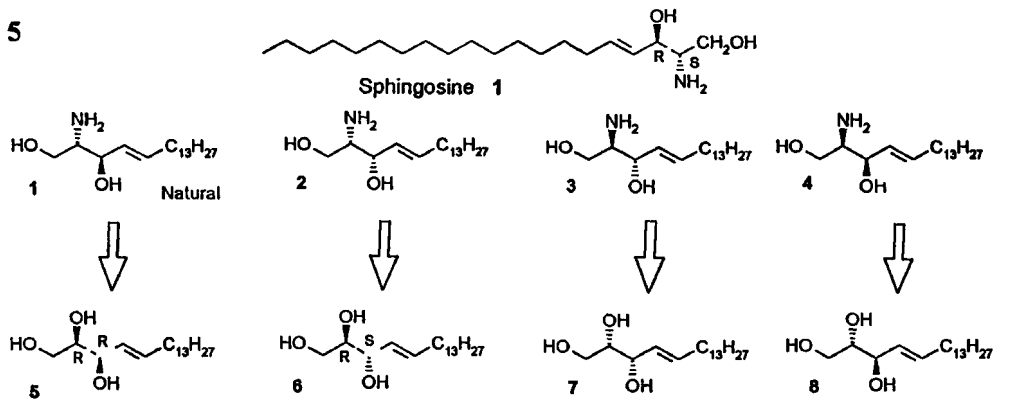


Scheme 4 synthesis of mosquito oviposition attractant pheromone from both glyceraldehyde acetonide.

Syntheses of precursors of all sphingosine stereoisomers

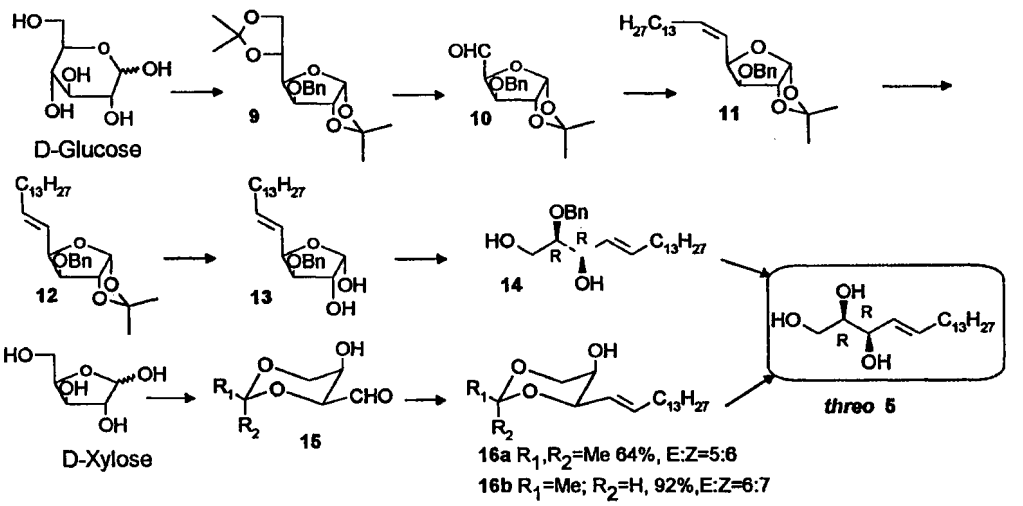
Sphingosine **1** is a biologically interesting compound and also is the basic skeleton of sphingomyelin. A number of chemists have reported its synthesis, among which preparation from a triol precursor is a facile approach. All the four stereoisomers(**1-4**) could be synthesized from corresponding four triols (**5-8**) as shown in the retrosynthesis (Scheme 5).

Scheme 5



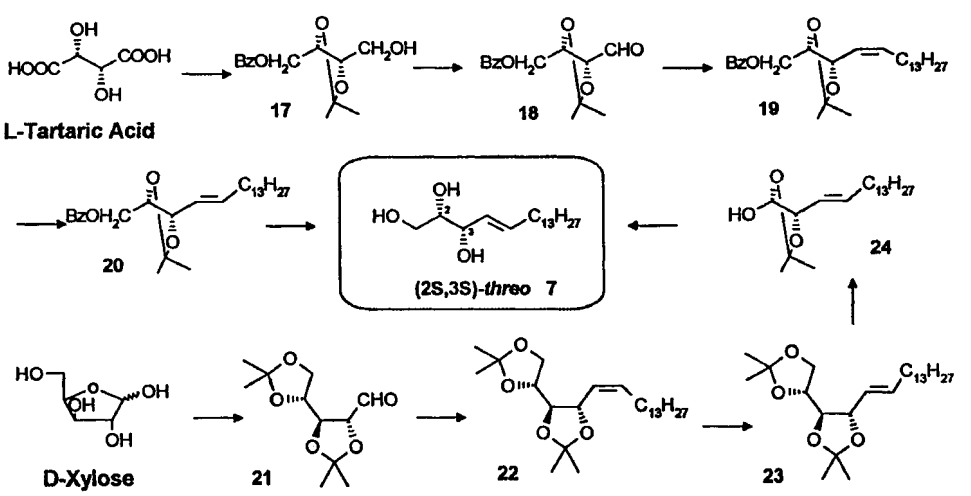
1,2R,3R-Trihydroxy-4E-octadecene **5**, the precursor[3] of natural sphingosine **1**, is in *threo*-configuration, so it should be synthesized from corresponding *threo* chiral starting material. Two approaches have been performed. Selective deacetonide and diol-cleavage in one pot[4] of compound **9** prepared from D-glucose gives aldehyde **10**, which is then suffered a series of reactions to afford the desired 2R,3R-target **5**. The second approach is utilizing D-xylose as the chiral pool. In both syntheses the chiral centers are taken from C_3-C_4 of glucose or xylose. In the case of glucose, the long chain connects with C_5, however it connects with C_2 of xylose in the second approach.(Scheme 6)[5].

Scheme 6



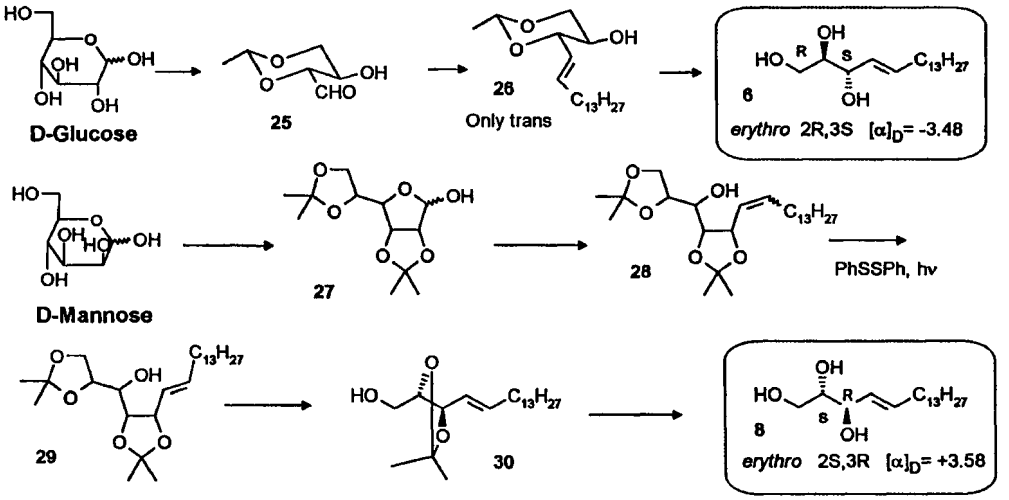
The another *threo*-isomer **7** is synthesized from the antipode of chiral pool used in the synthesis of isomer **5**. Its chiral centers are taken from L-tartaric acid or xylose. In the later case C_2-C_3 instead of C_3-C_4 of xylose is incorporated into the target molecule and the deacetonization-cleavage with periodic acid[4] is used again (Scheme 7)[5].

Scheme 7



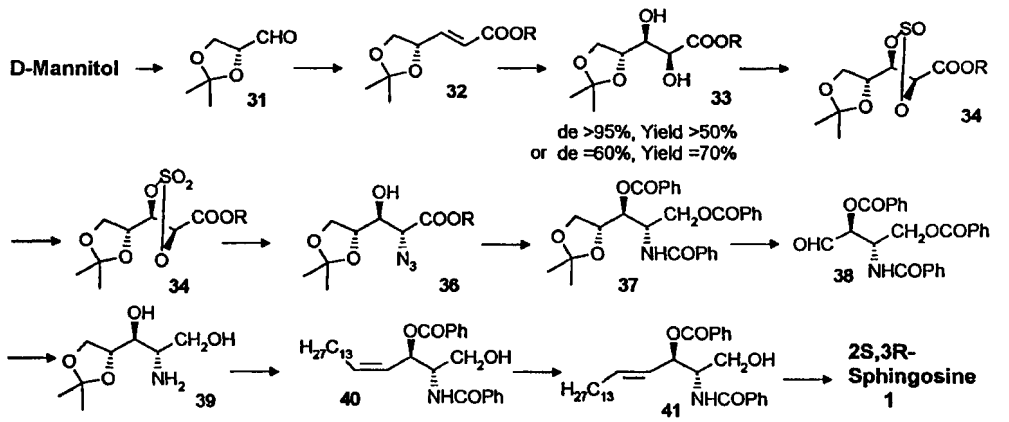
The pair of *erythro*-isomers **6** and **8** are synthesized from D-glucose and D-mannose respectively. In the former case, C_3-C_6 of glucose becomes to the C_1-C_4 segment of compound **6** and Wittig reaction of **25** gives only the desired trans olefin directly. However the C_1-C_4 segment of compound **8** is taken from C_1-C_4 of mannose and the deacetonization-diol cleavage[4] of compound **29** with periodic acid in ether removes the remainder two carbons of mannose (Scheme 8)[5].

Scheme 8



The chiral vicinal diol or aminoalcohol product also could be synthesized by asymmetric reaction in the presence of chiral catalyst or auxiliary group. Dihydroxylation of **32** without chiral catalyst give compound **33** in 70% yield and 60% d.e., however in the presence of hydroquinidine 4-chlorobezoate and potassium ferricyanide (K_3FeCN_6)[6] the d.e. value will be about 95% and the yield drops to ~50%. Formation of cyclic sulfate[7] and then regioselective opening of the sulfate with NaN_3 gives compound **36** and at last sphingosine[8] (Scheme 9).

Scheme 9



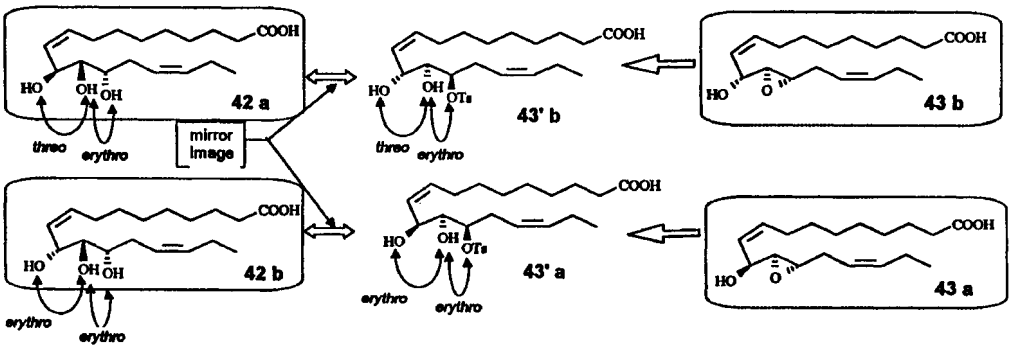
Syntheses of substances against rice blast disease (SARBD)

In 1986 Kato reported that several oxygenated C_{18} fatty acid, such as **42a, 42b, 43a, and 43b**, were isolated from rice plants suffering from rice blast disease, and could act as self-defense substances against the fungus. Their structures are shown in the scheme 10. We consider that substance **43b** and **43a** can be synthesized from **43'b** and **43'a** respectively. **43'b** and **43'a** are the enantiomers of **42a** and **42b**, and these upper substances are the epimers of lower ones.

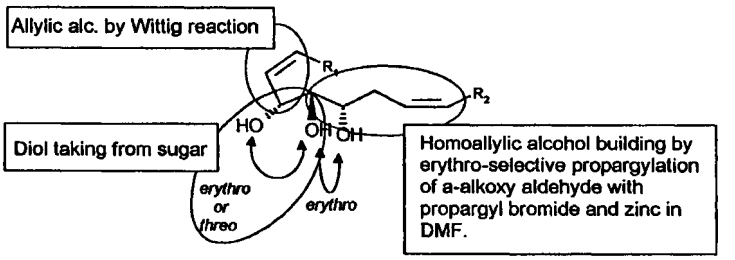
Their structures and the structure of trioxilin/ hepoxilin B_3, we will mentioned lately, might be generalized as shown in scheme 11. And our synthetic strategy will be : 1, formation of allylic alcohol by Wittig reaction; 2, the *erythro* or *threo* diol could be taken from sugar or hydroxy acid; 3, the homoallylic alcohol segment could be built up by an *erythro*-selective propargylation of α-alkoxy with propargyl bromide and zinc in DMF, which facile method have been summarized and submitted to the journal for publication[9].

As we mentioned above, substance **42a** is an enantio-isomer of **43'b**, the precursor of **43b**, and both are in *threo*-configuration at C_{11}-C_{12}. Their syntheses are performed using L(+)- and D(-)-tartaric acid respectively as the chiral pool[10] (Scheme 12).

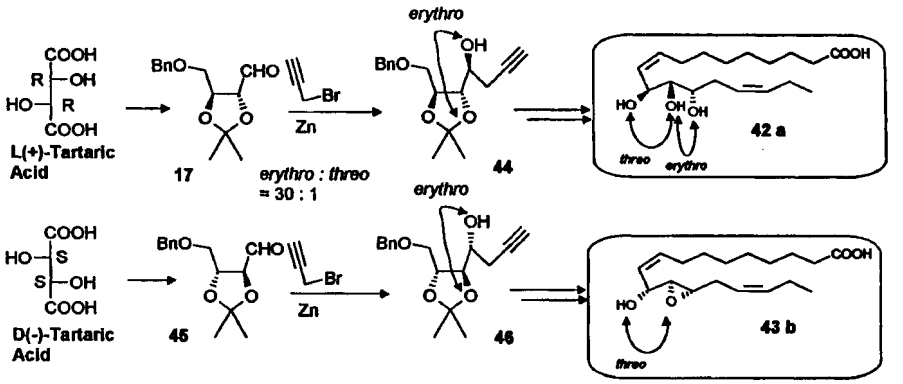
Scheme 10



Scheme 11

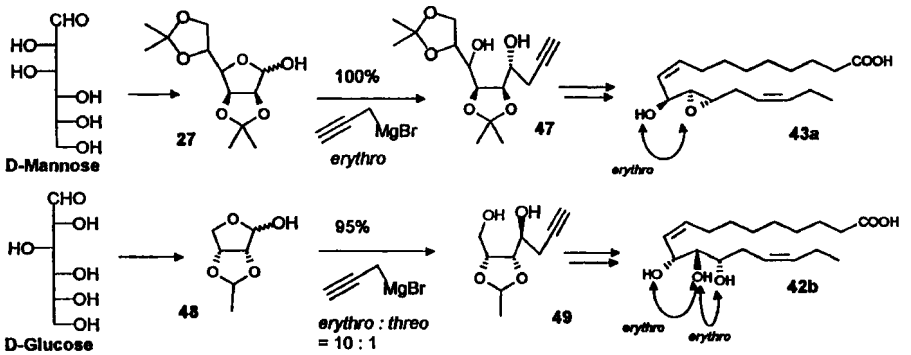


Scheme 12



For another pair of *erythro*-substances, the C_4-C_1 *erythro*-segment of D-mannose and C_6-C_3 *erythro*-segment of D-glucose are inserted into C_{10}-C_{13} position of **43a** and **42b** respectively. The third chiral hydroxy group is formed by *erythro*-selective propargylation of lactol with Grignard reagent[11] (Scheme 13).

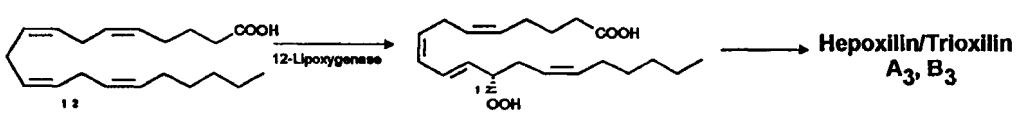
Scheme 13



Syntheses of trioxilin/ hepoxilin B_3

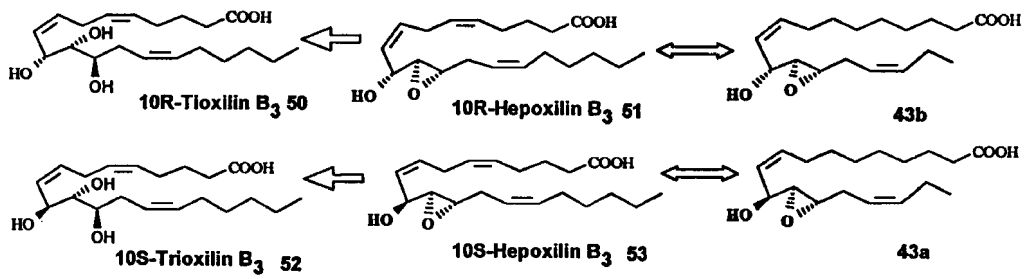
Hepoxilin/ Trioxilin A_3 and B_3 , the 12-lipoxigenase metabolites of arachidonic acid, are another interesting compounds in the eicosanoid family (Scheme 14).

Scheme 14



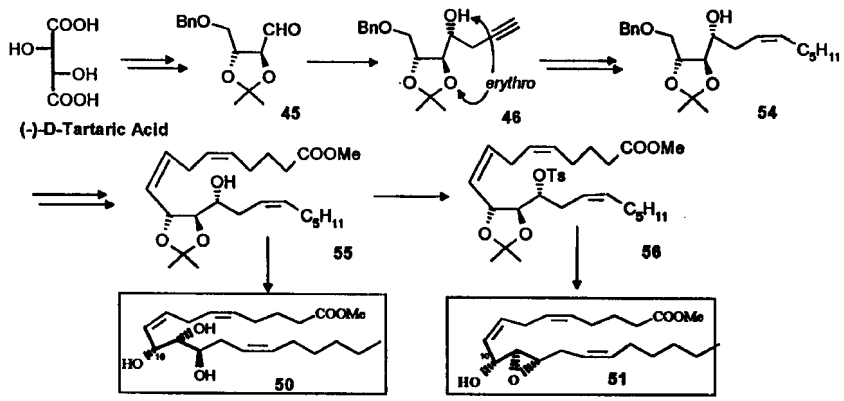
Both trioxilin B_3 and hepoxilin B_3 consist of two C_{10}-diastereoisomers **50, 52** and **51,53**. The central part, including all three asymmetric centers, of hepoxilin B_3 **51** or **53** is the same as one of substance against rice blast disease **43b** or **43a**. From the viewpoint of retrosynthesis hepoxilin B_3 can be synthesized from corresponding trioxilin B_3 as shown in the scheme 15.

Scheme 15



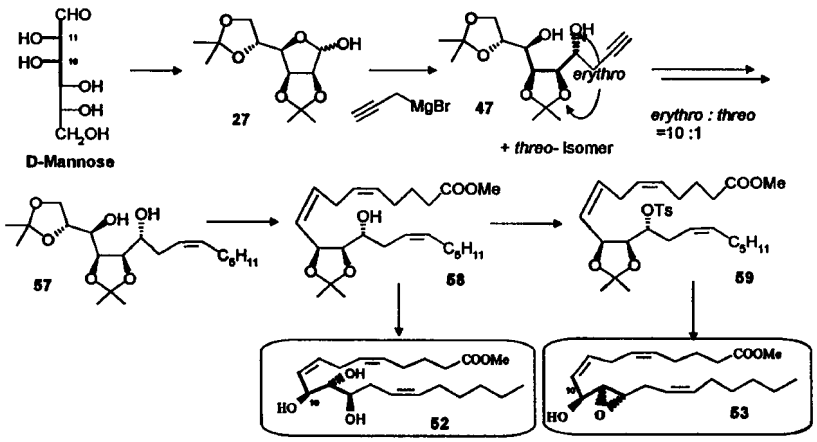
Following the same strategy used in the synthesis of substance against rice blast disease, *threo*-10S-hepoxilin/trioxilin B_3 is synthesized from (-)-D-tartaric acid[12] (Scheme 16). Stereoselective propargylation with propargyl bromide and zinc dust in DMF is again used for the introduction of third chiral center.

Scheme 16

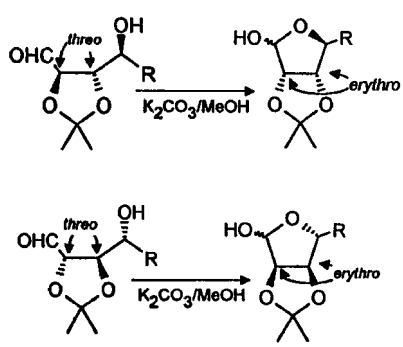


Erythro-10R-hepoxilin/ trioxilin is synthesized from D-mannose with a similar synthetic reaction sequence of SARBD **43a** (Scheme 17)[13].

Scheme 17



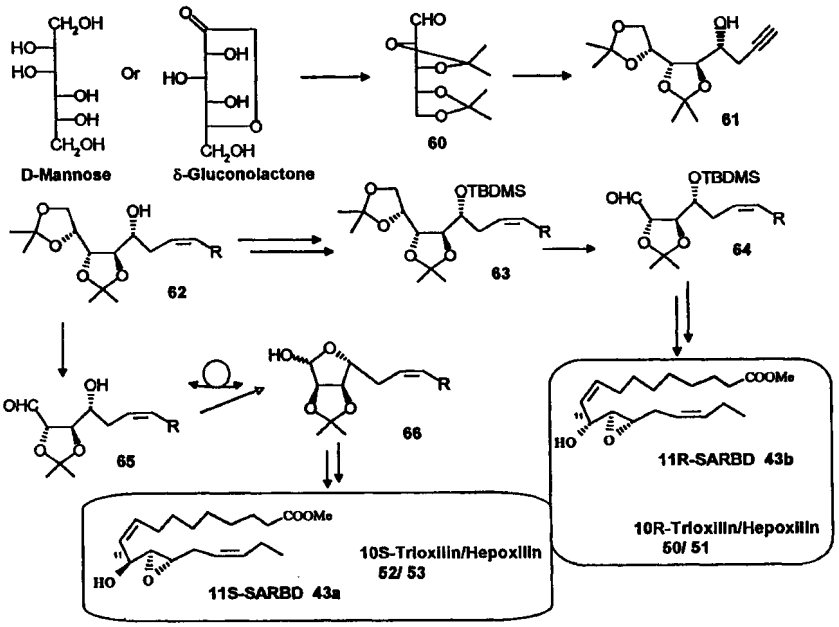
Scheme 18



Configuration conversion of *threo* to *erythro*

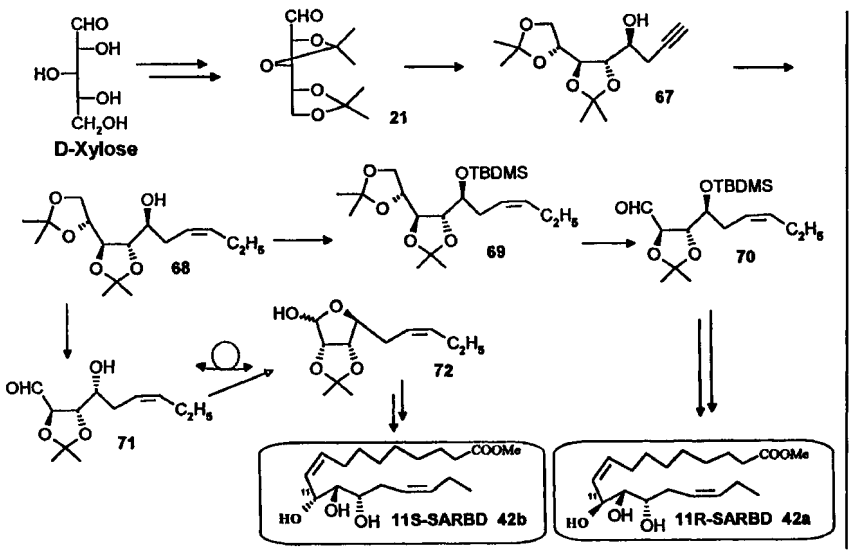
So far we have synthesized a series of vicinal diol natural products, during which studies *threo*-product comes from *threo*-chiral pool and *erythro*-product from *erythro*-chiral pool. However, we find that in the presence of γ-hydroxy group the acetonide of *threo*-2,3 dihydroxy aldehyde could be transformed into the *cis*-fused five-membered ring lactol with C_2-epimerization (scheme 18).

Scheme 19

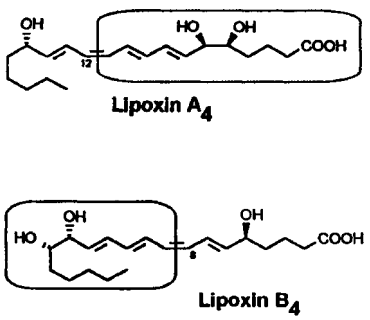


Using this *threo-erythro* conversion combined with our propargylation method and deacetonide-cleveage procedure, all four trioxilin/ hepoxilin B_3 compounds **52/53, 50/51** and two epoxide SARBD **43a, 43b** could be synthesized from one chiral pool **60**, obtained easily from D-mannose or δ-gluconolactone[14,15] (Scheme 19). While the reminder two triol SARBD **42a, 42b** could be synthesized from D-xylose with the same reaction sequence[15] (Scheme 20).

Scheme 20



Scheme 21

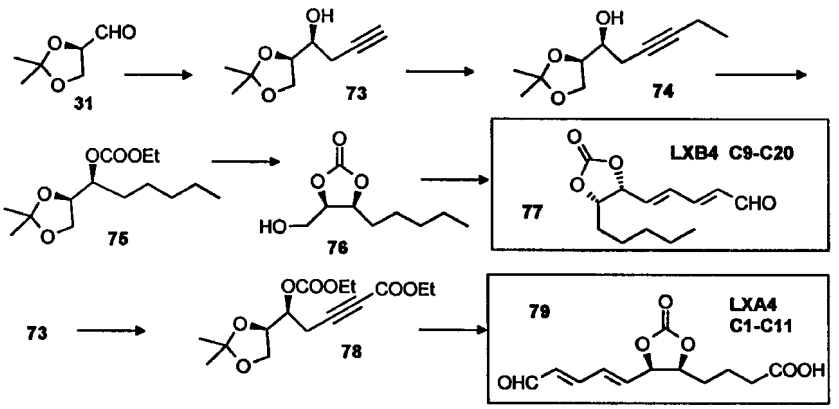


Synthesis of diol segment of lipoxin

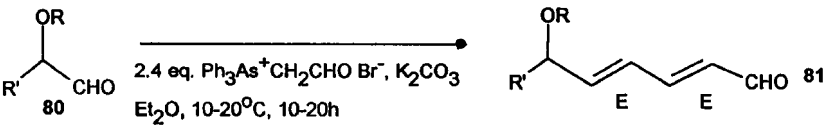
Lipoxin A_4 and B_4 is another metabolite of arachidonic acid. Both of them contain a vicinal diol segment as shown in scheme 21.

Propargylation of D-glyceraldehyde acetonide **31** gives stereoselectively the *erythro*-intermediate **73**, which is then converted to compound **75, 78** respectively. Formation of cyclic carbonate and Swern oxidation of thus obtained primary alcohol affords cyclic carbonate aldehyde, which is treated with 2 equivalent fomylmethyl triphenylarsonium bromide and potassium carbonate[16] to give the double formylolefination product **77** and **79** with pure trans, trans-configuration (Scheme 22), (scheme 23). As the next steps are known[17], synthesis of lipoxin A_4 and B_4 is also reached.

Scheme 22



Scheme 23



Summery

A series of chiral diol natural products have been synthesized through chiron approach or asymmetric reaction in our laboratory. It is demostrated that the consideration of molecular symmetry may facilitate the synthetic design and these most common sugars, such as glucose, mannitol, and xylose, may serve as the versatile chiral pool. Especially the most abundant sugar-glucose contained all possible *threo* and *erythro* segment may be the most useful chiral resource. However, there still are a lot of research work to be exploited before we could achieve such ideal outcome.

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