

De novo synthesis of carbohydrates and related natural products

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Abstract - Two synthetic strategies from achiral precursors especially useful for sugars requiring unusual functional groups, deoxy and branched sugars, as well as partially O-protected sugars, are outlined. One strategy employs inverse-type hetero-Diels-Alder reaction with highly functionalized 1-oxa-1,3-dienes. Their reaction with electron rich hetero-dienophiles (enol ethers, etc.) and subsequent diastereoselective transformation of the CC-double bond in the dihydropyran adducts obtained gives convenient access to deoxy sugars (for instance, D- and L-olivose) and related compounds, which also contain C-branching (for instance, ramulosin). The other versatile strategy starts from racemic or meso-divinyl glycols. Kinetic resolution via Sharpless epoxidation again gives direct access to partially O-protected carbohydrates. This method is exemplified in deoxy sugar synthesis (for instance, D- and L-digitoxose and -chalcose) and also in the synthesis of the pheromone exobrevicomin.

INTRODUCTION AND STRATEGIES

Carbohydrate derivatives and related natural products are mainly synthesized by transformation of readily available sugars (ref. 1). However, the high density of functional groups of comparable reactivity requires regioselective protection and deprotection measures and stereospecific functional group exchange quite often resulting in multistep syntheses. Several methods have been developed in the last years which are useful in the diastereoselective and enantioselective generation of new stereocenters (ref. 2). Therefore "de novo syntheses" or "total syntheses" of natural products from achiral starting materials have become competitive or even superior (ref. 3-8).

For the generation of several subsequent chiral centers two different key step reactions are applicable: (i) stereoselective CC-bond formation and (ii) stereoselective functionalisation of compounds having already the required carbon skeleton. In the de novo synthesis of carbohydrates these two principles, having led to great progress in natural product synthesis, are especially well illustrated (ref. 5-7).

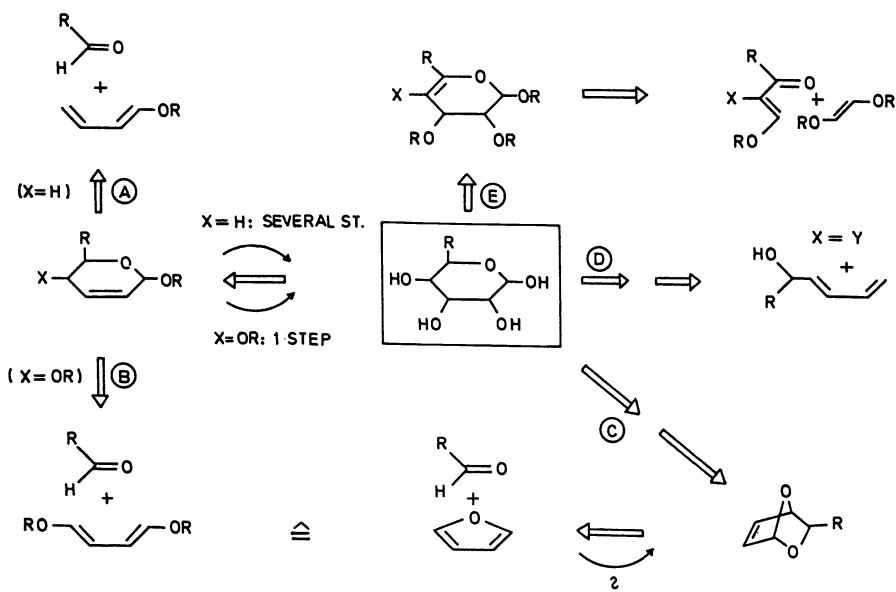
The stereoselective formation of the carbon skeleton is frequently attained by diastereofacial selectivity in carbon nucleophile additions to carbonyl and imine systems where either the nucleophile or the electrophile or both contain chiral groups in order to induce the preferred formation of one enantiomer (ref. 9, 10). Also Diels-Alder reaction has become a powerful tool in natural product synthesis because it combines CC-bond formation with diastereoselectivity at several centers (ref. 11). Due to supra-suprafacial reaction, polarity controlled orientation, and endo- or exo-selectivity of diene and dienophile, very often only one pair of enantiomers is obtained out of the maximum of thirty two possible isomers (ref. 7). Recently even enantioselectivity could be incorporated successfully into the Diels-Alder reaction leading to preferential or exclusive formation of one single isomer (ref. 12).

Aiming at the pyranose form of sugars hetero-Diels-Alder reactions were extensively used for the synthesis of functionally substituted dihydropyran and tetrahydropyran systems which are important targets in the "chiron approach"

* De novo Synthesis of Carbohydrates and Related Natural Products, Part 25. - Part 24, see ref. 23.

to natural product syntheses (ref. 1). Scheme 1 summarizes the routes followed by us and others, which start from electron rich 1,3-dienes and carbonyl compounds as dienophiles (routes A-C) and from functionally substituted dienes and diheterodienophiles (route D) (ref. 3-8). However, low reactivity, low diastereoselectivity, and/or eliminative loss of functional groups were frequently encountered as problems in these reactions. Therefore we turned our attention to inverse-type hetero-Diels-Alder reactions between functionally substituted 1-oxa-1,3-dienes and electron rich dienophiles for dihydropyran synthesis (Scheme 1, route E) (ref. 7, 13,14). The advantage and versatility of this route will be discussed in the first section of this paper.

Scheme 1



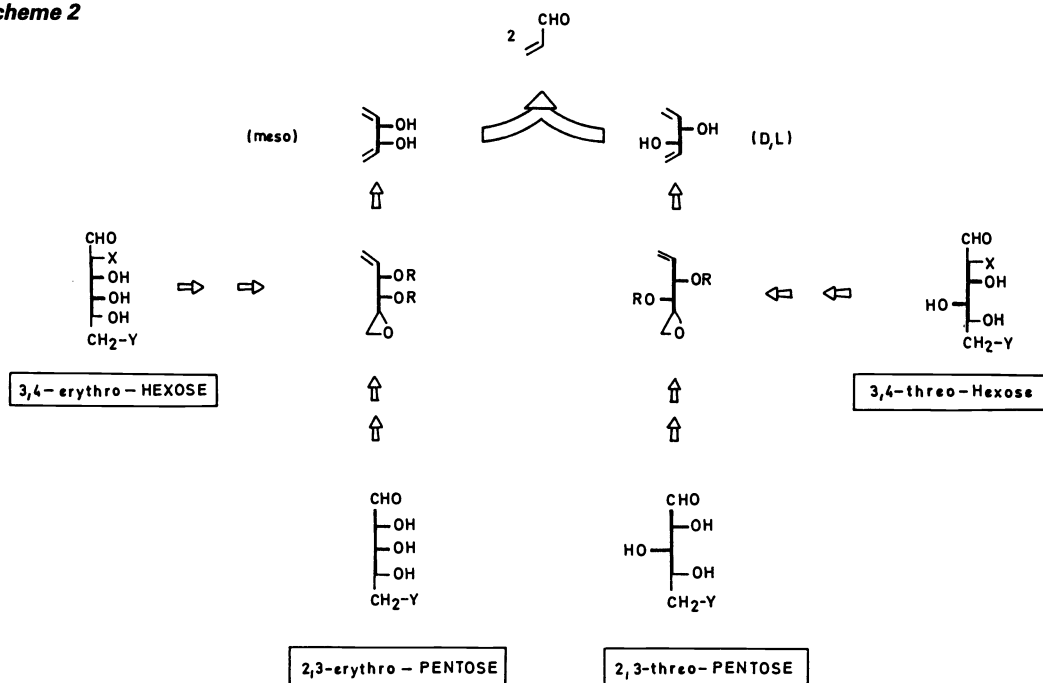
The stereoselective functionalization of a carbon skeleton is usually based on site selective carbon-heteroatom bond formation with CC-double bonds. For instance, vicinal diols are formed via cis- or trans-specific dihydroxylation. For allyl alcohols and allyl ethers a relative erythro stereochemistry was preferentially found between the hydroxy or alkoxy group, respectively, and the newly formed vicinal hydroxy group (ref. 15). A breakthrough in asymmetric synthesis was Sharpless epoxidation of allyl alcohols (ref. 16). Primary allyl alcohols are directly transformed into optically active α -hydroxy-methyl epoxides. Secondary allyl alcohols usually lead to enantiomerically pure epoxides with concomitant kinetic racemate resolution leaving behind an enantiomerically enriched allyl alcohol (ref. 17, 18). Methods for the stereoselective opening of epoxides with oxygen, nitrogen, hydrogen, and carbon nucleophiles are available (ref. 19). The synthetic potential of this method was exemplified, for instance, by Sharpless and Masamune in the synthesis of all eight L-hexoses from butene-1,4-diol (ref. 18).

Allyl alcohols are therefore valuable starting materials for stereoselective syntheses which contain in the CC-double bond a multivalent precursor for a variety of transformations. Molecules with an allyl alcohol function having more than one CC-double bond should be especially suitable for carbohydrate and related natural product syntheses. Therefore we have developed a versatile strategy for the synthesis of enantiomerically pure deoxy sugars starting from racemic or *meso*-divinyl glycols as outlined in Scheme 2 (ref. 20-23). Kinetic resolution via site-selective oxidation plays an important role in this approach, which will be discussed in the second section.

INVERSE TYPE HETERO-DIELS-ALDER REACTION

Hetero-Diels-Alder reactions with inverse electron demand, as for instance between α,β -unsaturated carbonyl compounds (1-oxa-1,3-dienes) as dienes and enol ethers as dienophiles, are an attractive route for the synthesis of 3,4-dihydro-2H-pyrans (ref. 24). Recent investigations have demonstrated that electron withdrawing substituents at the α -position increase the rate of this reaction strongly (ref. 25). This reaction would be of great potential for natural product syntheses provided that additional electron donating functional substituents could be introduced in the β -position, that enol ethers,

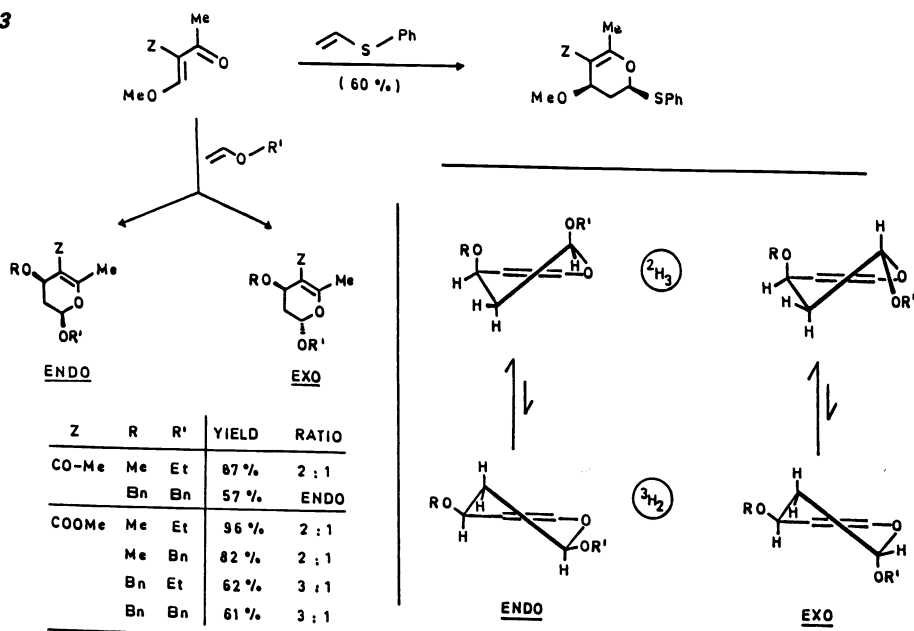
Scheme 2



enediol ethers, ketene acetals, and alkyl substituted derivatives could react as dienophiles, and that high diastereoselectivities could be obtained.

We first turned our attention to α -methoxymethylene substituted 1,3-dicarbonyl compounds as 1-oxa-1,3-diene, which were readily obtained from acetylacetone and alkyl acetoacetate, respectively (Scheme 3); and indeed, with enol ethers the expected 3,4-dihydro-2H-pyrans were usually obtained in high yields (ref. 13, 14, 26). However, the *endo/exo*-selectivity was very often low. Correspondingly low diastereoselectivities were already observed in more simple cases (ref. 24); they were explained in terms of secondary orbital overlap of the HOMO of the dienophile and the LUMO of the heterodiene (ref. 24). According to this principle the *endo*-selectivity could be increased by having electron donating substituents at the dienophile and/or electron withdrawing substituents at the heterodiene. This is exemplified in the reaction of benzyloxymethylene acetylacetone with benzyl vinyl ether and of methoxymethylene acetylacetone with benzyl vinyl thioether (Scheme 3). Similar behavior was also exhibited by α -nitro and α -sulfonyl substituted α,β -unsaturated carbonyl compounds (ref. 27). $^1\text{H-NMR}$ results indicate that the

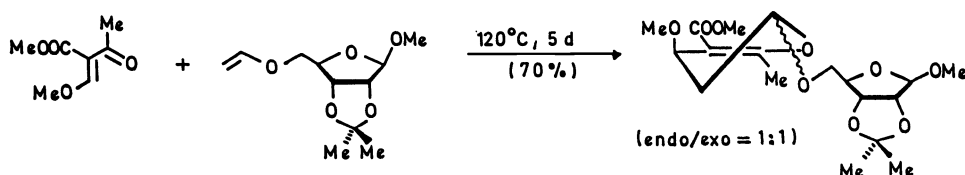
Scheme 3



endo-product and the exo product prefer the 2H_3 -conformation over the 3H_2 -conformation due to stereoelectronic effects (anomeric and allylic effect, ref. 28). However, the equilibrium is influenced by steric effects.

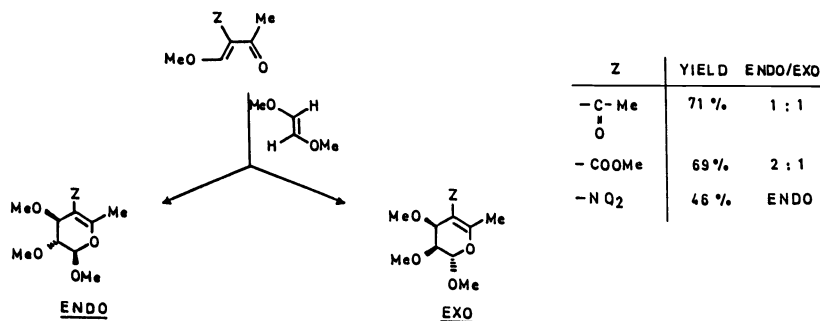
This hetero-Diels-Alder reaction was successfully extended to sugar vinyl ethers as indicated in Scheme 4, a result which could be of interest in terms

Scheme 4



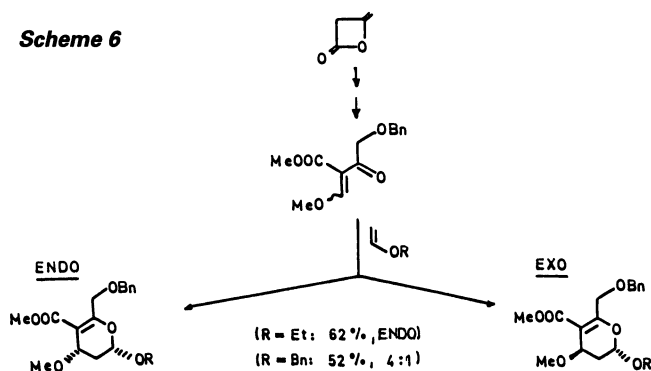
of glycoside bond formation to 2-deoxy sugars (ref. 29). It is particularly noteworthy that also enediol ethers were substrates in this reaction affording fully substituted dihydropyrans in good yields (Scheme 5). Again the

Scheme 5

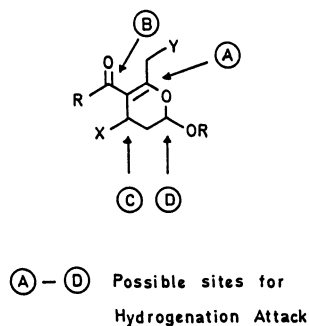


endo/exo-selectivity was found from 1:1 to only endo-product in good agreement with the influence of secondary orbital overlap. For carbohydrate syntheses it was also important to include an alkoxyethyl substituent in 6-position of the 3,4-dihydropyran skeleton (Scheme 6). The required benzyloxymethyl substituted 1-oxa-1,3-diene was readily obtained from diketene in two convenient steps. This heterodiene reacted cleanly with enol ethers to the desired dihydropyrans (ref. 14). The results in Scheme 6 underline again that electron withdrawing substituents at the heterodiene favor endo-product formation. The general substituent influence on dienophile reactivity is exhibited in differences in the required reaction temperature which depends on the electron donating character of the alkoxy substituents. Therefore it is not surprising that ketene acetals already react at room temperature with the 1-oxa-1,3-diene systems shown in Schemes 3-6 (ref. 14).

Scheme 6



Scheme 7

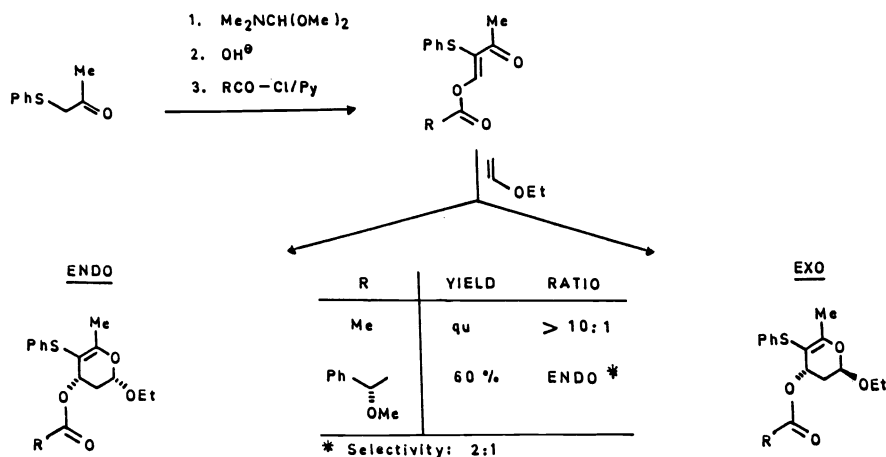


The scope of this cycloaddition reaction was very promising. However, removal of the CC-double bond and stereoselective functionalisations at positions 5 and 6 (pyran numbering) would be required for the synthesis of carbohydrates and related natural products, providing C-4 branched carbohydrate derivatives (or C-4 heteroatom substituted derivatives after carbon/heteroatom exchange reactions). For instance, diastereospecific hydrogenation of the push-pull substituted olefin moiety in these compounds (Scheme 7, A-attack) would yield branched hexopyranosides of controlled stereochemistry with up to five successive chiral centers in a two step procedure. However, hydrogenation of

such systems with various hydrogen donors has mainly resulted in low yields and/or side reactions (B- to D-attack) due to the inherent stability of the CC-double bond (ref. 25).

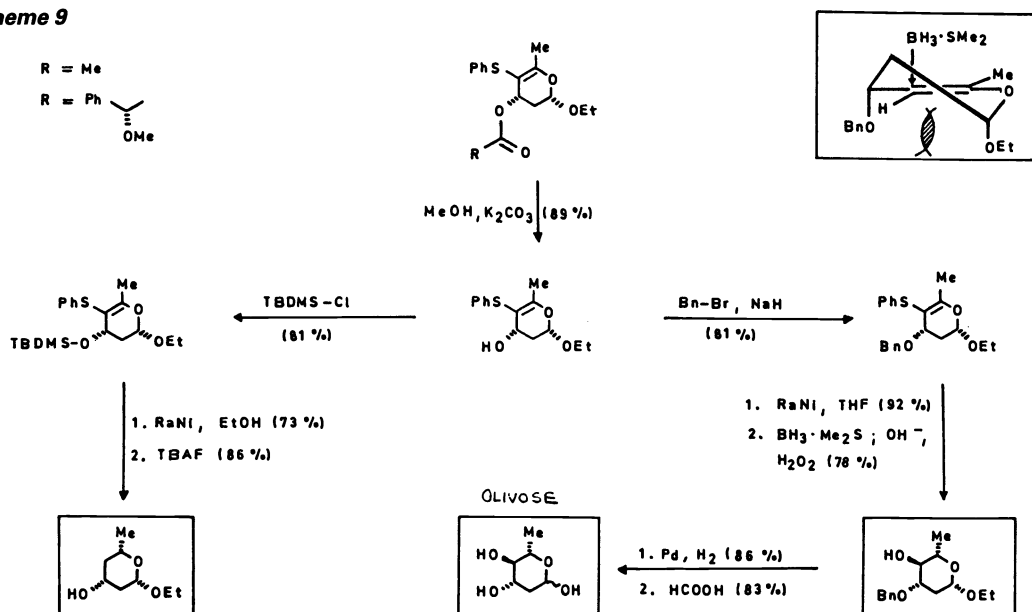
However, the aim of using this method for the synthesis of carbohydrates and related compounds makes a carbon substituent in 4-position (5-position in pyran numbering) redundant; instead, a functional heterosubstituent is required. However, β -alkoxy α,β -unsaturated carbonyl compounds having no electron withdrawing substituent in the α -position are very unreactive towards enol ethers (ref. 30). Therefore, we undertook investigations aimed at introducing a versatile functional substituent in the 4-position, which (i) increases the rate and the diastereoselectivity of the cycloaddition reaction and (ii) enables a straightforward introduction of hydroxy, amino, methyl, hydrogen, and perhaps other substituents in a diastereospecific manner. Results with β -acyloxy- α -phenylthio α,β -unsaturated carbonyl compounds as heterodienes demonstrate that the α -phenylthio group in combination with a β -acyloxy group fulfills these requirements (Scheme 8) (ref. 7, 14, 31). 4-Functionalization and derivatisation in general is predisposed by the phenylthioenol ether structure.

Scheme 8



The starting material was readily obtained from phenylthioacetone (Scheme 8) (ref. 7, 14). Reaction with enol ethers, enediol ethers, and especially ketene acetals went quite smoothly with high yields, and afforded exclusively or almost exclusively the endo-3,4-dihydropyran. With the O-methyl mandeloyl group as chiral auxiliary, in addition, preferential formation of one enantiomer could be achieved. As indicated in Scheme 9, removal of the acyl group and protection of the 3-hydroxy group with either tert.-butyldimethylsilyl or

Scheme 9

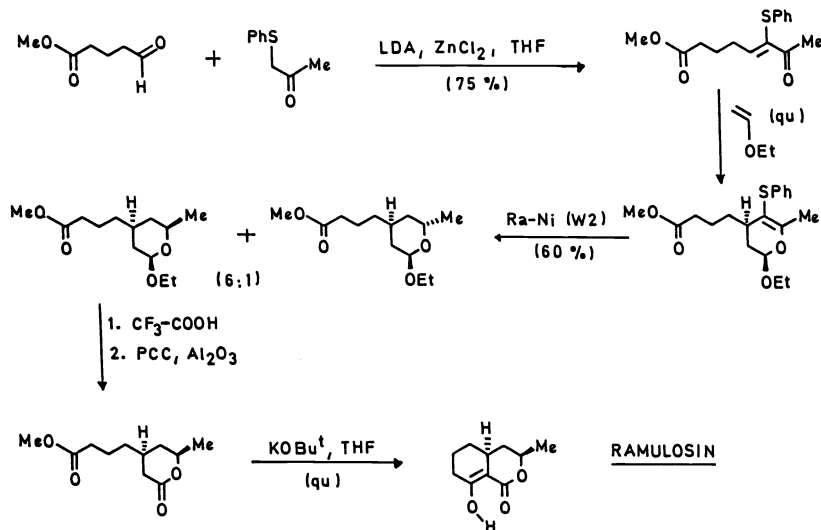


benzyl gave two 3,4-dihydropyran intermediates which were diastereo-specifically converted into 2,6-dideoxy-L-arabino- and 2,4,6-trideoxy-L-threo-hexopyranosides, respectively. As indicated in the box of Scheme 9, due to the anomeric and allylic effect one conformer is preferred which is diastereospecifically attacked by the borane reagent or by Raney nickel from the less hindered site. The partially O-protected L-arabino compound was easily converted into known L-olivose (ref. 7). This reaction could be recently successfully extended to heterodienes having a benzyloxy instead of a methyl substituent (Ref. 31, 32) and also to heterodienes having an acylamino instead of an acyloxy substituent (ref. 33).

Thus the inverse-type hetero-Diels-Alder reaction based hexopyranoside synthesis is high yielding and permits the diastereospecific generation of up to four chiral centers. Concomitant stereocontrolled generation of a fifth chiral center in the 2-position (3-position in pyran numbering) is under investigation (ref. 34). The direct access to partially O-protected derivatives with different O-protecting groups is an additional advantage of this method because carbohydrates are usually required for regioselective glycoside bond formation.

The simplicity, efficiency, and versatility of this method can be demonstrated in different areas. For instance, chemoselective reactions could be also carried out with β -unsubstituted α -phenylthio-substituted α,β -unsaturated carbonyl compounds and enol ethers which finally led to natural 2,3,6-trideoxy and to 4-amino-2,3,4,6-tetradeoxy tetradecyloxy sugars very readily (ref. 35). The usefulness of this approach with carbon substituents at β -position can be demonstrated in the synthesis of the antibiotics ramulosin and actinobolin, which recently gained importance because of interesting biological properties (ref. 36). We have just finished the synthesis of ramulosin according to this approach (Scheme 10) (ref. 35). The hetero-Diels-Alder reaction gave quantitatively the desired *endo*-3,4-dihydropyran adduct which upon Raney-nickel treatment afforded mainly *cis*-relation of the C-4 and C-6 carbon substituents. This product was then transformed in three convenient steps into (+)-ramulosin.

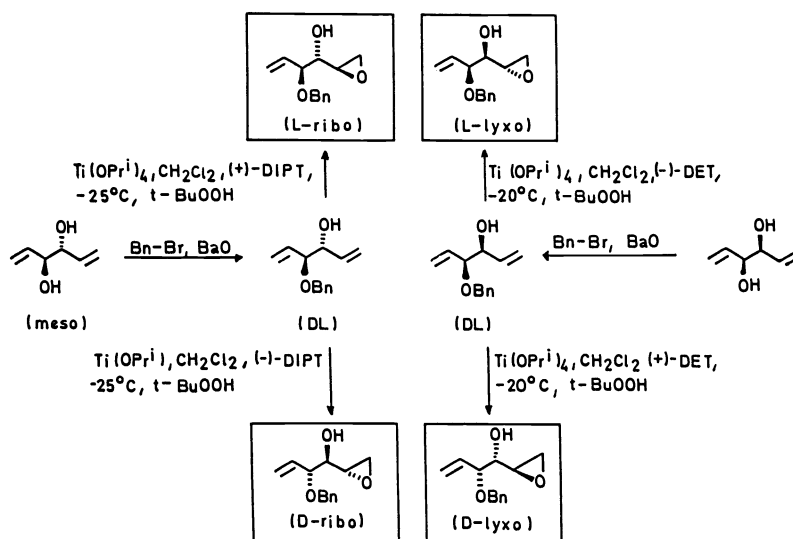
Scheme 10



DIVINYLGLYCOLS IN CARBOHYDRATE AND RELATED NATURAL PRODUCT SYNTHESIS

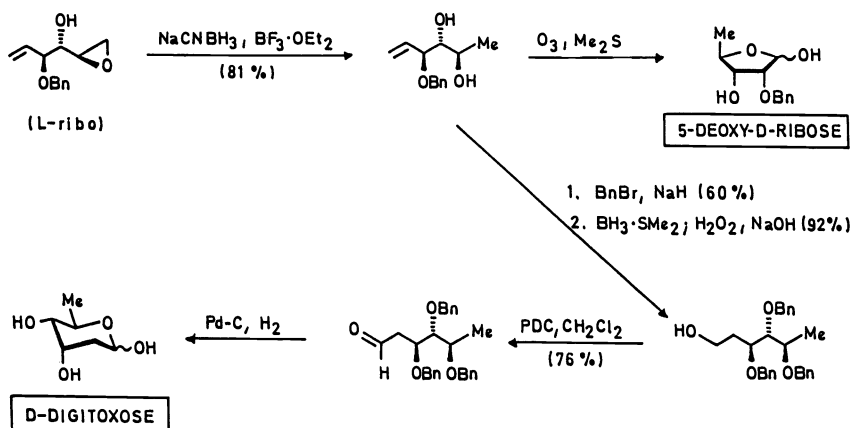
As outlined in the introductory section allyl alcohol systems with the required carbon skeleton may be advantageously used in hexose and pentose syntheses. Divinylglycols were already investigated earlier for hexitol syntheses (ref. 37, 38). However, mainly mixtures of stereoisomers were obtained. The usefulness of these precursors is based on (i) one step synthesis in large quantity from inexpensive chemicals, (ii) vicinal diol structure, (iii) C₂- or δ -symmetry in the DL- or *meso*-isomer, respectively, and (iv) high functionalization. The problems to be solved for the successful application of these compounds in the synthesis of highly functionalized compounds are (i) convenient *meso*-/DL-separation, (ii) racemate resolution, and (iii) chemo- and diastereoselective functionalization of the CC-double bonds (Scheme 2).

Scheme 11



After having accomplished the meso-/DL-separation by simple crystallization techniques (ref. 39, 40) we could overcome the other problems mainly with the help of Sharpless epoxidation. Application of this procedure to mono-O-benzylated meso- or DL-divinylglycols (Scheme 11) afforded in one step via kinetic resolution the enantiomerically pure D- and L-ribo- and D- and L-lyxo-monoepoxi-hexenediols (ref. 22). These readily available compounds, containing one epoxy, one hydroxy, one benzyloxy, and one vinyl group, are highly functionalized with different groups and therefore predisposed for regioselective reactions. The usefulness of these compounds in a variety of carbohydrate syntheses is demonstrated in one example (Scheme 12). The L-ribo-monoepoxi-hexenediol is transformed via regioselective reductive epoxide cleavage to the aldehyde stage, and hydrogenolytic O-deprotection into D-digitoxose, which is found in the oligosaccharide moiety of cardiac glycosides (ref. 22, 41). In our opinion this approach competes successfully with semisynthetic approaches from other carbohydrates (ref. 41) or other total syntheses (ref. 41, 42). The utility of these intermediates is also demonstrated in the 2-O-benzyl protected 5-deoxy-D-ribose synthesis by simple ozonolysis (ref. 40).

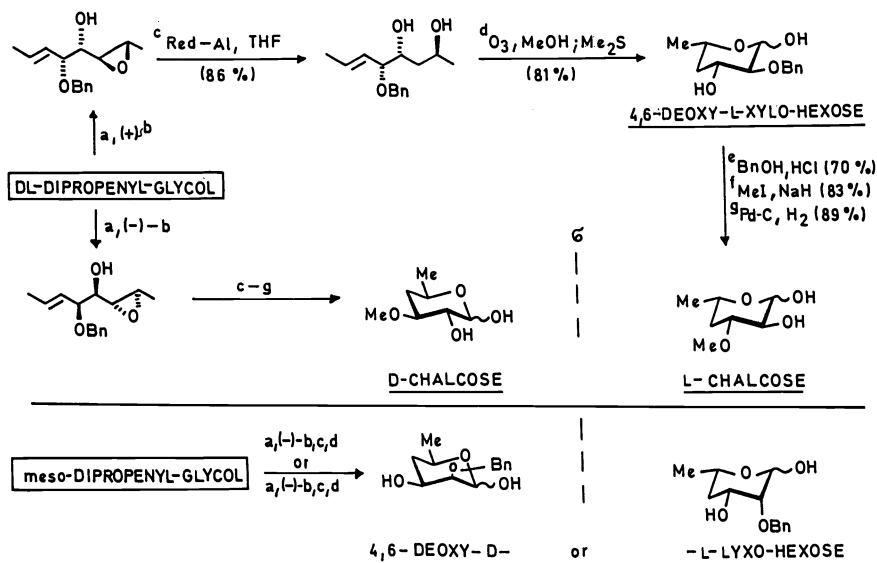
Scheme 12



The retrosynthetic analysis in Scheme 13 demonstrates that dipropenylglycols should be of advantage for 6-deoxy hexose syntheses. In this case the 2,3-diol moiety of the derived molecule provided by the precursors which require for C-4 and C-5 modification the selective functionalization of one of the CC-double bonds and for the generation of the aldehyde group ozonolysis of

lytic debenzoylation afforded the desired L- and D-chalcose, respectively, in convenient high yielding steps. This again demonstrates the versatility of this strategy for the synthesis of enantiomerically pure sugars from divinylglycol and derivatives. The method generally requires only a few steps and it gives also convenient access to partially O-protected carbohydrates. A similar methodology was recently applied to divinylcarbinols (ref. 46) which contain a C₅-carbon skeleton. Therefore their use is restricted to pentose syntheses.

Scheme 15



The wide applicability of divinylglycols in organic synthesis is exhibited by the synthesis of the pheromone *exo*-brevicomine from DL-divinylglycol (ref. 21). Bis-O-benzoylation, selective ω -hydroxylation of one CC-double bond, oxidation of the hydroxymethyl group to the aldehyde stage, chain extension by Wittig reaction, and hydrogenation under loss of CC-double bonds and O-benzyl protective groups with concomitant ring closure afforded d,l-*exo*-brevicomine. The same methodology applied to *meso*-divinylglycol will lead to the corresponding *endo*-isomer and combination with Sharpless epoxidation will readily provide these compounds in enantiomerically pure form.

Acknowledgement

I am grateful to my young colleagues M. Maier, U. K fner, B. Haag, K. Vogt and K. Frische who developed the methodologies described here during master and doctoral theses at the University of Konstanz. - This research was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

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