SYNTHETIC CONTROL LEADING TO NATURAL PRODUCTS

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Abstract - A variety of highly stereoselective reactions,
based on the concept of 'Synthetic Control', are described.
Some natural products are successfully synthesized by the
application of these reactions.

INTRODUCTION

The concept of 'Synthetic Control' is characterized by the utilization of chelate complexes
of common metals for the intra- or intermolecular interactions of reacting species, leading
to highly stereospecific or entropically advantageous reactions.   In this article, a
variety of highly stereoselective reactions, such as asymmetric reactions, intramolecular
Diels-Alder reactions, and useful reactions for the synthesis of sugar derivatives, guided
by the principle of 'Synthetic Control', are summarized.

### ASYMMETRIC SYNTHESIS BASED ON THE CHIRAL HETEROCYCLIC COMPOUNDS.

A variety of optically active compounds are obtained in much higher enantiomeric purities,
compared with the compounds synthesized by the conventional methods, by use of chiral
heterocyclic compounds, such as chiral pyrrolidine or oxazepine derivatives, which have
strong interactions with organometallic reagents, to form tight complexes as intermediates.

Asymmetric synthesis of optically active secondary alcohols.
Optically active secondary alcohols are obtained by reduction of prochiral ketones with
the chiral hydride reagent (1) prepared from $LiAlH_4$ and (S)-2-(substituted aminomethyl)-
pyrrolidines, derived easily in four steps from commercially available (S)-proline (Ref. 1).

PhCOEt   96 % ee
α-Tetralone   86 % ee

An alternative way for the preparation of optically active secondary alcohols, that is, the
enantioselective addition of organometallic reagents to aldehydes, is also attained by
employing the lithium salt of amino alcohol (2), synthesized from (S)-proline (Ref. 2).


R^1Li + R^2CHO

54-94 % ee
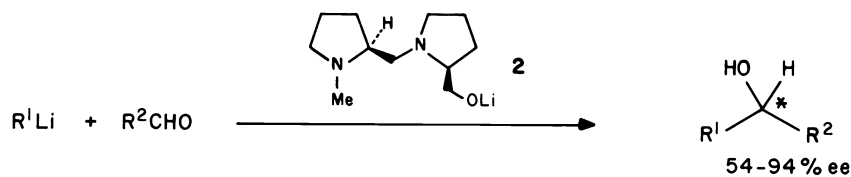
Asymmetric synthesis of optically active aldehydes.

A general and versatile method for the preparation of α-hydroxyaldehydes is developed by
using the diamine (3) as chiral adjuvant.   Such aldehydes, in the desired configuration,
are obtained by the following reaction sequence: i) reaction of one kind of Grignard
reagent (R^1MgX) with the aminal of methyl glyoxylate, ii) diastereoselective addition of a
second kind of Grignard reagent (R^2MgX) to the ketoaminal, and iii) hydrolysis of the
resulting α-hydroxyaminal (Ref. 3).
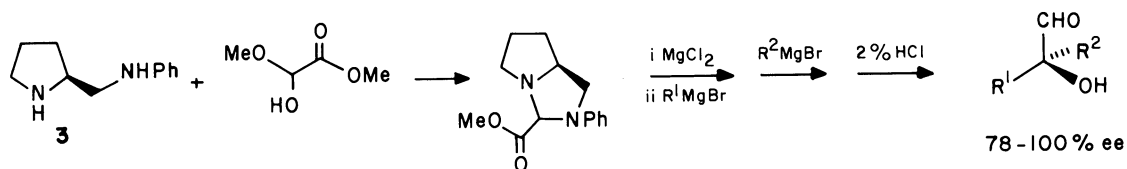
The two enantiomers of frontalin, a pheromone of several species of beetles belonging to
the genus Dendroctonus, and a marine antibiotic, (-)-malyngolide, discovered in the marine
blue-green alga, Lyngbya majuscula Gomont, are synthesized in high optical yields by
applying this asymmetric procedure (Refs. 4 and 5).

(−) 84 % ee   (+) 100 % ee   95 % ee
        Frontalin   (−)-Malyngolide
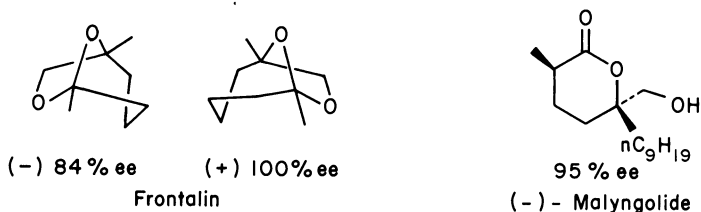
Asymmetric synthesis of carboxylic acids and their derivatives.

(2R, 3S)-3,4-Dimethyl-2-phenylperhydro-1,4-oxazepine-5,7-dione (4) is prepared from the
half-ester of malonic acid and l-ephedrine.   Optically active β-substituted alkanoic acids
are obtained by the reaction of the 6-alkylidene derivatives of 4 (5), easily prepared from
4 and aldehydes, with Grignard reagents in the presence of a catalytic amount of $NiCl_2$,
followed by hydrolysis (Ref. 6).

4   5 76-99 % ($E:Z$ =100:0-85:15)   82 -> 99 % ee
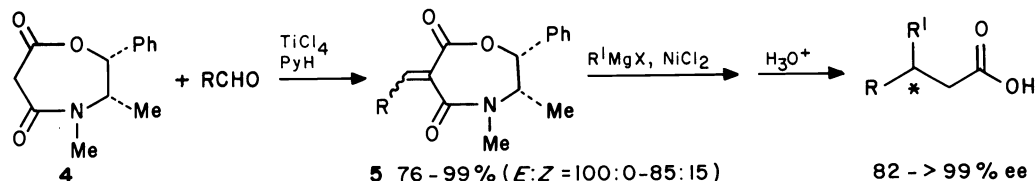
The antibiotic indolmycin is synthesized in high optical purity (Ref. 7).

93 % ee
5 S, 6 R - Indolmycin
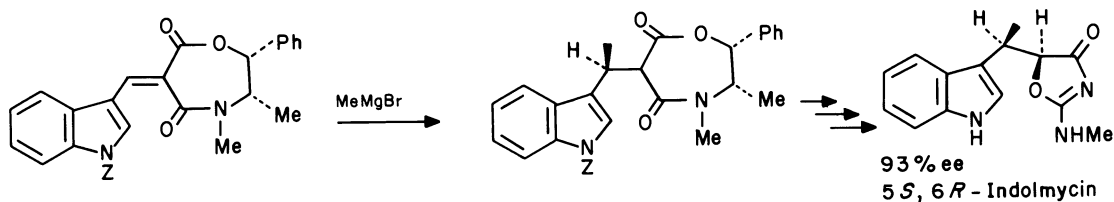
Optically active cyclopropane dicarboxylic acids and β-substituted γ-butyrolactones are also
obtained by using dimethylsulfoxonium methylide or phenylthiomethyl-lithium in place of the
Grignard reagents in the reaction (Refs. 8 and 9).

Catalytic enantioselective 1,4-addition of thiols to 2-cyclohexenone.

A chiral amino-alcohol (6), derived from l-4-hydroxyproline, is found to be a superior
catalyst for the enantioselective 1,4-addition of thiols to 2-cyclohexenone.   The resulting
(R)-3-arylthiocyclohexanone is successfully converted into optically active cyclohexenol
derivatives (7) and (8) respectively (Refs. 10 and 11).
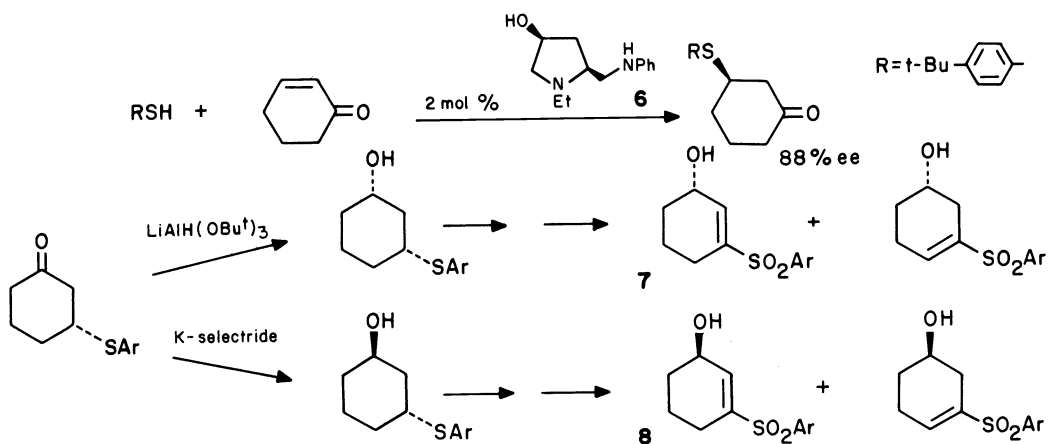
INTRAMOLECULAR DIELS-ALDER REACTION ASSISTED BY INTRAMOLECULAR INTERACTION.

The Diels-Alder reaction is one of the most important reactions in organic synthesis and has been applied to the synthesis of various natural products which possess a 6-membered ring system.   However, there are some limitations to the structures of dienes and dienophiles.   For example, the Diels-Alder adducts between furan derivatives and β,β-dimethylacrylic acid derivatives have not yet been isolated.   The adducts of some sterically hindered dienophile and furan derivatives are successfully obtained in good yields by the intramolecular Diels-Alder reaction of the diene and dienophile, activated by an intramolecular alkoxymagnesium salt coordination.   The acceleration of the reaction is apparently due to the coordination of the dienophile and a proximity effect which makes the reaction entropically advantageous.   This process is applied to the synthesis of the Karahana ether (Ref. 13).
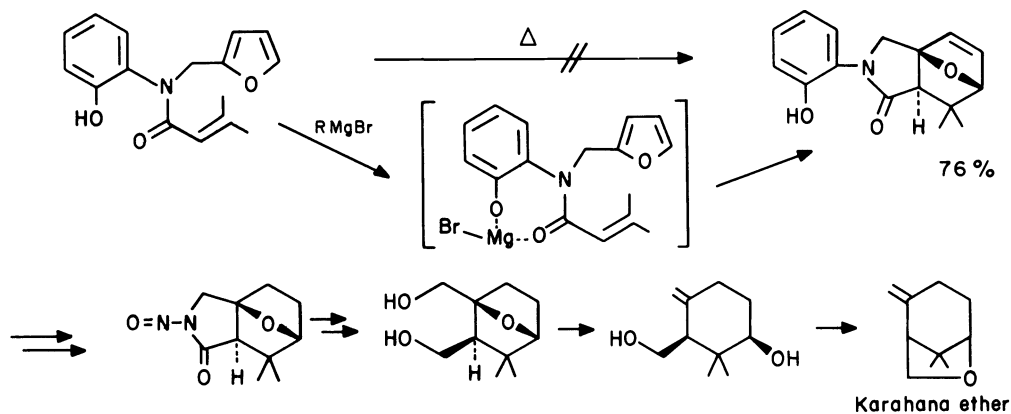
The above sequence is adapted to the asymmetric Diels-Alder reaction.   The reaction of the β,β-dimethylacrylic acid derivative (9), derived from (R)-2-amino-2-phenylethanol, afforded preferentially one diastereomer (10) in good yield, as in the case of the crotonic acid derivative.
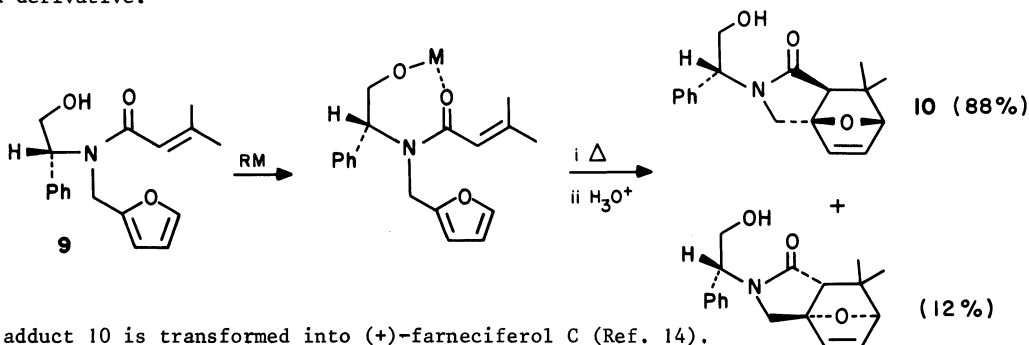
The adduct 10 is transformed into (+)-farneciferol C (Ref. 14).
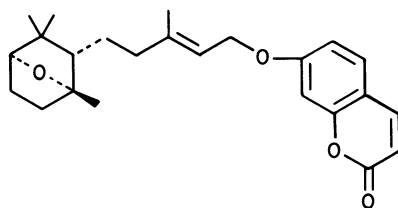
(+)-Farneciferol

This methodology, i.e., the introduction of an intramolecular chelate effect for highly
selective reaction, is further extended to the asymmetric 1,4-addition.   The reaction of
the amide (11) with Grignard reagents, followed by hydrolysis, constitutes a simple procedure
for preparing highly optically pure carboxylic acids (Ref. 15).
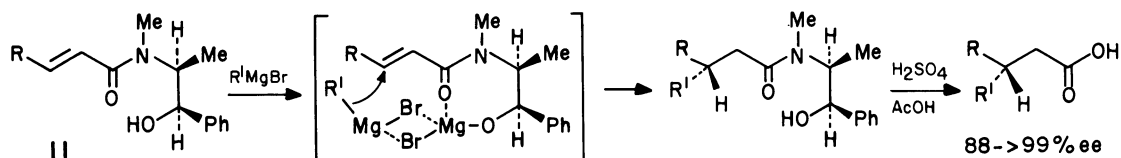
STEREOSPECIFIC REACTIONS LEADING TO SUGAR DERIVATIVES.

Various monosaccharides are generally synthesized starting from the easily available
monosaccharides, such as glucose, galactose, etc..   In recent years, there has been much
interest in the synthesis of such compounds starting from the simple organic molecules,
with the development of various highly stereoselective reactions in the acyclic system.
Recently, several new and useful methods have been exploited, and convenient syntheses of
a variety of monosaccharides, have been developed.

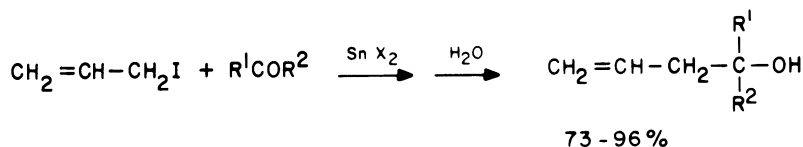Asymmetric aldol type reaction using optically active imine.
The metal enolate of imine (12), which is derived from an atrolactic acid derivative and
t-butyl glycinate, reacts with aldehydes to give the adduct (13) in high stereoselectivity
and in high optical purity (Ref. 16).
2-Acetamido-2-deoxy-D-arabinose and 2-acetamido-2-deoxy-D-ribose are synthesized by the
reaction of imine (12) or its antipode (14) and 2,3-O-isopropylidene-D-glyceraldehyde,
respectively (Ref. 17).

2-Acetamido-2-deoxy-D-arabinose

2-Acetamido-2-deoxy-D-ribose
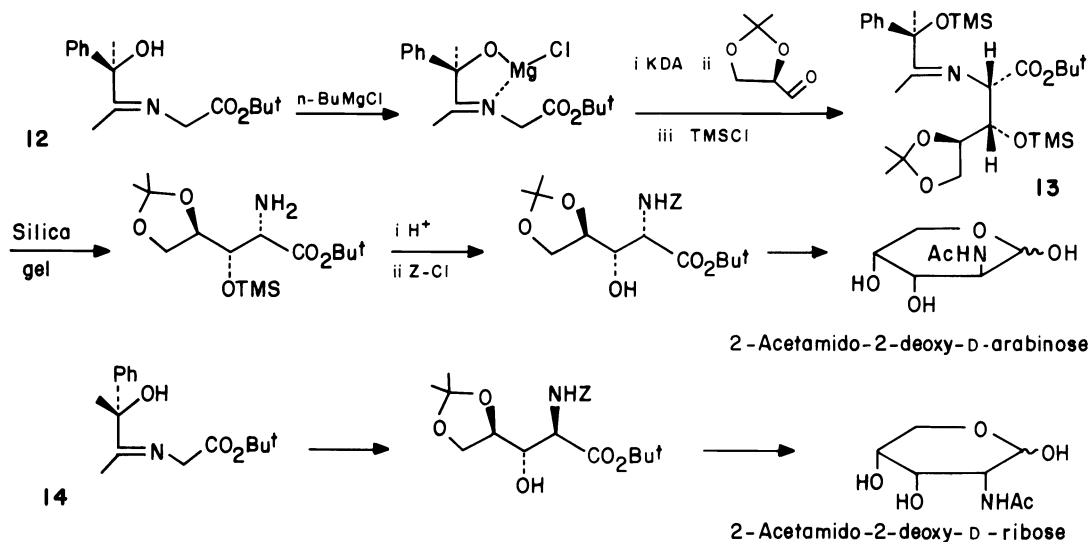
New and useful synthetic reactions by the use of stannous fluoride or metallic tin.
Allyltin dihaloiodide, formed in situ by the oxidative addition of SnF_2 to allyl iodide, is
found to react with carbonyl compounds to give homoallylic alcohols under mild reaction
conditions (Ref. 18).

$$CH_2=CH-CH_2I + R^1COR^2 \xrightarrow{Sn\ X_2} \xrightarrow{H_2O} CH_2=CH-CH_2-\underset{R^2}{\overset{R^1}{\underset{|}{\overset{|}{C}}}}-OH$$

73-96%

This reaction is applied to the synthesis of 2-deoxy-D-ribose (Ref. 19).


(erythro:threo=81:19)   74%

2-Deoxy-D-ribose
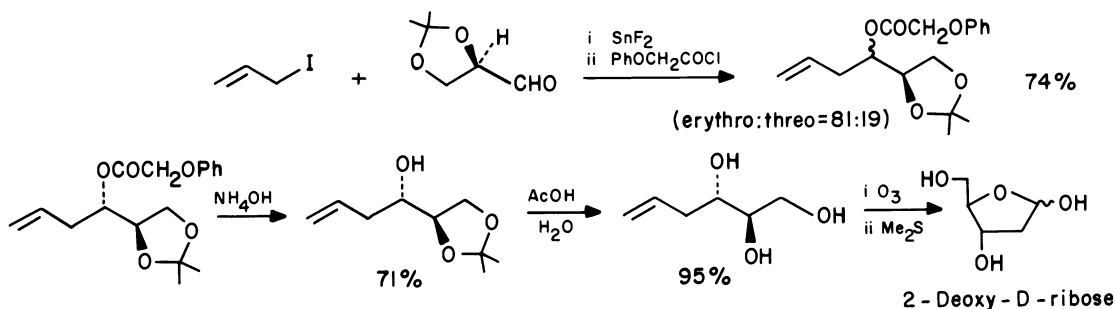
Metallic tin, Sn(0), is more effectively employed; for example, allylation proceeds even with allyl bromide (Ref. 20), and the α-haloesters react with carbonyl compounds in the presence of Sn(0) to give β-hydroxyesters in good yields (Ref. 21). 2,2,2-Tribromoethanol derivatives are also obtained by the reaction of carbon tetrabromide and aldehydes in the presence of SnF_2. 2,3-Di-O-acetyl-D-erythronolactone is synthesized as shown below (Ref. 22).


3:1

61%

57%
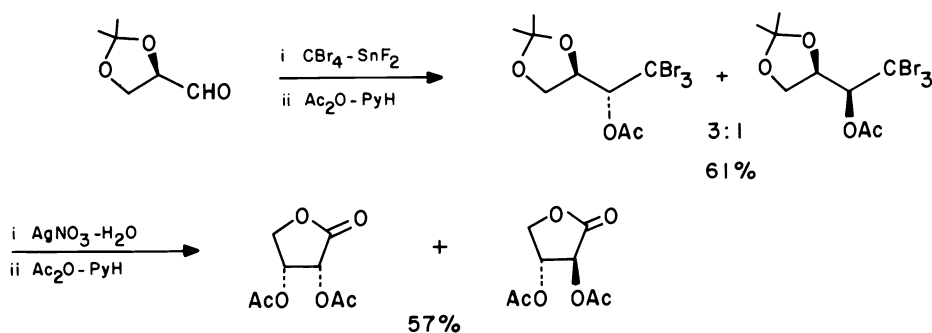
Stereoselective aldol reaction by the use of boron or stannous enolates.

The aldol reaction is one of the most fundamental and useful carbon-carbon bond forming reactions in organic synthesis, and enol borate is proven to be the most efficient as an intermediate, in the view of its mild reaction conditions and stereoselectivity (Ref. 23). Recently, stannous enolates have been found to have a characteristic property; those generated from α-bromoketones and Sn(0) react with aldehyde with high regiospecificity and high erythro selectivity (Ref. 24).

63-99% (erythro:threo = 90:10-94:6)
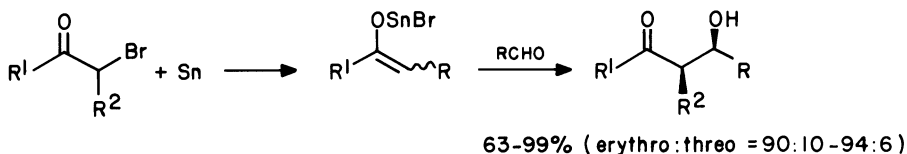
A successful method for the generation of stannous enolates has been newly developed. The stannous enolate, generated from various ketones and $Sn(OTf)_2$, is highly reactive and reacts even with ketones to give the corresponding aldols in high yields (Ref. 25).

71-86% (erythro:threo = 86:14 -> 95:<5)

76-84%
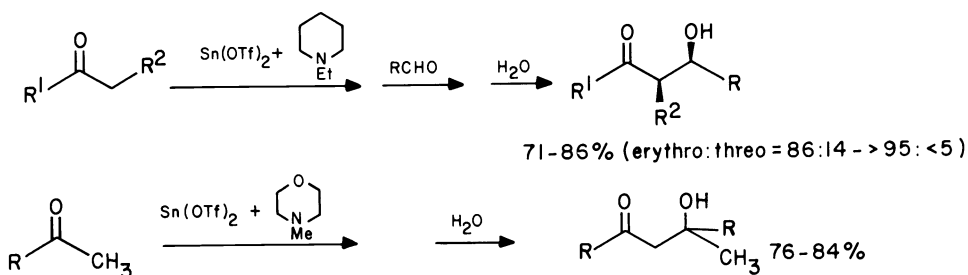
α,β-Dihydroxy-ketones are obtained by the reaction of α-dicarbonyl compounds and aldehydes in the presence of Sn(0), prepared from SnCl$_2$ and K, via the stannous enediolate.

3-4:1
70-87%
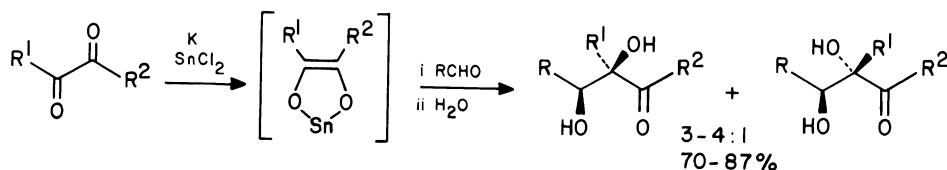
Stereoselective reactions by the use of 2-allyloxybenzimidazole derivatives.

The cadmium salt of the 2-allyloxybenzimidazole derivative (16) reacts with various aldehydes to afford adducts (17) with high regio- and stereoselectivity. The adducts (17) are subsequently transformed into trans-vinyloxiranes (18) (Ref. 26).

$R^2 = -(CH_2CH_2O)_3 Me$

57-98%
(α: γ = 75:25 -90:10)

18
(60-91%)
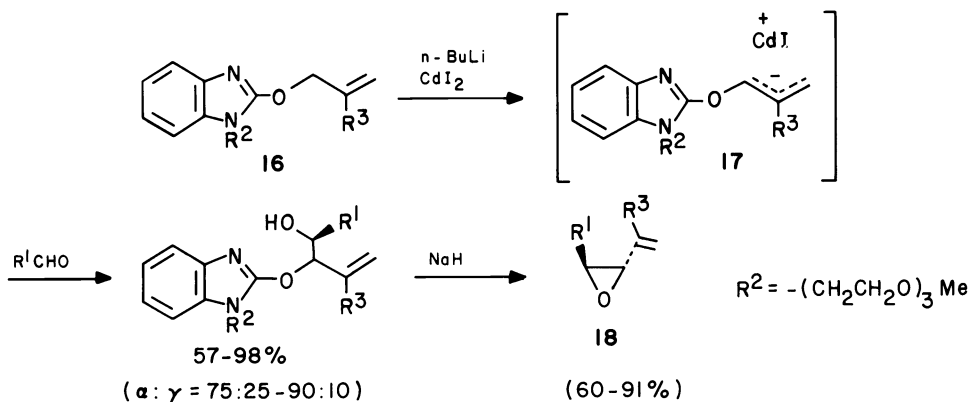
D- and L-Ribose are synthesized, starting from 2,3-O-isopropylidene-D- or-L-glyceraldehyde, respectively, by the application of this reaction (Ref. 27).

63%

82%

52%   54%

D-Ribose   91%

Imd =
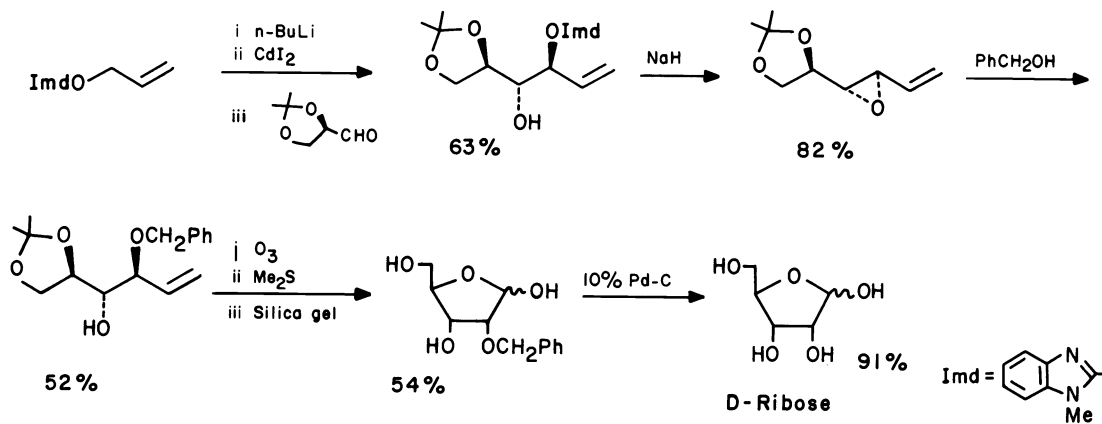
Convenient methods for the preparation of cis-vinyloxiranes (19) or homoallylic alcohols (20) are also explored by employing Et_3Al or R_3B in place of CdI_2 in the reaction (Refs. 28 and 29).
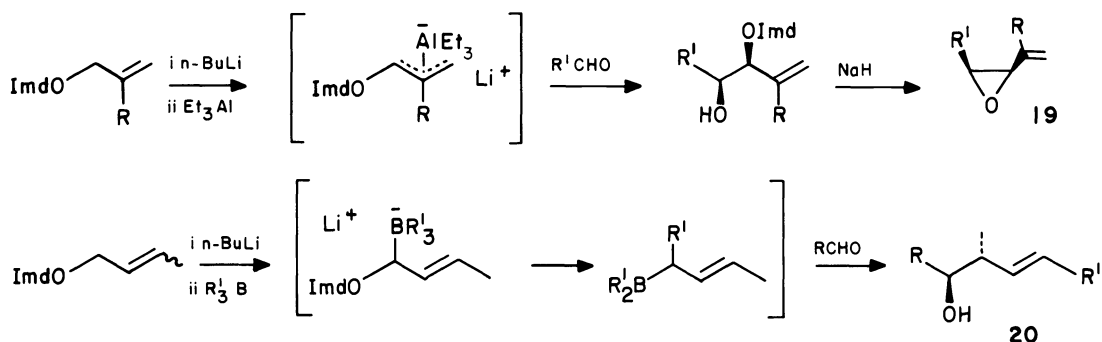

Novel 4-carbon building block for sugar synthesis.

Several sugar derivatives are successfully synthesized by employing the newly devised stereoselective carbon-carbon bond forming reactions starting from 2,3-O-isopropylidene-D- or-L-glyceraldehyde, as mentioned above. With these results in mind, a new and potentially useful 4-carbon building block for the L-sugars, 4-O-benzyl-2,3-O-isopropylidene-L-threose (21), is prepared conveniently starting from L-tartaric acid (Ref. 30).
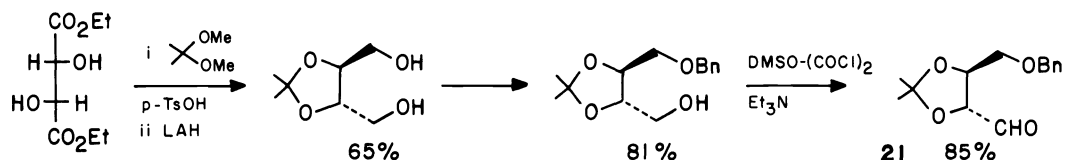
L-Tagatose and L-2-deoxygalactose are synthesized conveniently from the aldehyde (21) (Ref. 31).


1,2;3,4-Di-O-isopropylidene-L-tagatose
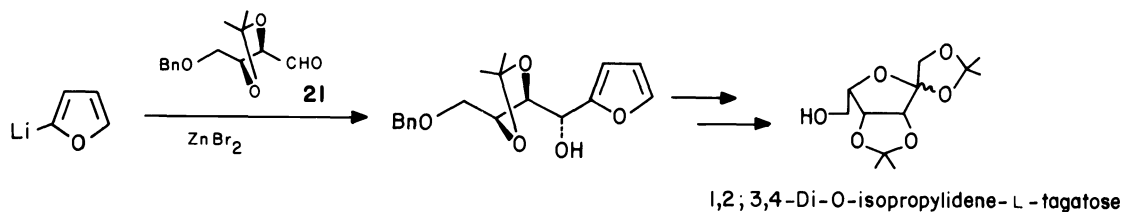
STEREOSELECTIVE GLYCOSYLATION REACTIONS.

In addition to the stereoselective synthesis of various monosaccharides, stereoselective reactions for the preparation of glycosides represent an important problem in the field of synthetic carbohydrate chemistry. However, the classical methods, which require the assistance of heavy metal salts or drastic reaction conditions, are still mostly employed in the synthesis of such compounds. Taking these disadvantages into consideration, new glycosylation reactions, which proceed under mild reaction conditions with high selectivity, are exploited.

Stereoselective synthesis of α-glucosides

Glucosides and disaccharides are prepared in good yields from 2-benzothiazoyl 2,3,4,6-tetra-O-benzyl-1-thio-D-glucopyranoside and various alcohols in the presence of cupric triflate. α-Glucosides are obtained predominantly by this method (Ref. 32).


86-94% ($\alpha:\beta$ = 60:40 -87:13)
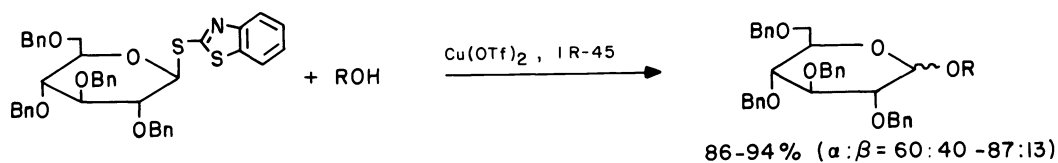
To achieve higher stereoselectivity, the combination of various sugar derivatives and activating reagents is examined. As a result, α-glucosides are prepared with high stereoselectivity by the reaction of β-glucosyl fluoride (22) with various hydroxy-compounds in the presence of SnCl$_2$ and AgClO$_4$ (Ref. 33).

76-96% (α:β = 80:20 - 92:8)
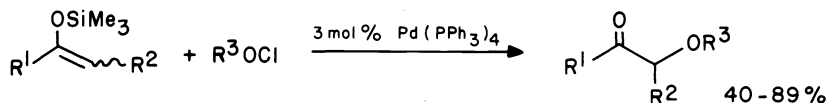
Stereoselectivity synthesis of β-glucosides.

The reaction of 3,5-dinitro-2-pyridyl-α-glucopyranoside (23), readily derived from 1α-hydroxysugar and 2-chloro-3,5-dinitropyridine, with alcohols proceeds smoothly in the presence of BF$_3$OEt$_2$ to afford the corresponding β-glucosides in good yields (Ref. 34).
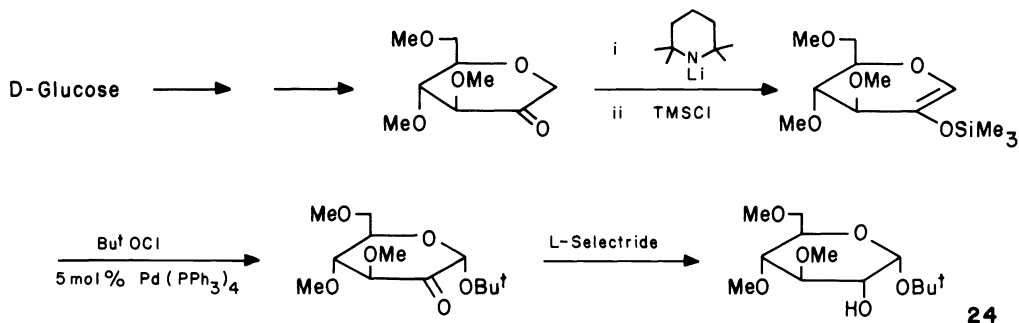

65-100% (α:β = 5:95 - 15:85)
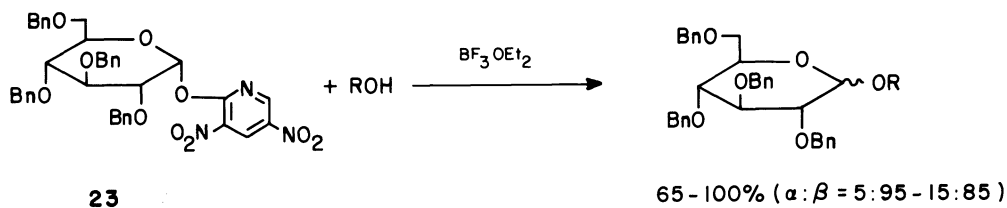
New approaches for the synthesis of glucosides.

An alkoxylation of silyl enol ethers   α-Alkoxyketones and α-ketoacetals are prepared in good yields from silyl enol ethers and alkyl hypochlorites, catalyzed by (Ph$_3$P)$_4$Pd (Ref. 35).


The reaction is applied to the synthesis of α-glucoside (24) as shown in the following equation.

A cyclization of hydroxy enol ethers   A stereoselective cyclization of (Z)-(2R, 3R, 4R)-6-cyclohexyloxy-1,3,4-tribenzyloxy-5-hexen-2-ol (25), promoted by Hg(OCOCF$_3$)$_2$ or PhSeCl, is successfully achieved. The 2-deoxy-α-hexopyranoside derivative (26) is obtained almost exclusively by the treatment of 25 with Hg(OCOCF$_3$)$_2$, followed by reductive work-up, while predominant formation of the β-anomer (27) is achieved by the reaction of 25 with PhSeCl, followed by deselenation (Ref. 36).
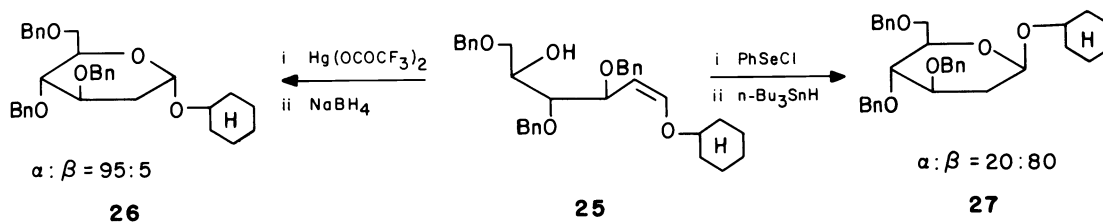
N-Iodosuccinimide also promotes the cyclization to give the α-glucoside derivative, and the disaccharide derivative (29) is synthesized with high stereoselectivity starting from the hydroxy vinylether (28).
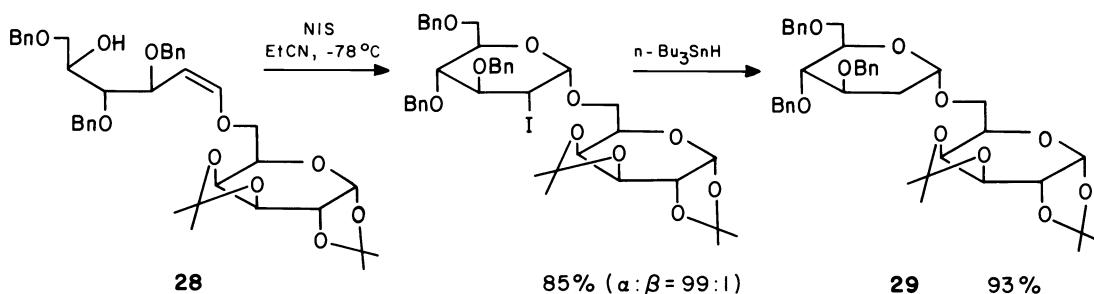
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