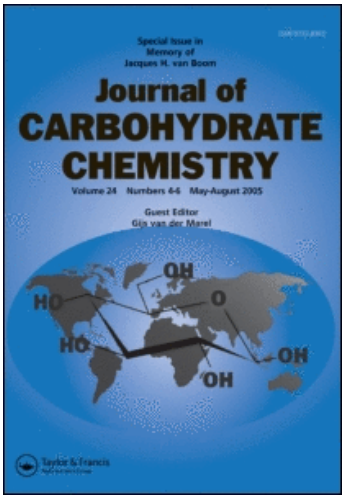

Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Acyclic Stereoselective Synthesis of Carbohydrates

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To cite this Article McGarvey, Glenn J. , Kimura, Masayuki , Oh, Taeboem and Williams, J. Michael(1984) 'Acyclic Stereoselective Synthesis of Carbohydrates', Journal of Carbohydrate Chemistry, 3: 2, 125 — 188
To link to this Article: DOI: 10.1080/07328308408058813
URL: http://dx.doi.org/10.1080/07328308408058813

J. CARBOHYDRATE CHEMISTRY, 3(2), 125-188 (1984)

REVIEW ARTICLE

ACYCLIC STEREOSELECTIVE SYNTHESIS OF CARBOHYDRATES

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ABSTRACT

This review examines recent syntheses of carbohydrates in which the target compounds are viewed as acyclic carbon frameworks. The synthetic approaches are divided into two categories in which critical asymmetry is placed either by (a) stereoselective carbon-carbon bond formation, or (b) stereoselective carbon-heteroatom bond formation. This account focuses its attention on the methodology utilized to place acyclic stereocenters as the key feature of the synthetic strategy.

INTRODUCTION

Throughout the past century, the chemical and biological fields have benefitted enormously from insights provided through carbohydrate-based investigations. Indeed, this class of compounds still has much to teach us, and, consequently, there is a considerable amount of present research effort devoted to the study of carbohydrates. This is certainly the case in the area of organic synthesis where interest in these compounds has substantially intensified in recent years. One indication of this

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trend is the increasing use of monosaccharides as chiral starting materials for the synthesis of complex natural products.[1,2] Perhaps even more telling is the ever-growing number of reported syntheses that have targeted the sugar structures themselves. Carbohydrates are attractive goals for synthetic effort by a number of criteria. The structures of these compounds are densely functionalized and highly asymmetric, thereby providing demanding tests of existing methodology and affording an excellent opportunity for the development of new methods. Additionally, carbohydrates are a ubiquitous class of compounds possessing appealing diversity of structure. Furthermore, these compounds fulfill crucial roles in key biological processes,[3] thus elevating the importance of synthetic access to rare naturally-occurring species and unnatural analogs for the investigation of these phenomena at a molecular level.

Synthetic approaches to carbohydrates may be divided into two broad categories: 1. those which transform existing carbohydrates into a new sugar species, and 2. those that afford the targeted compound through elaboration of "pro-sugar" substrates.[4] While the former approach has enjoyed substantial success,[5] often affording efficient access to rare or unusual sugar structures, many carbohydrates of interest are not well-served by this strategy since readily available sugars may be converted to the desired product only after an excessive number of synthetic operations. On the other hand, the "pro-sugar" approach draws upon a much wider range of available starting materials[6] and incorporates the potential to synthesize the product as either optical antipode or as a racemic modification.

This latter approach may be further subdivided into two categories based upon the type of substrate utilized in critical stereochemical operations to include: a. those featuring stereoselective manipulation of cyclic species, and b. syntheses involving asymmetric elaboration of acyclic carbon frameworks. The first of these approaches takes advantage of the vast body of knowledge that has been accumulated on selective transformations

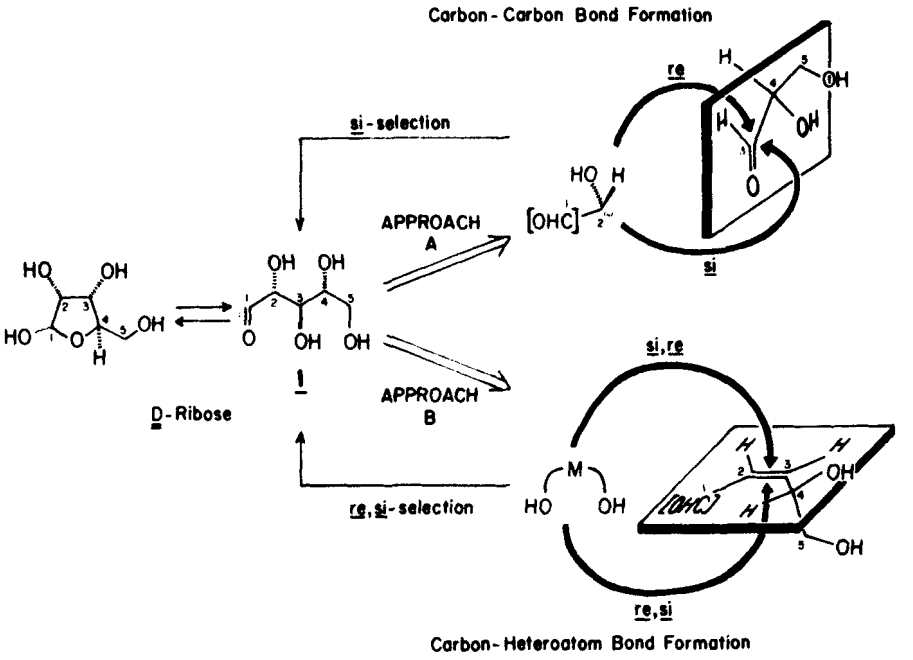


FIG. 1.

of five- and six-membered rings and has been recently reviewed.[7] This account will focus on the second of these approaches, one which has seen rapid development paralleling the impressive recent advances in the general area of acyclic stereoselective methodology.[8] The structures of carbohydrates clearly dictate that any synthetic assault on these compounds must concentrate on the task of controlling the asymmetric placement of heteroatoms on the carbon skeleton. As such, the following discussion will be organized according to the key stereochemical operation used in establishing the integrity of the asymmetric array.

Most of the present acyclic approaches are represented by the two pathways depicted in Fig. 1. A monosaccharide (e.g., D-ribose) may be viewed as a polyhydroxylated straight-chain species 1. From this perspective, most of the successful syntheses rely upon either: a. stereoselective carbon-carbon bond

formation (Approach A), or b. stereoselective carbon-heteroatom bond formation (Approach B).[9] As indicated, the requisite stereochemistry results from facial selection of the reagent acting on a suitable π-system, the steric preference being conferred by either the unsaturated substrate or the reagent.

This review will emphasize studies that have been carried out in the past ten years and will attempt to minimize overlap with existing compilations.[7] Discussion will also stress stereorational elaborations of "pro-sugar" species and will not address, for example, processes such as telomerization.[11] Additionally, space will not permit the inclusion of sugar-like molecules, in spite of the fact that synthetic approaches to these compounds will undoubtedly uncover chemistry useful for the preparation of carbohydrates.[12] Finally, it is not the endeavor of this account to detail every stereoselective acyclic synthesis culminating in a sugar, but, rather, to convey what the successful strategies entail, with particular attention being given to the stereoselective bond-forming processes.

APPROACHES via STEREOSELECTIVE CARBON BOND FORMATION

The first general group of approaches features the stereoselective addition of carbon centers to carbonyl compounds and imines. Through this strategy the carbon skeleton of the sugar is assembled with simultaneous establishment of one or more of the required stereocenters. These condensation reactions fall into two categories: 1. alkylation reactions, and 2. cycloaddition reactions, including Diels-Alder reactions and dipolar cycloadditions.

1. Alkylation Reactions

A concise route to carbohydrates is offered by asymmetric alkylation reactions with suitable electrophiles in the manner suggested in Fig. 2. The key feature of this "hypothetical" synthesis of D-ribose is the control of the stereocenters at C2 and C3 during the carbon-carbon bond-forming process. Further

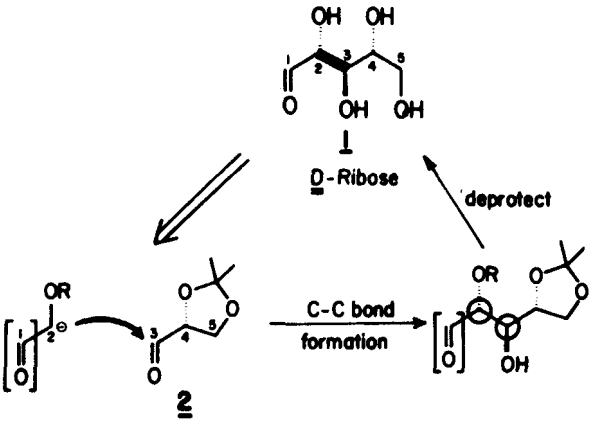
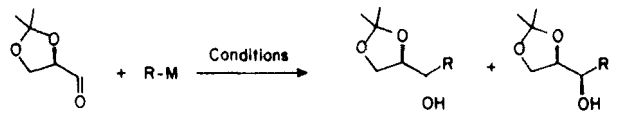


FIG. 2.

enhancing the attractiveness of this route is the availability of pro-sugar species 2 in either enantiomeric form through straightforward degradation of inexpensive sugars.[13] A variety of appropriate nucleophilic reaction partners are easily imagined which may allow placement of all new stereocenters in the product relative to the single fixed position in 2.

It is not surprising, therefore, that 2,3-O-isopropylidene-D (or -L)-glyceraldehyde (2) has become an extremely valuable chiral building block for carbohydrate synthesis. Investigations examining the critical question of stereoselection resulting from nucleophilic attack upon this aldehyde have yielded the data compiled in Tables 1, 2, 3, and 4. At this point, it is appropriate to discuss in general terms the rationale for stereoselection in these bond-forming processes, since such lays the groundwork for many of the diastereoselective syntheses that are addressed later in this review. Fig. 3 applies the various transition state models that have been proposed to explain asymmetric induction in the kinetic alkylation of carbonyl compounds. Both syn and anti product selection may be predicted by one chelated (A and B, respectively) and two non-chelated models (C,D and E,F, respectively). Recent theoretical findings

TABLE I. Condensation of 2 with Localized Carbanionic Species



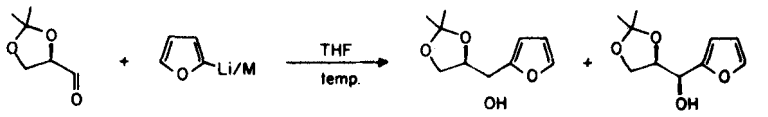
2 anti syn

Entry	R	M	Conditions	anti : syn	Ref.
1	Me	MgI[a] or MgBr	Et_2O/0°[a],-50°	67 : 33	14[a],15
2		Li	Et_2O/-50°	60 : 40	15
3	n-Bu	MgBr	Et_2O/-78°	75 : 25	15
4		Li	Et_2O/-78°	69 : 31	15
5		$Ti(Oi\text{-}Pr)_3$	Et_2O/22°	90 : 10	15
6	Ph	MgBr or Li	Et_2O/-78°	48 : 52	15
7		0.5 Zn	Et_2O/-40°	79 : 21	15
8		$Ti(Oi\text{-}Pr)_3$	Et_2O/-78°	24 : 76	15
9		$Ti(Oi\text{-}Pr)_3$	THF/-78°	9 : 91	15
10	$Me_2\overset{\oplus}{S}-\overset{\ominus}{C}H_2$	—	THF-DMSO/-13°	60 : 40[b]	16
11	$Me_2\overset{\oplus}{S}(O)-\overset{\ominus}{C}H_2$	—	THF-DMSO/RT	70 : 30[b]	16
12	$H_2C=CH$	MgCl	THF/21-60°	60 : 40	17
13	$HC\equiv C$	MgBr	THF/RT	44 : 56	18
14	Br_3C	$SnBrF_2$	DMSO/RT	75 : 25	19
15	Cl_3C	—[c]	Cl_4C-Cl_3CH	67 : 33	20
16	$(EtO)_2CHC\equiv C$	MgBr	—[d]	major : minor	21
17	$H_2C=CCH(OEt)_2$	Li	THF/-70°	70 : 30	22

[a] Identity of major and minor isomers made by analogy. [b] Products are the corresponding epoxides.
[c] Nucleophile is generated electrochemically. [d] Conditions not specified.

argue strongly in favor of Felkin model F over the alternative non-chelated models.[3,4] In the case at hand, the nucleophile would be expected to approach the carbonyl at an oblique angle near the adjacent hydrogen with the vicinal oxygen substituent occupying a position perpendicular to the carbonyl π-system. The data in the tables may then be evaluated in terms of models A, B, and F. The experimental results reveal a reasonably general trend toward anti-selection in these condensations, with only a few exceptions

TABLE 2. Effect of Metals on Stereoselectivity.[23]

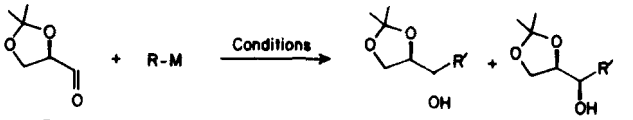


2 anti syn

Entry	M/temp.	anti : syn	Yield
1	none/-78°	40 : 60	69%
2	$MgBr_2$/0°	50 : 50	49%
3	$SnCl_4$/0°[a]	95 : 5	58%
4	$ZnCl_2$/0°	90 : 10	60%
5	$ZnCl_2$/-78°	>95 : <5	10%
6	$ZnBr_2$/0°	95 : 5	75%
7	ZnI_2/0°	>95 : <5	57%

[a] Carried out in PhMe.

TABLE 3. Condensation of 2 with Allylic Carbanion Species.

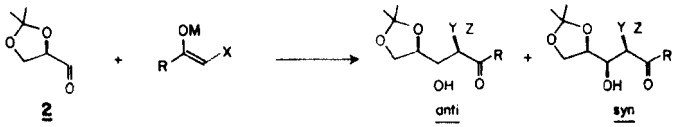


2 anti syn

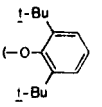
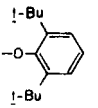
Entry	R-M	Conditions	R'	anti : syn	Ref.
1	Allyl-MgBr	Et_2O/-78°	Allyl	60 : 40	15
2	Allyl-Ti(O-i-Pr)$_3$	THF/-100°	Allyl	71 : 29	15
3	$(Allyl)_2Cr$	THF/25°	Allyl	70 : 30	15
4	$(Allyl)_2Zn$	Et_2O/-78°	Allyl	84 : 16	15
5	$(Allyl)_2Zn$	THF/-78°	Allyl	91 : 9	15
6	Allyl-I/SnF_2	DMI[a]-DMF/0°	Allyl	81 : 19	24
7		THF/-100°		100 : 0[c]	25

[a] DMI = 1,3-dimethyl-2-imidazolidinone. [b] Imd = 1-methyl-benzimidazole. [c] About 8% γ-attack was observed.

TABLE 4. Aldol Condensations with Aldehyde 2.



2

Entry	M	R	X	Y	Z	anti : syn	Ref.
1	Li	OMe	H	H	H	85 : 15	26
2	BPh_2[a]	OEt	H or HgOAc	H	H	93 : 7 (>90 : 10)[b]	27
3	Li		H	H	H	66 : 34	26
4	Li	t-Bu	H	H	H	>95 : >1	26
5	Li		H	H	H	66 : 34	26
6	Li	OMe	Me	Me H	H Me	40 : 0 60 : 0	26
7	Li		Me	Me H	H Me	0 : 15 85 : 0	26
8	Li	t-Bu	Me	Me H	H Me	0 : 15 85 : 0	26
9	Li		Me	Me H	H Me	47 : 5 17 : 31	26
10	ZnCl[c]	OEt	Cl	Cl H	H Cl	80 : 20[d]	28

[a] Prepared by mixture of EtOC≡CH, Ph_2BOH, $Hg(OAc)_2$ [b] Product with the hydroxyl group acetylated. [c] Prepared by treatment of EtOC≡CH with $HgCl_2$ and pyridinium-N-oxide, then Zn* [d] Anti:syn products were isolated as an epimeric mixture of chlorides.

(most notably, entries 8 and 9 in Table 1). While occasional participation by chelate B cannot be discounted, these data are most generally rationalized in terms of Felkin's model F (although these models complement each other). Regardless, the control over the formation of the new stereocenter is seen to depend upon a sensitive balance of reaction conditions, metal ion identity, and the nature of the nucleophile.

These condensations often proceed with useful levels of stereoselection to afford promising substrates for carbohydrate

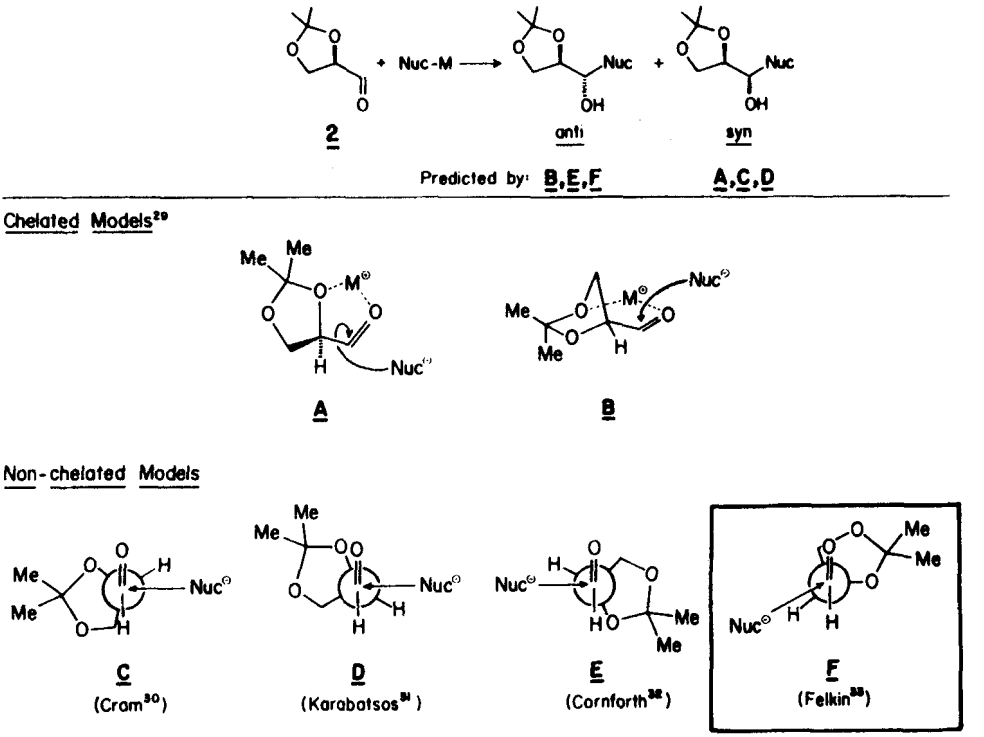


FIG. 3.

synthesis. For example, 2-deoxy-D-*erythro*-pentose (i.e., "2-deoxy-D-ribose") may be obtained through straightforward manipulation of allylation and aldol products (3 and 4 in Fig. 4). The preparation of more highly functionalized sugars results from the use of more sophisticated nucleophiles. Some representative examples are depicted below (Fig. 5). In the first route, one from Mukaiyama's laboratory, all the stereocenters are placed for D-*erythro*-pentulose (i.e., "D-ribulose"), in the initial adduct 5, the product being realized through simple degradative unmasking of the appended furan.[23] In a synthesis of D-ribose by the same group, two stereocenters are fixed in the oxyallylation of chiral aldehyde 2 to result in 6, which is poised for conversion to the final product.[25] By a completely analogous

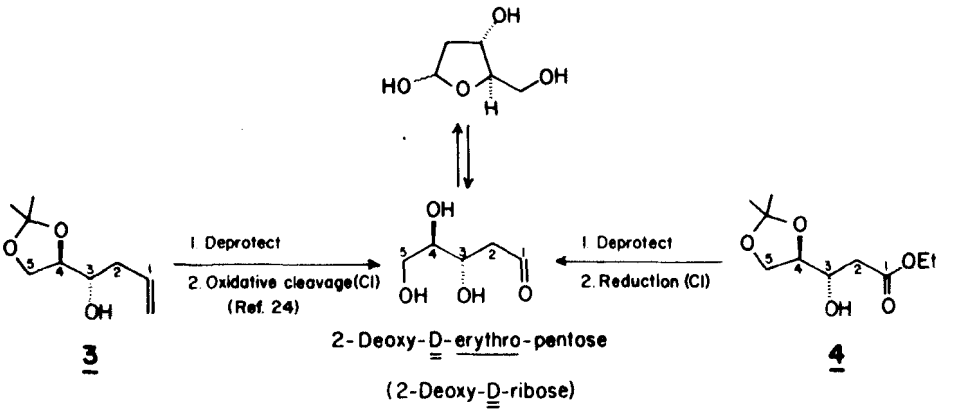


FIG. 4.

sequence germinating from enantio-2, the rarer L-ribose was also efficiently prepared. The last two routes feature the placement of the ultimate stereocenter by taking advantage of intervening cyclic species. Depezay and Le Merrer cyclized adduct 7 to pyranose 8 which was subsequently subjected to direct epoxidation/ring-opening to give only the required axial alcohol at C2 for the methyl glycoside of hamamelose.[22] In another contribution from the Mukaiyama laboratories, the epimeric center at C2 in condensation product 9 is corrected through base-induced ring-closure/equilibration to yield the more stable 10. This epoxide was then utilized to introduce nitrogen to afford the precursor to an amino sugar 11.[28]

In another approach to aminopentoses, the condensation of nucleophiles already incorporating nitrogen has been examined. A Japanese group has condensed both bisglycinatocopper(II) 12 and N-pyruvylideneglycinatoaquocopper(II) 13 with aldehyde 2 to give compound 11 as the predominating isomer (Fig. 6).[35] In a strategically similar approach, Mukaiyama's group studied the selection afforded by enolates of glycine bearing enantiomeric chiral auxiliaries (14 and 15) upon addition to 2 (Fig. 7).[36] In this way, selection between the D-arabino (16) or D-ribo (17)

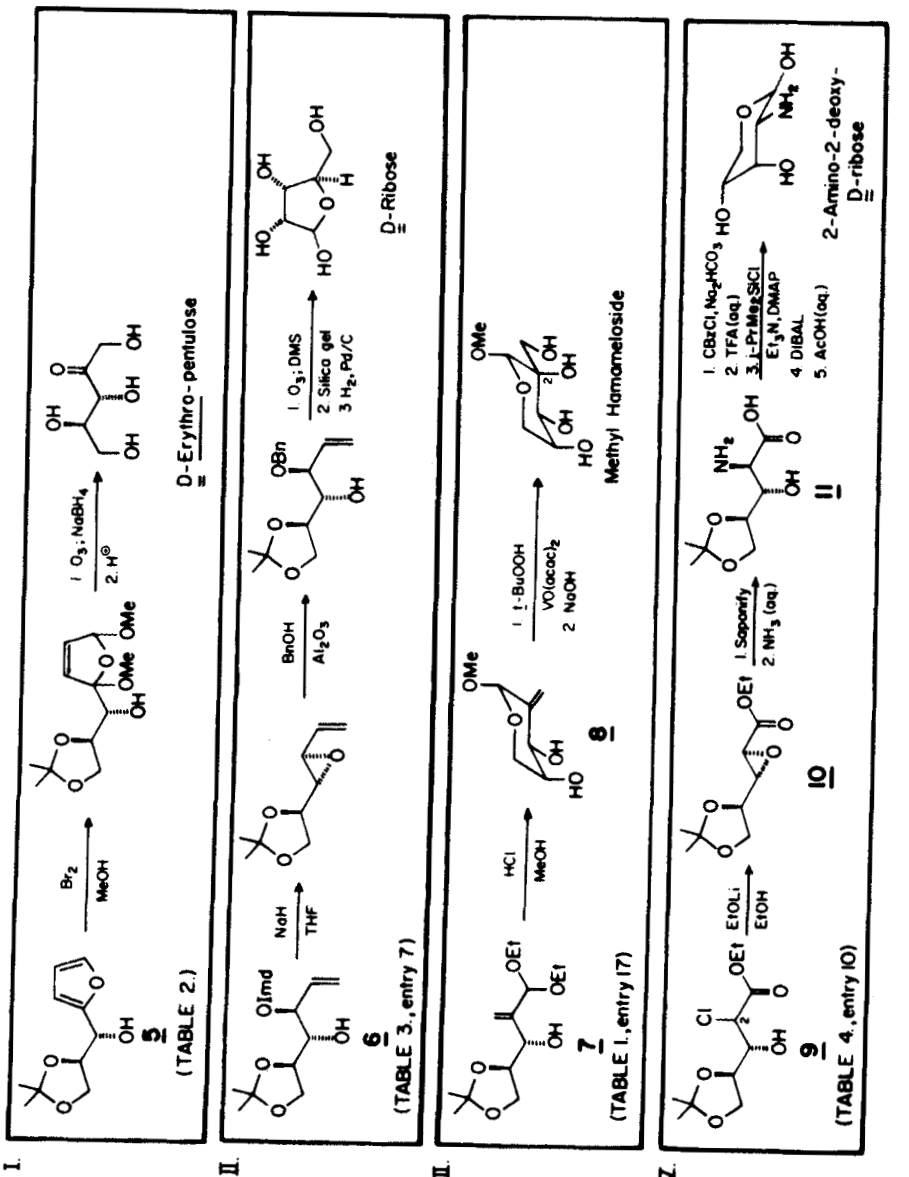


FIG. 5.

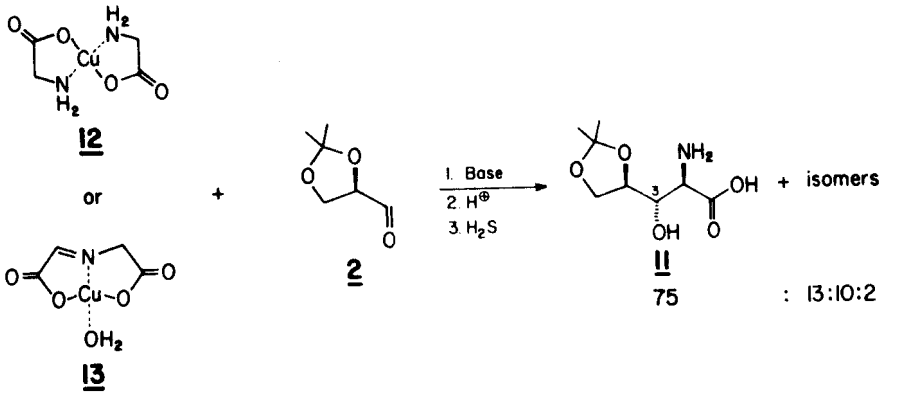


FIG. 6.

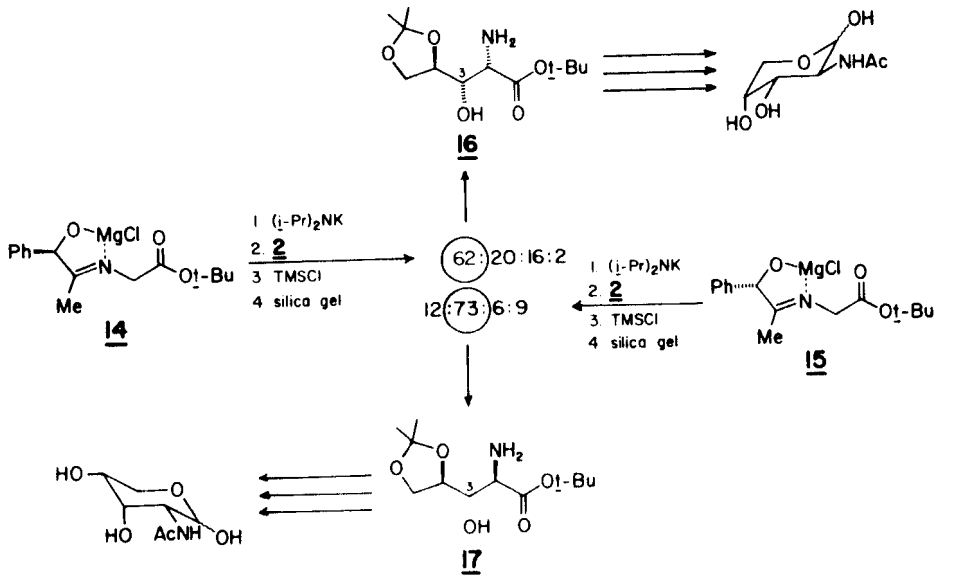


FIG. 7.

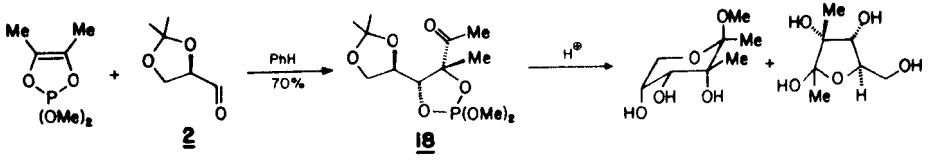


FIG. 8.

arrays is available. It bears noting that Felkin-predicted[33] attack on aldehyde 2 once again controls the stereochemistry at C3.

In a unique approach to various branched-chain hexoses, David and co-workers have exploited the Ramirez dioxophospholen condensation to obtain adducts solely of stereostructure 18 (Fig. 8).[37] The stereoselection of this four-carbon nucleophile is consistent with the stereochemical arguments of the previous examples.

With exception of the David synthesis, discussion has been directed toward the preparation of pentoses through two-carbon homologation of aldehyde 2. This strategy is very simply extended to the hexoses by substituting a four-carbon pro-sugar electrophile. Attention will now be turned to compounds 19-22 (Fig. 9), which are available in optically-pure form through enzymatic and chemical methods from inexpensive starting materials.[38] It is clear that through similar means many other useful fragments should be obtainable which would further extend the preparative utility of this approach.

Once again, the crucial question of stereoselectivity during the carbon-carbon bond-forming process must be considered. Specifically, what effect will the additional asymmetric center at the β-position in 19-22 have upon condensation reactions? This problem is addressed by the data in Tables 5, 6, and 7. In general, these results follow the Felkin model[33] prediction of anti-stereoselection seen previously. As was the case with aldehyde 2, however, there are exceptions to this trend which serve as a reminder that the factors influencing this acyclic stereoselection are still imperfectly understood.

Nevertheless, many of these condensations exhibit high selectivity and afford materials that are well-suited for elaboration into carbohydrates. The efficiency of this approach to hexoses is nicely illustrated by Roush's synthesis of a fully derivatized D-fucose (Fig. 10).[46] Condensation of the allyl boronate 23 with 21 (prepared from L-threonine) completes the carbon skeleton and places all the stereocenters with greater than

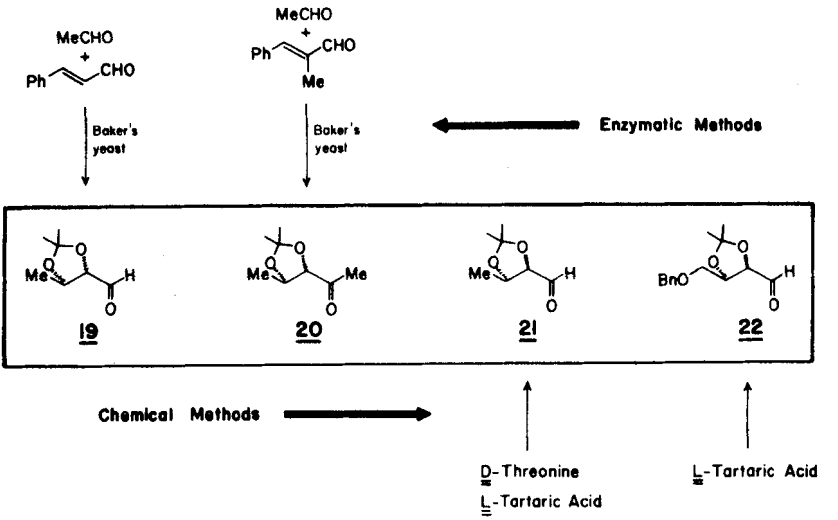
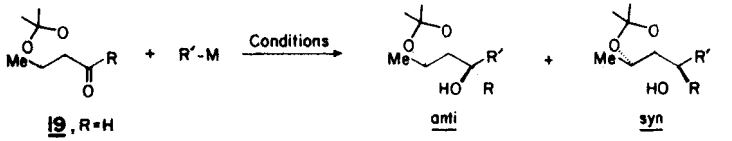
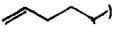
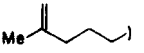


FIG. 9.

TABLE 5. Stereoselective Condensations of **19**/**20** with Carbon Nucleophiles.

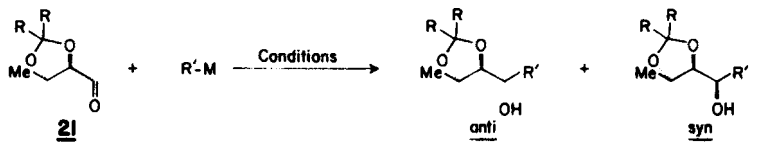


19, R=H
20, R=Me

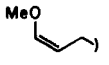
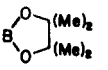
Entry	R	R′	M	Conditions	anti : syn	Ref.
1[a]	H	Et	MgBr	THF/-78°	40 : 60	39
2	H		MgBr	THF/-70°	40 : 60	40
3	H	n-Decyl	MgBr	THF/-78°	60 : 40	41
4	H	Allyl	MgBr	THF/-78°	60 : 40	42
5	H	Allyl	MgBr	Et_2O/-78°	70 : 30	43
6	H	Allyl	0.5 Zn	Et_2O/-78°	~95 : 5	43
7	Me	$ArCH_2CH_2$	MgBr	THF/-78°	0 : 100	44
8	Me		MgBr	Et_2O/2°	0 : 100	45
9	Me	Allyl	MgBr	Et_2O/-78°	100 : 0	43
10	Me	Allyl	0.5 Zn	Et_2O/-78°	100 : 0	43

[a] Cyclohexylidene derivative was used in place of the isopropylidene species.

TABLE 6. Stereoselective Condensations of **21** with Carbon Nucleophiles.

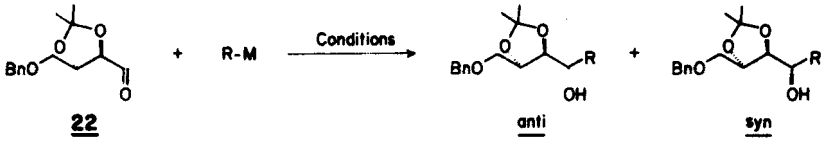


21 anti syn

Entry	R	R′	M	Conditions	anti : syn	Ref.
1	$(CH_2)_5$	Et	MgBr	THF/-78°	20 : 80	39
2	Me	Allyl	MgBr	THF/-78°	20 : 80	42
3	Me	Allyl	MgBr	Et_2O/-78°	70 : 30	43
4	Me	Allyl	0.5Zn	Et_2O/-78°	95 : 5	43
5[a]	$(CH_2)_5$			Hex./-78°→RT	>95 : <5[b]	46

[a] The enantiomer of **21** was used. [b] The product possesses anti,syn-relationships about the two newly formed stereocenters. See text for more complete description.

TABLE 7. Stereoselective Condensations of **22** with Carbon Nucleophiles.



22 anti syn

Entry	R	M	Conditions	anti : syn	Ref.
1		Li	THF/-78°	63 : 37	47
2		$Li/ZnBr_2$	THF/-78°	98 : 2	47
3	Allyl	$0.5SnBr_2$	THF/-100°	90 : 10	48
4	Allyl	$SnIF_2$	THF/0°	92 : 8	49
5	$Me_3SiC{\equiv}C$	Li	DME/-78°	80 : 20	49
6	EtO_2CCH_2	Li	THF/-78°	83 : 17	49
7	EtO_2CCH_2	Li	THF/-100°	90 : 10	49
8	t-BuO_2CCH_2	Li	THF/-78°	74 : 26	49
9	EtO_2CCH_2	SnBr	THF/RT	87 : 13	49

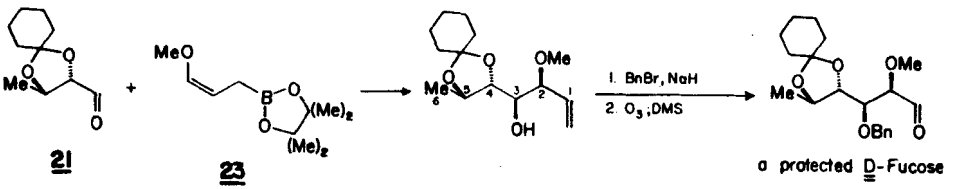


FIG. 10.

95% diastereoselection. Routine protection and oxidative cleavage completes the three-step sequence.[50] Exemplifying the versatility of this synthetic strategy is Mukaiyama's recent study that incorporates the extremely useful pro-sugar compound 22 (Fig. 11).[48] Stereoselective allylation affords 24, which is in a form that allows selective manipulation of the positions that become C3 and C6 in the final hexose. This was exploited to furnish several rare L-sugars, including an amino sugar through replacement of the C3 hydroxyl group by an amine with inversion (24 → 25).

Amino sugars are compelling targets for synthetic studies because of their role in biological processes and their presence in many important therapeutic agents. An alternative approach to these compounds is offered by replacing the carbonyl with an imine in the electrophilic component of the carbon-carbon bond-forming sequence. A summary of stereoselective condensations of this type is presented in Table 8. Any rationalization of these results must recognize the electron-donating abilities of nitrogen and, therefore, give more consideration to possible chelate models for transition states leading to products. However, unlike organomagnesium and organolithium reagents, stabilized organozinc nucleophiles favor exclusive formation of anti products, suggesting intervention of the Felkin or β-chelate model (or both, see B and F in Fig. 3). These adducts have been efficiently converted into protected forms of the important amino sugars L-daunosamine and L-ristosamine (Fig. 12).[52,54]

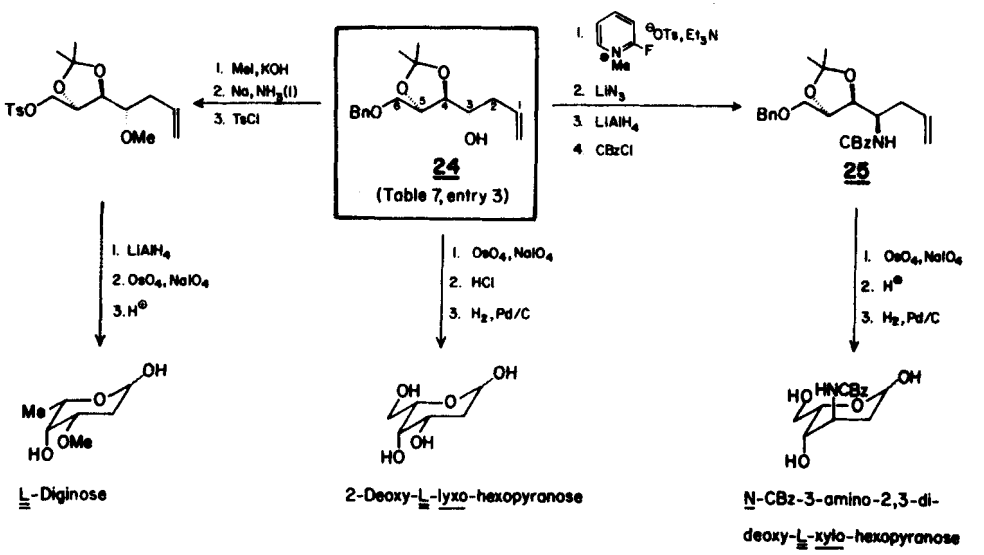
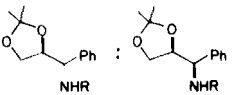
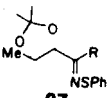
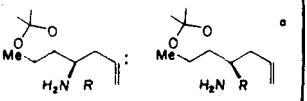
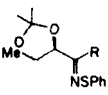
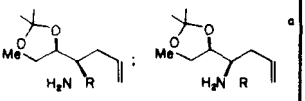
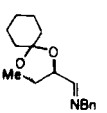
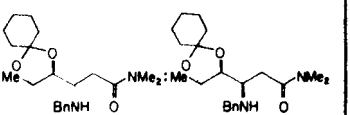
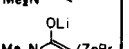


FIG. 11.

2. Cycloaddition Approaches

Another conceptually attractive approach targets not the acyclic form of carbohydrates but, rather, the pyranose form. Viewing an unsaturated species such as 30 as a precursor to the desired hexose, a heteroatom Diels-Alder reaction offers an efficient means of assembling the carbon skeleton in one operation (Fig. 13). While the Diels-Alder reaction of substituted butadienes with carbonyl compounds has been known for sometime, its utility has been attentuated principally by problems in reactivity.[55] This problem was circumvented in earlier work through the use of activated carbonyl components, such as ketomalonates and glyoxylates.[56] More germane to the emphasis of this review, attempts have been made to prepare optically active carbohydrate precursors by this method through the attachment of chiral auxiliaries to either the diene,[57] the dienophile,[58] or both.[59] While the level of asymmetric induction in these condensations has, in general, been disappointing, some notable

TABLE 8 Stereoselective Condensations with Imines

Entry	Imine	Nucleophile	Products (anti : syn)	Ref
	 **26**			
1	R = H	PhLi	26 : 74	51
2	R = Bn	PhLi	37 : 63	51
3	R = H	PhMgBr	91 : 9	51
4	R = Bn	PhMgBr	78 : 22	51
	 **27**		 [a]	
5	R = H		30 : 70	52
6	R = Me		0 : 100 [b]	53
7	R = H		100 : 0	52
	 **28**		 [a]	
8	R = H		55 : 45	52
9	R = Me		0 : 100 [b]	53
10	R = H		100 : 0	52
	 **29**			
11			33 : 67	54
12			100 : 0	54

[a] Products after acid hydrolysis. [b] This result was obtained starting with a mixture of **27** and **28** (R = Me).

successes have been realized. For example, David and co-workers have used this approach to prepare the antigenic determinant of blood group A (Fig. 14).[59b] In this case, chiral dienophile 31 and chiral diene 32 conspire to favor, following Lewis acid-induced equilibration, adduct 33 in respectable yield. Fucosylation gives the trisaccharide precursor 34, which is converted by a straightforward sequence to the final product.[60]

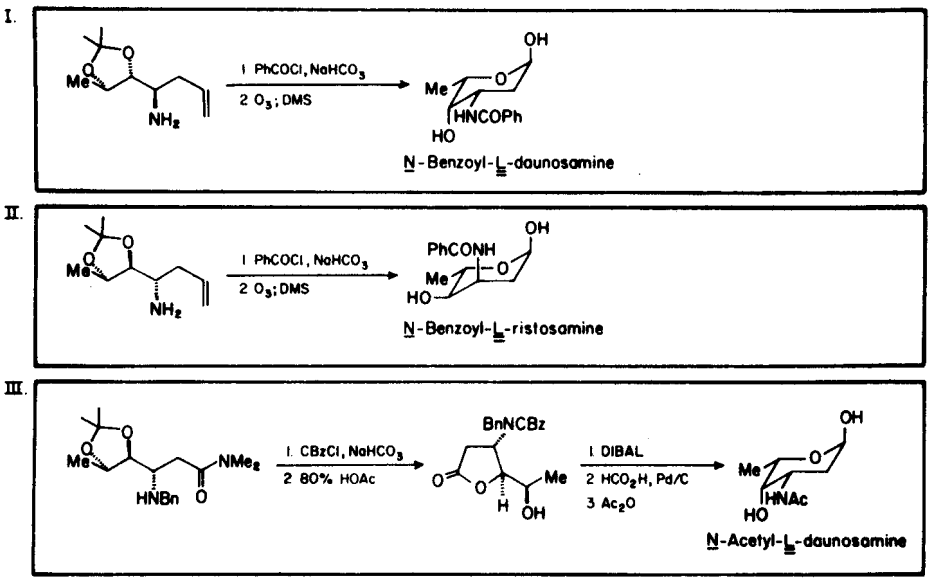
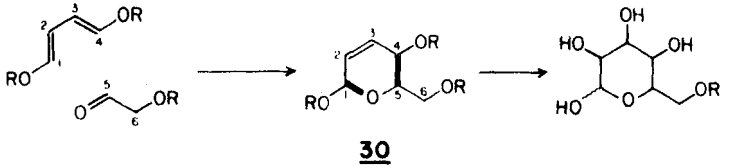


FIG. 12.

The heteroatom Diels-Alder approach as described above suffers from the structural limitations placed upon the reaction partners. In an effort to overcome this shortcoming, the use of high pressure to facilitate the cycloaddition process has been examined. It was found by Jurczak and co-workers that pressures of 15-23 kbar forced the condensation to take place with simple unactivated carbonyl compounds at moderate temperatures (20°C-65°C). As part of the development of a general strategy for the synthesis of sugars, these workers examined the high pressure cycloaddition of 1-methoxybutadiene with aldehyde 2 (Fig. 15).[62] The adducts are formed in high yield with a strong preference for the Felkin-predicted[33] approach to the chiral aldehyde 2, along with a respectable endo-preference. The elaboration of these adducts into carbohydrates awaits future disclosure.

The most significant development in this area of Diels-Alder chemistry has been the use of electron-rich dienes with Lewis acid catalysis. In particular, Danishefsky and co-workers have



30

FIG. 13.

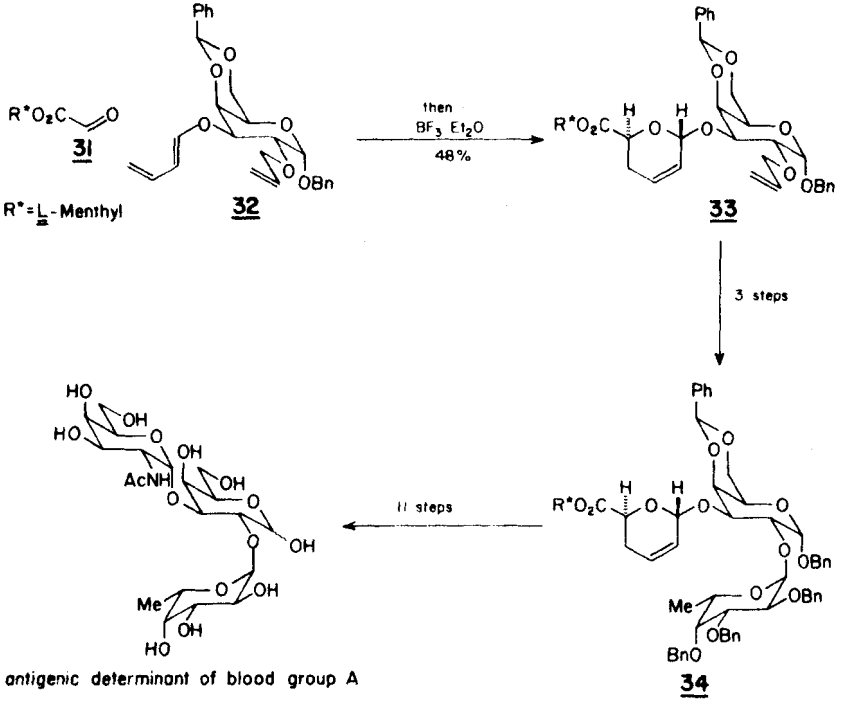


FIG. 14.

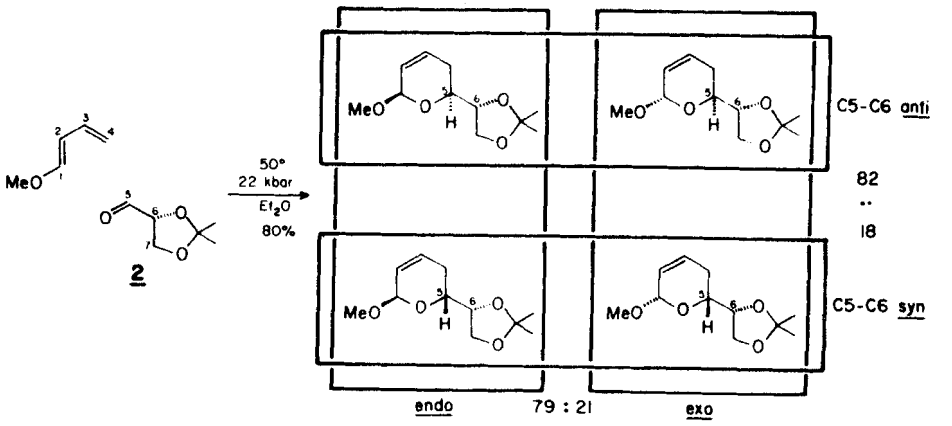


FIG. 15.

found that many highly oxygenated dienes smoothly condense with unactivated aldehydes in the presence of such catalysts as $ZnCl_2$ or $BF_3 \cdot Et_2O$ to give 2-substituted 2,3-dihydro-β-pyrones.[63,64] As illustrated in Fig. 16, these cycloadducts are efficiently transformed into a variety of sugar species. These cyclocondensations were presumed to proceed through the intermediacy of a methoxy-enol ether species such as 38, which is transformed under the reaction conditions to the observed enones 39-42. Diene 35 offers efficient entry to 4-deoxyhexoses (I and II), while the completely oxidized sugar series are realized by simply using more highly oxygenated dienes (e.g., 36 and 37), as exemplified by the syntheses of derivatives of DL-talose and DL-lincosaminide(III and IV).

The mechanistic details of this condensation have also been the subject of investigations by the Danishefsky group. The results of this study indicate that these reactions proceed via a pericyclic transition state unless a very aggressive Lewis acid is used (e.g., $BF_3 \cdot Et_2O$), in which case, a stepwise aldol-like process may be promoted.[65] As a consequence of the availability of two mechanistic pathways, products of different relative stereochemistries may be selected through judicious choice of the reaction conditions employed (See I and II in Fig. 17). An important facet of these cyclocondensations is the high level of diastereofacial discrimination often exhibited in reactions with aldehydes bearing α-asmmetry (See boxed stereorelationships in Fig. 17). As in the case of nucleophilic additions to chiral aldehydes, the major diastereomer is consistent with a transition state resembling the Felkin model.[33,68]

The value of this high degree of stereocontrol has been preliminarily demonstrated in the context of carbohydrate synthesis (Fig. 18).[67] Adduct 43, available in either enantiomeric form, may be transformed into pentoses or hexoses depending upon which carbon(s) is(are) oxidatively excised. Without removal of part of the carbon skeleton, this approach is also applicable to heptose synthesis.

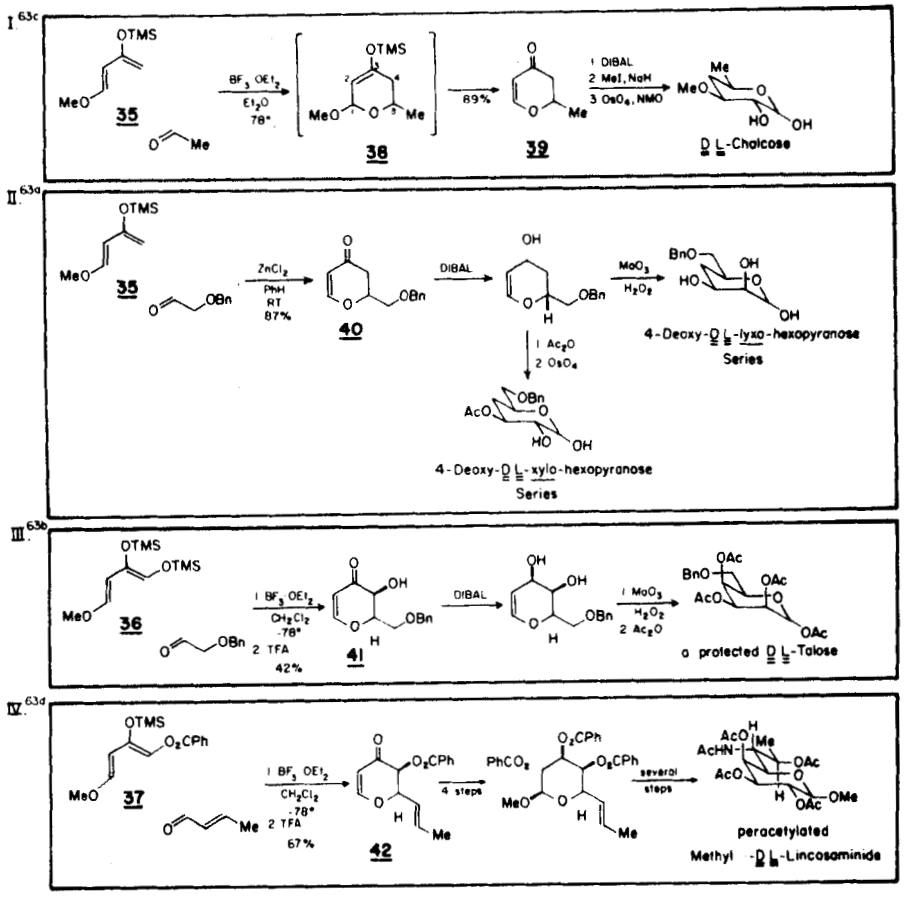


FIG. 16.

In an important recent discovery, the Danishefsky group has found that the lanthanides [e.g., $Eu(fod)_3$][69] act as extremely mild catalysts for these reactions, cleanly affording methoxy-enol ethers of the type 38 without *in situ* decomposition to an enone.[70] Moreover, the products are isolated in high yield favoring the *cis*-disposition of the groups at C1 and C5. Of conspicuous importance is the observation that optically active europium catalysts afford products with enantiomeric enhancement.[70] It has been recently demonstrated that adducts possessing high enantio-

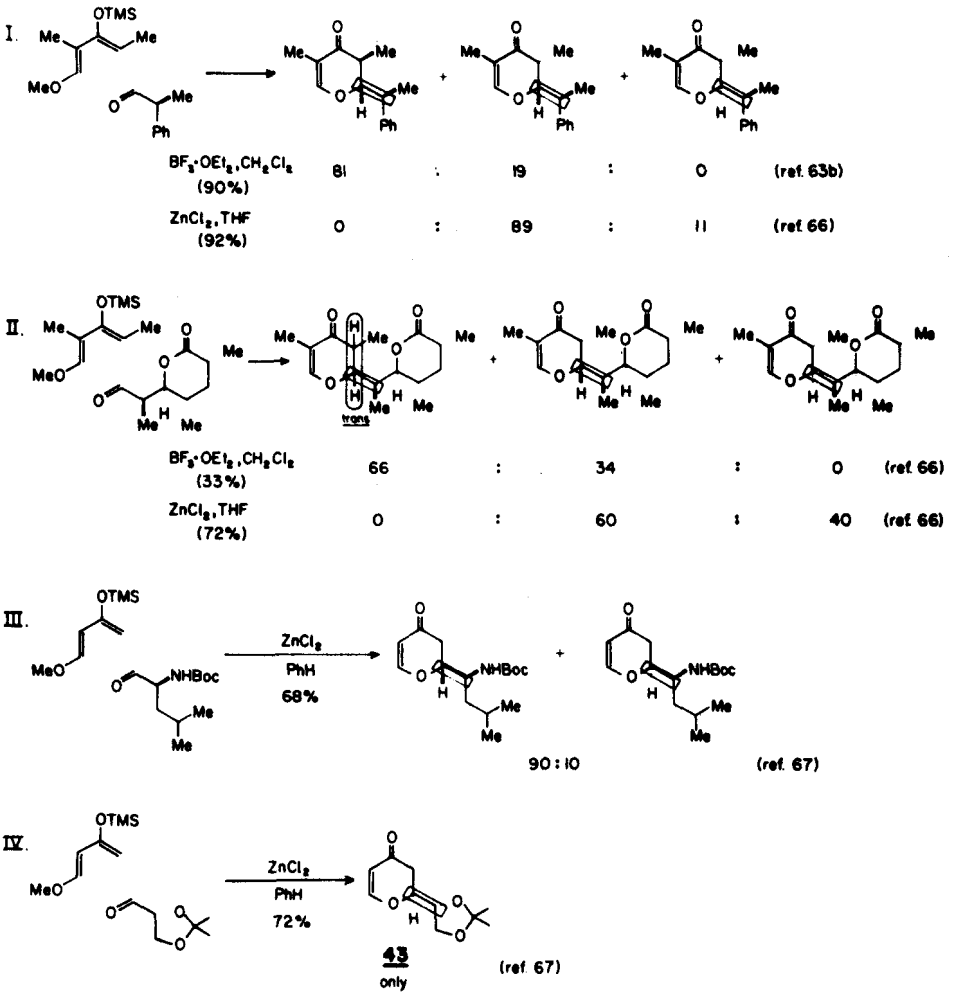


FIG. 17.

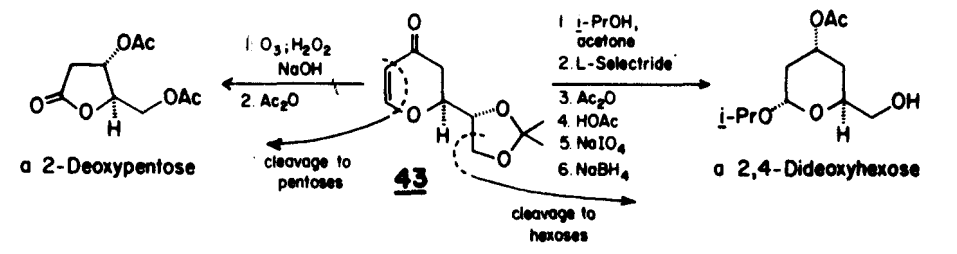


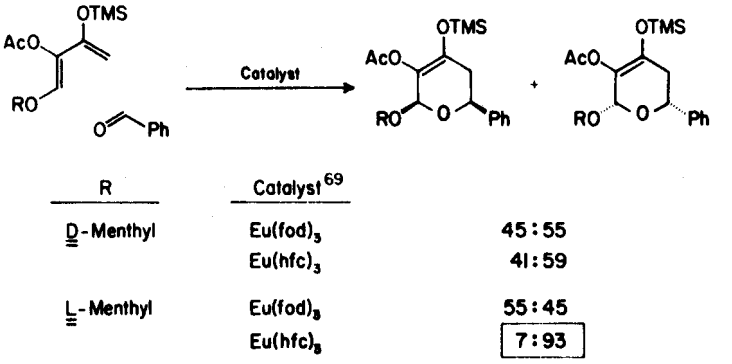
FIG. 18.

meric excesses may be realized by augmenting the directing effects of the chiral catalyst with an appropriate chiral auxiliary on the diene (Fig. 19).[70c] While the mechanistic features of this process are unclear at present, the considerable synthetic utility of this condensation has been demonstrated in the preparation of an optically pure 4-deoxy-L-gluconic acid derivative.[70c]

Complementing the Diels-Alder approach to carbohydrates, several sugar syntheses have successfully utilized dipolar cycloadditions of nitrile oxides and nitrones. For example, Muller and Jäger have condensed the nitrile oxide derived from the t-butyl ether of 2-nitroethanol 44 with furan to give a bicyclic array 45 (Fig. 20).[71] This rigid structure may be used as a vehicle for establishing acyclic stereocenters, as exemplified by its two step conversion to a protected version of 5-epi-norjirimycin with $\geq$95% diastereoselection in about 26% overall yield.

Toward the preparation of carbohydrates in optically discrete form, chiral nitrones, which are readily formed from chiral aldehydes, have been examined in several studies. In the approach of Vasella and Voeffray to norjirimycin and 1-deoxy-norjirimycin, a sugar is used as a chiral auxiliary for the nitrone (Fig. 21).[72] The nitrone (47) derived from the condensation of chiral oxime 46 with t-butyl glyoxalate undergoes a remarkably stereocontrolled cycloaddition with furan to afford adduct 48. Hydroxylation of this bicyclic structure, followed by reductive cleavage of the N-O bond, hydrolytic removal of the chiral auxiliary, and adjustment of oxidation states, leads to protected furanose 49, which has been previously converted to norjirimycin and 1-deoxy-norjirimycin.[73] The overall yield in this sequence to norjirimycin is a creditable 19.5%. As in the previous example, this strategy relies upon stereocontrolled ring-formation/fragmentation to establish acyclic stereorelationships.

In a related approach, DeShong and Leginus have utilized pro-sugar 22, available either in optical antipode or in racemic form, to prepare nitrone 50 as a single isomer (Fig. 22).[74] Regio- and stereospecific cycloaddition with ethyl vinyl ether



R	Catalyst[69]	
D-Menthyl	$Eu(fod)_3$	45:55
	$Eu(hfc)_3$	41:59
L-Menthyl	$Eu(fod)_3$	55:45
	$Eu(hfc)_3$	7:93

FIG. 19.

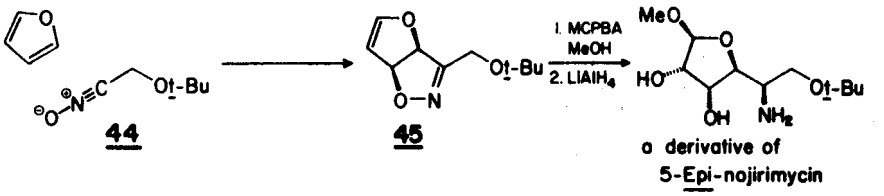


FIG. 20.

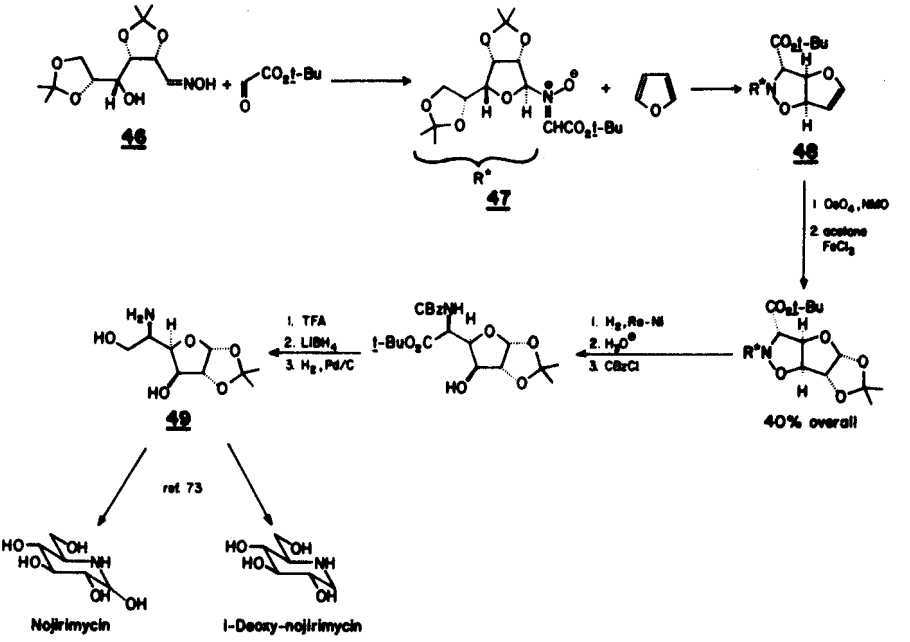


FIG. 21.

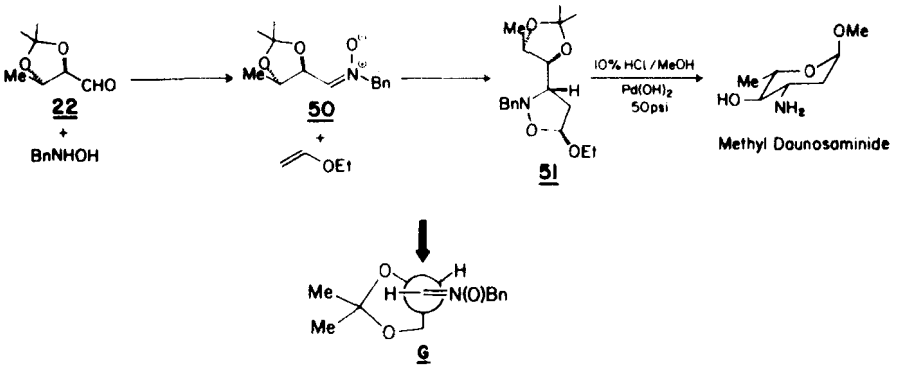


FIG. 22.

affords adduct 51, which is converted in one step to the methyl glycoside of daunosamine in 58% overall yield. Interestingly, the stereoselection of the cycloaddition is rationalized by Felkin transition state G, in which the adjacent alkyl substituent and not the oxygen substituent occupies the position perpendicular to the π-system.

Using an intramolecular variant of the nitrone cycloaddition, Wovkulich and Uskokovic successfully prepared the methyl glycosides of L-acosamine and L-duanosamine (Fig. 23).[75] In situ formation of chiral nitrone 52 with subsequent cycloaddition selectively afforded diastereomer 53. It is noteworthy that the normal regioselectivity of these cycloadditions has been reversed as a result of restraints placed by intramolecular approach of the nitrone and olefin. Cleavage of the N-O bond, partial reduction, and removal of the chiral auxiliary yields key intermediate 54, which may be hydrolyzed directly to L-acosamine or inverted at C4 to give L-duanosamine. An abbreviated route to L-acosamine from 53 was also reported that features simultaneous cleavage of the N-O bond and the chiral directing group through hydrogenolysis.

Kozikowski and Ghosh have examined the effect of allylic asymmetry in the dipolarophile in a study that led to an expedient synthesis of 2-deoxy-D-erythro-pentose.[76] Several nitrile oxides

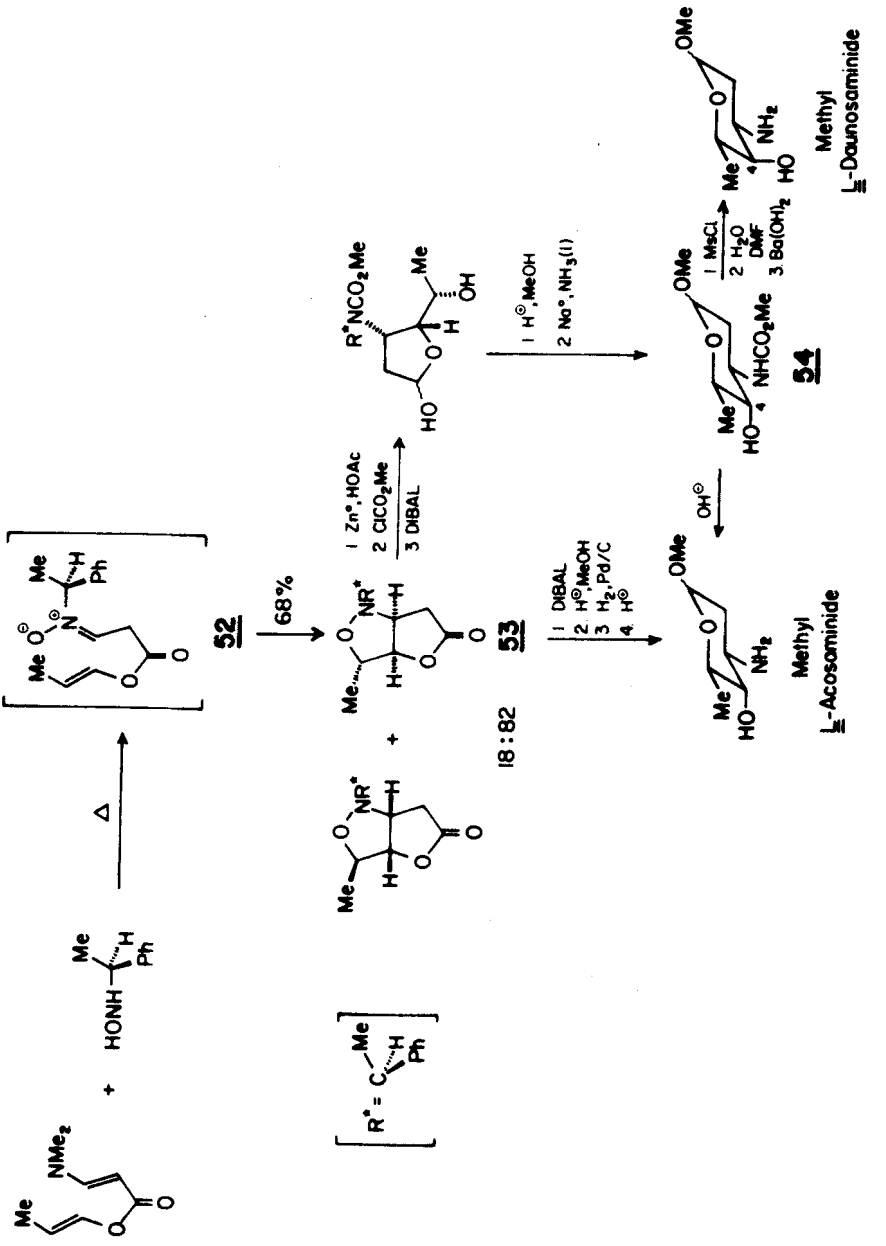
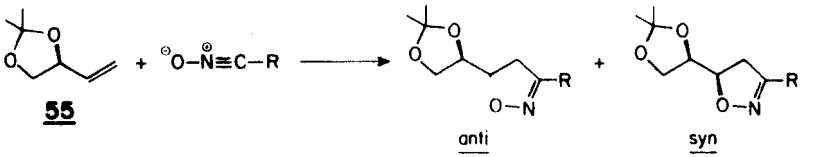


FIG. 23.

TABLE 9. Effect of Dipole Structure Upon Stereoselectivity.



Entry	R	anti : syn
1	CO_2Et	80:20
2	Me	88:12
3	CH_2OTHP	>94:<6

were condensed with butenediol 55 (readily prepared from 2) with the result that the anti-isomer predominated in varying degrees depending upon the structure of the dipole (Table 9). This stereoselection is again consistent with a transition state resembling the Felkin model[33] with the allylic oxygen in 55 occupying the perpendicular position (F in Fig. 3). This selectivity was exploited in the synthesis of 2-deoxy-D-erythro-pentose by converting the major isomers 56 and 57 to protected triol ester 58, which is routinely converted to the pentose (Fig. 24).

APPROACHES via STEREOSELECTIVE CARBON-HETEROATOM BOND FORMATION

In contrast to the strategies discussed in the above section, which focus on the stereoselective construction of the carbon skeleton of the carbohydrate, the following discussion will address approaches that begin with the carbon framework essentially assembled, then stereoselectively attach the required heteroatoms (See Fig. 1). Almost without exception, this features π-facial discrimination of an olefin during a process leading to a carbon-oxygen or carbon-nitrogen bond. This section will sequentially treat the two important approaches of: 1. amination of double bonds, and 2. oxygenation of double bonds.

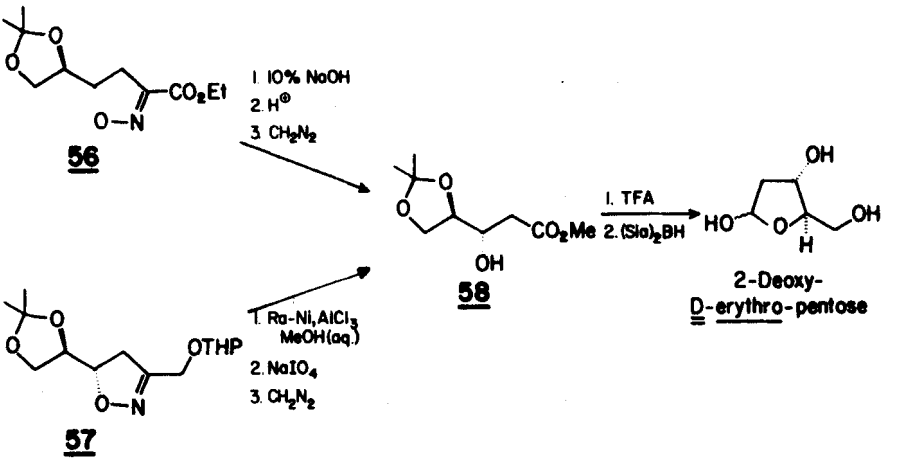
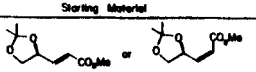
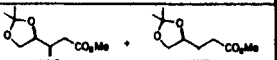
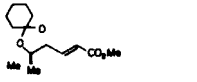
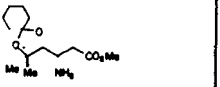
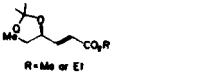
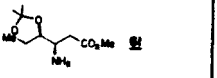
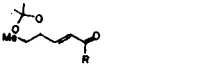
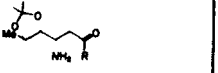
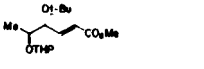
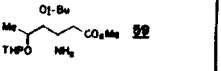
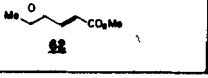
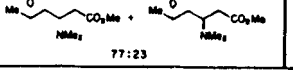
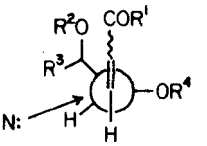


FIG. 24.

TABLE 10 Stereoselective Conjugate Addition of Amines

Entry	Starting Material	Amine	Products	Ref.
		$BnNH_2$		
1	Reaction temperature : 0°		80 : 20	77
2	-20°		94 : 6	77
3	-50°		100 : 0	77
4		NH_3 in MeOH		78
5	 R=Me or Et	NH_3 in MeOH	 61	79,80
6	 R=OEt	NH_3 in MeOH	 R=OMe, NH_2 60	81
7	R=Me		R=Me	78
8		NH_3	 59	82
9	 62	Me_2NH	 77:23	80



H

1. Amination of Double Bonds

The propensity of the amines to undergo conjugative addition to α,β-unsaturated carbonyl compounds has been exploited to introduce the critical nitrogen in amino sugars. In the application to acyclic substrates, the amine must be biased toward one face of the π-system through the influence of existing stereocenters on the carbon skeleton. As the data in Table 10 demonstrate, such aminations are subject to a high degree of stereocontrol, often affording a single diastereomer. As indicated by entries 1-3, this remarkably selective condensation is independent of the geometry of the starting disubstituted double bond since the separated E and Z-isomers gave essentially identical results over a range of temperatures. Furthermore, the presence of an additional stereocenter at the homoallylic position has a negligible effect on the outcome of these reactions (see entries 5-8). These results correlate very well with the Felkin model[33] transition state H, with the allylic oxygen substituent occupying the customary position perpendicular to the π-system. Finally, the stereocomplementary nature of these reactions with the allylation of asymmetric imines bears emphasis (Table 8).

The amine adducts in Table 10 represent quite advanced intermediates for the synthesis of amino sugars and have been exploited in this regard. The facile conversion of adducts 59, 60, and 61 to several biologically important carbohydrates is illustrated in Fig. 25.

It is noteworthy that the mode of amine addition to epoxy compounds such as 62 (entry 9) can be modified by replacing the ester functionality with a carboxylic acid group. Dyong and co-

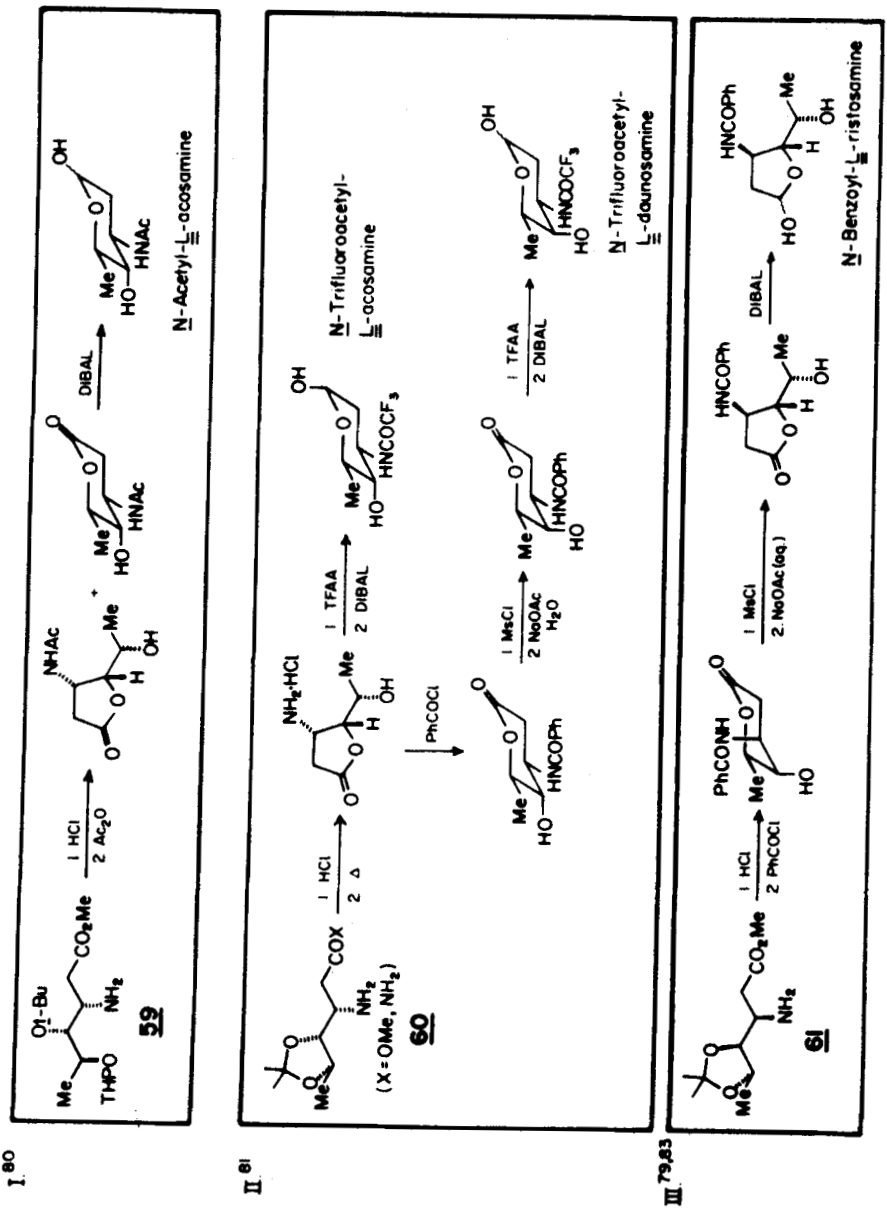


FIG. 25.

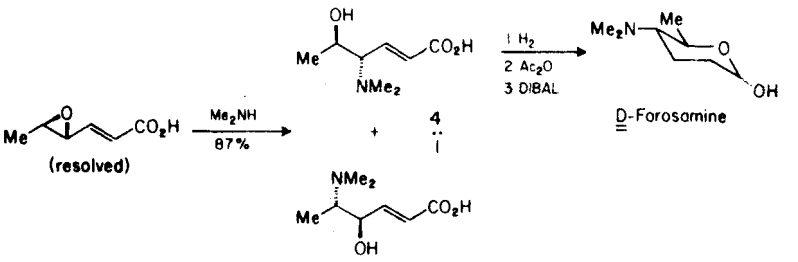


FIG. 26.

workers took advantage of this in an efficient synthesis of D-forosamine (Fig. 26).[84]

2. Oxygenation of Double Bonds

In view of the high oxygen content of carbohydrates, it is not surprising that approaches designed about the addition of oxygen to carbon-carbon double bonds have been numerous and successful. The discussion of these approaches is conveniently organized according to the process by which the oxygen is introduced: oxidative cyclization of an acyclic precursor, hydroxylation, and epoxidation.

In the first strategy, an unsaturated, acyclic molecule is activated toward ring formation via an electrophilic oxidant. An interesting example of this approach was reported by Current and Sharpless wherein ArSeBr initiates a three-component condensation which may be controlled to favor either thermodynamic (63, 62%) or kinetic (64, 68%, two isomers) products (Fig. 27).[85] The selenide 63 has been oxidatively eliminated to olefinic compound 65, which is suitable for further functionalization.

Nagakawa's group investigated the halolactonization of hydroxypentenoic acid 66 with aqueous N-bromosuccinimide and found that a single bromolactone 67 resulted (Fig. 28).[86] This compound could be readily transformed to the deoxypentose 68 (with inversion at C4) or to the dideoxy species 69. The stereoselection of this route is a result of thermodynamic control, as

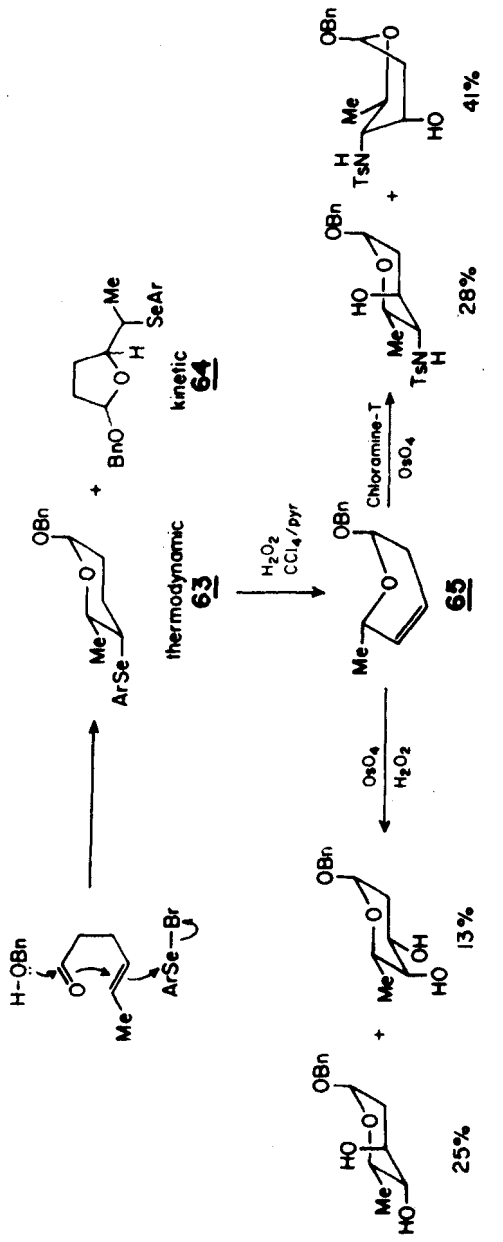
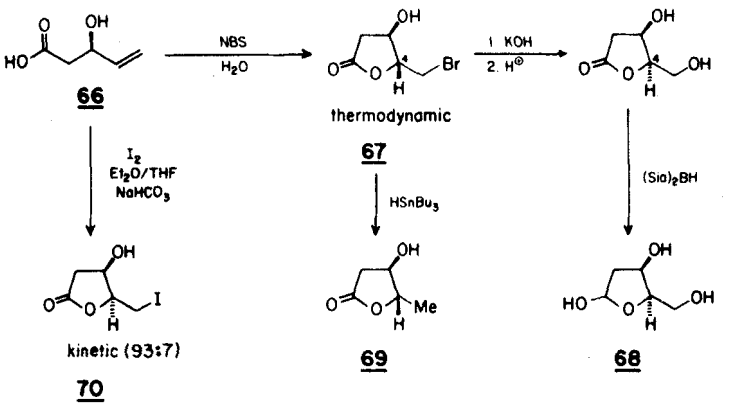


FIG. 27.



66 67 68 69 70

FIG. 28.

evidenced by Chamberlin's kinetic iodolactonization of 66 which strongly favors the opposite isomer 70 (93:7).[87]

In view of their relevance to the present discussion, note should be made of several cyclization studies which effect the stereoselective conversion of existing carbohydrates to O-glycosides and C-glycosyl compounds (Fig. 29).[88-90] The direct, electrophile-induced cyclizations carried out by Mukaiyama (I)[88] and Sinaÿ (II)[89] favor the preparation of α-anomeric products to the virtual exclusion of the β-isomer, while the asymmetric expoxidation (vide infra)/ ring-opening procedure of Sharpless and Masamune (III)[90] allows selective preparation of either anomer.[91] The cyclization approach to carbohydrates may be expected to play an important role in future syntheses, as judged by the amount of effort presently being directed toward understanding such processes.[92]

In another strategy, an acyclic olefin may be oxidized without cyclization to afford, ultimately, a geminal diol. The most direct methods involve cis-hydroxylation of the double bond by one of the several methods presently available. Until very recently only isolated examples of highly selective oxidations of this type have been observed, such as Iwai and Tomita's synthesis

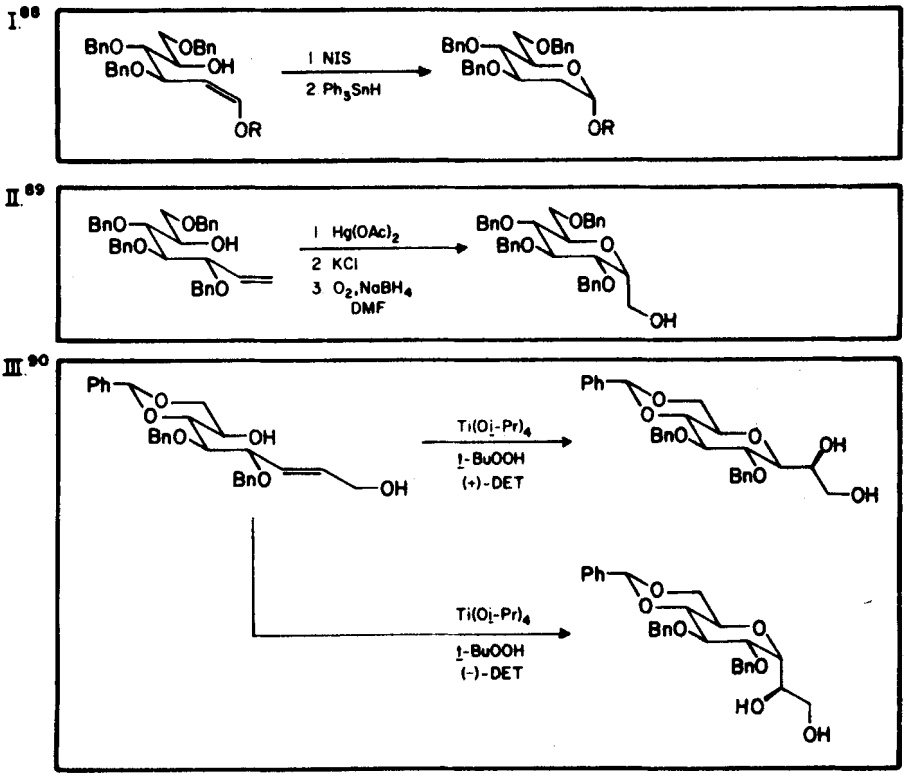


FIG. 29.

of DL-arabinose, which features a stereospecific permanganate oxidation (Fig. 30).[93] More often the levels of stereoselection have been disappointingly low. For syntheses that rely on essentially stereorandom hydroxylation, reference is made to previous reviews on carbohydrate synthesis.[7] There have been, however, several reports of efficient routes to sugars in spite of the modest stereoselection of the key hydroxylation reactions. The following examples are illustrative.

Bognár and Herczegh hydroxylated olefin 71 with OsO_4 to produce an unequal mixture of protected pentoses 72a/b (Fig. 31).[94] These are easily unmasked to afford the racemic pentoses; DL-

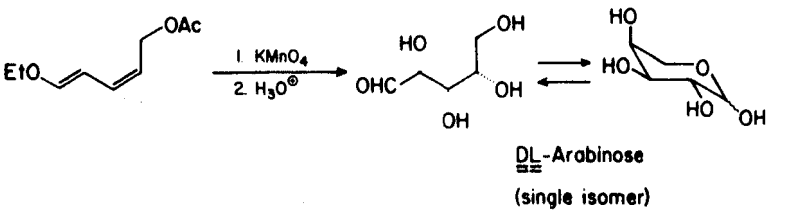


FIG. 30.

ribose and DL-arabinose. This route remains preparatively useful, in spite of the low level of stereoselection in the formation of 72a/b, through its brevity.

Several successful syntheses featuring the hydroxylation of allylic amines have been reported. Recently, Hauser and Rhee disclosed a concise synthesis of N-benzoyl-DL-daunosamine in which all the relative stereochemistry is placed in a selective osmylation of olefin 73 (Fig. 32).[95] It is worth noting that the relative asymmetric induction, as well as the isomer ratio, closely follow the previous example.

Dyong's group has carried out a series of experiments targeting several important amino sugars that also depend upon hydroxylation of allylic amines to introduce key stereorelationships. Protection of a readily available aldehyde with (+)-dimethyl tartrate afforded 74 which, in turn, was aminated at the C3 position in a virtually random manner (Fig. 33).[96] Following separation, the major isomer could be oxidized to favor the lyxo (75a) or xylo (75b) configurations, depending upon the conditions employed. Routine transformations subsequently led to the targeted sugars. Through minor modification of this route, optically pure N-tosyldaunosamine could be realized in 10-gram quantities.[96c] A slightly different starting material has led, by essentially the same strategy, to fully protected DL-vancosamine (Fig. 34).[97]

Very recently, reports have appeared that demonstrate that these hydroxylation reactions may be carried out with preparatively useful levels of stereoselection (Fig. 35). It bears noting

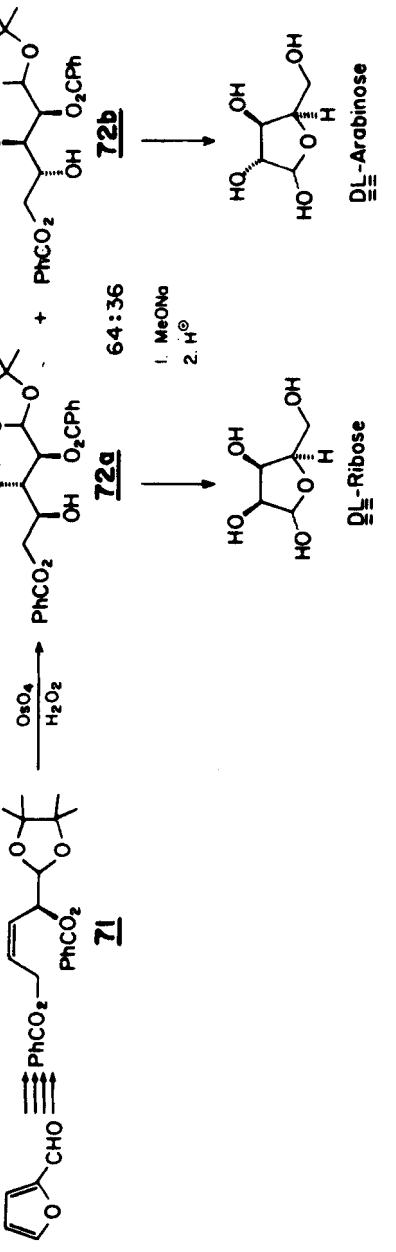


FIG. 31.

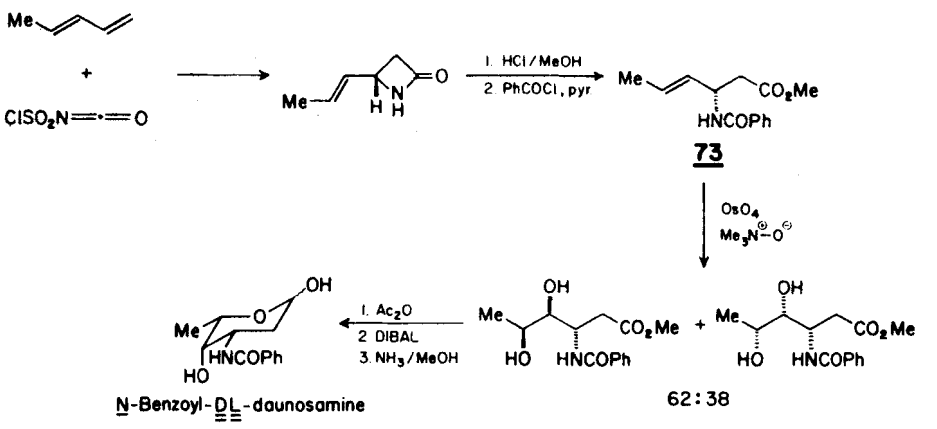


FIG. 32.

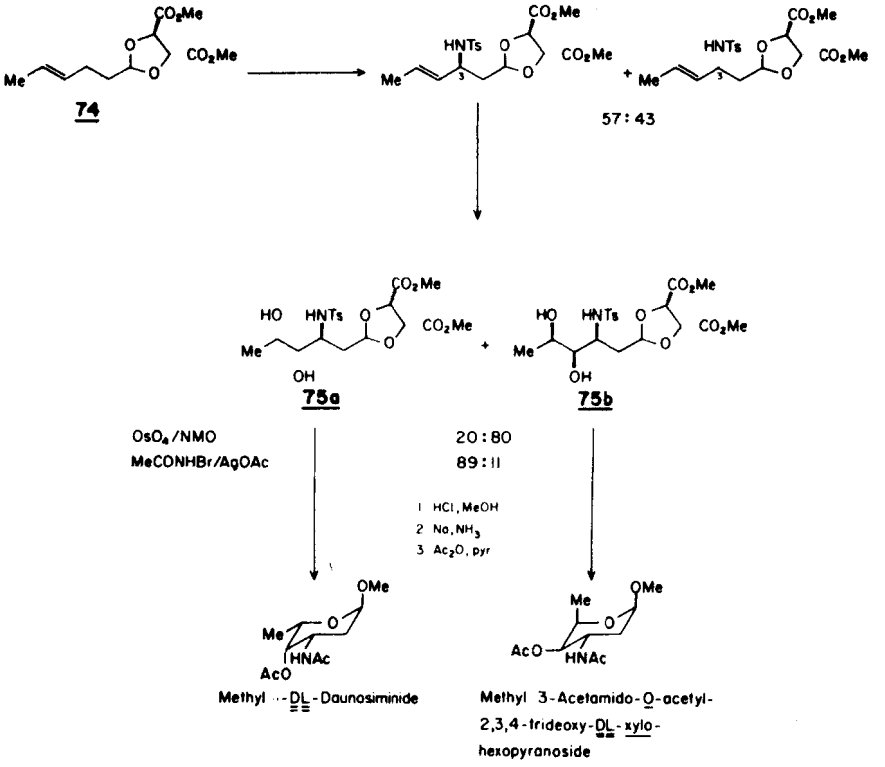


FIG. 33.

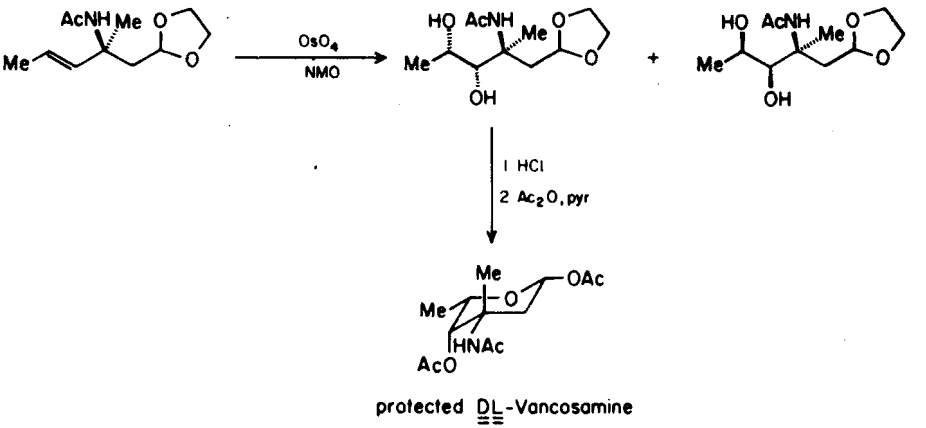
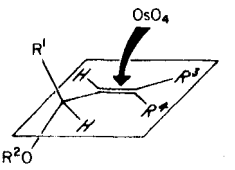


FIG. 34.

that in every example in the figure the same sense of 1,2-asymmetric induction was observed. Kishi has suggested an empirical model 76 to account for the stereochemical outcome of these reactions and has demonstrated considerable predictive value for this formulation.[100] Stork has supplied an alternative explanation for substrates which have electron-withdrawing substituents attached to the double bond.[99] Clearly, these reactions offer a powerful method for preparing carbohydrates of diverse structures and will become increasingly useful as mechanistic details of these oxidations are uncovered through systematic studies such as those carried out by Kishi.[100]

In contrast, epoxidation has already emerged as an exceptionally useful tool for carbohydrate synthesis. Abundant data has been amassed with regard to the stereoselection of these reactions, especially as influenced by asymmetric allylic heteroatom substituents.[101,8c,8i,8j] Consider, for example, the peracid epoxidation of simple allylic alcohols 77 (Fig. 36). Involving a hydrogen-bonding interaction with the reagent, two diastereomeric transition states 78s and 78a contribute to the formation of syn and anti epoxy alcohols. Predictably, replacing R=H with the more sterically demanding R=Me increases the indicated 1,3-interaction



76

in 78a and results in a substantial enhancement in syn-selectivity of the reaction. The utility of such stereocontrolled oxidation of allylic alcohols in carbohydrate synthesis is obvious and has been exploited in this regard.

Peracid epoxidation of simple dienyl systems has been examined in an effort to prepare 5- and 6-carbon polyols of specified relative configurations. While the oxidation of conjugated dienyl substrates has been hampered by low yields,[102] the use of divinyl methanol as a pentitol precursor has enjoyed modest success. Chautemps observed an unequal distribution of stereoisomers favoring the ribo-configuration when the parent compound (79,R=H) was treated with p-nitroperoxybenzoic acid (Fig. 37).[103] Holland and Stoddart, on the other hand, similarly epoxidized the corresponding acetate (79,R=Ac) in a stepwise fashion, with low levels of selectivity observed for each step.[104] While the former study reports clean base-induced ring opening of the hydroxy diepoxides to the corresponding pentitols, the latter investigators observed considerable stereochemical erosion in the acetate-induced ring cleavage of the acetoxy diepoxides.[105]

Holland and Stoddart have recently disclosed a stereoselective synthesis of xylitol which takes advantage of the product's symmetry (Fig. 38).[106] Cyclopentadiene was converted to bisallylic alcohol 80, which was epoxidized to give a mixture of products favoring the syn-epoxide as expected. Ring opening of the mixture, however, heavily favored the pentitol with the desired xylo configuration. This selectivity results from the anticipated cleavage of the syn-isomer directly to the target compound and acetate participation in the cleavage of the anti-epoxide to

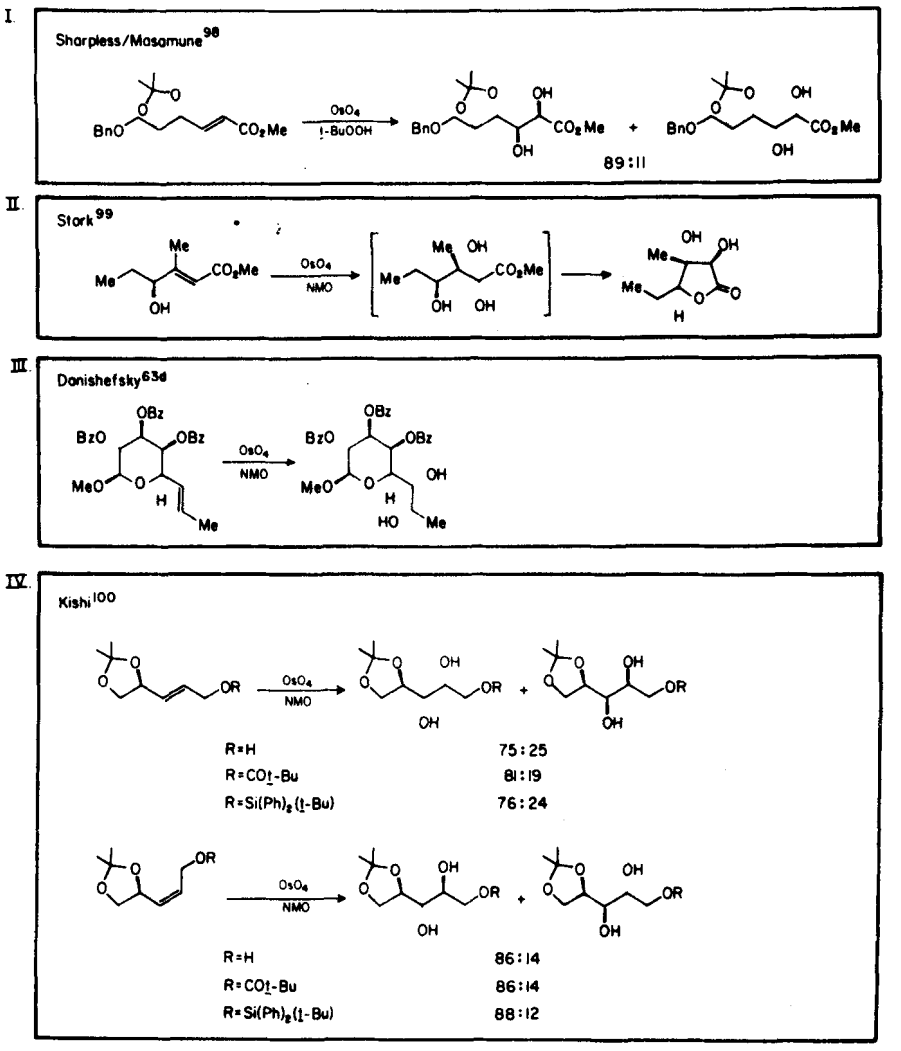


FIG. 35.

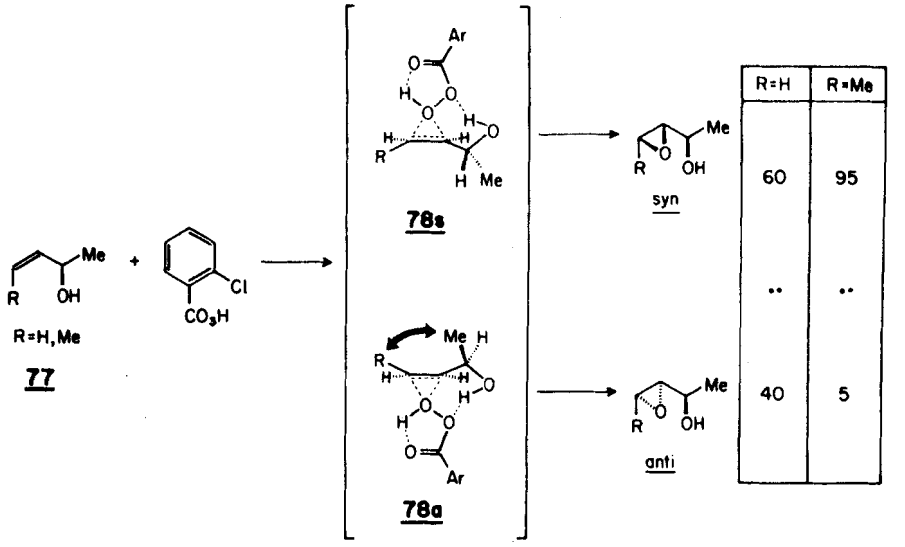


FIG. 36.

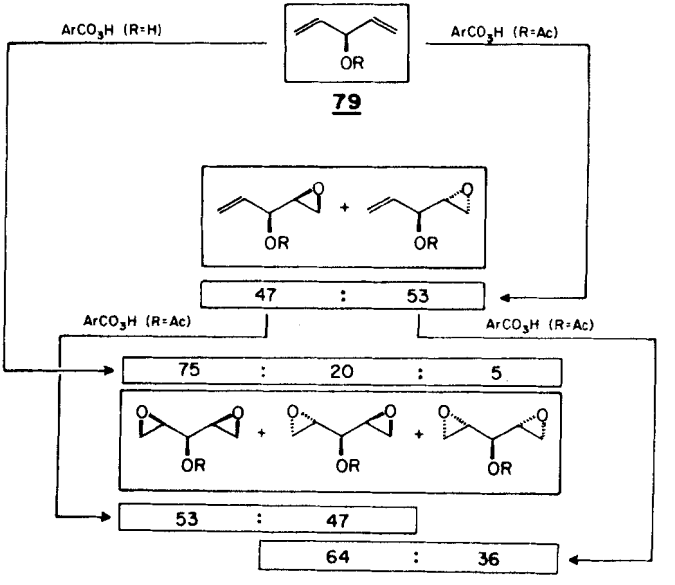


FIG. 37.

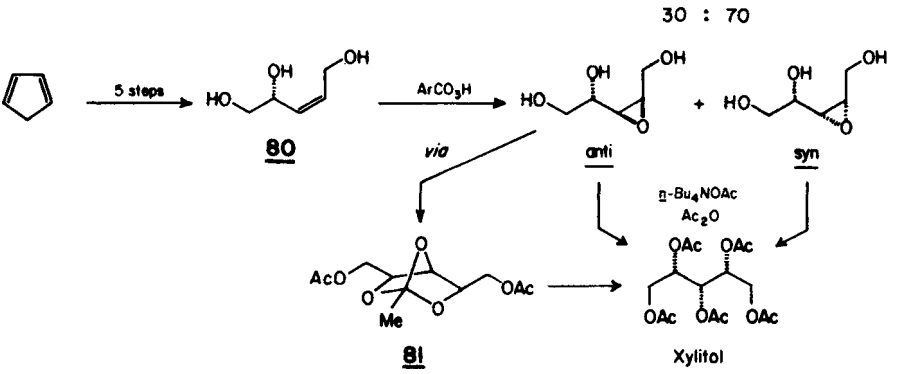
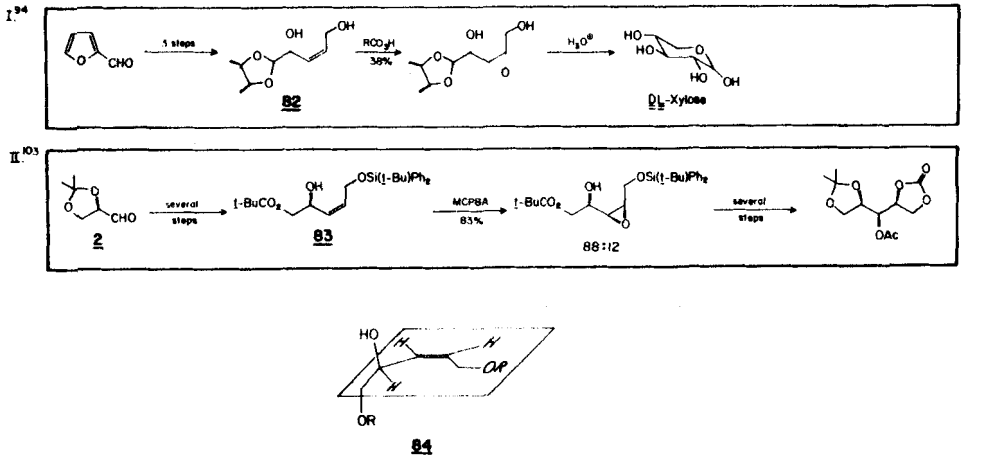


FIG. 38.

give symmetrical bicyclic intermediate intermediate 81 which collapses to give the xylo-isomer as well.

Closely related approaches to polyols with the xylo relative stereochemistry have been carried out by Bognár and Herczegh (Route I)[94] and Kishi's group (Route II,[107] Fig. 39). In contrast to the previous example, however, epoxidation of bisallylic alcohol species 82 and 83 takes place with high stereoselection to allow direct preparation of xylo-isomers. As a result of extensive studies which examined a range of olefinic substrates, Kishi has formulated a transition state for these epoxidations which proceeds via a conformation that minimizes allylic 1,3-interactions (84).[108,81] Additional steric bias may be conferred by involving both allylic oxygen substituents with the peracid in the transition state.[109]

Epoxidation of acyclic allylic alcohols is the key feature of two approaches to L-olivomycose (Fig. 40). In the first route, Dyong and Glittenberg epoxidized the Reformatsky product 85 to isolate a single product.[110,111] Simple hydrolysis, followed by partial reduction, affords the desired material. The optically pure product was realized through the use of resolved ester 85. In the approach of Fuganti and co-workers, an optically active pro-sugar unit 86, prepared through a microbial transformation,



84

FIG. 39.

also underwent stereospecific syn-epoxidation.[112] A straightforward sequence subsequently affords the enantiomerically discrete sugar.

Recent advances in epoxidation have had a dramatic impact on carbohydrate synthesis. This may be attributed principally to the pioneering studies of the Sharpless group on metal-catalyzed oxidations of olefins with t-butyl hydroperoxide.[8j] These epoxidations are chemoselective toward double bonds possessing proximal hydroxyl groups, with allylic, homoallylic, and bishomoallylic alcohols all serving as substrates for this reaction. In addition, the stereoselectivity of the $VO(acac)_2$-catalyzed epoxidation of acyclic allylic alcohols has been extensively investigated and is often found to complement peracid stereoselection (Fig. 41). This selectivity is a consequence of unfavorable interactions between the Cl methyl, R groups on the double bond, and ligands on the metal center in transition states 87s and 87a.[8j,113]

Depazay and co-workers have incorporated this method of epoxidation in a versatile synthesis of branched-chain pentoses.[115] Illustrative of these studies, compound 7 (See Table 1,

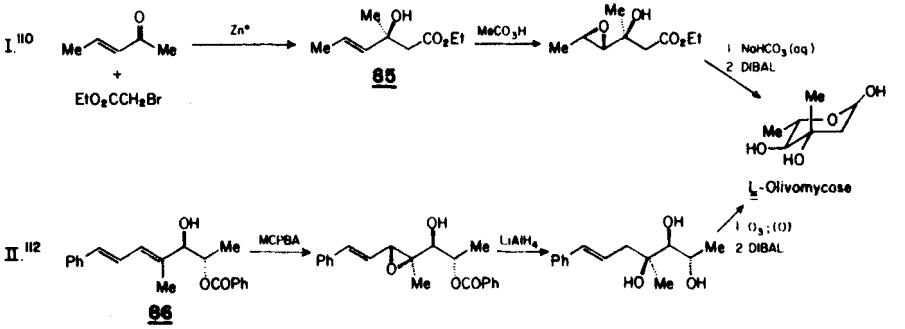


FIG. 40.

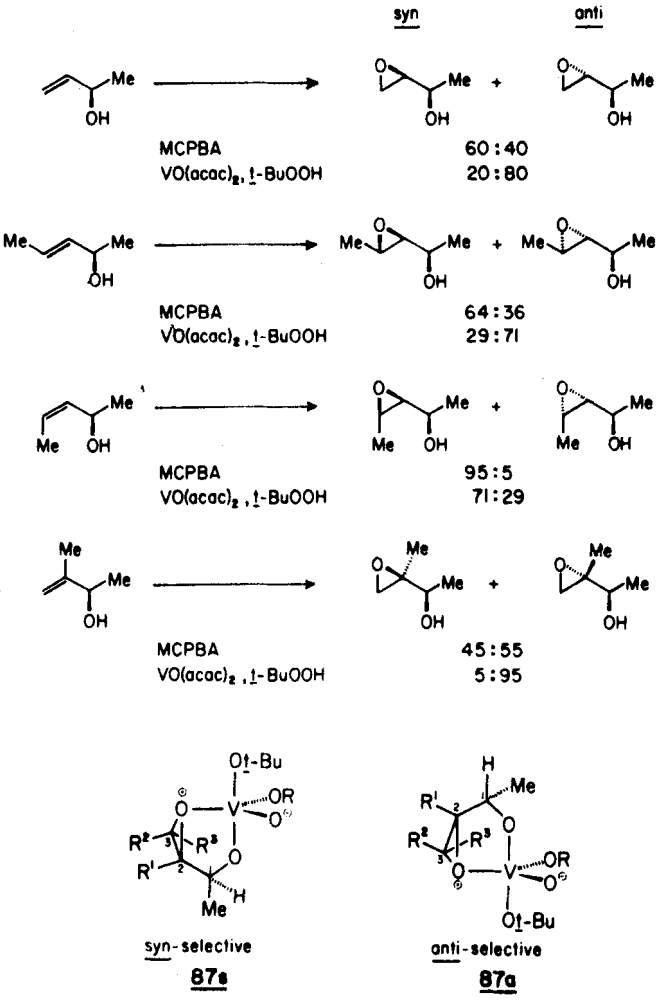


FIG. 41.

entry 17) was oxidized to give a single isomer 88, which could be regiospecifically opened with wide range of nucleophiles (Fig. 42). If the epoxide was cleaved with aqueous base, subsequent acid-induced hydrolysis and lactol formation afforded the ethyl glycoside of epi-hammamelose. As pointed out earlier, the epimeric sugar could be prepared by first cyclizing 7 to 8, then carrying out epoxidation using the directing effect of the axial C4 hydroxyl group.

Roush and Brown have reported a synthesis of racemic olivose which features the establishment of all the relative stereochemistry through a metal-catalyzed epoxidation/ring opening sequence (Fig. 43).[113] Diene 89 was regio- and stereoselectively converted to epoxide 90 with greater than 95% isomeric purity. The epoxide was opened with clean inversion of the C4 position through Lewis acid-mediated participation of a carbamate at C5. Base cleavage of the resulting cyclic carbonates and ozonolytic unmasking of the C1 aldehyde furnished the desired product.

Through a modification of this strategy, these workers were also able to prepare carbohydrates in optically active form.[116] Advantage was taken of a procedure developed in the Sharpless group that kinetically resolved allylic alcohols through asymmetric epoxidation (vide infra).[117] Through this method, racemic 91 was converted to enantiomerically pure epoxy alcohol 92 and highly enriched allylic alcohol 93 (Fig. 44). Paralleling the previous route, epoxide 92 was regioselectively opened via intramolecular carbamate participation, then routinely transformed into L-(+)-olivose. On the other hand, asymmetric epoxidation of alcohol 93, accompanied by further resolution, gave 94, the enantiomer of compound 92. Direct, regiospecific ring opening without intramolecular assistance gives a triol with an alternative relative stereorelationship (95) which is straightforwardly converted to L-(+)-digitoxose.

A breakthrough in asymmetric synthesis, alluded to in the synthesis above, was disclosed by Sharpless and Katsuki in 1980 when they reported the first practical method for asymmetric

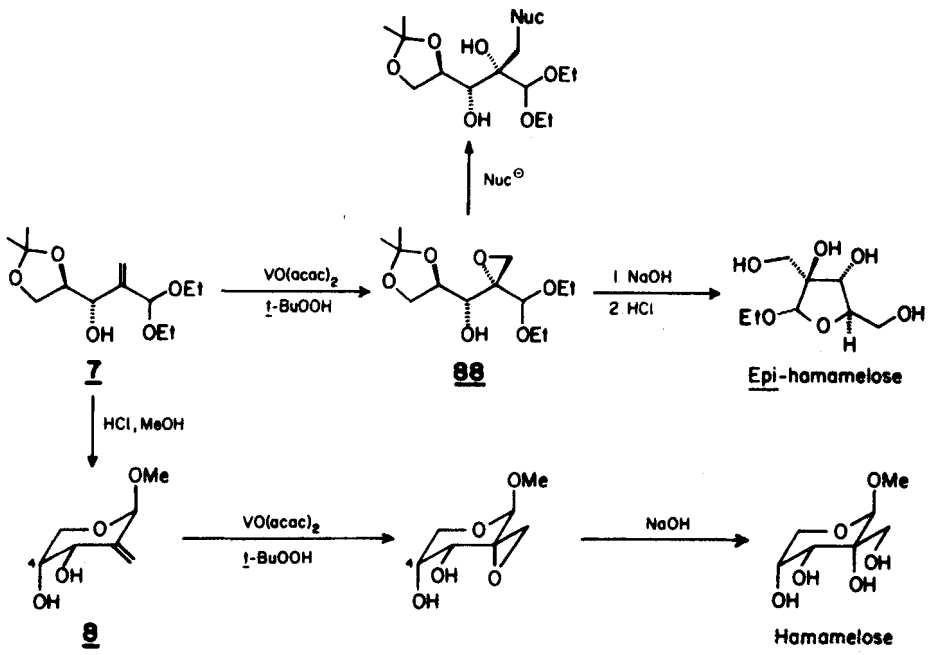


FIG. 42.

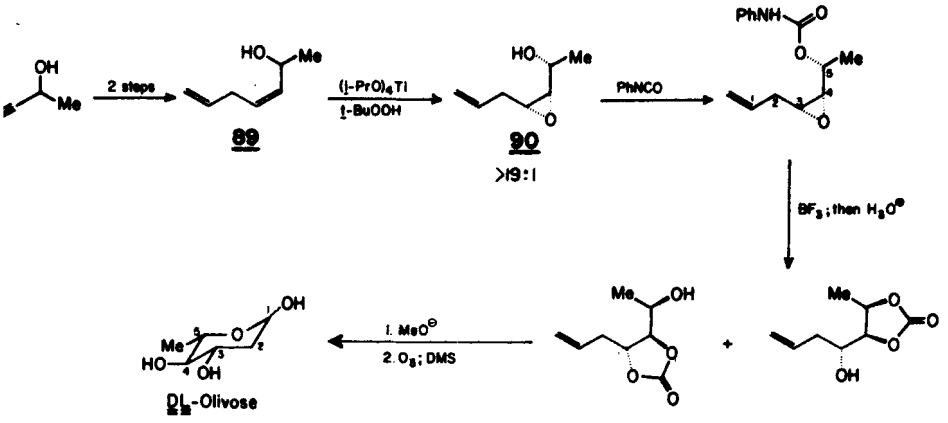


FIG. 43.

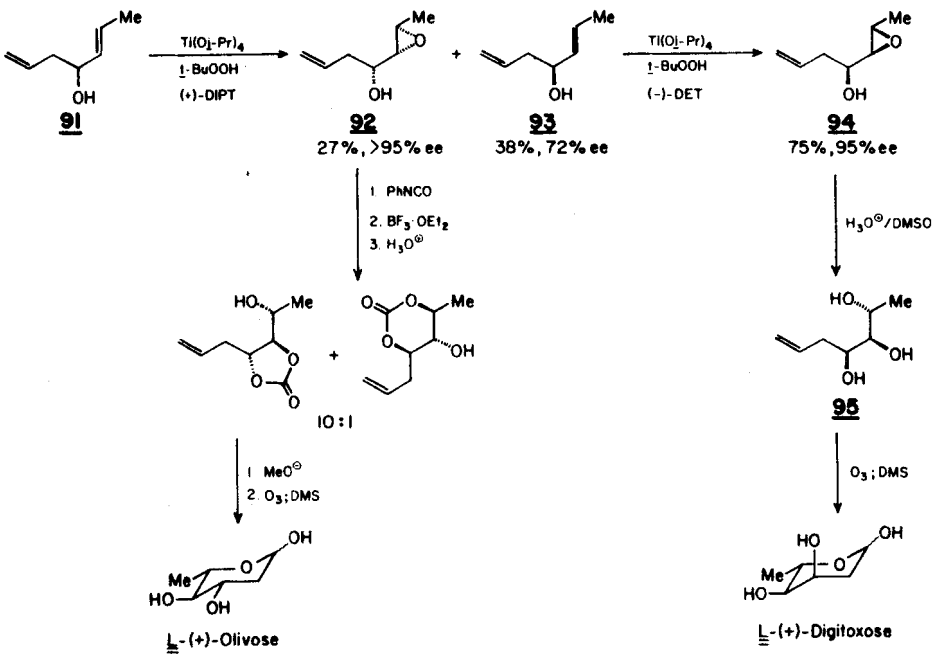


FIG. 44.

epoxidation, using a system of Ti(Oi-Pr)$_4$/t-BuOOH modified by D-(+) or L-(-)-tartaric acid.[118] This discovery broadened the synthetic access to optically pure materials enormously through asymmetric epoxidation of primary allylic alcohols.[119] By a procedure developed shortly thereafter, the kinetic resolution of secondary allylic alcohols was made possible.[117,120] In the present context, this has led to the first truly general protocol for the preparation of all the isomeric tetroses, pentoses, and hexoses principally through the efforts of the Sharpless and Masamune groups in collaboration[8c,98,101,121] and the Kishi group.[107]

The route starts with an isomerically defined olefin, such as 96E or 96Z, which is asymmetrically epoxidized with induction favoring either of the two possible oxides depending upon which enantiomer of the chiral modifier is employed (Fig. 45).[98,107]

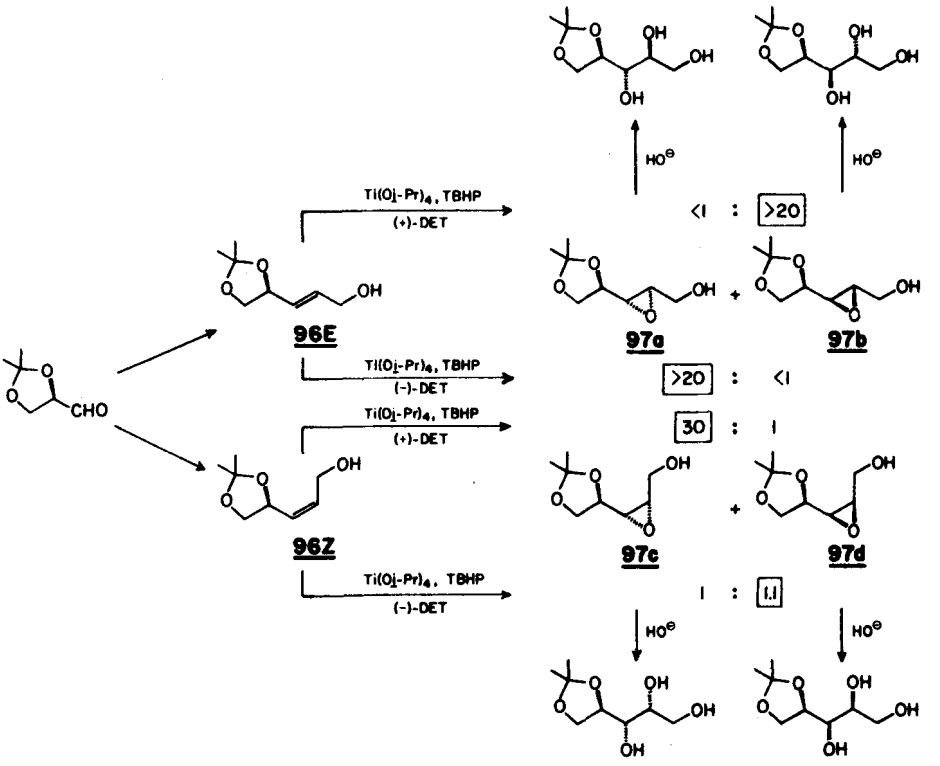


FIG. 45.

An important feature of these epoxidations is the relation of the epoxide asymmetry to the reagent's chirality without regard (generally) to asymmetry in the olefinic substrate. A notable exception to this observation is the almost stereorandom oxidation of the Z-isomer (96Z) with the (-)-reagent, a point that will be addressed shortly. In any event, the hydrolytic ring opening of these epoxides (under a specified set of conditions) affords four selectively protected pentitols.[9 8]

Obviously, successful conversion of epoxides such as 97a-d to sugars requires regiospecific cleavage of the ring. This has been realized through several methods, often taking advantage of an intramolecular delivery of a nucleophile. Pro-

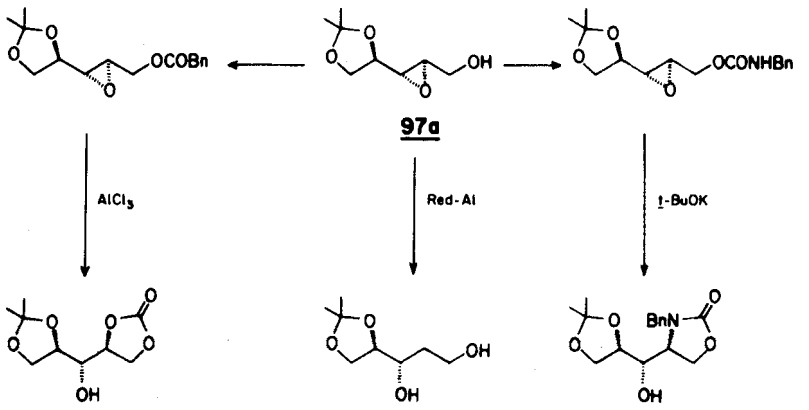


FIG. 46.

cedures have been developed for site-specific nucleophilic attack by oxygen,[98,107,116] nitrogen,[107,116] and hydrogen[121a,122] (Fig. 46; for additional examples see reference 101b). Another important method by which the epoxide may be selectively cleaved takes advantage of the Payne rearrangement which describes the equilibration between two hydroxy epoxides such as 98 and 99 (Fig. 47).[123] This equilibrium can be intercepted by nucleophiles, such as thiolate ions, at the most reactive position (C1) to afford regiospecific ring-opened products.[98]

This manipulation plays an important role in the development of a simple procedure for overcoming the problem of the disappointing levels of selectivity sometimes observed in the asymmetric epoxidation of Z-olefins (see epoxidation of 96Z using (-)-DET in Fig. 45). Since high levels of stereoselection are always observed with E-olefins, a strategy was conceived to convert the diol derived from the E-epoxide to the diol which would result from the Z-olefin (Fig. 48).[121b] Epoxide 97b, which is cleanly prepared from E-olefin 96E, may be opened via the Payne rearrangement to diol 100. Protection as the cyclic acetal, followed by an oxidation using the Pummerer rearrangement, leads to aldehyde 101. This aldehyde suffers highly selective

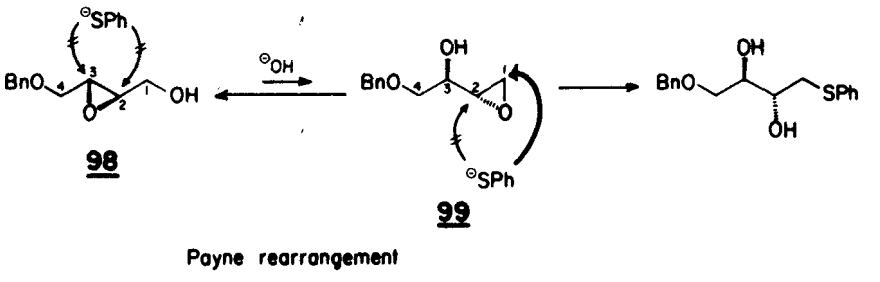


FIG. 47.

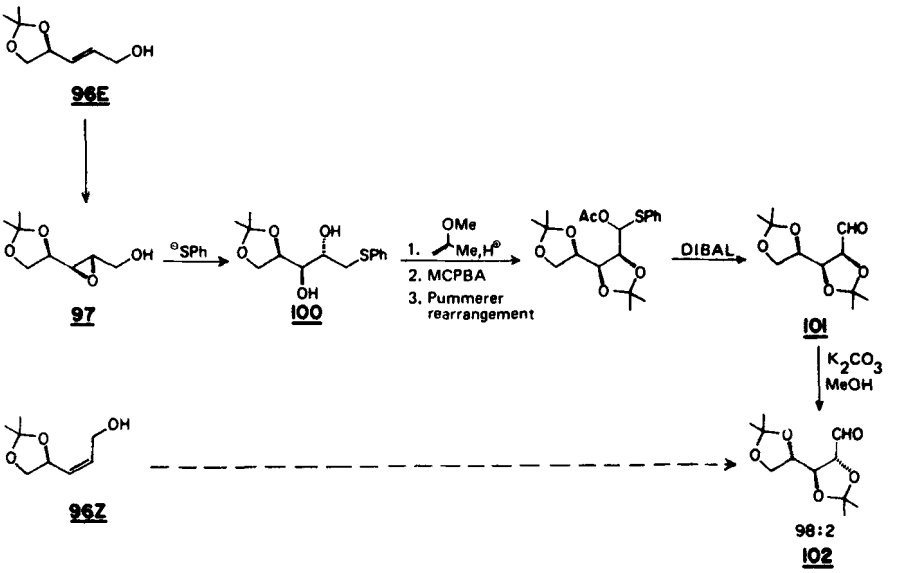


FIG. 48.

epimerization, without competitive β-elimination, to the more stable trans-acetonide 102, which is effectively the product of applying the asymmetric epoxidation/hydrolysis sequence to olefin 96Z.

The net result of all the above developments is an extremely flexible, reiterative two-carbon extension procedure that is applicable to the preparation of all possible stereoisomers of the trioses, tetroses, pentoses, hexoses, and beyond. It is fitting

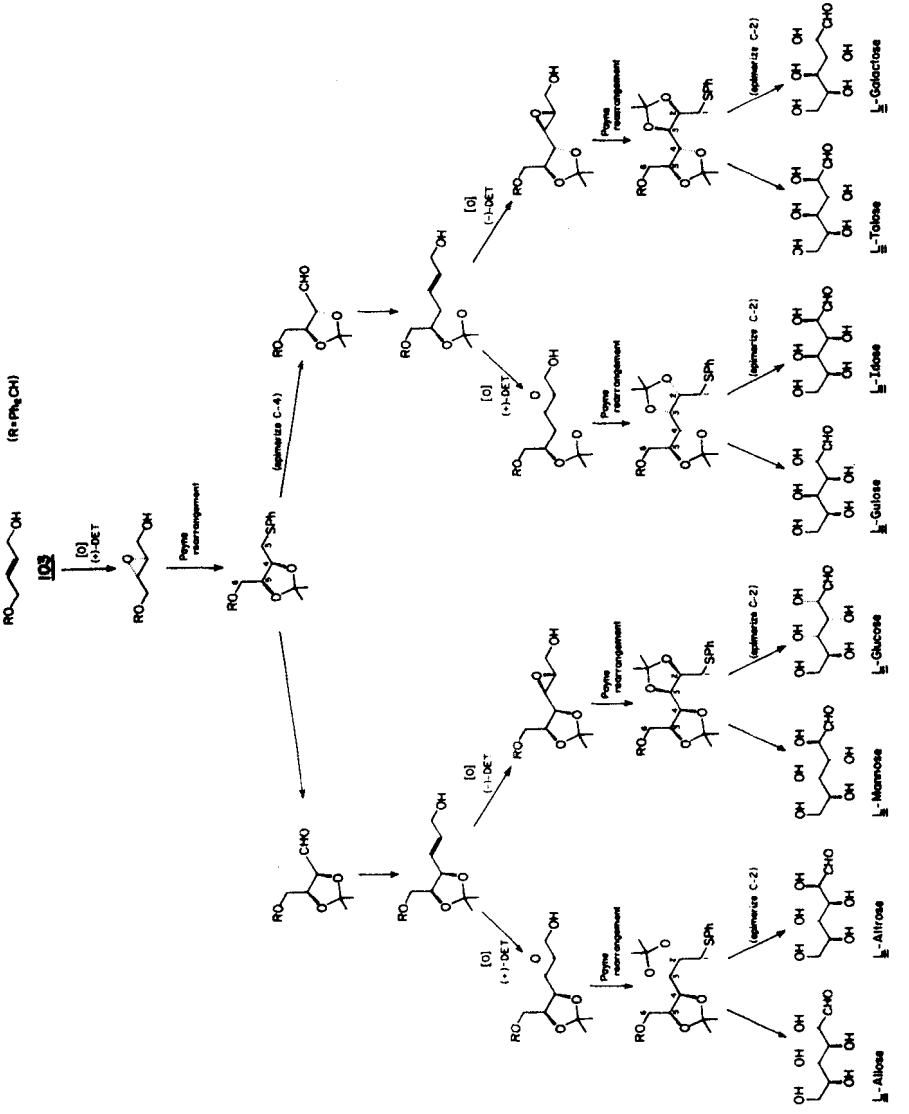


FIG. 49

to bring to a close the discussion in this review with a demonstration of the power of the asymmetric epoxidation strategy in the synthesis of carbohydrates. This has been impressively carried out by the Sharpless/Masamune groups in a synthesis of all eight possible L-hexoses starting from a single, monoprotected butenediol 103 and using the transformations described in Fig. 45 and 48 (Fig. 49).[121c]

CONCLUSION

The preceeding discussion has detailed recent advances in the chemical synthesis of carbohydrates that feature acyclic stereoselective placement of the requisite sites of asymmetry. Since one is dealing with a conformationally flexible carbon framework, it is often possible to create relative stereochemical relationships that are difficult to attain when starting with ring substrates. Not surprisingly, the growth in this area has paralleled the explosive advances in the general area of acyclic stereoselection and has provided an attractive test of existing methodologies, creating impetus for the development of new chemistry.

The future of this field would seem secure. While acyclic strategies for preparing carbohydrates will not supplant all the existing routes to uncommon sugars, especially those in which the product is readily attainable from inexpensive carbohydrate precursors, these methods will strongly complement the better syntheses available and expand the range of structural types that may be efficiently prepared. Carbohydrates have been instrumental in gaining a better understanding of basic chemical principles; it is now reasonable to expect that chemistry will increasingly turn its attention toward a deeper understanding of the fundamental roles that carbohydrates assume in living systems.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the National Institutes of Health (AI18889), which has supported our own efforts in this area during the preparation of this manuscript.

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