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The Synthetic Methodology of Nonracemic Glycidol and Related 2,3-Epoxy Alcohols

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Contents

Robert M. Hanson was born in 1957 in Madison, WI, and received his secondary education in Littleton, CO. He received his B.S. in 1979 from the California Institute of Technology and his Ph.D. in 1984 from Columbia University in the City of New York, studying natural products synthesis with Prof. Gilbert Stork as a National Science Foundation Pre-Doctoral Fellow. He then spent two years as an *NIH postdoctoral fellow with Prof. K. Barry Sharpless at the* Massachusetts Institute of Technology, where he discovered the benefit of adding molecular sieves to the asymmetric epoxidation reaction. In 1986 he accepted a position at St. Olaf College in Northfield, MN, where he is currently an assistant professor and maintains a research group of four to six undergraduates. In 1989 he received a National Science Foundation Presidential Young Investigator Award, one of the first ever given to a faculty member of an undergraduate-only institution. His research interests include the development of reagents and analytical methods for stereo*selective and enantioselective synthesis and the total synthesis of* natural products.

I. Introduction

A. Scope

After a discussion of the general methods of synthesis of nonracemic[1] glycidol ((*R*)-1 and (*S*)-1) in section II, a comprehensive discussion of the reactivities of nonracemic glycidol and a few related 2,3-epoxy alcohols with and without protecting and activating groups will be presented (section III). In sections IV and V of this review, the chemistry of glycidol is put into the perspective of natural product and synthetic analogue synthesis, with particular emphasis on the strategy used for the incorporation of the three carbons of glycidol into the target molecule. An attempt has been made to cover all pertinent literature published between 1980 and early 1990. Particular emphasis will be on the regioselectivity of these reactions. Included in this discussion will be the reactions of selected alkyl- and aryl-substituted glycidols in order to emphasize the effect of substituents upon 2,3-epoxy alcohol reactivity. This discussion stops short of reviewing the reactivity of *all* known 2,3-epoxy alcohols. (Reviews relating to general 2,3-epoxy alcohol reactivity can be found elsewhere.[2,3])

Instead, other than glycidol itself, only the minimally substituted derivatives given in Table 1 are discussed. For these derivatives, the discussion is comprehensive, regarding both racemic and nonracemic compounds. However, because of the vast number of references to racemic glycidol with and without protecting groups (over 11 000 compounds and several thousand references), the discussion of glycidol itself is comprehensive only in relation to the nonracemic form. Several references to reactions of racemic glycidol are given, but they are meant only to be illustrative.

B. Rationale and Method

Epoxides (oxiranes) in general, due to their ease of formation and ready reactivity toward nucleophiles, are important starting materials and intermediates in organic synthesis. Because there are two competing sites

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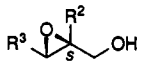
TABLE 1. 2,3-Epoxy Alcohols Dealt with in This Review (For Reference, Only One Enantiomer Is Shown)



1-4

R^3	R^2	name used here	*Chemical Abstracts* name
H	H	glycidol (1)	oxiranemethanol
Ph	H	*trans*-3-phenylglycidol (2)	*trans*-3-phenyloxiranemethanol
Me	H	*trans*-3-methylglycidol (3)	*trans*-3-methyloxiranemethanol
H	Me	2-methylglycidol (4)	2-methyloxiranemethanol

of reactivity in every epoxide, much work has gone into understanding what factors influence the regioselectivity of epoxide opening. In glycidol and its derivatives the presence of a CH_2OX group (where X = H or a protecting or activating group) besides introducing a third potentially electrophilic center also profoundly influences the reactivity of the oxirane. By concentrating on glycidol and its simple derivatives, an attempt is made to shed light on the influence of alkyl and aryl substituents, protecting groups, and activating groups on 2,3-epoxy alcohol reactivity in general.

Both (*R*)- and (*S*)-glycidol are of special interest synthetically due to their recent availability from either achiral, nonracemic, or racemic starting materials. The technology to synthesize related nonracemic 2,3-epoxy alcohols on an industrial scale is now at hand. Several patents describe the synthesis of nonracemic glycidol or its simple derivatives (vide infra).

It is the intent of this review to present a comprehensive discussion of the *synthetically useful* reactions of nonracemic glycidol and its derivatives. Thus, many of the references cited are to natural product and pharmaceutical syntheses which involved nonracemic glycidol at some stage. In most cases nonracemic glycidol was used to introduce at least one stereocenter of known configuration into the molecule of interest. Many very interesting syntheses of racemic compounds have also been published, but they are not included here.

The references in this review were generated through an extensive set of Chemical Abstract Service CAS-ONLINE searches carried out several times in 1990. Searches were based both on registry numbers for racemic and nonracemic forms of 1–4[4] and on results of substructure searches for all derivatives of these compounds bearing a C, S, or Si instead of H on the oxygen atom. Preliminary screening involved removal of references and compounds explicitly relating to polymers, plastics, and adhesives (virtually all of which relate to racemic glycidol). Due to the very large number of references to glycidol, articles related only to *racemic* glycidol ([556-52-5]) were investigated further only if they related explicitly to reactivity or synthesis. At this point approximately 1200 articles were in the database. Each abstract and title was then checked for relevance. Journal articles were reproduced and read thoroughly; patents were analyzed solely on information in their *Chemical Abstracts* abstract.

C. Nomenclature

The assignment of *R* or *S* to the C^2 position of the enantiomers of glycidol and its derivatives is not always a trivial matter. As depicted in Figure 1, the O atom

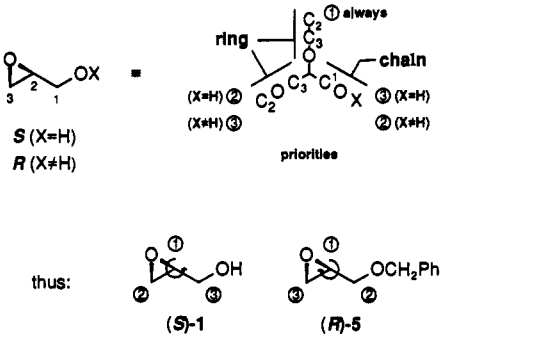
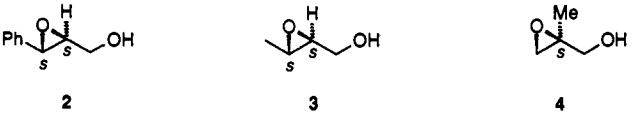


Figure 1. Stereochemical analysis of glycidol derivatives.



2 3 4

Figure 2. Stereochemical nomenclature for compounds 2–4.

at C^2 has first priority, but what about the ring vs the chain? In the original outlining of rules for stereochemical nomenclature, the assignment for certain glycidyl derivatives (particularly *O*-benzylglycidol, **5**) was ambiguous. The rules for assignment of stereochemical priority around the C^2 stereocenter in glycidol and its derivatives were clarified by Prelog and Helmchen in 1982.[5] A new rule was established: For stereocenters embedded in cyclic structures, the stereocenter itself must be included as a "phantom atom" at the end of *both* ring-derived groups. Thus, for glycidol itself (X = H in Figure 1), the ring-derived group C^3–O–C^2 has higher priority than the chain-derived group C^1–O–H. For essentially all O-substituted derivatives, on the other hand, the chain-derived group (C^1–O–X) has higher priority than the ring-derived one. *Thus, derivatization of glycidol results in a switching of the stereochemical designation.*[6] For example, simple benzylation of (*S*)-1 gives (*R*)-**5**.

Unfortunately, not all investigators have been aware of or accepting of this rule, and the literature is replete with erroroneous assignments of *R* and *S* to glycidyl derivatives, particularly *O*-benzylglycidol. In a sample of 25 references examined, only 4 had assigned the stereochemistry to *O*-benzylglycidol on the basis of the guidelines outlined in Figure 1. It is wise to be very careful in reading any of the literature in this area and to double-check all stereochemical assignments. Often it is not enough simply to look at the drawing of the glycidyl derivative, as many are drawn ambiguously, and a few are even incorrect. Rather, it is necessary to check the stereochemistry in context by looking carefully at the stereochemistry of other compounds in a scheme of reactions.

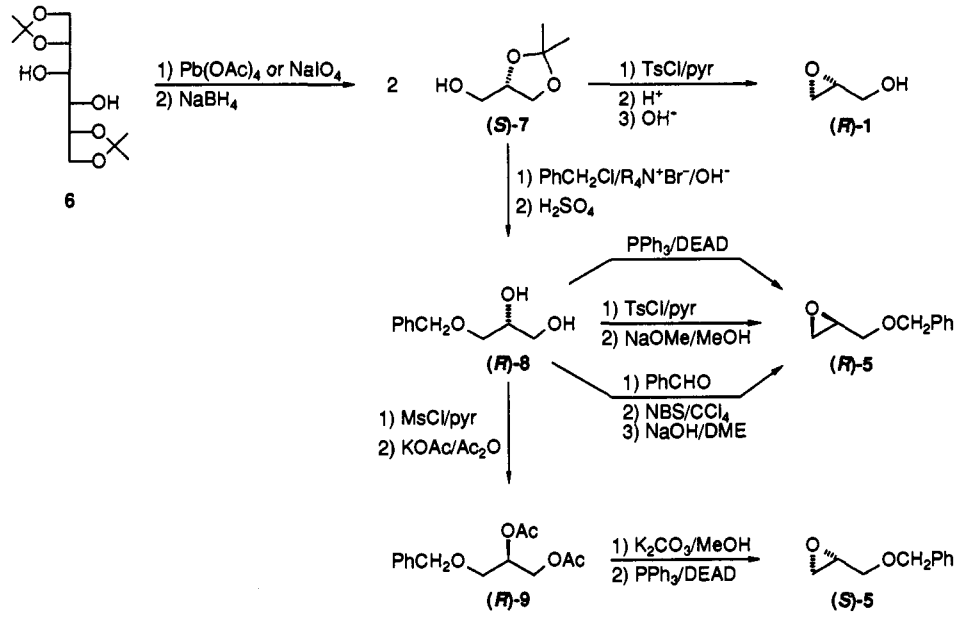
The assignments for C-alkylated and C-arylated glycidols are more straightforward (see Figure 2). In the C^2- and C^3-alkylated cases, the assignments are as for glycidol. Upon derivatization of either **2** or **3**, the stereochemical assignments remains unchanged due to the C^3 appendage's overwhelming priority.

II. Syntheses of Nonracemic Glycidol

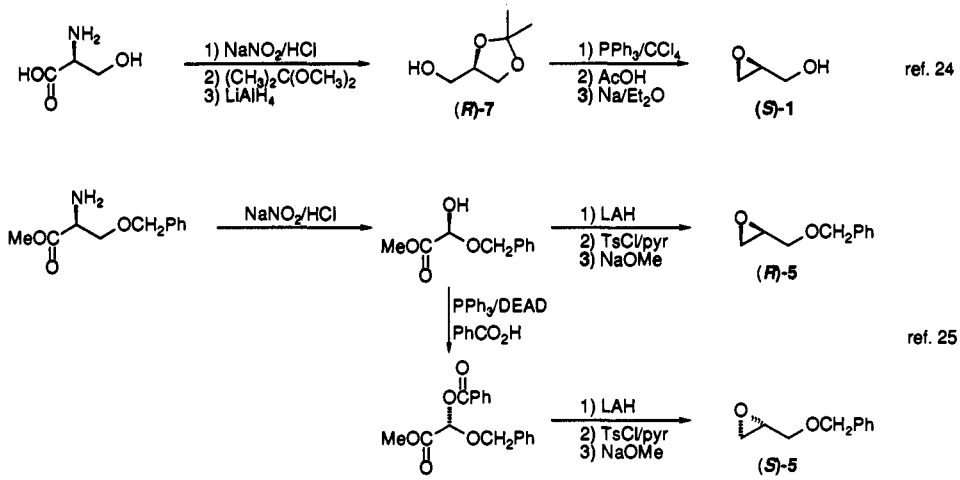
A. Syntheses from D-Mannitol and L-Serine

The earliest approach to nonracemic glycidol was based on the cleavage of the diacetonide of D-mannitol

SCHEME 1



SCHEME 2



(6, Scheme 1). The easily obtainable acetonide[7-11] is oxidized with either lead tetraacetate[12,13] or sodium periodate,[14-16] and the resultant aldehyde is reduced immediately with sodium borohydride to give alcohol (*S*)-7. The enantiomeric purity of 7, though in principle extremely good, is in practice variable.[12,13] The problem is that not only is the intermediate aldehyde sensitive to acid- and base-catalyzed epimerization, but also the product is sensitive to acid-catalyzed ketal migration.[12] Both processes lead to racemization.

Tosylation, acetonide removal, and base-induced ring closure leads to (*R*)-glycidol.[12] This method has the advantage of being very efficient in its use of the carbon atoms of mannitol, but has the drawback of producing only the *R* enantiomer of glycidol.

Through a slightly different sequence, also outlined in Scheme 1, both enantiomers of *O*-benzylglycidol have also been prepared. In this sequence alcohol (*S*)-7 is protected as the benzyl ether and then treated with acid to remove the acetonide and gives diol (*R*)-8.[15,16] At this point a number of options can be taken. The first method devised involves ring closure via the tosylate to give (*R*)-5.[15,17] Later methods developed to accomplish the same goal include treatment with triphenylphosphine/diethyl azodicarboxylate (DEAD)[18,19] and oxidation of the benzaldehyde acetal with use of *N*-bromosuccinimide (NBS)[20] followed by base treatment of the resulting 1-bromo-2-benzoate.[21,22]

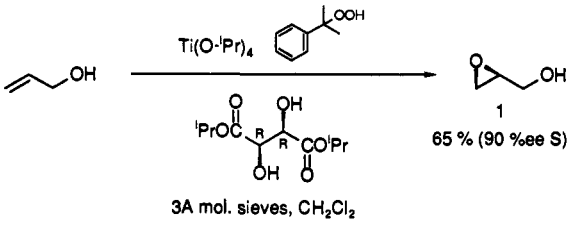
The *S* enantiomer of 5 is available by a sequence involving displacement at C^1 and C^2 of the dimesylate of (*R*)-8 to give diacetate 9 followed by deacylation and ring closure.[18]

Another method of synthesis of nonracemic glycidol from natural sources involves the transformation of L-serine into (*S*)-glycidol (Scheme 2). This sequence takes advantage of the reaction of α-amino acids with sodium nitrite to replace the NH_2 by OH *with retention of configuration*.[23] Chlorination using PPh_3/CCl_4, acetonide removal, and ring closure gives (*S*)-1, thus nicely complementing the mannitol approach. With *O*-benzyl-L-serine methyl ester used as starting material, either enantiomer of *O*-benzylglycidol is similarly available.

B. Syntheses via Asymmetric Epoxidation

Both enantiomers of glycidol are now commercially available in about 88–91% ee from allyl alcohol when

SCHEME 3



refs. 27, 28

asymmetric epoxidation employing titanium(IV) isopropoxide, cumene hydroperoxide, diisopropyl tartrate, and 3A molecular sieves is used (the catalytic Sharpless epoxidation,[26] Scheme 3). Since both the natural (+)-(*R*,*R*) and the unnatural (−)-(*S*,*S*) tartrates are available, this approach leads just as easily to one enantiomer of glycidol as to the other. Early problems with the synthesis were due to the requirement for 50–100 mol % "catalyst," which contributed significantly to the cost of the process and made workup difficult. These problems were solved in 1986 with the introduction of molecular sieves to the reaction mixture, thus allowing the catalyst loading to be in the range 5–10%.

Several patents have been issued on the basis of this process, which has been commercialized.[29-32] Coreagents other than molecular sieves have been reported to be successful (although not specifically for the synthesis of glycidol), including calcium hydride[33] and montmorillonite clay.[34]

Due to the much lower amounts of titanium and reagent derived alcohols in the reaction mixture, the molecular sieves method now allows for in situ derivatization of glycidol,[28,35,36] thus making isolation even easier (since derivatization leads to decreased water solubility and often produces a crystalline compound). In some cases it is preferable to reduce the excess hydroperoxide by using a phosphine or phosphite prior to derivatization.

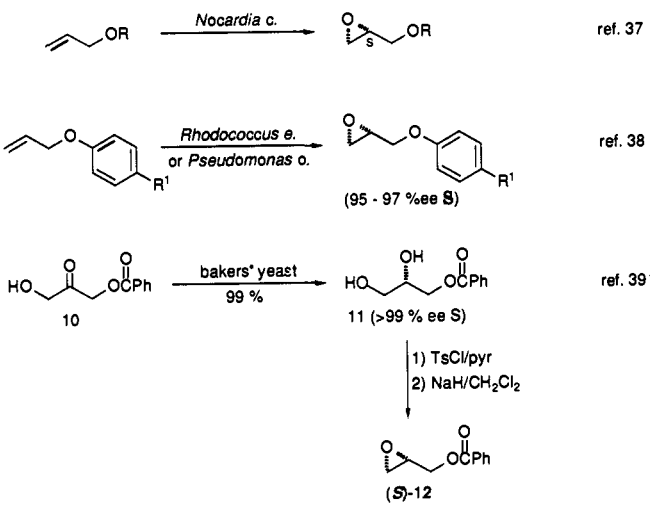
C. Syntheses Employing Enzymatic Transformation of Achiral Substrates

Enzymes as well as titanium(IV) complexes have been used to produce O derivatives of glycidol from achiral substrates (Scheme 4). In the first case, allyl ethers are epoxidized stereoselectively to give ethers of (*S*)-glycidol by using one of several microorganisms, including *Nocardia corallina* (R = alkyl),[37] *Rhodococcus equi* ($R^1 = CH_2CH_2OCH_3$),[38] and *Pseudomonas oleovorans* ($R^1 = CH_2CO_2CH_3$, CH_2CONH_2).[38] Alternatively, enzymatic reduction of achiral ketone **10** by bakers' yeast gives diol ester (*S*)-**11**.[39] Tosylation and ring closure then leads to (*S*)-glycidyl benzoate, (*S*)-**12**.

D. Syntheses Employing Enzymatic Resolution of Racemic Substrates

Specific esters and ethers of glycidol have also been produced via enzymatic resolution. In this approach, a racemic material is allowed to react in the presence of an enzyme. Two modes of reaction are possible. In the first, the reaction is allowed to go to only about 20–30% completion. The resultant product, which must be separated from large amounts of starting material, is generally isolated in high stereochemical purity.

SCHEME 4



Because of the practical limitations of this mode, it will not be discussed further (even though many of the reports cited propose it to be viable.) A second mode is to allow the reaction to proceed to 50–60% completion. One of the enantiomers is hydrolyzed or otherwise destroyed by the enzyme, leaving the starting material highly enriched in the other enantiomer, which is then isolated. The advantage of this second mode over the first is that it allows for a higher yield to be obtained. Nonetheless, the yield is never greater than about 40–45% of the starting mass of the racemic starting material (80–90% theoretical based on the desired enantiomer).

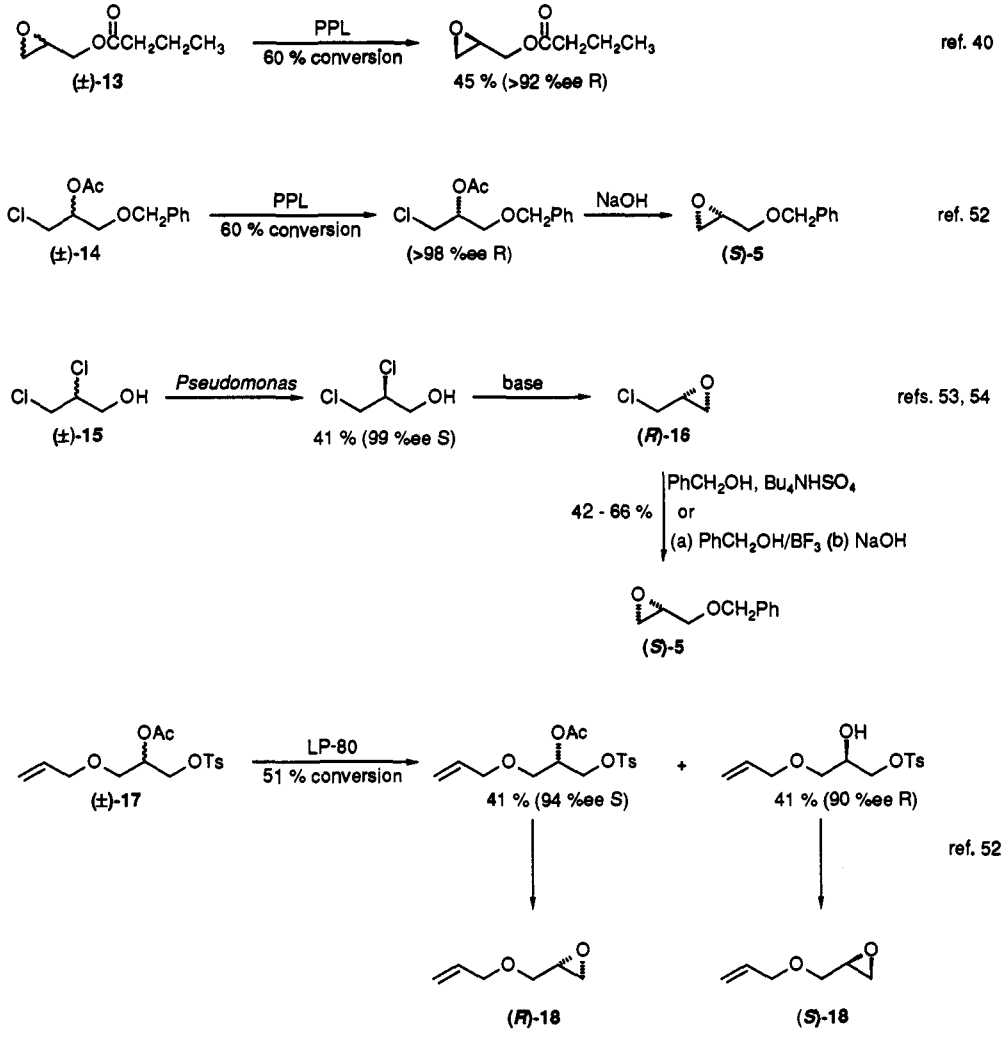
Whitesides pioneered an industrially important process using lipase from porcine pancreas (PPL) to resolve racemic glycidyl butyrate (**13**, Scheme 5).[40] The original process involved an aqueous mixture of **13** and PPL with the pH kept at 7.8 by the controlled addition of 7 M NaOH. After 60% completion, isolation of starting material gave the *R* enantiomer in >92% enantiomeric excess and 45% yield (89% of the theoretical 50% of racemic starting material). Several patents have been issued for this resolution.[41-44] It has been shown that the selectivity can be improved by purification of the enzyme,[45,46] and Ladner has since modified the procedure to use immobilized lipase.[47-49] The process has also been tested with membrane-enclosed lipase, but with somewhat less success.[50] Use of PPL to effect the enantioselective transesterification of glycidol with vinyl ethers has also been attempted.[51]

Using similar conditions, C. H. Wong has reported the enzymatic resolution of racemic acetate **14**. After a second step, (*S*)-*O*-benzylglycidol (**5**) of high enantiomeric purity was produced.

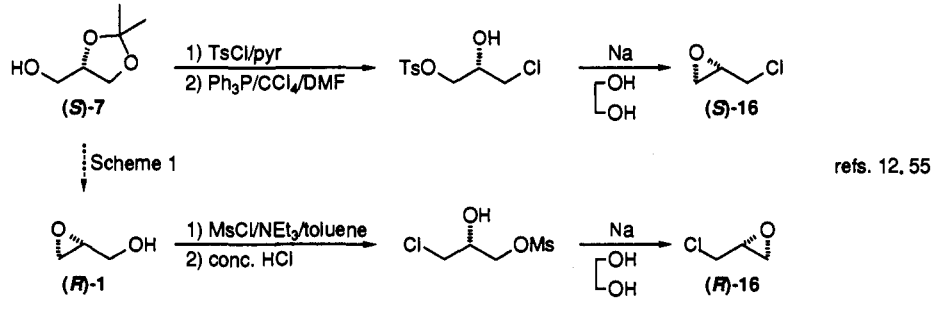
Takano has made (*S*)-*O*-benzylglycidol by enzymatic resolution.[53,54] His procedure involves racemic 2,3-dichloro-1-propanol (**15**) and uses immobilized *Pseudomonas*. In this case, the initial product is treated with base to give (*R*)-epichlorohydrin ((*R*)-**16**). Ring opening and reclosure then gives (*S*)-*O*-benzylglycidol ((*S*)-**5**).

Finally, Wong has also reported the extremely selective hydrolysis of racemic acetate **17** catalyzed by a purified lipase from *Pseudomonas* (LP-80). In this case, after reaction to 51% completion, both the remaining acetate and the product alcohol were isolated, each in 41% yield (82% of the theoretical 50% of racemic

SCHEME 5



SCHEME 6



starting material). Both products were of high enantiomeric purity and were easily transformed into the corresponding enantiomers of 18.

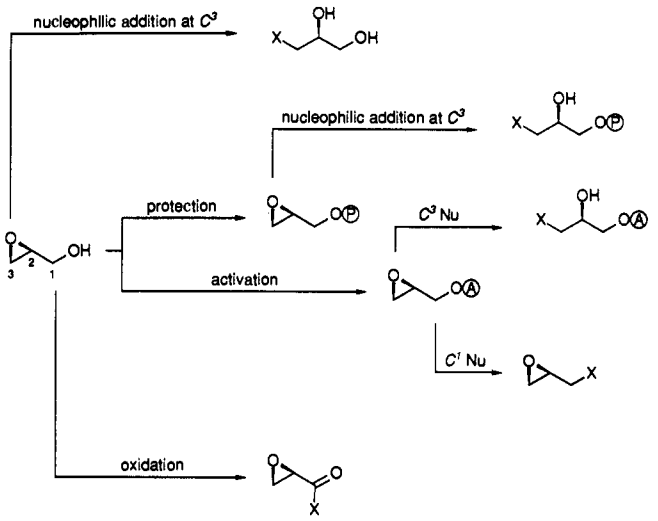
Historically, nonracemic epichlorohydrin (16) has held an important role as a sort of "activated" glycidol. A full discussion of its synthesis and reactivity is beyond the scope of this review. However, both enantiomers are available from mannitol. One of these syntheses involves glycidol explicitly, and for completeness sake both are depicted in Scheme 6.

E. Glycidol Synthesis Summary

There are advantages and disadvantages to each of these different approaches to nonracemic glycidol. Thus, syntheses employing D-mannitol or L-serine provide material of high stereochemical purity, but in their simplest form provide only one enantiomer of glycidol (mannitol giving *R*; serine giving *S*). If *O*-benzylglycidol is required, then either enantiomer is available, but the *S* enantiomer does require several additional steps in either approach. Some of the reagents involved are fairly expensive and/or toxic substances.

Asymmetric synthesis from allyl alcohol has the advantages that both enantiomers of glycidol are readily available in one step, although <0 °C temperatures are generally required. In situ derivatization makes available a whole range of derivatives, still in just one step. The major drawback of asymmetric epoxidation

SCHEME 7



of allyl alcohol is that the optical purity of the resultant product (88–91% ee) is somewhat lower than generally observed for other substrates (≥95% ee). The contamination of the product by 5–7% of the undesired enantiomer is generally only a problem if no later recrystallization is possible. Catalytic asymmetric epoxidation has recently become an important industrial process.

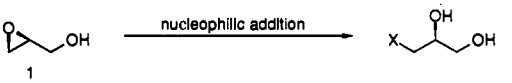
The enzymatic approaches have the advantages that few reagents are required, that the processes are capable of being scaled up to industrial scale, and that the resultant optical purity is excellent. The disadvantages are that careful control of reaction conditions are necessary, that glycidol *itself* is not produced by these methods, that substituted glycidols are not available (or have not been investigated), and that from any given process only one enantiomer of ether or ester is available. In addition, the starting materials for enzymatic resolution are not always readily available. The enzymatic resolutions, of course, give a maximum of 50% yield. Despite these drawbacks, there is a substantial amount of industrial interest in these enzymatic resolutions.

III. Reactivity of Nonracemic Glycidol and Related 2,3-Epoxy Alcohols

Virtually all of the reactions of nonracemic glycidol can be classified into one of four categories (Scheme 7): nucleophilic opening at C^3, protection or activation of the hydroxyl group followed by nucleophilic addition either at C^1 or C^3, and oxidation of the hydroxyl group to give an aldehyde or acid. These reactions will be discussed in turn. Along with each will be a discussion of the effect of substituents on reactivity.

Of course, virtually all of the reactions of nonracemic glycidol work with racemic glycidol as well. *However, the reverse is not as generally true.* Thus, for example, a reaction which works fine on racemic glycidol may lead to partial racemization in the case of nonracemic glycidol. Even reactions which work on nonracemic glycidol may not work the same with the racemate, especially if crystallization is involved. Since this review focuses on *nonracemic* glycidol, reactions only reported for racemic glycidol will be introduced selectively and will generally not be pictured. In the cases where reactions of racemic glycidol are of special note and are diagrammed or tabulated, an explicit mention will be made to the effect that these reactions were carried out only on racemic glycidol. To make the comparisons easier in this section, any reactions carried out on either enantiomer will be depicted *as if* carried out on the enantiomer derived from (*S*)-glycidol (as in Scheme 7).

TABLE 2. Simple Nucleophilic Additions to Glycidol



1

entry	reagent	X	yield (%)	ref
1	$EtMgBr/Li_2CuCl_4$/THF -5 °C	Et	71	56
2	sat. NH_3/^{i}PrOH/3 days	H_2N	93	57
3	R_2NH/base	R_2N	40-90	58
4	$R_2NH/Ti(O^iPr)_4$ *in situ*	R_2N	>68	36
5	$ROH/Ti(OR)_4$	RO	45-69	59
6	$ArONa/Ti(O^iPr)_4$/^{t}BuOH *in situ*	ArO	40	36, 60, 61
7	$RCO_2H/Ti(O^iPr)_4/Et_2O$ 0 °C	RCO_2	25-40	62
8	PhSH/NaOH/dioxane	PhS	71	63
9	$PhSH/Ti(O^iPr)_4$ *in situ*	PhS	88	36
10	HCl (gas)	Cl	96	64

A. Nucleophilic Addition

1. Nucleophilic Addition to Nonracemic Glycidol

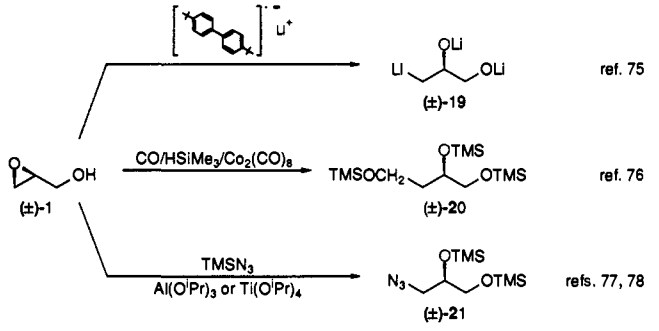
Simple nucleophilic additions to nonracemic glycidol are summarized in Table 2. The entries are ordered with respect to the stereochemical priority of the newly formed group. Note that addition occurs exclusively at C^3.

Addition of organomagnesium reagents is catalyzed by Li_2CuCl_4 (entry 1). This reagent, besides opening epoxides, has also been used to couple organomagnesium reagents with halides[65] and tosylates.[66] Use of a methyllithium/copper(I) bromide/tributyl phosphine reagent with racemic glycidol, on the other hand, resulted in selective *reduction* of the epoxide to the secondary alcohol, even in the presence of ketones.[67]

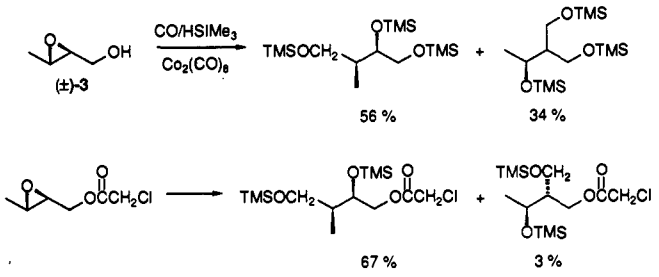
Ammonia can be added easily to glycidol in high yield as a saturated solution in 2-propanol (entry 2). The reaction has also been carried out in a high-pressure reactor.[57] The addition of secondary amines to glycidol is successful (entries 3 and 4), but most work has been done on racemic glycidol or protected glycidol and is not included in this particular table. In entry 4, the amine was added in situ after asymmetric epoxidation.

The addition of small aliphatic alcohols such as methanol to glycidol has been reported only for racemic material.[68] Catalysis by the quaternary ammonium hydroxide Triton B ($PhCH_2Me_3N^+OH^-$) is successful. However, the base-catalyzed addition of long-chain aliphatic alcohols to glycidol (of interest in the lipid field) is not successful due to the problem of competitive polymerization, which leads to a highly branched water-soluble solid.[69,70,71] The solution to this problem is to use a Lewis acid instead of a base to facilitate the reaction (entry 5). It was found that the best addition was with titanium alkoxide derived from the same alcohol that was to be added (in this case primary aliphatic alcohols). Use of titanium(IV) isopropoxide instead led to a significant amount of competitive addi-

SCHEME 8



SCHEME 9



tion of 2-propanol. Tin(IV) chloride has also been used with the racemate.[72] These reactions were based on reports of similar reactions involving *trans*-3-propylglycidol.[73]

Phenolates add readily to glycidol in reasonable yield (entry 6). In this case, the yield may be lower because it includes the asymmetric epoxidation step. Addition of benzenethiolate also poses no problem under either basic (entry 8) or Lewis acid (entry 9) conditions.

The addition of long-chain aliphatic acids is also of great interest in lipid chemistry. Opening of the epoxide with carboxylic acids in the presence of tributylamine is effective for racemic glycidol,[74] but in the case of glycidol it was shown that the high yields of addition to *racemic* glycidol are not reproducible with nonracemic material. Johnson[62] proved that the problem is due to ester migration from one end of the molecule to the other, which in the case of nonracemic glycidol leads to racemization. Use of titanium(IV) isopropoxide (entry 7) gives only a moderate yield of nonracemic product.

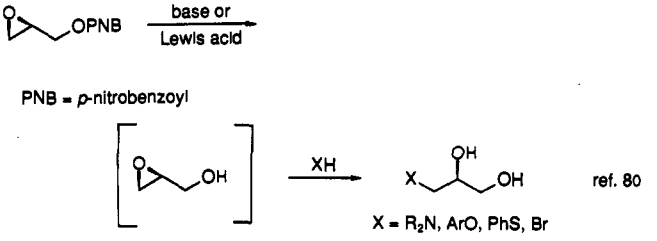
The addition of halide under acidic conditions (entry 10) is successful. The chloride, when derived from (*S*)-glycidol (as depicted here), has male antifertility activity.[64] Interestingly, the product from (*R*)-glycidol is inactive.

Three additional reactions only reported for racemic glycidol are notable (Scheme 8).

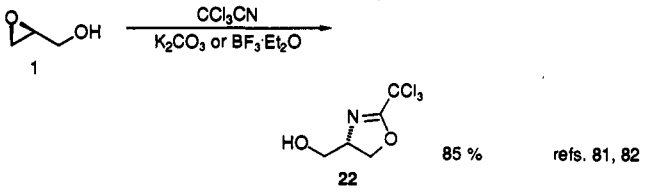
Reaction with lithium 4,4′-di-*tert*-butylbiphenylide (LDBB) in THF at −78 °C results in alkyllithium reagent **19** being produced. Addition of reagent **19** to *p*-methoxybenzaldehyde was only moderately successful (27% yield of the triol adduct). Use of a protected glycidol (methoxymethyl) was somewhat more successful.[75]

Reaction of racemic glycidol with trimethylsilane and CO in the presence of $Co_2(CO)_8$ results in addition of a CH_2O unit at C^3 followed by silylation of all three free hydroxyls to give compound **20** in excellent yield (92% by GLC). This reaction is formally equivalent to reaction with LDBB followed by addition to formaldehyde. The same reaction carried out on *trans*-3-methylglycidol (**3**, Scheme 9) was less selective, leading to a 56:34 ratio of opening at C^3 vs C^2. This selectivity could be improved to 67:3 by use of the chloroacetyl protecting group on **3**.

SCHEME 10



SCHEME 11



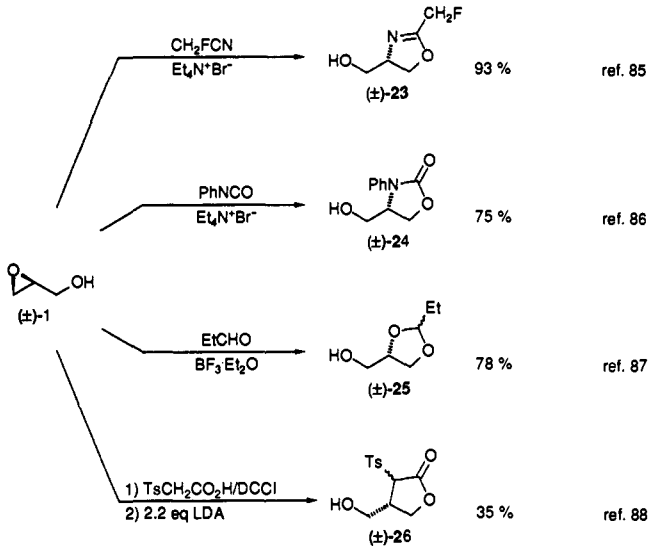
Finally, reaction with trimethylsilyl azide ($TMSN_3$) to give the bis(silyloxy) azide **21** (also Scheme 8) can be facilitated either with aluminum[77] or titanium[78] alkoxides. The reactions were carried out at room temperature for 4–6 days, giving a 59% yield of **21** in the case of aluminum and 90% yield in the case of titanium. In both cases the regioselectivity was excellent. Other workers have observed somewhat less selectivity in cases where there is an alkyl substituent at C^3.[79]

A clever method of generating glycidol in situ has been devised by Sharpless (Scheme 10). In this method, glycidol of about 85–90% ee is produced by asymmetric epoxidation and protected in situ as the *p*-nitrobenzoate. (Though crystalline, this ester does not lend itself to enantiomeric enrichment through recrystallization.) Treatment of the ester under many conditions similar to those in Table 2 results in in situ generation of glycidol and subsequent opening. Nucleophiles that were examined include amines, phenols, thiols, and bromide.

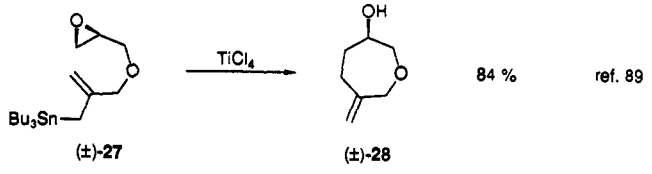
Whereas there are no reports of the direct addition of a nucleophile to nonracemic glycidol at C^2, one addition of note involes initial reaction at the OH followed by intramolecular displacement at C^2 (Scheme 11). Thus, oxazoline **22** is formed in 85% yield when glycidol is treated with trichloroacetonitrile and either a catalytic amount of K_2CO_3[81] or $BF_3{\cdot}Et_2O$.[82]

Several similar reactions have been reported for racemic glycidol (Scheme 12). For example, heating racemic **1** with CH_2FCN in the presence of tetraethylammonium bromide gives oxazoline **23**. Reaction with phenyl isocyanate under similar conditions gives oxazolidinone **24**. Benzoylisocyanate has also been used in a related reaction.[83,84] Besides nitriles and isocyanates, aldehydes also react with glycidol, for example giving dioxolane **25**. Finally, esterification of glycidol as the α-toluenesulfonylacetate using dicyclocarbodiimide and treatment with lithium diisopropylamide results in ring closure, forming lactone **26**. This reaction, which leads to C–C bond formation, is less successful with trans-substituted glycidols due to steric hindrance. In each reaction depicted in Scheme 12,

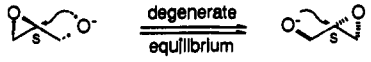
SCHEME 12



SCHEME 13



SCHEME 14



initial reaction occurs at the hydroxyl to give a species which can further react to displace the epoxide bond at C^2.

In contrast to this regioselectivity is the titanium(IV)-catalyzed reaction of racemic allylstannane **27** (Scheme 13) to give oxepane **28**, the product of opening at C^3. This reaction is successful with a variety of substituted glycidols, including **2** and **4**. The allylstannanes are easily made from 2,3-epoxy alcohols.

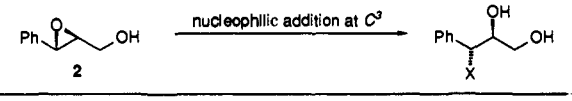
It should be noted that many of the conditions listed in Table 2 are basic. For all 2,3-epoxy alcohols exposed to basic conditions there is always the possibility of Payne rearrangement,[90] whereby the alcoholate displaces the epoxide internally to form a new 2,3-epoxy alcoholate (Scheme 14). In the case of glycidol *specifically*, this rearrangement is degenerate, however, and poses no problem (except for isotopically labeled glycidol). Racemization does not occur.

In summary, reactions involving glycidol with highly nucleophilic reagents (such as amines, thiolates, and phenolates) or under acidic conditions (HCl) are reasonably successful. The problems mentioned above regarding polymerization in the case of base-catalyzed addition of alcohols and product rearrangement/racemization in the case of addition of carboxylic acids are largely solved by the use of protecting groups, as discussed below.

2. Nucleophilic Addition to Substituted Glycidol

In this section all of the reactions of compounds **2–4**, both nonracemic and racemic, reported since 1967 are summarized. Only the nonracemic reactions are tabulated. The goal is to give a sense both of what has and has not been done in this area and, more important, to illustrate the effects of substitution around the oxirane skeleton on nucleophilic substitution.

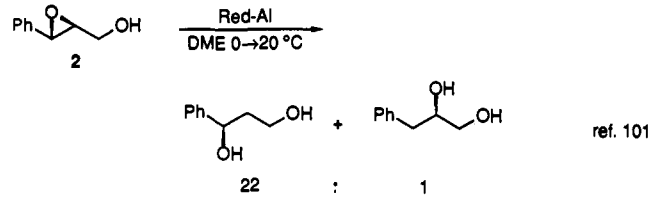
TABLE 3. Simple Nucleophilic Additions to 3-Phenylglycidol



entry	reagent	X[a]	yield (%)	ref
1	H_2 Pd/C	H	88	91
2	PhC≡C--BF_2	PhC≡C	90	91
3			96	91
4	R_2CuLi or $R_2(CN)CuLi_2$	R	78-88	91, 92
5	$Ti(O^iPr)_2(N_3)_2$	N_3	76	93
6	NaN_3/NH_4Cl	N_3	>95	91, 93
7	R_2NH/KOH	R_2N	84	94
8	ROH/BF_3·Et_2O	RO	74-99	91, 95
9	ArONa	ArO	83	96
10	PhCOH/$Ti(O^iPr)_4$	PhCO	~90	97, 98
11	$^iPr_2NH$·3HF 110 °C, 8 h	F	39	99
12	PhSH/NaOH	PhS	81	91

[a]Dashed line indicates point of attachment.

SCHEME 15



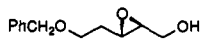
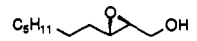
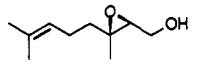
a. *trans*-3-Phenylglycidol. Reactions of nonracemic *trans*-3-phenylglycidol (**2**) with nucleophiles are compiled in Table 3. Although four of the conditions listed (entries 4, 7, 10, and 12) are similar to some of those in Table 2, the other eight involve reactions yet to be reported with glycidol itself. The major differences between the reactivity of **2** and **1** seem to be due to the phenyl group of **2** activating the C^3 position toward acid-catalyzed and organometallic addition. The effect on base-catalyzed reactions is less evident.

Takano[91] has carefully examined the addition of nucleophiles to *trans*-3-phenylglycidol. Much of his work, along with the work of several others, is summarized in this table. Several entries deserve mention.

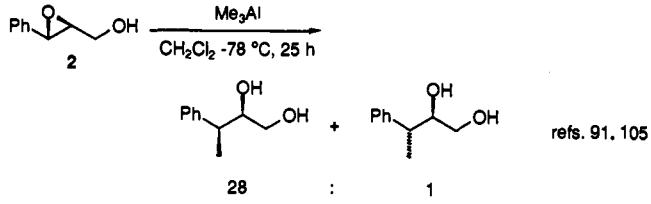
Reduction of **2** is effected by palladium-catalyzed hydrogenation (entry 1). Titanium(IV)-facilitated reduction by $LiBH_4$ has been carried out on the racemate with similar results.[100] Both methods are highly regioselective, giving >98% selectivity for opening at C^3. Not all reductions are selective for C^3, however. Reduction of **2** using sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) is selective for reduction at C^2 (Scheme 15).

This reaction is presumed to occur through initial attachment of the aluminum to the primary OH followed by intramolecular hydride reduction. These results are opposite those of Table 3, entry 1. Lithium

TABLE 4. Selectivities of Reductions of Four 2,3-Epoxy Alcohols

compd	reduction selectivity C^3 vs. C^2			ref
	$LiBH_4/Ti(O^iPr)_4$	Red-Al	$LiAlH_4$	
	98 : 2			100
		4 : 96		101
		1 : 99		102
			50 : 50	102
	99 : 1			100
		1 : 99		103
			20 : 80	103
	87 : 13			100
		1 : 99		103
			0 : 100	104

SCHEME 16



aluminum hydride ($LiAlH_4$) has also been used to reduce 2,3-epoxy alcohols and appears to react with more similarity to Red-Al than to $LiBH_4/Ti(O^iPr)_4$. However, $LiAlH_4$ appears to be generally less selective. Four comparative examples are given in Table 4. Note the complementary nature of the reactions of $LiBH_4/Ti(O^iPr)_4$ and Red-Al.

In the addition of organometallic reagents to **2** (Table 3, entries 2–4) there are also a few surprises. Use of trimethylaluminum instead of $Me_2(CN)CuLi_2$ results in addition with *retention of configuration* at C^3 (Scheme 16).[91,105] Other trialkylaluminum reagents are less selective. $PhC{\equiv}CAlEt_2$, for example, gives only a 3.2:1 ratio of retention vs inversion. Triethylaluminum gives a 1:1 mixture of diastereomers.

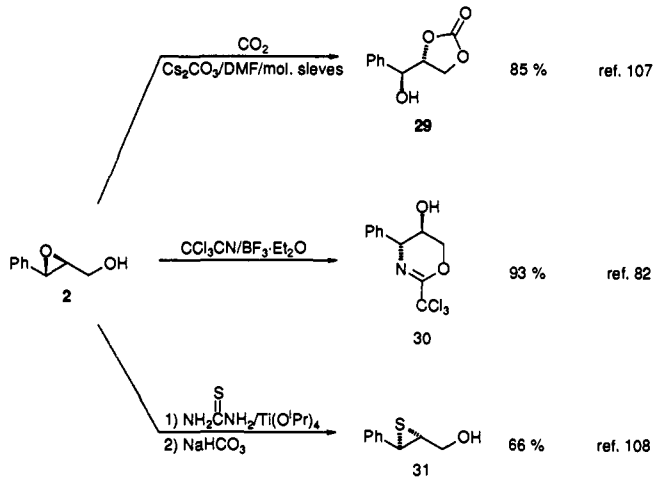
Two reagents, NaN_3 and $Ti(O^iPr)_2(N_3)_2$, are successful for the addition of azide (Table 3, entries 5 and 6). For this particular substrate, $Ti(O^iPr)_2(N_3)_2$ holds no advantage. With other substrates it is faster and more regioselective than NaN_3.[93]

Addition of secondary amines to *trans*-3-phenylglycidol in the presence of strong base (entry 7) is only moderately successful, the product being contaminated by about 12% of the regioisomer from Payne rearrangement (Scheme 14) followed by addition at C^1.[94] The fact that 3-*alkyl*-substituted glycidols under these conditions undergo much higher amounts of addition at C^1 indicates that the presence of the phenyl group in **2** facilitates base-catalyzed nucleophilic opening at C^3 compared to other substituents and minimizes the danger of Payne rearrangement.

The Lewis acid catalyzed addition of alcohols (entry 8) is also facilitated by the phenyl group in **2**. Thus, **2** reacts smoothly and in high yield with small molecular weight alcohols such as methanol, allyl alcohol, and propargyl alcohol in the presence of $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at −30 to −40 °C. Phenols in the presence of NaOH also add readily and highly selectively (entry 9),[96] as do thiophenols (entry 12).[91]

Carboxylic acid addition in the presence of $Ti(O^iPr)_4$ (entry 10) is far more successful with **2** than with glycidol, yields being high enough to continue without purification.

SCHEME 17



Addition of fluoride (entry 11) occurs in only moderate yield with the 1:3 complex of diisopropylamine with HF at 110 °C for 8 h.[99] About 5% of the product of retention of configuration at C^2 is also formed. Although the yield is low, the reaction is notable in that no isolable fluorinated materials could be obtained when other fluorinating reagents were employed.

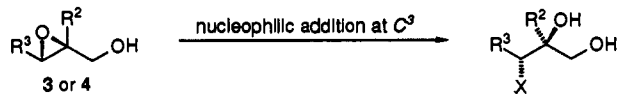
Three additional reactions of nonracemic *trans*-3-phenylglycidol are of note (Scheme 17). In the presence of Cs_2CO_3, carbon dioxide adds first to the OH of **2**, then opens the epoxide at C^2 (much as is observed for nitriles and isocyanates with glycidol, Scheme 12) to give **29**. The dioxolanone formed by carbonate migration to the C^2/C^3 positions is also found in 8% yield. A similar reaction with formaldehyde (giving structure **29** without the carbonyl group) has been reported with racemic *trans*-3-phenylglycidol.[106] Similarly, trichloroacetonitrile reacts with the OH, but then opens the ring at the C^3 position, giving heterocycle **30**. Compare this result with that found for glycidol presented in Scheme 11.

Also included in Scheme 17 is the titanium(IV)-catalyzed reaction of **2** with thiourea to give the unstable episulfide **31** in 66% yield. Evidently in this case reaction first occurs at C^3 due to initial *titanium* complexation between the OH and the epoxide oxygen. Displacement at C^2 then occurs. No product was isolable prior to base treatment.

b. ***trans*-3-Methylglycidol and 2-Methylglycidol.** Reported reactions of nonracemic *trans*-3-methylglycidol (**3**) and 2-methylglycidol (**4**) with nucleophiles are compiled in Table 5. Of particular note are the organometallic reactions. Homoallylic organomagnesium reagents, usually quite sluggish, added readily to **4** in the presence of dilithium tetrachlorocuprate (entry 2).

In addition, much work has been done in discovering the best way to add tritiated methyllithium to **3**. Thus it was found that methyllithium prepared from methyl iodide and butyllithium in hexane ("lithium iodide free" MeLi) gave the desired addition (entry 3). On the other hand, reaction of **3** with $Me_2(CN)CuLi_2$ results in a 50:50 mixture of addition at C^2 and C^3.[118,119] Use of methyllithium prepared from methyl iodide and lithium metal resulted only in the formation of diol **32** (Scheme

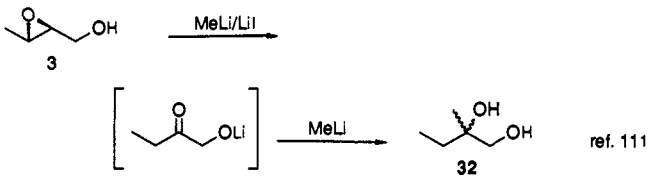
TABLE 5. Simple Nucleophilic Additions to 2-Methylglycidol and 3-Methylglycidol



entry	R^3 R^2	compd	reagent	X[a]	yield (%)	ref
1	Me H	3	$Et_2AlC{\equiv}CR$	RC≡C	38	109
2	H Me	4			85	110
3	Me H	3	LiI-free [^{3}H]-MeLi	[^{3}H]-Me	50	111, 112, 113, 114
4	H Me	4	PhSH/NaOH/dioxane	PhS	~35	115
5	H Me	4	$LiI{\cdot}2H_2O$/HMPT/$CHCl_3$	I	64-70	116, 117

[a]Dashed line indicates point of attachment.

SCHEME 18



18).[111] It would be interesting to note if such a difference is observed with glycidol or *trans*-3-phenylglycidol. Lithium iodide, in fact, adds readily to **4** in chloroform in the presence of hexamethylphosphoric triamide (HMPT), as shown in entry 5.

Concentrated ammonia reacts with racemic **3** selectively at C^3 in almost quantitative yield.[120] The reaction is run at 85 °C for 4 h.

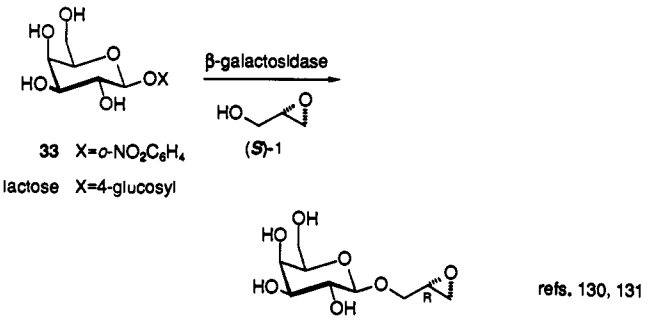
c. Substituent Effects Summary. In summary, all reported reactions of nonracemic glycidol occur at C^3 with high selectivity. The effect of a phenyl group attached at this position is to activate the C^3 position further toward acid-catalyzed and organometallic reactions. However, for nucleophilic reactions, a phenyl group at C^3 has mixed effect, depending upon reagent and conditions. Most dramatic is reduction with Red-Al, which occurs selectively at C^2. Reactions of **2** with organometallic reagents can even go with retention of configuration at C^3. The effect on regioselectivity of a methyl substituent at C^2 is not significant. A methyl at C^3, on the other hand, results in proportionally less addition at that position and can even lead to rearrangement prior to addition, as in the case of methyllithium that is not lithium iodide free.

B. Protection

Protection as defined here means any process which serves to prevent unwanted reactions by changing a functional group (in this case OH) into a less reactive group. The protecting groups discussed include alkyl and silyl ethers and carboxylic esters. Activation is defined as any process which serves to facilitate a desired reaction by changing a functional group into a more reactive one. A variety of sulfonic acid esters have been used to activate glycidol. They will be discussed later.

It is important to realize that although glycidol is an alcohol, it is a fairly reactive one, susceptible to base-catalyzed decomposition. Thus not all "standard" procedures for alcohol protection and activation are

SCHEME 19



successful with glycidol. What special precautions must one take? Which groups have been successfully applied? In addition, activation of glycidol poses a special challenge in that an already electrophilic molecule becomes even more electrophilic. After activation, which site will be more reactive, C^1 or C^3? The discussion below focuses on these questions and is organized along the lines of Scheme 7.

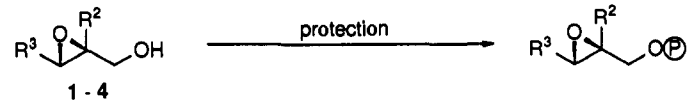
1. Protection of Nonracemic Glycidol and Related Small 2,3-Epoxy Alcohols

Since there is much similarity in reactivity among 2,3-epoxy alcohols **1**–**4** toward protection, reports of their protection will be summarized together (Table 6). The references in this table include details of the preparation of the indicated derivative. References in which a derivative is made by "standard" procedures or by procedures "described elsewhere" are not included. Thus, some compounds which are discussed later in this review are not presented here. The table is organized by the nature of the derivative, in increasing stereochemical precedence: alkyl, alkoxyalkyl, acyl, and silyl. Several entries in the table refer to protections which were carried out in situ after asymmetric epoxidation. Yields for those entries include the epoxidation reaction.

(*S*)- and (*R*)-*O*-(Triphenylmethyl)glycidol (tritylglycidol, entry 1) are crystalline solids with melting point 99–100 °C. Recrystallization allows for a "free" increase in enantiomeric purity after asymmetric epoxidation of allyl alcohol and in situ protection.[122] The trityl ether of (2*S*,3*S*)-*trans*-3-methylglycidol (entry 2) has also been prepared.

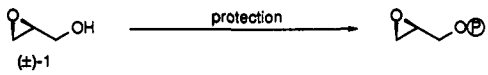
2,3-Epoxy alcohols are more robust toward mild acid than one might expect, and protection as mixed acetals and ketals is successful when standard conditions are

TABLE 6. Protection of Glycidol and Related Small 2,3-Epoxy Alcohols



entry	R^3 R^2	compd	OⓅ (abbr)	reagent	yield (%)	ref
1	H H	1	$OCPh_3$ (Tr)	TrCl/Et_3N/toluene or *in situ*	80	121, 122
2	Me H	3	(Tr)	TrCl/Et_3N/DMAP/CH_2Cl_2	89	123
3	H H	1	 (THP)	DHP/TsOH/CH_2Cl_2	88	124, 125
4	Me H	3		 /cat. $POCl_3/CCl_4$	---	126
5	H Me	4	$OCCH_3$ (Ac)	Ac_2O/pyr	100	127
6	H H	1	 (PNB)	PNBCl/Et_3N/CH_2Cl_2 *in situ*	61	28
7	Me H	3	(PNB)	"	65	28
8	H Me	4	(PNB)	"	78	28
9	H H	1	OSi^tBuMe_2 (TBS)	TBSCl/Et_3N/CH_2Cl_2 *in situ*	68	28
10	H H	1	OSi^tBuPh_2 (TBDPS)	TBDPSCl/Et_3N/CH_2Cl_2 *in situ*	45	28
11	Me H	3	(TBDPS)	"	76	128
12	H Me	4	(TBDPS)	TBDPSCl/DMAP/Et_3N/CH_2Cl_2	78	129

TABLE 7. Selected Procedures for the Protection of Racemic 1



entry	OⓅ (abbr)	reagent	yield (%)	ref
1	OCH_2Ph (Bn)	BnBr/NaH/THF	75	132, 133
2	 (MEM)	MEMCl/$^iPr_2NH$/CH_2Cl_2	92	134
3	 (EE)	CH_2=CHOEt/HOTs	---	135, 136
4		 /pyr/Et_2O	---	40
5		$(C_{15}H_{31}C)_2O$/hexane	80	74
6		 /$ZnCl_2$/CH_2Cl_2	84	137
7		 /pyr/Et_2O	78	121

used (entries 3 and 4). A related reaction is the β-galactosidase-catalyzed transacetalation of lactose or *o*-nitrophenyl galactopyranoside (33, Scheme 19). Either enantiomer of glycidol may be used, however the yield is only about 30%.

In situ procedures following asymmetric epoxidation have been used not only for making trityl ethers but also for making *p*-nitrobenzoates (entries 6–8) and silyl ethers (entries 9–11). These yields include the epoxidation reaction. In the case of the acetate of 4 (entry 5), the epoxy alcohol was isolated first, then protected.

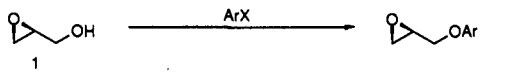
Several procedures for protecting glycidol have been reported only for the racemate. Selected examples are tabulated in Table 7.

For example, although (*S*)-*O*-benzylglycidol ((*S*)-5) has been made from (*R*)-glycidol,[138] the procedure for benzylation has only been reported for the racemate (entry 1). Care must be taken to moderate the temperature of the benzylation reaction.

Racemic glycidyl (methoxyethoxy)methyl (MEM) ether has been made by using diisopropylamine and MEM chloride (entry 2). Acidic conditions have been used to make diastereomeric mixtures of ethoxyethyl (EE) ethers (entry 3). The ethoxyethyl ether of racemic 4 has also been reported.[139]

Acid chlorides (entries 4 and 7), anhydrides (entry 5), and ketenes (entry 6) have all been used to make aliphatic esters of racemic glycidol. The anhydride used in entry 5 was palmitic anhydride. It would be interesting to know how general this reaction is. The alternative esterification procedure using palmitoyl chloride in pyridine has also been investigated,[24,140] but indications are that the anhydride procedure is preferable.[74] A careful study comparing methods of ester synthesis has been carried out on racemic glycidol.[140]

TABLE 8. Nucleophilic Aromatic Substitutions Involving Nonracemic Glycidol

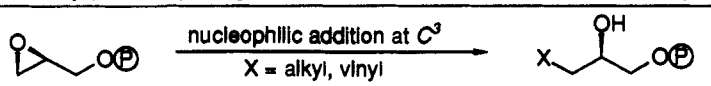


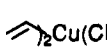
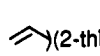
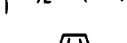
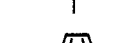
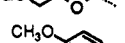
entry	ArX	conditions	yield (%)	ref
1		ArX/NaH/DMF 0 °C 1 h → 20 °C 16 h	55	143
2		ArX/NaH/DMF 0 °C 1 h → 20 °C 16 h	38	143
3		"base"	---	144

2. Preparation of Nonracemic Glycidyl Aromatic Ethers via Nucleophilic Aromatic Substitution

Several reactions involving the transformation of the OH of glycidol to OAr by nucleophilic aromatic substitution to produce glycidyl aromatic ethers are known, both for the racemate[141,142] and nonracemate (Table 8). These compounds are not "protected" in the sense defined above, because the aromatic group is never removed. Nonetheless, their syntheses from glycidol are

TABLE 9. Additions of Alkyl, Alkenyl, and Aryl Organometallics to Protected Nonracemic Glycidol



entry	OP	reagent	X[a]	yield (%)	ref
1	OBn	MeMgCl/Li_2CuCl_4/THF -78 °C	Me	99	145
2	OBn	 /THF 0 °C		95	146
3	OBn	 /THF -30 °C		86	147
4	OBn	 /THF 0 °C		90	148
5	OBn	/THF -78→0 °C		90	149
6	OBn	/THF -78→0 °C		95	149
7	OBn	 /LiCl or BF_3·Et_2O/DME		---	138
8	OBn	 /CuCN/THF -78 °C		98	150
9	OBn	 THF -30 °C		87	151

[a]Dotted lines indicate point of attachment.

described here because they are examples of a fundamentally different reaction involving glycidol. All of these syntheses involve the reaction of glycidol with a halogenated aromatic system with displacement of the halogen. That is, the C–O bond in glycidol remains intact. Reactions which form similar products by in situ activation and displacement of the OH of glycidol are discussed later in this review (see Table 16).

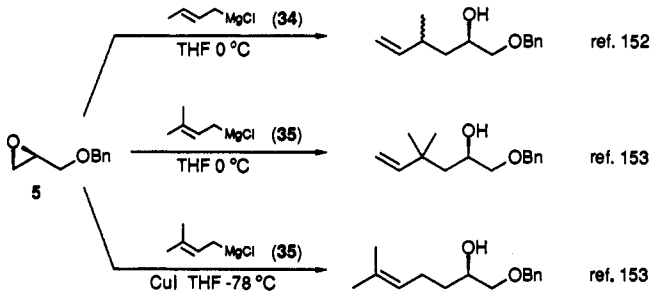
3. C^3-Reactivity of Protected Nonracemic Glycidol

a. Toward Alkyl, Alkenyl, and Aryl Organometallics. Additions of alkyl, alkenyl, and aryl organometallic reagents to protected nonracemic glycidol are summarized in Table 9. Although it would be reasonable to use a variety of protecting groups for such reactions, only the use of benzyl (Bn, compound **5**) has been reported.

All of these reactions have been carried out with use of fairly similar conditions, namely, in ethereal solvents at subambient temperatures. Although the reaction of allylmagnesium chloride (entry 2) is straightforward, the reactions of other allylmagnesium reagents depend dramatically upon conditions (Scheme 20). Thus reactions of either **34** or **35** at 0 °C *in the absence of Cu(I) salts* leads to addition at the more substituted allylic position. When 10 mol % of CuI is used at −78 °C, on the other hand, addition occurs at the less-substituted allylic position. All of the reactions in Scheme 20 are reported to occur in about 90% yield.

Lipshutz[147,148] has studied the addition of a number of reagents derived from vinyllithium to **5**. Use of $(vinyl)_2CuLi$ gave only a 73% yield as compared to the 86% yield of a higher order cyanocuprate (Table 9, entry 3) and 90% with a higher order mixed cyanocuprate (entry 4). Use of the lower order cuprate (vinyl)Cu(CN)Li gave a yield of only 11%.

SCHEME 20

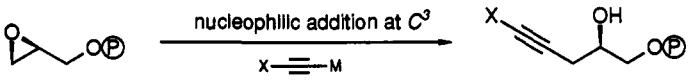


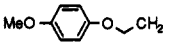
Two aryllithium species have been added. Thus Ireland[138] added the lithiofuran of entry 7 in unreported but presumably high yield in the presence of either lithium chloride or boron trifluoride, and Takano[150] added a cuprate reagent derived from *p*-bromoanisole (entry 8). A 2-lithiofuran has also been added to racemic **5** in excellent yield with boron trifluoride used as coreagent.[154]

b. Toward Acetylides. Reactions of acetylides with protected nonracemic glycidol are summarized in Table 10. Acetylene itself, either as the sodium or the lithium salt, has been employed (entries 1 and 2). Use of lithium (trimethylsilyl)acetylide (entry 3) allows for optional removal of the TMS group by using KF in methanol. For substituted acetylides, the reaction can be carried out in THF without (entry 5) or with the aid of *N,N,N′,N′*-tetramethylethylenediamine (entry 4), boron trifluoride (entry 6), or hexamethylphosphoramide (entries 7 and 8).

Takano has found that the adduct of acetylene with **5** can be isomerized to the internal alkyne **36** (Scheme 21) using potassium *tert*-butoxide in DMSO.[159,164] No racemization is observed. This isomerization thus leads

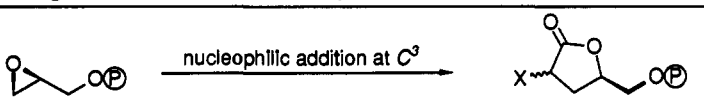
TABLE 10. Nucleophilic Additions of Acetylides to Protected Nonracemic Glycidol

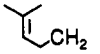
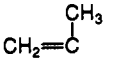


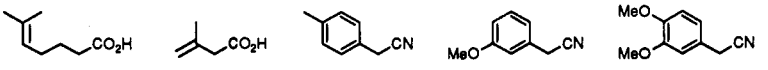
entry	OP	M	conditions	X[a]	yield (%)	ref
1	OBn	Na	DMSO	H	87	155, 156, 157
2	OBn	Li	NH_2⌒NH_2 /DMSO 0 °C	H	89	158, 159
3	OBn	Li	BF_3·Et_2O/THF -78 °C	TMS	82	132
4	OTHP	Li	TMEDA/THF -78→25 °C	Et	77	124
5	OBn	Li	THF -30→25 °C		74	160
6	OTBS	Li	BF_3·Et_2O/THF -78 °C	$THPOCH_2$	80	161
7	OBn	Li	HMPA/THF -70→25 °C		76	162
8	OBn	Li	HMPA/THF -25→25 °C		84	163

[a]Dotted lines indicate point of attachment.

TABLE 11. Lactonizations Involving Protected Nonracemic Glycidol



entry	OP	reagent/conditions	X	yield (%)	ref
1	OBn	a) EtOCCH$_2$COEt/NaOEt/EtOH	EtOC	75-84	15, 166
2	OBn	a) RCH_2CN/LiN(TMS)$_2$/THF 0 °C b) KOH/EtOH (c) toluene Δ	R	72	167, 168
3	OBn	a) **37**/LDA/THF -30→25 °C b) toluene Δ		80	169
4	OBn	a) **38**/LDA/THF -78→25 °C b) toluene Δ (c) LDA/THF (d) HCl		62	170, 171
5	OBn	a) **39**/LDA/THF -78→25 °C b) toluene Δ	*p*-MeC_6H_4	65	172
6	OBn	a) **40**/LDA/THF -78→25 °C b) KOH/EtOH (c) H^+	*m*-$MeOC_6H_4$	63	173, 174
7	OBn	a) **41**/LDA/THF -78→25 °C b) KOH/EtOH (c) H^+	3,4-$(MeO)_2C_6H_3$	64	175



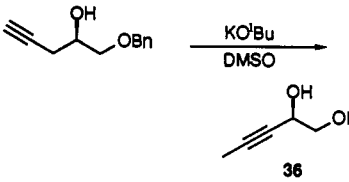
37 **38** **39** **40** **41**

to an alternative method of forming nonracemic α-acetylenic alcohols.[165]

c. Toward Stabilized Carbanions. Several reagents have been used to make a C–C bond at C^3 with concomitant formation of a lactone to the newly formed OH at C^2. These reactions are summarized in Table 11. Nucleophiles include β-keto ester enolates (entry 1), α-lithionitriles (entries 2 and 5–7), and carboxylic acid dianions (entries 3 and 4).

Initially in all of these reactions, close to a 50:50 mixture of syn- and anti-substituted lactones is produced. In the case of diethyl malonate (entry 1), decarboxylation using $MgCl_2$ in N,N-dimethylacetamide removes the stereocenter α to the carbonyl completely.[166] In entry 4, additional deprotonation/protonation steps were taken to reduce the mixture (including a

SCHEME 21



36 93 % refs. 157, 159

SCHEME 22

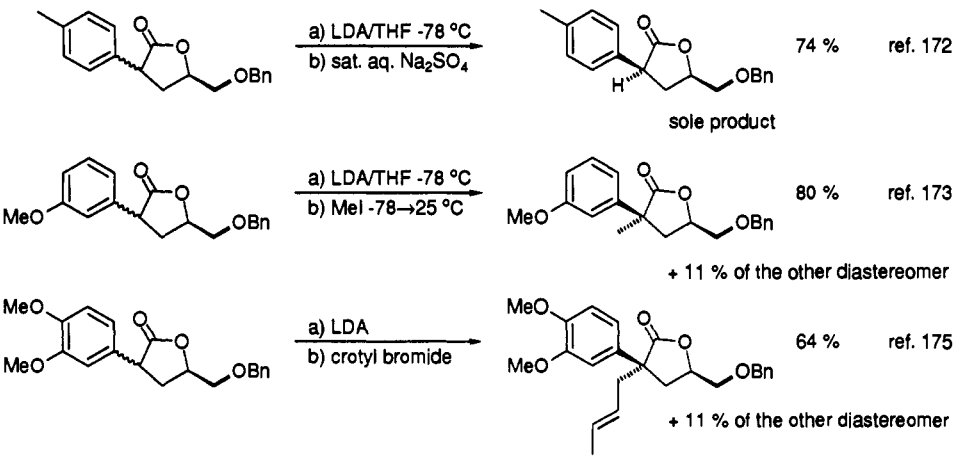
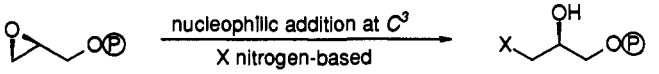


TABLE 12. Reactions of Protected Nonracemic Glycidol with Nitrogen-Based Nucleophiles



entry	OP	reagent	X	yield (%)	ref
1	OBn	NH_3/^{i}PrOH 3 days	H_2N	100	57
2	OAr	^{i}PrNH$_2$/alcohol Δ 1-20 h	^{i}PrN(H)	30-80	60, 187, 188, 189, 179, 190, 191
3	OAr	^{i}PrNH$_2$/neat	^{i}PrN(H)	80-85	192, 193, 194, 195, 196
4	OAr	^{t}BuNH$_2$	^{t}BuN(H)	---	197, 198
5	OAr	RNH$_2$ neat	RN(H)	---	199, 181, 200, 201
6	OAr	RNH$_2$/Me$_3$Al/CH$_2$Cl$_2$	RN(H)	---	144
7	OPNB	R$_2$NH/HOAc 7 d	R_2N	58	202
8	OC(=O)^{n}Pr	R$_2$NH/CH$_3$CN Δ 8 h	R_2N	---	203
9	OAr	RBnNH/alcohol Δ	RBnN	---	183, 204, 205
10	OAr	ZN⟨⟩NH /alcohol	ZN⟨⟩N	---	184, 185, 186
11	OPNB	NaN$_3$/pyr·HOTs/DMF	N_3	65-88	80

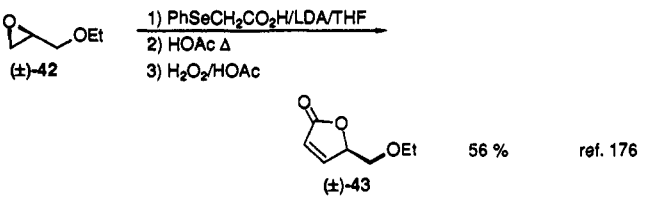
conjugated isomer) to a sole product, the syn lactone.

The fate of the stereocenters in entries 5–7 are depicted in Scheme 22. (In each of these reactions, (*R*)-**5** was used, as depicted in this scheme.) Deprotonation of the lactones and "kinetic" quenching at low temperature clearly increased the diastereomeric purity of the product.

Such a sequence of depronation followed by quenching at low temperature is not always so successful. In entry 2, the R group is a tetracyclic steroidal unit connected via the D ring at C^{17} (see also Figure 14 in section IV.3.6). Thus both components of the alkylation are nonracemic, and in this case only the adduct with (*S*)-**5** could be successfully quenched to give a single lactone. The *R* isomer, on the other hand, gave a 3:1 mixture upon quenching with aqueous sodium sulfate at −78 °C. The product of entry 3 could at best be transformed into a 5.4:1 ratio of syn to anti, this by quenching of the lactone enolate with trimethylsilyl chloride, followed by treatment with trifluoroacetic acid at −70 °C.

A similar reaction has been carried out on racemic *O*-ethylglycidol (**42**) with use of the dianion of α-phenylselenenylacetic acid (Scheme 23). Oxidation with acidic hydrogen peroxide gave butenolide **43** in 56% overall yield.

SCHEME 23



Three interesting reactions involving stabilized anions are shown in Scheme 24. In the first case, the dimethylhydrazone of acetone is deprotonated and used to open (*R*)-**5** at C^3. This product was not isolated but rather deprotonated again and treated a second time with (*R*)-**5** to give a bis-adduct. In a second reaction, treatment of glycidol with 2 equiv of sodium (methylsulfinyl)methide in dimethyl sulfoxide also resulted in opening at C^3. Heating the intermediate sulfoxide in refluxing *o*-dichlorobenzene led to sulfoxide elimination and the formation of allylic alcohol **44**. Interestingly,

SCHEME 24

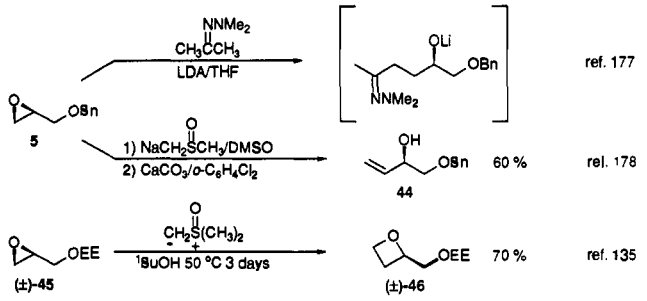
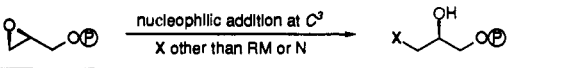


TABLE 13. Reactions of Other Nucleophiles with Protected Nonracemic Glycidol



entry	OP	reagent	X	yield (%)	ref
1	OC_5H_{11}	$LiAlH_4/Et_2O$ 1 h	H	72	206
2	OPNB	$KCN/(CH_3)_2C(CN)(OH)$	N≡C	85	80
3	OPNB	Et_2AlCN	N≡C	71	80
4	OPNB	$MeOH/H_2SO_4$	MeO	85	80
5	OTBDPS	$C_{16}H_{33}OH/BF_3{\cdot}Et_2O/CH_2Cl_2$	$C_{16}H_{33}O$	74	207
6	OBn	$C_{18}H_{37}ONa$/DMF 80 °C 2 h	$C_{18}H_{37}O$	46	208
7	OC^nPr	ArOH/$R_4N^+X^-$/toluene Δ	ArO	75	209
8	OR	phosphorylcholine/KOAc/AcOH Δ	RPO_3	42	210
9	OTr	LiSR/THF 0 °C	RS	82	122
10	OBn	NaSPh/THF 0 °C	PhS	89	211
11	OPNB	PhSH/Et_3N or pyr	PhS	97-100	80
12	OTr	RCSH <10 min	RCS	94	122
13	OR	$AlCl_3/CHCl_3$ 0 °C 1 h	Cl	69	212
14	OPNB	NaI/NaOAc/AcOH/$EtCO_2H$	I	89	80

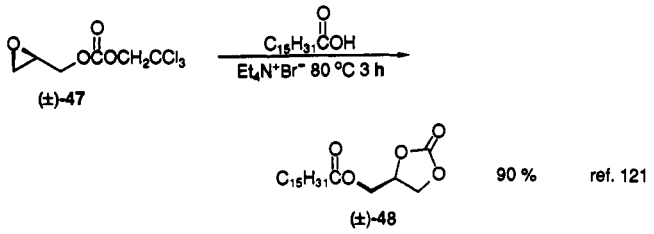
reaction of racemic *O*-(1-ethoxyethyl)glycidol (**45**) with the related dimethyloxosulfonium methylide results in ring expansion to give oxetane **46** in 70% yield, in analogy to that reagent's reactions with ketones to give epoxides.

d. Toward Nitrogen-Based Nucleophiles. Reactions of nitrogen-based nucleophiles with protected nonracemic glycidol are summarized in Table 12. Ammonia (entry 1), primary amines (entries 2–6), and secondary amines (entries 7–10) have all been used under a variety of conditions. Of special interest in the pharmaceutical industry have been the reactions of primary and secondary amines with glycidyl aromatic ethers (entries 2–6, 9, and 10). Several more complex primary amines have also been used.[179–183] In entry 10, Z has been either aryl[184] or alkyl.[185,186]

Addition of amines to nonracemic glycidyl esters is also successful (entries 7 and 8). In the reaction with azide (entry 11), some ester migration occurred due to the basic conditions employed. An alternative method of azide addition is the one presented for glycidol in Scheme 8, namely the reaction of trimethylsilyl azide catalyzed by aluminum or titanium(IV) isopropoxide. Racemic acetates and ethers give excellent selectivity and yields in the range of 70–80%.[77,78]

e. Toward Other Nucleophiles. Other nucleophiles used to open protected glycidol are shown in Table 13. These include hydride, cyanide, alcohols, acids, thiols, and halides.

SCHEME 25



The reduction of glycidyl *n*-pentyl ether has been effected using lithium aluminum hydride (entry 1). Comparing this result with those depicted in Table 4, it would appear that such a reduction would not be successful on 3-substituted glycidyl ethers.

Cyanide has been added to glycidyl *p*-nitrobenzoate either as potassium cyanide in the presence of acetone cyanohydrin (entry 2) or as diethylaluminum cyanide (entry 3). Acetone cyanohydrin acts as a "time-release" buffer, allowing no build-up of potassium alkoxide, which would cause problems with the benzoate group.

Alcohols have been added to protected nonracemic glycidol by using three different methods (entries 4–6). Thus, treatment of glycidyl *p*-nitrobenzoate with methanol in the presence of sulfuric acid (entry 4) gave the methyl ether. Racemic glycidyl acetate has also been opened with methanol by using a heterogeneous tin–phosphorus catalyst.[213] Treatment of silylated glycidol with hexadecyl alcohol in the presence of a catalytic amount of boron trifluoride gave the hexadecyl ether (entry 5). Use of basic conditions is also successful with *O*-benzylglycidol (entry 6). Similar treatment of the glycidyl butyrate, however, led to ester hydrolysis and partial racemization.[70] The addition of phosphorylcholine ($Me_3NCH_2CH_2OPO_3^-$) in buffered acetic acid (entry 8) to a glycidyl alkyl ether leads to substances related to platelet activating factor (see also Table 21). Alumina has been used to catalyze the addition of *tert*-butyl hydroperoxide to a racemic glycidyl aryl ether.[214]

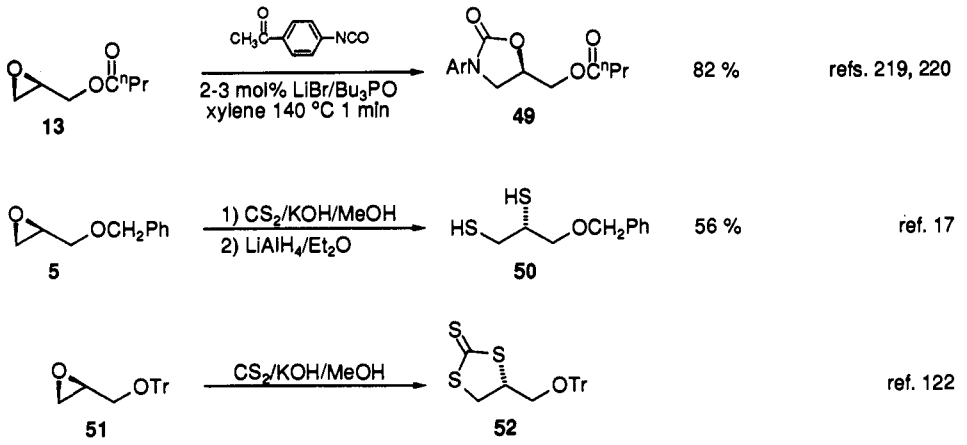
Quaternary ammonium salts nicely catalyze the reactions of glycidyl butyrate with phenols (entry 7). These conditions have also been used to add carboxylates to racemic *O*-benzylglycidol.[121] Interestingly, the reaction of racemic mixed carbonate **47** (Scheme 25) under the same conditions gave carbonate **48** in high yield. The same product was formed from glycidyl trichloroacetate (with loss of $CHCl_3$).

Reactions with thiols can be achieved in high yield by using several different conditions (entries 9–12). In the case of the *p*-nitrobenzoate, once again some ester migration occurs.[80]

Halides have been added either as the buffered anion (entry 14) or as the group III compound (entry 13). In a related reaction, dimethylboron bromide has been used to add bromide to a racemic aryl ether of glycidol.[215]

Three additional reactions of note are shown in Scheme 26. In the first reaction, glycidyl butyrate (**13**) was treated with an isocyanate to form oxazolidinone **49** in quantitative yield. This reaction is catalyzed by lithium bromide (solubilized as a phosphine oxide complex) and was first developed by using racemic **5**.[216] Presumably the bromide first opens the epoxide, the resultant alcohol reacts with the isocyanate, and, finally,

SCHEME 26



13 49 5 50 51 52

the nitrogen intramolecularly displaces the primary bromide.[217,218] This reaction is thus very similar (and complementary) to the one shown in Scheme 11.

The reagent derived from carbon disulfide and potassium hydroxide in methanol leads to displacement at both C^3 and C^2, giving, upon reduction with lithium aluminum hydride, dithiol **50**. In the case of **51**, trithiocarbonate **52** was isolated prior to reduction.

4. C^3 Reactivity of Other Protected Nonracemic 2,3-Epoxy Alcohols

Several reactions involving derivatives of **3** and **4** bearing protecting groups are shown in Table 14.

As in the case of glycidol, organomagnesium compounds in the presence of Cu(I) salts are the reagents of choice for addition of alkyl groups at the C^3 position of protected **3** (entry 1). Unlike glycidol, which reacts completely at C^3, in this case the regioselectivity was only 90:10 C^3/C^2. Trimethylaluminum has also been used with racemic *trans*-3-methylglycidol to add a methyl at C^3 (forming an isopropyl group) with >99% regioselectivity.[225] The reaction is strongly catalyzed by butyllithium.

In entry 2 a lower order cuprate was used, which probably explains the very low yield (along with the fact that the epoxide was in excess). Use of a higher order mixed cuprate in place of the lower order vinyl cuprate might have significantly increased this yield without sacrificing the precious alkenyl reagent, since a similar reaction using a higher order mixed 2-thienyl cuprate reagent worked well on racemic glycidyl benzoates.[226]

Less than ideal selectivity (7:1 C^3/C^2) was observed for the copper-catalyzed addition of a vinyl organomagnesium reagent to the trityl ether of **3** (entry 3). However, a closely related α-silyl reagent (entry 4) added exclusively at C^3. In entry 5, where the mixed ketal of acetone was used as the protecting group, the ratio of C^3 to C^2 addition was once again about 90:10. The reagent in this case was the (presumably) sterically undemanding ethylenediamine complex of lithium acetylide.

The success of α-lithio sulfone addition to silyl-protected **4** (entry 6) was very sensitive to sulfone structure. The authors report that only allylic α-lithio sulfones were successful (see also Figure 5). Such sulfones have also been successfully added to a racemic silyl ether of glycidol as *dianions*.[227] Addition of α-lithio dithianes to a silyl ether of **3** (entry 7) occurred in good yield.

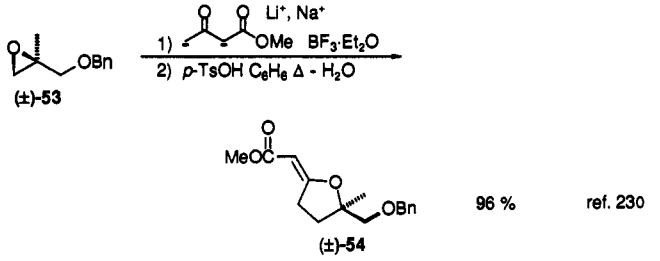
Iodide addition to the *p*-nitrobenzoate of **3** (entry 8) was highly selective, but the authors also report that phenylthiolate addition was not.

In analogy to some of the reactions known for protected glycidol with dianions (see Table 9), the dianion of methyl acetoacetate reacts with racemic **53** (Scheme 27), opening at C^3. Enol formation occurs in a second acid-catalyzed step, giving **54**. Similar reactions have also been carried out by using racemic glycidyl silyl[228] and benzyl[229] ethers.

Under Lewis acid conditions, silyl-protected *trans*-3-phenylglycidol (**55**, Scheme 28) has been observed to give aldehyde **56**. In this reaction, the entire C^1 appendage migrates to the C^3 position with concomitant formation of an aldehyde at the original C^2 position and no loss of enantiomeric purity. An alternative mechanism, involving phenyl migration via a phenonium ion[231] was ruled out, as it would produce an aldehyde of the opposite absolute configuration.

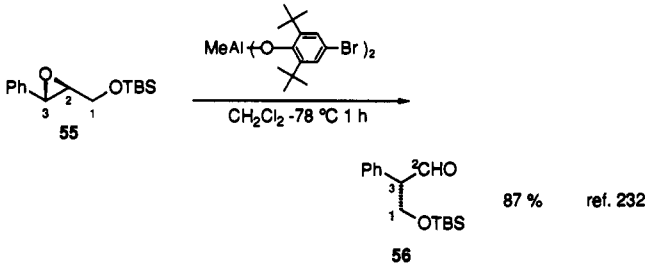
Thus, as in the case of protected glycidol, reactions of protected 2-alkyl-substituted glycidol should be expected to occur exclusively at C^3. In the case of protected *trans*-3-alkyl-substituted glycidols, reactions are

SCHEME 27



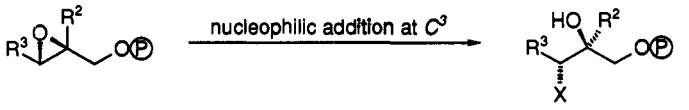
(±)-53 (±)-54

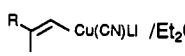
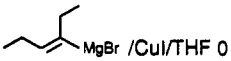
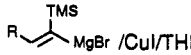
SCHEME 28



55 56

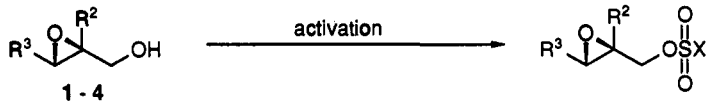
TABLE 14. Reactions of Other Protected Nonracemic 2,3-Epoxy Alcohols



entry	R^3	R^2	OP	reagent	X[a]	yield (%)	ref
1	Me	H		^{n}PrMgBr/CuI/THF	^{n}Pr	>40	221
2	Me	H	OTBS	 /Et_2O -40 °C		17	222
3	Me	H	OTr	 /CuI/THF 0 → 25 °C 2 days		68	223
4	Me	H	OTr	 /CuI/THF 0 °C		84	123, 224
5	Me	H		HC≡CLi(en) DMSO 25 °C 36 h	HC≡C	90	126
6	H	Me	OTBDPS	 /HMPA/THF		48	129
7	Me	H	OTBDPS	 /DMPU/THF 0 °C		76	128
8	Me	H	OPNB	NaI/NaOAc/AcOH/$EtCO_2H$	I	95	80

[a]Dotted lines indicate point of attachment.

TABLE 15. Activation as Alkyl and Aryl Sulfonic Acid Esters



entry	R^3	R^2	compd	X (abbr)	reagent	yield (%)	ref
1	H	H	1	CH_3 (Ms)	MsCl/Et_3N/toluene <0 °C	61	233
2	H	H	1	p-$CH_3C_6H_4$ (Ts)	TsCl/Et_3N/CH_2Cl_2 *in situ* (-10 °C)	40	28, 35
3	Ph	H	2	(Ts)	TsCl/pyr -10 °C	70	234
4	Me	H	3	(Ts)	TsCl/Et_3N/DMAP/CH_2Cl_2 *in situ*	70	28
5	H	Me	4	(Ts)	TsCl/Et_3N/DMAP/CH_2Cl_2 *in situ*	69	28
6	H	H	1	2-$NO_2C_6H_4$ (^{2}Ns)	^{2}NsCl/Et_3N/THF 0 °C	60	190
7	H	H	1	3-$NO_2C_6H_4$ (^{3}Ns)	^{3}NsCl/Et_3N/CH_2Cl_2 *in situ*	57	35, 32
8	H	H	1	4-$NO_2C_6H_4$ (^{4}Ns)	^{4}NsCl/Et_3N/CH_2Cl_2 *in situ*	48	35, 235
9	H	H	1	2-naphthyl (^{2}Nps)	^{2}NpsCl/Et_3N/CH_2Cl_2 *in situ*	75	35
10	H	Me	4	(^{2}Nps)	"	83	236
11	H	H	1	CF_3 (Tf)	Tf_2O/pyr/CH_2Cl_2 -20 to -65 °C	57	237

expected to always favor C^3, but not necessarily with extraordinarily high selectivity.

C. Activation

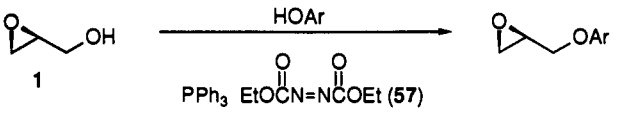
1. Activation of Nonracemic Glycidol and Related Small 2,3-Epoxy Alcohols

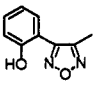
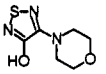
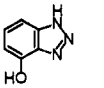
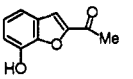
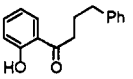
Sulfonyl groups have been used extensively to activate compounds 1–4 at the C^1 position. Reported procedures for their formation are summarized in Table 15. In situ refers to asymmetric epoxidation with in situ activation. Yields in these cases include the epoxidation reaction.

Perhaps the most salient point regarding these conditions is that low temperatures are important in order to minimize the risk of polymerization and chloride displacement of the newly formed tosylate.[238] Some of these products are not very stable and cannot be stored for long periods of time. The triflate in particular (entry 11) is quite unstable and is best used immediately or stored at −80 °C.[239] Besides mesylates (entry 1), other alkylsulfonates that have been made by using racemic glycidol include isopropyl and *n*-butyl.[240]

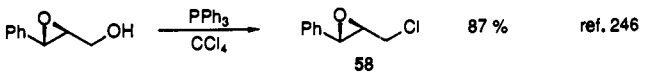
Quite a lot of work was done in the Sharpless group[35] investigating a variety of crystalline sulfonates (many not listed in Table 15) in hopes of finding ones which

TABLE 16. Reactions of Nonracemic Glycidol with Phenols



entry	HOAr	conditions	yield (%)	ref
1		THF 0→25 °C 16 h	48	184
2		toluene 25 °C 1 h	93	241
3		8 - 10 °C	---	183
4		THF 0→25 °C 3 h	80	242, 243, 244
5		---	---	200

SCHEME 29



are both reasonably stable and increase in enantiomeric purity upon recrystallization. Of all those tested, the *m*-nitrobenzenesulfonyl derivative (^{3}Ns, entry 7) was by far the best.

Several derivatives, though crystalline, could not be increased in enantiomeric purity beyond 85–90% ee. This curious behavior was attributed largely to the fact that for many (though not all) of these troublesome derivatives the racemate has a *higher* melting point than the individual enantiomers. Thus the racemate would crystallize first upon cooling, leading to no improvement in *ee*. Such is the case for both the ^{4}Ns derivative (entry 8) and the ^{2}Nps derivative (entry 9). (The ^{2}Ns derivative, entry 6, is an oil.) The enantiomerically pure ^{3}Ns derivative, on the other hand, melts 15–20 °C higher than its racemate.

Although 4-(dimethylamino)pyridine (DMAP) has been used to facilitate the reaction of sulfonyl chlorides with alcohols, its use in these cases is optional and not necessarily recommended even though it was used in the original work.

An example of a reaction in which a substrate is activated in situ and allowed to react further without isolation of an intermediate is the Mitsunobu reaction with phenols.[19] In this case nonracemic glycidol is treated with a phenol in the presence of triphenylphosphine and diethyl azodicarboxylate (DEAD, **57**). The aryl groups that have been used to date are shown in Table 16. In all cases, these reactions proceed by direct displacement at C^1.

A related reaction, shown in Scheme 29, is that between nonracemic *trans*-3-phenylglycidol and the reagent derived from triphenylphosphine and carbon tetrachloride[245] to give chloride **58**. Although this reaction is general for trans-3-substituted glycidols, it has not been reported for glycidol itself.

2. Reactivity of Activated Glycidol

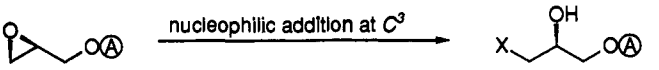
a. C^3 Reactivity of Activated Glycidol. One might think that the reason to activate glycidol would be so that it would react with displacement at C^1, and indeed a few such reactions are known for nonracemic glycidol. In most cases, however, activated glycidol reacts similarly to what we have seen already for glycidol itself and protected glycidol, that is, by ring-opening displacement at C^3. All of the reported reactions of nucleophiles with activated nonracemic glycidol at C^3 are summarized in Table 17. Note that in every case, the reactions are carried out in the presence of either a Lewis or Brønsted acid. Notable in their absence from this table of nucleophiles are acetates and phenolates. Those nucleophiles will be discussed later.

An important study done in the Sharpless group[35] carefully explored the reactivity of nonracemic glycidyl tosylate. Several of their findings are given in the table. For example, borohydride reduction (entry 1), copper-catalyzed organomagnesium addition (entries 2 and 3), aryllithium addition (entry 4), and diethylaluminum cyanide addition[254] (entry 6) all occur at C^3 *without* displacement of the tosylate.

In the addition of phenyllithium catalyzed by boron trifluoride (entry 4), 38% of the starting material was also isolated. When a cuprate reagent was used instead (Scheme 30), the major product was the epoxide formed by secondary in situ tosylate displacement by the oxygen atom on C^2.

This sort of secondary reactivity, although actually quite generally desirable, has been the bane of the activated glycidol story. Prior to careful studies involving nonracemic glycidyl sulfonates, it was never known (nor, perhaps, of any interest) whether such an indirect displacement of the activating group occurs. A first "Occam's razor" analysis might be that such mechanisms involve simple S_N2 displacement of the activating group. On the other hand, when *nonracemic* activated

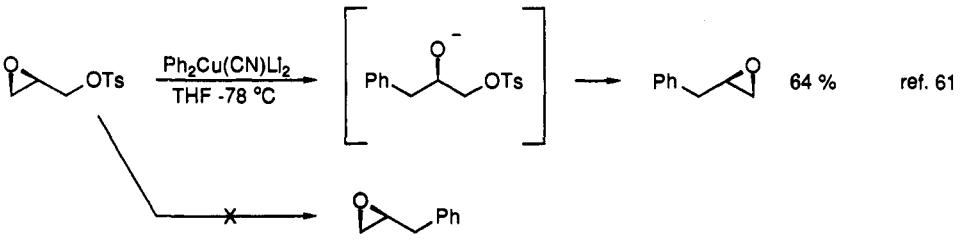
TABLE 17. Reactions of Activated Nonracemic Glycidol at C^3



entry	OⒶ	reagent	X[a]	yield (%)	ref
1	OTs	BH_3/cat. $NaBH_4$/THF 0 °C	H	81	35
2	OTs	RMgCl/Li_2CuCl_4 or CuI/Et_2O -40 to -50 °C	R	69-74	35
3	OTs	 /Li_2CuCl_4/THF -35 °C		49	35
4	OTs	PhLi/BF_3·Et_2O/THF -78 °C	Ph	61	35
5	O^3Ns	RC≡CLi/BF_3·Et_2O	RC≡C	71	247
6	OTs	Et_2AlCN/toluene 20 min	NC	96	35
7	OTs	R_2NH/HOAc 5 days	R_2N	56	202
8	OTs	H_2SO_4/^{i}PrOH/H_2O Δ 1 h	HO	30-50	203
9	OTs	BnOH/BF_3·Et_2O/CH_2Cl_2 0 → 20 °C	$PhCH_2O$	81-93	248, 249, 250
10	OTs	ROH/BF_3·Et_2O/CH_2Cl_2 20 °C 18 h	RO	79-83	250, 251, 252
11	O^3Ns	"	RO	73-83	250, 251
12	OTs	PhSH/BF_3·Et_2O/CH_2Cl_2 4 °C 18 h	PhS	81-83	250
13	OMs	conc. HCl 30 min	Cl	80-85	12, 55, 233
14	OTs	"	Cl	---	233, 253

[a]Dotted line indicates point of attachment.

SCHEME 30



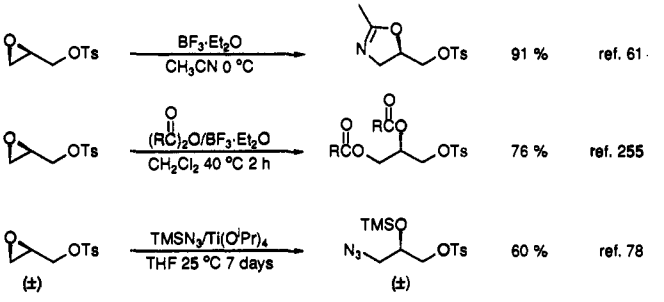
glycidol is used, displacement at C^1 leads to the opposite enantiomer as displacement at C^3 followed by internal displacement. Thus, any lack of *regioselectivity* translates into a loss of enantiomeric purity. More will be said regarding this problem in the discussion of Table 18.

Nonracemic glycidyl tosylate also reacts with amines (entry 7), water (entry 8), alcohols (entries 9 and 10), and thiols (entry 12) all in the presence of acid to give opening at C^3 and no further reaction. The alcohols used in entry 10 were long-chain aliphatic alcohols. In that case, the *m*-nitrobenzenesulfonate (entry 11) was also tested and found to be as good as the tosylate. In fact, since it is available in higher enantiomeric purity than the tosylate (vide supra), the *m*-nitrobenzenesulfonate is superior. Racemic glycidyl mesylate also reacts with secondary amines at C^3.[240]

The *m*-nitrobenzenesulfonate has also been used to add an acetylenic group at C^3 (entry 5), again with use of Lewis acid catalysis.

Finally, both the mesylate (entry 13) and the tosylate (entry 14) react with HCl to give chloride opening exclusively at C^3. Treatment of the resultant hydroxysulfonate with base gives nonracemic epichlorohydrin (16, Scheme 6). Similar opening with chloride has also been observed for racemic glycidyl sulfonates.[240]

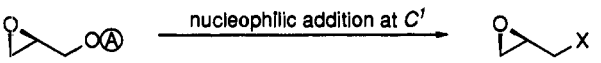
SCHEME 31



Three additional reactions of glycidyl tosylate have been reported (Scheme 31). These reactions are similar to those already mentioned in relation to protected glycidol.

b. C^1 Reactivity of Activated Glycidol. The known reactions of activated nonracemic glycidol occurring at C^1 are compiled in Table 18. Three clear differences between this table and the last stand out. First of all, the conditions are basic, in sharp contrast to the acidic conditions of Table 17. Second, triflates appear here and not in Table 17. Third, the reactions involve fairly classic nucleophilic additions, rather than the organometallic reactions found in Table 17.

TABLE 18. Reactions of Activated Nonracemic Glycidol at C^1



entry	OⒶ	reagent	X	yield (%)	ref
1	O^4Ns	(a) Me_3N (b) anion exchange	$Cl^- Me_3N^+$	---	256
2	O^3Ns	NaN_3/18-crown-6/DMSO	N_3	---	235
3	OMs	R_2C=NONa/THF 48 h	R_2C=NO	30-57	257, 258
4	OTf	R_2C=NONa/THF 1 h	R_2C=NO	>20	237
5	OTs	ArONa/DMF 4 h	ArO	72-89	35, 60
6	OTf	ArONa	ArO	---	200
7	O^2Ns	ArONa/THF 60 °C 13 h	ArO	60	190, 201
8	OTf	PhOH/K_2CO_3/CH_2Cl_2 40 h	PhO	93	259
9	OTf	PhONa/CH_2Cl_2/THF 10 min	PhO	91	259
10	OTf	ArOK/DMF 5 min	ArO	---	260
11	OTs	KF/Kryptofix 222/THF 95 °C 12 min	F	60-80	239

Both trimethylamine (entry 1) and azide (entry 2) have been reported to add exclusively at C^1. Similar reactivity has also been observed with an aromatic amide.[261]

McClure et al., at E. M. Merck,[259] did the initial careful studies comparing the regioselectivities of addition of phenol to epichlorohydrin, glycidyl mesylate, and glycidyl triflate. They found that the selectivity for direct C^1 displacement increased in that order. Epichlorohydrin expresses more C^3 opening than direct C^1 displacement, with selectivity on the order of 7–20:1. On the other end of the spectrum, the substrate most selective for C^1 addition is the triflate, for which there is no known reaction which goes by initial C^3 addition.

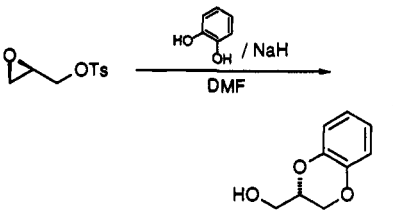
The Sharpless group,[35] using information also from McClure's study, were able to correlate the ratio of C^1:C^3 addition of phenol to the acid strength of the conjugate acid of the leaving sulfonate. Thus, they found that roughly log (C^3/C^1) = 2.06 × pK_a + 12.05. Thus, the *stronger* the conjugate acid (the lower the pK_a), the *less* C^3 addition takes place. This finding is consistent with the intuitive idea that the stronger the conjugate acid of the leaving group is, the better the leaving group will be, thus the less direct *epoxide* opening (i.e., addition at C^3) will occur.

Thus, mesylates, having the weakest conjugate acid (MsOH, pK_a −6.2), result in the most C^3 addition when phenol was used (1:5.7, in favor of C^1). Tosylates (*p*-TsOH, pK_a −6.6) are intermediate (1:32, still more in favor of C^1). *m*-Nitrobenzenesulfonates (^{3}NsOH, pK_a −7.1) show essentially no C^3 opening by phenol.

All of the results for sulfonates are in sharp contrast to the reaction of epichlorohydrin, which *never* exhibits substantial amounts of direct Cl displacement. In fact, except for possible arguments relating to availability, it is hard to imagine a reason to use nonracemic epichlorohydrin, since the *m*-nitrobenzenesulfonate is crystalline and exhibits higher (albeit reversed) regioselectivity in its reactions.

In the case of racemates, both glycidyl tosylate[262] and *o*-nitrobenzenesulfonate[263] have been treated with phenols with (apparent) reaction at C^1. Reaction of racemic glycidyl mesylate with sodium acetate has also been observed, giving apparent addition at C^1, but due to the racemic nature of the material, it was not determined how exactly the displacements occurred.[240] Racemic glycidyl triflate has also been treated with a derivatized α-naphthol with displacement of the triflate.[260]

SCHEME 32



refs. 61, 264

Radioactive fluoride (Table 18, entry 11) also has been added to nonracemic glycidyl tosylate. In this study, due to the short half-life of ^{18}F (less that 2 h), the key to success is speed, not necessarily selectivity. Much work was done to determine the best conditions for the reaction, including examining the use glycidyl triflate. The triflate turned out to be too unpredictable for this work. The less reactive *m*-nitrobenzenesulfonate, however, was not tried. It would have been a cleaner starting material and would have allowed for use of lower reaction temperatures than those necessary for the tosylate.

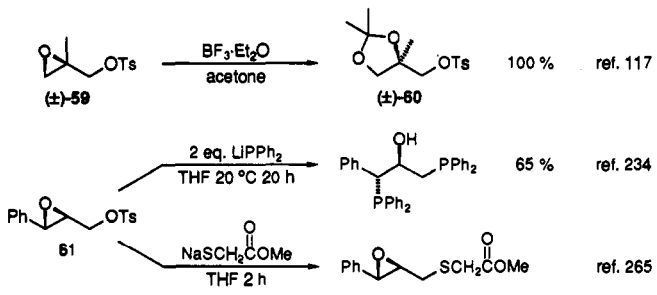
One reaction of activated nonracemic glycidol involving C^1 displacement followed by intramolecular C^2 opening of the epoxide has been reported and is shown in Scheme 32. In this reaction, once the first C–O bond with catechol was made, the second followed rapidly.

3. Reactions of Related Activated Nonracemic 2,3-Epoxy Alcohols

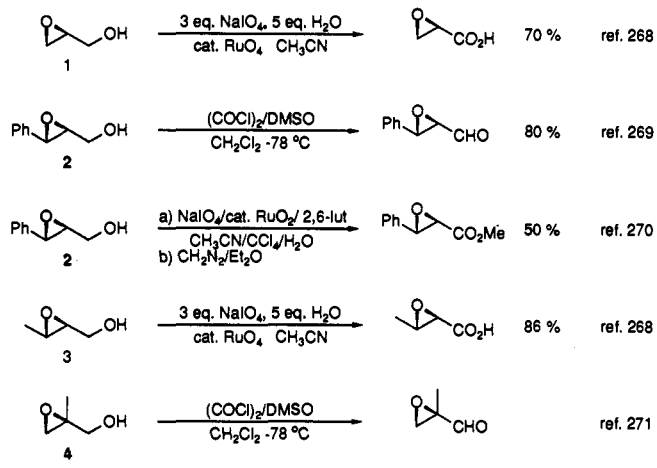
Very little work has been reported which involves the reactions of either racemic or nonracemic activated derivatives of alcohols **2**–**4**. The few that are known are shown in Scheme 33.

Thus, treatment of racemic tosylate **59** with boron trifluoride in acetone results in (presumed) opening at C^3 and formation of racemic acetonide **60**. Treatment

SCHEME 33



SCHEME 34



of nonracemic tosylate **61** with either lithium diphenylphosphide or the sodium salt of methyl thioacetate results in displacement at C^1. In the case of the phosphide, a second equivalent of $LiPPh_2$ then adds at C^3. (It is also possible that in this case reaction occurs first at C^3.)

D. Oxidation at C^1

Finally, the oxidation of 2,3-epoxy alcohols **1–4** to aldehydes and/or acids has been reported (Scheme 34). Thus, aldehydes are made by using Swern[266] conditions. Acids are formed by ruthenium tetroxide by using a method developed by Sharpless,[267] optionally followed with esterification with diazomethane. The Sharpless method has recently been modified to minimize decomposition by using close to a stoichiometric amount of water.[268]

IV. Natural Product Syntheses Involving Nonracemic Glycidol and Related 2,3-Epoxy Alcohols

It is important to realize that many of the reactions presented in section III were carried out in the context of a larger synthetic scheme. As such, the chemists involved had a bigger picture in mind than simply the reaction of glycidol. In particular, they were interested in establishing the absolute and relative stereochemistry of complex substances. In this section the focus is on how the stereochemistry of compounds **1–4** can form the basis of a stereoselective synthesis. In section IV.A are presented several small molecules that have been made from glycidol and hold great potential as early

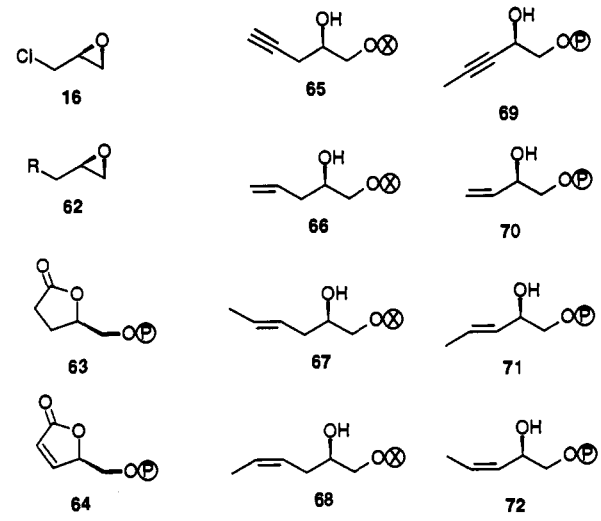


Figure 3.

intermediates in stereoselective synthesis. Then, in section IV.B, the 46 natural product related targets which have been made to date using the technology presented in section III are discussed. (Pharmaceutical analogues are discussed in section V.)

A. Small Synthetic Intermediates Available from Glycidol

Complex syntheses begin with small molecules. A dozen representative small molecules having only one or two stereocenters (if you count alkenes) which are available in just a few steps from glycidol are shown in Figure 3. Each will be discussed briefly.

Epichlorohydrin (**16**) has been introduced already. As mentioned in section III, glycidyl *m*-nitrobenzenesulfonate is a crystalline solid and exhibits higher selectivity than **16**. Nonetheless, (*R*)-**16** has been made from (*R*)-**1** (see Scheme 6) and so is mentioned here. Addition of organometallics to glycidyl sulfonates at C^3 (see Table 17 and Scheme 30) followed by treatment with base gives terminal alkyl epoxides (**62**). Lactones **63** and **64** both hold prominent places in natural products synthesis in their own right. Both are available from glycidol (Table 11, entry 1 and Scheme 23, respectively). Alkyne **65** and alkenes such as **66**, **67**, and **68**, where X is either a protecting or an activating group, are all available (Tables 9, 10, and 17, respectively). Propargylic alkyne **69** is available from **65** (Scheme 21), and the synthesis of allylic alkene **70** has been described (Scheme 24). Finally, both **71** and **72** are available from **69** by standard methods.

A comprehensive discussion of how these compounds have been used is outside the scope of this review. The following discussion includes syntheses involving the compounds of Figure 3 only if those syntheses refer explicitly to using nonracemic glycidol as a starting material.

B. Synthetic Strategies

The discussion of natural product syntheses in this review is organized along theoretical lines, involving glycidol as a synthon. (In contrast, the discussion of synthetic analogues will be organized along functional lines, involving the biological function of the analogue

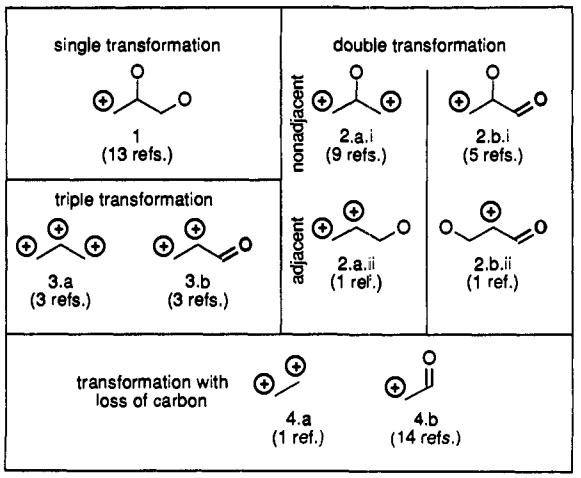


Figure 4. The synthons of glycidol and related 2,3-epoxy alcohols used to date in natural product syntheses and their subheading designator for this review.

itself.) The nine synthons relating to glycidol *that have been used in natural product syntheses* are summarized in Figure 4. The designation below each synthon refers to the subsection of this review which addresses all syntheses employing that synthon. A "+" indicates the equivalent of an electrophilic site, which at some point in the strategy is intercepted by a nucleophile. A carbonyl in the synthon indicates a position which gets oxidized. Thus, for example, the three references discussed in subsection 3.b, below, refer to a common strategy involving the oxidation of one of the carbons of glycidol and nucleophilic addition to the other two. If multiple transformations occur at the same position (for example, oxidation, then nucleophic addition, then another oxidation), only the first is shown.

The nine synthons fall into four distinct classes, depending upon how much transformation of the basic glycidyl unit occurs. Furthermore, three of the four classes (2, 3, and 4) are subdivided into subclasses depending upon the type of transformation involved (a or b, without or with oxidation, respectively). Finally, the second class is further subdivided on the basis of the adjacency of the two transformations on the three-carbon glycidyl framework (i or ii, nonadjacent or adjacent, respectively).

The starting points of the syntheses to be discussed all involve nonracemic compounds 1–4 or one of their protected or activated forms. For information regarding the syntheses of these starting compounds, see section III of this review. In each of the several figures to follow, the portion of the target molecule is highlighted which arose from the carbons and oxygens of the particular 2,3-epoxy alcohol used. In addition, the numbers 1, 2, and 3 on the target molecule refer to the carbons of the *original* 2,3-epoxy alcohol which have been incorporated. (This should not be confused with any official numbering scheme of the target molecule. No such official numbers will be necessary for the discussion.) Next to each molecule is a bold arrow with the reference indicated in italics.

Note that the drawings of epoxides in this part of the review are drawn *as the specific enantiomer used.* Whereas in section III of this review the epoxy alcohols have all been drawn with the same orientation, here they are drawn in as close a resemblence to the target molecule as feasible. Thus, at first glance, some of the depictions of glycidol and its derivatives in this section may seem ambiguous. To remove any ambiguity, each depiction is accompanied by labels of *R* or *S*, as appropriate.

Finally, a depiction of the essentials of the transformation are given. The abbreviations are "Nu" for nucleophile, "[Ox]" for oxidation, "[H]" for reduction, and "El" for electrophile. Note that in terms of synthons, reduction (as was also done in section III) is grouped with nucleophilic addition, since hydrides can be considered nucleophilic reagents. For multiple transformations, each is numbered to indicate the temporal order in which those transformations occurred.

1. *Single Transformations*

The simple use of glycidol for its electrophilic properties at C^3 leads to the introduction of a diol moiety into a molecule. The syntheses involving this straightforward strategy are summarized in Figure 5. In all of these syntheses, the C^2 stereochemistry remains intact and both oxygens are used. Each will be briefly discussed with particular emphasis on stereoselectivity and regioselectivity.

For **73**, acetylide addition (Table 10, entry 1) followed by carboxylation with CO_2 introduced the needed carbons. The rigidity of the lactone was used to translate the C^2 stereochemistry to the second center with high selectivity.

The objective in the case of **74** was to develop a reiterative route to all-syn polyols. Here stereochemistry is established by vinyl cuprate addition (Table 9, entry 3) and propagated by epoxidation of the resultant homoallylic alcohol.

Addition of thiophenol to the C^3 position of **1** (Table 1, entry 8) or **4** (Table 5, entry 4) followed by protection as the acetonide, oxidation to the sulfoxide, and Pummerer rearrangement[272] led to **75** and **76**, respectively. Note that aldehyde **75** is of stereochemistry *opposite* that derived from mannitol (Scheme 1).

The successful addition of the deprotonated allylic sulfone derived from farnesol in the case of **77** has already been mentioned (Table 14, entry 6). Further acid- or selenium-catalyzed cyclization, however, was unsuccessful.

Several syntheses of (*S*)-(−)-frontalin (**78**) have employed unprotected, unactivated **4**, which thus sets the absolute stereochemistry for both tertiary centers in the target cyclic ketal. Similarly, use of **3** for the synthesis of (+)-α-multistriatin (**79**) established three of the four stereocenters in the product. The other methyl substituent was not introduced in a stereocontrolled manner, although the two diastereomers could be equilibrated.

Finally, in the synthesis of **80**, the yield of lower order vinyl cuprate addition (Table 14, entry 2) was very low, as mentioned in section III. Nonetheless, the strategy here was an important one: the coupling of two independently generated sets of absolutely defined stereocenters. Evans' oxazolidinone enolate chemistry[273] was used to generate the other three stereocenters selectively.

Also in this category are the two syntheses summarized in Figure 6. Note that in both cases a *second* transformation involving the glycidic unit was carried out after the initial nucleophilic addition. That

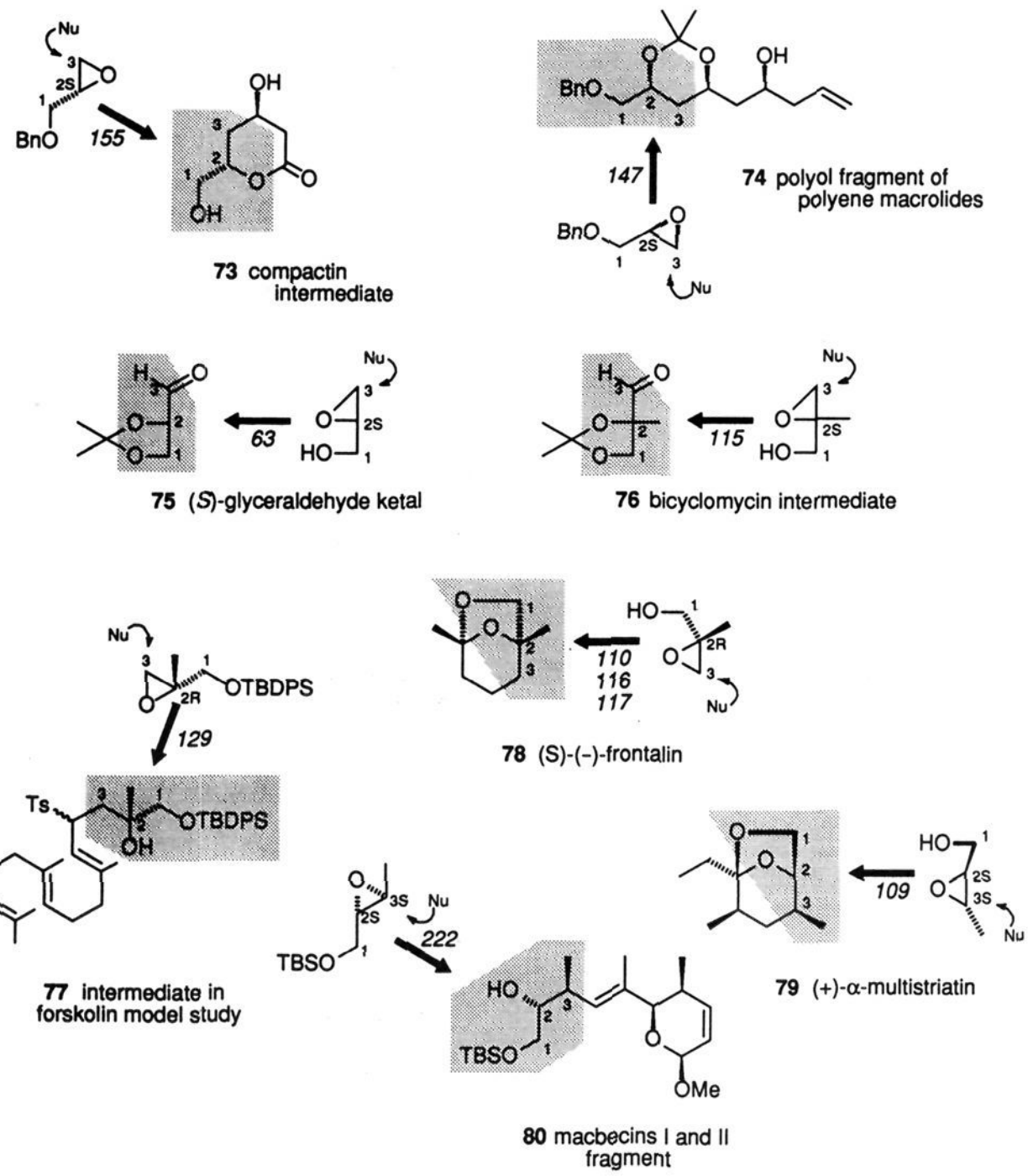
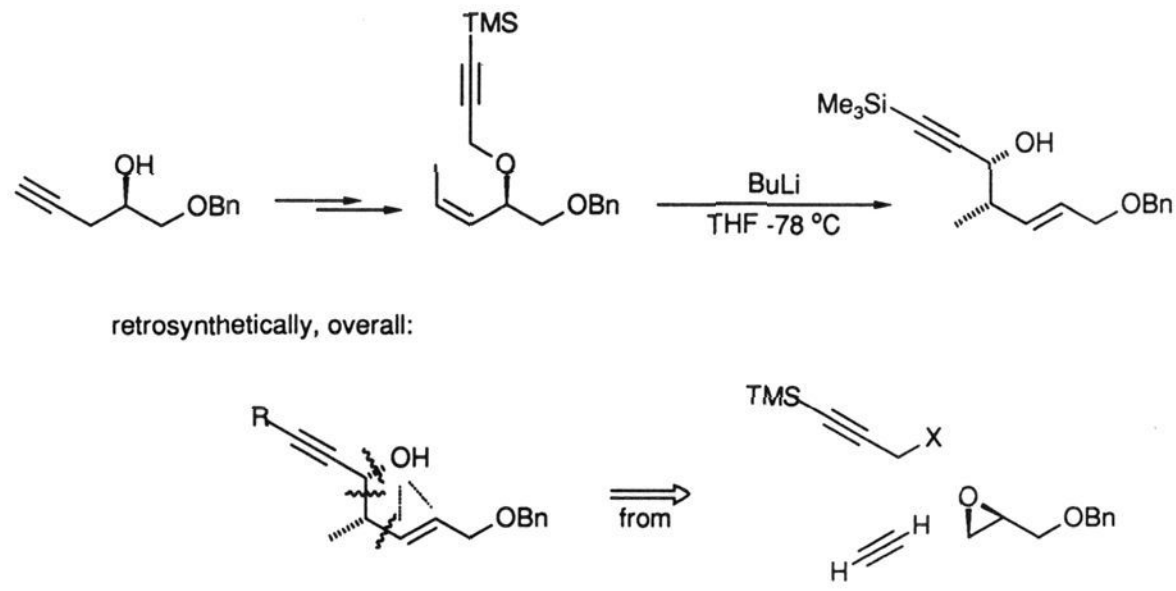


Figure 5.

SCHEME 35



transformation is depicted in Scheme 35. Without going into details, the initial acetylide adduct was treated with base as shown in Scheme 21, above, and reduced to give the *Z* alkene, which was functionalized as the ether shown here. Treatment with butyllithium resulted in an anionic electrocyclic rearrangement, which resulted in the stereoselective transposition of the double bond and the creation of two new stereocenters α to the original glycidic unit. Retrosynthetically, the result is the very interesting transformation shown also in Scheme 35.

2. *Double Transformations*

All of the other natural product syntheses to be discussed involve more extensive changes to the glycidyl framework. When two such transformations occur,

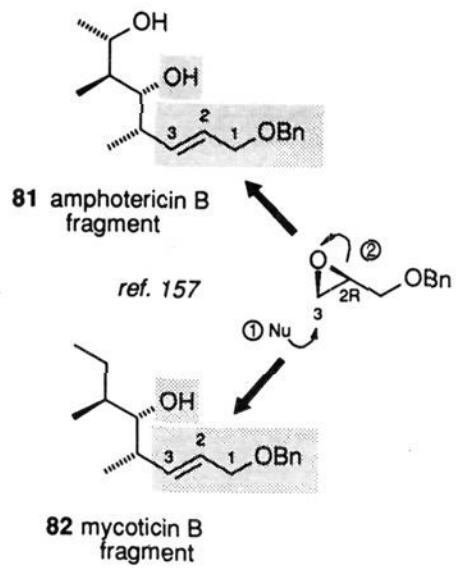


Figure 6.

several possibilities ensue, as shown in Figure 4.

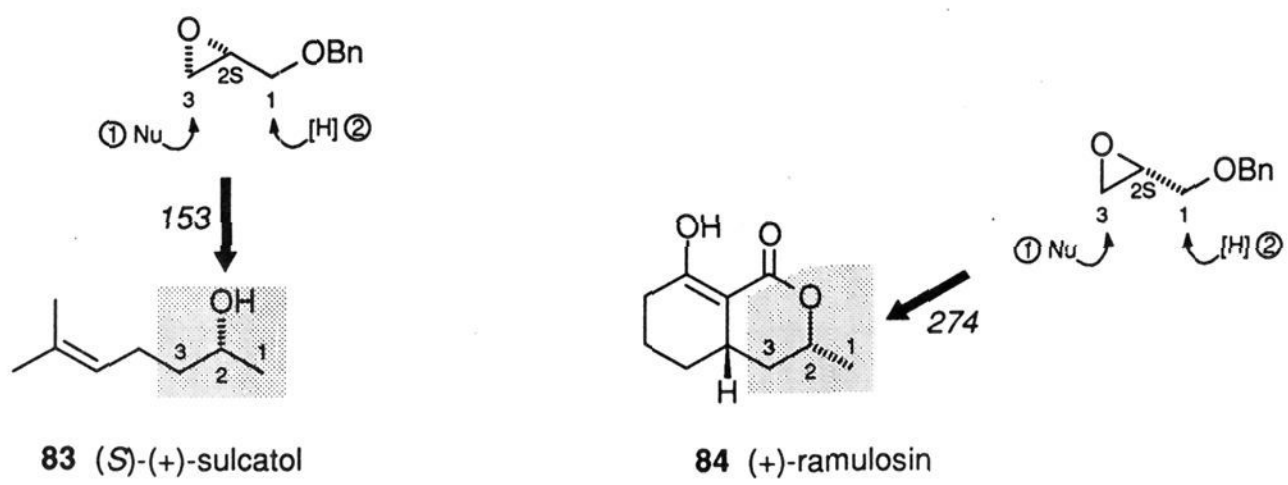
a. Addition of Two Nucleophiles. When two nucleophiles are added, they may be added either one at each end (nonadjacently) or one to an end and one to the middle carbon (adjacently). These two possibilities have both been explored and will be considered separately.

i. Nonadjacent Addition. The nine syntheses employing the nonadjacent addition of two nucleophiles, one to C^3 and one to C^1, are depicted in Figures 7 and 8, respectively.

In the cases of sulcatol (**83**) and ramulosin (**84**), the second "nucleophilic" addition was actually reduction. The initial organometallic additions are described in Scheme 20 and Table 10 (entry 1, ref 155), respectively. In the case of **84**, the stereochemistry at C^2 was transmitted to the ring fusion position by governing the conformation of an unsaturated lactone.

For **85**, after addition of a functionalized acetylide (Table 10, entry 6), intramolecular ketalization gave a compound reminiscent of frontalin (**78**). Reduction then proceeded with excellent selectivity. The second nucleophile was finally added after this reduction.

The adjacent hydroxyl and methyl stereocenters in **86** were established cleanly by hydroboration of the corresponding 2,3-dihydrofuran. So in this case the stereochemistry at C^2 governed which side of the di-



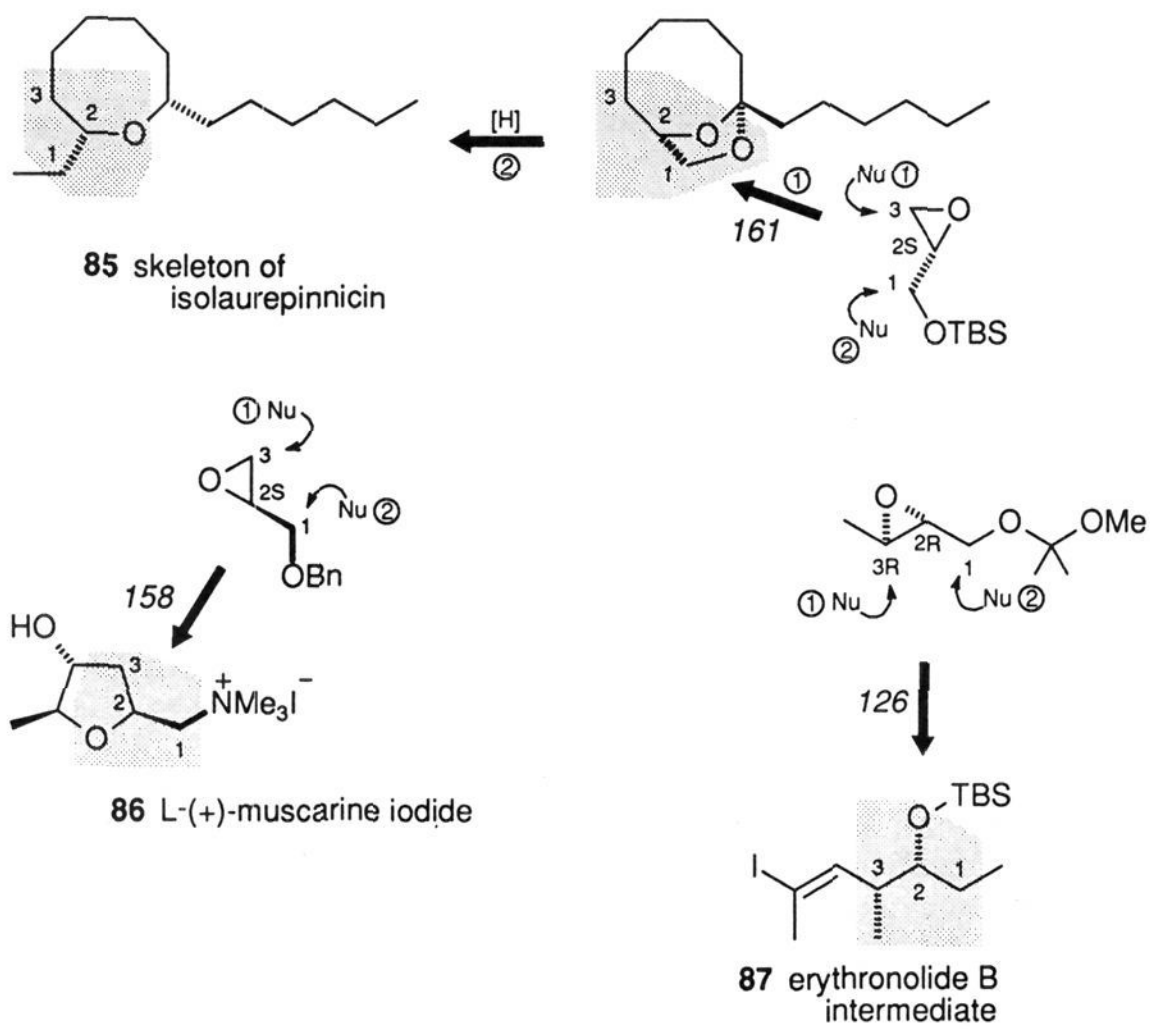


Figure 7.

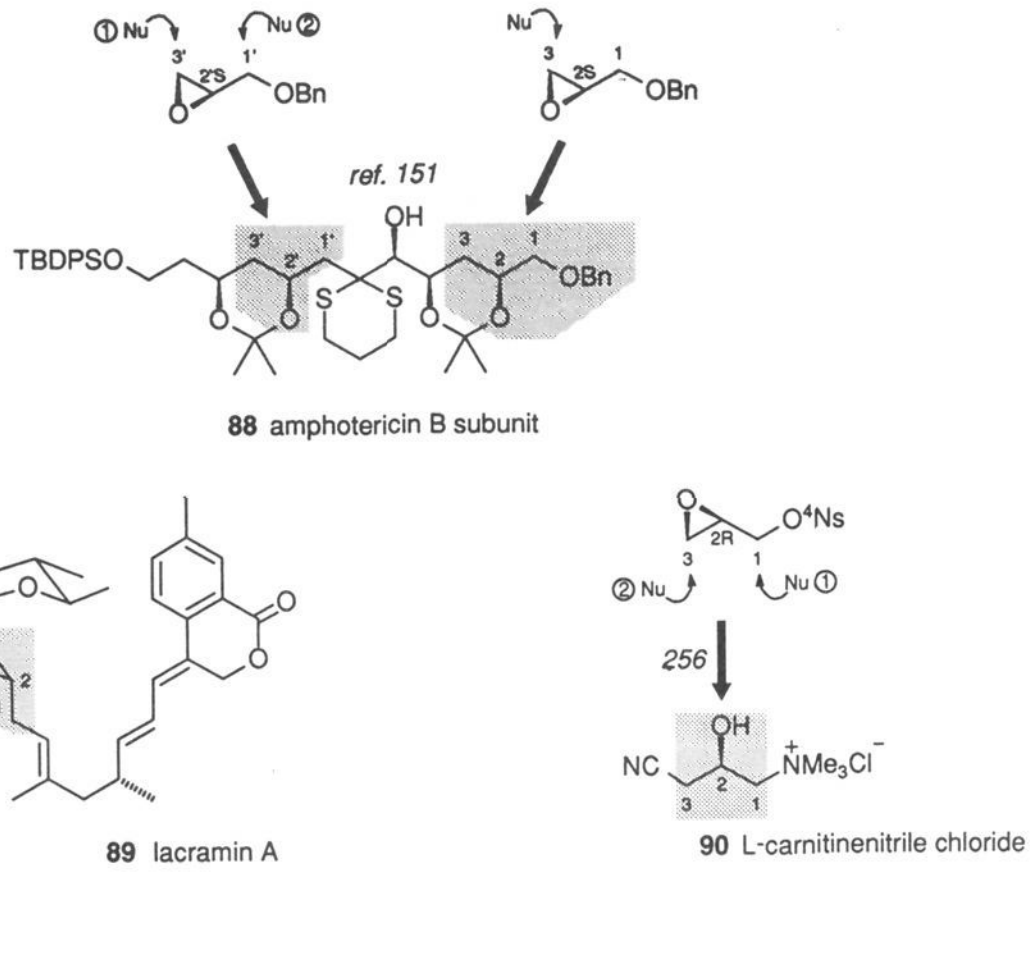
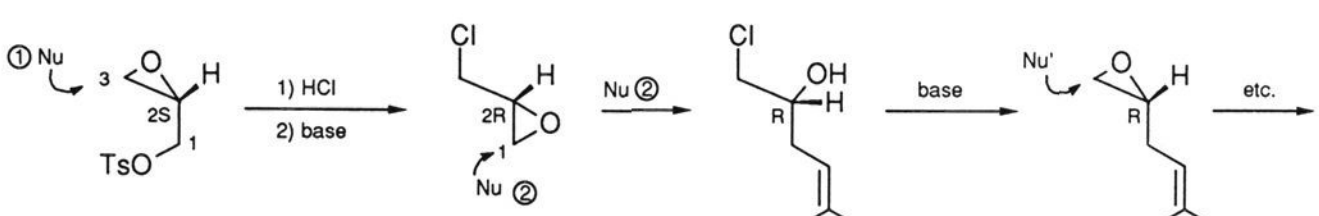


Figure 8.

SCHEME 36



hydrofuran was approached by the borane. The second nucleophile, trimethylamine, was added in the last step of the synthesis.

Finally, use again of *trans*-3-methylglycidol in the synthesis of **87** established two adjacent stereocenters bearing methyl and hydroxyl in a syn arrangement when drawn in zig-zag form. The nucleophile in this case was lithium acetylide (Table 14, entry 5).

In Figure 8, an especially efficient use of (*S*)-*O*-benzylglycidol (Table 9, entry 9) established all *five* of the stereocenters of **88** with excellent selectivity. In this molecule, each of the central three carbons were from dithiane. Counting all connections, deprotonated dithianes were used *six* times as nucleophiles!

In the synthesis of lacramin A (**89**), initial addition at C^3 was by *chloride* (Table 17, entry 14). Ring closure then gave (*R*)-epichlorohydrin (Scheme 36). The second nucleophile, a vinylaluminum ate complex, was then used to open the epoxide ring (at the original C^1 position). The use of such complexes with glycidyl sulfonates has not been reported, but since cuprates add nicely (Table 17), it is quite possible that aluminum ate complexes might be successful as well. If so, then by using glycidyl *m*-nitrobenzenesulfonate the intermediacy of epichlorohydrin might have been avoided. The second carbanionic nucleophile (Nu' in Scheme 36) was a lithiated methoxyallene.

Note that all of the syntheses discussed so far involve addition first at C^3, then at C^1. However, in the case of **90** (Figure 8), we have one of the first reported uses in natural product synthesis of a nitrobenzenesulfonate group to effect initial C^1 displacement. (It is not clear why the *p*-nitrobenzenesulfonate was used in this case rather than the more generally useful meta derivative.) Trimethylamine cleanly displaces at C^1 (Table 18, entry 1) to give an intermediate epoxypropylammonium salt, which was then opened with cyanide.

These two syntheses illustrate the flexibility of glycidyl sulfonates. In the case of **89**, acidic conditions are used to add to C^3; in the case of **90**, basic conditions are used to add to C^1. Use of a nitrobenzenesulfonate in the case of **90** ensures against loss of enantiomeric purity.

ii. Adjacent Addition. Clearly the strategy of addition of two nucleophiles, one at C^3 and one at C^1, has been widely appreciated. A different strategy, which utilizes addition at C^2, although certainly described in section III, has not yet been as widely used. All such

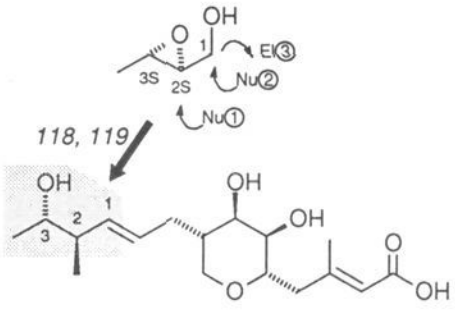
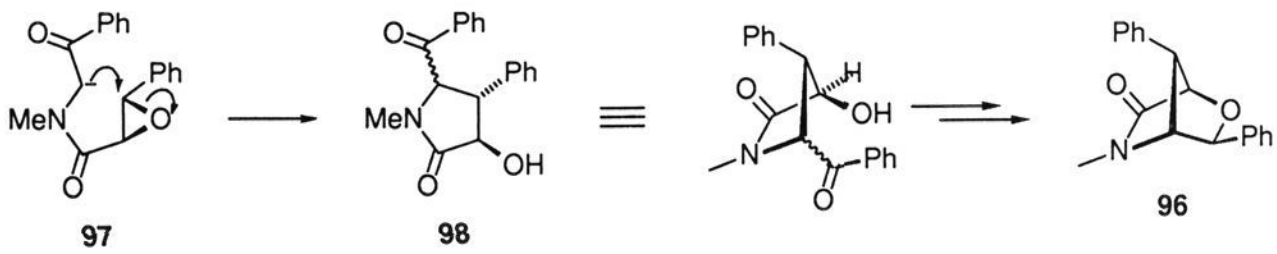


Figure 9.

SCHEME 37



reports except one are presented later, because they all involve further transformation of the glycidic unit. The single report that does fit here, the synthesis of monic acid C (**91**), is depicted in Figure 9.

Especially surprising should be the addition of the first nucleophile, $Me_2(CN)CuLi_2$, *to* C^2. Were this a selective process, it would be unprecedented. The key to the success here, however, relies not on selectivity, but rather chromatography. The reaction was, in fact, not selective, giving a 1:1 ratio of C^2/C^3 addition. However, the strategy here was to remove the unwanted regioisomer by chromatography and accept the loss in yield. Though perhaps not particularly elegant, the strategy worked. The second nucleophile in this case was iodide. The resultant iodide was made into a phosphonium salt and coupled with an aldehyde with disappointingly low stereoselectivity. Thus, this strategy, like the one for **80** also involved the coupling of two independently generated sets of absolutely defined stereocenters. In this case, the two enantiomers of the other half of the couple were resolved by chromatography.

b. One Nucleophilic Addition and One Oxidation. As for the case of transformations involving two nucleophilic additions, transformations involving one nucleophilic addition and one oxidation fall into two subclasses, nonadjacent and adjacent, which will be discussed separately.

i. Nonadjacent Addition/Oxidation. Four of the five reported addition/oxidation transformations involving C^3 and C^1 (that is, nonadjacent) are depicted in Figure 10.

Note that in each case addition is carried out first, oxidation second. In the first three cases, the purpose of the oxidation was to generate an aldehyde, which could then undergo coupling with a second independently nonracemic component. In the fourth case, all of the stereocenters are generated from the two in the starting epoxide.

The strategy for the synthesis of clavulone II (**92**) involved intermediate **63** (Figure 3), where the protecting group is the benzyl ether. Deprotection and Swern oxidation thus completes the transformation to an aldehyde. The coupling carried out involved Wittig reaction with a reagent derived (eventually) from L-(+)-diethyl tartrate.

For lipoxin A_5 (**93**), addition of butyne (Table 10, entry 4) followed by reduction gave a *cis*-alkene. After some protecting group changes, the primary alcohol was oxidized to the aldehyde and treated with chromium(II) chloride and iodoform (CHI_3) to give a vinyl iodide. This iodide was then coupled with palladium catalysis to the other half, the stereochemistry of which was derived from asymmetric epoxidation of a secondary allylic alcohol.

In the synthesis of **94**, protected *trans*-3-methylglycidol is opened with a dithiane (Table 14, entry 7),

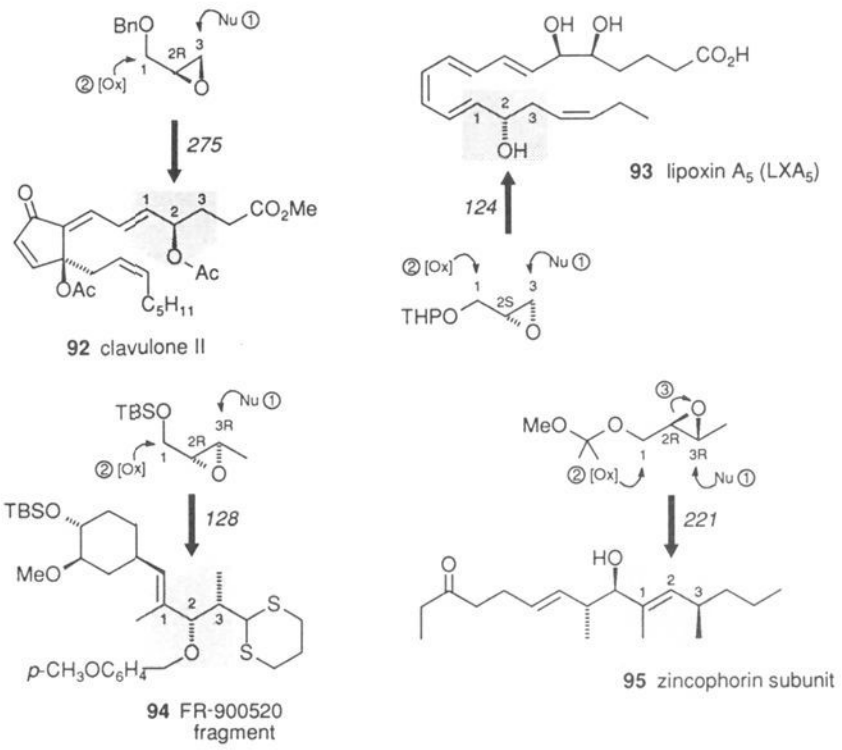


Figure 10.

thus once again setting the stereochemistry for two adjacent centers bearing methyl and hydroxyl. The *p*-methoxybenzyl group was put in place by DIBAL reduction of the corresponding acetal between the oxygens of C^1 and C^2. Oxidation gave the aldehyde. Coupling in this case involved an α-lithio sulfone derived from an asymmetric Diels–Alder reaction.

Finally, the strategy for **95** also employs *trans*-3-methylglycidol, this time protected as the mixed acetonide with methanol. The nucleophile was *n*-propylmagnesium bromide (Table 14, entry 1). Here, too, the stereochemistry at C^2 and C^3 was used to produce a syn orientation of methyl and hydroxyl, but this time a secondary transformation translated the hydroxyl center stereochemistry to a new position. The strategy used is too involved to describe here, but essentially relies on the C^2 stereochemistry to direct an addition of an acetylenic organomagnesium reagent to the oxidized C^1 position. The stereochemistry is further propagated down the chain via an anionic electrocyclic reaction similar to that shown in Scheme 35.

One last reaction that employs an addition/oxidation strategy is shown in Figure 11. Several aspects of this strategy are very interesting. As denoted in the figure, oxidation came first. In terms of natural product total syntheses, this is the only report to date of initial oxidation of *nonracemic* glycidols **1**–**4** prior to nucleophilic addition. The oxidation was carried out as depicted in Scheme 34 to give the methyl ester.

After amide–ester exchange, the precursor to anion **97** (Scheme 37) was produced. Treatment with a catalytic amount of tetramethylammonium hydroxide produced **97**, which cyclized to lactam **98** as a 3:1 mixture of epimers. Only the major diastereomer was carried on. It was reduced, tosylated, and treated with base to give **96**.

SCHEME 38

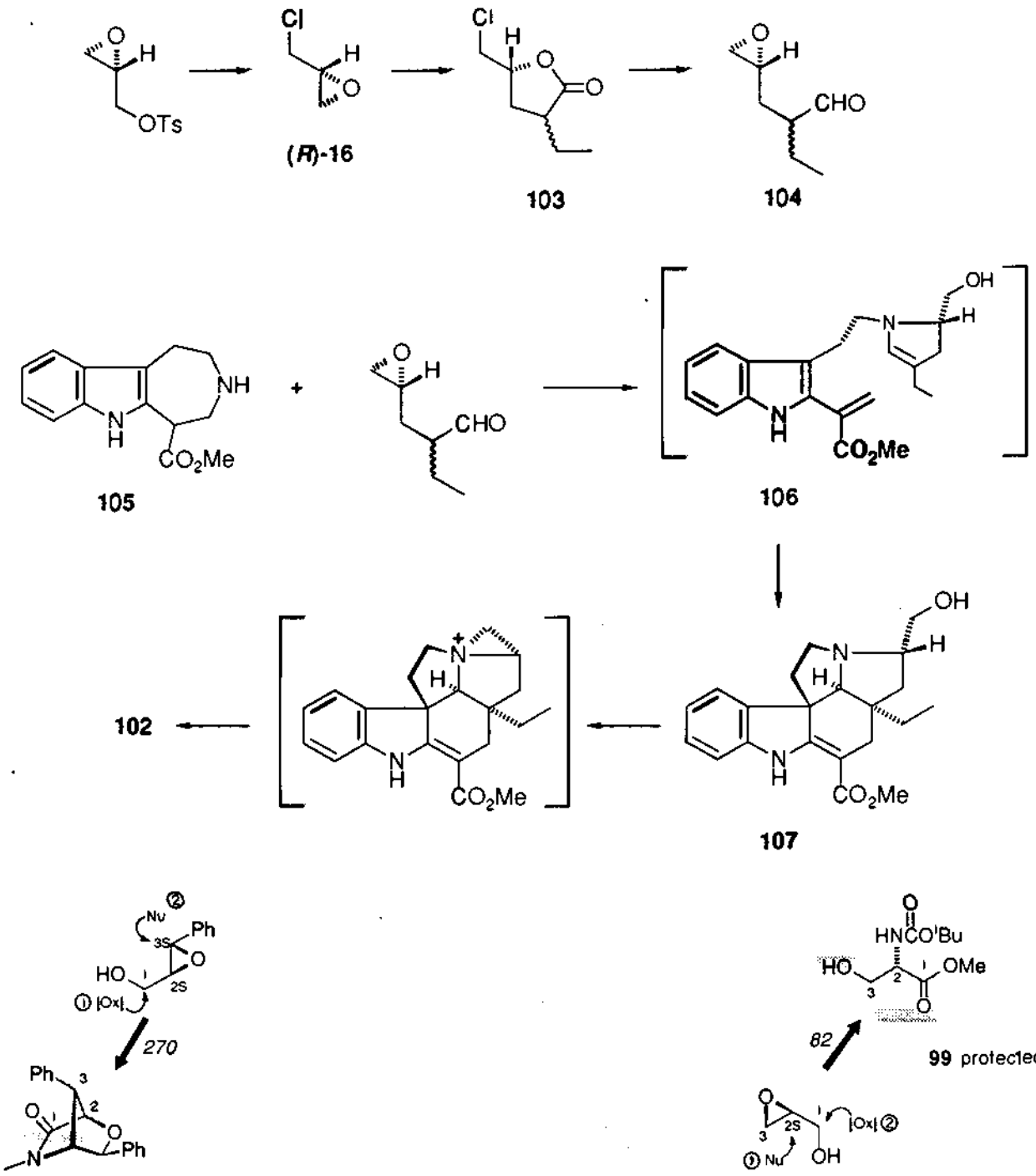


Figure 11.

Figure 12.

ii. Adjacent Addition/Oxidation. There is one report involving the directed addition of a nucleophile to C^2 followed by oxidation at C^1. It is depicted in Figure 12 and involves the reaction of glycidol with trichloroacetonitrile (see Scheme 11). The adduct, **22**, is converted easily to *N*-BOC-protected serine methyl ester. (Thus one can make glycidol from serine *and* vice versa!)

3. Triple Transformation

There are just a handful of reports of nucleophilic additions and oxidations involving all three centers of compounds **1**–**4**. They are depicted in Figures 13 and **14**.

a. Addition of Three Nucleophiles. The three reported strategies involving nucleophilic addition at all three glycidic carbons are depicted in Figure 13.

The clever strategy for the synthesis of gloeosporone (**100**) required two glycidyl units. The three-carbon chain linking their C^3 centers was provided by 2-fold nucleophilic addition of the dimethylhydrazone of acetone to (*R*)-*O*-benzylglycidol (see Scheme 24). The C_2-symmetric compound thus obtained was transformed into a bis-epoxide and treated with $(^nBu)_2CuLi$, opening at C^1. The other end of the molecule ($C^{1'}$) was opened with a functionalized acetylide. The 14-member lactone was then produced by Mitsunobu[19] displacement at C^2.

In the strategy for the synthesis of **101** the initial nucleophile, at C^3, was an aryllithium (Table 9, entry 8). Here the tosylate (or, perhaps, the *m*-nitrobenzenesulfonate) would have been more straightforward to use, since the next part of the strategy involved formation of an epoxide between C^1 and C^2, much like the one shown in Scheme 30. It was opened with acetylide. The final transformation of the glycidic unit involved Mitsunobu displacement at C^2 again, this time by phthalide. A series of seven steps then led to **101**.

A particularly creative strategy utilizing glycidol was used by Kuehne in the synthesis of vincadifformine (**102**). Notice that in this case the entire glycidic unit has been transformed into a simple alkyl chain, translating all of the inherent stereochemistry of glycidol to the three stereocenters of **102**. The key to Kuehne's overall plan was to use the stereochemistry at C^2 as "scaffolding" to direct a Diels–Alder reaction, and then to remove it later, revealing the desired skeleton. Such a subtle strategy is well worth considering further. An outline of this synthesis is depicted in Scheme 38.

The synthesis begins with (*R*)-**16**, which is derived from (*S*)-glycidyl tosylate as described previously

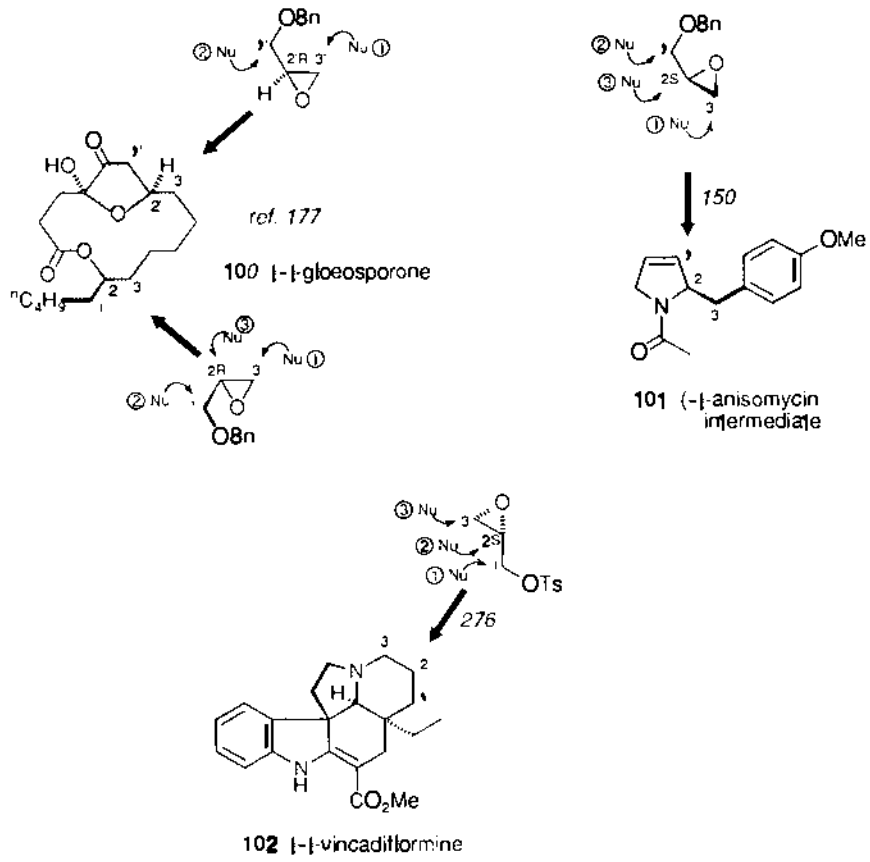


Figure 13.

(Scheme 6 and Table 17, entry 14). Opening with diethyl ethylmalonate, lactonization, and decarboxylation gives lactone **103**. Lactone opening, treatment with base to reform the *original* oxirane system, and reduction gave aldehyde **104**. Unfortunately, the authors did not find reducing conditions that were selective for the ester, and yields were no greater than 31% for that step.

Treatment of this aldehyde with indoloazepine **105** gave (presumably) enamine **106**, which spontaneously underwent intramolecular Diels–Alder addition to give **107**. Note that in this key step the stereochemistry at C^2 is the only directing influence for the Diels–Alder addition. Almost certainly the addition to the nonterminal side of an epoxide was directed intramolecularly *after* enamine formation. Product corresponding to the six-member ring enamine (from addition at the terminal position of the epoxide) was also found in 14% yield. It was transformed into another alkaloid, (−)-tabersonine. Transfer of the nitrogen atom from the original C^2 to the C^3 position involved a quaternary aziridinium salt, which upon reduction gave **102**. The enantiomeric excess of **102** (>97% ee) is a measure of the amount of influence of the stereochemistry at C^2 in the Diels–Alder addition, which was thus excellent.

b. Two Nucleophilic Additions and One Oxidation. The three reported strategies involving two nucleophilic additions and one oxidation are shown in Figure 14. In each case, *O*-benzylglycidol was used, and the sequence was addition to C^3 first, displacement at C^2 second, and oxidation at C^1 last.

In the syntheses of **108** and **109**, the essential feature involved allowing *O*-benzylglycidol to react with deprotonated nitriles (Table 11, entries 2 and 5, respectively). The α-disposed methyl groups adjacent to C^3 in **108** and **109** originate from the CN of these nitriles. The stereochemistry was set by kinetic quenching of the deprotonated lactone product (see Scheme 22). In each case, the synthesis is completed by reduction of both the lactone and C^2, followed by oxidation to an aldehyde at C^1 and Wittig reaction.

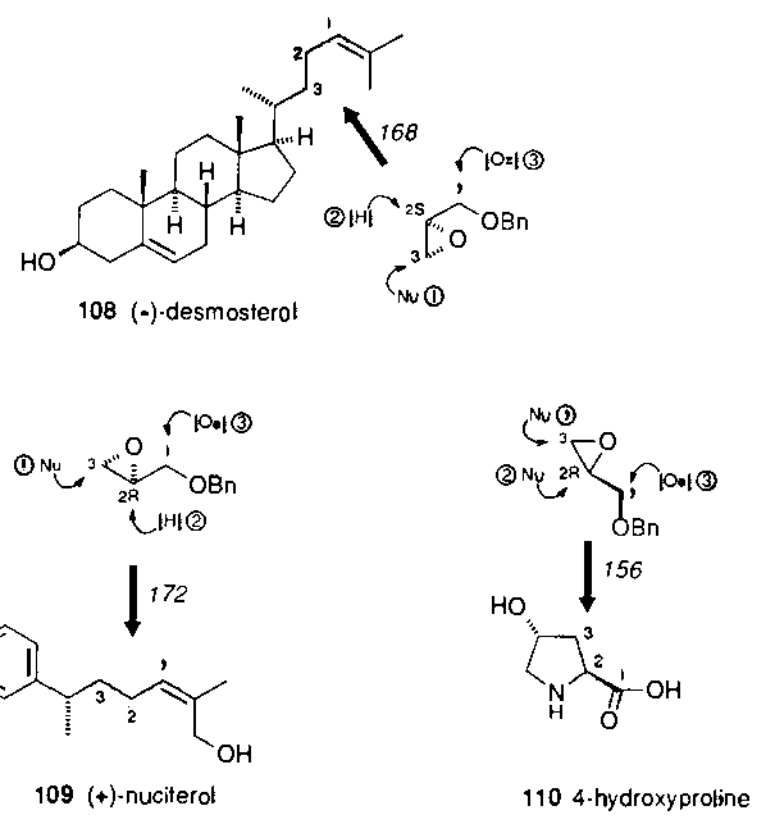


Figure 14.

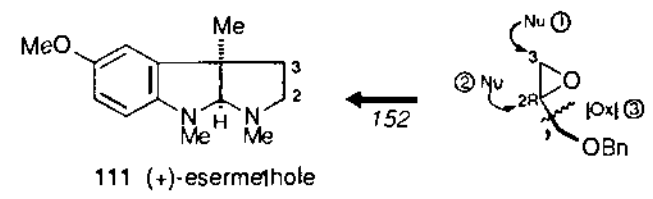


Figure 15.

The final synthesis in this set (**110**) involves a straightforward plan very similar to that used for the synthesis of **101** (Figure 13), but simpler. Again acetylide was added at C^3 followed by Mitsunobu reaction with phthalide at C^2. After ring formation, oxidation to the acid completed the synthesis.

4. Transformation with Loss of Carbon

Several reports involve the use of nonracemic glycidol to incorporate only two carbons into the framework of a synthetic target. In all of these cases, the C^1 position was removed oxidatively. In one approach, discussed in subsection 4.a, nucleophilic addition at C^2 precedes C^1 removal. The vast majority of the syntheses, however, involve the simpler addition at C^3 followed by 1,2-diol oxidation of C^2 and C^1 together, with concomitant loss of C^1. These syntheses are discussed in subsection 4.b.

a. Nucleophilic Addition at C^3 and C^2 with Loss of C^1. The single reported synthesis employing the strategy of nucleophilic addition at C^3 followed by nucleophilic addition at C^2 and finally oxidative removal of C^1 is depicted in Figure 15.

In this synthesis of esermethole (**111**), addition of a crotylmagnesium reagent (see Scheme 20) followed by Mitsunobu addition of phthalide provided all of the framework carbon atoms as well as the nitrogen atom adjacent to C^2. Removal of C^1 involved decarbonylation of an α-aminoaldehyde. The two stereocenters, however, were not introduced in a selective manner.

b. Nucleophilic Addition at C^3 and Oxidation at C^2 with Loss of C^1. A total of 14 syntheses have used strategies involving addition of a nucleophile at C^3 followed by oxidative elimination of C^1 and further transformation of the resultant carbonyl group at C^2. These syntheses are presented in Figures 16–20.

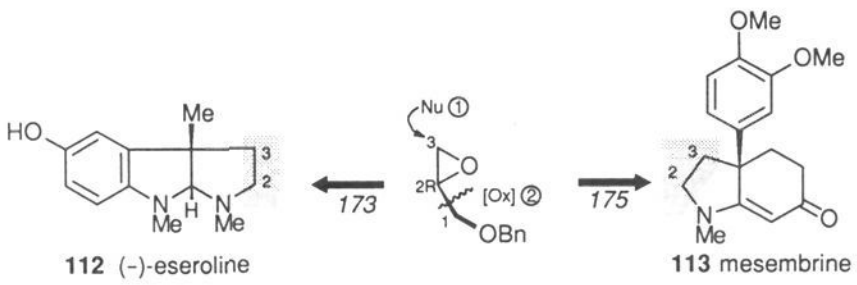


Figure 16.

The strategy depicted in Figure 16 for both eseroline (**112**) and mesembrine (**113**) is typical. This approach, which is similar to that discussed above for **108** and **109** employs addition of an α-lithio nitrile to C^3 followed by lactonization (Table 11, entries 6 and 7, respectively). In these cases, however, the resultant lactone was stereoselectively alkylated (Scheme 22) to provide the necessary quaternary center adjacent to C^3. The benzyloxymethyl substituent was ultimately removed by sodium periodate cleavage of a C^1–C^2 diol, reduction with sodium borohydride, and relactonization.

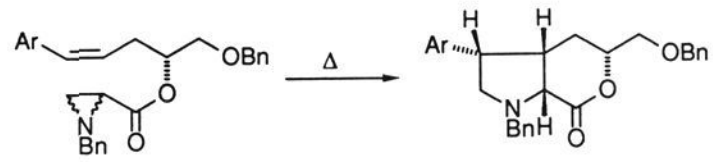
The use of carboxylic acid dianions to produce lactones (Table 11, entries 3 and 4) has been applied to five syntheses of natural products (Figure 17). In these cases, the stereochemistry at C^2 was transmitted to the appendage by kinetic protonation.

In the case of citronellol (**114**), the lactone carbonyl became a methyl substituent in the final product, much as was done in the syntheses of **108** and **109**. In the other four syntheses, the lactone carbonyl was used to introduce alkenes into the molecules either by reduction and elimination (**115**) or by Wittig reaction (**116–118**).

A strategy involving the addition of functionalized acetylenes to nonracemic *O*-benzylglycidol (see Table 10) has resulted in the syntheses of three natural products (Figure 18). The pyrrolidine system in these compounds was derived from the intramolecular electrocyclic addition of an aziridine to an alkene (Scheme 39). The reaction was highly stereoselective in each case.

The two reported syntheses involving nonracemic *trans*-3-methylglycidol are depicted in Figure 19. In

SCHEME 39



both strategies the oxidative removal of C^1 resulted in the formation of an aldehyde at C^2, which was then reacted with an organometallic nucleophile. Thus, in both of these cases, the stereochemistry at C^2 was *not* utilized (although there is no obvious reason why it might not have been in the case of **122**).

Finally, nonracemic *trans*-3-phenylglycidol has been used for the syntheses of two amino acids (Figure 20). Addition at C^3 was effected either directly in the case of **124** (as azide; Table 3, entry 6) or intramolecularly in the case of **125** (to give **30**, Scheme 17). Oxidation to the acid was effected by periodate either in combination with Mn(VII) or catalyzed by ruthenium salts.

C. Summary of Synthetic Strategies

Among all of the synthetic strategies involving compounds **1–4**, two stand out as the most productive to date. Referring to Figure 4, they are strategy 1 (simple addition at C^3, Figures 5 and 6) and strategy 4.b (addition at C^3 followed by oxidative removal of C^1, Figures 16–20). Two additional approaches have led to a moderate number of syntheses, namely strategy 2.a.i (addition at both C^3 and C^1, Figures 7 and 8) and strategy 2.b.i (addition at C^3 and oxidation at C^1, Figures 10 and 11). All of the other strategies of Figure 4 were used in fewer syntheses. This is not to say that these less-used strategies are less effective, merely less obvious or less general.

V. Analogue Syntheses Involving Nonracemic Glycidol and Related 2,3-Epoxy Alcohols

Besides natural products, a large number of biologically and/or pharmaceutically important compounds (analogues) have been made from nonracemic **1–4** or

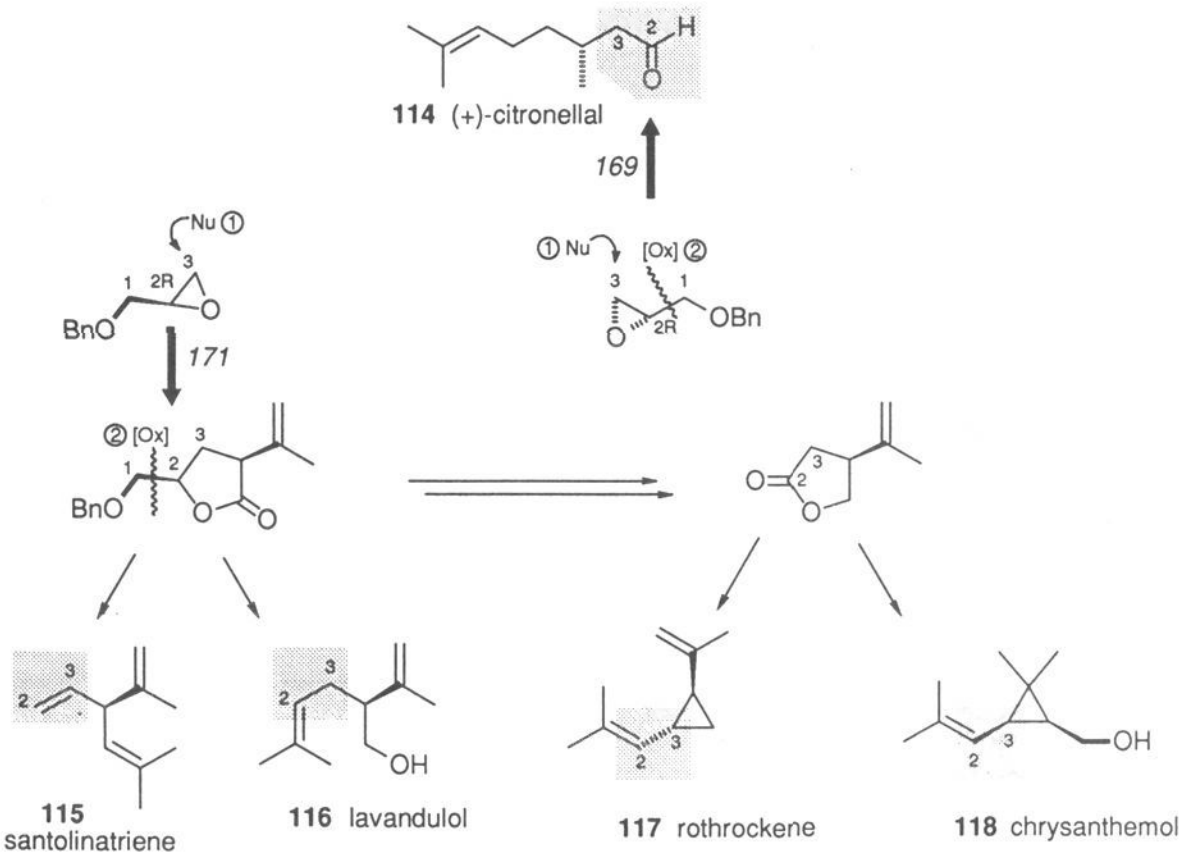


Figure 17.

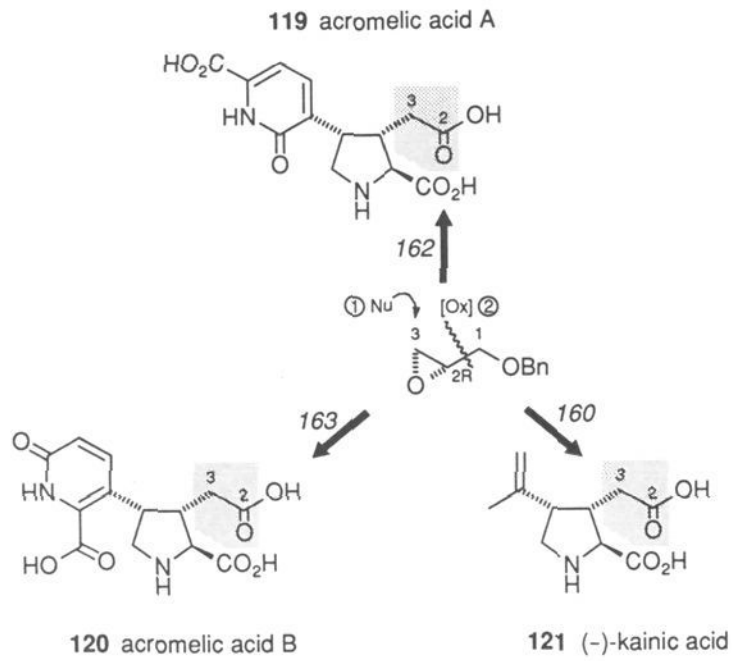


Figure 18.

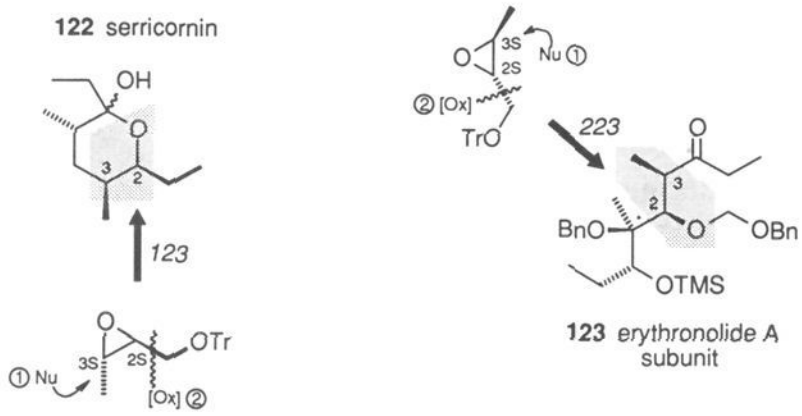


Figure 19.

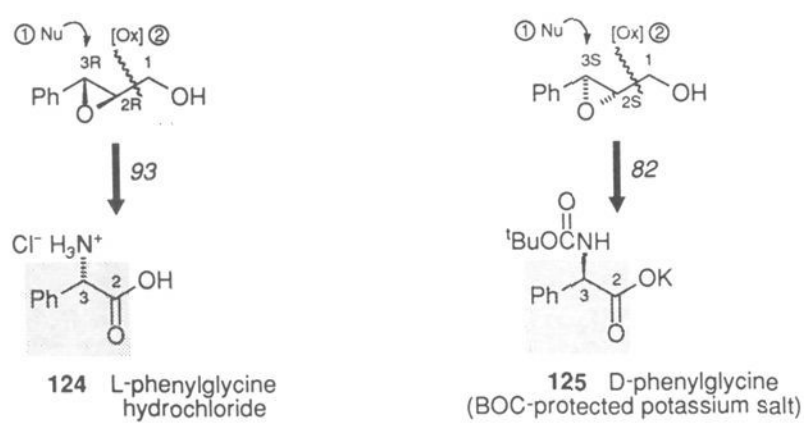


Figure 20.

their protected or activated derivatives. In this section, those synthetic analogues are reviewed. Due to space limitations, detailed discussions of the strategies involved in these compounds' syntheses will not be presented, especially since most of the strategies involved have already been presented. References to those strategies refer to Figure 4 and subsections of section IV.B.

This discussion is divided into four categories: cardiovascular agents, antibiotics, biochemical probes, and miscellaneous pharmaceuticals. Of course, many of these compounds have been made in a variety of ways not involving glycidol, and similar compounds have been produced by using strategies not within the scope of this review. Whole reviews have been dedicated to the pharmacology of these compounds, and it is not the intent here to provide any rigorous pharmacological review. Nonetheless, it is hoped that this discussion will provide a much needed reference point for workers in the field. In seeing the variety of nonracemic bioactive compounds that *have* been made, perhaps these workers will be guided to discover what compounds *might* be made from nonracemic glycidol.

Figure 21.

A. Cardiovascular Agents

Three fundamental goals of cardiovascular drugs are the lowering of high blood pressure (antihypertensives), return of the heart to rhythmic beating (antiarrhythmics), and the general improvement of heart muscle tone (cardiotonics). Biochemically, it is known that at least five mechanisms of action are involved with these activities, four of which involve the adrenergic system. This hormonal system provides the communications link between the sympathetic nervous system and involuntary muscle. Especially important are the neurotransmitters epinephrine (adrenalin) and norepinephrine, the active forms of which are shown in Figure 21.

There are four known receptors for these molecules: α_1, α_2, β_1, and β_2.[277,278] The α receptors are acted upon by norepinephrine in arterial and heart muscle and have been implicated in the maintenance of blood pressure. In particular, the α_1 receptors are postsynaptic and appear to be closely linked with hypertension and arrhythmia. The α_2 receptor is associated with presynaptic and postsynaptic nonspecific action, and α_2 activity is generally considered to be an undesirable side effect of drugs.

Blocking of the β receptor system reduces the overall activity of the sympathetic nervous system. Agents which are β-blockers are thus used to increase life expectancy after the occurrence of a heart attack. There are two known β receptors, β_1 and β_2. Compounds which are "β_1-specific" act on the heart *specifically* and are especially important potential cardiac drugs. Compounds which are "β_2-specific" have been found to be active on smooth respiratory muscle. Even though much of the hypertensive activity of drugs seems to lie with the α receptor system, all β-blockers are potential antihypertensives, since there is often substantial activity of a drug toward both α and β receptors.

A fifth way that a cardiovascular drug may act is by direct influence upon Ca^{2+} transport in cells. By inhibiting the transport of Ca^{2+} across cell membranes, these drugs dilate arteries and reduce heart rate.

The series of cardiovascular drugs derived from nonracemic glycidols will be presented in the following order: general β-blockers, β_1-/β_2-selective blockers, α- or combined α-/β-blockers, and drugs with adrenergic activity but of unspecified biochemical mechanism. In each case, the ordering of the compounds in each figure will be roughly chronological so as to emphasize the continuing progress being made in this area.

1. General β-Adrenergic Blockers

The general β-blockers that have been made from nonracemic glycidols are shown in Figure 22.

Except for **132** and **133**, these compounds were made by addition of an amine to a nonracemic glycidyl aryl ether at C^3. These aryl ethers were made in a variety

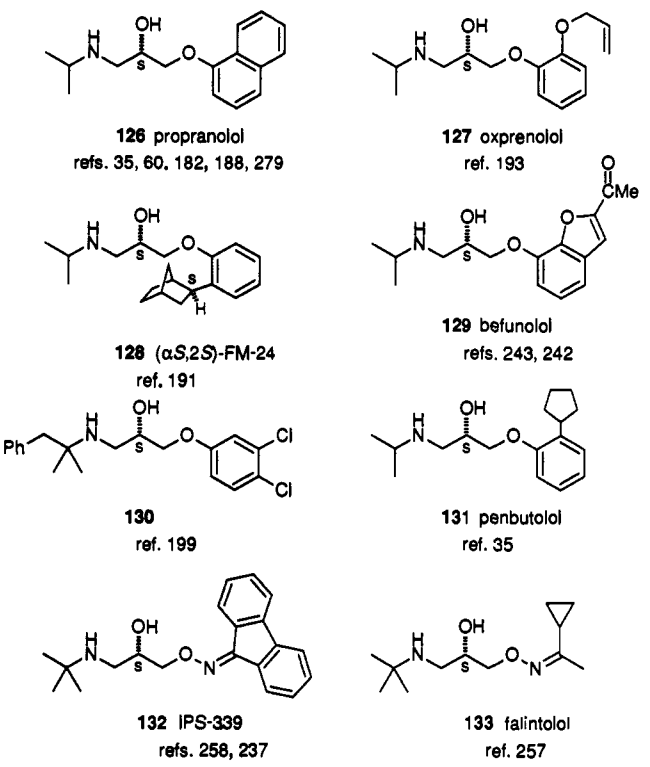


Figure 22. General β-adrenergic blockers.

of ways, including microbial oxidation of an allyl aryl ether (see Scheme 4), nucleophilic aromatic substitution of glycidol (Table 8), Mitsunobu reaction with glycidol itself (Table 16), and several other methods not involving glycidol per se. In the case of propranolol (**126**), the sodium salt of α-naphthol was reacted with (*S*)-glycidyl *m*-nitrobenzenesulfonate derived from asymmetric epoxidation.

Of the two enantiomers of each of these compounds except **132** and **133**, the *S* enantiomer, which is the one more similar to the structure of epinephrine (Figure 21), is more active. In the cases of **132** and **133**, however, both enantiomers show roughly the same activity. Interestingly, although both enantiomers were active, related compounds without the C^2 hydroxyl were inactive. The authors suggest that the "pseudosymmetry" of the molecules explains this unprecedented phenomenon.

2. β_1-Specific Adrenergic Blockers

β-Blockers that have been made from nonracemic glycidols and show differential β_1 or β_2 activity are depicted in Figure 23. Once again the *S* enantiomer is the more active enantiomer.

With regard to **141a** and **141b**, the second stereocenter (labeled 6) also influenced the drug activity, especially in regard to β_2 activity. The relative importance of the two stereocenters in **141a** and **141b** can be evaluated by stereochemical factor analysis,[281] the results of which are shown in Table 19. This analysis is not so much in terms of the absolutely most effective drug for an application as it is in the relative *selectivity* within a series of drugs. For both β_1 and β_2 receptors, the CF_3 derivative (**141a**) shows a tremendous influence of stereochemistry—in fact, slightly more so at position 6 than at position 2. The CH_3 derivative (**141b**) shows less overall influence of stereochemistry, this time with relatively more influence at C^2 than at C^6 (by a factor

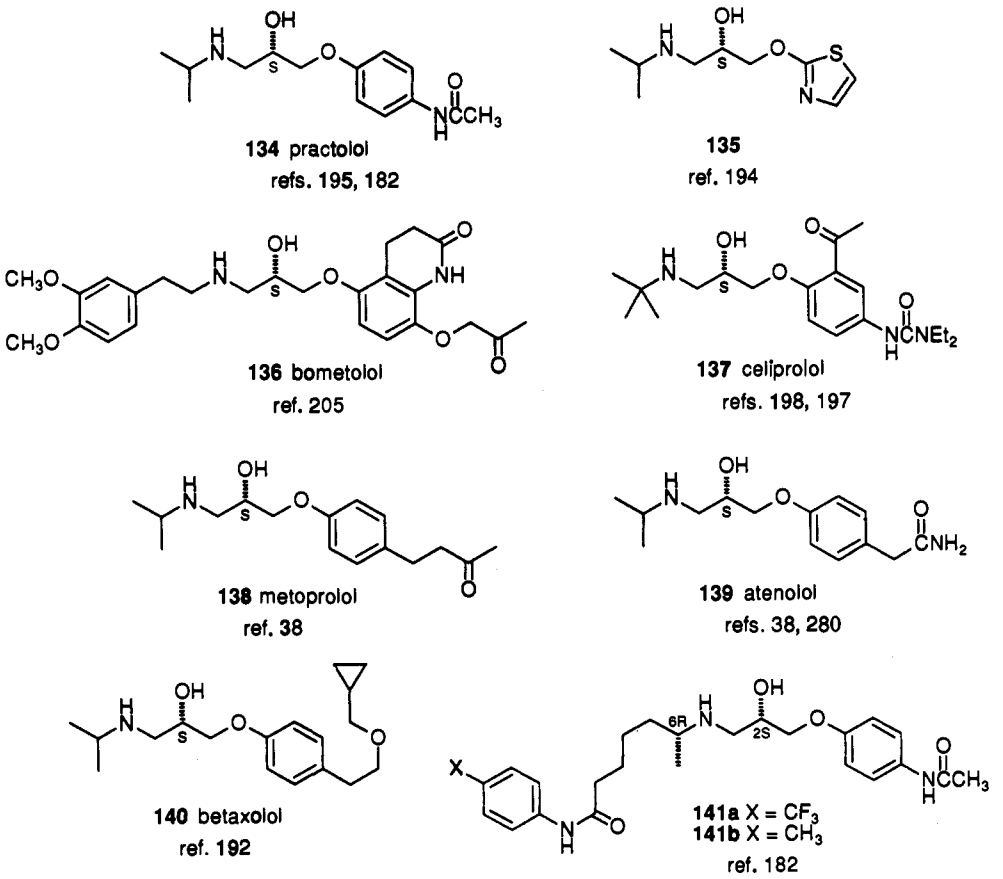


Figure 23. β_1-Specific adrenergic blockers.

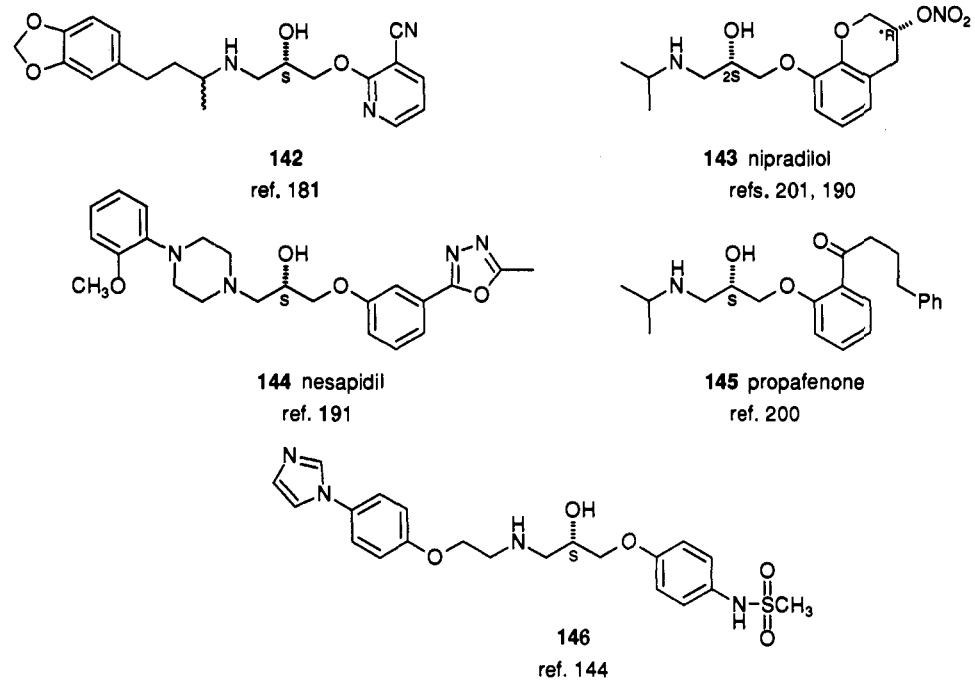


Figure 24. α-Blockers or combined α/β-blockers.

TABLE 19. Stereochemical Factor Analysis of β-Blocking Ability of 141a and 141b[a]

compd	receptor	$K_{rel}(R/S)_2$	$K_{rel}(S/R)_6$	$K_{rel}(l/u)$
141a	β_1	12.2 ± 2.1	17.8 ± 3.0	0.63 ± 0.11
	β_2	18.0 ± 4.0	23.6 ± 5.2	0.83 ± 0.17
141b	β_1	3.6 ± 0.2	2.8 ± 0.1	2.1 ± 0.1
	β_2	6.3 ± 0.8	1.8 ± 0.2	10.6 ± 1.3

[a] Data are from ref 182. $K_{rel}(R/S)_x$ is the relative contribution to the receptor–inhibitor dissociation constant, K_I, of stereocenter x. Larger dissociation constants indicate *lower* activity. Thus, the *RS* isomer of **141a** (CF_3) is 217 times *less* active at the β_1 receptor than the *SR* isomer, since $K_I(RS)/K_I(SR) = K_{rel}(R/S)_2 \times K_{rel}(S/R)_6 = 12.2 \times 17.8 = 217$. See also note 281.

of 3.6 to 2.8 in the case of the β_1 receptor and 6.3 to 1.8 in the case of the β_2 receptor).

The third column of numbers in Table 19, $K_{rel}(l/u)$, indicates the influence of the *relative* stereochemistry of the two centers (like, *RR* or *SS*, vs unlike, *RS* or *SR*). $K_{rel}(l/u)$ would be expected to be close to 1 in a situation where the two stereocenters are acting *independently*. The large value of 10.6 for **141b** at the β_2 receptor, if it is accurate, can only mean one thing: in this case the binding to the receptor is much more dependent upon the *relative* stereochemistry of the two stereocenters than it is upon the *absolute* stereochemistry of those centers. This is an extraordinarily interesting and perhaps unprecedented result.

Note that such an analysis as was done above is of potentially great practical import in the area of drug development. In a biological system such as this one, where several types of receptors are involved, the development of *selective* drugs is at least as important as the development of *potent* ones. Stereochemical factor analysis pinpoints that selectivity in relation to diastereomers.

3. α-Blockers or Combined α-/β-Blockers

Several compounds have been made from nonracemic glycidols and tested explicitly for α activity (as potential antihypertensives and antiarrhythmics). They are compiled in Figure 24.

TABLE 20. Stereochemical Factor Analysis of Relative Active Doses of 143[a]

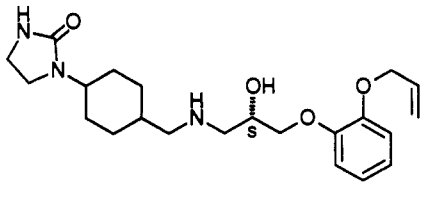
receptor	$C_{rel}(R/S)_2$	$C_{rel}(S/R)_6$	$C_{rel}(u/l)$
β_1 (right atrium)	130 ± 32	41 ± 10	1.6 ± 0.4
β_2	60 ± 17	37 ± 11	1.0 ± 0.3
α	2.0 ± 0.4	25 ± 5	0.8 ± 0.2
direct K^+	0.80 ± 0.14	37 ± 6	1.0 ± 0.2

[a] Data are from ref 190. See also notes 281 and 282.

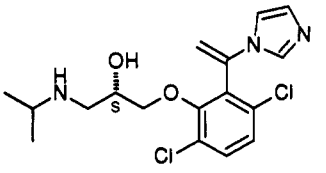
Most notable about this series is that *the α-adrenergic activity is essentially independent of absolute configuration.* Thus, both enantiomers are of similar activity with this receptor. It is important to realize that the lack of importance of stereochemistry for the compounds of Figure 24 does not necessarily mean that one might as well have synthesized the racemic mixture. Rather, *for the primary effect*, either enantiomer would be effective (and should be available by independent synthesis), whereas in terms of undesired *secondary effects*, the two enantiomers are likely to behave differently. For example, it is known that many of these compounds also affect the β-adrenergic system, where stereochemistry is of great importance. Such secondary effects could well account for observations of differential metabolism and toxicity of two enantiomeric forms of the same compound.

Such variation in two enantiomers' activities can be put to practical use. For example, in the case of **145**, the *R* enantiomer, with lower β activity has been suggested to be prescribed for hypertension in cases where β activity needs to be minimized, whereas the *S* enantiomer might be prescribed when cardiac-specific β activity is desired. It is even conceivable that a series of drugs based on the ratio of enantiomers of a single substance might be of therapeutic use.

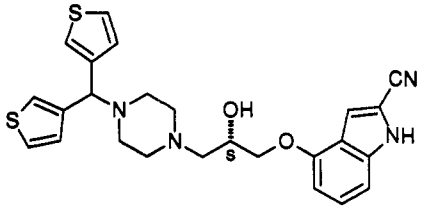
In the case of **143**, the second stereocenter turned out to be decisive in terms of the amount of both α activity



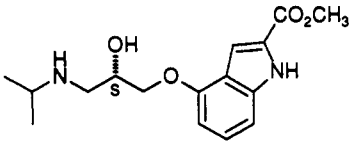
147 adrenergic
ref. 283



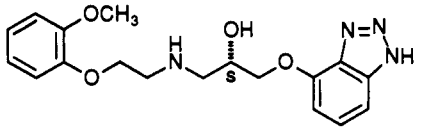
148 antiarrhythmic
ref. 179



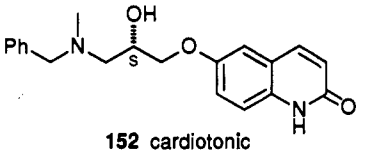
149 adrenergic
ref. 186



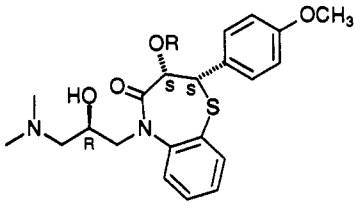
150 antihypertensive
ref. 187



151 for glaucoma
ref. 183



152 cardiotonic
ref. 204



153 Ca antagonist
ref. 261

Figure 25. Analogues exhibiting unspecified adrenergic activity.

and direct effect upon K^+ transport (Table 20). Much information can be derived from this table. For example, the C_{rel}(u/l) data indicate that the two stereocenters act essentially independently in all cases. The stereocenter marked with the asterisk is important for all activity, even for direct influence upon the K^+ channel. The C^2 stereochemistry, on the other hand, is important only for β-adrenergic blocking.

Note that in this case the data are *relative concentrations* required to achieve an equivalent effect,[282] so higher numbers again correlate to lower activity. Multiplying or dividing numbers in the same row of Table 20 gives the relative selectivity for two isomers. For example, the *RS* isomer is 5300 times less active than the *SR* isomer at the β_1 receptor (130 × 41 = 5300) but only 50 times less active at the α-adrenergic receptor (2.0 × 25 = 50) and only 30 times less active with respect to K^+ transport (0.80 × 37 = 30).

4. *Unspecified Adrenergic Activity*

In several cases, at least in the reports relating to synthesis, only general activity has been reported. These compounds are depicted in Figure 25.

Except for **153**, these compounds were all synthesized from nonracemic glycidyl aryl ethers. These aryl ethers were produced in a variety of ways, including reactions of *O*-benzylglycidol (**147**), glycidyl tosylate (**150**), glycidol itself (**151**), and epichlorohydrin (**152**). In the case of **153**, (*R*)-glycidyl tosylate was reacted with a 7-membered ring lactam.

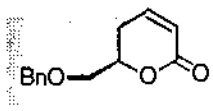
B. Antibiotics

Several antibacterial and potential (though in these cases inactive) antiviral agents have been synthesized beginning with nonracemic glycidols. They are depicted in Figure 26.

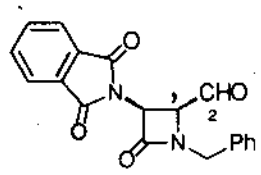
Most of these syntheses were fairly straightforward, involving the addition of acetylide (**154**), isocyanates (**156** and **157**), methyllithium (**158**), or an amine (**159**) to nonracemic protected glycidol. In the case of **155**, (2*R*,3*R*)-*trans*-3-phenylglycidol was oxidized to the aldehyde (Scheme 34), transformed into an epoxyimine, and reacted with 2-phthalimidoacetyl chloride. The resultant epoxylactam was then oxidized to remove the original phenyl ring and C^3 and give the aldehyde shown.

C. Biochemical Probes

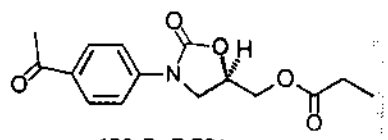
Many of the compounds derived from nonracemic glycidols have not been used as pharmaceuticals per se, but rather as probes into the mechanism of enzyme systems. A good example is the use of nonracemic glycidol for the synthesis of glycerophosphocholines (also called phosphatidylcholines or PCs, Table 21).



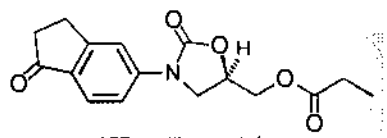
154 antibacterial
ref. 284



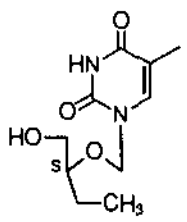
155 potential antibiotic intermediate
ref. 269



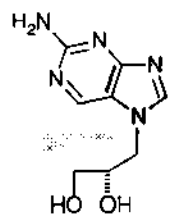
156 DvP 721
refs. 219, 285



157 antibacterial
ref. 220

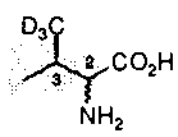


158 potential antiviral
ref. 145

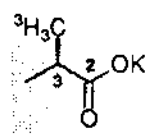


159 potential antiviral
ref. 202

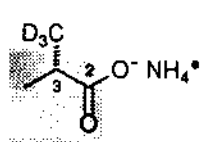
Figure 26. Antibiotics.



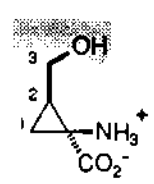
160 labeled valine
refs. 111, 112



161 labeled potassium isobutyrate
ref. 113



162 labeled ammonium isobutyrate
ref. 114



163
ref. 233

Figure 27. Biochemical probes.

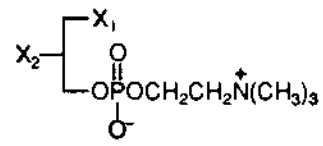
The compounds listed were synthesized for a variety of reasons, primary among them the study of phospholipase enzymes. Entries 1 and 2 also have potent antitumor activity. These compounds are methyl ether analogues of entries 3 and 4, which are known as platelet activating factors[286] and have acetates at position 2. Entries 5–11 constitute a whole series of additional synthetic glycerophosphocholines that have been investigated. The thioethers and thioesters of entries 12–14, though not technically glycerophosphocholines, are included here as PC analogues since they were used as substrates for phospholipase A_1 and A_2.

All of these syntheses begin with reactions already discussed in section III, including reaction of nonracemic glycidol (Table 2), protected glycidol (Table 8 and Scheme 26), and activated glycidol (Table 17).

Four additional compounds have been made specifically to be used as biochemical tools. They are presented in Figure 27.

Amino acid **160** was of use in the study of β-lactam biosynthesis. Salts **161** and **162** were of use in the study of asparagusic acid biosynthesis and L-valine metabolism, respectively. The syntheses of **160–162** involved the addition of isotopically labeled methyllithium to nonracemic *trans*-3-methylglycidol (Table 5). Amino acid **163** was synthesized as a potential ligand in affinity chromatography for the separation of the enzymes associated with ethylene biosynthesis. Its synthesis involved the addition of diethyl malonate to (*R*)-epichlorohydrin, which was derived from (*S*)-glycidyl mesylate.

TABLE 21. Glycerophosphocholines Derived from Nonracemic Glycidol



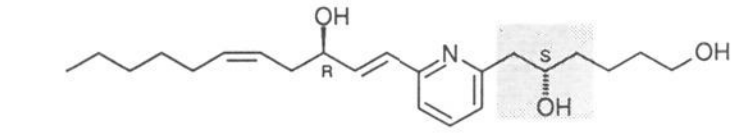
entry	X_2	X_1	ref
1	CH_3O	$O(CH_2)_{15}CH_3$	207
2	CH_3O	$O(CH_2)_{17}CH_3$	208
3	CH_3CO	$O(CH_2)_{15}CH_3$	251, 252
4	CH_3CO	$O(CH_2)_{17}CH_3$	208, 210
5	CH_3CH_2CO	$O(CH_2)_{17}CH_3$	208
6	$CH_3CH_2CH_2CO$	$O(CH_2)_{17}CH_3$	208
7	$CH_3(CH_2)_{14}CO$	$O(CH_2)_{15}CH_3$	251
8	$CH_3(CH_2)_{17}O$	$OCCH_3$	208
9	$CH_3(CH_2)_{15}O$	$OC(CH_2)_{14}CH_3$	248
10	$CH_3(CH_2)_9O$	$OC(CH_2)_{16}CH_3$	248
11	$CH_3(CH_2)_{16}CO$	$OC(CH_2)_{16}CH_3$	62
12	$CH_3(CH_2)_8CO$	$S(CH_2)_{17}CH_3$	122
13	$CH_3(CH_2)_8CO$	$SC(CH_2)_8CH_3$	122
14	$CH_3(CH_2)_8CS$	$SC(CH_2)_8CH_3$	122

D. Miscellaneous Synthetic Analogues

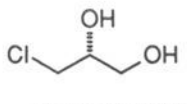
Seven additional synthetic analogues have been made from nonracemic glycidols. They are depicted in Figure 28.

The *RR*, *RS*, *SR*, and *SS* isomers of **164** were produced independently (the second stereocenter being generated by resolution prior to coupling). The hydroxypropyl chain in this compound came from a functionalized acetylene, which was added to glycidyl *m*-nitrobenzenesulfonate (Table 17, entry 5). This synthesis nicely illustrates the use of glycidyl sulfonates without the intermediacy of epichlorohydrin. Although it has not been thoroughly investigated, it is clear from this study and those listed in Table 17 that organometallics add to glycidyl sulfonates exactly as they do to epichlorohydrin (with ring-opening displacement at C^3). Several of the syntheses described in this review might have been simplified had the chemistry of glycidyl sulfonates been more widely known. For example, in the synthesis of **89** (Figure 8 and Scheme 36), the use of glycidyl *m*-nitrobenzenesulfonate might have reduced the number of steps by two.

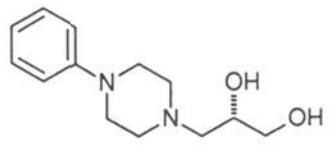
Diols **165** and **166** were produced by addition to (*R*)-glycidol itself. Finally, compounds **167–169** were all synthesized from (2*R*,3*R*)-*trans*-3-phenylglycidol.



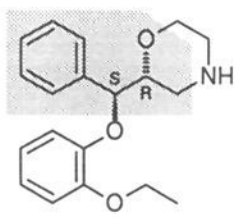
164 leukotriene antagonist U-75302
ref. 247

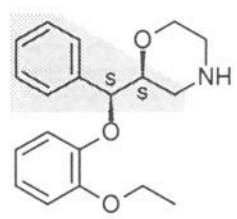


165 male antifertility
ref. 64

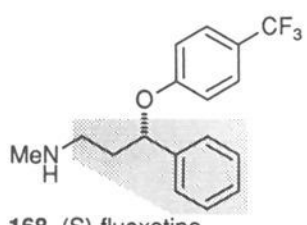


166 dropropizine
(sedative, antitussive)
refs. 58, 203

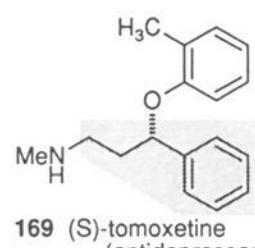




167a and **167b**
ref. 96 reserpine anagonist (+)-FCE20124



168 (S)-fluoxetine
(antidepressant)
ref. 101



169 (S)-tomoxetine
(antidepressant)
ref. 101

Figure 28. Miscellaneous synthetic analogues.

For **167a** and **167b**, phenolate addition occurred at C^3 (Table 3, entry 9); in the case of **168** and **169**, initial reaction involved reduction by Red-Al at C^2 (Scheme 15).

VI. Summary

This review has presented the chemistry of nonracemic glycidols **1–4**, including protected and activated derivatives. Several approaches to the synthesis of nonracemic glycidol and several of its derivatives have been detailed. These include transformation of D-mannitol and L-serine, asymmetric epoxidation and enzymatic transformation of achiral substrates, and enzymatic resolution of racemates.

Protection and activation of nonracemic glycidol is not generally a problem if care is taken to avoid extremes of temperature, acidity, and basicity. Some of the approaches to O derivatives of glycidol, in fact, involve in situ derivatization or bypass glycidol itself completely. The most widely used protecting group is benzyl, partially due to its robustness toward acids and bases, and partially due to the history of development in this field. Thus, for a long time, the only source (and still the most widely used source) of nonracemic glycidol was in the form of *O*-benzylglycidol from D-mannitol. The recent advances in asymmetric synthesis and enzyme-catalyzed reactions are clearly having a major impact on choice of substrate, with a wide range of substrates now available, including both enantiomers of glycidol itself in high stereochemical purity.

The reactivities of nonracemic compounds **1–4** toward nucleophiles have been examined in detail with selected references to reactions of racemates. For unprotected **1**, all reactivity occurs at C^3 (epoxide ring opening) unless directed intramolecularly, in which case opening occurs at C^2. Substituents have substantial effects, generally decreasing reactivity at the site of their attachment. The presence of a phenyl ring at C^3 in **2**, on the other hand, tends to increase the reactivity at that center, and may even lead to reaction with retention of configuration.

Protecting groups serve three functions besides the obvious one of preventing involvement of the primary hydroxyl. In the case of glycidol itself, protection allows for easier handling by (a) reducing the hydrophilicity of the compound and (b) sometimes producing a crystalline derivative. In the case of *trans*-3-methylglycidol, protection has a moderate influence upon the regioselectivity of reactions, increasing the selectivity at C^3 at the expense of reaction at C^2. Finally, proper choice of protecting group can have an effect upon later development of stereocenters ("transfer of chirality") in complex syntheses.

Activating groups have been studied in detail, especially with **1**, and have been found to have different effects depending upon the type of nucleophile. Thus, "hard" nucleophiles such as amines and alkoxides react selectively with glycidyl sulfonates with direct displacement at C^1. "Soft" nucleophiles such as organometallics react selectively with epoxide opening at C^3. Acidic conditions also strongly favor reaction at C^3. Historically nonracemic epichlorohydrin (**16**) has been important as a synthetic starting material. The selectivity observed with **16**, however, is not exceptionally high, and much greater selectivity is observed for glycidyl *m*-nitrobenzenesulfonate, which is available in both enantiomeric forms from asymmetric epoxidation.

Many of the reactions of compounds **1–4** have been employed in the context of natural products or synthetic analogue synthesis, especially reactions of **1**. Of all of the strategies used (summarized in Figure 4), only four have gained widespread recognition and application. These include simple nucleophilic addition at C^3, nucleophilic addition at both C^3 and C^1, and nucleophilic addition at C^3 followed at some point by either oxidation at C^1 or oxidative removal of C^1. Nonetheless, several other strategies have been used, many of them very creatively, including some that radically transform the glycidyl framework.

Clearly the need for enantiomerically pure pharmaceuticals has driven much of this research. In most exploratory work, both enantiomers have to be made, not so much because it is unpredictable which will have the higher activity, but rather because the two enantiomers may have dramatically different side effects due to the presence of multiple receptor sites, each of which may have different selectivities for the two enantiomers. Furthermore, exciting work is being done in the development of pharmaceuticals having more than one stereocenter, and in several cases different diastereomers have been observed to have tremendously different effects. Stereochemical factor analysis is useful in determining which of the stereocenters is most influential in this selectivity.

In terms of the useful products derived from glycidol, this is only the tip of the iceberg. Thousands of glycidyl derivatives have been made, and only a handful have

been synthesized asymmetrically. Yet, in most cases the racemate and the individual isomers have different physical and biological properties. In the 10 years since asymmetric syntheses (including enzyme-catalyzed syntheses) of these substances have been available it is clear that a dramatic revolution has occurred in the whole approach to natural product and synthetic analogue synthesis. The syntheses described here, involving glycidol and related 2,3-epoxy alcohols, are at the forefront of the asymmetric synthesis revolution.

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References

(1) In this review the name glycidol will be used rather than the more cumbersome name oxiranemethanol. For the *Chemical Abstracts* names of the 2,3-epoxy alcohols mentioned, see Table I. Also, the term nonracemic will be used instead of "optically active", "enantiomerically enriched", or "homochiral", for any material that contains a mixture of enantiomers which is not 50:50. In fact, all of the references to such material in this review are to material of at least 85% enantiomeric excess. Where the enantiomeric excess is known and is important to the discussion, the material will be referred to in a way which indicates clearly the stereochemistry at the C^2 carbon. For purposes of clarity of presentation, racemic substances in schemes and tables will be explicitly labeled as such. Furthermore, in section III, involving reactions of nonracemic substances *not in the context of complex syntheses*, all pictures of nonracemic substances will be presented *as though* the enantiomer which is reacting is that derived from (*S*)-glycidol, even though in actuality the other enantiomeric might have been used. In section III in particular no stereochemical designators (*R* or *S*) will be used. Thus, a picture of glycidol with no stereochemical descriptor indicates the nonracemic substance *of either enantiomer*. Finally, in parts IV and V, involving synthetic schemes, every reference to an epoxy alcohol will include explicit mention of the exact enantiomer that was used. It is hoped that this perhaps unconventional approach to nomenclature will set a rigorous standard for discussions relating to chiral substances.

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(280) Phillips, G. T.; Bertola, M. A.; Marx, A. F.; Koger, H. S. Eur. Patent Appl. EP 256,586, 1988; *Chem. Abstr.* **1989**, *110*, 7868n.
(281) Stereochemical factor analysis is a simple method discovered in our group at St. Olaf College for the analysis of the contribution of each stereocenter to the overall selectivity of a reaction or interaction. In our laboratory it has primarily been applied to double diastereoselective reactions. However, it is shown here to be especially valuable for the analysis of substrate–receptor binding in which the substrate has more than one stereocenter. In this analysis, the raw data for rate constants, product ratios, equilibrium constants, or inhibition constants are transformed from a *molecular* basis set (data for the *RR*, *RS*, *SR*, *SS* stereoisomers) into a *stereochemical* basis set (factors for the two stereocenters involved). The stereochemical basis consists of three selectivity factors, one for each center, and one very important factor relating the two centers. They are designated in this case as $K_{rel}(R/S)_2$, $K_{rel}(S/R)_6$, and $K_{rel}(l/u)$, respectively, where the subscripts 2 and 6 refer to the stereocenters of **141a** and **141b**, l stands for like (*RR* and *SS*), and u stands for unlike (*RS* and *SR*). (This l/u nomenclature is from Seebach, D.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 654–660.) These unitless factors are derived from the experimental data as follows:

$$K_{rel}(R/S)_2 = [(K_{RR} \times K_{RS})/(K_{SR}/K_{SS})]^{1/2}$$

$$K_{rel}(S/R)_6 = [(K_{RS} \times K_{SS})/(K_{RR} \times K_{SR})]^{1/2}$$

$$K_{rel}(l/u)_2 = [(K_{RR} \times K_{SS})/(K_{RS} \times K_{SR})]^{1/2}$$

where K_{RR}, K_{RS}, K_{SR}, and K_{SS} are the data for the respective stereoisomers. (In this case K_{RS} refers to the K_1 for the 2*R*,6*S* stereoisomer.) (For concentration data expressed logarithmically, simply replace "×" by "+", "/" by "−", and divide by 2 instead of taking the square root.) Note that the choice of R/S vs S/R in these expressions is arbitrary and is only made the way it is here so that predominantly the tables will have values greater than 1. Thus, $K_{rel}(R/S) = [K_{rel}(S/R)]^{-1}$ for a given stereocenter. These measures are true factors in the sense that they multiply pair wise to give the original relative selectivity data. For example,

$$K_{RS}/K_{SR} = K_{rel}(R/S)_2 \times K_{rel}(S/R)_6$$

$$K_{RR}/K_{SR} = K_{rel}(R/S)_2 \times K_{rel}(l/u)$$

$$K_{SS}/K_{SR} = K_{rel}(S/R)_6 \times K_{rel}(l/u)$$

$$K_{RR}/K_{SS} = K_{rel}(R/S)_2 \times K_{rel}(R/S)_6 = K_{rel}(R/S)_2/K_{rel}(S/R)_6$$

The merit of this approach is not in that the original data can be derived backward in this way, but rather that the discussion can focus on the relative effect of changes in specific *stereocenters* of a substrate (or reagent) involved in a particular reaction or interaction, with specific weight given to each stereocenter's absolute configuration *as well as* the stereocenters' relative configuration.
(282) The concentration here refers to the concentration of test compound required to shift the dose–response curve of a standard agonist (isoproterenol) in parallel to a 2-fold higher dose. Reported data were in the form of the reciprocal logarithm of this quantity.
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