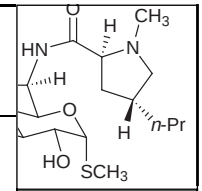
The tethered nitrogen in natural products synthesis



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A variety of nitrogen-containing natural products, including aminosugars and aminocyclitols, have been synthesized by routes that feature the intramolecular delivery of a temporarily-tethered nitrogen nucleophile to an electrophilic site. This general tactic for amino group introduction frequently provides entropic advantages, as well as improved site selectivity and stereoselectivity, compared with the corresponding intermolecular approach. An occasional additional benefit is that the resulting cyclized products can be more easily manipulated toward the desired target than the corresponding free amino compounds. These aspects are illustrated in a discussion of several natural products syntheses from the author's laboratory.

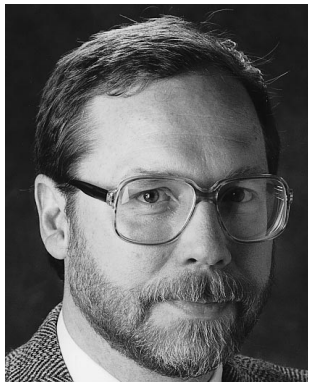
'Help from without is often enfeebling in its effects, but help from within invariably invigorates'

Samuel Smiles, *Self-Help*, 1859

1 Introduction

There are many ways in which the synthetic chemist can view potential targets for synthesis. One approach, which is certainly not favored by everyone, would be to look for interesting patterns of functionality in a group of natural products, judge whether existing methodology is fully up to the task, and then perhaps set about devising new methods for the installation of this functionality. If the methods have worth, they ought to be applicable to the syntheses of the very natural products that inspired their development.

Spencer Knapp was born in 1951 in Baytown, Texas, and raised in Tallmadge, Ohio. As a Fellow of the Ford Foundation Six-Year BA-PhD Program, he received his BA in 1972 and his PhD in 1975 from Cornell University, both under the mentorship of Jerrold Meinwald. Following an NIH postdoctoral fellowship at Harvard University with E. J. Corey, he joined the faculty of Rutgers University in 1977. His research interests include the synthesis of natural products, enzyme inhibitors, and complex ligands, and the development of new synthetic methods. He has received an NCI Young Investigator Award, an American Cyanamid Faculty Award, and a Hoechst-Celanese Innovative Research Award, and serves on the Editorial Board of the Journal of Carbohydrate Chemistry.



Nature has provided chemists with an amazing variety of densely functionalized small molecules that contain amino and hydroxy groups sprinkled about an otherwise simple carbocyclic or heterocyclic framework. A few examples relevant to the present discussion are shown in Fig. 1. This list includes

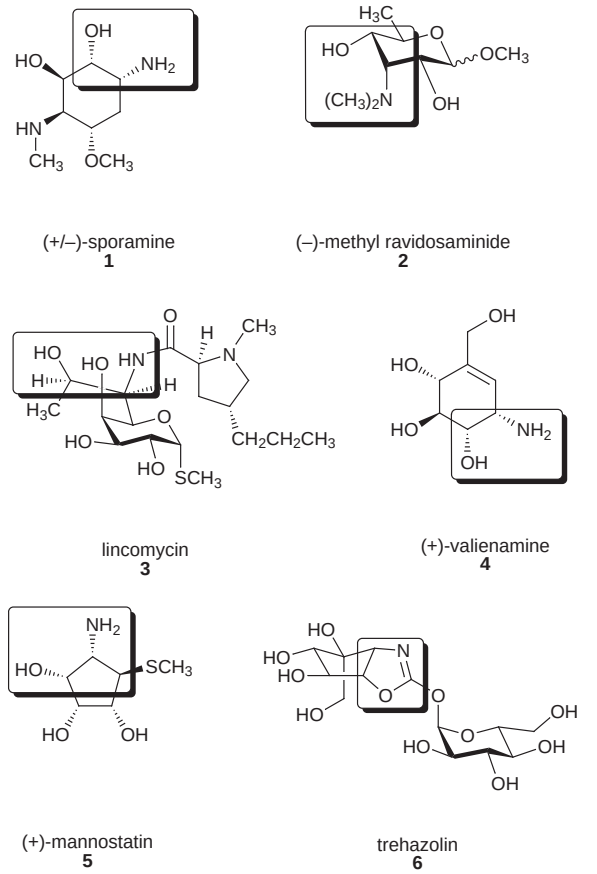
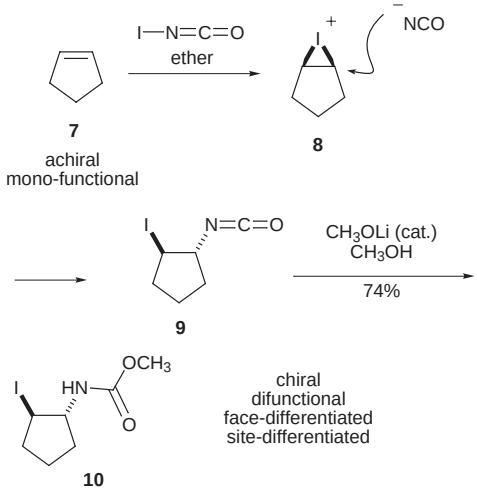


Fig. 1 Synthetic targets with *cis*, vicinal amino alcohol functional grouping.

representatives from both the aminosugar (*e.g.*, lincomycin **3**) and aminocyclitol (*e.g.*, valienamine **4**) families of natural products. One could easily add representatives from other classes of natural products, such as alkaloids, amino acids, and sphingosines. Clearly, no synthesis of these molecules should be contemplated without paying attention to the problem of how to introduce amino and hydroxy groups with control of site and stereochemistry.

A recurring 'functional grouping', or pattern of functionality, that can be identified in these molecules is the vicinal amino alcohol, and for each molecule in Fig. 1 an example of this functional grouping has been boxed-in to show how it occurs in context. Apart from this context, however, one can consider general methods of introducing vicinal functionality, and the

most obvious is in many ways also the best: electrophilic functionalization of an alkene. An old example[1] will suffice to show the power of this approach (Scheme 1). *Trans*-addition to



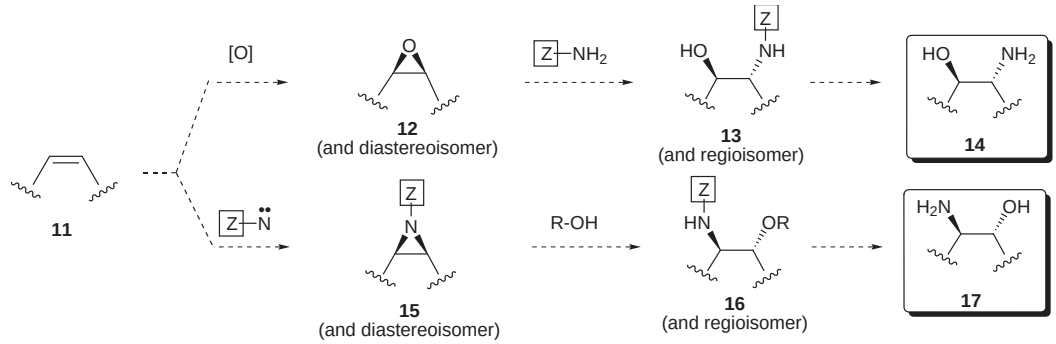
Scheme 1 Alkene *trans*-functionalization.

cyclopentene (**7**) of iodonium isocyanate, generated *in situ* from iodine and sodium cyanate, occurred by way of a cyclic iodonium ion **8** to give the *trans*-iodo isocyanate **9**. The isocyanato group was converted to the methyl carbamate (**10**) by addition of methoxide. Displacements of iodo may be contemplated for the further synthesis of derived vicinal functionality. The overall transformation is from the achiral, monofunctional cyclic alkene **7** to the chiral, difunctional, face-differentiated, and site-differentiated iodo carbamate **10**, and this represents a tremendous increase in the complexity, or level of functionality, or functional group content, of the cyclopentane.

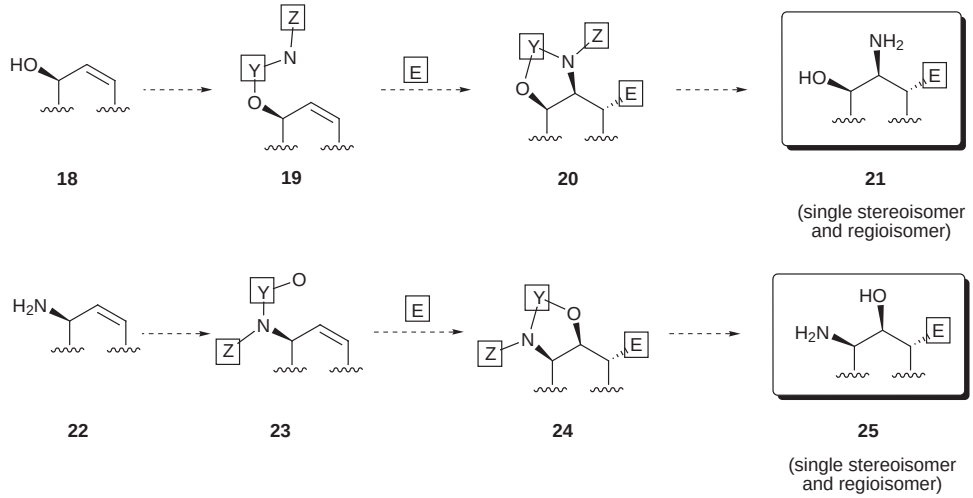
Cyclic vicinal amino alcohols come in two types: *trans* and *cis*. One can imagine functionalizing a cyclic alkene from opposite faces to arrive at the former, and from the same face to arrive at the latter. The *trans* introduction of amino and hydroxy groups can be accomplished in a straightforward manner (Scheme 2): ring-opening of an epoxide **12** by a nitrogen nucleophile, or ring-opening of an aziridine **15** by an oxygen nucleophile. Of course, the use of an amino protecting, activating, or precursor group, such as *N*-sulfonyl or azido, may be desirable, and similarly for the hydroxy. Note that unless the cyclic system **11** is symmetric, or has special features that differentiate the two alkene sites and the two alkene faces, mixtures of diastereoisomers and regioisomers (relative to a preexisting stereogenic center or substituent, say) may be expected.

Introducing the *cis*, vicinal amino alcohol functionality is typically more complicated. Two possibilities are: displacement of a *trans*-difunctional precursor such as **13**, or *syn*-addition of both the nitrogen and oxygen atoms by way of a reagent like $O_3Os{=}NHR$.[2] One can still expect site- and face-differentiation to be a problem. In the late 1970's, when we first began thinking about approaches to potential synthetic targets such as those in Fig. 1, it was clear that there was a need for additional methods tailored specifically for the *cis*, vicinal amino alcohol functional grouping. It was also clear that the concept of neighboring group participation[3,4] could be put to use for managing the activation, and site and stereochemistry of introduction, of the nitrogen or oxygen nucleophile. Scheme 3 shows this idea in generalized form.

The basis of the neighboring group participation approach to the synthesis of vicinal amino alcohols is to use the hydroxy group as a handle (that is, directing group) onto which a



Scheme 2 Synthesis of *trans*, vicinal amino alcohols by attack of an external nucleophile on a 3-membered intermediate. 'Z' represents an amino activating or protecting group; 'O' represents an epoxidizing reagent.



Scheme 3 Synthesis of *cis*, vicinal amino alcohols by attack of a tethered, internal nucleophile on an electrophilic intermediate. 'Y' represents the tether; 'Z' represents an amino activating or protecting group; 'E' represents an electrophilic reagent such as iodonium.

nitrogen nucleophile can be tethered (**19**), or alternatively, to use the amino as a handle for tethering a nucleophilic oxygen (**23**). Intramolecular delivery of the nitrogen (or oxygen) nucleophile to an electrophile-activated alkene affords excellent control of the site and stereochemistry of the eventual amino (hydroxy). For most alkene cyclizations involving participation across five atoms, the nucleophilic nitrogen (oxygen) will be delivered kinetically at the proximal carbon and *cis* to the directing group (**20** and **24**). Although special cases could arise where steric hindrance, C=C polarization, reversibility, or other effects alter this result, it is nevertheless possible to design and execute synthetic routes with intramolecular participation as the key element for installing the *cis*,vicinal amino alcohol functional grouping. Furthermore, recognizing the appropriate allylic alcohol (amine) precursor for this sequence serves as a tremendous simplification of the synthetic planning, and for some targets the appropriate allylic precursor is actually known in optically pure form, or is easily envisioned as the product of a short sequence.

This review describes the use of neighboring group participation for the synthesis of the naturally occurring *cis*, vicinal amino alcohols shown in Fig. 1. For most examples this involves the intramolecular delivery of an O-tethered nitrogen nucleophile. Within this narrowly defined operational format, however, there has been considerable opportunity for the author's research group to develop new cyclization chemistry, and to take advantage of some of the special features of the cyclized but not yet deprotected intermediates. As a result, this approach has proven to be surprisingly versatile, and fully complementary, or perhaps even superior, to many other methods for introduction of nitrogen into organic substrates. One might ask: When is an intramolecular method preferred to intermolecular N-substitution? The answer seems to be: whenever the latter fails, or, importantly, whenever an efficient route can be devised.

The literature concerned with amino alcohol synthesis by N-cyclization methods has been reviewed previously,[3,4] and there are numerous contributions over the last twenty years whose description can fill chapters. At the risk of slighting some excellent work by imaginative researchers, the author would venture a personal short list of some of the important early contributors to ideas in this field. Overman[5] demonstrated in 1974 that trichloroacetimidates could be used as a source of O-tethered nitrogen in an aza-Claisen process. Iodocyclization of these derivatives was later used by Fraser-Reid[6,7] and Cardillo[8,9] to synthesize ristosamine and daunosamine. Roush,[10] Kishi,[11] and Vasella[12] used *N*-benzylcarbamate cyclizations to synthesize sphingosines, ceramide, and 2-amino-2-deoxy-D-pentitols from epoxy alcohols, themselves the products of Sharpless asymmetric epoxidation. Other investigators have developed analogous tethered-N-delivery processes, but not many of them have been applied in natural products syntheses. Of course, there are many excellent synthetic methods that still await their most elegant applications, but as a general rule, the use of a particular synthetic method in a complex synthesis further validates it in the eyes of the organic synthesis community. One need only think of reactions such as the Wittig reaction and hydroboration to appreciate how synthetic applications reflect the power and usefulness of certain transformations.

2 Carbonimidothioate cyclizations: model studies[13,14]

Amide carbonyls, and in fact many other types of carbonyls, have long been recognized as excellent O-participating groups, especially through five-membered ring transition states.[15] This is due to the presence of a considerable amount of electron density on the carbonyl oxygen, as represented by the resonance structure **27** in Fig. 2. The amide nitrogen is only weakly Lewis

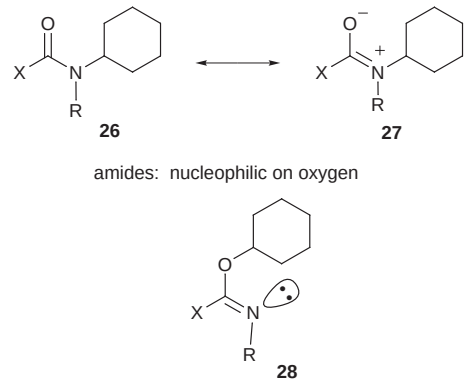


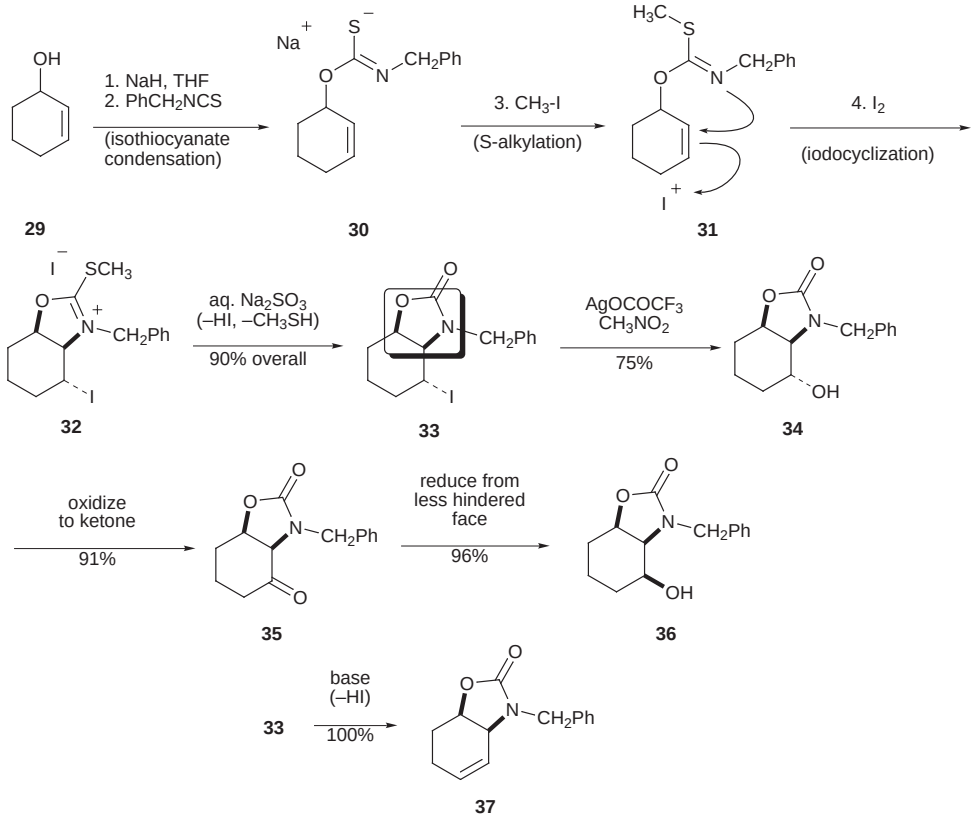
Fig. 2 Nucleophilicities of amides *vs*. imino ethers.

basic. In contrast, the nitrogen atom of an *imino ether*, as represented by **28**, is fully capable of participating as a Lewis base through its lone pair of electrons. Furthermore, *N*-alkylated salts of imino ethers are easily converted to *N*-alkylated amides by hydrolysis. Therefore the device of using an imino ether as an N-participating group could allow the intramolecular nucleophilic introduction of amino, in protected form, to an electropositive site five or six atoms away.

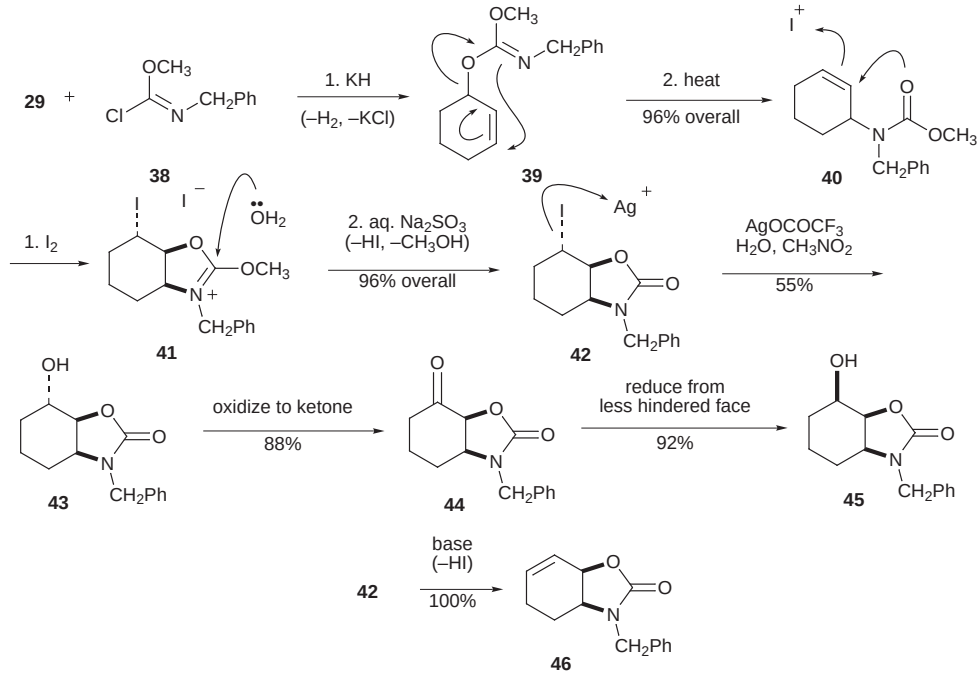
Model studies, based on cyclohexenol **29**, of the use of iodo (N and O)-cyclizations to introduce *cis*,vicinal functionality are shown in Schemes 4 and 5. Condensation (Scheme 4) of the sodium salt of **29** with benzyl isothiocyanate led to the ambident anion **30** (anionic character at both N and S), which reacted with iodomethane exclusively on sulfur (the softer atom) to afford the *S*-methyl carbonimidothioate derivative **31**. This rather exotic but easily prepared imino ether derivative cyclized under treatment with iodine to give the iodo iminium salt **32**, which in turn hydrolyzed upon quenching to give the iodo oxazolidinone **33**. One can see buried within this structure the protected *cis*, vicinal amino alcohol functional grouping (boxed), here flanked by an iodo substituent that offers opportunities for further transformation. For example, the iodo was displaced under silver-assisted solvolysis conditions to give the *trans*-hydroxy oxazolidinone **34**, and this could be oxidized to the corresponding ketone **35**, and then reduced from the less hindered side to give the *trans*-hydroxy oxazolidine **36**. The iodo could also be eliminated as H–I under E2 conditions by treatment with the amidine base DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), affording the unsaturated oxazolidinone **37**. Note that the transformations subsequent to iodocyclization benefit from the presence of the *cis*-fused oxazolidinone, which not only ties up the otherwise reactive hydroxy and amino groups, but also lends some face- and site-bias to the nearby cyclohexyl carbons.

Scheme 5 shows a complementary route to fused oxazolidinones based on an O-cyclization. Reaction of cyclohexenol (**29**) with carbimidoyl chloride **38** led to the imino ether derivative **39**, which on heating rearranged smoothly to carbamate **40** by a [3.3] sigmatropic pathway. Iodocyclization of **40** occurred with O-participation to give an iodo iminium intermediate **41** (compare **32**), and hydrolysis upon quenching led to the *trans*-iodo oxazolidinone **42**. As before, the iodo could be replaced by hydroxy (**43** or **45**) or keto (**44**), or eliminated to the alkene (**46**).

These model studies, published during 1982–1984,[13,14] established the synthetic links between a cyclic allylic alcohol precursor and a variety of derived amino alcohol, amino diol, and other functional groupings that might appear as part of interesting synthetic targets. The model transformations turned out to hold up well to the much more rigorous test of multistep synthesis with polyfunctional substrates.



Scheme 4 Carbonimidothioate iodocyclization model studies.

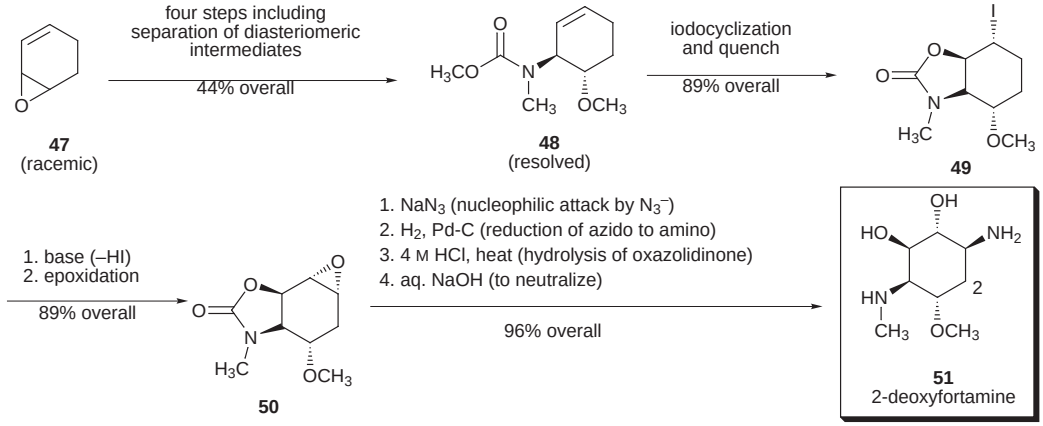


Scheme 5 [3,3]-Sigmatropic rearrangement and iodocyclization model studies.

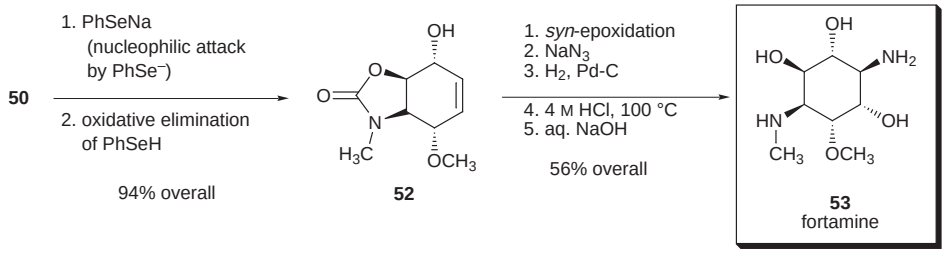
3 Synthesis of the aminocyclitols 2-deoxyfortamine, fortamine, and sporamine[16,17,18]

2-Deoxyfortamine (**51**, Scheme 6), fortamine (**53**, Scheme 7), and sporamine (**1**, Scheme 8) are aminocyclitol components of the antibiotics istamycin A, fortamicin A, and sporaricin A, respectively. They are structurally analogous, but differ in the nature of the substituents at C-1 and C-2. Thus divergent synthetic routes could perhaps be developed from a common intermediate already bearing appropriate functionality at C-3 to C-6. As events transpired, that common intermediate is the epoxy oxazolidinone **50**, and an efficient synthesis of this compound in optically active form was devised (Scheme 6). The three aminocyclitols bear vicinal amino alcohol functional groupings, both *trans* and *cis*, in several places, so the synthetic planning essentially became an exercise in matching the epoxide-based methods and the new iodocyclization methods to this functionality.

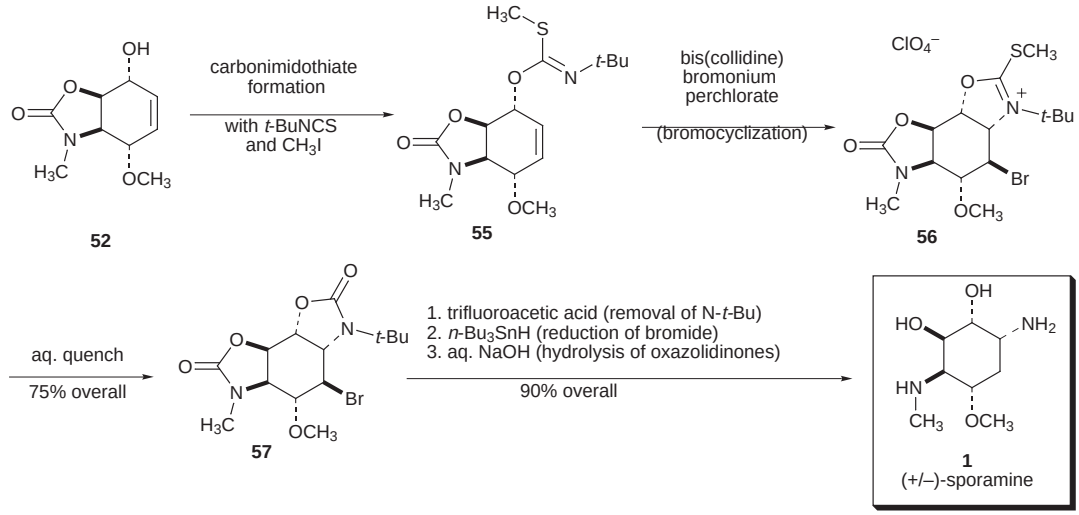
3,4-Epoxycyclohexene (**47**, Scheme 6) preferentially opens with amine nucleophiles at the allylic C–O bond, and this allowed the straightforward synthesis[16,17] of resolved allylic carbamate **48**. Iodocyclization and quenching as previously described (Scheme 5) gave the iodo oxazolidinone **49**, which



Scheme 6 Synthesis of 2-deoxyfortamine.



Scheme 7 Synthesis of fortamine.



Scheme 8 Synthesis of sporamine.

was dehydroiodinated as in the model studies, and then epoxidized from the less-hindered (convex) face. Site-selective reaction of the epoxide **50** with azide anion, reduction of the azido to amino, and then deprotection led to the simplest aminocyclitol target, 2-deoxyfortamine **51**. In this route, and in those that follow, the *cis*, vicinal amino alcohol substructure was formed by a cyclization reaction, whereas the *trans*, vicinal amino alcohol substructures were made by S_N2 epoxide opening with nitrogen nucleophiles.

Scheme 7 shows the transformation of epoxy oxazolidinone **50** to fortamine (**53**).[16] Another site-selective nucleophilic opening of the epoxide ring, this time with the sodium salt of selenophenol, led to a hydroxy selenoether, which in turn was converted to allylic alcohol **52** by the dependable oxidative *syn*-elimination method (with loss of PhSeOH). Epoxidation *syn* to the allylic hydroxy, another well-precedented reaction, was followed by site-selective azide attack on the epoxide and conversion as before to the aminocyclitol product **53**.

Once again the epoxide-opening reaction proved its merit for *trans*, vicinal amino alcohol preparation. Not only were these reactions highly site-selective, but the site could also be predicted (and the synthesis planned, or at least rationalized) based on the simple principle that the ring openings tend to occur in *trans*-diaxial fashion from the predominant half-chair conformation. For epoxides **50** and **54**, this is displayed as Fig. 3.

The sporamine synthesis (Scheme 8)[18] used allylic alcohol **52** as the starting point for a carbonimidothioate cyclization. *tert*-Butyl isothiocyanate was employed to allow for convenient removal of the *N*-alkyl substituent. For this case a bromocyclization was carried out [bis(collidine)bromonium perchlorate is an effective source of Br^+], and aqueous quenching gave rise to

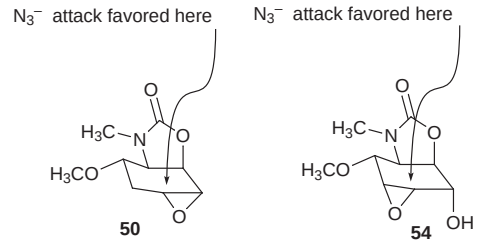


Fig. 3 Pseudo-axial attack by azide to afford a *trans*-diaxial product.

bromo oxazolidinone (**57**). Three operations finished the route: S_N1 acidolysis of the *N*-*tert*-butyl, radical-based reductive debromination, and basic hydrolysis of the two *cis*-fused oxazolidinones.

4 Synthesis of the amino sugar methyl ravidosaminide[19]

Ravidosamine, 3,6-dideoxy-3-(*N*,*N*-dimethylamino)altropyranose (absolute configuration unknown), is the aminosugar component of the aromatic C-glycoside antibiotic ravidomycin (it also lacks the O-4 acetyl of the antibiotic). The *cis*,vicinal amino alcohol functional grouping at C-3,4 (shown as the methyl glycoside **2**, Scheme 9), suggested that a carbonimidothioate iodocyclization could be employed for its synthesis in a manner analogous to that used previously on carbocyclic systems. Furthermore, one of the *N*-methyls could be introduced as methyl isothiocyanate, and the other could come from reduction of the oxazolidinone carbonyl. In this way, ravidosamine, or a simple derived glycoside, should serve as an interesting aminosugar target to further test the generality of the tethered nitrogen delivery method.

There are of course differences between substituted cyclohexyl substrates and pyranosides that could obstruct the direct transfer of a successful reaction from one realm to the other. One important difference is that the pyranose skeleton is more electron-rich at the anomeric carbon, but more electron-poor at other carbons compared with the cyclohexyl skeleton, both characteristics attributable to the presence of the ring oxygen. Thus S_N1 or solvolytic substitutions are generally easier to carry out at C-1 of the pyranose (resonance effect), but slower at C-2 (inductive effect). S_N2 reactions can be difficult at secondary carbons for *both* classes of substrates because of the steric hindrance imposed by the various substituents. With additional electron-withdrawing substituents, S_N1 reactions are further inhibited for both classes. The *intramolecular* delivery of a nucleophile can in principle help compensate for the reduced reactivity, but *intermolecular* displacements subsequent to the cyclization are still subject to the usual limitations.

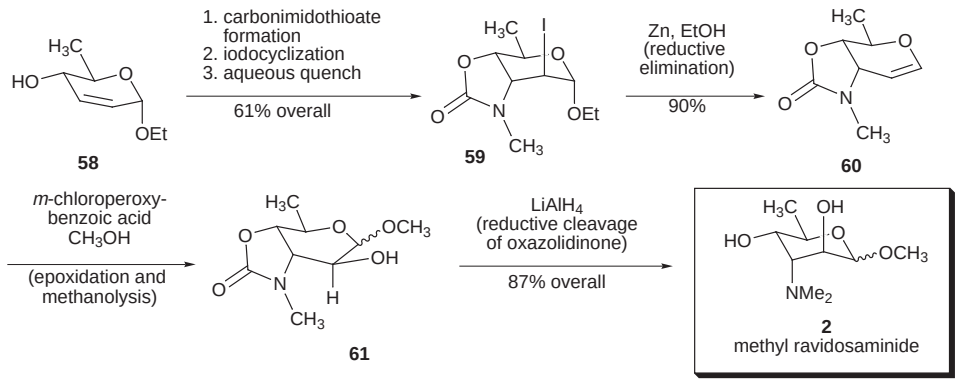
The appropriate saccharidal allylic alcohol substrate for carbonimidothioate cyclization is **58** (Scheme 9), available from commercial triacetyl-D-glucal in several steps.[19] Anionic condensation with methyl isothiocyanate followed by S-methylation, iodocyclization, and quenching as before led indeed to the iodo oxazolidinone **59**. The stereochemistry is presumably a result of kinetically favored pseudo-*trans*-diaxial addition of the electrophile and nucleophile. At this point, replacement of iodo by hydroxy would complete the installation of functionality on the pyranose ring.

The reaction designed to accomplish this functional group exchange had been worked out in model studies on a cyclohexyl substrate (Scheme 4).[14] However, reaction of iodo oxazolidinone **59** with silver trifluoroacetate in nitromethane gave no *trans*-hydroxy oxazolidinone; in fact, it gave no reaction at all, at least up to 90–100 °C, by which temperature slow destruction of starting material set in. The model displacement had occurred at 0 °C, perhaps with N-participation accounting for the clean stereochemical result. The reduced reactivity of the pyranoside substrate **59** relative to the cyclohexyl model **33** can be attributed to the two additional electron-withdrawing oxygens two atoms away from the carbon undergoing displacement. Thus, an alternative to the direct, or even N-assisted, solvolytic displacement of iodide had to be found.

Sometimes in synthesis one has to jettison hard-won functionality in order to open up new pathways to the target, and this was the case for **59** (Scheme 9). Treatment of **59** with zinc powder gave the glycal **60**, the result of a reductive vicinal elimination. In spite of the fact that stereochemical and functional complexity at C-2 was lost, it could be recovered immediately by epoxidizing **60** in methanol to give the methyl glycoside **61** as a mixture of anomers. Alternatively, alkene **60** was hydroxylated with osmium tetroxide, and the resulting vicinal diol was converted to the same methyl glycoside under acidic methanolysis conditions. Both oxidative transformations occur from the less-hindered *exo*-face of glycal **60**, as the *cis*-fused oxazolidinone again serves as a stereochemical directing element. Lithium aluminum hydride reduction of the oxazolidinone ring of **61** led to the target aminosugar **2**.

5 *N*-Benzoylcarbamate cyclizations: synthesis of aminosugars[20,21]

An often-used strategy for the synthesis of aminosugars from carbohydrate starting materials is simply to replace one of the hydroxys of the carbohydrate with an amino group, usually by means of an S_N2 substitution on a sulfonate ester or epoxide with a good nitrogen nucleophile such as azide anion. One can take advantage of the wide variety of enantiomerically pure and stereochemically rich carbohydrate starting materials that are commercially available or made by literature procedures in a few steps. The obvious drawback of this approach is that substitutions on secondary carbons of pyranosides and furanosides, for reasons mentioned in the previous section, can be



Scheme 9 Synthesis of methyl ravidosaminide.

quite low-yielding. Iodocyclization of an unsaturated imino ether offers one alternative to intermolecular substitution, as the nucleophilic nitrogen is well-positioned, prior to alkene activation, for participation at the intended carbon. However, this requires an allylic alcohol precursor. A more general strategy would be to arrange for intramolecular delivery of a tethered nitrogen *anion* in an S_N2 fashion to a sulfonate or epoxide carbon center. Both kinds of electrophiles can be made from poly-hydroxy starting materials by well-precedented transformations.

Our candidate for the tethered nitrogen nucleophile for intramolecular 'S_N2' is the anion of an *N*-benzoylcarbamate, prepared simply by reaction of benzoyl isocyanate with an appropriately positioned hydroxy (Scheme 10).[20,21] Because the reaction with benzoyl isocyanate occurs rapidly under mild and neutral conditions, sensitive substrates such as epoxy alcohols and diol monotriflates can be used, and many of these are available in enantiomerically pure form. As a model, cinnamyl alcohol **62** was converted to its *N*-benzoylcarbamate derivative, epoxidized, and then treated with sodium hydride to generated the sodium salt of the *N*-benzoylcarbamate anion, **64**. Intramolecular cyclization occurred at the proximal epoxide carbon to give the *N*-benzoyloxazolidinone **65**, which subsequently underwent N→O benzoyl migration to produce the final product, **66**. Although the benzylic carbon might have also undergone substitution in an intermolecular displacement, the intramolecular reaction using the five-atom tether was highly site-selective. McCombie co-discovered the *N*-benzoylcarbamate cyclization,[22] and several other examples of this cyclization to afford protected amino diols have been reported more recently.[23–29]

Pyranoside substrates can also be used for a direct sugar-to-aminosugar transformation (Scheme 11).[20,21] Thus methyl 4,6-*O*-benzylidene-α-D-glucopyranoside **67**, a *trans*-vicinal diol, was selectively converted to its 2-*O*-trifluoromethanesulfonate ester by reaction with triflic anhydride. Monotriflation of diols under these conditions tends to occur preferentially at the hydroxy flanked by a *cis*,vicinal heteroatom, here the methoxy oxygen, presumably because of intramolecular H-bonding and an accompanying increase in the electron density at the hydroxy oxygen. The less-reactive hydroxy, here O-3, is now available for condensation with benzoyl isocyanate under conditions that do not disturb the heat- and base-sensitive 2-*O*-triflate. The resulting *N*-benzoylcarbamate **68** was cyclized as its sodium salt to afford the *N*-benzoyloxazolidinone **69**, and deprotection by basic hydrolysis led to the aminosugar derivative **70**. The overall change is hydroxy-to-amino at a defined site, C-2.

Two other examples of pyranoside diol mono-triflate-mono-*N*-benzoylcarbamates were successfully cyclized (**71** and **72**, Fig. 4), but two other examples failed (**73** and **74**). In the latter

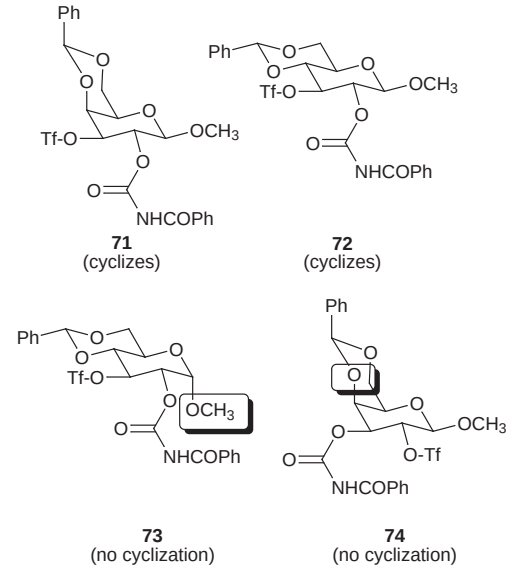
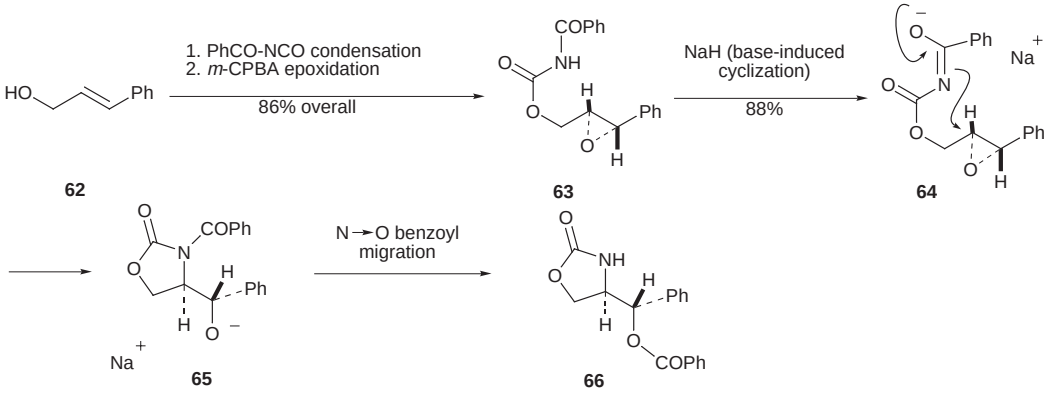
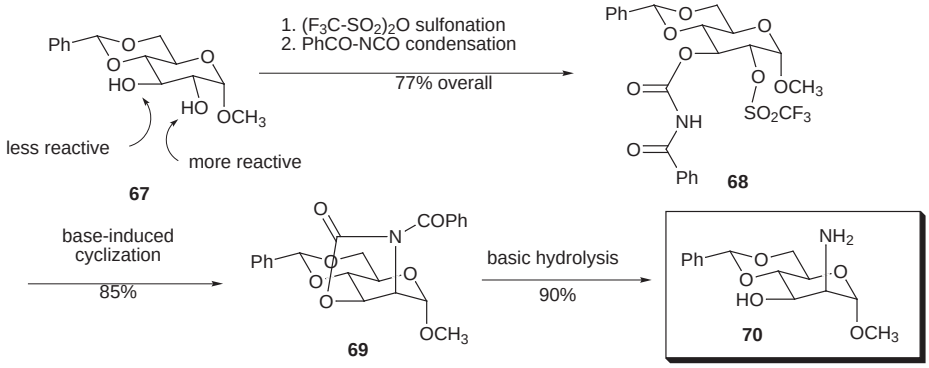


Fig. 4 Additional examples of *N*-benzoylcarbamate cyclizations.



Scheme 10 *N*-Benzoylcarbamate cyclization.



Scheme 11 Sugar to aminosugar transformation.

cases, nearby axial substituents (shown in boxes) can be blamed for blocking the approach of the *N*-benzoyl nitrogen.

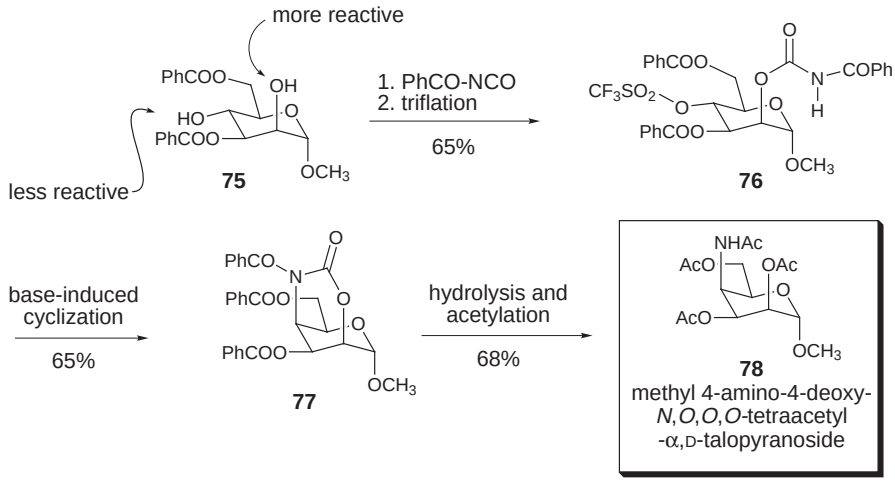
Two solutions presented themselves: the offending axial substituent can be removed, as in **72**, or it can be used *itself* to deliver the tethered nitrogen nucleophile. Scheme 12 shows the application of the latter idea to the hydroxy-to-amino transformation of 3,5-dibenzoylmannopyranoside **75**.

6 Synthesis of the antibiotic lincomycin[30]

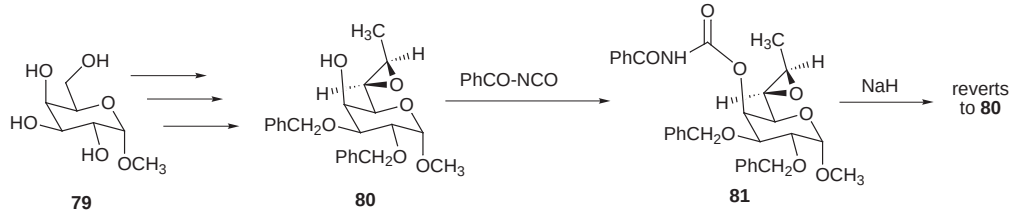
Lincomycin (**3**) is an antibacterial used to treat infections in humans and animals. It consists of two components joined by an amide link: an aminooctose thioglycoside termed methyl thiolincosaminide (**86**), and L-*trans*-*n*-propylhygric acid (**87**, Scheme 14). Coupling of **86** and **87** to regenerate **3** has been achieved, so that the synthesis of **86** constitutes a formal synthesis of the antibiotic. From the standpoint of aminosugar synthesis, the structure of **86** presents a particularly challenging feature: the location of the amino group, C-6, is extremely hindered, and intermolecular introduction of a nitrogen nucleophile at this position can be expected to be very difficult. There are other challenges presented by a synthesis of **86**, to be sure, but it seemed to be a good aminosugar test case for our methods of tethered nitrogen delivery.

We selected a strategy that asked the axial C-4 hydroxy to deliver the tethered nitrogen nucleophile to C-6 over a six-membered ring transition state. Commercially available methyl α-D-galactopyranoside (**79**, Scheme 13) was protected at C-2,3 and chain-extended at C-6 to produce the epoxy alcohol **80** after several steps. Condensation of **80** with benzoyl isocyanate was successful, but treatment of the *N*-benzoylcarbamate **81** with sodium hydride as before (Schemes 10–12) caused reversion to **80**. We infer that the reactivity of this anion is not sufficient to overcome the steric barrier to closure at C-6; one evidently needs a more reactive and less-hindered nitrogen nucleophile.

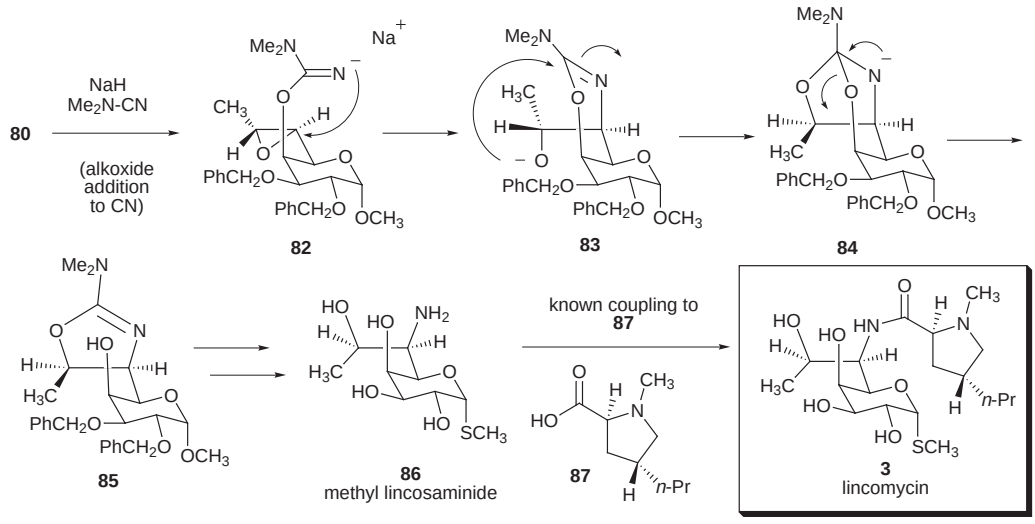
After experimenting with several nitriles and other potential tethers,[31] we found conditions for inducing the intramolecular epoxide opening (Scheme 14). Condensation of the sodium salt



Scheme 12 *N*-Benzoylcarbamate cyclization to non-vicinal site.



Scheme 13 Attempted *N*-benzoylcarbamate cyclization for lincomycin.



Scheme 14 Synthesis of lincomycin.

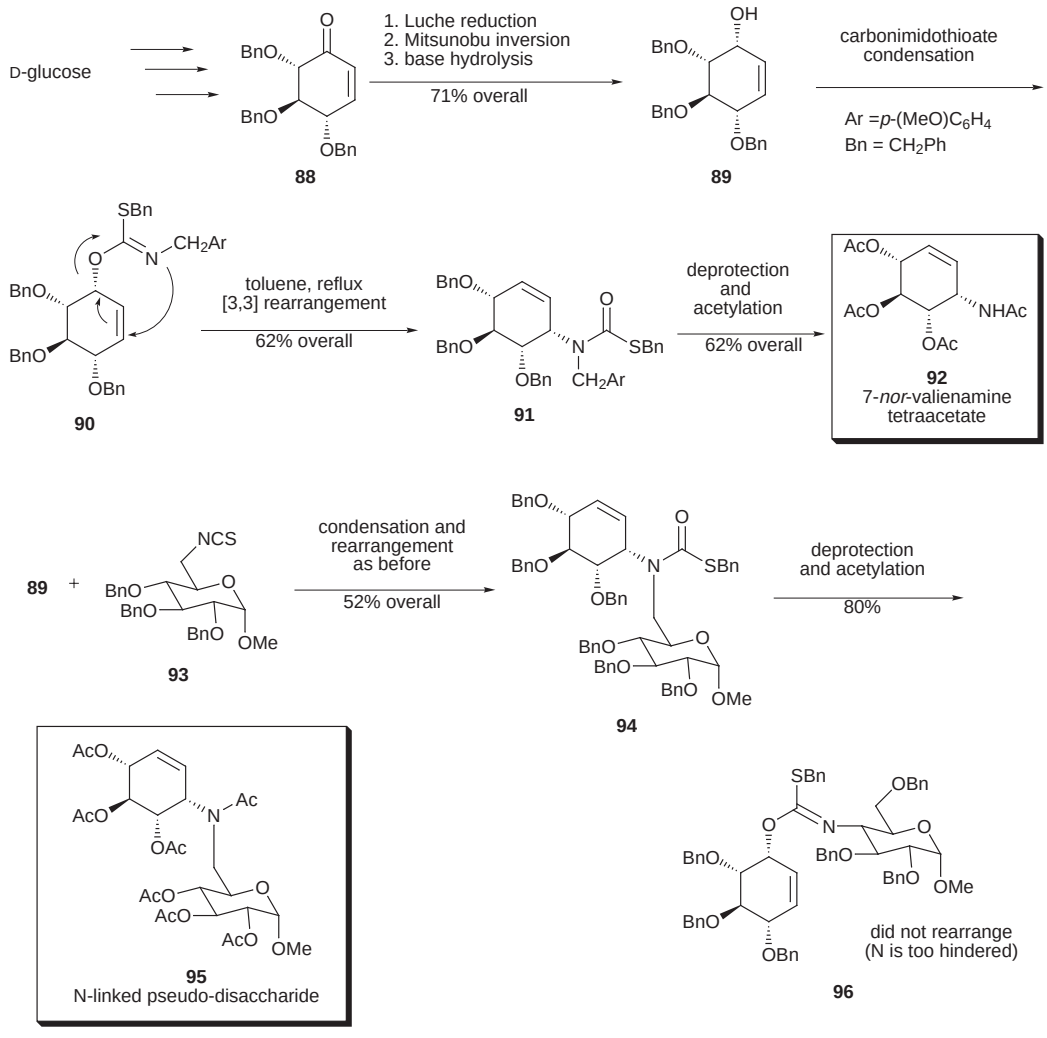
of epoxy alcohol **80** with *N*,*N*-dimethylcyanamide gave rise to an isourea anion (**82**), which evidently closed at C-6 to give a dihydrooxazine, **83**. This intermediate immediately rearranged, however, to the more stable C-6,7 oxazoline (**85**) by way of the tetrahedral intermediate **84**. The overall result was not only effective delivery of the tethered nitrogen to C-6, but also creation of a well-protected form of the C-6,7 amino alcohol. This proved to be critical for subsequent transformations at C-1 to install the axial methylthio group (**85** → **86**). It is also a demonstration of another advantage that intramolecular introduction of the nitrogen substituent can bestow. *Intermolecular* attack (by azide or phthalimide, for example) leads simply to a protected amine; *intramolecular* introduction of amino leads to an intermediate with two protected groups that can be deprotected simultaneously or otherwise manipulated to advantage. There are further examples of these features in the syntheses in the sections below.

7 Synthesis of the aminocyclitol valienamine and related pseudo-sugars[32]

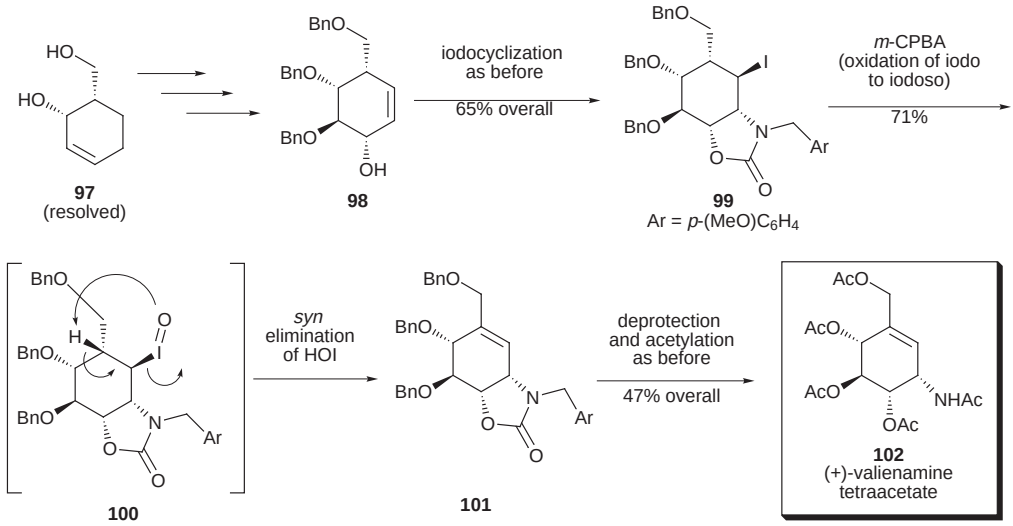
For the remaining sections we return to the aminocyclitol arena. Valienamine (**4**) is a seven-carbon unsaturated amino tetrol that shows α-glucosidase inhibitory activity. It is also found as a component of several other pseudo-oligosaccharide glycosidase inhibitors, wherein the amino is linked to C-4 of a glucopyranoside. Both of the carbon-bonds to this nitrogen are secondary, congested, and difficult to form by intermolecular reactions such as halide displacements, reductive amination, and epoxide aminolysis. Our previous work with carbonimidothioate chemistry[6] indicated that even bulky *N*-substituents such as *tert*-butyl are tolerated, and the conditions are mild enough that functionalized *N*-substituents might also be compatible. We therefore set out to synthesize **4** and some related compounds, and also to use the tethered nitrogen delivery methods for linking the *N*-substituent to the aminocyclitol (Scheme 15).[32]

The conversion of D-glucose to the cyclohexenone **88** (Scheme 16) followed a literature route. Selective reduction of the carbonyl from the less-hindered face, and then inversion of the resulting allylic alcohol by the Mitsunobu protocol led efficiently to the protected conduritol derivative **89**. A word about the Mitsunobu inversion sequence is appropriate here.[33] This procedure, which involves treating an alcohol with diethyl azodicarboxylate, triphenylphosphine, and benzoic acid, and then hydrolyzing the resulting (inverted) allylic benzoate, is particular efficient in the cyclohexenol cases we and others have studied. In fact, it is so dependable that we can incorporate into our synthetic planning the preparation of the *wrong* allylic alcohol, knowing that the stereochemistry can be 'fixed' at a later point in the route. A couple of extra steps are spent, but they are very high-yielding and lead to the desired product with greater stereoselectivity. Of course, one frequently makes compromises of this type in organic synthesis — the use of protecting groups is a prime example — but these tactics simply add to our capabilities until we are able to find a more direct solution.

Conversion of **89** to an *S*-benzylcarbonimidothioate (**90**) set the stage for [3,3]-sigmatropic rearrangement (reminiscent of Scheme 5) to the allylic amine derivative **91**, which was deprotected to afford 7-*nor*-valienamine (**92**). When the



Scheme 15 Synthesis of valienamine analogues.



Scheme 16 Synthesis of valienamine.

carbonimidothioate was prepared with the glucose-derived isothiocyanate **93** as the condensation partner, the [3,3] rearrangement led, after deprotection, to a pseudo-disaccharide of 7-*nor*-valienamine, **95**. This is a fairly complex and hindered N-substituent, but there are limits. The corresponding carbonimidothiate **96** derived from a protected 4-isothiocyanatoglucose did not rearrange, but instead underwent elimination to form a cyclohexadiene.

For the synthesis of valienamine itself (Scheme 16),[32] we prepared the cyclohexenediol **97** as the enantiomer shown, and converted it, by a multistep route capped with a Mitsunobu inversion procedure, to the allylic alcohol **98**. Iodocyclization of the carbonimidothioate derived from *p*-methoxybenzylisothiocyanate led to the iodo oxazolidinone **99**.

At this point, *syn*-elimination of H–I to the alkene is required. Previous model studies (Scheme 4) include an E2 dehydroiodination promoted by DBU, but this is almost certainly a *trans*-vicinal process, and it is blocked in the case of **99**. The *syn* elimination has only limited literature precedent — Reich had shown that oxidation of iodides to the corresponding iodoso derivatives (see **100**) led to some *syn* elimination of HOI, accompanied by other, cationic, processes such as substitution.[34] It is here that the role of the research director, as opposed to the poor soul carrying out the actual experiments, comes into prominence in a way that can be compared to the role of a priest, pastor, or other mediator of faith. The *syn* oxidative dehydroiodination had not, to the research director's knowledge, been used in a synthetic route, nor did it appear especially promising, because of the cationic side reactions. However, heavily oxygenated substrates, such as carbohydrates and cyclitols and **99**, do not readily give S_N1 or solvolytic products for reasons already alluded to (Section 4). Hence, the *syn* elimination pathway might be more prominent for these substrates. More worrisome, however, was the prospect that the product alkene would be more susceptible to oxidation than the starting material, so that at temperatures appropriate for elimination, over-oxidation at the alkene site might take preference to iodoso formation. But in this case, the research director reasoned, the product alkene would be flanked by three electron-withdrawing allylic heteroatoms, which ought to significantly reduce the reactivity of the alkene toward epoxidation. As often happens in synthesis, there is no appropriate model for this elimination reaction that is easier to make than the actual substrate **99**, except perhaps the racemate. Thus faith (there is no better word for it) is required on the part of the experimentalist that an investment of many synthetic steps will be rewarded by a successful elimination reaction, deep into the route, that is without adequate precedent. The same experimentalist should not be reminded at this point that there might well be similar cases of misplaced faith that have never been brought to light. As it happened, oxidation of iodo oxazolidinone **99** with *m*-chloroperoxybenzoic acid at −10 °C for two and a half days led to the formation of the protected valienamine derivative **101** in good yield, and deprotection and acetylation gave the desired target as its peracetate **102**.

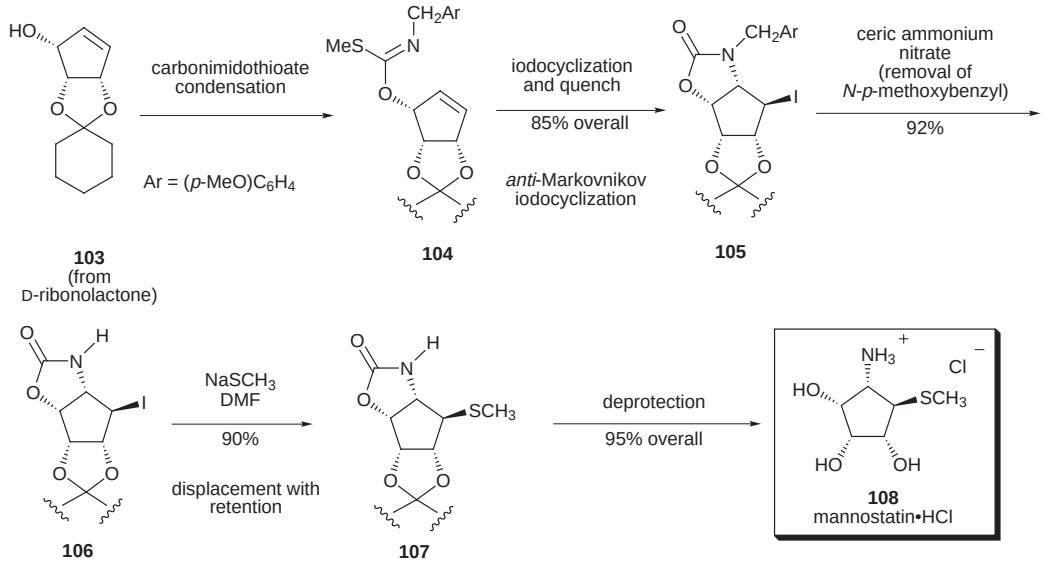
8 Synthesis of the mannosidase II inhibitor mannostatin A[35]

By the early 1990's, tether-based aminocyclitol synthesis had been brought to a point where the mere sighting of a *cis*,vicinal amino alcohol functional grouping reflexively triggered the author's urge to try another carbonimidothioate iodocyclization. Mannostatin (**5**) is a powerful and selective inhibitor of Golgi processing mannosidase II. Its *cis*, vicinal amino alcohol substituents at C-4,5 are flanked by a C-1 *trans*-methylthio group (see **108**, Scheme 17). The allylic alcohol precursor (**103**) was obvious, and, if fact, known in optically pure form. What wasn't known was an electropositive 'methylthio' electrophile that could initiate cyclization. Our experiments to develop such a reagent were unsuccessful, but Fuchs later found that $CH_3S–OSO_2CF_3$ functioned extremely well in this role.[36] Nevertheless, a carbonimidothioate iodocyclization was carried out to give the iodo oxazolidinone **105** in excellent overall yield, and the oxazolidinone nitrogen was oxidatively dealkylated as before.

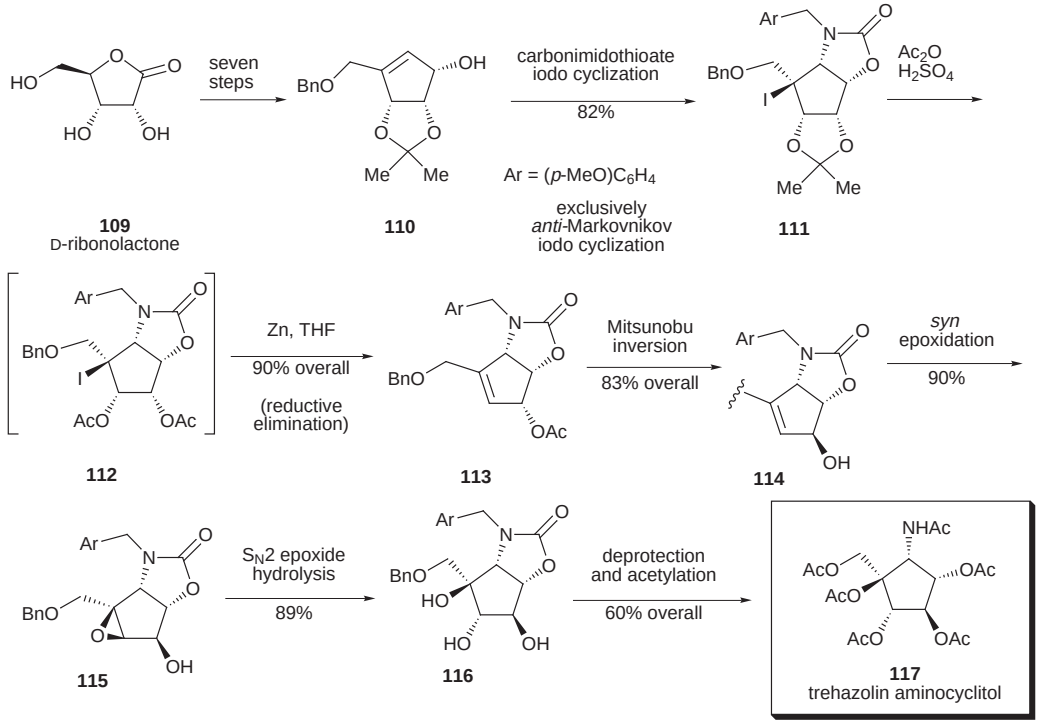
Replacement of iodo by methylthio with retention of configuration at C-1 was achieved under basic conditions (NaSMe in dimethylformamide solution). We had hoped, in another instance of faith, that the oxazolidinone nitrogen of **106** would participate in this displacement, so that the methylthiolate would then open an *N*-acylaziridine intermediate.[14,37] Whether or not this was actually the course of the mechanism, the *trans*-methylthio oxazolidinone **107** formed with apparently complete stereoselectivity, and was obtained in satisfying yield. Basic hydrolysis of the oxazolidinone followed by acidic removal of the cyclohexylidene ketal gave mannostatin A as its hydrochloride **108**.

9 Synthesis of the trehalase inhibitor trehazolin and a related glucosidase-inhibiting trehazoloid pseudo-disaccharide[38]

Was everything worth knowing known about carbonimidothioate iodocyclizations? Perhaps, but the structure of the



Scheme 17 Synthesis of mannostatin.

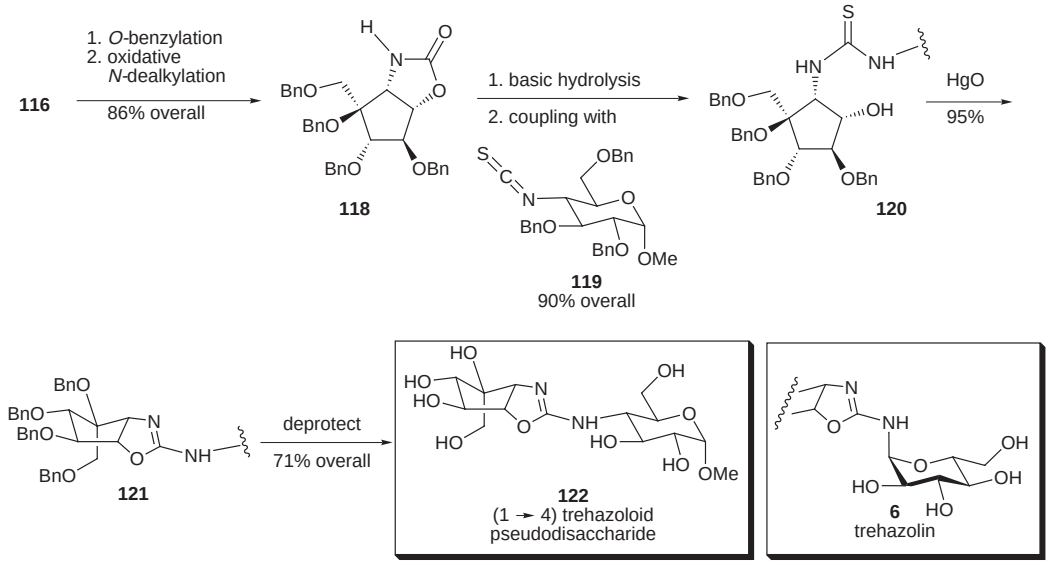


Scheme 18 Synthesis of the trehazolin aminocycitol.

trehazolin aminocyclitol (**117**, Scheme 18) was thought-provoking. Here, the *cis*,vicinal amino alcohol functional grouping is improperly oriented for a Markonikov iodocyclization onto a trisubstituted alkene, and anti-Markovnikov iodocyclizations were unknown, or at least very rare. And yet, the appropriate allylic alcohol precursor **110** was available in optically pure form by a short literature sequence. What did the anti-Markovnikov cyclization have going for it? Kinetic iodocyclizations of various types (iodolactonizations,[39] iodolactamizations,[40] *etc*.[3,4]) usually favor fused mode over bridged mode, and five-membered rings (5-*exo*) over six-membered rings (6-*endo*). Furthermore, heavily oxygenated ring systems, as we have seen, are not 'normal'. The two allylic heteroatom substituents distal to the cyclizing iminoether might be expected to modify the normal polarizability of the trisubstituted alkene such that development of partial positive change at that (distal) disubstituted alkene carbon is somewhat discouraged. Thus, it was another instance of faith, but not an instance of acting without guidance.

Iodocyclization of the carbonimidothioate derived from **110** gave the desired iodo oxazolidinone **111** resulting from anti-Markovnikov addition. Modification of the previous (Scheme 9) reductive vicinal elimination reaction entailed prior conversion of the acetonide to vicinal diacetate **112**, which was then reduced *in situ* with zinc metal to afford the unsaturated oxazolidinone **113**. Mitsunobu inverson and *syn*-epoxidation, directed by the nearby hydroxy, were followed by hydrolytic conversion to the *trans*,vicinal diol **116**, and then deprotection and acetylation gave the trehazolin aminocyclitol as its hexaacetate **117**.

The coupling of an appropriately protected form of the trehazolin aminocyclitol (**118**) with a 4-isothiocyanatoglucose derivative **119** to produce the (1→4)-trehazoloid pseudodisaccharide glucosidase inhibitor **122** is shown in Scheme 19. The oxazolidinone ring serves triple duty here in that it forms as the result of the iodocyclization, survives the installation and protection of the remaining hydroxys, and then falls away obligingly following N-dealkylation and basic hydrolysis.



Scheme 19 Synthesis of trehazoloids.

Condensation of the liberated amino with isothiocyanate **119** led to a thiourea, **120**, which was cyclized by treatment with freshly prepared, dry, yellow mercuric oxide to produce the *cis*-fused isourea **121**. (one is tempted to devise a direct cyclization route to this isourea!). Deprotection gave the (1→4)-trehazoloid pseudo-disaccharide glucosidase inhibitor **122**, which was of interest as an analogue of the naturally-occurring trehalase inhibitor trehazolin (**6**). Soon afterwards the natural product itself was also synthesized following a similar route employing the corresponding 1-isothiocyanatoglucose derivative.[41]

10 Summary and concluding remarks

Tethered nitrogen delivery is an effective strategy for natural products synthesis. In addition to the expected entropic advantage of using an intramolecular displacement, one gains excellent site- and stereoselectivity in the placement of the eventual amino group. Furthermore, the cyclization initially produces a *cis*,vicinal amino alcohol functional grouping wrapped in a heterocyclic cloak that can direct and facilitate subsequent transformations. The dependability of these transformations late in the route benefits both the planning and the completion of the synthesis. Exploring tethered nitrogen delivery has given the author and his coworkers opportunities to enjoy functionality-centered (not just skeleton-centered) and method-based (not just target-based) natural products synthesis. Samuel Smiles, the original self-help guru who advocated perseverance and courage as the route to success, would certainly have approved.

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