Synthesis of Complex Nucleoside Antibiotics

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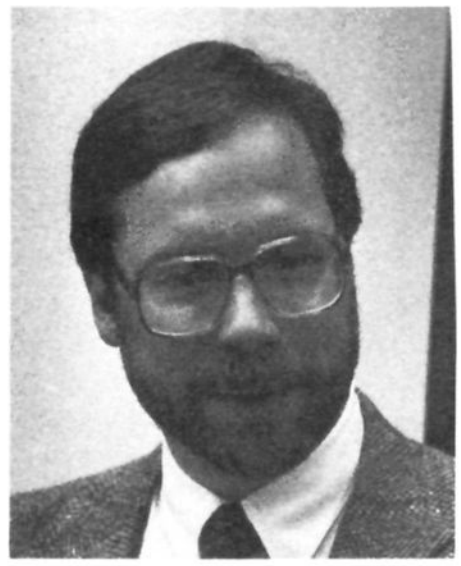
Received February 28, 1995 (Revised Manuscript Received April 24, 1995)

Contents



Spencer Knapp was born in Baytown, TX, raised in Tallmadge, OH, and received his B.A. degree in 1972 from Cornell University. After graduate studies at the University of California San Diego and Cornell University with Professor Jerrold Meinwald, and an NIH postdoctoral stint at Harvard University with Professor E. J. Corey, he joined the faculty at Rutgers University, where he is now Professor of Chemistry. His research interests have included the synthesis of natural products, enzyme inhibitors, and complex ligands, and the development of new synthetic methods.

I. Assessment of Current Status

A. Introduction and Coverage

Complex nucleoside antibiotics comprise an extensive array of natural products notable for combining the structural features of nucleosides, higher monosaccharides, disaccharides, peptides, and lipids. In some representatives there is unusual functionality that even goes beyond these contexts. The complex nucleoside antibiotics exhibit a variety of biological activities, including antifungal, anthelmintic, herbicidal, insecticidal, antiviral, and antitumor.

This review will discuss, with emphasis on the impressive accomplishments of the last several years (1988 to mid-1995), the strategies and tactics that have led to the synthesis of a growing collection of complex nucleoside antibiotics. The review by Garner[1] has detailed synthetic approaches to these compounds through 1987, and the 1988 and 1991 reviews by Isono[2,3] describe the structures, biological activities, and biosynthesis of nucleoside antibiotics including a number of simpler nucleoside and nucleotide analogues that will not be covered here. In 1991, Lerner[4] reviewed the synthesis and properties of various disaccharide nucleosides, including some with relatively simple pyranoside and furanoside components that likewise will not be covered in this review. Thus the emphasis here is on the most *complex* of the complex nucleoside antibiotics (presented in Charts 1 and 2), those whose synthesis challenges existing methods for carbohydrate and nucleoside chain elaboration, for glycosylation, and for functional group introduction, modification, protection, and deprotection.

B. Completed Syntheses 1973–1994

Chart 1 shows the structures of naturally-occurring complex nucleoside antibiotics whose syntheses have been completed at this writing. Interest in the synthesis of the complex nucleoside antibiotics originated in the early 1970s with the work of Moffatt[5] and Emoto,[6] who studied the synthesis of the polyoxins. Emoto's synthesis[7,8] of the dipeptidyl nucleoside antibiotic polyoxin J (**1**) in 1973 and Sorm's two syntheses of thuringiensin (**3**)[9–11] in 1976 can be seen in the context of Chart 1 as pioneering efforts—they predate by several years the next entry, Moffatt's 1982 sinefungin (**2**) synthesis.[12] The 1980s saw an intensification of effort that led to the synthesis of tunicamycin V (**4**),[13–17] octosyl acid A (**5**),[18–20] and nikkomycin B_x (**6**)[21,22] (as well as the aforementioned sinefungin **2**, the target of no less than four syntheses[23–25]). In the early 1990s nikkomycin B (**7**),[26] tunicamycin V (**4**, again),[27–29] polyoxin J (**1**, again),-30 hikizimycin (**8**),[31,32] and capuramycin (**9**),[33] succumbed to synthesis. Numerous other research groups also reported model studies and partial syntheses related to these targets. Facing this compilation, the reader must surely be impressed with the rich store of functionality and stereochemistry embodied in the nucleoside antibiotics, and with the

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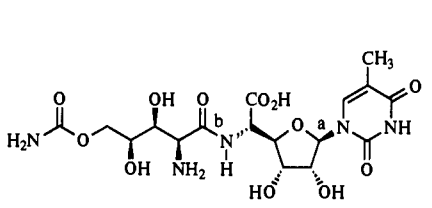
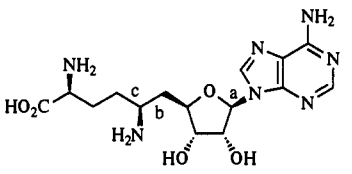
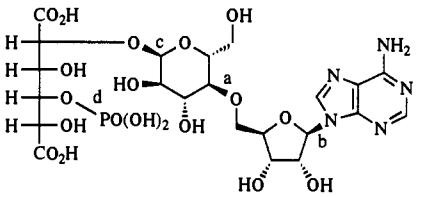
Chart 1. Complex Nucleoside Antibiotics—Completed Syntheses: Bonds Made



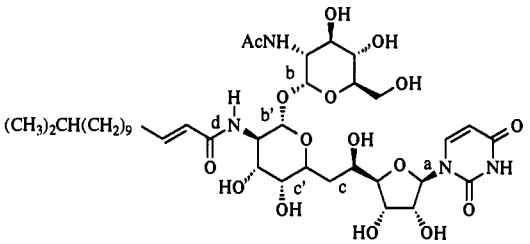
1
polyoxin J
Emoto, 1973: (a), b (ref. 6-8)
Ogawa, 1994: a, b (ref. 30)



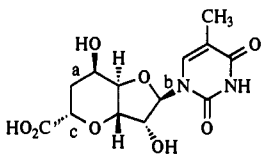
2
sinefungin
Moffatt, 1982: (a), b, c (ref. 12)
Fourey, 1983: (a), b, c (ref. 23)
Buchanan/Wightman, 1986: (a), b, c (ref. 24)
Rapoport, 1990: b, a (ref. 25)



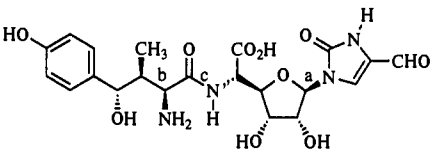
3
thuringiensin
Sorm, 1976: a, b, c, d (ref. 9-11)



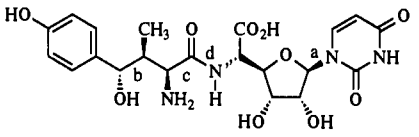
4
tunicamycin V
Suami, 1984: c,a, b', d (ref. 13-15)
Danishefsky, 1989: (a), c, c', (b'), (d) (ref. 16-17)
Myers, 1993: (a), b, c, d (ref. 27-29)



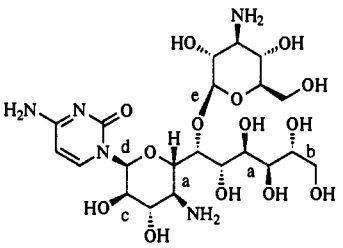
5
octosyl acid A
Danishefsky, 1986: a, b, c (ref. 18,19)
Hanessian, 1986: (b), a, c (ref. 20)



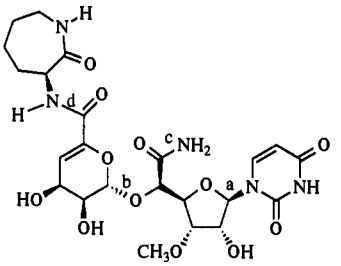
6
nikkomycin B_x
Konig, 1987: (a), b, c (ref. 21,22)



7
nikkomycin B
Barrett, 1990: (a), b, c, d (ref. 26)



8
hikizimycin
Schreiber, 1990: a, b, c, d, e (ref. 31-32)



9
capuramycin
Knapp, 1994: a, b, c, d (ref. 33)

power and sophistication of modern organic synthesis that brings these molecules within reach. The growth through the decades may not be as apparent, but should be made clear by this review—more recent syntheses are distinguished by the increasing complexity of the targets, the improvements in methods for controlling stereochemistry and for joining subunits, and the ever more skillful manipulation of multiple functional groups.

C. Notable Targets Approached but Not Yet Synthesized

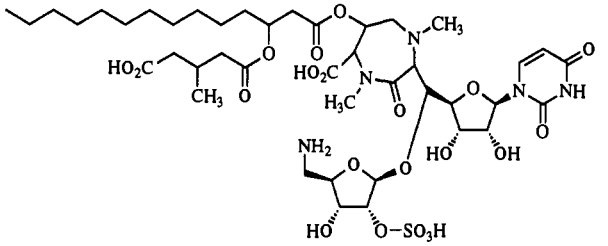
Chart 2 shows the structure of five complex nucleoside antibiotics that have been subjects for synthetic studies, but whose synthesis has not yet been accomplished. The ezomycins (e.g. **12**), in particular, have aroused intense and widespread synthetic efforts over the last 19 years,[34-48] but they present complexities that have thwarted all attempts thus far. Two antibiotics with unique but related higher monosaccharide components, miharamycin B (**13**) and amipurimycin (**14**), have been studied by Garner,[1,49-52] Casiraghi and Spanu,[53,54] Hara,[55] Sinay,[56] and Czernecki.[57] Gallagher,[58-61] Whiting,[62,63] and Vogel[64] have reported progress toward herbicidin (**11**). Liposidomycin C (**10**) contains several unassigned stereocenters, and thus synthetic studies[65-68] may well play a role in determining its structure. With its unusual sulfonated aminoribofuranoside, diazapanone peptidyl region, and attached lipid portion, liposidomycin C presents one of the most bizarre and synthetically challenging structures in this class. It is apparent that the synthesis of complex nucleoside antibiotics is an ongoing challenge that has been taken up by a growing group of investigators around the world.

II. Analysis of Synthetic Strategy

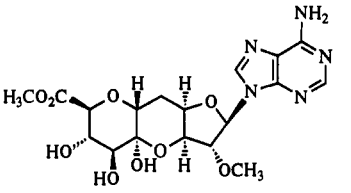
A. Convergence

Because the complex nucleoside antibiotics typically consist of easily-definable components, such as purine or pyrimidine, the higher monosaccharide, the peptidyl portion, and so forth, synthetic strategy is greatly simplified. One generally plans to (1) prepare the individual components in suitably protected form, (2) couple them with the required stereochemistry, and (3) deprotect and isolate the target compound. This simplification also means that the synthesis will be convergent to some degree, since steps involved in preparing one or more of the components will not be part of the longest linear sequence. Optimally, one might like to join two nearly equally complex and fully elaborated moieties as close to the end of the route as possible, but this has only occasionally been realized in practice.

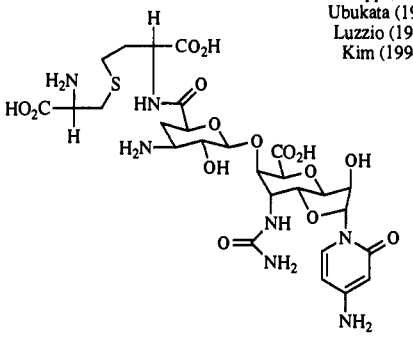
Chart 2. Notable Targets Approached but Not Yet Synthesized



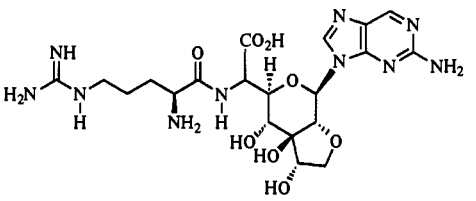
10
Ilposidomycin C
Knapp (1992)
Ubukata (1992)
Luzzio (1994)
Kim (1994)



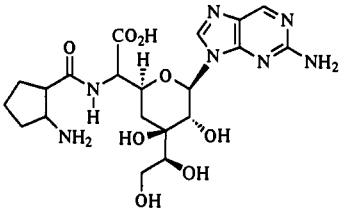
11
herbicidin
Gallagher (1993)
Vogel (1993)
Whiting (1993, 1995)



12
ezomycin A_1
Zamojski (1975)
Ogawa (1975)
Khorlin (1981)
Hanessian (1981, 1984)
Szarek (1981, 1982)
Suami (1986, 1987)
Schmidt (1990)
Knapp (1988, 1994)



13
mlharamycin B
Garner (1986, 1988, 1990, 1992)
Hara (1987)
Casiraghi/Spanu (1991)
Czernecki (1994)
Sinay (1995)



14
amipurimycin
Garner (1986, 1988, 1990, 1992)
Casiraghi/Spanu (1991)
Czernecki (1994)

The structures in Chart 1 have been marked with letters showing the key bonds formed in each successful synthesis; the order in which the bonds were formed is indicated under each structure. Bond letters in parentheses indicate that the bond was not actually formed in the synthesis, but rather was either present in the starting material, or in the case of tunicamycin V (**4**),[17] was formed in another synthesis that formally completed the route. It is obvious that, for the targets that have been the subject of two or more successful syntheses, the key bonds can be formed in different order. Some of the compounds, such as tunicamycin V (**4**), octosyl acid A (**5**), hikizimycin (**8**), and perhaps sinefungin (**2**), do not break down into two obvious components of equal complexity. The polyoxins (**1**) and nikkomycins (**6**, **7**) do, however, and all of the syntheses of these compounds take advantage by forming the centrally-located peptide bond late in the route.

An important point emerges particularly from our own synthesis of capuramycin (**9**),[33] the synthesis of tunicamycin V (**4**) by Myers,[30] and Sorm's synthesis of thuringiensin (**3**):[11] the simplification of synthetic strategy due to the joined-component nature of the complex nucleoside antibiotics is also a severe restriction that may not be obvious to those who have not tried to assemble such components. This is simply because there is no way around the formation of these key bonds—and they can be very difficult to form. In these cases the strategy plays a secondary role to the tactics required for the joining steps, or, put another way, the strategy had better allow for some flexibility in the method and timing of the couplings, because some of these will fail or give poor yields.

For example, capuramycin (**9**) contains three obvious bonds where components can (or perhaps must) be assembled: the *N*-glycosylation bond *a*, and *O*-glycosylation bond *b*, and the peptide bond *d*. Interestingly, the timing of formation of the amide bond *c* and the C=C bond of the mannuronamide portion also turned out to be critical. At first glance, the centrally-located bond *b* (representing an *O*-glycosylation) would appear to be the bond that ought to be formed latest in the route so that two approximately equally complex pieces could be joined. However, Lewis basic amide groups are frequently deleterious to glycosylations, so we planned to form bonds *c* and *d* after the *O*-glycosylation. The successful Myers route to tunicamycin V (**4**)[28-29] likewise delays formation of both amides (at N-10′ and N-2″) until after the *O*-glycosylation, whereas a glycosylation with an acetamido-containing component failed. Suami's tunicamycin glycosylation[14,15] did involve a 2-acetamidoglycosyl acceptor, but the yield of the desired coupled product was only 18%. The capuramycin route was further distorted from convergence when reaction failures made it clear that the oxidation at C-6′ and elimination at C-4″ would also have to be delayed until after the *O*-glycosylation. Thus, a coupling step that perhaps should have been penultimate was placed instead, and by necessity, eight steps from the end.

Another example of a Hobson's choice in synthesis arose during Myers's tunicamycin studies.[27-29] There is no obvious dissection into two equally complex portions, but the route efficiently joined four components at bonds *b*, *c*, and *d*, in that order (bond *a* was purchased as uridine). Given Myers's wonderfully stereoselective intramolecular radical coupling method for formation of bond *c* (section III.E.1), as demonstrated in his earlier synthesis of tunicaminyluracil,[27] one might imagine the synthesis of tunicamycin V (**4**) to involve just further attachment of the 2-acetamido-2-deoxy-α-D-glucopyranosyl unit by glycosylation at O-11′, and then amide formation at C-10′. However, even apart from the formidable protecting group logistics, this is a plan loaded with difficulties. Earlier work on tunicamycin by Suami[13-15] and Danishefsky,[16,17] and studies on simpler systems,[29] had shown that yields and stereoselectivity are low for this type of glycosylation, which must involve making either the [donor-α → acceptor-β], or the [donor-β → acceptor-α], trehalose linkage (bonds *b* and *b′*, respectively). The prospect of placing the further demand on this step that it must use a complex nucleoside component, with its Lewis basic uracil ring, as either the donor or acceptor apparently convinced Myers to form the trehalose linkage early in the route, and attach the uridine portion (via bond *c*) later. Furthermore, only bond *b* could be formed efficiently; attempts to make bond *b′* by a glycosylation with a 2-acetamido-2-deoxy-α-D-glucopyranose acceptor were disappointing. Here again, the tactics required for a key coupling step dictated the order of assembly, and the synthesis was completed only after exhausting several other seemingly plausible approaches to the joining of components.

For the synthesis of thuringiensin (**3**),[9-11] Sorm considered the 24 ways in which to order the formation of bonds *a*–*d*. Preliminary experiments showed, however, that the central ether bond *a* had to be made first, with some sacrifice in convergency, and the phosphorylation (bond *d*) had to be done last. This left only two possibilities, and one of them (*a*, *c*, *b*, *d*) "could not be realised to a full extent".[11] Thus the required order became ether formation, *O*-glycosylation, *N*-glycosylation with the entire sugar portion, and finally phophorylation.

B. Early vs Late *N*-Glycosylation

For those complex nucleoside antibiotics that contain an *O*-glycosyl linkage in addition to the nucleoside (*N*-glycosyl) linkage, the strategic question naturally arises as to which bond should be formed first. This question has been answered in the syntheses of thuringiensin (**3**), tunicamycin (**4**), hikizimycin (**8**), and capuramycin (**9**), and must yet be addressed if routes to ezomycin A_1 (**12**) and liposidomycin C (**10**) are to be successful. A related question for complex nucleoside antibiotics that contain key peptide-type linkages [polyoxin J (**1**), tunicamycin (**4**), capuramycin (**9**), and the nikkomycins (**6** and **7**)] is whether *N*-glycosylation should precede peptide bond formation, and the answer seems to be that it should. As discussed above, this is a combination of the desire for convergency and a recognition of the fact that Lewis basic amide bonds can interfere with, although not necessarily always doom, glycosylations.

Concerning *O*- vs *N*-glycosylation, Chart 1 shows that in the relevant syntheses the nucleoside is either assembled last [one case, thuringiensin (**3**)], first [hikizimycin (**8**), tunicamycin (**4**), and capuramycin (**9**)], or separately (Myers's tunicamycin work). The tactics involved in these glycosylations are discussed in section III, but as far as strategy is concerned, it is probably wrong to conclude that *N*-glycosylation should precede *O*-glycosylation. Firstly, nucleoside *O*-glycosylation is far from trivial, as it typically requires that the glycosyl donor find an acceptor hydroxyl in the presence of a pyrimidine or acylated purine ring. Both of these contain Lewis basic amide carbonyls, and thus can potentially interfere with the desired reaction. Usually an excess of the glycosyl donor is required. Secondly, there are now plenty of examples of *N*-glycosylation with a disaccharide donor or with a higher sugar donor, although these situations require greater than usual attention to the protecting groups and to donor stability under Lewis acid or Bronsted acid conditions. Thirdly, the design of syntheses of complex nucleoside antibiotics needs to be as flexible as possible, and having the option to form the *O*-glycosyl and *N*-glycosyl bonds in either order could be advantageous in cases where one order of coupling steps fails.

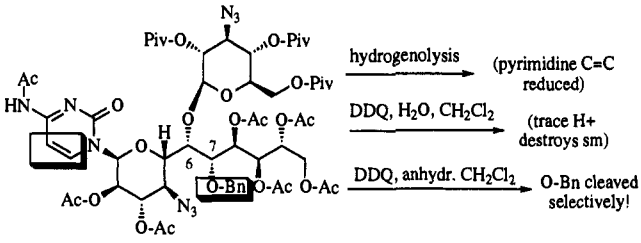
III. Analysis of Tactics

A. Final Deprotection

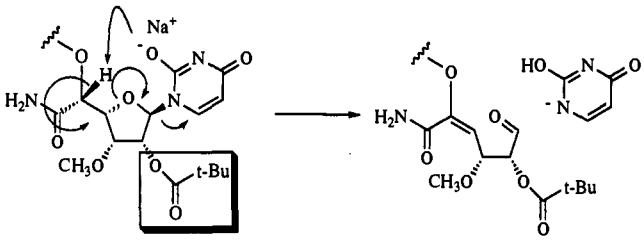
Part of any strategy for the synthesis of a complex nucleoside antibiotic is the use of protecting groups. Their role is unusually critical in this context because they serve a dual purpose: they must facilitate the synthesis of their own particular component (the higher sugar, the peptidyl portion, the nucleoside, etc.), and also they must direct the site and stereochemistry of the joining steps. Obviously it is advantageous to use the same protecting group for both purposes at each site where a functionality must be protected or stored as a precursor, rather than changing protecting groups along the way. For efficiency, the same, or same kind of, protecting group should be used at more than one site, so that the number of deprotection steps can be minimized. For someone planning the synthesis of a complex nucleoside antibiotic, there is perhaps no better place to look for advice on the choice of protecting groups than the final deprotection steps in the successful syntheses. Despite the structural differences in the targets, protecting groups themes (and other tactics as well) are recognizable throughout.

Chart 3 shows the final deprotection steps and isolation procedures from the syntheses of the targets in Chart 1. The pattern that emerges is one of conservative simplicity: there few exotic hydroxyl protecting groups, and *O*-acetyls, *O*-benzyls and acetonides predominate. The nitrogen protecting or precursor groups (*N*-Cbz, *N*-BOC, $-N_3$, $-NO_2$) are also fairly standard. It is apparent in some cases that protecting groups that have been successful for earlier syntheses, such as the sinefungin (entries 10–12) and tunicamycin (entries 7, 8) acetonides and the polyoxin J (entry 14) *O*-benzyls and *N*-Cbz, are adopted for later ones. On the other hand we have

Scheme 1. Debenzylation in the Hikizimycin Synthesis



Scheme 2. Base-Promoted Destruction of Capuramycin



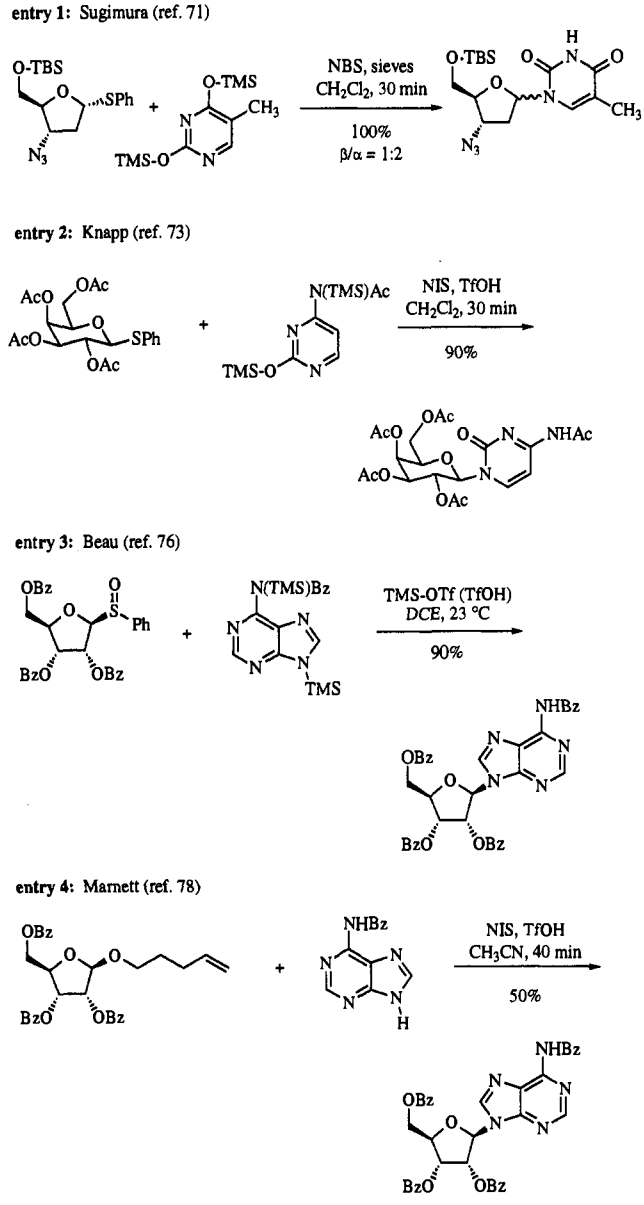
the contrapuntal Rapoport route to sinefungin (entry 13), which deviates from the three previous syntheses with respect to each of the five protecting/precursor groups. The Myers tunicamycin route (entry 7) keeps some but modifies several (*O*-TBS, *O*-BOM, *N*-3-BOC) of the original Suami protecting groups (entry 8).

A possible explanation for the conservative approach to protecting group chemistry in the synthesis of complex nucleoside antibiotics is that the researchers' interests may lie elsewhere—in the synthesis of the unusual components, in the C–C bond-forming steps, in the glycosylations. There is also the natural inclination to want to avoid surprises at the end of a long synthetic route, and the difficulty of optimizing the final steps when only limited amounts of material (natural *or* synthetic) are available. The less-than-quantitative deprotection and isolation sequences shown in Chart 3, however, illustrate that there is considerable room for improvement in this aspect of synthetic chemistry.

The final deprotections shown in Chart 3 do hold a surprise or two. In Ikemoto and Schreiber's synthesis of hikizimycin,[30,31] hydrogenolytic removal of the O-7′ benzyl (in box, Scheme 1) was complicated by competing reduction of the cytosine ring (in box). An oxidative method (DDQ, CH_2Cl_2, H_2O) that had proven successful on the neighboring O-6′ benzyl earlier in the synthesis was tried, but this cleavage was slower, and acidic products of DDQ hydrolysis apparently decomposed the starting material. A clean debenzylation was achieved, however, by omitting the water and conducting the reaction with DDQ in dry dichloromethane at 58 °C for 2 days. The 10 electron-withdrawing acyl groups probably protect against oxidation at the anomeric centers and elsewhere in the substrate.

In our synthesis of capuramycin,[33] the last step, a planned base-promoted hydrolysis of two acetates and a pivaloate, met with unexpected difficulties (Scheme 2). Hydrolysis of the acetates occurred readily, but the pivaloate (in box) hydrolyzed slowly, and over time the nucleoside was destroyed completely. We found that dilute methanolic sodium hydroxide converted most of the pivaloate to capuramycin if the reaction was stopped promptly at 2.5 h. The partially deacylated product could then be recovered by chromatography and resubjected to the reaction conditions to provide additional capuramycin (total 60%). What is the source of the base sensitivity of capuramycin when virtually every other complex nucleoside antibiotic is base stable? One possibility, as yet untested, is suggested in Scheme 2. Fragmentation of the nucleoside could occur if base removes the proton at C-5′, perhaps with assistance by the nearby deprotonated cytosine. If operative, this mechanism indicates that *concentrated* hydroxide at lower temperature should be more selective at pivaloate cleavage, as the fragmentation side reaction should not depend on base concentration.

Scheme 3. *N*-Glycosylations with Thioglycoside Donors

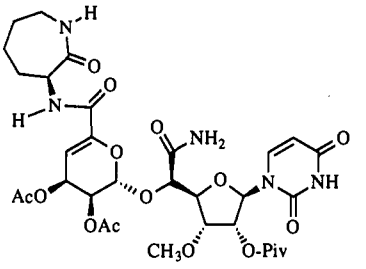


B. *N*-Glycosylation (Nucleoside Formation)

Progress in the synthesis of complex nucleoside antibiotics has paralleled improvements in methods

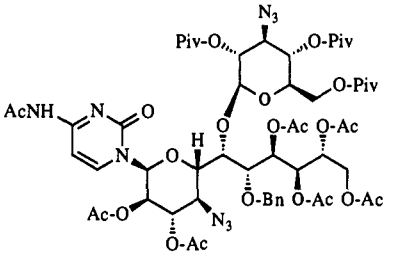
Chart 3. Final Steps and Deprotections

entry 1: capuramycin (**9**, ref. 33)



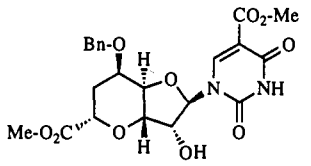
1. NaOH, aq MeOH, 2.5 h (cleaves O-Ac's and O-Piv)
2. aq NaOH, MeOH, 3 h (resubject to finish O-Piv)
3. aq $KHSO_4$ to pH 6
4. chrom., SiO_2, 5:1 $CHCl_3$/MeOH (60% overall yield)

entry 2: hikizimycin (**8**, ref. 31-32)



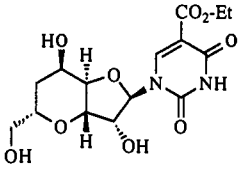
1. DDQ, CH_2Cl_2, 58 °C, 43 h (cleaves O-Bn)
2. chrom., SiO_2, prep tlc, 17:3 EtOAc/hexane (52% yield + 17% sm)
3. n-Bu_4NOH, MeOH, reflux, 2 h (cleaves 10 acyls)
4. ion-exchange, weak H+ (100% yield)
5. H_2, Lindlar, H_2O (reduces 2 azides, 100% yield)

entry 3: octosyl acid A (**5**, ref. 18,19)



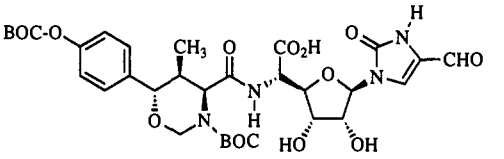
1. H_2, $Pd(OH)_2$, THF (cleaves O-Bn)
2. chrom., SiO_2, 1:9 MeOH, $CHCl_3$ (80% yield)
3. LiOH, aq THF, 2 h (cleaves esters)
4. Dowex IR-40 (H+ resin) (78% yield)

entry 4: octosyl acid A (**5**, ref. 20)



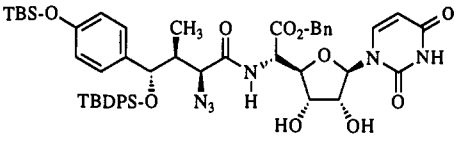
1. O_2, Pt, aq $NaHCO_3$, 90 °C (oxidizes C-8')
2. H+ to protonate, EtOH
3. Dowex-50 (H+) (70% overall yield)

entry 5: nikkomycin B_x (**6**, ref. 21,22)



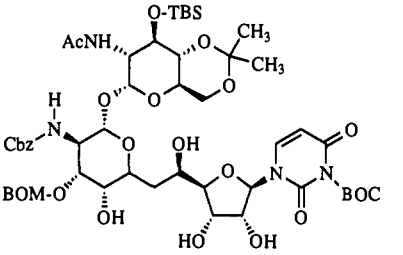
1. TFA, 0 °C, 15 min (cleaves O- and N-BOC)
2. H_2O, then lyophilize (cleaves acetal)
3. chrom., Sephadex G-10, H_2O
4. lyophilize (61% overall yield)

entry 6: nikkomycin B (**6**, ref.26)



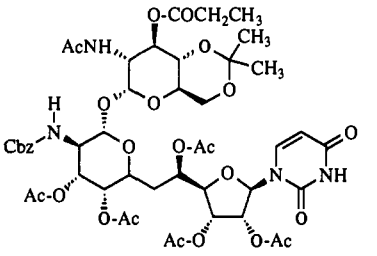
1. n-Bu_4NF, THF, 30 min (cleaves 2 O-SiR_3)
2. H_2, 10% Pd-$BaSO_4$, aq MeOH, 30 min (cleaves benzyl ester and reduces -N_3, 39% overall yield)

entry 7: tunicamycin V (**4**, ref. 28,29)



1. 10% HCO_2H, Pd, 1.5 h (cleaves O-BOM, N-Cbz)
2. 13% HCO_2H, MeOH, 40 °C, 5 h (cleaves N-BOC, acetonide)
3. HF, MeOH, CH_3CN (cleaves O-TBS)
4. $(CH_3)_2CH(CH_2)_9CH{=}CHCO_2H$, DCC, CH_2Cl_2 (forms amide)
5. chrom., reverse phase, 1:1:1 MeOH/pyridine/H_2O (83% overall yield)

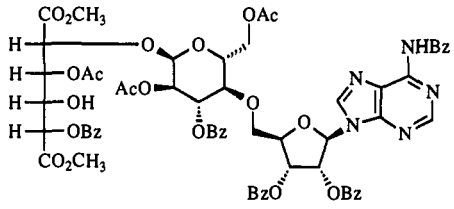
entry 8: tunicamycin V (**4**, ref. 14,15)



1. 0.1 M NaOMe, MeOH, 2 h (cleaves 6 O-acyl groups)
2. chrom., SiO_2, 5:1 $CHCl_3$/MeOH (83% yield)
3. H_2, Pd, MeOH, 1.5 h (cleaves N-Cbz)
4. $(CH_3)_2CH(CH_2)_9CH{=}CHCO_2H$, DCC, CH_2Cl_2 (forms amide)
5. chrom., SiO_2, 5:1 $CHCl_3$/MeOH (45% overall yield)
6. 70% aq HOAc, 40 °C, 20 min (cleaves acetonide, 100% yield)

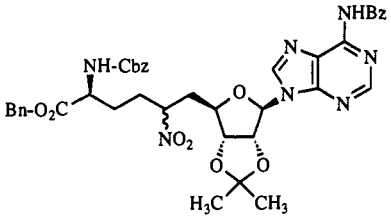
Chart 3. Continued

entry 9: thuringiensin (**3**, ref. 10,11)



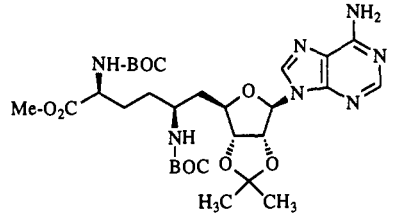
1. $POCl_3$, pyridine, benzene, 100 min (phosphorylates O-3‴)
2. NaOMe, MeOH, H_2O, dioxane, 22 h (cleaves 8 acyls and 2 esters)
3. Dowex 50 (pyridine form)
4. chrom., paper Whatman No. 3 MM, 55:10:35 n-PrOH/NH_4OH/H_2O (42% overall yield)

entry 10: sinefungin (**2**, ref. 12)



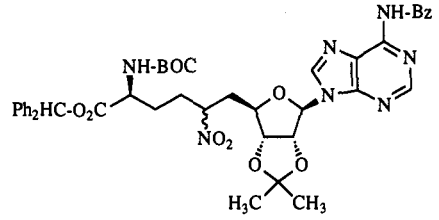
1. 90% TFA, 20 min (cleaves acetonide)
2. chrom., SiO_2, 19:1 CH_2Cl_2, MeOH (100% yield)
3. H_2 (50 psi), Pd-C, MeOH, 20 h (cleaves O-Bn, N-Cbz)
4. H_2, PtO_2, as above (reduces -NO_2)
5. reverse phase HPLC, H_2O, CH_3CN, NH_4OAc
6. NH_4OH, MeOH, 18 h (cleaves N-Bz)
7. reverse phase HPLC as above
8. lyophilize (22% overall yield as N-6′ mix)

entry 11: sinefungin (**2**, ref. 23)



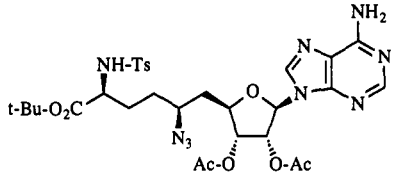
1. K_2CO_3, aq MeOH (cleaves methyl ester)
2. TFA, 0 °C, 1 min (cleaves 2 N-BOC)
3. 80% aq HCO_2H, overnight (cleaves acetonide)

entry 12: sinefungin (**2**, ref. 24)



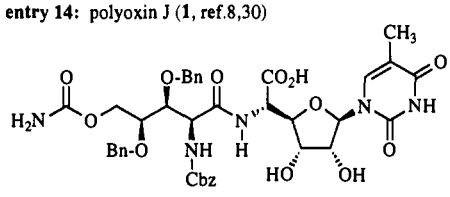
1. $ZnBr_2$, MeOH, 20 h (cleaves N-Bz)
2. chrom., SiO_2, 98:2 CH_2Cl_2/MeOH (88% yield)
3. 80% aq TFA, 45 min 84% (cleaves acetonide, N-BOC, O-$CHPh_2$)
4. T-4 RaNi, MeOH, NH_4+HCO_2-, 18 h (reduces -NO_2)
5. chrom., Dowex 50 (H+) (43% yield)

entry 13: sinefungin (**2**, ref. 25)



1. K_2CO_3, MeOH, 30 min (cleaves 2 O-Ac)
2. HOAc, 45 min
3. chrom., SiO_2, 95:5 EtOAc, MeOH (88% overall yield)
4. H_2 (60 psi), $Pd(OH)_2$, MeOH, 44 h (reduces -N_3, 91% yield)
5. 90% TFA, 1 h (cleaves O-tBu)
6. Na, NH_3, -78 °C, 1.5 min (cleaves N-Ts)
7. NH_4Cl quench
8. chrom., Dowex 50W-X8 (H+), aq NH_4OH
9. reverse phase HPLC, H_2O, CH_3CN, NH_4OAc
10. lyophilize (49% overall yield, steps 5-10)

entry 14: polyoxin J (**1**, ref.8,30)



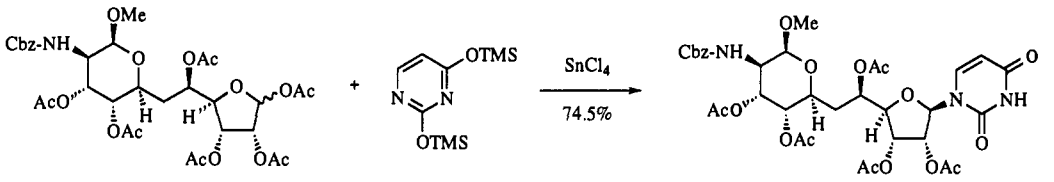
1. H_2, Pd-C, aq MeOH (cleaves 2 O-Bn + N-Cbz)
2. chrom., avicel, n-BuOH/HOAc/H_2O
3. adsorb on carbon, H_2O/acetone

for *N*-glycosylation of purines and pyrimidines, and for good reason: unless one starts with a commercially available nucleoside, this reaction is the *sine qua non* of nucleoside synthesis. The classic Hilbert–Johnson synthesis, involving an *O*-alkylated pyrimidine acceptor and an glycosyl halide donor, was used throughout the 1960s and 1970s to prepare simple nucleosides.[4] However, it was really Vorbruggen's use of silylated pyrimidines and acylated purines as acceptors, glycosyl acetates as donors, and stannic chloride or TMS-OTf as promoter[69] that stimulated the widespread incorporation of *N*-glycosylation into long synthetic routes. The first synthesis in Chart 1 to feature a pyrimidine *N*-glycosylation is the 1983 Suami synthesis of tunicamycin,[13–15] which also, not coincidentally, makes use of a Vorbruggen modification. Vorbruggen-type couplings have also been used to advantage in the Danishefsky syntheses of octosyl acid A[18,19] and tunicaminyluracil,[16–17] the Rapaport sinefungin synthesis,[25] and the Schreiber route to hikizimycin.[31–32]

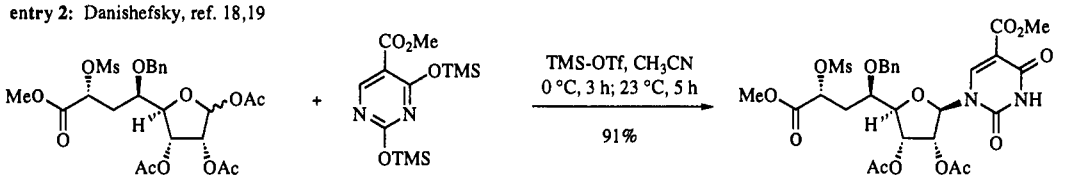
The 1990s have seen further development in methods for *N*-glycosylation that borrow from the progress made in *O*-glycosylation,[70] particularly with regard to new glycosyl donors and promoters (Scheme 3). Thus, Sugimura reported[71] that phenyl 1-thiopentofuranosides could be activated for reaction with silylated thymine by using *N*-bromosuccinimide as the promotor, a reaction developed by Lemieux, Nicolaou, and others[70] for the synthesis of disaccharides (Scheme 3, entry 1). Much earlier, Hanessian had used a bromine/thioglycoside coupling to attach the adenine unit of "quantamycin", a designed lincomycin-complex nucleoside hybrid.[42] Young has also activated a thioglycoside, for 2′-deoxynucleoside synthesis.[72] Noting the desirability of a site-selective low-temperature *N*-glycosylation method for the synthesis of complex nucleoside antibiotics, we showed[73]

Chart 4. Preparation of Nucleosides from Higher Carbohydrate Donors

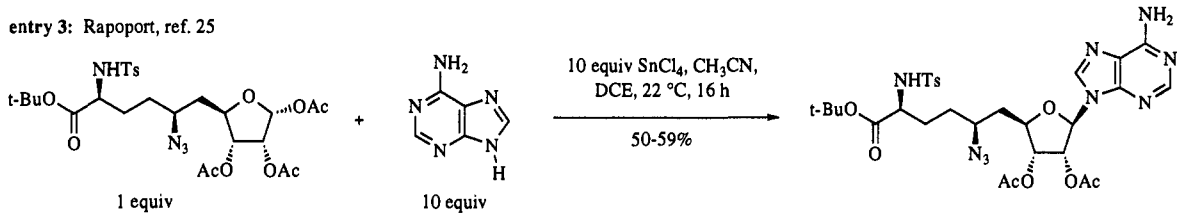
entry 1: Suami, ref. 13,15



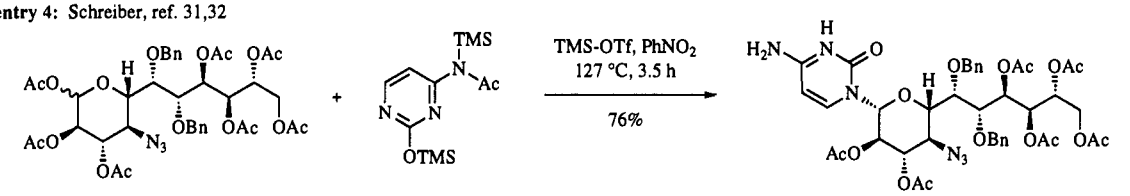
entry 2: Danishefsky, ref. 18,19



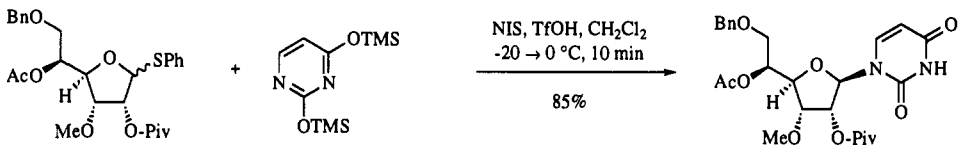
entry 3: Rapoport, ref. 25



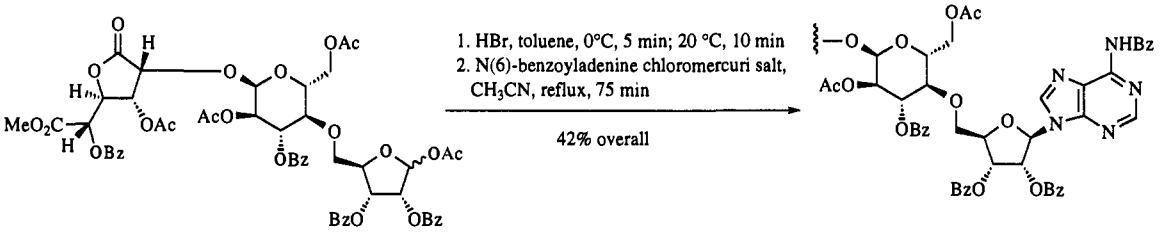
entry 4: Schreiber, ref. 31,32



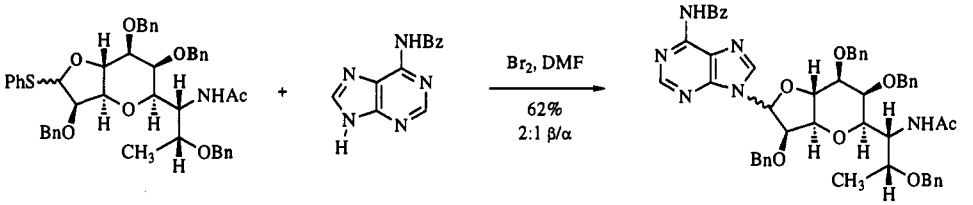
entry 5: Knapp, ref. 33



entry 6: Sorm, ref. 10



entry 7: Hanessian, ref. 42



entry 8: Suami, ref. 39

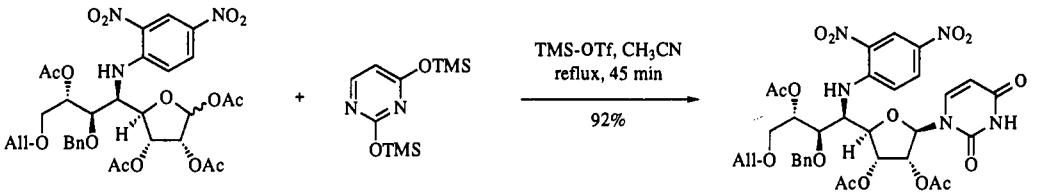
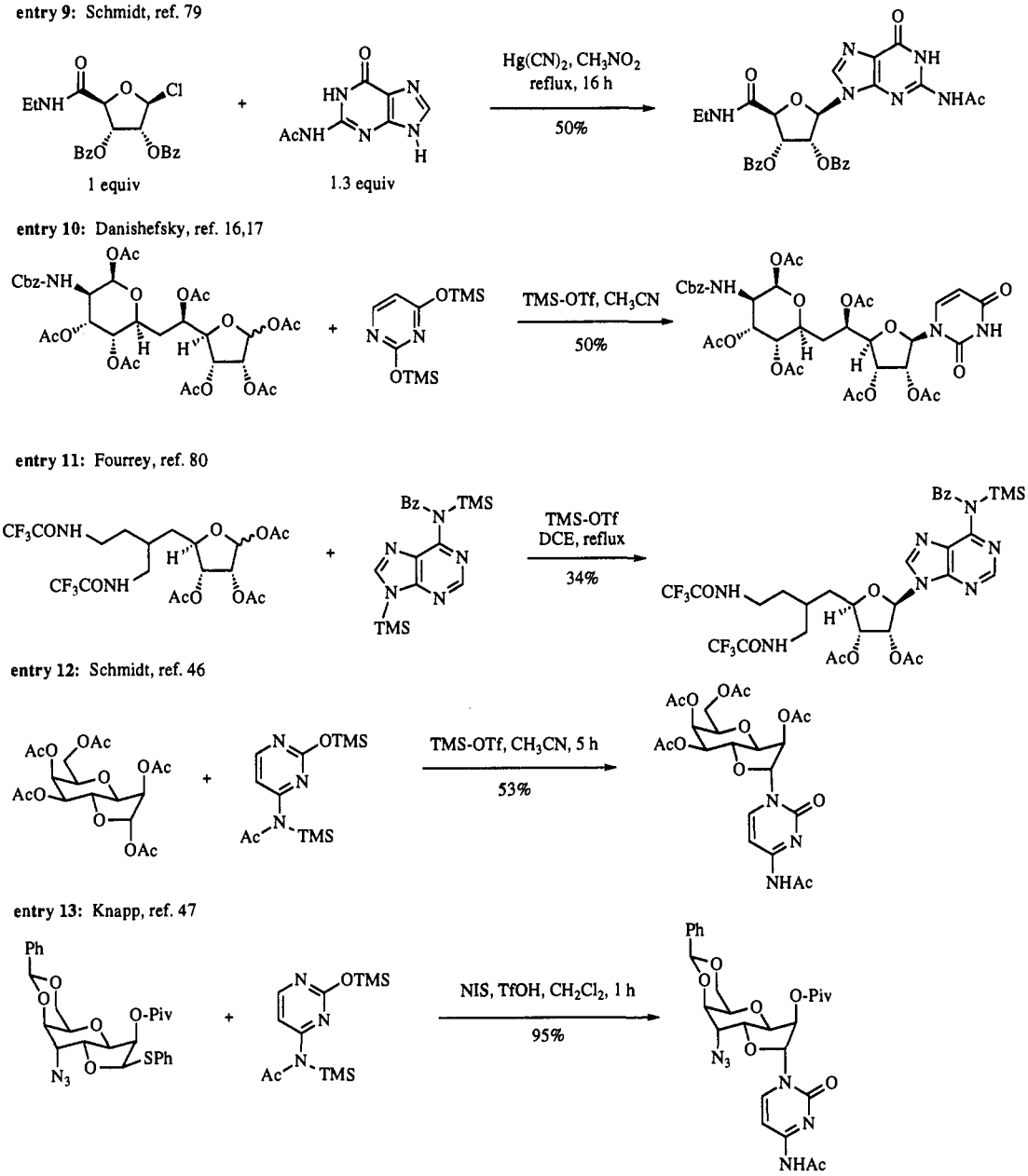


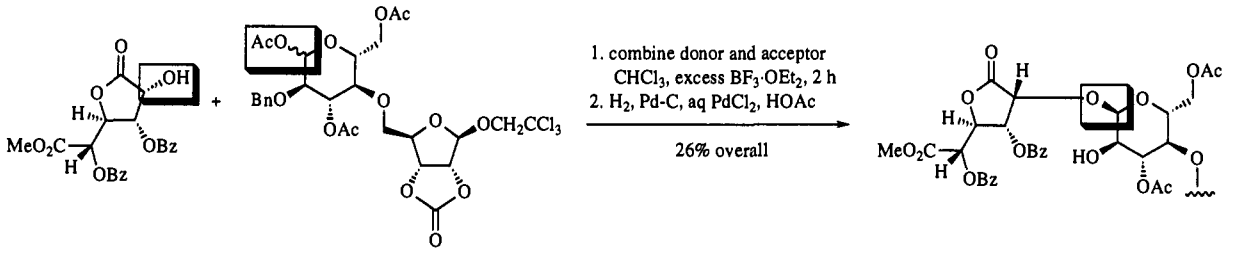
Chart 4. Continued



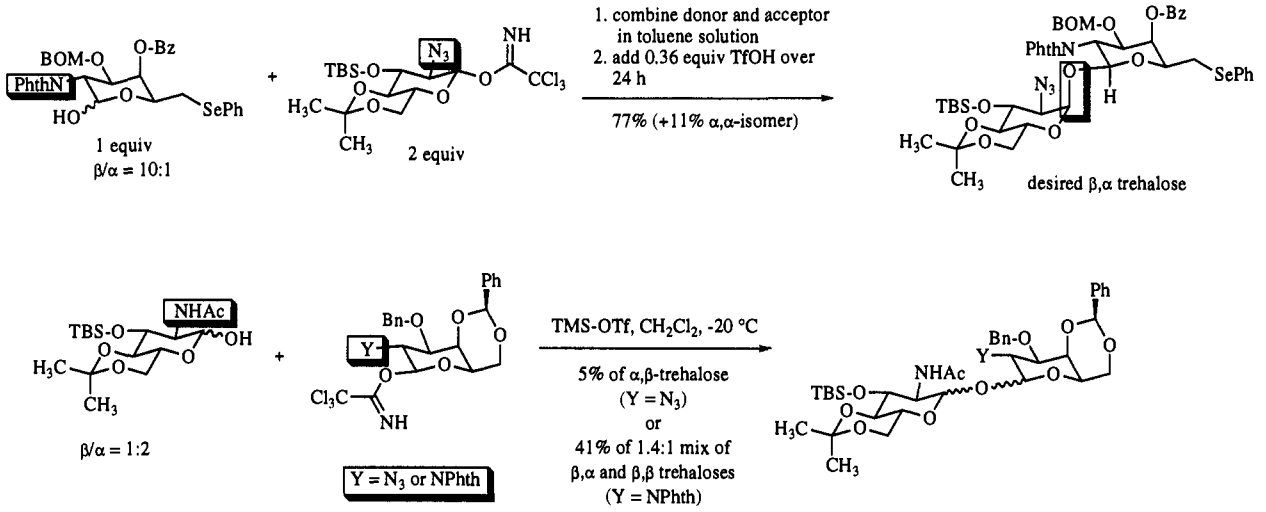
that the van Boom conditions[74] (*N*-iodosuccinimide, triflic acid) applied to nucleoside synthesis allowed the efficient conversion of (alkyl or aryl) 1-thiopyranosides and 1-thiofuranosides to various pyrimidine and purine nucleosides (Scheme 3, entry 2). This reaction was later used as a key step in our capuramycin synthesis,[33] and Garner has used it for selective N-7 purine glycosylation.[52] Beau showed in 1992 that phenyl 1-deoxy-1-thio-2,3,5-tri-*O*-benzoyl-D-ribofuranoside *S*-oxide reacted with silylated nucleobases in the presence of trimethylsilyl trifluoromethanesulfonate (an adaptation of the Kahne glycosylation[75]) to give the nucleosides in good yields, and used the reaction to prepare (1′-^{13}C) labeled 2′-deoxynucleoside building blocks (Scheme 3, entry 3).[76] More recently, Marnett has used pentenyl glycosides (originally developed by Fraser Reid[77]) as precursors to purine nucleosides (Scheme 3, entry 4).[78]

N-Glycosylation with "higher" carbohydrate donors, that is, chain-extended or otherwise elaborated pyranosyl and furanosyl substrates, is obviously an important aspect of complex nucleoside antibiotics synthesis. Chart 4 shows examples of such transformations drawn mostly from this context: the first six reactions are taken from completed syntheses represented in Chart 1, while most of the others are from studies of the synthesis of the nucleoside components of complex nucleoside antibiotics. An interesting feature of this collection of results is how efficient the nucleoside *N*-glycosylation reaction has become. Despite the complexity and variety of carbohydrate donors represented here, the *N*-glycosylation reaction is usually not one of the lowest yielding or "bottleneck" steps. It might even be argued (after viewing sections C and D) that *N*-glycosylations are typically the *most* efficient of the component-joining steps. This is not to say the reactions are easy; indeed, the entries in Chart 4 represent considerable optimization of reaction conditions. Several published approaches to complex nucleoside antibiotics (section III.E.2) stop short of the key *N*-glycosylation step, probably because exten-

Scheme 4. Thuringiensin *O*-Glycosylation



Scheme 5. Tunicamycin *O*-Glycosylations



sion experimentation with protecting groups and activation methods, as well as sufficient quantities of donor, are still required. What can be said is that there are many successful examples, the reaction is relatively well understood, and that a synthesis can be planned with *N*-glycosylation as a late step.

C. *O*-Glycosylation (Disaccharide Formation)

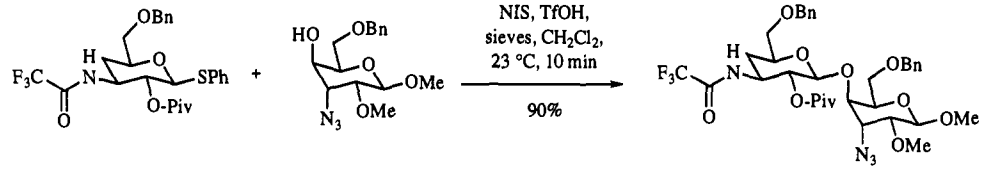
1. O-Glycosylation of Sugars

The considerable progress made in oligosaccharide synthesis in recent years has been reviewed.[70] Of particular importance to the synthesis of complex nucleoside antibiotics are the improvements in activatable anomeric groups, such as trichloroacetimidato, phenylthio, and phenylsulfenyl, and the development of selective and mild methods for their activation. This is because the functionality in these targets can be diverse and (Lewis and Brønsted) acid sensitive, and because the linkages themselves can be unusual and quite challenging.

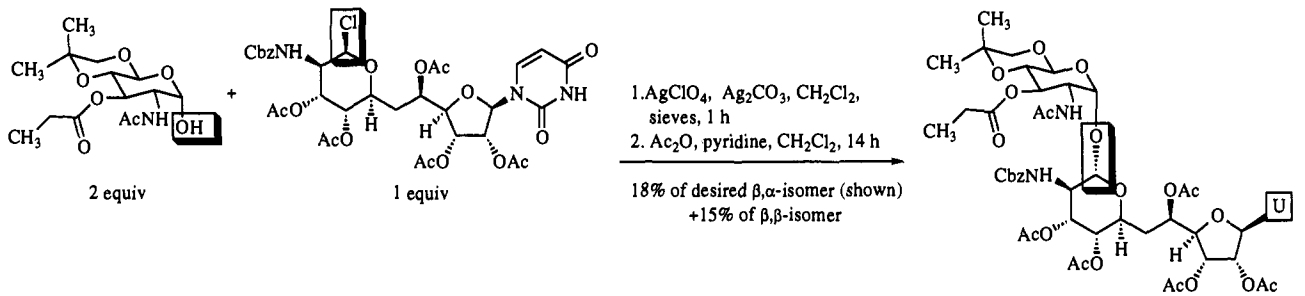
Among the syntheses of complex nucleoside antibiotics that contain an *O*-glycoside linkage in addition to the *N*-glycosyl bond, the disaccharide is assembled first or separately in two: Sorm's thuringiensin work,[10,11] and Myers's tunicamycin synthesis.[28,29] Each features an *O*-glycosylation that is instructive even in the absence of the nucleoside heterocycle. In his first thuringiensin route[10] (Scheme 4), Sorm constructed the glycosidic linkage by using an anomeric acetate as the glycosyl donor, a hydroxyl lactone derived from allose as the acceptor, and boron trifluoride etherate as the promoter (stannic chloride was ineffective). The neighboring O-2′ benzyloxy substituent in the donor allowed formation of the α-anomer as the major coupled product, which was then debenzylated as shown to facilitate its isolation. In retrospect, the low yield might be attributed to the complexation of boron trifluoride with the acceptor, which would reduce the reactivity of the latter. A modified version of the glycosylation (with O-2 and O-3 benzoyls and O-3″ benzyl) was used in the second route,[11] but this was less successful (13%).

Myers faced the difficult task of assembling the tunicamycin trehalose linkage with stereocontrol at both anomeric carbons[28,29] (Scheme 5). For the donor, a 2-azido-2-deoxy-α-D-glucopyranose was prepared, and converted to the Schmidt trichloroacetimidate derivative. The azido group was chosen as the acetamido precursor at C-2″ (tunicamycin numbering) because it is a nonparticipating group likely to favor the desired α-anomer at the adjacent anomeric center C-1″. The acceptor was a D-galactopyranose derivative with phthalimido at C-10′ and a free hydroxyl at C-11′. The anomeric configuration of the acceptor was 11:1 with the β (equatorial) anomer predominating, perhaps as a result of an unfavorable steric interaction between the phthalimido carbonyl and the axial hydroxyl. Triflic acid was found to be the best promoter (trimethylsilyl trifluoromethanesulfonate and boron trifluoride were also tried), and the glycosylation proceeded at −20 °C to give the tunicamycin disaccharide as the major product, with only a small amount of the α,α-disaccharide formed as the result of glycosylation of the minor anomer of the acceptor. Myers also tried an alternative approach to formation of the trehalose linkage that used a 2″-acetamido-2″-deoxyglucopyranose as the acceptor and a donor based on either 10″-azido or 10″-phthalimido galactopyranose derivative, but these

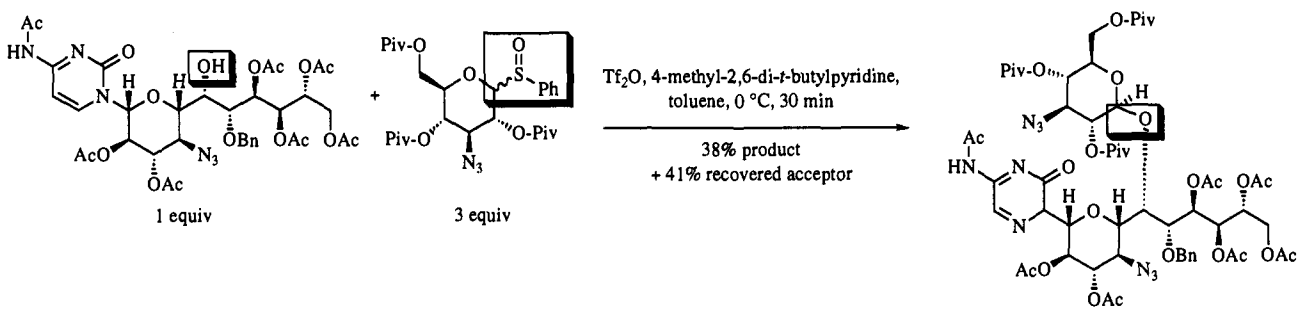
Scheme 6. Ezomycin Model Glycosylation



Scheme 7. Tunicamycin Nucleoside *O*-Glycosylation



Scheme 8. Hikizimycin Nucleoside *O*-Glycosylation



combinations gave low yields and poor stereoselectivity.

In our model study for the synthesis of ezomycins (Scheme 6), we examined a glycosylation involving a surrogate for the ezomycin octose acceptor (lacking the tetrahydrofuran ring and the pyrimidine) and an ezoaminuroic acid donor carrying C-6″ as a benzyl-protected carbinol.[48] The donor, a phenylthio pyranoside, was activated under the van Boom conditions[73,74] (*N*-iodosuccinimide and triflic acid), and glycosylation took place rapidly at room temperature to afford the desired β-linked disaccharide in high yield. Although this glycosylation does not ensure success with the octosyl nucleoside as acceptor, it shows how one might glycosylate the hindered C-6′ hydroxyl with compatible protecting groups on both the donor and acceptor components.

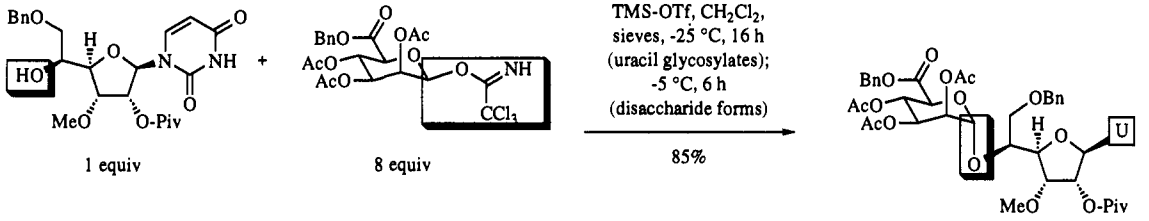
2. *O*-Glycosylation of Nucleosides

Nucleoside purines, pyrimidines, and their "protected" versions contain Lewis basic amide carbonyls and amine nitrogens that can potentially interfere with glycosylations of hydroxyls elsewhere in the nucleoside. Nevertheless, a number of successful *O*-glycosylations of simple nucleosides have been reported.[4,81,82] The reaction typically requires an excess of the glycosyl donor and careful attention to reaction conditions so that other processes, such as depurination or uracil *N*(3)-glycosylation, can be monitored and/or minimized. In the context of complex nucleoside synthesis, three nucleoside *O*-glycosylations have been reported, all involving elaborated pyrimidine nucleoside substrates.

If one theme plays throughout the various approaches to tunicamycin, it is the challenge presented by the unavoidable trehalose linking step. In Suami's synthesis of tunicamycin V, the key reaction involved the difficult glycosylation of a 2-acetamido-α-D-glucopyranose acceptor with a tunicaminyluracil donor (Scheme 7).[14,15] The expensive donor, an elaborated galactopyranosyl chloride with a participating *N*-benzyloxycarbonyl group at C-10′, was combined with a 2-fold excess of the less-precious acceptor in the presence of silver perchlorate. The anomeric hydroxyl of the acceptor evidently can equilibrate under the reaction conditions, as products from both acceptor anomers were isolated. The relatively hindered acceptor hydroxyl reacts quickly under mild conditions, although the modest yield might be the result of competition involving the Lewis basic uracil ring (compare the capuramycin example, below). A related trehalose coupling with similar but nonnucleoside components was reported by Myers[29] to give comparable yield and stereoselectivity, whereas Danishefsky and co-workers were unable to couple the Suami intermediates on a smaller scale.[17]

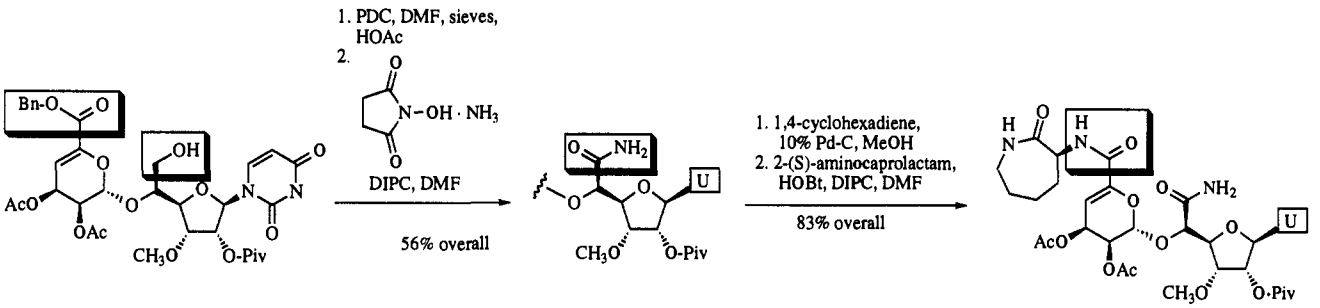
In the Schreiber synthesis of hikizimycin, the especially challenging glycosylation of a hindered undecanose nucleoside hydroxyl was required (Scheme 8).[31,32] The donor, a phenylsulfenyl glycoside related to kanosamine, was taken in 3-fold excess, activated by addition of triflic anhydride according to the procedure of Kahne,[75] and then exposed to the acceptor to give the β-linked coupled product in good yield based on 41% recovered acceptor. A number

Scheme 9. Capuramycin Nucleoside *O*-Glycosylation

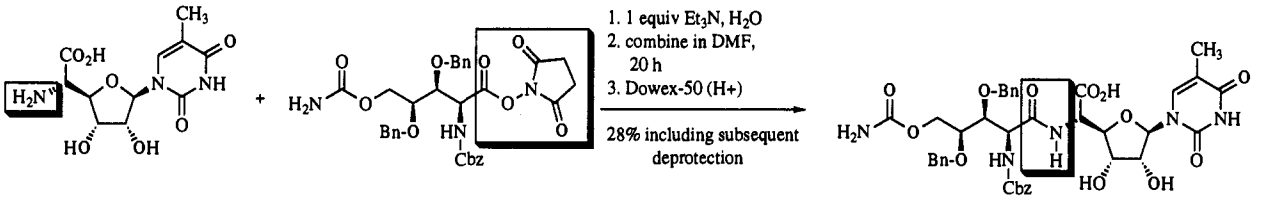


Scheme 10. Peptide and Amide Formation

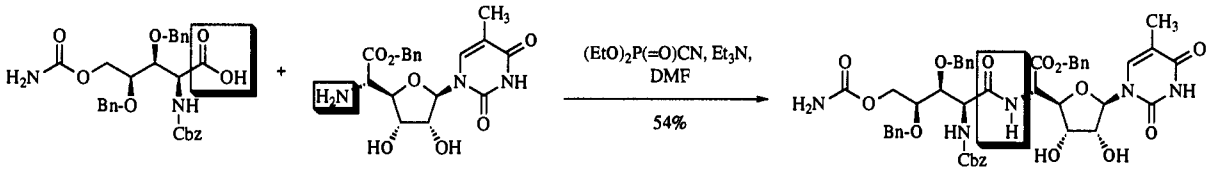
entry 1: Knapp, ref. 33



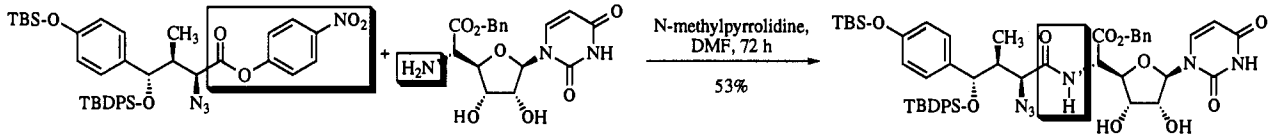
entry 2: Emoto, ref. 7,8



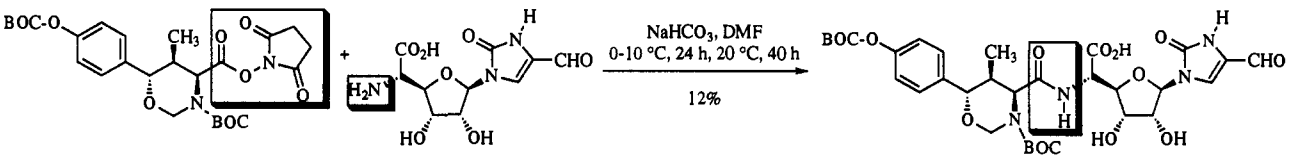
entry 3: Ogawa, ref. 30



entry 4: Barrett, ref. 26



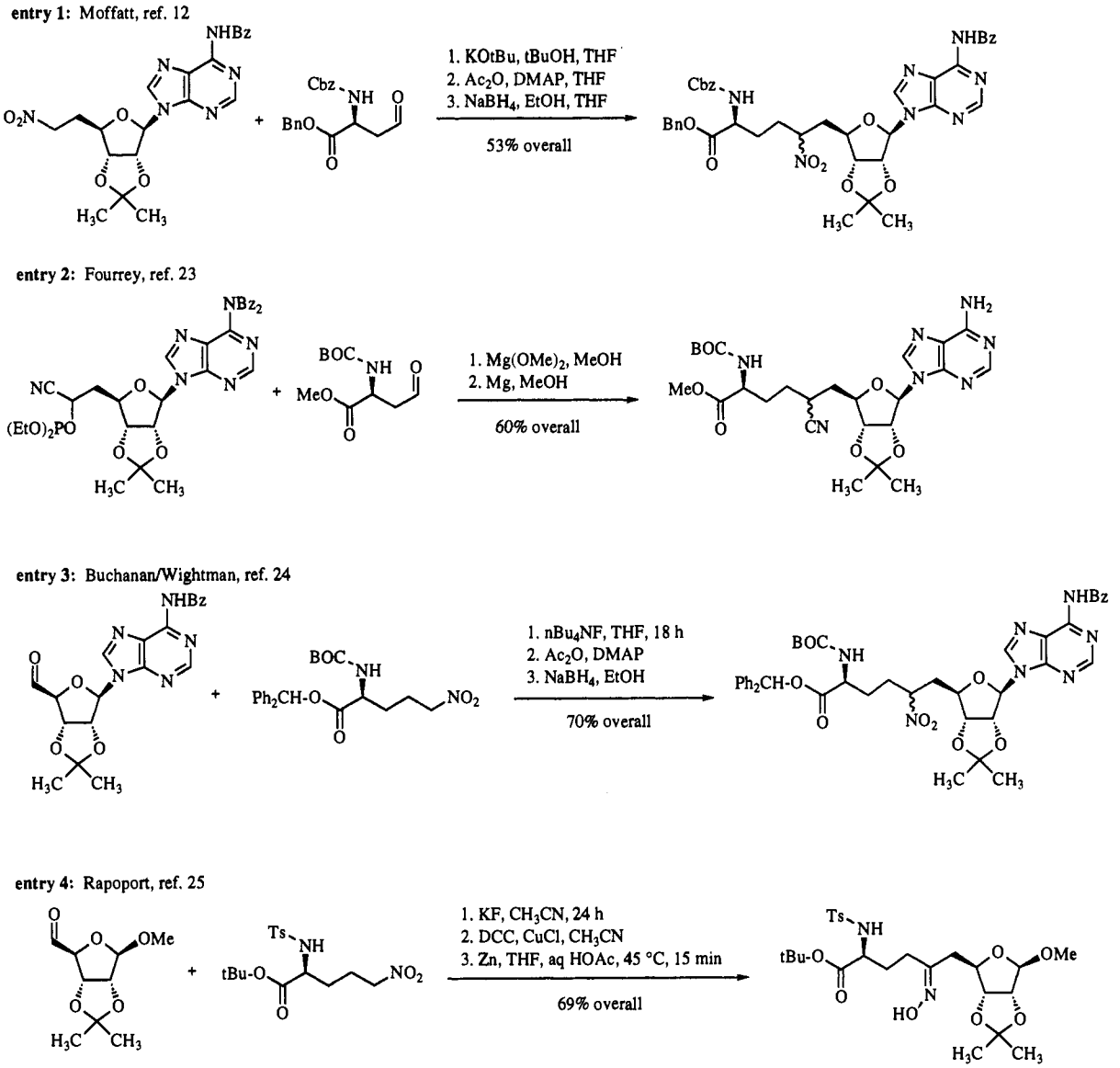
entry 5: Konig, ref. 22



of other coupling procedures were tried without success; perhaps they failed because of the hindered nature of the acceptor hydroxyl and competing glycosylation of the cytosine O-2 or N-3. The coupling also failed when acetamido replaced the C-4′ azido group of the acceptor, due to facile intramolecular cyclization to an imidate. Pivaloate was recommended as the donor O-2 protecting group rather than acetyl to minimize othoester formation.

Our synthesis of capuramycin depended on the glycosylation of a L-*talo*-uridine derivative at the hindered C-5′ hydroxyl (Scheme 9).[33] The donor was a D-*manno*-pyranuronate derivative activated according to Schmidt.[83] After exposure to the activated donor at −25 °C, the nucleoside suffered apparent glycosylation on the uracil ring, as evidenced by the

Scheme 11. C–C Bond Formation in the Sinefungin Syntheses



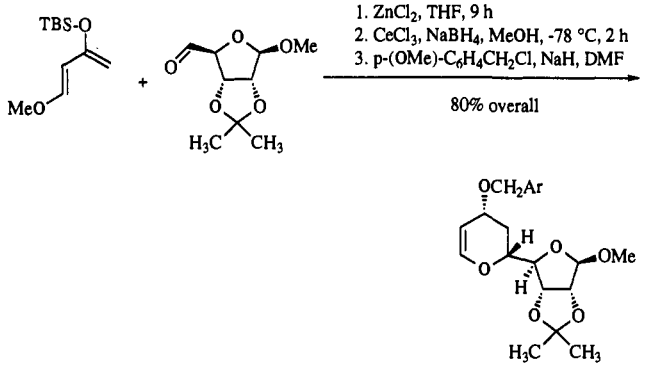
observation by TLC of a new product that reverted to starting acceptor upon aqueous bicarbonate workup. A parallel reaction warmed subsequently to −5 °C gave upon workup the required disaccharide in high yield, provided that 8 equiv of the donor was used to assure complete reaction. Lichtenthaler has shown that purine bases glycosylate and has also postulated that pyrimidine *N*-glycosylation occurs during the *O*-5′-glycosylation of an uridine.[81] Quite possibly this side reaction has also taken place during other nucleoside *O*-glycosylations, but was not observed because it is reversible under forcing reaction conditions or because the bond hydrolyzes during workup. For a hindered acceptor hydroxyl, glycosylation on the nucleoside base can be taken as the kinetically favored reaction. It would be desirable, therefore, to explore pyrimidine protecting methods for use in those cases where the donor component is expensive and one wants to minimize the number of equivalents required.

D. Peptide Bond Formation

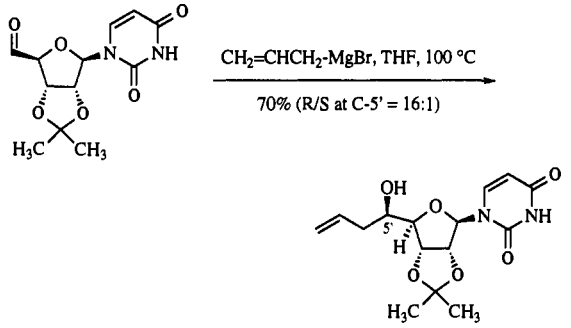
A number of the complex nucleoside targets listed in Charts 1 and 2 contain peptide-like linkages; that is, amide bonds involving at least one α-amino acid component that is susceptible to epimerization at the α-carbon. The extensive catalog of coupling procedures developed for oligopeptide synthesis[84–86] should be applicable to formation of these amide bonds as well. Scheme 10 shows the amide-forming steps taken from the syntheses in Chart 1 (one amide-forming reaction, namely attachment of the lipid side chain of tunicamycin V, was included in Chart 3 instead). The "peptide" bonds (shown in boxes) are in fact formed by application of peptide coupling procedures and reagents, including the use of *N*-hydroxysuccinimide-, *N*-hydroxybenzotriazole-, and nitrophenol-based activated esters, and the dehydrating reagents diisopropylcarbodiimide and diethylphosphoryl cyanide. Given the efficiency of these coupling procedures in the oligopeptide arena, it is perhaps surprising that the yields for coupling complex nucleoside components are generally not high. Some of the excuses offered earlier can be applied here as well: forming the peptide bond may not have been the principal focus of the research; the amount of material available for optimizing the coupling step may have been very limited; and the components

Scheme 12. C–C Bond Formation in the Octosyl Acid A Syntheses

entry 1: Danishefsky, ref. 18,19



entry 2: Hanessian, ref. 20



contain nucleophilic sites such as (deprotonated?) uracil and thymine rings that might acylate in competition with the amino group.

E. Synthesis of the Components

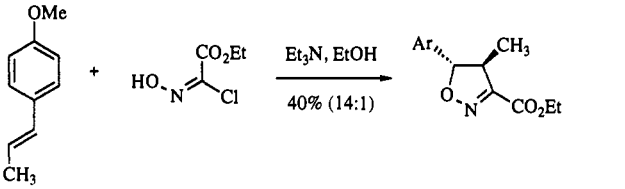
1. C–C Bond Formation in the Completed Syntheses

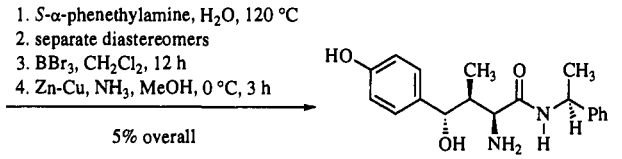
Complex nucleoside antibiotics cannot really be said to possess carbon "skeletons" in the way that, say, terpenoids do, because most of the linkages between components are through heteroatoms. Many of the components (pyrimidines, purines, furanosides, pyranosides, higher sugars) are *themselves* heterocyclic. Carbon–carbon bond formation is therefore not the foremost problem to be solved, typically, but it is clearly an important step for the synthesis of those targets with chain-extended carbohydrate or α-amino acid components. Given the historical fascination of synthetic chemists with carbon–carbon bond-forming reactions, it is natural that the "higher" sugars and amino acids should get their share of attention, and sinefungin (**2**), octosyl acid A (**5**), the nikkomycins (**6**, **7**), tunicamycin V (**4**), and hikizimycin (**8**) present interesting challenges for stereoselective chain extension of densely functionalized substrates. Most of these syntheses have been completed in more than one way, so it is instructive to examine how and where the carbon–carbon bonds are formed. One conclusion can be stated in advance of the discussion: there are many dependable ways to form carbon–carbon bonds, even with highly functionalized components; however, the complex nucleoside antibiotics have much to teach us about the *stereoselectivity* of bond formation.

All four sinefungin syntheses (Scheme 11) form a carbon–carbon bond to C-6′ where an amino group

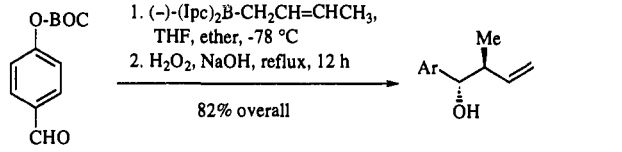
Scheme 13. C–C Bond Formation in Nikkomycin Syntheses

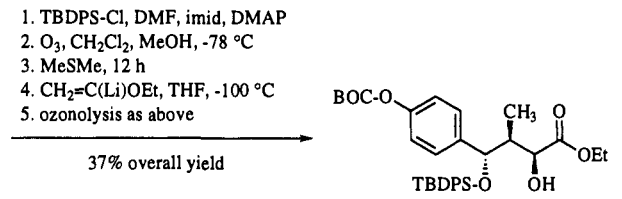
entry 1: Konig, ref. 22





entry 2: Barrett, ref. 26

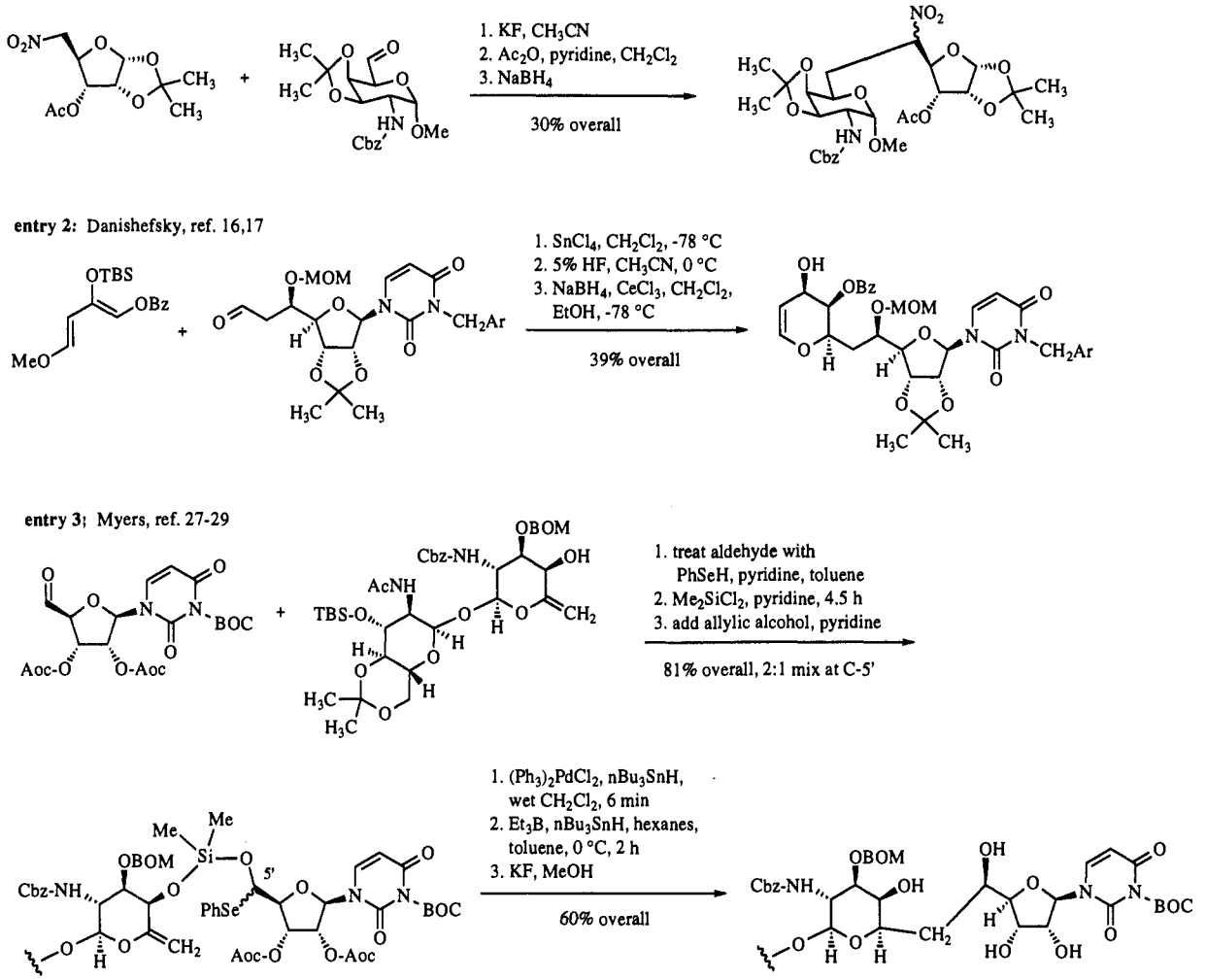




will eventually reside (see **2**, Chart 1). Nitro aldol chemistry is used in three, and the other (entry 2) relies on a Wadsworth–Horner–Emmons chain extension, but in no case is the C–C bond formed with stereoselectivity at C-6′. The recent Rapoport route (entry 4) eventually provides an (*S*)-C-6′ amino substituent, but direct stereoselective reduction of the oxime (for which there is no obvious precedent) was unsuccessful.[25] Therefore, this much-studied and seemingly simple target could still serve as a stimulus for further investigation.

In the octosyl acid A syntheses (Scheme 12), the stereoselective chain extension of a D-ribonic C-5 aldehyde was performed, but by completely different means. The Danishefsky route[16,17] (entry 1) established the C-5′ carbinol stereochemistry of the target (**5**, Chart 1) with a Lewis acid-promoted cyclocondensation of the "Danishefsky diene" with the back face of a D-ribose-derived carboxaldehyde. The resulting dihydropyrone was reduced stereoselectively at C-7′ to provide a carbinol that was later derivatized for cyclization to the tetrahydropyran ring of **5**. Hanessian (entry 2) was able to form the C-5′ carbinol directly on a uridine carboxaldehyde by stereoselective addition of allylmagnesium bromide.[20] The C-7′ stereochemistry was set later in the route by a mercuric ion-mediated cyclization. These contrasting approaches illustrate the questions of timing that arise when a special *N*-glycosylated pyrimidine, and also an extended carbon chain, must be built into a synthetic target. In the Danishefsky route, the pyrimidine was judged to be incompatible with the chain-extension chemistry, and was thus introduced

Scheme 14. C–C Bond Formation in the Tunicamycin Syntheses

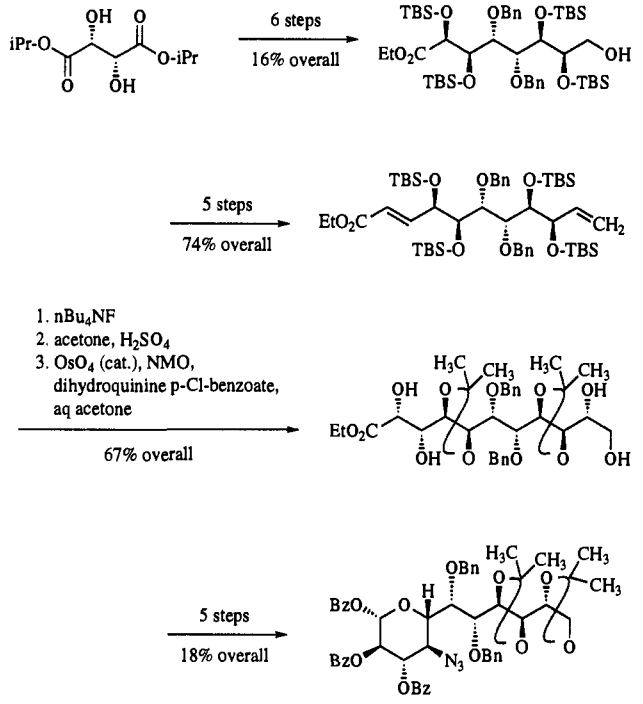


later in the sequence. In the Hanessian route, the uracil ring survived the Grignard reagent, but had to be protected and later elaborated by carboxylation to provide the octosyl acid A pyrimidine.

The polyoxins and nikkomycins (see **1**, **6**, and **7**, Chart 1) present a useful feature not seen among the other complex nucleoside antibiotics, in that an elaborated amino acid component and a nucleoside portion can be procured separately, and joined late in the route. The compatibility of the nucleoside with the carbon–carbon bond-forming steps in the amino acid component is therefore not an issue. There are, nevertheless, a variety of ways to tackle the preparation of the latter, and the syntheses of the nikkomycins (**6** and **7**, Chart 1) by Konig[21,22] and Barrett,[26] respectively, offer two contrasting approaches (Scheme 13). For the synthesis of nikkomycin B_x (entry 1), the cycloaddition of ethyl cyanoformate *N*-oxide ($EtO_2C-CN-O$, generated *in situ* by dehydrochlorination) with a substituted styrene derivative was employed. The resulting isoxazoline was converted to a pair of diastereomeric carboxamides, which were separated, and then the desired isomer was taken on to the γ-hydroxy-α-amino carboxylic acid derivative by reductive opening of the isoxazoline. Although this approach is not high yielding, it provided a variety of amino acid stereoisomers in pure form for incorporation into nikkomycin analogues. Barrett (entry 2) used the highly stereoselective addition of (−)-(*E*)-crotyldiisopinocamphenylborane to 4-(pivaloyloxy)benzaldehyde to generate two stereogenic centers, and then a Felkin–Ahn-type addition (6:1 stereoselectivity) to a derived aldehyde to create the third. The synthesis of the nikkomycin B amino acid component was completed by replacement of hydroxyl by azido by way of the corresponding iodo derivative, followed by activation of the carboxylate for coupling. In both approaches, the benzylic hydroxyl was appropriately protected before carboxylate activation in order to avoid cyclization to a lactone (see Scheme 10).

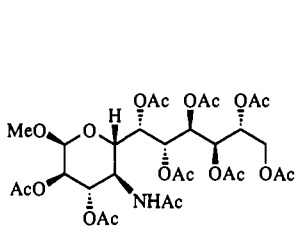
The tunicamycin (**4**) syntheses by Suami,[13–15] Danishefsky,[16,17] and Myers[27–29] (Scheme 14, entries 1–3, respectively) provide three approaches to the undecanose chain extension that are so different from one another that comparison is difficult. Carbon–carbon bond formation takes place at different times (early, midway, and late in the route, respectively) and by different means (nitro aldol, cyclocondensation, and intramolecular radical addition, respectively). It was stated earlier that having to assemble and couple various components can be taken as a restriction, but it is clear from these tunicamycin syntheses that the synthetic chemist can still exercise considerable imagination in formulating the synthetic route to individual components.

Scheme 15. Chain Elongation and Functionalization in the Hikizimycin Synthesis (Schreiber, refs 31 and 32)

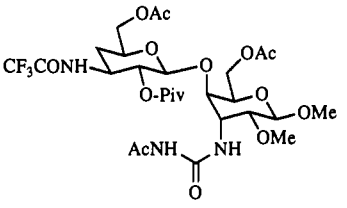


The Ikemoto and Schreiber synthesis of hikizimycin[31,32] (**8**, Chart 1) illustrates the unique application of two-directional chain synthesis[87] to the synthesis of a complex nucleoside antibiotic. In this context (namely, Chart 1) it is the only example of a *de novo* synthesis of a higher sugar that does not depend on a commercially available pyranose or furanose precursor. Instead, L-(−)-diisopropyltartrate serves as the four-carbon starting point, as summarized in Scheme 15. Double two-carbon chain extension is achieved by Horner–Emmons chemistry, and stereoselective[88] bis-osmylation serves to introduce hydroxyls at carbons that will become C-4′, C-5′, C-8′, and C-9′. The ends of the carbon chain are differentiated by means of a selective DIBAL reduction, and then further extended by Tebbe and Horner–Emmons olefinations. A second bis-osmylation creates three additional stereogenic carbons, and further modifications lead to the protected and fully-functionalized 4-azido-undecanose derivative. This route is thus highly stereoselective and provides adequate material for optimizing the challenging *N*- and *O*-glycosylation steps en route to **8**. One advantage that *de novo* sugar synthesis enjoys over more traditional pyranoside modification chemistry is illustrated here: functional groups can be protected as they are introduced, rather than having to be selectively deprotected, modified, and reprotected. This can lead to a more efficient route, provided the important matters of enantiomer resolution and stereoselectivity are attended to. *De novo* sugar synthesis has not yet caught up with carbohydrate modification chemistry, but the hikizimycin synthesis is a significant recent advance.

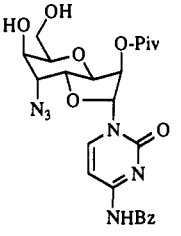
Chart 5. Components Synthesized in Model Studies and Approaches 1988–1995



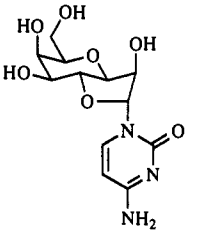
15
hikizimycin (**8**) studies
Danishefsky, ref. 89,90



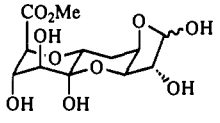
16
ezomycin (**12**) studies
Knapp, ref. 48



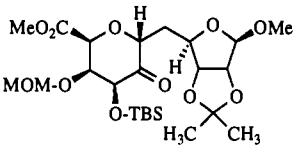
17
ezomycin (**12**) studies
Knapp, ref. 47



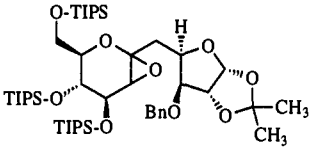
18
ezomycin (**12**) studies
Schmidt, ref. 46



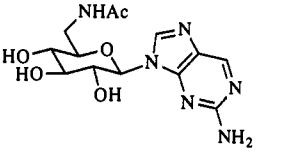
19
herbicidin (**11**) studies
Gallagher, ref. 58-61



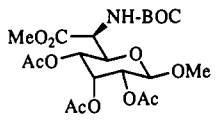
20
herbicidin (**11**) studies
Vogel, ref. 64



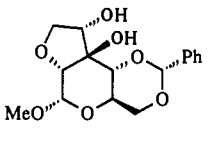
21
herbicidin (**11**) studies
Whiting, ref. 62,63



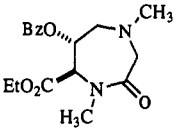
22
amipurimycin/miharamycin (**13**, **14**) studies
Garner, ref. 52



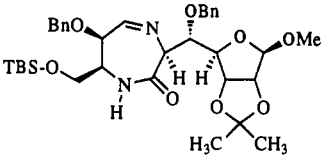
23
amipurimycin/miharamycin (**13**, **14**) studies
Casiraghi/Spanu, ref. 53,54



24
miharamycin (**13**) studies
Sinay, ref. 58



25
liposidomycin (**10**) studies
Knapp, ref. 66



26
liposidomycin (**10**) studies
Ubukata, ref. 65

2. Components Synthesized in Model Studies and Approaches, 1988 to Mid-1995

The complex nucleoside antibiotics have been the subject of intensive investigation apart from the completed syntheses in Chart 1. A number of model studies and synthetic approaches have been published during the period 1988 to mid-1995 (the earlier studies have been reviewed[1]), and these also address many of the strategic and tactical aspects discussed above: early vs late *N*-glycosylation, protecting groups, amide bond formation, C–C bond formation, etc. Chart 5 shows the structures of compounds that have been made in the course of these studies, and one can assess the degree to which these structures resemble the appropriate complex nucleoside antibiotic targets (compare Charts 1 and 2).

The Danishefsky synthesis of methyl α-peracetylhikosaminide (**15**) from galactose (Chart 5)[89,90] illustrates the thoughtful application of the aldehyde–diene cyclocondensation to higher sugar synthesis.[91] Excellent stereoselectivity is obtained throughout. The product matched the compound prepared by Secrist in his pioneering 1980 study.[92] Three recent synthetic studies on ezomycins have been published: Schmidt's preparation of the octosyl nucleoside (**18**) from galactose,[46] our synthesis of a similar compound (**17**) with the ureido precursor already installed,[47] and our model ezomycin glycosylation, which led to the disaccharide **16**.[48] The next major obstacle to be overcome in the ezomycin area is the *O*-6′-glycosylation of the octosyl nucleoside itself. Gallagher,[58–61] Whiting,[62,63] and Vogel[64] have published synthetic studies on the herbicidin glycoside. The Gallagher undecanose (**19**)[61] would seem to require "only" installation of the purine base, undoubtedly a more difficult task than it appears. Garner has continued his studies on amipurimycin and miharamycin with the preparation of related 2-aminopurine nucleosides (**22**).[52] Selective *N*-7-glycosylation was accomplished with several coupling procedures, including the mild van Boom conditions (thioglycoside donor, silylated purine base, *N*-iodosuccinimide, triflic acid, dichloroethane, room temperature).[73] Czernecki and co-workers,[57] Casiraghi and Spanu,[53,54] and Sinay[56] have also reported progress toward amipurimycin and miharamycin. The latter group has prepared a precursor **24** whose structure was confirmed by X-ray crystallography, and was shown to be different from that of a compound claimed earlier to be **24**.[55] Work in the liposidomycin area includes two studies on the unusual diazapanone ring. We published a method for the synthesis of the heterocycle **25** by a reductive amination reaction,[66] and Ubukata prepared the model **26** by chain-extending methyl β-D-ribofuranoside.[65] Luzzio has also reported the chain extension of uridine for application to liposidomycin,[67] and Kim et al. have reported synthetic studies on the liposidomycin aminoribofuranside.[68]

Note Added in Proof

The following recent articles describe tunicamycin studies: (a) Sarabia-Garcia, F.; Lopez-Herrera, F. J.; Gonzolez, M. S. P. *Tetrahedron* **1995**, *51*, 5491–5500. (b) Karpiesiuk, W.; Banaszek, A. *Carbohydr. Res.* **1994**, *261*, 243–253. The full paper on 2′-deoxynucleoside synthesis from thioglycosides has appeared: Sugimura, H.; Osumi, K.; Kodaka, Y.; Sujino, K. *J. Org. Chem.* **1994**, *59*, 7653–7660. An elegant synthesis of the cyclic nucleotide phosphodiesterase inhibitor griseolic acid from glucose has been reported by a Shering-Plough group: Tulshian, D. B.; Czarniecki, M. *J. Am. Chem. Soc.* **1995** *117*, 7009–7010.

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CR9411132