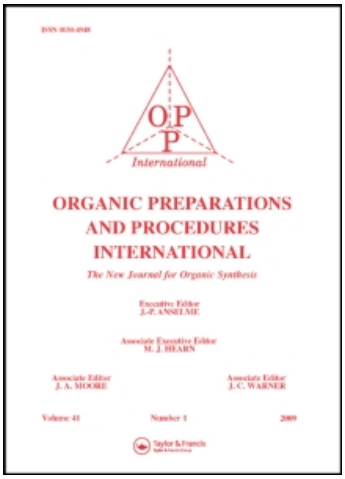

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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To cite this Article More, Jesse D.(2007) 'SYNTHESIS OF FUROPYRANYL PYRIMIDINE NATURAL PRODUCTS. A REVIEW', Organic Preparations and Procedures International, 39: 2, 107 — 133
To link to this Article: DOI: 10.1080/00304940709356007
URL: http://dx.doi.org/10.1080/00304940709356007

ORGANIC PREPARATIONS AND PROCEDURES INT., 39 (2), 107-133 (2007)

SYNTHESIS OF FUROPYRANYL PYRIMIDINE NATURAL PRODUCTS. A REVIEW

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INTRODUCTION

Certain bacterial species of the genus *Streptomyces* produce structurally and biologically interesting higher-carbon sugars. The most striking feature of these compounds is a *trans*-fused perhydrofuropyran ring system, formally derived from the addition of two carbons to C5' of a ribonucleoside and the linkage of the two-carbon chain with the oxygen atom at C3'. These metabolites also contain a natural or modified pyrimidine base. The ezomycins (*Fig. 1*), discovered in the early 1970's by Sakata and co-workers, are the most complex members of this family of natural products.[1-4]

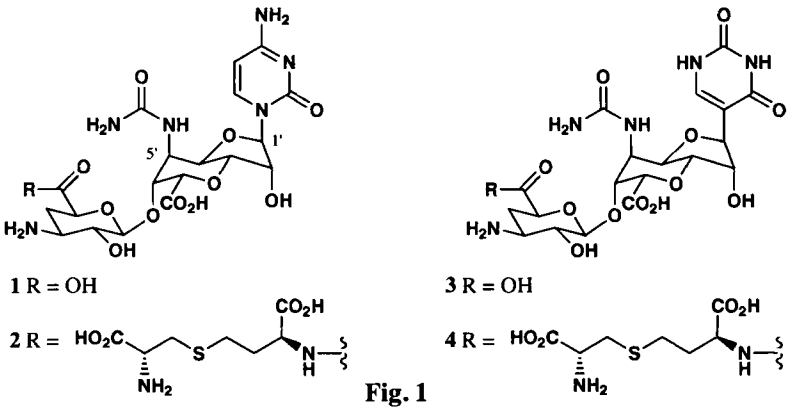
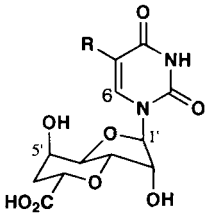


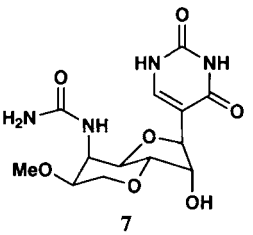
Fig. 1

There are eight known ezomycins but only ezomycins A_1 (**1**), A_2 (**2**), B_1(**3**), and B_2(**4**) contain the *trans*-fused perhydrofuropyran ring system. All ezomycins contain a urea at C5' and an axial hydroxyl group at C6' which is α-glycosylated with an aminohexose. Ezomycins indicated with a "1" subscript contain a cystathionine peptide residue while those in the "2" series exist as free acids. The other main structural variable in the ezomycin family is the nucleoside base. Ezomycins in the "A" series contain a cytosine linked as an N-glycoside while those in the "B" series have a C-linked uracil ring.

The discovery and structural elucidation of octosyl acids A (**5**) and B (**6**) (*Fig. 2*) were reported a few years after the ezomycins.[5] Structurally, **5** and **6** are much simpler than the ezomycins as they contain only the perhydrofuropyran portion and lack oxygenation at C6'. The most recently discovered member of the perhydrofuropyran nucleosides, malayamycin A **7**,[6] is a pseudouridine C-glycoside (a structural motif also found in ezomycins in the B series). Unique structural features of **7** include the absence of the C7' carboxylic acid group present in the ezomycins and the octosyl acids and an equatorial methoxy substituent at C6'.



5 R = CO_2H
6 R = CH_2OH



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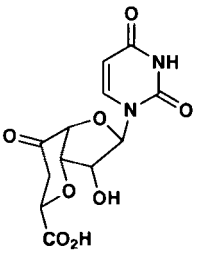

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Fig. 2

The unique and somewhat strained bicyclic framework of these natural products, rich with stereogenic centers and polar functionality, has piqued the interest of synthetic chemists for many years. This review will cover synthetic efforts directed towards octosyl acid, ezomycin A_1 and malayamycin A. The broad field of nucleoside antibiotic synthesis has been reviewed a number of times,[7,8] most recently by Knapp in 1995.[9] In the present review special emphasis is placed on the method of constructing the perhydrofuropyran ring system. Other synthetic challenges associated with these natural products are also highlighted.

I. OCTOSYL ACID

Octosyl acids A (**5**) and B (**6**) were isolated from the fermentation broth of *Streptomyces cacaoi var. asoensis* and their structures determined by degradation and spectroscopy.[5] Octosyl acid C (**8**) was discovered as a co-metabolite and has two unique features: it is oxidized at C5' and has a *cis*-ring fusion. Although the octosyl acids do not possess any biological activity, they do show structural similarities to cyclic nucleotides such as the intracellular signaling molecule adenosine 3',5'-cyclic monophosphate (cAMP, **9**, *Fig. 3*). Indeed, a synthetic adenine analog

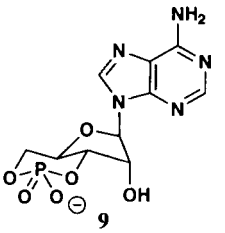

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Fig. 3

of octosyl acid was shown to be a competitive inhibitor of cyclic nucleotide phosphodiesterases from various animal tissues.[10]

To date, three total syntheses of octosyl acid A (**5**) have been reported, along with several partial syntheses and synthetic studies. Most of the synthetic studies have used a ribose or uridine derivative to supply the five-membered ring, with the six-membered ring annulated by forming either bond *a* or bond *b* (*Fig. 4*). The syntheses discussed below are arranged by the

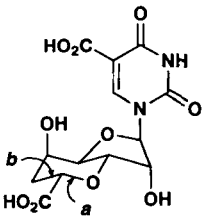
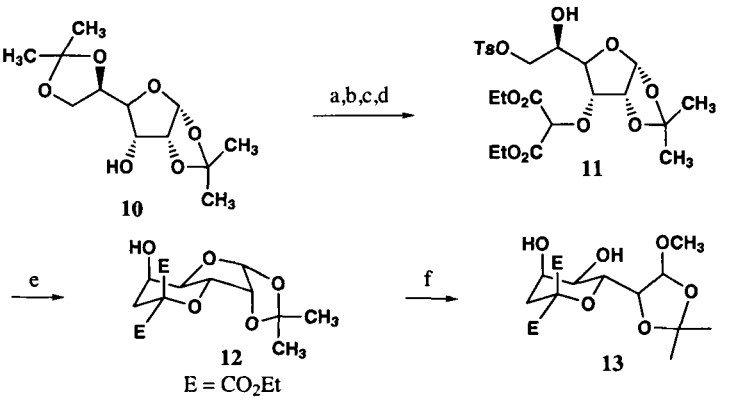


Fig. 4

method of formation of the six-membered ring: intramolecular alkylation, electrophile-induced etherification, and miscellaneous. Within each section, the studies are arranged chronologically. Synthetic efforts before 1988 have been reviewed by Hannessian and are not discussed in as much detail as the more recent studies.[11]

1. Intramolecular Enolate or Alkoxide Alkylation Approaches

A popular strategy in the octosyl acid field has been formation of bond *a* or bond *b via* an intramolecular alkylation. Bond *a* can be forged with a C3' alkoxide with a C7' electrophile or bond *b* with a C3' O-glycolate enolate and a C6' electrophile. The latter strategy was chosen by Anzai and Saito in the first report of synthetic efforts towards octosyl acid A.[12] Starting with glucose derived *bis*(acetonide) **10** (*Scheme 1*), a suitable cyclization substrate **11** was constructed



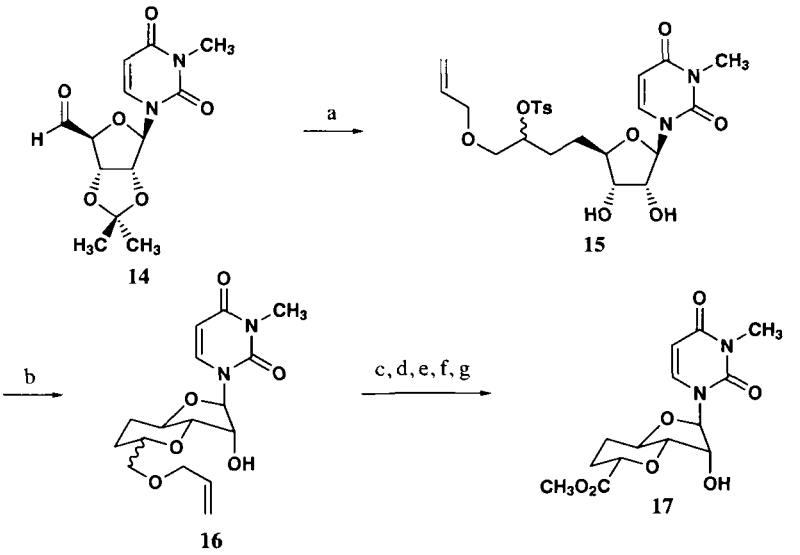
a) NaH, ethyl bromoacetate, 84%; b) NaH, diethyl carbonate; c) HOAc, 37°, 84%, two steps; d) 1 eq TsCl, pyridine, -15°C, 70%; e) NaH, THF, RT; f. 0.1N HCl.

Scheme 1

via an O-alkylation/Claisen condensation sequence followed by acetonide removal and selective activation of the primary alcohol as a tosylate.

Compound **11** was cyclized to give **12** upon stirring with NaH in THF for 20 hours. The desired product **12** was contaminated with a significant amount of epoxide by-product derived from cyclization of the C5' alkoxide with the adjacent tosylate, but **12** could nonetheless be purified. Progress beyond compound **12** was thwarted by its instability to even mildly acidic conditions; all attempts to remove the acetonide group of **12** led to opening of the bicyclic ring system to give **13**. Despite the recalcitrant acetonide protecting group, this work is notable for its rapid buildup of the skeleton of **5**. By establishing intramolecular alkylation as a viable method for the construction of the octose framework of **5**, this model study laid the foundation for much of the future work in the synthesis of furopyranyl pyrimidine natural products. The same researchers published a slightly more advanced model system a few years later for which few details were reported.[13]

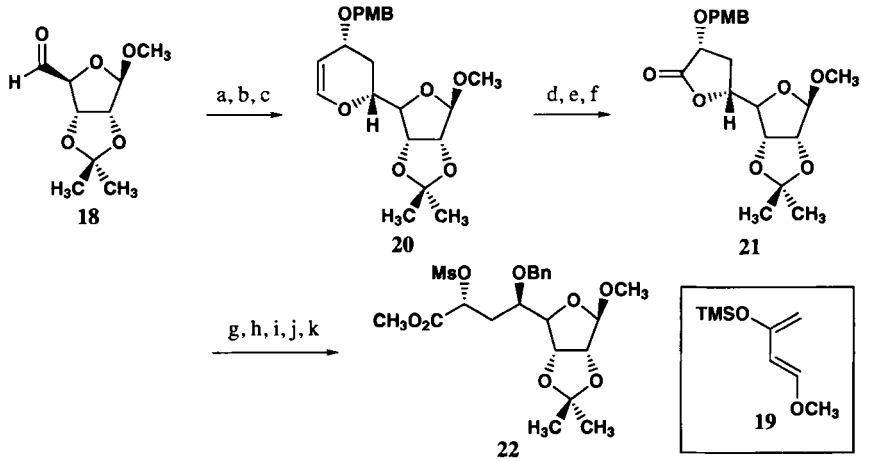
In 1981, Kim and Szarek synthesized a simple octosyl acid model system (lacking oxygenation at C5') through formation of bond *b via* alkylation (*Scheme 2*).[14] N-methyl uridine derivative **14** was converted to diol **15** *via* a nine-step sequence. The lengthy but efficient route from **14**→**15** consisted of a Wittig homologation and several routine functional group manipulations. Compound **15** was cyclized *via* the alkoxide to give **16** as a mixture of diastereomers. The isomers **16** could be separated by silica gel chromatography following conversion of the allyl ether to an enol ether with Wilkinson's catalyst. The relative stereochemistry of the individual diastereomers was established *via* examination of ^{13}C chemical shifts of derivatives of **16** (not shown). Model system **17** was completed *via* hydrolysis of the vinyl ethers, oxidation, and esterification.



a) 9 steps, 24% overall; b) NaH, DME, 50%; c) $RhCl(PPh_3)_3$, EtOH, Δ, 45% desired epimer; d) BzCl, pyr; 0.1N HCl, 88%; e) NaOMe/MeOH, 98%; f) Pt/C, O_2, 70°C, 75%; g) 5%HCl/MeOH, 81%.

Scheme 2

The first total synthesis of **5** was reported in 1986 by Danishefsky and Hungate, who used a novel maneuver to form bond *a via* alkoxide alkylation.[15,16] Starting with ribosyl aldehyde **18** (*Scheme 3*), cycloaddition with the Danishefsky-Kitahara diene **19** incorporated the remaining carbons of the octosyl skeleton and established the stereochemistry at C5'. Stereoselective Luche reduction (7:1 mixture of diastereomers favoring the one shown) followed by protection as a *p*-



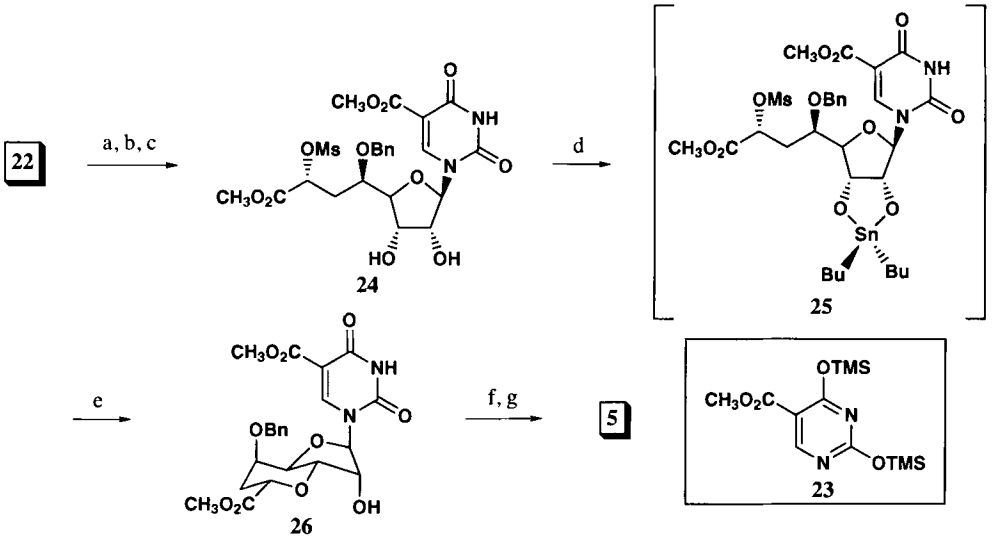
a) **19**, $ZnCl_2$, THF, 89%; b) $NaBH_4$, $CeCl_3$, MeOH; c) PMBCl, NaH, 90%, two steps; d) OsO_4 (cat), $NaIO_4$; e) K_2CO_3/MeOH, 93% 2 steps; f) Ag_2CO_3, Celite, xylenes, reflux, 86%; g) LiOH, THF; h) NaH, BnBr, DMF; i) CH_2N_2/Et_2O, 53%, three steps; j) DDQ, CH_2Cl_2/H_2O, 62%; k) MsCl, NEt_3, 52%

Scheme 3

methoxybenzyl (PMB) ether gave an intermediate dihydropyran **20**, which contains all of the stereochemical elements of **5**, but has an extraneous carbon. The superfluous carbon was excised by oxidative cleavage and formate ester hydrolysis to give a lactol, which was oxidized to the lactone **21** with silver carbonate in boiling xylenes. Saponification of **21** gave an acid which was protected as a C5' benzyl ether. Treatment with diazomethane was followed by two-step conversion to mesylate **22**.

Mesylation served a dual purpose; C7' was activated for S_N2 reaction and the C7' hydroxyl group was protected for the next several transformations (*Scheme 4*). Replacement of the acetonide in **22** with acetates followed by anomeric acetolysis gave an intermediate triacetate (not shown). N-glycosylation of this intermediate under Vorbrüggen conditions with **23** followed by deacylation gave diol **24** ready for alkylative ring formation.[17] It is notable that the mesylate emerged unscathed from this sequence of both acidic and basic reagents. Several attempts to cyclize **24** under conventional conditions failed and thus a novel route was devised to forge the required ring. Refluxing **24** with *bis*(tributyltin)oxide converted the diol *in situ* to a stannylene acetal **25**, which was not isolated, but treated with cesium fluoride in hot dimethylformamide (DMF). This combination of reagents produced the bicyclic structure **26** in 77% yield. The stannylene acetal presumably served to both protect the C2' alcohol and activate the C3' alcohol as a tin alkoxide. Debenzylation and saponification of **26** gave synthetic material with properties identical to those of natural **5**.

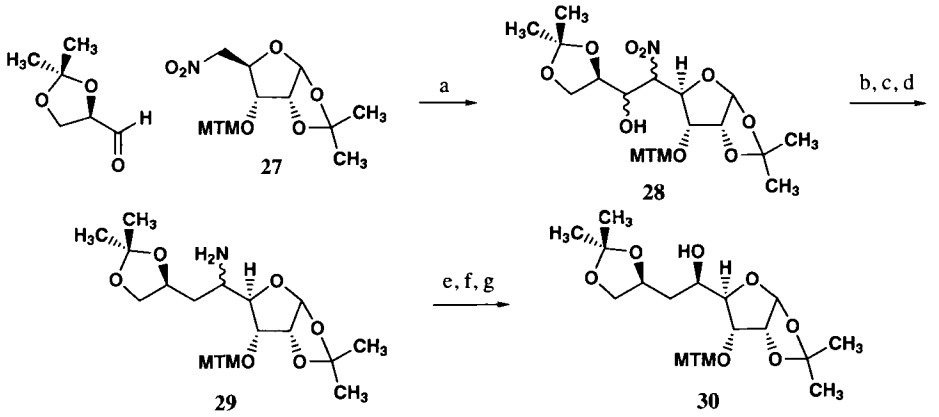
In 1988, a lengthy formal total synthesis of **5** using an intramolecular alkylation approach was reported.[18] Union of nitrosugar **27** and D-glyceraldehyde acetonide *via* fluoride-mediated Henry reaction gave **28** as a mixture of diastereomers (*Scheme 5*). Several steps were



a) 1M HCl/MeOH, reflux; Ac_2O/pyr; Ac_2O/HOAc conc. H_2SO_4, 76%; b) **23**, TMSOTf, CH_3CN, RT, 91%; c) NaOMe/MeOH, 86%; d) Bu_2SnO, MeOH, reflux; e) CsF, DMF, 60°C 77%, two steps; f) H_2, $Pd(OH)_2$, THF, 80%; g) LiOH, THF, 78%.

Scheme 4

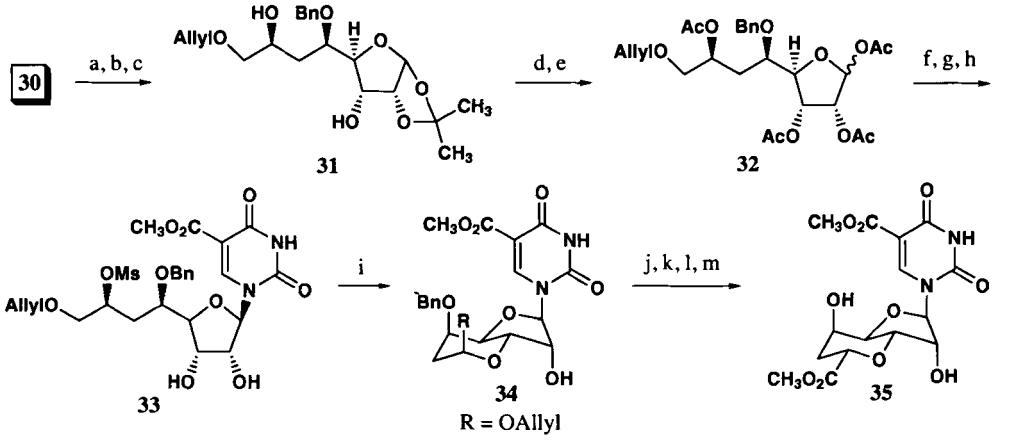
then used to set the stereochemistry at C5' and remove the extraneous C6' hydroxyl group. Conversion of **28** to an acetate and elimination gave a nitroolefin which was reduced to saturated amine **29** *via* hydrogenation over Raney nickel. Conversion of the primary amine to a ketone with Corey's method was followed by a non-selective reduction which yielded 55% of the desired **30** along with 32% of the undesired C5' epimer.[19] Fortunately, the diastereomers could be separated with standard silica gel flash chromatography.



a) KF, nBu_4NI, $PhCH_3$; b) Ac_2O/pyr, DMAP; c) $NaBH_4$, 45%, three steps; d) H_2, Ra-Ni, 70%; e) 4,5-di-*tert*-butyl *o*-quinone, oxalic acid, 66%; f) $NaBH_4$; 55% desired epimer. MTM = methylthiomethyl

Scheme 5

Standard protecting and functional group manipulations on **30** gave diol **31** (*Scheme 6*). Removal of the acetonide group in **31** was followed by conversion to glycosyl donor **32** which gave a single intermediate N-glycoside (not shown) upon Vorbrüggen reaction.[17] Deacylation,



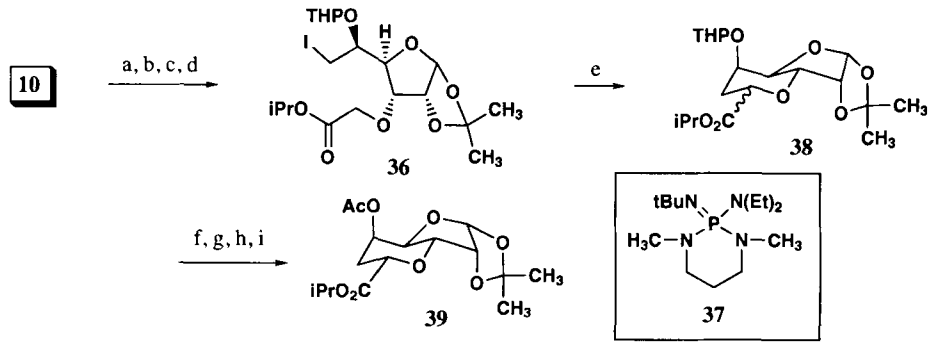
a) BnBr, NaH, DMF; HOAc, 100%; b) AllylBr, NaH, THF, 72%; c) MeI, aq. acetone; d) aq. HOAc; e) Ac_2O/pyr, 96%; f) TMSOTf, **23**, 80%; g) NaOMe/MeOH; DMP/TsOH, DMF; h) MsCl, pyr; aq. TFA, 81%; i) NaH, DMSO; HCl, MeOH, 45%; j) BzCl, pyr, 86%; k) SeO_2, HOAc, 86%; l) CrO_3, aq. acetone; HCl, MeOH, 67%; m) NaOMe/MeOH, reflux; HCl, MeOH.

Scheme 6

acetonide protection, mesylation, and acetonide removal then gave **33**. Intramolecular alkoxide alkylation of **33** was effected with sodium hydride in DMSO. After treatment with methanolic HCl (to re-esterify some saponified ester), compound **34** was isolated in 45% yield. All that remained in the synthesis was oxidation of C8' and epimerization of the C7' stereocenter to the more stable equatorial position. Protection of **34** as the benzoate was followed by allyl ether deprotection under rather harsh conditions (selenium dioxide, acetic acid/dioxane, reflux), which gave the free alcohol in 77% yield. Jones oxidation and esterification gave a fully protected derivative of octosyl acid which was treated with sodium methoxide. This epimerized the C7' stereocenter, removed the C2' benzoate and, apparently, the C5' benzyl ether. Esterification gave **35**, the dimethyl ester of octosyl acid.

Knapp's group at Rutgers recently reported a very short synthesis of **5** by revisiting the glycolate alkylation approach first explored some 30 years earlier by Anzai and Saito.[20] Commercially available *bis*(acetonide) **10** was O-alkylated with isopropyl bromoacetate in the presence of phosphazene base **37** (*Scheme 7*).

Selective acetonide removal, conversion of the primary alcohol to an iodide, and protection of the C5' alcohol gave glycolate **36**. Addition of ester **36** to a dilute solution of lithium diisopropylamide (LDA) in tetrahydrofuran (THF) generated an enolate which displaced the primary iodide intramolecularly to give a mixture of diastereomers **38** in 65% yield. The identity of the new compounds as C7' epimers of the desired bicyclic structure was secured upon removal

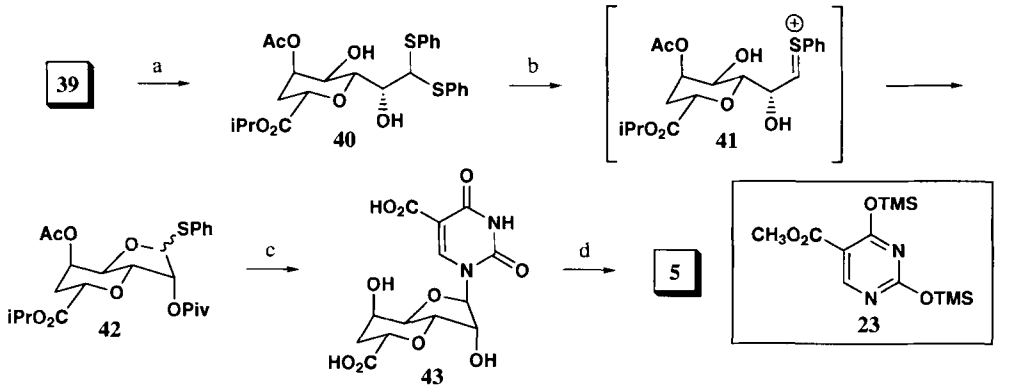


a) isopropyl bromoacetate, **37**, THF, 95%; b) aq. HOAc; c) I_2, PPh_3, MeCN/DMF; d) DHP, PPTS, CH_2Cl_2, 56%, three steps; e) LDA, THF, -78°C, 65%; f) *t*-BuOK/*t*-BuOH; g) *i*-PrI, NaH, DMF; h) aq. HOAc/THF, 45°C; i) Ac_2O/pyr, 74%, four steps.

Scheme 7

of the tetrahydropyranyl (THP) group and acylation (not shown). Examination of ^1H-^1H coupling constants in the separated, acylated isomers revealed the relative stereochemistry. Fortunately, the original mixture of diastereomers from the alkylation converged to a single compound **39** after a high-yielding four-step sequence involving epimerization and conversion of the THP group to an acetate.

With the furopyran skeleton intact, all that remained was to convert the isopropylidene sugar to an appropriate glycosyl donor and install the nucleoside base (*Scheme 8*). The usual tactic for installing a nucleoside base involves converting a stable anomeric protecting group to a

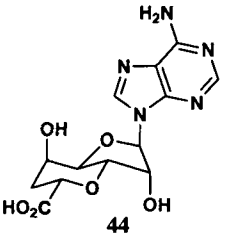


a) PhSH, BF_3OEt_2, 87%; b) $AgClO_4$, $NaHCO_3$, CH_3NO_2, 4Å MS; PivCl, DMAP, CH_2Cl_2, 57%; c) **23**, NIS, TfOH, 58%; d) LiOH, aq. MeOH, 70%. MS = molecular sieves

Scheme 8

1-O-acyl group, which then serves as a leaving group in the glycosylation reaction. Previous studies by Anzai and Saita had shown that cleavage of the C1'-C2' acetonide to a glycosyl donor was difficult and the five-membered ring, once opened, could not be reconstituted.[12] To circum-

vent this problem, the acetonide in **39** was first converted to a dithioacetal **40** with excess thiophenol and boron trifluoride diethyl etherate (BF_3•OEt_2). Upon activation with $AgClO_4$, a putative thionium ion **41** was generated and trapped by the C4' alcohol to give a thiophenyl sugar, which was converted to its C2' pivaloate ester **42**. The use of a reactive thionium ion allowed for facile formation of the five-membered ring and produced an anomeric thiophenyl group; thiophenyl glycosides are latent electrophiles that can be easily converted to leaving groups upon activation with an appropriate thiophile. In the event, treatment of **42** with N-iodosuccinimide (NIS) and catalytic trifluoromethanesulfonic acid (TfOH) in the presence of *bis*(trimethylsilyl)uracil derivative **23** gave a 58% yield of the nucleoside **43**. The four base-labile protecting groups were then cleaved with aqueous hydroxide in methanol to yield the natural product. An adenine analog **44** was also prepared using an analogous sequence. Despite the low stereoselectivity in the reaction of **36** to **38**, this synthesis is a highly efficient method to prepare octosyl acid and related congeners.

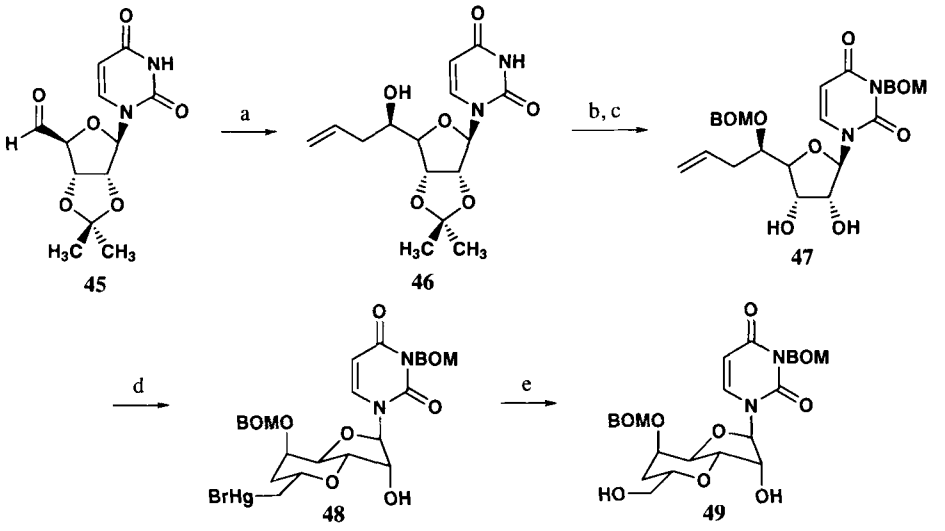


44

2. Electrophile-induced Cyclizations

Another general tactic used for the formation of the six-membered ring of octosyl acid is the activation of an olefin with an electrophilic species followed by trapping with the C3' hydroxyl group to form bond *a* (see *Fig. 4*). Electrophilic mercury and selenium species have been used to induce ring closure to construct the octosyl acid skeleton.

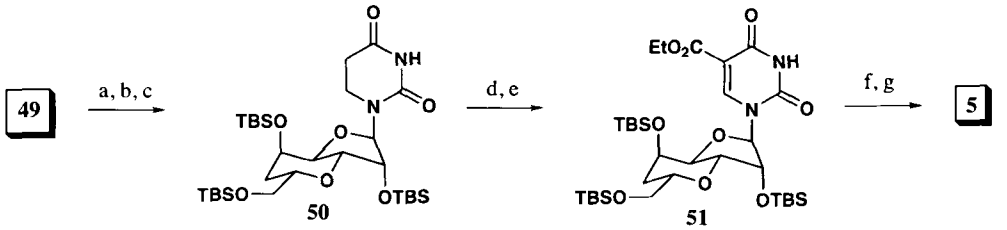
Shortly after Danishefsky's synthesis of octosyl acid,[15] Hanessian's group reported a total synthesis using an intramolecular oxymercuration reaction as the key ring-forming reaction.[21] Hanessian used uridine derivative **45** as starting material which alleviated the necessity of glycosylation subsequent to ring closure, but required modification of the uracil ring to incorporate the 5-carboxy moiety. Addition of allylmagnesium bromide to a cold solution of aldehyde **45** in THF proceeded selectively to give alcohol **46** in 70% yield (*Scheme 9*). This reaction incorporated all of the necessary carbons of the octosyl acid skeleton. Sequential benzyloxymethyl (BOM) protection of the free hydroxyl group and the uracil nitrogen followed by acetonide removal gave diol **47**, ready for cyclization. In the event, stirring **47** with mercuric acetate for 36 hours followed by addition of NaBr gave isolable organomercury compound **48** along with a minor amount of a separable diastereomer. Oxidative demercuration ($NaBH_4$, O_2 gas) gave alcohol **49** in a respectable 54% yield in two steps.



a) AllylMgBr, THF, -100°C 70%; b) BOMCl, DBU, DMF, 94%; BOMCl, *i*Pr$_2$NEt, THF, 70°C; c) HOAc, aq. THF, 65°C, 70%; d) Hg(OAc)$_2$, THF, 36h; NaBr; e) NaBH$_4$, O$_2$, DMF, 54%, two steps.

Scheme 9

With the furopyran ring system constructed, the remainder of the synthesis focused on installation of the 5-carboxy group and oxidation of the C8' carbon (*Scheme 10*). Removal of the BOM groups, saturation of the uracil ring and persilylation gave compound **50**, ready for introduction of the 5-carboxy group. α-Deprotonation with LDA and quenching with ethyl chloroformate gave the C5 ester as a mixture of diastereomers (not shown). A selenation-oxidation-elmination sequence then re-introduced the uracil alkene as seen in structure **51**. After removal of the silyl ethers, the primary alcohol at C8' was selectively and cleanly oxidized with platinum oxide to yield a carboxylic acid which was saponified to give the natural product. Despite the need for modification of the uracil ring, this work was a concise solution to the octosyl acid problem.

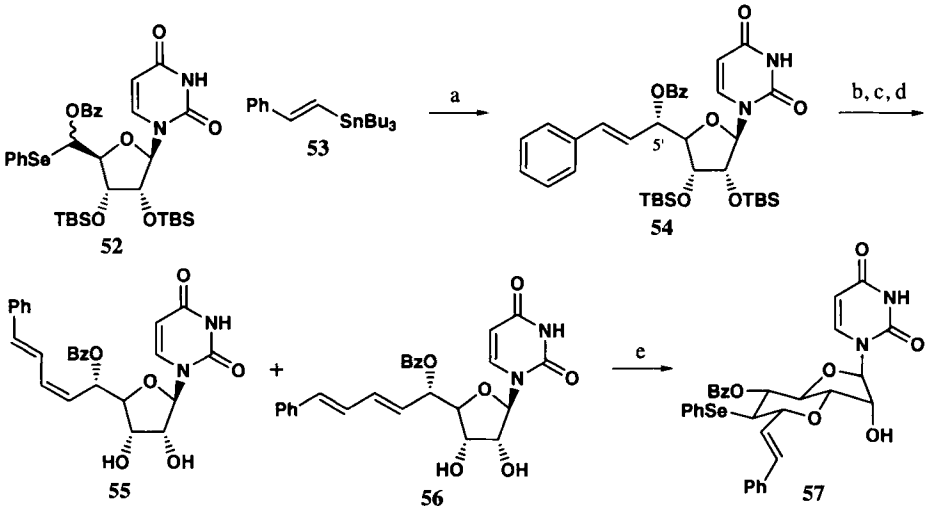


a) H$_2$, Pd(OH)$_2$/C, MeOH, 99%; b) 5% Rh/alumina, MeOH, 99%; c) TBSCl, *i*Pr$_2$NEt, DMAP, DMF 68%; d) LDA, THF; ClCO$_2$Et; e) PhSeCl, pyr; H$_2$O$_2$, 88%; f) TBAF, THF, 97%; g) PtO$_2$, NaHCO$_3$, H$_2$O, 90°C; LiOH/H$_2$O; Dowex H$^+$ resin, 70%, three steps.

Scheme 10

In 1998, a team of Japanese workers reported a synthesis of a protected derivative of nikkomycin Sz, the uracil analog of octosyl acid.[22] Their approach relied on a stereoselective

radical vinylation to establish the C5' stereochemistry and a selenoetherification of a conjugated diene to construct the bicyclic ring system (*Scheme 11*). The radical vinylation was carried out on selenoacetal **52**; irradiation of a benzene solution of **52**, styryl stannane **53**, and hexabutylditin

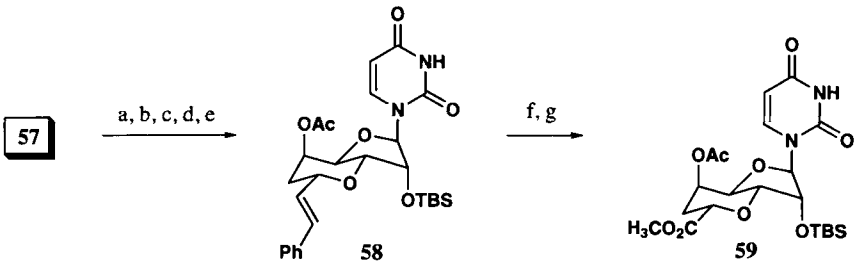


a) $(Bu_3Sn)_2$, hv, PhH, RT; b) OsO_4, $NaIO_4$, quant.; c) PPh_3=CHCH=CHPh, THF, 0°C; d) desilylation, quant. e) 2 eq. PhSeCl, 20:1 CH_2Cl_2/MeCN, 0°C, 75%.

Scheme 11

gave protected alcohol **54** as a single diastereomer. The high selectivity is notable, but the stereochemistry obtained at C5' is opposite to that found in the natural product. While **54** could be cyclized cleanly with PhSeCl (not shown), it was found more advantageous to convert **54** to conjugated dienes **55** and **56** *via* a sequence of Johnson-Lemieux oxidation, Wittig reaction and desilylation. Interestingly, exposure of either **55** or **56** to PhSeCl gave the same isomer of cyclized product **57** in 75% yield. The authors propose that the intermediate selenonium ion undergoes bond rotation prior to ring closure, resulting in the production of the thermodynamically favored isomer **57**.

After protection of the C2' hydroxyl (conditions not provided), the selenophenyl group was removed *via* triethylborane-initiated radical reduction (*Scheme 12*). Protecting

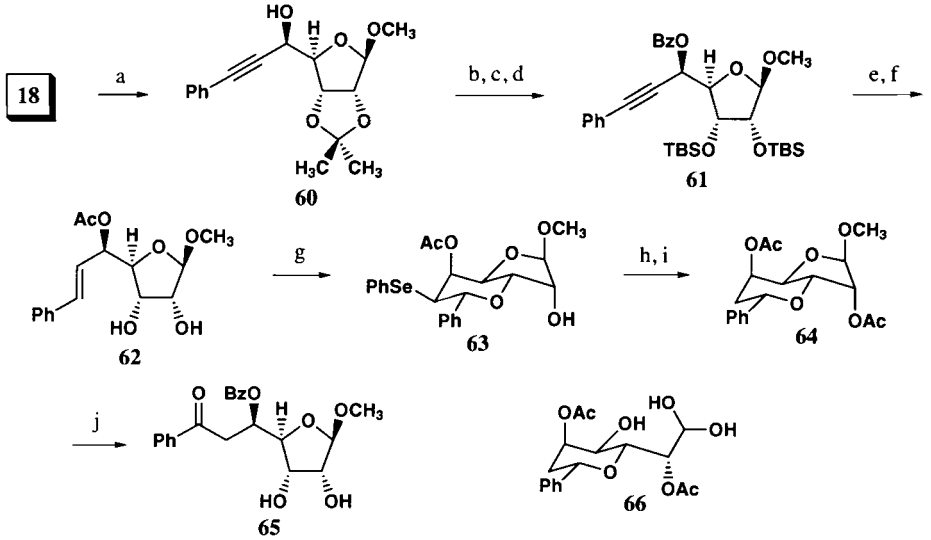


a) silylation, 79%; b) Bu_3SnH, Et_3B, O_2, -78°C, 90%; c) TBAF; TBSCl, imid., DMF, 60°C; NaOMe/MeOH; d) $ClCH_2SO_2Cl$, pyr, quant.; e) CsOAc, 18-c-6, PhH, reflux, 76%; f) OsO_4, $NaIO_4$, aq. dioxane, 76%; g) PDC, MeOH/DMF

Scheme 12

group manipulations gave an equatorial C5' alcohol (not shown) which was converted to its chloromethanesulfonate ester and then exposed to cesium acetate and 18-crown-6 in refluxing benzene to give axial acetate **58** in good overall yield. Oxidative cleavage of the olefin followed by pyridinium dichromate (PDC) oxidation in methanol/DMF gave methyl ester **59**, a protected derivative of nikkomycin S_z.

Recently, More and Finney reported a similar selenoetherification approach to the synthesis of the octosyl acid ring system.[23] Using an extension of Carreira's zinc acetylide methodology, ribosyl aldehyde **18** was homologated with complete reagent-controlled diastereoselectivity to give alcohol **60** (*Scheme 13*).



a) PhCCH, NEt_3, (-)-N-Methylephedrine, $PhCH_3$; b) BzCl, NEt_3, DMAP, 92%; c) Bio-Rad 50W H^+ resin, MeOH, 70°C, 53% anomer shown; d) TBSOTf, 2,6-lutidine, 96%; e) $LiAlH_4$, THF, 50°C then Ac_2O, DMAP, 82%; f) TBAF, THF, 92%; g) PhSeCl, $NaHCO_3$, CH_2Cl_2, RT, 41%; h) Ac_2O, NEt_3, DMAP, 92%; i) $(CH_3Si)_3SiH$, AIBN, $PhCH_3$, 110°C, 90%; j) $RuCl_3/NaIO_4$ (**65**) or $RuCl_3/HIO_4$ (**66**)

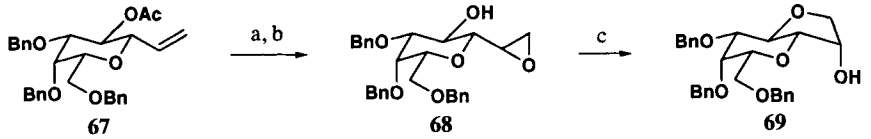
Scheme 13

Protection as a benzoate ester, removal of the acetonide and separation of the resulting anomers gave a diol which was protected as *bis*(*tert*-butyldimethylsilyl) ether **61**. Treatment of **61** with excess $LiAlH_4$ in warm THF reduced the benzoate and the alkyne, presumably *via* alkoxide assisted hydroalumination and hydrolysis of the intermediate vinyl aluminum species. Acylation and removal of the silyl ethers gave intermediate **62**, poised for cyclization. Under optimized conditions, treatment of **62** with PhSeCl and a large excess of $NaHCO_3$ gave cyclic ether **63** in a reproducible 41% yield along with recovered starting material. The HCl liberated from the reaction of the olefin and PhSeCl decomposed the starting olefin if the reaction medium was not buffered. Acylation of the C2' alcohol followed by removal of the selenophenyl group with excess *tris*(trimethylsilyl)silane and catalytic 2,2'-azobis(2-methylpropionitrile) (AIBN) in refluxing toluene gave **64**. Unfortunately, all attempts to oxidize the aromatic ring in **64** to a

carboxylic acid resulted either in acid mediated opening of the 5-membered ring to give **66** or benzylic oxidation followed by hemi-acetal opening to give **65**. Potential adaptation of this route to the synthesis of **5** would require substitution of the phenyl ring in **64** with a more readily oxidized (electron-rich) aryl ring. Although the diastereoselective acetylide addition and seleno-etherification reactions led to a rapid construction of compound **64**, the ultimate failure of this route once again highlights the sensitivity of the strained bicyclic framework of the furanopyranyl natural products.

3. Miscellaneous

In an early effort, Hanessian *et al.* synthesized a simple octosyl acid model system starting from D-galactose derived C-glycoside **67**.[24] This study is the only one directed towards octosyl acid that starts with a 6-membered ring and annulates the five-membered ring of the furopyran system (*Scheme 14*). Methanolysis of the acetate in **67** followed by epoxidation of the olefin with *m*-chloroperoxybenzoic acid (mCPBA) gave **68** in good yield. Cyclization to **69** was accomplished cleanly by refluxing hydroxy-epoxide **68** in 1,2-dichloroethane (DCE) containing a small amount of camphorsulfonic acid (CSA). Despite the fact that **69** lacks oxygenation at C1', its synthesis was a significant early accomplishment in the field of octosyl acid synthesis.

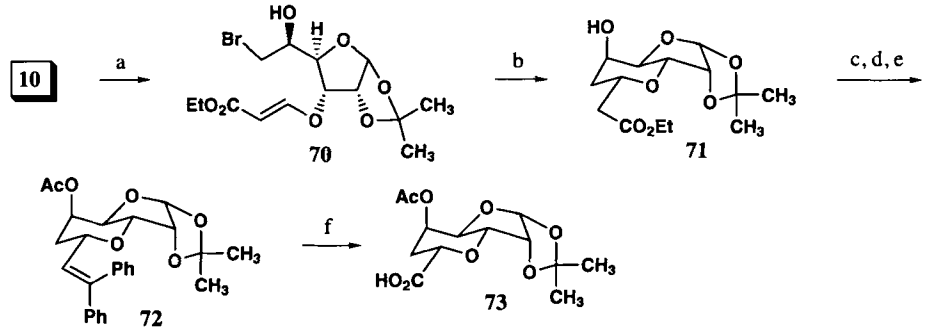


67 **68** **69**

a) NaOMe/MeOH; b) mCPBA, CH_2Cl_2, RT, 75%; c) CSA, DCE, Δ, 61%

Scheme 14

In 1989, Araki and co-workers demonstrated that the octosyl acid ring system could be constructed *via* cyclization of an alkyl radical to an olefin.[25] Slow addition of tributyltin hydride to a refluxing solution of AIBN and bromide **70** (synthesized in a few steps from **10**) yielded the bicyclic structure **71** in a very respectable 80% yield (*Scheme 15*). It is noteworthy that cyclization



70 **71** **72** **73**

a) 3 steps no yield given; b) Bu_3SnH, AIBN, PhH, reflux, 80%; c) excess PhMgBr. 88%; d) Ac_2O, pyr, 98%; e) $SOCl_2$, pyr, 56%; f) RuO_2, $NaIO_4$, 68%

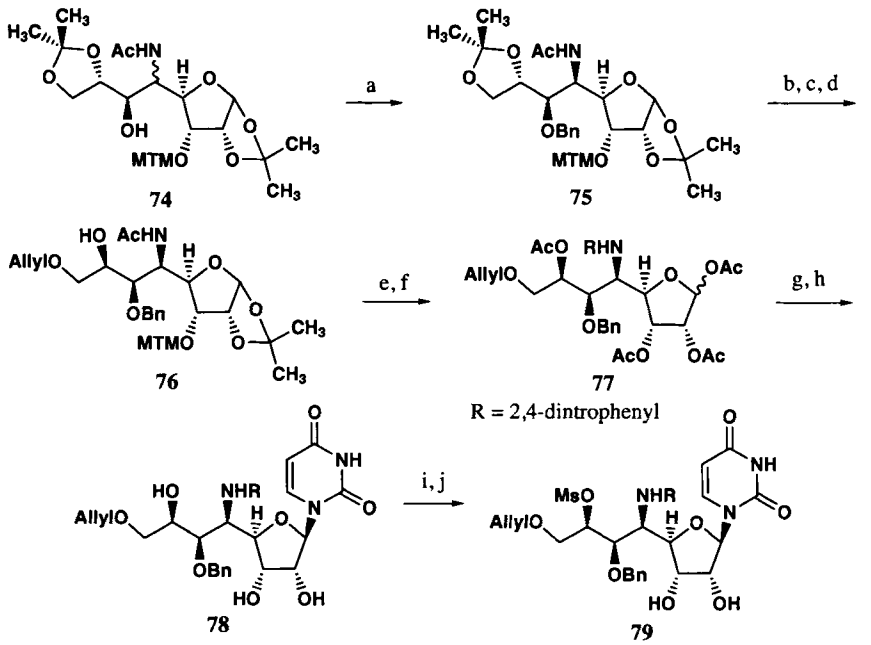
Scheme 15

to the somewhat strained ring system is faster than direct reduction of the C6' carbon radical. To complete the synthesis of **73**, a model system for octosyl acid, it was necessary to remove a carbon from the side chain at C8'. This was accomplished in four steps by first reacting ester **71** with excess PhMgBr to give a diol, which was selectively acylated at the secondary alcohol. Reaction of the tertiary alcohol with $SOCl_2$ and pyridine gave olefin **72**, which upon oxidative cleavage gave acid **73** in 68% yield. Although this radical methodology gave a rapid build up of the octosyl acid core, no further studies were reported. Esterification of compound **73** would give Knapp's intermediate **39** and thus constitute a formal synthesis of **5**.[20]

II. EZOMYCIN A_1

The ezomycin antibiotics possess structural complexities that make them much more difficult synthetic targets than octosyl acid A. These features include a C5' urea, a C6' axial hydroxyl group that is glycosylated with an ezoaminuroic acid moiety and (in some cases) a cystathionine attached *via* an amide linkage. Additionally, ezomycins in the B, C, and D series are C-glycosides. No member of the ezomycin family has yet succumbed to synthesis, although their potent antifungal activity and unusual structures have inspired many attempts. Three groups have reported syntheses of model systems of varying complexity most closely resembling ezomycin A_1 (**1**) or A_2 (**2**). Considering just the bicyclic core of the ezomycins, many of the challenges are similar to the issues faced in the synthesis of **5**. However, two of the three synthetic studies described below used very different tactics than those used most often in the octosyl acid series.

Contemporaneously with their studies on octosyl acid, the Suami group reported the synthesis of a protected version of the core aglycone of ezomycin A_1.[26] As in their previous studies, a convergent, but stereorandom Henry reaction was used to link a ribose derived nitrosugar with a glyceraldehyde derivative and the six-membered ring portion of the furopyran system was constructed using intramolecular alkylation (*Scheme 16*). Union of L-glyceraldehyde acetonide and **27**, followed by reduction and acylation (not shown) gave **74** as a mixture of diastereomers. O-Benzylation of **74** and chromatography gave **75** as a single isomer with the proper stereochemistry at C5'. Acetonide hydrolysis, selective allylation and epimerization gave **76**, where all of the hydroxyl groups had been differentiated. Basic hydrolysis of the N-acetyl group in hot, aqueous dimethoxyethane (DME) gave a free amine (not shown) which was protected as a 2,4-dinitrophenyl (DNP) amine in 96% overall yield. Removal of the methylthiomethyl (MTM) and acetonide protecting groups with aqueous trifluoroacetic acid (TFA) gave an intermediate triol which was prepared for introduction of the nucleoside base *via* conversion to the tetraacetate **77**. Subjection to standard Vorbrüggen conditions with *bis*-(trimethylsilyl)uracil followed by basic methanolysis gave **78** in 92% yield. A sequence of acetonide protection, mesylation, and acetonide removal produced **79**.

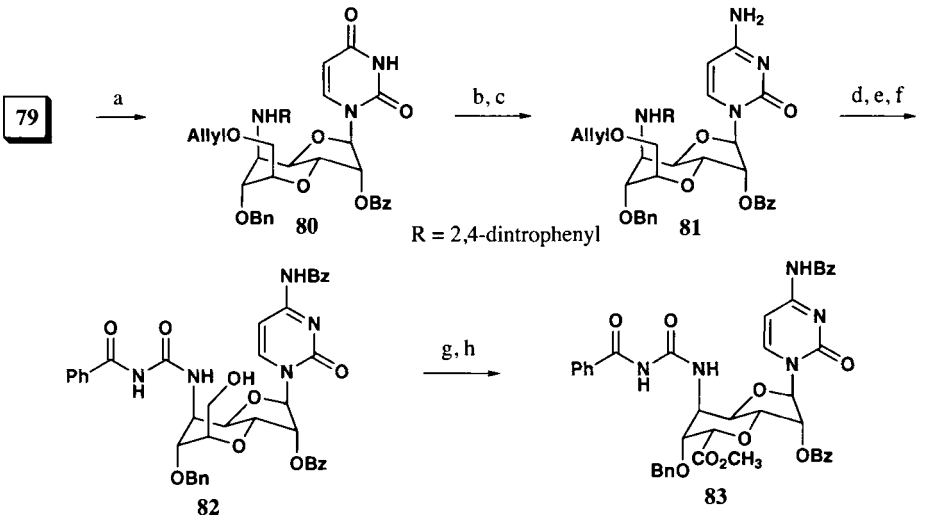


a) BnBr, NaH, DMF, 49% desired epimer; b) aq. HOAc, 91%; c) AllylBr, NaH, 65%; d) MsCl, pyr; NaH, DMF; SiO_2, 97%; e) NaOH, aq. DME; 2, 4-dinitrofluorobenzene, NEt_3, THF, 96%; f) aq. TFA; Ac_2O, pyr, 82%; g) *bis*(TMS)uracil, TMSOTf, CH_3CN, 92%; h) NaOMe/MeOH; i) DMP, pTsOH, DMF; j) MsCl, pyr; aq. TFA, 82%. DMP = 2,2-dimethoxypropane

Scheme 16

Stirring mesylate **79** in DMSO with NaH effected bicyclization to give compound **80** cleanly, although the C7' stereochemistry in **80** is opposite to that of the natural product (*Scheme 17*). After protection of the C2' hydroxy group as a benzoate, the uracil ring was converted to a cytosine (**81**) *via* treatment with oxalyl chloride and a catalytic amount of DMF followed by methanolic ammonia. After removal of the DNP group with basic ion-exchange resin, a urea (not shown) was installed in mediocre yield (31%) *via* treatment with sodium cyanate and acetic acid. The distal urea nitrogen and the cytosine amine were then converted to benzamides and the allyl ether removed with selenium dioxide in hot dioxane to produce **82**. A Jones oxidation-esterification sequence on the primary alcohol gave a methyl ester (not shown) in 47% overall yield from **82**. With the proper oxidation state at C7', the stereocenter could be inverted *via* the enolate by stirring with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) for 2 days. Although produced by a long sequence, **83** is a protected version of the core of ezomycin A_1.

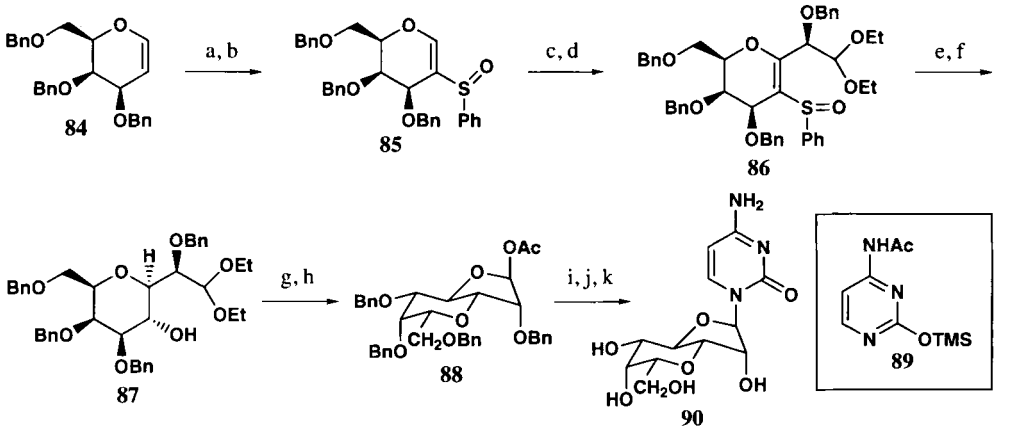
In 1990, Schmidt and co-workers reported the synthesis of compound **90**, a model for the bicyclic system of ezomycin A_1.[27] Although **90** lacks several key elements of ezomycin A such as the carboxylic acid at C8' and the urea at C5', it does contain the *trans*-fused core (*Scheme 18*). Schmidt's approach differed from that of Suami's in that the six-membered ring was forged first, followed by the 5-membered ring. The main carbon-carbon bond forming reactions of this



a) NaH, DMSO, 87%; b) BzCl, pyr, 98%; c) $(COCl)_2$, cat. DMF; NH_3/MeOH, 5 days, 80%; d) Amberlite OH resin, acetone/MeOH; aq. HOAc, NaOCN, 31%; e) BzCl, pyr, 62%; f) SeO_2, HOAc, dioxane, 73%; g) CrO_3, acetone, H_2SO_4; MeOH, HCl, reflux, 47%; h) DBU, RT, 2 days; HOAc, 60%.

Scheme 17

synthesis relied on the novel use of a 2-phenylsulfinyl glycal as a progenitor to a nucleophilic carbanion. Tri-(O-benzyl) galactal **84** was converted into the 2-phenylsufinyl derivative **85** *via* chlorosulfenation/elimination followed by peracid oxidation (mixture of diastereomers at sulfur).



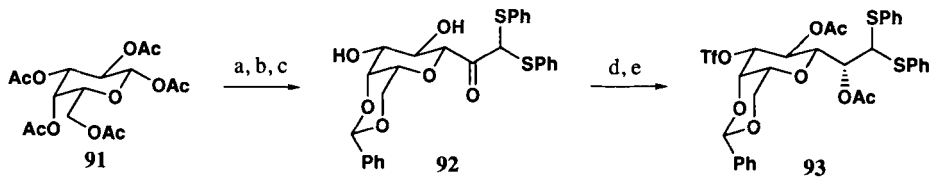
a) PhSCl, CCl_4; DBU, 50°C, 34%; b) mCPBA, CH_2Cl_2, 98%; c) LDA, HMPT/THF, -90°C, glyoxal monodiethylacetal; d) BnBr, NaH, DMF, 85%; e) Ra-Ni, THF, 81%; f) BH_3SMe_2, THF; NaOH, H_2O_2, 67%; g) aq. TFA, $CHCl_3$, 78%; h) Ac_2O, pyr, 79%; i) H_2, Pd/C;Ac_2O, pyr, 76%; j) **89**, TMSOTf, 53%; k) NH_3/MeOH, 80%.

Scheme 18

Lithiation with LDA followed by addition of glyoxal monodiethylacetal gave a virtually stereo-random mixture of alcohols; the stereocenters on the carbanion influenced the stereochemical outcome of the reaction to a very small extent. The secondary carbinol (not shown) was

protected as a benzyl ether to give **86** and the sulfoxide group, having served its purpose, was removed with Raney nickel. Hydroboration-oxidation of the derived enol ether (not shown) was highly regio- and stereoselective, giving the galacto-C-glycoside **87** in 67% yield. Acidic hydrolysis of the diethylacetal gave an aldehyde, which upon treatment with acetic anhydride, yielded the bicyclic ring system **88**. Hydrogenolysis of the benzyl groups followed by acylation gave a pentaacetate which was reacted with **89** to give an intact nucleoside. Removal of all five acyl groups with ammonia in methanol gave the final model compound **90**. Although compound **90** was constructed in only eleven steps from **84**, the low stereoselectivity in the synthesis of **86** and the lack of hydroxyl group differentiation in compound **88** conspire to make this route challenging for the synthesis of **1**.

Knapp and co-workers have reported the most advanced studies to date towards the ezomycins. Their synthesis of the bicyclic core was communicated in 1994 and resembled the work by Schmidt only in that D-galactose was the ultimate starting material. In the Knapp work, the hexose was an electrophilic bonding partner and the introduction of the C2' stereocenter was highly selective (*Scheme 19*).[28]

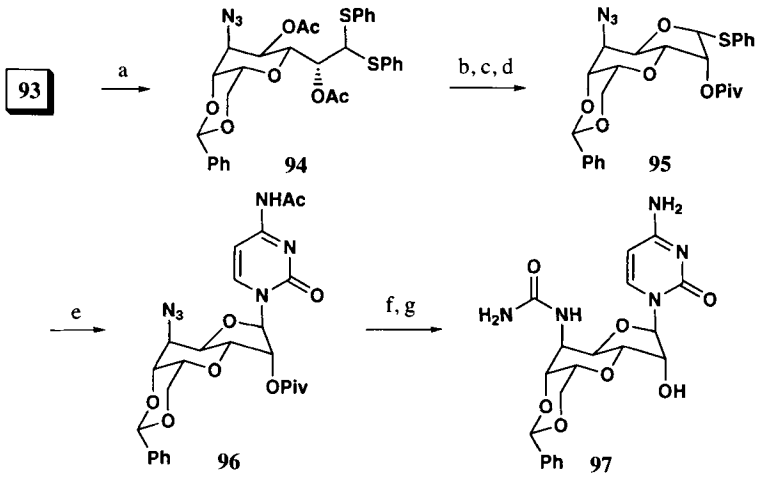


a) TMSCN, BF_3OEt_2; b) NH_3/MeOH; PhCHO, $ZnCl_2$, 92%; c) $(PhS)_2CHLi$, THF; aq. H_3PO_4, 78%; d) Tf_2O, pyr, CH_2Cl_2, 94%; e) DIBAL-H, THF, -78°C; Ac_2O, NEt_3, DMAP, 75%

Scheme 19

Galactosyl pentaacetate **91** was reacted with trimethylsilyl cyanide and BF_3•OEt_2 to give an anomeric nitrile which was protected as a benzylidene acetal *via* a high-yielding two-step sequence. Addition of [*bis*(phenylthio)methyl]lithium to the anomeric nitrile gave an imine which was hydrolyzed *in situ* to give ketone **92**. With all of the carbons of the bicyclic ring system in place, it was found that the C2' stereocenter could be introduced with high selectivity using substrate control. In the event, the C5' carbinol was converted to a triflate and the resulting hydroxyketone was exposed to a large excess (eight equiv) of diisobutylaluminum hydride (DIBAL-H) to give a single alcohol (not shown). Presumably, excess DIBAL-H is needed because one equivalent of the reducing agent forms an aluminum complex with the C4' alcohol (not shown). This complex effectively shields the front face of the ketone and allows for stereoselective reduction with another equivalent of DIBAL-H. Acylation of the intermediate alcohol gave **93**.

High-yielding S_N2 reaction with the organic soluble azide source nBu_4NN_3 introduced the nitrogen atom at C5' to give **94** (*Scheme 20*). Stirring **94** with ammonia in methanol gave a diol which was converted to furopyran **95** (NIS/TfOH) followed by protection with pivaloyl

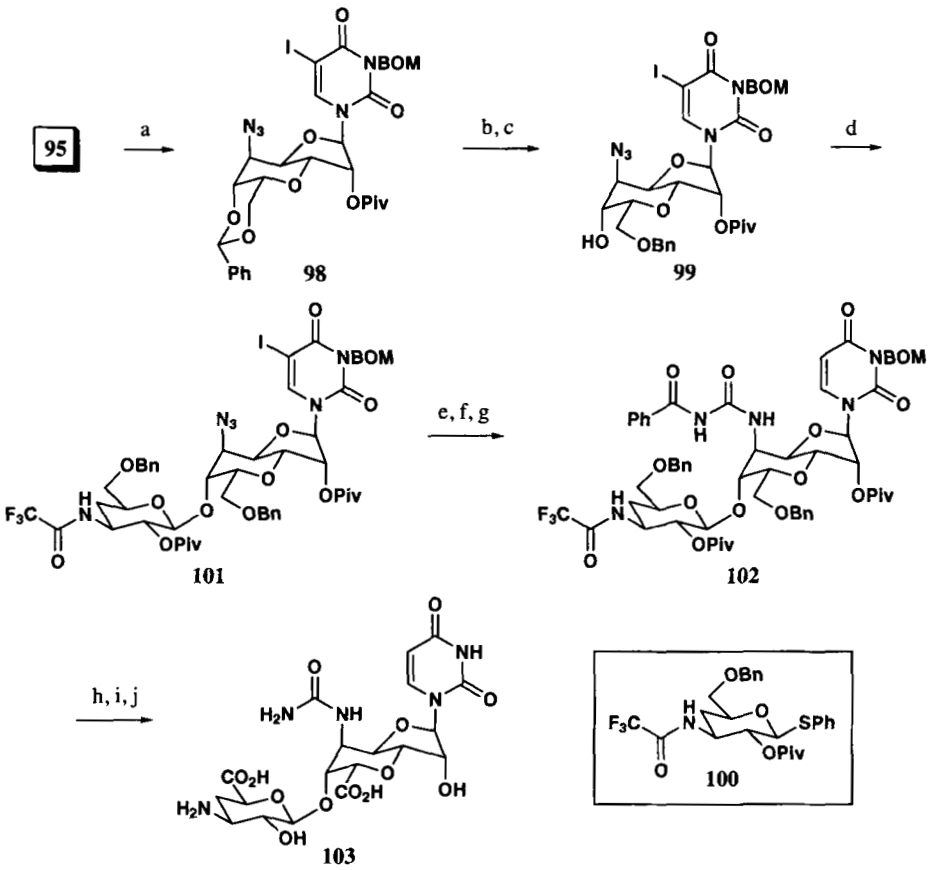


a) nBu_4NN_3, PhH, 95%; b) NH_3/MeOH; c) NIS, TfOH, 0°C, 73%; d) PivCl, pyr, DMAP, NEt_3, 99%; e) NIS, TfOH, **89**, RT, 95%; f) PMe_3, THF/H_2O, 93%; g) $Cl_3CCONCO$, CH_2Cl_2; $MeNH_2$/MeOH, 76%

Scheme 20

chloride. N-Acetylcytosine was incorporated *via* activation of the anomeric thioglycoside with NIS/TfOH followed by addition of *bis*(trimethylsilyl)-N-acetylcytosine **89** to give **96** in excellent yield. Finally, the C5' azide was converted to a urea *via* Staudinger reduction followed by sequential treatment with trichloroacetyl isocyanate and methylamine. Methylamine also removed the pivaloyl and N-acetyl groups to give model compound **97**. In relatively short order (15 steps from **91**), Knapp's group built an advanced intermediate towards ezomycin A_1.

In 2000, Knapp and Gore expanded on the work described above and reported a related model system which was the first to incorporate the ezoaminuroic acid glycoside.[29] Starting with thioglycoside **95**, a uracil ring was introduced using the NIS/TfOH methodology, and in the process the uracil ring was iodinated to give **98** (*Scheme 21*). After protection of the uracil imide nitrogen as a BOM ether, the benzylidene acetal was opened regioselectively to give a free secondary alcohol and a primary benzyl ether **99**. Activation of thioglycoside **100** with NIS/TfOH and nucleophilic trapping with alcohol **99** gave compound **101** with complete β-selectivity. A series of functional group manipulations was then carried out to complete the model system. The uracil iodine atom was removed by reduction, and the azide reduced with Lindlar's catalyst to give a crude amine which was reacted with benzoyl isocyanate to give compound **102** in 54% overall yield. The benzyl and BOM ethers, which survived two prior hydrogenations, were removed with Adams' catalyst and the liberated primary alcohols oxidized to the diacid with a two-step procedure. Finally, all of the protecting groups were removed with ammonia in warm methanol, and the final product was subjected to HPLC purification to give **103** in 65% overall yield. This chiral pool approach to **103** is the most advanced progress towards ezomycin A_1 reported to date and has several notable features. The plethora of Lewis basic groups present in the molecule was handled by selective manipulation of protecting groups



a) *bis*(TMS)uracil, NIS, TfOH, DCE, 73%; b) BOMCl, **37**, THF; c) $NaCNBH_3$, HCl, THF/Et_2O, 81%, two steps; d) 3.6 eq **100**, NIS, TfOH, DCE, 78%; e) H_2, Pd/C, EtOAc; f) H_2, Lindlar's catalyst, THF; g) PhCONCO, CH_2Cl_2, 54%, three steps; h) H_2, $Pd(OH)_2$/C, EtOAc/EtOH; i) $PhI(OAc)_2$, TEMPO, aq. MeCN; $NaClO_2$, NaH_2PO_4, isoprene, aq. *t*BuOH, 49%, three steps; j) NH_3/MeOH, 55°C, 65%

Scheme 21

and the use of thioglycoside methodology for the attachment of the uracil ring and the ezoaminouroic acid group. All that remains for the synthesis of **1** is the conversion of the uracil ring of **103** to a cytosine or the inclusion of a cytosine ring directly *via* glycosylation (vis-à-vis **95→98**).

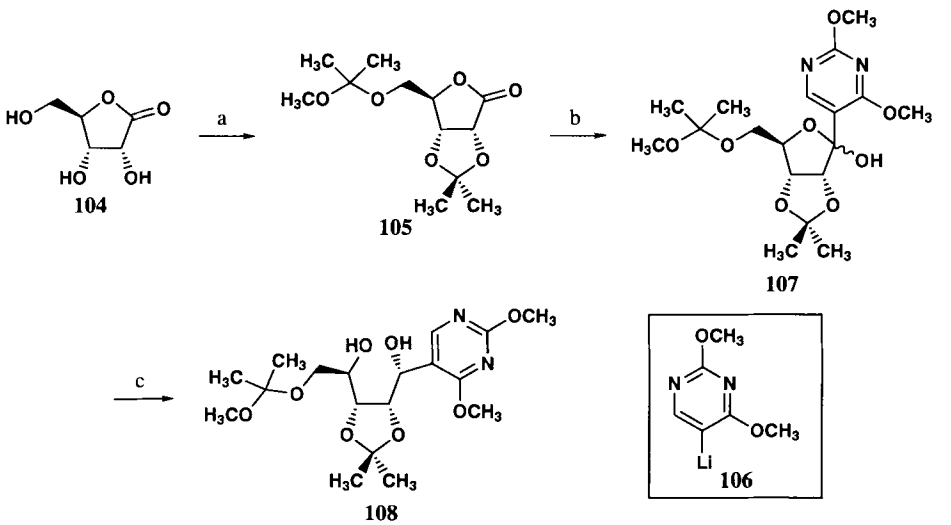
III. MALAYAMYCIN A

Malayamycin A (**7**) is the most recently discovered member of the pyrimidinal furopyran nucleosides. First reported in the patent literature,[6] **7** was isolated from *Streptomyces malaysiensis* and possessed fungicidal properties that may bode well for agrochemical applications. Structurally, **7** can be regarded as a hybrid between octosyl acid A and ezomycin A_1. Besides being a pseudo-uridine C-glycoside, **7** has one less carbon than the other furopyran

natural products, as it does not possess the carboxylic acid group at C7'. Malayamycin A also contains the C5' urea grouping common to the ezomycins but the methoxy substituent at C6' is epimeric to the hydroxyl group seen in the ezomycins. Despite some structural similarities, the strategy taken to synthesize **7** differs drastically from that of the other compounds discussed in this review.

1. Natural Malayamycin A

Hanessian communicated a total synthesis of malayamycin A in 2003,[30] followed by a full account three years later.[31] The synthesis, although highly linear, was stereoselective and efficient. The overall strategy was to construct the pseudo-uridine C-glycoside on a ribose template and then to annulate the six-membered ring. The main difficulties in the synthesis involved protecting group manipulations and stereoselective functionalization of the resulting dihydropyran. Reaction of D-ribonolactone **104** with dimethoxypropane in the presence of anhydrous sodium sulfate protected the diol as an acetonide and the primary alcohol as a mixed acetal (see **105,** *Scheme 22*). Stereoselective synthesis of the C-glycoside required a three-step procedure.

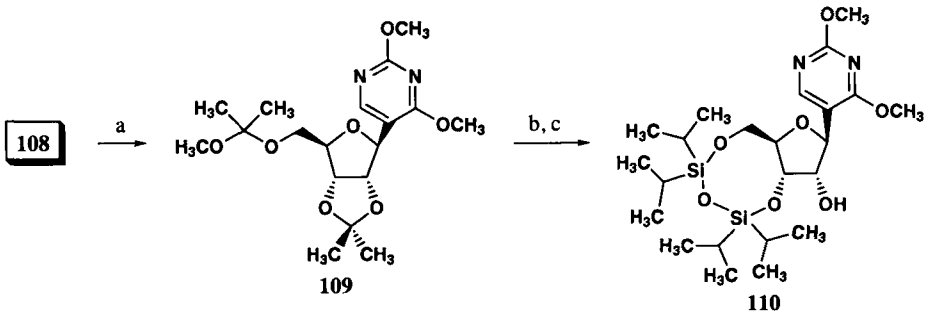


a) 2,2 dimethoxypropane, Na_2SO_4, PPTS, 94%; b) **106**, 75%; c) L-Selectride, $ZnCl_2$, CH_2Cl_2, 86%

Scheme 22

First, addition of organolithium reagent **106** to lactone **105** gave a mixture of lactol isomers **107**, which *via* ring-chain tautomerism, were in equilibrium with an open chain ketone (not shown). Reduction of this ketone with a mixture of L-Selectride® and $ZnCl_2$ gave primarily diol **108** *via* a chelation-controlled hydride addition. Finally, the tetrahydrofuran ring was reconstituted using a Mitsunobu-type intramolecular S_N2 reaction to give **109** in 91% yield (*Scheme 23*).

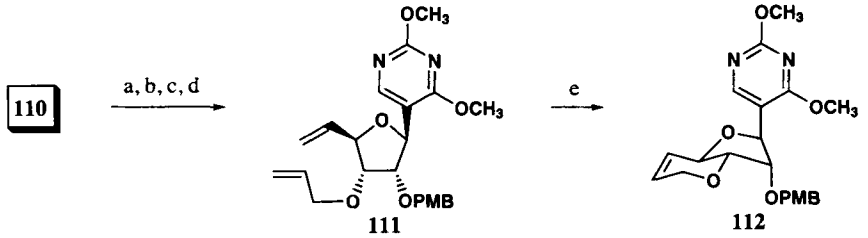
With the C-glycoside in place, the next task was construction of the six-membered ring. Appending olefinic substituents on the C3' and C5' alcohols, removal of the acetonide and



a) DIAD, PPh_3, THF, 91%; b) 70% HOAc, 85%; c) 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane, pyr, 89%

Scheme 23

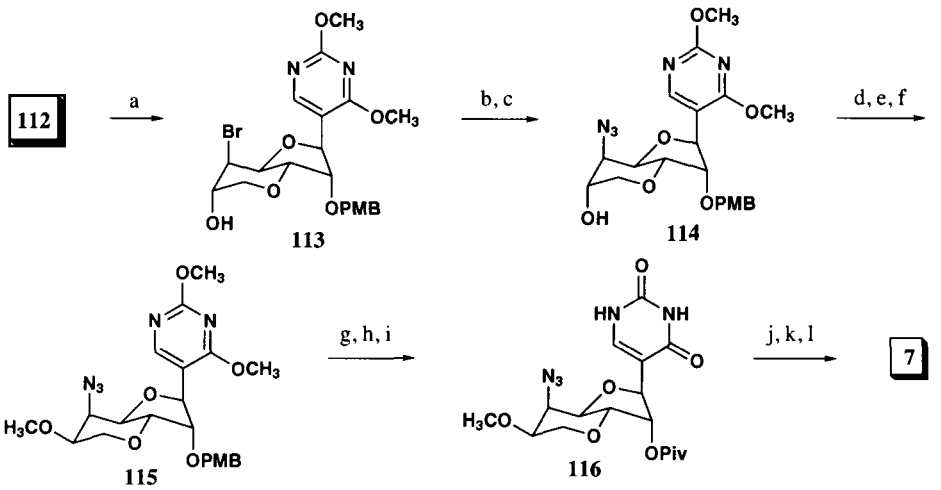
protection of the C3' and C5' hydroxyl groups as a seven-membered disiloxane gave **110** (*Scheme 23*). Installation of a C2' OPMB group and mild acidic hydrolysis liberated the C5' hydroxyl to give an intermediate silanol (not shown), which was converted *via* a Swern-Wittig sequence to a C5'-C6' olefin (*Scheme 24*). O-Allylation gave **111**, and exposure of **111** to the Grubbs first-generation catalyst under high-dilution conditions gave cyclic olefin **112** in 89% yield.



a) NaH, PMBBr, DMF/THF, 84%; b) 1N HCl, dioxane, 88%; c) DMSO, $(COCl)_2$, *i*-Pr_2NEt, CH_2Cl_2, Ph_3PCH_3Br, NaHMDS, THF, 36%; d) allylBr, NaH, DMF, 93%; e) $Cl_2RuCHPh(PCy_3)_2$, CH_2Cl_2, reflux, 89%.

Scheme 24

With the furopyran ring in place, the remainder of the synthesis focused on functionalization of the olefin in **112** to properly situate the *vic*-amino-alcohol substituents about the ring. A *cis*-oxyamination of olefin **112** (*Scheme 25*) was effected through the reaction of olefin **112** with N-bromosuccinimide (NBS) and H_2O to give bromohydrin **113** presumably *via* initial addition of NBS to the more hindered convex face of the bicyclic molecule followed by diaxial opening of the bromonium ion with water. Exposure of **113** to sodium hydroxide gave an epoxide which was opened regioselectively with sodium azide to give *trans*-hydroxy azide **114** in 41% over 3 steps. The hydroxyl group was inverted *via* an oxidation-reduction sequence and then methylated to give **115**. Exchanging the PMB group for a pivaloate ester was followed by decomposition of the *bis*(lactim ether) with *in situ* generated trimethylsilyl iodide (TMSI) to give pseudo-uridine **116**. Finally, Staudinger reduction, urea formation, and treatment with methylamine gave the natural product **7** in 60% yield in three steps. This work provided a convenient route to the C-glycoside framework of **7** and structural analogs.



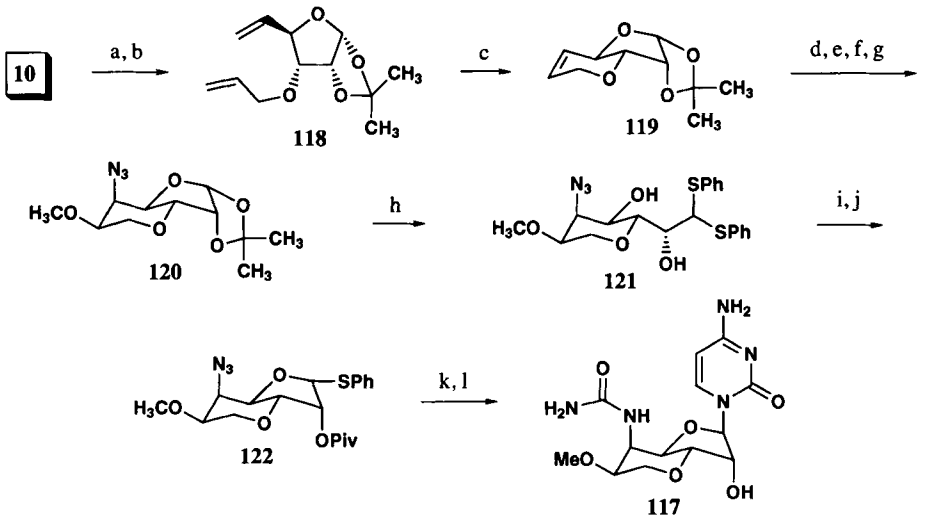
a) NBS, H_2O, THF; b) NaOH, THF; c) NaN_3, methoxyethanol, 41% 3 steps; d) Dess-Martin periodinane, CH_2Cl_2; e) $NaBH_4$, MeOH; f) NaH, MeI, DMF, 93% three steps; g) DDQ, H_2O/CH_2Cl_2, 84%; h) PivCl DMAP, NEt_3/pyr; i) TMSCl, NaI, MeCN, 42%, two steps; j) PMe_3, THF/H_2O; k) $Cl_3CCONCO$, CH_2Cl_2; l.$MeNH_2$/MeOH, 60%, three steps

Scheme 25

2. 1-Cytosinyl-N-malayamycin A

Upon completion of the synthesis of malayamycin A, the Hanessian group synthesized a number of analogs of **7** and tested them for fungicidal activity.[32] One such analog, 1-cytosinyl-N-malayamycin **117**, was found to be a potent fungicide, and was targeted for commercial development. In collaboration with workers at Syngenta Crop Protection, a large-scale synthesis of **117** was developed and reported in 2006.[33] The synthesis of **117** is greatly simplified compared to that of natural **7**, as the N-glycoside is much simpler to construct than the natural C-glycoside. Nonetheless, much of the methodology used in the synthesis of **117** overlapped with that in the synthesis of **7**.

Starting with commercially available **10** (*Scheme 26*), the C3' alcohol was allylated and the more labile acetonide was selectively removed to give a diol (not shown). Conversion to a dimesylate and reaction with NaI in hot dimethylacetamide (DMA) directly gave olefin **118** which was cleanly cyclized with 3.5 mole% of Grubbs first-generation catalyst to give **119**. A similar six-step sequence to that described above for the synthesis of **7** incorporated the *cis*-methoxy-azido functionality (**119→120**). It is notable that despite the structural and potential conformational differences between this system and the natural system, selectivity was quite high in all of the reactions. Installation of the cytosine ring and the urea group were accomplished using methodology similar to that from Knapp's ezomycin studies (*see Scheme 20*). The acetonide in **120** was first converted to a glycosyl donor *via* a four-step sequence. Treatment of **120** with excess thiophenol and acidic resin opened the furanose ring with subsequent elimination of acetone to yield dithioacetal **121**. Treatment of **121** with NIS at 0°C gave a thionium ion



a) allylBr, NaOH, $PhCH_3$; aq. HOAc, 84%; b) MsCl, NEt_3; NaI, DMA, 100°C, 93%; c) 3.5 mole% $Cl_2RuCHPh(PCy_3)_2$, CH_2Cl_2, reflux, 85%; d) NBS, H_2O, THF; NaOH, THF, reflux; e) NaN_3, methoxyethanol, 48%, three steps; f) Dess-Martin periodinane, CH_2Cl_2; g) $NaBH_4$, MeOH; NaH, MeI, THF, 56%, three steps; h) Amberlyst-15, PhSH, 84%; i) NIS, CH_2Cl_2, 70%; j) PivCl, pyr, DMAP, 100%; k) **89**, NIS, TfOH, RT, 96%; l) PMe_3, THF/H_2O; $Cl_3CCONCO$, CH_2Cl_2; $MeNH_2$/MeOH, 45%, three steps.

Scheme 26

which cyclized to give a thioglycoside (not shown) and protection as a C2' pivaloate ester gave **122**. Finally, glycosylation, azide reduction, and urea formation completed the synthesis of the malayamycin analog **117**.

CONCLUSIONS

The perhydrofuropyran pyrimidines have captivated the attention and inspired the creativity of synthetic chemists for nearly thirty years. Unabated synthetic activity in this area continues to produce interesting and important results. The ezomycins have not yet succumbed to synthesis and the ezomycins and malayamycin (and analogs) show promise as potential anti-fungal agents. The field of perhydrofuropyran pyrimidine synthesis should not be considered mature and will continue to be an active and fertile area of research.

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(Received November 28, 2006; in final form January 25, 2007)