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Recent progress in the synthesis of six-membered aminocyclitols (2008-2017)

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Dedicated to Prof. Gordon W. Gribble in honor of his lifetime contributions to organic synthesis

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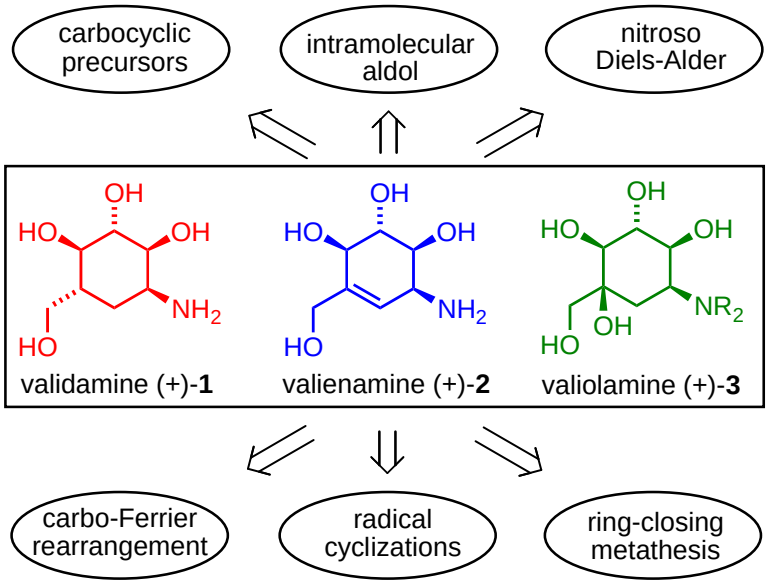
Abstract

Aminocyclitols are of interest as glucosidase inhibitors, as probes for the study of pseudoglycosyltransferases, and as potential therapeutics for the treatment of Gaucher's disease. The synthesis of these targets was reviewed in early 2008, and the aim of this review is to cover material relevant to the synthesis of aminocyclitols since that time. While not a focus of this review, biological evaluation of compounds will be presented where it is recorded in the literature.



Keywords: Aminocyclitols, stereoselective synthesis, ring-closing metathesis, cyclizations, chiral pool

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1. Introduction

As defined by Delgado,[1] aminocyclitols are "cycloalkanes containing at least one free or one substituted amino group and three additional hydroxyl groups on ring atoms". Examples of naturally occurring C7N aminocyclitols include validamine, valienamine, and valiolamine (**1**, **2**, and **3** respectively, Fig. 1) which exhibit α-glucosidase inhibitory activity. Validamine and valienamine both appear as subunits within the anti-fungal antibiotic N-linked pseudo saccharide validamycin A (**5**). Likewise, aminocyclitols lacking the hydroxymethylene sidechain, such as 2-deoxy-*scyllo*-inosamine (DOIA, **6**), are known biosynthetic intermediates in the production of 2-deoxystreptamine (2-DOS, **7**), a subunit of streptamine antibiotics such as kanamycin A (**8**).

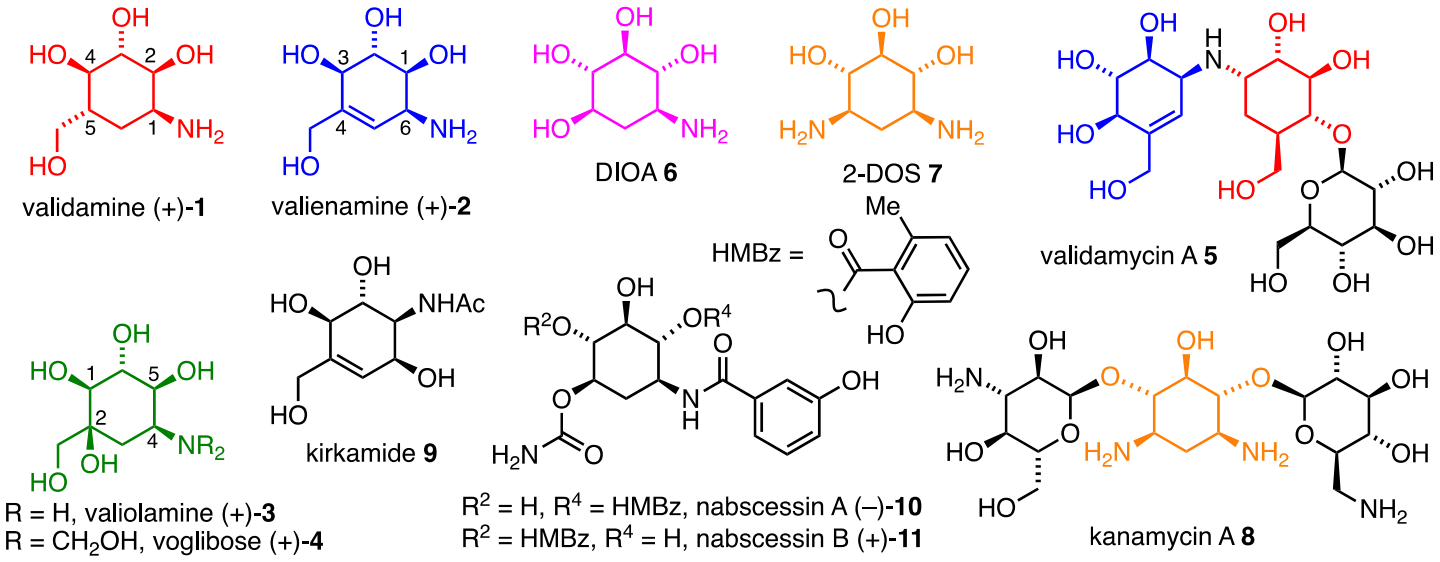


Figure 1. Structures of naturally occurring C_7 and C_6 aminocyclitols (CAS atom numbering).

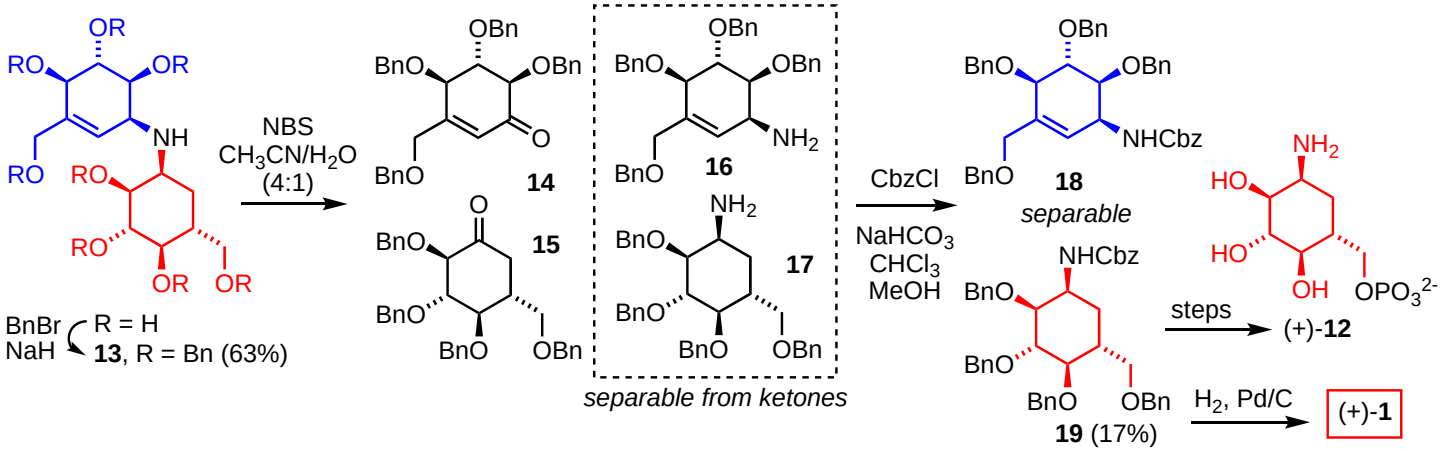
New aminocyclitols continue to be isolated, including kirkamide (**9**),[2] a positional isomer of valienamine, and nabscessins A and B (**10** and **11**).[3]

There are several excellent reviews[1,4-7] concerning aminocyclitols covering the literature through 2007 and a recent review reports on polyhydroxylated medium-ring carbocycles including larger ring aminocyclitols;[8,9] the reader is directed to these for literature prior to 2008. The present review will cover synthetic efforts toward six-membered aminocyclitols, excluding dihydroconduramines (4-amino-1,2,3-cyclohexanetriols), from 2008 to present. While not a focus of this review, biological evaluation of compounds will be presented where it is recorded in the literature.

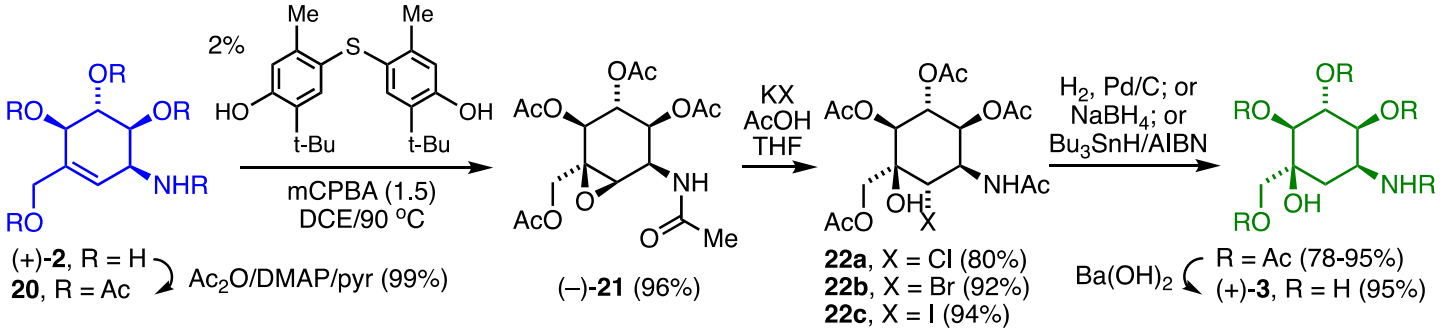
2. Preparation from 6-Membered Carbocycles

2.1 Degradation/semi-synthesis

As part of studies on validamycin A biosynthesis, Mahmud's group required validamine 7-phosphate (**12**, Scheme 1) as a substrate for pseudoglycosyltransferases.[10] To this end, they utilized the Ogawa NBS oxidative cleavage reaction[11] on perbenzylated validoxylamine A (**13**) to afford a mixture of ketones **14**/**15** and amines **16**/**17**, where the mixture of amines was separable from the ketones. Generation of the benzyloxycarbonyl protected amines allowed for their chromatographic separation. The minor product (**19**) could be further elaborated to (+)-**1** or to the desired 7-phosphonate (+)-**12**.



Scheme 1. Preparation of validamine 7-phosphate by degradation of validoxylamine A.



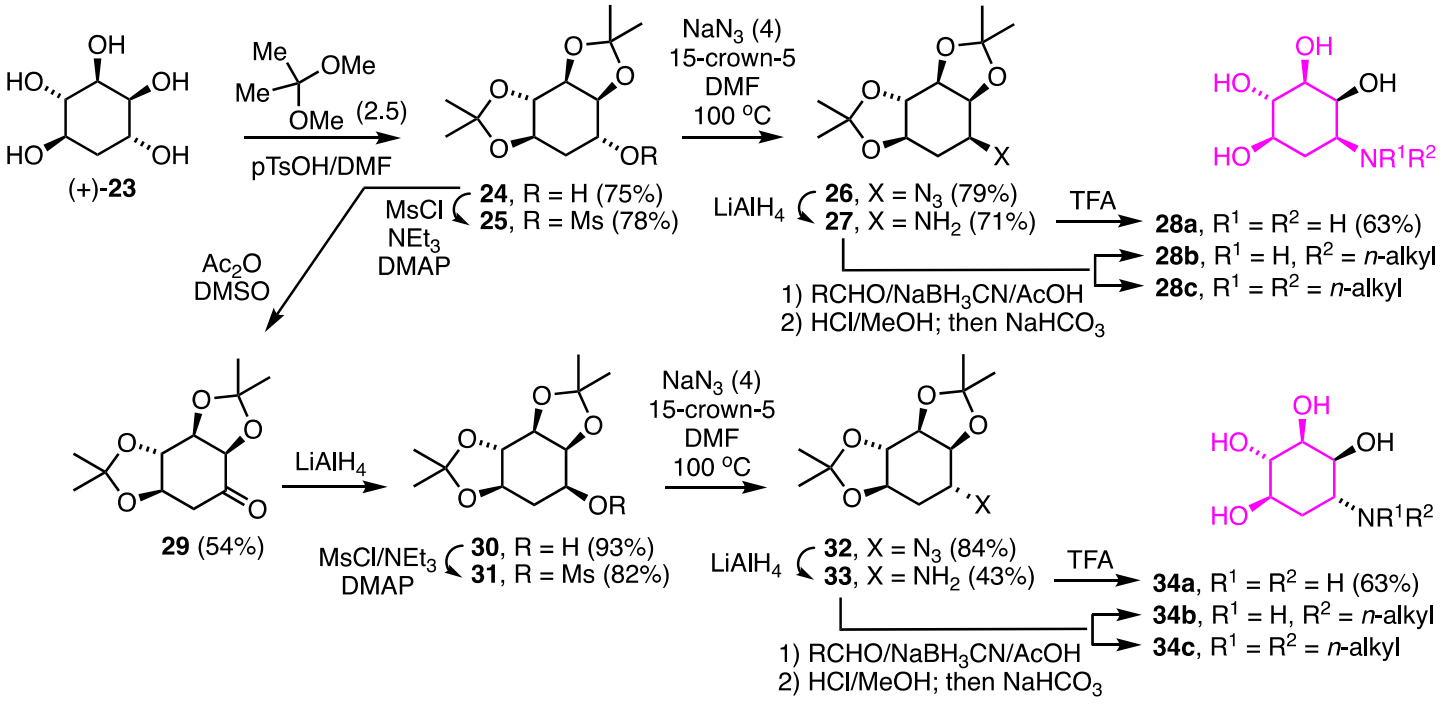
Scheme 2. High yielding conversion of valienamine into valiolamine.

Chen and co-workers reported a semi-synthesis of valiolamine from more abundant valienamine (Scheme 2).[12] Epoxidation of the tetraacetate amide (+)-**20** with mCPBA gave (–)-**21**. The yield of this reaction was nearly

doubled with 2% of radical inhibitor [4,4'-thiobis(6-*t*-butyl-*m*-cresol)]. The authors propose that the stereoselectivity for this epoxidation is directed by hydrogen bonding between the acetamido substituent and mCPBA. While attempted reduction of the epoxide was not productive, ring opening with potassium halides proceeded regioselectively to give the chloride, bromide or iodide **22a**, **b**, or **c** respectively. Reductive dehalogenation afforded protected valiolamine, which upon hydrolysis with $Ba(OH)_2$ afforded (+)-**3** (5 steps, 80.6% overall yield).

2.1 Chiral pool precursors

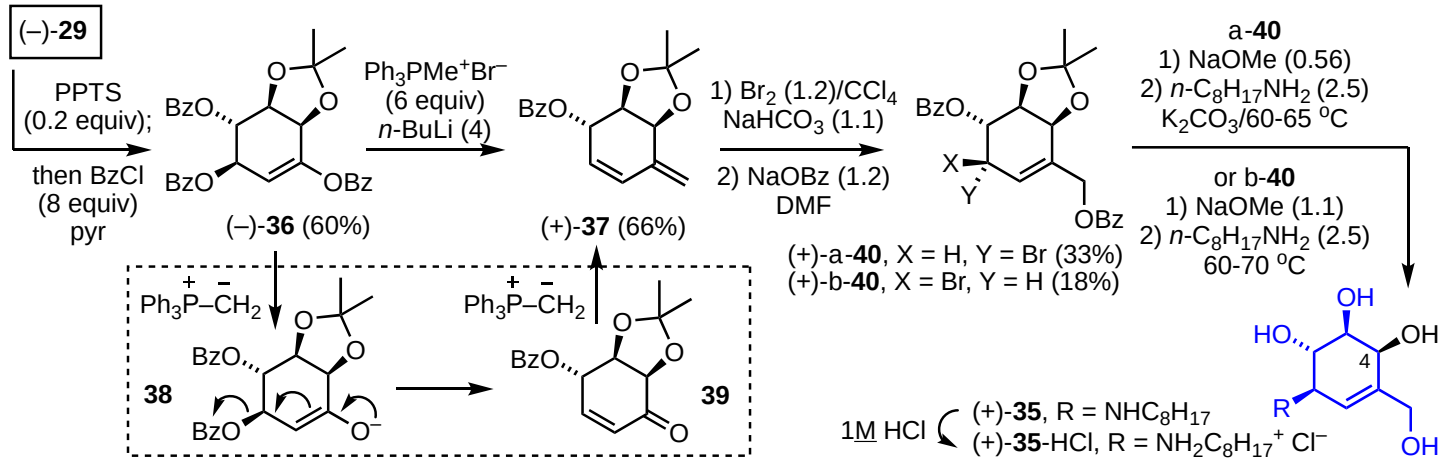
(+)-*proto*-Quercitol (**23**, Scheme 3) is a cyclohexanepentaol isolated from the stems of *Arfeuillea arborescens* (ca. 0.6 weight %). A racemic synthesis of (±)-**23** from the simple hydrocarbon 1,4-cyclohexadiene was reported in 1997.[13] Phuwapraisirisan and co-workers accomplished the synthesis of aminocyclitols from naturally occurring material (+)-**23**.[14] Selective bis-ketalization of **23** gave **24**, which also allowed for determination of its absolute configuration by NMR analysis of the *R*- and *S*-Mosher's esters. Generation of **28a** relies on S_N2 displacement of mesylate **25** by azide, followed by reduction and hydrolysis. Oxidation of **24** followed by stereocontrolled reduction gave the diastereomeric alcohol **30**, which was transformed into the diastereomeric aminocyclitol **34a** by a similar sequence of reactions. This group also prepared 2° and 3° amine derivatives **28b/c** and **34b/c** from the stereoisomeric protected aminocyclitols **27** and **33**, using standard reductive amination methodology.[15] The aminocyclitols **28a** and **34a** exhibit dramatically different inhibitory activity against α-glucosidase from Baker's yeast (**28a**, IC_{50} = 2890 μM; **34a**, IC_{50} = 12.5 μM), suggesting that the orientation of the amino functionality was essential for mimicking the oxocarbenium ion intermediate involved in the enzyme active site. The most potent 2° and 3° amines are **34b**, R = *n*-pentyl (IC_{50} = 0.24 μM) and **34c**, R = methyl (IC_{50} = 5.0 μM) and these were identified as competitive inhibitors.



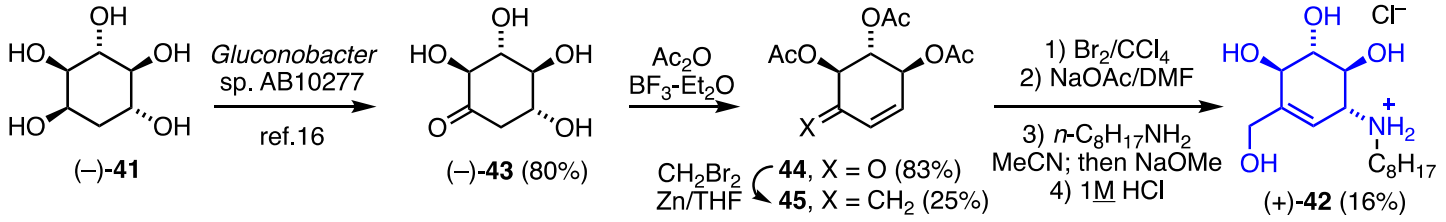
Scheme 3. Phuwapraisirisan synthesis of aminocyclitols.

Kuno, *et al.*, also utilized the bis-acetonide ketone **29**, derived from *proto*-quercitol, for the preparation of an *N*-octyl valienamine stereoisomer (**35**, Scheme 4).[16,17] Partial deprotection of the *trans*-acetonide, followed

by treatment with benzyl chloride gave the enol benzoate (–)-**36**. Treatment of **36** with excess methylene ylide afforded the exocyclic diene (+)-**37**. The authors propose[17] that this proceeds via addition–elimination at the enol benzoate carbonyl to generate the enolate anion **38** (see insert), which undergoes β-elimination to generate the enone **39**. 1,4-Addition of bromine to **37**, followed by displacement of the 1° bromide gave a separable mixture of allyl bromide epimers α-**40** and β-**40**; each epimer was separately transformed into the α-*N*-octylamine (+)-**35** by varying the equivalents of sodium methoxide. A similar strategy was used for the synthesis of *N*-octyl-β-valienamine (**42**) from (–)-*vibo*-quercitol (**41**) (Scheme 5).[16] Biooxidation of **41** with *Glactonobacter* sp. AB10277 was previously reported by Ogawa's group to afford (–)-**43**.[18] Acetylation of **43** proceeded with β-elimination to give the cyclohexenone **44**. While reaction of **44** with Wittig ylide lead to further elimination, reaction with the Nysted reagent gave the exocyclic diene **45**, albeit in attenuated yield. Transformation of **45** into **42** followed in a fashion similar to the preparation of **35**-HCl from **37**. The hydrochloride salt (+)-**35**-HCl exhibited inhibitory activity against bovine liver β-galactosidase, green coffee bean α-galactosidase, and almond β-glucosidase (IC_{50} = 4.5 μM, 4.5 μM and 8.1 μM respectively) but was relatively inactive toward α- and β-mannosidase and α-fucosidase (IC_{50} > 1 mM). In comparison, (+)-**42** was a more potent inhibitor of β-galactosidase (IC_{50} = 2.9 μM) than for β-glucosidase (IC_{50} = 47 μM).[16]



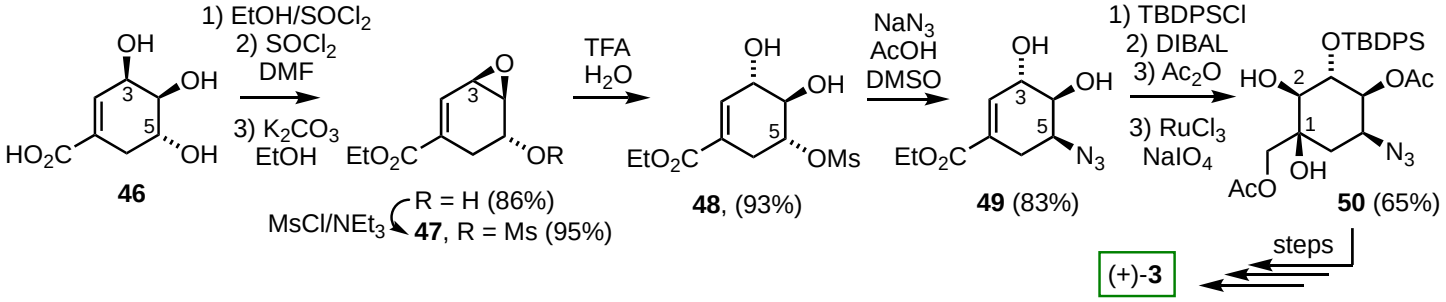
Scheme 4. Kuno synthesis of NOEV (*N*-octyl-*epi*-β-valienamine).



Scheme 5. Kuno synthesis of NOV (*N*-octyl-β-valienamine).

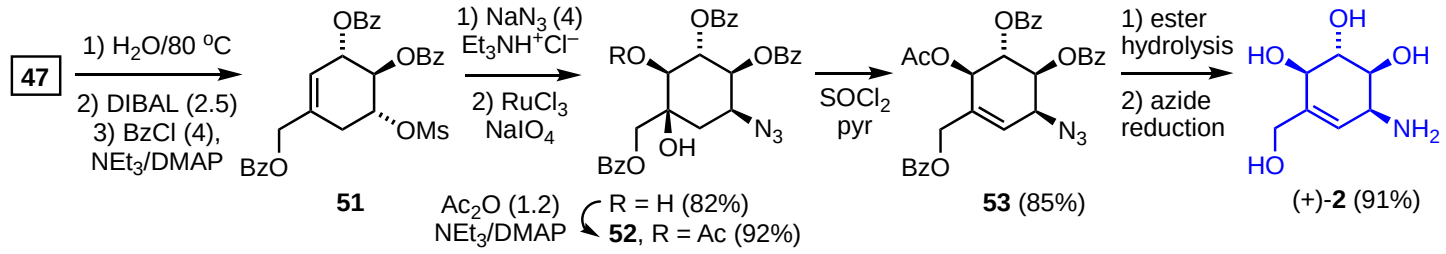
Shikimic acid (**46**), isolated from *Illicium verum* (Chinese star anise, 3-7%) or *Liquidambar styraciflua* (sweetgum fruit, 1.5%), has been used as a chiral pool precursor for the synthesis of a variety of targets, most notably the antiviral agent oseltamivir (tamiflu). Xiao-Xin Shi and co-workers utilized **46** for the synthesis of (+)-valiolamine (**3**, Scheme 6).[19] This sequence requires two inversions, at the C3 and C5 hydroxyl groups. The first inversion is achieved by hydrolysis of the epoxide **47** under acidic conditions to generate **48**. Regioselective nucleophilic attack of water occurs at the C3 position of the protonated epoxide due to allylic stabilization of

the partial positive charge. The second inversion proceeds via S_N2 displacement by azide ion of the C5 mesylate present in **48**. After reduction of the ethyl ester and hydroxyl group protection, the C1 and C2 hydroxyl groups were introduced by Ru catalyzed oxidation. This occurred stereoselectively on the olefin face opposite to the sterically bulky TBDPS ether group. Further functional group manipulation and deprotection afforded (+)-**3**.



Scheme 6. Shi synthesis of (+)-valiolamine from shikimic acid.

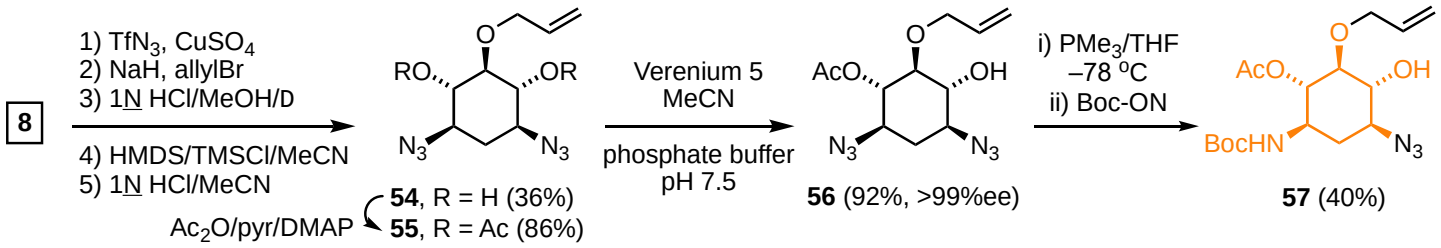
Shi's group also utilized shikimic acid as a precursor for the preparation of (+)-valienamine (Scheme 7).[20] In a fashion similar to their synthesis of valiolamine, hydrolysis of the epoxide **47** and S_N2 displacement by azide generate the required C3 and C1 stereocenters respectively (valienamine numbering). Furthermore, asymmetric Ru-catalyzed dihydroxylation establishes the C-4 alcohol functionality. Finally, dehydration of the tertiary alcohol of **52** was achieved using thionyl chloride to give **53**.



Scheme 7. Shi synthesis of (+)-valienamine from shikimic acid.

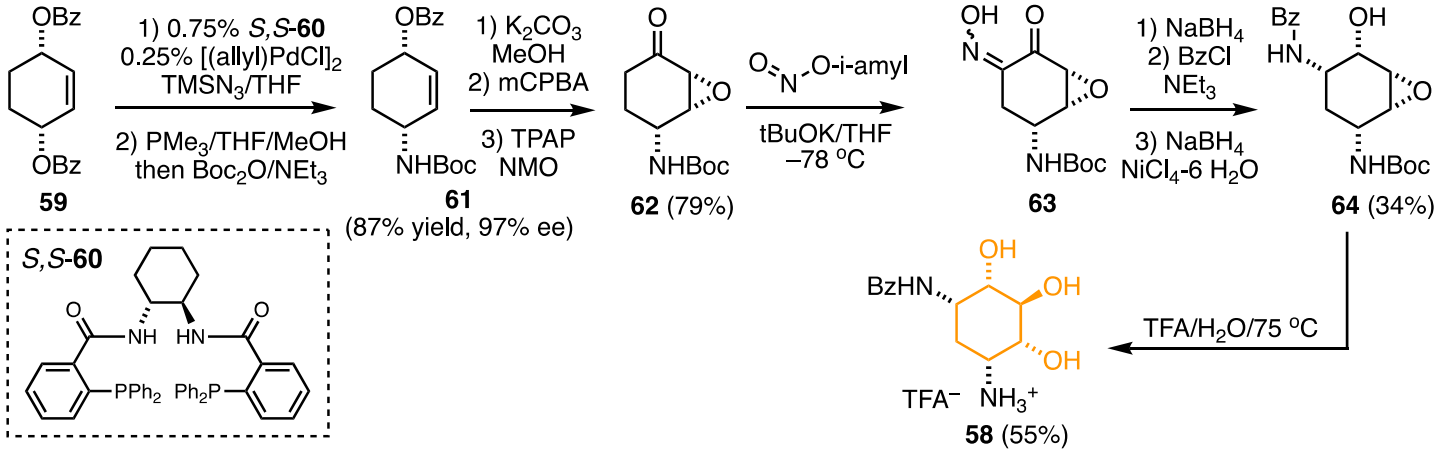
2.2 Achiral/meso precursors

The van Delft group reported the synthesis of an optically active, orthogonally protected 2-deoxystreptamine synthon which utilized an enzymic desymmetrization (Scheme 8).[21] The meso diacetate **55** was obtained by degradation of kanamycin A (**8**). This involved diazotransfer using triflyl azide, exhaustive allylation of the free hydroxyl groups, and acidic methanolysis of the glucoside linkages. Chromatographic separation of the desired 1,3-diazido-1,3-dideamino-5-*O*-allyl-2-deoxyptreptamine (**54**) and the resultant methyl glucosides was challenging. However reaction with TMS and HMDS afforded the bis-TMS derivative of **54**, the chromatographic separation of which from the methyl glucosides was considerably easier. Acidic hydrolysis of the bis-TMS derivative regenerated pure **54** in 36% overall yield from kanamycin A. Desymmetrization of the meso diacetate (**55**) proved elusive using commercially available esterases, however use of Verenium esterase 5 (Venerium Corporation), an esterase specifically engineered for sterically hindered substrates, in acetonitrile and pH 7.5 phosphate buffer, gave the mono acetate **56** in high yield and with excellent enantioselectivity. Staudinger mono-reduction and Boc protection gave **57**.



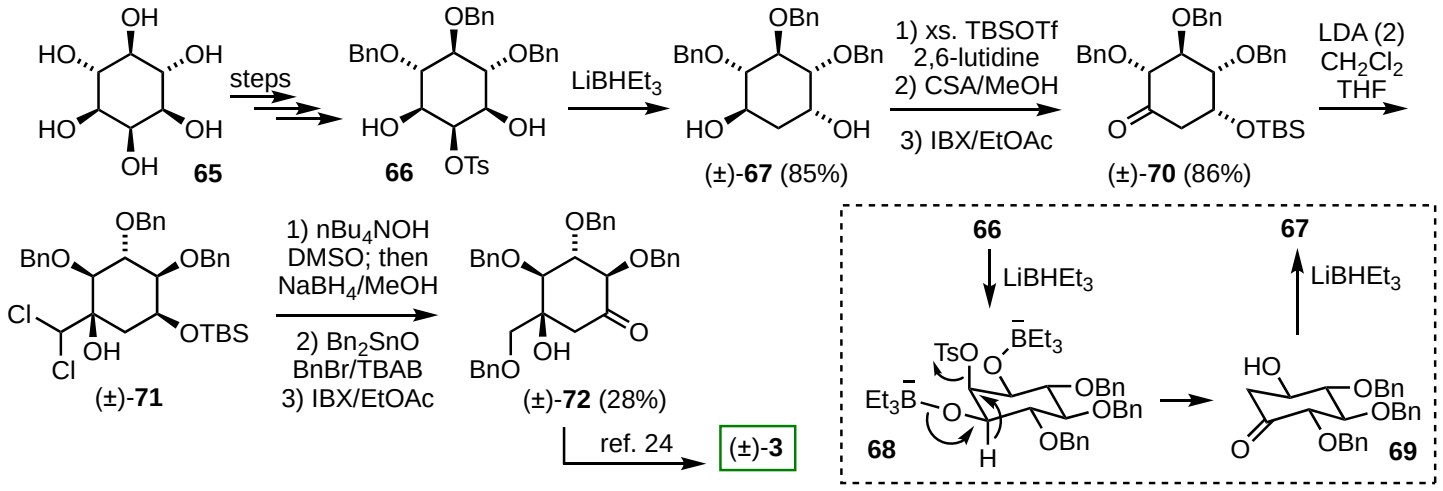
Scheme 8. Enzymatic desymmetrization of meso-diacetate **55**.

More recently, Trost and Molhotra reported a synthesis of the optically active mono-protected 2-DOS derivative **58** (Scheme 9).[22] Their route relied on a desymmetrization of meso-dibenzoate **59** with 1.2 equivalents of trimethylsilyl azide, using Pd-catalysis with the chiral bis-phosphine ligand *S,S*-**60**. Staudinger reduction of the resultant allylic azide, followed by Boc protection gave **61** with excellent enantioselectivity. Methanolysis of the optically active benzoate, followed by hydroxyl directed stereoselective epoxidation, and Ley oxidation gave the epoxyketone **62**. Generation of the enolate from **62** and reaction with *iso*-amyl nitrite gave the oxime **63**, which was stereoselectively reduced and benzoylated at both the 2° alcohol and the oxime. Nickel-boride reduction of the benzoyl oxime was followed by migration of the O-benzoyl group to nitrogen to afford **64**. Acidic hydrolysis of the epoxide was accompanied by cleavage of the Boc carbamate to afford the optically active benzoylated 2-DOS derivative **58**.



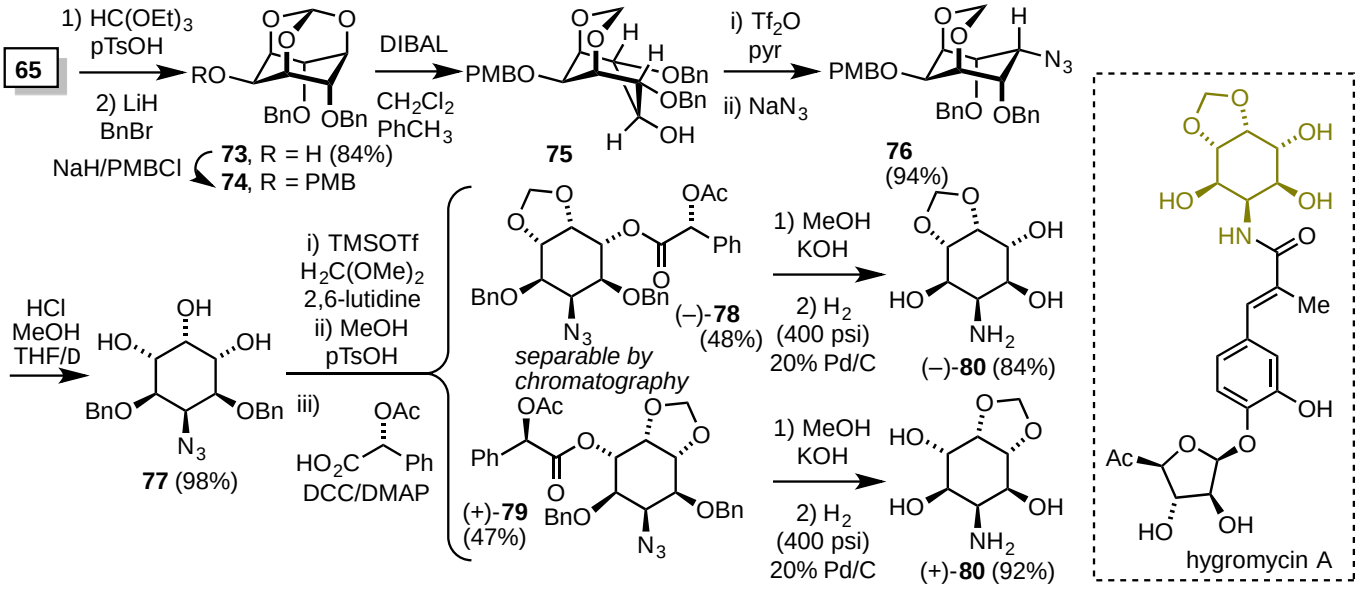
Scheme 9. Pd-catalyzed desymmetrization of meso dibenzoate **59**.

Shashidhar's group reported a formal synthesis of racemic valiolamine from relatively abundant *myo*-inositol **65** (Scheme 10).[22] Several steps transform the precursor into axial tosylate **66**. Reduction of meso **66** with lithium triethylborohydride gave diol (±)-**67**. The authors propose a hydride migration from the *bis*-boryl ether **68** which displaces the axial tosylate group (see insert, Scheme 10). The ketone **69** thus formed then undergoes reduction with $LiBHEt_3$ to generate racemic 2,3,4-tribenzyl *vibo*-quercitol **67**. The hydroxymethyl substituent is introduced by reaction of dichloromethyl lithium with ketone **70** to give **71**. Hydrolysis of the dichloromethyl group, reduction of the resultant aldehyde, benzyl protection and oxidation of the remaining 2° hydroxyl affords (±)-**72**. Preparation of (±)-**72** constitutes a formal synthesis of *rac*-valiolamine, since this intermediate has previously been transformed into **3**.[24]



Scheme 10. Shashidhar synthesis of *rac*-valiolamine.

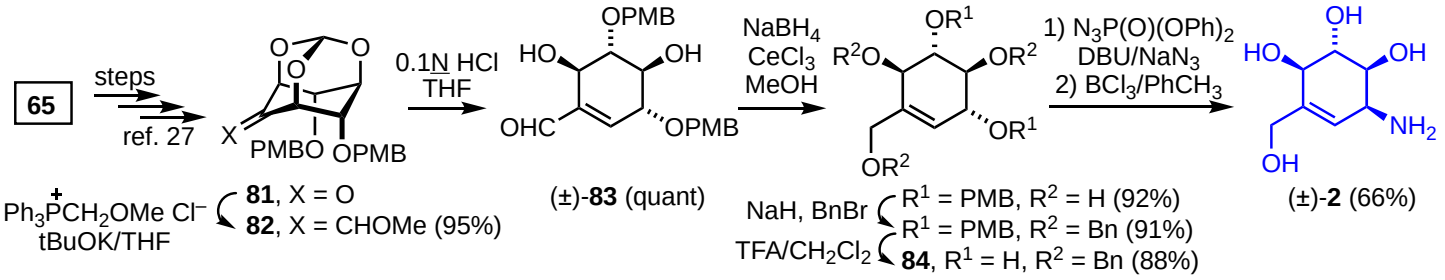
More recently, this group utilized *myo*-inositol (**65**) in the synthesis of the aminocyclitol portion of hygromycin A, a peptidyl transferase inhibitor and broad-spectrum antibiotic (Scheme 11).[25] Regioselective reduction of the tetracyclic orthoester **74** gave alcohol **75**. The authors rationalized this regioselectivity on the basis of complexation of DIBAL with the OPMB ether. Triflation and azide substitution gave **76** in excellent yield (94%) from **73**. Methanolysis of the methylidene acetal and the *p*-methoxybenzyl groups was accomplished with concentrated HCl to afford the meso triol **77**. Reaction of **77** with dimethoxymethane/TMSOTf, followed by hydrolysis of the methoxymethyl ether generated a racemic mono-alcohol. Coupling with the racemate with (R)-*O*-acetylmandelic acid gave a mixture of diastereomeric esters (–)-**78** and (+)-**79**, which could be separated by flash chromatography on a >1 g scale. Methanolysis of the individual diastereomers and subsequent azide reduction gave the enantiomeric aminocyclitols (–)-**80** and (+)-**80**.



Scheme 11. Shashidhar preparation of hygromycin A aminocyclitol segment via diasteremeric separation.

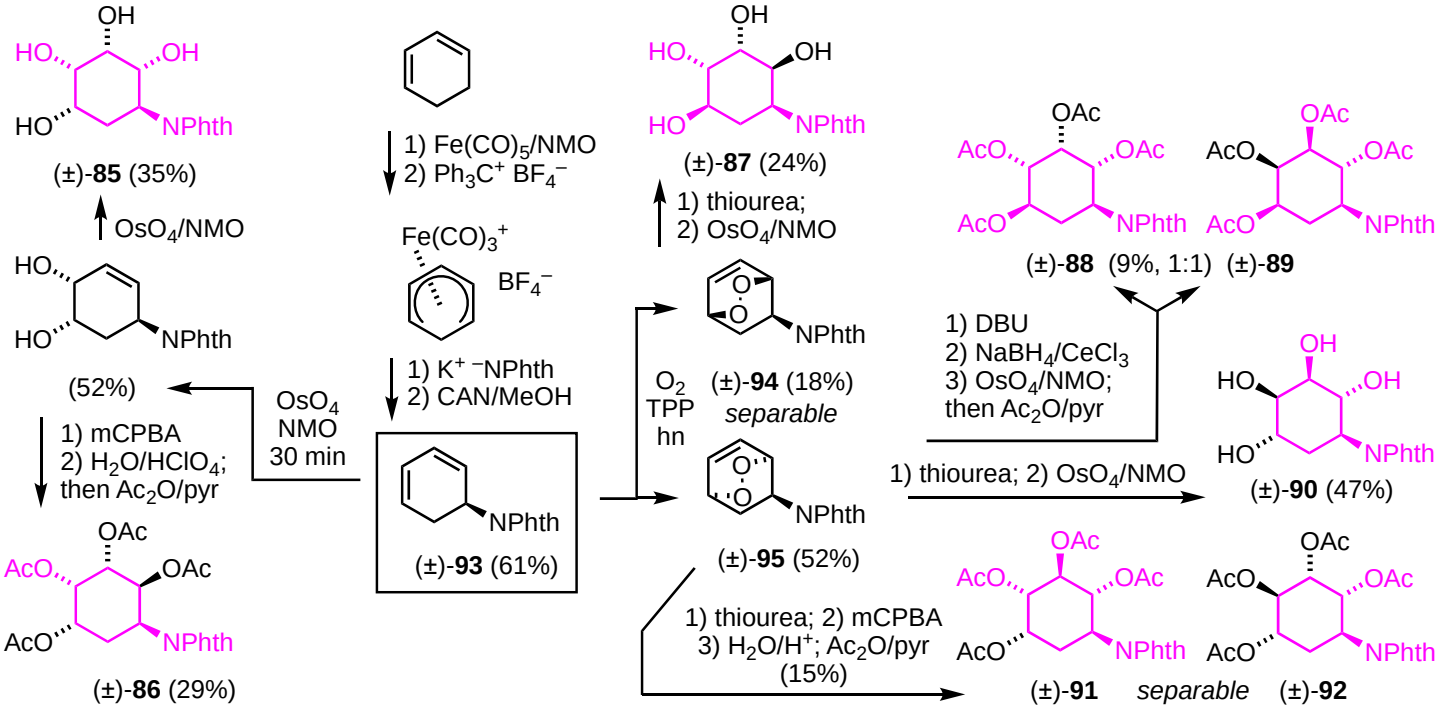
Sureshan's group also utilized *myo*-inositol in the synthesis of a variety of racemic cyclitol natural products, including valienamine (±)-**2** (Scheme 12).[26] A series of protection and oxidation steps afforded the *meso*-ketone **81**,[27] which underwent Wittig olefination to give the methyl vinyl ether **82**. Treatment with 0.1N HCl, led to hydrolysis of both the cyclic ortho ester and the enol ether and β-elimination to yield the enal (±)-**83**. The allylic

alcohol **84**, derived from **83**, underwent Mitsunobu inversion in the presence of diphenyl-phosphoryl azide and sodium azide. Treatment with BCl_3 afforded (±)-**2**.



Scheme 12. Sureshan synthesis of *rac*-valienamine.

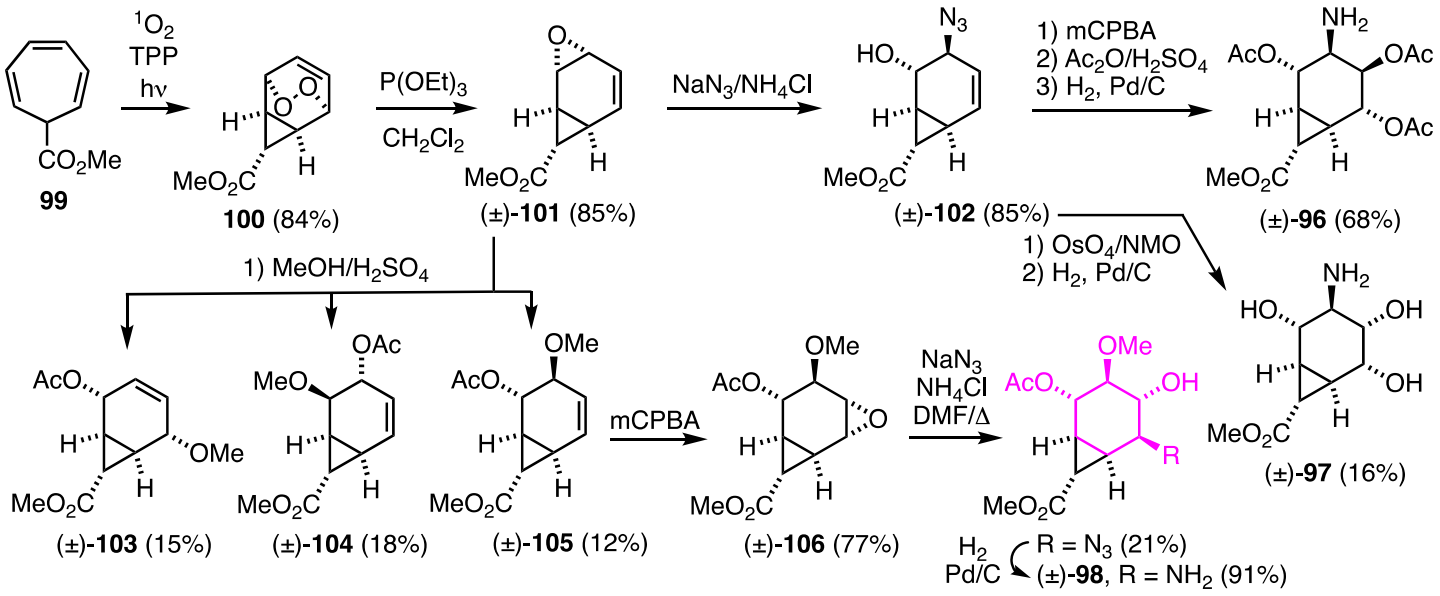
Sar and Donaldson prepared a library of eight protected stereoisomeric aminocyclitols **85**-**92** from racemic (2,4-cyclohexadien-1-yl)phthalimide (**93**, Scheme 13).[28] The precursor could be prepared in two steps from (cyclohexadienyl)$Fe(CO)_3^+$ cation. Cycloaddition of **93** with singlet oxygen gave a separable mixture of endoperoxides **94** and **95**; the stereochemistry of each was confirmed by X-ray crystallography. Further transformation by endoperoxide cleavage, Kornblum-DeLaMare rearrangement, dihydroxylation or epoxidation/hydrolysis generated the hydroxyl substituents in a stereocontrolled fashion. The relative stereochemistries of these products was tentatively assigned on the basis of $^3J_{H\text{-}H}$ coupling constants; the assignments for **85**, **88**, **91** and **92** were eventually corroborated by X-ray crystal structures.



Scheme 13. Sar and Donaldson synthesis of stereochemical diverse library of aminocyclitols.

Sengul and co-workers reported the synthesis of a unique trio of bicyclic aminocyclitols **96**-**98** from methyl 1,3,5-cycloheptatriene-7-carboxylate (**99**, Scheme 14).[29] Photooxygenation of **99** is known to proceed via the norcaradiene to generate meso tricyclic endoperoxide **100**.[30] Reduction of **100** with triethylphosphite yields the racemic epoxide (±)-**101** in good yield. Ring opening of **101** with sodium azide proceeds selectively at the allylic

epoxide carbon. Epoxidation/hydrolysis and azide reduction led to (±)-**96** while osmium catalyzed dihydroxylation and azide reduction led to (±)-**97**. Alternatively, methanolysis of epoxide **101** followed by acetylation gave a separable mixture of acetates **103**-**105**. Reaction of **105** with mCPBA gave a single epoxide **106**, which underwent regioselective opening with azide ion. Reduction gave aminocyclitol (±)-**98**.

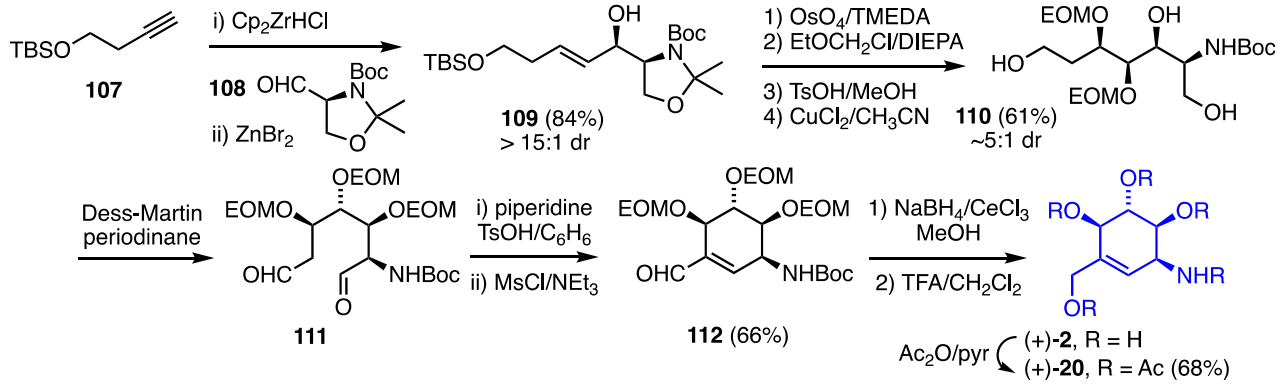


Scheme 14. Sengul synthesis of bicyclic aminocyclitols.

3. Intramolecular Cyclizations

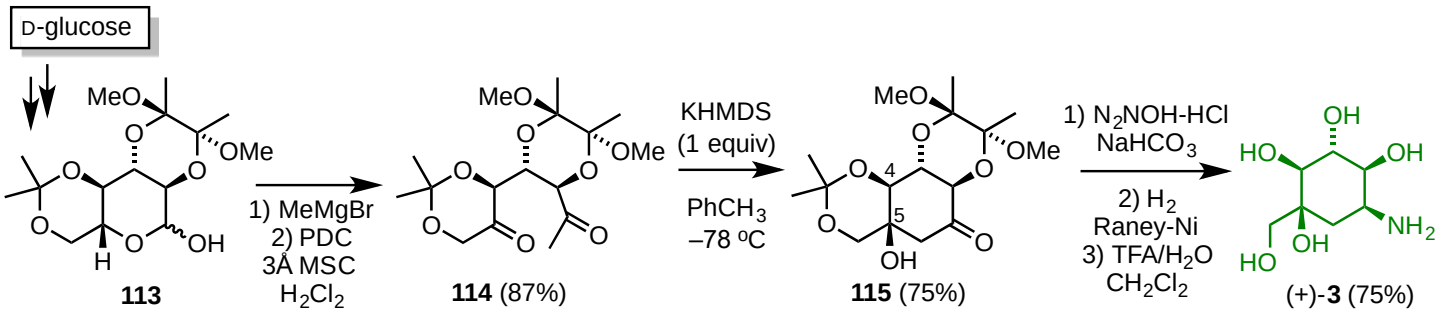
3.1 Intramolecular aldol condensation

Two syntheses reported during this period feature generation of the cyclohexyl ring of aminocyclitols via intramolecular aldol condensation. This reaction results in the desirable β-hydroxycarbonyl functionality present within the carbocyclic ring. The Li group began their synthesis with addition of the alkenyl zirconium reagent derived from alkyne **107** to Garner's aldehyde **108**, in the presence of zinc bromide, to afford the allylic alcohol **109** with excellent diastereoselectivity thus establishing the required C5 stereocenter (Scheme 15).[31] A sequence of dihydroxylation, protection, deprotection and primary alcohol oxidation gave the 1,7-dial **111**. Intramolecular aldol condensation with piperidine followed by mesylation–elimination afforded **112**. Reduction of **112** under Luche conditions, and global deprotection gave (+)-**2**.



Scheme 15. The Li group synthesis of peracetylated valienamine (EOM = ethoxymethyl).

Shing's group at the University of Hong Kong utilized an intramolecular aldol condensation for the synthesis of valiolamine (Scheme 16).[32,33] D-Glucose was transformed into the differentially protected lactol **113** via a 4 step procedure.[28] Methyl Grignard addition followed by oxidation afforded the diketone **114**. Extensive experimentation revealed that aldol condensation using potassium hexamethyldisilazane led to the formation of the β-hydroxyketone **115**. Imine formation, catalytic reduction and global deprotection completed the synthesis of (+)-**3**.



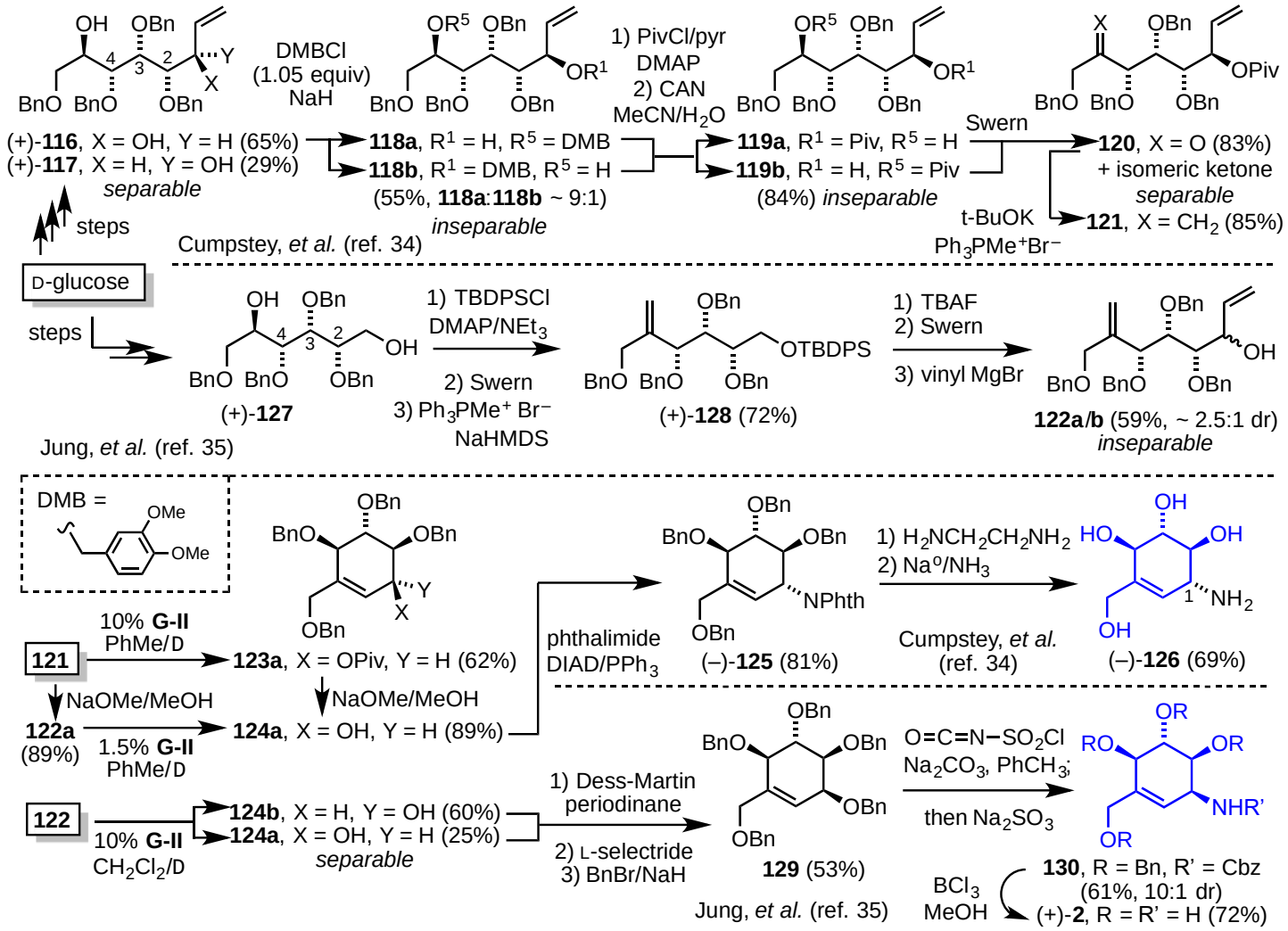
Scheme 16. The Shing group synthesis of valiolamine via intramolecular aldol condensation.

3.2 Ring-closing metathesis

Ring-closing metathesis (RCM) has played a prominent role in the synthesis of aminocyclitols, and the reader is directed to earlier reviews for prior examples.[1,6] RCM is particularly attractive since the product possesses an olefin that can serve as a handle for the introduction of further hydroxyl groups.

Two groups utilized D-glucose as a precursor since the C2, C3, and C4 stereocenters present in D-glucose match those in (+)-valienamine. Cumpstey's group reported[34] a variety of routes to protected 1,7-octadienes (Scheme 17). Addition of vinyl Grignard to 2,3,4,6-tetra-*O*-benzyl glucose gave a separable mixture of allylic alcohols **116** and **117**. Selective protection of diol **116** proved challenging, however benzylation with 3,4-dimethoxybenzyl chloride (DMBCl) proceeded predominantly at the non-allylic alcohol. Protection/deprotection and subsequent Swern oxidation gave a separable mixture of the C6 ketone **120** and the regioisomeric enone. In order to avoid the problems of selective protection of diol **116** Cumpstey also reported a route from L-sorbose. Ring-closing metathesis of allylic pivalate **121**, or its derived allylic alcohol **122a**, proceed in good yield using Grubbs' 2nd generation catalyst. Cumpstey's group eventually completed a synthesis of β-valienamine **126** by displacement of the cyclic allylic alcohol **124a** with phthalimide under Mitsunobu conditions.

About 5 years later, Jung's group reported a selective route to valienamine from D-glucose.[35] Olefin (+)-**128** was generated via a sequence of standard transformations (Scheme 17).[34] Addition of vinyl Grignard to the aldehyde generated from **128** gave an inseparable mixture of diastereomeric allylic alcohols **122a**/**b**. Ring- closing metathesis of **122a**/**b** gave a separable mixture of **124a** (25%) and **124b** (60%), which could be converted into the perbenzyl pentaol **129** via oxidation/stereoselective reduction/benzylation. Treatment of **129** with chlorosulfonyl isocyanate led to the Cbz protected amine **130**, via an S_Ni substitution with retention of configuration. Debenzylation gave valienamine (±)-**2**.

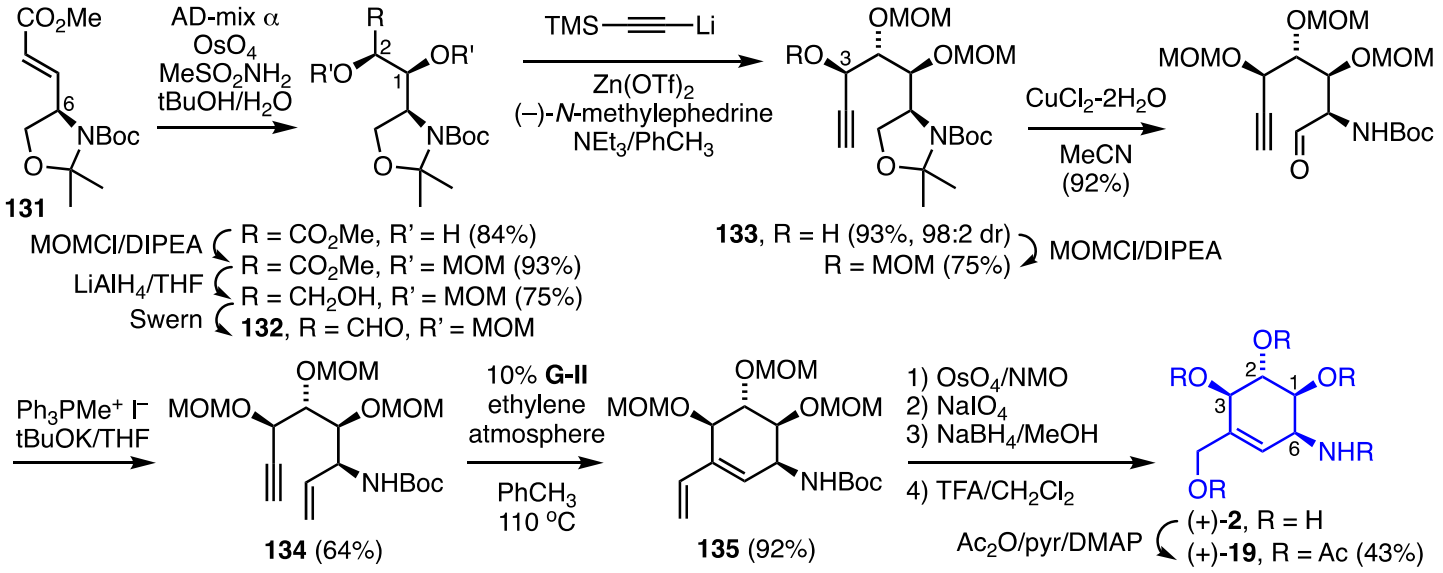


Scheme 17. Synthesis of β-valienamine **126** and valienamine **2** via RCM from D-glucose.

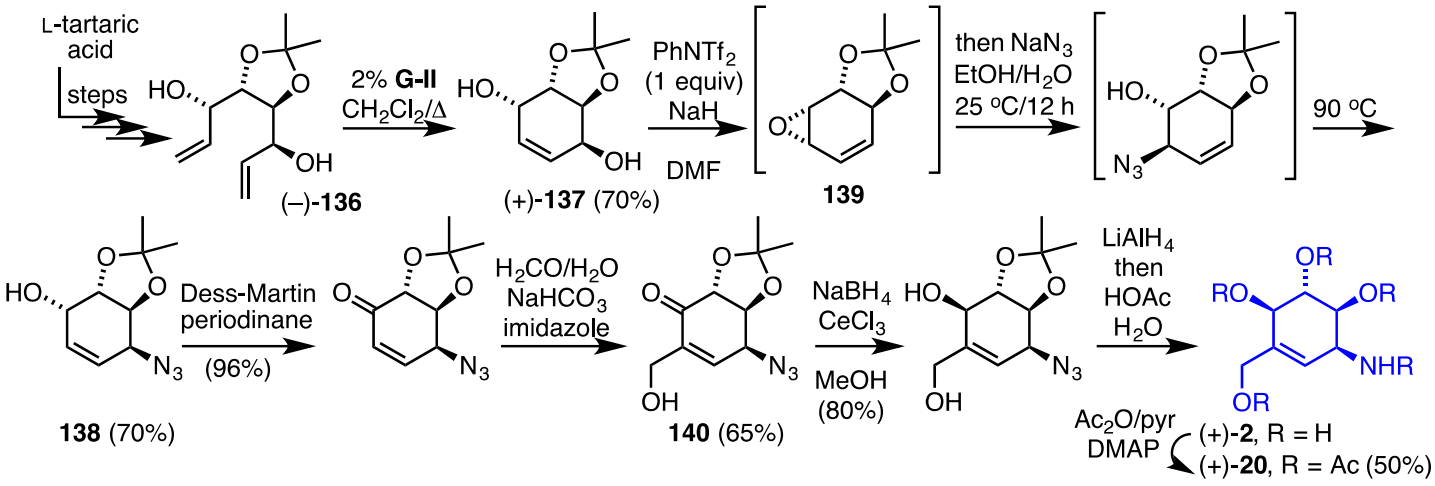
Krishna and Reddy utilized an enyne ring-closing metathesis for preparation of (+)-valienamine (Scheme 18).[36] The C6 stereocenter (CAS numbering) was derived from Garner's aldehyde, while the C1-C3 stereocenters were respectively introduced by Sharpless asymmetric dihydroxylation of **131**, and Carreira asymmetric alkynylation of aldehyde **132** in the presence of (–)-*N*-methylephedrine. Ring-closing metathesis of enyne **134** was accomplished using Grubbs' 2nd generation catalyst, under an atmosphere of ethylene, to afford the vinylcyclohexene **135** in high yield. Oxidative excision of the terminal methylene carbon afforded a cyclohexenecarboxaldehyde, which after reduction and global deprotection gave (+)-**2**. This was characterized as its peracetylated derivative (+)-**20**. Use of (+)-*N*-methylephedrine in the Carreira alkynylation gave the diastereomer of **133**, which gave peracetylated 3-*epi*-valienamine (CAS numbering) in a similar fashion.

Tu-Hsin Yan's group reported the synthesis of valienamine (Scheme 19).[37] The precursor, L-tartaric acid, was converted into the C2 symmetric 1,7-octadiene (–)-**136** which underwent RCM with Grubbs' 2nd generation catalyst to afford the C_2 symmetric cyclohexene (+)-**137**, according to the procedure of Madsen, *et al.*[38] Activation of **137** with phenyl-bis(trifluoromethanesulfonimide) and reaction with sodium azide gave **138**. This reaction is believed to proceed via generation of the epoxide **139**, regioselective ring opening and a [3,3]-sigmatropic rearrangement to yield **138** with apparent retention of configuration. The required hydroxymethyl substituent was introduced by oxidation of the allylic alcohol and Baylis-Hillman condensation with aqueous

formaldehyde to yield **140**. Luche reduction of the resultant enone, azide reduction and acetonide hydrolysis completed the synthesis of (+)-**2**.



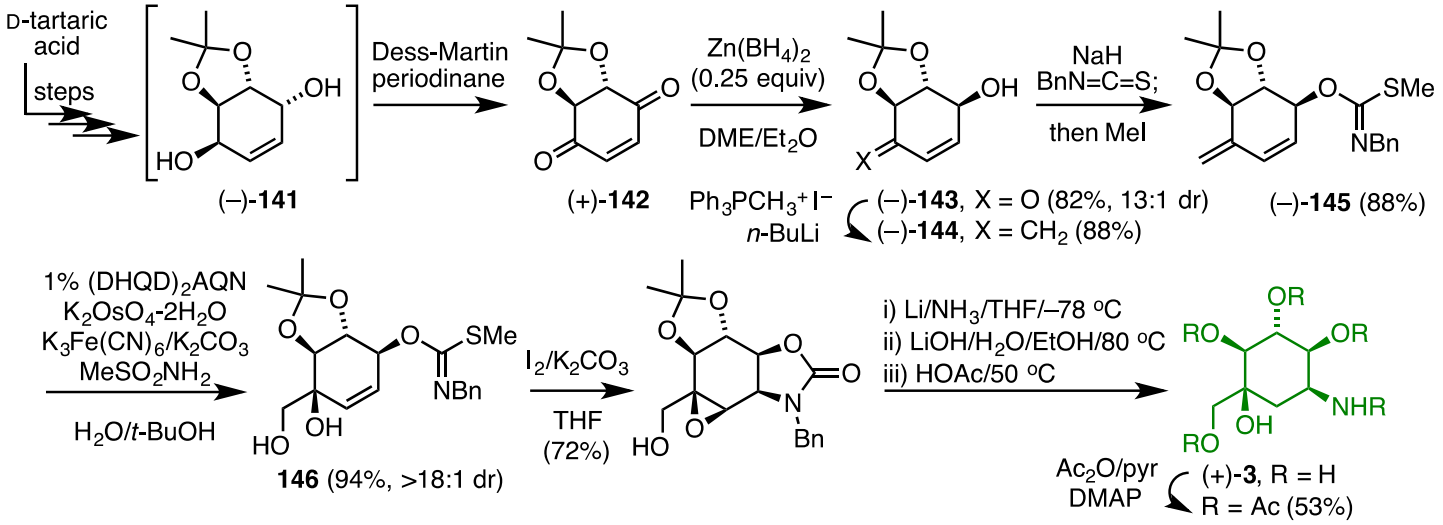
Scheme 18. Krishna and Reddy enyne ring-closing metathesis route to valienamine.



Scheme 19. The Yan group synthesis of valienamine.

More recently, this group completed a synthesis of (+)-valiolamine (Scheme 20).[39] In this case, D-tartaric acid was transformed into (–)-**141**; double oxidation and semi-reduction gave acetonide protected 4,5,6-trihydroxycyclohexenone **143** along with the diastereomer (13:1 dr). Methenylation of **143** required considerable experimentation. Peterson olefination or reaction with the ylide generated from methyltriphenyl phosphonium bromide proceed with partial epimerization at the α-carbon. Successful olefination without epimerization was achieved by using the phosphonium iodide to afford exclusively **144**, which was converted into carbonimidothioate **145**. Sharpless asymmetric dihydroxylation of the exocyclic olefin of **145** proved to be the next challenging step. While the standard 1,3-phthalazinediyl (PHAL) or pyrimidine (PYR) linked bis-cinchona ligands gave low to modest diastereoselectivity, Yan's group found that 1% of the anthraquinone linked ligand

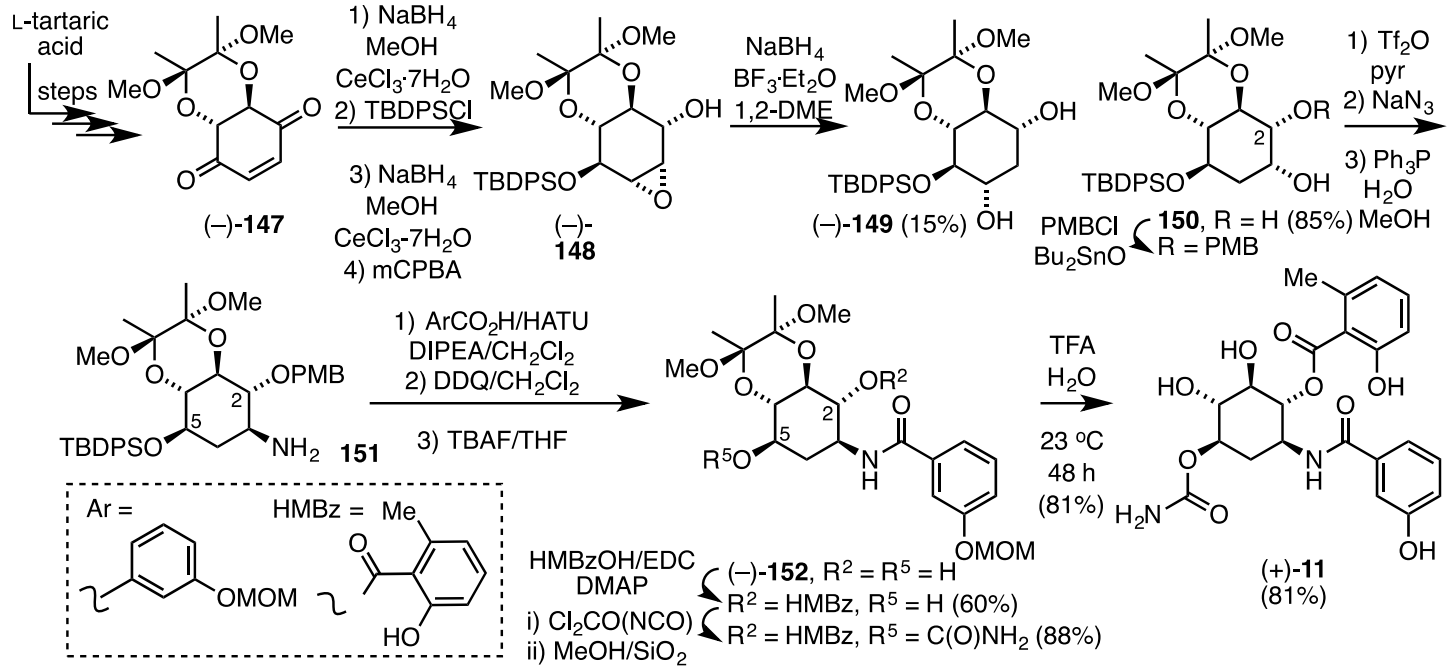
$(DHQD)_2AQN$ afforded the desired **146** with >18:1 dr. Cyclization of the carbonimidothioate with iodine generated the required amine stereocenter, which was eventually transformed into (+)-**3**.



Scheme 20. The Yan group synthesis of valiolamine.

Very recently, Banwell's group reported the first synthesis of nabscessin B (Scheme 21).[40] Their route uses L-tartaric acid as starting material to produce (–)-**147**,[41] the enantiomeric 1,2-diacetal protected analog of (+)-**142**. Stereoselective mono-carbonyl reduction, protection, reduction of the remaining carbonyl and stereoselective hydroxyl directed epoxidation affords the epoxy alcohol (–)-**148**. Lewis acid activated reduction of **148** gave a mixture of diols (–)-**149** and (–)-**150**, which were separable on a >1 g scale. The major product arises via a diaxial epoxide ring opening (Furst-Plattner rule). Selective protection of the equatorial hydroxyl at C2 of **150**, followed by activation, azide displacement and Staudinger reduction yielded the amine **151**.

Amidation of **151** with 3-(methoxymethoxy)benzoic acid and HATU, and removal of the PMB and TBDPS ethers generated the diol (–)-**152**. Esterification with 6-methylsalicylic acid, formation of the carbamate and acidic cleavage of the cyclic 1,2-diacetal and the methoxymethyl ether finally led to (+)-**11**.

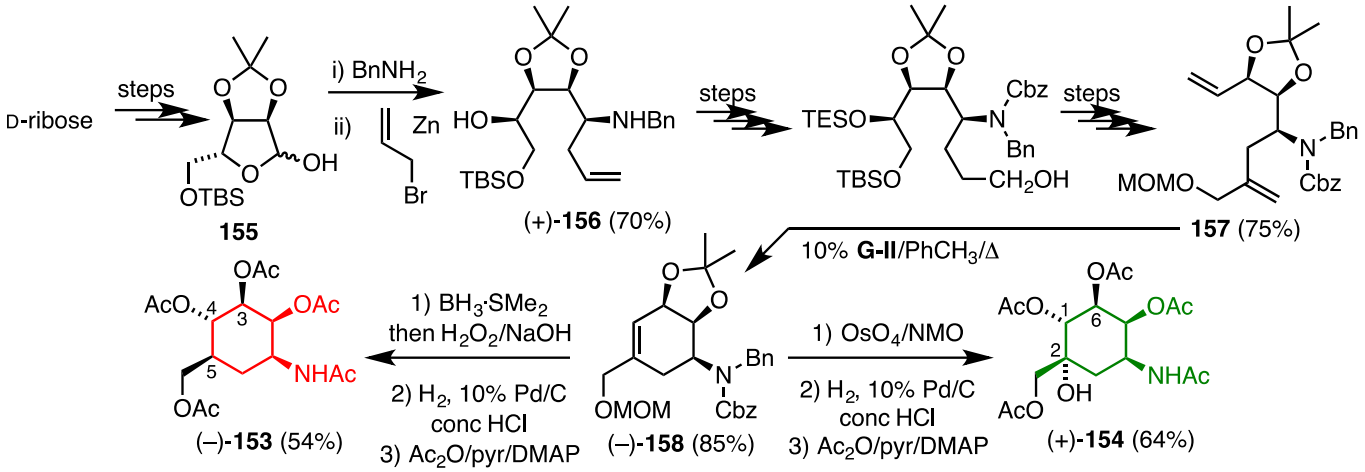


Scheme 21. The Banwell group synthesis of nabcessin B.

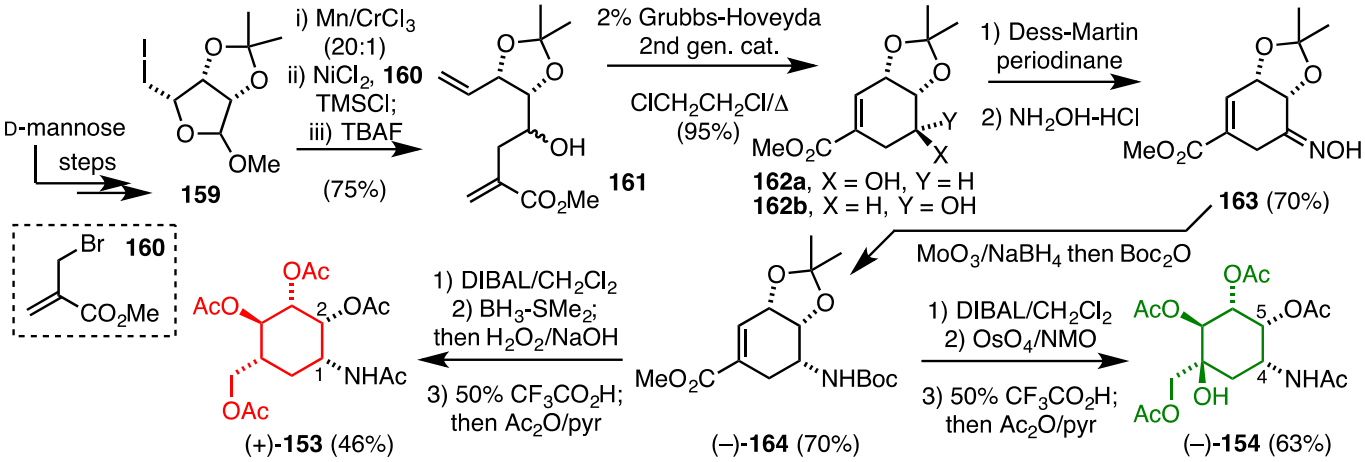
Venkateswara Rao's group prepared peracetylated *ent*-1,2-*bis*-*epi*-validamine (–)-**153** and peracetylated *ent*-4,5-*bis*-*epi*-valiolamine (+)-**154** from D-ribose (Scheme 22).[42] Stereoselective introduction of the secondary amine utilized addition of allyl zinc bromide to the imine derived from **155** to afford (+)-**156**. This olefin was transformed to 1,7-octadiene **157** over several steps. Ring-closing metathesis of **157** with Grubbs' 2nd generation catalyst gave the cyclohexene (–)-**158** in good yield. The remaining stereocenters in *ent*-1,2-*epi*-validamine and *ent*-4,5-*epi*-valiolamine were generated by diastereoselective hydroboration-oxidation and osmium catalyzed dihydroxylation respectively. More recently, this group prepared the enantiomeric compounds (+)-**153** and (–)-**154** from D-mannose (Scheme 23).[43] Treatment of the iodide **159** with Mn/$CrCl_3$, followed by transmetallation with $NiCl_2$ and methyl 2-bromomethyl)acrylate **160** effected a Nozaki-Hiyama-Kishi coupling to afford a mixture of diastereomeric alcohols **161**. Ring-closing metathesis of the 1-substituted acrylate **161** required the use of the Grubbs-Hoveyda 2nd generation catalyst to prepare acetonide protected *ent*-methyl shikimate (**162a**) and its C5 epimer (**162b**). The amine stereocenter was introduced by oxidation, reaction of the resultant unstable ketone with hydroxylamine, and stereoselective reduction of the resultant oxime **163** to afford (–)-**164**. After reduction of the ester, the allylic alcohol was processed in a fashion similar to that in Scheme 18 to give (+)-**153** or (–)-**154**.

Ring-closing metathesis also played a prominent role in the preparation of an aminocyclitol mimic **165** of α-galactosylceramide (Scheme 24).[44] Precursor aldehyde **166** was prepared from D-xylose which was subjected to an Evans' chiral oxazolidinone directed anti-aldol for introduction of the C4-C5 bond. Reductive removal of the auxiliary afforded 1,7-octadiene **167**. Ring closing metathesis with Grubbs' 2nd generation catalyst and benzylation of the 1° alcohol yielded the cyclohexene **168**. Installation of the required C1 alcohol proved challenging. Unlike the Banwell synthesis of nabcessin B, epoxidation of cyclohexene **168** (or various derivatives) either failed to proceed or gave unstable products. Eventually the authors found that hydroboration-oxidation, followed by oxidation to the ketone and stereoselective reduction gave a separable mixture of **169** and the desired (+)-**170**. Mesylation of **170**, S_N2 displacement with azide and reduction gave tetrabenzyl 4-*epi*-validamine **171**. Conversion of **171** to the phytoceramide yielded **165** (HS161). This compound proved to be a

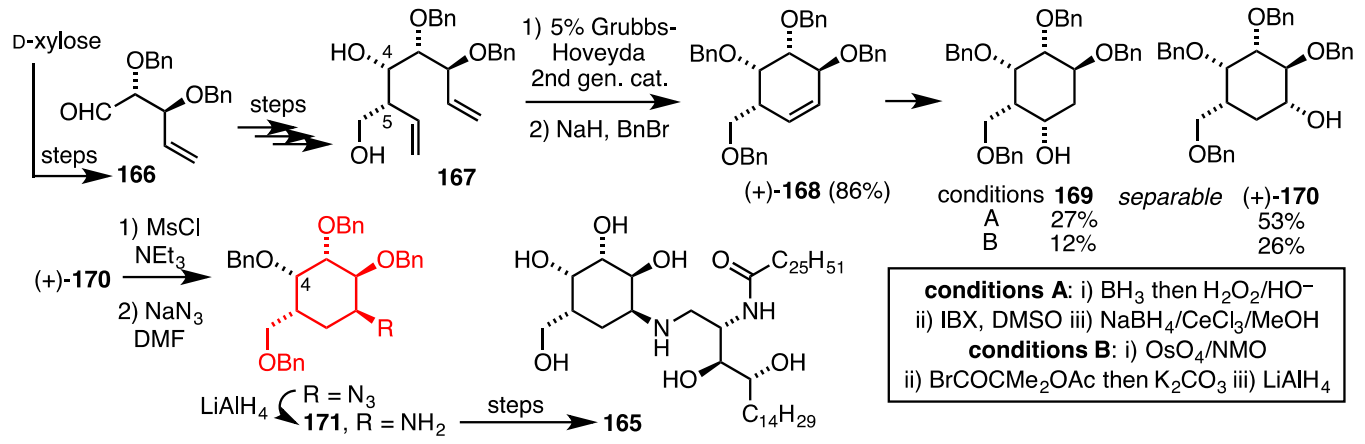
invarient Natural Killer T cell (iNKT) agonist, inducing Interferon-γ production in spleen cell culture, as well as by intraperitoneal administration in mice (1 μg dose).



Scheme 22. Venkateswara Rao synthesis of *ent*-1,2-*bis*-*epi*-validamine and *ent*-4,5-*bis*-*epi*-valiolamine.

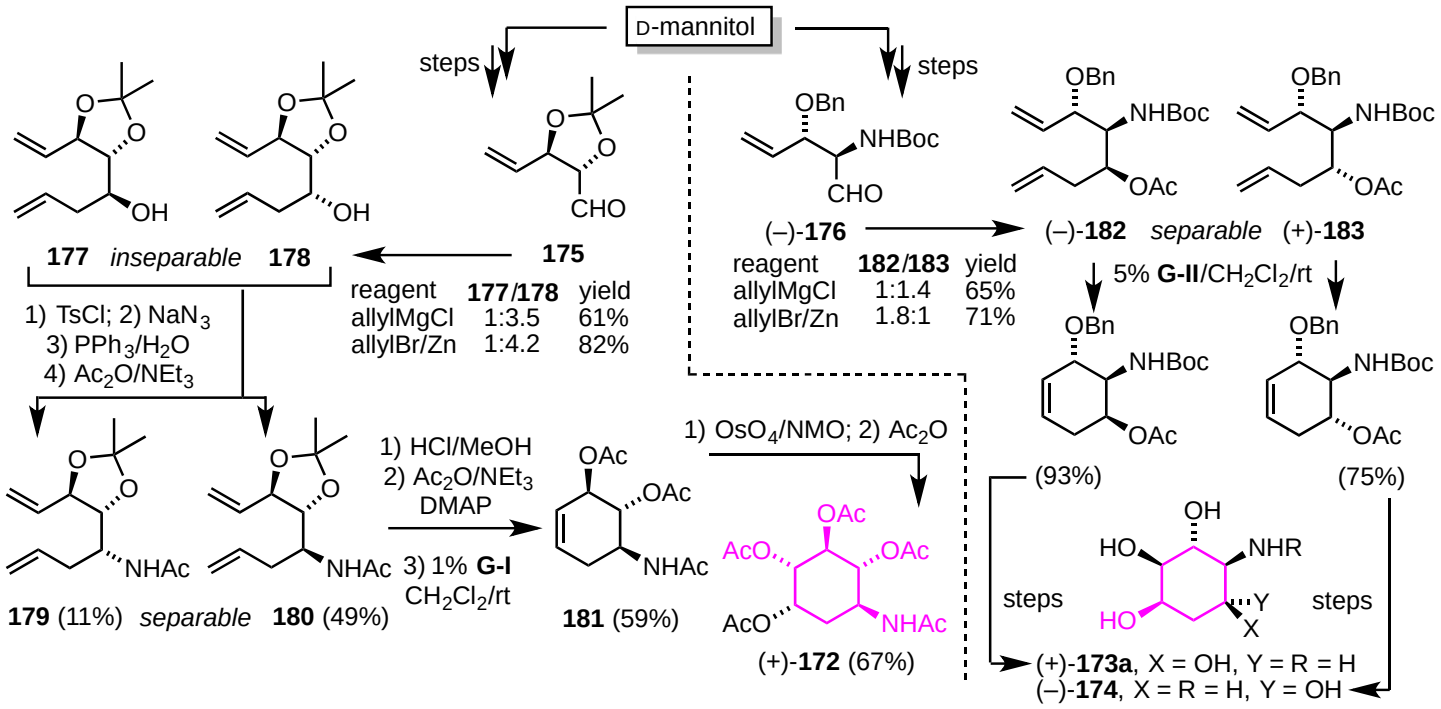


Scheme 23. Venkateswara Rao synthesis of 1,2-*bis*-*epi*-validamine and 4,5-*bis*-*epi*-valiolamine.



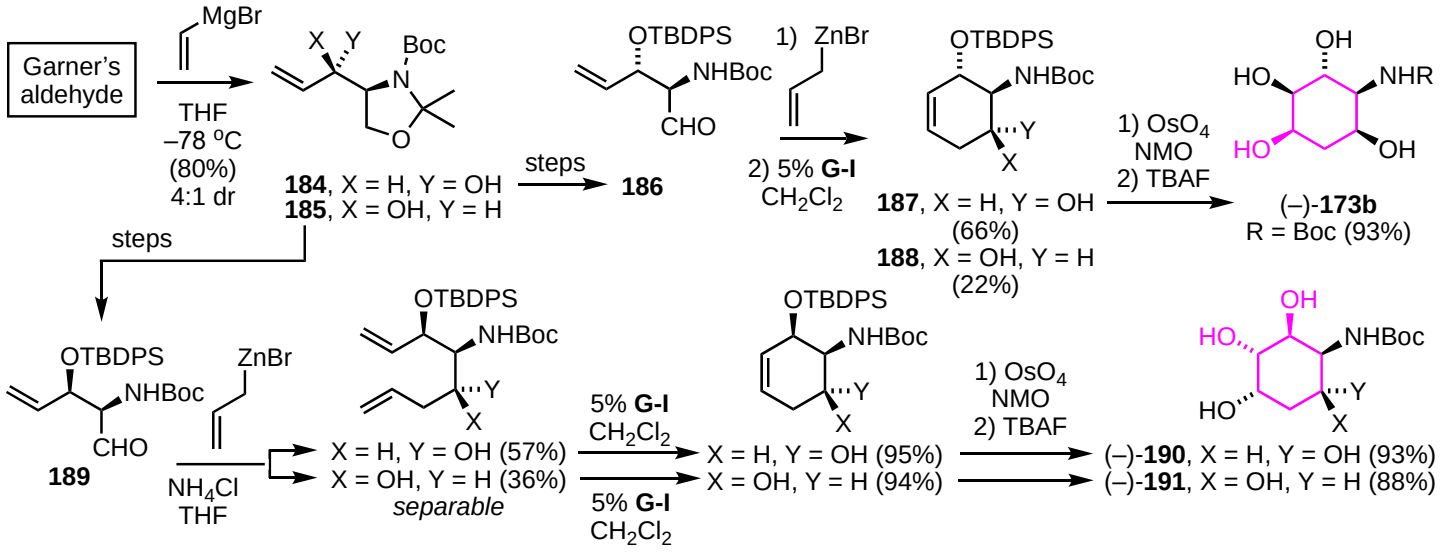
Scheme 24. Institut de Quimica Avancada de Catalunya synthesis of α-galactosylceramide aminocyclitol mimic.

Vankar's group reported the known 5-amino-5-deoxy-D-*vibo*-quercitol pentaacetate (+)-**172** and two new positional isomers, (+)-**173a** and (–)-**174** (Scheme 25).[45,46] D-mannitol was transformed into the chiral aldehydes **175** and **176** respectively. The addition of allyl magnesium chloride or allylzinc to **175** gave an inseparable mixture of diastereomers **177**/**178** (~ 1:4 dr); conversion of the mixture via tosylate displacement, reduction and acetylation gave a separable mixture of 1,7-octadienes **179** and **180**. After adjusting the protecting groups, ring-closing metathesis was accomplished with Grubbs' 1st generation catalyst; stereocontrolled dihydroxylation of **181** and acetylation yielded (+)-**172**. In contrast, addition of allyl magnesium chloride or allylzinc to **176** proceeded with low diastereoselectivity, however in this case the derived acetates **182** and **183** were separable by chromatography. Ring closing metathesis and dihydroxylation of the individual diastereomeric cyclohexenes occurred in a stereoselective fashion rendering (+)-**173a** and (–)-**174** respectively, after global deprotection.



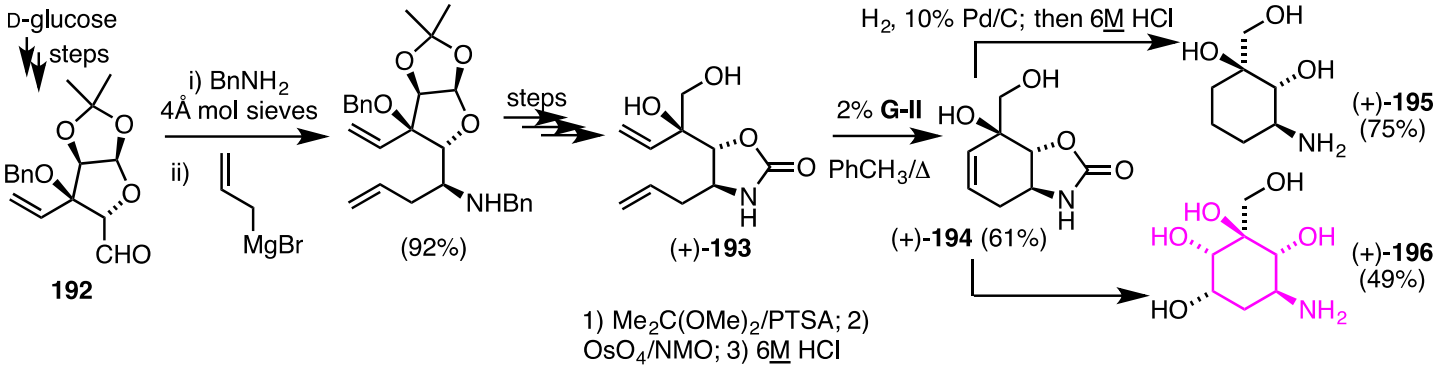
Scheme 25. Vankar synthesis of aminocyclitols.

Chattopadhyay's group reported a route to (–)-**173b** (Scheme 26),[47] the *N*-Boc protected analog, which shares some similarity to the methodology outlined in the previous Scheme. Beginning with Garner's aldehyde, addition of vinyl magnesium bromide gave a separable mixture of allylic alcohols **184** and **185**.[48] The major diastereomer (**184**) was converted into **186** (the TBDPS protected analog of **176**). Barbier reaction of **186**, followed by ring-closing metathesis with Grubbs' 1st generation catalyst gave a separable mixture of **187** and **188**. While dihydroxylation of **187** proceeded in a stereoselective fashion yielding exclusively (–)-**173b** after desilylation, applying the same sequence to **188** gave an inseparable mixture of epimeric products. The minor aldehyde **185** was processed to diastereomeric aminocyclitols (–)-**190** and (–)-**191**.



Scheme 26. Chattophadhyay synthesis of aminocyclitols.

Venkateswara Rao's group reported the synthesis of two novel aminocyclohexitols from D-glucose (Scheme 27).[49] The amino chiral center was generated by addition of allyl Grignard to the imine derived from **192**. Ring-closing metathesis of (+)-**193** with Grubbs' 2nd generation catalyst gave modest yields of (+)-**194**. Reduction or dihydroxylation, followed by cleavage of the oxazolidinone gave (+)-**195** or (+)-**196** respectively. The novel triol **195** inhibited yeast α-glucosidase (IC_{50} = 1.02 mM), while the pentaol **196** inhibited both yeast α-glucosidase (IC_{50} = 0.82 mM) and green coffee bean α-galactosidase (IC_{50} = 1. 2 mM). Neither compound inhibited β-glucosidase or β-galactosidase.

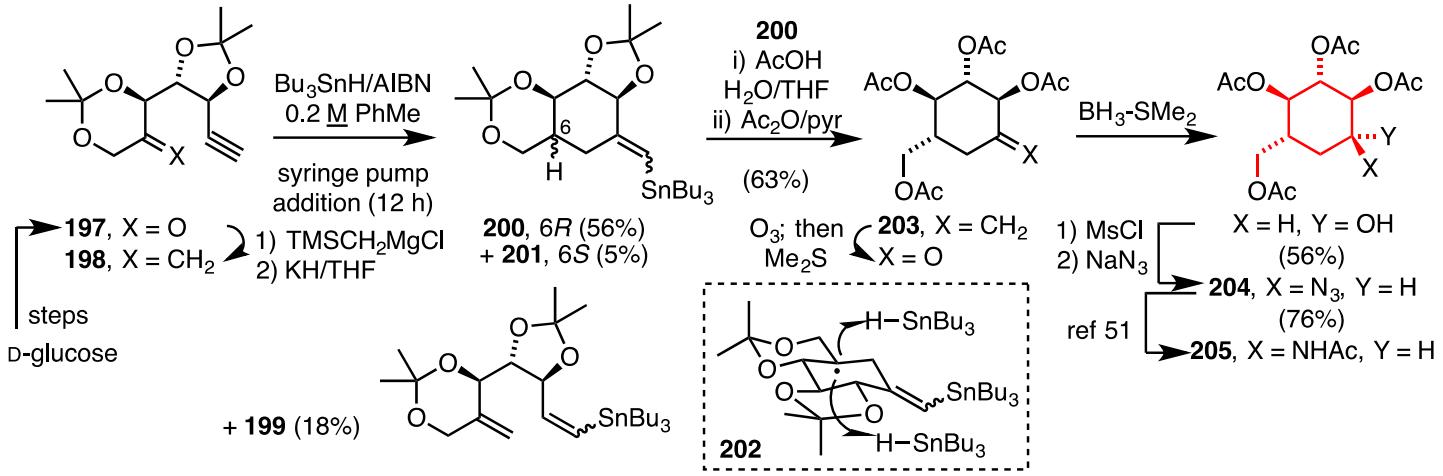


Scheme 27. Venkateswara Rao synthesis of novel aminocyclitols.

3.3 Radical cyclization

A group under the direction of Ana Gomez and Cristobal Lopez explored radical addition-cyclization for the preparation of a variety of carbahexopyranones.[50] D-Glucose was converted into the ynone **197**; Peterson olefination gave the cyclization precursor **198** (Scheme 28). Reaction of a mixture of **198** and tributyltin hydride under standard conditions gave only addition product **199**. However when the tin-hydride was added slowly via syringe pump a separable mixture of desired **200** (56%) and its C6 epimer **201** (5%), created via a 6-*endo*-trig radical cyclization, along with minor amounts of acyclic addition product **199** (18%) was produced. The diastereomers **200** and **201** are formed by hydrogen atom abstraction from either the α- or β-face respectively

of the 3° radical intermediate **202** (see insert). The cyclic constraints inherent in the bis(acetonide) protected intermediate were crucial for this level of diastereoselectivity (>10:1 dr); attempted cyclization of either the tetrabenzyl- or tetraacetyl- analogues of **198** gave only modest α:β selectivity (ca. 1.5:1 dr). Treatment of **200** with acetic acid resulted in acetonide hydrolysis and protodestannylation; the resulting tetraol was peracetylated to afford **203**. The olefin was converted into azide **204** by ozonolysis, stereoselective ketone reduction, mesylation and S_N2 displacement by azide. This constituted a formal synthesis of validamine pentaacetate, as Ogawa's group[51] had previously demonstrated this transformation.

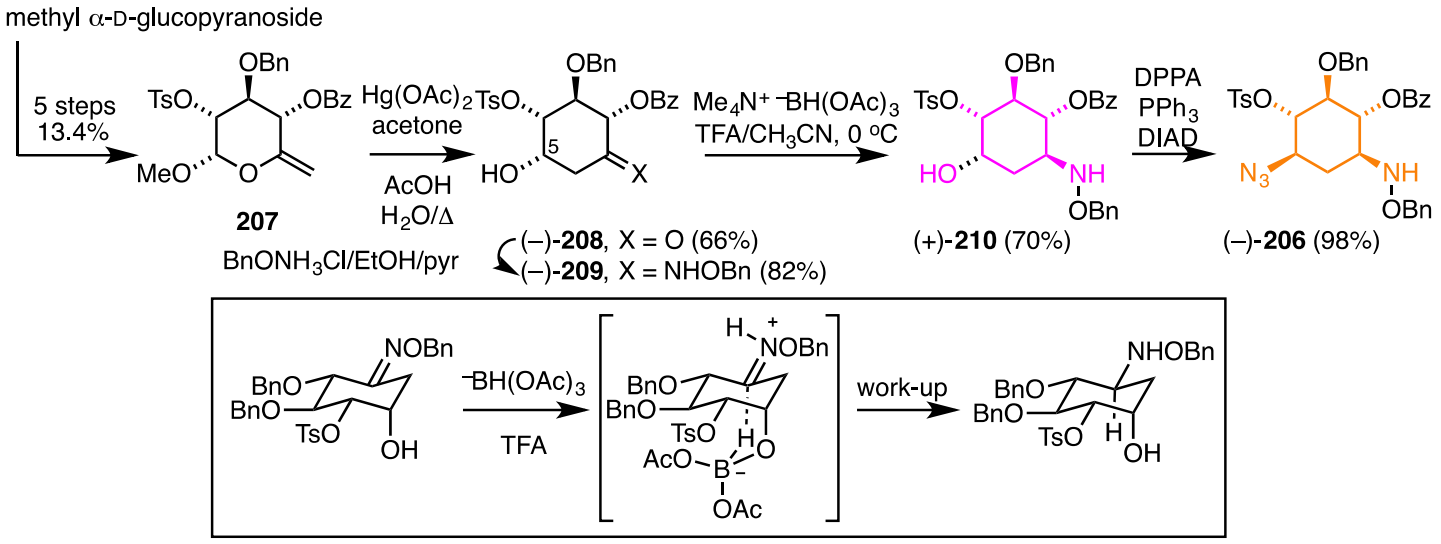


Scheme 28. The Gomez/Lopez formal synthesis of validamine pentaacetate.

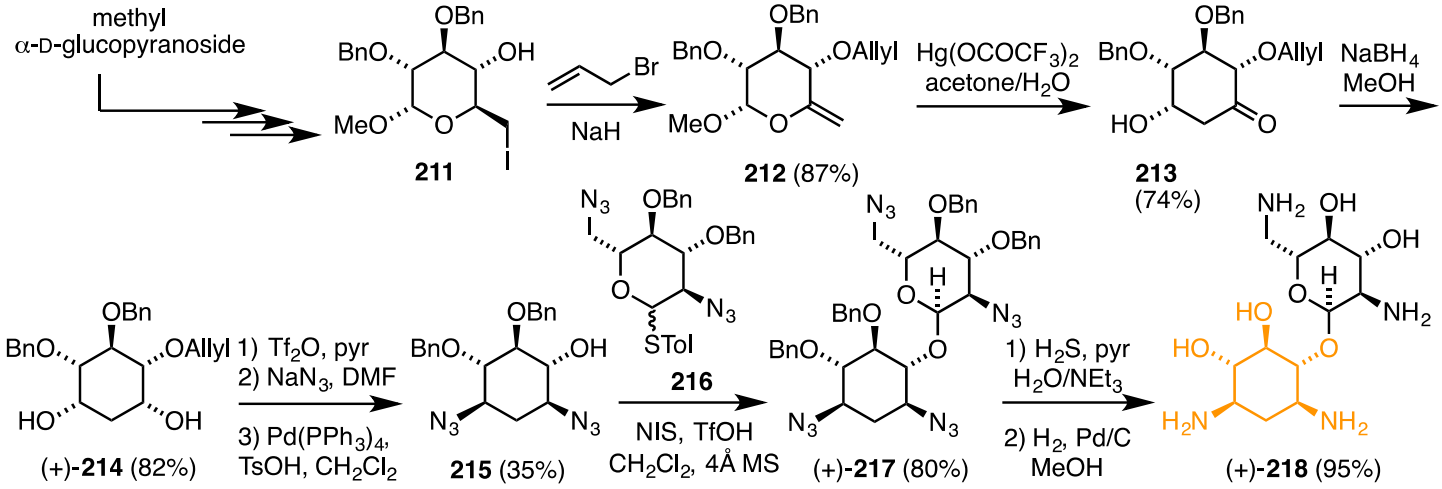
3.4 Carbo-Ferrier rearrangement

The biosynthetic pathway for 2-deoxy-*scyllo*-inosamine (DIOA, **6**) and 2-deoxystreptamine (DOS, **7**) involves transformation of glucose-6-phosphate into 2*S*,3*R*,4*S*,5*R*-tetrahydroxycyclohexanone (2-deoxy-scyllo-inosose, DOI) catalysed by 2-deoxy-*scyllo*-inosose synthase, via a carbo-Ferrier-type reaction.[52] In 2008, Bauder reported a bioinspired synthesis of an orthogonally protected 2-deoxystreptamine precursor (–)-**206** (Scheme 29).[53] The exocyclic enol ether **207** was prepared from methyl α-D-glucopyranoside. Treatment of **207** with mercuric acetate led to a carbo-Ferrier rearrangement to afford the cyclohexanone **208**, in which the C5 hydroxyl occupies an axial orientation. The *O*-benzyl oxime **209**, derived from **208**, underwent stereoselective reduction with triacetoxyborohydride in trifluoroacetic acid/acetonitrile to afford (+)-**210**. The axial addition of hydride was rationalized on the coordination of the acetoxyborohydride reagent to the axial C5 hydroxyl substituent. Mitsunobu substitution of **210** with diphenylphosphoryl azide afforded the orthogonally protected 2-deoxystreptamine derivative (–)-**206**.

The Ye group reported a similar approach to the synthesis of the 2-DOS subunit of neamine (Scheme 30).[54] Methyl α-D-glucopyranoside was transformed into the 1° iodide **211** by literature procedures.[55] Treatment of **211** with sodium hydride and allyl iodide effected both *O*-allylation as well as dehydrohalogenation to afford the exocyclic enol ether **212**. Carbo-Ferrier rearrangement of **212**, using mercuric trifluoroacetate, gave a mixture of diastereomeric 5-hydroxycyclohexanones (5:1 ratio) with **213** as the major product. Stereoselective reduction of **213** gave the differentially protected cyclohexanediol **214**. Activation with triflic anhydride, followed by double displacement with azide and Pd-catalyzed cleavage of the allyl ether generated the alcohol **215**. N-Iodosuccinimide mediated coupling of thioglucoside donor **216** with **215** gave the tetraazide **217**, which upon azide reduction and benzyl deprotection afforded (+)-neamine (**218**).

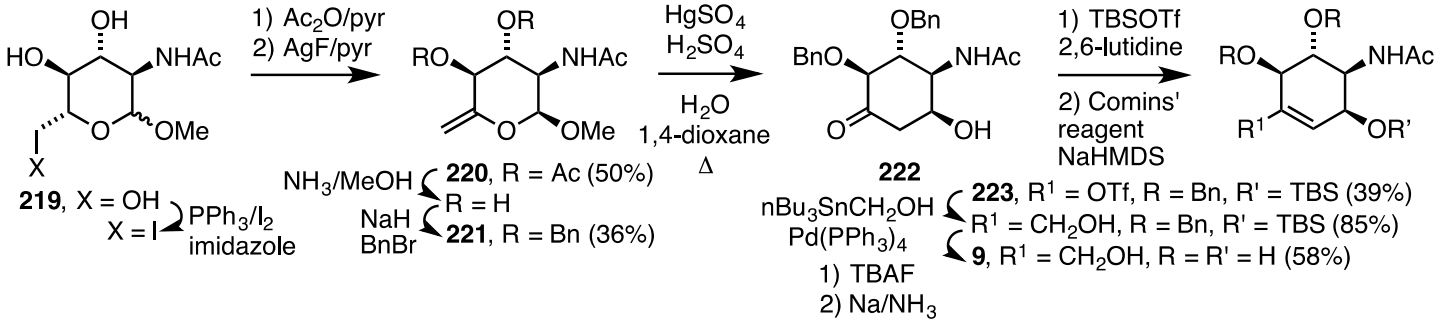


Scheme 29. Bauder synthesis of orthogonally protected 2-deoxystreptamine derivative.



Scheme 30. Ye synthesis of (+)-neamine (**218**).

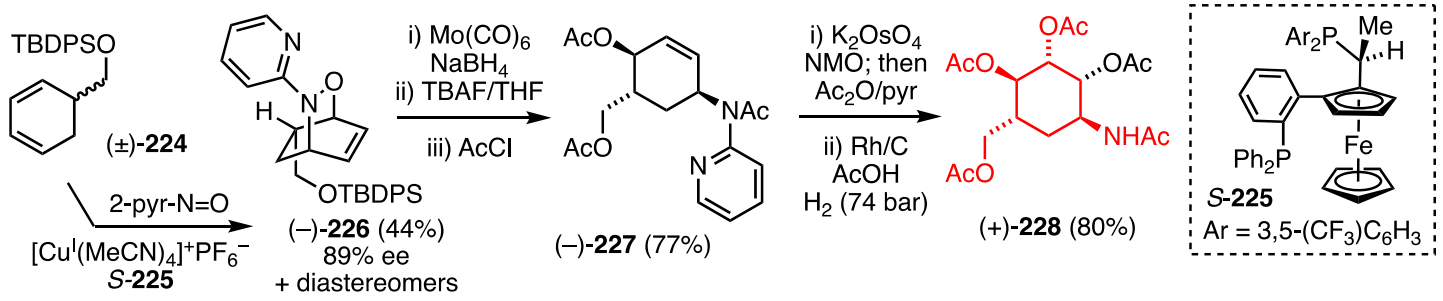
The Gademann group used an NMR-guided fractionation approach to identify a new C7N aminocyclitol (**9**, Scheme 31) from the obligate leaf nodule symbiont bacterium *Burkholderia kirkii*.[2] After isolation by reverse phase HPLC and prep TLC, the structure of **9** was assigned on the basis of its on NMR and MS spectral data and eventually confirmed by single crystal X-ray diffraction. Total synthesis of **9** commenced with methyl-*N*-acetyl-D-glucosamine **219**. Iodination, acetylation and elimination with silver fluoride gave the enol ether **220**. Protecting group reorganization gave **221** which underwent a carbo-Ferrier rearrangement upon treatment with $HgSO_4$ and sulfuric acid to afford the cyclohexanone **222**. The hydroxymethyl substituent was introduced by generation of the enol triflate **223** and Pd-catalyzed coupling with hydroxymethylstannane. Deprotection generated the natural product **9**. This compound, which the authors termed kirkamide, was found to be toxic to aquatic arthropods and insects with an LD_{50} = 0.48 mg/mL.



Scheme 31. Gademann synthesis of kirkamide (**9**).

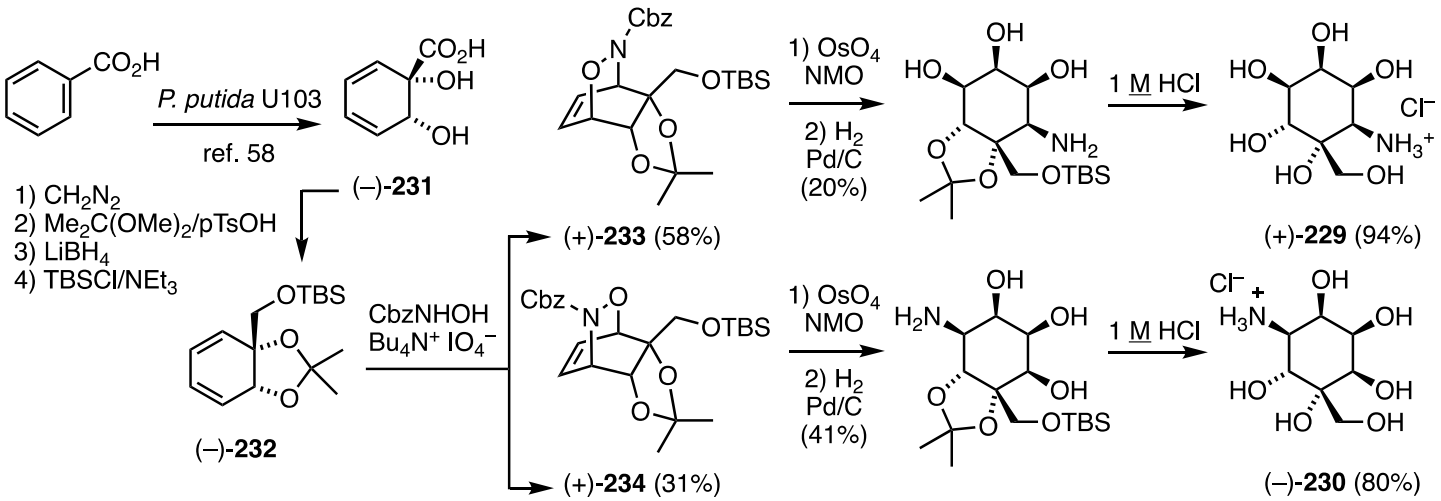
4. Nitroso Diels-Alder Cycloadditions

Jana and Studer studied Cu-catalyzed regiodivergent [2+2]-cycloadditions of 2-nitrosopyridine with racemic 5-substituted-1,3-cyclohexadienes (Scheme 32).[56] For example, the reaction of (±)-**224** with 2-nitrosopyridine can, in principle, result in 8 different regio- and stereoisomers. In the presence of walphos ligand (*S*)-**225**, cycloaddition resulted in (–)-**226** (89% ee), which was separable from the other stereoisomers. Reduction of the oxazine N–O bond, desilylation and acetylation gave the cyclohexene (–)-**227**. Dihydroxylation and reductive removal of the 2-pyridyl group afforded peracetylated 2-*epi*-validamine (+)-**228**.



Scheme 32. Jana and Studer synthesis of 2-epi-validamine via regiodivergent nitroso cycloaddition.

Lewis and co-workers prepared novel aminocyclitol analogs (+)-**229** and (–)-**230** beginning with inexpensive achiral starting material benzoic acid (Scheme 33).[57] Dihydroxylation of benzoic acid with *P. putida* U103 is known to afford the *ipso,ortho*-diol (–)-**231**,[58] which is transformed into the acetonide (–)-**232** after four steps. Cycloaddition of **232** with the acylnitroso generated from *N*-(benzyloxycarbonyl)hydroxyl-amine gave a separable mixture of two bicyclooxazines (+)-**233** and (+)-**234** respectively. Formation of the heterocycle on the face opposite to the bulky acetonide functionality was confirmed by NOESY correlations, while the regiochemistry of the cycloaddition was established by X-ray crystal structure of a derivative of **234**. Facial selective dihydroxylation, reductive cleavage of the oxazine N–O bond, and deprotection gave the regioisomeric aminocyclitols hydrochloride salts (+)-**229** and (–)-**230**. These novel aminocyclitols exhibited no inhibitory activity against α-glucosidase, β-glucosidease, β-galactosidase or β-glucuronidase at 100 μM.



Scheme 33. Lewis synthesis of optically active novel aminocyclitols via acylnitroso cycloaddition.

5. Conclusions

While aminocyclitols have been known and prepared numerous times, synthesis of these targets is still attractive, as evidenced by these examples from 2008 to present. Certain of these targets have been prepared by numerous routes during this period. For example valienamine, (+)-**2**, was prepared from cyclic chiral pool precursors (Scheme 7), from amino acid precursors via aldol condensation (Scheme 15) or via RCM (Scheme 18), or from sugar or tartaric acid precursors via RCM (Schemes 17, 19) while (±)-**2** was prepared from achiral *myo*-inositol (Scheme 12). The routes from *cyclic* chiral pool starting materials are particularly attractive, since no ring forming reactions are required and the multiple stereocenters inherent in these precursors can be translated into stereocenters in the target molecule. In contrast, those syntheses involving ring formation, such as RCM, aldol condensations or radical cyclizations may require significant experimentation with reaction conditions or conformational contraints in order to optimize the yields and or stereochemical outcome. Alternatively, synthetic routes proceeding via cyclohexene or cyclohexadiene intermediates provide an advantage for the generation of stereochemical diversity, since complementary oxidative functionalization reactions allow for variations in hydroxyl stereochemistry. Finally, the on-going efforts in natural product isolation should continue to provide new aminocyclitol targets.

Acknowledgements

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Author's Biography

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