Approaches to the Total Synthesis of Conduramines: A Review

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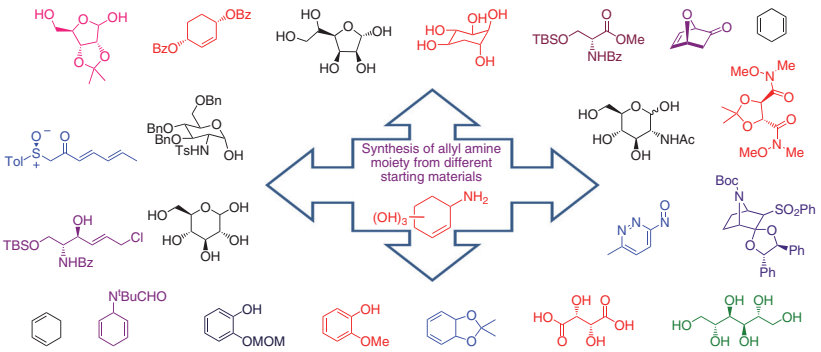

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Abstract This review reports on the total synthesis of conduramines, which are formally derived from conduritols, mainly containing a trihydroxy aminocyclohexene core. Analysis of the different strategies developed to prepare these aminocyclohexene triols and their derivatives has been carried out with special attention paid to the methods employed for the insertion of the chiral amine moiety.

Key words conduritols, conduramines, aminocyclitols, total synthesis, cyclohexenes

Conduramines are aminocyclohexenetriols formally derived from conduritols, in which one of the hydroxyl groups is exchanged with an amino group.[1] Many of these conduramines exhibit significant glycosidase inhibitory activity. The conduramines are also chiral building blocks for natural products such as (+)-narciclasine, (+)-valienamine, and (+)-lycoricidine.[2] They are also important as synthetic precursors of amino cyclitols and many of these constitute the aglycon portion of therapeutically useful aminoglycoside antibiotics.[3] In addition, the conduramines are used as intermediates in the synthesis of aminosugars, sphingosines, azasugars, and narcissus alkaloids.[4] Conduramines are classified into different types, based on the position of the amino group on the cyclohexene ring. The group in which the amino group occupies an allylic position on the ring comprises conduramines A, A-1, B-1, *ent*-C-1, D-1, E-1, F-1, C-4, E-4, *ent*-F, and F-4 and when the amino group is sandwiched between two hydroxyl groups, conduramine B-2 and F-2 (Figure 1).

Different methods have been designed for the synthesis of conduramines starting from carbohydrate and non-carbohydrates precursors. In this review article we described the total syntheses of conduramines that have been published since 2006.

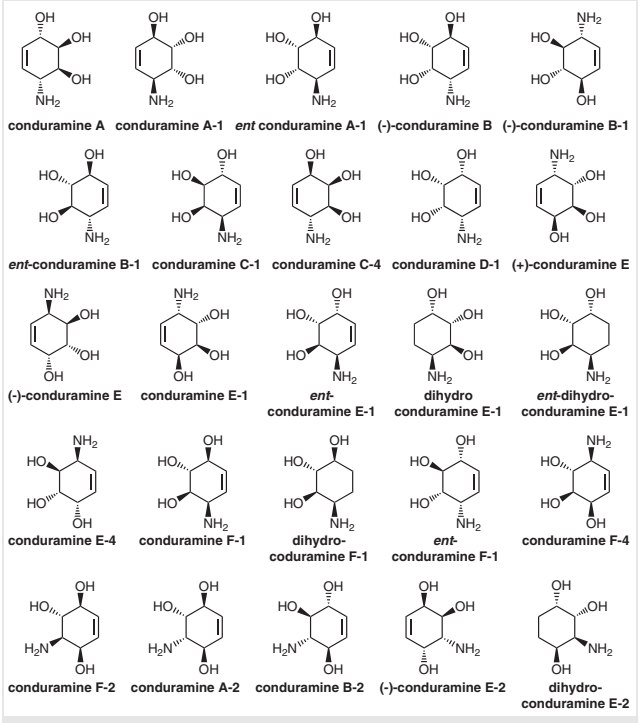


Figure 1 The conduramine family

Earlier approaches have been covered in review articles published by Vogel *et al.*, in 2006[5] and enzymatic methods of synthesis by Hudlicky *et al.*, in 2011.[6] In this review, most of the reported approaches have focused on conduramines with an allylic amine moiety.

Vogel *et al.*, in 2006,[7] reported the synthesis of (–)-conduramine F-1 from (±)-7-oxabicyclo[2.2.1]hept-5-en-2-one **1** (compound **1** was prepared by using their earlier protocol[8]).

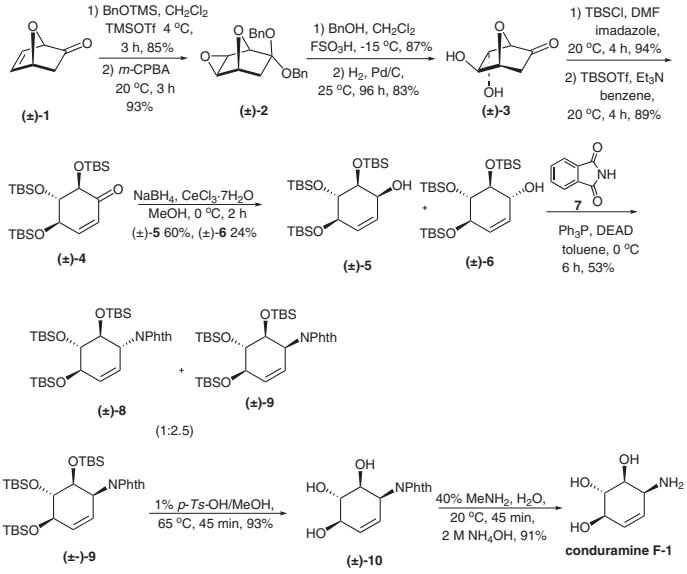
Biographical Sketches

Dr. B. Venkateswara Rao was born in 1960 in Nellore, Andhra Pradesh, India. He graduated in Chemistry (1981) from Sri Venkateswara University, Tirupati, India and obtained his M.Sc. degree (1983) from Sri Krishna Devaraya University, Anantapur, India. He received his Ph.D. in Chemistry (1990) under the supervision of Dr. A. V. Rama Rao from Osmania University. He joined as a Scientist in 1992 at the Indian Institute of Chemical Technology (CSIR-IICT), Hyderabad, and also worked as postdoctoral fellow under the guidance of Prof. Bert Fraser Reid from 1990 to 1992 at Duke University, Durham, USA. His research interests are in the areas of development of new synthetic routes, methodologies and their application in the synthesis of natural and unnatural products and carbohydrate mimics and process development under the principles of green chemistry. He has published more than 120 publications and filed 12 patents to his credit. He recently retired as a Chief Scientist from CSIR-IICT in 2020 and is currently working as CSIR-Emeritus Scientist at CSIR-IICT, Hyderabad.

Dr. H. Bharathkumar was born in 1988 Anantapur, Andhra Pradesh, India. He graduated in Chemistry (2009) from Sri Venkateswara University and obtained his M.Sc. degree (2011) from Sri Venkateswara University. He also received his Ph.D. in Chemistry (2016) under the supervision of Professor Basappa from Bangalore University. Later he worked at Indian Pharmacopoeia as a Research Associate. Recently he joined as a Research Associate at the CSIR-Indian Institute of Chemical Technology under the leadership of Dr. B. Venkateswara Rao working on sugar chemistry.

Dr. J. Siva Krishna, was born in 1992, in Bhimavaram, Andhra Pradesh, India. He graduated in chemistry (2012) from Andhra University and obtained his M.Sc degree (2014) from Andhra University. He received his PhD under the supervision of Dr. B. Venkateswara Rao from the Indian Institute of Chemical Technology, Hyderabad. Currently he is working at GVK biosciences, Hyderabad.

Dr. B. Surender was born in 1990 Mahabubabad, Telangana, India. He graduated in Chemistry (2010) from Kakatiya University and obtained his M.Sc. degree (2013) from Osmania University. He received his Ph.D. in Chemistry (2021) under the supervision of Dr. B. Venkateswara Rao from the Indian institute of Chemical Technology, Hyderabad. Currently he is working at IIT Hyderabad as a member of the Technical Staff.



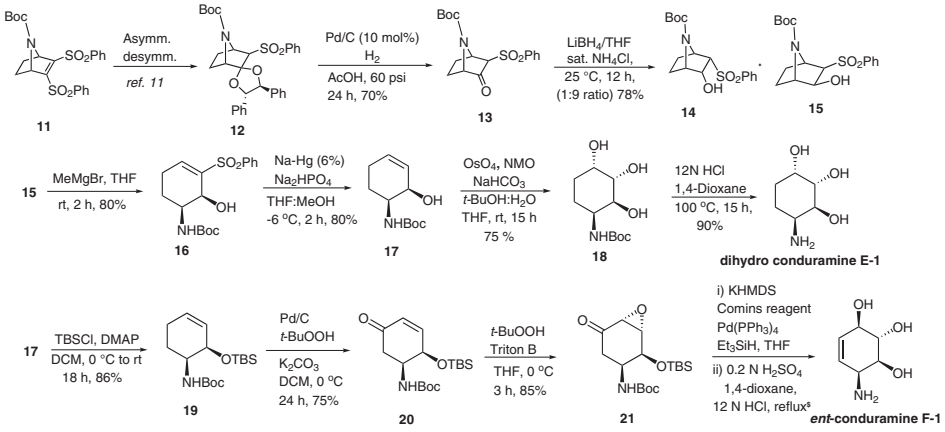
Scheme 1 Synthesis of conduramine F-1

Reduction of cyclohexenone **4** (which was obtained from **1** via **2** and **3**[9]) using $NaBH_4/CeCl_3$ in aqueous methanol gave a mixture of compounds **5** and **6**, respectively (Scheme 1).

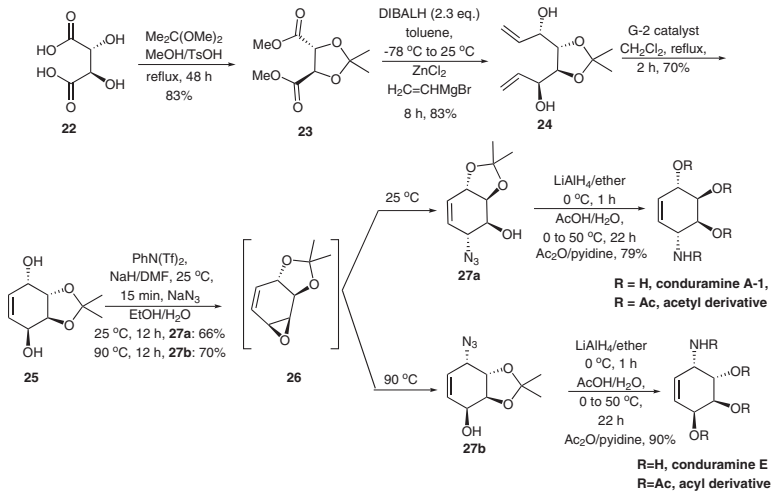
This mixture was treated with diethyl azodicarboxylate, phthalimide **7**, and triphenylphosphine in anhydrous toluene to give a mixture of *N*-substituted phthalimides **8** and **9** (1:2.5), which were separated by flash chromatography. Racemic **9** was subjected to desilylation, followed by aminolysis with 40% aq. CH_3NH_2, to give pure conduramine F-1 (Scheme 1).

Pandey *et al.*, in 2008,[10] reported the synthesis of dihydroconduramine E-1 and *ent*-conduramine F-1 from 7-azabicyclo[2.2.1]heptane-2-ol **11** (Scheme 2). Asymmetric desymmetrization of *meso*-compound **11** gave the desymmetrized compound **12** in 80% yield (99% *de*) using a reported protocol.[11] The ketal moiety was removed from **12** by hydrogenation to give **13**, which, on reduction with lithium borohydride, afforded a mixture of diastereomeric alcohols **14** and **15** (1:9). Ring opening of **15** with excess of MeMgBr in THF at room temperature gave compound **16**, which was treated with 6% Na/Hg in CH_3OH to furnish **17**. Compound **17** was subjected to oxidation with OsO_4 and *N*-methylmorpholine *N*-oxide (NMO) to give **18**, and subsequent Boc deprotection gave dihydroconduramine E-1.

Compound **17** was also subjected to TBS protection to give **19**, allylic oxidation of which with Pd/C and *tert*-butyl hydroperoxide in dichloromethane at 0 °C gave enone **20** (Scheme 2). This was subjected to nucleophilic epoxidation using Triton-B and *tert*-butyl hydroperoxide in THF at 0 °C to give the single product **21** due to facial selectivity. Compound **21** was treated with KHMDS/ Comins' reagent to yield the enol triflate, which was further treated with



Scheme 2 Synthesis of dihydro conduramine E-1 and *ent*-conduramine F-1. [a] Neither yield nor time were mentioned in reference paper.

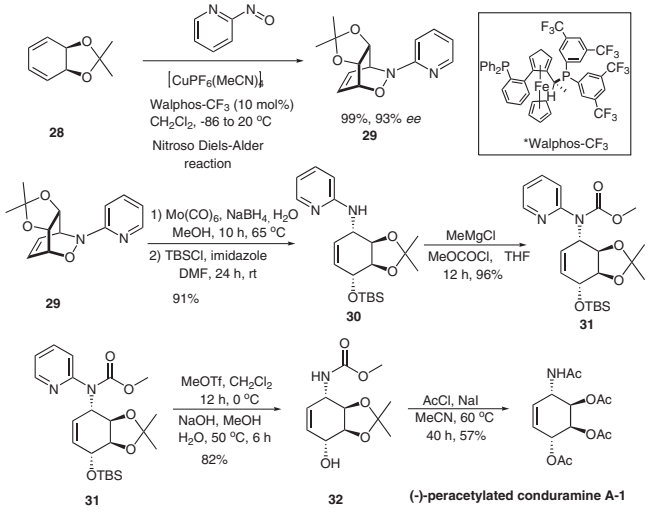


Scheme 3 Synthesis of conduramine A-1 and conduramine E

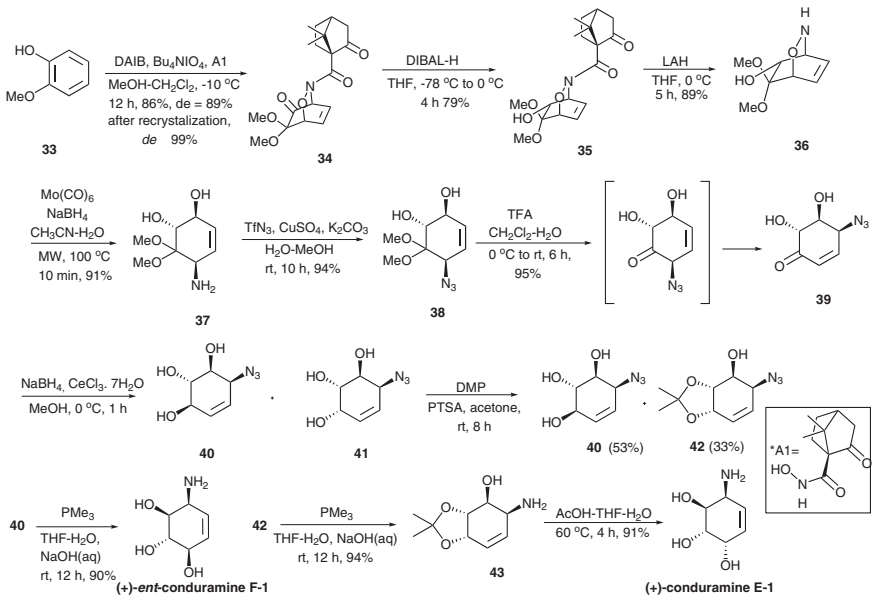
$Pd(PPh_3)_4$ and triethylsilane to afford the corresponding olefin derivative. Epoxide ring opening and deprotection with 0.1 M H_2SO_4 and 10 M HCl in dioxane under reflux conditions afforded *ent*-conduramine F-1.

Chang *et al.*, in 2009,[12] synthesized conduramines A-1 and E from L-tartaric acid **22** (Scheme 3). Treatment of **22** with 2,2-dimethoxypropane gave dimethyl 2,3-*O*-isopropylidenetartrate **23**, which was subjected to reduction with DIBAL-H, followed by diastereoselective divinyl zinc addition to the *in situ* generated dialdehyde to furnish the desired vinyl carbinol **24**. RCM of compound **24** afforded the corresponding cyclic diol **25**; subsequent epoxidation, followed by heating with azide at different temperatures gave the allylic azides **27a** and **27b**. Compounds **27a** and **27b**, on treatment with LAH and then quenching with H_2O/AcOH, gave conduramines A-1 and E, respectively.

Jana *et al.*, in 2009,[13] reported the synthesis of (–)-peracetylated conduramine A-1 from diene **28** and 2-nitrosopyridine (Scheme 4). They achieved good diastereoselectivity and enantioselectivity in the Diels–Alder reaction (**29**, 99%, d.r. >99:1, 93% *ee*). This nitroso-Diels–Alder product **29** was then used to synthesize peracetylated conduramine A1. In compound **29**, the N–O bond was cleaved with $Mo(CO)_6/NaBH_4$ followed by silylation to give the protected alcohol **30**. The amine group of compound **30** was subjected to carbamoylation by treatment of the corresponding magnesium amide with methyl chloroformate to give **31** (96%), which was subjected to *N*-methylation and removal of the pyridyl group by hydrolysis of the pyridinium salt to give compound **32**. Finally, removal of the carbamate and acetal groups and peracetylation using AcCl in combination with sodium iodide in CH_3CN, gave protected (–)-conduramine A-1 in a one-pot conversion.



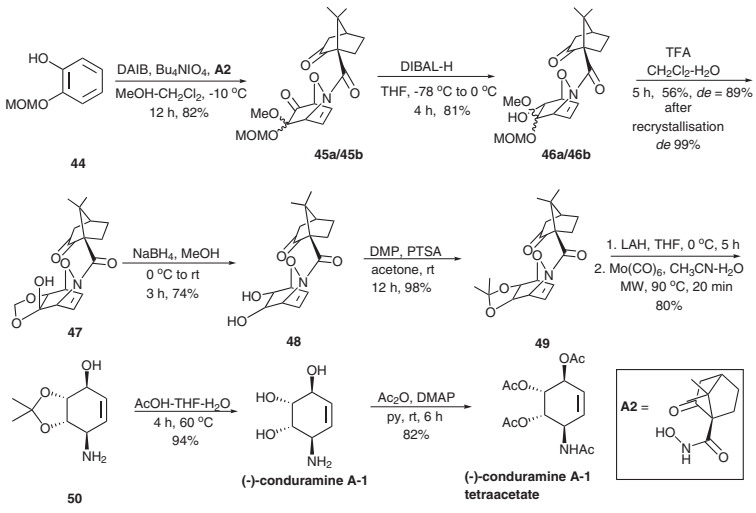
Scheme 4 Synthesis of (–)-peracetylated conduramine A-1



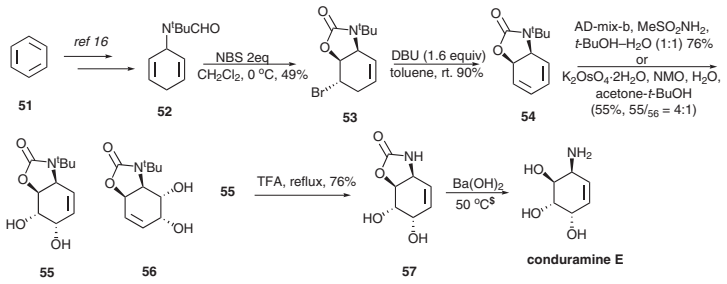
Scheme 5 Total synthesis of (+)-*ent*-conduramine F-1 and conduramine E-1

Lu *et al.*, in 2010,[14] reported the synthesis of (+)-*ent* conduramines F-1 and E-1, (–)-conduramine A-1 and A-1-tetraacetate from masked *O*-benzoquinones with enantiomerically pure nitroso dienophiles (Scheme 5). The nitroso compound **34** was prepared from the chiral auxiliary A1 (prepared from (1*S*)-(+)-10-camphorsulfonic acid) and 2-methoxyphenol **33**. Then compound **34** was treated with DIBAL-H to give hydroxy-compound **35**, which was treated with LAH to give oxazine **36**. Subjecting **36** to reductive cleavage of the N–O bond in the presence of $Mo(CO)_6/NaBH_4$ afforded the amino alcohol **37**. The amine group in compound **37** was converted into azide **38** using trifluoromethanesulfonylazide and $CuSO_4$ and this was subjected to ketal hydrolysis with TFA to afford enone **39**. Enone **39** was reduced using Luche's reagent to furnish an inseparable mixture of alcohols **40** and **41** (53:33). This alcoholic mixture was treated with DMP to give the protected *cis*-diol **42**. Alcohol **40** was treated with trimethylphospine in THF/H_2O to give the (+)-*ent*-conduramine F-1. A similar strategy was applied to prepare **43** from **42** and subsequent ketal deprotection gave (+)-conduramine E-1.

For the synthesis of conduramine A-1, the MOM protected compound **44** was treated with chiral auxiliary A2, derivative of (1*R*)-(–)-10-camphorsulfonic acid to give an inseparable mixture of compounds **45a** and **45b** (Scheme 6). These compounds further reacted with DIBAL-H to afford **46a** and **46b**. Compounds **46a** and **46b** were subjected to hydrolysis with TFA to give hemiketal **47**, and was sub-



Scheme 6 Syntheses of (–)-conduramine A-1 and A-1 tetraacetate



Scheme 7 Synthesis of conduramine E. [a] Reaction yield was not noted in the reference paper.

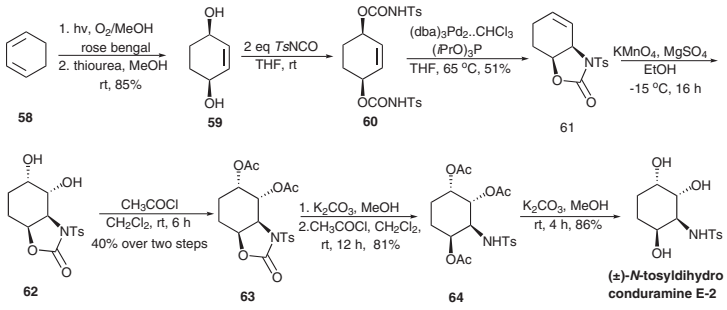
jected to reduction by $NaBH_4$ to give diol **48**. Compound **48** was further reacted with DMP to afford ketal **49** and this was reacted with $LiAlH_4$ and $Mo(CO)_6$ to give amino alcohol **50**. Deprotection of **50** gave the target (–)-conduramine A-1 and further acetylation gave (–)-conduramine A-1 acetate.

Russell *et al.*, in 2010,[15] reported the synthesis of conduramine E. Compound **52** was obtained by using a reported procedure[16] from benzene **51** (Scheme 7). Treatment of **52** with two equivalents of NBS gave the oxazolidinone **53** in 49% yield, and treatment of this with DBU gave the diene **54** in 90% yield. Compound **54** was subjected to regio- and stereoselective dihydroxylation with ADmix-β for 5 hours between 0 °C and –5 °C, furnishing **55** as a single region- and stereoisomer in 76% yield, or with $K_2OsO_4{\cdot}2H_2O$, NMO, H_2O, acetone, *t*-BuOH (55%, **55**/**56** = 4:1). Deprotection of compound **55** with TFA followed by hydrolysis with $Ba(OH)_2$ gave conduramine E.

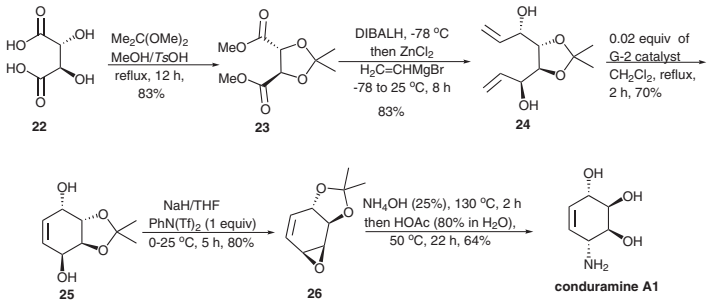
Kelebekli *et al.*, in 2010,[17] reported the synthesis of *N*-tosyldihydroconduramine E-2 from diene **58** (Scheme 8). Compound **58** was subjected to photochemical peroxidation using rose bengal in MeOH followed by treatment with thiourea to give the allylic *cis*-diol **59**. Diol **59** was reacted with *p*-TsNCO in THF to obtain the bis-carbamate **60**, then the reaction mixture was heated to 65 °C and the resulting solution was treated with 15 mol% triisopropyl phosphate and 5 mol% of tris(dibenzylideneacetone) dipalladium chloroform complex at the same temperature to give oxazolidinone **61**. The latter was subjected to dihydroxylation with $KMnO_4$ to give oxazolidinone *cis*-diol **62**. Compound **62** was treated with acetyl chloride in dichloromethane to give oxazolidin-2-one diacetate **63** and hydrolysis of **63** with K_2CO_3 in CH_3OH at room temperature and then treatment with acetyl chloride gave compound **64**. Finally, global deprotection of all the acetate groups with K_2CO_3 in methanol gave the *N*-tosyldihydroconduramine E-2.

Chang *et al.*,[18] in 2010, reported the synthesis of (+)-conduramine A-1 starting from L-tartaric acid **22**, forming compound **26** using the procedure outlined in Scheme 3. Epoxide **26** was treated with ammonium hydroxide (25%) followed by acetal deprotection to afford conduramine A-1 (Scheme 9).

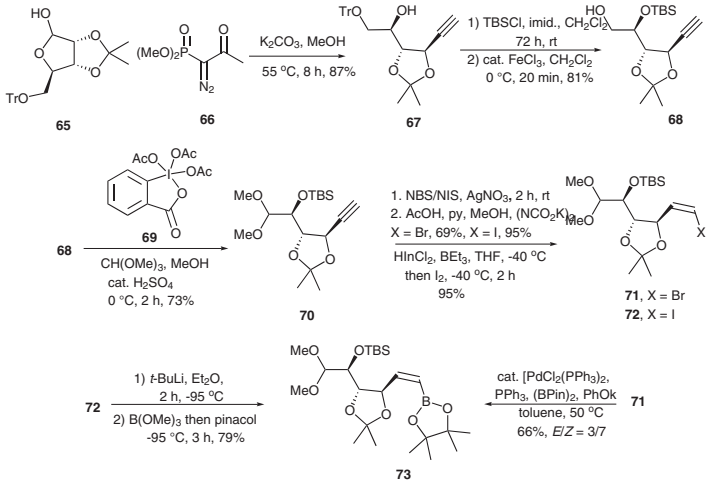
Norsikian *et al.*, in 2012,[4] synthesized *ent*-conduramine A-1 and conduramine C-4 from D-ribose (Scheme 10). The D-ribofuranose derivative **65** was treated with dimethyl-(1-diazo-2-oxopropyl) phosphonate **66** under Demailly's conditions to give compound **67**. The secondary alcohol of **67** was subjected to TBS protection and subsequent trityl group removal with iron trichloride gave intermediate **68**. The primary alcoholic group of **68** was subjected to DMP oxidation followed by trimethylorthoformate treatment to form acetal **70**. Compound **72** was directly prepared from **70**, using triethyl borane induced hydrometallation followed by iodolysis of the corresponding *Z*-alkenylindium species. Bromide **71** and iodide **72** were also synthesized in two steps by halogenation of the alkyne with NBS or NIS in the presence of silver nitrate followed by diimide *cis*-hydrogenation. The alkenyl bromide **71** underwent palladium-catalyzed cross coupling with bis(pinacolato)diboron to give the alkenyl boronic acid pinacol ester **73** in a *Z*/*E* ratio



Scheme 8 Synthesis of (±)-*N*-tosyldihydroconduramine E-2



Scheme 9 Synthesis of conduramine A-1

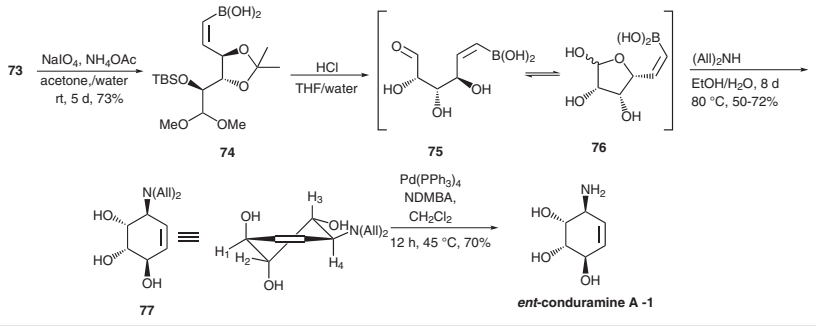


Scheme 10 Preparation of boronic ester **73**

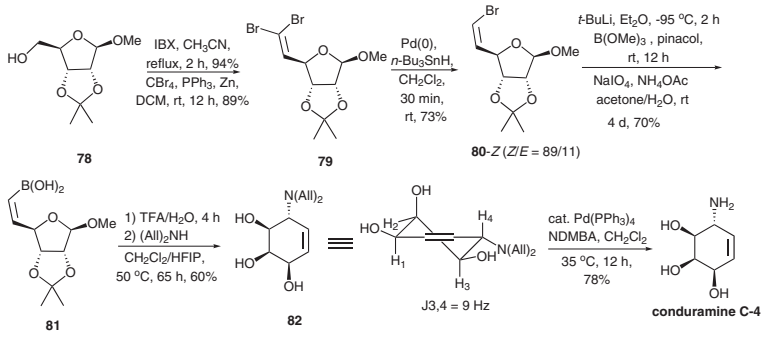
of 70:30. Alternatively, compound **72** was subjected to halogen–metal exchange followed by treatment with trimethyl borate and pinacol to give the boronic ester **73**.

A large excess of trimethyl borate (20 equiv) was required to obtain boronic ester **73** in a good yield. Treatment of boronic ester **73** with $NaIO_4$ afforded the corresponding boronic acid **74**. Removal of all the protecting groups with 6 M HCl in THF followed by treatment with excess of diallylamine in EtOH/H_2O at 80 °C for 19 hours gave the cyclized product **77**. Deprotection of the allyl group in compound **77** gave *ent*-conduramine A-1 (Scheme 11).

In their synthesis of conduramine C4, oxidation of β-D-ribofuranoside derivative **78** gave the aldehyde moiety and the resultant aldehyde was treated with PPh_3 and CBr_4 in the presence of activated Zn to give the dibromalkene **79** (Scheme 12). Pd-catalyzed hydrogenolysis of **79** with *n*-



Scheme 11 Synthesis of *ent*-conduramine A-1

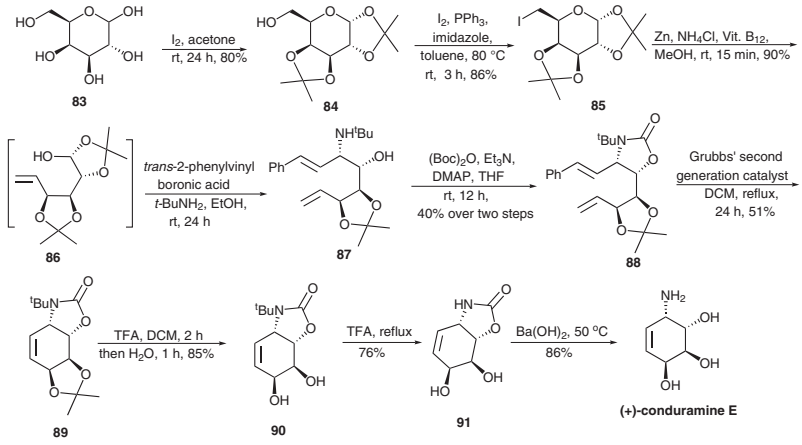


Scheme 12 Synthesis of conduramine C-4

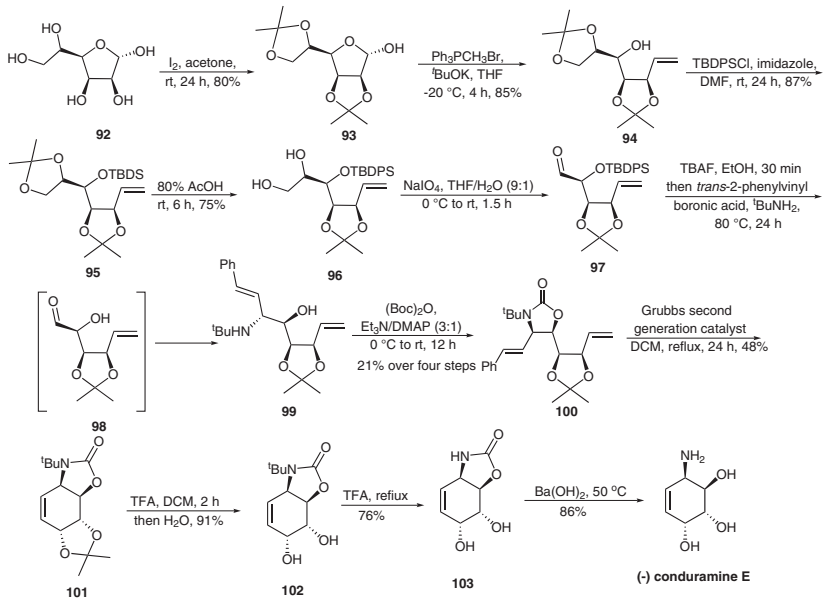
Bu_3SnH afforded **80**, which was subjected to boronic acid exchange to give compound **81**. Complete deprotection of **81** with TFA and treatment with diallylamine in EtOH/H_2O or in CH_2Cl_2/hexafluoroisopropanol afforded compound **82**, and deprotection of allyl group using palladium tetrakis(triphenylphosphine) gave conduramine C-4.

Ghosal *et al.*, in 2012,[19] reported the synthesis of (–)- and (+)-conduramine E. 1,2,3,4-Di-*O*-isopropylidine-α-D-galactopyranoside **84**, gave the iodo compound **85** on iodination, which was treated with zinc dust and catalytic cyanocobalamine to give hemiacetal **86** (Scheme 13). This was treated with *tert*-butylamine and *trans*-phenylvinyl boronic acid to give *erythro*-1,2-amino alcohol **87** exclusively. The amino alcohol **87** was reacted with Boc anhydride in the presence of DMAP/TEA in THF to give oxazolidinone **88** and this was subjected to RCM in the presence of Grubbs' 2nd generation catalyst to give the conduramine core moiety **89**. Deprotection of the acetonide group with TFA gave the diol **90**, which is a known intermediate for (±)-conduramine E synthesis. Deprotection of the *tert*-butyl group in compound **90** using TFA gave oxazolidinone **91** and basic hydrolysis of **91** using $Ba(OH)_2$ gave (+)-conduramine E.

2,3,5,6-Di-*O*-isopropylidine-α-D-mannofuranose hemiacetal **93** was synthesized from D-mannose **92** by the standard procedure (I_2/acetone). The anomeric carbon of compound **93** was subjected to Wittig methylenation to give the alkene **94**, and the free hydroxy group of **94** was protected with TBDPSCl to give compound **95** (Scheme 14). Selective deprotection of the terminal acetonide in **95** with 80% aq. acetic acid gave diol **96**. Oxidative cleavage of the diol fragment in compound **96** using $NaIO_4$ gave aldehyde **97**, and removal of the silyl group from aldehyde **97** with TBAF yielded the α-hydroxy aldehyde intermediate **98**. Subsequently, aldehyde **98** was subjected to Petasis borono-Mannich reaction with *trans*-2-phenylvinyl boronic acid and *tert*-butylamine under reflux to give the desired amine **99**, which was protected with Boc anhydride in the presence of base to give oxazolidinone **100**. RCM of diene compound **100** using Grubbs' 2nd generation catalyst gave the carbocyclic moiety of (–)-conduramine E **101**. Conversion of **101** into (–) conduramine E was carried out by a similar set of reactions to those detailed in Scheme 13.

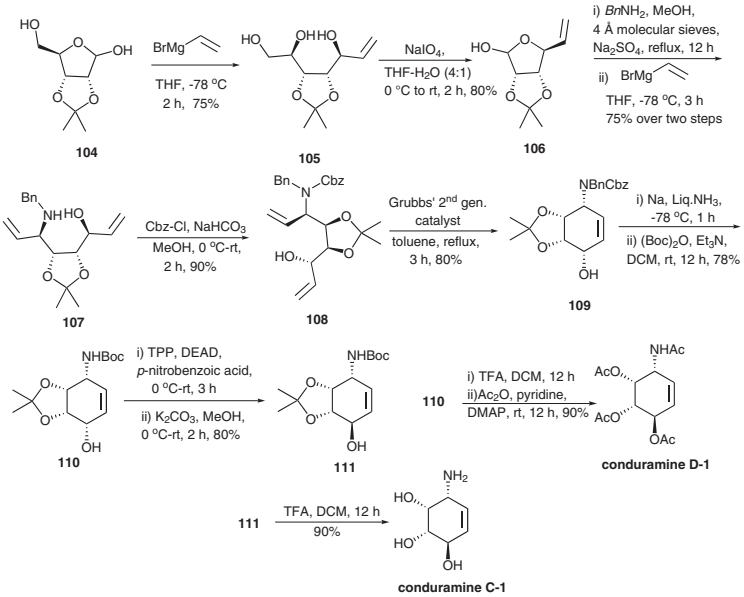


Scheme 13 Synthesis of (+)-conduramine E

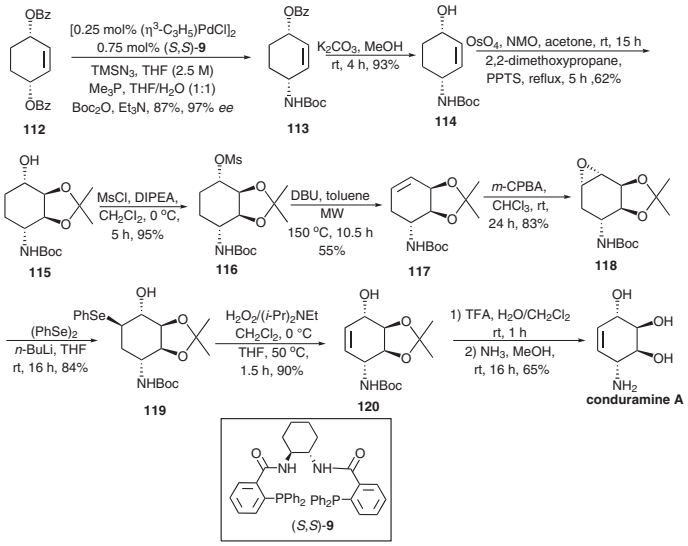


Scheme 14 Synthesis of (–)-conduramine E

Rao *et al.*, in 2013,[1] reported the synthesis of conduramine C-1 and conduramine D-1 from D-ribofuranose (Scheme 15). The derivative **104** was reacted with vinyl magnesium bromide at –78 °C in anhydrous THF to give triol **105**. The 1,2-diol was subjected to oxidative cleavage using $NaIO_4$ in THF/H_2O (4:1) to afford the lactol **106**, which underwent condensation with benzylamine in MeOH under reflux to give the glycosylamine. Stereoselective Grignard addition of the glycosylamine with vinyl magnesium bromide gave the *anti*-amino alcohol **107** exclusively. Amino alcohol **107** was subjected to Cbz protection to yield the diene compound **108** and this was subjected to RCM in the presence of 10 mol% Grubbs' 2nd generation catalyst at reflux in toluene to afford the desired cyclohexeneamine compound **109**. Compound **109** was then subjected to deprotection with Na/liq. NH_3, followed by protection with Boc anhydride to give **110**, which then underwent global deprotection with TFA in dichloromethane to afford condu-



Scheme 15 Synthesis of conduramine D-1 and conduramine C-1



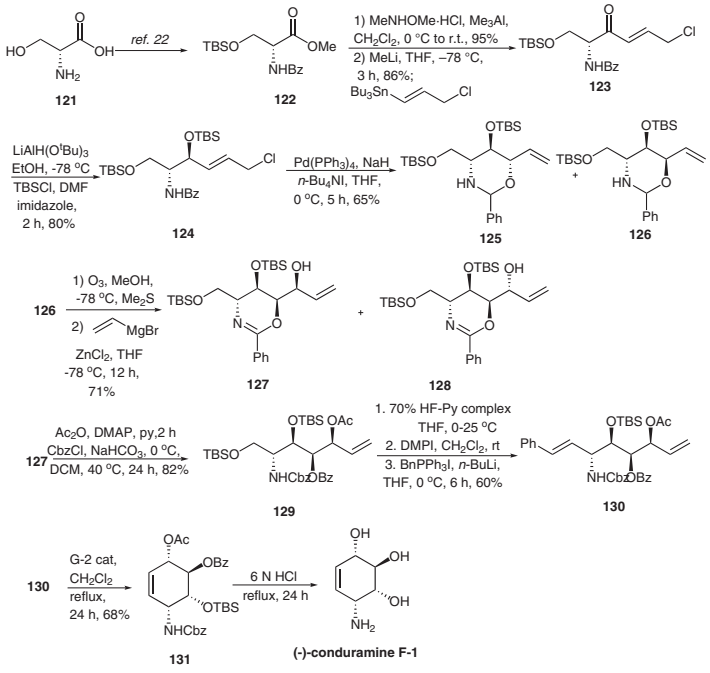
Scheme 16 Synthesis of conduramine A

ramine D-1. The free hydroxyl group of compound **110** underwent inversion under Mitsunobu conditions to yield the epimer **111**, and then deprotection gave conduramine C-1.

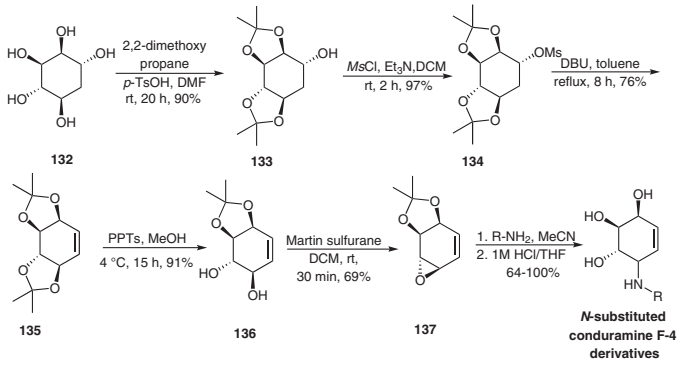
Trost and Malhotra, in 2014,[20] reported the preparation of conduramine A, through palladium-catalyzed asymmetric allylic azidation for the desymmetrization of *meso*-dibenzoate **112**; a procedure developed earlier to synthesize enantiomerically pure amino alcohols. The carbamate **113** was prepared from dibenzoate **112** by using a similar strategy (Scheme 16). Compound **113** then underwent benzoate hydrolysis to give allylic alcohol **114**, and diastereoselective OsO_4 catalyzed *cis*-dihydroxylation of **114** gave the triol, with subsequent protection with acetone giving the acetonide **115**. Treatment of alcohol **115** with mesyl chloride gave mesylate **116** and elimination under microwave conditions gave the alkene **117**. Epoxidation of **117** gave the epoxide **118** as a single isomer, which was treated with Li-phenyl selenide to give **119**. The product was further subjected to selenoxide cycloelimination to obtain conduramine A derivative **120**. Removal of protecting groups gave conduramine A.

Ham *et al.*, in 2015,[21] reported the synthesis of conduramine F-1. The *N*-benzoyl serine methyl ester **122** was prepared from serine **121** by using a reported procedure (Scheme 17).[22] The serine derivative **122** was then treated with *N*,*O*-dimethylhydroxylamine in the presence of $Al(CH_3)_3$ to give the corresponding Weinreb amide that was reacted with vinyl tin and CH_3Li at –78 °C in THF to give α,β-unsaturated ketone **123**. Compound **123** was subjected to reduction using Li-tri *t*-butoxyaluminohydride to give the *anti*-aminoalcohol, and subsequent TBSCl protection gave compound **124**. The latter was subjected to stereoselective intramolecular cyclization in the presence of $Pd(PPh_3)_4$, NaH, and TBAI in THF at 0 °C to give the *syn*,*syn*-oxazine **125** and *syn*,*anti*-oxazine **126** in a 9.5:1 mixture. Interestingly, when the authors increased the reaction temperature to 50 °C, the diastereoselectivity of the reaction was changed and the major isomer was *syn*,*anti*-oxazine **126** (1:9 mixture), in 73% yield. Ozonolysis of **126** gave the aldehyde, which was treated with vinylmagnesium bromide in the presence of $ZnCl_2$ in THF to give the allylic alcohols **127** and **128** in a ratio of 8:1 with 71% yield. The alcohol group in compound **127** was protected with acetic anhydride and treated with Cbz-Cl in the presence of aq. $NaHCO_3$ to generate carbamate **129**. TBS protection of the primary alcoholic group was removed with HF-Py complex, and the resultant alcohol group, on oxidation with DMP followed by treatment with triphenylphosphonium benzyl iodide, gave the phenyl-substituted diene **130**, and subsequent ring-closing metathesis gave **131**. Finally, global deprotection with 6N·HCl in MeOH gave the (–)-conduramine F-1.

Ogawa *et al.*,[23] in 2015, reported the synthesis of *N*-substituted conduramine F-4 derivatives (Scheme 18). Initially the (+)-*proto*-quercitol **132** was treated with 2,2-dimethoxypropane in DMF to afford diacetonide **133**. The hydroxy group on compound **133** was subjected to sulfonylation to give the mesylate **134**. Treatment of compound **134** with excess DBU under reflux conditions in toluene gave the cyclohexene compound **135**. The *trans*-isopropylidene group of compound **135** was then removed selectively by using a catalytic amount of pyridinium-*p*-toluenesulfonate (PPTS) in MeOH to give the diol compound **136**. Subsequent epoxidation of compound **136** with a slight excess of Martin sulfurane afforded the epoxide compound **137**. Finally, incorporation of various amine groups at the C-1 position of compound **137** via simple addition reactions with alkylamines and treatment with HCl/aq. THF afforded the *N*-substituted (+)-conduramine F-4 derivatives as HCl salts.



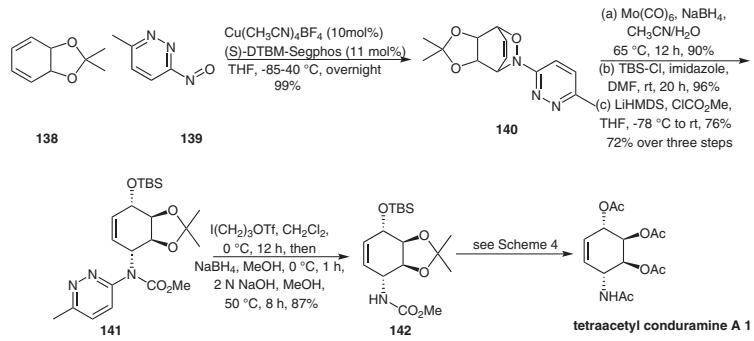
Scheme 17 Synthesis of (–)-conduramine F-1



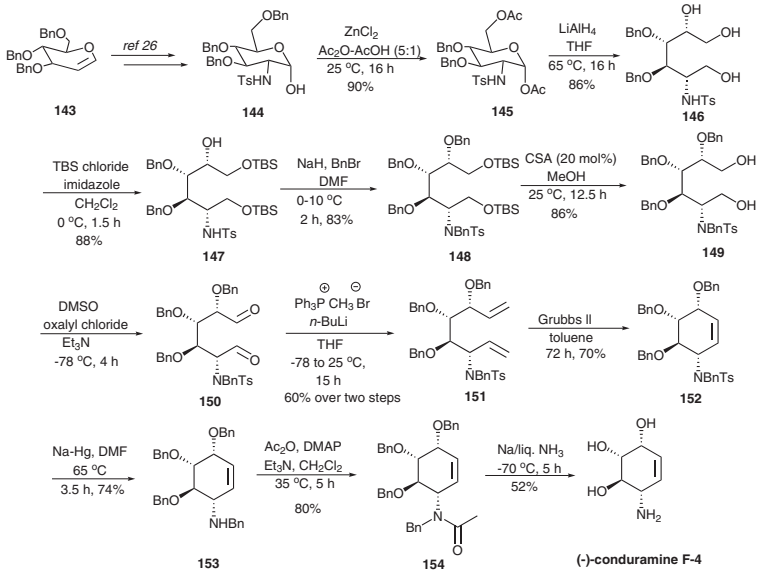
Scheme 18 Total synthesis of *N*-substituted (+)-conduramine F-4 derivatives

Maji and Yamamoto,[24] in 2015, reported the synthesis of conduramine A-1 (Scheme 19). The acetal protected *meso*-cyclohexa-3,5-diene-1,2-diol **138** was treated with **139** in the presence of a Cu catalyst to afford **140** with excellent enantio- and diastereoselectivity (d.r. >99:1 and >99% *ee*). Compound **140** was treated with $Mo(CO)_6$ to mediate reductive N–O bond cleavage, and O and N protection afforded **141**. Subsequent removal of the pyridazyl group by quaternization with 3-iodopropyl triflate, reduction with $NaBH_4$, and then a second quaternization and hydrolysis using NaOH in one pot, afforded **142**. Deprotection and acylation of **142** using the procedure described in Scheme 4[13] gave tetraacetyl conduramine A-1.

Harit and Ramesh, in 2016,[25] reported the synthesis of conduramine F-4 from D-glucose derived 1,6-diol **144** (3,4,5-tri-*O*-benzyl-2-deoxy-2-(*N*-benzyl-*N*-*p*-toluenesulfonyl)-amino-D-glucitol), prepared by using a reported procedure.[26] Selective debenzylative acetylation was carried out with zinc chloride in acetic acid–acetic anhydride in a ratio of 1:5 to give the 1,6-*O*-diacetate **145**, which was then treated with an excess of LAH to furnish triol **146** (Scheme 20). The primary alcohol groups in compound **146** were protected with TBS to give compound **147**, then benzylation of the secondary alcoholic group with benzyl bromide gave the fully protected compound **148**. Deprotection of compound **148** with camphorsulfonic acid gave the 1,6-diol **149**.



Scheme 19 Total synthesis of tetraacetyl conduramine A-1

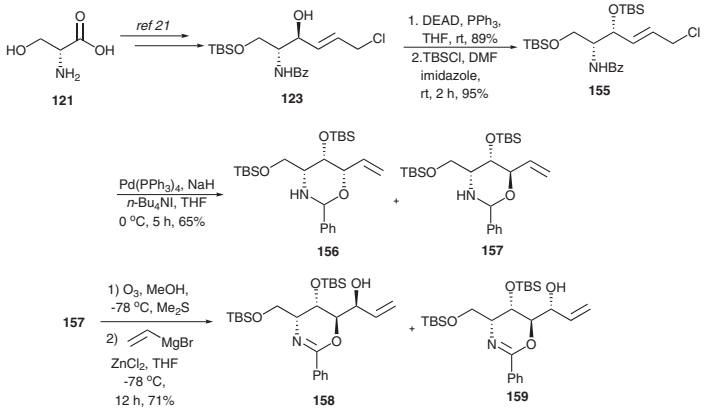


Scheme 20 Synthesis of conduramine F-4

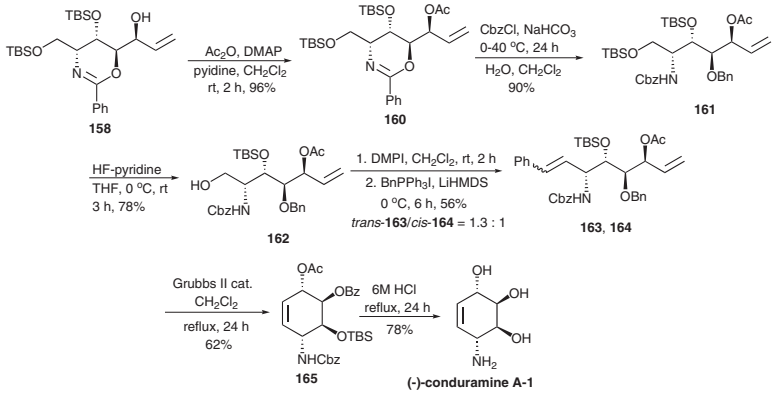
The diol **149** underwent Swern oxidation followed by Wittig reaction to furnish diene **151**. The ring closing of diene **151** with Grubbs' 2nd generation catalyst furnished protected (–)-conduramine F-4 **152**. *N*-Detosylation of **152** with Na-Hg gave the amino derivative **153**, which was subjected to acylation followed by deprotection using Na/liq. NH_3 to afford (–)-conduramine F-4 (Scheme 20).

Ham *et al.*, in 2016,[27] reported the synthesis of (–)-conduramine A-1 from D-serine by using the series of reactions shown in Scheme [17][21] (Scheme 21 and Scheme 22).

Raghavan *et al.*, in 2016,[28] reported the synthesis of (–)-conduramine B (Scheme 23). Initially compound **166** was treated with LDA and the anion was treated with ethyl sorbate **167** to give the β-keto sulfoxide **168**, which was subjected to diastereoselective reduction using DIBAL-H in the presence of anhydrous $ZnCl_2$ to give the diene alcohol **169**. Diene **169** was then treated with *N*-bromosuccinimide in dichloromethane to give the bromodiol **170**. The hydroxyl groups of **170** were protected as TBS ethers to give **171**, and reduction of the sulfinyl group using TFAA and NaI gave sulfide **172**. Treatment of **172** with *N*-chlorosuccinimide gave the α-chlorosulfide, which, on treatment with vinyl zinc bromide, gave diene sulfide **173** as the sole product. The silyl protecting groups of **173** were removed to give the bromodiol, which, on acetylation, afforded diacetate **174**. The crude diacetate was then treated with acetic anhydride to give the triacetate compound **175**. RCM of **175** using Grubbs' 2nd generation catalyst gave the allylic sulfide **176**. The acetate groups in **176** were subsequently hydrolyzed and the resultant product was protected by benzylation to give **177**. Treatment of **177** with *N*-chloro *N*-*tert*-butyloxy carbamate at 0 °C and heating the reaction mixture to room temperature gave the allylic amino derivative, which, upon treatment with $NaBH_4$ in CH_3OH, gave the (–)-conduramine-B derivative.



Scheme 21 *syn*,*anti*,*syn*-Oxazine approach

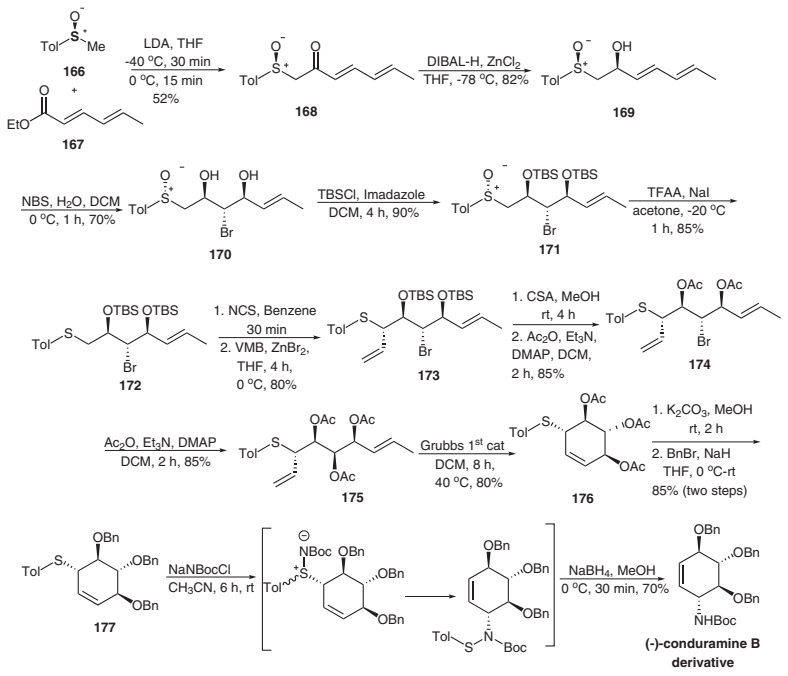


Scheme 22 Total synthesis of (–) conduramine A-1

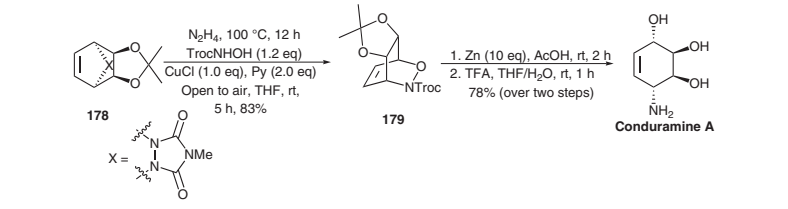
Sarlah *et al.*,[29] in 2016, reported the application of dearomative dihydroxylation for the synthesis of conduramine A via the corresponding 1,2,4-triazoline-3,5-dione-benzene adduct **178** through a modified hydrolysis oxidation that installed an additional 1,4-*syn*-aminohydroxy functionality via successive urazole hydrolysis, hydrazine/oxamic acid oxidation in one pot, and subsequent hetero-Diels–Alder reaction to afford the bicyclic product **179** in 83% yield. Subsequent N–O cleavage and removal of the trichloroethoxycarbonyl group, followed by acid-mediated deprotection of the acetonide, afforded conduramine A (Scheme 24).

Rao *et al.*, in 2017,[30] reported the synthesis of *N*-benzyl conduramine F-1, *N*-benzyl *ent*-conduramine E-1, dihydroconduramine F-1 and *ent*-dihydroconduramine E-1 from D-mannitol (Scheme 25). Initially they prepared diol **182** using a described protocol from D-mannitol. Aldehyde **183** was prepared using $NaIO_4$ via oxidative cleavage and was treated with vinyl magnesium bromide to give separable diastereomeric mixture of **184** and **185** (1:1.3). Deprotection of the primary acetonide and oxidative cleavage of compound **184** using H_5IO_6 gave aldehyde **186**, which was subsequently treated with benzylamine to give aldimine **187**. Nucleophilic addition on **187** using vinyl magnesium bromide in THF at –10 °C gave the *anti* product **188** exclusively. Amine **188** was subjected to Boc protection using $(Boc)_2O$ in the presence of sodium bicarbonate in CH_3OH to give **189**, which, on ring-closing metathesis using Grubbs' 2nd generation catalyst in dichloromethane, gave the cyclized product **190**. Treatment with 6 M HCl to give *N*-benzyl conduramine F-1, and reduction of the alkene and complete deprotection yielded dihydroconduramine F-1.

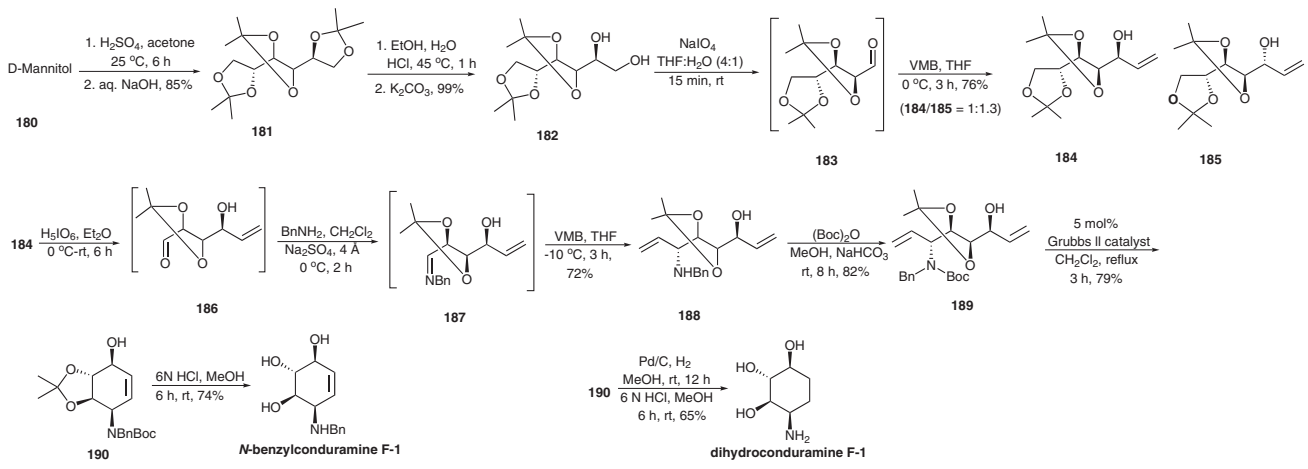
A similar sequence of reactions was carried out for the synthesis of *N*-benzyl *ent*-conduramine E-1 and *ent*-dihydroconduramine E-1 from compound **185** (Scheme 26).



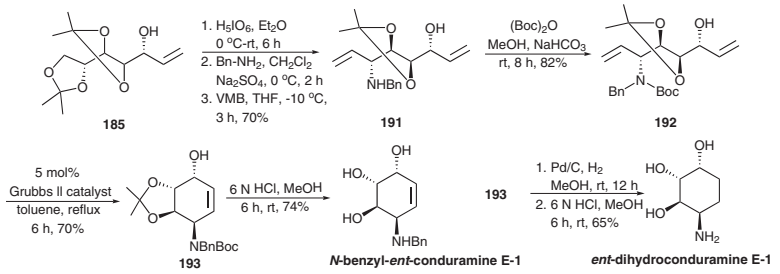
Scheme 23 Synthesis of conduramine (–)-B



Scheme 24 Synthesis of conduramine A



Scheme 25 Synthesis of *N*-benzyl-conduramine F-1 and dihydroconduramine F-1

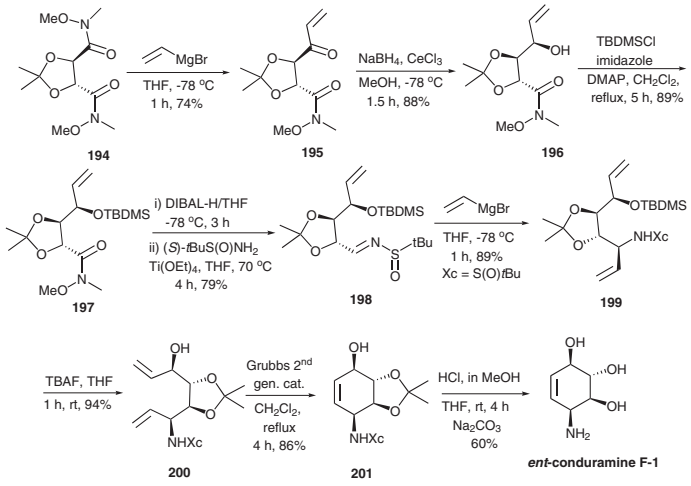


Scheme 26 Synthesis of *N*-benzyl *ent*-conduramine E-1 and *ent*-dihydroconduramine E-1

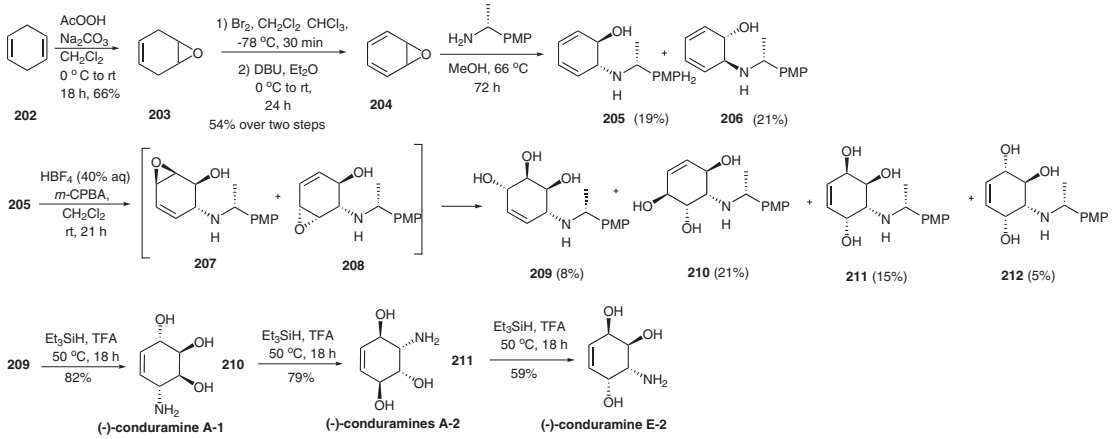
Prasad and Rangari, in 2018,[31] reported the synthesis of *ent*-conduramine F-1 from tartaric acid (Scheme 27). Vinyl magnesium bromide was added to the bis-Weinreb amide **194** to give the mono ketoamide **195**. The carbonyl group of compound **195** was subjected to stereoselective Luche reduction to give the alcohol **196** (*de* 99:1). The hydroxyl group of **196** was then protected as its *tert*-butyldimethylsilyl ether to give **197**. Treatment of **197** with DIBAL-H gave the corresponding aldehyde, and further reaction with (*S*)-*tert*-butylsulfinamide gave the sulfinimine **198**. Addition of vinyl magnesium bromide to **198** gave the sulfonamide **199** and TBS deprotection of **199** gave the diene **200**. Treatment of intermediate **200** with Grubbs' 2nd generation catalyst gave the cyclized product **201**. Removal of the sulfinyl and acetonide groups in **201** using HCl in methanol, followed by $NaHCO_3$ treatment gave *ent*-conduramine F-1.

Da Silva Pinto *et al.*, in 2019,[32] reported the synthesis of (–)-conduramines A-1, A-2, and E-2 (Scheme 28). Initially, **202** was subjected to oxidation in the presence of peracetic acid in dichloromethane to give the cyclohexa-1,4-diene monoepoxide **203**. Compound **203** was then subjected to bromination in a mixture of dichloromethane and chloroform to give the corresponding dibromide, which, on treatment with DBU, gave the benzene oxide **204**. The latter underwent ring opening with enantiopure (*R*)-α-methyl-*p*-methoxybenzylamine to afford a mixture of two compounds, **205** and **206**. Treatment of **205** with 40% aqueous HBF_4 and then *m*-CPBA gave a mixture of four compounds in a ratio of 17:37:32:14. These compounds were separated using preparative TLC and identified as *N*-α-methyl-*p*-methoxybenzyl derivatives of conduramine A1 (**209**), A2 (**210**), E2 (**211**), and F2 (**212**), respectively. Finally, removal of the α-methyl-*p*-methoxybenzyl fragment from **209**–**211** with Et_3SiH in the presence of TFA gave (–)-conduramine A-1, A-2, and E-2, respectively.

Harit and Ramesh,[33] in 2019, reported the synthesis of *ent*-conduramine F-2 and conduramine B-2 from precursor **143** (Scheme 29). Initially, intermediate **213** was prepared from compound **143** using a reported procedure.[29] Compound **213** was then heated at 50 °C with 1 equiv of $NaBH_4$ in THF and MeOH (1:1) to give **214**. Compound **214** was then subjected to chemoselective debenzylation and acetylation of the primary benzyloxy group at C-6 with $ZnCl_2$ in an acetic acid acetic anhydride mixture to furnish 6-*O*-acetate **215**, which was then hydrolyzed to alcohol **216** with sodium carbonate in methanol. Compound **216** was then converted into iodo compound **217** using PPh_3, I_2 and imidazole, and **217**, under sonication with Zn at 40 °C, under-



Scheme 27 Synthesis of *ent*-conduramine F-1



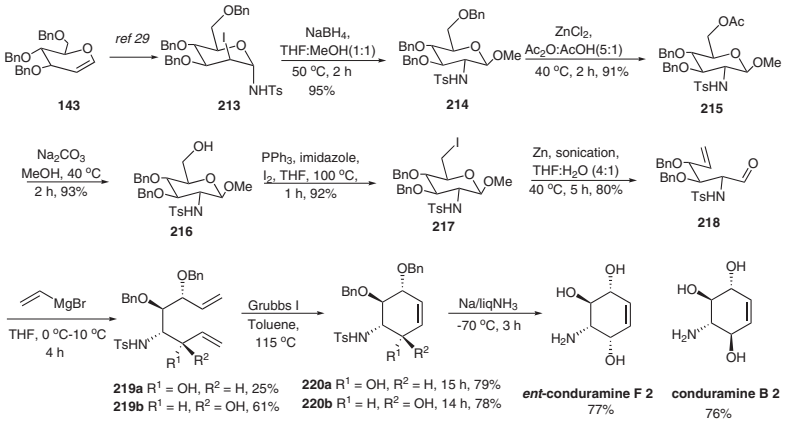
Scheme 28 Synthesis of (–)-conduramines A-1, A-2, and E-2

went Vasella reductive elimination to give the formylalkene **218**. Subsequently, **218** was treated with vinyl magnesium bromide in THF at 0–35 °C to give the dienes **219a** and **219b** as a separable mixture of diastereomers, in a ratio of 1:2.5, respectively.

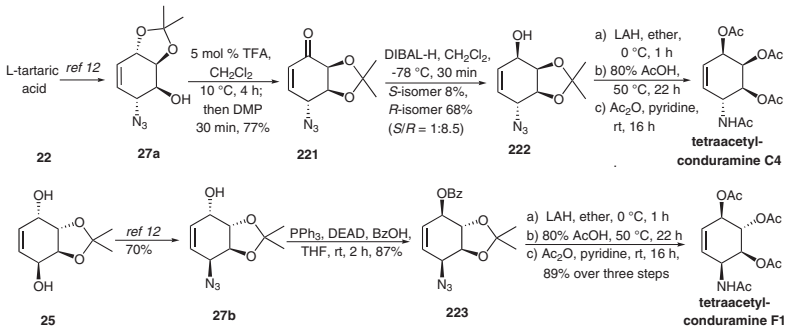
The dienes **219a** and **219b** were independently subjected to RCM in the presence of Grubbs' 1st generation catalyst to give **220a** (79%) and **220b** (78%), respectively. Global removal of the benzyloxy and tosyl protecting groups in compounds **220a** and **220b** with Na/liq. NH_3 afforded *ent*-conduramine F-2 and conduramine B-2 in 77 and 76% yield, respectively (Scheme 29).

Yan *et al.*,[34] in 2019, reported the synthesis of tetraacetyl conduramines B-1, *ent*-C-1, C-4, D-1, *ent*-F-1, and *ent*-F-4. Initially compound **27a** was prepared from L-tartaric acid **22** using a reported procedure (Scheme 3).[12] The azido alcohol **27a** was treated with trifluoroacetic acid (TFA) and oxidation of the allylic alcohol with DMP gave enone **221** (Scheme 30). Treatment of enone **221** with DIBAL-H at –78 °C afforded **222** in good yield with good selectivity (68%, *S*/*R* = 1:8.5). Treatment of compound **222** with LAH and subsequent acetonide deprotection and peracylation afforded the desired tetraacetyl conduramine C-4. The 1,4-*anti*-azido alcohol compound **27b** was synthesized from cyclic diol **25** (for details, see Scheme 3). Subsequently, treatment of **27b** with DEAD, benzyl alcohol, and PPh_3 in THF for 2 h afforded the 1,4-*syn*-azido alcohol **223**. Reduction of compound **223** with LAH, followed by acetonide removal and peracylation, yielded tetraacetyl *ent*-conduramine F-1 (Scheme 30).

Bromohydrin **224** was prepared from allylic epoxide **26** in a regioselective manner (see Scheme 3)[12,35] and was subjected to nucleophilic substitution with sodium azide to give azido alcohol **225** (Scheme 31). Compound **225** underwent TFA-catalyzed rearrangement to give the thermodynamically preferred *cis*-fused acetonide, and oxidation with DMP gave enone **226**. Luche reduction of enone **226** afforded the 1,4-*cis*-azido alcohol **227**. Subsequent acetonide re-



Scheme 29 Total synthesis of conduramine B-2 and *ent*-conduramine F-2

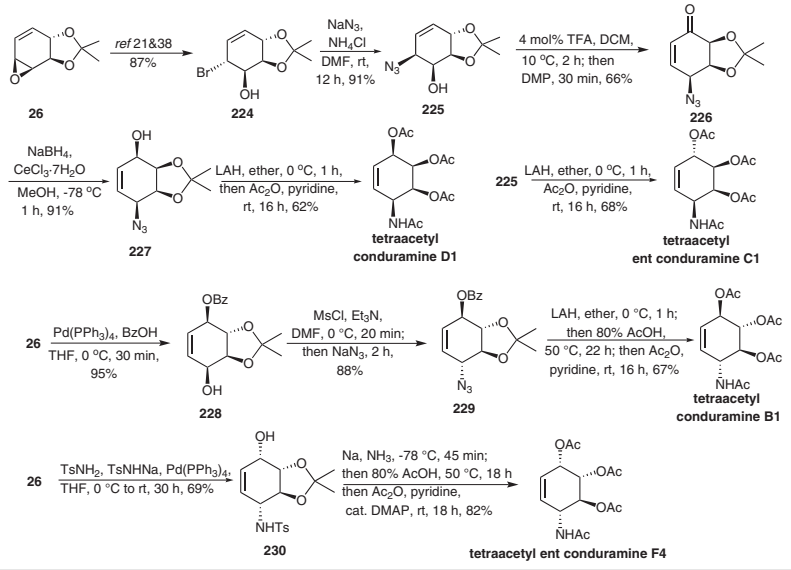


Scheme 30 Total synthesis of conduramine C-4 and tetra-acetyl conduramine F-1

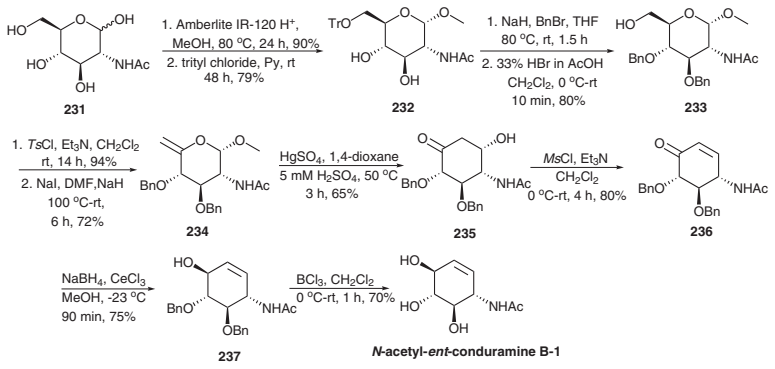
moval and peracylation of compound **227** resulted in conduramine D-1 tetraacetate. Treatment of compound **225** with LAH and subsequent acetonide deprotection and peracylation yielded the tetraacetyl *ent*-conduramine C-1.

The allylic epoxide **26** was treated with benzoic acid in the presence of 2 mol% $Pd(PPh_3)_4$, to give 1,4-*syn*-allylic alcohol **228**. The allylic alcohol unit of compound **228** was subjected to mesylation, followed by nucleophilic displacement with sodium azide, affording allylic azide **229**. Reduction of **229** with LAH, followed by acetonide removal and peracylation yielded tetraacetyl conduramine B-1. Compound **26** underwent palladium-catalyzed nucleophilic opening of the allylic epoxide with $TsNH_2$/TsNHNa in acetonitrile at 40 °C to give the 1,4-*syn*-amide **230**. The amide was then treated with Na/NH_3, followed by acetonide removal and peracetylation, to give tetraacetyl *ent*-conduramine F-4 (Scheme 31).

Narayana *et al.*, in 2021,[36] reported the synthesis of *N*-acetyl *ent*-conduramine B-1 from commercially available *N*-acetyl-D-glucosamine **231** (Scheme 32). Initially **231** was heated to reflux in CH_3OH in the presence of Amberlite IR-120-H1 resin to give the corresponding methylglycoside and this was treated with triphenylmethyl chloride in pyridine to give 6-*O*-trityl derivative **232**. Trityl derivative **232** was subjected to benzylation followed by removal of the trityl group to give **233**, which was subjected to tosylation followed by iodination and dehydrohalogenation at room temperature to furnish **234**.[37] Subsequently, **234** was subjected to $HgSO_4$ catalyzed Ferrier carbocyclization in 1,4-dioxane and 5 mM H_2SO_4(2:1) at 50 °C, to give cyclohexanone **235**. Compound **235** was treated with excess methanesulfonyl chloride and TEA to give the α,β-unsaturated ketone **236**, which underwent stereoselective Luche reduction to give a mixture of diastereomeric alcohols (α/β = 1:9). Finally, debenzylation of compound **237** using Lewis acid gave *N*-acetyl *ent*-conduramine B-1 (Scheme 32).



Scheme 31 Total synthesis of conduramine B-1, *ent*-C-1, D-1, and *ent*-F-4



Scheme 32 Synthesis of *N*-acetyl *ent*-conduramine B-1

In conclusion, a range of conduramines have been synthesized in recent years, as well as some of their enantiomers. Many elegant strategies for the total synthesis of these derivatives have been developed.

In the synthesis of conduramines, the insertion of amine moiety and extension of the corresponding substrate to different conduramines is one of the key aspects in the strategies. The amine group has been introduced at different stages of synthesis. Most approaches focus on constructing the allylic amine using benzylamine, allyl amine, NaN_3, *N*-*tert*-butylcyclohexa-2,5-dienylamine, α-methyl-*p*-methoxy benzyl amine, *P*-*Ts*NCO, *t*-$BuNH_2$, $TMSN_3$, NaNBocCl, and phthalimide on appropriate precursors. Details of the amine sources are listed in Table 1 and the synthetic approaches are summarized and classified in Table 2.

Table 1 Synthesis of Conduramine Derivatives from 2007 to 2021

Entry	Conduramine derivative	Source of nitrogen	Reference
1	conduramine A	$TMSN_3$	20
2	conduramine A	TrocNHOH	29
3	conduramine A-1	NaN_3	12
4	conduramine A-1	3-methyl-6-nitrosopyridazine	24
5	conduramine A-1	NH_4OH	18
6	(–)-conduramine A-1	(*R*)-α-methyl-*p*-methoxybenzylamine	32
7	peracetylated conduramine A-1	2-nitrosopyridine	13
8	(–)-conduramine A-1	D-serine	27
9	(–) conduramine A-1	Bu_4NIO_4	14
10	*ent*-conduramine A-1	allyl amine	4
11	(–)-conduramine A-2	(*R*)-α-methyl-*p*-methoxybenzylamine	32
12	(–)-conduramine B	*N*-chloro-*N*-*tert*-butyloxycarbamate	28
13	*N*-acetyl *ent* conduramine B-1	*N*-acetyl-D-glucosamine	36
14	tetracetyl conduramine *B-1*	sodium azide	34
15	conduramine B-2	*p*-toluene sulfonamide	33
16	conduramine C-1	benzyl amine	1
17	tetracetyl *ent*-conduramine C-1	sodium azide	34
18	conduramine C-4	allyl amine	4
19	tetraacetyl conduramine C-4	azide ion	34
20	conduramine D-1	benzyl amine	1
21	tetracetyl conduramine D-1	sodium azide	34
22	conduramine E	*N*-*tert*-butylcyclohexa-2,5-dienylamine	15

Entry	Conduramine derivative	Source of nitrogen	Reference
23	conduramine E	NaN_3	12
24	(+)-conduramine E	*tert*-butyl amine	19
25	(–)-conduramine E	*tert*-butyl amine	19
26	dihydro conduramine E-1	7-azabicyclo[2.2.1]heptane-2-ol	10
27	*ent*-dihydroconduramine E-1	benzylamine	30
28	(+)-*ent*-conduramine E-1	Bu_4NIO_4	14
29	*N*-benzyl *ent* conduramine E-1	benzylamine	30
30	(–)-conduramine E-2	(*R*)-α-methyl-*p*-methoxybenzylamine	32
31	*N*-tosyl dihydroconduramine E-2	*p*-toluenesulfonyl isocyanate	17
32	conduramine F-1	phthalimide	7
33	*ent*-conduramine F-1	7-azabicyclo[2.2.1]heptane-2-ol	10
34	(+)-*ent*-conduramine F-1	Bu_4NIO_4	14
35	(–)-conduramine F-1	D-serine	21
36	*N*-benzyl conduramine F-1	benzylamine	30
37	dihydro conduramine F-1	benzylamine	30
38	*ent*-conduramine F-1	bis-Weinreb amide	31
39	tetraacetyl *ent*-conduramine F-1	azide ion	34
40	*ent*-conduramine F-2	*p*-toluene sulfonamide	33
41	(–)-conduramine F-4	*p*-toluene sulfonamide	25
42	tetracetyl *ent*-conduramine F-4	sodium azide	34
43	*N*-substituted conduramine F-4	alkyl amine	23

Table 2 Synthetic Approaches to Conduramine Targets

Entry	Conduramine name	No. of synthetic routes reported	Reference
1	conduramine A and its isomers	11	4,12,13,14,18,20,24,27,29,32
2	conduramine B and its isomers	4	28,33,34,36
3	conduramine C and its isomers	3	1,4,34
4	conduramine D and its isomers	2	1,34
5	conduramine E and its isomers	10	10,12,14,15,17,19,30,32
6	conduramine F and its isomers	12	7,10,14,21,23,30,31,33,34

Conflict of Interest

The authors declare no conflict of interest.

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