Approaches to the Total Synthesis of Conduramines: A Review

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Figure 1 The conduramine family

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, aminocycloptols, total synthesis, cyclohexenes

Conduramines are aminocyclohexenetriols formally derived from conduritols, in which one of the hydroxyl groups is exchanged with an amino group. Many of these conduramines exhibit significant glycosidase inhibitory activity. The conduramines are also chiral building blocks for natural products such as (+)-narciscin, (+)-valienamine, and (+)-lycoricidin. They are also important as synthetic precursors of amino cyclitols and many of these constitute the aglycon portion of therapeutically useful aminoglycoside antibiotics. In addition, the conduramines are used as intermediates in the synthesis of aminosugars, sphingosines, azasugars, and narcissus alkaloids. 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.
Earlier approaches have been covered in review articles published by Vogel et al., in 2006\textsuperscript{7} and enzymatic methods of synthesis by Hudlicky et al., in 2011.\textsuperscript{6} In this review, most of the reported approaches have focused on conduramines with an allylic amine moiety. Vogel et al., in 2006\textsuperscript{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\textsuperscript{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 Ph.D under the supervision of Dr. B. Venkateswara Rao from the Indian Institute of Chemical Technology, Hyderabad. Currently he is working at GVK biosciences, Hyderabad.

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Reduction of cyclohexenone 4 (which was obtained from 1 via 2 and 3) using NaBH₄/CeCl₃ 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. CH₃NH₂ 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 CH₂OH to furnish 17. Compound 17 was subjected to oxidation with OsO₄ 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...
Pd(Ph₃P)₄ and triethylsilane to afford the corresponding olefin derivative. Epoxide ring opening and deprotection with 0.1 M H₂SO₄ and 10 M HCl in dioxane under reflux conditions afforded ent-conduramine F-1.

Chang et al., in 2009, synthesized conduramines A-1 and E from L-tartaric acid (Scheme 3). Treatment of 22 with 2,2-dimethoxypropane gave dimethyl 2,3-O-isopropylidene-tartrate 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 H₂O/AcOH, gave conduramines A-1 and E, respectively.

Jana et al., in 2009, 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/NaBH₄ 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 CH₃CN, gave protected (+)-conduramine A-1 in a one-pot conversion.

Scheme 3 Synthesis of conduramine A-1 and conduramine E

Scheme 4 Synthesis of (+)-peracetylated conduramine A-1
Lu et al., in 2010, reported the synthesis of (+)-ent-conduramine 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 was prepared from the chiral auxiliary A1 (prepared from (1S)-(+)10-camphorsulfonic acid) and 2-methoxyphenol. Then compound was treated with DIBAL-H to give hydroxy-compound, which was treated with LAH to give oxazine. Subjecting to reductive cleavage of the N–O bond in the presence of Mo(CO)6/NaBH4 afforded the amino alcohol. The amine group in compound was converted into azide using trifluoromethanesulfonylazide and CuSO4 and this was subjected to ketal hydrolysis with TFA to afford enone. Enone was reduced using Luche’s reagent to furnish an inseparable mixture of alcohols and (53:33). This alcholic mixture was treated with DMP to give the protected cis-diol. Alcohol was treated with trimethylphospine in THF/H2O to give the (+)-ent-conduramine F-1. A similar strategy was applied to prepare from and subsequent ketal deprotection gave (+)-conduramine E-1.

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

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

Scheme 6 Syntheses of (–)-conduramine A-1 and A-1-tetraacetate
The reaction mixture was heated to 65 °C and the resulting thiourea to give the allylic tion using rose bengal in MeOH followed by treatment with hydrolysis with Ba(OH)$_2$ gave conduramine E.

Kelebekli et al., in 2010, 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 phosphite and 5 mol% of tris(dibenzylideneacetone) palladium chlo-roform complex at the same temperature to give oxazolidinone 61. The latter was subjected to dihydroxylation with K$_2$MnO$_4$ 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$_2$CO$_3$ in CH$_3$OH at room temperature and then treatment with acetyl chloride gave compound 64. Finally, global deprotection of all the acetylated groups with K$_2$CO$_3$ in methanol gave the N-tosyldihydroconduramine E-2.

Chang et al., 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, 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 trimethylorthofomate treatment to form acetol 70. Compound 72 was directly prepared from 70, using triethyl borane induced hydrometallation followed by iodolysis of the corresponding Z-alkenyllidium 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 reduction. 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 7 Synthesis of conduramine E. a Reaction yield was not noted in the reference paper.
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 NaIO₄ 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/H₂O 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 PPh₃ and CBr₄ in the presence of activated Zn to give the dibromalkene 79 (Scheme 12). Pd-catalyzed hydrogenolysis of 79 with n-
Bu₃SnH 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/H₂O or in CH₂Cl₂/hexafluoroisopropanol afforded compound 82, and deprotection of allyl group using palladium tetras(triphenylphosphine) gave conduramine C-4.

Ghosal et al., in 2012,¹⁹ reported the synthesis of (−)- and (+)-conduramine E. 1,2,3,4-Di-O-isopropylidene-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-aminoo 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-isopropylidene-α-D-mannofuranose hemiacetal 93 was synthesized from D-mannose 92 by the standard procedure (I₂/acetonite). The anomic carbon of compound 93 was subjected to Wittig methylation 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 NaIO₄ 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 boron-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.
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Rao et al., in 2013, 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 NaIO4 in THF/H2O (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. NH3, followed by protection with Boc anhydride to give 110, which then underwent global deprotection with TFA in dichloromethane to afford conduramine E.

Scheme 14  Synthesis of (–)-conduramine E

Scheme 15  Synthesis of conduramine D-1 and conduramine C-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, 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 benzene hydrolysis to give allylic alcohol 114, and diastereoselective OsO4 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, 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). The serine derivative 122 was then treated with N0-dimethylhydroxylamine in the presence of Al(CH3)3 to give the corresponding Weinreb amide that was reacted with vinyl tin and CH3Li 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(PPh3)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 ZnCl2 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 acetyl anhydride and treated with Cbz-CI in the presence ofaq. NaHCO3 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., in 2015, reported the synthesis of N-substituted conduramine F-4 derivatives (Scheme 18). Initially the (+)-proto-querctol 132 was treated with 2,2-dimethoxypropene 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-toluene sulfonate (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.
Maji and Yamamoto,\textsuperscript{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\textsuperscript{13} gave tetraacetyl conduramine A-1.

Harit and Ramesh, in 2016,\textsuperscript{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-\textomega-glucitol), prepared by using a reported procedure.\textsuperscript{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 benzylolation 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 $149$. 

\[ 	ext{Scheme 17 Synthesis of } (-)-\text{conduramine F-1} \]

\[ 	ext{Scheme 18 Total synthesis of } N\text{-substituted } (+)-\text{conduramine F-4 derivatives} \]
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. NH₃ to afford (−)-conduramine F-4 (Scheme 20).

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

Raghavan et al., in 2016, 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 ZnCl₂ 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 sulfanyl group using TFAA and NaI gave sulfide 172. Treatment of 172 with N-chlorosuccinimide gave the 1-stchlorosulfide, 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-butyloxycarbamate at 0 °C and heating the reaction mixture to room temperature gave the allylic amino derivative, which, upon treatment with NaBH₄ in CH₃OH, gave the (−)-conduramine-B derivative.
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 NaIO₄ 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 H₃IO₆ 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 CH₃OH 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
Prasad and Rangari, in 2018,\(^{31}\) reported the synthesis of \(\text{ent-}\)conduramine F-1 from tartaric acid (Scheme 27). Vinyl magnesium bromide was added to the bis-Weinreb amide 195. The carbonyl group of compound 195 was subjected to stereoselective Luche reduction to give the alcohol 196 (\(\text{de}=99:\%\)). The hydroxyl group of 196 was then protected as its tert-butylsulfinamide to give the sulfinimine 197. Treatment of 197 with DIBAL-H gave the corresponding aldehyde, and further reaction with \((\text{S})\)-t-BuS(O)NH\(_2\) gave the silyl ether to give \((\text{S})\)-conduramines A-1, A-2, and E-2 (Scheme 28). Initially, compound 199 was subjected to chemoselective debenzylation and acetylation of the primary benzyloxy group at C-6 with ZnCl\(_2\) in THF and MeOH (1:1) to give 200. Removal of the sulfinyl and acetamide groups in 201 using HCl in methanol, followed by NaHCO\(_3\) treatment gave \(\text{ent-}\)conduramine F-1.

Da Silva Pinto \textit{et al.}, in 2019,\(^{32}\) reported the synthesis of \((\text{R})\)-conduramines A-1, A-2, and E-2 (Scheme 28). Initially, compound 202 was subjected to oxidation in the presence of peracetic acid in dichloromethane to give the cyclohexa-1,4-diene monoeponoxide 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 \((\text{R})\)-\(\alpha\)-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 \(N\)-\(\alpha\)-methyl-\(p\)-methoxybenzyl derivatives of conduramine A1 (209), A2 (210), E2 (211), and F2 (212), respectively. Finally, removal of the \(\alpha\)-methyl-\(p\)-methoxybenzyl fragment from 209–211 with Et\(_2\)SiH in the presence of TFA gave \((\text{R})\)-conduramine A-1, A-2, and E-2, respectively.

Harit and Ramesh,\(^{33}\) in 2019, reported the synthesis of \(\text{ent-}\)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-
went Vasella reductive elimination to give the formyl-alkene 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. NH3 afforded enone 221 (Scheme 29).

Yan et al.,24 in 2019, reported the synthesis of tetracyclic conduramines B-1, 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 = 1:3.5). Treatment of compound 222 with LAH and subsequent acetonide protection and peracetylation 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 PPh3 in THF for 2 h afforded the 1,4-syn-azido alcohol 223. Reduction of compound 223 with LAH, followed by acetonide removal and peracetylation, 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-
moval and peracylation of compound 227 resulted in conduramine D-1 tetraacetate. Treatment of compound 225 with LAH and subsequent acetonide deprotection and peracetylation yielded the tetraacetyl ent-conduramine C-1.

The allylic epoxide 26 was treated with benzoic acid in the presence of 2 mol% Pd(PPh₃)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 peracetylation yielded tetraacetyl conduramine B-1. Compound 26 underwent palladium-catalyzed nucleophilic opening of the allylic epoxide with TsNH₂/TsNHNa in acetonitrile at 40 °C to give the 1,4-syn-amide 230. The amide was then treated with Na/NH₃, followed by acetonide removal and peracetylation, to give tetraacetyl ent-conduramine F-4 (Scheme 31).

Narayana et al., in 2021, 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 CH₃OH 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. Subsequently, 234 was subjected to HgSO₄ catalyzed Ferrier carbocyclization in 1,4-dioxane and 5 mM H₂SO₄(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).
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, NaN₃, N-tert-butylcyclohexa-2,5-dienylamine, P-TsNCO, t-BuNH₂, TMSN₃, 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conduramine derivative</th>
<th>Source of nitrogen</th>
<th>Reference</th>
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<tbody>
<tr>
<td>1</td>
<td>conduramine A</td>
<td>TMSN₃</td>
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</tr>
<tr>
<td>2</td>
<td>conduramine A</td>
<td>TrocNH₂OH</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>conduramine A-1</td>
<td>NaN₃</td>
<td>12</td>
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<tr>
<td>4</td>
<td>conduramine A-1</td>
<td>3-methyl-6-nitrosopyridazine</td>
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</tr>
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<td>5</td>
<td>conduramine A-1</td>
<td>NH₂OH</td>
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<td>(R)-α-methyl-p-methoxybenzylamine</td>
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<td>2-nitrosopyridine</td>
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<td>d-serine</td>
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</tr>
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<td>Bu₄NIO₄</td>
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<td>10</td>
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<td>allyl amine</td>
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</tr>
<tr>
<td>11</td>
<td>(–)-conduramine A-2</td>
<td>(R)-α-methyl-p-methoxybenzylamine</td>
<td>32</td>
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<tr>
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<td>(–)-conduramine B</td>
<td>N-chloro-N-tert-butylxocarbamate</td>
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<tr>
<td>13</td>
<td>N-acetyl ent conduramine B-1</td>
<td>N-acetyl-d-glucosamine</td>
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<td>tetracetyl conduramine B-1</td>
<td>sodium azide</td>
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<td>15</td>
<td>conduramine B-2</td>
<td>p-toluene sulfonamide</td>
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Table 2 Synthetic Approaches to Conduramine Targets

<table>
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<th>Reference</th>
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<td>25</td>
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<tr>
<td>27</td>
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<td>benzylamine</td>
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<td>28</td>
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<td>Bu(_4)N(_3)</td>
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Conflict of Interest

The authors declare no conflict of interest.

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References

(26) Kumar, V.; Ramesh, N. G. Tetrahedron 2006, 62, 1877.