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Tetrahedron 62 (2006) 2733–2768

Tetrahedron report number 753

Synthesis of amino- and diaminoconduritols and their applications

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Received 16 November 2005

Available online 20 December 2005

Contents

Keywords: Conduritols; Conduramines; Diaminoconduritols; Asymmetric synthesis.

Abbreviations: Ac, acetyl; aq, aqueous; AIBN, 2,2′-azobis(isobutyronitrile); Bn, benzyl; Boc, *tert*-butyloxycarbonyl; *n*-Bu, *n*-butyl; *s*-Bu, *sec*-butyl; *t*-Bu, *tert*-butyl; Bz, benzoyl; CAN, ceric ammonium nitrate; Cbz, benzyloxycarbonyl; CC, column chromatography; *m*-CPBA, 3-chloroperbenzoic acid; CSA, camphorsulfonic acid; dba, dibenzylideneacetone; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DEAD, diethyl azodicarboxylate; △, solvent heated under reflux; DHP, dihydropyran; DIPEA, diisopropylethylamine; DMAP, 4-(*N*,*N*-dimethylamino)pyridine; DME, 1,2-dimethoxyethane; DMF, *N*,*N*-dimethylformamide; DMP, 1,3-dimethoxypropane; DMSO, dimethylsulfoxide; dppe, 1,2-(diphenylphosphino)ethane; Et, ethyl; FC, flash chromatography; FVT, flash vacuum thermolysis; HMPA, hexamethylphosphoric triamide; Imd, imidazole; $LiAlH_4$, lithium aluminium hydride; LHMDS, lithium hexamethyldisilazane; Me, methyl; MOM, methoxymethyl; MPM, *p*-methoxybenzyl; Ms, methanesulfonyl (mesyl); NBS, *N*-bromosuccinimide; NMO, *N*-methylmorpholine *N*-oxide; Phth, phthaloyl; PPL, porcine pancreatic lipase; PPTS, pyridinium *p*-toluenesulfonate; Py, pyridine; rt, room temperature; Red-Al, sodium bis(2-methoxyethoxy)aluminium hydride; TBAF, *tetra*-butylammonium fluoride; TBME (*t*-BME), *tert*-butyl methyl ether; TBSOTf, *tert*-butyldimethylsilyl triflate; TBS (TBDMS), *tert*-butyldimethylsilyl; TEA, triethylamine; TES, triethylsilyl; TESOTf, triethylsilyl triflate; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TMEDA, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; TMS, trimethylsilyl; TMSOTf, trimethylsilyl triflate; Troc, 2,2,2-trichloroethoxycarbonyl; Ts, tosyl=*para*-toluenesulfonyl; *p*-TsOH, *para*-toluenesulfonic acid; $Cu(acac)_2$, copper(II) acetylacetonate.

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doi:10.1016/j.tet.2005.11.046

1. Introduction

Conduritols **1**–**6** (cyclohex-5-ene-1,2,3,4-tetrols) are a class of polyols valuable as starting materials for the synthesis of biologically active compounds.[1] The ten possible stereoisomers, two *meso*-forms (conduritols A and D) and four couples of enantiomers (conduritols B, C, E and F), have been obtained in enantiomerically pure forms[1] (Fig. 1).

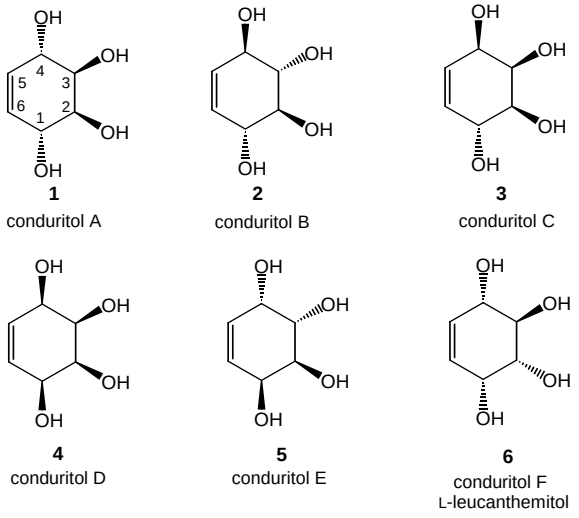


Figure 1.

In nature, the occurrence of only two conduritols A and F, has been established.[1]

Conduramines are purely synthetic aminocyclohexenetriols,[1a,b,h] formally derived from conduritols, in which one of the OH groups is exchanged for an amino moiety (Fig. 2). Conduramines and their analogues are important intermediates in the synthesis of amino- and diaminocyclitols.[2] Some aminoconduritols have shown interesting inhibitory activities towards glycosidases.[3] The syntheses of aminoconduritols have been partially reviewed.[1a,b,g,h,4] Conduramines have also been used as intermediates in the preparation of azasugars,[5] aminosugars,[6] sphingosines,[7] lactams,[8] and narcissus alkaloids.[9]

Aminoconduritols are also structural elements of many naturally occurring biological active compounds. A number of *Amaryllidaceae* alkaloids, for example, compounds **7** and **8**, having a [1,3]-dioxolophenanthridone skeleton, contain the conduramine A structure and show interesting inhibitory activity towards some glycosidases.[10] Most of these alkaloids contain the hydroxylated aminoconduritol A-1 subunit, for example, compounds **9** and **10** (Fig. 3).

In this review, we survey the general synthetic strategies applied to the preparation of amino- and diaminoconduritols and their analogues. We also give a short summary of the activities found for conduramines and diaminoconduritols as glycosidase inhibitors.

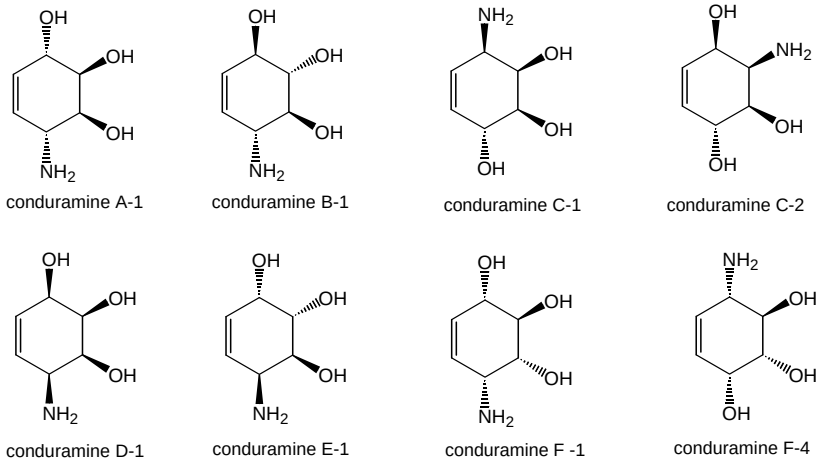


Figure 2.

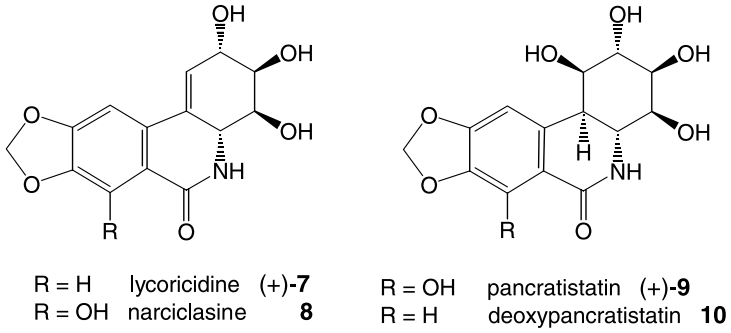


Figure 3.

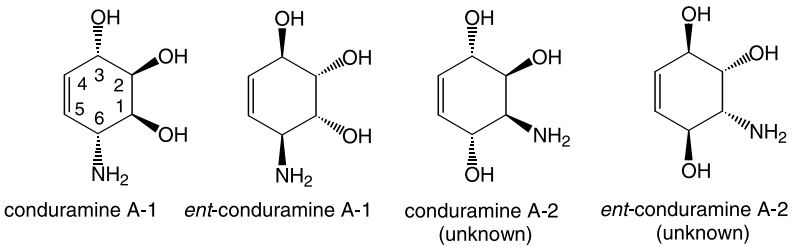


Figure 4.

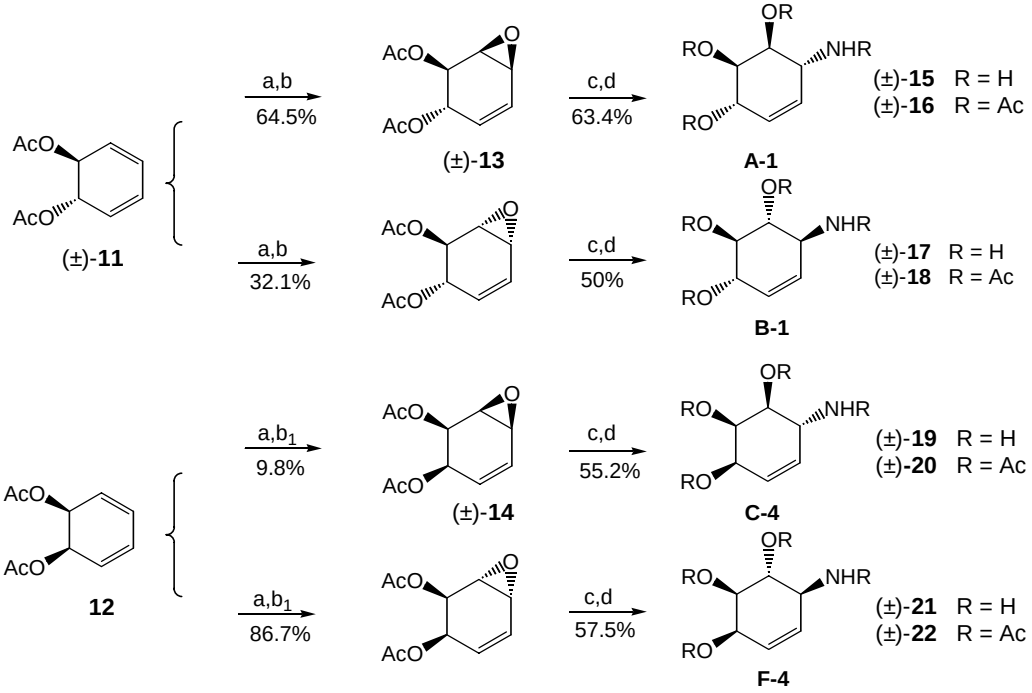
2. Aminoconduritols

2.1. Synthesis of aminoconduritols A

There are two types of conduramines A, conduramine A-1 and its enantiomer (*ent*-A-1), and conduramine A-2 and its enantiomer (*ent*-A-2) (Fig. 4). The two latter compounds have not yet been described. In this review, we will use numbering for conduramines according to the IUPAC recommendations.[11] The trivial nomenclature of conduramines arises from their correlation with naturally occurring conduritols, for example, conduritols A and F. Thus, if the trivial numbering of conduritols is used, replacement of the hydroxy group at C(1) of conduritol A with an amino moiety produces conduramine A-1. Similarly, replacement of HO–C(4) in conduritol F produces conduramine F-4. Moreover, if the corresponding conduritol is naturally occurring, its conduramine analogue is described as 'pseudo-natural', for example, conduramines A-1 and F-1. The corresponding conduramine enantiomers which virtually do not have natural conduritol analogues are referred to as *ent*.

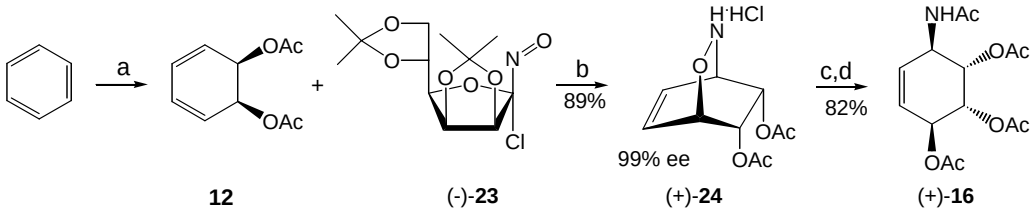
2.1.1. Synthesis of aminoconduritol A-1 and analogues. The first successful synthesis of racemic conduramines A-1, B-1, C-4 and F-4 was achieved by Nakajiama et al.[12] in 1962. Their syntheses involved the epoxidation of racemic *trans*-**11** or *cis*-cyclohexa-3,5-diene-1,2-yl diacetate **12** that were derived from tetrachlorocyclohexane. The reaction gave a mixture of two isomers, one of which [(±)-**13** or (±)-**14**] could be separated by crystallization. *Anti*-openings of the corresponding epoxides were carried out in NH_3/MeOH, giving four aminoconduritols, (±)-**15**, (±)-**17**, (±)-**19** and (±)-**21**, that were characterized as the corresponding crystalline tetraacetates, (±)-**16**, (±)-**18**, (±)-**20** and (±)-**22**. Other regioisomers were not formed, because ammonia attacks the epoxide ring selectively in the allylic positions (Scheme 1).

The hetero-Diels–Alder addition of *cis*-cyclohexa-3,5-diene-1,2-yl diacetate **12** with the nitroso compound (−)-**23** derived from D-mannose allowed the preparation of the corresponding dihydrooxazine (+)-**24** with very high optical purity (99% ee).[13] Selective reduction of the N–O bond of (+)-**24** (Zn/HCl) provided the enantiomerically



Reagents and conditions: a) $PhCO_3H$, $CHCl_3$, rt, 3 d; b: separation of (±)-**13** by crystallization; b_1: separation of (±)-**14** by crystallization; c) MeOH, NH_3; d) Ac_2O, Py.

Scheme 1.

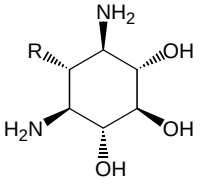


Reagents and conditions: a) (i) microbial dioxygenase oxidation; (ii) Ac_2O/Py, 4 h, rt (96%); b) $CHCl_3$/EtOH, -70 °C, then 4 d at - 40 °C; c) Zn/HCl-H_2O, 5 °C, 7 h; d) Ac_2O/Py.

Scheme 2.

enriched conduramine A-1 tetraacetate (+)-**16** in 82% yield (Scheme 2).

The majority of aminoglycoside antibiotics contain 2-deoxystreptamine (2-DOS) **25** and streptamine **26** as aminocyclitol subunits (Fig. 5).[14] Isomers of aminocyclitols



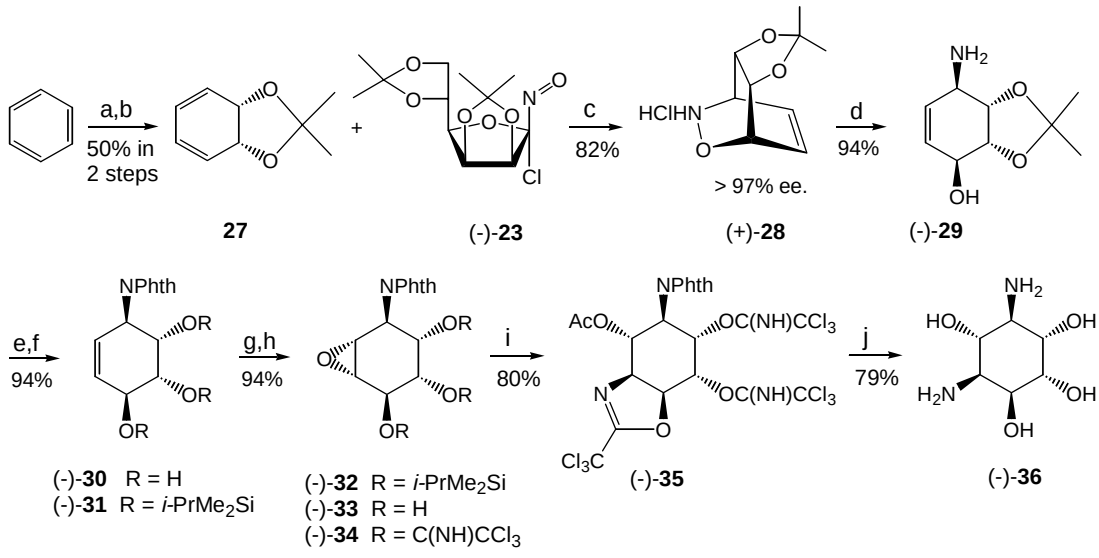
25 R = H
26 R = OH

Figure 5.

25 and **26** in which the configuration of the amino groups is not changed are attractive targets for stereoselective synthesis. They have found several applications including the generation of new antibiotics able to combat mutagenesis of bacteria,[15] and as ligands in the construction of cytostatic platinum complexes.[16]

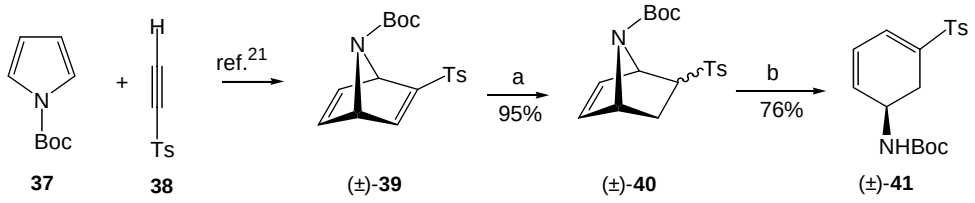
Piepersberg and co-workers[17] presented a stereoselective route to optically pure *cis*-1,3-diamino-1,3-dideoxycyclitol (−)-**36** based on the hetero-Diels–Alder reaction of nitroso dienophile (−)-**23** with protected *cis*-cyclohexa-3,5-diene-1,2-diol **27** (Scheme 3).

The starting diol,[18] which was obtained from benzene by microbial oxidation, was protected as its stable 1,2-*O*-isopropylidene derivative **27**.[19] The *meso*-diene **27** was subjected to a hetero-Diels–Alder reaction with (−)-furanosyl chloride **23** and gave the dihydrooxazine (+)-**28**



Reagents and conditions: a) *Pseudomonas putida*; b) *p*-TsOH, Me_2CO, 0-5 °C, 3 h; c) Et_2O-EtOH, -30 °C, 7 d; d) Al/Hg, aq. THF (20:1), 0 °C, 2 d; e) *N*-ethoxycarbonylphthalimide, Na_2CO_3, Me_2CO, $CaSO_4$, 30 °C, 1 d; f) (i) 80% AcOH, 65 °C, 2 h; (ii) *i*-$PrMe_2SiCl$, Imd, CH_2Cl_2, rt, 12 h; g) (i) *p*-$O_2NC_6H_4CO_3H$; (ii) 75% AcOH, rt, 2 d; h) Cl_3CCN, DBU, CH_2Cl_2, -30 °C, 3 d; i) (i) Et_3Al, DME, 0 °C, 3 h; (ii) EtOH, 30 min; (iii) Ac_2O/Py, rt, 12 h; j) (i) 1 mol dm^{-3} HCl, rt, 3 h; (ii) N_2H_4, EtOH-$CHCl_3$, 80 °C, 12 h.

Scheme 3.



Reagents and conditions: a) $NaBH_4$, MeOH, 0 °C; b) LHMDS, THF, -78 °C to rt.

Scheme 4.

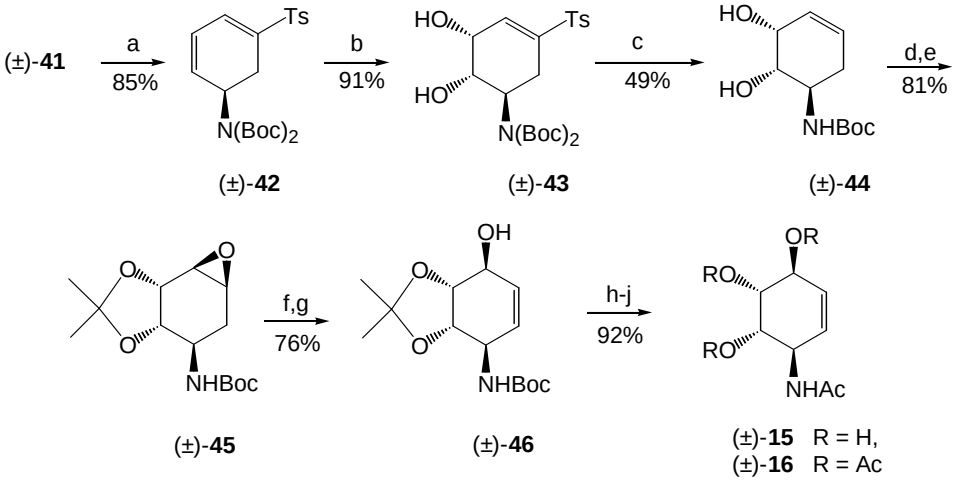
(>97% ee). After reduction (Al/Hg, aq THF) of the N–O bond, aminocyclohexenol (−)-**29** was obtained in 94% yield. Amine (−)-**29** was protected by phthaloylation[20] to give the corresponding phthalimide that was then hydrolyzed into the triol (−)-**30**. Epoxidation of the corresponding silyl diether (−)-**31** with *p*-nitroperbenzoic acid led to the *trans*-epoxide (−)-**32** exclusively (Scheme 3).

The silyl protective groups in (−)-**32** were removed by acidic hydrolysis ((−)-**33**) and were replaced by trichloroacetimidato functions to give derivative (−)-**34**. The second nitrogen function was introduced by stereoselective epoxide ring opening by the vicinal trichloroacetimidato residue in the presence of Et_3Al. 3,4-Dihydro-1,3-oxazole (−)-**35** was obtained in 80% yield. Hydrolytic cleavage of the oxazine ring (aq HCl) preceded the complete, simultaneous removal of all protective groups, yielding (−)-**36** (Scheme 3).

Starting from the Diels–Alder adduct (±)-**39** of the acetylene **38** and *N*-*t*-butoxycarbonylpyrrole (**37**) (Scheme 4), a compound described first by Altenbach et al.,[21] Muchowski and co-workers[22] have developed a synthetic pathway for (±)-conduramine A-1 [(±)-**15**] (Scheme 5), (±)-conduramine C-1 tetraacetate, (±)-conduramine D-1 and (±)-conduramine F-1. Reduction of (±)-**39** with $NaBH_4$ gave 7-azanorbornene (±)-**40**, which was then converted into the racemic diene **41** on treatment with a strong base [$(Me_3Si)_2NLi$].

From (±)-**41** and applying a chemo- and face-selective dihydroxylation of the di-Boc- protected amine (±)-**42**, diol (±)-**43** was obtained in good yield (Scheme 5). The same reaction applied to (±)-**41** gave a 1:1 mixture of two diastereomeric diols.

Reduction of the sulfone moiety of (±)-**43** with Na/Hg afforded (±)-**44**. After protection of its diol unit as an acetonide and face-selective epoxidation of its alkene moiety, epoxide (±)-**45** was isolated in 81% yield. Regioselective ring opening of epoxide (±)-**45** was possible with PhSeLi, which attacked (S_N2) the less sterically hindered center. The selenide obtained was not isolated, but directly oxidized with H_2O_2, which led to the regioselective formation of the allylic alcohol (±)-**46**. After deprotection, (±)-conduramine A-1 [(±)-**15**] was obtained and characterized as its peracetate acetamido derivative [(±)-**16**].

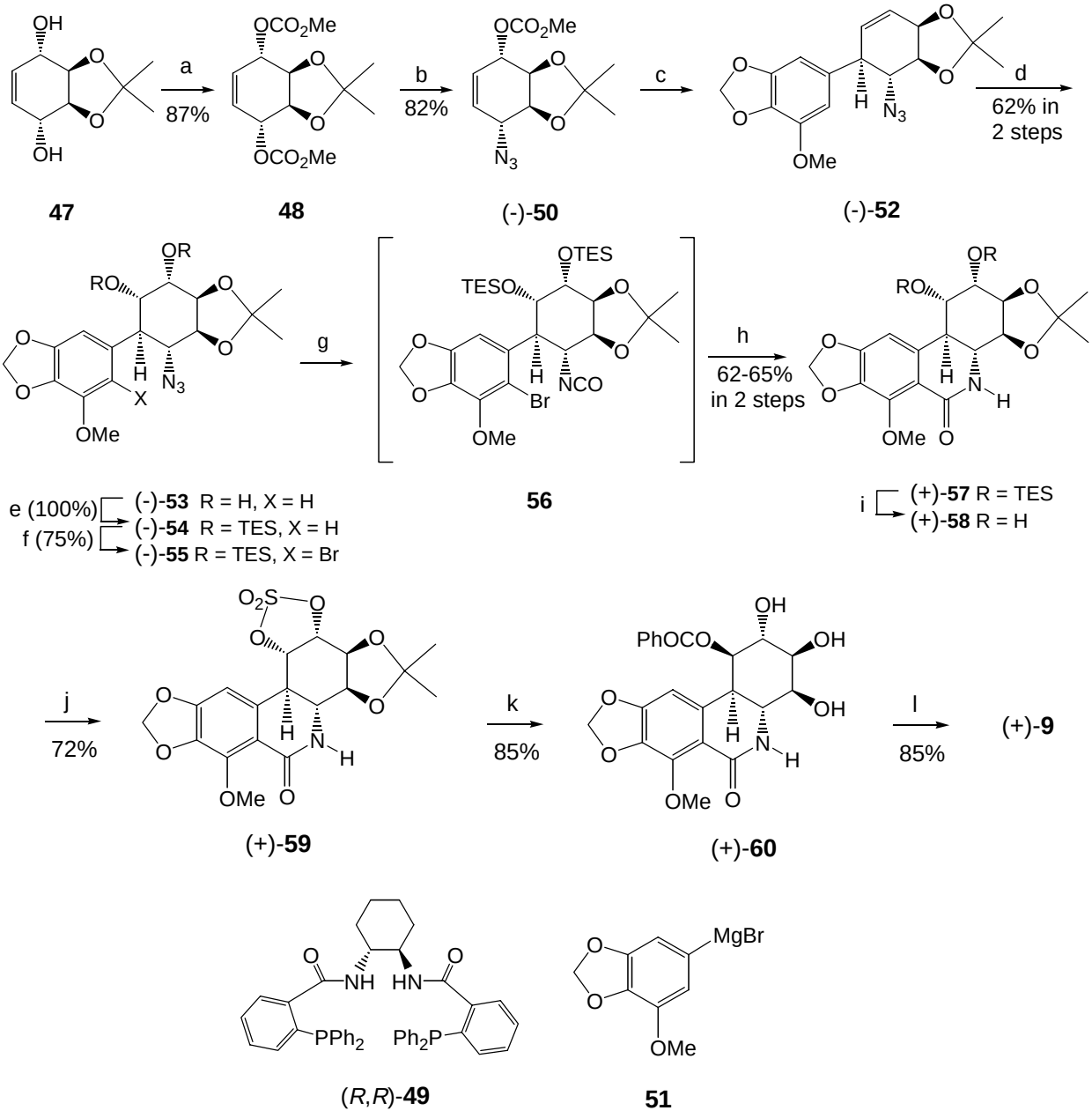


Reagents and conditions: a) $(Boc)_2O$, DMAP, MeCN; b) OsO_4-NMO, $NaHCO_3$, *t*-BuOH, H_2O, THF, rt; c) 6% Na/Hg, Na_2HPO_4, MeOH-THF, -12 °C; d) $Me_2C(OMe)_2$, Me_2CO, *p*-TsOH, rt; e) *m*-CPBA, $NaHCO_3$, CH_2Cl_2; f) $(PhSe)_2$, *n*-BuLi, THF; g) (i) H_2O_2, DIPEA, CH_2Cl_2, 0 °C; (ii) THF, reflux; h) TFA, H_2O/CH_2Cl_2; i) NH_3/ MeOH; j) Ac_2O/Py, DMAP.

Scheme 5.

As already mentioned, pancratistatin **9** which contains a hydroxylated conduramine structure is a member of the *Amaryllidacene* group of alkaloids. It has been used in folk medicine since ancient Greek times[23] and was isolated by Pettit and co-workers from the root the Hawaiian plant *Pancratium littorale*.[24]

Trost and Pulley[25] have described a synthetic strategy for (+)-pancratistatin, where they have used the conduramine A-1 analogue (−)-**50** and Grignard reagent **51** for the coupling reaction as the key step (Scheme 6). The synthesis started from the readily available diol **47**, which was converted into the dicarbonate **48**. The desymmetrization



Reagents and conditions: a) (i) *n*-BuLi, THF, 0 ^{o}C; (ii) $ClCO_2Me$; b) 0.5 mol% $(\pi\text{-}C_3H_7PdCl)_2$, 0.75 mol% (*R*,*R*)-**49**, $TMSN_3$, CH_2Cl_2, rt; c) **51**, CuCN, THF-Et_2O, 0 ^{o}C; d) cat. OsO_4, $NMO{\cdot}H_2O$, CH_2Cl_2, rt; e) TESOTf, 2,6-lutidine, CH_2Cl_2; f) NBS, DMF; g) (i) Me_3P, THF, H_2O; (ii) $COCl_2$, THF, Et_3N; h) *t*-BuLi, Et_2O, -78 ^{o}C; i) TBAF, THF, -78 to 0 ^{o}C; j) (i) $SOCl_2$, Et_3N; (ii) cat. $RuCl_3{\cdot}H_2O$, $NaIO_4$, CCl_4, MeCN, H_2O, rt; k) $PhCO_2Cs$, DMF, then work up with THF, H_2O, cat. H_2SO_4; l) (i) MeOH, K_2CO_3, rt; (ii) LiI, DMF, 80 ^{o}C .

Scheme 6.

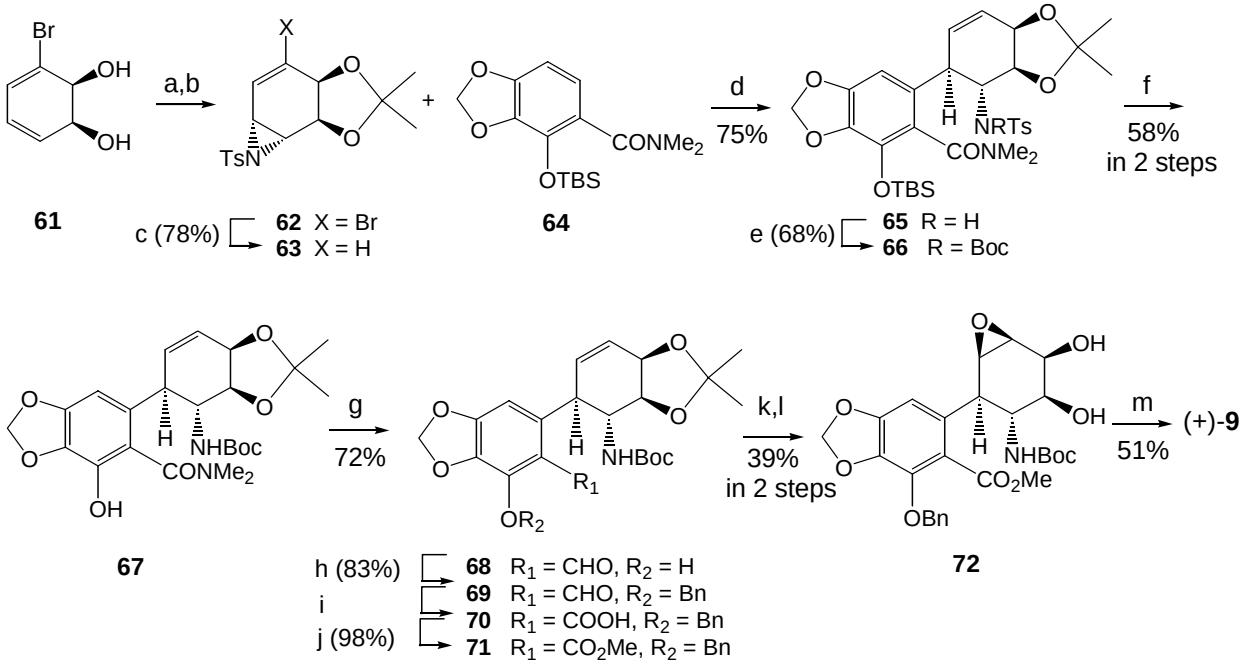
which utilizes a Pd complex derived from (*R*,*R*)-ligand **49** and π-allylpalladium chloride gave azide (−)-**50** in 82% yield with >95% ee. Addition of the Grignard reagent **51** to the mixture of azide (−)-**50** and CuCN led to the desired adduct (−)-**52**. Cis-dihydroxylation ($NMO \cdot H_2O$, cat. OsO_4, CH_2Cl_2) gave diol (−)-**53** which was transformed into (−)-**55** in two steps via (−)-**54**. The isocyanate **56** was formed by reacting (−)-**55** with $Me_3P/THF/H_2O$ and $COCl_2$. Treatment of **56** with *t*-BuLi led to metal/halogen exchange, the latter reaction being faster than addition to the isocyanate. The resultant aryllithium underwent spontaneous addition to form lactam (+)-**57**. Deprotection (TBAF, THF, −78 °C) of the silyl ether (+)-**57**→(+)-**58**, followed by trans-diaxial ring opening of the cyclic sulfate (+)-**59** in which the acetonide cleaves simultaneously with hydrolysis of the alkyl sulfate, provided derivative (+)-**60**. Simple removal of the benzoyl and methyl ether groups in (+)-**60** completes the synthesis of (+)-pancratistatin [(+)-**9**] (Scheme 6).

Independently, Hudlicky and co-workers[26] have developed an alternative enantioselective total synthesis of (+)-pancratistatin **9**. The key step in their synthesis was the coupling reaction of tosylaziridine **63** with amide **64** via *ortho*-metallation of the latter compound (Scheme 7).

The commercially available diol **61** was converted into conduramine A-1 precursor **62**, which was subsequently reduced (Bu_3SnH/AIBN, THF) into **63** in 78% yield. Amide **64** was subjected to *ortho*-metallation below −90 °C and converted in situ into the corresponding lithium cyanocuprate species $[Ar_2Cu(CN)Li_2]$, the addition of which to **63** produced tosylamide **65**. Amide **65** was converted into the Boc derivative **66** and, subsequently, reductive detosylation (Na/anthracene, DME) gave phenol **67**. Reduction of the dimethylamide **67** with Red-Al into aldehyde **68** and protection of the phenol moiety afforded **69**. The latter compound was oxidized into acid **70** and converted into the methyl ester **71** in 98% yield. Deprotection and $VO(acac)_2$-catalyzed epoxidation with *t*-BuO_2H, afforded the β-epoxide **72** selectively (lateral control by the free hydroxyl group). Near-neutral conditions (H_2O, cat. BzONa, 100 °C, 6d) transformed epoxide into (+)-pancratistatin [(+)-**9**] in 51% yield (Scheme 7).

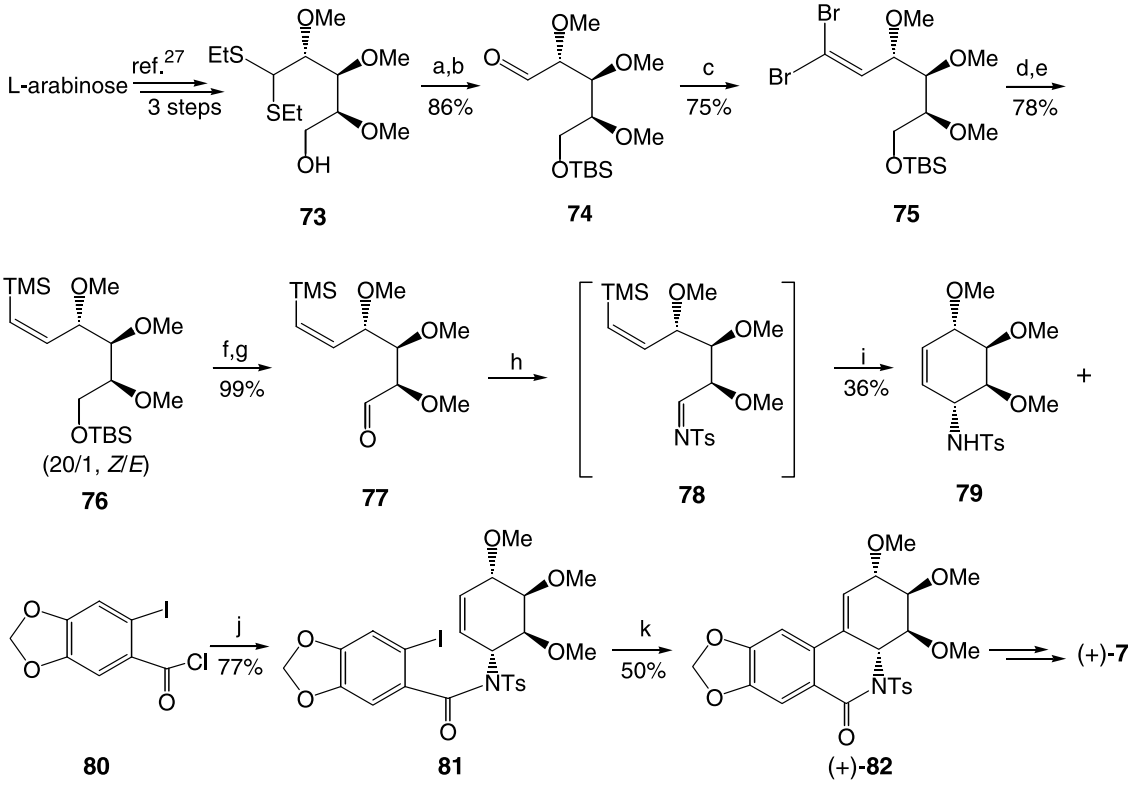
A convergent synthesis of a protected version of (+)-lycoricidine [(+)-**7**] has been accomplished by McIntosh and Weinreb.[10] In their synthesis, conduramine A-1 derivative **79** was an important synthetic intermediate (Scheme 8).

The synthesis starts from L-arabinose, which was converted in three steps into dithioacetal **73**.[27] The primary OH function of **73** was protected as a silyl ether. Subsequent hydrolysis of the dithioacetal gave aldehyde **74** in 86%



Reagents and conditions: a) DMP, *p*-TsOH, CH_2Cl_2; b) PhI=NTs, $Cu(acac)_2$, MeCN; c) Bu_3SnH, AIBN, THF; d) (i) *s*-BuLi, TMEDA, THF, -90 °C, 1.5 h; (ii) CuCN, -90 to -20 °C; (iii) **64**, -78 °C, $BF_3 \cdot Et_2O$, then to rt over 8 h; e) (i) *s*-BuLi, THF, 0 °C, 15 min; (ii) $(Boc)_2O$, reflux, 4 d; f) (i) Na/anthracene, DME, -78 °C, 15 min; (ii) TBAF, THF, 0 °C, 1.5 h; g) Red-Al, morpholine, THF, -45 °C, 31 h; h) BnBr, K_2CO_3, DMF, rt, 4 h; i) 2-methyl-2- butene, $NaClO_2$, KH_2PO_4, *t*-BuOH, H_2O, rt, overnight; j) CH_2N_2; k) AcOH, aq. THF, 75 °C, 3 h; l) *t*-BuO_2H; $VO(acac)_2$, PhH, 60 °C, 2 h; m) H_2O, BzONa (cat.), 100 °C, 6 d.

Scheme 7.



Reagents and conditions: a) TBSCl, DMAP, Imd, DMF, rt, 16 h; b) HgO, $HgCl_2$, Me_2O-H_2O (9:1), 50 °C, 1 h; c) PPh_3, CBr_4, CH_2Cl_2, Et_3N, -78 °C, 5 min; d) (i) *n*-BuLi, THF, TMEDA, -78 °C; (ii) TMSCl, -78 °C, 3 h, then 3 h at rt; e) H_2/5% Pd/$BaSO_4$ (2 mol %), Py, rt, 20 h; f) AcOH/H_2O (2:1), rt, 12 h; g) Swern oxidation; h) TsNCO (2 eq.), $(CH_2)_2Cl_2$, 80 °C, 24 h; i) $BF_3{\cdot}Et_2O$, 0 °C to rt; j) Et_3N, DMAP, CH_2Cl_2, rt, 36 h; k) Pd(dppe)$_2$ (20 mol %), TlOAc, DMF, 68 °C, 36 h.

Scheme 8.

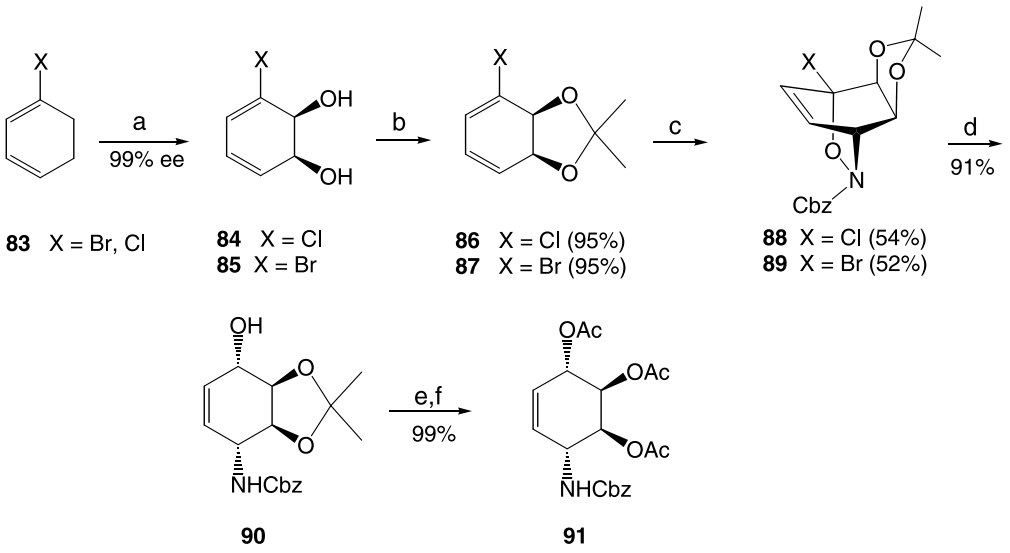
yield. In the next step, the Corey–Fuchs procedure was applied [PPh_3 (2 equiv)/CBr_4, Et_3N, −78 °C, 5 min] for one-carbon homologation and under these conditions, olefin **75** was obtained in 75% yield. Compound **75** was then transformed into the corresponding acetylene. Subsequent catalytic hydrogenation of the ethynylsilane using H_2/Pd/$BaSO_4$ gave the vinylsilane **76** with good *Z*/*E* stereoselectivity (20:1). The silyl ether **76** (inseparable mixture of *Z*/*E* isomers) was cleaved under mild conditions and the alcohol obtained was oxidized to give **77** in very good yield. Vinylsilane aldehyde **77** was converted into *N*-sulfonylimine **78** under neutral conditions. The imine **78** was treated in situ with $BF_3{\cdot}Et_2O$ in order to induce electrophilic ring cyclization into the conduramine A-1 derivative **79** (Scheme 8). Coupling of 6-iodopiperonyl chloride **80** and conduramine **79** afforded the *N*-acylsulfonamide **81**. Cyclization of **81** using a variation of the Ogawa procedure [Pd(dppe)$_2$, TlOAc, DMF] afforded the desired protected (+)-lycoricidine [(+)-**82**].

Hudlicky and co-workers[28–30] have devised a very effective synthetic strategy to produce either (+)- or (−)-conduramine A-1 derivatives from a single, optically pure, chloro- (**84**) or 1-bromodiol (**85**). Diols **84** and **85** were obtained form the corresponding inexpensive halobenzenes **83** by fermentation with a *Pseudomonas putida* strain, Pp 39D (Scheme 9). Protection of diols **84** and **85** as the acetonides **86** and **87**, respectively, and their subsequent hetero-Diels–Alder addition with CbzN=O[31] gave the corresponding oxazolidines **88** and **89**.

Reduction of bromide **89** and subsequent cleavage of the N–O bond were accomplished with Al/Hg and this afforded **90**. Acidic treatment of **90** and subsequent acetylation of the free hydroxyl groups led to the fully protected conduramine A-1 derivative **91** (Scheme 9).

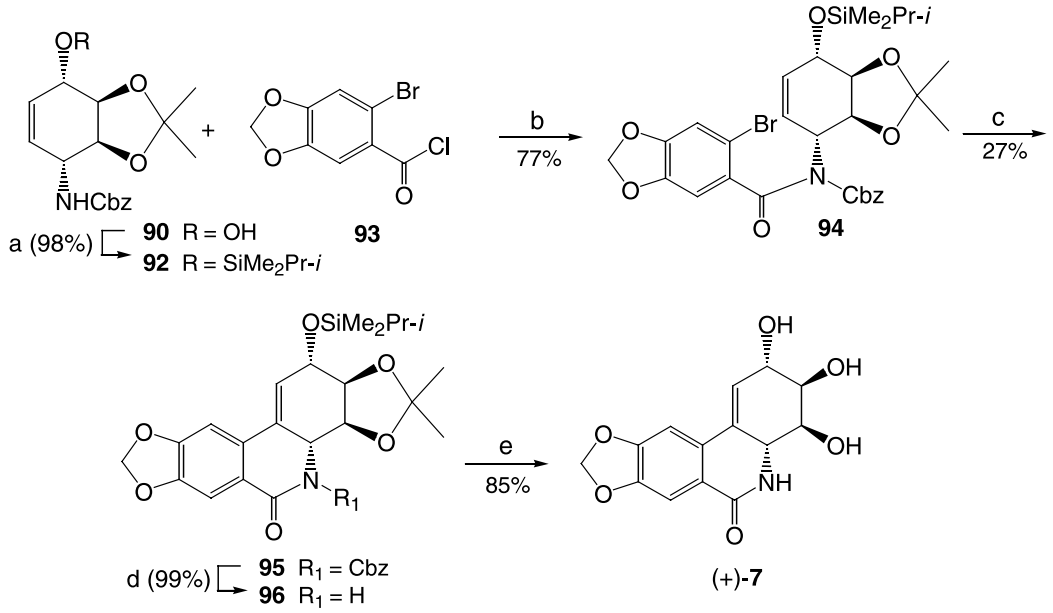
The same synthetic scheme has been used by Hudlicky and Olivo[28] in their total synthesis of (+)-lycoricidine [(+)-**7**] (Scheme 10). The starting alcohol **90** (Scheme 9) was silylated with *i*-PrMe_2SiCl to afford **92** in 98% yield. Reaction of **92** with **93** gave the amide **94**. The ring closure of **94** into **95** was accomplished in 27% yield by means of a modified Heck cyclization [Pd(OAc)$_2$, TlOAc, dppe, anisole]. Amide **95** was then deprotected with Pd/C to yield the derivative **96**. Treatment of **96** with CF_3CO_2H at 0 °C afforded optically pure (+)-lycoricidine [(+)-**7**].

More recently, Hudlicky and Akgün[30] have applied a similar synthetic methodology, leading to the first total synthesis of *ent*-7-deoxypancratistatin via a protected form of *ent*-conduramine A-1 [(+)-**101**] and diol **98**. The latter



Reagents and conditions: a) *Pseudomonas putida*, Pp 39D; b) DMP, Me_2CO, *p*-TsOH; c) Bu_4NIO_4 and CbzNHOH; d) Al/Hg, THF-H_2O; e) AcOH-THF-H_2O; f) Ac_2O/Py.

Scheme 9.

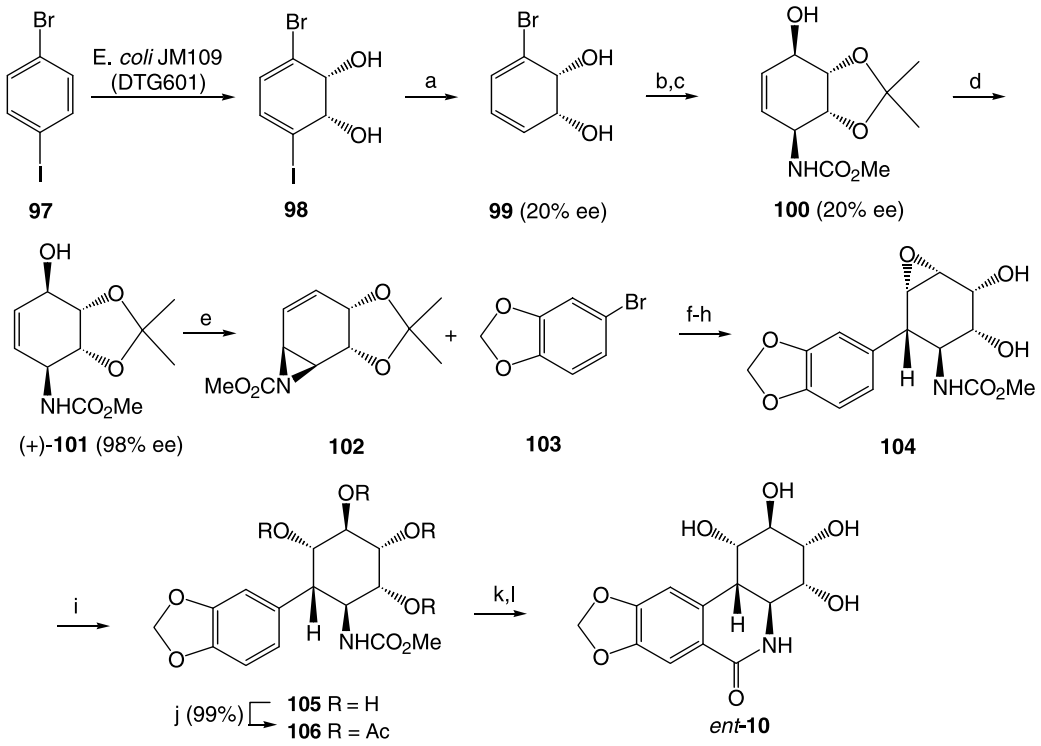


Reagents and conditions: a) $ClSiMe_2Pr$-*i*, Imd, CH_2Cl_2; b) (i) *n*-BuLi, THF, -78 °C; c) $Pd(OAc)_2$, TlOAc, dppe, anisole; d) Pd(C), cyclohexene-EtOH; e) TFA, 0 °C.

Scheme 10.

compound was generated by an improved chemoenzymatic means (Scheme 11). Oxidation of *p*-bromoiodobenzene **97** gave the diol **98**, which was subjected to Bu_3SnH reduction. The *ent*-diol **99** was isolated with 20% ee only. The Diels–Alder reaction of **99** with $MeCO_2NHOH$ proceeded with excellent regio- and stereospecifity to afford the bromooxazine, which was then transformed into the intermediate **100**.

Enantiomerically enriched compound (+)-**101** (>98% ee) was subjected to a Mitsunobu reaction[32] to give aziridine **102** (Scheme 11). Regioselective addition of the cuprate derived from **103** (*n*-BuLi, Cu) provided, after deprotection (95%), a diol, which was then subjected to vanadium oxide-catalyzed epoxidation, giving **104**. Acidic hydrolysis of the epoxide **104** provided the tetrol **105** that was then acetylated into **106**. Exposure of **106** to modified Bischler–Napieralski



Reagents and conditions: a) Bu_3SnH, AIBN, THF; b) (i) DMP, Me_2CO, *p*-TsOH; (ii) $HONHCO_2Me$, $NaIO_4$, H_2O, MeOH; c) Al/Hg, THF-H_2O; d) PPL, pH 7; e) PPh_3, DEAD, THF; f) *n*-BuLi, Cu, $BF_3{\cdot}Et_2O$, -78 °C; g) Dowex-50W, MeOH; h) $VO(acac)_2$, *t*-BuOH, PhH, 70 °C; i) BzONa, H_2O, 100 °C; j) Ac_2O/Py; k) Tf_2O, DMAP, CH_2Cl_2, 0 °C; l) K_2CO_3, MeOH.

Scheme 11.

conditions[33] and subsequent deprotection furnished the alkaloid, *ent*-7-deoxypancratistatin (*ent*-**10**).

Protected forms of the enantiomer of conduramine A-1 have been obtained by Johnson and co-workers.[9c] The Diels–Alder addition of diene **27** with PhCON═O (formed in situ by oxidation of benzohydroxamic acid with Et_4NIO_4) provided (±)-**107**. Reduction of the N–O bond of (±)-**107** gave (±)-**108**. Treatment of (±)-**108** with *Pseudomonas cepacia* (Amano P-30) lipase in isopropenyl acetate gave a 1:1 mixture of the acetate (+)-**110** and alcohol (−)-**109** that were readily separated by column chromatography. Acetate (+)-**110** was treated with NH_3 in MeOH to give (+)-**111**. Treatment of (+)-**111** and (−)-**109** under acidic conditions led to both enantiomers of *N*-benzoyl conduramine A-1, (+)-**112** and (−)-**112**, respectively (Scheme 12).

Fortamine (**113**) and 2-deoxyfortamine (**114**) are the aminocyclitol portions of the broad- spectrum antibiotics, fortimicin A (**115**) and istamycin A (**116**), respectively (Fig. 6).[34]

The syntheses of racemic fortamine [(±)-**113**] and 2-deoxyfortamine [(±)-**114**] have been reported by Knapp and co-workers in 1983.[35] Monoepoxidation of cyclohexa-1,3-diene (**117**) gave epoxide (±)-**118**, the reaction of which with $MeNH_2$ was highly regioselective and furnished (±)-**119** (Scheme 13).

N-Acylation and *O*-methylation of (±)-**119** led to (±)-**120**, which was then bromocyclized into (±)-**121**. This established the protected *cis*-4,5-methylaminoalcohol and E_2 elimination (DBU) gave an alkene that was epoxidized into a 9:1 (to 23:1) mixture of oxiranes. The major epoxide (±)-**122** was converted into the conduramine A-2 analogue (±)-**123** by a selenophenolate addition/selenoxide elimination sequence. Epoxidation of (±)-**123** gave (±)-**124** as a single isomer. This epoxide reacted with NaN_3 to give an azide, the reduction of which led to (±)-**125**. Acidic treatment of (±)-**125** and neutralization gave racemic fortamine (±)-**113**.

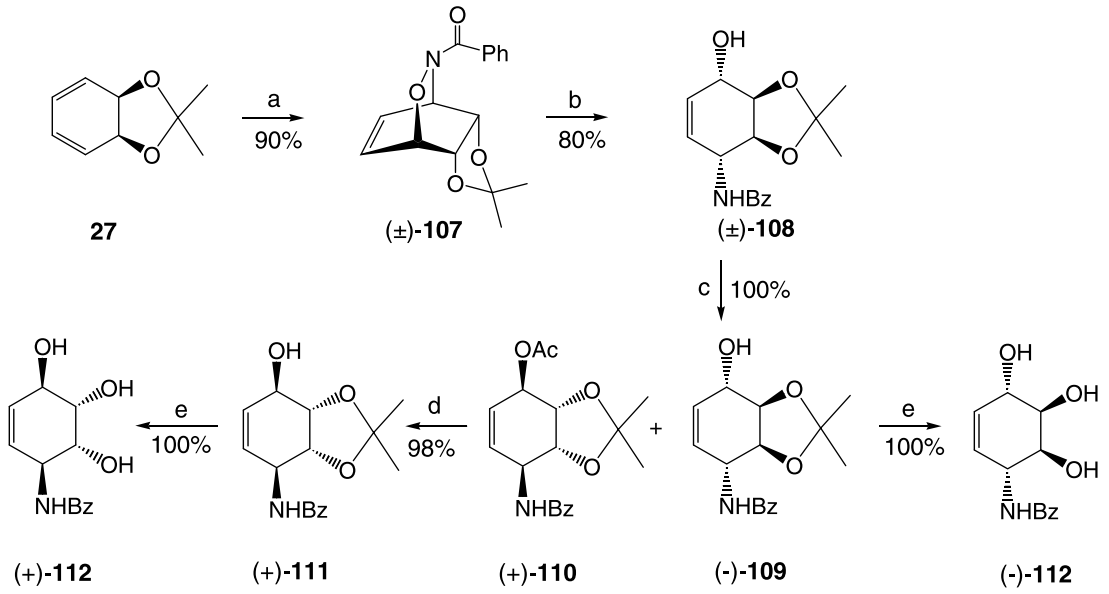
In 1986, the same team[36] described a synthesis of (−)-fortamine [(−)-**113**] and (+)-deoxyfortamine [(+)-**114**].

2.2. Synthesis of aminoconduritols B

There are two types of conduramines B, conduramine B-1 and its enantiomer (*ent*-B-1), and conduramine B-2 and its enantiomer (*ent*-B-2) (Fig. 7). Both conduramine B-2 and *ent*-B-2 are unknown compounds.

2.2.1. Synthesis of aminoconduritol B-1 and analogues. The first synthesis of racemic conduramine B-1 peracetate [(±)-**18**] has been reported by Nakajima et al.[12] (Scheme 1).

A protected form of enantiomerically pure (−)-conduramine B-1 has been obtained through dynamic kinetic



Scheme 12.

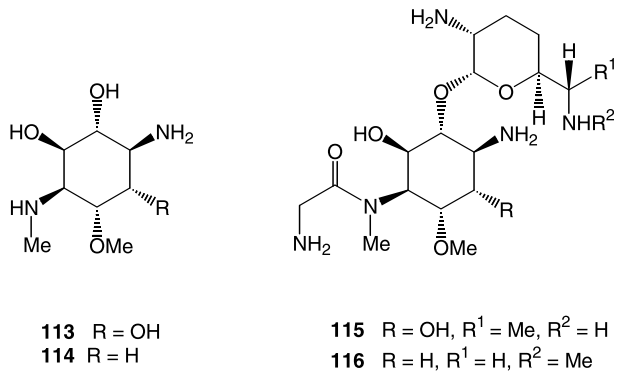
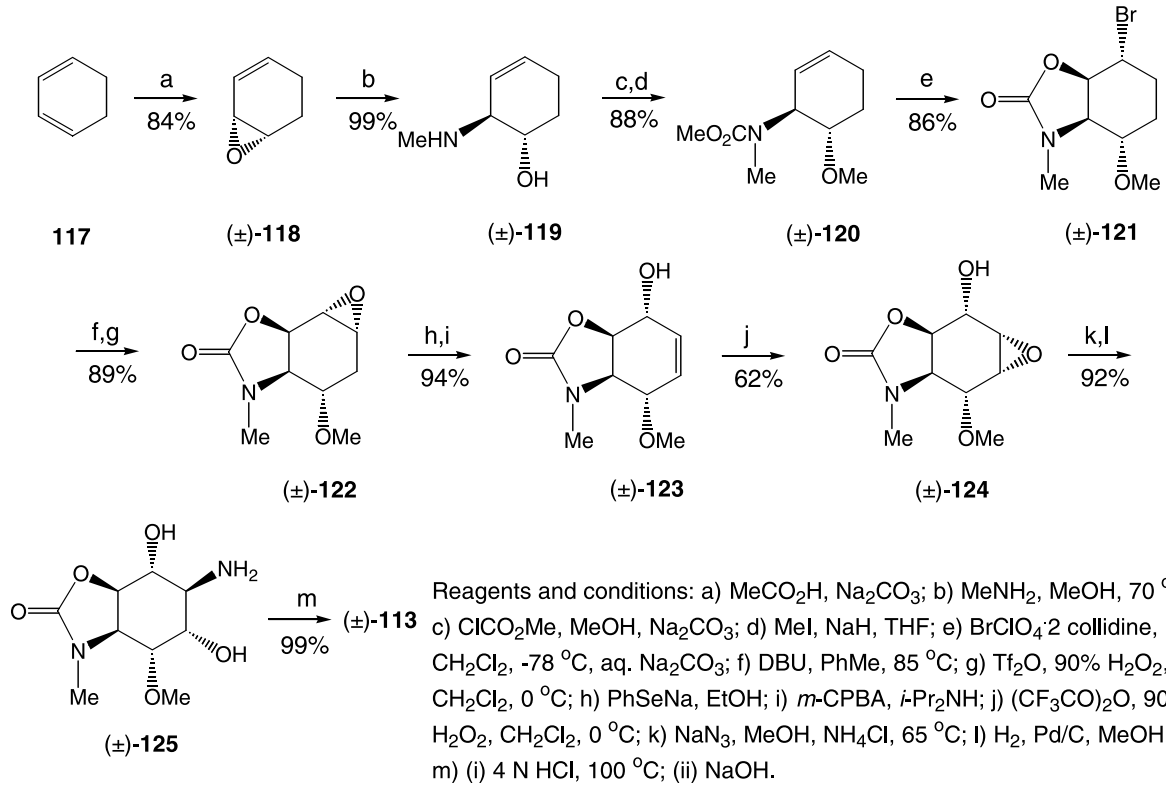


Figure 6.

asymmetric transformation (DYKAT) of the fully protected (±)-conduritol B (±)-**126** by Trost and co-workers.[37] This racemic conduritol tetraacetate (±)-**126** was prepared in three steps from benzoquinone by a simple modification of Guo's method.[38] Tetratrichloroethyl carbonate (±)-**127** was derived from (±)-**126** by a two-step, one-pot procedure. Phthalimidation of (±)-**127** in the presence of 2.5 mol% of $(dba)_3Pd_2\cdot CHCl_3$ and the chiral ligand (*R*,*R*)-**49** gave the protected conduramine B-1 derivative (−)-**128a** in 37% yield and 97% ee (Scheme 14). When the catalyst loading was increased to 5 mol%, the reaction proceeded to give a 61% yield (95% ee) in a process that is, at least in part, a DYKAT. When dibenzylamine was used, a DYKAT was observed, since complete conversion into (−)-**128b** in 89% yield (95% ee) could be achieved.

Unprotected conduramine B-1 hydrochloride [(−)-**135**·HCl] was first prepared by Stick and co-workers (Scheme 15).[39] Methyl α-D-glucopyranoside **129** was transformed into enone **130**[40] and then into the allylic alcohol **131** under Luche's conditions ($NaBH_4$, $CeCl_3\cdot 7H_2O$, MeOH).[41] The alcohol **131** was converted into the amide (−)-**133** through an Overman rearrangement[42] of the trichloroacetamidate (+)-**132** and hydrolysis of (−)-**133** gave the amine (−)-**134**. Debenzylation of (−)-**134** (Na/NH_3/THF) followed by treatment with 1 N HCl gave conduramine B-1 hydrochloride [(−)-**135**·HCl], which was characterized as the amide (−)-**18**.

(−)-Conduramine B-1 [(−)-**17**] has been prepared recently by Vogel and co-workers.[43] Aminoconduritol (−)-**17** has been derived from (+)-7-oxabicyclo[2.2.1]hept-5-en-2-one[44] [(+)-**136** (Scheme 16), a naked sugar of the first generation[45]], applying chemistry reported for the synthesis of (−)-conduritol F.[46] Dibenzyl acetal (+)-**137** was obtained from ketone (+)-**136** in two steps. Treatment of (+)-**137** with strong acid (HSO_3F) led to the partially protected *trans*-diol, which, after Pd-catalyzed hydrogenolysis, gave (+)-**138** (92%, two steps) and ketone (−)-**139** was obtained in two more steps. Reduction of cyclohexenone (−)-**139**[41] with $NaBH_4/CeCl_3\cdot 7H_2O$ in MeOH (0 °C, 3 h) gave a 2.5:1 mixture of conduritol F and conduritol B derivatives, (−)-**140** and (−)-**141**, respectively, in 98% yield. Treatment of this mixture with phthalimide, diethyl azodicarboxylate (DEAD) and triphenylphosphine (all in 1.25 equiv)[32,47] in dry toluene (0 °C, 12 h) provided a 3.8:1 mixture of *N*-substituted phthalimides, (−)-**142** and (−)-**143** (87%), that were separated by FC on silica gel. Under acidic conditions (1% *p*-TsOH in MeOH, 65 °C, 45 min), (−)-**142** was converted into triol (−)-**144** in 95% yield. Transaminolysis of (−)-**144** with $MeNH_2$ (41% in H_2O, 20 °C) and purification on a Dowex-50W-X2 (H^+ form) column provided pure (−)-conduramine B-1 [(−)-**17**] in 95% yield (Scheme 16).



Scheme 13.

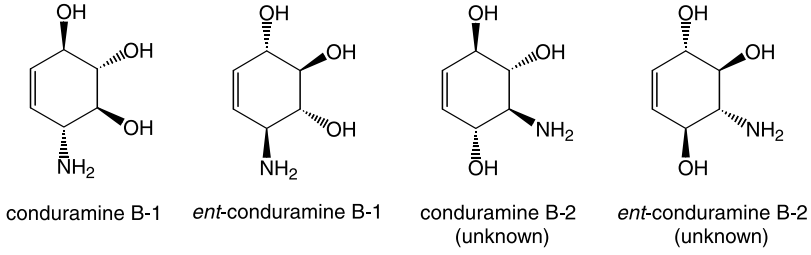
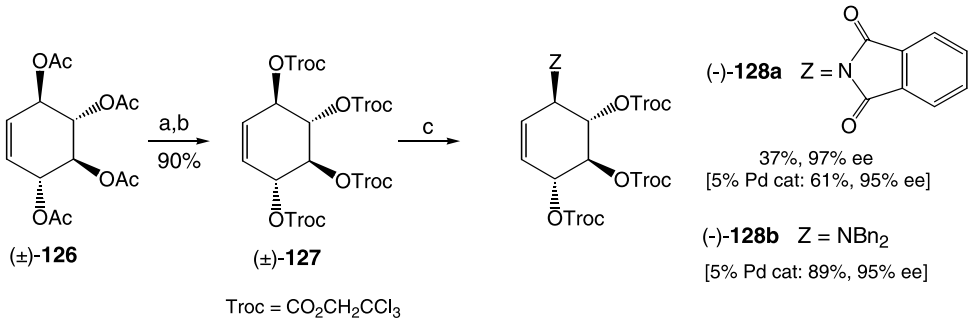
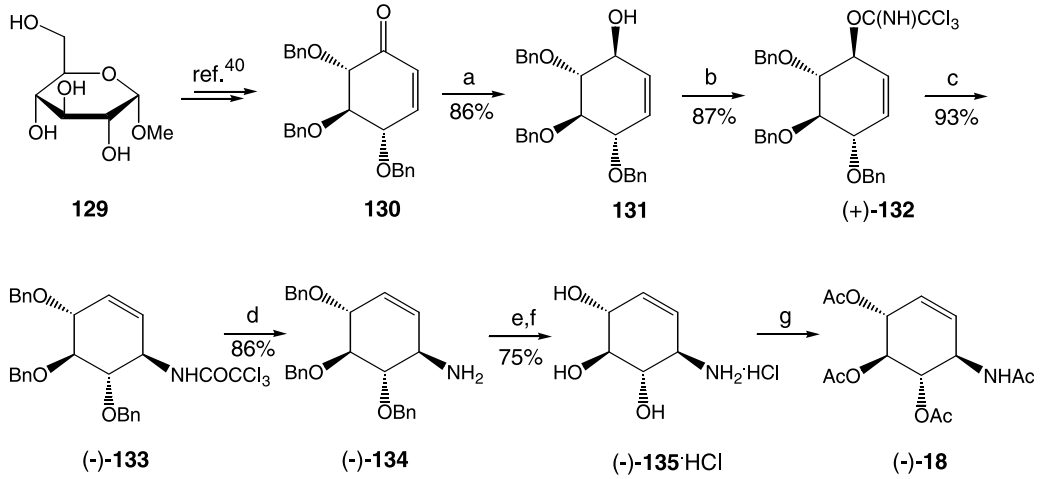


Figure 7.

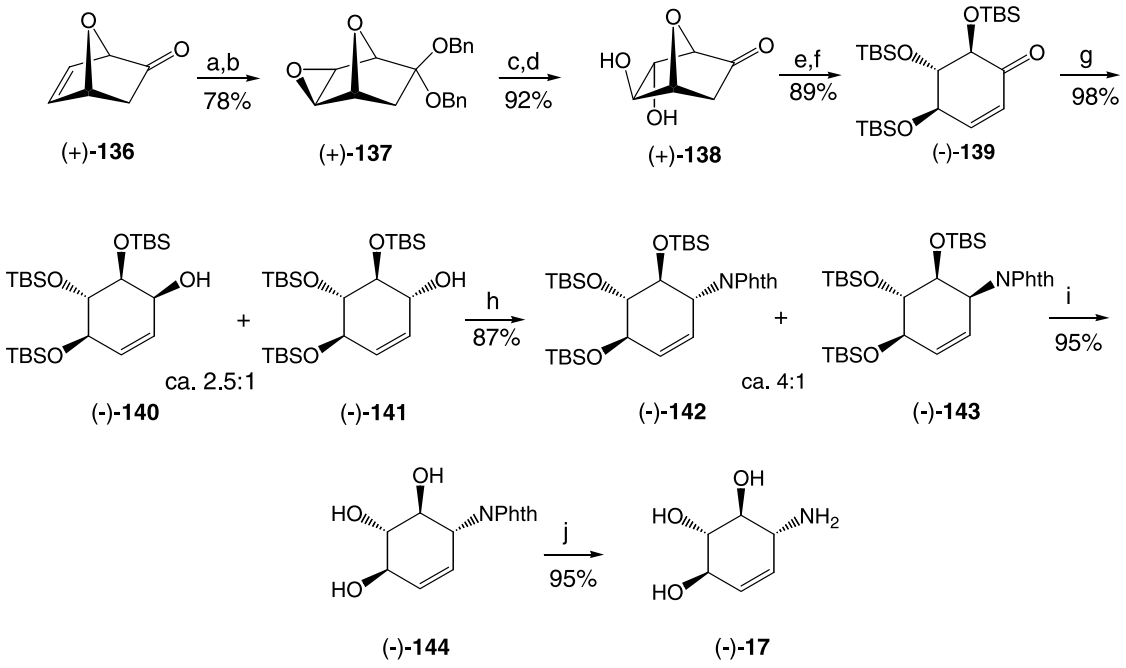


Scheme 14.



Reagents and conditions: a) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C; b) Cl_3CCN, NaH, CH_2Cl_2, rt, 1 h; c) xylene, Δ, 9 h; d) 6 N NaOH, EtOH, rt, overnight; e) Na/NH_3, THF,-78 °C, 1 h; f) 1 N HCl; g) Ac_2O/Py, DMAP, rt.

Scheme 15.



Reagents and conditions: a) BnOTMS, TMSOTf, CH_2Cl_2 4 °C, 4 h; b) *m*-CPBA, $CHCl_3$, rt, 6 h; c) BnOH, CH_2Cl_2, HSO_3F, -15 °C to rt, overnight; d) H_2, 10% Pd/C, EtOH:H_2O (9:1 v/v), 4 d; e) TBSCl, Imd, DMF, rt, 6 h; f) TBSOTf, Et_3N, PhH, 6 h; g) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C; h) PPh_3, phthalimide, DEAD, PhMe, 0 °C, 12 h, separation by CC, i) 1% *p*-TsOH in MeOH, reflux, 45 min; j) 40% $MeNH_2$ in H_2O, rt, 1 h, filtration on Dowex-50W-X2 (H^+ form)/2 N NH_4OH.

Scheme 16.

The same method starting from (−)-**136** allowed the synthesis of (+)-*ent*-conduramine B-1 [(+)-**17**] for the first time.[43]

2.3. Synthesis of aminoconduritols C

There are four types of conduramines C, conduramine C-1 and its enantiomer (*ent*-C-1), conduramine C-2 and *ent*-C-2, conduramine C-3 and *ent*-C-3, and conduramine C-4 and *ent*-C-4 (Fig. 8). Conduramines C-2, C-3 and C-4 in both enantiomeric forms are unknown compounds.

2.3.1. Synthesis of aminoconduritol C-1 and analogues. In 1992, Johnson and co-workers[9c] reported the first

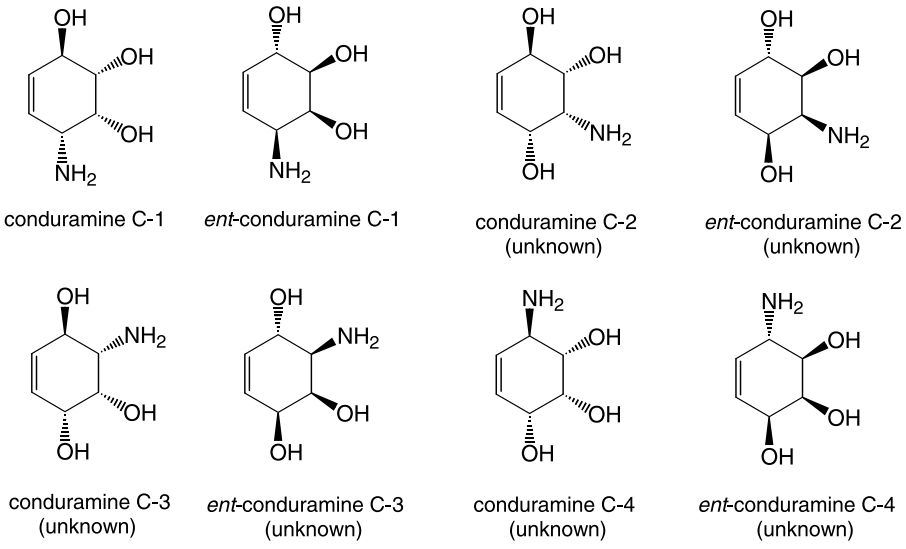
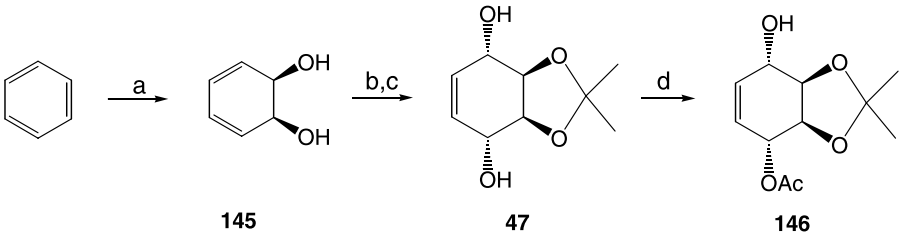


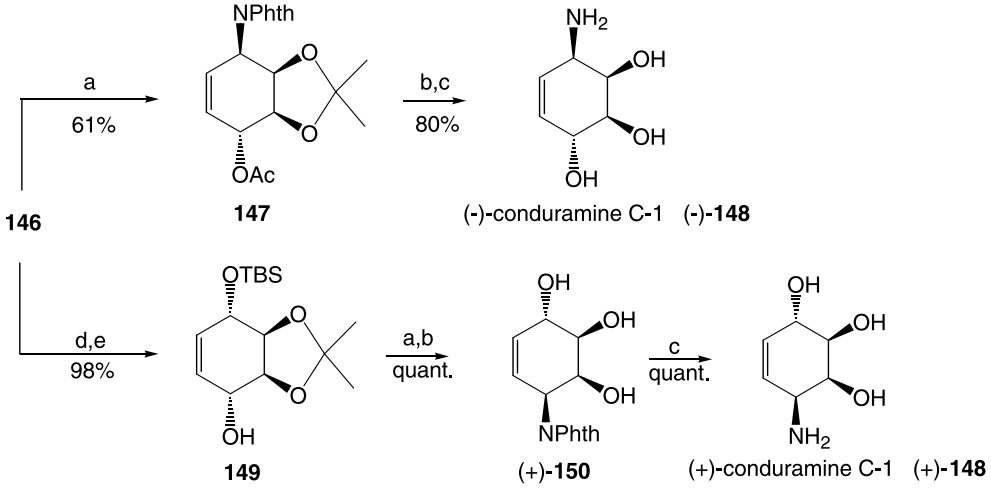
Figure 8.



Reagents and conditions: a) *Pseudomonas putida*; b) 2,2-dimethoxypropane, *p*-TsOH; c) O_2 then $(NH_2)_2CS$; d) *Pseudomonas cepacia* lipase (Amano P-30), isopropenyl acetate, 55 °C.

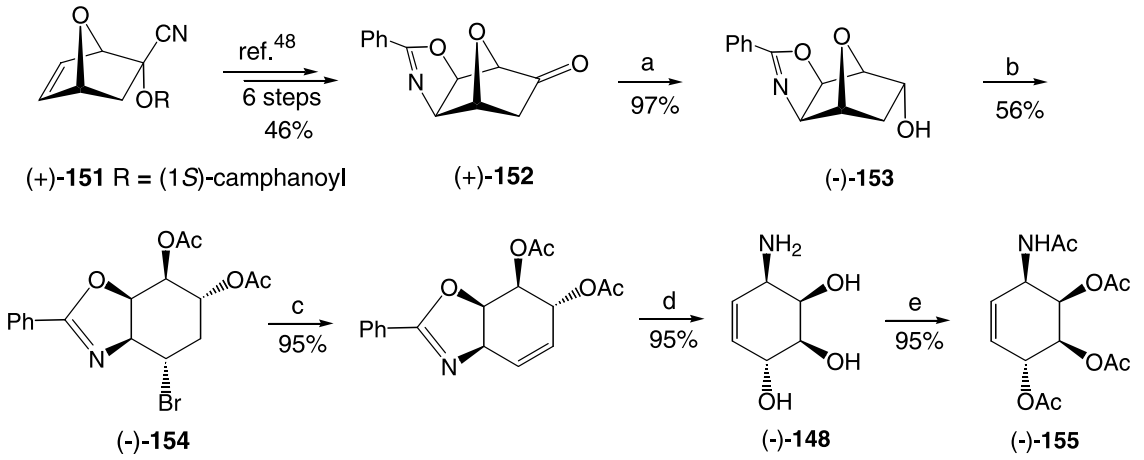
Scheme 17.

syntheses of (−)- and (+)-conduramine C-1, (−)-**148** and (+)-**148** (Schemes 17 and 18). Microbial oxidation of benzene into cyclohexa-3,5-diene-1,2-diol (**145**), followed by treatment with $(MeO)_2CMe_2$ under acidic conditions, produced *meso*-2,3-*O*-isopropylideneconduritol A (**47**). Its desymmetrization to **146** was realized by *Pseudomonas cepacia* lipase-catalyzed monoacetylation in pure isopropenyl acetate (Scheme 17).



Reagents and conditions: a) PPh_3, phthalimide, DEAD, PhMe, 0 °C, 1 h, b) *p*-TsOH, MeOH, reflux; c) 40% aq. $MeNH_2$; d) TBSCl, Imd, DMF; e) K_2CO_3, MeOH.

Scheme 18.



Reagents and conditions: a) $NaBH_3CN$, MeOH, 0 °C, then 5.5 h, rt; b) 33% HBr in AcOH, 60° C, 3 d; c) DBU, PhMe, Δ, 2 h; d) (i) 5 N HCl, Δ 2 h; (ii) Dowex (500 x 4); e) Ac_2O/Py.

Scheme 19.

Treatment of **146** with phthalimide applying the Mitsunobu protocol[32] gave the fully protected conduramine C-1 derivative **147** which, under acidic conditions followed by treatment with 40% aq $MeNH_2$, gave (−)-conduramine C-1 [(−)-**148**]. Silylation/deacetylation of **146** gave alcohol **149**. Deprotection (*p*-TsOH in MeOH) afforded triol (+)-**150** which, upon aminolysis, gave (+)-conduramine C-1 [(+)-**148**] (Scheme 18).

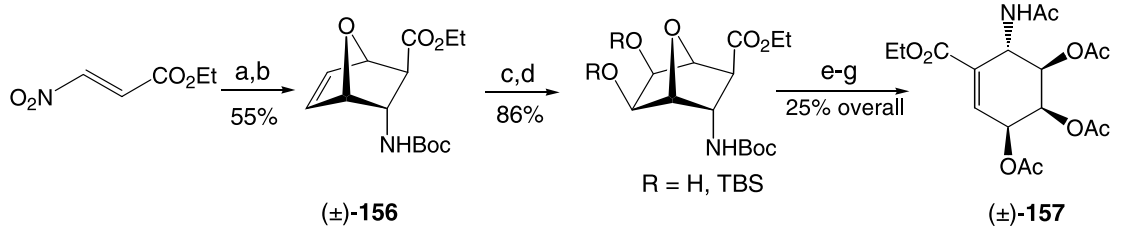
An alternative approach to the asymmetric synthesis of (−)-conduramine C-1 was developed by Allemann and Vogel,[2j] who used the naked sugar (+)-**151** as the starting material. The tricyclic ketone (+)-**152**[48] was obtained in six steps with an overall yield of 46%. Ketone (+)-**152** was reduced to the corresponding *endo*-alcohol (−)-**153**, the treatment of which with boiling HBr/AcOH provided the diacetate (−)-**154**. Regioselective *anti*-eliminaton of HBr with DBU and acidic hydrolysis furnished (−)-conduramine C-1 [(−)-**148**], which was also characterized as its peracetate (−)-**155** (Scheme 19).

A substituted racemic conduramine C-1 derivative that is, in fact, a β-amino acid derivative [(±)-**157**] was described by Masesane and Steel.[49] Their synthesis started with the oxanorbornene derivative (±)-**156**, obtained by Diels–Alder addition of ethyl (*E*)-nitroacrylate and furan. The selective *exo*-dihydroxylation of the alkene moiety of (±)-**156**, followed by base-induced fragmentation (LiHMDS, THF, −50 °C) of the oxanorbornane skeleton (E_1cb elimination), provided the desired conduramine derivative (±)-**157** (Scheme 20).

An approach to racemic conduramine C-1[21] is presented in Scheme 21 in which an initial OsO_4-catalyzed hydroxylation of (±)-**39** and subsequent protection gave acetonide (±)-**158**. Reduction of (±)-**158** ($NaBH_4$, MeOH) give a mixture (ca. 5.5:1) of the *exo* and *endo* isomers of (±)-**159**. Reaction of this mixture with LHMDS led to derivative (±)-**160**. Reductive desulfonylation gave compound (±)-**161** that was converted into the conduramine C-1 derivative (±)-**162** by a three-step process. After deprotection and acetylation of (±)-**162**, racemic conduramine C-1 tetraacetate [(±)-**155**] was obtained.

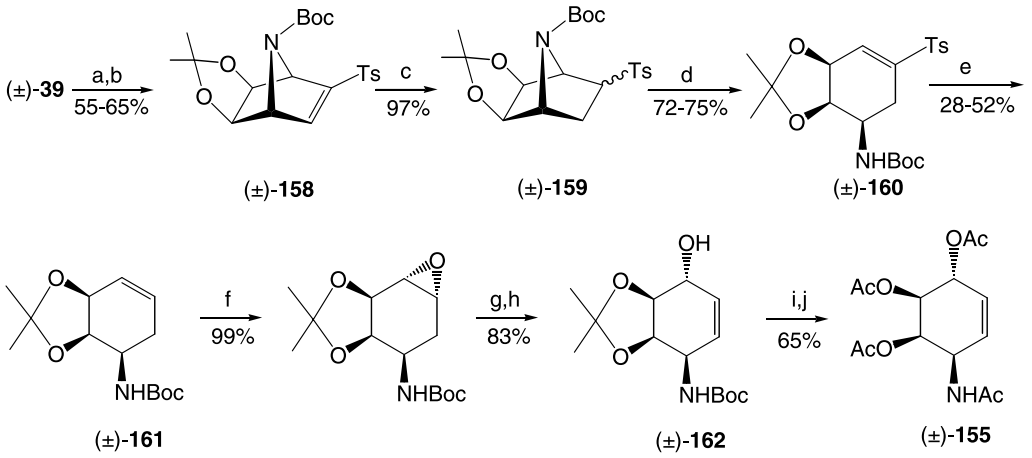
2.3.2. Synthesis of aminoconduritol C-2 analogues. Hygromycin A **163** is an antibiotic produced by cultures of several types of *Streptomyces*[50] and is widely used against Gram-positive and Gram-negative bacteria.[50a,b] It contains the unique aminocyclitol structure **164** (Fig. 9).

In 1989 Ogawa and co-workers[51] reported the total synthesis of this antibiotic from D-glucose. The key aminocyclitol (−)-**164** was obtained from the conduramine C-2 derivative **169** (Scheme 22).[51a] The known 5-enopyranoside **165** was



Reagents and conditions: a) furan, $CHCl_3$, -20 °C; b) (i) Zn/HCl, EtOH; (ii) Boc_2O, TEA; c) cat. OsO_4, $Me_3NO{\cdot}H_2O$, Me_2CO; d) TBSCl, Imd, CH_2Cl_2; e) LiHMDS, THF, -50 °C to 25 °C; f) TBAF, THF; g) Ac_2O/Py.

Scheme 20.



Reagents and conditions: a) cat. OsO_4, NMO, $NaHCO_3$, *t*-BuOH, H_2O, THF; b) $Me_2C(OMe)_2$-Me_2CO, *p*-TsOH; c) $NaBH_4$, MeOH; d) LHMDS, THF, -78 °C to rt; e) SmI_2/THF-HMPA, -23 °C; f) *m*-CPBA, $NaHCO_3$, CH_2Cl_2; g) $(PhSe)_2$, *n*-BuLi, THF; h) H_2O_2, CH_2Cl_2 then *i*-Pr_2NEt, THF, Δ; i) TFA, H_2O/CH_2Cl_2; j) NH_3/MeOH; j) Ac_2O/Py, DMAP.

Scheme 21.

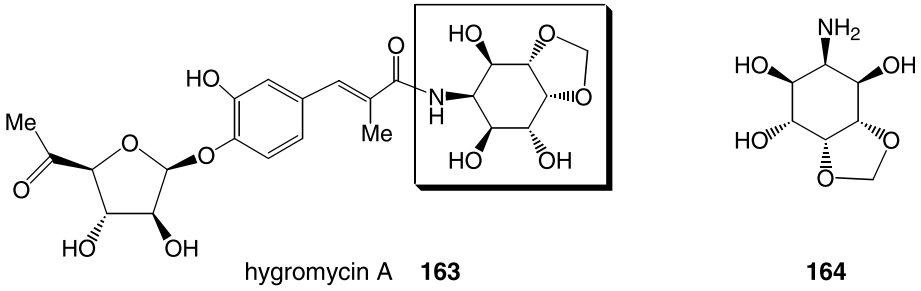
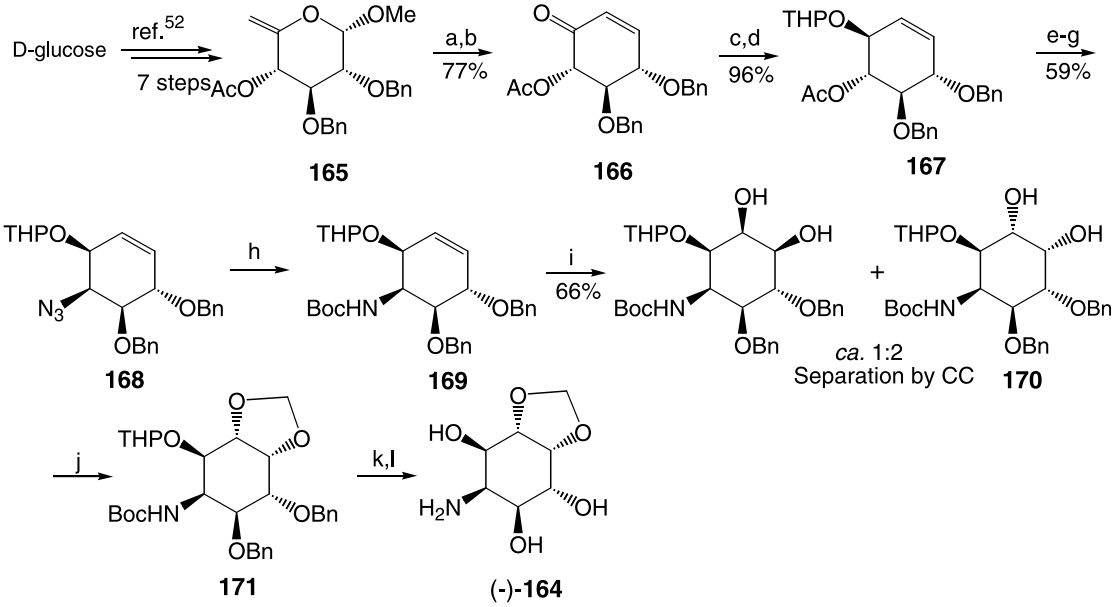
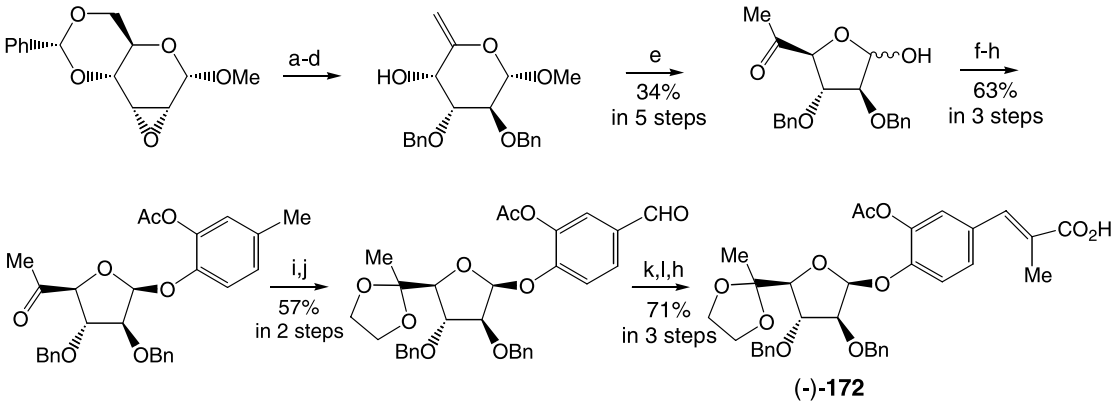


Figure 9.



Reagents and conditions: a) $HgCl_2$, Me_2O-H_2O (1:2), Δ; b) MsCl, Et_3N, CH_2Cl_2; c) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C; d) DHP, PPTS, CH_2Cl_2; e) MeONa, MeOH; f) MsCl, Py, 50 °C; g) NaN_3, HMPA, 100 °C; h) (i) $LiAlH_4$, Et_2O, 0 °C, (ii) $(Boc)_2O$, Et_3N, CH_2Cl_2; i) cat. OsO_4, NMO, DMF-H_2O (4:1), 75 °C; j) NaH, CH_2Br_2, DMF, 0 °C to rt; k) $H_2/Pd(OH)_2$, EtOH; l) TFA, $CHCl_3$, rt.

Scheme 22.



Reagents and conditions: a) (i) NaOH, H_2O, Δ, 48 h; (ii) BnCl, DMSO, rt, 4 h; b) 80% AcOH, 80 °C, 30 min; c) MeI, PPh_3, DEAD, THF, rt, 19 h; d) DBU, PhMe, 80 °C, 23 h; e) IR-120B resin (H^+ form), THF-H_2O (5:2), rt, 22 h; f) 3-benzyloxy-4-hydroxybenzaldehyde, PPh_3, DEAD, THF, rt, 2.5 h; g) H_2, $Pd(OH)_2$, AcOEt, rt, 30 min; h) Ac_2O/Py, rt, 30 min; i) $(CH_2OMe_3Si)_2$, TMSOTf, CH_2Cl_2, -5 °C, 8 h; j) CAN, MeCN-H_2O (1:2), 5 °C; k) $Ph_3P{=}C(Me)CO_2Et$, CH_2Cl_2, rt, 14 h; l) 1M NaOH, MeOH, 50 °C, overnight.

Scheme 23.

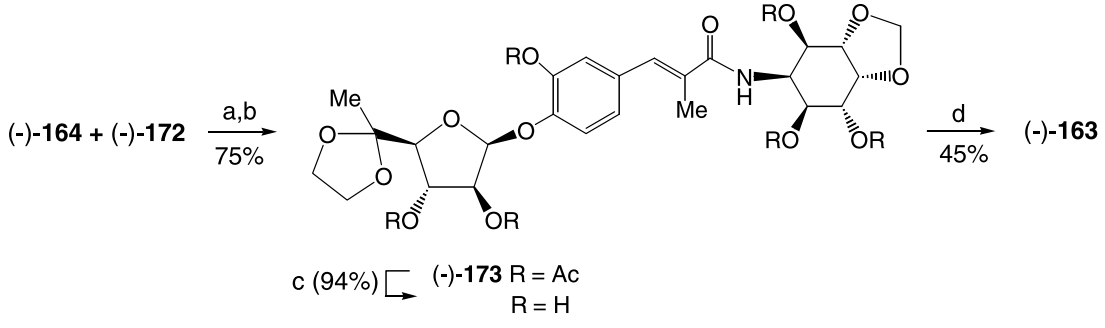
prepared from D-glucose in seven steps.[52] Ferrier reaction of **165**, followed by dehydration, afforded the cyclohexene derivative **166** (77%). Reduction of the carbonyl group of **166** ($NaBH_4/CeCl_3\cdot 7H_2O$) proceeded stereoselectively to give a single alcohol, which was isolated as the THP ether **167**, as a mixture of two diastereoisomers (96%). *O*-Deacetylation of **167** followed by treatment with MsCl gave the mesylate and subsequent treatment with NaN_3 in HMPA gave the azide **168** (59%). Azide **168** was reduced with $LiAlH_4$ and the amine obtained was converted into its Boc-derivative **169**. Dihydroxylation of **169** (OsO_4) gave a 1:2 mixture of two compounds in 66% yield. From this mixture, the *neo*-inosamine-2 derivative **170** was isolated by column chromatography. Further transformations (three steps) via **171** gave aminocyclitol (−)-**164** (Scheme 22).

The second fragment of (−)-hygromycin A containing 2-methylcaffeic acid [(−)-**172**] was prepared as outlined in Scheme 23.

The coupling reaction of the optically active aminocyclitol (−)-**164** and sugar fragment (−)-**172** was conducted under Shioiri's protocol[53] [$(EtO)_2P(O)CN$, Et_3N, DMF] and the condensate was obtained as the acetate (−)-**173**, *O*-deacetylation and acid hydrolysis giving (−)-hygromycin A [(−)-**163**] (Scheme 24).

In 1995, Plumet and co-workers[54] applied a highly diastereoselective dihydroxylation of an amino-deoxy-conduritol C-2 analogue, easily accessible from a 7-oxanorbornenic derivative, in the synthesis of the aminocyclitol moiety of hygromycin A.

2.3.3. Synthesis of aminoconduritol C-4 analogues. The synthesis of (±)-conduramine C-4 was reported for the first time by Nakajima et al.,[12] starting from *cis*-benzene diacetate **12**. Epoxidation of **12** followed by opening of the epoxide [(±)-**14**] with NH_3 in MeOH provided the (±)-aminoconduritols C-4 [(±)-**19**] (Scheme 1).

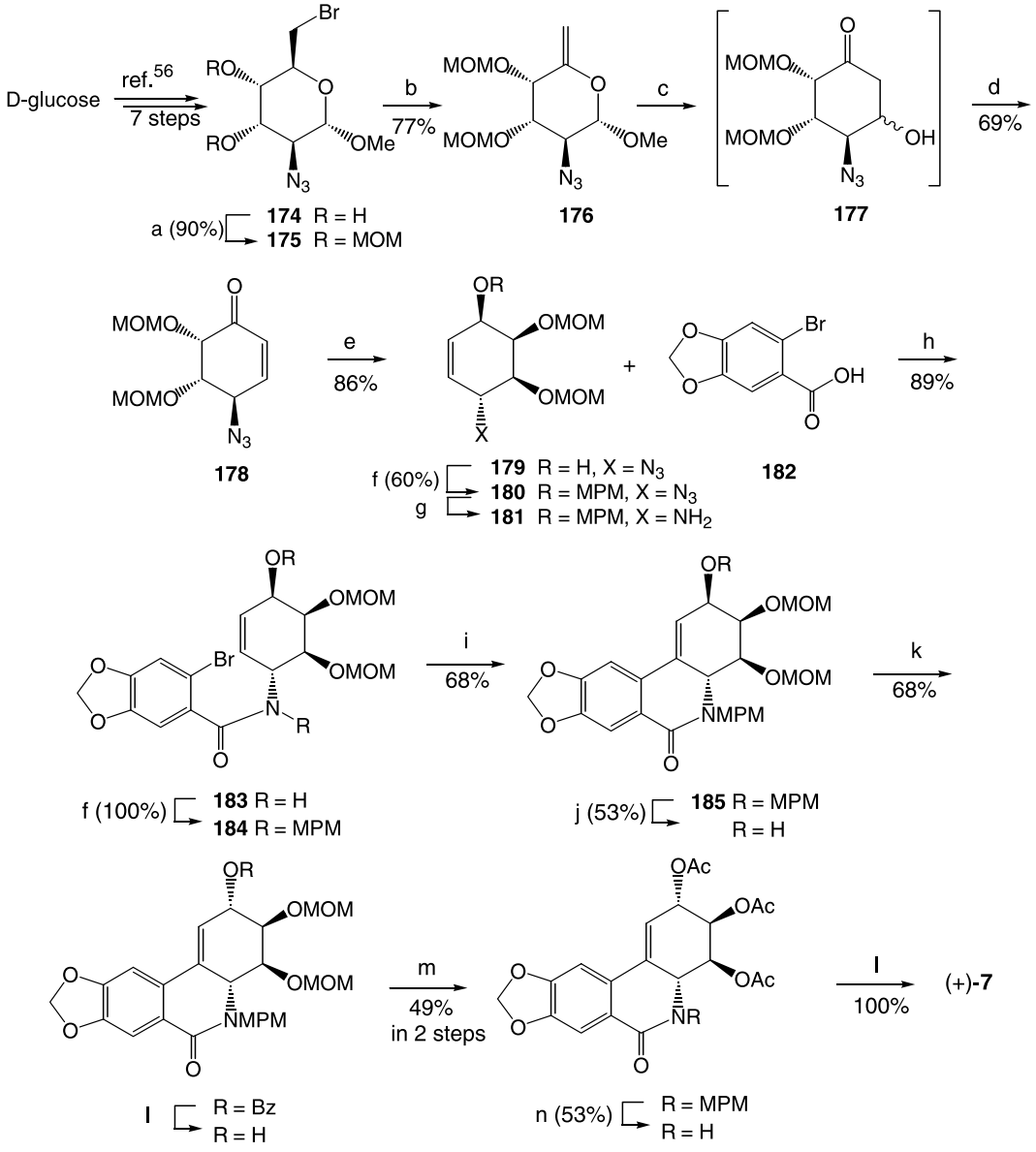


Reagents and conditions: a) $(EtO)_2P(O)CN$, Et_3N, DMF, 0 °C, 2.5 h; b) Ac_2O/Py, rt, 2 h; c) MeONa, MeOH, 0 °C, 30 min; d) TFA-H_2O (3:2), rt, 1 h.

Scheme 24.

Ogawa and co-workers[55] designed an elegant synthesis for optically active (+)-lycorcidine (+)-**7** starting from D-glucose. The key step in their synthesis is the Ferrier rearrangement used to construct the optically active cyclohexenone **178** which was then converted into the conduramine C-4 derivative **181** (Scheme 25).

The hydroxyl groups in **174**, obtained in seven steps from D-glucose,[56] were protected as the methoxymethyl diether **175**. This latter compound was then treated with DBU to afford **176** in good yield. The catalytic Ferrier rearrangement of **176** induced by $(CF_3CO_2)_2Hg$ provided the cyclohexanone derivative **177**, which was dehydrated in situ (MsCl, Et_3N) to give enone **178**. Reduction of the carbonyl group of **178** ($NaBH_4$, $CeCl_3\cdot 7H_2O$, MeOH) proceeded with good stereoselectivity, and alcohol **179** was obtained as a single product and was protected as a *p*-methoxybenzyl ether **180**. Reduction of the azido function of **180** gave the corresponding amine **181**, which was reacted with carboxylic acid **182** to give amide **183** (89% overall yield, based on **180**). Protection of the amide nitrogen (*p*-$MeOC_6H_4CH_2Cl$, NaH) led to compound **184**. Treatment of the fully protected amide **184** under modified Heck conditions (see Scheme 10) afforded a product **185** (68% yield) possessing the phenanthridone skeleton. This compound was subsequently converted into the final product [(+)-**7**] in six additional steps, as outlined in Scheme 25.



Reagents and conditions: a) MOMCl, DIPEA, CH_2Cl_2; b) DBU, PhMe, Δ; c) $(CF_3CO_2)_2Hg$ (1 mol %), Me_2CO-H_2O (2:1), rt; d) MsCl, Et_3N, CH_2Cl_2; e) $NaBH_4$, $CeCl_3\cdot 7H_2O$, MeOH; f) NaH, MPMCl, DMF; g) $LiAlH_4$, Et_2O; h) $(EtO)_2P(O)CN$, Et_3N, DMF; i) $Pd(OAc)_2$ (20 mol %), dppe (40 mol %), TlOAc, DMF, 140 °C; j) DDQ, CH_2Cl_2/H_2O (19:1); k) Ph_3P, DEAD, $PhCO_2H$, THF; l) MeONa, MeOH, rt; m) (i) 1M HCl aq./THF (1:1), 50 °C; (ii) Ac_2O/Py; n) TFA/$CHCl_3$ (1:1), rt, 2 h.

Scheme 25.

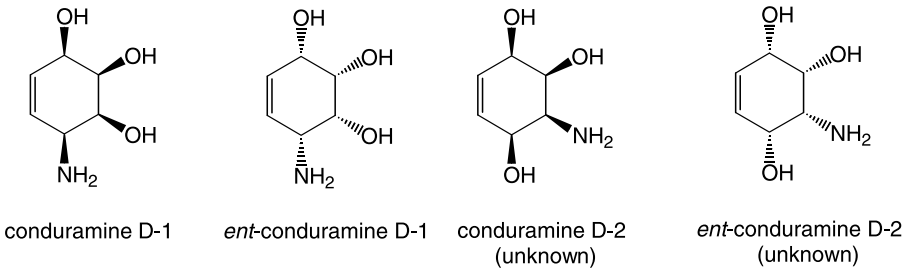


Figure 10.

2.4. Synthesis of aminoconduritols D

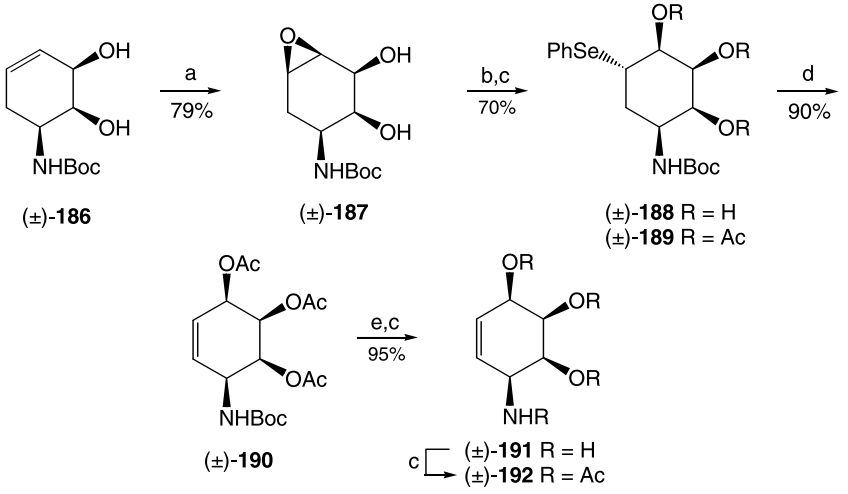
There are two types of conduramines D, conduramine D-1 and its enantiomer (*ent*-D-1), and conduramine D-2 and its enantiomer (*ent*-D-2) (Fig. 10). The two latter compounds have not yet been described.

2.4.1. Synthesis of aminoconduritol D-1 analogues. Conduramine D-1 [(±)-**191**] was first prepared by Muchowski and co-workers[21] as the racemic form using *cis*-diol (±)-**186** as the starting material. Oxidation of (±)-**186** with *m*-CPBA gave epoxide (±)-**187** with five contiguous cis substituents exclusively. The transformation of (±)-**187** into conduramine D-1 (±)-**191** and its crystalline peracetate derivative (±)-**192** (Scheme 26) was then effected by a methodology similar to that used for the generation of several other conduramines (Schemes 5, 21 and 34) and which implies the regioselective epoxide ring opening (±)-**187**→(±)-**188**, subsequent esterification of (±)-**188** into (±)-**189** and oxidative *syn*-elimination of the selenide to give alkene intermediate (±)-**190**. Final deacetylation of (±)-**190** produced the unprotected (±)-aminoconduritol D-1 [(±)-**191**], which was characterized as its peracetate (±)-**192**.

2.5. Synthesis of aminoconduritols E

There are two types of conduramines E, conduramine E-1 and its enantiomer (*ent*-E-1) and conduramine E-2 and its enantiomer (*ent*-E-2) (Fig. 11). The two latter compounds are unknown.

2.5.1. Synthesis of aminoconduritol E-1 and analogues. In 1995, Trost and Pulley[57] described an efficient



Reagents and conditions: a) *m*-CPBA, $NaHCO_3$, CH_2Cl_2; b) $(PhSe)_2$, *n*-BuLi, THF; c) Ac_2O/Py, DMAP; d) H_2O_2, DIPEA, CH_2Cl_2, 0 °C, then THF, Δ; e) 5 N HCl/Δ.

Scheme 26.

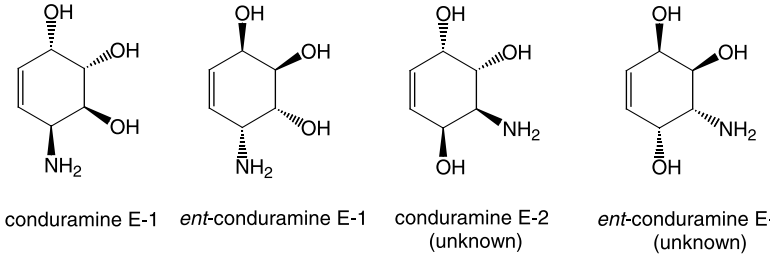
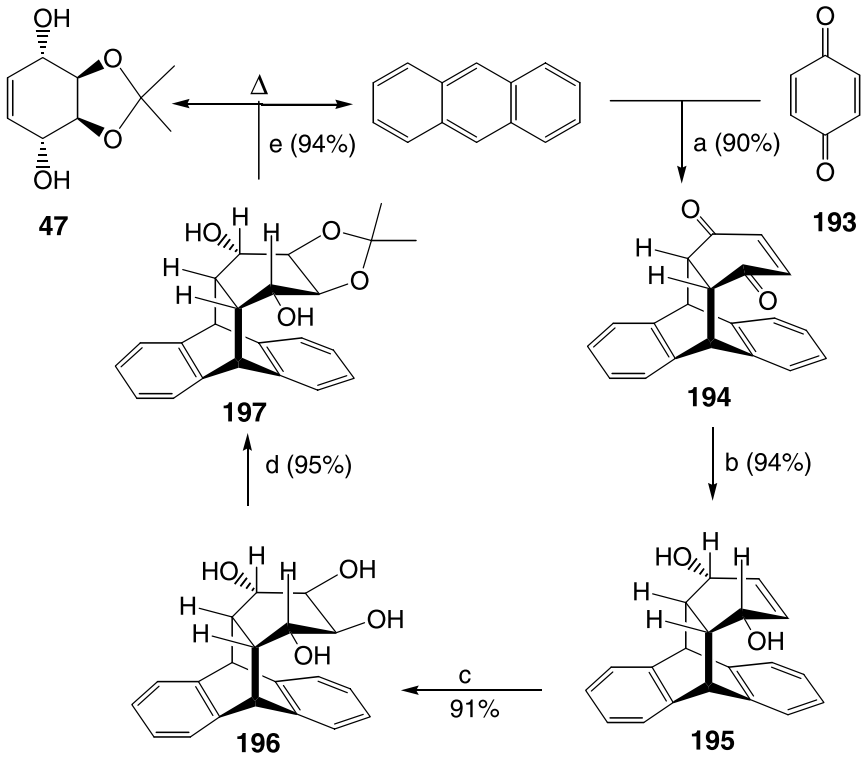


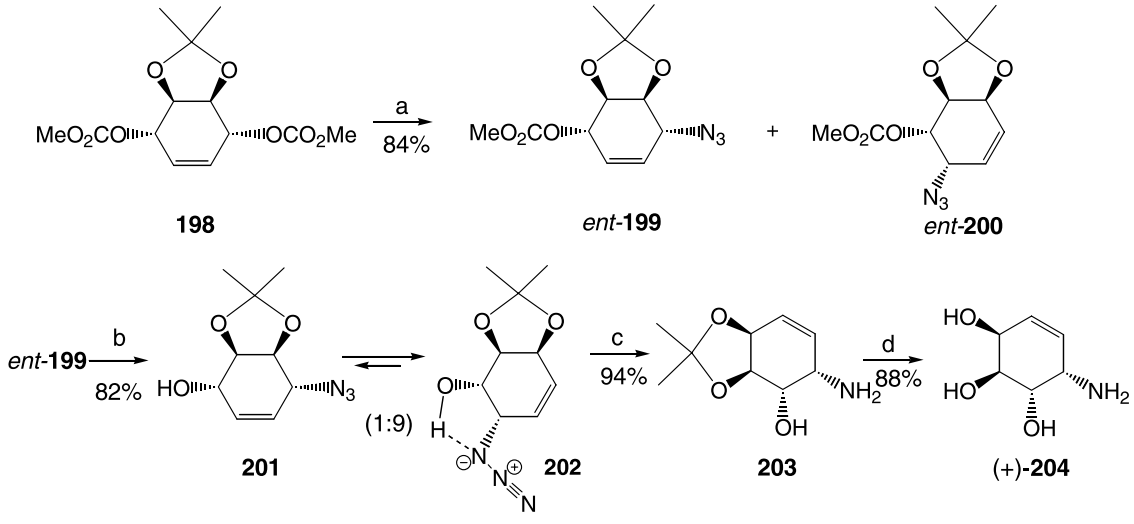
Figure 11.



Reagents and conditions: a) xylene, Δ; b) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, CH_2Cl_2; c) cat. OsO_4, $NMO{\cdot}2H_2O$, Py, *t*-BuOH, H_2O, D; d) Me_2CO, $Me_2C(OMe)_2$, *p*-TsOH; e) FVT, 500 °C.

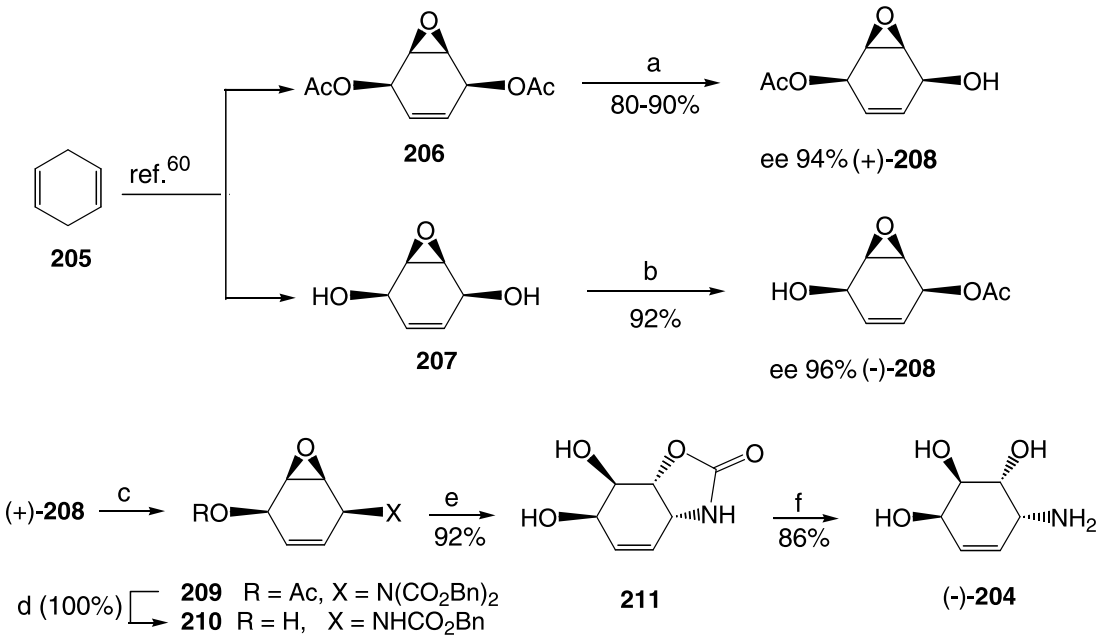
Scheme 27.

preparation of (+)-conduramine E-1 [(+)-**204**]. Conduritol A acetonide **47** was prepared as shown in Scheme 27 using a modification of the method of Cambie et al.[58] *p*-Benzoquinone (**193**) added to anthracene giving adduct **194**. Reduction of the dione under Luche's conditions provided **195** with high stereoselectivity (steric factor). Dihydroxylation of the cyclohexene moiety **195** gave tetrol **196** that was converted into its monoacetonide **197** (Scheme 27). Flash high vacuum pyrolysis furnished diol **47**, which was then converted into the dimethyl carbonate **198** (Scheme 28).



Reagents and conditions: a) 1.5% (*R,R*)-**49**, 0.5% $[\eta^3\text{-}C_3H_5PdCl]_2$, $TMSN_3$, CH_2Cl_2, 0 °C, 2 h; b) K_2CO_3, MeOH, 50 °C; c) Me_3P, THF, H_2O; d) 2 N HCl, H_2O, THF.

Scheme 28.



Reagents and conditions: a) *n*-hexane, 0.2 N pH 7 phosphate buffer, SP 523 (4% w/w), rt; b) TBME-vinyl acetate, Lipozyme IM (5% w/w), rt; c) nucleophile [$HN(CO_2Bn)_2$], PPh_3, DEAD, THF, rt; d) NH_3/MeOH, rt; e) AcOH, H_2O, 110 °C; f) $Ba(OH)_2$, 50 °C.

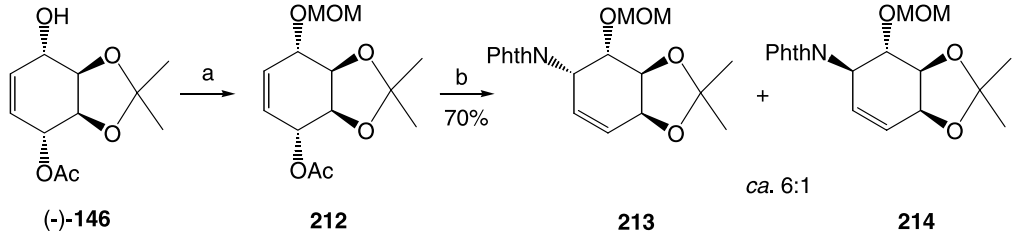
Scheme 29.

Using $[\eta^3\text{-}C_3H_5PdCl]_2$ as the palladium(0) source and the homochiral diphosphine (*R*,*R*)-**49** (see Scheme 6) compound **198** was converted into a mixture of two allylic azides, *ent*-**199** and *ent*-**200**, with high enantioselectivity. Subjecting *ent*-**199** to hydrolysis (K_2CO_3, MeOH), a 1:9 mixture of alcohols **201** and **202** was obtained. Compound **202** was isolated in 82% yield. A simple Staudinger-type reduction of **202** to amine **203**, followed by acidic hydrolysis, led to (+)-conduramine E-1 [(+)-**204**, ee >95%] (Scheme 28).

Recently, Prinzbach and co-workers[59] have reported a synthesis of (−)-conduramine E-1, starting from 1,4-cyclohexadiene (**205**). The epoxy-diacetate **206** and diol **207**, prepared according to a procedure that they had already disclosed in 1972,[60] were submitted to enantioselective lipase-catalyzed hydrolysis, giving either allylic alcohol (+)-**208** or its enantiomer (−)-**208**, depending upon the type of enzymes used (Scheme 29). Mitsunobu substitution of (+)-**208** with $HN(CO_2Bn)_2$ provided **209**. Selective removal of one of the two benzyl carbamate moieties gave **210** quantitatively. Treatment of **210** under acidic conditions provided a regioselective ring opening of the epoxide under assistance by the neighbouring carbamate group. This generated isoxazolone **211**, the hydrolysis of which under basic conditions produced (−)-conduramine E-1 [(−)-**204**].

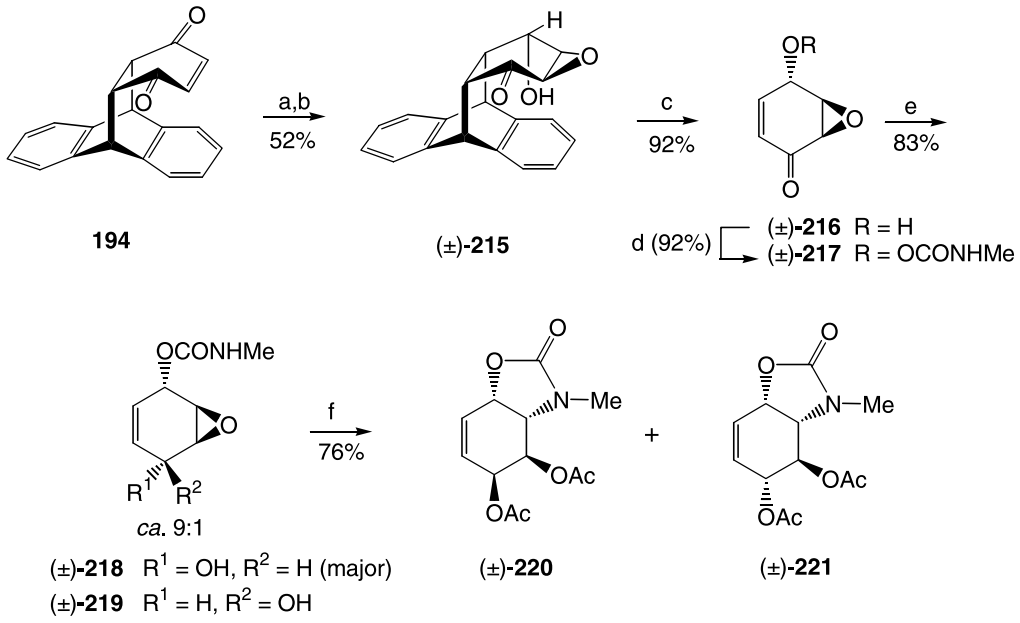
Fully protected conduramine E-1 derivative **213** and conduramine F-4 derivative **214** have been obtained by Johnson and co-workers.[9c] Treatment of **212** (derived from (−)-**146** by treatment with MOMCl, DIPEA) under the conditions shown in Scheme 30, gave two protected aminoconduritols **213** and **214** in a ratio of ca. 6:1.

The racemic forms of conduramine E-2 derivative (±)-**220** and conduramine F-2 derivative (±)-**221** have been obtained applying the method used by Combie and



Reagents and conditions: a) MOMCl, DIPEA; b) $Pd(PPh_3)_4$, DMF, dppe, 50 °C, potassium phthalimide.

Scheme 30.



Reagents and conditions: a) 27% aq. H_2O_2, K_2CO_3, CH_2Cl_2/MeOH (1:1), 40 min; b) $NaBH_4$, $ZnCl_2$, THF, 1 h; c) pyrolysis, 460 °C, 0.2 mmHg, 30 min; d) MeNCO, cat. Me_2SnCl_2 (2 mol %), CH_2Cl_2, rt, 3 h; e) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 0 °C, 10 min; f) (i) *t*-BuOK, THF, 2 h, rt; (ii) Ac_2O/Py, rt.

Scheme 31.

co-workers[61] in their synthesis of 3-*O*-demethylfortamine. The Diels–Alder adduct **194** of anthracene and 1,4-benzoquinone was converted into a mixture of (±)-**220** and (±)-**221** in five steps and 33% overall yield. Epoxidation of the enedione moiety of **194** and subsequent stereoselective reduction of one of the two ketone groups gave the alcohol (±)-**215**. Flash vacuum pyrolysis of (±)-**215** liberated (±)-**216** and anthracene. Reaction of (±)-**216** with methyl isocyanate furnished the corresponding methyl carbamate (±)-**217**. Reduction of the carbonyl group of (±)-**217** under Luche′s conditions led to an inseparable mixture of two diastereomeric allylic alcohols (±)-**218** and (±)-**219**. Treatment of this mixture with *t*-BuOK promoted the intramolecular ring opening of the epoxides and formation of the corresponding oxazolinone-diols that were acetylated into a 1:2 mixture of (±)-**220** and (±)-**221** (Scheme 31).

2.6. Synthesis of aminoconduritols F

There are four types of conduramines F, conduramine F-1 and its enantiomer (*ent*-F-1), conduramine F-2 and *ent*-F-2, conduramine F-3 and *ent*-F-3 and conduramine F-4 and *ent*-F-4 (Fig. 12). Conduramines F-2 and F-3 in both enantiomeric forms are unknown.

2.6.1. Synthesis of aminoconduritol F-1. The first examples of optically pure conduramines and derivatives were presented by Paulsen and co-workers,[62] who obtained

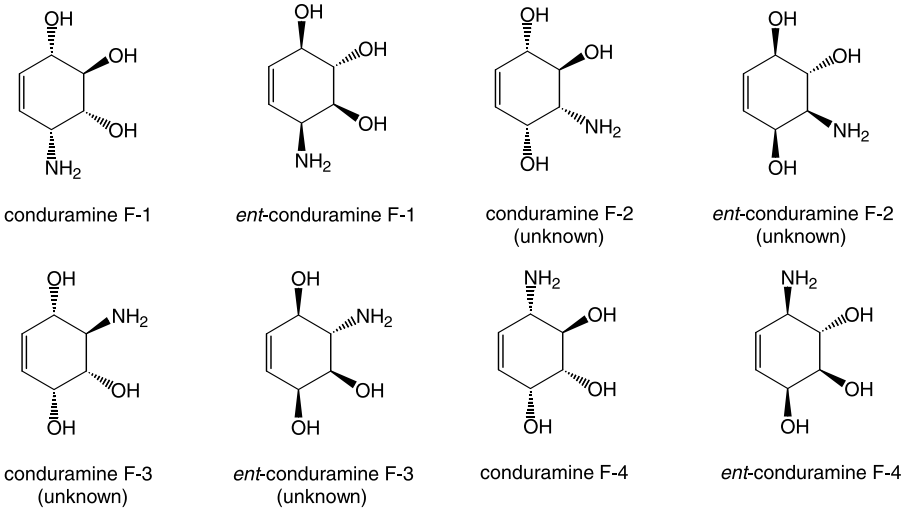
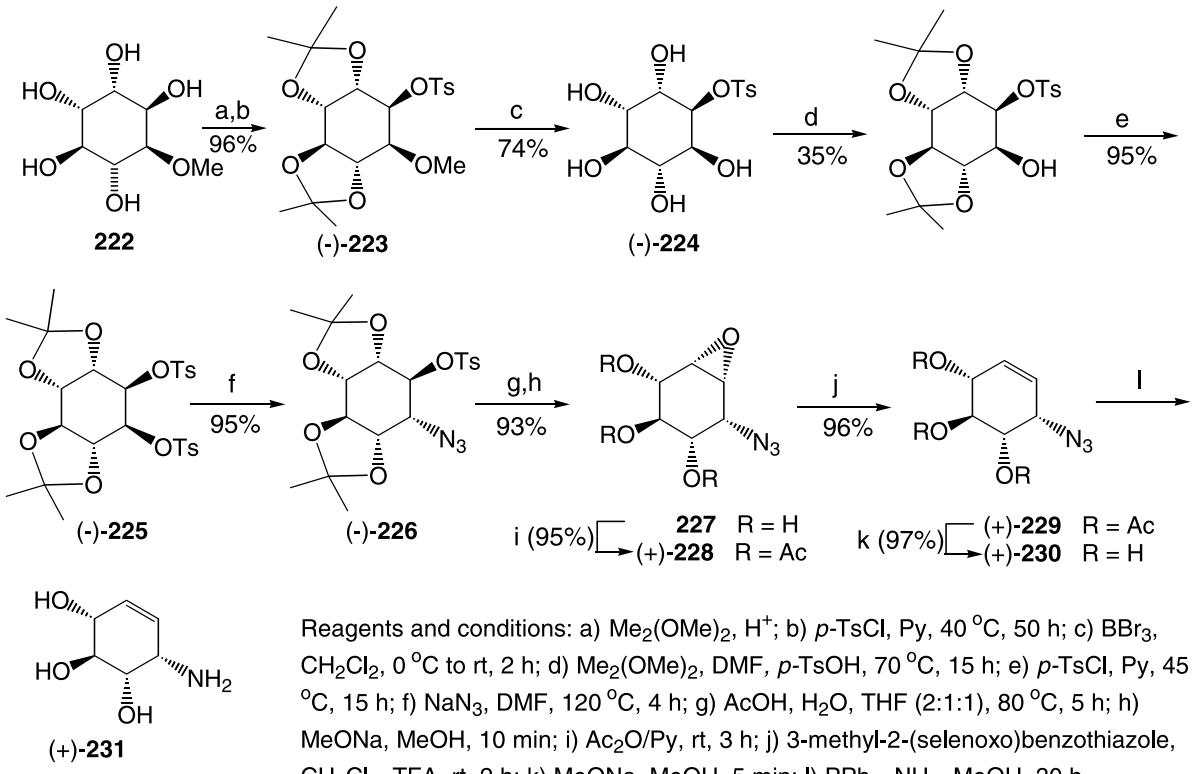


Figure 12.



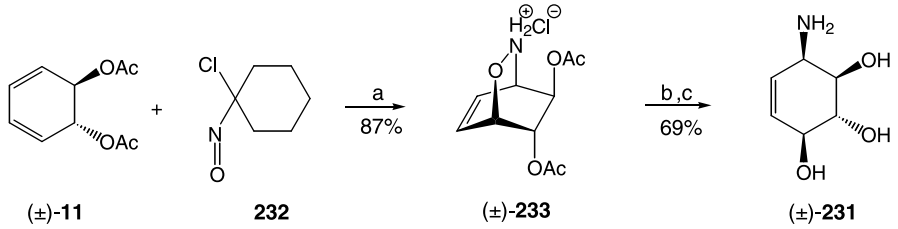
Scheme 32.

(+)-conduramine F-1 [(+)-**231**] (Scheme 32) from natural quebrachitol (2-*O*-methyl-L-*chiro*-inositol) **222**.

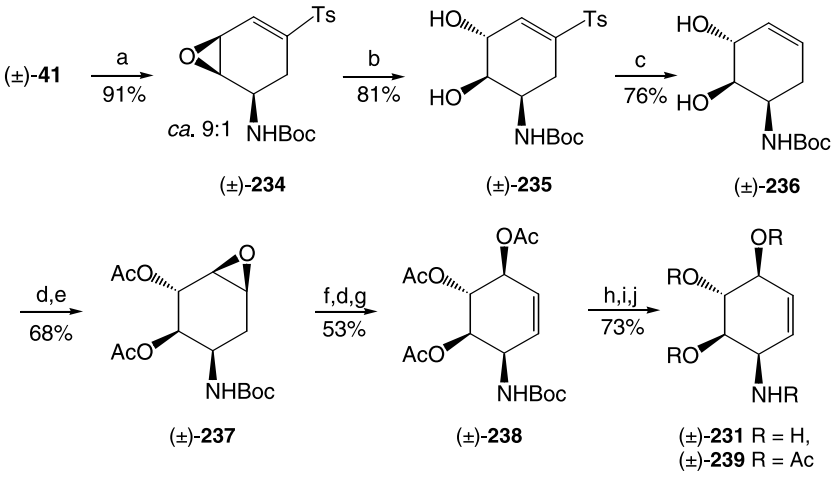
Treatment of **222** with 2,2-dimethoxypropane under acidic conditions followed by classical tosylation afforded di-*O*-isopropylidene-tosylate (−)-**223**. Compound (−)-**223** reacted with BBr_3 in CH_2Cl_2 to give after aqueous work-up 1-*O*-tosylate (−)-**224** which was converted into the ditosylate (−)-**225** in two steps. Selective displacement of the equatorial tosyloxy group of (−)-**225** by NaN_3 gave (−)-**226**. Acidic hydrolysis of the diacetonide and subsequent treatment under basic conditions led to the formation of the azido-epoxide **227**, which, after acetylation, gave triol (+)-**228**. Deoxygenation of the epoxide (+)-**228** provided the cyclohexene derivative (+)-**229**. Zemplen's methanolysis gave triol (+)-**230** which was converted into (+)-conduramine F-1 [(+)-**231**] (Scheme 32).[62]

Kresze and Dittel[63] have developed a short, elegant, four-step route to racemic conduramine F-1 [(±)-**231**]. The adduct (±)-**233** obtained by hetero-Diels–Alder addition of 1-chloro-1-nitrosocyclohexane **232** and *trans*-1,3-cyclohexadiene-5,6-diyl diacetate (±)-**11** in EtOH solution was treated with NH_3/MeOH. Subsequent reduction of the N–O bond produced (±)-**231** in good yield (Scheme 33).

More recently, Muchowski and co-workers[21] have synthesized (±)-conduramine F-1 [(±)-**231**] starting from diene (±)-**41** (for details, see Scheme 4). Peracid oxidation of (±)-**41** gave a 9:1 mixture of the corresponding epoxides. The major compound (±)-**234** underwent acid-promoted epoxide hydrolysis. The reaction is highly stereoselective due to the allylic activation and gave the *trans*-diol (±)-**235** in 81% yield. After reductive desulfonylation of (±)-**235**, giving enediol (±)-**236**, acetylation of the diol and epoxidation of the cyclohexene



Scheme 33.



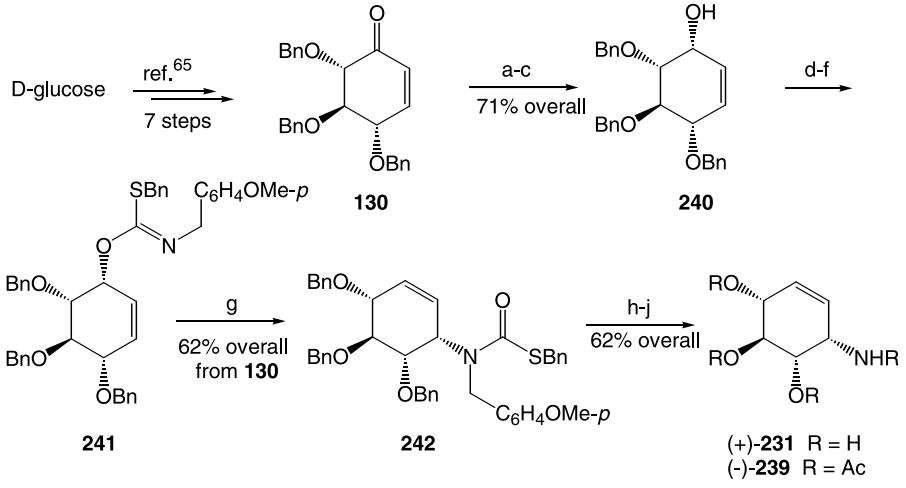
Reagents and conditions: a) *m*-CPBA, CH_2Cl_2; b) H_2O, H_2SO_4, THF, 70 °C; c) 6% Na/Hg, Na_2HPO_4, MeOH, THF, -23 °C; d) Ac_2O/Py; e) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 45 °C; f) $(PhSe)_2$, *n*-BuLi, THF; g) H_2O_2, *i*-Pr_2NEt, CH_2Cl_2, THF, 50 °C; h) 10% HCl, THF, Δ; i) NH_3/MeOH; j) Ac_2O/Py, DMAP.

Scheme 34.

moiety provided (±)-**237**. Five more steps converted (±)-**237** into (±)-conduramine F-1 [(±)-**231**]. The steps involved epoxide ring opening with PhSeLi and subsequent oxidative *syn*-elimination of the intermediate selenide. This generated the fully protected (±)-conduramine F-1 derivative (±)-**238**. Deprotection of (±)-**238** gave (±)-**231** that was characterized as its peracetylated derivative (±)-**239** (Scheme 34).

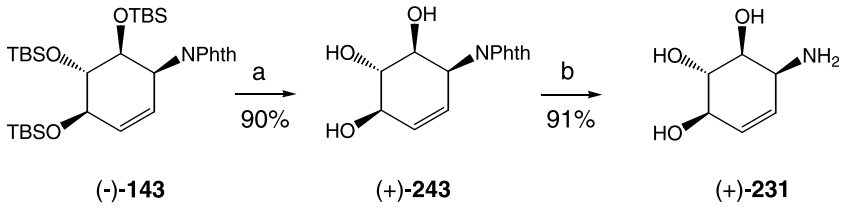
A new route to optically active conduramine F-1 was developed by Knapp and co-workers,[64] based on the [3,3]sigmatropic rearrangements of carbonimidothioate **241** derived from the allylic alcohol **240**, which was prepared from enone **130**[65] (see Scheme 15). Reduction of ketone **130** under Luche's conditions provided **131**, which was inverted into **240** by a Mitsunobu displacement reaction and alkaline methanolysis. Condensation of the sodium alcoholate of **240** with *p*-methoxybenzyl isocyanate, followed by quenching with benzyl bromide, led to carboimidothionate **241**. This latter compound underwent rearrangement in refluxing toluene to give the thiocarbamate **242** (44% overall from **240**). Removal of the *N*-(*p*-methoxybenzyl) group, followed by exhaustive debenzylation (Na/NH_3, THF), provided (+)-7-*nor*-valienamine [(+)-**231**], which was isolated as its peracetate (+)-**239** (Scheme 35).

(+)-*ent*-Conduramine F-1 [(+)-**231**] has been prepared recently by Łysek et al.[66] Under acidic conditions (1% *p*-TsOH in MeOH), compound (−)-**143** was converted into triol (+)-**243** in 90% yield. Transaminolysis of (+)-**243**



Reagents and conditions: a) $NaBH_4$, aq. $CeCl_3$, MeOH; b) $PhCO_2H$, DEAD, Ph_3P; c) aq. KOH, MeOH, 60 °C; d) NaH, THF; e) *p*-(MeO)$C_6H_4CH_2NCS$; f) BnBr; g) PhMe, Δ, 48 h; h) TFA, 2 h; i) Na/NH_3, THF, -55° C, 3 min; j) Ac_2O/Py, DMAP, 12 h, rt.

Scheme 35.



Reagents and conditions: a) 1% *p*-TsOH in MeOH, reflux, 40 min; j) 40% $MeNH_2$ in H_2O, rt, 1 h, filtration on Dowex-50W-X2 (H^+ form)/2 N NH_4OH.

Scheme 36.

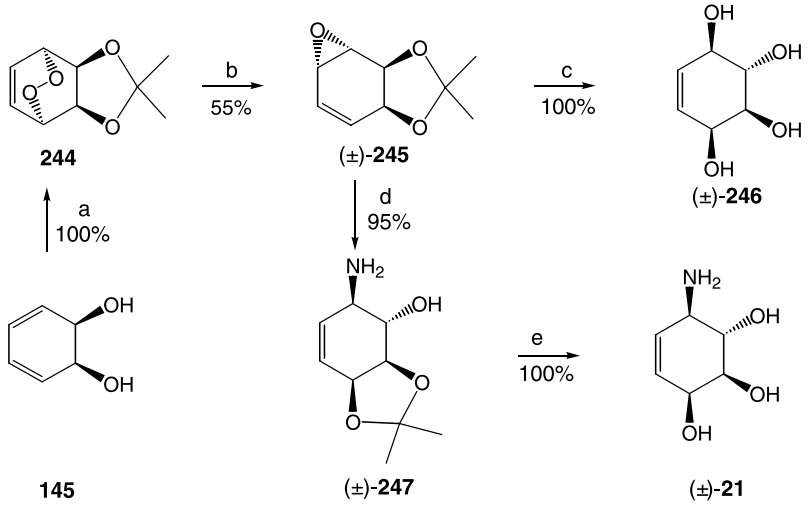
(41% $MeNH_2/H_2O$) and purification on a Dowex-50W-X2 (H^+ form) column gave pure (+)-conduramine F-1 [(+)-**231**] in 91% yield (Scheme 36).

2.6.2. Synthesis of aminoconduritol F-4 and analogues. As shown in Scheme 1, racemic conduramine F-4 was prepared for the first time by Nakajima et al.[12] *cis*-Benzene diacetate **12** was converted in two steps into (±)-aminoconduritol F-4 [(±)-**21**], which was characterized as its tetraacetate (±)-**22**.

The stereospecific synthesis of racemic conduramine F-4 [(±)-**21**] has also been achieved by Balci and co-workers.[67] The cyclohexadiene diol **145**, available from benzene by microbial oxidation using *Pseudomonas putida* (see Scheme 17), was protected as an acetonide and was then submitted to photosensitized oxidation of its diene moiety. The hetero-Diels–Alder reaction of singlet oxygen was highly face-selective for steric reasons and provided the *endo*-peroxide **244**, treatment of which with $POEt_3$ gave the allylic epoxide (±)-**245**, which can be hydrolyzed into (±)-conduritol F [(±)-**246**][68] or ammonolyzed with ammonia in methanol, giving the semiprotected (±)-conduramine F-4 derivative (±)-**247**. Acidic hydrolysis of the acetonide (±)-**247** provided (±)-**21** (Scheme 37).

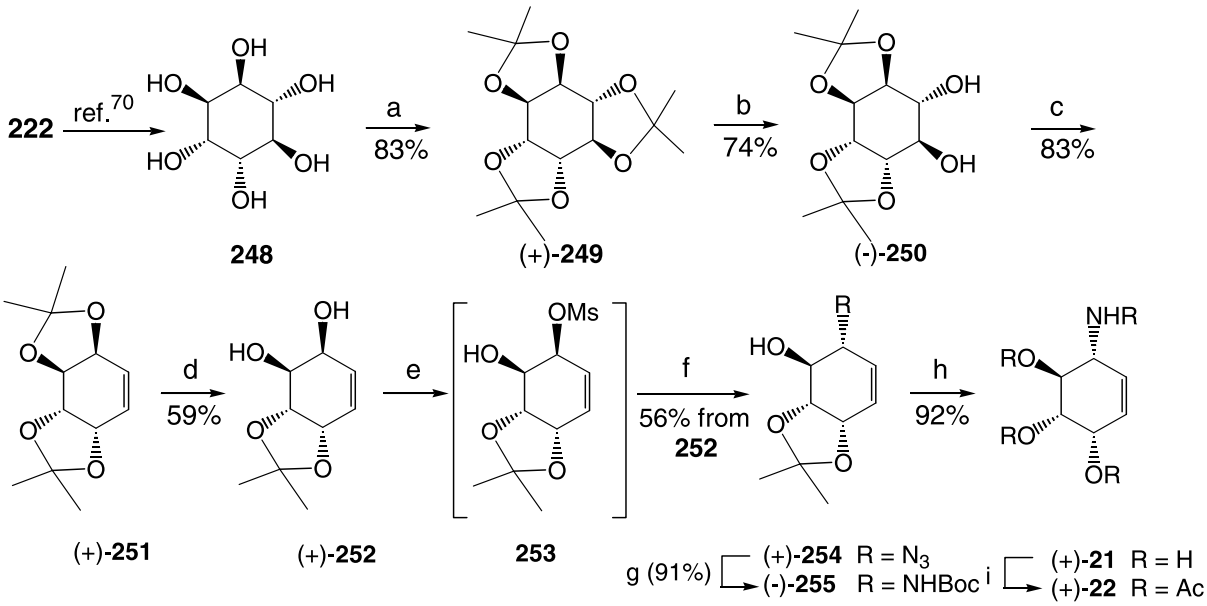
Later, (+)-conduramine F-4 [(+)-**21**] was obtained by Chida et al.,[69] who used this amine in their total synthesis of the novel cerebrosides, acanthacerebroside A and astrocerebroside A, isolated from starfish. L-*chiro*-Inositol **248** was prepared from L-quebrachitol **222** by a known procedure.[70] Treatment of **248** with 2,2-dimethoxypropane afforded the tris-acetonide (+)-**249** and its *trans*-*O*-isopropylidene group (ring strain relief) was removed selectively under acidic conditions to give the known diol (−)-**250** in 74% yield (Scheme 38).

The reaction of (−)-**250** with PPh_3, imidazole and I_2 in toluene cleanly generated the protected conduritol E derivative (+)-**251**. Treatment of (+)-**251** with an acidic resin afforded the mono-*O*-isopropylidene derivative (+)-**252**. The reaction of (+)-**252** with MsCl at −45 °C gave the allylic mesylate **253**, which was reacted with NaN_3 in situ to provide the single allylic azide (+)-**254** in 56% yield. It should be pointed out that it is well known that allylic azides exist as equilibrating mixtures of two isomers.[71] The reduction of azide (+)-**254**, followed by carbamate formation, gave (−)-**255**. Removal of the protecting groups in (−)-**255** afforded (+)-**21**, which was identified as the known conduramine F-4 tetraacetate (+)-**22** (Scheme 38).



Reagents and conditions: a) (i) $(MeO)_2CMe_2$, *p*-TsOH; (ii) O_2, tetraphenylporphyrin, hν, CCl_4, 4 h; b) $CHCl_3$, $POEt_3$, 0 °C to rt, 1 h; c) 1 N H_2SO_4, rt, 1 h; (ii) $BaCO_3$, 10 min; d) NH_3/MeOH, rt, 24 h; e) (i) 1 N H_2SO_4, rt, 3 h; (ii) $BaCO_3$, 10 min.

Scheme 37.



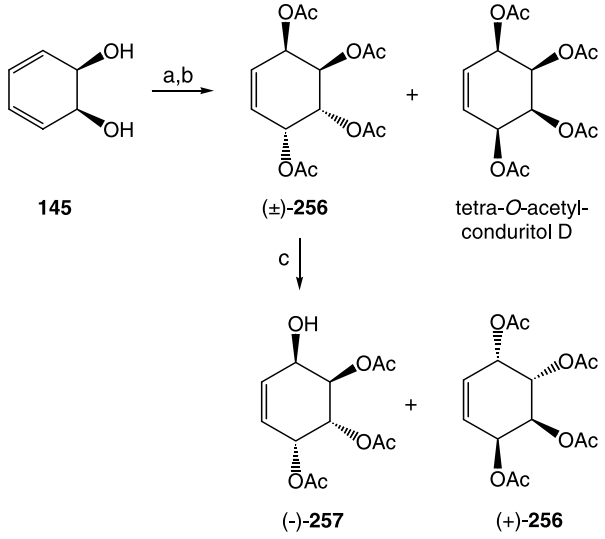
Reagents and conditions: a) 2,2-dimethoxypropane, DMF, *p*-TsOH, 70 °C, 42 h; b) CSA, THF, MeOH, 0 °C, 9 h; c) PPh_3, I_2, Imd, PhMe, D, 1 h; d) Amberlite IR-120B (H^+ form), THF, MeOH, rt, 12 h; e) MsCl, Py, CH_2Cl_2, -45 °C, 2 h; f) NaN_3, DMF, rt, 13 h; g) (i) $LiAlH_4$, THF, 0 °C to rt, 3 h; (ii) Boc_2O, rt, 4 h; h) (i) TFA, CH_2Cl_2, 0 °C to rt, 1 h; (ii) H_2O, 0 °C to rt, 3 h; i) Ac_2O/Py, rt, 4 h (90%).

Scheme 38.

In 1997, Nicolosi and co-workers[72] developed an efficient enzymatic preparation of (+)- and (−)-conduritol E. The triacetyl derivative of conduritol E (−)-**257** has been used in the synthesis of (−)-conduramine F-4 [(−)-**21**] (see Scheme 40). Compound (±)-**256** was prepared according to the Carless procedure[73] from **145**. Dihydroxylation of **145** with NMO in the presence of OsO_4 followed by acetylation led to (±)-**256** (63% yield). Minor amounts of protected conduritol D were also isolated (27% yield) (Scheme 39).

The ester (±)-**256** was subjected to alcoholysis with *n*-BuOH in *tert*-butyl methyl ether using lipase from *Mucor miehei* (Lipozyme® IM) (conv. 22%, 5 h) as catalyst. GC analysis of the reaction mixture showed the presence of unreacted ester (+)-**256** and a single product (−)-**257** (ee >95%).

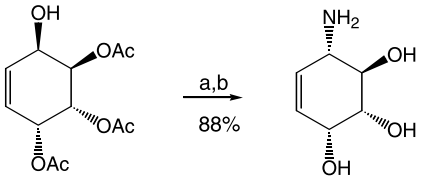
The free hydroxyl group of (−)-**257** makes this compound suitable for the synthesis of cyclitols and conduramines.



Reagents and conditions: a) cat. OsO_4, NMO, CH_2Cl_2, 4 °C, 24 h; b) Ac_2O/Py; c) Lipozyme(R) IM, *n*-BuOH, *t*-BEM, 45 °C, 300 rpm, 5 h, (conv. 22%, ee > 95%).

Scheme 39.

Amination of (−)-**257** (Mitsunobu conditions[32]) yielded the corresponding phthalimide derivative which, on treatment with 40% aq $MeNH_2$, gave (−)-conduramine F-4 [(−)-**21**] (Scheme 40).



(-)-**257** (-)-**21**

Reagents and conditons: a) phthalimide, PPh_3, DEAD, rt, 3 h; b) 40% aq. $MeNH_2$, rt, 15 min.

Scheme 40.

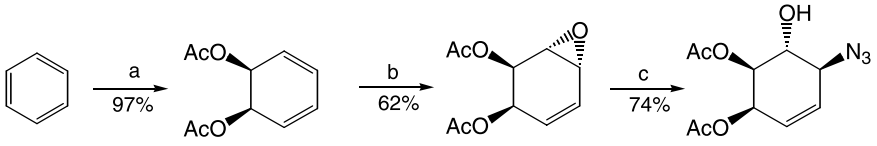
The racemic precursor of conduramine F-4 (**259**) was described by Lehmann and Moritz.[74] Diacetate **12** derived from benzene underwent selective *anti*-epoxidation, giving (±)-**258**. Subsequent ring opening of the oxirane with NaN_3 in AcOH gave the azide (±)-**252** (74%) (Scheme 41).

3. Diaminoconduritols

Diaminoconduritols are important intermediates in the synthesis of diaminoinositols and antibiotics.[75] They have also been used as ligands in antitumor platinum complexes.[76]

Glycosylation of conduramines generates unusual pseudodisaccharides and disaccharides of biological interest. Diazide (+)-**265** was obtained by the β-D-galactosylation of (±)-**263** and *o*-niphegal **264** (Scheme 42). It is a competitive inhibitor of β-D-galactosidase from *Escherichia coli*.[77] In the first two steps, the benzophenone **193** was converted into the diol (±)-**261**. Treatment of (±)-**261** with KOH, followed by ring opening of the dioxirane (±)-**262**[78] and subsequent glycosidation, gave (+)-**265**. Diazide (±)-**263** can be easily converted into the respective diaminoconduritol via Paulsen's method.[62]

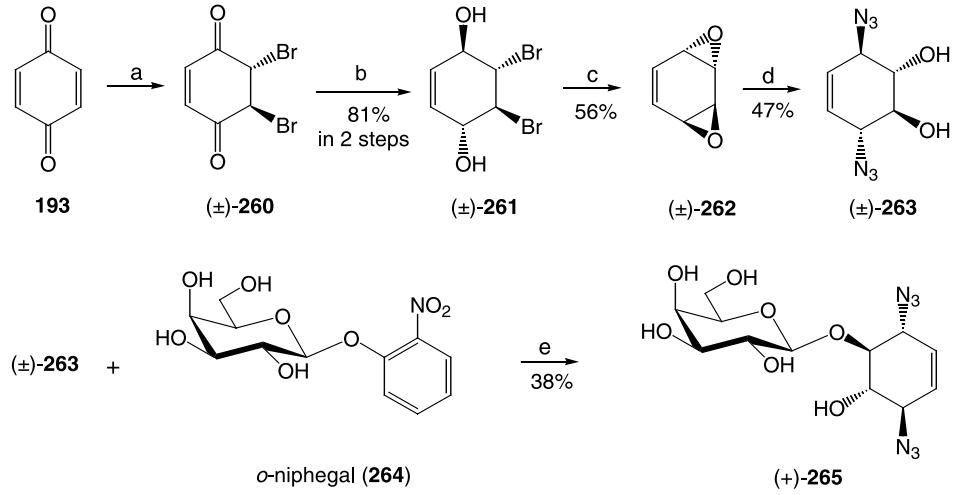
In 1979, Vogel and co-workers[79] described the synthesis of *meso*-diaminoconduritol **268**. Reaction of *syn*-benzene dioxide **266** with NaN_3 ($MeOH$, $MgCl_2$) led to regioselective (allylic activation) ring opening of the two oxirane rings to form the diazide **267**. Reduction was effected by



12 (±)-**258** (±)-**259**

Reagents and conditions: a) (i) chemical oxidation; (ii) Ac_2O/Py (1:2), rt; b) *m*-CPBA, CH_2Cl_2, Na_2CO_3, rt, 1 d; c) 70% AcOH, NaN_3, 60 °C.

Scheme 41.

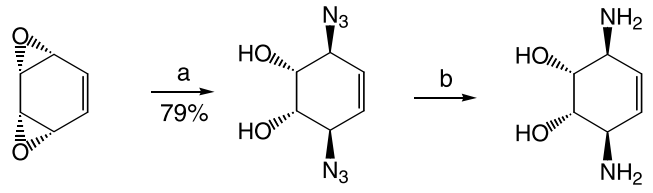


193 (±)-**260** (±)-**261** (±)-**262** (±)-**263**

o-niphegal (**264**) (+)-**265**

Reagents and conditions: a) Br_2, CCl_4, 0 °C; b) $NaBH_4$, H_2O, Et_2O, rt; c) KOH, $MgSO_4$, Et_2O, 0 °C; d) NaN_3, $ZnSO_4{\cdot}H_2O$, MeOH, Δ, 90 min; e) Na-K-phosphate buffer, β-D-galactosidase from *E. coli*, 6 h, rt, then 95 °C, 5 min.

Scheme 42.

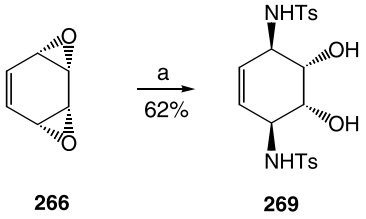


Reagents and conditions: a) NaN_3, $MgCl_2$, MeOH; b) PPh_3, MeOH/NH_3, Py.

Scheme 43.

PPh_3/MeOH/NH_3 and gave meso-diaminoconduritol **268** (Scheme 43).

Prinzbach and co-workers[80] have used a similar procedure to that outlined in Scheme 43 for the synthesis of meso-diaminoconduritol derivative **269** (Scheme 44). Nucleophilic opening of the two epoxides in **266** gave the diol **269** in 62% yield.



Reagents and conditions: a) chloramine T, $ZnSO_4$, MeOH, rt, 18 h.

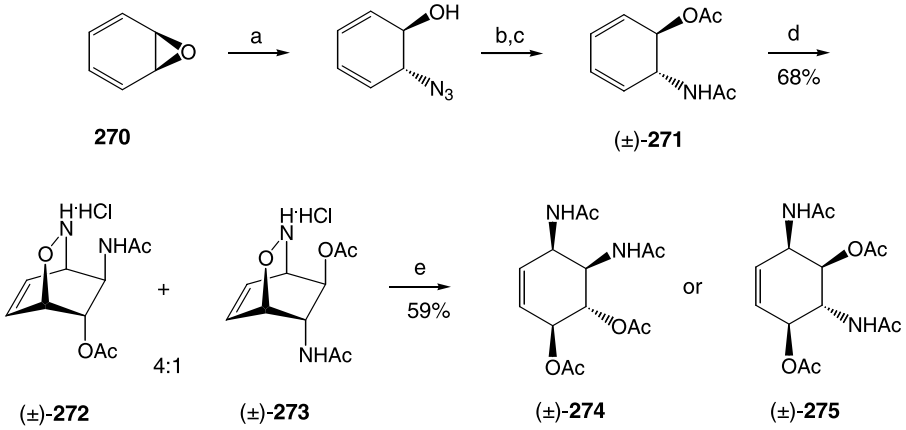
Scheme 44.

Kresze and co-workers[81] have applied the hetero-Diels–Alder reaction of racemic cyclohexadiene derivative (±)-**271**, derived from benzene epoxide **270**. The cycloaddition of (±)-**271** with 1-chloro-1-nitrosocyclohexane **232** gave a 4:1 mixture of adducts (±)-**272** and (±)-**273**. The major isomer (±)-**272** was treated with Zn in aqueous HCl to reduce the N–O bond. After work-up with acetic anhydride, the peracetylated diaminoconduramine derivative (±)-**274** was obtained (Scheme 45). The minor isomer (±)-**273** can also be converted into derivative (±)-**275** using the same method.

A very simple approach to 1,4-diaminoconduritols has been proposed by Kozlov et al.[82] As shown in Scheme 46, treatment of *anti*-benzene dioxide (±)-**262** with 2 equiv of piperidine gave the *trans*-3,6-dipiperidin-1-yl-cyclohex-4-ene-1,2-diol (±)-**276** in 34% yield. Analogous reactions with an excess of primary or secondary amines ($EtNH_2$, $PhNH_2$, $BnNH_2$, cyclohexyloamine, pyrrolidine, morpholine, Me_2NH, Et_2NH) led to the *N*-substituted diaminoconduritol derivatives (±)-**276** in 51–94% yield.

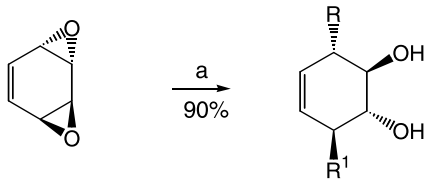
The synthesis of racemic fortamine, the aglycone of antibiotics such as fortimicins A and B, was described by Kuo et al.[83] Hetero-Diels–Alder addition of dimethyl azodicarboxylate to *trans*-1,3-cyclohexadiene-5,6-diol diacetate [(±)-**11**] gave (±)-**277** that can be converted into the 1,4-diaminoconduramine derivative (±)-**278** by reductive cleavage of the N–N bond (Scheme 47).

A few diaminoconduritol derivatives of the type **294** (see Scheme 49) were obtained as optically pure intermediates during the enantioselective synthesis of (−)-fortamine described by Ohno et al.[84] These authors used pig liver esterase (PLE) to convert racemic diester (±)-**279** into



Reagents and conditions: a) NaN_3, H_2O; b) $LiAlH_4$; c) Ac_2O/Py, DMAP, Et_2O, 0 °C (65%); d) **232**, EtOH:hexane (2:1), -22 °C; d) EtOH:hexane (2:1), -22 °C, 6 w; e) (i) Zn/HCl, H_2O, 0 °C, 7 h, (ii) Ac_2O/Py, rt, 20 h.

Scheme 45.



(±)-**262** (±)-**276**

R = R^1 = piperidino, EtNH, PhNH, BnNH, cyclohexylamino, pyrrolidino, morpholino, Me_2N, Et_2N

Reagents and conditions: a) piperidine or amines in excess.

Scheme 46.

optically active monoester **280** (>96% ee), which was then converted into all of the stereoisomers of the β-amino esters **281**–**284**, in a stereoselective manner (Scheme 48).

One of the nitrogen functions was introduced by Curtius rearrangement[84a] and the second by stereoselective ring opening of the epoxide by an azide [(−)-**289**→(−)-**290**]. The crucial step of this synthesis was the conversion of the acid (−)-**293** into the alkene (+)-**294** via a reaction first described by Barton and co-workers[85] (Scheme 49) and that implies radical intermediates. The key intermediate (−)-**289** was derived from **284**. After acidic hydrolysis of the *tert*-butyl ester with CF_3CO_2H, iodolactonization and treatment with DBU provided lactone (−)-**285**. *N*-metylation of (−)-**285** gave (−)-**286**, which was then methanolyzed into the methyl ester (+)-**287**. Esterification of alcohol (+)-**287** with methanesulfonyl chloride and Et_3N gave (−)-**288**, the epoxydation of which with MCPBA was highly face selective producing epoxide (−)-**289**. Treatment of epoxide (−)-**289** with Me_3SiN_3, followed acidic work-up and catalytic hydrogenation provided (−)-**291** that was silylated into the (+)-**292**. Saponification of (+)-**292** furnished carboxylic acid (−)-**293**.

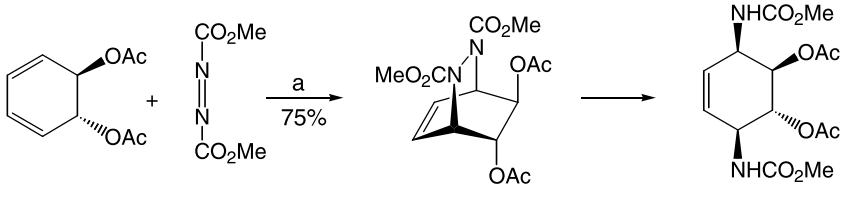
The first example of a 2,3-diaminoconduritol has been reported by Cerè and co-workers in 1998.[86] Starting with the thiepane derivative (−)-**295**, derived from D-mannitol,[87] they reacted this with NaN_3 and the azido derivative (−)-**296** obtained was oxidized to the corresponding sulfone (−)-**297**. Olefination applying the Ramberg-Bäcklung conditions gave the diazido compound (−)-**298**. Reduction of the azido functions led to the *O*-protected diaminoconduritol derivative (−)-**299** (Scheme 50).

More recently, the same authors[88] have published the synthesis of enantiomerically pure deprotected diaminoconduritol **300** (Scheme 51) using a similar methodology.

4. Biological importance of aminoconduritols and aminocyclitols

It has been shown that a conduramine F-4 derivative plays an important role in the synthesis of 1,5-lactams, which act as therapeutic agents for viral infections, particularly HIV infections.[8]

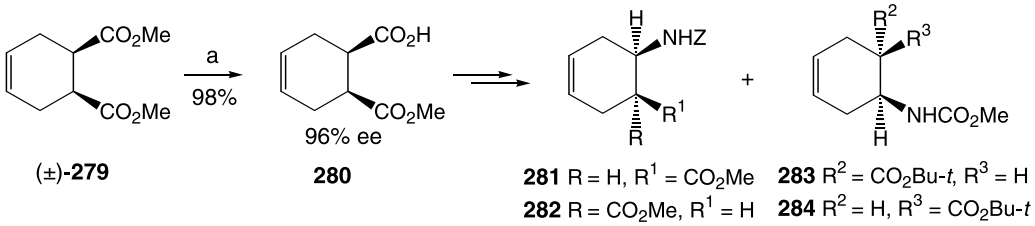
Aminocyclitols and diaminocyclitols, derived from conduramines and their analogues, comprise parts of aminoglycoside antibiotics, which are among the oldest and best known antibiotics.[2,89] It has been shown that antibiotics[90] such as kanamycin B, tobramycin B and their analogues[91]



(±)-**11** (±)-**277** (±)-**278**

Reagents and conditions: a) cyclohexane, hν, 46-50 °C, 24 h.

Scheme 47.

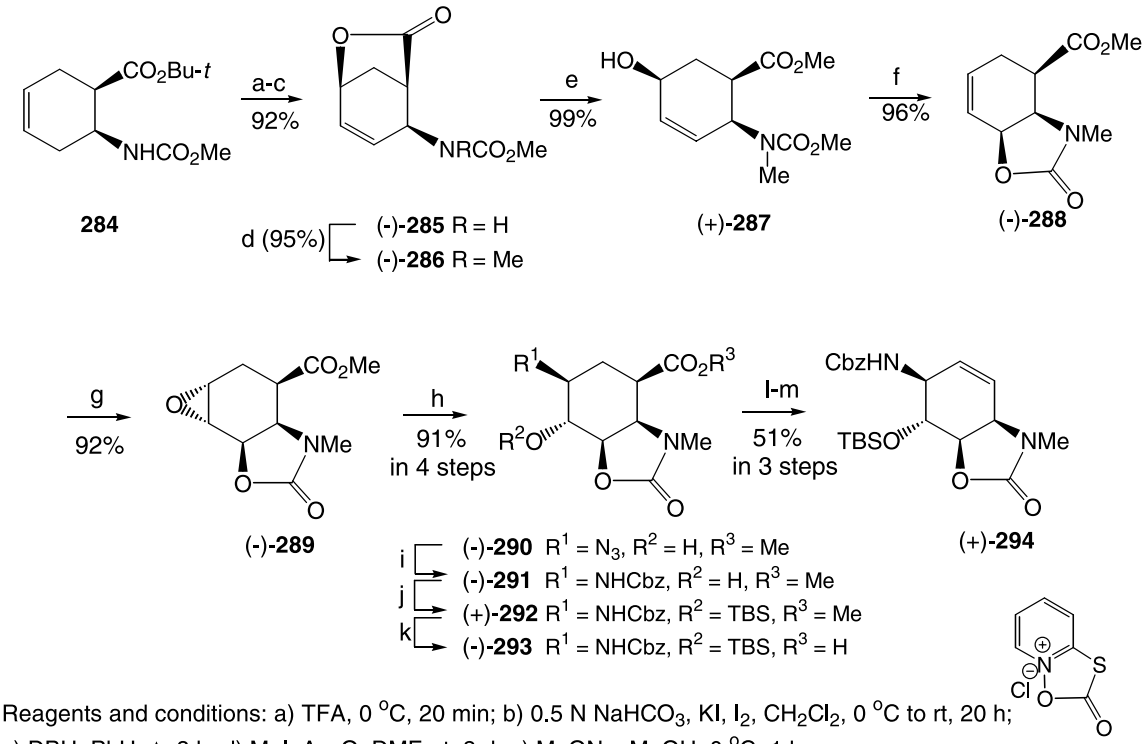


(±)-**279** **280**

281 R = H, R^1 = CO_2Me **283** R^2 = CO_2Bu-*t*, R^3 = H
282 R = CO_2Me, R^1 = H **284** R^2 = H, R^3 = CO_2Bu-*t*

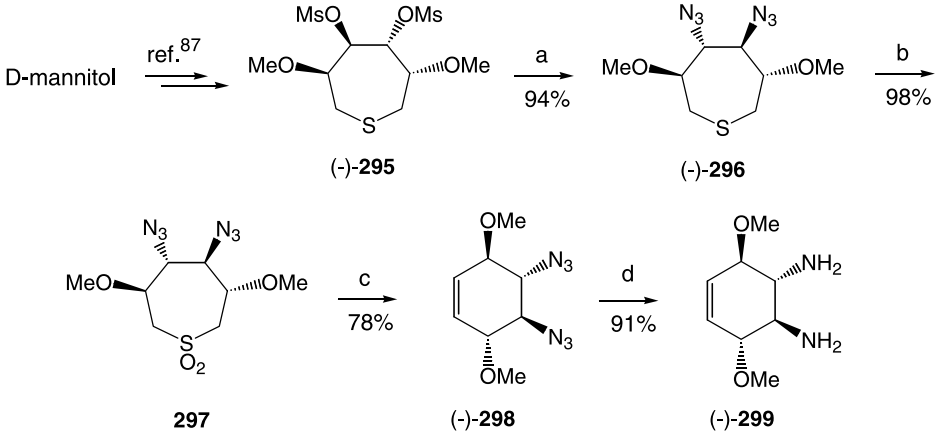
Reagents and conditions: a) pig liver esterase (PLE).

Scheme 48.



Reagents and conditions: a) TFA, 0 °C, 20 min; b) 0.5 N $NaHCO_3$, KI, I_2, CH_2Cl_2, 0 °C to rt, 20 h; c) DBU, PhH, Δ, 3 h; d) MeI, Ag_2O, DMF, rt, 2 d; e) MeONa, MeOH, 0 °C, 1 h; f) (i) MsCl, Et_3N, CH_2Cl_2, 2 h, 0 °C; (ii) Δ, 1 h; g) *m*-CPBA, CH_2Cl_2, 0 °C to rt, 2 d; h) (i) $TMSN_3$, $ZnCl_2$, $ClCH_2CH_2Cl$, Δ, 1.5 h; (ii) HCl/MeOH, rt; i) (i) H_2, Pd/C, MeOH, rt; (ii) benzyl chloroformate, dioxane, 0.5 N $NaHCO_3$, 0 °C to rt, 1 h; j) TBSCl, Imd, DMF, rt, 12 h; k) 1 N NaOH, MeOH, rt, 12 h; l) (i) Barton's reagent, DMAP, PhH, phosgene dimer, 0 °C to rt, 12 h (ii) $CBrCl_3$, Δ, 10 h; (ii) DBU, PhMe, Δ, 12 h.

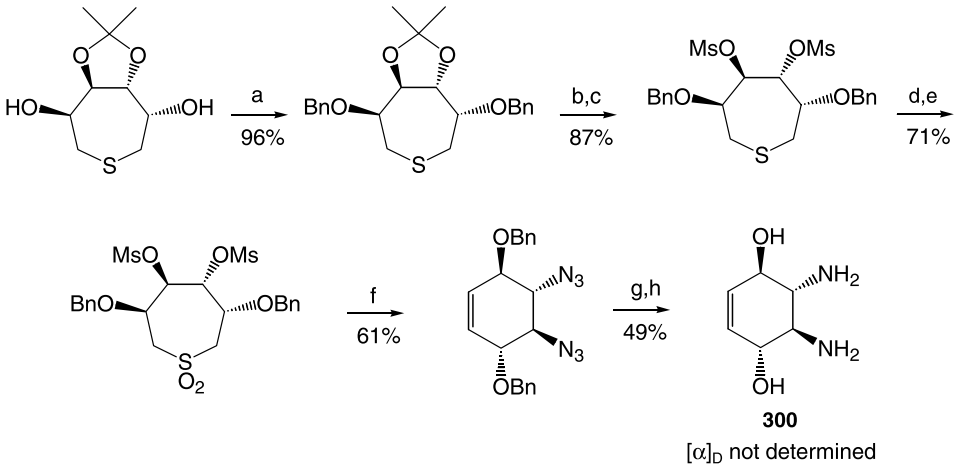
Scheme 49.



Reagents and conditions: a) NaN_3, DMSO, 120 °C, 20 h; b) *m*-CPBA, CH_2Cl_2, 3 h, rt; c) CCl_4, BuOH, H_2O, KOH, 3 h, rt; d) $LiAlH_4$, THF, 5 h, Δ.

Scheme 50.

interact with a number of RNA sequences including two important HIV regulatory domains, RRE[92] and TAR.[93] The binding between RNA and aminoglycosides reveals the interplay between the hydroxyl and their neighboring ammonium groups.[94] These discoveries demonstrate that compounds that possess arrays of hydroxyl and amino groups are potentially interesting systems, as they can target pivotal RNA sites, and are thus candidates for drug



Reagents and conditions: a) NaH, BnBr, KI, THF, rt, 19 h; b) TFA, H_2O (1:10), MeCN, 24 h, 95 °C; c) MsCl, Py, 5 h, 15 °C; d) NaN_3, DMSO, 2 h, 120 °C; e) *m*-CPBA, CH_2Cl_2, rt, 4 h; f) CCl_4, *t*-BuOH, H_2O, KOH, 7 h, rt; g) Et_3N, $HS(CH_2)_3SH$, MeOH, 48 h, rt; h) BCl_3, CH_2Cl_2, -78 °C, 2 h then 0 °C, 12 h.

Scheme 51.

discovery.[95] Aminocyclitols and their analogues can also be glycosidase inhibitors and thus be potential anticancer or antiviral agents.[96]

The fermentation-derived aminocyclitol, valienamine (**301**)[97] (Fig. 13), and several analogues[98] exhibit α-glucosidase inhibitory activity by virtue of a protonated amino group aptly positioned where a protonated interpyranosidic oxygen might bind in the enzyme active site.[99] Valienamine-based *pseudo*-oligosaccharides such as acarbose (**302**),[100] adiposin-1 (**303**),[101] and trestatin A[102] show enhanced α-glucosidase inhibition, presumably because two or more *pseudo*-sugar units bind more strongly than a single monosaccharide mimetic.[103] Even simple alkyl substitution (e.g., 2-phenethyl or β-hydroxyphenethyl) on the nitrogen of valienamine enhances inhibition of porcine maltase and sucrase.[104] In Table 1, we have summarized the inhibitory data reported for conduramine and diaminoconduritol derivatives **300** and **304–314**.

Recently, we reported that (−)-conduramine B-1 [(−)-**17**, Scheme 16] does not inhibit β-glucosidases and β-xylosidases, although this compound mimics β-glycopyranosides and β-xylopyranosides. We found, however, that *N*-benzyl derivatives of (−)-**17** are good competitive inhibitors of these enzymes. The most potent β-glucosidase inhibitor, **308** (−)-*N*-(*p*-phenylbenzyl)-conduramine B-1 [(−)-*N*-[(1,1′-biphenyl)-4-ylmethyl]-conduramine B-1], was also the most selective inhibitor in assays involving α-glucosidases from rice and yeast, amyloglucosidase from *Aspergillus niger* and *Rhizopus* mold, β-glucosidases from almonds and *Caldocellum saccharolyticum* and β-xylosidase form *Aspergillus niger*.[43a] Thus, *N*-benzyl

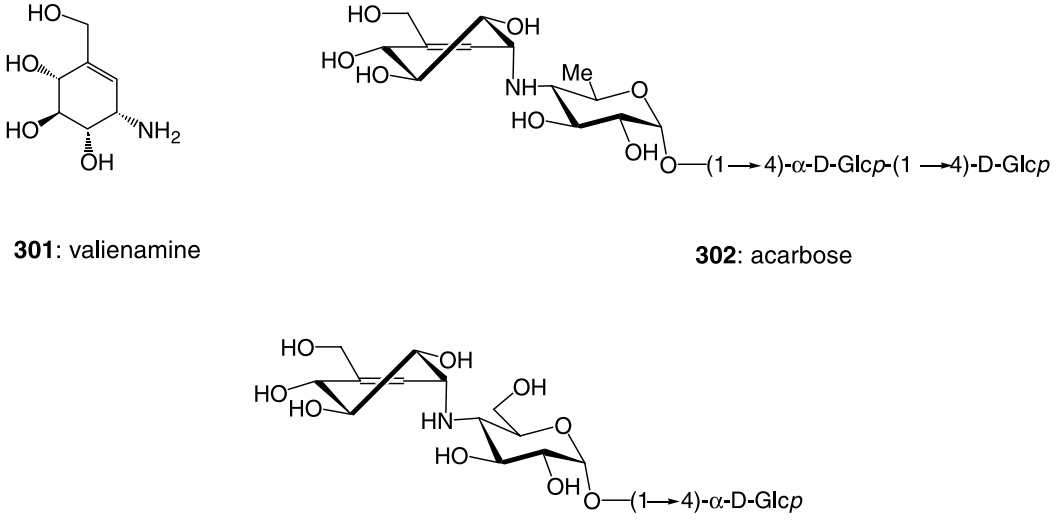
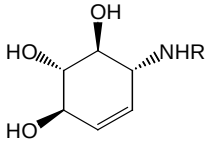
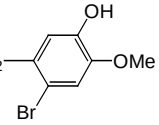
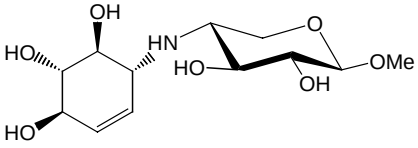
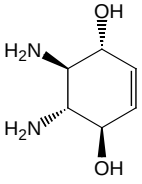
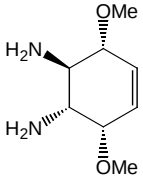
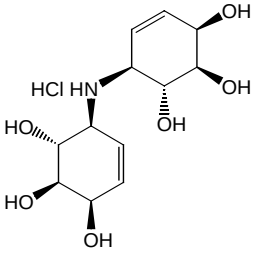
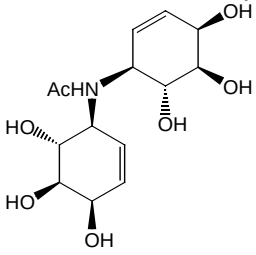


Figure 13.

Table 1. Glycosidase inhibitory activities for amino- and diaminoconduritols (IC_{50}, K_i in μM)

β-Glucosidase inhibitors	α-Mannosidase inhibitors
	
304 [43a], R = Bn, IC_{50} = 32; K_i = 10 (almonds)	**304** [43b], R = Bn, IC_{50} = 171 (jack beans), IC_{50} = 225 (almonds)
305 [43a], R = $CH_2C_6H_4OH$-*p*, IC_{50} = 72 (almonds)	**305** [43b], R = $CH_2C_6H_4OH$-*p*, IC_{50} = 100 (jack beans), IC_{50} = 183 (almonds)
306 [43a], R = $CH_2C_6H_4OMe$-*p*, IC_{50} = 52; K_i = 25 (almonds)	**306** [43b], R = $CH_2C_6H_4OMe$-*p*, IC_{50} = 91 (jack beans), IC_{50} = 86 (almonds)
307 [43a], R = $CH_2C_6H_4Cl$-*p*, IC_{50} = 35 (almonds), IC_{50} = 185 (*Caldocellum saccharolyticum*)	**307** [43b], R = $CH_2C_6H_4Cl$-*p*, IC_{50} = 91 (jack beans), IC_{50} = 77 (almonds)
308 [43a], R = $CH_2C_6H_4Ph_4$-*p*, IC_{50} = 32; K_i = 8 (almonds), IC_{50} = 35 (*Caldocellum saccharolyticum*)	**308** [43b], R = $CH_2C_6H_4Ph$-*p*, IC_{50} = 29; K_i = 4.8 (jack beans), IC_{50} = 32; K_i = 16 (almonds)
309 [43a], R = $CH_2C_6H_4OPh$-*p*, IC_{50} = 43; K_i = 13 (almonds), IC_{50} = 52 (*Caldocellum saccharolyticum*)	**309** [43b], R = $CH_2C_6H_4OPh$-*p*, IC_{50} = 40; K_i = 14 (jack beans), IC_{50} = 63 (almonds)
	310 [43b], R = A **310** [43b], R = 
	IC_{50} = 154 (jack beans)
β-Xylosidase inhibitors	
	
311 [39], K_i = 40 (*Thermoanaerobacterium saccharolyticum*)	
α-Glucoside inhibitors	
	
300 [88], K_i = 190 (baker's yeast)	**312** [88], K_i = 700 (baker's yeast)
	
313 [3], IC_{50} = 1400	**314** [3], IC_{50} = 1350
β-Galactosidase inhibitors	
313 [3], IC_{50} = 620	**314** [3], IC_{50} = 100

derivatives of (−)-conduramine B-1 should be tested for their ability to act as chemical chaperones and for their therapeutic potential against Gaucher's disease.[105] With a structure having one hydroxymethyl group less than that in β-valienamine derivatives,[106] which have been shown to act as chemical chaperones[107] to accelerate transport and maturation of F2/3I mutant β-glucosidase,[106] the *N*-benzyl derivatives of (−)-conduramine B-1 are expected to be more hydrophobic than the corresponding valienamine derivatives and thus to have a better chance to become orally active drugs in the treatment of Gaucher's disease.

Recently, Ogawa and co-workers[108] reported that β-valienamine, as (−)-conduramine B [(−)-**17**] does not inhibit β-glucosidase from almonds, but is a weak inhibitor (IC_{50} = 190 μM) of α-mannosidase from jack beans. Similarly, (−)-conduramine B-1 has been found to inhibit α-mannosidases from jack beans and from almonds, whereas it does not inhibit any of the other glycosidases (α-L-fucosidase, α-galactosidases, β-galactosidases, α-glucosidases, amyloglucosidases, β-glucosidases, β-mannosidase, β-xylosidase, α-*N*-acetylgalacto-saminidases, or β-*N*-acetyl glucosaminidases). As for the inhibition of β-glucosidases from almonds and from *Saccharomyces*

cerevisiae, **308** presented the highest inhibitory activity toward α-mannosidases. Expectedly, (+)-conduramine B-1 and its *N*-substituted derivatives did not inhibit these enzymes at 1 mM concentration.[43b]

5. Conclusions

In recent years, a number of highly efficient and enantioselective syntheses of conduramines (aminoconduritols) and diaminoconduritols have been developed. The methods rely on pure chemical processes or on combinations of the latter with enzymatic or microbiological pathways. Because of their alkene moieties, conduramines and diaminoconduritols can be seen as synthetic intermediates for the aminocyclitols and more complicated polyfunctional compounds of biological interest. The fact that these systems display arrays of amines and polyols will make them partners of sublibraries for the combinatorial preparation of biopolymer ligands by analogy with the known information for aminoglycoside antibiotics that recognize specific structural elements of RNA. Conduramines have interesting inhibitory activities toward various glycosidases. In the case of (−)-conduramine B-1, *N*-benzylation generates good inhibitors of β-D-glucosidases and of α-D-mannosidases with K_i values in the low micromolecular range.

Acknowledgements

Financial support from SRE (Bern, European TRIoH project) and from the Swiss NSF is gratefully acknowledged.

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