Total Synthesis of Natural *tert*-Alkylamino Hydroxy Carboxylic Acids

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Contents

1. Introduction

Amino hydroxy carboxylic acids are prevalently distributed in nature. They are non-proteinogenic amino acids where the requisite polar functionalities—amino, carboxylic, and hydroxyl groups—are arranged in the molecules with various combinations. In particular, the amino hydroxy acids containing the amino functionality at the quaternary carbon center have been considered as challenging synthetic targets due to their intriguingly complex structures as well as their potent biological activities. In the context of total synthesis of natural products, the enantioselective construction of a quaternary carbon center has been recognized as one of the abstruse issues in the synthetic community during the past decades, and numerous attempts to synthesize quaternary carbon-containing molecules have been reported.[1] Nevertheless, the stereoselective construction of a quaternary carbon center with a nitrogen heteroatom is still a demanding challenge for the streamlined synthesis of natural products. With this point of view, it is valuable to discuss synthetic approaches to the specific class of amino hydroxy carboxylic acids. Herein we describe recent efforts for the total synthesis of the natural products, manzacidins, sphingofungins, lactacystin, kaitocephalin, altemicidin, neooxazolomycin, and tetrodotoxin (Figure 1). The discussions are limited mainly to the their synthesis and focus on the strategies for construction of the functionalities.

Most target molecules presented in this paper are metabolites of microorganisms, except manzacidins and tetrodotoxin. The various biological activities of the molecules have attracted growing attention from pharmaceutical and synthetic chemists. Manzacidins belong to the class of bromopyrrole alkaloids, which are the most common metabolites of sponge origin.[2] However, the structures are unique in the animal kingdom because they contain the unprecedented tetrahydropyrimidine moiety, which was found previously in bacterial siderophores.[3] Manzacidins A and C were isolated from the Okinawan sponge *Hymeniacidon* sp.,[4] and manzacidin D was from the coralline demosponge *Astrosclera willeyana*.[5] According to the preliminary biological tests, the bromopyrrole alkaloids were known to have useful activities as α-adenoreceptor blockers, serotonin antagonists, and actomyosin ATPase activators.[4]

Sphingosines are constituents of sphingolipids, membrane components involved in signal transduction. Sphingofungins, sphingosine analogues of fungal origin, are known to have potent antifungal activity and inhibitory activity against serine palmitoyltransferase (SPT), which is an essential enzyme for sphingosine biosynthesis.[6] Sphingofungins E and F[7] have received particular attention due to their structural similarity to myriocin,[8] a compound having a very potent immunosuppressive activity. They were separated from fermentation broths of *Paecilomyces variotii* (ATCC 74079) by the Merck group in 1992.[7]

Lactacystin, a highly functionalized γ-lactam thioester, is a metabolite found in *Streptomyces* sp. OM-6519 by Omura et al. in 1991.[9] It has attracted considerable interest due to its significant inhibition of 20S proteosome, which is essential for the turnover of cellular proteins including regulatory proteins to control cell growth and metabolism.[10] The 20S proteosome also plays a vital role for removing damaged, misfolded, and mistranslated proteins. Because of this inhibitory activity against 20S proteosome, lactacystin possesses pharmaceutical potential for the treatment of arthritis, asthma, and stroke.[11]

Kaitocephalin was purified from *Eupenicillium shearii* PF1191 in 1997 by Shin-ya and Seto et al.[12] It has a highly functionalized pyrrolidine core structure, and an amino group is protected with the dichlorohydroxybenzoyl group. It exhibits a potent glutamate receptor antagonist activity which can be used for the treatment of disorders of the central nervous system (CNS) such as epilepsy, cerebrovas-

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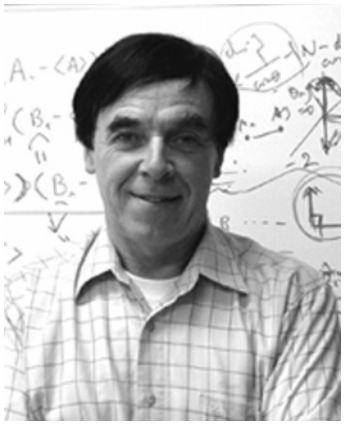
Sung Ho Kang was born in 1949 in Sancheong, Korea. He studied chemistry at Seoul National University, where he earned his B.S. (1972) and M.S. (1977) degrees. He moved to the University of Texas at Austin in 1977 and worked on the total synthesis of terpenoids such as zizanol and quadrone containing the bicyclo[3.2.1^{1,5}]octane skeleton to receive his Ph.D. degree in 1982 under the supervision of Professor S. Monti. After his study in Texas he joined the group of Professor Y. Kishi at Harvard University as a postdoctoral fellow, studying the total synthesis of palytoxin. From 1984 to 1985 he was hired as a principal scientist at Lucky Research Institute in Korea. His major research projects were new process development of pyrethroid insecticides and development of new insecticides. In 1985 he took a faculty position in the Department of Chemistry at Korea Institute of Technology, which merged with the Korea Advanced Institute of Science and Technology (KAIST). The merged Institute was named as the latter one (KAIST). He has been a full professor since 1992. His research interests include total synthesis of natural products and development of asymmetric reactions. In most of his natural product syntheses he has employed electrophile-promoted cyclization as one of the key features. He has established stereoselective synthesis of *syn*- and *anti*-β-amino alcohols by utilizing electrophile-promoted cyclization of allylic and homoallylic trichloroacetimidates. The developed protocol has been applied to the total synthesis of various physiologically valuable natural products such as indolizidine and pyrrolizidine alkaloids, (+)-furanomycin, (+)-lactacystin, sphingosines, etc. Recently his group succeeded in developing asymmetric catalysts for enantioselective mercuriocyclization and iodocyclization.

Suk Youn Kang was born in 1975 in Seoul, Korea. He graduated from the Department of Chemistry at Yonsei University to receive his Bachelor's degree in 1998. Then he was admitted to the Department of Chemistry at the Graduate School of KAIST. He received his Master's degree in 2000 and his Ph.D. degree in 2004 under the supervision of Professor Sung Ho Kang. He studied the total synthesis of (+)-lasonolide A. He is now working as a postdoctoral fellow in the same group.

Hee-Seung Lee was born in Seoul in 1967. He received his B.S. (1990) and M.S. (1992) degrees in Organic Chemistry from KAIST. He continued his doctoral study at KAIST and completed his Ph.D. degree in Organic Synthesis in 1996 under the guidance of Professor Sung Ho Kang. He worked on the synthesis of key intermediates to 1β-methylcarbapenem antibiotics. After he spent 3 years at Samsung Fine Chemicals Co. Ltd. as a senior scientist, he joined the group of Professor Sam Gellman at the University of Wisconsin in Madison as a postdoctoral fellow. His research focused on the development of helical β-peptide foldamer, which comprise the synthesis of unnatural β-amino acids and β-peptides (β-amino acid oligomers) that show antibacterial and anticancer activities. In 2003 he returned to KAIST, where he is currently an assistant professor. His research interest lies in the synthesis of biologically active molecules including unnatural amino acids and development of foldamers that can mimic various structures and functions of natural oligomers.



Alan J. Buglass was born in 1946 in Whitehaven, England. He graduated with his B.Sc. degree from the Chemistry Department at the University of Nottingham in 1968 and then his Ph.D. degree from the Chemistry Department at the University of Essex in 1972. His Ph.D. work was on the mechanisms of hydrolysis of some weakly basic organic substrates in strongly acidic media and under the guidance of Dr. J. G. Tillett. After a number of junior teaching and postdoctoral appointments, including one at Imperial College with Dr. B. C. Challis, he took a teaching post at the present Anglia Polytechnic University (APU) from 1974 to 2002, where he was subsequently promoted to a senior post. At APU he was course leader for some chemistry courses, such as part-time Graduateship of the Royal Society of Chemistry, designed primarily for personnel in local chemical industries. Since 2002 he has been a professor at Korea Advanced Institute of Science and Technology (KAIST). His present research interests are in mechanistic organosulfur chemistry and analytical organic chemistry, particularly the analysis of wine (and similar) components, both volatile and nonvolatile. Interest in the former came from previous mechanistic work, mainly on nitrogenous organic compounds, and interest in the latter grew from work on volatile animal semiochemicals. He is a Fellow of the Royal Society of Chemistry (since 1995).

cular ischemia, stroke, pain, and neurodegenerative diseases.[13]

Altemicidin was isolated from the actinomycete strain *Streptomyces sioyaensis* SA-1758 by Takahashi and colleagues in 1989.[14] It has a 6-azaindene core with a terminal sulfonamide. It possesses strong inhibitory activity against tumor cell growth as well as a potent acaricidal activity.

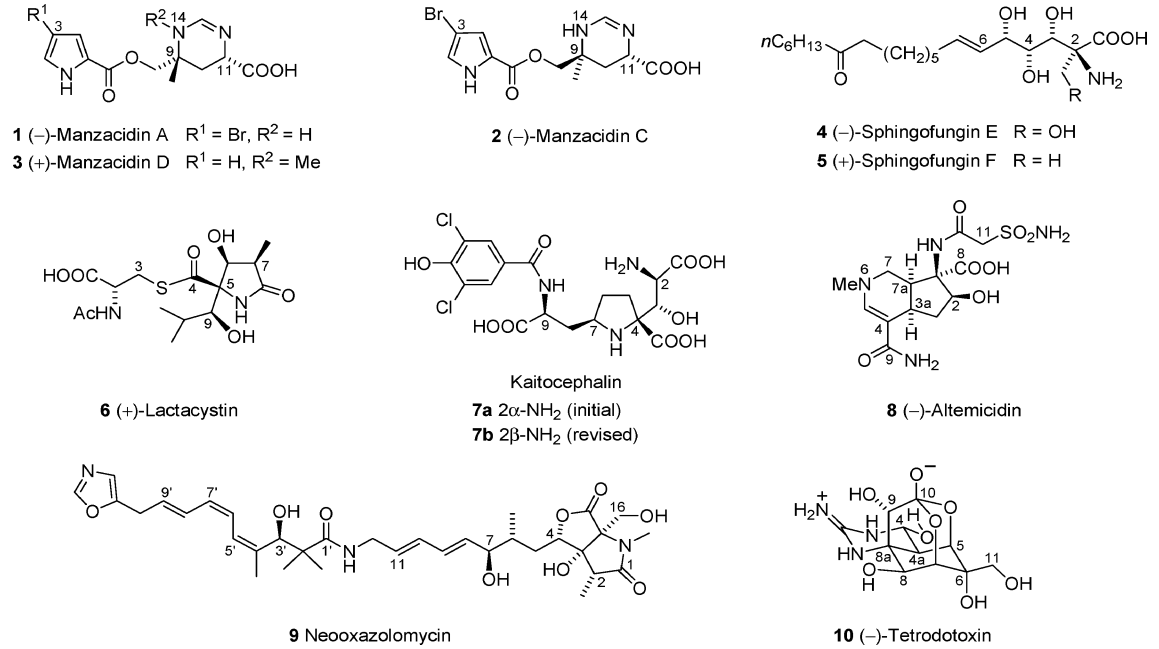
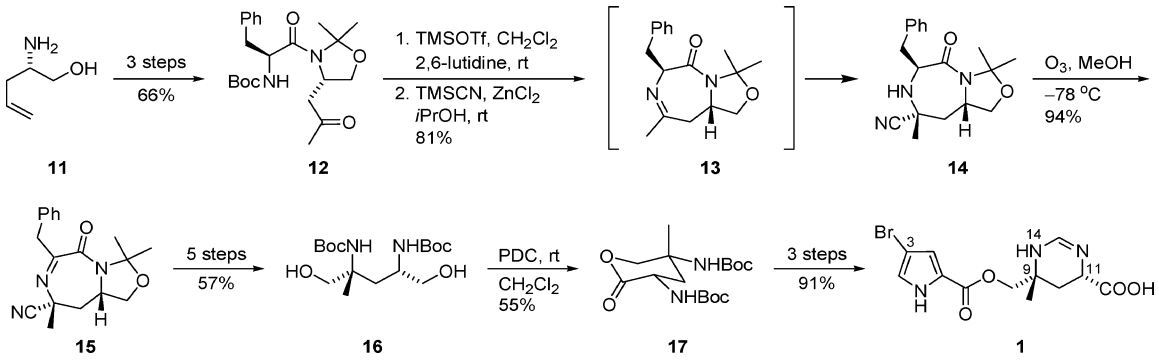


Figure 1.

Scheme 1



Natural antitumor antibiotic neooxazolomycin was obtained from *Streptomyces* strains by Uemura and co-workers in 1985.[15] It is the γ-lactone congener of oxazolomycin,[16] which was found to exhibit potent antibiotic activity against Gram-positive bacteria, in vivo antitumor activity, as well as antiviral activity against vaccinia, herpes simplex type I, and influenza A.[17] Neooxazolomycin is a highly functionalized molecule containing oxazole, polyene, and fused lactam–lactone groups. Interestingly, the highly functionalized γ-lactam core bears structural resemblance to lactacystin.

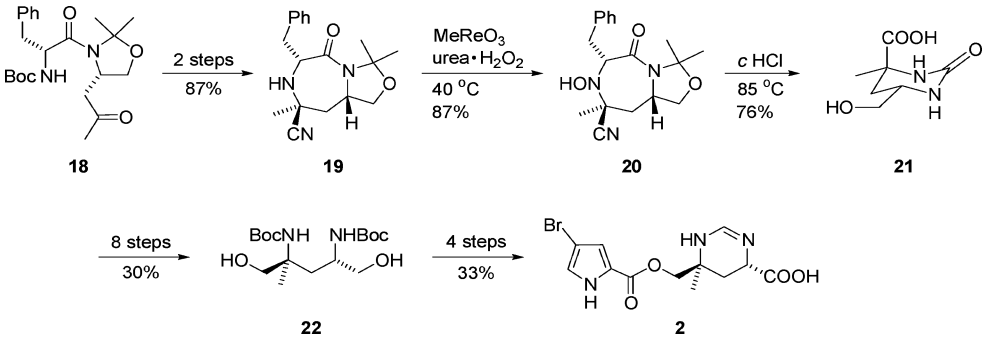
Tetrodotoxin, a toxic principle of puffer fish poisoning, is one of the most famous marine natural products. It was originally separated from puffer fish in 1909,[18] but recently its analogues have been purified from other animals.[19] Tetrodotoxin has been widely used as an important biochemical tool in physiological studies due to its specific activity as a voltage-gated sodium channel blocker.[20] The structure was elucidated in 1964 by the independent efforts of three groups.[21] Since the racemic total synthesis of tetrodotoxin was published by the Kishi group in 1972,[22] accomplishment of the asymmetric total synthesis of tetrodotoxin has been delayed for 30 years because of the difficulties in stereoselective construction of the two quaternary carbon centers containing different heteroatoms (one is nitrogen and the other is oxygen) in the molecule as well as its cage structure.[23] Furthermore, tetrodotoxin has unusual chemical properties, existing as an equilibrium mixture of ortho ester, anhydride, and lactone forms.

2. Synthesis of Manzacidins A, C, and D

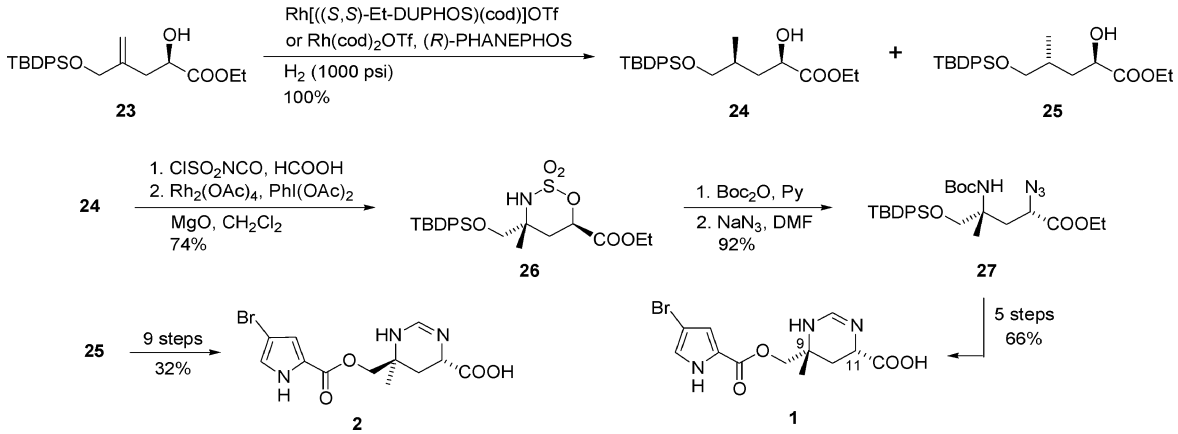
Manzacidins consist of pyrrolecarboxylic acid and tetrahydropyrimidine units in which the two amino groups of the latter are attached to secondary and tertiary stereogenic carbon centers. While manzacidins A and C are diastereomeric at the C9 position, manzacidins A and D have different substituents at the C3 and N14 positions.

Ohfune et al.[24] used asymmetric Strecker synthesis[25] for the C9 chiral center of manzacidin A **1**. The readily available allyl glycinol **11**[26] was converted to the amino ketone **12** through coupling with the protected phenylalanine and Wacker oxidation (Scheme 1). Deprotection of the Boc group of **12** induced the seven-membered imine **13** as the proposed Strecker substrate. Cyanide anion as a hydroxymethyl surrogate was added to **13** exclusively from its α-face to engender the amino cyanide **14** with the requisite C9 asymmetric center. The stereochemistry was presumably directed by steric repulsion from the benzyl

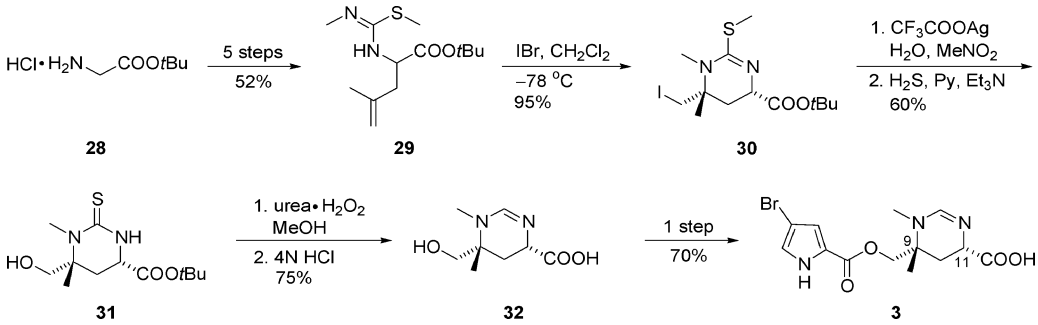
Scheme 2



Scheme 3



Scheme 4



group. To eliminate the pendent benzylacetyl substituent from the amino group of **14**, it was oxidized to the imine **15**[27] and hydrolyzed. Subsequent modification of the functional groups lead to the diol **16**. After chemoselective oxidation of its sterically less hindered hydroxyl group, the resulting lactone **17** was elaborated to manzacidin A **1**.

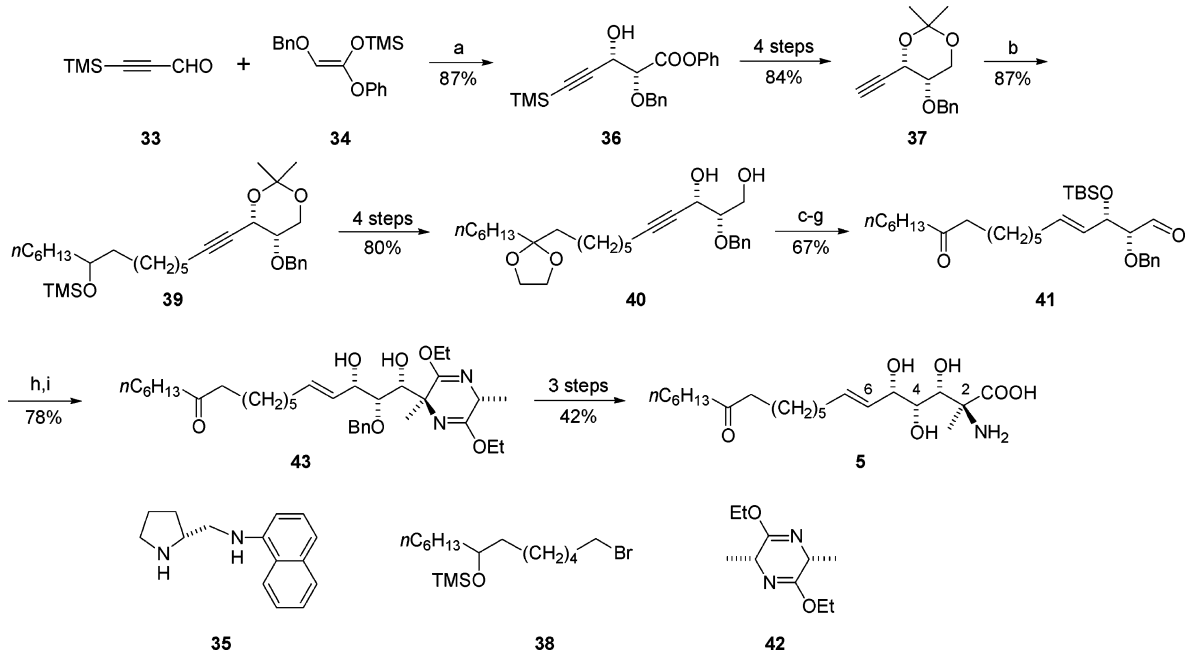
Synthesis of manzacidin C **2** was also completed from the amide ketone **18** diastereomeric to **11** by a similar process to the aforementioned.[24] Another Strecker reaction of **18** afforded the amino cyanide **19** as the sole stereoisomer (Scheme 2). Since it was difficult to generate the corresponding imine from **19**, it was oxidized to the hydroxylamine **20**[28] and hydrolyzed to the cyclic urea **21**. After conversion of **21** to the diol **22**, manzacidin C **2** was elicited from **22** by the same sequence as applied to **16**.

Du Bois and Wehn[29] conceived that Rh(I)-catalyzed C−H insertion of nitrene[30] would establish the C9 stereocenter of manzacidin A **1**. Their synthesis commenced with diastereoselective hydrogenation[31] of the homoallylic alcohol **23,** readily prepared from ethyl glyoxalate via Evans' asymmetric ene reaction,[32] to offer either of the methylated alcohols **24** or **25** as the major product depending on the chiral Rh(I) catalyst (Scheme 3). For manzacidin A synthesis **24** was sulfamoylated and cyclized oxidatively via nitrene to oxathiazinane **26** to forge the C9 chiral center stereospecifically. After completing the remaining C11 asymmetric center by a sequential protection and substitution of **26**, the acquired azido ester **27** was converted to manzacidin A **1**.

The same synthetic route as described for **24** was also suited for manzacidin C synthesis[29] starting from the diastereomeric methylated alcohol **25**.

MacKay's group[33] considered intramolecular iodoamination to arrange the relative C9 and C11 stereochemistry of racemic manzacidin D **3**. Glycine ester **28** was methylated and added to methyl isothiocyanate to provide the isothiourea **29** (Scheme 4). Iodocyclization of **29** secured the desired relative stereochemistry with >95:5 diastereoselectivity.[34]

Scheme 5[a]



[a] Reagents and conditions: (a) **35**, $Sn(OTf)_2$, SnO, EtCN, −78 °C; (b) *n*BuLi, HMPA, THF, **38**, −78 to 0 °C; (c) MMTrCl, DMAP, Et_3N, CH_2Cl_2, 0 °C; (d) $LiAlH_4$, THF, reflux; (e) TBSCl, imidazole, DMF; (f) HCOOH, Et_2O; (g) Swern oxidation; (h) **42**, *n*BuLi, $SnCl_2$, THF, −78 °C; (i) TBAF, THF.

The generated iodoisothiourea **30** was subjected to substitution of the iodo group, oxidative removal of the methylthio group via the thiourea **31**, hydrolysis of the ester group, and coupling of the resultant carboxylic acid alcohol **32** with trichloroacetylpyrrole to procure (±)-manzacidin D **3**.

3. Synthesis of Sphingofungins E and F

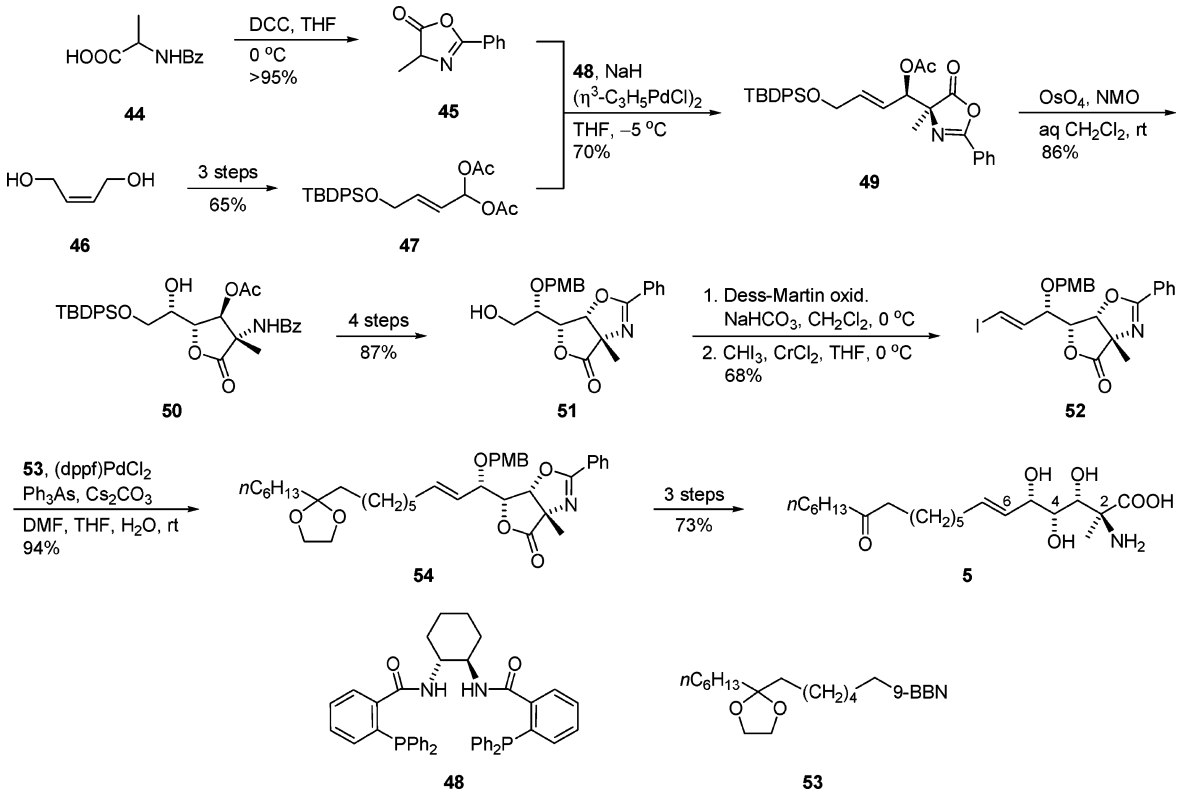
The only structural difference between sphingofungins E and F is due to different C2 substituents, a hydroxymethyl group in the former and a methyl group in the latter. The sphingofungins are composed of a functional polar head and lipid tail and contain four contiguous chiral centers with an amino group attached to a tertiary carbon.

Kobayashi et al.[35] exercised Sn(II)-catalyzed aldol condensation using a chiral pyrrolidine[36] for the C4 and C5 asymmetric centers of sphingofungin F **5** and another aldol reaction with Sn(II) azaenolate of Schöllkopf's bislactim[37] for its C2 and C3 stereocenters. The propargyl aldehyde **33** was condensed with the enol ether **34** in the presence of the complex between Sn(II) and the chiral diamine **35** to afford a 97:3 mixture of the syn product **36** with 91% ee and its anti isomer (Scheme 5). **36** was functionalized to the acetonide **37,** and then the hydrophobic tail was coupled to give rise to the diol **39**. A series of reactions of **39** including reduction of the acetylene to the (*E*)-alkene afforded the aldehyde **41**, which was reacted with the Sn(II) azaenolate from the bislactim ether **42** to form the requisite C1−C3 functional groups. Removal of the silyl group produced the latent carboxylic acid **43** as the major product with 70:25:5:0 diastereoselectivity. Global deprotection of **43** furnished sphingfungin F **5**.

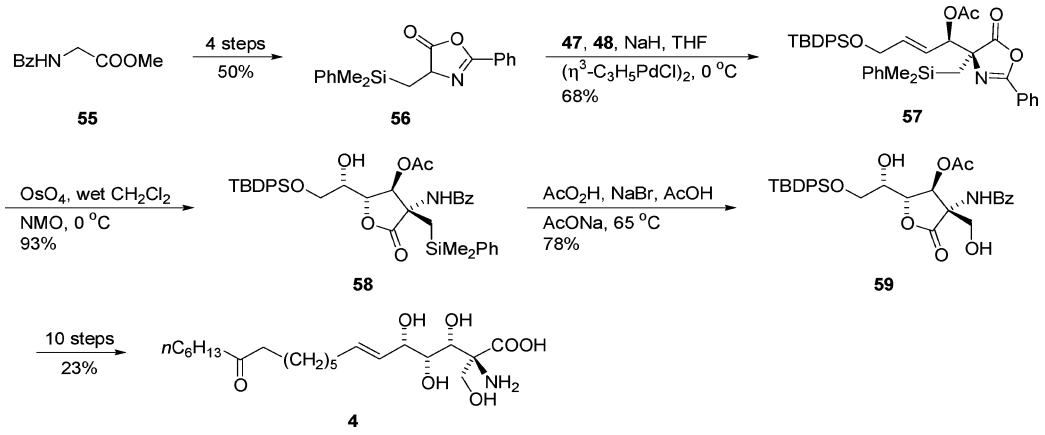
Trost and Lee[38] utilized asymmetric allylic alkylation[39] using a (*R*,*R*)-1,2-diaminocyclohexane-derived chiral ligand and the ensuing dihydroxylation[40] for the formation of the C1−C4 functionality of the two sphingofungins. The oxazole **45** was allylated with the allylic diacetate **47**[41] in the presence of a Pd(II) complex with the chiral ligand **48**[42] to deliver a 10.5:1 mixture of the alkylated product **49** with 89% ee and its diastereomer (Scheme 6).[38a] Dihydroxylation of **49** proceeded with 8:1 diastereoselectivity, and the desired diol was concomitantly rearranged to the lactone **50**. After formation of the bicyclic lactone **51** through intramolecular inversion of the C3 acetate group of **50**, it was subjected to Takai olefination[43] and subsequent Suzuki−Miyaura coupling[44] to provide the sphingofungin F skeleton, which was readily demasked to sphingofungin F **5**. A similar sequence was applied for the synthesis of sphingofungin E **4**. The initial asymmetric allylic alkylation was performed with the oxazolinone silane **56** instead of **45** to yield a 2.4:1 mixture of the allylated product **57** with 96% ee and its diastereomer (Scheme 7).[38b] **57** was dihydroxylated with 21:1 diastereoselectivity, and the silane group of the resulting lactone **58** was oxidized under modified Fleming conditions.[45] The generated alcohol **59** was protected and treated with essentially the same sequential reactions as in the aforementioned synthesis to procure sphingofungin E **4**.

Lin and colleagues[46] employed Hatakeyama rearrangement[47] of epoxy trichloroacetimidate to oxazoline for the C2 and C3 stereogenic centers of sphingofungin F **5**. The alcohol **60** was converted to the allylic alcohol **61,** which was then epoxidized to give a 3:1 mixture of the α-epoxy alcohol **62** and its stereoisomer (Scheme 8). Wittig olefination of **62** with the phosphonium salt **64** via the aldehyde **63** supplied the cis olefinic alcohol **65**. Conversion of **65** to the trichloroacetimidate followed by Lewis-acid-

Scheme 6



Scheme 7

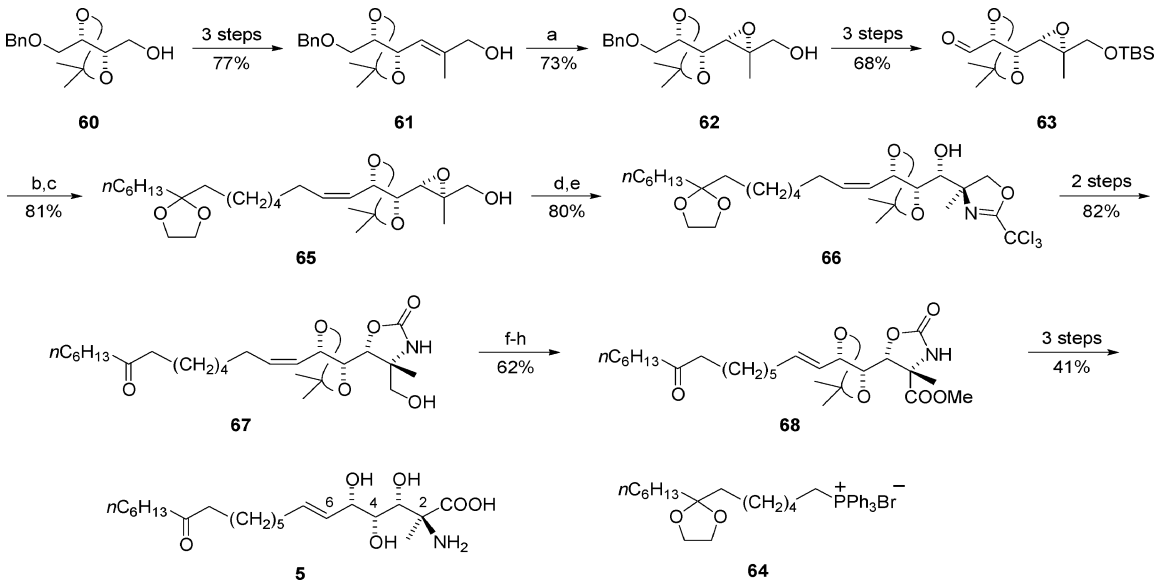


induced rearrangement afforded the oxazoline alcohol **66** with the crucial C2−C5 stereochemistry. The protecting groups of **66** were reorganized, and the acquired oxazolidinone alcohol **67** was subjected to oxidation, double-bond isomerization, and full deprotection to produce sphingfungin F **5**. For the synthesis of sphingofungin E **4**[48] the aldehyde **69** was reacted with acrylate to give rise to a 7:3 mixture of the Baylis−Hillman products in favor of the desired *β*-hydroxy ester **70** (Scheme 9). Dihydroxylation of **70** was completely stereoselective, and the resulting single stereoisomeric triol **71** was functionalized to the α-epoxy alcohol **72**. A similar reaction sequence used with **65** transformed **72** to sphingofungin E **4**.

Chida's group[49] established the C2−C5 stereochemistry of sphingofungin E **4** by Overman rearrangement[50] of the furanose scaffold. The synthetic route started with preparation of the allylic alcohol **76** from diacetone-D-glucose **75** comprising the C3−C5 chiral centers (Scheme 10). **76** was rearranged to the amide **77** with 62% de via the corresponding trichloroacetimidate to construct the C2 asymmetric center. Involvement of ozonolysis, acidic hydrolysis, Horner−Emmons olefination, and DIBAL reduction led **77** to the allylic bromide **79** via the conjugated ester **78**. The lipophilic moiety was attached to **79** using sulfone **80** to offer the diacetonide alcohol **81**, which was converted to sphingofungin E **4** through oxidation and deprotection.

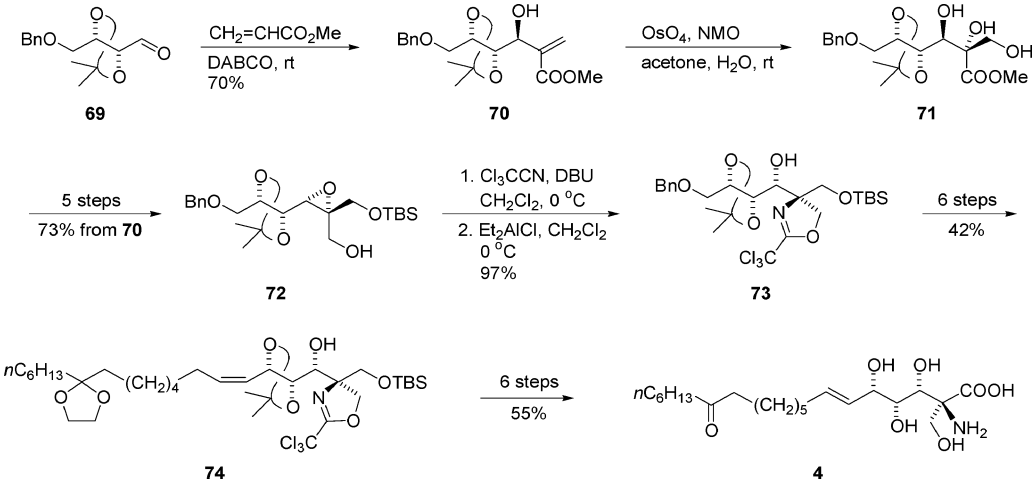
Shiozaki and Nakamura[51] made use of a regioselective opening reaction of the chloroepoxy group,[52] installed at the C2 position of a glucoside, for the C2 stereogenic center of sphingofungin E **4**. Oxidation of the known allyl glucoside **82**[53] was followed by addition of dichloromethyllithium exclusively to the *si* face of the ketone due to the bulky anomeric allyloxy group, and subsequent cyclization gave the chloroepoxide **83** (Scheme 11). The regioselective

Scheme 8[a]



[a] Reagents and conditions: (a) L-diisopropyl tartrate, Ti(O*i*Pr)$_4$, *t*BuOOH, 4 Å ms, CH_2Cl_2, −20 °C; (b) **64**, *n*BuLi, THF, −78 °C; (c) TBAF, THF, rt; (d) Cl_3CCN, DBU, CH_2Cl_2, 0 °C; (e) $BF_3{\cdot}Et_2O$, CH_2Cl_2, −23 °C; (f) PDC, DMF, rt; (g) CH_2N_2, Et_2O, 0 °C; (h) $(PhS)_2$, *hν*, cyclohexane, dioxane.

Scheme 9



epoxide opening of **83** with azide anion and the ensuing reduction engendered the pyranose **84** with the essential C2 chiral center. The functional groups of **84** were modified to the amide **86** via the pyranose **85**. Removal of the PMB group of **86** and subsequent cyclization delivered the lactone **87**. The lipid tail was connected to **87** through chemoselective desilylation, Takai iodoolefination,[43] and a Suzuki−Miyaura cross-coupling reaction.[44] The resultant ketal lactone **89** was deprotected and hydrolyzed to sphingofungin E **4**.

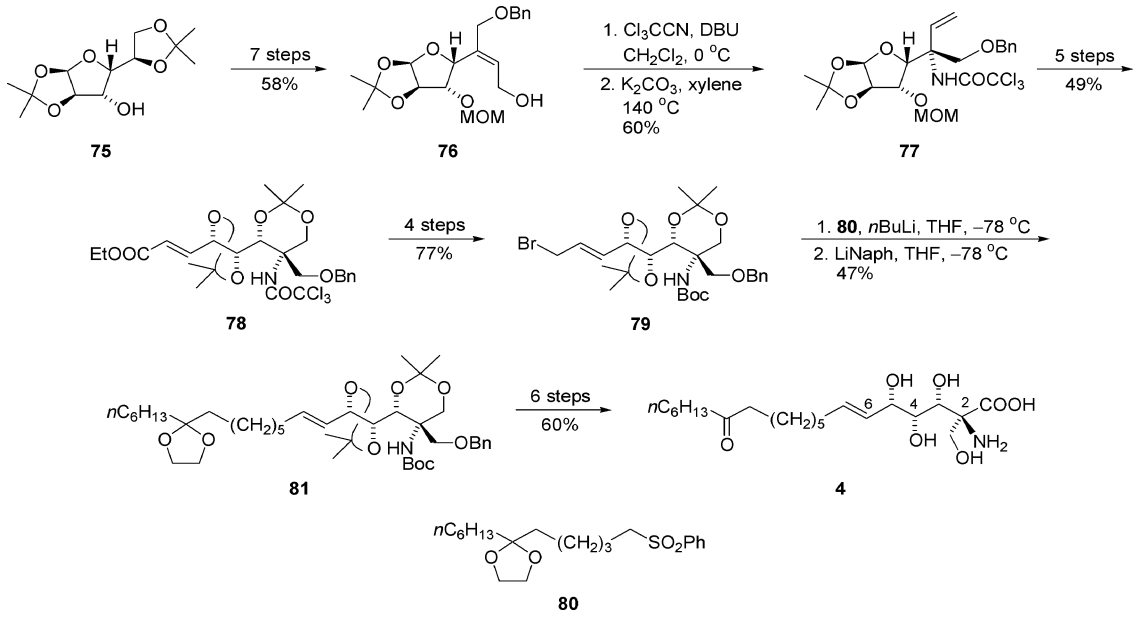
Ham and co-workers[54] relied on Pd(0)-catalyzed *trans*-oxazoline formation[55] and Mg(II)-promoted allylic stannane addition[56] for the C2−C5 stereocenters of sphingofungin F **5**. Treatment of the acetates **91** prepared from the protected serinol **90** provided the *trans*-oxazoline **92** as a single stereoisomer (Scheme 12). After oxidation of **92** to the ester **93** it was methylated to furnish a 20:1 mixture of the desired methyloxazoline **94** and its diastereomer.[57] After ozonolysis of **94** the generated aldehyde was coupled with the γ-silyloxy allylic stannane **95** in the presence of $MgBr_2$ to give the *cis*-dihydroxylated product **97** as the major product with >20:1 diastereoselectivity. The reaction can be rationalized by the most sterically and electronically favored transition state **96**. The remaining sequence was basically identical to the previously described Trost route[38] except that Negishi's protocol[58] was used instead of Suzuki−Miyaura's[44] in the coupling of the lipophilic tail.

4. Synthesis of Lactacystin

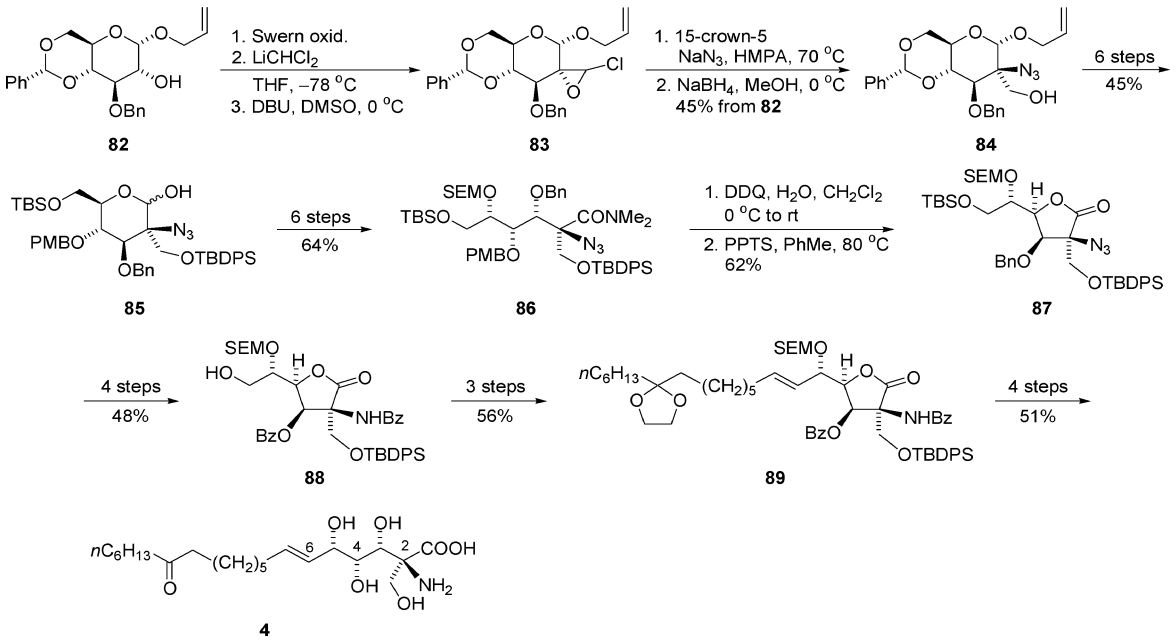
Lactacystin is a nonprotein γ-lactam thioester consisting of (*R*)-*N*-acetylcysteine and a pyroglutamic acid residue. The pyroglutamate residue is an α,α-disubstituted α-amino acid, and there are four contiguous asymmetric centers arrayed in its compact frame. Since two reviews[59] on (+)-lactacystin have appeared to date, this one will present a brief description of them and then focus on the synthetic efforts which have not been covered in these reviews.

While the C5 quaternary carbon was established mostly by aldol condensation[60−64] with an exceptional

Scheme 10



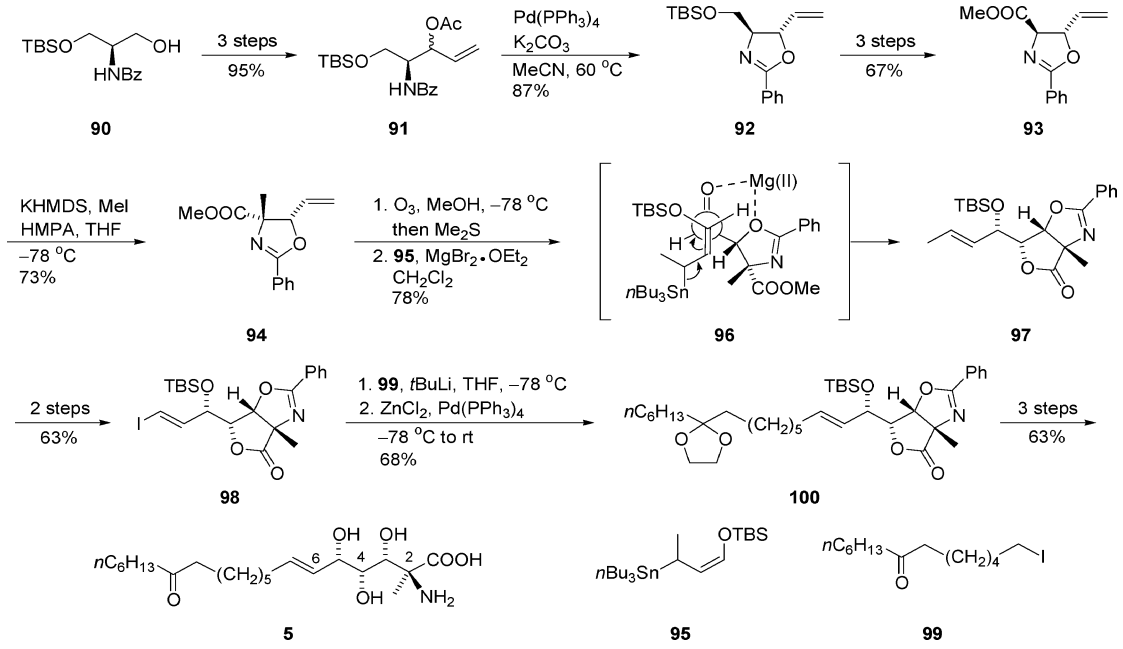
Scheme 11



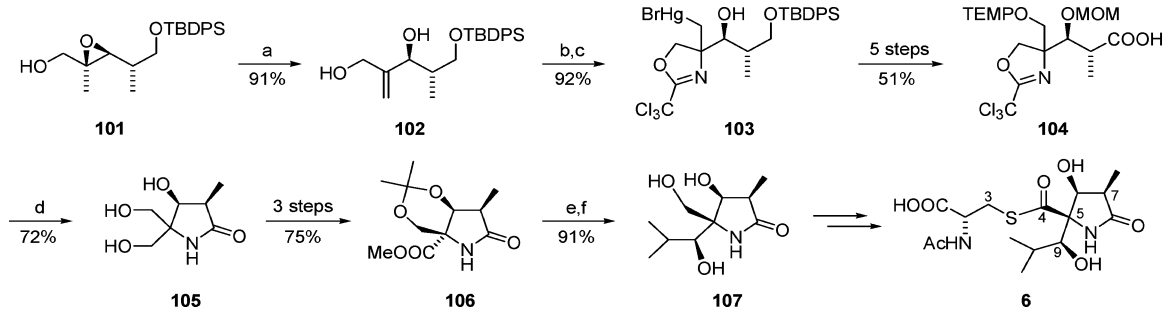
Overman rearrangement,[65] the C9 isopropyl carbinol functionality was set up by aldol condensation,[60a,62,63] Grignard addition,[60b,65] Sharpless asymmetric epoxidation,[61] dihydroxylation,[64] or aminohydroxylation.[63] Construction of the C6 and C7 asymmetric centers was implemented by aldol condensation,[60a,64] diastereoselective ketone reduction and the subsequent hydrogenolytic desulfurization,[60b] Brown's asymmetric crotylboration,[61,66] diastereoselective dihydroxylation followed by chemoselective deoxygenation,[62] crotylsilylation,[63] or chiral pools.[64,65]

Kang et al. developed two synthetic routes, characterized by mercuriocyclization of allylic trichoroacetimidate, to install the C5 stereogenic center. The first pathway[67] was initiated by ring opening of the known epoxide **101** containing the C6 and C7 chiral centers to the allylic alcohol **102** (Scheme 13). Conversion of the primary hydroxyl group of **102** to the trichloroacetimidate followed by mercuriocyclization[68] yielded a 1:1 diastereomeric mixture of the oxazolines **103**. Since oxidative demercuration and hydrolysis of the oxazoline ring of **103** were expected to generate the two identical hydroxymethyl groups, the diastereoselectivity was not significant. After conversion of **103** to the carboxylic acid **104**, its cyclization and the subsequent reductive cleavage of the N−O bond gave the triol **105**. The two hydroxymethyl groups of **105** were differentiated by acetonide formation, and the remaining hydroxymethyl group was oxidized to provide the ester **106**. Treatment of **106** with excess amounts of *i*PrMgBr consummated not only Grignard addition but also perfectly stereoselective reduction of the engendered carbonyl group to furnish the trihydroxy pyrrolidinone **107**, Baldwin's intermediate.[62]

Scheme 12

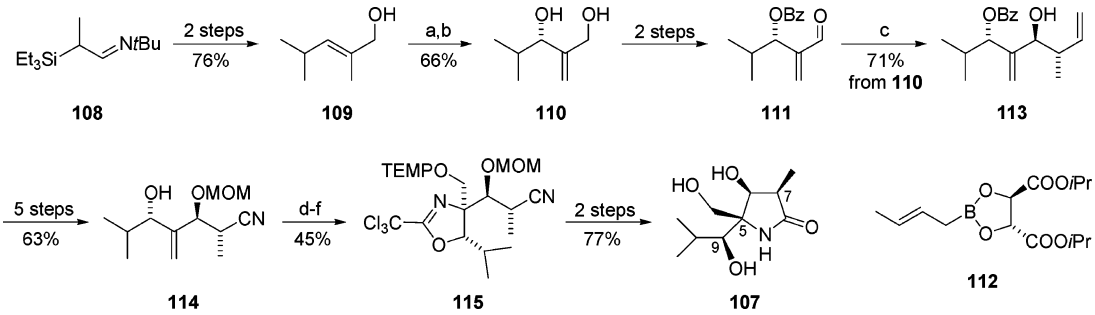


Scheme 13[a]



[a] Reagents and conditions: (a) LDA, THF, 0 °C to room temperature; (b) Cl_3CCN, DBU, EtCN, −78 °C; (c) $Hg(CF_3COO)_2$, K_2CO_3, THF, 0 °C, then aq KBr; (d) *c* HCl, EtOH, AcOH, reflux, then Zn, reflux; (e) *i*PrMgBr, THF, −20 to 0 °C; (f) TsOH, MeOH, 60 °C.

Scheme 14[a]

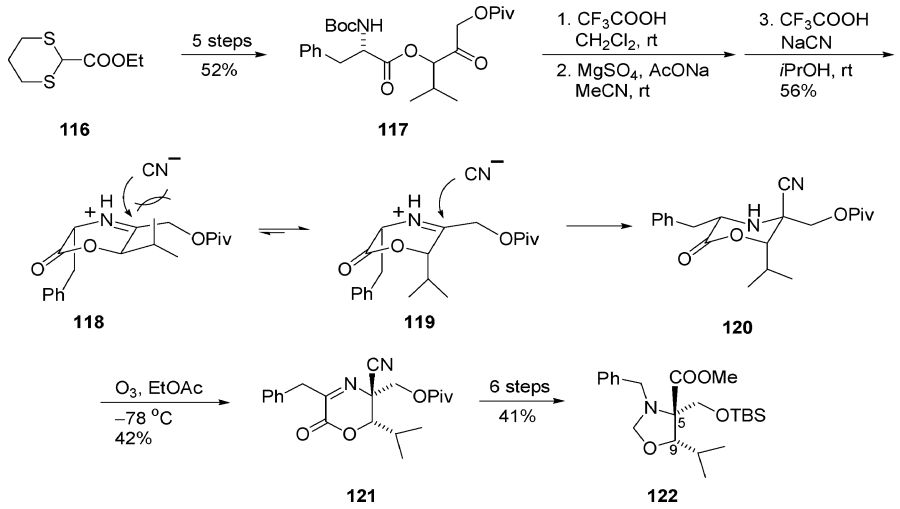


[a] Reagents and conditions: (a) L-diethyl tartrate, $Ti(OiPr)_4$, *t*BuOOH, CH_2Cl_2, −20 to −15 °C; (b) LDA, THF, 0 °C to room temperature; (c) **112**, 4 Å ms, PhMe, −78 °C; (d) Cl_3CCN, DBU, EtCN, −20 °C; (e) $Hg(CF_3COO)_2$, THF, PhH, rt, then aq KBr; (f) TEMPO, $LiBH_4$, THF, −20 °C.

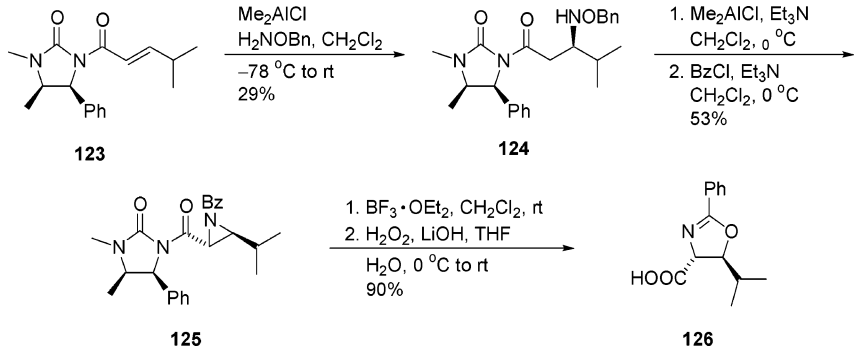
The second synthesis[69] was opened with Peterson olefination[70] of the silane **108** to produce the allylic alcohol **109** (Scheme 14). Sharpless epoxidation[71] of **109** followed by epoxide opening delivered the diol **110**. The C6 and C7 functional groups were introduced by Roush's asymmetric crotylation[72] of the aldehyde **111** obtained through chemoselective allylic oxidation of **110**. After transformation of the resultant alkene **113** to the cyanide **114**, its imidate was exposed to mercuriocyclization to secure the oxazoline **115** as a single diastereomer having the essential stereochemistry at the C5 and C9 positions. Hydrolytic cyclization of **115** led to the trihydroxy pyrrolidinone **107**.[62]

Ohfune and colleagues[73] utilized asymmetric Strecker synthesis[25] for the consecutive C5 and C9 stereocenters. Their route began with preparation of the ketone **117** from the dithiane **116** through aldol condensation and esterification (Scheme 15). Acidic deprotection and dehydration of **117** gave rise to ketimine, to which cyanide anion was added under acidic conditions. The acquired amino cyanide **120**

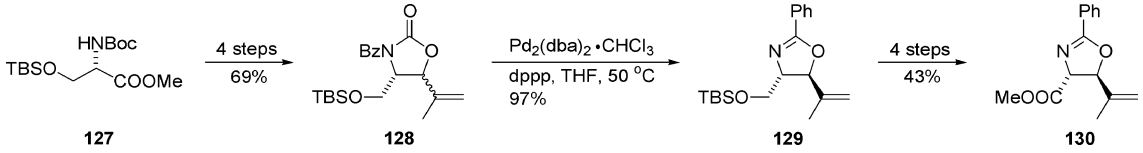
Scheme 15



Scheme 16



Scheme 17



turned out to be the only diastereomer, presumably through the kinetically favored transition state **119,** due to the sterically encumbered transition state **118**. After ozonolytic oxidation of **120** to the imine **121**,[27] it was transformed to the oxazolidine **122**, Corey's intermediate,[60a] through adjustment of the functional groups.

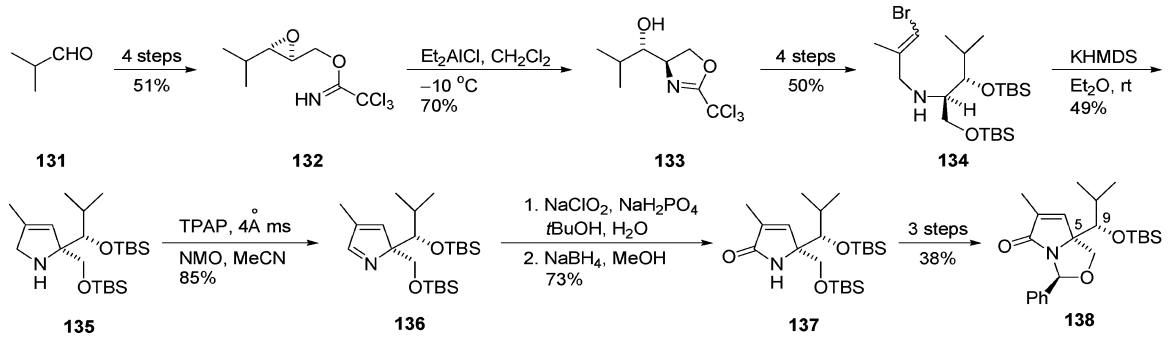
Cardillo's approach[74] relied on the Lewis-acid-induced ring expansion[75] of *N*-acyl aziridine to oxazoline. The conjugate addition of benzyloxyamine to the chiral imidazolidinone-attached amide **123** was performed to offer the desired amide **124** as the minor product with a 3:7 diastereomeric ratio (Scheme 16). After Lewis-acid-mediated intramolecular amination of **124**, the resulting aziridine **125** was rearranged, probably through a SNi mechanism, to afford the *trans*-oxazoline **126**, Omura and Smith's intermediate.[61]

Cook and Shanker[76] also synthesized the same *trans*-oxazoline intermediate from the protected L-serine **127**. It was readily functionalized to an isomeric mixture of the oxazolidinones **128** through Grignard reaction and cyclization (Scheme 17). Exposure of the allylic carbamate **128** to Pd(II) effected oxazoline formation and equilibration to procure the *trans*-oxazoline **129** as the only stereoisomer,[55] which was oxidized to the ester **130**.[61]

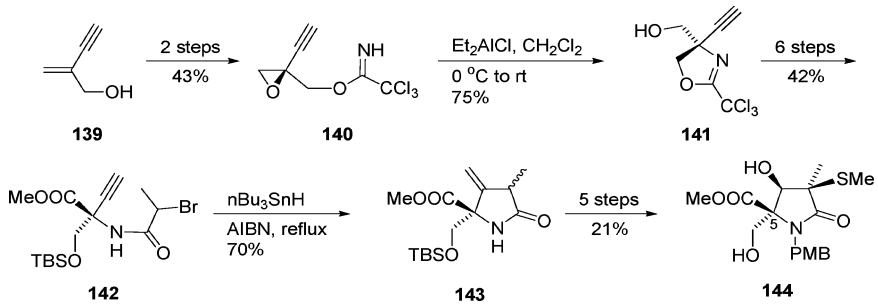
Hayes group[77] employed the Hatakeyama rearrangement[47] of epoxy trichloroacetimidate and C−H insertion of alkylidene carbene[78] to set up the C5 and C9 asymmetric centers. Sharpless epoxidation was involved to form the epoxy imidate **132** from isobutyaldehyde **131** (Scheme 18). Lewis-acid-mediated rearrangement of **132** yielded the oxazoline **133** comprising the indispensable isopropyl carbinol group. **133** was converted to the vinyl bromide **134** through hydrolysis and allylation. Generation of the alkylidene carbene from **134** resulted in 1,5-CH insertion to give the pyrroline **135** with the established C5 chiral center. **135** was oxidized to the pyrrolinone **137** via the cyclic imine **136**[79] and protected as benzylidene to provide the bicyclic lactam **138**, another Baldwin intermediate.[62]

Pattenden et al.[80] applied Hatakeyama oxazoline formation[47] to the C5 stereogenic center construction and radical cyclization to the pyrrolidinone ring formation. After preparation of the epoxy imidate **140** from the allylic alcohol **139** through Sharpless ep-

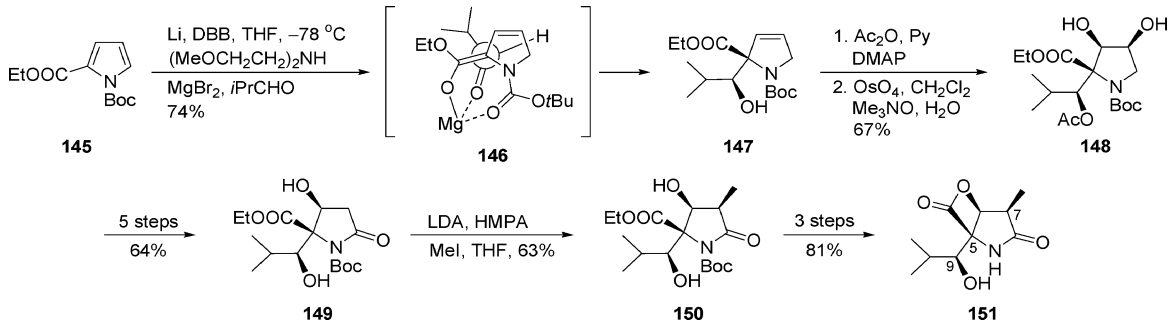
Scheme 18



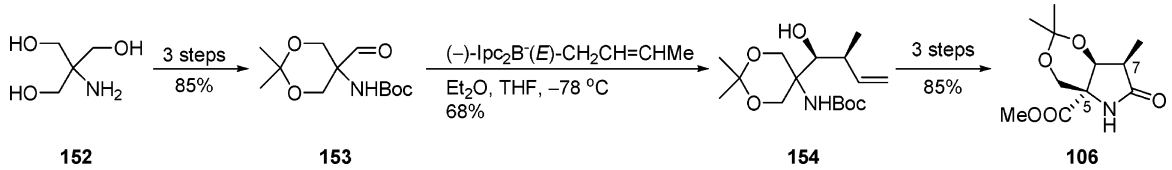
Scheme 19



Scheme 20



Scheme 21

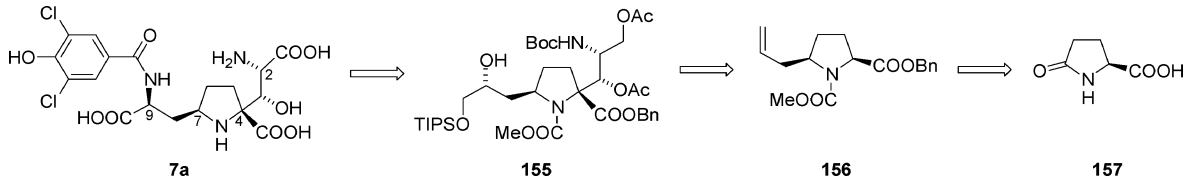


oxidation, it was rearranged to the oxazoline **141**, and the following adjustment of the protecting groups, acylation, and oxidation of **141** furnished the α-bromopropionamide **142** (Scheme 19). This was subjected to radical cyclization to offer the pyrrolidinone **143**, which was transformed to another Corey intermediate **144**[60b] in a straightforward manner.

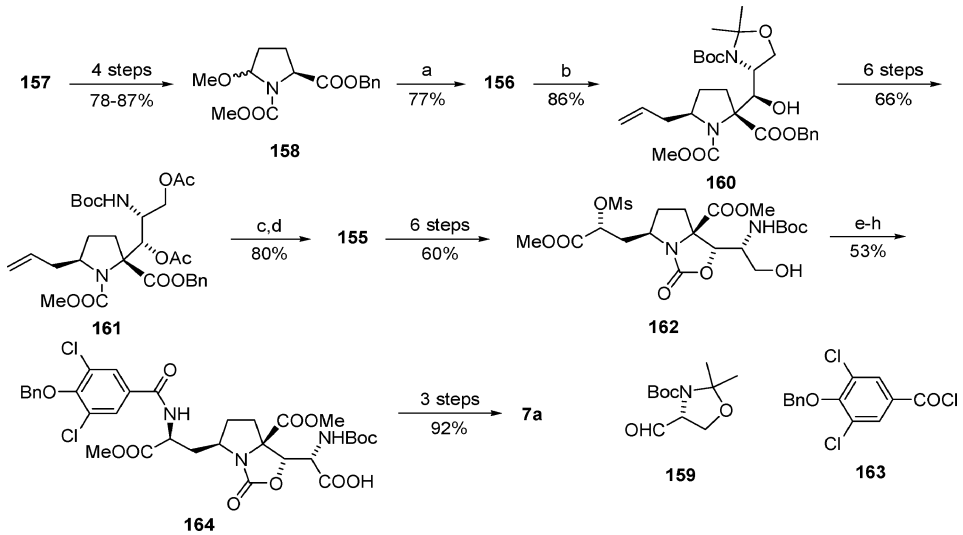
Donohoe and colleagues[81] engaged in synthesis of racemic lactacystin β-lactone, the true inhibitor, using reductive aldol condensation[82] for the C5 and C9 stereocenters. (*Z*)-Enolate generated from the pyrrole carboxylate **145** with lithium di-*tert*-butylbiphenylide was condensed with isobutyraldehyde in the presence of $MgBr_2$ to produce the anti aldol adduct **147** with an anti selectivity greater than 20:1, conceivably through the chelated transition state **146** (Scheme 20). **147** was functionalized to the pyrrolidinone **149** via diol **148** through stereoselective dihydroxylation, deoxygenation, and oxidation of the methylene group adjacent to the nitrogen. Methylation of **149** could be attained to afford a 9:1 mixture of the desired 7β-methyl product **150** and its 7α-methyl isomer. Deprotection of **150** and the subsequent lactonization supplied the lactacystin β-lactone **151**.

Hatakeyama and co-workers[83] made use of Brown's asymmetric crotylation[66] for the C6 and C7 stereocenters, the former of which ultimately controlled the stereochemistry of the C5 position. The aldehyde **153**, secured from the amino triol **152**, was crotylated enantioselectively to give the olefinic carbamate **154**, which was converted to the pyrrolidinone carboxylate **106**, Kang's intermediate,[67] through ozonolysis, lactam formation, and acetonide rearrangement (Scheme 21).

Scheme 22



Scheme 23[a]



[a] Reagents and conditions: (a) $CH_2{=}CHCH_2SiMe_3$, $TiCl_4$, CH_2Cl_2, −78 °C; (b) LiHMDS, **159**, THF, −78 °C; (c) $K_2OsO_2(OH)_4$, $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, *t*BuOH, H_2O, rt; (d) *i*Pr_3SiCl, DMAP, Et_3N; (e) NaN_3, DMF, 30 °C; (f) H_2, Pd/C; (g) **163**, Et_3N, CH_2Cl_2, rt; (h) Jones oxidation.

5. Synthesis of Kaitocephalin

Kaitocephalin is a novel tri-α-amino acid with a trisubstituted pyrrolidine ring as the structural core. Its structure was originally proposed as **7a** with the 2α-amino group and later revised as **7b** with the 2*β*-amino group. Total synthesis of kaitocephalin has been reported by two groups. While Ma et al.[84] asserted their synthesis of the initially assigned kaitocephalin **7a**, Kitahara and colleagues[85] claimed that of the revised kaitocephalin **7b**. Both syntheses utilized aldol condensation to settle the C4 position. The C7 position was elaborated by Ti(IV)-promoted allylation of an iminium ion in the Ma approach and by a novel alkylzinc addition to a nitrone in the Kitahara route.

5.1. Ma Synthesis of the Initial Structure 7a

Removal of the amide group from **7a** was planned to generate the trisubstituted pyrrolidine **155** (Scheme 22). Retroaldol cleavage disconnected **155** into the allylated proline **156**. Allylation of proline was retrosynthetically realized from (*S*)-pyroglutamic acid **157**.

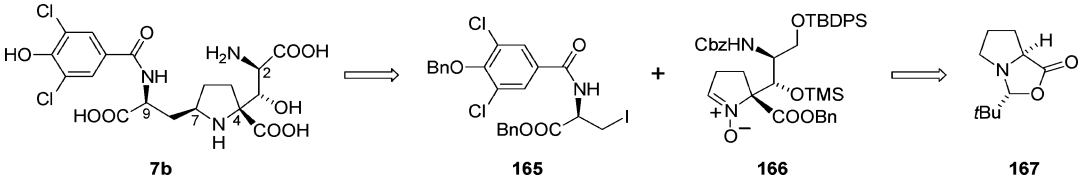
The aminal **158**, prepared from **157** via DIBAL reduction, was subjected to Ti(IV)-induced allylation[86] through an iminium cation to supply the *cis*-2,5-disubstituted pyrrolidine **156** (Scheme 23). The enolate of **156** was reacted with (*R*)-Garner aldehyde **159**[87] to afford the C1−C8 subunit **160** with the correct stereocenter at C4 but the wrong one at C3. While the benzyloxycarbonyl group controlled the stereochemistry of the C7 position, the allyl group dictated the C4 chiral center. After inversion of the C3 hydroxyl group of **160**, the resultant allyl pyrrolidine **161** was dihydroxylated[88] and silylated to give rise to a 6.8:1 mixture of the 9*β*-hydroxyl product **155** and its isomeric alcohol. Mesylation, protecting-group adjustment, and oxidation of **155** offered the mesylate ester **162**. The C9 position containing a mesylate group of **162** was aminated with inversion, acylated, and oxidized to furnish the protected kaitocephalin **164**, hydrogenolytic and hydrolytic deprotection of which produced kaitocephalin **7a** with the 2α-amino group.

5.2. Kitahara Synthesis of the Revised Structure 7b

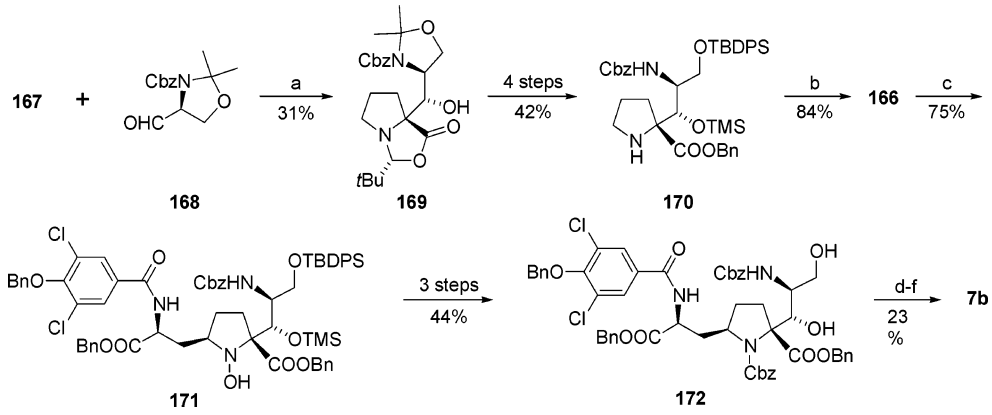
It was contemplated that kaitocephalin **7b** could be formed by connecting the C1−C7 nitrone subunit **166** and the C8−C10 iodide subunit **165** (Scheme 24). The amino acid moiety of **165** and the amino alcohol moiety of **166** were delivered from L-serine. Synthesis of **166** was presumed through Seebach's aldol condensation[89] of the oxazolone **167** with (*S*)-Garner aldehyde **168**.[87]

167 was coupled with **168** to yield a 3:2 mixture of the α-hydroxy pyrrolidine **169** and its *β*-hydroxy isomer, the *β*-hydroxyl group of which was inverted by an oxidation−reduction process (Scheme 25). The aldehyde **168** was attached exclusively to the convex face of the enolate of **167**, the *tert*-butyl group of which suppressed its conformational flipping, thus directing the attacking face. After demasking the acetal group of **169**, the generated amino group of

Scheme 24

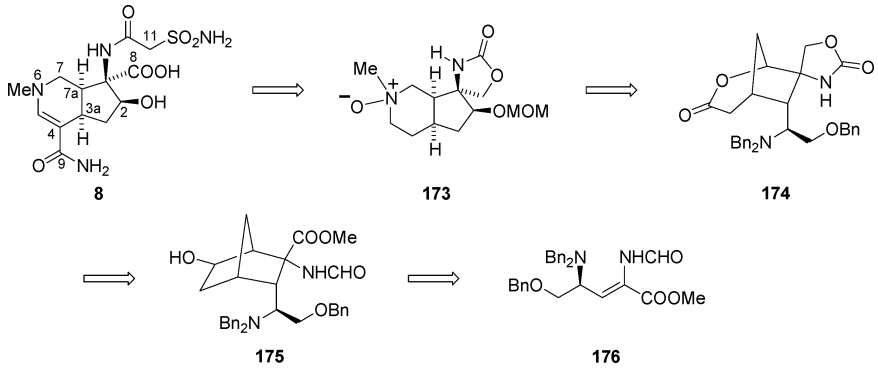


Scheme 25[a]



[a] Reagents and conditions: (a) LDA, THF, −78 °C; (b) $MeReO_3$, urea·H_2O_2, MeOH, rt; (c) **165**, Zn, CuI, THF, H_2O, ultrasound, rt; (d) 4-methoxy-TEMPO, KBr, satd $NaHCO_3$, CH_2Cl_2, 0 °C; (e) $NaClO_2$, NaH_2PO_4, $MeCH{=}CMe_2$, *t*BuOH, H_2O, rt; (f) H_2, 20% $Pd(OH)_2$/C, EtOH, $CHCl_3$, rt.

Scheme 26



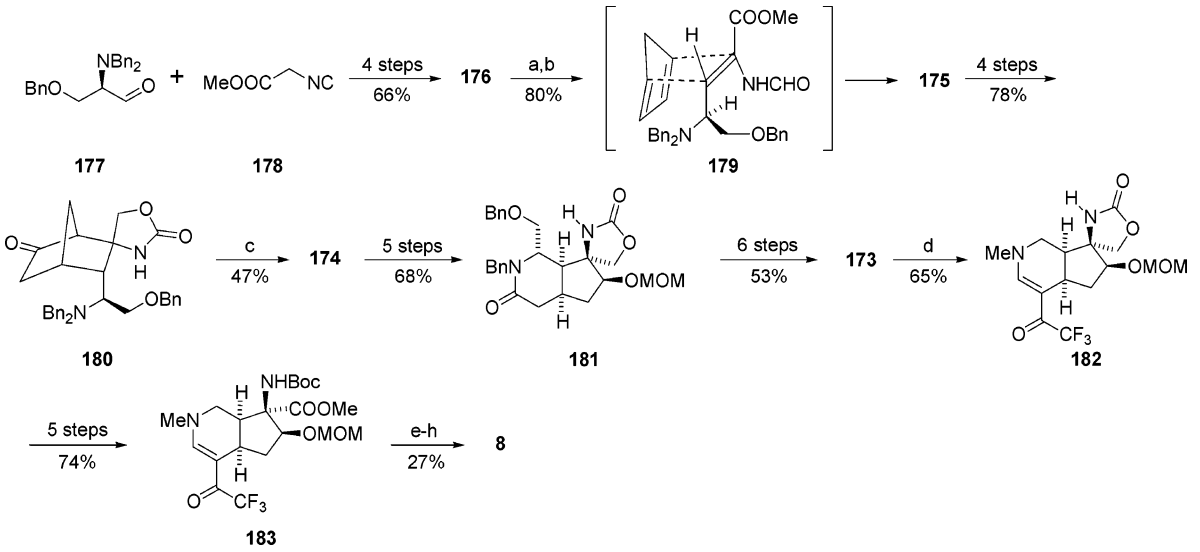
the pyrrolidine **170** was oxidized[28,90] and ultrasonicated with **165** in the presence of Cu(I)-activated Zn[91] to build the hydroxylamine **171** comprising the whole framework of kaitocephalin **7b**. A sequence of reduction, protection, and desilylation functionalized **169** to the diol **172**. The primary hydroxyl group of **172** was chemoselectively oxidized,[92] and the resulting carboxylic acid was deprotected to procure kaitocephalin **7b** with the 2β-amino group.

6. Synthesis of (−)-Altemicidin

The unique structural feature of altemicidin **8** is a tetrahydro-6-azaindan monoterpene alkaloid comprising a *cis*-ring junction, a carbamoyl enamine, and four successive asymmetric centers. Potier−Polonovski rearrangement[93] was considered by Kende et al. as a critical step to form the carbamoyl enamine functionality of (−)-altemicidin from the bicyclic *N*-oxide **173** (Scheme 26).[94] The bicyclic framework of **173** could be constructed by the transannular amide bond formation between the ester group and the benzyl-protected amino group of the lactone **174**. Its [3.2.1] bicyclic lactone ring was expected by Baeyer−Villiger oxidation of the [2.2.1] bicyclic system in the norbornane **175**, which was acquired through the known Diels−Alder reaction[95] of the formamido alkene **176**.

The dienophile **176** was prepared via Schöllkopf condensation[96] of the aldehyde **177** and the isocyanide **178** (Scheme 27). Cycloaddition of **176** with cyclopentadiene proceeded with complete diastereoselectivity and endo selectivity with respect to the formamido group through the conformationally controlled transition state **179**. The [4 + 2] cycloaddition not only provided the bicyclic ring element, but also established the stereochemistry of the carbamoyl-containing tertiary carbon and the ring junctions. The resulting norbornene was subjected to Rh(I)-catalyzed hydroboration[97] to yield the *exo*-norborneol **175** exclusively. After transformation of **175** to the ketone **180**, it was oxidized with peracid to furnish a 5:4 mixture of the expected bridgehead-migrated lactone **174** and the undesired methylene-migrated lactone. Adjusting the protective groups and rings of **174** founded the hydroazaindane skeleton and the C2 chiral center of **8**. The generated lactam **181** was

Scheme 27[a]



[a] Reagents and conditions: (a) cyclopentadiene, Et_2AlCl, 0 °C; (b) catecholborane, $(cod)_2RhCl$, Ph_3P, THF, −3 °C, then H_2O_2, NaOH; (e) CF_3CO_3H, CH_2Cl_2, 0 °C; (d) $(CF_3CO)_2O$, Py, CH_2Cl_2; (e) *B*-bromocatecholborane, CH_2Cl_2, rt; (f) (aminosulfonyl)acetic acid, 1,1′-carbonyldiimidazole, THF; (g) *n*PrSLi, HMPA, rt; (h) $NaNH_2$, DABCO, PhH, 80 °C.

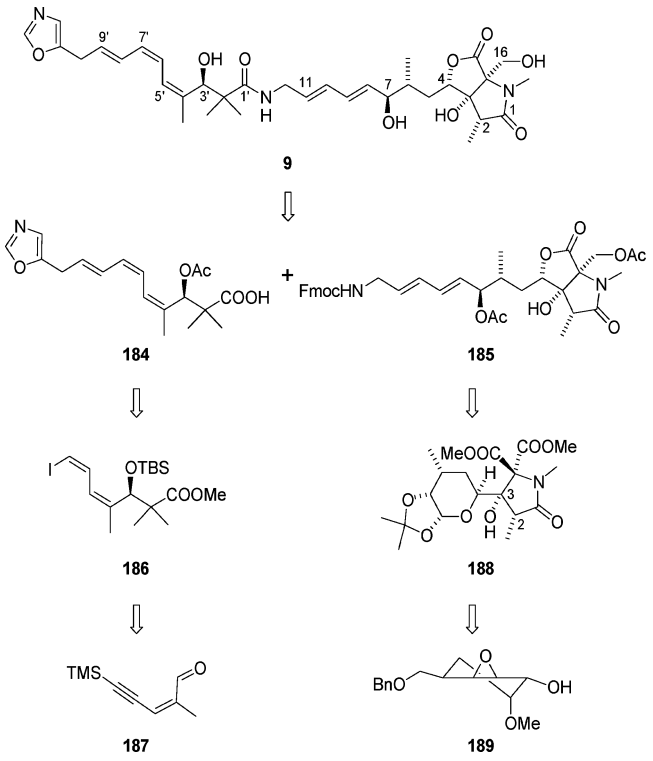
converted to the *N*-oxide **173** for the Potier−Polonovsky rearrangement through reduction, decarbonylation, and oxidation. The rearrangement of **173** delivered the vinylogous trifluoromethylamide **182**. Hydrolysis of its cyclic carbamate followed by oxidation of the demasked primary hydroxyl group and esterification provided the ester **183**. Involvement of deprotection, acylation, and substitution of the trifluoromethyl group by the amide group (Haller−Bauer fragmentation)[98] led **183** to (−)-altemicidin **8**.

7. Synthesis of Neooxazolomycin

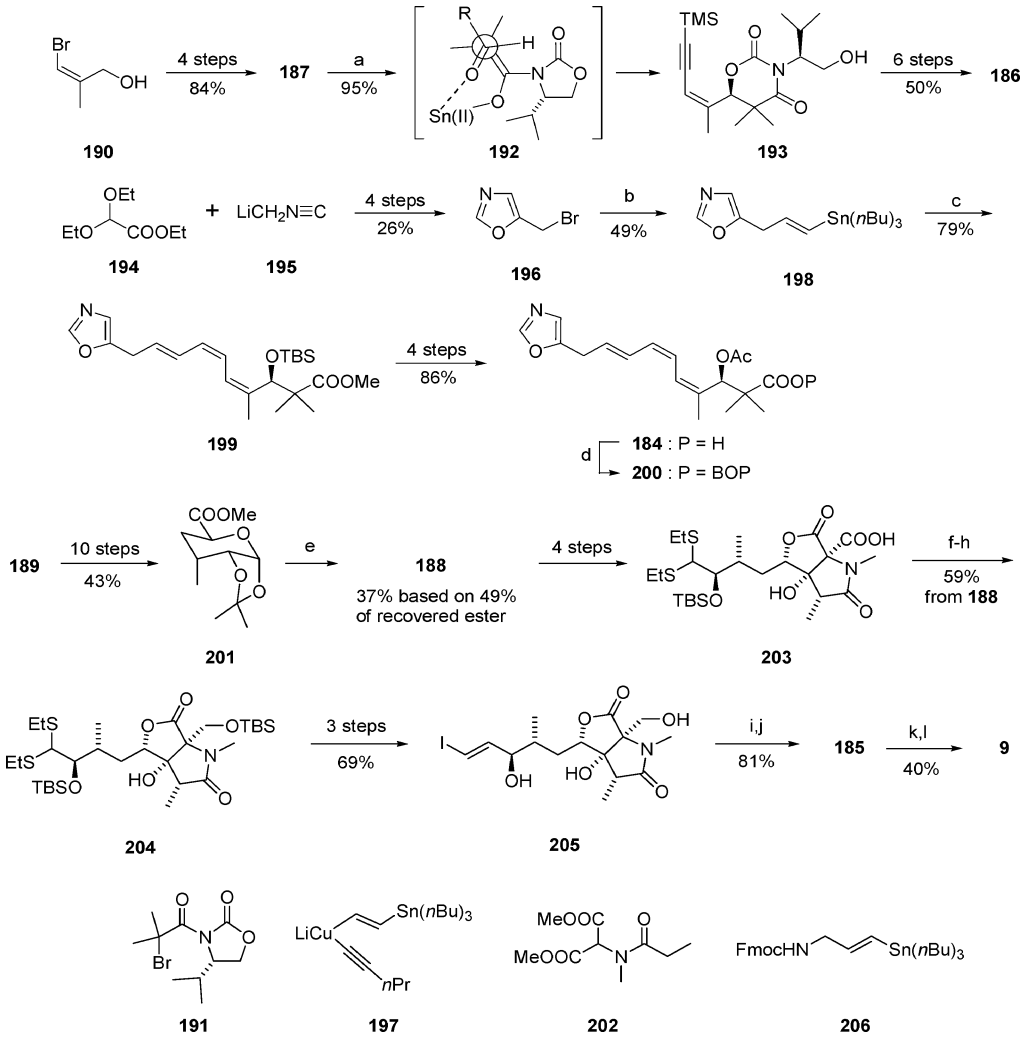
Neooxazolomycin **9** is formed by the amide linkage between an oxazole triene carboxylic acid and a diene amine. The amine subunit comprehends a novel fused γ-lactone and γ-lactam bicyclic system with chiral substituents at all the ring carbons. Retrosynthetic disconnection of the amide bond led to the carboxylic acid **184** and the carbamate **185** (Scheme 28).[99] Construction of the trienyl group of **184** was planned by Stille coupling[100] of the (*Z*)-vinyl iodide **186** and the corresponding oxazole-containing (*E*)-vinyl tin compound. The (*Z*)-iodoalkenyl and alkoxy groups of **186** were derived from the conjugated aldehyde **187** by diimide reduction[101] and Reformatsky-type condensation.[102] On the other hand, another Stille coupling was conceived to construct the dienyl group of **185**. The required (*E*)-iodovinyl group was installed by Cr(II)-promoted olefination[43] at the hemiacetal group of the glycoside **188** and the quaternary asymmetric carbon center by formation of the [3.3.0] bicyclic lactone ring to desymmetrize the two carbomethoxy groups. The tetrahydropyranyl moiety of **188** originated from the anhydrogalactoside **189**[103] and its lactam ring from propionamidomalonate through cyclocondensation.[104]

Starting from the vinyl bromide **190**[105] the conjugated enyne aldehyde **187** was obtained by Sonogashira coupling[106] and reacted with the Sn(II) enolate derived from the chiral bromoacyloxazolidinone **191** to secure the C1′−C7′ segment (Scheme 29). The segment was afforded as the 1,3-oxazine **193** in >99% de in accordance with the chelated transition state **192**[107] and further functionalized to the (*Z*)-vinyl iodide **186** as the substrate of the first Stille coupling. The oxazole bromide **196** prepared via Schöllkopf condensation[108] of the ester **194** and lithiated methyl isocyanide **195** was substituted by the vinyl tin cuprate reagent **197**,[109] and the resulting (*E*)-vinyl tin product **198** was combined with **186** to give rise to the triene **199**, which was activated to the mixed anhydride **200**[110] for the amide bond formation of the natural product **9**.

Scheme 28



Scheme 29[a]



[a] Reagents and conditions: (a) $SnCl_2$, $LiAlH_4$, THF, rt, then **191** in THF, rt, then **187** in THF, rt; (b) **187**, THF, −78 to −10 °C; (c) **186**, $PdCl_2(MeCN)_2$, DMF, rt; (d) BOPCl, Et_3N, CH_2Cl_2, rt; (e) **202**, *t*BuLi, TMEDA, THF, −78 °C, then addition to **201** in THF, −78 °C; (f) $[Me_2N{=}CHCl]^+Cl^-$, MeCN, THF, 0 °C; (g) $NaBH_4$, DMF, −78 °C to room temperature; (h) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt; (i) **206**, $PdCl_2(MeCN)_2$, DMF, rt; (j) Ac_2O, Py, rt; (k) DBU, CH_2Cl_2, rt, then addition to **200**, rt; (l) LiOH, THF, H_2O, rt, then 1N HCl.

A series of reactions including stereoelectronically controlled epoxide opening drove the anhydrogalactoside **189** to the ester **201** corresponding to the C3−C8 segment. The next sequence was to insert the [3.3.0] bicyclic framework. The ester group of **201** was condensed with the dianion of the amidomalonate **202** to offer a 1:1.4 mixture of the desired lactam (2α-Me, 3α-OH) **188** and its diastereomer (2*β*-Me, 3α-OH). Involvement of glycoside opening and lactone formation distinguished the two ester groups to produce the lactone lactam **203**. **203** was converted to the bicyclic (*E*)-vinyl iodide **205** via the thioacetal **204** through Fujisawa reduction[111] of the carboxylic acid group using Vilsmeier reagent and Takai iodovinylation. Stille reaction of **205** with the (*E*)-vinyl tin **206** induced the protected dienylamine **185**, which was deprotected, coupled with the activated carboxylic acid **200,** and deacetylated to provide neooxazolomycin **9**.

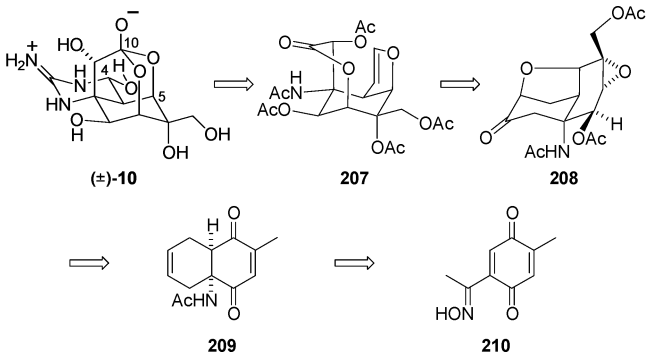
8. Synthesis of Tetrodotoxin

Tetrodotoxin **10** is structurally characterized by a highly hydroxylated cyclohexane to form a dioxaadamantane framework with an orthoacid functionality. The cage-shaped natural product also possesses a cyclic guanidine hemiaminal fused with the cyclohexane ring. Since the first synthesis of (±)-tetrodotoxin by Kishi et al.[22] in 1972, two groups recently reported enantioselective synthesis of (−)-tetrodotoxin. While Kishi's group employed stereoselective epoxidation and Beckmann rearrangement for the tertiary hydroxyl and C8a amino groups, Isobe and co-workers[112] installed them using epoxidation and Michael addition or Overman rearrangement. In the Kishi synthesis the starting 1,4-benzoquinone served as the cyclohexane ring, and the Isobe group assembled it using aldol condensation or Diels−Alder reaction. Instructively, Du Bois and Hinman[113] applied carbene C−H insertion to concomitant formation of the tertiary hydroxyl group and the cyclohexane ring and nitrene C−H insertion to creation of the C8a amino group.

8.1. Kishi Synthesis

Retrosynthetic consideration to cleave the ortho ester bond between the C5 oxygen and C10 and

Scheme 30



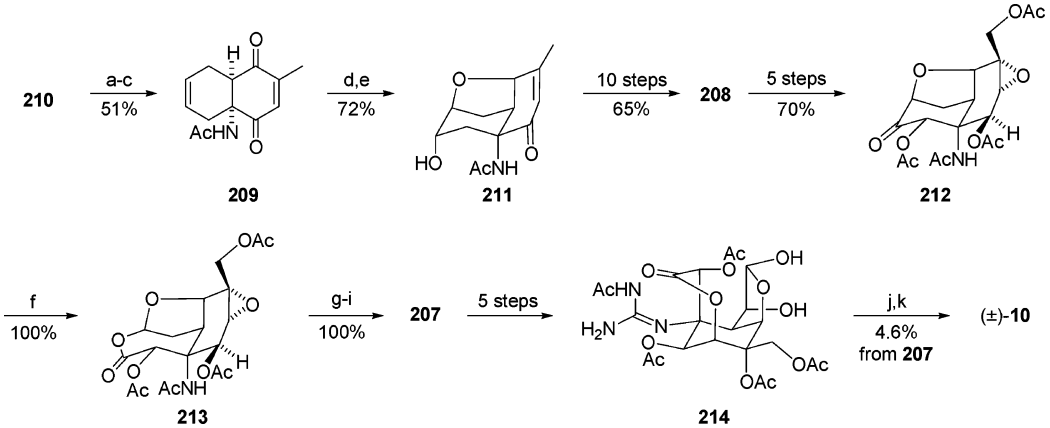
connect the C5 oxygen and C4 suggested the tricyclic dihydrofuran **207** as a precursor of racemic tetrodotoxin (±)-**10** (Scheme 30). Its assembly from **207** would need to involve guanidine formation and oxidative cleavage. Reframing **207** led to the tricyclic epoxide **208**, the forward conversion of which would need Baeyer−Villiger oxidation and acid-catalyzed intramolecular epoxide-opening cyclization. The carbon framework of **208** arose from the bicyclic conjugated dione **209**, obtained by Diels−Alder reaction of the benzoquinone **210**.

The synthesis commenced with attaching the two carbons of the ortho ester bridge and the one carbon of the hemiaminal moiety by cycloaddition[114] of **210** to afford a decalin derivative, Beckmann rearrangement[115] of which set up the tertiary alkyl amido group (Scheme 31). The generated dione **209** was reduced, epoxidized chemo- and stereoselectively from the convex face, and ensuingly cyclized to give rise to the tetrahydrofuran **211**. Installation of the tetrahydrofurano linkage was consequential to control the correct stereochemistry of the remaining oxygen functional groups as well as the intended migration in a later Baeyer−Villiger oxidation step. **211** was converted to the epoxy ketone **208** through a series of reactions using oxidations, Meerwein−Ponndorf−Verley reduction, and protections. The next sequence, to oxidize the α-position to the carbonyl group of **208**, was implemented via epoxidation of the enol ether procured by thermolysis of the diethyl ketal of **208** to deliver the α-acetoxy ketone **212**. To form the ortho ester bridge and the aminal carbon, the cyclohexanone ring was disposed by the regioselective Baeyer−Villiger oxidation of **212** to provide the seven-membered lactone **213**, which was reorganized to the six-membered lactone and eliminated by pyrolysis to the dihydrofuran **207**. To secure all the functional groups and the whole carbon skeleton of tetrodotoxin, the acetamido group of **207** was transformed to a monoacetylguanidino group using *S*,*S*-diethyliminodithiocarbonimidate and its olefinic double bond was oxidatively cleaved via the diol **214** to produce the racemic tetrodotoxin (±)-**10**.

8.2. Isobe Synthesis

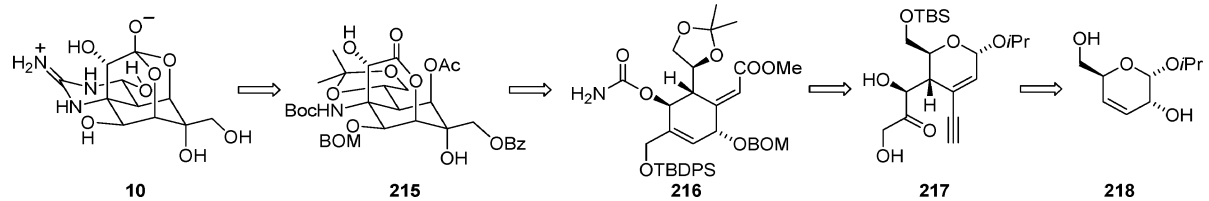
Isobe's group developed two synthetic routes to (−)-tetrodotoxin **10**. The first synthesis[112a] took the lactone **215** as an ortho ester precursor equivalent to the Kishi lactone **207** (Scheme 32). The two adjacent tertiary and lactonic oxygens were replaced by an endocyclic double bond, and removal of the carbamate group placed an exocyclic double bond to propose the cyclohexenol **216** as another retrosynthetic intermediate. **216** was built from the keto acetylene **217** by an intramolecular aldol condensation between the keto group and the acetylene group as an acetyl surrogate, which were attached to the

Scheme 31[a]

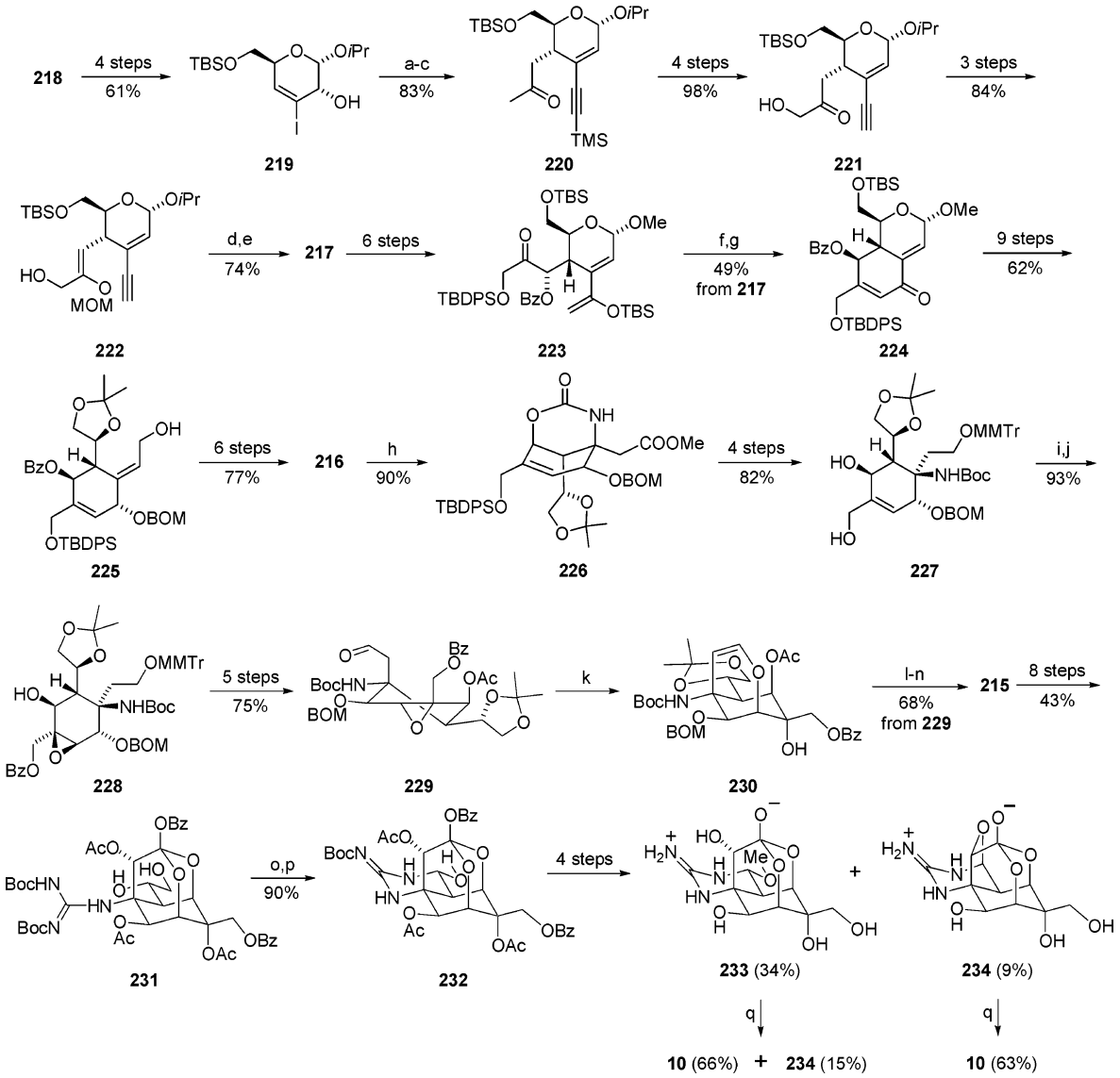


[a] Reagents and conditions: (a) CH_2=CHCH=CH_2, $SnCl_4$, MeCN, rt; (b) MsCl, Et_3N; (c) H_2O, reflux; (d) $NaBH_4$, MeOH, 0 °C; (e) *m*CPBA, CSA; (f) *m*CPBA, CH_2Cl_2, rt; (g) KOAc, AcOH, 90 °C; (h) Ac_2O, CSA, 100 °C; (i) high vacuum, 290−300 °C; (j) $NaIO_4$, aq THF, 0 °C; (k) NH_4OH, aq MeOH, rt.

Scheme 32



Scheme 33[a]

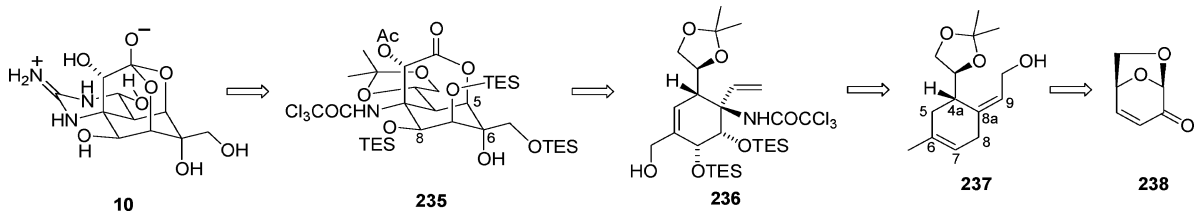


[a] Reagents and conditions: (a) $HCCSiMe_3$, $Pd(OAc)_2$, CuI, Ph_3P, Et_3N, PhH, rt; (b) $H_2C{=}C(Me)OMe$, PPTS, THF, rt; (c) K_2CO_3, *o*-dichlorobenzene, 150 °C; (d) *m*CPBA, K_2CO_3, CH_2Cl_2, rt; (e) Amberlyst 15, THF, H_2O, rt; (f) TBAF, THF, H_2O, 0 °C; (g) Cl_3CCOCl, DMAP, Py, rt; (h) *t*BuOK, THF, −78 to −15 °C; (i) *m*CPBA, Na_2HPO_4, $ClCH_2CH_2Cl$, rt; (j) BzCl, Et_3N, CH_2Cl_2, −42 °C; (k) DBU, *o*-dichlorobenzene, 130 °C; (l) OsO_4, NMO, acetone, H_2O, rt; (m) *o*-OIC_6H_4COOH, DMSO, 55 °C; (n) $NaBH_4$, MeOH, −78 °C; (o) $NaIO_4$, MeOH, H_2O, rt; (p) CF_3COOH, MeOH, rt; (q) CF_3COOH, H_2O, rt.

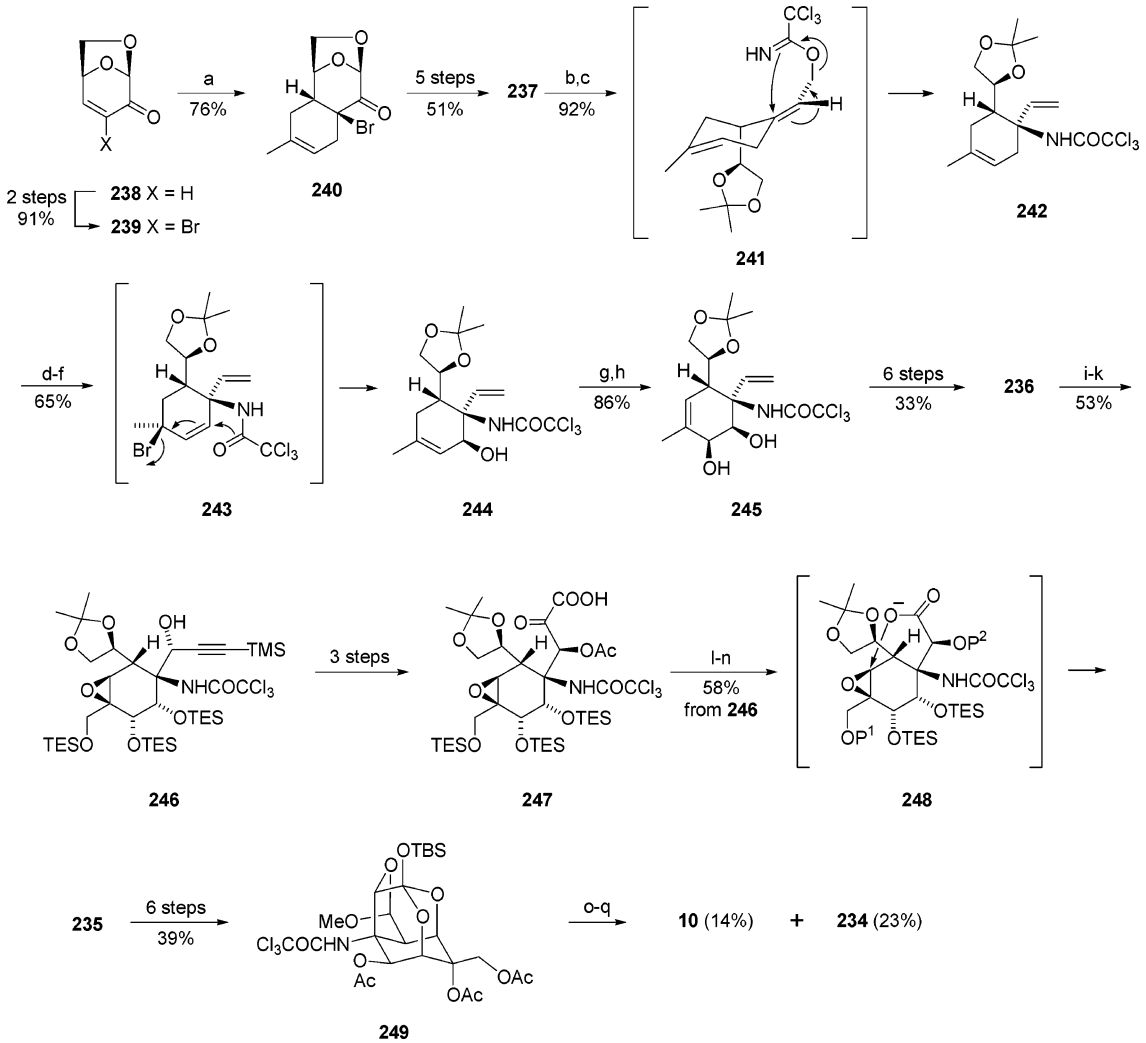
dihydropyran **218** by Claisen rearrangement and Sonogashira coupling reaction.

Synthesis started with iodination[116] of **218**[117] using the corresponding conjugated ketone (Scheme 33). The resulting vinyl iodide **219** was coupled with trimethylsilylacetylene[106] and subjected to [3,3] sigmatropic rearrangement to yield the methyl ketone **220**. The next event was hydroxylation of the two α positions to the carbonyl group. While the outer methyl group was readily oxidized, the inner methylene group was resistant to enolization. Oxidation of the hydroxyl group of the ketone **221** to aldehyde induced the spontaneous enolization to acquire the enol ether **222**. Epoxidation of **222** and the subsequent acidic hydrolysis effected the intended hydroxylation to furnish the α,α′-dihydroxy ketone **217**. The stereoselectivity was 7 to 1 in favor of the desired β stereochemistry. The enol ether **223** derived from **217** was cyclized and dehydrated for formation of the cyclohexene ring. The prepared cyclohexenone **224** was transformed to the allylic alcohol **225** through a series of reactions, including a stereoselective Luche reduction.[118] To equip the amino group at the tertiary carbon, the trichloroacetimidate of **225** was submitted to Overman rearrangement, which resulted in a 1,3-shift rather than the expected 3,3-shift. Alternatively, after the allylic alcohol was oxidized to the carboxylic acid, intramolecular Michael addition[119] of the generated carbamate **216**[120] gave rise to the cyclic carbamate **226**. Since an epoxy group should be installed from the β-face of the cyclohexene ring, **226** was converted to the allylic alcohol **227** and the following hydroxyl-directing epoxidation provided the desired epoxide **228** exclusively. With inversion of the secondary hydroxyl group of **228**, it was converted to the aldehyde **229**. Initially, it was oxidized to the corresponding carboxylic acid to cyclize to the hydroxy lactone spontaneously. However, its methylene

Scheme 34



Scheme 35[a]



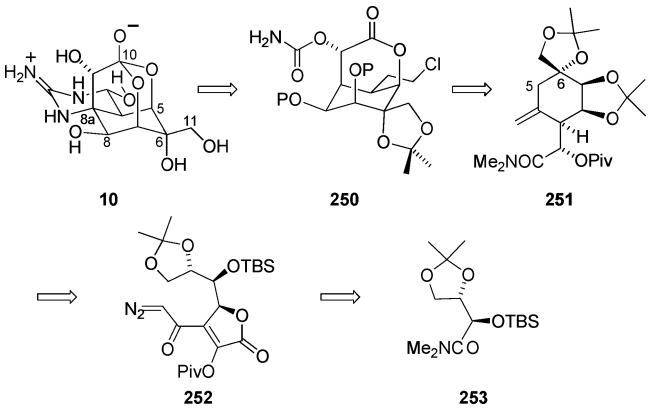
[a] Reagents and conditions: (a) CH_2=CMeCH=CH_2, BF_3·OEt_2, MeCN, 0 °C to room temperature; (b) Cl_3CCN, DBU, CH_2Cl_2, 0 °C; (c) K_2CO_3, xylene, reflux; (d) PyHBr_3, K_2CO_3, CH_2Cl_2, 0 °C; (e) DBU, DMF, rt; (f) TsOH, Py, H_2O, 70 °C; (g) *m*CPBA, Na_2HPO_4, CH_2Cl_2; (h) Ti(O*i*Pr)$_4$, $ClCH_2CH_2Cl$, reflux; (i) *m*CPBA, Na_2HPO_4, CH_2Cl_2, rt; (j) O_3, CH_2Cl_2, −78 °C, then Et_3N; (k) $Me_3SiC{\equiv}CMgBr$, THF, 0 °C; (l) 30% H_2O_2, $NaHCO_3$, MeOH, rt; (m) TESOTf, 2,6-lutidine, CH_2Cl_2, −40 °C; (n) Ac_2O, Py, rt; (o) DIBAL, CH_2Cl_2, −40 °C; (p) BocN=C(SMe)NHBoc, $HgCl_2$, Et_3N, DMF, rt; (q) CF_3COOH, H_2O, rt.

group α to the carboxyl group could not be hydroxylated. **229** was found to cyclize as its enol form to the cyclic vinyl ether **230**. A sequential oxidation and reduction of **230**[121] supplied the α-hydroxy lactone **215** as a single isomer. Involvement of deacetylation, deprotection, and guanidinylation[122] using *N,N′*-diBoc-*S*-methylisothiourea[123] transformed **215** to the ortho ester **231**. Oxidative cleavage of the vicinal diol and removal of one of the two Boc groups offered the cyclic guanidine aminal **232** from **231**. Adjustment of the protecting groups of **232** produced (−)-tetrodotoxin **10** via 4-methoxytetrodotoxin **233** and 4,9-anhydrotetrodotoxin **234**.

In the second approach[112b] another lactone **235**, having the lactone linkage with the C5 oxygen, was suggested as a promising intermediate (Scheme 34). Retrosynthetic cleavage of the two C5 and C6 oxygens led to the cyclohexene **236**, the trichloroacetamido group of which was equipped by Overman rearrangement[50] of the allylic trichloroacetimidate derived from the allylic alcohol **237**. The cyclohexene ring and the rest of the functional groups of **237** were constructed by Diels−Alder reaction of the levoglucosenone **238**.

The synthetic route was initiated by bromination[124] of **238** and immediate cycloaddition[125] of the gener-

Scheme 36



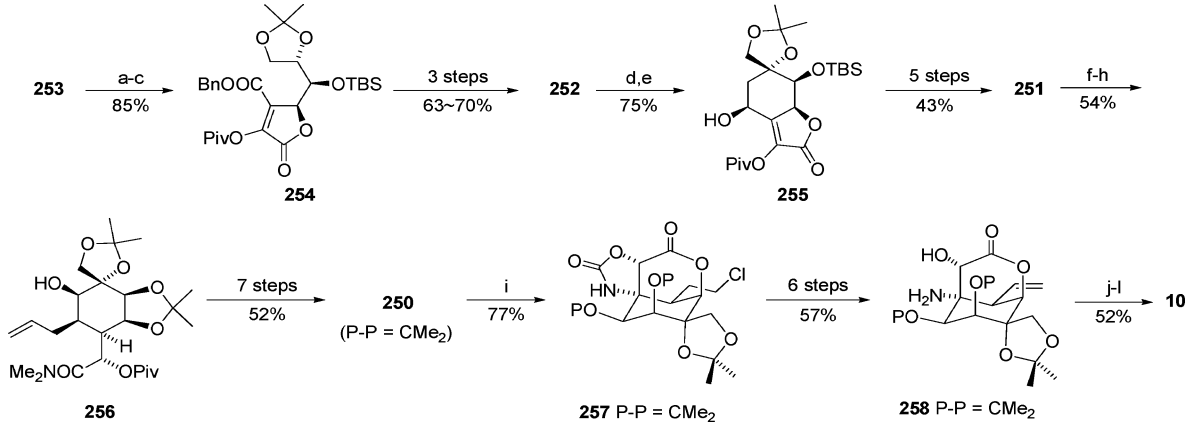
ated bromide **239** to secure the cyclohexane ring of (−)-tetrodotoxin **10** with a 15:1 regioselectivity[126] (Scheme 35). The acquired cyclohexene **240** was functionalized to **237** in a straightforward manner, and its trichloroacetimidate was exposed to [3,3] sigmatropic rearrangement to set up the indispensable C8a amino group of the allylic amide **242** through the conformation of **241** due to $A^{1,3}$-strain. The next event was introduction of the two C7 and C8 hydroxyl groups. The operation was conducted through an intramolecular SN2′ fashion as depicted in **243**,[127] and the ensuing Ti(IV)-promoted ring opening[128] of the epoxide prepared the allylic alcohol **244** to offer the diol **245** with the wrong stereochemistry of the two hydroxyl groups.[129] Involvement of their inversion and allylic oxidation[130] furnished the allylic alcohol **236**. To install the tertiary hydroxyl group and the ortho ester bridge, the endocyclic double bond of **236** was epoxidized and then its exocyclic double bond converted to a propargylic hydroxyl group via Grignard addition to deliver a 4:1 mixture of the desired propargylic alcohol **246** with the α-hydroxyl group and its stereoisomer. Oxidative cleavage[131] of the acetylenic group of **246** induced the keto carboxylic acid **247**, which was cyclized to the lactone **235** via the carboxylate **248** by alkaline hydrogen peroxide. A series of reactions including deprotection and oxidative cleavage was applied to **235** to generate the ortho ester acetal **249**. Reductive removal of the trichloroacetyl group of **249** and the subsequent guanidinylation and acidic deprotection produced (−)-tetrodotoxin **10** along with 4,9-anhydrotetrodotoxin **234**, readily convertible to (−)-tetrodotoxin **10**.

8.3. Du Bois Synthesis

Detachment of the nitrogen from the C8a position and the C7 oxygen from the C10 position engendered the lactone **250** as a prospective intermediate to (−)-tetrodotoxin **10** (Scheme 36). It was envisaged that **250** could be attained from the alkene **251** by allylic oxidation and Michael addition of a chloromethyl surrogate. Since construction of the cyclohexane ring of **251** was planned by carbene C−H insertion,[132] the C5−C6 bond was cleaved to give rise to the diazoketone **252**, which was obtained by a stereoselective aldol condensation using the amide **253**.

The synthesis began[133] with aldol condensation of the aldehyde derived from the amide **253**[134] to dispose the C8 hydroxyl group along with the ortho ester bridge carbons (Scheme 37). The stereoselectivity was higher than 10:1 in favor of the anti stereoisomer expected from the Felkin−Ahn model. After converting the prepared ester **254** to the diazoketone **252** in the usual manner, Rh(I)-catalyzed C−H insertion[135] of **252** was carried out to establish not only the requisite cyclohexane ring but also the tertiary hydroxyl group with the correct stereochemistry. The ensuing stereoselective reduction of the carbonyl group afforded the cyclohexanol **255**, which was further functionalized to the alkene **251** by a series of reactions including hydrogenation from the convex face to settle the C8a and C9 stereochemistry. Allylic oxidation[136] of **251** followed by cuprate addition[137] and reduction provided the homoallylic alcohol **256** containing the C5 hydroxyl group and hemiaminal carbon. Adaptation of the functional groups of **256** supplied the lactone **250** suitable for amidation of the C8a position. Rh(I)-catalyzed nitrene C−H insertion[138] of **250** was executed under oxidative conditions to deliver the five-membered carbamate **257**. The carbamate group and the chloromethyl group were demasked to the aminohydroxy alkene **258**. Guanidi-

Scheme 37[a]



[a] Reagents and conditions: (a) DIBAL, *n*BuLi, THF, hexane; (b) $BnO_2CCH_2COCO_2Bn$, NaOAc, THF; (c) *t*BuCOCl, Py, THF; (d) $Rh_2(HNCOCPh_3)_4$, CCl_4; (e) $H_3B{\cdot}NH_3$, CH_2Cl_2, MeOH; (f) Ph_2Se_2, $PhIO_2$, Py, PhCl, 100 °C; (g) $CH_2{=}CHMgBr$, CuI, THF; (h) *t*$BuNH_2{\cdot}BH_3$, $ClCH_2CH_2Cl$; (i) $Rh_2(HNCOCPh_3)_4$, $PhI(OAc)_2$, MgO, PhH, 65 °C; (j) $BocN{=}C(SMe)NHBoc$, $HgCl_2$, Et_3N, MeCN, CH_2Cl_2; (k) O_3, CH_2Cl_2, MeOH, then Me_2S; (l) aq CF_3COOH.

nylation of **258** and the subsequent ozonolysis and deprotective cyclization formed the cyclic guanidino hemiacetal to render (−)-tetrodotoxin **10**.

9. Summary and Concluding Remarks

We described the synthesis of biologically significant natural products with amino hydroxy carboxylic acid functionalities as a core structural feature. In particular, they contain a quaternary carbon with an amino group. One of the most challenging aspects in the synthesis of these complex molecules is construction of quaternary stereogenic centers. The intriguing methodologies applied to the culminating steps include asymmetric Strecker synthesis for manzacidins and lactacystin, nitrene C−H insertion for manzacidins and tetrodotoxin, Lewis-acid-induced Hatakeyama rearrangement for sphingofungins and lactacystin, Overman rearrangement for sphingofungin E and tetrodotoxin, aldol condensation of α-amino ester for lactacystin, kaitocephalin, and neooxazolomycin, iodocyclization of isothiourea for manzacidin D, asymmetric allylic alkylation using chiral Pd(II) complex for sphingofungins, epoxide opening reaction with azide anion for sphingofungin E, aldol condensation of Schöllkopf's bislactam and alkylation of oxazoline ester for sphingofungin F, mercuriocyclization of allylic trichloroacetimidate for lactacystin, Diels−Alder cycloaddition for altemicidin, and Beckmann rearrangement and Michael addition of carbamate to conjugated ester for tetrodotoxin.

A variety of valuable protocols have been established depending upon the targeted structures. Most of the implemented methods have relied on the preexisting asymmetric centers to set up the requisite stereochemistry. There is no doubt that their utility will continue in future organic synthesis. In addition, development of enantioselective formation of tertiary alkyl amino groups will not only be complementary to the described methods but also open novel ways in natural product synthesis.

10. References

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