Total Synthesis of Selected Bioactive Natural Products: Illustration of Strategy and Design

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1. Introduction

Anybody can draw a picture, but pictures painted by famous painters such as van Gogh, Monet, and Picasso are praised as "art". At the present time, anyone may be able to synthesize natural products, even those having complicated structure by advanced organic chemistry. Hence, "art" is much more essential to be introduced into the organic synthesis. That is the significance of the synthesis and development of bioactive compounds. The authors are of the opinion that "art" is a sublimate of originality, and, in the 21st century, it should be accompanied with some additional features.

In bioactive natural products, several antibiotics, called "the big four antibiotics", were the foremost subject of research at the time one of the authors, Tatsuta, started his study of antibiotic synthesis through the 1960s into the 1970s. They were macrolide (carbomycin, leucomycins, tylosin, oleandomycin), aminoglycoside (kanamycin, apramycin, saccharocin), β-lactam (thienamycin), and tetracycline (tetracycline) antibiotics. Tatsuta's group has fortunately succeeded in completing the total syntheses of 82 diverse bioactive natural products including the above-mentioned representatives of the big four antibiotics, and 77 of them are the first total syntheses. It is noteworthy that most of the optically active compounds have been synthesized efficiently even by using carbohydrates as chiral sources to determine the absolute structure and to clarify their structure−activity relationships.

The first total syntheses especially required the creation of original synthesis concepts and methodologies and included the definition of the absolute structure of the bioactive natural products as well as the verification of their biological activities.

In the present paper, the authors would like to introduce the dynamic as well as elegant parts of their total synthesis of practically useful bioactive compounds, focusing not only on "art" but also on the significance of the total synthesis.[1]

2. Total Synthesis of Cochleamycin A: 10 Membered Ring Constructions

Cochleamycin A (**1**) was isolated by the Kirin Brewery group from a cultured broth of *Streptomyces*

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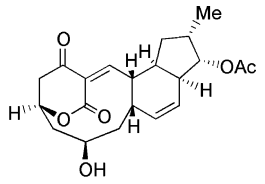
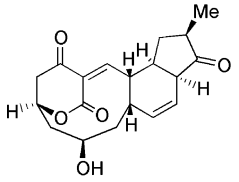
Kuniaki Tatsuta received his Ph.D. from Keio University, Japan, in 1969 working under the direction of Prof. S. Umezawa and joined the faculty as Assistant. Immediately after he was appointed as Assistant Professor in 1973, he joined Prof. R. B. Woodward's group at Harvard University as Postdoctoral Fellow (1973–1975), and, in 1985, he was promoted to Professor of Organic Chemistry, Keio University. In 1993, he moved to Waseda University as Professor of Bioactive Substances Science and, in 2004, was appointed as Dean of the Graduate School of Science and Engineering. He has been Visiting Professor of Cambridge University and Paris VI University in 1988 and 1994. Professor Tatsuta has been the recipient of the Divisional Award of the Chemical Society of Japan (1986), the Award of the Synthetic Organic Chemistry Japan (1998), Distinguished Award of the Chemical Society of Japan (2001) and Imperial Medal with Purple Ribbon of Japan (2002). He is the project leader of the 21st Century COE Program of MEXT "Practical Nano-Chemistry" (2002–2006). His research program focuses on total syntheses of bioactive natural products to develop new medicines as well as strategies, and he has already accomplished total syntheses of 84 kinds of natural products including the representative compounds of the so-called big four antibiotics: aminoglycoside, β-lactam, macrolide, and tetracycline antibiotics. In 1988, his anticancer agent, THP-adriamycin, was marketed as pirarubicin.

Seijiro Hosokawa was born in Kurashiki, Japan, in 1968. He received his BS and MS degrees from Hokkaido University under the supervision of Professor Haruhisa Shirahama and his Ph.D. from Nagoya University under the supervision of Professor Minoru Isobe in 1996. After a year of postdoctoral research at Nagoya University and an additional year at the Scripps Research Institute under the supervision of Professor K. C. Nicolaou, he was appointed as Assistant in Susumu Kobayashi's group in Tokyo University of Science. In 2003, he moved to Tatsuta's group in Waseda University as a lecturer. His research interests include the development of new synthetic methods and synthesis of bioactive compounds.

sp. to show cytotoxicity against P388 leukemia cells and antimicrobial activities.[2] The structure including the relative stereochemistry was elucidated by exhaustive NMR studies to be endowed with a 5−6−10−6 membered tetracyclic core (Figure 1).[3] After the isolation, its analogues, macquarimicins (**2**) were



Cochleamycin A (1)



Macquarimicin A (2)

Figure 1.

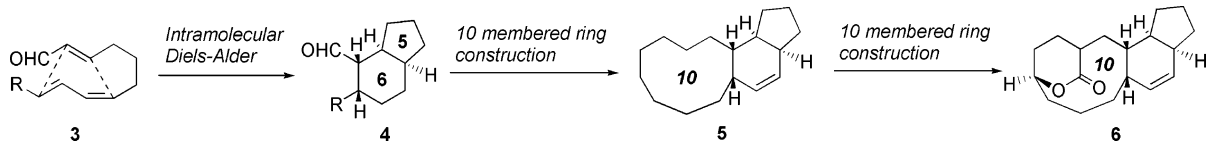
independently isolated by the Abbott group.[4] Not surprisingly, the combination of architectural complexities and bioactivities has engendered considerable interest, resulting in impressive synthetic studies from the groups of Paquette and Tadano using Diels−Alder reactions.[5,6] After our first total synthesis of cochleamycin A,[7] Tadano's group reported the total synthesis of macquarimicin A,[6a] and Roush's group disclosed its total synthesis of cochleamycin A.[8] Both groups took *transannular* Diels−Alder reactions to construct a cochleamycin skeleton, while we used an *intramolecular* Diels−Alder reaction followed by direct construction of the 10 membered ring. Here, we describe the first total synthesis of cochleamycin A accomplished in our laboratory.[7]

Our strategy to construct the skeleton of cochleamycin A is shown in Scheme 1. An acyclic triene **3** would be subjected to intramolecular Diels−Alder reaction to give 5−6 membered ring **4**,[9] which might be followed by 10 membered ring constructions to obtain the cochleamycin skeleton **6**. Although it is well-known that 10 membered ring construction is difficult due to the transannular repulsion, we decided to take this challenging route.

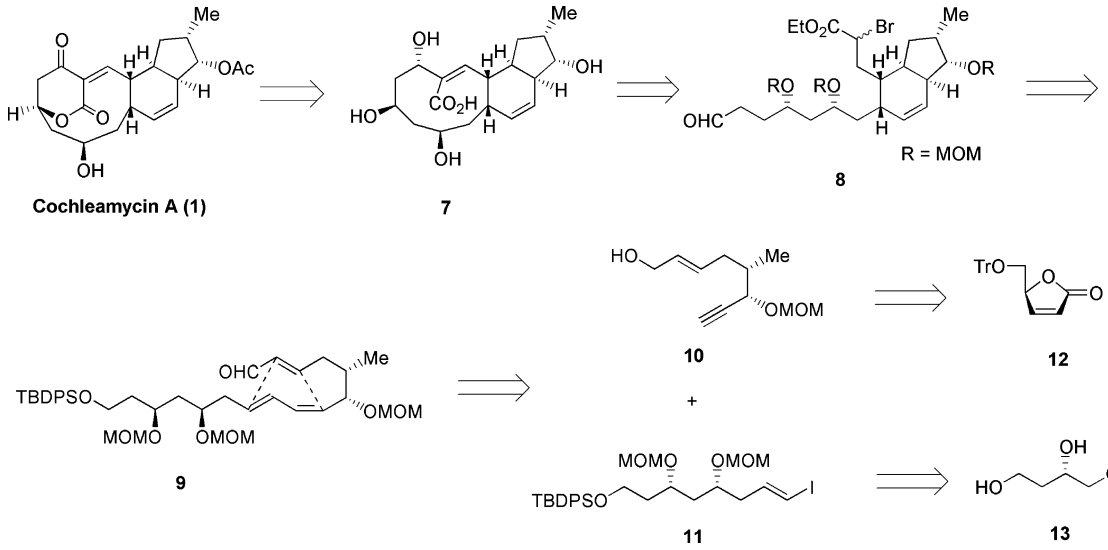
On the basis of this strategy, we planned the total synthesis of cochleamycin, as shown in Scheme 2. For maximum convergency, the acyclic precursor of the Diels−Alder reaction (**9**) was constructed by connection of two chiral segments, **10** and **11**. Segments **10** and **11** were prepared from readily available γ-lactone (**12**) and (*S*)-1,2,4-trihydroxybutane (**13**), respectively, by our previously developed methodologies.[10]

The first total synthesis of cochleamycin to determine the absolute structure was achieved as shown in Schemes 3−5. Lactone **12** was methylated stereoselectively by Michael addition with MeMgBr[10a] in the presence of CuBr·Me_2S and trimethylsilyl chloride (TMSCl) to give **14** as a single isomer (Scheme 3). Reduction with $LiAlH_4$ afforded acyclic diol **15**, which was followed by selective manipulation of alcohols to obtain aldehyde **16**. The aldehyde was converted to the acetylene **17** by treatment with dimethyl-1-diazo-2-oxopropylphosphonate[11] in the presence of K_2CO_3. The primary alcohol moiety of **17** was transformed to the allylic alcohol to give segment **10**. On the other hand, (*S*)-1,2,4-trihydroxybutane (**13**) was converted to the epoxide **18**,[12] which was

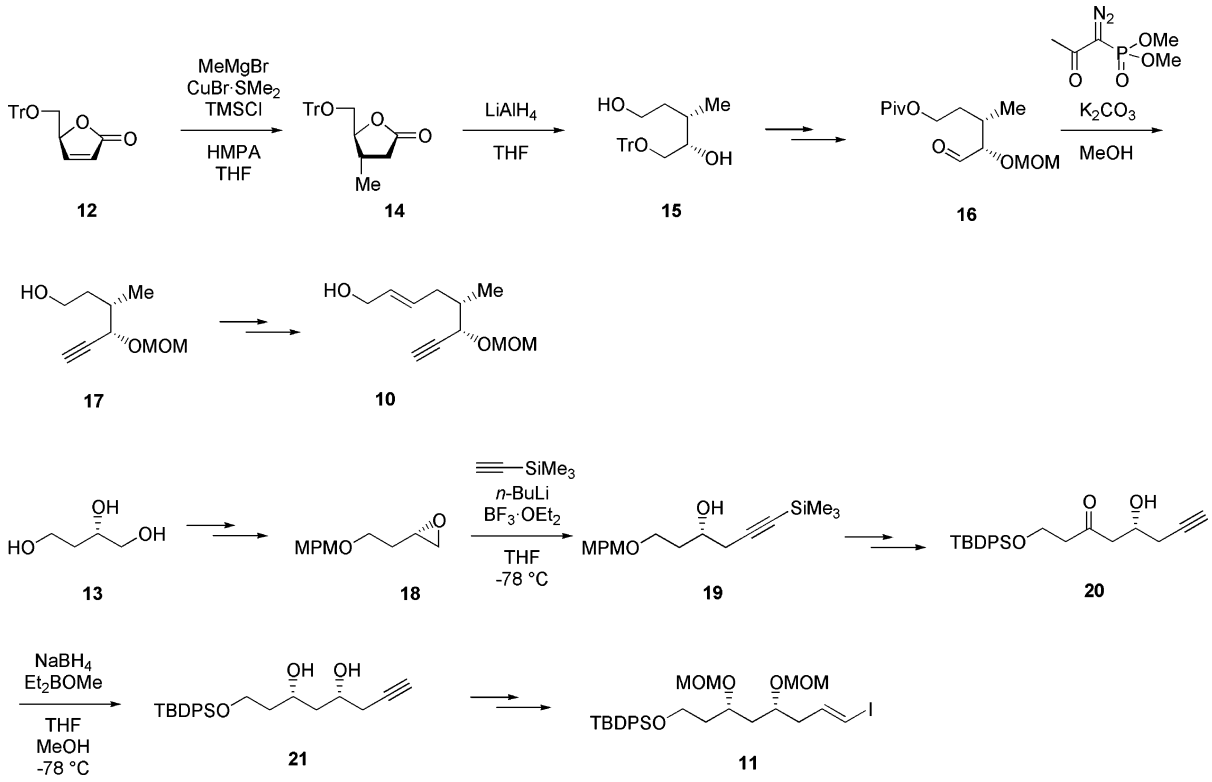
Scheme 1



Scheme 2



Scheme 3

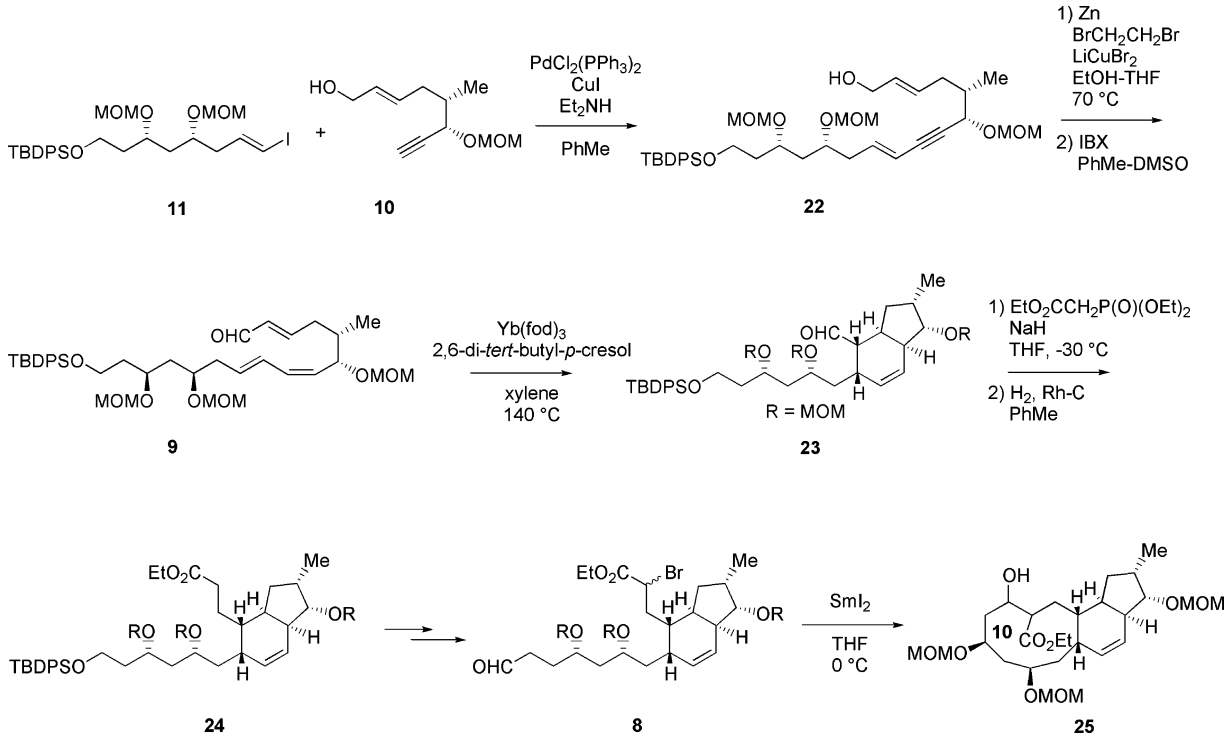


submitted to introduction of acetylene to afford **19**. Compound **19** was transformed to β-hydroxyketone **20** in several steps, which was reduced stereoselectively to give syn diol **21** with $NaBH_4$ in the presence of Et_2BOMe.[13] Further manipulation of **21** gave the other segment, (*E*)-1-iodoalkene **11**.

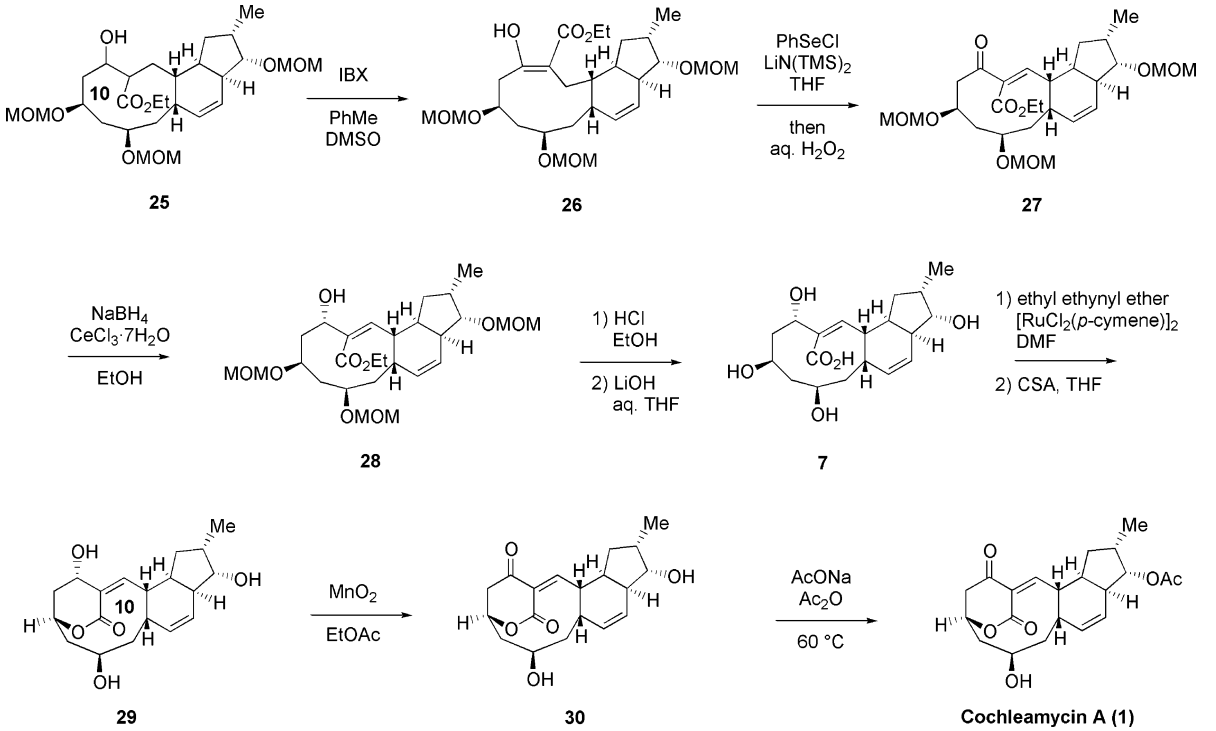
With both segments **10** and **11** in hand, we turned to the assembly of the carbon backbone of **1** (Scheme 4).

Coupling of **10** and **11** smoothly proceeded to give the alcohol **22** in quantitative yield. This was selectively reduced to the *cis*,*trans*-diene structure, which was crucial to the construction of the desired A−B ring by intramolecular Diels−Alder reaction. Oxidation of the allylic alcohol gave the α,β-unsaturated aldehyde **9**, which was submitted to intramolecular Diels−Alder reaction in the presence of $Yb(fod)_3$ at 140 °C.[14] The desired adduct **23** was obtained as a

Scheme 4

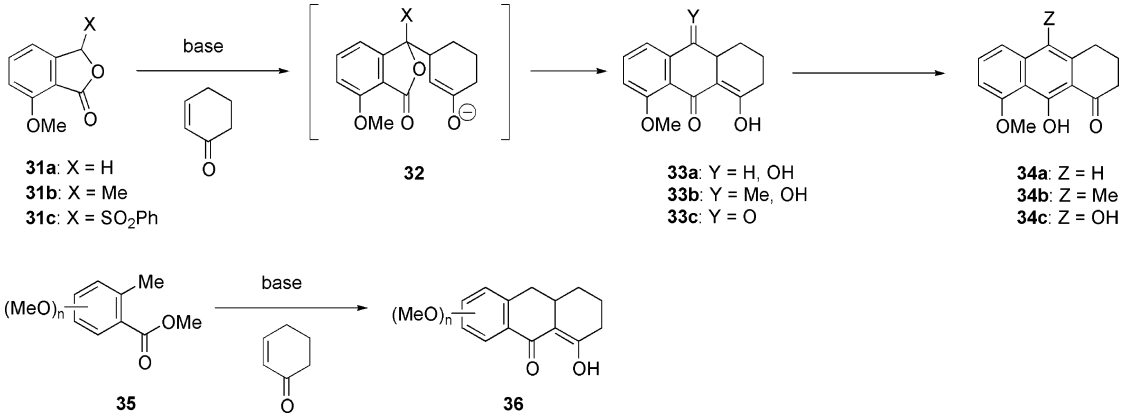


Scheme 5



single product in high yield. This intramolecular Diels−Alder reaction produced four critical stereocenters as expected. The Hornor−Emmons reaction of **23** was followed by selective reduction to give the ester **24**, which was converted to α-bromo ester **8**, the precursor of the 10 membered ring. The desired cyclization of **8** was accomplished with SmI_2 to give 10−6−5 membered tricyclic product **25** as a single product,[15] comprising the fully elaborated structure ready for conversion to the requisite seco-acid **7** (Scheme 5). The configurations of the newly produced stereocenters of **25** were not determined, because they disappeared on the following steps. IBX oxidation of **25** gave the corresponding ketone, which was transformed to the *cis*-enol **26** during silica gel column chromatography (Scheme 5). The enol **26** was converted to α,β-unsaturated ester **27** possessing the desired *Z*-olefin by phenylselenenylation and oxidative elimination. However, deprotection of **27** for lactonization resulted in β-elimination of the functional group. Therefore, the ketone was reduced to the β-alcohol **28**. Deprotection of **28** followed by

Scheme 6



saponification gave tetrahydroxyl carboxylic acid **7**. Each of the four hydroxyl groups of **7** was discriminated from others. Lactonization of **7** was tested under the various conditions to construct a C−D ring, and the best result was realized by using Kita's conditions[16] to afford the δ-lactone **29**, which possessed another 10 membered lactone ring. The allylic alcohol of the lactone **29** was oxidized to α,β-unsaturated ketone **30** by exposure to MnO_2. Finally, selective acetylation was accomplished with NaOAc and Ac_2O at 60 °C to afford cochleamycin A (**1**). The synthetic **1** was identical in all respects including the optical rotation with natural cochleamycin A, completing the first total synthesis to establish the absolute structure.

3. Total Syntheses of Natural Products Possessing Fused Aromatic Rings

3.1. Total Synthesis of Tetracycline: Tandem Michael–Dieckmann Cyclization

3.1.1. Tandem Michael–Dieckmann Cyclization

During total syntheses of bioactive natural products possessing aromatic rings and oxygenated cyclohexanes, we developed a novel methodology to synthesize those structures in short steps with convergency, meaning tandem Michael−Dieckmann cyclization (Scheme 6).[1] Lactones **31a**−**c** can be converted to tricyclic **33a**−**c** through Michael adduct **32** by coupling with cyclohexenone under the basic conditions. Aromatization of **33a**−**c** gives naphthalenes **34a**−**c**. Similarly, treatment of ester **35** with base can produce benzylic anion, which is coupled with cyclohexanone to afford ketone **36**. This procedure is suitable for constructing polycyclic compounds, especially aromatic ring-fusing compounds.

By this methodology containing tandem Michael−Dieckmann cyclization and following aromatization, total syntheses of some bioactive natural products were achieved including nanaomycin D,[17] kalafungin,[17] medermycin,[18] MS-444,[19] ES-242-4,[20] tetracycline,[21] napyradiomycin A1,[22] UCE-6,[23] and BE-54238B.[24] Herein, we describe our first total synthesis of (−)-tetracycline,[21] which included this methodology as a key step.

3.1.2. First Total Synthesis of (–)-Tetracycline

For almost a half-century, tetracycline (**37**) has been well-known as a major antibiotic from the viewpoint of its unique structural features as well as antibacterial activities[25] (Figure 2). The total

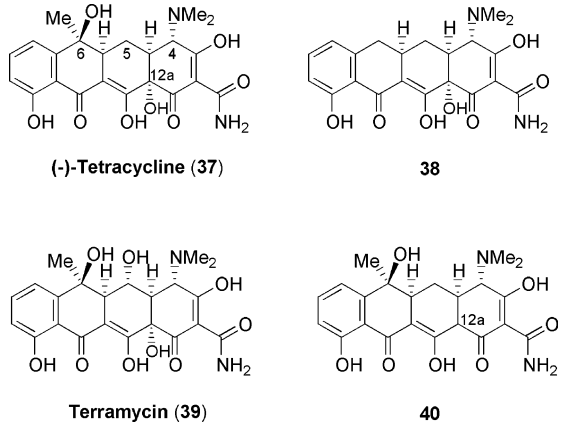


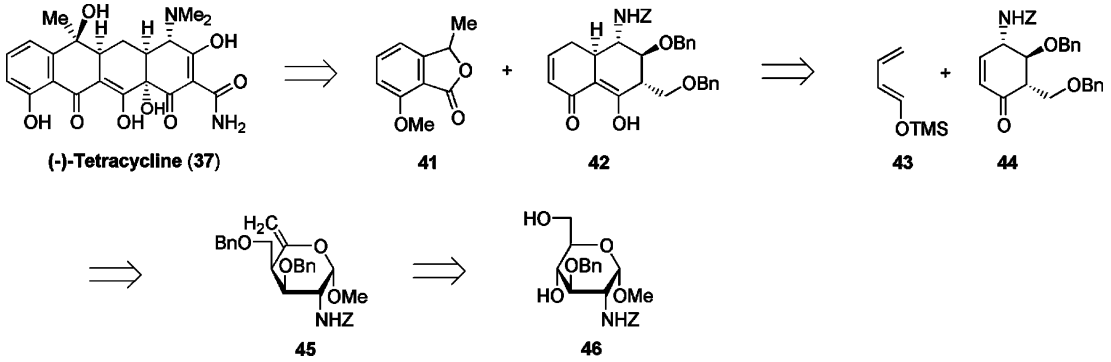
Figure 2.

synthesis of tetracycline families was initiated by Woodward's 6-demethyl-6-deoxytetracycline (**38**) synthesis in 1962,[26] followed by Muxfeldt's terramycin (**39**) synthesis in 1968,[27] and culminated by Stork's 12a-deoxytetracycline (**40**) synthesis in 1996.[28] However, all those syntheses have been accomplished only in racemic forms. The total synthesis of natural (−)-tetracycline (**37**) had remained an unanswered challenge, until achievements in our laboratory in 2000.[21] Recently, another success to the total synthesis of (−)-tetracycline was presented by the Myers group.[29] Herein, we focus on the first total synthesis of (−)-tetracycline (**37**) accomplished in our laboratory.[21]

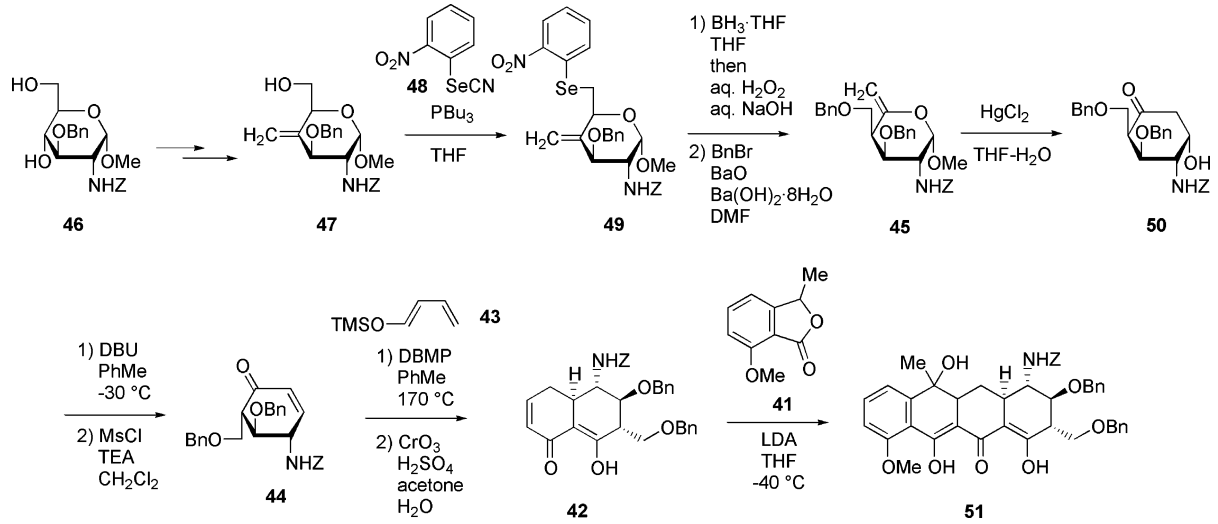
Our retrosynthetic analysis is shown in Scheme 7. The tetracycline structure is expected to be accessible by tandem Michael−Dieckmann type reaction of **41** with **42**. The suitably substituted chiral intermediate **42** would be synthesized by Diels−Alder reaction of cyclohexanone **44** and the siloxybutadiene **43**. The regio- and stereoselectivities are established as a consequence of the dienophile geometry according to Gleiter's theory.[30] Compound **44** could be obtained from **46** through Ferrier reaction of **45**.

The starting **46** derived from D-glucosamine[31] was converted to olefinic alcohol **47**, which was submitted

Scheme 7



Scheme 8

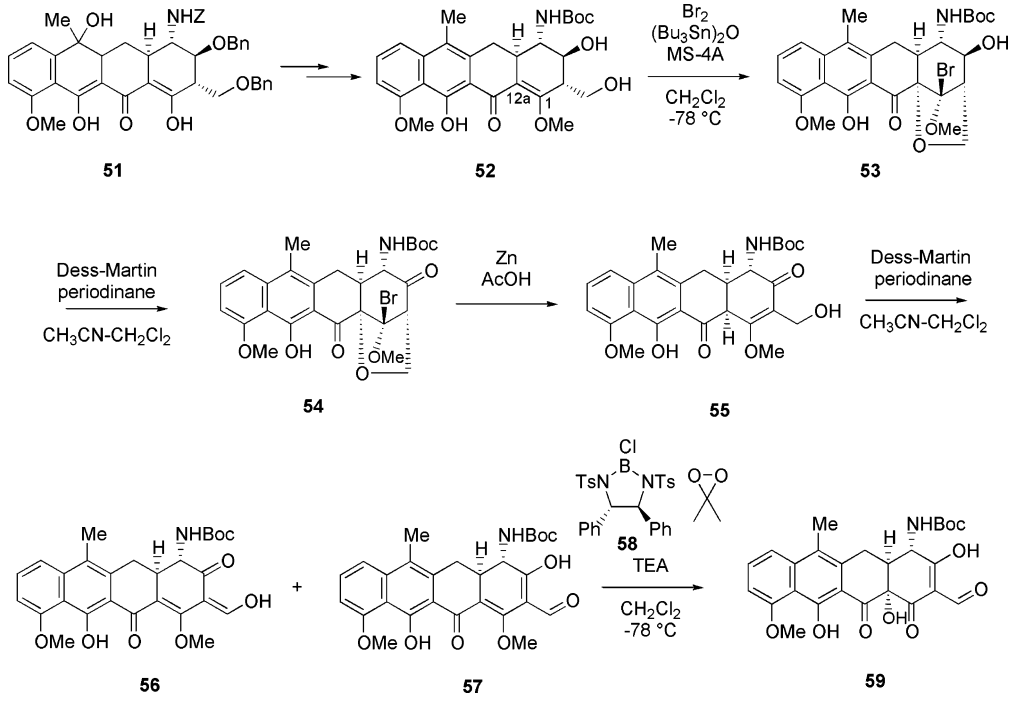


to selenylation[32] to give **49** (Scheme 8). Treatment of **49** with borane followed by H_2O_2 oxidation gave stereoselectively the alcohol **45** by simultaneous formation of a new olefin group, which was followed by benzylation to afford **45**. Enol ether **45** was subjected to Ferrier reaction to give β-hydroxyketone **50**.[33] Epimerization at the C-2 position of **50**, possessing two benzyloxy groups and one hydroxyl group at β-positions, was realized by treatment with DBU at −30 °C, and following elimination of hydroxyl group was proceeded in a one-pot mesylation−β-elimination sequence to give enone **44**. Diels−Alder reaction of **44** and **43** in the presence of 2,6-di-*tert*-butyl-4-methylphenol (DBMP) proceeded from the β-face of **44** regio- and stereoselectively as expected. This highly stereoselective reaction gave a labile adduct, which upon acidic oxidation was transformed to the α,β-unsaturated ketone **42**. The tandem Michael−Dieckmann type reaction of **42** with the isobenzofuranone **41**[34] gave tetracyclic compound **51**.

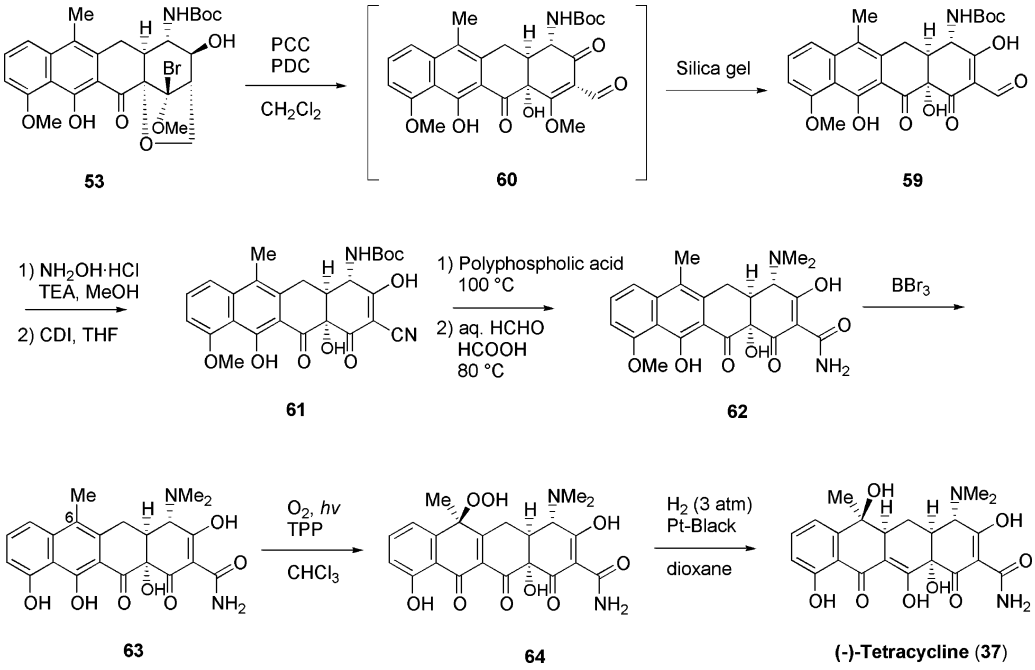
With the tetracyclic **51** in hand, we turned to the oxidation of the right ring (Scheme 9). Especially, stereoselective introduction of an hydroxyl group at C-12a was one of the key problems of this synthesis. Aromatization and manipulation of protective groups gave diol **52**, which was adequate for oxidation of the right wing. The primary alcohol of **52** participated to the bromination of the C-1−C-12a olefin. After oxidation of the secondary alcohol **53**, the primary alcohol appeared again with migration of the double bond by treatment with Zn in AcOH[35] to provide **55**. This was oxidized with Dess−Martin periodinane to a mixture of the enols **56** and **57**. The mixture was submitted to epoxidation using dimethyldioxirane with the chiral cyclic borane **58**,[36] where the reaction occurred from the α-face as expected, affording predominantly the C-12a alcohol **59**. Thus, desired **59** was obtained in 4 steps from **53**.

Recently, the direct conversion of **53** into **59** was established (Scheme 10). Treatment of **53** with a mixture of pyridinium chlorochromate (PCC) and pyridinium dichromate (PDC) in dichloromethane followed by purification with silica gel afforded **59** in 61% yield. This transformation, probably via intermediate **60**, realized concurrent oxidation of primary and secondary alcohols accompanied with introduction of the C-12a hydroxyl group in one pot. The resulting **59** was transformed to the nitrile **61** by our newly developed method, treatment of aldehyde **59** with hydroxylamine followed by dehydration with 1,1′-carbonyldiimidazole (CDI). Hydrolysis of cyanide **61** to give the amide with concomitant removal of the *N*-Boc group was followed by *N*-dimethylation to produce **62**. De-*O*-methylation gave anhydrotetracycline (**63**), which was identical with a naturally derived sample in all respects.[37] The final stage was to introduce stereoselectively the hydroxyl group into the C-6 position according to the reported procedures.[37] By

Scheme 9



Scheme 10



photooxidation of **63**, the peroxide **64** was obtained. Reduction of **64** by hydrogenolysis on Pt-black gave (−)-tetracycline (**37**), which was neutralized with HCl in MeOH to afford the hydrochloride. This was identical with the hydrochloride of natural (−)-tetracycline (**37**) in all respects, completing the first total synthesis.

3.2. Total Syntheses of Pyranonaphthoquinone Antibiotics Using Novel Strategies

Pyranonaphthoquinone antibiotics (**65**−**70**) have been shown to possess significant antimicrobial activities and potential antitumor activities.[38,39] These unique structures have drawn attention both for syntheses with developing new methodologies and for creation of novel biologically active compounds. We have already reported the first total syntheses of related antibiotics such as nanaomycin D[40] (**66**), kalafungin[41] (**67**), and medermycin[42] (**68**) (Figure 3) and developed a synthetic strategy for the stereoselective construction of densely functionalized pyranonaphthoquinones from carbohydrates.[17,18,43,44]

3.2.1. Total Syntheses of Nanaomycin D and Kalafungin: "Enantiodivergent" Total Synthesis

Carbohydrates have been used widespread as chiral sources in asymmetric syntheses of natural

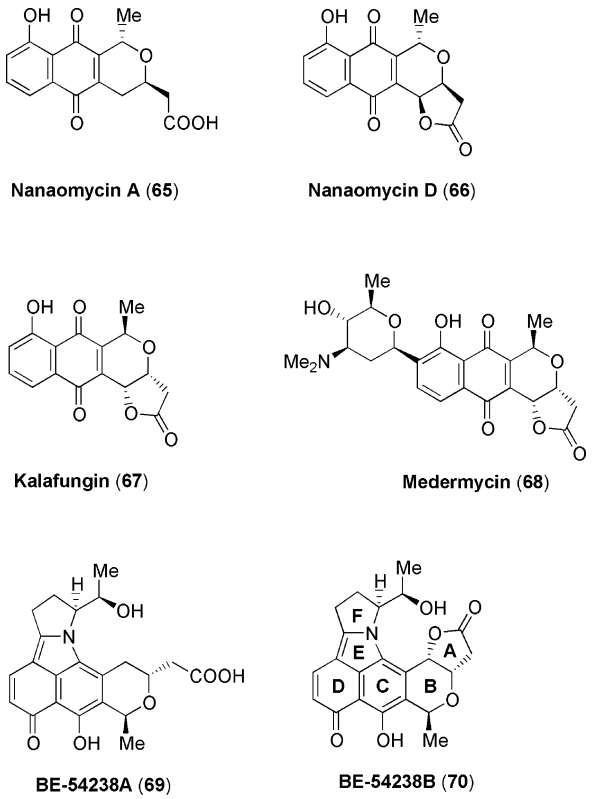


Figure 3.

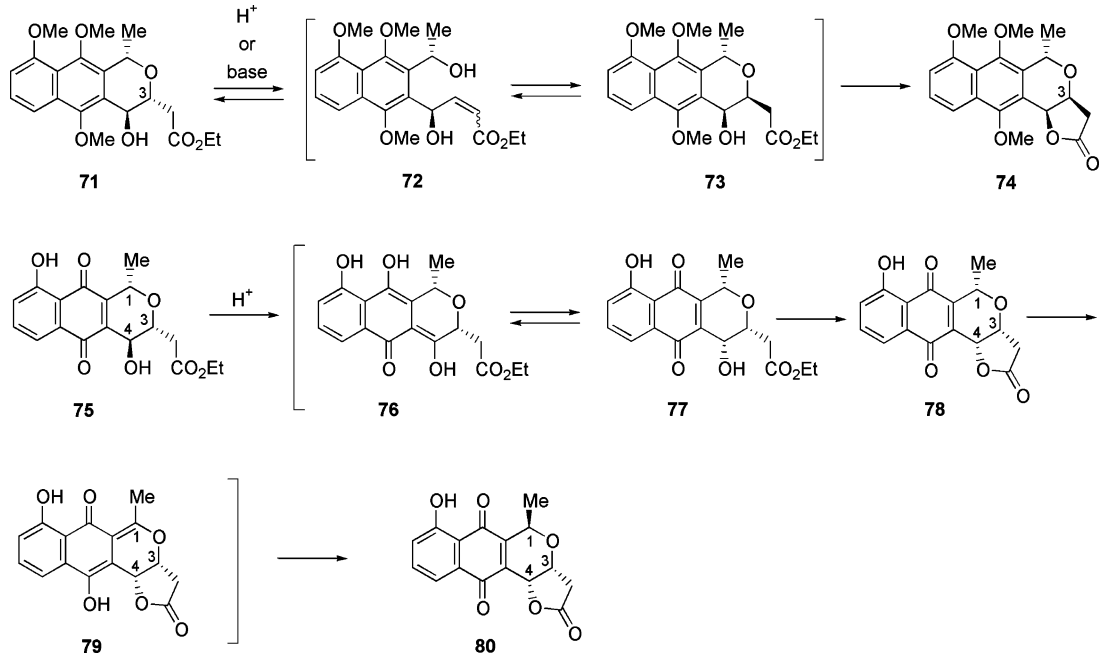
products.[45] Although various carbohydrates are available, in most of them one enantiomer is naturally abundant but another isomer is difficult to get in much quantity. Thus, it is hopeful that both enantiomeric chiral synthons in total synthesis are derived from one enantiomer of a carbohydrate.

During synthetic studies on nanaomycin D (**66**) and kalafungin (**67**), a new methodology to enable synthesis of both enantiomers from one enantiomeric carbohydrate had been developed in our laboratory, meaning "enantiodivergent synthesis".[17,46,47] The point of the methodology was catalytic isomerization of stereocenteres (Scheme 11). On the protected hydroquinone **71**, the isomerization at the C-3 position was accomplished to obtain the lactone **74** by elimination−recyclization equilibrium under the basic conditions. On the other hand, on the quinone **75**, the isomerization at C-1 and C-4 positions was realized to afford the lactone **80** by enolization−protonation equilibrium under the acidic conditions. This methodology was widely applied to the construction of pyranonaphthoquinone antibiotics.

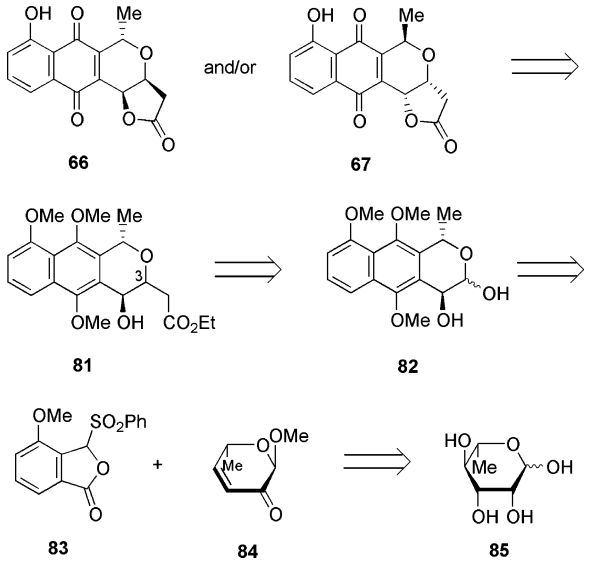
On the basis of this methodology, the retrosynthetic analysis for **66** and **67** has been suggested, as shown in Scheme 12. The substrate **81** for enantiodivergent synthesis would be obtained by Wittig reaction with lactol **82**. The pyranonaphthalene skeleton of **82** might be synthesized by tandem Michael−Dieckmann reaction to connect lactone **83**[48] and enone **84**.[49] The chiral enone **84** would be derived from commercially available L-rhamnose **85**.

Actually, the enantiodivergent synthesis of nanaomycin D and kalafungin based on this strategy is shown in Scheme 13. Methyl L-rhamnoside **86** was converted into the methyl 2,3-di-*O*-carboxyl-6-deoxy-4-*O*-tosylmannose **87** in 80% overall yield in a one-pot reaction with trichloromethyl chloroformate and then tosyl chloride in pyridine. Treatment of **87** with zinc powder and sodium iodide in reflux aqueous acetonitrile gave the unsaturated alcohol **88**.[50] Oxidation of **88** with pyridinium chlorocromate afforded the stable α,β-unsaturated ketone **84**. Michael−Dieckmann condensation of **84** with 4-methoxy-3-(phenylsulfonyl)-1(*3H*)-isobenzofuranone **83** prepared by Hauser's procedure[48] gave naphthopyranone **89**, which was transformed to lactol **82** in three steps. The lactol **82** was submitted to Wittig reaction, which afforded the lactone **74** and the hydroxyl ester **90**.[51] The lactone **74** was oxidized

Scheme 11



Scheme 12



to the quinone **91**, which was de-*O*-methylated to give **66**. On the other hand, the hydroxyl ester **90** was converted to the quinone **75**, which was subjected to acidic isomerization to produce **67**, the enantiomer of **66**.

Epimerization by *retro*-Michael and Michael reactions also proceeded under the acidic conditions, which was shown in the total synthesis of medermycin (**68**, Scheme 14).[18] It is quite interesting that the hydroquinone **92** was epimerized at C-3 to produce **93** by *retro*-Michael and Michael reactions without epimerization at any other positions, whereas quinone **75** was epimerized at C-1 and C-4 positions by enolization without C-3 epimerization.

3.2.2. Total Synthesis of BE-54238B: Iminoquinone Isomerization

Pyranonaphthoquinone antibiotics, BE-54238A (**69**) and -B (**70**), were isolated by the Banyu group from he culture broth of *Streptomyces* sp. A54238 to show antitumor activities.[52] The absolute structure of **70** was determined by NMR studies and X-ray analysis to be a nanaomycin analogue fused with a pyrrolidine ring, and, therefore, to belong to a family of pyranonaphthoquinone antibiotics (Figure 4).

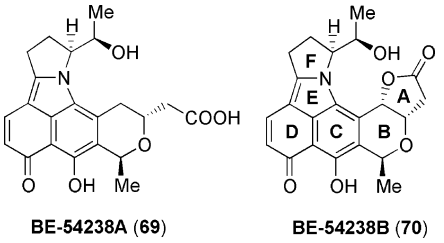
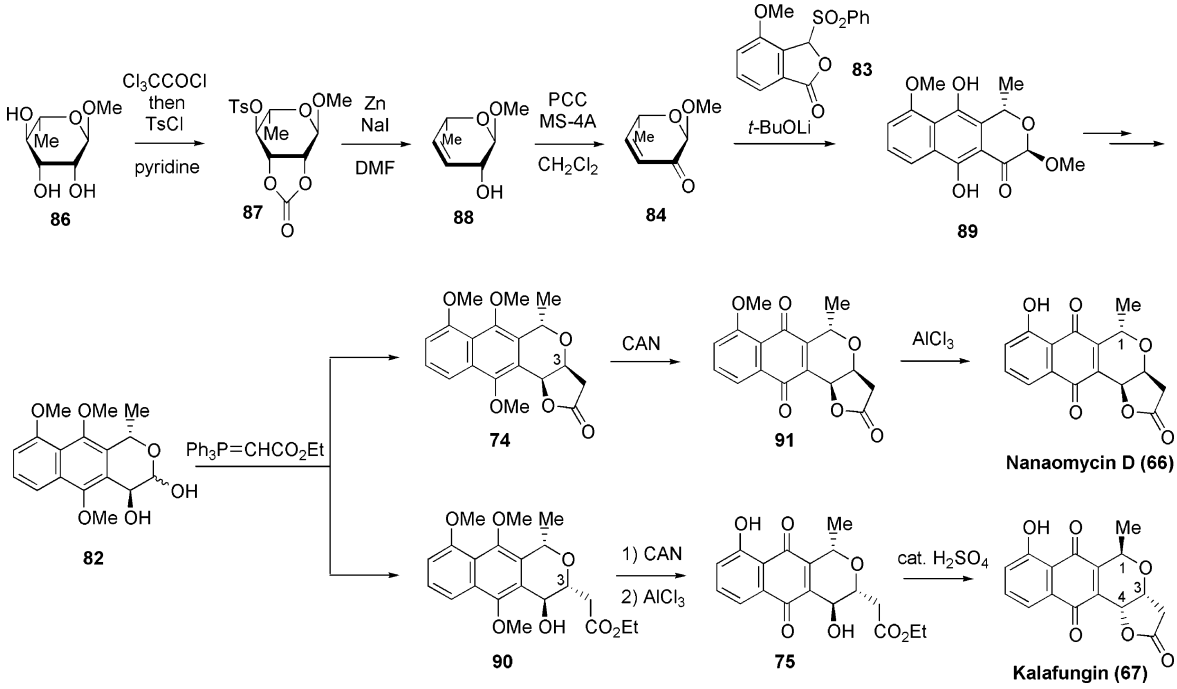
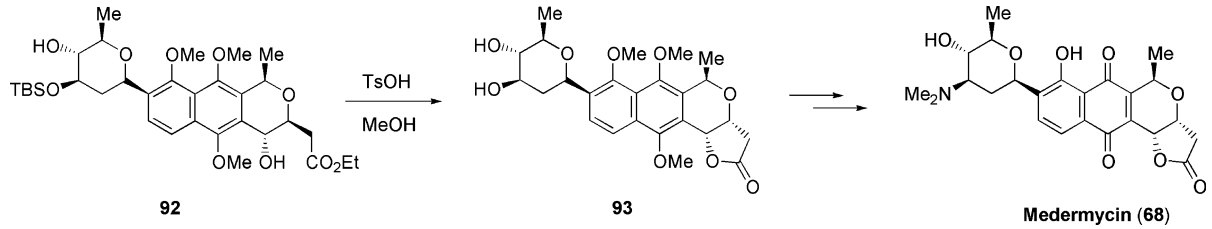


Figure 4.

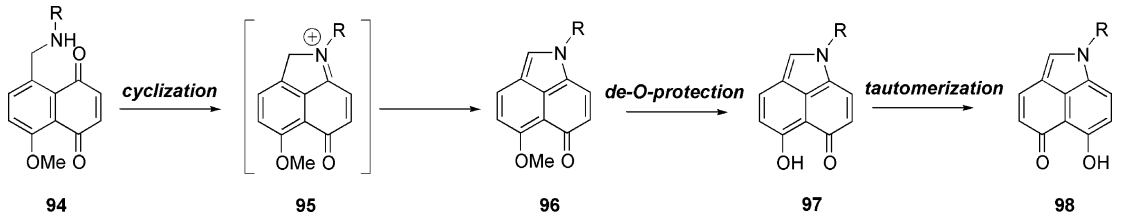
Scheme 13



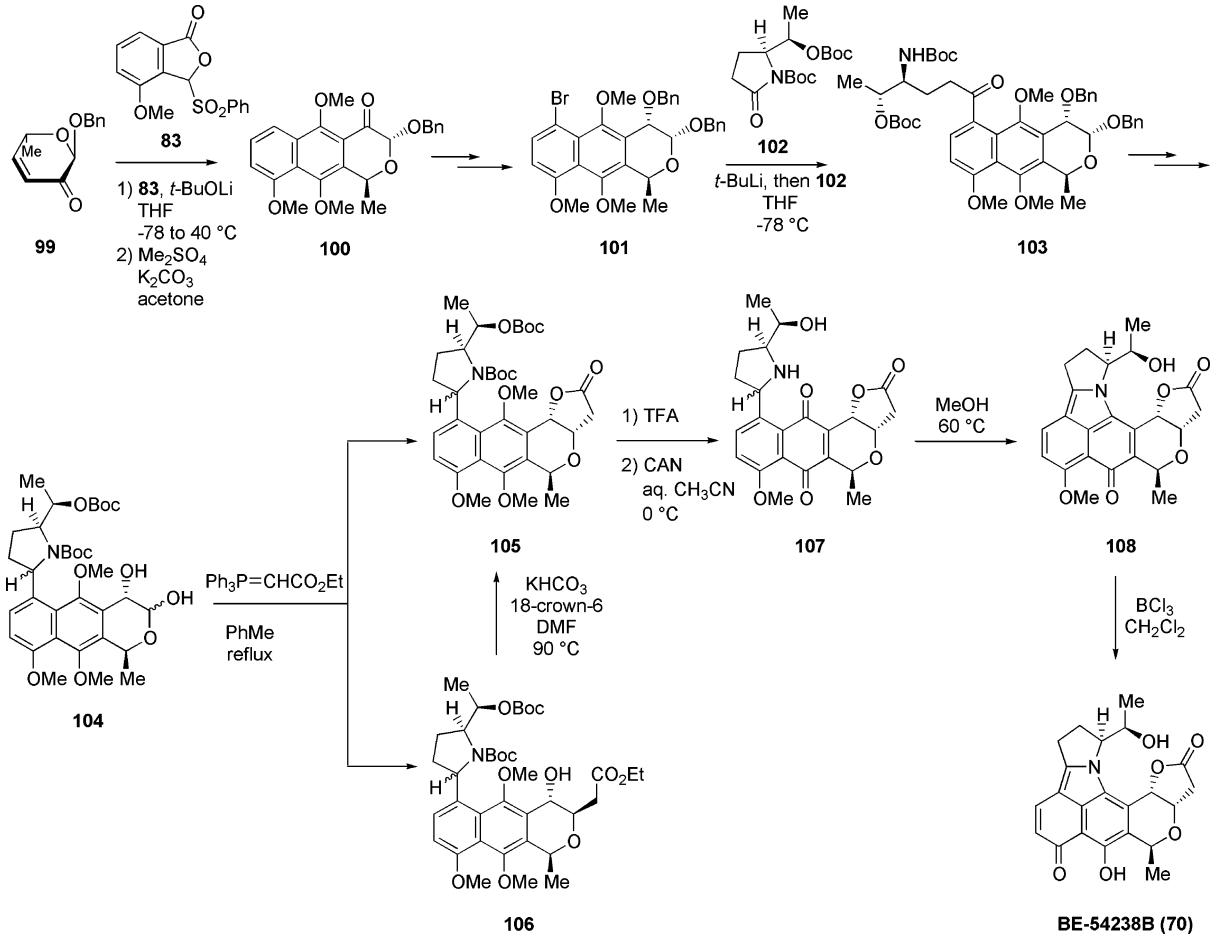
Scheme 14



Scheme 15



Scheme 16



On the total synthesis of BE-54238B (**70**), we planned the construction of the CDE ring as described in Scheme 15. Methoxy benzoquinone **94** would be cyclized to afford tricyclic **96** via imminium ion **95**. De-*O*-methylation of **96** might give **97**, which should be tautomerized to **98**.

We achieved the enantioselective total synthesis of **70** to confirm its absolute structure (Scheme 16).[24] The *O*-benzyl precursor **100** was prepared according to our reported procedures from the enone **99** and lactone **83**,[17] which were derived from L-rhamnose and *m*-methoxybenzoyl chloride, respectively. Pyranohydronaphthoquinone **100** was converted to the bromide **101**, which was lithiated to couple with L-pyrrogultamic acid derivative **102** to obtain the ketone **103**. After construction of pyrrolidine **104**, Wittig reaction gave the lactone **105** and hydroxyl ester **106**, in 67 and 22% yields, respectively. The lactone **105** was suitable for the synthesis of the natural product **70**, while the hydroxyl ester **106** was transformed to **105** in high yield by heating with $KHCO_3$ and 18-crown-6 in dimethylformamide (DMF). Acidic removal of two Boc groups in **105** was followed by oxidative de-*O*-methylation to give the quinone **107**. This was effectively cyclized to **108** as expected above. Compound **108** was de-*O*-methylated by BCl_3 to give the tautomerized compound **70** as a hydrochloride salt, which was identical in all respects with the salt of the natural BE-54238B (**70**).

Therefore, the efficient route to pyranonaphthoquinone antibiotics was established: (1) the pyran moiety possessing stereocenters is derived from commercially available carbohydrates, (2) the pyranonaphthalene skeleton is constructed by tandem Michael−Dieckmann type reaction, and (3) the final step is elaboration of stereocenters and the oxidation state.

These syntheses of pyranonaphthoquinone antibiotics show the power of the enantiodivergent synthesis to construct any arrangement of stereocenters from an abundant carbohydrate.

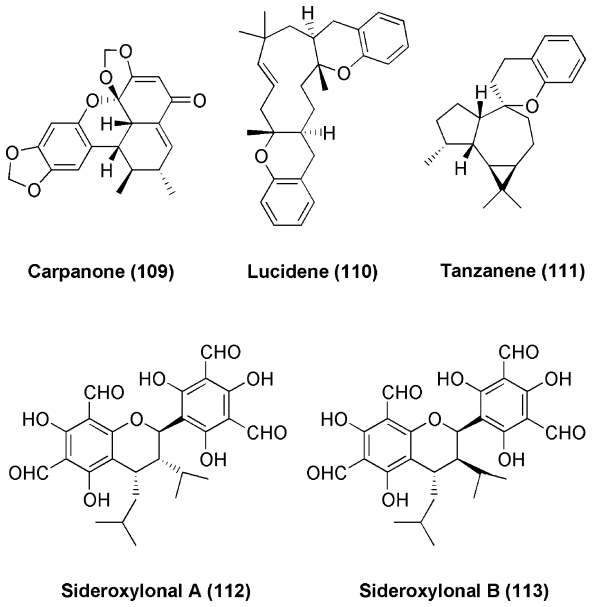


Figure 5.

3.3. Total Synthesis of Sideroxylonal: "Self-Divergently Assembled" [4 + 2] Cycloaddition of *o*-Quinone Methide

3.3.1. o-Quinone Methide in Natural Product Syntheses

Benzopyran skeletons are frequently found in natural products. Some of them including those in Figure 5 are considered to be produced with *o*-quinone methide, as shown in Scheme 17.[53] Despite its potential in the synthesis of a diverse range of natural products, only a few syntheses have employed *o*-quinone methide. Many methods to generate this highly reactive species have been developed; however, most of them include severe conditions.[53]

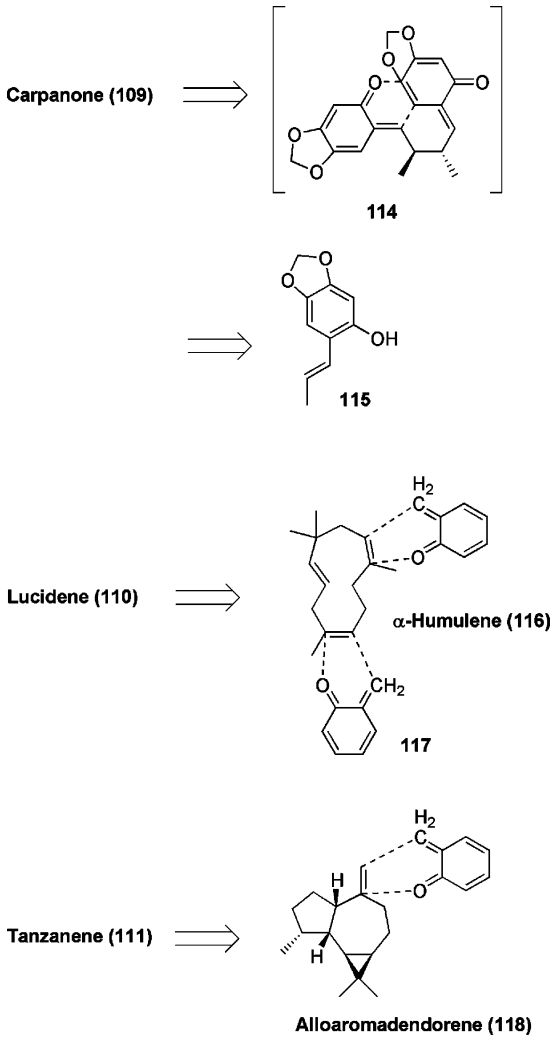
The early and impressive synthesis using *o*-quinone methide is Chapman's synthesis of carpanone (**109**),[54] which was realized by oxidative dimerization of **115** (Scheme 17). Recently, lucidene (**110**) and tanzanene (**111**) were synthesized by coupling of *o*-quinone methide (**117**) with α-humulene (**116**) and alloaromadendorane (**118**), respectively.[55,56]

3.3.2. First Total Synthesis of Sideroxylonal B

Sideroxylonals A (**112**) and B (**113**) are racemic flavanoid components isolated from extracts of *Eucalyptus sideroxylon*, which show biological activities against gram-positive bacteria, HeLa S-3 cells, and aldose reductase and inhibit attachment of blue mussels.[57] These structures were established by spectroscopic analysis to have a fully functionalized 2-phenyl-1-benzopyran skeleton as a common core (Figure 5). Biogenetically, these compounds apparently are formed from isopentenyl phloroglucinol precursors by a hetero-Diels–Alder coupling process.[58]

The first total synthesis of **113** was accomplished in our laboratory (Scheme 18).[59] The critical element in the design of the synthetic plan was inspired by the proposed biosynthetic sequence as shown in the retrosynthetic sequence to assemble the 2-phenyl-1-benzopyran skeleton, which was obtained from the isopentenyl phloroglucinol precursor **123** through

Scheme 17

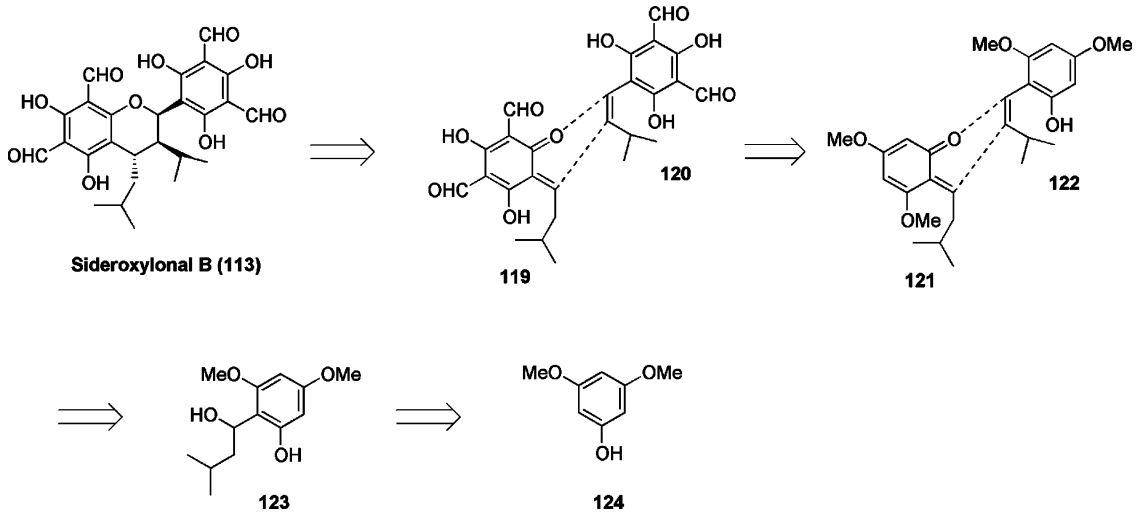


self-divergently assembled cycloaddition of the *o*-quinone methide **121** and the isopentenyl intermediates **122**.

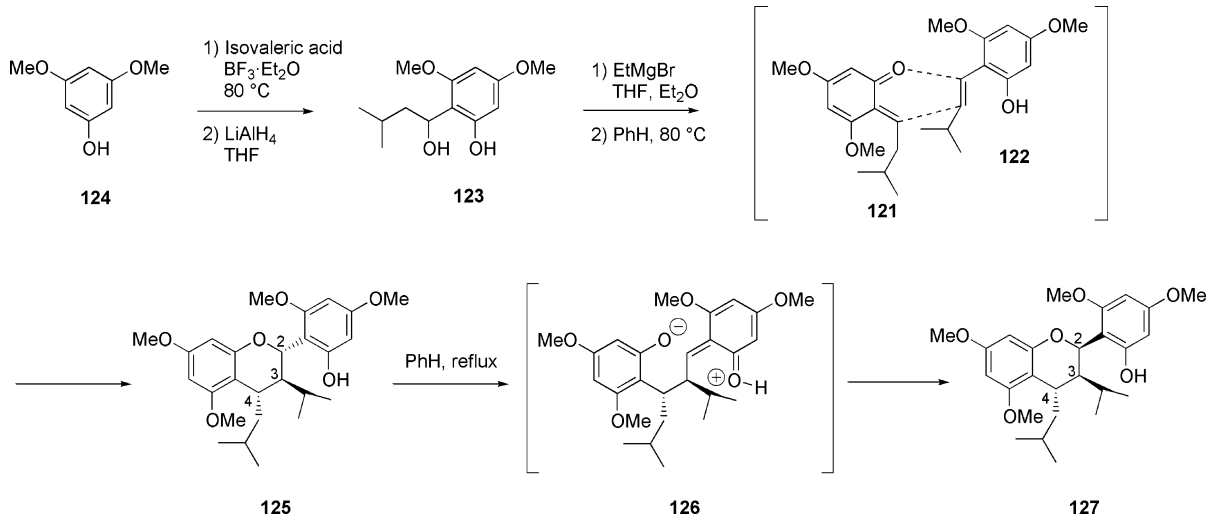
The synthesis of the core structure was constructed along this route (Scheme 19). The key intermediate **123** was prepared from 3,5-dimethoxyphenol (**124**). Reaction of **124** with isovaleric acid in the presence of $BF_3 \cdot Et_2O$ gave the ketone, which was reduced to the alcohol **123**. The hetero-Diels–Alder reaction was realized by treatment of **123** with EtMgBr[60] to give simultaneously the *o*-quinone methide **121** and the isopentenyl derivative **122** in situ, a mixture of which was submitted to the cycloaddition in question. The all-*trans*-isomer **125** was obtained as a major adduct in 78% yield as expected by the predicted transition state in Scheme 19. On the other hand, longer refluxing time (29 h) afforded the 2,3-*cis*-isomer **127** as a major product in 74% yield. This result indicated that the 2,3-trans isomer **125** was thermodynamically changed to the *cis*-isomer **127** through pyran ring-opening and -closing process[61] as shown in Scheme 19. Generation of the *o*-quinone methide intermediate **126** was the key of this process, tandem *retro*-Michael–Michael cyclization.

Accomplishment of the total synthesis is shown in Scheme 20. *O*-Methylation of **127** to give the fully protected compound **128** was followed by bromina-

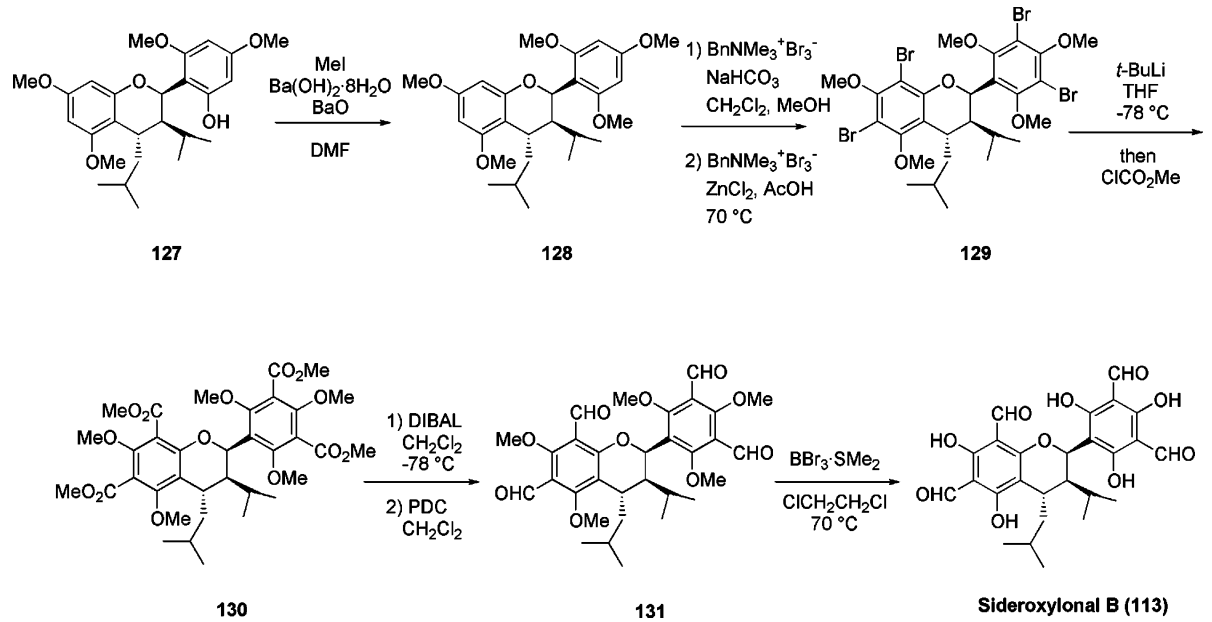
Scheme 18



Scheme 19



Scheme 20



tion[62] to obtain tetrabromide **129**. Lithiation of **129** with *t*-BuLi followed by treatment with methyl chloroformate afforded the methyl ester **130**. The ester **130** was submitted to hydride reduction with diisobutylaluminum hydride (DIBAL) to give the tetraol, which was oxidized with PDC to provide the aldehyde

131. De-*O*-methylation was effectively achieved with $BBr_3 \cdot SMe_2$ to give sideroxylonal B (**113**).

3.4. Total Synthesis of Lymphostin: Nitrogen Substitution of Quinones

Polycyclic heteroaromatic compounds have been studied as both synthetic targets to develop new methodologies and biological activities to discover new drugs. Recently, lymphostin (**132**)[63] and plakinidine (**133**)[64] have been isolated as significant bioactive compounds, possessing interesting structures with multi-heteroaromatic rings containing a tetranitrogen-substituted benzene ring (Figure 6).

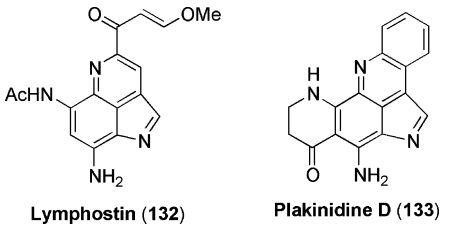


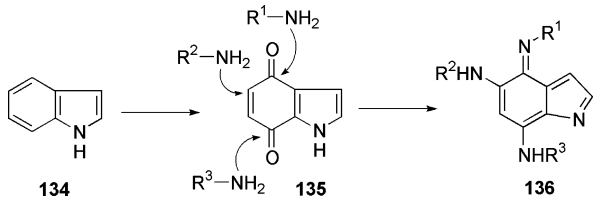
Figure 6.

Until our first total synthesis of lymphostin,[65] there had been no examples to synthesize such structures.

Lymphostin (**132**) was isolated by the Kyowa Hakko group from a culture broth of *Streptomyces* sp. as an immunosuppressant to show potent inhibitory activity against lymphocyte kinase. The structure was elucidated by thorough NMR studies to be a novel tricyclic aromatic alkaloid with a pyrroloquinoline skeleton (Figure 6). In addition to its novel mechanism of action, impinged on a crucial biological cascade, the structure of **132** interested us as a focused target for total synthesis.

The feature of the structure of lymphostin **132** includes a benzene ring possessing four nitrogen atoms. Our strategy for the synthesis of this structure is described in Scheme 21. The starting indole **134**

Scheme 21



would be oxidized to the indolequinone **135** which might be subjected to the nucleophilic attack of amines to give diaminopyrroloiminoquinone **136**.

The critical element of the synthetic plan was inspired by our proposed biosynthetic sequence as shown in the retrosynthetic perspective to assemble the tricyclic core **137** from the quinone **139** through cyclization and oxidation to give the intermediary iminoquinone **138** (Scheme 22).

The starting *N*-carbobenzyloxy-L-tryptophan methyl ester (**140**) was converted to the racemic ketophenol **141**,[66] which was further transformed to the indolequinone **142** (Scheme 23). Regioselective reaction of the quinone **142** with benzylamine[67] followed by oxidation to obtain aminoindolequinone **143** was achieved in one pot by exposure of **142** to benzylamine under air at room temperature. Hydrogenolysis of **143** afforded the diamino derivative **139**. This was cyclized concomitant with aromatization by heating in DMF with air followed by acetylation to give the desired iminoquinone **138**.[68] The transformation of the iminoquinone **138** to the diaminopyrroloquinone **145** was realized by the introduction of an azido group and subsequent reduction. Treatment of **138** with Tf_2O followed by n-Bu_4NN_3 afforded the tautomerized azide **137**. **137** was reduced on the Lindlar catalyst and protected by an *o*-nitrobenzenesulfonyl (Ns) group[69] to afford **145**. Manipulation of **145** to construct the side chain and removal of Ns group gave lymphostin **132**.

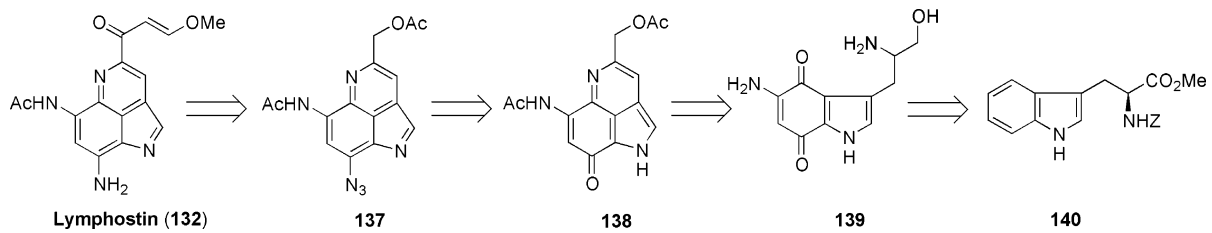
4. Total Syntheses of Nitrogen-Containing Polyhydroxy Compounds: Skeletal Rearrangement of Glycosamines

A variety of carbohydrates have been used for stereospecific syntheses of natural products as chiral sources.[1,46,70] However, little has been reported using amino sugars,[71] because of their scanty derivatives. The methodology to use glycosamine such as D-glucosamine **150** would enable construction of nitrogen-containing polyhydroxy compounds frequently seen in natural products (Figure 7). The utility of glycosamines in syntheses of optically active compounds has been developed in our laboratory.[72,73] Herein, we describe the novel methodology to use amino sugars, which includes the specific reaction of glycosamines.

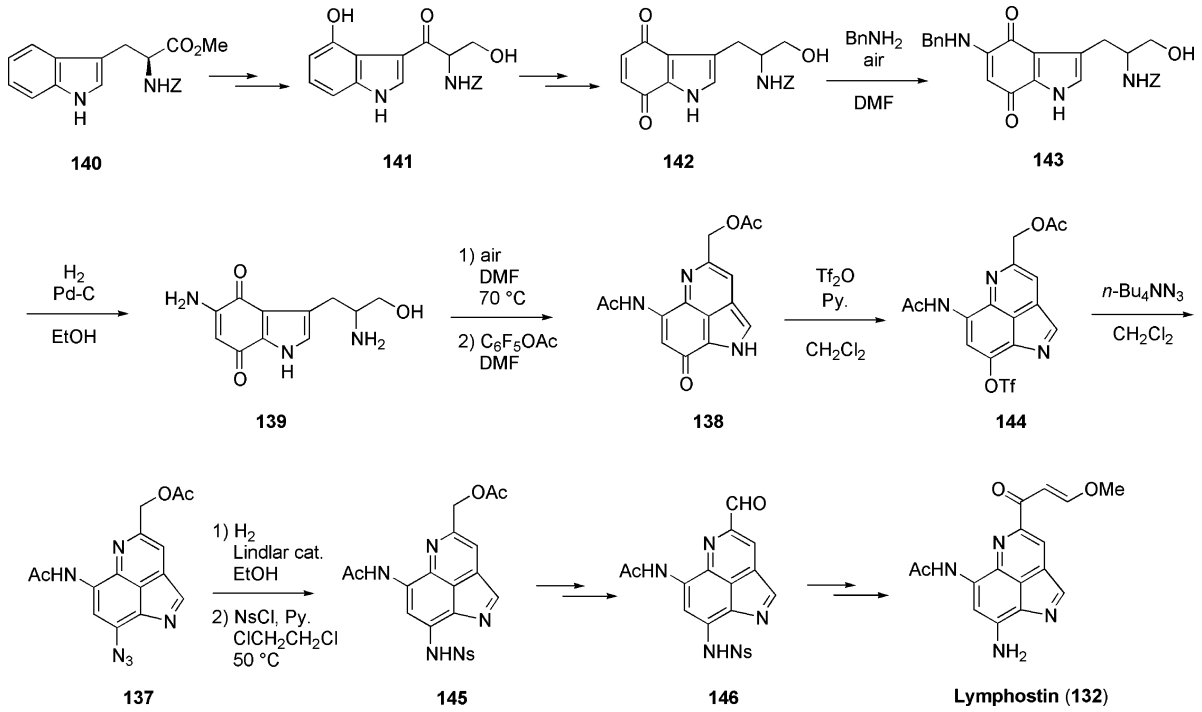
4.1. Novel Rearrangement with Ring Contraction of Glycosamines

The key reaction of our methodology includes a rearrangement of cyclic disulfonate derivative of glycosamines (Scheme 24).[72] The starting methyl α-D-glucosaminide **151** reacted with **152** to give exclusively cyclic sulfonate **153**. Compound **153** was subjected to rearrangement to produce [3,0,3]-bicylic compound **156** via 5 membered ring **155**. The N−S bond of **156** was cleaved by the Birch reduction to

Scheme 22



Scheme 23



give free amine **157**, which was protected by selective acylation. The bicyclic **158** possesses protected amine and four oxygen-attached carbons which are different from each other. Therefore, **158** is able to be converted to a variety of structures.

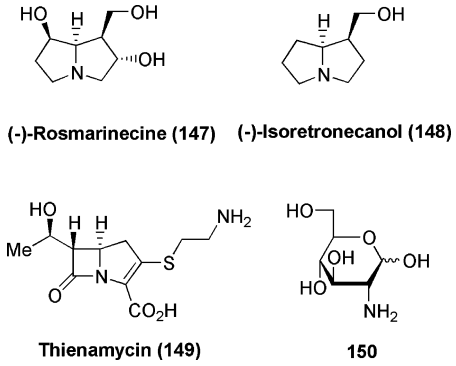


Figure 7.

4.2. Stereoselective Total Synthesis of (−)-Rosmarinecine

The pyrrolizidine alkaloids, which occur naturally in various plant species, have drawn attention for syntheses because of their structure and biological properties. Until total syntheses of (−)-rosmarinecine (**147**) and (−)-isoretronecanol (**148**, Figure 7) in our laboratory,[73] there had not been reported on completely stereoselective syntheses of optically active pyrrolizidine alkaloids.[74−76] The stereoselective synthesis of (−)-rosmarinecine is summarized in Scheme 25.

The sulfonate **156** was converted to the triol **159**, which contained already felicitously placed functional groups and an anomeric carbon of potential value for the stereoselective introduction of hydroxyl groups and a carbon chain. Silylation to protect primary alcohols of **159** gave the corresponding disilyl furanoside, which was submitted to Grignard reaction with allylmagnesium bromide in ether to afford the single *threo* amimo alcohol **170** by chelation control approach.[77] Further manipulation of **170** gave the ester **171**, which was subjected to hydrogenolysis of the benzyloxycarbonyl group accompanied with cyclization to give γ-lactam and subsequent de-*O*-silylation to afford diol **172**. Selective methoxymethylation and subsequent mesylation of **172** gave the mesylate **173**. Treatment of **173** with borane−methyl sulfide[78] to give the pyrrolizidine skeleton with intramolecular S_N2 displacement of the intermediary pyrrolidine derivative, followed by cleavage of MOM protecting groups under acidic conditions, afforded (−)-rosmarinecine (**147**).

With a similar strategy, the stereoselective synthesis of (−)-isoretronecanol (**148**) was accomplished.[73]

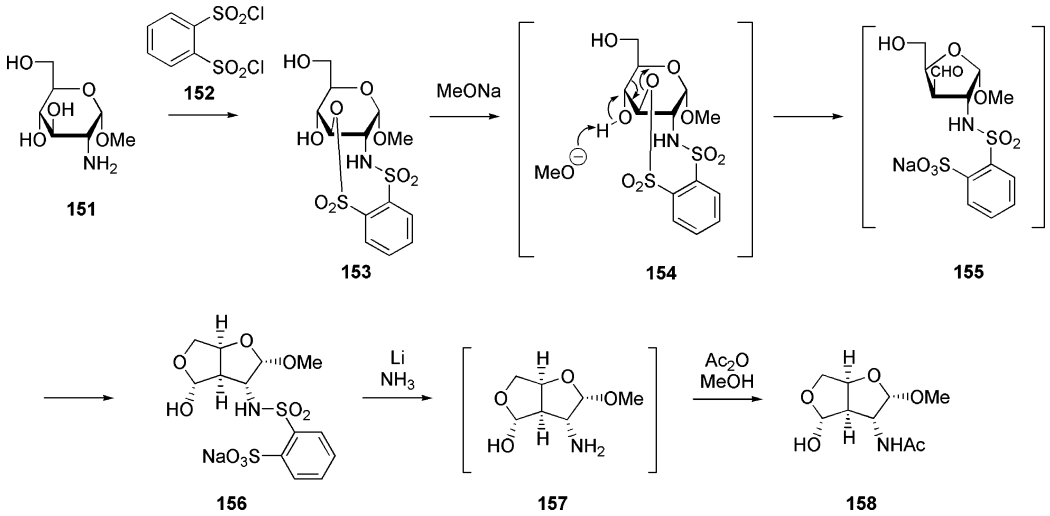
4.3. Formal Total Synthesis of (+)-Thienamycin

The molecular architecture associated with the β-lactam antibiotics has posed some of the greatest challenges in synthetic chemistry, and this family has provided the stimulus for the development of the methodology for the construction of their skeletons and side chains.

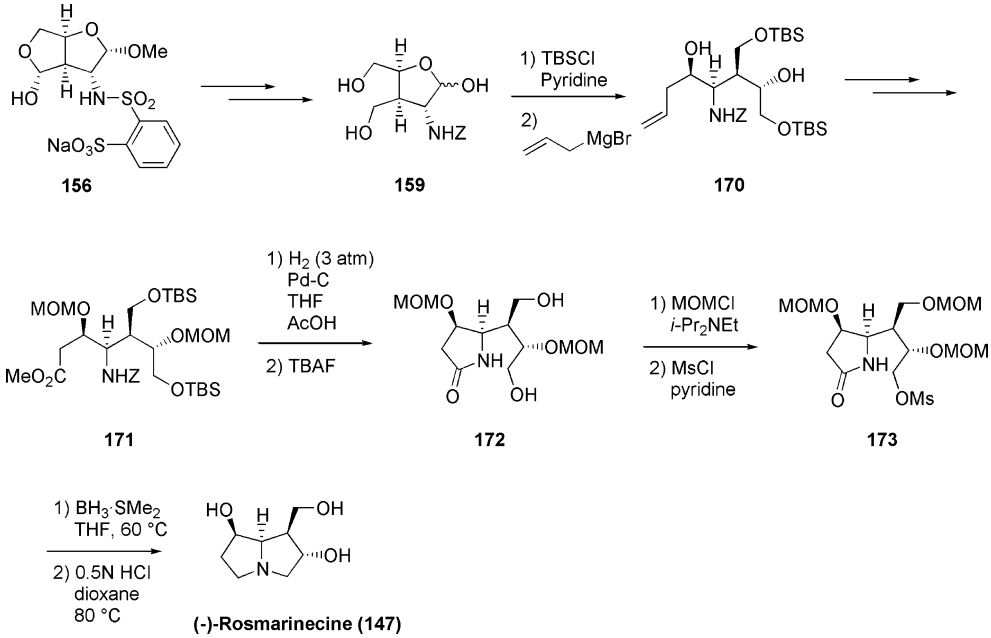
(+)-Thienamycin (**149**) was discovered in fermentation broth of *Streptomyces cattleya* to show exceptional antibacterial potency and spectrum.[79] The first stereocontrolled synthesis of **149** has been reported by the Merck group,[80] and the transformation of (+)-4-acetoxy-3-hydroxy-2-azetidinone (**174**) to (+)-thienamycin (**149**) was also made more attractive by another Merck group (Figure 8).[81] Consequently, the synthesis of (**174**) constitutes a formal total synthesis of (+)-thienamycin (**149**).

(+)-4-Acetoxy-3-hydroxy-2-azetidinone (**174**) and its derivatives have been well-known as the highly

Scheme 24



Scheme 25



versatile intermediates[82] for the synthesis of carbapenem antibiotics such as thienamycin (**149**),[79] imipenem, meropenem,[83] and so on.

The synthesis of **174** was initiated by the Sankyo group,[84] followed by the Merck group,[85] and culminated in the practical preparation by two Japanese companies[86] using Noyori-Murahashi's asymmetric procedures and chem-enzymatic procedures, respectively.

Herein is described our enantiospecific synthesis of **174** from a carbohydrate through a skeletal rearrangement and stereoselective epimerization.[87] The starting material is commercially available methyl

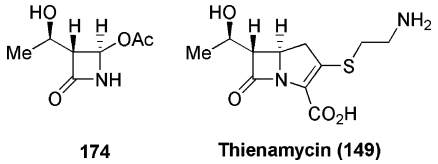


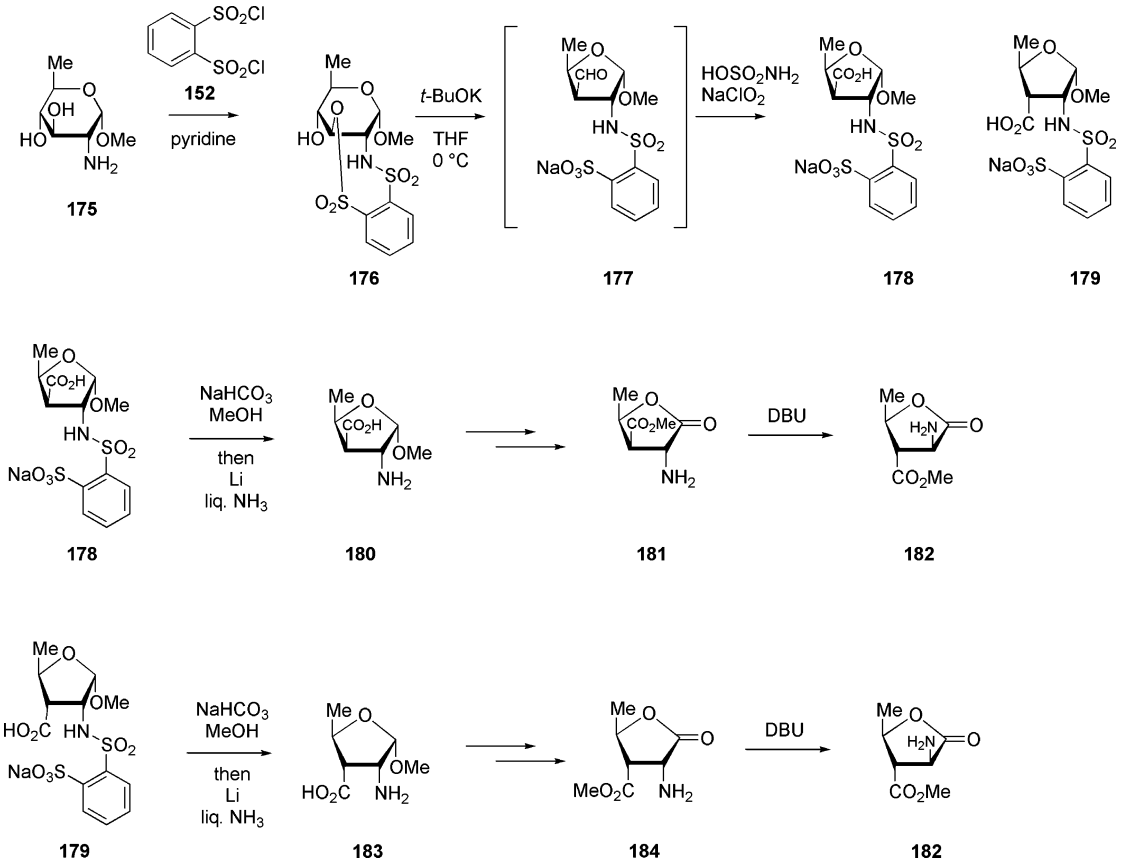
Figure 8.

2-amino-2,6-dideoxy-α-D-glucopyranoside (**175**), which has been also isolated from natural sources. [88]

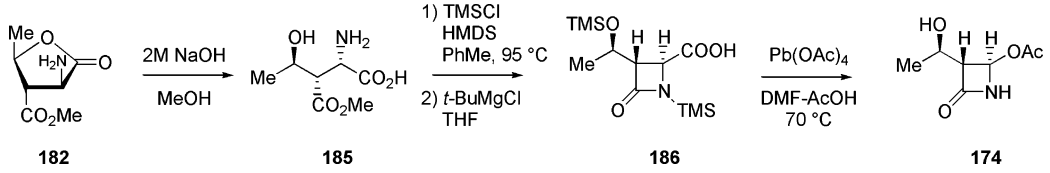
Reaction of **175** with *o*-benzenedisulfonyl dichloride (**152**) gave the cyclic sulfate **176**, which was submitted to the rearrangement with potassium *tert*-butoxide. The ring contraction reaction was quenched immediately after disappearance of **176**, and subsequent oxidation gave carboxylic acid **178** predominantly. The very minor product **179**, which increased prolonged reaction time of rearrangement, was readily separated by silica gel column chromatography. Practically, both compounds could be used for the synthesis without separation, because they were found to be efficiently converted to a single lactone **182** by stereoselective epimerization later on. However, the synthesis from each of the two compounds **178** and **179** is described as follows (Scheme 26).

Removal of the *N*-sulfonyl group of **178** by Birch reduction produced the corresponding amino acid **180** in 92% yield. This was transformed to the lactone **181**, which was submitted to epimerization at C2 and

Scheme 26



Scheme 27



C3 positions, one of the key operations of this synthesis. After a variety of conditions had been examined, the best result was realized by using DBU in MeOH at room temperature to afford predominantly the desired amino ester **182**. Similarly, the epimer **179** was transformed to **182** through **183** and **184** in 57% overall yield. These results indicated that the C4 configuration of **181** or **184** controlled the stereoselective construction of the C2 and C3 configurations of **182** through the cis repulsions.

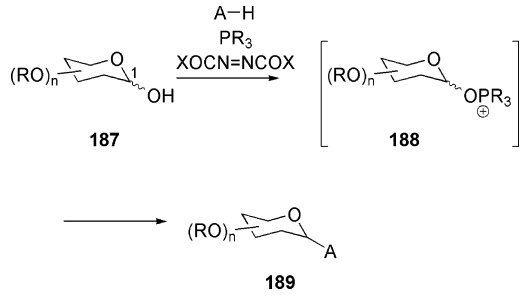
The resulting amino ester **182** was transformed to (+)-4-acetoxy-3-hydroxy-2-azetidinone (**174**), as shown in Scheme 27. Hydrolysis of **182** according to the reported procedures[89] led to the hydroxyl acid **185**, which was in turn submitted to the β-lactam formation. For our purpose, a Grignard-mediated cyclization of the silylated derivative seemed most promising.[90] Thus, **185** was silylated with trimethylsilyl chloride and hexamethyldisilazane (HMDS), and subsequent treatment with *tert*-butylmagnesium chloride gave the bis-silylated β-lactam **186**. Oxidative decarboxylation[81] of **186** gave exclusively the desired (+)-4-acetoxy-3-hydroxy-2-azetidinone (**174**) with removal of trimethylsilyl groups. Overall, the yield was approximately 32% in 12 steps from **175**.

Utility of amino sugars in syntheses of optically active compounds has been expanded as above. The rearrangement with ring contraction gave useful intermediary *N*-sulfonylamino aldehydes such as **155** and **177**, which are ready to be converted to various formations and configurations by manipulation including oxidation, reduction, and epimerization.

5. Total Synthesis Using Glycosylation under Mitsunobu Conditions

There have been created a number of glycosylation reactions and various activated sugars have been used to the syntheses of natural products. We have developed novel glycosylation methodologies,[91,92] and found that Mitsunobu conditions were quite effective for direct coupling of a C-1 (anomeric) hydroxyl group and an aglycon (A−H) possessing an acidic proton (Scheme 28).[93] Recently, Mukaiyama has established a novel glycosylation using sugars activated as phosphonium ion intermediate, which is produced in situ from glycosyl phosphinite,[94] bromide,[95] or acetate.[96] On the other hand, our methodology is so convenient that coupling can be accomplished in one pot with an unactivated sugar and suitable to use the aglycone possessing acidic proton (Scheme 28). Herein, we

Scheme 28



describe application of this methodology to syntheses of natural products.

5.1. Total Synthesis of Pyralomicin 2c

Pyralomicin 2c (**193**) has been isolated from the culture broth of *Microtetraspora spiralis* as novel antibiotics.[97] We synthesized pyralomicin 2c (**193**) to confirm the absolute structure (Scheme 29).[93] The aglycone, pyralomicinone (**190**), possesses the 5-hydroxy[1]benzopyrano[2,3-*b*]pyrrol-4-(1*H*)-one structure in which the proton on pyrrole nitrogen is slightly acidic. Thus, Mitsunobu conditions would be suitable to the glycosylation step. Coupling of **190** with **191** [a mixture of α- and *β*-anomers (approximately 1:1)] was accomplished to give predominantly the desired *N*-*β*-glucoside **192**, which was submitted to methanolysis to produce pyralomicin 2c (**193**). The synthetic product **193** was identical with the natural product in all respects, including optical rotation; thus, the first synthesis and determination of the absolute structure have been completed.

5.2. Total Synthesis of the Ellagic Acid Derivative

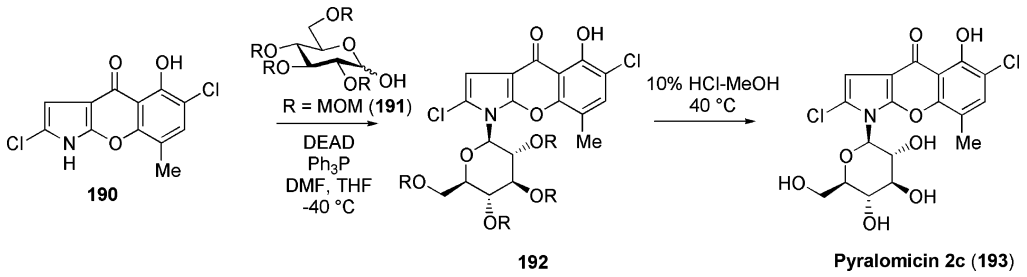
Ellagic acid glycosides show a variety of bioactivity, and a number of ellagic acid glycosides have been isolated so far. However, their syntheses have not been reported because of the difficulties with *O*-glycosylation.

Recently, 4-(4″-*O*-acetyl-α-L-rhamnopyranosyl)ellagic acid (**197**) was isolated from the branches of *Combretum yunnanensts* to show inhibitory activity on HIV protease and growth inhibitory activity toward tumor cells including adriamycin-resistant cells.[98] We attempted the synthesis of **197** to confirm its structure, including the absolute configurations as follows (Scheme 30).[99] The starting material, 3,3′-di-*O*-benzylellagic acid (**194**), was derived from ellagic acid in four steps according to the reported procedures.[100,101] Another starting material, 4-*O*-acetyl-2,3-di-*O*-benzyl-L-rhamnose (**195**), was selectively synthesized from L-rhamnose according to Koto's procedure.[102] Although the glycosylation of **194** with **195** was attempted under various known conditions,[91] the corresponding rhamnoside **196** was not produced in a good yield. The best result was obtained by our developed method using Tsunoda's conditions (tri-*n*-butylphosphine and *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide)[103,104] to give exclusively the desired α-rhamnoside **196** in 64% yield. The α-rhamnoside was expected to be preferentially produced, because the formation of *β*-rhamnoside was well-known to be restricted by the instability factor due to the 1,2-cis configuration in the transition state. Debenzylation of **196** gave **197**, which was identical in all respects with the natural product, confirming the absolute structure.

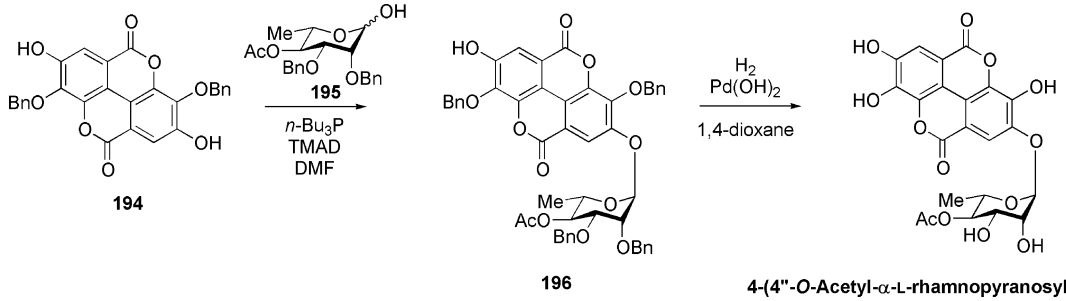
5.3. Synthesis of (*O*-Glycosyl)hydroxyamine Derivatives

The introduction of *N*-hydroxyphthalimide to the pyranose derivatives under the Mitsunobu conditions had been accomplished by Nicolaou group in total synthesis of calicheamicin *γ*.[105,106] They observed inversion of stereochemistry at the anomeric position and concluded that under their conditions (in THF, ambient temperature, 30 min.) *the intermediate*

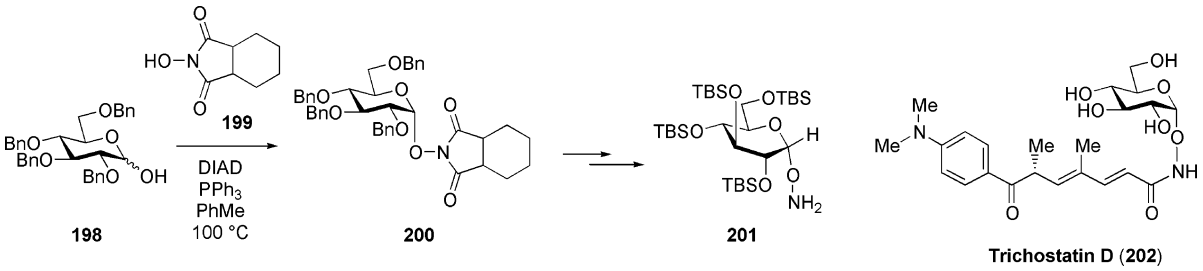
Scheme 29



Scheme 30



Scheme 31



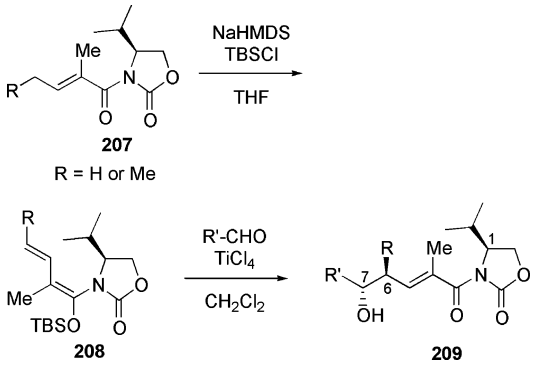
phosphonium ion did not dissociate to form an oxionium ion prior to attack by the nucleophile.[105] In our total synthesis of trichostatin D (**202**),[107] synthesis of *O*-glucosylhydroxyamine (**201**) had been achieved from the mixture of anomers in which the major one possessed the α hydroxy group (Scheme 31).

Treatment of the suitably protected D-glucose **198** (α:β = 2:1) and hydroxyimide **199**[108] with diisopropyl azodicarboxylate and triphenylphosphine at 100 °C in toluene gave the *O*-glucosylhydroxyamines in 83% yield with α:β = 5:1 selectivity. After isolation of α-anomer **200** by silica gel column chromatography, de-*O*-benzylation followed by subsequent silylation and de-*N*-protection gave the *O*-glucosylhydroxyamine **201**.

6. Total Synthesis Using Stereoselective Vinylogous Mukaiyama Aldol Reaction

There have been discovered various acyclic polyketides as bioactive molecules and have been developed a number of methodologies of stereoselective construction of polyketide skeletons.[1,109] Although such endeavors enable synthesis of a variety of arrangements of functions and stereocenters, it still remains a problem to construct a multifunctional unit possessing some stereocenters in short steps with high stereoselectivity. The structure analogous to **203** is frequently seen as a functional component in many kinds of polyketide compounds.[110] Figure 9 shows some bioactive polyketides including trichostatin D (**202**),[111] rasfonin (**204**),[112] TMC-151C (**205**),[113] and khafrefungin (**206**).[114] Recently, we have developed a novel methodology to construct the unit **203** in high stereoselectivity from a simple starting material **207** (Scheme 32).[115]

Scheme 32



6.1. Remote Stereoinduction Using Stereoselective Vinylogous Mukaiyama Aldol Reaction

In contrast to the methods of controlling acyclic stereochemistry at sites in close proximity to one another,[109] there are a few precedents for C−C bond formation with such a high degree of remote asymmetric induction in an acyclic system.[116,117,118] Herein, we describe the stereoselective vinylogous Mukaiyama aldol reaction[119,120] using the vinylketene silyl *N,O*-acetals, which provides a efficient and hitherto

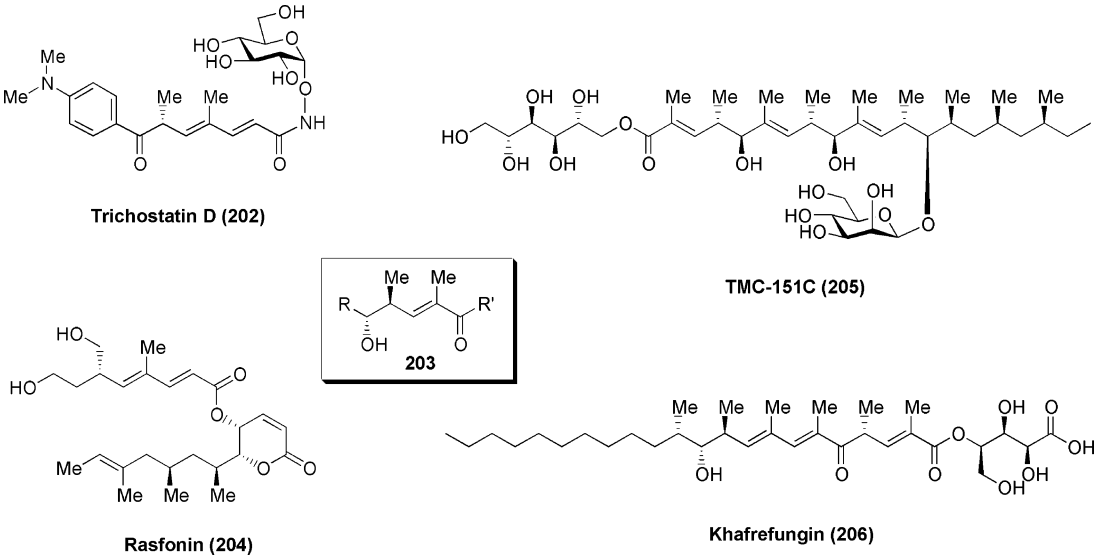
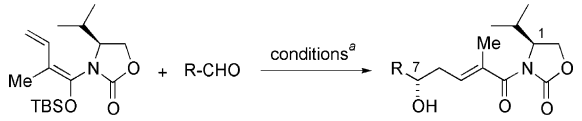


Figure 9.

unprecedented high degree of remote (1,7- and 1,6,7-) asymmetric induction.[115]

Table 1 summarizes the results of 1,7-stereoinduction of the vinylketene silyl *N,O*-acetal **210** by vinylogous Mukaiyama aldol reaction with typical aldehydes. Excellent diastereoselectivity was achieved using aliphatic aldehydes (entries 1−3), whereas the reaction with conjugated aldehydes, such as crotonaldehyde and 2-methyl-2-pentenal, gave moderate yield and high selectivity (entries 4 and 5).

Table 1. 1,7-Stereoinduction with Vinylketene Silyl *N,O*-Acetal 210



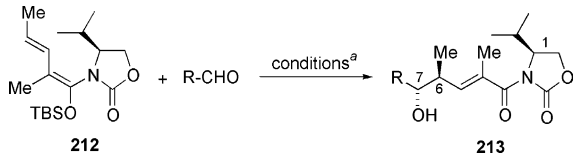
210 **211**

entry	R	Yield (%)	ds[c]
1	$CH_3(CH_2)_4$	97	42:1
2	$CH_3(CH_2)_{10}$	92	94:1
3	$(CH_3)_2CH$	95	40:1
4	$(E)CH_3CH{=}CH$	54 (87[b])	20:1
5	$(E)CH_3CH_2CH{=}C(CH_3)$	55 (65[b])	86:1
6	Ph	94	30:1

[a] 1.0 equiv of $TiCl_4$, 2.0 equiv of aldehyde, 1.0 equiv of **210**, 0.1 M in CH_2Cl_2, −78 °C. [b] Conversion yield. [c] Determined by HPLC analysis.

1,6,7-Stereocontrolled reaction was also examined with the vinylketene silyl *N,O*-acetal **212**. Results are summarized in Table 2. The $TiCl_4$-mediated vinylogous Mukaiyama aldol reaction of **212** with isobutyraldehyde gave the aldol adduct **213** (R = $(CH_3)_2CH$) in quantitative yield as an almost single isomer (entry 2). In all cases (entries 1−4), the major isomer has *anti*-stereochemistry. The excellent stereoselectivity in this strategy with **212** is noteworthy.

Table 2. 1,6,7-Stereoinduction with Vinylketene Silyl *N,O*-Acetal 212

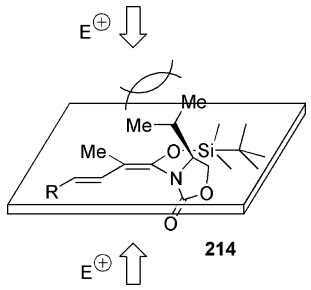


212 **213**

entry	R	temp (°C)	yield (%)	ds[c]
1	$CH_3(CH_2)_4$	−78	87	>50:1
2	$(CH_3)_2CH$	−78	99	>50:1
3	$(E)CH_3CH_2CH{=}C(CH_3)$	−78 to −40	67 (81[b])	>50:1
4	Ph	−78 to −55	90	20:1

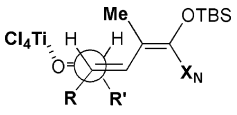
[a] 1.0 equiv of $TiCl_4$, 2.0 equiv of aldehyde, 1.0 equiv of **210**, 0.1 M in CH_2Cl_2, −78 °C. [b] Conversion yield. [c] Determined by HPLC analysis.

The methyl group at the α-position is important in achieving a high level of stereoselectivity in the present vinylogous Mukaiyama aldol reaction.[115] We propose the transition state depicted in Figures 10 and 11. It is assumed that the oxazolidin-2-one ring is almost perpendicular to the dienol ether plane and that the isopropyl group overhangs the upper face of the dienol ether.[121] The aldehyde presumably approaches from the less hindered side to give the 6*S* stereochemistry (**214**). The stereochemical behavior of **208** can be rationalized by the Newman projection models shown in Figure 11 (**215**). The aldehyde was submitted to nucleophilic attack of the silyl *N,O*-acetal from *Si* face to produce the observed stereochemistry at the C-7 position.



214

Figure 10.

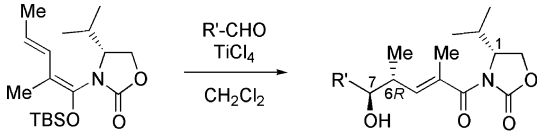


215

Figure 11.

Additionally, we investigated the origin of the stereoselectivity by X-ray crystallographic studies of the starting silyl ketene-*N,O*-acetal **216**, the enantiomer of **212** (Scheme 33, Figure 12).[107] The isopropyl group covered the β face of the dienolate and the rotation of oxazolidone was restricted by the *tert*-butyldimethylsilyl (TBS) group and the dienolate chain. It is quite reasonable that in the solution the dienolate **216** would take a conformation similar to **218** at low temperature and be submitted to attack of an electrophile from the α face to afford the 6*R* configuration (Figures 13 and 14).

Scheme 33



216 **217**

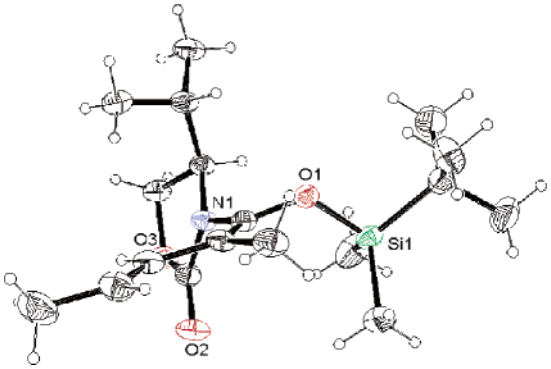


Figure 12.

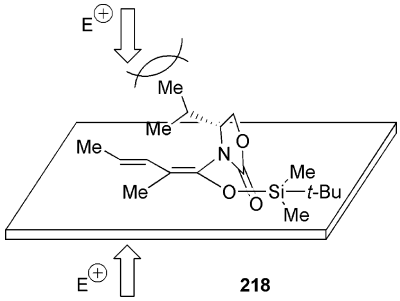


Figure 13.

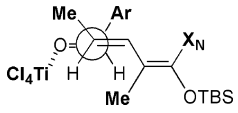
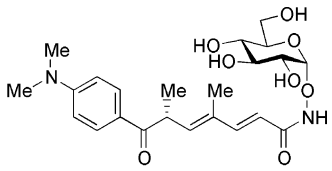


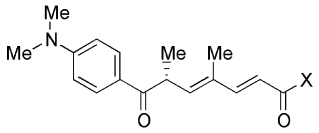
Figure 14.

6.2. Total Synthesis of Trichostatin D

Trichostatin D[111] (**202**) was isolated as an inducer of phenotypic reversion in oncogene-transformed cells from broth of an actinomycete *Streptomyces violaceusniger* (Figure 15). Because various oncogenes



Trichostatin D (**202**)



Trichostatic acid : X = OH (**219**)
Trichostatin A : X = NHOH (**220**)

Figure 15.

correlate with tumor phenotypes, the inducers of phenotypic reversion in oncogene-transformed cells are expected to be selective antitumor agents. On the other hand, trichostatin A[122] (**220**) has been used widely as a histone deacetylase inhibitor to a variety of biological research.[123] Therefore, trichostatin families are interested in biological activities.

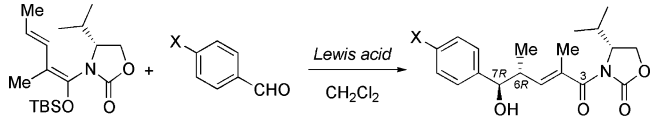
Trichostatic acid[124] (**219**), the common ketodiene unit of trichostatin families, and trichostatin A, have been synthesized to determine their absolute structures.[125]

Our remote stereoinduction with silyl ketene-*N,O*-acetals[115] is ideally suited for the syntheses of trichostatin families. Herein, we describe a novel stereoselective synthesis of trichostatic acid (**219**) as well as the first synthesis of trichostatin D (**202**).[107] At first, we examined stereoselective vinylogous Mukaiyama aldol reaction with the chiral silyl ketene-*N,O*-acetal **216** and *p*-dimethylaminobenzaldehyde **221a** (Table 3). Only the conditions described as entry 1 gave the coupling products in high yield with fairly good selectivity. The major product was determined to be the (6*R*,7*R*)- isomer by X-ray crystallographic analysis. Although the major product possessed the desired stereochemistry at the C-6 position, the reaction took a long time with difficult separation from other isomers bearing unknown stereochemistries. Therefore, we further examined such remote stereoinduction with *p*-bromobenzaldehyde which could be transformed to the *N,N*-dimethylaniline derivative (entries 2−4). With *p*-bromobenzaldehyde **211b**, the reaction proceeded smoothly and the coupling products were obtained in excellent yield with high stereoselectivity. The detectable isomers were the only two in which the (6*R*,7*R*)-isomer was produced predominantly as expected from Figures 13 and 14. The minor product was determined to be the (6*R*,7*S*)-isomer. Both isomers were found to have the desired 6*R* stereochemistry.

The major product of the remote stereoinduction with *p*-bromobenzaldehyde **221b** was isolated, after *O*-TBS protecting, by silica gel column chromatography (Scheme 34). Thus, we chose the product **222b** as an intermediate for the enantioselective synthesis of trichostatins.

Syntheses of (+)-trichostatic acid (**219**) and trichostatin D (**202**) are shown in Scheme 34. The imide **223** was directly converted to the α,β-unsaturated aldehyde **224** in high yield (91%) by treatment with DIBAL at −78 °C. Wittig reaction followed by hydrolysis gave the carboxylic acid **225**, which was submitted to the next palladium-catalyzed amination to give **226**.[126] Oxidation at the benzyl position of **226**

Table 3. Asymmetric Remote Stereoinduction with 4-Substituted Benzaldehyde

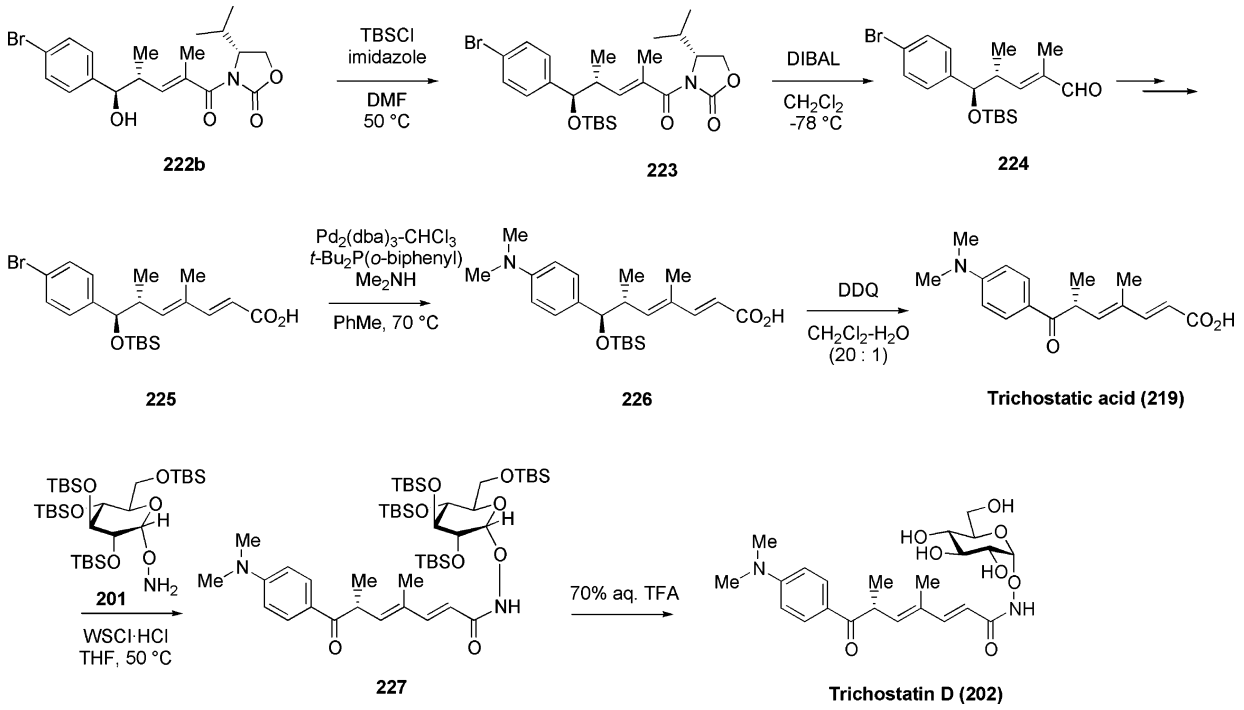


216 **221a: X = Me_2N** **221b: X = Br** **222a: X = Me_2N** **222b: X = Br**

entry	aldehyde	Lewis acid	temp (°C)	time	product	yield (%)	diastereo ratio[a]
1	221a	BF_3·OEt_2	−30	5 days	222a	88	89:8:1.5:1.5
2	221b	BF_3·OEt_2	−50	6 h	222b	85	94:6:<1:<1
3	221b	$TiCl_4$	−50	4 h	222b	97	96:4:<1:<1
4	221b	$SnCl_4$	−50	4 h	222b	98	96:4:<1:<1

[a] The diastereo ratio was determined by ^1H NMR spectroscopy.

Scheme 34



gave (+)-trichostatic acid (**219**), which was identical with the natural product in NMR, IR, mass spectral analysis, and optical rotation.

Finally, condensation of **219** with **201** followed by de-*O*-protection afforded (+)-trichostatin D (**202**).[107]

7. Conclusion

Most of the total syntheses that have been completed in our laboratories are the first ever accomplished. The achievement of successful results in research is, of course, of prime importance. Yet, prior to undertaking research, it is essential that the objectives of the research are clearly understood and defined. Hence, it may be no exaggeration to say that the selection of target molecules decides, above all, the value of the research itself in bioactive compounds synthesis.

In one view, the authors believe that the most important is to make utmost efforts toward realizing one's dream, that is, to synthesize a target molecule by one's own concept and developed strategies. Such effort will certainly produce the "art" as mentioned in the Introduction, in the reactions and/or products.

In short, there is no royal road to success in total synthesis and development of useful bioactive compounds—steady efforts are the only way to achieve that goal.

8. Acknowledgment

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