Total Syntheses of Useful Bioactive Compounds

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Abstract: The first total syntheses of a variety of useful bioactive compounds have been accomplished by practically useful strategies. In addition, practically useful intermediates have been developed, analogues of natural products have been prepared, their structure-activity relationships studied, and the large-scale preparations of medically useful compounds established. The target molecules are antibiotics, antifungals, antitumor antibiotics, compounds related to β-lactam antibiotics, enzyme inhibitors, central nervous system-affecting products, non-steroidal progesterone receptor ligands, mussel-attachment inhibitors, and so on.

Keywords: antibiotics; bioactivity; carbohydrates; rearrangements; total synthesis

1 Introduction

When a stone is thrown into a pond, several waves are produced in succession, gradually spreading until they finally cover the whole pond. The big stone thrown in the natural product synthesis pond was Woodward's reserpine synthesis in 1959. Some waves correspond to Corey's longifolene synthesis in 1961 and Kishi's palitoxin synthesis in 1994, among others.[1] Syntheses of these types are praised as "art", because they couple experimental skill with creative ingenuity, often involving the discovery of new reactions, reagents, or catalysts and resulting in a deeper understanding of the chemical processes involved. At the present time, a competent synthetic chemist may be able to synthesize many natural products, even those having a rather complicated structure, by utilizing the tools of modern organic synthesis. Nevertheless, in consideration of the challenge of the 21st Century that chemical processes should have 100% yield with 100% selectivity without waste or toxicity, "art" is called for more than ever. When applied to bioactive compounds, the author is of the opinion that the art of organic synthesis should incorporate some additional features:

1) The established synthetic method should be feasible for application to large-scale industrial production.
2) The synthetic approach should be amenable to the facile synthesis of analogues and derivatives, so as to find ones that show higher desired bioactivities than the parent natural products, that are less toxic and/or to clarify the structure-activity relationships.
3) The developed method should be useful in the elucidation of the biosynthetic mechanism.

In short, one of the most important factors in organic synthesis is "the preparation of useful compounds by practical methods".[2]

In the present paper, the author would like to present some of his recent efforts to achieve the practical total syntheses of useful bioactive compounds. It is noteworthy that most of optically active compounds have been synthesized efficiently by using carbohydrates as chiral sources so as to allow the determination of absolute structures and the clarification of structure-activity relationships.[2]

The syntheses of natural products from carbohydrates have been well-known as Hanessian's "chiron approach";[3] the present article describes syntheses from carbohydrates in which there has been a focus on "practicality" in order to increase their versatility.[4]

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Kuniaki Tatsuta received his Ph. D. from Keio University in 1969 working under the direction of Prof. S. Umezawa and joined the faculty as an assistant. He was promoted to a professor of the Department of Applied Chemistry, Keio University in 1986, and he then moved to Waseda Universty in 1993 as the professor of bioactive substances science. He was a postdoctoral fellow at Harvard University with Prof. R. B. Woodward from 1973 to 1975 and visiting professors of Cambridge University in 1988 and Paris VI University in 1994. He has received several awards including the Award of the Chemical Society of Japan (1986) and the Award of Synthetic Organic Chemistry Japan (1998). His research program focuses on the study of total syntheses of natural products, especially useful bioactive compounds, and the applications of these studies to the industrial preparation. Also, his research includes the developments of new antibiotics and medicines. In 1988, his anticancer agent, THP-adriamycin was marketed.

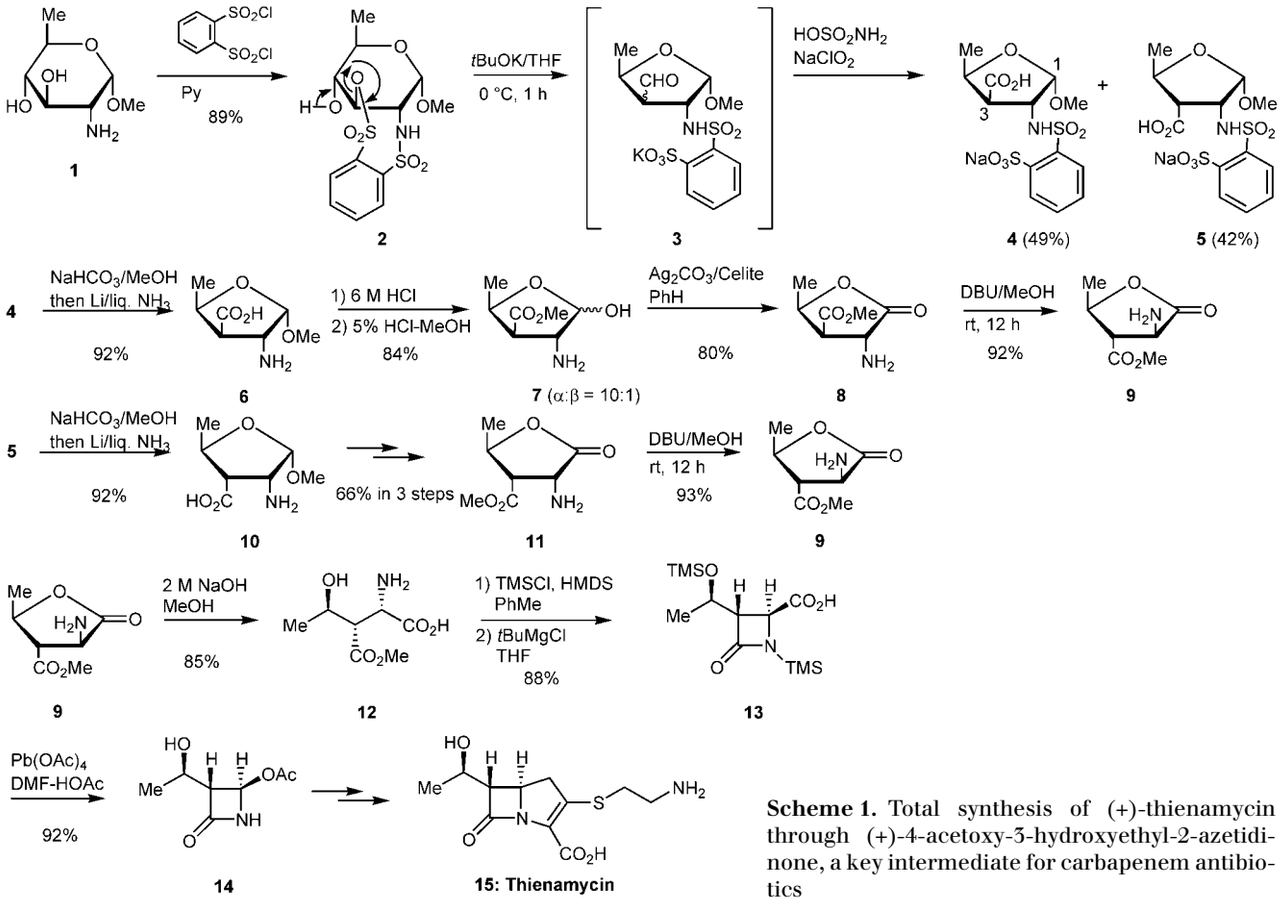
2 Synthesis and Development of Key Intermediates for β-Lactam Antibiotics Using Skeletal Rearrangement

Execution of a skeletal rearrangement is, in a sense, a brilliant factor in the field of organic synthesis. It enables beautifully the realization of the envisioned aims.

2.1 Practical Preparation of (+)-4-Acetoxy-3-hydroxyethyl-2-azetidinone, A Key Intermediate for Carbapenem Antibiotics. A 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 methodology for the construction of their skeletons and side chains. Especially in cephem antibiotics, the fourth generation has been already developed.

(+)-4-Acetoxy-3-hydroxyethyl-2-azetidinone, that is (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1′-hydroxyethyl]-2-azeti-



Scheme 1. Total synthesis of (+)-thienamycin through (+)-4-acetoxy-3-hydroxyethyl-2-azetidinone, a key intermediate for carbapenem antibiotics

dinone (**14**), and its derivatives are well-known as the highly versatile intermediates[5] for the synthesis of carbapenem antibiotics such as thienamycin (**15**), imipenem, meropenem and so on (Scheme 1).

Work on the synthesis of **14** was initiated by the Sankyo group, followed by the Merck group, and culminated in the practical preparation by two Japanese companies using Noyori-Murahashi's asymmetric procedures[6] and chemenzymatic procedures, respectively.

(+)-Thienamycin (**15**) was discovered in fermentation broths of *Streptomyces cattleya* and found to show an exceptional antibacterial potency and spectrum of action. The stereocontrolled synthesis of **15** has been reported by the Merck group, and the transformation of **14** to (+)-thienamycin (**15**) was also made more attractive by another group at Merck.[7] Consequently, the synthesis of (+)-4-acetoxy-3-hydroxyethyl-2-azetidinone (**14**) constitutes a formal total synthesis of (+)-thienamycin (**15**).

Here, a novel enantiospecific synthesis of **14** from a carbohydrate through a skeletal rearrangement and stereoselective epimerization is described. The starting material is commercially available methyl 2-amino-2,6-dideoxy-α-D-glucopyranoside (**1**), which has been also isolated from natural sources.[5]

Reaction of **1** with *o*-benzenedisulfonyl dichloride gave the cyclic sulfonate **2**, which was submitted to our developed skeletal rearrangement[8] including ring-contraction with potassium *tert*-butoxide. The resulting 3-formylfuranoside **3** was oxidized to a mixture of the carboxylic acids, which were readily separated on silica gel column chromatography ($CHCl_3$–MeOH, 8 : 1) to give the sodium salt **4** and its C3 epimer **5**, in 49% and 42% yields, in 2 steps from **2**, respectively. Practically, both compounds could be used for the synthesis without separation, because they were found to be efficiently converted to a single lactone **9** by stereoselective epimerization later on. However, the synthesis from each of the two compounds **4** and **5** is described as follows.

Removal of the *N*-sulfonyl group of **4** by Birch reduction produced the corresponding amino acid **6**. This was hydrolyzed and then esterified to give the furanose **7**. Oxidation of **7** to the lactone **8** was the key step of our strategy, although the lactone could not be obtained under usual oxidation conditions. Finally, we found that, on exposure to Ag_2CO_3/Celite in benzene, the furanose **7** was smoothly oxidized to the γ-lactone **8** in spite of the presence of the amino group.

The next important operation in the synthesis was to epimerize stereoselectively the configurations at the C2 and C3 positions of **8**. After a variety of conditions had been examined, the best result was realized by using DBU in MeOH to afford predominantly the desired amino ester **9**.

Similarly, the epimer **5** was transformed to **9** through **10** and **11** in 57% overall yield. The structure of **9** was reasonably confirmed by the NMR studies of **8**, **9** and **11**. These results indicated that the C4 configuration of **8** or **11** controlled the stereoselective construction of the C2 and C3 configurations of **9**.

Hydrolysis of **9** with 2 M NaOH according to the reported procedures led to the hydroxy acid **12**, which was in turn submitted to the β-lactam formation. For our purpose, a Grignard-mediated cyclization of the silylated derivative seemed most promising. Thus, **12** was silylated with trimethylsilyl chloride and hexamethyldisilazane (HMDS), and subsequent treatment with *tert*-butylmagnesium chloride gave the bis-silylated β-lactam **13**.

Oxidative decarboxylation of **13** by $Pb(OAc)_4$ gave exclusively the desired (+)-4-acetoxy-3-hydroxyethyl-2-azetidinone (**14**) with removal of silyl groups.[7] This was identical in all respects with the authentic sample, which was prepared from the commercially available *O-tert*-butyldimethylsilyl derivative.

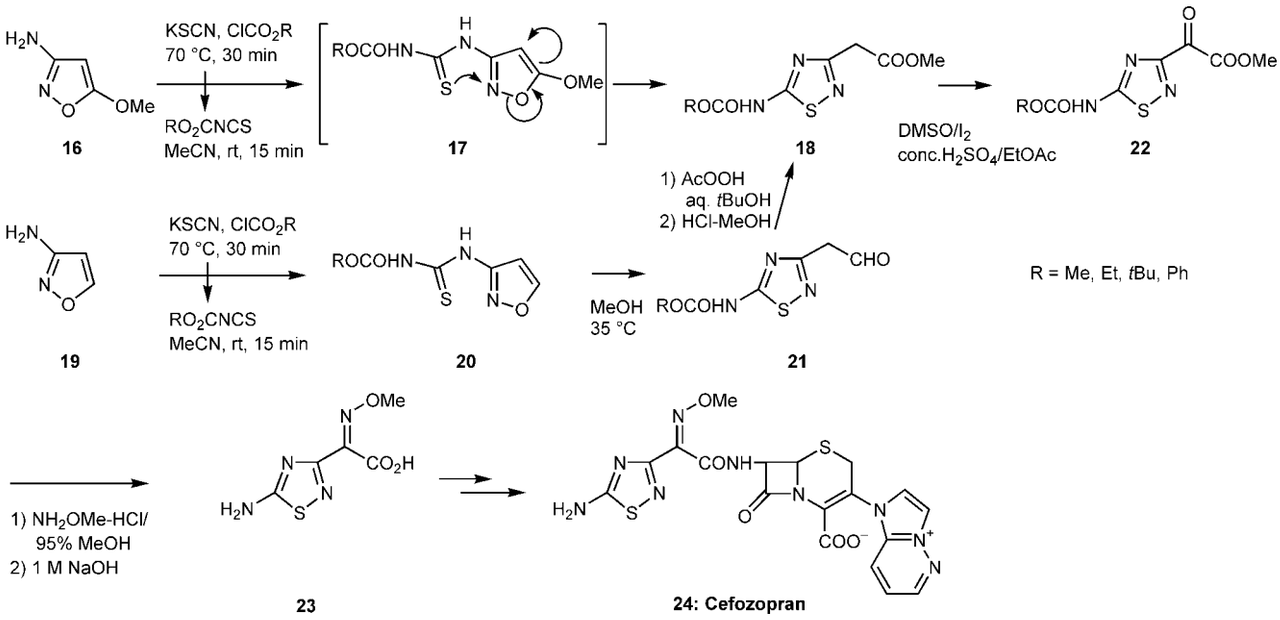
Overall, the yield was approximately 32% in 12 steps from **1**. Key steps include our developed skeletal rearrangement with ring-contraction, oxidation of the 2-aminofuranose, and stereoselective epimerization to the desired configurations.

2.2 Practical Preparation of (*Z*)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetic Acid, a Side-Chain of the Fourth Generation of Cephem Antibiotics

Recently, (*Z*)-7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(alkoxyimino)acetamido]cephalosporins such as cefozopran (**24**) have been reported as clinically useful antibiotics having excellent antimicrobial activities.[9] Their common acyl moiety at the C7 position corresponds to the *Z*-isomer (for example, **23**) of 2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(alkoxyimino)acetic acid. The *E*-isomer is known to be of no value for useful β-lactam antibiotics, as yet. Consequently, it was our intention to successfully develop a general method of entry into the *Z*-isomer by our own strategy, although several methods have been reported for the production of **23**.

The novel and concise preparation directed toward the mass production of the (*Z*)-methoxyimino compound: (*Z*)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(methoxyimino)acetic acid (**23**) is based on the skeletal rearrangement of the aminoisoxazoles **16** or **19** (Scheme 2).[9]

The starting 3-amino-5-methoxyisoxazole (**16**) was prepared from malononitrile through 3,3-dimethoxyacrylonitrile. Compound **16** was subjected to the skeletal rearrangement in question. A suspension of methyl chloroformate and KSCN in acetoni-



Scheme 2. Practical preparation of side-chains for the fourth generation of cephem antibiotics

trile was stirred at 70 °C for 30 min to give methoxycarbonyl isothiocyanate *in situ* which, in turn, reacted with **16** to afford methyl 2-(5-methoxycarbonylamino-1,2,4-thiadiazol-3-yl)acetate (**18**) in 86% yield by the skeletal rearrangement of the intermediate thiourea derivative **17**. This reaction mechanism was reasonably supported by the isolation of the similar intermediate **20** from 3-aminoisoxazole (**19**). The use of ethyl chloroformate, phenyl chloroformate and benzyl chloroformate for this reaction instead of methyl chloroformate led to the corresponding alkoxycarbonylamino derivatives in fairly good yields.

Compound **18** was converted into methyl 2-(5-alkoxycarbonylamino-1,2,4-thiadiazol-3-yl)-2-oxoacetates (**22**) by oxidation with DMSO and I_2 in the presence of catalytic amounts of H_2SO_4 and isolated in 83% yield. The moderate yield was ascribed to the difficult purification due to the polar nature of the compounds. Without isolation of the keto-ester, the methyl ester **18** was *quantitatively* converted into the desired methyl (*Z*)-2-(5-methoxycarbonylamino-1,2,4-thiadiazol-3-yl)-2-(methoxyimino)acetate (**23**) in a one-pot procedure. Namely, **18** was oxidized under the above-mentioned conditions followed by treatment with *O*-methylhydroxylamine to give the methyl ester of **23** in quantitative yield. Saponification of the methyl ester with 1 M NaOH provided the target product, (*Z*)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(methoxyimino)acetic acid (**23**) in quantitative yield, which was derivatized to cefozopran (**24**) for marketing.[10]

3 Practical Syntheses of Carbocyclic Compounds by New Methodologies

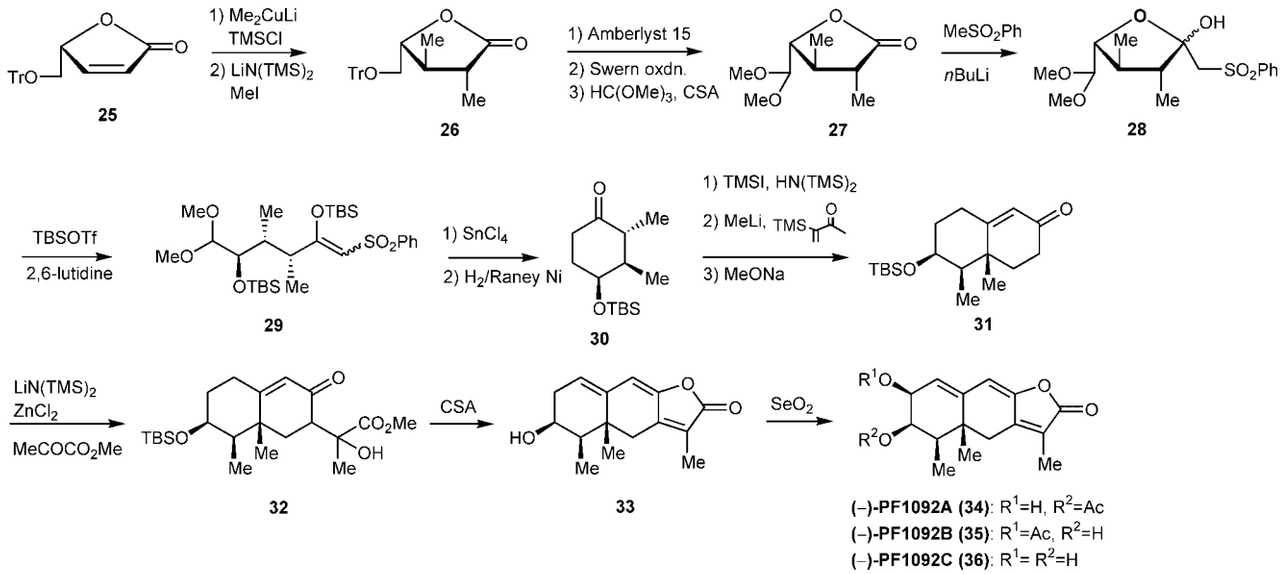
3.1 The First Total Synthesis of Progesterone Receptor Ligands, PF1092A, B, and C

The microbial metabolites (–)-PF1092A, B and C (**34**, **35**, and **36**) were isolated as new non-steroidal progesterone receptor ligands from the culture broth of *Penicillium oblatum*, and their absolute structures were finally determined by X-ray crystallographic analysis. Structurally, they belong to the complex eremophilane-type sesquiterpenes, with four contiguous *cis*-substituents on an octalone skeleton fused with a butenolide ring.[11]

The first enantiospecific total synthesis of (–)-PF1092A, B, and C (**34**–**36**) is based on the $SnCl_4$-promoted cyclization of an α-keto methyl sulfone and dimethyl acetal followed by a Stork annulation which gives the octalone core (Scheme 3).[11]

The critical step was the direct opening of the furanose ring (**28** to **29**) by silylation with simultaneous formation of the enol silyl ether, because the one-step opening of the furanose ring is generally difficult.

The synthesis was initiated with the stereoselective introduction of two methyl groups onto the tritylated butenolide **25** to give the dimethylated lactone **26** (67%) along with the C2 epimer (13%). As this stereocenter will be lost in the Stork annulation (see below), both epimers could be used in the total synthesis of **36**. Their structures were confirmed by the NOE enhancements observed in **26**. After detritylation, the



Scheme 3. The first total synthesis of PF1092A, B, and C, progesterone receptor ligands

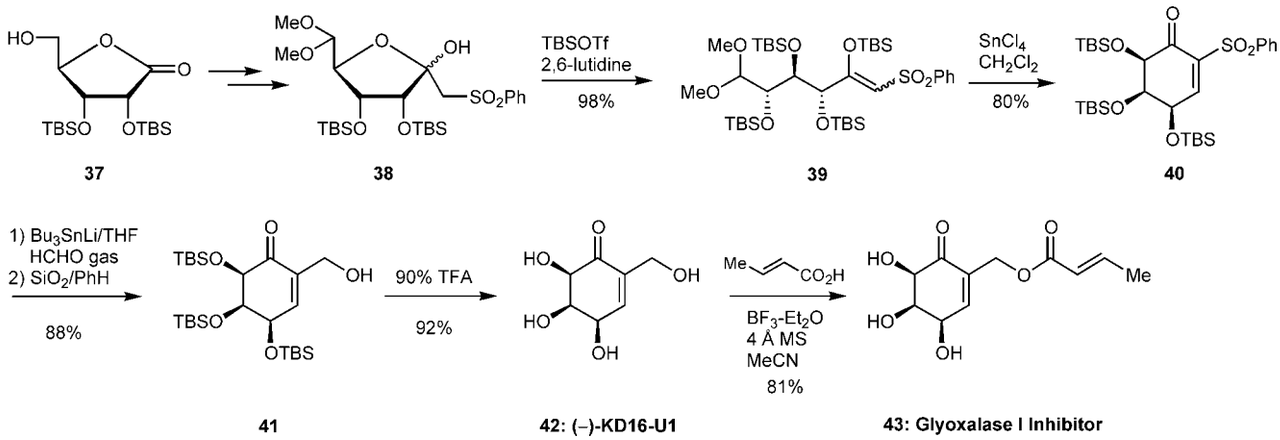
resulting alcohol was transformed to the dimethyl acetal **27**. Reaction with lithiated $MeSO_2Ph$ gave the lactol **28**, which was silylated to the open-chain compound **29** having the enol silyl ether unit (91%). These reactions seem to depend on the readiness of the enol silyl ether formation.

After investigating various derivatives and Lewis acids, the desired aldol-type cyclization of **29** with β-elimination was realized by treatment with $SnCl_4$. Desulfurization on Raney Ni with concomitant reduction of the olefin gave the cyclohexanone **30** (69%). These procedures feature general methods of entry into optically active cyclohexanes and cyclohexanols. The annulation of **30** was carried out according to Stork's procedure[12] by silylation to give the silyl enol ether, followed by successive treatment with a silylated methyl vinyl ketone and with MeONa to give the desired octalone **31** in 60% overall yield. The introduction of the ethyl methyl ketone moiety to C2 in **30** was expected to occur with addition *trans* to the C3 methyl group to afford the natural configurations in **31**. The NOE enhancement was clearly detected between the two methyl signals to support the *cis*-dimethyl structure. Compound **31** was converted into the Zn enolate and reacted with methyl pyruvate to give **32** quantitatively as a diastereomeric mixture. Closure to the desired lactone **33** was effected upon heating **32** with CSA. Finally, stereospecific SeO_2 oxidation of **33** with the aid of the hydroxy group afforded the *cis*-diol **36**, identical with the natural product (–)-PF1092C (**36**) in all respects.

Since (–)-PF1092C (**36**) has already been transformed into (–)-PF1092A and B (**34** and **35**) by selective acetylation, the synthesis of **36** constitutes the completion of the total synthesis of **34** and **35**.[11]

3.2 Total Synthesis of Glyoxalase I Inhibitor and Its Precursor KD16-U1

A glyoxalase I inhibitor (**43**) was isolated in 1975 from the culture broth of *Streptomyces griseosporeus* by Umezawa and coworkers. The absolute structure was determined by chemical studies and X-ray analysis. Its precursor, (–)-KD16-U1 (**42**), had already been isolated in 1974 from the culture broth of *Streptomyces filipinensis* by a chemical screening method developed in our laboratories,[13] and converted to the aforementioned glyoxalase I inhibitor by treatment with crotonic acid and $BF_3 \cdot Et_2O$. The glyoxalase system, which consists of glyoxalase I, glyoxalase II, and reduced glutathione, catalyzes the conversion of α-keto aldehydes to α-hydroxy acids. The glyoxalase I inhibitor (**43**) has also been reported to exhibit antitumor activities. The structures and bioactivities of compounds **42** and **43** have attracted our attention because of our program in developing novel methodology for the preparation of densely-functionalized carbocycles from carbohydrates. The first synthesis was achieved by Vasella et al. in which methyl α-D-glucopyranoside was effectively used as starting material.[14] As mentioned in the synthesis of the PF1092s (**34–36**),[11] the $SnCl_4$-promoted, aldol-like cyclization of phenylsulfonyl enol silyl ethers containing a dimethyl acetal has been explored extensively in our laboratories. This transformation is ideally suited to the synthesis of carbocycle-containing natural products and carbasugars, since the core skeleton arises after appropriate replacement of the phenylsulfonyl group. Accordingly, the novel synthesis of the (–)-glyoxalase I inhibitor (**43**) and its precursor, (–)-KD16-U1 (**42**) has been accomplished by the similar manner (Scheme 4).[15]



Scheme 4. Total synthesis of glyoxalase I inhibitor and its precursor KD16-U1

The key step was the introduction of the hydroxymethyl group onto the α-phenylsulfonylcyclohexenone **40** through the Michael type addition of tributylstannyllithium followed by trapping with formaldehyde and desulfonylation.

The cyclohexenone **40** would arise from the enol silyl ether containing the dimethyl acetal **39**, which originates from a one-step opening of the phenylsulfonylmethyl furanose **38**. Thus, the starting material simplifies to commercially available D-ribonic acid γ-lactone.

In practice, the silylated lactone **37** was converted into **38** by acetal formation followed by reaction with lithiated methyl phenyl sulfone.[11] Compound **38** was silylated to produce, as expected, the labile enol silyl ether **39** having a simultaneously silylated hydroxy group. The $SnCl_4$-promoted cyclization of **39** resulted in the formation of the cyclohexenone **40**. Addition of tributylstannyl-lithium to **40** was followed by trapping of the intermediate β-tributylstannyl sulfone with formaldehyde. This reaction gave an adduct which, upon treatment with silica gel, was converted through simultaneous elimination of the phenylsulfonyl and tributylstannyl groups to the desired α-hydroxymethylcyclohexenone **41**. De-*O*-silylation with 90% TFA afforded **42**, which was identical with the natural (–)-KD16-U1 (**42**) in all respects.[13]

The synthetic (–)-KD16-U1 (**42**) was treated with crotonic acid and $BF_3 \cdot Et_2O$, as previously reported in our laboratories,[15] to give the selectively acylated product **43**, identical with the natural glyoxalase I inhibitor (**43**).

3.3 Novel Syntheses of the Natural Pseudo-Aminosugars (+)-Valienamine and (+)-Validamine

(+)-Valienamine (**49**) and (+)-validamine (**53**) have been found to be key components for biological activities in pseudo-aminosugars and pseudo-oligosaccharides such as validamycins, acarbose, and trestatines.[11] Both pseudo-aminosugars **49** and **53** were also isolated from the fermentation broth of *Streptomyces hygroscopicus* subsp. *limoneus* IFO 12703 and found to show some biological activities.

Only few syntheses of the optically active compounds **49** and **53** have been reported by using L-quebrachitol, (–)-quinic acid, and D-glucose derivatives, although the racemates of **49** and **53** have been synthesized by a variety of methodologies (Scheme 5).

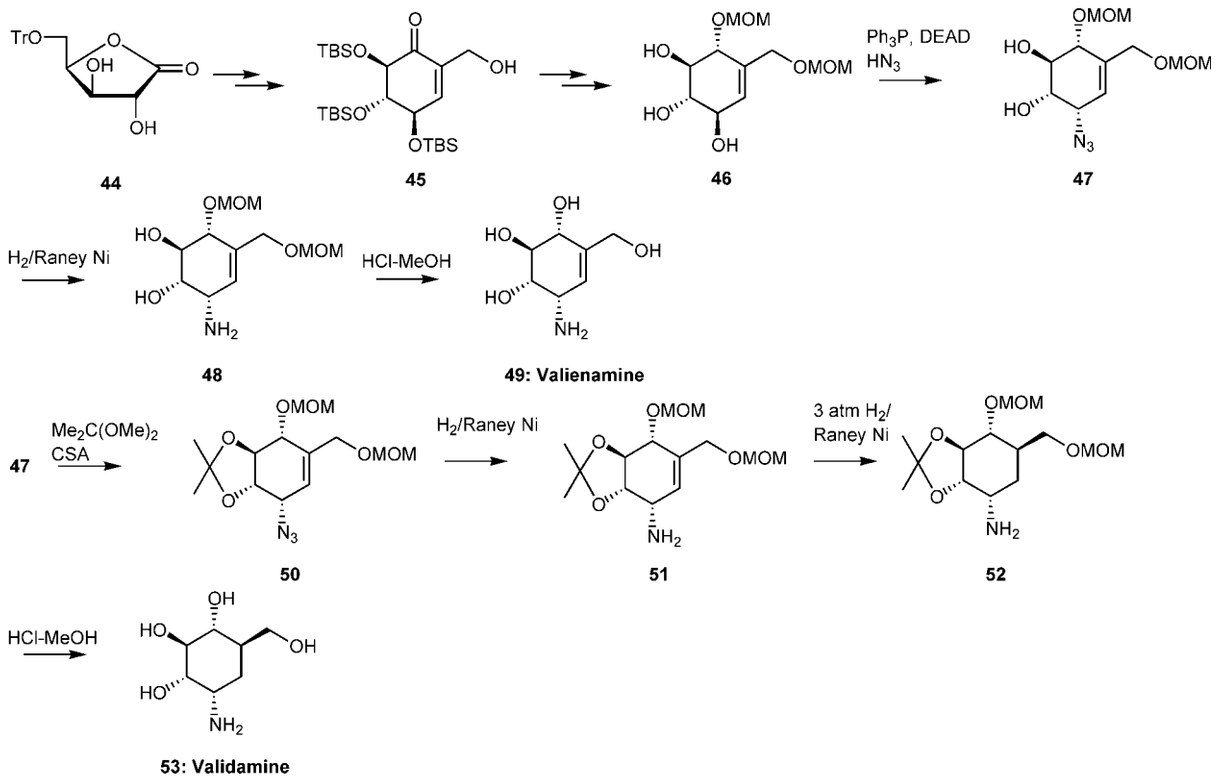
As mentioned above for the synthesis of the glyoxalase I inhibitor (**43**) and its biosynthetic precursor **42**, we have extensively developed the one-step opening of a furanose ring containing a phenylsulfonylmethyl group followed by aldol condensation as a general method for the construction of optically active carbasugars.[13]

Now, both the utility and the versatility of our method are demonstrated in the stereoselective synthesis of natural (+)-valienamine (**49**) and (+)-validamine (**53**) (Scheme 5).[13] Furthermore, the anchor effect of an amino group will be described in the stereoselective hydrogenation of the olefin of **51** to give **52** (Figure 1).

The starting compound **44**, which was prepared from D-xylose by bromine oxidation and tritylation, was converted into **45** by procedures similar to those used in the synthesis of **41**.

Stereoselective reduction of the carbonyl group in **45** by $Zn(BH_4)_2$ in ether to give the α-alcohol was followed by exchange of the protecting groups to give the properly protected alcohol **46**. Although **46** possessed three hydroxy groups, the allylic hydroxy group at C1 was expected to be more reactive than others.

As expected, Mitsunobu inversion of the allyl alcohol **46** using HN_3 gave predominantly the α-azide **47**. Mild hydrogenation of **47** with 1 atm of hydrogen over Raney Ni produced the corresponding amino com-



Scheme 5. Total synthesis of the natural pseudo-aminosugars (+)-valienamine and (+)-validamine

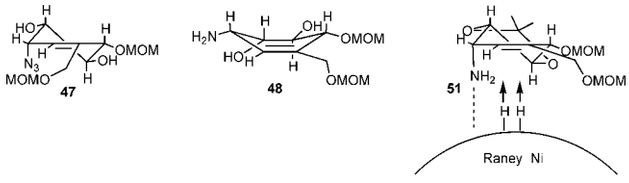


Figure 1. Conformations of key intermediates and the anchor effect of the amino group in **51** over Raney Ni

pound **48** in a quantitative yield without any significant reduction of the olefin.

Deprotection of **48** with methanolic hydrogen chloride gave the hydrochloride of (+)-valienamine (**49**), which was chromatographed on Dowex 1X2 (OH-type) with water to provide, after recrystallization from a small amount of water, needles of the free base **49** as a monohydrate. Both the hydrochloride and the free base of **49** were identical in all respects with the authentic samples of the natural product.[17]

In the final stage to synthesize validamine (**53**), extensive efforts were directed toward achieving a stereoselective hydrogenation of the olefin **48** that would ensure the configuration of the hydroxymethyl group at C5. Unfortunately, catalytic hydrogenation of **48** either on Raney Ni or Pd–C gave an approximately 1 : 1 mixture of the diastereomers due to C5.

^{1}H-NMR studies of **47** and **48** indicated that their conformations were different (Figure 1). Compound **47** adopts the usual half-chair form with the *quasi*-axial azido group, while the amino compound **48** exists in the boat-like form with the *quasi*-equatorial amino group. The latter form, **48**, might be due to an interaction such as hydrogen bonding between the C1 amino and C2 hydroxy groups.

The *quasi*-axial amino group or hydroxy group of methylcyclohex-2-enylamines or 2-enols has been known to act as an anchor toward the surface of Raney Ni on catalytic hydrogenation to give preferentially the *trans*-isomer.[18] Accordingly, the *quasi*-equatorial amino group of **48** could not participate in the anchor effect for stereoselective hydrogenation.

We expected that the conformations of the acetonated derivatives **50** and **51** would be much more rigid than **48** to keep the half-chair form having the *quasi*-axial amino group. Mild catalytic hydrogenation of **50** gave quantitatively the corresponding amino compound **51**.

As a mixture of dioxane and H_2O was used for catalytic hydrogenation, the ^{1}H-NMR spectra of **48** and **51** were measured in dioxane-d_8 and D_2O to support that **51** existed in the half-chair form with the *quasi*-axial amino group (Figure 1).

The *quasi*-axial amino group of **51** was expected to assist the anchor effect giving the desired 1,5-*trans* isomer **52**. As expected, catalytic hydrogenation of **51**

over Raney Ni in a mixture of dioxane and H_2O gave, after evaporation of the solvent, the *trans*-isomer **52** as a single product in quantitative yield. Direct hydrogenation of **50** to **52** was also achieved in quantitative yield with 3 atm of hydrogen on Raney Ni.

Acidic deprotection of **52** gave quantitatively the hydrochloride of (+)-validamine (**53**), which was chromatographed on Dowex 1X2 (OH-type) with water to yield the free base of **53**. Both the hydrochloride and the free base of **53** were identical in all respects with the authentic samples of the natural product.[17] The absolutely stereoselective hydrogenation of **50** and **51** to give (+)-validamine (**53**) is particularly noteworthy.

3.4 The First Total Synthesis of Pyralomicins 1 c and 2 c

Pyralomicins 1 c and 2 c (**60** and **62**) have been isolated from the culture broth of *Microtetraspora spiralis* as novel antibiotics also exhibiting antitumor activities. Structurally, **60** and **62** are endowed with the 5-hydroxy-8-methyl-[1]benzopyrano[2,3-*b*]pyrrol-4-(1*H*)-one structure **56** as a common core binding a carbasugar and a sugar moiety, respectively. The first total syntheses of pyralomicins 1 c and 2 c (**60** and **62**) have been effectively accomplished in our laboratories (Scheme 6).[19,20]

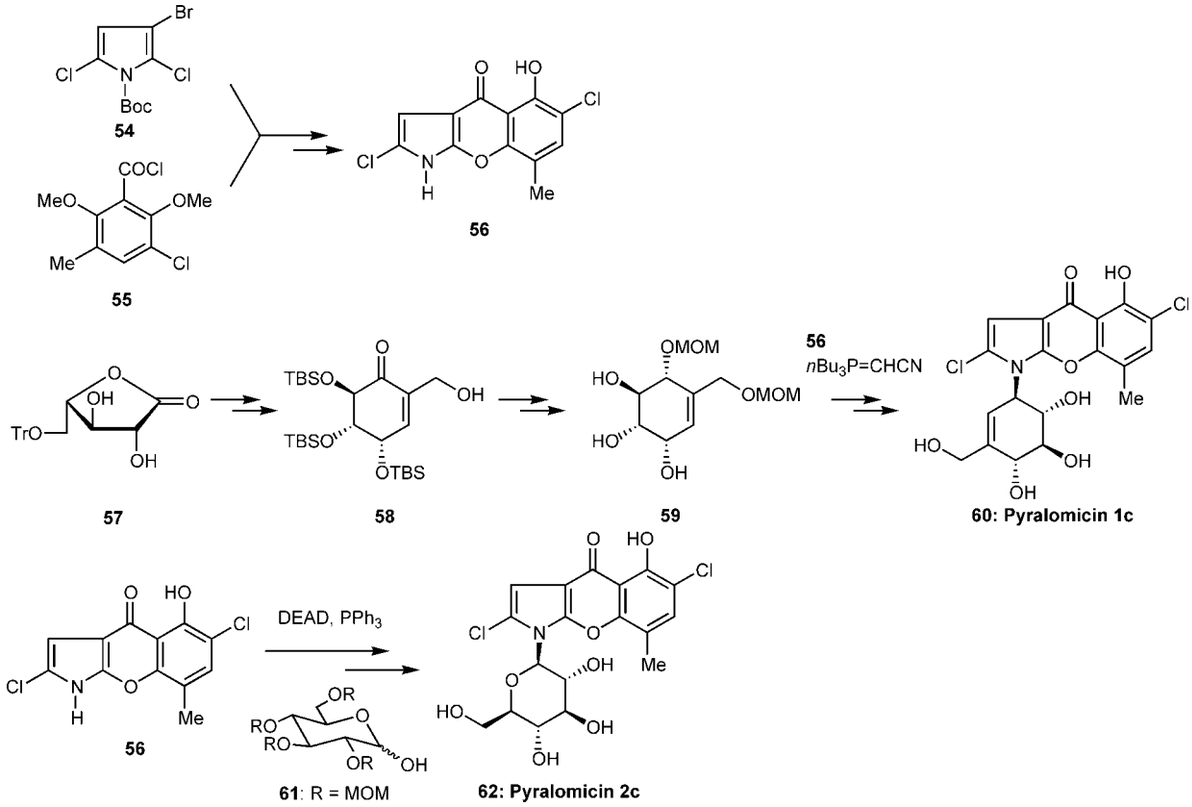
Since pyralomicinone (**56**) has been synthesized from pyrrole and 2,4-dihydroxytoluene derivatives (for example, **54** and **55**), the first aim in the synthesis of pyralomicin 1 c (**60**) is the effective construction of the carbasugar moiety **59**.[19]

We expected the regio- and stereoselective connection of **59** with pyralomicinone (**56**) to be controlled under Mitsunobu conditions with inversion. Furthermore, it was anticipated that the carbasugar **59** could be synthesized by similar strategies as developed by us in the syntheses of glyoxalase I inhibitor (**43**) and its precursor, KD16-U1 (**42**).[15]

The starting material in this synthesis was L-arabinonic acid γ-lactone **57**, which was readily derived from L-arabinose by tritylation and bromine oxidation. Conversion of **57** to **58** was carried out by procedures similar to those for the preparation of **41** and **45**.

The stereoselective reduction of the carbonyl group of **58** was examined under a variety of conditions, and the best result was realized by using $NaBH_4$ and $CeCl_3 \cdot 7H_2O$ to give the desired α-alcohol in 69%. This was protected with a methoxymethyl group followed by de-*O*-silylation to give quantitatively the triol **59**. Although **59** possessed three free hydroxy groups, the allylic hydroxy group at C1 was expected to be more reactive than others.

With pyralomicinone (**56**) and the alcohol **59** in



Scheme 6. The first total syntheses of pyralomicins 1 c and 2 c, including carbasugar and D-glucose

hand, we turned to their connection. Both components **56** and **59** were coupled under modified Mitsunobu conditions using a novel reagent, nBu$_3$P=CHCN to give predominantly the desired N–C product with inversion,[21] which was deprotected under acidic conditions to give pyralomicin 1 c (**60**). This was identical with the natural product in all respects, completing the first total synthesis. As expected, the by-products which would result from the reaction of other hydroxy groups with **56** were not observed in any significant amounts.

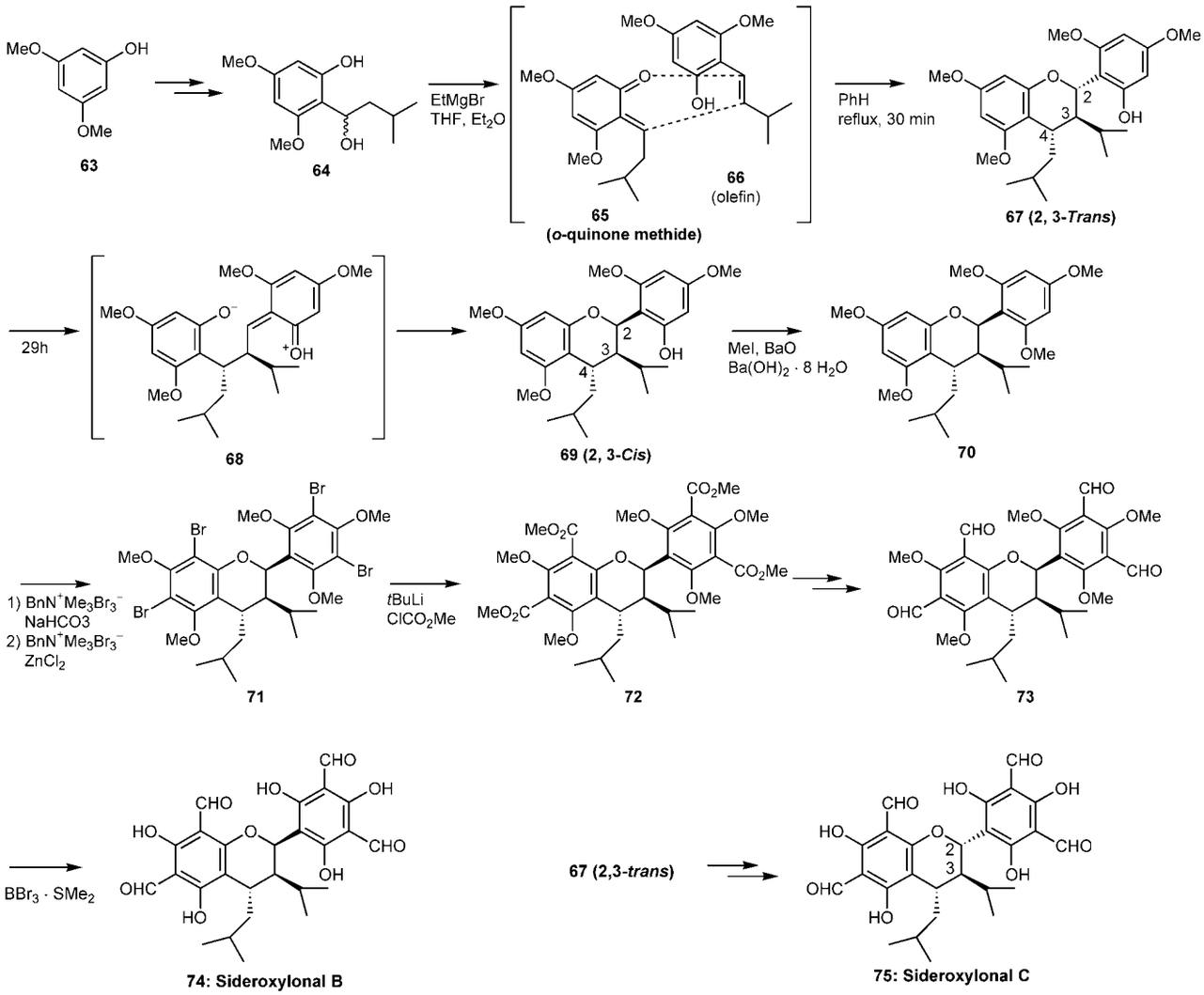
Next, pyralomicin 2 c (**62**) was synthesized from **56** and **61**.[20] The glucosyl donor **61** was prepared from benzyl α-D-glucopyranoside by methoxymethylation followed by hydrogenolysis. The stereoselective *N*-glucosylation of **61** with **56** was effectively accomplished by using Mitsunobu conditions to give **62**, after acidic deprotection. This was identical in all respects with the natural product **62**.

The total syntheses of pyralomicins 1 c (**60**) and 2 c (**62**) indicated that Mitsunobu conditions were useful for the stereoselective construction of N–C bonds.

4 Practical Synthesis using a Novel Diels–Alder Reaction and/or Tandem Michael–Dieckmann Type Reaction

4.1 The First Total Synthesis of Sideroxylonals

Sideroxylonal B (**74**) is a racemic flavanoid component isolated from extracts of *Eucalyptus sideroxylon*, which shows strong attachment-inhibiting activities against blue mussels. The structure was established by spectroscopic analysis to have a fully functionalized 2-phenyl-1-benzopyran skeleton. Biogeneti-



Scheme 7. The first total syntheses of sideroxylonals B and C

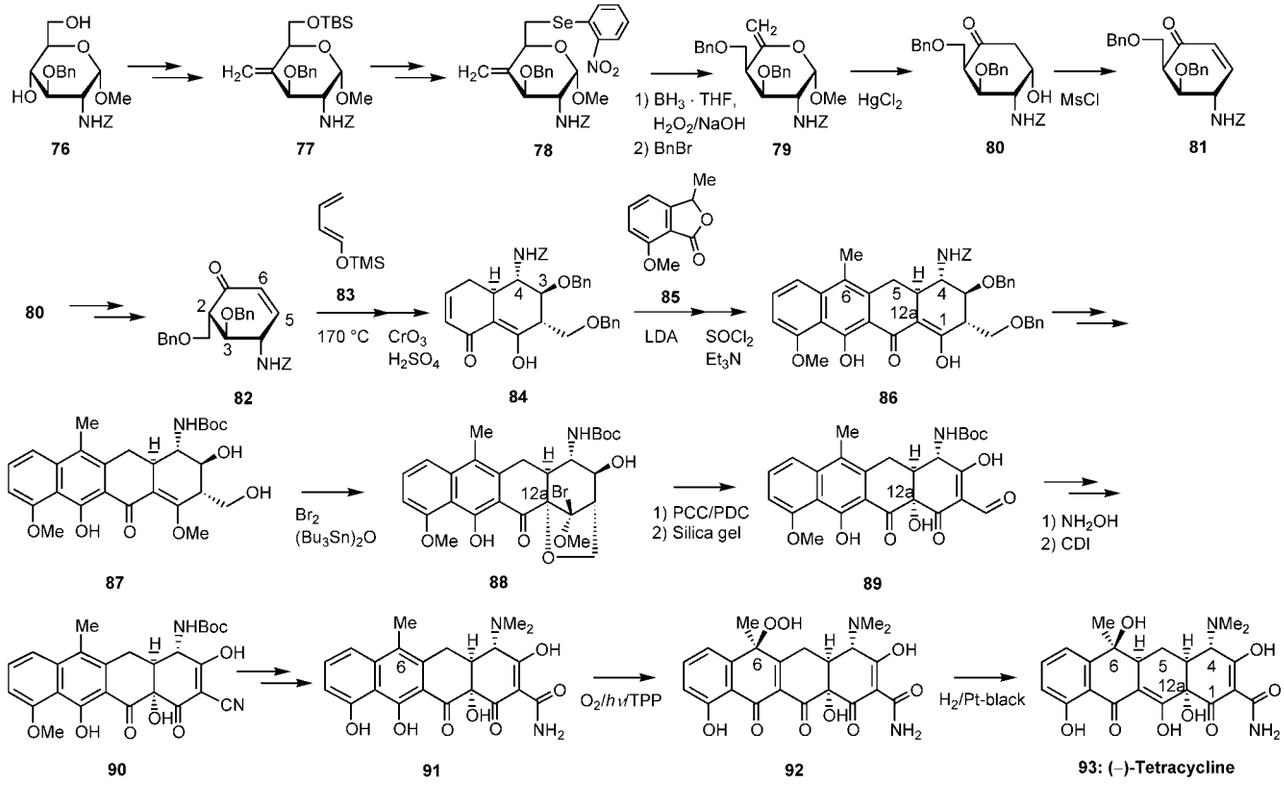
cally, this compound is apparently formed from isopentenyl-phloroglucinol precursors by a hetero-Diels–Alder coupling process.

Recently, we have reported the implementation of a novel biomimetic strategy for the first total syntheses of sideroxylonals B (**74**) and C (**75**) (Scheme 7).[22] The critical element in the design of the synthetic plan was inspired by the proposed biosynthetic sequence as shown in retrosynthetic sequence to assemble the 2-phenyl-1-benzopyran skeleton from the isopentenyl-phloroglucinol precursor **64** through cycloaddition of the *o*-quinonemethide and the isopentenyl intermediates (**65** and **66**), which could be simultaneously produced *in situ*.

The key intermediate **64** was prepared from 3,5-dimethoxyphenol (**63**) and isovaleric acid, followed by reduction. The hetero-Diels–Alder reaction was assayed under various conditions using Lewis acids, bases, and so on. The best result was obtained by treatment of **64** with EtMgBr to give simultaneously the *o*-quinonemethide **65** and the isopentenyl derivative **66** *in situ*, a mixture of which was submitted to the cycloaddition in question. On refluxing for 30 min, the 2,3-*trans* isomer **67** was obtained as the major adduct in 39% yield (theoretically 78%). The isomer **67** was reasonably expected to be produced through reaction of the *trans*-isomer **66** with **65** in the transition state. On the other hand, longer refluxing time (29 h) afforded the 2,3-*cis*-isomer **69** as the major product in 37% yield (theoretically 74%). This result indicated that the 2,3-*trans*-isomer **67** was thermodynamically changed to the 2,3-*cis*-isomer **69** through pyran ring-opening to **68** and ring-closing processes as shown in Scheme 7.

The 2,3-*cis*-isomer **69**, which has the same configuration as that of sideroxylonal B (**74**), was converted into the natural product **74**. *O*-Methylation of **69** gave the fully protected compound **70**, followed by perbromination with benzyltrimethylammonium tribromide under basic conditions and then acidic conditions to produce the tetrabromide **71**. Lithiation of **71** with *t*BuLi followed by treatment with methyl chloroformate afforded the methyl ester **72**. This was submitted to hydride reduction with DIBAL to give the tetraol, which was oxidized with PDC to provide the aldehyde **73**. De-*O*-methylation was effectively achieved with $BBr_3 \cdot SMe_2$ to give sideroxyronal B (**74**).

The 2,3-*trans*-analogue **75**, which is conveniently named as sideroxylonal C, was also synthesized from the 2,3-*trans*-intermediate **67** by similar procedures. After completion of our synthesis, sideroxylonal C (**75**) was also isolated from natural sources. Both compounds **74** and **75** showed much stronger attachment-inhibiting activities than $CuSO_4$ against blue mussels.



Scheme 8. The first total synthesis of (–)-tetracycline

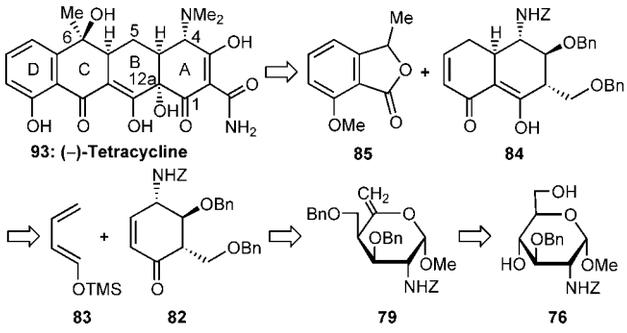


Figure 2. Retrosynthesis of (–)-tetracycline

4.2 The First Total Synthesis of Natural (–)-Tetracycline

For almost half a century, tetracycline (**93**) has been well-known as a major antibiotic from the viewpoint of its unique structural features as well as antibacterial activities.[23] The total synthesis of the tetracycline families was initiated by Woodward's 6-demethyl-6-deoxytetracycline synthesis in 1962,[24] followed by Muxfeldt's terramycin synthesis in 1968,[25] and culminated by Stork's 12a-deoxytetracycline synthesis in 1996.[26] However, all these syntheses have been accomplished only in racemic forms. The total synthesis of natural (–)-tetracycline (**93**) remained an unanswered challenge, despite the remarkable achievements as described above.

Very recently, the first total synthesis of (–)-tetracycline (**93**) has been completed in our laboratories[23] by using D-glucosamine as a chiral starting material, which stereospecifically constructs the densely and sensitively functionalized A ring (Scheme 8).

From the retrosynthetic perspective (Figure 2), the tetracyclic structure is expected to be accessible by a tandem Michael-Dieckmann type reaction of **84** with **85**. The suitably substituted chiral intermediate **84** could be synthesized by Diels-Alder reaction of the cyclohexenone **82** and the silyloxybutadiene **83**. The regio- and stereoselectivities are established as a consequence of the dienophile geometry according to Gleiter's theory.[23] Compound **82** could be obtained from **76** through Ferrier reaction of **79**.

As a viable synthetic relay from anhydrotetracycline (**91**) to tetracycline (**93**) has been reported by Wasserman and Scott via a two-step hydration at the 5a,6-position,[27] compound **91** was our first target. A reliable 12a-hydroxylation is required for the synthesis of **91**, although evidence of such hydroxylation has been reported.[26]

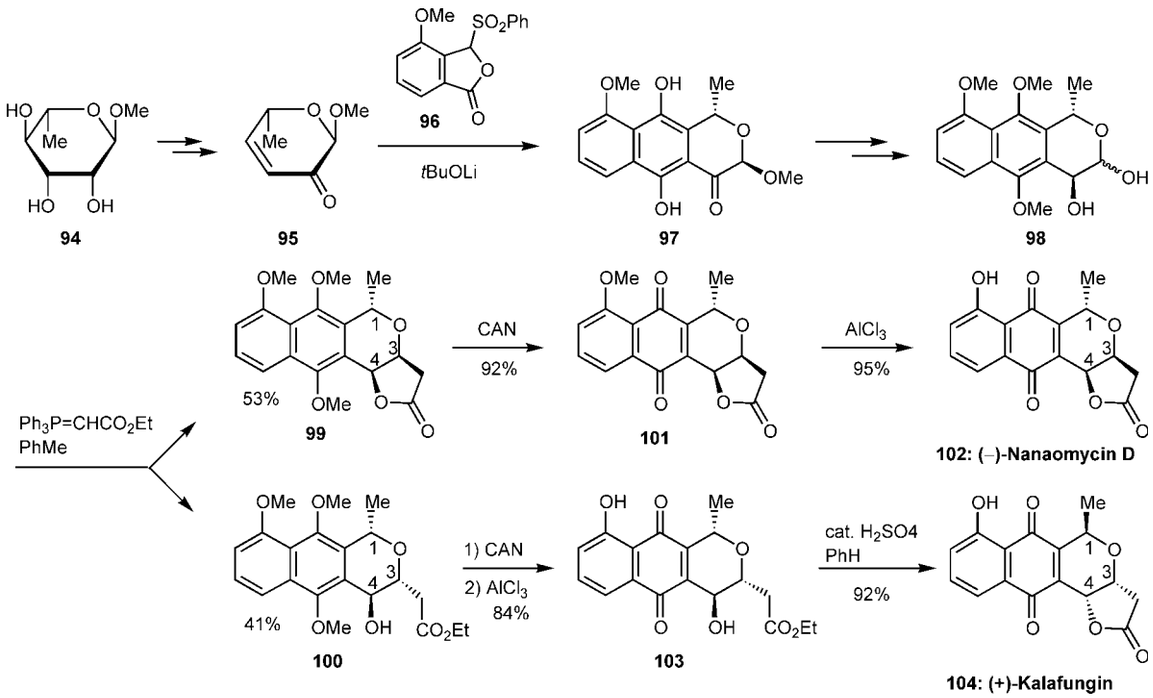
The starting **76**, which was prepared from D-glucosamine, was converted into the olefin **77** by selective silylation, oxidation and Wittig olefination (Scheme 8). After de-*O*-silylation of **77**, the resulting alcohol was transformed to the selenide **78**. Treatment of **78** with borane followed by H_2O_2 oxidation gave stereoselectively the alcohol by simultaneous formation of a new olefin group, which was benzylated to **79**. This was submitted to Ferrier reaction[28] with $HgCl_2$ to give the cyclohexanone **80**. The [4+2] cycloaddition of **81**, which was derived from **80** by dehydration, with the butadiene **83** did not proceed because of the steric repulsion. Therefore, **80** was epimerized at C2 and dehydrated to the isomer **82**. The α-hydroxymethyl group was an important factor for the stereospecific introduction of the hydroxy group at C12a in **88** and **89**. This cycloaddition with **83** in the presence of 2,6-di-*tert*-butyl-4-methylphenol proceeded from the β-face of **82** 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 **84**. The tandem Michael-Dieckmann-type reaction of **84** with the isobenzofuranone **85** gave the tetracyclic compound, which was in turn aromatized to **86** in high yield.

After selective de-*O*-benzylation of **86** with BBr_3, the alcohol was converted into **87** by exchange of the *N*-protecting group followed by *O*-methylation of the enol. Treatment of **87** with Br_2 gave stereoselectively the bromide **88**. The opening of the pyran ring was examined under a variety of conditions. PCC-PDC oxidation of the alcohol of **88** was found to give the C12a alcohol **89** followed by β-elimination and oxidative opening of the pyran. Compound **89** was transformed to the nitrile **90** by our newly developed method. Hydrolysis of **90** to give the amide with concomitant removal of the *N*-Boc group was followed by *N*-dimethylation and de-*O*-methylation to produce anhydrotetracycline (**91**). This was identical with a naturally derived sample in all respects.

The final stage was to introduce stereoselectively the hydroxy group into the C6 position according to the reported procedures.[27] By photooxidation of **91**, the corresponding C6 peroxide **92** was obtained. The subsequent hydrogenolysis on Pd-C gave no significant product,[26,27] while the desired reduction proceeded smoothly on Pt black to give (–)-tetracycline (**93**) in a fairly good yield, which was neutralized with HCl in MeOH to give the hydrochloride. This was identical with the hydrochloride of natural (–)-tetracycline in all respects, completing the first total synthesis.[23]

4.3 The First and Enantiodivergent Total Synthesis of Nanaomycins and Their Enantiomers, Kalafungins

Nanaomycin D (**102**) and kalafungin (**104**) are members of a growing family of pyranonaphthoquinone (benzoisochromanquinone) antibiotics, which have been shown to possess significant antimicrobial and



Scheme 9. The first and enantiodivergent total synthesis of (–)-nanaomycin D and (+)-kalafungin

antifungal activities. Remarkably, nanaomycin D (**102**) and kalafungin (**104**) are enantiomers with each other, and both antipode systems have been found as major constituents of many kinds of pyranonaphthoquinone antibiotics such as medermycin.[29] These unique structural features as well as the opportunity to develop synthetic strategies for the construction of more diverse analogues of these interesting antibiotics have prompted intensive investigation into their syntheses.

We have completed the first, enantiospecific total syntheses of nanaomycin D (**102**), its 4-deoxy analogue, nanaomycin A, as well as their enantiomers, kalafungin (**104**) and 4-deoxykalafungin from a common optically active intermediate **98** by the "enantiodivergent" strategies (Scheme 9).[30] The common intermediate **98** is expected to be derived from condensation of **95** with **96**.

Methyl α-L-rhamnoside (**94**) was converted into the stable α,β-unsaturated ketone (**95**). Condensation of **95** with the lithiated anion of **96** gave the hydroquinone **97**, which was treated with dimethyl sulfate followed by stereoselective hydride reduction to afford, after hydrolysis, exclusively **98**.

The hemiacetal **98** was submitted to Wittig reaction to give two products as expected: **99** and **100** in 53% and 41% yields. The lactone **99** results from a two-step sequence including the intramolecular Michael cyclization of the intermediate Wittig α,β-unsaturated ester and concomitant lactonization of the resultant 3,4-*cis*-hydroxy ester. The other 3,4-*trans*-hydroxy ester **100** results from the Michael cyclization without lactonization.

The lactone **99** was treated with ammonium cerium(IV) nitrate to give 9-*O*-methylnanaomycin D (**101**). De-*O*-methylation with aluminium chloride provided (–)-nanaomycin D (**102**).

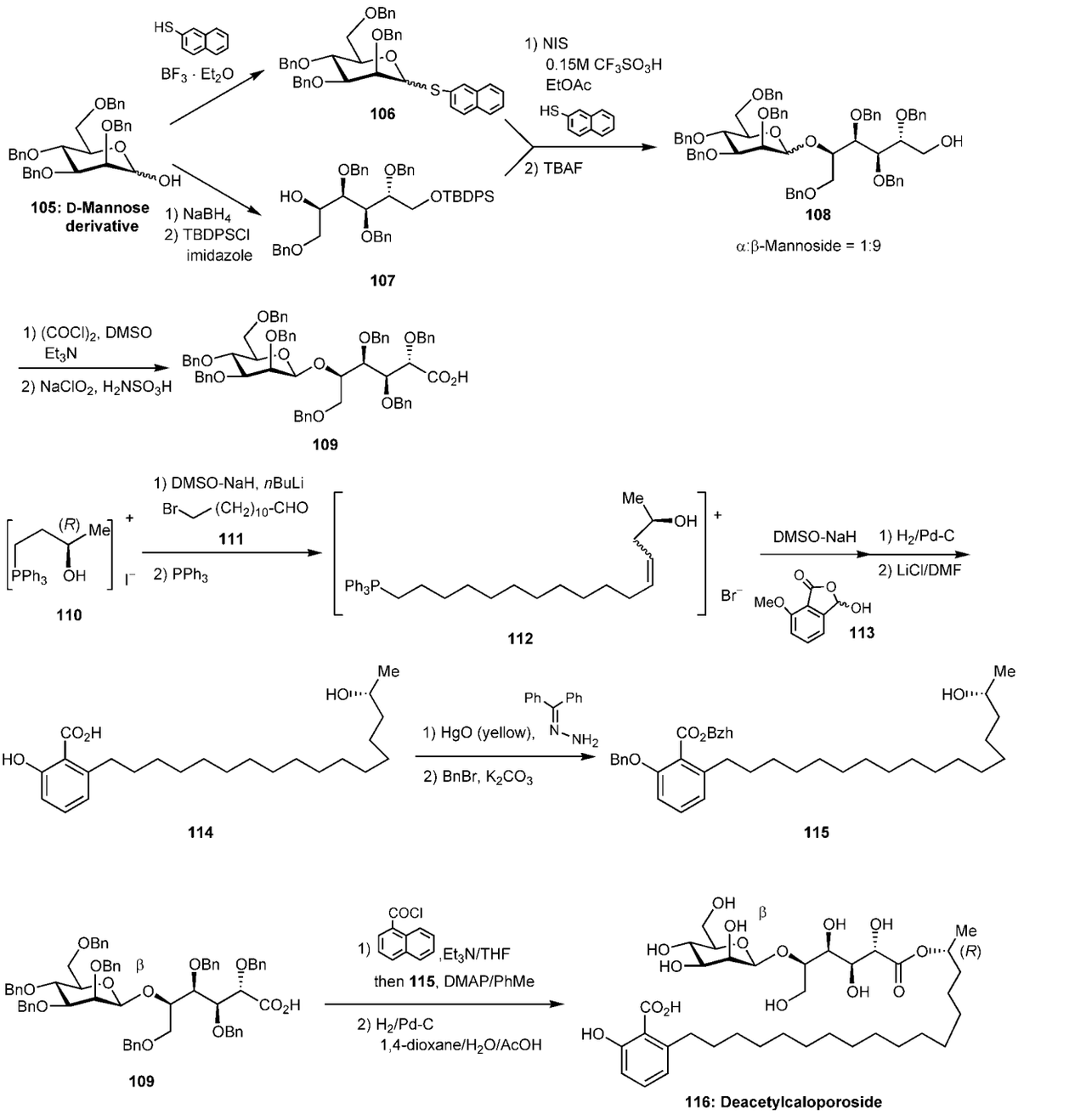
On the other hand, the ester **100** was converted by the aforesaid cerium(IV) oxidative demethylation and de-*O*-methylation into **103**. In the final stage, the favored epimerization of the C1 and C4 positions was realized by exposure to sulfuric acid in benzene along with some lactonization, followed by refluxing in toluene to complete the lactonization, affording (+)-kalafungin (**104**).[30] The epimerization was reasonably based on the keto-enol tautomerism due to both quinone carbonyl groups.

Hydrogenolysis of nanaomycin D (**102**) and kalafungin (**104**) furnished quantitatively their 4-deoxy analogues, nanaomycin A and 4-deoxykalafungin, respectively, which were found to show strong antimicrobial and antifungal activities at almost the same concentrations.[30]

5 Synthetic Organic Analysis of Mode of Action

5.1 The First Total Synthesis and Development of Deacetylcaloporosides

Deacetylcaloporoside (**116**) is a novel fungal inhibitor of the binding of [^{35}S]-labelled *tert*-butylbicyclophosphorothionate ([^{35}S]-TBPS) to the $GABA_A$/benzodiazepine chloride channel receptor complex *in vitro*.



Scheme 10. The first total synthesis of deacetylcaloporoside

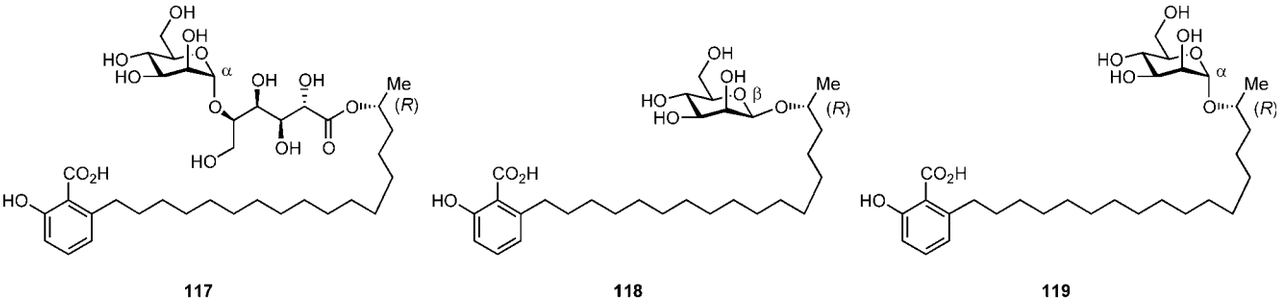


Figure 3. Caloporoside analogues

On the other hand, the analogous caloporoside has been reported to inhibit phospholipase C. It would, therefore, be important to examine the inhibitory activities of their analogs (**114** and **116–119**) (Scheme 10 and Figure 3).

Structurally, these compounds are salicylic acid derivatives containing the β-mannopyranoside, preparation of which is well-known to be generally difficult. Therefore, the selective β-mannopyranoside formation is a challenging problem.

The first total synthesis of deacetylcaloporoside (**116**) is based on coupling of a disaccharide-like segment (**109**) with a hydroxyheptadecyl salicylic acid segment (**115**).[31] The segment **109** was synthesized from methyl α-D-mannopyranoside through a common intermediate **105**. Methyl α-D-mannopyranoside was transformed to **105**, which reacted with 2-naphthalenethiol to afford the 1-thiomannoside **106** as a glycosyl donor on the one hand. On the other hand, $NaBH_4$ reduction of **105** followed by selective silylation gave the alcohol **107** as a glycosyl acceptor. In the β-D-mannosylation of **107**, a large number of methods including glycosyl donors [phenyl-1-thio- and (pyridine-2-yl)-1-thiomannosides, etc.] and solvents used were examined. The best result was realized by using the bulky glycosyl donor **106** and the acceptor **107** in EtOAc with NIS and TfOH, but a very important factor was the addition of 0.2 equivalents of 2-naphthalenethiol to the reaction mixture. This reaction could be explained as follows: both α- and β-thioglycosides **106** give the same intermediate oxocarbenium ion in the first stage. On the one hand, from the α-site of the oxocarbenium ion, the naphthalenethiol and alcohol can approach the anomeric carbon, but the thiol has a much stronger nucleophilicity than the alcohol. Therefore, the α-thioglycoside is reversibly produced. On the other hand, from the β-site, the naphthalenethiol is too bulky to approach the anomeric carbon because of the C2 axial and ring oxygen atoms. Then, the alcohol can approach there to react with the oxocarbenium ion gradually but irreversibly. Finally, the desired β-mannopyranoside is preferentially obtained. Thus, this process gave, after de-*O*-silylation, the desired β-mannoside **108** as the major product (72%) accompanied by the α-mannoside (8%). Swern oxidation of **108** followed by sodium chlorite oxidation afforded the corresponding carboxylic acid **109**.

The other segment **115** was synthesized from the phosphonium salt **110**, which was prepared from (*R*)-1,3-butanediol in our laboratories.[32] The Wittig reaction of **110** with the aldehyde **111** in the presence of DMSO-NaH and *n*BuLi gave the bromo-olefin, which was treated with PPh_3 to give the new phosphonium salt **112**. The use of both bases was critical for the complete Wittig reaction. The second Wittig reaction of **112** with the hemiacetal **113** afforded a mixture of olefins, which was submitted to catalytic reduction to yield the saturated alcohol, followed by de-*O*-methylation to give a salicylic acid derivative **114**. This was identical with the natural product, dihydromerulinic acid. Benzhydryl esterification of **114** followed by selective benzylation gave the alcohol **115**.

Table 1. Inhibitory activities [IC_{50} (μM/ml)] of caloporoside analogues in phospholipase C and $GABA_A$ receptor assays

Assays\Compounds	**116**	**117**	**118**	**119**	**114**
Phospholipase C	12	12	22	18	16
$GABA_A$	39	57	10	40	>100

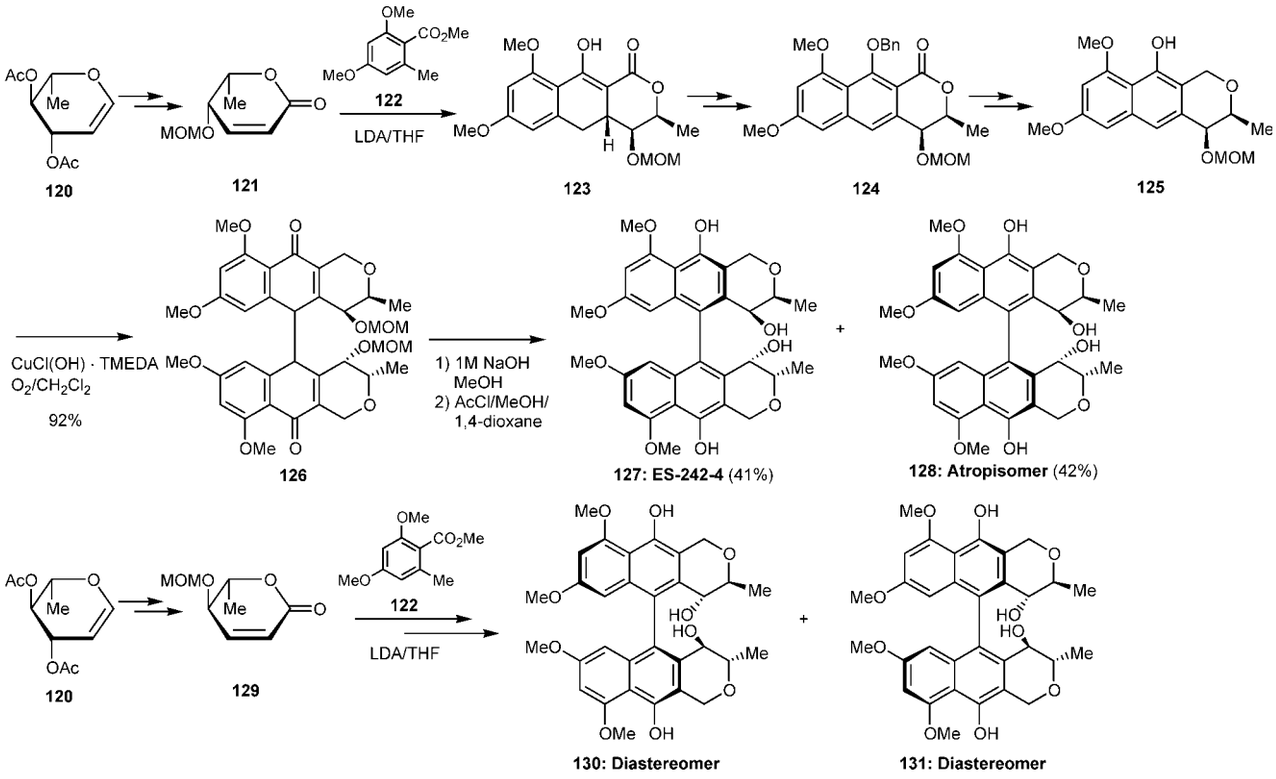
The final stage, coupling of the carboxylic acid **109** with the alcohol **115**, was accomplished by our mixed anhydride method.[33] After treatment of **109** with 1-naphthoyl chloride, the resulting mixed anhydride reacted with the alcohol **115** to give the ester. The following hydrogenolysis furnished the desired product **116**, which was identical with natural deacetylcaloporoside in all respects, including bioactivities. Similarly, the α-mannoside analogue **117** was obtained from the minor mannoside.

The direct β- and α-mannosides **118** and **119** were synthesized to further understand the structure-activity relationships. The glycosylation of **106** with the chain portion **115** was carried out under the above-mentioned conditions to give, after hydrogenolysis, **118** and **119**.[34]

The inhibitory activities for phospholipase C (rat brain) and the binding of the ligand to the $GABA_A$/benzodiazepine chloride channel receptor complex (rat brain) were assayed *in vitro* and are summarized in Table 1. All caloporoside analogues **116–119** were found to show significant biological activities and inhibit strongly phospholipase C activities in almost the same values. In the $GABA_A$ receptor ion channel, however, the β-mannoside analogues **116** and **118** showed stronger inhibitory activities of the binding of the ligand than their α-analogues **117** and **119**. Remarkably, the intact salicylic chain **114** exhibited strong inhibitory activity against phospholipase C, but no activity against the binding of the ligand in the $GABA_A$ receptor, suggesting that at least the chain portion **114** is essential for the appearance of the phospholipase C inhibitory activities.[34]

5.2 The First Total Synthesis and Development of *N*-Methyl-D-aspartate Receptor Antagonists, ES-242s

A bioxanthracene (–)-ES-242–4 (**127**) was isolated from the culture broth of *Verticillium* sp. in 1992 as one of eight antagonists for the *N*-methyl-D-aspartate (NMDA) receptor.[35] These novel natural products are reported to inhibit the [^3H]thienylcyclohexylpiper-



Scheme 11. The first total synthesis of ES-242s, *N*-Methyl-D-aspartate receptor antagonists

idine binding to rat crude synaptic membranes, and therefore, are of potential therapeutic interest for the treatment of neurodegenerative diseases. (–)-ES-242–4 (**127**) is structurally remarkable in having an axially chiral binaphthalene core that is adorned with two pyrans of the same absolute chirality. Our interest in the construction of densely functionalized naphthopyran ring systems, via tandem Michael–Dieckmann reactions, promoted us to attempt the first stereocontrolled total synthesis of (–)-ES-242–4 (**127**) (Scheme 11).[35]

To this end, the naphthopyran derivative **125** was our first target, which could be derived from the α,β-unsaturated lactone **121** and the *o*-methylbenzoate **122** through Michael and Dieckmann reactions. It was expected that the pivotal conversion of a monomer **125** to a dimer **127** could be accomplished by oxidative coupling (Scheme 11).

The α,β-unsaturated lactone **121**, which was derived from di-*O*-acetyl-L-rhamnal (**120**) according to reported procedures,[36] was submitted to Mitsunobu inversion with HCO_2H, followed by hydrolysis and methoxymethylation to afford **121**. On the other hand, the *o*-methylbenzoate **122** was obtained from 3,5-dihydroxytoluene under the protocols described by Solladié.[35]

Addition of lithiated **122** to **121** was followed by Dieckmann reaction to provide a single product **123** as expected from *trans* addition to the C4 *O*-MOM group. Aromatization of **123** was followed by *O*-benzylation to give **124**. Hydride reduction of **124** to the lactol was followed by treatment with Et_3SiH and TFA. The pyran **125** was obtained. Oxidative dimerization of **125** was examined under several conditions with a variety of metals such as Fe(II), Mn(II), and Cu(II). The best result was realized by the protocols reported by Noji, Nakajima and Koga using CuCl(OH) · TMEDA,[37] which was prepared from CuCl and TMEDA under oxygen. The diastereomeric mixture of **126** was produced as a stable intermediate (IR [KBr] $\nu = 1648\ cm^{-1}$). Finally, **126** was aromatized with aqueous NaOH followed by acid hydrolysis to remove the *O*-MOM group. Expectedly, two atropisomers were produced and isolated by silica gel column chromatography to give **127** and **128** in 37% and 38% overall yields, respectively. The former **127** was identical in all respects with an authentic sample of the natural (–)-ES-242–4.[35]

Furthermore, the diastereomeric analogues (**130** and **131**) of ES-242–4 (**127**) were synthesized from **120** by the similar synthetic strategies but without isomerization of the C4 hydroxy group to understand the structure-activity relationships. Similarly, Michael–Dieckmann-type reaction of **129** with **122** gave the tricyclic compound , which was converted into the atropisomers **130** and **131**.[38,39]

The absolute and atropisomeric structures of all

Table 2. Inhibitory activities [IC_{50} (μM/ml)] of ES-242s against the binding of [^3H]MK-801

Compounds	**127**	**128**	**130**	**131**
Activities	40	14	>200	0.4

isomers **127**, **128**, **130** and **131** were determined by their chemical derivation and the X-ray crystallographic analysis of the *O*-benzyl derivative of **130**.[35]

Finally, the structure-activity relationships were disclosed as follows (Table 2):[40] Two hydroxy groups at C-4 and C-4′ in **127** (ES-242–4) and **130** are observed to be far apart, while two hydroxy groups in **128** and **131** are close together. The shorter distance between these two hydroxy groups may be responsible for the stronger inhibitory activities against [^3H]MK-801 binding to the NMDA receptor.[40] Namely, **128** and **131** showed stronger activities than **127** and **130** suggesting that the appearance of their activities may be attributed to the intramolecular metal chelation formation between their two hydroxy groups.

6 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 author believes that the most important is to make utmost efforts towards realizing one's dreams, that is, to synthesize a target molecule by one's own concept and developed strategies. Such efforts will certainly produce the "art" as mentioned in the Introduction, in the reactions and/or products.

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