Review

Total synthesis and development of bioactive natural products

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Abstract: The first total synthesis and development of a variety of bioactive natural products have been accomplished by using carbohydrates as a chiral source. In addition, practically useful intermediates have been created, analogs of natural products have been prepared, their structure-activity relationships studied, and the large-scale preparations of medicinally useful compounds established. The key target molecules have been the "Big Four" antibiotics (macrolides, aminoglycosides, β-lactams and tetracyclines), pyranonaphthoquinone antibiotics, glycosidase inhibitors, and a side-chain of cephem antibiotics.

Keywords: natural products, antibiotics, total synthesis, enantiospecific synthesis, carbohydrates, glycosidase inhibitors

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, many chemists are able to synthesize natural products, even those having complicated structure, using advanced organic chemistry. However, not all such synthesis is above the mundane and can thus be raised to the level of "art". Hence, the unique significance of the synthesis and development of compounds which possess bioactivity. The author is of the opinion that "art" is a sublimate of originality, and has inherent special characteristics, and, in the 21st century, it should be recognized as such.

Among bioactive natural products, several antibiotics, termed the "Big Four", were the foremost subject of research at the time the author started his study of antibiotic synthesis.[1] As shown in Fig. 1, they were the macrolides (oleandomycin (**1**), erythromycin A (**2**), carbomycin, leucomycin A_3 (**3**), tylosin (**4**)), aminoglycosides (kanamycin (**5**), apramycin (**6**), saccharocin), β-lactams (thienamycin (**7**)) and tetracyclines (tetracycline (**8**)). The author's group has fortunately succeeded in completing the total syntheses of 93 diverse bioactive natural products, including the above-mentioned representatives of the big four antibiotics, and 86 of them represented the first total synthesis of the respective compounds.[2] It is noteworthy that most of optically active compounds have been synthesized efficiently using carbohydrates as chiral sources, to help determine the absolute structure and to clarify their structure-activity relationships. The methodologies devised are now established as the usual way in the natural product synthesis.[2),3]

The first total synthesis requires the creation of original synthesis concepts and methodologies, including 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 author introduces the dynamic as well as elegant parts of his total synthesis of practically-useful bioactive natural products, focusing not only on "art" but also on the significance of the total syntheses, and featuring his concept of "total synthesis reveals all".

2. Syntheses of the big four antibiotics from carbohydrates

2.1. Total synthesis of macrolide antibiotics and the related macrolactone antibiotics.

When a stone is thrown into a pond, several ripples

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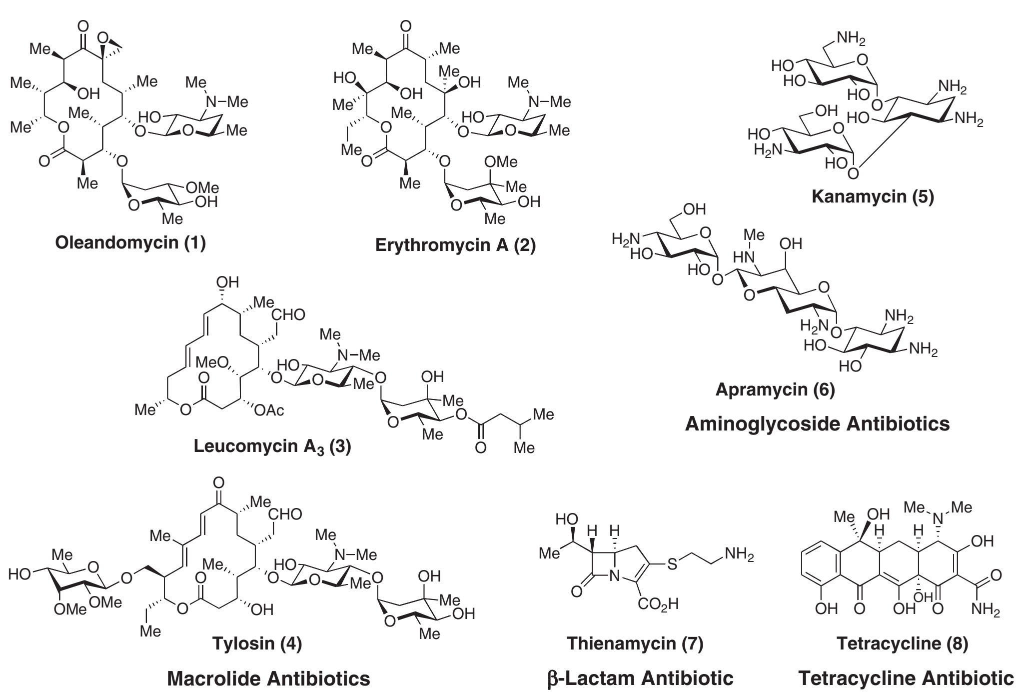

Fig. 1. The representatives of big four antibiotics.

are produced in succession, gradually radiating outward from the point of entry until they finally cover the whole pond. The 'stone' in macrolide synthesis was the news that R. B. Woodward had begun the total synthesis of erythromycin A (**2**) in 1973. His group accomplished the total synthesis in 1981. Some ripples from this point of origin are represented by Masamune's methymycin synthesis in 1977, Corey's erythronolide synthesis in 1978 and our syntheses of carbomycin B, leucomycin A_3 (**3**) and tylosin (**4**) in 1977 and 1981.[1),2)] The major targets, leucomycin A_3 and tylosin, were developed and marketed as medicinally useful antibiotics by Ōmura's group.[4)]

The first total syntheses of the 16-membered macrolide antibiotics, A26771B, carbomycin B, leucomycin A_3 (josamycin) and tylosin were accomplished in our laboratories.[1),2)] These syntheses were based on the stereoselective construction of the carbon skeletons from D-glucose as shown in Fig. 2.

2.1.1. *The first total synthesis of* 16-*membered macrolide antibiotics.* The first total synthesis of tylosin (**4**) was accomplished by coupling of the C1-C10 (**13**) and C11-C15 (**14**) segments derived from D-glucose, and the stereo- and regio-selective introduction of the three sugar moieties (**17**, **19** and **22**) (Scheme 1).[5)] The *C*-methyl compound **9**, derived from D-glucose, was converted into the unsaturated ester **10**, which was transformed to the methyl ketone **13** through a Michael addition with lithiated methyl methylthiomethyl sulfoxide to give the branched ester **12**. This addition of the lithiated reagent to the correct position from the desired side was effectively assisted by the metal chelation between the isopropylidene oxygen and the carboxyl oxygen of the transition state **11**, to give only the natural configuration at C6, as expected. This step was the first key component in completion of the synthesis.

The aldehyde **14** was also derived from D-glucose through the branched alcohol. Aldol condensation of **13** with **14** gave the unsaturated keto-ester **15**, which was transformed to the seco-acid, followed by lactonization according to Corey's procedure[6)] to give a tylonolide derivative **16**, following formation of the acetal of the aldehyde group. The ethylene acetal **16** was submitted to initial glycosylation with D-mycaminosyl bromide **17**, yielding the *β*-glycoside **18** after methanolysis. The second glycosylation, accomplished by our particular method,[7)] using the glycal of mycarose

Fig. 2. Total synthesis of 16-membered macrolide antibiotics from D-glucose.

Scheme 1. Total synthesis of tylosin.

19 plus 1,3-dibromo-5,5-dimethylhydantoin, to give the 2-bromo-2-deoxy-α-glycoside **20** followed by deprotection and debromination afforded de-mycinosyl tylosin (**21**). The third glycosylation, using the mycinosyl bromide **22** under Koenigs-Knorr conditions, followed by deprotection, completed the total synthesis of tylosin (**4**). The intermediary **21** was found to show strong antibiotic activities, even

Scheme 2. Total synthesis of oleandomycin.

Scheme 3. Total synthesis of erythromycin A.

against Gram-negative bacteria, while tylosin itself was not known to possess significant activities against them.[8]

2.1.2. *The first total synthesis of* 14-*membered macrolide antibiotics.* The author's group accomplished the first total synthesis of a 14-membered macrolide antibiotic, oleandomycin (**1**) (Scheme 2).[9] As mentioned above, this is also based on the construction of the skeleton from carbohydrates, L- and D-rhamnosides, **23** and **24**, and then cyclization by intramolecular Horner-Emmons reaction after esterification of the C1-C7 and C8-C14 segments, **27** and **28**, which were derived from the enantiomeric intermediates **25** and **26**. The sugar moieties **30** and **31** were regio- and stereoselectively introduced on the aglycone, oleandolide (**29**), to give oleandomycin (**1**).

The total synthesis of erythromycin A (**2**) was also accomplished in our laboratories via an original stereo- and regioselective introduction of sugar moieties to the aglycone **32** (Scheme 3).[10] The glycosylation to the C3 hydroxyl group of **29** and erythronolide derivative **33** predictively posed an extremely difficult problem, due to the low reactivity connected with the sterically crowded nature of the C3 hydroxyl group and the formation of a hydrogen bond between its hydroxyl group and C1 carbonyl group. However, our glycosylation, using the 2,6-anhydro-2-thio sugar **34** worked very efficiently to give the desired α-glycoside **35** in 92% yield. This was converted to erythromycin A (**2**) through desulfurization to give the 2,6-dideoxyglycoside.

We also developed several other glycosylation methods to synthesize many natural products.[11]

2.1.3. *Total synthesis of the macrolactone antibiotic, tubelactomicin A.* Tubelactomicin A (**46**) was isolated from the culture broth of *Nocardia* sp. MK703-102F1 and showed strong and specific antimicrobial activities against drug-resistant *Mycobacterium* sp.[12] Its structure was determined by X-ray crystallographic analysis to be the 16-membered lactone fused with a trans-decalin skeleton. Our total synthesis was completed from L-arabinose,[13] although, independently, another successful synthesis was reported.[14]

Scheme 4. Total synthesis of (+)-tubelactomicin A.

The stereochemical array of the northern part of the compound was derived from L-arabinose (**36**) (Scheme 4). The lactone **37** was submitted to stereoselective methylation and reductive ring-opening to give the diol **38**, possessing functionality to be the northern part **39**. The decalin moiety **43**, the southern part of tubelactomicin A, was constructed by intramolecular Diels-Alder reaction. Citronerol (**40**) was converted to the triene **41**. The stereoselective Diels-Alder reaction to construct the additional four chiral centers was realized by heating **41** in xylene, which gave the adduct **42** as a single product. This was converted to **43** to couple with the northern part **39**.

Treatment of the mixture of **39** and **43** under the conditions of Suzuki coupling gave the tetraene seco-acid **44** after desilylation.[15] The seco-acid **44** was submitted to the macrolactonization by the Shiina method[16] to construct the lactone **45**. Deprotection and selective oxidation afforded (+)-tubelactomicin A (**46**).

2.1.4. *The first total synthesis and determination of the absolute structure of (+)-cochleamycin A, which exhibits a unique 10-membered lactone.* (+)-Cochleamycin A (**58**) was isolated by the Kirin Brewery group from a cultured broth of *Streptomyces* sp. and showed cytotoxicity against P388 leukemia cells and antimicrobial activities.[17] The relative stereochemistry was elucidated and detected a 5-6-10-6-membered tetracyclic core (Scheme 5). We accomplished the first total synthesis of cochleamycin A, which facilitated determination of the absolute structure, by using intramolecular Diels-Alder reaction followed by direct construction of the 10 membered rings,[18] which was well-known to be difficult. After our first total synthesis, Roush's group reported another synthesis route.[19]

For maximum convergency, the acyclic precursor **52** of the Diels-Alder reaction was constructed by connection of two chiral segments, **48** and **50**, which were prepared from a small carbohydrate **47** and (*S*)-1,2,4-trihydroxybutane (**49**), respectively, by our previously developed methodologies.[20] Coupling of **48** and **50** proceeded smooth-

Scheme 5. Total synthesis of cochleamycin and tetrodecamycin.

ly to give the alcohol **51** in quantitative yield. This was selectively reduced to the *cis,trans*-diene structure, which was crucial to the construction of the desired 5-6-membered ring by intramolecular Diels-Alder reaction. Oxidation of the allylic alcohol gave the α,β-unsaturated aldehyde **52**, which was submitted to intramolecular Diels-Alder reaction in the presence of $Yb(fod)_3$ at 140 °C. The desired adduct **53** was obtained as a single product in good yield. This intramolecular Diels-Alder reaction produced four critical stereocenters, as expected. The desired cyclization of the bromo-aldehyde **54** was accomplished with SmI_2 to give the 10-6-5-membered tricyclic product **55** as a single product, comprising the fully elaborated structure ready for conversion to the cochleamycin (**58**). Lactonization of the seco-acid **56** was realized under Kita's conditions[21] to afford the 10-membered lactone concomitant with the formation of the δ-lactone ring. The allylic alcohol of the lactone **57** was oxidized to α,β-unsaturated ketone by exposure to MnO_2, followed by selective acetylation with AcONa and Ac_2O at 60 °C to afford (+)-cochleamycin A (**58**). The synthetic **58** was identical in all respects, including the optical rotation, with natural cochleamycin A, completing the first total synthesis to establish the absolute structure.

Thus, the simplest carbohydrate **47** was efficiently used for the total synthesis. In addition, the first total synthesis of another tetracyclic antibiotic having a unique γ-lactone, tetrodecamycin (**59**), was also accomplished by using **47** in our laboratories.[22]

2.2. Total synthesis of aminoglycoside antibiotics. The author's synthetic studies on antibiotics began with the determination of the absolute structure and the total synthesis of kanamycins (**5**) (Fig. 1).[23] Subsequently, in 1982, the author had another chance to undertake work on the total synthesis of aminoglycoside antibiotics, namely, apramycin (**6**) and saccharocin (**69**) (Scheme 6).

2.2.1. *The first total synthesis of apramycin and saccharocin.* Apramycin (**6**) and saccharocin (**69**)

Scheme 6. Total synthesis of apramycin and saccharocin.

are antibiotics active against Gram-positive and Gram-negative bacteria, including strains resistant to other aminoglycoside antibiotics. Structurally, **6** and **69** contain the unusual bicyclic aminooctodialdose and, in addition, 4-amino-4-deoxy-D-glucose and D-glucose units respectively.[24),25)] The first total synthesis of apramycin and saccharocin was accomplished in our laboratories in 1983.[26)] Our starting point was the known aminoglycoside antibiotic, neamine (**60**), which had already been synthesized by us. Neamine was converted into the aldehyde **61** by effective oxidation of the primary amino group (Scheme 6). The aldehyde **61** was converted by our carbon-elongation method to the acetyl glycal **62**. This was submitted to azidonitration using sodium azide and ammonium ceric nitrate to give azidoglycosyl nitrate **63**. The C3 position of the dimesylate **64** was selectively chlorinated to form the 3′-chloro compound, which was dechlorinated with tributylstannane to give the 3′-deoxy compound **65**. Epimerization of the 6′-hydroxy group, by heating **65** with sodium acetate trihydrate, yielded the *cis* cyclic carbamate **66** needed for the apramycin skeleton. Removal of all protecting groups gave aprosamine (**67**: Z = H), which was *N*-benzyloxy-carbonylated to **67**. In the glycosylation studies on **67**, the best result was realized under modified Mukaiyama conditions[27)] using 4-azido-2,3,6-tri-*O*-benzyl-4-deoxy-β-D-glucopyranosyl fluoride (**68**) to give the glycoside, subsequently deprotected by hydrogenolysis to furnish apramycin.

Similarly, saccharocin was synthesized by glycosylation of **67** with 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl fluoride.

2.3. Total synthesis and developments of β-lactam antibiotics. 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 development of novel methodologies for construction of their skeletons and side chains. Among the cephem antibiotics, the fourth generation has been especially noteworthy (Scheme 8).

2.3.1. *Total synthesis of the β-lactam antibiotic, (+)-thienamycin.* Thienamycin (**7**) was discovered in fermentation broths of *Streptomyces cattleya* and showed exceptional antibacterial potency and spectrum.[28)] (+)-4-Acetoxy-3-hydroxyethyl-2-azetidinone (**80**) has been well-known as a highly versatile intermediate for the synthesis of carbapenem antibiotics, such as thienamycin (Scheme 7).[29)] The synthesis of **80** was initiated by the Sankyo group, followed by the Merck group, and culmi-

Scheme 7. Total synthesis of thienamycin.

Scheme 8. Preparation of a side-chain of the fourth generation of cephem antibiotics.

nated in the practical preparation by two Japanese companies, using Noyori-Murahashi's asymmetric procedures and chem-enzymatic procedures, respectively.[29] The first stereocontrolled synthesis of (+)-thienamycin (**7**) was reported by the Merck group, and the transformation of **80** to **7** was also made more attractive by a second Merck group. Consequently, the synthesis of the azetidinone **80** constitutes a formal total synthesis of (+)-thienamycin (**7**).[30]

We reported a novel enantiospecific synthesis of **80** from a carbohydrate through our developed skeletal rearrangement and stereoselective epimerization (Scheme 7).[31] Our starting material was the commercially-available methyl 2-amino-2,6-dideoxy-α-D-glucopyranoside (**70**), which has also been isolated from natural sources.[31] Reaction of **70** with *o*-benzenedisulfonyl dichloride gave the cyclic sulfonate **71**, which was submitted to our skeletal rearrangement, including ring-contraction with potassium *tert*-butoxide. The resulting 3-formyl-furanoside **72** was oxidized to the carboxylic acid **73** in 91% yield. Removal of the *N*-sulfonyl group of **73** by Birch reduction produced the corresponding amino acid **74**. This was hydrolyzed and then esterified to give the furanose **75**. Oxida-

tion of **75** to the lactone **76** was the key step of our strategy, although the lactone could not be obtained under usual oxidation conditions. We finally discovered that, on exposure to Ag_2CO_3/Celite in benzene, the **75** was smoothly oxidized to the γ-lactone **76** despite the presence of the amino group.

The next important operation in the synthesis was to epimerize stereoselectively and simultaneously the configurations at the C2 and C3 positions of **76**. The best result was realized by using DBU in MeOH to afford predominantly the desired amino ester **77**. This result indicated that the C4 configuration of **76** controlled the stereoselective construction of the C2 and C3 configurations of **77**. Hydrolysis with 2M NaOH led to the hydroxy acid **78**, 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, **78** was silylated with trimethylsilyl chloride and hexamethyldisilazane (HMDS), followed by treatment with *tert*-butylmagnesium chloride to give the bis-silylated β-lactam **79**. Oxidative decarboxylation by $Pb(OAc)_4$ gave exclusively the desired (+)-4-acetoxy-3-hydroxyethyl-2-azetidinone (**80**), with removal of silyl groups. This was identical in all respects to the authentic sample.[30] Overall, the yield was approximately 35% in 11 steps from **70**. Key steps include our original skeletal rearrangement with ring-contraction, oxidation of the 2-aminofuranose, and stereoselective epimerization to the desired configurations.

2.3.2. *Practical preparation of (Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxy-iminoacetic 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 (**89**), have been reported as clinically useful antibiotics having excellent antimicrobial activities.[32] Their common acyl moiety at the C7 position corresponds to the *Z*-isomer (for example, **88**) of 2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(alkoxyimino)acetic acid (Scheme 8). The *E*-isomer is known to be of little value for β-lactam antibiotic use. Consequently, it was our intention to successfully develop a novel general method of entry into the *Z*-isomer, even though several methods have already been reported for the production of **88**.

We devised a 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 (**88**) based on the skeletal rearrangement of the amino-isoxazoles **81** or **84**, and stereoselective formation of **88** (Scheme 8).[33] 3-Amino-5-methoxyisoxazole (**81**) was subjected to the skeletal rearrangement in question. A suspension of methyl chloroformate and KSCN in acetonitrile was stirred at 70 °C for 30 min to give methoxycarbonyl isothiocyanate *in situ*, which in turn reacted with **81** to afford methyl 2-(5-methoxycarbonylamino-1,2,4-thiadiazol-3-yl)acetate (**83**) in 86% yield, through skeletal rearrangement of the intermediary thiourea derivative **82**. This reaction mechanism was reasonably supported by the isolation of the similar intermediate **85** from 3-aminoisoxazole (**84**). The compound **85** was also converted to **83** through **86**. Oxidation of **83** gave the 2-oxoacetates **87** (with DMSO and I_2 in the presence of catalytic amounts of H_2SO_4) in 83% yield. The moderate yield was ascribed to purification difficulties due to their polar nature. Without isolation of the keto-ester, the methyl ester **83** was quantitatively converted into the desired *Z*-isomer of 2-(methoxyimino)-acetate. Saponification provided the target product **88** in quantitative yield. This was derived to cefozopran (**89**), which was marketed in 1995.[34]

2.4. Total syntheses and developments of tetracycline antibiotic and relating antibiotics. For almost half a century, tetracycline (**8**) has been widely recognised as a major antibiotic, due to both its unique structural features as well as antibacterial activities.[35] The total synthesis of tetracycline families was initiated by Woodward's 6-demethyl-6-deoxytetracycline synthesis in 1962, followed by Muxfeldt's terramycin synthesis in 1968, culminating Stork's 12a-deoxytetracycline synthesis in 1996.[1),36] However, all these syntheses have been accomplished only in racemic forms. The total synthesis of natural (−)-tetracycline (**8**) remained an unanswered challenge, despite the remarkable achievements as described above. In 2000, the first total synthesis of (−)-tetracycline (**8**) was completed in our laboratories using D-glucosamine as a chiral starting material, which allows stereospecific construction of the densely and sensitively functionalized A ring (Scheme 9).[37] In 2005, Myers' group presented a second synthesis of (−)-tetracycline.[38]

Scheme 9. Total synthesis of natural (−)-tetracycline.

Scheme 10. Total synthesis of UCE6.

Synthetic studies on related tetracyclic antibiotics were also carried out in our laboratories, and the first total synthesis of UCE-6 (**110**) was accomplished (Scheme 10).[39]

2.4.1. *The first total synthesis of natural (−)-tetracycline.* Anhydrotetracycline (**103**) was our first target (Scheme 9)[37] as it provides a viable synthetic relay from **103** to tetracycline (**8**) via a two-step hydration at the 5a,6-position.[36] A reliable 12a-hydroxylation is required for the synthesis of **103**. The starting-point glucosaminide **90**, which was prepared from D-glucosamine, was converted into the selenide **91**. Treatment of **91** with borane followed by H_2O_2 oxidation stereoselectively gave the alcohol by simultaneous formation of a new olefin group, which was benzylated to the olefin **92**. This was submitted to Ferrier reaction with $HgCl_2$ to give the cyclohexanone **93**. The $[4+2]$ cycloaddition of the cyclohexenone, which was derived from **93** by dehydration, with the butadiene **95** did not proceed because of the steric repulsion. Therefore, **93** was epimerized at C2 and dehydrated to the isomer **94**. The α-hydroxymethyl group was an important factor for stereospecific introduction of the hydroxy group at 12a to give a furan derivative **100**. The cycloaddition with **95** in the presence of 2,6-di-*tert*-butyl-4-methylphenol (DBMP) proceeded from the β-face of **94**, 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 **96**. The tandem Michael-Dieckmann type reaction of **96** with the isobenzofuranone **97** gave the tetracyclic compound **98**.[40] One of the key problems of

this synthesis was the stereoselective introduction of a hydroxyl group at C12a. Manipulation of the protective groups of **98** gave the diol **99**, which was adequate to oxidate the right wing. The primary alcohol of **99** participated in the bromination of C1-12a olefin to give the desired **100**. Treatment of **100** with a mixture of PCC and PDC in dichloromethane, followed by purification with silica gel, afforded the aldehyde **101** in 61% yield. This transformation realized the concurrent oxidation of primary and secondary alcohols accompanied by introduction of the C12a hydroxyl group. The resulting **101** was converted to the nitrile **102** by a newly-developed method using hydroxylamine followed by dehydration with 1,1′-carbonyldiimidazole (CDI). The nitrile **102** was transformed through **103** and the perhydroxide **104** into (−)-tetracycline (**8**), which was identical with natural (−)-tetracycline in all respects, thus completing the first total synthesis. Our tetracycline synthesis was the first to be accomplished, some 50 years after its structure had been determined.

2.4.2. *The first total synthesis of the tetracyclic antibiotic, UCE6.* The tetracyclic UCE6 (**110**) was isolated from fermentation broth of Actinomycetes strain and possessed strong antitumor ability.[41] From the retrosynthetic perspective, the tetracyclic skeleton is expected to be accessible by the tandem Michael-Dieckmann-type reaction of the benzofuranone **108** with the cyclic α,β-unsaturated ketone **107** (Scheme 10). The **108** was derived from 2-methylresorcinol and the **107** was prepared by $[4 + 2]$ cycloaddition of the cyclohexenone **105** with the diene **106**.[39] The coupling of **107** and **108** was effectively carried out under basic conditions to give the tetracyclic product, which was aromatized to the alcohol **109** as a single product, under mild oxidation conditions concomitant with removal of one of the O-methoxymethyl groups. Deprotection of **109** afforded racemic UCE6 (**110**), which was identical with the natural product.

3. Total synthesis of pyranonaphthoquinone antibiotics from carbohydrates using novel strategies

Pyranonaphthoquinone antibiotics (**111**–**116**) have been shown to possess significant antimicrobial, antifungal and antitumor activities (Fig. 3). Structurally, the stereo-alignment of nanaomycin D (**112**) is included in nanaomycin A (**111**) and BE-54238B (**116**), while that of kalafungin (**113**) is in medermycin (**114**) and BE-52440A (**115**). The representative antibiotics are nanaomycin A (**111**) and D (**112**), which were isolated and developed by Ōmura's group.[42] These unique structures have drawn attention both for their synthesis using new methodologies and for the creation of novel biologically active compounds. The author's group accomplished the first total syntheses of these antibiotics, and developed a synthetic strategy for the stereoselective construction of densely-functionalized pyranonaphthoquinones from carbohydrates.[2]

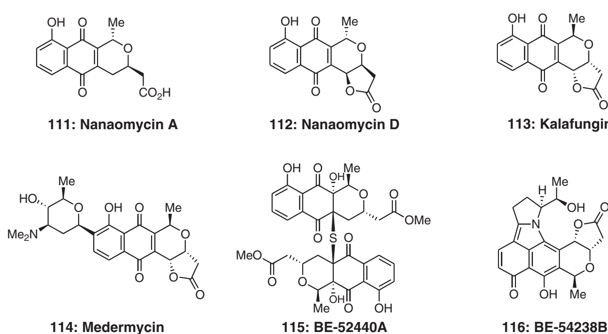

Fig. 3. Representative pyranonaphthoquinone antibiotics.

3.1. The first total synthesis of nanaomycin D and its enantiomer, kalafungin — the "enantiodivergent" total synthesis. Carbohydrates have been used widely as chiral sources in stereospecific syntheses of natural products, as mentioned above.[3] Although various carbohydrates are available, in most of them one enantiomer is abundant while another isomer is difficult to get in much quantity. Thus, it is hoped that both enantiomeric chiral synthons in the total synthesis are derived from only one abundant enantiomer of a carbohydrate. During synthetic studies on nanaomycin D (**112**) and its enantiomer, kalafungin (**113**), in our laboratories, a new methodology was developed to enable synthesis of both enantiomers from a single enantiomeric carbohydrate, creating "enantiodivergent synthesis".[43] The critical point of the methodology was catalytic isomerization of stereocenters (Scheme 11). On the protected hydroquinone **117**, the isomerization at the C3 position was carried out to obtain the lactone **118** by elimination-recyclization equilibrium under basic conditions. Using the quinone **119**, the isomerization at C1 and C4 positions was realized to afford the lactone **120** by

Scheme 11. Enantiodivergent methodologies for synthesis of pyranonaphthoquinone skeletons.

Scheme 12. Enantiodivergent total synthesis of nanaomycin D and its enantiomer, kalafungin.

enolization-protonation equilibrium under acidic conditions. This methodology was widely applied to the construction of pyranonaphthoquinone antibiotics. The enantiodivergent synthesis of nanaomycin D (**112**) and kalafungin (**113**) based on this strategy is shown in Scheme 12.[43)]

Methyl L-rhamnoside (**121**) was converted into the 2,3-di-*O*-carbonyl-4-*O*-tosyl derivative **122** in 80% overall yield in a one pot reaction, with trichloromethyl chloroformate and then tosyl chloride in pyridine (Scheme 12). Treatment of **122** with zinc powder and sodium iodide in reflux aqueous acetonitrile gave the unsaturated alcohol **123**. This olefin formation was also developed in our laboratories. Oxidation of **123** with pyridinium chlorochromate afforded the stable α,β-unsaturated ketone **124**. Michael-Dieckmann condensation of **124** with 4-methoxy-3-(phenylsulfonyl)-1(3*H*)-isobenzofuranone prepared by Hauser's procedures gave naphthopyranone **125**, which was transformed to the lactol **126** in three steps. The lactol **126** was submitted to Wittig reaction, which afforded the *cis*-lactone **127** and the *trans*-hydroxyl ester **128**. The lactone **127** was oxidized to the quinone **129**, which was subsequently de-*O*-methylated to give nanaomycin D (**112**). The hydroxyl ester **128** was converted to the quinone **130**, which was subjected to the above-mentioned acidic isomerization to produce kalafungin (**113**), the enantiomer of nanaomycin D (**112**).

3.2. The first total synthesis of BE-52440A and nanaomycin E. (+)-BE-52440A (**115**) was

Scheme 13. Total synthesis of nanaomycin E and BE-52440A.

Scheme 14. Enantiodivergent total synthesis of BE-54238B.

reported as an antitumor agent, produced by a *Streptomyces* strain, by the Banyu group in 2000.[44] The structure was identified as a dimer of nanaomycin derivatives bridged with sulfur (Scheme 13), although the relative configuration remained unknown. The first total synthesis of **115** was accomplished by us to help determine the absolute structure.[45] We assumed that **115** would be biogenetically synthesized by epoxy-opening dimerization of OM-173 αE (**132**), which was isolated by the Ōmura group.[46] It was possible to obtain the antibiotic **132** by stereospecific epoxydation of pyranonaphthoquinone **131**, which could be derived from the lactone **127** and γ-hydroxyester **128** by our enantiodivergent strategy, as mentioned above.[43] The key reaction sequence is a regioselective epoxy-opening dimerization of the tetra-substituted **132** with Na_2S by S_N2 reaction of the intermediary *tert*-thiolate.

Firstly, both enatiomeric intermediates [(−)- and (+)-**131**] were selectively synthesized from the key intermediates **127** and **128**. Subsequent epoxidation afforded (+)- and (−)-OM-173 αE [(+)- and (−)-**132**]. The one epimer, (+)-**132**, was hydrolyzed to natural (+)-nanaomycin E (**133**),[47] which was also isolated by Ōmura's group, while the other (−)-**132**, on treatment with Na_2S, was converted to natural (+)-BE-52440A (**115**). Thus their absolute structures were determined.

3.3. The first total synthesis of BE-54238B — the iminoquinone isomerization. We achieved the enantioselective total synthesis of BE-54238B (**116**) to confirm its absolute structure (Scheme 14).[48] The bromo precursor **134** was

Scheme 15. Total synthesis of β-D-glucosidase inhibitor, cyclophellitol.

prepared as mentioned above for the synthesis of nanaomycin D (**112**). The **134** was lithiated to couple with the L-pyroglutamic acid derivative **135** to obtain the ketone **136**. After construction of the pyrrolidine **137**, Wittig reaction gave the *cis*-lactone **138** and the *trans*-hydroxyl ester, in 67% and 22% yields, respectively. The lactone **138** was suitable for the synthesis of the natural product **116**, while the hydroxyl ester could also be transformed to **138** in high yield by heating with $KHCO_3$ and 18-crown-6 in DMF. Acidic removal of two Boc groups in **138** was followed by oxidative de-*O*-methylation to give the quinone **139**. This was effectively cyclized to the hexacyclic product **140** through proton-tautomerization. This was de-*O*-methylated by BCl_3 to give the re-tautomerized compound **116**, which was identical in all respects with natural BE-54238B.

4. Total syntheses of useful glycosidase inhibitors and synthetic organic analysis of their mode of action

4.1. The first total synthesis and chemical design of useful glycosidase inhibitors. In recent years, much attention has been focused on the synthesis and development of glycosidase inhibitors because of an increasing awareness of the vital role played by carbohydrates in biological processes. Therefore, the chemical and biochemical studies on glycosidase inhibitors may lead to understanding of the molecular basis of intractable diseases such as diabetes mellitus, cancer and AIDS, and may also provide therapeutic approaches to them. As part of an ongoing program to clarify the mode of action of glycosidase inhibitors, we have synthesized cyclophellitol (**147**), nagstatin (**158**), pyralomicin 1c (**172**), valienamine (**173**) and validamine (**174**), and their analogs which have different configurations and functionalities. These syntheses have featured general methods of entry into the carbasugars and their nitrogenous analogs.[49)–51)]

4.1.1. *Cyclophellitol and its analogs.* Cyclophellitol (**147**) is a novel β-D-glucosidase inhibitor isolated from culture filtrates of a mushroom, *Phellinus* sp., and structurally, is a fully oxygenated cyclohexane, corresponding to a carba analog of D-glucopyranose.[49)] The first total synthesis of **147** was mainly based on the stereospecific intramolecular $[3+2]$ cycloaddition of a nitrile oxide to an olefin (Scheme 15).[50)] Its analogs **148**–**151**, including the aziridine and thiirane analogs, have also been enantiospecifically synthesized in our laboratories to clarify their mode of action in glycosidase inhibition (Table 1).[51)]

Intramolecular cycloaddition of the oxime **142**, which was derived from L-glucose (**141**), was realized by using NaOCl via the intermediary nitrile oxide **143** to afford the isoxazoline **144** as a single product. The stereospecific reaction was found to be governed by the configuration of the C2 substituent. The isoxazoline opening was achieved by reduction of **144** with Raney Ni-W4 in the presence of AcOH to afford the keto-diol, which was silylated with diethylisopropylsilyl triflate to give the protected ketone **145**. The diethylisopropylsilyl (DEIPS) group was developed in our laboratories and effectively used as an *O*-protecting group,[52)] because this silyl group was found to be readily removed under hydrogenolysis conditions using $Pd(OH)_2$. The mesylate **146** was subjected to hydrogenolysis followed by epoxidation to give cyclophellitol (**147**), thereby completing the first total synthesis.

From the fact that cyclophellitol exhibits a

Table 1. Glycosidase inhibitory activities of cyclophellitol (**147**), nagstatin (**158**) and their analogs

Glycosidases	Inhibitors (IC_{50} : μg/ml)		
α-D-Glucosidase	**148 (10)**		
β-D-Glucosidase	**147 (0.8)**	**149 (0.22)**	**159 (0.14)**
β-D-Galactosidase	**150 (10)**	**160 (0.0016)**	**163 (0.081)**
α-D-Mannosidase	**151 (19)**		
β-D-Mannosidase	**161 (0.0023)**	**164 (0.078)**	
***N*-acetyl-β-D-Glucosaminidase**	**157 (0.0015)**	**158 (0.004)**	**162 (0.0017)**

very high β-D-glucosidase inhibiting activity, we expected that 1,6-*epi*-cyclophellitol (**148**) and α-*manno* analog **151** would inhibit α-D-glucosidase and α-D-mannosidase activities, respectively.[53)] *Epi*-cyclophellitol (**148**), β-*galacto* and α-*manno* analogs (**150** and **151**) were similarly synthesized from methyl α-D-galactopyranoside. The aziridine analog **149** and thiirane analogs were also prepared from **147** and **148**. The thiirane analogs having an S atom showed no bioactivity.[53),54)]

4.1.2. *Nagstatin and its analogs.* Nagstatin (**158**) is an *N*-acetyl-β-D-glucosaminidase inhibitor isolated from the fermentation broth of *Streptomyces amakusaensis*.[55)] Nagstatin (**158**) and a variety of its analogs **157**–**164** were first synthesized from carbohydrates through the inter- and intramolecular nucleophilic reactions with the imidazole and triazole moieties to clarify the structure-activity relationships (Table 1). These compounds were expected to serve as antagonists of the corresponding β-glycopyranosides. As a starting point, de-branched nagstatin (**157**) and its hydroxyl analog **160** were effectively synthesized from 2,3,5-tri-*O*-benzyl-L-ribofuranose (**152**) (Scheme 16).[56)] Reaction of **152** with lithiated *N*-tritylimidazole gave the L-*allo* (**153**) and L-*altro* (**154**) derivatives in a ratio of approximately 1:1. This lack of selectivity was expected from unspecified chelation of **152** and both products were useful for the synthesis of analogs. De-*N*-tritylation and the S_N2-type intramolecular cyclization of **153** or **154** were effectively realized in a one-pot by reaction with $BnSO_2Cl$ in pyridine to give, preferentially, the 5-*O*-sulfonate which, after treatment with Ac_2O gave the desired acetate, which was de-*O*-acetylated to the nitrogenous D-talose analog **155** or D-galactose analog **156**. The analog **156** was deprotected to the *galacto* analog **160** of nagstatin (Table 1). The effective de-*N*-tritylation seemed to be affected by the pyridinium acetate produced. The inversion of the hydroxyl group in **155** using HN_3 afforded the azido derivative, which was subjected to hydrogenolysis and *N*-acetylation, leading to the *N*-acetyl-D-galactosamine analog **157**, which corresponded to de-branched nagstatin.

Similarly, nitrogenous D-glucose (**159**), D-mannose (**161**) and *N*-acetyl-D-glucosamine (**162**) analogs were efficiently prepared from an L-xylofuranose derivative. The triazole analogs **163** and **164** were predominantly synthesized from the aforesaid **152** and L-xylofuranose by reaction with lithiated triazole.[57)] The enantiospecific synthesis of nagstatin (**158**) was achieved by introduction of an acetic acid unit on **157** through the *C*-

Scheme 16. Total synthesis of nagstatin.

allylation.[58] Synthetic nagstatin (**158**) was identical with the natural product, confirming the absolute structure.

4.1.3. *Analysis of mode of action by structure-activity relationships.* With regard to bioactive compounds, our interest goes far beyond total synthesis methodologies. Thus we have elucidated the mechanism of action of various natural products through detailed investigation of their structure-activity relationships exploiting our synthetic organic analysis.[2] For example, the glycosidase inhibiting activities of cyclophellitol (**147**), 1,6-*epi*-cyclophellitol (**148**), nagstatin (**158**) and their analogs, **148**–**151** and **157**–**164**, were generally assayed according to the method reported by Saul *et al.* and are shown in Table 1.[51] In dramatic contrast to natural cyclophellitol (**147**), the *epi*-epoxide **148** exhibited inhibiting activity only against α-D-glucosidase. The β-*galacto* **150** and α-*manno* **151** analogs, as expected, showed inhibitory activity against β-galacto- and α-mannosidases, respectively, and the β-aziridine analog **149** showed very high inhibitory activity against β-glucosidase. Structurally, cyclophellitol and its aziridine analog **149** have *quasi*-equatorially oriented C1-O and C1-N bonds, which correspond to the equatorial C1-O bond of β-D-glucopyranosides, whereas *epi*-cyclophellitol and α-*manno* analog **151** have *quasi*-axial C1-O bonds, corresponding to the axial C1-O bond of α-D-glycopyranosides. Their glycosidase-inhibiting activities emphasized that the α- and β-glycosidases recognized specifically the C1 positions and the residual portions as corresponding to those of α- and β-glycopyranosides. Consequently, these glycosidase inhibitors, **147**–**151**, serve as antagonists of the corresponding α- and β-D-glycopyranosides.

The nitrogenous α-glucosidase inhibitors such as valienamine (**173**) and validamine (**174**) were synthesized and found to serve as antagonists of the corresponding α-D-glucopyranoside (Scheme 17).[59] In fact, a validamine derivative, voglibose (**175**), was developed and marketed as the anti-diabetes drug “Basen”.[60]

It was also found that *N*-acetyl-D-galactosamine analog **157** exhibited strong bioactivity, even against *N*-acetyl-β-D-glucosaminidase, similar to nagstatin (**158**). Consequently, it was expected to inhibit *N*-acetyl-β-D-galactosaminidase, although this glycosidase is no longer available. Other synthesized analogs, **157**–**164**, showed strong inhibitory activity specifically against each of their corresponding β-D-glycosidases (Table 1).[53],[56],[57] All analogs possess a *quasi*-equatorially oriented C8a-N1 bond, which corresponds to an equatorial C1-O bond of β-glycopyranosides, due to the fused imidazole and triazole rings. The configurations from C8a to C5 of the analogs parallel the alignment from C1 to C5 of the corresponding glycopyranosides. Their substrate-specific activities emphasized that the analogs serve essentially as antagonists of the corresponding stereochemically oriented β-D-glycopyranosides. These findings are similar to those of cyclophellitol and its analogs.

Thus, these results demonstrated the theoretical possibility of chemically creating inhibitors against all glycosidases (Table 1).

4.2. The first total synthesis of a glucosidase inhibitor, pyralomicin 1c. Pyralomicin 1c (**172**) was isolated from a culture broth of *Microtetraspora spiralis* and found to have novel antitumor properties, including glucosidase-inhibiting activities.[61] We therefore synthesized **172** to

Scheme 17. Total synthesis of pyralomicin 1c and carba-sugars.

confirm the absolute structure (Scheme 17).[62) The aglycone, pyralomicinone (**170**), possesses the 5-hydroxy[1]benzopyrano[2,3-b]pyrrol-4-(1*H*)-one structure in which the proton on the pyrrole nitrogen is slightly acidic. Thus, Mitsunobu conditions would be suitable for the glycosylation step, which was first developed in our laboratories.[63)]

We had already synthesized **170** during the first total synthesis of pyralomicin 2c, the glucose analog of **172**.[64)] The carba-sugar moiety **169** was prepared from L-arabinonic acid γ-lactone **165**, which was derived from L-arabinose. This methodology had already been developed for synthesis of progesterone receptor ligands, PF1092s in our laboratories,[65)] and applied to the total synthesis of valienamine (**173**) and validamine (**174**).[59)] The phenylsulfonate **166** was silylated to the opened chain enolate **167** in one step by simultaneous formation of an enol silyl ether and an *O*-silyl secondary alcohol. The $SnCl_4$-promoted aldol condensation of **167** resulted in the formation of the cyclohexenone **168**, which was converted to **169** through the introduction of a hydroxymethyl group. Although **169** possessed three free hydroxyl groups, the allyl hydroxyl group at C1 was expected to be more reactive than the others. Both components, **169** and **170**, were coupled under modified Mitsunobu's conditions to give, predominantly, the desired product **171** with inversion. Acid deprotection produced pyralomicin 1c, which was identical with the natural product.

5. Conclusion

Recent progress in the total syntheses and development of selected bioactive natural products is reviewed. Most of the total syntheses that have been completed in our laboratories have been the first ever accomplished. Establishment of the total syntheses by use of carbohydrates as chiral sources created a comprehensive method to investigate a variety of bioactive natural products. 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, particularly with respect to bioactive natural product synthesis. In essence, the author believes that the most important factor is to make the utmost effort towards realizing one's goals, that is, to synthesize a target molecule by one's own concepts and strategies. However, through completion of such enterprise and skill, one can certainly produce the "art", as mentioned in the Introduction, which becomes manifest in the reactions and/or products.

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Profile

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