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 A3 (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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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 A3 (3) and tylosin (4) in 1977 and 1981.1,2 The major targets, leucomycin A3 and tylosin, were developed and marketed as medicinally useful antibiotics by Omura’s group.4)

The first total syntheses of the 16-membered macrolide antibiotics, A26771B, carbomycin B, leucomycin A3 (josamycin) and tylosin (4) 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. 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 ketoester 15, which was transformed to the seco-acid, followed by lactonization according to Corey’s procedure6) 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.
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
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, oleandomylene (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)
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 tetaene seco-acid 44 after desilylation. The seco-acid 44 was submitted to the macrolactonization by the Shiina method 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. 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, which was well-known to be difficult. After our first total synthesis, Roush’s group reported another synthesis route.

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. Coupling of 48 and 50 proceeded smoothly.
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 SmI₂ 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 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 MnO₂, followed by selective acetylation with AcONa and Ac₂O 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)
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 3'-chloro compound 63. The C3 position of the dimesylate 64 was selectively chlorinated to form the 3'-chboro 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-benzoyloxy-carbonylated to 67. In the glycosylation studies on 67, the best result was realized under modified Mukaiyama conditions27) 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 cephalosporin 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-
nated in the practical preparation by two Japanese companies, using Noyori-Murahashi’s asymmetric procedures and chem-enzymatic procedures, respectively. 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).

We reported a novel enantiospecific synthesis of 80 from a carbohydrate through our developed skeletal rearrangement and stereoselective epimerization (Scheme 7). Our starting material was the commercially-available methyl 2-amino-2,6-deoxy-α-D-glucopyranoside (70), which has also been isolated from natural sources. 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$_2$CO$_3$/Celite in benzene, the 75 was smoothly oxidized to the $\gamma$-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 $\beta$-lactam 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 $\beta$-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-butyllimagnesium chloride to give the bis-silylated $\beta$-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. 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-amino furanose, 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)-7,7'-[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. 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 $\beta$-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 aminoisoxazoles 81 or 84, and stereoselective formation of 88 (Scheme 8).

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 methoxy carbonyl 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$_2$SO$_4$) 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.

2.4. Total syntheses and developments of tetracycline antibiotic and relating antibiotics. For almost half a century, tetracycline (8) has been widely recognized as a major antibiotic, due to both its unique structural features as well as antibacterial activities. 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. 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). In 2005, Myers’ group presented a second synthesis of (−)-tetracycline.
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 H2O2 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 HgCl2 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 /C11-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 /C12-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
was the first to be accomplished, some 50 years the first total synthesis. Our tetracycline synthesis the diene 106 (107) methylresorcinol and the 8 tetracycline (108) followed by dehydration with 1,1 anone Michael-Dieckmann-type reaction of the benzofur skeleton is expected to be accessible by the tandem From the retrosynthetic perspective, the tetracyclic resulting introduction of the C12a hydroxyl group. The protective groups of this synthesis was the stereoselective introduction of primary and secondary alcohols accompanied by transformation realized the concurrent oxidation 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. From the retrosynthetic perspective, the tetracyclic skeleton is expected to be accessible by the tandem Michael-Dieckmann-type reaction of the benzo furanone 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 Omura’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) 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 stereo-specific 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
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(3H)-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
reported as an antitumor agent, produced by a \textit{Streptomyces} strain, by the Banyu group in 2000.\textsuperscript{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 \textsuperscript{115} was accomplished by us to help determine the absolute structure.\textsuperscript{45) We assumed that \textsuperscript{115} would be biogenetically synthesized by epoxy-opening dimerization of OM-173 $\alpha$E (\textsuperscript{132}), which was isolated by the O¯ mura group.\textsuperscript{46) It was possible to obtain the antibiotic \textsuperscript{132} by stereospecific epoxydation of pyranonaphthoquinone \textsuperscript{131}, which could be derived from the lactone \textsuperscript{127} and $\gamma$-hydroxyester \textsuperscript{128} by our enantiodivergent strategy, as mentioned above.\textsuperscript{43) The key reaction sequence is a regioselective epoxy-opening dimerization of the tetra-substituted \textsuperscript{132} with Na$_2$S by $\text{S}_2$N$_2$ reaction of the intermediary tert-thiolate.

Firstly, both enantiomeric intermediates [(-)- and (+)-\textsuperscript{131}] were selectively synthesized from the key intermediates \textsuperscript{127} and \textsuperscript{128}. Subsequent epoxidation afforded (+)- and (-)-OM-173 $\alpha$E [(-)- and (+)-\textsuperscript{132}]. The one epimer, (+)-\textsuperscript{132}, was hydrolyzed to natural (+)-nanaomycin E (\textsuperscript{133}), which was also isolated by O¯ mura’s group, while the other (-)-\textsuperscript{132}, on treatment with Na$_2$S, was converted to natural (+)-BE-52440A (\textsuperscript{115}). Thus their absolute structures were determined.

\subsection*{3.3. The first total synthesis of BE-54238B — the iminoquinone isomerization.}

We achieved the enantioselective total synthesis of BE-54238B (\textsuperscript{116}) to confirm its absolute structure (Scheme 14).\textsuperscript{48) The bromo precursor \textsuperscript{134} was}
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-hydroxy 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 KHCO₃ 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 BCl₃ 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 carbohydrates 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
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 thirane analogs were also prepared from 147 and 148. The thirane 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, debranched 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 Sβ2-type intramolecular cyclization of 153 or 154 were effectively realized in a one-pot by reaction with BuSO2Cl in pyridine to give, preferentially, the 5-O-sulfonate which, after treatment with Ac2O 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 HN3 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-

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

| Glycosidases          | Inhibitors (IC50 : µg/ml) |
|-----------------------|---------------------------|
| α-D-Glucosidase       |                           |
| β-D-Glucosidase       | 148 (10)                  |
| β-D-Galactosidase     | 147 (0.8)                 |
| α-D-Mannosidase       | 150 (10)                  |
| β-D-Mannosidase       | 151 (19)                  |
| β-D-Galactosaminidase | 157 (0.0015)              |
| N-acetyl-β-D-Glucosaminidase | 158 (0.004)  |

Nagstatin (158) and its analogs (150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164) 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 Sβ2-type intramolecular cyclization of 153 or 154 were effectively realized in a one-pot by reaction with BuSO2Cl in pyridine to give, preferentially, the 5-O-sulfonate which, after treatment with Ac2O 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 HN3 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-
allylation. Synthetic nagstatin (158) was identical with the natural product, confirming the absolute structure.

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. 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 1.41 In dramatic contrast to natural cyclophellitol (147), the epiperoxide 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 epicyclophellitol 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).49 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 C8α-N1 bond, which corresponds to an equatorial C1-O bond of β-glycopyranosides, due to the fused imidazole and triazole rings. The configurations from C8α 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 glycosidase-inhibiting activities.61 We therefore synthesized 172 to
confirm the absolute structure (Scheme 17). The aglycone, pyralomicinone (170), possesses the 5-hydroxy[1]benzopyrano[2,3-b]pyrrol-4-(1H)-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.

We had already synthesized 170 during the first total synthesis of pyralomicin 2c, the glucose analog of 172. The carba-sugar moiety 169 was prepared from L-arabinonic acid/C13-lactone 165, which was derived from L-arabinose. This methodology had already been developed for synthesis of progesterone receptor ligands, PF1092s in our laboratories, and applied to the total synthesis of valienamine (173) and validamine (174). 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 SnCl4-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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