REVIEW ARTICLE

Total synthesis of the big four antibiotics and related antibiotics

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The first total syntheses of a variety of antibiotics have been accomplished by using carbohydrates as a chiral source. The key target molecules were members of the ‘Big Four’ classes of antibiotics (macrolides, aminoglycosides, β -lactams and tetracyclines), naphthoquinone antibiotics and their related antibiotics.

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INTRODUCTION

‘Antibiotic’ was one of the greatest scientific discoveries in the 20th century and the masterpiece of the total synthesis of antibiotics and bioactive natural products is a display of beauty, achieving a status of ‘art’ in organic chemistry.

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’. The author is of the opinion that ‘art’ is a sublimation of originality, and has inherent special characteristics, and, even in the 21st century, it should be recognized as such.

Among bioactive natural products, several antibiotics, termed as the ‘Big Four’, were the foremost subject of research at the time the author started his study of antibiotic synthesis.¹ As shown in Figure 1, they were the macrolides (oleandomycin (1), erythromycin A (2), leucomycin A₃ (3), tylosin (4)), aminoglycosides (kanamycin A (5), apramycin (6)), β -lactams (thienamycin (7)) and tetracyclines (tetracycline (8)). The author’s group has fortunately succeeded in completing the total syntheses of 102 diverse bioactive natural products, including the above-mentioned representatives of the big four antibiotics, and 95 of them represented the first total synthesis of the respective compounds.^{2–6} 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.^{2–6}

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 big four antibiotics and related compounds, focusing not only on ‘art’ but also on the significance of the total syntheses, and featuring his concept of ‘all begins from total synthesis’.

TOTAL SYNTHESIS OF MACROLIDE ANTIBIOTICS AND THE RELATED MACROLACTONE ANTIBIOTICS

When a stone is thrown into a pond, several ripples 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 including the author 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.^{1–6}

The first total synthesis of 16-membered macrolide antibiotics

The first total syntheses of the 16-membered macrolide antibiotics, A26771B (1980),⁷ carbomycin B (1980),^{8,9} leucomycin A₃ (josamycin, 1980),^{8,9} and tylosin (1982)^{10,11} were accomplished in our laboratories.^{1–6} These syntheses were based on the stereoselective construction of the carbon skeletons from D-glucose as shown in Figure 2.

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) (Figure 3).^{10,11} 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

Figure 1 Representatives of big four antibiotics.

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

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 procedure¹² to give a tylosin 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,^{8,13} using the glycal of mycarose 19 and 1,3-dibromo-5,5-dimethylhydantoin, to give the 2-bromo-2-deoxy- α -glycoside 20 followed by deprotection and debromination to afford de-mycinosyl tylosin (21). This product was also isolated from the natural sources.¹⁴ The third glycosylation, using the mycinosyl bromide 22 under Koenigs–Knorr conditions, followed by deprotection, completed the total synthesis of tylosin (4).

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** (Figure 5).¹⁷ 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.^{18,19}

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.²⁰ 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,²¹ although, independently, another successful synthesis was reported.²²

The stereochemical array of the northern part of the compound was derived from L-arabinose (**36**) (Figure 6). After stereoselective introduction of C-methyl group, the lactone **37** was submitted to 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.²³ The seco-acid **44** was submitted to the macrolactonization by the Shiina method²⁴ to construct the lactone **45**. Deprotection and selective oxidation afforded (+)-tubelactomicin A (**46**).

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.²⁵

The relative stereochemistry was elucidated and detected a 5-6-10-6-membered tetracyclic core (Figure 7). 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,²⁶ which was well-known to be difficult. After our first total synthesis, Roush's group reported another synthesis route.²⁷

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.²⁸ Coupling of **48** and **50** proceeded smoothly 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 conditions²⁹ 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.³⁰

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 A (**5**), B and C (Figure 1).^{31,32} Subsequently, in 1982, the author had another chance to undertake work on the total synthesis of aminoglycoside antibiotics, namely, apramycin (**6**) and saccharocin (**69**) (Figure 8).

Figure 5 Total synthesis of erythromycin A.

Figure 6 Total synthesis of (+)-tubelactomicin A.

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 amino-octodialdose and, in addition, 4-amino-4-deoxy-D-glucose and D-glucose units, respectively.^{33,34} The first total synthesis of apramycin and saccharocin was accomplished in our laboratories in 1983.³⁵ 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 (Figure 8). 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 conditions³⁶ 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.

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 (Figure 9). Among the cephem antibiotics, the fourth generation has been especially noteworthy (Figure 10).

Total synthesis of the β-lactam antibiotic, (+)-thienamycin

Thienamycin (**7**) was discovered in fermentation broths of *Streptomyces cattleya* and showed exceptional antibacterial potency

Figure 7 Total synthesis of cochleamycin A and tetrodecamycin.

and spectrum.³⁷ (+)-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 (Figure 9).³⁸ The synthesis of **80** 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 and chem-enzymatic procedures, respectively.³⁸ 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**).^{39,40}

We reported a novel enantiospecific synthesis of **80** from a carbohydrate through our developed skeletal rearrangement and stereoselective epimerization (Figure 9).⁴¹ 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.⁴¹ 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**. Oxidation 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, **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 2 M 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, followed by treatment with *tert*-butylmagnesium chloride to give the bis-silylated β -lactam **79**. Oxidative decarboxylation by $\text{Pb}(\text{OAc})_4$ 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 $\sim 35\%$ 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.

Figure 8 Total synthesis of apramycin and saccharocin.

Figure 9 Total synthesis of thienamycin.

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)-7 β -(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.⁴² 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 (Figure 10). 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

Figure 10 Practical preparation of a side-chain of the fourth generation of cephem antibiotics.

on the skeletal rearrangement of the aminoisoxazoles **81** or **84**, and stereoselective formation of **88** (Figure 10).^{43,44} 3-Amino-5-methoxyisoxazole (**81**) was subjected to the skeletal rearrangement in question. A suspension of methyl chloroformate and potassium thiocyanate 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-oxoacetate **87** (with DMSO and I₂ in the presence of catalytic amounts of H₂SO₄) in 83% yield. The moderate yield was ascribed to purification difficulties due to their polar nature. Without isolation of the keto-ester **87**, 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 1995.⁴⁵

CHALLENGE TO THE TOTAL SYNTHESIS OF TETRACYCLINE ANTIBIOTICS AND RELATED 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.⁴⁶ 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.^{1,47} 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 (Figure 18).⁴⁸ In 2005, Myers' group presented the second synthesis of (–)-tetracycline.⁴⁹

Before and during the challenge to the total synthesis of tetracycline, we have been synthesizing naphthoquinone antibiotics to develop our own methodologies for the construction of the skeleton. Namely, pyranonaphthoquinone antibiotics (**90–95**) were synthesized by unique strategies including Michael–Dieckmann cyclization. After the tetracycline synthesis, the author completed the first total synthesis of a furanonaphthoquinone antibiotic, lactonamycin (**120**), and a pseudo-dimer of tetracycline, hibarimicinone (**150**), which represented the culmination of synthetic strategies and methodologies on antibiotics by the author.

Total synthesis of naphthoquinone-related antibiotics using carbohydrates and novel strategies

Pyranonaphthoquinone antibiotics (**90–95**) have been shown to possess significant antimicrobial, antifungal and antitumor activities (Figure 11). Structurally, the stereo-alignment of nanaomycin D (**91**) is included in nanaomycin A (**90**) and BE-54238B (**95**), while that of kalafungin (**92**) is in medermycin (**93**) and BE-52440A (**94**). The representative antibiotics are nanaomycin A (**90**) and D (**91**), which were isolated and developed by Ōmura's group.^{50,51} Moreover, a furanonaphthoquinone antibiotic, lactonamycin (**120**), was found to have the hexacyclic system and the glycosidic bond at the tertiary alcohol. 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 naphthoquinones using carbohydrates.^{2–6}

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.^{1–6} 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

Figure 11 Representative pyranonaphthoquinone antibiotics.

carbohydrate. During synthetic studies on nanaomycin D (**91**) 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'.^{52–54} The critical point of the methodology was catalytic isomerization of stereocenters (Figure 12). On the protected hydroquinone **96**, the isomerization at the C3 position was carried out to obtain the lactone **97** by elimination-recyclization equilibrium under basic conditions. Using the quinone **98**, the isomerization at C1 and C4 positions was realized to afford the lactone **99** by enolization–protonation equilibrium under acidic conditions. This methodology was widely applied to the construction of pyranonaphthoquinone antibiotics. The enantiodivergent synthesis of nanaomycin D (**91**) and kalafungin (**92**) based on this strategy is shown in Figure 13.^{52–54}

Methyl L-rhamnoside (**100**) was converted into the 2,3-di-O-carbonyl-4-O-tosyl derivative **101** in 80% overall yield in a one pot reaction, with trichloromethyl chloroformate and then tosyl chloride in pyridine (Figure 13). Treatment of **101** with zinc powder and sodium iodide in reflux aqueous acetonitrile gave the unsaturated alcohol **102**. This olefin formation was also developed in our laboratories. Oxidation of **102** with pyridinium chlorochromate afforded the stable α,β -unsaturated ketone **103**. Michael–Dieckmann condensation of **103** with 4-methoxy-3-(phenylsulfonyl)-1-(3*H*)-isobenzofuranone prepared by Hauser's procedures gave naphthopyranone **104**, which was transformed to the lactol **105** in three steps. The lactol **105** was submitted to Wittig reaction, which afforded the *cis*-lactone **106** and the *trans*-hydroxyl ester **107**. The lactone **106** was oxidized to the quinone **108**, which was subsequently de-O-methylated to give nanaomycin D (**91**). The hydroxyl ester **107** was converted to the quinone **109**, which was subjected to the above-mentioned acidic isomerization to produce kalafungin (**92**), the enantiomer of nanaomycin D (**91**).

The first total synthesis of BE-52440A and nanaomycin E. (+)-BE-52440A (**94**) was reported as an antitumor agent, produced by a *Streptomyces* strain, by the Banyu group in 2000.⁵⁵ The structure was identified as a dimer of nanaomycin derivatives bridged with sulfur (Figure 14), although the relative configuration remained unknown. The first total synthesis of **94** was accomplished by us to help determine the absolute structure.⁵⁶ We assumed that **94** would be

biogenetically synthesized by epoxy-opening dimerization of OM-173 α E (**111**), which was isolated by the Ōmura group.⁵⁷ It was possible to obtain the antibiotic **111** by stereospecific epoxidation of pyranonaphthoquinone **110**, which could be derived from the lactone **106** and γ -hydroxyester **107** by our enantiodivergent strategy, as mentioned above.^{52–54} The key reaction sequence is a regioselective epoxy-opening dimerization of the tetra-substituted **111** with Na₂S by S_N2 reaction of the intermediary *tert*-thiolate.

Firstly, both enantiomeric intermediates ((–)- and (+)-**110**) were selectively synthesized from the key intermediates **106** and **107**. Subsequent epoxidation afforded (+)- and (–)-OM-173 α E ((+)- and (–)-**111**). The one epimer, (+)-**111**, was hydrolyzed to natural (+)-nanaomycin E (**112**),⁵⁸ which was also isolated by Ōmura's group, while the other (–)-**111**, on treatment with Na₂S, was converted to natural (+)-BE-52440A (**94**). Thus, their absolute structures were determined.

The first total synthesis of BE-54238B—the iminoquinone isomerization. We achieved the enantioselective total synthesis of BE-54238B (**95**) to confirm its absolute structure (Figure 15).⁵⁹ The bromo precursor **113** was prepared as mentioned above for the synthesis of nanaomycin D (**91**). The **113** was lithiated to couple with the L-pyrogutamic acid derivative **114** to obtain the ketone **115**. After construction of the pyrrolidine **116**, Wittig reaction gave the *cis*-lactone **117** and the *trans*-hydroxyl ester, in 67% and 22% yields, respectively. The lactone **117** was suitable for the synthesis of the natural product **95**, while the hydroxyester could also be transformed to **117** in high yield by heating with KHCO₃ and 18-crown-6 in dimethylformamide. Acidic removal of two Boc groups in **117** was followed by oxidative de-O-methylation to give the quinone **118**. This was effectively cyclized to the hexacyclic product **119** through proton-tautomerization. This was de-O-methylated by BCl₃ to give the retautomerized compound **95**, which was identical in all respects with natural BE-54238B.

The first total synthesis of a furanonaphthoquinone antibiotic, lactonamycin. Lactonamycin (**120**, Figure 16) was isolated from a culture broth of *Streptomyces rishiriensis* MJ773-88K4 by Matsumoto *et al.*⁶⁰ in 1996. Lactonamycin (**120**) showed potent antimicrobial activities against gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* as well

Figure 12 Enantiodivergent methodologies for synthesis of pyranonaphthoquinone skeletons.

Figure 13 Enantiodivergent total synthesis of nanaomycin D and its enantiomer, kalafungin.

as antitumor activities.^{60,61} The unique structure of **120** was determined by X-ray crystallography and degradation studies. By the remarkable structure and activities, many groups have been attracted and challenged to synthesize this compound,^{62,63} nevertheless, the total synthesis has been unprecedented.

We accomplished the first total synthesis of lactonamycin (**120**) through Michael–Dieckmann type cyclization.⁶⁴ The stereoselective glycosylation of the tertiary alcohol with the 2,3-deoxysugar is challenging, and rhodinoside derivative **123** was used as a resolving agent for racemic **121**.

Thioester **122** corresponding to the DEF segment was synthesized from 4-bromo-3,5-dimethylphenol **124** (Figure 17). *O*-Methylation of **124** and subsequent lithiation followed by methoxycarbonylation gave the ester **125**, which was transformed to the bicyclic **126**. After exchange of *O*-Me to *O*-Bn group, the bromide was converted into the sulfone **122**.

The synthesis of the ABC segment **121** started from mono-*O*-methyl-dihydroxybenzoic acid **127** (Figure 17). Reduction of methyl ester and the successive oxidation of the aromatic ring in the presence of ethylene glycol gave quinone mono-acetal **128**. Dihydroxylation of

the tri-substituted olefin of **128** provided the triol, which was subjected to stereoselective reduction and protection to obtain the diol **129**. After oxidation of the secondary alcohol of **129**, the tertiary alcohol was protected as triethylsilyl ether to yield **130**. Methyl propiolate was introduced in the stereospecific manner under the basic conditions to give the *cis*-tertiary diol **131**. De-silylation and the conjugate addition of the resulting primary alcohol proceeded to afford **132**. Treatment of the ester **132** in methanol under the acidic conditions to give the γ -lactone, followed by oxidation to the 1,4-diketone **121**.

Rhodinoside thioether derivative **123** was synthesized from *L*-rhamnal through Ferrier reaction and inversion of the configuration of the secondary alcohol by Mitsunobu reaction.

The racemic **121** was subjected to glycosylation with **123** in the presence of silver triflate¹⁸ to give a diastereomeric mixture of only α -glycosides under a strong anomeric effect (Figure 17). The mixture was separated by silica gel column chromatography to give the optically pure **133** in 42% (practically 84%).

Michael–Dieckmann type condensation^{2–6} of the enone **133** with the thioester **122** gave the protected lactonamycin **134**.

Figure 14 Total synthesis of OM-173 E, nanaomycin E and BE-52440A.

Figure 15 Enantiodivergent total synthesis of BE-54238B.

Figure 16 Retrosynthesis of lactonamycin.

Hydrogenolysis of **134** afforded lactonamycin (**120**), completing the total synthesis.

The first total synthesis of natural (–)-tetracycline

Anhydrotetracycline (**147**) was our first target (Figure 18)^{48,65} as it provides a viable synthetic relay from **147** to tetracycline (**8**) via a two-step hydration at the 5a, 6-position.⁴⁷ A reliable 12a-hydroxylation is required for the synthesis of **147**. The starting-point glucosaminide **135**, which was prepared from D-glucosamine,

was converted into the selenide **136**. Treatment of **136** with borane followed by H₂O₂ oxidation stereoselectively gave the alcohol by simultaneous formation of a new olefin group, which was benzylated to the olefin **137**. This was submitted to Ferrier reaction with HgCl₂ to give the cyclohexanone **138**. The [4 + 2] cycloaddition of the cyclohexenone, which was derived from **138** by dehydration, with the butadiene **140** did not proceed because of the steric repulsion. Therefore, **138** was epimerized at C2 and dehydrated to the isomer **139**. The α -hydroxymethyl group was an important factor for

Figure 17 Total synthesis of lactonamycin.

stereospecific introduction of the hydroxy group at C12a to give a furan derivative **145**. The cycloaddition with **140** in the presence of 2,6-di-*tert*-butyl-4-methylphenol proceeded from the β -face of **139**, 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 **141**. The tandem Michael–Dieckmann type reaction of **141** with the isobenzofuranone **142** gave the tetracyclic compound **143**.⁶⁶ One of the key problems of this synthesis was the stereoselective introduction of a hydroxyl group at C12a. Manipulation of the protective groups of **143** gave the diol **144**, which was adequate to oxidate the right wing. The primary alcohol of **144** participated in the bromination of C1–12a olefin to give the desired **145**. Treatment of **145** with a mixture of pyridinium chlorochromate and pyridinium dichromate in dichloromethane, followed by purification with silica gel, afforded the aldehyde **146** in 61% yield. This transformation realized the concurrent oxidation of primary and secondary alcohols accompanied by introduction of the C12a hydroxyl group. The resulting **146** was converted to the nitrile **147** by a newly-developed method using hydroxylamine followed by dehydration with 1,1'-carbonyldiimidazole. The nitrile **147** was transformed through **148**

and the perhydroxide **149** 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.⁴⁸

The first total synthesis of a pseudo-dimer of tetracycline, hibarimicinone

Hibarimicins, isolated from the culture broth of *Microbispora rosea* subsp. *hibaria*, have been known to possess *v*-Src tyrosine kinase inhibitory activity and differentiation inducing activity of HL-60 cells.^{67,68} Among them, hibarimicinone (**150**) has the most potent activity of *v*-Src tyrosine kinase inhibition without differentiation inducing activity. The structure of hibarimicinone (**150**) has been disclosed to be a fascinating pseudo-dimer of tetracycline, which includes 13 stereogenic centers as well as the axial chirality (Figure 19). On this final chapter, the author presents the first total synthesis of hibarimicinone (**150**).^{69,70}

The strategy chosen to construct the eight-ring skeleton was a double Michael–Dieckmann type cyclization^{2–6,64,71} using the chiral biaryl thiolactone **152** (DE segment) and the chiral decalin **151**

Figure 18 Total synthesis of natural (–)-tetracycline.

Figure 19 Retrosynthesis of hibarimicinone.

(AB and GH segments) in Figure 19. Difference of the oxidation stage of thiolactones in biaryl **152** should reflect the oxidation stage of CD and EF rings. At first, the synthesis of decalin **151**, the common structure of AB and GH rings, started from the enone **157**,^{72–74} which was derived from D-arabinose **153** through D-arabinonic acid γ -lactone **154** (Figure 20). This methodology had already been developed for synthesis of progesterone receptor ligands, PF1092s in our laboratories,⁷² and applied to the total syntheses of pyralomicin **1c**,⁷³ valienamine and validamine.⁷⁴ The phenylsulfonate **155** was silylated to the opened chain enolate **156** in one step by simultaneous formation of an enol silyl ether and an O-silyl secondary alcohol. The

SnCl₄-promoted aldol condensation of **156** resulted in the formation of the key enone **157**. Diels–Alder reaction proceeded stereoselectively to give adduct **158**, which possessed the desired 9R configuration (hibarimicinone numbering). Jones oxidation, converting the allyl trimethylsilyl ether to the enone, and the subsequent reduction with SmI₂ to remove the sulfone gave the Sm(III) enolate **159**, which was oxidized to provide stereoselectively the tertiary alcohol **160**. The C10 α -alcohol **160** was converted into the β -alcohol **161** through regio- and stereoselective de-O-silylation, oxidation and reduction. Protection of the tertiary alcohol of **161** accompanied with formation of the dienyl silyl ether **162** as desired in the right ring, and the subsequent Grignard reaction introduced an allyl group in a stereoselective manner to give the tertiary alcohol **163**. After silylation of the tertiary alcohol, treatment of the dienyl silyl ether with DBU in hot toluene in the presence of *i*-PrOH promoted the regioselective de-silylation, followed by hydrogenation of the *exo* olefin to yield the enone decalin segment **151** corresponding to the AB and GH segments (Figure 20).

For constructing the DE segment, the chiral biaryl thiolactone **152** was obtained as shown in Figure 21. The commercially available carboxylic acid **164** was converted into **165** through *ortho*-lithiation-methylation of the corresponding amide and regioselective de-O-methylation. Phenol **165** was subjected to oxidative dimerization by using silver trifluoroacetate, and the resulting bisphenol was protected as benzoate **166**. Two benzylic positions of **166** were brominated and the sequential substitution with thioacetate ion and methanolysis produced the thiolactones **167** with free phenols. The racemic biaryl **167** was converted to the diastereo-mixture of mono-camphanate, which was resolved by column chromatography and subsequent crystallization to give the optically pure **168** ($R^* = (-)$ -camphanyl group) in good yield. The desired isomer **168** was converted into symmetrically protected **169**. Mono-bromination of **169** and

Figure 20 Synthesis of AB and GH segments of hibarimicinone.

Figure 21 Synthesis of DE segment of hibarimicinone.

substitution with *n*-butanol were performed in one pot to give the chiral biaryl **152**.

With both segments **151** and **152** in hand, their conversion to an eight-ring skeleton in a one-pot reaction was explored (Figure 22). In preliminary studies, we found that Michael–Dieckmann type cyclization using the non-substituted benzothiolactone (the left ring type of **152**) proceeded in THF, while the cyclization with the alkoxybenzothiolactone (the right ring type) was promoted in toluene. Pyridine suppressed generation of polymerized products. Therefore, the enone **151** and bis-thiolactone **152** were treated with base in the mixed solvent including THF, toluene and pyridine to promote double Michael–Dieckmann type cyclization to give the eight rings, and the resulting thiolates were methylated to provide the enol form **170** and

its labile keto form in G ring, the latter of which was smoothly converted into the enol **170** in the presence of LiCl. Hydrolysis of semithioacetal was performed with AgNO₃, and the subsequent treatment with DBU gave the hydroquinone at the C ring, followed by oxidation of the C ring and aromatization of F ring, including elimination of thioether and tautomerization to afford **171** in one pot. The ether bond crossing the AB rings was formed with excess amounts of LiI by enolization at the BC rings, followed by conjugate addition to the enone **172**. The simultaneous de-*O*-methoxymethylation gave the free phenols (D and E rings) in **173**. The resulting **173** was immediately oxidized to the quinone **174**. Finally, de-*O*-silylation as well as de-*O*-methylation and tautomerization at the CD rings were achieved under the acidic conditions to give hibarimicinone (**150**),

Figure 22 Total synthesis of hibarimicinone.

completing the first total synthesis.^{69,70} This is the 102nd accomplishment of total syntheses by the author.

CONCLUSION

The total synthesis of the big four antibiotics as well as the related antibiotics are 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, before 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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Structures of the 102 Synthesized Compounds

1: Neamine
(1967)

2: Trehalosamine
(1967)

3: Kanamycin A
(1968)

4: Kanamycin B
(1968)

5: Kanamycin C
(1968)

6: Chymostatin A: X=L-Leu
(1973)

7: Chymostatin B: X=L-Val
(1973)

8: Chymostatin C: X=L-Ile
(1973)

9: Carbomycin B
(1977)

11: Leucomycin A₃
(1980)

10: Hirsutene
(1979)

12: Coriolin
(1980)

13: A26771B
(1980)

14: Erythromycin A
(1981)

15: Tylosin
(1981)

16: Isotronecanol
(1982)

17: Rosmarinecine
(1982)

18: Apramycin
(1983)

Structures of the 102 Synthesized Compounds (continued)

19: Saccharocin
(1983) **20: Arphamenine A (2*R*,5*S*)**
21: Epi-arphamenine A (2*S*,5*S*)
(1983) **22: Nanaomycin D**
(1985) **23: Kalafungin**
(1985) **24: Nanaomycin A**
(1985) **25: Elaiophyllin**
(1986) **26: Indisocin**
(1987) **27: N-Methylindisocin**
(1987) **28: Erbstatin**
(1987) **29: Azepinomycin**
(1987) **30: Oleandomycin**
(1988) **31: Pyridomycin**
(1989) **32: Rifamycin W**
(1990) **33: Cyclophellitol**
(1990) **34: Medermycin (Lactoquinomycin)**
(1990) **35: Allosamizoline**
(1991) **36: Herbimycin A**
(1991) **37: Maniwamycin A**
(1993) **38: Maniwamycin B**
(1993) **39: Neopyrrolomycin**
(1993)

Structures of the 102 Synthesized Compounds (continued)

40: Pyrzinostatin
(1994)

41: AB3217-A
(1994)

42: Nagstatin
(1995)

43: Gualamycin
(1995)

44: Deacetyl-caloporoside
(1996)

45: Calbistrin A
(1997)

46: PF1092A
(1997)

47: PF1092B
(1997)

48: PF1092C
(1997)

49: MS-444
(1997)

50: Terpestacin
(1998)

51: KD16-U1
(1998)

52: Glyoxalase I Inhibitor
(1998)

53: ES-242-4
(1998)

54: ES-242-5
(1999)

55: Sideroxylonal B
(1999)

56: Sideroxylonal C
(1999)

57: Pyralomicin 2c
(1999)

58: PF1163A
(1999)

59: PF1163B
(1999)

Structures of the 102 Synthesized Compounds (continued)

60: Pyralomicin 1c
(2000) **61: PC-3 (SF2420B)**
(2000) **62: YM-30059**
(2000) **63: Validamine**
(2000) **64: Valienamine**
(2000) **65: Tetracycline**
(2000) **66: Thienamycin**
(2000) **67: Asterriquinone B1**
(2001) **68: Demethylasterriquinone B1**
(2001) **69: Quinolactacin B**
(2001) **70: LL-Z1640-2**
(2001) **71: Luminacin C₁**
(2001) **72: Luminacin C₂**
(2001) **73: Napyradiomycin A1**
(2002) **74: UCE6**
(2002) **75: 4-O-(4''-O-Acetyl-α-L-rhamnopyranosyl)-ellagic acid**
(2003) **76: Cochleamycin A**
(2003) **77: Lymphostin**
(2004) **78: BE-54238B**
(2004) **79: Trichostatin D**
(2005) **80: Xanthocillin X dimethylether**
(2005) **81: Xanthocillin X**
(2005) **82: YM182029**
(2005) **83: AM6898D**
(2005)

Structures of the 102 Synthesized Compounds (continued)

84: Tubelactomicin A
(2006)

85: Tetrodecamycin
(2006)

86: Actinopyrone A
(2006)

87: Lagunamycin
(2006)

88: Vinaxanthone
(2007)

89: YCM1008A
(2007)

90: TMC-66
(2007)

91: OM-173αE
(2007)

92: Nanaomycin E
(2007)

93: (+)-BE-52440A
(2007)

94: (-)-TMC-264
(2008)

95: Nidulalin A
(2009)

96: Benzopyrenomycin
(2009)

97: Epi-cochlioquinone A
(2010)

98: Lactonamycin
(2010)

99: K1115 B_{1α}
(2011)

100: K1115 B_{1β}
(2011)

101: XR774
(2011)

102: Hibarimicinone
(2012)

List of 102 synthesized compounds

No	The big four antibiotics (aminoglycoside, beta-lactam, macrolide and tetracycline antibiotics)		Compounds	Year	Journal title	Volume no.	Issue no.	Page range
	The first total synthesis							
1	○	○	Neamine	1967	<i>J. Antibiot.</i>	20	1	53–54
2	○	○	Trehalosamine	1967	<i>J. Antibiot.</i>	20	6	388–389
3	○	○	Kanamycin A	1968	<i>J. Antibiot.</i>	21	5	367–388
4	○	○	Kanamycin B	1968	<i>J. Antibiot.</i>	21	6	424–425
5	○	○	Kanamycin C	1968	<i>J. Antibiot.</i>	21	2	162–163
6	○		Chymostatin A: X = L-Leu	1973	<i>J. Antibiot.</i>	26	11	625–646
7	○		Chymostatin B: X = L-Val	1973	<i>J. Antibiot.</i>	26	11	625–646
8	○		Chymostatin C: X = L-Ile	1973	<i>J. Antibiot.</i>	26	11	625–646
9	○	○	Carbomycin B	1977	<i>J. Am. Chem. Soc.</i>	99	17	5826–5827
10			Hirsutene	1979	<i>J. Am. Chem. Soc.</i>	101	20	6116–6118
11	○	○	Leucomycin A3	1980	<i>Tetrahedron Lett.</i>	21	29	2837–2840
12	○		Coriolin	1980	<i>J. Antibiot.</i>	33	1	100–102
13	○		A26771B	1980	<i>Tetrahedron Lett.</i>	21	15	1479–1482
14	○	○	Erythromycin A	1981	<i>J. Am. Chem. Soc.</i>	103	11	3210–3213
				1981	<i>J. Am. Chem. Soc.</i>	103	11	3213–3215
				1981	<i>J. Am. Chem. Soc.</i>	103	11	3215–3217
15	○	○	Tylosin	1981	<i>Tetrahedron Lett.</i>	23	33	3375–3378
16	○		Isoretronecanol	1982	<i>J. Am. Chem. Soc.</i>	105	12	4096
17	○		Rosmarinecine	1982	<i>J. Am. Chem. Soc.</i>	105	12	4096
18	○	○	Apramycin	1983	<i>Tetrahedron Lett.</i>	24	44	4868–4870
19	○	○	Saccharocin	1983	<i>Tetrahedron Lett.</i>	24	44	4868–4870
20	○		Arphamenine	1983	<i>J. Antibiot.</i>	36	12	1787–1788
21	○		Epi-arphamenine	1983	<i>J. Antibiot.</i>	36	12	1787–1788
22	○		Nanaomycin D	1985	<i>J. Antibiot.</i>	38	5	680–682
23	○		Kalafungin	1985	<i>J. Antibiot.</i>	38	5	680–682
24	○		(–)-Nanaomycin A	1985	<i>Bull. Chem. Soc. Jpn.</i>	58	6	1699–1706
25	○	○	Elaiohylin	1986	<i>Tetrahedron Lett.</i>	27	39	4741–4744
26	○		Indisocin	1987	<i>J. Antibiot.</i>	40	8	1202–1203
27	○		N-Methylindisocin	1987	<i>J. Antibiot.</i>	40	8	1202–1203
28	○		Erbstatin	1987	<i>J. Antibiot.</i>	40	8	1207–1208
29	○		Azepinomycin	1987	<i>J. Antibiot.</i>	40	10	1461–1463
30	○	○	Oleandomycin	1988	<i>Tetrahedron Lett.</i>	29	32	3975–3978
31	○		Pyridomycin	1989	<i>Tetrahedron Lett.</i>	30	52	7419–7422
32	○	○	Rifamycin W	1990	<i>Tetrahedron</i>	46	13–14	4629–4652
33	○		Cyclophellitol	1990	<i>Tetrahedron Lett.</i>	31	8	1171–1172
34	○		Medermycin	1990	<i>Tetrahedron Lett.</i>	31	38	5495–5498
35			Allosamizoline	1991	<i>Tetrahedron Lett.</i>	32	39	5363–5366
36	○	○	Herbimycin A	1991	<i>Tetrahedron Lett.</i>	32	42	6015–6018
37	○		Maniwamycin A	1993	<i>Tetrahedron Lett.</i>	34	38	6095–6098
38	○		Maniwamycin B	1993	<i>Tetrahedron Lett.</i>	34	38	6095–6098
39	○		Neopyrrolomycin	1993	<i>Tetrahedron Lett.</i>	34	52	8443–8444
40	○		Pyrizinoastatin	1994	<i>J. Antibiot.</i>	47	3	389–390
41	○		AB3217-A	1994	<i>Tetrahedron Lett.</i>	35	19	3099–3102
42	○		Nagstatin	1995	<i>Tetrahedron Lett.</i>	36	37	6721–6724
43	○		Gualamycin	1995	<i>Tetrahedron Lett.</i>	36	37	6717–6720
44	○		Deacetyl-caloporoside	1996	<i>Tetrahedron Lett.</i>	37	14	2453–2456
45	○		Calbistrin A	1997	<i>Tetrahedron Lett.</i>	38	4	583–586
46	○		PF1092 A	1997	<i>Tetrahedron Lett.</i>	38	8	1439–1442
47	○		PF1092 B	1997	<i>Tetrahedron Lett.</i>	38	8	1439–1442
48	○		PF1092 C	1997	<i>Tetrahedron Lett.</i>	38	8	1439–1442
49	○		MS-444	1997	<i>J. Antibiot.</i>	50	3	289–290
50	○		Terpestacin	1998	<i>Tetrahedron Lett.</i>	39	1	83–86
51			KD16-U1	1998	<i>Tetrahedron Lett.</i>	39	6	401–402
52	○		Glyoxalase I inhibitor	1998	<i>Tetrahedron Lett.</i>	39	6	401–402
53	○		ES-242-4	1998	<i>Tetrahedron Lett.</i>	39	13	1771–1772

(Continued)

The big four antibiotics (aminoglycoside, beta-lactam, macrolide and tetracycline antibiotics)								
No	The first total synthesis		Compounds	Year	Journal title	Volume no.	Issue no.	Page range
54	○		ES-242-5	1999	<i>J. Antibiot.</i>	52	4	422–425
55	○		Sideroxylonal B	1999	<i>Tetrahedron Lett.</i>	40	10	1925–1928
56	○		Sideroxylonal C	1999	<i>Tetrahedron Lett.</i>	40	10	1925–1928
57	○		Pyralomicin 2c	1999	<i>Tetrahedron Lett.</i>	40	10	1929–1932
58	○		PF1163A	1999	<i>J. Antibiot.</i>	52	12	1146–1151
59	○		PF1163B	1999	<i>J. Antibiot.</i>	52	12	1146–1151
60	○		Pyralomicin 1c	2000	<i>J. Antibiot.</i>	53	1	88–91
61	○		PC-3	2000	<i>J. Antibiot.</i>	53	4	418–421
62	○		YM-30059	2000	<i>J. Antibiot.</i>	53	4	418–421
63			Valienamine	2000	<i>J. Antibiot.</i>	53	4	430–435
64			Validamine	2000	<i>J. Antibiot.</i>	53	4	430–435
65	○	○	Tetracycline	2000	<i>Chem. Lett.</i>	2000	6	646–647
66		○	Thienamycin	2000	<i>J. Antibiot.</i>	53	10	1231–1234
67	○		Asterriquinone B1	2001	<i>J. Antibiot.</i>	54	1	105–108
68	○		Demethylasterriquinone B1	2001	<i>J. Antibiot.</i>	54	1	105–108
69	○		Quinolactacin B	2001	<i>J. Antibiot.</i>	54	1	109–112
70	○		LL-Z1640-2	2001	<i>Chem. Lett.</i>	2001	2	172–173
71	○		Luminacin C1	2001	<i>Tetrahedron Lett.</i>	42	43	7625–7628
72	○		Luminacin C2	2001	<i>Tetrahedron Lett.</i>	42	43	7625–7628
73	○		Napyradiomycin A1	2002	<i>Chemistry Lett.</i>	2002	1	14–15
74	○	○	UCE 6	2002	<i>J. Antibiot.</i>	55	12	1076–1080
75	○		4-O-(4''-O-acetyl- α -L-rhamnopyranosyl)-ellagic acid	2003	<i>J. Nat. Prod.</i>	66	5	729–731
76	○		Cochleamycin A	2003	<i>J. Antibiot.</i>	56	6	584–590
77	○		Lymphostin	2004	<i>Tetrahedron Lett.</i>	45	13	2847–2850
78	○		BE-5423B	2004	<i>J. Antibiot.</i>	57	4	291–297
79	○		Trichostatin D	2005	<i>Tetrahedron Lett.</i>	46	2	333–337
80	○		Xanthocillin X dimethyl ether	2005	<i>Tetrahedron Lett.</i>	46	30	5017–5020
81	○		Xanthocillin X	2005	<i>Tetrahedron Lett.</i>	46	30	5017–5020
82	○		YM182029	2005	<i>Ogura, T. Doctor Thesis, Waseda Univ.</i>			
83	○		AM6898D	2005	<i>Ogura, T. Doctor Thesis, Waseda Univ.</i>			
84			Tubelactomicin A	2006	<i>Tetrahedron Lett.</i>	47	14	2439–2442
85	○		Tetrodecamycin	2006	<i>Tetrahedron Lett.</i>	47	21	3595–3598
86	○		Actinopyrone A	2006	<i>Tetrahedron Lett.</i>	47	30	5415–5418
87	○		Lagunamycin	2006	<i>Tetrahedron Lett.</i>	47	35	6183–6186
88	○		Vinaxanthone	2007	<i>Chemistry Lett.</i>	32	1	10–11
89	○		YCM1008A	2007	<i>Tetrahedron Lett.</i>	48	24	4187–4190
90	○		TMC-66	2007	<i>Tetrahedron Lett.</i>	48	41	7305–7308
91	○		OM-173 α E	2007	<i>Tetrahedron Lett.</i>	48	45	8018–8021
92	○		Nanaomycin E	2007	<i>Tetrahedron Lett.</i>	48	45	8018–8021
93	○		BE-52440 A	2007	<i>Tetrahedron Lett.</i>	48	45	8018–8021
94	○		TMC-264	2008	<i>Tetrahedron Lett.</i>	49	25	4036–4039
95	○		Nidulalin A	2009	<i>J. Antibiot.</i>	62	8	469–470
96	○		Benzopyrenomycin	2009	<i>Tetrahedron Lett.</i>	50	48	6701–6704
97	○		Epi-cochlioquinone A	2010	<i>Tetrahedron Lett.</i>	51	42	5532–5536
98	○		Lactonamycin	2010	<i>Tetrahedron Lett.</i>	51	42	5546–5549
99	○		K1115 B1 α	2011	<i>Tetrahedron Lett.</i>	52	9	983–986
100	○		K1115 B1 β	2011	<i>Tetrahedron Lett.</i>	52	9	983–986
101	○		XR774	2011	<i>Kataoka, Y. Master Thesis, Waseda Univ.</i>			
102	○	○	Hibarimicinone	2012	<i>Tetrahedron Lett.</i>	53	4	422–425