Total syntheses of bioactive natural products from carbohydrates

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Abstract

Total syntheses of bioactive natural products recently accomplished in our laboratories are described. They are classified by structures of target molecules and are focused on our original approach to their own structures. The target molecules include nanaomycin, kalafungin, BE-54238B, tetracycline, rosmarinecine, thienamycin, luminacines C1 and C2, tetrodecamycin, cochleamycin A, and tubelactomicin A, which have been synthesized as optically pure form from carbohydrates.

Keywords: Total synthesis; Natural product; Carbohydrate; Structural determination; Enantiodivergent synthesis; Michael–Dieckmann cyclization; Intramolecular Diels–Alder reaction

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1. Introduction

Anybody can draw a picture, but pictures painted by famous painters such as van Gogh, Monet and Picasso are praised as “art”. At the present time, anyone may be able to synthesize natural products, even those having...
describe the total syntheses of tandem Michael–Dieckmann cyclization\[1–3\]. Herein, we developed a novel methodology to synthesize those possessing aromatic rings and oxygenated cyclohexanes, compounds. During total syntheses of natural products methodologies and for creation of novel biologically active chlorocromate afforded the stable oxidized to the quinone \[13\] and the hydroxyl ester \[14\] with zinc powder and sodium trichloromethyl chloroformate and then tosyl chloride in pyridine. Treatment of \[6\] in 80% over all yield in one pot reaction with trichloromethyl chloroformate and then tosyl chloride in pyridine. Treatment of \[6\] with pyridinium chlorochromate afforded the stable \(\alpha,\beta\)-unsaturated ketone \[7\]. Michael–Dieckmann condensation of \[8\] with isobenzofuranone \[9,42\] gave naphthopyranone \[10\], which was transformed to lactol \[11\] in three steps. The lactol \[11\] was submitted to Wittig reaction, which afforded the lactone \[12\] and the hydroxyl ester \[13\] \[43,44\]. The lactone \[12\] was oxidized to the quinone \[14\], which was de-O-methylated to give nanaomycin \(D\) \([1\]) on the other hand, the hydroxyl ester \[13\] was converted to the quinone \[15\], which was subjected to acidic isomerization to produce kalafungin \(2\), the enantiomer of nanaomycin \(D\) \([1\]).

2. The total syntheses of pyranonaphthoquinone antibiotics using tandem Michael–Dieckmann cyclization

Pyranonaphthoquinone antibiotics \([1–3]\) and tetracycline \([4]\) are well-known antibiotics possessing significant antimicrobial activities and unique structures. These compounds have densely functionalized and aromatic ring-fusing polycyclic system. These unique structures have drawn attention both for syntheses with developing new methodologies and for creation of novel biologically active compounds. During total syntheses of natural products possessing aromatic rings and oxygenated cyclohexanes, we developed a novel methodology to synthesize those structures in short steps with convergency, meaning tandem Michael–Dieckmann cyclization \([1–3]\). Herein, we describe the total syntheses of \([1–4]\) using Michael–Dieckmann cyclization combined with carbohydrate chemistry \([1–4]\).

2.1. The total syntheses of nanaomycin \(D\) and kalafungin

Pyranonaphthoquinone antibiotics \([1–3]\) have been shown to possess significant antimicrobial activities and potential antitumor activities \([5–7]\). We have already reported the first total syntheses of related antibiotics such as nanaomycin \(D\) \([8]\), kalafungin \(2\) \([9,10]\), and BE-52534B \([3]\) \([11]\) (Fig. 1), and developed synthetic strategy for the stereoselective construction of densely-functionalized pyranonaphthoquinones from carbohydrates \([12–24]\). During synthetic studies on nanaomycin \(D\) \([1]\) and kalafungin \(2\), a new methodology to enable to synthesize both enantiomers from one enantiomeric carbohydrate had been developed in our laboratory, meaning “enantiodivergent synthesis” \([12,13,25–30]\).

Carbohydrates have been used widespread as chiral sources in asymmetric syntheses of natural products \([31–37]\). Although various carbohydrates are available, in most of them one enantiomer is natural abundant but another isomer is difficult to get in much quantity. Thus, it is hopeful that both enantiomeric chiral synths in total synthesis are derived from one enantiomer of a carbohydrate. This concept was realized as shown in Scheme 1.

Methyl \(L\)-rhamnoside \(5\) was converted into the carbonate \(6\) in 80% over all yield in one pot reaction with trichloromethyl chloroformate and then tosyl chloride in pyridine. Treatment of \(6\) with zinc powder and sodium iodide in refluxing aqueous acetonitrile gave the unsaturated alcohol \(7\) \([38–40]\). Oxidation of \(7\) with pyridinium chlorochromate afforded the stable \(\alpha,\beta\)-unsaturated ketone \(8\). Michael–Dieckmann condensation of \(8\) with isobenzofuranone \(9\) \([41,42]\) gave naphthopyranone \(10\), which was transformed to lactol \(11\) in three steps. The lactol \(11\) was subjected to acidic isomerization to produce kalafungin \(2\), the enantiomer of nanaomycin \(D\) \([1]\).

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

2.2. The total synthesis of BE-54238B

Pyranonaphthoquinone antibiotics, BE-54238 B \(3\), were isolated by the Banyu group from the culture broth of \(Streptomyces\) sp. A54238 to show antitumor activities \([11]\). The absolute structure of \(3\) was determined by NMR studies and X-ray analysis to be a nanaomycin analog.
fused with a pyrrolidine ring, and therefore, to belong to a family of pyranonaphthoquinone antibiotics (Fig. 1).

We achieved the enantioselective total synthesis of 3 to confirm its absolute structure (Scheme 2) [45]. The O-benzyl precursor 17 was prepared according to our reported procedures from the lactone 9 [12,13] and the enone 16 derived from L-rhamnose. Pyranohydronaphthoquinone 17 was converted to the bromide 18 which was lithiated to couple with L-pyrogultamic acid derivative 19 to obtain the ketone 20. After construction of pyrrolidine 21, Wittig reaction gave the lactone 22 and hydroxyl ester 23, in 67% and 22% yields, respectively. The lactone 22 was suitable for the synthesis of the natural product 3, while the hydroxyl ester 23 was transformed to 22 in high yield by heating with KHCO₃ and 18-crown-6 in DMF. Acidic removal of two Boc groups in 22 was followed by oxidative de-O-methylation to give the quinone 24. This was effectively cyclized to 25 as expected. 25 was de-O-methylated by BCl₃ to give the tautomerized compound 3 as the hydrochloride salt, which was identical in all respects with the salt of the natural BE-54238B (3).

2.3. The first total synthesis of (−)-tetracycline

For almost half a century, tetracycline (4) has been well known as a major antibiotic from the viewpoint of its unique structural features as well as antibacterial activities [46] (Fig. 1). The total synthesis of tetracycline families was initiated by Woodward’s 6-demethyl-6-deoxytetracycline synthesis in 1962 [47], followed by Muxfeldt’s terramycin synthesis in 1968 [48], and culminated by Stork’s 12a-deoxytetracycline synthesis in 1996 [49]. However, all those syntheses have been accomplished only in racemic forms. The total synthesis of natural (−)-tetracycline (4) had remained an unanswered challenge, until achievements in our laboratory in 2000 [50]. Recently, another success to the total synthesis of (−)-tetracycline was presented by Meyers group [51,52]. Herein, we focus on the first total synthesis of (−)-tetracycline (4) accomplished in our laboratory [50].

The starting 26 derived from α-glucosamine [53] was converted to olefin alcohol 27, which was submitted to selenylation [54] to give 29 (Scheme 3). Treatment of 29 with borane followed by H₂O₂ oxidation gave stereoselectively the alcohol by simultaneous formation of a new olefin group, which was followed by benzylation to afford 30. Enol ether 30 was subjected to Ferrier reaction to give β-hydroxyketone 31 [55]. Epimerization at C₂ position of 31, possessing two benzyloxy groups and one hydroxyl group at β-positions, was realized by treatment with DBU at 1°C, and following elimination of hydroxyl group was proceeded in one pot mesylation-β-elimination sequence to give enone 32. Diels–Alder reaction of 32 and 33 in the presence of 2,6-di-tert-butyl-4-methylphenol (DBMP) proceeded from the β-face of 32 regio- and stereo-selectively as expected [56]. This highly stereoselective reaction gave a labile adduct, which upon acidic oxidation was transformed to the α,β-unsaturated ketone 34. The tandem Michael-Dieckmann type reaction of 34 with the isobenzofuranone 35 [57] gave tetracyclic compound 36.

The tetracyclic 36 in hand, we turned to the oxidation of the right ring. Especially, stereoselective introduction of hydroxyl group at C₁₂α was one of the key problems of this
synthesis. Aromatization and manipulation of protective groups gave diol 37, which was adequate to oxidation of the right wing. The primary alcohol of 37 participated in the bromination of C_{1-12a} olefin to give the secondary alcohol 38. Treatment of 38 with a mixture of PCC and PDC in dichloromethane followed by purification with silica gel afforded 40 in 61% yield. This transformation, probably via intermediate 39, realized concurrent oxidation of primary and secondary alcohols accompanying with introduction of C_{12a} hydroxyl group in one pot. The resulting 40 was transformed to the nitrile 41 by our newly developed method, treatment of aldehyde 40 with hydroxylamine followed by dehydration with 1,1'-carbonyldiimidazole (CDI). Cyanide 41 was transformed to \((-\text{C}0\)-tetracycline (42) in a few steps, which was neutralized with HCl in MeOH to afford the hydrochloride. This was identical with the hydrochloride of natural \((-\text{C}0\)-tetracycline (42) in all respects, completing the first total synthesis.

3. The total syntheses of nitrogen-containing polyhydroxy compounds using the skeletal rearrangement of glucosamines

A variety of carbohydrates have been used for stereospecific syntheses of natural products as chiral sources [1–3,25,26,58]. However, little has been reported using amino sugars [59], because of their scanty derivatives. The methodology to use glycosamine would enable to construct nitrogen-containing polyhydroxy compounds frequently seen in natural products. The utility of glycosamines in syntheses of optically active compounds has been developed in our laboratory [60,61]. Herein, we describe the novel methodology to use amino sugars, which includes the specific reaction of glucosamines.

3.1. The stereoselective total synthesis of \((-\text{C}0\)-rosmarinecine

The pyrrolizidine alkaloids, which occur naturally in various plant species, have drawn attention for syntheses because of their structure and biological properties. Until total syntheses of \((-\text{C}0\)-rosmarinecine (42) (Fig. 2) in our laboratory [61], there had not been reported on completely stereoselective syntheses of optically active pyrrolizidine alkaloids [62–65]. The stereoselective synthesis of \((-\text{C}0\)-rosmarinecine (42) is summarized in Scheme 4.

The key reaction of our methodology includes a rearrangement of cyclic disulfonate derivative of a glycosamine. The starting methyl \(\alpha\)-D-glucosaminide 45 reacted with 46 to give exclusively cyclic sulfonate 47. 47 was subjected to rearrangement to produce [3,0,3]-bicyclic compound 50 via 5 membered ring 49. The sulfonate 50
was converted to the triol 51, which contained already felicitously placed functional groups and an anomeric carbon of potential value for the stereoselective introduction of hydroxyl groups and carbon chain. Silylation to protect primary alcohols of 51 gave the corresponding disilyl furanoside, which was submitted to Grignard reaction with allylmagnesium bromide in ether to afford the single threo amino alcohol 52 by chelation control approach [66,67]. Further manipulation of 52 gave (−)-rosmarinecine (42) through the lactam 53.

3.2. The formal total synthesis of (+)-thienamycin

The molecular architecture associated with the β-lactam antibiotics has posed some of the greatest challenges in synthetic chemistry, and this family has provided the stimulus for the development of methodology for the construction of their skeletons and side chains.
(+)-Thienamycin (43) (Fig. 2) was discovered in fermentation broth of *Streptomyces cattleya* to show exceptional antibacterial potency and spectrum [68]. The first stereocontrolled synthesis of 43 has been reported by Merck group [69], and the transformation of (+)-4-acetoxy-3-hydroxyethyl-2-azetidinone (44) to (+)-thienamycin (43) was also made more attractive by another Merck group [70]. Consequently, the synthesis of 44 constitutes a formal total synthesis of (+)-thienamycin (43).

(+)-4-Acetoxy-3-hydroxyethyl-2-azetidinone (44) (Fig. 2) and its derivatives have been well known as the highly versatile intermediates [71] for the synthesis of carbapenem antibiotics such as thienamycin (43) [68], imipenem, meropenem [72] and so on.

The synthesis of 44 was initiated by Sankyo group [73], followed by Merck group [74], and culminated in the practical preparation by two Japanese companies [75,76] using Noyori-Murahashi’s asymmetric procedures and chem-enzymatic procedures, respectively.

Herein is described our enantiospecific synthesis of 44 from a carbohydrate through a skeletal rearrangement and stereoselective epimerization (Scheme 5) [77]. The starting material is commercially available methyl 2-amino-2,6-dideoxy-α-D-glucopyranoside (54), which has been also isolated from natural sources [78].

Reaction of 54 with ω-benzenedisulfonyl dichloride (46) gave the cyclic sulfate 55, which was submitted to the rearrangement with potassium t-butoxide. The ring contraction reaction was quenched immediately after disappearance of 55, and subsequent oxidation gave carboxylic acid 57 predominantly. The very minor product 58, which increased prolonged reaction time of rearrangement, was readily separated by silica gel column chromatography. Practically, both compounds could be used for the synthesis without separation, because they were found to be efficiently converted to a single lactone 61 by stereoselective epimerization later on. The synthesis of 61 from each of the two compounds 57 and 58 was realized as follows.

Removal of the N-sulfonyl group of 57 by Birch reduction produced the corresponding amino acid 59 in 92% yield. This was transformed to the lactone 60, which was submitted to epimerization at C2 and C3 positions, one of the key operations of this synthesis. After a variety of conditions had been examined, the best result was realized by using DBU in MeOH at room temperature to afford predominantly the desired amino ester 61. Similarly, the epimer 58 was transformed to 61 through 62 and 63 in 57% overall yield. Hydrolysis of 61 according to the reported procedures [79] led to the hydroxyl acid 64, which was in turn submitted to the β-lactam formation. For our purpose, a Grignard-mediated cyclization of the silylated derivative seemed most promising [80]. Thus, 64 was silylated with trimethylsilyl chloride and hexamethyldisilazane (HMDS), and subsequent treatment with tert-butylnagnesium chloride gave the bis-silylated β-lactam 65. Oxidative decarboxylation [70] of 65 gave exclusively the desired (+)-4-acetoxy-3-hydroxyethyl-2-azetidinone (44) with removal of trimethylsilyl groups. Overall, the yield was approximately 32% in 12 steps from 54.

Utility of amino sugars in syntheses of optically active compounds has been expanded as above. The rearrangement with ring-contraction gave useful intermediary

![Scheme 4. Total synthesis of (−)-rosmarincine.](image-url)
**4. The total syntheses of highly oxidized compounds using carbanion–aldehyde coupling**

Highly-oxidized compounds containing several stereo-dynamic centers have been challenging target molecules for organic chemists. Stereoselective construction of such compounds requires a well-elaborated synthetic plan including convergent steps with functionalized segments. Herein, we present the total syntheses of luminacins and tetrodecamycin (Fig. 3), in which the carbanion produced from a multi-functionalized segment by hydrogen-alkali metal substitution was coupled with an aldehyde.

**4.1. The total synthesis of luminacins $C_1$ and $C_2$**

Luminacins $C_1$ and $C_2$ were isolated from *Streptomyces* sp. as novel angiogenesis inhibitors. Their structures, including the relative configuration of the carbohydrate portion, were determined mainly by NMR studies [81]. As a result, they were found to have the same planar structure as SI-4228 and UCS15A, which were reported to be microbial products showing antimicrobial, immuno-suppressive, antitumor and bone resorption inhibitory activities [82,83]. However, the absolute structure of luminacins $C_1$ and $C_2$ had remained undetermined until our total...
The total synthesis of luminacins C1 and C2 is described in Scheme 6 [84].

D-glucal (69) was transformed to the ketone 70, which was submitted to Wittig reaction using n-PrPPh3Br and n-BuLi and subsequent hydrolysis to afford acetal 71. Wittig reaction of 71 with 72 was followed by O-Michael addition cyclization to give 2'S-isomer 73 as a single isomer. The configuration of 73 at C20 was epimerized by treatment with NaOMe in MeOH to obtain 74. After transformation to cyclic sulfate 75 [85], introduction of the phenylselenyl group at C7 position and removal of sulfate by acidic hydrolysis gave 76, which was exposed to H2O2 to afford the exo-olefin 77. The exo-olefin 77 was converted to the diol 78, which was submitted further manipulation to the aldehyde 79, the right half of luminacins.

The 2'R-isomer 79 was coupled with 1''R-isomer 80 to give, after oxidation, (1''R, 2'R)-isomer 81, which was converted to (+)-luminacin C1 (66). By the same procedure, coupling of 79 and 82 followed by oxidation gave (1''S, 2'R)-isomer 83, which was transformed to (−)-luminacin C2 (67).

4.2. Total synthesis of (−)-tetrodecamycin

(−)-Tetrodecamycin (68) was isolated from the culture broth of Streptomyces sp. MJ885mF8 to show antimicrobial activities especially against Pasteurella piscicida [86,87]. The structure is distinguished by X-ray crystallography as a tetronic acid-containing tetracyclic skeleton, the one cyclohexane ring of which is fully and diversely substituted [88]. Moreover, the quaternary carbons are located at C7 and C13 [89]. The imposing structure and optical medicinal importance of this molecule have attracted a great deal of attention from the other researchers since the disclosure of the structure [90–95], although the total synthesis had not been reported until our synthesis [96].
The total synthesis was initiated with the stereoselective conversion of the carbohydrate derivative 84 (Scheme 7) [20–24,97]. Michael addition and following methylation gave 2,3-dimethyl derivative 85. Reaction of the lithiated 85 with the cyclohexanone was followed by dehydration to stereoselectively give the quaternary product 86 [20–24], which was submitted to hydride reduction to give diol 87. After transformation to keto-aldehyde 88, SmI₂-mediated pinacol coupling proceeded to afford cis-diol 89 as a single product [98]. Michael addition of 90 to diethyl acetylene-dicarboxylate (91) gave the adduct 92, which was converted to aldehyde 93. Treatment of 93 with NaHMDS constructed the seven membered ring [99] smoothly and the resulting alcohol was oxidized to ketone 94. Diester 94 was submitted to regioselective saponification to give monocarboxylic acid, which was transformed to the thioester 95. Reduction of 95 with Et₃SiH to the corresponding aldehyde [100] accompanied the cyclization to the acetal 96. Further reduction to lactone 96 was realized by our newly developed method using CBr₄ and PPh₃ [101,102]. Deacetonation of 97 afforded the diol 98, which, upon treatment with Eschenmoser’s reagent [103], underwent introduction of an exo-methylene group to give (−)-tetrodecamycin (68).

5. The total syntheses of macrolides using intramolecular Diels–Alder reaction

Intramolecular Diels–Alder reaction has been widely used to construct 6-membered ring-fused compounds including a functionalized decalin. The key function for control of stereoselectivity is arrangement of functional groups to lead to the desired transition state as well as stereoselective construction of olefins. Herein are described total syntheses by highly stereoselective intramolecular Diels-Alder reaction using carbohydrates as chiral sources.

Scheme 7. Total synthesis of tetrodecamycin.
5.1. The total synthesis of cochleamycin A

Cochleamycin A (99) was isolated by Kirin Brewery group from a cultured broth of *Streptomyces* sp. to show cytotoxicity against P388 leukemia cells and antimicrobial activities [104]. The structure including the relative stereochemistry was elucidated by exhaustive NMR studies to be endowed with a 5-6-10-6 membered tetracyclic core (Fig. 4) [105]. After the isolation, its analog, macquarimicin A (100) (Fig. 4) was independently isolated by Abbott group [106]. Not surprisingly, the combination of architectural complexities and bioactivities has engendered considerable interest, resulting in impressive synthetic studies from the groups of Paquette and Tadano using Diels–Alder reactions [107–110]. After our first total synthesis of cochleamycin A [97], Tadano’s group reported the total synthesis of macquarimicin A (100) [109,110], and Roush’s group disclosed his total synthesis of cochleamycin A [111]. Both groups took transannular Diels–Alder reactions to construct cochleamycin skeleton, as the formation of a 10-membered ring had been well known to be difficult. We used intramolecular Diels–Alder reaction followed by direct constructions of the 10-membered rings. Here, we describe the first total synthesis of cochleamycin A (99) accomplished in our laboratory [97].

The first total synthesis of cochleamycin A to determine the absolute structure was achieved as shown in Scheme 8. The lactone 84 was methylated stereoselectively by Michael addition with MeMgBr [112,113] in the presence of CuBr·Me2S and TMSCl to give 102 as a single isomer. Reduction with LiAlH4 afforded acyclic diol 103, which was transformed to give the segment 104 in several steps. On the other hand, (S)-1,2,4-trihydroxybutane (105) was converted to the epoxide 106 [114], which was submitted to introduction of acetylene to afford 107. 107 was transformed to the other segment, (E)-1-iodoalkene 108.

Coupling of 104 and 108 smoothly proceeded to give the alcohol 109 in quantitative yield. This was selectively reduced to the cis, trans-diene structure, which was crucial to the construction of the desired A–B ring by intramolecular Diels–Alder reaction. Oxidation of the allylic alcohol gave the z,β-unsaturated aldehyde 110, which was submitted to intramolecular Diels–Alder reaction in the presence of Yb(fod)3 at 140 °C [115]. The desired adduct 111 was obtained as a single product in high yield. This intramolecular Diels–Alder reaction produced four critical stereocenters as expected. 111 was converted to z-bromoester 112, the precursor of 10 membered ring. The desired cyclization of 112 was accomplished with SmI2 to give 10-6-5 membered tricyclic product 113 as a single product [116], comprising the fully elaborated structure ready for conversion to the requisite seco-acid 114 (Scheme 5). Each of the four hydroxyl groups of 113 was discriminated from others. Lactonization of 114 was tested under the various conditions to construct C–D ring and the best result was realized by using Kita’s conditions [117] to afford the δ-lactone 115 which possessed another 10 membered lactone ring. The allylic alcohol of the lactone 115 was oxidized to z,β-unsaturated ketone 116 by exposure to MnO2. Finally, selective acetylation was accomplished with NaOAc and Ac2O at 60 °C to afford cochleamycin A (99). The synthetic 99 was identical in all respects including the optical rotation with natural cochleamycin A, completing the first total synthesis to establish the absolute structure.

5.2. The total synthesis of (+)-tubelactomicin A

Tubelactomicin A (101) (Fig. 4) was isolated from the culture broth of *Nocardia* sp. MK703-102F1 to show strong and specific antimicrobial activities against drug-resistant *Mycobacterium* [118]. The structure was determined by X-ray crystallographic analysis to be the 16-membered lactone fused with a trans decalin skeleton. As the morbidity of tuberculosis with the drug resistant strains has increased worldwide, new effective drugs are needed for treatment of *Mycobacterium tuberculosis* [119]. The interesting chemical structure, combined with its antitubercular activities, has made (+)-tubelactomicin A an attractive target for synthesis, although the total synthesis has already been accomplished by the Tadano group using intramolecular Diels–Alder reaction [120,121]. Independently, we accomplished the total synthesis of (+)-tubelactomicin A (101), which was presented herein (Scheme 9) [122].

The stereochemical array of the northern part was derived from l-arabinose (117). Lactone 118 [123] was submitted to the stereoselective methylation and reductive ring opening to give diol 120, possessing functionality to be the northern part 121.
The decalin moiety, the southern part of tubelactomicin A, was constructed by intramolecular Diels–Alder reaction [97,124]. The citronerol 122 was converted the triene 123. The stereoselective Diels–Alder reaction to construct additional four chiral centers was realized by heating 123 in xylene, which gave 124 as a single product. The decalin 124 was converted to the alcohol 125 to couple with the northern part 121.

Treatment of the mixture of 121 and 125 under the conditions of Suzuki coupling gave the tetraen product 126 [125]. The seco-acid derivative 126 was submitted to the macro lactonization by Shiina’s method [126] to construct lactone 128. Deprotection and selective oxidation afforded (+)-tubelactomicin A (101).

6. Conclusion

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

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

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

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The carbon-numbering protocol parallels conveniently that of the natural product 68 as references 86 and 88.

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