Award Review

Synthetic and Structure-Activity Relationship Studies on Bioactive Natural Products

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This review summarizes our research into the synthesis and structure-activity relationships of epolactaene, neoechinulin A, plakevulin A, pseudodeflectusin and ustusorane C. These natural products are attractive in view of their apoptosis-inducing activity, cytoprotective activity against peroxynitrite, inhibitory activity against DNA polymerases, and cytotoxicity in cancer cells.

Key words: natural product; synthesis; structure-activity relationship

Microorganisms and plants produce many secondary metabolites that have unique structures, bioactivities, and interesting mechanisms of action. They can be used as lead compounds in the development of novel drugs and pesticides, and thus play important roles in medicinal chemistry and agrochemistry. They can also be utilized as probes to elucidate biological phenomena. This review describes our synthetic and structure-activity relationship studies on biologically active natural products.

I. Epolactaene

Epolactaene (1) was isolated from Penicillium sp. BM16899-P by Kakeya et al. (Fig. 1). The characteristic features of 1 include a highly functionalized α,β-epoxyγ-lactam and a conjugated triene moiety in the side chain. Epolactaene is present in a 5:1 tautomeric mixture derived from epimerization at the hemiaminal moiety. The absolute configuration of epoxide in 1 was determined independently by Hayashi and Kogen.

Kakeya et al. have reported that epolactaene promoted neurite outgrowth and induced G0/G1 cell cycle arrest in a human neuroblastoma cell line, SH-SYSY, and inhibited the growth of human cancer cell lines. They found that epolactaene bound to human Hsp60 and inhibited its chaperone activity. Ikekita et al. found that 1 induced apoptosis in a human leukemia B cell line, BALL-1. Mizushima et al. found that 1 inhibited mammalian DNA polymerase and DNA topoisomerase activities and had anti-inflammatory properties in a TPA (12-O-tetradecanoylphorbol 13-acetate)-induced inflammation model.

I. Synthesis of epolactaene

The attractive biological activities as well as the structural complexity of epolactaene have stimulated intensive synthetic interest, culminating in several total syntheses. Our group accomplished the total synthesis of epolactaene by a convergent approach utilizing a fluoride anion catalyzed aldol-type reaction of a silyl epoxylac tone (Scheme 1). We established large-scale preparation of enantiomerically pure 3, starting from (S)-ethyl lactate (Scheme 2). The Z-selective Horner–Emmons reaction of ethyl diphenylphosphonoacetate with (S)-2-(tert-butyldimethylsilyloxy)propanal afforded a 20:1 mixture of Z and E-α,β-unsaturated esters. Treatment of 6 with aqueous HF in CH3CN led to desilylation and cyclization to form β-angelica lactone (7). Epoxidation of 7 by a modification of Font’s procedure gave enantiomerically pure β-angelica lactone epoxide (8) in 60% yield and 98% ee by HPLC. After treatment of 8 with K2CO3 in MeOH, the resulting alcohol was protected as TBS ether. A solution of 9 in THF was added to a solution of LDA and TMSCI in THF, affording a 5.5:1 mixture of silyl epoxyesters in 80% yield. Selective desilylation with aqueous HF in CH3CN and recyclization with a catalytic amount of CSA in refluxing benzene gave the desired 3 in 75% yield.

We prepared tetraene aldehyde via Stille coupling of dienyl iodide and vinylstannane (Scheme 3). Dienyl iodide was prepared by Wittig reaction of (13) with phosphonium salt (14). Desilylation of 15 with K2CO3 in MeOH, and carbometallation of 16 with Cp2TiCl2–Me3Al, followed by treatment with iodine. Vinylstannane was prepared by oxidation of stannyl alcohol into carboxylic acid, followed...
Scheme 1. Synthetic Approach for Epolaetaene (1).

Scheme 2. Large-Scale Preparation of Enantiomerically Pure Silyl Epoxylactone 3.

1. Synthesis of dienyl iodide 11

2. Synthesis of vinyl stannane 12

3. Synthesis of tetraene aldehyde 14

Scheme 3. Preparation of Tetraene Aldehyde 4.
by esterification with CH$_3$I and t-BuOK. Stille coupling$^{25}$ of 11 and 12 with a catalytic amount of PdCl$_2$(CH$_3$CN)$_2$ in the presence of CuI in DMF gave 19 in 91% yield. The PMB group in 19 was cleaved with 4 M aq. HCl/dioxane (1:4) affording 21 in 89% yield. After Swern oxidation$^{26}$ of 20, a Wittig reaction between the resulting aldehyde 21 and the known phosphorane$^{27}$ afforded 4.

The key aldol-type reaction of 3 with 4 was performed using TBAF as fluoride source (Scheme 4). Treatment of 3 and 4 with a catalytic amount of TBAF in the presence of MS4A in THF-hexane (1:1) gave the desired alcohol 2 in 39% yield (78% yield based on recovered 4). Oxidation of 2 with trifluoroacetic anhydride (TFAA) and DMSO produced the corresponding ketone 22. After ammonolysis of 22, the resulting hydroxymidade 23 was oxidized with Dess–Martin periodinane$^{28}$ to give epolactaene (1), which was isolated as an approximately 5:4:1 diastereomeric mixture at the hemiaminal. We successfully prepared epolactaene (1) on a large scale ($>1$ g) by this synthetic route. The most significant feature of this approach is that silyl epoxylactone serves as a key intermediate in the synthesis of various epolactaene analogs. Several analogs were synthesized and evaluated for their biological activities.

## II. Neoechinulin A

Neoechinulin A (25), an indole alkaloid, has been isolated from Aspergillus sp.,$^{33–42}$ ascomysete Xylaria euolus,$^{43}$ endophytic fungus Chaetomium globosum,$^{44}$ Bridelia ferruginea (Euphorbiaceae),$^{45}$ Eurotium sp.,$^{46–49}$ Penicillium griseofulvum,$^{50}$ and the aerial parts of Plumbago zeylanica.$^{51}$ The structural features of 25 include a diketopiperazine, a Z-enamide, and an isopenyl group attached to an indole moiety (Fig. 3).

Yagi et al. found that 25 showed strong antioxidative activity on ferric thiocyanate and TBA (thiobarbituric acid) tests.$^{39}$ Li et al.$^{41}$ and Wang et al.$^{42}$ independently reported that 25 exhibited significant radical-scavenging activity against DPPH (1,1-diphenyl-2-picrylhydrazyl). Arai et al. demonstrated that 25 scavenged...
peroxynitrite generated from SIN-1 (3-(4-morpholino)-sydnonimine hydrochloride)).52) They reported that treatment of primary neuronal cells and NGF-differentiated PC12 cells with 25 rendered the cells resistant to peroxynitrite-induced cytotoxicity. Watanabe and Arai et al. have suggested that neoechinulin A confers cytoprotection against nitrosative stresses by elevating cellular reserve capacity for NAD(P)H generation, which can offset the crippling of energy-supplying systems due to nitrosative stress.53) They also found that 25 protected PC12 cells from the cytotoxicity of 1-methyl-4-phenylpyridine (MPP+) and rotenone, neurotoxins capable of provoking acute Parkinson’s-like neurodegeneration in humans.54,55) Pettit et al. have reported that neoechinulin A and preechinulin, 61–63) were prepared and evaluated for antinitration activity against peroxynitrite-Mediated Tyrosine Nitration, Anti-Oxidant Activity in Lipid Peroxidation, and Cytoprotective Activity against Peroxynitrite from SIN-1 in PC12 Cells.

(−)-neoechinulin A (25). The enantiomeric excess of synthetic 25 was established to be 95% ee by chiral HPLC analysis. The optical rotation of synthetic 25 ([α]D23 = −54° (c 0.1, MeOH)) was consistent with that of natural product ([α]D23 = −54° (c 0.1, MeOH)).47) Thus the absolute configuration of neoechinulin A was determined to be S. By this synthetic methodology, several analogs including (+)-neoechinulin A and preechinulin,61–63) were prepared and evaluated for their biological activities.

2. Structure-activity relationships of neoechinulin A

Our synthetic neoechinulin A and its derivatives were evaluated for antinitration activity against peroxynitrite-mediated tyrosine nitration, antioxidant activity as to lipid peroxidation, and cytoprotective activity against peroxynitrite from SIN-1 in PC12 cells.64–66) The C-8/C-9 double bond, which constitutes a conjugate system with the indole and diketopiperazine moieties of neoechinulin A, is essential for antinitration and antioxidant activities as well as protection against SIN-1 cytotoxicity (Fig. 4). The presence of an intact diketopiperazine moiety is an additional requirement for antinitration activity, but is not essential for the antioxidant and cytoprotective activities. The antioxidant activity or electrophilic nature of the C-8 carbon, both of which are afforded by the C-8/C-9 double bond, may play a role in the cytoprotective properties of this alkaloid. The stereochemistry of C-12 does not influence these activities, since no difference in biological activities between (−)-neoechinulin A and (+)-neoechinulin A was observed.

![Scheme 5. Synthesis of Neoechinulin A (25).](image)

![Fig. 3. Structure of Neoechinulin A (25).](image)

![Fig. 4. Structure-Activity Relationships of Neoechinulin A for Anti-Nitration Activity against Peroxynitrite-Mediated Tyrosine Nitration, Anti-Oxidant Activity in Lipid Peroxidation, and Cytoprotective Activity against Peroxynitrite from SIN-1 in PC12 Cells.](image)
III. Plakevulin A

The cytotoxic oxylipin plakevulin A was isolated from an Okinawan sponge, *Plakortis* sp., by Tsuda and Kobayashi *et al.* (Fig. 5).67 Natural plakevulin A was optically active ([α]D30 = +19° (c 2.0, CHCl3)). The absolute configurations at three chiral centers were assigned by spectroscopic data of the reductive product of (+)-plakevulin A and a modified Mosher's method. Although the proposed structure was the levulinyl ester, as depicted for 31a, our synthetic studies and enzyme-inhibitory assays revealed that the structure of plakevulin A is as shown for 31 (Fig. 5).68,69 Compound 31 exhibited cytotoxicity against murine leukemia L1210 and epidermoid carcinoma KB cells. It has also been exhibited cytotoxicity against murine leukemia L1210 and plakevulin A is as shown for 31a (Fig. 5).70,71 Compound 31 inhibited the activities of DNA polymerases α and γ. Plakevulin A can be synthesized biogenetically by reduction of untenone A (32), a related cyclopentenone derivative isolated from the Okinawan sponge *Plakortis* sp.

1. Synthesis of plakevulin A

The first synthesis of (+)-plakevulin A (31) and revision of the proposed structure (31a) was achieved by our group.68 Enantioselective total synthesis of (+)-31 was accomplished by Honda.72 Total syntheses of untenone A (32) have been reported by Takeda,73 Asami,74 Yamada,75 Whitehead,76,77 Honda,72 and Nakami,78

Our synthetic approach towards the proposed structure of plakevulin A (31a) was based on an assumed biosynthetic pathway (Scheme 6). Reduction of untenone A (32), followed by esterification of the resulting alcohol, should provide 31a. Our synthetic route to untenone A was based on a modification of the protocol reported by Yamada *et al.*

After protection of the alcohol (±)-33 as a TMS ether, methoxycarboxylation of (±)-34 with LDA and NCCO2CH3 afforded (±)-35 as a 4:2:1 mixture of inseparable diastereomers. Reduction of (±)-35 with DIBAL (2 eq.) in CH2Cl2 gave (±)-36 in 41% yield. Mitsunobu esterification of (±)-36 with levulinic acid afforded (±)-37 in 52% yield. Deprotection of TMS ether (±)-37 with TBAF yielded the revised structure of plakevulin A (31a). The 1H and 13C NMR spectral data for (±)-31a were different from those for natural plakevulin A. In particular, both the proton and carbon signals at C-1 in (±)-31a appeared further downfield from those in natural plakevulin A. These observations suggested that natural plakevulin A is not the levulinyl ester, but the delevulinyl form. Thus, removal of the levulinyl moiety of (±)-31a with hydrazine in pyridine and acetic acid gave alcohol (±)-31 in 92% yield. The 1H NMR and 13C NMR spectral data for synthetic (±)-31 were in good agreement with those for natural plakevulin A, except for the peaks derived from levulinic acid. Thus the sample of natural plakevulin A was estimated to be a 1:1 mixture of (+)-31 and levulinic acid. By the same methodology, we prepared (+)-31 and (−)-31, starting from compounds 38 and 40, respectively (Scheme 7).69

2. Structure-activity relationships of plakevulin A

We examined the structure-activity relationships of plakevulin A for inhibition of DNA polymerases α and β.69,70 We found that the methyl ester of 31 was important for the inhibitory activities (Fig. 6). The inhibitory activity of (−)-31 against DNA polymerases α and β was slightly more potent than that of (+)-31.

IV. Pseudodeflectusin and Ustusorane C

Pseudodeflectusin (42) is an isochroman derivative isolated from the culture broth of *Aspergillus pseudodeflectus* (Fig. 7).80 Mizushina *et al.* have reported that pseudodeflectusin exhibited cytotoxicity in stomach

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![Fig. 5. Structures of Plakevulin A (31), Proposed Structure of Plakevulin A (31a), and Untenone A (32).](image-url)
(NUGC-3), cervix (HeLa-S3), and peripheral blood (HL-60) cells. They also reported that 42 induced depletion of intramolecular glutathione, which decreased cell viability. Structurally related natural products such as pergillin, ustusolanes, and penicisochroman A–F were isolated from the fungus Pseudodeflectusin (Scheme 7). The reported NMR spectroscopic data (flectusin.85–87) for aspergione A (43), ustusorane C (44), and natural pseudodeflectusin were identical to those for natural ustusorane C. But, the absolute configuration of (++)-pseudodeflectusin (Scheme 8) was determined to 7α,95 by chiral HPLC and X-ray crystallographic analysis. (+)-Ustusorane C (43) was prepared by treatment of (+)-42 with p-TsOH in MeOH. The 1H and 13C NMR data for our synthetic pseudodeflectusin were different from those reported for aspergione A and ustusorane C. But, the optical rotation of synthetic 43 ([α]D25 = +54.3 (c 0.12, MeOH)) was also greater than that of natural 43 ([α]D31 = +6 (c 0.1, MeOH)).82 We believe that the sample of natural 43 isolated by Hong and Zhu might have contained impurities that caused a decrease in the observed optical rotation or might have been approximately racemic.

We also prepared the proposed structure of aspergione A and B (Scheme 9). The addition of ethylmagnesium bromide to (±)-49 gave a 1:1 diastereomeric mixture of the alcohol, which was oxidized by MnO2 to afford a ketone (±)-55. The ketone was converted into 2,3-dimethylpyran-4-one (±)-56 by intramolecular cyclization with Ac2O in pyridine. Reduction of (±)-56 with DIBAL gave the proposed structure of aspergione B (45). The hemiacetal in (±)-45 was converted into its methyl acetal (±)-44, the proposed structure of aspergione A (44). The 1H and 13C NMR data for our synthetic 44 and 45 were different from those reported for aspergione A and B, respectively. This result indicates that the structures of natural aspergione A
and B are identical to those ustusorane C and pseudodeflectusin, respectively.

2. Structure-activity relationships of pseudodeflectusin

Several analogs as well as synthetic intermediates are now undergoing biological studies in our laboratory. The structure-activity relationships of pseudodeflectusin governing its cytotoxic activity against various cancer cells were examined. These studies will be reported in due course.

V. Conclusion

This review focuses on our synthetic and structure-activity relationship studies of epolactaene, neoechinulin A, plakevulin A, pseudodeflectusin and ustusorane C. An efficient synthetic method of epolactaene via a novel oxiranyl anion derived from \( \beta \)-epoxy-\( \gamma \)-lactone was established. Using this synthetic methodology, several epolactaene derivatives were prepared to investigate structure–activity relationships. The total synthesis of neoechinulin A led to determination of the absolute configuration of natural neoechinulin A and evaluation of its biological properties. Our synthetic studies on plakevulin A, pseudodeflectusin, and ustusorane C revealed the structural revisions of plakevulin A, aspergione B, and aspergione A, respectively. Furthermore, all synthetic natural products and several analogs were tested to evaluate their potential biological activities. We hope that our studies will support the development of new drugs, pesticides, and chemical probes for biological studies.

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