Synthesis of 6-Halo-Substituted Pericosine A and an Evaluation of Their Antitumor and Antiglycosidase Activities

Yoshihide Usami 1,*, Yoshino Mizobuchi 1, Mai Ijuin 1, Takeshi Yamada 2, Mizuki Morita 1, Koji Mizuki 1, Hiroki Yoneyama 1 and Shinya Harusawa 1

1 Department of Pharmaceutical Organic Chemistry, Osaka University of Pharmaceutical Sciences, Nasahara 4-20-1, Takatsuki 569-1094, Osaka, Japan; e16101@gap.oups.ac.jp (Y.M.); e14509@gly.oups.ac.jp (M.I.); e12546@gap.oups.ac.jp (M.M.); e12007@gap.oups.ac.jp (K.M.); hiroki.yoneyama@ompu.ac.jp (H.Y.); harusawa@gly.oups.ac.jp (S.H.)

2 Department of Medicinal Molecular Chemistry, Osaka University of Pharmaceutical Sciences, Nasahara 4-20-1, Takatsuki 569-1094, Osaka, Japan; takeshi.yamada@ompu.ac.jp

* Correspondence: yoshihide.usami@ompu.ac.jp; Tel.: +81-796-90-1087; Fax: +81-796-90-1005

Abstract: The enantiomers of 6-fluoro-, 6-bromo-, and 6-iodopericosine A were synthesized. An efficient synthesis of both enantiomers of pericoxide via 6-bromopericosine A was also developed. These 6-halo-substituted pericosine A derivatives were evaluated in terms of their antitumor activity against three types of tumor cells (p388, L1210, and HL-60) and glycosidase inhibitory activity. The bromo- and iodo-congeners exhibited moderate antitumor activity similar to pericosine A against the three types of tumor cell lines studied. The fluorinated compound was less active than the others, including pericosine A. In the antitumor assay, no significant difference in potency between the enantiomers was observed for any of the halogenated compounds. Meanwhile, the (−)-6-fluoro- and (−)-6-bromo-congeners inhibited α-glucosidase to a greater extent than those of their corresponding (+)-enantiomers, whereas (+)-iodopericosine A showed increased activity when compared to its (−)-enantiomer.

Keywords: synthesis; 6-halogenated pericosine A analogues; antitumor; glycosidase inhibition; enantiomer; pericoxide

1. Introduction

Chemical modification of bioactive natural products is one of the most common methods used in drug development [1–8]. In addition to increasing the pharmacological activity, which is the major aim of chemical modification, decreasing side effects, improving the solubility or stability, and reducing costs remain problems to be resolved during drug development. Chemical modification based on marine natural products has been extensively studied due to the discovery of new lead compounds suitable for drug discovery [9–12].

The isolation of pericosine A (1Cl) and B (2) as metabolites of the marine-derived fungus Periconis byssoides N133 was first reported in 1997, and pericosines C–E (3–6) were discovered in 2008 [13–15]. The unique carbasugar structures constituting the highly functionalized cyclohexene ring are shown in Figure 1. Recently, the chemistry of carbasugars has received an increasing amount of research attention due to their wide range of biological activity [16–18]. In addition, many total syntheses of pericosines A–C (1–3) have been reported due to the antitumor activity of pericosine A (1Cl) [19–30]. However, the chemical modification of the pericosines has not been reported to date with the exception of our synthetic study on pericosine E analogs bearing chloro- or methoxy-substituents at C-6, which were used as α-glucosidase inhibitors [31,32]. Figure 1 also includes (+)-pericoxide (7) and (−)-maximiscin, which were discovered by Cichewitcz and coworkers from Tolypocladium sp. [33,34]. The fact that pericosine 1Cl was obtained together with
pericoxide 7 in their work suggests that 7 may be a biosynthetic precursor of 1Cl. Therefore, 7 should be classified as a member of the pericosine family.

![Diagram of pericosines and related molecules](image)

**Figure 1.** Structures of the pericosines and their related natural products.

In our recent report on pericosine A, natural 1Cl was isolated from *Periconia* sp. as an enantiomeric mixture. In addition, we confirmed that both synthesized enantiomers of 1Cl exhibit antitumor activity with similar potency against three tumor cell lines (P388, LH-6, and L1210). Furthermore, (−)-1Cl showed moderate α-glucosidase inhibitory activity (IC₅₀ = 2.25 mM), whereas (+)-1Cl was inactive [35]. As we are interested in the biological activities of pericosine congeners bearing other halogen atoms, the fermentation of *Periconia* sp in artificial seawater containing fluoride, bromide, or iodide sources has been examined as an alternative to chloride. It should be mentioned here that 6-halogenated pericosines bearing F, Br, or I atoms were not obtained in our preceding paper. Consequently, we have attempted the synthesis of non-natural 6-halo-substituted pericosine A. Our recent synthetic work on pericosine E analogs has suggested that the presence of a chlorine atom at C6 is an important factor for α-glucosidase inhibitory activity. The preparation of other 6-halo-congeners is also required for our continuous synthetic studies on new pericosine E analogs.

Herein, we describe the synthesis and evaluation of the antitumor and antiglycosidase inhibitory activities of both enantiomers of newly designed 6-halo-congeners of pericosine A. In addition, an efficient synthesis of closely related pericoxide 7 via 6-bromo pericosine 1Br has also been reported.

### 2. Results & Discussion

#### 2.1. Synthesis of Both Enantiomers of 6-Halo-Substituted Pericosine A

A similar reaction to the hydrochlorination of epoxide intermediate 8 used in the synthesis of pericosine A 1Cl [21,29] using commercially available HBr and HI aqueous solutions was envisioned in this study, in which the deprotection of the hydroxyl groups and hydrolysis of the ester moiety will occur (Scheme 1). Subsequently, we began this work by searching for suitable reagents used to introduce the required fluorine, bromine, or iodine atoms.
Scheme 1. Synthesis of 6-halogenated pericosine A. (a) Synthesis of (-)-1 from (-)-shikimic acid; (b) Synthesis of (+)-1 from (-)-quinic acid.

For bromination, BBr₃ was initially examined as the bromide source to react with epoxide (−)-8, which can be prepared from bromohydrin (+)-9 via an intramolecular S₅N₂ reaction [29,31]. However, careful addition of BBr₃ [0.33 equivalents (eq)] to (−)-8 in dry diethyl ether (Et₂O) at −78 °C afforded the desired product (10Br) in only 14% yield. Using 1.0 eq of BBr₃ slightly improved the yield (38%), but increasing the reaction temperature led to the formation of a complicated mixture including the undesired regioisomer. After investigating a variety of brominating reagents, we found mono-bromoborane dimethyl sulfide complex (BH₂Br·SMe₂) to be the most suitable for the desired reaction [36,37]. The reaction of 8 with 1.0 eq of BH₂Br·SMe₂ at −78 °C in Et₂O dramatically improved the yield of (−)-10Br to 94% yield. The reactions performed at higher temperatures led to a decreased yield of (−)-10Br (78% at −20 °C and 58% at 0 °C). Subsequent deprotection of the cyclohexylidene moiety was also a delicate process. The optimum reaction conditions were found after investigating a variety of conditions. Treatment of (−)-10Br with Dowex-XW50-H hydrogen form (Dowex® 50WX50-H: Acidic ion-exchange resin) in MeOH at room temperature (rt) for 56 h gave (−)-1Br in an excellent 87% yield when compared to the conventional reaction using trifluoroacetic acid (TFA) in MeOH (66%) (Scheme 1A). This deprotection process with Dowex-XW50-H was examined in detail because could also be applied in the subsequent synthesis of pericoxide 7 (see Supplementary Material, Table S1).
The corresponding (+)-enantiomer of \( \text{I}_\text{Br} \) was prepared in the same way using (+)-8 derived from (-)-quinic acid (Scheme 1B). Iodohydrination of (-)-8 was then achieved upon careful addition of 0.33 eq of aluminum iodide (AlI\(_3\)) at 0 °C to give the desired product [(−)-10\(_\text{I} \)] in 63% yield [38]. When 1.0 eq of AlI\(_3\) was used under the same reaction conditions, the yield of (−)-10\(_\text{I} \) was reduced to 15%. The reaction of (−)-8 with 1.0 eq of tetrabutylammonium iodide and a catalytic amount of BF\(_3\)·Et\(_2\)O in dry dichloromethane at −78 °C afforded (−)-10\(_\text{I} \) in 17% yield. Finally, deprotection of (−)-10\(_\text{I} \) was achieved under conventional TFA/MeOH conditions to give (−)-1\(_\text{I} \) in 76% yield, whereas treatment of (−)-10\(_\text{I} \) with Dowex\textsuperscript{®} 50WX8-H resulted in no reaction. The (+)-enantiomer of 1\(_\text{I} \) was prepared using a similar approach from (+)-8 via (+)-10\(_\text{I} \).

The introduction of a fluorine atom into (−)-8 was accomplished using the (HF)\(_n\)/py complex. The reaction of (−)-8 with this complex at 0 °C for 15 min in a polypropylene tube afforded the desired fluorohydrine product [(−)-10\(_\text{F} \)] in 46% yield. A longer reaction time (1 h) led to a more complex product mixture, giving a low yield of (−)-10\(_\text{F} \) (32%). Subsequent treatment of (−)-10\(_\text{F} \) with TFA in MeOH afforded (−)-1\(_\text{F} \) in 43% yield. Similarly, (+)-1\(_\text{F} \) was successfully obtained using (+)-8. It should be noted that 10\(_\text{I} \) and 1\(_\text{I} \) are relatively unstable when compared to the other halogenated congeners, so they were stored in a freezer prior to further use.

### 2.2. Synthesis of Pericoxide

The synthesis of 7, which was not reported prior to 2019, was also conducted, as shown in Scheme 2. The direct deprotection of epoxide 8 was examined in our preliminary efforts to prepare 7. Treatment of (−)-8 with trifluoroacetic acid in t-BuOH at room temperature (rt) did not afford pericoxide 7 despite the complete consumption of 8. Changing the acid catalyst to Dowex\textsuperscript{®} 50WX8-H resulted in no reaction and microwave (MW) heating afforded a small amount of methyl 3,4-dihydroxybenzoate along with the recovery of the starting material [(−)-8].

\[
\text{Scheme 2. Synthesis of (−)- and (+)-pericoxide (7): (a) (−)-Pericoxide from (−)-shikimic acid; (b) (+)-pericoxide from (−)-quinic acid.}
\]

In our next experiment, bromotrion 11 derived from bromohydrin 9 was treated with 3.0 eq of lithium hexamethyldisilazide (LHMDS) in THF at −78 °C because if the C6
hydroxide anion attacked the C5 center faster than the C4 hydroxide anion, the formation of 7 via an intramolecular SN2 process was expected to occur. However, the spectral data of epoxide 12 did not agree with those of 7. The structure of 12 was determined using NMR spectroscopy; epoxy carbon atoms C6 (δ 55.5 ppm) and C1 (δ 56.0 ppm) were detected in the high field region in the 13C-NMR spectrum and the HMBC cross peaks corresponding to H1/C3 and H6/C4 indicated the structure of 12 (see Supplementary Materials).

Finally, (−)-bromopericosine A (1Br) was treated with 3.0 eq of LHMDS at −78 °C to give (−)-7, which is an enantiomer of the natural product. The isolated yield of (−)-7 upon purification via conventional acidic silica gel column chromatography was only 23%, but this was improved to 77% using neutral silica gel. The spectral data agree with those of natural pericoside with the exception of the sign of its specific rotation. Unfortunately, (−)-7 was so unstable that it decomposed upon storage at rt in methanol, exhibiting a smaller optical rotation within a couple of days. Furthermore, the decomposed residue exhibits a positive specific rotation, although freshly synthesized 7 was negative. Regrettably, biological assays of 7 could not be performed because of this inherent instability.

Treatment of 1Br with 2.0 eq of LHMDS led to a decreased yield of 7 (57%) along with the recovered starting material (1Br, 34%). Alternatively, intramolecular epoxidation of (−)-1Cl with LHMDS (3.0 eq) gave (−)-7 in 12% yield along with the recovery of (−)-1Cl (20%).

This experiment indicates the significance of bromo-derivative 1Br as the starting material. Using the same synthetic process, natural (+)-7 was synthesized via (+)-1Br starting from (−)-quinic acid. A similar synthesis of (+)-7 from (+)-1Cl has been previously reported by Cichewitz in 2019 [39].

2.3. Evaluation of the Biological Activities of Enantiomerically Pure Pericosine A and Its 6-Halogenated Congeners
2.3.1. Antitumor Assay

The antitumor activity of halo-compounds 1 was evaluated against three types of tumor cell lines: Basic P388 (mouse lymphocytic leukemia), L1210 (mouse lymphocytic leukemia), and LH60 (human promyelocytic leukemia) cell lines, along with a previously reported procedure using 5-fluorouracil (5-FU) as a positive control [35]. The results are presented in Table 1, including those obtained for pericosine A (1Cl), which has been previously reported in the literature, for comparison. All compounds showed antitumor activity against the three types of tumor cell lines studied. Bromo- and iodo-pericosine (1Br and 1I) show similar activities to 1Cl, but fluorinated compound 1F was less active than all of the other compounds, including 1Cl. Because pericosine C (3), which exists as an enantiomeric mixture in nature and has the same relative configuration to 1s, was reported to be inactive against P-388 cell line [14], present results implied the importance of the presence of halogen atom at C-6 in pericosine core structure for antitumor activity. In addition, it is noteworthy that no significant difference in the potency was observed between the enantiomers, similar to pericosine A.

| Compound                        | P388 (µM) | L1210 (µM) | HL-60 (µM) |
|---------------------------------|-----------|------------|------------|
| (+)-Pericosine A (1Cl)          | 5.00      | 6.12       | 2.03       |
| (−)-Pericosine A (1Cl)          | 4.85      | 3.96       | 2.33       |
| (+)-6-Fluoropericosine A (1F)   | 9.91      | 44.0       | 10.8       |
| (−)-6-Fluoropericosine A (1F)   | 9.03      | 38.0       | 9.46       |
| (+)-6-Bromopericosine A (1Br)   | 5.39      | 5.66       | 5.57       |
| (−)-6-Bromopericosine A (1Br)   | 5.65      | 6.30       | 6.08       |
| (+)-6-Iodopericosine A (1I)     | 6.17      | 8.18       | 6.78       |
| (−)-6-Iodopericosine A (1I)     | 5.91      | 8.27       | 6.45       |
| 5-FU (positive control)         | 3.86      | 0.63       | 0.22       |
2.3.2. Glycosidase Inhibitory Activity Assay

There have been several excellent studies on the development of pseudosugar-type glycosidase inhibitors [40–50]. The compounds synthesized in this study were also applied to an glycosidase inhibitory assay against five kinds of enzymes: α-glucosidase from yeast, β-glucosidase from Jack bean, α-galactosidase from green coffee bean, β-galactosidase from bovine liver, and α-mannosidase from bovine liver. The results are presented in Table 2 along with the previous results obtained for pericosine A (1Cl) for comparison [35]. (−)-1F, (−)-1Br, and (−)-1I exhibit comparable inhibitory activities to (−)-1Cl (IC₅₀ = 2.25 mM) against α-glucosidase with IC₅₀ values of 1.95, 1.79, and 3.60 mM, respectively, whereas they were less active than the positive control [deoxynojirimycin (DNJ)]; IC₅₀ = 0.0965 mM]. (+)1Br showed less potent activity (IC₅₀ = 5.05 mM) when compared to (−)-1Br, and (+)-1F was inactive similar to (+)--1Cl. Surprisingly, (+)-1I exhibited the most potent α-glucosidase inhibitory activity (IC₅₀ = 1.15 mM) among the eight compounds studied and was active against α-galactosidase (IC₅₀ = 3.56 mM). This is the only example of an α—galactosidase inhibitor among the pericosines and their congeners reported to date.

Table 2. Glycosidase inhibitory activity of the synthetic 6-halo-congeners of pericosine A.

| Compound | α-Glucosidase | β-Glucosidase | α-Mannosidase | α-Galactosidase | β-Galactosidase |
|----------|---------------|---------------|---------------|----------------|----------------|
| (+)-1Cl35 | NI f           | NI            | NI            | NI              | NI             |
| (−)-1Cl35 | 2.25          | NI            | NI            | NI              | 5.38           |
| (+)-1F    | 1.95          | NI            | NI            | NI              | NI             |
| (−)-1F    | 1.79          | NI            | NI            | NI              | 5.60           |
| (+)-1Br   | 5.05          | NI            | NI            | NI              | NI             |
| (−)-1Br   | 1.15          | NI            | NI            | 3.56            | NI             |
| (+)-1I    | 3.60          | NI            | NI            | NI              | NI             |
| DNJ (positive control) | 0.0965 | 0.195 | – | – | – |

a Yeast, b Sweet almond, c Jack bean, d Green coffee bean, e Bovine liver, f NI: No inhibition (IC₅₀ >9.25 mM).

All of the synthesized compounds were inactive against β-glucosidase and α-galactosidase. Interestingly, (−)-1Br showed dual activity against β-galactosidase and α-glucosidase similar to (−)-1Cl, but they were less active than those reported for some pericosine E derivatives [33].

3. Materials and Methods

General methods: HRMS was performed on a JMS-700 (2) mass spectrometer (JEOL, Tokyo, Japan). NMR spectra were recorded at 27 °C on 300- and 400-MR-DD2, INOVA-500 and 600-DD2 spectrometers (Agilent Technologies, CA, USA) in CDCl₃ or acetone-d₆ using tetramethylsilane (TMS) as an internal standard. Specific rotations were measured using a DIP1000 digital polarimeter (JASCO Co., Tokyo, Japan). Liquid column chromatography was conducted on silica gel (BW-127ZH) (Fuji Silysia, Tokyo, Japan) or neutral silica gel (CHROMATOREX DIOL MB100–75/200) (Fuji Silysia, Tokyo, Japan). Analytical TLC was performed on precoated silica gel 60 plates (Merck & Co., Inc., Darmstadt, Germany) and the compounds were viewed by dipping the plates in an ethanol solution of phosphomolybdic acid, followed by heating. Microwave-aided reactions were performed using Initiator® (Biotage, Uppsala, Sweden). Flash chromatography was performed using Isolera One® (Biotage, Uppsala, Sweden). (−)-Shikimic acid was purchased from Carbosynth Ltd. (UK). (−)-Quinic acid was purchased from Merck & Co., Inc. (Darmstadt, Germany). Al₃I, HCl, BH₃Br, SMₑ₂, and Dowex® 50WX8-H were purchased from Sigma-Aldrich (St. Louis, MO). n-BuLi in hexane was purchased from Nacalai Tesque (Kyoto, Japan). Hexamethyldisilazane and (HF)ₙ/py complex were purchased from TCI (Tokyo, Japan). Trifluoroacetic acid, dry MeOH, CH₂Cl₂, Et₂O, and tetrahydrofuran (THF) were purchased from Wako Pure Chemical Industries (Osaka, Japan).
3.1. Synthesis of Both Enantiomers of The 6-Halopericosine A Analogs

3.1.1. Synthesis of Methyl

(--)3,4-O-Cyclohexyldiene-6-Fluoro-3,4,5-Trihydroxy-1-CycloHexene Carboxylate (10f)

To a solution of (--)8 (13.4 mg, 0.050 mmol) in CH₂Cl₂ (1.0 mL) in a polyethylene tube and cooled at 0 °C was added 12.5 mL of (HF)a/pyridine complex (67% w/v HF; 4.0 mmol). The resulting mixture was stirred at 0 °C for 15 min and quenched upon adding saturated (sat.) NaHCO₃ (aq) (10 mL). The mixture was then extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were dried over MgSO₄, filtered, and evaporated to afford the crude product, which was purified by column chromatography on neutral silica gel (eluent = Hexane:EtOAc = 9:1) to afford (--)10f as a colorless oil (6.6 mg, 46%). [α]D 20° = -41.1 (c 0.12, CHCl₃); 1H-NMR (CDCl₃, 500 MHz) δ 1.22–1.71 (10H, m), 2.51 (1H, dd, J = 4.1, 1.6 Hz, 5-CH₃), 3.83 (3H, s, -COOCH₃), 4.20 (1H, ddd, J = 10.3, 5.5, 4.3, 3.2 Hz, H-5), 4.56 (1H, ddd, J = 6.2, 3.2, 3.0 Hz, H-4), 4.76 (1H, ddd, J = 6.2, 5.5, 3.2, 0.9 Hz, H-3), 5.56 (1H, dd, J = 4.0, 5.5 Hz, H-6), 7.01 (1H, br dd, J = 3.2, 2.8 Hz, H-2); 13C-NMR (CDCl₃, 125 MHz) δ 23.6 (CH₂), 23.9 (CH₂), 24.9 (CH₂), 34.5 (CH₂), 36.6 (CH₂), 52.4 (CH₃), 67.6 (d, JCF = 24.9 Hz, CH, C-5), 70.9 (d, JCF = 2.4 Hz, CH, C-3), 73.4 (d, JCF = 5.8 Hz, CH, C-4), 86.2 (d, JCF = 168.8 Hz, CH, C-6), 111.2, 128.5 (d, JCF = 17.7 Hz, CH, C-1), 139.4 (d, JCF = 5.8 Hz, CH, C-2), 165.2 (Cq, COOME); HREIMS m/z calcd for C₁₄H₁₉O₂F [M]+ 286.1217, found 286.1218.

(+)10f (7.1 mg, 43%) was synthesized from (+)-8 (15.5 mg, 0.058 mmol) in the same manner as (--)10f. [α]D 20° +37.6 (c 0.13, CHCl₃); 1H-NMR (CDCl₃, 400 MHz) δ 1.22–1.70 (10H, m), 2.51 (1H, dd, J = 3.0 Hz, 5-CH₃), 3.83 (3H, s, -COOCH₃), 4.17–4.24 (1H, m, H-4), 4.56 (1H, dd, J = 6.3, 3.1 Hz, H-4), 4.76 (1H, ddd, J = 6.0, 5.5, 3.1 Hz, H-3), 5.56 (1H, dd, J = 48.1, 5.5 Hz, H-6), 7.01 (1H, br dd, J = 2.8, 2.5 Hz, H-2); 13C-NMR (CDCl₃, 100 MHz) δ 23.6, 23.9, 24.9, 34.5, 36.6, 52.4, 67.6 (d, JCF = 25.2 Hz, C-5), 70.9 (d, JCF = 2.3 Hz, C-3), 73.4 (d, JCF = 5.4 Hz, C-4), 86.2 (d, JCF = 168.6 Hz, C-6), 111.2 (Cq), 128.5 (d, JCF = 17.6 Hz, CH, C-1), 139.4 (d, JCF = 5.3 Hz, C-2), 165.2 (Cq, COOME); HREIMS m/z calcd for C₁₄H₁₉O₂F [M]+ 286.1217, found 286.1215.

3.1.2. Synthesis of (--)6-Fluoropericosine A (1f)

To a solution of (--)10f (7.5 mg, 0.026 mmol) in MeOH (1.0 mL) was added TFA (2.0 mL) at 0 °C with stirring. The reaction mixture was stirred for another 3.5 h at rt, then condensed under reduced pressure to give the crude product, which was purified by column chromatography on neutral silica gel (eluant = 5% MeOH in CH₂Cl₂) to afford (--)1f as a colorless oil. [α]D 20° -78.7 (c 1.4, MeOH); 1H-NMR (MeOH-d₄, 600 MHz, ppm) δ 3.76 (3H, s, -OME), 3.97 (1H, ddd, J = 13.6, 6.1, 2.0 Hz, H-5), 4.03–4.06 (1H, m, H-4), 4.41–4.44 (1H, m, H-3), 5.42 (1H, ddd, J = 49.6, 6.7, 1.7, 0.6 Hz, H-6), 6.81–6.82 (1H, m, H-2); 13C-NMR (MeOH-d₄, 150 MHz, ppm) δ 52.3 (CH₃, COOME), 68.2 (CH, C₃, JCF = 2.3 Hz), 72.7 (CH, C₄, JCF = 0.9 Hz), 73.3 (CH, C₅, JCF = 20.9 Hz), 90.7 (CH, C-6, JCF = 167.6 Hz), 129.1 (Cq, Cl, d, JCF = 18.5 Hz), 144.4 (CH, C-2, d, JCF = 5.8 Hz), 166.3 (Cq, COOME); HREIMS m/z calcd for C₈H₁₂O₃F [M]+ 207.0669, found 207.0668.

(+)1f (3.5 mg, 59%) was synthesized from (+)-8 (8.2 mg, 0.029 mmol) in the same manner as (--)1f. Colorless oil. [α]D 20° +67.7 (c 0.95, MeOH); 1H-NMR (MeOH-d₄, 600 MHz, ppm) δ 3.73 (3H, s, -OME), 3.92 (1H, ddd, J = 17.0, 6.1, 2.0 Hz, H-5), 4.03–4.05 (1H, m, H-4), 4.40–4.43 (1H, m, H-3), 5.34 (1H, ddd, J = 49.9, 6.5, 2.1, 0.6 Hz, H-6), 6.75–6.77 (1H, m, H-2); 13C-NMR (MeOH-d₄, 150 MHz, ppm) δ 52.4 (CH₃, COOME), 68.3 (CH, C₃), 73.0 (CH, C₄, JCF = 6.9 Hz), 73.1 (CH, C₅, JCF = 20.8 Hz), 90.8 (CH, C-6, d, JCF = 167.6 Hz), 129.0 (Cq, Cl, d, JCF = 18.5 Hz), 144.4 (CH, C-2, d, JCF = 6.9 Hz), 166.5 (Cq, COOME); HREIMS m/z calcd for C₈H₁₂O₃F [M]+ 207.0669, found 207.0675.

3.1.3. Synthesis of Methyl

(--)-6-Bromo-3,4-O-Cyclohexyldiene-3,4,5-Trihydroxy-1-CycloHexene Carboxylate (10Bb)

To a solution of syn-epoxide (--)8 (112.8 mg, 0.42 mmol) in Et₂O (5 mL) was added a solution 1.0 M BH₂Br-SMe₂ in CH₂Cl₂ (0.48 mL, 0.42 mmol) at −78 °C. After stirring at
−78 °C for 5 h, the reaction mixture was quenched with saturated NH₄Cl aq., and extracted with CH₂Cl₂ (10 mL × 3). The combined organic layers were dried over MgSO₄, filtered, and evaporated to give the crude product, which was almost pure, but purified via silica gel column chromatography (eluents; EtOAc:Hexane = 1:3) to afford (-)-10Br (139.7 mg, 94%). [α]D²⁰ = −207.4 (c 0.30, CHCl₃); IR (KBr) νmax 3471 (OH), 1724 (C=O), 1652 (C=C) cm⁻¹; ¹H-NMR (acetate-d₆, 600 MHz, ppm) δ 1.37–1.71 (10H, m, 5 × CH₂), 3.80 (3H, s, -OMe), 4.17 (1H, d, J = 4.1 Hz, OMe), 4.29 (1H, ddd, J = 4.4, 4.1, 3.5 Hz, H-5), 4.71 (1H, br dd, J = 7.0, 3.5 Hz, H-4), 4.88 (1H, br dd, J = 7.0, 3.2 Hz, H-3), 4.99 (1H, br d, J = 4.4 Hz, H-6), 6.99 (1H, dd, J = 3.2, 1.5 Hz, H-2); ¹³C-NMR (acetone-d₆, 150 MHz, ppm) δ 24.4 (CH₂), 24.7 (CH₂), 25.8 (CH₂), 34.91 (CH₂), 34.93(CH₂), 36.8 (CH₂), 44.0 (CH, C-6), 52.6 (Cq, -OCH₃), 68.9 (CH, C-5), 70.8 (CH, C-3), 73.6 (CH, C-4), 111.1 (Cq), 131.6 (Cq, C-1), 138.6 (CH, C-2), 165.8 (Cq, COOMe); ¹H-NMR (CDCl₃, 600 MHz, ppm) δ 1.40–1.73 (10H, m, 5 × CH₂), 2.70 (1H, d, J = 2.3 Hz, OMe), 3.83 (3H, s, -OMe), 4.35–4.37 (1H, m, H-5), 4.75–4.79 (2H, m, overlapped, H-3,4), 4.88 (1H, br dd, J = 7.0, 3.2 Hz, H-3), 5.09 (1H, d, J = 3.8 Hz, H-6), 7.17 (1H, dd, J = 1.8, 1.1 Hz, H-2); ¹³C-NMR (CDCl₃, 150 MHz, ppm) δ 23.5 (CH₂), 23.9 (CH₂), 25.1 (CH₂), 33.3 (CH₂), 36.0 (CH₂), 40.4 (CH-C6), 52.5 (Cq, -OCH₃), 67.0 (CH, C-5), 69.4 (CH, C-3), 71.6 (CH, C-4), 110.7 (Cq), 130.7 (Cq, C-1), 137.4 (CH, C-2), 164.7 (Cq, COOME); C₈H₁₄O₅S¹⁷Br [M⁺] 348.0395 found 348.0395. HREIMS m/z calcd for C₁₄H₁₉O₅S¹⁷Br [M⁺] 348.0416 found 348.0415, C₁₄H₁₉O₅S¹⁷Br (M⁺) 348.0395 found 348.0395.

(+)-10Br (57.6 mg, 83%) was synthesized from (+)-8 (53.2 mg, 0.20 mmol) in the same manner as (−)-10Br. Colorless crystals (CH₂Cl₂); mp 117–120 °C; [α]D²⁰ +204.0 (c 0.29, CHCl₃); ¹H-NMR (acetone-d₆, 600 MHz, ppm) δ 1.38–1.72 (10H, m, 5 × CH₂), 3.81 (3H, s, OMe), 4.19 (1H, d, J = 4.1 Hz, H-3), 4.27–4.30 (1H, m, H-5), 4.71 (1H, br dd, J = 7.0, 3.5 Hz, H-4), 4.88 (1H, br dd, J = 7.0, 2.9 Hz, H-3), 4.99 (1H, d, J = 4.4 Hz, H-6), 6.99 (1H, dd, J = 3.3, 1.5 Hz, H-2); ¹³C-NMR (acetone-d₆, 150 MHz, ppm) δ 24.4 (CH₂), 24.7 (CH₂), 25.8 (CH₂), 34.9 (CH₂), 36.8 (CH₂), 44.0 (CH, C-6), 52.6 (CH₃, COOMe), 68.9 (CH, C5), 70.8 (CH, C3), 73.6 (CH, C4), 111.1 (Cq), 131.6 (Cq, C-1), 138.7 (CH, C-2), 165.8 (Cq, COOME); HREIMS m/z calcd for C₁₄H₁₉O₅S¹⁷Br [M⁺] 348.0416 found 348.0415, C₁₄H₁₉O₅S¹⁷Br (M⁺) 348.0395 found 348.0395.

3.1.4. Synthesis of (−)-6-Bromopericosaine A (1Br)

Table S1, entry 4: To a solution of (−)-10Br (41.3 mg, 0.12 mmol) in MeOH (2.0 mL) was added Dowex® 50WX8-H (102.5 mg) and the resulting mixture was stirred for 56 h at room temperature. The reaction mixture was filtered and the filtrate concentrated under reduced pressure to give a crude residue, which was purified with silica gel column chromatography (eluents; CH₂Cl₂:MeOH = 95: 5) to afford (−)-1Br (27.6 mg, 87%) and recovered (−)-10Br (5.5 mg, 13%).

(+)-1Br (37.7 mg, 78%) was synthesized from (+)-10Br (57.6 mg, 0.166 mmol) in the same manner as (−)-1Br. Amorphous solid; mp 96–99 °C; [α]D²⁰ +130.8 (c 1.38, MeOH); IR (film) νmax 3219 (OH), 1712 (C=O) cm⁻¹; ¹H-NMR (CD₂OD, 600 MHz, ppm) δ 3.80 (3H, s, COOME), 4.10 (1H, dd, J = 4.4, 2.1 Hz, H-4), 4.18 (1H, ddd, J = 4.4, 2.0 Hz, H-5), 4.36 (1H, br dd, J = 4.4, 4.1 Hz, H-3), 4.94 (1H, dd, J = 4.4, 0.9 Hz, H-6), 6.86 (1H, d, J = 4.1 Hz, H-2); ¹³C-NMR (CD₂OD, 150 MHz, ppm) δ 48.7 (CH, C-6), 52.8 (CH₃, COOME), 67.6 (CH, C3), 69.3 (CH, C-4), 76.2 (CH, C-5), 131.8 (Cq, C-1), 141.6 (CH, C-2), 167.3 (Cq, COOME); HREIMS m/z calcd for C₈H₁₀O₅⁻¹⁷Br [M − H]⁺ 266.9868 found 266.9869.
3.1.5. Synthesis of Methyl
(−)-3,4-5-O-Cyclohexyldiene-3,4,5-Trihydroxy-6-iodo-1-CycloHexene Carboxylate (10)

To a solution of (−)-8 (14.4 mg, 0.056 mmol) in CH₂Cl₂ (1.0 mL) was added All₃ (7.9 mg, 0.019 mmol) at 0 °C with stirring. After stirring for 2 h at 0 °C, the reaction was quenched by adding sat. NaHCO₃ (aq) (5 mL). The resulting mixture was then extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were dried over MgSO₄, filtered, and evaporated to afford the crude product, which was purified by silica gel column chromatography (eluent = Hexane:EtOAc = 5:1) to afford (−)-10 (15.5 mg, 60%) as a white powder. mp 97–100 °C; [α]D¹⁰ -261.4 (c 0.09, CHCl₃); ¹H-NMR (CDCl₃, 600 MHz, ppm) δ 1.43–1.74 (10H, m), 2.70 (1H, d, J = 2.3 Hz, 5-OH), 3.82 (3H, s, -OMe), 4.36 (1H, dd, J = 4.1, 3.2, 2.3 Hz, H-5), 4.74 (1H, dd, J = 7.9, 3.2 Hz, H-3), 4.86 (1H, dd, J = 7.9, 4.1 Hz, H-4), 5.21 (1H, d, J = 3.2 Hz, H-6), 7.10 (1H, d, J = 3.2 Hz, H-2); ¹³C-NMR (CDCl₃, 150 MHz, ppm) δ 16.8 (CH₂), 23.5 (CH₂), 24.0 (CH₂). 25.1 (CH₂), 33.3 (CH₂), 36.0 (CH, C-6), 52.5 (CH₃, COOME), 68.0 (CH, C-5), 69.1 (CH, C-3), 72.6 (CH, C-4), 110.4 (Cq), 132.5 (Cq, C-1), 135.8 (CH, C-2), 164.7 (Cq, COOME); HREIMS m/z calc for C₁₄H₁₀O₃I [M]+ 394.0277, found 394.0279.

(+)·10 (17.6 mg, 72%) was synthesized from (+)-8 (16.5 mg, 0.062 mmol) in a similar manner as (−)-10. White powder; mp 97–100 °C; [α]D¹⁰ +262.0 (c 0.13, CHCl₃); ¹H-NMR (CDCl₃, 400 MHz, ppm) δ 1.43–1.74 (10H, m), 2.71 (1H, d, J = 1.6 Hz, 5-OH), 3.82 (3H, s, -OMe), 4.34–4.38 (1H, m, H-5), 4.74 (1H, dd, J = 7.8, 3.1 Hz, H-3), 4.86 (1H, dd, J = 7.8, 3.5 Hz, H-4), 5.21 (1H, d, J = 3.3 Hz, H-6), 7.10 (1H, d, J = 3.2 Hz, H-2); ¹⁳C-NMR (CDCl₃, 150 MHz, ppm) δ 16.8, 23.5, 23.9, 25.0, 33.2, 35.9, 52.5, 68.0, 69.1, 72.5, 110.4, 132.4, 135.8, 164.6; HREIMS m/z calc for C₁₄H₁₀O₃I [M]+ 394.0277, found 394.0279.

3.1.6. Synthesis of (−)-6-Iodopericosine A (1)

To a solution of (−)-10 (4.3 mg, 0.011 mmol) in CH₃OH (1.0 mL) was added TFA (0.13 mL) at 0 °C with stirring. After stirring for another 3 h at rt, the reaction mixture was stirred under reduced pressure to give a crude residue, which was purified by column chromatography with neutral silica gel (eluent = 5% MeOH in CHCl₃) to afford (−)-I₁ as a colorless oil (2.6 mg, 76%). [α]D²⁰ +11.7 (c 0.10, MeOH); ¹H-NMR (acetone-d₆, 600 MHz, ppm) δ 3.79 (3H, s, -OMe), 4.21 (1H, dd, J = 4.7, 2.1 Hz, H-4), 4.33 (1H, br dd, J = 3.5, 2.1 Hz, H-5), 4.43 (1H, br t, J = 4.7, H-3), 5.16 (1H, dd, J = 3.5, 0.6 Hz, H-6), 6.88 (1H, d, J = 4.4 Hz, H-2); ¹⁳C-NMR (acetone-d₆, 150 MHz, ppm) δ 26.8 (CH, C-6), 52.6 (CH₃, COOCH₃), 66.6 (CH, C₅), 67.7 (CH, C-4), 76.9 (CH, C-5), 132.8 (Cq, C₁), 139.5 (CH, C-2), 166.4 (Cq, COOME); HREIMS m/z calc for C₁₄H₁₁O₃I [M]⁺ 319.9652, found 319.9649.

(+)·1 (1.9 mg, 77%) was synthesized from (+)-10 (3.1 mg, 0.0079 mmol) in a similar manner as (−)-1. Colorless oil; [α]D²⁰ +11.7 (c 0.10, MeOH); ¹H-NMR (acetone-d₆, 600 MHz, ppm) δ 3.79 (3H, s, -OMe), 4.21 (1H, dd, J = 4.7, 2.1 Hz, H-4), 4.33 (1H, br dd, J = 3.5, 2.1 Hz, H-5), 4.43 (1H, br t, J = 4.7, H-3), 5.16 (1H, dd, J = 3.5, 0.6 Hz, H-6), 6.88 (1H, d, J = 4.4 Hz, H-2); ¹⁳C-NMR (acetone-d₆, 150 MHz, ppm) δ 26.8 (CH, C-6), 52.6 (CH₃, COOCH₃), 66.7 (CH, C-3), 67.7 (CH, C-4), 76.9 (CH, C-5), 132.8 (Cq, C₁), 139.5 (CH, C-2), 166.4 (Cq, COOME); HREIMS m/z calc for C₁₄H₁₁O₃I [M]⁺ 319.9652, found 319.9655.

3.2. Synthesis of Pericoxide

Synthesis of Methyl (3R,4R,5R,6S)-5-Bromo-3,4,6-Trihydroxycyclohex-1-ene-1-carboxylate (11) from 9

A solution of 9 (264 mg, 0.76 mmol) in dry MeOH (4.0 mL) in a microwave (MW) vial was added to Dowex (760 mg). The vial was then sealed and heated under MW irradiation at 100 °C for 30 min. After cooling, the reaction mixture was filtered, the filtrate concentrated under reduced pressure to give the crude product, which was purified via column chromatography (eluent: CH₂Cl₂:MeOH = 95:5) to afford 11 (164 mg, 80%); [α]D²⁰ -71.1 (c 1.285, MeOH); IR (liquid film) νₘₐₓ 3417 (OH), 1714 (C=O), 1650 (C=C) cm⁻¹; ¹H-NMR (CD₂OD, 600 MHz, ppm) δ 3.78 (3H, s, OMe), 3.84 (1H, dd, J = 8.2, 4.1 Hz, H-4), 4.29 (1H, dd, J = 8.2, 5.3 Hz, H-5), 4.47 (1H, t, J = 4.1 Hz, H-3), 4.64 (1H, d, J = 5.3 Hz, H-6), 6.77
(1H, dd, J = 4.1, 0.6 Hz, H-2); 13C-NMR (CD3OD, 150 MHz, ppm) δ 52.5 (COOMe-C8), 55.1 (CH, C5), 67.0 (CH, C3), 71.4 (CH, C4), 71.5 (CH, C6), 138.6 (CH, C2), 167.8 (COOMe-C7); HREIMS m/z calcd for C9H12O5.5Br1 [M + H]+ 266.9864 found 266.9865, C8H10O5.5Br1 [M + H]+ 268.9848 found 268.9850.

3.3. Intramolecular Epoxidation of Bromotriol 11

To a solution of 1,1,1,3,3,3-hexamethyldisilazane (HMDS) (0.22 mL, 1.07 mmol) in THF (5 mL) was added n-BuLi (0.66 mL, 1.06 mmol) at −78 °C to prepare a solution of lithium hexamethyldisilazide (LHMDS). After stirring for 30 min, the LHMDS solution was added dropwise to a solution of 11 (92.7 mg, 0.35 mmol) in THF (5 mL) at −78 °C. After stirring the reaction mixture at −78 °C for 1 h, the resulting mixture was warmed to rt and stirred for another 1 h. The reaction mixture was then treated with sat. NH4Cl aq. (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over MgSO4, filtered, and evaporated to give the crude product, which was purified by column chromatography (CH2Cl2: MeOH = 95: 5) to afford methyl 13C-dihydroxy-7-oxabicyclo[4.1.0]hept-3-ene-3-carboxylate (12) (27.4 mg, 42%). [α]D20 = 27.2 (c 0.29, MeOH); IR (liquid film) νmax = 3391 (OH), 1713 (C=O), 1655 (C=C) cm−1; 1H-NMR (CD3OD, 600 MHz, ppm) δ 3.05 (1H, ddd, J = 4.4, 2.1, 1.5 Hz, H-6), 3.54 (1H, dd, J = 4.1, 2.9 Hz, H-1), 3.76 (3H, s, COOMe), 4.49 (1H, dd, J = 4.4, 2.3 Hz, H-5), 4.58 (1H, s, OH), 4.68 (1H, dd, J = 2.6, 1.2 Hz, H-2), 6.43 (1H, dd, J = 4.1, 2.3 Hz, H-4); 13C-NMR (CD3OD, 150 MHz, ppm) δ 52.4 (CH3, COOME), 55.4 (CH, C-6), 56.0 (CH, C-1), 64.1 (CH, C-2), 65.9 (CH, C-5), 131.5 (Cq, C-3), 137.8 (CH, C-4), 168.0 (Cq, COOME); HREIMS m/z calcd for C8H11O5 [M + H]+ 187.0606 found 187.0604.

3.4. Synthesis of (−)-Pericoxide (7)

A solution of 1.6 M n-BuLi in hexane (0.17 mL, 0.27 mmol) was added to a solution of HMDS (0.089 mL, 0.43 mmol) in THF (2 mL) at −78 °C with stirring to prepare an LHMDS solution. After 40 min, the prepared LHMDS solution was added to a solution of 10B (22.1 mg, 0.085 mmol) in THF (2 mL) at −78 °C. After stirring for 1.5 h at −78 °C, the reaction mixture was quenched with sat. NH4Cl aq. (20 mL) and extracted with EtOAc (7 × 20 mL). The combined organic layers were dried over MgSO4, filtered, and concentrated under reduced pressure to give the crude product, which was purified via column chromatography (eluent: CH2Cl2:MeOH = 97:3) using neutral silica gel (DOL MB100–75/200, Fiji Silysia Co.) to afford (+)-3 (11.9 mg, 77%); Colorless oil; [α]D20 = −68.3 (c 0.60, MeOH); IR (film) νmax = 3414 (OH), 1720 (C=O), 1651 (C=C) cm−1; 1H-NMR (CD3OD, 600 MHz, ppm) δ 3.63 (1H, ddd, J = 4.4, 2.1, 1.5 Hz, H-5), 3.81 (3H, s, COOMe), 3.97 (1H, d, J = 4.1 Hz, H-6), 3.98 (1H, d, J = 4.4 Hz, H-4), 4.21 (1H, ddd, J = 6.2, 5.0, 2.1 Hz, H-3), 4.58 (1H, s, OH), 7.12 (1H, dd, J = 6.5, 2.4 Hz, H-2); 13C-NMR (CD3OD, 150 MHz, ppm) δ 50.1 (CH-C6), 52.8 (COOME-C8), 58.7 (CH-C5), 66.6 (CH-C3), 68.6 (CH-C4), 132.0 (CH, C-1), 143.3 (CH, C-2), 167.3 (Cq, COOME); HREIMS m/z calcd for C8H10O5 [M]+ 186.0528, found 186.0523.

(+)-7 (3.7 mg, 87%) was synthesized from (+)-10B (6.2 mg, 0.023 mmol) in the same manner. Colorless oil; [α]D20 = +65.8 (c 0.60, MeOH); 1H-NMR (CD3OD, 600 MHz, ppm) δ 3.63 (1H, ddd, J = 4.4, 2.1, 1.5 Hz, H-5), 3.81 (3H, s, COOMe), 3.96–3.98 (2H, m, H-4, H-6), 4.21 (1H, ddd, J = 6.2, 5.0, 2.1 Hz, H-3), 4.57 (1H, s, OH), 7.12 (1H, dd, J = 6.5, 2.4 Hz, H-2); 13C-NMR (CD3OD, 150 MHz, ppm) δ 50.1 (CH-C6), 52.8 (COOME-C8), 58.7 (CH-C5), 66.6 (CH-C3), 68.6 (CH-C4), 132.0 (CH, C-1), 143.3 (CH, C-2), 167.2 (Cq, COOME), *some degradation was detected when measuring the 13C-NMR spectrum; HREIMS m/z calcd for C8H10O5[M]+ 186.0528, found 186.0525; Literature data of (+)-7 [34]: [α]D +74 (c = 0.13, MeOH); 1H-NMR (CD3OD, 400 MHz, ppm) δ 3.64 (1H, m, H-5), 3.81 (3H, s, COOMe), 3.96 (1H, m, H-6), 3.96 (1H, m, H-4), 4.21 (1H, m, H-3), 4.58 (1H, s, OH), 7.10 (1H, dd, J = 6.4, 2.3 Hz, H-2); 13C-NMR (CD3OD, 100 MHz, ppm) δ 50.1 (CH, C-6), 52.8 (CH3, COOME), 58.6 (CH, C-5), 66.4 (CH, C-3), 68.5 (CH, C-4), 131.2 (CH, C-1), 143.2 (CH-2), 167.2 (Cq, C-7); HREIMS m/z calcd for C8H10O5Na [M + Na]+ 209.0420, found 209.0416.
3.5. Biological Assay

Antitumor and glucosidase inhibitory assays were performed using the same procedures as those described in our previous paper [35].

4. Conclusions

The synthesis of both enantiomers of pericosine A analogs bearing F, Br, and I atoms was achieved for the first time and their antitumor activity against P388, L1210, and HL-60 cell lines was evaluated. Although all of the synthesized compounds were moderately active against the three types of tumor cell lines studied, significant differences between their enantiomers and differences between the halogens, except for fluorine, were not observed. The fluorinated derivatives showed weaker activities than the other analogs and pericosine A.

Form glycosidase inhibitory assay, five synthesized molecules of 1 except for (+)-1F were elucidated to exhibit α-glucosidase inhibitory activity at mM level of IC50. As well, (−)-1Br and (+)-1Br showed inhibitory activities against β-galactosidase and α-galactosidase, respectively, at mM level of IC50.

In addition, both enantiomers of pericoxide were synthesized using 6-bromopericosine A as a suitable synthetic precursor.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/md20070438/s1, Figure S1. 1H-NMR spectrum of (−)-10F in CDCl3 (600 MHz), Figure S2. 13C-NMR spectrum of (−)-10F in CDCl3 (150 MHz); Figure S3. 1H-NMR spectrum of (−)-10F in CDCl3 (400 MHz); Figure S4. 13C-NMR spectrum of (−)-10F in CDCl3 (100 MHz); Figure S5. 1H-NMR spectrum of (−)-1F in acetone-d6 (600 MHz); Figure S6. 13C-NMR spectrum of (−)-1F in acetone-d6 (150 MHz); Figure S7. 1H-NMR spectrum of (−)-1F in acetone-d6 (600 MHz); Figure S8. 1H-NMR spectrum of (−)-1F in CDCl3 (600 MHz); Figure S9. 1H-NMR spectrum of (−)-1F in acetone-d6 (150 MHz); Figure S10. 1H-NMR spectrum of (−)-10Br in acetone-d6 (600 MHz); Figure S11. 13C-NMR spectrum of (−)-10Br in acetone-d6 (150 MHz); Figure S12. 1H-NMR spectrum of (−)-10Br in acetone-d6 (600 MHz); Figure S13. 13C-NMR spectrum of (−)-10Br in acetone-d6 (150 MHz); Figure S14. 1H-NMR spectrum of (−)-1Br in methanol-d4 (600 MHz); Figure S15. 13C-NMR spectrum of (−)-1Br in methanol-d4 (150 MHz); Figure S16. 1H-NMR spectrum of (−)-1Br in methanol-d4 (600 MHz); Figure S17. 13C-NMR spectrum of (−)-1Br in methanol-d4 (150 MHz); Figure S18. 1H-NMR spectrum of (−)-1Br in methanol-d4 (600 MHz); Figure S19. 13C-NMR spectrum of (−)-1Br in CDCl3 (600 MHz); Figure S20. 1H-NMR spectrum of (−)-1Br in CDCl3 (150 MHz); Figure S21. 13C-NMR spectrum of (−)-1Br in CDCl3 (100 MHz); Figure S22. 1H-NMR spectrum of (−)-1Br in acetone-d6 (600 MHz); Figure S23. 13C-NMR spectrum of (−)-1Br in acetone-d6 (150 MHz); Figure S24. 1H-NMR spectrum of (−)-1Br in acetone-d6 (600 MHz); Figure S25. 13C-NMR spectrum of (−)-1Br in acetone-d6 (150 MHz); Figure S26. 1H-NMR spectrum of (−)-11 in methanol-d4 (600 MHz); Figure S27. 13C-NMR spectrum of (−)-11 in methanol-d4 (150 MHz); Figure S28. 1H-NMR spectrum of (−)-12 in methanol-d4 (600 MHz); Figure S29. 13C-NMR spectrum of (−)-12 in methanol-d4 (150 MHz); Figure S30. HMBC spectrum of (−)-12 in methanol-d4 (600 MHz); Figure S31. 1H-NMR spectrum of (−)-7 in methanol-d4 (600 MHz); Figure S32. 13C-NMR spectrum of (−)-7 in methanol-d4 (150 MHz); Figure S33. 1H-NMR spectrum of (−)-7 in methanol-d4 (600 MHz); Figure S34. 13C-NMR spectrum of (−)-7 in methanol-d4 (150 MHz) Table S1. Deprotection of (−)-10Br; with Dowex® 50WX-8-H.

Author Contributions: Y.U. conceived and designed the experiments and wrote the manuscript. M.M. and K.M. synthesized pericoxide. H.Y. and S.H. wrote the manuscript.

Funding: This study received no external funding.

Data Availability Statement: Not applicable.

Acknowledgments: All experimental works described in this paper were performed at Osaka University of Pharmaceutical Sciences (OUPS) until March 2021. The OUPS was renamed Osaka Medical and Pharmaceutical University (OMPU) in April 2021. The authors thank K. Minoura M. Fujitake and M. Shibano of our University for measurement of the NMR, mass spectra, and useful advice on the
antiglucosidase assay, respectively. Y. Nakai, S. Fukuda, R. Yamashita, S. Nakagawa, A. Hirokawa, and R. Wakahara of our laboratory are appreciated for their extensive experimental support.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Gerry, C.J.; Schreiber, S.L. Chemical probes and drug leads from advances in synthetic planning and methodology. Nat. Rev. Drug Discov. 2018, 17, 333–352. [CrossRef] [PubMed]
2. Campos, K.R.; Coleman, P.J.; Alvarez, J.C.; Dreher, S.D.; Garbaccio, R.M.; Terrett, N.K.; Tillyer, R.D.; Truppo, M.D.; Parmee, E.R. The importance of synthetic chemistry in the pharmaceutical industry. Science 2019, 363, eaat0805. [CrossRef] [PubMed]
3. Lee, K.H. Discovery and development of natural product-derived chemotherapeutic agents based on a medicinal chemistry approach. J. Nat. Prod. 2010, 73, 500–516. [CrossRef] [PubMed]
4. Szychowski, J.; Truchon, J.F.; Bennani, Y.L. Natural products in medicine: Transformational outcome of synthetic chemistry. J. Med. Chem. 2014, 57, 9292–9308. [CrossRef] [PubMed]
5. Ermert, P. Design, properties and recent application of macrocycles in medicinal chemistry. Chimia 2017, 71, 678–702. [CrossRef] [PubMed]
6. Bauer, A.; Broenstrup, M. Industrial natural product chemistry for drug discovery and development. Nat. Prod. Rep. 2014, 31, 35–60. [CrossRef]
7. Koehn, F.E. Biosynthetic medicinal chemical of natural product drugs. Med. Chem. Comm. 2012, 3, 854–865. [CrossRef]
8. Ghosh, A.K.; Brindisi, M.; Shahabi, D.; Chapman, M.E.; Mesecar, A.D. Drug development and medicinal chemistry efforts toward SARS-Coronavirus and COVID-19 therapeutics. Chem. Med. Chem. 2020, 15, 907–993. [CrossRef]
9. Lu, W.Y.; Li, H.J.; Li, Q.Y.; Wu, Y.C. Application of marine natural products in drug research. Bioorg. Med. Chem. 2021, 35, 11605. [CrossRef] [PubMed]
10. Villa, F.A.; Gerwick, L. Marine natural product drug discovery: Leads for treatment of inflammation, cancer, infections, and neurological disorders. Immunopharmacol. Immunotoxicol. 2010, 32, 228–237. [CrossRef]
11. Kobayashi, J. Search for new bioactive marine natural products and application to drug development. Chem. Pharm. Bull. 2016, 64, 1079–1083. [CrossRef] [PubMed]
12. Khalifa, S.A.M.; Elias, N.; Farag, M.A.; Chen, L.; Saeed, A.; Hegazy, M.E.F.; Moustafa, M.S.; Abd El-Wahed, A.; Al-Mousawi, S.M.; Musharraf, S.G.; et al. Marine natural products: A source of novel anticancer drugs. Mar. Drugs 2019, 17, 491. [CrossRef] [PubMed]
13. Numata, A.; Iritani, M.; Yamada, T.; Minoura, K.; Matsumura, E.; Yamori, T.; Tsuruo, T. Novel antitumour metabolites produced by a fungal strain from a sea hare. Tetrahedron Lett. 1997, 38, 8215–8218. [CrossRef]
14. Yamada, T.; Iritani, M.; Ohishi, H.; Tanaka, K.; Doi, M.; Minoura, K.; Numata, A. Pericosines, antitumour metabolites from the sea hare-derived fungus Periconia byssoides. Structures and biological activities. Org. Biomol. Chem. 2007, 5, 3979–3986. [CrossRef] [PubMed]
15. Usami, Y. Synthesis of marine-derived carbasugar pericosines. In Studies in Natural Product Chemistry; Atta-ur-Rahman, A.Z., Ed.; Pergamon: Oxford, UK, 2014; Volume 41, pp. 287–319. [PubMed]
16. Arjona, O.; Gomez, A.M.; Lopez, J.C.; Plumet, J. Synthesis, and conformational and biological aspects of carbasugars. Mini-Rev. Med. Chem. 2007, 7, 679–691. [CrossRef]
17. Donohoe, T.J.; Blades, K.; Hellilwell, M.; Waring, M.J.; Newcombe, N.J. The synthesis of (+)-pericosine B. Tetrahedron Lett. 1998, 39, 8755–8758. [CrossRef]
18. Usami, Y.; Takaoka, I.; Ichikawa, H.; Horibe, Y.; Tomiyama, S.; Ohtsuka, M.; Imanishi, Y.; Arimoto, M. First total synthesis of antitumor natural product (+)- and (−)-pericosine A: Determination of absolute stereostructure. J. Org. Chem. 2007, 72, 6127–6134. [CrossRef]
19. Usami, Y.; Ohsugi, M.; Mizuki, K.; Ichikawa, H.; Arimoto, M. Facile and efficient synthesis of naturally occurring carbasugars (+)-pericosines A and C. Org. Lett. 2009, 11, 2699–2701. [CrossRef]
20. Usami, Y.; Suzuki, K.; Mizuki, K.; Ichikawa, H.; Arimoto, M. Synthesis of (−)-pericosine B, antipode of cytotoxic marine natural product. Org. Biomol. Chem. 2009, 7, 315–318. [CrossRef] [PubMed]
21. Boyd, D.R.; Sharma, N.D.; Acaru, C.A.; Malone, J.F.; O'Dowd, C.R.; Allen, C.C.R.; Stevenson, P.J. Chemoenzymatic synthesis of carbasugars (+)-pericosines A–C from diverse aromatic cis-dihydrodiol precursors. Org. Lett. 2010, 12, 2206–2209. [CrossRef] [PubMed]
22. Tripathi, S.; Shaikh, A.C.; Chen, C. Facile carbohydrate-based stereoregulated divergent synthesis of (+)-pericosines A and B. Org. Biomol. Chem. 2011, 9, 7306–7308. [CrossRef] [PubMed]
25. Reddy, Y.S.; Kadigachalam, P.; Basak, R.K.; Pal, A.P.J.; Vankar, Y.D. Total synthesis of (+)-pericosine B and (+)-pericosine C and their enantiomers by using the Baylis–Hillman reaction and ring-closing metathesis as key steps. *Tetrahedron*. 2012, 53, 132–136. [CrossRef]

26. MunirRaju, C.; Rao, J.P.; Rao, B.V. Stereoselective synthesis of (+)-pericosine B and (+)-pericosine C using ring closing metathesis approach. *Tetrahedron Asymmetry* 2012, 23, 86–93. [CrossRef]

27. Li, L.S.; Hou, D.R. Diastereoselective vinylamination for the synthesis of pericosine A, B and C. *RSC Adv.* 2014, 4, 91–97. [CrossRef]

28. Babu, D.C.; Rao, C.B.; Venkastesh, K.; Selvam, J.P.; Venkasteswaralu, Y. Toward synthesis of carbasugars (+)-gabosine C, (+)-COTC, (+)-pericosine B, and (+)-pericosine C. *Carbohydr. Res.* 2014, 388, 130–137. [CrossRef][PubMed]

29. Mizuki, K.; Iwashashi, K.; Murata, N.; Ikeda, M.; Nakai, N.; Yoneyama, H.; Harusawa, S.; Usami, Y. Synthesis of marine natural product β-~-pericosine E. *Org. Lett.* 2014, 16, 3760–3763. [CrossRef]

30. Bidus, N.; Banachowicz, P.; Buda, S. Application of a tandem seleno-michael/aldol reaction in the total syntheses of (+)-pericosine B, (+)-pericosine C, (+)-COTC and 7-chloro-analogue of (+)-Gabosine C. *Tetrahedron* 2020, 76, 131997. [CrossRef]

31. Usami, Y.; Nakamura, K.; Mizobuchi, Y.; Yoneyama, H.; Harusawa, S. Synthesis of natural O-linked carba-disaccharides, (+)- and (−)-pericosine E, and their analogues as α-glucosidase inhibitors. *Mar. Drugs* 2017, 15, 22. [CrossRef]

32. Usami, Y.; Higuchi, M.; Mizuki, K.; Yamamoto, M.; Kanki, M.; Nakasone, C.; Sugimoto, Y.; Shibano, M.; Uesawa, Y.; Nagai, J.; et al. Syntheses and glycosidase inhibitory activities, and in silicon docking studies of pericosines E analogs methoxy-substituted at C6. *Mar. Drugs* 2020, 18, 221. [CrossRef][PubMed]

33. Du, L.; Robles, A.J.; King, J.B.; Powell, D.R.; Miller, A.N.; Mooberry, S.L.; Cichewicz, R.H. Crowd sourcing natural products discovery to access uncharted dimensions of fungal metabolite diversity. *Angew. Chem. Int. Ed.* 2014, 53, 804–809. [CrossRef][PubMed]

34. Du, L.; You, J.; Nicholas, K.M.; Cichewicz, R.H. Chemoreactive natural products that afford resistance against disparate antibiotics and toxins. *Angew. Chem. Int. Ed.* 2016, 55, 4220–4225. [CrossRef][PubMed]

35. Usami, Y.; Nakamura, K.; Mizobuchi, Y.; Yoneyama, H.; Harusawa, S.; Yamada, T. Enantiomeric composition of natural pericosine A derived from *Periconia byssoides* and α-glycosidase inhibitory activity of (−)-enantiomer. *Chirality* 2022, 1–8. [CrossRef]

36. Brown, H.C.; Roy, C.D. Dibromoborane-dimethyl sulfide and monobromoborane–dimethyl-sulfide as superior reagents for the brominative cleavage of terminal epoxides into vicinal bromohydrins. *Molecules* 1998, 2, 114–120. [CrossRef]

37. Roy, C.D.; Brown, H.C. Monobromoborane-dimethyl sulfide-a highly promising reagent for the region- and chemoselective brominative cleavage of terminal epoxides into vicinal bromohydrins. *Aust. J. Chem.* 2007, 60, 139–145. [CrossRef]

38. Bhatt, M.V.; Babu, J.M. New reagents 3: Alumi.ium iodide—A highly regioselective ether-cleaving reagent with novel cleavage pairs for validating scoring functions. *Phytochemistry* 2005, 66, 3547–3550. [CrossRef][PubMed]

39. Dada, L.; Manzano, V.E.; Varela, O. Design and synthesis of 2-acetamido-2,3-dideoxythiodisaccharides via diastereoselective opening of oxiranes to bromohydrins. *Tetrahedron Lett.* 1984, 25, 3497–3500. [CrossRef]

40. Kumar, K.S.A.; Rathee, J.S.; Subramanian, M.; Chattopadhyay, S. Divergent synthesis of 4-epi-fagomine, 3,4-dihydroxypropilic acid, and a dihydroxyindolizidine and their β-galactosidase inhibitory and immunomodulatory activities. *J. Org. Chem.* 2013, 78, 7406–7413. [CrossRef]

41. Dada, L.; Manzano, V.E.; Varela, O. Design and synthesis of 2-acetamido-2,3-dideoxythiodisaccharides via diastereoselective conjugate addition to sugar enone O-acetyl oximes. galactosidase inhibition studies. *Org. Lett.* 2018, 20, 6225–6228. [CrossRef]

42. Front, S.; Gallienne, E.; Charollais-Thueng, J.; Demotz, S.; Martin, O.R. N-Alkyl-, 1-C-silyl-, and 5-C-Alkyl-1,5-dideoxy-1,5-imino-(L)-ribitols as galactosidase inhibitors. *Phytochemistry* 2016, 11, 133–141. [CrossRef][PubMed]

43. Govindaraj, R.G.; Manavalan, B.; Lee, G.; Choi, S. Molecular modeling-based evaluation of hTLR10 and identification of potential ligands in toll-like receptor signaling. *PloS ONE* 2010, 5, e12713. [CrossRef][PubMed]

44. Yamamoto, K.; Miyake, H.; Kusunoki, M.; Osaki, S. Crystal structures of isomaltase from Saccharomyces cerevisiae and in complex with its competitive inhibitor maltose. *FEBS J.* 2010, 277, 4205–4214. [CrossRef][PubMed]

45. Tang, H.; Zhao, D.; Xue, Z. Exploring the interaction between Salvia miltiorrhiza and α-glucosidase: Insights from computational analysis and experimental studies. *RSC Adv.* 2018, 8, 24701–24710. [CrossRef][PubMed]

46. Kalinowsky, L.; Weber, J.; Balasupramaniam, S.; Baumann, K.; Proschak, E. A diverse benchmark based on 3D matched molecular pairs for validating scoring functions. *ACS Omega* 2018, 3, 5704–5714. [CrossRef][PubMed]

47. Rivera-Chavez, J.; Gonzalez-Andrade, M.; Gonzalez Mdel, C.; Glenn, A.E.; Mata, R. Thielavins A, J and K: α-Glucosidase inhibitors from MEXU 27095, an endophytic fungus from Hintonia latiflora. *Phytochemistry* 2013, 94, 198–205. [CrossRef][PubMed]

48. Murtugesu, S.; Ibrahim, Z.; Ahmed, Q.U.; Yusoff, N.I.N.; Uzir, B.F.; Perumal, V.; Abas, F.; Saari, K.; El-Seedi, H.; Khatib, A. Characterization of α-glucosidase inhibitors from *Clinacanthus nutans* lindau leaves by gas chromatography-mass spectrometry-based metabolomics and molecular docking simulation. *Molecules* 2018, 23, 2402. [CrossRef]
49. Murugesu, S.; Ibrahim, Z.; Ahmed, Q.U.; Uzir, B.F.; Yusoff, N.I.N.; Perumal, V.; Abas, F.; Shaari, K.; Khatib, A. Identification of α-glucosidase inhibitors from Clinacanthus nutans leaf extract using liquid chromatography-mass spectrometry-based metabolomics and protein-ligand interaction with molecular docking. *J. Pharm. Anal.* 2019, 9, 91–99. [CrossRef]

50. Gopalan, G.; Prabha, B.; Joe, A.; Reshmitha, T.R.; Sherin, D.R.; Abraham, B.; Sabu, M.; Manojkumar, T.K.; Radhakrishnan, K.V.; Nisha, P. Screening of Musa balbisiana Colla. seeds for antidiabetic properties and isolation of apiforol, a potential lead, with antidiabetic activity. *J. Sci. Food Agric.* 2019, 99, 2521–2529. [CrossRef]