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Facile and Efficient Synthesis of Naturally Occurring Carbasugars (+)-Pericosines A and C†

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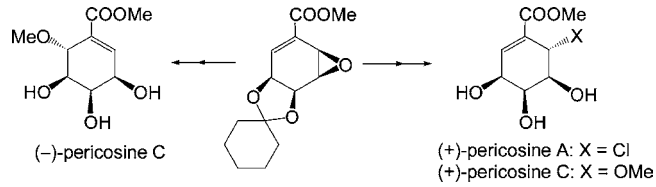
ABSTRACT



An efficient synthesis of antitumor marine natural product (+)-pericosine A was achieved from (−)-quinic acid in 11.7% overall yield, which is 20 times better than our previously reported synthesis. The crucial steps of this synthesis include the regio- and stereoselective bromohydrination of an unstable diene and the ring opening of an epoxide. This synthetic route was applicable to a synthesis of (+)-pericosine C and also to a synthesis of (−)-pericosine C.

The isolation of pericosines A−E, **1**−**5**, respectively, as cytotoxic metabolites of *Periconia byssoides* OUPS-N133 originally separated from the sea hare, *Aplysia kurodai*, was reported in 1997 and 2007.[1,2] Because this series of compounds have a multifunctionalized cyclohexene core that is typical of carbasugars,[3,4] we have been interested in their syntheses and the synthesis of their related compounds.[5−9] Among them, pericosine A (**1**) is the most important one because it was reported to possess significant inhibitory activity against protein kinase EGFR (epidermal growth factor receptor) and human topoisomerase II in addition to antitumor activity against P388 in vivo.[2] The absolute configurations of **1**−**4** were determined by their total syntheses.[6−8,10] However, the overall yields in the first total synthesis of (−)- and (+)-**1** were not satisfactory, although the absolute configuration of natural **1** was elucidated.[7]

Therefore, we desired to devise a more efficient synthetic route for (+)-**1** in the hope that it could be amenable to the construction of analogues. Naturally occurring pericosine C (**3**) was reported to be an enantiomeric mixture,[2] and we have reported the synthesis of (+)-**3**,[6] which exists as a minor component in nature. We are also interested in the synthesis of (−)-**3**.

† This paper is dedicated to Professor Kaoru Fuji on the occasion of his retirement from Hiroshima International University.

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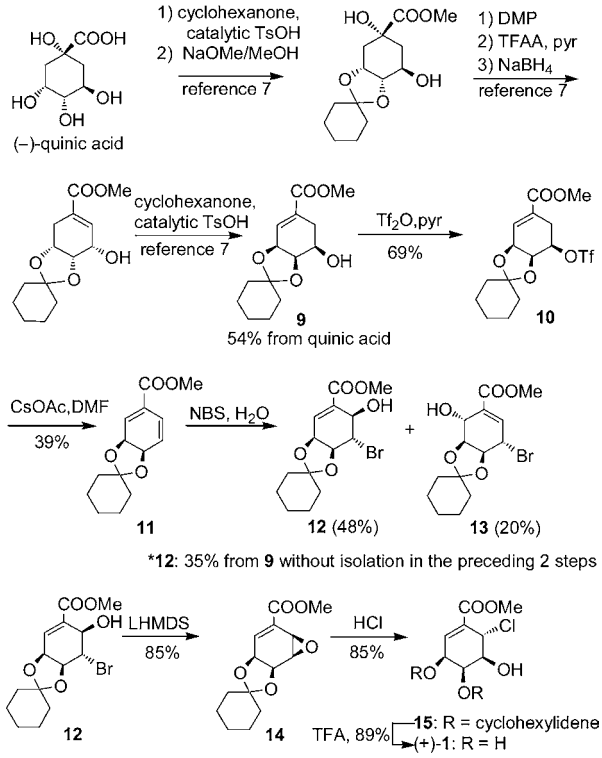
In 1990, two Japanese groups jointly reported the isolation of the first chlorine-containing shikimate-related metabolite (**6**) from two fungi.[11] In 1993, an Italian group isolated cyathiformines C (**7**) and A (**8**)[12] from the *Basidiomycetous* fungus, and **7** was synthesized from **6** in a previous study.[11] Two papers on the synthesis of **7** via **8** based on the biosynthetic hypothesis were published independently.[13,14] Structurely, these chlorine-containing natural products are closely related to pericosines. Inspired by these series of studies, we have devised a simpler and more effective synthetic route for (+)-**1**. The key reactions of our new avenue involve the regio- and stereoselective bromohydrination of an unstable diene and the regio- and stereoselective ring opening of an epoxide. Described herein are the simple, facile, and efficient synthesis of (+)-**1** from (−)-quinic acid in 12 steps and its application to the synthesis of both enantiomers of pericosine C. The synthesis of (+)-**1** is summarized in Scheme 1. Commercially available (−)-quinic

Scheme 1. Synthesis of (+)-Pericosine A



acid was converted into methyl *ent*-3-epiquinate derivative **9** according to a literature method.[7] Alcohol **9** was esterified into triflate **10**, which was eliminated with CsOAc to afford an unstable diene **11**[15,16] in 39% isolated yield. Diene **11** was reacted with NBS in a H_2O/1,4-dioxane solvent system

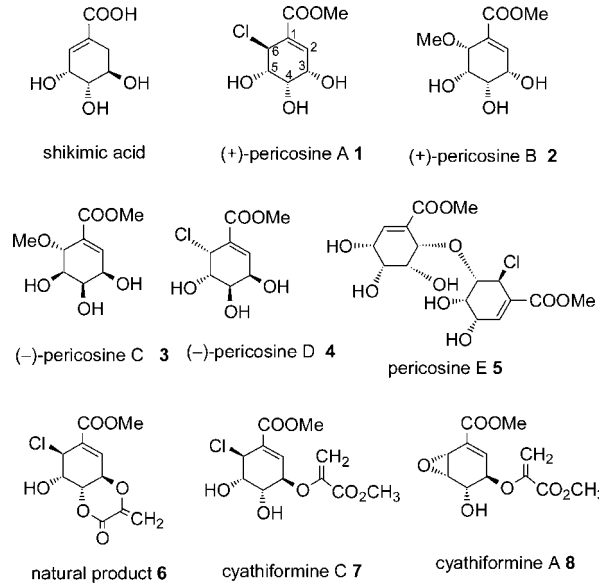


Figure 1. Structures of naturally occurring pericosines and related compounds.

at room temperature to give bromohydrins **12** and **13** in 48% and 20% yields, respectively. The constitution of **12** and **13** were determined on the basis of 2D-NMR analysis, including COSY, HSQC, and HMBC. The relative stereochemistry of **12** was determined on the basis of NOESY analysis where cross peaks H-4/H-6 and 6-OH/H-5 were observed. The relative stereochemistry of **13** was determined by comparing the coupling constants in the ^{1}H NMR spectra with those of related compounds that were synthesized previously.[8] A plausible explanation for production of **12** is formation of the cyclic bromonium cation on the less hindered α-face by NBS followed by S_N2-type ring opening. A probably minor part of the cyclic bromonium cation was opened with the double bond rearrangement into an incipient carbocation, which was attacked from the less hindered α-face by water, affording **13**. The same reaction at 0 °C lowered the product yield.

Bromohydrin **12** was treated with LHMDS to afford epoxide **14** in 85% yield. The relative configuration of **14** was confirmed by comparing with the *trans*-epoxide that appeared in our previous paper.[7] This assignment supported the relative stereochemistry of **12** and **13**. Epoxide **14** was treated with HCl in dry diethyl ether to give chlorohydrin **15** in 85% yield as the sole product, whereas a similar reaction involving the corresponding *trans*-epoxide afforded several isomers in our previous study.[8] The ring-opening reaction of **14** excluded the S_N'-type side reaction. A plausible explanation for this excellent selectivity is illustrated in Figure 2. The original π^*_{C1-C2} orbital for the S_N'-type reaction is distorted to become highly reactive, which means that the energy level is lowered, and more extended in the

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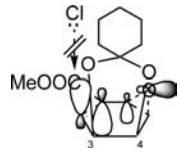


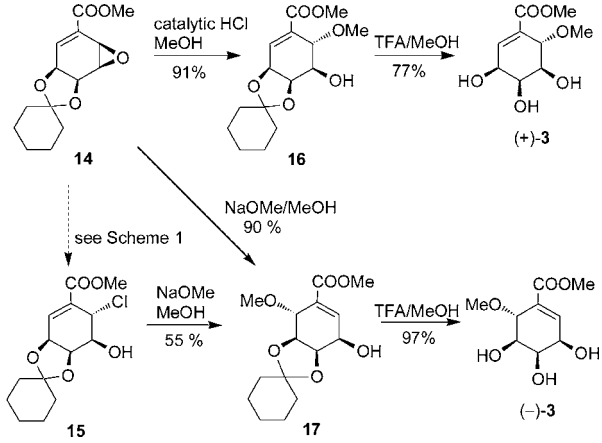
Figure 2. Inhibition of S_N' reaction attacking distorted π^* in **14**.

β-face by orbital mixing with σ^*_{C6-O} in phase.[17,18] However, the β-face is markedly sterically hindered by the 3,4-*O*-cyclohexylidene moiety in **15** such that a side reaction could not occur. Assigned relative configuration of **15** was supported by agreement of the spectral data with those of the reported acetonide of natural pericosine A.[1,2]

The enantiospecific synthesis was completed by adding TFA in MeOH to give desired (+)-**1** in 89% yield. When the conversion of **9** into **12** was performed without purification of intermediates, the isolated yield of **12** was improved to 35% for the three steps. Thus, the overall yield of this 12-step synthesis from (−)-quinic acid was 11.7%, which is 20 times better than that of our initially reported synthesis.[7]

Not only is this synthetic route efficient, it is also applicable to the synthesis of pericosine analogues. Therefore, we demonstrated the synthesis of (+)-pericosine C (**3**), as illustrated in Scheme 2. Treatment of epoxide **14** with

Scheme 2. Synthesis of (+)- and (−)-Pericosine C



catalytic HCl in MeOH as solvent at room temperature afforded 5-α-methoxyalcohol **16** in 91% yield. Relative configuration of **16** was also assigned by comparison of the NMR spectral data to those of an acetonide of natural pericosine C reported in the literature.[2] Deprotection of **16** with TFA in MeOH afforded desired (+)-**3** in 77% yield.

Another application of this new synthetic route toward (+)-pericosine B (**2**) was also attempted. Chlorohydrin **15** was treated with NaOMe in MeOH aiming for the S_N2 process. To our surprise, the product of this reaction was not the precursor of **2** but alcohol (−)-**17**[6] in 55% yield, which is the precursor of naturally preferred enantiomer (−)-**3** as shown in Scheme 2. The S_N2 process around C-6 was completely inhibited by steric hindrance by the neighboring 3,4-*O*-cyclohexylidene moiety. One possible explanation for formation of (−)-**17** is the α-face-selective S_N' reaction[17,18] on **15** as seen in the first synthesis of **1**[7] and the other is the S_N'-type reaction on **14**, which should be regenerated from **15** under the basic condition. Then **14** was treated with NaOMe in order to elucidate the mechanism. Production of (−)-**17** in 90% yield suggested the latter explanation is reasonable.

The synthesis of (−)-**3** was completed by treating (−)-**17** with TFA in MeOH in 97% yield. Noteworthy is the fact that both enantiomers were prepared from single intermediate **14**. This finding might give us a hint to understand the biosynthetic pathway of naturally occurring **3** as an enantiomeric mixture, as mentioned above. At the same time, this result implies that there is a more rapid way to access (+)- and (−)-**3**, because the antipode of **11** can be prepared in four steps from (−)-quinic acid, whereas eight steps are required from (−)-quinic acid to **11**.

In summary, we have developed a facile and efficient total synthesis of (+)-pericosine A (**1**). The overall yield of this total synthesis from (−)-quinic acid improved to reach 11.7% compared to 0.57% for the first synthesis. Using this new synthetic route, both enantiomers (+)- and (−)-pericosine C were prepared. Development of a more rapid preparation of pericosine analogues via the antipode of **11** as mentioned above and biological evaluation of synthesized pericosines are ongoing.

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Supporting Information Available: Experimental procedures and copies of ^1H and ^{13}C NMR spectra of all new compounds and synthesized (+)-**1**, (+)-**3**, (−)-**3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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