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Synthesis of Marine Natural Product (−)-Pericosine E

Koji Mizuki, Kaoru Iwahashi, Naoko Murata, Mayuko Ikeda, Yutaka Nakai, Hiroki Yoneyama, Shinya Harusawa, and Yoshihide Usami*

Laboratory of Pharmaceutical Organic Chemistry, Osaka University of Pharmaceutical Sciences, 4-20-1 Nasahara, Takatsuki, Osaka 569-1094, Japan

Supporting Information

ABSTRACT: The first synthesis of (−)-pericosine E (**6**), a metabolite of the *Periconia byssoides* OUPS-N133 isolated originally from the sea hare *Aplysia kurodai*, has been achieved. Efficient and regioselective synthetic procedures for the synthesis of key intermediates, *anti*- and *syn*-epoxides **9** and **10**, were developed using an *anti*-epoxidation of diene **12** with TFDO and a bromohydrination of **12** with NBS in CH_3CN/H_2O (2:3), respectively. In addition, comparison of the specific optical rotations between synthetic **6** and natural **6** elucidated that the naturally preferred enantiomer of pericosine E had the same absolute configuration as (−)-**6** synthesized from chlorohydrin (−)-**8** and *anti*-epoxide (+)-**9**.

The identification of possible drug candidates from marine sources has been developing progressively over recent decades.[1,2] However, the traditional natural product research style of isolating biologically active compounds from whole marine animals or plants has the potential of destroying large areas of natural habitat. An alternative approach for the discovery of biologically active molecules from marine animals or plants has emerged recently.[3,4] To this end, Numata and co-workers reported the isolation and structural determination of pericosines A−E (**1**−**6**), metabolites of the fungus *Periconia byssoides* OUPS-N133, which were originally isolated from the sea hare *Aplysia kurodai*.[5−7] All of these compounds, with the exception of pericosine E (**6**), have unique C_7-cyclohexenoid structures containing multifunctional groups on the six-membered ring, as shown in Figure 1. The absolute configurations in Figure 1 represent the preferential enantiomers that occur in Nature. It is worth noting that pericosines **2**, **3**, and **6** exist as enantiomeric mixtures in Nature.[6,8]

(+)-pericosine A (**1**) (+)-pericosine B (**2**)* (-)-pericosine C (**3**)*

(−)-pericosine D (**4**) (+)-pericosine D_o (**5**) (-)-pericosine E (**6**)*

*existing as enantiomeric mixture in Nature

Figure 1. Structures of naturally occurring pericosines.

Pericosine A (**1**) has previously shown remarkable physiological activities: (i) in vitro growth inhibition of breast cancer cell line HBC-5 and the central nervous system cell line SNB-75; (ii) inhibition against the protein kinase epidermal growth factor receptor; (iii) topoisomerase II inhibitory activity.[6] Thus, research into the total synthesis of pericosines has received much attention in recent years.[9−20]

Of particular interest to us, pericosine E (**6**) is a unique natural product. It appears to be formed by connection of (−)-**1** and (+)-**2**, with the opposite enantiomer of the natural pericosine A forming the right half of **6**, while the left half adopts the intrinsic configuration of pericosine B (Figure 1). As the chemistry of **6** is complicated, the synthesis presents an exciting new challenge toward a compound with potentially valuable biological activity (ED_{50} value of **6**: 15.5 μg/mL in in vitro growth inhibition activity against murine P388 cell line[6]).

If a synthetic route were established, it would allow the biological activity of **6** to be determined and improve the understanding of the biosynthetic route toward **6**. Herein, we disclose the first stereoselective total synthesis of (−)-**6** which clarifies the absolute configuration of the naturally occurring preferential enantiomer.

We envisioned the retrosynthesis of **6** as summarized in Scheme 1. In our previous synthetic studies on pericosine A [(+)-**1**] and C [(+)- or (−)-**3**],[20,21] asymmetric synthesis of the bromohydrin (−)-**11** afforded only a low yield of the desired product. Moreover, in our work toward (−)-pericosine D (**4**), the low regioselectivity (ca. 1:1) in the epoxidation of (+)-**12** using *m*CPBA led to an inseparable mixture of epoxide (−)-**9** and its regioisomer.[18,22] Thus, a more efficient and regioselective synthesis of the enantiomerically pure intermediates

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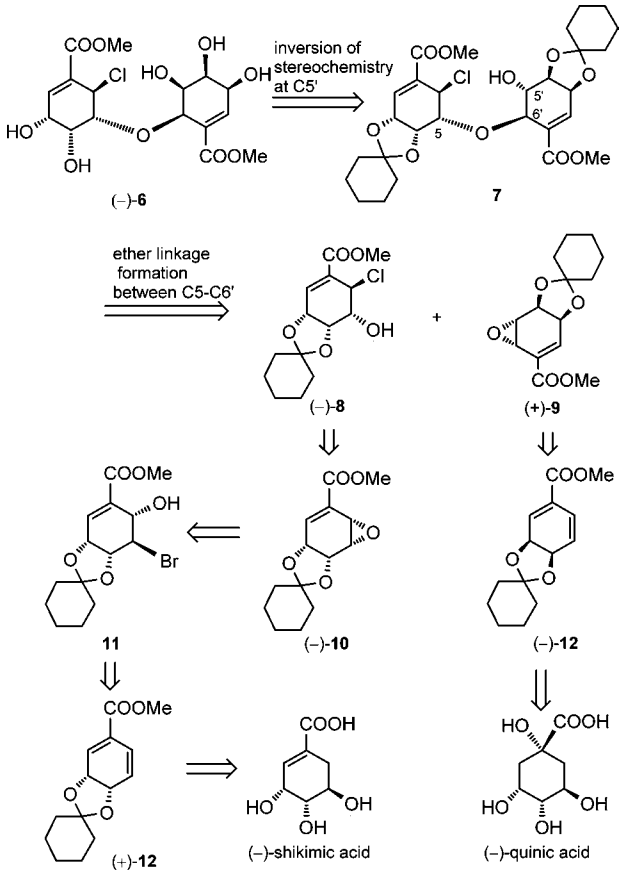
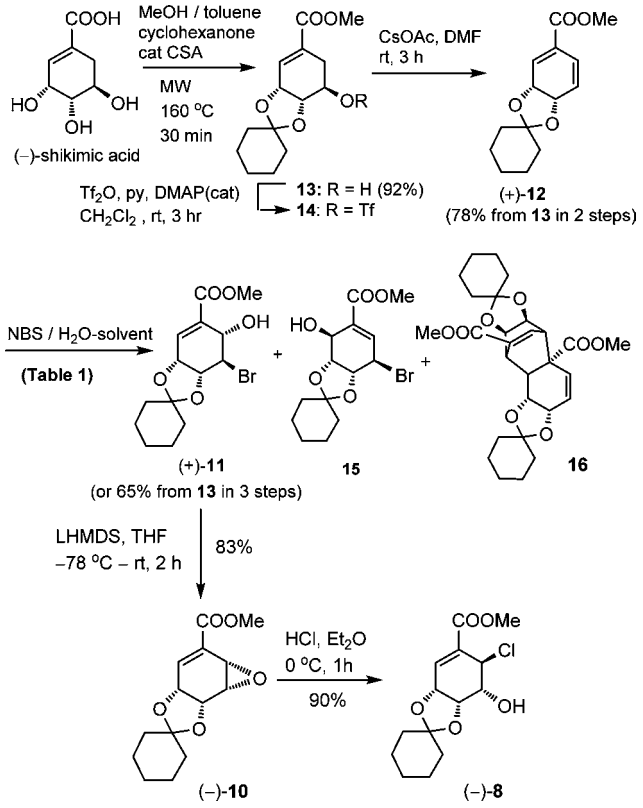
Scheme 1. Retrosynthetic Strategy of Pericosine E (6)



Scheme 2. Synthesis of Chlorohydrin (−)-8 from (−)-Shikimic Acid



(+)-**11** and (+)-**9** was essential for the synthesis of (−)-pericosine E (**6**) (Scheme 1).

Initially, the synthesis of (−)-**8** was undertaken, as illustrated in Scheme 2. (−)-Shikimic acid was converted to alcohol **13** under microwave irradiation (MW; 160 °C, 30 min) in 92% yield. Triflate **14** derived from **13** was treated with CsOAc in DMF to afford diene (+)-**12** in two steps (78%).

The bromohydrination of (+)-**12** with NBS was examined in detail using various solvent systems and substrate concentrations within a fixed reaction time (20 h), as summarized in Table 1. The best selectivity for desired product (+)-**11** was achieved using an acetonitrile−water (2:1) solvent system, with isomer **15** and byproduct **16** also formed within the reaction (Scheme 2 and Table 1, entries 1−5 and 7). The regio- and stereochemistry of byproduct **16** was established using ^{1}H−^{1}H COSY, NOESY, HSQC, and HMBC experiments (see Supporting Information). From these results, acetonitrile−water was chosen as the optimal solvent system for the bromohydrination. The ratio of acetonitrile to water was further explored (entries 6−10), using a 5 mg/mL concentration of (+)-**12**, with 2:3 acetonitrile−water giving the best selectivity (entry 9). The concentration of (+)-**12** was investigated but did not improve the selectivity of the desired product (entries 11 and 12). Finally, it was found that a 4 h reaction time gave almost the same result compared to 20 h (entry 9 and 13). Using the optimized conditions, the three-step conversion of alcohol **13** to (+)-**11** was achieved in 65% yield without purification. The bromohydrin obtained was treated with LHMDS in THF at −78 °C to afford (−)-**10** in 83% yield, which was then converted to (−)-**8** by treatment with HCl in 90% yield.

Table 1. Bromohydrination of (+)-12 to (+)-11[20,21]

			product ratio[b] (%)		
entry[a]	concn of **12** (mg/mL)	solvent	(+)-**11**	**15**	**16**
1	5	dioxane−H_2O (2:1)	36	49	15
2	5	*t*BuOH−H_2O (2:1)	43	27	30
3	5	DMSO−H_2O (2:1)	insoluble		
4	5	acetone−H_2O (2:1)	72	12	16
5[c]	5	THF−H_2O (2:1)	33	46	
6	5	MeCN−H_2O (4:1)	38	45	17
7	5	MeCN−H_2O (2:1)	76	8	16
8	5	MeCN−H_2O (1:1)	74	13	13
9	5	MeCN−H_2O (2:3)	80	7	13
10	5	MeCN−H_2O (1:2)	75	12.5	12.5
11	2.5	MeCN−H_2O (2:3)	74	9	17
12	7.5	MeCN−H_2O (2:3)	75	11	14
13	5	MeCN−H_2O (2:3)	80	8	12

[a]Reaction time in all entries was set to 20 h except entry 13 (4 h). [b]Ratios were determined by analysis of ^{1}H NMR spectra of crude reaction mixtures. [c]Recovered diene **12** at a ratio of 21%.

Next, the formation of epoxy intermediate (+)-**9** was explored using readily accessible diene (+)-**12**, the enantiomer of intermediate (−)-**12** for pericosine D synthesis (Table 2). It is worth noting that both enantiomers of **12** can be accessed from (−)-quinic acid[23] or (−)-shikimic acid. Oxidation of **12**

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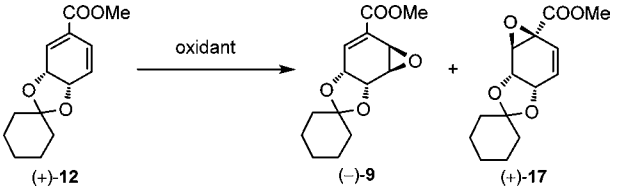
Table 2. Examination of the Epoxidation of (+)-12



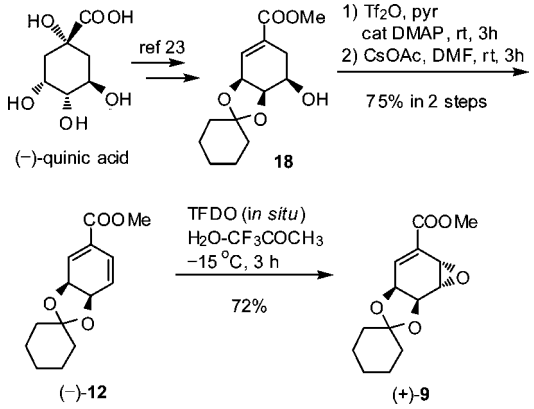
					product yield[a] (%)	
entry	oxidant	solvent	reaction time (h)	temp (°C)	9	17
1[b]	*m*CPBA	CH_2Cl_2	10	40	35	35
2[c]	DMDO[d]	H_2O–acetone	10	0 to rt	24	18
3	TFDO[d]	H_2O–CF_3COCH_3	3	0 to rt	57.4	3.3
4	TFDO[d]	H_2O–CF_3COCH_3	3	0	65	0
5	TFDO[d]	H_2O–CF_3COCH_3	3	−15	72	0

[a]Yields were calculated as combined yield from ^{1}H NMR spectrum of crude products. [b]From ref 18. [c]Experiment was carried out with the procedure described in ref 8. [d]Prepared in situ.

using dimethyldioxirane (DMDO) gave an improved 4:3 ratio of (−)-**9** and (+)-**17** (entry 2) compared to oxidation using *m*CPBA (entry 1).[18] Furthermore, oxidation of **12** with methyl(trifluoromethyl)dioxirane (TFDO)[24,25] provided a 16:1 mixture of **9** and **17** in 61% combined yield (entry 3). Performing the reaction at 0 °C for 3 h afforded only **9** in 65% isolated yield (entry 4). Two explanations for better selectivity with TFDO against DMDO are plausible. Bulkiness of the trifluoromethyl group in TFDO might inhibit oxidation of the double bond bearing a methoxycarbonyl group in **12**, or increased electrophilicity of TFDO from inductive effect of the trifluoromethyl group might accelerate the reaction to another double bond, which does not bear an electron-withdrawing methoxycarbonyl group in **12**. Finally, reduction of the reaction temperature to −15 °C increased the yield of (−)-**9** to 72% (entry 5).

Next, the synthesis of *anti*-epoxide (+)-**9** was carried out, as shown in Scheme 3. Starting from (−)-quinic acid, known

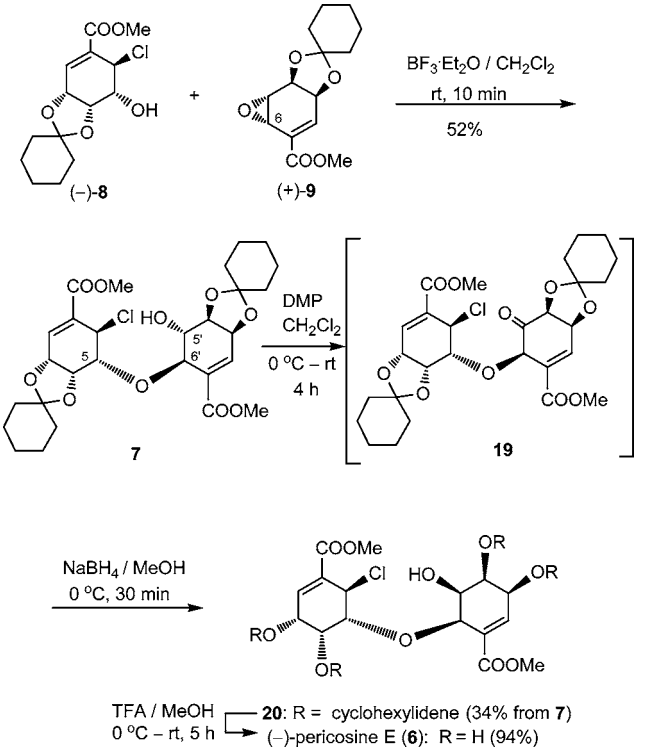
Scheme 3. Synthesis of (+)-9 from (−)-Quinic Acid



alcohol **18**[23] was converted to cyclohexadiene (−)-**12** in two steps according to a literature procedure in 75% yield.[20] Using the optimized epoxidation conditions, (−)-**12** was successfully oxidized to (+)-**9** in 72% yield.

With required molecules (−)-**8** and (+)-**9** in hand, attention turned to the synthesis of (−)-pericosine E (**6**) (Scheme 4). Ether linkage formation between (−)-**8** and (+)-**9** was carried out by treatment with BF_3–Et_2O (0.1 equiv) in CH_2Cl_2 at room temperature, affording condensation product **7** in 52%

Scheme 4. Synthesis of (−)-Pericosine E (6) from (−)-8 and (+)-9



isolated yield (see Table SI-1 in the Supporting Information on the model studies of the coupling reaction). The regioselective outcome of the nucleophilic epoxide opening was determined to be at C6 of (+)-**9**, on the basis of 600 MHz ^{1}H–^{1}H COSY analysis of **7** in $CDCl_3$. The NOESY cross-peak H6′/H4′ suggested the configuration at C6′ in **7**, as shown in Scheme 3. An oxidation–reduction sequence was applied for inversion of the remaining C5′-hydroxyl group of **7**. Alcohol **7** was treated with Dess-Martin periodinane to give a crude inseparable mixture of ketone **19** and an undefined compound. Subsequently, the crude mixture including **19** was reduced with $NaBH_4$ to afford the desired epimeric alcohol **20** in 34% yield from **7**. The cross-peak H3′/H5′ in the NOESY spectrum of **20** in acetone-d_6 (600 MHz) confirmed the configuration of a newly generated stereocenter at C5′. Finally, treatment of **20**

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with trifluoroacetic acid in methanol completed the total synthesis of **6**. Spectral data obtained for product **6** were consistent with those of the naturally occurring product except for the specific rotation.[6] The specific rotation for synthesized **6** was $[\alpha]_D$ −68.3, whereas that for reported natural **6** is −31.5. This indicates that the absolute configuration of the naturally dominant enantiomer of (−)-**6** is assigned to (3*R*,4*R*,5*R*,6*R*)-methyl 6-chloro-3,4-dihydroxy-5-{[(1*R*,4*S*,5*S*,6S)-4,5,6-trihydroxy-2-(methoxycarbonyl)cyclohex-2-en-1-yl]oxy}cyclohex-1-enecarboxylate. Accordingly, the ratio of (−)-**6**/(+)-**6** in natural pericosine E would roughly correlate to 3:1.

In conclusion, the total synthesis of pericosine E has been achieved for the first time and allowed the elucidation of the absolute configuration of the naturally preferred pericosine E as (−)-**6**. Regioselectivities in the synthesis of epoxides **9** and **10**, which are the key intermediates in pericosine synthesis, were efficiently improved. Bromohydrination of cyclohexadiene **12** in the CH_3CN−H_2O (2:3) solvent system was proved to be the optimum conditions for the formation of bromohydrin **11**, which was subsequently converted to epoxide **10**. Epoxidation of **12** with TFDO formed in situ afforded epoxide **9** with complete regiocontrol. We believe that the synthesis could be scaled up to meet the demand in the search of novel bioactive analogues of pericosine E.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and ^1H and ^{13}C NMR spectra for new compounds described therein. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: usami@gly.oups.ac.jp. Tel.: +08-729-690-1087. Fax: +08-729-690-1005.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2004**, *67*, 1216−1238.
(2) Newman, D. J.; Cragg, G. M. *Curr. Drug Targets* **2006**, *7*, 279−304.
(3) Newman, D. J.; Hill, R. T. *J. Ind. Microbiol. Biotechnol.* **2006**, *33*, 539−544.
(4) Fenical, W.; Jensen, P. R. *Nat. Chem. Biol.* **2006**, *2*, 666−673.
(5) Numata, A.; Iritani, M.; Yamada, T.; Minoura, K.; Matsumura, E.; Yamori, T.; Tsuruo, T. *Tetrahedron Lett.* **1997**, *38*, 8215−8218.
(6) Yamada, T.; Iritani, M.; Ohishi, H.; Tanaka, K.; Doi, M.; Minoura, K.; Numata, A. *Org. Biomol. Chem.* **2007**, *5*, 3979−3986.
(7) Usami, Y.; Mizuki, K. *J. Nat. Prod.* **2011**, *74*, 877−881.
(8) Usami, Y.; Okada, Y.; Yamada, T. *Chirality* **2011**, *23*, E7−E11.
(9) Donohoe, T. J.; Blades, K.; Helliwell, M.; Warning, M. J.; Newcombe, N. J. *Tetrahedron Lett.* **1998**, *39*, 8755−8758.
(10) Boyd, D. R.; Sharma, N. D.; Acaru, C. A.; Malone, J. F.; O'Dowd, C. R.; Allen, C. C. R.; Stevenson, P. J. *Org. Lett.* **2010**, *12*, 2206−2209.
(11) Tripathi, S.; Shaikh, A. C.; Chen, C. *Org. Biomol. Chem.* **2011**, *9*, 7306−7308.
(12) Reddy, Y. S.; Kadigachalam, P.; Basak, R. K.; John Pal, A. P.; Vankar, Y. D. *Tetrahedron Lett.* **2012**, *53*, 132−136.
(13) MuniRaju, C.; Rao, J. P.; Rao, B. V. *Tetrahedron: Asymmetry* **2012**, *23*, 86−93.
(14) Li, L.-S.; Hou, D.-R. *RSC Adv.* **2014**, *4*, 91−97.
(15) Babu, D. C.; Rao, C. B.; Venkastesham, K.; Selvam, J. J. P.; Venkasteswarlu, Y. *Carbohydr. Res.* **2014**, *388*, 130−137.
(16) Usami, Y.; Hatsuno, C.; Yamamoto, H.; Tanabe, M.; Numata, A. *Chem. Pharm. Bull.* **2004**, *52*, 1130−1133.
(17) Usami, Y.; Takaoka, I.; Ichikawa, H.; Horibe, Y.; Tomiyama, Y.; Otsuka, M.; Imanishi, Y.; Arimoto, M. *J. Org. Chem.* **2007**, *72*, 6127−6134.
(18) Usami, Y.; Mizuki, K.; Ichikawa, H.; Arimoto, M. *Tetrahedron: Asymmetry* **2008**, *19*, 1460−1463.
(19) Usami, Y.; Suzuki, K.; Mizuki, K.; Ichikawa, H.; Arimoto, M. *Org. Biomol. Chem.* **2009**, *7*, 315−318.
(20) Usami, Y.; Ohsugi, M.; Mizuki, K.; Ichikawa, H.; Arimoto, M. *Org. Lett.* **2009**, *11*, 2699−2701.
(21) (a) Huntley, C. F. M.; Wood, H. B.; Ganem, B. *Tetrahedron Lett.* **2000**, *41*, 2031−2034. (b) Chuanjun, S.; Shende, J.; Gurdial, S. *Synlett* **2001**, *12*, 1983−1985.
(22) Bowles, S. A.; Campbell, M. M.; Sainsbury, M.; Davies, G. M. *Tetrahedron* **1990**, *46*, 3981−3992.
(23) Ulibarri, G.; Nadler, W.; Skrydstrup, T.; Audrain, H.; Chianori, A.; Riche, C.; Grierson, A. A. *J. Org. Chem.* **1995**, *60*, 2753−2761.
(24) Bach, R. D.; Dmitrenko, O.; Adam, W.; Schambony, S. *J. Am. Chem. Soc.* **2003**, *125*, 924−934.
(25) Annese, C.; D'Accolti, L.; Dinoi, A.; Fusco, C.; Gandolfi, R.; Curci, R. *J. Am. Chem. Soc.* **2008**, *130*, 1197−1204.