J. Antibiot. 61(3): 136–141, 2008

ORIGINAL ARTICLE

THE JOURNAL OF ANTIBIOTICS

Colletoic Acid, a Novel 11β-Hydroxysteroid Dehydrogenase Type 1 Inhibitor from *Colletotrichum gloeosporioides* SANK 21404

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Received: February 22, 2008/Accepted: February 28, 2008

Abstract Colletoic acid, a novel 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitor, was found and isolated from the cultured broth of the producing fungus *Colletotrichum gloeosporioides* SANK 21404. Its structure was determined to be a novel acorene-type sesquiterpene by several spectroscopic methods. The absolute structure of colletoic acid was established using a modified Mosher's method and single-crystal X-ray diffraction analysis.

Keywords colletoic acid, 11β-HSD1 inhibitor, *Colletotrichum gloeosporioides*, taxonomy, fermentation, isolation, structure

Introduction

11β-Hydroxysteroid dehydrogenase type1 (11β-HSD1) intracellularly converts inert glucocorticoid (11-dehydrocorticosterone in rats and mice, cortisone in humans) into active glucocorticoid (corticosterone in rats and mice, cortisol in humans) *in vivo*. As glucocorticoids oppose the insulin effect, several studies on mice lacking [1] or overexpressing [2] 11β-HSD1 reported that 11β-HSD1 plays an important role in Type 2 diabetes and metabolic syndrome.

Our preceding paper described the discovery of novel 11β-HSD1 inhibitors named sterenin A, B, C and D [3]. Here, we report the discovery of a novel 11β-HSD1 inhibitor, colletoic acid (Fig. 1), produced by a fungus identified as *Colletotrichum gloeosporioides* SANK 21404.

Materials and Methods

General

The ^{1}H- and ^{13}C-NMR spectra were recorded at 298 K on an AVANCE 500 spectrometer equipped with a cryogenic probe (Bruker BioSpin) operating at 500 MHz and 125 MHz, respectively. The samples for NMR characterization were dissolved in DMSO-d_6 or $CDCl_3$. The optical rotation and IR spectrum were measured with a DIP-370 (JASCO) and a VALOR-III (JASCO), respectively. The mass

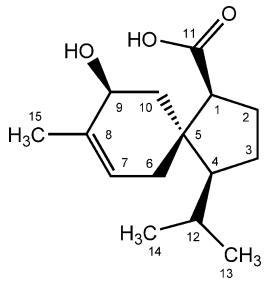

Fig. 1 Structure of colletoic acid.

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spectrum and high-resolution mass spectrum were measured with a JMS700QV Mstation (JEOL). The HPLC analysis was carried out with an HP1100 system (Agilent). All measurements of the X-ray crystallographic analysis were made on a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Cu-Kα radiation at a temperature of -100 ± 1°C.

Detection of Colletoic Acid

The progress of purification was monitored by HPLC (column; Capcell pak C18 UG120, 4.6×250 mm, mobile phase; CH_3CN - H_2O (45 : 55) containing 0.05% HCOOH, flow rate; 1.0 ml/minute, detection; UV at 210 nm, retention time; 7.9 minutes).

Esterification of Colletoic Acid

Colletoic acid (60 mg) was dissolved in methanol (1.5 ml) and trimethylsilyl (TMS)-diazomethane (0.8 ml) was added. After 5 hours at room temperature, the reaction mixture was applied to a preparative HPLC (column; Capcell pak C18 UG120, 20×250 mm, mobile phase; CH_3CN - H_2O (65 : 35) containing 0.05% HCOOH, flow rate; 10 ml/minute, detection; UV at 210 nm). The collected fraction was evaporated under reduced pressure to remove the CH_3CN followed by freeze drying to give pure colletoic acid methylester (34.3 mg).

Colletoic Acid Methylester

^{1}H-NMR (DMSO-d_6, the remaining DMSO signal was used for an internal standard as δ_H 2.50); 0.78 (H-14, 3H, d, J=6.6 Hz), 0.85 (H-13, 3H, d, J=6.8 Hz), 1.53 (H-4, 1H, m), 1.62 (H-3, 2H, m), 1.63 (H-15, 3H, br. s), 1.71 (H-2, 1H, m), 1.72 (H-10, 1H, m), 1.74 (H-12, 1H, m), 1.78 (H-2, 1H, m), 1.80 (H-6, 1H, br. d), 1.86 (H-10, 1H, m), 1.88 (H-6, 1H, br. d), 2.60 (H-1, 1H, t, J=8.1 Hz), 3.55 (11-OCH_3, 3H, s), 3.98 (H-9, 1H, m), 4.56 (9-OH, 1H, br. d, J=5.9 Hz), 5.32 (H-7, 1H, br. s).

Preparation of MTPA Derivatives

Colletoic acid methylester (1.0 mg) was dissolved in pyridine (1.0 ml), and (*R*)-(−)- or (*S*)-(+)-2-methoxy-2-(trifluoromethyl)phenylacetyl chloride (MTPA-Cl, 150 μl each) was added. After 14 hours at room temperature, each reaction mixture was applied to an HPLC (column; Senshu pak Pegasil ODS, 10×250 mm, mobile phase; CH_3CN - H_2O (85 : 15) containing 0.05% HCOOH, flow rate; 5.0 ml/minute, detection; UV at 210 nm). The collected fraction was evaporated under reduced pressure to remove the solvent, followed by freeze drying to give pure (*S*)- or (*R*)-MTPA derivative of colletoic acid methylester (800 μg each).

(*S*)-MTPA Derivative of Colletoic Acid Methylester

^{1}H-NMR ($CDCl_3$, TMS was used for an internal standard as δ_H 0.00); 0.84 (H-14, 3H, d, J=6.5 Hz), 0.92 (H-13, 3H, d, J=6.7 Hz), 1.44 (H-4, 1H, m), 1.56 (H-2, 1H, m), 1.65 (H-15, 3H, br. s), 1.68 (H-3, 2H, m), 1.73 (H-12, 1H, m), 1.76 (H-10, 1H, m), 1.79 (H-2, 1H, m), 1.97 (H-6, 1H, br. d, 18 Hz), 2.07 (H-6, 1H, br. d, 18 Hz), 2.17 (H-10, 1H, dd, J=14.1, 6.5 Hz), 2.46 (H-1, 1H, dd, J=8.9, 6.2 Hz), 3.50 (11-OCH_3, 3H, s), 3.60 (MTPA-OCH_3, 3H, s), 5.57 (H-9, 1H, br. t), 5.59 (H-7, 1H, br. s), 7.41 (MTPA-Ph, 3H), 7.57 (MTPA-Ph, 2H).

(*R*)-MTPA Derivative of Colletoic Acid Methylester

^{1}H-NMR ($CDCl_3$, TMS was used for an internal standard as δ_H 0.00); 0.85 (H-14, 3H, d, J=6.7 Hz,), 0.93 (H-13, 3H, d, J=6.7 Hz), 1.45 (H-15, 3H, br. s), 1.53 (H-4, 1H, m), 1.69 (H-2, 1H, m), 1.70 (H-3, 2H, m), 1.74 (H-12, 1H, m), 1.87 (H-2, 1H, m), 1.91 (H-10, 1H, dd, J=13.8, 6.2 Hz,), 1.99 (H-6, 1H, br. d, J=18 Hz), 2.06 (H-6, 1H, br. d, J=18 Hz), 2.21 (H-10, 1H, dd, J=13.8, 6.5 Hz), 2.58 (H-1, 1H, br. t), 3.52 (11-OCH_3, 3H, s), 3.59 (MTPA-OCH_3, 3H, s), 5.55 (H-7, 1H, br. s), 5.61 (H-9, 1H, br. t), 7.41 (MTPA-Ph, 3H), 7.58 (MTPA-Ph, 2H).

X-Ray Crystallographic Analysis

A colorless block crystal of colletoic acid crystallized from hexane - EtOAc solution was mounted on a glass fiber. The crystal data are as follows: Space group $P2_12_12_1$, a=10.521(6) Å, b=10.842(8) Å, c=25.32(2) Å, V=2887(3) Å^3, Z=8, Dc=1.16 g/cm^3. The structure was determined by direct methods with the program SIR92 and refined by full-matrix least-squares methods based on F. The final R and Rw values were 0.035 and 0.042 for $I>3.00(I)$ data, respectively. All calculations were performed using a CrystalStructure crystallographic software package (version 3.6.0, Rigaku/MSC).

Biological Assays

11β-HSD1 reductase and 11β-HSD2 dehydrogenase inhibitory activities were evaluated by the method described in the preceding paper [3].

Results

Taxonomy of the Producing Organism

The producing microorganism, *Colletotrichum gloeosporioides* SANK 21404, was isolated from a leaf collected in Fukuoka Prefecture, Japan. Colonies on potato dextrose agar (PDA) was attained 82～88 mm in 7 days at 25°C, and were greenish grey to white. The colonies were

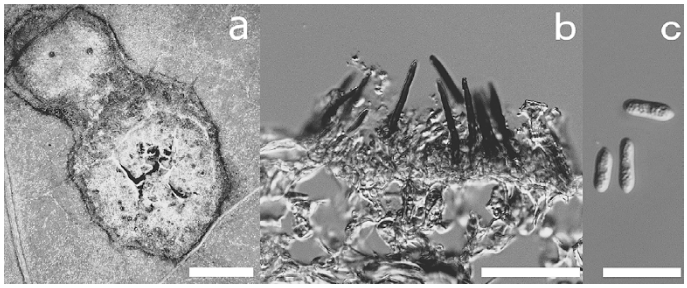

Fig. 2 *Colletotrichum gloeosporioides* SANK 21404.

a, Symptoms associated with *Colletotrichum gloeosporioides*. b, Vertical section of a conidioma. c, Conidia on PDA. Scales: a=1.0 mm, b=50 μm, c=20 μm.

floccose, consisting of aerial mycelia and submerged vegetative hyphae, rarely producing conidia. Conidiomata, ascomata, and sclerotia were absent. The colonies on the leaf were circular to irregular, light brown, and formed conidiomata on the surface and reverse side. The conidiomata were acervular, epidermal to peridermal, with setae, producing white to light pink conidia in masses. The setae were dark brown to black, 27.9～51.3×3.0～4.7 μm, and septate. The conidiophores were hyaline to brown, and septate, and were formed from the upper cells of the conidiomata. The conidia were hyaline, 27.9～51.3×3.0～4.7 μm, aseptate, straight, smooth, ellipsoidal to cylindrical, and apex obtuse. The appressoria were 5.3～14.8×4.1～8.0 μm, and clavate to irregular.

Based on these taxonomic properties, the strain SANK 21404 was identified as *Colletotrichum gloeosporioides* (Penz.) Penz. & Sacc [4]. It has been deposited at the National Institute of Advanced Industrial Science and Technology, Japan, under the accession number FERM BP-10309.

Fermentation

The culture of the strain *Colletotrichum gloeosporioides* SANK 21404 on an agar slant was inoculated into 30 ml of sterilized seed medium consisting of glycerol 3.0%, glucose 3.0%, soluble starch 2.0%, soybean meal 1.0%, gelatin 0.25%, yeast extract 0.25%, NH_4NO_3 0.25% in 100-ml Erlenmeyer flask. The flask was incubated on a rotary shaker at 23°C, 210 rpm for 5 days. The seed culture (2.0 ml) was transferred into two 500-ml Erlenmeyer flasks containing 80 ml of sterilized producing medium consisting of glycerol 5.0%, potato 5.0%, malt extract 0.5%, yeast extract 0.5%, and incubated on a rotary shaker at 23°C, 210 rpm for 7 days.

Isolation of Colletoic Acid

The Me_2CO (200 ml) was added to the harvested broth (160 ml) and the colletoic acid was extracted for 30 minutes. After centrifuging, the resulting supernatant was adjusted to pH 3.0 with 6 M HCl. The solution was extracted twice with EtOAc (200 ml), and the upper layers were combined. The solvent layer (500 ml) was washed with brine (200 ml), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to dryness to yield an oily material (188 mg). The material was dissolved in 10 ml of MeOH - H_2O (2 : 3) containing 0.3% triethylamine phosphate (pH 3.0) and was applied onto 50 ml of an ODS column (Cosmosil 140 C18 OPN, Nacalai Tesque) which was equilibrated with CH_3CN - H_2O (3 : 7) containing 0.3% triethylamine phosphate (pH 3.0). The adsorbed substance was eluted successively with 200 ml of CH_3CN - H_2O (30 : 70, 35 : 65 and 40 : 60) containing 0.3% triethylamine phosphate (pH 3.0). An CH_3CN - H_2O fraction in the ratio of 40 : 60 was collected, concentrated, and then the compound was extracted twice with EtOAc. The EtOAc layer (500 ml) was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to dryness to yield an oily material (14 mg). After the material was dissolved in 500 μl of MeOH, a 100-μl portion of it was charged to the preparative HPLC (column; Capcell Pak C18 UG120, 20×250 mm, mobile phase; CH_3CN - H_2O (48 : 52) containing 0.05% HCOOH, flow rate; 10 ml/minute, detection; UV at 210 nm). After preparations were performed 5 times, the active fractions were combined and evaporated under reduced pressure to remove the solvent, which was followed by freeze drying to give pure colletoic acid as a white powder (7.4 mg).

Physico-chemical Properties

The physico-chemical properties of the colletoic acid are summarized in Table 1.

Colletoic acid was soluble in several organic solvents, including EtOAc, MeOH and DMSO. The UV spectrum showed end absorption. The IR absorptions at 3282 and

Table 1 Physico-chemical properties of colletoic acid

Appearance	White powder
$[\alpha]_D^{25}$	+17.8° (*c* 0.73, MeOH)
Molecular weight	252
Molecular formura	$C_{15}H_{24}O_3$
FAB-MS (*m*/*z*)	275 $(M+Na)^+$
HRFAB-MS (*m*/*z*)	
Found:	275.1633
Calcd.:	275.1623
UV absorption (MeOH)	End absorption
IR $\nu_{max}^{Thin\ film}$ cm^{-1}	3282, 2957, 2877, 2637, 1687, 1548, 1450, 1410, 1392, 1367, 1308, 1276, 1256, 1215, 1193, 1169, 1100, 1078, 1053, 1034, 985, 962, 926
Solubility	
Soluble	EtOAc, MeOH, DMSO

Table 2 NMR spectral data of colletoic acid in DMSO-d_6

Position	δ_C (multiplicity[a])	δ_H (multiplicity, *J* in Hz)
1	55.2 (d)	2.47 (1H, t, *J*=8.4 Hz)
2	26.1 (t)	1.69 (1H, m),
		1.80 (1H, m)
3	23.7 (t)	1.58 (2H, m)
4	55.2 (d)	1.50 (1H, m)
5	47.1 (s)	
6	27.3 (t)	1.88 (1H, br. d, *J*=18.1 Hz)
		1.94 (1H, br. d, *J*=18.1 Hz)
7	122.6 (d)	5.34 (1H, br. s)
8	135.9 (s)	
9	66.8 (d)	3.99 (1H, br. t, *J*=6.5 Hz)
10	45.8 (t)	1.78 (1H, m),
		1.85 (1H, m)
11	176.1 (s)	
		12.07 (br. s)
12	27.1 (d)	1.75 (1H, m)
13	25.2 (q)	0.85 (3H, d, *J*=6.8 Hz)
14	19.2 (q)	0.78 (3H, d, *J*=6.6 Hz)
15	19.6 (q)	1.63 (3H, br. s)

The solvent signal was used for an internal standard as δ_H 2.50 and δ_C 39.51.

[a] Multiplicity by DEPT experiment

1686 cm^{-1} suggested the presence of a carboxyl group in the structure. The molecular weight was determined to be 252 by FAB-MS and the molecular formula was established as $C_{15}H_{24}O_3$, which was calculated to have four degrees of unsaturation, from the results of the high resolution FAB-MS and additional data from the NMR studies.

Structure Elucidation

Planar Structure of Colletoic Acid

The ^{13}C- and ^1H-NMR data (DMSO-d_6) of colletoic acid are shown in Table 2.

The ^{13}C-NMR data revealed the presence of three methyls, four sp^3 methylenes, four sp^3 methines, one sp^2 methine, one sp^3 quaternary carbon, one sp^2 quaternary carbon and one carbonyl carbon.

DQF-COSY, HSQC, ^1H-^{13}C HMBC and phase-sensitive 2D-INADEQUATE [5] studies in DMSO-d_6 were applied to elucidate the planar structure.

As shown in Fig. 3, INADEQUATE spectrum analysis allowed us all the C–C bond linkages except for C-7 to C-8. Finally, the key H–C long-range couplings between H-1 to C-5/C-10 and H-4 to C-5/C-10 observed in the HMBC spectrum confirmed a bicyclo-ring system and correlations between H-7 to C-9/C-15, H-9 to C-7 and H-15 to C-7 followed by a DQF-COSY study clarified the propene system.

Thus, the planar structure of colletoic acid was elucidated as a novel acorene-type sesquiterpene.

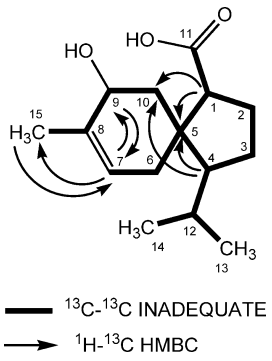

Fig. 3 $^1J_{C-C}$ and key H–C long-range couplings of colletoic acid.

Stereochemistry of Colletoic Acid

The absolute configuration of C-9 was determined by a modified Mosher's Method [6, 7]. Because the presence of carboxylic acid at C-1 was not favorable for the application of this method, the carboxyl residue was esterified (Materials and Methods section). Treatment of the methyl ester derivative with (*R*)-(−)- and (*S*)-(+)-MTPA-Cl afforded the (*S*)- and (*R*)-MTPA esters, respectively.

As shown in Fig. 4, differences in the chemical shifts of

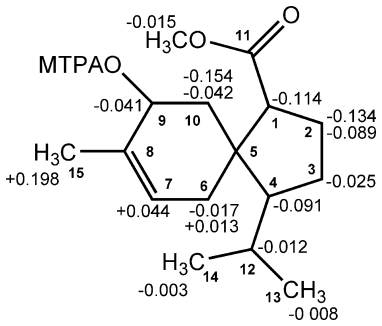

Fig. 4 Distribution of $\Delta\delta_{S\text{-}R}$ values of the (*S*)- and (*R*)-MTPA esters of colletoic acid methylester.

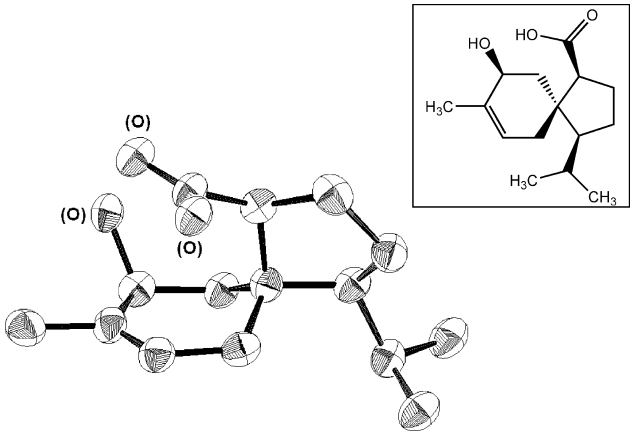

Fig. 5 An ORTEP drawing of colletoic acid.

each MTPA derivative ($\Delta\delta_{S\text{-}R}$) at H-7 and H-15 showed significantly positive values, while those at H-1, H-2, H-3, H-4 and H-10 were apparently negative clearly indicating that C-9 is an *S*-configuration.

Consequently, along with the relative configuration obtained by X-ray crystallographic analysis, the configurations of all four asymmetric carbons in colletoic acid were determined to be *S*.

Thus, the absolute structure of colletoic acid was elucidated as shown in the ORTEP drawing in Fig. 5.

Biological Activities

As shown in Table 3, colletoic acid potently inhibited human 11β-HSD1 activity in a dose-dependent manner with the IC_{50} value of 13 nM. However, colletoic acid weakly inhibited mouse 11β-HSD1 with the IC_{50} value of 460 nM, and did not inhibit its isoform of human 11β-HSD2. To analyse the 11β-HSD1 inhibition mechanism of colletoic acid, we performed kinetic analysis. The Lineweaver-Burk plots revealed that colletoic acid behaved as a competitive inhibitor of the human 11β-HSD1 (Fig. 6).

Table 3 Inhibitory activities of colletoic acid to 11β-HSDs

Enzyme	IC_{50} (nM)
Human 11β-HSD1	13
Mouse 11β-HSD1	460
Human 11β-HSD2	>10000

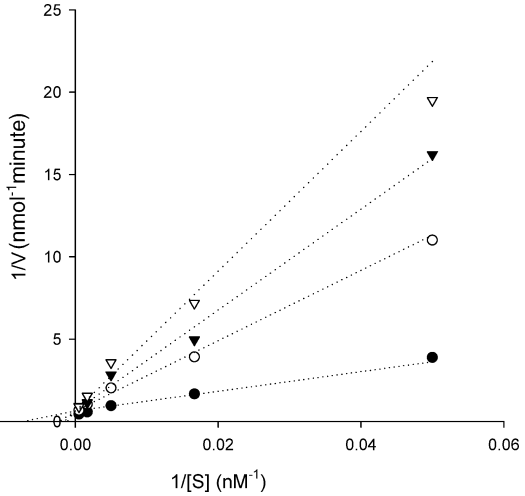

Fig. 6 Lineweaver-Burk plots for inhibition of human 11β-HSD1 by colletoic acid.

● None, ○ 8 nM, ▼ 12 nM, ▽ 27 nM.

The *Ki* value of colletoic acid was calculated to be 3.9 nM.

Discussion

In the present study, we have reported the discovery of a novel acorene-type sesquiterpene, named colletoic acid, in a cultured broth of the producing fungus, *Colletotrichum gloeosporioides* SANK 21404.

To date, various kinds of related sesquiterpenes have been reported [8]. Among them, the structures of 3-hydroxy-4-acorene [9], alaskene and acoradiene from liverwort [10], tricho-acorenol from *Trichoderma koningii* [11], acorenones [12] and AC-1 through AC-4 [13] from rhizome of calamus (*Acorus calamus*), acorenone-B from *Bothriochloa intermedia* [14] were noted to be similar to that of colletoic acid. However, their planar structures were distinct from that of colletoic acid, which was fully oxidized to carboxylic acid at C-11. Considering the stereochemistries of these acorene-type compounds, it is noteworthy that only acorenone-B possesses the same absolute structure as that of colletoic acid. Although

acorenone-B was reported to be isolated from the plant, it is interesting that colletoic acid has the same configuration despite originating from a fungus. Since AC-4 was reported as a germination inhibitor of lettuce seeds, no further information about the activity of the others has been reported. Therefore, we determined whether the extract of *Acorus calamus* root possesses 11β-HSD1 inhibitory activity, but no activity was observed (data not shown). In addition, the methylester derivative of colletoic acid had no 11β-HSD1 inhibitory activity, suggesting that the carboxyl group plays a critical role in the inhibitory action. Although many other structurally similar acorene-type sesquiterpenes might be produced in the fermentation broth of the strain SANK 21404, we could not find any acoren-type compounds with inhibitory effects on 11β-HSD1 activity other than colletoic acid. These findings imply that the inhibitory properties of colletoic acid are strictly the result of its unique stereochemistry and the carboxyl group at C-1. X-ray crystallographic analysis of its enzyme complex will be reported elsewhere.

Acknowledgements We are deeply grateful to Dr. Shuichiro Ito for his useful advice and support in the X-ray crystallographic analysis.

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