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First synthesis of (*S*)-(+)-hymenoic acid, a DNA polymerase λ inhibitor isolated from *Hymenochaetaceae* sp

Kensuke Takahashi, Miki Matsui, Masaki Kuse and Hirosato Takikawa

Department of Agrobioscience, Graduate School of Agricultural Science, Kobe University, Kobe, Japan

ABSTRACT

Hymenoic acid, isolated from cultures of the fungus, *Hymenochaetaceae* sp., is a specific inhibitor of DNA polymerase λ. The first synthesis of (*S*)-(+)-hymenoic acid was achieved by starting from *trans*-1,4-cyclohexanedimethanol and methyl (*R*)-(−)-3-hydroxyisobutyrate, and Julia–Kocienski olefination was employed as the key step.

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Synthesis; hymenoic acid; sesquiterpene; DNA polymerase; Julia–Kocienski olefination

In 2007, Nishida et al. reported the isolation and structure elucidation of hymenoic acid (**1**) from a fungus, *Hymenochaetaceae* sp [1]. This fungus had been isolated from a coral collected from Hachijo Island, Japan. Hymenoic acid (**1**) is a monocyclic sesquiterpene dicarboxylic acid. Its absolute configuration at C-5′ was determined to be *S*, as shown in Figure 1. Although the well-known sesquiterpene juvabione (**2**) and its relatives such as **3** are known to exist [2], only two structurally analogous marine natural products, namely phorbacins H and I (**4** and **5**), have been reported to date [3]. Nishida et al. also reported that **1** could potently inhibit only the activity of human and plant DNA polymerase (pol) λ [1]. Thus, **1** might be useful not only as a specific inhibitor against pol λ, but also as a lead compound for design of new antitumor agents.

Inspired by its interesting biological profiles, we initiated studies toward the synthesis of **1** as a continuation of our synthetic studies on pol inhibitors [4,5]. Here, we report the first synthesis of (*S*)-(+)-**1**.

Results and discussion

The synthetic plan for **1** is shown in Scheme 1. The basic skeleton of the target compound **1** would be synthesized using Julia–Kocienski (J–K) olefination [6–9] between a sulfone **A** and an aldehyde **B**. Although J–K olefination between **A′** and **B′** was also possible, this method was not adopted because early model studies on J–K olefination showed that the (*E*)-selectivity in the coupling between a secondary sulfone and an aldehyde was much better than that between a ketone and a primary sulfone. Intermediates **A** and **B** would be preparable from *trans*-1,4-cyclohexanedimethanol (**C**) and methyl (*R*)-(−)-3-hydroxyisobutyrate (**D**), respectively.

Scheme 2 illustrates the synthesis of **1**. The starting material, *trans*-1,4-cyclohexanedimethanol **6** (= **C**), was converted to the known aldehyde **7** (53% in two steps) [10]. Treatment of **7** with MeMgI afforded **8** (89%). The alcohol **8** was converted into the corresponding sulfide, which was immediately oxidized with *m*-CPBA to give the key 1-phenyl-1*H*-tetrazol-5-yl (PT) sulfone **9** (= **A**; 56% in two steps). Despite considerable effort, the corresponding benzothiazole-2-yl (BT) sulfone could not be prepared in an acceptable yield. By starting from methyl (*R*)-(−)-3-hydroxyisobutyrate **10** (=**D**), the known aldehyde **12** (= **B**) was prepared. Although several methods of preparation have been reported, [11–13] we prepared the ester **11** (48% in four steps) according to Chandrasekhar's procedure [14] and reduced **11** with DIBAL to give **12** (quant.).

With the two intermediates (**9** and **12**) in hand, J–K olefination was attempted. As stated in review articles, [8,9] the formation of a trisubstituted olefin via J–K olefination is difficult as there are only a limited number of (*E*)-selective options available for the coupling between a secondary sulfone and an aldehyde [15–17]. However, because the successful formation of a trisubstituted olefin is usually performed using an alkaline metal hexamethyldisilazide (HMDS) in an ethereal solvent, the coupling between **9** and **12** with three alkaline HMDSs in THF is examined. As a result of this strategy, the desired olefin **13** was obtained (55% yield based on **11**; *E*:*Z* = ca. 4:1) only when LiHMDS was used as a base. The use of NaHMDS and KHMDS gave

CONTACT Hirosato Takikawa takikawa@kobe-u.ac.jp

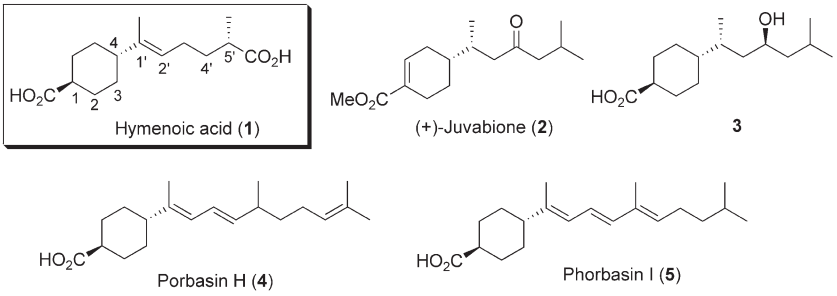
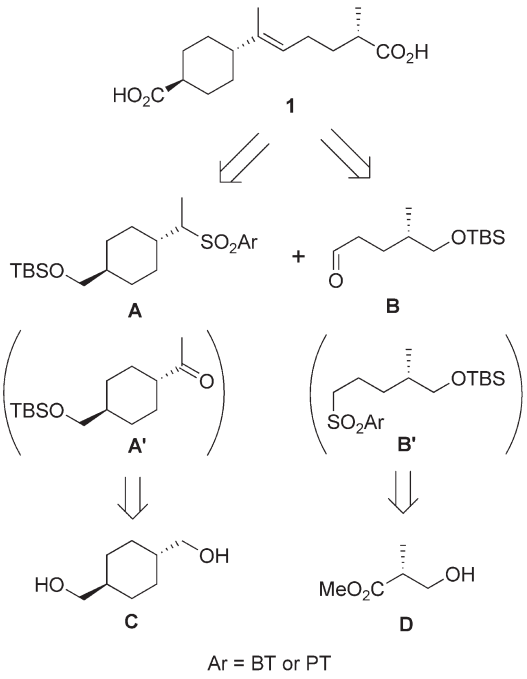


Figure 1. Structures of hymenoic acid (**1**) and the related natural products.



Scheme 1. Synthetic plan for **1**.

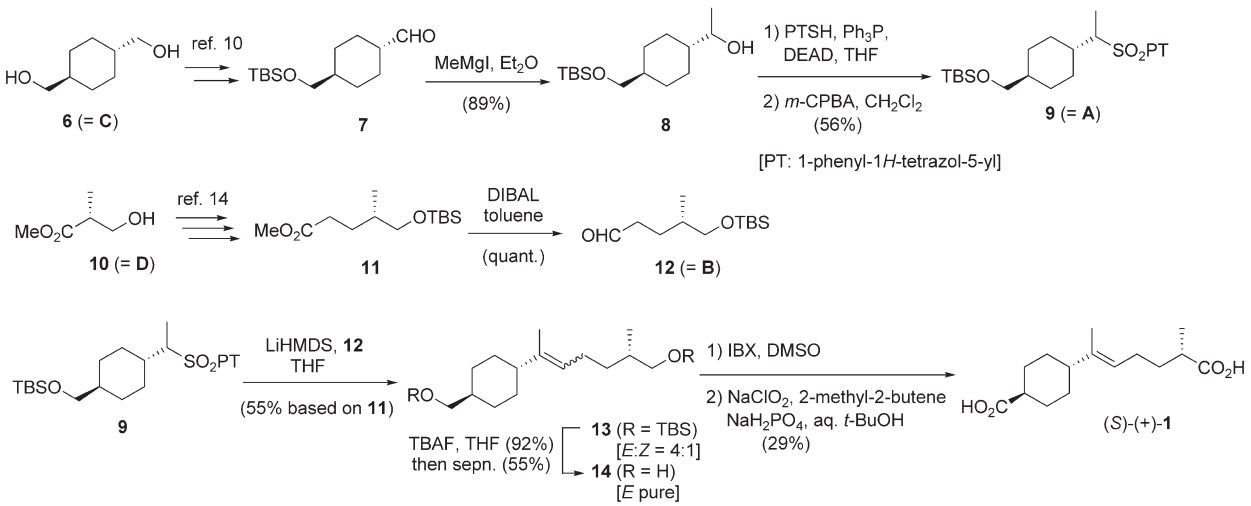
no desired adduct. Furthermore, it is important to note that this base dependency is also observed in early model studies. Upon treatment with TBAF, two TBS groups of **13** were removed (92%), and the resulting diol **14** was carefully separated by SiO_2 column chromatography to afford (*E*)-**14**. Finally, (*E*)-**14** was stepwisely oxidized in the conventional manner to give (*S*)-(+)-**1** (29%). The various spectral data of synthetic (*S*)-(+)-**1** were in good agreement with those of the naturally ocurring **1**.

In conclusion, the first synthesis of (*S*)-(+)-hymenoic acid (**1**) was accomplished by employing Juila–Kociensky olefination as the key step. This synthetic rout is straightforward and enables the synthesis of a wide range of hymenoic acid analogs. To clarify the structure-activity relationship, the synthesis of hymenoic acid analogs is an ongoing focus of this research.

Experimental

General procedures

^{1}H-NMR spectra were recorded at 300 MHz with a Jeol JNM-AL300 spectrometer. TMS or the residual solvent peak in $CDCl_3$ (at δ_H = 7.26) or CD_3OD (at δ_H = 3.30), was used as the internal standard. ^{13}C-NMR spectra were recorded at 75 MHz with the Jeol JNM-AL300 spectrometer, the peak for $CDCl_3$ (at δ_C = 77.0) or CD_3OD (at δ_C = 49.0) being used as the internal standard. Optical rotations were taken with a HORIBA SEPA-300 polarimeter. Mass spectra were measured with a Jeol JMS-SX102A spectrometer. Anhydrous THF (Cat. No. 41001–84) was purchased from Kanto Chemical Co., Inc., and other anhydrous solvents were dried over MS 3A/4A.



Scheme 2. Synthesis of (*S*)-(+)-hymenoic acid (**1**).

1-[trans-4′-(t-Butyldimethylsilyloxymethyl)-cyclohexyl]ethanol (8)

To an ice-cooled solution of MeMgI (ca. 1.0 M in Et_2O; 35 mL, 35 mmol), a solution of **7** (1.84 g, 7.19 mmol) in dry Et_2O (15 mL) was added dropwise. After removal of an ice-bath, the stirring was continued for 1.5 h. The reaction mixture was quenched with sat. NH_4Cl aq. and extracted with EtOAc. The organic layer was washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give **8** (1.74 g, 89%). NMR δ_H ($CDCl_3$): 0.03 (6H, s, Si-*Me*), 0.89 (9H, s, *t*-Bu), 0.88–1.60 (6H, m), 1.17 (3H, d, *J* = 6.3 Hz, CH-*Me*), 1.65–1.94 (4H, m), 3.40 (2H, d, *J* = 6.3 Hz, O-*CH*$_2$), 3.56 (1H, m, O-*CH*). NMR δ_C ($CDCl_3$): −5.4, 18.4, 20.5, 26.0, 27.7, 28.1, 29.2, 29.3, 40.5, 45.3, 68.7, 72.2. HREIMS *m/z* $[M]^+$: calcd. for $C_{15}H_{32}O_2Si$, 272.2172; found, 272.2198.

5-{1-[trans-4′-(t-Butyldimethylsilyloxymethyl)-cyclohexyl]ethanesulfonyl}-1-phenyl-1H-tetrazole (9)

To an ice-cooled solution of **8** (270 mg, 0.993 mmol) in dry THF (10 mL), 5-mercapto-1-phenyl-1*H*-tetrazole (0.53 g, 3.0 mmol), Ph_3P (0.79 g, 3.0 mmol) and DEAD (2.2 M in toluene; 1.4 ml, 3.1 mmol) were added successively under Ar. After stirring overnight at room temperature, the reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to give the residue (0.36 g). To a solution of this residue in CH_2Cl_2 (10 mL), *m*-CPBA (75%, 0.58 g, 2.5 mmol) was added at 0 °C. After stirring overnight at room temperature, the reaction mixture was diluted with sat. $NaHCO_3$ aq. and extracted with CH_2Cl_2. The organic layer was washed with 10% $Na_2S_2O_3$ aq., sat. $NaHCO_3$ aq., and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give **9** (257 mg, 56% in two steps). NMR δ_H ($CDCl_3$): 0.03 (6H, s, Si-*Me*), 0.89 (9H, s, *t*-Bu), 0.88–1.60 (6H, m), 1.45 (3H, d, *J* = 7.2 Hz, CH-*Me*), 1.65–1.98 (4H, m), 2.27 (1H, m), 3.38 (2H, d, *J* = 6.3 Hz, O-*CH*$_2$), 3.98 (1H, dq, *J* = 2.4, 7.2 Hz, SO_2-*CH*), 7.53–7.69 (5H, m, Ph). NMR δ_C ($CDCl_3$): −5.4, 9.5, 18.4, 25.9, 26.9, 28.8, 29.5, 30.8, 36.4, 39.9, 65.2, 68.3, 125.4, 129.6, 131.4, 133.3, 153.3. HREIMS *m/z* $[M]^+$: calcd. for $C_{22}H_{36}N_4O_3SSi$, 464.2277; found, 464.2273.

(S)-5-(t-Butyldimethylsilyloxy)-4-methylpentanal (12)

To a solution of **11** (78 mg, 30 mmol) in toluene (2 mL), DIBAL (1.0 M in toluene; 0.33 mL, 33 mmol) was slowly added at −78 °C under Ar. After stirring for 2 h at −78 °C, the reaction mixture was quenched with MeOH and then diluted with hexane. The resulting mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure to give **12** (88 mg, quant.). This was used for the next step immediately.

(5′S)-trans-1-(t-Butyldimethylsilyloxymethyl)-4-(6′-t-butyldimethylsilyloxy-1′,5′-dimethyl-1′-hexenyl)-cyclohexane (13)

To a solution of **9** (140 mg, 0.301 mmol) in dry THF (2 mL), LiHMDS (1.09 M in THF; 0.45 mL, 0.49 mmol) was added dropwise at −78 °C under Ar. After stirring for 30 min, a solution of **12** (88 mg) in THF (1 mL) was added, and the mixture was stirred overnight with gradual warming to room temperature. It was then quenched with sat. NH_4Cl aq. and extracted with Et_2O. The organic layer was washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give a mixture of (*E*)- and (*Z*)-**13** (77 mg, 55% based on **11** in two steps, *E*:*Z* = ca. 4:1). $[\alpha]_D^{21}$ = −0.58 (*c* 1.04, $CHCl_3$). NMR δ_H ($CDCl_3$): 0.03, 0.04 (12H, each s, Si-Me), 0.84–0.90 (12H, m), 0.90–2.40 (15H, m), 1.56 (3H, br s, 1′-Me), 3.32–3.48 (4H, m, O-CH_2), 5.05 (1/5H, t, *J* = 6.9 Hz, *Z*-2′-H), 5.11 (4/5H, t, *J* = 6.9 Hz, *E*-2′-H). NMR δ_C ($CDCl_3$): −5.34, −5.32, 14.3, 16.71, 16.73, 18.36, 18.40, 19.6, 24.7, 25.3, 25.97, 26.00, 29.7, 29.8, 30.4, 31.3, 33.4, 33.8, 35.4, 35.5, 39.8, 40.3, 40.4, 47.4, 68.3, 68.4, 68.87, 68.90, 122.9, 124.7, 139.7, 139.9. HREIMS *m/z* $[M]^+$: calcd. for $C_{27}H_{56}O_2Si_2$, 468.3819; found, 468.3818.

(2S,5E)-6-[trans-4-(Hydroxymethyl)cyclohexyl]-2-methylhept-5-en-1-ol (14)

To a solution of **13** (93 mg, 0.20 mmol) in THF (3 mL), TBAF (1.0 M in THF; 0.6 mL, 0.6 mmol) was added. After stirring for 2 h at room temperature, the reaction mixture was diluted with sat. NH_4Cl aq. and extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give a mixture of (*E*)- and (*Z*)-**14** (44 mg, 92%). Further chromatographic purification of this mixture was carefully performed to give the pure (*E*)-**14** (24 mg, 55%). $[\alpha]_D^{23}$ = −5.8 (*c* 0.33, $CHCl_3$). NMR δ_H ($CDCl_3$): 0.93 (3H, d, *J* = 6.6 Hz, 2-Me), 0.96–1.06 (2H, m), 1.10–1.30 (2H, m), 1.39–1.58 (2H, m), 1.60 (3H, s, 6-Me), 1.75–2.15 (8H, m), 3.43 (1H, dd, *J* = 10.2, 6.3 Hz), 3.46 (2H, d, *J* = 6.0 Hz), 3.51 (1H, dd, *J* = 10.2, 5.8 Hz), 5.12 (1H, t, *J* = 6.9 Hz, 5-H). NMR δ_C ($CDCl_3$): 14.4, 16.5, 25.1, 29.6, 31.1, 33.2, 35.4, 40.3, 47.2, 68.3, 68.7, 122.6, 140.0. HREIMS *m/z* $[M]^+$: calcd. for $C_{15}H_{28}O_2$, 240.2089; found, 240. 2097.

(S)-(+)-Hymenoic acid (1)

To a solution of **14** (12.3 mg, 51.2 μmol) in DMSO (0.2 mL), IBX (57.8 mg, 0.206 mmol) in DMSO (0.7 mL) was added. After stirring at room temperature for 4 h, the reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to give the crude products, which was immediately dissolved into *t*-BuOH (0.2 ml) and water (0.2 mL). To this solution were added 2-methyl-2-butene

(0.55 mL, 5.1 mmol), NaH_2PO_4 (30.5 mg, 0.196 mmol), $NaOCl_2$ (26.4 mg, 0.292 mmol). After stirring for 3.5 h at room temperature, the reaction mixture was diluted with sat. NH_4Cl aq. and extracted with CH_2Cl_2. The organic layer was washed brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give (*S*)-(+)-**1** (4.0 mg, 29% in two steps). $[\alpha]_D^{25}$ = + 7.9 (*c* 0.080, CH_3OH). It should be noted that the absolute value of specific rotation of the synthesized **1** has fluctuated considerably due to unknown reason. NMR δ_H (CD_3OD): 1.13 (3H, d, *J* = 6.9 Hz), 1.21–1.34 (2H, m), 1.37–1.49 (3H, m), 1.58 (3H, s), 1.62–1.77 (3H, m), 1.84 (1H, tt, *J* = 11.7, 3.0 Hz), 1.99–2.06 (4H, m), 2.21 (1H, tt, *J* = 12.0, 3.6 Hz), 2.33–2.42 (1H, m), 5.15 (1H, t, *J* = 6.9 Hz). NMR δ_C (CD_3OD): 14.4, 17.7, 26.5, 30.5, 32.1, 35.0, 40.3, 44.4, 47.9, 123.3, 141.5, 180.1, 180.8. HREIMS *m/z* $[M]^+$: calcd. for $C_{15}H_{24}O_4$, 268.1675; found, 268.1682.

Author contribution

H.T. designed the synthetic route and wrote the manuscript. K.T. and M.M. conducted the synthetic experiments with the aid of M.K. M.K. specially contributed to analytical works.

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Disclosure statement

No potential conflict of interest was reported by the authors.

References

[1] Nishida M, Ida N, Horio M, et al. Hymenoic acid, a novel specific inhibitor of human DNA polymerase λ from a fungus of *Hymenochaetaceae* sp. Bioorg Med Chem. 2008;16:5115–5122.

[2] Numata A, Hokimoto K, Takemura T, et al. Plant constituents biologically active to insects. II. Juvabione analogs from *Abies sachalinensis* Mast. (1). Chem Pharm Bull. 1983;31:436–442.

[3] Lee HS, Park SY, Sim CJ, et al. Phorbasins G–I: three new diterpenoids from the sponge *Phorbas gukulensis*. Chem Pharm Bull. 2008;56:1198–1200.

[4] Takikawa H, Nozawa D, Kayo A, et al. Synthesis of sulfobacin A, B and flavocristamide A, new sulfonolipids isolated from *Chryseobacterium* sp. J Chem Soc Perkin Trans. 1999;1:2467–2477.

[5] Takikawa H, Kamatani N, Nakanishi K, et al. Synthetic studies on kohamaic acids: synthesis of structurally simplified analogs of kohamaic acid A. Biosci Biotechnol Biochem. 2008;72:3071–3074.

[6] Baudin JB, Hareau G, Julia SA, et al. A direct synthesis of olefins by reaction of carbonyl compounds with lithio derivatives of 2-[alkyl- or (2′-alkenyl)- or benzyl-sulfonyl]-benzothiazoles. Tetrahedron Lett. 1991;32:1175–1178.

[7] Blakemore PR, Cole WJ, Kocienski PJ, et al. A stereoselective synthesis of *trans*-1,2-disubstituted alkenes based on the condensation of aldehydes with metallated 1-phenyl-1*H*-tetrazol-5-yl sulfones. Synlett. 1998;26–28.

[8] Blakemore PR. The modified Julia olefination: alkene synthesis via the condensation of metallated heteroarylalkylsulfones with carbonyl compounds. J Chem Soc Perkin Trans. 2002;1:2563–2585.

[9] Aïssa C. Mechanistic manifold and new developments of the Julia–Kocienski reaction. Eur J Org Chem. 2009;12:1831–1844.

[10] Fotsop DF, Roussi F, Leverrier A, et al. Biomimetic total synthesis of meiogynin A, an inhibitor of Bcl-xL and Bak interaction. J Org Chem. 2010;75:7412–7415.

[11] Marshall JA, Yanik MM. Synthesis of a C1–C21 subunit of the protein phosphatase inhibitor tautomycin: a formal total synthesis. J Org Chem. 2001;66:1373–1379.

[12] Molli SD, Qi J, Yajima A, et al. Structure-activity relationship of α hormones, the mating factors of phytopathogen *Phytophthora*. Bioorg Med Chem. 2012;20:681–686.

[13] Williams BD, Smith AB III. Total synthesis of (±)-18-*epi*-latrunculol A. Org Lett. 2013;15:4584–4587.

[14] Chandrasekhar S, Reddy CR. Towards a synthesis of epothilone A: asymmetric synthesis of C(1)-C(6) and C(7)-C(15) fragments. Tetrahedron: Asymmetry. 2002;13:261–268.

[15] Huang H, Panek JS. Total synthesis of callipeltoside A. Org Lett. 2004;6:4383–4385.

[16] Werneburg M, Hertweck C. Chemoenzymatic total synthesis of the antiproliferative polyketide (+)-(*R*)-aureothin. ChemBioChem. 2008;9:2064–2066.

[17] Tan D-X, Xu Z-J, Chen H-J, et al. Synthesis and configurations of (−)-furospongin-1 and (+)-dihydrofurospongin-2. Eur J Org Chem. 2016;5:946–957.