Synthesis Y. Ichikawa et al. Paper

Bioinspired Synthesis of the Central Core of Halichonadin H: The Passerini Reaction in a Hypothetical Biosynthesis of Marine Natural Products

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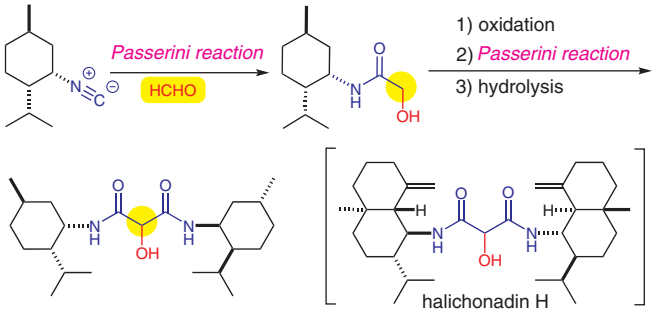

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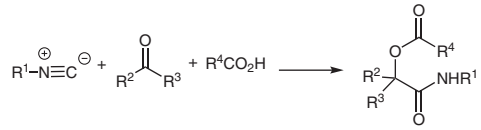
Abstract A pathway is proposed for the biosynthesis of the unique homodimeric terpene, halichonadin H. The proposed biosynthetic pathway involves two key Passerini reactions of eudesmane-type terpene isocyanides. The Passerini reaction of a model terpene isocyanide and formaldehyde afforded an α-hydroxy acetamide, which was further subjected to oxidation and a second Passerini reaction. This reaction sequence furnished an α-hydroxy malonamide connected with two identical terpene units which is the identical structural motif found in halichonadin H.

Key words marine natural products, terpenes, isocyanides, biosynthesis, Passerini reaction

The Passerini reaction,[1] discovered in 1921 by Mario Passerini in Italy, is a multicomponent process in which an isocyanide reacts with a carbonyl compound in the presence of an acid to produce an α-acyloxy amide (Scheme 1). This process has attracted growing interest in combinatorial diversity-oriented organic synthesis.[2] In contrast, there has been no report to date that Nature employs the Passerini reaction in biosynthetic pathways.

During our ongoing research project to explore bioinspired syntheses of marine natural products,[3] a unique homodimeric terpene halichonadin H (**1**) arrested our attention (Figure 1). This substance was isolated in 2011 by the Kobayashi group at Hokkaido University from the light-brown marine sponge *Halichondria* sp. collected at Unten Port on Okinawa Island.[4] In particular, we aimed to address a question about the biosynthetic origin of the unique central core structure of **1** in which two identical eudesmane sesquiterpenoid units are connected with α-hydroxy malonic acid through amide bonds.



Scheme 1 The three-component Passerini reaction

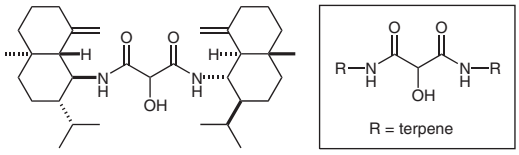
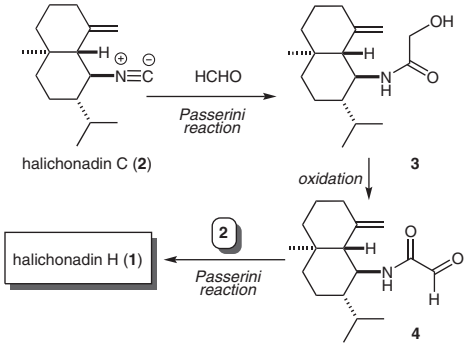


Figure 1 Structure of halichonadin H and its central core structure

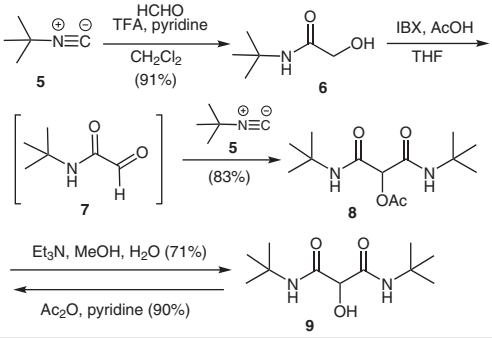
In contemplating a plausible pathway for the biosynthesis of halichonadin H, we reasoned that the terpene isocyanide halichonadin C (**2**) would be a likely biogenetic precursor (Scheme 2). Isolation and structural elucidation of halichonadin C was reported in 2005 by the Kobayashi group from the same marine sponge found at Unten Port.[5] In accord with this proposal, a key step in the biosynthetic pathway would be the Passerini reaction of halichonadin C (**2**) with formaldehyde to produce α-hydroxy acetamide **3**. Oxidation of **3** would form the corresponding glyoxamide **4**, which would subsequently undergo the Passerini reaction with halichonadin C (**2**) to produce halichonadin H (**1**). In order to experimentally evaluate the feasibility of the proposed biosynthetic pathway, we embarked on a study



Scheme 2 Plausible biosynthesis of halichonadin H illustrating its origin from halichonadin C and formaldehyde

aimed at the synthesis of the central structural motif of halichonadin H in which two identical terpene units are joined to α-hydroxy malonic acid through amide bonds.

In the first phase of the exploratory effort, we selected *tert*-butyl isocyanide (**5**) as a structurally simple starting material and focused on the modified Passerini reaction reported by Lumma[6] (Scheme 3). Trifluoroacetic acid promoted Passerini reaction of *tert*-butyl isocyanide (**5**) and aqueous formaldehyde in the presence of pyridine in dichloromethane generated the crystalline α-hydroxy acetamide **6** in 92% yield. In order to circumvent difficulties associated with the synthesis and isolation of glyoxamide **7** due to its facile hydration and air sensitivity,[7] we utilized Zhu's protocol that advantageously uses in situ oxidation of alcohols to produce carbonyl substrates in the Passerini reaction.[8] In the event, oxidation of α-hydroxy acetamide **6** with *o*-iodoxybenzoic acid (IBX) followed by reaction of the in situ generated glyoxamide **7** with *tert*-butyl isocyanide (**5**) and acetic acid in THF produced the α-acetoxy malonamide **8** in 83% yield after chromatographic purification. Finally, removal of the acetyl group in **8** with triethylamine in aqueous methanol provided α-hydroxy malonamide **9** in 71% yield.



Scheme 3 Model synthesis of the central structure of halichonadin H

Although the NMR data of **9** are fully consistent with the structure depicted in Scheme 3, we were puzzled over an unusual TLC behavior of **9** in comparison with **8**. Since alcohol **9** is considered to be a more polar substance than acetate **8**, migration of **9** on TLC is expected to be lower than that of **8**. Contrary to this expectation, the R_f value of **9** was considerably higher than that of **8**.[9] Fortunately, we obtained **8** as nice white crystals suitable for X-ray structural analysis,[10] which unambiguously confirmed the structure of **8** (Figure 2). In addition, analysis through re-formation of acetate **8** by treatment of **9** with acetic anhydride and pyridine (Scheme 3) indicated no change had occurred during the hydrolysis of **8** to form **9**.

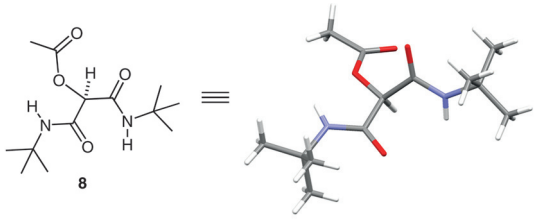
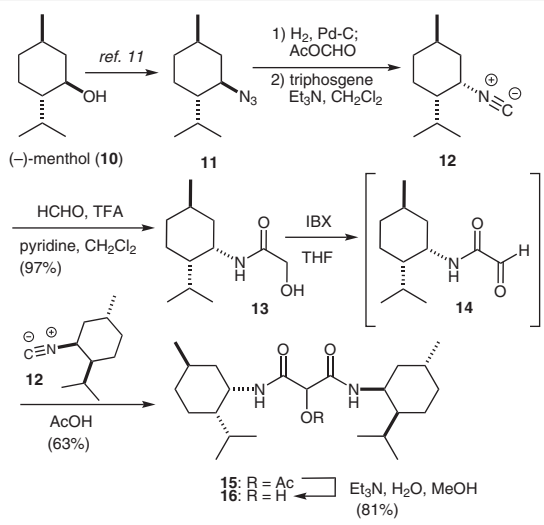


Figure 2 Plot of the X-ray crystallographic data of acetate **8**

Our attention next turned to a terpene model for the biomimetic synthesis of the central core structure of halichonadin H (Scheme 4). For this purpose, terpene isocyanide **12** was prepared from known azide **11**, which was synthesized from (–)-menthol (**10**).[11] Transformation of **11** to terpene isocyanide **12** was performed using our previously reported method involving: i) catalytic hydrogenation of azide **11**, ii) in situ formylation of the produced amine with acetic formic anhydride, and iii) dehydration of the resulting formamide with triphosgene and triethylamine.[3b] The Passerini reaction of **12** with aqueous formaldehyde using



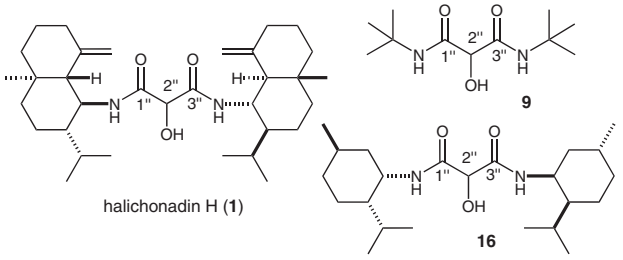
Scheme 4 Synthesis of the central core structure of halichonadin H

similar reaction conditions to those depicted in Scheme 3 was found to generate α-hydroxy acetamide **13** in 97% yield. The ensuing Passerini reaction of isocyanide **12** with the carbonyl surrogate **13**, to avoid isolation of glyoxamide **14**, furnished the product **15** in one pot in 63% yield. Finally, hydrolytic removal of the acetate group in **15** gave rise to the menthyl analogue **16** of halichonadin H in 81% yield.[12]

Selected ^{13}C and ^{1}H NMR data of halichonadin H (**1**) and the *tert*-butyl and menthyl model compounds **9** and **16** are listed in Table 1. The ^{13}C NMR chemical shifts associated with carbons in the α-hydroxy malonamide moieties of the model compounds **9** and **16** closely match those of halichonadin H (**1**). Most of the ^{1}H NMR data of model compounds **9** and **16**, measured in pyridine-d_5 solution, are consistent with those of halichonadin H (**1**). However, some notable differences exist in the chemical shifts of the H-2″ (halichonadin H numbering) and OH hydrogens in the menthyl derivative **16** (5.12 and 7.69 ppm), which are located downfield from those of the corresponding hydrogens in halichonadin H (**1**; 4.86 and 7.22 ppm) and the *tert*-butyl model compound **9** (4.77 and 7.05 ppm).[13] These differences in chemical shift may be a consequence of stereoisomeric differences imparted by steric effects of the *N*-substituents on the bis-amide and by a hydrogen-bonding network within the α-hydroxy malonamide moiety. Specifically, the more sterically encumbering nature of the two *trans*-decalin fragments in halichonadin H (**1**), compared with the menthyl moieties in **16**, could be responsible for stereoisomeric and chemical shift differences. This interpretation is supported by the observation that the corresponding chemical shifts of the protons in **9**, which contains the sterically more crowded *tert*-butyl groups, are similar to those in halichonadin H (**1**).

Although a direct comparison of the hydrogen-bonding networks in **9** and **16** is difficult, key clues about their differences came from the results of experiments in which the hydrogen in the OH group was exchanged by deuterium in order to assign the OH signals. Each pyridine-d_5 solution of **9** and **16** in an NMR tube was treated with two drops of CD_3OD as exchangeable deuterium source. Because ensuing proton-by-deuterium exchange in **9** is a slow process (Figure 3), the mixture was allowed to stand at room temperature for 4 days. This resulted in a decrease in the intensity of the OH signal at δ 7.05 ppm by only 57%, implying that a tight intramolecular hydrogen-bonding network in **9** attenuates the rate of proton exchange between OH and CD_3OD. In contrast, exchange of the OH proton (7.69 ppm) in **16** occurred within 4 hours (Figure 4). This observation suggests that the OH hydrogen in menthyl compound **16** is engaged in hydrogen bonding with pyridine-d_5, resulting in smooth hydrogen exchange of OH by deuterium. In addition, this intermolecular hydrogen bond in **16** could bring about a deshielding effect that causes the chemical shift of the OH proton to appear at a higher frequency. In the case of OH in **9**, the bulky *tert*-butyl group would interfere with the hydrogen-bonding interaction with solvent pyridine-d_5.

Table 1 Comparison of Selected ^{13}C and ^{1}H NMR Data of Halichonadin H (**1**) and Model Compounds **9** and **16**



	^{13}C NMR (pyridine-d_5)		
	1[a]	**9**	**16**
1′′	169.7	169.2	169.5
2′′	71.8	72.8	72.4
3′′	169.1	–	168.7
	^{1}H NMR (pyridine-d_5)		
	1[a]	**9**	**16**
2′′	4.86 (s, 1 H)	4.77 (s, 1 H)	5.12 (s, 1 H)
NH	7.73 (d, *J* = 9.8 Hz, 1 H)	7.70 (br s, 2 H)	7.83 (d, *J* = 9.8 Hz, 1 H)
NH	7.94 (d, *J* = 9.9 Hz, 1 H)		7.98 (d, *J* = 9.2 Hz, 1 H)
OH	7.22 (br s, 1 H)	7.05 (br s, 1 H)	7.69 (br s, 1 H)

[a] Literature NMR data of **1**.[4]

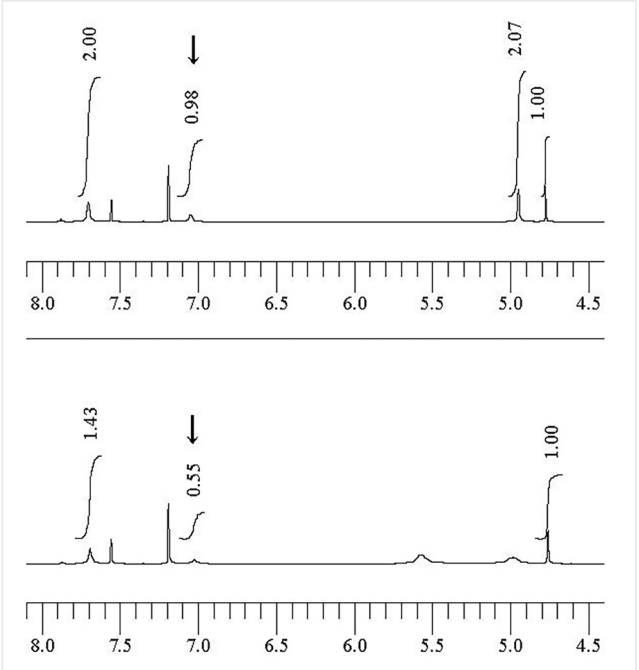


Figure 3 ^{1}H NMR spectrum of **9** in pyridine-d_5 (upper trace) and in the deuterium-exchange experiment with CD_3OD (lower trace)

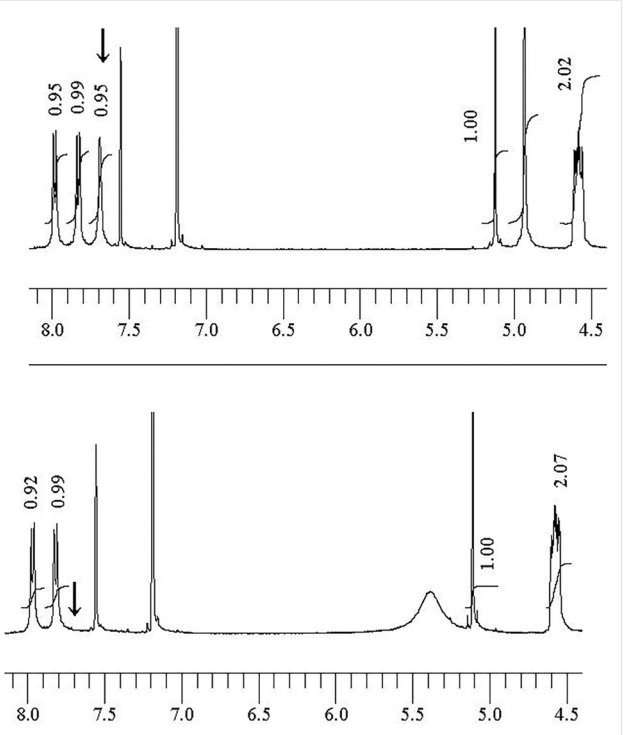


Figure 4 ^{1}H NMR spectrum of **16** in pyridine-d_5 (upper trace) and in the deuterium-exchange experiment with CD_3OD (lower trace)

The suggestion that pyridine-d_5 participates in a hydrogen-bonding network with the α-hydroxy malonamide in **16** gains further support from the ^{1}H NMR spectra of **9** and **16** measured in $CDCl_3$ (Table 2). No hydrogen-bonding interaction with solvent $CDCl_3$ can occur, which is consistent with similarities in the chemical shifts and coupling constants in the ^{1}H NMR spectra of **9** and **16** measured in $CDCl_3$.

Table 2 Comparison of Selected ^{1}H NMR Data of Model Compounds **9** and **16** Measured in $CDCl_3$

	^{1}H NMR (500 MHz, $CDCl_3$)	
	9	**16**
2′′	4.23 (d, *J* = 2.9 Hz, 1 H)	4.45 (d, *J* = 2.3 Hz, 1 H)
NH	7.09 (br s, 2 H)	7.41 (d, *J* = 9.2 Hz, 1 H)
NH		7.51 (d, *J* = 8.5 Hz, 1 H)
OH	4.65 (d, *J* = 2.9 Hz, 1 H)	4.64 (d, *J* = 2.3 Hz, 1 H)

In conclusion, we have tested the chemical features of our proposed biosynthesis of halichonadin H. Our synthetic endeavor utilizing model terpene isocyanide **12** and formaldehyde along our proposed Passerini-type biogenetic pathway led to the synthesis of an identical structural motif to that found in halichonadin H. The bioinspired synthesis presented here clearly demonstrates the feasibility of our proposal that Nature utilizes Passerini-type reactions in the biosynthetic pathway for the formation of halichonadin H. To the best of our knowledge, this is the first hypothesis proposing that the Passerini reaction operates in the biosynthesis of natural products.

Melting points were recorded on a Yanaco MP-S3 micro melting point apparatus and are not corrected. Optical rotations were measured at the sodium D line with a 100 mm path length cell on a JASCO DIP-370 digital polarimeter, and are reported as follows: $[\alpha]_D^T$, concentration (g/100 mL), solvent. IR data were obtained on a JASCO FT/IR-460 spectrophotometer; spectral bands are reported in wavenumbers (cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded on a JEOL ECA 500 spectrometer. ^{1}H NMR chemical shifts are reported in ppm with chloroform (7.26 ppm) and pyridine (7.19 ppm) as internal standards. ^{13}C NMR chemical shifts are reported in ppm relative to $CDCl_3$ (77.0 ppm) and pyridine-d_5 (123.5 ppm) as internal standards. High-resolution mass spectra (HRMS) were measured on a BRUKER, FT-ICRMS, solariX XR spectrometer. Moisture- and/or oxygen-sensitive reactions were conducted under an argon atmosphere. CH_2Cl_2 was dried over 3 Å molecular sieves. Pyridine and Et_3N were stocked over anhydrous KOH. All other commercially available reagents were used as received.

N-tert-Butyl-2-hydroxyacetamide (6)

To a solution of *tert*-butyl isocyanide (**5**; 357 mg, 4.30 mmol), aqueous formaldehyde (37%, 1.11 mL) and pyridine (1.74 mL, 21.6 mmol) in CH_2Cl_2 (4.0 mL), cooled to 0 °C, was added TFA (0.30 mL, 3.98 mmol). After stirring at 0 °C for 90 min, the cooling bath was removed, and stirring was continued for 2.5 h. The solution was concentrated to afford a residue (1.94 g), which was purified by silica gel chromatography (EtOAc/hexane, 2:1) to afford **6** as a colorless crystalline solid; yield: 514 mg (91%); mp 77–78 °C (recrystallized from EtOAc/hexane).

IR (KBr): 3362, 3236, 1636, 1540, 1082 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.43 (br, 1 H), 3.97 (s, 2 H), 3.60 (br, 1 H), 1.38 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.8, 62.1, 50.9, 28.6.

HRMS (ESI): *m*/*z* calcd for $C_6H_{14}NO_2$ $[M + H]^+$: 132.1019; found: 132.1018.

1,3-Bis(*tert*-butylamino)-1,3-dioxopropan-2-yl Acetate (8)

AcOH (0.36 mL, 6.36 mmol), α-hydroxy acetamide **6** (100 mg, 0.76 mmol) and *tert*-butyl isocyanide (**5**; 0.12 mL, 1.06 mmol) were added successively to a suspension of IBX (594 mg, 2.12 mmol) in THF (3.0 mL). The mixture was stirred at 40 °C for 3 h. Additional THF (1.0 mL) was added, and stirring was continued at 40 °C for 2 h. The reaction mixture was diluted with Et_2O, filtered through Celite and poured into aqueous $NaHCO_3$. The aqueous layer was separated and extracted with Et_2O. The combined organic layer was washed with H_2O and brine, and dried (Na_2SO_4). Concentration under reduced pressure afforded a residue (222 mg), which was purified by silica gel chromatography (EtOAc/hexane, 1:2) to afford **8** as a white crystalline solid; yield: 173 mg (83%); mp 159–161 °C (recrystallized from EtOAc/hexane).

IR (KBr): 3359, 2977, 1746, 1687, 1671, 1540, 1245 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.59 (br s, 2 H), 5.35 (s, 1 H), 2.26 (s, 3 H), 1.34 (s, 18 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.3, 163.8, 72.6, 51.6, 28.4, 20.7.

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{25}N_2O_4$ $[M + H]^+$: 273.1809; found: 273.1806.

N^1,*N*^{3}-Di-*tert*-butyl-2-hydroxymalonamide (9)

A solution of **8** (90 mg, 0.34 mmol), Et_3N (0.10 mL), H_2O (0.10 mL) and MeOH (2.0 mL) was stirred at room temperature for 3 h. The solution was concentrated under reduced pressure, and the resulting residue (74 mg) was purified by silica gel chromatography (EtOAc/hexane, 1:5 followed by 5:1) to afford **9** as a white solid; yield: 55 mg (71%); mp 122–123 °C (recrystallized from EtOAc/hexane).

IR (KBr): 3432, 3357, 3277, 3080, 2972, 1653, 1542, 1219, 1116 cm^{-1}.

^{1}H NMR (500 MHz, pyridine-d_5): δ = 7.70 (br s, 2 H), 7.05 (br, 1 H), 4.77 (s, 1 H), 1.34 (s, 18 H).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.09 (br s, 2 H), 4.65 (d, *J* = 2.9 Hz, 1 H), 4.23 (d, *J* = 2.9 Hz, 1 H), 1.36 (s, 18 H).

^{13}C NMR (125 MHz, pyridine-d_5): δ = 169.2, 72.8, 51.1, 28.5.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.7, 70.5, 51.4, 28.4.

HRMS (ESI): *m*/*z* calcd for $C_{11}H_{23}N_2O_3$ $[M + H]^+$: 231.1701; found: 231.1703.

2-Hydroxy-*N*-((1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)acetamide (13)

TFA (0.20 mL, 2.67 mmol) was added to a solution of isocyanide **12** (250 mg, 1.50 mmol), aqueous formaldehyde (37%, 0.58 mL) and pyridine (0.72 mL, 9.8 mmol) in CH_2Cl_2 (4.0 mL) at 0 °C. After stirring at 0 °C for 4 h, the cooling bath was removed, and stirring was continued for 4 h. Concentration of the reaction mixture under reduced pressure afforded a residue (973 mg), which was purified by silica gel chromatography (EtOAc/hexane, 1:1) to afford **13** as a white solid; yield: 309 mg (97%); mp 71–72 °C (recrystallized from hexane).

$[\alpha]_D^{30}$ +35.5 (*c* 1.00, $CHCl_3$).

IR (KBr): 3395, 3296, 2958, 2925, 1656, 1535, 1081 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.85–6.75 (br, 1 H), 4.40–4.34 (m, 1 H), 4.07 (s, 2 H), 3.50–2.50 (br, 1 H), 1.88–1.80 (m, 2 H), 1.78–1.72 (m, 1 H), 1.52–1.40 (m, 1 H), 1.38–1.27 (m, 1 H), 1.13–1.03 (m, 3 H), 1.00–0.80 (m, 10 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.7, 62.0, 46.1, 45.7, 40.0, 34.6, 29.4, 26.7, 25.2, 22.1, 20.9, 20.7.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{24}NO_2$ $[M + H]^+$: 214.1800; found: 214.1802.

1,3-Bis((1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexylamino)-1,3-dioxopropan-2-yl Acetate (15)

To a suspension of IBX (291 mg, 1.04 mmol) in THF (5.0 mL) was added successively AcOH (0.18 mL, 3.12 mmol), α-hydroxy acetamide **13** (111 mg, 0.52 mmol) and isocyanide **12** (120 mg, 0.73 mmol). After stirring at 40 °C for 24 h, the reaction mixture was diluted with Et_2O (7.0 mL) and filtered through Celite. The filtrate was poured into aqueous $NaHCO_3$. After stirring for 20 min, the aqueous layer was separated and extracted with Et_2O. The combined organic layer was washed with H_2O and brine, and dried (Na_2SO_4). Concentration under reduced pressure afforded a residue (184 mg), which was purified by silica gel chromatography (EtOAc/hexane, 1:5) to afford **15** as a white solid; yield: 142 mg (63%); mp 101–102 °C (recrystallized from hexane).

$[\alpha]_D^{27}$ +43.3 (*c* 1.00, $CHCl_3$).

IR (KBr): 3566, 3321, 2949, 2921, 1762, 1683, 1531, 1372, 1216 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.10 (d, *J* = 9.2 Hz, 1 H), 6.95 (d, *J* = 9.2 Hz, 1 H), 5.65 (s, 1 H), 4.34 (m, 2 H), 2.30 (s, 3 H), 1.90–1.65 (m, 6 H), 1.52–1.16 (m, 4 H), 1.12–0.98 (m, 6 H), 0.96–0.80 (m, 20 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.4, 164.2, 163.6, 72.0, 46.62, 46.58, 46.25, 46.15, 39.8, 34.5, 29.39, 29.32, 26.8, 26.7, 25.28, 25.26, 22.14, 22.12, 21.0, 20.9, 20.70, 20.67, 20.6.

HRMS (ESI): *m*/*z* calcd for $C_{25}H_{45}N_2O_4$ $[M + H]^+$: 437.3374; found: 437.3367.

2-Hydroxy-*N*^{1},*N*^{3}-bis((1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)malonamide (16)

To a solution of **15** (129 mg, 0.30 mmol) dissolved in a mixture of H_2O (0.10 mL) and MeOH (2.0 mL) was added Et_3N (0.10 mL). The solution was stirred at room temperature for 3 h and then concentrated under reduced pressure. The resulting residue (106 mg) was purified by silica gel chromatography (EtOAc/hexane, 1:5) to afford **16** as a white solid; yield: 95 mg (81%); mp 101–102 °C (recrystallized from hexane).

$[\alpha]_D^{28}$ +51.8 (*c* 1.00, $CHCl_3$).

IR (KBr): 3405, 3349, 2959, 2923, 1671, 1516, 1116 cm^{-1}.

^{1}H NMR (500 MHz, pyridine-d_5): δ = 7.98 (d, *J* = 9.2 Hz, 1 H), 7.83 (d, *J* = 9.8 Hz, 1 H), 7.69 (br s, 1 H), 5.12 (s, 1 H), 4.63–4.54 (m, 2 H), 1.93–1.88 (m, 2 H), 1.73–1.61 (m, 2 H), 1.60–1.38 (m, 5 H), 1.35–1.27 (m, 1 H), 1.14–0.89 (m, 5 H), 0.99 (d, *J* = 6.3 Hz, 3 H), 0.97 (d, *J* = 6.3 Hz, 3 H), 0.87 (d, *J* = 6.9 Hz, 3 H), 0.83–0.71 (m, 3 H), 0.82 (d, *J* = 6.9 Hz, 3 H), 0.77 (d, *J* = 6.3 Hz, 3 H), 0.75 (d, *J* = 6.9 Hz, 3 H).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.51 (d, *J* = 8.5 Hz, 1 H), 7.41 (d, *J* = 9.2 Hz, 1 H), 4.64 (d, *J* = 2.3 Hz, 1 H), 4.45 (d, *J* = 2.3 Hz, 1 H), 4.36–4.29 (m, 2 H), 1.90–1.73 (m, 6 H), 1.52–1.40 (m, 2 H), 1.32–1.21 (m, 2 H), 1.12–1.00 (m, 6 H), 0.97–0.83 (m, 20 H).

^{13}C NMR (125 MHz, pyridine-d_5): δ = 169.5, 168.7, 72.4, 46.64, 46.57, 46.49, 46.35, 40.4, 34.9, 29.62, 29.61, 26.91, 26.87, 25.5, 25.4, 22.4, 21.18, 21.06, 21.00, 20.95.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.1, 167.5, 70.2, 46.8, 46.6, 46.3, 46.2, 40.0, 34.6, 29.4, 29.3, 26.7, 26.6, 25.2, 22.2, 21.0, 20.9, 20.7, 20.6.

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{43}N_2O_3$ $[M + H]^+$: 395.3268; found: 395.3263.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610867.

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(9) The R_f value of **9** on silica gel TLC (EtOAc/hexane, 1:2) is approximately 0.56, while that of **8** is ca. 0.25. For details of the TLC experiments, see the Supporting Information.

(10) CCDC 1887491 (**8**) contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

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(12) The TLC behaviors of **15** and **16** are similar to those of **8** and **9**. For details of the TLC experiments, see the Supporting Information.

(13) We have demonstrated that the NH and OH proton resonances in the ^{1}H NMR spectra of **9** and **16** in pyridine-d_5 and $CDCl_3$ are concentration independent. This is a likely consequence of the rigid intramolecular hydrogen-bonding network in α-hydroxy malonamides, which decreases the proton-exchange rate. For details, see the Supporting Information.