Enantioselective Synthesis of Four Isomers of 3-Hydroxy-4-Methyltetradecanoic Acid, the Constituent of Antifungal Cyclodepsipeptides W493 A and B

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Four possible stereoisomers of 3-hydroxy-4-methyltetradecanoic acid were enantioselectively synthesized by using Sharpless epoxidation and a subsequent epoxide-ring opening reaction with trimethylaluminum as the key steps. The absolute configuration of the β-oxyacid component of antifungal cyclodepsipeptides W493 A and B was consequently determined as 3S,4R.

Key words: Sharpless epoxidation; W493 A; W493 B; cyclodepsipeptide; 3-hydroxy-4-methyltetradecanoic acid

By bioassay-guided fractionation, two cyclodepsipeptides, W493 A (1) and B (2) (Fig. 1), were isolated from the culture broth of Fusarium sp. and characterized as potent antifungal substances with unique activity for inducing morphological change to hypha in several fungal species.1,2) Both compounds contain a novel β-oxyacid component, 3-hydroxy-4-methyltetradecanoic acid (HMTA), which may influence their antifungal potency.3,4)

In order to further investigate the antifungal mode of action based on derivative synthesis, it was necessary to stereoselectively synthesize the four HMTA isomers, (3R,4R)-HMTA (3), (3S,4S)-HMTA (4), (3S,4R)-HMTA (5), and (3R,4S)-HMTA (6).

The absolute configuration of the naturally occurring HMTA had previously been determined to be 3S,4R by a comparison of the 1H-NMR spectrum of the corresponding 2-naphthylmethoxyacetic acid (2NMA) ester5) with those of the four chemically synthesized stereoisomers. A synthetic study on HMTAs has previously been reported by Flippin et al.9) However, no optically pure HMTAs had been obtained so that its chirality remained unclear. We describe here details of a convenient synthesis of the four stereoisomers and their properties.

Epoxy alcohols 7 and 8 were enantioselectively synthesized in a high yield as previously reported, but with slight modifications (Scheme 1).7) The ring-opening reaction of 7 by Me3Al proceeded in a regio- and stereoselective manner to produce 1,2-diol 9.8) After selectively tosylating the primary hydroxyl group in 9, the secondary alcohol obtained was converted to β-oxyacid 3 via successive steps of cyanide substitution and alkaline hydrolysis. Likewise, 4 was synthesized from epoxy alcohol 8.

Selective inversion at C-2 in 9 was needed in order to furnish β-oxyacid 5. Accordingly, the primary alcohol moiety in 9 was protected as a TBS ether and then the remaining secondary alcohol moiety was tosylated. The removal of the TBS protecting group with excess TBAF at 40°C provided epoxide 10 in one pot. Desired β-oxyacid 5 was obtained by cyanide substitution and hydrolysis of 10. Compound 6 was synthesized from 8 by the same steps as those used for obtaining 5 from 7.

The synthetic HMTAs, 3, 4, 5 and 6, were converted...
into the corresponding (S)-2NMA esters, 11, 12, 13 and 14, via their methyl esters. The $^1$H-NMR assignment of 13 derived from (3S,4R)-HMTA (5) was in complete agreement with that of the (S)-2NMA ester from natural HMTA. The absolute configuration of natural HMTA was consequently determined to be 35,4R.

**Experimental**

All melting point (mp) values are uncorrected. Optical rotation was measured with a Horiba SEPA-300 high-sensitivity polarimeter. HREI-MS data were measured with a Jeol JMX-AX500 spectrometer, and $^1$H- and $^13$C-NMR spectra (400 MHz and 100 MHz) were measured with a Jeol JNM-CX200 spectrometer. All melting point (mp) values are uncorrected. Optical rotation was measured with a Horiba SEPA-300 high-sensitivity polarimeter. HREI-MS data were measured with a Jeol JMX-AX500 spectrometer, and $^1$H- and $^13$C-NMR spectra (400 MHz and 100 MHz) were measured with a Jeol JNM-CX200 spectrometer.

(2S,3R)-3-Methyl-1,2-tridecanediol (9). To a solution of 7 (0.50 g, 2.33 mmol) in CH$_2$Cl$_2$ (20 ml) at 0 °C was carefully added 6.50 ml of Me$_2$Al (1.08 M in hexane, 7.02 mmol) under argon atmosphere. The reaction mixture was stirred at room temperature for 10 h and then quenched with 3 M HCl (10 ml) at 0 °C. After filtering through a pad of Celite, the mixture was extracted with CH$_2$Cl$_2$. The organic layer was washed with brine and dried over Na$_2$SO$_4$. Concentration in vacuo and subsequent silica gel chromatography with EtOAc–hexane (1:4) gave 9 (0.49 g, 91%) as a colorless oil. [a]$_D^{20}$ +8.55° (c 1.0, CHCl$_3$). IR $v$$_{max}$ (film) cm$^{-1}$: 3377, 2924, 1467, 1066, 1014. $^1$H-NMR (CDCl$_3$) $\delta$: 0.88 (3H, t, $J$ = 6.6 Hz), 0.91 (3H, d, $J$ = 6.8 Hz), 1.26 (18H, m), 1.53 (1H, m), 2.05 (1H, bs), 2.68 (1H, bs), 3.55 (3H, m). $^13$C-NMR (CDCl$_3$) $\delta$: 14.6, 14.6, 22.7, 27.1, 29.4, 29.6, 29.7, 29.9, 31.9, 33.0, 35.8, 65.2, 75.8. HREI-MS m/z (M$^+$–OH): calcd. for C$_{14}$H$_{29}$O, 213.2219; found, 213.2185.

(3R,4R)-3-Hydroxy-4-methyltetradecanoic acid (3) and (3S,4S)-3-hydroxy-4-methyltetradecanoic acid (4). To a solution of 9 (0.20 g, 0.87 mmol) in a mixture of pyridine–CH$_2$Cl$_2$ (1:6, 7 ml) at 0°C was added TsCl (0.17 g, 0.89 mmol). After being stirred at 0°C for 1 h and at 10°C for 5 h, the mixture was diluted with CH$_2$Cl$_2$ (20 ml). The organic layer was successively washed with a saturated CuSO$_4$ solution and brine, and then filtration and concentration gave a crude tosylate. The tosylate in aqueous 40% EtOH (8 ml) was heated to reflux with NaCN (0.74 g, 15.1 mmol) for 8 h. After removing most of the EtOH in vacuo, the residue was extracted with ether. The organic layer was washed with brine and dried over Na$_2$SO$_4$, filtration and concentration gave a crude cyanide. The cyanide in aqueous 40% EtOH (8 ml) was heated to reflux with KOH (1.34 g, 23.9 mmol) for 6 h. Most of the EtOH was removed in vacuo, and the residue was washed with ether. The aqueous layer was carefully acidified to pH 2 with concentrated HCl while ice-cooling under a hood and then extracted with CH$_2$Cl$_2$. The organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was subjected to silica gel chromatography, eluting with EtOAc–hexane (1:4), and crystallization from hexane gave 3 (83 mg, 37%) as colorless needles, mp 68–71°C. [a]$_D^{20}$ +17.20° (c 1.0, CHCl$_3$). IR $v$$_{max}$ (film) cm$^{-1}$: 2916, 1705, 1309, 1066. $^1$H-NMR (CDCl$_3$) $\delta$: 0.88 (3H, t, $J$ = 6.8 Hz), 0.92 (3H, d, $J$ = 6.8 Hz), 1.16 (18H, m), 1.55 (1H, m), 2.53 (1H, bs), 2.68 (1H, bs), 3.55 (3H, m). $^13$C-NMR (CDCl$_3$) $\delta$: 14.1, 14.2, 22.7, 27.2, 29.4, 29.6, 29.7, 31.9, 33.0, 35.8, 65.2, 75.8. HREI-MS m/z (M$^+$–OH): calcd. for C$_{15}$H$_{31}$O, 259.2273; found, 259.2287. According to essentially the same procedure, 4 (83 mg, 33%) was synthesized from 8 as colorless needles, mp 67–69°C.

**Scheme 1.** Synthesis of (3R,4R)-HMTA (3), (3S,4S)-HMTA (4), (3S,4R)-HMTA (5) and (3R,4S)-HMTA (6).

Reagents: (a) H$_2$, 5%Pd/C, H$_2$SO$_4$, quinoline, MeOH; (b) TBHP, Ti(O-i-Pr)$_4$, d-DET, CH$_2$Cl$_2$; (c) TBHP, Ti(O-i-Pr)$_4$, l-DET, CH$_2$Cl$_2$; (d) Me$_2$Al, CH$_2$Cl$_2$; (e) TsCl, pyridine/CH$_2$Cl$_2$; (f) NaCN, EtOH/H$_2$O; (g) KOH, EtOH/H$_2$O; (h) TBSCI, imidazole, DMF; (i) TSCI, pyridine; (j) TBAF, THF.

![Scheme 1](image-url)
(2R)-[(1R)-1-methylundecyl]-oxirane (10). To a solution of 9 (0.80 g, 3.47 mmol) and imidazole (0.48 g, 7.05 mmol) in DMF (4 ml) at 0 °C was added TBSCI (0.53 g, 3.52 mmol). After being stirred at 0 °C for 0.5 h and then at room temperature for 2 h, the reaction mixture was diluted with CH₂Cl₂ (6 ml). The organic layer was washed with brine and dried over Na₂SO₄, subsequent filtration and concentration giving a crude silyl ether. TsCl (0.63 g, 3.30 mmol) was added to a solution of this silyl ether in pyridine (5 ml) at 0 °C. After being stirred at 0 °C for 1 h and then at room temperature for 5 h, the reaction mixture was diluted with CH₂Cl₂ (10 ml). The organic layer was washed with a saturated CuSO₄ solution and dried over Na₂SO₄, subsequent filtration and concentration giving a crude tosylate. To a solution of this tosylate in THF (2 ml) was dropwise added 5.50 ml of TBAF (1.0M in THF, 5.50 mmol). The reaction mixture was stirred at 40 °C for 6 h and then cooled to room temperature. After being diluted with CH₂Cl₂, the organic layer was washed with brine and dried over Na₂SO₄. Concentration in vacuo and subsequent silica gel chromatography with EtOAc–hexane (2:1) gave 10 (0.55 g, 75%) as a colorless oil, [α]D₂⁰ -17.50° (c 1.0, CHCl₃). The ¹H- and ¹³C-NMR, HREI-MS, and IR spectral data were in complete agreement with those of 3.

Preparation of the (S)-2NMA esters. Each HMTA ester (2.0 mg, 7.8 μmol) was dissolved in ether (1 ml), and etheral CH₂Cl₂ was added until the yellow color was retained. After evaporating, the residue was purified by silica gel chromatography, eluting with EtOAc–hexane (1:4), to give the HMTA methyl ester as a colorless oil, being used in the next step without further purification.

To each HMTA methyl ester, DMAP (0.4 mg, 3.3 μmol) and (S)-2NMA (1.8 mg, 8.3 μmol) dissolved in 0.3 ml of CH₂Cl₂ were added EDC (3.0 mg, 15.6 μmol) and Et₃N (1.5 mg, 14.8 μmol) at 0 °C. After stirring for 12 h, the reaction mixture was diluted with CH₂Cl₂. The organic layer was successively washed with a diluted aqueous citric acid solution, saturated aqueous NaHCO₃ solution, water and brine, dried over Na₂SO₄, and evaporated. The crude product was purified by HPLC in a silica gel column (8.0 × 250 nm, Develosil 60-10, Nomura Chemical Co.), eluting with EtOAc–hexane (1:4) at 2.0 ml/min to give the (S)-2NMA ester as a colorless oil. The enantiomeric excess (ee) was calculated on the basis of the peak area ratio between the diastereomers in an HPLC analysis at 254 nm.

Methyl (3R,4R)-3-[(S)-2-naphthylmethoxyacyl]oxycarbonyl-4-methyltetradecanoate (11). This was obtained in an 85% yield (tg 16.2 min, 92.3% ee). ¹H-NMR (CDCl₃) δ: 0.87 (3H, d, J = 6.8 Hz, 0.85 (3H, t, J = 6.8 Hz), 1.09–1.30 (18H, m), 1.29 (1H, m), 2.39 (1H, dd, J = 15.6, 4.4 Hz), 2.47 (1H, dd, J = 15.6, 8.8 Hz), 3.24 (3H, s), 3.46 (3H, s), 4.91 (1H, s), 5.27 (1H, ddd, J = 8.8, 4.4, 4.0 Hz), 7.52 (3H, m), 7.83 (3H, m), 7.90 (1H, s).

Methyl (3S,4R)-3-[(S)-2-naphthylmethoxyacyl]oxycarbonyl-4-methyltetradecanoate (12). This was obtained in an 80% yield (tg 22.9 min, 85.2% ee). ¹H-NMR (CDCl₃) δ: 0.69 (3H, d, J = 6.8 Hz, 0.89 (3H, t, J = 6.8 Hz), 0.77–1.31 (18H, m), 1.52 (1H, m), 2.49 (1H, dd, J = 15.6, 4.4 Hz), 2.53 (1H, dd, J = 15.6, 8.8 Hz), 3.46 (3H, s), 3.60 (3H, s), 4.90 (1H, s), 5.26 (1H, ddd, J = 8.8, 4.4, 4.0 Hz), 7.50 (3H, m), 7.82 (3H, m), 7.90 (1H, s).

Methyl (3S,4R)-3-[(S)-2-naphthylmethoxyacyl]oxycarbonyl-4-methyltetradecanoate (13). This was obtained in a 73% yield (tg 23.1 min, 77.8% ee). ¹H-NMR (CDCl₃) δ: 0.62 (3H, d, J = 6.8 Hz, 0.89 (3H, t, J = 6.8 Hz), 0.94–1.30 (18H, m), 1.56 (1H, m), 2.53 (2H, m) 3.46 (3H, s), 3.58 (3H, s), 4.90 (1H, s), 5.26 (1H, td, J = 6.0, 5.6 Hz), 7.51 (3H, m), 7.83 (3H, m), 7.91 (1H, s).

Methyl (3S,4S)-3-[(S)-2-naphthylmethoxyacyl]oxycarbonyl-4-methyltetradecanoate (14). This was obtained in a 70% yield (tg 16.1 min, 75.2% ee). ¹H-NMR (CDCl₃) δ: 0.85 (3H, d, J = 6.8 Hz, 0.88 (3H, t, J = 6.8 Hz), 1.18–1.33 (18H, m), 1.81 (1H, m), 2.40 (1H, dd, J = 15.6, 4.4 Hz), 2.45 (1H, dd, J = 15.6, 8.8 Hz), 3.12 (3H, s), 3.45 (3H, s), 4.90 (1H, s), 5.26 (1H, ddd, J = 8.8, 5.2, 4.4 Hz), 7.51 (3H, m), 7.83 (3H, m), 7.90 (1H, s).

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References


