Synthesis and Absolute Configuration of (+)-8-Hydroxyhexadecanoic Acid, an Endogenous Inhibitor for Spore Germination in *Lygodium japonicum*

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(+)-2-Aminodecanoic acid was converted in 9 steps to (+)-8-hydroxyhexadecanoic acid, an endogenous inhibitor for spore germination in *Lygodium japonicum*, establishing its absolute configuration to be S.

In 1965 Tulloch isolated (+)-8-hydroxyhexadecanoic acid 1a from the spores of *Lycopodium complanatum*1). The structural proposal was based on its conversion to methyl 8-oxohexadecanoate which was identical with the synthetic ester prepared by chain elongation of 6-oxotetradecanoic acid.1) However, no attempt has been reported during these seventeen years to determine the absolute configuration at C-8 of (+)-1a. Due to the remote location of the asymmetric carbon atom from the terminal carboxyl group, it is rather difficult to clarify its absolute configuration either by degradation or by synthesis. Re-isolation of (+)-1a as an endogenous inhibitor for spore germination in *Lygodium japonicum* was reported in 1980 by Yamane et al.2) This information prompted us to undertake the stereochemical studies on the acid by synthetic means. Our synthesis started from (+)-(−)-2-aminodecanoic acid (decylene) 2a and allowed us to assign the S-configuration to (+)-1a as depicted in the formula.** The key-step in the present synthesis is the nucleophilic ring opening of an optically active epoxide (S)-1.

(+)-2-Aminodecanoic acid 2a was prepared in the usual manner starting from n-octyl bromide and diethyl acetaminomalonate in 78.5% yield. The acid (±)-2a gave the corresponding N-chloroacetyl derivative (±)-2b in 61.5% yield.3) Enzymatic resolution of (±)-2b with *Aspergillus* amino acylase yielded the known (S)-(−)-2-aminodecanoic acid 2a, \([\alpha]^{D}_{D} +28.7^\circ\) (AcOH) [lit.3) \([\alpha]^{D}_{D} +31.0^\circ\) (AcOH)]. This was deaminated with nitrous acid in the usual manner4) to give (S)-(−)-2-hydroxydecanoic acid 3, mp 73～74°C, \([\alpha]^{D}_{D} +5.0^\circ\) (CHCl₃) [lit.5) mp 77.6～78.0°C, \([\alpha]^{D}_{D} +5.3^\circ\) (CHCl₃)], in 57.7% yield. The deamination is known to proceed with retention of the configuration.6) The optical purity of our (S)-3 was estimated to be ∼94% \([5.0/5.3 \times 100]\) by comparison of its specific rotation with that of Horn's (S)-3 which was prepared from optically pure (S)-malic acid.5) This estimation was supported by the NMR measurements of the methyl esters of (±)-3 and (S)-3 in the presence of tris [3-(heptafluoropropylhydroxy-methylene)-d-camphorato] europium(III) [Eu(hfc)₃]. In the case of the methyl ester of (±)-3, splitting of the OCH₃ signal was observed when Eu(hfc)₃ was added, while in the case of the methyl ester of (S)-3, the OCH₃ signal remained as a singlet even in the presence of the shift reagent. This means that

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** The synthesis was first carried out starting from (±)-2a so as to establish the reaction condition for each step. The synthesis of both (±)-1a and (+)-1a is described in Experimental.
our \((S)-3\) was nearly optically pure. Reduction of \((S)-3\) with lithium aluminum hydride gave a crystalline diol \((S)-4\) in 92.4\% yield. Conversion of the diol \((S)-4\) into the key epoxide \((S)-7\) was executed in a similar manner to that described previously for other epoxides.\(^7\)\(^8\) The diol \((S)-4\) was first treated with 30\% hydrogen bromide in acetic acid to give a mixture of the acetoxy–bromides \(5\) and \(6\). The mixture afforded the desired epoxide \((S)-7\) upon treatment with sodium methoxide in methanol in a yield of 68.1\%. The epoxide \((S)-7\) was treated with 6-tetrahydropyranoylhexylmagnesium bromide\(^9\) in the presence of 10 mol\% of cuprous iodide\(^10\) to give a crystalline alcohol \((S)-8a\) in 86.1\% yield. Acetylation of \((S)-8a\) with acetic anhydride and pyridine in the presence of 4-(\(N,N\)-dimethylamino)pyridine afforded the corresponding acetate \((S)-8b\) in 93.2\% yield. Deprotection of the tetrahydropyranoylated hydroxyl group was effected with \(p\)-toluenesulfonic acid in methanol to give a diol monoacetate \((S)-8c\) in 92.4\% yield. This was oxidized with the Jones chromic acid to give an oily acetoxy acid \((S)-\)\(8b\), which was hydrolyzed to give \((S)-8\)-hydroxyhexadecanoic acid \(1a\), mp 77~79.5\(^\circ\)C, \([\alpha]_D\)\(^{12}\) +0.3° (c=19.5, CHCl\(_3\); lit.\(^2\) mp 78~79\(^\circ\)C, \([\alpha]_D^{25}\) +0.6° (c=3.3, MeOH)), in 59.8\% yield from \((S)-8c\). Our synthetic acid \(1a\) was proved to be identical with the natural acid kindly provided by Professor N. Takahashi and Dr. H. Yamane on the basis of mixed mp determination and IR spectral comparison. Therefore, in conclusion, the \(S\) absolute configuration was unequivocally assigned to \((+)-8\)-hydroxyhexadecanoic acid by the present synthesis of the natural product itself.

**EXPERIMENTAL**

All bps and mps were uncorrected. IR spectra were determined as films or as nujol mulls on a Jasco A-102 spectrometer. NMR spectra were recorded at 60 MHz with TMS as an internal standard on a Hitachi R-24A spectrometer. Optical rotations were measured on a Jasco DIP-140 automatic polarimeter.

\((\pm)-2\)-Aminodecanoic acid \((\pm)-2a\). A solution of sodium ethoxide in ethanol was prepared from sodium (3.47 g) and ethanol (75 ml). To this solution was added a solution of diethyl acetaminomalonate (32.58 g) in ethanol (80 ml). After the addition of \(n\)-octyl bromide (35 g), the mixture was stirred and heated under reflux for 16 hr. It was then concentrated \textit{in vacuo} to remove the ethanol. The residue was diluted with water and extracted with ether. The ether extract was concentrated \textit{in vacuo}. The residue was mixed with concentrated hydrochloric acid (72 ml)
and water (24 ml) and the mixture was stirred and heated under reflux for 24 hr. After cooling, the mixture was neutralized with aqueous ammonia. The precipitated crystals were collected on a filter and washed with ice-water, methanol and ether. The solid was dried in vacuo over phosphorus pentoxide to give 22.0 g (78.5%) of (±)-2a, mp 202°C (dec.), \( \nu_{\text{max}} \) cm\(^{-1}\): 3000 ~ 2870 (br, vs), 2700 (sh, s), 2600 (m), 2120 (w), 1660 (s), 1625 (s), 1610 (s), 1590 (s), 1520 (s), 1470 (s), 1465 (s), 1450 (s), 1415 (s), 1380 (m), 1370 (m), 1355 (s), 1342 (s), 1310 (m), 1280 (w), 1275 (w), 1245 (w), 1210 (w), 1160 (w), 1130 (w), 1090 (s), 1060 (w), 1035 (w), 960 (w), 890 (w), 850 (w), 795 (w), 775 (w), 750 (w), 725 (m), 705 (m); Anal. Found: C, 64.13; H, 11.23; N, 7.28. Calcd. for \( \text{C}_{10}\text{H}_{20}\text{O}_{3} \): C, 64.70; H, 10.71%.

(±)-2-Chloroacetamidodecanoic acid (±)-2b. Chloroacetyl chloride (67.8 g) and 2-n-hydroxydodecyl alcohol (525 ml) were added simultaneously during 1 hr to an ice-cooled and vigorously stirred solution of (±)-2a (56.1 g) in 2-n-hydroxydodecyl alcohol (150 ml). Subsequently the mixture was left to stand for 2 hr at room temperature and acidified with hydrochloric acid to pH 1.7. The precipitated solid was collected on a filter and dissolved in ethyl acetate. The solution was washed with water, dried over magnesium sulfate and concentrated in vacuo. The residue was recrystallized from acetonitrile–petroleum ether to give 51.7 g (61.5%) of (±)-2b, mp 86 ~ 87°C, \( \nu_{\text{max}} \) cm\(^{-1}\): 3375 (s), 3100 ~ 3000 (br. s), 2900 (m), 2800 (s), 2600 ~ 2500 (br. m), 2400 (m), 1720 (s), 1700 (s), 1620 (s), 1530 (s), 1420 (m), 1400 (m), 1350 (w), 1340 (sh, w), 1302 (w), 1280 (w), 1238 (m), 1216 (m), 1180 (m), 1144 (m), 1120 (w), 1106 (w), 998 (w), 900 (m), 848 (w), 780 (m), 770 (sh, m), 740 (w), 650 (w), NMR \( \delta \) (CDCl\(_3\)) 0.85 (3H, deformed t, \( \nu = 5.5\)Hz), 1.0 ~ 2.2 (14H, m, 12.2 br. s), 4.00 (2H, s), 4.50 (1H, m), 7.00 (1H, d, \( J = 7\)Hz), 13.50 (1H, s, -CO\(_2\)H); Anal. Found: C, 54.77; H, 8.25; N, 5.27.

Calcd. for \( \text{C}_{12}\text{H}_{22}\text{O}_{3} \): C, 54.64; H, 8.41, N, 13.50%. Calcd. for \( \text{C}_{12}\text{H}_{22}\text{O}_{3} \): C, 54.77; H, 8.15; N, 13.50%.

1.2-Decanediol 4.

(a) Racemate: A solution of (+)-3 (984 mg) in dry THF (1.2 ml) was added dropwise to a stirred suspension of LAH (369 mg) in dry THF (6 ml). The mixture was stirred and heated under reflux for 2 hr. After cooling, the excess LAH was destroyed by the addition of a 10% potassium hydroxide solution (0.43 g) and water (0.68 ml). The mixture was stirred and heated under reflux for 10 min and filtered with suction. The solid was washed with hot THF and the combined filtrate and washings were concentrated in vacuo. The residue was dissolved in ether. The ether solution was dried over sodium sulfate and concentrated in vacuo to give 777 mg (85.3%) of (±)-4, mp 42°C after recrystallization from ether–petroleum ether, \( \nu_{\text{max}} \) cm\(^{-1}\): 3360 (br. s), 1130 (w), 1060 (br. m), 930 (w), 870 (w), 720 (w); NMR \( \delta \) (CDCl\(_3\)) 0.88 (3H, deformed t, \( J = 5.5\)Hz), ~ 1.28 (14H, br. s), 3.05 ~ 3.80 (3H, m), 4.20 (2H, s, -OH); Anal. Found: C, 69.36; H, 12.47.

(b) (S)-Enantiomer: In the same manner as described above (S)-(+)-2a (5.0 g) yielded 2.9 g (57.7%) of (S)-3, mp 73 ~ 74°C, \( [\alpha]_{D}^{2} \) + 5.0° (c = 0.8, CHCl\(_3\)); IR \( \nu_{\text{max}} \) cm\(^{-1}\): 3450 (m), ~ 3200 ~ 2800 (br. s), 1740 (s), 1460 (m), 1375 (w), 1260 (s), 1180 (w), 1135 (m), 1090 (s), 1030 (w), 900 (w), ~ 840 (br. w), 760 (w), 720 (w), 650 (w). The NMR spectrum of (S)-3 was identical with that of the racemate.

2-Hydroxydecanoic acid 3.

(a) Racemate: (±)-2a (2.74 g) was dissolved in 2N-sulfuric acid (11 ml) by heating at 80°C. Then a solution of sodium nitrite (1.61 g) in water (19 ml) was added dropwise to the stirred solution of (±)-2a during 5 hr. The mixture was left to stand overnight at room temperature. This was extracted with ether and the extract was concentrated in vacuo. The residue was next mixed with benzene and the mixture was concentrated in vacuo. This procedure was repeated three times to remove water. The residue was recrystallized from ether–petroleum ether to give 1.1 g (40%) of (±)-3, mp 63°C, \( \nu_{\text{max}} \) cm\(^{-1}\): 3450 (m), 3400 (s), ~ 3200 ~ 2800 (br. vs), 2600 (br. m), 1705 (vs), 1465 (s), 1460 (s), 1375 (m), 1335 (m), 1310 (m), 1290 (m), 1250 (m), 1220 (s), 1200 (m), 1125 (m), 1090 (s), 1030 (w), 960 (w), 930 ~ 900 (br. w), 770 (m), 720 (w), 690 (m); NMR \( \delta \) (CDCl\(_3\)) 0.85 (3H, deformed t, \( J = 5.5\)Hz), ~ 1.25 (14H, br), 4.20 (1H, t, \( J = 6\)Hz), 7.28 (2H, br, -OH and -CO\(_2\)H); Anal. Found: C, 63.65; H, 10.62. Calcd. for \( \text{C}_{12}\text{H}_{20}\text{O}_{3} \): C, 63.80, H, 10.71%.

(b) (S)-Enantiomer: In the same manner as described above (S)-(+)-2a (5.0 g) yielded 2.9 g (57.7%) of (S)-3, mp 73 ~ 74°C, \( [\alpha]_{D}^{2} \) + 5.0° (c = 0.8, CHCl\(_3\)); IR \( \nu_{\text{max}} \) cm\(^{-1}\): 3450 (m), ~ 3200 ~ 2400 (br. s), 1740 (s), 1460 (m), 1375 (w), 1260 (s), 1180 (w), 1135 (m), 1090 (s), 1030 (w), 900 (w), ~ 840 (br. w), 760 (w), 720 (w), 650 (w). The NMR spectrum of (S)-3 was identical with that of the racemate.

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C_{10}H_{22}O_2: C, 68.92; H, 12.72%.

(b) (S)-Enantiomer. In the same manner as described above (S)-3 (2.9 g) yielded 2.48 g (92.4%) of (S)-4, mp 53~54°C, [\alpha]_D^{22} +11.9° (c = 0.431, MeOH); IR \nu_{\text{max}} cm^{-1}: 3350 (br. s), 2920 (s), 2850 (s), 2550 (w), 2430 (w), 2350 (w), 1470 (s), 1460 (m), 1370 (w), 1330 (m), 1300 (m), 1200 (w), 1130 (m), 1100 (s), 1060 (s), 1040 (m), 1015 (m), 1000 (m), 970 (m), 920 (w), 870 (s), 840 (m), 750 (w), 720 (m); NMR (CDCl_3): 0.86 (3H, deformed t, J = 5.5 Hz), 1.28 (14H, br. s), 3.2~3.8 (5H, m); Anal. Found: C, 68.86; H, 12.75. Calcd. for C_{10}H_{22}O_2: C, 68.92; H, 12.72%.

1,2-Epoxydecane 7.

(a) Racemate: A 30% solution of hydrogen bromide in acetic acid (5.2 g) was added to stirred and ice-cooled (+)-4 (1.28 g). The ice-bath was removed after 5 min and the mixture was stirred for 3 hr at room temperature. The mixture was diluted with ice-water, neutralized with sodium carbonate and extracted with ether. The ether extract was dried over magnesium sulfate and concentrated in vacuo to give 1.66 g of a mixture of (+)-5 and (+)-6, IR \nu_{\text{max}} cm^{-1}: 3050 (w), 2950 (s), 2930 (vs), 2850 (s), 1745 (vs), 1460 (m), 1430 (w), 1370 (m), 1230 (vs), 1020 (m), 930 (w), 720 (w). The mixture of 5 and 6 was stirred with a solution of potassium hydroxide (1.84 g) in ethylene glycol (2 ml) and water (2 ml) for 2 hr at room temperature, diluted with water and extracted with a small amount of ether. The ether solution was washed with water and brine, dried over potassium carbonate, concentrated through a Vigreaux column and the residue distilled in vacuo, bp 125~131°C/95 mmHg. The distillate was further purified by preparative TLC to give 209 mg (18.2%) of (±)-7, IR \nu_{\text{max}} cm^{-1}: 3050 (w), 2950 (m), 2925 (s), 2850 (s), 1745 (vs), 1640 (m), 1430 (w), 1370 (w), 1230 (vs), 1020 (m), 930 (w), 720 (w); NMR (CDCl_3) 0.87 (3H, deformed t, J = 5.5 Hz), 1.26 (14H, br. s), 2.18~2.35 (1H, m), 2.45~2.82 (2H, m).

(b) (S)-Enantiomer. In the same manner as described above (S)-4 (2.38 g) yielded 3.64 g of a mixture of (5)-5 and (5)-6. To the stirred solution of the mixture above (S)-4 (2.38 g) yielded 2.48 g of a mixture of (5)-5 and (5)-6, IR \nu_{\text{max}} cm^{-1}: 3050 (w), 2950 (m), 2925 (s), 2850 (s), 1745 (vs), 1640 (m), 1430 (w), 1370 (w), 1230 (vs), 1020 (m), 930 (w), 720 (w); NMR (CDCl_3) 0.87 (3H, deformed t, J = 5.5 Hz), 1.26 (14H, br. s), 2.18~2.35 (1H, m), 2.45~2.82 (2H, m).

1-Tetrahydropyranyloxy-8-hexadecanol 8a.

(a) Racemate: A Grignard reagent was prepared from 6-tetrahydropyranyloxyhexyl bromide (1.696 g) and magnesium (0.154 g) in dry THF (12 ml). This was added dropwise to a stirred and cooled suspension of cuprous iodide (122 mg) in dry THF (5 ml) at ~30°C under argon. Stirring was continued for 5 min after this addition and then a solution of (±)-7 (0.2 g) in dry THF (2 ml) was added to the stirred mixture. The dry ice-acetone bath was removed, the mixture kept at 0°C for 2 hr, then poured into an ice-ammonium chloride solution and extracted with n-hexane. The hexane solution was washed with brine, dried over magnesium sulfate and concentrated in vacuo. The residue was purified by column chromatography followed by preparative TLC to give 41 mg (9.4%) of (±)-8a, IR \nu_{\text{max}} cm^{-1}: 3450 (m), 2930 (vs), 2850 (vs), 1465 (m), 1450 (m), 1440 (m), 1380 (w), 1365 (w), 1350 (m), 1320 (w), 1280 (w), 1270 (w), 1260 (w), 1200 (m), 1180 (m), 1140 (s), 1120 (s), 1080 (s), 1030 (s), 1020 (s), 985 (m), 900 (m), 865 (m), 810 (m), 720 (w); NMR (CDCl_3) 0.86 (3H, deformed t, J = 5.5 Hz), 1.0~1.8 (34H, m), 3.0~3.9 (5H, m), 4.43 (1H, s).

(b) (S)-Enantiomer: In this case the procedure was slightly modified: i) The Grignard reagent was prepared under argon. ii) The amount of cuprous iodide was increased to 17 mol%. iii) Three equivalents of the Grignard reagent was used for 1 eq of (S)-7. iv) During the addition of (S)-7 to the Grignard reagent, the mixture was kept at ~30°C, the temperature then raised to 0°C and finally the mixture stirred overnight at 5°C. By this procedure the yield was significantly improved. Starting from 1.18 g of (S)-7, 2.22 g (86.1%) of (S)-8a was obtained after chromatographic purification. A portion was recrystallized from ether petroleum ether to give an analytical sample, mp 28~29°C, [\alpha]_D^{22} +1.7° (c = 2.2, MeOH); Anal. Found: C, 73.63; H, 12.25. Calcd. for C_{22}H_{45}O_2: C, 73.63; H, 12.36%. The IR and NMR spectra were identical with those of the racemate.

8-Acetoxy-1-tetrahydropyranyloxyhexadecane 8b.

(a) Racemate: Acetic anhydride (0.5 ml) and 4-(N,N-dimethylamino) pyridine (5 mg) was added to a solution of (±)-8a (41 mg) in dry pyridine (1 ml) and the mixture stirred overnight at room temperature. It was then poured into ice-water and extracted with n-hexane. The hexane solution was washed with cupric sulfate solution, water, sodium bicarbonate solution and water, dried over sodium sulfate and concentrated in vacuo to give 43.7 mg of (±)-8b as an oil, IR \nu_{\text{max}} cm^{-1}: 2930 (vs), 2850 (s), 1740 (w), 1645 (m), 1460 (m), 1370 (m), 1350 (m), 1320 (w), 1240 (vs), 1200 (m), 1180 (w), 1160 (w), 1135 (m), 1120 (m), 1080 (m), 1070 (m), 1030 (s), 1020 (s), 985 (m), 970 (m), 900 (w), 870 (w), 840 (w), 810 (w), 720 (w); NMR (CDCl_3) 0.85 (3H, deformed t, J = 5.5 Hz), 1.0~1.8 (34H, m), 1.93 (3H, s), 3.0~3.9 (4H, m), 4.50 (1H, s), 4.6~5.0 (1H, br).
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(b) (S)-Enantiomer In the same manner as described above (S)-8b (1.89 g) yielded (S)-8b (1.98 g). A small portion was purified by preparative TLC for analytical purposes, \( R_f = 0.459 \); \( \delta_{31} = 0.31^\circ (c = 1.8, \text{ hexane}) \); Anal. Found: C, 71.91; H, 11.66. Calcd. for C_{23}H_{44}O_4: C, 71.83; H, 12.02.

The IR and NMR spectra were identical with those of the racemate.

8-Acetoxy-1-hexadecanol 8c.

(a) Racemate: A trace amount of \( p \)-toluenesulfonic acid was added to a solution of \((\pm)-8b\) (43.7 mg) in methanol (1 ml). The mixture was stirred for 6 hr at room temperature, poured into water and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate and concentrated in vacuo. The residue was added to a solution of (±)-8b (43.7 mg) in acetone (1 ml). The mixture was stirred for 6 hr at room temperature, poured into water and extracted with ether. The ether solution was then poured into water, acidified with hydrochloric acid and extracted with ether. The ether solution was washed with brine, dried over sodium sulfate and concentrated in vacuo to give 5 mg (23% from \((\pm)-8c\)) of \((\pm)-1a\) after recrystallization from acetone, mp 73~74°C, IR \( \nu_{max} \text{ cm}^{-1} \): 3640 (w), 3400 (s), 3200~2400 (br. m), 1700 (br s), 1410 (m), 1340 (m), 1310 (w), 1290 (w), 1270 (w), 1250 (w), 1230 (w), 1210 (w), 1195 (w), 1130 (w), 1100 (w), 1070 (w), 1050 (w), 1020 (m), 990 (w), 900 (m), 855 (w), 840 (w), 790 (w), 720 (m), 680 (w); NMR \( \delta \) (CDCl_3) 0.85 (3H, m), 1.0~1.8 (24H, br. s), 1.93 (3H, s), 2.1 (2H, t, \( J = 5.5 \text{ Hz} \)), 4.5~5.0 (1H, br. m).

(b) (S)-Enantiomer In the same manner as described above (S)-8b (43.7 mg) yielded 0.359 g of (S)-1a (59.8%) from (S)-8c, which was recrystallized from acetone to give fine needles, mp 77~78.5°C, IR \( \nu_{max} \text{ cm}^{-1} \): 3320 (s), 3300 (s), 3000~2400 (br. m), 1700 (vs), 1410 (m), 1350 (m), 1230 (m), 1285 (m), 1265 (w), 1250 (w), 1230 (w), 1205 (w), 1190 (w), 1150 (w), 1130 (m), 1100 (m), 1065 (m), 1050 (m), 1030 (w), 1010 (w), 990 (w), 930 (br, m), 900 (m), 850 (w), 790 (w), 720 (m); Anal. Found: C, 70.39; H, 11.84%. The IR spectrum was identical with that of the natural product, mp 76~77°C.

NMR measurements of the methyl esters of \((\pm)-3\) and \((\pm)-3\) in the presence of Eu(hfc)_3. The racemate (57 mg) and Eu(hfc)_3 (80 mg) were dissolved in CCl_4 (0.2 ml). The OCH_3 signal was observed as a doublet (\( \Delta \delta \approx 0.05 \)). With a solution of the (S)-isomer (62 mg) in CCl_4 (0.2 ml) in the presence of Eu(hfc)_3 (80 mg), no splitting of the OCH_3 signal was observed.

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