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Synthesis of the Four Stereoisomers of 2,6-Dimethyloctane-1,8-dioic Acid, a Component of the Copulation Release Pheromone of the Cowpea Weevil, *Callosobruchus maculatus*

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A diastereomeric mixture and the four stereoisomers of 2,6-dimethyloctane-1,8-dioic acid (2), a copulation release pheromone of the cowpea weevil, *Callosobruchus maculatus*, were synthesized. The stereoisomeric purities of the four synthetic isomers of 2 were determined by the HPLC analyses of their bis-2-(2,3-anthracenedicarboximide)-1-cyclohexyl esters.

Key words: copulation release pheromone; cowpea weevil; *Callosobruchus maculatus*; 2-(2,3-anthracenedicarboximide)-1-cyclohexyl ester

The cowpea weevil, *Callosobruchus maculatus*, and the azuki bean weevil, *C. chinensis*, are serious cosmopolitan pests of stored products such as cowpea, azuki, and-or other pulses. Various studies have been conducted on the pheromones of the azuki bean weevil, *C. chinensis*,[1–7] and the copulation release pheromone (electin) was identified as callosobruchusic acid {(*E*)-3,7-dimethyl-2-octene-1,8-dioic acid (**1**)} by Yamamoto *et al.* in 1981 (Fig. 1).[1] Synthetic studies[2–7] and the biological activities[4] of **1** were reported, but the absolute configuration of the natural product remains obscure. On the other hand, during the course of pest-management programs, evidence for the presence of the sex pheromone of *C. maculatus* was reported by Rup and Sharma in 1978.[8] The biology associated with female calling and the production of the pheromone were reported by Qi and Burkholder in 1982.[9] Identification of the sex pheromones of *C. maculatus* was reported by Phillips *et al.* in 1996.[10] Recently, Ohsawa and his co-workers identified a copulation release pheromone of *C. maculatus* from the acidic fraction of the crude extracts of about 3,000 females (Fig. 1) (K. Ohsawa, personal communication). The pheromone induces protrusion of the genital organ with the neutral fraction of the extracts, which contain some hydrocarbons. The structure of the pheromone was proposed to be 2,6-dimethyloctane-1,8-dioic acid (**2**) on the basis of the GC–MS spectrum of the corresponding partially purified methyl esters. Since a pure sample of **2** was unavailable due to the scarcity of the material, such physical properties as IR, NMR, and $[\alpha]_D$ of the natural product were unavailable. In order to determine the absolute configuration of the natural product and clarify the biological activity-structure relationship, we became interested in synthesizing the four possible stereoisomers of **2**. This paper describes the synthesis of the diastereomeric mixture and the four stereoisomers of 2,6-dimethyloctane-1,8-dioic acid (**2**), a copulation release pheromone of the cowpea weevil, *C. maculatus*. It also describes HPLC analyses of their bis-2-(2,3-anthracenedicarboximide)-1-cyclohexyl esters.[11–18]

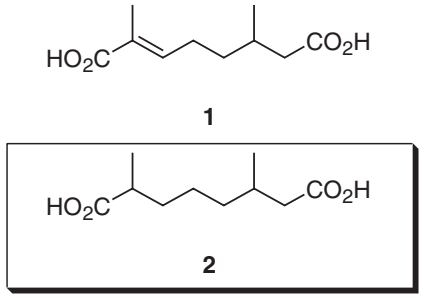

Fig. 1. The Structures of Copulation Release Pheromones of Azuki Bean and Cowpea Weevils.

Results and Discussion

Our synthetic plans of **2** are shown in Scheme 1. We first planned to synthesize a diastereomeric mixture for the authentic sample of **2**. Diacid (2*RS*,6*RS*)-**2** was obtained by oxidation of corresponding diol **A**. Diol **A**

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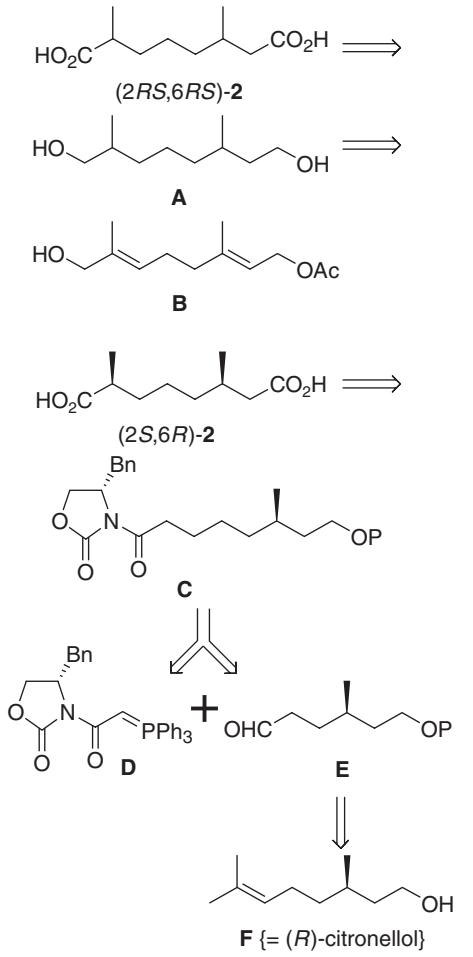
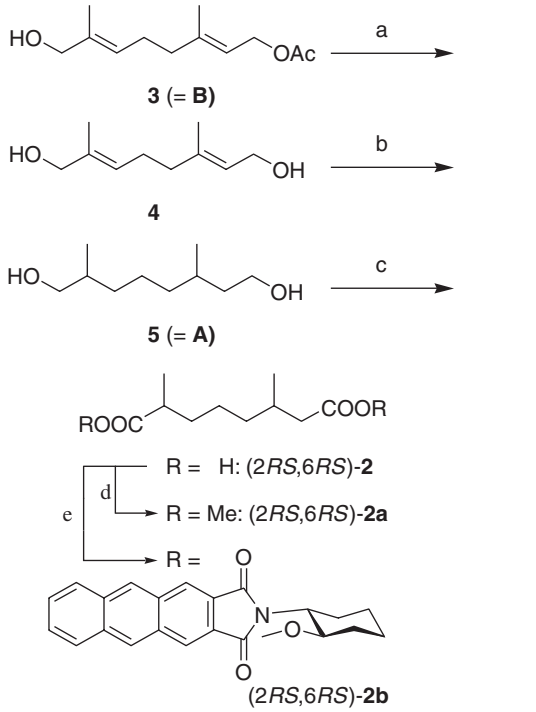


Scheme 1. Retrosynthetic Analyses of (2*RS*,6*RS*)- and (2*S*,6*R*)-**2**.



Scheme 2. Synthesis of (2*RS*,6*RS*)-**2**.
(a) KOH, MeOH, rt (97% yield). (b) PtO_2, H_2, MeOH, rt (74% yield). (c) Jones reagent, acetone, 0 °C (quant.). (d) CH_2N_2. ether (97% yield). (e) (1*S*,2*S*)-2-(2,3-anthracenedicarboximide)-1-cyclohexanol, EDC, DMAP, toluene, CH_3CN.

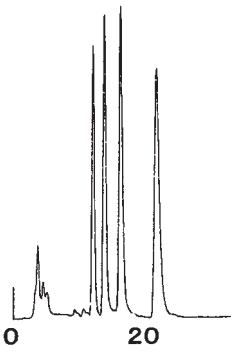
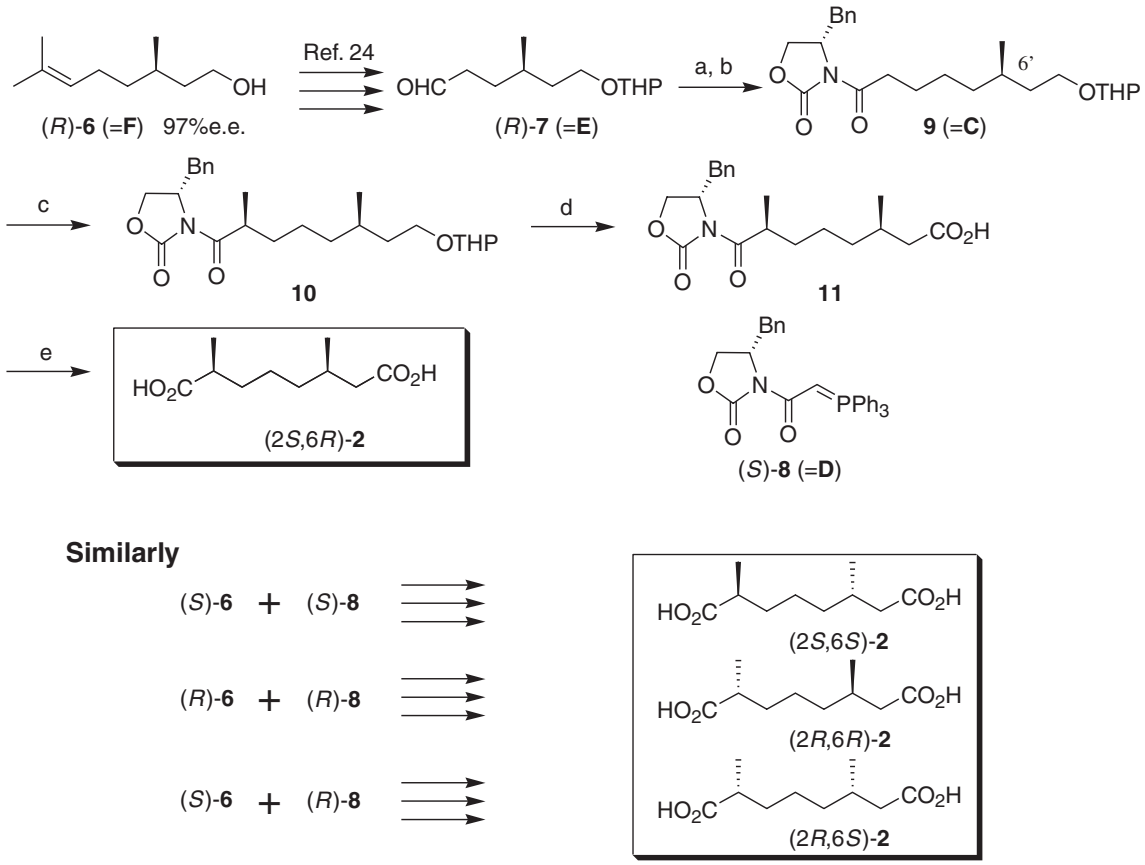


Fig. 2. Chromatogram of (1*R*,2*R*)-2Acyclo-O Ester of (2*RS*,6*RS*)-**2** (**2b**), Column: Develosil ODS-A-3, Mobile Phase: MeOH, Flow Rate: 0.8 ml/min, 20 °C.

was derived from the known compound **B**.[19] In the synthesis of optically active **2**, the methyl group of C-2 was introduced by diastereoselective Evans alkylation[20,21] of **C**. The chiral auxiliary group **D**[22,23] connected with known aldehyde **E**[24] by Wittig condensation. Aldehyde **E** was prepared from optically active citronellol (**F**). Hence we selected citronellol (**F**) as the origin of the C-6 chiral center.

Scheme 2 summarizes the synthesis of (2*RS*,6*RS*)-**2**. The known compound **3**,[19] derived from geraniol, was hydrolyzed and subsequent catalytic hydrogenation on PtO_2 gave saturated diol **5** (= **A**). Jones oxidation of **5** gave (2*RS*,6*RS*)-**2**. Since the structure of the natural **2** has been determined by GC–MS analysis of the corresponding dimethyl ester, the synthetic (2*RS*,6*RS*)-**2** was derived to dimethyl ester by treating with diazomethane to give (2*RS*,6*RS*)-**2a**. The retention time on GC analysis and the MS spectrum of the synthetic **2a** are identical with those of the natural product (K. Ohsawa, unpublished data). In order to discriminate the diastereomers, diacid (2*RS*,6*RS*)-**2** and diester (2*RS*,6*RS*)-**2a** were subjected to various analyses such as GC and HPLC with chiral or achiral stationary phases, but the diastereomers were inseparable. This problem was solved by the Ohrui–Akasaka method.[11–18] Namely, the diacid (2*RS*,6*RS*)-**2** was converted to bis-(1*R*,2*R*)-2-(2,3-anthracenedicarboximide)-1-cyclohexyl (2Acyclo-O) ester (**2b**). HPLC analysis of **2b** with an ODS column gave the four peaks (Fig. 2). This means that it is possible to discriminate the stereochemistry not only of synthetic but also of natural **2** using this method. Since the Ohrui–Akasaka method uses not UV but a fluorescence detector on HPLC analysis, the required amount of the sample is sufficient at the fmol level.[12] Thus it is a powerful tool for pheromone chemistry, which often suffers from scarcity of the requisite pheromones.



Scheme 3. Synthesis of the Four Stereoisomers of **2**.
(a) (*S*)-**8**, benzene, reflux (b) catalyst, H_2, AcOEt (2 steps, 80% yield). (c) NaHMDS, MeI, THF, −78 °C (84% yield). (d) Jones reagent, acetone (89% yield). (e) LiOH, H_2O_2, THF, H_2O (96% yield).

Although we succeeded in discriminating the four isomers of **2** by the Ohrui–Akasaka method, the absolute configuration of each component remained unidentified. In order to determine their absolute configurations, we synthesized the four stereoisomers of **2**. Scheme 3 summarizes our stereoselective synthesis of **2**. Optically active (97% e.e.) citronellol (*R*)-**6** (= **F**) was converted to known aldehyde **7** (= **E**) in the reported manner.[24] Aldehyde **7** was coupled with a chiral auxiliary group (*S*)-**8** (= **D**)[22,23] by Wittig reaction, followed by catalytic hydrogenation to give **9** (= **C**). In this step, we initially used Pd/C for the syntheses of (2*S*,6*R*)- and (2*R*,6*S*)-**2**. However, as discussed below, partial racemization at C-6′ of **9** was observed. In order to avoid this racemization, we turned to the use of PtO_2 as a catalyst for the synthesis of (2*R*,6*R*)- and (2*S*,6*S*)-**2**. The diastereoselective Evans alkylation[20,21] of **9** with methyl iodide in the presence of NaHMDS as a base gave **10**. Deprotection of the THP group and simultaneous oxidation of **10** were carried out by Jones oxidation to give **11**. Finally, the chiral auxiliary group of **11** was removed by LiOOH[25] to give (2*S*,6*R*)-**2**. The overall yield of (2*S*,6*R*)-**2** was 57% from the known compound **7**. Similarly, the other three isomers of **2** were synthesized.

With the four stereoisomers of **2** in hand, the purities of each sample were determined by the Ohrui–Akasaka method. Figure 3 shows the chromatograms of each sample. The fastest-moving isomer was (2*S*,6*R*)-**2b**, and the retention times were prolonged as follows: (2*S*,6*S*) < (2*R*,6*R*) < (2*R*,6*S*). Table 1 shows the chromatographic data for the samples. According to the HPLC analysis data, the diastereoselectivities of Evans alkylation of C-2 were estimated to be about 93:7 (entry 4) to 97:3 (entry 3). On the other hand, partial racemization at C-6 of the two samples was observed by comparison with the enantiomeric purity of the starting (*R*)- and (*S*)-citronellol (**6**) (entries 1 and 4). The enantiomeric purity of both the starting (*R*)- and (*S*)-citronellol (**6**) was 97% e.e., but those of the synthetic (2*S*,6*R*)- and (2*R*,6*S*)-**2** at C-6 were 94.4 and 88.8% e.e. respectively. This partial racemization is probably caused by catalytic hydrogenation of the double bond with Pd/C as a catalyst. Indeed, this partial racemization was not observed in entries 2 and 3 (97% e.e. at C-6), in which we used PtO_2 as a catalyst in the hydrogenation step. In the course of hydrogenation, the related palladium catalyst-mediated partial racemization was observed at a branched chain.[26] In spite of the possibility of partial racemization, palladium catalysts

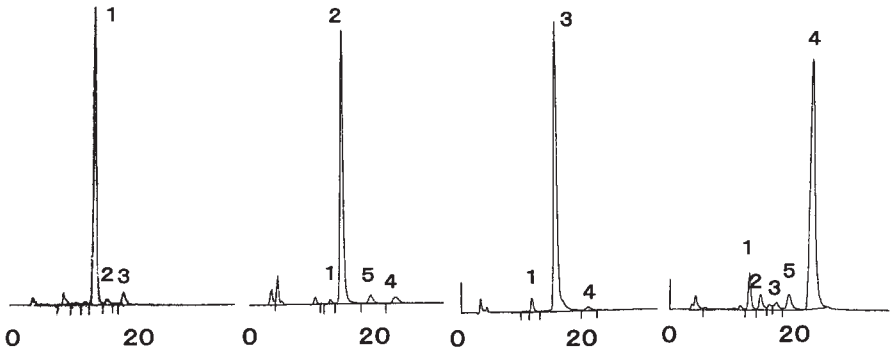


Fig. 3. Chromatograms of (1*R*,2*R*)-2Acyclo-O Esters of Synthetic **2**; 1: (2*S*,6*R*), 2: (2*S*,6*S*), 3: (2*R*,6*R*), 4: (2*R*,6*S*), 5: Unknown.

Table 1. Stereoisomeric Purities of the Synthetic **2** Determined by HPLC Analyses of **2b**

Entry	Sample	Retention time (min)[b]	Peak area ratio (%)[a]			
			(2*S*,6*R*)	(2*S*,6*S*)	(2*R*,6*R*)	(2*R*,6*S*)
1	(2*S*,6*R*)-**2b**	12.6	91.9	2.8	5.3	nd[c]
2	(2*S*,6*S*)-**2b**	14.4	1.0	94.7	nd[c]	4.3
3	(2*R*,6*R*)-**2b**	16.9	3.3	nd[c]	95.2	1.5
4	(2*R*,6*S*)-**2b**	22.6	5.4	1.9	0.2	92.5

[a]The detail of the analytical conditions are described in Experimental.
[b]The retention time of the major peak.
[c]Not detected.

are widely used in synthetic studies. The maintenance of the stereoisomeric purity of a synthetic product with a branched-chain after the hydrogenation step by such a highly sensitive analytical method as the Ohrui–Akasaka method should be confirmed. Although the stereoisomeric purity of some synthetic sample was slightly diminished, the purity of each sample was estimated to be $>91\%$. In order to study the enantio-specifity of pheromone perception, it is known that samples with $>85\%$ optical purity are suitable in most cases.[27] Thus our synthetic samples can be used to study the enantio-specifity of the pheromone perception of *C. maculatus*.

Conclusion

Synthesis of the diastereomeric mixture and the four stereoisomers of **2** was achieved. The four synthetic stereoisomers were discriminated from each other by HPLC analysis of the corresponding bis-(1*S*,2*S*)-2-(2,3-anthracenedicarboximide)-1-cyclohexyl ester. The optical purities of the synthetic **2** were determined by the same method. Our synthetic samples were pure enough to use in the study of the enantio-specifity of the pheromone perception of *C. maculatus*. Since the Ohrui–Akasaka method requires an fmol level sample, it is a powerful tool for the determination of the absolute configuration of the natural product. Bioassay of the synthetic samples and determination of the absolute configuration of the natural product using this analytical method are currently under way.

Experimental

Optical rotation values were measured on a Jasco DIP-140. IR spectra were measured using a Shimadzu IR-470 spectrometer. NMR spectra were recorded with a Jeol JNM-A400 operating at 400 MHz for ^{1}H spectra and 100 MHz for ^{13}C NMR spectra. Chemical shifts are reported as ppm relative to $CHCl_3$ measured from the solvent resonance (7.24 ppm). Mass spectra were recorded with a Shimadzu GCMS-QP 2000A running in the EI scan mode. Elemental compositions were analyzed on a J-Science Microcorder JM10. Column chromatography was carried out using silica gel (Wakogel C-200).

*(2E,6E)-2,6-Dimethyl-2,6-octadiene-1,8-diol (**4**).* Acetate **3** (50 mg, 0.24 mmol) was dissolved in MeOH (8 ml), then 2 M KOH (4 ml) was added. The reaction mixture was stirred for 5 min and then poured into water, and the aqueous mixture was extracted with ether and the organic phases were washed with brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by column chromatography with hexane/EtOAc (5:1) to give **4** as a colorless oil (39 mg, 97%). IR ν_{max} (film) cm^{-1}: 3330 (br. s, O–H), 2900 (s, C–H), 1000 (s, C–O), 590 (w). NMR δ_H ($CDCl_3$): 1.65 (s, 3H, 6-CH_3), 1.67 (s, 3H, 2-CH_3), 2.01–2.19 (m, 4H, 4, 5-H), 3.98 (s, 2H, 1-H), 4.14 (d, $J = 7.3$ Hz, 2H, 8-H), 5.36 (m, 2H, 3, 7-H). Found: C, 70.55%; H, 10.55%. Calcd. for $C_{10}H_{18}O_2$: C, 70.55%; H, 10.66%.

*(2RS,6RS)-2,6-Dimethyloctane-1,8-diol (**5**).* A solution of **4** (444 mg, 2.60 mmol) in MeOH (8 ml) was charged with PtO_2 (10 mg, 0.05 mmol). The reaction mixture was stirred vigorously under an atmosphere of hydrogen for 2 h. The catalyst was removed by filtration with Celite and rinsed with methanol. The solvent was evaporated and the residue was purified by column chromatography with hexane/EtOAc (5:1) to give **5** as a colorless oil (336 mg, 74%). IR ν_{max} (film) cm^{-1}: 3330 (br. s, O–H), 2900 (s, C–H), 1470 (m, C–H), 1390 (m, C–H), 1040 (s, C–O), 690 (w). NMR δ_H ($CDCl_3$): 0.87 (d, $J = 6.8$ Hz, 3H, 6-CH_3), 0.89 (d, $J = 6.8$ Hz, 3H, 2-CH_3), 1.02–1.41 (m, 6H, 3, 4, 5, 6-H), 1.55–1.63 (m, 3H, 2, 7-H), 3.37–3.51 (m, 2H, 1-H), 3.61–3.72 (m, 2H, 8-H). Found: C, 69.03%; H, 12.51%. Calcd. for $C_{10}H_{22}O_2$: C, 68.92%; H, 12.72%.

*(2RS,6RS)-2,6-Dimethyloctane-1,8-dioic acid (**2**).* To a solution of **5** (50 mg, 0.29 mmol) in acetone (4 ml), Jones reagent was added dropwise until an orange-brown color persisted. Thereafter, the reaction mixture was poured into water, the aqueous mixture was extracted with EtOAc and organic phases were washed successively with water and brine, and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by column chromatography with hexane/EtOAc (5:1) to give **2** as a colorless oil (70 mg, quant.). IR ν_{max} (film) cm^{-1}: 3100 (m, O–H), 2930 (s, C–H), 1700 (s, C=O), 1440 (m), 1300 (m), 1240 (s, C–H), 1170 (m), 1130 (w), 1020 (w), 950 (m), 800 (w), 740 (w), 690 (w), 640 (w). NMR δ_H ($CDCl_3$): 0.95 (d, $J = 6.8$ Hz, 3H, 6-CH_3), 1.16 (d, $J = 6.8$ Hz, 3H, 2-CH_3), 1.19–1.47 (m, 5H, 3, 4, 5-H), 1.65 (m, 1H, 3-H), 1.95 (m, 1H, 6-H), 2.11–2.20 (m, 1H, 7-H), 2.26–2.23 (m, 1H, 7-H), 2.46 (m, 1H, 2-H). NMR δ_C ($CDCl_3$): 16.8 (C-9), 19.7 (C-10), 24.3 (C-4), 29.8 (C-6), 33.4 (C-3), 36.2 (C-5), 39.2 (C-2), 41.3 (C-7), 179.4 (C-8), 182.9 (C-1). Found: C, 59.49%; H, 8.98%. Calcd. for $C_{10}H_{18}O_4$: C, 59.39%; H, 8.97%.

*Dimetyl (2RS,6RS)-2,6-dimetyloctanedioate (**2a**).* A solution of **2** (48 mg, 0.25 mmol) in ether (2 ml) was treated with CH_2N_2. After stirring until a yellow color persisted, the reaction mixture was evaporated to give **2a** (53 mg, 97%). IR ν_{max} (film) cm^{-1}: 2950 (s, C–H), 1740 (s, C=O), 1450 (m), 1385 (m), 1200 (br. m) (1050 (w), 840 (w), 750 (w). NMR δ_H ($CDCl_3$): 0.89 (d, $J = 6.8$ Hz, 3H, 6-CH_3), 1.12 (d, $J = 6.8$ Hz, 3H, 2-CH_3), 1.23–1.41 (m, 4H, 4, 5-H), 1.59 (m, 2H, 3-H), 1.92 (m, 1H, 6-H), 2.09 (dd, $J = 6.8$, 15.1 Hz, 1H, 7-H), 2.28 (m, 1H, 7-H), 2.41 (sxt, $J = 6.8$ Hz, 1H, 2-H), 3.64 (s, 3H, CH_3–O), 3.65 (s, 3H, CH_3–O). GC–MS analysis; column: DB-5 (30 m × 0.25 mm), carrier gas He (1.3 ml/min), 100 °C (2 min) to 220 °C (4 °C/min), $t_R = 14.2$, *m/z*: 199 (M–CH_3O^+), 171, 166, 157, 143, 139, 125, 111, 97, 88, 83, 74, 69, 59, 55 (100), 43, 41. Found: C, 62.61%; H, 9.52%. Calcd. for $C_{12}H_{22}O_4$: C, 62.58%; H, 9.63%. The retention time and MS spectrum were identical with those of the dimethylester of the natural product (K. Ohsawa, unpublished data).

*Preparations and HPLC analyses of bis-(1R,2R)-2-(2,3-anthracenedicarboximide)-1-cyclohexyl ester of 2,6-dimethyloctane-1,8-dioic acid (**2b**).* To a solution of 2,6-dimethyloctane-1,8-dioic acid (**2**) in MeCN:toluene (1:1), (1*R*,2*R*)-2-(2,3-anthracenedicarboximide)-1-cyclohexanol (2ACyclo–OH) (10 eq.), 4-*N*,*N*-dimethylaminopyridine (DMAP, catalytic amount), and 2-(3-dimethylaminopropyl)-1-ethylcarbodiimide hydrochloride (EDC, 30 eq.) were successively added. The mixture was stirred at 40 °C overnight. An aliquot was then loaded onto silica gel TLC plate (10 cm length, Silicagel 60 F_{254}, Art −5744, Merck) and developed with hexane/EtOAc (4:1, v/v). The target spot detected by fluorescence was collected, packed in a Pasteur pipette, and eluted with EtOAc/EtOH (4:1, v/v). After evaporation of the solvent with an N_2 gas stream, the residue was dissolved in MeOH and directly used for HPLC analysis. HPLC analyses: The prepared **2b** was separated on a reverse-phase column (Develosil ODS-A-3, 4.6 mm i.d. × 150 mm, Nomura Chemical, Aichi, Japan). Detection was carried out by monitoring the fluorescence intensity at 462 nm (excitation at 298 nm). The separation was performed with MeOH at a flow rate 0.8 ml/min. The column temperature was kept at 20 °C; $t_R(2S,6R) = 12.6$, $t_R(2S,6S) = 14.4$, $t_R(2R,6R) = 16.9$, $t_R(2R,6S) = 22.6$.

*(4S,6′R)-3-[6′-Methyl-8′-(tetrahydro-2H-pyran-2-yl-oxy)octanoyl]-4-phenylmethyl-1,3-oxazolidin-2-one (**9**).* A mixture of (*R*)-**7** (400 mg, 1.87 mmol) and (*S*)-**8** (1.34 g, 2.81 mmol) was dissolved in benzene. The reaction mixture was refluxed at 60 °C for 4 d and then the solvent was evaporated. The residue was purified by column chromatography with hexane/EtOAc (20:1) to give coupling compound (738 mg). This was dissolved in AcOEt (50 ml), and the solution was charged with Pd/C (6 mg, 0.03 mmol). The reaction mixture was stirred vigorously under an atomosphere of hydrogen for 2 h. The catalyst was removed by filtration with Celite and rinsed with methanol. The solvent was evaporated and the residue was purified by column chromatography with hexane/EtOAc (10:1) to give (4*S*,6′*R*)-**9** as a colorless oil (716 mg, 80%). $[\alpha]_D^{22}$ +48° (*c* 0.12, $CHCl_3$). IR ν_{max} (film) cm^{-1}: 2930 (s, C–H), 1780 (s, C=O), 1700 (s, C=O), 1460 (s), 1390 (s), 1230 (m, C–H), 1140 (m), 1030 (m), 900 (m), 870 (m), 810 (m), 750 (m), 700 (m). NMR δ_H ($CDCl_3$): 0.88 (d, $J = 6.8$ Hz, 3H, 6′-CH_3), 1.16–1.83 (m, 15H, 3′, 4′, 5′, 6′, 7′, 3″, 4″, 5″-H), 2.74 (dd, $J = 9.8$, 13.7 Hz, 1H, C*H*H–Ph), 2.91 (m, 2H, 2′-H), 3.28 (dd, $J = 3.4$, 13.7 Hz, 1H, CH*H*–Ph), 3.34–3.52, 3.72–3.87 (m, total 4H, 8′, 6″-H), 4.14 (m, 2H, 5-H), 4.55 (m, 1H, 2″-H), 4.62–4.68 (m, 1H, 4-H), 7.17–7.34 (m, 5H, Ph). Found: C, 69.08%; H, 8.48%; N, 3.39%. Calcd. for $C_{24}H_{35}NO_5$: C, 69.04%; H, 8.45%; N, 3.35%.

(4R,6′S)-isomer. In the same manner as described above, (4*R*,6′*S*)-**9** was obtained from 8.70 g of (*S*)-**7** (15.2 g, 76%). $[\alpha]_D^{22}$ −38.2° (*c* 1.10, $CHCl_3$). IR and ^{1}H NMR spectra were indistinguishable from those of (4*S*,6′*R*)-isomer. Found: C, 69.04%; H, 8.41%; N, 3.45%. Calcd. for $C_{24}H_{35}NO_5$: C, 69.04%; H, 8.45%; N, 3.35%.

(4S,6′S)-isomer. In the same manner as described above, except for using PtO_2 as a catalyst in the hydrogenolysis, (4*S*,6′*S*)-**9** was obtained from 5.27 g of (*S*)-**7** (8.60 g, 68%). $[\alpha]_D^{22}$ +33° (*c* 0.12, $CHCl_3$). IR and ^{1}H NMR spectra were indistinguishable from those of (4*S*,6′*R*)-isomer. Found: C, 69.03%; H, 8.39%; N, 3.55%. Calcd. for $C_{24}H_{35}NO_5$: C, 69.04%; H, 8.45%, N, 3.35%.

(4R,6′R)-isomer. In the same manner as described above, (4*R*,6′*R*)-**9** was obtained from 3.0 g of (*R*)-**7** (5.4 g, 81%). $[\alpha]_D^{22} = -34°$ (*c* = 0.22, $CHCl_3$). IR and ^{1}H NMR spectra were indistinguishable from those of (4*S*,6′*R*)-isomer. Found: C, 69.05%; H, 8.38%; N, 3.49%. Calcd. for $C_{24}H_{35}NO_5$: C, 69.04%; H, 8.45%; N, 3.55%.

*(4S,2′S,6′R)-3-[2′,6′-Dimethyl-8′-(tetrahydro-2H-pyran-2-yloxy)octanoyl]-4-phenylmethyl-1,3-oxazolidin-2-one (**10**).* To a cooled solution of (4*S*,6′*R*)-**9** (300 mg, 0.629 mmol) in THF (5 ml) at −78 °C, 1 M NaHMDS (0.69 ml, 0.69 mmol) in THF was added dropwise. After the reaction mixture was stirred for 30 min at the same temperature, MeI (120 ml, 1.89 mmol) was added. The solution was stirred overnight and then the reaction mixture was poured into water. The aqueous mixture was extracted with three portions of ether, and the organic phases were washed successively with water and brine and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography with hexane/EtOAc (10:1) to give **10** as a colorless oil (259 mg, 84%). $[\alpha]_D^{22}$ +49.9° (*c* 1.05, $CHCl_3$). IR ν_{max} (film) cm^{-1}: 2930 (s, C–H), 1780 (s, C=O), 1700 (s, C=O), 1460 (m), 1380 (m), 1230 (m, C–H), 1030 (m), 900 (w), 870 (w), 700 (m), 500 (w). NMR δ_H ($CDCl_3$): 0.86 (d, *J* = 6.8 Hz, 3H, 6′-CH_3), 1.16–1.83 (m, 15H, 3′, 4′, 5′, 6′, 7′, 3″, 4″, 5″-H), 1.20 (d, *J* = 6.8 Hz, 3H, 2′-CH_3), 2.74 (dd, *J* = 9.6, 13.2 Hz, 1H, C*H*H–Ph), 3.25 (dd, *J* = 3.2, 13.2 Hz, 1H, CH*H*–Ph), 3.32–3.52, 3.68–3.88 (m, total 5H, 2′, 8′, 6″-H), 4.14 (m, 2H, 5-H), 4.55 (m, 1H, 2″-H), 4.66 (m, 1H, 4-H), 7.18–7.33 (m, 5H, Ph). Found: C, 69.62%; H, 8.73%; N, 3.30%. Calcd. for $C_{25}H_{37}NO_5$: C, 69.58%; H, 8.64%; N, 3.25%.

(4S,2′S,6′S)-isomer. In the same manner as described above, (4*R*,2′*R*,6′*R*)-**10** was obtained from 7.20 g (4*S*,6′*S*)-**9** (5.87 g, 80%). $[\alpha]_D^{22}$ +46.3° (*c* 1.00, $CHCl_3$). IR and ^{1}H NMR spectra were indistinguishable from those of (4*S*,2′*S*,6′*R*)-isomer. Found: C, 69.64%; H, 8.57%; N, 3.18%. Calcd. for $C_{25}H_{37}NO_5$: C, 69.58%; H, 8.64%; N, 3.25%.

(4R,2′R,6′R)-isomer. In the same manner as described above, (4*S*,2′*S*,6′*S*)-**10** was obtained from 3.3 g of (4*R*,6′*R*)-**9** (2.8 g, 82%). $[\alpha]_D^{22}$ −49.1° (*c* 1.00, $CHCl_3$). IR and ^{1}H NMR spectra were indistinguishable from those of (4*S*,2′*S*,6′*R*)-isomer. Found: C, 69.63%; H, 8.72%; N, 3.22% Calcd. for $C_{25}H_{37}NO_5$: C, 69.58%; H, 8.64%; N, 3.25%.

(4R,2′R,6′S)-isomer. In the same manner as described above, (4*R*,2′*R*,6′*S*)-**10** was obtained from 270 mg of (4*R*,6′*S*)-**9** (230 mg, 83%). $[\alpha]_D^{22}$ −46° (*c* 0.50, $CHCl_3$). IR and ^{1}H NMR spectra were indistinguishable from those of (4*S*,2′*S*,6′*R*)-isomer. Found: C, 69.61%; H, 8.68%; N, 3.22%. Calcd. for $C_{25}H_{37}NO_5$: C, 69.58%; H, 8.64%; N, 3.25%.

*(4S,2′S,6′R)-3-(2′,6′-Dimethyl-7′-carboxyheptanoyl)-4-phenylmethyl-1,3-oxazolidin-2-one (**11**).* To a solution of (4*S*,2′*S*,6′*R*)-**10** (79 mg, 0.16 mmol) in acetone (6 ml), Jones reagent was added dropwise until an orange-brown colour persisted. Thereafter, the reaction mixture was poured into water, the aqueous mixture was extracted with three portions of EtOAc, and the organic phases were washed successively with water and brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by column chromatography with hexane/EtOAc (5:1) to give (4*S*,2′*S*,6′*R*)-**11** as a colorless oil (60 mg, 89%). $[\alpha]_D^{22}$ +55.7° (*c* 1.00, $CHCl_3$). IR ν_{max} (film) cm^{-1}: 3300 (br. m, O–H), 2930 (s, C–H), 1780 (s, C=O), 1700 (s, C=O), 1460 (w) 1390 (s), 1230 (s, C–H), 1100 (w), 1050 (w), 1020 (w), 970 (w), 920 (w), 740 (s), 700 (m). NMR δ_H ($CDCl_3$): 0.94 (d, *J* = 6.8 Hz, 3H, 6′-CH_3), 1.15–1.40 (m, 5H, 3′, 4′, 5′-H), 1.20 (d, *J* = 6.8 Hz, 3H, 2′-CH_3), 1.74 (m, 1H, 3′-H), 1.94 (m, 1H, 6′-H), 2.13 (dd, *J* = 6.8, 15.1 Hz, 1H, 7′-H), 2.31 (dd, *J* = 6.8, 15.1 Hz, 1H, 7′-H), 2.74 (dd, *J* = 9.6, 13.2 Hz, 1H, C*H*H–Ph), 3.24 (dd, *J* = 3.2, 13.2 Hz, 1H, CH*H*–Ph), 3.69 (sxt, *J* = 6.8 Hz, 1H, 2′-H), 4.08 (m, 2H, 5-H), 4.66 (m, 1H, 4-H), 7.18–7.32 (m, 5H, Ph). Found: C, 66.49%; H, 7.63%; N, 3.80%. Calcd. for $C_{20}H_{27}NO_5$: C, 66.46%; H, 7.53%; N, 3.88%.

(4S,2′S,6′S)-isomer. In the same manner as described above, (4*S*,2′*S*,6′*S*)-**11** was obtained from 5.5 g of (4*S*,2′*S*,6′*S*)-**10** (4.5 g, 95%). $[\alpha]_D^{22}$ +48° (*c* 0.70, $CHCl_3$). IR and ^{1}H NMR spectra were indistinguishable from those of (4*S*,2′*S*,6′*R*)-isomer. Found: C, 66.42%; H, 7.64%; N, 3.85%. Calcd. for $C_{20}H_{27}NO_5$: C, 66.46%; H, 7.53%; N, 3.88%.

(4R,2′R,6′R)-isomer. In the same manner as described above, (4*R*,2′*R*,6′*R*)-**11** was obtained from 2.7 g of (4*R*,2′*R*,6′*R*)-**10** (2.3 g, 95%). $[\alpha]_D^{22}$ −55° (*c* 0.30, $CHCl_3$). IR and ^{1}H NMR spectra were indistinguishable from those of (4*S*,2′*S*,6′*R*)-isomer. Found: C, 66.31%; H,

7.69%; N, 3.92%. Calcd. for $C_{20}H_{27}NO_5$: C, 66.46%; H, 7.53%; N, 3.88%.

(4R,2′R,6′S)-isomer. In the same manner as described above, (4*R*,2′*R*,6′*S*)-**11** was obtained from 200 mg of (4*R*,2′*R*,6′*S*)-**10** (160 mg, 93%). $[\alpha]_D^{22}$ −57.6° (*c* 1.10, $CHCl_3$). IR and ^1H NMR spectra were indistinguishable from those of (4*S*,2′*S*,6′*R*)-isomer. Found: C, 66.49%; H, 7.34%; N, 3.87%. Calcd. for $C_{20}H_{27}NO_5$: C, 66.46%; H, 7.53%; N, 3.88%.

*(2S,6R)-2,6-Dimethyloctane-1,8-dioic acid (**2**).* A solution of (4*S*,2′*S*,6*R*)-**11** (50 mg, 0.12 mmol) in THF (2 ml) and water (6 ml) was treated with 30% H_2O_2 (58 ml, 0.48 mmol) followed by solid LiOH (12 mg, 0.24 mmol). After stirring for 30 min, the reaction was treated with a solution of aq. Na_2SO_3 followed by 0.5 N $NaHCO_3$. Following removal of THF *in vacuo* on a rotary evaporator, the residue was diluted with water and extracted with three portions of CH_2Cl_2. The aqueous phase was acidified to pH 1–2 with 5 N HCl and extracted with three portions of AcOEt. The AcOEt extracts were combined, and dried with Na_2SO_4, and the solvent was evaporated and the residue purified by column chromatography with hexane/EtOAc (1:5) to give (2*S*,6*R*)-**2** as a colorless oil (28 mg, 96%). $[\alpha]_D^{22}$ +20° (*c* 0.30, $CHCl_3$). IR ν_{max} (film) cm^{-1}: 2930 (s, C–H), 2700 (br. m, O–H), 1700 (s, C=O), 1440 (m), 1300 (m), 1240 (s, C–H), 1170 (m), 1130 (w), 1020 (w), 950 (m), 800 (w), 740 (w), 690 (w), 640 (w). NMR δ_H ($CDCl_3$): 0.95 (d, $J = 6.8$ Hz, 3H, 6-CH_3), 1.16 (d, $J = 6.8$ Hz, 3H, 2-CH_3), 1.20–1.44 (m, 5H, 3, 4, 5-H), 1.64 (m, 1H, 3-H), 1.95 (m, 1H, 6-H), 2.17 (dd, $J = 6.8$, 15.1 Hz, 1H, 7-H), 2.29 (dd, $J = 6.8$, 15.1 Hz, 1H, 7-H), 2.46 (sxt, $J = 6.8$ Hz, 1H, 2-H). NMR δ_C ($CDCl_3$): 16.9 (C-9), 19.7 (C-10), 24.5 (C-4), 29.9 (C-6), 33.4 (C-3), 36.3 (C-5), 39.3 (C-2), 41.5 (C-7), 179.6 (C-8), 183.2 (C-1). Found: C, 59.44%; H, 8.89%. Calcd for $C_{10}H_{18}O_4$: C, 59.39%; H, 8.97%.

(2S,6S)-isomer. In the same manner as described above, (2*S*,6*S*)-**2** was obtained from 2.00 g of (4*S*,2′*S*,6′*S*)-**11** (900 mg, 93%). $[\alpha]_D^{22}$ +9.3° (*c* 0.41, $CHCl_3$). IR ν_{max} (film) cm^{-1}: 2930 (s, C–H), 2700 (br. m, O–H), 1700 (s, C=O), 1440 (m), 1300 (m), 1240 (s, C–H), 1170 (m), 1130 (w), 1020 (w), 950 (m), 800 (w), 740 (w), 690 (w), 640 (w). NMR δ_H ($CDCl_3$): 0.95 (d, $J = 6.8$ Hz, 3H, 6-CH_3), 1.16 (d, $J = 6.8$ Hz, 3H, 2-CH_3), 1.33–1.44 (m, 3H, 5, 6-H), 1.64 (m, 2H, 4-H), 1.95 (m, 2H, 3-H), 2.17 (dd, $J = 6.8$, 15.1 Hz, 1H, 7-H), 2.29 (dd, $J = 6.8$, 15.1 Hz, 1H, 7-H), 2.46 (sxt, $J = 6.8$ Hz, 1H, 2-H). NMR δ_C ($CDCl_3$): 16.8 (C-9), 19.8 (C-10), 24.3 (C-4), 29.8 (C-6), 36.1, 36.1 (C-3,5), 39.1 (C-2), 41.3 (C-7), 179.4 (C-8), 183.0 (C-1). Found: C, 59.44%; H, 8.84%. Calcd. for $C_{10}H_{18}O_4$: C, 59.39%; H, 8.97%.

(2R,6R)-isomer. In the same manner as described above, (2*R*,6*R*)-**2** was obtained from 2.2 g of (4*R*,2′*R*,6′*R*)-**11** (1.0 g, 96%). $[\alpha]_D^{22}$ −11° (*c* 0.30, $CHCl_3$). Found: C, 59.41%; H, 8.69%. Calcd. for $C_{10}H_{18}O_4$: C, 59.39%; H, 8.97%. IR, ^1H and ^{13}C NMR spectra were identical to those of (2*S*,6*S*)-**2**.

(2R,6S)-isomer. In the same manner as described above, (2*R*,6*S*)-**2** was obtained from 190 mg of (4*R*,2′*R*,6′*S*)-**11** (90 mg, 98%). $[\alpha]_D^{22}$ −17.2° (*c* 2.02, $CHCl_3$). Found: C, 59.55%; H, 8.82%. Calcd. for $C_{10}H_{18}O_4$: C, 59.39%; H, 8.97%. IR, ^1H and ^{13}C NMR spectra were identical to those of (2*S*,6*R*)-**2**.

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