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Synthesis of (*S*)- and (*R*)-3-Hydroxy-4-butanolide and (2*S*,4*S*)-, (2*R*,4*S*)-, (2*S*,4*R*)-, and (2*R*,4*R*)-2-Hydroxy-4-hydroxymethyl-4-butanolide and Their Satiety and Hunger Modulating Activities

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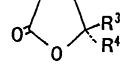
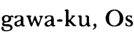
Two endogenous γ-lactones, 3-hydroxy-4-butanolide (**1**) and 2-hydroxy-4-hydroxymethyl-4-butanolide (**2**) have been identified as substances that enhance, respectively, satiety and hunger by their effects on the feeding behavior and the central neurons of rats. To determine the stereochemistry of the physiologically active isomers, all the stereoisomers of these two lactones were synthesized and their effects on the feeding behavior and humoral factors were assessed by infusion into the rat third cerebroventricle. Among four isomers, (2*S*,4*S*)-2-hydroxy-4-hydroxymethyl-4-butanolide (**2a**) was most effective in elicitating the feeding and caused potent hypoglycemia with hyperinsulinemia. (*S*)-3-Hydroxy-4-butanolide (**1a**) suppressed the food intake more potently than the antipode and caused humoral responses reciprocal to those of **2a**. From these facts, it was concluded that **1a** and **2a** are physiologically active forms for conveying intrinsic signals of satiety and hunger to neurons in the hypothalamus.

Sufficient evidence has been accumulated to show that some endogenous blood factors such as glucose, free fatty acids, insulin, glucagon, and some peptides contribute to the induction of hunger and satiety.[1)] In search of humoral factors that might be related to hunger and satiety, Oomura and coworkers analyzed human and rat blood serum, identified many organic acid derivatives in a gas chromatography-mass spectrometry system and investigated the effect of starvation on their blood serum levels.[2)] From the observed patterns of changes of their serum levels at various stages of hunger, they postulated that two of them, structurally simple γ-lactones, 3-hydroxy-4-butanolide (**1**) and 2-hydroxy-4-hydroxymethyl-4-butanolide (**2**), might modulate food intake.[3)] To confirm this assumption, they injected the synthesized lactones into the third cerebral ventricle of rats. Interestingly, the injection of 2.5 μmol of **1** suppressed both food intake and single neuron activity in the lateral hypothalamic area (LHA). The same treatment with **2** elicited feeding and increased LHA single neuron activity. From the high correlation between the feeding behavior and changes in LHA neuron activity, Oomura concluded that 3-hydroxy-4-butanolide (**1**) acts as an endogenous satiety substance and that 2-hydroxy-4-hydroxymethyl-4-butanolide (**2**) acts as a hunger substance.[4,5)] The question arose as to which stereoisomers of the two possible isomers of **1** and the four isomers of **2** were really responsible for the suppression or elicitation of food intake. The question had been left unsolved since the materials used for the infusion tests were the racemate of **1** and the mixture of two pairs of diastereomers of **2**. Though the report that (*S*)-3,4-dihydroxybutanoic acid exists in human blood and urine suggests the possibility of (*S*)-3-hydroxy-4-butanolide (**1a**) to be the active isomer,[6)] no report had been published about the natural occurrence of **2**.[7)] It seemed to be impractical to isolate these two lactones from rat blood serum to decide their stereochemistry because of their paucity.[8)] We decided to synthesize all the stereoisomers of these two lactones, **1a**, **b** and **2a**—**d**, in order to examine the effects on feeding activities and humoral factors of each isomer by direct infusion into rats. In this paper, we wish to report on the synthesis of these lactones and give a brief summary of the results of infusion test which led to the conclusion that (*S*)-3-hydroxy-4-butanolide (**1a**) and (2*S*,4*S*)-2-hydroxy-4-hydroxymethyl-4-butanolide (**2a**) are the physiologically active isomers.



1
a: R^1=H, R^2=OH
b: R^1=OH, R^2=H



2
a: R^1=OH, R^2=H, R^3=CH_2OH, R^4=H
b: R^1=H, R^2=OH, R^3=CH_2OH, R^4=H
c: R^1=OH, R^2=H, R^3=H, R^4=CH_2OH
d: R^1=H, R^2=OH, R^3=H, R^4=CH_2OH

Results and Discussion

Both optically active forms of **1** had been prepared by several methods.[9)] Though a few reports had been published concerning the preparation of optically

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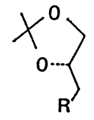
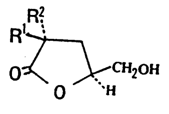
active isomers of **2** from some sugars, these preparation methods did not necessarily seem to be suitable for obtaining all the stereoisomers.[10)] We adopted a different approach. As common starting materials for the preparation of both lactones, we selected (*S*)-[11)] and (*R*)-3,4-*O*-isopropylidene-3,4-dihydroxybutanal,[9b)] (**3** and **3′**) which had been derived from (*S*)- and (*R*)-malic acid, respectively. For the preparation of **1a**, the method reported by Mori et al.[9b)] was modified. (*S*)-Aldehyde (**3**) was oxidized to a carboxylic acid (**4**) in 65% yield with $RuCl_3$ and $NaIO_4$ according to the method reported by Sharpless et al.[12)] This made the very water-soluble product (**4**) isolation much easier compared with Mori's method which used Jones' reagent. Deprotection and lactonization with *p*-TsOH gave **1a** with $[\alpha]_D^{20}$ −75.7° in 94% yield. The same treatment of (*R*)-aldehyde (**3′**) gave **1b** with $[\alpha]_D^{20}$ +78.2°.



3: R=CHO
4: R=COOH
5: R=CH(OH)CH=CH_2
6: R=CH(OBz)CH=CH_2
7: R=CH(OBz)COOH



8a: R^1=OBz, R^2=H
b: R^1=H, R^2=OBz

The preparation of **2a** and **2b** was carried out as follows. After some unsuccessful attempts to incorporate one carbon atom into (*S*)-aldehyde (**3**) by some reactions such as cyanosilylation,[13)] vinylmagnesium bromide was treated with **3** to give a mixture consisting of two diastereomeric vinyl alcohols (**5**) in 95% yield. No essential diastereoselectivity was observed. No effort to increase the selectivity was carried out in this study. After benzoylation, the mixture (**6**) was subjected to double-bond cleavage with $RuCl_3$ and $NaIO_4$ by the method of Sharpless[12)] to afford a mixture of two carboxylic acids (**7**) in high yield. All attempts to separate the two diastereomeric mixtures at stages **5**, **6**, and **7** were unsuccessful. However, the treatment of **7** with *p*-TsOH also gave a mixture of two diastereomeric benzoylated lactones in quantitative yield, which could be separated by preparative thin-layer chromatography (TLC) to obtain two benzoylated lactones, **8a** with $[\alpha]_D^{20}$ +21.1° and **8b** with $[\alpha]_D^{20}$ +41.9° in a ratio of 6 : 5. The hydrolysis and lactonization of **8a** and **8b** gave the desired optically active lactones, **2a** and **2b**, respectively, which showed $[\alpha]_D^{20}$ +23.2° and $[\alpha]_D^{20}$ +50.3°.

The stereochemistry of the benzoylated lactones, **8a** and **8b**, and the lactones, **2a** and **2b**, must be either (2*S*,4*S*) or (2*R*,4*S*), since the starting aldehyde (**3**) had the (*S*)-configuration. The nuclear magnetic resonance (NMR) signal of the proton at the 4-position of the benzoylated lactone, **8b**, appeared at 0.16 ppm down-field, compared with that of **8a**, while no significant difference of chemical shifts was observed between 4-positioned protons of **2a** and **2b**. This observation means that the 4-positioned proton of **8b** is apparently in the deshielding region of the benzoyloxyl group at the 2-position, and strongly suggests that the benzoyloxyl group and the proton at the 4-position locate at the same side of the lactone ring in **8b**. This means that **8b**, and then **2b**, have the (2*R*,4*S*)-configuration and that **8a** and **2a** have the (2*S*,4*S*)-configuration. This assignment was confirmed by reducing both lactones. As expected,[14)] the lithium aluminum hydride reduction of **2a** gave an optically active tetrol (**9a**) with a (2*S*,4*S*)-configuration, which showed $[\alpha]_D^{20}$ −44.8° after benzoylation.[15)] However, an optically inactive meso product (**9b**) was obtained by the reduction of **2b**, which did not show any essential optical rotation after benzoylation.[16)] According to the same procedure started with (*R*)-aldehyde (**3′**), we obtained two lactones, **2d**, with a (2*R*,4*R*)-configuration and $[\alpha]_D^{20}$ −22.0° and **2c**, with a (2*S*,4*R*)-configuration and $[\alpha]_D^{20}$ −45.6°.

A preliminary comparison of 2-hydroxy-4-hydroxymethyl-4-butanolide in rat and human sera with the four lactone isomers of **2** was carried out after trimethylsilylation by gas chromatography. The retention time of the lactone from a natural source coincided with that of one pair of diastereomer, **2a** and **2d**, but no signal corresponding to that of **2b** and **2c** was observed in rat or human sera. This excluded the possibility of the stereochemistry of the natural lactone to be (2*R*,4*S*) or (2*S*,4*R*).

The effects of each isomer (**1a**, **1b**, **2a**, **2b**, **2c**, and **2d**) on feeding behavior and humoral factors were assessed by infusion into the rat third cerebroventricle in a laboratory of internal medicine I, faculty of medicine, Kyushu University. Details regarding the experiments and results are published elsewhere, but a brief summary of the results is given here. Adult male Wister King A rats were implanted with a cannula aimed at the third cerebroventricle[17)] and used for tests after food and water intake, body weight and ambulatory activity returned to normal following surgery. Ten μl of a 0.25

Table 1. Ingestive and Ambulatory Behavior in a One-Hour Test Period Following Infusion of Each Stereoisomer of 2-Hydroxy-4-hydroxymethyl-4-butanolide (**2**) at Doses of 2.5 μmol or Phosphate Buffered Saline (PBS)

	2a	2b	2c	2d	PBS
Feeding incidence (%)	75[a)]	17	0	0	0
Drinking incidence (%)	0	0	0	0	0
Ambulation	+++	+			

a) $p<0.05$, compared to PBS.

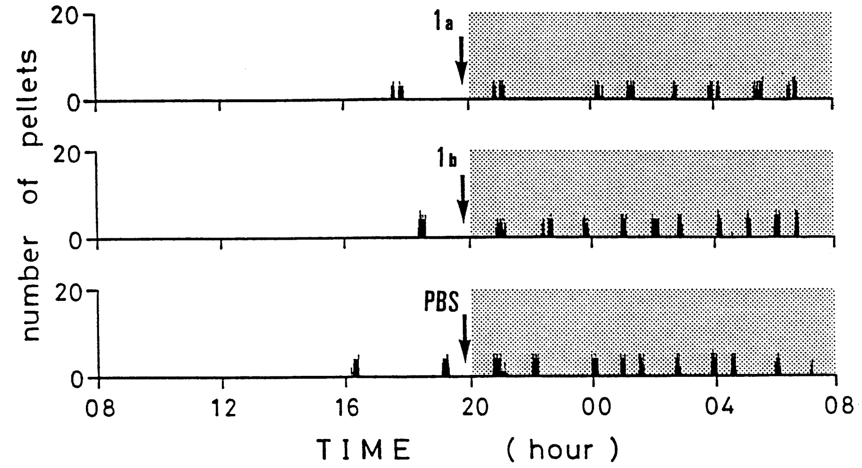


Fig. 1. Typical feeding patterns for rats after infusion of 2.5 μmol of **1a**, **1b**, and PBS solution into the third cerebro-ventricle. Shaded, dark time.

M solution (1 M=1 mol dm^{-3}) of each isomer in phosphate buffered saline (PBS. pH 7.3) was infused at a rate of 1 μl/1 min. The incidence and duration of eating and drinking, meal size, postprandial intermeal interval, and number of pellets and water-droplets ingested during meals[18,19] were recorded with a pellet-sensing eatometer and photoresistor drinkometer.[20] The ambulatory activity was measured by counting the crossings of 3×4 arrays of photobeams.[21] A statistical evaluation was carried out by either Fisher's exact probability test,[22] or by an analysis of the variance with replication. Typical feeding patterns after injection of **1a**, **1b**, and PBS are shown in Fig. 1. Compared with **1b** and PBS control groups which did not show any significant feeding suppression, the injection of **1a** potently suppressed food intake ($p<0.01$). In addition, **1a** prolonged the postprandial intermeal intervals and decreased the ambulatory bursts. The injection of **1a** raised the serum glucose level and decreased the serum insulin level over a 30-min testing period, while **1b** and PBS did not change these values.[23]

The injection of **2a** induced feeding more (75%) (Table 1), with a shorter latency to eat and a longer duration of meals than any other. Among the remaining isomers, **2b** elicited feeding (17%), but **2c**, **2d**, and PBS did not affect feeding. The intensity and frequency of ambulation were parallel to feeding. The effect to humoral factors was examined with **2a** and **2b**. In contrast to **1a**, injection of **2a** decreased the serum glucose level and raised the serum insulin level over a 30 min-testing period, but **2b** and PBS had no effect.[24]

From the facts described above, it seems quite reasonable to conclude that (*S*)-3-hydroxy-4-butanolide (**1a**) and (2*S*, 4*S*)-2-hydroxy-4-hydroxymethyl-4-butanolide (**2a**) are compounds that exist in human and rat sera and physiolosically active forms for conveying intrinsic signals to the LHA in feeding modulation.

Experimental

The ^{1}H NMR and ^{13}C NMR spectra were recorded at 90 and 25 MHz with a JEOL JNM-FX90Q spectrometer using Me_4Si as an internal standard. The IR spectra were taken with a Hitachi R-215 spectrometer. The MS spectra were taken with a JEOL-OISG-2 spectrometer. Optical rotations were measured on a Yanagimoto OR-50 polarimeter. Kieselgel F-254 (Merck) was used for column chromatography and glass plates precoated with silica gel 60F-254 (0.25 mm, Merck) were used for TLC and preparative TLC.

(*S*)-3-Hydroxy-4-butanolide (1a). A solution of $RuCl_3$-$(H_2O)_n$ (4.8 mg) in water (0.5 ml) was added to a mixture of (*S*)-3,4-*O*-isopropylidene-3,4-dihydroxybutanal[11] (**3**, 150 mg, 1.04 mmol), $NaIO_4$ (912 mg, 4.27 mmol), CCl_4 (2 ml), CH_3CN (2 ml), and water (3 ml). The brown color of the solution changed to deep green immediately. The solution was stirred for 2 h at room temperature and the product was extracted with CH_2Cl_2. After drying and evaporation of the solvent, the residue was chromatographed on a short column of silica gel (AcOEt) to give a crude acid (**4**) as an oil (108 mg, 65%). This was used for the next step without further purification. *p*-TsOH (8.3 mg) was added to a solution of **4** (69.5 mg, 0.434 mmol) in CH_2Cl_2 (5 ml) and the solution was stirred at room temperature overnight. Triethylamine (7 μl) was added to the solution and the solvent was evaporated in vacuo. The residue was subjected to silica-gel chromatography (AcOEt) to give **1a** (42 mg, 94.8%). Colorless oil, $[\alpha]_D^{20}$ −75.7° (*c* 0.806, MeOH). (lit,[9d] $[\alpha]_D^{9}$ −85.9° (*c* 2.2, EtOH)). IR (neat) 3350, 1760, 1180, 1085, 1050, 992, and 965 cm^{-1}. ^{1}H NMR (CD_3OD) δ=2.45 and 2.68 (2H, H-2, and H-2′, dd and dd, $J_{2,2'}$=18 Hz, $J_{2,3}$=2.5 Hz, $J_{2',3}$=5.5 Hz), 4.2—4.8 (3H, H-3, H-4, and H-4′, m). ^{13}C NMR ($CDCl_3$) δ=37.45, 66.96, 76.14, and 177.03. Found: *m/z* 102.0311. Calcd for $C_4H_6O_3$: M, 102.0317. Found: C, 46.83; H, 6.01%. Calcd for $C_4H_6O_3$: C, 47.06; H, 5.92%.

(*R*)-3-Hydroxy-4-butanolide (1b) was prepared according to the same procedure starting with (*R*)-3,4-*O*-isopropylidene-3,4-dihydroxybutanal (**3′**).[9b] Colorless oil, $[\alpha]_D^{20}$ +78.2° (*c* 0.972, MeOH). (lit,[9b] $[\alpha]_D^{23}$ +77.3° (*c* 2.0, EtOH). Found: *m/z* 102.0317. Calcd for $C_4H_6O_3$: M, 102.0317. Found: C, 46.62;

H, 6.06%. Calcd for $C_4H_6O_3$: C, 47.06; H, 5.92%. The other spectroscopic properties are same as those of **1a**.

A Mixture of (3*S*,5*S*)- and (3*R*,5*S*)-5,6-*O*-Isopropylidene-1-hexene-3,5,6-triol (5). A solution of vinylmagnesium bromide which was prepared from vinyl bromide (1.11 ml, 15.8 mmol) and Mg (486 mg, 20 mmol) in THF (5 ml) was added dropwise to a cold solution (ice bath) of **3** (760 mg, 5.27 mmol) in THF (5 ml). The solution was stirred for 2 h at room temperature and quenched with an aqueous NH_4Cl solution. After extraction with ether and drying with $MgSO_4$, the evaporation of the solvent gave crude products. Purification by silica-gel chromatography (hexane : AcOEt =5 : 2) gave a mixture of (3*S*,5*S*)- and (3*R*,5*R*)-products (**5**, 865 mg, 95.3%). Colorless oil.[25] Found: C, 62.43; H, 9.11%. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36%.

A Mixture of (3*S*,5*S*)- and (3*R*,5*S*)-3-Benzoyloxy-5,6-*O*-isopropylidene-1-hexene-5,6-diol (6). Benzoyl chloride (507 μl, 4.35 mmol) was added to a solution of **5** (500 mg, 2.9 mmol) in pyridine (2.5 ml) at room temperature. After stirring overnight, the mixture was treated with an aqueous $NaHCO_3$ solution and the products were extracted with ether. After washing with an aqueous $NaHCO_3$ solution and water, the evaporation of the solvent gave a mixture of the benzoates (**6**) in a quantitative yield. The purification by silica-gel chromatography (CH_2Cl_2 : hexane=3 : 1) gave **6** as a colorless oil (788 mg, 98.2%).[25] Found: C, 69.72; H, 7.29%. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.29%.

A Mixture of (2*S*,4*S*)- and (2*R*,4*S*)-2-Benzoyloxy-4-hydroxymethyl-4-butanolide (8a and 8b). A solution of $RuCl_3(H_2O)_n$ (3.1 mg) in water (1 ml) was added to a mixture of **6** (186 mg, 0.673 mmol), $NaIO_4$ (590 mg, 2.76 mmol), CCl_4 (2 ml), CH_3CN (2 ml), and water (2 ml). The solution was vigorously stirred at room temperature. The color of the solution changed to deep green immediately and to yellowish green after 2 h; the products were extracted with CH_2Cl_2. After drying with $MgSO_4$ and filtration through a short column of celite, evaporation of the solvent gave a mixture of acids (**7**, 187 mg, 95.4%). This was employed for the next step without further purification. *p*-TsOH (9.2 mg, 0.048 mmol) was added to a solution of **7** (141.8 mg, 0.482 mmol) in CH_2Cl_2 (3 ml) and stirred at room temperature overnight. After adding triethylamine (8 μl, 0.058 mmol), the solution was concentrated in vacuo and the residue was chromatographed on a short column of silica-gel (AcOEt) to give a mixture of lactones (120 mg, 75.5%). For the separation of **8a** and **8b**, the lactone mixture (400 mg) was subjected to preparative thin-layer chromatography (hexane : AcOEt=3 : 2). Since the difference of R_f-values was small (R_f-values, 0.1 and 0.15), development was repeated four times. From the lower zone, **8a** was obtained as colorless solids (120 mg). Mp 50—51 °C. $[\alpha]_D^{20}$ +21.1° (*c* 0.9, MeOH). IR (neat) 3490, 2950, 1790, 1721, 1278, 1200, 1130, and 718 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=2.38 and 2.68 (2H, H-3, and H-3′, dt and ddd, $J_{3,3'}$=14.0 Hz, $J_{2,3}$=$J_{3,4}$=11.2 Hz, $J_{2,3'}$=9.8 Hz, $J_{3',4}$=6.8 Hz), 2.95 (1H, s, -OH), 3.72 and 3.96 (2H, H-5, and H-5′, ddd, $J_{5,5'}$=12.5 Hz, $J_{4,5}$=2.6 Hz, $J_{4,5'}$=4.8 Hz), 4.65 (1H, H-4, m), 5.78 (1H, H-2, dd, $J_{2,3}$=9.0 Hz, $J_{2,3'}$=10.5 Hz), 7.30—8.60 (5H, aromatic, m). Found: *m/z* 236.0819. Calcd for $C_{12}H_{12}O_5$: M, 236.0684. Found: C, 60.58; H, 5.22%. Calcd for $C_{12}H_{12}O_5$: C, 61.01; H, 5.12%. **8b** was obtained from the upper zone as colorless solids (100 mg). Mp 84—86 °C. $[\alpha]_D^{20}$ +41.9° (*c* 1.0, MeOH). IR (neat) 3450, 1785, 1765, 1610, 1460, 1390, 1365, 1292, 1235, 1000, 725, and 720 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=2.48 and 2.78 (2H, H-3, and H-3′, dt and ddd, $J_{3,3'}$=14.0 Hz, $J_{2,3}$=$J_{3,4}$=8.9 Hz, $J_{2,3'}$=10.0 Hz, $J_{3',4}$=9.8 Hz), 2.90 (1H, s, -OH), 3.70 and 3.98 (2H, H-5 and H-5′, ddd, $J_{5,5'}$=12.5 Hz, $J_{4,5}$=2.9 Hz, $J_{4,5'}$=2.4 Hz), 4.81 (1H, H-4, m). Found: *m/z* 236.0717. Calcd for $C_{12}H_{12}O_5$: M, 236.0684. Found: C, 60.64; H, 5.21%. Calcd for $C_{12}H_{12}O_5$: C, 61.01; H, 5.12%.

(2*S*,4*R*)- and (2*R*,4*R*)-Isomers (8c and 8d) were prepared starting with (*R*)-aldehyde (**3′**) according to the same method described above. **8c**, Colorless solides. Mp 82—85 °C. $[\alpha]_D^{20}$ −42.1° (*c* 1.12, MeOH). Found: *m/z* 236.0647. Calcd for $C_{12}H_{12}O_5$: M, 236.0684. Found: C, 60.88; H, 5.22%. Calcd for $C_{12}H_{12}O_5$: C, 61.01, H, 5.12%. **8d**, colorless solids. Mp 49—50 °C. $[\alpha]_D^{20}$ −20.3° (*c* 0.87, MeOH). Found: *m/z* 236.0685. Calcd for $C_{12}H_{12}O_5$: M, 236.0685. Found: C, 60.91; H, 5.03%. Calcd for $C_{12}H_{12}O_5$: C, 61.01; H, 5.12%. The other spectroscopic properties of these lactones are same as those of **8b** and **8a**, respectively.

(2*S*,4*S*)-2-Hydroxy-4-hydroxymethyl-4-butanolide (2a). A mixture of **8a** (98.9 mg, 0.49 mmol), an aqueous NaOH solution (10%, 0.5 ml), and MeOH (0.5 ml) was stirred overnight at room temperature. The mixture was acidified with a diluted HCl solution and the solvents were evaporated in vacuo as much as possible. The product was extracted with AcOEt. After evaporation of the solvent, the residue was subjected to silica-gel chromatography (AcOEt) to give **2a** (40 mg, 72.2%) as a colorless oil. $[\alpha]_D^{20}$ +23.2° (*c* 3.61, MeOH). IR (neat) 3450, 2930, 1760, 1325, 1200, 1130, 995, 960, 900, and 803 cm^{-1}. ^{1}H NMR (CD_3OD) δ=1.93 and 2.53 (2H, H-3, and H-3′, dt and ddd, $J_{3,3'}$=12.3 Hz, $J_{2,3}$=$J_{3,4}$=10.6 Hz, $J_{2,3'}$=8.5 Hz, $J_{3',4}$=5.7 Hz), 3.59 and 3.81 (2H, H-5, and H-5′, ddd, $J_{5,5'}$=12.7 Hz, $J_{4,5}$=3.1 Hz, $J_{4,5'}$=4.8 Hz), 4.34—4.67 (2H, H-2, and H-4, m.). ^{13}C NMR (CD_3OD) δ=33.48, 63.76, 69.04, 78.48, and 178.59. Found: C, 44.92; H, 6.03%. Calcd for $C_5H_8O_4$: C, 45.46; H, 6.10%.[25]

(2*R*,4*S*)-, (2*S*,4*R*)-, and (2*R*,4*R*)-Isomers (2b, 2c, and 2d) were prepared by the same procedure described above from **8b**, **8c**, and **8d**, respectively. **2b**, colorless oil. $[\alpha]_D^{20}$ +50.3° (*c* 1.75, MeOH). IR (neat) 3400, 2950, 1775, 1640, 1460, 1357, 1205, 1115, 980, and 803 cm^{-1}. ^{1}H NMR (CD_3OD) δ=2.12 and 2.48 (2H, H-3, and H-3′, dt and ddd, $J_{3,3'}$=13.1 Hz, $J_{2,3}$=$J_{3,4}$=8.3 Hz, $J_{2,3'}$=8.5 Hz, $J_{3',4}$=3.2 Hz), 3.58 and 3.76 (2H, H-5, and H-5′, ddd, $J_{5,5'}$=13.1 Hz, $J_{4,5}$=2.6 Hz, $J_{4,5'}$=3.4 Hz), 4.47—4.73 (2H, H-2, and H-4, m). ^{13}C NMR (CD_3OD) δ=33.93, 64.35, 68.19, 79.59, and 179.17. Found: C, 45.56; H, 6.19%. Calcd for $C_5H_8O_4$: C, 45.46; H, 6.10%.[25] **2c**, colorless oil. $[\alpha]_D^{20}$ −45.6° (*c* 1.60, MeOH). Found: C, 44.99; H, 6.21%. Calcd for $C_5H_8O_4$: C, 45.46; H, 6.10%.[25] **2d**, colorless oil. $[\alpha]_D^{20}$ −22.2° (*c* 1.26, MeOH). Found: C, 44.96; H, 6.33%. Calcd for $C_5H_8O_4$: C, 45.46; H, 6.10%.[25] The other spectroscopic properties of **2c** and **2d** are the same as those of **2b** and **2a**, respectively.

(2*S*,4*S*)-1,2,4,5-Tetrakis(benzoyloxy)pentane (10a). A solution of **2a** (20 mg, 0.15 mmol) in THF (2 ml) was added to a solution of LAH (30 mg, 0.79 mmol) in THF (2 ml) and the mixture was stirred for 2 h at room temperature. The mixture was decomposed by the addition of a few drops of water and filtered and the residue was extracted thoroughly with a 2 : 1 mixture of THF and water. The concentration of the combined filtrate and extracts gave the residue which was dissolved in pyridine (1 ml) and treated with benzoyl chloride (120 mg, 0.85 mmol) overnight at room temperature. The mixture was treated with water, extracted with ether, and washed with diluted HCl and Na_2CO_3 solutions. After drying over Na_2SO_4, removing the solvent gave a residue which was purified by silica-gel chromatography to give **10a** as a gum (59 mg, 76%). (lit,[26] a gum.) $[\alpha]_D^{20}$ −44.8° (c 1.12, AcOEt). ^{1}H NMR ($CDCl_3$) δ=2.39 (2H, H-3, and H-3′, dd, $J_{2,3}=J_{3,4}$=6.1 Hz, $J_{2,3'}=J_{3',4}$=7.0 Hz), 4.60 (4H, $OCH_2\times 2$, m), 5.70 (2H, H-2, and H-4, m), 7.20—8.10 (20H, aromatic).

(*meso*)-1,2,4,5-Tetrakis(benzoyloxy)pentane (10b) was prepared according to the same procedure. Colorless solids. Mp 98—101 °C. (lit,[16] mp 104—105 °C). $[\alpha]_D^{20}$ ±0°. ^{1}H NMR ($CDCl_3$) δ=2.41 (2H, H-3, and H-3′, m), 4.60 (4H, $OCH_2\times 2$, m), 5.70 (2H, H-2, and H-4, m), 7.20—8.10 (20H, aromatic).

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