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Chemical Transformation of Terpenoids. IX.[1] Ionophoretic Activities of Macrocyclic Lactone Epoxides Synthesized from *E*,*E*-Farnesol

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Two diastereomeric macrocyclic lactone epoxides, *i.e.*, a 13-membered-ring monomeric lactone diepoxide (FL_1E_2, 7) and a 26-membered-ring dimeric lactone tetraepoxide (FL_2E_4, 8), were synthesized from *E*,*E*-farnesol by employing a new lactonization reaction with sodium hydride. Examinations by using a W-07 apparatus (liquid-membrane type) and by means of the human erythrocyte membrane method, have shown that FL_2E_4 (8) exhibits not only ion-transport activity for K^+ ion but also ion-permeation activity for K^+ ion across the human erythrocyte membrane, while FL_1E_2 (7) decreases the Na^+ ion concentration inside human erythrocytes. Furthermore, we studied the dependence of the ionophoretic activities for K^+ ion upon the epoxide configurations by using six diastereomers of FL_2E_4 (8).

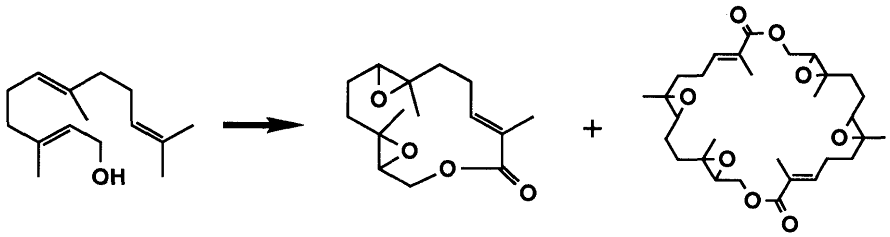
Keywords farnesol-*E*,*E*; lactone epoxide macrocyclic; lactonization; ion-transport activity; ionophoretic activity; X-ray analysis

In the course of our studies on the chemical transformation of readily available acyclic terpenoids, we have reported preparations of menthofuran and juvabione from geraniol and nerol[2] and a synthesis of (±)-costunolide, an antitumor sesquiterpene lactone, from *E*,*E*-farnesol.[3] On the other hand, ionophores, which transport metal-cations across artificial or biological membranes, have recently received much attention because of their various important biological activities. Our interest in ionophores led us to develop three methods for the determination of ionophoretic activities; *e.g.*, the W-07 apparatus[4] for measuring ion-transport activity and the W-08 apparatus[5] for measuring ion-transport as well as ion-binding activities, both of glass-cell liquid-membrane type, and a method using human erythrocyte membrane[6] for measuring ion-permeation intensity. Since then, we have been engaged in the characterization of naturally occurring ionophores by means of those methods[4–6] (*e.g.*, Ca^{2+}-ionophores of soya-cerebrosides[5]), as well as synthetic studies of podant- and coronand-type terpenoid ionophores.[7] Recently, we have investigated Ca^{2+}-ionophoretic activities of several synthetic analogs of soya-cerebroside II from the viewpoint of structure–activity relationship.[8]

As a continuation of these studies, we describe in this paper: 1) syntheses of two macrocyclic lactone epoxides, *i.e.*, a monomeric lactone diepoxide (FL_1E_2, **7**) and a dimeric lactone tetraepoxide (FL_2E_4, **8**), from *E*,*E*-farnesol (**1**), 2) ionophoretic activities of FL_1E_2 (**7**) and FL_2E_4 (**8**) for Na^+, K^+, and Ca^{2+} ions, and 3) comparisons of the ionophoretic activities of six diastereomers (**8a**—**8f**) of FL_2E_4 (**8**).[9]

Syntheses of Monomeric Lactone Diepoxide (FL_1E_2) (7) and Dimeric Lactone Tetraepoxide (FL_2E_4) (8) from *E*,*E*-Farnesol (1) Oxidation of *E*,*E*-farnesyl acetate (**1a**), which was prepared from *E*,*E*-farnesol (**1**) by ordinary acetylation (Ac_2O–pyridine), with one equivalent of selenium dioxide in aqueous 95% ethanol furnished ω-hydroxyfarnesyl acetate (**2**) in 39% yield with 30% recovery of **1a**. The *E* geometry of the newly introduced ω-hydroxyl function of **2** was presumed on the basis of the reaction mechanism of selenium dioxide oxidation[10] and was substantiated by the ^{1}H-NMR data for the ω-aldehydic derivative (**2a**) ($\delta_{C\underline{H}O}$ 9.39),[11] which was synthesized quantitatively by manganese dioxide oxidation of **2**. Treatment of **2a** with manganese dioxide and sodium cyanide in AcOH–MeOH[12] under Corey's oxidation conditions provided a methoxycarbonyl derivative (**3**) in 59% yield. Subsequent methanolysis of **3** furnished an ω-methoxylcarbonyl farnesol (**4**), which was the substrate of the following lactonization reaction.

At first, we attempted lactonization of an ω-carbonyl farnesol (**4a**), prepared from the ω-methoxycarbonyl farnesol (**4**) by alkaline treatment, under several known lactonization conditions.[13] However, neither a monomeric lactone (FL_1, **5**) nor a dimeric lactone (FL_2, **6**) was obtained. Afterwards, we found that treatment of ω-methoxycarbonyl farnesol (**4**) with 5 eq of sodium hydride in an aprotic solvent [tetrahydrofuran (THF), benzene, or



E, *E*-farnesol (**1**) FL_1E_2 (**7**) FL_2E_4 (**8**)

Chart 1

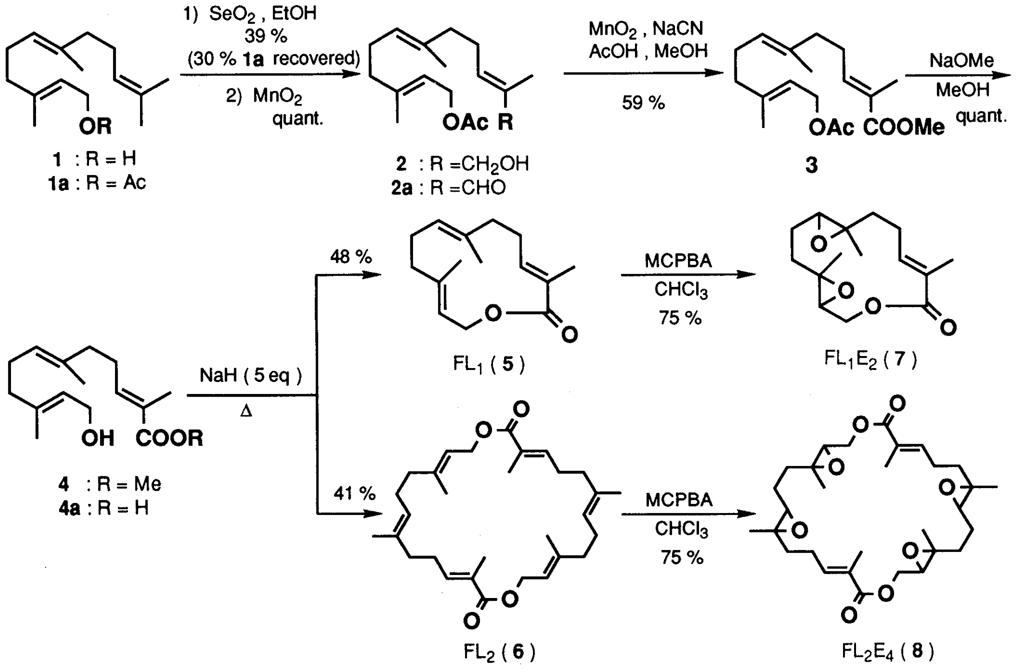


Chart 2

Table I. Lactonization of ω-Methoxycarbonyl Farnesol (4) by Making Use of NaH (5.0 eq)

Solvent	Initial concentration of **4** (mol/l)	Yield (%)[a]	
		FL_1 (**5**)	FL_2 (**6**)
THF	1.0×10^{-2}	8	72
THF	1.0×10^{-3}	46	36
Benzene	1.0×10^{-2}	14	61
Benzene	1.0×10^{-3}	55	33
Toluene	1.0×10^{-2}	48	41
Toluene	1.0×10^{-3}	72	24

a) Calculated from the isolated products.

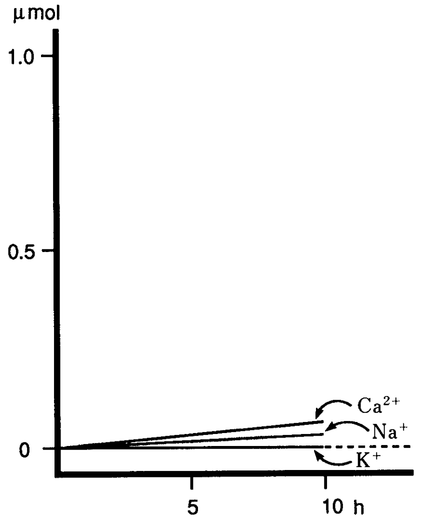


Fig. 1. Ion-Transport Activity of FL_1E_2 (**7**) for Metal Ions

Initial concentration of sample: 0.03 mol/l in $CHCl_3$.

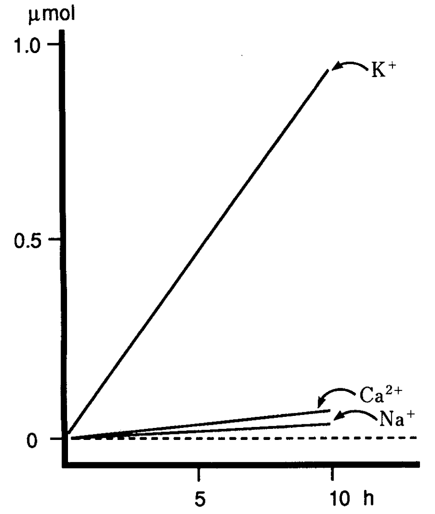


Fig. 2. Ion-Transport Activity of FL_2E_4 (**8**) for Metal Ions

Initial concentration of sample: 0.03 mol/l in $CHCl_3$. $m_K = 9.38 \times 10^{-8}$ mol/h.

toluene] under reflux afforded both desired lactones (**5**, **6**) in excellent combined yield. The ratio of FL_1 (**5**) and FL_2 (**6**) in the reaction product was affected by the kind of solvent used as well as by the initial concerntration of the substrate **4**, as shown in Table I. Thus, when the initial concentration of **4** was 1.0×10^{-2} mol/l in THF, the dimeric lactone (FL_2, **6**) was obtained in high yield (72%) with a small amount (8%) of the monomeric lactone (FL_1, **5**). On the other hand, when the initial concentration of **4** was 1.0×10^{-3} mol/l in toluene, the lactonization reaction resulted in 72% yield of FL_1 (**5**) and 24% yield of FL_2 (**6**).

The monomeric lactone (FL_1, **5**) and the dimeric lactone (FL_2, **6**) were then each subjected to *m*-chloroperbenzoic acid oxidation to obtain their epoxide derivatives, FL_1E_2 (**7**) and FL_2E_4 (**8**), both as diastereomeric mixtures.

Ionophoretic Activities of FL_1E_2 (7) and FL_2E_4 (8) The ionophoretic activities of the monomeric and dimeric lactone epoxides FL_1E_2 (**7**) and FL_2E_4 (**8**), as diastereomeric mixtures, for Na^+, K^+, and Ca^{2+} ions were initially examined by using a W-07 apparatus.[4] It was found that

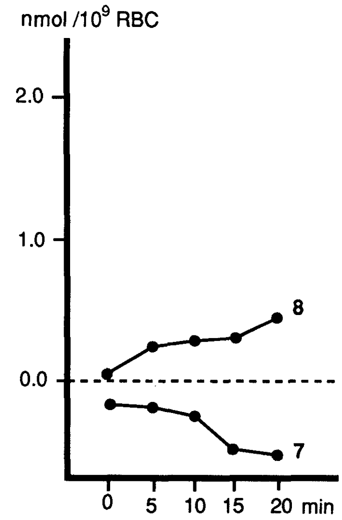


Fig. 3. Ion-Permeation Activities of FL_1E_2 (**7**) and FL_2E_4 (**8**) for Na^+ Ion

Initial concentration of sample: 0.25 mmol/10^9 red blood cells (RBC).

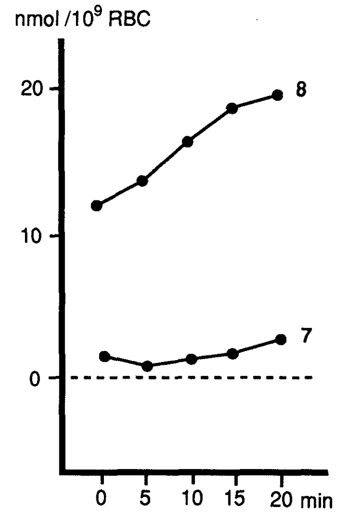


Fig. 4. Ion-Permeation Activities of FL_1E_2 (**7**) and FL_2E_4 (**8**) for K^+ Ion

Initial ion concentration of sample: 0.25 mmol/10^9 RBC.

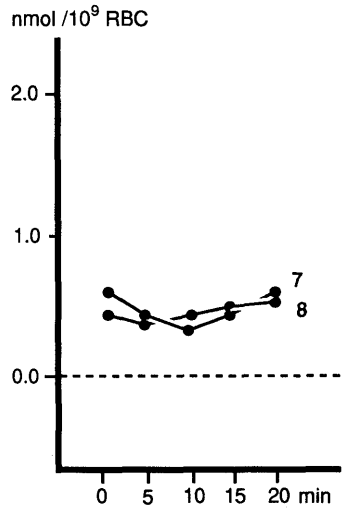


Fig. 5. Ion-Permeation Activities of FL_1E_2 (**7**) and FL_2E_4 (**8**) for Ca^{2+} Ion

Initial ion concentration of sample: 0.25 mmol/10^9 RBC.

FL_2E_4 (**8**, 0.03 mol/l in chloroform) exhibited ion-transport activity (9.38×10^{-8} mol/h) only for K^+ ion (Fig. 2), while FL_1E_2 (**7**) did not show any ionophoretic activity for Na^+, K^+, or Ca^{2+} ion (Fig. 1).

Next, **7** and **8** were examined by using the human erythrocyte membrane method.[6] It was found that FL_2E_4 (**8**) increased the concentration of K^+ ion inside erythrocytes (Fig. 4), whereas FL_1E_2 (**7**) slightly decreased the concentration of Na^+ ion inside erythrocytes (Fig. 3). However, **7** and **8** did not significantly affect the Ca^{2+} ion concentration inside erythrocyte (Fig. 5).

TABLE II. Torsion Angles at the Ring Atoms of FL_2E_4-1 (**8a**), FL_2E_4-3 (**8c**), FL_2E_4-4 (**8d**), and FL_2E_4-5 (**8e**)

	8a	**8c**	**8d**	**8e**
O1–C1–C2–C3	−0.4 (5)	−174.2 (3)	164.8 (3)	171.4 (4)
O4′–C1–C2–C3	179.6 (3)	6.0 (4)	−17.4 (4)	−9.2 (6)
C2–C1–O4′–C12′	175.1 (2)	−178.0 (3)	−173.4 (3)	−170.8 (3)
O1–C1–O4′–C12′	−4.9 (4)	2.1 (5)	4.3 (5)	8.7 (6)
C1–C2–C3–C4	−178.2 (4)	175.9 (3)	−178.3 (3)	−178.2 (4)
C2–C3–C4–C5	−176.7 (4)	178.5 (3)	−124.2 (3)	−95.6 (5)
C3–C4–C5–C6	178.1 (4)	62.3 (3)	66.6 (3)	164.4 (4)
C4–C5–C6–C7	−93.4 (4)	−103.7 (3)	−92.4 (3)	17.8 (6)
C4–C5–C6–O2	−159.6 (3)	−169.9 (3)	−159.5 (3)	−50.1 (5)
C5–C6–C7–C8	157.4 (3)	154.3 (3)	155.3 (3)	156.0 (4)
C5–C6–C7–O2	−100.5 (3)	−100.0 (3)	−101.5 (3)	−100.9 (4)
O2–C6–C7–C8	−102.2 (3)	−105.6 (3)	−103.2 (3)	−103.1 (5)
C5–C6–O2–C7	110.1 (3)	111.0 (3)	110.7 (3)	114.1 (4)
C6–C7–C8–C9	−92.3 (4)	−92.2 (3)	−100.2 (3)	137.1 (4)
O2–C7–C8–C9	−162.2 (3)	−163.1 (3)	−170.0 (3)	66.2 (5)
C8–C7–O2–C6	117.4 (3)	115.8 (3)	116.3 (3)	118.0 (4)
C7–C8–C9–C10	−55.2 (4)	−176.5 (2)	−176.9 (2)	62.3 (5)
C8–C9–C10–C11	101.5 (3)	92.5 (3)	85.9 (3)	−97.4 (5)
C8–C9–C10–O3	167.9 (2)	158.6 (3)	153.5 (3)	−163.0 (4)
C9–C10–C11–C12	−152.8 (3)	−154.5 (3)	−152.6 (3)	162.7 (4)
C9–C10–C11–O3	101.4 (3)	101.6 (3)	105.1 (3)	−99.8 (4)
O3–C10–C11–C12	105.8 (3)	103.9 (3)	102.3 (3)	−97.5 (5)
C9–C10–O3–C11	−110.2 (3)	−110.2 (3)	−108.3 (3)	110.6 (4)
C10–C11–C12–O4	−158.2 (3)	−153.5 (3)	−146.0 (3)	−118.7 (5)
O3–C11–C12–O4	−88.2 (3)	−84.0 (3)	−76.4 (3)	173.0 (3)
C12–C11–O3–C10	−112.6 (3)	−113.6 (3)	−116.0 (3)	118.9 (4)
C11–C12–O4–C1′	−147.0 (3)	−169.7 (3)	−80.7 (3)	89.2 (4)
O4–C1′–C2′–C3′	−161.5 (3)	−11.2 (4)	14.8 (4)	9.2 (6)
O1′–C1′–C2′–C3′	18.2 (5)	169.5 (3)	−162.9 (3)	−171.4 (4)
C2′–C1′–O4–C12	−179.2 (2)	175.4 (3)	172.3 (3)	170.8 (3)
O1′–C1′–O4–C12	1.0 (4)	−5.3 (5)	−9.8 (5)	−8.7 (6)
C1′–C2′–C3′–C4′	174.1 (3)	−177.2 (3)	−179.5 (3)	178.2 (4)
C2′–C3′–C4′–C5′	132.9 (4)	144.5 (3)	120.3 (3)	95.6 (5)
C3′–C4′–C5′–C6′	167.3 (3)	73.0 (3)	−64.0 (3)	−164.4 (4)
C4′–C5′–C6′–C7′	−103.1 (3)	−99.1 (3)	91.3 (3)	−17.8 (6)
C4′–C5′–C6′–O2′	−169.3 (3)	−165.0 (3)	157.1 (3)	50.1 (5)
C5′–C6′–C7′–C8′	156.5 (3)	157.1 (3)	−156.2 (3)	−156.0 (4)
C5′–C6′–C7′–O2′	−101.0 (3)	−100.0 (3)	100.6 (3)	100.9 (4)
O2′–C6′–C7′–C8′	−102.5 (3)	−102.9 (3)	103.2 (3)	103.1 (5)
C5′–C6′–O2′–C7′	109.7 (3)	110.7 (3)	−110.7 (3)	−114.1 (4)
C6′–C7′–C8′–C9′	−91.4 (4)	−99.0 (3)	93.5 (3)	−137.1 (4)
O2′–C7′–C8′–C9′	−161.7 (3)	−169.4 (3)	163.9 (3)	−66.2 (5)
C8′–C7′–O2′–C6′	117.3 (3)	117.3 (3)	−116.2 (3)	−118.0 (4)
C7′–C8′–C9′–C10′	−51.0 (4)	−174.8 (2)	179.0 (3)	−62.3 (5)
C8′–C9′–C10′–C11′	99.3 (3)	135.1 (3)	−82.0 (3)	97.4 (5)
C8′–C9′–C10′–O3′	165.4 (3)	69.4 (3)	−147.1 (3)	163.0 (4)
C9′–C10′–C11′–C12′	−153.6 (3)	155.4 (3)	152.9 (3)	−162.7 (4)
C9′–C10′–C11′–O3′	101.5 (3)	−100.8 (3)	−102.1 (3)	99.8 (4)
O3′–C10′–C11′–C12′	104.9 (3)	−103.8 (3)	−104.9 (3)	97.5 (5)
C9′–C10′–O3′–C11′	−109.2 (3)	110.0 (3)	108.8 (3)	−110.6 (4)
C10′–C11′–C12′–O4′	−175.4 (3)	157.7 (3)	145.3 (3)	118.7 (5)
O3′–C11′–C12′–O4′	−105.1 (3)	88.4 (4)	73.9 (3)	−173.0 (3)
C12′–C11′–O3′–C10′	−114.0 (3)	113.0 (3)	115.4 (3)	−118.9 (4)
C11′–C12′–O4′–C1	171.9 (3)	−175.4 (3)	84.9 (3)	−89.2 (4)

Relative Stereostructures of Six Diastereomers of FL_2E_4 (8) Since the diastereomeric mixture FL_2E_4 (**8**) exhibited ion-transport and ion-permeation activities for K^+ ion, we next examined the diastereostructure–ionophoretic activity relationship of **8**. Thus, FL_2E_4 (**8**) was subjected to high-performance liquid chromatography (HPLC) and the six anticipated diastereomers, FL_2E_4-1 (**8a**), -2 (**8b**), -3 (**8c**), -4 (**8d**), -5 (**8e**), and -6 (**8f**), were separated in a ratio of 1:5:6:4:3:3.

The relative stereostructures of FL_2E_4-1 (**8a**), -3 (**8c**), -4 (**8d**), and -5 (**8e**) were determined by X-ray crystallographic analysis. PLUTO drawings of these dilactone-tetraepoxides are shown in Fig. 6 and torsion angles at the ring atoms are given in Table II. As is apparent from Table II, the torsion angles of O1–C1–C2–C3 and O1′–C1′–C2′–C3′ indicate that the carbonyl moieties (O1–C1, O1′–C1′) of

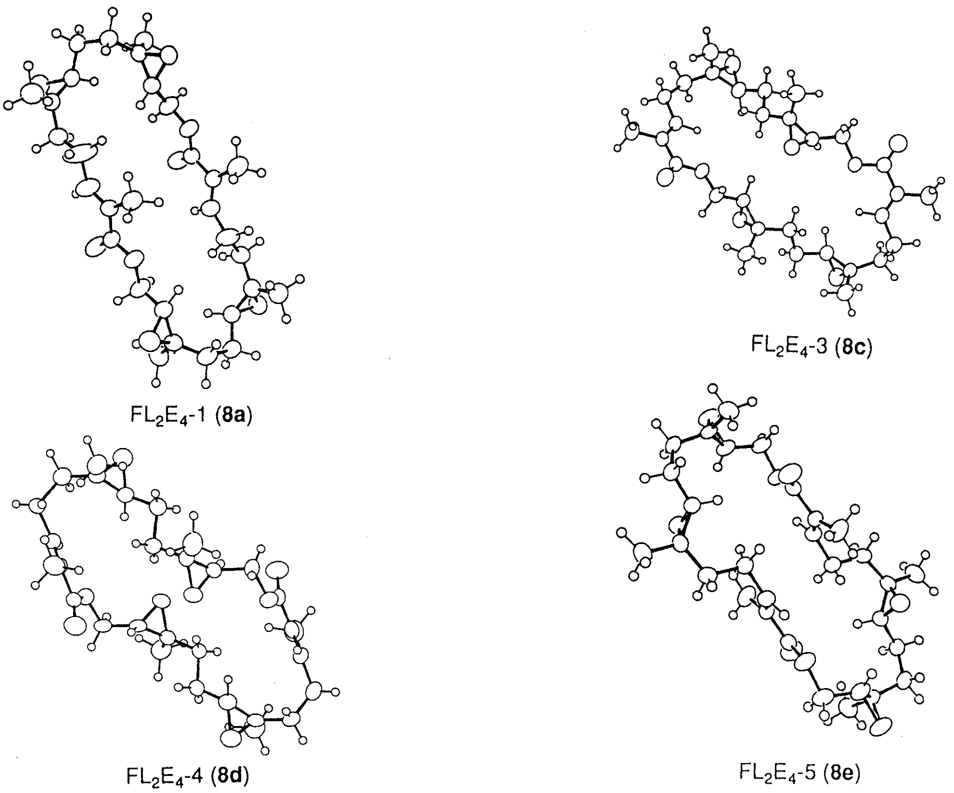
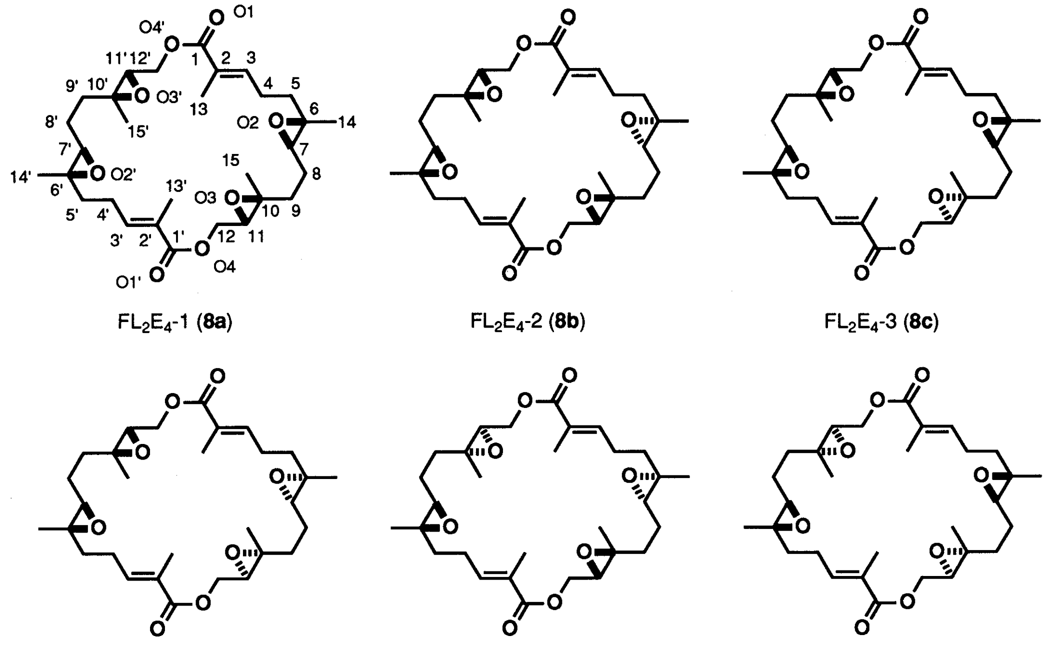

FL_2E_4-1 (**8a**) FL_2E_4-3 (**8c**) FL_2E_4-4 (**8d**) FL_2E_4-5 (**8e**)

Fig. 6. PLUTO Drawings of FL_2E_4



FL_2E_4-1 (**8a**) FL_2E_4-2 (**8b**) FL_2E_4-3 (**8c**)
FL_2E_4-4 (**8d**) FL_2E_4-5 (**8e**) FL_2E_4-6 (**8f**)

Chart 3

FL_2E_4-3 (**8c**), FL_2E_4-4 (**8d**), and FL_2E_4-5 (**8e**) take an *anti* conformation with respect to the double bonds at C2–C3 and C2′–C3′, while the corresponding carbonyls of FL_2E_4-1 (**8a**) are in *syn* conformation.

As for the stereostructures of FL_2E_4-2 (**8b**) and -6 (**8f**), it has been shown that **8b** is asymmetric while **8f** is symmetric from a consideration of the ^{1}H-NMR signals due to the methyls attached to the epoxide rings of **8b** (δ 1.26, 1.27, 1.35, 1.37, 3H each, all s) and **8f** (δ 1.19, 1.28, 6H each, both s). Consequently, the structures of **8b** and **8f** are assigned as shown in Chart 3.

Thus, FL_2E_4-1 (**8a**) and FL_2E_4-6 (**8f**) are C_2-symmetrical and FL_2E_4-4 (**8d**) and FL_2E_4-5 (**8e**) are S_2-symmetrical, whereas FL_2E_4-2 (**8b**) and FL_2E_4-3 (**8c**) are asymmetrical.

Ionophoretic Activities of Six Diastereomers of FL_2E_4 In order to clarify the relationship between the ionophoretic activities and the stereostructures, we next examined the ionophoretic activities of the diastereomers of FL_2E_4 (**8**). Among the six diastereomers, FL_2E_4-1 (**8a**), FL_2E_4-5 (**8e**) and FL_2E_4-4 (**8d**), having symmetrical structures, were shown to exhibit stronger K^+ ion transport activities than the parent diastereo-mixture (**8**), whereas FL_2E_4-2 (**8b**), FL_2E_4-6 (**8f**) and FL_2E_4-3 (**8c**) exhibited weaker activities. On the other hand, in regard to the K^+ ion-permeation activity across human erythrocyte membrane, it was found that FL_2E_4-3 (**8c**), FL_2E_4-1 (**8a**) and FL_2E_4-2 (**8b**) exhibited stronger activities than the other three diastereomers (**8d**—**8f**).

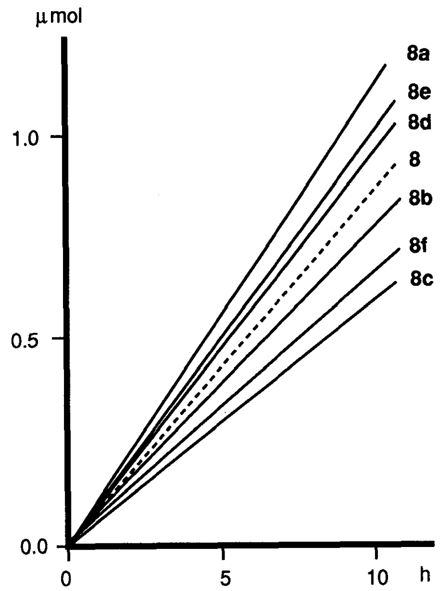


Fig. 7. K^+-Ion Transport Activities of FL_2E_4-1—6 (**8a**—**f**)
Initial concentration of sample: 0.03 M in $CHCl_3$.

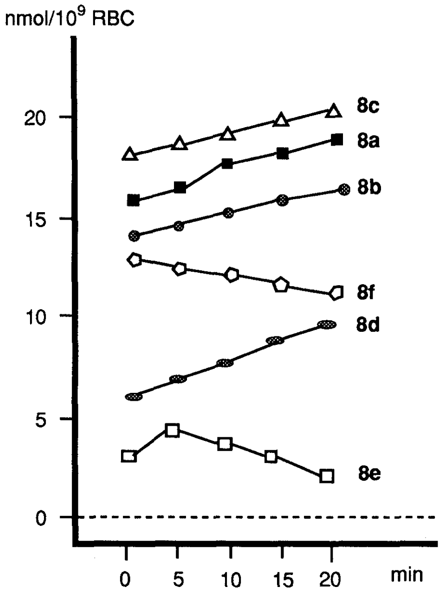


Fig. 8. K^+-Ion Permeation Activities of FL_2E_4-1—6 (**8a**—**f**)
Initial concentration of sample: 0.25 mmol/10^9 RBC.

The results revealed that FL_2E_4-1 (**8a**) possesses quite strong ion-transport and ion-permeation activities[4,6] for K^+ ion. In order to establish the mode of association between **8a** and K^+ ion in solution, we next compared the ^{1}H-NMR spectra of FL_2E_4-1 (**8a**) taken in the absence and in the presence of K^+ ion. The ^{1}H-NMR spectrum of **8a** taken in $CDCl_3$ saturated with D_2O showed a 12-proton singlet at δ 1.25 attributable to four methyl groups attached to epoxide rings and a 6-proton singlet at δ 1.83 due to two vinyl methyls. On the other hand, the spectrum of **8a**, taken in the same solvent system containing potassium tetrachloroplatinate (K_2PtCl_4), showed two 6-proton singlets at δ 1.25 and 1.60 ascribable to four methyl groups together with a 6-proton singlet signal of vinyl methyls at δ 1.83. These findings suggest that some epoxide oxygens in the molecule of FL_2E_4-1 (**8a**) are involved in the association with K^+ cation. Furthermore, the conformation of FL_2E_4-1 (**8a**) in the solution may change in the presence of K^+ ion for binding with the cation, since four epoxide rings in **8a** have been shown by X-ray analysis to be directed equally towards the outside of the plane of the macrocyclic dilactone ring.

Finally, it is noteworthy that FL_2E_4-3 (**8c**) showed the weakest ion-transport but the strongest ion-permeation activities among the six diastereomers. The apparently different ionophoretic activities observed in two different activity tests suggested that the increase of K^+ ion inside erythrocytes may result from the operation of an active transport system, but further investigation is needed on this point.

Experimental

Melting points were determined on a Yanagimoto micro-melting point apparatus and recorded as observed. Optical rotations were measured in a 0.5 cm tube with a JASCO DIP-370 polarimeter. MS and high-resolution mass specta (high MS) were taken on a JEOL JMS-D300 spectrometer. Infrared (IR) spectra were taken on a Hitachi 260-30 spectrometer. Ultraviolet (UV) spectra were taken on a Hitachi 330 UV-VIS spectrophotometer. ^{1}H-NMR spectra were recorded on JEOL GX-500 (500 MHz), EX-270 (270 MHz), and FX-90Q (90 MHz) spectrometers with tetramethylsilane (TMS) as an internal standard. Chemical shifts are given on the δ scale (ppm). The following abbreviations are used: s = singlet, d = doublet, t = triplet, m = multiplet and br = broad. Coupling constants (*J* value) are given in hertz (Hz). HPLC was carried out on Shimadzu LC-5A, LC-6A, and Waters C-201 chromatographs. X-Ray crystallographic data were collected on a Rigaku AFC-5 diffractometer using graphite-monochromated CuK_α radiation. Column chromatography was performed on Kieselgel 60 (Merck, 70—230 mesh), and thin-layer chromatography (TLC) was carried out with pre-coated Kieselgel 60F_{254} plates (Merck).

Selenium Dioxide Oxidation of *E,E*-Farnesyl Acetate (1a) A solution of *E,E*-farnesyl acetate (**1a**, 15.0 g, 56.8 mmol), which was prepared from *E,E*-farnesol (**1**, 14.2 g) by treatment with Ac_2O (8 ml) and pyridine (15 ml), in aqueous 95% EtOH (1 l) was treated with SeO_2 (6.62 g, 56.8 mmol, 1.0 eq) and the mixture was stirred vigorously at 60 °C for 2 h. After rapid cooling to room temperature, the reaction mixture was poured into ice-water and the whole was extracted with EtOAc. The EtOAc extract was washed with aqueous saturated $NaHCO_3$ and aqueous saturated NaCl, then dried over $MgSO_4$. Removal of the solvent under reduced pressure from the EtOAc extract gave a product (21 g), which was purified by column chromatography (SiO_2 1.0 kg, *n*-hexane : EtOAc = 5 : 1) to furnish **2** (6.2 g, 22.1 mmol, 39%) and recovered **1a** (4.5 g, 17 mmol, 30%).

2: A colorless oil. IR (film): 3600—3100 (br), 1730, 1660 cm^{-1}. ^1H-NMR (90 MHz, $CDCl_3$) δ: 1.62, 1.68, 1.71 (3H each, all br s, vinyl methyl × 3), 2.06 (3H, s, $-OCOC\underline{H}_3$), 4.00 (2H, br s, $-C\underline{H}_2OH$), 4.59 (2H, d, $J=7$ Hz, $-C\underline{H}_2OAc$), 5.0—5.2 (1H, m, olefinic proton), 5.2—5.5 (2H, m, olefinic protons). MS *m/z* (%): 280 (M^+, 2.6), 220 ($M^+ -$AcOH, 13.7), 93 (100). High-resolution MS *m/z*: Calcd for $C_{17}H_{28}O_3$: 280.204. Found: 280.206 (M^+).

Manganese Dioxide Oxidation of 2 A solution of **2** (6.2 g, 22.1 mmol) in *n*-hexane–$CHCl_3$ (10 : 1, 550 ml) was treated with MnO_2[14] (39 g) and the whole mixture was stirred vigorously at room temperature for 5 h. After removal of the solid matter by filtration, the solvent was evaporated off under reduced pressure to yield the aldehydic derivative **2a** (6.61 g, 22.1 mmol, quantitative).

2a: A colorless oil. IR (film): 1745, 1690, 1645 cm^{-1}. UV λ_{max}^{EtOH} nm (ε): 204 (16000), 228 (15000). ^1H-NMR (90 MHz, $CDCl_3$) δ: 1.61, 1.67, 1.71 (3H each, all br s, vinyl methyl × 3), 2.01 (3H, s, $-OCOC\underline{H}_3$), 4.55 (2H, d, $J=7$ Hz, $-C\underline{H}_2OAc$), 5.0—5.5 (2H, m, olefinic protons), 6.44 (1H, br t, $J=$ *ca.* 6 Hz, olefinic proton), 9.35 (1H, s, $-C\underline{H}O$). MS *m/z* (%): 278 (M^+, 1.4), 218 ($M^+ -$AcOH, 46.9), 93 (100). High-resolution MS *m/z*: Calcd for $C_{17}H_{26}O_3$: 278.188. Found: 278.187 (M^+).

Oxidation of 2a with MnO_2–NaCN–AcOH–MeOH NaCN (95%, 2.49 g, 50.8 mmol, 2.3 eq), MnO_2 (57.6 g, 0.66 mol, 30 eq) and freshly distilled AcOH (3.50 ml, 61.0 mmol, 2.8 eq) were added successively to a solution of **2a** (6.61 g, 22.1 mmol) in dry MeOH (500 ml), and the whole mixture was stirred vigorously at room temperature for 36 h. After removal of the solid matter by filtration, the filtrate was poured into ice-water and the whole was extracted with EtOAc. The EtOAc extract was washed with aqueous saturated $NaHCO_3$ and aqueous saturated NaCl, then dried over $MgSO_4$. Removal of the solvent under reduced pressure from the EtOAc extract gave a product (8.0 g), which was purified by column chromatography (SiO_2 500 g, *n*-hexane : EtOAc = 1 : 1) to furnish **3** (4.03 g, 13.1 mmol, 59%).

3: A colorless oil. IR (film): 1732, 1710, 1645 cm^{-1}. UV λ_{max}^{EtOH} nm (ε): 206 (18000), 216 (sh), 233 (sh). ^1H-NMR (90 MHz, $CDCl_3$) δ: 1.62, 1.72, 1.84 (3H each, all br s, vinyl methyl × 3), 2.06 (3H, s, $OCOC\underline{H}_3$), 3.74 (3H, s, $-COOC\underline{H}_3$), 4.60 (2H, d, $J=7$ Hz, $-C\underline{H}_2OAc$), 5.0—5.5 (2H, m, olefinic protons), 6.74 (1H, br t, $J=$ *ca.* 6 Hz, olefinic proton). MS *m/z* (%): 308 (M^+, 0.8), 248 ($M^+ -$AcOH, 40.2), 93 (100). High-resolution MS *m/z*: Calcd for $C_{18}H_{28}O_4$: 308.199. Found: 308.199 (M^+).

Alkaline Hydrolysis of 3 A solution of **3** (1.84 g, 5.97 mmol) in dry MeOH (20 ml) was treated with 10% KOH–MeOH (20 ml) and the whole was stirred at room temperature for 30 min. The reaction mixture was poured into ice-water and then extracted with EtOAc. Work-up of the EtOAc extract in the usual manner gave **4** (1.58 g, 5.97 mmol, quantitatively).

4: A colorless oil. IR (film): 3600—3100 (br), 1705, 1645 cm^{-1}. UV λ_{max}^{EtOH} nm (ε): 208 (16000), 217 (sh). ^1H-NMR (90 MHz, $CDCl_3$) δ: 1.63, 1.69, 1.85 (3H each, all br s, vinyl methkl × 3), 3.74 (3H, s, $-COOC\underline{H}_3$), 5.14, 5.41 (1H each, both m, olefinic protons), 6.75 (1H, br t, $J=$ *ca.* 7 Hz, olefinic proton). MS *m/z* (%): 266 (M^+, 1.7), 206 ($M^+ -$AcOH, 41.5), 93 (100). High-resolution MS *m/z*: Calcd for $C_{16}H_{26}O_3$: 266.372. Found: 266.373 (M^+).

Lactonization of 4 Giving 5 and 6 I) 1.0×10^{-2} mol/l in THF: A solution of **4** (15 mg, 5.64×10^{-2} mmol) in dry THF (5.64 ml) was treated with 60% NaH (11.3 mg, 0.282 mmol, 5.0 eq) and the mixture was heated under reflux for 2 h. After cooling, the reaction mixture was poured into aqueous saturated NH_4Cl and the whole was extracted with EtOAc. The EtOAc extract was washed with aqueous saturated NaCl, and then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a product (25 mg), which was purified by column chromatography (SiO_2 5 g, *n*-hexane : EtOAc = 20 : 1) to furnish FL_1 (**5**, 1.1 mg, 4.70×10^{-3} mmol, 8.3%) and FL_2 (**6**, 9.5 mg, 2.03×10^{-2} mmol, 72%).

II) 1.0×10^{-3} mol/l in THF: A solution of **4** (15 mg, 5.64×10^{-2} mmol) in dry THF (56.4 ml) was treated with 60% NaH (11.3 mg, 0.282 mmol, 5.0 eq) and the mixture was heated under reflux for 3 h. After cooling, the reaction mixture was poured into aqueous saturated NH_4Cl and the whole was extracted with EtOAc. Work-up of the EtOAc extract as described above gave a product (26 mg), which was purified by column chromatography (SiO_2 5 g, *n*-hexane: EtOAc = 20 : 1) to afford FL_1 (**5**, 6.0 mg, 2.56×10^{-2} mmol, 46%) and FL_2 (**6**, 4.8 mg, 1.03×10^{-2} mmol, 36%).

III) 1.0×10^{-2} mol/l in Benene: A solutio of **4** (15 mg, 5.64×10^{-2} mmol) in dry benzene (5.64 ml) was treated with 60% NaH (11.3 mg, 0.282 mmol, 5 eq) and the mixture was heated under reflux for 2 h. After cooling, the reaction mixture was poured into aqueous saturated NH_4Cl and the whole was extracted with EtOAc. Work-up of the extract as described above gave a product (24 mg), which was purified by column chromatography (SiO_2 5 g, *n*-hexane : EtOAc = 20 : 1) to afford FL_1 (**5**, 1.8 mg, 7.69×10^{-3} mmol, 14%) and FL_2 (**6**, 8.0 mg, 1.71×10^{-2} mmol, 61%).

IV) 1.0×10^{-3} mol/l in Benzene: A solution of **4** (15 mg, 5.64×10^{-2} mmol) in dry benzene (56.4 ml) was treated with 60% NaH (11.3 mg, 0.282 mmol, 5.0 eq) and the mixture was heated under reflux for 3 h. Work-up of the reaction mixture as described above gave a product (24 mg), which was purified by column chromatography (SiO_2 5 g, *n*-hexane : EtOAc = 20 : 1) to furnish FL_1 (**5**, 7.2 mg, 3.08×10^{-2} mmol, 55%) and FL_2 (**6**, 4.3 mg, 9.19×10^{-3} mmol, 33%).

V) 1.0×10^{-2} mol/l in Toluene: A solution of **4** (15 mg, 5.64×10^{-2} mmol) in dry toluene (5.64 ml) was treated with 60% NaH (11.3 mg, 0.282 mmol, 5.0 eq) and the mixture was heated under reflux for 2 h. Work-up of the reaction mixture as above gave a product (27 mg), which was purified by column chromatography (SiO_2 5 g, *n*-hexane : EtOAc = 20 : 1) to furnish FL_1 (**5**, 6.2 mg, 2.70×10^{-2} mmol, 48%) and FL_2 (**6**, 5.4 mg, 1.15×10^{-2} mmol, 41%).

VI) 1.0×10^{-3} mol/l in Toluene: A solution of **4** (15 mg, 5.64×10^{-2} mmol) in dry toluene (56.4 ml) was treated with 60% NaH (11.3 mg, 0.282 mmol, 5.0 eq) and the mixture was heated under reflux for 3 h. Work-up of the reaction mixture as above gave a product (26 mg), which was purified by column chromatography (SiO_2 5 g, *n*-hexane : EtOAc = 20 : 1) to afford FL_1 (**5**, 9.5 mg, 4.06×10^{-2} mmol, 72%) and FL_2 (**6**, 3.2 mg, 0.68×10^{-2} mmol, 24%).

FL_1 (**5**): Colorless fine crystals (from petroleum ether), mp 49 °C. IR (KBr): 1689, 1651 cm^{-1}: UV λ_{max}^{EtOH} nm (ε): end absorption, 205 (sh), 218 (sh), 237 (sh). ^1H-NMR (90 MHz, $CDCl_3$) δ: 1.58, 1.64, 1.82 (3H each, all br s, vinyl methyl × 3), 4.70 (2H, d, $J=8$ Hz, $-C\underline{H}_2OCO-$), 4.6—5.0 (1H, m, olefinic proton), 5.48 (1H, t, $J=8$ Hz, olefinic proton), 6.51 (1H, t, $J=6$ Hz, olefinic proton). MS *m/z* (%): 234 (M^+, 4.7), 82 (100). High-resolution MS *m/z*: Calcd for $C_{15}H_{22}O_2$: 234.162. Found: 234.162 (M^+).

FL_2 (**6**): Colorless fine crystals (from petroleum ether), mp 45 °C. IR (KBr): 1704, 1646 cm^{-1}. UV λ_{max}^{EtOH} nm (ε): end absorption, 208 (sh), 218 (sh), 239 (sh). ^1H-NMR (90 MHz, $CDCl_3$) δ: 1.59, 1.71, 1.80 (6H each, all br s, vinyl methyl × 6), 4.63 (4H, d, $J=7$ Hz, $-C\underline{H}_2OCO-$), 4.9—5.2 (2H, m, olefinic protons), 5.33 (2H, t, $J=7$ Hz, olefinic protons), 6.69 (2H, t, $J=6$ Hz, olefinic protons). MS *m/z* (%): 468 (M^+, 5.8), 82 (100). High-resolution MS *m/z*: Calcd for $C_{30}H_{44}O_4$: 468.324. Found: 468.324 (M^+).

Epoxidation of FL_1 (5) A solution of **5** (80 mg, 0.34 mmol) and 70% MCPBA (253 mg, 1.02 mmol, 3.0 eq) in $CHCl_3$ (20 ml) was stirred at room temperature for 2.5 h. The reaction mixture was poured into aqueous saturated Na_2SO_3 and the whole was extracted with EtOAc. The EtOAc

TABLE III. Experimental Data for the X-Ray Diffraction Studies of FL_2E_4-1 (**8a**), -3 (**8c**), -4 (**8d**), and -5 (**8e**)

	FL_2E_4-1 (**8a**)	FL_2E_4-3 (**8c**)	FL_2E_4-4 (**8d**)	FL_2E_4-5 (**8e**)
Formula	$C_{30}H_{44}O_8$	$C_{30}H_{44}O_8$	$C_{30}H_{44}O_8$	$C_{30}H_{44}O_8$
Formula weight	532.304	532.304	532.304	532.304
F (000)	1160	1152	576	576
System	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/C$	$P2_1/C$	$P2_1$	$P2_1/C$
a (Å)	8.897 (3)	10.400 (3)	10.058 (4)	5.940 (5)
b (Å)	31.005 (6)	22.238 (6)	6.157 (2)	12.869 (3)
c (Å)	11.237 (3)	12.770 (3)	23.611 (9)	19.351 (4)
α (°)	90.0	90.0	90.0	90.0
β (°)	108.660 (3)	91.92 (2)	91.80 (4)	106.31 (3)
γ (°)	90.0	90.0	90.0	90.0
V (Å)	2937 (1)	2952 (1)	1461.3 (9)	1417.18 (5)
Z	4	4	2	4
F_O used	3657	4613	2553	1474
No. of parameters	475	344	344	238
R	0.0579	0.0402	0.0468	0.0763
R_w	0.0579	0.0503	0.0507	0.0763

TABLE IV. Fractional Coordinates of Non-H Atoms and Equivalent Isotropic Temperature Factors with e.s.d.'s in Parentheses

Atom	x	y	z	B_{eq}/B_{iso} (Å^2)
FL$_2$E$_4$-1 (**8a**)				
C1	1.1317 (4)	0.40551 (11)	0.4359 (3)	3.98 (11)
C2	1.0245 (4)	0.43136 (11)	0.3313 (3)	4.03 (10)
C3	1.0533 (5)	0.47264 (14)	0.3311 (5)	6.86 (16)
C4	0.9603 (10)	0.5049 (2)	0.2333 (8)	11.8 (3)
C5	1.0071 (5)	0.54869 (14)	0.2572 (4)	5.29 (13)
C6	0.9124 (4)	0.58032 (12)	0.1610 (3)	4.48 (11)
C7	0.7766 (4)	0.60090 (11)	0.1844 (3)	4.03 (11)
C8	0.6391 (4)	0.62047 (12)	0.0869 (3)	4.13 (11)
C9	0.5022 (4)	0.58901 (13)	0.0355 (3)	4.37 (11)
C10	0.4433 (4)	0.56838 (11)	0.1344 (3)	3.98 (10)
C11	0.4931 (4)	0.52421 (11)	0.1738 (3)	3.97 (10)
C12	0.5050 (6)	0.50762 (12)	0.3013 (4)	4.88 (13)
C13	0.8911 (5)	0.40904 (14)	0.2344 (4)	5.24 (13)
C14	0.9205 (6)	0.5763 (2)	0.0303 (5)	6.9 (2)
C15	0.3936 (6)	0.59917 (14)	0.2184 (5)	5.56 (16)
C1′	0.5803 (4)	0.43933 (11)	0.3977 (3)	3.87 (10)
C2′	0.5624 (4)	0.39184 (11)	0.3824 (3)	3.81 (10)
C3′	0.6722 (5)	0.36809 (12)	0.4628 (4)	4.56 (12)
C4′	0.6891 (6)	0.31994 (13)	0.4610 (4)	5.47 (14)
C5′	0.7132 (5)	0.29984 (13)	0.5893 (4)	4.59 (12)
C6′	0.7677 (4)	0.25344 (12)	0.5968 (3)	4.22 (11)
C7′	0.9369 (4)	0.24461 (12)	0.6611 (3)	3.88 (10)
C8′	1.0246 (5)	0.20564 (12)	0.6402 (4)	4.41 (12)
C9′	1.1027 (5)	0.21293 (12)	0.5387 (4)	4.60 (13)
C10′	1.2040 (4)	0.25297 (11)	0.5585 (3)	3.79 (10)
C11′	1.1324 (4)	0.29134 (11)	0.4855 (3)	3.69 (10)
C12′	1.1798 (5)	0.33600 (12)	0.5275 (3)	4.74 (12)
C13′	0.4268 (6)	0.37421 (14)	0.2770 (4)	5.95 (15)
C14′	0.6652 (6)	0.22318 (15)	0.5006 (5)	6.12 (15)
C15′	1.3394 (5)	0.25681 (16)	0.6797 (4)	5.14 (13)
O1	1.2403 (3)	0.41922 (8)	0.5210 (3)	6.08 (9)
O2	0.9264 (3)	0.62393 (8)	0.2107 (3)	5.85 (9)
O3	0.3362 (3)	0.53233 (8)	0.0861 (2)	4.99 (8)
O4	0.4960 (3)	0.46060 (7)	0.2938 (2)	4.52 (8)
O1′	0.6608 (3)	0.45738 (8)	0.4905 (3)	5.87 (9)
O2′	0.8198 (3)	0.23710 (9)	0.7250 (2)	5.21 (9)
O3′	1.2446 (3)	0.26515 (8)	0.4472 (2)	4.83 (8)
O4′	1.0918 (3)	0.36369 (7)	0.4252 (2)	4.41 (7)
FL$_2$E$_4$-3 (**8c**)				
C1	1.1281 (3)	0.1103 (1)	0.1964 (2)	3.8 (1)
C2	1.1534 (3)	0.1048 (1)	0.3099 (2)	3.7 (1)
C3	1.0595 (3)	0.0936 (1)	0.3741 (2)	3.7 (1)
C4	1.0758 (3)	0.0912 (2)	0.4913 (2)	4.2 (1)
C5	0.9520 (3)	0.0790 (2)	0.5481 (3)	4.5 (1)
C6	0.8499 (3)	0.1268 (2)	0.5319 (2)	4.0 (1)
C7	0.7400 (3)	0.1140 (2)	0.4595 (3)	4.4 (1)
C8	0.6617 (3)	0.1604 (2)	0.4019 (3)	4.7 (2)
C9	0.7174 (3)	0.1714 (2)	0.2947 (3)	4.2 (1)
C10	0.6414 (3)	0.2149 (1)	0.2264 (2)	3.8 (1)
C11	0.5424 (3)	0.1908 (1)	0.1533 (2)	3.8 (1)
C12	0.4298 (3)	0.2272 (2)	0.1158 (3)	4.4 (1)
C13	1.2913 (4)	0.1150 (2)	0.3469 (3)	6.2 (2)
C14	0.8891 (4)	0.1898 (2)	0.5592 (3)	5.2 (2)
C15	0.6357 (4)	0.2787 (2)	0.2668 (3)	5.3 (2)
C1′	0.2753 (3)	0.2256 (2)	−0.0215 (3)	4.1 (1)
C2′	0.2282 (3)	0.1978 (1)	−0.1216 (2)	3.9 (1)
C3′	0.2827 (3)	0.1494 (2)	−0.1593 (3)	4.2 (1)
C4′	0.2368 (4)	0.1175 (2)	−0.2570 (3)	5.0 (2)
C5′	0.2519 (3)	0.0491 (2)	−0.2523 (2)	4.1 (1)
C6′	0.3891 (3)	0.0270 (1)	−0.2592 (2)	3.7 (1)
C7′	0.4591 (3)	0.0109 (1)	−0.1619 (2)	3.9 (1)
C8′	0.6026 (3)	0.0094 (2)	−0.1466 (3)	4.4 (1)
C9′	0.6540 (3)	0.0664 (1)	−0.0930 (2)	3.9 (1)
C10′	0.7957 (3)	0.0630 (1)	−0.0685 (2)	3.5 (1)
C11′	0.8428 (3)	0.0830 (2)	0.0356 (2)	3.9 (1)
C12′	0.9785 (3)	0.1045 (2)	0.0542 (2)	4.5 (1)
C13′	0.1127 (4)	0.2285 (2)	−0.1725 (3)	6.2 (2)
C14′	0.4572 (4)	0.0426 (2)	−0.3573 (3)	5.7 (2)
C15′	0.8827 (3)	0.0613 (2)	−0.1601 (3)	5.2 (2)
FL$_2$E$_4$-3 (**8c**)				
O1	1.2094 (2)	0.1251 (1)	0.1351 (2)	5.9 (1)
O2	0.7277 (2)	0.1083 (1)	0.5717 (2)	5.7 (1)
O3	0.6653 (2)	0.2085 (1)	0.1158 (2)	4.4 (1)
O4	0.3884 (2)	0.2039 (1)	0.0149 (2)	4.16 (9)
O1′	0.2186 (3)	0.2646 (1)	0.0233 (2)	6.4 (1)
O2′	0.4021 (3)	−0.0351 (1)	−0.2275 (2)	5.1 (1)
O3′	0.8278 (2)	0.0197 (1)	0.0141 (2)	4.18 (9)
O4′	1.0071 (2)	0.0975 (1)	0.1648 (2)	4.6 (1)
FL$_2$E$_4$-4 (**8d**)				
C1	1.0396 (4)	−0.0698 (9)	0.4139 (2)	3.0 (2)
C2	0.9115 (5)	−0.1440 (9)	0.4378 (2)	3.4 (2)
C3	0.8281 (5)	0.0037 (9)	0.4586 (2)	3.5 (2)
C4	0.6974 (5)	−0.032 (1)	0.4857 (2)	3.7 (3)
C5	0.5841 (6)	0.104 (1)	0.4530 (2)	4.7 (3)
C6	0.5554 (5)	0.025 (1)	0.3931 (2)	4.0 (3)
C7	0.6258 (5)	0.124 (1)	0.3474 (2)	4.0 (3)
C8	0.6511 (5)	0.016 (1)	0.2908 (2)	4.6 (3)
C9	0.7907 (5)	−0.073 (1)	0.2894 (2)	4.0 (3)
C10	0.8209 (5)	−0.1709 (9)	0.2323 (2)	3.5 (2)
C11	0.8679 (5)	−0.0259 (9)	0.1888 (2)	3.3 (2)
C12	0.8477 (5)	−0.064 (1)	0.1270 (2)	3.4 (2)
C13	0.8872 (6)	−0.3713 (9)	0.4415 (2)	4.0 (3)
C14	0.5033 (6)	−0.206 (1)	0.3867 (3)	6.4 (4)
C15	0.7458 (7)	−0.373 (1)	0.2178 (3)	5.6 (4)
C1′	0.9657 (6)	0.234 (1)	0.0853 (2)	4.0 (3)
C2′	1.0932 (5)	0.2980 (8)	0.0610 (2)	2.8 (2)
C3′	1.1733 (5)	0.149 (1)	0.0412 (2)	3.4 (2)
C4′	1.3071 (6)	0.190 (1)	0.0156 (2)	5.0 (3)
C5′	1.4169 (5)	0.079 (1)	0.0468 (2)	4.0 (3)
C6′	1.4400 (5)	0.155 (1)	0.1060 (2)	4.2 (3)
C7′	1.3692 (5)	0.041 (1)	0.1528 (2)	4.1 (3)
C8′	1.3411 (5)	0.140 (1)	0.2080 (2)	4.2 (3)
C9′	1.2039 (5)	0.246 (1)	0.2102 (2)	3.7 (3)
C10′	1.1794 (5)	0.3389 (9)	0.2660 (2)	3.3 (2)
C11′	1.1336 (5)	0.1887 (9)	0.3110 (2)	3.5 (2)
C12′	1.1578 (5)	0.225 (1)	0.3719 (2)	4.0 (3)
C13′	1.1129 (6)	0.556 (1)	0.0658 (3)	5.0 (3)
C14′	1.4963 (6)	0.374 (1)	0.1124 (3)	5.4 (3)
C15′	1.2474 (6)	0.555 (1)	0.2799 (3)	4.8 (3)
O1	1.1278 (4)	−0.1883 (7)	0.4052 (2)	5.1 (2)
O2	0.4917 (4)	0.1837 (8)	0.3581 (2)	5.7 (2)
O3	0.9589 (3)	−0.1712 (7)	0.2178 (2)	4.2 (2)
O4	0.9588 (3)	0.0153 (6)	0.0969 (1)	3.8 (2)
O1′	0.8687 (4)	0.3547 (7)	0.0938 (2)	5.4 (2)
O2′	1.5095 (4)	−0.0100 (9)	0.1426 (2)	6.2 (3)
O3′	1.0384 (3)	0.3285 (7)	0.2820 (2)	4.1 (2)
O4′	1.0391 (3)	0.1410 (6)	0.4021 (1)	3.9 (2)
FL$_2$E$_4$-5 (**8e**)				
C1	0.3208 (10)	1.2187 (5)	0.4712 (3)	3.0 (2)
C2	0.3562 (11)	1.1200 (5)	0.4336 (3)	3.3 (2)
C3	0.2161 (13)	1.0395 (6)	0.4306 (4)	3.9 (2)
C4	0.2461 (14)	0.9360 (6)	0.3971 (4)	4.1 (2)
C5	0.0935 (14)	0.9263 (6)	0.3203 (4)	4.0 (2)
C6	0.1569 (12)	0.8393 (5)	0.2769 (3)	3.4 (2)
C7	0.3008 (12)	0.7519 (5)	0.3112 (4)	3.4 (2)
C8	0.3050 (14)	0.6446 (6)	0.2811 (4)	3.7 (2)
C9′	0.4495 (14)	1.3966 (6)	0.7065 (4)	3.9 (2)
C10′	0.3174 (11)	1.4144 (5)	0.6281 (4)	3.1 (2)
C11′	0.1511 (12)	1.3338 (6)	0.5921 (4)	3.7 (2)
C12′	0.0496 (13)	1.3196 (6)	0.5121 (5)	4.2 (3)
C13′	0.567 (2)	1.1226 (8)	0.4065 (6)	5.2 (3)
C14	−0.009 (2)	0.8301 (7)	0.2026 (5)	0.076 (4)
C15′	0.4252 (16)	1.4886 (6)	0.5885 (5)	4.5 (3)
O1	0.4567 (9)	1.2892 (4)	0.4826 (3)	5.1 (2)
O2	0.4059 (9)	0.8353 (4)	0.2810 (3)	4.26 (16)
O3′	0.0643 (8)	1.4260 (4)	0.6183 (3)	4.6 (2)
O4′	0.1164 (8)	1.2212 (4)	0.4874 (3)	3.99 (15)

extract was washed with aqueous saturated $NaHCO_3$ and aqueous saturated NaCl, then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a product (200 mg), which was purified by column chromatography (SiO_2 20 g, *n*-hexane : EtOAc = 4 : 1) to furnish FL$_1$E$_2$ (**7**, 76 mg, 0.29 mmol, 84%).

FL$_1$E$_2$ (**7**): A white powder. IR (film): 1708, 1644 cm^{-1}. UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ε): 216 (10500). ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.20, 1.28 (3H each, both s, methyl × 2), 1.83 (3H, br s, vinyl methyl), 2.60 (1H, t, $J=4$ Hz), 3.01 (1H, dd, $J=4$, 8 Hz), 3.9—4.8 (2H, m), 6.6—6.9 (1H, m, olefinic proton). MS *m*/*z* (%): 266 (M^+, 0.1), 111 (100). High-resolution MS *m*/*z*: Calcd for $C_{15}H_{22}O_4$: 266.152. Found: 266.150 (M^+).

Epoxidation of FL$_2$ (6) A solution of **6** (200 mg, 0.43 mmol) and 70% MCPBA (461 mg, 2.14 mmol, 5.0 eq) in $CHCl_3$ (30 ml) was stirred at room temperature for 4 h. The reaction mixture was poured into aqueous saturated Na_2SO_3 and the whole was extracted with EtOAc. The EtOAc extract was washed with aqueous saturated $NaHCO_3$ and aqueous saturated NaCl, then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a product (264 mg), which was purified by column chromatography (SiO_2, 30 g, *n*-hexane : EtOAc = 4 : 1) to furnish FL$_2$E$_4$ (**8**, 170 mg, 0.32 mmol, 75%).

FL$_2$E$_4$ (**8**): A white powder. IR (film): 1706, 1642 cm^{-1}. UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ε): 218 (21000). ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.23, 1.31 (6H each, both s, methyl × 4), 1.82 (6H, br s, vinyl methyl × 2), 2.5—2.8 (2H, m), 2.9—3.1 (2H, m), 3.8—4.5 (4H, m), 6.73 (2H, m, olefinic protons). MS *m*/*z* (%): 532 (M^+, 3.0), 111 (100). High-resolution MS *m*/*z*: Calcd for $C_{30}H_{44}O_8$: 532.304. Found: 532.304 (M^+).

HPLC Separation of FL$_2$E$_4$ (8) Giving Six Diastereomers (8a—8f) FL$_2$E$_4$ (**8**, 232 mg) was subjected to HPLC separation (Merck Hibar LiChrosorb Si60, *n*-hexane : EtOAc = 3 : 1) to provide FL$_2$E$_4$-1 (**8a**, 11 mg), FL$_2$E$_4$-2 (**8b**, 53 mg). FL$_2$E$_4$-3 (**8c**, 63 mg), FL$_2$E$_4$-4 (**8d**, 42 mg), FL$_2$E$_4$-5 (**8e**, 32 mg), and FL$_2$E$_4$-6 (**8f**, 31 mg).

FL$_2$E$_4$-1 (**8a**): Colorless needles, mp 114—115 °C (*n*-hexane–EtOAc). IR ($CHCl_3$): 1708, 1644 cm^{-1}. UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ε): 217 (23000). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.36, 1.27 (6H each, both s, 6-CH_3, 10-CH_3, 6′-CH_3, 10′-CH_3), 1.86 (6H, br s, 2-CH_3, 2′-CH_3), 2.71 (2H, br t, 11-H, 11′-H), 3.03 (2H, t, $J=6.8$ Hz, 7-H, 7′-H), 4.17 (2H, dd, $J=6.2$, 12.2 Hz, 12-H_a, 12′-H_a), 4.34 (2H, dd, $J=4.8$, 12.2 Hz, 12-H_b, 12′-H_b), 6.77 (2H, t-like, 3-H, 3′-H). ^{1}H-NMR (500 MHz, $CDCl_3$ saturated with D_2O) δ: 1.25 (12H, br s, CH_3 × 4), 1.83 (6H, br s, CH_3 × 2), 2.72 (2H, t, $J=5.6$ Hz, 11-H, 11′H), 3.04 (2H, t, $J=5.9$ Hz, 7-H_a, 7′-H_a), 4.16 (2H, dd, $J=6.3$, 12.2 Hz, 12-H_a, 12′-H_a), 4.35 (2H, dd, $J=4.6$, 11.8 Hz, 12-H_b, 12′-H_b), 6.78 (2H, t-like, 3-H, 3′-H). ^{1}H-NMR (500 MHz, $CDCl_3$ saturated with a saturated solution of K_2PtCl_4 in D_2O) δ: 1.25 (6H, br s, CH_3 × 2), 1.60 (6H, br s, CH_3 × 2), 1.83 (6H, br s, CH_3 × 2), 2.72 (2H, t, $J=5.6$ Hz, 11-H, 11′-H), 3.03 (2H, t, $J=5.9$ Hz, 7-H_a, 7′-H_a), 4.16 (2H, dd, $J=6.3$, 12.2 Hz, 12-H_a, 12′-H_a), 4.35 (2H, dd, $J=4.6$, 11.8 Hz, 12-H_b, 12′-H_b), 6.78 (2H, t-like, 3-H, 3′-H). MS *m*/*z* (%): 532 (M^+, 1.6), 95 (100). High-resolution MS *m*/*z*: Calcd for $C_{30}H_{44}O_8$: 532.303. Found: 532.302 (M^+).

FL$_2$E$_4$-2 (**8b**): Colorless needles, mp 111—112 °C (*n*-hexane–EtOAc). IR ($CHCl_3$) cm^{-1}: 1710, 1645. UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ε): 216 (18000). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.26, 1.27, 1.35, 1.37 (3H each, all s, CH_3 × 4), 1.86 (6H, br s, CH_3 × 2), 2.63 (1H, t, $J=6.1$ Hz, 7-H or 7′-H), 3.23 (1H, br t, 11-H or 11′-H), 3.71 (1H, t, $J=6.1$ Hz, 7-H or 7′-H), 3.96 (1H, br t, 11-H or 11′-H), 4.03 (1H, dd, $J=6.4$, 12.2 Hz), 4.08 (1H, dd, $J=6.4$, 12.2 Hz), 4.29 (1H, dd, $J=4.9$, 12.2 Hz), 4.31 (1H, dd, $J=4.9$, 12.2 Hz), (12-H_2, 12′-H_2), 6.69 (2H, t, $J=6.5$ Hz, 3-H, 3′-H). MS *m*/*z* (%): 532 (M^+, 2.0), 95 (100). High-resolution MS *m*/*z*: Calcd for $C_{30}H_{44}O_8$: 532.303. Found: 532.303 (M^+).

FL$_2$E$_4$-3 (**8c**): Colorless needles, mp 112—113 °C (*n*-hexane–EtOAc). IR ($CHCl_3$) cm^{-1}: 1709, 1644. UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ε): 216 (13000). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.19, 1.21, 1.26, 1.28 (3H each, all s, CH_3 × 4), 1.79 (6H, br s, CH_3 × 2), 2.64 (1H, t, $J=5.8$ Hz, 7-H or 7′-H), 2.99 (2H, dd, $J=3.7$, 7.3 Hz, 11-H, 11′-H), 3.65 (1H, t, $J=6.4$ Hz, 7-H or 7′-H), 3.97 (1H, dd, $J=7.3$, 15.9 Hz), 4.01 (1H, dd, $J=7.3$, 15.9 Hz), 4.36 (2H, m) (12-H_2, 12′-H_2), 6.69 (2H, t-like, 3-H, 3′-H). MS *m*/*z* (%): 532 (M^+, 2.2), 95 (100). High-resolution MS *m*/*z*: Calcd for $C_{30}H_{44}O_8$: 532.303. Found: 532.302 (M^+).

FL$_2$E$_4$-4 (**8d**): Colorless needles, mp 112—113 °C (*n*-hexane–EtOAc). IR ($CHCl_3$) cm^{-1}: 1708, 1646. UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ε): 216 (23000). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.21, 1.25 (6H each, both s, CH_3 × 4), 1.80 (6H, br s, CH_3 × 2), 2.68 (2H, br t, 11-H, 11′-H), 3.02 (2H, dd, $J=3.1$, 7.9 Hz, 7-H, 7′-H), 4.16 (2H, dd, $J=6.6$, 12.0 Hz), 4.25 (2H, $J=4.6$, 12.0 Hz) (12-H_2, 12′-H_2), 6.62 (2H, t-like, 3-H, 3′-H). MS *m*/*z* (%): 532 (M^+, 2.0), 95 (100). High-resolution MS *m*/*z*: Cacld for $C_{30}H_{44}O_8$: 532.303. Found: 532.302 (M^+).

FL$_2$E$_4$-5 (**8e**): Colorless needles, mp 113—114 °C (*n*-hexane–EtOAc). IR ($CHCl_3$) cm^{-1}: 1705, 1643. UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ε): 215 (15000). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.28, 1.38 (6H each, both s, CH_3 × 4), 1.86 (6H, br s, CH_3 × 2), 2.77 (2H, t, $J=6.1$ Hz, 7-H, 7′-H), 3.09 (2H, dd, $J=4.6$, 6.4 Hz, 11-H, 11′-H), 4.12 (2H, dd, $J=6.4$, 12.2 Hz), 4.21 (2H, dd, $J=4.6$, 12.2 Hz), (12-H_2, 12′-H_2), 6.77 (2H, t, $J=7.6$ Hz, 3-H, 3′-H). MS *m*/*z* (%): 532 (M^+, 2.2), 95 (100). High-resolution MS *m*/*z*: Calcd for $C_{30}H_{44}O_8$: 532.303. Found: 532.302 (M^+).

FL$_2$E$_4$-6 (**8f**): Colorless needles, mp 112—113 °C (*n*-hexane–EtOAc). IR ($CHCl_3$) cm^{-1}: 1711, 1645. UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ε): 216 (21000). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.19, 1.28 (6H each, both s, CH_3 × 4), 1.79 (6H, br s, CH_3 × 2), 2.64 (1H, t, $J=5.9$ Hz, 7-H or 7′-H), 2.70 (1H, t, $J=6.2$ Hz, 7-H or 7′-H), 2.96 (1H, br t), 2.98 (1H, br t), (11-H, 11′-H), 4.03 (1H, dd, $J=6.1$, 12.1 Hz), 4.10 (1H, dd, $J=6.1$, 12.1 Hz), 4.28 (1H, dd, $J=4.9$, 12.1 Hz), 4.35 (1H, dd, $J=4.9$, 12.1 Hz), (12-H_2, 12′-H_2), 6.6—6.8 (2H, m, 3-H, 3′-H). MS *m*/*z* (%): 532 (M^+, 2.2), 95 (100). High-resolution MS *m*/*z*: Calcd for $C_{30}H_{44}O_8$: 532.303. Found: 532.302 (M^+).

Ion-Transport and Ion-Permeation Activity Tests Ion-transport tests using a W-07 apparatus were carried out by the procedure described in the literature,4) and ion-permeation activity employing human erythrocyte membrane was assayed by the procedure described in the literature.6)

References and Notes

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