Studies on the Chemical Modification of Monensin. III. Synthesis and Sodium Ion Transport Activity of Macrocyclic Monensylamino Acid-1,29-lactones

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Monensylglycine (2a) was lactonized to macrocyclic monensylglycine-1,29-lactone (3a) by Corey's method. Lactonization of monensylamino acids (2b—d) to monensylamino acid-1,29-lactones (3b—d) was carried out by utilizing the template effect of K^+ ion. Monobenzyl esters of dicarboxylic monensylamino acids (5e—f) also were lactonized followed by debenzylation to yield carboxylic monensylamino acid-1,29-lactones (3e—f). Sodium ion transport activity of monensin (1) and the lactones (3) was measured in a liquid membrane and in guinea pig erythrocyte membrane. Monensylaspartic acid-1,29-lactone (3e) exhibited 2.5 times higher activity than 1 in the liquid membrane. Monensylalanine-1,29-lactone (3b), monensylphenylalanine-1,29-lactone (3c), and monensyltyrosine-1,29-lactone (3d), having smaller Na^+ ion transport activity than 3e, showed weak antibacterial activity, while 3e was inactive in biological tests, probably due to the lower lipophilicity.

Keywords monensin; monensylamino acid-1,29-lactone; macrolactonization; Na^+ ion transport activity; lipophilicity; antibacterial activity

The antibiotic monensin (**1**, Fig. 1) is a typical representative of the polyether carboxylic ionophore family, and is known to preferentially transport Na^+ ion across biological membranes.[1] This ability results in a variety of biological activities,[2] anticoccidial activity[3] and a positive inotropic effect (PIE) on isolated guinea pig papillary muscle.[4]

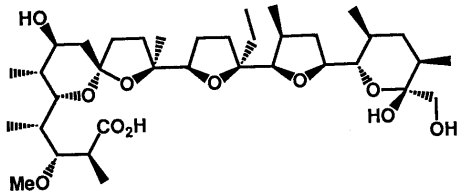

Fig. 1. Chemical Structure of Monensin (**1**)

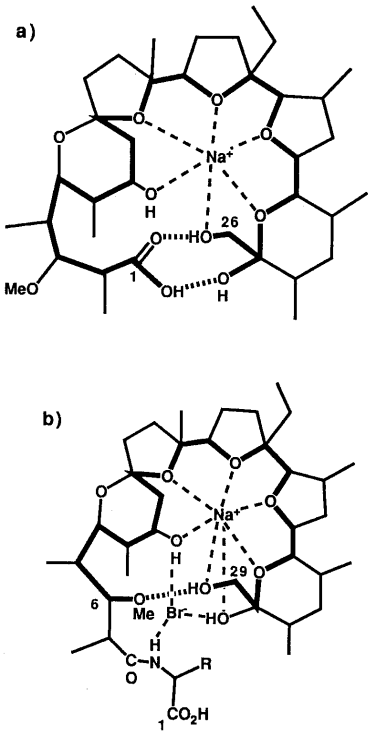

Fig. 2. Pseudocyclic Structure of a) NaBr Complex of Monensin (**1**) and b) NaBr Complexes of Monensylamino Acids (**2**)

We have recently synthesized a series of monensylamino acids (**2a—f**) by condensing the carboxylic group with optically active amino acids, and established, on the basis of X-ray analysis, that the NaBr complexes of **2a—f** (Fig. 2b) are quite different from the NaBr complex of **1** (Fig. 2a).[5] In addition, our technique to measure the Na^+ ion transport ability across the membrane of living guinea pig erythrocytes by using sodium-23 nuclear magnetic resonance (^{23}Na-NMR) spectroscopy revealed that **2a—f** showed much smaller initial increasing rates of Na^+ ion transport than **1**, probably due to their lower lipophilicity.[6] These observations suggested that chemical modifications of **2a—f** to produce more lipophilic compounds might lead to new monensin analogs with high initial increasing rate and potent biological activity.

Suzuki *et al.* found that monensin-1,26-lactone (Fig. 3) is a highly Li^+-selective ionophore[7] because the lactonization caused a reduction of the radius of the cavity at the position of Na^+ ion coordination. This interesting result prompted us to prepare monensylamino acid-1,29-lactones with increased lipophilicity which may have optimal cavity size for selective complexation with Na^+ ions. In the present paper, we describe the synthesis, Na^+ ion transport activity,

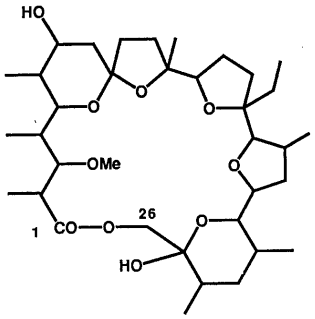

Fig. 3. Monensin 1,26-Lactone

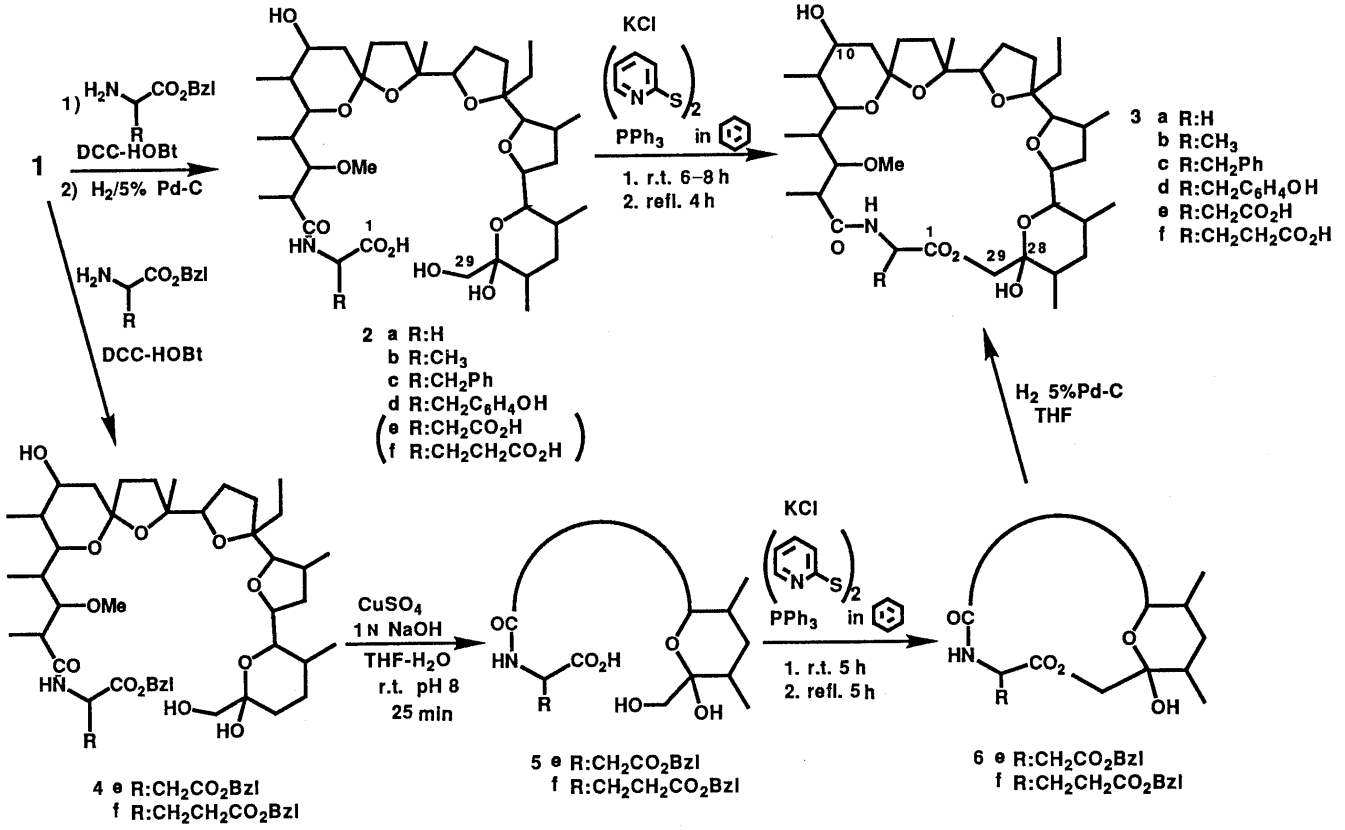

Chart 1

and biological activity of monensylamino acid-1,29-lactones (**3a**—**f**, Chart 1).

Results

Chemistry The preparation of macrocyclic monensylamino acid-1,29-lactones (**3a**—**d**) from monocarboxylic monensylamino acids (**2a**—**d**) was carried out according to Corey's method[8] as outlined in Chart 1, and compound **3a** was obtained from **2a** in 84% yield. The binding of the carboxyl group through oxygen to the C_{29} methylene is clear from the appearance in the ^{1}H-NMR spectrum of an AB doublet of doublets due to the C_{29} methylene of **3a** with doublet A at δ 3.71 ppm and doublet B at δ 4.92 ppm (J=11 Hz). The observed chemical shift values for H_A and H_B of the C_{29} methylene in **2a** itself are δ 3.56 and 3.65 (J=11 Hz), as summarized in Table I. The downfield shift of the C_{29} methylene protons of **3a** relative to **2a** and also the large chemical shift between H_A and H_B in **3a** offer reasonable evidence for structure **3a** and argue against the isomeric 1→10 or 1→28 lactones.

Lactonization of **2b** was similarly carried out, but the yield (57%) of **3b** was disappointingly low. This result stimulated us to utilize template cations[9] which hold two reacting groups in the correct orientation to allow easy lactonization. Thus, NaBr was initially added to the lactonization reaction as a source of readily available template cation. The yield of **3b**, however, was unsatisfactory (61%). This low yield appears to be attributable to the strong hydrogen bonding between the C_{29} hydroxy group and the C_6 methoxy oxygen[5] (Fig. 2b). We hence expected that the strong hydrogen bonding may be weakened, and consequently the C_{29} hydroxy and carboxylic groups may be more readily accessible to each other, if the cavity of complexed **2b** could be enlarged by using template cations with larger ion radius than that of Na^+ ion. We thus attempted the lactonization of **2b** in the presence of various template cations such as KCl, KBr, RbCl, RbBr, and $BaCl_2$. Among these cations, KCl was found to be the most effective compound to give **3b** in good yield (73%), while other compounds gave **3b** in 35—65% yields. Although the reasons for these differences in yield remain unclear, unambiguous evidence for weakened C_6–C_{29} hydrogen bonding in the **2b**–KCl complex was obtained from the ^{13}C-NMR spectrum. In the ^{13}C-NMR ($CDCl_3$) spectrum, the signal of the C_6 carbon of **2b**–NaBr complex appeared 4.13 ppm downfield compared to that of the free acid (**2b**), whereas the corresponding C_6 carbon signal of **2b**–KCl complex was shifted only 1.27 ppm downfield. These chemical shift differences arose from the appreciably weaker hydrogen

Table I. Reaction Times, Yields, and ^{1}H-NMR Data for Lactones

Compound	Reaction time (h)		Yield (%)	Chemical shifts of $C_{(29)}H_2$ (δ ppm) (each 1H, each d, J=11 Hz)	
	Stirring at r.t.	Reflux		Lactones **3** or **6**	ω-Hydroxy acids **2** or **5**
3a	8	4	84	3.71, 4.92	3.56, 3.65
3b	6	4	73	3.55, 4.96	3.54, 3.62
3c	6	4	75	3.49, 4.99	3.60, 3.70
3d	6	4	73	3.51, 5.00	3.60, 3.66
6e	5	5	72	3.53, 4.93	3.54, 3.57
6f	5	5	67	3.50, 4.94	3.52, 3.63

bonding between C_6 oxygen and C_{29} hydrogen. Guided by these results, other monensylamino acids (**2c—d**) were also reacted in the presence of KCl to give **3c—d** in the yields shown in Table I. The structures of **3c—d** were confirmed by the spectral data.

In order to prepare carboxylic lactones (**3e—f**), we examined a different approach as illustrated in Chart 1. Dibenzyl esters (**4e—f**) of monensylaspartic acid and monensylglutamic acid were selectively debenzylated in the presence of aqueous NaOH and $CuSO_4$[10] in tetrahydrofuran (THF) to give **5e—f**. In the ^{1}H-NMR spectra, the methine protons of amino acid moiety appeared downfield relative to the corresponding methines of **4e—f**. This finding demonstrates that selective debenzylation has indeed taken place. Lactonization of **5e—f** in the presence of KCl followed by debenzylation of **6e—f** over Pd–C provided the lactone compounds (**3e—f**).

We finally examined the lipophilicity of macrocyclic lactones (**3a—f**) by measuring *Rm* values.[11] All the lactones measured showed increased lipophilicity over the corresponding monensylamino acids (**2a—f**), and compounds **3a—d** were more lipophilic than monensin (**1**), as illustrated in Table II.

Ion Transport Activity Na^+ ion transport and binding activities of lactones in a $CHCl_3$ liquid membrane system were measured using the W-08 apparatus (Fig. 4).[12] The amount of Na^+ ion transported from the ion-containing water phase into the pure water phase and the amount of Na^+ ion in the $CHCl_3$ phase were determined by counting radioactivity with a γ-counter (Aloka NDW-35E). Interestingly, compound **3e** showed 1.5 times stronger binding activity and 2.5 times stronger transport activity than monensin (**1**), while the other lactones did not have any activity, as shown in Table III.

We also determined the Na^+ ion transport activity in a biological membrane. We employed the living erythrocytes of guinea pig and measured the concentration of intracellular Na^+ ion ($[Na^+_{in}]$) using ^{23}Na-NMR[6] spectros-

TABLE II. Rm_{50} Values of Monensin Derivatives

Compound	Rm_{50}	Compound	Rm_{50}[6]
1	1.83		
3a	1.86	**2a**	0.65
3b	1.99	**2b**	0.73
3c	2.54	**2c**	1.17
3d	1.94	**2d**	0.83
3e	0.82	**2e**	−0.04
3f	0.54	**2f**	−0.08

TABLE III. Na^+ Ion Transport and Binding Activities

Compound	Na^+ ion (nmol)	
	Transport	Binding
1	67.37	36.39
3a	0	0
3b	9.96	2.11
3c	2.51	0.08
3d	5.35	0.53
3e	170.03	56.93
3f	24.13	7.03

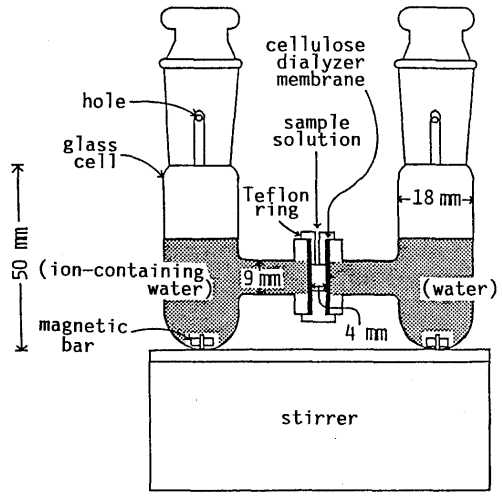

Fig. 4. Apparatus W-08 for Measurements of Ion-Transport and Ion-Binding Activity

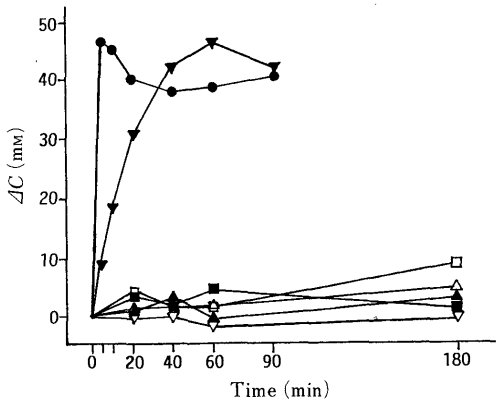

Fig. 5. Corrected Time–Dependent Change of $\Delta[Na_{in}]$ (ΔC)

●, **1**; ▲, **3a**; △, **3b**; ■, **3c**; □, **3d**; ▼, **3e**; ▽, **3f**. DMSO caused a slight decrease of $[Na_{in}]$, and therefore the corrected time dependent change of $\Delta[Na_{in}]$, ΔC ($=\Delta[Na_{in}]^i_t-\Delta[Na_{in}]^{DMSO}_t$) were indicated. $\Delta[Na_{in}]^i_t=[Na_{in}]^i_t-[Na_{in}]^i_0$.

TABLE IV. Minimum Inhibitory Concentrations of Monensin (**1**) and Lactones (**3**) against Anaerobic Bacteria

Organisms	MIC (ppm)						
	1	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**
Peptococcus anaerobius B-40	0.20	>50	12.5	6.25	12.5	>50	>50
Peptostoreptococcus anaerobius B-30	1.56	>50	25	25	50	>50	>50
Propionibacterium acnes ATCC 11828	0.39	>50	25	12.5	6.25	>50	>50
Eubacterium entum BEERENS 515	1.56	>50	25	25	>50	>50	>50
Lactobacillus acidophilus ATCC 4356	0.78	>50	25	>50	1.56	>50	>50
Clostridium perfringens 7-heart	6.25	>50	50	50	25	>50	>50

copy. Among the lactones, compound **3e** showed the most remarkable increasing rate of $[Na^+_{in}]$ (Fig. 5). However, Fig. 5 indicates that the initial increasing rate of $[Na^+_{in}]$ within 0—5 min is markedly slower than that in the case of monensin (**1**).

Biological Activity The values of minimum inhibitory concentration against various bacteria were measured. Compounds **3b—d** showed weak antibacterial activity against anaerobic bacteria, as shown in Table IV, while compounds **3e—f** were inactive. Compounds **3a—f** showed no anticoccidial activity in *Eimeria tennella*-infected chicks. Compound **3e** showed a tendency to decrease the contraction of papillary muscle rather than to develop PIE.

Discussion

We found that the lactonization proceeded in satisfactory yield when KCl was added to Corey's reagents. The improved yields may be attributed to the template effect of K^+ ion.

Compounds **3e—f** showed effective Na^+ ion transport and binding activities in a $CHCl_3$ liquid membrane. In particular, the remarkable activity of **3e** suggested that the carboxylic acid group contributed to the stable complex formation with Na^+ ion by taking the most appropriate position to encapsulate the Na^+ ion in the cavity, as shown in Fig. 6. Compound **3f** may also complex with Na^+ ion in a similar fashion to **3e**, but the carboxylic side arm in this case seems unsuitable to shield the Na^+ ion completely.

Contrary to our expectation, compounds **3e—f** were less active in a variety of biological tests. These findings suggested that appearance of biological activity might depend not on the Na^+ ion transport activity but on the lipophilic character of the molecule. Low lipophilicity of **3e—f** obviously results from the hydrophilic carboxylic acid group appended to the periphery of the macrocyclic molecules. It is, therefore, difficult for **3e—f** to penetrate the bacterial cell membrane.

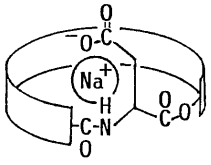

Fig. 6. Probable Structure of Complexed **3e**

The Na^+ ion is in a hydrophilic central cavity of the cyclic molecule and is covered by the ionic carboxylic arm.

In summary, we have synthesized macrocyclic monensylamino acid-1,29-lactones in sufficient yields, and investigated the Na^+ ion transport activity and the biological activity. Compound **3e** showed the largest Na^+ ion transport activity in the liquid membrane system, but **3e** did not show any biological activity, possibly due to its less lipophilic character resulting from the presence of the carboxylic acid group. Consequently, introduction of lipophilic substituents at the α-position to the carboxylic acid group will increase the lipophilicity of **3e** and improve membrane permeability. Our forthcoming paper will focus on further elaboration of **3e** analogues.

Experimental

The fast atom bombardment mass spectra (FAB-MS) were measured with a JEOL JMS DX-300 mass spectrometer, and the infrared (IR) spectra with a JASCO IRA-2 spectrometer. The ^{1}H-NMR spectra were recorded with a JEOL GSX-400 spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard. The following abbreviations are used: d, doublet; dd, doublet of doublets; br, broad. Column chromatography was carried out on silica gel BW-200 (Fuji Davison Chemicals, Ltd.). High-performance liquid chromatography (HPLC) was carried out on C.I.G. ODS-C_{18}-10/20 (22 mm i.d. × 100 mm, Kusano Kagakukikai Co.).

Monensinamidoacetic Acid-1,29-lactone (3a) A solution of **2a** (100 mg), 2,2′-dithiodipyridine (10 eq) and triphenylphosphine (10 eq) in benzene (100 ml) was stirred for 8 h at room temperature followed by the addition of benzene (100 ml) and subsequent gentle boiling for 4 h. The solution was evaporated and the residue was chromatographed on silica gel (hexane–acetone) to afford **3a** as a syrup (82 mg, 84%). ^{1}H-NMR data for **3a** are summarized in Table I. The IR and FAB-MS data and physicochemical data for **3a** are shown in Table V.

General Procedure for Preparations of Lactones (3b—d) A solution of **2b—d** (100 mg) in $CHCl_3$ (5 ml) was treated with an equivalent amount of KCl in MeOH (5 ml). The mixture was evaporated to dryness to give syrups, which were subjected to lactonization using the same procedure as described for **3a** to give **3b—d** as syrups. The yield, the reaction time, and ^{1}H-NMR data for **3b—d** are summarized in Table I. The IR and FAB-MS data and physicochemical data for **3b—d** are shown in Table V.

3b: 2-Methylmonensinamidoacetic acid-1,29-lactone, **3c**: 2-phenylmethylmonensinamidoacetic acid-1,29-lactone, **3d**: 2-(4-hydroxyphenyl)-methylmonensinamidoacetic acid-1,29-lactone.

Monensylaspartic Acid β-Benzyl Ester (5e) and Monensylglutamic Acid γ-Benzyl Ester (5f) Compounds **4e, f** (200 mg) were each dissolved in THF

TABLE V. Physicochemical Data for Monensylamino Acid-1,29-lactones (**3**)

3	R	IR ν_{max}^{KBr} cm^{-1} (C=O)	$[\alpha]_D^{20}$ (c, $CHCl_3$)	FAB-MS m/z $(M+Na)^+$	Formula	Analysis (%) Found (Calcd)		
						C	H	N
a	H	1745, 1650	31.92 (0.30)	732	$C_{38}H_{63}NO_{11}\cdot 1/2H_2O$	63.50 (63.49)	9.20 8.97	1.71 1.94)
b	CH_3	1750, 1670	14.64 (0.38)	746	$C_{39}H_{65}NO_{11}$	64.49 (64.72)	9.31 9.05	1.72 1.93)
c	CH_2Ph	1735, 1665	−11.45 (0.50)	822	$C_{45}H_{69}NO_{11}$	67.61 (67.56)	8.78 8.69	1.41 1.75)
d	$CH_2C_6H_4OH$	1735, 1660	−10.30 (0.42)	838	$C_{45}H_{69}NO_{12}\cdot 1/2H_2O$	65.44 (65.51)	8.52 8.55	1.35 1.70)
e	CH_2CO_2H	1740, 1660	8.54 (0.41)	790, 812[a]	$C_{40}H_{64}NNaO_{13}$[b]	60.75 (60.82)	8.47 8.17	1.68 1.77)
f	$CH_2CH_2CO_2H$	1735, 1660	3.95 (0.30)	804	$C_{41}H_{67}NO_{13}$	62.78 (62.97)	8.79 8.63	1.79 1.79)

a) Pseudomolecular peak of $(M+2Na-H)^+$. *b*) Elemental analysis of **3e** was carried out as the sodium salt.

(10 ml) and aqueous $CuSO_4 \cdot 5H_2O$ (50 mg, 1 ml) was added. The pH was raised to pH 8 with 1 M NaOH and the solution was maintained at pH 8 for 30 min at room temperature, then extracted with AcOEt. The AcOEt layer was washed with 10% citric acid, 4% $NaHCO_3$, and water. The AcOEt layer was dried over $MgSO_4$, filtered, and evaporated to dryness. The residue was chromatographed on silica gel ($CHCl_3$–MeOH) to give the syrups **5e** and **5f**. **5e**: 2-Monensinamidobutanedioic acid β-benzyl ester, yield: 160 mg (88%). $[\alpha]_D^{23}$: 60.4° ($c=0.3$, $CHCl_3$). FAB-MS: 920 $(M+2Na-H)^+$. IR ν_{max}^{KBr} cm^{-1}: 1735, 1720, 1650. ^{1}H-NMR δ (ppm): 5.13 (1H, br, –NH–CH), 5.13, 5.15 (each 1H, each d, $J=12$ Hz, OCH_2Ph). **5f**: 2-Monensylamidopentanedioic acid γ-benzyl ester, yield: 151 mg (83%). $[\alpha]_D^{23}$: 42.0° ($c=0.3$, $CHCl_3$). FAB-MS: 912 $(M+Na)^+$, 934 $(M+2Na-H)^+$. IR ν_{max}^{KBr} cm^{-1}: 1735, 1720, 1650. ^{1}H-NMR δ (ppm): 4.73 (1H, dd, $J=14$, 8 Hz, NH–CH), 5.10, 5.11 (each 1H, each d, $J=12$ Hz, OCH_2Ph).

The elemental analysis of **5e, f** was carried out on their sodium salts. A solution of **5e, f** (20 mg) in $CHCl_3$ was washed with 4% $NaHCO_3$ in water. The $CHCl_3$ layer was separated, dried over Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by HPLC to give an amorphous power.

Sodium Salt of **5e**: IR ν_{max}^{KBr} cm^{-1}: 1735, 1640, 1590. *Anal.* (%) Calcd for $C_{47}H_{72}NNaO_{14}$: C, 62.86; H, 8.08; N, 1.56. Found: C, 62.57; H, 8.22; N, 1.38.

Sodium Salt of **5f**: IR ν_{max}^{KBr} cm^{-1}: 1735, 1640, 1610. *Anal.* (%) Calcd for $C_{48}H_{74}NNaO_{14}$: C, 63.21; H, 8.18; N, 1.54. Found: C, 63.09; H, 8.40; N, 1.38.

2-Benzyloxycarbonylmethylmonensinamidoacetic Acid-1,29-lactone (6e) and 2-(2-Benzyloxycarbonylethyl)monensinamidoacetic Acid-1,29-lactone (6f) Compounds **5e, f** were cyclized to **6e, f** by the same procedure as described for **3b—d**. The reaction times, the yields, and ^{1}H-NMR data for **6e, f** are summarized in Table I. **6e**: syrup. $[\alpha]_D^{22}$: −7.7 ($c=0.3$, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1745, 1735, 1670. FAB-MS: 880 (M + Na): **6f**; Syrup. $[\alpha]_D^{22}$: 5.0 ($c=0.3$, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1740, 1735, 1675. FAB-MS: 894 $(M+Na)^+$.

2-Hydroxycarbonylmethylmonensinamidoacetic Acid-1,29-lactone (3e) and 2-(2-Hydroxycarbonylethyl)monensinamidoacetic Acid-1,29-lactone (3f) Compounds **6e** (96 mg) and **6f** (131 mg) were each hydrogenated in the presence of 5% palladium on charcoal (10 mg) in THF (4 ml) at atmospheric pressure of hydrogen for 30 min. The catalyst was filtered off and the filtrate was evaporated to dryness followed by silica gel chromatography ($CHCl_3$–MeOH) of the residue to give syrups (**3e, f**, respectively). The IR and FAB-MS data and physicochemical data for **3e, f** are summarized in Table V. **3e**: Yield: 85 mg (99%). ^{1}H-NMR δ (ppm): 3.63, 5.00 (each 1H, each d, $J=11$ Hz, CH_2–O–CO). **3f**: yield: 111 mg (95%). ^{1}H-NMR δ (ppm): 3.53, 5.08 (each 1H, each d, $J=11$ Hz, CH_2–O–CO).

The elemental analysis of **3e** (Table V) was performed as the sodium salt, which was prepared by the same procedure as described for the sodium salts of **5e, f**.

Sodium Salt of **3e**: IR ν_{max}^{KBr} cm^{-1}: 1740, 1640, 1595.

***Rm* Values** The *Rm* values were measured by the reported method.[6,11] The MeOH solution of a compound was spotted on precoated TLC plates of Silica gel 60 F_{254} silanized (layer thickness 0.25 mm, Merck no. 5747), and developed with 65, 70, 75, and 80% (w/v) aqueous MeOH solutions. The *Rm* values were calculated from *Rf* values by means of the following equation.

$$Rm = \log(1/Rf - 1)$$

Determination of Ion Transport Activity in a Liquid Membrane The ion transport activity of the lactones (**3**) and monensin (**1**) in a liquid membrane was determined using the W-08 apparatus by essentially the same method as described previously.[12] Two glass cells containing ion-containing water (6 ml, 1 mmol/l, $Na^+ : {}^{22}Na^+ = 12185 : 1$) and pure water (6 ml) sandwich the Teflon cell containing sample solution (0.03 mol/l in $CHCl_3$ saturated with water). The aqueous phases were gently stirred at 25 °C. After 10 h, each phase was sampled. The molar amounts of ions in the pure water phase and in the organic solution phase were calculated by using the equations in the previous paper.[12]

Determination of Ion Transport Activity in Erythrocyte Membrane Na^+ ion transport activity in guinea pig erythrocyte membrane was measured by essentially the same method as we have reported, using ^{23}Na-NMR.[6] ^{23}Na-NMR spectra were recorded using a JEOL EX-270 spectrometer at 71.32 MHz and 37 °C. The tube combination (1 mm o.d. tube inside a 5 mm o.d. NMR tube) contained 0.45 ml of guinea pig blood obtained by cardiocentesis, 0.05 ml of 100 mM dysprosium triethylenetetramine hexacetate ($DyTTHA^{3-}$) in water, and 5 μl of 10^{-2} M lactone in DMSO in the annular space. The inner tube contained an external reference (20 mM dysprosium sodium triphosphate, $Na_7Dy(PPPi) \cdot 3NaCl$). The intracellular Na^+ ion concentrations were calculated by using the reported equation.[6]

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