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Enantiomer Recognition of Organic Ammonium Salts by Podand- and Crown-Type Monensin Amides: New Synthetic Strategy for Chiral Recep

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Abstracts: Podand- and crown-types of new chiral receptors, characterized by a chiral polyether skeleton and an amide junction, were derived from naturally occurring monensin ionophore. Their chiral recognition ability was investigated by ion-selective electrode and ^{1}H-NMR spectroscopic methods. Several podand-type monensin amides formed 1:1 complexes with chiral amine salts and exhibited excellent enantiomer selectivity. Since biological monensin and its macrocyclic derivatives were less effective for chiral recognition, a molecular combination of pseudo-cyclic monensin cavity, chiral polyether skeleton and neutral amide moiety offered high enantiomer selectivity. Chemical modification of biological monensin allowed remarkable development of new ionophoric functions and provided an effective synthetic strategy for chiral receptors.

INTRODUCTION

The synthesis of new chiral receptors is one of the most interesting subjects in host-guest chemistry, biomimetic chemistry, organic chemistry and related fields. Several research groups have developed a variety of chiral receptors and successfully applied them in catalysis, separation, detection, enzyme mimic and so on.[1] Chiral crown-type receptors have been extensively investigated.[2] Cram, Lehn and others have demonstrated that their crown-type receptors offer chiral recognition of organic ammonium salts in solvent extraction, liquid membrane transport, chromatography and asymmetric reactions. Although their synthetic concepts were useful and suggestive, their practical syntheses usually included multi-step reactions and many laborious procedures. Therefore, there is a need for a new and facile method to prepare chiral receptors.

We recently succeeded in deriving a new series of chiral receptors from naturally occurring ionophores.[3] We prepared various ester derivatives of polyether-type ionophores such as monensin, lasalocid, nigericin and salinomycin. Although they were themselves incapable of discriminating between optical isomers of amine salts,

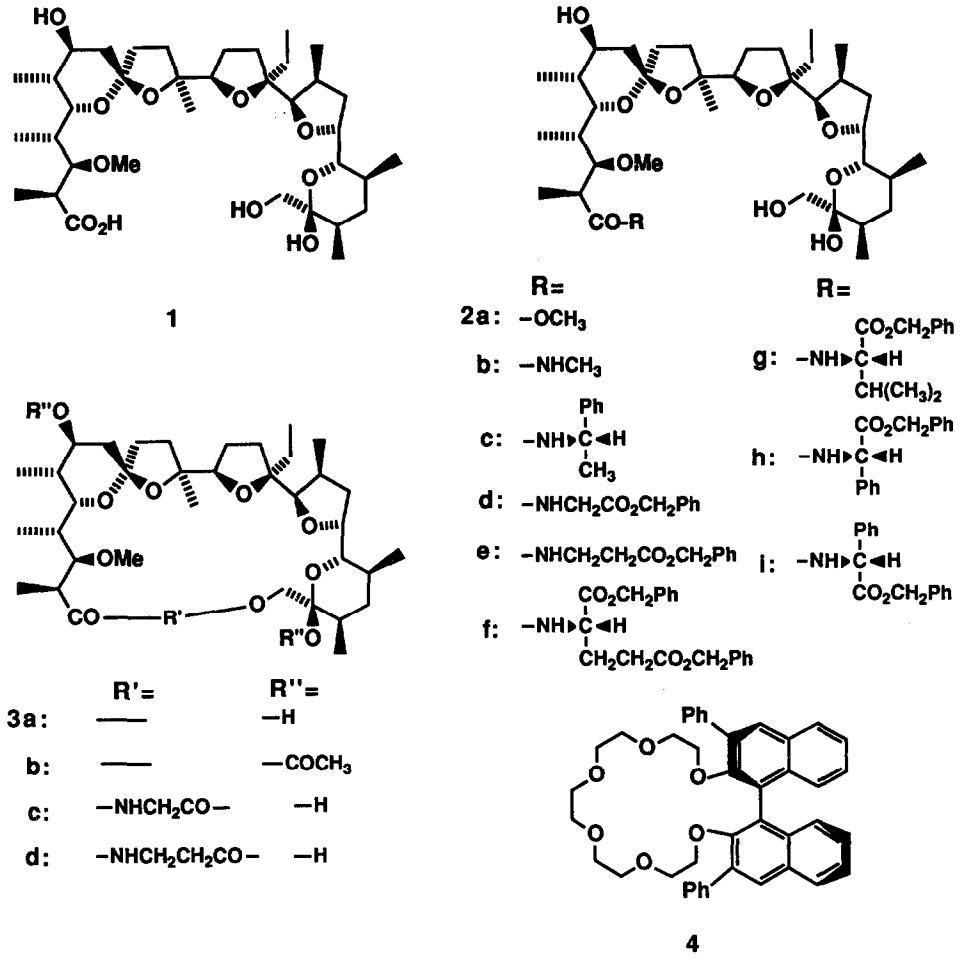


Figure 1. Podand- and Crown-Type Monensin Amides and Related Receptors

their ester derivatives, interestingly, exhibited chiral recognition ability. These polyether-type ionophores are known to accommodate alkali and alkaline earth metal cations in their pseudo-cyclic cavities and to transport them specifically across the biomembrane.[4] Since they are composed of several optically active segments, they are thought to have chiral, ordered pseudo-cyclic cavities suitable for enantiomer selective binding of ammonium cations. A limited number of successful examples has previously been reported.[5] Westley et al. first applied biological lasalocid to the preferential crystallization of salts with racemic amines. More recently, Lindoy and coworkers reported that lasalocid mediated selective enantiomeric transport of chiral metal complexes through a $CHCl_3$ membrane. These findings clearly offered the interesting possibility that excellent chiral receptor may be derivable from naturally occurring ionophore.

Here, we report a facile synthesis of monensin amide derivatives which offer chiral recognition ability comparable to that of Cram's chiral crown ether.[6] Monensin is a typical biological ionophore and mediates specific biomembrane transport of Na^+ ion.[4] Since K^+, Ag^+, Pb^{2+} and $R\text{-}NH_3^+$ cations are also accommodated in its pseudo-cyclic cavity,[7] monensin was chemically modified so that other interesting receptor

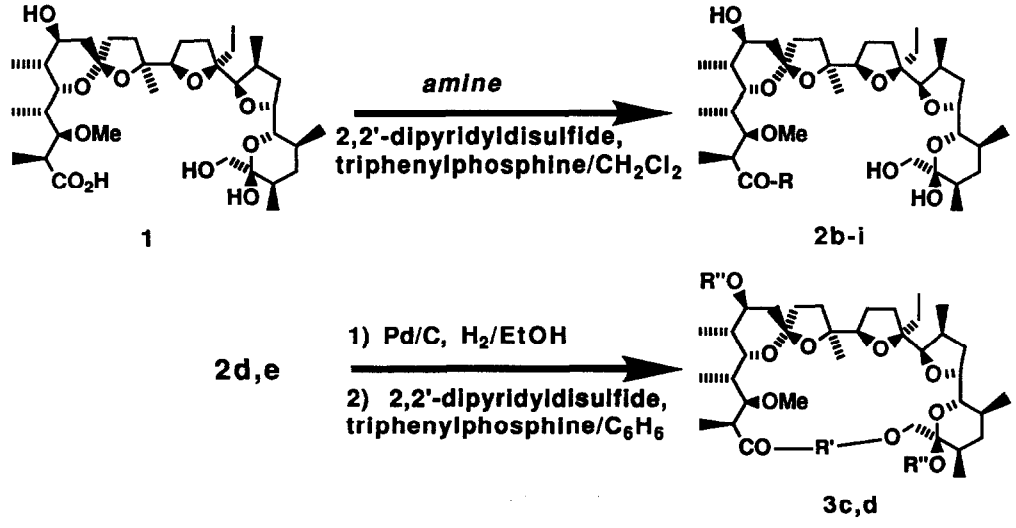
functions might be developed.[3,6,8] We prepared both podand- and crown-types of monensin amides in good yields, though the parent monensin is an unstable and complicated molecule. The ion-selective electrode and ^{1}H-NMR titration experiments clearly demonstrated that several podand-type amide derivatives formed enantiomer selective, 1:1 complexes with certain chiral ammonium salts and exhibited higher enantiomer selectivity than related monensin esters as reported earlier.[3] A new series of chiral receptors was readily developed through chemical modification of biological materials.

RESULTS AND DISCUSSION

Synthesis of Monensin Amides.

We prepared two different types of monensin amide derivatives: podand-type, **2b-2i**, and crown-type derivatives, **3a-3d** (Figure 1). Since the parent monensin **1** has a spiro-ketal structure and is very unstable especially under acidic conditions, its chemical modification requires mild reaction conditions. Corey et al. reported one-step lactonization of the monensin in 1975.[9] Treatment of monensin free acid with 2,2'-dipyridyldisulfide and triphenylphosphine afforded intramolecularly cyclized product **3a**. We applied this reaction to the intermolecular amide formation and obtained a new series of podand-type monensins having various terminal substituents **2b-2i** in good yields (Scheme 1).

Crown-type monensin derivatives **3c** and **3d** were readily synthesized by debenzylation of podand-type monensins **2d** and **2e** and successive cyclization as shown in Scheme 1. Since Suzuki et al. recently reported that monensin macrocycle **3a** acted as a specific carrier of Li^+ cation,[10] we inserted glycine and ß-alanine moieties into the monensin ring system and obtained large membered crown-type compounds suitable for binding of organic ammonium cations. We further prepared crown-type compound **3b** which included monensin macrocycle and functionalized side arms. The chiral recognition properties of these crown-type monensins were compared with those of the podand-type.



Scheme 1. Synthetic Route to Monensin Amide Derivatives

Ion-Selective Electrode Studies on Cation Recognition of Monensin Amides.

The cation recognition property of monensin amides was investigated by ion-selective electrode technique.[11] We employed the same system as the convenient metal ion-selective electrodes: the monensin derivative was incorporated into the poly(vinyl chloride) membrane and the membrane potentials were measured. In this paper, the potentiometric guest selectivity coefficient k_{ba} was defined as $10^{(Ea-Eb)/0.058}$ for monocation and $10^{(Ea-Eb)/0.029}$ for dication at 20°C, where E_a and E_b represented the potentials for the guest-containing solutions. This means that nonselective binding occurs if $k_{ba}=1$. When **a** and **b** are enantiomers, k_{ba} is indicative of chiral recognition and can be correlated with the stability constants of the complexes between receptors and optically active guests in the membrane phase.[11]

All monensin amides employed showed near Nernstian responses to several alkali and alkaline earth metal cations in the range of 10^{-1} to 10^{-4} mol/L. The Na^+ selectivity coefficient k_{Na^+i} values were calculated and typical results are illustrated in Figure 2.[12] The podand-type monensin amides such as **2d** and **2f** exhibited the same Na^+ selectivity as biological monensin **1** and its ester **2a**. Thus, attachment of amide-substituent to the monensin terminal slightly influenced the size of cation binding cavity. On the other hand, crown-type monensin derivatives **3a**, **3c** and **3d** favored K^+ cation. Although they apparently have different membered rings, their effective cavity-sizes seemed to be similar.

Podand-type monensin amides **2b-i** were confirmed to exhibit near Nernstian responses to the sample solutions containing optically active ammonium cations such as PhglyOMe·HCl (α-phenylglycine methyl ester hydrochloride) and LeuOMe·HCl. Typically, linear relations between membrane potentials and log(activity) were

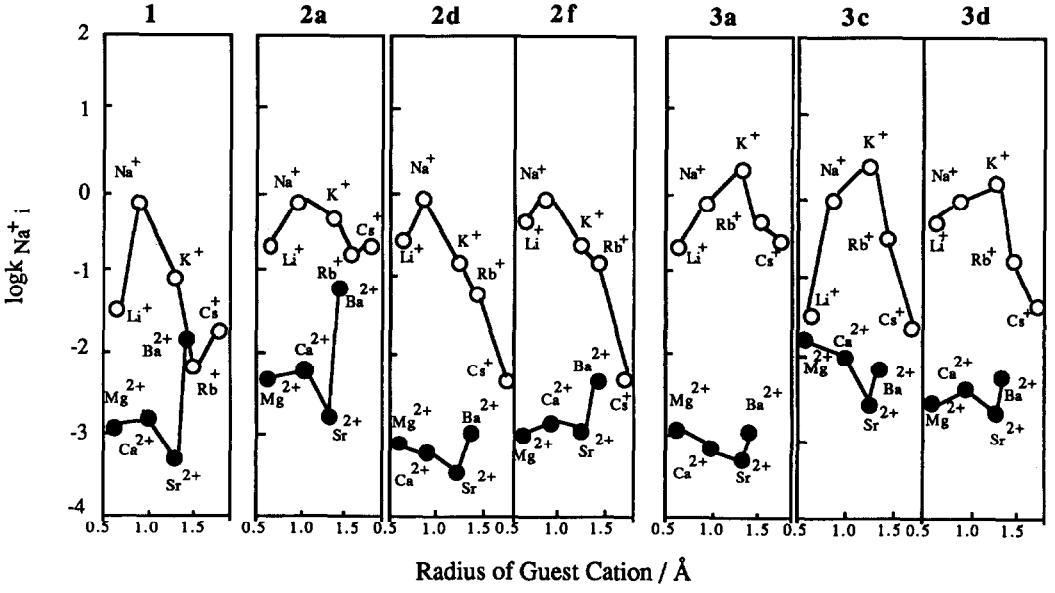


Figure 2. Ion Selectivity Coefficient (logk $_{Na^+\ i}$ i: interfering ion) [a] of Monensin Derivatives for Alkali and Alkaline Earth Metal Cations [b]

a) logk $_{Na^+\ i}$ was defined as $k=10^{(E_i - E_{Na^+})/0.059}$ for alkali metal cations and $k=10^{(E_i - E_{Na^+})/0.029}$ for alkaline earth metal cations at 25°C. b) Membrane composition: 67wt% *o*-nitrophenyl octyl ether, 30wt% poly(vinyl chloride), 3wt% receptor. Solutions containing guest cations were not bufferized.

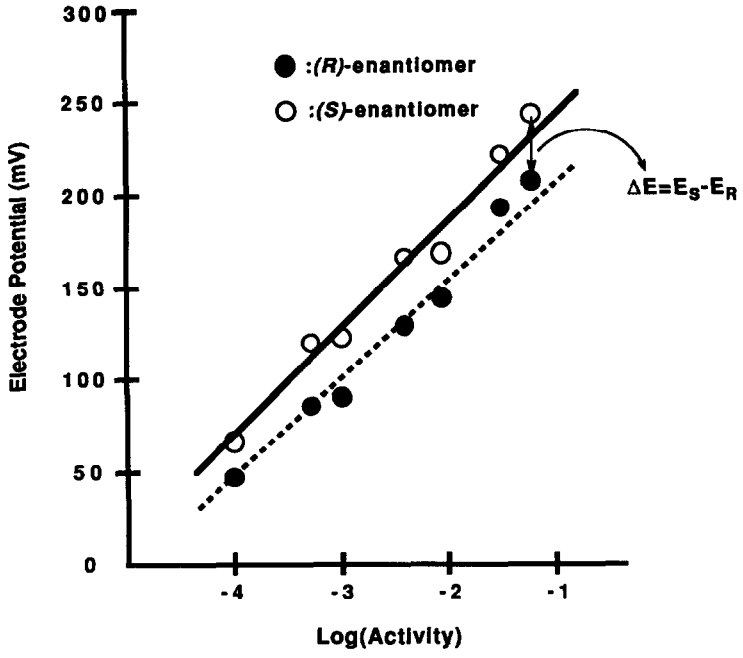


Figure 3. Response of Electrode Containing 2g to *(S)*- and *(R)*-Phenylalanine Methyl Ester•HCl Solution

established in the monensin amide **2g**-PheOMe·HCl system (Figure 3), and k_{RS} value was estimated as 6.2. The enantiomer selectivity coefficients k_{RS} were similarly determined for podand-type amides **2b-2i** (Table 1). Biological monensin **1**, its ester **2a** and chiral crown ether **4** were also examined for comparison.

Podand-type monensin amides **2b-2i** exhibited enantiomer selectivity for certain chiral ammonium cations similar to or higher than monensin ester **2a**. Since biological monensin **1** rarely discriminated between the enantiomers of each amine salt, a new receptor function could be developed by terminal-functionalization of monensin. The chiral recognition ability strongly depended on the nature of amide-substituent. Monensin amides having bulky groups **2c**, **2g**, **2h** and **2i** showed larger k_{RS} values for PhglyOMe, PheOMe and LeuOMe salts than those having small groups **2b**, **2d** and **2e**. The potential differences, E_S-E_R, reached 30-51 mV for monensin amides **2c**, **2g**, **2h**, and **2i** and their k_{RS} values were calculated as 3.3-7.6. The attachment of bulky residues remarkably enhanced chiral recognition ability. The stereochemistry of the introduced amide-substituent also influenced chiral recognition behavior. Monensin amide **2h** having *(S)*-phenylglycine moiety showed higher enantiomer selectivity for various ammonium cations than did its diastereomer **2i**. Therefore, the chirality and bulkiness of the amide-substituent should be carefully chosen when this type of receptor is designed. Crown ether **4**[2] was also examined under the same conditions. Although this is recognized as an excellent receptor for chiral recognition of ammonium cations,[13] monensin amides **2c**, **2g** and **2h** exhibited higher enantiomer selectivities for PheOMe and 1-phenethylamine salts. Since these monensin amides have a great synthetic advantage over crown ether **4**, chemical modification of biological ionophore can be considered as a facile and effective methodology for development of a specific chiral receptor.

Three crown-type monensins of different ring sizes, **3a**, **3c** and **3d** were similarly characterized by the electrochemical method (Table 2). These exhibited near Nernstian responses to the solutions of primary

Table 1 Enantiomer Selectivity Coefficient k_{RS} of Podand-Type Monensin Amides and Related Receptors.

Receptor	k_{RS} at 20°C							
	PhglyOMe[b] •HCl	PheOMe[b] •HCl	LeuOMe[b] •HCl	ProOMe[b] •HCl	1-Phenethyl-amine[b] •HCl	1-(1-Naphthyl)ethyl-amine[b] •HCl	LysOMe[c] •2HCl	ArgOMe[c] •2HCl
1	1.1	1.2	1.3	1.0	0.90	0.76	d)	d)
2a	3.4	2.6	2.7	1.0	0.50	0.47	1.1	0.84
2b	2.1	1.8	2.3	1.0	1.0	0.62	2.3	0.84
2c	5.1	6.2	6.0	1.2	0.43	0.59	3.3	2.2
2d	2.7	2.1	1.9	1.0	0.59	0.63	2.7	0.63
2e	2.3	2.2	2.6	0.80	0.44	0.57	2.5	0.62
2f	2.8	1.6	1.7	1.0	0.96	0.93	1.7	1.0
2g	5.1	6.2	7.6	1.0	0.40	0.48	2.6	3.1
2h	4.9	5.7	5.3	1.1	0.42	0.62	2.7	3.1
2i	3.3	4.3	3.4	1.0	0.53	0.62	2.0	0.94
4	18.4	4.0	10.4	1.3	0.49	0.46	3.0	3.0

a) Reproducibility: <±0.3 for monoammonium, <±0.5 for diammonium. b) not bufferized. c) bufferized to pH 3.0±0.1.
d) not responded.

ammonium salts, but could not discriminate between the enantiomers of chiral amine salts. Since they bound both enantiomers of these guest cations, acyclic monensin skeleton must be essential for chiral recognition. In contrast, functionalized monensin derivative **3b** was confirmed to bind the ammonium cations only weakly, indicating that the blocking of two -OH groups completely prevented binding of ammonium salts. Thus, a combination of pseudo-cyclic polyether skeleton, amide junction and chiral, bulky residue provided excellent chiral recognition function.

Table 2 Enantiomer Selectivity Coefficient k_{RS} of Crown-Type Monensin Amides.

Receptor	k_{RS} at 20°C							
	PhglyOMe[b] •HCl	PheOMe[b] •HCl	LeuOMe[b] •HCl	ProOMe[b] •HCl	1-Phenethyl-amine[b] •HCl	1-(1-Naphthyl)ethyl-amine[b] •HCl	LysOMe[c] •2HCl	ArgOMe[c] •2HCl
3a	1.1	1.0	1.0	d)	1.0	0.94	d)	d)
3c	1.0	1.0	1.0	d)	0.86	0.62	d)	d)
3d	1.0	1.0	1.0	d)	1.0	1.2	d)	d)

a) Reproducibility: <±0.3 for monoammonium, <±0.5 for diammonium. b) not bufferized. c) bufferized to pH 3.0±0.1.
d) not responded.

^{1}H-NMR Studies on Enantiomer Selective Complexation Behaviors of Monensin Amides.

The enantiomer selective complexation behavior of monensin derivatives was investigated in $CDCl_3$ by ^{1}H-NMR spectroscopy. Figures 4 and 5 indicate the guest-induced changes in the chemical shifts of selected proton signals of biological monensin **1** and podand-type monensin amide **2g**. In both cases, averaged signals were observed upon addition of guest salts. Since discrete signals were not observed for the complex and the free receptor at intermediate stoichiometries, fast binding kinetics was suggested.

Biological monensin sodium salt showed characteristic spectral changes in the presence of *(R)*- or *(S)*-1-(1-naphthyl)ethylamine·AcOH salt (Figure 4). Addition of these ammonium cations caused changes in chemical shifts of the signals of several protons attached to the carbons surrounding the pseudo-cyclic cavity such as those positioned at 2, 5, 7, 17, 20, 26 and 31. Although the monensin was reported to extract several organic ammonium cations into $CHCl_3$ phase from aqueous phase,[7] the shifted values were too small to determine the stoichiometry and stability constant accurately. Probably, the guest ammonium cation appeared to be in loose contact with the polyether linkage in the complex. Since both enantiomers of guest salt induced almost the same spectral changes, biological monensin could not discriminate between these enantiomers. Electrostatic interaction between the terminal carboxylate anion of monensin and guest ammonium cation is probably not effective for enantiomer selective binding.

Figure 5 illustrates the spectral changes of podand-type monensin amide **2g**. Its shifted values were much larger than those observed with biological monensin **1**, and the guest ammonium cation is believed to be located at the center of the pseudo-cyclic cavity and to effectively interact with several oxygen atoms of the monensin chain. Furthermore, the protons on the amide-substituent shifted greatly, indicating that amide junction also acted as a potential binding site for guest ammonium cation. When *(R)*-1-(1-naphthyl)ethylamine·AcOH salt was added to a solution of monensin amide **2g**, the signal for proton positioned at 21-carbon shifted to 83.6 Hz lower field, while the *(S)*-guest cation induced a shift to 3.0 Hz higher field. The fact that the shifted values exhibited the opposite signs demonstrated that podand-type monensin amide **2g** formed complexes with these chiral

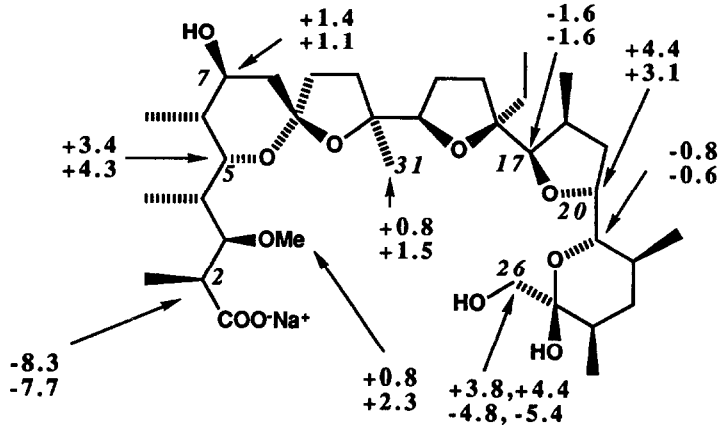


Figure 4. Guest-Induced Changes in ^{1}H-NMR Chemical Shifts (Hz)[a] of Monensin Sodium Salt in $CDCl_3$[b]

a) upper : +15 eq. of *(R)*-1-(1-Naphthyl)ethylamine·AcOH
lower : +15 eq. of *(S)*-1-(1-Naphthyl)ethylamine·AcOH.
b) Conc. of Monensin : 0.0146 mol/L

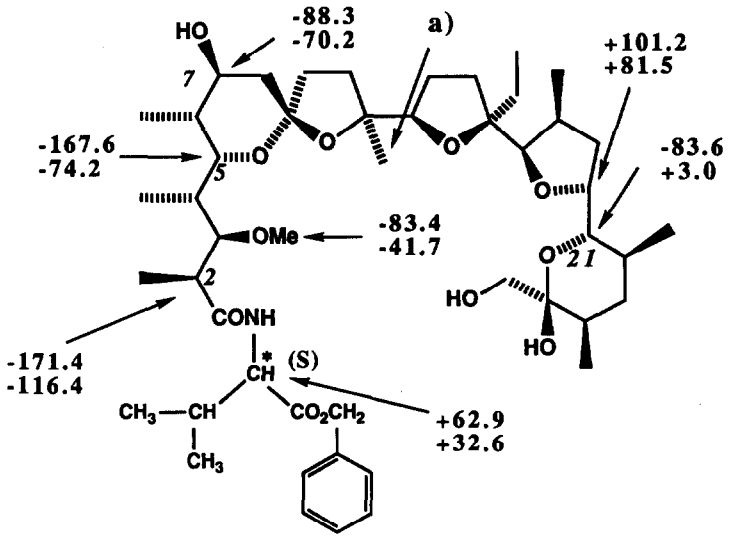


Figure 5. Guest-Induced Changes in ^{1}H-NMR Chemical Shifts (Hz)[b] of Podand-Type Monensin Amide 2g in $CDCl_3$[c]

a) These signals could not be identified, because of their large shifts.
b) upper : +15 eq. of *(R)*-1-(1-Naphthyl)ethylamine·AcOH
lower : +15 eq. of *(S)*-1-(1-Naphthyl)ethylamine·AcOH.
c) Conc. of Monensin Derivative **2g** : 0.0146 mol/L

ammonium cations having different structures.

Figure 6 illustrates plots of the guest-induced changes in chemical shifts of the proton signal positioned at carbon 2 *vs.* mole ratio of *(S)*- or *(R)*-1-(1-naphthyl)ethylamine·AcOH / monensin amide **2g**. These titration curves gave good fits for 1:1 complexation and the thermodynamic stability constants were calculated by nonlinear least-squares treatment: K_R=89 L/mol for the *(R)*-isomer and K_S=30 L/mol for the *(S)*-isomer in $CDCl_3$ at 25°C. We also calculated stability constants based on changes of other proton signals and obtained similar values. Thus, monensin amide **2g** formed a more stable complex with *(R)*-1-(1-naphthyl)ethylamine·AcOH than with *(S)*-isomer and k_{RS} value was smaller than 1. Other podand-type monensin amides offered parallel spectral changes but their guest-induced shifts were smaller than those of monensin amide **2g**.

Crown-type monensin **3a** also bound chiral ammonium cations. Its enantiomer-induced shifts for protons at 2-, 5-, 17-, 21- and 26-positioned carbons showed the opposite signs, but shifted values were much smaller than those with podand-type monensin amide **2g** (Figure 7). Since its titration curves were somewhat flat and not well fitted for 1:1 complexation, crown-type skeleton was less effective for chiral recognition than podand-type skeleton.

Table 3 summarizes thermodynamic stability constants, K_S and K_R, of the monensin ester **2a** and amide **2g**, compared with electrochemical enantiomer selectivity coefficients k_{RS}. Monensin amide **2g** gave much larger stability constants for four ammonium salts than monensin ester **2a**. Introduction of a chiral, bulky amide-substituent effectively stabilized the complexes and enhanced chiral recognition ability. As reported earlier,[11] the electrochemically obtained k_{RS}^{-1} was confirmed to be correlated with K_R/K_S in these systems. These observations clearly demonstrate that monensin derivative exhibiting large spectral changes upon complexation

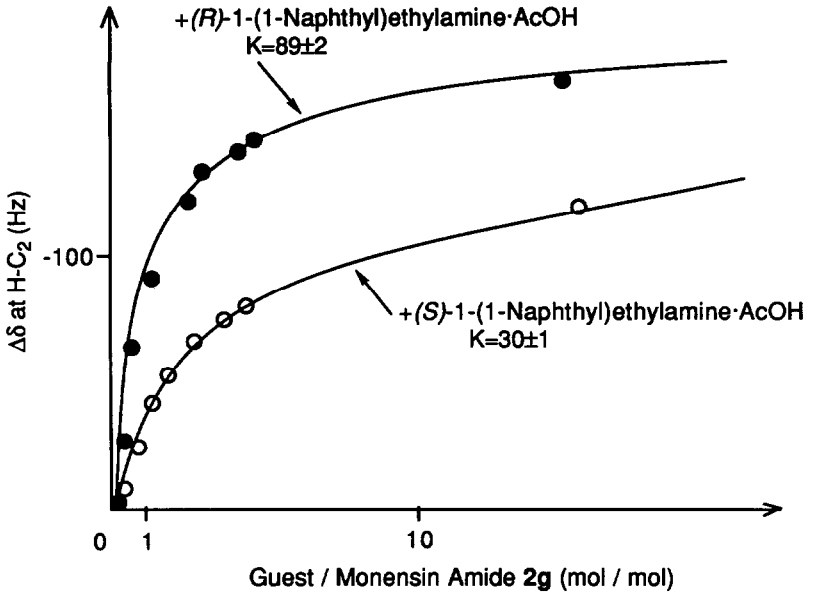


Figure 6. Titration Curves of Monensin Amide 2g with *(S)*- and *(R)*-1-(1-Naphthyl)ethylamine·AcOH in $CDCl_3$

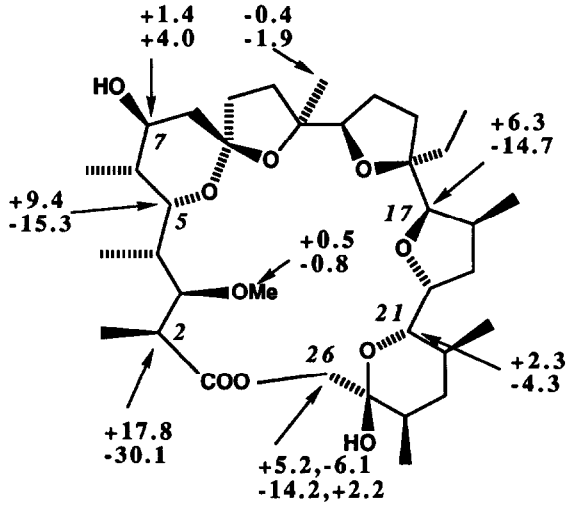


Figure 7. Guest-Induced Changes in ^{1}H-NMR Chemical Shifts (Hz)[a] of Crown-Type Monensin 3a in $CDCl_3$[b]

a) upper : +15 eq. of *(R)*-1-(1-Naphthyl)ethylamine·AcOH
lower : +15 eq. of *(S)*-1-(1-Naphthyl)ethylamine·AcOH.
b) Monensin Derivative 3a: 0.0146 mol/L.

Table 3. Stability Constants and Enantiomer Selectivity Coefficients of Monensin Derivatives 2a and 2g.

Receptor	Guest·AcOH	H-Cn[a]	^{1}H-NMR Method		Electrode Method
			K_R or K_S[b]	K_R/K_S	k_{RS}^{-1}
2a	*(R)*-1-(1-Naphthyl)ethylamine·AcOH	2	13	2.3	2.2
	(S)-1-(1-Naphthyl)ethylamine·AcOH	2	6		
	(R)-1-Phenethylamine·AcOH	17	9	-	1.9
	(S)-1-Phenethylamine·AcOH	c)	c)		
2g	*(R)*-1-(1-Naphthyl)ethylamine·AcOH	2	89	3.0	2.6
	(S)-1-(1-Naphthyl)ethylamine·AcOH	2	30		
	(R)-1-Phenethylamine·AcOH	2	73	2.5	2.5
	(S)-1-Phenethylamine·AcOH	2	30		

a) Cn indicates carbon number of carbon atoms of monensin skeleton. b) K_R and K_S indicate the stability constants with *(R)*- and *(S)*-enantiomers calculated by means of ^{1}H-NMR titration method at 25°C. c) could not be calculated because their changes in chemical shifts were too small.

provides excellent enantiomer selectivity both in the homogeneous solution and at the membrane surface in the electrochemical sensory system.

We successfully obtained a new series of chiral receptors from naturally occurring monensin ionophore. Some podand-type monensin amides formed encapsulated complexes with certain chiral ammonium cations. Guest cations were comfortably included in these complexes by chiral and pseudo-cyclic monensin skeleton and further coordinated by the amide junction introduced. Further modification of naturally occurring ionophores and related biological materials may offer promising means of development of a new and specific chiral receptor molecule.

EXPERIMENTAL SECTION

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a JEOL GSX-400 (Department of Chemistry, Kyoto University) or a Varian VXR-500 (SC-NMR Laboratory, Okayama University) spectrometer with Me_4Si as internal reference at 25°C. IR spectra were run on a JASCO IRA-1 spectrophotometer.

Monensin sodium salt and its methyl ester **2a** are commercially available (Wako and Calbiochem, respectively) and were used without further purification. Solvents and other reagents were used after usual purification. Amino acid esters are also commercially available (Sigma Co. and Wako Pure Chemical Industries).[14] Monensin lactone **3a** and its diacetate **3b** were prepared by methods described in the literature.[9]

3a: ^{1}H-NMR(400MHz, $CDCl_3$), δ=0.85-2.29(similar to parent monensin, 45H), 2.99(m, 1H), 3.39(s, 3H), 3.45(br.s, 1H), 3.62(m, 1H), 3.65(d, J=11.0Hz, 1H), 3.85(br.s, 1H), 3.97(dd, J=10.0, 3.0Hz, 1H), 4.09(d, J=4.2Hz, 1H), 4.27(br.d, J=10.5Hz, 1H), 4.31(m, 1H), 4.45(d, J=11.3Hz, 1H); IR ν_{max}($CHCl_3$) 1740cm^{-1}.

3b: ^{1}H-NMR(400MHz, $CDCl_3$), δ=0.85-2.31(similar to parent monensin, 44H), 2.05(s, 3H), 2.09(s,

3H), 2.76(m, 1H), 3.00(m, 1H), 3.49(s, 3H), 3.52-3.55(m, 2H), 3.90(d, J=3.6Hz, 1H), 4.03(dd, J=7.2, 2.2Hz, 1H), 4.28(m, 1H), 4.67(d, J=18.0Hz, 1H), 4.71(br.s, 1H), 4.76(d, J=10.0Hz, 1H), 4.84(d, J=18.0Hz, 1H); IR ν_{max}($CHCl_3$) 1725-1735cm^{-1}.

All new monensin derivatives were confirmed as pure materials by TLC analysis and had correct elemental compositions determined by high-resolution FAB-mass spectroscopy (JEOL JMS HX-110). These are "hazardous compounds" and require careful handling and disposal.

Modification of Monensin. Typically, podand-type monensin amide **2g** was synthesized as follows. In the presence of 2,2'-dipyridyldisulfide (30mg) and triphenylphosphine (45mg), monensin free acid (30mg) was treated with L-ValOBz (100mg, Bz=-$CH_2C_6H_5$) in methylene chloride at room temperature for 1 day. After refluxing for 1 day, the reaction mixture was washed with dil. HCl and then with saturated sodium hydrogen carbonate solution. Chromatography (silica gel: Wako gel C-200, CH_2Cl_2/AcOEt) gave pure monensin derivative **2g** (24mg).

Crown-type monensin amides **3c** and **3d** were derived from the podand-type compounds **2d** and **2e**. These precursors were reductively debenzylated under H_2 in the presence of 5% Pd/C catalyst (1 day at room temperature in EtOH). After filtration and evaporation, the obtained free acids were treated with 2,2'-dipyridyldisulfide and triphenylphosphine in benzene. After usual workup, chromatographic purification (silica gel; Wako gel C-200, CH_2Cl_2/AcOEt) gave crown-type monensin derivatives. Selected spectroscopic data for new monensin derivatives are described below.[15]

2b: colorless oil; ^{1}H-NMR(400MHz, $CDCl_3$), δ=0.85-2.30 (similar to parent monensin, 45H), 2.46(m, 1H), 2.78(d, J=6.0Hz, 3H), 3.43(s, 3H), 3.35-3.57(m, 4H), 3.81(br.s, 1H), 3.94(dd, J=11.9, 3.0Hz, 1H), 3.96(d, J=3.0Hz, 1H), 4.16(d, J=7.2Hz, 1H), 4.33(m, 1H), 4.73(br.s, 1H), 5.27(br.s, 1H), 6.95(br.s, 1H); IR ν_{max}($CHCl_3$) 1650cm^{-1}; High Resolution Mass Spectrum(HRMS), Found: m/z 706.4439. Calcd for $C_{37}H_{65}O_{10}NNa$: $(M+Na)^+$, 706.4506; Yield 80%.

2c: colorless oil; ^{1}H-NMR(400MHz, $CDCl_3$), δ=0.90-2.30 (similar to parent monensin, 45H), 1.54(d, J=9.6Hz, 3H), 2.91(m, 1H), 3.38(m, 3H), 3.51(s, 3H), 3.58(m, 1H) 3.80(m, 2H), 4.03(d, J=3.7Hz, 1H), 4.12(dd, J=6.9, 0.9Hz, 1H), 4.18(m, 1H), 4.44(m, 1H), 5.08(m, 1H), 5.35(br.s, 1H), 7.18-7.61(m, 6H); IR ν_{max}($CHCl_3$) 1650cm^{-1}; HRMS, Found: m/z 796.4943. Calcd for $C_{44}H_{71}O_{10}NNa$: $(M+Na)^+$, 796.4976; Yield 60%.

2d: colorless oil; ^{1}H-NMR(400MHz, $CDCl_3$), δ=0.80-2.30 (similar to parent monensin, 45H), 2.54(m, 1H), 3.42(s, 3H), 3.45(m, 1H), 3.47(br.s, 2H), 3.53(m, 1H) 3.77(br.s, 1H), 3.92(dd, J=11.9, 3.4Hz, 1H), 3.97(d, J=4.8Hz, 1H), 4.04(d, J=6.5Hz, 1H), 4.06(d, J=6.5Hz, 1H), 4.11(dd, J=8.5, 2.4Hz, 1H), 4.32(m, 1H), 5.05(br.s, 1H), 5.16(s, 2H), 7.35(m, 5H); IR ν_{max}($CHCl_3$) 1660cm^{-1}, 1740cm^{-1}; HRMS, Found: m/z 840.4855. Calcd for $C_{45}H_{71}O_{12}NNa$: $(M+Na)^+$, 840.4874; Yield 70%.

2e: colorless oil; ^{1}H-NMR(400MHz, $CDCl_3$), δ=0.80-2.30 (similar to parent monensin, 45H), 2.69(t, J=7.7Hz, 2H), 2.92(m, 1H), 3.30-3.43(m, 2H), 3.53(s, 3H), 3.60(m, 1H) 3.50-3.60(br.s, 2H), 3.80(m, 2H), 3.99(br.s, 1H), 4.03(d, J=4.1Hz, 1H), 4.21(d, J=7.2Hz, 1H), 4.45(m, 1H), 5.11(s, 2H), 5.41(br.s, 1H), 7.19(br.s, 1H), 7.34(m, 5H); IR ν_{max}($CHCl_3$) 1650cm^{-1}, 1720cm^{-1}; HRMS, Found: m/z 854.4975. Calcd for $C_{46}H_{73}O_{12}NNa$: $(M+Na)^+$, 854.5031; Yield 60%.

2f: colorless oil; ^{1}H-NMR(400MHz, $CDCl_3$), δ=0.90-2.45 (similar to parent monensin, 45H, and -$NCCH_2CH_2$-, 4H), 2.57(m, 1H), 3.35(s, 3H), 3.43-3.52(m, 3H), 3.58(m, 1H), 3.73(br.s, 1H) 3.86(dd,

J=9.8, 3.3Hz, 1H), 3.93(d, J=4.9Hz, 1H), 4.11(dd, J=8.1, 1.6Hz, 1H), 4.29(m, 1H), 4.62(m, 1H), 5.09(s, 2H), 5.13(d, J=12.7Hz, 1H), 5.17(d, J=12.7Hz, 1H), 7.00(d, J=5.6Hz, 1H), 7.35(m, 10H); IR ν_{max}(CHCl3) 1650cm^{-1}, 1740cm^{-1}; HRMS, Found: m/z 1002.5550. Calcd for $C_{55}H_{81}O_{14}NNa$: $(M+Na)^+$, 1002.5556; Yield 70%.

2g: colorless oil; ^{1}H-NMR(400MHz, CDCl3), δ=0.90-2.30 (similar to parent monensin, 45H, and -NCCH$(CH_3)_2$, 7H), 2.57(m, 1H), 3.38(s, 3H), 3.47-3.52(m, 3H), 3.60(m, 1H), 3.75(br.s, 1H) 3.84(dd, J=9.6, 3.0Hz, 1H), 3.92(d, J=4.5Hz, 1H), 4.13(dd, J=7.5, 2.4Hz, 1H), 4.28(m, 1H), 4.39(br.s, 1H), 4.56(m, 1H), 5.17(d, J=12.0Hz, 1H), 5.20(d, J=12.0Hz, 1H), 6.73(d, J=9.7Hz, 1H), 7.34(m, 5H); IR ν_{max}(CHCl3) 1650cm^{-1}, 1720cm^{-1}; HRMS, Found: m/z 882.5318. Calcd for $C_{48}H_{77}O_{12}NNa$: $(M+Na)^+$, 882.5343; Yield 80%.

2h: colorless oil; ^{1}H-NMR(400MHz, CDCl3), δ=0.80-2.30 (similar to parent monensin, 45H), 3.12(br.s, 1H), 3.32(t, J=11.2Hz, 1H), 3.52(s, 3H), 3.40-3.53(m, 2H), 3.60(m, 1H), 3.78(m, 1H), 3.82(dd, J=11.2, 4.5Hz, 1H), 4.01(br.s, 1H), 4.05(d, J=4.0Hz, 1H), 4.28(d, J=6.3Hz, 1H), 4.43(m, 1H), 5.13(d, J=13.5Hz, 1H), 5.17(d, J=13.5Hz, 1H), 5.40(br.s, 1H), 5.55(d, J=5.8Hz, 1H), 7.21-7.38(m, 10H), 7.54(d, J=6.5Hz, 1H); IR ν_{max}(CHCl3) 1650cm^{-1}, 1720cm^{-1}; HRMS, Found: m/z 916.5205. Calcd for $C_{51}H_{75}O_{12}NNa$: $(M+Na)^+$, 916.5187; Yield 60%.

2i: colorless oil; ^{1}H-NMR(400MHz, CDCl3), δ=0.70-2.30 (similar to parent monensin, 45H), 2.78(m, 1H), 3.42(s, 3H), 3.52-3.60(m, 3H), 3.73(dd, J=10.4, 3.1Hz, 1H), 3.82(m, 1H), 3.90(br.s, 1H), 3.98(d, J=3.5Hz, 1H), 4.06(d, J=10.4Hz, 1H), 4.20(br.s, 1H), 4.42(m, 1H), 4.77(br.s, 1H), 5.19(s, 2H), 5.55(d, J=7.0Hz, 1H), 7.21-7.50(m, 11H); IR ν_{max}(CHCl3) 1650cm^{-1}, 1720cm^{-1}; HRMS, Found: m/z 916.5177. Calcd for $C_{51}H_{75}O_{12}NNa$: $(M+Na)^+$, 916.5187; Yield 60%.

3c: colorless oil; ^{1}H-NMR(400MHz, CDCl3), δ=0.85-2.39 (similar to parent monensin, 45H), 2.69(m, 1H), 3.07(dd, J=9.7, 1.6Hz, 1H), 3.37(s, 3H), 3.40(m, 1H), 3.72(d, J=11.0Hz, 1H) 3.79(dd, J=9.7, 1.9Hz, 1H), 3.81(br.s, 1H), 3.89(dd, J=10.6, 2.3Hz, 1H), 3.97(d, J=3.5Hz, 1H), 3.98(dd, J=19.4, 3.2Hz, 1H), 4.25(dd, J=19.4, 3.2Hz, 1H), 4.29(m, 1H), 4.92(d, J=10.0Hz, 1H), 6.30(br.s, 1H); IR ν_{max}(CHCl3) 1600cm^{-1}, 1720cm^{-1}; HRMS, Found: m/z 732.4309. Calcd for $C_{38}H_{63}O_{11}NNa$: $(M+Na)^+$, 732.4299; Yield from **2d**: 60%.

3d: colorless oil; 1H-NMR(400MHz, CDCl3), δ=0.85-2.30 (similar to parent monensin, 45H), 2.36(m, 1H), 2.59(t, J=5.8Hz, 2H), 3.42-3.48(m, 2H), 3.44(s, 3H), 3.53(m, 1H), 3.64(m, 1H), 3.79(br.s, 1H), 3.92(dd, J=10.6, 2.3Hz, 1H), 3.95(d, J=10.4Hz, 1H), 3.96(br.s, 1H), 4.11(br.s, 1H), 4.29(m, 1H), 4.92(d, J=8.9Hz, 1H), 5.71(br.s, 1H), 6.16(br.m, 1H); IR ν_{max}(CHCl3) 1600cm^{-1}, 1720cm^{-1}; HRMS, Found: m/z 746.4473. Calcd for $C_{39}H_{65}O_{11}NNa$: $(M+Na)^+$, 746.4459; Yield from **2e**: 70%.

Method of Evaluation for Stability Constants (K). For the ^{1}H-NMR titration experiments, we usually prepared ten samples with different guest / receptor ratios. The guest / receptor ratio was also confirmed by comparing integrated values of some protons in the ^{1}H-NMR spectrum. The stability constant (K) for 1:1 complex formation is given by equation (1):

$$K=[C]/\{[R]_O-[C]\}\{[G]_O-[C]\} \quad \cdots\cdots\cdots\cdots(1)$$

where [C], $[R]_O$ and $[G]_O$ represent the concentration of complex in the equilibrated state, and initial concentrations of receptor and guest, respectively. Supposing that guest-induced change in the chemical shift of proton signal (Δδ) can be related to $\Delta\delta_\infty$ (saturated Δδ) as equation (2),

$$\Delta\delta=[C]\Delta\delta_\infty/[R]_O \quad \cdots\cdots\cdots\cdots(2)$$

one can derive equation (3) by substitution of equation (1) with equation (2).

$$\Delta\delta=\{[R]_O+[G]_O+1/K-\{\{([R]_O+[G]_O+1/K)^2-4[R]_O[G]_O\}^{1/2}\}/(2[R]_O/\Delta\delta_\infty) \cdots\cdots (3)$$

Substituting measured $\Delta\delta$, $[R]_O$ and $[G]_O$ in equation (3), we determined stability constant (K) with nonlinear least squares treatment (Gauss-Newton method). Curves indicated in Figure 6 are computer-calculated titration curves according to equation (3).

Methods for Ion-Selective Electrode Measurements. Ion-selective electrode measurements were carried out as follows. Cell composition was Ag/AgCl; 0.01M NaCl; membrane; sample solution; reference electrode (ORION 0.3M NH_4NO_3; AgCl/Ag). Membrane potentials were measured by an EA-920 ion analyzer (ORION) and recorded within ±0.3mV stability with a microcomputer system. We used a DKK membrane electrode kit: 1mg of potassium tetrakis(*p*-chrolophenyl)borate, 3mg of receptor, 30mg of poly(vinyl chloride) and 66mg of *o*-nitrophenyl octyl ether were dissolved in 1mL of tetrahydrofuran (THF).[16] After the solution became homogeneous, twenty drops were spread on a Teflon sheet put on the electrode tip. After 12 hours, the electrode tip was immersed in 0.01M NaCl solution for 6 hours and then mounted on an electrode body for measurement. The emf values measured at 0.1M were set into the Nicolsky-Eisenman equation for calculation of selectivity coefficient k_{ba} by the separate solution method. Activity coefficients were calculated according to the Debye-Hückel equation. We confirmed near-Nernstian response for each experiment.

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REFERENCES AND NOTES

1. Recent examples: Kaneda, T.; Hirose, K.; Misumi, S. *J. Am. Chem. Soc.* **1989**, *111*, 742-743; Castro,P. P.; Georgiadis, T. M.; Diederich, F. *J. Org. Chem.* **1989**, *54*, 5835-5838; Potin, D.; Williams, K.; Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1420-1422; Liu, R.; Sanderson, P. E. J .; Still, W. C. *J. Org. Chem.* **1990**, *55*, 5184-5186; Colonna, S.; Manfredi, A.; Annunziata, R.; Gaggero, N. *J. Org. Chem.* **1990**, *55*, 5862-5866; Arimura, T.; Kawabata, H.; Matsuda, T.; Muramatsu, T.; Satoh, H.; Fujio, K.; Manabe, O.; Shinkai, S. *J. Org. Chem.* **1991**, *56*, 301-306.
2. Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1009-1027; Lehn, J. -M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 90-112; Hofmeister, G. H.; Hahn, F. E.; Pedersen, S. F. *J. Am. Chem. Soc.* **1989**, *111*, 2318-2319; Aoki, S.; Sasaki, S.; Koga, K. *Tetrahedron Lett.* **1989**, *30*, 7229-7230; Zinic, M.; Frkanec, L.; Skaric, V.; Skaric, J.; Trafton, J.; Gokel, G. W. *J. Chem. Soc., Chem. Commun.* **1990**, 1726-1728; Bradshaw, J. S.; Huszthy, P.; McDaniel, C. W.; Zhu, C. Y.; Dalley, N. K.; Izatt, R. M. *J. Org. Chem.* **1990**, *55*, 3129-3137; Yamamoto, K.; Ikeda, T.; Kitsuki, T.; Okamoto, Y.; Chikamatsu, H.; Nakazaki, M. *J. Chem. Soc., Perkin Trans. I* **1990**, 271-276.
3. Tsukube, H.; Sohmiya, H. *Tetrahedron Lett.* **1990**, *31*, 7027-7030; Tsukube, H.; Sohmiya, H. *J. Org. Chem.* **1991**, *56*, 875-878.

4. Agtarap, A.; Chamberlin, J. W.; Pinkerton, M.; Steinrauf, L. K. *J. Am. Chem. Soc.* **1967**, *89*, 5737-5739; Duesler, E. N.; Paul, I. C. *'Polyether Antibiotics: Naturally Occurring Acid Ionophores,'* Vol 2, ed. by Westley, J. W.; Marcel Dekker, New York, **1982**; Painter, G. R.; Pressman, B. C. *Topics in Current Chemistry'*, Vol. *101*, Springer, Berlin, **1982**, p. 1; Choy, E.; Evans, D. F.; Cussler, E. L. *J. Am. Chem. Soc.* **1974**, *96*, 7085-7090; Duax, W. L.; Smith, G. D.; Strong, P. D. *ibid.* **1980**, *102*, 6725-6729; Pangborn, W.; Duax, W. L.; Langs, D. *ibid.* **1987**, *109*, 2163-2165; Reed, W. P. *'Polyether Antibiotics: Naturally Occurring Acid Ionophores,'* Vol *1*, ed. by Westley, J. W., Marcel Dekker, New York, **1982**; Cox, B. G.; Truong, N. V.; Rzeszotarsta, J.;Schneider, H. *J. Am. Chem. Soc.* **1984**, *106*, 5965-5969.
5. Westley, J. W.; Evans, R. H.; Blout, J .F. *J. Am. Chem. Soc.* **1977**, *99*, 6057-6061; Chia, P. S. K.; Lindoy, L. F.; Walker, G. W.; Everett, G. W. *J. Am. Chem. Soc.* **1991**, *113*, 2533-2537.
6. Preliminary communication; Maruyama, K.; Sohmiya H.; Tsukube, H. *J. Chem. Soc., Chem. Commun.* **1989**, 864-865.
7. Tsukube, H.; Takagi, K.; Higashiyama, T.; Iwachido, T.; Hayama, N. *J. Chem. Soc., Chem. Commun.* **1986**, 448-449; Tsukube, H.; Sohmiya, H. *Inorg. Chim. Acta.* **1989**, *166*, 27-29.
8. Some kinds of monensin derivatives have been prepared: Westley, J. W.; Evans, R. H., Jr.; Sello, L. H.; Troupe, N.; Liu, C.; Miller, P. A. *J. Antibiotic.* **1981**, *34*, 1248-1252; Westley, J. W.; Liu, C.; Evans, R. H., Jr.; Sello, L. H.; Troupe, N.; Hermann, T. *J. Antibiotic.* **1983**, *36*, 1195-1200.; Asukabe, H.; Yoneyama, H.; Mori, Y.; Harada , K.; Suzuki, M. *J. Chromatography* **1987**, *396*, 261-271; Sakakibara, J.; Nakamura, A.; Nagai, S.; Ueda, T.; Ishida, T. *Chem. Pharm. Bull.* **1988**, *36*, 4776-4784; Smith, P. W. Still, W. C. *J. Am. Chem. Soc.* **1988**, *110*, 7917-7919.
9. Corey, E. J.; Nicolaou, K. C.; Melvin, L. S., Jr. *J. Am. Chem. Soc.* **1975**, *97*, 653-654.
10. Suzuki, K.; Tohda, K.; Sasakura, H.; Inoue, H.; Tatsuta, K.; Shirai, T. *J. Chem. Soc., Chem. Commun.* **1987**, 932-934.
11. Moody, G. J.; Thomas, J. D. R. *'Selective Ion-Sensitive Electrode'*, Merrow, London, **1971**; Bussman, W.; Simon, W. *Helv. Chim. Acta* **1981**, *64*, 657-661
12. Metal selectivity of monensin and its esters has been characterized in several electrochemical sensory systems. The natures of the membrane solvent and other additives seriously affected the guest selectivity : Arnold, M. A.; Solsky, R. L. *Anal. Chem.* **1986**, *58*, 84R-101R; Suzuki, K.; Tohda, K.; Aruga, H.; Matsuzoe, M.; Inoue, H.; Shirai, T. *Anal. Chem.* **1988**, *60*, 1714-1721; Tohda, K.; Suzuki, K.; Kosuge, N.; Watanabe, K.; Inoue, H.; Shirai, T. *Anal. Chem.* **1990**, *62*, 936-942; Davies, O. G.; Moody, G. J.; Thomas, J. D. R. *Analyst* **1988**, *113*, 497-500; Schindler, J. G.; Schindler, M. M. *Frezenius Z. Anal. Chem.* **1985**, *320*, 258-260.
13. Shinbo, T.; Yamaguchi, T.; Nishimura, K.; Kikkawa, M.; Sugiura, M. *Anal. Chim. Acta* **1987**, *193*, 367-371.
14. Only PhglyOBz was not commercially available and was prepared according to the following literature: Loose, G.; Wagner, R.; Neuland, P.; Rateitschak, J. *Chem. Ber.* **1958**, *91*, 2410-2417; Hakimelaki, G. H. Just, G. *Can. J. Chem.* **1979**, *57*, 1939-1944.
15. Some signals of hydroxy and amide protons were not observed. NMR assignment: Robinson, J. A.; Turner, D. L. *J. Chem. Soc., Chem. Commun.* **1982**, 148-151; Ajaz, A. A.; Robinson, J. A. *J. Chem. Soc., Perkin Trans. I* **1987**, 27-36.
16. Potassium tetrakis(*p*-chlorophenyl)borate was not used in metal-selective electrode experiments. See Fig.2.