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TETRAHEDRON

NOVEL ACYCLIC LIGANDS FOR METAL CATIONS BASED ON THE ADJACENT BISTETRAHYDROFURAN AS ANALOGS OF NATURAL *ANNONACEOUS* ACETOGENINS

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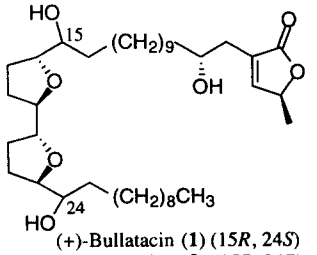
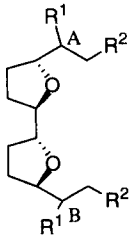
Abstract: The acyclic ligands with an adjacent bistetrahydrofuran (THF) skeleton have been synthesized as analogs of bullatacin, a representative natural product in a family of *Annonaceous* acetogenins, and their binding properties toward metal cations have been investigated. The dihydroxyl bis-THF ligands with alkyl chains showed specific binding toward Ca^{2+}, and those with acetamido groups exhibited potent binding with Ca^{2+} and Mg^{2+}. The ligand with ether chains showed higher affinity toward Mg^{2+}. These binding properties which depend on the nature of side chains and their stereochemistry have been analyzed by molecular modeling.

INTRODUCTION

Annonaceous acetogenins are a relatively new family of natural products with tetrahydrofurans and have attracted much attention in view of their diverse biological effects.[1] Among them, extremely potent *in vitro* antitumor activities have been exhibited by the compounds with an adjacent bistetrahydrofuran (THF) skeleton such as bullatacin (**1**).[2] Biological studies on the mode of action have revealed the inhibition of the mitochondorial respiration at the site of the complex I and the NADH oxidase in the plasma membrane, leading to induction of apoptosis through decrease in ATP production.[3] Although no ionophoric activity of these compounds has been found for living cells,[4] it has been presumed from the structural analogy with compounds with oligo-tetrahydropyrans,[5] tetrahydrofurans,[6] and synthetic ionophores[7] that they may possess affinity toward metal cations and such properties might be related to their biological activities. Our preliminary studies have shown that compounds with an adjacent bis-THF skeleton, including natural products (+)-squamocin G (bullatacin) and (+)-squamocin H (asimicin), exhibit selective affinity to Ca^{2+} in solution, and it turned out that the bis-THF derivatives construct a new family of ligands for metal cations.[8] Recently, another group also reported NMR studies of Ca^{2+} complexes of *Annonaceous* acetogenins.[9]



(+)-Bullatacin (**1**) (15*R*, 24*S*)
(+)-Asimicin (**2**) (15*R*, 24*R*)



	(*A*, *B*)	R^1=	R^2=
3:	(*R*, *R*)	OH	CH_3
4:	(*R*, *S*)	OH	CH_3
5:	(*S*, *S*)	OH	CH_3
6:	(*R*, *R*)	OH	$(CH_2)_8CH_3$
7:	(*R*, *S*)	OH	$(CH_2)_8CH_3$
8:	(*S*, *S*)	OH	$(CH_2)_8CH_3$
9:	(*R*, *R*)	OH	$(OCH_2CH_2)_2OEt$
10:	(*R*, *S*)	OH	$(OCH_2CH_2)_2OEt$
11:	(*R*, *R*)	NHAc	$(CH_2)_8CH_3$
12:	(*R*, *S*)	NHAc	$(CH_2)_8CH_3$
13:	(*S*, *S*)	NHAc	$(CH_2)_8CH_3$

We further synthesized new bis-THF ligands with different side chains and stereochemistry to investigate structural effects on the binding of metal cations. In this report, we wish to describe in detail the binding prop-

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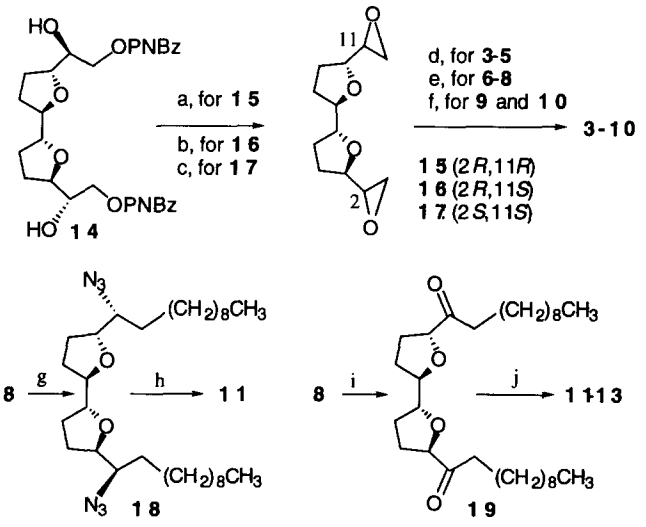
erties of the new bis-THF ligands together with the previously reported ones with focusing on the following aspects: 1) the effects of the stereochemistry on the binding, 2) theoretical analysis of the metal cation selectivity by molecular modeling, and 3) the molecular assembly depending on the side chain structures.

SYNTHESIS

The synthesis of the ligands started with di-*p*-nitrobenzoate of (2*S*,3*R*,6*R*,7*R*,10*R*,11*S*)-3,6:7,10-diepoxydodecane-1,2-diol (**14**) which was prepared from D-tartrate as the key intermediate in the synthesis of bullatacin[10] (Scheme 1). The secondary hydroxyl groups of **14** were mesylated with MsCl and then treated with *n*-Bu_4NOH in THF to produce the (2*R*,11*R*)-diepoxide **15**. Treatment of **14** with one equivalent of MsCl gave the monomesylate, which afforded monoepoxide by the treatment with *n*-Bu_4NOH. The remaining primary hydroxyl group was selectively tosylated *via* cyclic stannate and then subjected to the epoxide formation with K_2CO_3 to give (2*R*,11*S*)-diepoxide **16**. On the other hand, **14** was hydrolyzed with K_2CO_3 in methanol followed by *n*-Bu_2SnO to yield bis-cyclic stannate, which then gave the corresponding ditosylate of the primary hydroxyl groups by the reaction with *p*-toluenesulfonyl chloride in $CHCl_3$. Subsequent treatment with K_2CO_3 produced the (2*S*,11*S*)-epoxide **17**. The alkylations of these epoxides were carried out with the use of *n*-nonylMgBr or MeLi in the presence of CuBr to afford the dihydroxyl ligands (**3-8**). The ligands with ether side chains (**9** and **10**) were obtained from the epoxides **15** and **17**, respectively, by the reaction with a sodium alcoholate of 2-(2-ethoxyethoxy)ethanol.

Scheme 1[a]



[a](a) 1) MsCl (2.2.eq), TEA, THF, 0 °C, 2) *n*-Bu_4NOH, THF, 0 °C, (b) 1) MsCl (1.1 eq) , TEA, THF, 0 °C, 2) *n*-Bu_4NOH, THF, 0 °C, 3) *n*-Bu_2SnO, MeOH, reflux, 4) TsCl, $CHCl_3$, rt, 5) K_2CO_3, EtOH, (c) 1) *n*-Bu_2SnO, MeOH, reflux, 2) TsCl, $CHCl_3$, rt, 3) K_2CO_3, EtOH, (d) MeLi, CuBr, THF, 0 °C, (e) $CH_3(CH_2)_8MgBr$, CuBr, THF, 0 °C, (f) NaH, $CH_3(CH_2OCH_2)_2CH_2OH$, rt, (g) 1) TsCl, pyridine, 0 °C, 2) NaN_3, DMSO, 100 °C, (h) 1) $LiAlH_4$, THF, 0 °C to rt, 2) Ac_2O, pyridine, rt, (i) PCC, Celite, CH_2Cl_2, (j) 1) $NaBH_3CN$, NH_4OAc, MeOH, rt, 2) Ac_2O, pyridine, 0 °C to rt.

The ligand **11** with acetamido groups was synthesized through S_N2 displacement of the ditosylate of **8** following $LiAlH_4$ reduction and acetylation. The ketone derivative **19** was obtained from **8** and then subjected to the reductive amination using $NaBH_3CN$ in the presence of $AcONH_4$ following acetylation to give a mixture

of stereoisomers (**11-13**). The isomers were successfully separated by preparative HPTLC, and the structures were determined unambiguously by comparison of the TLC movements and the ^{1}H-NMR spectra with those of **11**, with distinguishable chemical shifts of the amido protons; 5.62 ppm for (11*R*,20*R*)-**11**, 5.61 and 5.43 ppm for (11*R*,20*S*)-**12**, and 5.48 ppm for (11*S*,20*S*)-**13**. Interestingly, the ratio of the isomers changed in the presence of additional metal salts: the ratio of **11**:**12**:**13** = 50:33:17 was changed to 10:53:37 or 10:59:31 in the presence of CaI_2 or MgI_2, respectively. These ratios may reflect the affinities of these compounds to the metal cations.

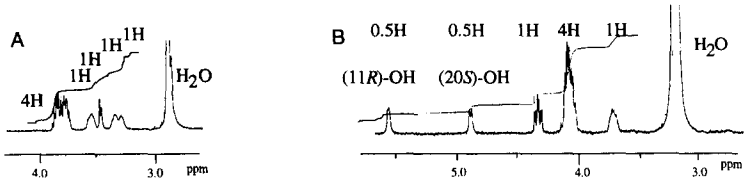


Fig.1. ^{1}H-NMR of **7** in the absence (A) and in the presence (B) of $Ca(SCN)_2$ (one equivalent to **7**) in d_6-Acetone.

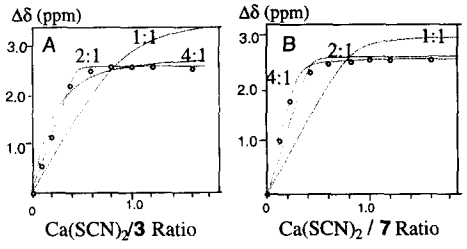


Fig. 2. Comparison of the Experimental Δδ and the Theoretical Curves Obtained by the Indicated Ligand-to-Metal Raio. A: **3** and $Ca(SCN)_2$; B: **7** and $Ca(SCN)_2$.

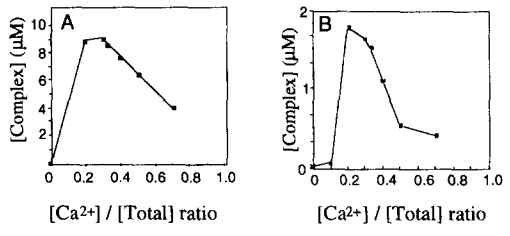


Fig.3. Job's Plots for Complexation with $Ca(SCN)_2$ by **3** (A) and by **7** (B). Total Concentration; [**3**]+[$Ca(SCN)_2$]=13 μM, [**7**]+[$Ca(SCN)_2$]=8.6 μM.

NMR TITRATION

Complexation properties of the ligands were investigated by ^{1}H-NMR titration in d_6-acetone.[8a] Signals of the free and the complexed ligands were assigned by COSY measurement, indicating remarked downfield shifts of the hydroxyl protons by the addition of metal salts. Fig. 1 illustrates examples of ^{1}H-NMR spectra of **7** in the absence (Fig.1A) and in the presence of $Ca(SCN)_2$ (Fig.1B). The facts that these downfield shifts were inhibited by the addition of 18-crown-6 as a competitive binder to the metal salt and that its diacetate did not show any significant change of the ^{1}H-NMR spectra by the addition of $Ca(SCN)_2$[8a] apparently indicate that the shifts are caused by the binding with the metal salt and the hydroxyl groups are directly involved in the complexation. Thus, the chemical shift changes of the hydroxyl groups were subjected to the curve-fitting method to obtain complex stability constants (*K*s) and maximum changes of chemical shifts ($\Delta\delta_{max}$).[11] The binding parameters obtained by this method have been recently shown to be almost equal to those obtained by the analysis of ^{13}C-NMR signals.[9]

Interestingly, it turned out that the ligands used in this study tend to form molecular assembly in the binding with metal cations. For example, the experimental data obtained with **3** and $Ca(SCN)_2$ were well fitted to the theoretical curve with r^2>0.999 only when the 2:1 ligand-to-salt ratio was assumed (Fig. 2A). On the

the other hand, the experimental data obtained between **7** and $Ca(SCN)_2$ were successfully analyzed using the 4:1 ligand-to-salt ratio (Fig. 2B). These ligand-to-salt ratios were consistent with those determined by the Job's plot, in which the maximum complex concentration was obtained at the ligand-to-salt ratio of 2:1 for **3** (Fig. 3A) and at the 4:1 ratio for **7** (Fig. 3B). The *K*s, $\Delta\delta_{max}$ and the ligand-to-salt ratios obtained by the above curve-fitting method are recorded in Tables 1-4. It is noteworthy that the integral ratios of the shifted hydroxyl protons sometimes showed less than unity, such as shown in Fig. 1. As the hydroxyl groups are attributable to metal binding, their integration ratios may reflect the number of hydroxyl groups tightly binding to metal cations, and four of the eight hydroxyl groups are thought to bind Ca^{2+} in the 4:1 complex of **7**•$Ca(SCN)_2$. In contrast, the spectrum of the 2:1 complex of **3**•$Ca(SCN)_2$ showed a simple integral ratio, and all of the four hydroxyl groups of the two ligands are regarded to bind Ca^{2+}. These estimated number of hydroxyl groups coordinating with a cation have been taken into account in molecular modeling of the complex structures.

BINDING PROPERTIES

Effects of Stereochemistry. Binding properties of the ligands (**3-5**) with short alkyl chains are listed in Table 1. These ligands tend to form complexes of 2:1 ligand-cation ratio. Among them, highest selectivity toward Ca^{2+} was exhibited by **3** with (3*R*,12*R*)-stereochemistry. The binding affinity of **3** with Ca^{2+} (*K*s = 9.00×10^3 M^{-1}) was shown to be comparable to that of 18-crown-6, and seems to be superior to the known ligands such as carboxylic antibiotic A23187 (calcimycin)[12] or macrocyclic criptands.[13] Interestingly, the other stereoisomer (3*R*,12*S*)-**4** and (3*S*, 12*S*)-**5** showed only diminished affinity toward Ca^{2+}, hence the selectivity disappeared. In order to rationalize the effects of stereochemistry on the binding affinity, the complex structures of **3**, **4**, and **5** with $Ca(SCN)_2$ were analyzed by molecular modeling. The most stable structures of a metal-free ligand and plausible complex structures of 2:1 ligand-to-Ca^{2+} were searched by MD with MM2 parameters.[14] Fig. 4 illustrates a complex structure of $\mathbf{3}_2$•$Ca(SCN)_2$ which was further optimized with ZINDO. A ligand structure was taken from such calculated complex and optimized again with MM2, and its steric

Table 1. Binding Properties of the Bis-THF Ligands (**3-4**) with Short Alkyl Chains.[a]

Ligand	Metal	Ligand/ Metal	*K*s (10^3 M^{-1})	$\Delta\delta$max (ppm)
3	Ca^{2+}	2:1	9.00	2.58
3	Mg^{2+}	2:1	0.04	2.66
3	K^+	-	-	-
3	Na^+	-	-	-
4	Ca^{2+}	2:1	0.83	2.53
4	Mg^{2+}	2:1	0.06	2.65
4	K^+	-	-	-
4	Na^+	-	-	-
5	Ca^{2+}	2:1	0.05	2.06
5	Mg^{2+}	2:1	0.07	0.72
5	K^+	-	-	-
5	Na^+	-	-	-

[a]Binding experiments were done at 23 °C using metal thiocyanates in d_6-acetone. Blank columns indicate no binding observed.

Table 2. Comparison of the Steric Energies of the Free and the Complexed Ligand.[a]

Ligand	*K*s (10^3 M^{-1})	ΔSteric energy (kcal/mol)
3 (*R*,*R*)	9.00	0.40
4 (*R*,*S*)	0.83	1.84
5 (*S*,*S*)	0.05	5.94

[a]The most stable conformation of the ligand was searched by MD, followed by optimization by MM2 with augmented parameter. Complex structure was similarly searched, followed by optimization by ZINDO. Ligand conformation in the complex was reoptimized by MM2 after removal of the rest constituents of the complex.

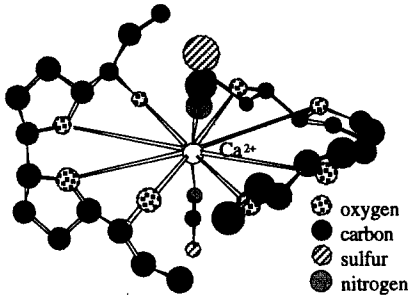


Fig. 4. A Possible Complex Structure of 3_2•Ca(SCN)$_2$ Simulated with ZINDO. Hydrogens are not shown for clarity.

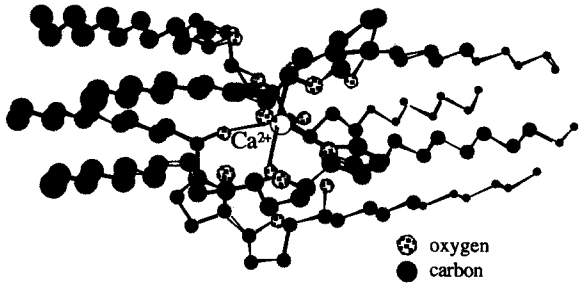


Fig. 5. A Possible Complex Structure of 7_4•Ca(SCN)$_2$ Simulated with MM2. Thiocyanates and hydrogens are not shown for clarity.

energy was compared with that of the corresponding free ligand (Table 2). Apparently, **3** needs much less conformational change for complexation with Ca^{2+} than either the stereoisomers **4** or **5**. Eventually, it turned out that the structure of **3** is preorganized for the complexation with Ca^{2+}. As Mg^{2+} has a smaller ionic radii than Ca^{2+}, the two ligands come closer to the metal in the 3_2•Mg(SCN)$_2$ complex than in 3_2•Ca(SCN)$_2$ (Fig. 4) and cause steric repulsion between the alkyl chains.

Table 3. Binding Properties of the Bis-THF Ligands with Long Alkyl or Ether Chains (**1, 2, 6-10**).[a]

Ligand	Metal	Ligand/ Metal	*K*s ($10^3 M^{-1}$)	Δδmax (ppm)
1	Ca^{2+}	2:1	3.10	2.27
2	Ca^{2+}	4:1	5.50	2.74
6	Ca^{2+}	4:1	0.15	2.7
6	Mg^{2+}	4:1	0.09	1.84
6	K^+	4:1	0.13	1.13
6	Na^+	4:1	0.04	1.10
7	Ca^{2+}	4:1	1.50	2.59
7	Mg^{2+}	4:1	0.21	1.44
8	Ca^{2+}	4:1	0.10	2.16
9	Ca^{2+}	1:1	0.08	3.70
9	Mg^{2+}	1:1	0.62	2.05
10	Ca^{2+}	1:1	0.06	4.76
10	Mg^{2+}	1:1	0.11	3.38

[a]Binding experiments were done at 23 °C using metal thiocyanates of Ca^{2+}, Mg^{2+}, K^+, and Na^+ in d_6-acetone. Only the data indicative of binding are listed.

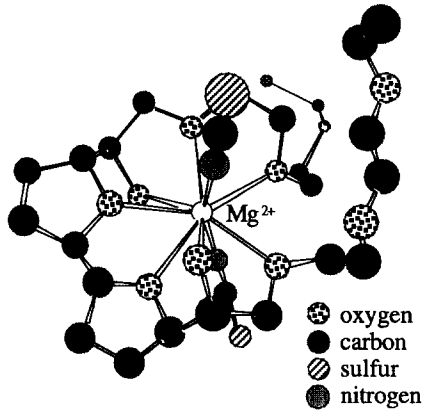


Fig. 6. A Possible Complex Structure of **9**•Mg(SCN)$_2$ Simulated with MOPAC. Hydrogens are not shown for clarity.

Effects of Side Chain Structure on the Binding Properties. The binding properties of the ligands with long alkyl chains (**1, 2** and **6-8**) and ether chains (**9, 10**) are listed in Table 3. In contrast to the ligands with short alkyl chains, the ligands with long alkyl chains formed complexes of 4:1 ligand-to-cation ratio. Among them, only the (11*R*,20*S*)-**7** retains selective affinity toward Ca^{2+}. The fact that ligands with long alkyl chains tend to form higher assembly than those with short chains indicates that the long alkyl chains may

contribute to the molecular assembly probably due to the van der Waals interactions. Fig. 5 proposes such a supramolecular assembly, in which four ligands provide four coordinating hydroxyl groups surrounding Ca^{2+}. Interestingly, the natural products (**1** and **2**) exhibited potent affinity toward Ca^{2+} with high selectivity. The lactone at the end of the alkyl chain of the natural product apparently contributes to produce high affinity as well as assembly states. Recent NMR studies of the complexes of $Ca(SCN)_2$ with squamocin, a structural isomer of **1**, have suggested that the carbonyl oxygen of the lactone may interact with Ca^{2+}.[9] The effects of stereochemistry of the hydroxyl groups and the lactone of the natural products have not yet been well analyzed by molecular modeling because of their high aggregate states. The ligand with ether chains (**9** and **10**) showed a striking difference in that they form complexes of 1:1 ligand-to-metal ratio with selectivity toward Mg^{2+}. Molecular modeling of the complex structure was performed by MD and then PM3, and it was suggested that ether oxygens of the side chains wrap around the magnesium ion (Fig. 6).

The diacetamido ligands (**11, 12, 13**) were not soluble in d_6-acetone; therefore these binding properties were investigated in a mixture of d_6-acetone and $CDCl_3$ (1: 1) (Table 4). The downfield shifts of the amide NH signals were observed upon complexation with metal salts similarly with changes as observed for the dihydroxyl ligands. These acetamido ligands exhibited higher binding affinities compared to the corresponding hydroxyl ligands. The ligand **11** gained selectivity toward Mg^{2+}. Very high binding affinity was exhibited by (11*S*,20*S*)-**13** with the *K*s value as high as $>10^5\ M^{-1}$ to both Mg^{2+} and Ca^{2+} in the formation of 2:1 ligand-to-metal complexes. The molecular modeling with MOPAC on the complex of **13**•$Ca(SCN)_2$ has suggested that the acetamido groups take a stable conformation in which the carbonyl oxygen may be oriented to the metal cation within the cavity (Fig. 7). This calculated structure also indicates that Mg^{2+} may be bound by **13** in the 2:1 ligand-to-metal complex without causing steric repulsion between the alkyl chains.

Table 4. Binding Properties of the Bis-THF Ligands (**6-8, 11-13**) in d_6-Acetone/$CDCl_3$ (1:1).[a]

Ligand	Metal	Ligand/ Metal	*K*s ($10^3\ M^{-1}$)	Δδmax (ppm)
6	Ca^{2+}	4:1	0.20	3.22
7	Ca^{2+}	4:1	3.70	2.67
8	Ca^{2+}	4:1	0.80	2.16
11	Ca^{2+}	4:1	0.66	1.13
11	Mg^{2+}	2:1	4.80	1.31
11	K^+	4:1	0.25	0.68
11	Na^+	4:1	0.28	0.67
12	Ca^{2+}	4:1	9.60	1.36
12	Mg^{2+}	4:1	3.00	1.32
12	K^+	2:1	1.00	0.46
12	Na^+	4:1	1.20	0.48
13	Ca^{2+}	2:1	>100	1.31
13	Mg^{2+}	2:1	>100	1.52
13	K^+	4:1	1.60	0.63
13	Na^+	4:1	3.40	0.54

[a]Binding experiments were done at 35 °C using metal thiocyanates.

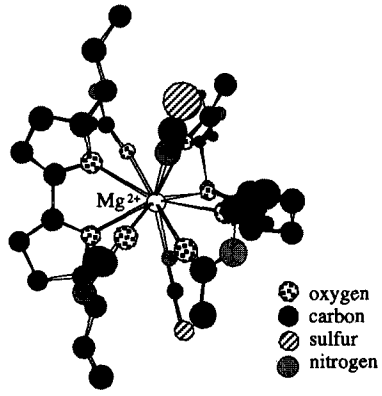


Fig. 7. A Possible Complex Structure of **13**$_2$•$Mg(SCN)_2$ Simulated with MOPAC. Calculation was done using the structure of **13** with R=CH_3 instead of $(CH_2)_2CH_3$. Hydrogens are not shown for clarity.

CONCLUSION

We have revealed the unique binding properties of bis-THF lignads as structural analogs of the antitumor natural products, *Annonaceous* acetogenins. Binding affinity, metal cation selectivity, and ligand assembly highly depend on the stereochemistry of the coordination sites and the nature of the alkyl side chains. Molecular modeling of the complexes have suggested that supramolecular assembly of the ligand with the bis-THF skeleton may produce a suitable cavity to bind metal cations. It is interesting that among the bis-THF compounds used in this study only those with long alkyl chains exhibit *in vitro* antitumor activity,[10] although the relationship between binding properties of these bis-THF compounds and biological activity is not yet clear. These new ligands will be useful for applications such as in ion-selective electrodes as well as a lead structure to develop new antitumor agents.

EXPERIMENTAL

General. ^{1}H NMR spectra were taken at 500, or 270 MHz. Analytical TLC was carried out on Merck precoated TLC plates (Kiesel gel 60 F254, 0.2 nm). Column chromatography was done using silica gel FL60D (Fuji Division).

(-)-(2*R*,3*R*,6*R*,7*R*,10*R*,11*R*)-1,2:3,6:7,10:11,12-Tetraepoxydodecane (15). Methanesulfonyl chloride (46 μL, 0.59 mmol) was added into a solution of triethylamine (0.11 mL, 0.79 mmol) and **14** (55 mg, 0.098 mmol) in dry THF (2 mL) at 0 °C under an argon atm. After 30 min, the mixture was diluted with AcOEt, and the whole was washed successively with saturated aqueous NH_4Cl and brine, dried over Na_2SO_4 and filtered, then evaporated. The residue was chromatographed on a silica gel column ($CHCl_3$/AcOEt = 3/2 to AcOEt) to give the corresponding dimesylate as a colorless oil (65 mg, 93%). A solution of *n*-Bu_4NOH in methanol (0.20 mL of 1.0 M solution) was added into a solution of the above mesylate (85 mg, 0.12 nmol) in dry THF (5 mL) at 0 °C under an argon atm, and the mixture was stirred for 4 h at rt. The mixture was diluted with AcOEt (30 mL), the whole was washed with brine, dried over Na_2SO_4, filtered, and evaporated. The residue was chromatographed on a silica gel column (AcOEt) to give the pure **15** as a colorless oil (24 mg, 90%): $[\alpha]_D$ = -6.53° (*c* 0.94, $CHCl_3$); IR (neat) 1270, 1060 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.00-3.89 (4H, m), 2.95 (2H, ddd, *J* = 6.2, 5.2, 3.8 Hz), 2.75 (2H, dd, *J* = 5.2, 4.2 Hz), 2.65 (2H, dd, *J* = 4.2, 3.8 Hz), 2.30-1.69 (8H, m); FABMAS *m/z*: 226 $(M)^+$, 207 $(M\text{-}OH)^+$; HRFABMS calcd for $C_{12}H_{19}O_4$ 227.1283, found 227.1283.

(-)-(2*R*,3*R*,6*R*,7*R*,10*R*,11*S*)-1,2:3,6:7,10:11,12-Tetraepoxydodecane (16). The same procedure as described above using methanesulfonyl chloride (26 μL, 0.34 mmol), triethylamine (0.10 mL, 0.72 mmol), and **14** (191 mg, 0.341 mmol) in dry THF (3 mL) gave the corresponding monomesylate (80.6 mg, 37%) together with recovered **14** (109 mg, 57%). A similar epoxidation of the above mesylate (21 mg, 0.033 mmol) in dry THF (1 mL) with *n*-Bu_4NOH (69 mL of 1.0 M in methanol solution) following a general workup produced the pure epoxydiol as a colorless oil (7.4 mg, quantitative). A mixture of the above oil (6 mg, 0.025 mmol) and *n*-Bu_2SnO (30 mg, 0.12 mmol) in absolute methanol (1 mL) was heated under reflux for 2 h, and the solvent was evaporated. The residue was dissolved in $CHCl_3$ and followed by the addition of *p*-toluenesulfonyl chloride (18 mg, 0.094 mmol), and the mixture was stirred for 2 h at rt. The mixture was diluted with AcOEt, and the whole was washed successively with saturated aqueous Na_2SO_4, water, and brine, dried over Na_2SO_4, and filtered, then evaporated. The residue was chromatographed on a silica gel column ($CHCl_3$/AcOEt = 1/1 to AcOEt) to afford the corresponding monotosylate (8 mg, 81%). Subsequently, a mixture of the above tosylate (4.5 mg, 0.013 mmol) in ethanol (0.1 mL) and 1.0 M aqueous solution of K_2CO_3 (0.24 mL) was stirred for 10 min at rt. The reaction was quenched with saturated aqueous NH_4Cl and diluted with AcOEt. The whole was washed with brine, dried over Na_2SO_4, filtered, and evaporated. The residue was chromatographed on a silica gel column (AcOEt) to give the pure **16** as a colorless oil (2.0 mg, 80 %): $[\alpha]_D$ = -2.67° (*c* = 0.90, $CHCl_3$); IR (neat) 1270, 1060 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.00-3.83 (4H, m), 3.10-2.95 (2H, m), 2.85-2.70 (3H, m), 2.60 (1H, dd, *J* = 5.2, 4.4 Hz), 2.20-1.50 (8H, m); FABMAS *m/z*: 226 $(M)^+$, 207 $(M\text{-}OH)^+$; HRFABMS: calcd for $C_{12}H_{19}O_4$; 227.1283, found 227.1284.

(-)-(2*S*,3*R*,6*R*,7*R*,10*R*,11*S*)-1,2:3,6:7,10:11,12-Tetraepoxydodecane (17). A mixture of **14** (172 mg, 0.31 nmol) and K_2CO_3 (4 mg, 0.029 mmol) in absolute methanol (3 mL) was stirred for 2 h at rt. *n*-Bu_2SnO (175 mg, 0.7 mmol) was added into the above mixture and the whole was heated under reflux for 2.5 h, and the solvent was evaporated. The residue was dissolved in $CHCl_3$ followed by the addition of *p*-toluenesulfonyl chloride (555 mg, 2.28 mmol). The mixture was stirred for 3.5 h at rt and diluted with AcOEt. The whole was washed successively with saturated aqueous Na_2SO_4, water, and brine, dried over Na_2SO_4,

and filtered, then evaporated. The residue was chromatographed on a silica gel column ($CHCl_3$/AcOEt = 2/1 to AcOEt/ethanol = 6/1) to give the ditosylate (175 mg, quantitative). The mixture of the above oil (20 mg, 0.035 mmol) and 0.5 M aqueous K_2CO_3 (0.42 mL, 0.21 mmol) in ethanol (2 mL) was stirred for 1 h at rt, then diluted with AcOEt. The whole was successively washed with saturated aqueous NH_4Cl and brine, dried over Na_2SO_4, filtered, and evaporated. The residue was chromatographed on a silica gel column ($CHCl_3$/AcOEt = 1/1) to give pure **17** as a colorless oil (7 mg, 92 %): $[\alpha]_D$ = -2.1° (*c* = 1.22, $CHCl_3$); IR (neat) 3450, 1360, 1180 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.99-3.84 (4H, m), 3.03, (2H, ddd, *J* = 5.0, 4.0, 2.6 Hz), 2.79 (2H, dd, *J* = 5.0, 4.0 Hz), 2.58 (2H, dd, *J* = 5.0, 2.6 Hz), 2.12-1.60 (8H, m); FABMAS *m/z* 226 $(M)^+$, 207 $(M\text{-}OH)^+$; HRFABMS calcd for $C_{12}H_{19}O_4$ 227.1283, found 227.1283.

(+)-(3*R*,4*R*,7*R*,8*R*,11*R*,12*R*)-4,7:8,11-Diepoxy-3,12-dihydroxytetradecane (3). A solution of MeLi (0.4 mL of 1.16 M in ether, 0.46 mmol) was added into a solution of **15** (10 mg, 0.044 mmol) and CuBr (50 mg, 0.35 mmol) in dry THF at 0 °C under an argon atm. The mixture was stirred for 1 h and quenched by the addition of saturated aqueous NH_4Cl-30% NH_4OH (9:1). The reaction mixture was diluted with ether and the whole was successively washed with water and brine, dried over Na_2CO_3, filtered, and evaporated. The residue was chromatographed on a silica gel column (hexane/ether = 4/1) to give pure **3** as a colorless oil (10 mg, 91%): $[\alpha]_D$ = +3.2° (*c* = 0.56, $CHCl_3$); IR (neat): 3500-3200, 1060 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.00-3.80 (4H, m), 3.40-3.28 (2H, m), 2.55-2.45 (2H, bs), 2.10-1.40 (12H, m), 1.00 (6H, t, *J* = 7.3 Hz); FABMAS 259 $(M+H)^+$; HRFABMS calcd for $C_{14}H_{27}O_4$ 259.1909, Found 259.1924.

(3*R*,4*R*,7*R*,8*R*,11*R*,12*S*)-4,7:8,11-Diepoxy-3,12-dihydroxytetradecane (4). The title compound was obtained by the same procedure as described for **3** in 60%: IR (neat): 3500-3200, 1060 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.01-3.72 (5H, m), 3.34 (1H, ddd, *J* = 7.9, 6.8, 4.3 Hz), 2.05-1.35 (12H, m), 1.02 (3H, t, *J* = 7.4 Hz), 1.01 (3H, t, *J* = 7.4 Hz); FABMAS *m/z*: 259 $(M+H)^+$; HRFABMS calcd for $C_{14}H_{27}O_4$ 259.1909, found 259.1908

(+)-(3*S*,4*R*,7*R*,8*R*,11*R*,12*S*)-4,7:8,11-Diepoxy-3,12-dihydroxytetradecane (5). The title compound was obtained by the same procedure as described for **3** in 41%: $[\alpha]_D$ = +14.5° (*c* = 0.69, $CHCl_3$); IR (neat): 3500-3200, 1060 cm^{-1}; ^1H NMR (270 MHz, d_6-acetone) δ 3.82-3.78 (2H, m), 3.74-3.70 (2H, m), 3.41-3.37 (2H, m), 3.36 (2H, d, *J* = 4.3 Hz), 1.89-1.82 (4H, m), 1.78-1.70 (2H, m), 1.69-1.61 (2H, m), 1.53-1.44 (2H, m), 1.25 (2H, dq, *J* = 14.0, 7.3 Hz), 0.90 (6H, t, *J* = 7.3 Hz); FABMAS *m/z*: 259 $(M+H)^+$; HRFABMS calcd for $C_{14}H_7O_4$ 259.1909, found 259.1908.

(+)-(11*R*,12*R*,15*R*,16*R*,19*R*,20*R*)-12,15:16,19-Diepoxy-11,20-dihydroxytriacontane (6). The same procedure as described for **3** using **4** (24.2 mg, 0.108 mmol), $CH_3(CH_2)_8MgBr$ (1.3 mL of 0.5 M THF solution, 0.65 mmol) and CuBr (25.4 mg, 0.177 mmol) gave **6** as white crystals (36.2 mg, 70%): mp 38.5-39.5 °C (hexane); $[\alpha]_D$ = +6.48° (*c* = 1 .32, $CHCl_3$); IR (neat): 3500-3200, 1070 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.92-3.80 (4H, m), 3.42-3.35 (2H, m), 2.43 (2H, bs), 2.15-1.90 (4H, m), 1.82-1.22 (40H, m), 0.88 (6H, t, *J* = 6.9 Hz); FABMAS *m/z* 521 $(M+K)^+$, 505 $(M+Na)^+$, 483 $(M+H)^+$; HRFABMS calcd for $C_{30}H_{59}O_4$; 483.4413, found 483.4420; Anal Calcd for $C_{30}H_{58}O_4$: C, 74.63; H, 12.11. Found: C, 74.37; H 12.11.

(+)-(11*R*,12*R*,15*R*,16*R*,19*R*,20*S*)-12,15:16,19-Diepoxy-11,20-dihydroxytriacontane (7). The same procedure as described for **6** gave **7** as white crystals in 70%: mp 47-48 °C; $[\alpha]_D$ = +9.2° (*c* = 0.5, $CHCl_3$); IR (neat): 3500-3250, 1070 cm^{-1}, ^1H NMR (270 MHz, $CDCl_3$) δ 4.00-3.82 (5H, m), 3.48-3.35 (1H, m), 2.51-2.45 (1H, m), 2.00-1.25 (45H, m), 0.88 (6H, t, *J* = 6.9 Hz); FABMAS *m/z* 505 $(M+Na)^+$, 483 $(M+H)^+$; HRFABMS calcd for $C_{30}H_{59}O_4$ 483.4413, found 483.4402.

(+)-(11*S*,12*R*,15*R*,16*R*,19*R*,20*S*)-12,15:16,19-Diepoxy-11,20-dihydroxytriacontane (8). The same procedure as described for **6** gave **8** as a white powder in 65%: mp 72-75 °C; $[\alpha]_D$ = +2.1° (*c* = 0.58, $CHCl_3$); IR (neat) 3500-3200, 1050 cm^{-1}; ^1H NMR (270 MHz, d_6-acetone) δ 3.80 (2H, dt, *J* = 1 1.0, 5.5 Hz), 3.74-3.70 (2H, m), 3.50-3.47 (2H, m) 3.34 (2H, d, *J* = 4.9 Hz), 1.88-1.82 (4H, m), 1.78-1.62 (4H, m), 1.46-1.42 (4H, m), 1.30-1.18 (32H, m), 0.83 (6H, t, *J* = 7.3 Hz); FABMAS *m/z* 965 $(2M+H)^+$, 482 $(M\text{-}H)^+$; HRFABMS calcd for $C_{30}H_{59}O_4$ 483.4413, found 483.4409.

(-)-(2*R*,3*R*,6*R*,7*R*,10*R*,11*R*)-1,12-Bis(ethoxyethoxyethoxy)-3,6:7,10-diepoxy-2,11-dihydroxydodecane (9). A solution of **15** (10 mg, 0.04 nmol) in 2-(2-ethoxyethoxy)ethanol (0.25 mL) was added into a suspension of NaH (60% in oil, 35 mg, 0.87 mmol) in 2-(2-ethoxyethoxy)ethanol (0.25 mL) under an argon atm, and the mixture was stirred for 1 h at rt, then the solvent was removed under reduced pressure (5 mmHg, 100 °C). The residue was chromatographed on a silica gel column ($CHCl_3$/methanol = 30/1 to 5/1) to give pure **9** as a colorless oil (13.7 mg, 78%): $[\alpha]_D$ = -4.8° (*c* = 0.71, $CHCl_3$); IR (neat): 3400, 1120, 1060 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.02-3.87 (4H, m), 3.78-3.51 (26H, m), 2.81 (2H, m), 2.04-1.62 (8H, m), 1.21 (6H, t, *J* = 5.0 Hz); FABMAS *m/z* 495 $(M+H)^+$, 5 17 $(M+Na)^+$; HRFABMS calcd for $C_{24}H_{47}O_{10}$ 495.3169, found 495.3170.

(-)-(2*R*,3*R*,6*R*,7*R*,10*R*,11*S*)-1,12-Bis(ethoxyethoxyethoxy)-3,6:7,10-diepoxy-2,11-dihydroxydodecane (10). The same procedure as described for **9** using **16** gave the title compound as a colorless oil in 51%: $[\alpha]_D$ = -4.1° (*c* = 1.03, $CHCl_3$); IR (neat): 3400, 1120, 1060 cm^{-1}; ^1H NMR (270 MHz,

$CDCl_3$) δ 4.03-3.81 (4H, m), 3.72-3.43 (26H, m), 2.76 (2H, m), 2.03-1.61 (8H, m), 1.21 (6H, t, J = 6.9 Hz); FABMAS *m/z* 495 $(M+H)^+$, 517 $(M+Na)^+$; HRFABMS calcd for $C_{24}H_{47}O_{10}$ 495.3169, found 495.3170

(+)-(11*R*,12*R*,15*R*,16*R*,19*R*,20*R*)-11,20-Diazido-12,15:16,19-diepoxytriacontane (18). *p*-Toluenesulfonylchloride (29 mg, 0.15 mmol) was added into a solution of **8** (12 mg, 0.024 mmol) in dry pyridine (0.5 mL) at 0 °C, and the whole was stored at the same temperature for 18 h. The mixture was diluted with AcOEt, and the whole was successively washed with 10% aqueous HCl, saturated aqueous Na_2SO_4, brine, and dried over Na_2SO_4, filtered, then evaporated. The residue was chromatographed on a silica gel column ($CHCl_3$/hexane = 1/6 then ether/hexane = 1/6) to give the corresponding tosylate as a colorless oil (17 mg, 92%). The mixture of the above tosylate (17 mg, 0.023 mmol) and NaN_3 (30 mg, 0.46 mmol) in dry DMSO (0.15 mL) was heated at 60 °C for 2 h and at 100 °C for 3 h. The mixture was diluted with AcOEt, and the whole was successively washed with water, brine, and dried over Na_2SO_4, filtered, then evaporated. The residue was chromatographed on a silica gel column (ether/hexane = 1/10 then $CHCl_3$/hexane = 1/2) to give the azide derivative as a colorless oil (5 mg, 42%): $[\alpha]_D$ = +29.2° (*c* = 0.39, $CHCl_3$); IR (neat): 2100 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.04-3.96 (4H, m), 3.13-3.06 (2H, m), 2.29-1.93 (6H, m), 1.75-1.27 (38H, m), 0.88 (6H, t, J = 6.6 Hz).

(+)-(11*R*,12*R*,15*R*,16*R*,19*R*,20*R*)-11,20-Diacetamido-12,15:16,19-diepoxytriacontane (11). The mixture of the above oil (5 mg, 9.3 μmol) and $LiALH_4$ (7 mg, 0.18 mmol) in dry THF (1 mL) was stirred at rt for 3.5 h, followed by the addition of water (7 μL), 15% aqueous NaOH (7 μL), and water (21 μL). The whole was filtered and evaporated to give a crude oil which was chromatographed on a silica gel column ($CHCl_3$/methanol = 9/1 to methanol) to give (11*R*,12*R*,15*R*,16*R*,19*R*,20*R*)-11,20-diamino-12,15:16,19-diepoxytriacontane as a colorless oil (4 mg, 89%). This diamine (1 mg, 2.1 μmol) was acetylated with Ac_2O (4 μL, 0.042 μmol) in dry pyridine (0.1 mL) at rt for 12 h. The mixture was diluted with AcOEt and the whole was successively washed with water, brine, dried over Na_2SO_4, filtered, and then evaporated. The residue was chromatographed on a silica gel column ($CHCl_3$/methanol = 40/1 then AcOEt/$CHCl_3$ = 2/1 to 4/1) to give the diacetamido **11** as a colorless oil (1.1 mg, 92%): $[\alpha]_D$ = +46.7° (*c* = 0.06, $CHCl_3$); IR (neat): 3280, 1650, 1640 cm^{-1}; 1H NMR (270 MHz, $CDCl_3$) δ 5.62 (2H, d, J = 9.9 Hz), 3.98-3.92 (4H, m), 3.84-3:80 (2H, m), 2.01 (6H, s), 2.00-1.91 (4H, m), 1.68-1.58 (4H, m), 1.40-1.23 (36H, m), 0.88 (6H, t, J = 6.6 Hz); FABMAS(m/Z): 565 $(M)^+$; HRFABMS calcd for $C_{34}H_{65}O_4N_2$ 565.4944, found 565.4944.

(+)-(12*R*,15*R*,16*R*,19*R*)-12,15:16,19-Diepoxytriacontane-11,20-dione (19). A mixture of **8** (3 mg, 6.2 μmol), PCC (8 mg, 0.037 mmol), and celite (9 mg) in dry CH_2Cl_2 (0.5 mL) was stirred at rt for 18 h, and filtered through a celite pad, then evaporated. The residue was chromatographed on a silica gel column (AcOEt/hexane = 1/9) to give the title compound as a white powder (3 mg, quantitative): mp 43-45 °C; $[\alpha]_D$ = +35.5° (*c* = 1.73, $CHCl_3$); IR (neat): 1710, 1050 cm^{-1}; 1H NMR (270 MHz, $CDCl_3$) δ 4.42 (2H, t, J = 7.9 Hz), 4.18-4.05 (2H, m), 2.60 (2H, dt, J = 11.9, 7.9 Hz), 2.49 (2H, dt, J = 12.0, 8.0 Hz), 2.05-1.82 (4H, m), 1.70-1.49 (4H, m), 1.40-1.20 (32H, m), 0.83 (6H, t, J = 7.3 Hz); FABMAS *m/z* 501 $(M+Na)^+$, 479 $(M+H)^+$; HRFABMS calcd for $C_{30}H_{54}O_4Na$; 501.3920, found 501.3920.

(11*R*,12*R*,15*R*,16*R*,19*R*,20S)- and (11*S*,12*R*,15*R*,16*R*,19*R*,20S)-11,20-Diacetamido-12,15:16,19-diepoxytriacontane (12 and 13). A mixture of **19** (3 mg, 6.2 μmol), NH_4OAc (12 mg, 0.16 mmol), and $NaBH_3CN$ (1.5 mg, 0.024 mmol) in absolute methanol was stirred for 12 h at rt, and additional 4 h after the addition of NH_4OAc (10 mg, 0.13 mmol) and $NaBH_3CN$ (1.0 mg, 0.016 mmol). The reaction was quenched by the addition of 10 % aqueous HCl (pH<2), followed by the addition of 10 % aqueous NaOH (pH>10). The mixture was extracted with ether, and the organic layers were dried over Mg_2SO_4, filtered, and then evaporated. The residue was dissolved in dry pyridine (0.3 mL) containing Ac_2O (30 μL, 0.32 mmol) and the mixture was stirred for 15 h at rt. The mixture was diluted with AcOEt, and the whole was successively washed with water and brine, dried over Na_2SO_4, filtered, then evaporated. The residue was chromatographed on a silica gel column (AcOEt/hexane = 1/6 to methanol) to give the mixture of the diacetamido compounds. The three isomers were separated by preparative HPTLC (acetone/$CHCl_3$x3) by monitoring at 200 nm. (11*R*,20*R*)-**11** as a white powder (0.6 mg, 7.5 %); Movement on a TLC plate, mp, IR, and ^1H NMR were identical with those obtained above. (11*R*,20*S*)-**12** as a white powder (0.8 mg, 10 %): Rf = 0.48; mp 65-67 °C; $[\alpha]_D$ = +4.0° (*c* = 0.05, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 5.61 (1H, d, J = 9.9 Hz), 5.43 (1H, d, J = 9.2 Hz), 3.98-3.91 (4H, m), 3.85-3.81 (2H, m), 2.00 (3H, s), 1.99 (3H, s), 1.98-1.88 (4H, m), 1.70-1.58 (4H, m), 1.40-1.23 (36H, m), 0.88 (6 H, t, J = 6.6 Hz); FABMASS (*m/z*) 565 $(M)^+$, 587 $(M+Na)^+$; HRFABMS calcd for $C_{34}H_{65}O_4N_2$ 565.4944, found 565.4940. (11*S*,20*S*)-**13** as a white powder (0.9 mg, 11%): Rf = 0.29; mp 175-175.5 °C; $[\alpha]_D$ = -36.0° (*c* = 0.05, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 5.48 (2H, d, J = 9.2 Hz), 0.98-3.92 (4H, m), 3.86-3.82 (2H, m), 1.99 (6H, s), 2.00-1.90 (4H, m), 1.75-1.60 (4H, m), 1.35-1.23 (36H, m), 0.88 (6H, t, J = 6.6 Hz); FABMAS *m/z* 565 $(M)^+$, 587 $(M+Na)^+$, 603 $(M+K)^+$; HRFABMS calcd for $C_{34}H_{65}O_4N_2$ 565.4944, found 565.4943. The same reductive amination was done in the presence of CaI_2 or MgI_2 (10 equivalent $NaBH_3CN$), and the subsequently acetylated products (**11**, **12**, and **13**) were found to contain three isomers in the ratio of 10:53:37 or 10:59:31, respectively, based on the analysis by HPTLC (acetone/$CHCl_3$ x3) by monitoring at 200 nm with a TLC densitometer.

NMR Titration. Metal thiocyanates were dried under vacuum for several hours at rt, and dissolved in d_6-acetone to make stock solutions. A mixture of D_2O-d_6-acetone (1:1) was used to prepare a stock solution of NaSCN or KSCN. The concentrations of stock solutions were adjusted so that the addition of 1 μL of a stock solution into a NMR sample tube (600 μL) became 0.1 equivalent to the ligand included. The ligands were used at the concentration ranged between 1-10 mM, in which no aggregation of the ligand was observed in the absence of a metal salt. ^{1}H NMR spectra were taken at either 270 or 570 MHz at rt (23 °C) with solutions of d_6-acetone, or at 35 °C with solutions of the amido ligand (**11-13**) in $CDCl_3$-d_6-acetone (1:1).

Computational Calculation. MD calculation was done with the augmented MM2 parameters at 300 °K for 10 picoseconds, and sampled every 1.0 femtosecond. A number of stable structures more than 20 were selected for further optimization by MM2, MOPAC (PM3), or ZINDO. Calculations were performed with CAChe-Group Server (IBM RS6000) system on Macintosh.

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14. The stable complex structures were initially searched by MD with augmented MM2 parameters, and further optimized by MOPAC or ZINDO. Calculations were performed with CAChe-Group Server (IBM RS6000) system on Macintosh.