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Synthetic studies on development of a novel macrolide ionophore: Configurational requirement of 16-membered macrodiolide for binding ability

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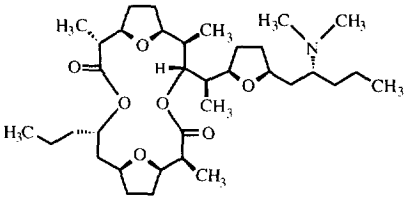
abstract: Twelve synthetic 16-membered macrodiolides were prepared from racemic homononactic acid. The compounds which have an anti-relationship between the ether linkage of THF and the adjacent methyl showed the cation-binding ability. Macrodiolide **12** exhibited the ion selectivity for Li^+.

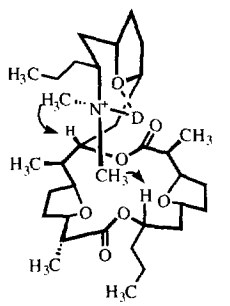
Molecular recognition is one of the most attractive topics in the field of organic chemistry. Ionophore belongs to the simplest compound having recognition site in the molecule and is generally classified into following three types[1]; i) podand that holds the cation in a pseudo-cyclic cavity; ii) cyclic polyether represented a crown ether; iii) armed macrocyclo compound that has a cyclic polyether and one or more side chain with functional group in the molecule. Our interest focuses on the armed macrocyclo compound because of enhancement of the cation binding ability and selectivity[2]. Recently, we reported[3] the isolation of pamamycin-607 (**1**) as an aerial mycelium-inducing factor of *Streptomyces alboniger* that has a very unique structure as shown in Fig.1. The NOE experiments of pamamycin-607 and other pamamycins exhibited that dimethyl amino group in the side chain overhung the 16-membered macrodiolide ring.[4] Although pamamycins did not have ionophore-like ability, this unique three dimensional structure seemed to be a good model to develop a novel armed ionophore.

It may be possible to predict that 16-membered macrodiolide ring containing with THF ring, which is the basic structure of pamamycin, has the cavity for Li^+ or Na^+ cation by recent reports[5]. But we can not predict that the 16-membered macrodiolide shows the ion binding ability or not. We report herein the synthesis of various 16-membered macrodiolide and their configurational requirement for a moderate ability as an ionophore.

The synthesis of 16-membered macrodiolides was initiated from racemic homononactic acid (**2**) and 2-*epi*-homononactic acid (**3**) obtained from alkaline hydrolysis of nactins[6](Fig. 2). Esterification of the hydrolysis products with benzyl bromide in the presence of cesium carbonate afforded to **2a** and **3a** after purification with



pamamycin-607 (**1**)



NOE enhancements of pamamycin-607•CF_3CO_2D

Fig. 1

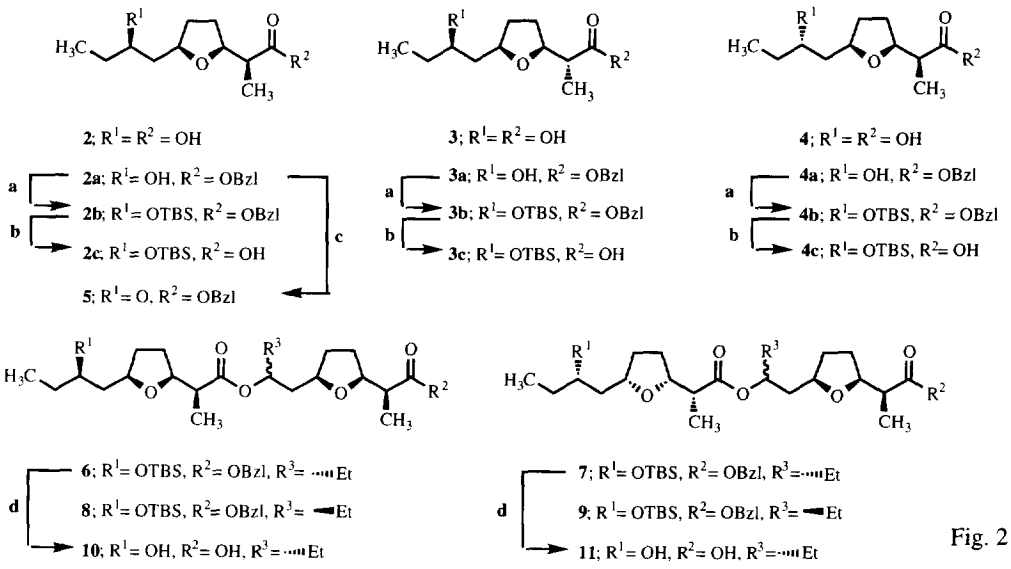


Fig. 2

a; TBSCl, imidazole, DMF, rt. **b**; 10%Pd-C, MeOH, rt. **c**; $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2. **d**; 1) aq. HF, $CHCl_3$. 2) 10%Pd-C, MeOH

silica gel column chromatography, then the hydroxy group of **2a** and **3a** was protected with TBS group to give **2b** and **3b**, respectively. For the synthesis of 8-*epi*-homononactate **4a**, **2a** was transformed to ketone **5** by use of Swern oxidation in 83% yield. Stereoselective reduction of **5** with L-selectride was already reported by J.D. White *et al.*[7], though the yield and stereoselectivity were unsatisfactory results. We succeed in improvement of diastereoselectivity with excellent ratio (**4a** : **2a** =12 : 1) and yield (90%) using $Zn(BH4)2$ in $Et2O$. Benzyl ester **2b**, **3b**, and **4b** were easily converted to carboxylic acid **2c**, **3c**, and **4c**, respectively, by hydrogenolysis over 10% Pd-C in MeOH. Now we had all racemic homononactate derivatives to prepare various macrolides with different configuration and ring size.

The coupling reactions of homononactic acid derivatives to give a desired linear dimeric compound were carried out with three different type coupling reagents (DCC, BOP-Cl, and Mukaiyama's reagent). These coupling reagents, however, resulted in poor yields or recovery of the starting materials. Consequently, using modified Yamaguchi's method[8] (rt, 6h, benzene) known as a powerful esterfication method, the coupling reaction of **2a** and **2c** was afforded to a mixture of **6** and **7** in 83% yield. On the other hand, Mitsunobu reaction accompanied with the inversion of hydroxy group was used for the coupling reaction. P.A. Bartlett *et al.*[9] demonstrated on this coupling afforded less than 30% yield due to steric hindrance in the presence of an adjacent methyl group. Using *n* -Bu3P in place of Ph3P, this coupling reaction of **2a** and **2c** was smoothly proceeded to give corresponding dimeric compound **8** and **9** as a mixture in 78% yield. After deprotection of silyl group and benzyl ester, macrolactonization was also accomplished with modified Yamaguchi's method under high dilution condition (rt, 2days, 1mM xylene). The mixture of **6** and **7** was converted to the desired macrodiolide **12** and **13** in 45% yield. According to this pathway, various macrodiolides as shown in Fig. 3, and macrotriolides, macrotetrolides, and macrohexolides from **2a** and **2c** were prepared for the examination of ionophore ability .

Cation-binding ability of these macrodiolide compounds was assessed by three different methods which involve the solvent extraction of alkali picrate established by Cram[10], cation transportation across liquid membrane[11] and FAB mass spectrometry[12]. The results of solvent extraction experiment are listed in Table 1.

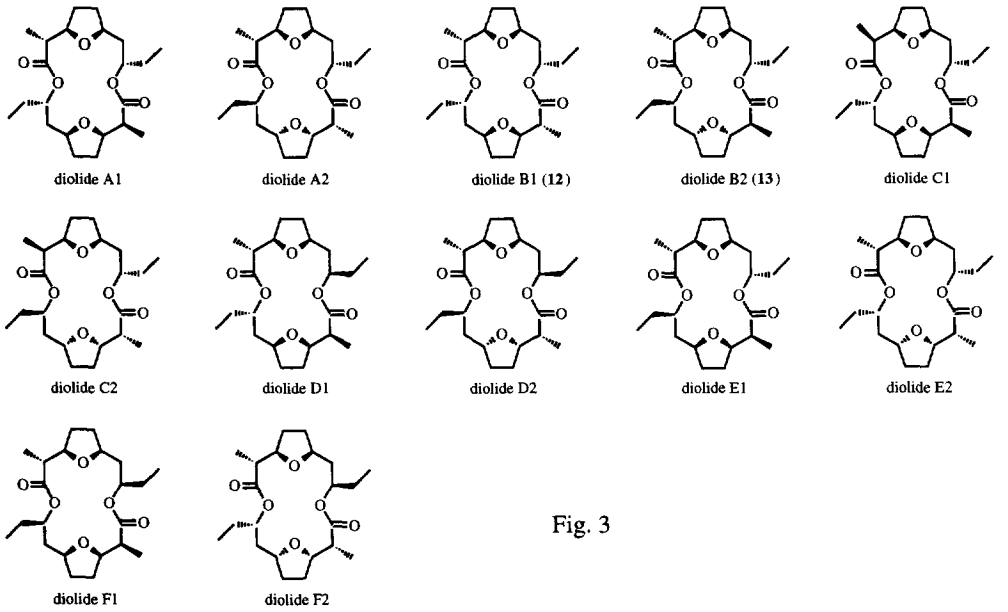


Fig. 3

Any macrocyclic compound examined did not diffuse from the chloroform layer to the aqueous layer. Among twelve macrodiolides, **12** and **13** showed a cation-binding ability comparable to 14-membered macrodiolide reported[5b]. Macrodiolide **12** also showed moderate selectivity for Li^+. The hexolide exhibited significant cation-binding ability but less ion selectivity indicated flexible frame and larger cavity. We guess that cation-binding ability of 16-membered macrodiolide is attributed to the configurational difference, because relationships between each ether linkage of THF rings and its adjacent methyl groups may affect coordination of cation to oxygen atoms. Anti-relationship should be required for coordination of cation from our results. Unfortunately, **12** did not have the cation transport function across liquid membrane called "hollow tube within a vial" established by R.M. Izatt *et al.* [11] (data not shown).

Since FAB technique have semi-quantitatively estimated the selectivity between metal cation and macrocyclo ligand, this method was applied to diolide **12**, triolide, tetrolide, and hexolide, and the results are listed in Table 3. These results indicated that increase of the relative ion intensity corresponding to cation complex reflects on the

Table 1 Comparative association constants (Ka) and binding free energies (-ΔG°)

Host molecules	K_a (M^{-1}) ; -ΔG° (kcal / mol)		
	Li^+	Na^+	K^+
diolide B1(**12**)	4.0×10^5 ; 7.6	1.1×10^5 ; 6.9	2.2×10^4 ; 5.9
diolide B2(**13**)	—	2.3×10^5 ; 7.3	2.3×10^4 ; 5.9
triolide	0	0	0
tetrolide[a]	—	6.6×10^6 ; 9.3	1.0×10^8 ; 11
hexolide	1.1×10^6 ; 8.2	2.5×10^6 ; 8.7	5.5×10^6 ; 9.2
15-crown-5	—	4.3×10^6 ; 9.0	6.7×10^5 ; 7.9

a) This compound is already known as a K^+ selective ionophore.

size of cavity, but not the ion selectivity of macrolides. Although we did not explain why the results did not reflect on the ion selectivity[13], it may be possible to measure the diameter of the cavity by use of related metal cations.

Further related studies on armed macrocyclo compound are under way, including development of a new guest for not only monovalent cations but also divalent cations.

Table 2 **FAB mass binding experiments**

host molecule	relative ion intensity		
	$M+Li^+$	$M+Na^+$	$M+K^+$
diolide B1(**12**)	0.5	1.0	<0.1
triolide	0.5	1.0	0.8
tetrolide	0.3	1.0	0.8
hexolide	<0.1	1.0	1.0

m-Nitrobenzyl alcohol was used as a matrix.

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References and notes

1) Tsukube, H. Cation Binding by Macrocycles; Marcel Dekker; New York, **1990**, p497-522, and references cited therein.
2) a) Tsukube, H.; Hori, K.; Inoue, T. *Tetrahedoron Lett.*, **1993**, *34*, 6749. b) Tsukube, H.; Uenishi, J.; Higaki, H.; Kikkawa, K.; Tanaka, T.; Wakabayashi, S.; Oae, S. *J. Org. Chem.*, **1993**, *58*, 4389.
3) a) Kondo, S.; Yasui, K.; Natsume, M.; Katayama, M.; Marumo, S. *J. Antibiot.*, **1988**, *41*, 1196. b) Kondo, S.; Yasui, M.; Katayama, M.; Marumo, S.; Kondo, T.; Hattori, H. *Tetrahedron Lett.*, **1987**, *28*, 5861. c) Natsume, M.;Kondo, S.; Marumo, S. *J. Chem. Soc.,Chem. Commun.*, **1989**, 1911.
4) Natsume, M.; Yasui, K.; Kondo, S.; Marumo, S. *Tetrahedron Lett.*, **1991**, *32*, 3087.
5) a) Keller-Schierlein, W.; Gerlach, H. *Fortschr. Chem. Org. Naturst*, **1968**, *26*, 162. b) Burke, S.D.; Porter , W.J.; Rancourt, J.; Kaltenbach, R.F. *Tetrahedron Lett.*, **1990**, *31*, 5285 and references cited therein.
6) a) Beck, J.; Gerlach, H.; Prelog, V.; Voser, W. *Helv. Chim. Acta*, **1962**, *45*, 620. b) Grelach, H.; Hutter, R.; Keller-Schierlein, W.; Seibl, J.; Zahner,H. *Helv. Chim. Acta*, **1967**, *50*, 1782. c) Commercialy available Polynactins (Chugai Pharmaceutical Company) as the souce of homononactic acid is a mixture of dinactin, trinactin, and tetranactin.
7) Arco, M.J., Trammell, M.H.; White, J.D. *J. Org. Chem.*, **1976**, *41*, 2075.
8) Hikota, M.; Sakurai, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.*, **1990**, *31*, 4613.
9) Bartlett, P.A.; Rico, J.G.; Oh, Y.I.; Codon, B.D. *J. Org. Chem.*, **1986**, *51*, 3388.
10) Koenig, K.E.; Lein, G.M.; Stuckler, P.; Tanada, T.; Cram, D.J. *J. Am. Chem. Soc.*, **1979**, *101*, 3553.
11) a) Izatt, R.M.; Deardon, D.V.; Brown, P.R.; Bradshaw, J.S.; Lamb, J.D.; Christensen, J.J. *J. Am. Chem. Soc.*, **1983**, *105*, 1785. b) Izatt, R.M.; LindH, G.C.; Bruening, R.L.; Huszthy, P.; MacDaniel, C.W.; Bradshaw, J.S.; Christensen, J.J. *Anal. Chem.*, **1988**, *60*, 1694
12) Johnstone, R.A.W.; Rose, M.E. *J. Chem. Soc., Chem. Commun.*, **1983**, 1268.
13) Michael, J.P.; Pattenden, G. *Angew. Chem. Int. Ed. Engl.*, **1993**, *32*, 1.

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