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Stereoselective Synthesis of (+)-SCH 351448: A Unique Ligand System for Sodium, Calcium, and Other Cations

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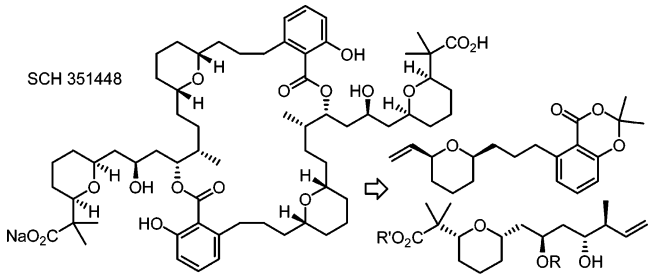

(+)-SCH 351448 (Na^+ salt A) was synthesized employing ring-closing olefin metathesis reaction of an open diene diester intermediate for construction of the 28-membered macrodiolide structure. The open diene diester was prepared from the monomeric hydroxy carboxylic acid and two different olefin fragments. The monomeric hydroxy acid was synthesized via Julia−Julia coupling reaction of intermediates derived from the same olefinic fragments. Oxane units in these fragments were prepared by radical cyclization reactions of β-alkoxyacrylates. Analogous SCH 351448 salts incorporating other mono- and divalent cations may be prepared. Under acidic conditions, SCH 351448 (Na^+ salt A) was the most stable complex, but SCH 351448 (Ca^{2+} salt) and (Na^+ salt B) appear to be physiologically important species.

Introduction

LDL uptake by the LDL receptor (LDL-R) is an important mechanism for clearing serum cholesterol. Selective activators of LDL-R transcription may be able to decrease serum LDL levels by increasing LDL uptake by the LDL-R. Screening the ethyl acetate extracts of several microbial fermentation broths, researchers at Schering-Plough Research Institute and Duke University recently found that a microorganism belonging to *Micromonospora* sp. yielded an extract that displayed distinct activity in the LDL-R assay, and identified the structure of SCH 351448 (**1**).[1] Purified SCH 351448 has an ED_{50} of 25 μM in the LDL-R promoter transcription assay using hGH as a reporter gene, but it did not activate transcription of hGH from the SRα promoter. Thus, **1** selectively activates transcription from the LDL-R promoter, and it is the first small molecule activator of the LDL-R promoter identified to date. The structure of **1** features a 28-membered macrodiolide consisting of two identical hydroxy carboxylic acid units (Figure 1). In the X-ray crystal structure of **1** reported by the Schering-Plough and Duke researchers, the sodium ion appears to be surrounded by seven oxygen atoms rendering a pseudo-C_2 symmetric structure for the complex. The unique bioactivity and the intriguing structure of **1** makes it an attractive target for synthetic chemists,[2] and we wish to describe here a full account of the first total synthesis.[3]

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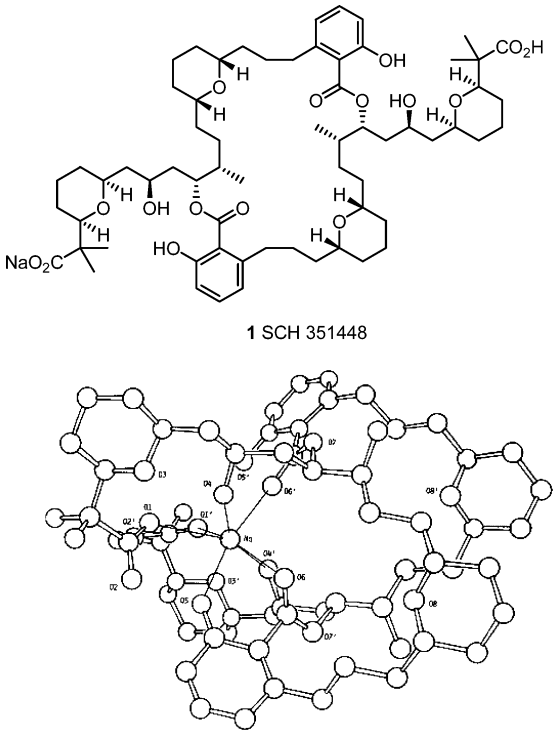


FIGURE 1. Structure of SCH 351448.

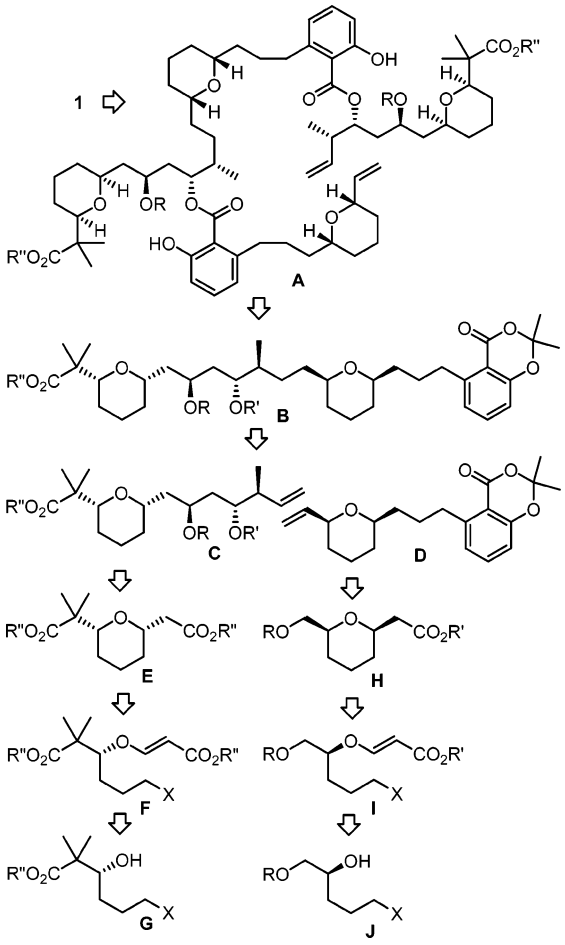
Total Synthesis

At the outset, ring-closing metathesis reaction of the diester intermediate **A** was envisaged for construction of the 28-membered ring macrodiolide structure. The diester intermediate **A** would be prepared from the monomeric unit **B** and fragments **C** and **D**. Fragments **C** and **D** are the basic modules in the synthetic plan as they may serve as precursors for the monomer **B**. Synthesis of fragments **C** and **D** calls for preparation of the oxane derivatives **E** and **H**, which may be formed via radical cyclization reactions of β-alkoxyacrylates **F** and **I** (Scheme 1).

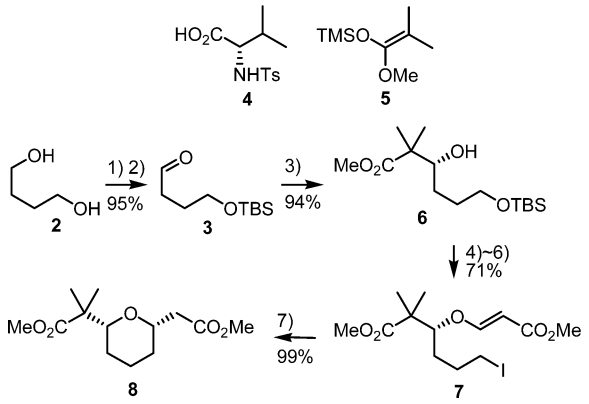
Synthesis of the fragment **E** started with a 2-step conversion of 1, 4-butanediol (**2**) into aldehyde **3**.[4] Mukaiyama aldol reaction of aldehyde **3** and silyl enol ether **5** was mediated by a chiral borane reagent[5] prepared from *N*-tosyl-l-valine (**4**). The secondary alcohol **6** thus obtained (>95% e.e.)[6] was converted into β-alkoxyacrylate **7** via reaction with methyl propiolate, TBS deprotection, and iodide substitution. Radical cyclization[7] in the presence of 1-ethylpiperidinium hypophosphite and triethylborane in ethanol[8] proceeded efficiently to yield the oxane diester **8** (Scheme 2).

The 3-(*R*)-configuration of the secondary alcohol **6** was confirmed by converting it into (*O*)-acetyl-(*S*)-mandelate

SCHEME 1. Retrosynthetic Analysis



SCHEME 2. Synthesis of the Fragment E[a]



[a] Reagents and conditions: (1) 0.7 equiv NaH, 0.7 equiv TBSCl, THF, 0 °C, 1 h; (2) 3.0 equiv SO_3·Pyr, 5.0 equiv TEA, DMSO-DCM (1:1), 0 °C, 30 min; (3) **4**, 1.0 equiv BH_3·THF, DCM, r.t. 30 min; 1.0 equiv **3**, 1.1 equiv **5**, −78 °C, 4 h; (4) 1.5 equiv $HCCCO_2Me$, 0.2 equiv NMM, MeCN, r.t. 48 h; (5) concentrated HCl, MeOH, r.t. 30 min; (6) 1.5 equiv I_2, 1.5 equiv Ph_3P, 3.0 equiv imidazole, THF, 0 °C, 2 h; (7) 5.0 equiv H_3PO_2, 5.0 equiv 1-ethylpiperidine, 1.5 equiv Et_3B, EtOH, r.t. 30 min.

(3) Kang, E. J.; Cho, E. J.; Lee, Y. E.; Ji, M. K.; Shin, D. M.; Chung, Y. K.; Lee, E. *J. Am. Chem. Soc*. **2004**, *126*, 2680−2681.

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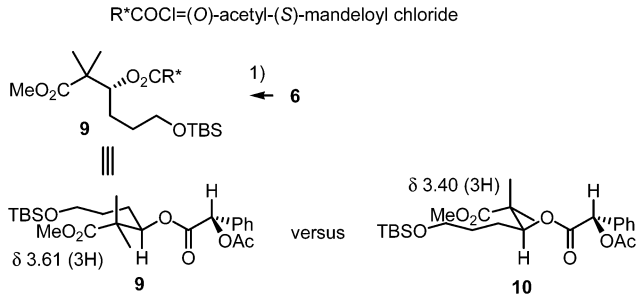
(6) Due to interference from other signals around δ 3.40 from the minor diastereomer **10**, the exact enantiomeric excess value was difficult to determine.

(7) For recent examples of β-alkoxyacrylate radical cyclization, see: (a) Song, H. Y.; Joo, J. M.; Kang, J. W.; Kim, D.-S.; Jung, C.-K.; Kwak, H. S.; Park, J. H.; Lee, E.; Hong, C. Y.; Jeong, S.; Jeon, K.; Park, J. H. *J. Org. Chem*. **2003**, *68*, 8080−8087. (b) Jeong, E. J.; Kang, E. J.; Sung, L. T.; Hong, S. K.; Lee, E. *J. Am. Chem. Soc*. **2002**, *124*, 14655−14662. (c) Lee, E.; Choi, S. J.; Kim, H.; Han, H. O.; Kim, Y. K.; Min, S. J.; Son, S. H.; Lim, S. M.; Jang, W. S. *Angew. Chem., Int. Ed. Engl*. **2002**, *41*, 176−178.

(8) Lee, E.; Han, H. O. *Tetrahedron Lett*. **2002**, *43*, 7295−7296.

SCHEME 3. Configuration at C-3[a]



[a] Reagents and conditions: (1) 3.0 equiv (*O*)-acetyl-(*S*)-mandeloyl chloride, 5.0 equiv pyridine, benzene, r.t. 5 h.

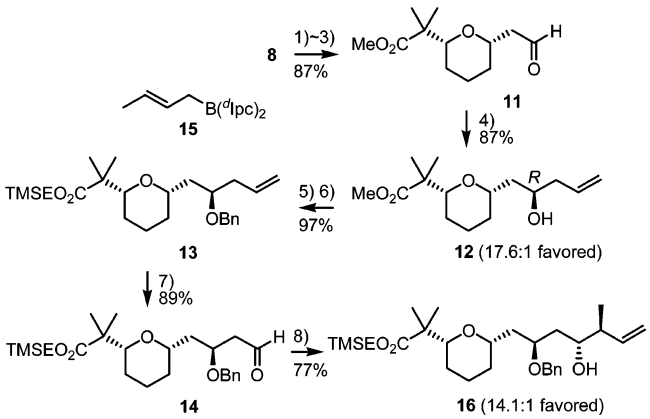
9. The ^{1}H NMR signal of the methyl ester moiety of **9** was located at δ 3.61 while the same signal of the 3-(*S*)-diastereomer **10** appeared at δ 3.40 (Scheme 3).

Reactivity of the two ester groups in **8** was vastly different, and basic hydrolysis of **8** provided a monocarboxylic acid. The corresponding aldehyde **11** was converted into the correct homoallylic alcohol **12** (dr = 17.6:1) via Brown allylation.[9] At this point, a crucial decision was made to proceed further after converting the methyl ester into the 2-trimethylsilylethyl ester moiety. Hydrolysis of the sterically crowded carboxylic ester group was anticipated to be the last step in the synthesis, and the 2-trimethylsilylethyl ester functionality made much more sense than the original methyl ester group. In practice, benzyl protection of **12** and transesterification[10] with 2-trimethylsilylethanol in the presence of titanium(IV) isopropoxide led to a new ester **13**. Aldehyde **14** was then obtained via oxidative cleavage, and it was converted into the homoallylic alcohol **16** (dr = 14.1:1) via Brown crotylation using the (*E*)-crotylborane reagent **15**[11] (Scheme 4).

The 9-(*R*)-configuration of **12** was confirmed by comparing the ^{1}H NMR data of the corresponding (*O*)-acetyl-(*S*)-mandelate **17** with those of the 9-(*S*)-epimer **18**. In particular, the vinyl proton signals of **17** appeared at δ 5.40 and 4.77, and those of **18** appeared at δ 5.73 and 5.07 (Scheme 5).

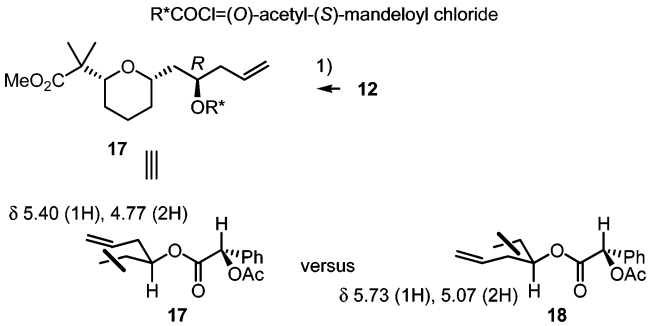
For synthesis of fragment **H**, D-mannitol (**19**) was converted into glyceraldyhyde acetonide, from which ester **20** was obtained via Horner-Emmons reaction.[12] Hydrogenation of **20**, LAH reduction, and tosylation led to the primary tosylate **21**.[13] Selenide **22** was obtained from **21** via selenide substitution and acetonide deprotection. Regioselective benzylation of **22** and reaction with methyl propiolate then led to β-alkoxyacrylate **23**. Radical cyclization of **23** proceeded smoothly in the presence of tributylstannane and AIBN to provide the oxane ester **24** in good yield (Scheme 6). Radical cyclization reaction of selenides such as **23** was sluggish in the presence of 1-ethylpiperidinium hypophosphite and triethylborane in ethanol.

SCHEME 4. Synthesis of the Fragment C[a]



[a] Reagents and conditions: (1) 0.3 N KOH, THF−H_2O-MeOH (3:1:1), r.t. 3 h; (2) 3.0 equiv BH_3·DMS, 3.0 equiv $B(OMe)_3$, THF, 0 °C, 3 h; (3) 3.0 equiv SO_3·Pyr, 5.0 equiv TEA, DMSO-DCM (1:1), 0 °C, 1 h; (4) 2.0 equiv (+)-DIPCl, 1.5 equiv CH_2CHCH_2MgBr, THF, −78 °C, 1 h; **11**, −78 C ∼ r.t. 2 h; NaOH, H_2O_2, r.t. 1 h; (5) 1.2 equiv NaHMDS, 1.5 equiv BnBr, THF-DMF (4:1), 0 °C ∼ r.t. 12 h; (6) 0.25 equiv Ti(O*i*-Pr)$_4$, 10 equiv $TMSCH_2CH_2OH$, DME, 120 °C, 48 h; (7) 0.05 equiv OsO_4, 3.0 equiv NMO, acetone-H_2O (3:1), r.t. 12 h; 3.0 equiv $NaIO_4$, r.t. 30 min; (8) 1.5 equiv **15**, THF, −78 °C, 4 h; NaOH, H_2O_2, −78 °C ∼ r.t. 1 h.

SCHEME 5. Configuration at C-9[a]



[a] Reagents and conditions: (1) 3.0 equiv (*O*)-acetyl-(*S*)-mandeloyl chloride, 5.0 equiv pyridine, benzene, r.t. 5 h.

Aldehyde **25** obtained from ester **24** was converted into the homologous vinylstannane **26** via a modified Corey-Fuchs protocol[14] and radical-mediated hydrostannylation. Efficient Stille coupling[15] of **26** and the known triflate **27**[16] led to an olefinic intermediate **28**. An alternative way to **28** involved coupling aldehyde **25** with the boronate reagent **29** following Takai protocol,[17] and subsequent Suzuki reaction[18] of boronate **30** with triflate **27**. Hydrogenation/ hydrogenolysis of **28** and oxidation led to aldehyde **31**, and the terminal olefin **32** was obtained via Wittig reaction (Scheme 7).

With the terminal olefin fragments **16** and **32** at hand, metathesis reaction appeared as the most attractive route toward the monomeric unit **B**. The cross metathesis reaction of **16** and **32** employing the second-generation

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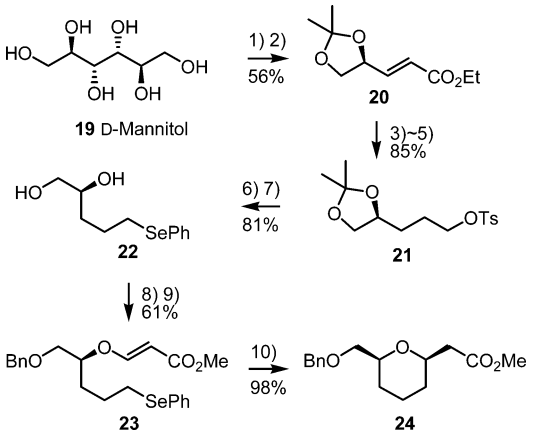
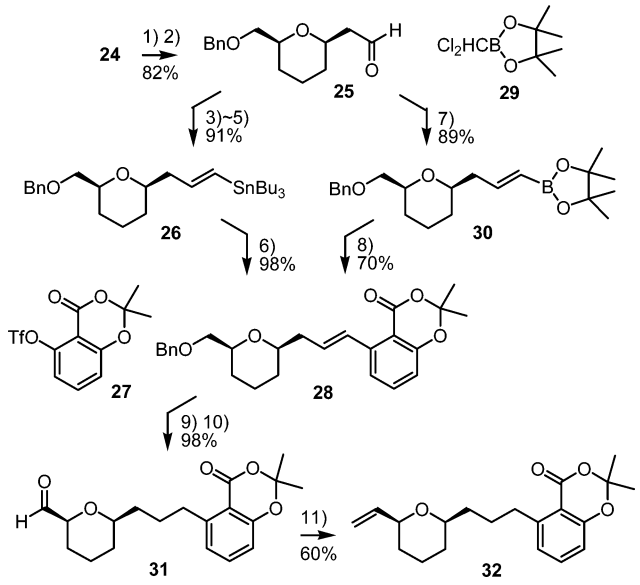
SCHEME 6. Synthesis of the Fragment H[a]



[a] Reagents and conditions: (1) 2.0 equiv $ZnCl_2$, acetone, r.t. 22 h; 2.0 equiv K_2CO_3; (2) 1.2 equiv $NaIO_4$, 5% $NaHCO_3$, H_2O, r.t. 1 h; 2.2 equiv $(EtO)_2POCH_2CO_2Et$, 6 N K_2CO_3, H_2O, r.t. 20 h; (3) H_2, 0.1 equiv $Pd(OH)_2$, MeOH, r.t. 2 h; (4) 1.0 equiv LAH, ether, 0 °C, 1 h; (5) 2.0 equiv *p*-TsCl, 3.0 equiv TEA, DCM, 0 °C, 12 h; (6) 0.6 equiv PhSeSePh, 1.3 equiv $NaBH_4$, EtOH, r.t. 1 h; (7) concentrated HCl, MeOH, r.t. 12 h; (8) 1.1 equiv Bu_2SnO, benzene, reflux ($-H_2O$), 16 h; 2.4 equiv BnBr, 1.1 equiv TBAI, benzene, reflux, 30 min; (9) 1.5 equiv $HCCCO_2Me$, 0.3 equiv NMM, MeCN, r.t. 12 h; (10) 1.2 equiv *n*-Bu_3SnH, 0.2 equiv AIBN, benzene (0.01 M), reflux, 5 h.

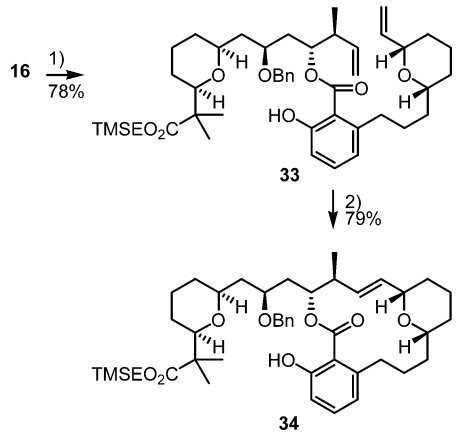
SCHEME 7. Synthesis of the Fragment D[a]



[a] Reagents and conditions: (1) 1.0 equiv LAH, THF, 0 °C, 2 h; (2) 4.0 equiv SO_3·Pyr, 8.0 equiv TEA, DMSO-DCM (1:1), 0 °C, 5 h; (3) 5.0 equiv CBr_4, 10 equiv HMPT, THF, −30 °C, 1 h; (4) 2.1 equiv *n*-BuLi, THF, −78 °C, 1 h; (5) 1.1 equiv *n*-Bu_3SnH, 0.05 equiv AIBN, benzene (0.02 M), reflux, 1 h; (6) 0.1 equiv $PdCl_2(PPh_3)_2$, 0.83 equiv **27**, 7.1 equiv LiCl, 0.5 equiv Ph_3P, DMF (0.1 M), 120 °C, 6 h; (7) 2.0 equiv **29**, 8.0 equiv $CrCl_2$, 4.0 equiv LiI, THF, r.t. 16 h; 8) 0.1 equiv $PdCl_2$(dppf), 0.91 equiv **27**, 1.5 equiv K_3PO_4, THF, 65 °C, 6 h; (9) H_2, 0.1 equiv Pd/C, MeOH, r.t. 2 h; (10) 4.0 equiv SO_3·Pyr, 8.0 equiv TEA, DMSO-DCM (1:1), 0 °C, 5 h; (11) 2.0 equiv $Ph_3PCH_3^+Br^-$, 1.9 equiv *n*-BuLi, THF, 0 °C, 1 h; 1.0 equiv **31**, THF, −78 °C ∼ r.t. 6 h.

Grubbs catalyst[19] did not proceed efficiently, and the cross metathesis product was isolated in low yield (<7%) accompanied by the homo dimer of **16**. For the ring-closing metathesis reaction, the diene ester precursor **33** was prepared smoothly from the sodium alkoxide of **16** and **32**, and it was converted into macrolide **34** in the presence of the first-generation Grubbs catalyst (Scheme 8). Unfortunately, it was not possible to obtain the required hydroxy carboxylic acid from macrolide **34** under hydrolytic conditions employing various acids and bases.

SCHEME 8. Synthesis of the Monomeric Macrolide[a]



[a] Reagents and conditions: (1) 2.5 equiv NaHMDS, THF, 0 °C, 30 min; 1.1 equiv **32**, 0 °C, 2 h; (2) 10 mol % $(PCy_3)_2RuCl_2(CHPh)$, DCM (3 mM), 45 °C, 6 h.

Alternative ways for joining units **16** and **32** were investigated, and the Julia−Julia reaction[20] appeared most promising. TBS-protection of **16**, oxidative cleavage, and sodium borohydride reduction led to the primary alcohol **35**. The boron-mediated anti aldol reaction[21] of aldehyde **14**, and subsequent 5-step transformations also produced **35**, but the route via **16** was more efficient. Sulfone **37** was obtained via Mitsunobu-type substitution of **35** with thiol **36** and selective oxidation. The coupling of sulfone **37** and aldehyde **31** required intensive tuning-up, but eventually, efficient synthesis of olefin **38** was possible using sodium hexamethyldisilazide in ether. The monomeric unit **39** was obtained from olefin **38** via diimide reduction (Scheme 9). Wittig reaction did not work between partners derived from **31** and **35**. Myers reductive coupling between appropriate partners was also unsuccessful.[22]

The final assembly of the fragments was initiated by reacting the sodium alkoxide derived from **16** with **39**. The coupled ester product **40** was then converted into another alkoxide after TBS-deprotection, which was used for the coupling with **32** to produce diester **41**. Ring-closing olefin metathesis of **41** mediated by the second-generation Grubbs catalyst **42** proceeded smoothly, and macrodiolide **43** was obtained in good yield (Scheme 10).

Macrodiolide **44** was obtained from **43** after hydrogenation/hydrogenolysis. The last step toward **1** was hydrolytic removal of the 2-trimethylsilylethyl ester functionalities in **44**. The macrodiolide diester **44** was treated

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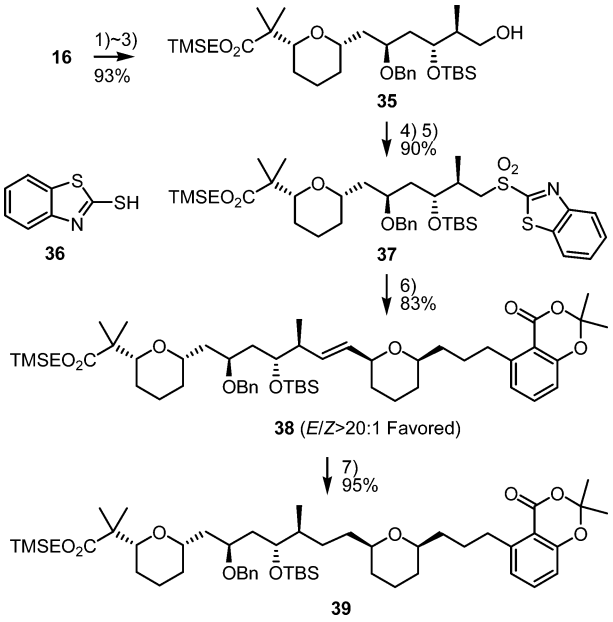
SCHEME 9. Synthesis of the Monomeric Unit B[a]



[a] Reagents and conditions: (1) 3.0 equiv TBSOTf, 4.0 equiv 2,6-lutidine, DCM, 0 °C, 3 h; (2) 0.05 equiv OsO_4, 3.0 equiv NMO, acetone−H_2O (3:1), r.t. 12 h; 3.0 equiv $NaIO_4$, r.t. 30 min; (3) 3.0 equiv $NaBH_4$, EtOH, r.t. 30 min; (4) 1.5 equiv **36**, 1.5 equiv DIAD, 1.5 equiv Ph_3P, THF, 0 °C, 1 h; (5) 2.0 equiv $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, 10 equiv H_2O_2, EtOH, 0 °C ∼ r.t. 12 h; (6) 1.1 equiv NaHMDS, ether, −78 °C, 15 min; 1.5 equiv **31** (syringe pump, 30 min), −78 °C ∼ r.t. 15 h; (7) 10 equiv $TsNHNH_2$, 16 equiv NaOAc, DME−H_2O (1:1), reflux, 4 h.

with tetrabutylammonium fluoride in THF, and a major product was produced after the usual workup. Unexpectedly, TLC analysis showed that the product was much more nonpolar than the starting material, and the NMR data of the product did not match those of the natural product provided by the Schering-Plough workers. Many different workup conditions were examined, and the sample of **1** (Na^+ salt) with the correct NMR (^1H and ^{13}C) and mass (MALDI *m/z* 1143.7) data was obtained when the reaction mixture was extracted with dichloromethane after equilibration with 4 N HCl saturated with sodium chloride (Scheme 11). This synthetic sample was designated as **1** (Na^+ salt A), which was found to be the (+)-enantiomer: $[\alpha]^{13}_D$ +31.2 (*c* 0.73, $CHCl_3$).[23]

Sodium (^{23}Na) NMR spectra of this sample were obtained (at 185.24 MHz) in $CDCl_3$ solution at an ambient probe temperature of ca. 22−23 °C relative to external 0.1 M NaCl in D_2O. The observed chemical shift (δ, −8 ppm) and the line width (∼590 Hz) suggest that the compound **1** (Na^+ salt A) wraps itself around the sodium cation to form strong coordination complex. The shielding effects on sodium ion were already observed and used in previous studies.[24] The line width (∼590 Hz), however, suggests that the complex in solution has a dissymmetric environment around the sodium cation.[25]

(23) The specific rotation of the natural sample is unknown.

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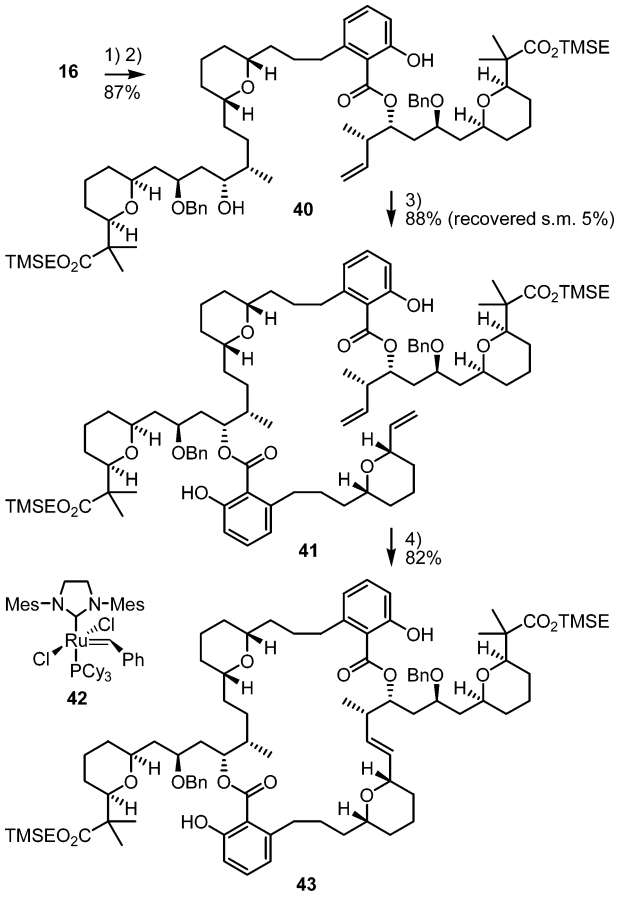
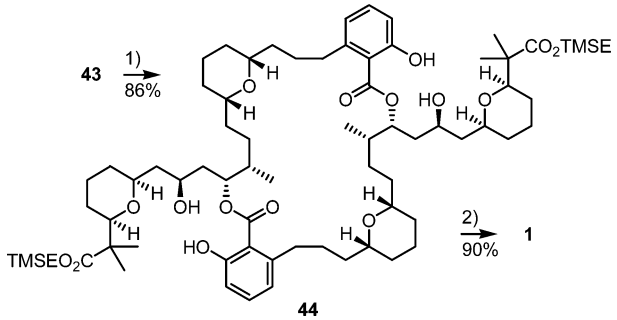
SCHEME 10. Synthesis of the Macrodiolide Intermediate[a]



[a] Reagents and conditions: (1) 3.0 equiv NaHMDS, THF, 0 °C, 30 min; 1.2 equiv **39**, r.t. 1 h; (2) concentrated HCl, MeOH, r.t. 1 h; (3) 4.0 equiv NaHMDS, THF, 0 °C, 30 min; 1.5 equiv **32**, 0 °C, 1 h; (4) 10 mol % **42**, DCM (0.003 M), 80 °C, 12 h.

SCHEME 11. Synthesis of SCH 351448[a]



[a] Reagents and conditions: (1) H_2, 0.1 equiv Pd/C, MeOH−EtOAc (3:1), r.t. 6 h; (2) 6.0 equiv TBAF, THF, r.t. 2 h; 4 N HCl (sat. with NaCl).

A different sample of **1** was obtained after equilibration of the reaction mixture with 2 N HCl saturated with sodium chloride: ^1H NMR analysis revealed that the sample was a mixture (1:1.6) of **1** (Na^+ salt A) and a different species. The new species was the sole product after equilibration with NaH_2PO_4/Na_2HPO_4 (pH 6.8) and AcOH/NaOAc (pH 5.0) buffer, and it was assigned as **1** (Na^+ salt B).[26] Sodium (^{23}Na) NMR spectra of **1** (Na^+ salt B) exhibited the same chemical shift and line width as those recorded for **1** (Na^+ salt A).

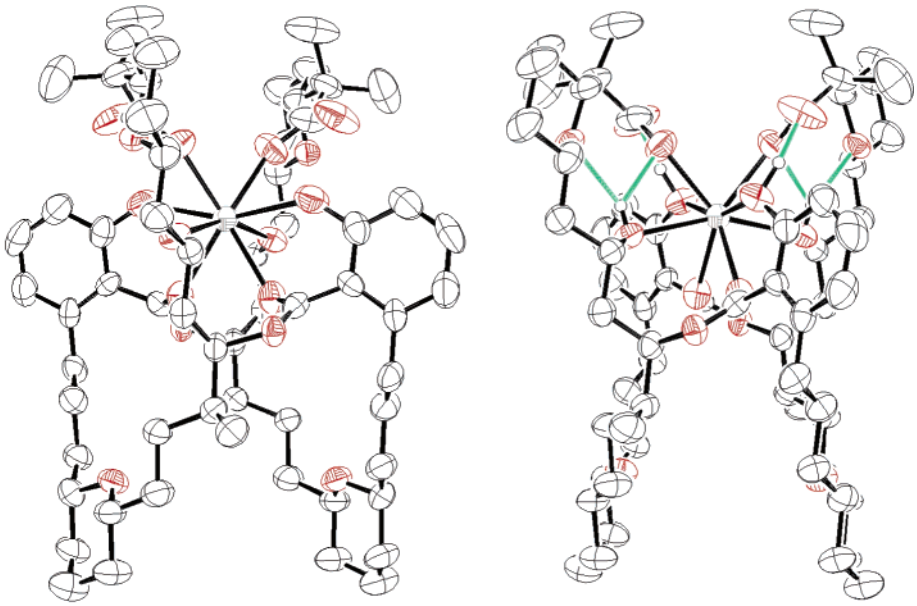


FIGURE 2. Crystal structure of **1** (Ca^{2+} salt): hydrogen bonds (green) are shown in (b).

Structural and Cation Exchange Studies

Crystallization of the crude product was difficult, and column chromatographic purification of the synthetic sample of **1** (Na^+ salt A, obtained after equilibration with 4 N HCl saturated with sodium chloride) was carried out using Merck silica gel 60 yielding crystals from the methanol solution of the purified sample. The crystallographic data reveals a C_2-symmetric structure in which the metal cation is surrounded by eight oxygen atoms (Figure 2a,b). Four different bond lengths (Å) are noted: 2.327 ($M-O_{carboxylate}$), 2.446 ($M-O_{ester\ carbonyl}$), 2.576 ($M-O_{hydroxy}$), and 2.657 ($M-O_{phenolic}$).[27] In the crystal structure, two sets of bifurcated hydrogen bonds between the hydroxyl protons and the (M^+-coordinating) carboxylate and oxane oxygens are prominent: the hydrogen bonds between the phenolic hydrogens and the (free) carboxylate oxygens are also present (Figure 2b). It was initially assigned as **1** (Na^+ salt A),[3] but curiously, different mass (MALDI *m/z* 1159.6) and NMR data were obtained for this crystalline sample. After much thought, it was realized that the crystal structure represented **1** (Ca^{2+} salt). The sodium salt was mysteriously transformed into the calcium salt upon chromatographic separation. The mystery was solved as it was discovered[28] that similar incidence was reported by Sodeoka and coworkers concerning RK-682.[29] Silica gel supplied by Merck contained a large amount of calcium ion.[30]

Crystals of **1** (Na^+ salt B) were later obtained as bis(dichloromethane) solvate from dichloromethane-methanol solution of the crude sample without chromatographic purification (Figure 3a,b). The crystal structure reveals that the sodium cation is surrounded by seven oxygen atoms as reported in the original report by Schering researchers.[1] One $M-O_{phenolic}$ bond is missing (4.037 Å), and the opposite $M-O_{hydroxy}$ bond is the shortest (2.407 Å) of the M−O bonds. Two sets of bifurcated hydrogen bonds between the hydroxyl protons and the (Na^+-coordinating) carboxylate and oxane oxygens are present: one hydrogen bond between a phenolic hydrogen and a (free) carboxylate oxygen is found, but the second phenolic hydrogen is bonded to the adjacent ester carbonyl oxygen forming a six-membered ring structure. (Figure 3b).

Crystals were also obtained from the dichloromethane-methanol solution of **1** (Na^+ salt A), but they were identical with the crystals of **1** (Na^+ salt B) as verified by NMR analysis of the redissolved samples of the crystals. It may be concluded that **1** (Na^+ salt A) was converted slowly to **1** (Na^+ salt B) in solution, and crystals were obtained as **1** (Na^+ salt B).

Realizing that cation exchange occurred on silica gel, it was decided to investigate systematically cation-binding selectivities of **1** guided by NMR and mass spectral analysis, and prepare salts containing other cations. As we were not able to prepare the free carboxylic

(26) Samples of **1** (Na^+ salt A) and **1** (Na^+ salt B) exhibited different ^1H NMR data. As for mass spectroscopic data, both samples gave similar ESI data (*m/z* 1143.7), but in the MALDI analysis, the strongest peak for **1** (Na^+ salt B) was at *m/z* 1165.6, as opposed to the normal *m/z* 1143.7 peak for **1** (Na^+ salt A). For this reason, **1** (Na^+ salt B) was initially thought to be a disodium salt. In solution (for example, hexane-DCM), **1** (Na^+ salt A) was slowly converted to **1** (Na^+ salt B).

(27) Slightly different values were found when the crystal structure was initially solved as a Na^+ salt. For simplicity, the values obtained as the Ca^{2+} salt are presented here.

(28) The authors thank Prof. Hyeongjin Cho of Inha University for the information on the Sodeoka paper.

(29) Sodeoka, M.; Sampe, R.; Kojima, S.; Baba, Y.; Morisaki, N.; Hashimoto, Y. *Chem. Phar. Bull.* **2001**, *49*, 206−212.

(30) Kanto silica gel 60 (spherical) had different characteristics and the sample of **1** (Na^+ salt A) survived column chromatographic separation.

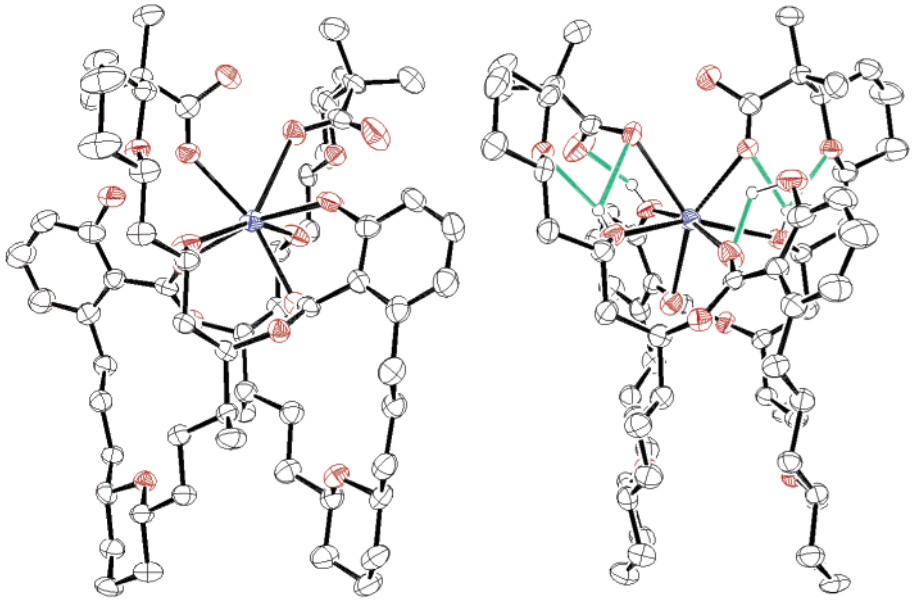


FIGURE 3. Crystal structure of **1** (Na^+ salt B, CH_2Cl_2 omitted): hydrogen bonds (green) are shown in (b).

TABLE 1. Exchange Reactions of 1 (Na^+ Salt A)

	additive (saturation)	analysis (^1H NMR)	analysis (MALDI & FAB)
4 N HCl solution	LiCl	(broad signals)	(*m/z* 1127.7)[a]
	KCl	(K^+ salt) & (Na^+ salt A) (3.8:1)	(*m/z* 1159.6 & 1143.7)[a]
	RbCl	(Rb^+ salt) & (Na^+ salt A) (2.9:1)	(*m/z* 1205.6 & 1143.7)[a]
	$CaCl_2$	(Na^+ salt A)	(*m/z* 1143.7)[a]
aqueous solution	$MgCl_2$	(Mg^{2+} salt)	(*m/z* 1143.6)[a]
	$CaCl_2$	(Ca^{2+} salt)	(*m/z* 1159.6)[a]
	$Cu(OAc)_2$[b]	(Cu^{2+} salt)	(*m/z* 1181.6)[c]
	$Mn(OAc)_2$[b]	(no spectrum)	(*m/z* 1227.5)[d]
	$Co(OAc)_2$	(no spectrum)	(*m/z* 1235.5)[d]

[a] MALDI data for protonated metal salts. [b] Metal ion exchange did not occur when equilibrated with relatively acidic sat. $CuCl_2$ solution and sat. $MnSO_4$ solution. [c] MALDI data for metal salts. [d] MALDI data for doubly metalated salts.

TABLE 2. Exchange Reactions of 1 (Ca^{2+} Salt)

	additive (saturation)	analysis (^1H NMR)	analysis (MALDI & FAB)
4 N HCl solution	LiCl	(broad signals)	(*m/z* 1127.7)[a]
	NaCl	(Na^+ salt A)	(*m/z* 1143.7)[a]
	KCl	(K^+ salt) & (Na^+ salt A) (3.6:1)	(*m/z* 1159.6 & 1143.7)[a]
	RbCl	(Rb^+ salt) & (Na^+ salt A) (2.1:1)	(*m/z* 1205.6 & 1143.7)[a]
aqueous solution	LiCl	(Ca^{2+} salt)	(*m/z* 1159.6)[a]
	NaCl	(Na^+ salt B) & (Ca^{2+} salt) (3.7:1)	(*m/z* 1143.7 & 1159.6)[a]
	$MgCl_2$	(Mg^{2+} salt) & (Ca^{2+} salt) (1:1.6)	(*m/z* 1143.6 & 1159.6)[a]

[a] MALDI data for protonated metal salts.

acid of **1** from the synthetic scheme[31] or from any of the salts, studies were limited on the relative stabilities of various salts under defined conditions. The results of the exchange experiments (NMR and mass data) using **1** (Na^+ salt A) in dichloromethane equilibrated with different metal salt solutions in 4 N HCl or water are presented in Table 1. The results of the exchange experiments using **1** (Ca^{2+} salt) are presented in Table 2. From the results, it was obvious that (Na^+ salt A) was the most stable form in 4 N HCl solutions. Alkali metal salts (Li^+, K^+, and Rb^+) may be prepared under highly acidic conditions, and alkaline earth metal salts (Mg^{2+} and Ca^{2+}) and others (Cu^{2+}, Mn^{2+}, and Co^{2+}) may be prepared under (near) neutral conditions. It is to be noted that **1** (Na^+ salt A) was stable under equilibrating conditions with 4 N HCl saturated with calcium chloride, but it was converted into **1** (Ca^{2+} salt) when equilibrated

(31) A variety of different deprotection procedures starting from **44** yielded **1** (Na^+ salt A) as the sole product. Treatment of **43** with tetrabutylammonium fluoride in THF produced a dicarboxylic acid, and hydrogenolysis (H_2, Pd/C, ethyl acetate, polypropylene vessel) yielded **1** (Na^+ salt A) and a polar product, which stayed unchanged upon treatment with sodium chloride.

TABLE 3. Studies on the Relative Stability of 1 (Na^+ Salt A) and 1 (K^+ Salt)[a]

KCl:NaCl	500:5	250:5	100:5	50:5	5:5
(K^+ salt):(Na^+ salt A)	1.53: 1	0.57: 1	0.35: 1	0.23: 1	~0: 1

[a] In each experiment, a DCM solution (5 mL) containing **1** (Na^+ salt A) (5 mg) was treated with 4 N HCl solution (5 mL) containing the given amounts (equiv.) of KCl and NaCl, and the mixture was stirred vigorously for 1 h. The ratios were determined by comparing the signals at δ 5.83 (K^+ salt) and δ 5.63 (Na^+ salt A) in the ^1H NMR spectra (300 MHz, $CDCl_3$). Mass spectral analyses were also carried out. ESI data gave similar results as the ^1H NMR data. MALDI data confirmed the relative stability of the (Na^+ salt A), but the exact ratios were not reliable because of the problems associated with extraneous cations.

TABLE 4. Studies on the Solvent Effects[a]

solvents (dielectric constants)	Hexane (1.9)	Et_2O (4.3)	DCM (9.1)	MeCN (38)
(K^+ salt):(Na^+ salt A)	~0: 1	~0: 1	3.8: 1	4.2: 1

[a] In each experiment, a solution (5 mL) containing **1** (Na^+ salt A) (5 mg) was treated with 4 N HCl solution (5 mL) saturated with KCl.

with saturated aqueous solution of calcium chloride.[32] A mixture of **1** (Na^+ salt B) and **1** (Ca^{2+} salt) resulted when **1** (Ca^{2+} salt) was equilibrated with saturated aqueous solution of sodium chloride. Higher stability of **1** (Ca^{2+} salt) over **1** (Mg^{2+} salt) under neutral conditions was also obvious from the equilibration experiment.

Relative stability of **1** (Na^+ salt A) and **1** (K^+ salt) in dichloromethane was investigated by equilibration experiments with 4 N HCl solutions containing different amounts of sodium and potassium chloride starting from **1** (Na^+ salt A) (Table 3). From the experiments, it is clearly shown that **1** (Na^+ salt A) is much more stable in dichloromethane than **1** (K^+ salt) under acidic conditions. Higher relative stability of **1** (Na^+ salt A) is obtained in nonpolar solvents, and remarkably, **1** (Na^+ salt A) was stable when equilibrated in hexane or ether with 4 N HCl solution saturated with potassium chloride.

More comments on **1** (Ca^{2+} salt) are deemed necessary aside from the story on its "surprise" formation on (Merck) silica gel columns. Octacoordination by oxygen is the most common chelate scheme for Ca^{2+} for small molecules and is also the most common in proteins.[33] The relative stability of **1** (Ca^{2+} salt) attests to the maximum stabilization of the calcium ion complex via intramolecular octacoordination:[34] intramolecular hydrogen bonds discussed above should also help stabilizing the complex. From the cation exchange studies, **1** (Ca^{2+} salt) appears to be the most stable species under (near) neutral conditions, and equilibrium between **1** (Ca^{2+} salt) and **1** (Na^+ salt B) is a distinct possibility under physiological conditions. Calcium is a second messenger in virtually all cells. In particular, calcium signals in the nucleus have effects on gene transcription and cell growth that are distinct from those of cytosolic calcium signals. Regulation of calcium signals in the nucleus is an important area of research.[35] The known bioactivity of **1** as a small molecule activator of the LDL-R promoter may then be related to the structural characteristics of **1** (Ca^{2+} salt) and **1** (Na^+ salt B) and also to their interconversion leading to calcium transport.

Conclusion

In the present studies, the two oxane fragments of SCH 351448 (Na^+ salt) were prepared stereoselectively via radical cyclization reactions of β-alkoxyacrylates. The monomeric unit was obtained via Julia-Julia coupling reaction, and the ring-closing olefin metathesis reaction was employed for the 28-membered macrodiolide ring formation. SCH 351448 analogues containing other cations were prepared, but SCH 351448 (Na^+ salt A) appeared to be the most stable complex under acidic conditions. SCH 351448 (Ca^{2+} salt), which is relatively stable under neutral conditions, may be a physiologically important species.

Experimental Section

Preparation of SCH 351448 1 (Na^+ Salt A). TBAF (1.0 M in THF, 0.1 mL, 0.1 mmol) was added to a solution of macrodiolide **44** (17 mg, 0.013 mmol) in THF (3 mL). After being stirred for 2 h at room temperature, the reaction mixture was diluted with hexane (10 mL) and washed with 4 N HCl solution (saturated with NaCl, 12 mL). The aqueous layer was extracted with hexane (3 × 8 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to afford a monosodium salt as a white solid without further purification (13.5 mg, 91%). R_f 0.62 (Hex−EtOAc, 2:1). ^1H NMR (500 MHz, $CDCl_3$): δ 7.23 (t, 2H, J = 7.8 Hz), 6.84 (d, 2H, J = 8.2 Hz), 6.69 (d, 2H, J = 7.3 Hz), 5.63−5.61 (m, 2H), 3.77−3.73 (m, 2H), 3.63−3.59 (m, 2H), 3.50 (d, 2H, J = 11.0 Hz), 3.17−3.09 (m, 6H), 2.53−2.59 (m, 2H), 2.03−1.97 (m, 2H), 1.85−1.76 (m, 8H), 1.73−1.57 (m, 8H), 1.51−1.35 (m, 20H), 1.28−1.15 (m, 12H), 1.15 (s, 6H), 1.12 (s, 6H), 1.00 (d, 6H, J = 6.2 Hz). ^{13}C NMR (75 MHz, CD_2Cl_2): δ 178.8, 171.2, 160.2, 145.2, 133.6, 122.4, 116.0, 115.7, 83.3, 79.3, 78.4, 78.2, 77.8, 67.6, 46.6, 43.7, 37.8, 37.6, 37.0, 36.8, 35.3, 33.1, 32.7, 32.0, 30.2, 29.7, 25.3, 24.4, 23.6, 23.4, 19.4, 15.2. MS *m/z* (FAB, relative intensity): 1143 (M^+ + 1, 47), 1121 (13), 1098 (6), 561 (31), 245 (39), 154 (65), 81 (100), 55 (82), 23 (71). HRMS (FAB): calcd for $C_{64}H_{96}O_{16}Na$ (M^+ + 1) 1143.6596, found 1143.6598. $[\alpha]^{13}_D$ +31.2 (*c* 0.73, $CHCl_3$).

Preparation of SCH 351448 1 (Na^+ Salt B). When the TBAF reaction mixture of **44** (as described above) was washed with NaH_2PO_4/Na_2HPO_4 (pH 6.8) or AcOH/NaOAc (pH 5.0) buffer, **1** (Na^+ salt B) was obtained as the sole product. It was also obtained when **1** (Na^+ salt A) was equilibrated with aqueous NaCl solution. ^1H NMR (500 MHz, $CDCl_3$): δ 7.16 (t, 2H, J = 7.9 Hz), 6.96 (d, 2H, J = 8.2 Hz), 6.63 (d, 2H, J = 7.4 Hz), 5.87−5.84 (m, 2H), 4.89 (s, 2H), 3.75 (d, 2H, J = 10.7 Hz), 3.73−3.67 (m, 2H), 3.59 (t, 2H, J = 10.6 Hz), 3.35 (td, 2H, J = 12.9, 4.4 Hz), 3.08−3.03 (m, 4H), 2.30 (td, 2H, J = 13.4, 3.9 Hz), 2.12−2.06 (m, 2H), 2.02−1.95 (m, 2H), 1.92−1.87 (m, 2H), 1.80−1.75 (m, 4H), 1.63−1.55 (m, 2H), 1.53−1.43 (m, 14H), 1.38−1.33 (m, 4H), 1.31−1.22 (m, 12H), 1.20−1.11 (m, 8H), 1.17 (s, 6H), 1.10 (s, 6H), 1.00 (d, 6H, J = 6.1 Hz). ^{13}C NMR (75 MHz, CD_2Cl_2): δ 185.2, 170.7, 159.4, 143.9,

(32) It was important to check the ratio with the crude equilibrium mixture. The usual drying over anhydrous $MgSO_4$ some times resulted in the formation of **1** (Na^+ salt A) regardless the original composition.

(33) Katz, A. K.; Glusker, J. P.; Beebe, S. A.; Bock, C. W. *J. Am. Chem. Soc*. **1996**, *118*, 5752−5763.

(34) For examples of intramolecular calcium ion octacoordination, read the following articles. (a) Adams, S. R.; Kao, J. P. Y.; Grynkiewicz, G.; Minta, A.; Tsien, R. Y. *J. Am. Chem. Soc.* **1988**, *110*, 3212−3220. (b) Ellis-Davies, G. C. R. *Tetrahedron Lett*. **1998**, *39*, 953−956.

(35) For introduction to this area of research, read the following articles. (a) Deisseroth, K.; Heist, E. K.; Tsien, R. W. *Nature* **1998**, *392*, 198−202. (b) Dolmetsch, R. E.; Pajvani, U.; Fife, K.; Spotts, J. M.; Greenberg, M. E. *Science* **2001**, *294*, 333−339. (c) Echevarria, W.; Leite, M. F.; Guerra, M. T.; Zipfel, W. R.; Nathanson, M. H. *Nature Cell Biol.* **2003**, *5*, 440−446.

132.8, 121.5, 117.9, 116.4, 82.7, 80.2, 78.4, 78.1, 76.0, 68.9, 46.9, 43.2, 38.2, 36.9, 36.3, 35.7, 33.5, 33.2, 32.5, 31.0, 30.5, 24.8, 24.5, 23.8, 23.7, 18.3, 14.4. MS *m/z* (FAB, relative intensity): 1187 ($M^+ - 1 + 2Na$, 28), 1165 ($M^+ + Na$, 100), 1143 ($M^+ + 1$, 90), 1098 (16), 1001 (11), 957 (4), 583 (3), 23 (71). HRMS (FAB): calcd for $C_{64}H_{95}O_{16}Na_2$ ($M^+ + Na$) 1165.6416, found 1165.6431. Crystals of **1** (Na^+ salt B) were obtained from DCM−MeOH (1:5) at 3 °C.

General Procedure for Exchange Reactions of 1 (Na^+ Salt A) or 1 (Ca^{2+} Salt). A sample (5 mg) of **1** (Na^+ salt A) or **1** (Ca^{2+} salt) in DCM (5 mL) was equilibrated with different saturated metal salt solutions in 4 N HCl or water (5 mL). After vigorous stirring for 1 h, the organic layer was separated and concentrated. The composition of the crude equilibrium mixture was checked by ^1H NMR and mass (MALDI and FAB) spectral analysis (Tables 1 and 2).

SCH 351448 1 (K^+ Salt). Ms *m/z* (FAB, relative intensity): 1197 ($M^+ + K$, 2), 1159 ($M^+ + 1$, 10), 1143 (2), 1114 (2), 973 (1), 599 (10), 555 (6), 55 (100). HRMS (FAB): calcd for $C_{64}H_{96}O_{16}K$ ($M^+ + 1$) 1159.6335, found 1159.6366.

SCH 351448 1 (Rb^+ Salt). MS *m/z* (FAB, relative intensity): 1290 ($M^+ + Rb$, 4), 1205 ($M^+ + 1$, 19), 1159 (6), 1143 (11), 1098 (2), 525 (2), 245 (3), 85 (100). HRMS (FAB): calcd for $C_{64}H_{96}O_{16}{}^{85}Rb$ ($M^+ + 1$) 1205.5816, found 1205.5844.

SCH 351448 1 (Mg^{2+} Salt). Ms *m/z* (FAB, relative intensity): 1166 ($M^+ - 1 + Mg$, 20), 1143 ($M^+ + 1$, 18), 1098 (4), 1001 (3), 623 (6), 605 (10), 583 (8), 23 (100). HRMS (FAB): calcd for $C_{64}H_{95}O_{16}{}^{24}Mg$ ($M^+ + 1$) 1143.6471, found 1143.6460.

SCH 351448 1 (Ca^{2+} Salt). ^1H NMR (500 MHz, $CDCl_3$): δ 7.17 (t, 2H, J = 7.9 Hz), 7.01 (d, 2H, J = 8.3 Hz), 6.60 (d, 2H, J = 7.4 Hz), 6.20−6.16 (m, 2H), 5.92 (s, 2H), 3.79−3.73 (m, 2H), 3.72 (d, 2H, J = 11.2 Hz), 3.46 (t, 2H, J = 10.3 Hz), 3.27 (td, 2H, J = 12.4, 4.2 Hz), 3.10 (t, 2H, J = 9.5 Hz), 3.03 (t, 2H, J = 10.7 Hz), 2.36−2.30 (m, 2H), 2.07−2.02 (m, 2H), 2.00−1.93 (m, 2H), 1.89 (t, 2H, J = 13.0 Hz), 1.80−1.74 (m, 4H), 1.63−1.41 (m, 22H), 1.38−1.30 (m, 10H), 1.25−1.12 (m, 8H), 1.11 (s, 6H), 1.03 (s, 6H), 0.98 (d, 6H, J = 6.6 Hz). ^{13}C NMR (75 MHz, CD_2Cl_2): δ 185.4, 173.5, 160.4, 142.7, 132.6, 120.2, 119.1, 116.9, 82.9, 81.6, 78.0, 77.8, 76.8, 71.5, 46.5, 41.5, 38.6, 36.8, 36.5, 36.1, 34.6, 33.3, 33.2, 32.1, 30.5, 30.2, 25.0, 24.4, 24.2, 24.1, 19.1, 13.7. MS *m/z* (FAB, relative intensity): 1159 ($M^+ + 1$, 65), 1143 (20), 1114 (13), 1098 (5), 1017 (4), 973 (4), 599 (27), 23 (100). HRMS (FAB): calcd for $C_{64}H_{95}O_{16}Ca$ ($M^+ + 1$) 1159.6246, found 1159.6266. Crystals of **1** (Ca^{2+} salt) were obtained from MeOH at room temperature.

SCH 351448 1 (Cu^{2+} Salt). ^1H NMR (500 MHz, $CDCl_3$): δ 7.12 (t, 2H, J = 7.8 Hz), 6.84 (d, 2H, J = 8.1 Hz), 6.63 (d, 2H, J = 7.4 Hz), 5.75−5.72 (m, 2H), 4.58 (s, 2H), 3.87 (d, 2H, J = 10.8 Hz), 3.85−3.82 (m, 2H), 3.61 (t, 2H, J = 10.5 Hz), 3.08−3.00 (m, 6H), 2.35−2.29 (m, 2H), 2.07−1.98 (m, 6H), 1.81−1.74 (m, 4H), 1.67−1.35 (m, 22H), 1.33−1.05 (m, 18H), 1.13 (s, 6H), 1.09 (s, 6H), 0.97 (d, 6H, J = 6.7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 184.0, 169.9, 156.4, 141.6, 131.0, 120.6, 115.3, 82.4, 80.6, 78.0, 77.9, 75.5, 68.7, 46.9, 42.7, 38.0, 37.0, 35.8, 35.7, 35.6, 33.3, 33.0, 32.3, 30.2, 29.9, 24.6, 24.2, 23.9, 23.5, 18.0, 13.9. MS *m/z* (FAB, relative intensity): 1181 (M^+, 4), 1159 (8), 1143 (3), 1114 (2), 1098 (1), 599 (1), 39 (100). HRMS (FAB): calcd for $C_{64}H_{94}O_{16}{}^{63}Cu$ (M^+) 1181.5838, found 1181.5811.

SCH 351448 1 (Mn^{2+} Salt). MS *m/z* (FAB, relative intensity): 1228 ($M^+ - 1 + Mn$, 20), 1144 (3), 1143 (2), 1098 (1), 1041 (2), 685 (13), 667 (30), 649 (8), 55 (100). HRMS (FAB): calcd for $C_{64}H_{93}O_{16}Mn_2$ ($M^+ - 1 + Mn$) 1227.5225, found 1227.5256.

SCH 351448 1 (Co^{2+} Salt). MS *m/z* (FAB, relative intensity): 1235 ($M^+ - 1 + Co$, 18), 1143 (4), 1049 (1), 693 (9), 675 (16), 618 (4), 305 (7), 55 (100). HRMS (FAB): calcd for $C_{64}H_{93}O_{16}Co_2$ ($M^+ - 1 + Co$) 1235.5128, found 1235.5151.

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Supporting Information Available: Experimental procedures and a collection of ^1H- and ^{13}C NMR spectra of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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