Natural Products Synthesis

Stereoselective Total Synthesis of the Ionophore Antibiotic Zincophorin**

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The ionophore antibiotics, often polyethers and peptides, are known to transport a specific metal ion or specific metal ions through membranes in organisms.[1,2] Ionophore antibiotics have also been shown to transport a specific metal cation by forming a metal chelate. Zincophorin (**1**), isolated from a strain of *Streptomyces griseus*, is a unique ionophore antibiotic with a very high affinity for Zn^{II} cations.[3,4] This affinity also extends to Mg^{II} ions.[3,4] Several novel structural features of zincophorin, as well as its strong antibacterial properties, render this ionophore a worthy target for synthetic exploration.[5] The Danishefsky group reported the first total synthesis of zincophorin methyl ester based on a hetero-

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[**] Financial support from the Ministry of Education, Culture, Sports, Science, and Technology, Japan (a Grant-in-Aid for Scientific Research (A) (No. 12304042) and a Grant-in-Aid for Scientific Research on Priority Areas (A): "Exploitation of Multi-Element Cyclic Molecules" (No. 13029003)) is gratefully acknowledged.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

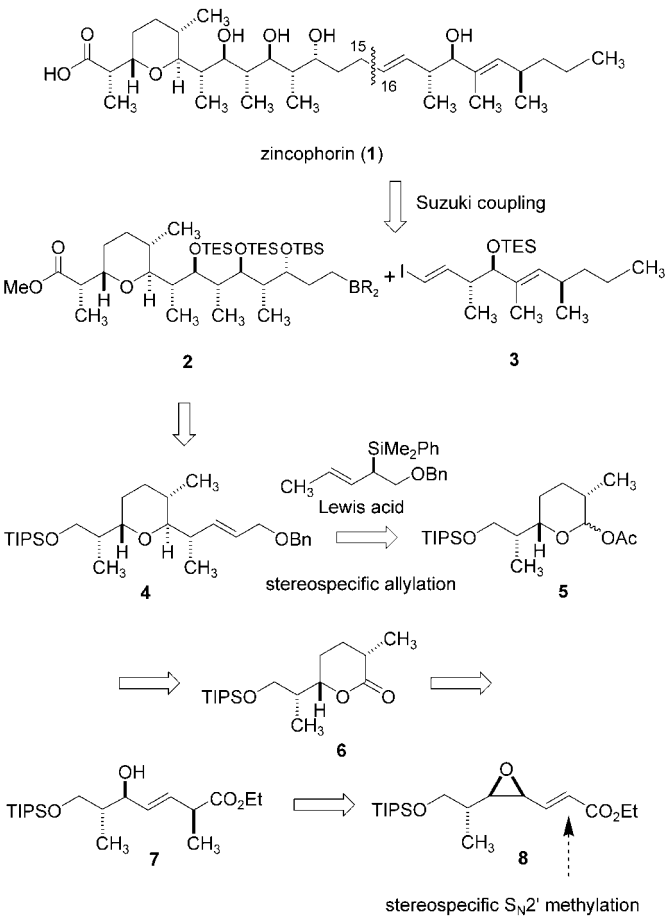
 DOI: 10.1002/ange.200460434 © 2004 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Diels–Alder strategy,[6] and very recently Cossy and coworkers also reported the successful synthesis of zincophorin methyl ester.[7] However, the total synthesis of zincophorin (**1**) itself has not been reported, probably because of the difficulty in characterizing the free acid.[6]

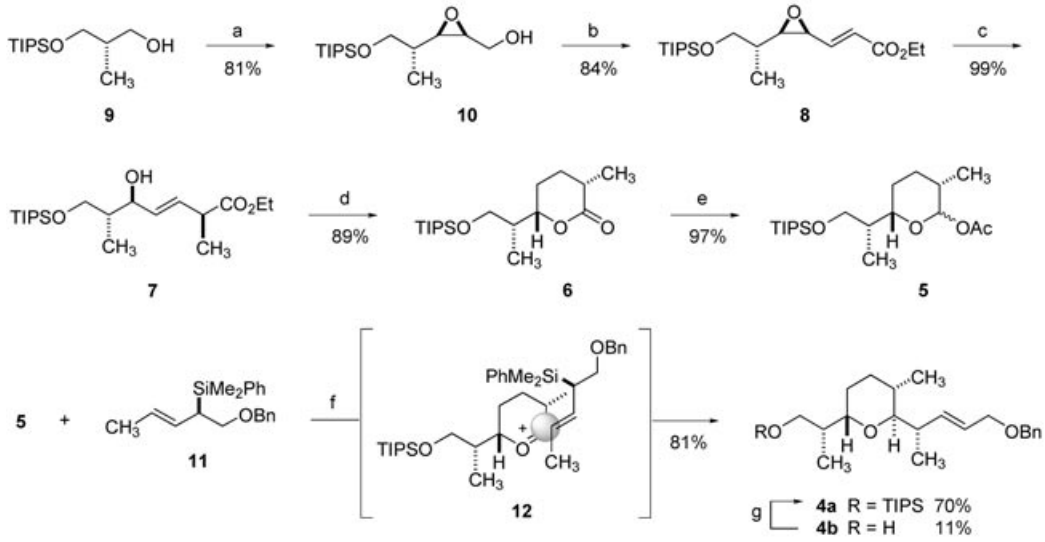
We report herein the first and highly stereoselective total synthesis of the free acid zincophorin based on our original strategy of acyclic stereocontrol (Scheme 1). Retrosynthetically, zincophorin (**1**) was disconnected at the C15–C16 bond and divided into the fragments **2**, which contains a terminal alkyl borane, and **3**, with a trisubstituted double bond and a terminal vinyl iodide. These two fragments could be connected by a Suzuki coupling.[8] Fragment **2**, which consists of the 2,5,6-trisubstituted tetrahydropyran moiety and a polypropionate-derived chain, contains eight contiguous asymmetric carbon atoms as well as two further stereogenic centers. Thus, the stereoselective synthesis of the trisubstituted tetrahydropyran moiety and construction of the contiguous stereogenic centers are the key points in the present synthesis.

To prepare the requisite trisubstituted tetrahydropyran **4** highly stereoselectively, we designed a synthetic route via the δ-lactone **6**. A stereospecific allylation reaction of the lactol **5** with a chiral allyl silane was envisaged. We planned to construct the crucial intermediate **6** stereoselectively by an S_N2' methylation reaction of the *cis*-epoxy unsaturated ester **8** to give **7**, since it has been reported that α methylation of δ-lactones that bear an alkyl substituent at the C5 position generally leads to a 1:1 mixture of stereoisomers.[9]

The trisubstituted tetrahydropyran **4** was synthesized highly stereoselectively according to Scheme 2. Thus, (*S*)-3-(triisopropylsilyloxy)-2-methylpropanol (**9**) was converted into the expected *Z* unsaturated ethyl ester by a Swern oxidation followed by a Horner–Emmons reaction with the



Scheme 1. Retrosynthetic analysis of zincophorin (**1**).



Scheme 2. Synthesis of the trisubstituted tetrahydropyran **4a**: a) 1. Swern oxidation; 2. $(o\text{-}CH_3C_6H_4O)_2P(O)CH_2CO_2Et$, NaH, THF, −78 °C, 92% (2 steps); 3. DIBAL-H, THF, −78→0 °C; 4. MCPBA, CH_2Cl_2, −78→−45 °C, 88% (2 steps); b) 1. Swern oxidation; 2. $(i\text{PrO})_2P(O)CH_2CO_2Et$, *t*BuOK, THF, −78 °C, 84% (2 steps); c) Me_2Zn–CuCN, DMF, 0 °C, 99% (α/γ = 97:3); d) 1. H_2, PtO_2, EtOH, room temperature; 2. $Ti(O\text{i}Pr)_4$, DMF, 100 °C, 89% (2 steps); e) DIBAL-H, CH_2Cl_2, −78 °C, then Ac_2O, pyridine, DMAP, −78 °C→RT, 97%; f) $TiCl_3(O\text{i}Pr)$, CH_2Cl_2, −78 °C, 81%; g) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 100%. Bn = benzyl, DIBAL-H = diisobutylaluminium hydride, MCPBA = *m*-chloroperoxybenzoic acid, DMF = *N*,*N*-dimethylformamide, DMAP = 4-(dimethylamino)pyridine, RT = room temperature, TIPS = triisopropylsilyl, Tf = trifluoromethanesulfonyl.

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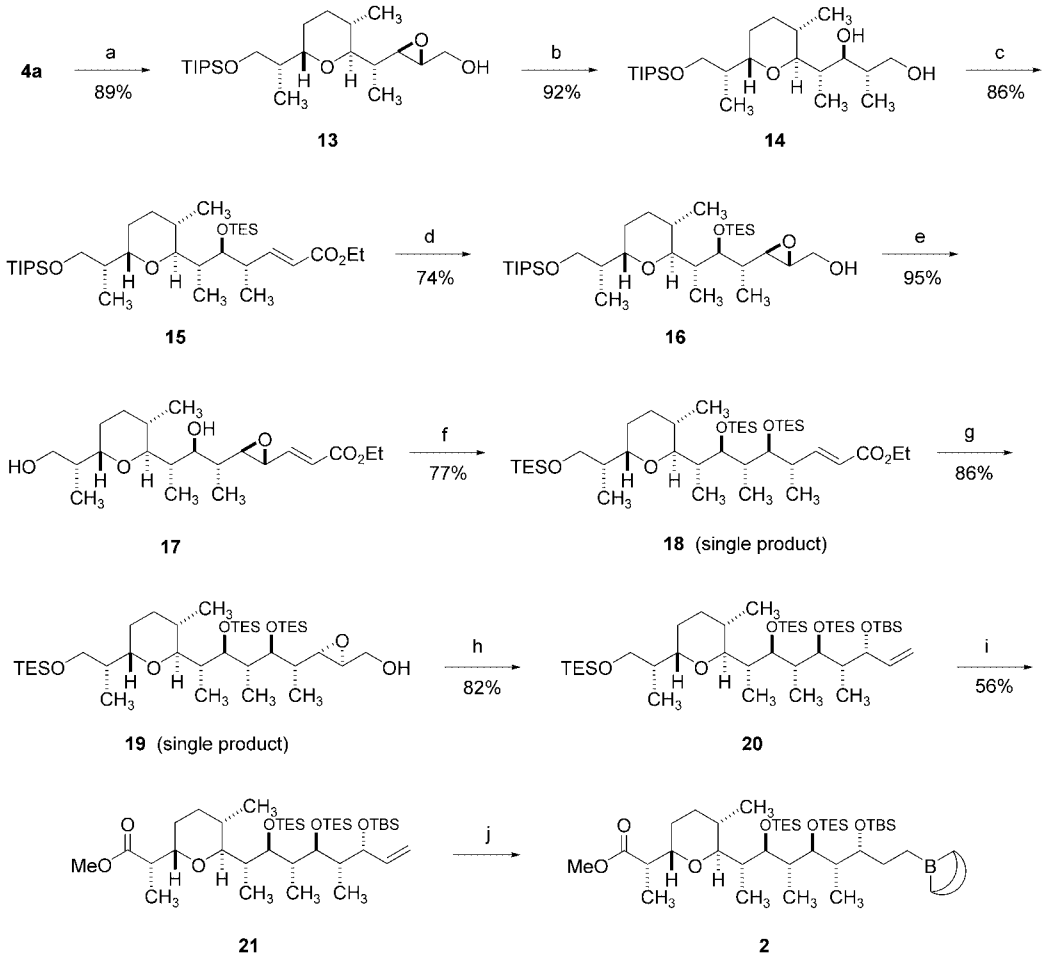
Ando reagent[10] in 92% yield ($Z/E = 93:7$). After reduction of the ester with DIBAL-H, the resulting Z allylic alcohol was oxidized stereoselectively with MCPBA to afford the β-epoxy alcohol **10** ($\alpha/\beta = 7:93$, 88% yield),[11] which was then transformed into the epoxy unsaturated ester **8** by a Swern oxidation followed by a Horner–Emmons reaction in 84% yield from **10**. The crucial S_N2' methylation reaction of **8** occurred highly stereoselectively in the presence of a new Me_2Zn–CuCN reagent in DMF recently discovered in our laboratory,[12] to give the product of S_N2' methylation **7** quantitatively. The *syn* product was obtained exclusively in this reaction and was readily converted into the key α-methyl-δ-lactone intermediate **6** by a two-step reaction sequence: 1) hydrogenation of the alkene double bond, and 2) lactonization with $Ti(OiPr)_4$ in DMF. The lactone was transformed routinely into the acetal **5** by reduction with DIBAL-H followed by acetylation of the resulting lactol in a one-pot operation.

The key allylation of **5** with the chiral allyl silane **11**[13] occurred stereospecifically in the presence of the Lewis acid $TiCl_3(OiPr)$ in CH_2Cl_2 at −78 °C to give **4a** and **4b**, each as a single stereoisomer, in 70 and 11% yield, respectively. The latter compound was readily converted quantitatively into the former by treatment with TIPSOTf. As expected, the allylation reaction of **5** proceeded highly stereoselectively, probably via the transition state **12** in which the double bond of the oxonium ion derived from **5** and that of the allyl silane occupy the favorable antiperiplanar conformation with maximum overlap of the π orbitals.[14]

Thus, the critical intermediate **4a** with five stereogenic centers was synthesized with complete stereoselectivity. Compound **4a** was then converted into the single α-epoxy alcohol **13** by removal of the benzyl group followed by asymmetric epoxidation (Scheme 3).[15] Upon the treatment of **13** with the Gilman reagent,[11b] compound **14** with seven stereogenic centers was obtained in 92% yield as the only



Scheme 3. Synthesis of **2**: a) 1. Ca, NH_3, THF, −78 °C; 2. $Ti(OiPr)_4$, D-(−)-DIPT, TBHP, MS (4 Å), CH_2Cl_2, −23 °C, 89% (2 steps); b) Me_2CuLi, Et_2O, −40→0 °C, 92%; c) 1. TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; 2. Swern oxidation; 3. $(iPrO)_2P(O)CH_2CO_2Et$, *t*BuOK, THF, −78 °C, 86% (3 steps); d) 1. DIBAL-H, THF, −78→0 °C; 2. $Ti(OiPr)_4$, D-(−)-DET, TBHP, MS (4 Å), CH_2Cl_2, −23 °C, 74% (2 steps), ($\alpha/\beta = 5:95$); e) 1. Swern oxidation; 2. $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C; 3. TBAF, THF, room temperature, 95% (3 steps); f) 1. Me_3Al–D_2O, CH_2Cl_2, −30 °C; 2. TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 77% (2 steps); g) 1. DIBAL-H, THF, −78→0 °C, 98%; 2. MCPBA, CH_2Cl_2, −78→0 °C, 88%; h) 1. PPh_3, I_2, imidazole, benzene, room temperature; 2. BuLi, THF, −78 °C, 92% (2 steps); 3. TBSCl, DMAP, DMF, room temperature, 89%; i) 1. Swern oxidation; 2. $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH, H_2O, THF, room temperature, then $TMSCHN_2$, CH_2Cl_2, room temperature, 56% (3 steps); j) 9-BBN, THF, 60 °C. DIPT = diisopropyl tartrate, TBHP = *tert*-butyl hydroperoxide, MS = molecular sieves, TES = triethylsilyl, DET = diethyl tartrate, TBAF = tetrabutylammonium fluoride, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl, 9-BBN = 9-borabicyclo[3.3.1]nonane.

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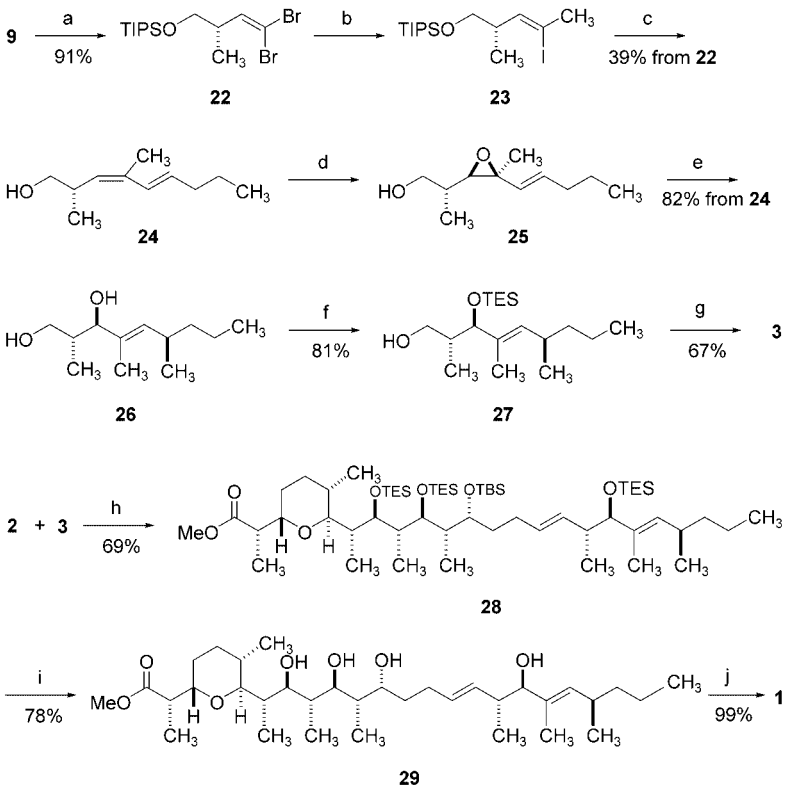
product. It was transformed into the unsaturated ester **15** by a three-step reaction sequence: 1) protection of the hydroxy groups as TES ethers, 2) Swern oxidation by the Spur protocol,[16] and 3) Horner–Emmons reaction, in 86% overall yield. After the reduction of **15** with DIBAL-H, asymmetric epoxidation of the resulting allylic alcohol furnished the epoxy alcohol **16** stereoselectively. Compound **16** was subjected to another Swern oxidation/Horner–Emmons olefination sequence, followed by removal of the silyl protecting groups with TBAF, to afford the epoxy unsaturated ester **17** (95% for the three steps). The key methylation reaction of **17** proceeded stereospecifically with a Me_3Al–water system[17] to give a single product with nine asymmetric carbon atoms. The treatment of this compound with TESOTf then afforded **18** (77% yield over two steps). When **18** was treated with DIBAL-H in THF and then with MCPBA in CH_2Cl_2, the α-epoxy alcohol **19** was obtained as a single product in 86% yield.[18]

Compound **19** was transformed in turn into the terminal olefin **20** by a three-step reaction sequence: 1) conversion into an epoxy iodide, 2) treatment with BuLi to give an allylic alcohol,[19] and 3) protection of the secondary alcohol with TBSCl (82% yield over three steps). All that remained in the synthesis of fragment **2** was the oxidation of the TES-protected primary alcohol moiety to the carboxylic acid and subsequent hydroboration of the terminal olefin. These transformations were performed successfully by a Swern oxidation[16] followed by $NaClO_2$ oxidation of the resultant aldehyde to the carboxylic acid, esterification with $TMSCHN_2$ (56% for the three steps), and further treatment of the product **21** with 9-BBN in THF. Thus, fragment **2** with ten stereogenic centers was synthesized in a straightforward and highly stereoselective manner by our original strategy based on acyclic stereocontrol.



Scheme 4. Synthesis of **3** and total synthesis of zincophorin (**1**): a) 1. Swern oxidation; 2. CBr_4, PPh_3, pyridine, CH_2Cl_2, 0°C, 91% (2 steps); b) Me_2CuLi, Et_2O, −78°C, then I_2, −40°C; c) 1. (*E*)-$CH_3(CH_2)_2CH{=}CHZrCp_2Cl$, $ZnBr_2$, $[PdCl_2(PPh_3)_2]$, DIBAL-H, THF, room temperature; 2. HF, THF, room temperature, 39% from **22**; d) MCPBA, CH_2Cl_2, −60→−30°C, (α/β = 7:93); e) Me_2CuLi, Et_2O, −78°C, 82% from **24**; f) 1. TESOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 96%; 2. HF–py, pyridine, THF, 0°C, 84%; g) 1. Dess–Martin periodinane; 2. $CrCl_2$, CHI_3, THF, 0°C, 67% (2 steps); h) aqueous Cs_2CO_3, $AsPh_3$, $[PdCl_2(dppf)]$, THF, DMF, room temperature, 69%; i) TEAF, DMF, room temperature, 78%; j) LiOH, H_2O, MeOH, THF, room temperature, then 1N HCl, 99%. py = pyridine, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, TEAF = tetraethylammonium fluoride.

We next focused on the synthesis of fragment **3**. Although we presumed that the synthesis of **3** would be difficult because of its densely functionalized stereostructure, we were able to synthesize **3** in a straightforward fashion according to Scheme 4. Thus, the dibromomethylene compound **22**, readily prepared from the same starting material **9** as used for the synthesis of fragment **2**, was treated with the Gilman reagent in Et_2O, and the *Z* vinyl copper species generated in situ was quenched with iodine to give the *Z* vinyl iodide **23**.[20] A Negishi coupling[21] with an (*E*)-1-pentenylzirconium reagent then furnished the desired *Z*,*E* conjugated diene **24** (39% yield over three steps). The homoallylic alcohol **24** was oxidized with MCPBA to produce the β-epoxy alcohol **25** stereoselectively (α/β = 7:93). The key S_N2' methylation reaction of **25** proceeded upon treatment with the Gilman reagent[22] in a highly stereoselective manner to afford the *syn* compound **26** as a single product in 82% yield from **24**. After protection of the secondary hydroxy group in **26** with a TES group in two steps, the product **27** was transformed into fragment **3** by Dess–Martin oxidation followed by the Takai reaction[23] in 67% yield.

With the segments **2** and **3** in hand, we had reached a critical stage in the total synthesis: the coupling of the two segments, removal of the protecting groups, and final hydrolysis of the methyl ester moiety. The key Suzuki coupling reaction[8,24] of **2** and **3** was performed under the conditions given in Scheme 4 and resulted in the formation of **28** in 69% yield. The removal of the four silyl groups in **28** with tetraethylammonium fluoride (TEAF) in DMF afforded zincophorin methyl ester (**29**) in 78% yield.

All spectral data of the synthetic compound **29** and its optical rotation value ($[\alpha]_D^{26} = +22$ ($c = 0.64$, $CHCl_3$)) were identical with those of the methyl ester derived from natural zincophorin ($[\alpha]_D^{24} = +21$ ($c = 2.0$, $CHCl_3$)).[4] Finally, hydrolysis of the methyl ester **29** with aqueous LiOH in MeOH and THF, followed by acidification with 1N HCl, provided zincophorin (**1**) in nearly quantitative yield.[25] The synthetic compound (free acid) was identical in all respects with naturally occurring zincophorin,[3] including spectroscopic

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characteristics (^{1}H and ^{13}C NMR, IR, and mass spectra), melting point (m.p. 65–69 °C; lit.:[3] m.p. 66–70 °C), and optical rotation ($[\alpha]_D^{24} = -1.9$ ($c = 0.59$, $CHCl_3$); lit.:[3] $[\alpha]_D^{25} = 0$ ($c = 1.0$, $CHCl_3$)).

In summary, we have reported the first, highly stereoselective total synthesis of zincophorin free acid through an original strategy based on acyclic stereocontrol without the use of aldol methodologies.

Received: April 24, 2004 [Z460434]

Keywords: allylation · antibiotics · natural products · stereoselectivity · total synthesis

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[25] To isolate zincophorin free acid, it is essential to protonate the lithium carboxylate by acidification and to isolate the resulting carboxylic acid by extraction, as purification by column chromatography on silica gel gives an inseparable mixture of zincophorin and zincophorin–metal (probably magnesium) complexes.

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