## Natural Products Synthesis

## Stereoselective Total Synthesis of the Ionophore Antibiotic Zincophorin\*\*

Kei Komatsu, Keiji Tanino, and Masaaki Miyashita\*

The ionophore antibiotics, often polyethers and peptides, are known to transport a specific metal ion or specific metal ions through membranes in organisms.<sup>[1,2]</sup> 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<sup>II</sup> cations.<sup>[3,4]</sup> This affinity also extends to Mg<sup>II</sup> ions.<sup>[3,4]</sup> Several novel structural features of zincophorin, as well as its strong antibacterial properties, render this ionophore a worthy target for synthetic exploration.<sup>[5]</sup> The Danishefsky group reported the first total synthesis of zincophorin methyl ester based on a hetero-

[*] K. Komatsu, Dr. K. Tanino, Prof. Dr. M. Miyashita	
Division of Chemistry, Graduate School of Science	
Hokkaido University	
060-0810 Sapporo (Japan)	
Fax: (+81)11-706-4920	
E-mail: miyasita@sci.hokudai.ac.jp	

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

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.<sup>[8]</sup> 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  $\delta$ -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  $\alpha$  methylation of  $\delta$ -lactones that bear an alkyl substituent at the C5 position generally leads to a 1:1 mixture of stereoisomers.<sup>[9]</sup>

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



stereospecific S<sub>N</sub>2' methylation

Scheme 1. Retrosynthetic analysis of zincophorin (1).



Scheme 2. Synthesis of the trisubstituted tetrahydropyran 4a: a) 1. Swern oxidation; 2.  $(o-CH_3C_6H_4O)_2P(O)CH_2CO_2Et$ , NaH, THF,  $-78^{\circ}C$ , 92% (2 steps); 3. DIBAL-H, THF,  $-78 \rightarrow 0^{\circ}C$ ; 4. MCPBA,  $CH_2Cl_2$ ,  $-78 \rightarrow -45^{\circ}C$ , 88% (2 steps); b) 1. Swern oxidation; 2.  $(iPrO)_2P(O)CH_2CO_2Et$ , tBuOK, THF,  $-78^{\circ}C$ , 84% (2 steps); c) Me<sub>2</sub>Zn–CuCN, DMF, 0°C, 99% ( $\alpha/\gamma = 97:3$ ); d) 1. H<sub>2</sub>, PtO<sub>2</sub>, EtOH, room temperature; 2. Ti(*OiPr*)<sub>4</sub>, DMF, 100°C, 89% (2 steps); e) DIBAL-H, CH<sub>2</sub>Cl<sub>2</sub>,  $-78^{\circ}C$ , then Ac<sub>2</sub>O, pyridine, DMAP,  $-78^{\circ}C \rightarrow RT$ , 97%; f) TiCl<sub>3</sub>(*OiPr*), CH<sub>2</sub>Cl<sub>2</sub>,  $-78^{\circ}C$ , 81%; g) TIPSOTf, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>, 0°C, 100%. Bn = benzyl, DIBAL-H = diisobutylaluminium hydride, MCPBA = *m*-chloroperoxybenzoic acid, DMF = N,N-dimethyl-formamide, DMAP = 4-(dimethylamino)pyridine, RT = room temperature, TIPS = triisopropylsilyl, Tf = trifluoromethanesulfonyl.

Ando reagent<sup>[10]</sup> 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  $\beta$ -epoxy alcohol **10** ( $\alpha/\beta = 7:93$ , 88% yield),<sup>[11]</sup> 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  $S_N 2'$  methylation reaction of 8 occurred highly stereoselectively in the presence of a new Me<sub>2</sub>Zn-CuCN reagent in DMF recently discovered in our laboratory,<sup>[12]</sup> to give the product of  $S_N 2'$  methylation 7 quantitatively. The syn product was obtained exclusively in this reaction and was readily converted into the key  $\alpha$ -methyl- $\delta$ -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**<sup>[13]</sup> occurred stereospecifically in the presence of the Lewis acid TiCl<sub>3</sub>(*OiPr*) in CH<sub>2</sub>Cl<sub>2</sub> 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  $\pi$  orbitals.<sup>[14]</sup>

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



**Scheme 3.** Synthesis of **2**: a) 1. Ca, NH<sub>3</sub>, THF,  $-78^{\circ}$ C; 2. Ti(OiPr)<sub>4</sub>, D-(-)-DIPT, TBHP, MS (4 Å), CH<sub>2</sub>Cl<sub>2</sub>,  $-23^{\circ}$ C, 89% (2 steps); b) Me<sub>2</sub>CuLi, Et<sub>2</sub>O,  $-40 \rightarrow 0^{\circ}$ C, 92%; c) 1. TESOTf, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>,  $0^{\circ}$ C; 2. Swern oxidation; 3. (*i*PrO)<sub>2</sub>P(O)CH<sub>2</sub>CO<sub>2</sub>Et, tBuOK, THF,  $-78^{\circ}$ C, 86% (3 steps); d) 1. DIBAL-H, THF,  $-78 \rightarrow 0^{\circ}$ C; 2. Ti(OiPr)<sub>4</sub>, D-(-)-DET, TBHP, MS (4 Å), CH<sub>2</sub>Cl<sub>2</sub>,  $-23^{\circ}$ C, 74% (2 steps), ( $\alpha/\beta = 5:95$ ); e) 1. Swern oxidation; 2. (EtO)<sub>2</sub>P(O)CH<sub>2</sub>CO<sub>2</sub>Et, NaH, THF,  $0^{\circ}$ C; 3. TBAF, THF, room temperature, 95% (3 steps); f) 1. Me<sub>3</sub>Al–D<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>,  $-30^{\circ}$ C; 2. TESOTf, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>,  $0^{\circ}$ C, 77% (2 steps); g) 1. DIBAL-H, THF,  $-78 \rightarrow 0^{\circ}$ C, 98%; 2. MCPBA, CH<sub>2</sub>Cl<sub>2</sub>,  $-78 \rightarrow 0^{\circ}$ C, 88%; h) 1. PPh<sub>3</sub>, I<sub>2</sub>, imidazole, benzene, room temperature; 2. BuLi, THF,  $-78^{\circ}$ C, 92% (2 steps); 3. TBSCl, DMAP, DMF, room temperature, 89%; i) 1. Swern oxidation; 2. NaClO<sub>2</sub>, NaH<sub>2</sub>PO<sub>4</sub>, 2-methyl-2-butene, tBuOH, H<sub>2</sub>O, THF, room temperature, then TMSCHN<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 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 = tetra-butylammonium 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,<sup>[16]</sup> 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<sub>3</sub>Al-water system<sup>[17]</sup> 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  $\alpha$ -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,<sup>[19]</sup> 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 TESprotected primary alcohol moiety to the carboxylic acid and subsequent hydroboration of the terminal olefin. These transformations were performed successfully by a Swern oxidation<sup>[16]</sup> followed by NaClO<sub>2</sub> oxidation of the resultant aldehyde to the carboxylic acid, esterification with TMSCHN<sub>2</sub> (56% for the three steps)

with TMSCHN<sub>2</sub> (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.

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.<sup>[20]</sup> A Negishi coupling<sup>[21]</sup> 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  $\beta$ -epoxy alcohol 25 stereoselectively ( $\alpha/\beta = 7:93$ ). The key S<sub>N</sub>2' methylation reaction of 25 proceeded upon treatment with the Gilman reagent<sup>[22]</sup> in a highly stereoselective manner to afford the syn compound 26 as a single product in 82% yield from 24. After



**Scheme 4.** Synthesis of **3** and total synthesis of zincophorin (1): a) 1. Swern oxidation; 2. CBr<sub>4</sub>, PPh<sub>3</sub>, pyridine, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 91% (2 steps); b) Me<sub>2</sub>CuLi, Et<sub>2</sub>O, -78 °C, then I<sub>2</sub>, -40 °C; c) 1. (*E*)-CH<sub>3</sub>(CH<sub>2</sub>)<sub>2</sub>CH=CHZrCP<sub>2</sub>Cl, ZnBr<sub>2</sub>, [PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>], DIBAL-H, THF, room temperature; 2. HF, THF, room temperature, 39% from **22**; d) MCPBA, CH<sub>2</sub>Cl<sub>2</sub>, -60  $\rightarrow$  -30 °C, ( $\alpha/\beta$ =7:93); e) Me<sub>2</sub>CuLi, Et<sub>2</sub>O, -78 °C, 82% from **24**; f) 1. TESOTf, 2,6lutidine, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 96%; 2. HF-py, pyridine, THF, 0 °C, 84%; g) 1. Dess-Martin periodinane; 2. CrCl<sub>2</sub>, CHI<sub>3</sub>, THF, 0 °C, 67% (2 steps); h) aqueous Cs<sub>2</sub>CO<sub>3</sub>, AsPh<sub>3</sub>, [PdCl<sub>2</sub>(dppf)], THF, DMF, room temperature, 69%; i) TEAF, DMF, room temperature, 78%; j) LiOH, H<sub>2</sub>O, MeOH, THF, room temperature, then 1 N HCl, 99%. py=pyridine, dppf=1,1'-bis(diphenylphosphanyl)ferrocene, TEAF=tetraethylammonium fluoride.

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<sup>[23]</sup> 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<sup>[8,24]</sup> 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  $([a]_{D}^{26} = +22 \ (c = 0.64, \text{ CHCl}_3))$  were identical with those of the methyl ester derived from natural zincophorin  $([a]_{D}^{24} = +21 \ (c = 2.0, \text{ CHCl}_3))$ .<sup>[4]</sup> 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.<sup>[25]</sup> The synthetic compound (free acid) was identical in all respects with naturally occurring zincophorin,<sup>[3]</sup> including spectroscopic



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

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.

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

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