Published in final edited form as:

Nat Prod Rep. 2009 April ; 26(4): 560–571.

Challenges in the Synthesis of a Unique Mono-Carboxylic Acid Antibiotic (+)-Zincophorin

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Abstract

(+)-Zincophorin, also referred to as M144255 or griseochellin, is a polyoxygenated ionophoric antibiotic that was isolated from *Streptomyces griseus* in 1984. It possesses strong in vivo activity against Gram-positive bacteria and *Clostridium coelchii*. Its methyl ester was reported in a patent as having strong inhibitory properties against influenza WSN/virus with reduced toxicity for the host cell. Its ability to strongly bind with Zn^{2+} , which is also present in its X-ray structure, is the basis for its name. Over the last two decades, (+)-zincophorin has attracted an impressive array of synthetic efforts including Danishefsky's first total synthesis along with two recent elegant total syntheses reported by Cossy and Miyashita as well as our own formal total synthesis. This Account provides a comparison of the different synthetic efforts on this novel mono-carboxylic acid antibiotic and documents its interesting isolation, structure determination, and biological activities.

1. Introduction

Many polyoxygenated ionophore-containing natural products exhibit potential antibiotic properties.¹ The activity is due to the ability of ionophores to form lipophilic complexes with various cations such as Li^+ , Na^+ , and K^+ , and divalent alkaline earth cations such as Ca^{2+} and Mg^{2+} . These complexes have been shown to affect the proton-cation exchange processes across biological membranes to disrupt transmembrane ion concentration gradient, which is required for the proper functioning and survival of microorganisms.

In 1984, Gräfe et al. reported the isolation of a new mono-carboxylic acid ionophore, griseocholin, from cultured strains of *Streptomyces griseus*.² The structure was established first by extensive NMR experiments.³ Just two months later, Poyser et al. reported the isolation of another ionophore named M144255 from the same strains.⁴ Its three-dimensional structure as well as the absolute configuration was finally ascertained by X-ray diffraction of the zinc-magnesium salt. In fact, it turned out that these two compounds are structurally identical. Based on its high affinity for divalent cations especially zinc, it was given the trivial name, (+)-zincophorin **1** [Figure 1].

Generally, chelation to the metal cation such as Zn is in an octahedral manner through the C1-carboxylate and the two hydroxy groups at C11 and C13 from TWO molecules of (+)-zincophorin. The pyran oxygen and the hydroxy groups at C9 and C19 do not coordinate to

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the metal cation [see ChemDraw replication of half of the octahedral Zn-complex in Figure 2]. Complexation studies have established a stability order: $\text{Zn} \approx \text{Cd} > \text{Mg} > \text{Sr} \approx \text{Ba} \approx \text{Ca}$. The carbon backbone of (+)-zincophorin suggests propionic acid as initiator and a number of propionic acid subunits were involved in the biosynthesis. The relatively low oxygen content of the metabolite may be accounted for by assuming either excessive reduction or dehydration following the assembly of the polyketide chain.

(+)-Zincophorin possesses strong *in vivo* activity against Gram-positive bacteria and *Clostridium coelchii* at ≤ 1 ppm, at which levels it also inhibited methane production and favorably altered volatile fatty acid ratios in the *in vitro* rumen fermentations. No biological activity has been observed against Gram-negative bacteria, yeasts and fungi. The ammonium and sodium salts of (+)-zincophorin exhibited significant anticoccidial activity against *Eimeria tenella* W/CAM in quantities above 100 $\mu\text{g}/\text{embryo}$ when using the mortality of chicken embryos as a measure. Moreover, its methyl ester **2** [Figure 1] was reported in a patent as having strong inhibitory properties against influenza WSN/virus with reduced toxicity for the host cells⁵.

In light of the novel structure and its profile of biological activity, (+)-zincophorin has attracted an impressive array of synthetic efforts over the last two decades. Three elegant total syntheses have been accomplished along with several synthetic approaches. This Account focuses on the comparison of the different strategies to introduce the first disconnection, to construct the functionalized tetrahydropyran moiety, to address the complex stereochemical issues, particularly of the challenge in accessing the *anti,anti,anti,anti* acyclic stereopentade array at C8–C12.

2. Danishefsky's Total Synthesis

In 1987, Danishefsky reported the first total synthesis of (+)-zincophorin⁶. Disconnection of C16–C17 *E*-olefin by Julia olefination generated two fragments: C1–C16 **3** and C17–C25 **4**, respectively [Scheme 1]. Other key strategies to install all the stereocenters in both fragments are shown in Scheme 1. They include Ferrier reaction to install C2 and C3 stereocenters, and Cram-chelation controlled Grignard addition for C13 and C14 in **3**; and Mukaiyama aldol for C18 and C19 in **4**. The most crucial and attractive one is the two-fold application of the Lewis acid-induced hetero Diels-Alder [hetero-DA] reaction to generate tetrahydropyran skeleton and install 6 contiguous stereocenters from C6 to C11.

2.1. Synthesis of the C1–C16 Fragment

The starting point of C1–C16 fragment is the known chiral aldehyde (*S*)-**5**, which underwent Cram addition with Grignard agent **6** to afford aldehyde **7** in 48% overall yield with complete stereocontrol at C13 [Scheme 2]. Chelation-controlled [see inside the box] hetero-Diels-Alder [hetero-DA] reaction of **7** with siloxydiene **8** generated the cycloadduct dihydropyranone **9** as a 7:1 mixture of diastereomers in favor of the C10–C11 *anti* relationship. In the proposed transition state, chelation of magnesium between the aldehyde carbonyl and OBOM favors a cyclic conformer [see inside the box]. Thus, the approaching nucleophilic diene would attack the *Re*-face of the aldehyde to establish the *anti* relationship between C11 and C12.⁷ In addition, this chelation also favors a sterically less encumbered *exo*-cycloaddition approach, thereby leading to an *anti*-pattern at C10 and C11 in the resulting pyran ring.⁸

Luche reduction of the cycloadduct **9** followed by a Ferrier reaction [see **step-e** and **f**] with 3,4-dimethoxybenzyl alcohol afforded **10** in 78% overall yield [Scheme 2]. Hydroboration [**step-g**] of C8–C9 double bond from α -face installed the required stereochemistry at C8. Though the configuration of C9 was opposite to that required in (+)-zincophorin, it was easily reversed through an oxidation/reduction sequence [**step-h** and **i**], leading to pyran **11** in 50%

overall yield. Pyran **11** was finally converted in 6 steps [step-j through o] into the C7–C16 fragment **12** ready for the second hetero-Diels-Alder [hetero-DA] reaction. It is noteworthy that the strategy of employing hetero-Diels-Alder cycloaddition followed by disassembly to access acyclic stereochemical manifold is very clever because it takes advantage of the better ability of cyclic systems in controlling of stereochemical courses, thereby providing an efficient construction of the challenging C8–C12-*anti,anti,anti,anti*-stereopentade.

In the presence of $\text{BF}_3 \cdot \text{OEt}_2$, the second hetero DA reaction of aldehyde **12** with siloxydiene **13** afforded pyranone **15** in 5–10% yield, as well as the aldol product **14** in 60% yield as a 4:1 mixture at C7 [Scheme 3]. The aldol product **14** could be easily transformed to **15** by acid-catalyzed cyclization. Introduction of the C2 and C3 stereocenters was achieved by using the carbon nucleophilic version of the Ferrier reaction with *E*-crotyltrimethylsilane [step-c] and generated a 3:1 mixture of the C2 epimers **16**.⁹ The ensuing 7 standard transformations [step-d through j] led to the C1–C16 fragment **3** in 18% overall yield.

2.2. Synthesis of the C17–C25 Fragment

Asymmetric alkylation of norephedrine-derived Evans oxazolidinone **17** with methyl iodide introduced the C22 methyl group and generated aldehyde **18** in 45% overall yield over 6 steps [see step-a through f in Scheme 4].¹⁰ Mukaiyama aldol of *E*-silyl ketene acetal **19** with **18** afforded an 8:1 mixture of *threo:erythro* isomers **21** in 50% yield. Reaction proceeded via a proposed transition state shown as **20** featuring the complexation of TiCl_4 , **18** and **19** as 1:1:1 ratio.¹¹ From diol **21**, a succession of 4 standard transformations [step-g through j] provided the C17–C25 fragment **4** in 66% overall yield.

2.3. Coupling of the C1–C16 and C17–C25 Fragments

The final steps of Danishefsky's synthesis involved Julia olefination¹² of aldehyde **3** with sulfone **4** and an 8:1 mixture of *E:Z* isomers **22** was obtained [Scheme 5]. Subsequent removal of protecting groups and re-esterification of the C1 carboxylic group [step-b through e] completed the synthesis of (+)-zincophorin methyl ester **2**.

2.4. Applications of the Hetero-Diels-Alder Reaction

Danish efsky's total synthesis of (+)-zincophorin provided some of the earliest examples for demonstrating the great power of the hetero-Diels-Alder [hetero-DA] reaction in constructing complex natural products. The siloxydienes, well-known today as Danishefsky's diene, can readily reacts with aldehydes or imines to afford the corresponding heterocycles.^{13a–e} Asymmetric fashion of this cycloaddition has also been developed.^{13f} A number of complex natural products [some examples shown in Scheme 6] have been synthesized employing this powerful methodology as the key strategy.¹⁴

Overall, given the timeliness of Danishefsky's synthesis in showcasing the hereto-Diels-Alder cycloaddition as an imminent synthetic strategy, and the subsequent impact of this method on organic synthesis, this very first total synthesis remains the best synthesis of (+)-zincophorin.

3. Cossy's Total Synthesis

Cossy's total synthesis of (+)-zincophorin¹⁵ incorporated an entirely different retrosynthetic disconnection, which occurred at C12–C13 bond employing a *syn*-aldol reaction between the *Z*-enolate derived from C1–C12 fragment **23** containing the ethyl ketone and aldehyde **24** [Scheme 7]. In addition, a unique sequence of oxymercuration of cyclopropane and reduction would generate the key tetrahydropyran moiety and the C8 methyl group in **23**. Introduction of the *anti* methyl-hydroxyl array at C9–C10 in **23** and C18–C19 in aldehyde **24** would be

achieved through a chiral allenylzinc addition. Finally, the C20–25 portion of **24** would involve a Claisen rearrangement.

3.1. Synthesis of the C1–C12 Fragment

Hydroboration/oxidation of alkene **26**, derived from chiral 3-oxabicyclo[3.1.0]hexan-2-one **25**,¹⁶ would introduce the required C6 stereochemistry with a 98:2 diastereoselectivity [see **step-c** in Scheme 8]. Subsequent standard transformations afforded aldehyde **27** in 61% yield. An ensuing *anti*-aldol condensation with *E*-boron enolate of aldehyde **28** [**step-h**] followed by desilylation [**step-i**] gave rise to the oxymercuration precursor **29**.¹⁷ Subjecting **29** to the oxymercuration conditions [**step-j**] and subsequent tin hydride reduction of the primary organo-mercury intermediate [**step-k**] led to the anticipated tetrahydropyran formation through an initial cyclopropane ring-opening with an inversion of configuration at C7 and a 93:7 diastereomeric ratio [see aldehydes **30** after standard transformations of **step-l** through **p**].¹⁸ This is a very creative construction of the pyranyl moiety while controlling the C7 and C8 relative stereochemistry.

Addition of aldehyde **30** with chiral allenylzinc (*P*)-**31** [generated *in situ*]¹⁹ introduced the *anti,anti* relative configuration at C9–C10. The desired homo-propargylic alcohol **32** formed in 63% yield and with an 80/12/8 diastereoselectivity, which might arise from a mismatched transition state in this doubly asymmetric allenylation. From alcohol **32**, the remaining synthesis of C1–C12 fragment **23** was completed in 6 steps [**step-r** through **w**] with a 56% overall yield.

3.2. Synthesis of the C13–C25 Fragment

A similar allenylzinc addition to aldehydes **33** using the chiral allenylzinc reagent (*M*)-**34** gave homo-propargylic alcohol **35** in 66% yield [Scheme 9]. Alkylation of the terminal alkyne [**step-a**] in **35** and a Cram-chelation controlled addition using (*Z*)-prop-1-enylmagnesium bromide [**step-d**] afforded tertiary alcohol **36**, which was converted in to β -ketoester **38** in 88% yield using diketene **37**. The subsequent Carroll-type Claisen rearrangement²⁰ and loss of CO₂ provided unsaturated ketone **40** with an *E/Z* ratio of 96:4, thereby completing the chirality transfer from C20 to C22 via the transition state **39**. The subsequent 8 standard transformations [**step-e** through **l**] of **40** would then give rise to the C13–C25 fragment **24** in 27% overall yield.

3.3. Coupling of the C1–C12 and C13–C25 Fragments

Aldol condensation of (*Z*)-titanium enolate derived from **23** with aldehyde **24** provided the requisite *syn* relative stereochemistry at C12–C13 with *dr* > 96:4,²¹ which was controlled in a 1,3-relay manner resulting with C10–C12 being *syn* and the overall stereochemical outcome being controlled by the C10 stereocenter exclusively as predicted [Scheme 10].^{21b} The aldol product **42** was then transformed to (+)-zincophorin **1** successfully in 48% yield in 3 steps [**steps-a** through **c**].

3.4. Application of the Oxymercuration Chemistry

One of the key steps in Cossy's total synthesis of zincophorin is the oxymercuration of cyclopropane that led to a facile access to the tetrahydropyran core and the related stereochemistry. Along with other variants, such as oxymercurations of alkenes²² [**43** to **44**] and allenes²³ [**45** to **46**], this type of reaction sequence provides an effective approach to the diastereoselective synthesis of tetrahydropyran and tetrahydrofuran rings [Scheme 11]. Successful applications in total syntheses of a wide range of natural products have also been reported as shown in Scheme 11.²⁴

Cossy's excellent total synthesis parlayed the oxymercuration method beautifully into an approach toward the pyranyl ring, thereby rendering their elegant total synthesis distinctly differentiated from that of Danishefsky. In addition, Cossy elected a very different retrosynthetic bond construction at C12–C13 instead of C16–C17 adopted by Danishefsky. Consequently, Cossy cleverly employed a sequence of allenylzinc addition, Cram-chelation controlled Grignard addition, and Carroll's rearrangement to construct C13–C25 fragment and install the C22-methyl stereochemistry in the C13. However, as elegant as this sequence is while deviating from Danishefsky's work, it did bear the cost of removing the carbon group at C24.

4. Miyashita's Total Synthesis

In contrast to Danishefsky and Cossy's total syntheses, Miyashita employed a Suzuki-Miyaura coupling as a retrosynthetic connection at C15–C16 bond.²⁵ This led to two major fragments: Alkyl borane **47** and vinyl iodide **48** [Scheme 12]. A chiral crotylsilane allylation of lactol formed the tetrahydropyran moiety along with installing the C7–C8 stereocenters. The *anti,anti,anti*-stereoquadrade at C9–C12 was to be generated by a two-fold methylation of epoxide process, while introduction of C3 and C6 stereocenters in **47**, and C19 and C22 stereocenters in **48** would feature a S_N2' methylation of epoxide reaction.

4.1. Synthesis of the C1–C15 Fragment

Epoxy ester **50** was obtained from (*S*)-3-(triisopropylsilyloxy)-2-methyl-propanol **49** via 6 standard transformations [**step-a** through **f** in Scheme 13]. Ring-opening of the epoxide in **50** via an interesting S_N2' methylation using $\text{Me}_2\text{Zn}/\text{CuCN}$ afforded **51** with a regiochemical ratio of 97:3 [S_N2' to S_N2], thereby setting up the desired stereochemistry at C3 and C6 [Scheme 13].²⁶ An ensuing 3 standard transformations [**step-g** through **i**] provided the crotylation precursor **52**.

The crucial asymmetric crotylation of **52** employing chiral crotylsilane **53**²⁷ occurred stereoselectively in the presence of $\text{TiCl}_3(\text{Oi-Pr})$ to give alkene **55** as a single diastereomeric isomer in 81% yield.²⁸ The reaction likely proceeded through the transition state **54** in which the double bond of oxocarbeniumion and that of the allylsilane assumed a favorable antiperiplanar conformation for the maximum overlap of respective *p*-orbitals.

The extension of the C1–C11 fragment embedded in **55** to C1–15 in epoxy alcohol **58** commenced with an iterative process featuring epoxidations that are followed by ring-opening of epoxides [Scheme 14]. The first two epoxidations are Sharpless asymmetric epoxidations [SAE] [**step-b** and **step h**] with each being followed by a methylative ring-opening of epoxide using Gilman reagent^{29a} [**step c** and see the diol product **56**] after the 1st SAE, and $\text{Me}_3\text{Al-D}_2\text{O}$ ^{29b} [**step-l** starting from epoxide **57**] after the 2nd SAE.

The 3rd epoxidation is a substrate-controlled epoxidation using *m*-CPBA [**step-o** and see epoxy alcohol **58**]. The ring opening of this 3rd epoxide featured an α -epoxy anion elimination [**step-p** and **q**]³⁰ to give the terminal olefin **59** in 82% yield. Consequently, this entire iterative process provides a unique approach to set up the *anti,anti,anti* relative stereochemistry from C9 through C12. An ensuing 3-step reaction sequence would 15 convert alkene **59** into alkyl borane species **47** [the C1–C15 fragment] in 56% overall yield.

4.2. Synthesis of the C16–C25 Fragment

A more straightforward route was utilized for the synthesis of C16–C25 fragment **48**. As shown in Scheme 15, vinyl dibromide **60** was prepared from the same starting alcohol **49** that was used in the synthesis of C1–C15 fragment. Transformation of **60** to epoxide **61** featuring a rather unique [details unpublished] sequence of methyl cuprate addition/iodine quenching,

Negishi coupling of the *Z*-vinyl iodide intermediate, and a stereoselective substrate-controlled MCPBA-epoxidation. Subsequent S_N2' methylation of epoxide **61** with Me_2CuLi would establish the desired C19 and C22 stereochemistry in **62**. Ensuing steps featuring Swern oxidation [step-i] and Takai reaction [step-j]³¹ would lead to vinyl iodide **48** in 54 % overall yield.

4.3. Coupling of the C1–C15 and C16–C25 Fragments

Coupling of C1–C15 fragment **47** and C16–C25 fragment **48** proceeded smoothly under Suzuki-Miyaura coupling condition and provided **63** in 69% yield [Scheme 16].³² Finally, removal of the silyl group and hydrolysis of the methyl ester gave rise to (+)-zincophorin **1** in 77% overall yield.

4.4. Applications of Allylsilane Additions in Synthesis

Chiral organosilanes as one of the chiral organometallic reagents have shown great potential in stereoselective transformations. Among them, chiral crotylsilane reagent **64** developed in Paneks' group is the most attractive one in synthesis [Scheme 17].²⁸ In general, it could react with aldehydes in either an addition-elimination^{28b} (stereoselective condensation) process or an [4 + 2] annulation manner³³ to give the *syn* methyl-hydroxyl acyclic array in **65**, or functionalized dihydropyran structure in **66**. By employing this highly stereoselective reaction manifold, a number of complex natural products have been synthesized successfully with some examples shown in Scheme 17.³⁴

With that, Miyashita's beautiful work differed from both Danishefsky and Cossy's total syntheses while adopting a number of elegant strategies including Sharpless epoxidation, and Suzuki-Miyaura and Negishi cross-couplings along with the aforementioned chiral allyl silane chemistry. At the very same time, the choice of C1–C15 fragment for the key Suzuki-Miyaura coupling, and the choice of constructing the C1–C15 fragment through allyl silane addition chemistry led to a rather repetitive sequence for stalling the C9–C12 stereoquadrade. Despite the fact it was concisely executed, and by no means was it unimaginative, it still provided a laborious or tedious appearance to the entire total synthesis.

5. Hsung's Formal Total Synthesis

In 2007, Hsung's group reported a formal total synthesis of (+)-zincophorin through intercepting Miyashita's³⁵ and Cossy's³⁶ advanced intermediates [Scheme 18]. The key strategy featured the first synthetic application of an inverse electron-demand hetero [4 + 2] cycloaddition of chiral allenamide **71** with heterodiene **70**, as well as a sequence of two-fold diastereoselective hydrogenation and stereoselective crotylation to form the tetrahydropyranyl intermediate **69**.

The efforts commenced with the synthesis of heterodiene **70**, which was obtained from (*R*)-3-hydroxy-2-methylpropionic ester **72** by 4 steps and in 50% yield [Scheme 19]. The key [4 + 2] cycloaddition of heterodiene **70** with the Close auxiliary substituted allenamide **71** led to pyran **74** as a single diastereomer. This was the first time a chiral heterodiene was used in this type of cycloaddition.³⁷ The high level of diastereoselectivity is a likely result of a matched transition state, in which the heterodiene **70** with an *s-cis* conformation should approach from the less hindered π -face of the internal olefin of allenamide **71** shown in its lowest energy conformation.

By the careful selection of Pt catalyst and H_2 pressure, stereoselective hydrogenation of the C6 *exo*- and C3 *endo*-cyclic double bond was achieved and gave **76** as a single isomer [Scheme 20]. Crotylation of **76** with (*Z*)-crotylsilane generated a 3:1 diastereomeric mixture **78** at C8 and with the completed stereocontrol at C7. Formation of the desired major isomer was

proposed to be via a dominant antiperiplanar transition state **77** having the minimum gauche interaction. From pyran **78**, Miyashita's intermediate was finally synthesized in 7 steps and in 18% yield,³⁵ while the Cossy's intermediate could be obtained in 5 steps and in 30% yield.³⁶

During the investigation of hydrogenations of the hetero [4 + 2] cycloadduct **74**, the authors discovered an unusual urea-directed Stork-Crabtree hydrogenation process³⁸ and the directed hydrogenation product **79** was obtained in 50% yield [Scheme 21]. These reaction conditions could also be applied to both oxy- and aza-cycles **80** and **81**. The respective directed hydrogenation products **82** and **83** have the opposite methyl stereochemistry to the corresponding products **84** and **85** attained from heterogeneous hydrogenations. A general mechanistic model is illustrated in the box to depict a urea-directed directed pathway.

6. Highlights of Various Synthetic Approaches

Following the first total synthesis of Zincophorin by Danishefsky, several approaches have been reported for the synthesis of various Zincophorin fragments. The efforts still focused on the construction of tetrahydropyran moiety and assembling the *all-anti*-stereopentade from C8 through C12.

6.1. Approaches Toward the Tetrahydropyran Unit

In 1988, Kallmerten³⁹ reported some of the earliest and very creative preparations of C1–C11 and C12–C25 fragments [Scheme 22]. By an acid-catalyzed cyclization of **86** [step-b], tetrahydropyranyl alcohol **87** was obtained in 49% overall yield, which was transformed to tertiary allylic ether **88** in 6 steps [step-c through h]. Subsequently, a [2,3]-Wittig rearrangement was utilized to install the C10 stereocenter and provide **89** as the only isolated product. Finally, preparation of diene **90** followed by a very nifty intramolecular delivery of hydroborating reagent provided diol **91** with the desired C8–C9 *anti*-stereochemistry.

A similar sequence was again used for the preparation of the C12–C25 fragment **95** starting from the allylic ether **92**, which yielded **93** upon rearrangement in 72% yield [Scheme 23]. The following acid-catalyzed lactonization gave rise to **94**, which was then converted into **95** in 6 steps [step-a through f].

Holzapfel⁴⁰ demonstrated a selective nucleophilic substitution to install the C2 and C3 stereocenters of the zincophorin pyran core from pseudo-glycals [Scheme 24]. First, palladium-catalyzed substitution of carbonate **96** followed by reductive cleavage of the phenylsulfonyl groups yielded alcohol **97** in 55% yield. Further substitution promoted by FeCl₃ at the anomeric position of **97** using a mixture of *cis*- and *trans*-enol acetate **98** gave diacetate **99** as a 45:55 diastereomeric mixture at C2, which was further transformed to the C1–C8 fragment **100**.

Burke's strategy⁴¹ involved a very clever tandem glycolate Claisen rearrangement/ring-closing metathesis [RCM] sequence to obtain the C1–C8 fragment **104** starting from glycolate **101** [Scheme 25]. Under the standard Ireland-Claisen conditions, [3,3]-sigmatropic rearrangement afforded metathesis precursor **103** with a reasonable yield as well as selectivity via silyl ketene acetal intermediate **102**. RCM using Grubbs generation-I catalyst subsequently led to the C1–C8 fragment **104**.

6.2. Approaches Towards the Stereopentade from C8 to C12

Marshall⁴² revealed an interesting application of their well-known allenyl tin chemistry. Specifically, chiral allenyltin reagent **A** was employed to invoke a chelation-controlled addition to aldehyde **105**, leading to the *anti,anti*-stereotriade in alcohol **107** [Scheme 26]. Alcohol

107 was then carried on through 8 standard transformations [**step-a** through **h**] to intercept Danishefsky's C7–C16 fragment **12** with the epoxy alcohol **108** as a key intermediate.

At the same time, Roush⁴³ also intercepted Danishefsky's C7–C16 fragment **12** and successfully prepared the all-*anti*-stereopentade at C8–C12 featuring a unique diastereoselective crotylation of α -methyl β -hydroxy aldehyde **110** employing (*Z*)-crotyltrifluorosilane [Scheme 27]. The proposed bicyclic transition state **111** accounts for the observed stereochemical induction in diol **112**, in which the β -hydroxy substituent of the aldehyde coordinates to the silicon center. Consequently, the addition to the aldehyde occurs opposite the α -methyl group.

In 2001, Guindon⁴⁴ reported an elegant iterative iodo-cyclofunctionalization/stereoselective tin-hydride reduction strategy to construct the polypropionate stereotriade and stereopentade of Zincophorin. Iodo-cyclofunctionalization of carbamate **115** gave cyclic carbonate **117** presumably through the transition state **116**, in which the addition of the nucleophilic carbamate oxygen to the double bond occurs antiperiplanar to electrophilic iodine [Scheme 28]. A highly stereoselective tinhydride reduction of iodide **117** yielded the stereotriade **118** with good selectivity based on the previously reported *exo-cyclic* effect. This iterative sequence was used again to generate the stereopentade from C8–C12 in Danishefsky's C7–C16 fragment **12** [**step-a** through **p**].

7. Conclusion

We have summarized here elegant efforts towards the novel mono-carboxylic acid antibiotic: (+)-zincophorin. We have not only illustrated how various different synthetic methodologies can play a crucial rule in resolving the same key issues effectively, but also more importantly, we have shown how these applications can lead to much better understanding of reaction mechanism and scope, and promote further development and applications in constructing other complex natural products.

Overall in the very context of zincophorin, it is awestruck that interests in a single natural product with significant biological profiles and an above average structural complexity could spring forth applications of a very rich and impressive array of synthetic methods such as hetero-Diels-Alder reaction of Danishefsky dienes, oxymercuration of cyclopropanes, chiral allylsilane additions, inverse electron-demand hetero-Diels-Alder reactions, asymmetric aldols, cross-couplings, asymmetric epoxidations, sigmatropic rearrangements, ring-closing metathesis, Pd- π -allyl chemistry, asymmetric allenylations, Stork-Crabtree directed hydrogenation, olefinations, and iodo-cyclizations. We hope this account has highlighted an important synergy between development of synthetic methodologies and applications in natural product syntheses, and a significant insight that they mutually drive one another forward.

Biographies

Zhenlei Song obtained his Ph.D. in Organic Chemistry from Lanzhou University with Professor Yongqiang Tu. From 2005 to 2008, he was a post-doctoral associate in Professor Richard Hsung's group. Currently, he is an Associate Professor in West China School of Pharmacy, Sichuan University in China. His research interests involve total syntheses of natural products and medicinal chemistry.

Andrew G. Lohse received his B.S. in Chemistry from Calvin College in Grand Rapids, MI, in 2007, and worked with Professors Ron Blankespoor and Eric Arnoys. Since 2007, he has been pursuing a Ph.D. degree in Organic Chemistry under the supervision of Professor Richard

Hsung at University of Wisconsin at Madison while working on [4 + 3] cycloadditions employing allenamides.

Richard P. Hsung attended The University of Chicago and received his Ph.D. degree in Organic Chemistry in 1994 under supervisions of Professor Bill Wulff. After pursuing post-doctoral stays with Professor Larry Sita and Professor Gilbert Stork at Columbia University, he moved to University of Minnesota as an Assistant Professor in 1997 and was promoted to Associate Professor in 2002. He was promoted to Professor and moved to University of Wisconsin in 2006. He has co-authored over 175 publications with research interests in developing cycloaddition and annulation approaches to natural product syntheses and stereoselective methods using allenamides, ynamides, enamides, and acetals.

Acknowledgments

NIH funding [GM066055] is greatly appreciated.

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Figure 1.
(+)-Zincophorin and (+)-Zincophorin Methyl Ester.

Figure 2.
Zn-Bound (+)-Zincophorin: X-Ray Structure in ChemDraw.

Scheme 1.
Retrosynthetic Analysis [Danishefsky].

Scheme 2.

Synthesis of the C7–C16 Fragment.

Reagents and Conditions: (a) Aldehyde **5** and Grignard reagent **6**, THF, -78°C to 0°C . (b) NaH, HMPA/THF, rt. (c) ClCH_2OPh , *i*-PrNH, rt. (d) O_3 , $\text{CH}_2\text{Cl}_2/\text{MeOH}$, -78°C . (e) NaBH_4 , $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, EtOH, rt. (f) 3,4-Dimethoxybenzyl alcohol, *p*-TsOH, benzene, rt. (g) $\text{BH}_3 \cdot \text{DMS}$, 0°C , then 1.0 *N* NaOH, 30% H_2O_2 , rt. (h) Oxalyl chloride, DMSO, CH_2Cl_2 , -78°C then NEt_3 [Swern oxidation]. (i) L-Selectride, THF, -78°C . (j) DDQ, $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$, rt. (k) LiBH_4 , THF, rt. (l) TBDPSCl, THF, rt. (m) 2,2-dimethoxypropane, CSA. (n) TBAF, DMF, rt. (o) Swern oxidation.

2nd hetero-DA

Scheme 3.

Expanding the C7–C16 Fragment to the C1–C16 Fragment.

Reagents and Conditions: (a) NaBH₄, CeCl₃·7H₂O, EtOH/CH₂Cl₂, –78 °C to –15 °C. (b) Acetic anhydride, NEt₃, DMAP, CH₂Cl₂, (c) *Trans*-crotylsilane, ZnBr₂, CH₃NO₂, –20 °C. (d) NMO, OsO₄, H₂O/THF. (e) NaIO₄, NaHCO₃, H₂O/THF. (f) Jones oxidation. (g) CH₂N₂, CH₂Cl₂, rt. (h) H₂, Pd/C, rt. (i) BzCl, Pyridine, DMAP, rt. (j) *p*-TsOH, acetone.

Scheme 4.

Synthesis of the C17–C25 Fragment.

Reagents and Conditions: (a) LDA, THF, -78°C then MeI. (b) LiAlH_4 , Et_2O , 0°C . (c) Swern oxidation. (d) DIBAL-H, CH_2Cl_2 , -78°C . (e) Swern oxidation. (f) $\text{Ph}_3\text{PC}(\text{CH}_3)\text{CO}_2\text{Et}$. (g) *p*-TsCl, Pyridine, DMAP, 60°C . (h) 60 TBSOTf, NEt_3 , CH_2Cl_2 , 0°C . (i) KSPH, DMF, 45°C , 1 h. (j) $\text{PhSeSePh}/\text{H}_2\text{O}_2$, $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$, 0°C .

Scheme 5.

Coupling of C1–C16 and C17–C25 Fragments.

Reagents and Conditions: (a) Sulfone **4**, *n*-BuLi, THF, -78°C , MgBr_2 , and then, aldehyde **3**.(b) THF/MeOH, 6% Na/Hg, -40°C . (c) 1.0 *N* HCl/MeOH/THF, 50°C . (d) 2.0 *N* LiOH/MeOH/THF, 50°C , and then, 1 *N* HCl. (e) CH_2N_2 , Et_2O .

Scheme 6.
Hetero-Diels-Alder Reaction in Natural Product Synthesis.

Scheme 7.
Retrosynthetic Analysis [Cossy].

Scheme 8.

Synthesis of the C1–C12 Fragment.

Reagents and Conditions: (a) MeLi (2 equiv), THF, 0 °C then TBDPSCl, imidazole, DMF, rt. (b) MsCl, NEt₃, DMAP, CH₂Cl₂, 0 °C. (c) BH₃·THF, THF, –30 °C to rt, and then NaOH, H₂O₂. (d) PCC oxidation with 4 Å MS. (e) (EtO)₂P(O)CH₂CO₂Et, NaH, THF. (f) H₂, cat PtO₂, EtOAc. (g) DIBAL-H, toluene, –78 °C. (h) Aldehyde **28**, *c*-Hex₂BCl, EtNMe₂, Et₂O, 0 °C, and then addition of aldehydes **27**, –78 to –23 °C. (i) HF·pyridine, THF. (j) Hg(OCOCF₃)₂, CH₂Cl₂, rt then KBr/H₂O. (k) *n*-Bu₃SnH, toluene/THF, rt to 60 °C then CCl₄. (l) *t*-BuPh₂SiCl, imidazole, DMF, rt. (m) LiBH₄, THF, 20 °C to rt then NaIO₄, MeOH, rt. (n) NaClO₂, NaH₂PO₄, 2-methyl-2-butene, *t*-BuOH/H₂O, rt. (o) Me₃SiCHN₂, MeOH/C₆H₆. (p) HF·pyridine, THF. (q) DMP oxidation. (r) Lindlar [H]. (s) TBSOTf, 2,6-lutidine, CH₂Cl₂, –78 °C. (t) OsO₄, NMO, acetone/H₂O. (u) NaIO₄, THF/H₂O. (v) Et₂CuLi, Et₂O, –78 °C. (w) DMP oxidation.

Scheme 9.

Synthesis of the C13–C25 Fragment.

Reagents and Conditions: (a) *n*-BuLi, THF, $-78\text{ }^\circ\text{C}$ and then $\text{BnO}(\text{CH}_2)_2\text{-CH}_2\text{Br}$, HMPA.(b) TBAF, THF. (c) DMP oxidation. (d) (Z)-Propenyl-MgBr, $\text{MgBr}_2\cdot\text{OEt}_2$, $\text{Et}_2\text{O/THF}$, $-78\text{ }^\circ\text{C}$.(e) DIBAL-H, Et_2O , $-78\text{ }^\circ\text{C}$. (f) MsCl, *i*-Pr₂NEt, CH_2Cl_2 , $0\text{ }^\circ\text{C}$. (g) LiAlH_4 , THF, reflux.(h) *p*-TsOH, MeOH. (i) LiAlH_4 , THF, reflux. (j) TBSOTf, 2,6-lutidine, CH_2Cl_2 , $-78\text{ }^\circ\text{C}$. (k)Li, NH_3 , THF/*t*-BuOH, $-78\text{ }^\circ\text{C}$. (l) DMP oxidation.

Scheme 10.

Coupling of the C1–C12 and C13–C25 Fragments.

Reagents and Conditions: (a) NaBH_4 , MeOH, $0\text{ }^\circ\text{C}$. (b) $\text{HF}\cdot\text{pyridine}$, THF, rt. (c) LiOH , $\text{H}_2\text{O}/\text{MeOH}/\text{THF}$ (1/1/2), $50\text{ }^\circ\text{C}$, and then, 35% aq HCl.

Scheme 11.
Applications of Oxymercuration in Organic Syntheses.

Scheme 12.
Retrosynthetic Analysis [Miyashita].

Scheme 13.

Synthesis of the C1–C11 Fragment.

Reagents and Conditions: (a) Swern oxidation. (b) (*o*-CH₃C₆H₄O)₂P(O)CH₂CO₂Et, NaH, THF, -78 °C. (c) DIBAL-H, THF, -78 °C. (d) MCPBA, CH₂Cl₂, -78 °C to -45 °C. (e) Swern oxidation. (f) (*i*-PrO)₂P(O)CH₂CO₂Et, *t*-BuOK, THF, -78 °C. (g) H₂, PtO₂, EtOH, rt. (h) Ti(O*i*-Pr)₄, DMF, 100 °C. (i) DIBAL-H, CH₂Cl₂, -78 °C, and then Ac₂O, pyridine, DMAP, -78 °C, rt.

Scheme 14.

Extension of the C1-C11 Fragment to the C1-C15 Fragment.

Reagents and Conditions: (a) Ca, NH₃, THF, -78 °C. (b) Ti(Oi-Pr)₄, D-(-)-DIPT, TBHP, 4 Å MS, CH₂Cl₂, -78 °C. (c) Me₂CuLi, Et₂O, -78 to 0 °C. (d) TESOTf, 2,6-lutidine, CH₂Cl₂, 0 °C. (e) Swern oxidation. (f) (*i*-PrO)₂P(O)CH₂CO₂Et, *t*-BuOK, THF, -78 °C. (g) DIBAL-H, THF, -78 °C. (h) Ti(Oi-Pr)₄, D-(-)-DET, TBHP, 4 Å MS, CH₂Cl₂, -23 °C. (i) Swern oxidation. (j) (EtO)₂P(O)CH₂CO₂Et, NaH, THF, 0 °C. (k) TBAF, THF, rt. (l) Me₃Al-D₂O, CH₂Cl₂, -30 °C. (m) TESOTf, 2,6-lutidine, CH₂Cl₂, 0 °C. (n) DIBAL-H, THF, -78 °C. (o) MCPBA, CH₂Cl₂, -78 to 0 °C. (p) PPh₃, I₂, imidazole, benzene, rt. (q) *n*-BuLi, THF, -78 °C. (r) TBSCl, DMAP, DMF, rt. (s) Swern oxidation. (t) Lindgren oxidation. (u) TMSCHN₂, CH₂Cl₂, rt. (v) 9-BBN, THF, 60 °C.

Scheme 15.

Synthesis of the C16–C25 Fragment.

Reagents and Conditions: (a) Swern oxidation. (b) CBr_4 , PPh_3 , pyridine, CH_2Cl_2 , 0°C . (c) Me_2CuLi , Et_2O , -78°C , then I_2 , -40°C . (d) $(E)\text{-CH}_3(\text{CH}_2)_2\text{CH=CHZrCp}_2\text{Cl}$, ZnBr_2 , $[\text{PdCl}_2(\text{PPh}_3)_2]$, DIBAL-H, THF, rt. (e) HF, THF, rt. (f) MCPBA, CH_2Cl_2 , -60 to -30°C . (g) TESOTf, 2,6-lutidine, CH_2Cl_2 , 0°C . (h) HF-pyridine, pyridine, THF, 0°C . (i) DMP oxidation. (j) CrCl_2 , CHI_3 , THF, 0°C .

Scheme 16.
Coupling of the C1-15 and C16-25 Fragments.
Reagents and Conditions: **(a)** TBAF, DMF, rt. **(b)** LiOH and 1 N aq HCl.

Scheme 17.
Application of Chiral Allylsilane Additions.

Scheme 18.
Retrosynthetic Analysis [Hsung].

Scheme 19.
Inverse Demand Hetero-[4 + 2] Cycloaddition.

Scheme 20.
Key Hydrogenations and Crotylation.

Scheme 21.

A Urea-Directed Stork-Crabtree Hydrogenation.

Reagents and Conditions: (a) 10 mol% Crabtree cat, 60 psi H₂, CH₂Cl₂. (b) 5–10% Heterogeneous catalyst [Pd/C, Pt/C or Lindar], 1 atm H₂.

Scheme 22.

Kallmerten: The C1–C11 Fragment.

Reagents and Conditions: (a) Pd/C, H₂, EtOAc. (b) CSA, CH₂Cl₂. (c) TPAP, NMO, CH₂Cl₂. (d) MeCC-MgBr, THF. (e) TPAP, NMO, CH₂Cl₂. (f) MeMgBr, THF, –78 °C. (g) LiAlH₄, THF. (h) 2-Chloromethyl-4,5-dihydro-4,4-dimethyloxazole, KH, DME. (i) CF₃CO₂H, H₂O, THF, and then LiAlH₄. (j) NaIO₄, acetone-H₂O. (k) PPh₃=CH₂, THF.

Scheme 23.

Kallmerten: The C12–C25 Fragment.

(a) DIBAL-H, toluene, $-78\text{ }^{\circ}\text{C}$. **(b)** $\text{PPh}_3=\text{CH}_2$, THF. **(c)** Ac_2O , DMAP, Et_3N , CH_2Cl_2 . **(d)** $\text{CH}_3\text{C}(\text{OEt})_3$, EtCO_2H , $120\text{ }^{\circ}\text{C}$. **(e)** LiOH. **(f)** EtLi.

Scheme 24.

Holzapfel: The C1–C8 Fragment.

Reagents and Conditions: (a) $\text{ClCO}_2(i\text{-Bu})$, pyridine. (b) FeCl_3 , Ac_2O , vinyl acetate **96**. (c) 10% Pd/C, H_2 , EtOH. (d) NaOMe, MeOH, 0 °C. (e) CrO_3 , H_2SO_4 , acetone. (f) CH_2N_2 , Et_2O , 0 °C.

Scheme 25.
Burke: The C1-C8 Fragment.

Scheme 26.

Marshall: The C7–C16 Fragment.

Reagents and Conditions: (a) Red-Al, THF. (b) SAE (c) $\text{Me}_2\text{Cu}(\text{CN})\text{Li}_2$. (d) $(\text{MeO})_2\text{CMe}_2$, CSA. (e) H_2 , Pd/C. (f) TPAP/NMO oxidation. (g) Grignard reagent **109**, THF, 0°C . (h) BOMCl, *i*-Pr₂NEt.

Scheme 27.

Roush: The C7–C16 Fragment.

Reagents and Conditions: (a) 2-Methoxypropene, PPTS, CH_2Cl_2 . (b) OsO_4 , NMO, $t\text{-BuOH/THF/H}_2\text{O}$ (10:3:1). (c) NaIO_4 . (d) Vinyl lithium **114**, THF, -90°C . (e) H_2 , Pd/C. (f) BOMCl, $i\text{-Pr}_2\text{NEt}$, CH_2Cl_2 .

Scheme 28.

Guindon: The C1–C8 Fragment.

Reagents and Conditions: (a) LiOH, H₂O-THF (1:3). (b) (CH₃)₂C(OMe)₂, *p*-TsOH. (c) DIBAL-H. (d) Swern oxidation. (e) (Ph)₃P=C(Me)CO₂*t*-Bu, toluene. (f) THF-HCl (1.0 M) (1:1). (g) TBDPSCl, imidazole, CH₂Cl₂. (h) CCl₃CONCO, CH₂Cl₂, 0 °C, then K₂CO₃, *t*-BuOH, reflux. (i) I₂, AgOTf, NaHCO₃, CH₃CN. (j) *n*-Bu₃SnH, Et₃B, THF, –78 °C. (k) LiOH, H₂O-THF (1:3), and then, *p*-TsOH, THF. (l) HNMe(OMe)·HCl, Me₂AlCl, THF, –78 °C. (m) (CH₃)₂C(OMe)₂, *p*-TsOH. (n) Alkyl lithium **121**, Et₃N, and then NH₄Cl. (o) L-Selectride, THF, –78 °C. (p) BOMCl, *i*-Pr₂NEt, CH₂Cl₂.