Review

Total synthesis of borrelidin

By Tohru NAGAMITSU,*) Yoshihiro HARIGAYA,*) and Satoshi ŌMURA**),†)
(Contributed by Satoshi ŌMURA, M. J. A.)

Abstract: Borrelidin is a natural product possessing a variety of biological activities. Its total synthesis has been reported by several groups including those of Morken, Hanessian, Theodorakis and ourselves and two other synthetic studies toward the total synthesis have also been described by the groups of Haddad and Negishi. All these synthetic methods are reviewed herein.

Key words: Borrelidin; potent anti-malarial activity; asymmetric synthesis; total synthesis.

Introduction. Borrelidin (**1**), a structurally unique 18-membered macrolide, was first isolated from *Streptomyces rochei* in 1949 by Berger *et al*. as an antibiotic possessing anti-*Borrelia* activity (Fig. 1).[1] The planar structure of borrelidin was elucidated by Keller-Schierlein in 1967,[2] and its absolute configuration was determined by Anderson *et al*. by X-ray crystallography of a chiral solvate.[3] Structural and functional features of borrelidin (**1**) include a deoxypropionate subunit consisting of four 1,3-alternating *C*-methyl groups with a distinctive *syn/syn/anti* relationship at C4-C10, a *Z*/*E* cyanodiene unit at C12-C15 and a cyclopentane carboxylic acid subunit at C17. These features turned out to be identical to the previously reported antibiotic, treponemycin.[4] Interesting biological activities of borrelidin (**1**) include antibacterial activity[1),5)] which involves selective inhibition of threonyl tRNA synthetase,[6] antiviral activity,[7] anti-angiogenesis activity,[8] and inhibitory activity toward cyclin-dependent kinase Cdc28/Cln2 of *Saccharomyces cerevisiae*.[9] Biosynthesis of borrelidin (**1**) was also reported by Salas *et al*.[10),11)]

Recently, we found borrelidin to exhibit potent antimalarial activity also against chloroquine-resistant strains, both *in vitro* and *in vivo*.[12] Borrelidin (**1**) was isolated from the cultured broth of an actinomycete strain OM-0060 in a research center for tropical diseases in the Kitasato Institute. The antimalarial activities of borrelidin (**1**) and the standard anti-malarial drugs against K1 and FCR3 strains of *Plasmodium falciparum in vitro* and against *P. berghei* and *P. yoelii* ssp. NS *in vivo* were summarized in Tables I and II.[13),14)] Borrelidin shows more potent antimalarial effects than artemether, artesunate, and chloroquine, both *in vitro* and *in vivo*.

This biological profile, as well as its structural complexity, prompted substantial synthetic efforts toward the total synthesis of borrelidin. Recently, four total syntheses of borrelidin were reported by the respective groups of Morken,[15] Hanessian,[16] Theodorakis,[17] and ours,[18] and two synthetic studies toward the total synthesis have been presented.[19),20)] This review will describe all these synthetic accomplishment.

Total synthesis of borrelidin. *Morken synthesis.*[15] The first total synthesis of borrelidin (**1**) was achieved by Morken and co-workers in 2003. The synthetic features included macrolactonization of the seco acid (**A**), hydrostannylation followed by cyanation (**B**), Sonogashira coupling of the C1-C13 segment **2** with the C14-C23 segment **3** (**C**), the iridium-indanepybox catalyzed enantioselective reductive aldol reaction developed originally by the same group (**D**), and construction of the cyclopentane carboxylic acid subunit by Yamamoto asymmetric carbocyclization (**E**) (Fig. 2).

The synthesis of the northern segment **2** started with aldehyde **4** (Scheme 1). The iridium-indanepybox **5** catalyzed the reductive aldol reaction of **4** with methyl

*) School of Pharmaceutical Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641, Japan.
**) Kitasato Institute for Life Sciences and Graduate School of Infection Control Sciences, Kitasato University and The Kitasato Institute, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641, Japan.
†) Correspondence to S. Ōmura.

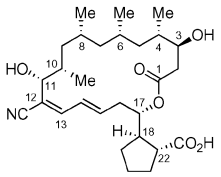


Fig. 1

Table I. *In vitro* antimalarial activities of borrelidin (**1**) and other drugs

Compound	IC_{50} (nM)	
	K1 strain	FCR3 strain
Borrelidin	1.9	1.8
Artemether	7.6	2.2
Artesunate	11	2.7
Chloroquine	357	29

Table II. *In vivo* subcutaneous antimalarial activities of borrelidin (**1**) and other drugs

Parasite	Compound	ED_{50} (mg/kg)	ED_{90} (mg/kg)
P. berghei N*	Borrelidin	0.18	2.0
	Artemether	0.95	3.8
	Artesunate	1.7	10.0
	Chloroquine	1.5	2.5
P. yoelii ssp. NS**	Borrelidin	0.07	0.8
	Artemether	1.1	5.1
	Artesunate	0.4	26.0
	Chloroquine	4.5	>100.0

* drug-sensitive strain ** chloroquine-resistant strain

acrylate, and gave the desired aldol adduct **6** with excellent enantio- (> 90% e.e.) and diastereocontrol (6 : 1 d.r.), which was then converted into the trisubstituted vinyl iodide **7** through functional group manipulation. The reductive aldol reaction with aldehyde **8** under the same conditions followed by transformation provided iodide **10** with similar stereoselectivities. The iodide **10** was subjected to Myer's asymmetric alkylation using (–)-pseudoephedrine propionamide to produce the amide **11** with high diastereoselectivity. Reductive removal of the chiral auxiliary followed by iodination of the resulting alcohol yielded iodide **12**, which was in turn treated with **7** under modified Negishi coupling conditions to furnish **13**. Following deprotection of the TBS ethers, directed hydrogenation led to diol **14** with the desired C6 stereochemistry. Conversion of **14** into **16** was carried out via the epoxide **15** in a standard manner. Subsequent alkyne formation from **16** produced the desired northern segment **2**.

The synthesis of the southern segment **3** commenced with the known chiral bis(*d*-menthyl) ester **17**, which was readily prepared from succinic acid by Yamamoto asymmetric carbocyclization (Scheme 2). Monosaponification followed by Rosenmund reduction gave aldehyde **18**, which was subjected to Brown allylboration to furnish alcohol **19** stereoselectively. The alcohol **19** was converted into the southern segment **3** by functional group manipulation involving 5 steps.

The critical cross coupling of **2** and **3** was efficiently achieved by a Sonogashira reaction that led to enyne **20**, after treatment with acetic anhydride (Scheme 3). Hydrostannylation of **20** followed by iodination and deacetylation of the resulting vinyl stannane led to a 1 : 1 mixture of vinyl iodide **21** and its regioisomer **22**. Subsequent palladium catalyzed cyanation of **21** quantitatively provided vinyl cyanide **23**. After a series of protections and deprotections, the crucial intramolecular macrolactonization of the resulting seco acid **24** was effectively accomplished by Yamaguchi procedure. Final deprotection of MOM ethers completed the first total synthesis of borrelidin (**1**).

Hanessian synthesis.[16] The second total synthesis of borrelidin (**1**) was achieved by Hanessian and coworkers in 2003. The synthetic features included macrolactonization of the seco acid (**A**), Julia-Kocienski olefination between the C1-C14 segment **25** and the C15-C23 segment **26** (**B**), Still-Gennari olefination with cyanoketone (**C**), conjugated additions of lithium dimethylcuprate to γ-substituted α,β-unsaturated esters relying on 1,2- or 1,3-induction (**D**), and Grubbs ring closing metathesis (**E**) (Fig. 3).

The synthesis of the C1-C14 segment **25** is summarized in Scheme 4. The synthesis of **28** with the desired C4 stereochemistry was established through a highly selective conjugate addition (1,2-induction) of lithium dimethylcuprate in the presence of TMSCl to a readily available enoate **27**. After conversion of **28** into the *tert*-butyl enoate **29**, the second conjugate addition (1,3-induction) under the same conditions to **29** led to a 4 :1 mixture of the desired *syn* isomer **30** and its C6 epimer. The repeated preparation of the *tert*-butyl enoate followed by conjugate addition (1,3-induction) under the same conditions gave a > 10 : 1 mixture of the adduct **32** with the desired *syn/syn* relationship and its C8 epimer. Although the additional trials for the synthesis of *tert*-butyl enoate and following cuprate conjugate

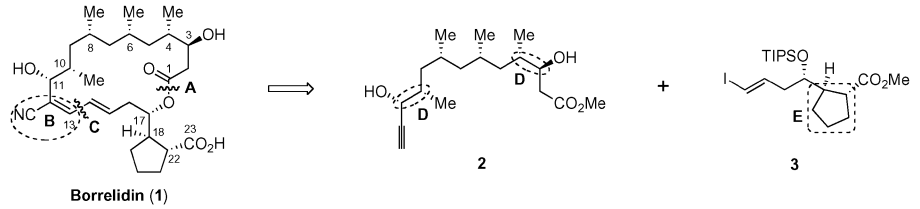
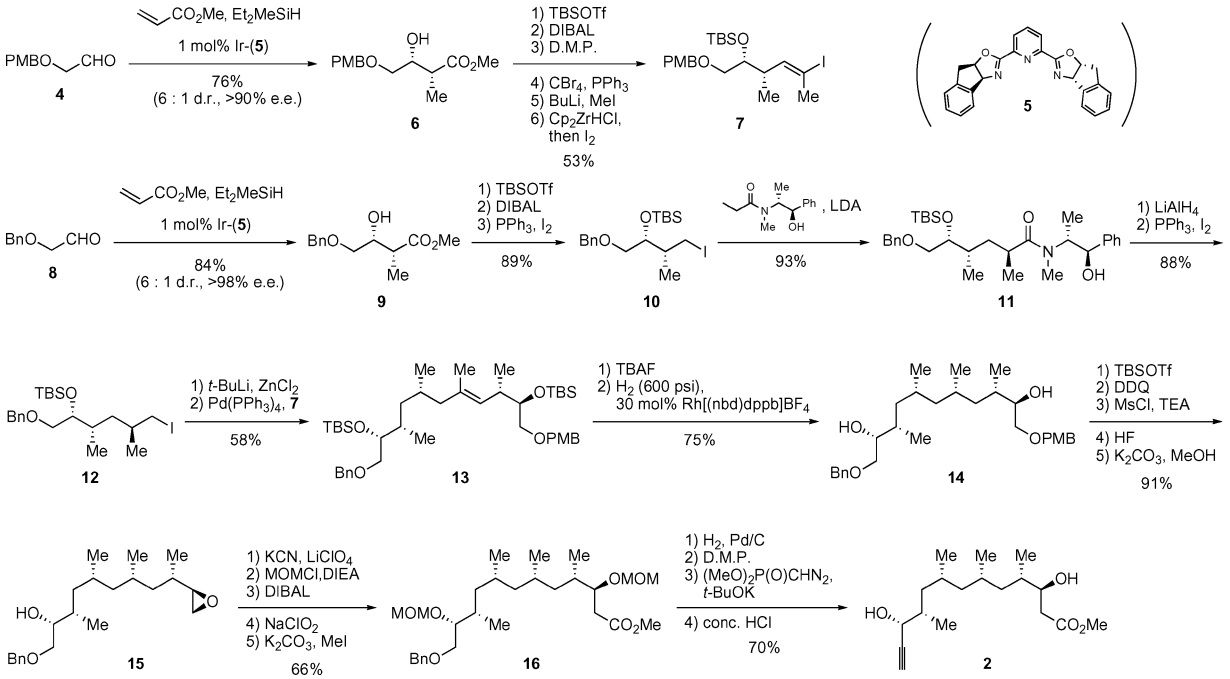
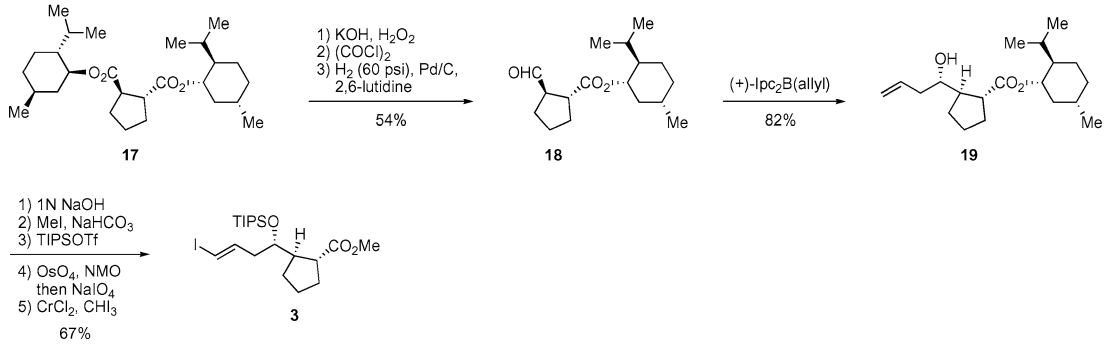


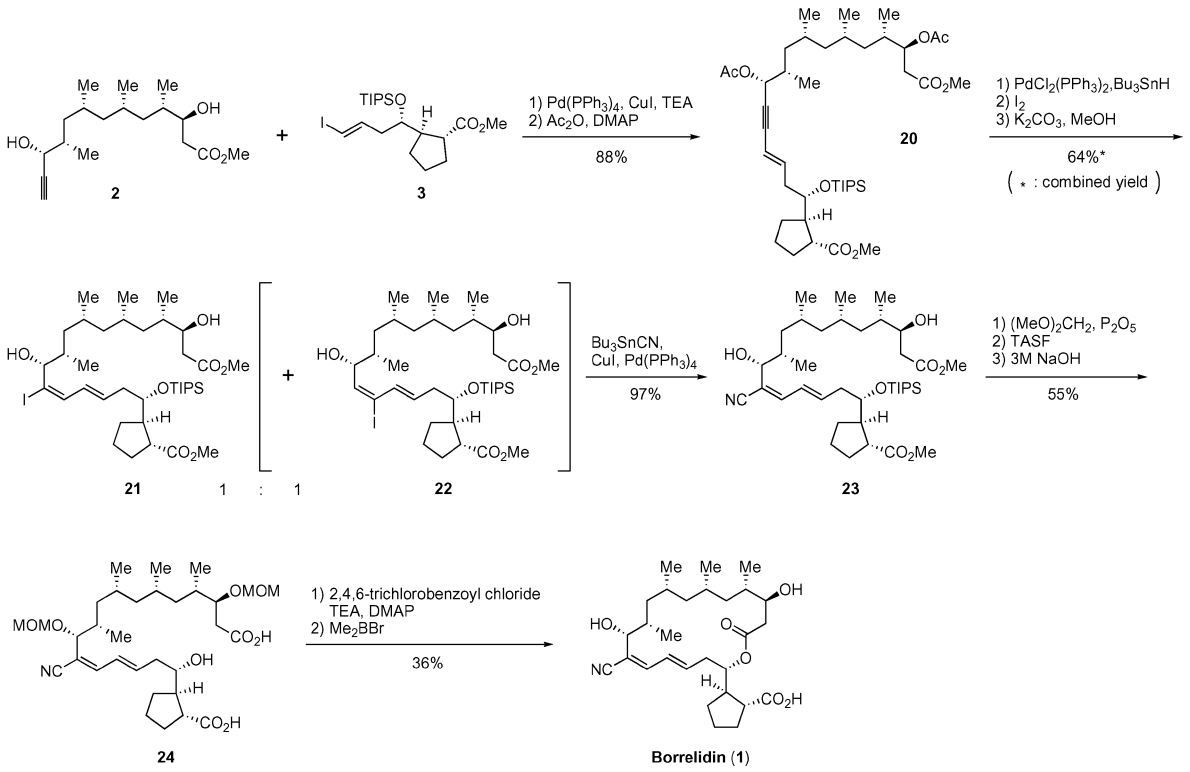
Fig. 2



Scheme 1



Scheme 2



Scheme 3

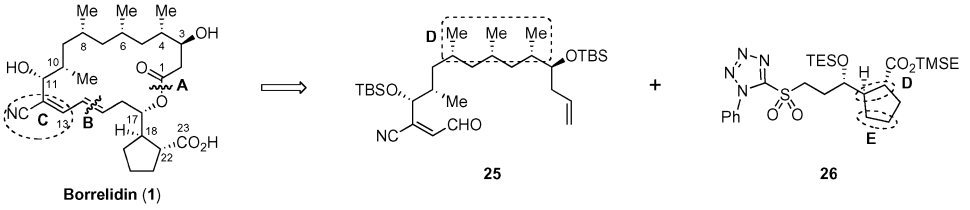
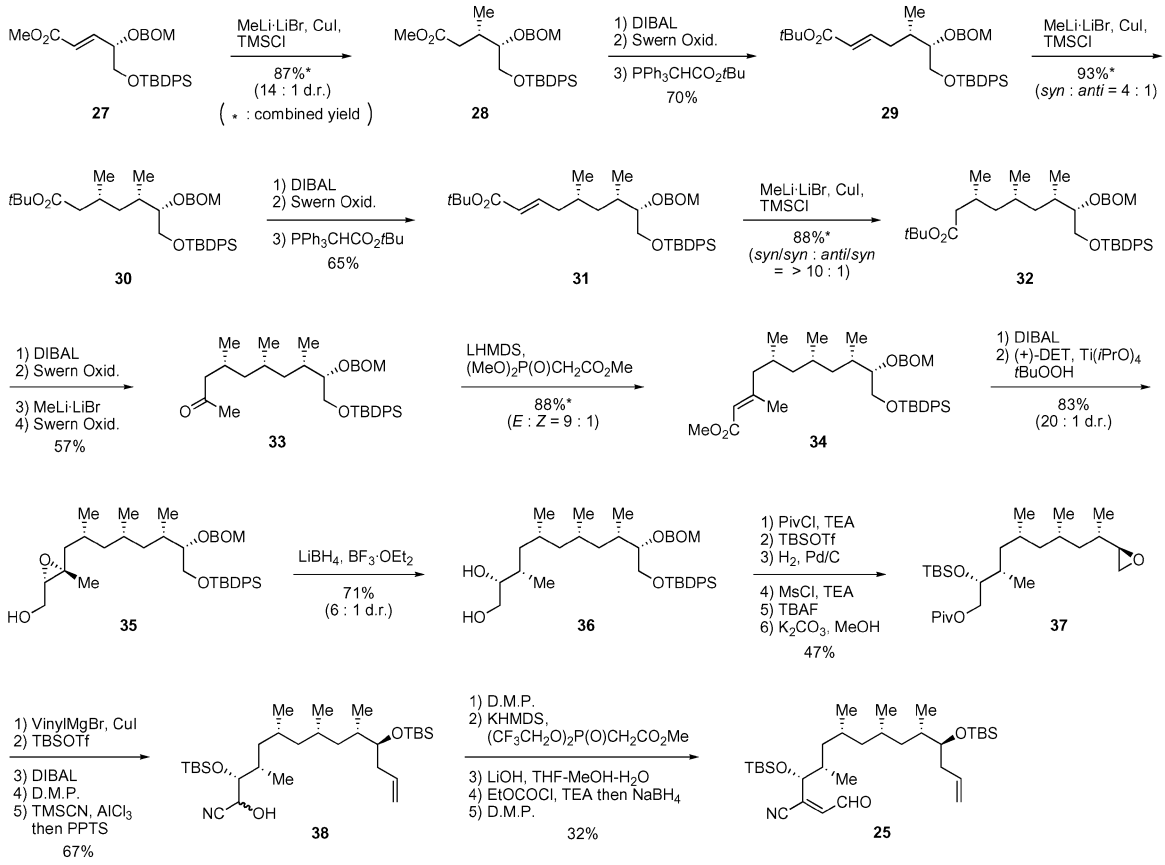


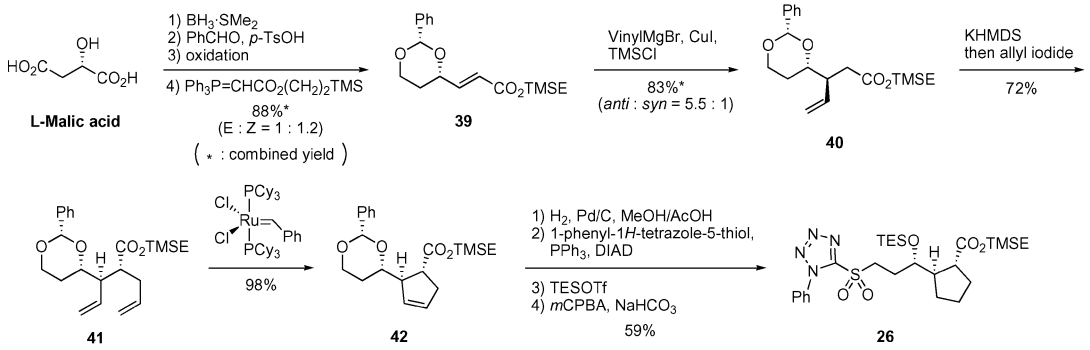
Fig. 3

addition to install the C10 stereochemistry was carried out, stereoselectivity of the resulting adducts was very low (all *syn* : *anti*/*syn*/*syn* = 2 : 1). Therefore, a different strategy was adopted to introduce the last C-methyl group at C10 having the desired stereochemistry. The adduct **32** was converted to **33** through a standard procedure, which was subjected to a Horner-Emmons reaction to produce the *trans*-trisubstituted ester **34** stereoselectively (*E* : *Z* = 9 : 1). DIBAL reduction followed by Sharpless-Katsuki epoxidation provided the desired epoxy alcohol **35** with excellent diastereoselectivity (20 : 1 d.r.). Subsequent regioselective ring opening of the epoxide by treatment with $LiBH_4$ in the presence of $BF_3 \cdot Et_2O$ furnished **36** as a major regioisomer in a ratio of 6 : 1. The diol **36** was converted to cyanohydrin **38** via epoxide **37** by a series of transformations. Finally, **38** was oxidized with Dess-Martin periodinane to the corresponding cyanoketone, which was subjected to Still-Gennari olefination, saponification, reduction through the formation of a mixed anhydride, and Dess-Martin oxidation to give the desired *Z*-trisubstituted aldehyde **25** as a single isomer.

The synthesis of C15-C23 segment **26** started with **39**, prepared from L-malic acid through a series of



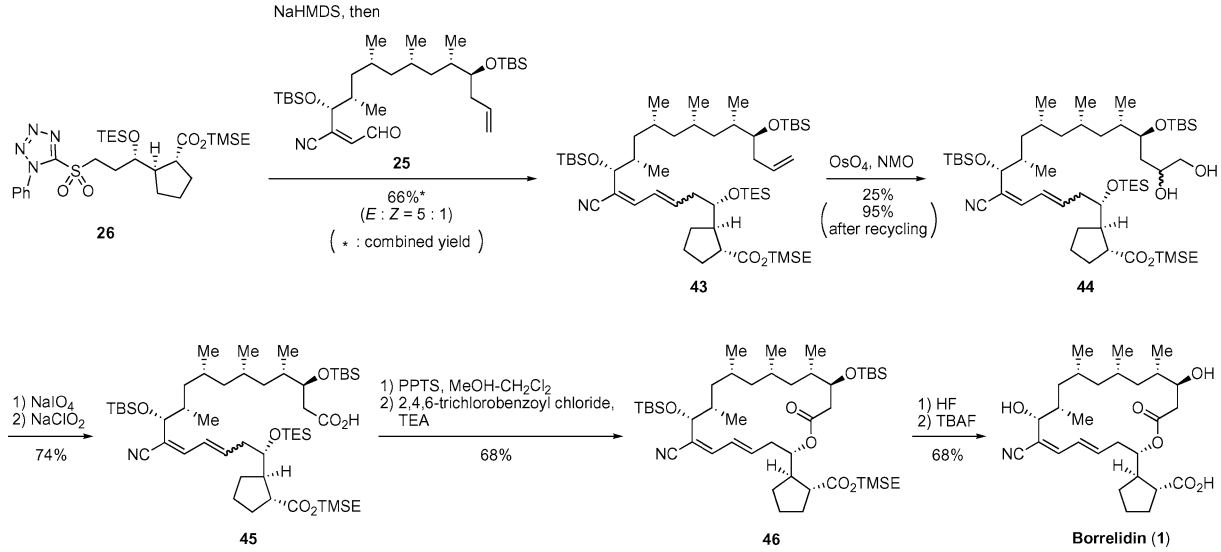
Scheme 4



Scheme 5

transformations (Scheme 5). Conjugate addition with vinylmagnesium bromide in the presence of TMSCl and copper iodide to **39** gave *C*-vinyl adduct **40** as the major isomer in a ratio of 5.5 : 1. Alkylation of potassium enolate of **40** with allyl iodide afforded allylated adduct **41** with excellent stereoselectivity, which was subjected to Grubbs ring closing metathesis to furnish cyclopentene **42** quantitatively. It was converted into the C15-C23 segment **26** by functional group manipulation.

The completion of the total synthesis of borrelidin (**1**) is described in Scheme 6. The Julia-Kocienski olefination of **25** and **26** afforded a 5 : 1 mixture of the



Scheme 6

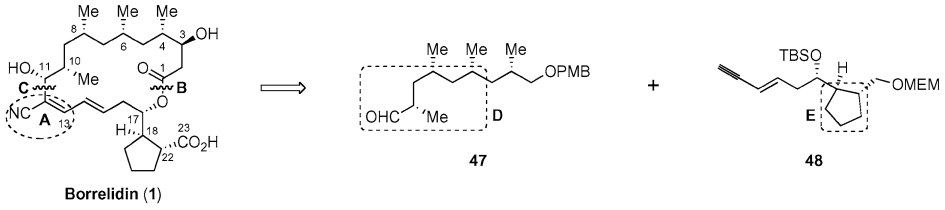


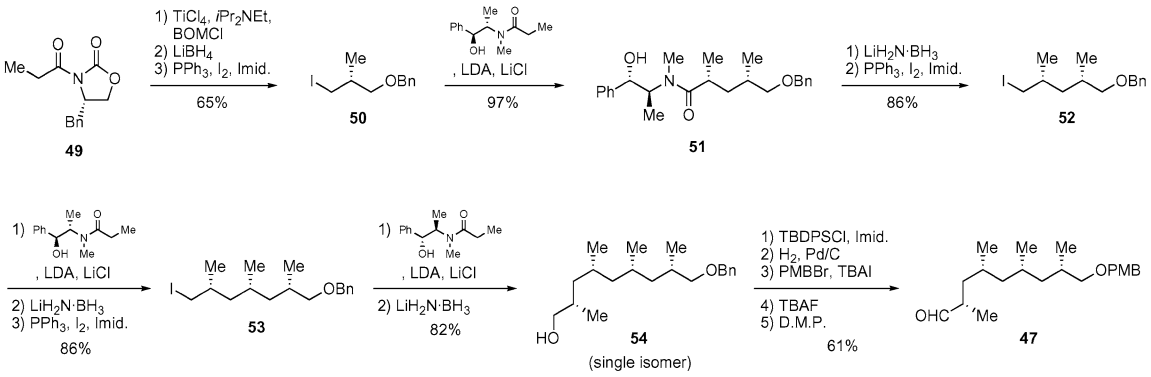
Fig. 4

desired *Z*/*E* cyanodiene **43** and its isomeric *Z*/*Z* product. Although subsequent selective dihydroxylation of the terminal olefin in **43** gave the desired diol **44** in a modest yield, the nonreacted **43** was easily recycled and converted to **44** in a high overall yield. Oxidative cleavage of **44** with $NaIO_4$ followed by Kraus oxidation of the resulting aldehyde provided the carboxylic acid **45**, which was subjected to Yamaguchi lactonization after selective deprotection of TES ether to afford **46**. Finally, deprotection of silyl protecting groups furnished the desired borrelidin (**1**).

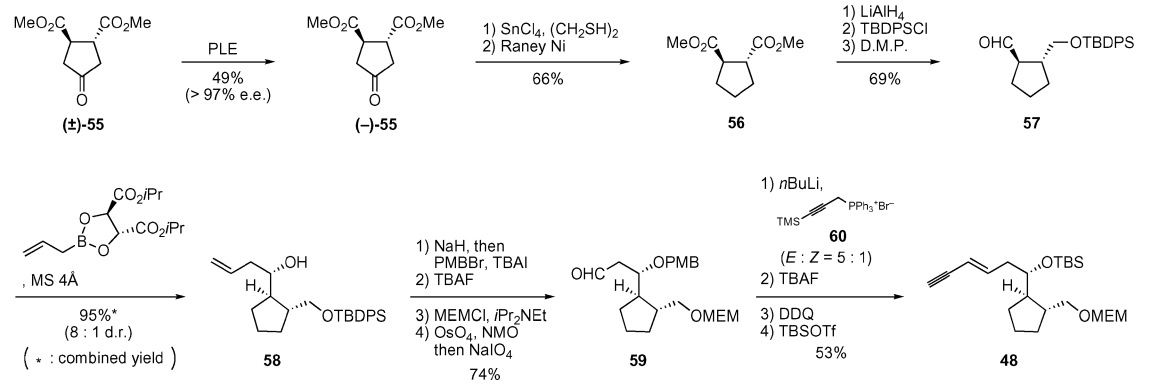
Theodorakis synthesis.[17] The total synthesis of borrelidin (**1**) by the Theodorakis group was accomplished in 2004 via a Mo(0)-catalyzed hydrostannylation followed by cyanation (**A**), macrolactonization of the seco acid (**B**), connection of aldehyde **47** and alkyne **48** (**C**), the Myer's asymmetric alkylation using pseudoephedrine propionamide (**D**), and enzymatic desymmetrization using pig liver esterase (PLE) (**E**) (Fig. 4).

The aldehyde **47** was synthesized from the readily available oxazolidinone **49** (Scheme 7). Evans asymmetric alkylation of **49** with BOMCl, reductive cleavage of the chiral auxiliary with $LiBH_4$, and iodination of the resulting alcohol gave iodide **50**, which was converted into iodide **53** by two repetitions of the following sequence of reactions: (1) Myer's asymmetric alkylation using (–)-pseudoephedrine propionamide, (2) reductive cleavage of the chiral auxiliary with $LiNH_2 \cdot BH_3$, and (3) iodination of the resulting alcohol. The additional Myer's asymmetric alkylation using (+)-pseudoephedrine propionamide of **53** followed by reductive cleavage of the chiral auxiliary with $LiNH_2 \cdot BH_3$ furnished alcohol **54** as a single diastereomer. Further functional group manipulations (5 steps) afforded the key aldehyde **47**.

The synthesis of alkyne **48** commenced with the racemic diester **55** (Scheme 8). Enzymatic desymmetrization using PLE led to the desired chiral diester



Scheme 7

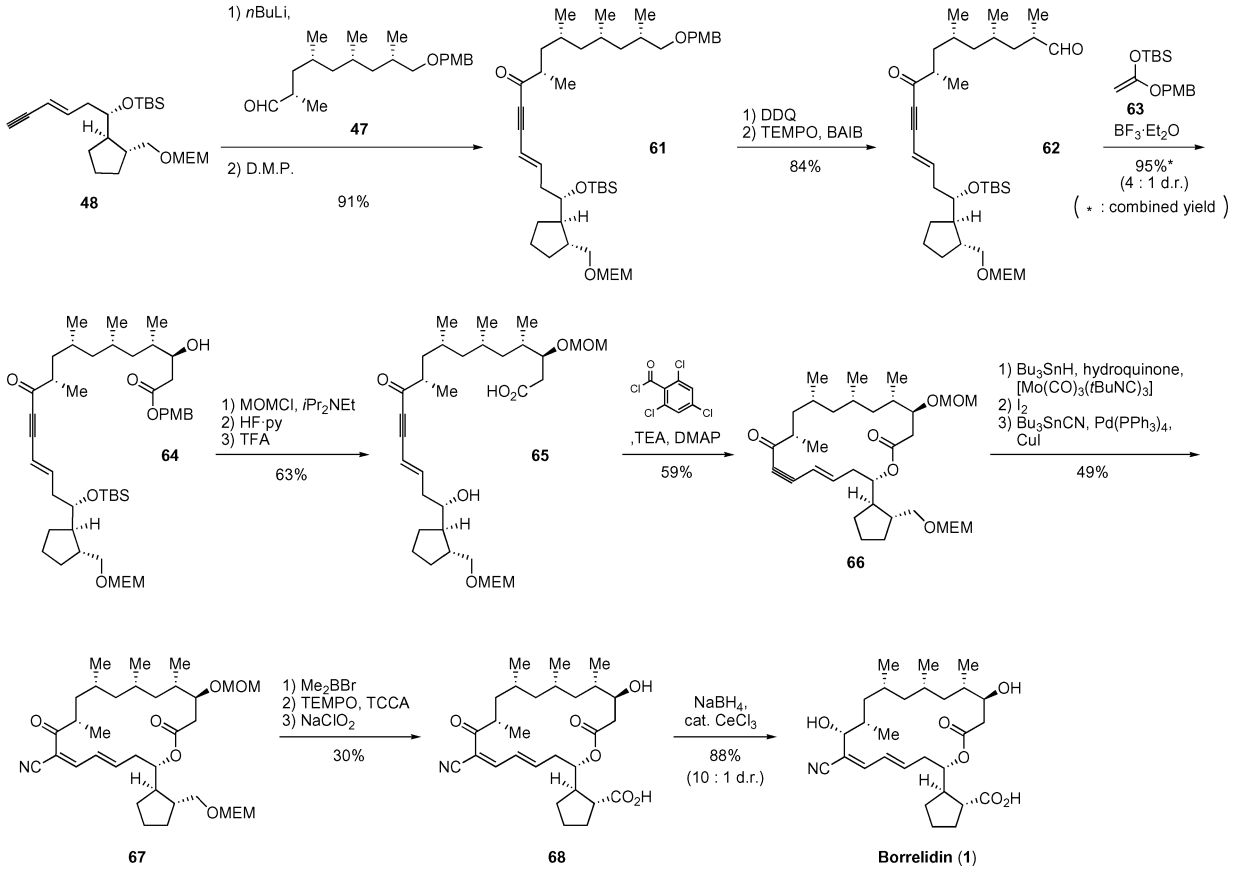


Scheme 8

(–)-55 with high enantioselectivity. Dithioacetalization of **(–)-55** followed by reductive desulfurization furnished **56**, which underwent a series of transformations to provide aldehyde **57**. Subsequent Roush allylboration of **57** gave an 8 : 1 mixture of homoallylic alcohol **58** with the desired C17 stereochemistry and its epimer. The alcohol **58** was converted into aldehyde **59** in a straightforward step. The aldehyde **59** was treated with lithium salt of Wittig reagent **60** to give the corresponding *E*-enyne as the major isomer in a ratio of 5 : 1, which was subjected to a final adjustment of the protecting groups to yield the alkyne **48**.

As shown in Scheme 9, 1,2-addition of lithium acetylide derived from **48** to **47** followed by Dess-Martin oxidation led to ketone **61**. Following conversion of **61** to aldehyde **62**, an aldol reaction with the silyl ketene acetal **63** under Mukaiyama conditions provided a 4 : 1 mixture of alcohol **64** with the desired C3 stereochemistry and its epimer. MOM protection of **64**, desilylation, and deprotection of PMB ester produced the seco acid **65**, which was subjected to macrolactonization under Yamaguchi conditions to give the macrolactone **66**. Next, regioselective installation of nitrile functionality to **66** was investigated. Although direct metal-catalyzed hydrocyanation and palladium-catalyzed hydrostannylation followed by cyanation after iodination were found to be unsuccessful, a molybdenum-based hydrostannylation of **66** gave the desired corresponding vinyl stannane with complete regioselectivity, which was converted to the vinyl cyanide **67** via iodination and palladium-catalyzed cyanation. Deprotection of MOM and MEM ethers and TEMPO oxidation of the resulting primary alcohol followed by Kraus oxidation led to the C11 keto-borrelidin **68**. The final Luche reduction of **68** provided synthetic borrelidin (**1**) with high diastereoselectivity (10 : 1 d.r.).

Ōmura and Nagamitsu synthesis.[18] The total synthesis of borrelidin (**1**) was also accomplished by our



Scheme 9

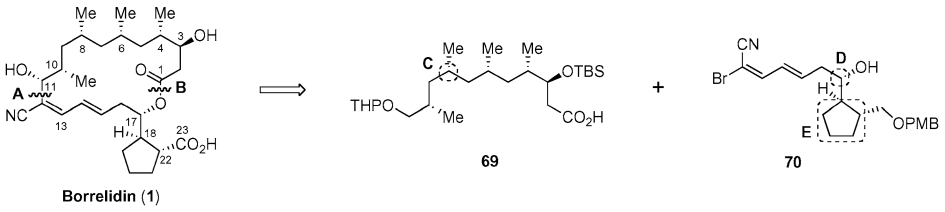
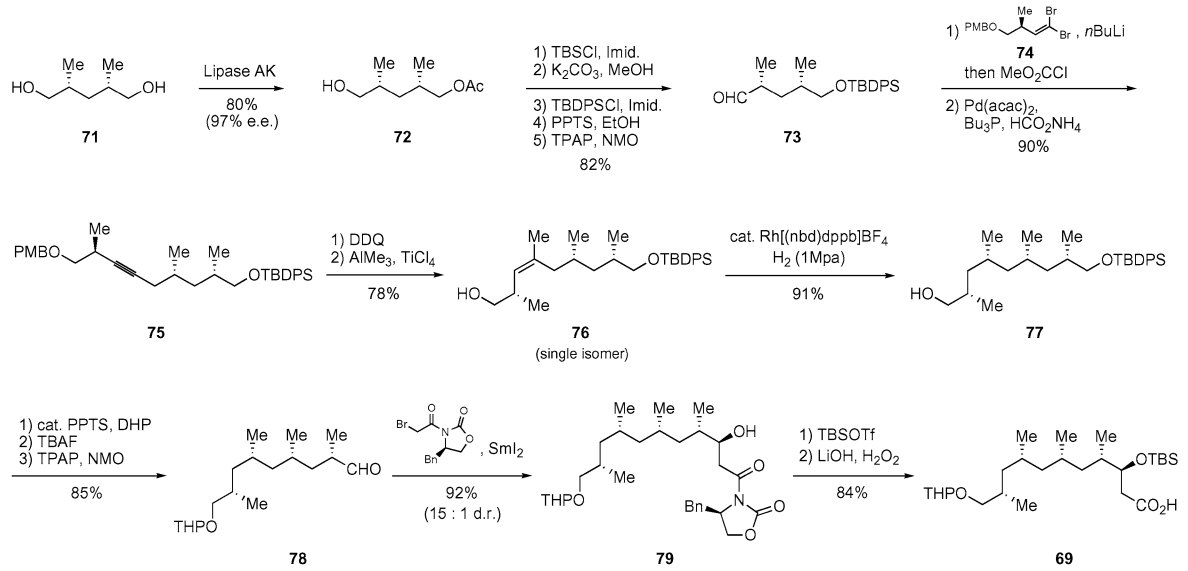


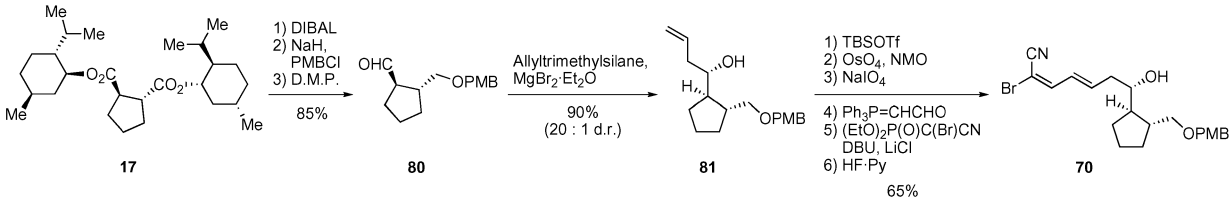
Fig. 5

group in 2004. Our synthetic strategy of borrelidin (**1**) is also convergent as shown in Fig. 5. All previous synthetic strategies directed towards the construction of the 18-membered ring of borrelidin (**1**) are by macrolactonization of the seco acid. However, we featured samarium iodide-mediated intramolecular Reformatsky-type reaction (**A**) to provide macrocyclization after esterification (**B**) between the C1-C11 segment **69** and the C12-C23 segment **70**. This strategy differed significantly from the total syntheses reported previously. Other synthetic features included regioselective methylation followed by directed hydrogenation (**C**), $MgBr_2 \cdot Et_2O$-mediated stereoselective allylation (**D**), and construction of the cyclopentane carboxylic acid subunit by Yamamoto asymmetric carbocyclization (**E**).

Formation of the C1-C11 segment **69** started with a known chiral acetate **72** (97% e.e.), which was readily obtained from a *meso*-diol **71** by enzymatic desymmetrization (Scheme 10). The conversion of **72** to the aldehyde **73** was efficiently accomplished by a series of



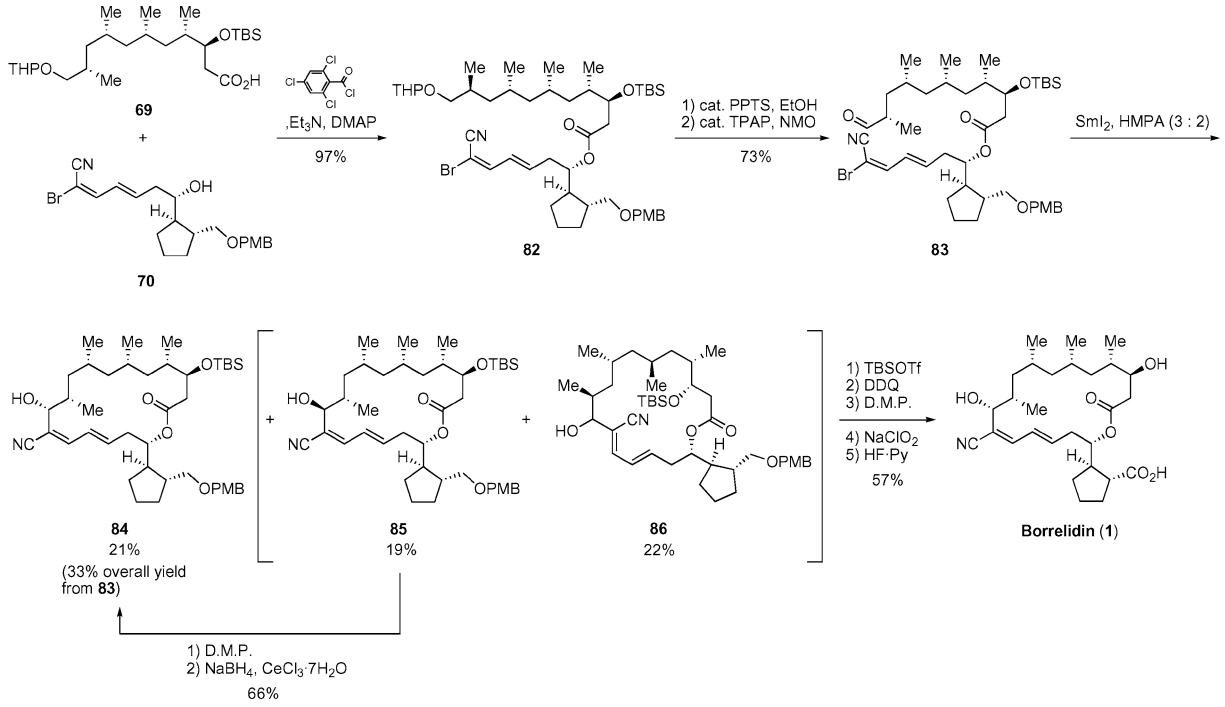
Scheme 10



Scheme 11

protections and deprotections followed by TPAP oxidation. 1,2-Addition of lithium acetylide, prepared from known dibromoolefin **74**, to aldehyde **73** was quenched with chloromethyl carbonate to furnish the corresponding methyl carbonate, which underwent decarbonation using a palladium catalyst to produce alkyne **75**. After PMB deprotection, regioselective methylation of the resulting homopropargylic alcohol under slightly modified Thompson's conditions produced the desired (*Z*)-trisubstituted olefin **76** as a sole product. Subsequent directed hydrogenation of **76** using a Rhodium catalyst under high pressure gave alcohol **77** with the desired C8 methyl stereocenter. THP ether formation, deprotection of the TBDPS ether, and TPAP oxidation efficiently produced aldehyde **78**. Stereoselective Reformatsky reaction of **78** with a chiral bromoacetyl oxazolidinone using samarium iodide under Fukuzawa's conditions afforded a 15 : 1 mixture of the desired adduct **79** and its C3 epimer. Finally, TBS protection followed by removal of the chiral auxiliary gave the C1-C11 segment **69**.

The C12-C23 segment **70** was prepared, starting from the known chiral diester **17** which was readily derived from succinic acid by Yamamoto asymmetric carbocyclization (Scheme 11). DIBAL reduction of **17**, monoselective PMB protection of the corresponding diol, and Dess-Martin oxidation gave the aldehyde **80**. To construct stereochemistry of C17, additional stereoselective allylation was needed. Reaction with allylmagnesium bromide or Brown's allylboration of **80** to produce the allyl adduct **81** resulted in a low stereoselectivity. Therefore, chelation controlled allylation of **80** with allyltrimethylsilane in the presence of Lewis acids was investigated. After the screening of Lewis acids, it was found that magnesium dibromide was the best to give **81** in high yield with high stereoselectivity (20 : 1 d.r.). The conversion of **81** into the desired C12-C23 segment **70**



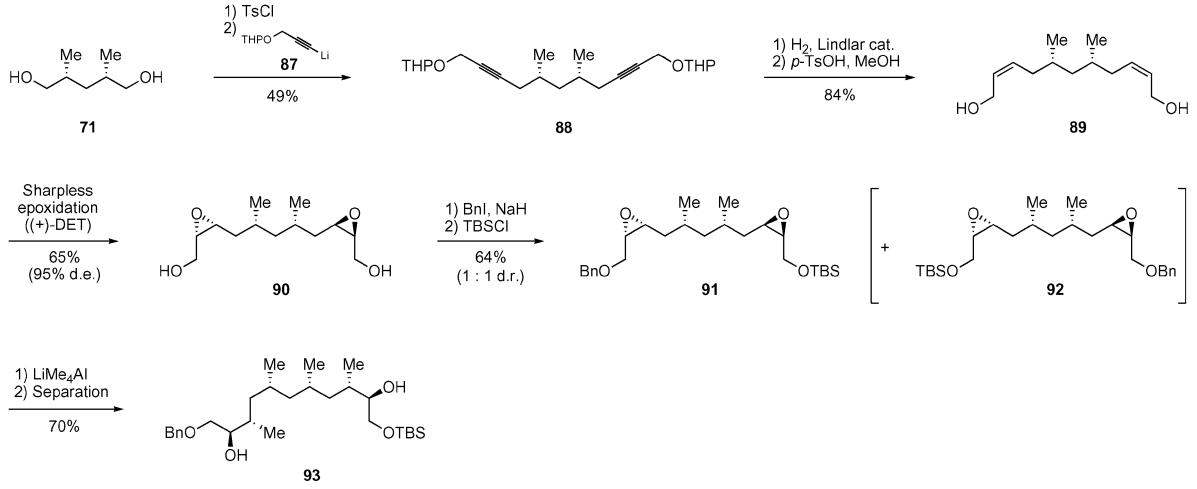
Scheme 12

was efficiently accomplished through a standard procedure.

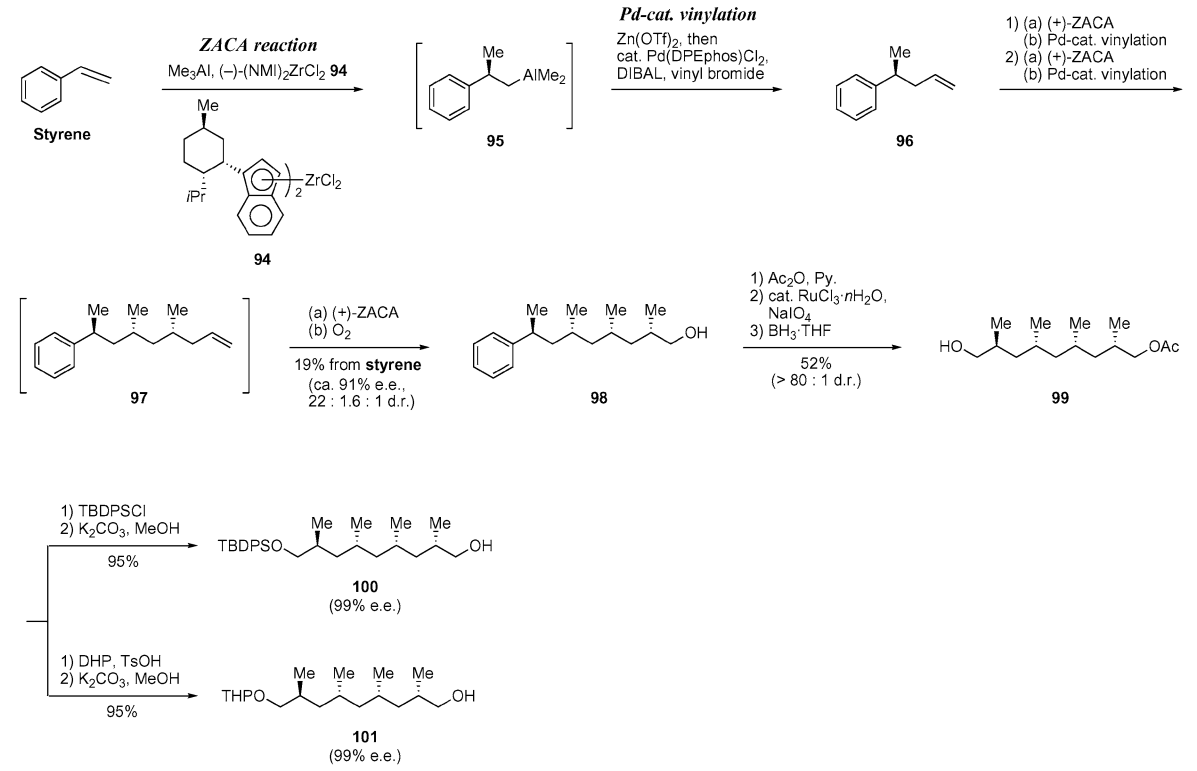
Esterification of the C1-C11 segment **69** and the C12-C23 segment **70** was performed under Yamaguchi's conditions to give the corresponding ester **82**, which was then converted to the key aldehyde **83**, by THP deprotection followed by TPAP oxidation (Scheme 12). Next, the SmI_2-mediated intramolecular Reformatsky-type reaction of **83** for macrocyclization was explored. Treatment of **83** with SmI_2 at –78 °C gave no reaction, and a rise in the reaction temperature (to 0 °C) led to decomposition. Then, effects of HMPA as an additive to enhance the reducing power of SmI_2 at –78 °C were examined. Consequently, treatment of **83** with a 3 : 2 ratio mixture of SmI_2 and HMPA under high dilution conditions at –78 °C gave the best result, affording the desired cyclized product **84** in 21% yield. At the same time, the cyclized C11 epimer **85** and the cyclized compound **86** with undesirable *E* stereochemistry at C12-C13, each in about 20% yield, were also obtained. Inversion of the C11-hydroxyl group of **85** by Dess-Martin oxidation followed by Luche reduction proved to be quite effective to give **84**. As a result, the conversion of **83** into **84** proceeded in 33% overall yield. Finally, TBS protection, removal of the PMB ether, a tandem approach of oxidation of the resulting primary alcohol, and deprotection of the TBS ether completed the total synthesis of borrelidin (**1**).

Synthetic studies toward total synthesis. *Haddad approach to the synthesis of C2-C12 segment.*[19] The first synthetic study toward total synthesis of borrelidin (**1**) was reported by Haddad and co-workers in 1997, in which the synthesis of C2-C12 segment **93** was efficiently achieved via Sharpless asymmetric epoxidation followed by regioselective methylation.

The synthesis of **93** was initiated with the known *meso*-diol **71** (Scheme 13). Tosylation of the diol followed by alkylation with lithium acetylide **87** produced the bis-alkyne **88**. Hydrogenation of **88** with lindlar catalyst and deprotection of the THP ethers furnished the bis-allyl alcohol **89**, which was subjected to Sharpless asymmetric epoxidation using (+)-DET to provide the bis-epoxy alcohol **90** with high diastereoselectivity. Unfortunately, subsequent monobenzylation and TBS protection of the resulting monoalcohol afforded a 1 : 1 diastereomeric mixture of the desired bis-epoxide **91** and its diastereomer **92**. Regioselective methylation of the mixture with $LiMe_4Al$ followed by careful separation



Scheme 13



Scheme 14

gave the desired C2-C12 segment **93**.

Negishi approach to the synthesis of C3-C11 segment.[20] Early this year (2005), Negishi and coworkers reported a practical synthesis of C3-C11 segment from inexpensive styrene via an originally developed zirconium catalyzed asymmetric carboalumination (ZACA) followed by palladium catalyzed vinylation (Scheme 14).

The synthesis of C3-C11 segment **99** commenced with styrene. ZACA reaction using (–)-$(NMI)_2ZrCl_2$ **94** of

styrene produced the corresponding chiral alkylaluminium **95**, which was subjected to palladium catalyzed vinylation to afford alkene **96**. Then, combination of ZACA reaction using (+)-$(NMI)_2ZrCl_2$ and palladium catalyzed vinylation was additionally repeated twice to convert **96** into **97**. The fourth ZACA reaction followed by oxidation with O_2 furnished the desired chiral alcohol **98** with high enantio- (ca. 91% e.e.) and diastereoselectivity (22 : 1.6 : 1 d.r.). Subsequent functional group manipulation involving 3 steps gave the C3-C11 segment **99**, whose purity was readily improved (> 80 : 1 d.r.). Further exchange of protecting groups led to TBDPS ether **100** and THP ether **101**, which are the key intermediates in the total synthesis of borrelidin (**1**) achieved by Theodorakis and our groups and were determined to be 99% e.e. by NMR analysis of the Mosher esters.

Conclusion. Total synthesis of borrelidin (**1**), an 18-membered macrolide possessing a variety of biological activities, and a synthetic study toward the total synthesis have only been documented intensively in the last three years (except for Haddad report) despite its initial isolation more than 50 years ago. These synthetic studies of borrelidin (**1**) will contribute to the production of borrelidin (**1**) in sufficient amounts for more detailed biological evaluations, synthesis of diverse derivatives, and biological mechanistic studies.

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Profile

Satoshi Ōmura is Professor and President of The Kitasato Institute, Professor of Kitasato Institute for Life Sciences and Graduate School of Infection Control Sciences, Kitasato University. He was born in Yamanashi Prefecture, Japan, in 1935 and received his Ph. D. in Pharmaceutical Sciences from the University of Tokyo in 1968 and in Chemistry from Tokyo University of Science in 1970. He was appointed as Professor of School of Pharmaceutical Sciences, Kitasato University in 1975. He has been the President of The Kitasato Institute since 1990. His research interests focus on chemistry and biology of microbial metabolites, including discovery; the biosynthesis and hybrid biosynthesis of new macrolide antibiotics; the breeding, genetic analysis and mapping of *Streptomyces avermectinius*; synthesis of the novel semi-synthetic macrolides; the organic synthesis of new compounds. He has received Japan Academy Prize (1990), ACS Nakanishi Prize (2000), ACS Ernest Guenther Award in the Chemistry of Natural Products (2005), and many other awards at home and abroad. He is a member of the National Academy of Sciences, USA (1999), the Japan Academy (2001), Institut de France, Académie des Sciences (2002), Russian Academy of Sciences (2004), and European Academy of Sciences (2005).