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Total Synthesis of Borrelidin

Tohru Nagamitsu,[†] Daisuke Takano,[†] Kaori Marumoto,[†] Takeo Fukuda,[†] Kentaro Furuya,[†] Kazuhiko Otoguro,[‡] Kazuyoshi Takeda,[§] Isao Kuwajima,[||] Yoshihiro Harigaya,[†] and Satoshi Ōmura*,[‡,||]

School of Pharmacy, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641, Japan, The Kitasato Institute, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8642, Japan, Department of Medicinal Chemistry, Yokohama College of Pharmacy, 601 Matanocyo, Hodogayaku, Yokohama-shi, Kanagawa 245-0066, Japan, and Kitasato Institute for Life Sciences and Graduate School of Infection Control Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641 Japan

omura-s@kitasato.or.jp

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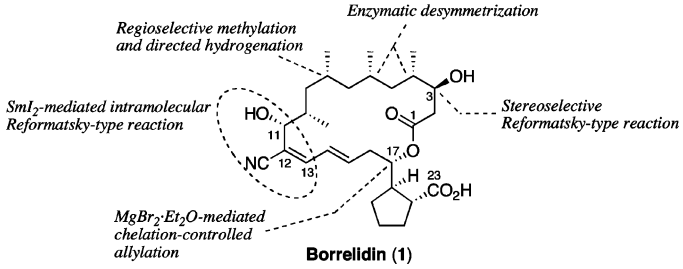

The total synthesis of borrelidin has been achieved. The best feature of our synthetic route is macrocyclization at C11−C12 for the construction of an 18-membered ring after esterification between two segments. A detailed examination of the macrocyclization led us to the samarium(II) iodide-mediated intramolecular Reformatsky-type reaction as the most efficient synthetic approach. The two key segments were synthesized through regioselective methylation, directed hydrogenation, stereoselective Reformatsky-type reaction, and $MgBr_2 \cdot Et_2O$-mediated chelation-controlled allylation.

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.[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 reduced polypropionate moiety with the 4,6,8,10-methyl groups (borrelidin numbering) possessing a distinctive syn/syn/anti relationship, 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] Borrelidin (**1**) possesses interesting biological activity including antibacterial activity,[1,5] which involves selective inhibition of threonyl tRNA synthetase,[6] antiviral activity,[7] antiangiogenesis activity,[8] and inhibitory activity toward cyclin-dependent kinase Cdc28/Cln2 of *Saccharomyces cerevisiae*.[9] The biosynthesis of borrelidin (**1**) has also been reported by Salas and co-workers.[10,11]

[†] School of Pharmacy, Kitasato University.
[‡] The Kitasato Institute.
[§] Yokohama College of Pharmacy.
[||] Kitasato Institute for Life Sciences and Graduate School of Infection Control Sciences, Kitasato University.

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TABLE 1. In Vitro Antimalarial Activities of Borrelidin (1) and Other Drugs

	IC_{50} (nM)	
compound	K1 strain	FCR3 strain
borrelidin	1.9	1.8
artemether	7.6	2.2
artesunate	11	2.7
chloroquine	357	29

TABLE 2. In Vivo Subcutaneous Antimalarial Activities of Borrelidin (1) and Other Drugs

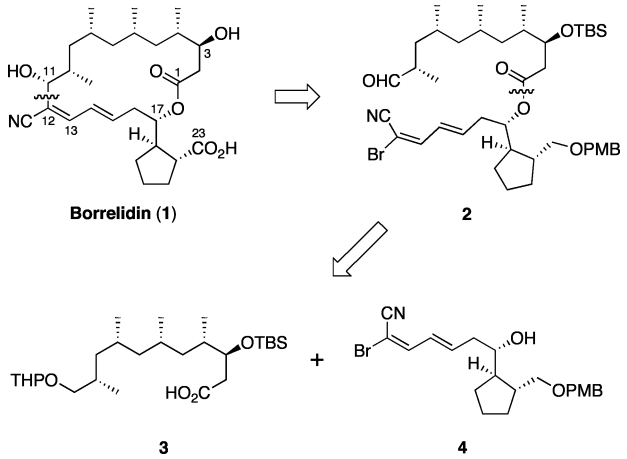
parasite	compound	ED_{50} (mg/kg)	ED_{90} (mg/kg)
P. berghei N[a]	borrelidin	0.18	2.0
	artemether	0.95	3.8
	artesunate	1.7	10.0
	chloroquine	1.5	2.5
P. yoelii ssp. NS[b]	borrelidin	0.07	0.8
	artemether	1.1	5.1
	artesunate	0.4	26.0
	chloroquine	4.5	>100.0

[a] Drug-sensitive strain. [b] Chloroquine-resistant strain.

Recently, we also found borrelidin to exhibit potent antimalarial activity 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 activity of borrelidin (**1**) and the standard antimalarial drugs used against K1 and FCR3 strains of *Plasmodium falciparum* in vitro, and against *P. berghei* and *P. yoelii* ssp. NS in vivo, are summarized in Tables 1 and 2.[13,14] Borrelidin is a more potent antimalarial drug than artemether, artesunate, and chloroquine, both in vitro and in vivo.

This interesting biological profile as well as the structural complexity of borrelidin has prompted substantial synthetic effort toward its total synthesis. Recently, four total syntheses of borrelidin have been reported by the representative groups of Morken,[15] Hanessian,[16] Theodorakis,[17] and ours,[18] and three studies toward the total synthesis have been presented.[19−21] Herein, we provide a complete account of our synthetic studies.

SCHEME 1. Retrosynthesis of Borrelidin (1)



Results and Discussions

Retrosynthetic Analysis. We envisioned a convergent approach toward borrelidin (**1**) via an intramolecular Reformatsky-type reaction[22] of α-bromo-α,*β*/*γ*,*δ*-unsaturated nitrile **2** with macrocyclization at C11−12 after esterification between acid **3** and alcohol **4**, as shown in Scheme 1. While the stereoselective constructions of the C11 stereogenic center and the trisubstituted olefin at C12−13 in the key reaction might cause difficulties, we expected that this synthetic strategy would afford a concise route to borrelidin (**1**) as elaboration of the long-chain seco acid, including stereogenic centers and a (*Z*,*E*)-diene, would not be necessary (Scheme 1).

Synthesis of Acid 3. We started from the known chiral monoacetate **6** (97% ee), which was readily obtained from the meso-diol **5** by enzymatic desymmetrization,[23] to give the acid **3** (Scheme 2). The conversion of **6** to aldehyde **8**[24] was efficiently accomplished by a series of protections and deprotections followed by TPAP oxidation of the resulting alcohol **7** (82% overall yield). The aldehyde **8** underwent clean addition of lithium acetylide, prepared from known dibromoolefin **9**,[25] by treatment with *n*-BuLi, and was then quenched with MeO_2-CCl to furnish the corresponding methyl carbonate **10**. Subsequent decarboxylation of **10** under Radinov conditions[26] furnished **11** in 90% yield over two steps. Removal of the PMB ether of **11** with DDQ led to homopropargyl alcohol **12** in 97% yield.

Next we turned to regioselective methylation of homopropargyl alcohol **12** to construct (*Z*)-homoallylic alcohol **13** (Table 3). Our first attempt under the conditions reported by Schiavelli

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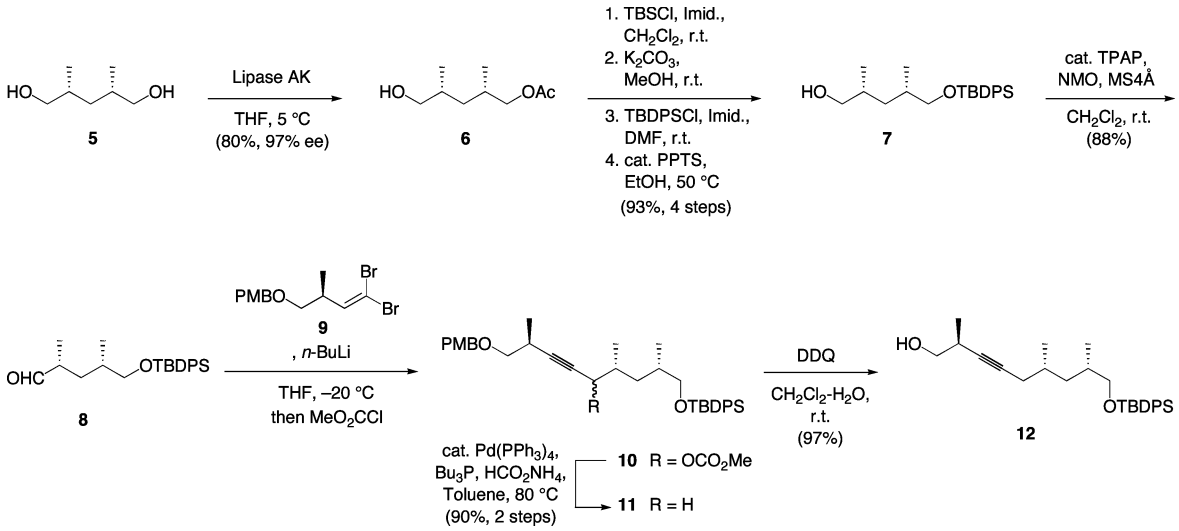
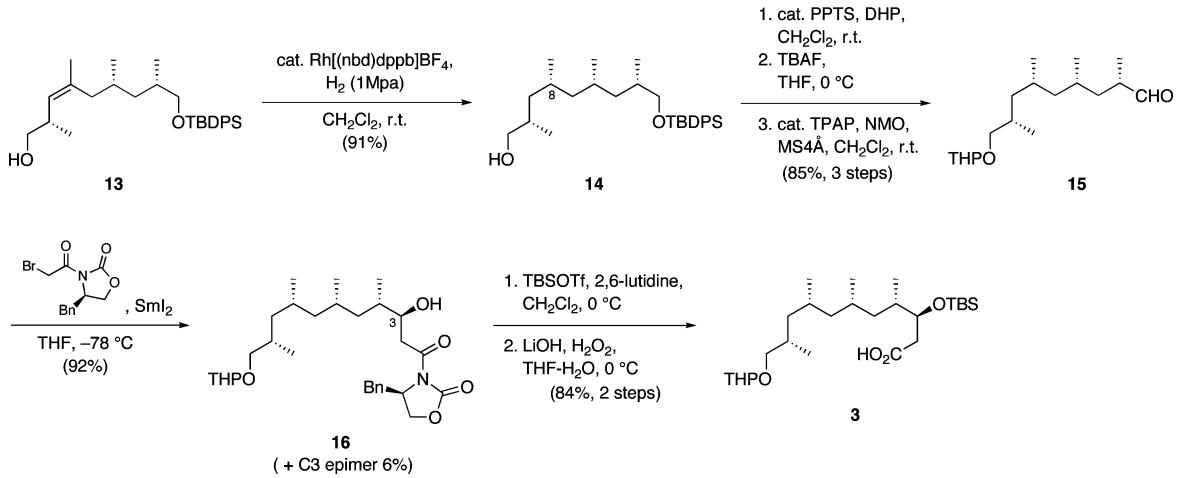
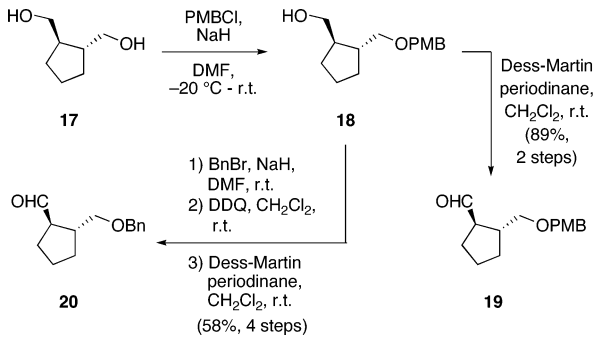
SCHEME 2. Synthesis of Homopropargyl Alcohol 12



SCHEME 3. Synthesis of Carboxylic Acid 3



SCHEME 4. Synthesis of Aldehydes 19 and 20



et al.[27] gave the desired product **13** in poor yield (16%) and recovered **12** (77%) (entry 1). Although it seemed likely that a rise in the reaction temperature would lead to side reactions such as oligomerization, we were pleased to find that this reaction could be effected in a much improved, 80%, yield and with a short reaction time if the reaction temperature was set at −5 °C and excess $Me_3Al-TiCl_4$ was used (entry 4). Reaction with other titanium reagents did not proceed at all (entries 5−7).

The *Z* stereochemistry of the constructed trisubstituted olefin **13** was confirmed by NOE experiments.

Subsequent directed hydrogenation[28] of (*Z*)-homoallylic alcohol **13** using a catalytic amount of Rh[(nbd)dppb]BF_4 under high pressure (1 MPa) gave alcohol **14** with the desired C8 stereochemistry[29] in 91% yield (Scheme 3). THP ether formation, deprotection of the TBDPS ether, and TPAP oxidation efficiently produced aldehyde **15** in 85% yield over three steps. Stereoselective Reformatsky-type reaction of the aldehyde **15** with a chiral bromoacetyl oxazolidinone using samarium(II) iodide under Fukuzawa's conditions[30] afforded the corresponding adduct **16** with the desired C3(*S*) stereochemistry in 92% yield; the absolute configuration was confirmed by application of the advanced Mosher ester analysis.[31] The product **16** was then subjected to TBS protection followed by removal of the chiral auxiliary to give the desired acid **3** in 84% yield over two steps.

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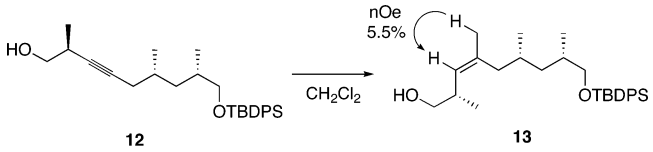
TABLE 3. Regioselective Methylation of Homopropargyl Alcohol 12

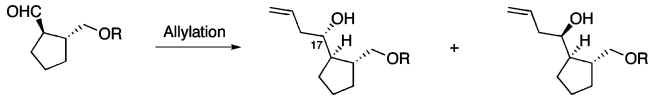


12 **13**

entry	reagents	temp	time	products (%)[a]
1	Me_3Al (2.2 equiv), $TiCl_4$ (1.1 equiv)	−78 °C	2 h	**13** (16), recovered **12** (77)
2	Me_3Al (2.2 equiv), $TiCl_4$ (1.1 equiv)	0 °C	5 min	**13** (50)
3	Me_3Al (2.6 equiv), $TiCl_4$ (1.3 equiv)	−20 °C	3 h	**13** (80)
4	Me_3Al (4.0 equiv), $TiCl_4$ (2.0 equiv)	−5 °C	15 min	**13** (80)
5	Me_3Al (2.2 equiv), $CpTiCl_3$ (1.1 equiv)	rt	12 h	no reaction
6	Me_3Al (2.2 equiv), Cp_2TiCl_2 (1.1 equiv)	rt	10 h	no reaction
7	Me_3Al (2.2 equiv), Cp_2TiCl_2 (1.1 equiv)	80 °C	5 h	no reaction

[a] Isolated yield

TABLE 4. Stereoselective Allylation of Aldehydes 19 and 20



19 R = PMB
20 R = Bn

21 R = PMB
23 R = Bn

22 R = PMB
24 R = Bn

entry	aldehyde	reagents	solvent	temp °C	time	products (%)[a]
1	**19**	allylMgBr	THF	−78	30 min	**21** (54), **22** (42)
2	**19**	allylMgBr, $ZnCl_2$	Et_2O	−78 to 0	2.5 h	**21** (18), **22** (16)
3	**19**	(−)-Ipc_2Ballyl	Et_2O	−78 to 0	1 h	**21** (30), **22** (25)
4	**19**	(−)-Ipc_2Ballyl	toluene	−78 to 0	1 h	**21** (33), **22** (30)
5	**20**	allyltrimethylsilane, $TiCl_4$	CH_2Cl_2	−78	10 min	**23** (75), **24** (24)
6	**20**	allyltrimethylsilane, $SnCl_4$	CH_2Cl_2	−78	10 min	**23** (44), **24** (16)
7	**19**	allyltrimethylsilane, $MgBr_2{\cdot}Et_2O$	CH_2Cl_2	0	6 h	**21** (90), **22** (4.5)
8	**19**	allyltrimethylsilane, $BF_3{\cdot}Et_2O$	CH_2Cl_2	−78	30 min	**21** (35), **22** (42)

[a] Isolated yield.

Synthesis of Alcohol 4. Next, we turned to preparation of the alcohol **4**, starting from the known chiral diol **17**, which was readily derived from succinic acid by Yamamoto asymmetric carbocyclization.[32] Monoselective PMB protection of the diol **17** followed by Dess−Martin oxidation of the resulting alcohol **18** afforded aldehyde **19** in 89% yield over two steps (Scheme 4). The alcohol **18** was also converted into aldehyde **20** via benzyl ether formation, deprotection of the PMB ether with DDQ, and Dess−Martin oxidation in 58% yield over four steps.

We then needed to perform stereoselective allylation of the aldehydes **19** and **20** to construct the C17(*S*)-hydroxy group (Table 4). Treatment with allylmagnesium bromide (entries 1 and 2) and Brown allylation[33] with (−)-Ipc_2Ballyl (entries 3 and 4) led to low stereoselectivity. We therefore investigated chelation-controlled allylation with allyltrimethylsilane in the presence of Lewis acids. After screening of Lewis acids (entries 5−7), it was found that magnesium dibromide[34] gave the best results, affording the desired C17(*S*)-allyl adduct **21** with high yield (90% yield) and diastereoselectivity (20:1 d.r.); the absolute configuration was again confirmed by application of the advanced Mosher ester analysis.[31]

Stereoselective allylation of **19** using the optimum conditions (entry 7 in Table 4) is thought to occur via chelation of magnesium dibromide with the formyl oxygen and the PMB ether oxygen, with the allyltrimethylsilane adding to the *si* face of the formyl carbon. The *re* face of the formyl group is considered to be sufficiently screened by the cyclopentyl group to favor highly selective formation of the desired allyl adduct **21** (Scheme 5). Nonstereoselective allylation in the presence of $BF_3{\cdot}Et_2O$ would support the chelation-controlled reaction mechanism (entry 8 in Table 4). TBS protection of the secondary alcohol followed by oxidative cleavage of the terminal olefin afforded the corresponding aldehyde **26** quantitatively, which

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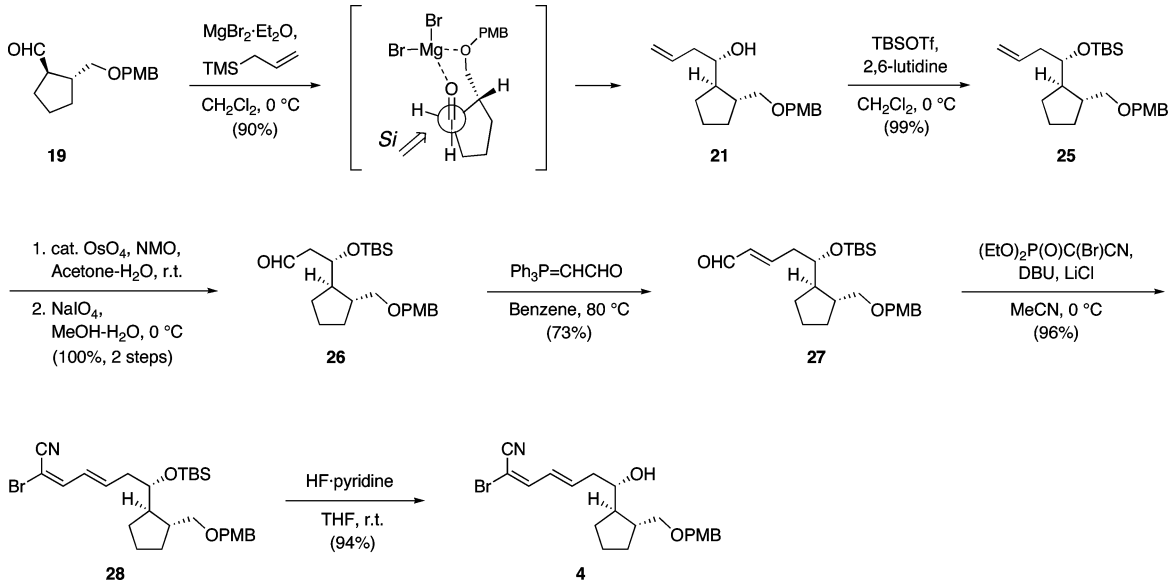
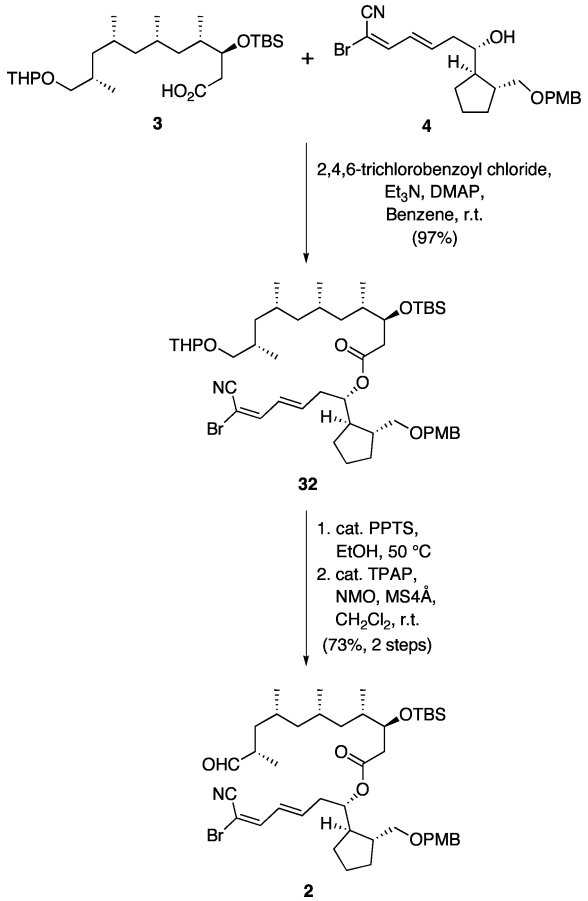
SCHEME 5. Synthesis of Alcohol 4



was then subjected to a Wittig reaction to give the (*E*)-unsaturated aldehyde **27** in 73% yield. Subsequent Horner−Emmons olefination of the aldehyde **27** with diethyl bromo(cyano)methylphosphonate[35] using DBU and LiCl[36] furnished the corresponding (*E*,*E*)-vinyl bromide **28**[37] as a single isomer in 96% yield. The TBS protecting group of **28** was finally removed by exposure to HF·pyridine to provide the desired alcohol **4** in 94% yield.

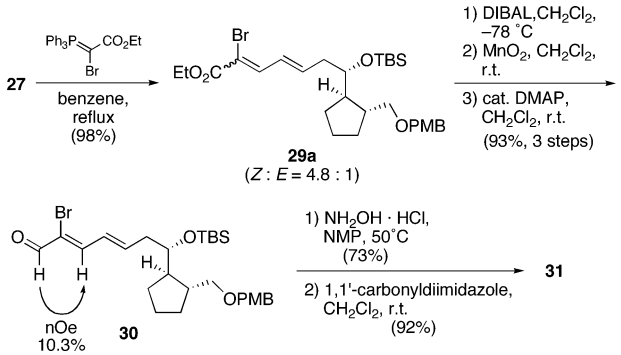
Synthesis of the Key Intermediate Aldehyde 2. The next step was to obtain the key intermediate **2** for the intramolecular Reformatsky-type reaction (Scheme 6). Esterification of the carboxylic acid **3** and the alcohol **4** was performed under Yamaguchi conditions[38] to give the corresponding ester **32** in 97% yield, which was then converted to the target aldehyde **2** by THP deprotection followed by TPAP oxidation in 73% yield over two steps.

SCHEME 6. Synthesis of Aldehyde 2



Macrocyclization 1: Intramolecular Reformatsky-Type Reaction. Prior to carrying out the intramolecular Reformatsky-type reaction, we conducted a study on the Reformatsky-type reaction using a model substrate **31**[37a] and isobutyraldehyde (Table 5). In this case, use of zinc reagents[39,40] and chromium

(37) (a) In early synthetic studies of borrelidin in our laboratory, the model substrate [(*Z*)-vinyl bromide] **31** had been synthesized by another route which required more steps as follows: (i) Wittig reaction, (ii) reduction, oxidation, and isomerization, (iii) conversion of aldehyde into nitrile.



(b) In early synthetic studies of borrelidin in our laboratory, this Reformatsky-type reaction using **31** and isobutyraldehyde had also been studied. The resulting trisubstituted olefin **33** was an *E*/*Z* mixture under any conditions, with the stereoselectivity dependent on the reducing agent (not shown in Table 5). These results showed that the stereochemistry of the trisubstituted olefin of the starting material would not be critical in the key macrolactonization and led us to first select **4** as the key intermediate for the total synthesis, rather than **31**, which could be synthesized from **27** in fewer steps.

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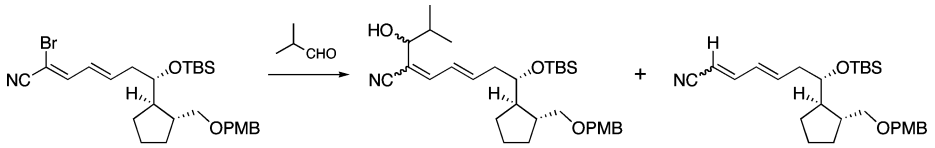
TABLE 5. Model Study on Reformatsky-Type Reaction Using 31 and Isobutyraldehyde

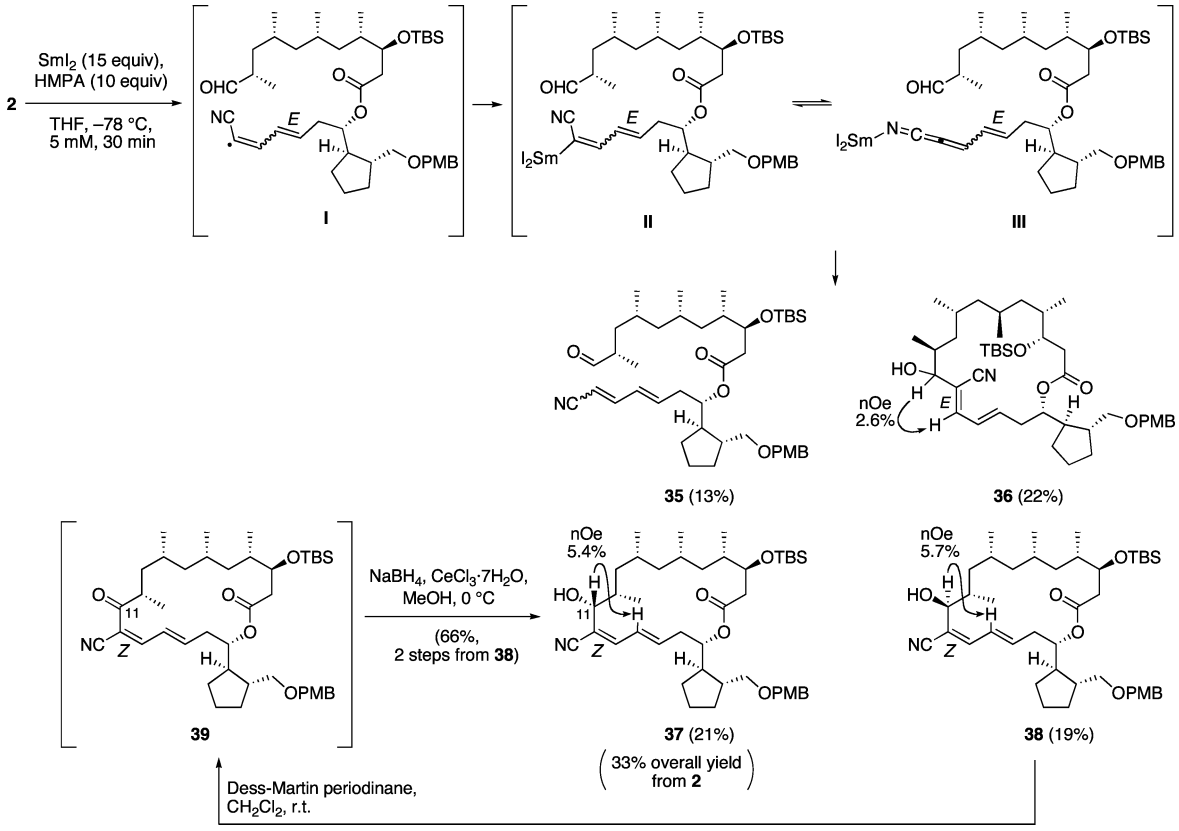


31 **33** **34**

entry	reagents	solvent	temp	time	products (%)[a]
1	Zn, Et_2AlCl, cat. CuBr, MS4A	THF	rt	2 h	**33** (20), **34** (61)
2	Et_2Zn, cat. $RhCl(PPh_3)_3$	THF	0 °C	2 h	degradation products
3	Zn/Cu	THF	rt	12 h	**33** (trace), **34** (82)
4	Zn/Cu, $BF_3{\cdot}Et_2O$	THF	rt	12 h	**33** (trace), **34** (73)
5	$CrCl_2$	THF	rt	2 h	no reaction
6	$CrCl_2$	DMF	rt	2 h	**33** (26), **34** (48)
7	SmI_2	THF	−78 °C	3 h	no reaction
8	SmI_2	THF	0 °C	2 h	**33** (29), **34** (35)
9	SmI_2−HMPA (1:4)	THF	−78 °C	30 min	**33** (42), **34** (2)
10	SmI_2−HMPA (3:2)	THF	−78 °C	30 min	**33** (65), **34** (32)

[a] Isolated yield.

SCHEME 7. SmI_2-Mediated Intramolecular Reformatsky-Type Reaction of 2



dichloride[41] in DMF resulted in low yields, and along with the desired product **33**, the debrominated side product **34** in 50 to ∼80% yield (entries 1, 3, 4, and 6). Next, treatment with samarium(II) iodide[22] at −78 °C gave no reaction, and the starting material was recovered quantitatively (entry 7). Although a rise in reaction temperature to 0 °C afforded a small amount of the desired adduct **33**, complex mixtures including **34** were also obtained (entry 8). To prevent decomposition of **31** and **33**, we next examined using HMPA as an additive to increase the reducing power of samarium(II) iodide at −78 °C.[42] Consequently, it was found that a 1:4 ratio mixture of samarium(II) iodide and HMPA gave the desired adduct **33** in 42% yield;

(40) Kanai, K.; Wakabayashi, H.; Honda, T. *Org. Lett.* **2000**, *2*, 2549−2551.

(41) Gabriel, T.; Wessjohann, L. *Tetrahedon Lett.* **1997**, *38*, 1363−1366.

(42) (a) Inanaga, J.; Ishikawa, M.; Yamaguchi, M. *Chem. Lett.* **1987**, 1485−1486. (b) Shabangi, M.; Flowers, R. A., II. *Tetrahedron Lett.* **1997**, *38*, 1137−1140. (c) Shabangi, M.; Sealy, J. M.; Fuchs, J. R.; Flawers, R. A., II. *Tetrahedron Lett.* **1998**, *39*, 4429−4432.

(43) In the following papers, the authors named similar reactions as the Baylis−Hillman reaction. (a)Youn, S. W.; Park, H. S.; Kim, Y. H. *Chem. Commun.* **2000**, 2005−2006. (b) Concellón, J. M.; Huerta, M.; García-Granda, S.; Díaz, M. R. *Chem. Eur. J.* **2003**, *9*, 5343−5347. (c) Concellón, J. M.; Huerta, M. *J. Org. Chem.* **2005**, *70*, 4714−4719.

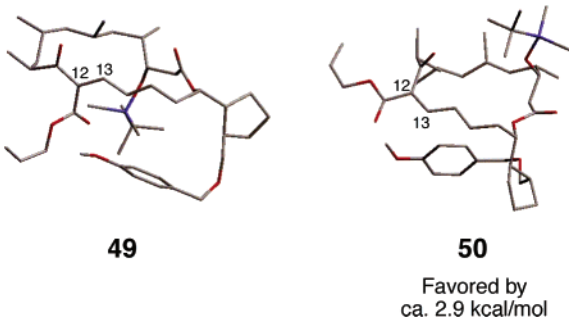
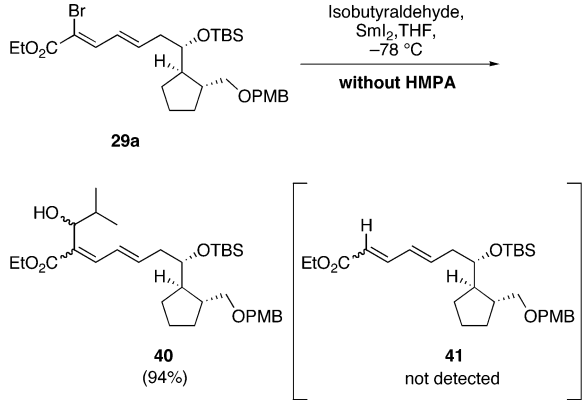
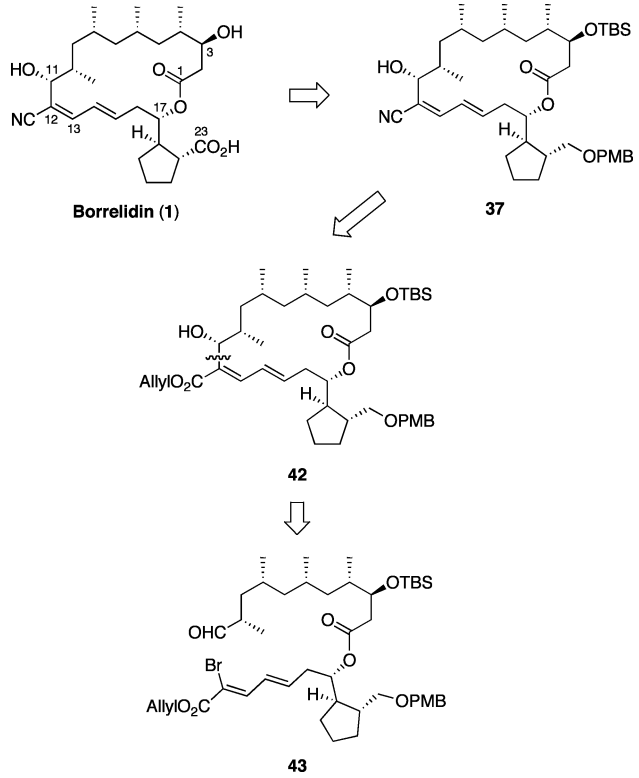


FIGURE 1. Conformational analysis of **49** and **50**.

SCHEME 8. Reformatsky-Type Reaction of 29a with Isobutyraldehyde

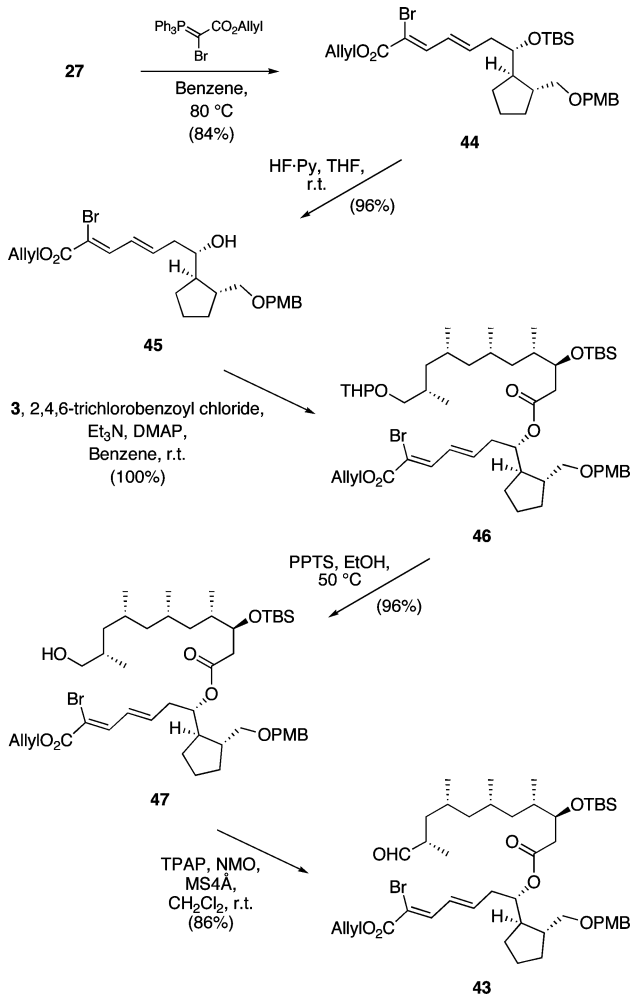


SCHEME 9. Second Retrosynthesis of Borrelidin (1)



however, many degradation compounds were also detected (entry 9). Careful follow-up experiments revealed that treatment of the aldehyde **31** with a 3:2 ratio mixture of samarium(II) iodide and HMPA at −78 °C afforded the desired adduct **33** in 65% yield, representing with the best results (entry 10).[37b]

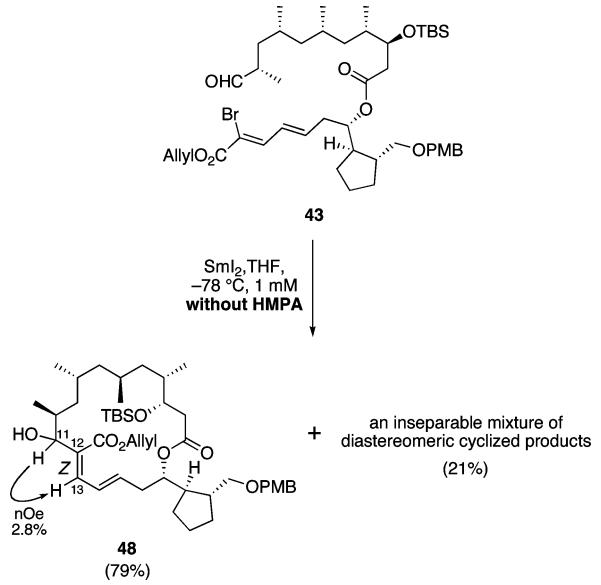
SCHEME 10. Synthesis of Aldehyde 43



Using the optimum conditions obtained in the model study (Scheme 7), we next attempted the intramolecular Reformatsky-type reaction. Treatment of the key aldehyde **2** under high dilution gave not only the desired cyclized product **37** (21% yield)[29] but also the debrominated uncyclized compound **35** (13% yield), the cyclized compound with undesirable *E* stereochemistry at C12−13 **36** (22% yield), and the cyclized C11 epimer **38** (19% yield).[29] The stereochemistries of the C12−13 olefin in the cyclized compounds were confirmed by NOE experiments. The key reaction would proceed through a formation of vinylsamarium species II.[43] Consequently, the likely equilibria between (*E*)- and (*Z*)-vinyl radical intermediates I[44] and between vinylsamarium species II and nitrile allenolate intermediate III would lead to nonstereoselective construction of the C11 stereogenic center and the trisubstituted olefin at C12−13 in macrocyclization. Not surprisingly, treatment of a stereoisomer **2**[45] with a C12−13(*Z*) trisubstituted olefin under the same conditions also gave similar results, as shown in Scheme 7. Fortunately, inversion of the hydroxyl group of the C11 epimer **38** by Dess−Martin oxidation followed by Luche reduction (d.r. = 12:1) was quite effective in affording **37** in 66% yield over two steps. As a result, we could obtain the desired product **37** from the key aldehyde **2** in 33% overall yield.

The key intermediate **2** for macrocyclization could be prepared by this convergent approach very efficiently; however, the subsequent samarium(II) iodide-mediated intramolecular Reformatsky-type reaction only afforded a moderate yield of

SCHEME 11. SmI_2-Mediated Intramolecular Reformatsky-Type Reaction of 43

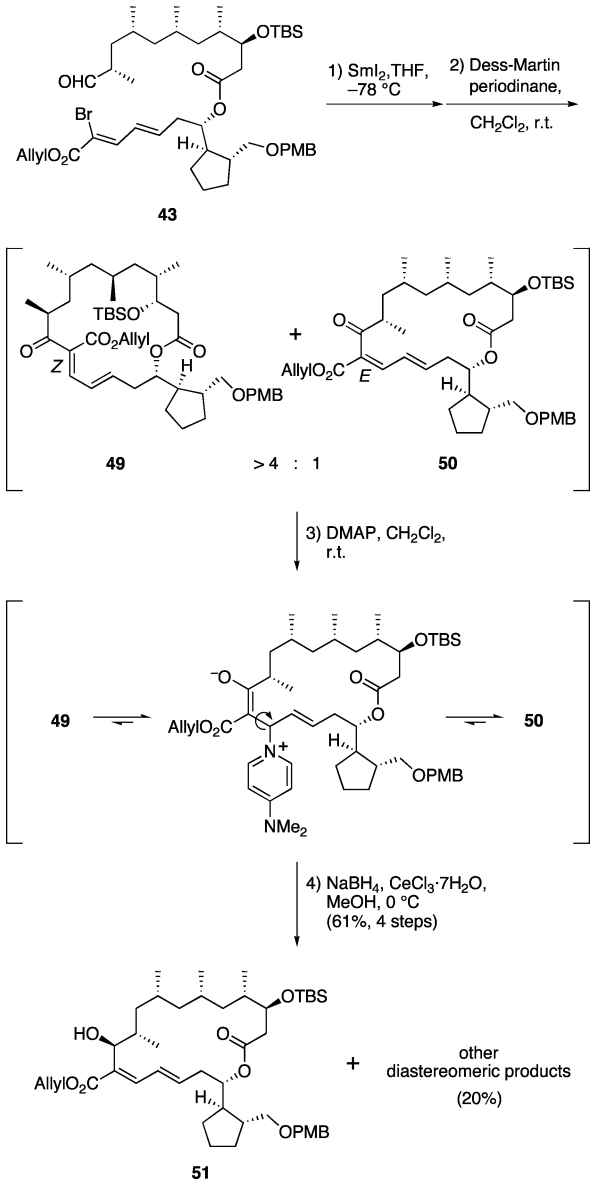


the desired product **37**. Further studies on the intramolecular Reformatsky-type reaction of aldehyde **2** proved very difficult because the cyclized products could be produced without decomposition only under a limited set of reaction conditions. Using a smaller amount of HMPA resulted in a lower yield of the desired product **37** along with the unreacted starting material **2**, and using $CrCl_2$ as an alternative reducing agent provided the debrominated uncyclized compound **35** as a major product (70% yield) with only a trace amount of the desired product **37**.

Macrocyclization 2: Attempts to Improve the Intramolecular Reformatsky-Type Reaction. In the course of the model studies of the samarium(II) iodide-mediated Reformatsky-type reaction mentioned above, we also found that α-bromo-α,*β*/*γ*,*δ*-unsaturated ester **29a**[37] was a much better substrate, affording the desired product **40** in excellent yield without the debrominated product **41**, even in the absence of HMPA (Scheme 8).

To improve the yield of the samarium(II) iodide-mediated intramolecular Reformatsky-type reaction, we next focused on the allyl ester **43** instead of **2**, which would afford the cyclized products including **42** without decomposition and without the formation of the debrominated uncyclized compound under milder conditions (Scheme 9). Although in this synthetic strategy

SCHEME 12. Conversion of 43 into 51 via Olefin Isomerization



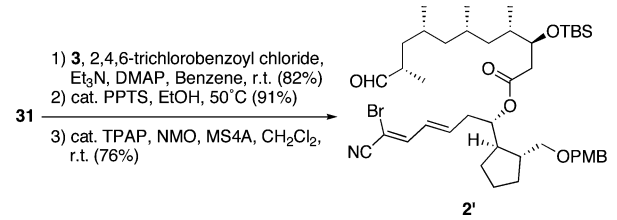
additional steps are required to convert allyl ester **42** into nitrile **37** for achievement of the total synthesis, we anticipated that the overall yield would improve and the desired cyclized intermediate **42** would give new borrelidin derivatives with modification at the nitrile group, which could not be synthesized from natural borrelidin.

The aldehyde **43** was derived from **27** without any difficulties according to the procedure shown above (Scheme 10). The aldehyde **27** was subjected to Wittig reaction with (allyloxycarbonylbromomethylidene)triphenylphosphorane[46] to furnish allyl ester **44** in 84% yield, which was treated with HF·pyridine for deprotection of the TBS ether to afford alcohol **45** in 96% yield. Subsequent esterification of **45** and **3** under Yamaguchi conditions provided diester **46** quantitatively. THP deprotection followed by TPAP oxidation afforded the aldehyde **43** in 86% yield over two steps.

We then turned to the samarium(II) iodide-mediated intramolecular Reformatsky-type reaction of **43** (Scheme 11). As we expected, the reaction proceeded smoothly even without the

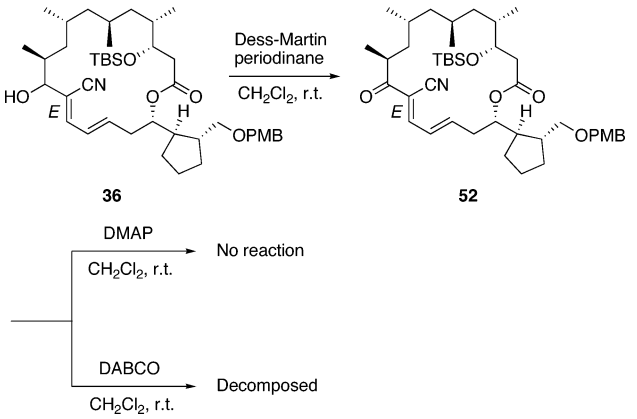
(44) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 4, pp 715.

(45) Also see the Supporting information:



(46) This reagent was synthesized from an allyl alcohol and bromoacetyl bromide, according to the following papers on the synthesis of (ethoxycarbonylbromomethylidene)triphenylphosphorane: (a) Denney, D. B.; Ross, S. T. *J. Org. Chem.* **1962**, *27*, 998. (b) Kayser, M. M.; Zhu, J.; Hooper, D. L. *Can. J. Chem.* **1997**, *75*, 1315.

SCHEME 13. Unsuccessful Olefin Isomerization of 36

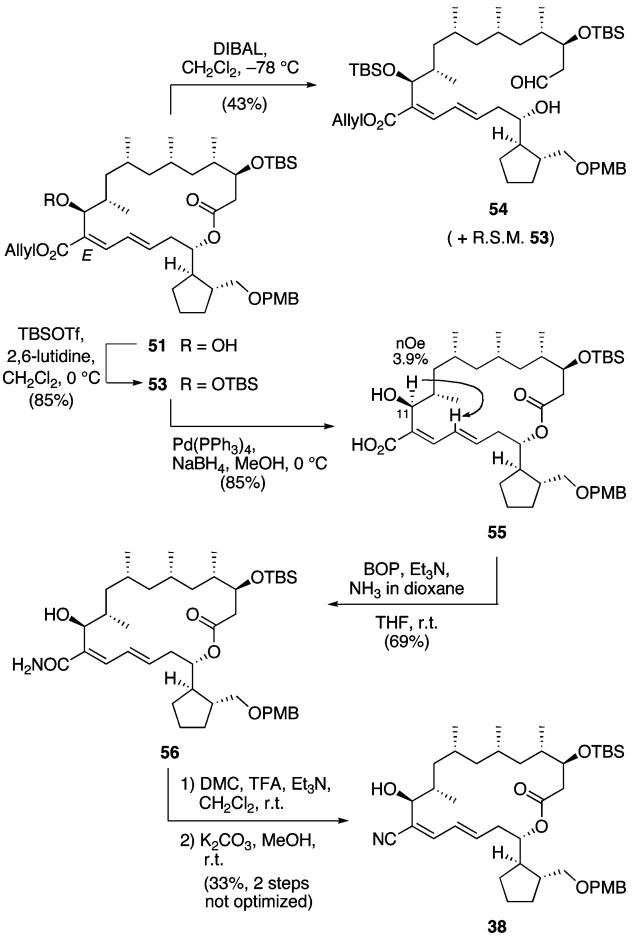


addition of HMPA to produce the separable major cyclized product **48** in 79% yield as a single diastereomer (C11 stereochemistry was not determined) and an inseparable mixture of diastereomeric cyclized products in 21% yield. However, the stereochemistry of the C12−13 olefin in the major product **48** was determined to be the undesired *Z* configuration by NOE experiments. Therefore, we next investigated olefin isomerization of the cyclized mixtures.[47]

Following a brief purification, the mixture of cyclized products obtained by the intramolecular Reformatsky-type reaction of **43** was subjected to Dess−Martin oxidation to produce a mixture of ketones **49** and **50** (>4:1), which underwent olefin isomerization without purification. Treatment with a stoichiometric amount of DMAP at room temperature for 7 days followed by Luche reduction afforded alcohol **51** in 61% yield over four steps from **43** (Scheme 12). The stereochemistries of the C11 hydroxy group and the C12−13 olefin of **51** were unknown at this stage. The other recovered diastereomeric products (∼20%) were again subjected to a sequence of olefin isomerizations as described to give alcohol **51**. Conformational analysis of **49** and **50** was carried out using the following protocol. First, conformational searching was carried out using the MMFF94 molecular mechanics force field with the program CONFLEX5.[48] Second, the conformation structures obtained were further optimized using density functional theory (DFT) together with the Perdew−Wang LDA functional (PWC)[49] and the double numerical plus d-functional (DND) basis set, using the DMol3 package of Accelrys Inc.[50,51] The calculations revealed that **50** is ca. 2.9 kcal/mol more stable than **49** (Figure 1). Therefore, the resulting olefin isomerization would proceed with an equilibrium existing between the ketones **49** and **50** upon addition and elimination of DMAP, and the thermodynamically favored **50** would be furnished as a major product.

We also tried the olefin isomerization using the previous undesired cyclized product **36** as shown in Scheme 13. Unfortunately, reaction of the product **52** obtained by Dess−Martin oxidation of **36** did not proceed with DMAP and led to decomposition of the substrates with DABCO.

SCHEME 14. Conversion of Allyl Ester 51 into Nitrile 38



We proceeded in turn to additional studies on the conversion of **51** into **37** (Scheme 14). Our first attempt was the construction of a nitrile via an aldehyde. Protection of the secondary alcohol of **51** furnished TBS ether **53** in 85% yield. Subsequent chemoselective DIBAL reduction of the allyl ester group was unsuccessful, affording the undesired aldehyde **54** as a major product with recovered **53** due to the high susceptibility of the lactone to DIBAL reduction. Therefore, we next focused on the construction of a nitrile through amide formation. Deprotection of allyl ester **53** under standard conditions with palladium catalyst gave carboxylic acid **55** in 85% yield with deprotection of the C11 TBS ether. At this stage, the *E* stereochemistry of the C12−13 olefin of **51** was confirmed by NOE experiments. Treatment of **55** with ammonia−dioxane solution in the presence of BOP and Et_3N provided amide **56** in 69% yield. Finally, dehydration of **56** with 2-chloro-1,3-dimethylimidazolinium chloride (DMC)[52] afforded the nitrile compound in 33% yield. Although the yield was unsatisfactory, priority was given to determination of the C11 stereochemistry of the nitrile compound over optimization of the reaction. After comparison of the spectral data, the nitrile compound proved to be the undesired **38**, not **37**. This result showed that Luche reduction of the *β*-keto allyl ester **50** afforded the undesired C11(*S*) alcohol stereoselectively in Scheme 12 and contrasted sharply with the results

(47) For a description of the previously observed nucleophilic equilibration of α,*β*-unsaturated carboxylic acid derivatives with DMAP, see: (a) Keck, G. E.; Boden, E. P.; Mabury, S. A. *J. Org. Chem.* **1985**, *50*, 709. (b) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497.

(48) (a) Goto, H.; Osawa, E. *J. Am. Chem. Soc.* **1987**, *111*, 8950. (b) Goto, H.; Osawa, E. *J Chem. Soc., Perkin Trans. 2* **1993**, 187. (c) Goto, H.; Ohta, K.; Kamakura, T.; Obata, S.; Nakayama, N.; Matsumoto, T.; Osawa, E. *CONFLEX5*; Conflex Corp.: Tokyo−Yokohama, Japan, 2004.

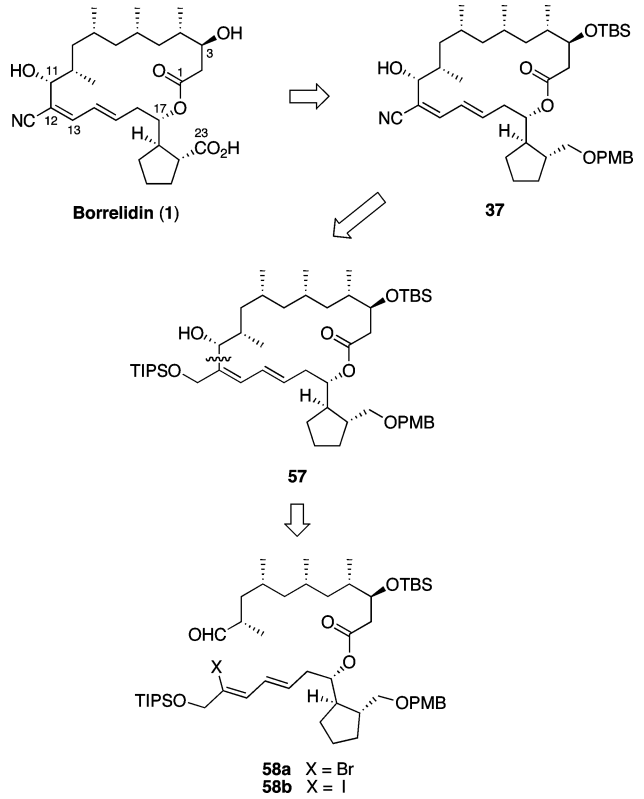
(49) Perdew, J. P.; Wang, Y. *Phys. Rev. B* **1992**, *45*, 13244.

(50) Delley, B. *J. Chem. Phys.* **1990**, *92*, 508.

(51) Delley, B. *J. Chem. Phys.* **2000**, *113*, 7756.

(52) Isobe, T.; Ishikawa, T. *J. Org. Chem.* **1999**, *64*, 6984.

SCHEME 15. Third Retrosynthesis of Borrelidin (1)



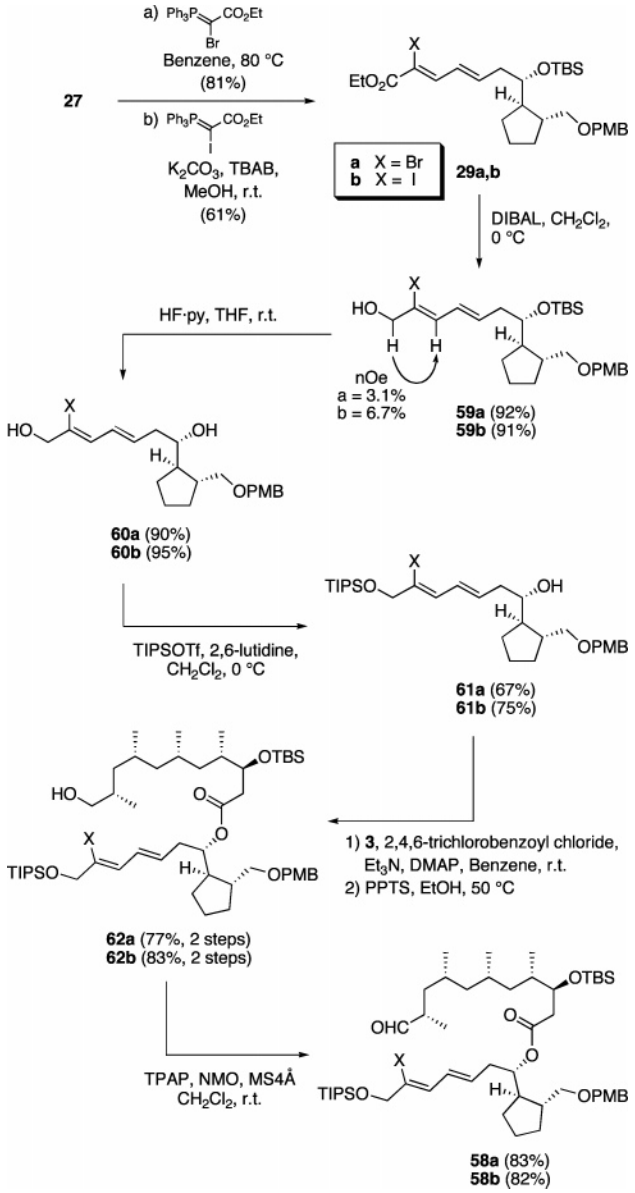
of Luche reduction of β-keto nitrile **39** in Scheme 7, in which the desired C11(*R*) alcohol was obtained stereoselectively. Although Mitsunobu reactions of **51** under conditions using DEAD/*p*-nitrobenzoic acid/PPh_3[53] and TMAD/*p*-anisic acid/Bu_3P[54] were also attempted, the desired product with the C11-(*R*) hydroxy group was not obtained.

As mentioned above, we found that samarium(II) iodide-mediated intramolecular Reformatsky-type reaction using the new precursor **43** instead of **2** was quite effective for the construction of the 18-membered macrocyclic ring even without HMPA. Subsequent olefin isomerization also proceeded smoothly to give the desired C12−13(*E*) olefin in good overall yield. However, we could not achieve efficient installation of the C11-(*R*) hydroxy group by this route.

Macrocyclization 3: Nozaki−Hiyama−Kishi Reaction. Seeking a more efficient synthetic strategy for the macrocyclization in the total synthesis of borrelidin, we selected the Nozaki−Hiyama−Kishi reaction,[55,56] since the reaction is very mild and tolerant of functional group diversity. In this case, however, we needed to construct the trisubstituted vinyl halides **58a** or **58b** stereoselectively and to perform several steps for elaboration of the nitrile group (Scheme 15). We expected that this route would lead to an improvement of overall yield.

Synthesis of the trisubstituted vinyl halides **58a** and **58b** was commenced with Wittig olefination of the aldehyde **27**. The

SCHEME 16. Synthesis of Aldehydes 58a and 58b



trisubstituted vinyl bromide **29a**[37] was obtained in 81% yield under standard conditions; however, synthesis of the trisubstituted vinyl iodide **29b** under the same conditions resulted in a low yield and decomposition. After screening of several conditions, Wittig olefination of the aldehyde **27** with (ethoxycarbonyliodomethylidene)triphenylphosphorane[57] in the presence of K_2CO_3 and a catalytic amount of tetrabutylammonium bromide[57b] was found to give the best results, affording the trisubstituted vinyl iodide **29b** in 61% yield (Scheme 16). The vinyl halides **29a** and **29b** were subjected to DIBAL reduction to produce allyl alcohols **59a** (92%) and **59b** (91%), whose stereochemistries at the C12−13 olefin were determined to be the desired *Z* configuration by NOE experiments. Exposure of **59a** and **59b** to HF·pyridine gave diols **60a** (90%) and **60b** (95%). Subsequent selective protection of the primary alcohol with TIPSOTf furnished alcohols **61a** (67%) and **61b** (75%). Esterification between the carboxylic acid **3** and the alcohols **61a** and **61b** under Yamaguchi conditions followed by deprotection of the THP ether led to esters **62a** (77%, two steps) and

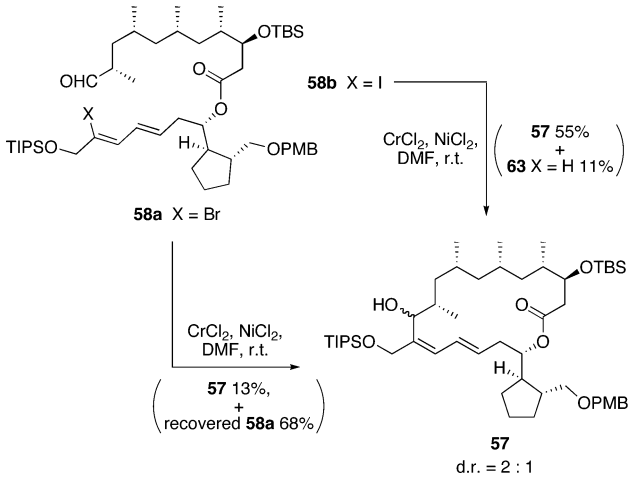
(53) Mitsunobu, O. *Synthesis* **1981**, 1.

(54) Tsunoda, T.; Yamamiya, Y.; Kawamura, Y.; Ito, S. *Tetrahedron Lett.* **1995**, *36*, 2529.

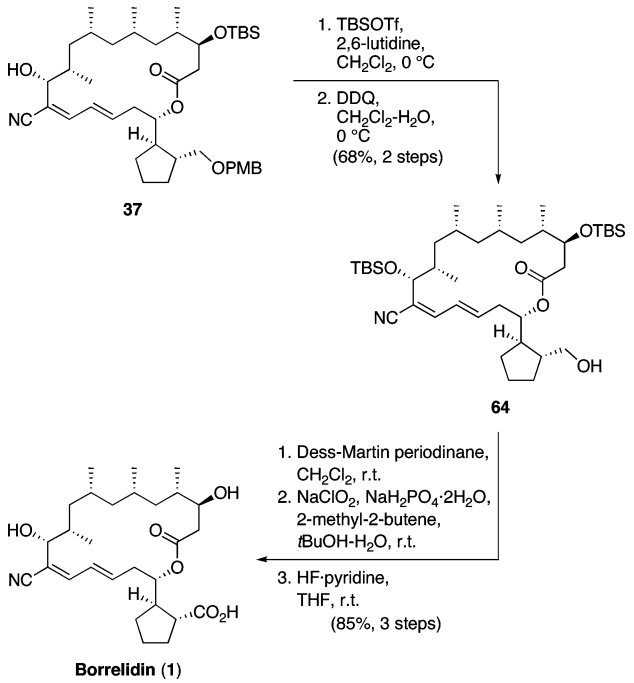
(55) (a) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644. (b) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048.

(56) For recent reviews on Cr-mediated reactions, see: (a) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991. (b) Wessjohann, L. A.; Scheid, G. *Synthesis* **1999**, 1. (c) Saccomano, N. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 1, p 173.

SCHEME 17. Nozaki−Hiyama−Kishi Reaction of Aldehydes 58a and 58b



SCHEME 18. Completion of the Total Synthesis of Borrelidin (1)



62b (83%, two steps). Finally, oxidation of the primary alcohol with TPAP afforded the desired aldehydes **58a** (83%) and **58b** (82%).

Intramolecular Nozaki−Hiyama−Kishi reaction of **58a** and **58b** was performed as shown in Scheme 17. In the reaction of the vinyl bromide **58a** with 10 equiv of chromium(II) chloride in the presence of a catalytic amount of nickel(II) chloride (1 mol %) in DMF (0.01M) at room temperature the cyclized product **57** was obtained in only 13% yield with low diastereoselectivity (2:1 d.r.)[58] along with recovered **58a** in 68% yield. This result was partly predictable due to use of the less reactive vinyl bromide, and we expected an improved result for intramolecular Nozaki−Hiyama−Kishi reaction of the more reactive vinyl iodide **58b** under the same conditions. However, this reaction resulted in a moderate yield (55%) of **57** with the same diastereoselectivity (2:1 d.r.), accompanied by a 11% yield of the proton substituted product **63**. Use of DMSO as a solvent gave no reaction, and increased amounts of chromium(II) chloride and nickel(II) chloride did not yield improved results. In this route, synthesis of the trisubstituted vinyl iodide **29b** by Wittig olefination and Nozaki−Hiyama−Kishi reaction as the key reaction were unsatisfactory.

We investigated three synthetic strategies for macrocyclization as mentioned above. The results demonstrated that among these strategies the initial samarium(II) iodide-mediated intramolecular Reformatsky-type reaction using aldehyde **2** was the most efficient route, providing the shortest number of steps and the highest overall yield of the key intermediate **37**. Therefore, we decided to adopt this initial macrocyclization approach for the total synthesis.

Completion of the Total Synthesis of Borrelidin. In the closing stages, TBS protection and removal of the PMB ether provided the corresponding alcohol **64** in 68% yield over two steps (Scheme 18), which was then subjected to a tandem approach of oxidation of the primary alcohol followed by deprotection of the TBS ether with HF·pyridine, affording borrelidin (**1**) in 85% yield over three steps. Synthetic borrelidin was identical to an authentic sample[1] in all respects.

Conclusion

In summary, we have accomplished the total synthesis of borrelidin. The best feature of our synthetic route is a samarium(II) iodide-mediated intramolecular Reformatsky-type reaction for macrocyclization, after esterification between two key intermediates prepared by concise and efficient synthetic routes. This strategy differs significantly from other total syntheses reported previously. Other key features of our total synthesis include regioselective methylation followed by directed hydrogenation, $MgBr_2 \cdot Et_2O$-mediated stereoselective allylation, and construction of the cyclopentane carboxylic acid subunit by Yamamoto asymmetric carbocyclization. Development of borrelidin analogues as antimalarial agents are currently in progress in our laboratory.

Experimental Section

(3S,4S,6S,8R,10S)-((S,3E,5E)-6-Bromo-6-cyano-1-{(1R,2R)-2-[(4-methoxybenzyloxy)methyl]cyclopentyl}hexa-3,5-dienyl) 3-(tert-Butyldimethylsilyloxy)-4,6,8,10-tetramethyl-11-(tetrahydro-2H-pyran-2-yloxy)undecanoate (32). To a stirred solution of **3** (113 mg, 0.239 mmol) in benzene (2.4 mL) was added triethylamine (67 μL, 0.479 mmol), followed by 2,4,6-trichlorobenzoyl chloride (41 μL, 0.263 mmol) at room temperature. The resulting solution was stirred for 1 h, treated with a solution of **4** (130 mg, 0.311 mmol) in benzene (1.4 mL) and DMAP (38.0 mg, 0.311 mmol) in benzene (1 mL), and stirred for an additional 30 min. The reaction was quenched with saturated aqueous $NaHCO_3$ solution, and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (25:1 hexanes/EtOAc) afforded **32** (204 mg, 97%) as a colorless oil. $[\alpha]^{24}_D$ −7.4° (*c* 0.76, $CHCl_3$); IR (KBr) 2957, 2927, 2856, 1732, 1259, 1092, 1034 cm^{-1}; ^{1}HNMR (270 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.07 (s, 3H), 0.80−0.92 (m, 23H), 0.99−1.42 (m, 5H), 1.46−1.94 (m, 16H), 2.07 (m, 1H), 2.31−2.60 (m, 4H), 3.10−3.39 (m, 3H), 3.45−3.59 (m, 2H),

(57) This reagent was synthesized from (carbethoxymethylene)triphenylphosphorane and I_2, according to the following papers on the synthesis of (ethoxycarbonyliodomethylidene)triphenylphosphorane: (a) Chenault, J.; Dupin, J.-F. E. *Synthesis* **1987**, 498. (b) Zhang, X.; Zhong, P.; Chen, F. *Synth. Commun.* **2004**, *34*, 1729.

(58) The C11 stereochemistry is unknown.

3.80 (s, 3H), 3.86 (m, 1H), 4.06 (m, 1H), 4.41 (d, 1H, J = 11.9 Hz), 4.44 (d, 1H, J = 11.9 Hz), 4.57 (m, 1H), 4.96 (m, 1H), 6.11 (m, 1H), 6.37 (dd, 1H, J = 15.2, 11.2 Hz), 6.87 (d, 2H, J = 8.6 Hz), 7.07 (d, 1H, J = 11.2 Hz), 7.24 (d, 2H, J = 8.6 Hz, ArH); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ −4.7, −4.4, 14.5, 16.4, 16.5, 18.0, 19.4, 19.5, 20.4, 20.6, 25.0, 25.5, 25.8, 26.9, 27.0, 27.2, 29.6, 30.1, 30.6, 30.8, 30.9, 35.4, 36.4, 39.6, 39.9, 40.8, 40.9, 41.4, 45.1, 45.7, 55.1, 61.9, 62.0, 71.5, 72.6, 73.7, 73.9, 74.0, 75.6, 85.0, 98.6, 98.9, 113.6, 114.4, 128.0, 128.9, 130.5, 141.5, 149.3, 159.0, 171.5; HRMS (FAB, *m*-NBA) [M + Na]$^+$ calcd for $C_{47}H_{76}O_7NBrSiNa$ 896.4472, found 896.4473.

(3S,4S,6S,8R,10S)-((S,3E,5E)-6-Bromo-6-cyano-1-{(1R,2R)-2-[(4-methoxybenzyloxy)methyl]cyclopentyl}hexa-3,5-dienyl) 3-(tert-Butyldimethylsilyloxy)-4,6,8,10-tetramethyl-11-oxoundecanoate (2). To a solution of **32** (195 mg, 0.223 mmol) in EtOH (5 mL) was added PPTS (28.0 mg, 0.112 mmol), and the resulting solution was stirred at 50 °C. After 10 h, the reaction mixture was diluted with water, and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (7:1 hexanes/EtOAc) afforded the corresponding alcohol[59] (164 mg, 93%) as a colorless oil. $[\alpha]^{25}_D$ −10.2° (*c* 0.31, $CHCl_3$); IR (KBr) 3500, 2956, 2927, 1733, 1250, 1172, 1084, 1036 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.07 (s, 3H), 0.80−0.91 (m, 24H), 0.94−1.41 (m, 4H), 1.45−1.81 (m, 9H), 1.88 (m, 1H), 2.06 (m, 1H), 2.31−2.60 (m, 4H), 3.24−3.47 (m, 4H), 3.80 (s, 3H), 4.06 (m, 1H), 4.37 (d, 1H, J = 11.9 Hz), 4.41 (d, 1H, J = 11.9 Hz), 4.93 (m, 1H), 6.10 (m, 1H), 6.36 (dd, 1H, J = 14.8, 11.2 Hz), 6.87 (d, 2H, J = 8.6 Hz), 7.06 (d, 1H, J = 11.2 Hz), 7.24 (d, 2H, J = 8.6 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ −4.7, −4.4, 14.4, 15.9, 18.0, 20.5, 20.6, 25.0, 25.8, 27.0, 27.2, 29.6, 30.1, 33.1, 35.4, 36.5, 39.5, 39.6, 41.0, 41.5, 45.1, 45.7, 55.1, 69.1, 71.7, 72.7, 73.9, 75.7, 85.0, 113.7, 114.4, 128.0, 129.0, 130.5, 141.5, 149.3, 159.0, 171.6; HRMS (FAB, *m*-NBA) [M + Na]$^+$ calcd for $C_{42}H_{68}O_6$-NBrSiNa 812.3897, found 812.3936.

To a solution of the alcohol (153 mg, 0.194 mmol) in CH_2Cl_2 (4 mL) were added dried MS4 Å (1 g), TPAP (3.40 mg, 9.70 μmol), and NMO (45.6 mg, 0.388 mmol) at room temperature. The resulting solution was stirred for 30 min and filtered through a silica pad. After evaporation of the filtrate, the residue was purified by flash chromatography (15:1 hexanes/EtOAc) to afford **2** (120 mg, 79%) as a colorless oil. $[\alpha]^{25}_D$ −3.7° (*c* 0.19, $CHCl_3$); IR (KBr) 2955, 2929, 2856, 1731, 1513, 1462, 1249, 1084 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.07 (s, 3H), 0.80−0.91 (m, 21H), 0.93−1.10 (m, 2H), 1.07 (d, 3H, J = 6.9 Hz), 1.18−1.43 (m, 2H), 1.47−1.76 (m, 9H), 1.86 (m, 1H), 2.05 (m, 1H), 2.30−2.59 (m, 4H), 3.23−3.38 (m, 2H), 3.80 (s, 3H), 4.05 (m, 1H), 4.40 (d, 1H, J = 11.9 Hz), 4.44 (d, 1H, J = 11.9 Hz), 4.96 (m, 1H), 6.10 (m, 1H), 6.36 (dd, 1H, J = 15.2, 11.2 Hz), 6.87 (d, 2H, J = 8.6 Hz), 7.07 (d, 1H, J = 11.2 Hz), 7.24 (d, 2H, J = 8.6 Hz), 9.61 (d, 1H, J = 1.6 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ −4.7, −4.4, 13.0, 14.6, 18.0, 20.4, 20.5, 25.0, 25.8, 27.3, 27.4, 29.7, 30.2, 35.4, 36.3, 36.5, 39.5, 40.7, 41.5, 44.1, 45.1,45.2, 55.2, 71.5, 72.7, 74.0, 75.6, 85.1, 113.6, 114.4, 128.1, 129.0, 130.5, 141.5, 149.3, 159.0, 171.6, 205.1; HRMS (FAB, *m*-NBA) [M + Na]$^+$ calcd for $C_{42}H_{66}O_6NBrSiNa$ 810.3740, found 810.3770.

(2S,4E,6Z,8R,9S,11R,13S,15S,16S)-16-(tert-Butyldimethylsilyloxy)-8-hydroxy-2-{(1R,2R)-2-[(4-methoxybenzyloxy)methyl]cyclopentyl}-9,11,13,15-tetramethyl-18-oxooxacyclooctadeca-4,6-diene-7-carbonitrile (37) (Intramolecular Reformatsky-Type Reaction of 2). To a solution of SmI_2 (0.1 M solution in THF, 20 mL, 2.00 mmol) was added HMPA (240 μL, 1.37 mmol) at room temperature. The resulting solution was cooled to −78 °C, and **2** (54.2 mg, 68.9 μmol) was added dropwise over 30 min. After exposure to oxygen gas, the reaction mixture was treated with silica gel (20.0 g) and hexane (20 mL) and stirred for 20 min at room temperature. The mixture was filtered through a pad of silica gel and concentrated in vacuo. The residue was purified by flash chromatography (10:1 to 5:1 hexanes/EtOAc) to afford **35** (6.10 mg, 13%), **36** (10.5 mg, 22%), the desired **37** (10.2 mg, 21%), and the C11 epimer **38** (9.20 mg, 19%) each as a yellow oil.

36 : $[\alpha]^{24}_D$ +16.2° (*c* 0.91, $CHCl_3$); IR (KBr) 3471, 2954, 2856, 2213, 1738, 1644, 1613, 1587, 1514, 1464, 1362, 1301, 1250, 1174, 1080, 1039, 973, 939, 836, 775, 758 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.10 (s, 3H), 0.16 (s, 3H), 0.67 (m, 1H), 0.76 (d, 3H, J = 6.6 Hz), 0.77 (d, 3H, J = 6.9 Hz), 0.72−1.66 (m, 26H), 1.67−2.19 (m, 6H), 2.20−2.62 (m, 4H), 3.27 (dd, 1H, J = 9.0, 7.5 Hz), 3.35 (dd, 1H, J = 9.0, 6.3 Hz), 3.69 (d, 1H, J = 9.0 Hz), 3.80 (s, 3H), 4.00 (dt, 1H, J = 8.8, 2.2 Hz), 4.39 (d, 1H, J = 11.7 Hz), 4.45 (d, 1H, J = 11.7 Hz), 5.15 (ddd, 1H, J = 11.2, 7.0, 3.8 Hz), 6.53 (ddd, 1H, J = 14.5, 11.2, 1.6 Hz), 6.60 (d, 1H, J = 11.2 Hz), 6.87 (d, 1H, J = 8.7 Hz), 7.26 (d, 1H, J = 8.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.0, −3.5, 15.4, 18.0, 18.1, 19.2, 20.1, 25.0, 25.6, 25.9, 26.1, 29.0, 29.7, 30.2, 35.3, 35.5, 36.4, 37.6, 41.7, 43.2, 46.8, 48.8, 55.2, 72.8, 73.0, 74.3, 74.9, 79.7, 113.8, 114.6, 116.0, 140.9, 144.5, 159.2, 171.5; HRMS (FAB, *m*-NBA) [M + Na]$^+$ calcd for $C_{42}H_{67}O_6NSiNa$ 732.4635, found 732.4640.

37: $[\alpha]^{24}_D$ −19.0° (*c* 0.54, $CHCl_3$); IR (KBr) 3470, 2956, 2926, 2853, 1737, 1513, 1463, 1249, 1079, 1036 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.10 (s, 3H), 0.11 (s, 3H), 0.79 (d, 3H, J = 6.9 Hz), 0.81 (d, 3H, J = 5.9 Hz), 0.86 (m, 3H), 0.89 (s, 9H), 1.03 (d, 3H, J = 6.6 Hz), 0.76−1.41 (m, 9H), 1.52−2.20 (m, 7H), 2.26−2.25 (m, 6H), 3.17 (dd, 1H, J = 8.9, 7.6 Hz), 3,34 (dd, 1H, J = 8.9, 4.9 Hz), 3.80 (s, 3H), 4.04 (m, 1H), 4.08 (d, 1H, J = 9.9 Hz), 4.38 (d, 1H, J = 11.9 Hz), 4.43 (d, 1H, J = 11.9 Hz), 5.02 (m, 1H), 6.17 (m, 1H), 6.30 (dd, 1H, J = 14.8, 10.9 Hz), 6.82 (d, 1H, J = 10.9 Hz), 6.87 (d, 2H, J = 8.6 Hz), 7.24 (d, 2H, J = 8.6 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ −5.4, −4.4, 14.9, 17.9, 18.6, 19.8, 20.7, 25.0, 25.9, 26.1, 26.2, 30.0, 30.3, 35.3, 35.6, 36.2, 36.4, 37.6, 42.7, 43.4, 43.6, 48.1, 55.3, 72.6, 72.9, 73.8, 74.0, 75.2, 77.2, 113.8, 115.5, 126.9, 128.9, 130.7, 139.7, 144.2, 159.1, 171.5; HRMS (FAB, *m*-NBA) [M + Na]$^+$ calcd for $C_{42}H_{67}O_6NSiNa$ 732.4635, found 732.4639.

38: $[\alpha]^{24}_D$ −17.6° (*c* 1.05, $CHCl_3$); IR (KBr) 3454, 2955, 2926, 2854, 1737, 1513, 1463, 1248, 1175, 1078 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.99 (s, 3H), 0.11 (s, 3H), 0.77 (d, 3H, J = 6.9 Hz), 0.78 (d, 3H, J = 5.9 Hz), 0.86 (s, 9H), 0.88 (m, 3H), 1.05 (d, 3H, J = 6.9 Hz), 0.72−1.17 (m, 5H), 1.21−2.12 (m, 13H), 2.18−2.40 (m, 4H), 3.27 (dd, 1H, J = 8.9, 7.3 Hz), 3.36 (dd, 1H, J = 8.9, 5.9 Hz), 3.80 (s, 3H), 4.00 (m, 1H), 4.40 (d, 1H, J = 11.9 Hz), 4.44 (d, 1H, J = 11.9 Hz), 4.54 (d, 1H, J = 3.3 Hz), 5.04 (m, 1H), 5.90 (m, 1H), 6.38 (dd, 1H, J = 14.2, 11.5 Hz), 6.74 (d, 1H, J = 11.5 Hz), 6.87 (d, 2H, J = 8.6 Hz), 7.25 (d, 2H, J = 8.6 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ −5.2, −4.3, 12.4, 17.9, 18.5, 19.9, 20.7, 25.0, 25.7, 25.9, 26.0, 29.4, 30.2, 35.7, 35.9, 37.0, 37.4, 37.5, 41.6, 43.8, 46.4, 48.4, 55.2, 72.0, 72.8, 73.2, 74.3, 74.7, 77.2, 112.4, 113.8, 126.7, 129.0, 130.7, 142.2, 145.8, 159.1, 171.3; HRMS (FAB, *m*-NBA) [M + Na]$^+$ calcd for $C_{42}H_{67}O_6NSiNa$ 732.4635, found 732.4642.

(2S,4E,6Z,8R,9S,11R,13S,15S,16S)-16-(tert-Butyldimethylsilyloxy)-8-hydroxy-2-{(1R,2R)-2-[(4-methoxybenzyloxy)methyl]-cyclopentyl}-9,11,13,15-tetramethyl-18-oxooxacyclooctadeca-4,6-diene-7-carbonitrile (37) (Oxidation/Reduction of 38). To a solution of **38** (13.2 mg, 18.6 μmol) in CH_2Cl_2 (1 mL) was added Dess−Martin periodinane (22.6 mg, 55.9 μmol). After stirring for 30 min, the reaction was quenched by saturated aqueous $Na_2S_2O_3$ solution and saturated aqueous $NaHCO_3$ solution, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue (**39**) was subjected to the next reaction without further purification.

To a solution of the crude **39** in MeOH (1 mL) at 0 °C was added cerium(III) chloride (14.0 mg, 37.2 μmol) followed by sodium borohydride (1.40 mg, 37.2 μmol). The reaction was stirred for 10 min and then poured into water. The aqueous phase was

(59) The chemical number of the alcohol in the Supporting Information is **32a**.

extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (8:1 hexanes/EtOAc) afforded **37** (8.50 mg, two steps 66%) and **38** (0.70 mg, two steps 5.3%).

(2S,4E,6Z,8R,9S,11R,13S,15S,16S)-8,16-bis(tert-Butyldimethylsilyloxy)-2-[(1R,2R)-2-(hydroxymethyl)cyclopentyl]-9,11,13,-15-tetramethyl-18-oxooxacyclooctadeca-4,6-diene-7-carbonitrile (64). To a solution of **37** (13.1 mg, 18.4 μmol) in CH_2Cl_2 (200 μL) cooled to 0 °C was added 2,6-lutidine (4 μL, 31.4 μmol) followed by TBSOTf (6 μL, 24.0 μmol). The resulting solution was stirred at 0 °C for 1 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (25:1 hexanes/EtOAc) afforded the corresponding bis-TBS ether[60] (11.4 mg, 75%) as a colorless oil. $[\alpha]^{25}_D$ −37.8° (*c* 0.69, $CHCl_3$); IR (KBr) 2956, 2928, 2856, 1738, 1612, 1513, 1250, 1084 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.05 (s, 3H), 0.10 (s, 3H), 0.12 (s, 3H), 0.78−1.20 (m, 17H), 0.90 (s, 9H), 0.91 (s, 9H), 1.23−2.09 (m, 11H), 2.16−2.33 (m, 5H), 2.52 (m, 1H), 3.17 (dd, 1H, *J* = 8.6, 8.3 Hz), 3.35 (dd, 1H, *J* = 8.9, 4.9 Hz), 3.80 (s, 3H), 3.98−4.10 (m, 2H), 4.39 (d, 1H, *J* = 11.9 Hz), 4.43 (d, 1H, *J* = 11.9 Hz), 5.02 (m, 1H), 6.09−6.32 (m, 2H), 6.75 (d, 1H, *J* = 10.6 Hz), 6.87 (d, 2H, *J* = 8.6 Hz), 7.23 (d, 2H, *J* = 8.6 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ −5.6, −4.9, −4.6, −3.5, 15.3, 17.9, 18.1, 18.5, 20.0, 20.7, 22.6, 25.0, 25.6, 25.7, 26.1, 26.2, 29.7, 30.0, 30.2, 35.6, 35.9, 36.3, 37.1, 42.9, 43.5, 48.1, 55.2, 72.6, 73.3, 73.9, 74.0, 75.3, 77.2, 113.8, 118.8, 127.1, 129.0, 130.7, 139.0, 142.9, 159.1, 171.5; HRMS (FAB, *m*-NBA) $[M + Na]^+$ calcd for $C_{48}H_{81}O_6NSi_2N$ 846.5500, found 846.5494.

To a solution of the bis-TBS ether (11.4 mg, 13.9 mmol) in CH_2Cl_2 (250 μL) and H_2O (50 μL) was added DDQ (3.70 mg, 16.6 mmol) at 0 °C. The reaction mixture was stirred for 15 min and then poured into water. The aqueous phase was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (8:1 hexanes/EtOAc) afforded **64** (8.80 mg, 90%, 68% for two steps) as a colorless oil. $[\alpha]^{25}_D$ −37.2° (*c* 0.36, $CHCl_3$); IR (KBr) 3447, 2956, 2927, 2856, 1740, 1464, 1386, 1292, 1253, 1081 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ −0.01 (s, 3H), 0.05 (s, 3H), 0.11 (s, 3H), 0.13 (s, 3H), 0.80 (d, 3H, *J* = 5.9 Hz), 0.81 (d, 3H, *J* = 7.3 Hz), 0.85 (d, 3H, *J* = 6.6 Hz), 0.90 (s, 9H), 0.91 (s, 9H), 0.94 (d, 3H, *J* = 6.3 Hz), 0.67−1.18 (m, 5H), 1.23−2.09 (m, 13H), 2.21−2.39 (m, 3H), 2.54 (m, 1H), 3.42 (dd, 1H, *J* = 10.6, 6.6 Hz), 3.51 (dd, 1H, *J* = 10.6, 5.9 Hz), 3.99 (d, 1H, *J* = 9.9 Hz), 4.08 (m, 1H), 5.02 (m, 1H), 6.15 (m, 1H), 6.28 (dd, 1H, *J* = 15.2, 10.6 Hz), 6.75 (d, 1H, *J* = 10.6 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ −5.6, −4.9, −4.6, −3.4, 15.3, 17.9, 18.1, 18.4, 20.0, 20.7, 22.7, 25.1, 25.7, 26.1, 26.2, 29.5, 29.7, 30.5, 35.6, 35.9, 36.2, 37.1, 43.4, 43.5, 45.5, 48.0, 66.7, 73.3, 73.9, 75.4, 77.2, 118.7, 127.2, 138.6, 142.8, 171.4; HRMS (FAB, *m*-NBA) $[M + Na]^+$ calcd for $C_{40}H_{73}O_5NSi_2$-Na 726.4925, found 726.4924.

Borrelidin (1). To a solution of **64** (8.80 mg, 12.5 μmol) at room temperature was added Dess−Martin periodinane (10.6 mg, 25.0 μmol). The mixture was stirred for 30 min. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ solution and saturated aqueous $Na_2S_2O_3$ solution, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting crude aldehyde was subjected to the next reaction without further purification.

The crude aldehyde was dissolved in *t*-BuOH (250 μL) and H_2O (250 μL) at room temperature. 2-Methyl-2-butene (7 μL, 62.8 μmol), sodium phosphate (5.80 mg, 37.5 μmol), and sodium chlorite (3.30 mg, 37.5 μmol) were added to the solution. After 30 min, the reaction mixture was poured into water and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo to give the corresponding carboxylic acid.

To a solution of the crude acid in THF (1.0 mL) and pyridine (1.0 mL) was added dropwise HF·pyridine (500 μL). The solution was stirred for 2 days. The resulting solution was filtered through a short plug of silica gel and concentrated in vacuo. Flash chromatography (30:1 hexanes/EtOAc) afforded borrelidin (**1**) (5.20 mg, 85% for three steps) as a white solid. $[\alpha]^{27}_D$ −26.7° (*c* 0.10, EtOH), lit[1] −28° (EtOH); mp 140−142 °C, authentic sample 141−143 °C, lit[1] 145−147 °C; IR (KBr) 3446, 2924, 2853, 1717, 1465, 1275, 1259 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.73 (m, 1H), 0.80 (d, 3H, *J* = 6.3 Hz), 0.83 (d, 3H, *J* = 7.2 Hz), 0.84 (d, 3H, *J* = 6.6 Hz), 1.05 (d, 3H, *J* = 6.6 Hz), 0.89−1.44 (m, 6H), 1.50−1.71 (m, 3H), 1.75−2.11 (m, 6H), 2.32 (dd, 1H, *J* = 16.8, 2.3 Hz), 2.44 (dd, 1H, *J* = 16.8, 9.9 Hz), 2.49−2.78 (m, 4H), 3.87 (dt, 1H, *J* = 9.9, 2.3 Hz), 4.11 (d, 1H, *J* = 9.6 Hz), 4.98 (dt, 1H, *J* = 10.6, 3.3 Hz), 6.20 (ddd, 1H, *J* = 14.5, 9.2, 5.3 Hz), 6.39 (dd, 1H, *J* = 14.5, 11.2 Hz), 6.83 (d, 1H, *J* = 11.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9, 16.9, 18.2, 20.1, 25.2, 26.2, 27.1, 29.7, 31.2, 35.2, 35.6, 35.9, 37.4, 39.3, 43.0, 45.8, 47.8, 48.4, 69.8, 73.1, 77.2, 115.9, 118.2, 127.0, 138.5, 144.0, 172.2, 180.6; HRMS (FAB, *m*-NBA) $[M + Na]^+$ calcd for $C_{28}H_{43}O_6Na$ 512.2988, found 512.2978.

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Supporting Information Available: Experimental procedures, ^{1}H and ^{13}C NMR and IR spectral data, optical rotations, HRMS, and additional information on key intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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(60) The chemical number of the bis-TBS ether in the Supporting Information is **37a**.