ORGANIC LETTERS

2004
Vol. 6, No. 11
1865−1867

# Total Synthesis of (−)-Borrelidin

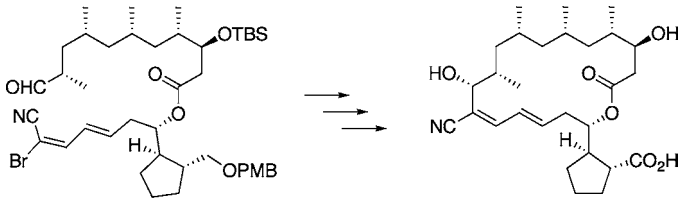
**Tohru Nagamitsu,[†] Daisuke Takano,[†] Takeo Fukuda,[†] Kazuhiko Otoguro,[‡] Isao Kuwajima,[§] Yoshihiro Harigaya,[†] and Satoshi Ōmura*[,‡,§]**

*School of Pharmaceutical Science, Kitasato University, Kitasato Institute for Life Sciences, Kitasato University, and The Kitasato Institute, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641, Japan*

*omura-s@kitasato.or.jp*

**Received April 8, 2004**

## ABSTRACT




**Borrelidin**

**The total synthesis of borrelidin has been achieved. The best feature of our synthetic route is $SmI_2$-mediated intramolecular Reformatsky-type reaction for macrocyclization after esterification between two segments. The two key segments were synthesized through chelation-controlled carbotitanation, chelation-controlled hydrogenation, stereoselective Reformatsky reaction, and $MgBr_2$·$Et_2O$-mediated chelation-controlled allylation.**

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] Other useful biological activities of borrelidin such as its inhibitory activities against threonyl-tRNA synthetase[2] and cyclin-dependent kinase[3] and its potent antiangiogenesis activity[4] were reported later. The planar structure of borrelidin was elucidated by Keller−Schierlein in 1967,[5] and the absolute configuration was determined by Anderson et al. through X-ray crystallography of a chiral solvate.[6] Recently, we found that borrelidin also shows potent antimalarial activity against chloroquine-resistant strains, both in vitro and in vivo.[7] This biological profile, as well as its structural complexity, prompted substantial synthetic effort toward the total synthesis of (−)-borrelidin. To date, two elegant total syntheses of borrelidin have been reported, by Morken et al.[8] and Hanessian et al.,[9] respectively, and two synthetic studies toward total synthesis have also been described.[10] We report herein the stereocontrolled total synthesis of (−)-borrelidin (**1**), by a convergent strategy that features $SmI_2$-mediated intramolecular Reformatsky-type reaction of α-bromo-α,*β*:*γ*,*δ*-unsaturated nitrile **2** for macrocyclization at C11−12 after esterification between acid **10** and alcohol **15**, as shown in Figure 1.

We started from a known chiral alcohol **3** (97% ee), which was readily obtained from the *meso*-diol by enzymatic desymmetrization,[11] to lead to the C1−C11 segment **10** (Scheme 1). The conversion of **3** to aldehyde **4**[12] was efficiently accomplished by a series of protections and deprotections followed by TPAP oxidation. 1,2-Addition of

[†] School of Pharmaceutical Science, Kitasato University.
[‡] The Kitasato Institute.
[§] Kitasato Institute for Life Sciences, Kitasato University.

(1) Berger, J.; Jampolsky, L. M.; Goldberg, M. W. *Arch. Biochem.* **1949**, *22*, 476.
(2) Paetz, W.; Nass, G. *Eur. J. Biochem.* **1973**, *35*, 331.
(3) Tsuchiya, E.; Yukawa, M.; Miyakawa, T.; Kimura, K.; Takahashi, H. *J. Antibiot.* **2001**, *54*, 84.
(4) Wakabayashi, T.; Kageyama, R.; Naruse, N.; Tsukahara, N.; Funahashi, Y.; Kitoh, K.; Watanabe, Y. *J. Antibiot.* **1997**, *50*, 671.
(5) Keller-Schierlein, W. *Helv. Chim. Acta* **1967**, *50*, 75.
(6) Anderson, B. F.; Herlt, A. J.; Rickards, R. W.; Robertson, G. B. *Aust. J. Chem.* **1989**, *42*, 717.
(7) Otoguro, K.; Ui, H.; Ishiyama, A.; Kobayashi, M.; Togashi, H.; Takahashi, Y.; Masuma, R.; Tanaka, H.; Tomoda, H.; Yamada, H.; Ōmura, S. *J. Antibiot.* **2003**, *56*, 727.
(8) Duffey, M. O.; LeTiran, A.; Morken, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 1458.
(9) Hanessian, S.; Yang, Y.; Giroux, S.; Mascitti, V.; Ma, J.; Raeppel, F. *J. Am. Chem. Soc.* **2003**, *125*, 13784.
(10) (a) Haddad, N.; Grishko, M.; Brik, A. *Tetrahedron Lett.* **1997**, *38*, 6075. (b) Vong, B. G.; Abraham, S.; Xiang, A. X.; Theodorakis, E. A. *Org. Lett.* **2003**, *4*, 1617.
(11) Fujita, K.; Mori, K. *Eur. J. Org. Chem.* **2001**, *66*, 493.

10.1021/ol049356w CCC: $27.50 
**Published on Web 05/08/2004**

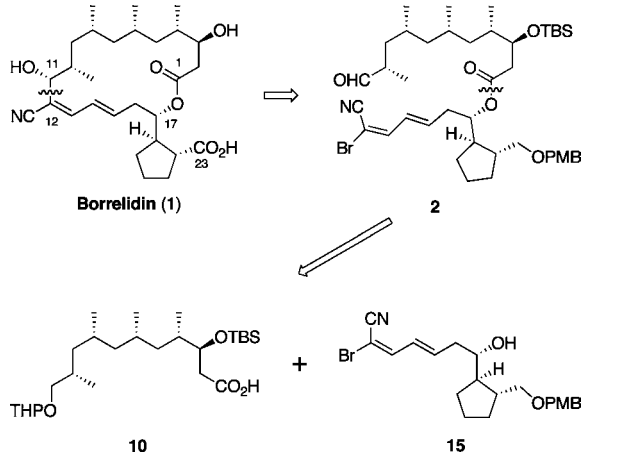
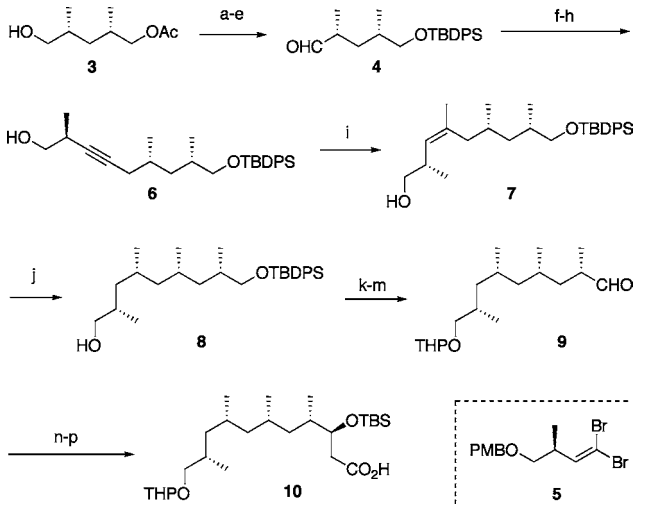



**Figure 1.** Structure and retrosynthesis of borrelidin (**1**).

lithium acetylide (which was easily prepared from **5**[13]) to **4** was quenched with $MeO_2CCl$ to furnish the corresponding methyl carbonate, which was treated with $Pd(acac)_2/Bu_3P/HCO_2NH_4$[14] to give **6** after PMB deprotection. Subsequent

**Scheme 1**[a]

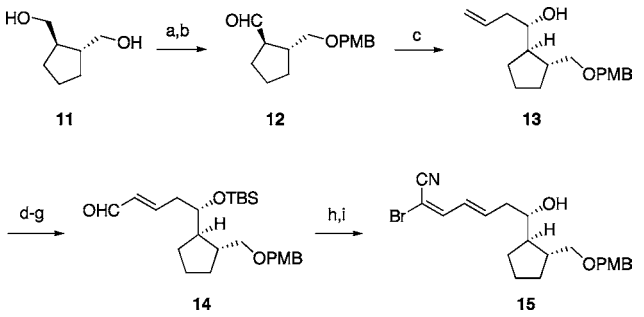



[a] Conditions: (a) TBSCl, imidazole (98%). (b) $K_2CO_3$, MeOH (98%). (c) TBDPSCl, imidazole. (d) PPTS (97%, two steps). (e) TPAP, NMO, 4 Å MS (88%). (f) (i) **5**, *n*-BuLi; (ii) **4**, then $MeO_2CCl$. (g) $Pd(acac)_2$, $Bu_3P$, $HCO_2NH_4$ (90%, two steps). (h) DDQ (97%). (i) $Me_3Al$, $TiCl_4$ (80%). (j) $H_2$ (1 MPa), Rh[(nbd)-dppb]$BF_4$ (91%). (k) Dihydropyrane, PPTS (100%). (l) TBAF (96%). (m) TPAP, NMO, 4 Å MS (89%). (n) (*R*)-4-Benzyl-3-bromoacetyl-2-oxazolidinone, $SmI_2$ (98%, 15:1). (o) TBSOTf, 2,6-lutidine. (p) LiOH, $H_2O_2$ (84%, two steps).

chelation-controlled carbotitanation of the homoallylic alcohol **6** under slightly modified Thompson's conditions[15] produced the desired trisubstituted (*Z*)-olefin **7** as the sole product.[16] Chelation-controlled hydrogenation[17] of **7** using catalytic Rh[(nbd)dppb]$BF_4$ under high pressure (1 MPa) gave rise to **8** with the desired C8 methyl stereocenter.[18] THP ether formation, deprotection of the TBDPS ether, and TPAP oxidation efficiently produced aldehyde **9**. Stereoselective Reformatsky reaction of **9** with (*R*)-4-benzyl-3-bromoacetyl-2-oxazolidinone using $SmI_2$ under Fukuzawa's conditions[19] afforded the corresponding adduct with the desired C3 stereochemistry (15:1),[20] which was subjected to TBS protection followed by removal of the chiral auxiliary to give carboxylic acid **10**.

The C12−C23 segment **15** was prepared from the known chiral diol **11**, which was readily derived from succinic acid by Yamamoto asymmetric carbocyclization[21] (Scheme 2).

**Scheme 2**[a]




[a] Conditions: (a) PMBCl, NaH; (b) Dess−Martin periodinane (89%, two steps); (c) allyltrimethylsilane, $MgBr_2 \cdot Et_2O$ (95%, 20:1); (d) TBSOTf, 2,6-lutidine (99%); (e) $OsO_4$, NMO; (f) $NaIO_4$ (100%, two steps); (g) $Ph_3P{=}CHCHO$ (73%); (h) $(EtO)_2P(O)CH$-(Br)CN, DBU, LiCl (96%); (i) HF·pyridine (94%).

Monoselective PMB protection of diol **11** followed by Dess−Martin oxidation gave aldehyde **12**. Reaction with allylmagnesium bromide or Brown's allylboration[22] of **12** to produce **13** led to low stereoselectivity. Therefore, chelation-controlled allylation of **12** with allyltrimethylsilane in the presence of Lewis acids was investigated. It was found that

(12) For another synthetic route, see: (a) Smith, A. B., III; Condon, S. M.; McCauley, J. A.; Leazer, J. L., Jr.; Leahy, J. W.; Maleczka, R. E., Jr. *J. Am. Chem. Soc.* **1997**, *119*, 947. (b) Smith, A. B., III; Maleczka, R. E., Jr.; Leazer, J. L., Jr.; Leahy, J. W.; McCauley, J. A.; Condon, S. M. *Tetrahedron Lett.* **1994**, *35*, 4911. Also see: Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Straub, J. A.; Palkowitz, A. D. *J. Org. Chem.* **1990**, *55*, 4117.

(13) Paquette, L. A.; Guevel, R.; Sakamoto, S.; Kim, I. H.; Crawford, J. *J. Org. Chem.* **2003**, *68*, 6096.

(14) Randinov, R.; Hutchings, S. D. *Tetrahedron Lett.* **1999**, *40*, 8955.

(15) Schiavelli, M. D.; Plunkett, J. J.; Thompson, D. W. *J. Org. Chem.* **1981**, *46*, 807.

(16) Stereochemistry was confirmed by NOE. Also see Supporting Information.

(17) Evans, D. A.; Morrissey, M. M.; Dow, R. L. *Tetrahedron Lett.* **1985**, *26*, 6005.

(18) Stereochemistries of C8 and C11 were confirmed by the achievement of the total synthesis of borrelidin (**1**).

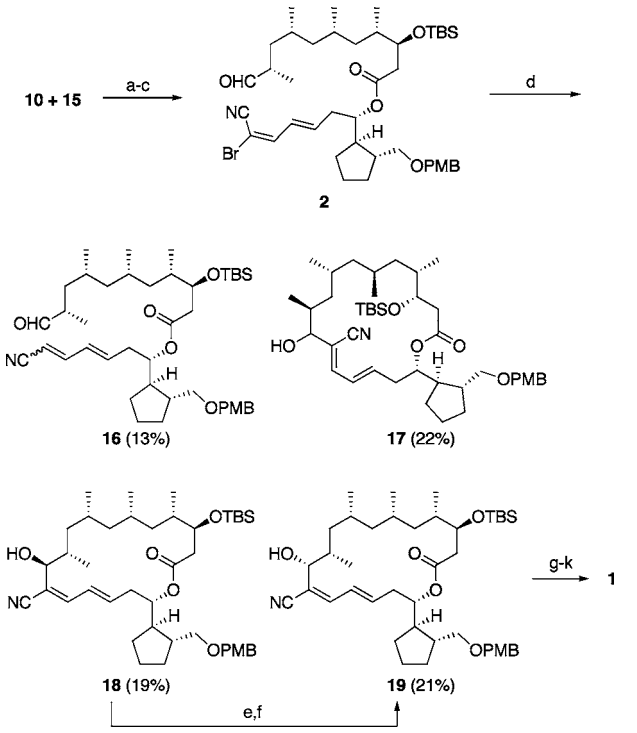
(19) Fukuzawa, S.; Matsuzawa, H.; Yoshimitsu, S. *J. Org. Chem.* **2000**, *65*, 1702.

(20) Stereochemistry was determined by the modified Mosher procedure; see: Ohtani, I.; Kusumi, J.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092. Also see Supporting Information.

(21) (a) Misumi, A.; Iwanaga, K.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 3343. (b) Fujimura, O.; de la Mata, F. J.; Grubbs, R. H. *Organometallics* **1996**, *15*, 1865.

(22) Brown, H. C.; Randad, R. S.; Bhat, K. S.; Zaidlewicz, M.; Racherla, U. S. *J. Am. Chem. Soc.* **1990**, *112*, 2389.

**Scheme 3**[a]




[a] Conditions: (a) **10**, 2,4,6-trichlorobenzoyl chloride, $Et_3N$ then **15**, DMAP (97%); (b) PPTS (93%); (c) TPAP, NMO, 4 Å MS (79%); (d) $SmI_2$, HMPA; (e) Dess−Martin periodinane; (f) $NaBH_4$, $CeCl_3 \cdot 7H_2O$; (71%, two steps, 12:1); (g) TBSOTf, 2,6-lutidine (75%); (h) DDQ (90%); (i) Dess−Martin periodinane; (j) $NaClO_2$, $NaH_2PO_4 \cdot 2H_2O$, 2-methyl-2-butene; (k) HF·pyridine (85%, three steps).

$MgBr_2 \cdot Et_2O$ gave the best result,[23,24] affording **13** with high yield and stereoselectivity (20:1).[20] Dihydroxylation after TBS protection of **13** followed by treatment with $NaIO_4$ afforded the corresponding aldehyde, which was subjected to a Wittig reaction with $Ph_3P{=}CHCHO$ to give (*E*)-unsaturated aldehyde **14**. Subsequent Horner−Emmons olefination of **14** with $(EtO)_2P(O)CH(Br)CN$[25] using DBU and LiCl[26] furnished the corresponding (*E*)-vinyl bromide as a single isomer, which was exposed to HF·pyridine to form alcohol **15**.

Esterification between **10** and **15** was performed under Yamaguchi conditions[27] to give rise to the corresponding ester, which was converted to the aldehyde, the key intermediate for the intramolecular Reformatsky-type reaction, by THP deprotection followed by TPAP oxidation. Next, we explored the $SmI_2$-mediated intramolecular Reformatsky-type reaction of **2**. Treatment of **2** with $SmI_2$ at −78 °C gave no reaction, and a rise in the reaction temperature (to 0 °C) afforded a trace amount of cyclized compounds accompanied by decomposition. We next examined the effect of HMPA as an additive at −78 °C.[28] Consequently, treatment of **2** with a 3:2 ratio mixture of $SmI_2$ and HMPA at −78 °C gave the best result, to produce cyclized products **18** and **19**[16,18] with the desired *Z* stereochemistry at C12−C13 in a 40% total yield, accompanied by the protonated uncyclized compound **16** (13%) and the cyclized compound **17** with the undesired *E* stereochemistry[16] at C12−C13 (22%). Inversion of the hydroxyl group at C11, namely, conversion of epimer **18** into **19**, by Dess−Martin oxidation followed by Luche reduction proved to be quite effective (12:1). TBS protection of **19**, removal of the PMB ether, and a tandem oxidation approach provided the corresponding carboxylic acid, which was subjected to deprotection of the TBS ether with HF·pyridine, to give borrelidin (**1**). Synthetic borrelidin (**1**) was identical to an authentic sample in all respects ($[\alpha]_D$, mp, $^1H$ and $^{13}C$ NMR, IR, FAB-MS).

In summary, we have achieved the total synthesis of borrelidin (**1**). The best feature of our synthetic route is $SmI_2$-mediated intramolecular Reformatsky-type reaction for macrocyclization after esterification between two segments, and this strategy differs significantly from those of the total syntheses reported previously. The other noteworthy features are as follows: chelation-controlled carbotitanation of a homoallylic alcohol to construct the trisubstituted (*Z*)-olefin **7**, $MgBr_2 \cdot Et_2O$-mediated stereoselective allylation of **12**, and effective inversion of the hydroxyl group for the conversion of **18** to **19**. Improvement of the key intramolecular Reformatsky-type reaction and development of borrelidin analogues as antimalarial agents are currently in progress in our laboratory.

**Acknowledgment.** This work was supported in part by a Grant from the 21st Century COE Program, Ministry of Education, Culture, Sports, Science and Technology, Japan. T.N. acknowledges a Kitasato University research grant for young researchers.

**Supporting Information Available:** Characterization data and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049356W

(23) Use of other Lewis acids led to low stereoselectivity.

(24) For the effectiveness of $MgBr_2 \cdot Et_2O$ in chelation-controlled allylation, see: Williams, D. R.; Klingler, F. D. *Tetrahedron Lett.* **1987**, *28*, 869.

(25) Iorga, B.; Ricard, L.; Savignac, P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3311.

(26) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

(27) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamagauchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

(28) Inanaga, J.; Ishikawa, M.; Yamaguchi, M. *Chem. Lett.* **1987**, 1485.