Total Synthesis of (–)-Borrelidin

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Received April 8, 2004

ORGANIC LETTERS 2004

Vol. 6, No. 11 1865-1867

ABSTRAC1



The total synthesis of borrelidin has been achieved. The best feature of our synthetic route is Sml2-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 MgBr₂·Et₂O-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 synthetase² and cyclindependent kinase³ and its potent antiangiogenesis activity⁴ 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

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10.1021/ol049356w CCC: \$27.50 © 2004 American Chemical Society Published on Web 05/08/2004

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- $\alpha,\beta;\gamma,\delta$ -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

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

lithium acetylide (which was easily prepared from 5^{13}) to 4 was quenched with MeO₂CCl to furnish the corresponding methyl carbonate, which was treated with Pd(acac)₂/Bu₃P/HCO₂NH₄¹⁴ to give **6** after PMB deprotection. Subsequent



^{*a*} Conditions: (a) TBSCl, imidazole (98%). (b) K₂CO₃, 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 MeO₂CCl. (g) Pd(acac)₂, Bu₃P, HCO₂NH₄ (90%, two steps). (h) DDQ (97%). (i) Me₃Al, TiCl₄ (80%). (j) H₂ (1 MPa), Rh[(nbd)-dppb]BF₄ (91%). (k) Dihydropyrane, PPTS (100%). (l) TBAF (96%). (m) TPAP, NMO, 4 Å MS (89%). (n) (*R*)-4-Benzyl-3-bromoacetyl-2-oxazolidinone, SmI₂ (98%, 15:1). (o) TBSOTf, 2,6-lutidine. (p) LiOH, H₂O₂ (84%, two steps).

chelation-controlled carbotitanation of the homoallylic alcohol **6** under slightly modified Thompson's conditions¹⁵ produced the desired trisubstituted (*Z*)-olefin **7** as the sole product.¹⁶ Chelation-controlled hydrogenation¹⁷ of **7** using catalytic Rh[(nbd)dppb]BF₄ 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 SmI₂ under Fukuzawa's conditions¹⁹ 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 carbocyclization²¹ (Scheme 2).



^{*a*} Conditions: (a) PMBCl, NaH; (b) Dess-Martin periodinane (89%, two steps); (c) allyltrimethylsilane, MgBr₂·Et₂O (95%, 20: 1); (d) TBSOTf, 2,6-lutidine (99%); (e) OsO₄, NMO; (f) NaIO₄ (100%, two steps); (g) Ph₃P=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 allylboration²² of **12** to produce **13** led to low stereoselectivity. Therefore, chelationcontrolled allylation of **12** with allyltrimethylsilane in the presence of Lewis acids was investigated. It was found that

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^{*a*} Conditions: (a) **10**, 2,4,6-trichlorobenzoyl chloride, Et₃N then **15**, DMAP (97%); (b) PPTS (93%); (c) TPAP, NMO, 4 Å MS (79%); (d) SmI₂, HMPA; (e) Dess—Martin periodinane; (f) NaBH₄, CeCl₃·7H₂O; (71%, two steps, 12:1); (g) TBSOTf, 2,6-lutidine (75%); (h) DDQ (90%); (i) Dess—Martin periodinane; (j) NaClO₂, NaH₂PO₄·2H₂O, 2-methyl-2-butene; (k) HF•pyridine (85%, three steps).

MgBr₂·Et₂O 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 NaIO₄ afforded the corresponding aldehyde, which was subjected to a Wittig reaction with Ph₃P=CHCHO to give (*E*)-unsaturated aldehyde **14**. Subsequent Horner–Emmons ole-fination of **14** with (EtO)₂P(O)CH(Br)CN²⁵ using DBU and LiCl²⁶ 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 conditions²⁷ 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 SmI₂-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 SmI₂ 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 stereochemistry¹⁶ 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 ¹³C NMR, IR, FAB-MS).

In summary, we have achieved the total synthesis of borrelidin (1). The best feature of our synthetic route is SmI₂-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, MgBr₂•Et₂O-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

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