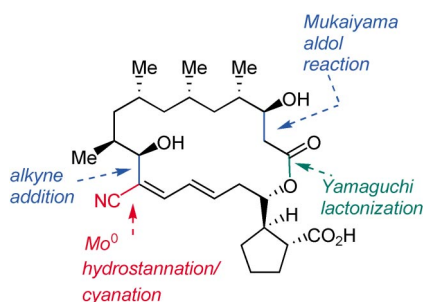


Natural Product Synthesis

Stereoselective Total Synthesis of (–)-Borrelidin



1: (–)-borrelidin

A convergent synthesis of (–)-borrelidin (1) is reported based on the retrosynthetic disconnections indicated in the picture.

Highlights of the strategy include the construction of a strained enynone-containing macrolide and the installation of a cyano group in a regioselective manner by a novel molybdenum-catalyzed hydrostannation of the alkyne.

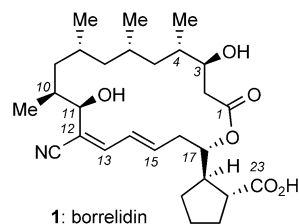
B. G. Vong, S. H. Kim, S. Abraham, E. A. Theodorakis* *_____* 3947–3951

Keywords: hydrostannation · macrolactonization · natural products · synthetic methods · total synthesis

2004 – 43/30

Stereoselective Total Synthesis of
(–)-Borrelidin**Binh G. Vong, Sun Hee Kim, Sunny Abraham, and
Emmanuel A. Theodorakis*

Borrelidin (treponemycin, **1**) is a biologically intriguing and structurally unique macrolide, first isolated by Berger et al. from a soil sample of *Streptomyces rochei* and subsequently



identified in other related *Streptomyces* species.^[1] Initial biological screening indicated that **1** exhibits broad antiviral^[2] and antibacterial^[3] activity, which presumably arises from its inhibition of threonyl-tRNA synthetase and protein synthesis.^[4] More recently, borrelidin was found to inhibit cyclin-dependent kinase (CDK) and thus display potent antimetabolic properties at low μM concentrations.^[5] Equally impressive are reports that **1** inhibits angiogenesis in rat aorta models at subnanomolar concentrations ($\text{IC}_{50} = 0.4 \text{ ng mL}^{-1}$) through a yet unknown mechanism of action.^[6] These results underline the significant potential of borrelidin as a lead compound for the development of novel antiangiogenesis drugs.

Chemical degradation^[7] and crystallographic studies^[8] revealed that borrelidin is an 18-membered macrolide with an unprecedented structure, composed of a repeated isopropyl subunit (C4–C10),^[9] a conjugated cyanodiene fragment (C12–C15), and a cyclopentane carboxylic acid substituent (C18–C23).^[10] The unique structure of **1** has spurred the development of several synthetic routes,^[11] which recently led to two elegant syntheses by the Morken^[12] and Hanessian^[13] research groups. Inspired by the structural and biological uniqueness of borrelidin, we devised a strategy toward its

[*] B. G. Vong, S. H. Kim, S. Abraham, Prof. E. A. Theodorakis
Department of Chemistry and Biochemistry
University of California, San Diego
9500 Gilman Drive, MC: 0358, La Jolla, CA 92093-0358 (USA)
Fax: (+1) 858-822-0386
E-mail: etheodor@chem.ucsd.edu

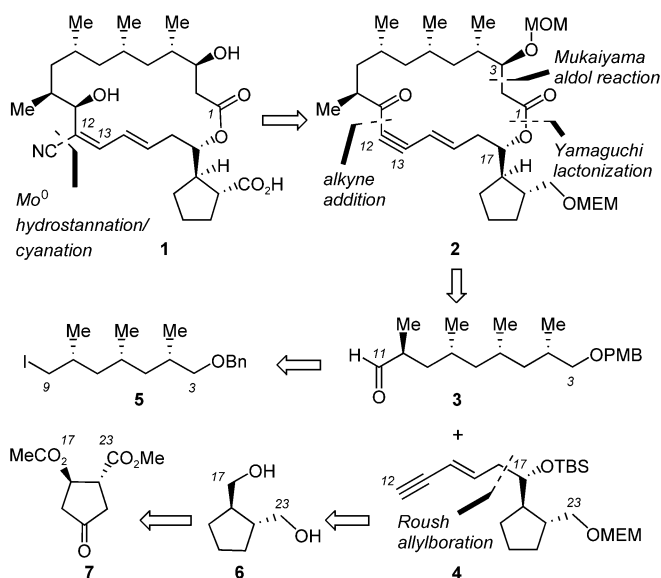
[**] In honor of Professor E. J. Corey, recipient of the 2004 Priestley Medal. Financial support from the NIH (CA 086079) is gratefully acknowledged. We also thank Dr. L. N. Zakharov and Dr. P. Gantzel (UCSD, X-ray Facility) for the reported crystallographic studies and Professor D. B. Ball, California State University, Chico, for a sample of natural borrelidin.



Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

synthesis. Crucial to our approach was the installation of the cyano group after the construction of the macrocyclic ring of **1**. The installation of the cyano group occurred with excellent regioselectivity by a novel Mo⁰-catalyzed hydrostannation of an enyne (at C11–C15).^[14] Herein we present the results of our study.

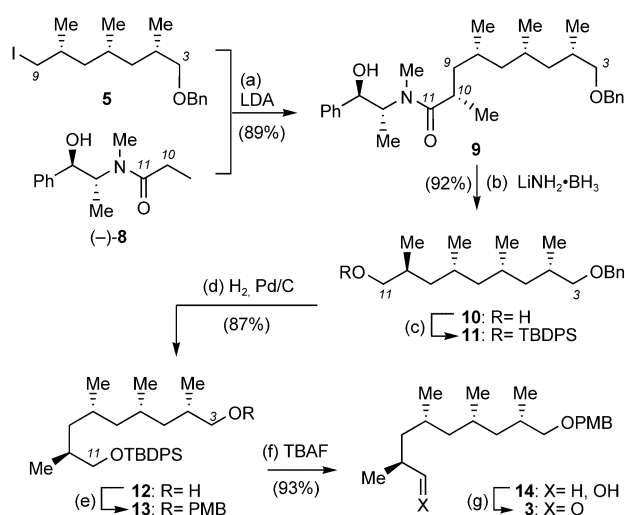
Our retrosynthetic strategy towards borrelidin (**1**) is illustrated in Scheme 1. We hypothesized that the *Z,E* cyanodiene motif of **1** could be constructed by the *syn*



Scheme 1. Strategic bond disconnections in the retrosynthesis of borrelidin (**1**). Bn = benzyl, MEM = (2-methoxyethoxy)methyl, MOM = methoxymethyl, PMB = *p*-methoxybenzyl, TBS = *tert*-butyldimethylsilyl.

addition of an H–CN unit across a C12–C13 triple bond, thus suggesting the use of macrolide **2**, which contains an enyne conjugated system, as a viable synthetic precursor. This disconnection raised two major challenges related to the overall construction of such a strained macrocycle and the regioselectivity of the HCN addition. Despite this risk we were intrigued by the possibilities offered by the macrolide **2** as a test case for the hydrocyanation reaction and as a scaffold for the synthesis of analogues to help in the evaluation of structure–activity relationships of the natural product. An additional advantage of this approach is that compound **2** could be disconnected into two major fragments **3** and **4**, thus adding to the convergence of our strategy. The postulated key bond-forming reactions would include the coupling of **4** with aldehyde **3**, extension of the northern fragment by using a Mukaiyama aldol reaction, and subsequent macrolactonization. Aldehyde **3** could be formed by the extension of alkyl iodide **5**,^[11d] whereas the cyclopentane subunit of **4** can be traced back to diol **6**, which is available from diester **7**.

The synthesis of aldehyde **3** is shown in Scheme 2. The Myers alkylation^[15] of iodide **5** with the lithium enolate of (–)-pseudoephedrine propionamide ((–)-**8**), followed by reduction of the resulting amide **9** with LiNH₂·BH₃, produced alcohol **10** as a single diastereomer (d.r. > 98:2) in 82%

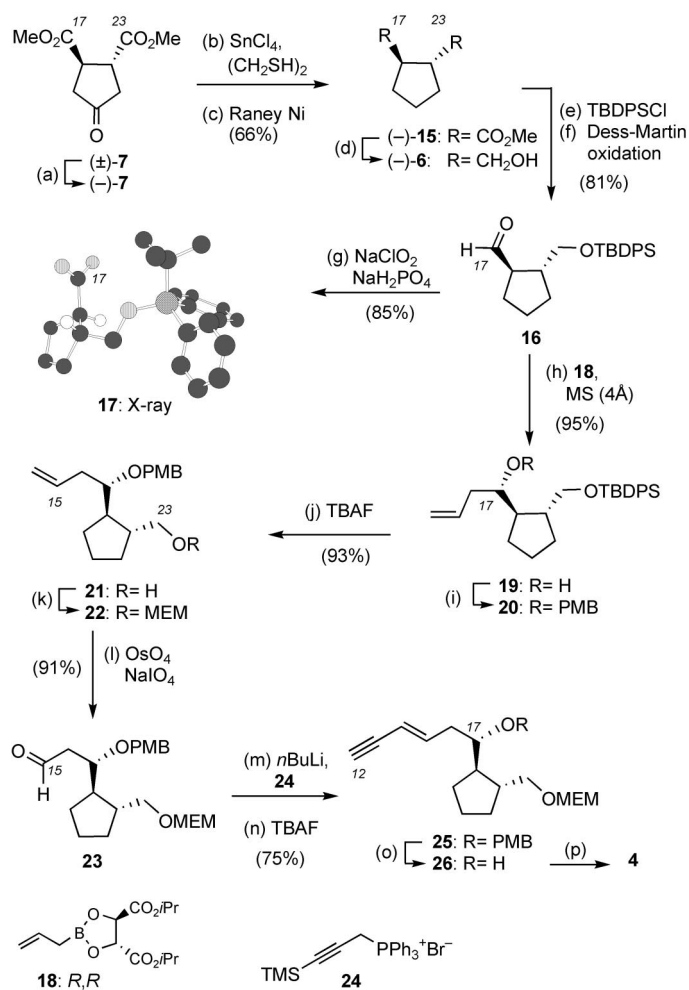


Scheme 2. Reagents and conditions: a) (–)-**8** (2.1 equiv), LDA (4.0 equiv), LiCl (12.2 equiv), THF, 0 °C, 18 h, 89%; b) LiNH₂·BH₃ (4.0 equiv), CH₂Cl₂, –78–0 °C, 3 h, 92%; c) TBDPSCI (2.0 equiv), imidazole (3.0 equiv), DMAP (0.1 equiv), 25 °C, 8 h, 95%; d) H₂, Pd/C, EtOH, 25 °C, 12 h, 87%; e) NaH (3.0 equiv), THF, 0 °C, 1 h; then PMBBR (2.0 equiv), TBAI (0.1 equiv), 25 °C, 12 h, 85%; f) TBAF (1.5 equiv), THF, 25 °C, 12 h, 93%; g) Dess–Martin periodinane (1.2 equiv), CH₂Cl₂, 25 °C, 1 h, 94%. DMAP = *N,N*-dimethylaminopyridine, LDA = lithium diisopropylamide, TBDPS = *tert*-butyldiphenylsilyl, TBAF = tetrabutylammonium fluoride, TBAI = tetrabutylammonium iodide.

overall yield.^[16] Adjustment of the protecting groups and oxidation of the hydroxy group at C11 produced the desired aldehyde **3** in 61% yield from **10**.

The synthesis of the southern fragment **4** of borrelidin is illustrated in Scheme 3. The cyclopentane diester subunit **7** was first prepared in an enantioselective manner by enzymatic resolution of racemic **7** with pig liver esterase (PLE) under conditions reported previously.^[17] During this reaction (+)-**7** was selectively hydrolyzed to the corresponding monoacid, thus allowing facile separation of the desired *R,R* ester (–)-**7** in excellent yield and with > 97% *ee*. This compound was converted into the corresponding dithioacetal, which underwent reductive desulfurization with Raney Ni to produce diester **15** in 66% yield from (–)-**7**. The reduction of both ester functionalities of **15**, followed by monosilylation by using the bulky reagent TBDPSCI and oxidation of the available hydroxy group with Dess–Martin periodinane produced aldehyde **16** (three steps, 75% yield). Single-crystal X-ray analysis of carboxylic acid **17**, obtained by oxidation of aldehyde **16**, confirmed the depicted relative stereochemistry of the cyclopentane ring in **16** unambiguously.^[18]

Aldehyde **16** underwent allylation with boronate ester **18** under the conditions of Roush and co-workers^[19] to give homoallylic alcohol **19** as an 8:1 mixture of isomers at the C17 center in favor of the desired compound and in 95% combined yield. Model studies towards esterification of the C17 hydroxy group of **19** under a variety of conditions led to the corresponding ester in low yields, presumably because of the bulkiness of the neighboring TBDPS group. To overcome this problem we decided to protect the alcohol at C23 with a



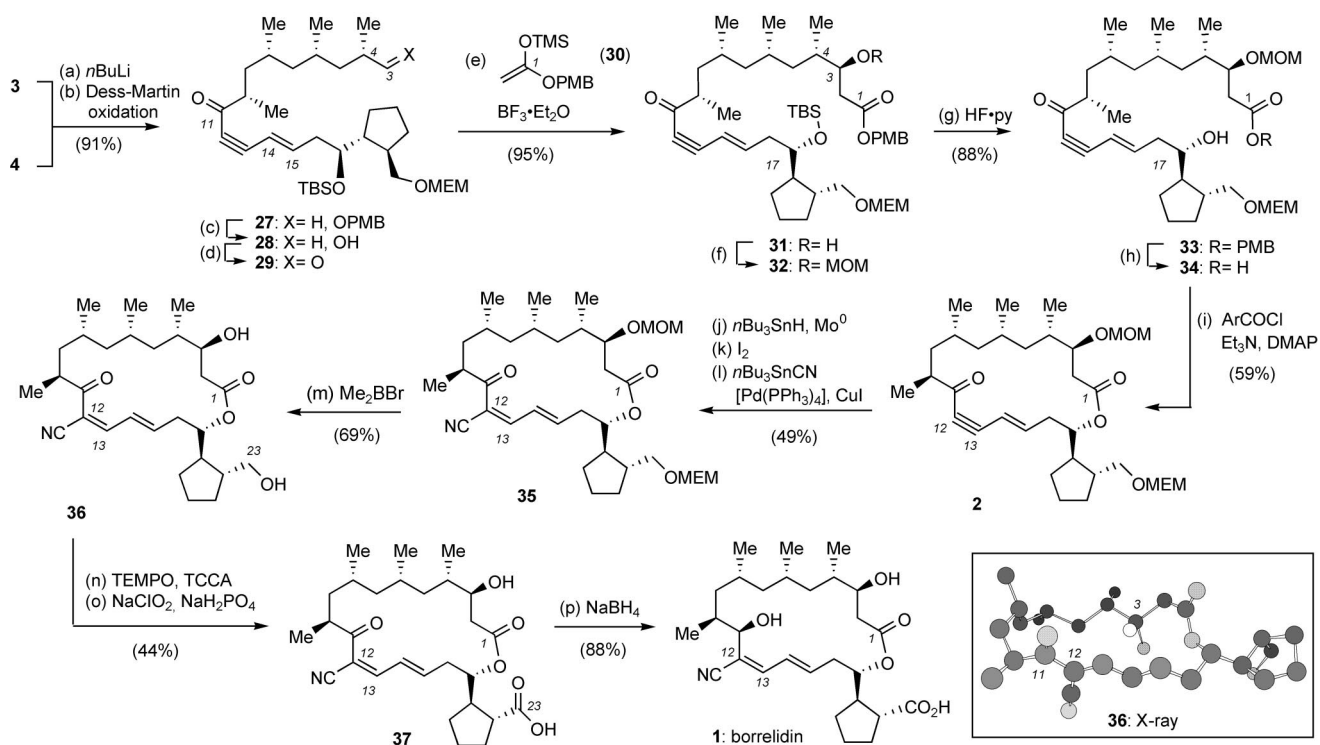
Scheme 3. Reagents and conditions: a) PLE (3.0 equiv), H_2O , phosphate buffer (pH 7.0), 1 h, 49% (from 50% maximum yield), $>97\%$ ee; b) SnCl_4 (5.0 equiv), 1,2-ethanedithiol (1.8 equiv), CH_2Cl_2 , $0 \rightarrow 25^\circ\text{C}$, 8 h, 72%; c) Raney Ni, MeOH, reflux, 3 h, 92%; d) LiAlH_4 (5.0 equiv), Et_2O , 25°C , 12 h, 92%; e) TBDPSCI (2.1 equiv), imidazole (2.1 equiv), DMAP (0.1 equiv), CH_2Cl_2 , 25°C , 8 h, 84% (+8% recovered **6**); f) Dess–Martin periodinane (1.2 equiv), CH_2Cl_2 , 25°C , 1 h, 89%; g) NaClO_2 (3.0 equiv), NaH_2PO_4 (3.0 equiv), 2-methyl-2-butene, $t\text{BuOH}/\text{H}_2\text{O}$ (2:1), 25°C , 0.5 h, 85%; h) **18** (1.4 equiv), MS (4 Å), toluene, -78°C , 1 h, 95% (8:1 ratio at C17); i) NaH (3.5 equiv), THF, 0°C , 1 h; then PMBBBr (3.5 equiv), TBAI (0.1 equiv), 12 h, 25°C , 94%; j) TBAF (2.0 equiv), THF, 25°C , 12 h, 93%; k) MEMCl (3.0 equiv), $i\text{Pr}_2\text{NEt}$ (5.0 equiv), CH_2Cl_2 , $0 \rightarrow 25^\circ\text{C}$, 8 h, 93%; l) OsO_4 (3 mol%), NMO (1.2 equiv), pyridine (0.1 equiv), acetone/ H_2O (10:1), 25°C , 12 h; then NaIO_4 (1.4 equiv), THF/ H_2O (5:4), 25°C , 2 h, 91%; m) **24** (3.0 equiv), $n\text{BuLi}$ (3.0 equiv), THF, -78°C , 1 h; then **23**, THF, -78°C , 2 h, 77% (5:1 *trans/cis*); n) TBAF (1.2 equiv), THF, 25°C , 0.5 h, 98%; o) DDQ (1.5 equiv), buffer (pH 7.0, 10 equiv), CH_2Cl_2 , 25°C , 1 h, 91%; p) TBSOTf (2.0 equiv), imidazole (3.1 equiv), DMAP (0.1 equiv), 40°C , 8 h, 93%. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, NMO = 4-methylmorpholine *N*-oxide, PLE = pig liver esterase, Tf = trifluoromethanesulfonyl.

sterically less imposing group, such as MEM. Compound **19** was therefore converted into its PMB ether **20**, which underwent fluoride-induced desilylation and alkylation of the alcohol group at C23 with MEMCl to give **22** in three steps and 81% yield.

Exposure of the protected homoallylic alcohol **22** to osmium tetroxide and sodium periodate furnished aldehyde **23**, which was treated immediately with deprotonated **24** as its lithium salt. Desilylation of the C12 center then gave enyne **25** (*trans/cis* 5:1) in 68% combined yield.^[20] Final adjustment of the protecting groups afforded enyne **4**, which represents the southern fragment of borrelidin (Scheme 3).

With the two major fragments **3** and **4** in hand, the stage was now set for the completion of the synthesis of borrelidin (Scheme 4). To this end, the lithiation of **4** followed by the addition of aldehyde **3** produced the coupled product as a 3:1 mixture of isomers at the C11 center (93% combined yield). During optimization attempts it was found that the use of a 1:1 solvent mixture of THF and DME together with molecular sieves led to an increase in the reactivity of the enyne nucleophile and a decrease in side reactions.^[21] At this step, the *trans* and *cis* isomers of the alkene functionality (C14–C15) became separable; the *cis* isomer was separated from the *trans* and was subjected to radical isomerization with sunlight in the presence of catalytic diphenyl sulfide to give a mixture of *cis* and *trans* alkenes in a ratio of 1:1.^[22] Oxidation of the alcohol functionality with Dess–Martin periodinane afforded ketone **27**, which was converted uneventfully into aldehyde **29** (84% yield).^[23] An aldol reaction with the silyl ketene acetal **30** under Mukaiyama conditions^[24] produced a 4:1 mixture of isomers at the C3 center in favor of the desired ester **31** and in 95% combined yield. The stereochemical outcome of this addition was efficiently controlled by the chirality of the neighboring C4 center. The protection of **31** with MOMCl, followed by a two-step unmasking of the C17 hydroxy group and the C1 carboxylic acid, furnished hydroxy acid **34** in 63% overall yield. The macrolactonization of **34** under the Yamaguchi conditions^[25] then afforded macrolide **2** in 59% yield. Similar yields were observed for the Mukaiyama macrolactonization procedure.^[26]

Several catalysts and conditions, such as $[\text{Ni}\{\text{P}(\text{OPh})_3\}_4]$ and HCN or acetone cyanohydrin,^[27] were evaluated for the regioselective installation of the nitrile functionality at the C12 center. As this direct metal-catalyzed hydrocyanation was found to be unsuccessful,^[28] we attempted an alternative sequence involving the regioselective hydrostannation of the C12–C13 alkyne, followed by conversion of the vinyl stannane into the corresponding vinyl iodide, which was then subjected to palladium-based cyanation. The problem with this sequence arose from the complete loss of regioselectivity observed during the initial hydrostannation reaction under the known Pd-based catalytic conditions.^[29] In an effort to improve this reaction, we attempted a molybdenum-based hydrostannation with $[\text{Mo}(\text{CO})_3(t\text{BuNC})_3]$ as the catalyst.^[14,30] We were delighted to observe that under these conditions the tributylstannane residue was installed exclusively at the C12 center. The regioselectivity of this addition was influenced by the presence of the C11 carbonyl group; in a related experiment with a macrolide containing an enyne–alcohol motif the hydrostannation was much less regioselective. To the best of our knowledge, this is the first example of the use of a Mo^0 -catalyzed hydrostannation in the context of complex natural product synthesis, and it clearly demonstrates the scope of this reaction. After iodination of the vinyl



Scheme 4. Reagents and conditions: a) **4** (1.3 equiv), **3** (1.0 equiv), *n*BuLi (1.3 equiv), THF/DME (1:1), MS (4 Å), -78°C , 1 h, 93%; b) Dess–Martin periodinane (1.2 equiv), CH_2Cl_2 , 25°C , 0.5 h, 98%; c) DDQ (1.5 equiv), H_2O (pH 7), CH_2Cl_2 , 25°C , 0.5 h, 89%; d) TEMPO (0.1 equiv), BAIB (1.5 equiv), CH_2Cl_2 , 25°C , 2 h, 94%; e) **30** (5.0 equiv), $\text{BF}_3\cdot\text{OEt}_2$ (3.0 equiv), MS (4 Å), THF, -78°C , 1 h, 95%; f) *i*Pr₂NEt (20 equiv), MOMCl (10 equiv), CH_2Cl_2 , 25°C , 12 h, 86%; g) HF-pyridine (20%), THF, 25°C , 12 h, 88%; h) TFA (3%), CH_2Cl_2 , 0°C , 8 h, 83%; i) 2,4,6-trichlorobenzoyl chloride (10 equiv), Et₃N (20 equiv), THF, 25°C , 3 h; then DMAP (10 equiv), toluene, 25°C , 12 h, 59%; j) hydroquinone (2.0 equiv), $[\text{Mo}(\text{CO})_3(\text{tBuNC})_3]$ (0.5 equiv), *n*Bu₃SnH (5.0 equiv), THF, 55°C , 12 h; k) I₂ (1.1 equiv), CH_2Cl_2 , 25°C , 54% (over two steps); l) *n*Bu₃SnCN (2.3 equiv), $[\text{Pd}(\text{PPh}_3)_4]$ (0.6 equiv), CuI (0.4 equiv), toluene, 80°C , 12 h, 90%; m) Me₂BBr (3.0 equiv), CH_2Cl_2 , -78°C , 1 h, 69%; n) TEMPO (0.01 equiv), TCCA (1.1 equiv), CH_2Cl_2 , 25°C , 1 h, 85%; o) NaClO₂ (3.0 equiv), NaH₂PO₄ (3.0 equiv), *t*BuOH/H₂O (2:1), 25°C , 0.5 h, 52%; p) NaBH₄ (1.2 equiv), CeCl₃ (cat.), 0°C , 0.5 h, 88%, 10:1 ratio of epimers at C11. BAIB = bis(acetoxy)iodobenzene, DME = dimethoxyethane, TCCA = trichloroacetic acid, TEMPO = 2,2,6,6-tetramethylpiperidine *N*-oxide, TCCA = trichloroacetic acid, TFA = trifluoroacetic acid.

stannane, a Pd-catalyzed cyanation produced macrolide **35** in 49% yield from **2**.

Further elaboration of **35** included the simultaneous removal of both the MOM and MEM groups to give diol **36**. Gratifyingly, **36** was found to be a crystalline solid, and single-crystal X-ray analysis confirmed the stereochemistry of the macrolide core (Scheme 4).^[18] The primary alcohol at C23 of diol **36** was oxidized selectively by using TEMPO/TCCA,^[31] and the resulting aldehyde was converted into carboxylic acid **37** upon treatment with NaClO₂ (44% yield from **36**). Reduction of acid **37** under Luche conditions with NaBH₄ and CeCl₃^[32] produced synthetic borrelidin in 10:1 diastereoselectivity with respect to the C11 center and in 88% yield. Spectroscopic and analytical data for synthetic borrelidin were in full agreement with those reported for the natural product.

In conclusion, a stereoselective total synthesis of borrelidin (**1**) has been reported. The strategy developed is distinguished by the construction of a strained enynone-containing macrocycle **2**, and the regioselective introduction of a cyano group by implementing a novel molybdenum-catalyzed hydrostannation reaction. The late installation of

the nitrile unit in a fully functionalized macrocyclic scaffold paves the way for the preparation of analogues of borrelidin that could be used to evaluate structure–activity relationships of this natural product.

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Keywords: hydrostannation · macrolactonization · natural products · synthetic methods · total synthesis

- [1] J. Berger, L. M. Jampolsky, M. W. Goldberg, *Arch. Biochem.* **1949**, *22*, 476–478; for the subsequent isolation of **1** from related *Streptomyces* strains, see: S. K. Singh, S. Gurusiddaiah, J. W. Whalen, *Antimicrob. Agents Chemother.* **1985**, *27*, 239–245; H. Maher, R. H. Evans, *J. Antibiot.* **1987**, *40*, 1455–1456.
- [2] M. Lumb, P. E. Macey, J. Spyvee, J. M. Whitmarsh, R. D. Wright, *Nature* **1965**, *206*, 263–265; L. Dickinson, A. J. Griffiths, C. G. Mason, R. F. N. Mills, *Nature* **1965**, *206*, 265–268.
- [3] M. Buck, A. C. Farr, R. J. Schnitzer, *Trans. N. Y. Acad. Sci. Ser. 2* **1949**, *11*, 207–209; E. Grunberg, D. Eldrige, G. Soo-Hoo, D. R. Kelly, *Trans. N. Y. Acad. Sci. Ser. 2* **1949**, *11*, 210–212; T. C. Schüz, H. Zähler, *FEMS Microbiol. Lett.* **1993**, *114*, 41–46; K.

- Otoguro, H. Ui, A. Ishiyama, M. Kobayashi, H. Togashi, Y. Takahashi, R. Masuma, H. Tanaka, H. Tomoda, H. Yamada, S. Omura, *J. Antibiot.* **2003**, *56*, 727–729.
- [4] J. S. Cantt, C. A. Bennett, S. M. Arfin, *Proc. Natl. Acad. Sci. USA* **1981**, *78*, 5367–5370; T. Hirakawa, H. Morinaga, K. Watanabe, *Agric. Biol. Chem.* **1974**, *38*, 85–89; W. Paetz, G. Nass, *Eur. J. Biochem.* **1973**, *35*, 331–337; G. Nass, K. Poralla, H. Zähler, *Naturwissenschaften* **1971**, *58*, 603–610; K. Poralla, H. Zähler, *Arch. Microbiol.* **1968**, *61*, 143–153; for a review on threonyl-tRNA synthetase, see: W. Friest, D. H. Gauss, *Biol. Chem. Hoppe-Seyler* **1995**, *376*, 213–224.
- [5] E. Tsuchiya, M. Yukawa, T. Miyakawa, K. Kimura, H. Takahashi, *J. Antibiot.* **2001**, *54*, 84–90; K. Poralla in *Mechanism of Action of Antimicrobial and Antitumor Agents* (Eds.: J. W. Corcoran, F. E. Hahn), Springer, Berlin, **1975**, pp. 365–388.
- [6] T. Wakabayashi, R. Kageyama, N. Naruse, N. Tsukahara, Y. Funahashi, K. Kitoh, Y. Watanabe, *J. Antibiot.* **1997**, *50*, 671–676; E. L. Eastwood, S. E. Schaus, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2235–2237.
- [7] K. Anderton, R. W. Rickards, *Nature* **1965**, *206*, 269; M. S. Kuo, D. A. Yurek, D. A. Kloosterman, *J. Antibiot.* **1989**, *42*, 1006–1007; W. Keller-Schierlein, *Experientia* **1966**, *22*, 355–359; W. Keller-Schierlein, *Helv. Chim. Acta* **1967**, *50*, 731–753.
- [8] The absolute stereochemistry of **1** was determined by incorporating a chiral solvent in the crystal lattice: B. F. Anderson, A. J. Herlt, R. W. Rickards, G. B. Robertson, *Aust. J. Chem.* **1989**, *42*, 717–730.
- [9] The repeated isopropyl motif constitutes a common structural element in many natural products of polyketide origin, including ionomycin, rapamycin, and related macrolides; for a recent monograph on macrolides, see: *Macrolide Antibiotics Chemistry, Biology, and Practice*, 2nd ed. (Ed.: S. Omura), Academic Press, London, **2002**, pp. 1–637.
- [10] For recent studies on the biosynthesis of this natural product, see: C. Olano, B. Wilkinson, C. Sanchez, S. J. Moss, R. Sheridan, V. Math, A. J. Weston, A. F. Brana, C. J. Martin, M. Oliynyk, C. Mendez, P. F. Leadlay, J. A. Salas, *Chem. Biol.* **2004**, *11*, 87–97; C. Olano, B. Wilkinson, C. Sanchez, S. J. Moss, A. F. Brana, C. Mendez, P. F. Leadlay, J. A. Salas, *Chem. Commun.* **2003**, 2780–2782.
- [11] a) N. Haddad, M. Grishko, A. Brik, *Tetrahedron Lett.* **1997**, *38*, 6075–6078; b) N. Haddad, A. Brik, M. Grishko, *Tetrahedron Lett.* **1997**, *38*, 6079–6082; c) C.-X. Zhao, M. O. Duffey, S. J. Taylor, J. P. Morken, *Org. Lett.* **2001**, *3*, 1829–1831; d) B. G. Vong, S. Abraham, A. X. Xiang, E. A. Theodorakis, *Org. Lett.* **2003**, *5*, 1617–1620; e) D. B. Ball, B. R. Taft, *Abstracts of Papers, CHED-933*, 227th ACS National Meeting, Anaheim, CA, **2004**; f) D. B. Ball, B. R. Taft, M. Mahoney, *Abstracts of Papers, CHED-597*, 225th ACS National Meeting, New Orleans, LA, **2003**.
- [12] M. O. Duffey, A. LeTiran, J. P. Morken, *J. Am. Chem. Soc.* **2003**, *125*, 1458–1459.
- [13] S. Hanessian, Y. Yang, S. Giroux, V. Mascitti, J. Ma, F. Raeppl, *J. Am. Chem. Soc.* **2003**, *125*, 13784–13792.
- [14] U. Kazmaier, D. Schauss, M. Pohlman, *Org. Lett.* **1999**, *1*, 1017–1019; U. Kazmaier, M. Pohlman, D. Schauss, *Eur. J. Org. Chem.* **2000**, *15*, 2761–2766; S. Braune, U. Kazmaier, *J. Organomet. Chem.* **2002**, *641*, 26–29.
- [15] A. G. Myers, B. H. Yang, H. Chen, J. L. Gleason, *J. Am. Chem. Soc.* **1994**, *116*, 9361–9362; A. G. Myers, B. H. Yang, H. Chen, L. McKinstry, D. J. Kopecky, J. L. Gleason, *J. Am. Chem. Soc.* **1997**, *119*, 6496–6511.
- [16] The use of other chiral auxiliaries in conjunction with β -branched iodides leads to low yields as a result of the reduced reactivity of the electrophile. However, such reduced reactivity is not observed in the pseudoephedrine-based alkylation reported by Myers and co-workers;^[15] see also: A. G. Myers, B. H. Yang, H. Chen, D. J. Kopecky, *Synlett* **1997**, 457–459.
- [17] L. Rosenquist, I. Kvarnström, S. C. T. Svensson, B. Classon, B. Samuelsson, *Acta Chem. Scand.* **1992**, *46*, 1127–1129; F. C. Acher, F. J. Tellier, R. Azerard, I. N. Brabet, L. Fagni, J.-P. R. Pin, *J. Med. Chem.* **1997**, *40*, 3119–3129; D. Nöteberg, J. Brånalt, I. Kvarnström, M. Linschoten, D. Musil, J.-E. Nyström, G. Zuccarello, B. Samuelsson, *J. Med. Chem.* **2000**, *43*, 1705–1713.
- [18] CCDC-234162 (**17**) and CCDC-234484 (**36**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).
- [19] L. K. Hoong, M. A. Palmer, J. C. Park, W. R. Roush, *J. Org. Chem.* **1990**, *55*, 4109–4117; L. K. Hoong, M. A. Palmer, J. C. Park, A. D. Palkowitz, W. R. Roush, *J. Org. Chem.* **1990**, *55*, 4117–4126.
- [20] The *cis/trans* isomers were easily separated by column chromatography after the coupling between **3** and **4**.
- [21] For a discussion on the activation of organolithium reagents, see: M. Schlosser, *J. Organomet. Chem.* **1967**, *8*, 9–16.
- [22] P. E. Sonnet, *Tetrahedron* **1980**, *36*, 557–604.
- [23] A. DeMico, R. Margarita, L. Parlanti, A. Vescovi, G. Piancarelli, *J. Org. Chem.* **1997**, *62*, 6974–6977.
- [24] T. Mukaiyama, K. Banno, K. Narasaka, *J. Am. Chem. Soc.* **1974**, *96*, 7503–7509.
- [25] J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.
- [26] T. Mukaiyama, M. Usui, K. Saigo, *Chem. Lett.* **1976**, 49–50.
- [27] W. R. Jackson, C. G. Lowel, *Aust. J. Chem.* **1983**, *36*, 1975–1982; W. R. Jackson, P. Perlmutter, A. J. Smallridge, *Aust. J. Chem.* **1988**, *41*, 251–261.
- [28] In our hands, direct hydrocyanation in the presence of $[\text{Ni}(\text{P}(\text{OPh})_3)_4]$ did not yield any addition product.
- [29] For selected reports on this issue, see: N. D. Smith, J. Mancuso, M. Lautens, *Chem. Rev.* **2000**, *100*, 3257–3282; M. B. Rice, S. L. Whitehead, C. M. Horvath, J. A. Muchnij, R. E. Maleczka, Jr., *Synthesis* **2001**, *10*, 1495–1504.
- [30] For recent applications of this reaction, see: S. Braune, M. Pohlman, U. Kazmaier, *J. Org. Chem.* **2004**, *69*, 468–474; U. Kazmaier, D. Schauss, M. Pohlman, S. Raddatz, *Synthesis* **2000**, 914–916.
- [31] L. DeLuca, G. Giacomelli, A. Porcheddu, *Org. Lett.* **2001**, *3*, 3041–3043.
- [32] J. L. Luche, L. Rodriguez-Hahn, P. Crabbe, *J. Chem. Soc. Chem. Commun.* **1978**, *14*, 601–602.