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Enantioselective Total Synthesis of Borrelidin

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Borrelidin (**1**) is a structurally unique macrolide first isolated from *Streptomyces rochei* in 1949 by Berger and co-workers.[1] The originally investigated antibiotic activity of borrelidin was ultimately found to arise from inhibition of threonyl-tRNA synthetase;[2] however, further development of the compound was abandoned when it was found to be a potent sensitizer.[3] In addition to its recently described CDK inhibitory activity,[4] borrelidin has re-emerged as a potent angiogenesis inhibitor with an IC_{50} of 0.8 nM, which is lower than its IC_{50} for tRNA synthetase inhibition.[5] This result implies an alternate biological target for borrelidin, which may have implications for anticancer therapy. The gross structure of borrelidin was first described in 1967,[6] and the absolute configuration was determined by Anderson et al. through crystal structure analysis of a chiral solvate.[7] The structure of borrelidin is characterized by an 18-membered macrolactone carrying a cyclopentane carboxylic acid and a unique conjugated cyanodiene (Figure 1). The structural novelty and relevant biological activity of borrelidin present an exciting challenge for chemical synthesis and are the focus of this report.[8]

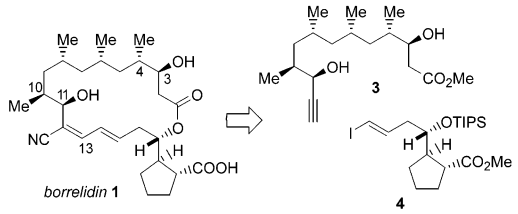
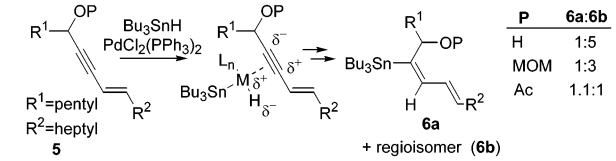


Figure 1. Structure of borrelidin and retrosynthetic disconnections.

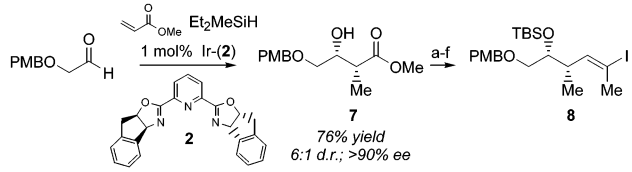
Our strategy for the synthesis of **1** focused on the use of an iridium-indanepybox (**2**)-catalyzed enantioselective reductive aldol reaction to establish the stereogenic centers at C3, C4, C10, and C11.[9] This represents the first example of the use of this transformation in the context of complex natural product synthesis. From a retrosynthetic perspective, disconnections of borrelidin at the C1 macrolactone and C13−C14 linkage led to two fragments, alkyne **3** and vinyl iodide **4**, respectively (Figure 1).

For the construction of the cyanodiene functionality, we sought to develop a method for the regio- and stereoselective introduction of the nitrile group at C12. While hydrostannylation of alkynes is frequently used for the synthesis of vinylstannanes,[10] which may be precursors to vinyl nitriles,[11] this method suffers from the lack of regiocontrol in the addition of tin hydride to internal unsymmetrical alkynes. Recent studies have established that branching α to the hydroxyl position of enynols promotes the formation of the distal vinylstannane.[12,13] To address the regiochemistry of the requisite hydrostannylation, we examined the reaction of model enyne **5** (Scheme 1). Varying the catalyst as well as reaction conditions had little effect on the regioisomer ratio of the reaction with the unprotected substrate (data not shown), and the undesired isomer **6b** was the major product. We then examined the impact of hydroxyl protecting groups because we suspected that electronic

Scheme 1

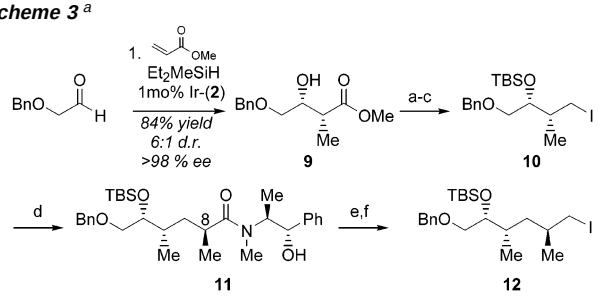


Scheme 2 [a]



[a] TBSOTf, 2,6-lutidine (90%); (b) DIBAL (79%); (c) Dess−Martin periodinane (92%); (d) CBr_4, PPh_3 (94%); (e) BuLi, MeI (97%); (f) (i) Cp_2ZrHCl, (ii) I_2 (89%).

Scheme 3 [a]



[a] (a) TBSOTf, 2,6-lutidine (99%); (b) DIBAL (94%); (c) PPh_3, I_2 (96%); (d) pseudoephedrine propionamide, LDA (93%); (e) LAB (93%); (f) PPh_3, I_2 (95%).

polarization of the alkyne by the C−O dipole might cause the hydride to preferentially add to the more electron-deficient end of the alkyne. This study revealed that by increasing the electron-withdrawing ability of the hydroxyl protecting group, the desired isomer **6a** could be obtained *albeit* only by a small margin.[14,15]

With a method for stereoselective introduction of the cyanodiene delineated, the synthesis of borrelidin commenced with reductive aldol coupling of methyl acrylate and *p*-methoxybenzyloxyacetaldehyde to provide aldol adduct **7** with excellent enantio- and diastereocontrol (Scheme 2). After protection of **7**, the methyl ester was converted to an aldehyde by a reduction/oxidation sequence, and the aldehyde was then converted to a terminal alkyne by a Corey−Fuchs reaction. Hydro-zirconation/iodination of the alkyne gave vinyl iodide **8**.

Alkyl iodide **12** was prepared by a second reductive aldol coupling between methyl acrylate and benzyloxyacetaldehyde to afford propionate **9** (Scheme 3). Compound **9** was converted to iodide **10**, which was then utilized in a Myers' asymmetric alkylation to properly set the C8 methyl stereocenter in **11**.[16] The auxiliary was reductively removed to give the primary alcohol, which was subsequently converted to alkyl iodide **12**.

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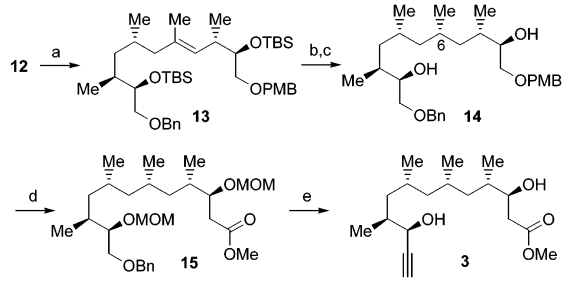
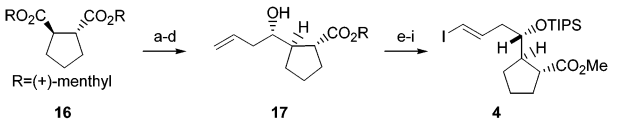
Scheme 4 [a]



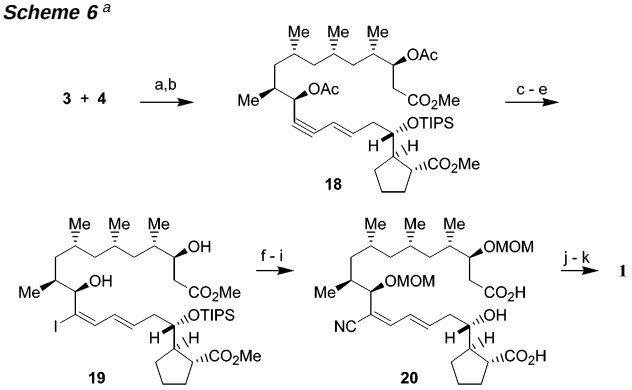
[a] (a) (i) *t*-BuLi, $ZnCl_2$, (ii) $Pd(PPh_3)_4$, **8** (58%); (b) TBAF (87%); (c) H_2 (600 psi), 30 mol % $Rh[(nbd)dppb]BF_4$ (86%); (d,e) see the Supporting Information for these details.

Scheme 5 [a]



[a] (a) KOH, H_2O_2, MeOH (73%); (b) $(COCl)_2$; (c) H_2 (60 psi), 10% Pd/C, 2,6-lutidine (74%, two steps); (d) (+)-Ipc_2B(allyl) (82%); (e) 1 N NaOH, MeOH (99%); (f) MeI, $NaHCO_3$ (92%); (g) TIPSOTf, 2,6-lutidine (96%); (h) OsO_4, NMO, then $NaIO_4$ (93%); (i) $CrCl_2$, CHI_3 (83%).

Scheme 6 [a]



[a] (a) $Pd(PPh_3)_4$, CuI, TEA (94%); (b) Ac_2O, DMAP (94%); (c) $PdCl_2(PPh_3)_2$, Bu_3SnH; (d) I_2 (97%, two steps, 1:1 regioisomer mixture); (e) K_2CO_3, MeOH, −25 °C (66%); (f) Bu_3SnCN, CuI, $Pd(PPh_3)_4$ (97%); (g) $(MeO)_2CH_2$, P_2O_5 (85%); (h) TASF (77%); (i) 3 M NaOH, THF (84%); (j) 2,4,6-trichlorobenzoyl chloride, TEA, DMAP; (k) Me_2BBr, −78 °C (36%, two steps).

Coupling of **8** and **12** ultimately allowed for synthesis of **3** (Scheme 4). In this approach, alkyl iodide **12** was converted to the mixed dialkyl zinc and used in a modified Negishi coupling with vinyl iodide **8** to give **13**.[17] After deprotection of the silyl ethers, the C6 stereocenter was established through a directed hydrogenation to give **14**.[18] Our attention then turned to the conversion of compound **14** to fragment **3**. This was accomplished in an expedient manner in a 35% overall yield through the intermediacy of **15**.[19]

Vinyl iodide **4**, which is required for coupling to alkyne **3**, was prepared from the known chiral bis-menthyl ester **16**, which was readily accessed via efficient carbocyclization of (+)-dimenthylsuccinate as described by Yamamoto (Scheme 5).[20] Monosaponification followed by Rosenmund reduction and Brown allylboration furnished the enantiopure alcohol **17**, which was converted to **4** in 32% overall yield from **16**.

The critical cross coupling of the subtargets **3** and **4** was best achieved by a Sonogashira reaction to give, after treatment with acetic anhydride, enyne **18** (Scheme 6).[21] Hydrostannylation of enyne **18**, followed by iodination and deacetylation of the resulting vinyl stannane, afforded vinyl iodide **19** along with its regioisomer, which was removed via silica gel chromatography (1:1 ratio, Scheme 6). Palladium-catalyzed cyanation of **19** using CuI as a cocatalyst[22] followed by MOM protection of the secondary alcohols, removal[23] of the TIPS ether, and saponification of the methyl esters provided a single stereoisomer of vinyl nitrile **20**. Selective macrolactonization of diacid **20** was subsequently performed by carboxyl activation with trichlorobenzoyl chloride.[24] Final deprotection of the MOM ethers produced synthetic borrelidin, whose spectral data (^1H, ^{13}C, and HRMS) are in agreement with the reported values for **1**.

In conclusion, we have reported the first total synthesis of borrelidin, which relied on our ability to execute large-scale asymmetric reductive aldol reactions and also required introduction of methods for reversing the usual regioselection in hydrostannylation of propargyl alcohols. Our synthesis sequence allows for late stage derivatization of the cyanodiene core, which may allow for discovery of nontoxic analogues of the natural product. These efforts are currently underway.

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

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