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Studies Towards Total Synthesis of Borrelidin, Stereoselective Synthesis of the Polysubstituted Macrolidic Part

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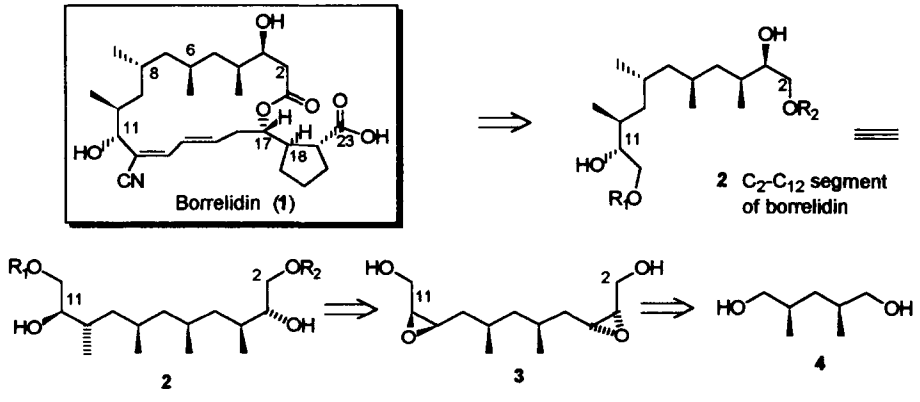
Abstract: Enantioselective synthesis of the polysubstituted macrolidic part of borrelidin (**1**) is presented. Six out of the nine stereogenic centers in **12** and **13** were achieved in >99.2 %ee in seven steps from *meso*-diol **4**. The synthesis is based on enantioselective formation of bis-epoxide **10** followed by regioselective alkylation of the epoxide functionalities. © 1997 Elsevier Science Ltd.

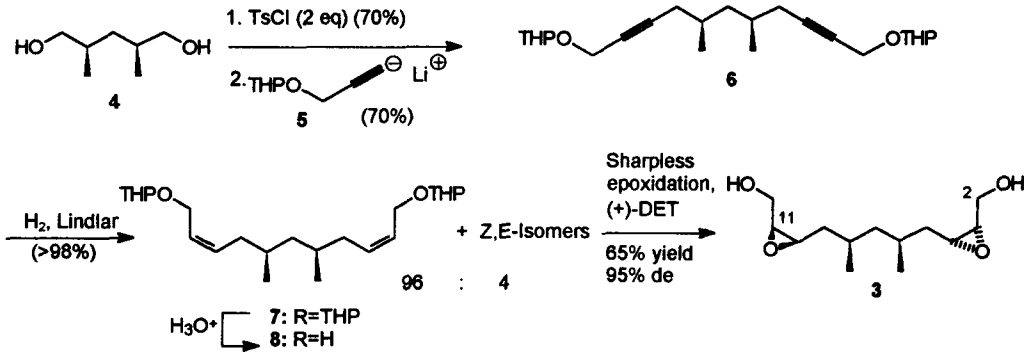
Borrelidin (**1**) is a structurally atypical 18-membered antibiotic macrolide,[1] first isolated from *Streptomyces rochei* by Berger et al[2] and so named because of specific activity against *Borrelia*, the spirochete of replacing fever.[3] Its activity has been found to extend to viruses *in vitro*[4] and to spirochetes of the genus Treponema.[5] Angiogenesis inhibition,[6] insecticidal and herbicidal activity has also been claimed recently.[7] The mode of its antibiotic action in sensitive microorganisms involves selective inhibition of threonyl-tRNA synthetase.[8] The terminal cyclopentane carboxylic acid and conjugated diene nitrile chromophore are unique to borrelidin. The nitrile, lactone and probably the hydroxyl functions are essential for the borrelidin molecule to show antimicrobial activity.[5b] Borrelidin has subsequently been isolated from several other sources.[9] The absolute configurations of its nine stereogenic centers have been determined[10] by X-ray diffraction of its crystal incorporating chiral solvent of known absolute configuration in the crystal lattice. The configuration of the stereogenic centers of borrelidin were determined to be: 3S, 4S, 6S, 8R, 10S, 11R, 17S, 18R, 22R.



Scheme 1

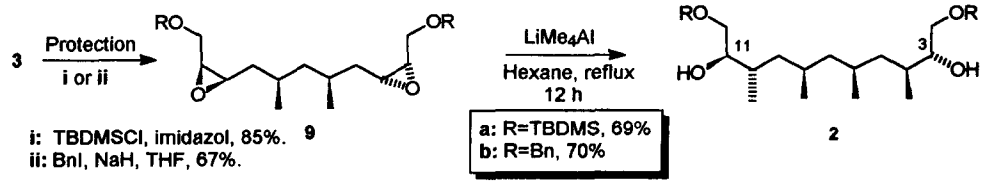
As a part of our studies towards total synthesis of borrelidin, we have developed a highly stereoselective and efficient approach for the synthesis of its C_2-C_{12} segment **2**, possessing six out of the nine stereogenic centers in the target molecule. The synthesis based on enantioselective formation of bis-epoxide **3** followed by

regioselective methylation at the C_4 and C_{10} positions as described in the retrosynthetic scheme (the numbering in **2** and **3** is related to the macrolactonic part of borrelidin). Bis-epoxide **3** was prepared starting from meso-2,4-dimethyl-1,5-pentandiol[11] (**4**) which was converted to the corresponding ditosylate (TsCl, Pyridin, 71% yield) then coupled on both sides with the protected acetylenic anion **5** (scheme 2) in refluxing dioxane[12] for three days, affording **6** in 70% yield with no detection of elimination products.[13] Catalytic hydrogenation of **6** using Lindlar's catalyst in hexane, afforded mixture of the desired *Z,Z*-diene **7** and its corresponding *Z,E*-dienes in 96:4 ratio respectively[14] and 98% yield. The *Z,E*-dienes were separated by column chromatography, using silica impregnated with silver nitrate.[15] Hydrolysis of the tetrahydropyran protection (p-TsOH, MeOH, 86%) afforded the bis-allylic alcohol **8** ready for introducing the chirality on both sides of the molecule using Sharpless epoxidation.[16] The desired chirality on both sides was achieved using (+)-diethyl tartrate which afforded bis-epoxide **3** in a mixture with 5% and 7% of the two corresponding diastereomers[14] in 65% yield. Based on the obtained diastereoselectivity, the enantiomer of **3** is expected to be formed in ca. 0.35% and the enantiomeric excess must be over 99.2 %ee.[17] Unselective epoxidation of **8** was expected to increase the formation of the undesired bis-epoxides. Indeed, epoxidation with MCPBA afforded mixture of **3** and its enantiomer (50%) along with 24% and 26% of its corresponding diastereomeric bis-epoxides in the statistically expected ratio of $2_{(racemic)}$: 1 : 1 respectively.



Scheme 2

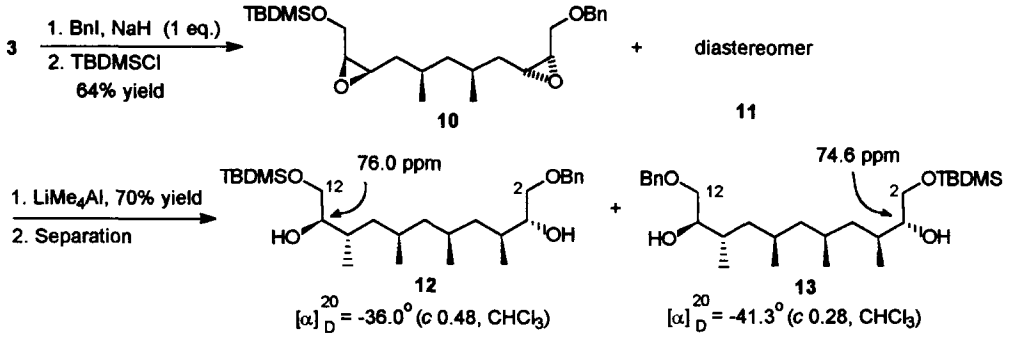
Regioselective methylations at the C_4 and C_{10} positions of bis-epoxide **3** was required in order to achieve the desired substitution at the six stereogenic centers in **2**. Protection of the hydroxyl groups with TBDMSCl[18] then treatment of the product **9a** with $LiMe_4Al$[19] afforded the desired product **2a** in high regioselectivity and 69% isolated yield.[20] Similar selectivity and yield was obtained when benzyl ethers[21] (**2b**) were used as protecting groups.



Scheme 3

The regioselectivity was defined by the downfield crosspeaks of both C_3 and C_{11} proton resonances with C_2 and C_{12} downfield protons in the 2D-Cosy NMR experiment of compounds **2** and their absence in the bis-1,3-diol regioisomer.[20] The ^{13}C-NMR resonances of C_3 and C_{11} in compound **2a** are 74.6 and 76.2 ppm respectively, as determined by transforming the corresponding monoepoxides of **8** to the *meso* or *diastereomeric* mixtures of 3,5,7-trimethylnonanoles[20].

At this stage, it is important to differentiate between the C_2 and C_{12} positions. Monoprotection of **3** with benzyl iodide afforded the desired monobenzyl ethers in a 1:1 mixture and 67% isolated yield, along with 22% yield of the dibenzyl product. Subsequent protection of the monobenzyl ethers with TBDMSCl afforded diastereomeric mixture **10** and **11** in 95% yield. Methylation of this mixture with $LiMe_4Al$ afforded the desired products **12** and **13** in 70% yield. Careful separation by column chromatography afforded the diastereomeric compounds **12** (C_3: 74.6 ppm) and **13** (C_{11}: 76.0 ppm) in over 95% purity.[22]



Scheme 4

In summary, we have developed a short and highly enantioselective synthesis of the polysubstituted macrolidic part of the naturally occurring compound borrelidin. The method is versatile since it allows preparation of a large number of related structures by simple modifications in the geometry of the bis-allylic alcohol, the enantioselectivity at the Sharpless epoxidation and the regioselectivity in the bis-epoxide alkylation. Synthetic studies towards the first total synthesis of borrelidin is currently underway in our laboratory.

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I: R=H, THP

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