

## Studies Towards Total Synthesis of Borrelidin, Regioselective Methylation of Bis-epoxides and Structure Determination

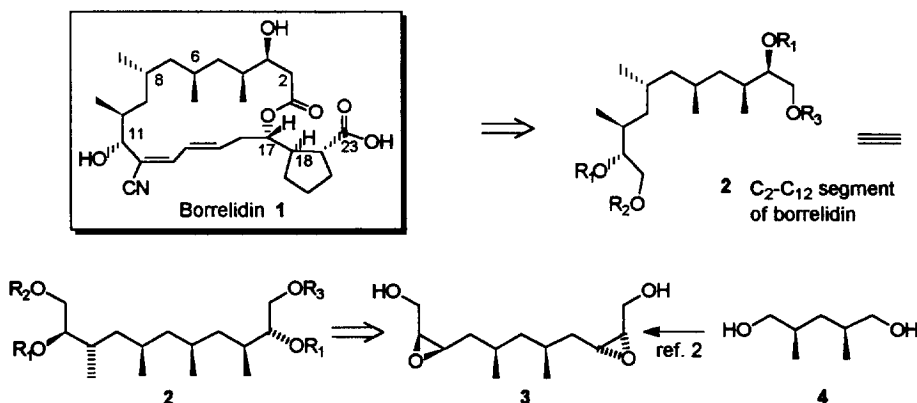
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**Abstract:** Regioselective methylation of bis-epoxides **9** were examined. Two examples of high regioselectivity and yield were achieved. Structure determination of the four possible regioisomers provide useful information for structure determination of structurally related flexible molecules. © 1997 Elsevier Science Ltd.

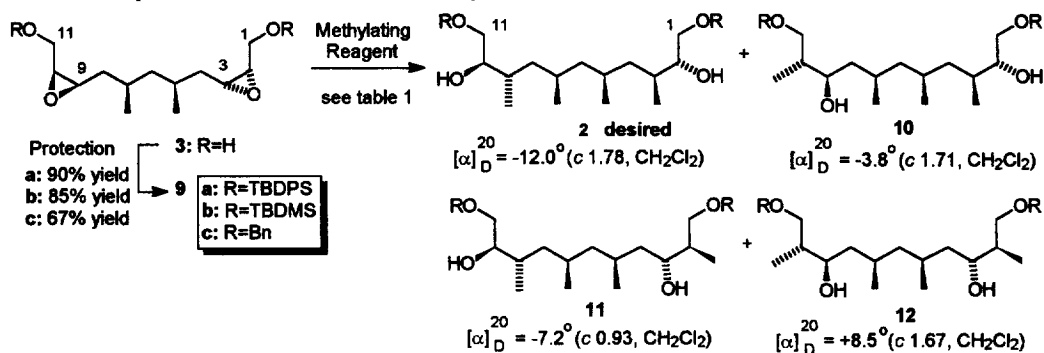
As part of our studies towards a total synthesis of borrelidin (**1**), and interest in studying the relation between relative configuration of polysubstituted alkanes and the conformational distribution of such "flexible molecules with defined shape",<sup>1</sup> we have developed a versatile and highly stereoselective approach for the synthesis of (**2**) (C<sub>2</sub>-C<sub>12</sub> segment of borrelidin) and related isomers.<sup>2</sup> The synthesis based on enantioselective preparation of bis-epoxide **3** (>99.2 %ee, 29% total yield of five steps starting from meso-diol **4**), followed by regioselective methylation of the bis-epoxide.<sup>2</sup>

Regioselective alkylation of *threo*-epoxides, derived from *E*-allylic alcohols, that produce 1,2-diols, is a well documented reaction<sup>3</sup>. However, the regioselectivity and yields of these reactions could be strongly decreased<sup>4</sup> when applied in the alkylation of *erythro*-epoxy alcohols. Regioselective addition of methyl substituents to the bis-epoxide **3**, structure determination of the four possible regioisomers and convenient method for the determination of C<sub>1</sub> and C<sub>11</sub> positions in **2** and its related regioisomers are presented.



Scheme 1

Four diastereomers should be obtained *via* unselective alkylation of bis-epoxide **3**. However, regioselective methylation at C<sub>3</sub> and C<sub>9</sub> positions is required for the synthesis of borrelidin. Treatment of **3** with Me<sub>3</sub>Al resulted in a sluggish transformation<sup>4</sup> to unidentified mixture of products. Partial selectivity was obtained upon treatment of the protected bis-epoxide **9a** (R=TBDPS) with Me<sub>2</sub>CuLi<sup>5</sup> (entry 2). Four diastereomers **2a**, **10a**, **11a** and **12a** obtained in this reaction in 40:25:25:10 ratio respectively. Similar selectivity, however, lower yield, obtained upon treatment of **9a** with Me<sub>2</sub>Cu(CN)Li<sub>2</sub> (entry 3) as methylating reagent.<sup>5</sup> The isomeric products were *easily* separated by flash chromatography (R<sub>f</sub> (Hexane:EtOAc, 4:1) = 0.55, 0.50, 0.45, 0.40 respectively). Structure determination of the desired product **2a** was achieved as follows: Compounds **10a** and **11a** are expected to be formed in a similar ratio in the case of similar regioselectivity on both sides of the bis-epoxide. <sup>1</sup>H-NMR of these compounds shows similarity in two signals at 3.95 and 3.5-3.7 ppm in the ratio of 1H:5H respectively. <sup>1</sup>H-NMR of the major product **2a** shows one signal at 3.5-3.7 ppm integrated to 6H whereas the minor isomer **12a** shows two signals at 3.95 and 3.5-3.7 ppm in the ratio of 2H:4H respectively. The major product **2a** was easily distinguished from isomer **12a** by characteristic cross peaks of the methylene protons of C<sub>1</sub> and C<sub>11</sub> with the downfield vicinal protons at C<sub>2</sub> and C<sub>10</sub> respectively in the 2D-Cosy spectrum, no such cross peaks were obtained in the 2D-Cosy of **12a**.



Scheme 2

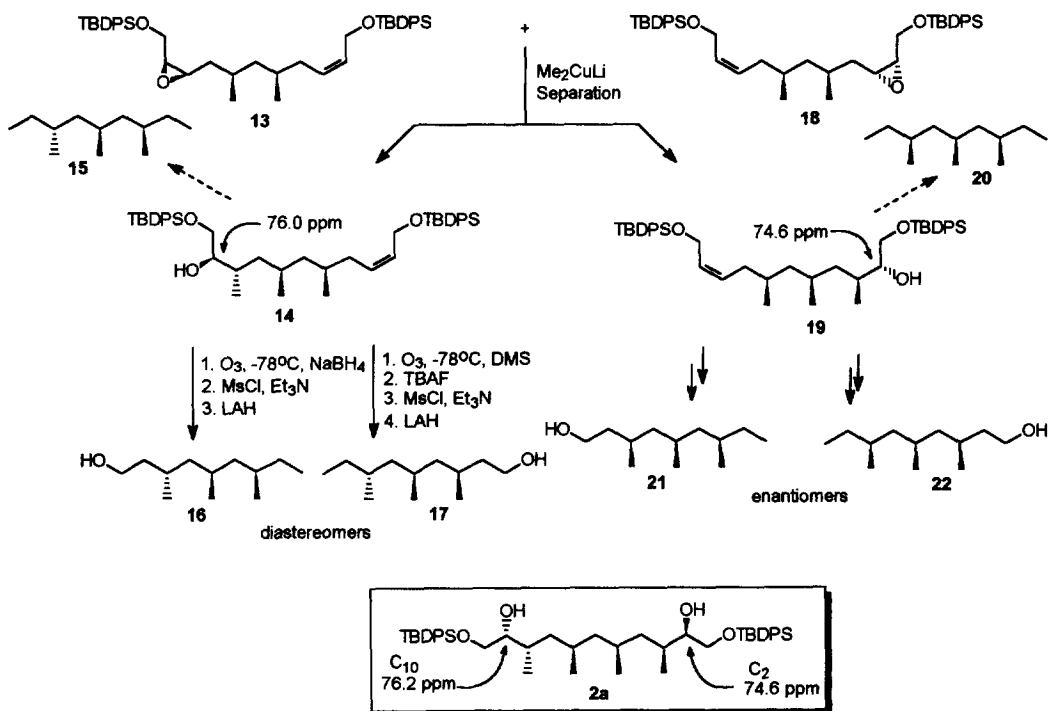
Table 1: Methylation of bis-epoxides **9**.

Entry	R	Methylating Reagent	Reaction Conditions	Total Yield	Regioselectivity 2 : 10 : 11 : 12
1	H	AlMe <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub> , 0°C	ca. 20%	undefined mixture
2	TBDPS	Me <sub>2</sub> CuLi	Et <sub>2</sub> O, -23°C	60%	40 : 25 : 25 : 10
3	TBDPS	Me <sub>2</sub> Cu(CN)Li <sub>2</sub>	Et <sub>2</sub> O, -23-0°C	40%	40 : 25 : 25 : 10
4	TBDMS	Me <sub>2</sub> CuLi	Et <sub>2</sub> O, -23°C	~60%	10 : 25 : 25 : 40
5	TBDPS	LiAlMe <sub>4</sub>	Hexane/Et <sub>2</sub> O, rt	no reaction	---
6	TBDMS	LiAlMe <sub>4</sub>	Hexane/Et <sub>2</sub> O, reflux, 12h	78%	88 : 6 : 6 : 0
7	Bn	LiAlMe <sub>4</sub>	Hexane/Et <sub>2</sub> O, reflux, 12h	80%	87 : 7 : 7 : 0

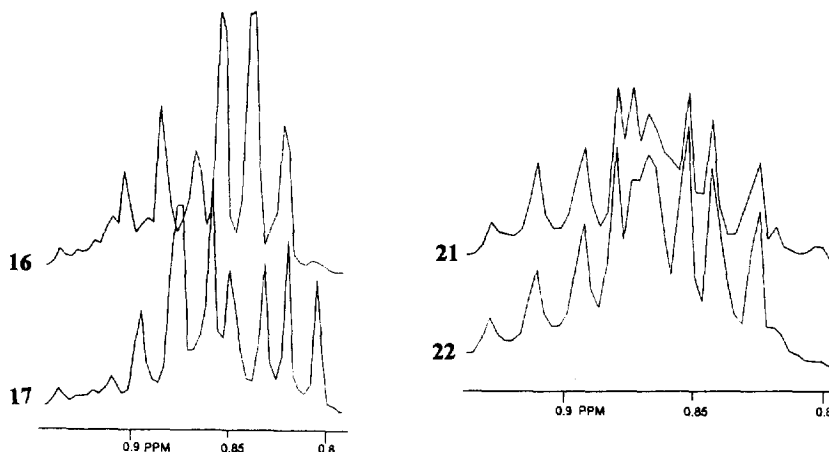
Decreasing the steric hindrance of the protecting silyl ethers (**9b**) (entry 4) resulted in converting the regioselectivity. On the other hand, treatment of epoxide **9a** with LiMe<sub>4</sub>Al<sup>6</sup> (entry 5) resulted in no reaction under the examined conditions, presumably due to steric hindrance of the silyl groups. However, replacement

of the TBDPS-protection with TBDMS-protection (entry 6) afforded the desired product **2b** in high selectivity and 69% isolated yield. Similar selectivity was obtained in entry 7, using benzyl ethers as protecting groups (BnI, NaH)<sup>7</sup> at the bis-epoxide **9c** and LiMe<sub>4</sub>Al as methylation reagent.

At this stage, it is important to distinguish between the C<sub>1</sub> and C<sub>11</sub> sides in the desired isomer **2a**, necessary to determine the position of monoprotection at one of the primary alcohols, required for the synthesis of borrelidin. The <sup>13</sup>C-NMR chemical shifts<sup>8</sup> of the secondary alcohols in the desired products **2** (76.1 and 74.6 ppm) are more downfield than for the undesired product **12a** (71.5 and 71.6 ppm). The <sup>13</sup>C-chemical shifts kept constant in **2a** and **2b**. Based on this, we have developed the following test to distinguish between C<sub>2</sub> and C<sub>10</sub> in the desired isomer **2a**. Monoepoxides **13** and **18** were prepared by partial asymmetric epoxidation, methylation of the monoepoxides afforded alcohols **14** and **19** which were separated (ptlc: EtOAc:Hexane, 1:30 respectively). The alcohol fraction that possesses the 76.2 ppm signal in its <sup>13</sup>C-NMR spectrum<sup>8</sup> was transformed *via* two different sequences (scheme 3) to afford the diastereomeric products **16** and **17** in ca. 50% total yield,<sup>9</sup> indicating the stereochemistry of alcohol **14**. Following the same transformations on the second alcohol fraction that possesses the 74.6 ppm signal in its <sup>13</sup>C-NMR spectrum, afforded two enantiomers **21** and **22** which must be formed from **19**. Based on these results we attribute the signal which appears at 74.6 ppm in the <sup>13</sup>C-NMR spectrum of **2a** to C<sub>2</sub> and that at 76.2 ppm to C<sub>10</sub> and distinguish between the isomeric structures of **10a** (74.5 ppm) and **11a** (76.2 ppm).<sup>8</sup>



Scheme 3



**Figure 1:** Selected  $^1\text{H}$ -NMR spectra of diastereomers **16** and **17** and enantiomers **21** and **22**.

In summary, high regioselectivity achieved in the methylation of bis-epoxides **2** and structure determination of the four possible regioisomers provide versatile and enantioselective synthesis of a large number of related diastereomers of types **2**, **10**-**12**.

#### Acknowledgment

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#### References and Notes

- # Presented in part at the 60th Annual Meeting of the Israel Chemical Society, February 1996, 108.
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  - $^{13}\text{C}$ -NMR (JMOD-XH,  $\text{CDCl}_3$ ) of: diol **2**: (-) 135.5, (+) 133.2, (-) 129.8, (-) 127.7, (-) 76.1, (-) 74.6, (+) 66.5, (+) 66.2, (+) 45.6, (+) 41.2, (+) 39.7, (-) 32.7, (-) 32.3, (-) 27.1, (-) 27.1, (-) 26.7, (-) 20.7, (-) 20.1, (+) 19.3, (-) 14.8, (-) 14.1; diol **10**: (-) 135.7, (-) 135.6, (-) 129.8, (-) 127.7, (-) 74.5, (-) 72.1, (+) 68.5, (+) 66.5, (+) 45.2, (+) 41.4, (+) 41.0, (-) 38.8, (-) 32.4, (-) 27.6, (-) 27.4, (-) 26.9, (-) 21.3, (-) 21.0, (+) 20.3, (-) 14.9, (-) 10.6; diol **11**: (-) 135.7, (-) 135.6, (+) 133.7, (-) 129.8, (-) 127.8, (-) 76.2, (-) 71.4, (+) 68.4, (+) 66.3, (+) 47.0, (+) 41.5, (+) 40.2, (-) 40.2, (-) 32.8, (-) 27.1, (-) 26.9, (-) 26.5, (-) 19.6, (-) 19.3, (+) 19.2, (-) 14.2, (-) 10.7; diol **12**: (-) 135.6, (-) 135.5, (-) 129.8, (-) 129.7, (+) 127.7, (-) 127.7, (-) 71.6, (-) 71.5, (+) 68.5, (+) 68.3, (+) 45.9, (+) 41.7, (+) 41.0, (-) 40.2, (-) 39.0, (-) 27.2, (-) 26.7, (-) 26.7, (-) 20.9, (-) 20.3, (+) 19.3, (-) 10.8, (-) 10.0; alcohol **14**: (-) 135.5, (+) 133.1, (-) 129.8, (-) 129.6, (-) 129.5, (-) 127.7, (-) 127.6, (-) 76.0, (+) 66.1, (+) 60.4, (+) 45.5, (+) 39.9, (+) 34.8, (-) 32.6, (-) 30.3, (-) 27.1, (-) 26.9, (-) 19.8, (-) 19.7, (+) 19.3, (-) 14.1; alcohol **19**: 135.6, 133.2, 130.0, 129.8, 129.5, 127.7, 127.6, 74.6, 66.4, 60.4, 44.2, 41.0, 34.1, 32.3, 30.5, 27.4, 26.8, 20.9, 20.9, 19.3, 14.9.
  - This experiment was favored over the alternative formation of chiral **15** from **13** and meso **20** from **18** based on the expected small  $\alpha_D$  value of these compounds as it was found in diols **2**, **10**, **11** and **12**.