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

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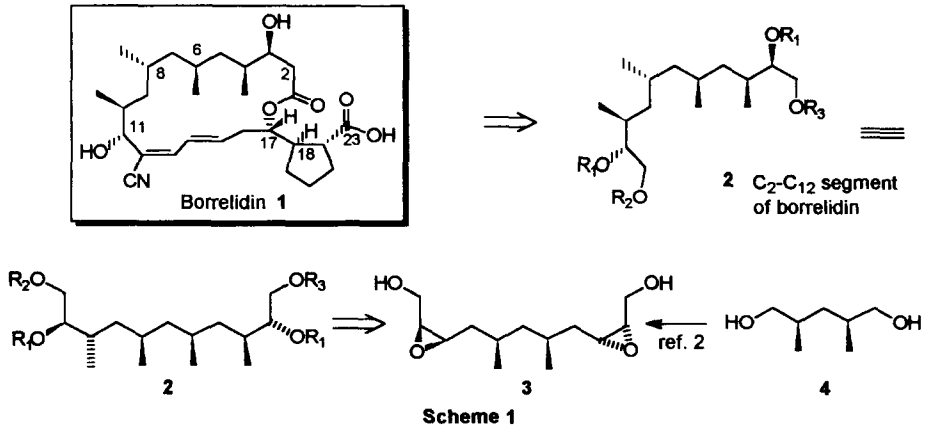
Abstract: Regioselective methylation of bis-epoxides **9** were examined. Two examples of high regioselectivity and yield were achieved. Structure determination of the four possible regioisomers provide useful information for structure determination of structurally related flexible molecules. © 1997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

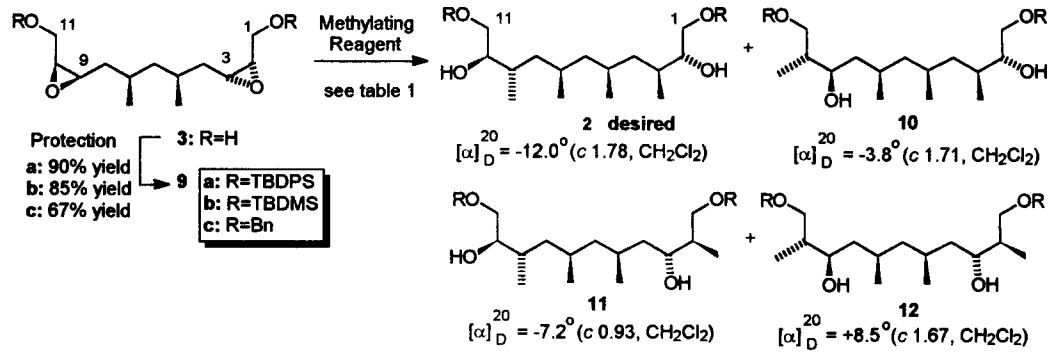
As part of our studies towards a total synthesis of borrelidin (**1**), and interest in studying the relation between relative configuration of polysubstituted alkanes and the conformational distribution of such "flexible molecules with defined shape",[1] we have developed a versatile and highly stereoselective approach for the synthesis of (**2**) (C_2-C_{12} segment of borrelidin) and related isomers.[2] 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.[2]

Regioselective alkylation of *threo*-epoxides, derived from *E*-allylic alcohols, that produce 1,2-diols, is a well documented reaction[3]. However, the regioselectivity and yields of these reactions could be strongly decreased[4] 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_1 and C_{11} 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_3 and C_9 positions is required for the synthesis of borrelidin. Treatment of **3** with Me_3Al resulted in a sluggish transformation[4] to unidentified mixture of products. Partial selectivity was obtained upon treatment of the protected bis-epoxide **9a** (R=TBDPS) with Me_2CuLi[5] (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 $Me_2Cu(CN)Li_2$ (entry 3) as methylating reagent.[5] The isomeric products were *easily* separated by flash chromatography (R_f (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. ^{1}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. ^{1}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_1 and C_{11} with the downfield vicinal protons at C_2 and C_{10} respectively in the 2D-Cosy spectrum, no such cross peaks were obtained in the 2D-Cosy of **12a**.



Scheme 2

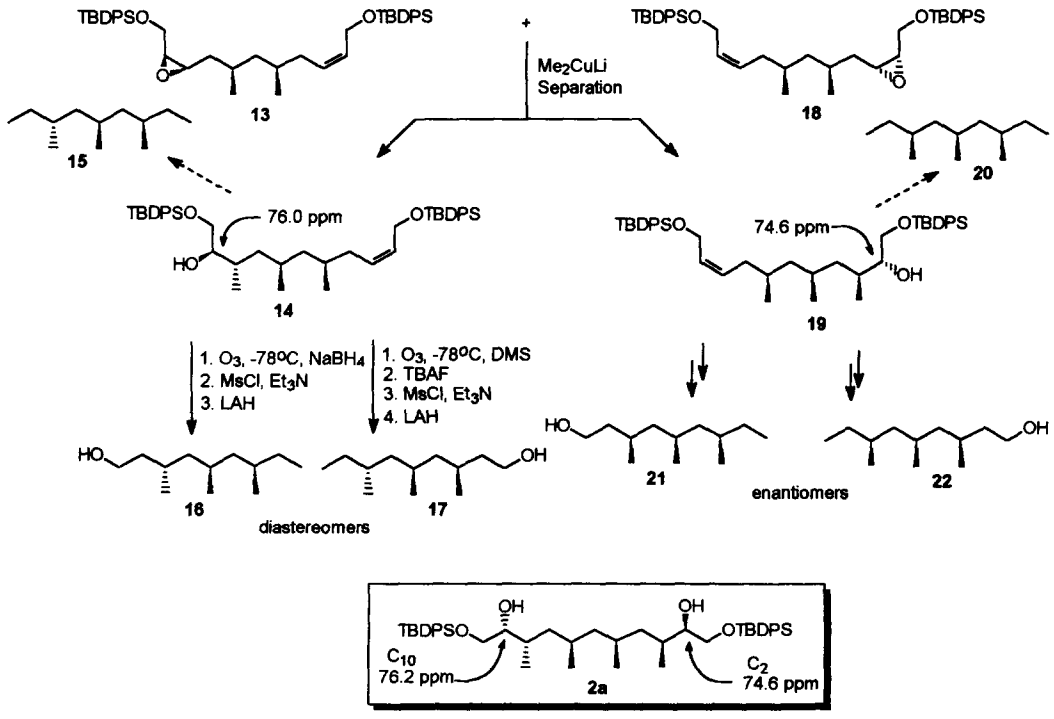
Table 1: Methylation of bis-epoxides **9**.

Entry	R	Methylating Reagent	Reaction Conditions	Total Yield	Regioselectivity 2 : 10 : 11 : 12
1	H	$AlMe_3$	CH_2Cl_2, 0°C	ca. 20%	undefined mixture
2	TBDPS	Me_2CuLi	Et_2O, -23°C	60%	40 : 25 : 25: 10
3	TBDPS	$Me_2Cu(CN)Li_2$	Et_2O, -23-0°C	40%	40 : 25 : 25: 10
4	TBDMS	Me_2CuLi	Et_2O, -23°C	~60%	10 : 25 : 25: 40
5	TBDPS	$LiAlMe_4$	Hexane/Et_2O, rt	no reaction	-----
6	TBDMS	$LiAlMe_4$	Hexane/Et_2O, reflux, 12h	78%	88 : 6 : 6 : 0
7	Bn	$LiAlMe_4$	Hexane/Et_2O, 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 $LiMe_4Al$[6] (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)[7] at the bis-epoxide **9c** and $LiMe_4Al$ as methylation reagent.

At this stage, it is important to distinguish between the C_1 and C_{11} 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 ^{13}C-NMR chemical shifts[8] 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 ^{13}C-chemical shifts kept constant in **2a** and **2b**. Based on this, we have developed the following test to distinguish between C_2 and C_{10} 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 ^{13}C-NMR spectrum[8] was transformed *via* two different sequences (scheme 3) to afford the diastereomeric products **16** and **17** in ca. 50% total yield,[9] indicating the stereochemistry of alcohol **14**. Following the same transformations on the second alcohol fraction that possesses the 74.6 ppm signal in its ^{13}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 ^{13}C-NMR spectrum of **2a** to C_2 and that at 76.2 ppm to C_{10} and distinguish between the isomeric structures of **10a** (74.5 ppm) and **11a** (76.2 ppm).[8]



Scheme 3

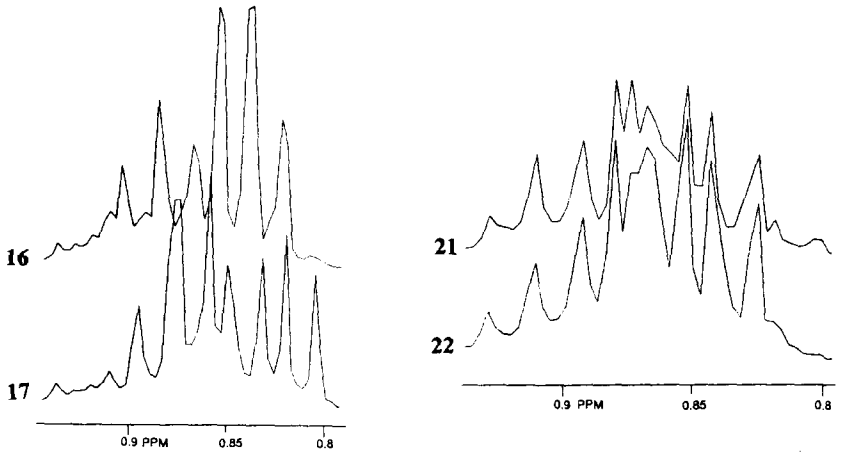


Figure 1: Selected ^{1}H-NMR spectra of diastereomers **16** and **17** and enantiomers **21** and **22**.

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**.

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8. ^{13}C-NMR (JMOD-XH, $CDCl_3$) 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.
9. This experiment was favored over the alternative formation of chiral **15** from **13** and meso **20** from **18** based on the expected small α_D value of these compounds as it was found in diols **2**, **10**, **11** and **12**.

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