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DIRECTIVE EFFECTS IN THE OPENING OF EPOXIDES WITH TRIMETHYLSILYL CYANIDE - ZINC IODIDE. THE ESTABLISHMENT OF THREE CONTIGUOUS CHIRAL CENTERS.

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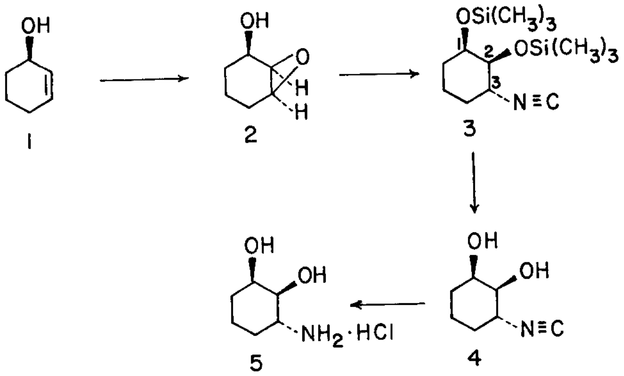
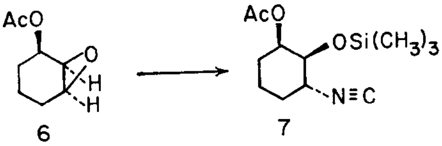
Summary: Adjacent hydroxyl, trimethylsiloxyl, and acetoxyl groups have been shown to provide complete control over the regiospecificity of the opening of epoxides by trimethylsilyl cyanide - zinc iodide. Thus, cyclohex-2-en-R*-1-ol can be readily converted into (1R*;2S*;3R*)-3-aminocyclohexan-1,2-diol.

β-amino alcohols are widely occurring in nature and often constitute a critical moiety in the structure of biologically active natural products. In many instances, these natural products contain an additional hydroxyl group in a specific arrangement of three contiguous chiral centers. Examples of such systems are certain amino sugars, such as daunosamine,[1] and the structurally simple aminoglycosidic antibiotics, such as fortimicin.[2]. Recently, we described a new path to β-amino alcohols which involved the opening of epoxides with trimethylsilyl cyanide - zinc iodide.[3]. In order to determine whether this synthetic methodology would be applicable to the establishment of a series of contiguous functionalized chiral centers, we combined our ring opening with the Sharpless epoxidation.[4] We now wish to report the results of this study.

Treatment of **1** under the conditions described by Sharpless and co-workers[4] or by other stereospecific methods[5] provided **2** in high purity. When **2** was treated with four equivalents of trimethylsilyl cyanide and 1.5 mol % of anhydrous zinc iodide in refluxing methylene chloride for 24 h, a 71% yield of **3** was obtained.[6] Both the regiochemistry of the epoxide opening and the stereochemistry of the contiguous centers were established by a combination of ^1H NMR and ^{13}C NMR on either **3**, or **4** and **5**. ^{13}C NMR of **3** showed nine different resonances, which precluded the reverse regiochemistry in the epoxide opening, since the observed spectrum required the product to be unsymmetrical. In addition, the coupling of C-3 with the isonitrile nitrogen firmly established the presence of the isonitrile moiety,[3,7] while ^1H NMR showed the presence of two trimethylsiloxyl substituents on the ring. When a methanolic solution of **3** containing five equivalents of potassium fluoride was stirred at 25° C for 14 h, a 93% yield of **4** was obtained. Subsequent hydrolysis of **4** with methanolic hydrochloric acid (5 equiv. for 24 h at 25° C gave 98% of **5** (mp 191-194° C), for an overall 61% yield of **5** from **2**. The 300 MHz ^{1}H NMR of **5** showed H-1 as an unsymmetrical quartet at 4.07, H-2 as a doublet of doublets at δ 3.56 (J=3.0 and 9.5 Hz), and H-3 as a six peak multiplet centered at δ 3.29. Decoupling of H-1 resulted in H-2 becoming a sharp doublet with J=9.5 Hz. This indicated that H-1 and H-2 were cis, while H-2 and H-3 were trans.[8]

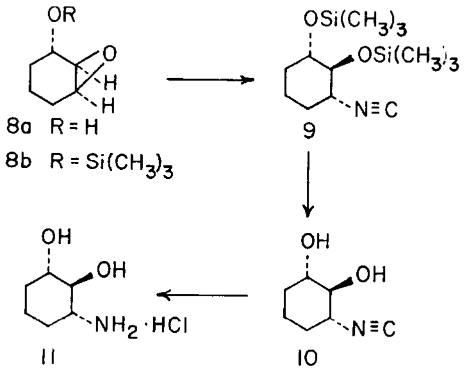


When the trimethylsilyl ether of **2** was subjected to our epoxide opening reaction conditions (2 equiv. TMSiCN, 14 h) a 68% yield of **3** was produced. When **2** was converted to the acetate, **6**, and **6** was subjected to the usual reaction conditions (4 equiv. TMSiCN, 24 h) an 82% yield of **7** was obtained. Interestingly, **7** was cleanly converted into **4** (94% yield) on treatment with three equivalents of potassium fluoride in methanol at 25° C.



The opening of the epoxide ring of **8a** under the conditions used for **2** gave a 70% yield of **9**. Fluoride treatment of **9** gave 73% of **10**. Conversion of the isonitrile group of **10** into the amino moiety of **11** using the procedure described above gave an 84% yield of crude product and a 62% yield of analytically pure material, mp 180-181° C.[9] When the trimethylsilyl ether of **8a** (**8b**) was used with three equivalents of trimethylsilyl cyanide for 20 h, a 51% yield of **9** was obtained.

The work described above provides substantial evidence for the directive effect of hydroxyl and protected hydroxyl groups on the opening of epoxides by trimethylsilyl cyanide - zinc iodide. As a result, this reaction shows considerable promise for the synthesis of molecules containing contiguous amino and hydroxyl groups in a rigorously controlled stereochemical and regiochemical relationship.



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(6) Satisfactory elemental analyses and/or exact mass molecular weights have been obtained on all new compounds. All compounds showed spectral properties which were consistent with the assigned structures.

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(8) Similar NMR analyses and decoupling experiments were used to establish the stereochemistry of the other products discussed in this report.

(9) No difference existed between the ^{1}H NMR spectra of the crude product and the analytically pure material.

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