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ACYCLIC STEREOSELECTION. 21. SYNTHESIS OF AN IONOPHORE SYNTHON HAVING FOUR ASYMMETRIC CARBONS BY SEQUENTIAL ALDOL ADDITION, CLAISEN REARRANGEMENT AND HYDROBORATION[1]

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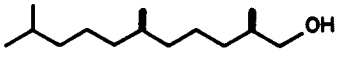
Abstract: Allylic alcohol **7**, obtained by a synthesis involving stereoselective aldol addition to an unsaturated aldehyde, is transformed by the Ireland variant of the Claisen rearrangement into unsaturated acid **9**. Subsequent elaboration of this material gives homoallylic alcohols **13** and **14**, which are hydroborated to obtain primarily **3** and **4**. It is shown that the hydroboration is intermolecular, rather than intramolecular.

We have recently demonstrated a strategy for 1,4 and 1,5 diastereoselection whereby 1,2 stereoselectivity obtained in an aldol addition to an unsaturated aldehyde is parlayed by stereoselective Claisen rearrangement of the resulting allylic alcohol.[3,4] The strategy was demonstrated for 1,5 stereoselection with a synthesis of the C_{14} vitamin E sidechain alcohol **1**[3] and for 1,4 stereoselection with a synthesis of the C_{30} hydrocarbon **2**, a substance related to the C_{30} diol from Messel shale kerogen.[4] In this Letter, we report the application of this strategy to the synthesis of diols **3** and **4**, synthons having four chiral centers and of potential use for the synthesis of polyether ionophores.



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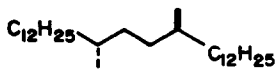

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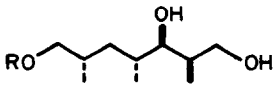
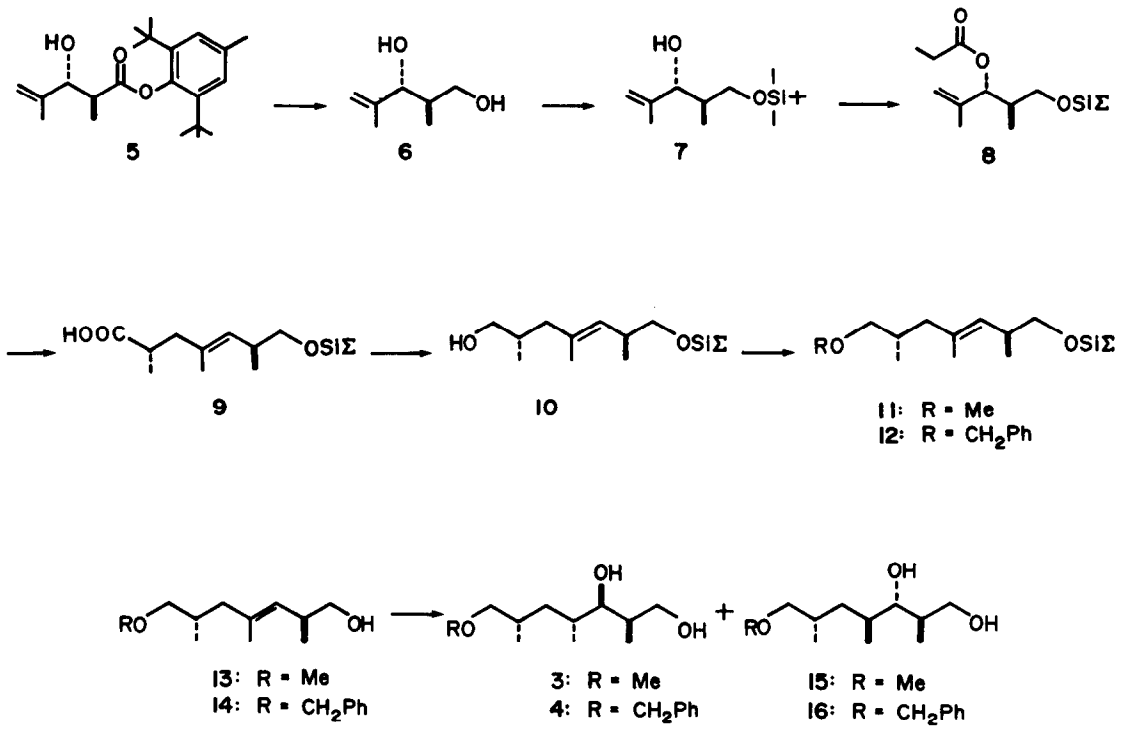


3: R = Me
4: R = CH_2Ph

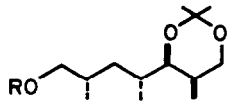
The synthesis is summarized in Scheme 1. Addition of the preformed lithium enolate of the BHT ester of propionic acid[5] to methacrolein gives adduct **5** (88% yield). Reduction of **5** with lithium aluminum hydride in refluxing THF provides unsaturated diol **6** (75% yield). This material is monoprotected with t-butyldimethylsilyl chloride, triethylamine, and 4-(N,N-dimethylamino)pyridine in CH_2Cl_2. The resulting monoether **7**, obtained in quantitative yield, is esteri-

Scheme I



fied by treatment with propionyl chloride and pyridine in CH_2Cl_2 to provide **8** (93% yield). Claisen rearrangement of **8** is accomplished by the method of Ireland[6]; unsaturated acid **9** is obtained in 63% yield. Reduction of **9** (lithium aluminum hydride, refluxing ether) gives monoprotected diol **10** (64%), which is converted into the methyl ether (**11**) and benzyl ether (**12**) by the standard method (NaH, THF, RBr, reflux); ethers **11** and **12** are produced in yields of 88% and 95%, respectively. The t-butyldimethylsilyl group is removed by treatment of **11** or **12** with aqueous acetic acid in THF; alcohols **13** and **14** are thereby obtained, each in 89% yield. The hydroboration of **13** and **14** was studied under a variety of conditions. A mixture of diols (**3** + **15** or **4** + **16**) is produced in a ratio of about 3:1 in yields of 80-90%.

The stereostructures of the major and minor diols were assigned on the basis of ^1H NMR decoupling experiments on the major acetonides (**17** and **18**). A portion of the spectrum of acetonide **17** is shown in Figure 1. The five protons adjacent to oxygen appear as five double doublets at the indicated positions.



17: R = Me
18: R = CH_2Ph

Irradiation of the methine resonance at δ = 1.86 ppm causes two of the double doublets (δ = 3.03 and 3.30 ppm) to collapse to doublets. Therefore, the 1.86 ppm methine must be the C-6 hydrogen. Of the remaining three double doublets, two (δ = 3.59 and 4.06 ppm) are coupled by a geminal coupling of J = 11.4 Hz. Hence, these two resonances must be from the C-1 hydrogens. The second couplings of these two double doublets are 2.7 and 1.7 Hz, values that are compatible with axial-equatorial and equatorial-equatorial couplings, but <u>not</u> with axial-axial coupling. It follows that the C-2 methyl must be axial if C-4 is equatorial, as seems reasonable.

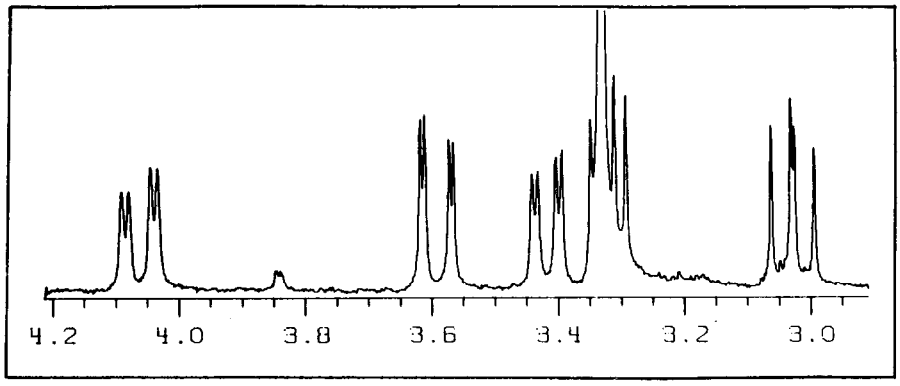
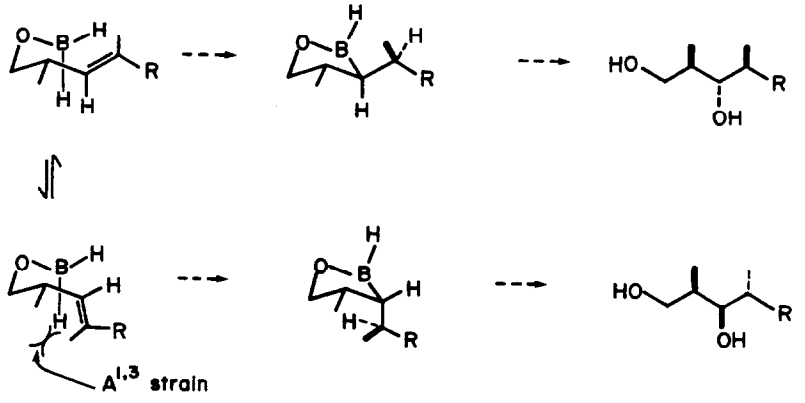


FIGURE 1. Part of the ^1H NMR Spectrum of acetonide 17.

The mechanism of the hydroboration reaction is of interest, since it is not unreasonable to expect that the stereochemistry of the reaction might be controlled by intramolecular reaction (see Scheme 2). However, the diastereofacial preference shown by unsaturated alcohols **13** and **14** is <u>not</u> that expected on the basis of intramolecular delivery of hydride. Instead, the stereostructures of the major diols are those predicted by the Kishi model for intermolecular hydroboration of similar chiral substrates.[7] The idea that the reaction is intermolecular, rather than intramolecular, is supported by other observations. Upon addition of one mole-equivalent of BH_3 to a THF solution of the alcohol, rapid hydrogen evolution is observed. However, tlc analysis of the reaction mixture

Scheme 2



shows that the addition product is not formed until a second mole-equivalent of BH_3 is added.

In summary, the strategy presented in this Letter may be used to prepare the useful synthons 3 and 4. The aldol addition and Claisen rearrangement steps both proceed with excellent stereoselectivity. The stereoselectivity in the hydroboration step is lower, but the overall stereoselectivity of 3:1 in the synthesis of a compound with four asymmetric centers is still attractive.

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References and Notes

1. For part 20, see S.-I. Kiyooka and C.H. Heathcock, Tetrahedron Lett., in press.

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