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# Highly Diastereoselective 5-Hexenyl Radical Cyclizations with Lewis Acids and Carbohydrate Scaffolds

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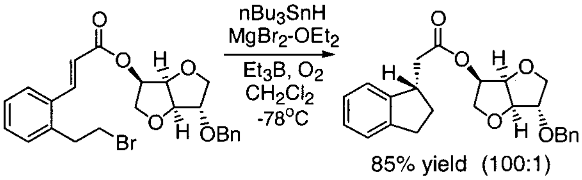
## ABSTRACT

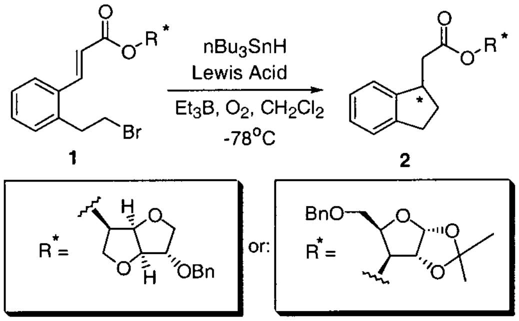


**Carbohydrates as removable chiral scaffolds for free radical cyclizations were examined for the first time. This investigation illustrates the utility of two inexpensive carbohydrate derivatives as sources of asymmetry for 5-hexenyl radical cyclizations. Diastereomeric ratios as high as 100:1 were achieved with an ester-appended (+)-isosorbide hexose and 70:1 for a diol-protected D-xylose pentose. Temperature dependence, Lewis acids, and solvents were all examined. By correlation with known compounds, the newly generated chiral centers were of the (*S*)-configuration.**

Radical cyclizations with activated olefins offer synthetic chemists a well-documented and reliable means of carbon−carbon bond formation.[1] Synthetic benefits include neutral reaction conditions and tolerance of various functional groups and protecting schemes. All of these advantages render this methodology attractive for a wide variety of synthetic sequences.[2] Recently, the diastereoselectivity of free radical reactions has been greatly enhanced due to the use of a combination of Lewis acids and appended chiral auxiliaries, scaffolds, and templates.[3−5] Although radical additions to activated olefins have been studied extensively,[2,6] 5-hexenyl cyclizations with chiral auxiliaries such as oxazolidinones, sulfoxides, and chiral esters have been far less investigated.[7]

Interestingly, carbohydrates as removable chiral auxiliaries for 5-hexenyl free radical cyclizations have not been studied. This investigation examined the utility of two inexpensive carbohydrate derivatives as sources of asymmetry for a 5-hexenyl radical cyclization of **1** at low temperatures (−78 °C) with tributyltin hydride, $BEt_3$, and $O_2$ (Scheme 1). Very

**Scheme 1**



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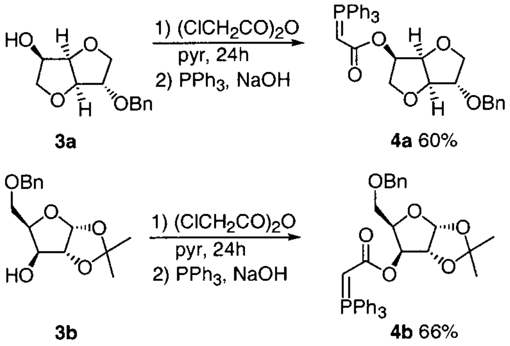
high diastereomeric ratios were achieved while the effects of temperature dependence, Lewis acids, and solvents were all studied. By correlation with known compounds, the newly generated chiral center in **2** in both carbohydrate-mediated cyclizations is of the (*S*)-configuration. With these high diastereomeric ratios, we believe these 5-hexenyl radical cyclizations are some of the most highly diastereoselective radical closures to date resulting from any removable appended chiral molecule.

Earlier investigations of auxiliaries used in various radical reactions have relied on a chiral oxazolidinone ring;[5,8] however, these investigations examined the commercially available and less expensive sugar auxiliaries (+)-isosorbide and (−)-D-xylose acetonide. Both carbohydrates are highly oxygenated and provide multiple sites for metal chelation. Thus, additional affinity that strongly attracts the Lewis acid was a key and desirable trait in selecting these auxiliaries.

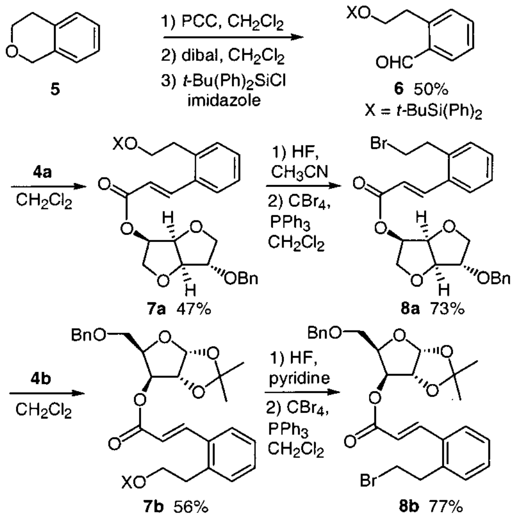
Precursor **1** was to be constructed via a Wittig reaction; the main framework was to be assembled via an unsaturated chiral ester and an aromatic aldehyde. Carbohydrate-derived Wittig reagents **4a** and **4b** were synthesized from monobenzyl ethers **3a** and **3b**, respectively, in two steps, as illustrated in Scheme 2. Monobenzylation of (+)-isosorbide and 1,2-*O*-isopropylidene-D-xylofuranose was achieved by etherification with benzyl bromide, affording **3a** and **3b**, respectively.[9] The remaining hydroxyl functionality was converted to a chloromethylene ester using chloroacetic anhydride in pyridine.[10] The corresponding ylides **4a** and **4b** were obtained from triphenylphosphine followed with base treatment.

**Scheme 2**



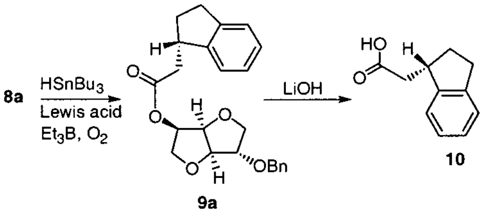
The Wittig reagents were then coupled with aromatic aldehyde **6** synthesized from commercially available isochroman (Scheme 3). Isochroman (**5**) was first oxidized with PCC to isochroman-1-one and then reduced using Dibal to isochroman-1-ol.[11] The aromatic lactol was then trapped in its acyclic form as an aldehyde with the bulky silylating agent *tert*-butylchlorodiphenylsilane. The desired aldehyde was achieved in three steps with an overall yield of 50%. Wittig reagents **4a** and **4b** and aldehyde **6** were reacted in methylene chloride, providing unsaturated chiral esters **7a** and **7b**. Further manipulations included deprotection of the silyl ether with HF followed by conversion to bromides **8a** and **8b** in 73% (isosorbide) and 77% (xylose), respectively.

**Scheme 3**



Once the unsaturated bromoester of each carbohydrate derivative had been synthesized, various reaction conditions for a 5-hexenyl radical cyclization were explored. *It was disquieting that the distance of the new cyclopentane center was a lengthy five atoms from the nearest controlling chiral alkoxy carbon on the tetrahydrofuran rings in* ***8a*** *and* ***8b***. Diastereomeric ratios of the isosorbide adduct **9a**, obtained via GC and HPLC, are shown in Table 1.

**Table 1.** Free Radical Cyclizations of **8a**



| entry | Lewis acid | temp-erature | solvent | % yield | ratio |
|---|---|---|---|---|---|
| 1 | none | 80 °C | benzene | 87 | 1.6:1 |
| 2 | none | 0 °C | $CH_2Cl_2$ | 85 | 2.2:1 |
| 3 | none | -78 °C | $CH_2Cl_2$ | 85 | 2.9:1 |
| 4 | $Et_2AlCl$ | -78 °C | $CH_2Cl_2$ | – | 7:1 |
| 5 | $MgBr_2$ | -78 °C | $CH_2Cl_2$-ether | 85 | >100:1 |
| 6 | $ZnCl_2$ | -78 °C | $CH_2Cl_2$-THF | 87 | >100:1 |
| 7 | $Yb(OTf)_3$ | -78 °C | $CH_2Cl_2$ | 75 | 1.6:1 |

At 80 °C, AIBN was used as a radical initiator; however, triethylborane and oxygen were utilized for the lower

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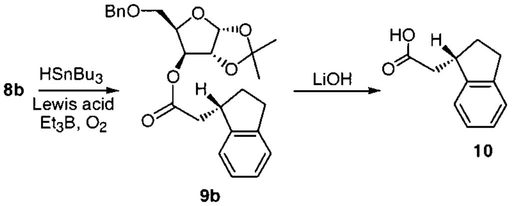
temperature studies. As expected, the radical cyclization of the (+)-isosorbide moiety **8a** proved to be more selective at lower temperatures. Without a Lewis acid, the diastereomer ratios were low, ranging from 1.6:1 to 2.9:1. When a Lewis acid was employed, diastereomeric ratios increased substantially, suggesting the formation of an activated metal chelate with the appended isosorbide auxiliary. Among the best of the Lewis acids studied, *zinc chloride and magnesium bromide etherate proved to be the most effective for the isosorbide chiral scaffold with diastereomeric values of >100:1 for each*.

The radical cyclization of D-xylose adduct **8b** proved successful as well, as shown in Table 2. Similar to Table 1, a temperature dependence and an improvement in diastereomeric ratios with Lewis acids were observed for these cyclizations. *Lewis acids, such as diethylaluminum chloride and titanium tetrachloride, provided diastereomeric ratios as high as 60:1 and 70:1, respectively*. For both sugars, lanthanides such as Eu(III) and Yb(III) were uniformly less effective in enhancing the diastereoselectivity of the cyclization. In some cases the lanthanide Lewis acids gave ratios that were similar to those reactions lacking any added Lewis acids. This was unexpected because lanthanide Lewis acids have demonstrated excellent results in recent radical studies.[2,12]

**Table 2.** Free Radical Cyclizations of **8b**



| entry | Lewis acid | temperature | solvent | % yield | ratio |
|---|---|---|---|---|---|
| 1 | none | 0 °C | $CH_2Cl_2$ | – | 5:1 |
| 2 | none | -78 °C | $CH_2Cl_2$ | 82 | 7:1 |
| 3 | $TiCl_4$ | -78 °C | $CH_2Cl_2$ | 81 | 70:1 |
| 4 | $Et_2AlCl$ | -78 °C | $CH_2Cl_2$ | 83 | 60:1 |
| 5 | $Eu(OTf)_3$ | -78 °C | $CH_2Cl_2$-ether | – | 2:1 |
| 6 | $ZnCl_2$ | -78 °C | $CH_2Cl_2$-THF | 83 | 6:1 |
| 7 | $Yb(OTf)_3$ | -78 °C | $CH_2Cl_2$ | 75 | 12:1 |

Once the diastereomeric ratios of each reaction parameter set had been determined, elucidation of the absolute stereochemistry of the newly formed chiral center was investigated. Both cyclized products **9a** and **9b** were subjected to saponification conditions using lithium hydroxide in water/THF. Carboxylic acid **10**, the major product in both saponifications, was then isolated. This compound was identical to (*S*)-(+)-indan acid as previously reported.[13]

In conclusion, the highly oxygenated nature of carbohydrate derivatives is extremely advantageous, offering ease in functionalization, multiple sites for Lewis acid chelation, and inexpensive ready availability. As chiral templates for free radical 5-hexenyl cyclizations, both (+)-isosorbide and (−)-D-xylose gave very high diastereomeric ratios. This high selectivity can be attributed to the multiple sites of chelation, firmly anchoring the Lewis acid to the polyoxygenated sugar.

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**Supporting Information Available:** Experimental and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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