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Aldehyde–alkene cyclizations via *O*-stannyl ketyl radicals using sugars as chiral auxiliaries

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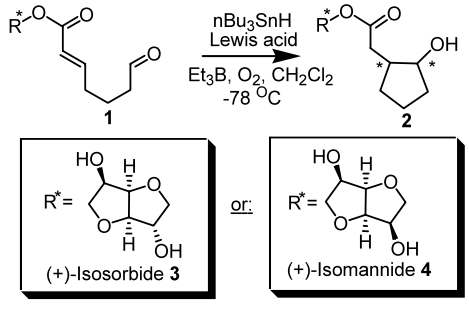
Abstract—This investigation illustrates the utility of two inexpensive carbohydrate derivatives as sources of asymmetry for aldehyde–alkene radical cyclizations. Diastereomeric ratios as high as 9:1 were achieved with an ester-appended (+)-isosorbide and 100:1 for (+)-isomannide. Temperature dependence, Lewis acids and solvents were all examined.

For more than 20 years tributyltin hydride (nBu_3SnH) has been used in a wide diversity of free radical cyclization reactions.[1] Almost all free radical reactions use nBu_3SnH with halides and other precursors to obtain a carbon-centered radical, which, upon cyclization with an alkene, result in a net loss of both functions in the end. We have actively reported on studies directed towards the use of *O*-stannyl ketyls in synthesis.[2] This interest began with simple carbonyl-alkene coupling reactions[3a] and tandem cyclizations[3c] using these potentially useful intermediates. Although there is still much to be learned, *O*-stannyl ketyl radical anions differs markedly from other radicals because (1) they have an inherent nucleophilic/anionic component to their properties, (2) they are more stable and less reactive due to resonance, and (3) they produce a useful alcohol function after the reaction.[3e]

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.[4a] Similar *O*-stannyl ketyl-mediated reactions have not been studied.[3] This investigation examined, for the first time, two carbohydrate derivatives as chiral auxiliaries for aldehyde–alkene radical cyclizations with a Lewis acid at low temperatures (−78°C) with tributyltin hydride, as shown in Scheme 1.

Note that there are two challenging problems to overcome in this transformation. First, two new non-racemic stereogenic centers are formed in this reaction, raising the possibility for four different stereoisomers to result in **2**. Thus, product mixtures have the potential to be complex. Second, the controlling asymmetric center in either (+)-isosorbide **3** or (+)-isomannide **4** is a distance of 5–6 atoms away from the newly formed stereogenic centers in **2**. Asymmetric synthesis over this span of atoms clearly has the potential to reduce diastereoselectivity. On the other hand, it is beneficial that both carbohydrate precursors are highly oxygenated and provide multiple sites for metal chelation. This oxophilicity for Lewis acids was a key and desirable trait in selecting these auxiliaries. We were pleased to obtain diastereomeric ratios as high as 9:1 for **1**→**2** with ester-appended (+)-isosorbide **3** and 100:1 for (+)-isommanide **4**.

A preliminary study of the diastereoselectivity of the cyclization without any chiral appendage was first



Scheme 1.

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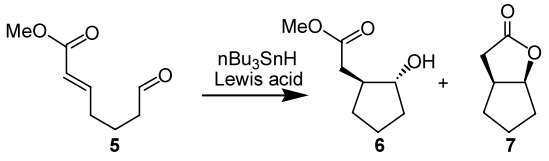
Table 1. Ratios of **6**:**7**

Entry	Lewis acid	Solvent	Temp. (°C)	% Yield[b]	**6**:**7**[c]
1[a]	None	Benzene	80	97	1.1:1
2	None	CH_2Cl_2	20	70	1.8:1
3	None	CH_2Cl_2	0	58	3:1
4	None	CH_2Cl_2	−78	30	7:1
5	$MgBr_2$–OEt_2	CH_2Cl_2–ether	−78	83	>100:1
6	CuOTf	CH_2Cl_2	−78	98	>100:1
7	$ZnCl_2$	CH_2Cl_2–ether	−78	90	>100:1

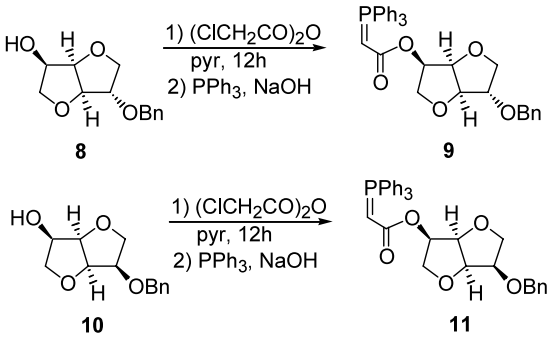
[a] AIBN was used as an initiator in entry 1; all other entries used BEt_3 and O_2.
[b] Isolated yields for material judged to be pure.
[c] Ratios determined by capillary GC.

examined. Previous studies had indicated that **6** should be favored in the reaction at 80°C, where the appendages avoid each other in the transition state.[3a] The studies are summarized in Table 1.

trans-Alcohol **6** was the major product in every reaction and, unlike **7**, it cannot spontaneously close to a bicyclic lactone due to high strain.[5] Without the use of Lewis acids in entries 1–4, the ratios gradually improved as the temperature was lowered to −78°C. In entry 4, we obtained a 7:1 ratio as the best attempt. Yields and ratios favoring **6** were dramatically improved with the addition of Lewis acids in entries 5–7. The minor *cis*-lactone **7** could only be observed in trace quantities here. The use of Lewis acid-mediated reactions gave ratios up to >100:1 in all cases (Scheme 2).

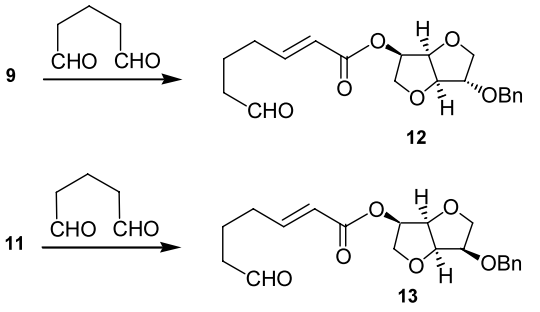


Scheme 2.



Scheme 3.

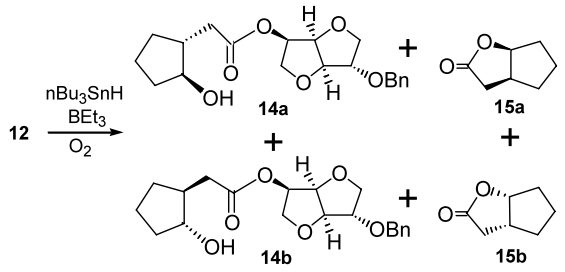
We next decided to prepare chiral auxiliaries of **1** with either ester-appended sugar **3** or **4**. Chiral cyclization precursors **12** and **13** (Scheme 4) were to be constructed via a Wittig reaction and the remaining framework was to be assembled via an unsaturated chiral ester and an aliphatic aldehyde. Starting monobenzyl ethers **8** and **10** prepared from **3** and **4** by standard treatment with benzyl bromide (1 equiv.), were used in Scheme 3. The remaining hydroxyl in each sugar was converted to a stabilized ylide by treatment with chloroacetic anhydride and pyridine, followed by triphenylphosphine and aqueous base. The Wittig reagents **9** and **11** were then coupled with freshly distilled glutaraldehyde to construct the chiral precursors **12** and **13**, respectively, as shown in Scheme 4.



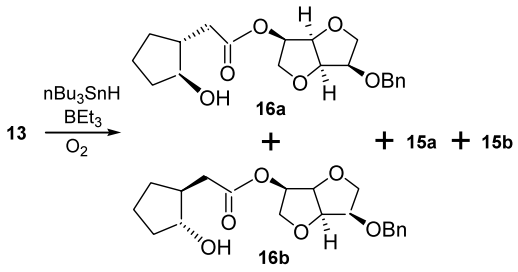
Scheme 4.

Once the α,β-unsaturated ester of each carbohydrate derivative had been synthesized, various reaction conditions for radical cyclizations were explored. The four different aldehyde–alkene products that can result from the cyclization of **12** are shown in Scheme 5. The conditions for the cyclizations we studied are summarized in Table 2. At 80°C, AIBN was used as a radical initiator; however, triethylborane and oxygen were utilized for the lower temperature studies. The lactones **15a** and **15b** were usually formed in smaller amounts, a trend we noticed in the cyclization of less complex compound **5**. Without a Lewis acid, the diastereomer ratios for **14a**:**14b** were very low, ranging from 1:1 to 1.1:1. When certain Lewis acids were employed, diastereomeric ratios increased. Among the most successful of the Lewis acids studied, zinc chloride proved to be the most effective for isosorbide chiral scaffold **12** with diastereomeric values of 9:1 in entry 6 in Table 2.[6]

The radical cyclization of isomannide adduct **13** proved to be even more successful and differed from **12** only by the stereochemistry of a single hydroxyl. The four different products that can result from the cyclization of **13** are shown in Scheme 6. The conditions for the



Scheme 5.



Scheme 6.

cyclizations we studied are summarized in Table 3. Similar to Table 1, much improvement in diastereomeric ratios with Lewis acids were observed for these cyclizations too. In general, the ratios were much higher in the case of **13** versus **12**. Isomannide gave a very high diastereomeric ratio of 100:1 for **16a**:**16b** with three different Lewis acids, including, $ZnCl_2$, $MgBr_2$–OEt_2, and CuOTf.

For both sugars, lanthanide-based Lewis acids such as Eu(III) and Yb(III) were uniformly ineffective 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 expected because lanthanide Lewis acids have demonstrated poor results in a previous study involving those sugars.[7]

Once the diastereomeric ratios of each reaction set had been determined, elucidation of the absolute stereochemistry of the major diastereomer was achieved by chemical correlation as shown in Scheme 7. Major isomer **16a**[8] from the radical cyclization of isomannide derivative **13** in presence of $ZnCl_2$ (entry 4, Table 3) was saponified and esterified, affording chiral methyl ester **17** with a specific rotation of +43.1. The specific rotation of **17** is known (+43.1).[9] The same process was done with **14a**,[6] the major isomer from the cyclization of the isosorbide adduct (entry 6, Table 2). A similar specific rotation +43.0 was obtained after careful chromatographic isolation.

A proposed working model of the transformation of **13** to **16a** using $ZnCl_2$ as a Lewis acid is shown in Scheme 8. The α-disposed benzyloxy function clearly plays a

Table 2. Product ratios from the cyclization of **12**

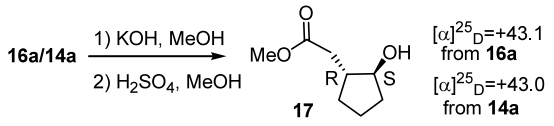
Entry	Lewis acid	Solvent	% Yield[b]	**14a**/**14b**:**15a**/**15b**[c]	**14a**:**14b**[c]
1[a]	None	Benzene[d]	84	2:1	1:1
2	None	CH_2Cl_2[e]	40	3.3:1	1:1
3	$Eu(OTf)_3$	CH_2Cl_2[e]	65	6:1	1.7:1
4	$MgBr_2$–OEt_2	CH_2Cl_2[f]	71	48:1	1.1:1
5	CuOTf	CH_2Cl_2[f]	70	48:1	2.3:1
6	$ZnCl_2$	CH_2Cl_2–THF[f]	73	48:1	9:1
7	$Yb(OTf)_3$	CH_2Cl_2[f]	68	48:1	1.4:1

[a] AIBN was used as an initiator in entry 1; all other entries used BEt_3 and O_2.
[b] Isolated yields for material judged to be pure by ^1H NMR.
[c] Ratios determined by HPLC.
[d] Run at 80°C.
[e] Run at 0°C.
[f] Run at −78°C.

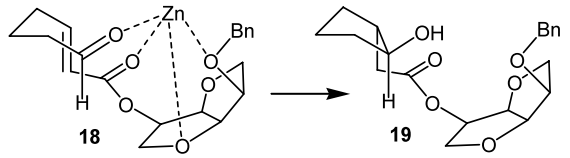
Table 3. Product ratios from the cyclization of **13**

Entry	Lewis acid	Solvent	% Yield[b]	**16a**/**16b**:**15a**/**15b**[c]	**16a**:**16b**[c]
1[a]	None	Benzene[d]	96	100:1	1:1
2	$MgBr_2$–OEt_2	CH_2Cl_2[e]	91	100:1	100:1
3	CuOTf	CH_2Cl_2[e]	89	100:1	100:1
4	$ZnCl_2$	CH_2Cl_2–THF[e]	93	100:1	100:1
5	$Yb(OTf)_3$	CH_2Cl_2[e]	68	100:1	2:1

[a] AIBN was used as an initiator in entry 1; all other entries used BEt_3 and O_2.
[b] Isolated yields for material judged to be pure by ^1H NMR.
[c] Ratios determined by HPLC.
[d] Run at 80°C.
[e] Run at −78°C.



Scheme 7.



Scheme 8.

role in the reaction because the β-benzyloxy in **12** leads to decreased diastereoselectivity. The polydentate zinc metal likely chelates the readily available oxygens with the isomannide forming a 'clamshell' to cup the metal in place in **18**. Using **16b**, the aldehyde oxygen points down and is not readily accessible to the Lewis acid and cannot partake in the metal chelate.

In conclusion, *O*-stannyl ketyl promoted aldehyde-alkene cyclizations with two appended carbohydrate derivatives. Diastereomeric ratios as high as 9:1 were achieved with an ester-appended (+)-isosorbide and 100:1 for (+)-isommanide were observed over a remote distance from the nearest asymmetric center.[10] Temperature dependence, Lewis acids and solvents were all examined.

Acknowledgements

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6. Partial spectroscopic data for **14a**: $[\alpha]_D^{25}=+125.4$ (*c* 0.1, MeOH); ^{1}H NMR δ 1.21 (m, 1H), 1.58 (m, 2H), 1.71 (m, 1H), 1.94 (m, 2H), 2.11 (m, 1H), 2.38 (dd, $J=16.5$, 7.8 Hz, 1H), 2.41 (ddd, $J=16.5$, 6.3, 1.0 Hz, 1H), 2.60 (br s, 1H), 3.82 (m, 8H), 4.23 (q, $J=6.3$ Hz, 1H), 4.81 (t, $J=6.3$ Hz, 1H), 5.12 (q, $J=6.6$ Hz, 1H), 7.23 (m, 5H); ^{13}C NMR ($CDCl_3$) 172.8, 137.2, 128.4, 127.6, 83.3, 79.0, 76.8, 75.5, 74.1, 72.2, 64.9, 64.2, 36.5, 32.0, 30.7, 23.7, 17.2.
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8. Partial spectroscopic data for **16a**: $[\alpha]_D^{25}=+137.6$ (*c* 0.1, MeOH); ^{1}H NMR δ 1.16–1.36 (m, 1H), 1.54–164 (m, 2H), 1.67–1.77 (m, 1H), 1.91–1.99 (m, 2H), 2.03–2.13 (m, 1H), 2.39 (dd, $J=16.3$, 8.0 Hz, 1H), 2.45 (ddd, $J=16.3$, 6.1, 1.0 Hz, 1H), 2.51 (br s, 1H), 3.40–4.08 (m, 7H), 3.85 (m, 1H), 4.20 (q, $J=6.5$ Hz, 1H), 4.85 (t, $J=6.4$ Hz, 1H), 5.15 (q, $J=6.4$ Hz, 1H), 7.14 (m, 5H); ^{13}C NMR ($CDCl_3$) 172.0, 137.2, 128.4, 127.6, 82.9, 79.2, 76.4, 75.6, 73.8, 72.2, 65.4, 64.6, 36.1, 31.8, 30.7, 23.5, 16.9 HRMS calcd for $C_{20}H_{26}O_6$ 362.1729, found 362.1747.
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