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An asymmetric Kharasch reaction mediated by D-xylose: long range diastereocontrol

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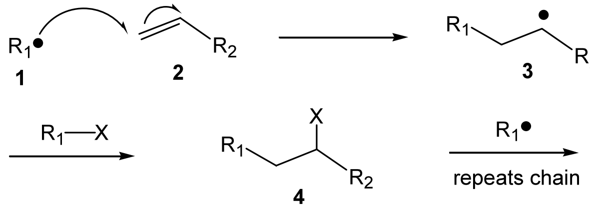
Abstract—An asymmetric Kharasch-type atom transfer reaction was studied under 13 different sets of reaction conditions in order to obtain the highest levels of diastereoselection. The highest ratio of 12.5:1 (71%) was observed at low temperatures (−78°C) using the Lewis acid $Eu(OTf)_3$. Because the new asymmetric center is so distant from the D-xylose, we propose a transition state involving two sugars. The conversion of the major product to a naturally occurring chiral γ-butyrolactone, under basic conditions, is described which also confirmed the diastereoselectivity and absolute stereochemistry of the Kharasch reaction. © 2003 Elsevier Science Ltd. All rights reserved.

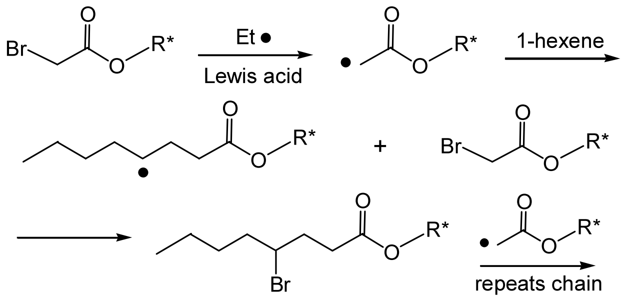
Free radical reactions involving atom transfer were studied by Kharasch many years ago as shown in Scheme 1.[1] Related efforts, particularly from Curran and others, have expanded on this work and led to a better understanding of atom transfer reactions in general.[2] Chiral versions of the Kharasch reaction are particularly scarce, however, Porter and co-workers have performed interesting experiments on these reactions using a chiral oxazolidinone auxiliary.[3] In this letter, we will describe our results in this area using an inexpensive D-xylose carbohydrate as an auxiliary that produced ratios varying from a low diastereoselectivity of 1.5:1 to a potentially synthetically useful 12.5:1.[4] The modern version of this radical transformation, shown in Scheme 2, represents a more useful and successful variation of the classic Kharasch reaction, in part due to the use of an electrophilic α-bromo ester and a Lewis acid.[3]



Scheme 1.

Particularly helpful in this newer Kharasch atom transfer reaction is the ability to run the reaction at lower temperatures. Thus, the potential for good diastereoselectivity in the introduction of the bromide was possible with some reasonable experimental design.

In our design it was recognized that the ester function represents a good functionality for the introduction of a removable chiral auxiliary. In these transformations, we wanted to study the asymmetric variation of this reaction by using D-xylose as a chiral auxiliary for the chiral R* as shown in Scheme 2. Particularly concerning was the long-range distance of several atoms from the controlling C-3 carbon on D-xylose not just in a free radical reaction but any asymmetric induction over that span. To the best of our knowledge, this is also the first example of any sugar auxiliary used in a Kharasch reaction.



Scheme 2.

Keywords: free radical; diastereoselective; atom transfer; Kharasch reaction.

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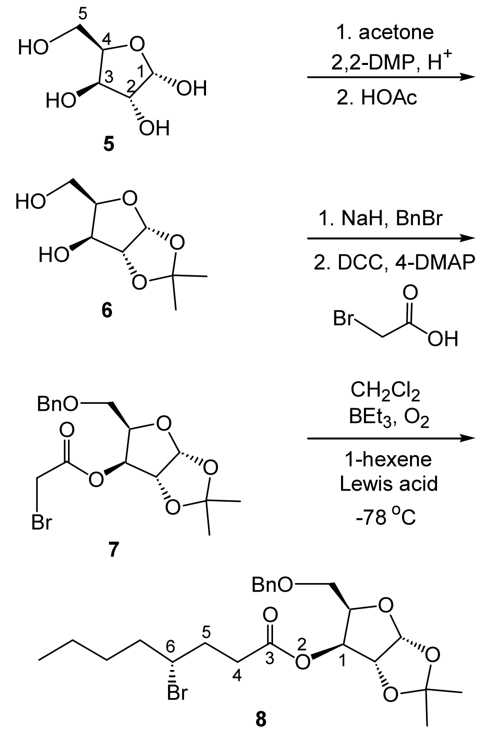


Scheme 3.

Our synthesis of the xylose auxiliary, shown in Scheme 3, begins by treatment of **5** with acetone and 2,2-dimethoxypropane to form the 1,2:3,5-diacetonide as a crystalline solid in 90% yield, followed by selective deprotection of the 3,5-acetonide with acetic acid (70% aq.) constructing diol **6** in 70% yield. Selective protection of the primary C-5 hydroxyl as its benzyl ether (60% yield) and esterification with bromoacetic acid gave **7** (89% yield) as the key starting compound for the asymmetric Kharasch reactions examined here.

The Kharasch reaction we are investigating involves a type of Lewis acid complexation that also appears to accelerate many examples of other radical reactions.[5] This occurs by weakening the C–Br bond or increasing the electrophilic nature of the radical. Researchers have found that a C–Br bond next to a carbonyl, as in **7**, is weakened by chelation with a Lewis acid.[3] Others[6] have also studied this bond-weakening effect suggesting that the carbonyl function destabilizes the C–Br bond dipole in the parent compound. This effect makes the parent species less stable than the radical formed from it. Thus, a carbon bearing a bromine (CHBr) is a weaker bond when placed adjacent to a metal-chelated carbonyl function.

In an attempt to improve the diastereoselectivity of the reaction, more than 13 different sets of conditions were examined for the Kharasch reaction of **7**→**8**, as summarized in Table 1. Temperatures at or above 0°C gave ratios that were not over 3:1. The reactions at −78°C were somewhat improved in d.e., while the best results were observed using $Eu(OTf)_3$ as a Lewis acid. The solvent gave some variation in ratios comparing ether in one case (7.3:1) to dichloromethane (12.5:1). The diethylether oxygen (Lewis base) ties up the $Eu(OTf)_3$ while access to the carbonyl is much better in CH_2Cl_2. Reactions under Kharasch conditions with 1-hexene and no Lewis acid did not produce any of the expected product **8** and no reaction was observed. We concluded that an external Lewis acid is critical to the outcome of the reaction; subsequently all the examples worked well when one was added. When one considers that the bromide is several atoms removed from the nearest asymmetric center, the 12.5:1 ratio with $Eu(OTf)_3$ in CH_2Cl_2 was very gratifying.[7]

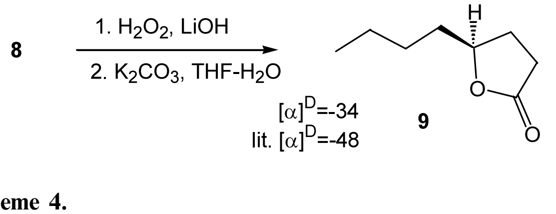
Table 1. Conditions for the Kharasch reaction

Lewis acid	Temp. (°C)	Solvent	d.e.[b]	Yield (%)[c]
$Eu(OTf)_3$	25	CH_2Cl_2	1.7:1	56
$ZnCl_2$	25	CH_2Cl_2/THF[a]	1.6:1	67
$Yb(OTf)_3$	25	CH_2Cl_2	1.7:1	63
$Zn(OTf)_2$	25	CH_2Cl_2/THF	1.5:1	57
$Yb(OTf)_3$	0	CH_2Cl_2	2.2:1	62
$ZnCl_2$	0	CH_2Cl_2/THF	2.5:1	56
$MgBr_2$	0	CH_2Cl_2/THF	1.5:1	62
$Eu(OTf)_3$	0	CH_2Cl_2	2.8:1	65
$Eu(OTf)_3$	−78	Ether	7.3:1	70
$ZnCl_2$	−78	CH_2Cl_2/THF	3.3:1	52
$MgBr_2$	−78	CH_2Cl_2/THF	3.0:1	56
$Yb(OTf)_3$	−78	CH_2Cl_2	4.1:1	65
$Eu(OTf)_3$	−78	CH_2Cl_2	12.5:1	71

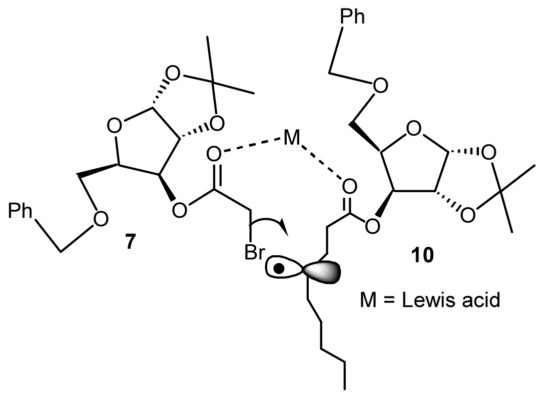
[a] A mixture of solvents was used for solubility.
[b] d.e. measured by gas chromatography.
[c] Yields are for isolated materials.

To confirm the stereochemistry of the major diastereomer **8**, it was cleaved with base along with concurrent cyclization of the acid to the naturally occurring chiral *S*-γ-butyrolactone **9**.[8] This lactone is ubiquitous and found in a number of natural fruit flavors such as apricots, peaches and strawberries. Clean closure by S_Ni backside displacement of the bromide from the reaction producing **8** in 12.5:1 ratio constructed **9** in 74% e.e. in our best attempt (Scheme 4).

Although we do not yet have a complete explanation for the origin of the diastereoselection, the delivery of the bromide from chiral bromoester **7** to **10**, the radical derived from **8**, may resemble that depicted in Figure 1. The possibility shows the two metal-coordinated sugar species in delivery of the bromide to the radical. Lewis acid M likely draws the bromide close to the intermediate radical species in an intramolecular-like internal delivery.



Scheme 4.



→**8.**

Figure 1. Transition state for **7**→**8**.

With non-bonded conformational preferences becoming important now. It should be noted that M probably has several other unknown sites of lone-pair polydentate interactions with both molecules. Molecular models indicate that the two sugars easily sandwich the reaction with one directly on top of the other. Because both sugars must be involved in this bromine atom transfer, the long distance from the controlling asymmetric center in **10**, may be just part of the picture in addition to how the two xylose sugars have nonbonded interactions and fit together.[9]

In conclusion, an asymmetric Kharasch-type atom transfer reaction was studied to obtain the highest levels of diastereoselection. The highest ratio of 12.5:1 (71%) was observed at low temperatures (−78°C) using the Lewis acid Eu(OTf)$_3$. Because the new asymmetric center is six atoms away from the D-xylose, we proposed a transition state involving two sugars. The conversion of the major product to a naturally occurring chiral *S*-γ-butyrolactone, confirmed the absolute stereochemistry of the Kharasch reaction.

Acknowledgements

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9. Selected spectral data. Bromoester **7**: ^{1}H NMR 7.30 (m, 5H), 6.00 (d, 1H, $J=3.5$), 4.71 (d, 1H, $J=11.9$), 4.60 (d, 1H, $J=3.5$), 4.45 (d, 1H, $J=11.9$), 4.43–4.34 (m, 3H), 3.81 (s, 2H), 3.69 (m, 1H), 1.45 (s, 3H), 1.31 (s, 3H); ^{13}C NMR δ 167.3, 137.3, 128.8, 128.4, 128.1, 112.2, 105.5, 82.3, 81.7, 76.9, 72.1, 64.1, 41.0, 27.0, 26.5. Bromoester **8**: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.30 (m, 5H), 5.98 (d, 1H, $J=3.8$), 4.72 (d, 1H, $J=11.8$), 4.65 (d, 1H), 4.45 (d, 1H, $J=11.9$), 4.39–4.34 (m, 4H), 4.01 (m, 1H), 3.99 (m, 2H), 2.52 (m, 2H), 2.15 (m, 1H), 2.01 (m, 1H), 1.85 (m, 2H), 1.50 (s, 3H), 1.33 (s, 3H), 1.25 (m, 2H), 0.8 (t, 3H, $J=7.31$); ^{13}C NMR δ 172.8, 137.4, 128.8, 128.3, 128.0, 112.1, 105.5, 82.3, 81.8, 78.3, 72.1, 62.6, 57.3, 39.2, 34.1, 32.4, 29.9, 27.0, 26.5, 22.3, 14.1.