ORGANIC LETTERS

2005
Vol. 7, No. 4
745−748

De Novo Enantioselective Syntheses of *Galacto*-Sugars and Deoxy Sugars via the Iterative Dihydroxylation of Dienoate

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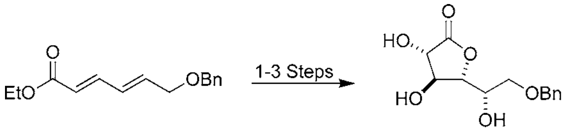
Received January 10, 2005

ABSTRACT



D-, L-, or *rac*-*galacto*-1,4-lactone

An efficient route to various sugar lactones has been developed. Key to the overall transformation is the sequential osmium-catalyzed dihydroxylation of 2,4-dienoates. The simplest (one-step/racemic) example of this reaction occurs when the dihydroxylation is performed with aqueous NMO in MeOH. When the first dihydroxylation is performed using the AD-mix procedure, an enantioselective variant results. When a matched AD-mix procedure is used for the second dihydroxylation, an exceedingly diastereo- and enantioselective synthesis of *galacto*-1,4-lactone results.

There has been a tremendous growth in our understanding of the important role carbohydrates play in biology.[1] While this new understanding certainly has and will continue to have a great impact on medicine, unfortunately this effect is limited by the medicinal chemist's inability to prepare unnatural sugar analogues and hence to do thorough structure activity relationship studies. This need is exemplified by the fact that of the 16 possible stereoisomers of the hexoses, only three are readily available from natural sources (D-glucose, D-mannose, and D-galactose).

Since the seminal work of Sharpless and Masamune,[2] the de novo enantioselective synthesis of the hexoses stands as a challenge to asymmetric catalysis.[3] Recently, McMillan reported a short iterative aldol strategy toward this goal.[4] Despite substantial efforts over the years,[3,5] there still does not exist a general and truly practical route to all the hexoses. As part of our program aimed at the use of catalysis for the synthesis of natural[6] and unnatural carbohydrates[7] and oligosaccharides,[8] we were interested in finding a highly diastereo- and enantioselective synthesis of a simple hexose, which could serve as a useful starting material for oligosaccharide assembly. Herein, we present our discovery of an expeditious route to either enantiomer of *galacto*-1,4-lactone using the Sharpless dihydroxylation for enantiocontrol. These studies resulted in a three-step synthesis of enantiopure *galacto*-1,4-lactone, a one-step variant to racemic material, as well as a five-step synthesis of *C*-4 deoxy sugars. All routes are amenable to various *C*-6 substituents.

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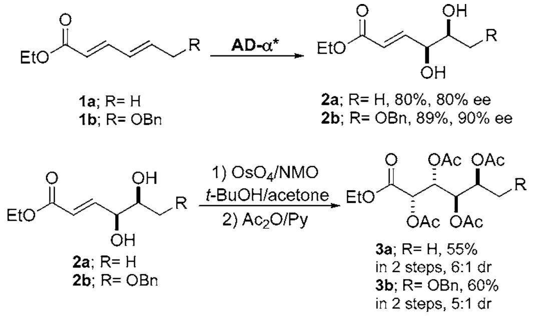
10.1021/ol050044i CCC: $30.25

We have targeted *galacto*-1,4-lactones **4a**/**b**[9,10] or the more easily isolated peracetates **5a**/**b** because they lacked an anomeric stereocenter and are common starting material in carbohydrate synthesis.[11,12] The ideal synthesis should also start from a commercially available starting material, and as such, we chose 2,4-dienoate esters, which are easily prepared[13] or commercially available. Thus our strategy, outlined below, is an iterative and highly stereocontrolled oxidation of both double bonds in dienoates **1a**/**b** to establish all four stereocenters in *galacto*-lactone (Scheme 1).

Scheme 1. Two-Step Enantioselective Synthesis of Ethyl Galactonate Sugars



AD-α* = 2% OsO$_4$, 2.1% (DHQ)$_2$PHAL, 3 eq K$_3$Fe(CN)$_6$, 3 eq K$_2$CO$_3$, 1eq MeSO$_2$NH$_2$ in 1:1 *t*-BuOH/H$_2$O.

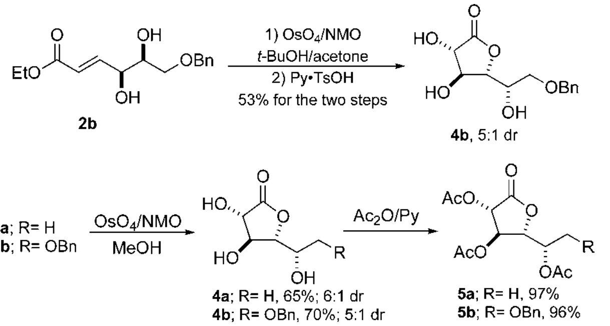
While conceptually a bis-dihydroxylation reaction appears ideal for an efficient carbohydrate synthesis, there were issues associated with regioselectivity (which double bond reacts first), enantioselectivity (the facial selectivity of the first dihydroxylation), and double diastereoselectivity (a balance between substrate and catalyst stereocontrol).[14,15] The solution to these problems emerged from our continuing study of the Sharpless dihydroxylation of di- and tri-enoates,[16] which we have used in natural product synthesis.[17]

To accomplish this goal we chose to start with dienoates **1a**/**b** (Scheme 1). Previously, Sharpless had demonstrated that the initial dihydroxylation could be controlled in terms of regio- and enantioselectivity (e.g. ethyl sorbate **1a** reacted with the AD-mix reagent to afford diol **2a** with good enantioselectivity).[18,19] Similarly, we found that dienoates **1a**/**b** reacted under the typical Sharpless AD-mix procedure (2% OsO$_4$/2.1% (DHQ)$_2$PHAL, 3 equiv of K$_3$Fe(CN)$_6$/K$_2$CO$_3$, 1 equiv of MeSO$_2$NH$_2$) to give diols **2a**/**b** in good yields (80% and 89%) and enantiomeric excess (80% ee and 90% ee).[20] While the double bond selectivity can easily be explained in terms of electron density of the π-system (i.e., the most electron-rich double bond reacts first), there is an underlying stereocontrol element to this reaction. The second double bond does not react under the reaction conditions because of conflicting diastereo-controlling issues (mismatching reagent and substrate control).

This substrate/reagent mismatch effect can be seen in the case when the ligand ((DHQ)$_2$PHAL) was removed from the AD-mix reaction condition (Scheme 1). Thus, when diols **2a**/**b** were exposed to the typical Upjohn procedure (OsO$_4$/NMO in *t*-BuOH/acetone), they reacted with achiral OsO$_4$ to afford tetrol products with good conversion, which could be isolated as their corresponding tetraacetates **3a**/**b** (55% for **3a**; 60% for **3b**). While these tetrol and tetraacetate products were difficult to isolate, it was determined that they were formed in about a 5:1 ratio of stereoisomers (*galacto* to *ido*).

We found it easier to isolate the dihydroxylation product as a lactone **4b** (Scheme 2). This less polar triol **4b** was formed by acid-catalyzed lactonization (Py·TsOH in MeOH/benzene) and isolated in a 53% yield. In general, we found that the triacetates **5a**/**b** had clearer ^{1}H NMR spectra, which facilitated spectroscopic comparison to known materials.[9] Thus, the *galacto*-triacetates **5a** and **5b** were prepared in 97% and 96% yields, respectively.

Scheme 2. Two-Step Enantioselective Synthesis of *galacto*-γ-Lactone



An improved and simplified procedure resulted from performing the second dihydroxylation reactions (OsO$_4$/NMO) in MeOH (**2a**/**b** to **4a**/**b**, Scheme 2), which—due to the basic reaction conditions—provides the lactones **4a**/**b** in one step (65% for **4a**; 70% for **4b**). Despite the solvent change, the diastereoselectivity for these dihydroxylations was found to be the same as before (6:1 for **4a** and 5:1 for

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[9] Although it is a rare sugar, L-*galacto*-1,4-lactone is a naturally occurring metabolite produced in plants as an intermediate in the biosynthesis of vitamin C, see: Smirnoff, N. *Nat. Biotechnol.* **2003**, *21*, 134−136.

[10] It has been suggested that the level of the important antioxidant ascorbic acid can be increased by treatment with L-*galacto*-1,4-lactone, see: Smirnoff, N. *Philos. Trans. R. Soc. London* **2001**, *335*, 1455−1464.

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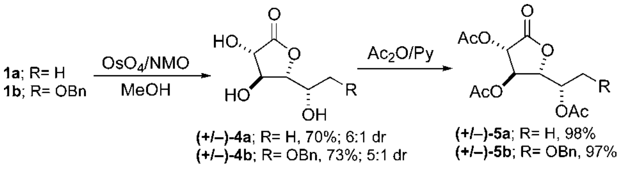
[19] Becker, H.; Soler, M. A.; Sharpless, K. B. *Tetrahedron* **1995**, *51*, 1345−1376.

[20] All enantioexcesses were determined by examining the ^{1}H NMR and/or ^{19}F NMR of a corresponding Mosher ester, see: Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143−2147.

4b). In the case of **5a**, the minor diastereomer was removed by silica gel chromatography, whereas for **5b** the minor isomer was removed by a selective crystallization of the major isomer from EtOAc/hexanes.

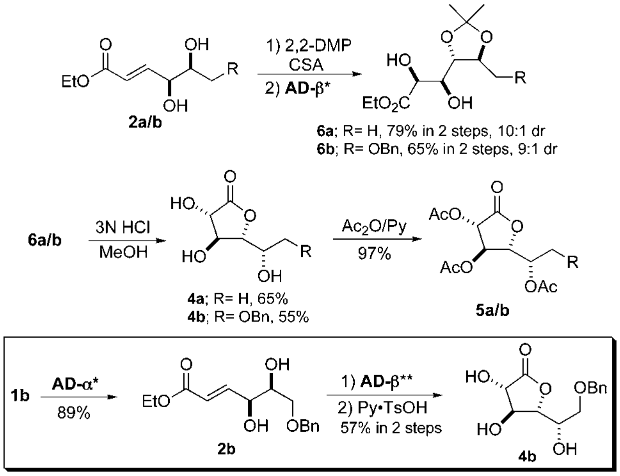
A highly efficient one-step protocol for the synthesis of racemic *galacto*-γ-lactone (±)-**4a**/**b** was easily achieved by subjecting the dienoates **1a**/**b** to the dihydroxylation/lactonization procedure (OsO_4/NMO in MeOH) (Scheme 3). Thus, exposing dienoates **1a**/**b** to a catalytic amount of OsO_4 with excess NMO in methanol provided racemic *galacto*-γ-lactone (±)-**4a**/**b** in 70% and 73% yields, respectively. The lactones (±)-**4a**/**b** were converted to the peracetates (±)-**5a**/**b** and shown to be identical with the previously prepared material in all ways except optical rotation. Evidence that the initial dihydroxylations occurred to give diols **2a**/**b** before subsequent dihydroxylation/lactonization was suggested by the identical diastereoselectivities for this one-step procedure as for the two-step procedure (Scheme 2).

Scheme 3. One-Step Racemic Synthesis of *galacto*-γ-Lactone



While these procedures (Schemes 2 and 3) are highly efficient in terms of yields and steps, they do suffer a drawback associated with less than perfect diastereocontrol. This issue of diastereoselectivity was easily resolved when the second dihydroxylation was performed in a diastereomerically matched sense between substrate and catalyst (Scheme 4). For isolation purposes, this was first carried out on an acetonide protected form of diols **2a**/**b**, which were dihydroxylated with the pseudo-enantiomeric reagent **AD-*β***** (2% OsO_4/2.1% $(DHQD)_2$PHAL, 3 equiv of $K_3Fe(CN)_6$, 3 equiv of K_2CO_3, and 1 equiv of $MeSO_2NH_2$) to give good yields of diols **6a**/**b** (79% for **6a** and 65% for **6b**) with improved diastereocontrol (dr = 10:1/9:1), once again with the *galacto*-stereoisomer prevailing. For both **6a** and **6b**, the minor isomers were easily removed by silica gel chromatography and the diasteromerically pure products **6a**/**b** were deprotected and lactonized to give **4a**/**b** (65% for **4a** and 55% for **4b**). As before, the triols **4a**/**b** were peracylated and the triacetates formed proved to be identical with the previously prepared **5a**/**b**. Because the enantiomeric impurity in **2a**/**b** is converted into the minor diastereomer during the second asymmetric dihydroxylation, the *galacto*-lactones **4a**/**b** formed by this procedure are essentially enantiomerically pure.

Scheme 4. Three- or Four-Step Highly Enantio- and Diastereoselective Synthesis of *galacto*-γ-Lactone



AD-α* = 2% OsO_4, 2.1% $(DHQ)_2$PHAL, 3 eq $K_3Fe(CN)_6$, 3 eq K_2CO_3, 1eq $MeSO_2NH_2$ in 1:1 *t*-BuOH/H_2O; **AD-β*** = 2% OsO_4, 2.1% $(DHQD)_2$PHAL, 3 eq $K_3Fe(CN)_6$, 3 eq K_2CO_3, 1eq $MeSO_2NH_2$ in 1:1 *t*-BuOH/H_2O; **AD-β**** = 10% OsO_4, 12% $(DHQD)_2$PHAL, 6 eq $K_3Fe(CN)_6$, 3 eq K_2CO_3, 3 eq $NaHCO_3$, 1eq $MeSO_2NH_2$ in 2:1 *t*-BuOH/H_2O

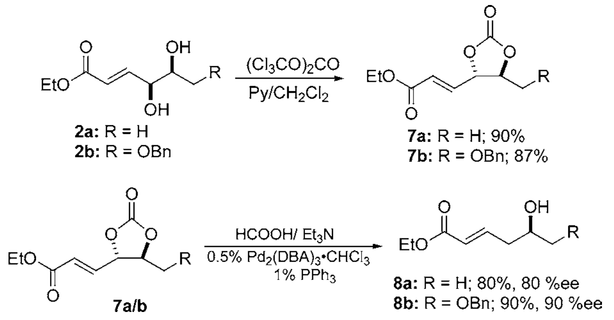
Our fully optimized procedure allows for a three-step conversion of achiral **1b** to optically pure **4b** (Scheme 4). The need for the inclusion of a protection step was finally eliminated when we realized that there was a competing hydrolysis reaction occurring during the dihydroxylation of **2b**, thus reducing the yield of **4b**. This competing reaction was easily overcome by simply increasing the catalyst loading from 2% OsO_4 to 10% OsO_4 and the ligand from 2.1% to 12%. Thus, exposing **2b** to the pseudo-enantiomeric reagent **AD-*β***** (10% OsO_4/12% $(DHQD)_2$PHAL, 6 equiv of $K_3Fe(CN)_6$, 3 equiv of $NaHCO_3$, 3 equiv of K_2CO_3, and 1 equiv of $MeSO_2NH_2$) provides, after lactonization with Py·TsOH, the *galacto*-γ-lactone **4b** in good yield (57%). The triol **4b** formed by this latter procedure was, for all practical purposes, both enantiomerically and diasteromerically pure (>96% ee and de).

Due to the fact that the substrate **2b** and the catalyst (OsO_4/$(DHQD)_2$PHAL) were synergistically directing the stereochemical course of the reaction, once again the product enantiopurity (>96% ee) was even greater than that of the original starting material (90% ee). This presumably resulted from the fact that the minor enantiomer (*ent*-**2b**) did not react with the mismatched OsO_4/$(DHQD)_2$PHAL catalyst system. Finally, this procedure also produced the enantiomer of **4b** (D-*galacto*-γ-lactone) equally well, by simply using the AD-mix reagent systems in reverse. That is to say, using OsO_4/$(DHQD)_2$PHAL for the conversion of **1b** to *ent*-**2b** and then OsO_4/$(DHQ)_2$PHAL for the conversion of *ent*-**2b** to *ent*-**4b**. Thus, our final optimized procedure also produced *ent*-**4b** in good yield (63% from *ent*-**2b**) and with virtually complete stereocontrol (>96% ee and de).

Further insights into the origins of the substrate stereocontrol in the dihydroxylation of diols **2a**/**b** were gained from the application of this methodology for the preparation of *C*-4 deoxy-sugar lactones (Schemes 6 and 7). In particular, we found that the substrate control essentially disappeared when the *C*-4 hydroxy group is removed as in the δ-hydroxyenoate **8a**/**b**.

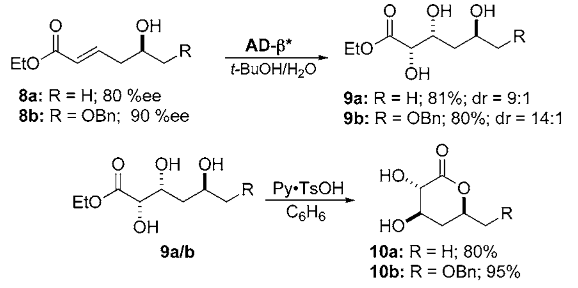
The enoates **8a**/**b** were easily prepared from cyclic carbonate **7a**/**b** by a Pd-catalyzed π-allyl reduction reaction with formic acid (hydride source). Exposure of diols **2a**/**b** to triphosgene ($(Cl_3CO)_2CO/Py$) gave good yields (~90%) of carbonates **7a**/**b**. Treatment of **7a**/**b** with a catalytic amount of palladium(0) source and triphenylphosphine (1 mol % of $Pd(0)/PPh_3$) and a mild hydride source (3 equiv of Et_3N/HCO_2H) gave the reduced alcohol **8a**/**b** in good yields (80 to 90%) and with no loss of enantiomeric excess.[21]

Scheme 5. Palladium-Catalyzed Reduction at *C*-4



The alcohols **8a**/**b** were subjected to Sharpless asymmetric dihydroxylation conditions (2% OsO_4 and 4% $(DHQD)_2$-PHAL) and gave triols **9a**/**b** in approximately 80% yield and >96% ee. The strong substrate diastereocontrol associated with the second dihydroxylation reaction is diminished with the removal of the *C*-4 hydroxyl group.[22] Thus, triols **9a**/**b** were formed with a minor diastereomer (*ent*-**11a**/**b**), where the formation of *ent*-**11a**/**b** comes primarily from the minor enantiomer present in **8a**/**b** (*ent*-**8a**/**b**). Once this minor diastereomer was removed by silica gel chromatography, triols **9a**/**b** were obtained in both diastereo- and enantiomerically pure form. As before, the stereochemistry of the triols was most easily assigned after lactonization (**9a**/**b** to **10a**/**b**). Treating triols **9a**/**b** with 5% Py·TsOH/C_6H_6 provided the desired deoxy-*gluco*-pyranones **10a**/**b** in excellent yields (80 to 95% yield) (Scheme 6).

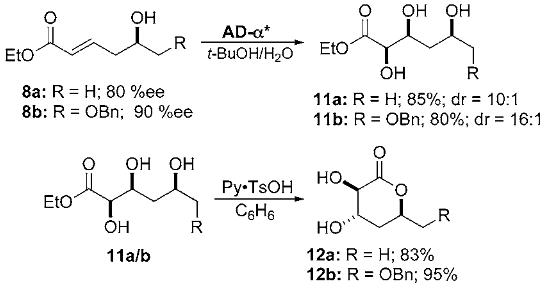
Scheme 6. Enantioselective Synthesis of L-4-Deoxy-*gluco*-δ-lactone



AD-β* = 2% OsO_4, 4% $(DHQD)_2PHAL$, 3 eq $K_3Fe(CN)_6$, 3 eq K_2CO_3, 1 eq $MeSO_2NH_2$

This same procedure (Scheme 6) can be used for the formation of **12a**/**b** (the *C*-2/*C*-3 bis-epimer of **10a**/**b**, Scheme 7), because **8a**/**b** has no strong facial bias.[22] Thus, exposing alcohols **8a**/**b** to the pseudo-enantiomeric Sharpless reagent system (2% OsO_4 and 4% $(DHQ)_2PHAL$) provided triols **11a**/**b** in similarly excellent yields, diastereomeric ratios,[23] and enantiomeric excesses (>96% ee). Finally, triols **11a**/**b** were lactonized by treatment with 5% Py·TsOH/C_6H_6. The desired lactones **12a**/**b** were isolated in excellent yields (83−95%). As with 4-deoxy-*gluco*-lactone **10a**/**b**, the 4-deoxy-*altro*-pyranone stereochemistry of **12a**/**b** was easily assigned from analysis of the relevant $^1H-^1H$ coupling constants.

Scheme 7. Enantioselective Synthesis of L-4-Deoxy-*altro*-δ-lactone



AD-α* = 2% OsO_4, 4% $(DHQ)_2PHAL$, 3 eq $K_3Fe(CN)_6$, 3 eq K_2CO_3, 1 eq $MeSO_2NH_2$

In summary, our strategy for the synthesis of either enantiomer of *galacto*-sugars provides rapid and practical access to an important sugar, which should be of use for further oligosaccharide synthesis. Thus in only one step, racemic **4a**/**b** was produced in excellent yield from achiral **1a**/**b**. Similarly, optically pure **4a** was prepared in four steps from **1a** (41%, overall yield) and optically pure **4b** was prepared in three steps from **1b** (51%, overall yield). In addition, a highly enantio- and diastereoselective procedure for the preparation of various sugar δ-lactones has been developed resulting in the syntheses of *C*-4 deoxysugars. Finally, by selecting the order in which the Sharpless reagents were used, both D- and L-sugars were produced. This second reagent choice in the *C*-4 deoxy series also determines which sugar diastereomer is formed (*gluco* vs *altro*). This approach serves as an excellent complement to the recently reported enantioselective aldol approach to hexoses,[4] because it provides a related and important stereoisomer.

Acknowledgment. We are grateful to NIH (GM63150) and NSF (CHE-0415469) for the support of our research program and NSF-EPSCoR (0314742) for a 600 MHz NMR at WVU.

Supporting Information Available: Complete experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[21] Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 1049−1052.

[22] This decrease in substrate control can be seen in that when **8a**/**b** were exposed to the achiral UpJohn conditions approximately 1:1 mixtures of **9a**/**b** to **11a**/**b** were formed.

[23] It is worth noting that because $(DHQ)_2PHAL$ is a diastereomer of $(DHQD)_2PHAL$ and not an enantiomer, the diastereomeric ratios for the conversion of **8a**/**b** to **9a**/**b** should be slightly different than the ratio for the conversion of **8a**/**b** to **11a**/**b**.