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De novo synthesis of *galacto*-sugar δ-lactones via a catalytic osmium/palladium/osmium reaction sequence

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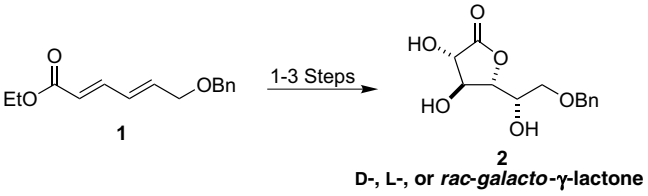
Abstract—A highly efficient route to various 1,5-*galacto*-sugar lactones from dienoates has been developed by using three catalytic reactions. These reactions include (i) an enantioselective osmium-catalyzed dihydroxylation, (ii) a regio- and diastereoselective palladium-catalyzed π-allyl alkylation with *p*-methoxyphenol for alcohol differentiation and protection, and (iii) a diastereoselective dihydroxylation that can be improved using matched enantioselective osmium-catalyzed dihydroxylation condition.

1. Introduction

The de novo enantioselective synthesis of carbohydrates and their analogous stands as a challenge to asymmetric synthesis,[2–5] as these compounds are integral components of many important pharmaceuticals and biomolecules.[1] Most existing syntheses are based on chemical manipulation of naturally occurring sugars, where most, if not all, of the stereocenters in the products are derived directly from the starting material. Despite some notable efforts by many, there still does not exist a practical route to all the hexoses.[2,3]

Recently we reported an expedient and practical synthesis of *galacto*-sugars from simple achiral precursors with complete stereocontrol.[4,5] This powerful new approach is based on the tandem use of the osmium-catalyzed Sharpless asymmetric dihydroxylation (AD) reaction (Scheme 1).[4] Herein we report our discovery of a practical and highly stereocontrolled synthesis of various *C*-4 protected *galacto*-sugar δ-lactones via the use of a catalytic Os/Pd/Os reaction sequence. A limitation to the above approach (Scheme 1) is the limit to five membered *galacto*-lactones. This problem was resolved when the *C*-4 hydroxyl group was removed, in which a Pd-π-allyl-catalyzed reduction was added to the sequence and resulted in a 5-step synthesis of either *altro*- or *gluco*-*C*-4 deoxy sugar lactones **3** and **4** (Scheme 2).[4]

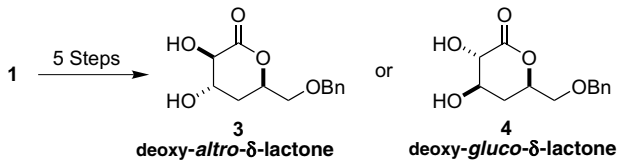


Scheme 1. Synthesis (1- to 3-step) of *galacto*-γ-sugar lactone.

In order to prevent five membered ring lactonization, a selective protection of the *C*-4 hydroxyl group was required. We were intrigued by the possibility of accomplishing this alcohol differentiation by means of the same Pd-π-allyl intermediate that was used for the deoxy-sugar synthesis (Scheme 2).

While many oxygen nucleophiles were investigated, only phenols gave good yields, reacting with excellent regio- and stereocontrol.[6] Because of its ability for oxidative removal, we pursued our synthetic investigations with *p*-methoxyphenol (vide infra).

As in our previous syntheses the diols **5a**–**c** can be easily synthesized from dienoate **1a/b** or from the commercially available ethyl sorbate **1c** in good yields and enantiomeric



Scheme 2. Synthesis (5-step) of *C*-4 deoxy-δ-sugar lactone.

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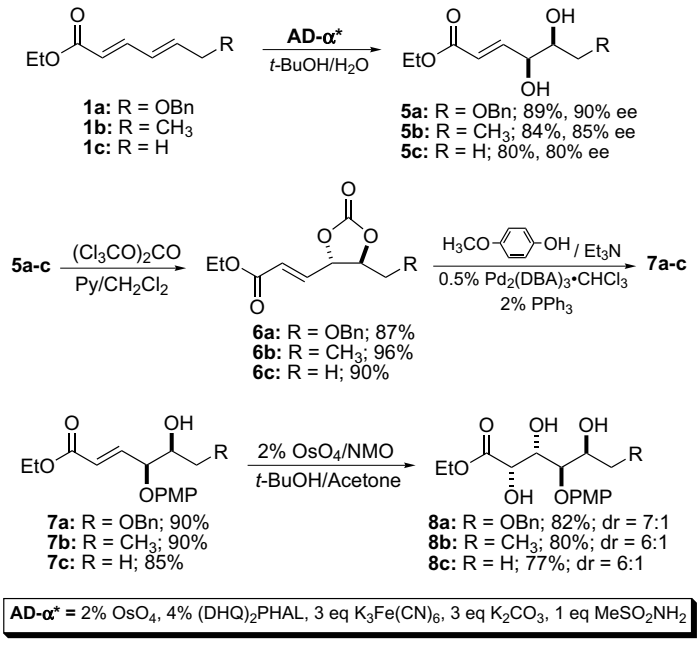


Scheme 3. Palladium-catalyzed hydroxyl protection at *C*-4.

excess (80–90% ee) (Scheme 3). The diol **5a** was converted into cyclic carbonate **6a** (87% yield). Treatment of **6a** with a catalytic amount of palladium(0) (1 mol% Pd(0)/2 mol% PPh_3) and *p*-methoxyphenol as the nucleophile provided the protected alcohol **7a** in 90% yield, with no loss of enantiomeric excess.[7] Finally the *C*-2/*C*-3 hydroxyl groups were installed, with *galacto*-stereochemistry, by means of a diastereoselective dihydroxylation of **7a**. Thus, exposure of **7a** to the Upjohn conditions (OsO_4/NMO) provided **8a** in a 7:1 diastereomeric ratio. Similar yields and selectivities were observed for the conversion of dienoates **1b/c** to *galacto*-triols **8b/c** (58% and 47% overall yield of **8b** and **8c**, respectively; Scheme 3). In all three cases (**8a–c**) the minor diastereomer was easily removed by silica gel chromatography.

While the triols **8a–c** were easily obtained in diastereomerically pure form, we were interested in improving both the diastereo- and enantiopurity of these triols. Thus we investigated the use of the Sharpless reagent for the second dihydroxylation (**7** to **8**).[8] In this improved procedure the triols **8a–c** were isolated to all practical purposes in both enantiomerically and diastereomerically pure form. When the alcohols **7a–c** were subjected to Sharpless asymmetric dihydroxylation reactions using the matched reagent system (2% OsO_4 and 4% $(DHQD)_2$ PHAL) triols **8a–c** were afforded as a single diastereomer and enantiomer.[9,10] Triol **8a** was isolated in 86% yield (>96% ee), triol **8b** was isolated in 85% yield (>96% ee) and triol **8c** was isolated in 83% yield (>96% ee). The pseudo-enantiomeric catalyst system (2% OsO_4/4% $(DHQ)_2$PHAL) reacted with the enantiomers of **7a–c** (*ent*-**7a–c**) to give *ent*-**8a–c** in similar yields and stereoselectivities (Scheme 4).

This improvement of enantiopurity results from the fact that both the substrates **7a–c** and the catalyst (OsO_4/$(DHQD)_2$PHAL) direct the stereochemical course of the reaction in concert (matched case); therefore, the product enantiopurity is even greater than the original starting material enantiopurity.[8,10,11] This presumably results from the fact that the minor enantiomers (*ent*-**7a–c**) do not react with the mismatched OsO_4/$(DHQD)_2$PHAL catalyst system.

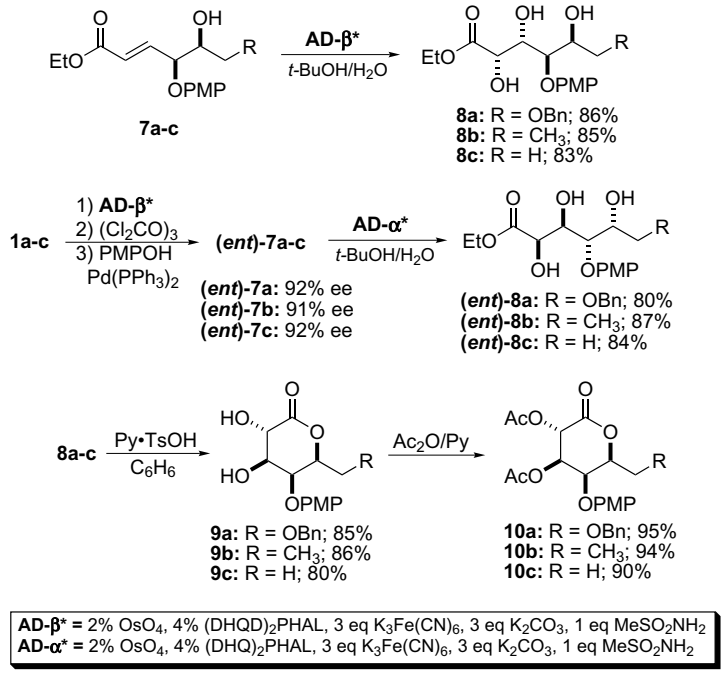
With the *C*-4 position differentiated, the triols **8a–c** could easily be lactonized giving the δ-lactones **9a–c** (Scheme 4). When triols **8a–c** were treated with 5% Py·TsOH/C_6H_6, the desired lactonization readily occurred providing the *galacto*-pyranones **9a–c** in 80–86% yield.[12] At this stage the relative stereochemistry could be assigned by analysis of ^1H–^1H-coupling constants.[13] This was easily accomplished on the diacetates **10a–c**, which were readily prepared using Ac_2O/Py in 90–95% yield (Scheme 4).[14]

In summary, a highly enantio- and diastereoselective procedure for the preparation of various *galacto*-sugar δ-lactones has been developed. Critical to the success of this approach was the unique use of a regio- and stereospecific Pd-π-allyl reaction for alcohol differentiation and protection. Finally, by selecting the order in which the Sharpless reagents were used, both D- and L-sugars were produced. Further investigation for the development of this methodology for the synthesis of biologically important carbohydrates is ongoing.

2. Experimental section

2.1. (*E*)-Ethyl 3-((4*S*,5*S*)-5-((benzyloxy)methyl)-2-oxo-1,3-dioxolan-4-yl)acrylate (6a)

Into a 250 mL round-bottomed flask was placed 6.5 g (23.2 mmol) of (*E*,4*S*,5*S*)-ethyl 6-(benzyloxy)-4,5-dihydroxyhex-2-enoate **5a** in 25 mL of dichloromethane



Scheme 4. Enantioselective synthesis of L-*galacto*-δ-lactone.

and 10 mL (116 mmol) of pyridine. The solution was cooled to 0 °C and 7.6 g (25.6 mmol) of triphosgene in 50 mL of dichloromethane was added slowly with an addition funnel. The reaction was stirred for 1.5 h and quenched with saturated aqueous NH_4Cl (40 mL). The layers were separated and the aqueous layer was extracted with ether (3×50 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate (30 mL), brine (25 mL), and dried over anhydrous sodium sulfate. After removal of the solvents in vacuo, flash chromatography on silica gel (7:3 (v/v) hexanes/EtOAc) afforded (*E*)-ethyl 3-((4*S*,5*S*)-5-((benzyloxy)methyl)-2-oxo-1,3-dioxolan-4-yl)acrylate **6a** as a clear, colorless oil (6.17 g, 87%): R_f (30% EtOAc/hexanes) = 0.37; $[\alpha]_D^{25}$ −54.7 (*c* 1.03, CH_2Cl_2); IR (thin film, cm^{-1}) 2983, 2938, 2908, 2872, 1806, 1721, 1665, 1496, 1454, 1369, 1304, 1272, 1174, 1111, 1032, 978 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.34 (m, 5H), 6.83 (dd, $J = 15.6$, 5.4 Hz, 1H), 6.14 (dd, $J = 15.6$, 1.4 Hz, 1H), 5.17 (ddd, $J = 6.6$, 5.4, 1.2 Hz, 1H), 4.64 (d, $J = 12$ Hz, 1H), 4.58 (d, $J = 12$ Hz, 1H), 4.46 (ddd, $J = 6.6$, 3.6, 3.6 Hz, 1H), 4.24 (q, $J = 7.2$ Hz, 2H), 3.75 (dd, $J = 11.4$, 3.6 Hz, 1H), 3.66 (dd, $J = 11.4$, 3.6 Hz, 1H), 1.30 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 164.9, 153.5, 139.7, 136.7, 128.5 (2C), 128.1, 127.7 (2C), 124.5, 79.3, 76.4, 73.7, 67.7, 61.0, 14.1; CIHRMS: Calcd for $[C_{16}H_{18}O_6+Na]^+$: 329.1001. Found: 329.1003.

2.2. (*E*,4*S*,5*S*)-Ethyl 4-(4-methoxyphenoxy)-6-(benzyloxy)-5-hydroxyhex-2-enoate (7a)

Into a 100 mL, round bottomed flask fitted with a condenser and maintained under nitrogen was placed 3 g (9.8 mmol) of (*E*)-ethyl 3-((4*S*,5*S*)-5-((benzyloxy)methyl)-2-oxo-1,3-dioxolan-4-yl)acrylate **6a**, 50.7 mg (0.49 mmol, 0.5 mol%) of $Pd_2(DBA)_3{\cdot}CHCl_3$, 51 mg (0.19 mmol, 2 mol%) of PPh_3, and 30 mL of CH_2Cl_2. Triethylamine 1.3 mL, (9.8 mmol) and *p*-methoxy phenol 2.43 g (19.6 mmol) were added and the mixture was allowed to reflux for 30 min. The reaction was cooled to room temperature and quenched with saturated aqueous sodium bicarbonate (20 mL). The aqueous layer was extracted with ether (3×30 mL). The organic layer was washed with brine (20 mL) and dried with anhydrous sodium sulfate. After removal of the solvents in vacuo, flash chromatography on silica gel (7:3 (v/v) hexanes/EtOAc) afforded (*E*,4*S*,5*S*)-ethyl 4-(4-methoxyphenoxy)-6-(benzyloxy)-5-hydroxyhex-2-enoate **7a** as a yellow oil (3.4 g, 90%): Mosher ester analysis of this alcohol shows 90% ee; R_f (30% EtOAc/hexanes) = 0.32; $[\alpha]_D^{25}$ 22.5 (*c* 1.1, CH_2Cl_2); IR (thin film, cm^{-1}) 3484, 2980, 2954, 2923, 2869, 1716, 1660, 1506, 1454, 1368, 1303, 1276, 1227, 1180, 1109, 1036, 983; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.33 (m, 5H), 6.98 (dd, $J = 15.6$, 5.4 Hz, 1H), 6.81 (m, 4H), 6.07 (dd, $J = 15.6$, 1.8 Hz, 1H), 4.86 (ddd, $J = 5.4$, 4.8, 1.8 Hz, 1H), 4.56 (d, $J = 12$ Hz, 1H), 4.53 (d, $J = 12$ Hz, 1H), 4.18 (q, $J = 7.8$ Hz, 1H), 4.16 (q, $J = 7.8$ Hz, 1H), 4.01 (ddd, $J = 10.2$, 6, 5.4 Hz, 1H), 3.76 (s, 3H), 3.68 (dd, $J = 9.6$, 4.8 Hz, 1H), 3.60 (dd, $J = 9.6$, 5.4 Hz, 1H), 2.58 (d, $J = 5.4$ Hz, 1H), 1.27 (t, $J = 7.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 165.7, 154.5, 151.6, 143.5, 137.6, 128.4 (2C), 127.8 (3C), 123.8, 117.0 (2C), 114.6 (2C), 78.4, 73.6, 72.3, 69.9, 60.6, 55.6, 14.1; CIHRMS: Calcd for $[C_{22}H_{26}O_6+Na]^+$: 409.1627. Found: 409.1621.

2.3. (2*S*,3*S*,4*R*,5*S*)-Ethyl 4-(4-methoxyphenoxy)-6-(benzyloxy)-2,3,5-trihydroxyhexanoate (8a)

Into a 50 mL round bottom flask was added 10 mL of *t*-BuOH, 10 mL of water, $K_3Fe(CN)_6$ (4.93 g, 15 mmol), K_2CO_3 (2.07 g, 15 mmol), $MeSO_2NH_2$ (475 mg, 5 mmol), $(DHQD)_2PHAL$ (155 mg, 0.2 mmol,

4 mol%), and OsO_4 (25 mg, 0.1 mmol, 2 mol%). The mixture was stirred at room temperature for about 15 min and then cooled to 0 °C. To this solution was added (*E*,4*S*,5*S*)-ethyl 4-(4-methoxyphenoxy)-6-(benzyloxy)-5-hydroxyhex-2-enoate **7a** (2.00 g, 5 mmol) in 4 mL CH_2Cl_2 and the reaction was stirred vigorously at 0 °C overnight. The reaction was quenched with solid sodium sulfite (100 mg) at room temperature and stirred for 15 min. Then the mixture was filtered through a pad of Celite/Florisil and eluted with 50 mL 50% Ethyl acetate/MeOH. The combined organic layers were dried over anhydrous sodium sulfate. After removal of the solvents in vacuo, flash chromatography on silica gel (6:4 (v/v) hexanes/EtOAc) afforded 1.8 g (86% yield) of (2*S*,3*S*,4*R*,5*S*)-ethyl 4-(4-methoxyphenoxy)-6-(benzyloxy)-2,3,5-trihydroxyhexanoate **8a** as a viscous oil: R_f (90% EtOAc/hexanes) = 0.43; $[\alpha]_D^{25}$ 5.4 (*c* 1.0, CH_2Cl_2); IR (thin film, cm^{-1}) 3533, 2983, 2957, 2869, 1747, 1653, 1593, 1506, 1466, 1455, 1372, 1296, 1220, 1184, 1044 ; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.28 (m, 5H), 6.98 (m, 2H), 6.80 (m, 2H), 4.49 (dd, J = 9, 1.8 Hz, 1H), 4.46 (d, J = 11.4 Hz, 1H), 4.43 (d, J = 11.4 Hz, 1H), 4.35–4.29 (m, 3H), 3.76 (s, 3H), 4.28 (q, J = 7.2 Hz, 1H), 4.26 (q, J = 7.2 Hz, 1H), 3.67 (dd, J = 9.6, 6 Hz, 1H), 3.55 (dd, J = 9.6, 6 Hz, 1H), 3.18 (d, J = 5.4 Hz, 1H), 2.89 (d, J = 8.4 Hz, 1H), 2.62 (d, J = 7.8 Hz, 1H), 1.29 (t, J = 7.2 Hz, 3H) ; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 173.4, 154.4, 152.4, 137.5, 128.4 (2C), 127.8 (3C), 117.1 (2C), 114.7 (2C), 76.6, 73.4, 71.1, 70.6, 70.1, 69.3, 62.1, 55.6, 14.1; CIHRMS: Calcd for $[C_{22}H_{28}O_8+Na]^+$: 443.1682. Found: 443.1668.

2.4. (3*S*,4*S*,5*S*,6*S*)-5-(4-Methoxyphenoxy)-6-((benzyloxy)methyl)-tetrahydro-3,4-dihydroxypyran-2-one (9a)

To a solution of (2*S*,3*S*,4*R*,5*S*)-ethyl 4-(4-methoxyphenoxy)-6-(benzyloxy)-2,3,5-trihydroxyhexanoate **8a** (200 mg, 0.48 mmol) in benzene (3 mL), was added Py·TsOH (6 mg, 0.03 mmol, 5 mol%) and the mixture was allowed to reflux for 5 h. The reaction was cooled to room temperature and quenched with saturated aqueous sodium bicarbonate (2 mL). The aqueous layer was extracted with ether (3 × 10 mL). The organic layer was washed with brine (10 mL) and dried with anhydrous sodium sulfate. After removal of the solvents in vacuo, flash chromatography on silica gel (4:6 (v/v) hexanes/EtOAc) afforded (3*S*,4*S*,5*S*,6*S*)-5-(4-methoxyphenoxy)-6-((benzyloxy)methyl)-tetrahydro-3,4-dihydroxypyran-2-one **9a** as a viscous oil (160 mg, 85%): R_f (90% EtOAc/ hexanes) = 0.40; $[\alpha]_D^{25}$ −26.8 (*c* 2, CH_2Cl_2); IR (thin film, cm^{-1}) 3396, 2929, 2922, 1740, 1506, 1455, 1368, 1328, 1220, 1103, 1034, 923, 830; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.26 (m, 3H), 7.03 (m, 4H), 6.78 (m, 2H), 4.8 (dd, J = 2.4, 1.8 Hz, 1H), 4.59 (d, J = 10.2 Hz, 1H), 4.54 (ddd, J = 7.2, 6.6, 1.8 Hz, 1H), 4.36 (d, J = 11.4 Hz, 1H), 4.28 (d, J = 11.4 Hz, 1H), 4.17 (ddd, J = 10.2, 1.8, 1.2 Hz, 1H), 3.81 (br s, 1H), 3.74 (s, 3H), 3.72 (d, J = 6.6 Hz, 2H), 3.21 (br s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 172.1, 154.8, 153.5, 137.0, 128.4 (2C), 127.9 (2C), 127.8, 117.7 (2C), 114.6 (2C), 78.2, 76.7, 73.5, 71.8, 70.4, 67.0, 55.7; CIHRMS: Calcd for $[C_{20}H_{22}O_7+Na]^+$: 397.1257. Found: 397.1285.

2.5. (3*S*,4*R*,5*R*,6*S*)-5-(4-Methoxyphenoxy)-6-((benzyloxy)methyl)-tetrahydro-3,4-diacetoxypyran-2-one (10a)

To a solution of (3*S*,4*S*,5*S*,6*S*)-5-(4-methoxyphenoxy)-6-((benzyloxy)methyl)-tetrahydro-3,4-dihydroxypyran-2-one **9a** (150 mg, 0.4 mmol) in CH_2Cl_2 (2 mL) was added excess Ac_2O (0.6 mL, 2 mmol), pyridine (0.3 mL, 4 mmol) and a catalytic amount of DMAP (2.5 mg, 5 mol%). The reaction was stirred for an hour, after which 10 mL ether and 10 mL of NH_4Cl was added to remove excess base. The organic layer was washed with 10 mL $CuSO_4$ solution, 10 mL brine and the aqueous layer was further extracted with ether (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuo. The crude product was purified by flash chromatography on silica gel (4:1 (v/v) hexanes/EtOAc) to yield (3*S*,4*R*,5*R*,6*S*)-5-(4-methoxyphenoxy)-6-((benzyloxy)methyl)-tetrahydro-3,4-diacetoxypyran-2-one **10a** (174 mg, 95% yield) as viscous oil. R_f (40% EtOAc/hexanes) = 0.38; $[\alpha]_D^{25}$ −59.7 (*c* 1.0, CH_2Cl_2); IR (thin film, cm^{-1}) 2953, 2922, 2876, 2863, 1754, 1507, 1455, 1373, 1209, 1087, 1034, 929; ^1H NMR ($CDCl_3$, 270 MHz): δ 7.29 (m, 3H), 7.19 (m, 2H), 6.94 (m, 2H), 6.79 (m, 2H), 5.49 (d, J = 10.2 Hz, 1H), 5.41 (dd, J = 10.2, 2.4 Hz, 1H), 5.04 (dd, J = 2.4, 1.4 Hz, 1H), 4.73 (ddd, J = 7.3, 7.1, 1.4 Hz, 1H), 4.46 (d, J = 11.4 Hz, 1H), 4.38 (d, J = 11.4 Hz, 1H), 3.78 (d, J = 7.1 Hz, 2H), 3.77 (s, 3H), 2.15 (s, 3H), 1.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 170.2, 170.1, 165.7, 154.9, 152.9, 136.9, 128.4 (2C), 128.0, 127.9 (2C), 117.7 (2C), 114.6 (2C), 76.5, 73.6, 73.2, 71.4, 69.4, 66.3, 55.6, 20.5, 20.4; CIHRMS: Calcd for $[C_{24}H_{26}O_9+Na]^+$: 481.1475. Found: 481.1466.

Acknowledgements

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7. We have found that this reaction works for various phenols, however, simple alcohols (e.g., BnOH) did not participate in this reaction.
8. Recently we have found that when the Sharpless reagent was used in a matched fashion on diols **5a/c**, tetrols were obtained in both excellent diastereoselectivity and enantioselectivity, see: Ref. 4.
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12. The overall sequence requires fewer steps (five vs eight) to a *galacto*-δ-lactone and occurs in a greater overall yield (40% vs 14%) than a related iterative aldol approach, see: Ref. 3e.
13. Particularly revealing coupling constants were the *J*'s between the two axial protons at *C*-2 and *C*-3 (e.g., for **10a**, $J_{2,3}$ = 10.2 Hz) and between the equatorial proton at *C*-4 and the two axial protons at *C*-3 and *C*-5 (e.g., for **10a**, $J_{3,4}$ = 2.4 Hz and $J_{4,5}$ = 1.4 Hz).
14. As a representative example of this approach we have included experimental details and spectral data for the conversion of **6a** to **10a**.