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De Novo Asymmetric Syntheses of D- and L-Talose via an Iterative Dihydroxylation of Dienoates

Md. Moinuddin Ahmed and George A. O'Doherty*

Department of Chemistry, West Virginia University, Morgantown, West Virginia 26506

Abstract

A short and highly efficient route to D- and L-*talo*- γ -lactones has been developed. The key transformation was the sequential osmium-catalyzed bis-dihydroxylation reaction of substituted 2,4-dienoates. When the first dihydroxylation reaction is performed on (2*Z*,4*E*)-dienoates using the Sharpless AD-mix procedure, a regio- and enantioselective dihydroxylation resulted along with an in situ lactonization. A subsequent dihydroxylation, using OsO₄/NMO in MeOH conditions resulted, in an exceedingly diastereo- and enantioselective synthesis of *talo*- γ -lactone.

In response to the growing importance carbohydrate structures play in biology,¹ considerable efforts have been made to develop new synthetic routes to monosaccharides. This need in particular is driven by medicinal chemist's desire for unnatural sugar analogues for structure activity relationship studies. For the unnatural sugars in particular, there has been a growing interest in preparing these carbohydrates from achiral starting material using enantioselective catalysis to set the asymmetry (de novo synthesis). This interest in de novo approach to the hexoses goes back to the seminal work of Sharpless and Masamune.² More recently this challenge has been taken up by McMillan (iterative aldol strategy)³ and us (both an Achmatowicz⁴ and an iterative dihydroxylation strategy^{5,6}). In contrast to the diastereoselective aldol approach to hexoses of McMillan and others, we investigated the possibility of using a diastereoselective osmium-catalyzed dihydroxylation approach to the hexoses (Scheme 1). These efforts resulted in our recently reported synthesis of *galacto*-sugars from simple achiral precursors with complete stereocontrol.⁵ Our optimized procedure affords either D-*galacto*- γ -lactone (conditions a, Scheme 1) or L-*galacto*- γ -lactone (conditions b, Scheme 1) in three steps.^{7,8} Alternatively, racemic *galacto*- γ -lactone (conditions c, Scheme 1) can be prepared in only one step. Key to the success of these transformations is the in situ lactonization of the initially formed tetraol products. The in situ lactonization along with peracylation significantly aid in isolation of the *galacto*-lactones **2**.

Herein, we present the expansion this iterative dihydroxylation strategy to the *talo*- γ -lactones using the Sharpless dihydroxylation for enantiocontrol.⁹ These studies resulted in a three-step synthesis of *talo*- γ -lactones, which are amenable to various C-6 substituents.

George.O'Doherty@mail.wvu.edu.

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

Results and Discussion

Conceptually a bis-dihydroxylation reaction, which installs a hydroxyl group at every carbon atom, appears to be an ideal method for an efficient carbohydrate synthesis. In practice however, 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).^{10,11} The solution to these problems emerged from our continuing study of the Sharpless dihydroxylation of di- and tri-enoates.^{12,13} As with the *galacto*-lactones, we planned to establish the C-2 to C-5 tetrol stereochemistry of the *talo*-lactones from (Z,E)-dienoates (i.e. **3** from **6**; Scheme 2).¹⁴ These (Z,E)-dienoates were easily prepared by a Still-Gennari olefination of 4-substituted crotyl aldehydes.¹⁵ Once again we targeted the γ -lactone **3**, for ease of isolation (Scheme 2).

Encouraged by our success with the de novo synthesis of *galacto*-lactones **2**, we decided to next examine the possibility of an iterative dihydroxylation on a double bond isomer for the preparation of sugar stereoisomers. Because the Sharpless dihydroxylation occurs with greater selectivity for *trans*-double bonds, we selected (2Z,4E)-dienoate **6** to study.¹⁴ To our surprise, when dienolate **6** was dihydroxylated neither diol **5** nor tetrol **4** were detected, instead a concomitant lactonization reaction also occurred.

In practice, the dienolate **6** was prepared by treating a THF solution of crotyl aldehyde **7** with both EtO₂CCH₂P(O)(OCH₂CF₃)₂ and KO^t-Bu in the presence of excess 18-crown-6 (Scheme 3). This procedure reliably prepared dienolate **6** in both excellent yield (95%) and double bond stereoselectivity (12:1 Z/E-ratio). Exposing (2Z,4E)-dienoate **6** to the typical Sharpless AD-mix procedure (2% OsO₄/2.1% (DHQ)₂PHAL, 3 equiv K₃Fe(CN)₆/K₂CO₃, 1 equiv MeSO₂NH₂),⁹ afforded lactone **8** in good yield (70%) and enantiomeric excess (90% ee). When the lactone **8** was further dihydroxylated under ligandless conditions (OsO₄/NMO in MeOH), the *talo*- γ -lactone **3** was produced in good yield (65%, 5:1 dr). As with the *galacto*-lactones (c.f. Scheme 1), the triol **3** was per-acylated giving **9** in an excellent yield (95%).

We next looked to improve the diastereoselectivity of the second dihydroxylation in the sequence by making the alcohol of **8** more sterically hindered (Scheme 4). To these ends, we protected the alcohol with TBSCl, affording **10** in good yield (80%). When the TBS-protected alcohol **10** was exposed to the same dihydroxylation conditions improved diastereoselectivity was observed (10:1 instead of 5:1). The *talo*-lactone **11** was isolated in good yield (70%). To prove the stereochemistry the lactone **11** was deprotected with TBAF to afford the identical *talo*- γ -lactone **3** in good yield (80%).

To perform a Mosher ester analysis, the diol **11** was protected as the acetonide and the TBS group was deprotected to give the alcohol **12** in good yield (70% for 2 steps). Conversion of **12** to the corresponding Mosher esters followed by NMR analysis indicated that **12** was formed in 91% ee. The *talo*-stereochemistry of **12** was assigned by a series of nOe experiments (see supporting information). Finally, this procedure was also used to produce the enantiomer of **3** (D-*talo*- γ -lactone) in similar overall yield and enantiopurity (43% and 93% ee), by simply switching to (DHQD)₂PHAL ligand system in the initial dihydroxylation.

Conclusion

Our strategy for the synthesis of either enantiomer of *talo*-sugars provides rapid and practical access to important sugars, which should be of further use for oligosaccharide synthesis. In contrast to the recently reported enantioselective aldol approach³ to hexoses, which uses a change in aldol mechanism to prepare stereoisomers, this approach can be used to prepare either *galacto*- or *talo*-sugars by simply changing the dienolate double bond geometry. Thus,

by simply changing one of the double bond geometry, optically pure **3** was prepared in two steps from (2*Z*, 4*E*)-dienoate **8** (45% overall yield).

Experimental Section¹⁶

(2*Z*, 4*E*)-Ethyl 6-(benzyloxy)hexa-2,4-dienoate (**6**)

A solution of (CF₃CH₂O)₂P(O)CH₂CO₂CH₂CH₃ (3 g, 9.0 mmol) and 18-crown-6 (7.1 g, 27.0 mmol) in THF (60 mL) was cooled to −78 °C and treated with *t*-BuOK (1.2 g, 10.8 mmol). After the mixture was stirred for 15 min, a solution of the aldehyde **7** (1.6 g, 9.1 mmol) in THF (10 mL, plus 5 mL of rinse) was added by cannula. The resulting mixture was stirred at −78 °C for 2.5 h and the reaction mixture was quenched by the addition of saturated aqueous NH₄Cl and the bulk of THF was removed under reduced pressure. The residue was extracted with ether (3 × 30 mL) and the organic extracts were washed with brine, dried (Na₂SO₄), filtered and concentrated. The crude product was purified by flash chromatography on silica gel (25:1 (v/v) hexane/EtOAc) to yield (2*Z*,4*E*)-Ethyl 6-(benzyloxy)hexa-2,4-dienoate **6** (2.1 g, 12:1 *Z/E* ratio, 95% yield) as a viscous oil. Major isomer (**6**): *R*_f (30% EtOAc/hexanes) = 0.6; IR (thin film, cm^{−1}) 2983, 2928, 2872, 1766, 1650, 1620, 1496, 1454, 1436, 1362, 1268, 1141, 1073, 1029, 953; ¹H NMR (CDCl₃, 600 MHz): δ 7.58 (dddd, *J* = 15.6, 11.4, 1.2, 1.2 Hz, 1H), 7.33 (m, 5H), 6.59 (dd, *J* = 11.4, 11.4 Hz, 1H), 6.12 (ddd, *J* = 15.6, 6, 6 Hz, 1H), 5.68 (d, *J* = 11.4 Hz, 1H), 4.54 (brs, 2H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.17 (d, *J* = 6 Hz, 1H), 4.16 (d, *J* = 6 Hz, 1H), 1.30 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 150 MHz): δ 166.2, 143.6, 139.3, 137.9, 128.4 (2C), 128.1, 127.7 (2C), 127.6, 118.1, 72.5, 70.0, 60.0, 14.2; CIHRMS: Calculated for [C₁₅H₁₈O₃+Na]⁺: 269.2914, Found: 269.2917.

(*S*)-5-((*S*)-2'-(Benzyloxy)-1'-hydroxyethyl)-furan-2(5*H*)-one (**8**)

Into a 100 mL round bottom flask was added 20 mL of *t*-BuOH, 20 mL of water, K₃Fe(CN)₆ (9.6 g, 29 mmol), K₂CO₃ (4.03 g, 29 mmol), MeSO₂NH₂ (0.93 g, 9.7 mmol), (DHQ)₂PHAL (158 mg, 0.2 mmol, 2.1 mol%), and OsO₄ (49 mg, 0.19 mmol, 2 mol%). The mixture was stirred at room temperature for about 15 minutes and then cooled to 0 °C. To this solution was added (2*Z*,4*E*)-ethyl 6-(benzyloxy)hexa-2,4-dienoate **6** (2.4 g, 9.7 mmol) and the reaction was stirred vigorously at 0 °C overnight. The reaction was quenched with solid sodium sulfite (100 mg) at room temperature. Ethyl acetate (30 mL) was added to the reaction mixture, and after separation of the layers, the aqueous phase was further extracted with the organic solvent (2 × 20 mL). The combined organic layers were washed with brine 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 1.6 g (70% yield) of (*S*)-5-((*S*)-2'-(benzyloxy)-1'-hydroxyethyl)-furan-2(5*H*)-one **8** as a white solid: mp 74–75 °C; *R*_f (50% EtOAc/hexanes) = 0.16; [α]_D²⁵ −52.33° (*c* 1.2, CH₂Cl₂); IR (thin film, cm^{−1}) 3424, 2927, 2899, 1745, 1602, 1500, 1475, 1454, 1399, 1365, 1340, 1266, 1217, 1167, 1096, 1072, 993, 913 cm^{−1}; ¹H NMR (CDCl₃, 600 MHz): δ 7.47 (dd, *J* = 6, 1.2 Hz, 1H), 7.33 (m, 5H), 6.14 (dd, *J* = 6, 1.8 Hz, 1H), 5.16 (ddd, *J* = 4.2, 1.8, 1.8 Hz, 1H), 4.58 (d, *J* = 12 Hz, 1H), 4.54 (d, *J* = 12 Hz, 1H), 4.01 (dddd, *J* = 6, 5.4, 4.8, 4.2 Hz, 1H), 3.64 (dd, *J* = 9.6, 5.4 Hz, 1H), 3.58 (dd, *J* = 9.6, 5.4 Hz, 1H), 2.42 (d, *J* = 6 Hz, 1H); ¹³C NMR (CDCl₃, 150 MHz): δ 172.9, 153.8, 137.2, 128.5 (2C), 128.0, 127.8 (2C), 122.2, 83.7, 73.6, 70.2, 70.0; CIHRMS: Calculated for [C₁₃H₁₄O₄+Na]⁺: 257.0784, Found: 257.0782; The COSY spectral analysis confirmed the formation of γ-lactone.

(3*R*,4*S*,5*R*)-5-((*S*)-2'-(Benzyloxy)-1'-hydroxyethyl)-3,4-dihydroxy-dihydrofuran-2(3*H*)-one (**3**)

Into a 25 mL round bottom flask was added (*S*)-5-((*S*)-2'-(benzyloxy)-1'-hydroxyethyl)-furan-2(5*H*)-one **8** (100 mg, 0.42 mmol) and 1 mL of MeOH and then cooled to 0 °C. To this solution 0.3 mL 50% NMO in H₂O (1.28 mmol) and OsO₄ (2.1 mg, 8 μmol, 2 mol%) was added and the reaction was stirred vigorously at 0 °C overnight. The reaction was quenched with solid sodium sulfite (150 mg) at room temperature. Then the reaction mixture was filtered

through a pad of celite/florisil and eluted with 20 mL 50% ethyl acetate/MeOH. The combined organic layers were dried over anhydrous sodium sulfate. After removal of the solvents *in vacuo* and flash chromatography on silica gel (1:9 (v/v) MeOH/EtOAc) afforded (3*R*,4*S*,5*R*)-5-((*S*)-2'-(benzyloxy)-1'-hydroxyethyl)-3,4-dihydroxy-dihydrofuran-2(3*H*)-one **3** (74 mg, 5:1 dr, 65% yield) as a viscous oil. R_f (2% MeOH/EtOAc) = 0.14; $[\alpha]^{25}_D$ 41.2° (c 1.1, MeOH); IR (thin film, cm^{-1}) 3396, 2928, 2874, 1779, 1455, 1366, 1316, 1215, 1179, 1092, 1027, 978, 905; ^1H NMR (CD_3OD , 600 MHz) δ 7.37 (m, 5H), 4.67 (d, J = 6 Hz, 1H), 4.61 (s, 2H), 4.52 (d, J = 1.8 Hz, 1H), 4.38 (dd, J = 6, 0.6 Hz, 1H), 4.02 (ddd, J = 7.2, 6.6, 1.8 Hz, 1H), 3.60 (dd, J = 9, 7.2 Hz, 1H), 3.56 (dd, J = (9, 6.6 Hz, 1H), 3.76 (br s, 3H); ^{13}C NMR (CD_3OD , 150 MHz) δ 178.9, 139.6, 129.5 (2C), 129.0, 128.9 (2C), 86.9, 74.5, 72.0, 71.7, 70.3, 70.2; CIHRMS: Calculated for $[\text{C}_{13}\text{H}_{16}\text{O}_6+\text{Na}]^+$: 291.0839, Found: 291.0830.

(3*R*,4*S*,5*R*)-5-((*S*)-2'-(Benzyloxy)-1'-acetoxylethyl)-3,4-diacetoxy-dihydrofuran-2(3*H*)-one (**9**)

To a solution of (3*R*,4*S*,5*R*)-5-((*S*)-2'-(benzyloxy)-1'-hydroxyethyl)-dihydro-3,4-dihydroxyfuran-2(3*H*)-one **3** (50 mg, 0.18 mmol) in CH_2Cl_2 (1 mL) was added excess Ac_2O (80 μL , 0.74 mmol), pyridine (120 μL , 1.5 mmol) and a catalytic amount of DMAP (1.1 mg, 5 mol%). The reaction was stirred for 6 h, after which 5 mL ether and 5 mL of NH_4Cl was added to remove excess base. The organic layer was washed with 5 mL CuSO_4 solution, 5 mL brine and the aqueous layer was further extracted with ether (3 $\times$ 5 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 (7:3 (v/v) hexane/EtOAc) to yield (3*R*,4*S*,5*R*)-5-((*S*)-2'-(benzyloxy)-1'-acetoxylethyl)-3,4-diacetoxy-dihydrofuran-2(3*H*)-one **9** (70 mg, 95% yield) as a viscous oil. R_f (40% EtOAc/hexanes) = 0.3; $[\alpha]^{25}_D$ 8.6° (c 1.0, CH_2Cl_2); IR (thin film, cm^{-1}) 2953, 2922, 2876, 2863, 1808, 1749, 1373, 1234, 1179, 1100, 1069, 1044; ^1H NMR (CDCl_3 , 600 MHz): δ 7.33 (m, 5H), 5.69 (d, J = 6 Hz, 1H), 5.39 (d, J = 6 Hz, 1H), 5.27 (ddd, J = 7.8, 5.4, 3 Hz, 1H), 4.86 (d, J = 3 Hz, 1H), 4.57 (d, J = 12 Hz, 1H), 4.54 (d, J = 12 Hz, 1H), 3.65 (dd, J = 9.6, 5.4 Hz, 1H), 3.60 (dd, J = 9.6, 7.8 Hz, 1H), 2.14 (s, 3H), 2.13 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (CDCl_3 , 150 MHz): δ 170.2, 169.5, 169.3, 169.1, 137.2, 128.5 (2C), 128.0, 127.8 (2C), 80.7, 73.6, 70.3, 69.8, 66.4, 66.1, 20.8, 20.4, 20.1; CIHRMS: Calculated for $[\text{C}_{19}\text{H}_{22}\text{O}_9+\text{Na}]^+$: 417.1156, Found: 417.1158.

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16. Only the procedures for our initial preparation of *talo*-sugar 9 are presented in the Experimental Section (Scheme 3). Complete experimental procedures and spectral data for all new compounds (Schemes 3 and 4) are presented in the Supporting Information.

- a:** 1) 2% OsO₄/4% (DHQ)₂PHAL, K₃Fe(CN)₆/MeSO₂NH₂; 2) 10% OsO₄/12% (DHQD)₂PHAL, K₃Fe(CN)₆/MeSO₂NH₂; 3) Py•TsOH; 4) Ac₂O/Py; 50% of **2**.
b: 1) 2% OsO₄/4% (DHQD)₂PHAL, K₃Fe(CN)₆/MeSO₂NH₂; 2) 10% OsO₄/12% (DHQ)₂PHAL, K₃Fe(CN)₆/MeSO₂NH₂; 3) Py•TsOH; 4) Ac₂O/Py; 61% of (*ent*)-**2**.
c: 1) 2% OsO₄/NMO; 2) Ac₂O/Py; 71% of (+/-)-**2**.

Scheme 1.

1 to 3-step stereoselective synthesis of *galacto*- γ -lactone

Scheme 2.
Retrosynthesis of *talo*- γ -lactones

AD-α* = 2% OsO₄, 2.1% (DHQ)₂PHAL, 3 eq K₃Fe(CN)₆,
3 eq K₂CO₃, 1eq MeSO₂NH₂ in 1:1 *t*-BuOH/H₂O

Scheme 3.

Two-step highly enantio- and diastereoselective synthesis of *talo*-γ-lactone

Scheme 4.
Four-step synthesis of *talo*- γ -lactone