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Three-step synthesis of protected L-altrose from D-galactose derived Perlin aldehyde

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A new short three-step strategy has been designed for the synthesis of L-hexoses that are rare antipodes of the common hexoses from the commercially available glycals. S_{N^2} inversion of the triflate derived from the easily accessible Perlin aldehydes, followed by the dihydroxylation, leads to L-hexoses in good yields. The strategy has been successfully demonstrated by synthesizing one of the most expensive L-sugars i.e. L-altrose from D-galactose derived Perlin aldehyde. Also, interesting reactivity of the 2,4-dintrosulfonate group and the reactivity of protected Perlin aldehydes under the oxidative conditions have been discussed.

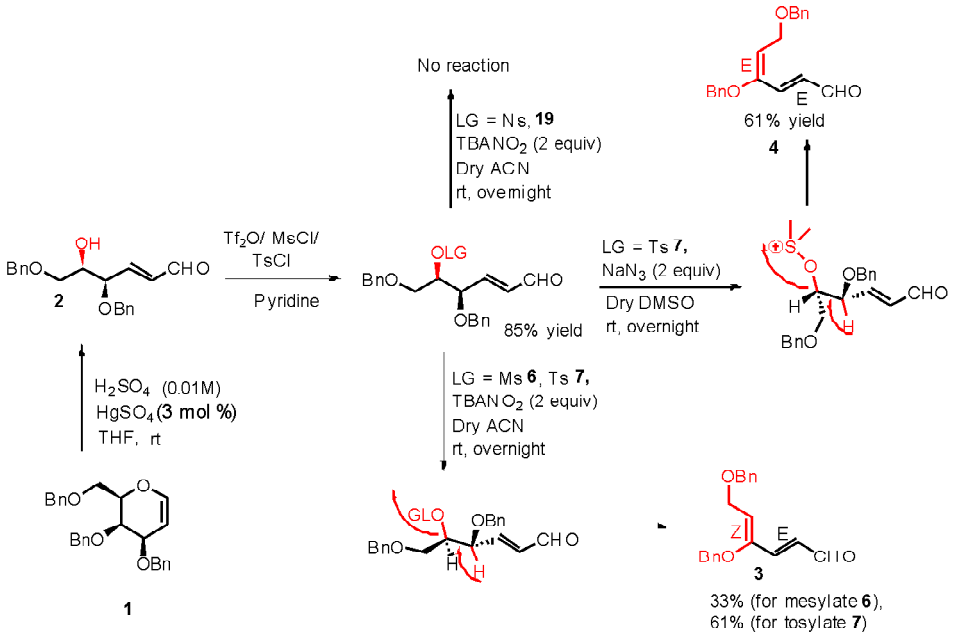
Keywords: Glycals, Perlin aldehyde, S_{N^2} inversion, L-sugars.

Introduction

L-Sugars[1], unlike their enantiomers the D-sugars, are rare[2] but are biologically important and play significant roles in nature. Some of these rare L-sugars find their use in the synthesis of low-calorie sweeteners[3], immunosuppresive agents[4], antiviral[5,6] compounds and also as chiral building blocks in the synthesis of natural products[7,8]. Some of these L-hexoses are a part of various antibiotics[9,10], terpene glycosides and also clinically important oligosaccharide like heparin[11]. Though commercially available, these L-sugars are hugely expensive. For example, the cost of L-altrose[1], a constituent of the extracellular polysaccharides from *Butyrivibrio fibrisolvens* strain CF3 is $11550 for 10 g and hence, the research on the interconversion of the commercially cheap D-sugars to L-sugars has gained continuous attention in carbohydrate chemistry. Numerous synthetic pathways for the synthesis of L-sugars have been reported including the epimerization of D-sugars[12,13], de novo synthesis[14,15], C-H activation[1,16] strategies, and asymmetric iterative aldol[17,18] reactions as well. However, a huge number of the reported syntheses in the literature deal with multi-step sequence including the protection and deprotection strategies that makes the synthesis of L-sugars also expensive.

Herein, we report a proof of concept for a short synthetic route towards the synthesis of L-sugars via the synthesis of L-altrose[19-21], one of the most expensive L-sugars. The synthesis has been achieved via Perlin aldehyde, an easily accessible synthetic intermediate from commercially available glycals.

Perlin aldehydes with a high degree of functionality (a) two well defined chiral centers, (b) unprotected alcohol and (c) an α,β-unsaturated system for further functionalization, have been attractive chiral pool synthons in organic chemistry. Ever since its first discovery by A. S. Perlin in 1975[22] on whose name this class of compounds were named after, these Perlin aldehydes have been used in the total synthesis of several natural products. Perlin aldehydes are easily accessible from the corresponding glycals in a single step. Treatment of the glycals with $HgSO_4$ in THF and 0.01 (*M*) H_2SO_4 at room temperature provides the corresponding Perlin aldehydes in almost quantitative yields. Non-mercurial Lewis acids have also been employed for the synthesis of these aldehydes although at elevated temperatures[23]. Though Perlin aldehydes have been utilized in the synthesis of various natural products, the synthetic potential of these chirally rich synthons has not been utilized for the synthesis of L-sugars. We envisaged that the stereo-inversion of the free hydroxyl group followed by simple dihydroxylation would lead to the synthesis of L-sugars. However, the approach poses a significant synthetic challenge as these compounds can undergo an E2 elimination process leading to a stable conju-

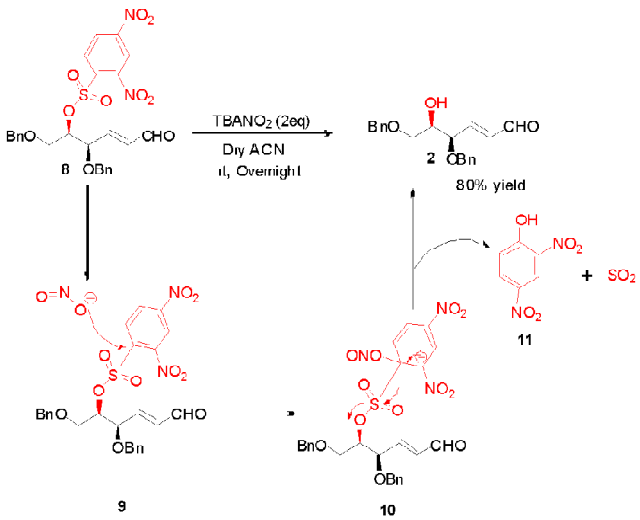


Scheme 1. Synthesis of Perlin aldehyde derivatives.

gate double bond with the already existing α,β-unsaturated aldehyde.

Here in this report, we present our initial reports of this three-step strategy towards the synthesis of protected L-sugars from Perlin aldehydes **2** and also some of the interesting observations that were made in the process of achieving the target.

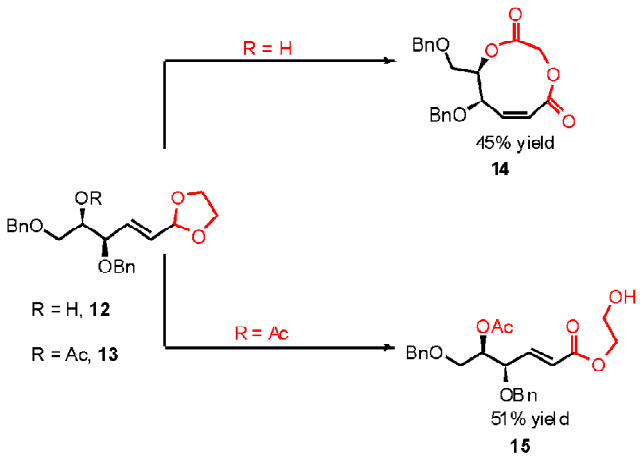
Our initial attempts started with the synthesis of Perlin aldehydes **2** with various leaving groups at the C-5 position. The D-galactose derived Perlin aldehyde **2** was chosen for this study. Hence, the galactose derived Perlin aldehyde **2** has been treated with mesyl chloride in the presence of pyridine that led to the formation of the corresponding mesylate **6** in 73% yield. Similarly, the corresponding tosylate **7**, nosylate **19**, 2,4-dinitrotosylate **8** and triflate **16** compounds were successfully synthesized by treating the alcohol **2** under the respective conditions (refer to the Experimental section for details). We then subjected the mesylate compound **6** for the stereo-inversion by reacting with tetrabutylammonium nitrite nucleophile in order to obtain the inverted alcoholic group. However, to our surprise, the isolated compound was observed to be an *E,Z*-dienal **3**, promoted via the E2 elimination in 33% (Scheme 1). Similarly, the tosylate compound **7**, when subjected to similar reaction conditions, also led to the formation of the eliminated compound **3** in a moderate yield of 61% (Scheme 1). Interestingly, when the reaction was performed in DMSO as a solvent instead of acetonitrile and NaN_3 as nucleophile, *E,E*-diene **4** has been obtained (Scheme 1). The change in stereochemistry of the olefinic product obtained can be attributed to the $S_{N}2$ attack of DMSO followed by E2 elimination reaction. Compound **19**, with nosylate as a leaving group (Scheme 1), when treated



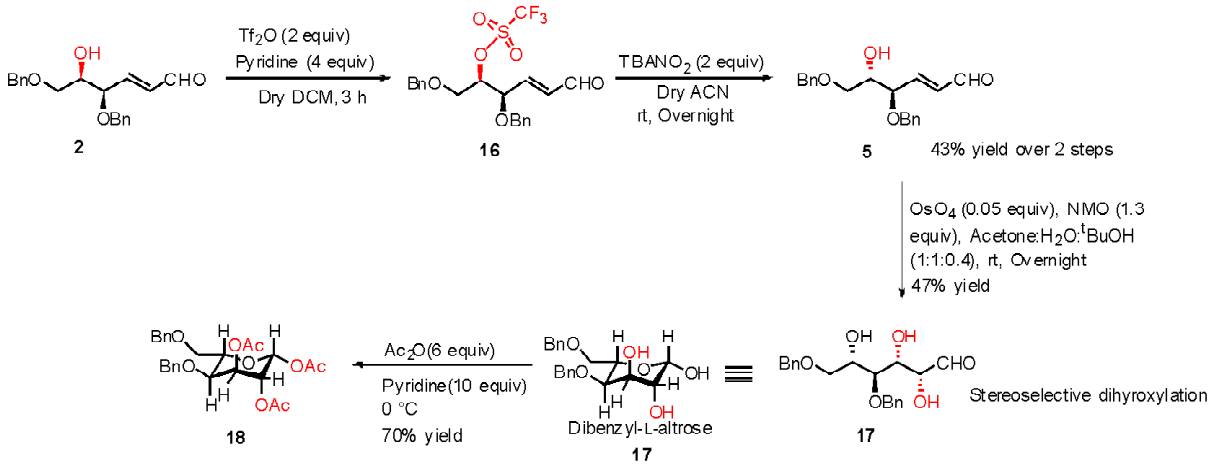
Scheme 2. Unusual behaviour of 2,4-dinitrosulfonate.

with $TBANO_2$, did not lead to any conversion. An intriguing observation has been made when 2,4-dinitrobezenesulfonyl group was used as a possible leaving group. Sulfonate **8** when treated with $TBANO_2$ as a nucleophile, we have obtained the alcohol **2** as the product, however, surprisingly with a stereo-retention instead of stereo-inversion. This phenomenon can be explained by an *ipso* attack of the nucleophile at the C-S bond followed by the elimination of sulfur dioxide giving rise to the stereo-retentive alcoholic product **2** along with 2,4-dinitrophenol **11** as a by-product. This observation is in accordance with a recent report by Mandal and co-workers[24] where the authors had explored the concept in a C-N bond forming reaction.

After many failed attempts with various leaving groups, we decided to test trifluoromethanesulfonate (triflate), a group with greater nucleofugal ability as a leaving group for the current desired transformation. Hence, the corresponding trilfate has been made by treating the alcohol **2** under Tf_2O/pyridine conditions that led to the formation of the desired compound **16**. The crude triflate compound **16** when treated with $TBANO_2$, underwent a smooth $S_{N}2$ inversion and yielded the compound **5**, a precursor of L-sugars in 43% overall yield over two steps. The product was confirmed by the disappearance of signals corresponding to the H-4 and H-5 at 4.29 and 3.87 ppm respectively in the D-isomer (**2**) and appearance of signals at 4.12 and 3.84 ppm respectively for the L-isomer (**5**) in ^{1}H NMR spectrum indicating the inversion of the stereocenter. The unique nature of the triflate group, despite being a better nucleofuge than the tosylate **7** and mesylate **6** did not undergo the competitive E2 elimination but provided the desired inversion of the stereocenter leading to the L-sugar **5**. Next, treatment of the resultant unprotected alcohol **5** with OsO_4 resulted in a stereoselective dihydroxylation reaction presumably controlled by the C-4 *O*-benzyl protecting group giving rise to L-altrose derivative **17**. The compound **17** has also been characterized as a triacetate **18**, after the acetylation under the standard conditions of Ac_2O/pyridine. Attempts to form an epoxide on the protected aldehydes **12** and **13** gave rise to allylic oxidation products **14** and **15** respectively (Scheme 3).



Scheme 3. Oxone mediated oxidation. Reaction conditions: 1 equiv. starting material, 1.2 equiv. oxone, 2.1 equiv. $NaHCO_3$, acetone, rt, 24 h. R = H **12**, R = Ac **13**.



Scheme 4. Synthetic route of L-altrose.

NOE experiments were also performed for the unambiguous structural assignment of compound **18**. Upon irradiation of anomeric proton (α-isomer) H-1 (δ 6.08 ppm), enhancement was observed in the signals corresponding to H-2 (δ 5.16 ppm) (3.72% w.r.t. H-1) and H-5 (δ 4.05 ppm) (2.93% w.r.t. H-1) which indicates that H-1 is in *cis* relation with both H-2 and H-5. Similarly, irradiation of H-2 (δ 5.16 ppm) led to a substantial enhancement of H-1 (δ 6.08 ppm) (3.67% w.r.t. H-2) and weak enhancement of H-3 (δ 5.51 ppm) (2.56% w.r.t. H-2) thus confirming the di-equatorial relation of H-2 and H-3 (Fig. 1). Besides, the coupling constants of H-1 (*J* 1.6 Hz), H-2 (*J* 1.6, 4.7 Hz), H-3 (*J* 4.5, 3.3 Hz), and H-4 (*J* 8.9, 3.1 Hz), also reveal the stereochemical relation of these protons. Based on these experiments, the structure of compound **18** has been assigned as L-altrose.

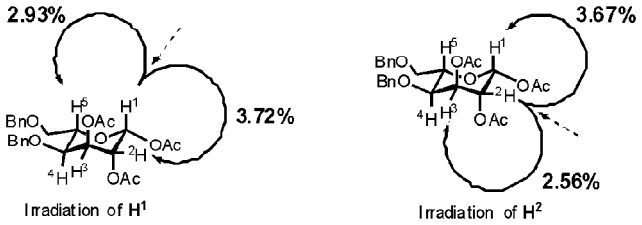


Fig. 1. NOE experiments on compound **18**.

In conclusion, we have developed a very practical, short, three-step synthesis of L-altrose from Perlin aldehydes that are easily accessible from the commercially available glycals via the stereo-inversion of the Perlin aldehyde derived triflate followed by the dihydroxylation. Also, the ability of various leaving groups towards the stereo-inversion has been discussed. An interesting observation of the 2,4-dinitrosulfonate esters undergoing *ipso* substitution has also been discussed. The strategy has the potential for the synthesis of all the possible eight L-sugars and will be pursued in due course.

Experimental

All solvents purchased were in commercial-grade. All the reagents purchased were from Sigma-Aldrich, Merck, Carbosynth, Spectrochem, Alfa Aesar and were used without further purification. Reactions were monitored by TLC on Kieselgel 60 F_{254} (Merck). Detection was done by examination under UV light (254 nm) and by charring with 10% sulfuric acid in water. Purification was performed by both Combi Flash Nextgen-100 chromatography and in normal phase using silica gel (Merck, 60–120 mesh). Extracts were concentrated *in vacuo* using both Büchi rotary evaporator (bath temperatures up to 40°C) at a pressure of either 15 mmHg (diaphragm pump) and 0.7 mmHg (oil pump), at rt. ^{1}H and ^{13}C NMR were recorded on Bruker Avance 600 MHz and 400 MHz spectrometers using $CDCl_3$ as solvent. Chemical shift values are reported in ppm with the solvent as the internal standard ($CDCl_3$: δ 7.26 for ^{1}H, δ 77.16 for ^{13}C). The data accounted as follows: chemical shifts (δ), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets, t = triplet, td = triplet of doublets, q = quartet, m = multiplet) etc., coupling constants *J* (Hz), and integration. High-resolution mass measurements were performed using Agilent technologies mass spectrometer.

*(4R,5R,E)-4,6-Bis(benzyloxy)-5-hydroxyhex-2-enal (**2**):*

To a solution of benzyl-protected galactal **1** (1 g, 2.4 mmol) in THF, 0.01 (*M*) sulphuric acid (5 ml) was added, followed by mercuric sulphate (0.02 g, 3 mol%) at rt. The reaction mixture was stirred for overnight. After completion of the reaction, THF was evaporated under reduced pressure. The crude residue was extracted with ethyl acetate (3×50 ml). The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The crude residue was purified through flash chromatography to afford colorless liquid **2**. R_f: 0.3 (30% ethyl acetate in hexane), yield = 85%.^{1}H NMR (600 MHz, $CDCl_3$): δ 9.55 (d, *J* 7.9 Hz, 1H), 7.39–7.28 (m, 10H), 6.78 (dd, *J* 15.9, 5.9 Hz, 1H), 6.34 (ddd, *J* 15.8, 7.9, 1.1 Hz, 1H), 4.63 (d, *J* 11.5 Hz, 1H), 4.53 (d, *J* 11.8 Hz, 1H), 4.48 (d, *J* 11.8 Hz, 1H), 4.43 (d, *J* 11.5 Hz, 1H), 4.29 (dd, *J* 8.0, 3.1 Hz, 1H), 3.87 (dd, 1H), 3.59 (dd, *J* 9.8, 4.7 Hz, 1H), 3.51 (dd, *J* 9.8, 5.4 Hz, 1H), 2.78 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 193.2, 153.2, 137.6, 137.2, 133.8, 128.6, 128.5, 128.2, 128.0, 128.0, 127.9, 78.6, 73.6, 72.3, 72.2, 70.1.

*(2E,4Z)-4,6-Bis(benzyloxy)hexa-2,4-dienal (**3**):*

To a solution of compound **6** (0.1 g, 0.25 mmol) in dry ACN, $TBANO_2$ was added at rt. The mixture was stirred for overnight under nitrogen atmosphere. After completion, water was added to freeze the reaction, extracted with ethyl acetate (3×40 ml). The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced

pressure. The crude residue was purified through flash chromatography to afford colorless liquid **3**. R_f: 0.7 (30% ethyl acetate in hexane), yield = 33%. HRMS Calcd. for $C_{20}H_{20}O_3Na$ $[M+Na]^+$: 331.1310, Found: 331.1322. ^1H NMR (600 MHz, $CDCl_3$): δ 9.64 (d, *J* 7.9 Hz, 1H), 7.38–7.28 (m, 11H), 6.92 (d, *J* 15.5 Hz, 1H), 6.39 (dd, *J* 15.5, 7.9 Hz, 1H), 5.77 (t, *J* 6.6 Hz, 1H), 4.75 (s, 2H), 4.46 (s, 2H), 4.13 (d, *J* 6.6 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 193.3, 153.1, 147.6, 137.7, 136.3, 129.0, 128.6, 128.5, 128.2, 127.9, 127.9, 127.0, 126.3, 74.7, 72.8, 64.6.

*(2E,4E)-4,6-Bis(benzyloxy)hexa-2,4-dienal (**4**):*

To a solution of compound **7** (0.1 g, 0.21 mmol) in dry DMSO, sodium azide (0.041 g, 0.63 mmol) was added at rt. The mixture was stirred for overnight under nitrogen atmosphere. After completion, water was added to freeze the reaction and extracted with ethyl acetate (3×40 ml). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified through flash chromatography to afford colourless liquid **4**. R_f: 0.7 (30% ethyl acetate in hexane), yield = 61%. HRMS Calcd. for $C_{20}H_{20}NaO_3$ $[M+Na]^+$: 331.1310, Found: 331.1318. ^1H NMR (600 MHz, $CDCl_3$): δ 9.59 (d, *J* 8.0 Hz, 1H), 7.40–7.30 (m, 11H), 7.19 (d, *J* 15.3 Hz, 1H), 6.62 (dd, *J* 15.3, 8.0 Hz, 1H), 5.36 (t, *J* 7.6 Hz, 1H), 4.88 (s, 2H), 4.54 (s, 2H), 4.23 (d, *J* 7.6 Hz, 2H).

*(4R,5S,E)-4,6-Bis(benzyloxy)-5-hydroxyhex-2-enal (**5**):*

To a solution of benzyl-protected perlin aldehyde (0.1 g, 0.31 mmol) in dry DCM, pyridine (0.1 ml, 4 equiv.) was added, followed by trifluoromethanesulfonic anhydride (0.1 ml, 0.62 mmol) at 0°C. The reaction mixture was stirred for 3 h at room temperature under nitrogen atmosphere. After completion of the reaction, ice-cold water was added to freeze the reaction. The product was extracted by ethyl acetate (3×40 ml). The organic layer was washed with 2 (*N*) HCl (30 ml), saturated solution of $NaHCO_3$ (2×50 ml), brine solution and dried over Na_2SO_4. The crude triflate was dissolved in dry acetonitrile, to this solution $TBANO_2$ (0.13 g, 0.44 mmol) was added at rt under nitrogen atmosphere, allowed for stirring overnight. After completion, water was added to freeze the reaction, extracted with ethyl acetate (3×40 ml). The combined organic layers were washed with brine solution, concentrated, purified through flash chromatography to afford compound **5**, as a colourless liquid. R_f: 0.3 (30% ethyl acetate in hexane). The overall yield was 43% over 2 steps. HRMS Calcd. for $C_{20}H_{26}NO_4$ $[M+NH_4]^+$: 344.1862, Found: 344.1860. ^1H NMR (400 MHz, $CDCl_3$): δ 9.59 (d, *J* 7.9 Hz, 1H), 7.38–7.23 (m, 10H), 6.88 (dd, *J* 15.9, 6.0 Hz, 1H), 6.34 (ddd, *J* 15.9, 7.9, 1.0 Hz, 1H), 4.60 (d, *J* 11.5 Hz, 1H), 4.50 (d, *J* 7.3 Hz, 2H), 4.43–4.39 (m, 1H), 4.12 (dd, *J* 6.1, 0.9 Hz, 1H), 3.84 (dd, *J* 10.6, 5.3 Hz, 1H), 3.59 (qd, *J* 9.6, 4.9 Hz, 2H), 2.42 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 193.4, 153.8, 137.5, 137.2, 133.9, 128.6, 128.5, 128.1, 128.0, 128.0, 127.9, 78.5, 73.5, 72.3, 72.0, 70.1.

*(2R,3R,E)-1,3-Bis(benzyloxy)-6-oxohex-4-en-2-yl methanesulfonate (**6**):*

To a solution of benzyl-protected perlin (0.2 g, 0.61 mmol) in dry DCM, pyridine (98 μL, 1.22 mmol) was added, followed by mesyl chloride (0.12 ml, 1.22 mmol) at 0°C. The mixture was stirred for 3 h at room temperature under nitrogen atmosphere. After completion, ice-cold water was added to freeze the reaction. The reaction mixture was extracted with ethyl acetate (3×40 ml). The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The crude residue was purified through flash chromatography to afford white solid **6**. R_f: 0.6 (40% ethyl acetate in hexane), yield = 73%. ^1H NMR (600 MHz, $CDCl_3$): δ 9.48 (d, *J* 7.8 Hz, 1H), 7.35–7.15 (m, 10H), 6.65 (dd, *J* 15.8, 5.3 Hz, 1H), 6.32 (ddd, *J* 15.8, 7.8, 1.2 Hz, 1H), 4.75 (td, *J* 6.3, 3.0 Hz, 1H), 4.55 (d, *J* 11.6 Hz, 1H), 4.47 (d, *J* 11.7 Hz, 1H), 4.41–4.37 (m, 3H), 3.65 (dd, *J* 11.1, 3.0 Hz, 1H), 3.55 (dd, *J* 11.1, 6.6 Hz, 1H), 2.90 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 193.3, 153.1, 147.7, 137.8, 136.4, 129.0, 128.7, 128.5, 128.3, 128.2, 128.0, 126.3, 74.7, 72.8, 64.6, 31.6.

*(2R,3R,E)-1,3-Bis(benzyloxy)-6-oxohex-4-en-2-yl 4-methylbenzenesulfonate (**7**):*

To a solution of benzyl-protected perlin (0.2 g, 0.61 mmol) in dry DCM, pyridine (98 μL, 1.22 mmol) was added followed by tosyl chloride (0.35 g, 1.82 mmol) at 0°C. The reaction mixture was stirred at room temperature for 4 h under nitrogen atmosphere. After completion of the reaction, ice-cold water was added to freeze the reaction. The reaction mixture was extracted with DCM (3×40 ml). The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The crude reaction mixture was purified by flash chromatography to afford colourless liquid **7**. R_f: 0.6 (30% ethyl acetate in hexane), yield = 78%. ^1H NMR (600 MHz, $CDCl_3$): δ 9.38 (d, *J* 7.9 Hz,

1H), 7.72 (d, *J* 8.2 Hz, 2H), 7.34–7.26 (m, 6H), 7.23–7.16 (m, 6H), 6.59 (dd, *J* 15.8, 5.4 Hz, 1H), 6.27–6.22 (m, 1H), 4.67 (q, *J* 5.0 Hz, 1H), 4.55 (d, *J* 11.7 Hz, 1H), 4.44 (dd, *J* 7.1, 2.9 Hz, 1H), 4.41 (d, *J* 3.8 Hz, 1H), 4.39 (d, *J* 3.9 Hz, 1H), 4.34 (d, *J* 11.8 Hz, 1H), 3.73 (dd, *J* 10.6, 4.8 Hz, 1H), 3.56 (dd, *J* 10.6, 5.6 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 192.7, 151.1, 144.0, 137.2, 136.8, 133.9, 133.2, 129.7, 128.5, 128.4, 128.1, 128.0, 127.9, 127.9, 127.8, 80.4, 76.3, 73.4, 72.4, 67.8, 21.6.

*(2R,3R,E)-1,3-Bis(benzyloxy)-6-oxohex-4-en-2-yl 2,4-dinitrobenzenesulfonate (**8**):*

To a solution of benzyl-protected perlin (0.2 g, 0.61 mmol) in dry DCM , pyridine (98 μL, 1.22 mmol) was added, followed by 2,4-dinitrobenzenesulfonyl chloride (0.325 g, 1.22 mmol) at 0°C. The reaction mixture was stirred for 5 h at room temperature under nitrogen atmosphere. After completion, ice-cold water was added to freeze the reaction. The reaction mixture was extracted by DCM (3×40 ml). The combined organic layers were washed with brine, concentrated under reduced pressure. The crude mixture was purified by flash chromatography to afford colourless liquid **8**. R_f: 0.4 (30% ethyl acetate in hexane), yield = 69%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.59 (d, *J* 7.7 Hz, 1H), 8.10 (dd, *J* 14.9, 5.3 Hz, 2H), 8.04 (dd, *J* 8.6, 2.0 Hz, 1H), 7.30–7.26 (m, 6H), 7.17–7.15 (m, 2H), 7.12–7.09 (m, 2H), 6.72 (dd, *J* 15.8, 5.4 Hz, 1H), 6.42 (dd, *J* 15.9, 7.7 Hz, 1H), 4.91 (td, *J* 6.4, 2.3 Hz, 1H), 4.59–4.56 (m, 1H), 4.52 (t, *J* 5.6 Hz, 1H), 4.43 (d, *J* 11.1 Hz, 1H), 4.37 (d, *J* 11.4 Hz, 1H), 4.25 (d, *J* 11.1 Hz, 1H), 3.75 (dd, *J* 11.4, 2.2 Hz, 1H), 3.65 (dd, *J* 11.4, 6.6 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 192.5, 149.7, 149.0, 136.6, 136.4, 135.2, 134.8, 132.4, 128.5, 128.4, 128.4, 128.4, 127.9, 127.8, 127.7, 126.0, 119.9, 84.7, 76.8, 73.6, 72.3, 68.5.

*(2R,3R,E)-1,3-Bis(benzyloxy)-5-(1,3-dioxolan-2-yl)pent-4-en-2-ol (**12**):*

To an oven dried RB, benzyl-protected perlin aldehyde (0.2 g, 0.61 mmol) was added, dissolved in dry benzene. 2,3,5-collidine (11 μL, 15 mol%) and D(+)-10-camphorsulfonic acid (0.021 g, 15 mol%), excess ethylene glycol (171 μL, 3.05 mmol) was added to it. The reaction mixture was refluxed under nitrogen for 3 h. After cooling down to rt, water (50 ml) and trimethylamine (0.1 ml) was added, extracted with ether (3×40 ml), dried over Na_2SO_4, concentrated under reduced pressure. The crude residue was purified through flash chromatography to afford colourless liquid **12**. R_f: 0.3 (30% ethyl acetate in hexane), yield 80%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.23 (m, 10H), 5.90 (dd, *J* 15.8, 7.3 Hz, 1H), 5.79 (dd, *J* 15.8, 5.6 Hz, 1H), 5.29 (d, *J* 5.7 Hz, 1H), 4.64 (d, *J* 11.6 Hz, 1H), 4.51 (q, *J* 12.0 Hz, 2H), 4.36 (d, *J* 11.6 Hz, 1H), 4.04–3.95 (m, 3H), 3.93–3.88 (m, 2H), 3.78 (dd, *J* 9.7, 5.1 Hz, 1H), 3.57 (dd, *J* 10.0, 4.0 Hz, 1H), 3.49 (dd, *J* 10.0, 5.4 Hz, 1H), 2.73 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 138.1, 137.9, 132.6, 131.2, 128.4, 128.4, 128.0, 127.8, 127.8, 127.7, 102.9, 79.3, 73.5, 72.9, 71.0, 70.5, 65.0.

*(2R,3R,E)-1,3-Bis(benzyloxy)-5-(1,3-dioxolan-2-yl) pent-4-en-2-yl acetate (**13**):*

To a solution of compound **12** (0.2 g, 0.54 mmol) in dry DCM, pyridine (87 μL, 1.08 mmol) was added, followed by acetic anhydride (102 μL, 1.08 mmol) at 0°C . The reaction mixture was stirred for 3 h at room temperature under nitrogen atmosphere. After completion of the reaction, ice-cold water was added to freeze the reaction. The reaction mixture was extracted by DCM (3×40 ml). The combined organic layers were washed with brine, concentrated under reduced pressure. The crude mixture was purified by flash chromatography to afford colourless liquid **13**. R_f: 0.6 (40% ethyl acetate in hexane), yield 70%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35–7.25 (m, 10H), 5.82 (t, *J* 5.1 Hz, 2H), 5.28 (d, *J* 4.6 Hz, 1H), 5.15 (dd, *J* 10.0, 5.3 Hz, 1H), 4.65 (d, *J* 12.0 Hz, 1H), 4.50 (d, *J* 12.0 Hz, 1H), 4.43 (d, *J* 12.0 Hz, 1H), 4.38 (d, *J* 12.0 Hz, 1H), 4.16 (t, *J* 5.3 Hz, 1H), 3.99–3.94 (m, 2H), 3.93–3.88 (m, 2H), 3.63 (dd, *J* 10.5, 4.3 Hz, 1H), 3.57 (dd, *J* 10.5, 5.7 Hz, 1H), 2.08 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 170.5, 144.5, 137.9, 131.6, 130.9, 128.4, 128.4, 128.4, 127.8, 127.7, 127.7, 102.8, 76.9, 73.5, 73.2, 71.1, 68.3, 65.0, 21.1.

*(8R,9R,Z)-8-(Benzyloxy)-9-((benzyloxy)methyl)-8,9-dihydro-5H-1,4-dioxonine-2,5(3H)-dione (**14**):*

To a solution of compound **12** (0.05 g, 0.13 mmol) in acetone (0.3 ml), $NaHCO_3$ (0.022 g, 0.26 mmol) was added at 0°C. After that, a solution of oxone (0.1 g, 0.16 mmol) in water (165 μL) was added dropwise. The mixture was stirred for 24 h. Upon completion of the reaction, acetone was removed under reduced pressure. The reaction mixture was extracted with ethyl acetate (3×40 ml). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified through flash chromatography to afford colourless liquid **14**. R_f: 0.4 (50% ethyl acetate in hexane), yield 45%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.27 (m, 10H), 6.98 (ddd, *J* 19.4, 15.8, 6.3 Hz, 1H), 6.12 (dd, *J* 15.5, 12.6 Hz, 1H), 4.64 (d, *J* 11.5 Hz, 1H), 4.59–4.46 (m, 2H), 4.40 (dd, *J* 11.5, 2.4 Hz, 1H), 4.29 (dd, *J* 5.1, 2.7 Hz, 1H), 4.19 (dd, *J* 11.5, 5.5 Hz, 1H), 3.85 (dt, *J* 9.7, 4.6 Hz, 2H), 3.58 (dd, *J* 9.8, 4.4 Hz, 1H), 3.50 (dd, *J* 9.9, 5.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.9, 165.1, 145.9, 144.3, 136.7, 136.3, 127.5, 127.4, 127.1, 127.0, 127.0, 127.0, 126.8, 122.3, 77.5, 72.5, 71.3, 70.9, 70.9, 69.1, 65.3, 60.2.

*2-Hydroxyethyl (4R,5R,E)-5-acetoxy-4,6-bis(benzyloxy) hex-2-enoate (**15**):*

To a solution of compound **13** (0.05 g, 0.12 mmol) in acetone (0.24 ml), $NaHCO_3$ (0.02 g, 0.24 mmol) was added at 0°C. After that, a solution of oxone (0.09 g, 0.14 mmol) in water (145 μL) was added dropwise. The mixture was stirred for 1 day. After completion of the reaction, acetone was removed under reduced pressure. The reaction mixture was extracted with ethyl acetate (3×40 ml). The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The crude residue was purified through flash chromatography to afford colourless liquid **15**. R_f: 0.6 (40% ethyl acetate in hexane), yield 51%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.27 (m, 10H), 6.90 (dd, *J* 15.7, 5.6 Hz, 1H), 6.15 (dd, *J* 15.7, 1.0 Hz, 1H), 5.17 (dd, *J* 10.1, 5.0 Hz, 1H), 4.64 (d, *J* 11.9 Hz, 1H), 4.52–4.41 (m, 3H), 4.33–4.27 (m, 3H), 3.87–3.83 (m, 2H), 3.65 (dd, *J* 10.5, 4.5 Hz, 1H), 3.55 (dd, *J* 10.4, 5.7 Hz, 1H), 2.07 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 170.5, 166.1, 144.6, 137.6, 137.4, 128.5, 128.4, 128.0, 127.9, 127.8, 127.7, 123.2, 76.4, 73.3, 73.0, 72.0, 68.0, 66.3, 61.2, 21.1.

*4,6-Di-O-benzyl L-altropyranose (**17**):*

To a stirred solution of compound **5** (0.1 g, 0.31 mmol) in 5 ml mixture of acetone:water:^{t}butanol (1:1:0.4) at rt was added NMO.H_2O (48 μL 0.4 mmol) followed by catalytic amount of 2% aqueous solution of OsO_4 (0.2 ml, 0.016 mmol). The reaction mixture was stirred for overnight. After completion of the reaction, it was treated with $Na_2S_2O_5$. The reaction mixture was stirred further for another 1 h and extracted with ethyl acetate (3×50 ml), washed with 1(*N*) HCl (50 ml), water, brine solution. Then, dried over Na_2SO_4, concentrated under reduced pressure, purified by column chromatography (ethyl acetate:hexane = 3:1) to afford colourless liquid **17**. R_f: 0.6 (100% ethyl acetate), yield 47%. HRMS Calcd. for $C_{20}H_{24}KO_6$ $[M+K]^+$ 399.1210, Found: 399.1249. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.12 (m, 10H), 5.04 (d, *J* 15.0 Hz, 1H), 4.68–4.40 (m, 5H), 4.19 (d, *J* 12.7 Hz, 1H), 3.99–3.78 (m, 3H), 3.68 (d, *J* 24.2 Hz, 3H), 2.41 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 136.7, 136.4, 127.6, 127.4, 127.2, 127.1, 127.0, 126.9, 93.9, 91.8, 72.6, 70.9, 69.6, 68.2, 67.0, 64.8.

*4,6-Di-O-benzyl 1,2,3-tri-O-acetyl-L-altropyranose (**18**):*

To a solution of compound **17** (0.1 g, 0.28 mmol) in dry DCM, pyridine (0.09 ml, 1.12 mmol) was added followed by acetic anhydride (0.11 ml, 1.12 mmol) at 0°C. The reaction mixture was stirred for 3 h at room temperature under nitrogen atmosphere. After completion of the reaction, ice-cold water was added to freeze the reaction, extracted by ethyl acetate (3×40 ml). The combined organic layers were washed with saturated $NaHCO_3$ to remove excess acid, brine solution and dried over Na_2SO_4, concentrated under reduced pressure. The crude residue was purified by flash chromatography (ethyl acetate:hexane = 1:2) to afford colourless liquid **18**. R_f: 0.5 (40% ethyl acetate in hexane), yield 70%. HRMS Calcd. for $C_{26}H_{34}NO_9$ $[M+NH_4]^+$ 504.2234, Found: 504.2234. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.17 (m, 10H), 6.08 (H^1, d, *J* 1.6 Hz, 1H), 5.51 (H^3, dd, *J* 4.5, 3.3 Hz, 1H), 5.16 (H^2, dd, *J* 4.7, 1.6 Hz, 1H), 4.64 (dd, *J* 9.3, 5.8 Hz, 1H), 4.59 (H^6, d, *J* 5.3 Hz, 1H), 4.52–4.49 (m, 1H), 4.37 (d, *J* 10.8 Hz, 1H), 4.05 (H^5, dd, *J* 8.0, 4.3 Hz, 1H), 3.94 (H^4, dd, *J* 8.9, 3.1 Hz, 1H), 3.73–3.70 (m, 2H), 2.15 (s, 3H), 2.11 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.5, 169.4, 168.8, 138.0, 137.2, 128.4, 128.4, 128.3, 128.2, 128.0, 127.7, 90.3, 74.4, 73.6, 72.1, 70.7, 68.9, 67.9, 66.3, 29.7, 21.0, 20.9.

*(2R,3R,E)-1,3-Bis(benzyloxy)-6-oxohex-4-en-2-yl 4-nitrobenzenesulfonate (**19**):*

To a solution of benzyl-protected perlin (0.2 g, 0.61 mmol) in dry DCM, pyridine (98 μL, 1.22 mmol) was added, followed by 4-nitrobenzenesulfonyl chloride (0.27 g, 1.22 mmol) at 0°C. The reaction mixture was stirred for 5 h at room temperature under nitrogen atmosphere. After completion of the reaction, ice-cold water was added to freeze the reaction. The reaction mixture was extracted by DCM (3×40 ml). The combined organic layers were washed with brine, concentrated under reduced pressure. The crude mixture was purified by flash chromatography to afford colourless liquid. R_f: 0.45 (20% ethyl acetate in hexane), yield 75%. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.55 (d, *J* 7. 7 Hz, 1H), 8.01 (d, *J* 8.9 Hz, 2H), 7.94 (d, *J* 8.9 Hz, 2H), 7.34–7.30 (m, 6H), 7.22–7.19 (m, 2H), 7.14–7.11 (m, 2H), 6.70 (dd, *J* 15.8, 5.4 Hz, 1H),

6.38 (ddd, *J* 15.8, 7.7, 1.1 Hz, 1H), 4.79 (td, *J* 6.1, 3.0 Hz, 1H), 4.58 (d, *J* 11.5 Hz, 1H), 4.48 (dd, *J* 7.8, 3.3 Hz, 1H), 4.38 (dd, *J* 22.1, 11.4 Hz, 2H), 4.26 (d, *J* 11.4 Hz, 1H), 3.71 (dd, *J* 11.2, 2.9 Hz, 1H), 3.54 (dd, *J* 11.2, 6.3 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 192.5, 150.4, 149.7, 141.9, 136.7, 136.5, 134.6, 129.2, 128.6, 128.5, 128.4, 128.3, 127.9, 127.9, 123.9, 82.5, 76.8, 73.6, 72.5, 68.3.

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