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Note

Serendipitous one-pot synthesis of chiral dienes from pyranosidic 2,4-bistriflates

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ABSTRACT

Attempted nucleophilic displacements of L-rhamnosyl 2,4-bistriflates led to serendipitous formation of a chiral diene via competing cascade eliminations. The reaction also followed the same pathway with D-rhamnosyl and D-mannosyl 2,4-bistriflates substrates providing access to dienes with opposite stereochemistry. The reaction presumably proceeds through *E*2 elimination of C2 triflate followed by allylic rearrangement. The easily accessible chiral dienes would be useful in the synthesis of natural products.

1. Introduction

A variety of rare deoxy amino sugars are exclusively present on bacterial cell surfaces [1]. The unusual sugars being absent on the host surfaces are looked upon as important targets for development of specific diagnostics, inhibitors and vaccines [2,3]. Our laboratory has developed a novel and efficient protocol for synthesis of a variety of rare deoxy amino D-sugars [4]. In this synthetic strategy, changing the sequence of addition of nucleophiles in a series of one-pot double displacement reactions using azide, phthalimide and nitrite ions as nucleophiles and mannose derived 2,4-bistrifluoromethanesulfonates (triflates) as electrophiles enabled rapid access to various orthogonally protected rare deoxy amino sugar building blocks. We also extended the S_N2 double displacement protocol to access deoxy amino L-sugars starting from L-rhamnose and L-fucose [5,6]. The success of the S_N2 displacements depends on the fine tuning of a variety of factors including solvent, temperature, reagent, and stoichiometry. Above all, the relative orientation of substituents on the sugar ring plays a crucial role in controlling the steric and stereo electronic factors [7]. All these factors should be carefully considered while designing a successful S_N2 reaction. In substrates having multiple reaction centres, oftentimes it is possible to position a bulky substituent to block the path of a particular reaction and guide the nucleophile to the desired reaction centre to obtain selectivity. However, it is commonly observed that sterically blocking the S_N2 reaction path of a nucleophile forces it to act as a base and thereby facilitates the competing *E*2 elimination reaction. In the course of our studies on S_N2 displacements of pyranosidic triflates, we serendipitously stumbled upon an interesting cascade elimination reaction that led to the formation of chiral dienes which are difficult to synthesize otherwise. In this note, we give an account of this novel reaction and our mechanistic explorations to understand how the cascade elimination proceeds.

2. Results and discussion

As shown in Scheme 1, treatment of known diol **1** [5] with Tf_2O and pyridine afforded 2,4-bistriflate **2**. Attempted S_N2 displacement of crude bistriflates with nucleophiles such as sodium azide or nitrite ($TBANO_2$, $NaNO_2$) led to elimination product **3** exclusively in very good yields (70–81%, over two steps). The structure of the unexpected diene was confirmed from analysis of ^1H NMR, ^{13}C NMR and 2D spectra (See the supporting information). Specifically, lack of peaks for PMP group, a highly downfield shift of H-1 (7.43 ppm), the appearance of only 4 sugar ring protons (H1, H2, H4, H5) with disappearance of H3 as indicated by COSY spectrum and the presence of 4 carbons in olefinic region (100–160 ppm) helped us to arrive at the unexpected structure.

Although the outcome of this reaction was far from our set goal of nucleophilic displacements leading to rare sugars, we took a moment to rationalize the course of the reaction. A closer inspection of transition state model (Fig. 1) revealed that, for an S_N2 reaction, the approach of a nucleophile from the top face of the pyranose ring at C2 centre is sterically hindered by the axially oriented O-*para*-methoxyphenyl group (OPMP) [5]. Likewise, the nucleophile is not able to achieve S_N2 transition state with the C4-triflate due to the unfavourable 1,3-diaxial

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repulsion from the axially oriented C-2 triflate. This together with equally unfavourable dipole-dipole repulsions practically thwart any chances of nucleophilic displacements. Because the nucleophile is not able to act as a nucleophile, it behaves as a base and finds a favourable antiperiplanar arrangement of C3–H and C2-OTf groups leading to a facile *E*2 elimination generating allylic triflate **4**, which being unstable probably undergoes a swift allylic rearrangement to afford the chiral 5 (*S*) diene **3**.

We anticipated that a similar reaction should take place in D-rhamno and D-manno series. This would allow us to obtain the chiral diene with opposite stereochemistry. For this purpose, we quickly synthesized the requisite D-series substrates as shown in Scheme 2.

Accordingly, D-mannose upon per-*O*-acetylation [8] followed by acid catalysed nucleophilic displacement of anomeric acetate with PMPOH afforded *α*-PMP glycoside **5** exclusively in 78% yield over two steps. The acetate groups were removed under Zemplén conditions using NaOMe in MeOH to obtain tetraol **6** which served as a common intermediate to synthesize substrates **8** and **10**. Regioselective O6 silylation of **6** afforded **7** (98%), which upon regioselective benzoylation in the presence of a highly catalytic amount of Me_2SnCl_2 [9,10] furnished the desired diol **8** in 96% yield. Likewise, regioselective tosylation of **6** followed by LAH reduction gave D-rhamno triol **9**, which upon tin catalysed benzoylation delivered diol **10** in 89% yield.

As expected, diols **8** and **10** upon triflation and attempted S_N2 displacements with azide and nitrite nucleophiles afforded similar dienes **12** and **14** (Scheme 3).

To probe the mechanism of this unusual elimination reaction we conducted a few experiments using $TBANO_2$ mainly due to its better solubility in acetonitrile as compared to the other nucleophiles $NaNO_2$ and NaN_3. We observed that although the pH of the $TBANO_2$ reaction is slightly acidic, conducting the same reaction in basic medium by adding 1.2 equiv of Hünig base had no effect on the course of the reaction. So, protonation may not be a necessary step in the mechanism. To see if radicals are involved, we conducted reaction in the presence of 2.0 equiv of TEMPO radical. This also did not have any effect on the reaction, ruling out the intervention of any radical pathway. In order to isolate or trap any reaction intermediates we conducted the reaction with lesser amount of $TBANO_2$ (Scheme 4). When we used 1.2 equiv of $TBANO_2$ we isolated upon column chromatography an inseparable 1:1 mixture of alkene **4** and diene **3**, along with unreacted bistriflate **2** and triflate hydrolysis product. Use of 2.5 equiv of $TBANO_2$ furnished a similar 1:1 mixture of **3** and **4**; albeit more conversion was seen and the extent of triflate hydrolysis and the unreacted starting material **2** was decreased. These side products viz. alkene **4** and starting material **2** or its hydrolysed product were not encountered when we conducted the reaction using 4 equivalents of $TBANO_2$. These experiments proved that the allylic triflate **4** is the reaction intermediate which being highly reactive gets rearranged to diene **3**. Moreover, both the sequential eliminations **2** → **4** → **3** are mediated by nitrite anions: 4 equivalents are necessary to complete the cascade elimination. So, it remains to see how the nitrite ions or azide ions are converting alkene **4** into diene **3** and how the anomeric functionality is displaced? To answer these questions, we carefully carried out the TLC analyses of reaction mixture. We did not observe any spot related to quinone side product. However, treating the crude mixture with Amberlite acidic resin resulted in a new spot on TLC which matched with para methoxy phenol standard. We isolated it and also confirmed by ^1H NMR. This observation placed the final piece of the puzzle in place, as it was confirmed that *para*-methoxy phenoxide is the side product of this reaction. Based on these experiments, a plausible mechanism is suggested in Scheme 5. Accordingly, 2,4-bistriflate **2** first undergoes an *E*2 elimination to generate allylic triflate **4**, which being highly reactive undergoes nitrite mediated allylic rearrangement to generate intermediate **15**. One more molecule of nitrite ion now attacks the nitrogen centre in **15** to trigger a cascade reaction via elimination of *para*-methoxy phenoxide ion to transiently fashion a bicyclic intermediate, which concomitantly gets dismantled with release of NO_2 gas resulting in the formation of the stable diene **3**. Azide nulecophiles will traverse a similar path.

3. Conclusions

*E*2 elimination is a common competing side reaction alongside an S_N2 reaction. However cascade eliminations are uncommon. In this note, we report a novel transformation of bistriflate **2** to diene **3**, which is not reported so far. The dienes **3** and **14** being a pair of enantiomeric dienes will be very useful in the synthesis of natural products. Diene **12** is C6-OTBDPS analogue of diene **14** and is also a useful synthon as it provides a handle for further functionalization at C6 position of the diene.

4. Experimental

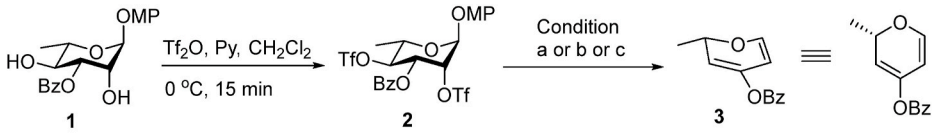
4.1. General methods

All reactions were conducted under the dry nitrogen atmosphere. Solvents (CH_2Cl_2 >99%, THF 99.5%, CH_3CN 99.8%, HMPA 99.5%, DMF 99.5%) were purchased in capped bottles and dried under sodium or CaH_2. All other solvents and reagents were used without further purification. All glassware used was oven dried before use. TLC was performed on pre-coated Aluminium plates of Silica Gel 60 F254 (0.25 mm, E. Merck). Developed TLC plates were visualized under a short-wave UV lamp and by heating plates that were dipped in ammonium molybdate/cerium (IV) sulfate solution. Silica gel column chromatography was performed using Silica Gel (100–200 mesh) and employed a solvent polarity correlated with TLC mobility. NMR experiments were conducted on 500 and 400 MHz instrument using $CDCl_3$ (D, 99.8%) as a solvent. Chemical shifts are relative to the deuterated solvent peaks and are in parts per million (ppm). ^1H–^1H COSY was used to confirm proton assignments. Mass spectra were acquired in the ESI mode. Specific rotation experiments were measured at 589 nm (Na) and 25 °C. IR spectra were recorded on an FT-IR spectrometer.

4.2. Experimental procedures

4.2.1. 4-Methoxyphenyl 3-O-benzoyl-α-L-rhamnopyranoside (1)

Me_2SnCl_2 (22 mg, 0.102 mmol) and DIPEA (0.71 mL, 4.08 mmol) were added to a stirred solution of 4-methoxyphenyl *α*-L-rhamnopyranoside (0.550 g, 2.04 mmol) in THF (5 mL). To this, BzCl (0.4 mL, 3.06 mmol) was added, after 4 h, the reaction mixture was quenched with 1 N HCl (5 mL) and extracted with EtOAc (10 mL x 2). The combined organic



a) $TBANO_2$ (4 equiv), CH_3CN, 12 h, 81%; b) $NaNO_2$ (6 equiv), HMPA, rt, 12 h, 80%;
c) NaN_3 (6 equiv), HMPA, 12 h, 70%

Scheme 1. Serendipitous formation of diene via cascade elimination.

layers were dried over Na_2SO_4, concentrated in vacuo, and purified by silica gel (100–200 mesh) column chromatography (30% ethyl acetate: petroleum ether) to afford **1** as a off-white solid (0.695 g, 92%). $[\alpha]^{25}_D$ −7.46 (c 0.06, $CHCl_3$); IR ($CHCl_3$) ν 3448, 3020, 2929, 2399, 1714, 1656, 1216, 929, 768, 669 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, J = 8.1 Hz, 2H, ArH), 7.62–7.59 (m, 1H, ArH), 7.48–7.46 (m, 2H, ArH), 7.04 (d, J = 9.1 Hz, 2H, ArH), 6.85 (d, J = 8.9 Hz, 2H, ArH), 5.51 (dd, J = 9.9, 3.1 Hz, 1H, H-3), 5.43(bs, 1H, H-1), 4.37 (bs, 1H, H-2), 3.98–3.88 (m, 2H, H-5, H-4), 3.80 (s, 3H, OMe), 1.37 (d, J = 5.9 Hz, 3H, H-6); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 155.0, 150.2, 133.6, 129.9, 129.5, 128.6, 117.6, 114.7, 98.4, 75.3, 71.4, 69.7, 69.4, 55.7, 17.6; HRMS calcd for $C_{20}H_{22}NaO_7$ $[M+Na]^+$ 397.1262, found 397.1258.

4.2.2. 4-Methoxyphenyl 3-O-benzoyl-2,4-bis-triflouromethanesulfonyl-1-α-L-rhamnopyranoside (2)

Triflouromethanesulfonic anhydride (0.23 mL, 1.39 mmol) was added to a solution of compound **1** (0.130 g, 0.35 mmol) in pyridine (0.17 mL, 2.08 mmol) and CH_2Cl_2 (2.0 mL) at 0 °C. After 15 min stirring at the same temperature, the reaction was quenched by addition of ice water and the mixture was extracted with CH_2Cl_2 (15 mL x 2). The combined organic layer was washed with 2 N HCl and aq. $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, and concentrated to give foam product **2**, which was used for the next step without any purification. For the confirmation, NMR characterization has been done for 2,4-bistriflate compound **2**. ^1H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, J = 7.3 Hz, 2H, ArH), 7.66–7.65 (m, 1H, ArH), 7.54–7.51 (m, 2H, ArH), 7.08–7.66 (m, 2H, ArH), 6.91–6.90 (m, 2H, ArH), 6.01 (dd, J = 9.9, 3.1 Hz, 1H, H-3), 5.57 (d, J = 1.3 Hz, 1H, H-1), 5.45–5.44 (m, 1H, H-2), 5.57 (t, J = 9.9 Hz, 1H, H-4), 4.38–4.33 (m, 1H, H-5), 3.82 (s, 3H, OMe), 1.50 (d, J = 6.3 Hz, 3H, H-6); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 155.0, 150.2, 133.6, 129.9, 129.5, 128.6, 117.6, 114.7, 98.4, 75.3, 71.4, 69.7, 69.4, 55.7, 17.6.

4.2.3. (S)-2-Methyl-2H-pyran-4-yl-benzoate (3)

To a solution of the 2,4-bistriflate in acetonitrile (2 mL) was added tetrabutylammonium nitrite (163 mg, 0.56 mmol) at rt. The reaction was kept at stirring for 12 h and then the solvent was evaporated on rotary evaporator. The residue was purified by silica gel (100–200 mesh) column chromatography using 15% EtOAc: pet ether as eluents to give **3** as a yellow viscous compound (41 mg, 81% over 2 steps). Similar results have been observed for the product **3** with the sodium azide in HMPA and $NaNO_2$ in HMPA. $[\alpha]^{25}_D$ −4.48 (c 0.067, $CHCl_3$); IR ($CHCl_3$) ν 3020, 2926, 2400, 1733, 1216, 769, 669, 628 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, J = 7.3 Hz, 2H, ArH), 7.61 (t, J = 7.4 Hz, 1H, ArH), 7.50–7.47 (m, 1H, 1H ArH), 7.43 (d, J = 6.1 Hz, 1H, H-1), 5.68 (d, J = 3.8 Hz, 1H, H-4), 5.56 (d, J = 5.9 Hz, 1H, H-2), 4.86–4.81 (m, 1H, H-5), 1.50 (d, J = 6.7 Hz, 3H, H-6); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 162.5, 133.6, 130.0, 128.9, 128.7, 128.5, 105.4, 77.1, 71.3, 14.2; HRMS calcd. for $C_{13}H_{13}O_3$ $[M+H]^+$ 217.0864, found 217.0859.

4.2.4. 4-Methoxyphenyl 2,3,4,6-tetra-O-acetyl-1-α-D-mannopyranoside (5)

To a mixture of D-mannose (5.0 g, 27.75 mmol) and acetic anhydride (15.7 mL, 166.5 mmol) was added freshly dried $Cu(OTf)_2$ (0.03 mol% of L-rhamnose) at 0 °C under nitrogen. The ice bath was removed, and the mixture was kept for stirring at room temperature for 15 min. When acetylation was completed (confirmed by TLC), PerAc compound was diluted with $CHCl_3$ and washed with $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated. The vacuum dried per-Ac compound was dissolved in dry CH_2Cl_2, and *p*-methoxy phenol (1.1 mL, 10.96 mmol) and $BF_3{\cdot}Et_2O$ (1.3 mL, 10.96 mmol) were sequentially added and the mixture was allowed to stir for 12 h. The reaction was quenched by addition of saturated $NaHCO_3$ and the mixture was extracted with $CHCl_3$ (100 mL x 2). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (20% ethyl acetate: petroleum ether) to afford the desired product **5** as a viscous liquid (74%, 9.30 g). $[\alpha]^{25}_D$ +56.52 (c 0.207, $CHCl_3$); IR ($CHCl_3$) ν 3019, 2400, 1735, 1503, 1422, 1217, 1042, 928, 771, 669, 625 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.96–6.95 (m, 2H, ArH), 6.77–6.75 (m, 2H, ArH), 5.48 (dd, J = 9.9, 3.1 Hz, 1H, H-3), 5.38–5.35 (m, 2H, H-1, H-2), 5.29 (t, J = 9.3 Hz, 1H, H-4), 4.23–4.20 (m, 1H, H-6), 4.09–4.01 (m, 2H, H-5, H-6'), 3.69 (s, 3H, OCH_3), 2.12 (s, 3H, $COCH_3$), 1.99 (s, 3H, $COCH_3$), 1.97 (s, 3H, $COCH_3$), 1.96 (s, 3H, $COCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 169.9, 169.8, 169.7, 155.4, 149.6, 117.8, 114.6, 96.6, 69.4, 68.9, 68.8, 65.9, 62.1, 55.5, 20.8, 20.6; HRMS calcd for $C_{21}H_{26}NaO_{11}$ $[M+Na]$ + 477.1365, found 477.1367.

4.2.5. 4-Methoxyphenyl 6-O-TBDPS-1-α-D-mannopyranoside (7)

To a solution of compound **5** (3.6 g, 9.22 mmol) in anhydrous MeOH (40 mL), NaOMe (0.81 g, 0.5 M) was added at room temperature. After complete consumption of the starting material, Amberlyte $IR120H^+$ (4 g, strong resin) was added to quench the excess sodium methoxide. After stirring for 10 min, the reaction mixture was filtered through funnel and washed with MeOH (100 mL). The solution was concentrated under reduced pressure and the crude product **6** (2.27 g, quant.) was as such used for the next step.

TBDPSCl (0.5 mL) was added to a solution of compound **6** (0.250 g, 0.87 mmol) in Py (2 mL) at 0 °C under nitrogen. The ice bath was removed, and the mixture was kept for stirring at room temperature for 12 h. When reaction was completed (confirmed by TLC), the reaction was diluted with ethyl acetate and quenched by addition of 2 N HCl, and the mixture was extracted with ethyl acetate (30 mL x 2). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (50% ethyl acetate: petroleum ether) to afford the desired product **7** as a viscous liquid (98%, 0.450 g). $[\alpha]^{25}_D$ +50.00 (c 0.14, $CHCl_3$); IR ($CHCl_3$) ν 3418, 3071, 2931, 2857, 1589, 1507, 1217, 1106, 1037, 970, 825, 749, 703, 614 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68–7.66 (m, 4H, ArH), 7.45–7.35 (m, 4H, ArH), 6.97–6.95 (m, 2H, ArH), 6.79–6.77 (m, 2H, ArH), 5.41 (s, 1H, H-1) 4.15–4.13 (m, 1H, H-2) 4.07 (dd, J = 9.2, 2.6 Hz, 1H, H-3), 3.97–3.89 (m, 3H, H-4, H-5, H-6'), 3.83–3.79 (m, 1H, H-6), 3.77 (s, 3H, OCH_3), 1.06 (s, 9H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.9, 150.2, 135.6, 135.6, 132.8, 129.9, 127.84, 127.8, 117.9, 114.6, 98.6, 71.5, 71.3, 71.2, 70.4, 70.2, 70.1, 65.0, 55.6, 26.8, 19.2; HRMS calcd for $C_{29}H_{36}NaO_7Si$ $[M+Na]$ + 547.2122, found 547.2123.

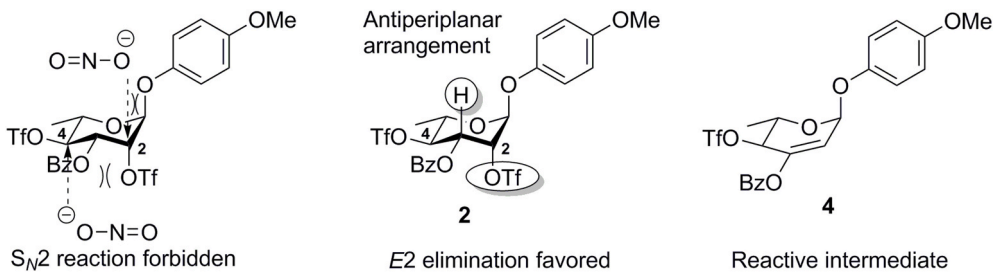
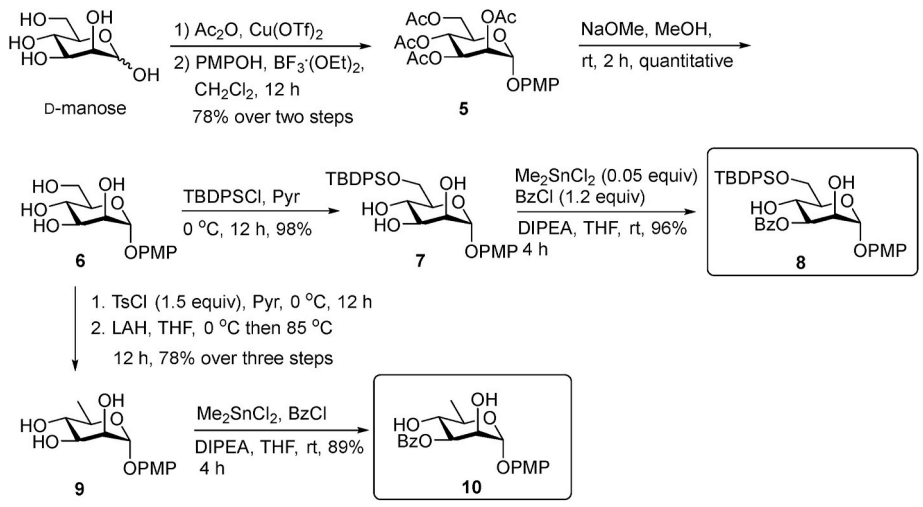
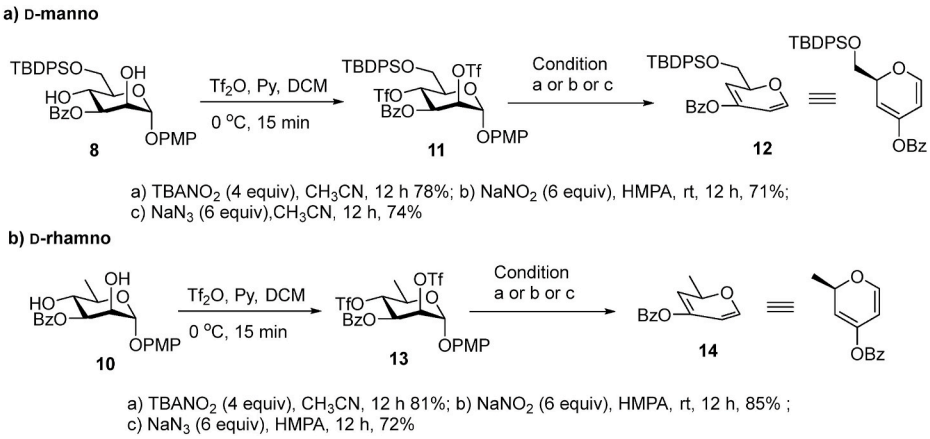


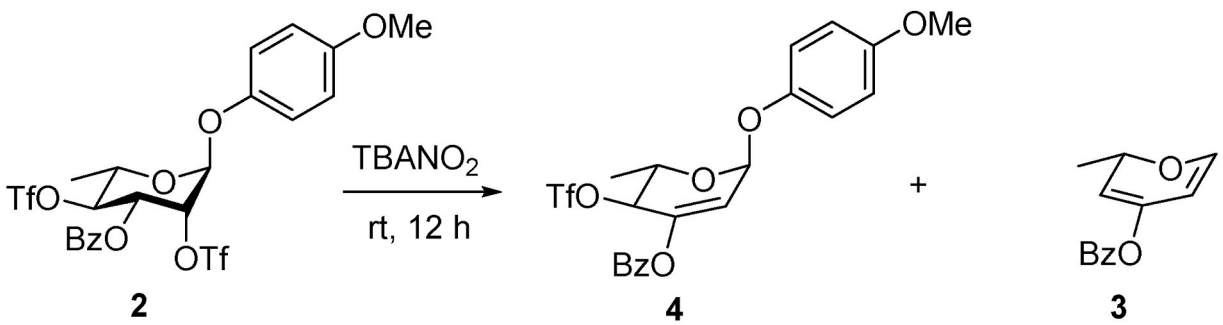
Fig. 1. Transition states for S_N2 Vs *E*2 reaction in **2**.



Scheme 2. Synthesis of D-manno and D-rhamno substrates.



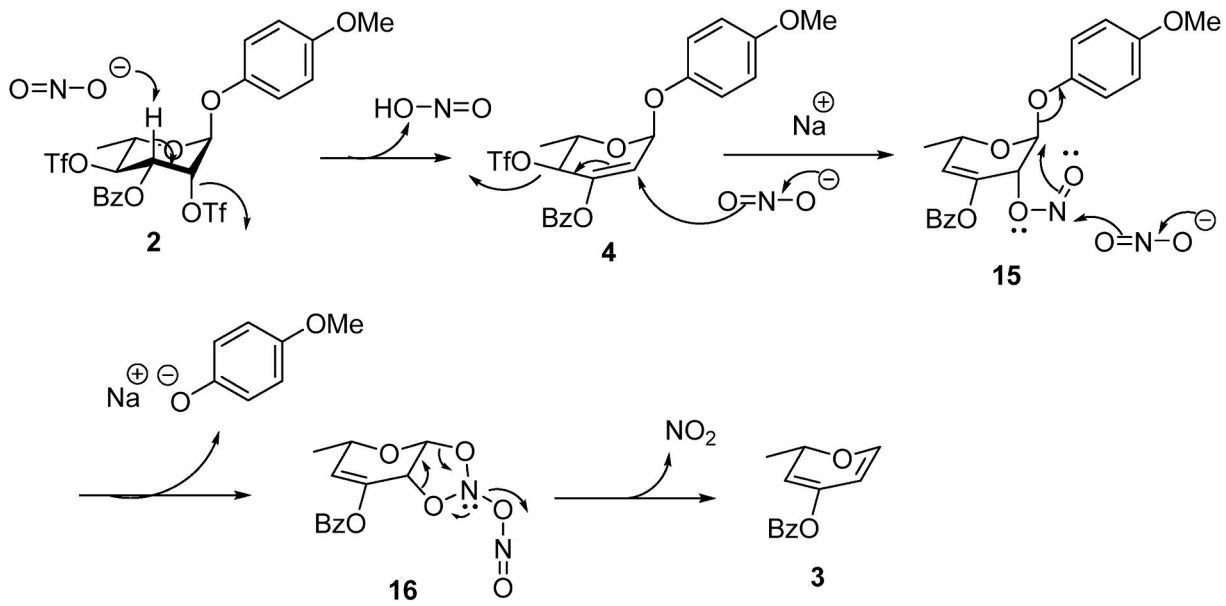
Scheme 3. Cascade eliminations in D-manno and D-rhamno series.



Scheme 4. Effect of reagent stoichiometry on elimination.

4.2.6. 4-Methoxyphenyl 3-O-benzoyl-6-O-TBDPS-1-α-D-mannopyranoside (8)

Me_2SnCl_2 (8.2 mg, 0.04 mmol) and DIPEA (0.30 mL, 1.49 mmol) were added to a stirred solution of **7** (0.390 g, 0.744 mmol) in THF (4 mL). To this, BzCl (0.13 mL, 1.12 mmol) was added, after 4 h, the reaction mixture was quenched with 1 N HCl (5 mL) and extracted with EtOAc (30 mL x 2). The combined organic layers were dried over Na_2SO_4, concentrated in vacuo, and purified by silica gel (100–200 mesh) column chromatography (30% ethyl acetate: petroleum ether) to afford **8** as a off-white solid (0.450 g, 96%). $[\alpha]^{25}_D$ +42.99 (c 0.107, $CHCl_3$); IR ($CHCl_3$) ν 3479, 3071, 3014, 2932, 2857, 1716, 1601, 1563, 1507, 1273, 1220, 1111, 1035, 826, 761, 667, 615 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.17–8.15 (m, 2H, ArH), 7.72–7.69 (m, 4H, ArH), 7.49–7.39 (m, 9H, ArH), 7.05–7.03 (m, 2H, ArH), 6.82–6.80 (m, 2H, ArH), 5.60 (dd, $J = 9.7$, 3.1 Hz, 1H, H-3), 5.45 (d, $J = 1.6$ Hz, 1H, H-1), 4.37–4.36 (m, 1H, H-2), 4.31 (t, $J = 9.3$ Hz, 1H, H-4), 3.99–3.95 (m, 3H, H-5, H-6, H-6'), 3.78 (s, 3H, OCH_3), 1.09 (s, 9H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 155.1, 150.2, 135.7, 135.6, 133.5, 133.0, 132.9, 132.98, 132.6, 130.0, 129.9,129.7, 128.5, 128.2, 127.8, 127.7, 117.9, 114.6, 98.7, 74.9, 72.6, 69.3, 67.3, 64.5, 55.7, 26.9, 19.2; HRMS calcd. for $C_{36}H_{40}NaO_8Si$ $[M+Na]^+$ 651.2383, found 651.2385.



Scheme 5. Proposed reaction mechanism.

4.2.7. 4-Methoxyphenyl 1-α-D-rhamnopyranoside (9)

TsCl (1.99 g, 10.48 mmol) was added to a solution of compound **6** (2.0 g, 6.99 mmol) in Py (20 mL) at 0 °C under nitrogen. The mixture was kept for stirring for 12 h. When reaction was completed (confirmed by TLC), the reaction was diluted with ethyl acetate and quenched by addition of 2 N HCl, the mixture was extracted using ethyl acetate (100 mL x 2). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The dried tosyl compound (3.0 g, 6.81 mmol) was dissolved in dry THF (15 mL) and slowly added through canula into a solution of LAH (0.776 g, 20.43 mmol) in THF (15 mL) at 0 °C under nitrogen. After the addition, the reaction was set for stirring at 85 °C for 6 h. After completion of reaction, LAH was quenched using ethyl acetate and 2 N H_2SO_4. The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (70% ethyl acetate: petroleum ether) to afford the desired product **9** as a white solid (71%, 1.33 g). $[\alpha]^{25}_D$ +100.65 (c 0.153, $CHCl_3$); IR ($CHCl_3$) ν 3778, 3682, 3369, 2931, 1618, 1508, 1448, 1219, 1108, 1040, 983, 827, 749 cm^{-1}; ^1H NMR (500 MHz, MeOD) δ 6.89–6.87 (m, 2H, ArH), 5.19 (d, J = 1.3 Hz, 1H, H-1) 3.90–3.88 (m, 1H, H-2), 3.73 (dd, J = 9.5, 3.4 Hz, 1H, H-3), 3.63 (s, 3H, OCH_3), 3.60–3.57 (m, 1H, H-5), 3.35 (t, J = 9.5 Hz, 1H, H-4), 2.1–2.0 (m, 1H, OH), 1.13 (d, J = 6.2 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, MeOD): δ 155.4, 150.8, 117.8, 114.5, 99.6, 72.8, 71.2, 71.1, 69.4, 55.0, 17.0; HRMS calcd for $C_{13}H_{18}O_6Na$ $[M+Na]^+$ 293.1014, found 293.0996.

4.2.8. 4-Methoxyphenyl 3-O-benzoyl-α-D-rhamnopyranoside (10)

Me_2SnCl_2 (29 mg, 0.13 mmol) and DIPEA (0.92 mL, 5.26 mmol) were added to a stirred solution of triol **9** (0.710 g, 2.63 mmol) in THF (8 mL). To this, BzCl (0.5 mL, 3.95 mmol) was added, after 4 h, the reaction mixture was quenched with 1 N HCl (5 mL) and extracted with EtOAc (30 mL x 2). The combined organic layers were dried over Na_2SO_4, concentrated in vacuo, and purified by silica gel (100–200 mesh) column chromatography (30% ethyl acetate: petroleum ether) to afford **10** as an off-white solid (0.860 g, 89%). $[\alpha]^{25}_D$ +118.00 (c 0.20, $CHCl_3$); IR ($CHCl_3$) ν 3457, 2935, 1704, 1507, 1451, 1316, 1280, 1215, 1113, 1028, 984, 829, 751, 713 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.11–8.10 (m, 2H, ArH), 7.61–7.58 (m, 1H, ArH), 7.47–7.44 (m, 2H, ArH), 7.04–7.02 (m, 2H, ArH), 6.85–6.83 (m, 2H, ArH), 5.50 (dd, J = 9.5, 3.2 Hz, 1H, H-3), 5.42 (d, J = 1.7 Hz, 1H, H-1), 4.37–4.36 (m, 1H, H-2), 3.96–3.89 (m, 2H, H-5, H-4), 3.80 (s, 3H, OMe), 1.36 (d, J = 5.9 Hz, 3H, H-6); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 155.0, 150.2, 133.6, 129.9, 129.5, 128.6, 117.6, 114.7, 98.4, 75.2, 71.3, 69.7, 69.3, 55.7, 17.6; HRMS calcd. for $C_{20}H_{22}NaO_7$ $[M+Na]^+$ 397.1256, found 397.1258.

4.2.9. 4-Methoxyphenyl 3-O-benzoyl-6-O-TBDPS-2,4-bis-triflouromethanesulfonyl-1-α-D-mannopyranoside (11)

Triflouromethanesulfonic anhydride (0.15 mL, 0.89 mmol) was added to a solution of compound **8** (0.140 g, 0.22 mmol) in pyridine (0.11 mL, 1.34 mmol) and CH_2Cl_2 (2.0 mL) at 0 °C. After 15 min stirring at the same temperature, the reaction was quenched by addition of ice water and the mixture was extracted with DCM (15 mL x 2). The combined organic layer was washed with 2 N HCl and aq. $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, and concentrated to give foam product **11**, which was used for the next step without any purification. For confirmation NMR characterization has been done for 2,4-bistriflate compound. ^1H NMR (500 MHz, $CDCl_3$) δ 8.21–8.19 (m, 2H, ArH), 7.79–7.66 (m, 4H, ArH), 7.57–7.42 (m, 9H, ArH), 6.89–6.88 (m, 2H, ArH), 6.82–6.79 (m, 2H, ArH), 6.01 (dd, J = 10.1, 3.1 Hz, 1H, H-3), 5.82 (t, J = 9.9 Hz, 1H, H-4), 5.50 (d, J = 1.5 Hz, 1H, H-1), 5.47–5.46 (m, 1H, H-2), 4.15–3.86 (m, 3H, H-5, H-6, H-6'), 3.80 (s, 3H, OCH_3), 1.15 (s, 9H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 155.8, 149.1, 136.2, 135.6, 134.2, 133.1, 132.7, 130.6, 130.3, 129.9, 129.8, 128.9, 128.7, 127.8, 127.7, 127.6, 117.4, 114.8, 95.6, 81.5, 75.7, 70.6, 68.2, 60.8, 55.7, 26.6, 19.2.

4.2.10. (R)-2-(Tertbutyl diphenyl silyloxy methyl)-2H-pyran-4-yl-benzoate (12)

To a solution of the 2,4-bistriflate (0.108 g, 0.121 mmol) in acetonitrile (1.5 mL) was added tetrabutylammonium nitrite (83.5 mg, 0.56 mmol) at rt. The reaction kept at stirring for 12 h and then solvent was evaporated on rotary evaporator. The residue was purified by silica gel (100–200 mesh) column chromatography using 10% EtOAc: pet ether as eluents to give **12** as a yellow viscous compound (41 mg, 81% over 2 steps). Similar results have been observed for the product **12** with the sodium azide in HMPA and $NaNO_2$ in HMPA. $[\alpha]^{25}_D$ +58.33 (c 0.20, $CHCl_3$); IR ($CHCl_3$) ν 3019, 2400, 1734, 1216, 1046, 924, 766, 669 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68–7.60 (m, 5H, ArH), 7.47–7.44 (m, 3H, ArH), 7.40–7.36 (m, 4H, ArH), 7.35 (d, J = 6.1 Hz, 1H, H-1), 7.31–7.29 (m, 3H, ArH), 5.89 (d, J = 4.8 Hz, 1H, H-4), 5.49 (d, J = 6.1 Hz, 1H, H-2), 4.79–4.76 (m, 1H, H-5), 4.07–3.97 (m, 2H, H6 & H6'),

1.05 (s, 9H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.5, 164.8, 162.0, 135.6, 135.5, 133.5, 132.6, 132.5, 130.3, 130.1, 129.9, 129.8, 128.9, 128.6, 128.5, 127.8, 127.7, 105.6, 80.6, 68.7, 61.2, 26.6, 19.1; HRMS calcd. for $C_{29}H_{31}O_4Si$ $[M+H]^+$ 471.1982, found 471.1986.

4.2.11. 4-Methoxyphenyl 3-O-benzoyl-2,4-bis-triflouromethanesulfonyl-1-α-D-rhamno pyranoside (13)

Triflouromethanesulfonic anhydride (0.23 mL, 1.39 mmol) was added to a solution of compound **10** (0.130 g, 0.35 mmol) in pyridine (0.17 mL, 2.08 mmol) and CH_2Cl_2 (2.0 mL) at 0 °C. After 15 min stirring at the same temperature, the reaction was quenched by addition of ice water and the mixture was extracted with CH_2Cl_2 (15 mL x 2). The combined organic layer was washed with 2 N HCl and aq. $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, and concentrated to give foam product **13**, which was used for the next step without any purification. For the confirmation NMR characterization has been done for 2,4-bistriflate compound **13**. ^1H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, $J = 7.3$ Hz, 2H, ArH), 7.68–7.65 (m, 1H, ArH), 7.54–7.51 (m, 2H, ArH), 7.08–7.66 (m, 2H, ArH), 6.91–6.90 (m, 2H, ArH), 6.01 (dd, $J = 10.3$, 3.2 Hz, 1H, H-3), 5.57 (d, $J = 1.3$ Hz, 1H, H-1), 5.45 (bs, 1H, H-2), 5.11 (t, $J = 9.9$ Hz, 1H, H-4), 4.38–4.33 (m, 1H, H-5), 3.82 (s, 3H, OMe), 1.50 (d, $J = 6.2$ Hz, 3H, H-6); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 155.9, 149.1, 134.2, 130.2, 128.6, 127.8, 119.6, 119.4, 117.7, 117.0, 116.9, 114.9, 95.7, 82.1, 81.9, 67.8, 66.5, 55.7, 17.3.

4.2.12. (R)-2-Methyl-2H-pyran-4-yl-benzoate (14)

To a solution of the 2,4-bistriflate (0.135 g, 0.21 mmol) in acetonitrile (2 mL) was added tetrabutylammonium nitrite (146 mg, 0.51 mmol) at rt. The reaction was kept at stirring for 12 h and then the solvent was evaporated on rotary evaporator. The residue was purified by silica gel (100–200 mesh) column chromatography using 15% EtOAc: pet ether as eluents to give **14** as a yellow viscous compound (38 mg, 83% over 2 steps). Similar results have been observed for the product **14** with the sodium azide in HMPA and $NaNO_2$ in HMPA. $[\alpha]^{25}_D$ +22.22 (c 0.027, $CHCl_3$); IR ($CHCl_3$) ν 3696, 3019, 2929, 2398, 1732, 1216, 929, 768, 669, 628 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, $J = 7.3$ Hz, 2H, ArH), 7.61 (t, $J = 7.4$ Hz, 1H, ArH), 7.49–7.47 (m, 1H, 1H ArH), 7.43 (d, $J = 6.1$ Hz, 1H, H-1), 5.67 (d, $J = 3.9$ Hz, 1H, H-4), 5.56 (d, $J = 6.1$ Hz, 1H, H-2), 4.86–4.81 (m, 1H, H-5), 1.50 (d, $J = 6.8$ Hz, 3H, H-6); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 162.5, 133.6, 130.0, 128.7, 128.5, 105.4, 77.1, 71.3, 14.2; HRMS calcd. for $C_{13}H_{13}O_3$ $[M+H]^+$ 217.0859, found 217.0859.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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