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General strategy for the synthesis of unsaturated carbasugars *via* a diastereoselective *seleno*-Michael/aldol reaction†

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Carbasugars are a diverse group of carbohydrate mimetics in which the ring oxygen is replaced by a methylene group. We have developed a simple and efficient carbasugar synthesis from D-aldopentoses *via* temporary protection of the hydroxyl moieties with TMS groups followed by consecutive intramolecular tandem Michael/aldol cyclisation. It is important to note that only the *n*-butylselenolate nucleophile is compatible with per-*O*-TMS-protected substrates. The desired products were obtained in five steps, with total yields reaching up to 40% with excellent diastereoselectivity of up to 19 : 1.

1 Introduction

Natural and synthetic carbasugars have demonstrated intriguing biological activities.[1–5] Since the 1960s, when McCasland and his team synthesised a series of derivatives in which the oxygen atom in the monosaccharide ring was substituted with a methylene group, coining the term 'pseudosugars' to describe these compounds, interest in carbasugars has grown steadily.[6–8] McCasland proposed that its structural similarity to parent sugars could enhance the recognition by enzymes or other biological systems as substitutes for natural sugars. The precise synthesis of polyhydroxylated carbasugars remains a compelling and complex challenge in organic chemistry due to factors such as structural intricacy, ring size and strain, functional group characteristics, stereochemical control, selection of synthetic approaches, and absence of straightforward synthetic pathways (Fig. 1).

Over the past two decades, numerous innovative methods have been developed, including aldol reactions,[9] Mukaiyama cyclization,[10] ring-closing metathesis (RCM),[11–14] transition metal catalysis,[15–17] and chemoenzymatic processes.[18] An alternative strategy involves using readily available natural substrates, such as polyalcohols[19,20] or gluconolactone.[21,22] However, these methods often require extensive and inefficient

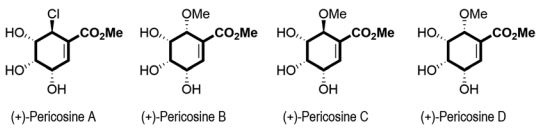
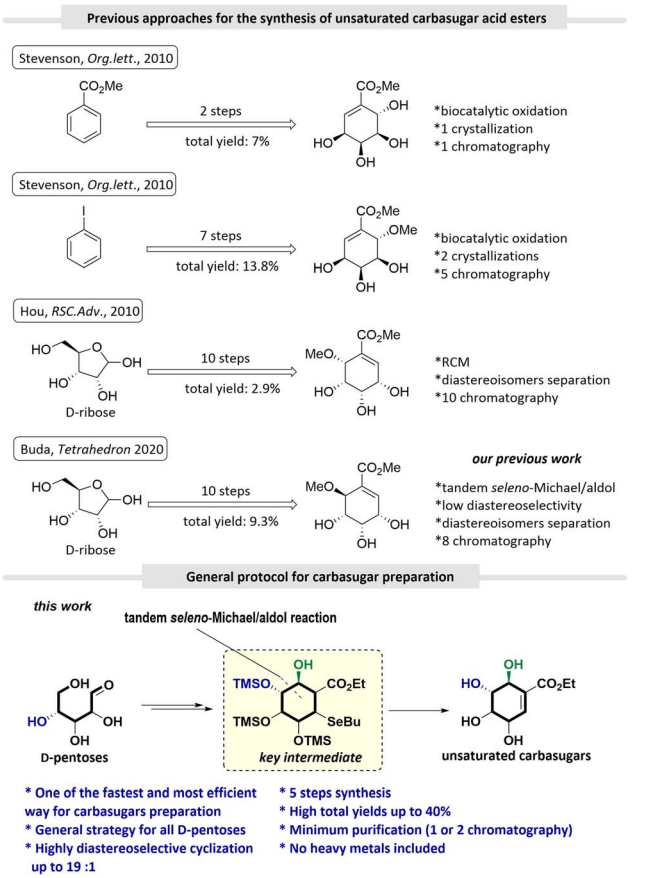


Fig. 1 Structures of pericosines A–D, examples of important unsaturated carbasugars.



Scheme 1 Examples of the previous synthetic routes leading to carbasugar acid esters and the proposed utilisation of trimethylsilyl ethers as a temporary protecting group shorten the overall process.

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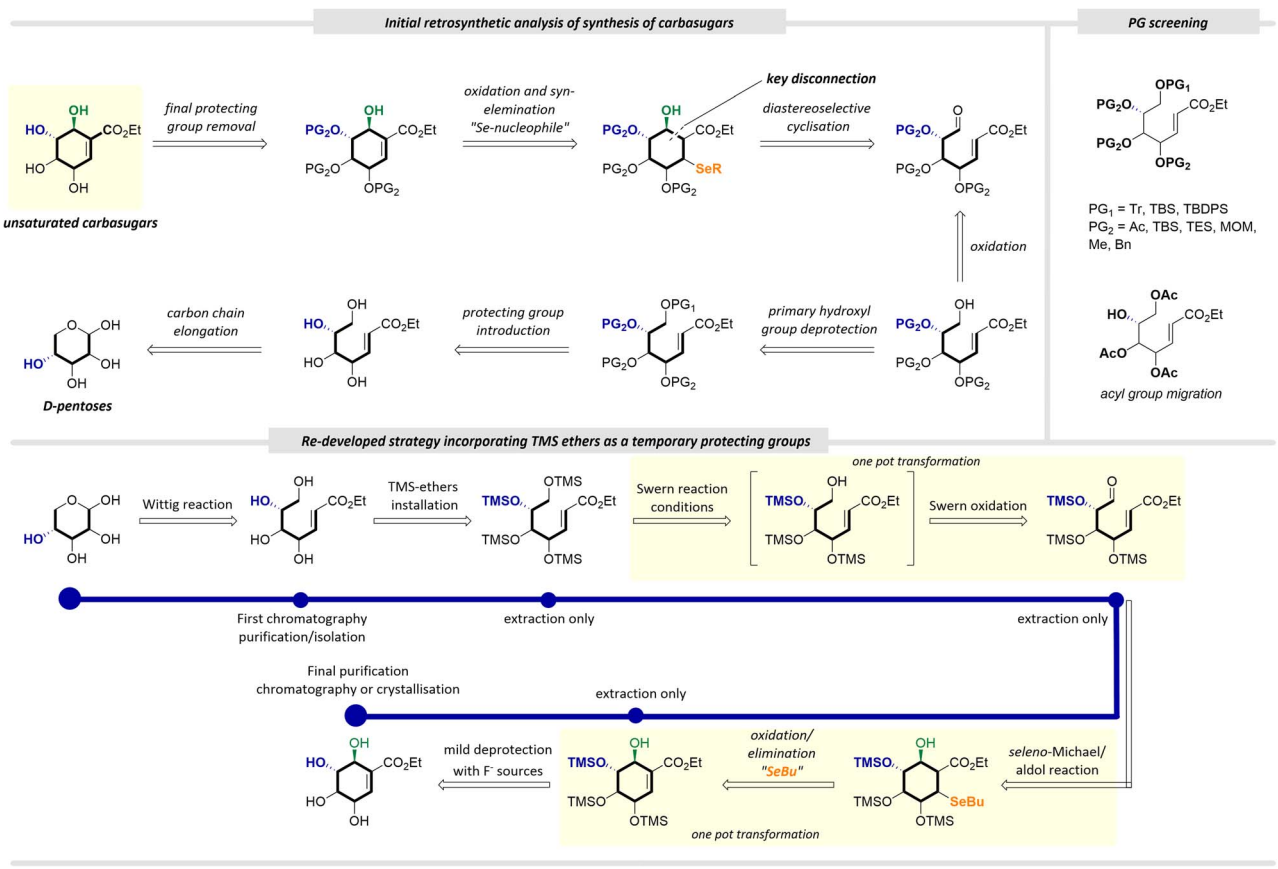
manipulation of protective groups. In response to these challenges, we introduce a practical approach to synthesising natural products using an intramolecular tandem *seleno*-Michael/aldol reaction.[23] Within the carbasugar family, unsaturated carbasugar acid esters hold significant biological importance. Pericosines A to C were initially isolated as metabolites of the fungus *Periconia byssoides*, located in the gastrointestinal tract of the sea hare *Aplysia kurodai*.[24] These compounds have attracted substantial interest due to their cytotoxicity against P388 lymphocytic leukemia cells, antitumor activity against murine P388 cells, and selective growth inhibition of human cancer cell lines HBC-5 and SNB-75.[25,26] Stevenson *et al.* proposed a concise, albeit inefficient, synthesis of pericosine derivatives utilising the biocatalytic oxidation of benzene derivatives.[18,27] Hou later employed a general method for carbasugar synthesis based on a ring-closing metathesis (RCM) protocol.[12] However, this approach was inefficient, requiring purification after almost every part of the 10-step synthesis. In our earlier work, we developed a total synthesis of pericosine derivatives using an intramolecular *seleno*-Michael/aldol reaction starting from D-pentose. While effective, this methodology had limitations, including lengthy substrate preparation, poor diastereoselective control during ring closure, the need for benzyl group protection, and harsh conditions for subsequent deprotection.[28] Here, we present an improved methodology for the total synthesis of carbasugars *via* a *seleno*-Michael/aldol reaction, incorporating the labile TMS protecting group. This modification significantly enhances efficiency, reduces the number of synthetic steps, achieves excellent diastereoselective control during ring closure, and minimises chromatography to only two purification steps (Scheme 1).

2 Results

Based on our retrosynthetic analysis (Scheme 2), we planned to prepare the carbasugar core according to the tandem *seleno*-Michael/aldol reaction protocol connected with oxidation and elimination of the selenium nucleophile. We have successfully achieved this transformation for several carbasugar molecules.[23,28,29] The previously described protocols suffered from only moderate or poor diastereoselectivity, long substrate preparation, and harsh conditions for deprotection of the OBn ethers in the presence of the double bond. Our initial strategy involved the application of an orthogonal protection group approach. As a model system for this optimisation, we chose the D-arabinose derivative (**6**), because it was the only crystalline material of the series. The installation of the bulky protective group ($\mathbf{PG_1}$) was successfully achieved for both Tr or TBDPS, but later we found that only acetyl ester was able to the fully attach to remaining hydroxyl group ($\mathbf{PG_2}$). Unfortunately, we found that the next step, the deprotection of the bulky primary ether, provided a complex mixture of the isomers as a result of the

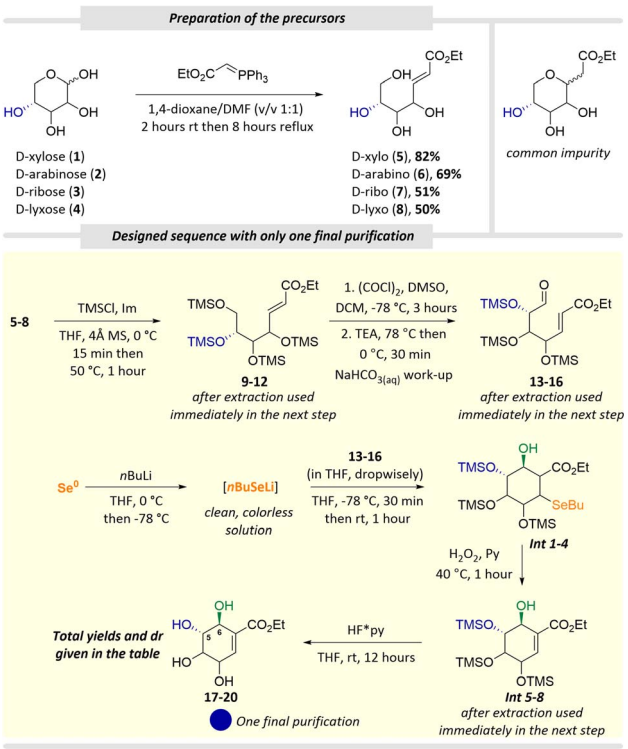


Scheme 2 Initial retrosynthetic analysis of the carbasugar synthesis, and revised concept incorporating trimethylsilyl ethers as protecting groups.

migration of secondary acetyl ester to the primary alcohol. Thus, we revised our strategy and decided to install labile TMS groups on each of the hydroxyl moieties, with the hope that the primary hydroxy component could be selectively deprotected later. After initial difficulties related to the bulky character of the TMS ethers (ESI, Table 1, entry 8†), we found that the addition of molecular sieves and the heating of the reaction mixture to 50 °C allowed us to successfully synthesise the tetra-*O*-TMS derivative (**10**). However, subjecting the per-*O*-silylated derivative directly to Swern conditions (typically −78 °C, 30 min) initially did not lead to complete deprotection of the primary hydroxyl group and also did not fully oxidise. The extension of the initial time from 30 minutes to 3 hours fortunately solved this problem, resulting in only one major product after oxidation (only one major spot in the TLC; other analyses were not possible due to the instability of the molecule). Having established a methodology for the preparation of a carbasugar precursor, we turned our attention to the practical aspect of the transformation by using other D-aldopentoses derivatives.

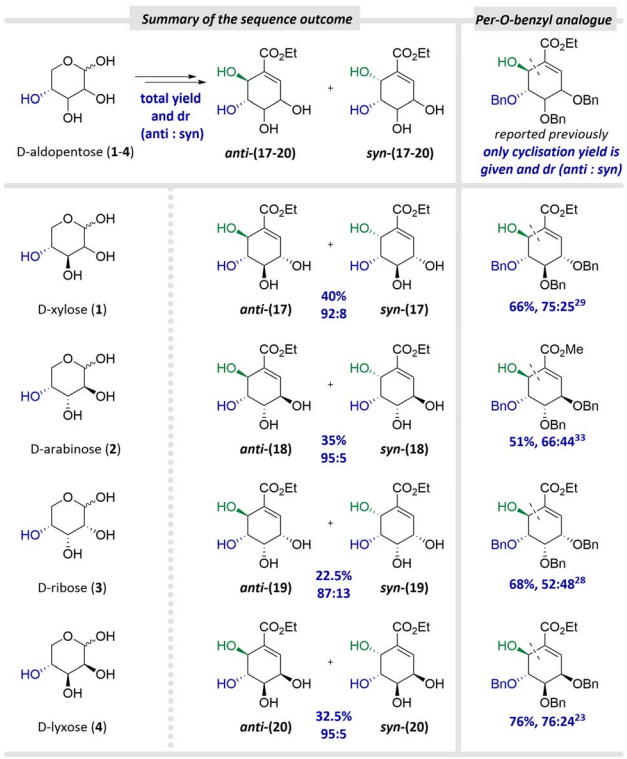
Starting from other commercially available monosaccharides, the reaction of pure D-aldopentoses (**1–4**) with ethyl (triphenylphosphoranylidene)acetate resulted mainly in *E*-unsaturated Wittig products (**5–8**) with yields ranging from 50% to 83%. Most of those transformations suffered from oxo-Michael side products, which were particularly visible for the D-ribo (**7**) and D-lyxo (**8**) derivatives, which significantly decreased the reaction yields (Scheme 3).

Adapting our revised concept of the formation of the derivatives (**9–12**), we subjected the Wittig reaction's product (**5–8**) to the mixture of trimethylsilyl chloride (TMSCl) and imidazole, which successfully accomplished the quadruple protection. Purification of compounds **9–12** was not possible due to the instability of the *O*-TMS group however, they were all sufficiently pure by TLC with only one major spot being observed. Then, the crude per-*O*-silylated olefin (**9–12**) was added to the activated DMSO/oxalyl chloride mixture at −78 °C. The selective primary TMS deprotection followed by the Swern oxidation conditions gave almost quantitatively pure aldehydes **13–16**.[30,31] The crucial cyclization was achieved by the *seleno*-Michael/aldol reaction with the oxidation/elimination process. Per-*O*-silylated aldehydes **13–16** were added to *n*-BuSeLi (generated *in situ* from Se^0 and *n*BuLi) at −78 °C.[30,31] After complete substrate consumption, we treated the reaction mixture with excess H_2O_2 in the presence of pyridine. The oxidation–elimination process of unstable selenide (**Int 1–4**) provides the desired protected 5a-carbasugar derivatives (**Int 5–8**). Aqueous work-up gave a complex mixture of partially protected products. Therefore, a crude mixture of the cyclic product was dissolved in THF and treated with an excess of the Olah reagent (HF·Py). The commercially available TBAF solution in THF gave only partial deprotection of the TMS groups. The deprotected products were purified by column chromatography or crystallisation. It is noteworthy that chromatographic purification was not needed in all cases until the last step.



Scheme 3 Total syntheses of unsaturated carbasugars.

Table 1 Summary of the total synthesis of unsaturated carbasugars[a,b,c]



[a] Diastereoisomeric ratios were assigned based on ^{1}H NMR of the crude reaction mixtures after the final step. [b] Relative configuration of C5 and C6 stereogenic centers were assigned by analogy to previously synthesized per-*O*-benzylated derivatives or known derivatives and confirmed by selected 2D-NMR spectra (see: ESI). [c] Configuration of **18** was additionally confirmed by detailed analysis of the NOESY spectra.

As presented in Table 1, products **17–20** were obtained as diastereoisomeric mixtures with very good or excellent selectivity. The lowest selectivity was observed with **19** (Table 1, entry 3) and is correlated with the *cis*-conformation of all hydroxyl groups from the monosaccharide. The diastereomeric ratio was determined by ^{1}H-NMR analysis and the main pure isomers were isolated by column chromatography. A detailed analysis of the NOESY spectra of compound **18** was needed due to the inconsistent assignment. A strong NOE effect was observed that confirmed the interaction between the H5–H6 proton pair. Furthermore, the structure of **18** was confirmed with the assignment to (6*S*)-6-hydroxy-4-*epi*-shikimic acid reported by Griesbeck.[32]

3 Conclusions

In conclusion, several polyhydroxylated cyclohex-1-ene carboxylated esters were prepared in a versatile manner from commercially available monosaccharides in good to excellent overall yields in a 5-step synthesis. The high diastereoselectivity of the cyclization reaction gave access to products with good diastereoselectivity (up to 19 : 1) on a gram scale. The use of TMS groups increased selectivity compared to those of benzyl ethers.[33] The TMS protected D-xylose moiety gave more than 10 : 1 *anti*/*syn* compared to the Bn protected substrate (up to 4 : 1 *anti*/*syn*). Even better results were observed for D-lyxose (*anti*/*syn*: TMS = 20 : 1 *vs.* Bn = 3 : 1). Our methodology is an interesting alternative to the known methods of carbasugar synthesis with significant improvements in terms of shorter reaction times and substrate scope. The efficiency and reduction of the purification steps are noticeable.

4 Experimental

4.1 General information

All starting materials and reagents were purchased from commercial sources and used without purification. Reactions were controlled using TLC on silica [aluplates (0.2 mm)]. The plates were visualised with UV light (254 nm) and treated with an aqueous cerium(IV) sulphate solution with molybdic and sulfuric acid followed by heating. All organic solutions were dried over anhydrous magnesium sulfate. The reaction products were purified by column chromatography using silica gel 60 (240–400 mesh). Optical rotations were measured at room temperature with a digital polarimeter. $CDCl_3$, D_2O, and CD_3OD were used as NMR solvents. ^{1}H spectra were recorded at 600 and 300 MHz and referenced relative to: $CDCl_3$ – residual solvent peak ($\delta = 7.26$ ppm); D_2O – residual solvent peak ($\delta = 4.79$ ppm); CD_3OD – solvent residual peak (δ = 3.31 ppm). Data are reported as follows: chemical shift in parts per million (ppm), multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, m = multiplet), coupling constants (in hertz) and integration. ^{13}C NMR spectra were measured at 150 and 75 MHz with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard: $CDCl_3$ (δ = 77.16 ppm); CD_3OD (δ = 49.00 ppm). High-resolution mass spectra were acquired using the ESI-TOF method.

4.2 General procedure for Wittig reaction

To a solution of (ethoxycarbonylmethylene)-triphenylphosphorane (3.02 g, 8.6 mmol) in anhydrous dioxane/DMF (v/v 1 : 1, 40 ml), D-aldopentose (1.00 g, 6.6 mmol) was added. The mixture was stirred under an atmosphere of argon at room temperature for 2 h, then warmed to 80 °C and stirred for 4 h. The resulting clear solution was concentrated *in vacuo* to give a semisolid residue. Water (25 ml) and methylene chloride (25 ml) were added. After phase separation, the organic layer was extracted a second time with water (25 ml). The combined water layers were washed twice with methylene chloride (2 × 25 ml). The water phase was concentrated under reduced pressure and the crude product was purified by crystallisation from ethanol or by column chromatography.

4.3 (*E*/*Z*)-(4*S*,5*R*,6*R*)-Ethyl 4,5,6,7-tetrahydroxy-hept-2-enoate (from D-xylose) (5)

The crude product was purified by column chromatography (chloroform/MeOH 3 : 1) to give the pure product as a colourless oil as a mixture of diastereoisomers *E*/*Z* > 95/5 (based on ^{1}H NMR spectra). Yield = 83% (1.21 g, 5.48 mmol); $[\alpha]_D^{26} = -17.6$ (c 0.5, MeOH); ^{1}H NMR (for *E* diastereoisomer) (600 MHz, D_2O) δ 7.03 (dd, J = 15.7, 5.3 Hz, 1H), 6.17 (dd, J = 15.8, 1.6 Hz, 1H), 4.49 (td, J = 5.3, 1.5 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 3.80–3.76 (m, 1H), 3.71 (dd, J = 11.7, 4.6 Hz, 1H), 3.69–3.63 (m, 2H), 3.35 (s, 1H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (for *E* diastereoisomer) (151 MHz, D_2O) δ 168.5, 147.4, 121.8, 72.8, 71.4, 71.3, 62.5, 61.7, 13.2.

4.4 (*E*)-(4*R*,5*S*,6*R*)-Ethyl 4,5,6,7-tetrahydroxy-hept-2-enoate (from D-arabinose) (6)

The crude product was purified by crystallisation from ethanol to give the pure product as white crystals. Yield = 69% (1.02 g, 4.61 mmol); $[\alpha]_D^{26} = +16.2$ (c 0.5, MeOH); mp 136–138 °C; ^{1}H NMR (600 MHz, D_2O) δ 7.07 (dd, J = 15.8, 4.6 Hz, 1H), 6.17 (dd, J = 15.8, 1.7 Hz, 1H), 4.69–4.59 (m, 1H), 4.24 (q, J = 7.1 Hz, 2H), 3.84 (dd, J = 11.8, 2.9 Hz, 1H), 3.81–3.75 (m, 1H), 3.71–3.62 (m, 2H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, D_2O) δ 168.6, 149.1, 121.2, 72.5, 70.8, 69.9, 62.8, 61.7, 13.2.

4.5 (*E*)-(4*S*,5*S*,6*R*)-Ethyl 4,5,6,7-tetrahydroxy-hept-2-enoate (from D-ribose) (7)

The crude product was purified by three consecutive column chromatographies (2 times chloroform/MeOH 3 : 1 and finally AcOEt/MeOH/H_2O 5 : 1 : 0.1) to give the pure product as white crystals. Yield = 51% (0.74 g, 3.37 mmol); $[\alpha]_D^{26} = -32.5$ (c 0.5, MeOH); mp 68.5–70 °C; ^{1}H NMR (600 MHz, D_2O) δ 7.08 (dd, J = 15.8, 5.5 Hz, 1H), 6.16 (dd, J = 15.8, 1.4 Hz, 1H), 4.61–4.57 (m, 1H), 4.24 (q, J = 7.1 Hz, 2H), 3.83–3.75 (m, 2H), 3.69–3.62 (m, 2H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, D_2O) δ 168.4, 146.4, 122.1, 73.5, 71.6, 71.0, 62.6, 61.7, 13.2; HRMS (ESI): calcd for $C_9H_{16}NaO_6$ $[M + Na]^+$ 243.0839, found 243.0836.

4.6 (*E*)-(4*R*,5*R*,6*R*)-Ethyl 4,5,6,7-tetrahydroxy-hept-2-enoate (from D-lyxose) (8)

The crude product was purified by three consecutive column chromatographies (2 times chloroform/MeOH 3 : 1 and finally AcOEt/MeOH/H_2O 5 : 1 : 0.1) to give the pure product as white crystals. Yield = 50% (0.73 g, 3.33 mmol); $[\alpha]_D^{26}$ = +36.7 (c 0.5, MeOH); mp 83.5–85 °C; ^{1}H NMR (600 MHz, D_2O) δ 7.13 (dd, J = 15.8, 5.4 Hz, 1H), 6.16 (dd, J = 15.8, 1.5 Hz, 1H), 4.44–4.39 (m, 1H), 4.24 (q, J = 7.1 Hz, 2H), 3.91 (ddd, J = 7.6, 5.2, 2.7 Hz, 1H), 3.71–3.64 (m, 2H), 3.61 (dd, J = 7.3, 2.7 Hz, 1H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, D_2O) δ 168.2, 148.1, 121.7, 72.7, 70.4, 70.3, 62.7, 61.7, 13.2; HRMS (ESI): calcd for $C_9H_{16}NaO_6$ $[M + Na]^+$ 243.0839, found 243.0837.

4.7 General procedure for the preparation of protected ω-oxo α,β-unsaturated esters (13–16)

Ethyl 4,5,6,7-tetrahydroxy-hept-2-enoate (**5–8**) (0.30 g, 1.36 mmol) was dissolved in anhydrous THF (13.6 ml) and cooled in an ice bath at 0 °C. Powdered molecular sieves (~0.40 g), imidazole (2.23 g, 33.7 mmol) and TMSCl (1.38 ml, 10.9 mmol) were added. The reaction mixture was kept for 15 min at 0 °C, 1 h at room temperature and finally warmed to 50 °C for 30 min to completely convert substrate to the tetra-*O*-silyl derivative (the reaction was monitored by a TLC plate in Hx/AcOEt 6 : 1, ESI, Table 1†). After the indicated time, the reaction mixture was filtered through a short Celite pad, and the product was eluted with two portions of ether (2 × 20 ml) directly into a separating funnel containing a 10% aqueous $NaHCO_3$ solution (30 ml). The water phase was extracted an additional time with ether (30 ml). The combined organic phases were washed with 5% aqueous $NaHCO_3$ solution (2 × 30 ml) and brine (30 ml) and dried over anhydrous $MgSO_4$. After solvent evaporation under reduced pressure (below 30 °C), a clear colourless oil formed, which was dried under high vacuum and used in the next step without further purification.

A solution of oxalyl chloride (0.35 ml, 4.08 mmol) in anhydrous methylene chloride (30 ml) was cooled to −78 °C, after which DMSO (0.58 ml, 8.17 mmol) was added dropwise and stirred for 30 min. The α,β-unsaturated ω-alcohol (**13–16**) from the previous step was dissolved in anhydrous methylene chloride (15 ml) and slowly added to the oxidative mixture and kept at −78 °C for 3 h (shorter reaction times do not undergo complete deprotection and oxidation). Triethylamine (1.72 ml, 12.3 mmol) was slowly added and stirring continued for the next 30 min, after which time, the reaction mixture was allowed to warm to 0 °C. The reaction was quenched with the addition of sat. NH_4Cl (5 ml), followed by the addition of 5% aqueous $NaHCO_3$ (30 ml). The aqueous layer was extracted with methylene chloride (2 × 30 ml) and combined organic layers were washed with 5% aqueous $NaHCO_3$ (2 × 30 ml) and brine (50 ml). The organic phase was dried over anhydrous $MgSO_4$, concentrated under reduced pressure (below 30 °C) and dried under high vacuum for a few seconds. The procedure synthesises quantitatively almost pure aldehydes to be obtained as viscous yellow oils which were used immediately in the next step.

4.8 General procedure for tandem *seleno*-Michael/aldol reaction, oxidation/elimination and deprotection steps

A suspension of elemental selenium (0.13 g, 1.63 mmol) in anhydrous THF (28 ml) was cooled in an ice bath and *n*BuLi (1.6 M in hexanes, 1.02 ml, 1.63 mmol) was added dropwise (a clear, colourless solution was produced) and the mixture was stirred 15 min at 0 °C. After that, the reaction mixture was cooled to −78 °C, a solution of aldehyde (**13–16**) from the previous step (in 15 ml of anhydrous THF) was added dropwise and stirring continued through the next 30 min and then the cryobath was removed and mixture was allowed to warm to room temperature and stirring was continued for the next 1 hour. After that time, the reaction was cooled to 0 °C and hydrogen peroxide (35% v/v, 1.20 ml, 13.6 mmol) and pyridine (0.55 ml, 6.82 mmol) were added. The ice bath was removed, and the mixture was heated to 40 °C for 1 h (solution became clear and colourless, TLC plate Hx/AcOEt 3 : 1; TLC plate-ESI-MS indicates partial deprotection of silyl ethers). The mixture was cooled to room temperature and transferred to a separatory funnel containing 50 ml of 10% $NaHCO_3$ solution. The water phase was extracted three times with AcOEt (3 × 30 ml). The combined organic layers were washed twice with brine (2 × 20 ml) and dried over anhydrous $MgSO_4$. After solvent removal under reduced pressure, most of the residual pyridine was removed under high vacuum. The crude oil was dissolved in anhydrous THF (15 ml), cooled to 0 °C and excess Olah reagent (HF·Py) was added (1.29 ml) and stirred at room temperature for 12 h. After the indicated time, solid $NaHCO_3$ was added until bubbling ceased. The solution was filtered through a short pad of Celite and the product was eluted with ethanol (2 × 20 ml). The solvent was evaporated under reduced pressure and then co-evaporated with toluene (30 ml) to remove most of the pyridine residue. The products were purified by column chromatography (chloroform/MeOH 4 : 1 to 3 : 1).

4.9 Ethyl (3*S*,4*R*,5*R*,6*S*)-3,4,5,6-tetrahydroxycyclohex-1-ene-1-carboxylate (from D-xylose) (17)

The crude mixture was purified by column chromatography (chloroform/MeOH 4 : 1 to 3 : 1) to obtain ethyl (3*S*,4*R*,5*R*,6*S*)-3,4,5,6-tetrahydroxycyclohex-1-ene-1-carboxylate (***anti*-17**) as a colourless syrup (0.141 g, 0.54 mmol, 39.7%); $[\alpha]_D^{26}$ = +25.4 (c 0.25, MeOH); ^{1}H NMR (600 MHz, CD_3OD) δ 6.56–6.53 (m, 1H), 4.39 (ddd, J = 7.3, 2.7, 1.3 Hz, 1H), 4.26–4.20 (m, 2H), 4.17 (dt, J = 8.1, 2.3 Hz, 1H), 3.50 (dd, J = 10.4, 7.4 Hz, 1H), 3.37 (dd, J = 10.3, 8.2 Hz, 1H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, CD_3OD) δ 167.7, 140.7, 133.6, 77.0, 76.4, 72.6, 72.4, 61.9, 14.4; HRMS (ESI): calcd for $C_9H_{14}NaO_6$ $[M + Na]^+$ 241.0683, found 241.0681; and (3*S*,4*R*,5*R*,6*S*/6*R*)-3,4,5,6-tetrahydroxycyclohex-1-ene-1-carboxylate as a mixture of 6*S*/6*R* isomers (ratio: 59 : 41) as a colourless syrup (0.028 g, 0.13 mmol, 9.4%).

4.10 Ethyl (3*R*,4*S*,5*R*,6*S*)-3,4,5,6-tetrahydroxycyclohex-1-ene-1-carboxylate (from D-arabinose) (18)

The crude mixture was purified by column chromatography (chloroform/MeOH 4 : 1 to 3 : 1) to obtain ethyl (3*R*,4*S*,5*R*,6*S*)-

3,4,5,6-tetrahydroxycyclohex-1-ene-1-carboxylate (***anti*-18**) as a colourless syrup (0.118 g, 0.65 mmol, 47.4%); $[\alpha]_D^{26} = -10.4$ (c 0.25, MeOH); ^{1}H NMR (600 MHz, CD_3OD) δ 6.82 (d, $J = 2.4$ Hz, 1H), 4.49 (d, $J = 3.2$ Hz, 1H), 4.31 (dd, $J = 8.1$, 2.3 Hz, 1H), 4.27–4.18 (m, 2H), 3.96–3.92 (m, 1H), 3.79 (dd, $J = 8.2$, 2.3 Hz, 1H), 1.30 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (151 MHz, CD_3OD) δ 167.7, 143.4, 131.5, 75.3, 72.1, 69.9, 69.1, 61.8, 14.4; HRMS (ESI): calcd for $C_9H_{14}NaO_6$ $[M + Na]^+$ 241.0683, found 241.0682; and (3*R*,4*S*,5*R*,6*S*/6*R*)-3,4,5,6-tetrahydroxycyclohex-1-ene-1-carboxylate as a mixture of 6*S*/6*R*/unknown (ratio: 16 : 48 : 36) as a colourless syrup (0.018 g, 0.51 mmol, 3.7%).

4.11 Ethyl (3*S*,4*S*,5*R*,6*S*)-3,4,5,6-tetrahydroxycyclohex-1-ene-1-carboxylate (from D-ribose) (19)

The crude mixture was purified by column chromatography (chloroform/MeOH 4 : 1 to 3 : 1) to obtain ethyl (3*S*,4*S*,5*R*,6*S*/6*R*)-3,4,5,6-tetrahydroxycyclohex-1-ene-1-carboxylate as a mixture of 6*S*/6*R* isomers. [(a) 6*S*/6*R*: 88.5 : 11.5 as a white solid, 0.102 g, 0.47 mmol, 32.7%; (b) 6*S*/6*R*: 72 : 28; 0.018 g, 0.082 mmol, 5.8%, (c) 6*S*/6*R*/unknown: 70 : 8 : 21, 4.5%].

4.12 Gram scale synthesis of ethyl (3*S*,4*S*,5*R*,6*S*)-3,4,5,6-tetrahydroxycyclohex-1-ene-1-carboxylate (from D-ribose) (19)

The procedure was started from (*E*)(4*S*,5*S*,6*R*) ethylene 4,5,6,7-tetrahydroxy-hept-2-enoate (from D-ribose) (1.50 g, 6.81 mmol). After the deprotection step with Olah's reagent, the main impurities were removed by flash chromatography (chloroform/MeOH 9 : 1 to 2 : 1). Analytical sample of ethyl (3*S*,4*S*,5*R*,6*S*)-3,4,5,6-tetrahydroxycyclohex-1-ene-1-carboxylate (***anti*-19**)was crystallised from AcOEt (white solid, 0.484 g, 2.21 mmol, 32.5%); $[\alpha]_D^{24} = +94.5$ (c 0.25, MeOH); mp 125–126.5 °C; ^{1}H NMR (600 MHz, D_2O) δ 6.72–6.68 (m, 1H), 4.59 (ddd, $J = 7.4$, 2.2, 1.4 Hz, 1H), 4.55 (dt, $J = 3.6$, 2.4 Hz, 1H), 4.33–4.25 (m, 2H), 4.14 (dt, $J = 3.6$, 1.8 Hz, 1H), 3.82 (dd, $J = 7.4$, 2.1 Hz, 1H), 1.31 (t, $J = 7.1$ Hz, 3H).; ^{13}C NMR (151 MHz, D_2O) δ 167.7, 139.9, 131.7, 73.5, 72.1, 68.1, 67.4, 62.1, 13.2; HRMS (ESI): calcd for $C_9H_{14}NaO_6$ $[M + Na]^+$ 241.0683, found 241.0682. The filtration medium was concentrated under reduced pressure and the product was isolated by column chromatography (chloroform/MeOH 4 : 1 to 3 : 1) as a mixture of 6*S*/6*R* isomers (ratio: 65 : 35) (0.15 g, 0.69 mmol, 10.1%).

4.13 Ethyl (3*R*,4*R*,5*R*,6*S*)-3,4,5,6-tetrahydroxycyclohex-1-ene-1-carboxylate from (D-lyxose) (20)

Crude mixture was purified by column chromatography (chloroform/MeOH 4 : 1 to 3 : 1) to obtain ethyl (3*R*,4*R*,5*R*,6*S*)-3,4,5,6-tetrahydroxycyclohex-1-ene-1-carboxylate (***anti*-20**) as a colorless syrup (0.166 g, 0.76 mmol, 53.4%); $[\alpha]_D^{26} = -80.5$ (c 0.25, MeOH); ^{1}H NMR (600 MHz, CD_3OD) δ 6.74 (d, $J = 3.8$ Hz, 1H), 4.36 (t, $J = 3.9$ Hz, 1H), 4.29 (d, $J = 4.7$ Hz, 1H), 4.27–4.20 (m, 2H), 3.97 (dd, $J = 7.4$, 4.7 Hz, 1H), 3.73 (dd, $J = 7.3$, 4.1 Hz, 1H), 1.31 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (151 MHz, CD_3OD) δ 167.8, 138.9, 134.2, 72.9, 71.4, 70.2, 67.2, 61.9, 14.4; HRMS (ESI): calcd for $C_9H_{14}NaO_6$ $[M + Na]^+$ 241.0683, found 241.0684; and a mixture of 6*S*/6*R*/unknown (ratio: 85 : 10 : 5) (0.036 g, 0.16 mmol, 10.9%).

Data availability

The data that support the findings of this study are openly available in Rodbuk at **https://doi.org/10.57903/UJ/V6NORN**.

Conflicts of interest

There are no conflicts to declare.

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