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Synthesis of novel seven-membered carbasugars and evaluation of their glycosidase inhibition potentials[†]

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Here, we report the synthesis of five novel seven-membered carbasugar analogs. We adopted a chiral-pool strategy starting from the cheap and readily available p-mannitol to synthesize these ring-expanded carbasugars. Apart from several regioselective protecting group manipulations, these syntheses involved Wittig olefination and ring-closing metathesis as the key steps. We observed an unprecedented deoxygenation reaction of an allylic benzyl ether upon treatment with H₂/Pd during the synthesis. Preliminary biological evaluation of the carbasugars revealed that these ring expanded carbasugars act as inhibitors of various glycosidases. This study highlights the importance of the synthesis of novel ring expanded carbasugars and their biological exploration.

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Introduction

Carbohydrate mimics¹ are important tools to unravel complex signalling pathways involving various carbohydrates² and carbohydrate-binding or metabolizing enzymes.3 They are also important for pharmaceutical interventions in diseases caused by the aberration in activities of these glycoenzymes.⁴ Carbasugars constitute an important family of glycomimetics wherein a one-carbon unit replaces the endocyclic oxygen of pyranoses.⁵ As carbasugars lack a hemiacetal or hemiketal functionality, they are stable towards glycosidases and often can be competitive inhibitors of these enzymes.6 Additionally, many of them show antiviral,7 antibiotic,8 antidiabetic9 and antitumor activities.¹⁰ More than 200 carbasugar natural products are known.¹¹ Most of the natural carbasugars have a six-membered ring as their core, and they are structural mimics of pyranoses.^{11a} Many of these natural pyranose mimics, and their unnatural derivatives have been synthesised.¹² The natural products, namely calystegines,¹³ a group of cyclitols with a seven-membered ring as core show attractive biological properties. Furthermore, many synthetic ring-expanded sugar analogs such as septanose,14 seven-membered iminocyclitols15 etc. show interesting biological activities. Due to the wide range of biological activities of ring-expanded analogs, there is great interest in synthesising novel analogs of this class of carbasugars.¹⁶ Several strategies have been implemented for the synthesis of sevenmembered carbasugar analogs. Both *de novo* synthesis from achiral fossil-derived fine chemicals involving a step of asymmetric induction¹⁷ and synthesis from naturally abundant chiral pool starting materials are known.¹⁸ From a practical point of sustainability, methods that use renewable natural chiral pools are attractive for synthesizing these densely hydroxylated products. We report the synthesis of five novel seven-membered carbasugars and their biological activities.

We have previously reported the total syntheses of various carbasugars such as cyclophellitol, valienamine, lincitols, uvacalols, gabosines and others.¹⁹ We found that (–)-gabosine J (1) and its reduced derivatives 2 and 3 (ref. 19*b*) inhibit various glycosidases. Notably, (–)-gabosine J inhibits α -mannosidase three times stronger than the well-known mannosidase inhibitor deoxymannojirimycin. This result inspired us to synthesize the homologous seven-membered analogs 4, 5 and 6 (Fig. 1a).



Fig. 1 (a) Chemical structures of gabosine J (1), gabosinol $J-\alpha$ (2), gabosinol $J-\beta$ (3) and corresponding seven-membered analogs 4, 5 and 6. (b) Retrosynthetic analysis of seven-membered analogs 4, 5 and 6.

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Paper

15 36 %

126 MeOH, rt,

A retrosynthetic analysis suggested that cheap and readily available D-mannitol is an ideal chiral pool starting material for the synthesis of these derivatives. These three molecules can be obtained from the diene 7 through Grubb's ring closing metathesis. The diene 7 can be obtained from enal **8** by a Barbier type allylation.²⁰ The enal **8** can be obtained from Dmannitol through several synthetic steps involving a Wittig olefination²¹ and several regio- and chemoselective protecting group manipulations (Fig. 1b).

Results and discussion

We synthesized aldehyde **10** in ten steps, starting from Dmannitol **9**.^{19d} The aldehyde **10** on Barbier allylation using metallic zinc and allyl bromide resulted in an inseparable mixture of diastereomers **11** in 70% yield. We could not calculate the ratio of isomers from the ¹H NMR spectrum due to the extensive overlapping of the peaks. The mixture of diastereomers **11** was directly cyclized using Grubb's second generation catalyst, to give a mixture of cyclic diastereomers **12**.

The ¹H NMR spectrum of this mixture was well resolved and we calculated the diastereomeric ratio as 1 : 0.3. Unfortunately, the mixture of diastereomers **12** was also chromatographically inseparable. Acetylation of the free hydroxyl of the diastereomers **12** resulted in a mixture of diastereomers, **13** and **14**, which could be separated by column chromatography. We assigned the stereochemistry at C-4, of the major isomer **13**, using NOESY experiment. H-4 of compound **13** showed a spatial interaction with H-5 and H-6, which confirms the *syn*



Scheme 1 Synthesis of seven-membered carbasugars 5 and 6. Reagents and conditions: (a) Zn, allylbromide, THF, 0 °C, 30 min, 70%; (b) Grubb's 2nd generation catalyst, DCM, reflux, 12 h, 81%; (c) Ac₂O, DMAP, pyridine, 3 h; (d) NaOMe, methanol, rt, 12 h; (e) BCl₃, DCM, -78 °C, 3 h; (f) Dess-Martin periodinane, DCM, rt, 4 h, 96%; (g) BCl₃ or BBr₃ or FeCl₃ (reagent conditions as per the literature).^{196,23}



16 22 %

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HO

17.27%

relationship of H-4 with H-5 and H-6. For the minor isomer 14, peaks corresponding to H-5, H-6 and H-7 merged in the range 3.93–3.87 ppm of ¹H NMR spectrum. Hence we could not confirm the stereochemistry at C-4 of this isomer. The major isomer 13 and the minor isomer 14 were deacetylated using sodium methoxide to get compounds 12β and 12α respectively.

As per the NOESY spectrum of compound 12β , H-4 showed *syn*-relationship with H-5. For compound 12α , H-4 did not spatially interact with H-5 indicating the *anti*-relationship between H-4 and H-5. Compounds 12β and 12α were debenzy-lated using BCl₃ to obtain pentaols 6 (84% yield) and 5 (65% yield) respectively (Scheme 1). We made the stereochemical assignments of both pentaols 5 and 6 using NOESY experiments. The cross peaks showing spatial interaction of H-4 with H-6 in the NOESY spectrum of the compound 6 indicate that they have *syn*-relationship. On the other hand, H-4 does not show cross peaks with H-6, in the NOESY spectrum of compound 5, and hence these two hydrogens have *anti*-relationship with each other.

The endocyclic double bond in these compounds in principle can be reduced to get a set of fully saturated cyclitols. To test this, we have treated compound 12β with H₂ in the presence of Pd/C (Scheme 2). Surprisingly, the reaction resulted in a mixture of products, as evidenced by TLC analysis. In the TLC, there were two well-separated spots having R_F 0.7 and 0.3, respectively when eluted using methanol–ethyl acetate (1 : 4, v/v). The polar spot corresponds to an inseparable mixture of two diastereomers 17 (27% yield) as evidenced by ¹H NMR spectroscopy. The non-polar spot also corresponds to two



Fig. 2 ORTEP diagram of compounds (a) 15 and (b) 23 with 50% probability level.

diastereomers, which could be separated when eluted using methanol–chloroform (1 : 6, v/v, $R_{\rm F}$ 0.3 and 0.25 respectively). We identified the non-polar compound among these two as compound **15** (36% yield) and the polar one as compound **16** (22% yield) by various NMR spectral studies, such as ¹H, ¹³C, DEPT, COSY and HMQC spectra. We identified the peaks corresponding to the newly formed methyl groups at 0.96 ppm and 0.86 ppm for compounds **15** and **16** respectively.

Stereochemistry of the methyl groups of cyclitols **15** and **16** was confirmed using NOESY experiment. In compound **15**, H-1 does not have spatial interaction with H-7, indicating that both have anti-relation with each other. Whereas in compound **16**, H-1 has spatial interaction with H-7, indicating the *syn*-relation between H-7 and H-1. Single crystal X-ray diffraction analysis further confirmed the stereochemical assignment of compound **15** (Fig. 2a). The crystal structure also validated the stereochemical assignments at position C-4, done using NOESY experiments of compound **15**, the hydroxyl substituents on C4, C6 and C7 are present in the equatorial position, and C-5 is in axial position. The bond angles and the torsional angles in the sevenmembered ring matched with a twist-chair conformation of cycloheptane (Table S2†).²²

To obtain compound 4, we oxidised compound 12 using Dess-Martin periodinane to ketone 18 (Scheme 1). Unfortunately, our attempts to debenzylate the cyclic ketone using BCl_3 , BBr_3 or FeCl_3 were not successful and resulted in a complex mixture of many inseparable compounds. Under these conditions, such reactions were successful in the case of sixmembered carbasugar derivatives with alkene and ketone functional groups.^{19b,23} This unexpected outcome necessitated a detour in the reaction sequence. Hence we decided to replace benzyl protecting groups in compound 12 with *p*-methoxybenzyl (PMB), since the latter can be deprotected under mild conditions.

We synthesized diacetal 19 from p-mannitol in an overall yield of 80% over two steps as reported.19b Stannylene-acetalmediated regioselective alkylation of 19 with p-methoxybenzylchloride gave PMB ether 20 (76% yield) as an oily liquid. Ether 20 on Swern oxidation²⁴ gave ketone 21 in good yield. Wittig reaction on the ketone resulted in alkene 22 in 76% yield. Then, the isopropylidene groups of compound 22 were deprotected using 0.1 M HCl to yield tetraol 23. We confirmed the structure of the tetraol 23 using single crystal X-ray diffraction analysis (Fig. 2b). The primary hydroxyl of the tetraol 23 was selectively tritylated to yield triol 24 in 88% yield. All the free hydroxyl groups of the triol 24 were protected by alkylation using pmethoxybenzyl chloride to get alkene 25. The trityl group was then cleaved by acidic hydrolysis to get compound 26. We then oxidised the free primary hydroxyl group of compound 26 under Swern oxidation conditions to obtain corresponding aldehyde 27. Barbier allylation of aldehyde 27, gave an inseparable mixture of diastereomers 28. The mixture of diastereomers 28 was directly treated with Grubb's second generation catalyst to obtain cyclised product 29 as an inseparable mixture of diastereomers in 83% yield. The free hydroxyl of compound 29 was oxidised using Dess-Martin periodinane²⁵ to obtain ketone 30,

which on treatment with a 1% solution of TFA in DCM (v/v) resulted in target compound 4 in 74% yield (Scheme 3). In the NOESY spectrum of compound 4, the peak corresponding to H-7 at 4.37 ppm does not couple with that of H-5 at 3.7 ppm. This confirms that H-7 has anti-relationship with H-5.

We have evaluated the inhibition potential of these novel cyclitols towards various glycosidases (Table 1). Fig. 3 shows a comparison of structural elements of carbasugars that are inhibitors of various enzymes with their natural substrates. Apart from this positional similarity, the 3D conformations of these molecules play major roles in their activity. All these compounds inhibited a-glucosidase from Saccharomyces cerevisiae with IC₅₀ values in the range 1-10 mM. On the other hand, none of these compounds inhibits a-glucosidase from Bacillus stearothermophilus. The difference in the sequence and 3D-structure of bacterial and fungal enzymes could be the reason for this difference in activities. Except compound 5, all other compounds inhibited β -glucosidase from almonds, but to a lesser extent compared to their activity towards a-glucosidases. While compounds 5, 15 and 16 inhibited jack bean α mannosidase, only compound 4 could inhibit β-mannosidase (from Helix pomatia). The activities of these compounds



Scheme 3 Synthesis of compound 4. Reagents and conditions: (a) Bu_2SnO , *p*-methoxybenzyl chloride, toluene, reflux, 24 h, 76%; (b) oxalyl chloride, DMSO, triethylamine, DCM, -78 °C, 2 h, 75%; (c) PPh₃PCH₃Br, ^{*n*}BuLi, THF, -78 °C, 3 h, 76%; (d) 0.1 M HCl, methanol, rt, 30 min, 76%; (e) trityl chloride, diisopropylethylamine, DCM, rt, 4 h, 88%; (f) *p*-methoxybenzyl chloride, NaH, DMF, 0 °C to rt, 3 h, 76%; (g) 0.05 M HCl, methanol/chloroform (3 : 1, v/v), rt, 30 min, 79%; (h) Zn, allylbromide, THF, 0 °C, 30 min, 70%; (i) Grubb's 2nd generation catalyst, DCM, 50 °C, 12 h, 83%; (j) Dess–Martin periodinane, DCM, rt, 4 h, 84%; (k) 5% TFA, DCM, 0 °C, 3 h, 74%.

| | Percentage inhibition (%) at 1 mM concentration of the inhibitor | | | | |
|--|--|--|--|--|--|
| Name of the enzymes | 4 | 5 | 6 | 15 | 16 |
| α-Glucosidase from | 41.1 (IC ₅₀ ^{<i>a</i>} = 1.5 \pm 0.1 | $3.3~(\mathrm{IC}_{50} = 11.5 \pm 0.1$ | 22.1 (IC ₅₀ = 2.9 ± 0.4 | 19.5 (IC ₅₀ = 9.5 \pm 1.8 | 24.3 (IC ₅₀ = 3.7 ± 0.6 |
| Saccharomyces cerevisiae | mM) | mM) | mM) | mM) | mM) |
| α-Glucosidase from <i>Bacillus</i> stearothermophilus | NI ^b | NI | NI | NI | NI |
| β-Glucosidase from almonds | 12.3 | NI | 3.2 | 14.1 | 29.8 |
| α-Mannosidase from jack bean | NI | 12.5 | NI | 10.6 | 35.1 (IC ₅₀ = 4.3 \pm 1.2 mM) |
| β-Mannosidase from <i>Helix</i> pomatia | 16.2 | NI | NI | NI | NI |
| α-Galactosidase from <i>E. coli</i> | 17.5 | NI | 20.7 (IC ₅₀ = 3.5 ± 0.3 mM) | 34.7 (IC $_{50} = 9.4 \pm 0.5$ mM) | 26.8 |
| α-Galactosidase from green coffee beans | NI | NI | 41.7 (IC ₅₀ = 1.3 ± 0.2 mM) | NI | NI |
| β-Galactosidase from <i>E. coli</i> | NI | NI | NI | NI | NI |
| β-Galactosidase from bovine | 5.9 | 42.1 (IC ₅₀ = 5.6 \pm 0.5 | $41.9~(IC_{50}=1.9\pm0.3$ | $48.8~(IC_{50}=1.9\pm0.5$ | $25.2(\mathrm{IC}_{50} = 4.6 \pm 0.04$ |
| liver | | mM) | mM) | mM) | mM) |
| β-Galactosidase from <i>Aspergillus</i> oryzae | NI | NI | NI | NI | 12.8 |

^a Concentration of inhibitor required for 50% inhibition of the enzyme. ^b NI - no inhibition up to 20 mM concentration.

Table 1 Glycosidase enzyme inhibition studies of synthesized seven-membered carbasugars

Fig. 3 Structural comparison of enzyme-inhibitors of various glycosidases with their natural substrates.

towards galactosidases varied greatly with the source of the enzyme. While all compounds except **5** inhibited bacterial (*E. coli*) α -galactosidase, only the compound **6** inhibited α -galactosidase from coffee beans. All the five compounds inhibit mammalian (bovine liver) β -galactosidase, but they are inactive towards bacterial (*E. coli*) β -galactosidase and only the compound **16** inhibits fungal (*Aspergillus oryzae*) β -galactosidase. It is clear that minor changes in the structure lead to a huge difference in activities and also the activity varies with the source of enzymes. This is, in fact, advantageous for finding a selective inhibitor for an organism-specific enzyme. Detailed

structure-activity relationship studies with various analogs would yield specific inhibitors having therapeutic potentials. In comparison to standard inhibitors, the seven-membered carbasugar analogs exhibited moderate inhibition potential.

Conclusions

We have synthesised five novel seven-membered carbasugar analogs by adopting a chiral pool approach, utilizing the inexpensive and readily available D-mannitol as the starting material. All the synthesised seven-membered cyclitols exhibited weak inhibition towards various glycosidases. The glycosidase inhibition exhibited by these novel seven-membered cyclitols shows the importance of developing ring expanded cyclitols for various biological explorations. Ring-expanded cyclitols, having more number of modifiable sites, allows the synthesis of a wide variety of derivatives. Extensive research on the synthesis of many such ring-expanded cyclitols and their structure-activity correlation might give many compounds that can unravel the signalling pathways and that are of high therapeutic potentials. This research also showed an unusual deoxygenation of an allyl benzyl ether. This deoxygenation pathway might have been influenced by the conformational features of the sevenmembered ring, and this warrants a systematic investigation.

Experimental section

General

All reagents and solvents were purchased from commercial sources and used without further purification. Pre-coated TLC silica gel 60 F_{254} plates were purchased from Merck. TLC analyses were carried out by visualizing the chromatograms under UV light and further by heating the plates after dipping into

ceric ammonium molybdate staining solution. Silica gel (200–400 mesh) was used for column chromatography. The ¹H NMR, COSY, DEPT, ¹³C NMR and HMQC spectra were recorded on an Avance III-500 (Bruker) NMR spectrometer. The chemical shifts of NMR spectra are reported in ppm (δ) relative to internal tetramethylsilane (TMS, δ 0.0 ppm). ¹³C NMR spectra were recorded with complete proton decoupling. All NMR data were collected at 25 °C. Elemental analyses were done on Elementar, vario MICRO cube elemental analyzer. High resolution mass spectra were recorded using Q Exactive TM-Benchtop-LC-HRMS. UV absorbance during enzyme assay was measured using multimode plate reader Infinite 200 PRO at 25 °C.

(5R,6S,7R)-8-((Benzyloxy)methyl)-5,6,7-tris((4-

methoxybenzyl)oxy)nona-1,8-dien-4-ol (11). To a cooled (0 °C) solution of aldehyde **10** (ref. 19*d*) (12 g, 0.019 mol) in 100 mL THF, Zn (5 g, 0.077 mol) and allyl bromide (6.6 mL, 0.077 mol) were added and the mixture was stirred for 30 minutes. A saturated solution of ammonium chloride (8 g in 20 mL water) was added slowly over 10 minutes at 0 °C. THF was evaporated under reduced pressure; the aqueous layer was transferred to a separating funnel and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na₂SO₄ and was concentrated under reduced pressure. The residue obtained was passed through a small pad of silica using ethyl acetate–petroleum ether (1 : 4, v/v) as eluent to remove any impurities and obtain the diastereomeric mixture **11** (9 g, 70% yield) as an yellow oily liquid. The mixture was used for the next reaction without further purification.

(5R,6S,7R)-4-((Benzyloxy)methyl)-5,6,7-tris((4-

methoxybenzyl)oxy) cyclohept-3-enol (12). To a solution of mixture of diastereomers **11** (1 g, 1.53 mmol) in DCM (300 mL), Grubb's second generation catalyst (0.063 g, 0.074 mmol) was added at room temperature and the mixture was refluxed for 12 h. The solvent was removed under reduced pressure and the residue obtained was purified by column chromatography using ethyl acetate/petroleum ether (1 : 2, v/v) as eluent, to yield the cyclized derivative **12** (0.78 g, 81%) as a brown oil, which consists of inseparable mixture of diastereomers in the ratio 1 : 0.3.

Acetylation of derivative 12

To a solution of mixture of diastereomers 12 (0.88 g, 1.37 mmol) in 5 mL anhydrous pyridine at 0 °C, acetic anhydride (0.16 mL, 1.7 mmol) and DMAP (0.017 g, 0.14 mmol) were added and the reaction mixture was stirred at room temperature for 3 h. At complete consumption of the starting material, pyridine was evaporated under reduced pressure. The residue thus obtained was diluted with ethyl acetate (50 mL) and taken into a separating funnel. The organic layer was washed successively with saturated NaHCO₃ solution (20 mL \times 2), brine and water. The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The mixture of diastereomers was separated by column chromatography using acetone/ petroleum ether (1:5, v/v) as eluent, to get the isomer 13 (0.65 g, 69% yield, $R_{\rm F}$ 0.3 in acetone/petroleum ether, 1 : 4, v/v) and 14 (0.2 g, 21% yield, $R_{\rm F}$ 0.25 in acetone/petroleum ether, 1:4, v/v) as yellow oily liquids.

Data for (1R,5R,6S,7R)-4-((benzyloxy)methyl)-5,6,7-tris((4methoxybenzyl)oxy)cyclohept-3-en-1-yl acetate (13). $[\alpha] =$ -20.3 (c 0.14, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ: 7.28-7.19 (m, 7H, Ar-H), 7.13 (d, J = 8.55 Hz, 2H, Ar-H), 7.06 (d, J =8.55 Hz, 2H, Ar-H), 6.8–6.7 (m, 6H, Ar-H), 5.72 (t, J = 6.5 Hz, 1H, H-2), 4.86 (dd, *J* = 7.5 Hz, *J* = 2.5 Hz, 1H, H-4), 4.65–4.59 (m, 3H, -CH₂Ph), 4.53 (d, J = 7.1 Hz, 1H, -CH₂Ph), 4.51 (d, J = 6.8 Hz, 1H, $-CH_2Ph$), 4.47 (d, I = 8.2 Hz, 1H, H-7), 4.6-4.4 (m, 3H, -CH₂Ph), 3.98 (s, 2H, H-8A and H-8B), 3.96 (s, 1H, H-5), 3.75-3.7 $(m, 9H, -OCH_3), 3.59 (dd, J = 8.1 Hz, J = 1.5 Hz, 1H, H-6), 2.67-$ 2.6 (m, 1H, H-3A), 2.15-2.06 (m, 1H, H-3B), 1.92 (s, 3H, -COCH₃); ¹³C NMR (125 MHz, CDCl₃) δ: 170.6 (CO), 159.0, 158.99, 158.91, 140.4, 138.5 (C-1), 131.2, 131.1, 130.9, 129.4, 129.2, 128.9, 128.3, 127.6, 127.4, 122.8 (C-2), 113.6, 80.8 (C-6), 79.5 (C-5), 75.9 (C-7), 73.4 (-CH₂Ph), 73.3 (-CH₂Ph), 73.1 (-CH₂Ph), 72.7 (C-8), 72.2 (-CH₂Ph), 72.1 (C-4), 55.3 (-OCH₃), 55.2 (-OCH₃), 26.5 (C-3), 21.3 (-COCH₃); elemental analysis calcd for C₄₁H₄₆O₉; C, 72.12; H, 6.79; found: C, 71.87; H, 6.95.

Data for (1S,5R,6S,7R)-4-((benzyloxy)methyl)-5,6,7-tris((4methoxybenzyl)oxy)cyclohept-3-en-1-yl acetate (14). $[\alpha] =$ -28.5 (c 0.2, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ : 7.28–7.19 (m, 5H, Ar-H), 7.16 (d, J = 8.5 Hz, 2H, Ar-H), 7.04 (d, J = 8.5 Hz, 2H, Ar-H), 7.0 (d, J = 8 Hz, 2H, Ar-H), 6.78 (d, J = 8.5 Hz, 2H, Ar-H), 6.75 (d, J = 9 Hz, 2H, Ar-H), 6.70 (d, J = 8.5 Hz, 2H, Ar-H), 5.86– 5.81 (m, 1H, H-2), 5.08 (t, J = 9 Hz, 1H, H-4), 4.58 (d, J = 12 Hz, 1H, $-CH_2Ph$), 4.50 (d, J = 11.5 Hz, 1H, $-CH_2Ph$), 4.45–4.38 (m, 3H, -CH₂Ph), 4.37-4.30 (m, 2H, -CH₂Ph), 4.17 (d, J = 10 Hz, 1H, $-CH_2Ph$), 3.93–3.87 (m, 3H, H-5, H-6 and H-7), 3.83 (d, J = 12, 1H, H-8A), 3.79-3.69 (m, 10H, H-8B and -OCH₃), 2.53-2.46 (m, 1H, H-3A), 2.27–2.19 (m, 1H, H-3B), 1.95 (s, 3H, -COCH₃); ¹³C NMR (125 MHz, CDCl₃) δ: 170.1 (CO), 159.08, 159.05, 159.02, 139.2, 138.4 (C-1), 130.8, 130.6, 129.4, 129.2, 129.0, 128.3, 127.7, 127.4, 125.5 (C-2), 113.6, 113.5, 81.6 (C-7), 76.7 (C-6) 75.0 (C-8), 74.8 (C-5), 73.1 (-CH₂Ph), 72.9 (-CH₂Ph), 71.9 (-CH₂Ph), 71.8 (C-4), 70.7 (-CH₂Ph), 55.3 (-OCH₃), 55.2 (-OCH₃), 29.3 (C-3), 21.3 (-COCH₃); elemental analysis calcd for C₄₁H₄₆O₉; C, 72.12; H, 6.79; found: C, 72.4; H, 6.67.

(1R,5R,6S,7R)-4-((Benzyloxy)methyl)-5,6,7-tris((4-

methoxybenzyl)oxy)cyclohept-3-enol (12β). To a solution of acetate 13 (0.2 g, 0.3 mmol) in anhydrous methanol (0.5 mL), added a methanolic solution of NaOMe (0.1 M, 0.6 mL) and stirred at room temperature for 12 h. At completion of reaction, as monitored by TLC analysis, the reaction mixture was neutralized using Dowex 50 H⁺ resin and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography to obtain the derivative **12**β (0.18 g, 96% yield) as a pale yellow oily liquid: $[\alpha] = -59.8$ (*c* 0.25, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ: 7.28-7.17 (m, 7H, Ar-H), 7.07 (d, J = 8.5 Hz, 2H, Ar-H), 6.96 (d, J = 9 Hz, 2H, Ar-H), 6.79 (d, J = 7 Hz, 2H, Ar-H), 6.76-6.70 (m, 4H, Ar-H), 5.89-5.85 (m, 1H, H-2), 4.62 (d, J = 11.4 Hz, 1H, -CH₂Ph), 4.57 (d, J = 11.5 Hz, 1H, -CH₂Ph), 4.48-4.04 (m, 3H, -CH₂Ph), 4.37 (d, J = 7.5 Hz, 1H, $-CH_2Ph$), 4.34 (d, J = 7 Hz, 1H, $-CH_2Ph$), 4.17 (d, J =11.5 Hz, 1H, -CH₂Ph), 4.13 (bs, 1H, H-4), 4.04-3.99 (m, 2H, H-6 and H-7), 3.88-3.81 (m, 2H, H-8A and H-8B), 3.76-3.70 (m, 10H, H-5 and -OCH₃), 2.52-2.45 (m, 1H, H-3A), 2.36-2.31 (m, 1H, H-

3B); ¹³C NMR (125 MHz, CDCl₃) δ : 159.2, 159.1, 159.0, 138.4 (C-5), 138.3, 130.6, 130.0, 129.6, 129.4, 128.9, 128.5 (C-2), 128.3, 127.7, 127.5, 113.8, 113.7, 113.6, 78.7 (C-5), 78.6 (C-6), 75.4 (C-8), 74.5 (C-7), 73.9 (-CH₂Ph), 71.9 (-CH₂Ph), 71.0 (C-4), 70.6 (-CH₂Ph), 70.5 (-CH₂Ph), 55.2 (-OCH₃), 30.8 (C-3); elemental analysis calcd for C₃₉H₄₄O₈; C, 73.10; H, 6.92; found: C, 72.94; H, 7.13.

(1S,5R,6S,7R)-4-((Benzyloxy)methyl)-5,6,7-tris((4-

methoxybenzyl)oxy)cyclohept-3-enol (12a). The procedure used for synthesis of compound 12β , was followed starting with the compound 14 (0.26 g, 0.38 mmol) to yield the derivative 12α (0.24 g, 98% yield) as a colourless oily liquid: $[\alpha] = -30.5$ (*c* 0.2, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ : 7.29–7.2 (m, 5H, Ar-H), 7.14 (d, J = 8.5 Hz, 2H, Ar-H), 7.08–7.02 (m, 4H, Ar-H), 6.81– 6.74 (m, 4H, Ar-H), 6.72 (d, *I* = 8.6 Hz, 2H, Ar-H), 5.95–5.91 (dd, *I* = 9.5 Hz, 4.1 Hz, 1H, H-2), 4.49 (d, J = 12 Hz, 1H, $-CH_2Ph$), 4.44-4.34 (m, 5H, -CH₂Ph), 4.29 (d, J = 11 Hz, 1H, -CH₂Ph), 4.17 (d, J = 11.5 Hz, 1H, -CH₂Ph), 4.0-3.96 (m, 2H, H-6 and H-7), 3.85-3.76 (m, 3H, H-4, H-8A and H-8B), 3.76-3.75 (m, 1H, H-5), 3.74-3.71 (m, 9H, -OCH₃), 2.71 (br s, 1H, OH), 2.48-2.39 (m, 1H, H-3A), 2.34–2.38 (m, 1H, H-3B); ¹³C NMR (125 MHz, CDCl₃) δ: 159.3, 159.1, 159.0, 138.3, 138.4, 130.7, 130.6, 130.1 (C-1), 129.6, 129.4, 129.0, 128.3, 127.7, 127.8 (C-2), 127.5, 113.9, 113.7, 113.6, 84.7 (C-5), 75.6 (C-8), 74.4 (C-6), 74.2 (C-7), 72.8 (-CH₂Ph), 71.9 (-CH₂Ph), 71.8 (-CH₂Ph), 70.6 (-CH₂Ph), 67.7 (C-4), 55.3 (-OCH₃), 55.2 (-OCH₃), 30.7 (C-3); elemental analysis calcd for C₃₉H₄₄O₈; C, 73.10; H, 6.92; found: C, 73.31; H, 7.08.

(1R,2R,3S,4R)-5-(Hydroxymethyl)cyclohept-5-ene-1,2,3,4tetraol (6). To a solution of the compound 12β (0.1 g, 0.16 mmol) in anhydrous DCM (5 mL) stirred at -78 °C, added BCl₃ (1.6 mL, 1 M solution in DCM) and the reaction mixture was stirred at -78 °C for 3 h. At completion, the reaction was quenched by adding methanol (0.3 mL) followed by pyridine (0.6 mL). The reaction mixture was warmed slowly to room temperature and evaporated under reduced pressure. The residue was dissolved in water (1 mL) and passed through a column filled with bicarbonate-form resin (prepared by passing NaHCO₃ through Cl⁻ resin) and then through Dowex H⁺ ion resin successively. The solution was evaporated under reduced pressure and the residue was purified by column chromatography using methanol-ethyl acetate (1:19, v/v) as eluent. The collected fractions were evaporated under reduced pressure to yield the carbasugar 6 (0.025 g, 84% yield) as a colourless oily liquid: $[\alpha] = -24.1$ (*c* 0.108, methanol); ¹H NMR $(500 \text{ MHz}, \text{CD}_3\text{OD}) \delta$: 5.75–5.72 (m, 1H, H-2), 4.63 (d, J = 8.5 Hz, 1H, H-7), 4.21–4.03 (m, 3H, H-5, H-8A and H-8B), 3.65 (d, J = 10 Hz, 1H, H-4), 3.55 (d, *J* = 8.5 Hz, 1H, H-6), 2.72–2.64 (m, 1H, H-3A), 2.12–2.03 (m, 1H, H-3B); ¹³C NMR (125 MHz, CD₃OD) δ: 143.6 (C-1), 121.1 (C-2), 74.4 (C-5), 73.3 (C-6), 70.6 (C-4), 67.7 (C-7), 64.1 (C-8), 28.0 (C-3); elemental analysis calcd for C₈H₁₄O₅; C, 50.52; H, 7.42; found: C, 50.71; H, 7.31.

(1S,2R,3S,4R)-5-(Hydroxymethyl)cyclohept-5-ene-1,2,3,4-

tetraol (5). The procedure for the synthesis of compound **6** was followed with the derivative 12α (0.24 g, 0.37 mmol) as starting material, to yield the carbasugar **5** (0.046 g, 65% yield) as an oily liquid: [α] = -10.9 (*c* 0.11, methanol); ¹H NMR (500 MHz, CD₃OD) 5.75–5.68 (m, 1H, H-2), 4.21 (d, *J* = 7.5 Hz, 1H, H-7),

3.94 (s, 2H, H-8A and H-8B), 3.88 (dd, J = 7.4 Hz, 2.55 Hz, 1H, H-6), 3.78 (dd, J = 7.9 Hz, 2.5 Hz, 1H, H-5), 3.60–3.55 (m, 1H, H-4), 2.35–2.29 (m, 1H, H-3A), 2.68–2.19 (m, 1H, H-3B); ¹³C NMR (125 MHz, CD₃OD) δ : 142.5 (C-1), 122.6 (C-2), 75.6 (C-5), 72.1 (C-6), 69.3 (C-4), 69.1 (C-7), 65.7 (C-8), 30.2 (C-3); elemental analysis calcd for C₈H₁₄O₅; C, 50.52; H, 7.42; found: C, 50.39; H, 7.68.

Reduction of compound 12β. To a solution of compound **12** β (0.2 g, 0.3 mmol) in methanol (5 mL), added palladium (6.6 mg, 10 wt% on carbon). The reaction mixture was purged with H₂ gas for 5 minutes to remove other gases and the reaction mixture was stirred at room temperature for 12 h in H₂ atmosphere. At completion of starting material, as monitored by TLC analysis, the reaction mixture was filtered through 0.2 micron syringe filter and the solvent was removed under reduced pressure. The residue was purified by column chromatography using MeOH/CHCl₃ (1 : 6, v/v) as eluent to give compound **15** (0.02 g, 36% yield, *R*_F 0.3) as a gum which crystallized from a mixture of MeOH–CHCl₃ (1 : 19, v/v), **16** (0.012 g, 22% yield, *R*_F 0.25) and **17** (0.016 g, 27% yield, inseparable mixture of diastereomers, *R*_F 0.2 in MeOH/CHCl₃, 1 : 3, v/v) as yellow oily liquids.

(1*R*,2*R*,3*S*,4*R*,5*S*)-5-Methylcycloheptane-1,2,3,4-tetraol (15). Mp 59–60 °C; $[\alpha] = -9.3$ (*c* 0.1, methanol); ¹H NMR (500 MHz, CD₃OD) δ : 3.89 (s, 1H, H-5), 3.72–3.67 (m, 1H, H-4), 3.42 (dd, *J* = 8 Hz, 1.5 Hz, 1H, H-6), 3.29 (t, *J* = 8 Hz, 1H, H-7), 1.75–1.66 (m, 1H, H-2A), 1.59–1.51 (m, 2H, H-2B and H-3A), 1.44–1.34 (m, 2H, H-1 and H-3B), 0.96 (d, *J* = 6.7 Hz, 3H, H-8); ¹³C NMR (125 MHz, CD₃OD) δ : 76.9 (C-6), 76.0 (C-7), 74.9 (C-5), 71.9 (C-4), 37.1 (C-1), 29.0 (C-2), 27.4 (C-3), 19.9 (–CH₃); elemental analysis calcd for C₈H₁₆O₄; C, 54.53; H, 9.15; found: C, 54.79; H, 8.96.

(1*R*,2*R*,3*S*,4*R*,5*R*)-5-Methylcycloheptane-1,2,3,4-tetraol (16). [α] = +1.2 (c 0.08, methanol); ¹H NMR (500 MHz, CD₃OD) δ : 3.89 (s, 1H, H-5), 3.69–3.64 (m, 1H, H-4), 3.63–3.59 (m, 1H, H-7), 3.55–3.52 (m, 1H, H-6), 2.09–1.99 (m, 1H, H-1), 1.79–1.69 (m, 1H, H-2A), 1.63–1.51 (m, 1H, H-2B), 1.40–1.28 (m, 1H, H-3A), 1.24–1.17 (m, 1H, H-3B), 0.86 (d, J = 7.25 Hz, 3H, H-8); ¹³C NMR (125 MHz, CD₃OD) δ : 76.6 (C-6), 76.3 (C-5), 75.9 (C-7), 73.1 (C-4), 35.0 (C-1), 31.6 (C-2), 25.4 (C-3), 17.6 (–CH₃); elemental analysis calcd for C₈H₁₆O₄; C, 54.53; H, 9.15; found: C, 54.75; H, 9.06.

(R)-2-((4-Methoxybenzyl)oxy)-1-((4R,4'R,5R)-2,2,2',2'-tetramethyl-[4,4'-bi(1,3-dioxolan)]-5-yl)ethanol (20). To a solution of diol 19 (ref. 19b) (15 g, 0.057 mol) in anhydrous toluene (250 mL), added Bu₂SnO (16.9 g, 0.068 mol) and the reaction mixture was heated to reflux for 12 h in a Dean-Stark apparatus. The reaction mixture was cooled to room temperature, added tetrabutylammonium iodide (25 g, 0.068 mol) and p-methoxybenzyl chloride (8.5 mL, 0.063 mol). The reaction mixture was refluxed for 3 h. At completion of reaction, as monitored by TLC analysis, the reaction mixture was quenched by adding triethylamine (24 mL, 0.17 mol) at room temperature and refluxed for additional 2 h. The reaction mixture was cooled to room temperature, the precipitate was filtered and the solvent was evaporated under reduced pressure. The residue was diluted with ethyl acetate (50 mL), transferred to a separating funnel and washed with water, brine and dried over anhydrous Na2SO4. The solvent was removed under reduced pressure and purified

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by column chromatography using ethyl acetate/petroleum ether (1 : 9, v/v) as eluent to yield compound **20** (16.6 g, 76% yield) as a colourless liquid: $[\alpha] = +11.9$ (*c* 0.21, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ : 7.28 (d, J = 8.5 Hz, 2H, Ar-H), 6.80 (d, J = 8.5 Hz, 2H, Ar-H), 4.55 (d, J = 11.9 Hz, 1H, -CH₂Ph), 4.52 (d, J = 11.85 Hz, 1H, -CH₂Ph), 4.18-4.14 (m, 1H, H-6A), 4.12-4.07 (m, 1H, H-5), 4.02-3.97 (m, 1H, H-6B), 3.92-3.82 (m, 3H, H-2, H-3 and H-4), 3.81 (s, 3H, -OCH₃), 3.7 (dd, J = 10 Hz, 2.5 Hz, 1H, H-1A), 3.57-3.54 (m, 1H, H-1B), 3.39 (s, 1H, -OH), 1.36 (s, 3H, -CH₃), 1.3-1.27 (m, 9H, -CH₃); ¹³C NMR (125 MHz, CDCl₃) δ : 159.2, 130.3, 129.3, 113.7, 110.0 (-C(CH₃)₂), 109.5 (-C(CH₃)₂), 80.6 (C-4), 79.9 (C-3), 76.2 (C-5), 73.1 (-CH₂Ph), 71.8 (C-2), 71.0 (C-1), 67.5 (C-6), 55.2 (-OCH₃), 27.0 (-CH₃), 26.9 (-CH₃), 26.4 (-CH₃), 25.1 (-CH₃); elemental analysis calcd for C₂₀H₃₀O₇; C, 62.81; H, 7.91; found: C, 62.72; H, 8.17.

2-((4-Methoxybenzyl)oxy)-1-((4R,4'R,5S)-2,2,2',2'-tetramethyl-[4,4'-bi(1,3-dioxolan)]-5-yl)ethanone (21). To a solution of oxalyl chloride (5.4 mL, 63 mmol) in anhydrous DCM (100 mL), added anhydrous DMSO (8.8 mL, 124 mmol) dropwise for 15 minutes at -78 °C. A solution of compound 20 (12 g, 31 mmol) in dry DCM (50 mL) was added and the reaction mixture was stirred at the same temperature for 1 h. Et₃N (21.6 mL, 155 mmol) was added and the mixture was stirred for an additional 1 h. The solvents were evaporated under reduced pressure and the residue obtained was diluted with ethyl acetate (250 mL). The contents were transferred to a separating funnel and successively washed the organic layer with saturated NaHCO₃ solution, water and brine. The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography using ethyl acetate-petroleum ether (1:6, v/v) as eluent to yield the ketone **21** (8.9 g, 75% yield) as an oily liquid: $[\alpha] =$ +4.08 (c 0.19, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ : 7.22 (d, J = 8.25 Hz, 2H, Ar), 6.81 (d, J = 8.25 Hz, 2H, Ar), 4.51-4.44 (m, 2H, -CH₂Ph), 4.39-4.29 (m, 3H, H-1A, H-1B and H-3), 4.16-4.08 (m, 2H, H-4 and H-5), 4.05–4.0 (m, 1H, H-6A), 3.89 (dd, J = 8.5 Hz, 4.8 Hz, 1H, H-6B), 3.74 (s, 3H, -OCH₃), 1.36 (s, 3H, -CH₃), 1.32 (s, 3H, -CH₃), 1.28-1.25 (m, 6H, -CH₃); ¹³C NMR (125 MHz, CDCl₃) δ: 204.5 (CO), 158.5, 128.7, 128.1, 112.8, 110.5 (-C(CH₃)₂), 108.8 (-C(CH₃)₂), 79.6 (C-3), 77.1 (C-4), 75.2 (C-5), 71.9 (-CH₂Ph), 71.5 (C1), 65.5 (C-6), 54.2 (-OCH₃), 25.8 (-CH₃), 25.4 (-CH₃), 25.0 (-CH₃), 24.1 (-CH₃); elemental analysis calcd for C₂₀H₂₈O₇; C, 63.14; H, 7.42; found: C, 63.35; H, 7.28.

(4S,4'R,5R)-5-(3-((4-Methoxybenzyl)oxy)prop-1-en-2-yl)-

2,2,2',2'-tetramethyl-4,4'-bi(1,3-dioxolane) (22). To a suspension of Ph_3PCH_3Br (9.3 g, 26 mmol) in anhydrous THF (150 mL) cooled at -78 °C, added *n*-butyl lithium (17 mL, 1.6 M in hexane) dropwise for 20 minutes and then a solution of ketone 21 (7 g, 18.4 mmol) in anhydrous THF (100 mL) was added at the same temperature. The reaction mixture was warmed to room temperature and stirred for 3 h. At completion of the reaction, as monitored by TLC analysis, the reaction mixture was evaporated under reduced pressure. The residue thus obtained was diluted with ethyl acetate (150 mL) and transferred into a separating funnel. The organic layer was washed successively with water and brine; and then concentrated under reduced

pressure. The residue was purified by column chromatography using ethyl acetate/petroleum ether (1 : 9, v/v) as eluent to give compound 22 (5.3 g, 76% yield) as an oily liquid: $[\alpha] = -3.54$ (*c* 0.23, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ : 7.19 (d, 2H, J = 8.5 Hz, Ar-H), 6.81 (d, J = 8.5 Hz, 2H, Ar-H), 5.33 (s, 1H, H-2A'), 5.27 (s, 1H, H-2B'), 4.43–4.33 (m, 3H, H-3 and –CH₂Ph), 4.09–4.05 (m, 2H, H-1A and H-5), 4.02–3.95 (m, 2H, H-1B and H-6A), 3.91–3.85 (m, 2H, H-4 and H-6B), 3.73 (s, 3H, –OCH₃), 1.34 (m, 6H, –CH₃), 1.30 (s, 3H, –CH₃), 1.26 (s, 3H, –CH₃); ¹³C NMR (125 MHz, CDCl₃): δ : 159.1 (Ar), 142.8 (C2), 130.3 (Ar), 129.3 (Ar), 115.6 (C-2'), 113.7 (Ar), 109.6 (–C(CH₃)₂), 109.2 (–C(CH₃)₂), 80.5 (C-3), 80.3 (C-4), 76.4 (C-5), 71.8 (–CH₂Ph), 69.5 (C-1), 66.7 (C-6), 55.2 (–OCH₃), 27.0 (–CH₃), 26.8 (–CH₃), 26.4 (–CH₃), 25.2 (–CH₃); elemental analysis calcd for C₂₁H₃₀O₆; C, 66.65; H, 7.99; found: C, 66.46; H, 8.22.

(2R,3S,4R)-5-(((4-Methoxybenzyl)oxy)methyl)hex-5-ene-1,2,3,4-tetraol (23). To a solution of 22 (4 g, 10.5 mmol) in methanol (25 mL) was added HCl (1.5 mL, 8 M). The mixture was stirred at room temperature for 30 minutes. The reaction mixture was guenched by slow addition of Et₃N (7 mL) at 0 °C, and solvent was removed under reduced pressure. The residue was purified by column chromatography using ethyl acetate as eluent to yield tetraol 23 (2.4 g, 76% yield) as a white solid: mp 90–92 °C; $[\alpha] = +5.3$ (c 0.19, methanol); ¹H NMR (500 MHz, CD_3OD) δ : 7.17 (d, J = 8.5 Hz, 2H, Ar-H), 6.79 (d, J = 8.55 Hz, 2H, Ar-H), 5.23 (s, 1H, H-2A'), 5.15 (s, 1H, H-2B'), 4.40 (s, 1H, H-3), 4.37 (d, J = 11.5 Hz, 1H, -CH₂Ph), 4.33 (d, J = 11.3 Hz, 1H, $-CH_2Ph$), 4.04 (d, J = 12.5 Hz, 1H, H-1A), 3.93 (d, J = 12.5 Hz, 1H, H-1B), 3.71-3.65 (m, 4H, H-6A and -OCH₃), 3.64-3.59 (m, 1H, H-5), 3.54–3.49 (m, 1H, H-6B), 3.47 (d, 1H, J = 7.85 Hz, H-4); $^{13}\mathrm{C}$ NMR (125 MHz, CD₃OD) δ : 159.4, 146.4, 130.0, 129.2, 113.4, 113.1 (C-2'), 72.5 (C-4), 71.6 (C-5), 71.5 (-CH₂Ph), 70.9 (C-3), 70.3 (C-1), 63.6 (C-6), 54.2 ($-CH_3$); elemental analysis calcd for C₁₅H₂₂O₆; C, 60.39; H, 7.43; found: C, 60.61; H, 7.31.

(2R,3S,4R)-5-(((4-Methoxybenzyl)oxy)methyl)-1-(trityloxy) hex-5-ene-2,3,4-triol (24). To a suspension of tetraol 23 (1 g, 3.4 mmol) in anhydrous DCM (50 mL), added anhydrous diisopropylethylamine (0.88 mL, 5 mmol) at 0 °C and trityl chloride (1.2 g, 4.42 mmol) portionwise. The reaction mixture was stirred at room temperature for 4 h. At completion of the reaction, as monitored by TLC analysis, the solvent was evaporated under reduced pressure and the residue thus obtained was purified by column chromatography using ethyl acetate-petroleum ether (2:5, v/v) as eluent to yield triol 24 (1.6 g, 88% yield) as a viscous liquid: $[\alpha] = +2.66 (c \ 0.2, \text{CHCl}_3); {}^{1}\text{H} \text{ NMR} (500 \text{ MHz}, \text{CDCl}_3) \delta$: 7.36 (d, J = 7.4 Hz, 6H, Ar-H), 7.25–7.19 (m, 6H, Ar-H), 7.19–7.16 (m, 3H, Ar-H), 7.13 (d, J = 8.5 Hz, 2H, Ar-H), 6.76 (d, J = 8.5 Hz, 2H, Ar-H), 5.16 (s, 1H, H-2A'), 5.14 (s, 1H, H-2B'), 4.39-4.33 (m, 3H, H-3 and -CH₂Ph), 4.05 (d, *J* = 11.25 Hz, 1H, H-1A), 3.89 (d, *J* = 11.25 Hz, 1H, H-1B), 3.86-3.8 (m, 1H, H-5), 3.7 (s, 3H, $-OCH_3$), 3.64–3.59 (m, 1H, H-4), 3.31 (dd, *J* = 9.5 Hz, 4.5 Hz, 1H, H-6A), 3.28–3.23 (m, 2H, OH (C-4) and H-6B), 2.95 (d, J = 6.05 Hz, 1H, OH (C-3)), 2.63 (d, J = 5 Hz, 1H, OH (C-5)); ¹³C NMR (125 MHz, CDCl₃) δ: 158.3, 143.9 (C-2), 142.6, 128.5, 128.2, 127.5, 126.9, 126.1, 116.1 (C-2'), 112.9, 85.9 (-C(Ph)₃), 72.3 (C-4), 71.9 (C-3), 71.2 (-CH₂Ph), 70.3 (C-5), 69.7 (C-1), 63.8 (C-6), 54.2 (-OCH₃);

elemental analysis calcd for $C_{34}H_{36}O_6$; C, 75.53; H, 6.71; found: C, 75.55; H, 6.41.

4,4',4"-((((2*R*,3*S*,4*R*)-5-(((4-Methoxybenzyl)oxy)methyl)-1-(trityloxy)hex-5-ene-2,3,4-triyl)tris(oxy))tris(methylene))

tris(methoxybenzene) (25). To a solution of triol 24 (1.5 g, 2.8 mmol) in anhydrous DMF (10 mL) at 0 °C, added NaH (0.67 g, 16.8 mmol, 60% suspension in wax) and stirred for 15 minutes. PMBCl (1.5 mL, 11.2 mmol) was added and the reaction mixture was stirred at room temperature for 3 h. At completion, the reaction was quenched by adding water (30 mL) at 0 °C and diluted with ethyl acetate (100 mL). The contents were transferred into a separating funnel and the aqueous layer was extracted with ethyl acetate (25 mL \times 3). The organic layer was washed with water and brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue obtained was purified by column chromatography using ethyl acetatepetroleum ether (1:4, v/v) as eluent to yield compound 25 (1.9 g, 76% yield) as a pale yellow liquid: $\left[\alpha\right] = -10.2$ (c 0.16, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ: 7.41–7.32 (m, 6H, Ar-H), 7.21–7.09 (m, 13H, Ar-H), 7.08 (d, J = 8 Hz, 2H, Ar-H), 6.81 (d, *J* = 8 Hz, 2H, Ar-H), 6.78–6.72 (m, 4H, Ar-H), 6.68 (d, *J* = 8.5 Hz, 2H, Ar-H), 6.6 (d, J = 8.5 Hz, 2H, Ar-H), 5.28 (s, 1H, H-2A'), 5.16 (s, 1H, H-2B'), 4.57 (d, J = 11 Hz, 1H, -CH₂Ph), 4.41-4.32 (m, 3H, $-CH_2Ph$), 4.32–4.24 (m, 2H, $-CH_2Ph$), 4.15 (d, 1H, J = 11 Hz, -CH₂Ph), 4.12-4.07 (m, 2H, H-3 and -CH₂Ph), 3.93 (d, J = 13 Hz, 1H, H-1A), 3.87 (d, 1H, J = 12.9 Hz, H-1B), 3.76-3.63 (m, 14H, H-4, H-5 and $-OCH_3 \times 4$), 3.42–3.35 (m, 1H, H-6A), 3.22–3.15 (m, 1H, H-6B); ¹³C NMR (125 MHz, CDCl₃) δ: 159.1, 159.0, 158.9, 144.1, 143.1, 131.1, 130.6, 130.5, 130.4, 129.8, 129.6, 129.1, 128.9, 128.8, 128.6, 127.7, 126.8, 115.4, 113.7, 113.6, 113.3, 86.5 (-C(CH₃)₃), 79.9 (C-4), 79.7 (C-3), 78.5 (C-5), 74.1 (-CH₂Ph), 72.3 (-CH₂Ph), 72.0 (-CH₂Ph), 70.5 (-CH₂Ph), 70.4 (C-1), 63.6 (C-6), 55.3 (-OCH₃), 55.2 (-OCH₃), 55.1 (-OCH₃); elemental analysis calcd for C₅₈H₆₀O₉; C, 77.31; H, 6.71; found: C, 77.49; H, 6.60. (2R,3S,4R)-2,3,4-Tris((4-methoxybenzyl)oxy)-5-(((4-

methoxybenzyl)oxy)methyl)hex-5-en-1-ol (26). To a solution of compound 25 (2 g, 2.2 mmol) in methanol (100 mL), added HCl (0.5 mL, 10 M) and the reaction mixture was stirred at room temperature for 30 minutes. At completion of the reaction, as monitored by TLC analysis, the reaction was quenched with Et₃N (3 mL) at 0 °C and the solvents were evaporated under reduced pressure. The residue thus obtained was purified by column chromatography using ethyl acetate/petroleum ether (3:7, v/v) as eluent to yield compound 26 (1.15 g, 79% yield) as an yellow oily liquid: $\left[\alpha\right] = -13.04 (c \ 0.14, \text{CHCl}_3); {}^{1}\text{H} \text{ NMR} (500)$ MHz, $CDCl_3$) δ : 7.19–7.11 (m, 6H, Ar-H), 7.04 (d, I = 8.5 Hz, 2H, Ar-H), 6.78-6.72 (m, 8H, Ar-H), 5.36 (s, 1H, H-2A'), 5.29 (s, 1H, H-2B'), 4.54 (d, J = 10.75 Hz, 1H, $-CH_2Ph$), 4.51 (d, J = 10.8 Hz, 1H, -CH₂Ph), 4.45 (d, J = 11.35 Hz, 1H, -CH₂Ph), 4.39 (d, J =11.45 Hz, 1H, -CH₂Ph), 4.36 (d, *J* = 11.45 Hz, 1H, -CH₂Ph), 4.21 $(d, J = 11.1 Hz, 1H, -CH_2Ph), 4.16 (d, J = 11.35 Hz, 1H, -CH_2Ph),$ 4.09-4.03 (m, 2H, H-3 and -CH₂Ph), 3.95 (d, J = 12.75 Hz, 1H, H-1A), 3.9 (d, J = 12.75 Hz, 1H, H-1B), 3.74–3.64 (m, 15H, H-4, H-6A and H-6B), 3.52–3.49 (m, 1H, H-5), 2.17 (t, 1H, J = 5.75 Hz, -OH); ¹³C NMR (125 MHz, CDCl₃) δ: 159.2, 159.1, 142.9 (C-2), 130.5, 130.4, 130.2, 129.9, 129.8, 129.2, 116.1 (C-2'), 113.8, 113.7, 113.6, 80.5 (C-3), 80.0 (C-4), 78.7 (C-5), 74.7 (-CH₂Ph),

72.4 (-CH₂Ph), 71.0 (-CH₂Ph), 70.3 (-CH₂Ph), 70.2 (C-1), 60.8 (C-6), 55.3 (-OCH₃), 55.2 (-OCH₃); elemental analysis calcd for $C_{39}H_{46}O_9$; C, 71.10; H, 7.04; found: C, 71.35; H, 6.98.

(2S,3S,4R)-2,3,4-Tris((4-methoxybenzyl)oxy)-5-(((4-

methoxybenzyl)oxy)methyl)hex-5-enal (27). To a solution of oxalyl chloride (0.26 mL, 3 mmol) in anhydrous DCM (3 mL), added anhydrous DMSO (0.43 mL, 6 mmol) dropwise during 15 minutes at -78 °C. A solution of compound 26 (1 g, 1.5 mmol) in anhydrous DCM (10 mL) was added and the reaction mixture was stirred at the same temperature for 1 h. Et₃N (1 mL) was added and the mixture was stirred for an additional 1 h. The solvent was evaporated under reduced pressure and the residue obtained was diluted with ethyl acetate (50 mL). The contents were transferred to a separating funnel and washed the organic layer successively with saturated NaHCO₃, water and then brine. The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography using ethyl acetate/petroleum ether (1: 4, v/v) to yield compound 27 (0.8 g, 81%) as an yellow liquid: $[\alpha] = +24.83$ (c 0.22, CHCl₃); ¹H NMR $(500 \text{ MHz}, \text{CDCl}_3) \delta$: 9.49 (s, 1H, HCO-), 7.16 (d, 2H, J = 8.5 Hz, Ar-H), 7.13-7.05 (m, 6H, Ar-H), 6.78-6.71 (m, 8H, Ar-H), 5.38 (s, 1H, C-2A'), 5.36 (s, 1H, C-2B'), 4.51 (d, J = 11.05 Hz, 1H, $-CH_2Ph$), 4.45 (d, J = 11.05 Hz, 1H, $-CH_2Ph$), 4.42 (d, J =11.3 Hz, 1H, -CH₂Ph), 4.37 (d, J = 11.5 Hz, 1H, -CH₂Ph), 4.33 (d, J = 11.4 Hz, 1H, -CH₂Ph), 4.32 (d, J = 11.2 Hz, 1H, -CH₂Ph), 4.18 $(s, 1H, -CH_2Ph), 4.15 (s, 1H, -CH_2Ph), 4.11 (d, J = 5.5 Hz, 1H, H-$ 3), 3.9-3.87 (m, 3H, H-5, H-1A and H-1B), 3.86-3.84 (m, 1H, H-4), 3.71 (s, 12H, -OCH₃); ¹³C NMR (125 MHz, CDCl₃) δ: 201.8 (HCO), 159.3, 159.2, 142.3 (C-2), 130.27, 130.20, 130.1, 129.8, 129.7, 129.5, 129.2, 117.1 (C-2'), 113.8, 113.7, 113.6, 83.3 (C-5), 81.2 (C-4), 80.5 (C-3), 74.1 (-CH₂Ph), 72.4 (-CH₂Ph), 72.1 (-CH₂Ph), 70.7 (-CH₂Ph), 70.0 (C-1), 55.2 (-OCH₃); elemental analysis calcd for C₃₉H₄₄O₉; C, 71.32; H, 6.75; found: C, 71.35; H, 6.63.

(5R,6S,7R)-5,6,7-Tris((4-methoxybenzyl)oxy)-8-(((4-

methoxybenzyl)oxy)methyl)nona-1,8-dien-4-ol (28). Procedure followed for synthesizing compound **11** was followed with aldehyde **27** (7 g, 0.011 mol) as starting material, using Zn (2.8 g, 0.042 mol), allyl bromide (3.6 mL, 0.042 mol) and saturated solution of ammonium chloride (8 g in 20 mL water). The residue obtained after evaporation of solvent was purified by column chromatography using ethyl acetate–petroleum ether (1 : 4, v/v) as eluent. Compound **28** (5.2 g, 70% yield) was obtained as an yellow oily liquid, which consists of mixture of diastereomers in the ratio 1 : 0.2.

(5R,6S,7R)-5,6,7-Tris((4-methoxybenzyl)oxy)-4-(((4-

methoxybenzyl)oxy)methyl)cyclohept-3-enol (29). To a solution of mixture of diastereomers **28** (0.5 g, 0.72 mmol) in DCM (150 mL), Grubb's second generation catalyst (30 mg, 0.036 mmol) was added at room temperature and the mixture was refluxed for 12 h. The solvent was removed under reduced pressure and the residue obtained was purified by column chromatography using ethyl acetate/petroleum ether (1 : 2, R_F 0.2) as eluent, to yield the cyclic derivative **29** (0.4 g, 83%) as a brown oil, which consists of mixture of isomers in the ratio 1 : 0.2.

(5R,6S,7S)-5,6,7-Tris((4-methoxybenzyl)oxy)-4-(((4-

methoxybenzyl)oxy)methyl)cyclohept-3-enone (30). To a solution of compound 29 (0.1 g, 0.15 mmol) in anhydrous DCM (10 mL), added Dess-Martin periodinane (0.098 g, 0.23 mmol) and the reaction mixture was stirred at room temperature for 4 h. At complete consumption of starting material, as monitored by TLC analysis, the reaction mixture was cooled to 0 °C and quenched with 20% Na₂S₂O₃ solution (1 mL). The reaction mixture was diluted with DCM (50 mL), washed with 20% $Na_2S_2O_3$ solution (10 mL \times 3) followed by saturated NaHCO₃ solution (10 mL \times 2) and then brine (10 mL). The organic layer was dried over anhydrous Na2SO4 and evaporated under reduced pressure. The residue thus obtained was purified by column chromatography using ethyl acetate-petroleum ether (1:5, v/v) as eluent to yield ketone 30 (84 mg, 84%) as a pale yellow liquid: $[\alpha] = -58.2$ (c 0.2, CHCl₃); ¹H NMR (500 MHz, $CDCl_3$) δ : 7.22–7.17 (m, 2H, Ar-H), 7.12 (d, J = 8.4 Hz, 2H, Ar-H), 7.08 (d, J = 8.45 Hz, 2H, Ar-H), 6.98 (d, J = 8.4 Hz, 2H, Ar-H), 6.81–6.71 (m, 8H, Ar-H), 5.72 (t, J = 5.8 Hz, 1H, H-2), 4.66 (d, J= 11.7 Hz, 1H, -CH₂Ph), 4.64-4.60 (m, 2H, H-5 and -CH₂Ph), 4.43 (d, I = 11.7 Hz, 1H, -CH₂Ph), 4.34 (d, I = 11.1 Hz, 1H, -CH2Ph), 4.29-4.24 (m, 4H, -CH2Ph, H-8A and H-8B), 4.10-4.07 (m, 1H, H-6), 4.02 (d, J = 5.55 Hz, 1H, H-7), 3.96-3.91 (m, 1H, -CH₂Ph), 3.77-3.68 (m, 13H, -CH₂Ph and -OCH₃), 3.28 (dd, J = 16.4 Hz, 4.75 Hz, 1H, H-3A), 3.04 (dd, *J* = 16.45 Hz, 7.1 Hz, 1H, H-3B); ¹³C NMR (125 MHz, CDCl₃) δ: 202.2 (CO), 158.2, 158.1, 136.2 (C-1), 129.2, 129.0, 128.6, 128.3, 120.1 (C-2), 112.7, 112.5, 83.6 (C-5), 77.8 (C-6), 73.8 (C-7), 73.0 (-CH₂Ph), 71.8 (-CH₂Ph), 70.9 (-CH₂Ph), 70.6 (-CH₂Ph), 70.5 (C-8), 54.2 (-OCH₃), 40.2 (C-3); elemental analysis calcd for C40H44O9; C, 71.84; H, 6.63; found: C, 72.08; H, 6.55.

(5R,6S,7S)-5,6,7-Trihydroxy-4-(hydroxymethyl)cyclohept-3enone (4). To a solution of ketone 30 (0.12 g, 0.18 mmol) in DCM (30 mL), added TFA (0.3 mL) at 0 °C and the reaction mixture was stirred at room temperature for 3 h. At complete consumption of the starting material, as monitored by TLC analysis, the solvent was evaporated under reduced pressure and the residue obtained was purified by column chromatography using ethyl acetate as eluent to yield the cyclitol 4 (0.025 g, 74%) as an yellow oily liquid: $\left[\alpha\right] = +35.7$ (c 0.11, methanol); ¹H NMR (500 MHz, CD₃OD) δ : 5.58–5.53 (m, 1H, H-2), 4.37 (d, J =6 Hz, 1H, H-7), 4.15 (dd, J = 9 Hz, 6.5 Hz, 1H, H-6), 3.91 (d, J = 13.15 Hz, 1H, H-8A), 3.86 (d, J = 13.1 Hz, 1H, H-8B), 3.96 (d, J = 9 Hz, 1H, H-5), 2.49 (dd, J = 17.5 Hz, 4.5 Hz, 1H, H-3A), 2.14 (d, J = 17.3 Hz, 1H, H-3B); ¹³C NMR (125 MHz, CD₃OD) δ : 138.7 (C-1), 121.8 (C-2), 104.7 (CO), 76.5 (C-7), 74.2 (C-5), 69.7 (C-6), 63.2 (C-8), 32.2 (C-3); HRMS (ESI-TOF) m/z calcd for $C_8H_{12}O_5$ [M-H] 187.18, found 187.0606.

Glycosidase inhibition. Spectrophotometric method²⁶ was used to study the glycosidase enzyme inhibition of sevenmembered cyclitols **4**, **5**, **6**, **15** and **16**. α-Glucosidase from *Saccharomyces cerevisiae*, α-glucosidase from *Bacillus stearothermophilus*, β-glucosidase from almonds, α-mannosidase from jack bean, β-mannosidase from *Helix pomatia*, α-galactosidase from *Escherichia coli*, α-galactosidase from green coffee beans, β-galactosidase from *Escherichia coli*, β-galactosidase

from bovine liver and β -galactosidase from Aspergillus oryzae were purchased from Sigma Aldrich. We made solutions of αglucosidase (pH 7.2), β -galactosidase (pH 7.2) and α -galactosidase enzymes (pH 6.8) in sodium phosphate buffer and; both α and β mannosidases in citrate buffer (pH 4.5). Concentration of each enzyme stock solution was adjusted such that the reading of absorbance of the final solution in the assay without the inhibitor was in the range of 1-1.5. Final concentrations of enzymes were in the range 0.01-0.05 U mL⁻¹. Solutions of respective p-nitrophenyl glycoside substrates (3 mM) and inhibitors (20 mM) were made in the same buffer as the corresponding enzymes. 96-well microplate was marked and partitioned for blank (solution containing only substrate and inhibitor), control (solution containing only substrate and enzyme) and reaction mixture (solution with enzyme, substrate and inhibitor). The inhibitor solution was added to the well corresponding to the blank and reaction mixture such that the at least five different final concentration (in range 0.1 mM to 15 mM) are achieved when made up to 150 µL. The enzyme solution (10 µL) was added to the control and reaction mixture. Corresponding buffers were added to make up all the solutions to 95 µL. The reaction was started by adding solutions of corresponding substrates (25 µL) and incubating the microplate at 37 °C for 30 minutes. The reaction was quenched by adding Na_2CO_3 solution (1 M, 30 µL) in all wells. The absorbance of pnitrophenol released from the substrate was read immediately using multimode plate reader Infinite 200 PRO at 25 °C. The absorbance values from blanks were subtracted from corresponding values of control and reaction mixture to get corrected absorbance A and B respectively. The percentage of inhibition was calculated using the equation, percent inhibition $= ((A - A))^2$ B)/A) \times 100. The IC₅₀ values were calculated from a plot of concentration of inhibitors versus percentage inhibition. The experiments were separately duplicated. Acarbose was used as positive control. IC₅₀ for acarbose against α-glucosidase from baker's yeast is obtained to be 166 \pm 0.4 $\mu\text{M},$ which is close to the reported value (178.0 \pm 0.27 μ M).²⁷

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- (a) A. Tamburrini, C. Colombo and A. Bernardi, *Med. Res. Rev.*, 2020, 40, 495; (b) L. Cipolla, B. L. Ferla, C. Airoldi, C. Zona, A. Orsato, N. Shaikh, L. Russo and F. Nicotra, *Future Med. Chem.*, 2010, 2, 587; (c) P. Compain, *Molecules*, 2018, 23, 1658.
- 2 (a) J. P. Ribeiro, T. Diercks, J. Jimenez-Barbero, S. Andre, H. J. Gabius and F. J. Canada, *Biomolecules*, 2015, 5, 3177;

(b) B. Wu, J. Ge, B. Ren, Z. Pei and H. Dong, *Tetrahedron*, 2015, **71**, 4023.

- 3 (a) M. Kitaoka, S. Ogawa and H. A. Taniguchi, *Carbohydr. Res.*, 1993, 247, 355; (b) L. I. Willems, T. J. M. Beenakker, B. Murray, S. Scheij, W. W. Kallemeijn, R. G. Boot, M. Verhoek, W. E. Donker-Koopman, M. J. Ferraz and E. R. van Rijssel, *J. Am. Chem. Soc.*, 2014, 136, 11622.
- 4 A. R. Sawkar, W.-C. Cheng, E. Beutler, C.-H. Wong,
 W. E. Balch and J. W. Kelly, *Proc. Natl. Acad. Sci. U. S. A.*, 2002, 99, 15428.
- 5 S. Roscales and J. Plumet, Int. J. Carbohydr. Chem., 2016, 2016, 4760548.
- 6 (a) M. Lefoix, A. Tatibouet, S. Cottaz, H. Driguez and P. Rollin, *Tetrahedron Lett.*, 2002, 43, 2889; (b) Q. Gao, C. Zaccaria, M. Tontini, L. Poletti, P. Costantinob and L. Lay, *Org. Biomol. Chem.*, 2012, 10, 6673; (c) E. Leclerc, X. Pannecoucke, M. Etheve-Quelquejeuc and M. Sollogoub, *Chem. Soc. Rev.*, 2013, 42, 4270; (d) G. Aydin, T. Savran, S. Baran and A. Baran, *Bioorg. Med. Chem. Lett.*, 2018, 28, 2555.
- 7 (a) A. D. Borthwick, K. Biggadike and J. L. Paternoster, *Bioorg. Med. Chem. Lett.*, 1993, 3, 2577; (b) J. Wang, Y. Jin, K. L. Rapp,
 M. Bennett, R. F. Schinazi and C. K. Chu, *J. Med. Chem.*, 2005,
 48, 3736; (c) J.-s. Yoon, G. Kim, D. B. Jarhad, H.-R. Kim,
 Y.-S. Shin, S. Qu, P. K. Sahu, H. O. Kim, H. W. Lee,
 S. B. Wang, Y. J. Kong, T.-S. Chang, N. S. Ogando,
 K. Kovacikova, E. J. Snijder, C. C. Posthuma, M. J. van
 Hemert and L. S. Jeong, *J. Med. Chem.*, 2019, 62, 6346.
- 8 M. S. Visser, K. D. Freeman-Cook, S. J. Brickner, K. E. Brighty, P. T. Le, S. K. Wade, R. Monahan, G. J. Martinelli, K. T. Blair and D. E. Moore, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 6730.
- 9 W.-L. Ng, H.-C. Li, K. K.-M. Lau, A. K. N. Chan, C. B.-S. Lau and T. K. M. Shing, *Sci. Rep.*, 2017, 7, 5581.
- 10 (a) Y. Usami, I. Takaoka, H. Ichikawa, Y. Horibe, S. Tomiyama, M. Ohtsuka, Y. Imanishi and M. Arimoto, J. Org. Chem., 2007, 72, 6127; (b) M. Li, Y. Li, K. A. Ludwik, Z. M. Sandusky, D. A. Lannigan and G. A. O'Doherty, Org. Lett., 2017, 19, 2410.
- 11 (a) O. Arjona, A. M. Gomez, J. C. Lopez and J. Plumet, *Chem. Rev.*, 2007, 107, 1919; (b) W. W. Kallemeijn, K.-Y. Li, M. D. Witte, A. R. A. Marques, J. Aten, S. Scheij, J. Jiang, L. I. Willems, T. M. Voorn-Brouwer, C. P. A. A. V. Roomen, R. Ottenhoff, R. G. Boot, H. V. D. Elst, M. T. C. Walvoort, B. I. Florea, J. D. C. Codee, G. A. V. D. Marel, J. M. F. G. Aerts and H. S. Overkleeft, *Angew. Chem., Int. Ed.*, 2012, 51, 12529.
- 12 (a) P. Wen, V. Vetvicka and D. Crich, J. Org. Chem., 2019, 84, 5554; (b) Y. Usami, in *Studies in Natural Products Chemistry*, ed. R. Atta-ur, Elsevier, 2014, vol. 41, p. 287.
- 13 (a) O. Duclos, M. Mondange, A. Dureault and J. C. Depezay, *Tetrahedron Lett.*, 1992, 33, 8061; (b) C. R. Johnson and S. J. Bis, *J. Org. Chem.*, 1995, 60, 615; (c) T. Faitg, J. Soulie, J.-Y. Lallemand and L. Ricard, *Tetrahedron: Asymmetry*, 1999, 10, 2165; (d) F.-D. Boyer and I. Hanna, *Tetrahedron Lett.*, 2001, 42, 1275.
- 14 J. Saha and M. W. Peczuh, *Adv. Carbohydr. Chem. Biochem.*, 2011, **66**, 121.

- 15 (a) H. Li, Y. Bleriot, C. Chantereau, J.-M. Mallet, M. Sollogoub, Y. Zhang, E. Rodríguez-García, P. Vogel, J. Jiménez-Barbero and P. Sinaÿ, Org. Biomol. Chem., 2004, 2, 1492; (b) H. Li, C. Schutz, S. Favre, Y. Zhang, P. Vogel, P. Sinaya and Y. Bleriot, Org. Biomol. Chem., 2006, 4, 1653.
- 16 (a) L. A. Paquette, G. Moura-Letts and G. P. Wang, J. Org. Chem., 2009, 74, 2099; (b) G. Mehta, K. Pallavi and S. Katukojvala, Tetrahedron Lett., 2009, 50, 4519; (c) R. Madsen, Eur. J. Org. Chem., 2007, 399; (d) G. Mehta, R. Mohanrao, S. Katukojvala, Y. Landais and S. Sen, Tetrahedron Lett., 2011, 52, 2893; (e) K. Ecer and E. Salamci, Tetrahedron, 2014, 70, 8389; (f) G. Moura-Letts and L. A. Paquette, J. Org. Chem., 2008, 73, 7663; (g) W. Wang, Y. Zhang, M. Sollogoub and P. Sinay, Angew. Chem., Int. Ed., 2000, 39, 2466; (h) L. A. Paquette and Y. Zhang, J. Org. Chem., 2006, 71, 4353; (i) Y. Zozik, E. Salamci and A. Kilic, Tetrahedron Lett., 2017, 58, 4822; (j) A. Osuch-Kwiatkowska and S. Jarosz, Curr. Org. Chem., 2014, 18, 1674.
- 17 (a) M. E. Sengul, A. Menzek and N. Saracoglu, J. Chem. Res., 2005, 2005, 382; (b) R. Beniazza, V. Desvergnes, G. Mehta, N. Blanchard, F. Robert and Y. Landais, J. Org. Chem., 2011, 76, 791; (c) M. F. El-Mansy, A. Sar, S. Lindeman and W. A. Donaldson, Chem.-Eur. J., 2013, 19, 2330; (d) D. A. Khlevin, S. E. Sosonyuk, M. V. Proskurnina and N. S. Zefirov, Eur. J. Org. Chem., 2013, 2381; (e) A. Pearson and S. Katiyar, Tetrahedron, 2000, 56, 2297; (f) A. A. Yadav, P. S. Sarang, M. Sau, S. Thirumalairajan, G. K. Trivedi and M. M. Salunkhe, Tetrahedron Lett., 2012, 53, 3599.
- 18 (a) Y. Bleriot, A. Giroult, J.-M. Mallet, E. Rodriguez, P. Vogel and P. Sinay, Tetrahedron: Asymmetry, 2002, 13, 2553; (b) E. Sisu, M. Sollogoub, J.-M. Mallet and P. Sinay, Tetrahedron, 2002, 58, 10189; (c) C. Jia, Y. Zhang and L. Zhang, Tetrahedron: Asymmetry, 2003, 14, 2195; (d) J. Marco-Contelles and E. de Opazo, J. Org. Chem., 2002, 67, 3705; (e) P. R. Skaanderup and R. A. Madsen, J. Org. Chem., 2003, 68, 2115; (f) J. Marco-Contelles and E. de Opazo, J. Carbohydr. Chem., 2002, 21, 201; (g) J. Marco-Contelles and E. Opazo, Tetrahedron Lett., 2000, 41, 5341; (h) I. Hanna and L. Ric, Org. Lett., 2000, 2, 2651; (i) J. Marco-Contelles and E. Opazo, J. Org. Chem., 2000, 65, 5416; (j) C. Gravier-Pelletier, W. Maton, T. Dintinger, C. Tellier and Y. L. Merrer, Tetrahedron, 2003, 59, 8705; (k) G. Rassu, L. Auzzas, L. Pinna, V. Zambrano, F. Zanardi, L. Battistini, E. Gaetani, C. Curti and G. Casiraghi, J. Org. Chem., 2003, 68, 5881.
- 19 (a) S. Mondal, A. Prathap and K. M Sureshan, J. Org. Chem., 2013, 78, 7690; (b) A. Vidyasagar and K. M. Sureshan, Eur. J. Org. Chem., 2014, 2349; (c) S. Mondal and K. M. Sureshan, Org. Biomol. Chem., 2014, 12, 7279; (d) A. Vidyasagar and K. M. Sureshan, Org. Biomol. Chem., 2015, 13, 3900; (e) S. Mondal and K. M. Sureshan, J. Org. Chem., 2016, 81, 11635; (f) R. Mohanrao, A. Asokan and K. M. Sureshan, Chem. Commun., 2014, 50, 6707.
- 20 J. H. Dam, P. Fristrup and R. Madsen, *J. Org. Chem.*, 2008, 73, 3228.

- 21 W. Huang, H.-Y. Rong and J. Xu, J. Org. Chem., 2015, 80, 6628.
- 22 S. Dey and N. Jayaraman, Pure Appl. Chem., 2014, 86, 1401.
- 23 (a) J. Yang, H. Xu, Y. Zhang, L. Bai, Z. Deng and T. Mahmud, Org. Biomol. Chem., 2011, 9, 438; (b) A. Scaffidi, K. A. Stubbs,
 D. J. Vocadlo and R. V. Stick, Carbohydr. Res., 2008, 343, 2744; (c) D. H. Mac, R. Samineni, A. Sattar,
 S. Chandrasekhar, J. S. Yadav and R. Gree, Tetrahedron, 2011, 67, 9305.
- 24 R. Ding, Y. Liu, M. Han, W. Jiao, J. Li, H. Tian and B. Sun, *J. Org. Chem.*, 2018, **83**, 12939.
- 25 A. Sonousi, A. Vasella and D. Crich, J. Org. Chem., 2020, 85, 7583.
- 26 A. Sevšek, M. Celan, B. Erjavec, L. Q. van Ufford, J. S. Torano, E. E. Moret, R. J. Pieters and N. I. Martin, *Org. Biomol. Chem.*, 2016, 14, 8670.
- 27 H. A. Jung, P. Paudel, S. H. Seong, B.-S. Min and J. S. Choi, *Bioorg. Med. Chem. Lett.*, 2017, 27, 2274.