RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2021, **11**, 9410

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

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Received 30th January 2021
Accepted 23rd February 2021

DOI: 10.1039/d1ra00804h

rsc.li/rsc-advances

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 D-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 H_2/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.

Introduction

Carbohydrate mimics[1] are important tools to unravel complex signalling pathways involving various carbohydrates[2] 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] antidiabetic[9] 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 iminocyclitols[15] *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 seven-membered carbasugar analogs. Both *de novo* synthesis from achiral fossil-derived fine chemicals involving a step of asymmetric induction[17] 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).

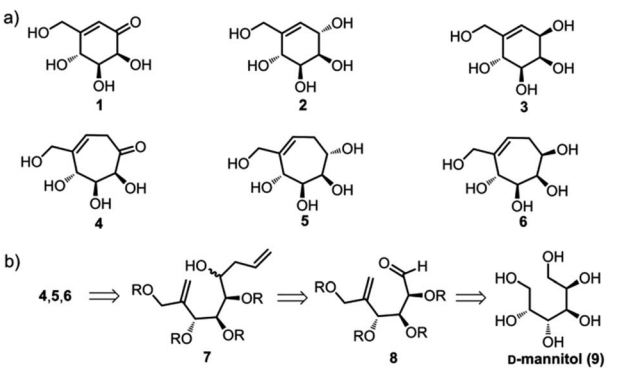

Fig. 1 (a) Chemical structures of gabosine J (**1**), gabosinol J-α (**2**), gabosinol J-β (**3**) and corresponding seven-membered analogs **4**, **5** and **6**. (b) Retrosynthetic analysis of seven-membered analogs **4**, **5** and **6**.

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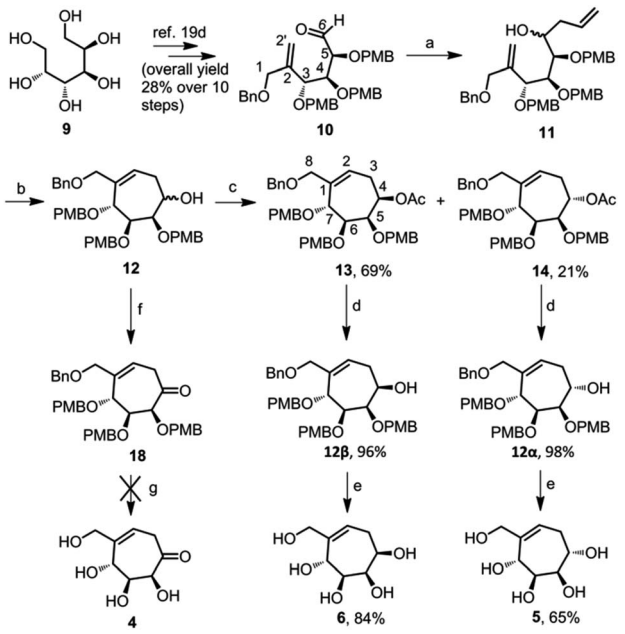
† Electronic supplementary information (ESI) available: Procedures and full characterization of compounds by ^{1}H NMR, ^{13}C NMR. CCDC 2046641 and 2046642. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1ra00804h

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 D-mannitol through several synthetic steps involving a Wittig olefination[21] and several regio- and chemoselective protecting group manipulations (Fig. 1b).

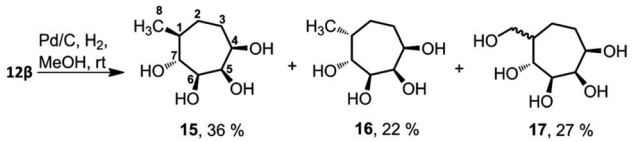
Results and discussion

We synthesized aldehyde **10** in ten steps, starting from D-mannitol **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 ^{1}H 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 ^{1}H 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* 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 ^{1}H 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.



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) Ac_2O, DMAP, pyridine, 3 h; (d) NaOMe, methanol, rt, 12 h; (e) BCl_3, DCM, −78 °C, 3 h; (f) Dess–Martin periodinane, DCM, rt, 4 h, 96%; (g) BCl_3 or BBr_3 or $FeCl_3$ (reagent conditions as per the literature).[19b,23]



Scheme 2 Hydrogenation of **12β** resulting in unusual reduction products **15** and **16**.

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 debenzylated using BCl_3 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 H_2 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 ^{1}H NMR spectroscopy. The non-polar spot also corresponds to two

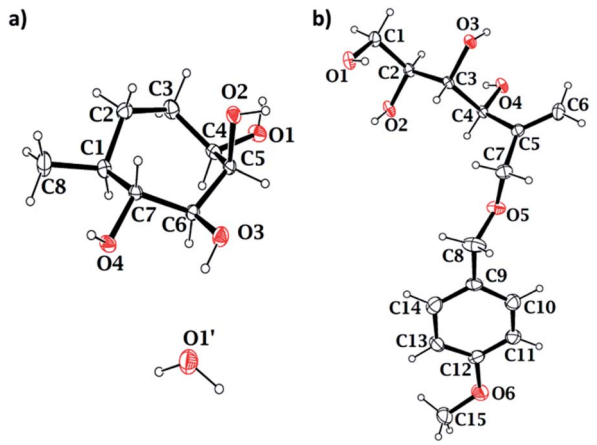


Fig. 2 ORTEP diagram of compounds (a) **15** and (b) **23** with 50% probability level.

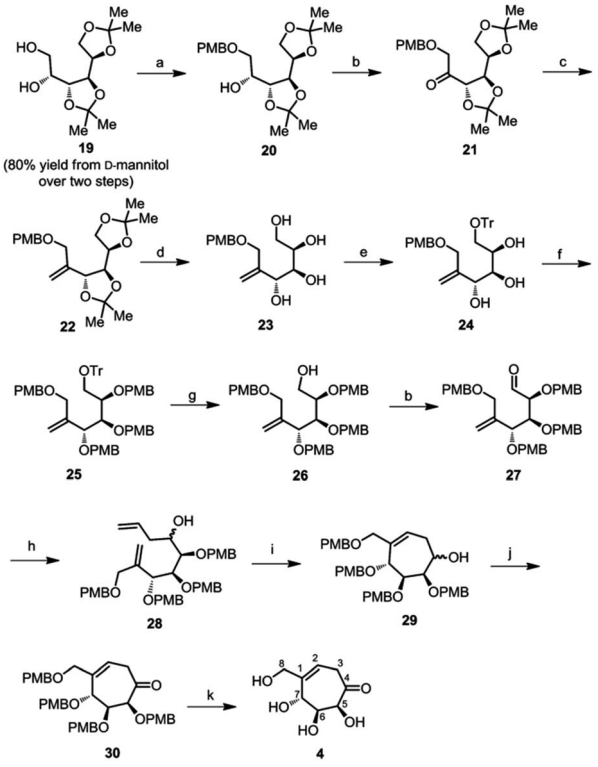
diastereomers, which could be separated when eluted using methanol–chloroform (1 : 6, v/v, R_F 0.3 and 0.25 respectively). We identified the non-polar compound among these two as compound **15** (36% yield) and the polar one as compound **16** (22% yield) by various NMR spectral studies, such as ^{1}H, ^{13}C, 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 compounds **12β** and its precursor. In the crystal structure 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 seven-membered 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 six-membered 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 D-mannitol in an overall yield of 80% over two steps as reported.[19b] Stannylene-acetal-mediated regioselective alkylation of **19** with *p*-methoxybenzyl-chloride gave PMB ether **20** (76% yield) as an oily liquid. Ether **20** on Swern oxidation[24] 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 *p*-methoxybenzyl 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 periodinane[25] 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 α-glucosidase from *Saccharomyces cerevisiae* with IC_{50} values in the range 1–10 mM. On the other hand, none of these compounds inhibits α-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 α-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) PPh_3PCH_3Br, ^{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%.

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

	Percentage inhibition (%) at 1 mM concentration of the inhibitor				
Name of the enzymes	4	5	6	15	16
α-Glucosidase from *Saccharomyces cerevisiae*	41.1 (IC_{50}[a] = 1.5 ± 0.1 mM)	3.3 (IC_{50} = 11.5 ± 0.1 mM)	22.1 (IC_{50} = 2.9 ± 0.4 mM)	19.5 (IC_{50} = 9.5 ± 1.8 mM)	24.3 (IC_{50} = 3.7 ± 0.6 mM)
α-Glucosidase from *Bacillus 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 ± 1.2 mM)
β-Mannosidase from *Helix pomatia*	16.2	NI	NI	NI	NI
α-Galactosidase from *E. coli*	17.5	NI	20.7 (IC_{50} = 3.5 ± 0.3 mM)	34.7 (IC_{50} = 9.4 ± 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 *E. coli*	NI	NI	NI	NI	NI
β-Galactosidase from bovine liver	5.9	42.1 (IC_{50} = 5.6 ± 0.5 mM)	41.9 (IC_{50} = 1.9 ± 0.3 mM)	48.8 (IC_{50} = 1.9 ± 0.5 mM)	25.2 (IC_{50} = 4.6 ± 0.04 mM)
β-Galactosidase from *Aspergillus 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.

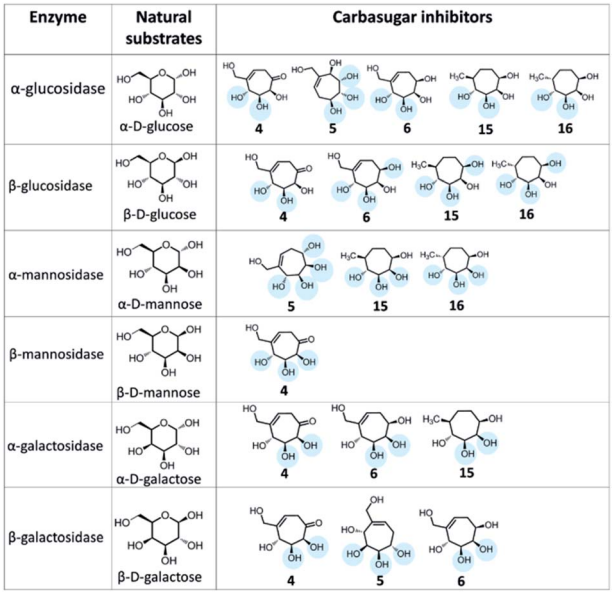


Fig. 3 Structural comparison of enzyme-inhibitors of various glycosidases with their natural substrates.

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 seven-membered 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 ^{1}H NMR, COSY, DEPT, ^{13}C 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). ^{13}C 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.

(5*R*,6*S*,7*R*)-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 Na_2SO_4 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.

(5*R*,6*S*,7*R*)-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 $NaHCO_3$ solution (20 mL × 2), brine and water. The organic layer was dried over anhydrous Na_2SO_4 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_F 0.3 in acetone/petroleum ether, 1 : 4, v/v) and **14** (0.2 g, 21% yield, R_F 0.25 in acetone/petroleum ether, 1 : 4, v/v) as yellow oily liquids.

Data for (1*R*,5*R*,6*S*,7*R*)-4-((benzyloxy)methyl)-5,6,7-tris((4-methoxybenzyl)oxy)cyclohept-3-en-1-yl acetate (13). [α] = −20.3 (*c* 0.14, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 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, –CH_2Ph), 4.53 (d, J = 7.1 Hz, 1H, –CH_2Ph), 4.51 (d, J = 6.8 Hz, 1H, –CH_2Ph), 4.47 (d, J = 8.2 Hz, 1H, H-7), 4.6–4.4 (m, 3H, –CH_2Ph), 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, –$COCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) 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 (–CH_2Ph), 73.3 (–CH_2Ph), 73.1 (–CH_2Ph), 72.7 (C-8), 72.2 (–CH_2Ph), 72.1 (C-4), 55.3 (–OCH_3), 55.2 (–OCH_3), 26.5 (C-3), 21.3 (–$COCH_3$); elemental analysis calcd for $C_{41}H_{46}O_9$; C, 72.12; H, 6.79; found: C, 71.87; H, 6.95.

Data for (1*S*,5*R*,6*S*,7*R*)-4-((benzyloxy)methyl)-5,6,7-tris((4-methoxybenzyl)oxy)cyclohept-3-en-1-yl acetate (14). [α] = −28.5 (*c* 0.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 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, –CH_2Ph), 4.37–4.30 (m, 2H, –CH_2Ph), 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 –OCH_3), 2.53–2.46 (m, 1H, H-3A), 2.27–2.19 (m, 1H, H-3B), 1.95 (s, 3H, –$COCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) 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 (–CH_2Ph), 72.9 (–CH_2Ph), 71.9 (–CH_2Ph), 71.8 (C-4), 70.7 (–CH_2Ph), 55.3 (–OCH_3), 55.2 (–OCH_3), 29.3 (C-3), 21.3 (–$COCH_3$); elemental analysis calcd for $C_{41}H_{46}O_9$; C, 72.12; H, 6.79; found: C, 72.4; H, 6.67.

(1*R*,5*R*,6*S*,7*R*)-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 **12β** (0.18 g, 96% yield) as a pale yellow oily liquid: [α] = −59.8 (*c* 0.25, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 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, –CH_2Ph), 4.57 (d, J = 11.5 Hz, 1H, –CH_2Ph), 4.48–4.04 (m, 3H, –CH_2Ph), 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, –CH_2Ph), 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 –OCH_3), 2.52–2.45 (m, 1H, H-3A), 2.36–2.31 (m, 1H, H-

3B); ^{13}C NMR (125 MHz, $CDCl_3$) 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 (–CH_2Ph), 71.9 (–CH_2Ph), 71.0 (C-4), 70.6 (–CH_2Ph), 70.5 (–CH_2Ph), 55.2 (–OCH_3), 30.8 (C-3); elemental analysis calcd for $C_{39}H_{44}O_8$; C, 73.10; H, 6.92; found: C, 72.94; H, 7.13.

(1*S*,5*R*,6*S*,7*R*)-4-((Benzyloxy)methyl)-5,6,7-tris((4-methoxybenzyl)oxy)cyclohept-3-enol (12α). 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, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 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, J = 8.6 Hz, 2H, Ar-H), 5.95–5.91 (dd, J = 9.5 Hz, 4.1 Hz, 1H, H-2), 4.49 (d, J = 12 Hz, 1H, –CH_2Ph), 4.44–4.34 (m, 5H, –CH_2Ph), 4.29 (d, J = 11 Hz, 1H, –CH_2Ph), 4.17 (d, J = 11.5 Hz, 1H, –CH_2Ph), 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, –OCH_3), 2.71 (br s, 1H, OH), 2.48–2.39 (m, 1H, H-3A), 2.34–2.38 (m, 1H, H-3B); ^{13}C NMR (125 MHz, $CDCl_3$) 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 (–CH_2Ph), 71.9 (–CH_2Ph), 71.8 (–CH_2Ph), 70.6 (–CH_2Ph), 67.7 (C-4), 55.3 (–OCH_3), 55.2 (–OCH_3), 30.7 (C-3); elemental analysis calcd for $C_{39}H_{44}O_8$; C, 73.10; H, 6.92; found: C, 73.31; H, 7.08.

(1*R*,2*R*,3*S*,4*R*)-5-(Hydroxymethyl)cyclohept-5-ene-1,2,3,4-tetraol (6). To a solution of the compound **12β** (0.1 g, 0.16 mmol) in anhydrous DCM (5 mL) stirred at −78 °C, added BCl_3 (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 $NaHCO_3$ 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); ^{1}H NMR (500 MHz, CD_3OD) δ: 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); ^{13}C NMR (125 MHz, CD_3OD) 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 $C_8H_{14}O_5$; C, 50.52; H, 7.42; found: C, 50.71; H, 7.31.

(1*S*,2*R*,3*S*,4*R*)-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: $[\alpha] = -10.9$ (*c* 0.11, methanol); ^{1}H NMR (500 MHz, CD_3OD) 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); ^{13}C NMR (125 MHz, CD_3OD) 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 $C_8H_{14}O_5$; C, 50.52; H, 7.42; found: C, 50.39; H, 7.68.

Reduction of compound 12β. To a solution of compound **12β** (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 H_2 gas for 5 minutes to remove other gases and the reaction mixture was stirred at room temperature for 12 h in H_2 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/$CHCl_3$ (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–$CHCl_3$ (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/$CHCl_3$, 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); ^{1}H NMR (500 MHz, CD_3OD) 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); ^{13}C NMR (125 MHz, CD_3OD) 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 (–CH_3); elemental analysis calcd for $C_8H_{16}O_4$; 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). $[\alpha] = +1.2$ (*c* 0.08, methanol); ^{1}H NMR (500 MHz, CD_3OD) 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); ^{13}C NMR (125 MHz, CD_3OD) 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 (–CH_3); elemental analysis calcd for $C_8H_{16}O_4$; C, 54.53; H, 9.15; found: C, 54.75; H, 9.06.

(*R*)-2-((4-Methoxybenzyl)oxy)-1-((4*R*,4′*R*,5*R*)-2,2,2′,2′-tetramethyl-[4,4′-bi(1,3-dioxolan)]-5-yl)ethanol (20). To a solution of diol **19** (ref. 19*b*) (15 g, 0.057 mol) in anhydrous toluene (250 mL), added Bu_2SnO (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 Na_2SO_4. The solvent was removed under reduced pressure and purified

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, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 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, –CH_2Ph), 4.52 (d, J = 11.85 Hz, 1H, –CH_2Ph), 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, –OCH_3), 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, –CH_3), 1.3–1.27 (m, 9H, –CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 159.2, 130.3, 129.3, 113.7, 110.0 (–$C(CH_3)_2$), 109.5 (–$C(CH_3)_2$), 80.6 (C-4), 79.9 (C-3), 76.2 (C-5), 73.1 (–CH_2Ph), 71.8 (C-2), 71.0 (C-1), 67.5 (C-6), 55.2 (–OCH_3), 27.0 (–CH_3), 26.9 (–CH_3), 26.4 (–CH_3), 25.1 (–CH_3); elemental analysis calcd for $C_{20}H_{30}O_7$; C, 62.81; H, 7.91; found: C, 62.72; H, 8.17.

2-((4-Methoxybenzyl)oxy)-1-((4*R*,4′*R*,5*S*)-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. Et_3N (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 $NaHCO_3$ solution, water and brine. The organic layer was dried over anhydrous Na_2SO_4 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, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 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, –CH_2Ph), 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, –OCH_3), 1.36 (s, 3H, –CH_3), 1.32 (s, 3H, –CH_3), 1.28–1.25 (m, 6H, –CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 204.5 (CO), 158.5, 128.7, 128.1, 112.8, 110.5 (–$C(CH_3)_2$), 108.8 (–$C(CH_3)_2$), 79.6 (C-3), 77.1 (C-4), 75.2 (C-5), 71.9 (–CH_2Ph), 71.5 (C1), 65.5 (C-6), 54.2 (–OCH_3), 25.8 (–CH_3), 25.4 (–CH_3), 25.0 (–CH_3), 24.1 (–CH_3); elemental analysis calcd for $C_{20}H_{28}O_7$; C, 63.14; H, 7.42; found: C, 63.35; H, 7.28.

(4*S*,4′*R*,5*R*)-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 quenched by adding water (5 mL) at 0 °C and THF 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, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 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 –CH_2Ph), 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, –OCH_3), 1.34 (m, 6H, –CH_3), 1.30 (s, 3H, –CH_3), 1.26 (s, 3H, –CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ: 159.1 (Ar), 142.8 (C2), 130.3 (Ar), 129.3 (Ar), 115.6 (C-2′), 113.7 (Ar), 109.6 (–$C(CH_3)_2$), 109.2 (–$C(CH_3)_2$), 80.5 (C-3), 80.3 (C-4), 76.4 (C-5), 71.8 (–CH_2Ph), 69.5 (C-1), 66.7 (C-6), 55.2 (–OCH_3), 27.0 (–CH_3), 26.8 (–CH_3), 26.4 (–CH_3), 25.2 (–CH_3); elemental analysis calcd for $C_{21}H_{30}O_6$; C, 66.65; H, 7.99; found: C, 66.46; H, 8.22.

(2*R*,3*S*,4*R*)-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 quenched by slow addition of Et_3N (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); ^{1}H 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, –CH_2Ph), 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 –OCH_3), 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}C NMR (125 MHz, CD_3OD) 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 (–CH_2Ph), 70.9 (C-3), 70.3 (C-1), 63.6 (C-6), 54.2 (–CH_3); elemental analysis calcd for $C_{15}H_{22}O_6$; C, 60.39; H, 7.43; found: C, 60.61; H, 7.31.

(2*R*,3*S*,4*R*)-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, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 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 –CH_2Ph), 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)); ^{13}C NMR (125 MHz, $CDCl_3$) 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 (–CH_2Ph), 70.3 (C-5), 69.7 (C-1), 63.8 (C-6), 54.2 (–OCH_3);

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 × 3). The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue obtained was purified by column chromatography using ethyl acetate–petroleum ether (1 : 4, v/v) as eluent to yield compound **25** (1.9 g, 76% yield) as a pale yellow liquid: $[\alpha] = -10.2$ (*c* 0.16, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 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, –CH_2Ph), 4.41–4.32 (m, 3H, –CH_2Ph), 4.32–4.24 (m, 2H, –CH_2Ph), 4.15 (d, 1H, J = 11 Hz, –CH_2Ph), 4.12–4.07 (m, 2H, H-3 and –CH_2Ph), 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 × 4), 3.42–3.35 (m, 1H, H-6A), 3.22–3.15 (m, 1H, H-6B); ^{13}C NMR (125 MHz, $CDCl_3$) 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 (–$C(CH_3)_3$), 79.9 (C-4), 79.7 (C-3), 78.5 (C-5), 74.1 (–CH_2Ph), 72.3 (–CH_2Ph), 72.0 (–CH_2Ph), 70.5 (–CH_2Ph), 70.4 (C-1), 63.6 (C-6), 55.3 (–OCH_3), 55.2 (–OCH_3), 55.1 (–OCH_3); elemental analysis calcd for $C_{58}H_{60}O_9$; C, 77.31; H, 6.71; found: C, 77.49; H, 6.60.

(2*R*,3*S*,4*R*)-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 Et_3N (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: $[\alpha] = -13.04$ (*c* 0.14, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.19–7.11 (m, 6H, Ar-H), 7.04 (d, J = 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, –CH_2Ph), 4.45 (d, J = 11.35 Hz, 1H, –CH_2Ph), 4.39 (d, J = 11.45 Hz, 1H, –CH_2Ph), 4.36 (d, J = 11.45 Hz, 1H, –CH_2Ph), 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 –CH_2Ph), 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 (–CH_2Ph), 72.4 (–CH_2Ph), 71.0 (–CH_2Ph), 70.3 (–CH_2Ph), 70.2 (C-1), 60.8 (C-6), 55.3 (–OCH_3), 55.2 (–OCH_3); elemental analysis calcd for $C_{39}H_{46}O_9$; C, 71.10; H, 7.04; found: C, 71.35; H, 6.98.

(2*S*,3*S*,4*R*)-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. Et_3N (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 $NaHCO_3$, water and then brine. The organic layer was dried over anhydrous Na_2SO_4 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, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 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, –CH_2Ph), 4.37 (d, J = 11.5 Hz, 1H, –CH_2Ph), 4.33 (d, J = 11.4 Hz, 1H, –CH_2Ph), 4.32 (d, J = 11.2 Hz, 1H, –CH_2Ph), 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, –OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 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 (–CH_2Ph), 72.4 (–CH_2Ph), 72.1 (–CH_2Ph), 70.7 (–CH_2Ph), 70.0 (C-1), 55.2 (–OCH_3); elemental analysis calcd for $C_{39}H_{44}O_9$; C, 71.32; H, 6.75; found: C, 71.35; H, 6.63.

(5*R*,6*S*,7*R*)-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.

(5*R*,6*S*,7*R*)-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.

(5*R*,6*S*,7*S*)-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% $Na_2S_2O_3$ solution (1 mL). The reaction mixture was diluted with DCM (50 mL), washed with 20% $Na_2S_2O_3$ solution (10 mL × 3) followed by saturated $NaHCO_3$ solution (10 mL × 2) and then brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4 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, $CHCl_3$); ^{1}H 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, –CH_2Ph), 4.64–4.60 (m, 2H, H-5 and –CH_2Ph), 4.43 (d, $J = 11.7$ Hz, 1H, –CH_2Ph), 4.34 (d, $J = 11.1$ Hz, 1H, –CH_2Ph), 4.29–4.24 (m, 4H, –CH_2Ph, 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, –CH_2Ph), 3.77–3.68 (m, 13H, –CH_2Ph and –OCH_3), 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 (–CH_2Ph), 71.8 (–CH_2Ph), 70.9 (–CH_2Ph), 70.6 (–CH_2Ph), 70.5 (C-8), 54.2 (–OCH_3), 40.2 (C-3); elemental analysis calcd for $C_{40}H_{44}O_9$; C, 71.84; H, 6.63; found: C, 72.08; H, 6.55.

(5*R*,6*S*,7*S*)-5,6,7-Trihydroxy-4-(hydroxymethyl)cyclohept-3-enone (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: $[\alpha] = +35.7$ (*c* 0.11, methanol); ^{1}H NMR (500 MHz, CD_3OD) 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); ^{13}C NMR (125 MHz, CD_3OD) 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 method[26] was used to study the glycosidase enzyme inhibition of seven-membered 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 α-glucosidase (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 *p*-nitrophenol 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 = $((A - B)/A) \times 100$. The IC_{50} values were calculated from a plot of concentration of inhibitors *versus* percentage inhibition. The experiments were separately duplicated. Acarbose was used as positive control. IC_{50} for acarbose against α-glucosidase from baker's yeast is obtained to be 166 ± 0.4 μM, which is close to the reported value (178.0 ± 0.27 μM).[27]

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

KMS thanks Department of Science and Technology, India for a SwarnaJayanti Fellowship.

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