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Studies on the synthesis of valienamine and 1-epi-valienamine starting from D-glucose or L-sorbose

Ian Cumpstey,* Sebastian Gehrke, Sayeh Erfan and Riccardo Cribiu

Department of Organic Chemistry, The Arrhenius Laboratory, Stockholm University, 106 91 Stockholm, Sweden

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Abstract—Two synthetic routes to a carbocyclic precursor to valienamine are reported, starting from either D-glucose or L-sorbose and using ring-closing metathesis as a key step. A low-yielding synthesis of 1-epi-valienamine is reported. Results from an abortive third possible route to valienamine based on an early introduction of nitrogen are discussed.

Keywords: Valienamine; Ring-closing metathesis; L-Sorbose

1. Introduction

Valienamine **1** is a highly functionalised cyclohexene that is found in nature as a substructure of acarbose or the validamycin family of antibiotics,[1] where it is coupled to carbohydrates or other carbohydrate-like species, and that can be considered to be a carbasugar (Fig. 1).[2] Valienamine shares its stereochemistry at C-1–C-4 with α-glucose,[†] and has been shown to act as an α-glucosidase inhibitor.[1] Pseudooligosaccharides containing a valienamine unit are linked by a bridging amine rather than by an acetal, so they are hydrolytically stable and may bind to glycoprocessing enzymes without the risk of hydrolysis, and natural and unnatural compounds containing a valienamine moiety have been found to have interesting biological properties.[3] We became interested in synthesising valienamine as part of our ongoing interest in the synthesis of oligosaccharide mimics.[4–6] We needed a route to large quantities of the unsaturated carbasugar or a suitable precursor. In this article, we report our results on the synthesis of a valienamine precursor **19** and also 1-epi-valienamine **2** (resembling β-glucose), starting from cheap carbohydrate starting materials, i.e. D-glucose or L-sorbose.

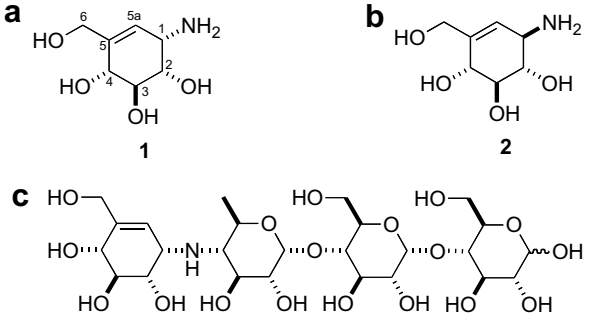

Figure 1. (a) Valienamine; (b) 1-epi-valienamine; (c) acarbose, a naturally occurring valienamine-containing pseudotetrasaccharide.

Various syntheses of valienamine have been reported,[1] including one by Vasella[7] where the carbocyclic ring was closed using a metathesis reaction. In this case, the C=C bond is not in the right position for valienamine, and an isomerisation is necessary. Since many papers using ring-closing metathesis of carbohydrate-derived substrates have been published,[8] we decided to investigate a metathesis-based route to a cyclohexene derivative with the

* Corresponding author. Tel.: +46 (0) 8 16 24 79; fax: +46 (0) 8 15 49 08; e-mail: cumpstey@organ.su.se

† Throughout this paper, carbocyclic derivatives are numbered as carbasugars formally derived from glucose (as shown in Fig. 1). Cyclic glucose and sorbose derivatives are numbered as the parent carbohydrates, while open-chain forms are numbered as shown in Scheme 1 (i.e., with a change in numbering on ring-opening of glucose, e.g., **3**→**4**, but not of sorbose, e.g., **32**→**39**).

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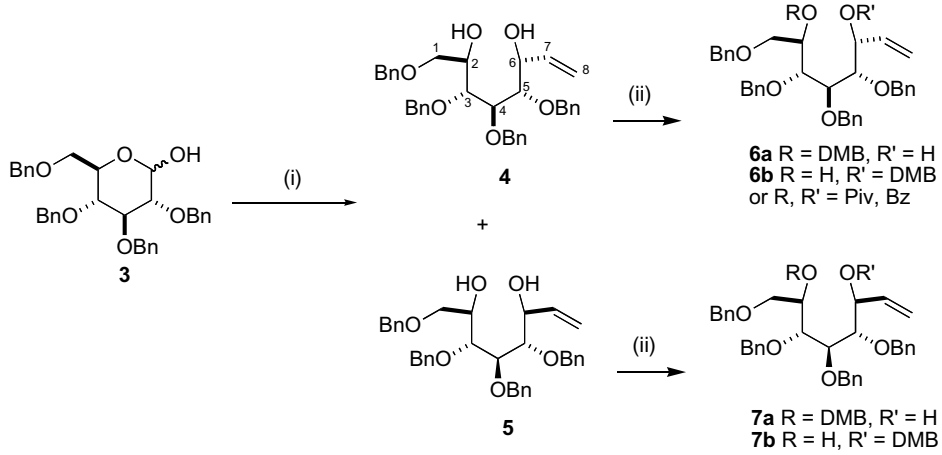
C=C bond in the correct position for valienamine.[9] Other groups have published similar metathesis approaches to C-5=C-5a unsaturated six-membered ring carbasugars starting from the respective aldoses.[10–12]

2. Results and discussion

Our first approach began from 2,3,4,6-tetra-*O*-benzyl glucose **3**, with the plan to introduce the two C=C bonds necessary for metathesis by vinyl Grignard addition to an aldehyde and Wittig methylenation of a ketone. Treatment of **3** with vinylmagnesium bromide gave the alkene diols **4** (65%) and **5** (29%) (Scheme 1; the stereochemistry of the products was assigned later, after ring closure). It has been shown in related systems that changing the solvent or counter-ion, or adding salts (e.g., $MgBr_2$) can effect significant changes in the stereoselectivity of Grignard addition.[13,14] However, for the formation of **4** and **5** from **3**, we were unable to find conditions to improve the stereoselectivity for the formation of **4**: using THF–Et_2O 1:1 as solvent gave virtually no change in yield or selectivity; using vinylmagnesium chloride in toluene–THF, 10:1 gave lower stereoselectivity and yield (**4**, 45%; **5**, 33%); using a $MgBr_2{\cdot}OEt_2$ (3 equiv) additive (vinylmagnesium bromide (5 equiv) in THF), resulted in slightly lower stereoselectivity and lower reaction yield (**4**, 41%; **5**, 21%). The formation of **4** as the major product can be rationalised by using a 1,2-chelate model;[15,16] however, variation in stereoselectivity between many similar reported additions to carbohydrate aldehydes or hemiacetals, for example, a dependence of stereoselectivity on protecting groups[17] or on the stereochemistry of substituents remote from the reaction centre,[18] suggests that a model to reliably account for observed selectivities must be rather more complex, as has been noted.[17]

There is some precedent in the literature for the selective protection of allylic secondary alcohols over non-allylic secondary alcohols,[19–21] and also for the propargylic case.[22,23] However, when we attempted to selectively protect the allylic alcohol of **4**, we failed to get good regioselectivity in favour of the allylic alcohol. Our results are summarised in Table 1. In all cases, the other major reaction components were either unreacted starting diol or diprotected compound. Rather good selectivity was found in the alkylation reaction with dimethoxybenzyl chloride,[24] but this alkylation was selective for the non-allylic secondary alcohol (Table 1, entry 4); regioisomers **6a** (R = DMB, R′ = H) and **6b** (R = H, R′ = DMB) were inseparable by column chromatography. We decided nevertheless to proceed with this mixture **6a/b** and use a protection-deprotection strategy to gain access to the required molecule with OH-2 free. In contrast, for the epimer **5**, treatment with dimethoxybenzyl chloride and sodium hydride in DMF



Scheme 1. Reagents and conditions: (i) Vinylmagnesium bromide, THF, 0 °C→rt; **4**, 65%; **5**, 29%; (ii) see Table 1.

Table 1. Attempted regioselective protection

Entry	Starting material	Conditions	X	Ratio (R = H, R′ = X)/(R = X, R′ = H)	Yield
1	**4**	BzCl, py	Bz	75:25	29%
2	**4**	BzCl, Bu_4NI, NaOH, H_2O, CH_2Cl_2	Bz	25:75	43%
3	**4**	PivCl, py	Piv	50:50	27%
4	**4**	DMBCl, NaH, DMF, 0 °C	DMB	9:91	55% (**6a/b**)[a]
5	**5**	DMBCl, NaH, DMF, 0 °C	DMB	65:35	33% (**7b**) + 18% (**7a**)[b]

DMB = 3,4-dimethoxybenzyl.

[a] Disubstituted compound (R = R′ = DMB), 26% was also isolated.

[b] Disubstituted compound (R = R′ = DMB), 9% was also isolated.

resulted in the selective protection of the allylic alcohol OH-6, albeit with a lower selectivity (Table 1, entry 5). In this case, though the regioisomers **7a** (R = DMB, R′ = H) and **7b** (R = H, R′ = DMB) could be partially separated by column chromatography.

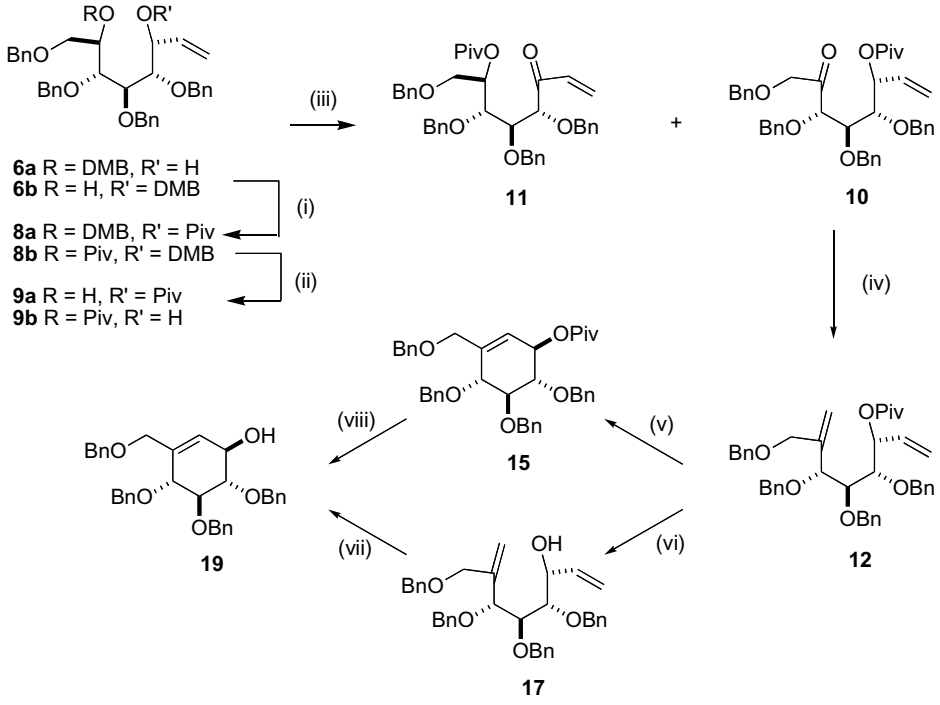
The inseparable mixture of selectively protected alcohols (**6a**:**6b**, 10:1) was treated with pivalyl chloride and pyridine to form pivalate esters at the remaining free OH groups, and the DMB ethers were then removed (Scheme 2). The free alcohols **9a,b** were oxidised under Swern conditions to give the ketones **10** and **11**, which could be separated by column chromatography. Ketone **10** was methylenated by treatment with a phosphonium ylid to give the diene **12**.

Having selectively protected the epimeric diol **5** (the minor diastereomer from Grignard addition), the free alcohol **7b** was subjected to the same Swern conditions, however, this failed to give the ketone product and only unreacted starting material could be recovered from the reaction mixture. Oxidation with PCC was more successful and gave ketone **13** in good yield (Scheme 3). Wittig methylenation of this ketone gave diene **14**.

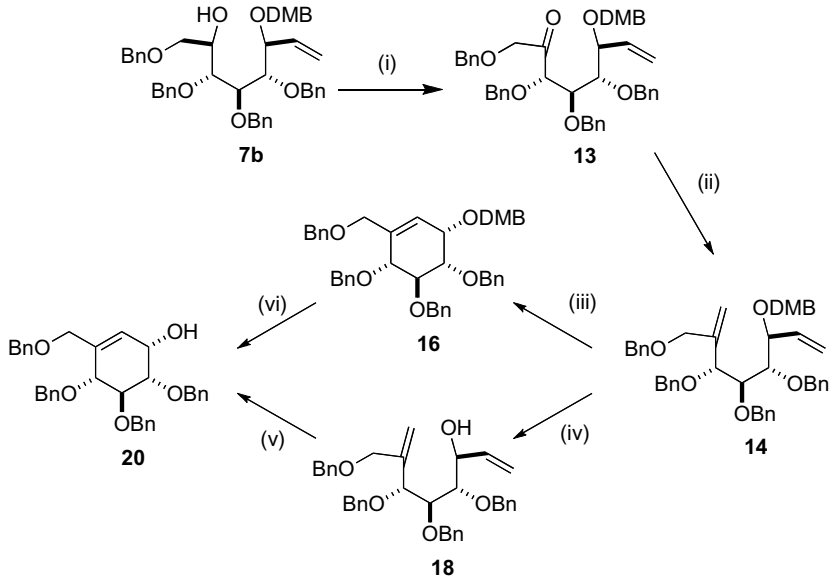
Our attention then turned to the metathesis reaction. Treatment of diene **12** with Grubbs' second generation catalyst (10%) gave the ring-closed carbocycle **15** after a rather long reaction time in reasonable yield (Scheme 2). Starting material still remained and addition of further catalyst did not induce further progress. Under the same conditions, **14** gave the ring-closed product **16** in a rather lower yield. We deprotected **12** and **14** to give C-6-epimeric allylic alcohols **17** and **18**, respectively. Metathesis of these two dienes **17** and **18** now proceeded quickly and with a lower catalyst loading to give the respective carbocycles **19** and **20** in good yield. Deprotected carbocycles **19** and **20** could also be accessed by deprotection after metathesis of **15** and **16**, respectively. The stereochemistry at C-1 could now be assigned using coupling constants in the ^{1}H NMR spectra.[25]

To complete the synthesis of valienamine and 1-epi-valienamine, it was necessary to introduce nitrogen at C-1 and deprotect the resulting molecules.[26] We first considered an alternative strategy based on Grignard addition to a glycosylamine (a hemiaminal): the resulting amino alcohol would not have the same problems of regioselective protection as diols **4** and **5**, and furthermore, the extra steps to introduce nitrogen after ring closure may be avoided.

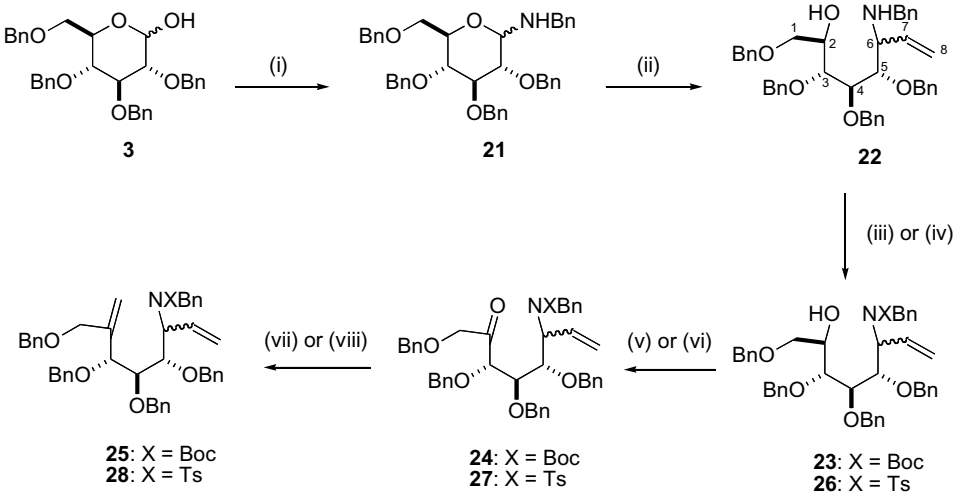
Thus, the benzyl-protected glucose hemiacetal **3** was treated with benzylamine to give the glycosylamine **21** (Scheme 4).[27–29] This was treated with vinylmagnesium bromide and the amino alcohols **22** were formed as a mixture of diastereomers (ratio ca. 2:1). Boc protection of the amine **22** was followed by oxidation of OH-2 and Wittig methylenation to give diene **25**. However, treatment of this diene **25** with Grubbs' second



Scheme 2. Reagents and conditions: (i) PivCl (4 equiv), DMAP (0.5 equiv), pyridine, 96%; (ii) CAN (3 × 1 equiv), MeCN, H_2O, 88%; (iii) $(COCl)_2$ (2.2 equiv), Me_2SO (4.4 equiv), CH_2Cl_2; then Et_3N (5 equiv), 83%; (iv) PPh_3CH_3Br (5 equiv), *t*-BuOK (4.8 equiv), toluene, 80 °C; then **12**, rt, 85%; (v) Grubbs' second generation catalyst (0.1 equiv), toluene, 60 °C, 24 h, 62%; (vi) NaOMe (3 equiv), MeOH, 45 °C, 48 h, 89%; (vii) Grubbs' second generation catalyst (0.015 equiv), toluene, 60 °C, 3 h, 89%; (viii) NaOMe, MeOH, 45 °C, 48 h, 88%.

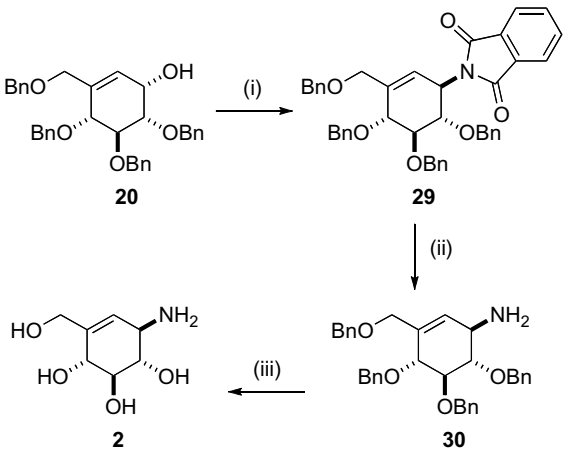


Scheme 3. Reagents and conditions: (i) PCC (3.9 equiv), NaOAc (1.3 equiv), 4 Å, CH_2Cl_2, 82%; (ii) PPh_3CH_3Br (5 equiv), *t*-BuOK (4.8 equiv), toluene, 80 °C; then **13**, rt, 88%; (iii) Grubbs' second generation catalyst (0.08 equiv), DCE, 60 °C, 48 h, 54%; (iv) DDQ (1.2 equiv), CH_2Cl_2, H_2O, 0 °C, 1 h 20 min, 75%; (v) Grubbs' second generation catalyst (0.01 equiv), toluene, 60 °C, 3 h, 90%; (vi) CAN (3 × 1.1 equiv), MeCN, H_2O, rt, 2 h 30 min, 74%.



Scheme 4. Reagents and conditions: (i) $BnNH_2$, CH_2Cl_2, 4 Å, CSA, 4 weeks, 69%; (ii) vinylmagnesium bromide (4 equiv), THF, 0 °C→rt, 42%; (iii) Boc_2O (2.5 equiv), CH_2Cl_2, rt, 48 h, **23**, 88%; (iv) TsCl (1 equiv), Et_3N (1.1 equiv), CH_2Cl_2, 0 °C→rt, 40 h, **26**, 48%; (v) $(COCl)_2$, Me_2SO, CH_2Cl_2 −60 °C, then Et_3N, rt, **24**, 69%; (vi) PCC (4 × 1.3 equiv), NaOAc (1.3 equiv), 4 Å, CH_2Cl_2, rt, **27**, 83%; (vii) Ph_3PMeBr (2 equiv), $NaN(SiMe_3)_2$ (1.6 equiv), −78 °C, **25**, 68%; (viii) PPh_3CH_3Br (1 equiv), *t*-BuOK (0.95 equiv), toluene, 90 °C then **27**, rt, **28**, 95%.

generation catalyst gave no reaction; only unreacted starting material was seen in the NMR spectrum of the crude reaction product. We tried also with the amine protected as its sulfonamide.[30] Thus, amino alcohol **22** was protected on nitrogen with tosyl chloride. Interestingly, one diastereomer of the starting material was much more reactive than the other, and it was possible to obtain a single diastereomer of the sulfonamide product **26** completely pure (according to NMR spectroscopy). Oxidation of OH-2 and Wittig methylenation of the resulting ketone gave the diene **28**. However, once again, Grubbs' second generation catalyst completely failed to give any product, and only starting material could be seen. The results from all our attempted metathesis reactions suggest that the nature of the substituent at the allylic position of one of the double bonds can have a profound effect on the outcome of the reaction, and are consistent with a steric explanation, i.e. that it is the increase in size of the allylic substituent along the sequence: alcohol **17** or **18** < ester **12** or ether



Scheme 5. Reagents and conditions: (i) Phthalimide (2 equiv), DIAD (8 equiv), PPh_3 (8 equiv), THF, 81%; (ii) Ethylene diamine, EtOH; 1:10, 89%; (iii) Na, NH_3, THF, −78 °C, 78%.

14 < doubly protected nitrogen **25** or **28** that is responsible for a decrease in reaction rate. However, they do not rule out alternative explanations based on the different reactivities of hydroxyl groups, esters, ethers, sulfonamides and carbamates towards the ruthenium catalyst. The effect of the stereochemistry and protecting group of an allylic substituent on the outcome of a metathesis reaction has been noted before. In some cases, having a free allylic hydroxyl was necessary for successful metathesis,[31] while for other examples, the yield of metathesis product is higher with a protected allylic hydroxyl (often with a smaller protecting group such as acetate) than with a free allylic alcohol.[32,33] It may be so that for our compounds **17** and **18**, potential side-reactions arising from the free hydroxyl groups are minimal, and that any benefit of running the metathesis reaction with protected hydroxyl groups is lost due to the steric crowding arising from the larger protecting groups in **12** or **14**. A related strategy towards the synthesis of Calystegine B_2 should be mentioned: a synthetic route based on ring-closing metathesis with a doubly protected nitrogen (NBnCbz) at the allylic position failed to give useful yields of the 7-ring carbocycle,[33] a failure ascribed to the steric bulk of the nitrogen group, whereas a metathesis reaction with a doubly protected nitrogen (NBnCbz) at the homoallylic position gave the 7-ring carbocycle in excellent yield.[33,34]

In any case, we abandoned this approach and returned to our original strategy. Key intermediate **19** could be converted to valienamine **1** following Fukase's procedure.[26] The route to 1-epi-valienamine **2** from **20** followed an analogous route: nitrogen was introduced at C-1 of **20** with inversion of configuration by Mitsunobu reaction of the allylic alcohol with phthalimide. Deprotection of phthalimide **29** using ethylene diamine gave the free amine **30**, which was then deprotected under Birch conditions to give 1-epi-valienamine **2** (Scheme 5).[35]

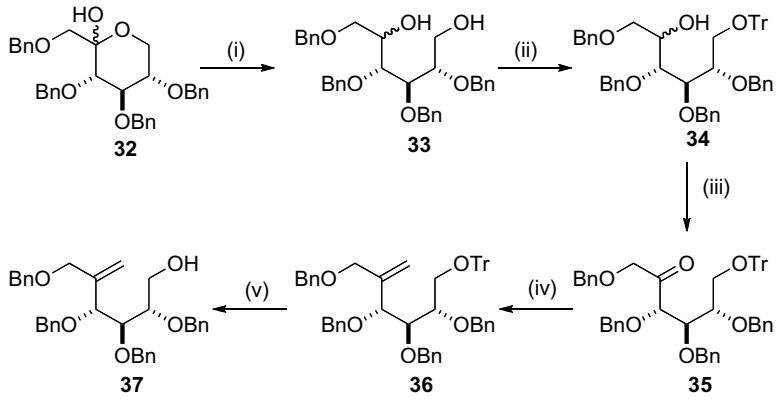
In a final, alternative, and ultimately most successful route to **19** and **20**, we decided to abandon glucose as starting material and instead use the unnatural ketose L-sorbose. D-Glucose is related to L-sorbose by formal reduction at C-1 and oxidation at C-5 (glucose numbering). As it was necessary to oxidise glucose at C-5 during our synthetic sequences described above, starting with this already oxidised ketose with a lack of stereochemical information at C-5 does not detract from the work. Moreover, L-sorbose is a very cheap starting material due to its being an intermediate in the industrial synthesis of vitamin C from glucose.[36] It has been used before both as a starting material for the synthesis of modified carbohydrates[37] and in the synthesis of effective organocatalysts.[38]

Hemiketal **32** is readily produced in three steps from L-sorbose **31** in excellent yield according to a slightly modified literature procedure (see Supplementary data).[39] Wittig reaction on hemiketal **32** would install the methylene group at C-2, and free OH-6 for oxidation to the aldehyde which could then undergo Grignard attack to give the same diene metathesis precursor (**17** or **18**) as we synthesised earlier. Unfortunately, when hemiketal **32** was treated with the ylid generated from *t*-BuOK and Ph_3PMeBr, elimination dominated and none of the desired product **37** could be detected.

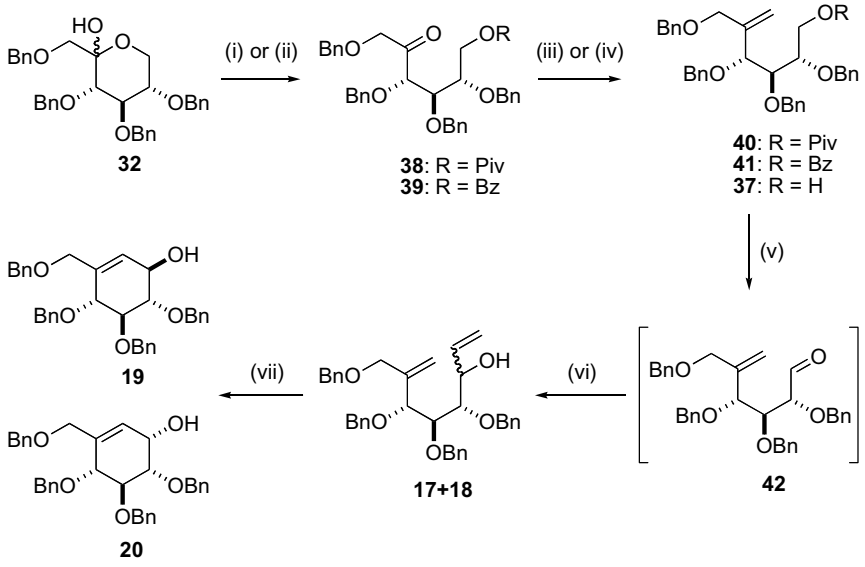
One solution to this was as follows: reduction of hemiketal **32** gave a mixture of diols **33** (Scheme 6). The primary alcohols could be selectively protected as their trityl ethers, and the secondary alcohols could be reoxidised to restore the ketone as described.[39] This ketone **35** underwent clean Wittig methylenation, and detritylation of the primary alcohol gave the desired compound **37**. However, despite high yielding reactions and a lack of selectivity problems, this route was rather long-winded, adding an extra four steps to the ideal, if unattainable, reaction sequence.

As the Wittig reaction worked so well on the C-6-protected ketone **35**, we wondered whether it would be possible to access such a compound directly from hemiacetal **32**, rather than going through the tedious reduction–oxidation procedure. We found that acylation of the hemiacetal with either pivalyl chloride or benzoyl chloride resulted in the exclusive high yielding formation of the OH-6 protected ketones **38** or **39**, respectively (Scheme 7). These ketones **38** and **39** underwent Wittig reaction to give the respective alkenes **40** and **41** with no elimination seen. In the case of the benzoate-protected compound **41**, however, some cleavage of the ester was seen (presumably occurring after methylenation), resulting in the formation of the free C-6 alcohol **37**.

We decided to pursue the benzoate route, due to the ease of deprotection, which was the next reaction step.



Scheme 6. Reagents and conditions: (i) $NaBH_4$ (3 equiv), MeOH, 0 °C→rt, 3 h, 85%; (ii) TrCl (1.5 equiv), DMAP (0.03 equiv), pyridine, 80 °C, 69%; (iii) PDC (7 equiv), 4 Å, CH_2Cl_2, rt, 22 h, 92%; (iv) PPh_3CH_3Br (6 equiv), *t*-BuOK (5.8 equiv), toluene, 80 °C then **37**, rt, >99%; HCOOH, Et_2O, rt, 2 h, 66%.



Scheme 7. Reagents and conditions: (i) PivCl (5 equiv), pyridine, 60 °C, 17 h, **38**, 83%; (ii) BzCl (3 equiv), pyridine, rt, 15 h, **39**, 85%; (iii) *t*-BuOK (4.8 equiv), Ph_3PMeBr (5 equiv), toluene, 80 °C; then **38**, rt; **40**, 91%; (iv) *t*-BuOK (2.4 equiv), Ph_3PMeBr (2.5 equiv), toluene, 80 °C; then **39**, 0 °C→rt; then NaOMe (1 equiv), MeOH; **37**, 92%; (v) $(COCl)_2$ (2.2 equiv), Me_2SO (4.4 equiv), CH_2Cl_2, −60 °C; then Et_3N (5 equiv), −60 °C→rt; (vi) vinylmagnesium bromide (2 equiv), THF, 0 °C→rt, (**17**:**18**, 2:1) 79% from **37**; (vii) Grubbs' second generation catalyst (3 × 0.01 equiv), toluene, 60 °C, 19 h; **19**, 53%; **20**, 21%.

Our best procedure for the Wittig reaction–deprotection, then, was to take the benzoate-protected ketone **39** and methylenate under standard Wittig conditions. Following complete conversion of the ketone to a mixture of the benzoate-protected **41** and free alcohol **37** olefinated compounds, the mixture was filtered and a sodium methoxide solution added, which effected cleavage of any remaining benzoate protection. The free alcohol **37** could in this way be isolated in good yield over two steps.

Oxidation of the primary alcohol in **37** under Swern conditions gave the aldehyde **42**, which was not isolated, but treated directly with vinylmagnesium bromide to give the dienes **17** and **18** as an epimeric mixture. The diastereomers were not separated at this stage, but underwent ring-closing metathesis mediated by Grubbs' second generation catalyst to give the cyclohexenes **19** and **20**, which could now be separated by column chromatography.

2.1. Conclusions

An advanced precursor to valienamine has been synthesised starting from D-glucose and from L-sorbose. The sorbose route is the shorter and more efficient, giving the Fukase intermediate **19** in eight steps from sorbose, and in 30% overall yield; it relies on a reaction in which a hemiketal is forced open by acyl protection,

exposing the naked carbonyl group, which was more amenable to Wittig methylenation than the original hemiketal. The behaviour of some carbohydrate derivatives differing only in the substituent at one allylic position in the ring-closing metathesis reaction is compared: their reactivity followed a trend that could be explained on steric grounds, with compounds bearing an allylic alcohol reacting fastest, and those with a doubly protected nitrogen completely unreactive. However, an alternative electronic explanation cannot be ruled out. The minor diastereomer from Grignard addition was converted into 1-epi-valienamine **2**.

3. Experimental

3.1. General methods

Melting points were measured using a Gallenkamp melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H) spectra were recorded on Bruker Avance II 400 (400 MHz), Varian 300 (300 MHz) or Varian Mercury 400 (400 MHz) spectrometers; multiplicities are quoted as singlet (s), doublet (d), doublet of doublets (dd), triplet (t), apparent triplet (at) or apparent triplet of doublets (atd). Carbon nuclear magnetic resonance (^{13}C) spectra were recorded on Bruker Avance II 400 (100 MHz), Varian Mercury 300 (75 MHz) or Varian Mercury 400 (100 MHz) spectrometers. Spectra were assigned using COSY, HSQC and DEPT experiments. All chemical shifts are quoted on the δ-scale in parts per million (ppm). Residual solvent signals were used as an internal reference. NMR spectra of the di-*N*-substituted carbamates showed a mixture of two rotamers and two diastereomers, and therefore assignments are not reported. Low- (ESI^+) and high-resolution electrospray mass spectra were recorded using a Bruker Microtof instrument or at the mass spectrometry unit, Universidad de Santiago de Compostela, Spain. MALDI spectra were recorded on a Bruker Biflex III spectrometer using 2′,4′,6′-trihydroxyacetophenone trihydrate (THAP) as matrix. Optical rotations were measured on a Perkin–Elmer 241 polarimeter with a path length of 1 dm; concentrations are given in g/100 mL. Thin layer chromatography (TLC) was carried out on Merck Kieselgel sheets, pre-coated with $60F_{254}$ silica. Plates were visualised with UV light and developed using 10% sulfuric acid, or an ammonium molybdate (10% w/v) and cerium (IV) sulfate (2% w/v) solution in 10% sulfuric acid. Flash column chromatography was carried out on silica gel (35–70 μm, Grace). CH_2Cl_2 was distilled from calcium hydride. Et_2O and THF were distilled from sodium benzophenone ketyl radical. Toluene was distilled from sodium. Reactions performed under an atmosphere of nitrogen or argon were maintained by an inflated balloon.

3.2. (2*R*,3*R*,4*R*,5*S*,6*R*)-1,3,4,5-Tetra-*O*-benzyl-oct-7-ene-1,2,3,4,5,6-hexaol (4) and (2*R*,3*R*,4*R*,5*S*,6*S*)-1,3,4,5-tetra-*O*-benzyl-oct-7-ene-1,2,3,4,5,6-hexaol (5)

Hemiacetal **3** (3.1 g, 5.6 mmol) was suspended in THF (10 mL) and cooled to 0 °C under N_2. Vinylmagnesium bromide (22 mL, 1 M in THF, 22 mmol) was added and the resulting solution stirred. After 22 h, NH_4Cl (satd aq) was added dropwise. The mixture was diluted with EtOAc (100 mL) and washed with brine (100 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (CH_2Cl_2–Et_2O 12:1→5:1) to give one diastereoisomer **5** (932 mg, 29%) as a pale yellow oil. $[\alpha]_D^{21}$ +1.5 (*c* 1.0, $CHCl_3$); IR (film); *ν* 3460 (OH) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 3.60 (1H, dd, $J_{1,2} = 4.9$ Hz, $J_{1,1'} = 10.0$ Hz, H-1), 3.62 (1H, dd, $J_{1',2} = 3.8$ Hz, H-1′), 3.70 (1H, dd, $J_{5,6} = 5.2$ Hz, $J_{4,5} = 4.2$ Hz, H-5), 3.83 (1H, dd, $J_{3,4} = 4.3$ Hz, $J_{2,3} = 7.0$ Hz, H-3), 3.91 (1H, at, $J = 4.3$ Hz, H-4), 4.00 (1H, m, H-2), 4.40 (1H, atat, $J = 5.2$ Hz, $J = 1.6$ Hz, H-6), 4.50, 4.56 (2H, ABq, $J_{AB} = 11.9$ Hz, PhCH_2), 4.57 (2H, s, PhCH_2), 4.61, 4.70 (2H, ABq, $J_{AB} = 11.2$ Hz, PhCH_2), 4.62, 4.67 (2H, ABq, $J_{AB} = 11.7$ Hz, PhCH_2), 5.20 (1H, dat, $J_{cis} = 10.4$ Hz, $J = 1.6$ Hz, H-8_{cis}), 5.34 (1H, dat, $J_{trans} = 17.2$ Hz, $J = 1.6$ Hz, H-8_{trans}), 5.84 (1H, ddd, $J_{6,7} = 5.4$ Hz, H-7), 7.21–7.37 (20H, m, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): 71.2, 73.2, 73.6, 74.0 (4 × t, C-1, 4 × Ph*C*H_2), 71.3, 72.4, 77.0, 78.8, 79.7 (5 × d, C-2, C-3, C-4, C-5, C-6), 116.5 (t, C-8), 127.9, 128.0, 128.0, 128.0, 128.1, 128.1, 128.2, 128.3, 128.5, 128.6, 128.7 (11 × d, Bn–CH), 137.6, 138.0, 138.0, 138.2 (4 × s, 4 × Bn–C), 137.6 (d, C-7). MALDI *m*/*z* 607 $[M+K]^+$, 591 $[M+Na]^+$. ESIMS *m*/*z*: $[M+Na]^+$ calcd for $C_{36}H_{40}O_6Na$, 591.2717; found, 591.2734.

And its epimer **4** (2.09 g, 65%) as a pale yellow oil, which solidified on standing. Recrystallisation was difficult, but gave some white crystals, mp 143–145 °C (MeOH); $[\alpha]_D^{21}$ +11.6 (*c* 1.0, $CHCl_3$); IR (film); *ν* 3453 (OH) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 3.64 (1H, dd, $J_{1,2} = 5.0$ Hz, $J_{1,1'} = 9.8$ Hz, H-1), 3.67 (1H, dd, $J_{1',2} = 3.8$ Hz, H-1′), 3.77–3.80 (2H, m, H-3, H-5), 4.00 (1H, dd, $J = 3.4$ Hz, $J = 7.4$ Hz, H-4), 4.08 (1H, m, $J_{2,3} = 7.0$ Hz, H-2), 4.17 (1H, m, H-6), 4.52, 4.57 (2H, ABq, $J_{AB} = 12.0$ Hz, PhCH_2), 4.54, 4.60 (2H, ABq, $J_{AB} = 11.5$ Hz, PhCH_2), 4.62, 4.77 (2H, ABq, $J_{AB} = 11.1$ Hz, PhCH_2), 4.64, 4.74 (2H, ABq, $J_{AB} = 11.2$ Hz, PhCH_2), 5.13 (1H, dat, $J_{cis} = 10.6$ Hz, $J = 1.5$ Hz, H-8_{cis}), 5.26 (1H, dat, $J_{trans} = 17.2$ Hz, $J = 1.5$ Hz, H-8_{trans}), 5.80 (1H, ddd, $J_{6,7} = 4.9$ Hz, H-7), 7.23–7.38 (20H, m, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): 70.9, 72.3, 77.5, 79.4, 81.7 (5 × d, C-2, C-3, C-4, C-5, C-6), 71.4, 73.2, 73.6, 75.0, 75.2 (5 × t, C-1, 4 × Ph*C*H_2), 115.6 (t, C-8), 127.9, 128.0, 128.1, 128.3, 128.4, 128.5, 128.5, 128.6, 128.6 (9 × d, Bn–CH),

137.9, 138.1, 138.3 (3 × s, 4 × Bn–C), 136.8 (d, C-7). MALDI *m/z* 607 $[M+K]^+$, 591 $[M+Na]^+$. ESIMS *m/z*: $[M+Na]^+$ calcd for $C_{36}H_{40}O_6Na$, 591.2717; found, 591.2746.

3.3. (2*R*,3*S*,4*R*,5*S*,6*R*)-1,3,4,5-Tetra-*O*-benzyl-2-*O*-(3,4-dimethoxybenzyl)-oct-7-ene-1,2,3,4,5,6-hexaol (6a), (2*R*,3*R*,4*S*,5*R*,6*R*)-1,3,4,5-tetra-*O*-benzyl-6-*O*-(3,4-dimethoxybenzyl)-oct-7-ene-1,2,3,4,5,6-hexaol (6b) and (2*R*,3*S*,4*R*,5*R*,6*R*)-1,3,4,5-tetra-*O*-benzyl-2,6-bis-*O*-(3,4-dimethoxybenzyl)-oct-7-ene-1,2,3,4,5,6-hexaol

Diol **4** (1.50 g, 2.64 mmol) was dissolved in DMF (20 mL) and cooled to 0 °C under N_2. Dimethoxybenzyl chloride (516 mg, 2.77 mmol) and NaH (60% in oil, 211 mg, 5.28 mmol) were added, and the mixture was stirred at 0 °C. After 1 h 30 min, TLC (CH_2Cl_2–Et_2O 19:1) showed the formation of mono- ($R_f = 0.4$) and disubstituted ($R_f = 0.6$) products, along with remaining starting material ($R_f = 0.3$). The mixture was diluted with Et_2O (200 mL), and washed with brine (200 mL). The aqueous phase was re-extracted with Et_2O (200 mL), and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (CH_2Cl_2–Et_2O 19:1→9:1) to give the disubstituted compound (589 mg, 26%) as a colourless oil. $[\alpha]_D^{21}$ −11.6 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 3.65–3.94 (6H, m, H-1, H-1′, H-2, H-3, H-4, H-5), 3.71, 3.73, 3.83, 3.85 (12H, 4 × s, 4 × OCH_3), 4.03 (1H, at, $J = 6.7$ Hz, H-6), 4.25 (1H, d, $J = 11.3$ Hz, ArC*H*H′), 4.40 (1H, d, $J = 11.5$ Hz, ArC*H*H′), 4.45–4.76 (9H, m, 9 × benzylic-H), 4.83 (1H, d, $J = 11.5$ Hz, ArCH*H*′), 5.10 (1H, d, $J_{trans} = 17.3$ Hz, H-8_{trans}), 5.19 (1H, d, $J_{cis} = 10.2$ Hz, H-8_{cis}), 5.69 (1H, ddd, $J_{6,7} = 7.7$ Hz, H-7), 6.72–6.84 (6H, m, DMB–H), 7.21–7.32 (20H, m, Bn–H); ^{13}C NMR (75 MHz, $CDCl_3$): 55.8, 55.8, 56.0, 56.0 (4 × q, 4 × OCH_3), 70.4, 70.5, 71.9, 73.4, 74.0, 74.7, 74.9 (7 × t, C-1, 4 × Ph*C*H$_2$, 2 × DMP*C*H$_2$), 79.4, 79.4, 79.7, 80.7, 82.2 (5 × d, C-2, C-3, C-4, C-5, C-6), 110.9, 111.0, 111.1, 111.7, 120.0, 120.8 (6 × d, 6 × DMB–H), 119.0 (t, C-8), 127.3, 127.5, 127.6, 127.8, 128.0, 128.3, 128.3, 128.4 (8 × d, Bn–CH), 130.8, 131.4 (2 × s, 2 × DMB–C), 135.8 (d, C-7), 138.5, 138.9, 139.0, 139.2 (4 × s, 4 × Bn–C), 148.4, 148.6, 148.9, 149.0 (4 × s, DMB–C). MALDI *m/z* 908 $[M+K]^+$, 892 $[M+Na]^+$. ESIMS *m/z*: $[M+Na]^+$ calcd for $C_{54}H_{60}O_{10}Na$, 891.4079; found, 891.4114.

The monoprotected compounds **6a/b** (1.04 g, 55%) as a colourless oil (**6a**:**6b** ratio ca. 10:1). ^1H NMR data for **6a** (300 MHz, $CDCl_3$): 3.65 (1H, dd, $J = 2.9$ Hz, $J = 6.4$ Hz, H-5), 3.74–3.79 (4H, m, OCH_3), 3.86 (s, OCH_3), 3.91–3.96 (4H, m), 4.16 (1H, m, H-6), 4.42, 4.60 (2H, ABq, $J_{AB} = 12.1$ Hz, ArCH_2), 4.56 (1H, d, $J = 11.3$ Hz, ArC*H*H′), 4.62 (1H, d, $J = 11.5$ Hz, ArC*H*H′), 4.64 (1H, d, $J = 11.3$ Hz, ArC*H*H′), 4.70 (1H, d, $J = 11.0$ Hz, ArCH*H*′), 4.71 (1H, d, $J = 11.5$ Hz, ArCH*H*′), 4.76 (1H, d, $J = 11.5$ Hz, ArCH*H*′), 5.09 (1H, dat, $J_{cis} = 10.4$ Hz, $J = 1.5$ Hz, H-8_{cis}), 5.22 (1H, dat, $J_{trans} = 17.3$ Hz, $J = 1.6$ Hz, H-8_{trans}), 5.71 (1H, ddd, $J_{6,7} = 5.0$ Hz, H-7), 6.77 (1H, d, $J = 8.1$ Hz, DMB–H), 6.82 (1H, dd, $J = 1.6$ Hz, $J = 8.1$ Hz, DMB–H), 6.87 (1H, d, $J = 1.6$ Hz, DMB–H), 7.23–7.34 (20H, m, Ar-H). MALDI *m/z* 757 $[M+K]^+$, 741 $[M+Na]^+$. ESIMS *m/z*: $[M+Na]^+$ calcd for $C_{45}H_{50}O_8Na$, 741.3398; found, 741.3385.

And recovered starting material **4** (261 mg, 17%), as a colourless oil.

3.4. (2*R*,3*S*,4*S*,5*R*,6*R*)-1,3,4,5-Tetra-*O*-benzyl-2-*O*-(3,4-dimethoxybenzyl)-6-*O*-pivalyl-oct-7-ene-1,2,3,4,5,6-hexaol (8a), (2*R*,3*S*,4*R*,5*R*,6*R*)-1,3,4,5-tetra-*O*-benzyl-6-*O*-(3,4-dimethoxybenzyl)-2-*O*-pivalyl-oct-7-ene-1,2,3,4,5,6-hexaol (8b)

Mixture **6a/b** (2.24 g, 3.12 mmol) was dissolved in pyridine. Pivalyl chloride (1.5 mL, 12.5 mmol) and DMAP (230 mg, 1.6 mmol) were added and the mixture was stirred at rt. After 22 h, TLC (pentane–EtOAc 3:1) showed the formation of a major product ($R_f = 0.7$) and the complete consumption of starting material ($R_f = 0.2$). The mixture was diluted with EtOAc (200 mL), washed with HCl (1 M, 200 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (pentane–EtOAc 4:1) to give the fully protected compounds **8a/b** (2.41 g, 96%) as a colourless oil. MALDI *m/z* 842 $[M+K]^+$, 826 $[M+Na]^+$. ESIMS *m/z*: $[M+Na]^+$ calcd for $C_{50}H_{58}O_9Na$, 825.3973; found, 825.3967.

3.5. (2*R*,3*R*,4*S*,5*R*,6*R*)-1,3,4,5-Tetra-*O*-benzyl-6-*O*-pivalyl-oct-7-ene-1,2,3,4,5,6-hexaol (9a), (2*R*,3*S*,4*R*,5*S*,6*R*)-1,3,4,5-tetra-*O*-benzyl-2-*O*-pivalyl-oct-7-ene-1,2,3,4,5,6-hexaol (9b)

Mixture **8a/b** (2.41 g, 3.0 mmol) was dissolved in MeCN (27 mL), and water (3 mL) was added. The mixture was cooled to 0 °C under N_2. Cerium ammonium nitrate (3 × 1.38 g, 3.0 mmol) was added in three portions at hourly intervals. After the final addition, the mixture was stirred at 0 °C for 1 h, after which time it was removed from the ice-bath and stirred for a further 2 h at rt. After this time, TLC (pentane–EtOAc 4:1) showed the formation of a major product ($R_f = 0.5$) and the complete consumption of starting material ($R_f = 0.4$). The mixture was diluted with CH_2Cl_2 (200 mL) and washed with NH_4Cl (satd aq, 200 mL). The aqueous phase was re-extracted with CH_2Cl_2 (100 mL), and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (pentane–EtOAc 5:1) to give the deprotected compounds **9a/b** (1.73 g, 88%) as

a colourless oil. MALDI *m/z* 691 $[M+K]^+$, 675 $[M+Na]^+$. ESIMS *m/z*: $[M+Na]^+$ calcd for $C_{41}H_{48}O_7Na$, 675.3292; found, 675.3312.

3.6. (3*S*,4*R*,5*R*,6*R*)-1,3,4,5-Tetra-*O*-benzyl-6-*O*-pivalyl-1,3,4,5,6-pentahydroxy-oct-7-en-2-one (10)

Oxalyl chloride (0.51 mL, 5.83 mmol) was dissolved in CH_2Cl_2 (6 mL) and cooled to −60 °C. Me_2SO (0.83 mL, 11.7 mmol) was dissolved in CH_2Cl_2 (6 mL) and added, and the mixture was stirred at −60 °C. After 30 min, alcohols **9a/b** were added by cannula under N_2, and the mixture was stirred at −60 °C. After 1 h, Et_3N (1.84 mL, 13.3 mmol) was added. The mixture was removed from the cooling bath and stirred further at rt. After 2 h, TLC (pentane–EtOAc 5:1) showed the formation of major ($R_f = 0.4$) and minor ($R_f = 0.5$) products, and the complete consumption of the starting material ($R_f = 0.3$). The mixture was diluted with CH_2Cl_2 (200 mL) and washed with water (200 mL). The aqueous phase was re-extracted with CH_2Cl_2 (100 mL), and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (pentane–EtOAc 6:1) to give the ketone **10** (1.43 g, 83%) as a colourless oil. $[\alpha]_D^{21}$ −4.7 (*c* 1.0, $CHCl_3$); IR (film); *ν* 1731 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.22 (9H, s, $C(CH_3)_3$), 3.84 (1H, at, $J = 5.2$ Hz, H-5), 3.91 (1H, at, $J = 4.5$ Hz, H-4), 4.09 (1H, d, $J_{3,4} = 3.8$ Hz, H-3), 4.22, 4.34 (4H, 2 × s, H-1, H-1′, PhCH_2), 4.41, 4.68 (2H, ABq, $J_{AB} = 11.6$ Hz, PhCH_2), 4.46 (1H, d, $J = 11.0$ Hz, PhCHH′), 4.59–4.63 (2H, m, PhCHH′, PhCHH′), 4.67 (1H, d, $J = 11.3$ Hz, PhCHH′), 5.11–5.21 (2H, m, H-8, H-8′), 5.40 (1H, at, $J = 5.6$ Hz, H-6), 5.80 (1H, ddd, $J_{cis} = 10.7$ Hz, $J_{trans} = 17.3$ Hz, $J_{6,7} = 6.0$ Hz, H-7), 7.17–7.39 (20H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): 27.3 (q, C(CH$_3$)$_3$), 39.1 (s, C(CH$_3$)$_3$), 73.3, 73.8, 74.5, 74.5, 74.6 (5 × t, C-1, 4 × PhCH$_2$), 73.7, 79.4, 80.1, 81.1 (4 × d, C-3, C-4, C-5, C-6), 117.4 (t, C-8), 127.8, 128.0, 128.0, 128.3, 128.4, 128.4, 128.4, 128.5, 128.7 (9 × d, Bn–CH), 133.7 (d, C-7), 137.1, 137.5, 137.6, 138.3 (4 × s, 4 × Bn–C), 177.5 (s, OC=O), 206.7 (s, C-2). MALDI *m/z* 689 $[M+K]^+$, 673 $[M+Na]^+$. ESIMS *m/z*: $[M+Na]^+$ calcd for $C_{41}H_{46}O_7Na$, 673.3136; found, 673.3155.

The α,β-unsaturated ketone **11** was also isolated for characterisation. A colourless oil; IR (film); *ν* 1729 (OC=O), 1698 (C=C–C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.19 (9H, s, $C(CH_3)_3$), 3.65 (1H, dd, $J_{7,8} = 5.8$ Hz, $J_{8,8'} = 10.2$ Hz, H-8), 3.90 (1H, dd, $J_{7,8'} = 5.2$ Hz, H-8′), 4.03–4.04 (2H, m, H-5, H-6), 4.22 (1H, br s, H-4), 4.33–4.71 (8H, m, 4 × PhCH_2), 5.23 (m, H-7), 5.52 (1H, dd, $J_{1,1'} = 1.6$ Hz, $J_{cis} = 10.4$ Hz, H-1$_{cis}$), 6.23 (1H, dd, $J_{trans} = 17.6$ Hz, H-1$_{trans}$), 6.66 (1H, dd, H-2), 7.13–7.36 (20H, m, Ar-H). MALDI *m/z* 689 $[M+K]^+$, 673 $[M+Na]^+$. ESIMS *m/z*: $[M+Na]^+$ calcd for $C_{41}H_{46}O_7Na$, 673.3136; found, 673.3139.

3.7. (3*R*,4*S*,5*R*,6*R*)-1,3,4,5-Tetra-*O*-benzyl-6-*O*-pivalyl-2-methylene-oct-7-ene-1,3,4,5,6-pentaol (12)

Methyltriphenylphosphonium bromide (3.3 g, 9.23 mmol) and potassium *tert*-butoxide (984 mg, 8.78 mmol) were suspended in toluene (20 mL) and the mixture was stirred at 80 °C. After 3 h, the mixture was removed from the heat bath and allowed to cool to rt. Ketone **10** (1.20 g, 1.85 mmol) was dissolved in toluene (20 mL) and added by cannula under N_2 and the mixture was stirred at rt. After 2 h, TLC (pentane–EtOAc 6:1) showed the formation of a major product ($R_f = 0.4$), and the complete consumption of starting material ($R_f = 0.3$). The mixture was filtered through Celite and concentrated in vacuo. The residue was purified by flash column chromatography (pentane–EtOAc 9:1) to give the diene **12** (1.02 g, 85%) as a colourless oil. $[\alpha]_D^{21}$ −17.9 (*c* 1.0, $CHCl_3$); IR (film); *ν* 1729 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.18 (9H, s, $C(CH_3)_3$), 3.73–3.80 (2H, m, H-4, H-5), 3.96 (1H, d, $J_{1,1'} = 13.0$ Hz, H-1), 4.04 (1H, d, H-1′), 4.26 (1H, d, $J_{3,4} = 5.2$ Hz, H-3), 4.31, 4.56 (2H, ABq, $J_{AB} = 11.5$ Hz, PhCH_2), 4.48, 4.53 (2H, ABq, $J_{AB} = 12.1$ Hz, PhCH_2), 4.63, 4.78 (2H, ABq, $J_{AB} = 11.0$ Hz, PhCH_2), 4.63, 4.76 (2H, ABq, $J_{AB} = 11.5$ Hz, PhCH_2), 5.06 (1H, dat, $J_{cis} = 10.2$ Hz, $J = 1.1$ Hz, H-8$_{cis}$), 5.12 (1H, dat, $J_{trans} = 17.3$ Hz, $J = 1.3$ Hz, H-8$_{trans}$), 5.26 (1H, s, H-2a), 5.40–5.45 (2H, m, H-6, H-2a′), 5.69 (1H, ddd, $J_{6,7} = 6.3$ Hz, H-7), 7.23–7.38 (20H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): 27.3 (q, C(CH$_3$)$_3$), 39.0 (s, C(CH$_3$)$_3$), 70.0, 71.1, 72.8, 74.1, 74.8 (5 × t, C-1, 4 × PhCH$_2$), 74.5, 80.1, 80.5, 81.7 (4 × d, C-3, C-4, C-5, C-6), 117.0, 117.8 (2 × t, C-2a, C-8), 127.4, 127.5, 127.8, 128.0, 128.3, 128.3, 128.4, 128.5, 128.5 (9 × d, Bn–CH), 134.0 (d, C-7), 138.2, 138.3, 138.8, 139.0 (4 × s, 4 × Bn–C), 142.7 (s, C-2), 177.4 (s, C=O). MALDI *m/z* 687 $[M+K]^+$, 671 $[M+Na]^+$. ESIMS *m/z*: $[M+Na]^+$ calcd for $C_{42}H_{48}O_6Na$, 671.3343; found, 671.3360.

3.8. (1*R*,2*R*,3*S*,4*R*)-2,3,4-Tri-*O*-benzyl-1-*O*-pivalyl-5-(benzyloxymethyl)-cyclohex-5-ene-1,2,3,4-tetrol (15)

Diene **12** (154 mg, 0.24 mmol) was dissolved in toluene (6 mL), and Grubbs' second generation catalyst (12% in wax, 168 mg, 0.024 mmol)[40] was added. The mixture was stirred at 60 °C under Ar. After 24 h, TLC (pentane–EtOAc 7:1) showed consumption of the starting material ($R_f = 0.8$) and the formation of a major product ($R_f = 0.7$). The mixture was concentrated in vacuo, and the residue was purified by flash column chromatography (pentane–EtOAc 12:1) to give the carbocycle **15** (92 mg, 62%) as white crystals, mp 92–93 °C (MeOH);

$[\alpha]_D^{21}$ −71.2 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): 1.21 (9H, s, $C(CH_3)_3$), 3.81 (1H, dd, $J_{1,2} = 7.9$ Hz, $J_{2,3} = 10.4$ Hz, H-2), 3.89 (1H, dd, $J_{3,4} = 7.5$ Hz, H-3), 3.92 (1H, d, $J_{6,6'} = 12.4$ Hz, H-6), 4.22 (1H, d, H-6′), 4.35 (1H, d, H-4), 4.48, 4.52 (2H, ABq, $J_{AB} = 11.8$ Hz, PhCH_2), 4.72, 4.85 (2H, ABq, $J_{AB} = 11.0$ Hz, PhCH_2), 4.74, 4.85 (2H, ABq, $J_{AB} = 11.0$ Hz, PhCH_2), 4.80, 4.95 (2H, ABq, $J_{AB} = 10.9$ Hz, PhCH_2), 5.55–5.58 (2H, m, H-1, H-5a), 7.25–7.36 (20H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): 27.3 (q, C(CH_3)$_3$), 38.9 (s, $C(CH_3)_3$), 70.0, 72.7, 75.0, 75.4, 75.6 (5 × t, C-6, 4 × PhCH_2), 74.2, 79.8, 82.0, 84.3 (4 × d, C-1, C-2, C-3, C-4), 124.2 (d, C-5a), 127.7, 127.7, 127.8, 127.8, 127.9, 128.0, 128.1, 128.5, 128.5, 128.6 (10 × d, Bn–CH), 138.0, 138.1, 138.4, 138.5, 138.6 (5 × s, 4 × Bn–C, C-5), 178.1 (s, C=O). MALDI *m*/*z* 659 $[M+K]^+$, 643 $[M+Na]^+$. ESIMS *m*/*z*: $[M+Na]^+$ calcd for $C_{40}H_{44}O_6Na$, 643.3030; found, 643.3011.

3.9. (3*R*,4*S*,5*S*,6*R*)-1,3,4,5-Tetra-*O*-benzyl-2-methylene-oct-7-ene-1,3,4,5,6-pentaol (17)

3.9.1. Method 1: deprotection of pivalate 12. Sodium (112 mg, 4.87 mmol) was dissolved in MeOH (10 mL) and added to a solution of diene **12** (1.02 g, 1.57 mmol) in MeOH (10 mL), and the mixture was stirred at 45 °C. After 48 h, TLC (pentane–EtOAc 5:1) showed little remaining starting material ($R_f = 0.9$) and the formation of a major product ($R_f = 0.5$). Silica was added, the mixture concentrated in vacuo, and the residue dry-loaded onto a column and purified by flash column chromatography to give the allylic alcohol **17** (786 mg, 89%) as a colourless oil. $[\alpha]_D^{22}$ −12.0 (*c* 1.0, $CHCl_3$); IR (film); *ν* 3464 (OH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 2.59 (1H, br s, OH-6), 3.67 (1H, dd, $J_{4,5} = 6.0$ Hz, $J_{5,6} = 3.0$ Hz, H-5), 3.85 (1H, dd, $J_{3,4} = 4.4$ Hz, H-4), 4.00–4.03 (2H, m, H-1, H-6), 4.09 (1H, d, $J_{1,1'} = 12.8$ Hz, H-1′), 4.27 (1H, d, H-3), 4.33 (1H. d, $J = 11.9$ Hz, PhCHH′), 4.51, 4.56 (2H, ABq, $J_{AB} = 12.0$ Hz, PhCH_2), 4.63–4.73 (5H, m, 2 × PhCH_2, PhCHH'), 5.10 (1H, dd, $J_{cis} = 10.6$ Hz, J_{gem} 1.5 Hz, H-8_{cis}), 5.20 (1H, dd, $J_{trans} = 17.2$ Hz, H-8_{trans}), 5.40, 5.49 (2H, 2 × s, H-2a, H-2a′), 5.78 (1H, ddd, $J_{6,7} = 5.3$ Hz, H-7), 7.24–7.39 (20H, m, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): 70.6 (t, C-1), 70.9, 72.8, 74.9, 75.3 (4 × t, 4 × PhCH_2), 72.3 (d, C-6), 80.1 (d, C-3), 81.0 (d, C-4), 81.8 (d, C-5), 115.6 (t, C-8), 116.8 (t, C-2a), 127.7, 127.7, 127.8, 127.8, 127.9, 128.0, 128.3, 128.4, 128.5, 128.5, 128.6 (11 × d, Ar-CH), 137.9, 138.3, 138.5, 138.6 (4 × s, 4 × Ar-C), 138.7 (d, C-7), 142.5 (s, C-2); ESI^+ *m*/*z* 582 $[M+NH_4]^+$, 100%. ESIMS *m*/*z*: $[M+NH_4]^+$ calcd for $C_{37}H_{44}O_5N$, 582.3214; found, 582.3206.

Also recovered starting material **12** (55 mg, 5%) as a colourless oil.

3.9.2. Method 2: oxidation of alcohol 37 and subsequent Grignard reaction. Oxalyl chloride (0.87 mL, 10.0 mmol) was dissolved in CH_2Cl_2 (5 mL) and cooled to −60 °C. Me_2SO (1.42 mL, 20.0 mmol) was dissolved in CH_2Cl_2 (5 mL) and added, and the mixture was stirred at −60 °C. After 30 min, alcohol **37** (2.45 g, 4.55 mmol) in CH_2Cl_2 (10 mL) was added by cannula under N_2, and the mixture was stirred at −60 °C. After 40 min, Et_3N (3.16 mL, 22.8 mmol) was added. The mixture was allowed to warm up slowly: After 2 h, it had reached −40 °C, and it was removed from the cooling bath and stirred further at rt. After 1 h at rt, TLC (pentane–EtOAc 3:1) showed the formation of a major product (R_f 0.6), and the complete consumption of the starting material ($R_f = 0.4$). The mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo.

The residue was dissolved in THF (5 mL) and cooled to 0 °C under N_2, and vinylmagnesium bromide (0.7 M, 13 mL, 9.1 mmol) was added. After 90 min, the reaction was quenched with NH_4Cl (100 mL) and extracted with EtOAc (2 × 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (pentane–EtOAc 6:1) to give the dienes **17** and **18** (2.02 g, 79%) as a colourless oil (**17**:**18**, 2:1).

3.10. (1*R*,2*S*,3*S*,4*R*)-2,3,4-Tri-*O*-benzyl-5-(benzyloxymethyl)-cyclohex-5-ene-1,2,3,4-tetrol (19)

3.10.1. Method 1: ring-closing metathesis after deacylation. Diene **17** (669 mg, 1.19 mmol) was dissolved in toluene (50 mL). Grubbs second generation catalyst (12% in wax, 126 mg, 0.018 mmol)[40] was added, and the mixture was stirred at 60 °C under Ar. After 3 h, TLC (pentane–EtOAc 3:1) showed the formation of a major product ($R_f = 0.3$), and the near-complete consumption of starting material ($R_f = 0.8$). The mixture was filtered and concentrated in vacuo. The residue was purified by flash column chromatography (pentane–EtOAc 3:1) to give the carbocycle **19** (569 mg, 89%) as white crystals, mp 73–74 °C (EtOAc/pentane), lit.[26] 74–75 °C. $[\alpha]_D^{21}$ −72.8 (*c* 0.5, $CHCl_3$), lit.[26] −66.9; ^1H NMR (400 MHz, $CDCl_3$): 3.57 (1H, dd, $J_{1,2} = 7.4$ Hz, $J_{2,3} = 9.8$ Hz, H-2), 3.85 (1H, dd, $J_{3,4} = 7.0$ Hz, H-3), 3.91 (1H, d, $J_{6,6'} = 12.4$ Hz, H-6), 4.25 (1H, d, H-6′), 4.29–4.34 (2H, m, H-1, H-4), 4.46, 4.52 (2H, ABq, $J_{AB} = 11.9$ Hz, PhCH_2), 4.70, 4.80 (2H, ABq, $J_{AB} = 10.9$ Hz, PhCH_2), 4.73, 4.97 (2H, ABq, $J_{AB} = 11.5$ Hz, PhCH_2), 4.82, 4.93 (2H, ABq, $J_{AB} = 11.1$ Hz, PhCH_2), 5.74 (1H, s, H-5a), 7.26–7.36 (20H, m, Ar-H).

3.10.2. Method 2: deacylation after ring closure. Sodium methoxide (3 mL of a 1 M solution, 3 mmol) was added to a solution of carbocycle **15** (162 mg, 0.26 mmol) in MeOH (3 mL), and the mixture

was stirred at 45 °C. After 48 h, TLC (pentane–EtOAc 5:1) showed little remaining starting material ($R_f = 0.8$) and the formation of a major product ($R_f = 0.1$). AcOH (0.3 mL) was added, and the mixture concentrated in vacuo. The residue was purified by flash column chromatography to give the alcohol **19** (123 mg, 88%) as a white solid, identical to that described above.

3.10.3. Method 3: starting from a diastereomeric mixture of dienes. Dienes **17** and **18** (2:1, 1.73 g, 3.06 mmol) were dissolved in toluene (130 mL), and Grubbs' second generation catalyst (26 mg, 0.03 mmol) was added. The mixture was stirred at 60 °C. Further catalyst (26 mg, 0.03 mmol) was added after 2 h, and again after a further 12 h. After a total of 19 h, TLC (pentane–EtOAc 3:1) showed little starting material ($R_f = 0.6$) and the formation of two products ($R_f = 0.15$ and 0.2). The mixture was concentrated and purified by flash column chromatography (pentane–EtOAc 3:1→2:1) to give the major diastereomer **19** (879 mg, 53%) as a white solid and the minor diastereomer **20** (343 mg, 21%) as a pale brown oil, identical to those described above. A further amount of a colourless oil was isolated and found to be a diastereomeric mixture of the two products (157 mg, 10%, **19**:**20**, 3:2).

3.11. (3*S*,4*R*,5*R*,6*S*)-1,3,4,5-Tetra-*O*-benzyl-6-*O*-(3,4-dimethoxybenzyl)-1,3,4,5,6-pentahydroxy-oct-7-en-2-one (13)

3.11.1. (2*R*,3*S*,4*R*,5*S*,6*S*)-1,3,4,5-Tetra-*O*-benzyl-2-*O*-(3,4-dimethoxybenzyl)-oct-7-ene-1,2,3,4,5,6-hexaol (7a), (2*R*,3*R*,4*S*,5*R*,6*S*)-1,3,4,5-tetra-*O*-benzyl-6-*O*-(3,4-dimethoxybenzyl)-oct-7-ene-1,2,3,4,5,6-hexaol (7b) and (2*R*,3*S*,4*R*,5*R*,6*S*)-1,3,4,5-tetra-*O*-benzyl-2,6-bis-*O*-(3,4-dimethoxybenzyl)-oct-7-ene-1,2,3,4,5,6-hexaol. Diol **5** (1.66 g, 2.90 mmol) was dissolved in DMF (15 mL) and cooled to 0 °C under N_2. Dimethoxybenzyl chloride (516 mg, 2.77 mmol) and NaH (60% in oil, 232 mg, 5.8 mmol) were added, and the mixture was stirred at 0 °C. After 1 h 45 min, TLC (CH_2Cl_2–Et_2O 19:1) showed the formation of three products ($R_f = 0.4$, 0.6 and 0.7), along with remaining starting material ($R_f = 0.3$). The mixture was diluted with Et_2O (200 mL) and washed with brine (200 mL). The aqueous phase was re-extracted with Et_2O (200 mL), and the combined organic extracts were washed with brine (200 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (CH_2Cl_2–Et_2O 40:1, more than one column was necessary) to give the disubstituted compound (223 mg, 9%) as a colourless oil. $[\alpha]_D^{23}$ +6.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): 3.70–3.78 (7H, m, H-1, 2 × OCH_3), 3.83–3.98 (11H, m, H-1′, H-2, H-3, H-4, H-5, 2 × OCH_3), 4.02 (1H, dd, $J_{5,6} = 4.3$ Hz, $J_{6,6'} = 7.7$ Hz, H-6), 4.13 (1H, d, $J = 11.3$ Hz, ArC*H*H′), 4.40, 4.56 (2H, ABq, $J_{AB} = 11.4$ Hz, $ArCH_2$), 4.47–4.50 (3H, m, $ArCH_2$, ArCH*H*′), 4.63–4.73 (5H, m, 2 × $ArCH_2$, ArC*H*H′), 4.80 (1H, d, $J = 11.3$ Hz, ArCH-*H*′), 5.33–5.39 (2H, m, H-8_{trans}, H-8_{cis}), 5.98 (1H, ddd, $J_{cis} = 10.2$ Hz, $J_{trans} = 17.6$ Hz, H-7), 6.72–6.83 (6H, m, DMB–H), 7.22–7.32 (20H, m, Bn–H); ^{13}C NMR (100 MHz, $CDCl_3$): 55.8, 55.8, 56.0, 56.0 (4 × q, 4 × OCH_3), 70.0, 70.4, 72.0, 73.4, 74.1, 74.2, 75.2 (7 × t, C-1, 6 × Ar*C*H_2), 79.3, 79.8, 80.9, 81.8 (4 × d, C-2, C-3, C-4, C-5, C-6), 110.9, 111.0, 111.2, 111.2, 120.1 (5 × d, 6 × DMB–CH), 119.5 (t, C-8), 127.4, 127.5, 127.6, 127.6, 127.7, 127.9, 128.0, 128.1, 128.3, 128.3, 128.4 (11 × d, Bn–CH), 131.2, 131.4 (2 × s, 2 × DMB–C), 136.1 (d, C-7), 138.6, 138.8, 139.0, 139.1 (4 × s, 4 × Bn–C), 148.5, 148.9 (2 × s, DMB–C); ESI$^+$ *m*/*z* 891 $[M+Na]^+$, 100%. ESIMS *m*/*z*: $[M+Na]^+$ calcd for $C_{54}H_{60}O_{10}Na$, 891.4079; found, 891.4054.

The monoprotected compound, major component **7a** (374 mg, 18%, **7a**:**7b**, 7:1) as a colourless oil. IR (film); *v* 3491 (OH) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 3.22 (1H, d, $J_{OH,6} = 6.2$ Hz, OH-6), 3.58 (1H, dd, $J_{4,5} = 4.1$ Hz, $J_{5,6} = 5.3$ Hz, H-5), 3.70–3.79 (4H, m, OCH_3, H-1), 3.81–3.91 (5H, m, OCH_3, H-1′, H-2), 3.94 (1H, dd, $J_{3,4} = 5.9$ Hz, H-4), 4.12 (1H, dd, $J_{2,3} = 3.9$ Hz, H-3), 4.39 (1H, m, H-6), 4.45–4.82 (10H, m, 5 × Ar*C*H_2), 5.18 (1H, dat, $J_{cis} = 10.6$ Hz, $J = 1.7$ Hz, H-8_{cis}), 5.36 (1H, dat, $J_{trans} = 17.2$ Hz, $J = 1.7$ Hz, H-8_{trans}), 5.79 (1H, ddd, $J_{6,7} = 5.1$ Hz, H-7), 6.78 (3H, m, DMB–H), 7.20–7.38 (20H, m, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): 55.8, 56.0 (2 × q, 2 × OCH_3), 69.8 (t, C-1), 71.9, 72.6, 73.5, 74.3, 74.6 (5 × t, 5 × Ar*C*H_2), 72.1 (d, C-6), 79.1, 79.2 (2 × d, C-2, C-3), 79.7 (d, C-4), 80.1 (d, C-5), 110.9, 111.1, 120.1 (3 × d, 3 × DMB–CH), 116.1 (t, C-8), 127.6, 127.7, 127.8, 127.8, 127.8, 128.1, 128.2, 128.3, 128.3, 128.4, 128.5 (11 × d, Bn–CH), 131.2 (s, DMB–C), 137.9 (d, C-7), 138.2, 138.2, 138.3, 138.6 (4 × s, 4 × Bn–C), 148.5, 148.9 (2 × s, 2 × DMB–C); ESI$^+$ *m*/*z* 741 $[M+Na]^+$, 100%. ESIMS: $[M+Na]^+$ calcd for $C_{45}H_{50}O_8Na$, 741.3398; found, 741.3396.

Monoprotected compound, major component **7b** (701 mg, 33%, **7a**:**7b,** 1:5.5) as a colourless oil. IR (film); *v* 3499 (OH) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 3.03 (1H, d, $J_{OH,2} = 4.5$ Hz, OH-2), 3.60 (1H, dd, $J_{1,2} = 5.4$ Hz, $J_{1,1'} = 10.0$ Hz, H-1), 3.63 (1H, dd, $J_{1',2} = 3.7$ Hz, H-1), 3.75 (1H, dd, $J = 4.1$ Hz, $J = 6.9$ Hz), 3.79, 3.86 (6H, 2 × s, 2 × OCH_3), 3.90 (1H, m), 3.99–4.05 (3H, m), 4.19 (1H, d, $J = 11.5$ Hz, ArCH*H*′), 4.49–4.73 (8H, m, 3 × Ar*C*H_2, ArC*H*H′, ArCH*H*′), 4.85 (1H, d, $J = 11.2$ Hz, ArCH*H*′), 5.34 (1H, dd, $J_{trans} = 17.4$ Hz, $J = 1.4$ Hz, H-8_{trans}), 5.39 (1H, dd, $J_{cis} = 10.2$ Hz, $J = 1.7$ Hz, H-8_{cis}), 6.00 (1H, ddd, $J_{6,7} = 7.3$ Hz, H-7), 6.78–6.88 (3H, m, DMB–H), 7.20–7.38 (20H, m, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): 55.8, 56.0 (2 × q, 2 × OCH_3), 70.0, 71.4, 73.1, 73.5, 74.4, 74.6 (6 × t, C-1, 5 × Ar*C*H_2), 71.0 (d, C-2), 77.5, 78.9, 80.8, 81.1 (4 × d, C-3, C-4, C-5, C-6), 111.0,

111.2, 120.2 (3 × d, 3 × DMB–CH), 119.6 (t, C-8), 127.5, 127.7, 127.7, 127.9, 127.9, 128.1, 128.2, 128.3, 128.4, 128.4, 128.4, 128.4, 128.5, 128.5 (14 × d, Bn–CH), 131.2 (s, DMB–C), 135.8 (d, C-7), 138.2, 138.2, 138.4, 138.7 (4 × s, 4 × Bn–C), 148.5, 149.0 (2 × s, 2 × DMB–C); ESI$^+$ *m*/*z* 741 [M+Na]$^+$, 100%. ESIMS *m*/*z*: [M+Na]$^+$ calcd for $C_{45}H_{50}O_8Na$, 741.3398; found, 741.3388.

And recovered starting material **5** (301 mg, 18%) as a colourless oil.

3.11.2. (3*S*,4*R*,5*R*,6*S*)-1,3,4,5-Tetra-*O*-benzyl-6-*O*-(3,4-dimethoxybenzyl)-1,3,4,5,6-pentahydroxy-oct-7-en-2-one (13).

4 Å Molecular sieves (ca. 350 mg) were suspended in CH_2Cl_2 (6 mL) and sodium acetate (34 mg, 0.42 mmol) and pyridinium chlorochromate (90 mg, 0.42 mmol) were added. Alcohol **7a**:**7b**, 5.5:1 (232 mg, 0.32 mmol) was dissolved in CH_2Cl_2 (6 mL) and added to the reaction mixture. The mixture was stirred at rt under N_2. Further PCC (2 × 273 mg, 1.27 mmol) was added after 1 h and after a further 1 h 30 min. After a further 1 h 15 min, TLC (pentane–EtOAc 4:1) showed the formation of a product ($R_f = 0.4$), and the complete consumption of starting material ($R_f = 0.3$). The mixture was loaded directly onto a silica column and purified by flash column chromatography (CH_2Cl_2–Et_2O 20:1) to give the ketone **13** (190 mg, 82%) as a colourless oil. $[\alpha]_D^{24}$ −6.8 (*c* 1.0, $CHCl_3$); IR (film); *v* 1729 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 3.81, 3.85 (6H, 2 × s, 2 × CH_3), 3.86–3.95 (2H, m, H-5, H-6), 4.02 (1H, at, $J = 4.9$ Hz, H-4), 4.16 (1H, d, $J_{3,4} = 4.4$ Hz, H-3), 4.17, 4.51 (2H, ABq, $J_{AB} = 11.3$ Hz, ArCH_2), 4.21, 4.33 (4H, 2 × s, H-1, H-1′, ArCH_2), 4.37, 4.54 (2H, ABq, $J_{AB} = 11.7$ Hz, ArCH_2), 4.44, 4.65 (2H, ABq, $J_{AB} = 11.2$ Hz, ArCH_2), 4.61, 4.70 (2H, ABq, $J_{AB} = 10.8$ Hz, ArCH_2), 5.32–5.40 (2H, m, H-8, H-8′), 5.92 (1H, ddd, $J_{cis} = 10.2$ Hz, $J_{trans} = 17.4$ Hz, $J_{6,7} = 7.4$ Hz, H-7), 6.78–6.86 (3H, m, DMB–H), 7.15–7.34 (20H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): 55.9, 56.0 (2 × q, 2 × OCH_3), 70.1, 73.3, 73.5, 74.4, 74.5, 75.1 (6 × t, C-1, 5 × PhCH_2), 80.1, 80.7, 80.9, 82.1 (4 × d, C-3, C-4, C-5, C-6), 111.0, 111.3, 120.4 (3 × d, DMB–CH), 120.0 (t, C-8), 127.5, 127.8, 127.8, 128.0, 128.2, 128.2, 128.3, 128.4, 128.4, 128.6 (10 × d, Bn–CH), 130.9 (s, DMB–C), 135.8 (d, C-7), 137.1, 137.6, 138.0, 138.6 (4 × s, 4 × Bn–C), 148.6, 149.0 (2 × s, 2 × DMB–C), 207.0 (s, C-2); ESI$^+$ *m*/*z* 739 [M+Na]$^+$, 100%, 734 [M+NH_4]$^+$, 15%. ESIMS *m*/*z*: [M+Na]$^+$ calcd for $C_{45}H_{48}O_8Na$, 739.3241; found, 739.3216.

3.12. (3*R*,4*S*,5*R*,6*S*)-1,3,4,5-Tetra-*O*-benzyl-6-*O*-(3,4-dimethoxybenzyl)-2-methylene-oct-7-ene-1,3,4,5,6-pentaol (14)

Methyltriphenylphosphonium bromide (1.30 g, 3.64 mmol) and potassium *tert*-butoxide (388 mg, 3.47 mmol) were suspended in toluene (10 mL) and the mixture was stirred at 80 °C. After 2 h, the mixture was allowed to cool to rt. Ketone **13** (521 mg, 0.73 mmol) was dissolved in toluene (10 mL) and added by cannula under N_2 and the mixture was stirred at rt. After 2 h, TLC (pentane–EtOAc 7:1) showed the formation of a major product ($R_f = 0.2$), and the complete consumption of starting material ($R_f = 0.1$). The mixture was filtered through Celite and concentrated in vacuo. The residue was purified by flash column chromatography (pentane–EtOAc 7:1→5:1) to give the diene **14** (456 mg, 88%) as a colourless oil. $[\alpha]_D^{22}$ −19.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): 3.79–3.90 (9H, m, H-4, H-5, H-6, 2 × CH_3), 4.01–4.08 (3H, m, H-1, H-1′, ArC*H*H′), 4.25 (1H, d, $J_{3,4} = 5.5$ Hz, H-3), 4.33, 4.59 (2H, ABq, $J_{AB} = 11.8$ Hz, PhCH_2), 4.43 (1H, d, $J = 11.5$ Hz, ArCH*H*′), 4.48, 4.52 (2H, ABq, $J_{AB} = 12.0$ Hz, ArCH_2), 4.61, 4.75 (2H, ABq, $J_{AB} = 11.2$ Hz, ArCH_2), 4.64, 4.85 (2H, ABq, $J_{AB} = 11.3$ Hz, ArCH_2), 5.26 (1H, dd, $J_{trans} = 17.4$ Hz, $J_{gem} = 1.6$ Hz, H-8$_{trans}$), 5.27 (1H, d, $J_{gem} = 1.1$ Hz, H-2a), 5.33 (1H, dd, $J_{cis} = 10.4$ Hz, H-8$_{cis}$), 5.45 (1H, d, H-2a′), 5.97 (1H, m, H-7), 6.77–6.83 (3H, m, DMB–H), 7.24–7.38 (20H, m, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): 55.8, 56.0 (2 × q, 2 × CH_3), 69.9, 70.1, 70.8, 72.7, 74.2, 75.3 (6 × t, C-1, 5 × ArCH_2), 80.3, 80.8, 81.2, 81.5 (4 × d, C-3, C-4, C-5, C-6), 111.0, 111.1, 120.0 (3 × d, DMB–CH), 116.5, 119.4 (2 × t, C-2a, C-8), 127.3, 127.4, 127.6, 127.8, 128.2, 128.2, 128.2, 128.4, 128.5 (9 × d, Bn–CH), 131.4 (s, DMB–C), 136.0 (d, C-7), 138.2, 138.4, 139.1, 139.2 (4 × s, 4 × Bn–C), 142.7 (s, C-2), 148.4, 148.9 (2 × s, 2 × DMB–C); ESI$^+$ *m*/*z* 737 [M+Na]$^+$, 100%. ESIMS *m*/*z*: [M+Na]$^+$ calcd for $C_{46}H_{50}O_7Na$, 737.3449; found, 737.3440.

3.13. (1*S*,2*R*,3*S*,4*R*)-2,3,4-Tri-*O*-benzyl-1-*O*-(3,4-dimethoxybenzyl)-5-(benzyloxymethyl)-cyclohex-5-ene-1,2,3,4-tetrol (16)

Diene **14** (52 mg, 0.073 mmol) was dissolved in dichloroethane (3 mL), and Grubbs' second generation catalyst (6 mg, 0.006 mmol) was added. The mixture was stirred at 60 °C under Ar. After 48 h, TLC (pentane–EtOAc 7:1) showed consumption of starting material ($R_f = 0.3$) and the formation of a major product ($R_f = 0.2$). The mixture was concentrated in vacuo, and the residue purified by flash column chromatography (pentane–EtOAc 5:1) to give the carbocycle **15** (27 mg, 54%) as a colourless oil; $[\alpha]_D^{23}$ +32.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): 3.59 (1H, dd, $J_{1,2} = 3.7$ Hz, $J_{2,3} = 10.1$ Hz, H-2), 3.80, 3.89 (6H, 2 × s, 2 × OCH_3), 3.96 (1H, d, $J_{6,6'} = 12.4$ Hz, H-6), 4.10 (1H, at, $J = 4.4$ Hz, H-1), 4.19–4.22 (2H, m, H-4, H-6′), 4.32 (1H, dd, $J_{3,4} = 7.1$ Hz, H-3), 4.44, 4.49 (2H, ABq, $J_{AB} = 11.9$ Hz, ArCH_2), 4.63–4.72 (3H, m,

ArCH_2, ArCHH′), 4.72, 4.76 (2H, ABq, $J_{AB} = 12.1$ Hz, ArCH_2), 4.81, 5.05 (2H, ABq, $J_{AB} = 11.0$ Hz, ArCH_2), 4.82 (1H, d, $J = 11.2$ Hz, ArCHH'), 5.90 (1H, d, $J_{1,5a} = 5.3$ Hz, H-5a), 6.82 (1H, d, $J = 8.1$ Hz, DMB–H), 6.89 (1H, dd, $J = 1.5$ Hz, DMB–H), 6.97 (1H, d, DMB–H), 7.26–7.38 (20H, m, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): 55.9, 56.0 (2 × q, 2 × OCH_3), 70.4 (t, C-6), 70.6 (d, C-1), 71.7, 72.6, 72.8, 73.9, 75.1 (5 × t, 5 × ArCH$_2$), 79.8, 80.1 (2 × d, C-2, C-4), 80.8 (d, C-3), 110.9, 111.4, 120.5 (3 × d, 3 × DMB–CH), 123.6 (d, C-5a), 127.6, 127.7, 127.8, 127.8, 127.8, 127.9, 128.1, 128.4, 128.5, 128.5 (10 × d, Bn–CH), 131.4 (s, DMB–C), 138.2, 138.7, 138.8, 139.0 (4 × s, 4 × Bn–C), 138.6 (s, C-5), 148.7, 149.2 (2 × s, 2 × DMB–C).

Also recovered starting material **14** (20 mg, 38%).

3.14. (3*R*,4*S*,5*S*,6*S*)-1,3,4,5-Tetra-*O*-benzyl-2-methylene-oct-7-ene-1,3,4,5,6-pentaol (18)

Diene **14** (252 mg, 0.35 mmol) was dissolved in CH_2Cl_2 (12 mL) and water (0.6 mL) was added. The mixture was cooled to 0 °C under N_2. DDQ (96 mg, 0.42 mmol) was added, and the mixture was stirred at 0 °C. After 1 h 20 min, $NaHCO_3$ (satd aq, ca. 5 mL) was added. The mixture was stirred for 5 min, then diluted with CH_2Cl_2 (50 mL) and washed with water (50 mL). The aqueous phase was re-extracted with CH_2Cl_2 (50 mL) and the combined organic extracts dried (Na_2SO_4), filtered and concentrated in vacuo. TLC (pentane–EtOAc 4:1) showed the formation of a major product ($R_f = 0.4$), and the complete consumption of starting material ($R_f = 0.3$). The residue was purified by flash column chromatography (pentane–EtOAc 5:1) to give the diene **18** (150 mg, 75%) as a colourless oil. $[\alpha]_D^{22}$ −35.2 (*c* 1.0, $CHCl_3$); IR (film); *ν* 3474 (OH) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 3.26 (1H, d, $J_{OH,6}$ 6.6 Hz, OH-6), 3.58 (1H, dd, $J_{4,5} = 3.6$ Hz, $J_{5,6} = 4.7$ Hz, H-5), 3.94 (1H, dd, $J_{3,4} = 6.7$ Hz, H-4), 3.97 (1H, d, $J_{1,1'} = 12.4$ Hz, H-1), 4.06 (1H, d, H-1′), 4.32–4.40 (3H. m, H-3, H-6, PhCHH′), 4.47–4.56 (4H, m, PhCH_2, PhCHH′, PhCHH'), 4.64, 4.86 (2H, ABq, $J_{AB} = 10.8$ Hz, PhCH_2), 4.70 (1H, d, $J = 11.5$ Hz, PhCHH'), 5.13 (1H, dat, $J_{cis} = 10.5$ Hz, $J = 1.5$ Hz, H-8$_{cis}$), 5.29–5.33 (2H, m, H-2a, H-8$_{trans}$), 5.43 (1H, d, $J = 1.1$ Hz, H-2a′), 5.74 (1H, ddd, $J_{6,7} = 5.1$ Hz, $J_{trans} = 17.1$ Hz, H-7), 7.24–7.39 (20H, m, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): 70.0 (t, C-1), 70.9, 72.4, 73.0, 74.9 (4 × t, 4 × PhCH$_2$), 71.8 (d, C-6), 79.9 (d, C-5), 80.7 (d, C-4), 82.7 (d, C-3), 116.0 (t, C-8), 117.8 (t, C-2a), 127.7, 127.8, 127.8, 127.9, 127.9, 128.3, 128.4, 128.5, 128.5, 128.6 (10 × d, Ar-CH), 137.9 (d, C-7), 138.2, 138.2, 138.3, 138.4 (4 × s, 4 × Ar-C), 142.7 (s, C-2); *m*/*z* (ESI$^+$) 582 [M+NH$_4$]$^+$, 100%. ESIMS *m*/*z*: [M+NH$_4$]$^+$ calcd for $C_{37}H_{44}O_5N$, 582.3214; found, 582.3206.

3.15. (1*S*,2*S*,3*S*,4*R*)-2,3,4-Tri-*O*-benzyl-5-(benzyloxymethyl)-cyclohex-5-ene-1,2,3,4-tetrol (20)

3.15.1. Method 1: ring-closing metathesis after deprotection. Diene **18** (149 mg, 0.26 mmol) was dissolved in toluene (12 mL). Grubbs second generation catalyst (12% in wax, 19 mg, 0.0026 mmol)[40] was added, and the mixture was stirred at 60 °C under Ar. After 3 h, TLC (pentane–EtOAc 4:1) showed the formation of a major product ($R_f = 0.1$), and the near-complete consumption of starting material ($R_f = 0.5$). The mixture was filtered and concentrated in vacuo. The residue was purified by flash column chromatography (pentane–EtOAc 3:1) to give carbocycle **20** (128 mg, 90%) as a colourless oil; $[\alpha]_D^{21}$ −7.8 (*c* 0.5, $CHCl_3$); IR (film); *ν* 3448 (OH) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 2.59 (1H, br s, OH-1), 3.61 (1H, dd, $J_{1,2} = 3.8$ Hz, $J_{2,3} = 9.2$ Hz, H-2), 3.95 (1H, d, $J_{6,6'} = 12.1$ Hz, H-6), 4.07 (1H, dd, $J_{3,4} = 6.8$ Hz, H-3), 4.16 (1H, d, H-4), 4.24 (1H, d, H-6′), 4.32 (1H, br m, H-1), 4.44, 4.50 (2H, ABq, $J_{AB} = 11.8$ Hz, PhCH_2), 4.65–4.82 (5H, m, 2 × PhCH_2, PhCHH′), 4.89 (1H, d, $J = 11.0$ Hz, PhCHH'), 5.92 (1H, d, $J_{1,5a} = 4.2$ Hz, H-5a), 7.26–7.33 (20H, m, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): 65.2 (d, C-1), 70.4 (t, C-6), 72.7, 73.0, 74.2, 74.9 (4 × t, 4 × PhCH$_2$), 78.9, 79.0, 79.2 (3 × d, C-2, C-3, C-4), 124.8 (d, C-5a), 127.7, 127.8, 127.8, 127.9, 128.1, 128.1, 128.2, 128.5, 128.5, 128.6, 128.7 (11 × d, Ar-CH), 138.1, 138.2, 138.7, 138.7 (4 × s, 4 × Bn–C), 139.9 (s, C-5); ESI$^+$ *m*/*z* 559 [M+Na]$^+$, 100%. ESIMS *m*/*z*: [M+Na]$^+$ calcd for $C_{35}H_{36}O_5Na$, 559.2455; found, 559.2461.

3.15.2. Method 2: deprotection after ring closure. Carbocycle **16** (33 mg, 0.048 mmol) was dissolved in a mixture of MeCN (1.8 mL) and water (0.2 mL). CAN (90 mg, 0.165 mmol) was added in three portions over 1 h. After a further 90 min, TLC (pentane–EtOAc 3:1) showed the conversion of the starting material ($R_f = 0.3$) into a major product ($R_f = 0.2$). The reaction mixture was added to ammonium bicarbonate (satd aq, 25 mL), and extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (CH_2Cl_2–Et_2O 30:1→20:1) to give the deprotected carbocycle **20** (19 mg, 74%), identical to that described above.

3.16. (1*R*,2*S*,3*S*,4*R*)-2,3,4-Tri-*O*-benzyl-5-(benzyloxymethyl)-1-phthalimidocyclohex-5-ene-2,3,4-triol (29)

Alcohol **20** (94 mg, 0.18 mmol) was dissolved in THF. Phthalimide (52 mg, 0.35 mmol) and triphenyl phosphine (371 mg, 1.41 mmol) were added. The mixture was cooled to 0 °C and then DIAD (0.27 mL, 1.41 mmol) was added. The mixture was then allowed to return to rt and stirred under N_2. After 24 h, the reac-

tion mixture was concentrated in vacuo and the residue was purified by flash column chromatography (CH_2Cl_2–Et_2O 40:1) to give the phthalimide derivative **29** (94 mg, 81%) as a colourless oil. $[\alpha]_D^{21}$ −155 (*c* 0.5, $CHCl_3$); IR (film); *ν* 1714 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 3.89 (1H, d, $J_{6,6'} = 13.0$ Hz, H-6), 4.00 (1H, dd, $J = 8.1$ Hz, $J = 10.2$ Hz, H-3), 4.28–4.36 (2H, H-2, H-6′), 4.43, 4.59 (2H, ABq, $J_{AB} = 12.0$ Hz, PhCH_2), 4.48–4.51 (2H, m, H-4, PhC*H*H′), 4.79–4.94 (5H, m, H-1, PhCH_2, PhC*H*H′, PhCH*H*′), 5.05 (1H, d, $J = 11.0$ Hz, PhC*H*H′), 5.46 (1H, s, H-5a), 6.76 (1H, t, $J = 7.4$ Hz, Bn–H), 6.85 (2H, at, $J = 7.3$ Hz, Bn–H), 7.03 (2H, d, $J = 7.0$ Hz, Bn–H), 7.23–7.41 (15H, m, Ar-H), 7.68 (4H, s, Phth-H); ^{13}C NMR (100 MHz, $CDCl_3$): 52.6 (d, C-1), 69.5 (t, C-6), 71.5, 74.9, 75.3, 75.8 (4 × t, 4 × Ph*C*H_2), 78.5 (d, C-2), 80.3 (d, C-4), 86.2 (d, C-3), 123.3, 133.8 (2 × d, Phth-CH), 123.9 (d, C-5a), 127.4, 127.6, 127.8, 128.0, 128.1, 128.1, 128.2, 128.4, 128.4, 128.5, 128.6 (11 × d, Ar-CH), 132.0 (s, Phth-C), 137.6, 138.0, 138.5, 138.6, 138.7 (5 × s, 4 × Bn–C, C-5), 167.7 (s, C=O); ESI^+ *m*/*z* 683 $[M+NH_4]^+$, 100%. ESIMS *m*/*z*: $[M+NH_4]^+$ calcd for $C_{43}H_{43}O_6N_2$, 683.3116; found, 683.3106.

3.17. 1-epi-Valienamine (2)

3.17.1. (1*R*,2*S*,3*S*,4*R*)-1-Amino-2,3,4-tri-*O*-benzyl-5-(benzyloxymethyl)cyclohex-5-ene-2,3,4-triol (30). Phthalimide derivative **29** (94 mg, 0.14 mmol) was dissolved in EtOH (8 mL) and ethylene diamine (0.8 mL), and the mixture was stirred at 70 °C. After 3 h, TLC (EtOAc) showed the presence of a single compound (R_f 0.3). The reaction mixture was concentrated in vacuo and the residue was purified by flash column chromatography (EtOAc; 1% triethylamine) to give the amine **30** (67 mg, 89%) as a colourless oil. $[\alpha]_D^{22}$ −82.3 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): 3.37 (1H, at $J = 9.0$ Hz, H-2), 3.47 (1H, d, $J_{1,2} = 8.6$ Hz, H-1), 3.85 (1H, dd, $J_{2,3} = 9.7$ Hz, $J_{3,4} = 7.7$ Hz, H-3), 3.88 (1H, d, $J_{6,6'} = 11.9$ Hz, H-6), 4.23 (1H, d, H-6′), 4.34 (1H, d, H-4), 4.45, 4.51 (2H, ABq, $J_{AB} = 11.8$ Hz, PhCH_2), 4.68–4.71 (2H, m, 2 × PhC*H*H′), 4.80–4.85 (2H, m, PhC*H*H′, PhCH*H*′), 4.94 (1H, d, $J = 11.2$ Hz, PhCH*H*′), 5.00 (1H, d, $J = 11.4$ Hz, PhCH*H*′), 5.65 (1H, s, H-5a), 7.23–7.35 (20H, m, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): 53.7 (d, C-1), 70.4 (t, C-6), 72.6, 74.7, 75.3, 75.4 (4 × t, 4 × Ph*C*H_2), 80.5 (d, C-4), 84.9 (d, C-3), 85.2 (d, C-2), 127.8, 127.8, 127.9, 128.0, 128.0, 128.3, 128.5, 128.6, 128.7 (9 × d, Ar-CH), 135.9 (s, C-5), 138.3, 138.6 (2 × s, Bn–C).

3.17.2. 1-epi-Valienamine (2). Benzyl ether protected compound **30** (67 mg, 0.12 mmol) was dissolved in THF (2 mL), and the solution cooled to −78 °C under N_2. Ammonia (ca. 10 mL) was condensed into the flask, and sodium (ca. 80 mg) was added. The mixture turned blue, and after the blue colour disappeared (10 min), further sodium (ca. 30 mg) was added. After a further 10 min, NH_4Cl was added to quench the reaction, then the mixture was allowed to warm to rt, and then concentrated in vacuo. The residue was taken up in MeOH (6 mL) and filtered, and the filtrate concentrated to dryness. The residue was dissolved in water (6 mL) and Dowex 50WX8 (H^+ form) was added. After 10 min, the mixture was filtered, and the resin washed with water. The resin was then washed with ammonia (2% aq, 30 mL), and the filtrate concentrated to give the deprotected compound **2** (17 mg, 78%) as an off-white solid. ^1H NMR (500 MHz, D_2O) 3.53–3.60 (2H, m, H-2, H-3), 3.82 (1H, m, H-1), 4.07–4.17 (3H, m, H-4, H-6, H-6′), 5.57 (1H, m, H-5a); ^{13}C NMR (125 MHz, D_2O) 54.1 (d, C-1), 61.4 (t, C-6), 72.0, 72.2 (2 × d, C-2, C-4), 76.1 (d, C-3), 117.5 (d, C-5a), 143.7 (s, C-5). ESIMS *m*/*z*: $[M+Na]^+$ calcd for $C_7H_{13}O_4NNa$, 198.0737; found, 198.0734.

3.18. 1,3,4,5-Tetra-*O*-benzyl-6-*O*-trityl-L-iditol and 1,3,4,5-tetra-*O*-benzyl-6-*O*-trityl-L-gulitol (34)

3.18.1. 1,3,4,5-Tetra-*O*-benzyl-L-iditol and 1,3,4,5-Tetra-*O*-benzyl-L-gulitol (33). Hemiacetal **32**[39] (2.96 g, 5.47 mmol) was suspended in MeOH (30 mL). The mixture was cooled to 0 °C, $NaBH_4$ (0.63 g, 16.6 mmol) was added, and the mixture was stirred at rt. After 3 h, TLC (toluene–EtOAc 6:1) indicated the complete consumption of starting material ($R_f = 0.6$) and the formation of the product ($R_f = 0.1$). The reaction mixture was poured into water, neutralised with NH_4Cl (10% aq, 10 mL), concentrated to less than half of its volume and extracted with EtOAc (100 mL, 2 × 30 mL). The organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (toluene–EtOAc 9:1) to afford the alcohols **33** (2.32 g, 85%) as a yellow oil, as a mixture. The isomers were partially separated by chromatography for characterisation. Isomer 1 $[\alpha]_D^{23}$ +13.8 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): 2.19 (1H, br s, OH-6), 2.99 (1H, d, $J_{OH,2} = 5.1$ Hz, OH-2), 3.56 (1H, m, H-6), 3.64 (2H, m, H-1, H-1′), 3.51–3.81 (3H, m, H-3, H-5, H-6′), 3.89 (1H, dd, J= 3.7 Hz, $J = 6.4$ Hz, H-4), 4.03 (1H, m, H-2), 4.49, 4.53 (2H, ABq, $J_{AB} = 11.9$ Hz, $PhCH_2$), 4.54, 4.58 (2H, ABq, $J_{AB} = 11.5$ Hz, $PhCH_2$), 4.61, 4.66 (2H, ABq, $J_{AB} = 11.6$ Hz, $PhCH_2$), 4.65, 4.71 (2H, ABq, $J_{AB} = 11.3$ Hz, $PhCH_2$), 7.20–7.36 (20H, m, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): 62.0 (t, C-6), 70.9 (d, C-2), 71.3 (t, C-1), 73.2, 73.4, 73.6, 74.7 (4 × t, 4 × $PhCH_2$), 77.5, 79.7 (2 × d, C-3, C-5), 79.3 (d, C-4), 127.9, 128.0, 128.1, 128.1, 128.1, 128.3, 128.6, 128.6, 128.6, 128.6 (10 × d, 10 × Ar-CH), 138.0, 138.0, 138.1, 138.3 (4 × s, 4 × Ar-C). ESIMS *m*/*z*: $[M+Na]^+$ calcd for $C_{34}H_{38}O_6Na$, 265.2561; found, 265.2561.

Isomer 2 $[\alpha]_D^{23}$ +16.3 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): 2.20 (1H, br s, OH-6), 2.64 (1H, d, $J_{OH,2} = 6.7$ Hz, OH-2), 3.37 (1H, dd, $J_{1,1'} = 9.3$ Hz, $J_{1,2} = 6.1$ Hz, H-1), 3.46 (1H, dd, $J_{1,1'} = 9.3$ Hz, $J_{1',2} = 6.4$ Hz, H-1′), 3.67 (1H, m, H-6), 3.70 (1H, m, H-5), 3.78 (1H, m, H-6′), 3.85 (1H, dd, $J_{3,4} = 6.9$ Hz, $J_{2,3} = 2.4$ Hz, H-3), 3.91 (1H, m, H-4), 3.94 (1H, m, H-2), 4.40, 4.46 (2H, ABq, $J_{AB} = 11.9$ Hz, $PhCH_2$), 4.54, 4.75 (2H, ABq, $J_{AB} = 11.2$ Hz, $PhCH_2$), 4.59, 4.63 (2H, ABq, $J_{AB} = 11.6$ Hz, $PhCH_2$), 4.65, 4.71 (2H, ABq, $J_{AB} = 11.4$ Hz, $PhCH_2$), 7.20–7.36 (20H, m, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): 61.8 (t, C-6), 69.7 (d, C-2), 71.4 (t, C-1), 72.7, 73.4, 74.8, 74.8 (4 × t, 4 × $PhCH_2$), 78.3 (C-3), 78.8 (C-5), 79.4 (C-4), 127.9, 128.0, 128.0, 128.0, 128.3, 128.4, 128.5, 128.6, 128.6 (9 × d, 9 × Ar-CH), 138.1, 138.2, 138.2 (3 × s, 3 × Ar-C). ESIMS *m*/*z*: Calcd $[M+Na]^+$ for $C_{34}H_{38}O_6Na$, 565.2561; found, 565.2556.

3.18.2. 1,3,4,5-Tetra-*O*-benzyl-6-*O*-trityl-L-iditol and 1,3,4,5-tetra-*O*-benzyl-6-*O*-trityl-L-gulitol (34). Diols **33** (2.32 g, 4.28 mmol) were suspended in pyridine (40 mL). Trityl chloride (1.79 g, 6.41 mmol) and DMAP (15 mg, 0.13 mmol) were added, and the mixture was stirred at rt and 10 h at 80 °C. After 14 h, TLC (toluene–EtOAc 6:1) indicated the complete consumption of starting material ($R_f = 0.5$) and the formation of major ($R_f = 0.7$) and minor ($R_f = 0.9$) products. The reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography (toluene–EtOAc 1:0→9:1) to afford alcohols **34** (2.33 g, 69%) as a pale yellow oil. (X and Y denote the two alcohols arbitrarily.) ^1H NMR (400 MHz, $CDCl_3$): 2.54 (1H, d, $J_{OH,2} = 6.2$ Hz, OH-2^X), 2.88 (1H, d, $J_{OH,2} = 5.5$ Hz, OH-2^Y), 3.20 (1H, dd, $J_{6,6'} = 10.3$ Hz, $J_{5,6} = 5.2$ Hz, H-6^Y), 3.27 (1H, dd, $J_{1,1'} = 9.4$ Hz, $J_{1,2} = 5.6$ Hz, H-1^X), 3.37–3.40 (3H, m, H-$1'^X$, H-6^X, H-$6'^X$), 3.43 (1H, dd, $J_{6',6} = 10.3$ Hz, $J_{5,6'} = 4.0$ Hz, H-$6'^Y$), 3.54–3.56 (2H, m, H-1^Y, H-$1'^Y$), 3.60 (1H, dd, $J_{3,4} = 3.7$ Hz, $J_{2,3} = 6.8$ Hz, H-3^Y), 3.71 (1H, dd, $J_{2,3} = 2.7$ Hz, $J_{3,4} = 7.0$ Hz, H-3^X), 3.73–3.77 (1H, m, H-2^X), 3.79–3.83 (1H, m, H-5^X), 3.91 (2H, m, H-2^Y, H-5^Y), 3.97 (1H, dd, $J_{4,5} = 3.7$ Hz, $J_{3,4} = 7.0$ Hz, H-4^X), 4.05 (1H, dd, $J_{2,3} = 5.6$ Hz, $J_{3,4} = 3.7$ Hz, H-4^Y), 4.15, 4.36 (2H, ABq, $J_{AB} = 11.4$ Hz, $PhCH_2$), 4.37, 4.41 (2H, ABq, $J_{AB} = 12.0$ Hz, $PhCH_2$), 4.46–4.68 (12H, m, $PhCH_2$), 7.10–7.44 (70H, m, Ar-CH); ^{13}C NMR (100 MHz, $CDCl_3$): 63.1 (t, C-6^Y), 63.4 (t, C-6^X), 70.1 (d, C-2^X), 70.9 (d, C-2^Y), 71.4 (t, C-1^Y), 71.5 (t, C-1^X), 73.0, 73.2, 73.3, 73.4, 74.5, 74.9, 75.0 (7 × t, $PhCH_2$), 77.9 (d, C-3^Y), 78.1 (d, C-5^X), 78.6 (d, C-3^X), 78.6 (d, C-4^X), 79.3 (d, C-5^Y), 79.4 (d, C-4^Y), 127.2, 127.2, 127.6, 127.7, 127.8, 127.8, 127.8, 127.8, 127, 9, 127.9, 128.0, 128.0, 128.0, 128.2, 128.3, 128.4, 128.4, 128.4, 128.5, 128.5, 128.5, 128.5, 128.6, 128.6, 128.9, 128.9, 129.2 (27 × d, Ar-CH), 138.2, 138.3, 138.4, 138.4, 138.5, 138.6 (6 × s, Ar-C) 144.1 (s, Tr-C). ESIMS *m*/*z*: $[M+Na]^+$ calcd for $C_{53}H_{52}O_6Na$, 807.3656; found, 807.3660.

3.19. 1,3,4,5-Tetra-*O*-benzyl-6-*O*-trityl-L-sorbose (35)

Alcohols **34** (2.33 g, 2.96 mmol) were suspended in CH_2Cl_2 (100 mL). Pyridinium dichromate (7.80 g, 21.0 mmol) and molecular sieves (4 Å, 14 g) were added under nitrogen. After 22 h, TLC (toluene–EtOAc 6:1) indicated complete consumption of starting material ($R_f = 0.6$) and the formation of a major product ($R_f = 0.7$). The mixture was filtered through silica, washed with CH_2Cl_2 and concentrated to afford ketone **35** (2.13 g, 92%) as a pale yellow oil. $[\alpha]_D^{23}$ −1.1 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): 3.15 (1H, dd, $J_{6,6'} = 10.4$ Hz, $J_{5,6} = 5.1$ Hz, H-6), 3.46 (1H, m, H-6′), 3.90 (1H, m, H-5), 3.95, 4.27 (2H, ABq, $J_{AB} = 11.4$ Hz, $PhCH_2$), 4.00 (1H, d, $J_{3,4} = 3.7$ Hz, H-3), 4.09, 4.17 (2H, ABq, $J_{AB} = 17.8$ Hz, H-1, H-1′), 4.18 (1H, dd, $J_{4,5} = 5.8$ Hz, H-4), 4.30, 4.35 (2H, ABq, $J_{AB} = 12.0$ Hz, $PhCH_2$), 4.43, 4.63 (2H, ABq, $J_{AB} = 11.3$ Hz, $PhCH_2$), 4.55, 4.63 (2H, ABq, $J_{AB} = 11.3$ Hz, $PhCH_2$), 7.23–7.44 (35H, m, Ar-CH); ^{13}C NMR (100 MHz, $CDCl_3$): 62.9 (t, C-6), 73.3, 73.4, 73.8, 74.5, 74.8 (5 × t, C-1, 4 × $PhCH_2$), 79.0 (d, C-5), 80.1 (d, C-4), 82.9 (d, C-3), 127.2, 127.8, 128.0, 128.0, 128.0, 128.1, 128.1, 128.2, 128.3, 128.5, 128.5, 128.6, 128.8, 128.9, 129.2, 130.0 (16 × d, 16 × Ar-CH), 137.1, 137.6, 137.9 (3 × s, 3 × Ar-C), 144.0 (s, Tr-C), 207.6 (C-2). ESIMS *m*/*z*: $[M+Na]^+$ calcd for $C_{53}H_{50}O_6Na$, 805.3500; found, 805.3516.

3.20. (3*R*,4*R*,5*S*) 1,3,4,5-Tetra-*O*-benzyl-2-methylene-6-*O*-trityl-hexane-1,3,4,5,6- pentaol (36)

Methyltriphenylphosphonium bromide (5.85 g, 16.4 mmol) and potassium *tert*-butoxide (1.78 g, 15.8 mmol) were suspended in toluene (50 mL). The mixture was stirred at 80 °C for 3 h, then a solution of ketone **35** (2.14 g, 2.73 mmol) in toluene (25 mL) was added. After 1 h, TLC (toluene–EtOAc 6:1) indicated the complete consumption of starting material ($R_f = 0.5$) and the formation of a major product ($R_f = 0.6$). The mixture was diluted with toluene, filtered through silica and concentrated in vacuo to afford alkene **36** (2.13 g, >99%). $[\alpha]_D^{23}$ −5.8 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): 3.16 (1H, dd, $J_{6,6'} = 10.0$ Hz, $J_{5,6} = 4.7$ Hz, H-6), 3.43 (1H, dd, $J_{5,6'} = 4.5$ Hz, H-6′), 3.77 (1H, aq, $J = 4.6$ Hz, H-5), 3.93, 4.37 (2H, ABq, $J_{AB} = 11.3$ Hz, H-1, H-1′), 3.94, 3.99 (2H, ABq, $J_{AB} = 13.5$ Hz, $PhCH_2$), 3.96 (1H, m, H-4), 4.12 (1H, d, $J_{3,4} = 5.5$ Hz, H-3), 4.40, 4.45 (2H, ABq, $J_{AB} = 12.1$ Hz, $PhCH_2$), 4.46, 4.60 (2H, ABq, $J_{AB} = 11.6$ Hz, $PhCH_2$), 4.62, 4.72 (2H, ABq, $J_{AB} = 11.1$ Hz, $PhCH_2$), 5.19 (1H, s, H-2a), 5.37 (1H, s, H-2a′), 7.24–7.41 (35H, m, Ar-CH); ^{13}C NMR

(100 MHz, $CDCl_3$): 63.0 (t, C-6), 70.2 (t, C-1), 71.3, 72.8, 73.2, 75.4 (4 × t, 4 × $PhCH_2$), 79.8 (d, C-5), 80.4 (d, C-4), 82.2 (d, C-3), 116.1 (t, C-2a), 127.2, 127.5, 127.6, 127.7, 128.0, 128.1, 128.2, 128.4, 128.4, 128.4, 128.6, 128.7, 128.9 (13 × d, Ar-CH), 138.5, 138.5, 138.8, 138.9 (4 × s, 4 × Ar-C), 144.2 (s, C-2), 143.0 (s, Tr-C). ESIMS *m/z*: $[M+Na]^+$ calcd for $C_{54}H_{52}O_5Na$, 803.3707; found, 803.3697.

3.21. (3*R*,4*R*,5*S*) 1,3,4,5-Tetra-*O*-benzyl-2-methylene-hexane-1,3,4,5,6-pentaol (37)

3.21.1. Method 1: deprotection of trityl ether 36. Protected alkene **36** (100 mg, 0.13 mmol) was dissolved in a mixture of formic acid and Et_2O (1:1, 0.5 mL). The mixture was stirred at rt. After 4 h, TLC (toluene–EtOAc 6:1) indicated complete consumption of starting material ($R_f = 0.7$) and the formation of major ($R_f = 0.2$) and minor ($R_f = 0.6$) products. The mixture was concentrated and the residue was purified by flash column chromatography ($CH_2Cl_2 \rightarrow CH_2Cl_2$–EtOAc 30:1) to afford deprotected alkene **37** (46 mg, 66%); $[\alpha]_D^{22}$ −13.3 (*c* 1.0, $CHCl_3$); IR (film); *v* 3458 (OH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 3.46 (1H, m, H-6), 3.61–3.64 (2H, m, H-5, H-6′), 3.78 (1H, at, $J = 4.7$ Hz, H-4), 3.98, 4.07 (2H, ABq, $J_{AB} = 12.7$ Hz, H-1, H-1′), 4.27 (1H, d, $J_{3,4} = 4.8$ Hz, H-3), 4.33, 4.57 (2H, ABq, $J_{AB} = 11.5$ Hz, $PhCH_2$), 4.46, 4.51 (2H, ABq, $J_{AB} = 11.9$ Hz, $PhCH_2$), 4.53, 4.58 (2H, ABq, $J_{AB} = 11.6$ Hz, $PhCH_2$), 4.67, 4.73 (2H, ABq, $J_{AB} = 11.3$ Hz, $PhCH_2$), 5.33 (1H, s, H-2a), 5.43 (1H, s, H-2a′), 7.21–7.27 (20H, m, Ar-CH); ^{13}C NMR (100 MHz, $CDCl_3$): 61.8 (t, C-6), 70.6 (t, C-1), 71.2, 72.8, 72.9, 75.1 (4 × t, 4 × $PhCH_2$), 79.3 (d, C-5), 80.7 (d, C-4), 81.0 (d, C-3), 117.0 (t, C-2a), 127.8, 127.8, 127.9, 127.9, 128.0, 128.4, 128.5, 128.6, 12.6, 128.8 (10 × d, 10 × Ar-CH), 138.1, 138.4, 138.4, 138.7 (4 × s, 4 × Ar-C), 142.7 (C-2). ESIMS *m/z*: $[M+Na]^+$ calcd for $C_{35}H_{38}O_5Na$, 561.2611; found, 561.2590.

And the 6-*O*-formate compound (25 mg, 34%) as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$): 3.73–3.81 (2H, m, H-3, H-4), 3.97, 4.07 (2H, 2 × d, $J_{1,1'} = 12.3$ Hz, H-1, H-1′), 4.13–4.20 (2H, m, H-6, H-6′), 4.30 (1H, m, H-5), 4.34, 4.56 (2H, ABq, $J_{AB} = 11.7$ Hz, $PhCH_2$), 4.46, 4.51 (2H, ABq, $J_{AB} = 11.8$ Hz, $PhCH_2$), 4.55, 4.60 (2H, ABq, $J_{AB} = 11.5$ Hz, $PhCH_2$), 4.64, 4.76 (2H, ABq, $J_{AB} = 11.3$ Hz, $PhCH_2$), 5.26 (1H, d, $J = 1.0$ Hz, H-2a), 5.41 (1H, d, $J = 1.3$ Hz, H-2a′), 7.21–7.35 (20H, m, Ar-CH), 7.76 (1H, s, CHO); ^{13}C NMR (100 MHz, $CDCl_3$): 63.3 (t, C-6), 70.5 (t, C-1), 71.1, 72.9, 73.3, 75.2 (4 × t, 4 × $PhCH_2$), 77.4, 79.4 (2 × d, C-3, C-4), 81.5 (d, C-5), 117.5 (t, C-2a), 127.8, 128.0, 128.3, 128.4, 128.5, 128.5, 128.6, 128.8 (8 × d, Ar-CH), 138.2, 138.3, 138.4, 138.5 (4 × s, 4 × Ar-C), 142.6 (s, C-2), 160.8 (d, CHO).

3.21.2. Method 2: Wittig reaction/deprotection of ketone 39. Methyltriphenylphosphonium bromide (4.23 g, 11.9 mmol) and potassium *tert*-butoxide (1.27 g, 11.4 mmol) were suspended in toluene (10 mL). The mixture was stirred at 80 °C for 90 min, then the mixture was removed from the heat and cooled to 0 °C. (Cooling the reaction mixture during the addition of ylid was necessary on larger scales to avoid elimination, presumably occurring via initial cleavage of the benzoate to restore the elimination-prone hemiketal.) A solution of ketone **39** (3.05 g, 4.73 mmol) in toluene (15 mL) was added. After addition was complete, the mixture was allowed to stir at rt. After 30 min, TLC (pentane–EtOAc 4:1) indicated the complete consumption of starting material ($R_f = 0.5$) and the formation of two products ($R_f = 0.8$ and 0.4). MeOH (ca. 6 mL) was added, and the mixture was filtered through Celite and concentrated in vacuo.

The residue was dissolved in MeOH (15 mL) and a sodium methoxide solution generated from sodium (109 mg, 4.74 mmol) and MeOH (10 mL) was added. After 1 h, TLC (pentane–EtOAc 4:1) showed the presence of a single major product ($R_f = 0.4$). The mixture was added to HCl (100 mL) and extracted with EtOAc (2 × 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (pentane–EtOAc 3:1) to give alkene **37** (2.34 g, 92%), identical to that described above.

Working up the reaction after the Wittig reaction but before methoxide deacylation allowed the isolation of the protected alkene **41** as well as the deprotected alkene **37**. Data for the benzoate-protected alkene **41** follow: colourless oil; $[\alpha]_D^{21}$ −19.7 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): 3.88 (1H, dd, $J_{3,4} = 6.1$ Hz, $J_{4,5} = 4.0$ Hz, H-4), 3.94–4.01 (2H, m, H-1, H-5), 4.08 (1H, d, $J_{1,1'} = 12.6$ Hz, H-1′), 4.36–4.42 (4H, m, H-3, H-6, H-6′, PhC*H*H′), 4.45, 4.49 (2H, ABq, $J_{AB} = 12.1$ Hz, PhCH_2), 4.57 (1H, d, $J = 11.6$ Hz, PhC*H*H′), 4.58 (1H, d, $J = 11.5$ Hz, PhCH*H*′), 4.71–4.72 (2H, m, PhC*H*H′, PhCH*H*′), 4.84 (1H, d, $J = 11.4$ Hz, PhCH*H*′), 5.30 (1H, m, H-2a), 5.43 (1H, m, H-2a′), 7.24–7.96 (25H, m, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$): 64.3 (t, C-6), 70.1 (t, C-1), 71.1, 72.7, 73.2, 75.1 (4 × t, 4 × $PhCH_2$), 77.4 (d, C-5), 79.5 (d, C-4), 82.0 (d, C-3), 117.3 (d, C-2a), 127.6, 127.7, 127.7, 127.8, 127.8, 127.9, 128.2, 128.3, 128.4, 128.4, 128.5, 128.5, 128.7 (13 × d, Ar-CH), 129.7 (d, Bz-CH), 130.2 (s, Bz-C), 133.1 (d, Bz-CH), 138.2, 138.5 (4 × s, Bn–C), 142.6 (s, C-2), 166.2 (s, C=O); ESI^+ *m/z* 665 $[M+Na]^+$, 100%. ESIMS *m/z*: $[M+Na]^+$ calcd for $C_{42}H_{42}O_6Na$, 665.2874; found, 665.2878.

3.22. 1,3,4,5-Tetra-*O*-benzyl-6-*O*-pivalyl-L-sorbose (38)

Hemiacetal **32** (200 mg, 0.37 mmol) was dissolved in pyridine (1.6 mL) and pivalyl chloride (0.23 mL,

1.85 mmol) added. The mixture was stirred at 60 °C for 17 h. After this time, TLC (pentane–EtOAc 3:1) showed complete conversion of starting material ($R_f = 0.4$) into a single product ($R_f = 0.8$). The mixture was diluted with CH_2Cl_2 (25 mL) and washed with HCl (1 M, 25 mL) and $NaHCO_3$ (satd aq, 25 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (pentane–EtOAc 6:1) to give the ketone **38** (192 mg, 83%) as a colourless oil. $[\alpha]_D^{23}$ −18.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): 1.22 (9H, s, $C(CH_3)_3$), 3.90 (1H, m, H-5), 3.95 (1H, m, H-4), 4.18 (1H, dd, $J_{5,6} = 6.4$ Hz, $J_{6,6'} = 11.9$ Hz, H-6), 4.23–4.26 (3H, m, H-3, H-1, H-1′), 4.36 (1H, dd, $J_{5,6'} = 3.2$ Hz, H-6′), 4.37, 4.43 (2H, ABq, $J_{AB} = 12.0$ Hz, PhCH_2), 4.50–4.65 (6H, m, 3 × PhCH_2), 7.22–7.35 (20H, m, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$): 27.3 (q, C(CH_3)$_3$), 38.8 (s, $C(CH_3)_3$), 63.8 (t, C-6), 73.3, 73.3, 73.7, 74.3, 74.4 (5 × t, 4 × PhCH_2, C-1), 76.7 (d, C-5), 79.2 (d, C-4), 81.3 (d, C-3), 127.8, 127.9, 127.9, 128.1, 128.1, 128.3, 128.4, 128.4, 128.5, 128.5, 128.6 (11 × d, Ar-CH), 136.9, 137.4, 137.4, 137.9 (4 × s, Ar-C), 178.1 (s, Piv-C=O), 207.1 (s, C-2); ESI$^+$ *m*/*z* 1271 [2M+Na]$^+$, 5%, 647 [M+Na]$^+$, 100%. ESIMS *m*/*z*: [M+Na]$^+$ calcd for $C_{39}H_{44}O_7Na$, 647.2979; found, 647.2970.

3.23. 1,3,4,5-Tetra-*O*-benzyl-6-*O*-benzoyl-L-sorbose (39)

Hemiacetal **32** (3.02 g, 5.55 mmol) was dissolved in pyridine (15 mL) and benzoyl chloride (1.92 mL, 16.7 mmol) added. The mixture was stirred at rt for 15 h. After this time, TLC (pentane–EtOAc 4:1) showed complete conversion of starting material ($R_f = 0.3$) into a single product ($R_f = 0.4$). The mixture was diluted with EtOAc (100 mL) and washed with HCl (1 M, 100 mL). The aqueous phase was re-extracted with EtOAc (100 mL), and the combined organic extracts washed with $NaHCO_3$ (satd. aq., 100 mL) then dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (pentane–EtOAc 5:1→4:1→7:2) to give the ketone **39** (3.05 g, 85%) as a colourless oil. $[\alpha]_D^{23}$ −24.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): 4.04–4.06 (2H, m, H-4, H-5), 4.25 (2H, s, H-1, H-1′), 4.33 (1H, d, $J_{3,4} = 3.6$ Hz, H-3), 4.38–4.41 (2H, m, H-6, PhC*H*H′), 4.44 (1H, d, $J = 11.9$ Hz, PhCH*H*′), 4.53 (1H, d, $J = 11.5$ Hz, PhC*H*H′), 4.56 (1H, d, $J = 11.5$ Hz, PhC*H*H′), 4.58–4.67 (5H, m, H-6′, 2 × PhCH*H*′, PhCH_2), 7.23–8.00 (25H, m, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$): 64.5 (t, C-6), 73.3, 73.4, 73.9, 74.3 (4 × t, 4 × PhCH_2), 74.5 (t, C-1), 76.5, 79.0 (2 × d, C-4, C-5), 81.6 (d, C-3), 127.9, 128.0, 128.0, 128.0, 128.1, 128.3, 128.3, 128.5, 128.5, 128.5, 128.5, 128.5, 128.6, 128.6, 128.7 (15 × d, Ar-CH), 129.7 (d, Bz-CH), 130.1 (s, Bz-C), 133.1 (d, Bz-CH), 136.9, 137.3, 137.4, 137.8 (4 × s, 4 × Bn–C), 166.3 (s, Bz-C=O), 207.4 (s, C-2); ESI$^+$ *m*/*z* 1311 [2M+Na]$^+$, 5%, 667 [M+Na]$^+$, 100%. ESIMS *m*/*z*: [M+Na]$^+$ calcd for $C_{41}H_{40}O_7Na$, 667.2666; found, 667.2633.

3.24. (3*R*,4*R*,5*S*) 1,3,4,5-Tetra-*O*-benzyl-2-methylene-6-*O*-pivalyl-hexane-1,3,4,5,6- pentaol (40)

Methyltriphenylphosphonium bromide (544 mg, 1.52 mmol) and potassium *tert*-butoxide (161 mg, 1.44 mmol) were suspended in toluene (2 mL). The mixture was stirred at 80 °C for 90 min, then the mixture was removed from the heat and allowed to cool to rt. A solution of ketone **38** (190 mg, 0.30 mmol) in toluene (4 mL) was added and the mixture was stirred at rt. After 90 min, TLC (pentane–EtOAc 6:1) indicated complete consumption of the starting material and the formation of a single product. The mixture was filtered through Celite and concentrated in vacuo. The residue was purified by flash column chromatography (pentane–EtOAc 8:1) to give the alkene **40** (172 mg, 91%). $[\alpha]_D^{21}$ −18.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): 1.19 (9H, s, $C(CH_3)_3$), 3.76 (1H, dd, $J_{3,4} = 6.1$ Hz, $J_{4,5} = 4.2$ Hz, H-4), 3.81 (1H, aq, $J = 5.0$ Hz, H-5), 4.02 (1H, d, $J_{1,1'} = 13.0$ Hz, H-1), 4.08 (1H, d, H-1′), 4.18 (1H, dd, $J_{5,6} = 5.7$ Hz, $J_{6,6} = 11.5$ Hz, H-6), 4.21 (1H, dd, $J_{5,6'} = 5.0$ Hz, H-6′), 4.35 (1H, d, H-3), 4.39, 4.59 (2H, ABq, $J_{AB} = 12.1$ Hz, PhCH_2), 4.50–4.54 (3H, m, PhC*H*H′, PhCH_2), 4.66–4.72 (2H, m, PhC*H*H′, PhCH*H*′), 4.57 (1H, d, $J = 11.6$ Hz, PhC*H*H′), 4.58 (1H, d, $J = 11.5$ Hz, PhCH*H*′), 4.83 (1H, d, $J = 11.3$ Hz, PhCH*H*′), 5.29 (1H, m, H-2a), 5.46 (1H, m, H-2a′), 7.28–7.37 (20H, m, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$): 27.3 (q, C(CH_3)$_3$), 38.8 (s, $C(CH_3)_3$), 63.9 (t, C-6), 70.0 (t, C-1), 71.1, 72.8, 73.1, 75.2 (4 × t, 4 × PhCH_2), 77.7 (d, C-5), 79.8 (d, C-4), 81.9 (d, C-3), 116.9 (d, C-2a), 127.6, 127.7, 127.7, 127.8, 127.8, 128.3, 128.4, 128.4, 128.5, 128.5, 128.6 (11 × d, Ar-CH), 138.2, 138.3, 138.5, 138.6 (4 × s, 4 × Bn–C), 142.7 (s, C-2), 178.2 (s, C=O); ESI$^+$ *m*/*z* 645 [M+Na]$^+$, 100%. ESIMS *m*/*z*: [M+Na]$^+$ calcd for $C_{40}H_{46}O_6Na$, 645.3187; found, 645.3201.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2008.04.010.

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