Synthesis of naturally occurring iminosugars from D-fructose by the use of a zinc-mediated fragmentation reaction†

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A short synthesis of 1,4-dideoxy-1,4-imino-D-arabinitol (DAB) and a formal synthesis of australine are described. In both cases, D-fructose is employed as the starting material and converted into a protected methyl 6-deoxy-6-iodo-furanoside. Zinc-mediated fragmentation produces an unsaturated ketone which serves as a key building block for both syntheses. Ozonolysis, reductive amination with benzylamine and deprotection affords 1,4-dideoxy-1,4-imino-D-arabinitol in only 7 steps and 11% overall yield from D-fructose. Alternatively, reductive amination with homoallylamine, ring-closing metathesis and protecting group manipulations give rise to an intermediate which can be converted into australine in 3 steps. The intermediate is prepared by two different strategies both of which use a total of 9 steps. The first strategy utilizes benzyl ethers for protection of fructose while the second and more effective strategy employs an isopropylidene acetal.

Introduction

Iminosugars are a class of polyhydroxylated alkaloids that have been found in a number of plants and microorganisms.[1] They can be regarded as analogues of monosaccharides in which the ring oxygen has been replaced by nitrogen. Many of these natural products are potent inhibitors of glycosidases due to their resemblance with the pyranosyl cation of the natural substrates.[2] Furthermore, numerous non-natural analogues have been prepared and investigated as glycosidase inhibitors.[3] As a consequence, iminosugars have been used as important lead compounds for the treatment of viral infections, cancer, diabetes and other metabolic disorders. Several iminosugars are currently in clinical development[4] and two *N*-alkylated derivatives of deoxynojirimycin have been approved as drugs for the treatment of Gauchers disease and type II diabetes.[5]

Iminosugars are divided into five sub-classes based on the ring system: pyrrolidines, piperidines, pyrrolizidines, indolizidines, and nortropanes. The synthesis of these molecules is often performed from a carbohydrate starting material.[6] However, it is still a challenge to introduce the amino group and to form the ring system in few steps.[7] We have recently developed a short synthetic route to the nortropane alkaloids (calystegines) from cheap aldohexoses.[8] Three of these alkaloids were prepared in 7 steps from the corresponding methyl glycopyranosides of D-glucose, D-galactose, and D-mannose.[8] One of the steps involved a zinc-mediated fragmentation of the benzyl-protected methyl 6-iodo-glycopyranosides.[9] This reaction has been widely used in carbohydrate chemistry for converting aldohexoses into unsaturated aldehydes, but has to the best of our knowledge never been applied to ketohexoses. We speculated that this fragmentation reaction could offer new ways of using D-fructose as a synthetic starting material and lead to short syntheses of other iminosugars.

Fructose is one of the most inexpensive carbohydrates and has structural similarity with several naturally occurring iminosugars. In connection with this, we were particularly interested in the pyrrolidine alkaloid 1,4-dideoxy-1,4-imino-D-arabinitol (DAB) and the corresponding pyrrolizidine alkaloid australine (Fig. 1). DAB is a strong inhibitor of yeast α-glucosidase[10] and several mammalian α-glucosidases.[11] It is also a powerful inhibitor of glycogen phosphorylase[12] and is a promising candidate for treatment of type II diabetes.[13] DAB was first isolated in 1985 from *Arachniodes standishii*[14] and *Angylocalyx boutiqueanus.*[15] It has also been found in a number of other plants and seems to be a fairly widespread secondary metabolite.[1] Several chemical syntheses of DAB have appeared which all employ a total of 10–12 steps starting from either a carbohydrate,[16] an amino acid,[17] or 2-butene-1,4-diol.[18] In addition, three enzyme-catalysed syntheses with an aldolase have also been described.[19]

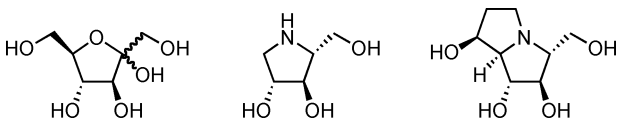

Fig. 1 Structure of D-fructofuranose, 1,4-dideoxy-1,4-imino-D-arabinitol, and australine.

Australine is a potent inhibitor of amyloglucosidase[20] and was first isolated in 1988 from the legume *Castanospermum australe.*[21] Only three *de novo* chemical syntheses of australine have been reported. White and Hrnciar developed a 16 step synthesis from D-mannitol by using a transannular cyclisation as the key step to form the pyrrrolizidine ring system (*vide infra*).[22] Denmark and Martinborough utilized two asymmetric cycloaddition reactions to afford the natural product in only 9 steps from 2,5-dihydrofuran[23] while Pearson and Hines obtained australine in 11 steps from L-xylose by using a reductive cyclisation

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of an azido epoxy tosylate.[24] In addition, australine has also been prepared from the indolizidine alkaloid castanospermine by a ring contraction reaction[25] and from 1,4-pentadien-3-ol by a chemo-enzymatic procedure with an aldolase.[26]

Herein, we describe a concise synthetic route to DAB and a formal synthesis of australine. Both syntheses have been achieved from fructose by the use of a zinc-mediated fragmentation reaction.

Results and discussion

Retrosynthesis

The structural resemblance between the two alkaloids and D-fructose is noteworthy (Fig. 1). The absolute configuration of the two hydroxyl groups in the pyrrolidine ring is the same as for the hydroxyl groups at position 3 and 4 in D-fructose. The hydroxymethyl group in DAB and australine is found in fructose at position 1. The amino group can be introduced by reductive amination from the ketone at position 2 in fructose. Thus, we envisaged that DAB and australine could both be derived from a common building block **A** (Fig. 2). Ozonolysis of the olefin in **A** followed by reductive amination would afford the pyrrolidine ring in DAB. On the other hand, reductive amination with homoallylamine followed by ring-closing metathesis and epoxidation would yield aminoepoxide **B**. The pyrrolizidine ring in australine can then be formed by a transannular cyclisation as demonstrated by White and Hrnciar in their synthesis of the natural product.[22] The key building block **A** can be prepared from fructose by a zinc-mediated fragmentation of the corresponding methyl 6-iodo-furanoside. This approach from fructose should be able to generate the two natural products in relatively few synthetic steps.

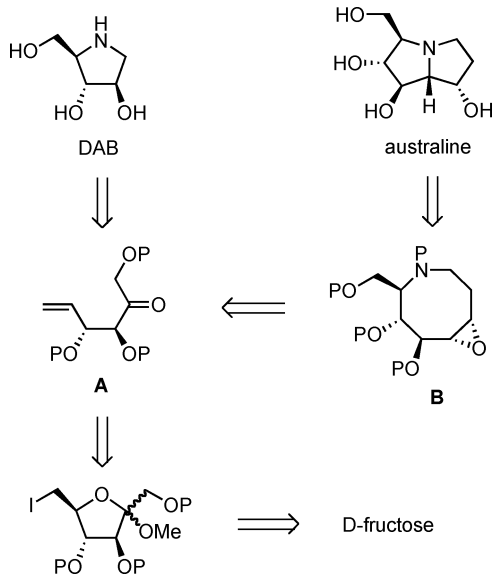
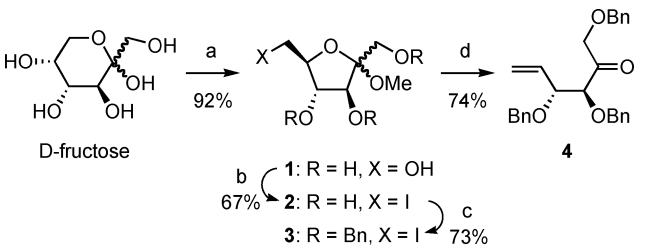


Fig. 2 Retrosynthesis for 1,4-dideoxy-1,4-imino-D-arabinitol and australine.

Zinc-mediated fragmentation of fructose

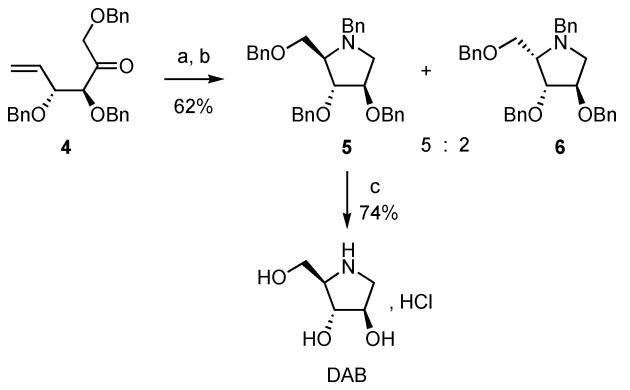
The iodofuranoside for the reductive fragmentation was prepared in three steps from fructose. First, the ketose was converted into the furanose form by a Fischer glycosylation with methanol under kinetic conditions[27] (Scheme 1). The product consisting of a 1 : 1 mixture of the α- and the β-furanoside was treated with 1.5 equivalents of iodine and triphenylphosphine.[28] Under these conditions only the primary hydroxyl group in the 6-position was replaced by iodine while the primary hydroxyl group at position 1 did not react. The obtained methyl 6-iodo-furanoside **2** was separated from triphenylphosphine oxide on a reverse-phase column and isolated in 67% yield. The hydroxyl groups at positions 1, 3, and 4 were protected as benzyl ethers by reaction with benzyl trichloroacetimidate under acidic conditions. The resulting tribenzyl ether **3** was isolated in 73% yield and then subjected to sonication with zinc in a THF–water mixture. This fragmentation reaction proceeded smoothly and afforded unsaturated ketone **4** in 74% yield after purification by silica gel chromatography. Ketone **4** is a useful chiral building block which has previously been prepared from D-arabinose in 5 steps by the use of a Wittig reaction and a chromium-mediated oxidation.[29] The current route from fructose utilizes 4 steps and avoids the use of a toxic metal.



Scheme 1 *Reagents and conditions*: (a) MeOH, H_2SO_4, rt;[27] (b) I_2, PPh_3, imidazole, THF, 65 °C; (c) $BnOC(NH)CCl_3$, TfOH, dioxane, 0 °C; (d) Zn, THF, H_2O, ultrasound, 40 °C.

1,4-Dideoxy-1,4-imino-D-arabinitol (DAB)

With the key building block **4** in hand, our attention then turned to the reductive amination. For the synthesis of DAB the C–C double bond in **4** was first cleaved by ozonolysis to afford the corresponding aldehyde (Scheme 2). This dicarbonyl compound existed as a mixture of hydrates and was not further purified or characterized. Instead, the crude product was submitted directly to a double reductive amination[30] with benzylamine, sodium cyanoborohydride and acetic acid in THF. This afforded a 5 : 2 mixture of benzyl-protected DAB **5** and the corresponding L-xylo compound **6**, which could be separated by column chromatography. The two isomers were isolated in 62% overall yield from olefin **4**. The yield and diastereoselectivity were lower when the more sterically demanding benzhydrylamine was used in the reductive amination. Attempts to use ammonium acetate as the amine source gave none of the desired product. Lower yield and diastereoselectivity were also observed when the reducing agent was changed to sodium triacetoxyborohydride or the acid was changed to a Lewis acid. The desired isomer **5** was isolated in 44% yield over two steps from olefin **4**. Finally, hydrogenolysis over palladium on carbon gave 1,4-dideoxy-1,4-imino-D-arabinitol, which crystallised as the hydrochloride salt in 74% yield. The spectral data and physical properties of synthetic DAB hydrochloride were in excellent accordance with those reported in the literature.[16] This

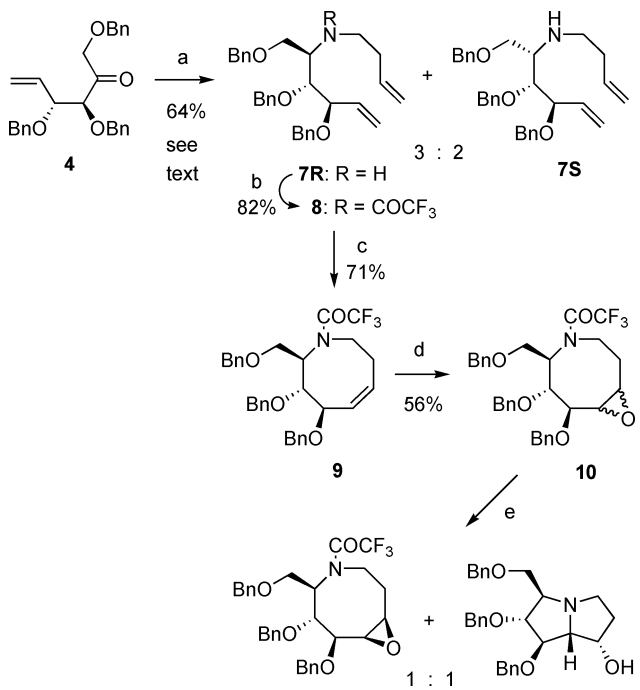


Scheme 2 *Reagents and conditions*: (a) O_3, MeOH, CH_2Cl_2, −78 °C, then Me_2S, rt; (b) $BnNH_2$, $NaCNBH_3$, AcOH, 3 Å MS, THF, rt; (c) H_2, HCl, MeOH, Pd/C, rt.

completes the synthesis of DAB from D-fructose in only 7 steps and gives rise to the natural product in 11% overall yield.

First generation approach to australine

With the successful preparation of DAB, the synthesis of the related pyrrolizidine alkaloid australine might also be realized from olefin **4**. In this case, the reductive amination will be performed with homoallylamine and the diastereoselectivity should be controlled to afford the (*R*)-isomer as the major product. Sinaÿ and co-workers have previously reacted **4** with allylamine, sodium cyanoborohydride and acetic acid to give a 3 : 2 ratio between the (*R*)- and the (*S*)-amine.[31] Hence, as the first experiment we treated olefin **4** with homoallylamine under these conditions at room temperature (Scheme 3). To our disappointment, this reaction



Scheme 3 *Reagents and conditions*: (a) homoallylamine, $NaCNBH_3$, $InCl_3$, 3 Å MS, THF, rt; (b) TFAA, Et_3N, CH_2Cl_2, rt; (c) $(PCy_3)(C_3H_4N_2Mes_2)Cl_2Ru{=}CHPh$, CH_2Cl_2, rt; (d) *m*-CPBA, CH_2Cl_2, rt; (e) $LiOH{\cdot}H_2O$, EtOH, H_2O, 100 °C.

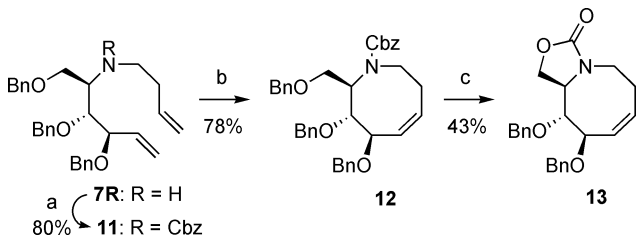
gave the two diastereomers in a 1 : 1 ratio. The two amines could be separated by column chromatography and were isolated in 67% yield. Attempts to use other reducing agents like sodium triacetoxyborohydride or L-selectride did not improve the reaction, but mainly led to reduction of the ketone. The reductive amination and the zinc-mediated fragmentation of iodide **3** could, however, be combined and performed as a tandem reaction.[32] When a mixture of iodide **3**, homoallylamine, acetic acid, zinc, and sodium cyanoborohydride was sonicated in a THF solution at 40 °C the two amines were isolated in 55% yield as a 1 : 1 mixture. Some reduction of the ketone also took place under these conditions which may be due to the higher temperature during the reductive amination. In order to improve the selectivity we decided to replace acetic acid by other additives. Therefore, ketone **4** was reacted with homoallylamine and sodium cyanoborohydride in the presence of lithium chloride, magnesium dibromide, and indium trichloride. The first two additives led to a similar yield and selectivity as obtained with acetic acid. Indium trichloride, on the other hand, gave a slightly improved 3 : 2 ratio of the two amines in favour of the (*R*)-isomer. In this case, the yield of the two amines was 64% and it was decided to continue the synthesis with this result.

The next step involved protection of the amine functionality since the ensuing metathesis reaction is severely hampered by the presence of a secondary amine. The amine protecting group should be labile to base in order to be removed under the alkaline conditions for the transannular cyclisation. The trifluoroacetyl group was chosen for this purpose and installed by reaction with trifluoroacetic anhydride to afford trifluoroacetamide **8**. The subsequent ring-closing metathesis reaction proceeded well with Grubbs 2nd generation catalyst[33] to form the eight-membered ring in 71% yield.

The following step called for a diastereoselective epoxidation of the C–C double bond. Unfortunately, treatment of olefin **9** with *m*-CPBA afforded a 1 : 1 mixture of the two epoxides in 56% yield. Changing the epoxidising agent to a dioxirane derived from either trifluoroacetone[34] or a fructose-derived ketone[35] gave the same 1 : 1 mixture in a slightly lower yield. The two epoxides could not be separated by column chromatography and were treated directly with aqueous lithium hydroxide. Notably, only the desired isomer underwent the transannular cyclisation while the other isomer was recovered unchanged.

The complete lack of selectivity in the epoxidation came as a surprise since White and Hrnciar performed an *m*-CPBA epoxidation on a very similar compound in 75% yield with complete stereocontrol.[22] The only difference is the nitrogen protecting group which in their case was an oxazolidinone ring with the hydroxymethyl group. Apparently, this additional ring changes the conformation of the eight-membered ring and the steric bias around the double bond. At this point, we decided to change the synthesis in order to introduce this oxazolidinone ring since a bicyclic ring system seems to be the best way to control the selectivity in the epoxidation. The synthesis of australine will then be a formal synthesis, but the route from fructose will still be shorter than the route from mannitol.

The bicyclic ring system was formed in four steps from amine **7*R***. First, the amine was protected with the Cbz group to afford carbamate **11** (Scheme 4). Ring-closing olefin metathesis then generated the medium-sized ring in 78% yield. Finally, the cyclic carbamate was installed in two steps by selective acetolysis of the



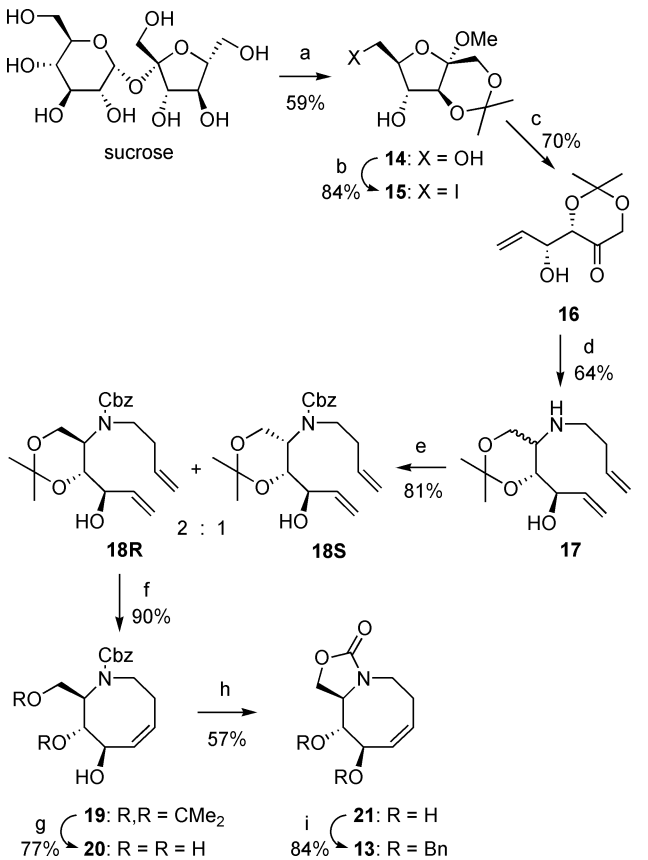
Scheme 4 *Reagents and conditions*: (a) CbzCl, $KHCO_3$, CH_2Cl_2, H_2O, rt; (b) $(PCy_3)(C_3H_4N_2Mes_2)Cl_2Ru{=}CHPh$, CH_2Cl_2, rt; (c) Ac_2O, TMSOTf, CH_2Cl_2, 0 °C, then NaOMe, MeOH, rt.

benzyl group on the primary alcohol followed by treatment with sodium methoxide. Oxazolidinone **13** was isolated in 43% yield over the last two steps with spectral data and optical rotation in complete agreement with those reported previously.[22] The overall yield of **13** from fructose is 3.4% over 9 steps. White and Hrnciar described the synthesis of australine from **13** in 3 steps and 75% overall yield.[22] Although, the route from fructose gives rise to a shorter synthesis of australine we were still not pleased with the diastereoselectivity in the reductive amination and the overall yield. As a result, we decided to investigate an alternative synthesis from fructose.

Second generation approach to australine

In this case, fructose will be protected with an isopropylidene group instead of benzyl ethers. The acetal protecting group will generate a cyclic ketone which may induce a better selectivity in the reductive amination. Initially, the 1,3-isopropylidene group was installed from methyl fructofuranoside **1** by reaction with 2,2-dimethoxypropane, acetone, and camphorsulfonic acid. However, since furanoside **1** is a 1 : 1 α–β mixture and only the α-anomer reacted with the acetal, the yield of methyl 1,3-*O*-isopropylidene-α-D-fructofuranoside (**14**) was only 35%. Instead, we turned our attention to a report by Richardson and co-workers where **14** was prepared from sucrose by cleavage of the glycosidic linkage.[36] In their work, sucrose was reacted with 2,2-dimethoxypropane and *p*-toluenesulfonic acid in dimethylformamide followed by work-up with basic ion-exchange resin and acetylation to afford acetylated **14** in 36% yield.[36] Although a moderate yield, it was noted that **14** was formed as the major product according to TLC. Thus, we envisioned that this procedure could be further optimized. In fact, by leaving out the ion-exchange resin, which often binds organic compounds, and by increasing the amount of acid, we were able to isolate **14** in 59% yield after purification by flash chromatography (Scheme 5).

With acetal **14** in hand, the next step required a substitution of the primary hydroxyl group with iodide. This reaction was conducted under the same conditions as described above to afford iodofuranoside **15** in 84% yield. Subsequent fragmentation with zinc proceeded uneventfully to give cyclic ketone **16** in 70% yield. Treatment of this compound with homoallylamine, sodium cyanoborohydride and acetic acid in THF gave a 2 : 1 mixture of the (*R*)- and the (*S*)-amine in 64% yield. This is only a slight improvement compared to the result with ketone **4**. Unfortunately, it was not possible in this case to enhance the selectivity by adding indium trichloride which mainly led to reduction of the ketone **16**. The two amines co-eluted by column chromatography, but



Scheme 5 *Reagents and conditions*: (a) $Me_2C(OMe)_2$, TsOH·H_2O, DMF, rt; (b) I_2, PPh_3, imidazole, THF, 65 °C; (c) Zn, THF, H_2O, ultrasound, 40 °C; (d) homoallylamine, $NaCNBH_3$, AcOH, 3 Å MS, THF, rt; (e) CbzCl, $KHCO_3$, CH_2Cl_2, H_2O, rt; (f) $(PCy_3)(C_3H_4N_2Mes_2)Cl_2Ru{=}CHPh$, CH_2Cl_2, rt; (g) AcOH, H_2O, rt; (h) NaOMe, MeOH, rt; (i) BnBr, NaH, THF, rt.[22]

could be separated after protection with the Cbz group. The major isomer **18*R*** was submitted to ring-closing metathesis to afford the eight-membered ring in 90% yield. Hydrolysis of the isopropylidene group then gave triol **20**, which upon treatment with base furnished oxazolidinone **21**. The spectroscopic data for **21** were in agreement with those reported by White and Hrnciar who described the following benzylation to give **13** in 84% yield.[22] This alternative synthesis of **13** requires 9 steps from sucrose and gives rise to the target molecule in 4.0% overall yield.

Conclusion

We have described a new synthesis of 1,4-dideoxy-1,4-imino-D-arabinitol and a formal synthesis of australine where the latter has been achieved by two different protecting group strategies. The synthesis of 1,4-dideoxy-1,4-imino-D-arabinitol requires 7 steps from D-fructose and occurs in 11% overall yield. This constitutes the shortest chemical synthesis of 1,4-dideoxy-1,4-imino-D-arabinitol reported to date. The formal synthesis of australine with benzyl protection gives rise to the key intermediate **13** in 9 steps from fructose and 3.4% overall yield. The alternative synthesis with isopropylidene protection affords **13** in 9 steps from sucrose and 4.0% overall yield. In their synthesis of australine

White and Hrnciar prepared the key intermediate **13** in 13 steps from D-mannitol and 4.2% overall yield.

The syntheses highlight the use of D-fructose as a synthetic starting material by exploiting the zinc-mediated fragmentation of the methyl 6-iodo-furanoside. Benzyl-protected ketone **4** is prepared from fructose in 4 steps while the isopropylidene-protected ketone **16** is obtained from sucrose in only 3 steps. Unsaturated ketones **4** and **16** are valuable building blocks for further synthesis.

Experimental

General

Reactions were conducted under an atmosphere of nitrogen when anhydrous solvents were used. CH_2Cl_2 was dried over activated 4 Å molecular sieves, while THF was distilled from sodium-benzophenone. Sonications were carried out in a Branson 1210 sonic bath. Zinc (Aldrich, particle size <0.01 mm) was activated and dried immediately before use: zinc dust (5 g) in 1 M HCl (50 mL) was stirred at room temperature for 15 min, and then filtered, washed with water (2 × 50 mL) and Et_2O (2 × 50 mL), and finally dried under high vacuum with a heatgun. All reactions were monitored with thin-layer chromatography using aluminium plates precoated with silica gel 60. Compounds were visualized by dipping in a solution of $Ce(SO_4)_2$ (10 g L^{-1}) and $(NH_4)_6Mo_7O_{24}$ (25 g L^{-1}) in 10% aqueous H_2SO_4 followed by heating. Flash column chromatography was performed with E. Merck silica gel 60 (particle size 0.040–0.063 mm) while reverse phase flash chromatography was conducted with Macherey-Nagel silica gel 60 C_{18} (particle size 0.040–0.063 mm). Optical rotations were measured on a Perkin Elmer 241 polarimeter while IR spectra were recorded on a Perkin Elmer 1720 Infrared Fourier Transform spectrometer. NMR spectra were recorded on a Varian Unity Inova 500 or a Varian Mercury 300 instrument. Chemical shifts are reported in parts per million (ppm) with the residual undeuterated solvent as internal reference for ^{1}H NMR and the deuterated solvent as reference for ^{13}C NMR.[37] Microanalyses and high resolution mass spectra were obtained at the Department of Chemistry, University of Copenhagen.

Methyl 6-deoxy-6-iodo-D-fructofuranoside (2). To a solution of **1**[27] (5.23 g, 26.9 mmol) in dry THF (200 mL) were added PPh_3 (10.6 g, 40.4 mmol) and imidazole (3.65 g, 53.6 mmol). The mixture was heated to reflux and a solution of I_2 (10.35 g, 40.8 mmol) in dry THF (80 mL) was added over 2 h. The reaction mixture was cooled to room temperature, filtered and concentrated. The residue was purified by reverse phase flash chromatography (H_2O–MeOH, 9 : 1). The appropriate fractions were concentrated and purified by silica gel flash chromatography (CH_2Cl_2–MeOH, 50 : 1 → 50 : 3) to give a mixture of the two epimers as a white solid (5.46 g, 67%).

For methyl 6-deoxy-6-iodo-α-D-fructofuranoside: R_f 0.67 ($CHCl_3$–MeOH, 5 : 1); $[\alpha]_D$ +78.8 (*c* 2.0, MeOH); ν_{max}(KBr)/cm^{-1}: 3347, 2926, 2876, 1451, 1041, 1024; δ_H (500 MHz, D_2O): 4.11 (d, J = 3.4 Hz, 1H), 3.89–3.83 (m, 2H), 3.75 (d, J = 12.2 Hz, 1H), 3.63 (d, J = 12.4 Hz, 1H), 3.47–3.42 (m, 1H), 3.36–3.30 (m, 1H), 3.27 (s, 3H); δ_C (75 MHz, D_2O): 108.9, 82.5, 81.5, 81.0, 58.3, 48.9, 5.9; Anal. calcd. for $C_7H_{13}IO_5$: C, 27.65; H, 4.31. Found: C, 27.90; H, 4.23%.

For methyl 6-deoxy-6-iodo-β-D-fructofuranoside: R_f 0.57 ($CHCl_3$–MeOH, 5 : 1); $[\alpha]_D$ −21.2 (*c* 2.1, MeOH); ν_{max}(KBr)/cm^{-1}: 3426, 2941, 1371, 1139, 1093, 1060, 1011; δ_H (300 MHz, D_2O): 4.20 (d, J = 8.1 Hz, 1H), 4.13 (t, J = 6.9 Hz, 1H), 3.89–3.83 (m, 1H), 3.74 (d, J = 12.3 Hz, 1H), 3.66 (d, J = 12.3 Hz, 1H), 3.50 (dd, J = 10.8, 5.1 Hz, 1H), 3.42–3.36 (m, 1H), 3.36 (s, 3H); δ_C (75 MHz, D_2O): 104.6, 81.0, 79.5, 77.9, 60.3, 50.2, 7.7; Anal. calcd. for $C_7H_{13}IO_5$: C, 27.65; H, 4.31. Found: C, 27.91; H, 4.23%.

Methyl 1,3,4-tri-*O*-benzyl-6-deoxy-6-iodo-D-fructofuranoside (3). A solution of **2** (1.49 g, 4.90 mmol) in freshly distilled dioxane (30 mL) was cooled to 0 °C followed by addition of freshly distilled benzyl trichloroacetimidate (3.3 mL, 17.7 mmol). Triflic acid was added (30 drops) to ensure that the mixture was strongly acidic and the solution was stirred for 12 min. The reaction was quenched with saturated aqueous $NaHCO_3$ (50 mL) and extracted with Et_2O (50 mL). The organic phase was dried (K_2CO_3) and concentrated. The residue was purified by flash chromatography (hexane–Et_2O, 7 : 1) to give the title compound (2.06 g, 73%) as a mixture of two diastereomers which could not be separated. Pure samples of both epimers were prepared from anomerically pure samples of **2**.

For methyl 1,3,4-tri-*O*-benzyl-6-deoxy-6-iodo-α-D-fructofuranoside: R_f 0.58 (hexane–EtOAc, 3 : 1); $[\alpha]_D$ +25.0 (*c* 2, $CHCl_3$); ν_{max}(neat)/cm^{-1}: 3029, 2868, 1496, 1454, 1113, 736, 699; δ_H (300 MHz, $CDCl_3$): 7.37–7.27 (m, 15H), 4.70–4.42 (m, 6H), 4.10 (d, J = 2.7 Hz, 1H), 3.97 (q, J = 5.3 Hz, 1H), 3.76 (dd, J = 5.5, 2.3 Hz, 1H), 3.66 (s, 2H), 3.31 (s, 3H), 3.29 (dd, J = 10.6, 5.7 Hz, 1H), 3.20 (dd, J = 10.7, 6.6 Hz, 1H); δ_C (75 MHz, $CDCl_3$): 138.0, 137.8, 137.7, 128.6, 128.5 (2C), 128.2, 128.1, 128.0, 127.9 (3C), 108.4, 87.6 (2C), 80.7, 73.7, 72.8, 72.2, 65.8, 48.8, 6.4; HRMS calcd. for $C_{28}H_{31}IO_5Na$ $[M + Na]^+$ m/z 597.1114, found m/z 597.1111.

For methyl 1,3,4-tri-*O*-benzyl-6-deoxy-6-iodo-β-D-fructofuranoside: R_f 0.58 (hexane–EtOAc, 3 : 1); $[\alpha]_D$ +21.6 (*c* 2.1, $CHCl_3$); ν_{max}(neat)/cm^{-1}: 2925, 1454, 1114, 1106, 736, 700; δ_H (300 MHz, $CDCl_3$): 7.36–7.25 (m, 15H), 4.74 (d, J = 11.8 Hz, 1H), 4.65–4.54 (m, 4H), 4.50 (d, J = 12.0 Hz, 1H), 4.32 (d, J = 6.8 Hz, 1H), 4.07 (t, J = 6.2 Hz, 1H), 3.99–3.93 (m, 1H), 3.59–3.57 (m, 2H), 3.41 (s, 3H), 3.31–3.26 (m, 2H); δ_C (75 MHz, $CDCl_3$): 138.1, 137.9, 137.8, 128.6 (2C), 128.5, 128.3, 128.0 (3C), 127.9 (2C), 104.7, 86.8, 85.4, 79.7, 73.7, 73.0, 72.8, 69.9, 50.3, 7.9; Anal. calcd. for $C_{28}H_{31}IO_5$: C, 58.54; H, 5.44. Found: C, 58.14; H, 5.40%.

(3*S*,4*R*)-1,3,4-Tris(benzyloxy)-hex-5-en-2-one (4). To a solution of **3** (2.42 g, 4.21 mmol) in THF (30 mL) and H_2O (8 mL) was added pre-activated zinc (2.7 g, 41.3 mmol) and the mixture was sonicated for 2 h at 40 °C. The mixture was then filtered through a short column of Celite, which was rinsed with CH_2Cl_2. The filtrate was washed with saturated aqueous $NaHCO_3$ (2 × 25 mL), dried and concentrated. The residue was purified by flash chromatography (hexane–EtOAc, 6 : 1) to afford ketone **4** (1.29 g, 74%). R_f 0.56 (hexane–EtOAc, 3 : 1); $[\alpha]_D$ −45.7 (*c* 1.7, $CHCl_3$); ν_{max}(neat)/cm^{-1}: 3032, 2864, 1733, 1496, 1455, 1104, 735; δ_H (300 MHz, $CDCl_3$): 7.29–7.14 (m, 15H), 5.90–5.78 (m, 1H), 5.27 (d, J = 17.2 Hz, 1H), 5.26 (d, J = 10.7 Hz, 1H), 4.54–4.34 (m, 5H), 4.29–4.27 (m, 2H), 4.22 (d, J = 11.8 Hz, 1H), 4.12 (dd, J = 7.9, 3.4 Hz, 1H), 3.94 (d, J = 3.2 Hz, 1H); δ_C (75 MHz, $CDCl_3$): 207.7, 137.6, 137.4, 136.9, 134.2, 128.6, 128.5 (2C), 128.4, 128.3,

128.2, 128.1, 128.0, 127.9, 119.9, 85.9, 80.9, 74.6, 74.4, 73.3, 70.9; Anal. calcd. for $C_{27}H_{28}O_4$: C, 77.86; H, 6.78. Found: C, 77.83; H, 6.67%.

2,3,5-Tri-*O*-benzyl-1,4-benzylimino-1,4-dideoxy-D-arabinitol (5) and -L-xylitol (6). A solution of ketone **4** (0.920 g, 2.21 mmol) in MeOH–CH_2Cl_2 (80 mL, 2 : 1) was cooled to −78 °C. N_2 was bubbled through the solution for 15 min followed by ozone for 30 min and then N_2 for 15 min. Me_2S (0.9 mL) was added and the reaction was warmed to room temperature. The mixture was concentrated and the residue dissolved in dry THF (70 mL). Molecular sieves (3 Å) were added followed by benzylamine (2 mL, 18.3 mmol) and then AcOH until pH ∼ 6–7. $NaCNBH_3$ (0.7 g, 11.1 mmol) was added at 0 °C and the reaction was stirred overnight at room temperature. The mixture was quenched with saturated aqueous $NaHCO_3$ (100 mL), filtered and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), concentrated and purified by flash chromatography (heptane–EtOAc, 8 : 1) to give a 5 : 2 mixture of **5** and **6** (0.674 g, 62%).

*For **5**.* R_f 0.35 (heptane–EtOAc, 3 : 1); $[\alpha]_D$ +25.8 (*c* 2, $CHCl_3$); δ_H (300 MHz, $CDCl_3$): 7.35–7.23 (m, 20H), 4.44 (s, 2H), 4.43 (s, 2H), 4.38 (d, $J = 12.4$ Hz, 1H), 4.30 (d, $J = 12.2$ Hz, 1H), 4.07 (d, $J = 13.1$ Hz, 1H), 3.84–3.82 (m, 2H), 3.54–3.52 (m, 2H), 3.41 (d, $J = 13.0$ Hz, 1H), 2.97 (d, $J = 10.5$ Hz, 1H), 2.79 (q, $J = 5.1$ Hz, 1H), 2.48 (dd, $J = 10.5$, 5.5 Hz, 1H); δ_C (75 MHz, $CDCl_3$): 139.0, 138.7, 138.5 (2C), 129.2, 128.6, 128.4, 128.0, 127.9, 127.8, 127.1, 86.1, 81.7, 73.5, 71.6, 71.5, 71.1, 68.7, 59.4, 57.2; HRMS calcd. for $C_{33}H_{36}NO_3$ $[M + H]^+$ *m/z* 494.2695, found *m/z* 494.2703.

*For **6**.* R_f 0.27 (heptane–EtOAc, 3 : 1); $[\alpha]_D$ +28.7 (*c* 2, $CHCl_3$) (lit.[38] $[\alpha]^{22}_D$ +30.5 (*c* 0.95, $CHCl_3$)); δ_H (300 MHz, $CDCl_3$): 7.32–7.26 (m, 20H), 4.64 (d, $J = 12.3$ Hz, 1H), 4.57 (d, $J = 12.3$ Hz, 1H), 4.53 (s, 2H), 4.42 (s, 2H), 4.15–4.00 (m, 3H), 3.87 (dd, $J = 9.6$, 6.2 Hz, 1H), 3.67–3.64 (m, 1H), 3.48 (d, $J = 13.0$ Hz, 1H), 3.30–3.25 (m, 1H), 3.15–3.13 (m, 1H), 2.35–2.31 (m, 1H); δ_C (75 MHz, $CDCl_3$): 139.1, 138.5 (2C), 138.2, 129.1, 128.5 (2C), 128.4, 128.3, 127.9, 127.8 (2C), 127.7 (2C), 127.6, 127.0, 83.6, 82.1, 73.6, 72.2, 71.5, 69.6, 65.4, 59.5, 57.3; HRMS calcd. for $C_{33}H_{36}NO_3$ $[M + H]^+$ *m/z* 494.2695, found *m/z* 494.2728.

1,4-Dideoxy-1,4-imino-D-arabinitol hydrochloride. Amine **5** (0.340 g, 0.689 mmol) was dissolved in 1.25 M HCl in MeOH (30 mL) and Pd/C (186 mg) was added. The reaction was stirred under 10 bar of H_2 for 4 days. The mixture was filtered through a short column of Celite, which was rinsed with MeOH. The filtrate was concentrated and co-concentrated with toluene to give a solid residue which was recrystallised from Et_2O–MeOH. This gave DAB hydrochloride as a white solid (0.086 g, 74%). Mp 110–112 °C (lit.[16a] mp 113–114 °C); $[\alpha]_D$ +31.1 (*c* 0.2, H_2O) (lit.[16a] $[\alpha]^{20}_D$ +34.7 (*c* 0.78, H_2O)); δ_H (300 MHz, D_2O): 4.30–4.27 (m, 1H), 4.04 (t, $J = 2.8$ Hz, 1H), 3.91 (dd, $J = 12.2$, 4.6 Hz, 1H), 3.78 (dd, $J = 12.0$, 8.5 Hz, 1H), 3.57–3.48 (m, 2H), 3.29 (dd, $J = 12.7$, 2.8 Hz, 1H); δ_C (75 MHz, D_2O): 76.4, 75.1, 67.3, 59.7, 50.7. NMR data are in accordance with literature values.[16]

(3*R*,4*R*)-1,3,4-Tris(benzyloxy)-2-(but-3-enylamino)-hex-5-ene (7). To a solution of ketone **4** (0.083 g, 0.199 mmol) in THF (8 mL) were added activated molecular sieves (3 Å), $InCl_3$ (0.226 g, 1.02 mmol), homoallylamine (0.145 g, 2.04 mmol) and $NaCNBH_3$ (0.024 g, 0.38 mmol). The mixture was stirred at room temperature for 3 h and then filtered. The filtrate was diluted with Et_2O (10 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL). The aqueous phase was extracted with Et_2O (3 × 5 mL) and the combined organic phases were dried (K_2CO_3) and concentrated. The residue was purified by flash chromatography (heptane–Et_2O–Et_3N, 66 : 33 : 1) to give **7** (0.060 g, 64%) as a 2 : 3 mixture of **7*S*** and **7*R***.

*For **7*S**.* R_f 0.35 (hexane–EtOAc, 3 : 1); $[\alpha]_D$ +9.5 (*c* 2, $CHCl_3$); ν_{max}(neat)/cm^{-1}: 2860, 1714, 1454, 1095, 734; δ_H (300 MHz, $CDCl_3$): 7.38–7.24 (m, 15H), 5.91–5.69 (m, 2H), 5.37–5.29 (m, 2H), 5.07–4.95 (m, 2H), 4.87 (d, $J = 11.2$ Hz, 1H), 4.60 (d, $J = 11.5$ Hz, 1H), 4.55 (d, $J = 11.4$ Hz, 1H), 4.37 (m, 3H), 4.17 (t, $J = 6.8$ Hz, 1H), 3.70 (dd, $J = 6.6$, 3.5 Hz, 1H), 3.45–3.43 (m, 2H), 2.93–2.88 (m, 1H), 2.76 (dt, $J = 11.2$, 7.1 Hz, 1H), 2.53 (dt, $J = 11.1$, 7.3 Hz, 1H), 2.18–2.11 (m, 2H); δ_C (75 MHz, $CDCl_3$): 139.2, 138.8, 138.5, 136.9, 136.0, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.7, 127.6, 127.5, 118.8, 116.0, 82.8, 81.7, 75.3, 73.2, 70.8, 69.7, 57.8, 47.4, 35.1; Anal. calcd. for $C_{31}H_{37}NO_3$: C, 78.95; H, 7.91; N, 2.97. Found: C, 78.62; H, 8.04; N, 2.96%.

*For **7*R**.* R_f 0.19 (hexane–EtOAc, 3 : 1); $[\alpha]_D$ −7.3 (*c* 1, $CHCl_3$); ν_{max}(neat)/cm^{-1}: 2862, 1454, 1095, 734, 699; δ_H (300 MHz, $CDCl_3$): 7.33–7.28 (m, 15H), 5.95–5.84 (m, 1H), 5.79–5.66 (m, 1H), 5.32–5.26 (m, 2H), 5.06–4.95 (m, 2H), 4.74 (d, $J = 11.5$ Hz, 1H), 4.64–4.59 (m, 2H), 4.52 (d, $J = 12.3$ Hz, 1H), 4.44 (d, $J = 12.0$ Hz, 1H), 4.35 (d, $J = 12.0$ Hz, 1H), 4.16 (dd, $J = 7.7$, 4.7 Hz, 1H), 3.67–3.56 (m, 3H), 2.95–2.91 (m, 1H), 2.61 (dt, $J = 11.3$, 7.0 Hz, 1H), 2.47 (dt, $J = 11.3$, 7.0 Hz, 1H), 2.10 (q, $J = 7.2$ Hz, 2H); δ_C (75 MHz, $CDCl_3$): 139.0, 138.7, 138.6, 136.9, 136.3, 128.4 (2C), 128.3, 128.2 (2C), 127.9, 127.6 (2C), 127.5, 118.4, 116.0, 81.6, 81.2, 74.9, 73.2, 70.7, 68.7, 58.3, 47.0, 34.9; Anal. calcd. for $C_{31}H_{37}NO_3$: C, 78.95; H, 7.91; N, 2.97. Found: C, 78.62; H, 8.04; N, 2.96%.

Methyl 1,3-*O*-isopropylidene-α-D-fructofuranoside (14). A mixture of sucrose (2.00 g, 5.84 mmol) and $TsOH{\cdot}H_2O$ (0.50 g, 2.63 mmol) in DMF (30 mL) was stirred at room temperature for 30 min. 2,2-Dimethoxypropane (8.0 mL, 66 mmol) was added and the resulting solution stirred for 48 h. The reaction was quenched with Na_2CO_3 (4.0 g) and stirred for an additional 1 h. The mixture was filtered and the filtrate concentrated at high vacuum. The residue was purified twice by flash chromatography (CH_2Cl_2–MeOH, 14 : 1 and then EtOAc–heptane, 2 : 1) to give **14** (0.804 g, 59%) as a syrup. R_f 0.40 (CH_2Cl_2–MeOH, 10 : 1); $[\alpha]_D$ +38.6 (*c* 2, $CHCl_3$) (lit.[36] $[\alpha]_D$ +42.5 (*c* 1, MeOH)); ν_{max}(neat)/cm^{-1}: 3416, 2989, 2944, 1378, 1219, 1096; δ_H ($CDCl_3$, 300 MHz): 4.08–4.05 (m, 1H), 4.00 (s, 1H), 3.95–3.85 (m, 3H), 3.77–3.75 (m, 2H), 3.27 (s, 3H), 3.08 (br s, 2H), 1.42 (s, 3H), 1.33 (s, 3H); δ_C (75 MHz, $CDCl_3$): 101.4, 98.8, 87.3, 79.9, 77.6, 62.8, 61.9, 48.7, 27.8, 19.5; δ_C (75 MHz, CD_3OD): 104.1, 100.4, 86.2, 83.4, 78.7, 63.4, 62.8, 48.6, 27.1, 21.3; HRMS calcd. for $C_{10}H_{19}O_6$ $[M + H]^+$ *m/z* 235.1182, found *m/z* 235.1179.

Methyl 6-deoxy-6-iodo-1,3-*O*-isopropylidene-α-D-fructofuranoside (15). To a solution of **14** (0.420 g, 1.79 mmol) in dry THF (16 mL) were added PPh_3 (0.71 g, 2.7 mmol) and imidazole (0.25 g, 3.7 mmol) and the mixture was heated to reflux. A solution of I_2 (0.7 g, 2.8 mmol) in dry THF (7 mL) was added quickly, and the reaction had gone to completion within a few minutes according to TLC. The mixture was cooled to room temperature, filtered and concentrated. The residue was purified by flash chromatography (hexane–EtOAc, 3 : 1) to afford **15** (0.520 g, 84%). R_f 0.19

(hexane–EtOAc, 4 : 1); $[\alpha]_D$ +26.1 (*c* 2, CH_2Cl_2); ν_{max}(neat)/cm^{-1}: 3445 (br), 2990, 2939, 1376, 1093; δ_H (300 MHz, $CDCl_3$): 4.19 (m, 1H), 4.02 (s, 1H), 3.97 (dd, $J = 9.9$, 1.7 Hz, 1H), 3.88 (d, $J = 1.2$ Hz, 1H), 3.36–3.29 (m, 2H), 3.28 (s, 3H), 2.87 (d, $J = 10.4$ Hz, 1H), 1.42 (s, 3H), 1.34 (s, 3H); δ_C (75 MHz, $CDCl_3$): 102.5, 98.8, 87.5, 80.2, 79.7, 61.9, 48.9, 27.9, 19.6, 5.6; Anal. calcd. for $C_{10}H_{17}IO_5$: C, 34.90; H, 4.98. Found: C, 35.24; H, 4.95%.

(1′*R*,4*S*)-2,2-Dimethyl-4-(1′-hydroxyallyl)-1,3-dioxan-5-one (16). To a solution of **15** (3.02 g, 8.78 mmol) in THF (50 mL) and H_2O (15 mL) was added pre-activated zinc (4.9 g, 75 mmol) followed by sonication for 1.5 h at 40 °C. The mixture was filtered through a short column of Celite and the column was rinsed with CH_2Cl_2. The filtrate was washed with saturated aqueous $NaHCO_3$ (100 mL). The aqueous layer was extracted with CH_2Cl_2 (100 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (CH_2Cl_2–MeOH, 49 : 1) to give **16** (1.14 g, 70%). R_f 0.19 (hexane–EtOAc, 4 : 1); $[\alpha]_D$ −164.9 (*c* 2, $CHCl_3$); ν_{max}(neat)/cm^{-1}: 3484 (br), 2988, 1750, 1377, 1227; δ_H (300 MHz, $CDCl_3$): 6.01–5.90 (m, 1H), 5.37 (dt, $J = 17.3$, 1.5 Hz, 1H), 5.22 (dt, $J = 10.5$, 1.5 Hz, 1H), 4.56 (br s, 1H), 4.27–4.21 (m, 2H), 3.99 (dd, $J = 17.1$, 1.2 Hz, 1H), 2.58 (br s, 1H), 1.45 (s, 3H), 1.44 (s, 3H); δ_C (75 MHz, $CDCl_3$): 208.2, 136.3, 116.8, 101.0, 77.2, 70.6, 67.2, 24.3, 23.5; HRMS calcd. for $C_9H_{14}O_4$ $[M]^+$ *m*/*z* 186.0892, found *m*/*z* 186.0903.

(1′*R*,4*R*)-5-(But-3-enylamino)-2,2-dimethyl-4-(1′-hydroxyallyl)-1,3-dioxane (17). To a solution of ketone **16** (0.058 g, 0.31 mmol) in dry THF (5 mL) were added activated molecular sieves (3 Å) and homoallylamine (0.24 g, 3.4 mmol). The mixture was cooled to 0 °C and AcOH was added until pH 6–7. $NaCNBH_3$ (0.095 g, 1.5 mmol) was then added and the reaction was stirred at room temperature for 1 h. The mixture was filtered and the filtrate was diluted with CH_2Cl_2 (10 mL) and washed with saturated aqueous $NaHCO_3$ (15 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL) and the combined organic phases were dried (K_2CO_3) and concentrated. The residue was purified by flash chromatography (CH_2Cl_2–MeOH, 19 : 1) to give **17** (0.048 g, 64%) as a 2 : 1 mixture of diastereomers which could not be separated. R_f 0.53 (CH_2Cl_2–MeOH, 9 : 1); ν_{max}(neat)/cm^{-1}: 3282, 2995, 2935, 1378, 1201, 1103; δ_H (300 MHz, $CDCl_3$): 6.05–5.64 (m, 4H), 5.43–5.00 (m, 8H), 4.36–4.34 (m, 1H), 4.24–4.21 (m, 1H), 3.93 (dd, $J =$ 11.5, 5.3 Hz, 1H), 3.85–3.83 (m, 2H), 3.70 (t, $J = 2.2$ Hz, 1H), 3.66 (dd, $J = 9.9$, 3.8 Hz, 1H), 3.45 (t, $J = 10.0$ Hz, 1H), 2.94–2.74 (m, 4H), 2.60–2.50 (m, 2H), 2.30–2.15 (m, 4H), 1.40 (s, 6H), 1.39 (s, 3H), 1.33 (s, 3H); δ_C (75 MHz, $CDCl_3$): 138.0, 137.3, 135.8 (2C), 117.0, 116.8, 115.8, 115.2, 99.3, 98.7, 75.6, 73.4, 73.2, 72.6, 63.6, 61.4, 55.1, 52.4, 46.0, 45.9, 34.6, 34.5, 29.6, 28.7, 19.3, 18.4; HRMS calcd. for $C_{13}H_{23}NO_3$ $[M]^+$ *m*/*z* 241.1678, found *m*/*z* 241.1672.

(1′*R*,4*R*,5*R*)-*N*-Benzyloxycarbonyl-5-(but-3-enylamino)-2,2-dimethyl-4-(1′-hydroxyallyl)-1,3-dioxane (18*R*) and (1′*R*,4*R*,5*S*)-*N*-benzyloxycarbonyl-5-(but-3-enylamino)-2,2-dimethyl-4-(1′-hydroxyallyl)-1,3-dioxane (18*S*). To a solution of aminodiene **17** (0.147 g, 0.609 mmol) in CH_2Cl_2 (20 mL) and H_2O (15 mL) was added $KHCO_3$ (0.49 g, 4.9 mmol) and the mixture was cooled to 0 °C. CbzCl (0.17 mL, 1.2 mmol) was added dropwise, and the stirring was continued for 45 min at room temperature. The organic phase was isolated and the aqueous phase extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (heptane–EtOAc, 3 : 1) to give **18*R*** (0.123 g, 54%) and **18*S*** (0.062 g, 27%).

For **18*R***: R_f 0.35 (hexane–EtOAc, 3 : 1); $[\alpha]_D$ −20.9 (*c* 2, $CHCl_3$); ν_{max}(neat)/cm^{-1}: 3459, 2990, 1679, 1429, 1227, 944; δ_H (300 MHz, $CDCl_3$): 7.39–7.26 (m, 5H), 5.94–5.63 (m, 2H), 5.32–5.00 (m, 6H), 4.55–4.39 (m, 1H), 4.17–4.04 (m, 2H), 3.80–3.47 (m, 3H), 3.20 (q, $J = 7.4$ Hz, 1H), 2.47–2.20 (m, 2H), 1.54, 1.38, 1.31, 1.16 (4s, 6H); δ_C (75 MHz, $CDCl_3$): 155.6, 137.8, 136.5, 135.1, 134.9, 128.9, 128.8, 128.7, 128.4, 128.2, 127.8, 117.3, 116.3, 116.2, 99.1, 72.0, 71.1, 70.8, 68.0, 67.2, 61.1, 60.2, 52.5, 49.1, 34.1, 33.4, 28.4, 20.3, 19.8; HRMS calcd. for $C_{21}H_{30}NO_5$ $[M + H]^+$ *m*/*z* 376.2124, found *m*/*z* 376.2114.

For **18*S***: R_f 0.18 (hexane–EtOAc, 3 : 1); $[\alpha]_D$ +10.6 (*c* 2.1, $CHCl_3$); ν_{max}(neat)/cm^{-1}: 3450 (br), 2990, 1696, 1422, 1384, 1288, 1228, 1200, 1148, 1011; δ_H (300 MHz, $CDCl_3$): 7.35–7.26 (m, 5H), 5.95–5.67 (m, 2H), 5.30–4.98 (m, 6H), 4.24–3.52 (m, 6H), 3.17 (d, $J = 5.0$ Hz, 1H), 2.43 (q, $J = 7.6$ Hz, 2H), 1.49 (s, 3H), 1.44 (s, 3H); δ_C (75 MHz, $CDCl_3$): 157.4, 136.5, 135.7, 135.1, 128.6, 128.2, 128.0, 116.5, 116.1, 99.6, 75.0, 71.7, 67.7, 64.6, 47.1, 45.8, 34.2, 29.5, 18.7; HRMS calcd. for $C_{21}H_{30}NO_5$ $[M + H]^+$ *m*/*z* 376.2124, found *m*/*z* 376.2112.

(1*R*,7*R*,8*R*)-*N*-Benzyloxycarbonyl-7-hydroxy-10,10-dimethyl-9,11-dioxo-2-azabicyclo[6.4.0]dodec-5-ene (19). A solution of diene **18*R*** (0.240 g, 0.639 mmol) in CH_2Cl_2 (30 mL) was degassed under argon. Grubbs 2nd generation catalyst (0.025 g, 0.029 mmol) was added and the reaction was stirred at room temperature overnight. The mixture was concentrated and the residue purified by flash chromatography (heptane–EtOAc, 2 : 1) to give **19** (0.200 g, 90%), which showed 2 rotamers by NMR. R_f 0.24 (heptane–EtOAc, 2 : 1); $[\alpha]_D$ +38.5 (*c* 2, $CHCl_3$); ν_{max}(neat)/cm^{-1}: 3476 (br), 2936, 1697, 1424, 1130; δ_H (300 MHz, $CDCl_3$): 7.37–7.31 (m, 5H), 5.65–5.46 (m, 2H), 5.12–4.92 (m, 2H), 4.74, 4.59 (2t, $J = 10.8$ Hz, $J = 9.4$ Hz, 1H), 4.34–3.78 (m, 3H), 3.67–3.57 (m, 1H), 2.93–2.81 (m, 2H), 2.32–2.10 (m, 2H), 1.64, 1.41, 1.31, 1.08 (4s, 6H); δ_C (75 MHz, $CDCl_3$): 156.1, 155.6, 136.3, 135.5, 134.4, 133.2, 129.2, 128.7 (2C), 128.5, 128.2, 128.1, 126.4, 125.9, 99.2, 99.0, 72.1, 72.0, 71.4, 69.6, 68.2, 66.9, 60.5, 59.5, 54.8, 54.0, 46.4, 46.1, 29.1, 28.9, 27.0, 26.8, 19.9, 19.4; HRMS calcd. for $C_{19}H_{26}NO_5$ $[M + H]^+$ *m*/*z* 348.1811, found *m*/*z* 348.1790.

(2*R*,3*R*,4*R*)-*N*-Benzyloxycarbonyl-5,6-didehydro-3,4-dihydroxy-2-hydroxymethyl-azocane (20). Cycloheptene **19** (0.171 g, 0.492 mmol) was dissolved in 80% AcOH (3 mL) and stirred at room temperature for 4 h. The mixture was concentrated and the residue was purified by flash chromatography (CH_2Cl_2–MeOH, 9 : 1) to afford **20** (0.117 g, 77%). R_f 0.48 ($CHCl_3$–MeOH, 9 : 1); $[\alpha]_D$ +69.6 (*c* 2, $CHCl_3$); ν_{max}(neat)/cm^{-1}: 3416 (br), 2948, 1678, 1436, 1235, 1058; δ_H (300 MHz, $CDCl_3$): 7.39–7.26 (m, 5H), 5.60 (dd, $J = 10.7$, 6.0 Hz, 1H), 5.51–5.44 (m, 1H), 5.14–4.98 (m, 2H), 4.27–3.76 (m, 5H), 2.94–2.87 (m, 2H), 2.32–2.14 (m, 2H); δ_C (75 MHz, $CDCl_3$): 157.6, 136.1, 134.7, 128.6, 128.4, 128.1, 125.6, 72.3, 69.3, 67.6, 65.4, 62.1, 46.2, 26.7; HRMS calcd. for $C_{16}H_{22}NO_5$ $[M + H]^+$ *m*/*z* 308.1498, found *m*/*z* 308.1491.

(9*R*,10*R*,10*aR*)-9,10-Dihydroxy-1,5,6,9,10,10*a*-hexahydro[1,3]-oxazolo[3,4-*a*]azocin-3-one (21). To a solution of the triol **20** (0.070 g, 0.228 mmol) in MeOH (2 mL) was added a 1 M solution of NaOMe in MeOH (0.1 mL). The mixture was stirred at room

temperature for 7.5 h and then concentrated. The residue was partitioned between CH_3CN (3 ml) and H_2O (5 mL) and the phases were separated. The aqueous phase was extracted with CH_3CN (2 × 3 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (CH_2Cl_2–MeOH, 9 : 1) to give **21** (0.026 mg, 57%). R_f 0.38 (CH_2Cl_2–MeOH, 9 : 1); ν_{max}(neat)/cm^{-1}: 3378 (br), 1746, 1423, 1215, 1065; δ_H (300 MHz, CD_3CN): 5.61–5.55 (m, 2H), 4.38 (dd, J = 8.9, 2.2 Hz, 1H), 4.28 (dd, J = 9.0, 7.8 Hz, 1H), 4.20 (dd, J = 9.7, 3.9 Hz, 1H), 3.75 (br s, 1H), 3.57–3.45 (m, 3H), 3.20–3.20 (m, 2H), 2.39–2.23 (m, 2H); δ_C (75 MHz, CD_3CN): 160.8, 135.6, 126.5, 75.4, 71.0, 68.8, 58.9, 44.6, 27.1; HRMS calcd. for $C_9H_{14}NO_4$ $[M + H]^+$ m/z 200.0923, found m/z 200.0956.

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